The University Of Sheffield.

Synthesis of Pyrroloquinolines and Pyrroloquinoxalinones Using Azomethine Ylide Cycloaddition Chemistry

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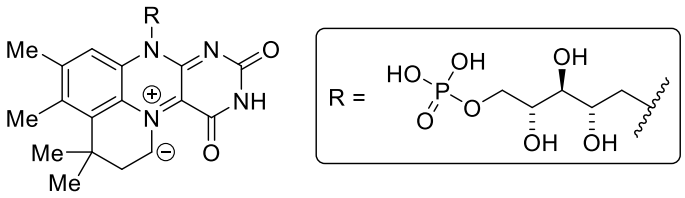
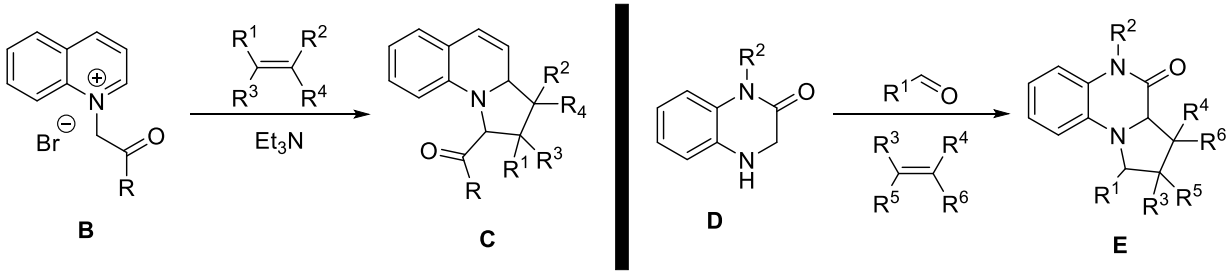
Abstract

This thesis describes the synthesis of pyrroloquinolines and pyrroloquinoxalinones in order to probe a decarboxylation mechanism which takes place in nature. The mechanism is believed to occur through an azomethine ylide cycloaddition reaction using ylide **A**. Simplifying this model, cycloadducts with the general structure of **C** were synthesised from quinolinium salts **B**. In addition, oxidation, reduction and Suzuki-Miyaura coupling reactions were carried out on the cycloadducts generated. Cycloadducts with the general structure of **E** were synthesised *via* ylides generated from the condensation of amine **D** with aldehydes. For both series of cyclodducts the substrate scope was limited, but reactions worked well with *N*-methylmaleimide. Unfortunately, attempts at generating cycloadducts with ylides more closely resembling **A** were unsuccessful.

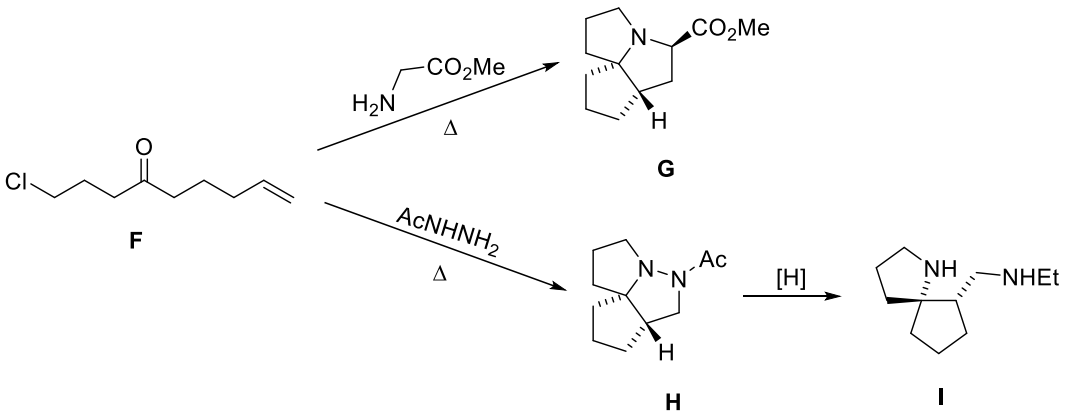


A

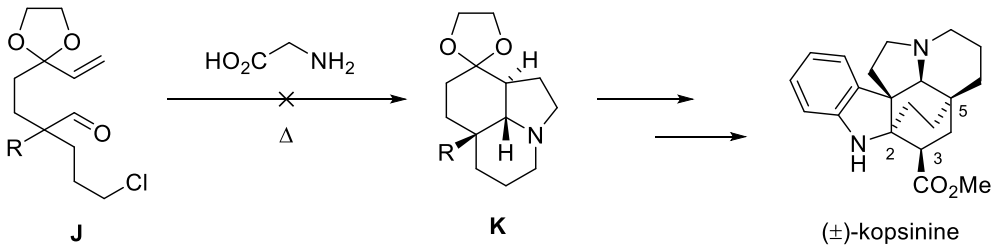


B **C** **D** **E**

Using a cascade process, the reaction of ketone **F** with either glycine or acetyl hydrazine gave tricyclic cycloadducts **G** and **H** through the corresponding azomethine ylide or imine. Although the substrate scope was limited with these reactions the N-N bond in **H** could be cleaved to give the spirocyclic compound **I**.



Finally, we envisaged that by applying a similar cascade process to aldehydes with the general structure of **J** then cycloadduct **K** could be obtained. Subsequent transformations on any of the cycloadducts generated would potentially lead to the natural product (±)-kopsinine. Although different analogues of aldehyde **J** were synthesised no cascade reactions took place to give **K**.



Acknowledgements

So, I suppose this is it…

First I would like to thank Prof Iain Coldham for giving me the opportunity to do my PhD in his group. The help and support throughout my time in the group has been much appreciated.

I would also like to thank everyone in the Coldham group over the past few years. Nick, Ruaa, Tahani, Ziad and Rungroj thanks for making my early days in the group more entertaining then what they may have been. However, I would like to say a special thanks to certain people. Ashraf I would make the joke and say thanks for all the proof reading, repair jobs, and lone master's students to look after, but in hindsight there were some good times. In particular, reminders about the correct pronunciation of the number "…eleven…" have provided much humour over the past few years. Jennifer thanks for putting up with me on a daily basis in my final year, even when I was in "bitey" mode, for showing me that peaches can look like radishes and for expressing your dislike of broccoli (actually most green vegetables) and carrots. I would list more things here (e.g. Star Wars, hair stroking, travel earrings, airplane mode, Korean love hearts and Chris Hemsworth) but more importantly thanks for being a good friend and for the laughs along the way. Beth thank-you as well: your joyful and bubbly personality has made my days a lot happier towards the end of my PhD, so keep on going and you'll be great. To all the master's students I've looked after officially (and un-officially, you know who you are) I would like to thank you all for making the lab a fun place work in and for the general humour, banter and (on occasion) sarcasm that has accompanied you all. Special thanks goes to Rebecca, Jemma, Matt and Robbie who have all been brilliant students and have "churned" whilst under my supervision on cycloaddition projects.

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Finally, I would like to thank my mum, dad, sister and Nelson (the cat) for their support throughout my PhD.

Contents

Abbreviations

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
UbiD or ubiD	3-octaprenyl-4-hydroxybenzoate decarboxylase
DMAP	4-dimethylaminopyridine
Ac	acetyl
Å	angstrom
atm	atmosphere
Bn	benzyl
TEBAC	benzyltriethylammonium chloride
b.p.	boiling point
BHT	butylated hydroxytoluene
CSA	camphorsulfonic acid
CDI	carbonyldiimidazole
cm	centimetre(s)
c	concentrated
Cy	cyclohexyl
°C	degrees Celsius
DFT	density functional theory
DCB	dichlorobenzene
DIBAL-H	diisobutylaluminium hydride
DME	dimethoxyethane
DMSO	dimethyl sulfoxide
DMF	dimethylformamide
DMPU	dimethylpropyleneurea
EDG	electron donating group
EI	electron impact
EWG	electron withdrawing group
ES	electrospray

ee	enantiomeric excess
eq	equivalent(s)
Fdc or fcd	ferulic acid decarboxylase
FAD	flavin adenine dinucleotide
FMN	flavin mononucleotide
UbiX or ubiX	flavin prenyltransferase
FT	fourier transform
FMO	frontier molecular orbital
g	gram(s)
Hz	hertz
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HOMO	highest occupied molecular orbital
h	hour(s)
IR	infrared
^{i}Pr	isopropyl
lit.	literature
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
m/z	mass to charge ratio
*m*CPBA	*m*-chloroperoxybenzoic acid
MHz	megahertz
m.p.	melting point
Mes	mesitylene
Ms	methanesulfonyl
µW	microwave
mg	milligram(s)
mL	millilitre(s)
min	minute(s)

M	molar
mol	mole(s)
MS	molecular sieves
nm	nanometre(s)
n-Bu	*n*-butyl
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
ppm	parts per million
Ph	phenyl
PPA	polyphosphoric acid
prFMN	prenylated flavin mononucleotide
Pad or pad	protein-arginine deiminase
rt	room temperature
Boc	*tert*-butoxycarbonyl
t-Bu	*tert*-butyl
TBDMS	*tert*-butyldimethylsilyl
TBAI	tetrabutylammonium iodide
THF	tetrahydrofuran
TBAF	tetra-*n*-butylammonium fluoride
TPP	tetraphenylporphyrin
TLC	thin layer chromatography
TOF	time of flight
Ts	toluenesulfonyl
TBA	tribromoacetic acid
TFAA	trifluoroacetic anhydride
Tf	trifluoromethanesulfonyl
TMS	trimethylsilyl
UV	ultraviolet
v/v	volume/volume percentage
w/v	weight/volume percentage

Chapter 1 – Introduction

1.1 Azomethine ylides

Azomethine ylides are an example of a nitrogen-based 1,3-dipole. Structurally they are planar molecules made up of three sp^2 hybridised atoms forming a C–N–C unit. The molecule contains 4 π-electrons spread over the three atoms and can be represented by 4 different resonance structures which are shown in Figure 1.[1]

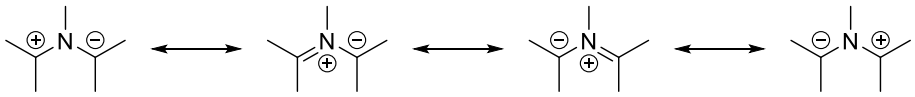


Figure 1 – Resonance forms of an azomethine ylide

In the presence of dipolarophiles, azomethine ylides can undergo 1,3-dipolar cycloaddition reactions to generate a variety of heterocycles.[2–6] Although they were first discovered in 1963 by Huisgen, the use of azomethine ylides in intramolecular cycloaddition reactions was not carried out until 1976.[1,7] However, since then they have been studied widely for the formation of 5-membered cyclic amines, such as pyrrolidines, dihydropyrroles and pyrroles. Importantly, 1,3-dipolar cycloaddition reactions have been used to generate a variety of products *via* regiocontrolled and stereocontrolled pathways.[8]

Applying the Woodward−Hoffmann rules to the reaction of a 1,3-dipole with a suitable dipolarophile, we can see the reaction involves 6 π-electrons [$_{\pi}4_s$ + $_{\pi}2_s$].[9] The reaction is suprafacial on both π-systems and is therefore thermally allowed. It is generally accepted that the reaction is a concerted process, where the two carbon-carbon σ-bonds form at the same time and on the same face of both the ylide and dipolarophile.[10] As a result, the relative stereochemistry of the alkene dipolarophile is maintained in the cycloadduct. A general diagram of the concerted process is shown in Figure 2.

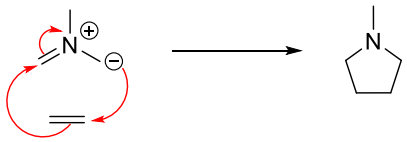


Figure 2 – A 1,3-dipolar cycloaddition reaction

The cycloaddition reaction can be explained using frontier molecular orbital (FMO) theory. The dominant orbital interaction in the cycloaddition reaction is between the highest occupied molecular orbital (HOMO) of the azomethine ylide and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile (Figure 3).[11] As a result of this, azomethine ylides prefer to react with electron poor dipolarophiles in intermolecular cycloadditions, whereas intramolecular cycloaddition reactions can occur with electron rich alkenes and this makes it difficult to see which frontier orbital interaction dominates.

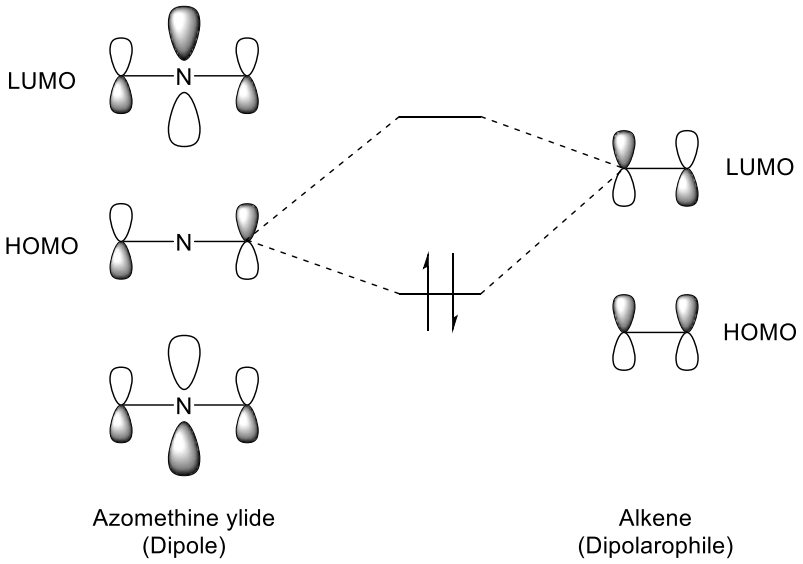


Figure 3 – Frontier Molecular Orbital Diagram

Stereochemistry is an important factor to consider in cycloaddition reactions, as up to four new stereocentres are formed in the cycloadduct. Therefore, this could potentially result in the formation of 16 stereoisomers for each regioisomer. The stereochemistry of the C2 and C5 atoms in the cycloadduct are determined by the shape of the azomethine ylide. There are four possible geometries an azomethine ylide can adopt, which are shown in Figure 4. The W-shaped and U-shaped ylides lead to the formation of the 2,5-*cis*-disubstituted pyrrolidine products; whereas the two S-shaped ylides lead to the formation of the 2,5-*trans*-disubstituted pyrrolidine products.

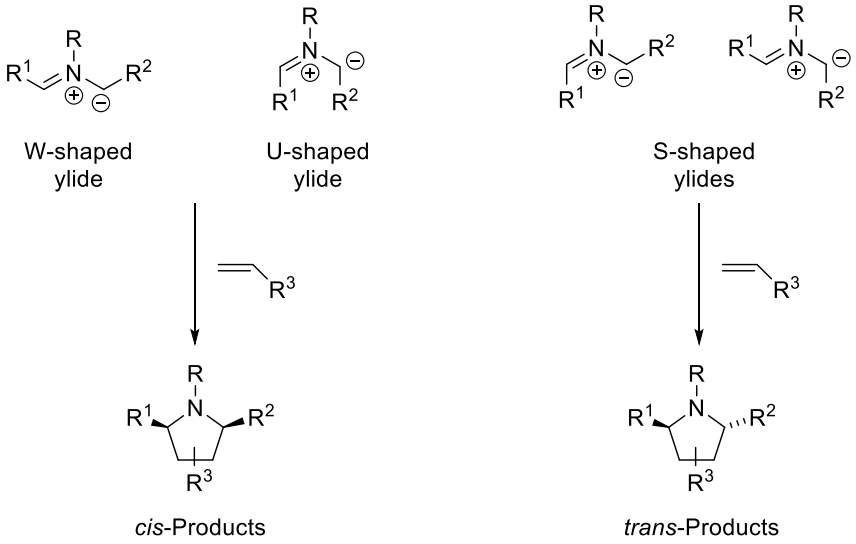


Figure 4 – Different shaped ylides forming cis or trans products

In comparison, the stereochemistry of the C3 and C4 atoms is determined by the relative orientation of the substituents in the dipolarophile. Due to cycloaddition reactions occurring *via* a concerted mechanism they are usually stereospecific with respect to the alkene. As a result, *trans*-disubstituted alkenyl dipolarophiles generally lead to the formation of the 3,4-*trans*-disubstituted pyrrolidine products, while *cis*-disubstituted alkenyl dipolarophiles lead to the formation of the 3,4-*cis*-disubstituted pyrrolidine products (Figure 5).

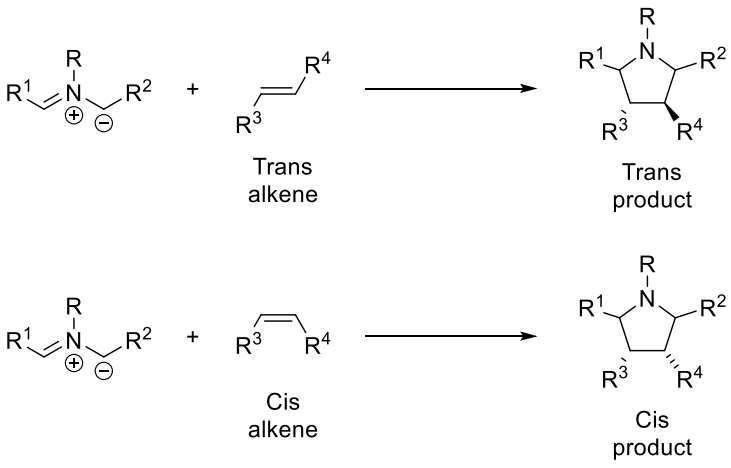


Figure 5 – Different shaped alkenes forming cis or trans products

The orientation of the dipolarophile with respect to the azomethine ylide is another important factor as this can lead to the formation of *endo* and *exo* diastereoisomers. In general, like Diels−Alder reactions, there is a preference for the substituents on the alkene dipolarophile to adopt an *endo*

orientation, rather than the *exo*, during the cycloaddition reaction. Therefore, in most reactions the *endo* product is preferred (Figure 6).

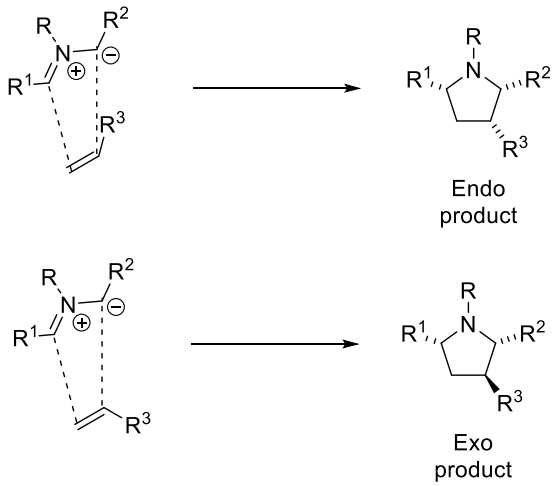


Figure 6 – Endo and Exo selectivity in cycloaddition reactions

Most cycloaddition reactions are highly regioselective, however if either the dipole and/or dipolarophile are unsymmetrical then regioselectivity is another important factor to consider (Figure 7).[12] This is usually determined by the sizes of the molecular orbitals involved in the reaction, where the preferred regioisomer is formed as a result of the maximum overlap between the orbitals in the reactants. The relative sizes of the molecular orbitals can be influenced by the presence of electron withdrawing groups (EWG) and electron donating groups (EDG) on each reactant. In addition, steric and electronic effects may also have an impact on the regioselectivity.

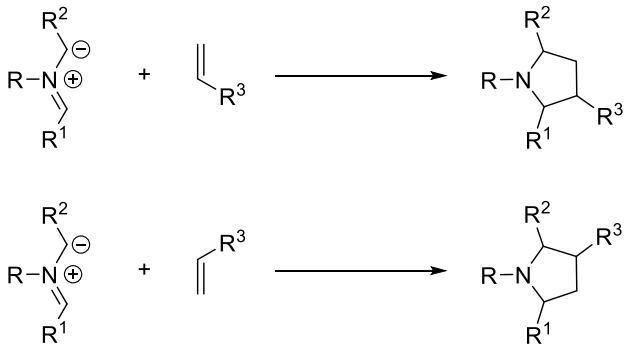
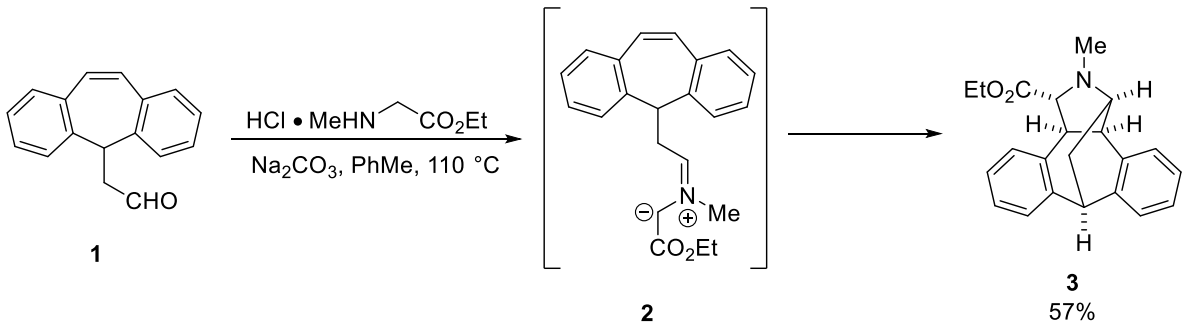


Figure 7 – Regioselectivity in cycloaddition reactions

1.2 Formation of azomethine ylides

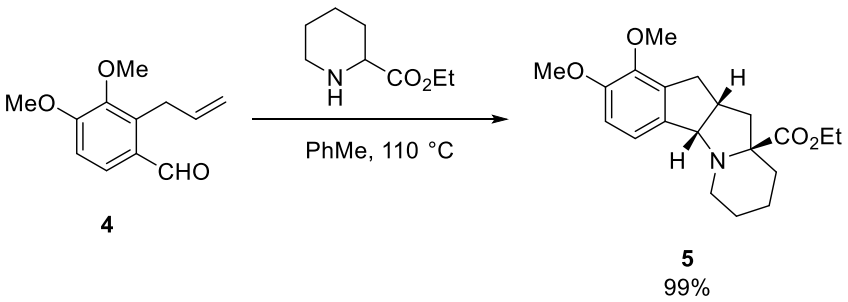
Due to their unstable nature, azomethine ylides are usually synthesised *in-situ*, and once formed can then react with dipolarophiles to generate cycloadducts *via* an intramolecular or intermolecular cycloaddition reaction.[1] Although there are many ways to generate azomethine ylides, this brief introduction will focus only on a few methods which will be used later in future chapters.

One of the simplest ways to generate azomethine ylides is by the reaction of an aldehyde or ketone with a primary or secondary amine. If the amine contains an electron withdrawing group in the α-position, such as an ester, then the resulting iminium ion can be deprotonated to give an azomethine ylide. Typical examples of amines used to generate azomethine ylides are α-amino esters due to their wide availability. One of the first reported examples of this chemistry was in 1983 by Confalone and co-workers.[13] An example is shown in Scheme 1 where aldehyde **1** was heated with *N*-methyl glycine ethyl ester hydrochloride and Na_2CO_3 in toluene. From this, cycloadduct **3** was isolated in 57% yield.



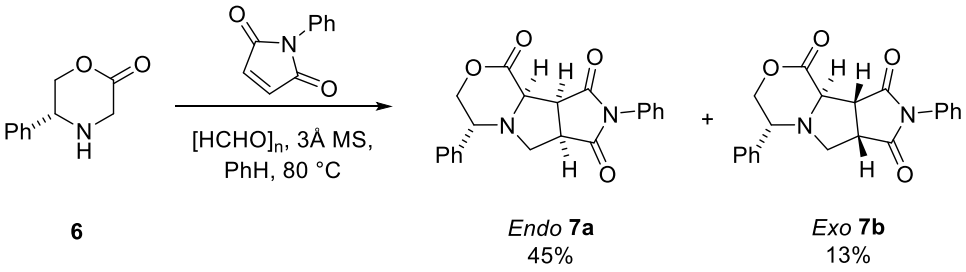
Scheme 1

The range of substrates was then later expanded by using different aldehydes and α-amino esters.[14,15] This generated a variety of different cycloadducts in good yields. An interesting example is shown in Scheme 2 where aldehyde **4** was reacted with pipecoline ethyl ester to give compound **5** in 99% yield.



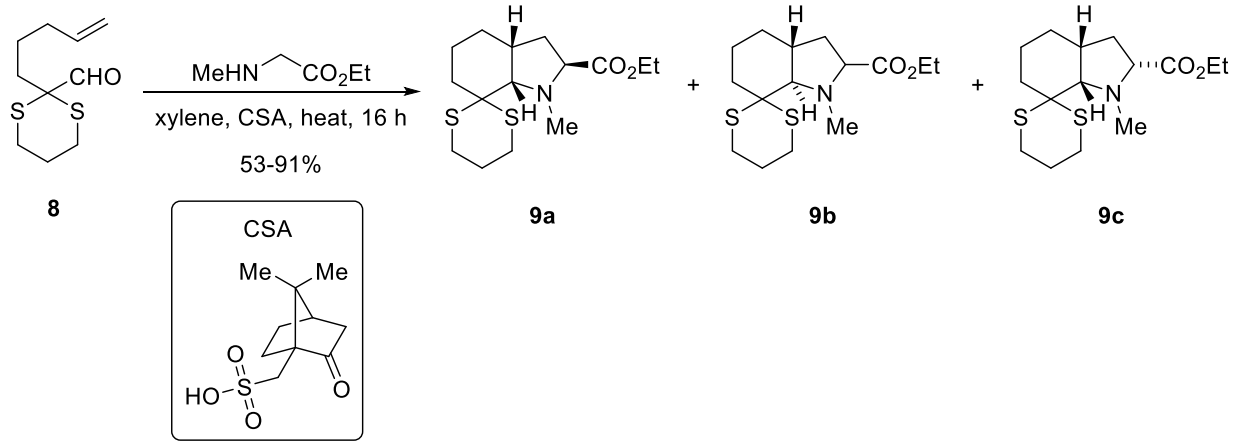
Scheme 2

Alongside this cyclic esters (lactones) have also been used to generate azomethine ylides, which in turn has allowed access to a variety of different polycyclic compounds. As shown in Scheme 3 Harwood and co-workers reacted lactone **6** with paraformaldehyde and *N*-phenylmaleimide to give cycloadducts **7a** and **7b**. Development of this chemistry eventually led to the synthesis of enantiomerically pure α-substituted proline derivatives, demonstrating the wider application of this chemistry.[16]



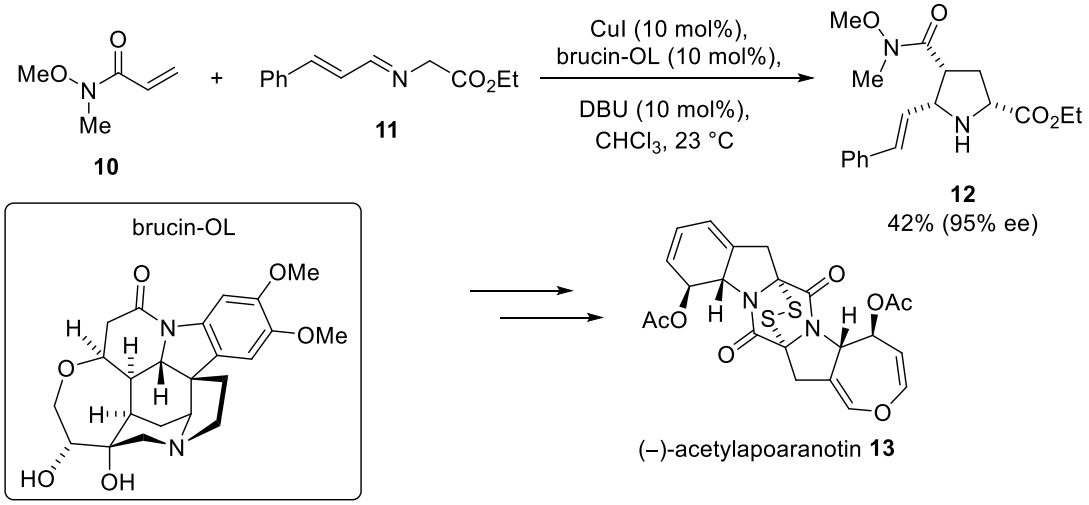
Scheme 3

It should be noted that most examples of this type of chemistry use aromatic aldehydes to generate the ylide.[17–21] However, aliphatic aldehydes can be used as well. An example of this chemistry has been done by Coldham and co-workers and is summarised in Scheme 4.[22] Aldehyde **8** was first reacted with *N*-methyl glycine ethyl ester in xylene with a Dean-Stark trap to give the major product **9a** (*via* the S-shaped ylide) and two other inseparable isomers, which were tentively assigned as the *trans*- fused cycloadduct **9b** and isomer **9c**.



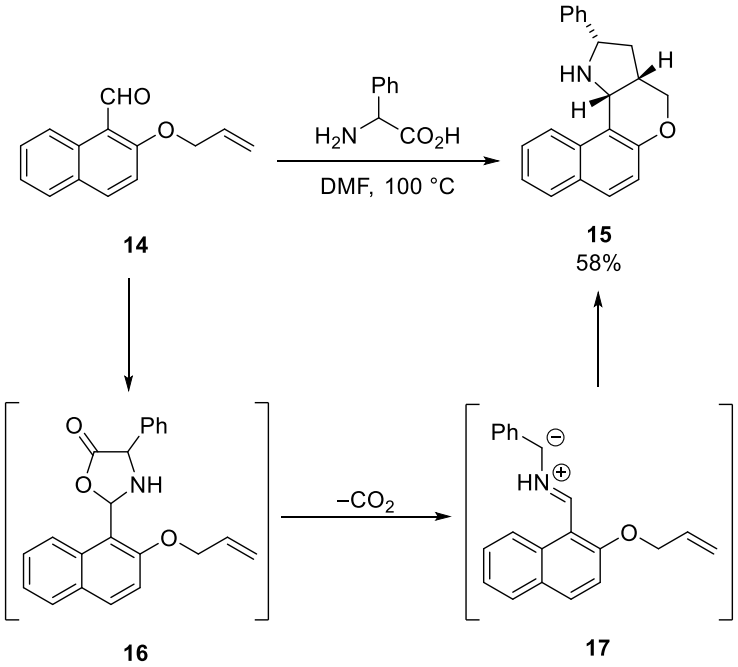
Scheme 4

In addition to using aliphatic aldehydes, additives and metal catalysts can be added to a cycloaddition reaction to induce selectivity. A recent example using α-amino esters is shown in Scheme 5 where Reisman and co-workers utilised a Cu(I)/brucin-OL catalysed 1,3-dipolar cycloaddition reaction between Weinreb amide **10** and imine **11**, derived from cinnamaldehyde and glycine ethyl ester, to synthesise pyrrolidine **12** in 42% yield and 95% enantiomeric excess (ee). Subsequent reactions on **12** then led to the total synthesis of (−)-acetylapoaranotin **13**.[23]



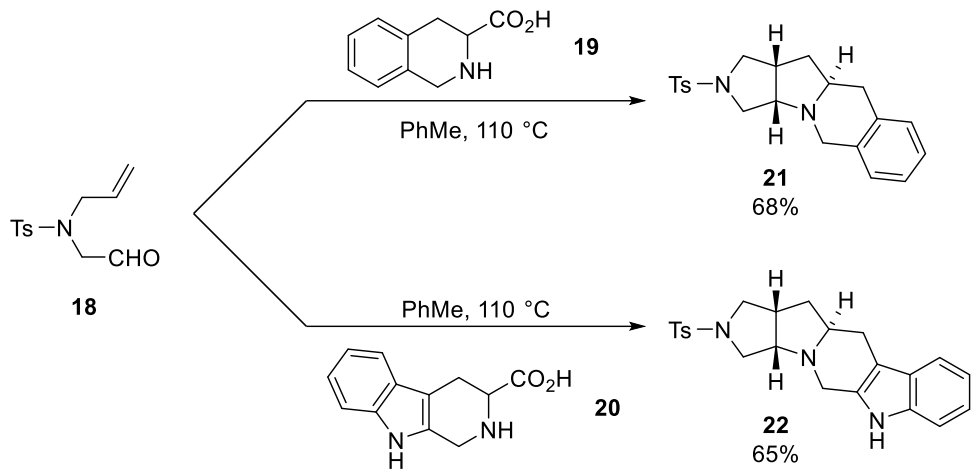
Scheme 5

One of the major drawbacks of using α-amino esters to generate azomethine ylides is that the ester group used to stabilise the ylide remains on the cycloadduct formed. While there are methods to remove the ester functional group, generating an unstabilised azomethine ylide *via* decarboxylation can be done to overcome this problem.[1] This type of chemistry has been widely studied by Grigg and co-workers and an example is shown in Scheme 6.[24,25] Heating aldehyde **14** with phenyl glycine in DMF formed product **15**, *via* the W-shaped ylide **17**, as a single diastereoisomer. It is thought that the reaction proceeds through the oxazolidinone intermediate **16**, which when heated releases carbon dioxide generating the unstabilised azomethine ylide **17**.



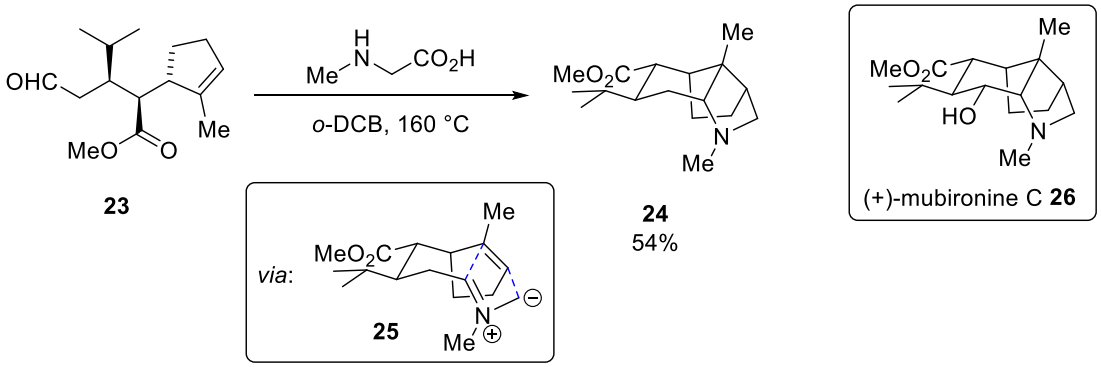
Scheme 6

This chemistry has been used to synthesise a number of potential drug molecules and natural products.[26,27] An example is shown in Scheme 7 where aldehyde **18** was heated separately with 1,2,3,4-tetrahydro-isoquinoline-2-carboxylic acid **19** and 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid **20** to give products **21** and **22** respectively.



Scheme 7

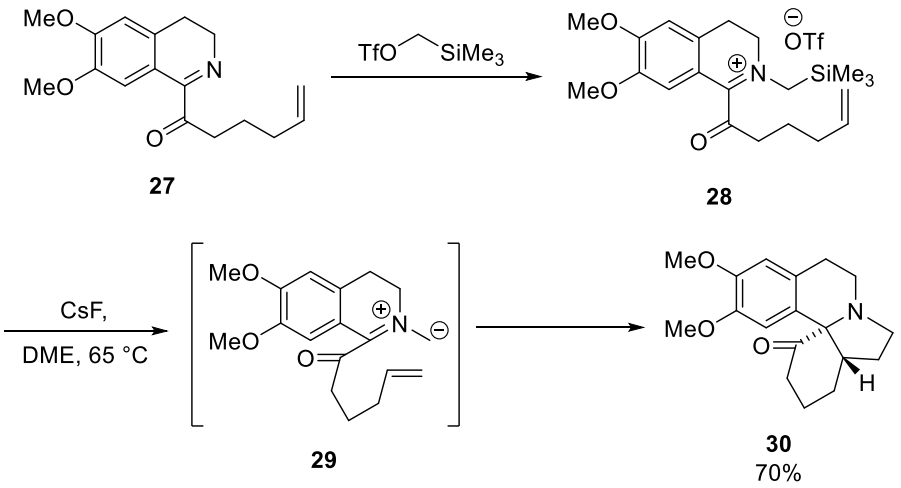
A more recent example using decarboxylation to form unstabilised ylides is shown in Scheme 8. This work was carried out by Trauner and co-workers where they managed to synthesise 5-deoxymubironine C **24** *via* a cycloaddition reaction of **23** with sarcosine.[28] It was thought that the reaction proceeded through azomethine ylide **25.** The synthesis of these carbon frameworks was particularly interesting as they can be seen in natural products such as (+)-mubironine C **26**.



Scheme 8

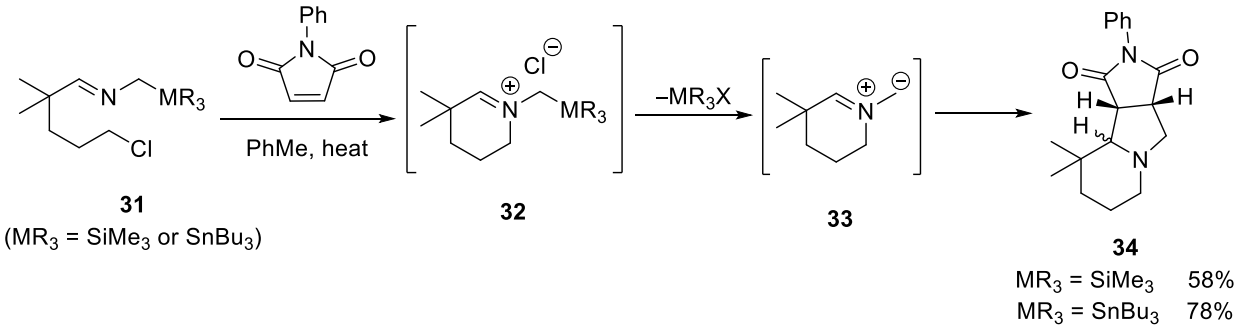
Another useful method that allows the formation of unstabilised ylides involves desilylation. One of the first examples of using this method is shown in Scheme 9. The work was carried out by Livinghouse and co-workers in 1986 and was towards synthesising the core structure of the erythrinane alkaloids. Imine **27** was alkylated with trimethylsilylmethyl triflate to form iminium **28**.

Using caesium fluoride then allowed the formation of azomethine ylide **29**, which underwent a cycloaddition reaction to afford cycloadduct **30** as a single diastereoisomer.[29,30]



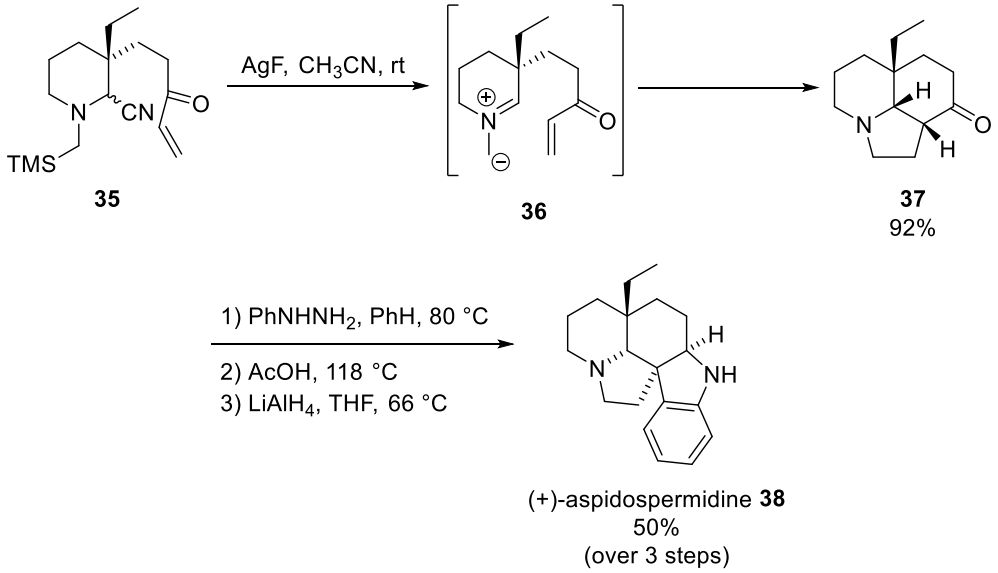
Scheme 9

In 1997 and then in 2004, Pearson and co-workers reported the formation of azomethine ylides *via* intramolecular *N*-alkylation of imines and subsequent desilylation.[31,32] These azomethine ylides were treated with a range of dipolarophiles to produce a series of indolizidine products through an intermolecular cycloaddition process. A destannylation method was also developed as well and through altering the chain length of the starting imine it was found that different cyclic azomethine ylides could be generated, forming products with larger ring sizes (five, six, seven, and eight but with a poorer yield). An example is shown in Scheme 10 where imine **31** was heated in toluene to give iminium **32**. The azomethine ylide **33** was then generated either through desilylation or destannylation, and a subsequent cycloaddition reaction with *N*-phenylmaleimide then gave the final product **34** in good yields as a 1:1 mixture of *endo* and *exo* isomers.



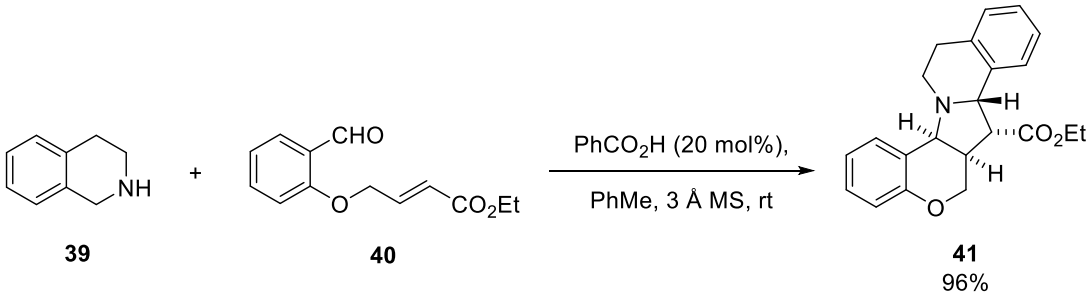
Scheme 10

A more recent application of desilylation to form an azomethine ylide is shown in Scheme 11. In 2016, Pandey and co-workers managed to synthesise (+)-aspidospermidine **38** where the key step involved an intramolecular cycloaddition reaction.[33] Mixing precursor **35** with silver fluoride in acetonitrile generated azomethine ylide **36** which underwent a cycloaddition reaction to form cycloadduct **37** in a very good yield of 92% as a single diastereoisomer. Subsequent Fischer indole and reduction reactions on cycloadduct **37** gave (+)-aspidospermidine **38** in 50% yield.



Scheme 11

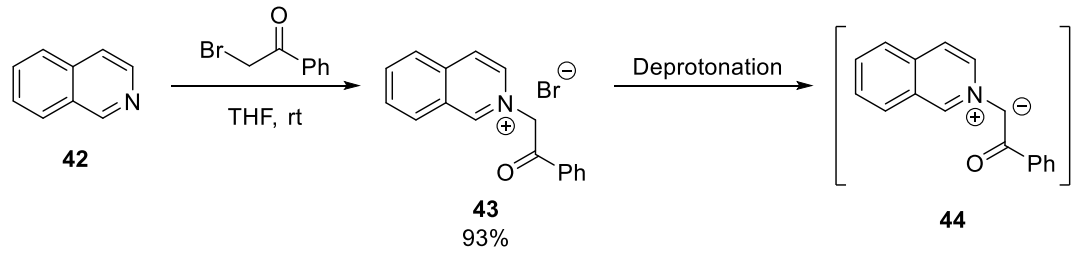
Unstabilised azomethine ylides can sometimes be generated through deprotonation without the need of a carbonyl group in the α-position of the amine or loss of TMS. This chemistry has been carried out by Siedel and co-workers and an example is shown in Scheme 12.[34] 1,2,3,4-Tetrahydroisoquinoline **39** first undergoes a condensation reaction with benzaldehyde derivative **40** in the presence of benzoic acid, 3 Å molecular sieves (MS) and toluene. This generates an azomethine ylide intermediate, which undergoes an intramolecular cycloaddition reaction to give compound **41** in 96% yield. The reaction scope was further expanded to include a variety of other amines, such as indoline, pyrrolidine and piperidine.



39 + **40** → **41** 96%

Scheme 12

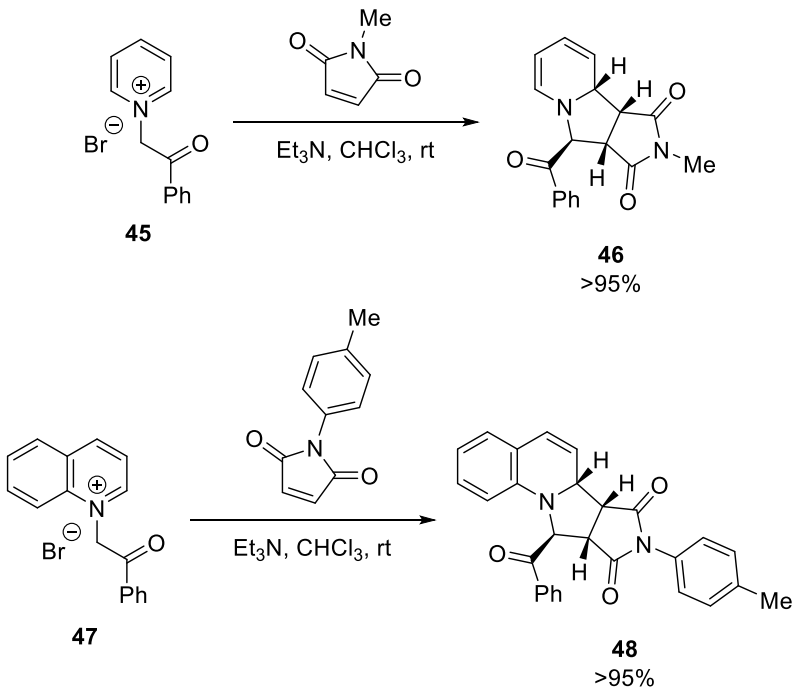
An alternative method to synthesise azomethine ylides is through the deprotonation of iminium salts, which can be generated through the N-alkylation of aromatic nitrogen containing heterocycles, such as pyridine, isoquinoline and other similar structures.[35–41] An example reaction is shown in Scheme 13 where salt **43** was formed from the reaction of isoquinoline **42** with 2-bromoacetophenone in tetrahydrofuran (THF). Subsequent deprotonation of **43** then generated the azomethine ylide **44**.



42 → **43** 93% → **44**

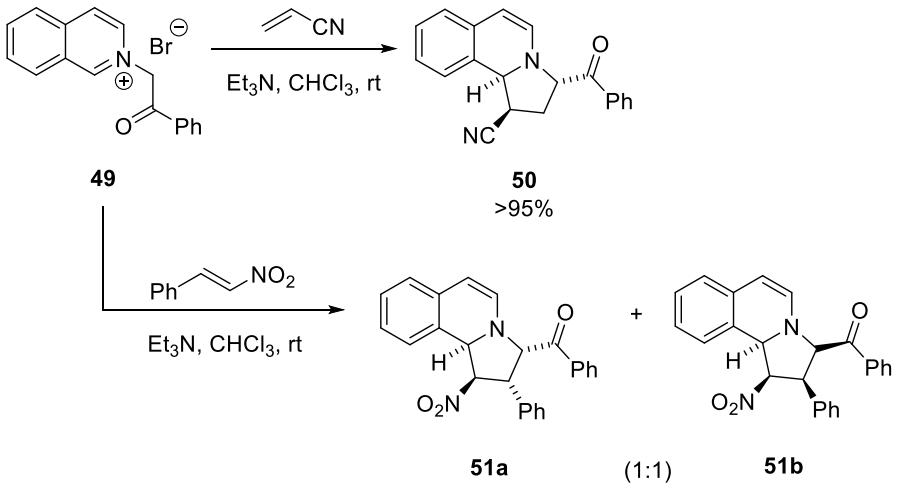
Scheme 13

This method of generating azomethine ylides has been used many times throughout the literature to synthesise a variety of cycloadducts. One of the first examples of this work was done by Tsuge and co-workers who managed to synthesise a wide range of iminium salts and react them with different symmetrical alkenes.[42] Some example reactions are shown in Scheme 14 where salts **45** and **47** were deprotonated using triethylamine and reacted with *N*-methylmaleimide and *N*-tolylmaleimide respectively. This gave cycloadducts **46** and **48** in quantitative yields.



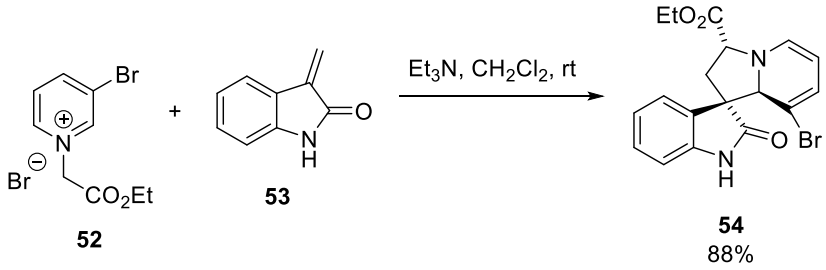
Scheme 14

Tsuge and co-workers then expanded the range of reactions to include a large number of unsymmetrical alkenes.[43] Two examples are shown in Scheme 15 where salt **49** was reacted with acrylonitrile or with *trans*-*β*-nitrostyrene to give products **50** and isomers **51a** and **51b** respectively. Isomers **51a** and **51b** were isolated in a 1:1 ratio, which implied that the reaction may not have occurred *via* a concerted process.



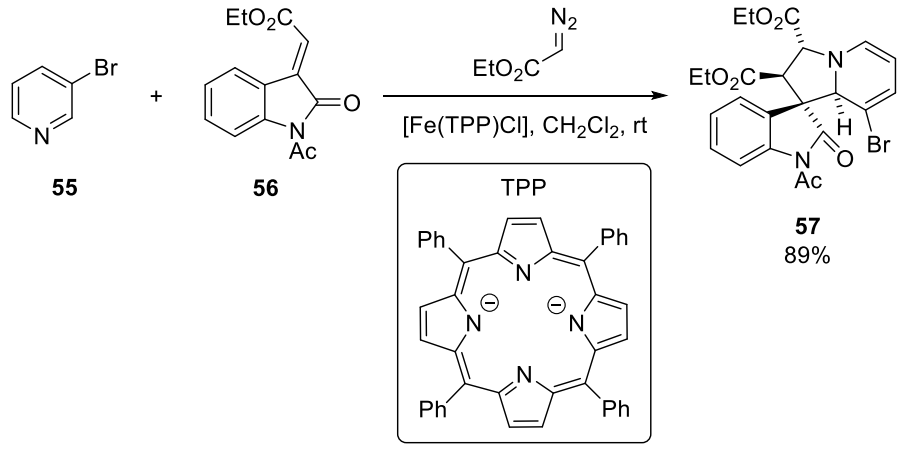
Scheme 15

Spirocyclic compounds can be synthesised using this chemistry. Some recent work in this area has been carried out by Dowden and co-workers and an example is shown in Scheme 16, where pyridinium salt **52** was reacted with 3-alkenyl oxindole **53** to give the spirocyclic compound **54** as a single diastereoisomer in 88% yield.[44] The substrate scope was then expanded using different substituted pyridinium salts and 3-alkenyl oxindoles, which gave a range of novel spirocyclic oxindoles in high yields and with very good regioselectivity and diastereoselectivity.



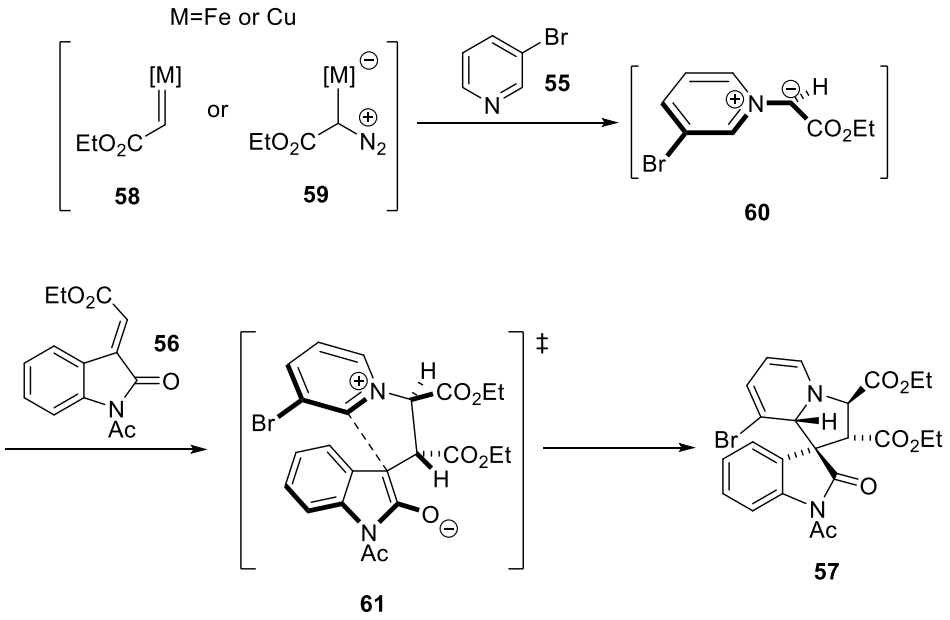
Scheme 16

This work was then developed further to synthesise a series of highly functionalized tetrahydroindolizidines in good yields with generally excellent diastereoselectivity.[45] An example is shown in Scheme 17 where the corresponding pyridinium ylide was generated from pyridine derivative **55** and ethyl diazoacetate in the presence of [Fe(TPP)Cl]. A subsequent *in-situ* cycloaddition with alkene **56** gave cycloadduct **57** in 89% yield as a single diastereoisomer.



Scheme 17

It is important to mention that mechanistic studies were carried out which suggested a stepwise process was taking place where once the pyridinium ylide formed, *via* nucleophilic addition to the metal carbene or diazonium ylide, it then underwent 1,4-addition to the alkenyloxindole. A subsequent cyclisation reaction would then generate the final product. A general mechanism using pyridine derivative **55**, ethyl diazoacetate and alkene **56** is shown in Scheme 18.



Scheme 18

To summarise this chapter, we have demonstrated that azomethine ylides can be generated in a number of different ways. Once they have been formed *in-situ* they can react with dipolarophiles *via* 1,3-dipolar cycloaddition reactions to give products usually in high yields and good selectivities. In future chapters we will discuss the application of this chemistry to synthesise novel compounds and its possible involvement in a biotransformation with a flavin heterocycle.

Chapter 2 – Synthesis of Pyrroloquinolines and Pyrroloquinoxalinones Towards Developing a Flavin Model

2.1 Introduction to Flavins and Function in Decarboxylases

Flavins are a group of organic compounds derived from the tricyclic heterocycle isoalloxazine **62**. The flavin moiety is utilised in many biochemical pathways where it is often covalently bonded to other functional groups to form biological cofactors, such as flavin adenine dinucleotide **63** (FAD) and flavin mononucleotide **64** (FMN). These cofactors bind to flavoenzymes not only as cofactors, but can also serve as substrates in some flavin-dependent reactions. The natural biochemical source of flavin comes from the vitamin riboflavin **65**, which is also known as vitamin B2. The structures of isoalloxazine, FAD, FMN and riboflavin are shown in Figure 8.[46]

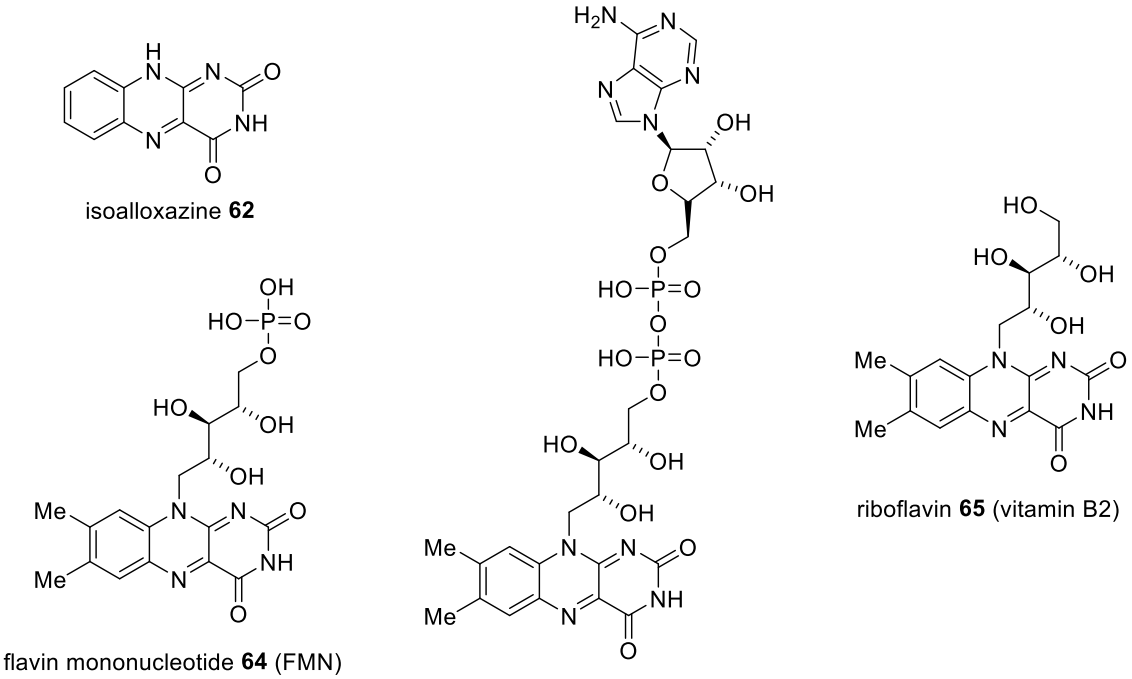
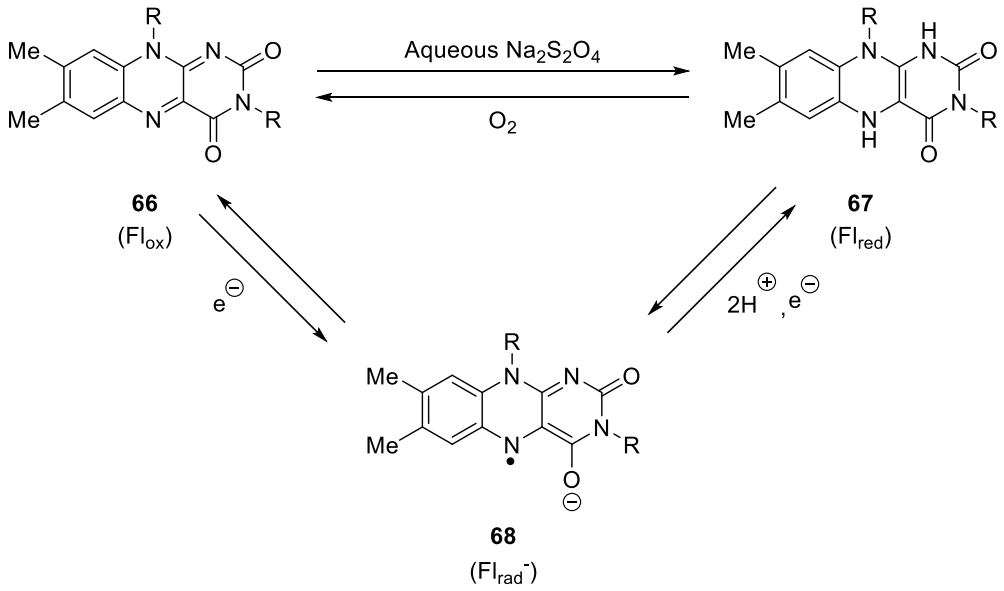


Figure 8 – Structure of isoalloxazine, FAD, FMN & riboflavin

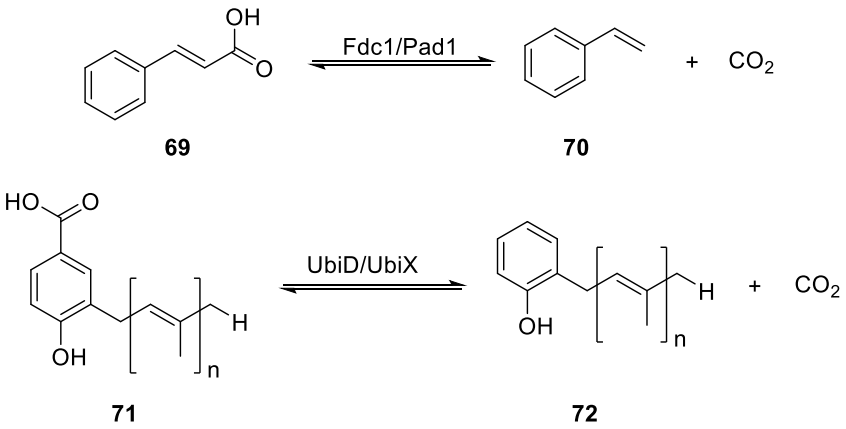
Flavins can undergo redox reactions either as a single two-electron reaction or as two single-electron reactions, forming an intermediate flavin free radical during the process. Sodium dithionite in protic or aqueous media is commonly used in the literature to reduce flavins. This process is

summarised in Scheme 19 where the oxidised flavin **66** (Fl_{ox}) is converted to the reduced flavin **67** (Fl_{red}) *via* the radical anion **68** (Fl_{rad}^{-}).[47–49]



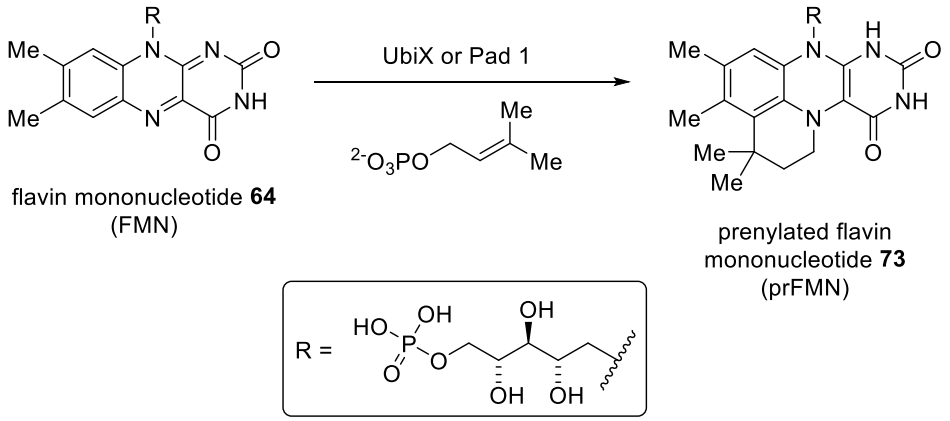
Scheme 19

The ability of flavins to undergo redox reactions is important for the function of flavoenzymes in biological pathways. In 2015, while researching the function of decarboxylase enzymes, work carried out by Leys and co-workers found a new enzyme cofactor, which was derived from FMN **64**.[50] Previous work in the area showed that the bacterial genes *ubiX* and *ubiD* (or the homologous fungal genes *fdc1* and *pad1*) coded proteins that were responsible for the non-oxidative reversible decarboxylation of aromatic substrates.[51] Example reactions done are shown in Scheme 20 where molecules **69** and **71** are decarboxylated to give compounds **70** and **72** respectively.



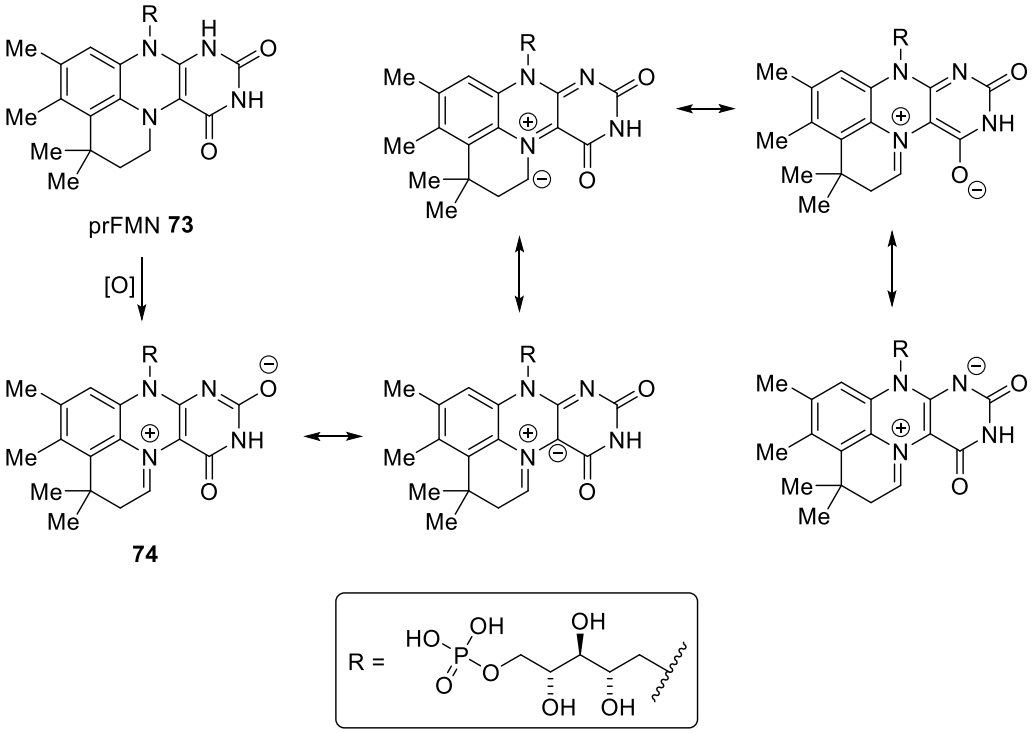
Scheme 20

Continuing on from this work, the *Aspergillus niger fdc1* gene was co-expressed with the *ubiX* gene from *E. coli*. This gave a co-expressed Fdc1 protein called Fdc1^{UbiX}. As expected the Fdc1^{UbiX} protein was able to successfully catalyse the reversible decarboxylation of a variety of cinnamic acid derivatives as shown by the UV-visible spectra data collected. Further atomic resolution data showed that the prenylated FMN **73** (prFMN) cofactor was involved in the reaction. In line with previous work it was suggested that prFMN **73** cofactor was formed from the prenylation of FMN **64** using dimethylallyl-monophosphate and the UbiX protein (or Pad1). This process is summarised in Scheme 21.[50,52,53]



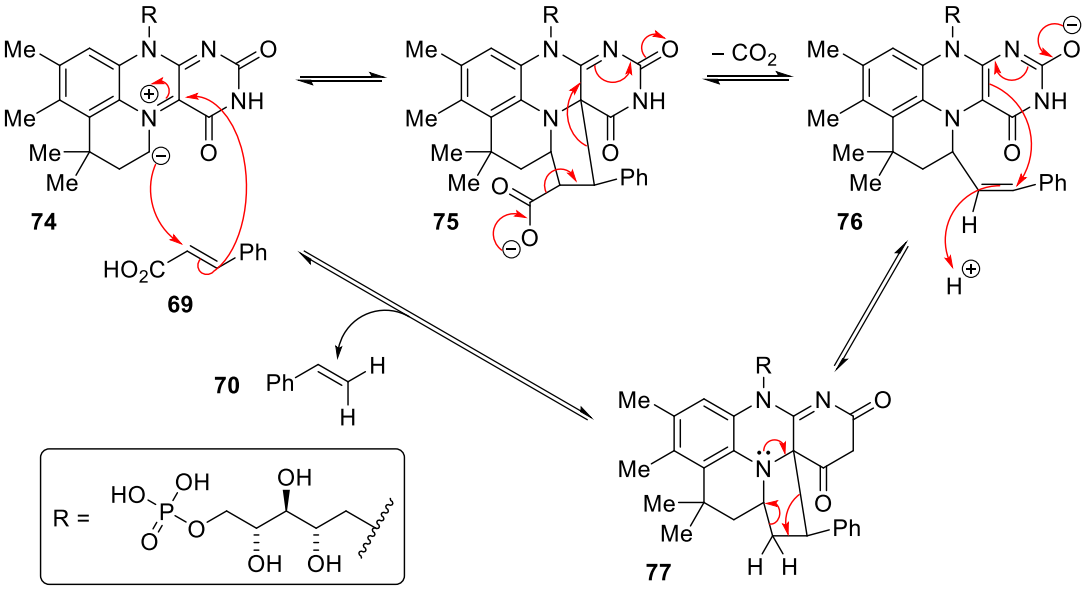
Scheme 21

It was found that activation of prFMN **73** was oxygen dependent. This indicated that prFMN **73** was oxidised to form an intermediate. Using data from high resolution mass spectrometry it was suggested that prFMN **73** was oxidised to form intermediate **74**. This intermediate contains a 1,3-dipole and is an example of an azomethine ylide. The oxidation process is shown in Scheme 22 alongside the resonance forms of the ylide.[50,54]



Scheme 22

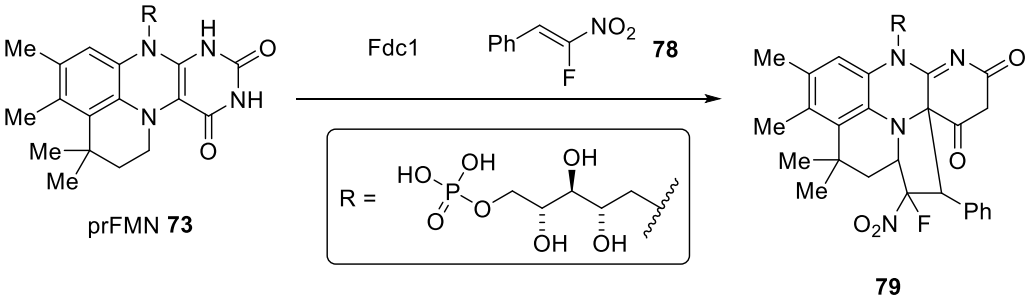
After further experiments, a mechanism for the decarboxylation of cinnamic acid **69** was proposed.[50,54] This is shown in Scheme 23 where intermediate **74** undergoes a 1,3-dipolar cycloaddition to give the pyrrolidine adduct **75**. Fragmentative decarboxylation could take place to give **76**, which is then protonated using a glutamic acid residue to give another pyrrolidine adduct **77**. A retro 1,3-dipolar cycloaddition then takes place reforming the azomethine ylide **74** and the desired product styrene **70**. It's important to mention that this mechanism has some reservations, in particular the first step where the 1,3-dipolar cycloaddition reaction occurs. Although 1,3-dipolar cycloaddition reactions occur widely in organic chemistry, this was believed to be the first example of an enzymatic azomethine ylide cycloaddition. As a result further research has been carried out by other research groups into this mechanism as discussed below. In addition to the cycloaddition reaction the feasibility of some of the remaining steps is questionable. The fragmentation of adduct **75** to give **76** is suspicious due to the molecular orbitals in **75** not being aligned, whereas in the third step cyclisation of **76** to **77** is potentially problematic as no similar examples of this process have been reported in the literature. However, as the whole decarboxylation process take place within an enzyme active site these steps may be feasible.



Scheme 23

The original mechanism was based on the crystal structures of Fdc1^{UbiX} complexed with a variety of substrate analogues.[50] However, further research into the area has provided some evidence to support this mechanism involving a 1,3-dipolar cycloaddition.[50,54] In 2016, Marsh and co-workers carried out a range of deuterium isotope studies to investigate the decarboxylation process.[55] Their results supported the proposed mechanism and also suggested that the rate determining step in the catalytic cycle was the final step, where the product-prFMN adduct undergoes a retro 1,3-dipolar cycloaddition. Furthermore, they postulated that by using a highly electron withdrawn vinyl substrate it may have been possible to stabilise the product-prFMN adduct and slow down the rate of reaction.

Continuing with this work, in 2017 Marsh and co-workers attempted to use (*Z*)-2-fluoro-2-nitro-vinylbenzene **78** to trap adduct **79** formed after a 1,3-dipolar cycloaddition with prFMN **73** in the presence of Fdc1 (Scheme 24).[56] Initially they struggled to use ^{19}F NMR and ^{1}H NMR to characterise adduct **79** due small amounts being released from the enzyme and its instability once it was released. To overcome this problem they used native mass spectrometry, which enables the study of intact protein, non-covalent protein-protein and protein-ligand complexes in their biological state. Using this technique they were able to dissociate adduct **79** from the enzyme, and record its mass spectrum *in-situ* detecting MK^+ and MH^+ for adduct **79**.



Scheme 24

Finally, density functional theory (DFT) calculations have been done by Chen and co-workers to investigate the Fdc1 decarboxylation mechanism with cinnamic acid.[57] Their calculations provided further support for the proposed mechanism, and like the other studies carried out, concluded that the last step where the styrene-prFMN adduct (e.g. **77**, Scheme 23) undergoes a retro 1,3-dipolar cycloaddition was rate-limiting with an overall barrier of 18.9 kcal mol^{-1}.

The discovery of this novel decarboxylation mechanism attracted a lot of attention when it was first published. If the decarboxylation mechanism is correct, then similar reactions could be done to generate a variety of different *α*-olefins, and once optimised the overall process could provide a new efficient route to many industrially important hydrocarbons and chemicals. Therefore, investigating the mechanism further is of interest, especially the 1,3-dipolar cycloaddition reaction.

2.2 Previous work

Previous research in the Coldham group has been focussed around the use of azomethine ylides to synthesise polycyclic molecules. As a result of the work mentioned in the previous section related to the decarboxylation of cinnamic acid **69** we wanted to investigate the pathway further by trying to provide some further evidence for the 1,3-dipolar cycloaddition step. Due to the complexity and large size of prFMN **74**, it was first important to simplify the flavin model. Looking at the site where the azomethine ylide forms, **74** can be simplified in a number of different ways. This is summarised in Figure 9 where removing some of the functional groups off the prenylated flavin and *N*-methylating the N(3) position would give intermediate **80**. Making further simplifications by removing the dihydrouracil ring would give intermediate **81** and then removing the amide functional group would give the simplest model **82**.

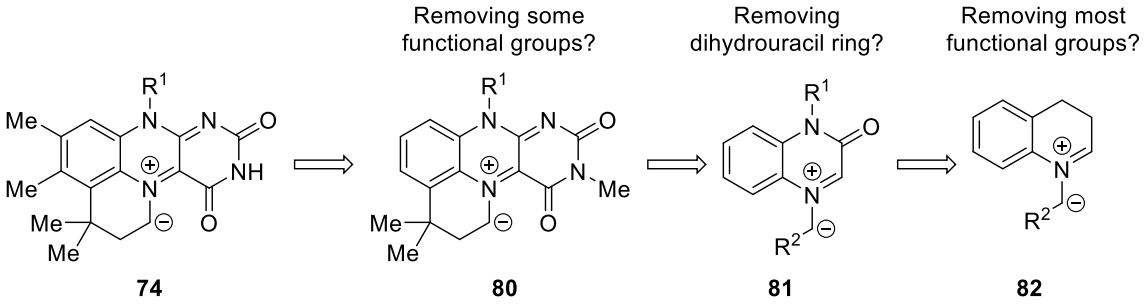
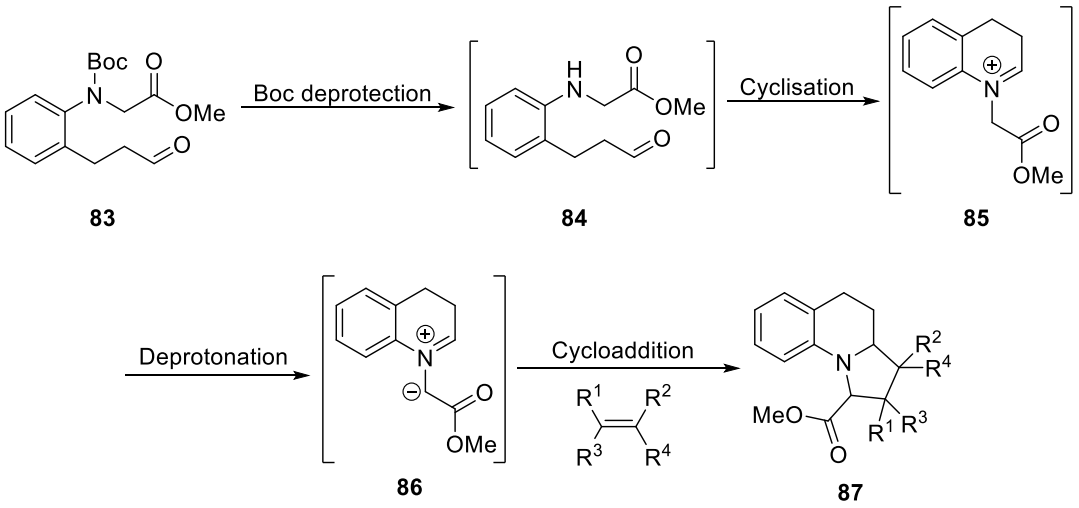


*Figure 9 – Simplifying intermediate **74***

Ultimately, if cycloaddition products could be successfully isolated from reactions of dipolarophiles with intermediate **80** then this could provide some further evidence for the 1,3-dipolar cycloaddition step. In addition, synthesis of cycloadducts *via* intermediates **81** and **82** may be useful as no examples were present in the literature.

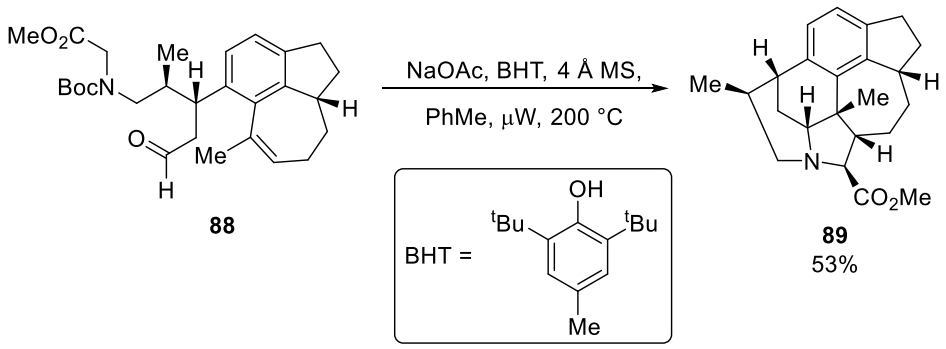
To begin work on investigating the cycloaddition reaction we chose to synthesise azomethine ylide **82**. The R^2 group was chosen to be a methyl ester due to its electron withdrawing capability, which would help stabilise azomethine ylide **86**. A potential way to form ylide **86** is shown in Scheme 25 *via* a Boc deprotection reaction on **83**. Subsequent cyclisation, followed by deprotonation, and cycloaddition with an appropriate dipolarophile would hopefully generate the core cycloadduct **87**.



Scheme 25

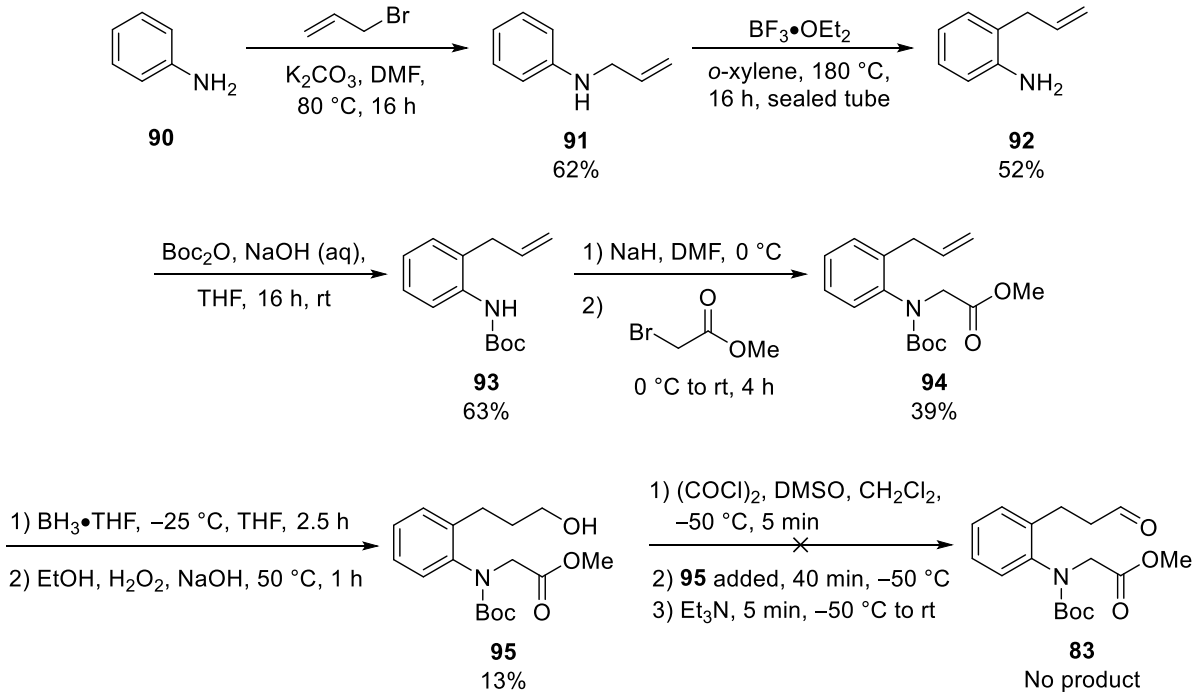
It's important to mention that similar work has been carried out by Fukuyama and co-workers to synthesise (–)-daphenylline.[58] The most important reaction to synthesise the main core of (–)-daphenylline is shown in Scheme 26, where cleavage of the Boc group from compound **88** by

heating in toluene at 200 °C triggered the formation of a cyclic azomethine ylide. This promoted an intramolecular cycloaddition reaction to give the core **89** in 53% yield.



Scheme 26

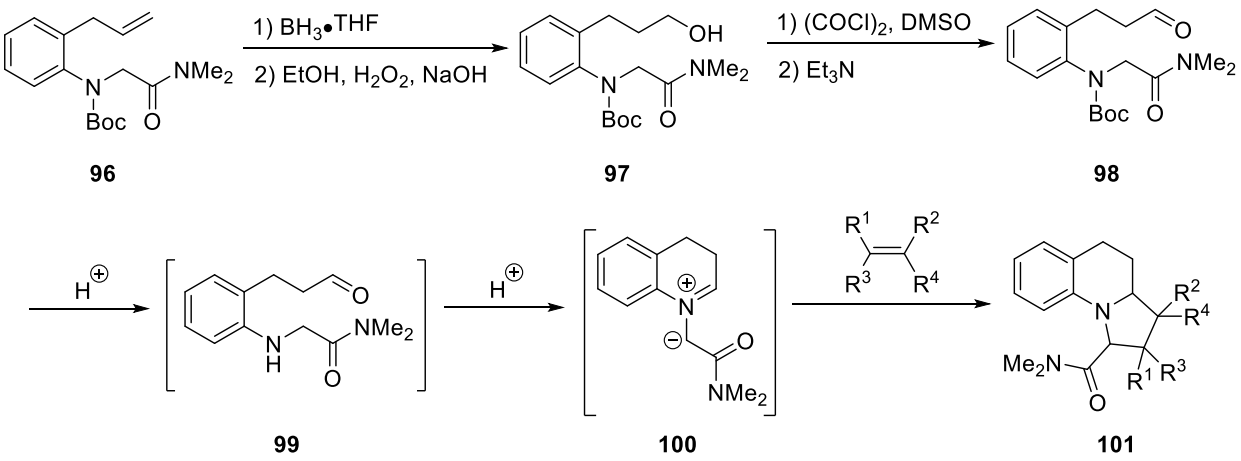
Early work began by attempting to synthesise compound **83** *via* the synthetic route shown in Scheme 27.[59] In the first step, aniline (**90**) was reacted with allyl bromide to give *N*-allyl aniline **91**, which was then converted into 2-allyl aniline **92**, *via* a 3,3-sigmatropic rearrangement. Subsequent Boc protection and alkylation with methyl bromoacetate using sodium hydride gave compound **94**. Hydroboration was carried out next to give primary alcohol **95**, however this reaction gave a very low yield. This may have been due to the hydrolysis of the methyl ester group. Unfortunately, an attempted Swern oxidation to try and obtain compound **83** was unsuccessful.



Scheme 27

2.3 Aims

In order to continue with this chemistry, it was decided that the hydroboration reaction to synthesise compound **95** would first need to be optimised. If the methyl ester functional group was being hydrolysed; therefore reducing the overall yield, then it may be more beneficial to replace the methyl ester group in compound **94** with the more robust *N,N*-dimethyl amide group to give compound **96**. Hydroboration and Swern oxidation steps would then hopefully give aldehyde **98**, which could then undergo subsequent Boc deprotection to give **99**. By using conditions similar to Fukuyama, cyclisation would then take place, forming azomethine ylide **100** which in the presence of a suitable dipolarophile would hopefully generate cycloadducts with the general structure of **101**. These steps are summarised in Scheme 28.

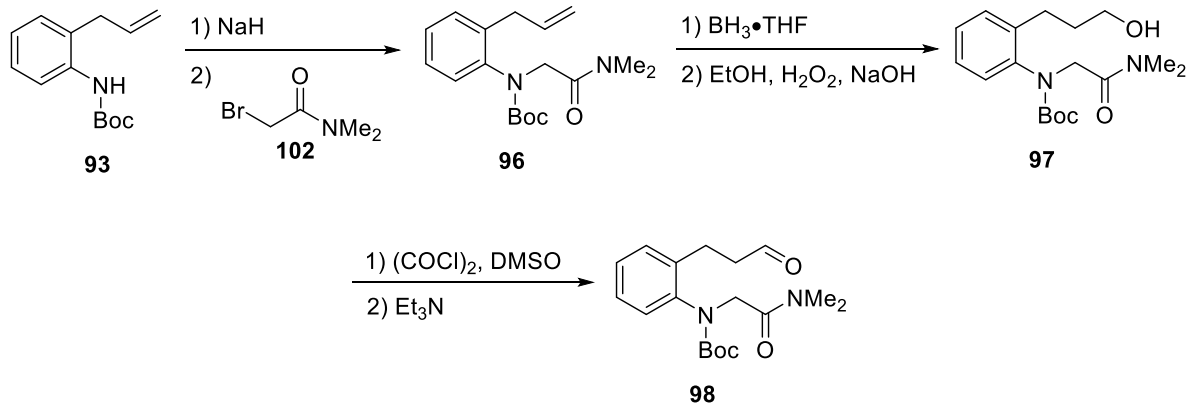


Scheme 28

If work on synthesising cycloadducts similar to **101** was successful then further work could lead to cycloadducts from intermediates **80** and **81** as well. Therefore, this could provide potential evidence that similar reactions take place within nature.

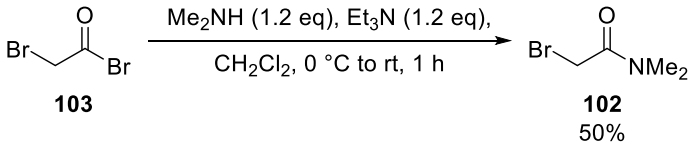
2.4 Synthesis of aldehydes 83 and 98

Before any cycloaddition reactions could be carried out it was important to try and synthesise aldehyde **98**. To achieve this the synthetic route shown in Scheme 29 was used which was based on previously developed chemistry in the group to access compound **93**. This could then undergo an alkylation reaction with 2-bromo-*N,N*-dimethylacetamide **102** to give compound **96**. Subsequent hydroboration and Swern oxidation steps would then hopefully allow aldehyde **98** to be isolated.



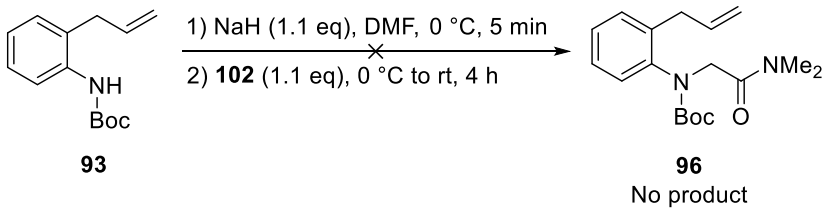
Scheme 29

Fortunately, we were provided with a previously synthesised sample of compound **93** to carry out the first alkylation reaction. Due to the cost of compound **102** it was decided to synthesise this compound first from the more readily available bromoacetyl bromide **103**. Using dimethylamine we were able to isolate acetamide **102** in 50% yield (Scheme 30).



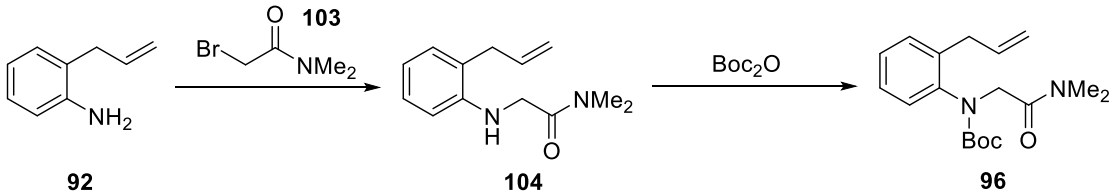
Scheme 30

However, when carrying out the alkylation of compound **93** with acetamide **102** in the presence of sodium hydride and DMF no desired product was isolated (Scheme 31). This reaction was repeated multiple times producing the same result. Furthermore, in each attempt no starting material was recovered and an unknown by-product was isolated instead. Initially from ^{1}H NMR spectroscopy we thought that the starting material may have cyclised to form 2-methylindoline, but the spectra were inconsistent with the literature data already known.



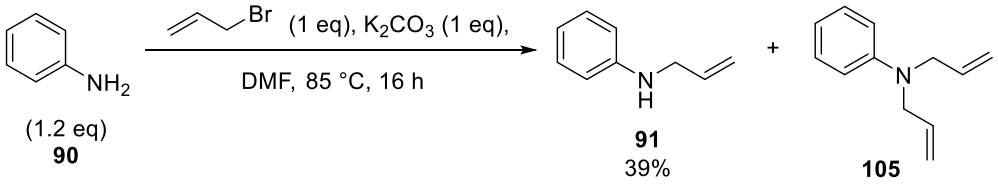
Scheme 31

A new synthetic route was then devised as shown in Scheme 32 where compound **92** was first alkylated with acetamide **102** to give compound **104**. This could then undergo a Boc protection reaction to give compound **96**, which after further reactions would allow aldehyde **98** to be isolated.



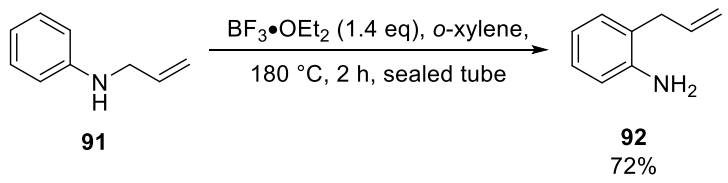
Scheme 32

As shown in Scheme 33, aniline (**90**) was first *N*-alkylated using allyl bromide and potassium carbonate in DMF at 85 °C to give compound **91** in a low yield of 39%. Initially, we thought that this may have been due to the difficult work-up procedure as lots of water was required to remove the DMF from the crude product. Furthermore, it was found that compound **91** could be alkylated again to give the disubstituted product **105** reducing the overall yield further.



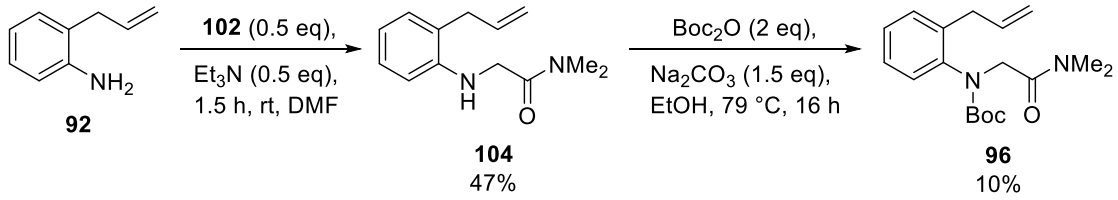
Scheme 33

Conversion of compound **91** to compound **92** using a Lewis acid catalysed 3,3-sigmatropic rearrangement was achieved using the conditions shown in Scheme 34. The reaction involved heating compound **91** in a sealed tube at 185 °C for 2.5 h to give **92** in 72% yield.



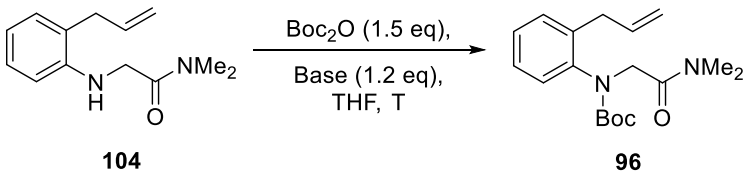
Scheme 34

The next two steps carried out are shown in Scheme 35. Compound **92** was first alkylated with acetamide **102** using triethylamine in the presence of DMF at room temperature. The isolated compound **104** was then protected using Na_2CO_3 and Boc_2O to obtain compound **96**. Unfortunately, compound **96** was obtained in a very low yield of 10%. Therefore, it was important to try and optimise the Boc protection reaction to obtain a better yield.



Scheme 35

It was thought that the choice of base may have played an important part in the synthesis of compound **96**. As a result, the Boc protection reaction to synthesise **96** was repeated multiple times using different bases and conditions. The results obtained are summarised in Table 1 and the general conditions are shown in Scheme 36.



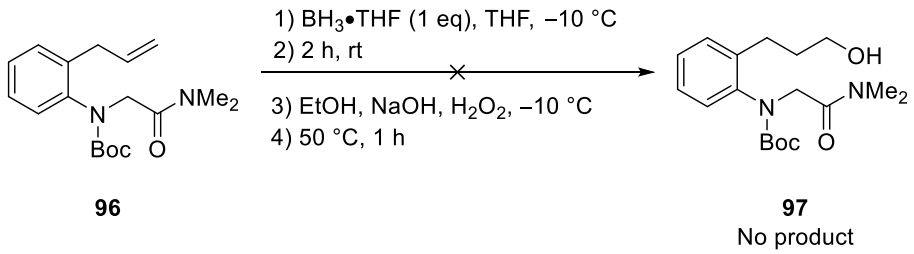
Scheme 36

Base	T	% Yield of **96**	Notes
NaOH	rt	15	
n-BuLi	−78 °C to rt	26	*n*-BuLi added to starting material before Boc_2O with 5 min wait
n-BuLi	−78 °C to rt	34	*n*-BuLi added to starting material before Boc_2O with 10 min wait
No base	rt	0	

Table 1

Looking at the data, using a slightly stronger base such as NaOH gave an improved 15% yield. The next base used was *n*-BuLi, which was added to the starting material at −78 °C and left to stir for 5 minutes before Boc_2O was added. The mixture was then warmed to room temperature over 16 h. This gave a much better yield of 26% and this was increased to 34% when leaving the reaction for 10 minutes before quenching with Boc_2O. Due to time constraints, no more reaction conditions were scoped for the Boc protection reaction and compound **96** was carried forward onto the next step.

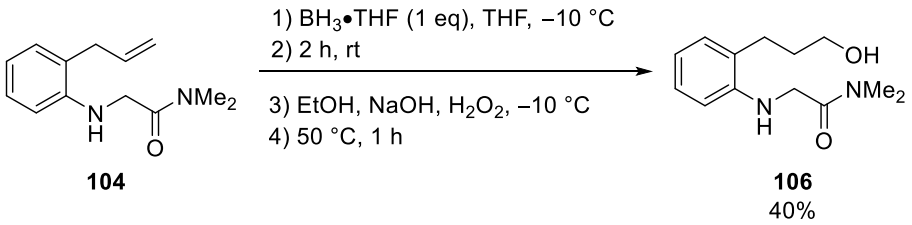
Unfortunately, the hydroboration-oxidation reaction of compound **96** was unsuccessful using the conditions shown in Scheme 37. Multiple repeats of the reaction were done and different boranes such as 9-BBN were also used. In all reactions no starting material was recovered and multiple spots could be seen on the TLC plate.



96 **97**
No product

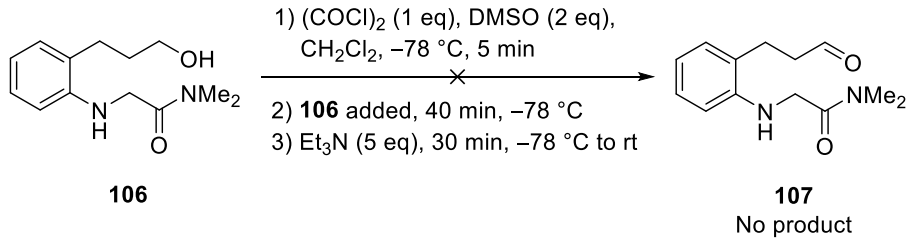
Scheme 37

In comparison, it was found when compound **104** was subjected to the same hydroboration-oxidation conditions shown in Scheme 37, the corresponding primary alcohol **106** was isolated in a 40% yield. More importantly, the reaction generated none of the potential secondary alcohol product. This is summarised in Scheme 38.



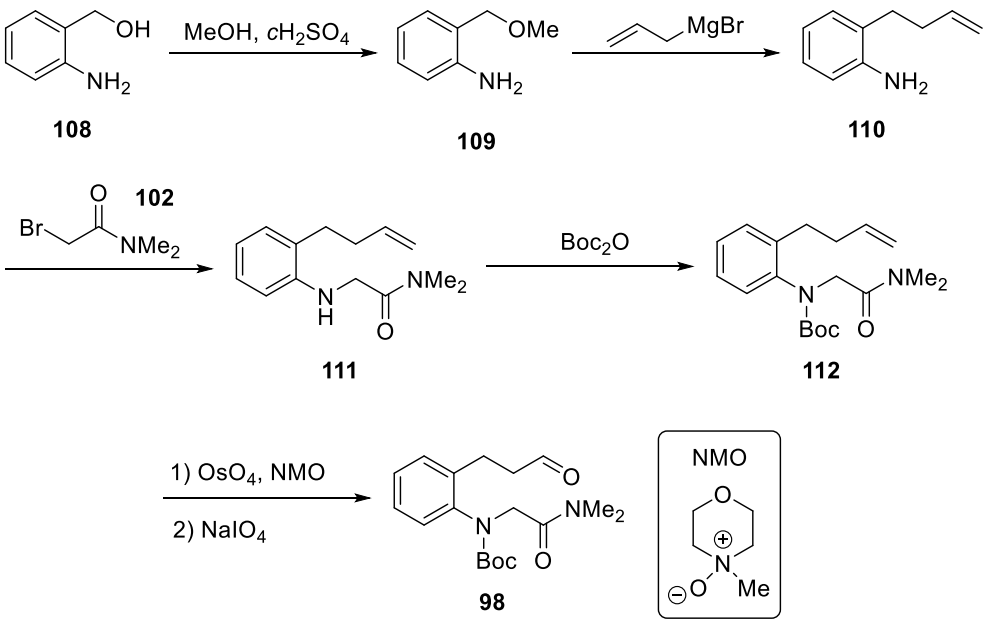
Scheme 38

It was decided to carry compound **106** forward to see whether the alcohol group could be converted into an aldehyde to obtain compound **107**. To achieve this, a Swern oxidation reaction was carried out as shown in Scheme 39. However, this generated no desired product and no starting material was recovered. As a result, a new synthetic route to try and synthesise aldehyde **98** needed to be designed.



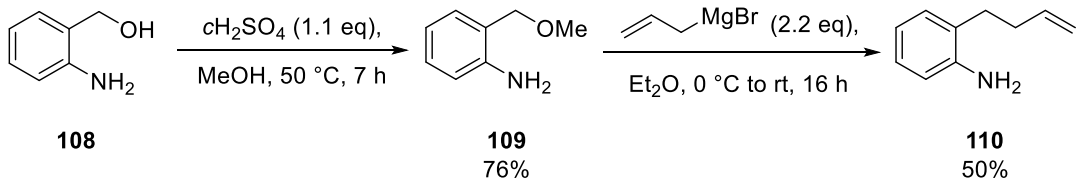
Scheme 39

The alternative route devised to synthesise aldehyde **98** is shown in Scheme 40. In the first step 2-aminobenzyl alcohol **108** is *O*-methylated to give **109**. A subsequent reaction with allyl magnesium bromide in the second step then gives the 2-substituted aniline **110**. Using similar alkylation and Boc protection methods as mentioned previously would then hopefully allow compound **112** to be isolated. The final step involves a dihydroxylation-diol cleavage reaction to form aldehyde **98**.



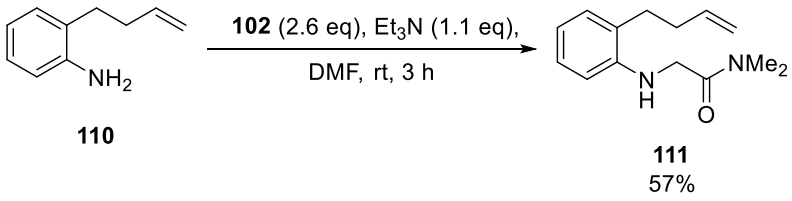
Scheme 40

Compound **110** was synthesised using a known literature method.[60] This is summarised in Scheme 41 where 2-aminobenzyl alcohol **108** was *O*-methylated using methanol and concentrated sulfuric acid to obtain compound **109** in 76% yield. This was then reacted with allyl magnesium bromide to give compound **110** in 50% yield.



Scheme 41

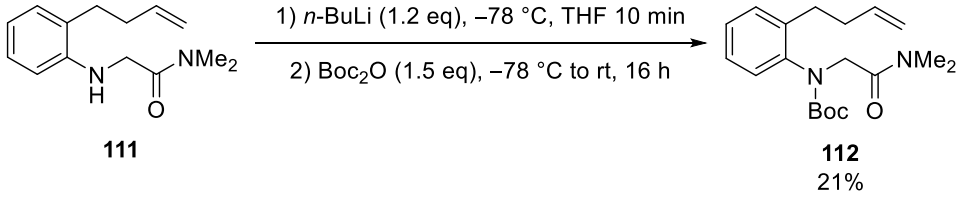
Next, compound **110** was alkylated using similar conditions to those mentioned previously (Scheme 35). It was found that using an excess of both 2-bromo-*N,N*-dimethylacetamide **102** and triethylamine gave a much better yield of compound **111**. However, full conversion of compound **110** to compound **111** was not achieved as starting material was recovered upon purification (Scheme 42).



110 **111** 57%

Scheme 42

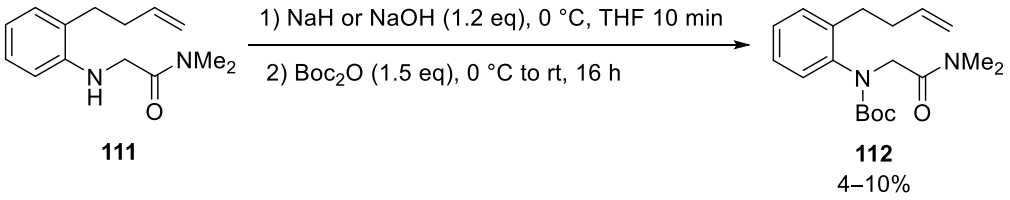
Moving forward to the Boc-protection step, the optimised conditions used to synthesise compound **96** were used again to convert compound **111** to compound **112**. These are summarised in Scheme 43 where the reaction was carried out using *n*-BuLi as the base at –78 °C. Disappointingly a low yield of 21% was obtained for compound **112**.



111 **112** 21%

Scheme 43

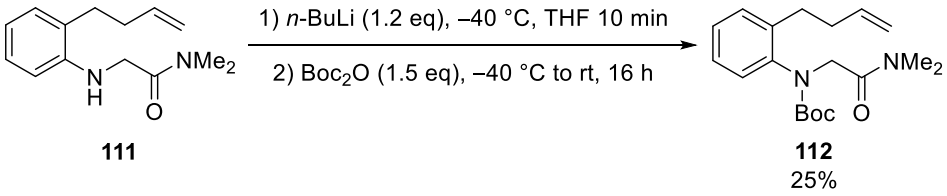
This indicated further optimisation needed to be done to try and improve the yield of compound **112**. Applying a similar method to before it was first decided to investigate how changing the base would affect the yield. The reaction conditions used are summarised in Scheme 44. Looking at the data collected and comparing with the synthesis of compound **112** using the conditions in Scheme 43, using a weaker base, such as sodium hydroxide, generated a lower yield of the Boc protected compound **112**. Therefore, although a low yield of compound **112** was obtained using *n*-BuLi, the initial results still indicated that using a stronger base was preferred.



111 **112** 4–10%

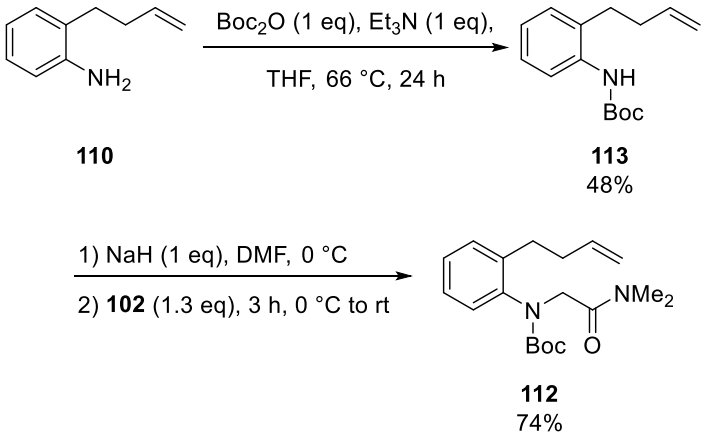
Scheme 44

The next parameter that was investigated was temperature. The reaction in Scheme 43 was repeated at −20 °C and −40 °C (Scheme 45). The reaction at a higher temperature of −20 °C proved less beneficial as a much lower yield of 16% of compound **112** was obtained. However, a slightly higher yield of 25% was obtained when the reaction was done at −40 °C.



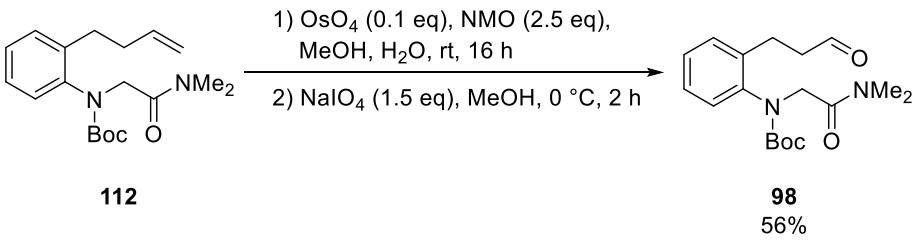
Scheme 45

Although a slightly higher yield of compound **112** was eventually obtained, this was still a low yield. In order to try and obtain a better yield of compound **112**, it was decided to swap the alkylation and Boc-protection steps around. Boc protection of compound **110** using triethylamine and Boc_2O, in THF, gave compound **113** in 48% yield. The isolated material was then alkylated with 2-bromo-*N,N*-dimethylacetamide **102** and sodium hydride to give compound **112** in a much better yield of 74%. Both these steps are summarised in Scheme 46.



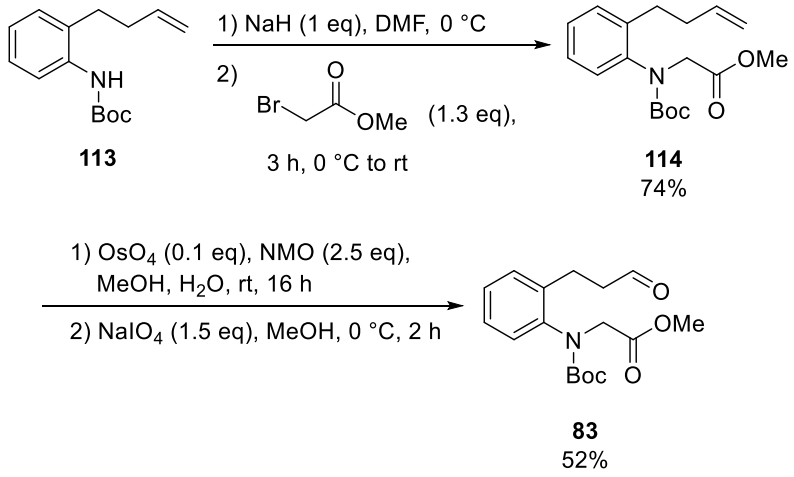
Scheme 46

The final step in the synthesis of aldehyde **98** is shown in Scheme 47 where compound **112** was dihydroxylated using osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO). Upon working up the reaction the crude product was carried forward onto the next step where the crude diol was cleaved using sodium periodate to give aldehyde **98** in 56% yield.



Scheme 47

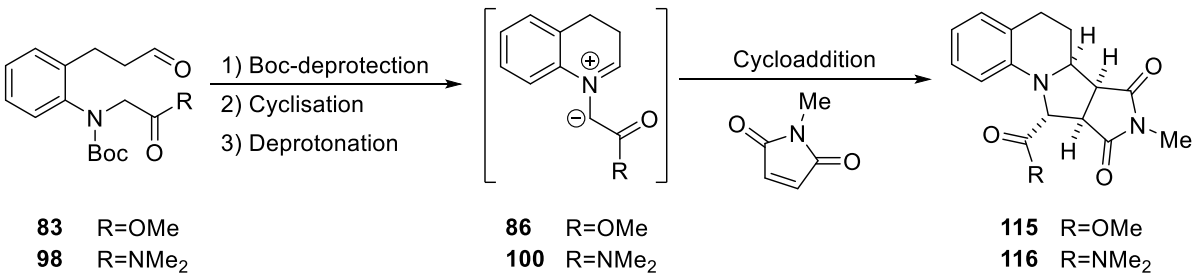
Before any cycloaddition reactions were attempted, the methyl ester analogue **83** was also synthesised using a similar route to compound **98**. The overall process is shown in Scheme 48 where in the first step, compound **113** was alkylated using methyl bromoacetate to give compound **114** in 74% yield. Subsequent dihydroxylation and diol cleavage steps generated compound **83** in 52% yield.



Scheme 48

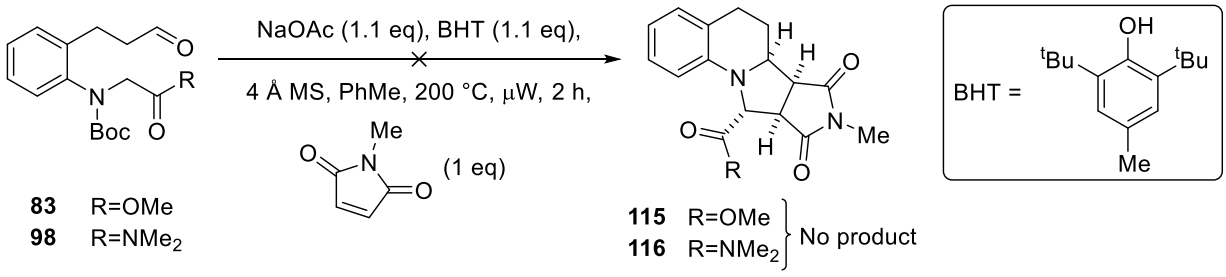
2.5 Attempted cycloaddition reactions with aldehydes 83 and 98

Once aldehydes **83** and **98** were isolated the final step in the synthetic route needed to be carried out. This involved a Boc-deprotection reaction followed by cyclisation to form an azomethine ylide intermediate. This could then react with a dipolarophile, such as *N*-methylmaleimide. This is summarised in Scheme 49 where the desired cycloadducts **115** and **116** are shown.



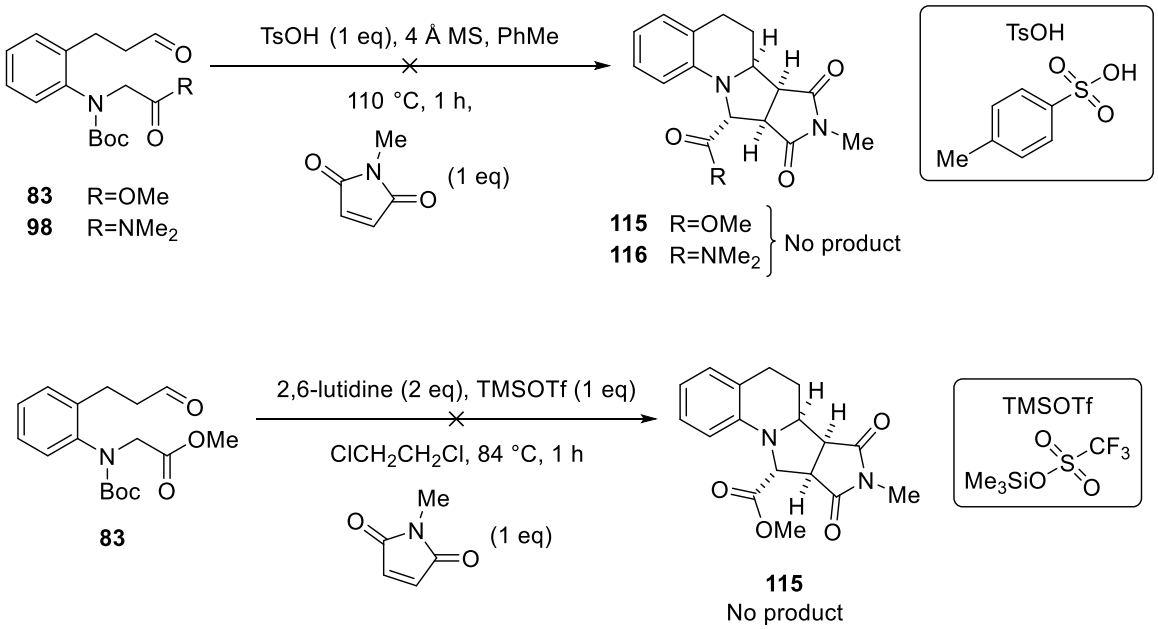
Scheme 49

The initial reaction conditions were the same as those used by the Fukayama group (Scheme 26).[58] These conditions were applied to compounds **83** and **98** and involved heating with NaOAc, butylated hydroxytoluene (BHT), and 4 Å molecular sieves in toluene at 200 °C under microwave conditions. This is summarised in Scheme 50. Unfortunately, after many attempts, no desired product was isolated and none of the original starting material was recovered.



Scheme 50

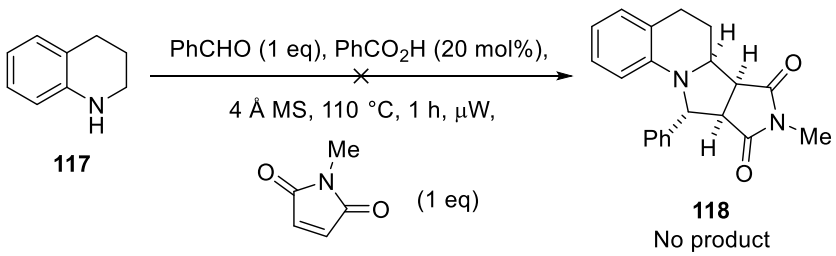
Following on from this many other conditions were used to try and isolate the desired products **115** and **116**. These are summarised in Scheme 51 where *p*-toluenesulfonic acid (TsOH) was first used to try and remove the Boc group in compounds **83** and **98**. This would have hopefully allowed cyclisation to take place and a cycloaddition reaction to occur. Another set of conditions used was based around the work done by Sato, Chida and co-workers.[61] This involved using trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 2,6-lutidine to try and remove the Boc group on compound **83**. Unfortunately, these methods were unsuccessful and none of the desired products were isolated. Due to the disappointing results obtained it was decided to stop work on this synthetic route and move towards alternative methods to synthesise the desired products.



Scheme 51

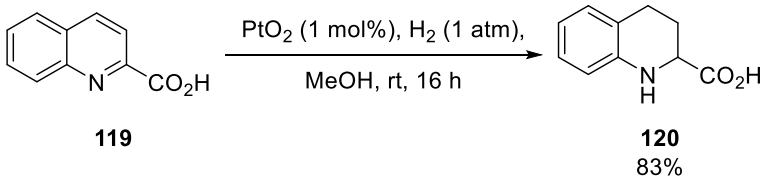
2.6 Alternative routes to pyrroloquinoline cycloadducts

From the work done so far it was clear that formation of azomethine ylides similar to **82** was problematic. Therefore the next step was to try and apply more conventional methods to form these ylides. As mentioned previously one of the simplest ways to form an azomethine ylide is by reacting an aldehyde with an amine. Deprotonation of the resulting iminium could then form an azomethine ylide. In an attempt to apply this chemistry to synthesise cycloadducts similar to **87** and **101**, it was decided to react tetrahydroquinoline **117** with benzaldehyde in the presence of benzoic acid and *N*-methylmaleimide. The conditions used were similar to those reported by Seidel and co-workers, [34] but after multiple attempts, no desired product **118** was isolated. This is summarised in Scheme 52.



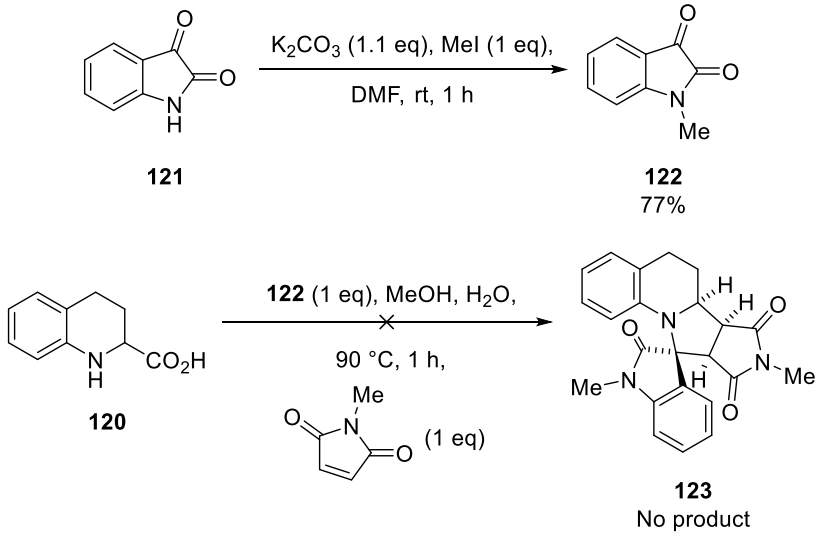
Scheme 52

A potential reason why these reactions didn't work is due to the α-proton in tetrahydroquinoline not being acidic enough for deprotonation. Therefore, no azomethine ylide was formed and no cycloaddition reaction could take place. An alternative way to generate azomethine ylides is from the decarboxylation of amino acids and using this idea we decided to investigate whether similar reactions could take place with 1,2,3,4-tetrahydroquinoline-2-carboxylic acid **120**. Before any reactions could be done compound **120** had to be synthesised. The conditions used are shown in Scheme 53 where quinaldic acid **119** was reduced using PtO_2 under a hydrogen atmosphere (1 atm). The desired product **120** was isolated in 83% yield.



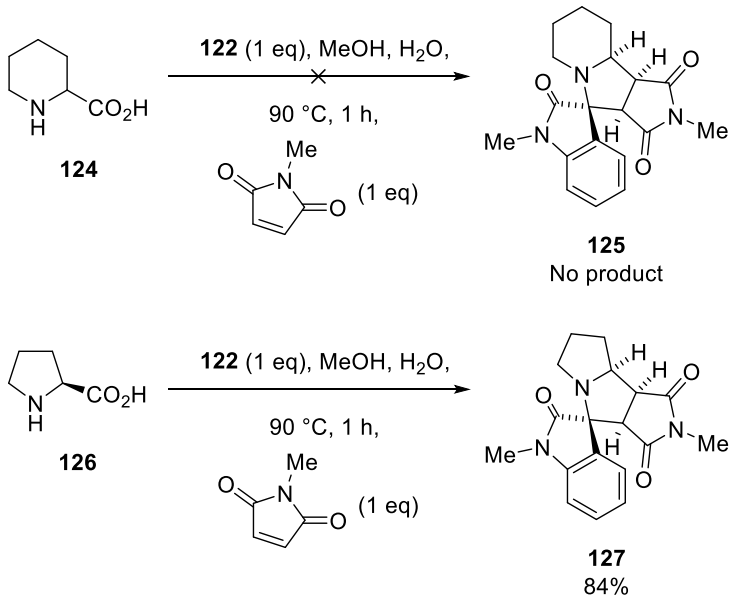
Scheme 53

Compound **120** was then subjected to similar cycloaddition reaction conditions as reported in the literature with other amino acids.[62–64] This is summarised in Scheme 54 where compound **120** was reacted with *N*-methylisatin **122** and *N*-methylmaleimide in methanol at 90 °C for 1 h. *N*-Methylisatin **122** was synthesised from isatin **121** using K_2CO_3 and methyl iodide. Unfortunately, when carrying out the cycloaddition reaction none of the desired cycloadduct product **123** was isolated.



Scheme 54

We repeated the reaction with similar amino acids such as L-proline and pipecolinic acid as shown in Scheme 55. The reaction with pipecolinic acid **124** was unsuccessful and TLC analysis of the crude product indicated that methylisatin **122** had not been consumed in the reaction. This suggested that no imine formation had taken place, and as a result none of the desired azomethine ylide was formed to generate cycloadduct **125**. In comparison, the reaction with L-proline **126** gave cycloadduct **127** in 84% yield. X-ray crystallography was done on compound **127** and confirmed that only one stereoisomer had been isolated (Figure 10 and Appendix 1). The methyl group appears as six protons due to individual molecules in unit cell being disordered, therefore an "average" orientation of the methyl group is shown.



Scheme 55

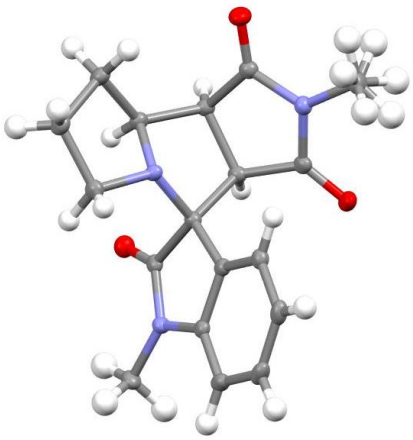
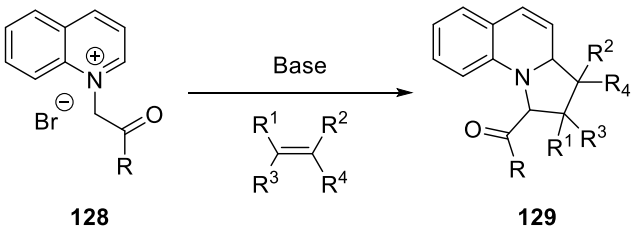


*Figure 10 – X-ray crystal structure of **127***

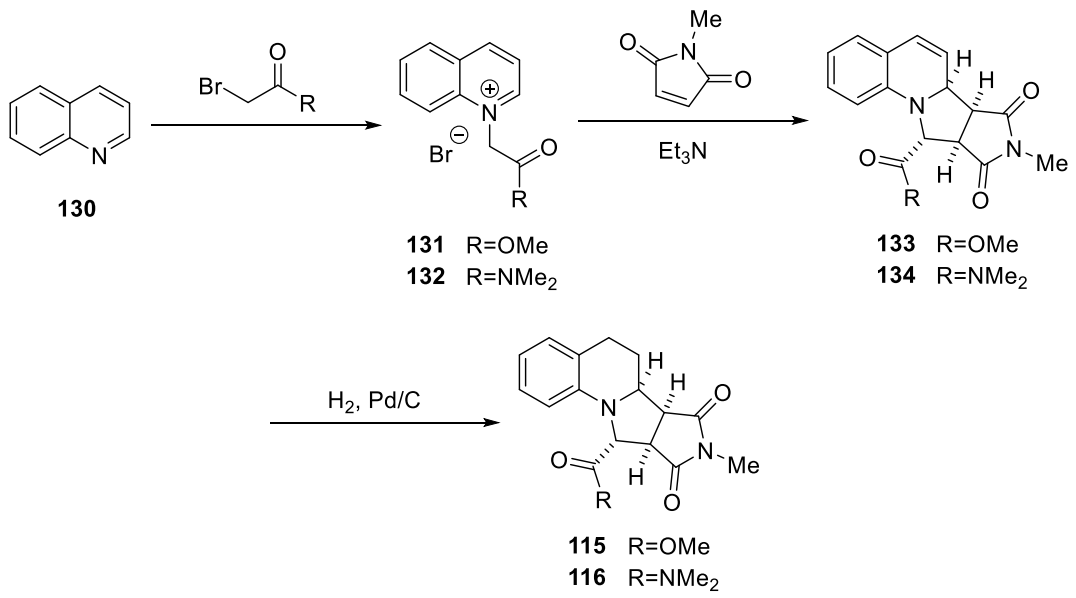
The initial results using decarboxylation methods to try and synthesise tetrahydroquinoline cycloadducts seemed discouraging. As a result, it was decided to take a different approach to try and synthesise these compounds *via* the deprotonation of iminium salts to generate azomethine ylides. Looking further through the literature, quinolinium salts with the general structure **128** had been exploited to synthesise a variety of pyrroloquinoline compounds with a structure similar to **129** (Scheme 56).[65–67] Most examples used ketones (R = aryl) as electron withdrawing groups to stabilise the intermediate azomethine ylide. Although carboxylic acid derivatives had been used, there were few examples of quinolinium salts which contained the ester and amide functional groups we were interested in.[68–70] Therefore, this provided us with a potentially viable route to the tetrahydroquinoline cycloadducts we were synthesising.



128 **129**

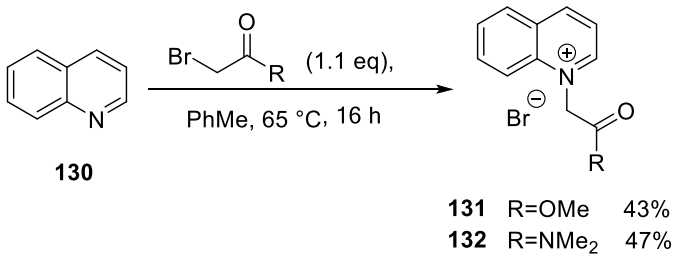
Scheme 56

The new synthetic approach taken to synthesise compounds **115** and **116** is shown in Scheme 57 and takes advantage of using quinolinium salts like **128**. Using a methyl ester or dimethyl amide functional group would give salts **131** and **132**, which could be synthesised from quinoline. Subsequent deprotonation using an appropriate base would then generate an azomethine ylide which could undergo a cycloaddition reaction with *N*-methylmaleimide to give compounds **133** and **134**. Hydrogenation of compounds **133** and **134** would then hopefully give compounds **115** and **116**.



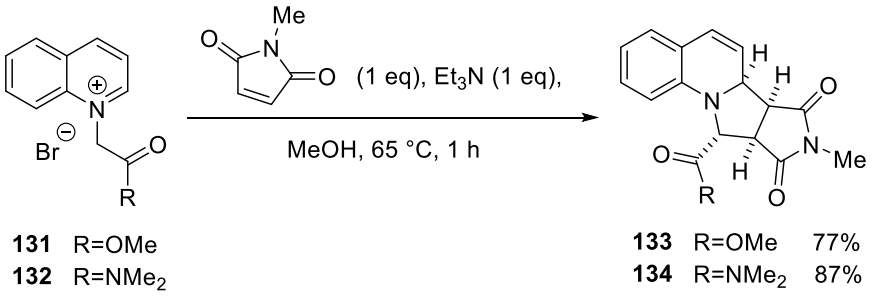
Scheme 57

Synthesis of salts **131** and **132** was achieved using the conditions shown in Scheme 58. Quinoline (**130**) was reacted with the appropriate bromide in toluene. The mixtures were heated at 65 °C for 16 h to give salts **131** and **132** in yields of 43% and 47% respectively.



Scheme 58

Once salts **131** and **132** were isolated they were both subjected to the cycloaddition conditions shown in Scheme 59 where triethylamine was used to deprotonate the salt forming an azomethine ylide intermediate, which then reacted with *N*-methylmaleimide to generate the cycloadducts **133** and **134** in good yields of 77% and 87% respectively. X-ray crystallography of compound **133** was useful in identifying its relative stereochemistry (Figure 11 and Appendix 2). Using the dihedral angles, determined from the X-ray crystallography data, between the C-H bonds on the pyrrolidine ring it was possible to assign protons in the ^{1}H NMR spectrum. This was done by applying the Karplus relationship to compare the relative sizes of the *J*-values with the corresponding dihedral angles. This is summarised on the correlation diagram shown in Figure 11.



Scheme 59

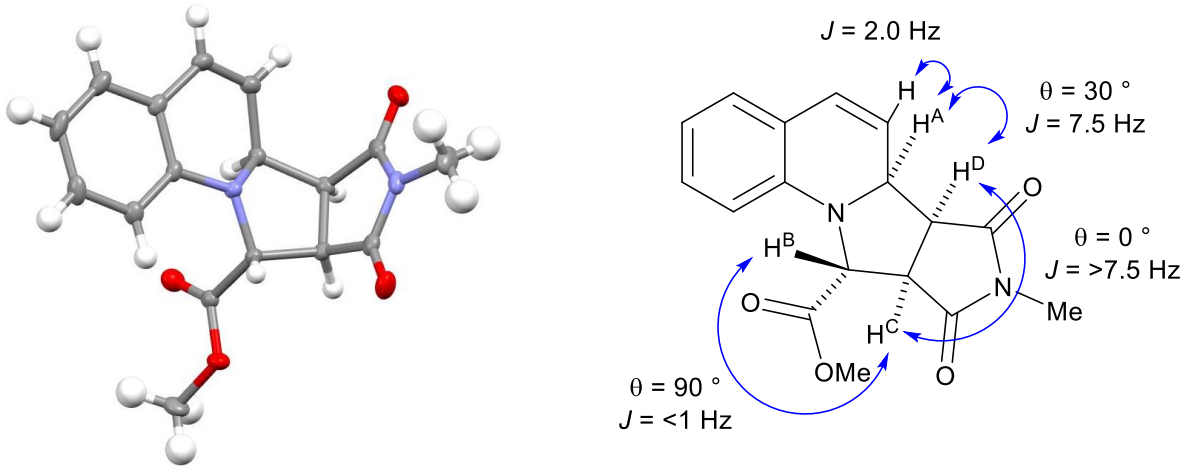
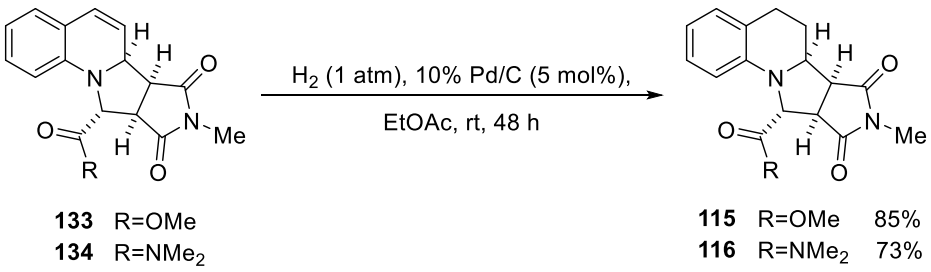


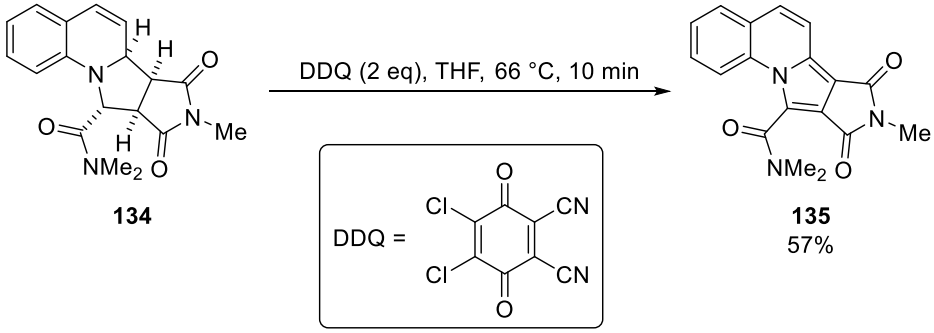
*Figure 11 – X-ray crystal structure of **133** with approximate dihedral angles (θ) & J-values shown*

Moving forward, the final step in the synthetic route involved the hydrogenation of compounds **133** and **134** to give compounds **115** and **116**. This was achieved by using the conditions shown in Scheme 60 where alkenes **133** and **134** were stirred with 10% Pd/C in ethyl acetate, under a hydrogen gas atmosphere (1 atm) at room temperature. ^{1}H NMR spectroscopy was used to monitor the reaction and showed that the starting materials were fully consumed after 48 h. This gave products **115** and **116** in yields of 85% and 73% respectively.



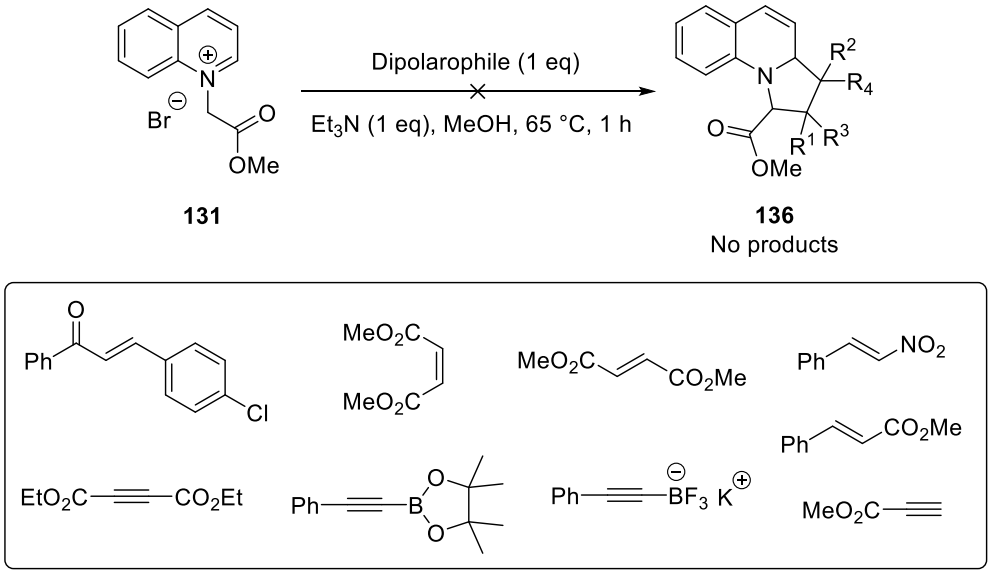
Scheme 60

It was also possible to oxidise compound **134** by heating in the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and THF. This gave pyrrole **135** in 57% yield as shown in Scheme 61.



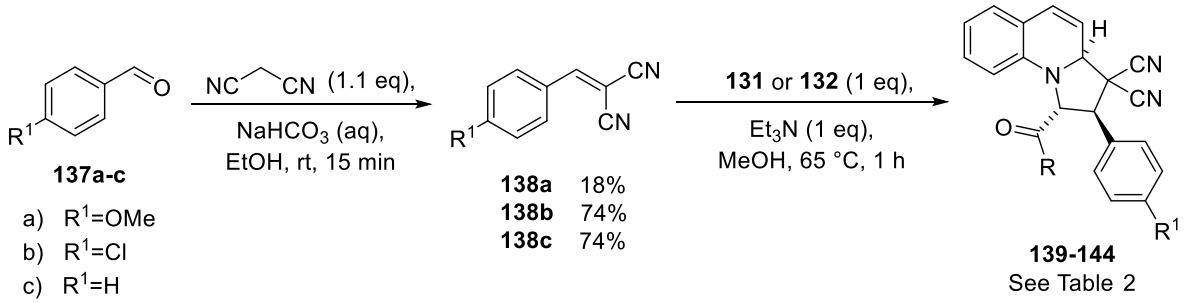
Scheme 61

In an attempt to expand the range of cycloadducts further, salt **131** was reacted with a small number of other dipolarophiles. Unfortunately with most alkenes and alkynes the reaction was unsuccessful generating none of the desired cycloadduct. Dipolarophiles that were unsuccessful are shown in Scheme 62. For all the reactions TLC analysis of the crude products indicated that the dipolarophile had not been consumed and no new spots were observed after heating the reactions for 1 h. Overall, we were unsure about why reactions with these dipolarophiles were unsuccessful. This was even more suprising when considering the high reactivity of some of the dipolarophiles due to the presence of electron withdrawing groups on the alkene or alkyne.



Scheme 62

Fortunately, aromatic malononitriles **138a-c** gave positive results when they were each reacted with salts **131** and **132**. The conditions used are summarised in Scheme 63 where compounds **138a-c** were synthesised first by reacting the substituted benzaldehydes **137a-c** with malononitrile in ethanol at room temperature, in the presence of aqueous $NaHCO_3$. Once the malononitriles were isolated, they were then each reacted with salts **131** and **132** to give the products **139–144**. When carrying out the reactions we found that prolonged heating caused the cycloadducts formed to decompose, therefore the reactions were heated for 1 h only. The structures and yields of compounds **139–144** are shown in Table 2. The stereochemistry of compound **139** was confirmed using X-ray crystallography (Figure 12 and Appendix 3).



Scheme 63

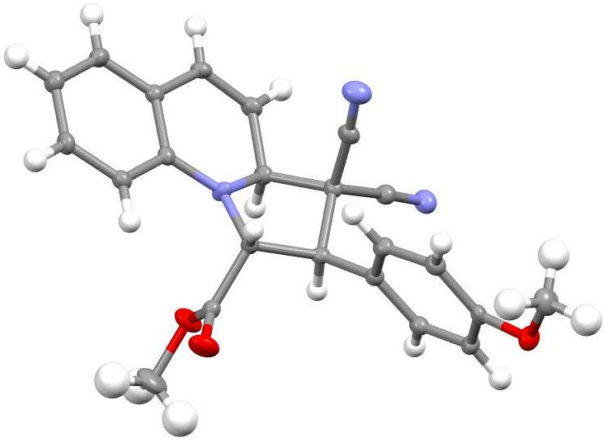


*Figure 12 – X-ray crystal structure of **139***

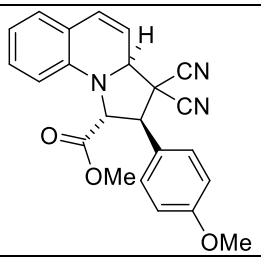
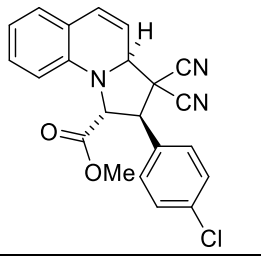
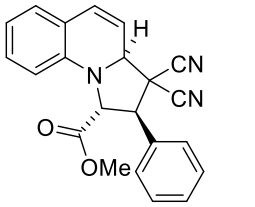
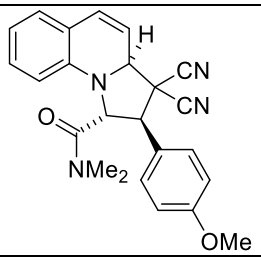
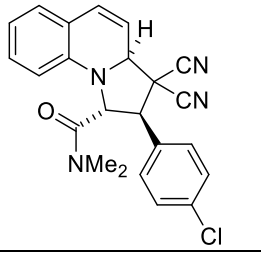
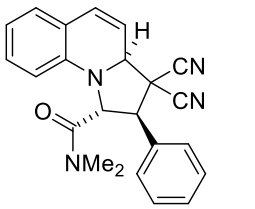
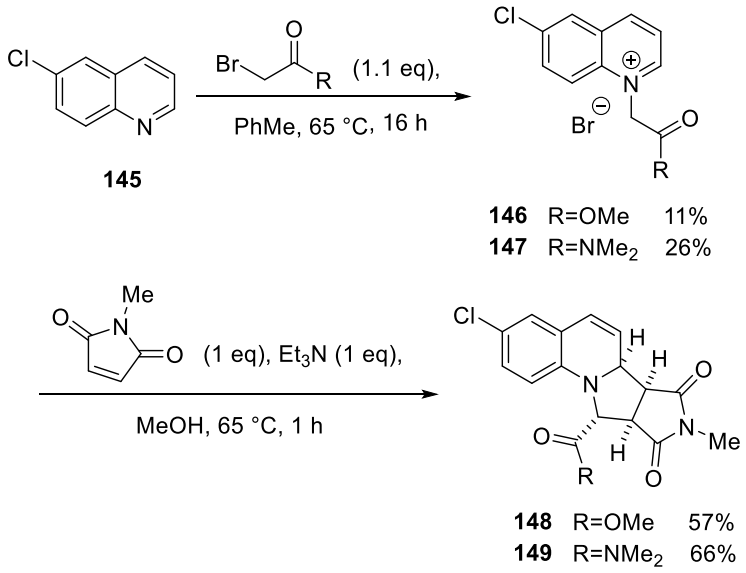
Compound	Group R and R^1	Structure	% Yield
139	R=OMe R^1=OMe		64
140	R=OMe R^1=Cl		67
141	R=OMe R^1=H		77
142	R=NMe_2 R^1=OMe		35
143	R=NMe_2 R^1=Cl		61
144	R=NMe_2 R^1=H		66

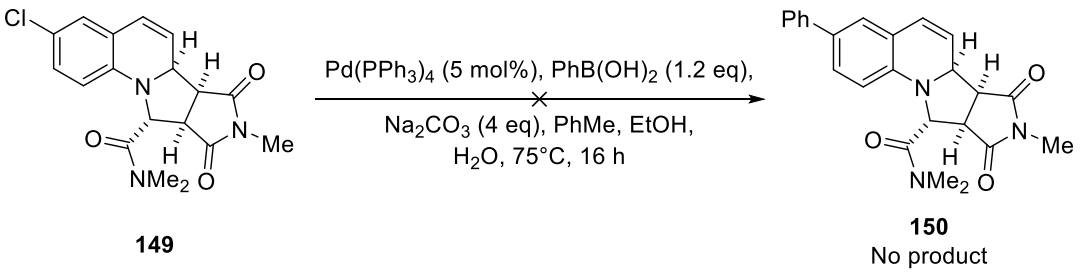
Table 2

To complete the work on the pyrroloquinolines we attempted to expand the substrate scope further by synthesising some compounds starting with 6-chloroquinoline **145**. This work was carried out alongside a MChem student in the group and the results are summarised in Scheme 64.[71] Starting with 6-chloroquinoline **145** the corresponding ester and amide quinolinium salts **146** and **147** were synthesised using the same conditions used previously. Salts **146** and **147** were isolated in 11% yield and 26% yield respectively. In comparison with salts **131** and **132** the 6-chloroquinoline derivatives were much more hygroscopic and harder to isolate, hence lower yields were obtained. Nonetheless, cycloaddition reactions of salts **146** and **147** with *N*-methylmaleimide gave the desired cycloadducts **148** and **149** in 57% yield and 66% yield respectively.



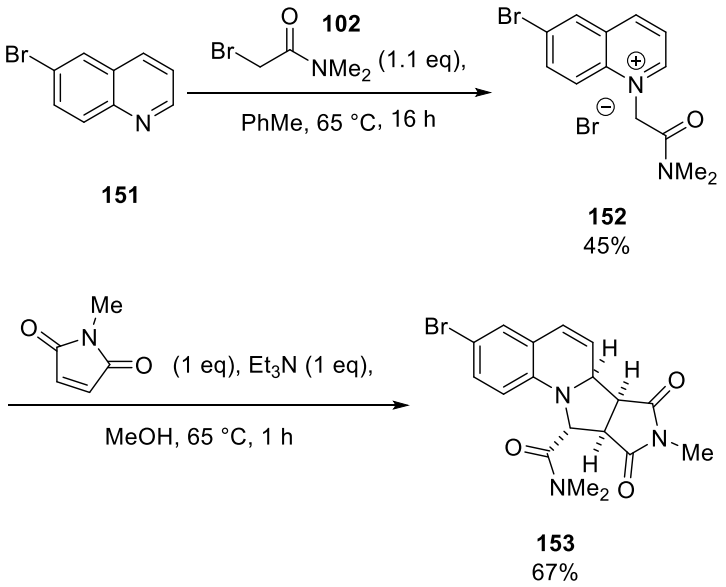
Scheme 64

We then attempted to do a Suzuki-Miyaura coupling reaction on compound **149**. The conditions used are shown in Scheme 65 where compound **149** was heated with tetrakis(triphenylphosphine)palladium(0), phenyl boronic acid and sodium carbonate. Unfortunately, none of the desired product **150** was isolated, however when repeating the reaction multiple times we managed to recover the starting material **149**. This indicated that oxidative addition of the palladium catalyst to compound **149** was not occurring and no coupling reaction was taking place.



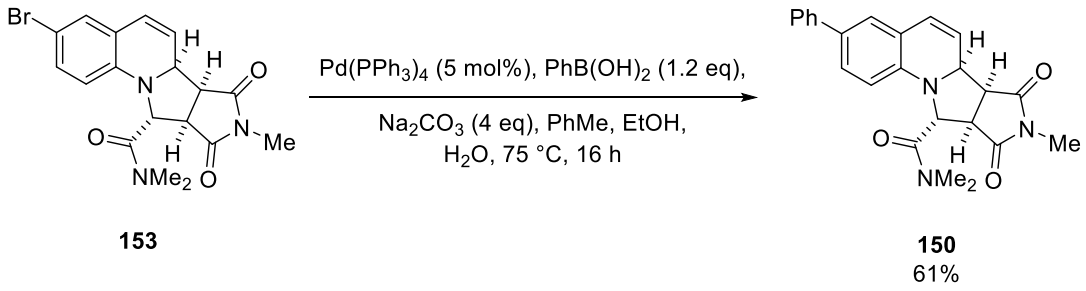
Scheme 65

To overcome this problem it was decided to synthesise the corresponding 6-bromo cycloadduct instead and repeat the Suzuki-Miyaura coupling. This is shown in Scheme 66 where starting from 6-bromoquinoline **151** the amide quinolinium salt **152** was first synthesised in 45% yield. Subsequent reaction of compound **152** with *N*-methylmaleimide gave cycloadduct **153** in 67% yield.



Scheme 66

We were now in a position to repeat the Suzuki-Miyaura coupling. Applying the same reaction conditions as before to cycloadduct **153** we were able to successfully isolate the coupled compound **150** in 61% yield. This is shown in Scheme 67.

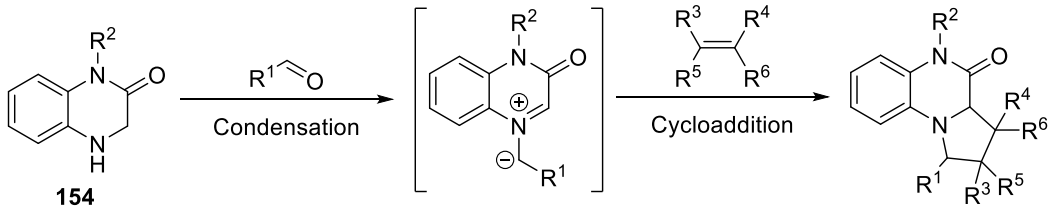


153 **150** 61%

Scheme 67

2.7 Synthesis of pyrroloquinoxalinone cycloadducts

With some successful results obtained with the pyrroloquinolines we decided to move forward onto the next flavin model based around synthesising cycloadducts from azomethine ylide **81**. To access these compounds we devised the synthetic route shown in Scheme 68 where the condensation reaction of dihydroquinoxalinone **154** with an aldehyde would generate an iminium species that could be deprotonated to give azomethine ylides **81**. Different alkenes could then be used to trap the azomethine ylides formed allowing cycloadducts with the general structure of **155** to be isolated.

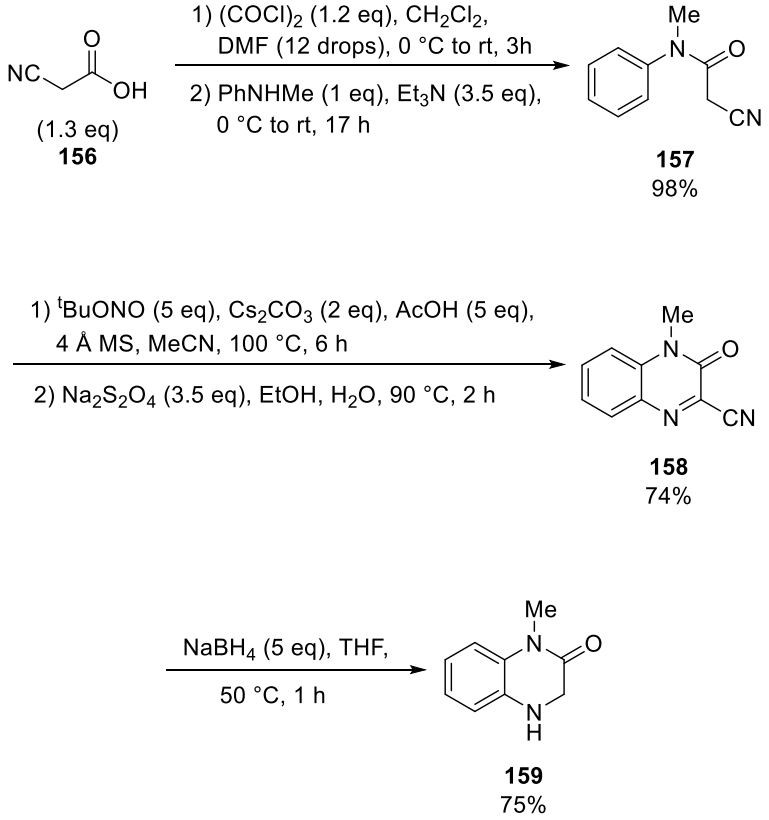


154 **81** **155**

Scheme 68

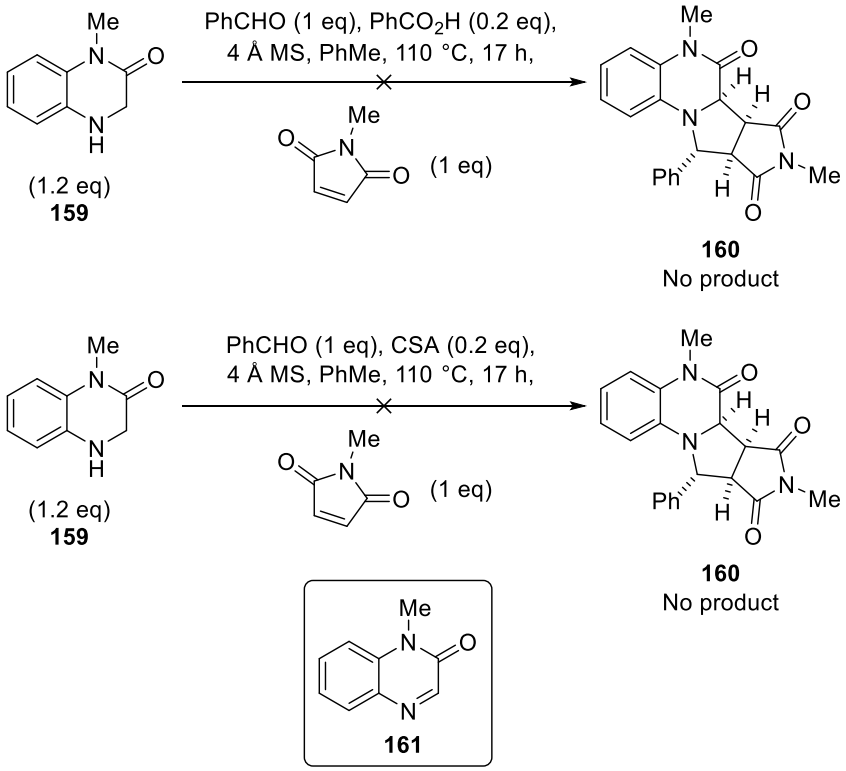
Before any work could be done, dihydroquinoxalinone **154** had to be synthesised. This was done using a known literature procedure as shown in Scheme 69.[72] Although R^2 has the potential to be any functional group we chose a methyl group to keep the model simple. The corresponding acid chloride of cyanoacetic acid **156** was first reacted with *N*-methylaniline to give amide **157** in 98% yield. This subsequently underwent a tandem nitrosation/cyclisation process with *t*-butyl nitrite in the presence of caesium carbonate, acetic acid and 4 Å MS in acetonitrile to give quinoxalin-2-one **158** in 74% yield. It's important to mention that the addition of sodium dithionite was required to reduce any of the quinoxalin-2-one **158** which may have oxidised further. In the final step

quinoxalin-2-one **158** was reduced using sodium borohydride to give dihydroquinoxalinone **159** in an overall yield of 75%.



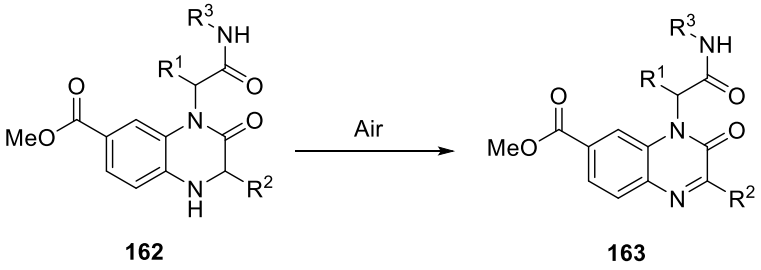
Scheme 69

With dihydroquinoxalinone **159** in hand we studied the use of conditions similar to those reported by Siedel and co-workers to try and synthesise the desired cycloadduct products.[34] As shown in Scheme 70, dihydroquinoxalinone **159** was heated with benzaldehyde, 4 Å MS, benzoic acid and *N*-methylmaleimide in toluene, but unfortunately none of the desired cycloaddition product **160** was isolated and only starting material was recovered. Changing to a stronger acid from benzoic to camphorsulfonic acid gave a similar result, but LCMS analysis of the crude product indicated that oxidised starting material **161** had been formed.



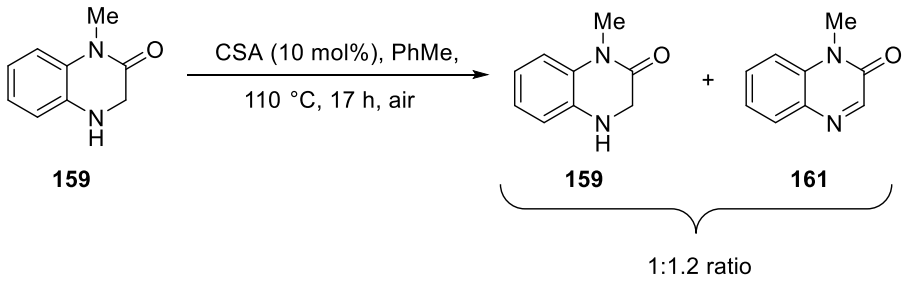
Scheme 70

It was clear that oxidation of the starting material was potentially interfering with the cycloaddition reaction. Looking in the literature, similar reactions have been reported where similar dihydroquinoxalinones were readily oxidised to form quinoxalin-2-one products. An example is shown in Scheme 71.[73]



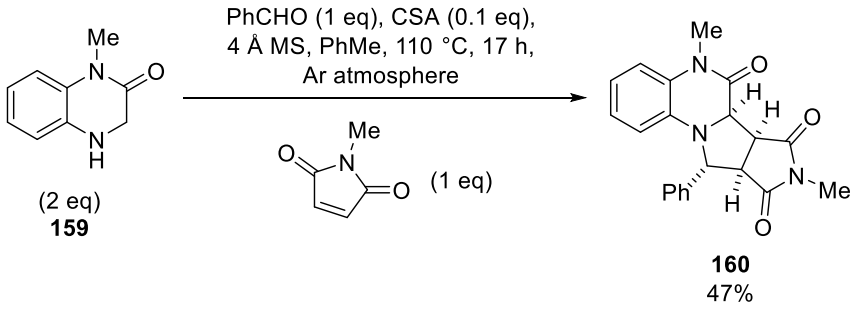
Scheme 71

To investigate the oxidation reaction, dihydroquinoxalinone **159** was heated under reflux in toluene with 10 mol% CSA as shown in Scheme 72. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy indicated a mixture of dihydroquinoxalinone **159** and its oxidised form **161** in a 1:1.2 ratio.



Scheme 72

When carrying out the same reaction under an inert argon atmosphere, ^{1}H NMR spectroscopy of the reaction mixture indicated no oxidised material **159** had been formed. Subsequently, repeating the cycloaddition reaction under an inert argon atmosphere as shown in Scheme 73 gave the desired cycloadduct **160**, as a single diastereoisomer in a moderate yield of 47%. In the reaction two equivalents of dihydroquinoxalinone **159** was used to cater for any potential oxidation of the starting material.



Scheme 73

The stereochemistry of compound **160** was confirmed by using X-ray crystallography (Figure 13 and Appendix 4), which indicated that compound **160** was presumably formed *via* the S-shaped ylide due to the *trans* configuration between the protons α to the amine nitrogen atom. Like with the pyrroloquinolines correlating the *J*-values with the dihedral angles, determined from the X-ray crystallography data, between the C-H bonds on the pyrrolidine ring allowed assignment of the protons in the ^{1}H NMR spectrum. This is summarised on the correlation diagram shown in Figure 13.

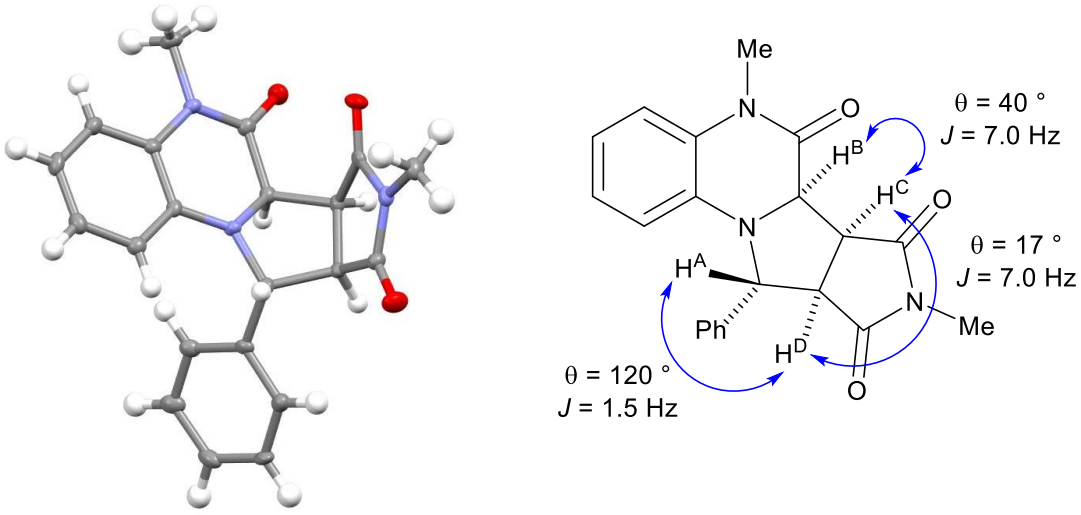
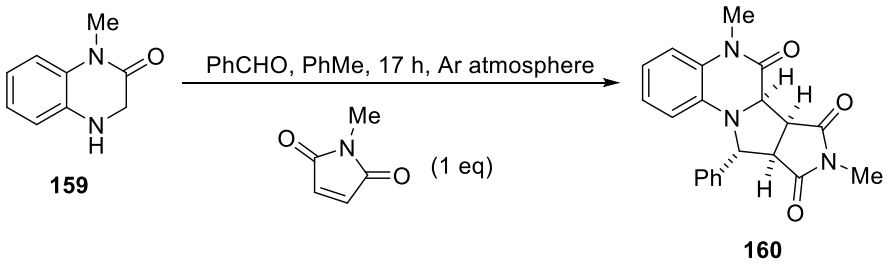


*Figure 13 – X-ray crystal structure of **160** with approximate dihedral angles (θ) & J-values shown*

The next step was to optimise the reaction conditions as shown in Scheme 74 and Table 3. Initially increasing the amount of CSA caused an increase in the yield of cycloadduct **160**, with a maximum yield of 57% being obtained when 15 mol% of CSA was added (entry 4). Decreasing the reaction temperature caused a decrease in the yield of cycloadduct **160** (entries 7 & 8). Addition of 4 Å molecular sieves to act as a drying agent seemed to improve the reaction yield (entry 10). Changing the molar ratio of dihydroquinoxalinone **159** and benzaldehyde gave variable yields for cycloadduct **160** (entries 11−15) with the best yield being obtained when the molar ratio of dihydroquinoxalinone **159**:benzaldehyde was 1.5:1 (entry 11). In a final attempt to improve the yield, the acid added to the reaction was changed from CSA to benzoic acid; however, this resulted in a decrease of the yield (entry 16).



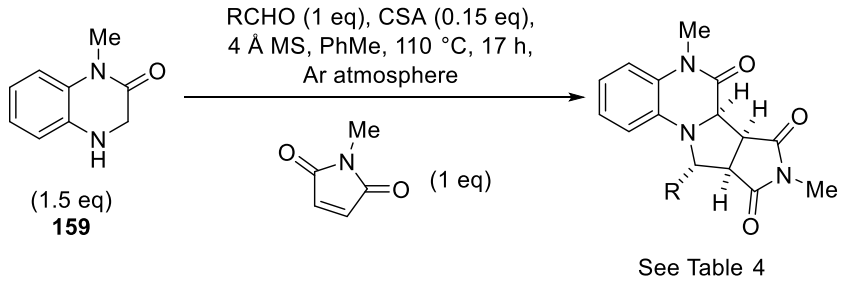
Scheme 74

Entry	Amine Eq	PhCHO Eq	Acid (mol%)	Temperature	Drying Agent	% Yield
1	2	1	No Acid	110 °C	None	0
2	2	1	CSA (5 mol%)	110 °C	None	14%
3	2	1	CSA (10 mol%)	110 °C	None	47%
4	2	1	CSA (15 mol%)	110 °C	None	57%
5	2	1	CSA (20 mol%)	110 °C	None	49%
6	2	1	CSA (50 mol%)	110 °C	None	47%
7	2	1	CSA (15 mol%)	90 °C	None	40%
8	2	1	CSA (15 mol%)	70 °C	None	31%
9	2	1	CSA (15 mol%)	110 °C	$MgSO_4$	48%
10	2	1	CSA (15 mol%)	110 °C	4 Å MS	63%
11	**1.5**	**1**	**CSA (15 mol%)**	**110 °C**	**4 Å MS**	**69%**
12	1.2	1	CSA (15 mol%)	110 °C	4 Å MS	40%
13	1	1	CSA (15 mol%)	110 °C	4 Å MS	54%
14	1.5	1.5	CSA (15 mol%)	110 °C	4 Å MS	38%
15	1	1.5	CSA (15 mol%)	110 °C	4 Å MS	25%
16	1.5	1	$PhCO_2H$ (15 mol%)	110 °C	4 Å MS	32%

Table 3

Using the optimised conditions (Scheme 75), we then explored the substrate scope of the reaction. By varying the aldehyde, we were able to obtain a range of different cycloadducts **164-167** in varying yields (Table 4). The reaction was successful with both electron-poor (entry 2) and electron-rich (entry 3) benzaldehydes, although the yield of cycloadduct **165** in the latter case was low. It was pleasing to find that the reaction was successful with a heteroaryl group (entry 4) and with the non-aromatic aldehyde cyclohexanecarbaldehyde, which gave the desired cycloadduct **167** in 31% yield. In all cases **164-167**, we obtained only a single stereoisomer and this was assumed to have the same stereochemistry as determined for cycloadduct **160**.

Although the reaction was successful with this range of aldehydes, when the reaction was carried out using 2-furaldehyde or 3-methyl-2-butenal no desired product was isolated. With 2-furaldehyde the starting material was recovered, whereas with 3-methyl-2-butenal a mixture of products was seen *via* TLC analysis.



Scheme 75

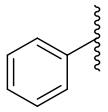
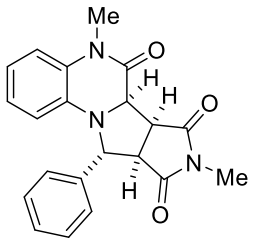
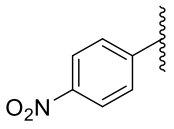
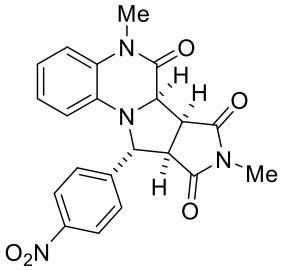
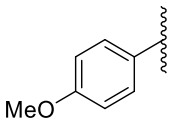
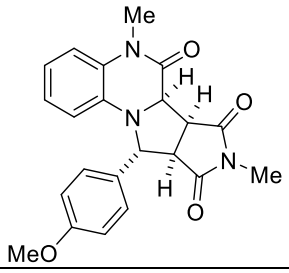
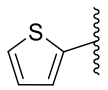
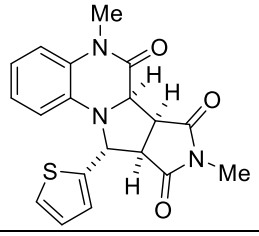
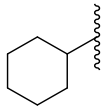
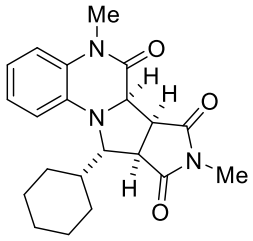
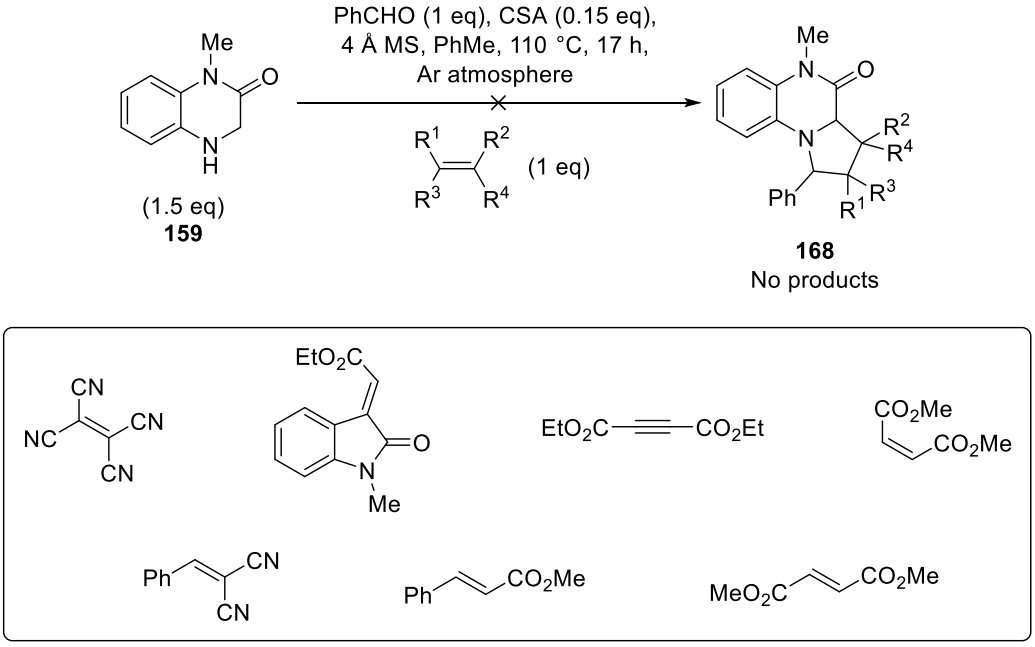
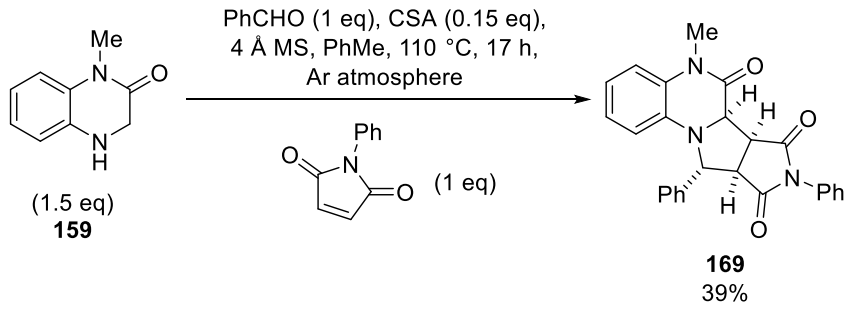
Entry	Compound	R Group	Product	% Yield
1	**160**			69%
2	**164**			46%
3	**165**			27%
4	**166**			59%
5	**167**			31%

Table 4

Continuing with the work we then looked into expanding the alkene scope. Like the pyrroloquinolines the cycloaddition reaction was unsuccessful with a variety of dipolarophiles including dimethyl furmarate, methyl *trans*-cinnamate and diethyl acetylenedicarboxylate. This is summarised in Scheme 76, where reactions with other failed dipolarophiles are shown. However, the reaction was successful with *N*-phenylmaleimide to give cycloadduct **169** in 39% yield (Scheme 77).

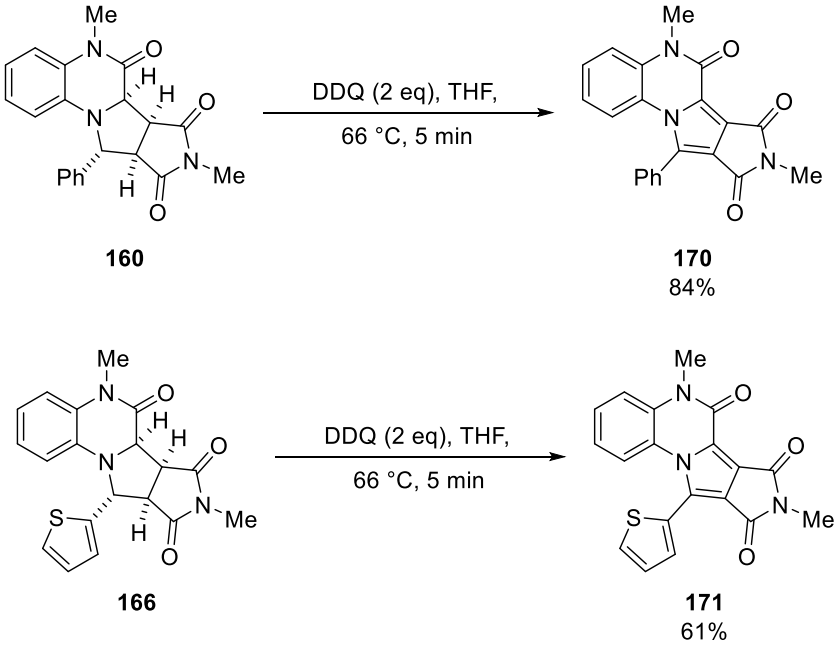


Scheme 76



Scheme 77

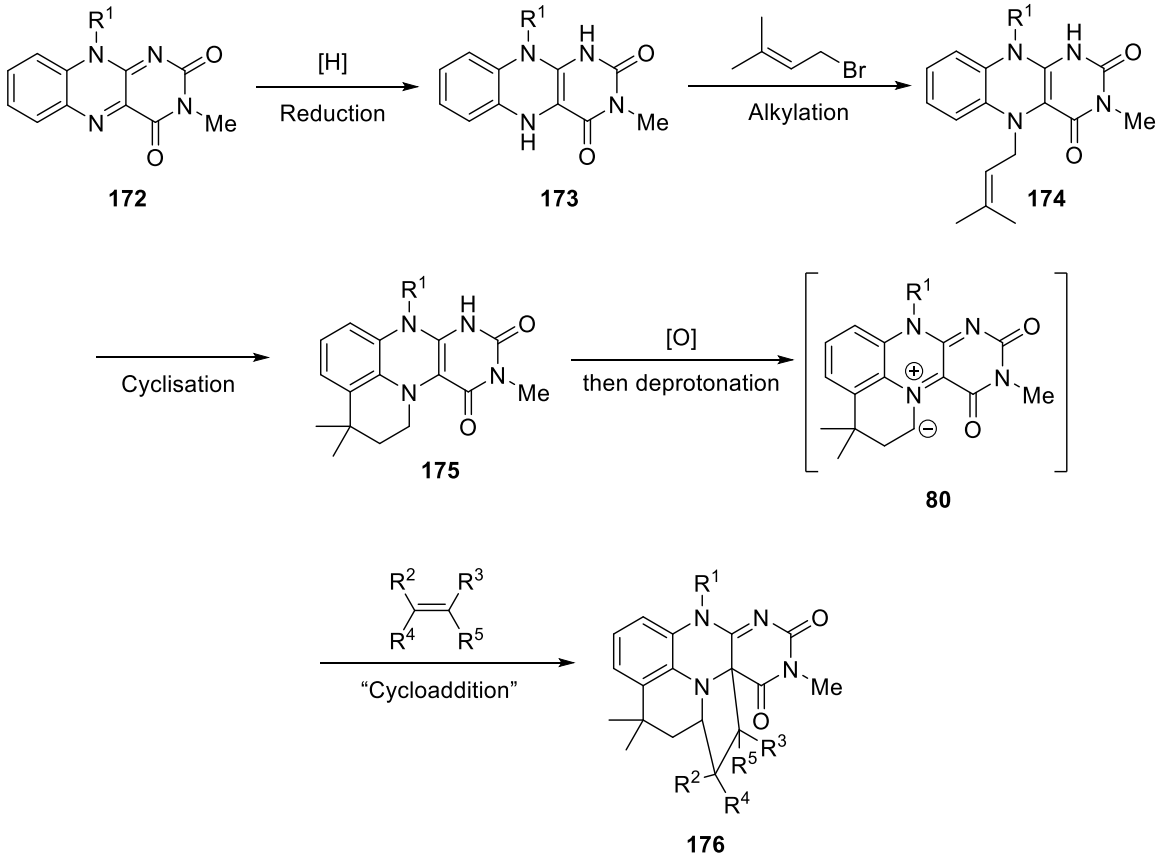
Finally, the scope of products was extended by oxidation of cycloadducts **160** and **166** using DDQ. Like the pyrroloquinolines, similar reaction conditions were used as shown in Scheme 78. This resulted in the formation of compounds **170** and **171** respectively in good yields.



Scheme 78

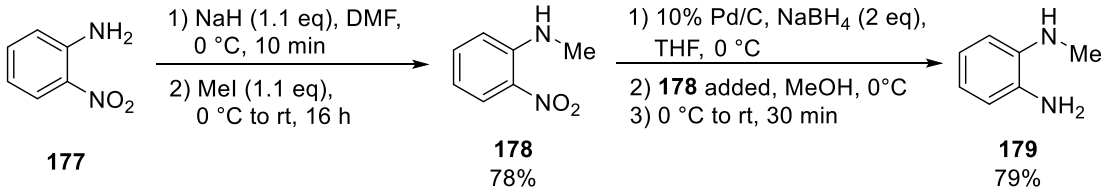
2.8 Moving towards the flavin model

Having now made progress towards synthesising pyrroloquinolines and pyrroloquinoxalinones we wanted to test the flavin model **80**. The synthetic route devised to access this model is shown in Scheme 79. Starting with flavin derivative **172** a reduction reaction could be done to generate the reduced species **173**.[49] This could then be alkylated with prenyl bromide to give **174**, which could then undergo a cyclisation reaction to form prenylated flavin **175**.[74,75] Subsequent oxidation and deprotonation would then result in azomethine ylide **80**.[76,77] Reactions of ylide **80** with alkenes would then allow cycloadducts with the general structure **176** to be accessed. This would hopefully provide some evidence that a 1,3-dipolar cycloaddition reaction could take place in the biochemical pathway of the decarboxylation of α,β-unsaturated carboxylic acids.



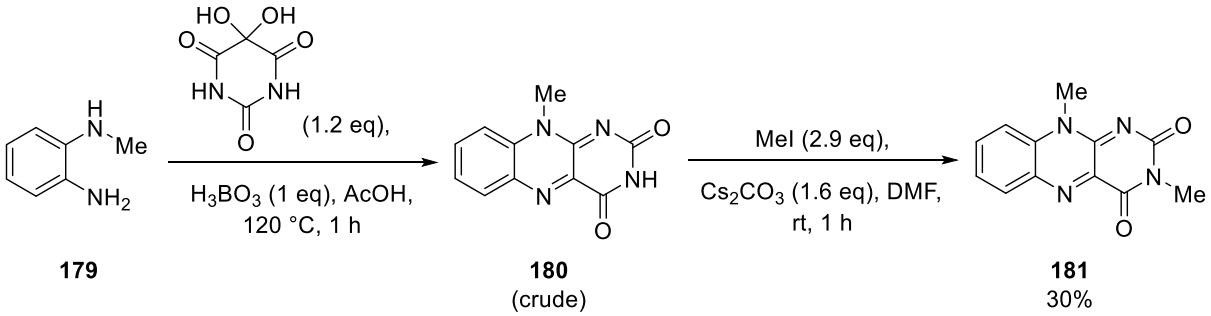
Scheme 79

Initial work began by attempting to synthesise derivatives of flavin **172**. To not overcomplicate the flavin structure we initially chose the R^1-group to be methyl. Therefore, as shown in Scheme 80, nitroaniline **177** was *N*-methylated using methyl iodide and sodium hydride to give compound **178** in 78% yield.[78] Subsequent reduction of compound **178** using a mixture of sodium borohydride and 10% Pd/C gave diamine **179** in 79% yield.[79]



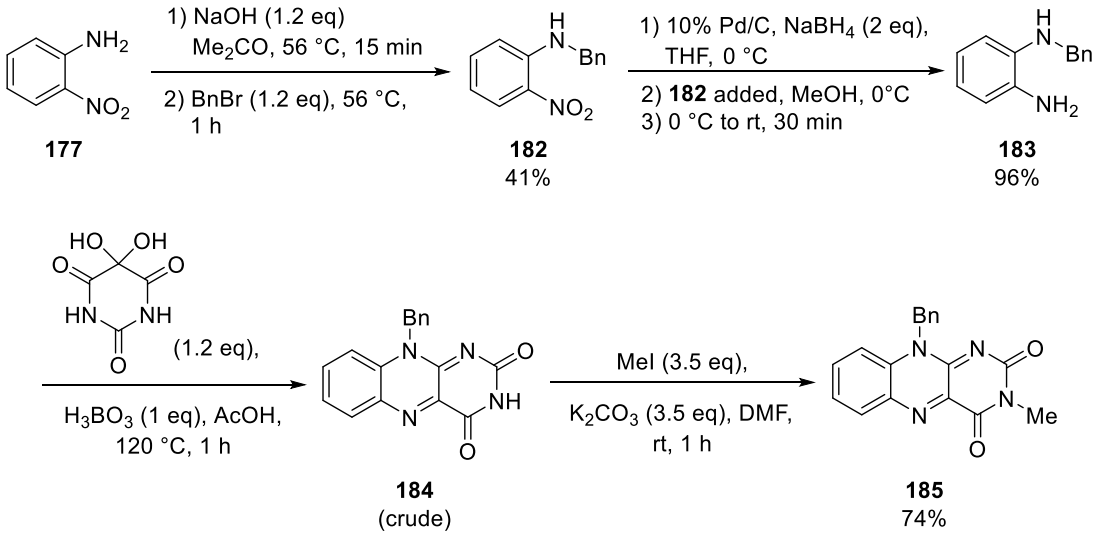
Scheme 80

Compound **179** was then reacted with alloxan monohydrate and boric acid in the presence of glacial acetic acid.[80] This gave the crude flavin **180**, which was then methylated using methyl iodide and Cs_2CO_3 in DMF.[81] Compound **181** was isolated in a yield of 30% over the two steps (Scheme 81). Unfortunately, when scaling up the reaction to synthesise larger amounts of compound **181,** very poor yields were obtained (<10%). This may have been due to the poor solubility of **181** in organic solvents.



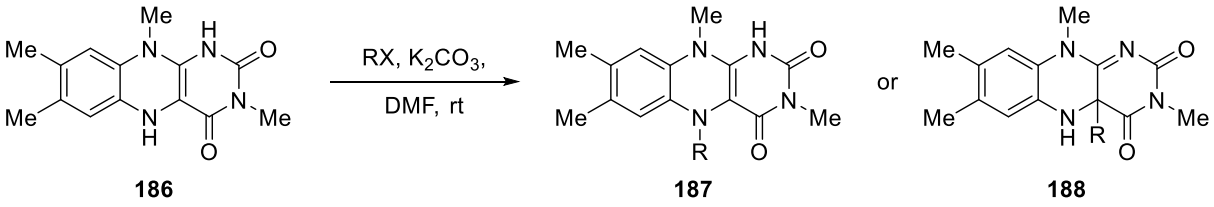
Scheme 81

To try and overcome this problem it was decided to replace the N(10) methyl group with a benzyl group to increase its solubility. As a result, a new synthetic route was devised as shown in Scheme 82. The route used is very similar to the route used to synthesise compound **181**. In the first step, nitroaniline **177** was *N*-alkylated using benzyl bromide and sodium hydroxide in acetone.[82] Heating under reflux for 1 h gave compound **182** in 41% yield. Subsequent reduction of compound **182** using sodium borohydride and 10% Pd/C gave diamine **183** in 96% yield. Crude flavin **184** was then synthesised by reacting **183** with alloxan monohydrate and boric acid in glacial acetic acid. The crude flavin **184** was then methylated using potassium carbonate and methyl iodide to give the flavin core **185** in a good yield of 74%. This route was more beneficial as the product **185** was isolated in a high yield when performing the reaction on a large scale.



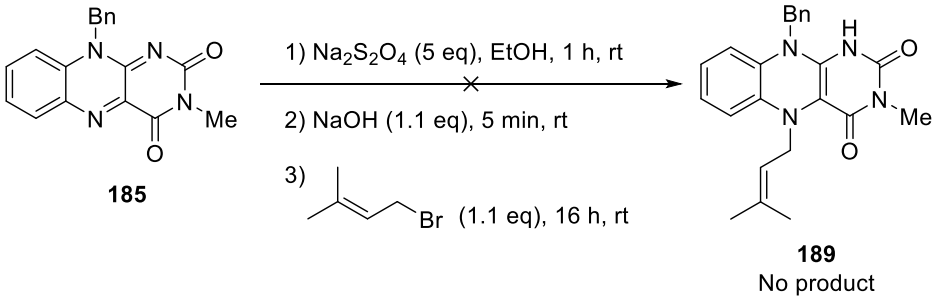
Scheme 82

With flavin core **185** in hand we now wanted to reduce and alkylate at the N(5) position. Looking further into the literature, we hoped that once we were able to reduce flavin **185** using a suitable reducing agent, such as sodium dithionite, then alkylation would occur readily. However, previous studies in the area have shown that the choice of alkylation agent is important as that different alkylating agents have the potential to alkylate in different positions on the flavin core (Scheme 83).[83]



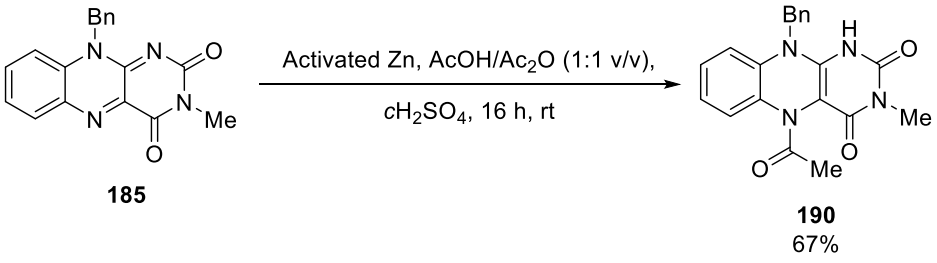
Scheme 83

The reaction conditions first used in an attempt to reduce compound **185** are shown in Scheme 84. Sodium dithionite was added to a solution of compound **185** in ethanol and left to stir under an argon atmosphere. Prenyl bromide was then added in the hope that alkylation would occur and produce compound **189**. Unfortunately after multiple attempts and switching to alternative alkylating agents including allyl bromide, benzyl bromide and ethyl bromide no desired alkylated flavin could be isolated.



Scheme 84

Looking at the potential issues, we thought there may have been a problem with the reduction process. According to the literature, the reduction of vitamin B2 normally results in a colour change from yellow to colourless.[84] When carrying out the reduction reactions shown in Scheme 84 we noticed that none of the reactions produced a similar colour change. As a result we decided to investigate other methods to reduce flavins, in particular using zinc and acid. Using the reaction conditions shown in Scheme 85 we were able to successfully reduce flavin **185** using activated zinc in acetic acid under an argon atmosphere. Upon the addition of activated zinc metal the reaction changed colour from yellow/orange to red (Figure 14) which was in agreement with a similar example in the literature and indicated that the reduction reaction had occurred.[85] Acylation of the reduced flavin with acetic anhydride then allowed the acylated flavin **190** to be isolated in 67% yield.



Scheme 85

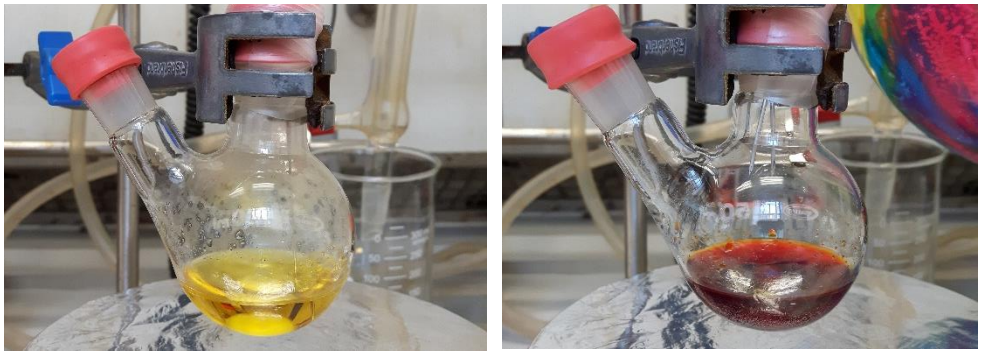
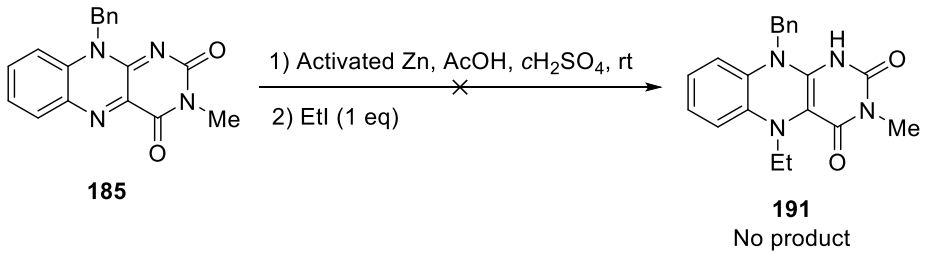


*Figure 14 – Yellow to red colour change during reduction of **185** using zinc*

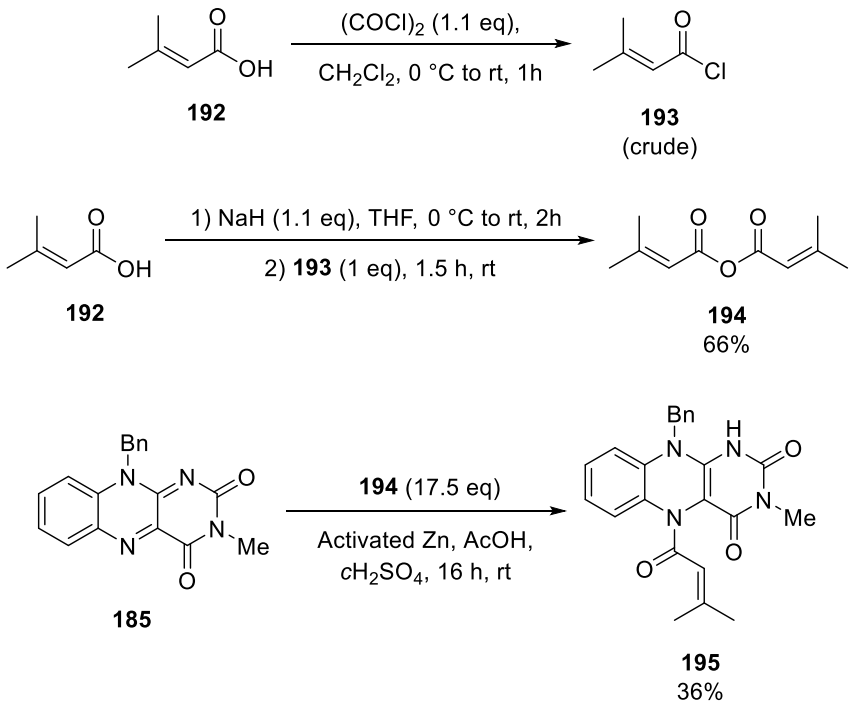
Having now found a method to reduce flavin **185** we then attempted an alkylation reaction using ethyl iodide as the alkylating agent (Scheme 86). Unfortunately, upon the addition ethyl iodide the reaction mixture began to vigorously bubble eventually causing the reaction vessel to fail and the mixture to be exposed to air. Based on the assumption that an organozinc reagent was being formed further attempts using different alkylating agents such as prenyl bromide, were not done.



185 **191** No product

Scheme 86

Moving forward, we then wanted to use a similar acylation reaction to the one shown in Scheme 85 to get closer to the prenylated flavin intermediate **80**. The anhydride **194** was prepared by converting 3,3-dimethylacrylic acid **192** into its corresponding acid chloride **193** using oxalyl chloride. This was then added to a mixture of 3,3-dimethylacrylic acid **192** and sodium hydride to give anhydride **194** in 66% yield. By applying a procedure similar to the reaction in Scheme 85 using anhydride **194**, acylated flavin **195** was isolated in 36% yield (Scheme 87). The structure of **195** was confirmed using X-ray crystallography which showed that flavin **185** had been acylated in the correct position on the N(5) atom (Figure 15 and Appendix 5).



Scheme 87

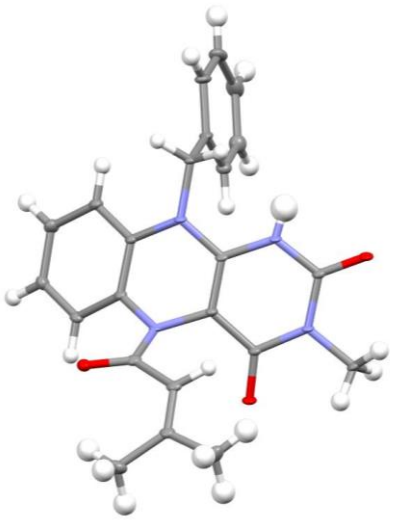
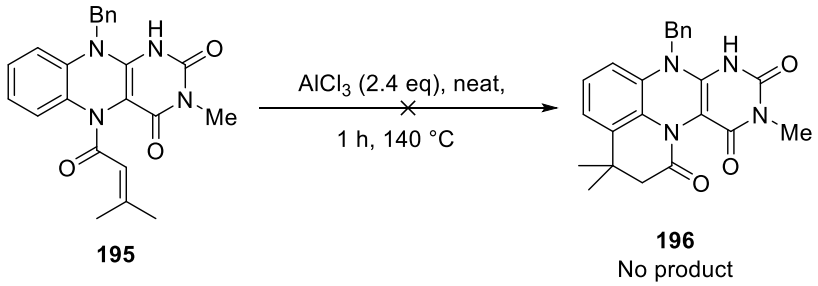


*Figure 15 – X-ray crystal structure of **195***

We then attempted to cyclise the alkene in acylated flavin **195** onto the aromatic core by heating it with $AlCl_3$ as shown in Scheme 88. Our idea was that the $AlCl_3$ may have been able to coordinate the two carbonyl groups to allow this process to take place, however after multiple attempts of the reaction no desired product was formed. This may have been potentially due to the preference of the undesired rotamer of the acyl group. The reaction was repeated at room temperature in CH_2Cl_2 but gave the same result.



Scheme 88

Unfortunately, due to the difficulties encountered, it was decided to stop work on trying to synthesise the final flavin model **80** and move onto a different project.

2.9 Conclusions and Future Work

In summary, although we were unsuccessful in providing further evidence for the initial 1,3-dipolar cycloaddition reaction in the decarboxylation pathway of cinnamic acid using prFMN **73**, we were able to synthesise a range of smaller cycloadducts with similar resemblance to the intermediate **75**.

Using quinolinium salts we successfully managed to perform cycloaddition reactions to isolate pyrroloquinolines. We were also able to carry out further reactions on these products, including reduction to form the corresponding tetrahydroquinoline and oxidation to form the corresponding pyrrole in good yields. Subsequently, we found that if the pyrroloquinoline contained a bromine atom in the C(6) position then a Suzuki-Miyaura coupling could be achieved. Shifting the focus towards the synthesis of pyrroloquinoxalinones, although the cycloaddition reactions were air sensitive, a small number of cyclodducts were synthesised in varying yield. In addition, like the pyrroloquinolines some of the molecules were oxidised to obtain the desired pyrrole products. Unfortunately, with both the pyrroloquinolines and the pyrroloquinoxalinones the dipolarophile scope was very limited, generally only working with a few alkenes such as *N*-methylmaleimide.

Efforts to synthesise a prenylated flavin analogue were unsuccessful. Essentially, this was mainly due to difficulty in installing the prenyl group onto the flavin core. Taking inspiration from biology, a potential method to overcome this problem is to use enzymes to prenylate the flavin.

Further work could be done on the pyrroloquinoxalinones as the products generated have the potential to be biologically active, therefore expanding the substrate scope could prove useful.[86–89] This could be achieved in a number of different ways as shown in Figure 16. Changing the aromatic ring, either by adding substituents to the benzene ring or by changing the benzene ring to a heteroaryl group is a simple way to expand the scope of products. Furthermore, changing the electron withdrawing group from an amide to an ester or thioester could be beneficial as well. Alternatively, another electron withdrawing group could be placed in the 2-position as shown. This is more likely to have an effect on the cycloaddition reaction and could lead to an expansion in the dipolarophile scope.

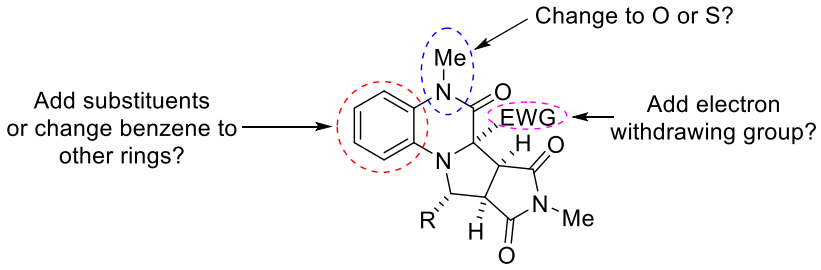


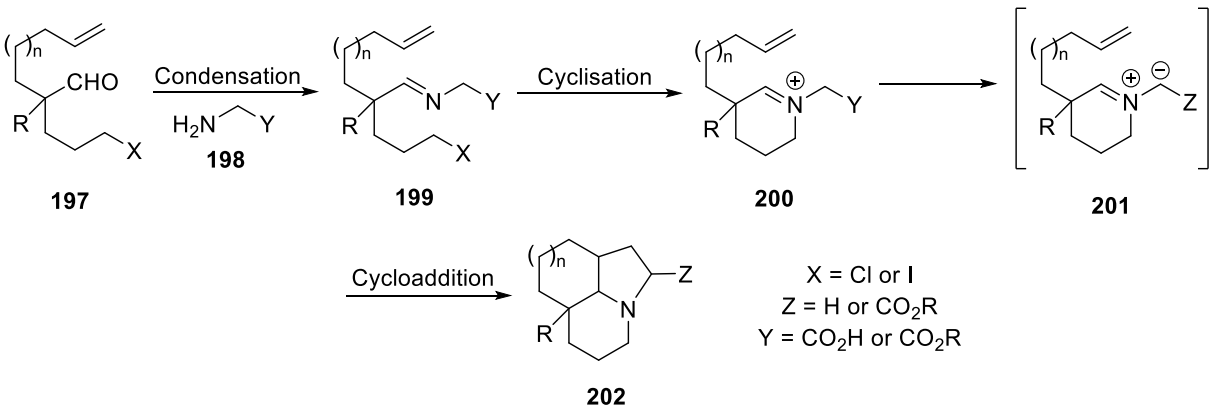
Figure 16 – Potential future work on pyrroloquinoxalinone compounds

Chapter 3 – Synthesis of Tricyclic Compounds Using Cascade Chemistry

3.1 Introduction to cascade chemistry

Within organic synthesis the ability to form complex molecules in an efficient manner is of vital importance, particularly when synthesising alkaloid natural products as most synthetic routes are generally long and contain multiple chemical reactions. A possible solution to overcome these long synthetic routes is to utilise cascade reaction processes. These processes involve using a series of chemical reactions which proceed successively due to the presence of highly reactive functional groups or reactive intermediates being formed in each step. As a result of this, intermediate compounds are usually not isolated or purified; and the addition of extra reagents or changes to reaction conditions are not required. Overall, this results in a highly efficient process, which is environmentally friendly when compared to using multiple stepwise reactions as less chemical waste is generated.[90,91]

Within the Coldham group we have successfully managed to utilise dipolar cycloaddition reactions in a cascade process, in particular using azomethine ylides. This is summarised in Scheme 89 where amine **198** first undergoes a condensation reaction with aldehyde **197**. This results in the formation of imine **199** that can cyclise to give the iminium **200**. Subsequent deprotonation or decarboxylation can then generate the desired azomethine ylide **201** and intramolecular cycloaddition would then result in the tricyclic product **202** being isolated. Formally, this process is referred to as a condensation, cyclisation, cycloaddition cascade.

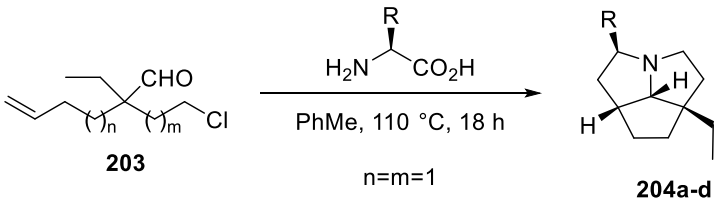


Scheme 89

In this chapter we will discuss the use of this cascade reaction towards the synthesis of small tricyclic compounds, which have become a common target in the group. However, it is important to mention that this research has also been used to synthesise the main cores of natural products. This will be discussed in the next chapter.

3.2 Previous work

One of the first synthetic methods used in the group to synthesise tricyclic compounds is shown in Scheme 90.[92] Using the acyclic aldehyde **203** and heating with a variety of amino acids in toluene allowed access to cycloadducts **204a-d** in good yields from 77-85% (Table 5). The reactions were highly stereoselective as only the all *cis* diastereoisomer was formed. A contributing factor to the high yields was due to the additional ethyl group on aldehyde **203** which prevented enolisation of the aldehyde and therefore any unwanted side products.

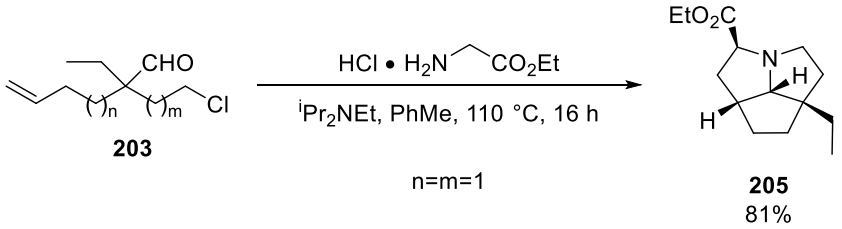


Scheme 90

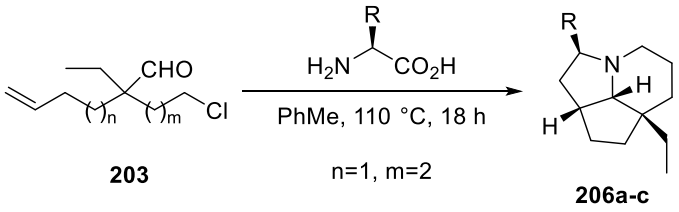
Compound	R Group	% Yield
204a	H	77
204b	Me	85
204c	CH_2Ph	85
204d	CH_2CHMe_2	78

Table 5

The substrate scope was then expanded by using glycine ethyl ester hydrochloride instead of glycine. The reaction conditions used are shown in Scheme 91 and gave product **205** in 81% yield. Furthermore, it was found that by altering the chain length of the two alkyl chains attached to the aldehyde, cycloadducts could be isolated in good yields that contained different ring sizes (Scheme 92, Table 6 and Scheme 93).



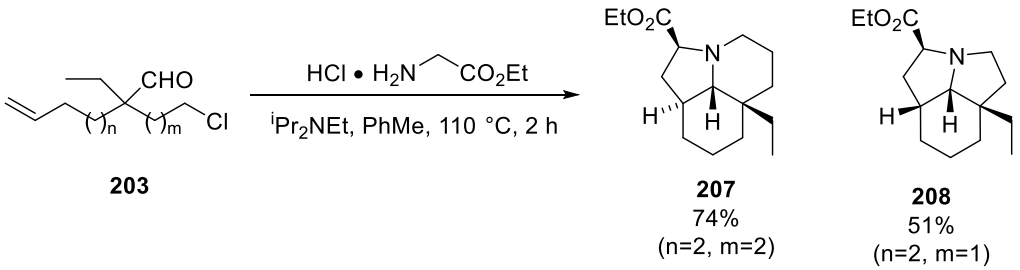
Scheme 91



Scheme 92

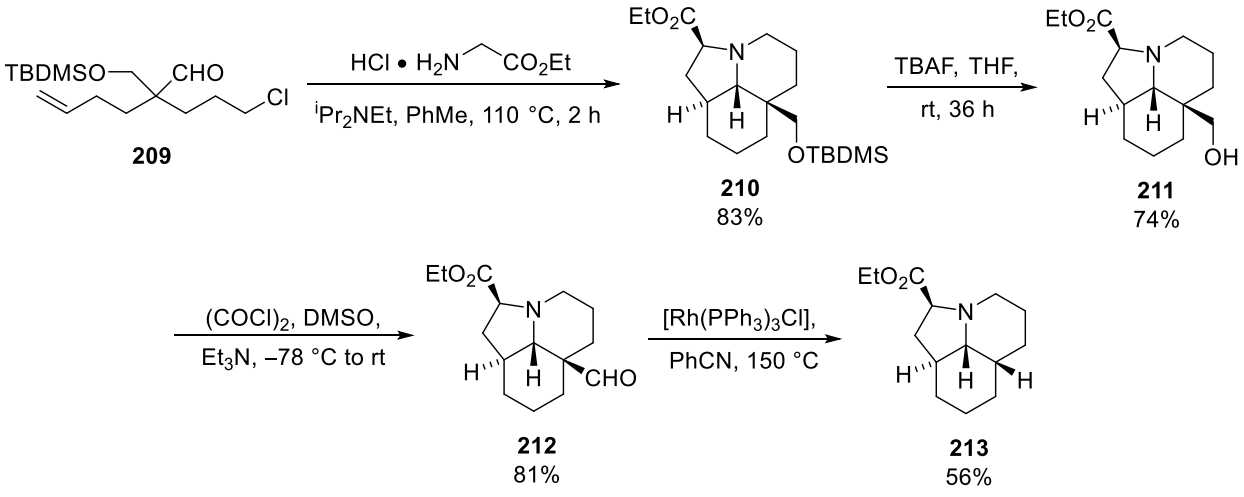
Compound	R Group	% Yield
206a	H	82
206b	Me	78
206c	CH_2Ph	60

Table 6



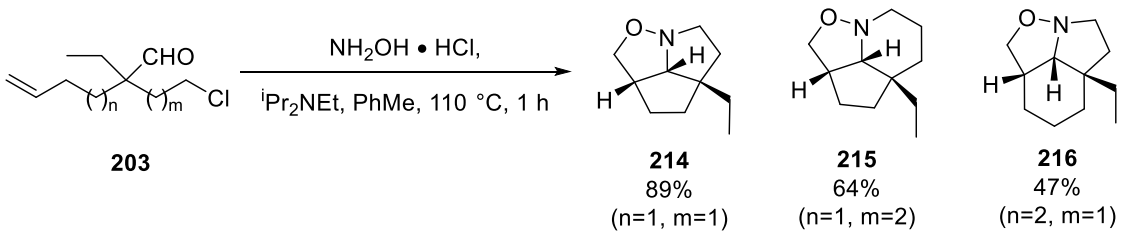
Scheme 93

Continuing with the work, it was found that by replacing the ethyl group on the α-carbon of the aldehyde starting material with a *tert*-butyldimethylsilyl (TBDMS) ether group gave access to a small series of novel cycloadducts.[93] An example is shown in Scheme 94 where aldehyde **209** was reacted with glycine ethyl ester hydrochloride in the presence of Hünig's base to give cycloadduct **210**. From here the TBDMS group could then be removed to give alcohol **211** and subsequent Swern oxidation and decarbonylation reactions gave the tricyclic amine **213**.

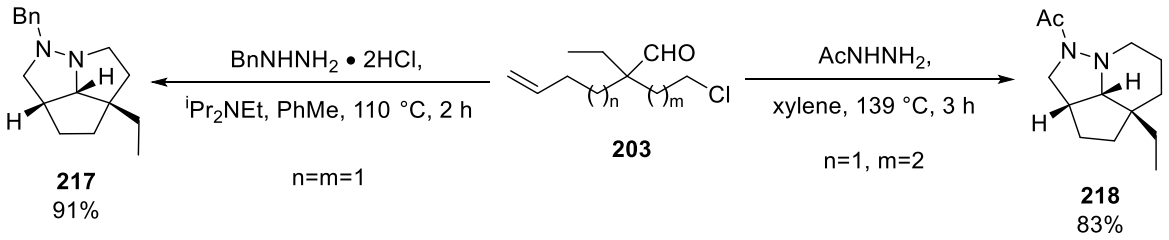


Scheme 94

Generating different dipoles instead of azomethine ylides also proved to be a successful way of expanding the substrate scope. Using hydroxylamine hydrochloride to generate nitrones, and applying the reaction conditions shown in Scheme 95 to aldehyde **203** gave the fused tricyclic isoxazolidine products **214−216** in good yields as a single diastereoisomer.[92] In comparison, using substituted hydrazines allowed the formation of tricyclic pyrazolidines such as **217** and **218** in very good yields of 91% and 83% respectively (Scheme 96).[94]

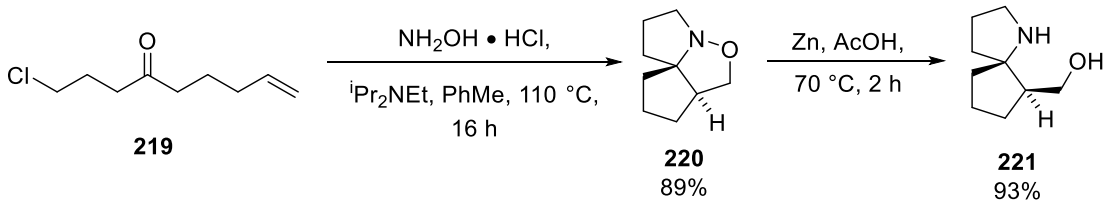


Scheme 95



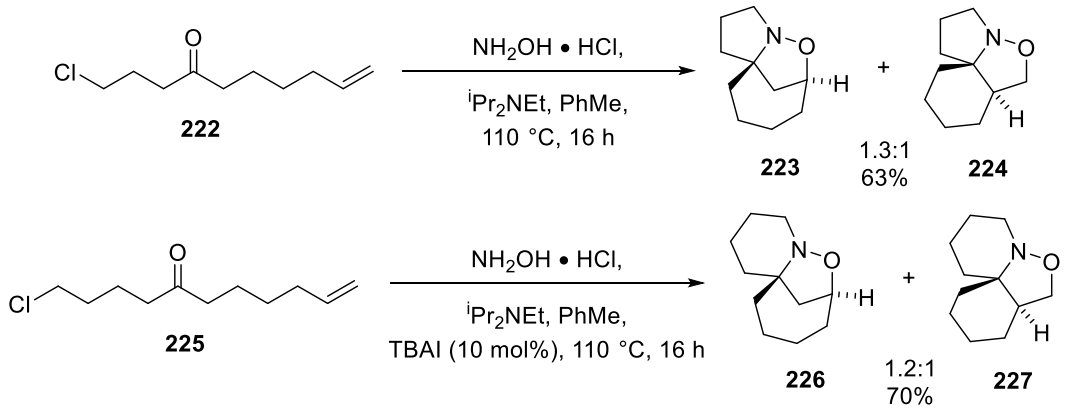
Scheme 96

More recently, research in the group has moved on to synthesising similar tricyclic compounds. However instead of using aldehydes, acyclic ketones were used. An example reaction is shown in Scheme 97 where ketone **219** was heated with hydroxylamine hydrochloride and Hünig's base in toluene.[95] This gave cycloadduct **220** in 89% yield as a single diastereoisomer. Furthermore, upon reduction of the N-O bond using zinc and acetic acid the spirocyclic compound **221** could be isolated.



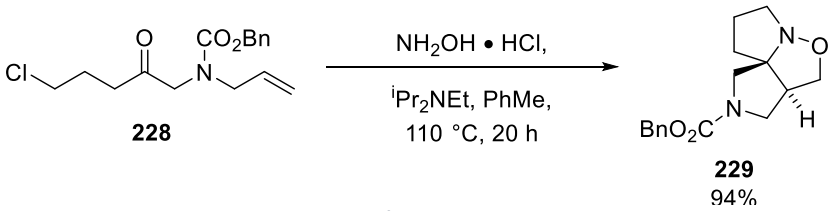
Scheme 97

Like with previous work, varying the alkyl chain length on either side of the ketone allowed access to a variety of alternative cycloadducts with different ring structures. It's important to mention that a mixture of inseparable regioisomers was obtained when ketones **222** and **225** were used (Scheme 98). However, upon the addition of zinc and acetic acid to the mixture of products gave spirocycles which could be separated using column chromatography and were isolated in good yields.

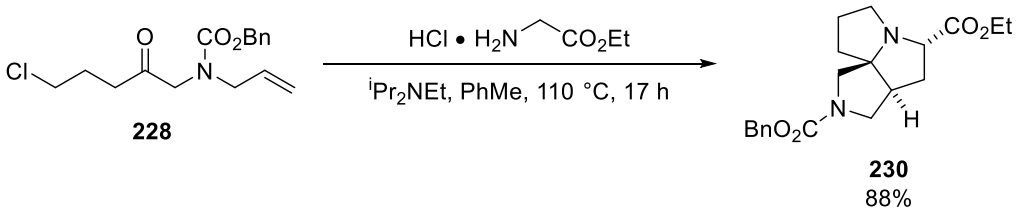


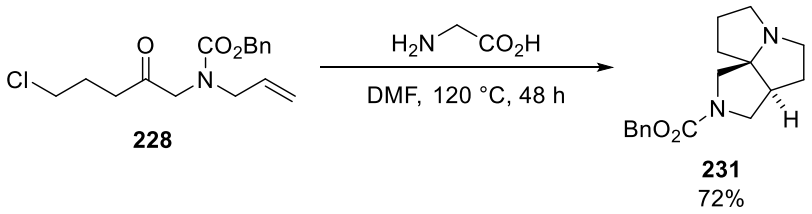
Scheme 98

Using ketone **228**, which contained a nitrogen atom between the alkene and ketone functional groups, allowed compound **229** to be synthesised in a 94% yield using hydroxylamine hydrochloride (Scheme 99). Furthermore, the use of glycine ethyl ester hydrochloride and glycine gave access to cycloadducts **230** and **231** respectively *via* the corresponding azomethine ylide when each reacted with ketone **228** (Scheme 100).[96] For the cycloaddition reaction using glycine it was found that changing the reaction solvent to *N,N*-dimethylformamide was required to help solubilise the glycine.



Scheme 99

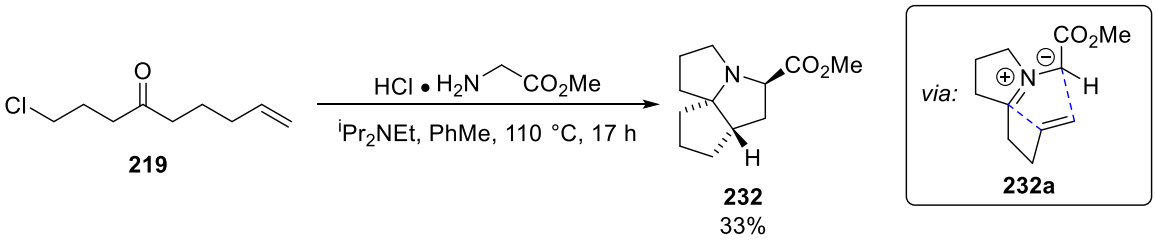




Scheme 100

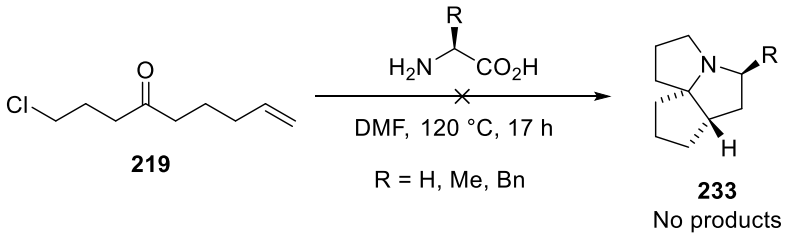
Synthesising compounds **230** and **231** demonstrated the versatility of the cascade cycloaddition chemistry with acyclic ketones. As a result of this it was decided to develop the chemistry further in an attempt to synthesise more tricyclic compounds *via* azomethine ylides. This work was originally carried out by a MChem student in the group under my supervision in the laboratory.[97] The first reaction attempted is shown in Scheme 101 where ketone **219** was heated with different methyl ester derivatives of amino acids in the presence of Hünig's base and toluene. Disappointingly the reaction was only successful with glycine methyl ester hydrochloride, which

gave cycloadduct **232** in 33% yield. It was thought that the reaction proceeded through azomethine ylide **232a**.



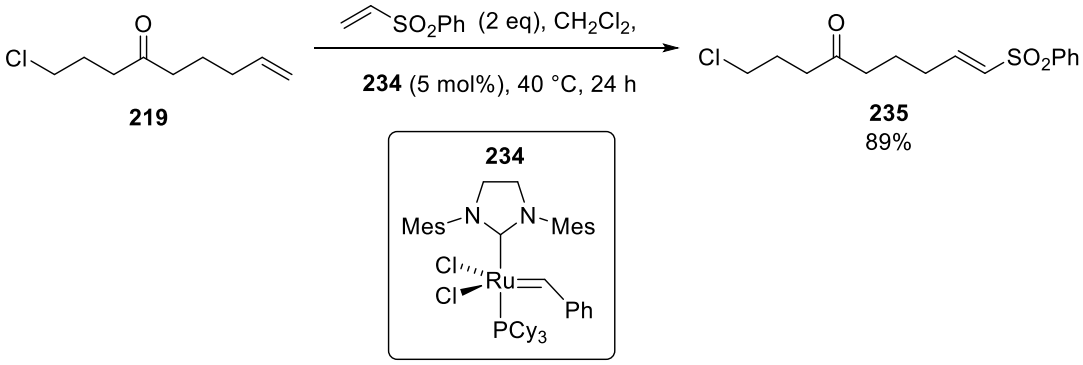
Scheme 101

Repeating the reactions using amino acids instead of their methyl ester derivative was unsuccessful. The reaction conditions used are shown in Scheme 102. In all of the reactions no desired products **233** were isolated after column chromatography, but LCMS analysis of the crude reaction mixtures indicated that the desired cycloadducts **233** had been formed.



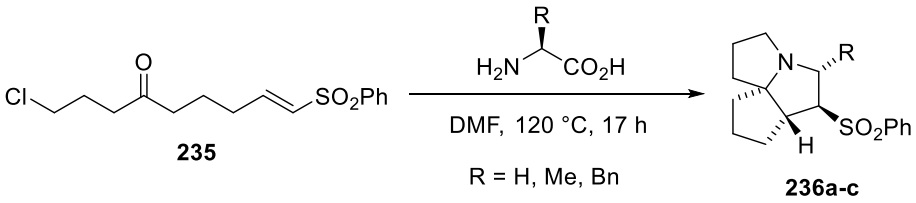
Scheme 102

It was then decided to activate the alkene functional group in ketone **219** by attaching a phenyl sulfone group in the terminal position. This was achieved using a Grubbs metathesis reaction as shown in Scheme 103 where ketone **219** was reacted with phenyl vinyl sulfone in the presence of Grubbs 2nd generation catalyst in CH_2Cl_2. Compound **235** was isolated in 89% yield.



Scheme 103

With compound **235** in hand the cycloaddition reactions using the amino acids shown in Scheme 104 were carried. The results are summarised in Table 7 where it was pleasing to find that when using glycine and phenylalanine the desired cycloadducts **236a** and **236c** were isolated in 56% and 12% yields respectively. Unfortunately, the reaction was unsuccessful when using L-alanine and none of the desired product **236b** was isolated. It's important to mention that although the addition of the phenyl sulfone group should have improved the rate of cycloaddition, when compared to ketone **219**, the reaction was less efficient when sterically more bulky amino acids were used.

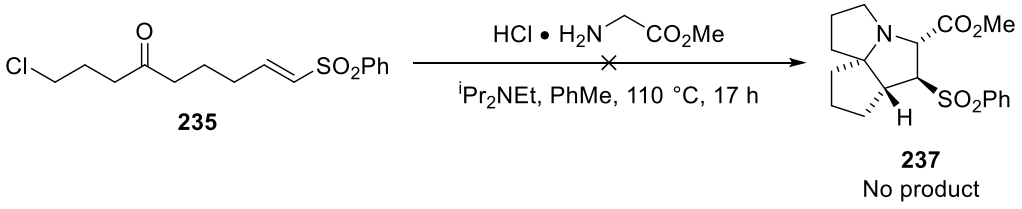


Scheme 104

Compound	R Group	% Yield
236a	H	56
236b	Me	0
236c	CH_2Ph	12

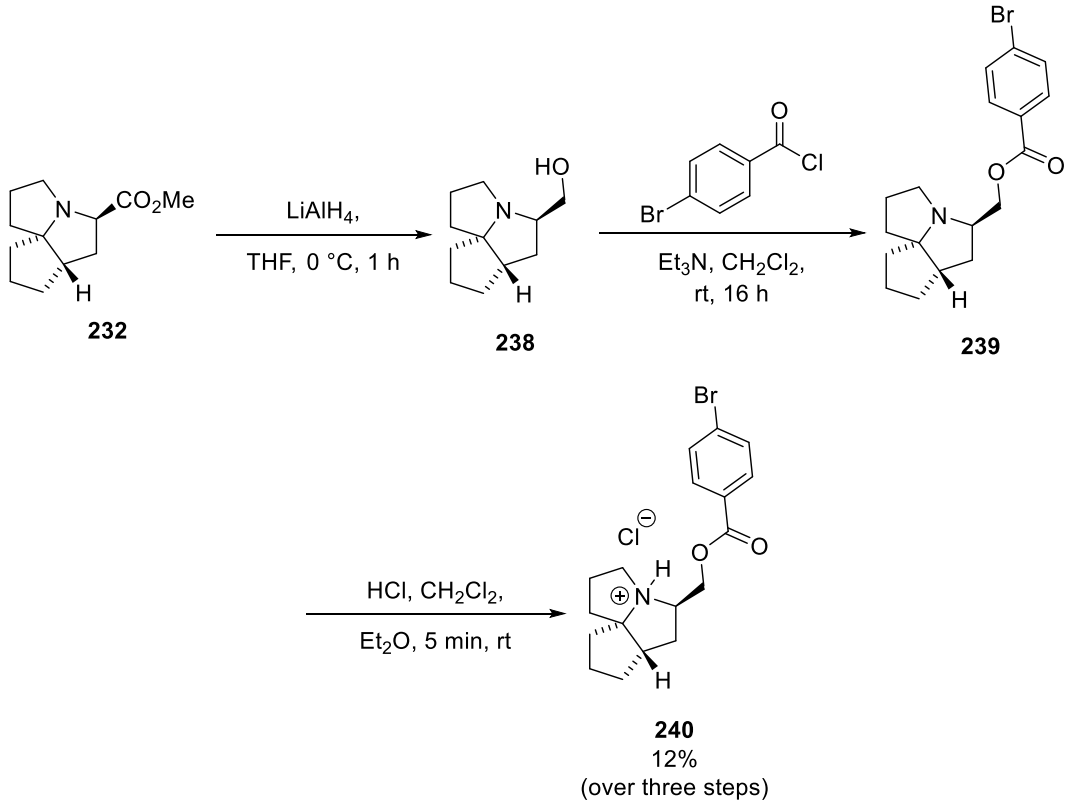
Table 7

To expand the substrate scope with ketone **235** it was then decided to see whether a cycloaddition reaction would take place with glycine methyl ester hydrochloride (Scheme 105). Although TLC analysis of the crude product indicated the starting ketone had been consumed none of the desired product **237** was isolated.



Scheme 105

Finally, the stereochemistry of cycloadduct **232** was confirmed *via* X-ray crystallography on compound **240** (Figure 17). This was synthesised using a three step process as shown in Scheme 106 where compound **240** was isolated in 16% yield over the three steps. As only a small sample of cycloadduct **232** had been synthesised and due to time constraints intermediates **238** and **239** were not isolated and characterised. The X-ray crystal structure of compound **240** confirmed that the cycloaddition reaction occurred *via* the S-shaped ylide.



Scheme 106

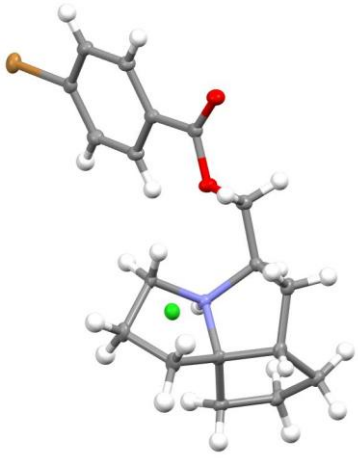
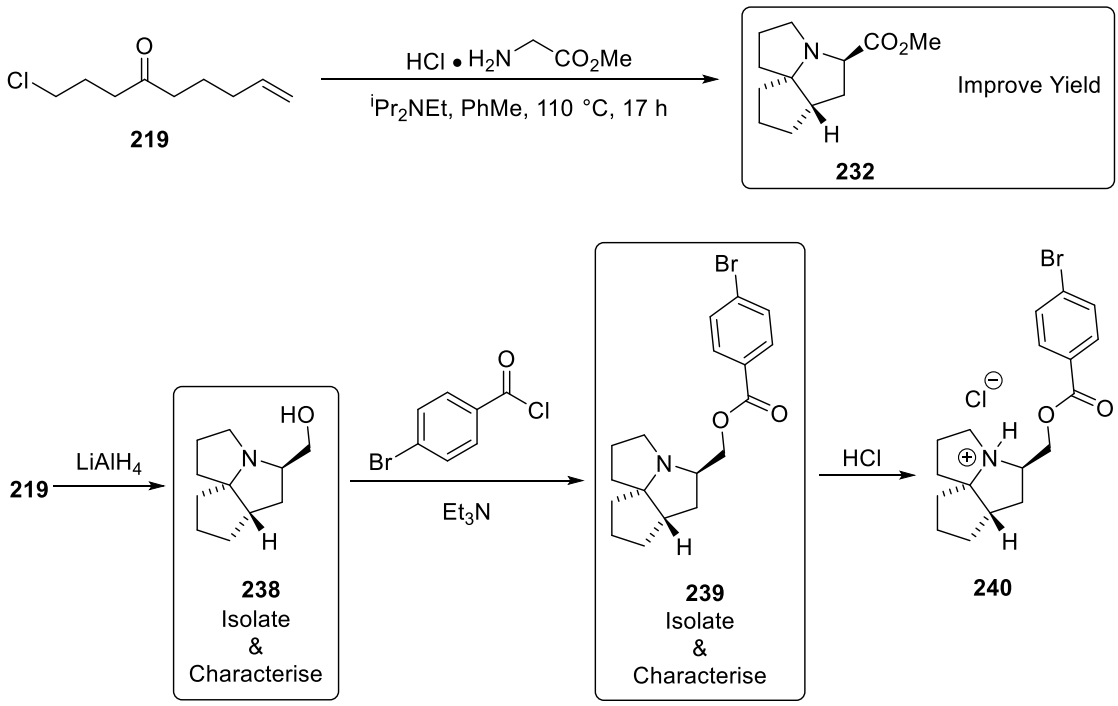


*Figure 17 – X-ray crystal structure of **240***

3.3 Aims

Continuing on from previous work done in the group it was important to improve the yields obtained when ketone **219** was reacted with glycine methyl ester hydrochloride to give cycloadduct **232**. Furthermore, although the stereochemistry of **232** was confirmed *via* X-ray crystallography on compound **240**, the intermediate compounds **238** and **239** were not characterised. Therefore, it was important to synthesise and isolate these compounds as well (Scheme 107).



Scheme 107

Following on from this the substrate scope needed to be expanded. This could be achieved using a variety of different ketones in place of ketone **219**. Some examples of ketones are shown in Figure 18 which would result in cycloadducts with different ring structures.

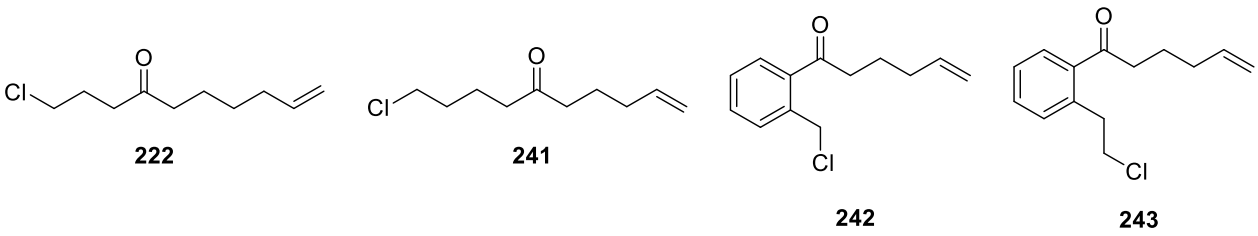
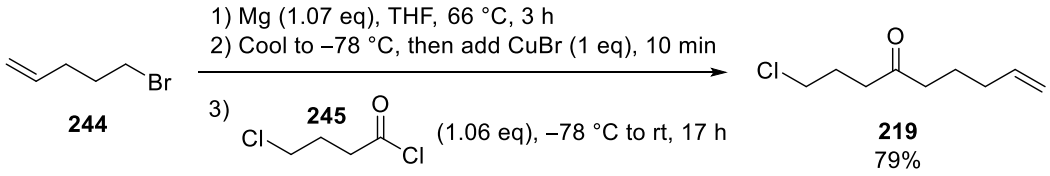


Figure 18 – Ketones to be synthesised

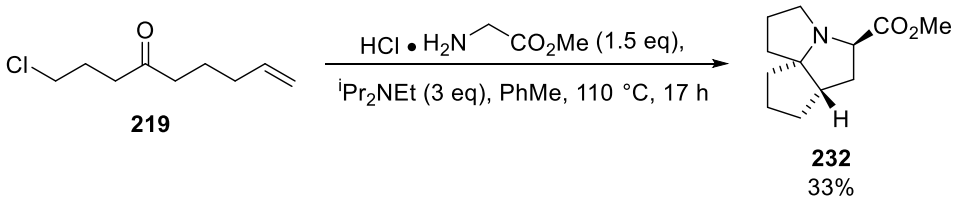
3.4 Synthesis of cycloadduct 232 and optimisation

Before any cycloaddition reactions could be done ketone **219** needed to be synthesised. The reaction conditions used are shown in Scheme 108 where bromopentene **244** was converted into its corresponding Grignard reagent using magnesium and THF. This was then cooled to −78 °C and copper(I) bromide was added and subsequent addition of acid chloride **245** then formed the desired ketone **219**, which was isolated in a yield of 79%.[95]



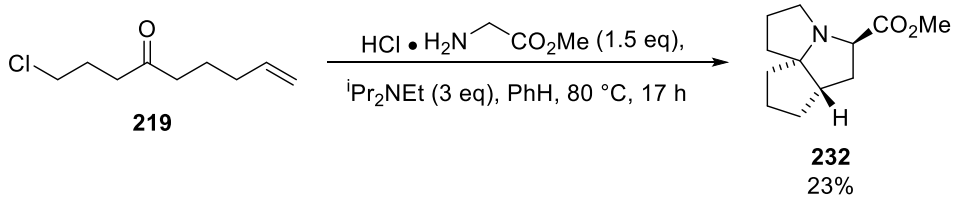
Scheme 108

Having obtained ketone **219** the next step was to repeat the initial cycloaddition reaction with glycine methyl ester hydrochloride as shown in Scheme 109. Repeating the reaction it was pleasing to find that we managed to obtain cycloadduct **232** in 33% yield. Although this was in agreement with the previously obtained result TLC analysis of the crude product indicated many side products had been formed.



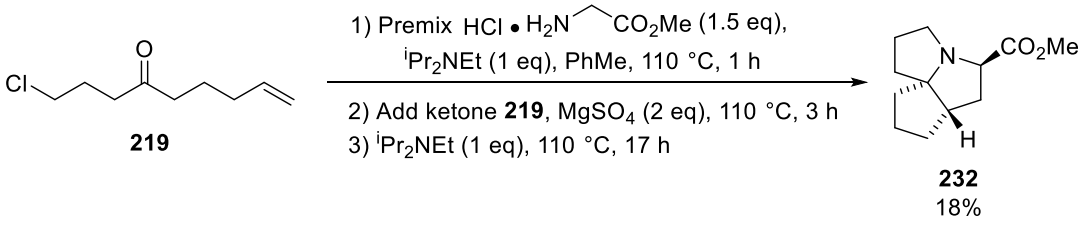
Scheme 109

We now wanted to optimise these reaction conditions. Repeating the reaction and varying the solvent didn't seem to benefit the reaction as no desired product was isolated when *o*-xylene or DMF were used and in both reactions ketone **219** was recovered. In comparison, the reaction was tolerated in benzene but a lower (23%) yield of compound **232** was obtained (Scheme 110).



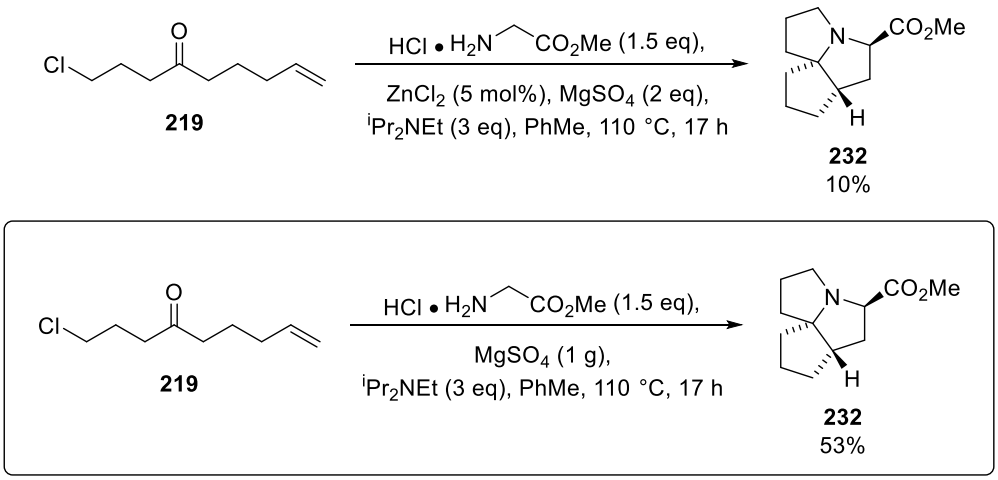
Scheme 110

We thought that there may have been a problem with the initial iminium formation. Therefore the reaction conditions shown in Scheme 111 were attempted as well. It was thought that by premixing the glycine methyl ester hydrochloride and a stoichiometric amount of Hünig's base would generate its free amine form in solution. Subsequently adding ketone **219** and magnesium sulfate would then allow the intermediate iminium ion to be formed more readily, which could then be deprotonated to form the desired azomethine ylide, and therefore cycloadduct **232** *via* the addition of another equivalent of Hünig's base. Unfortunately, compound **232** was isolated in a much lower yield of 18%.



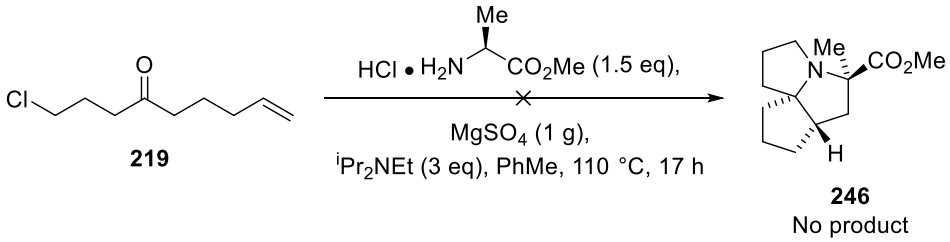
Scheme 111

In a final attempt to increase the yield of compound **232** we investigated the addition of different additives to the initial cycloaddition reaction in Scheme 109. To help with the imine formation we first added $ZnCl_2$ to the reaction to act as a Lewis acid, alongside magnesium sulfate which was added to remove any water formed. To our disappointment cycloadduct **232** was isolated only in 10% yield. However, to our surprise when repeating the initial reaction with a large excess of magnesium sulfate (1 g) cycloadduct **232** was isolated in a higher yield of 53% (Scheme 112).



Scheme 112

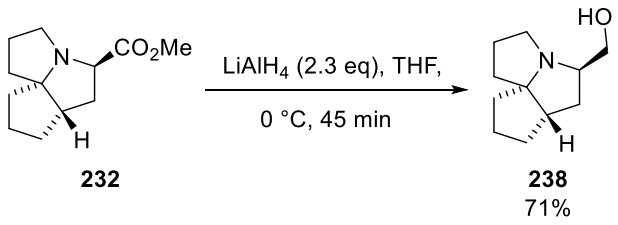
Having now obtained the optimised reaction conditions, we then repeated the cycloaddition reaction using L-alanine methyl ester hydrochloride (Scheme 113). Although TLC analysis indicated the starting material had been consumed during the reaction no desired product could be isolated.



Scheme 113

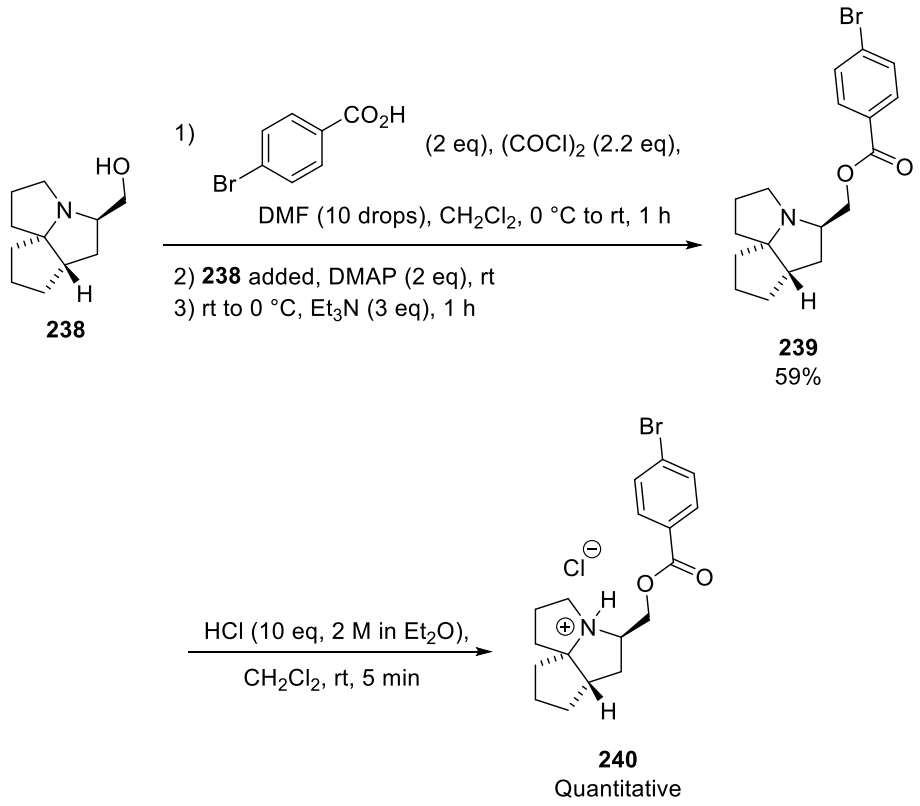
3.5 Synthesis of salt 240

We considered that it was important to re-synthesise compound **240** and in the process characterise compounds **238** and **239** as well. Cycloadduct **232** was first reduced using $LiAlH_4$ to give alcohol **238** in a good yield of 71% (Scheme 114).



Scheme 114

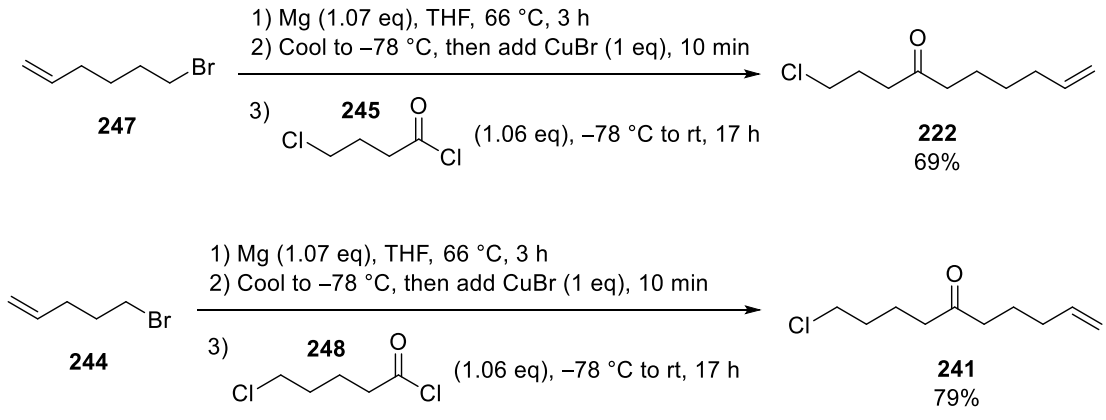
Next, compound **238** was reacted with 4-bromobenzoyl chloride which was generated from 4-bromobenzoic acid. Upon the addition of triethylamine, ester **239** was isolated in 59% yield. Finally using an ethereal solution of hydrogen chloride, ester **239** was converted into its hydrochloride salt **240** in a quantitative yield. These steps are summarised in Scheme 115.



Scheme 115

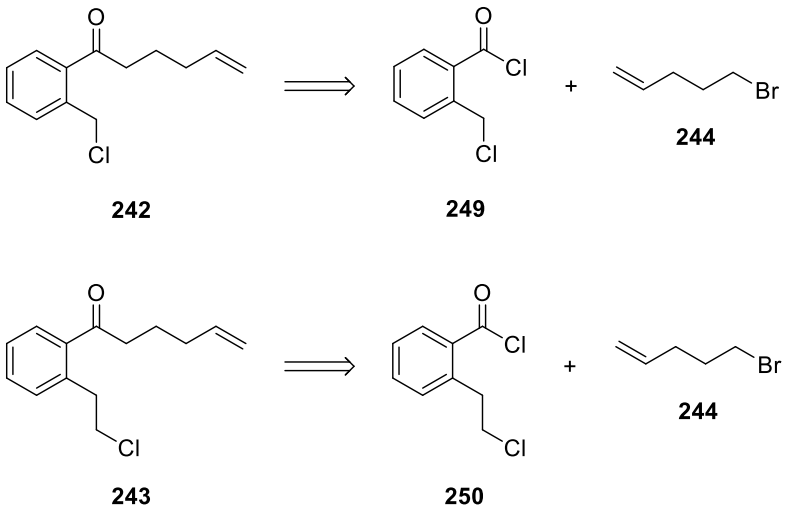
3.6 Expanding the substrate scope

To continue we now wanted to expand the substrate scope by using alternative ketones instead of **219**. Acyclic ketones **222** and **241** were synthesised using similar reaction conditions to those shown in Scheme 108. Ketone **222** was synthesised using bromohexene **247** and acid chloride **245** to give the desired product in 69% yield. In comparison, **241** was synthesised using bromopentene **244** and acid chloride **248** to give the desired product in 79% yield (Scheme 116).[95]



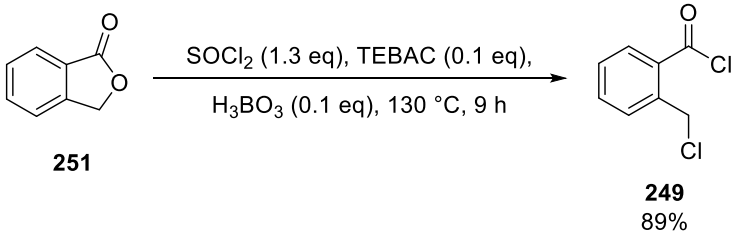
Scheme 116

We also decided to prepare aromatic ketones **242** and **243** as well. However to apply the same methods used previously we would have to first synthesise the appropriate acid chloride derivative as shown in Scheme 117.

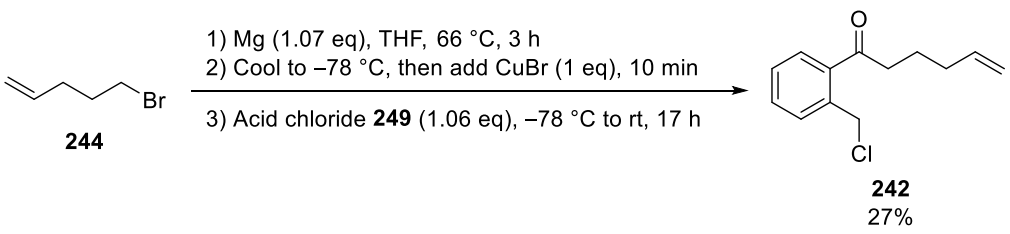


Scheme 117

Acid chloride **249** was synthesised using a known literature method where phthalide **251** was heated with thionyl chloride, benzyltriethylammonium chloride (TEBAC), and boric acid at 130 °C for 9 h (Scheme 118).[98] Upon working up the reaction the crude acid chloride **249** was isolated in 89% yield and was carried forward onto the next step without further purification. Using similar reaction conditions as mentioned previously ketone **242** was isolated in 27% yield (Scheme 119). This yield was low when compared to the aliphatic ketones **222** and **241**, which may have been caused by **249** being a less reactive acid chloride due to conjugation.

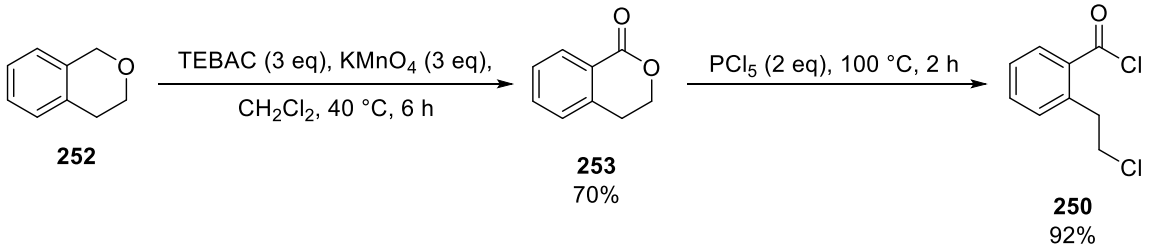


Scheme 118



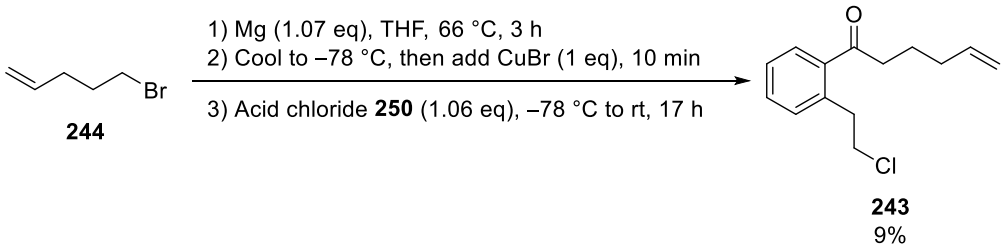
Scheme 119

In comparison, acid chloride **250** was synthesised using the route shown in Scheme 120. Isochroman **252** was first oxidised by using potassium permanganate to give the oxidised product **253** in 70% yield.[99] This was then carried forward onto the next step where phosphorus pentachloride was used to convert compound **253** into acid chloride **250** in 92% yield.[100]



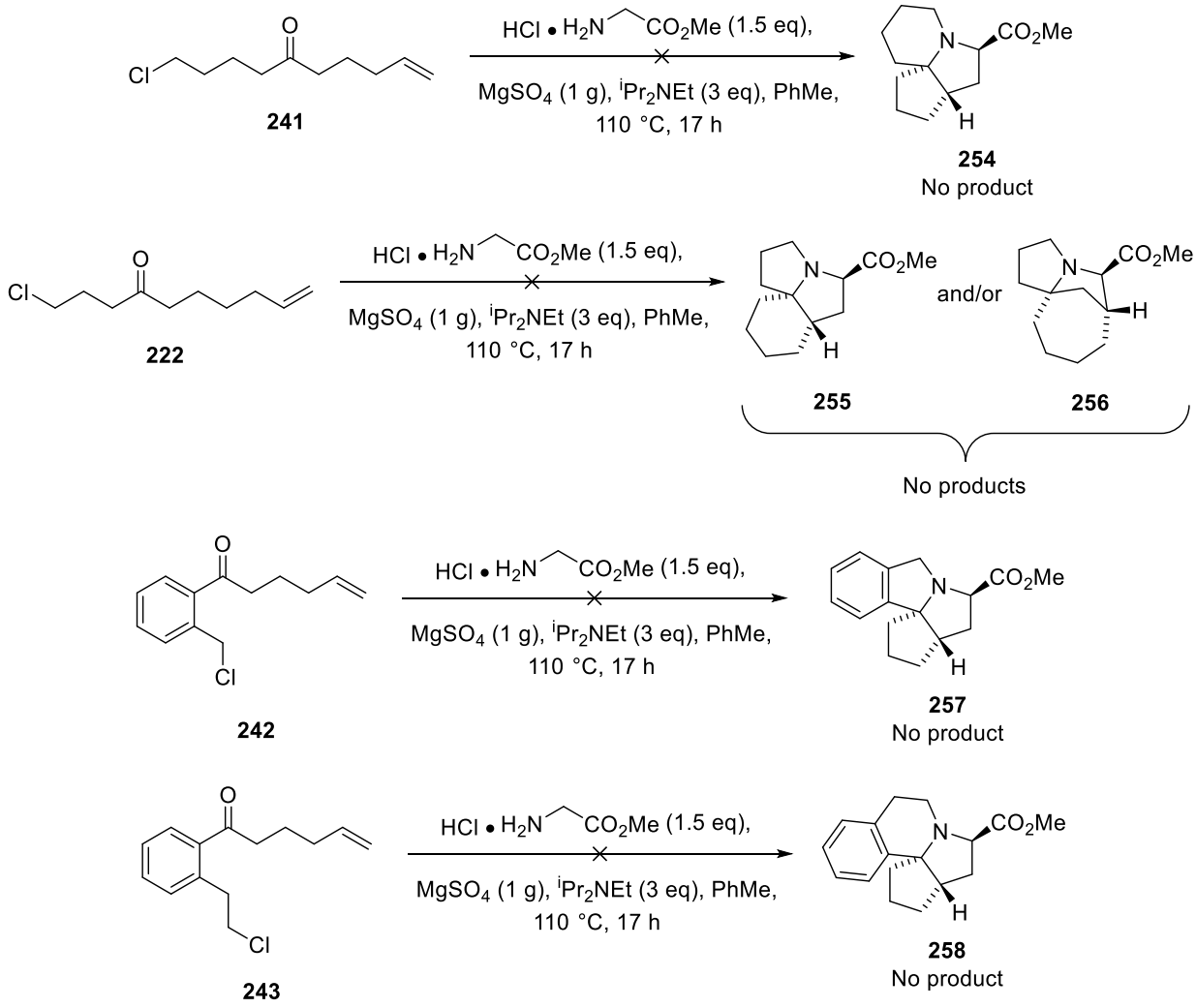
Scheme 120

Using the crude acid chloride **250** and applying the reaction conditions shown in Scheme 121, compound **243** was isolated in 9% yield. To our surprise this was much lower yield than expected when compared to the other ketones previously synthesised. However, initial TLC analysis of the crude product indicated many impurities had formed during the reaction, contributing to the low yield.



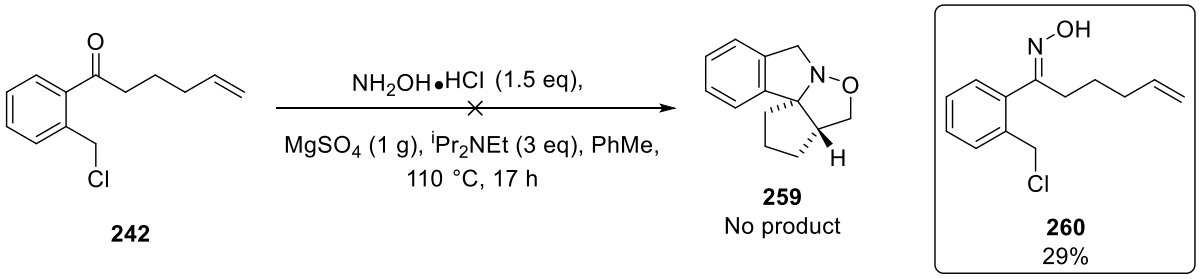
Scheme 121

With ketones in hand we reacted them each with glycine methyl ester hydrochloride using the same conditions as mentioned before (Scheme 122). Unfortunately in all reactions no desired product was isolated, but the starting ketone was recovered. This indicated that there may have been problems with the initial imine formation preventing the overall cascade process from occurring. Furthermore, the reaction using ketone **241** was repeated with the addition of 0.1 equivalents of tetrabutylammonium iodide (TBAI) to aid the cyclisation step, and potentially allow the cycloaddition to take place. However this was unsuccessful as only the starting ketone **241** was recovered.

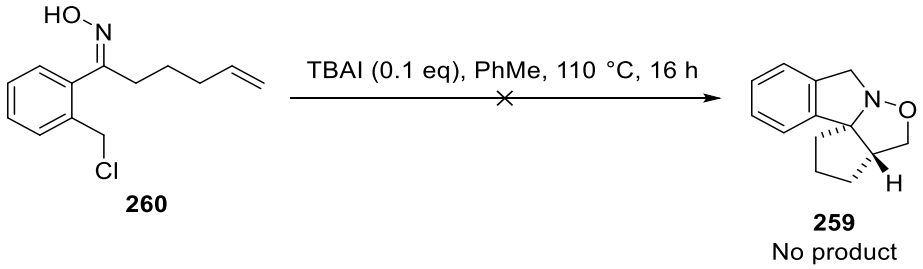


Scheme 122

Due to the success of the previous work done using nitrone cycloaddition chemistry with ketones **222** and **241**, we then decided to investigate whether a similar reaction would take place with ketone **242**. The reaction conditions used are shown in Scheme 123 where ketone **242** was heated with hydroxylamine hydrochloride and Hünig's base in the presence of magnesium sulfate and toluene. Although no desired cycloadduct **259** was isolated some starting material was recovered. In addition, an unknown compound was also isolated, and based on the ^{1}H NMR and ^{13}C NMR spectroscopic data seemed to suggest that the oxime **260** had been obtained. However, the mass spectrum was inconsistent with oxime **260** and did not show the correct molecular ion peak. On the assumption we had successfully isolated oxime **260** we then heated it with TBAI in toluene in an attempt to form cycloadduct **259**, but only the starting oxime **260** was isolated (Scheme 124).



Scheme 123



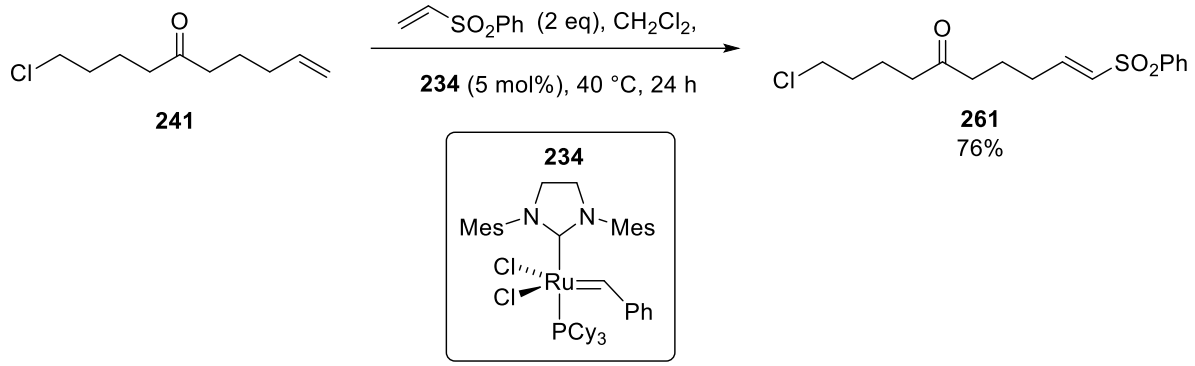
Scheme 124

Due to the unsuccessful results obtained so far with expanding the ketone substrate scope it was decided to focus on ketone **241** and investigate whether activating the terminal alkene would help allow a cycloaddition reaction to take place.

3.7 Activation of alkene in ketone 241

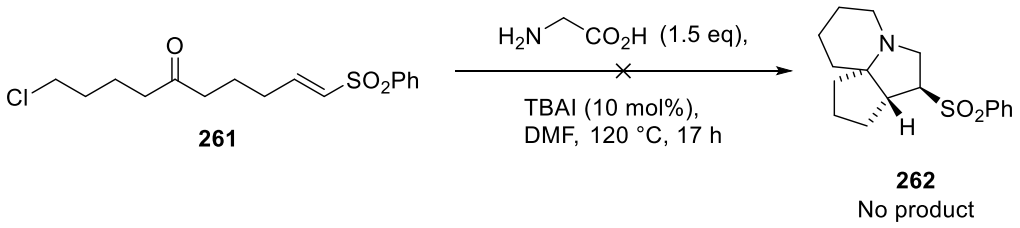
As mentioned earlier activation of ketone **219** proved to be beneficial towards allowing cycloaddition reactions to take place with amino acids such as glycine and phenylalanine. To achieve this a phenyl vinyl sulfone group was introduced in the terminal position of the alkene. As a result of this we now wanted to apply similar chemistry to ketone **241** in an attempt to allow a successful cycloaddition reaction to take place.

Starting with ketone **241** a Grubbs metathesis reaction was carried out. The conditions used are shown in Scheme 125 where ketone **241** was heated with phenyl vinyl sulfone in dichloromethane, in the presence of Grubbs second generation catalyst. In line with previous work done in the group on ketone **235**, to aid the purification process dimethylsulfoxide (DMSO) was added to the reaction mixture after 24 hours to remove any remaining ruthenium impurities in the reaction mixture.[101] Overall the activated ketone **261** was isolated in a good yield of 76%.



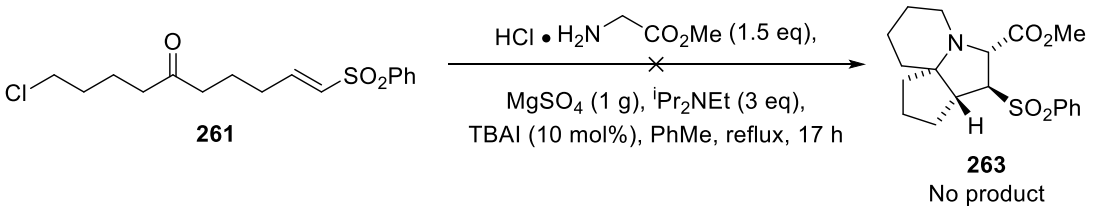
Scheme 125

With ketone **261** in hand it was subjected to similar cycloaddition reaction conditions as ketone **235** with glycine in DMF, with the addition of 10 mol% TBAI (Scheme 126). Unfortunately, none of the desired product was isolated and although TLC analysis of the reaction mixture indicated that the starting material had been consumed many spots could be observed. However, LCMS analysis of the crude product gave a peak that corresponded to the mass of the desired product **262**. From the data collected we thought that the desired cycloadduct **262** was potentially decomposing due to the high temperature. Repeating the reaction at 110 °C gave the same results and changing the reaction solvent to toluene, and heating at 110 °C gave back recovered starting material.



Scheme 126

Ketone **261** was then heated with glycine methyl ester hydrochloride, Hünig's base, magnesium sulfate and TBAI in an attempt to form cycloadduct **263** (Scheme 127). Similar to previous reactions, TLC analysis showed that the starting material had been consumed, and LCMS analysis produced a peak which corresponded to the mass of the desired product **263**. Unfortunately, after purification of the crude product none of the desired product could be isolated, indicating that it was potentially unstable.

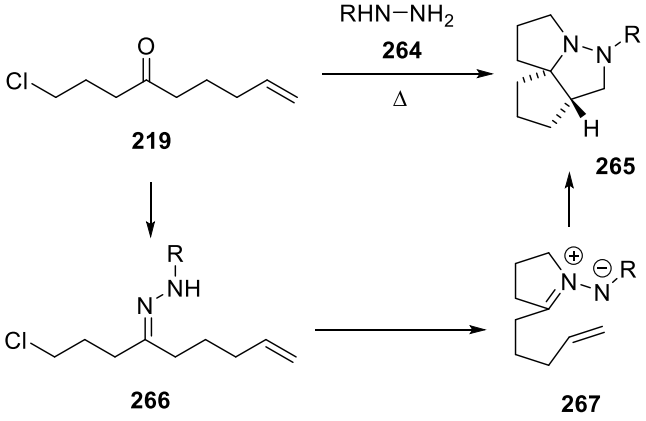


Scheme 127

Due to the unsuccessful results obtained so far with expanding the ketone substrate scope it was decided to stop work here and attempt to synthesise alternative cycloadducts from the ketones instead.

3.8 Tricyclic products from azomethine imines

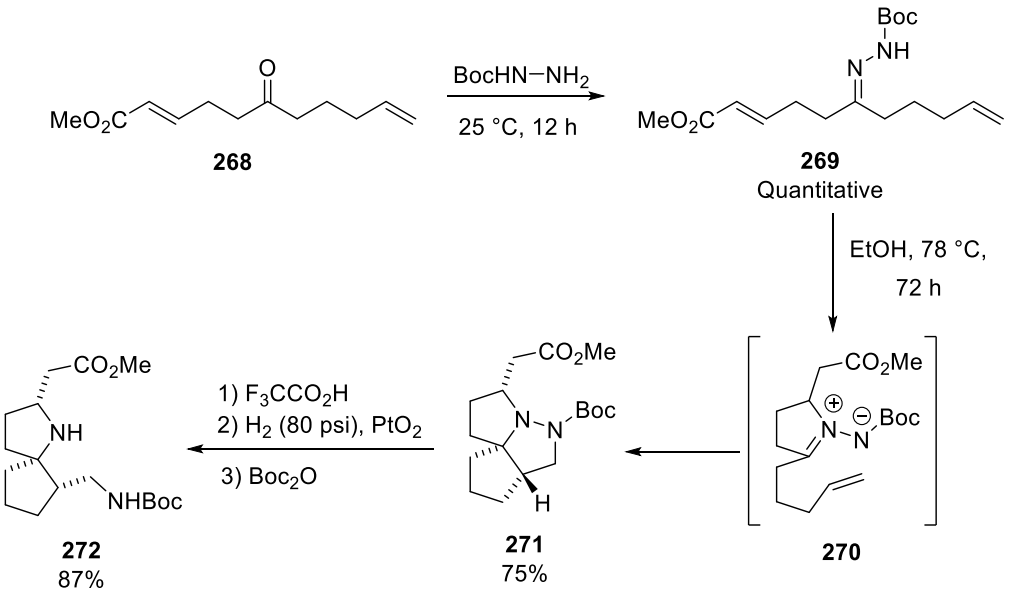
Taking inspiration from previous work in the group we then decided to investigate whether azomethine imines could be formed from some of the ketones already synthesised. This is outlined in Scheme 128 with ketone **219**. A reaction with hydrazine **264** would give hydrazone **266**, which could then cyclise and be deprotonated to give azomethine imine **267**. Intramolecular cycloaddition would then hopefully allow cycloadducts with the general structure of **265** to be isolated. If this work was successful then the substrate scope could be expanded using other ketones and hydrazine substrates.



Scheme 128

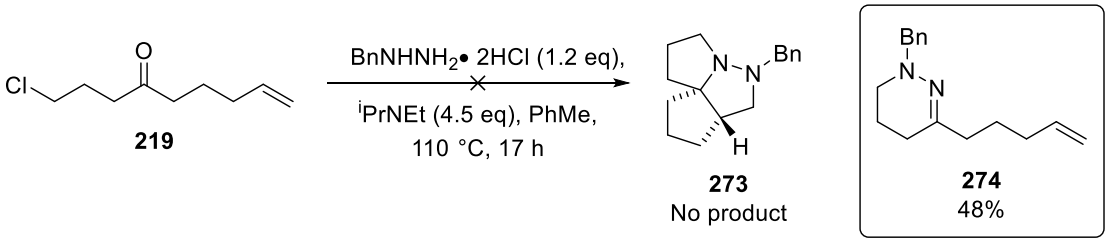
It's important to mention at this point that similar reactions had been done before in the literature, albeit the scope was very limited.[102] An example is shown in Scheme 129 where ketone **268** was reacted with *t*-butyl carbazate. The resulting hydrazone **269** then underwent an intramolecular Michael addition reaction and deprotonation to give azomethine imine **270**. A subsequent

cycloaddition reaction then gave **271** in a good 75% yield. Furthermore, it was also found that the N-N bond could be reduced to give the spirocyclic product **272** in 87% yield.



Scheme 129

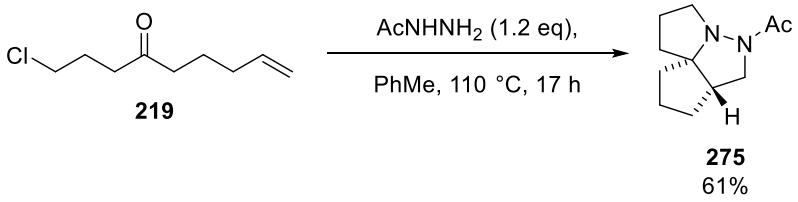
With this in mind we started to do similar reactions with ketone **219**. The first reaction attempted involved heating ketone **219** with benzylhydrazine dihydrochloride and Hünig's base in toluene to try and obtain cycloadduct **273**. However, instead of isolating compound **273** the 6-membered ring compound **274** was obtained in 48% yield. The formation of compound **274** was most likely due to the nucleophilicity of the NHBn in the intermediate hydrazine, cyclisation would then give compound **274** (Scheme 130).



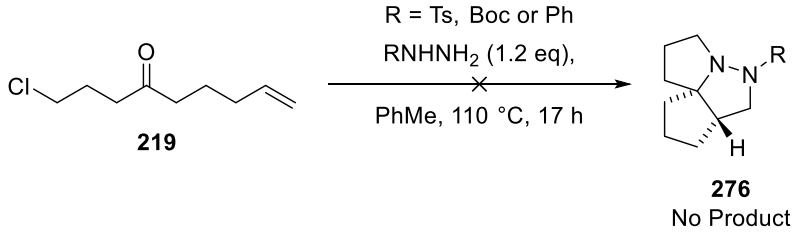
Scheme 130

In an attempt to overcome this problem the reaction was repeated using acetylhydrazine and this gave the desired cycloadduct **275** in 61% yield (Scheme 131). Unfortunately repeating the reaction with *p*-toluenesulfonyl hydrazide, *t*-butyl carbazate, or phenyl hydrazine gave no desired products

(Scheme 132). However TLC analysis indicated that the starting ketone was consumed in all three reactions.

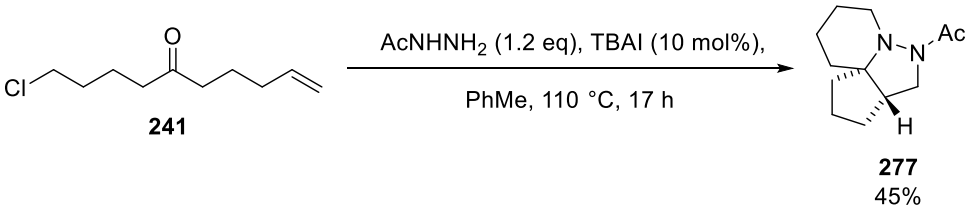


Scheme 131



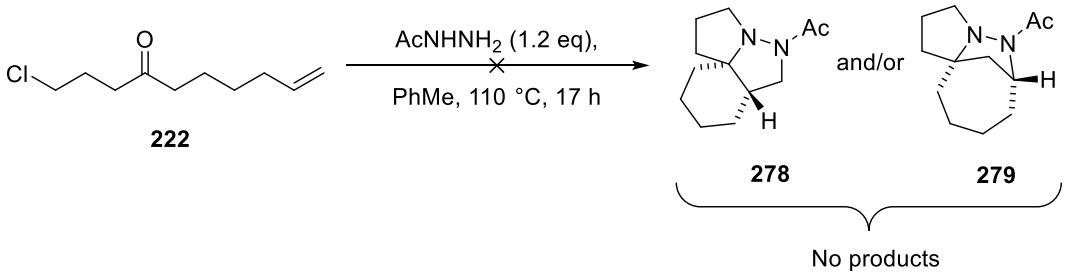
Scheme 132

Following on from the results obtained and using ketone **241** allowed cycloadduct **277** to be isolated in 45% yield. The reaction conditions used are shown in Scheme 133 where TBAI was added to aid the cyclisation step. This allowed the desired azomethine imine to be formed and therefore the desired cycloadduct **277** to be isolated.



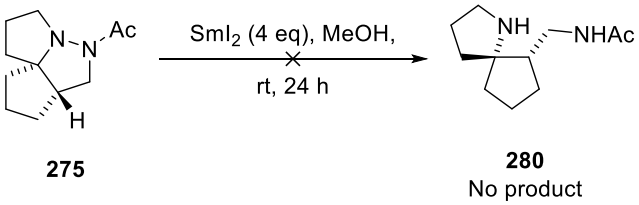
Scheme 133

When repeating the reaction using ketone **222** we expected to obtain a mixture of regiosiomers **278** and **279** based on previous results using hydroxylamine to generate nitrones.[95] Although TLC indicated that the starting material had been consumed in the reaction, no desired products could be isolated (Scheme 134).



Scheme 134

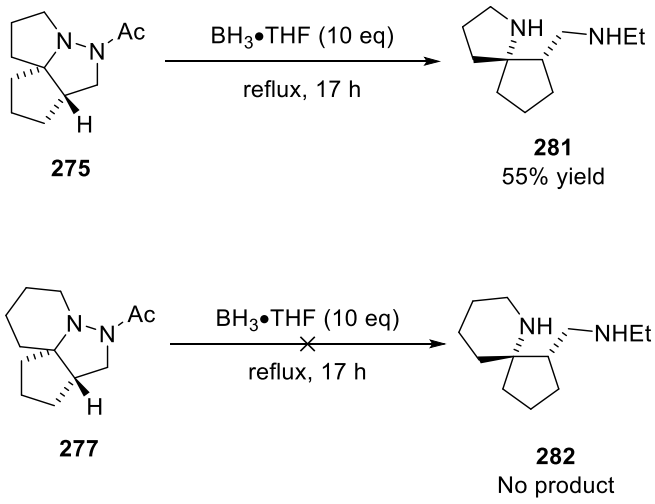
With the limited success of the cycloaddition reactions with azomethine imines our focus then shifted towards cleaving the N-N bond in cycloadducts **275** and **277**. Although similar reactions had been done before in the literature, they generally required Pd/C and hydrogen at high pressures.[102] In an attempt to use milder reaction conditions to cleave the N-N bond in our compounds, we first investigated using samarium diiodide as this had been shown to be a useful reagent in the literature.[103,104] The reaction conditions used are shown in Scheme 135 where samarium diiodide was first prepared using Imamoto's method by heating samarium metal with iodine in THF for 5 h.[105] During the reaction the mixture changed colour from orange, to yellow, to green, and eventually to the characteristic dark blue colour of samarium diiodide. Once the mixture was cooled to room temperature it was added to a solution of cycloadduct **275** in methanol. After 30 minutes TLC analysis of the reaction mixture indicated starting material was still present and no product **280** had been formed. Leaving the reaction mixture overnight gave the same result.



Scheme 135

Fortunately, we were able to cleave the N-N bond in cycloadduct **275** using borane, however by using this reagent the acyl group was reduced as well to give diamine **281** in a moderate yield of 55%.[106] The yield of diamine **281** was lower than expected, which may have been due to problems encountered during purification as the diamine was very polar. Unfortunately, when repeating the reaction with cycloadduct **277** no desired product was obtained. Although LCMS analysis of the

crude reaction mixture indicated the desired product **282** had formed during the reaction many impurity peaks could be seen as well (Scheme 136).



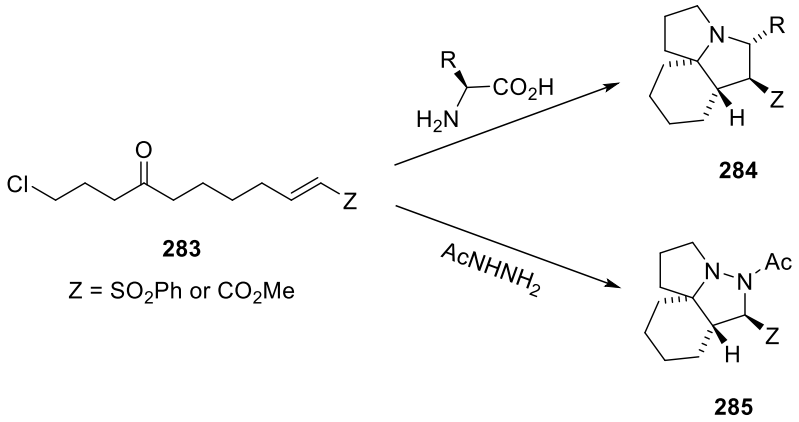
Scheme 136

3.9 Conclusion and Future Work

To conclude this chapter we were able to successfully improve on the initial results obtained in synthesising tricyclic amines from ketones using a condensation, cyclisation, cycloaddition cascade. In particular it was found that the addition of magnesium sulfate to the original cascade reaction helped to improve the yield of the desired cycloadduct. Unfortunately, this success was limited as using different ketones, including derivatives which contained aromatic rings did not generate any of the desired cycloadducts. In addition, activation of a ketone was achieved using a Grubbs metathesis reaction in the hope that the desired cascade process would take place, but this was unsuccessful as well.

Besides generating azomethine ylides, reacting acetyl hydrazine with some of the ketones gave access to the corresponding azomethine imines. This allowed the formation of a different set of cycloadducts which contained N-N bonds. Like previous reactions, the substrate scope was limited as the choice of substituted hydrazine was important. Finally, for one of the cycloadducts generated the N-N bond was cleaved using borane to give a diamine spirocyclic compound.

Although most of our efforts to expand the substrate scope have been unsuccessful future work could involve investigating other substituted ketones to see whether the desired cascade cycloaddition reaction will take place. Previous work in the group has indicated that activating the alkene in ketone **219** proved beneficial in allowing cycloaddition reactions to take place with amino acids.[97] Therefore, activating the alkene in ketone **222** by introducing an electron withdrawing group to give ketone **283** may prove beneficial and allow a cycloaddition reaction to take place *via* the corresponding azomethine ylide or azomethine imine intermediate (Scheme 137).



Scheme 137

Finally, to expand on the results obtained from using azomethine imines investigating other methods of cleaving the N-N bond in the cycloadducts generated would be of interest as this could be used to synthesise a wide range of spirocyclic compounds.

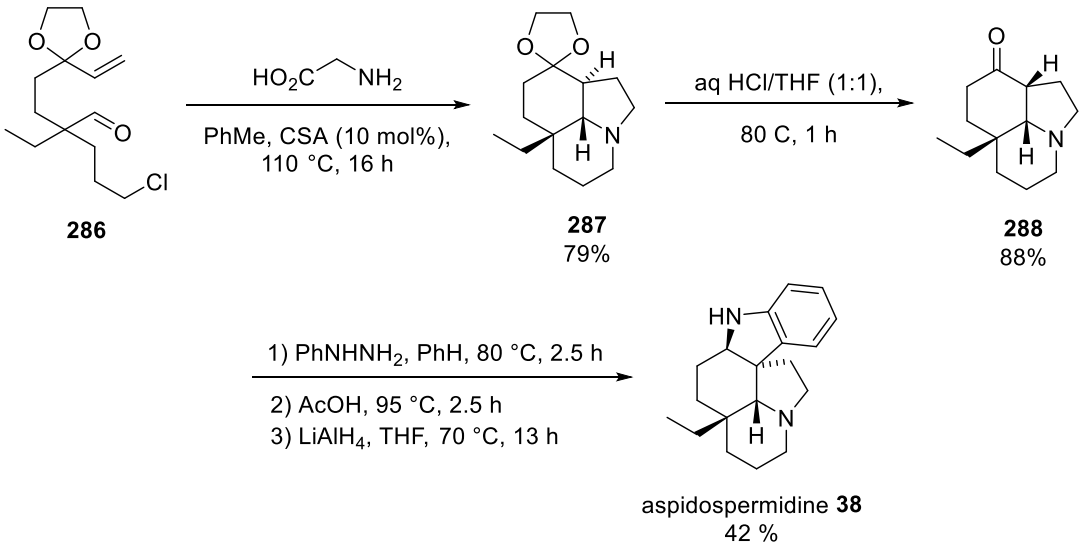
Chapter 4 – Towards the Synthesis of Kopsinine Using Cascade Chemistry

4.1 Introduction to indole alkaloids and previous work

As discussed in the previous chapter the development of the condensation, cyclisation, cycloaddition cascade process in the Coldham group has led to the successful synthesis of a range of complex polycyclic molecules with various ring structures. It so happens that many of these ring structures are present in natural products. Utilising the cascade process in the group has allowed efficient access to the main cores of many alkaloid structures, such as the Daphniphyllum, Stemona and Yuzurimine alkaloids.[107–109] Furthermore, the complete total synthesis of several natural products has also been achieved making use of the cascade process.[92,110]

Indole alkaloids have been of particular interest in the Coldham group. The monoterpenoid indole alkaloids represent one of the largest classes of natural products containing a diverse range of complex organic structures. The compounds are widely extracted from the *Apocynaceae*, *Loganiaceae*, and *Rubiaceae* plant families and are classified into five main groups according to their carbon skeleton. The five main groups are referred to as the *Aspidosperma, Ajmalan, Corynanthe, Iboga,* and *Quinoline* alkaloids.[111]

An example of previous work in the Coldham group using azomethine ylides is shown in Scheme 138 where three of the *Aspidosperma* alkaloids were synthesised.[112] Cycloadduct **287** was generated as a single diastereoisomer from the reaction of aldehyde **286** with glycine in toluene, in the presence of camphorsulfonic acid. Subsequent reaction of cycloadduct **286** with aqueous HCl and THF at 80 °C gave ketone **288**, which was then converted to aspidospermidine (**38**) under the Fischer indole synthesis conditions. Subsequent reactions on ketone **288** then allowed aspidospermine (**289**) and quebrachamine (**290**) to be synthesised as well (Figure 19).



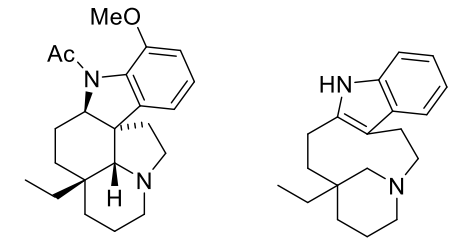
286

287
79%

288
88%

aspidospermidine **38**
42 %

Scheme 138

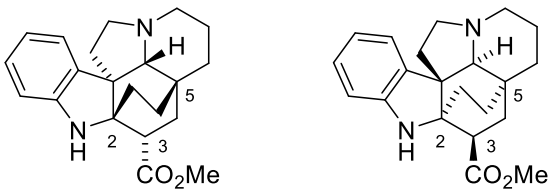


aspidospermine **289**

quebrachamine **290**

Figure 19

The ability to synthesise indole alkaloids by applying the cascade process is potentially a useful way to access other similar alkaloids. Another example is kopsinine (**291**) and the structure of both isomers is shown in Figure 20.[113] Overall, the structure is very similar to aspidospermidine (**38**) however, kopsinine contains an ethyl bridge connecting the C2 and C5 carbon atoms forming a bicyclic framework. The natural isomer (−)-kopsinine was first isolated from the *Kopsia arborea* tree, but has been isolated from other plants such as the *Vinca erecta*.[114] Generally, *Kopsia* is a genus of plant belonging to the family *Apocynaceae*. These plants are commonly found in China, Southeast Asia and Australia; and are a rich source of monoterpenoid indole alkaloids. A number of compounds have been isolated from these plants and due to their significant biological activity make them very interesting to research.[111]



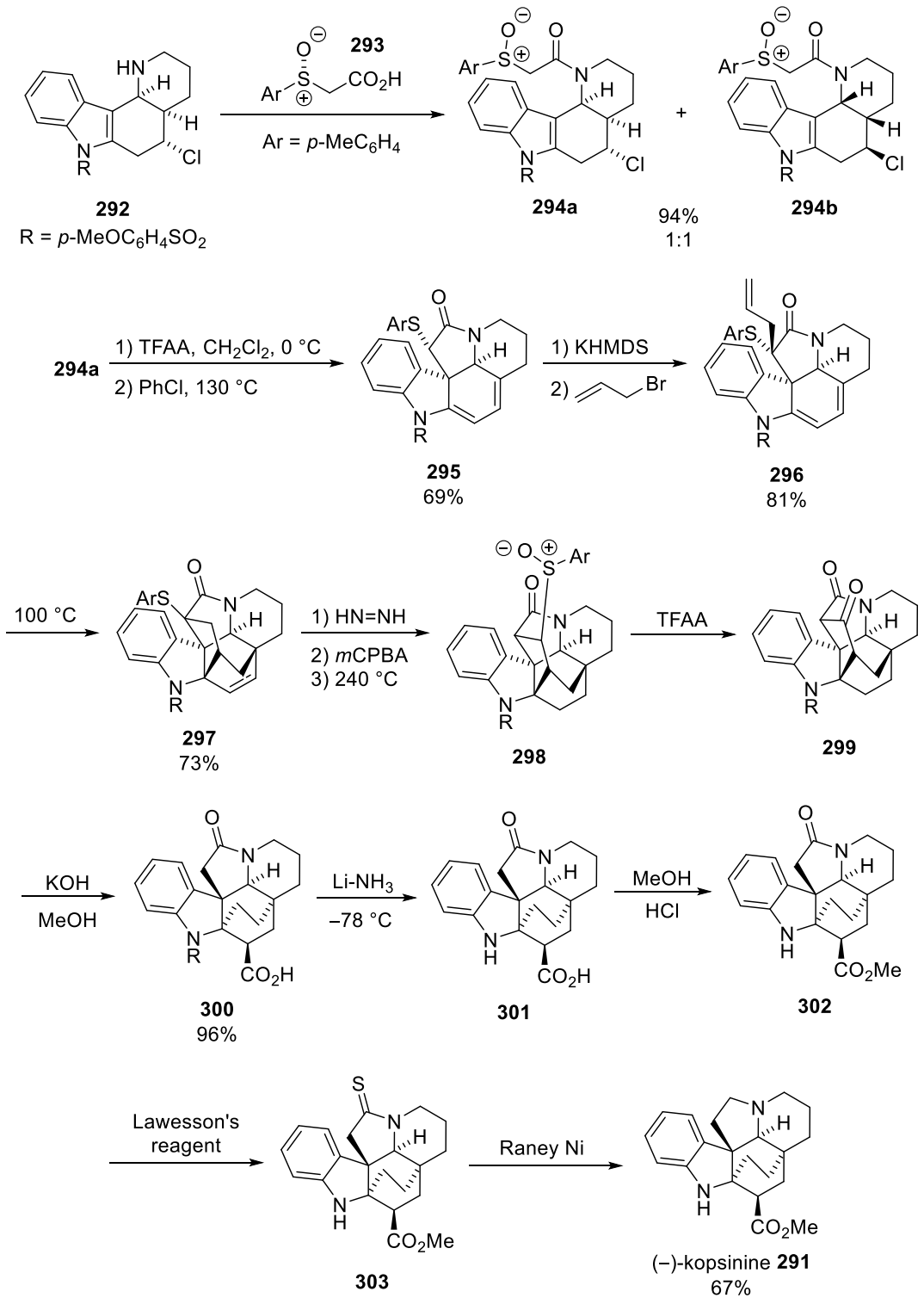
ent-(+)-kopsinine **291** (−)-kopsinine

Figure 20

The total synthesis of kopsinine has been achieved many times throughout the literature. However, before discussing a potential method of synthesising kopsinine using the cascade chemistry developed in the group, it's first important to look at the previous methods used to identify key intermediates and useful reactions which may help.

4.2 Previous synthetic routes towards Kopsinine

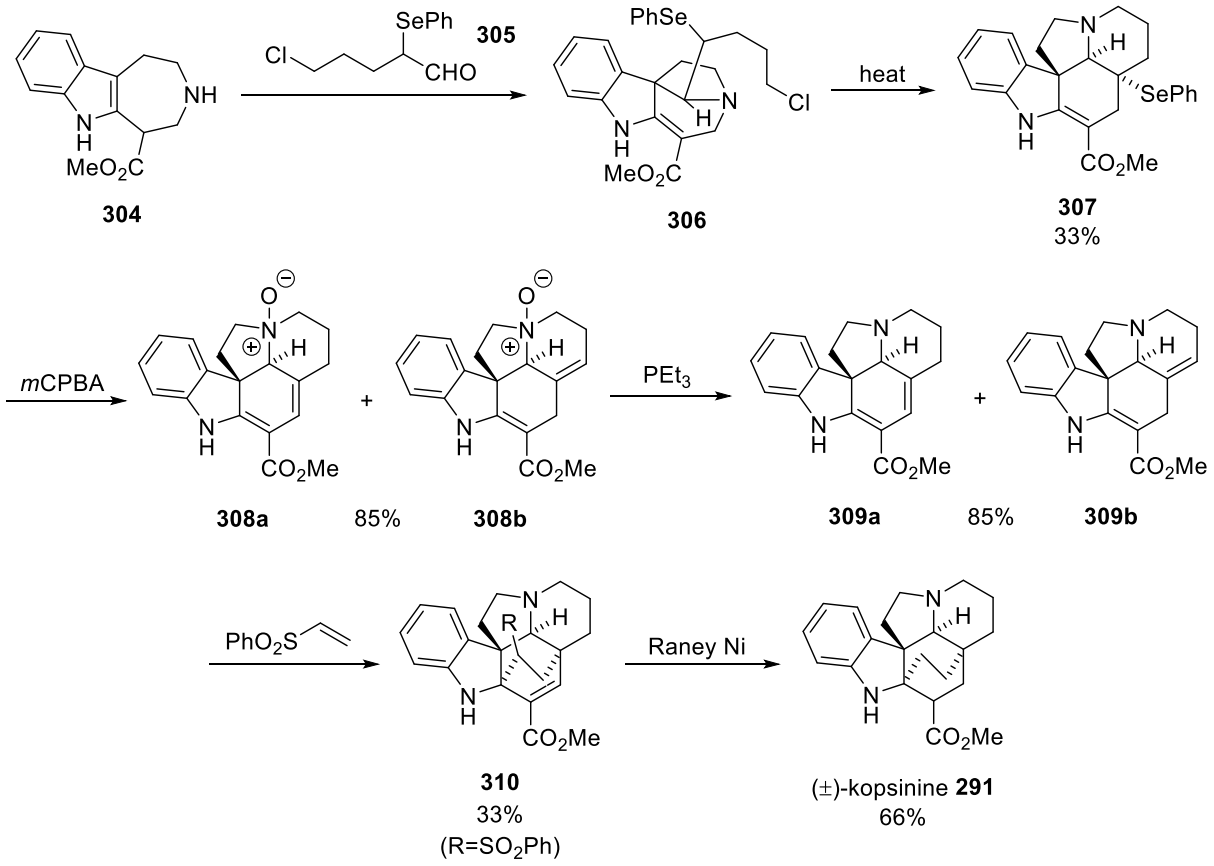
To the best of our knowledge there have only been six reports on the total synthesis of kopsinine. Each route varies in length and has its own advantages and disadvantages. In 1985, Magnus and Brown reported the first total synthesis of kopsinine consisting of 13 steps as shown in Scheme 139.[115] In the first step, amine **292** undergoes an amide coupling reaction with (*R*)-(+)-acetic acid **293** to give a mixture of separable diastereoisomers **294a** and **294b**. Isomer **294a** was then reacted with trifluoroacetic anhydride (TFAA) to give **295** and a subsequent alkylation reaction gave compound **296**. An intramolecular [4+2] cycloaddition reaction then allowed **297** to be isolated. Addition of diazene and mCPBA then resulted in the reduction of the alkene and oxidation of the sulfide in compound **297**. Heating then allowed **298** to be isolated which was then oxidised further with TFAA to give **299**. Potassium hydroxide was then used to form the carboxylic acid **300** *via* an addition-elimination reaction. The *p*-methoxysulfonyl group was then removed using Li-NH_3 to give compound **301**, an esterification reaction then gave compound **302**. The use of Lawesson's reagent converted the carbonyl in **302** to a thiocarbonyl resulting in compound **303** and in the final step a Raney nickel desulfurisation was used to obtain (−)-kopsinine (**291**).



Scheme 139

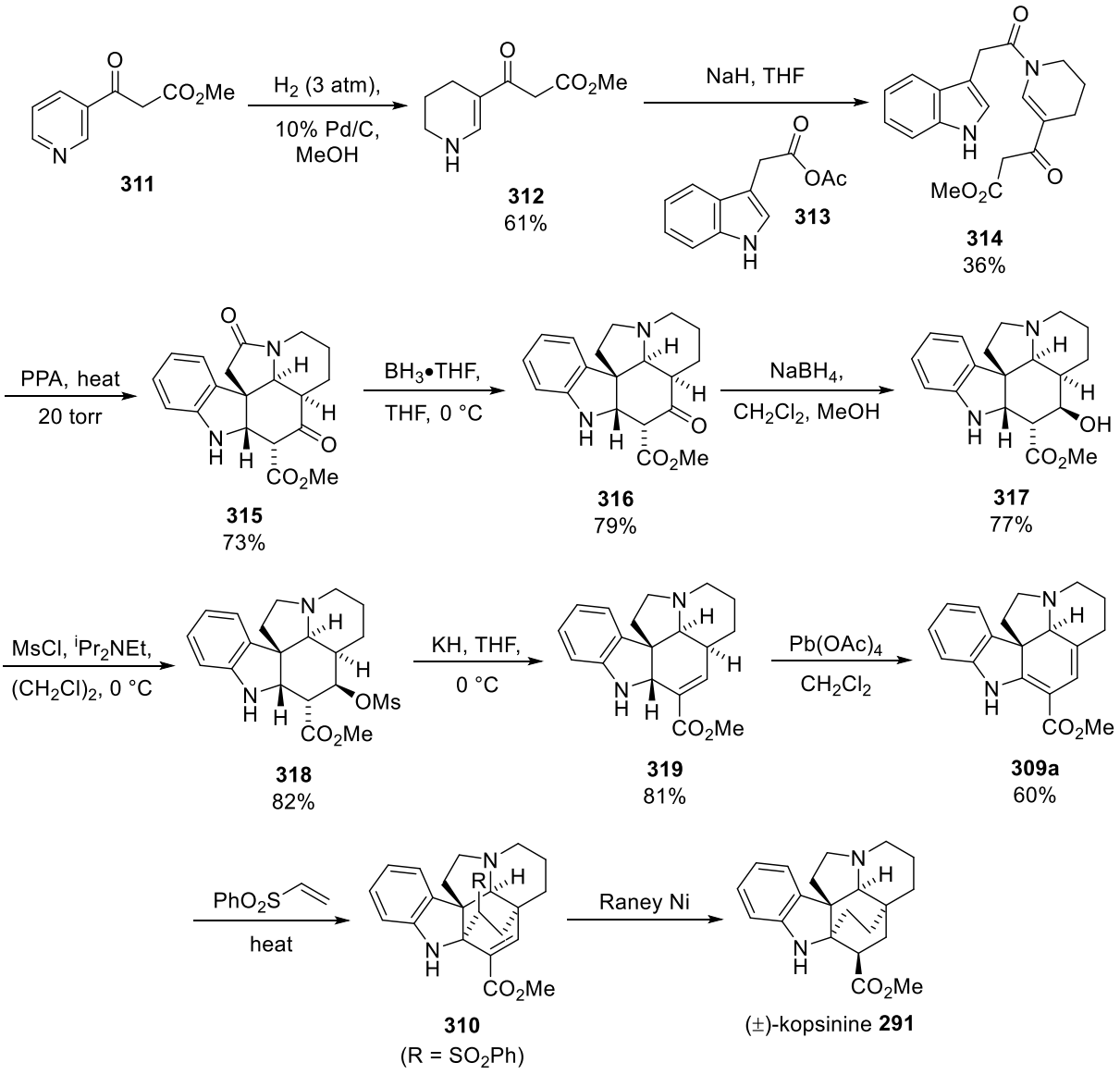
Soon after this method was published, within the same year Kuehne and Seaton reported a shorter synthetic route to synthesise a racemic mixture of kopsinine which consisted of 6 steps (Scheme 140).[116] Indolazepine **304** was first condensed with aldehyde **305** to give the bridged system **306** as a mixture of diastereoisomers. Heating the mixture of isomers resulted in the formation of **307**

as a single diastereoisomer. Oxidation of compound **307** then resulted in **308a** and **308b** in a 7:3 ratio and the addition of triethylphosphine then gave **309a** and **309b**. Heating this mixture with phenyl vinyl sulfone then gave **310** *via* a [4+2] cycloaddition and reduction using Raney nickel then gave the final product kopsinine.



Scheme 140

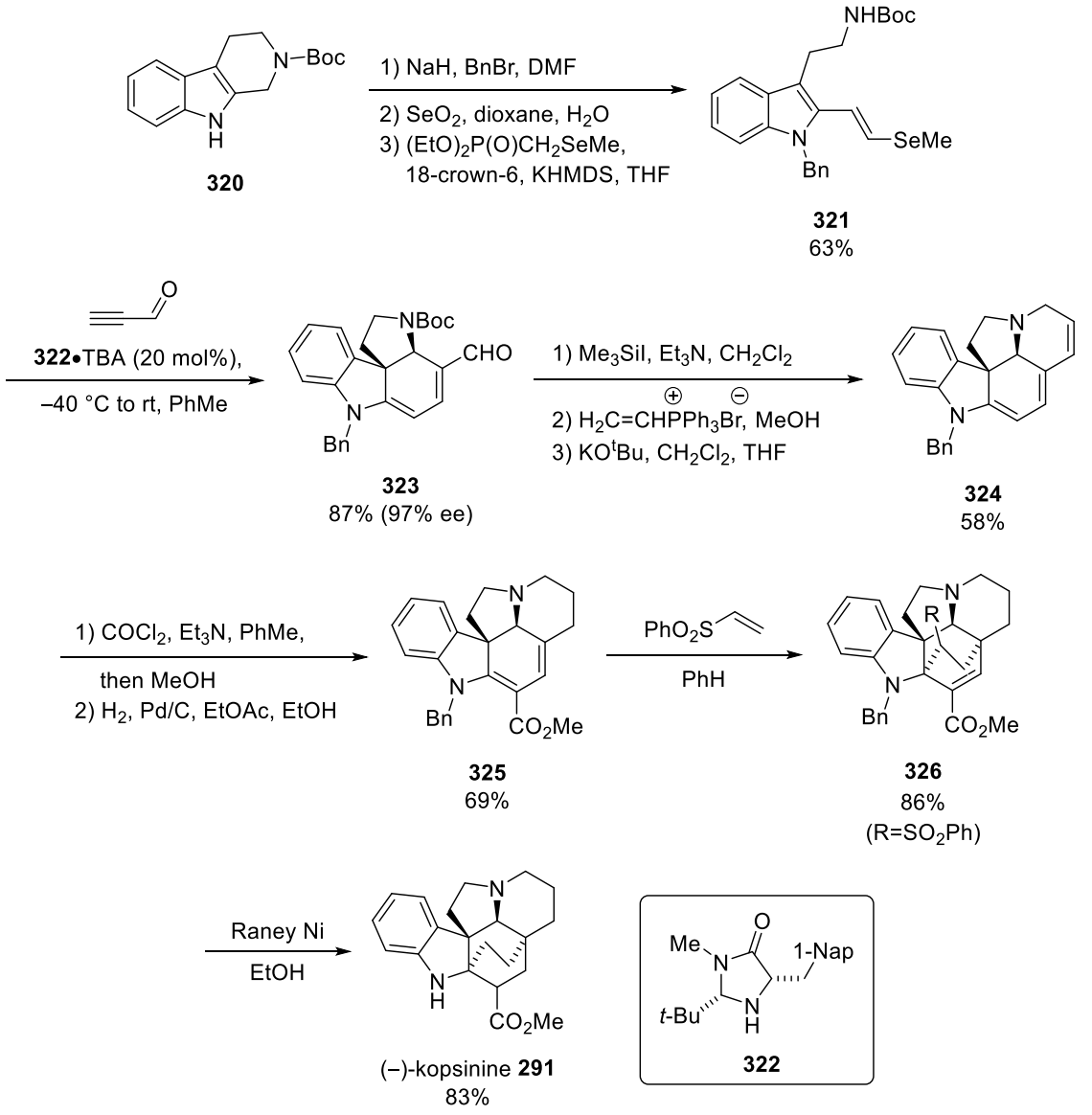
A few years later in 1988, Wenkert and Pestchanker published their route to kopsinine taking inspiration from Kuehne and Seaton.[117,118] The synthetic route is shown in Scheme 141 where pyridine **311** was first hydrogenated to give **312**. This was then reacted with indole derivative **313** to give **314** and treatment with polyphosphoric acid (PPA) then gave the pentacyclic compound **315**. Reduction of this compound using borane and sodium borohydride led to the formation of alcohol **317**, which was then mesylated to give **318**. Using potassium hydride allowed the successful β-elimination of **318** to give **319** and a successive oxidation reaction using lead tetraacetate then gave **309a**. Repeating the same Diels-Alder reaction with phenyl vinyl sulfone and reduction, as reported by Kuehne and Seaton, allowed the formation of kopsinine.



Scheme 141

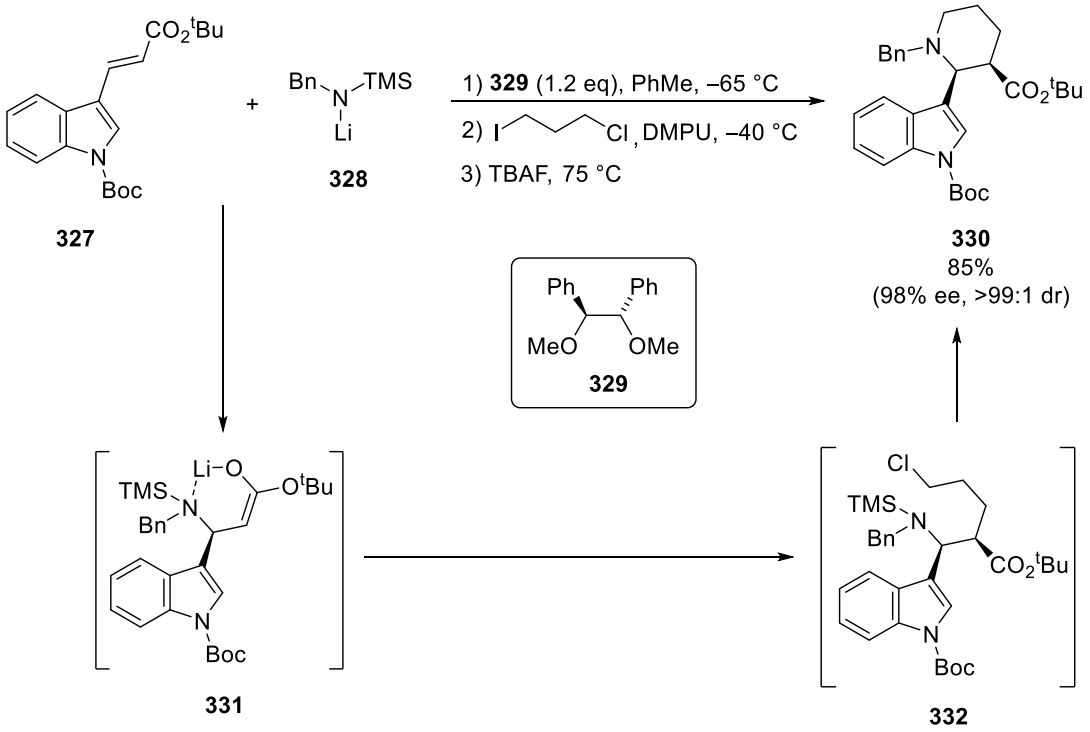
It would be at least another 20 years until another total synthesis of kopsinine was reported. In 2011, Macmillan and co-workers reported the synthesis of (−)-kopsinine and a small number of other natural products using an organocatalytic addition-cyclisation cascade process.[119] Starting with compound **320** this was converted into **321**, which was then subjected to the cascade process using the imidazolidine catalyst **322** and co-catalyst tribromoacetic acid (TBA). This gave compound **323** in a very good yield and high enantiomeric excess of 97%. This compound was then deprotected using trimethylsilyl iodide which allowed the resultant deprotected species to undergo a conjugate addition reaction with triphenylvinylphosphonium bromide. Addition of potassium *tert*-butoxide then induced a Wittig reaction to give compound **324**. Enamine α-

carbomethoxylation using phosgene and methanol, followed by the selective hydrogenation of **324** resulted in the formation of **325**. By applying similar methods used previously compound **325** was subjected to a [4+2] cycloaddition reaction with phenyl vinyl sulfone to give **326** and reduction using Raney nickel gave (−)-kopsinine (Scheme 142).[116]



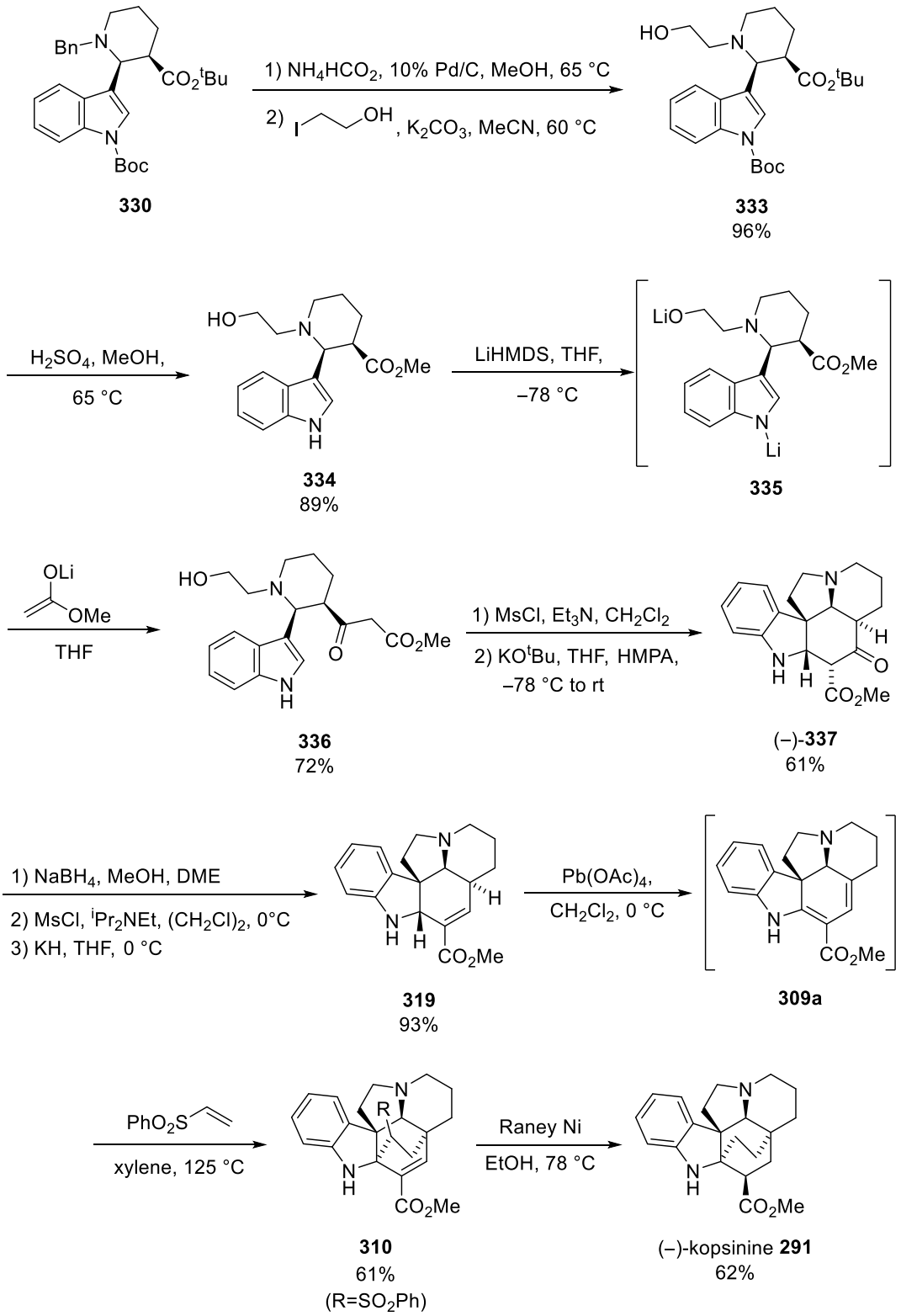
Scheme 142

In 2012, Tomioka and co-workers reported the synthesis of (−)-kopsinine utilising a one pot [N+2+3] cyclisation reaction to synthesise the main starting material **330**.[120] This reaction is shown in Scheme 143 where the organolithium **328** undergoes a conjugate addition reaction with indole **327** to give intermediate **331**. This is then alkylated with 1-chloro-3-iodopropane to give **332**, which then cyclises forming piperidine **330** upon the addition of tetrabutylammonium fluoride (TBAF).



Scheme 143

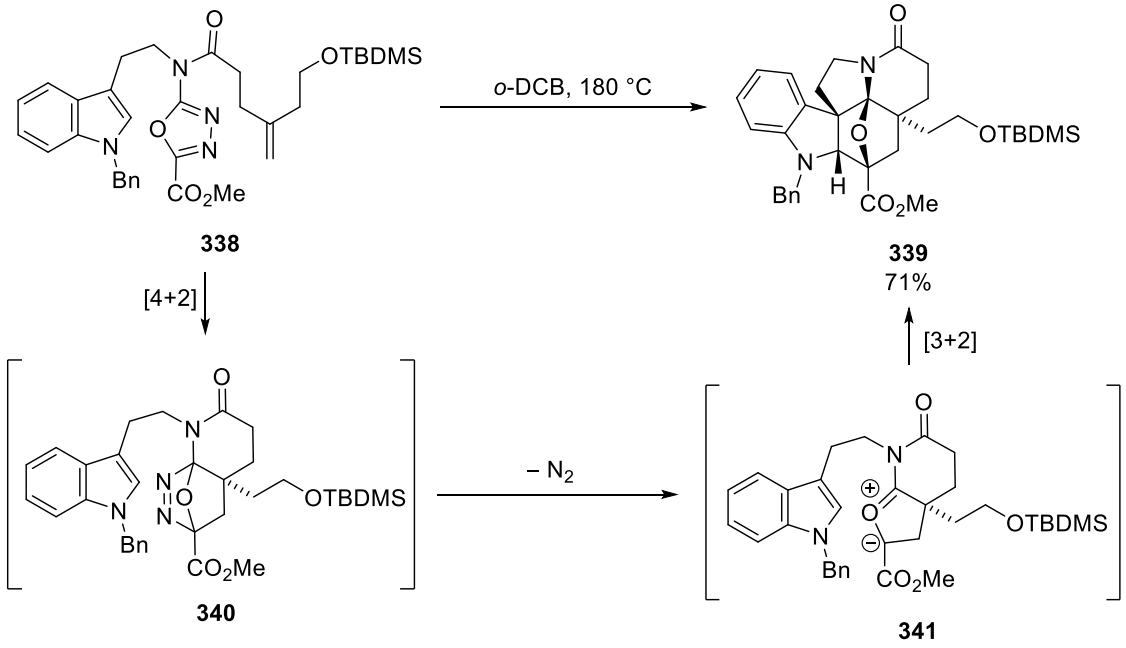
Hydrogenolysis and *N*-alkylation of **330** allowed compound **333** to be isolated, which then underwent a deprotection reaction to give compound **334**. Deprotonation using LiHMDS then gave the intermediate dianion **335** which could react *via* a Claisen condensation reaction to give ketoester **336**. The mesylation of **336** followed by the addition of potassium *tert*-butoxide then gave (−)-**337**. Applying similar conditions as proposed by Wenkert and Pestchanker then allowed the target compound (−)-kopsinine to be isolated (Scheme 144).[118]



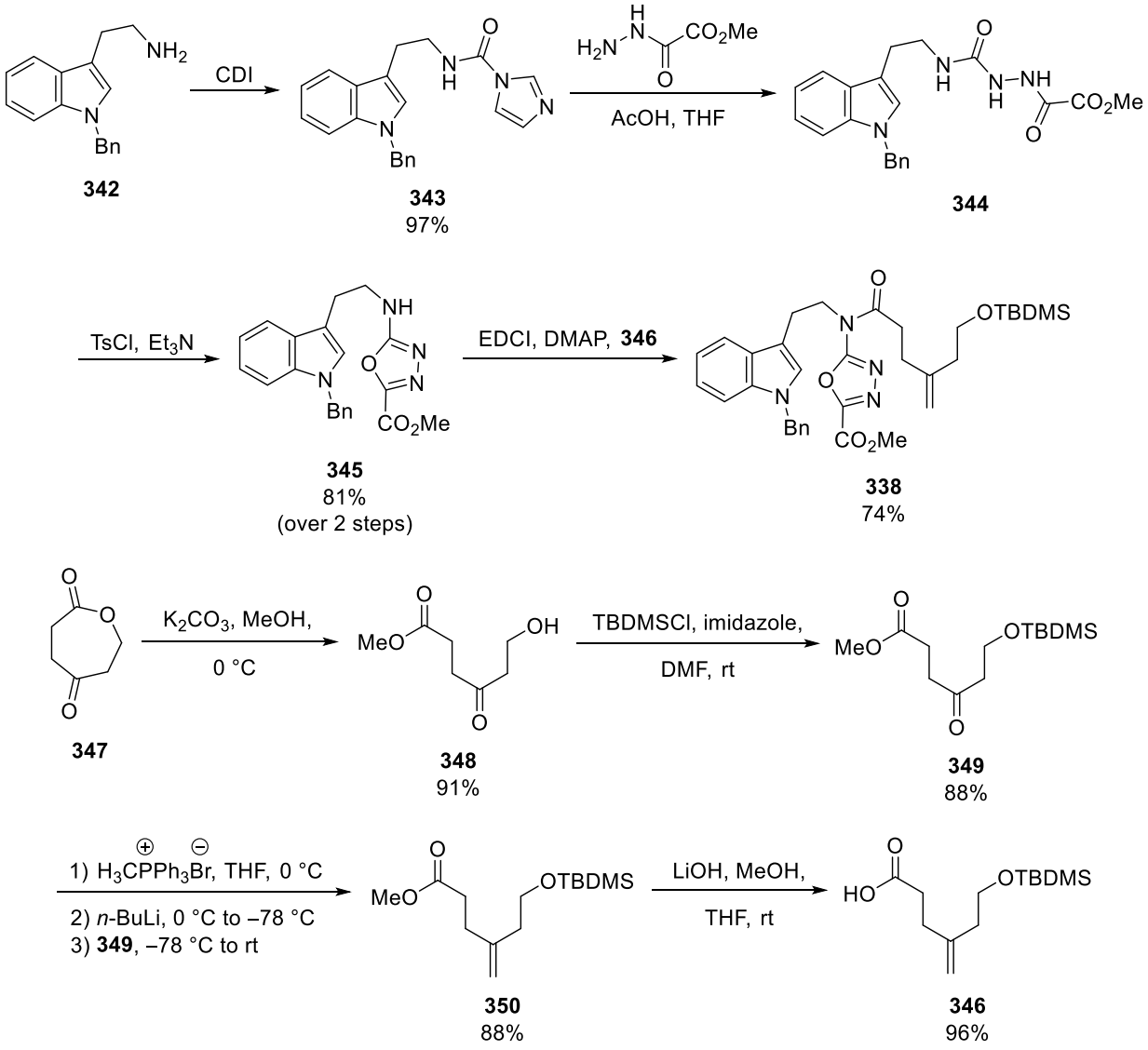
Scheme 144

A year later in 2013, Boger and co-workers proposed a synthetic route to kopsinine using a intramolecular [4+2]/[3+2] cycloaddition cascade reaction.[121] This reaction is shown in Scheme 145 whereby heating compound **338** in *o*-dichlorobenzene gave cycloadduct **339** in 71% yield. The

reaction proceeds through an initial [4+2] cycloaddition reaction to give intermediate **340**, which through the loss of nitrogen then generates intermediate **341**. A subsequent [3+2] cycloaddition then gives the desired cycloadduct. It's important to mention compound **338** was not commercially available and was synthesised in 4 steps from indole derivative **344** (Scheme 146). In the final step compound **346** also needed to be synthesised, which was achieved in 4 steps from lactone **347**.[122]



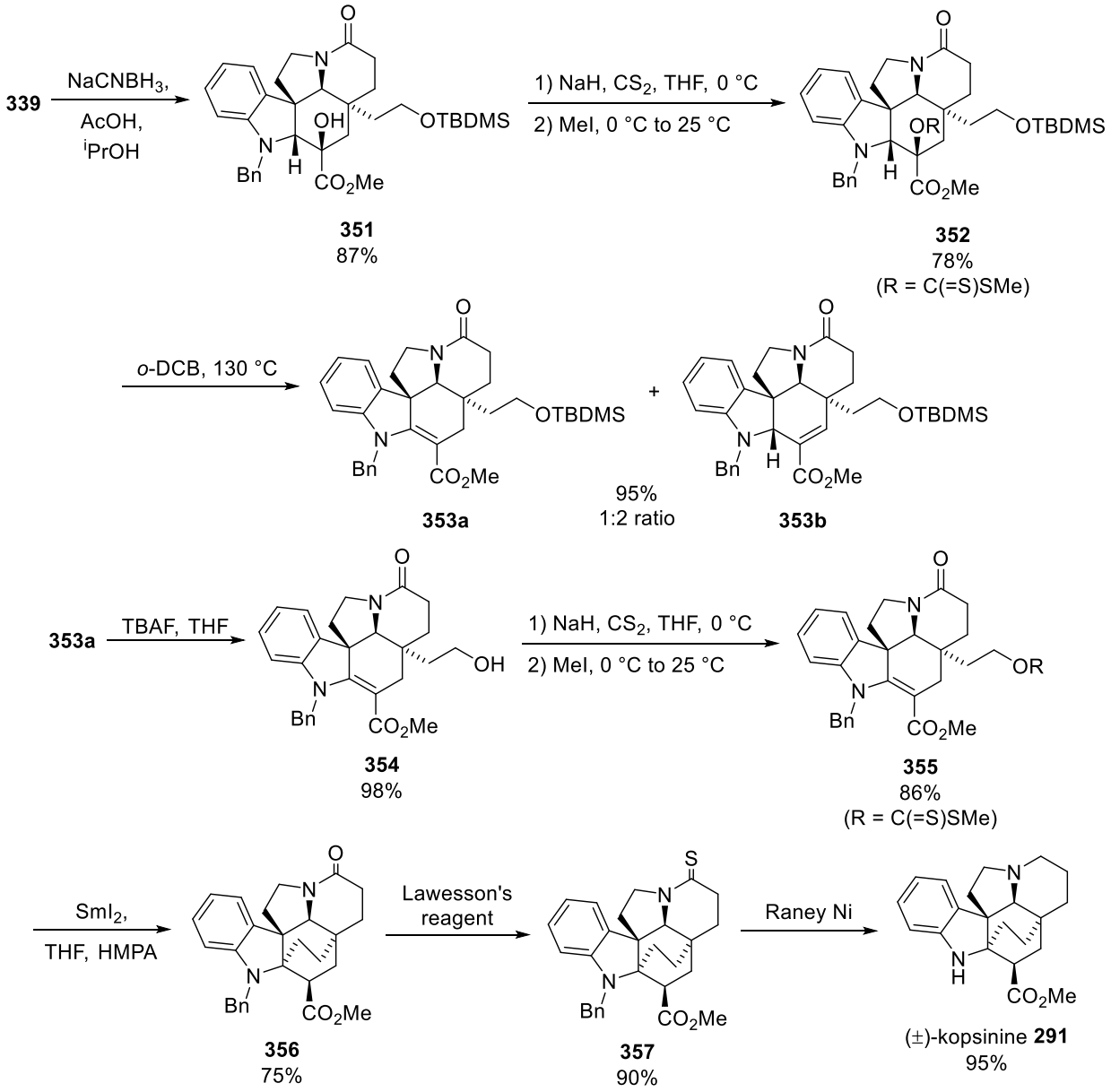
Scheme 145



Scheme 146

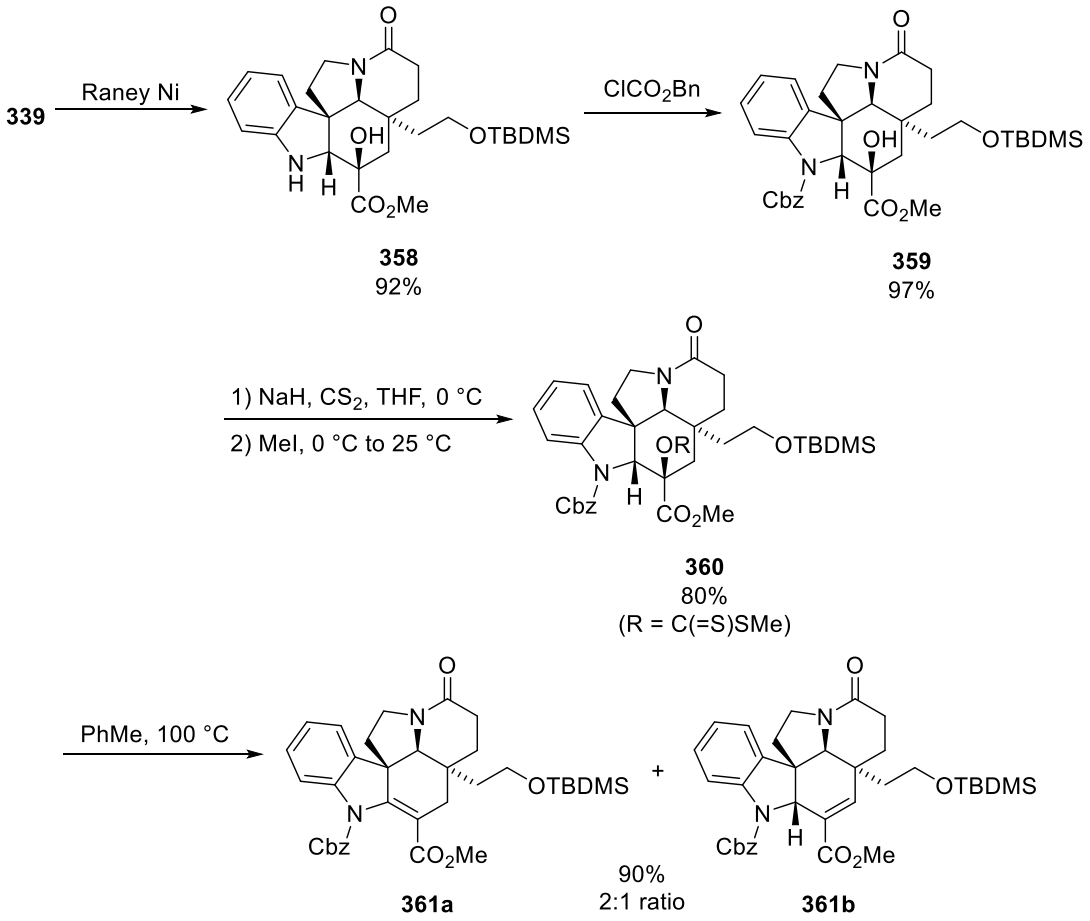
Cycloadduct **339** was then converted to alcohol **351** as a single diastereoisomer using sodium cyanoborohydride. Subsequent treatment of alcohol **351** with sodium hydride, carbon disulfide and methyl iodide then gave compound **352**, which underwent a Chugaev elimination to give regioisomers **353a** and **353b** in a 1:2 ratio. This was unfortunate as only compound **353a** was useful towards the synthesis of kopsinine. Nonetheless, deprotection of **353a** using TBAF gave alcohol **354**, which was then converted to **355**. The ethyl bridge was then installed using a SmI_2 cyclisation reaction to give **356** and the subsequent addition of Lawesson's reagent gave

thiolactam **357**. Upon treatment of **357** with Raney nickel kopsinine was formed as a racemic mixture. These steps are summarised in Scheme 147.



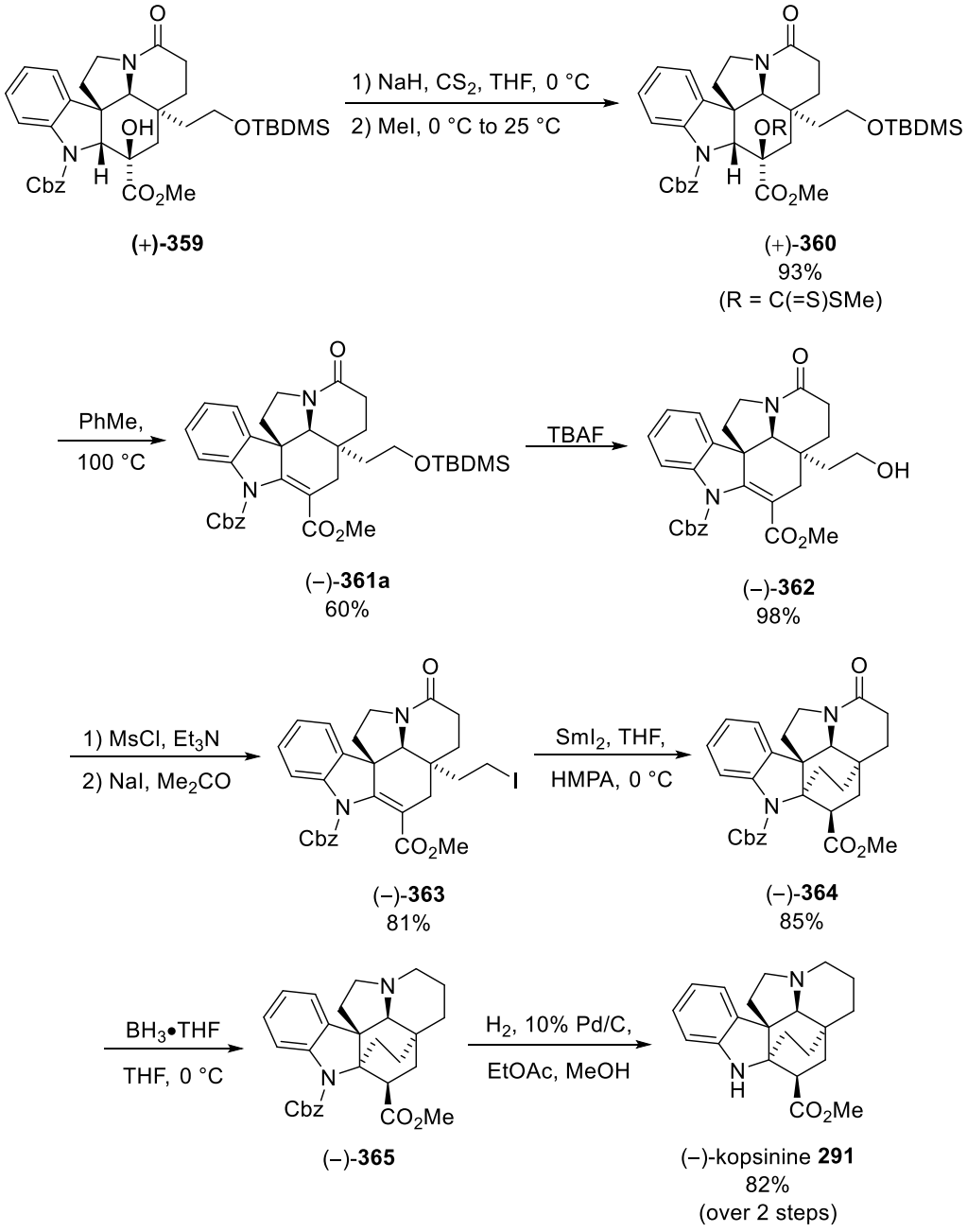
Scheme 147

Furthermore, within the same report it was found that by replacing the benzyl group in the indoline core of **351** with a Cbz group to give **359** led to an improvement in the regioselectivity of the Chugaev elimination step, still producing the mixture of isomers **361a** and **361b** but now in a much better 2:1 ratio (Scheme 148).



Scheme 148

Boger and co-workers then developed the synthetic route further in 2015 by synthesising enantiomerically pure (−)-kopsinine and its unnatural enantiomer *ent*-(+)-kopsinine.[123] Starting with a racemic mixture of alcohol **359** the enantiomers were separated using semi-preparative chiral HPLC to give (+)-**359** and *ent*-(−)-**359**. These were then converted to (−)-kopsinine and *ent*-(+)-kopsinine respectively. The synthetic route for (−)-kopsinine is shown in Scheme 149 and it's important to mention that some alterations were made to the original synthetic route. This can be seen in the last few steps where iodide (−)-**363** was used for the SmI_2 cyclisation reaction to give (−)-**364**. The amide moiety was then reduced with borane to give (−)-**365** and the Cbz group was finally removed *via* hydrogenation to give (−)-kopsinine.

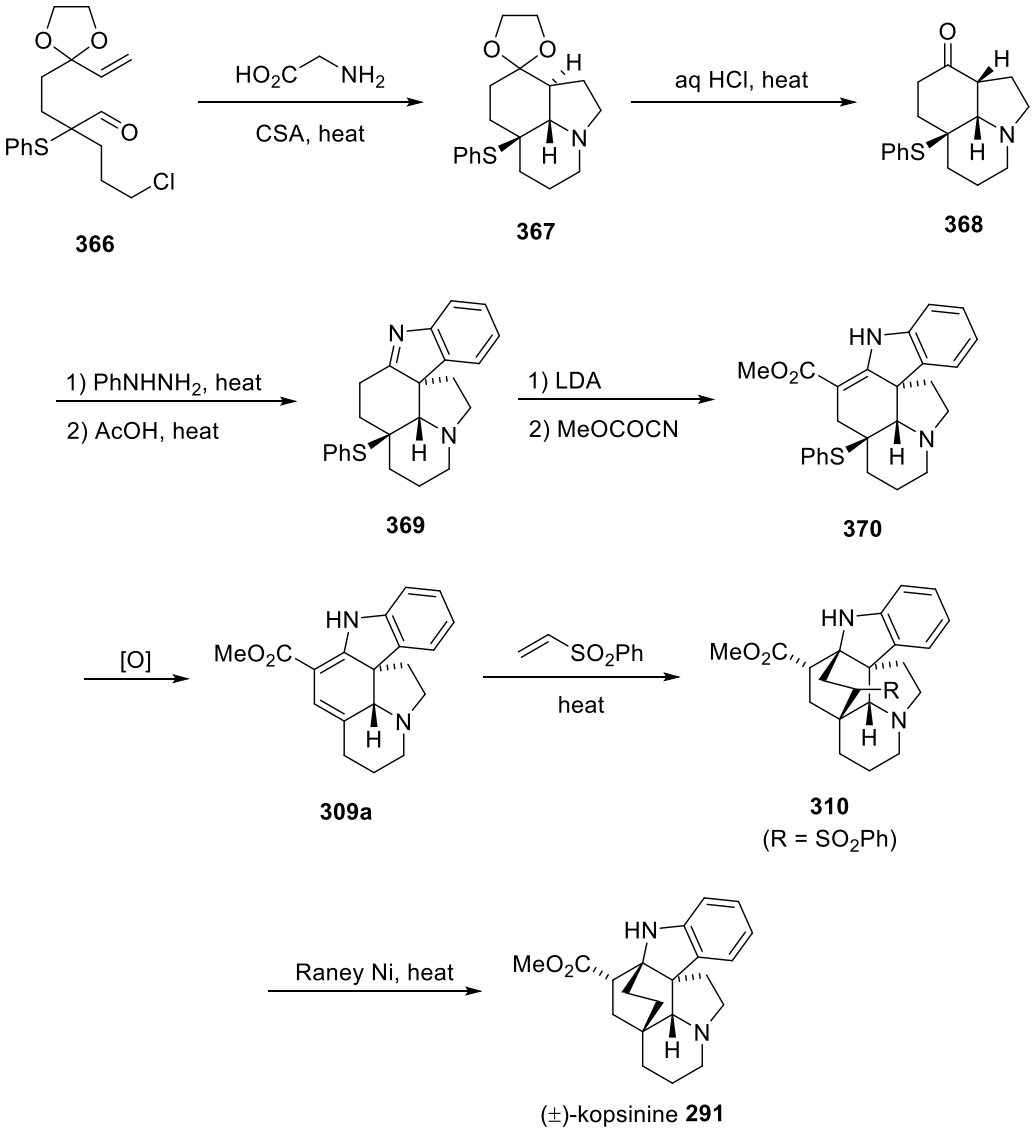


Scheme 149

To this date there have been no other reported syntheses of kopsinine. Looking at the previous routes used, in particular the work done by the Boger group, shows the potential that cycloaddition reactions provide a useful way to access the main core of kopsinine. This is further exemplified when looking at older synthetic routes where the ethyl bridge in kopsinine is usually inserted using a [4+2] cycloaddition reaction with phenyl vinyl sulfone. In addition, previous work done in the Coldham group has allowed the efficient synthesis of aspidospermidine, which is structurally similar to kopsinine.

4.3 Aims

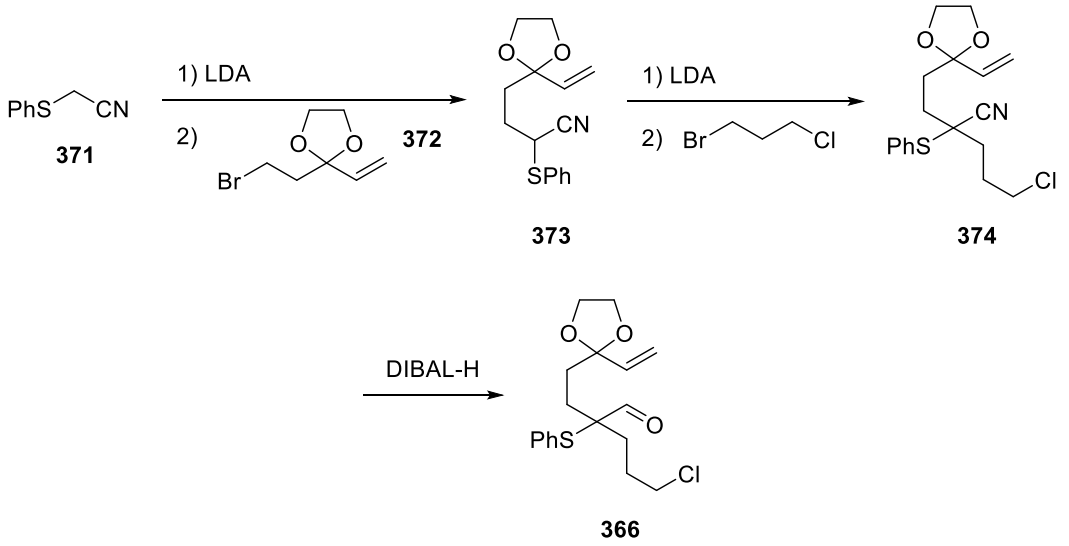
In line with previous work done in the group we wanted to investigate whether we could apply the cascade cycloaddition process developed to synthesise kopsinine. To achieve this the synthetic route shown in Scheme 150 was devised. Starting with aldehyde **366** and carrying out similar reactions previously done in the group would allow **369** to be accessed. Subsequent deprotonation and addition of methyl cyanoformate would then give **370** which could hopefully be converted to kopsinine using similar work done by Kuehne and Seaton.[124,125] Before any work could be done, aldehyde **366** needed to be first synthesised as it was not commercially available.



Scheme 150

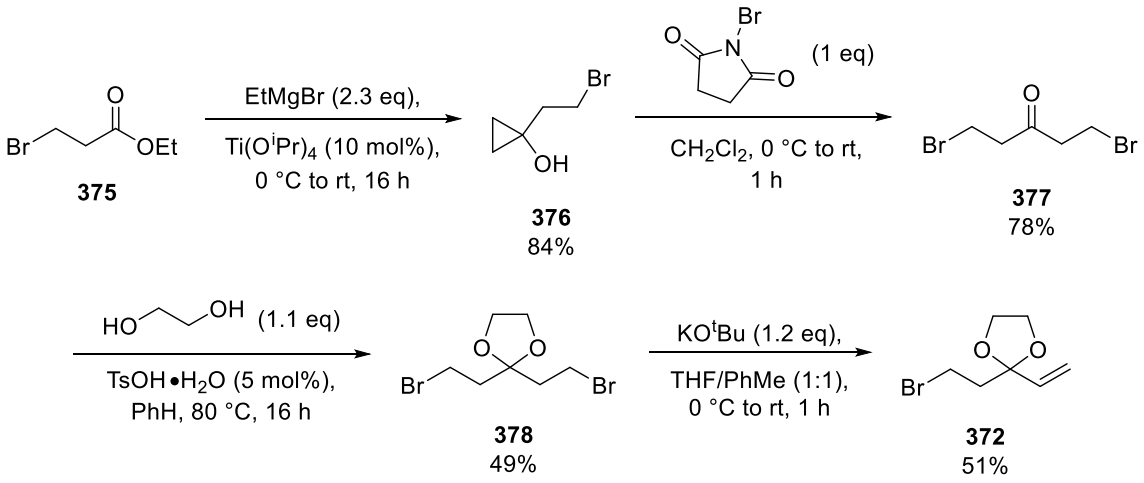
4.4 Synthesis of aldehyde 366 and cycloaddition reactions

To synthesise aldehyde **366** we wanted to use the synthetic route shown in Scheme 151. Deprotonation of (phenylthio)acetonitrile **371** and quenching with bromide **372** would give access to nitrile **373**, which could then be deprotonated again and through the addition 1-bromo-3-chloropropane would give nitrile **374**. Reduction of the nitrile group using DIBAL-H would then generated desired aldehyde **366**.[112]



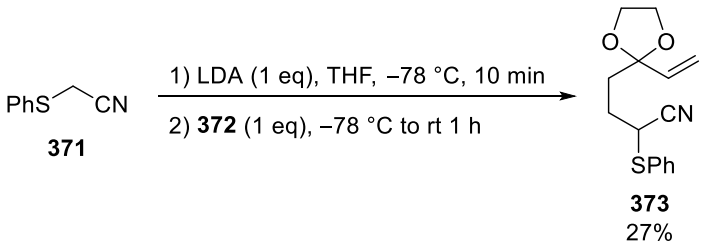
Scheme 151

Bromide **372** was synthesised in 4 steps using a method previously done in the group (Scheme 152).[112] Cyclopropanol **376** was isolated in a yield of 84% from a Kulinkovich reaction using ethyl 3-bromopropanoate **375**. Subsequent reaction of cyclopropanol **376** with *N*-bromosuccinimide then gave ketone **377** in 78% yield. It was pleasing to find that this reaction worked well in dichloromethane, rather than using carbon tetrachloride which was commonly used throughout the literature.[126] Ketone **377** was converted to ketal **378** by heating with ethylene glycol in benzene with the addition of TsOH. Finally, an elimination reaction on ketal **378** using potassium *tert*-butoxide then gave the desired bromide **372** in a reasonable yield of 51%.



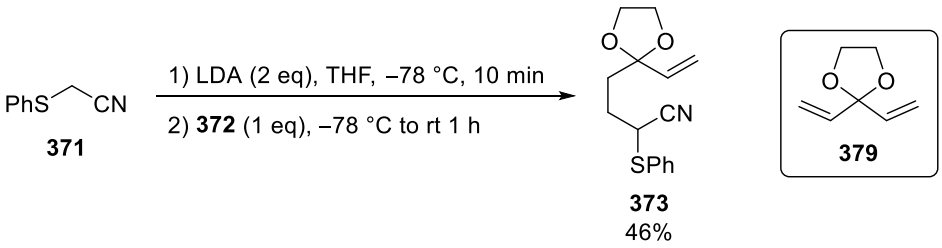
Scheme 152

Having isolated bromide **372** we were now able to prepare nitrile **373**. Some of the initial work was originally carried out by a MChem student in the group under my supervision in the laboratory.[127] Unfortunately, by applying reaction conditions used previously in the group, nitrile **373** was only isolated in 25% yield.[128] The reaction also gave a similar yield of nitrile **373** (27%) when repeated using only one equivalent of the nitrile starting material, rather than four equivalents (Scheme 153). In both reactions the starting bromide **372** was recovered in small amounts.



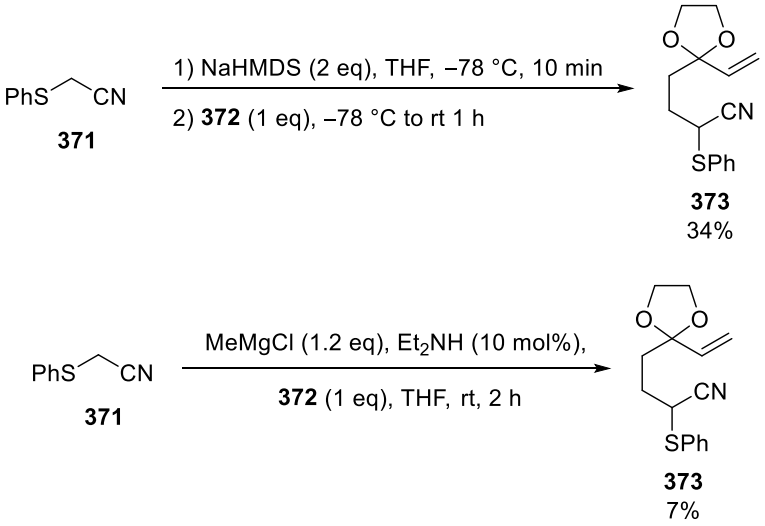
Scheme 153

Fortunately, repeating the reaction using two equivalents of lithium diisopropylamide (LDA) gave an increased yield of 46% for nitrile **373** with recovered bromide **372** (Scheme 154). To our disappointment, when scaling up the reaction the same result was not achieved as only a 6% yield of nitrile **373** was isolated. Furthermore, no bromide starting material was recovered and instead the eliminated product **379** was isolated in 30% yield with respect to bromide **372**.



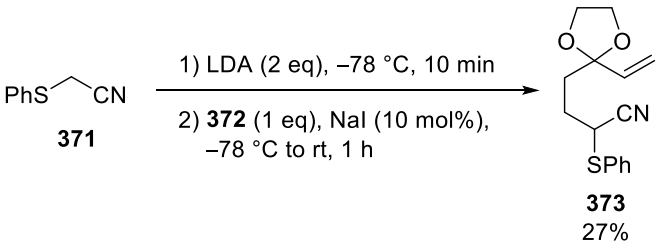
Scheme 154

Other methods to synthesise nitrile **373** were investigated as well. Repeating the reaction and changing the base to sodium bis(trimethylsilyl)amide gave nitrile **373** in lower yield of 34%. In comparison, using methyl magnesium chloride and applying similar alkylation conditions as found by the O'Leary group gave a much lower yield of nitrile **373** (7%), however bromide **372** was recovered in 52% yield.[129] These reactions are shown in Scheme 155.



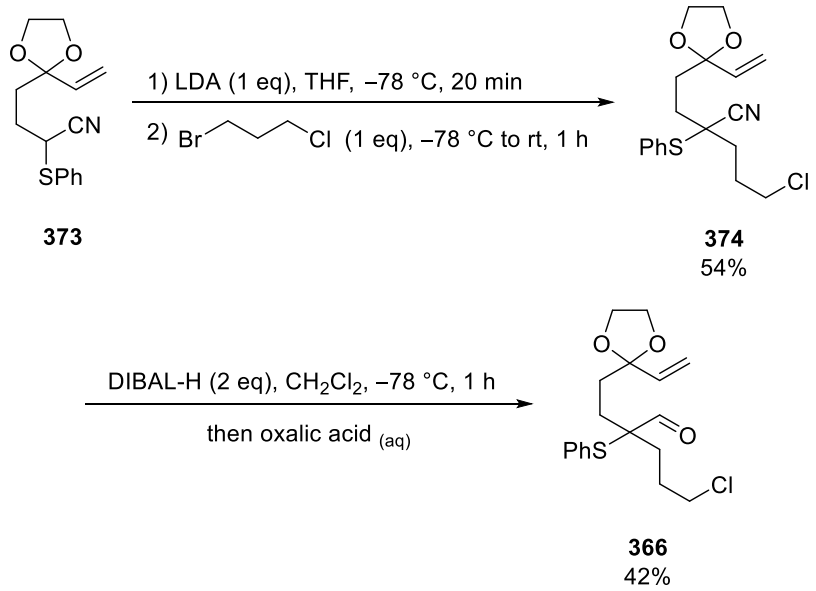
Scheme 155

The final method attempted is shown in Scheme 156 where bromide **372** was premixed with sodium iodide before it was added to the reaction. This hopefully would have allowed the more reactive alkyl iodide to be generated, but instead a low 27% yield of nitrile **373** was isolated with bromide **372** being recovered in 29% yield. Recovery of bromide **372** indicated that formation of the corresponding alkyl iodide may not have occurred as well as expected, however any iodide formed may have decomposed to form compound **379** but this was not isolated.



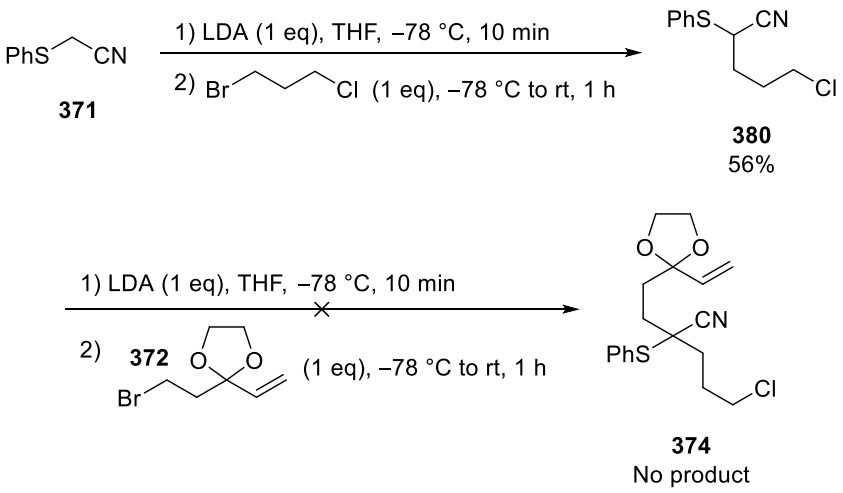
Scheme 156

It was then decided to carry on with the synthetic route towards aldehyde **366**. Alkylation of nitrile **373** with 1-bromo-3-chloropropane gave nitrile **374** in 54% yield and subsequent reduction using DIBAL-H gave the desired aldehyde **366** in 42% yield (Scheme 157).



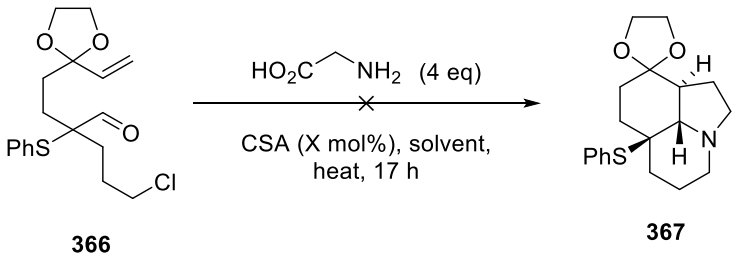
Scheme 157

At this point, in an attempt to increase the overall yield of nitrile **374** we decided to swap around the alkylation reactions. This is summarised in Scheme 158 where (phenylthio)acetonitrile **371** was alkylated with 1-bromo-3-chloropropane to give nitrile **380** in 56% yield. However, disappointingly the next alkylation step with bromide **372** was unsuccessful generating none of the desired product **374** and just gave recovered starting material.



Scheme 158

With aldehyde **366** in hand we then attempted the key cycloaddition reaction to obtain compound **367**. After multiple attempts of heating aldehyde **366** with glycine using various reaction conditions none of the desired cycloadduct **367** was formed (Scheme 159, Table 8). The reaction was carried out using different catalyst loadings of CSA and when changing the reaction solvent to *o*-xylene, and heating at a higher temperature the same results were achieved. TLC and LCMS analysis of all crude reaction mixtures showed that aldehyde **366** was still present and no desired cycloadduct **367** had been formed.



Scheme 159

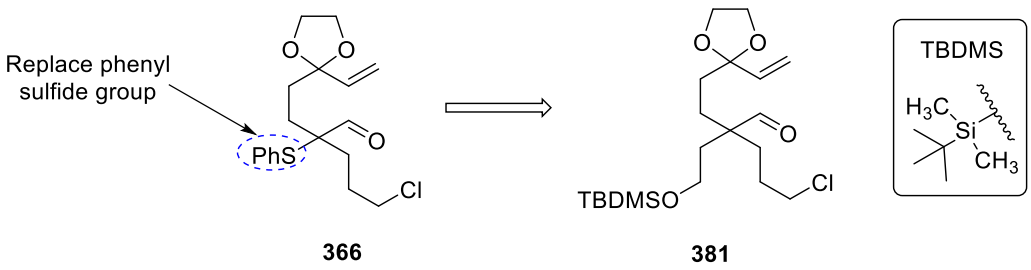
Entry	CSA mol%	Temperature	Solvent	Outcome
1	0	110 °C	PhMe	No Product
2	0.1	110 °C	PhMe	No Product
3	0.2	110 °C	PhMe	No Product
4	0.2	145 °C	*o*-Xylene	No Product

Table 8

Due to unsuccessful results obtained using aldehyde **366** it was then decided to investigate an alternative route to kopsinine using a different aldehyde in the hope that a cycloaddition reaction would take place.

4.5 Alternative routes towards kopsinine using different aldehydes

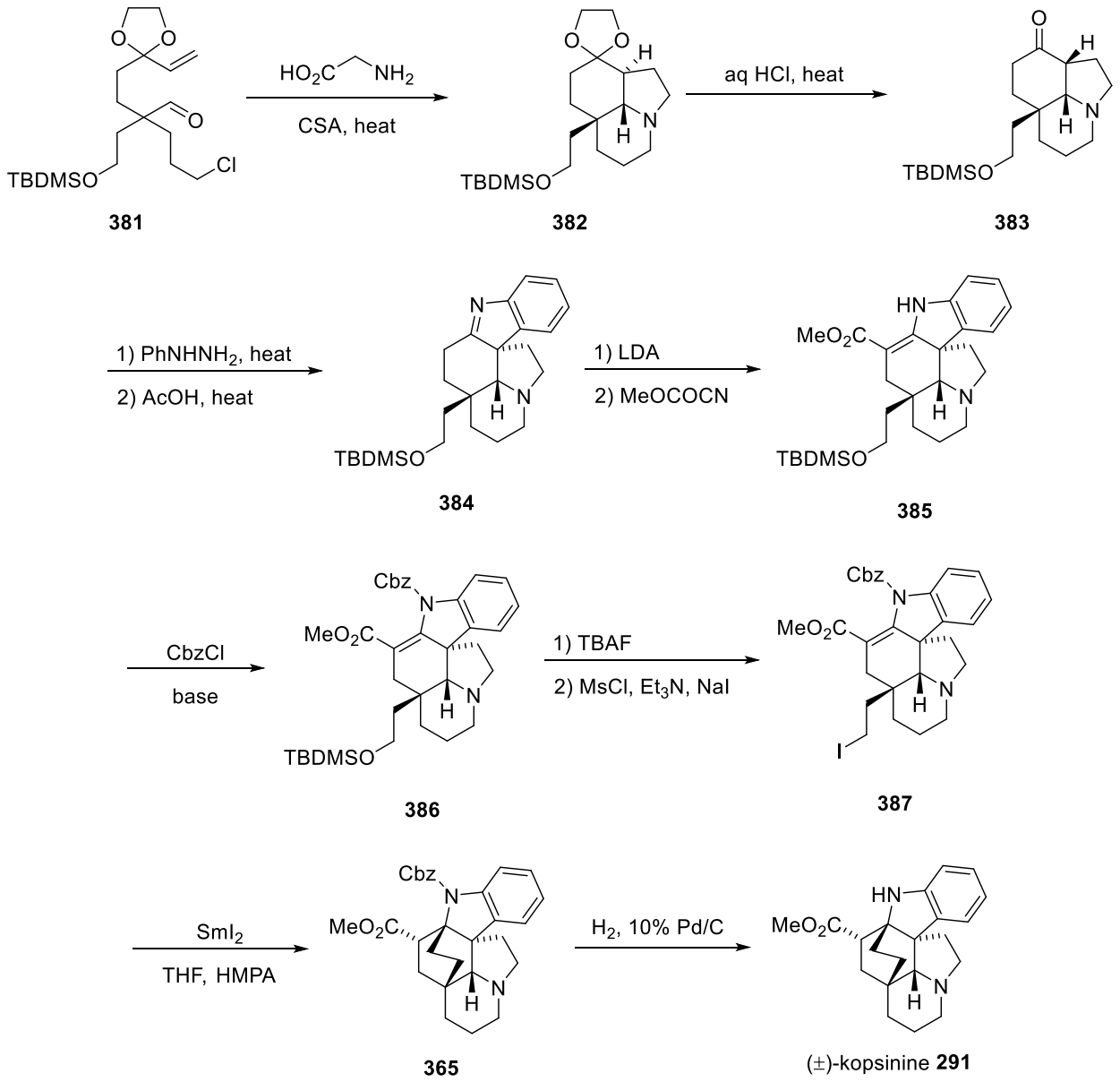
In order to continue applying the cascade chemistry developed in the group towards the total synthesis of kopsinine it was clear that the new aldehyde to be investigated needed to have a similar structure to aldehyde **366**, otherwise the main core of kopsinine would not be able to be synthesised. As a result of this there were very few changes that could have been made to aldehyde **366** to enable a cycloaddition reaction to take place, but the most obvious one was to replace the phenyl sulfide group. Taking inspiration from the work done by the Boger group a simple replacement for this group could be a TBDMS protected ethyl alcohol chain.[123] Ultimately, this would result in aldehyde **381** (Scheme 160) and a different method would be required to insert the ethyl bridge in kopsinine.



Scheme 160

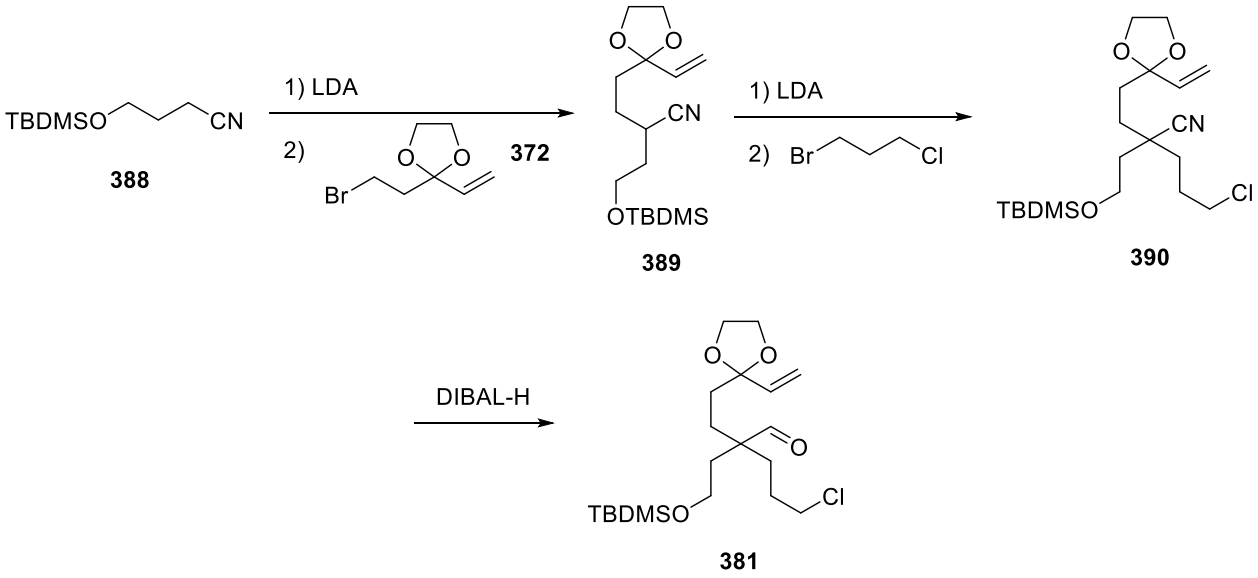
The next strategy that was applied towards the synthesis of kopsinine is shown in Scheme 161. Starting with aldehyde **381** and applying similar reaction conditions as used previously in the Coldham group could allow imine **384** to be obtained.[112] A subsequent deprotonation and addition of methyl cyanoformate would then hopefully give compound **385**.[124,125] Due to the nature in which the bicyclic structure of kopsinine is formed using the methods developed by the Boger group, it may also be beneficial to protect the basic nitrogen centre in compound **385** to prevent any unwanted side reactions taking place.[123] Using a carboxybenzyl (Cbz) protecting group would give compound **386** and carrying out similar reactions performed by the Boger group to install the ethyl

bridge would allow the kopsinine precursor **365** to be isolated. Finally, removal of the Cbz group would then give kopsinine.



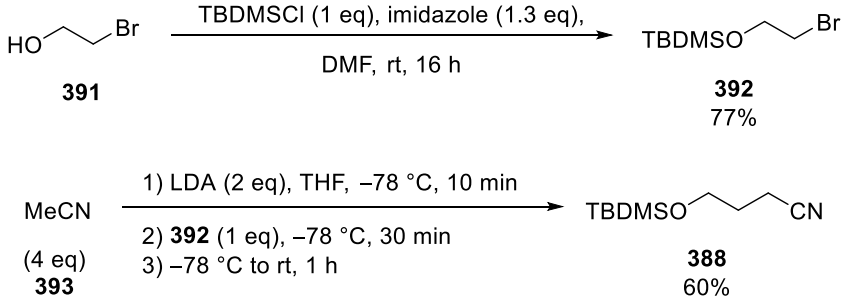
Scheme 161

To synthesise aldehyde **381** the route shown in Scheme 162 was devised. This route is very similar to the synthesis of aldehyde **366** where starting with nitrile **388** and alkylating with bromide **372** would give nitrile **389**. Repeating the alkylation reaction with 1-bromo-3-chloropropane would then give **390** and subsequent reduction of the nitrile group would give the desired aldehyde **381**.



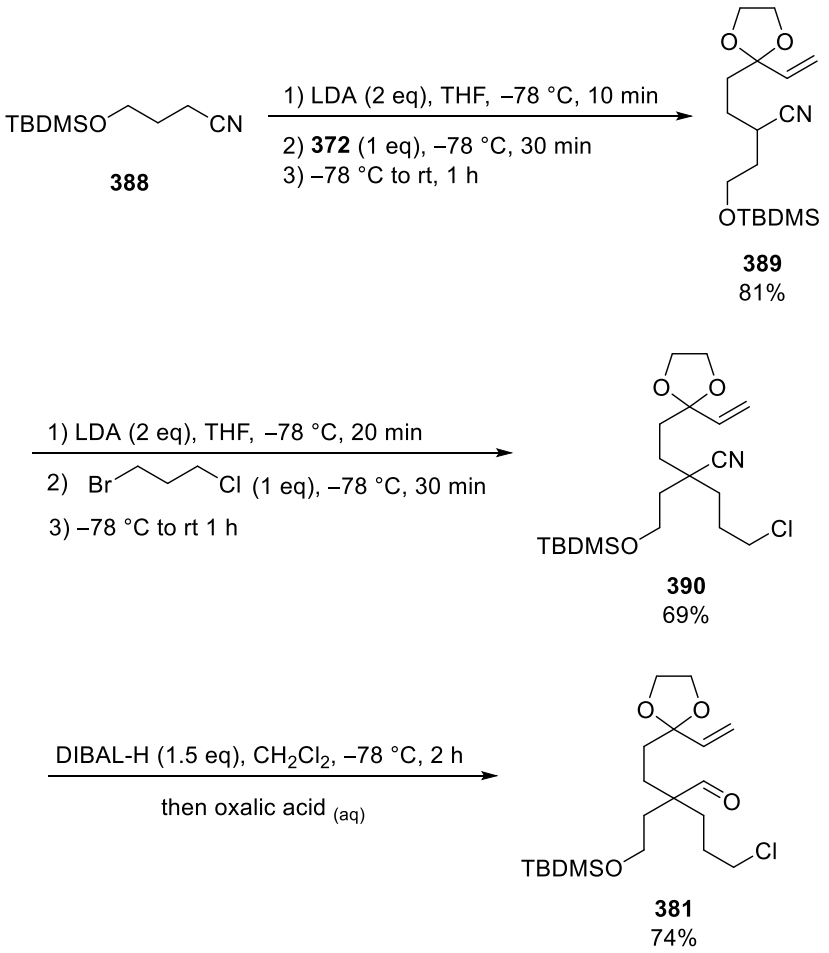
Scheme 162

As nitrile **388** was not commercially available it needed to be synthesised. Starting with 2-bromoethanol **391**, bromide **392** was obtained in 77% yield *via* a reaction with TBDMSCl in the presence of imidazole. This was then reacted with acetonitrile to give the desired nitrile **388** in a reasonable 60% yield (Scheme 163).[130]



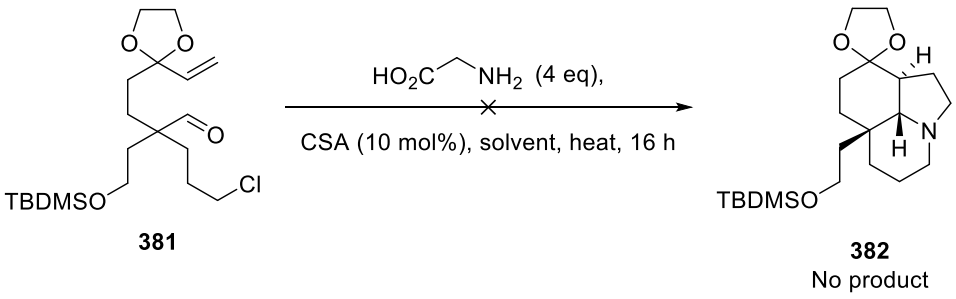
Scheme 163

With nitrile **388** in hand we could now start the synthesis of aldehyde **381** (Scheme 164). Alkylation of nitrile **388** with bromide **372** gave nitrile **389** in a good 81% yield. Subsequent alkylation of nitrile **389** with 1-bromo-3-chloropropane then gave nitrile **390** in a slightly lower yield of 69%. Finally, reduction of the nitrile group using DIBAL-H gave the desired aldehyde **381** in 74% yield. It was pleasing to see that unlike using (phenylthio)acetonitrile **371** the first alkylation reaction to give nitrile **389** occurred smoothly without any problems.



Scheme 164

Having isolated aldehyde **381** we now wanted to subject it to the cycloaddition conditions used previously to see whether we could generate the desired cycloadduct **382**.[112] Heating aldehyde **381** with glycine in the presence of 10 mol% CSA and toluene unfortunately failed to give any of the desired product. TLC analysis of the crude product indicated that the aldehyde **381** was present and had not been consumed in the reaction. Furthermore, repeating the reaction in *o*-xylene or DMF (heating at 120 °C) gave similar results. These results are summarised in Scheme 165 and Table 9.

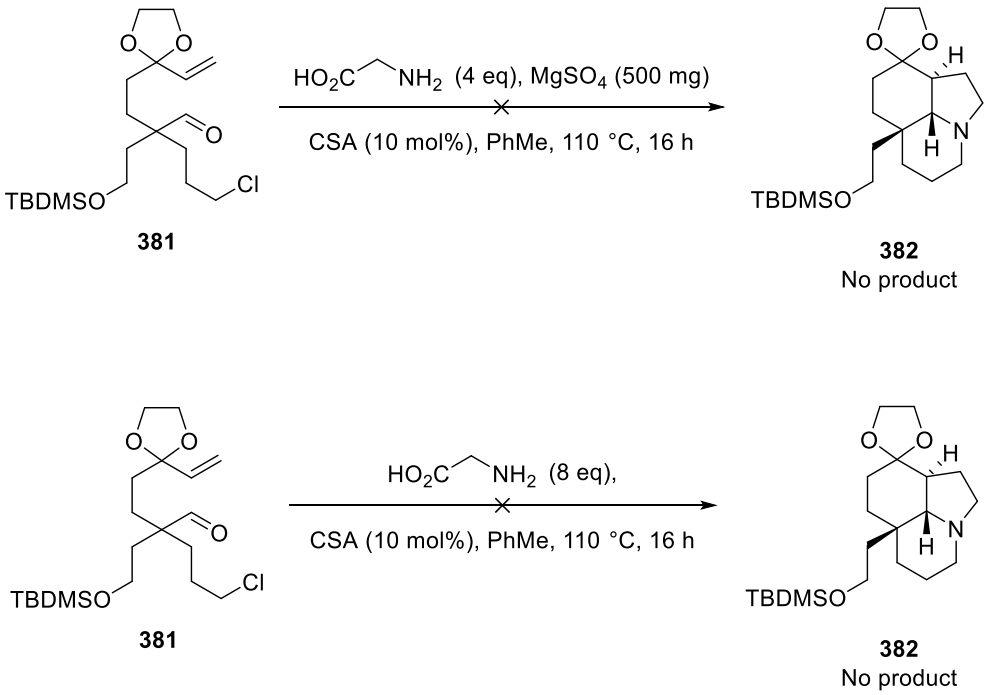


Scheme 165

Entry	Temperature	Solvent	Outcome
1	110 °C	PhMe	No Product
2	120 °C	DMF	No Product
3	145 °C	*o*-Xylene	No Product

Table 9

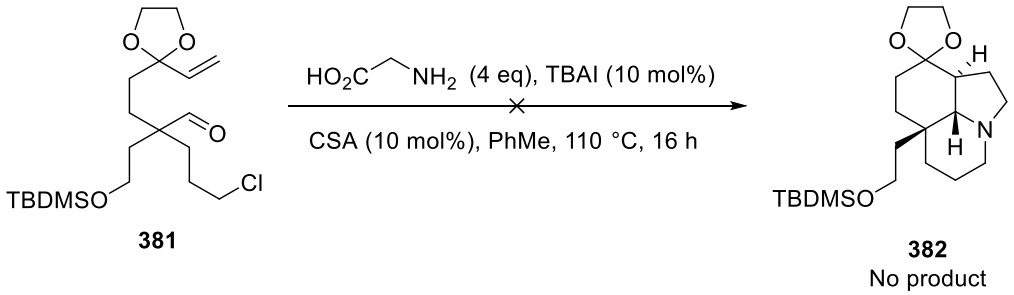
We initially thought there may have been a problem with the first step of the reaction where glycine reacts with the aldehyde to generate an imine. To potentially overcome this problem the reaction in Scheme 165 was repeated with the addition of magnesium sulfate to remove any water formed during the imine formation. Unfortunately, the same result was obtained and TLC analysis showed that the aldehyde starting material was present in the crude product. Carrying out the reaction using a large excess glycine (8 equivalents) was also unsuccessful and TLC analysis showed that starting material was still present. These results are summarised in Scheme 166.



Scheme 166

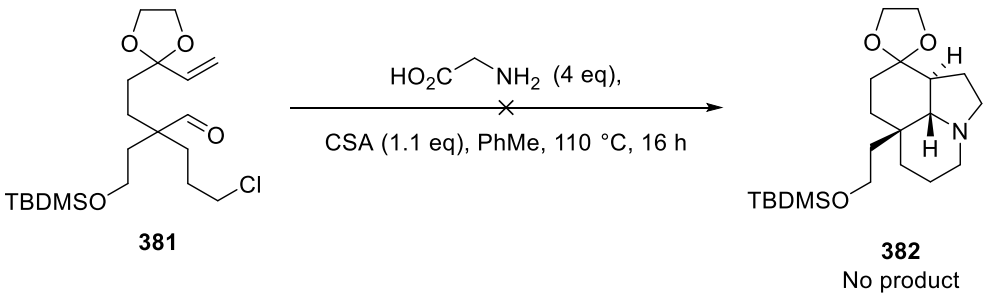
Moving forward, we thought that there may have been a potential problem with the cyclisation step. If the initial imine formed wasn't cyclising onto the chloride then no azomethine ylide was going to be formed, therefore no cycloaddition reaction would occur. To aid the cyclisation step the cycloaddition reaction was repeated with the addition of TBAI to allow the desired alkyl iodide to

be formed *in-situ* (Scheme 167). Unfortunately, no desired product was isolated and only aldehyde **381** was recovered.



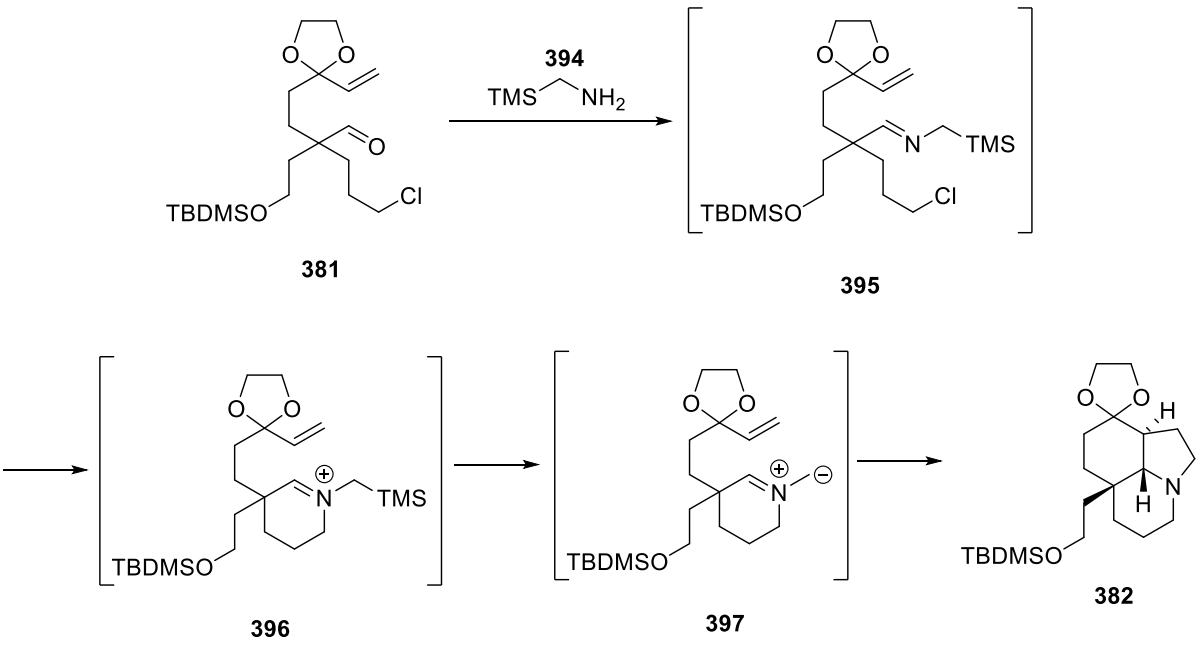
Scheme 167

Before trying alternative methods to form the desired azomethine ylide we also investigated increasing the concentration of CSA in the reaction. The CSA added to the reaction was originally meant to aid the imine formation between the aldehyde and glycine *via* coordination to the carbonyl group. Furthermore, the acid could also coordinate to one of the ketal oxygen atoms to allow activation of the alkene towards cycloaddition. If coordination was occurring at a different position, in particular the TBDMS protected alcohol, then imine formation or alkene activation would not take place. To test this theory the cycloaddition reaction was repeated with 1.1 equivalents of CSA in the reaction (Scheme 168). Unfortunately, TLC analysis of the crude reaction mixture showed many spots indicating the aldehyde starting material may have decomposed during the reaction. LCMS analysis also shown no desired product formation.



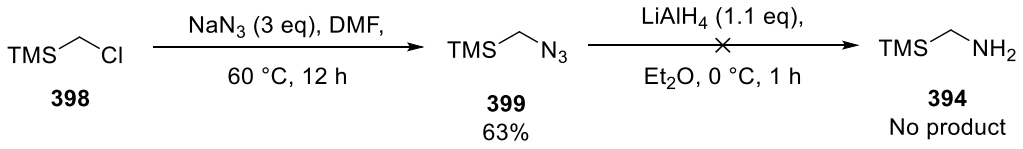
Scheme 168

We wanted to investigate alternative methods to form the azomethine ylide. Looking at the previous work done by the Pearson group we were interested in applying their methods using (trimethylsilyl)methylamine **394** in the hope that the desired cycloaddition reaction would occur through the cyclisation of the resultant imine **395** (Scheme 169).[32]



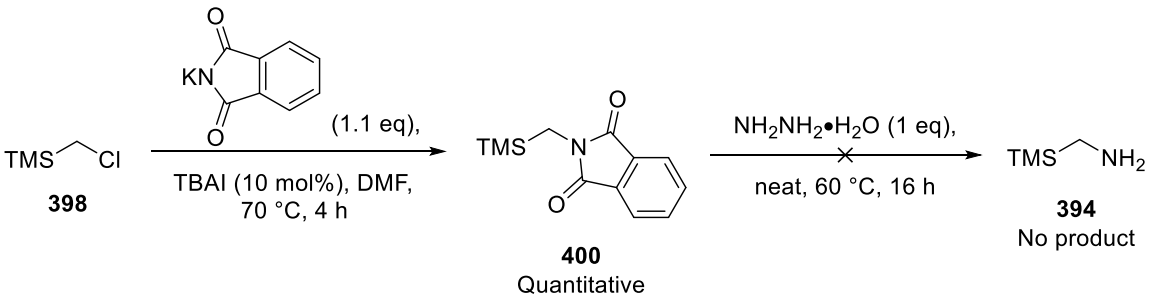
Scheme 169

Due to the high cost of (trimethylsilyl)methylamine **394** we wanted to first synthesise this reagent. Looking in the literature there were very few methods available. Starting with chloromethyltrimethylsilane **398** we were able to synthesise the corresponding organoazide **399** in 63% yield. However, in an attempt to reduce azide **399** using $LiAlH_4$ none of the desired amine **394** was isolated (Scheme 170).[131]



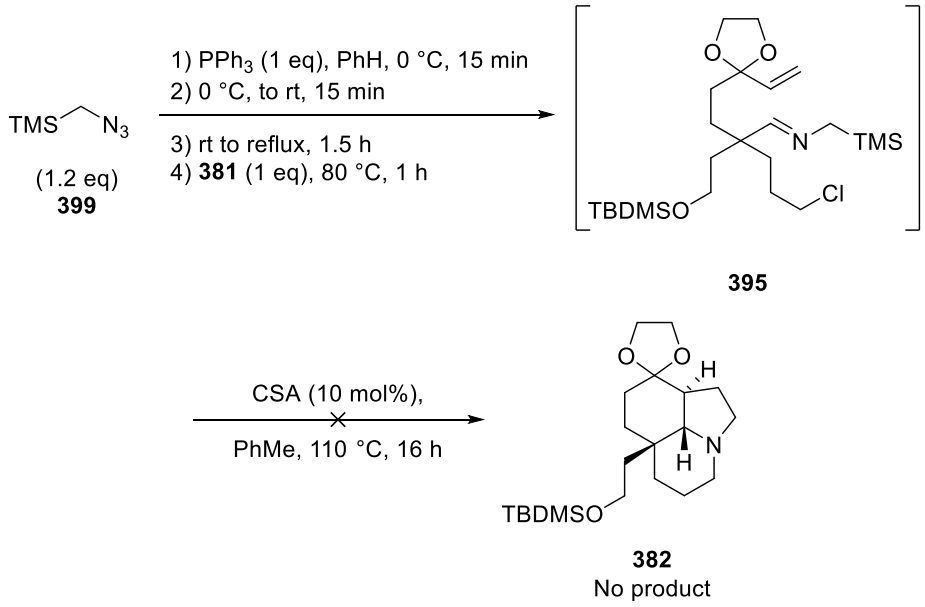
Scheme 170

As an alternative we tried to access amine **394** using the Gabriel synthesis.[132] This is summarised in Scheme 171 where compound **400** was synthesised in quantitative yield from chloride **398**. Unfortunately, subsequent reduction of compound **400** using hydrazine failed to give any of the desired amine **394**.



Scheme 171

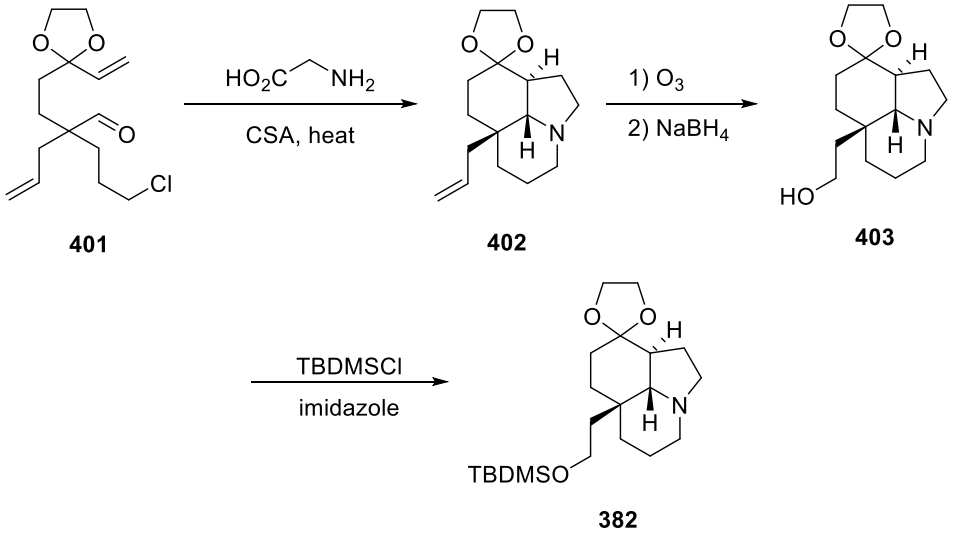
Moving on we then investigated trying to form intermediate **395** through the aza-wittig reaction of organoazide **399** with aldehyde **381**.[133] To our disappointment when applying the reaction conditions shown in Scheme 172 none of the desired product **381** was isolated and the starting aldehyde **381** was recovered. This was unexpected considering in the first step the formation of nitrogen gas was observed indicating the desired iminophosphorane ($TMSCH_2N{=}PPh_3$) and hopefully the imine **395** was being formed.



Scheme 172

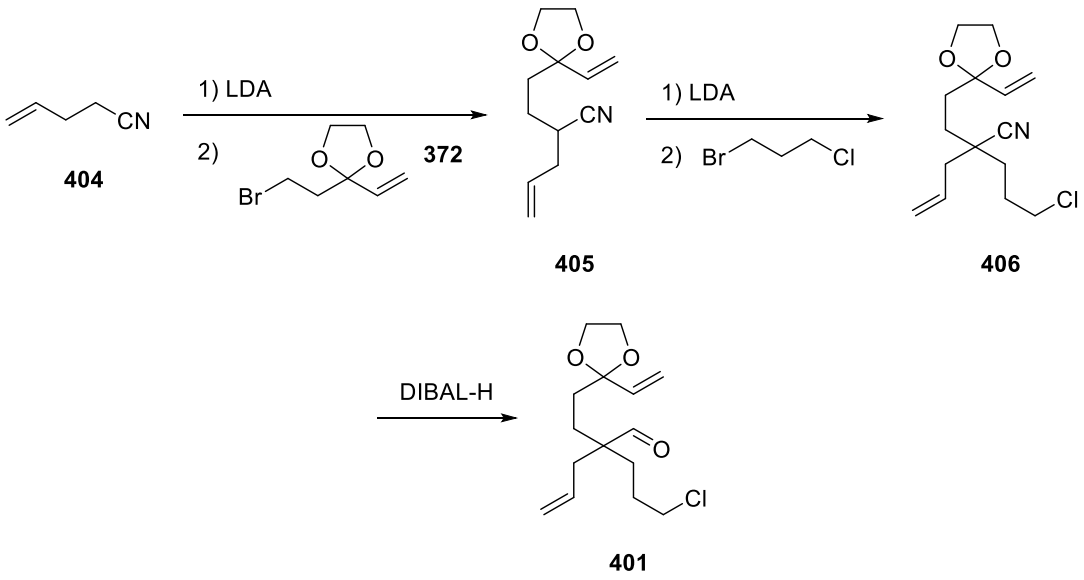
The results obtained so far attempting to carry out cycloaddition reactions on aldehyde **381** seemed discouraging. However, the use of the TBDMS protected ethyl alcohol side chain seemed like a useful way to install the ethyl bridge in kopsinine. As a result, in a final attempt to achieve a successful cycloaddition reaction we decided to modify aldehyde **381** by replacing the TBDMS protected ethyl alcohol side chain with an allyl group, which would result in aldehyde **401** (Scheme

173). If a successful cycloaddition reaction could be carried out on aldehyde **401** then the cycloadduct **402** could be isolated. Subsequent ozonolysis and reduction reactions would then result in alcohol **403**.[134] This could then be TBDMS protected to give the original cycloadduct **382** we were attempting to synthesise.



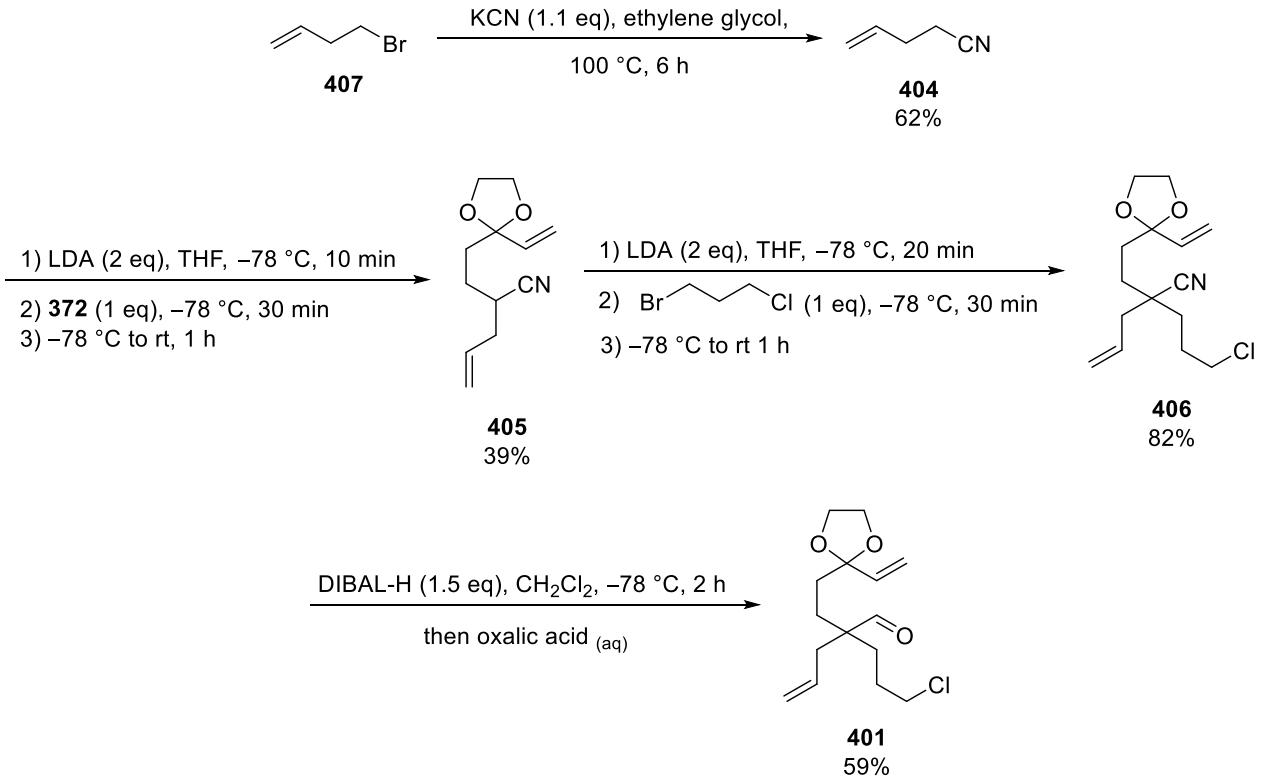
Scheme 173

Similar to the previous synthetic routes we first needed to synthesise the starting aldehyde **401**. To achieve this we devised the synthetic route shown in Scheme 174 where 4-pentenenitrile **404** was first alkylated with bromide **372** to give nitrile **405**. Another alkylation reaction with 1-bromo-3-chloropropane would then give nitrile **406**, which could then be reduced with DIBAL-H to give the desired aldehyde **401**.



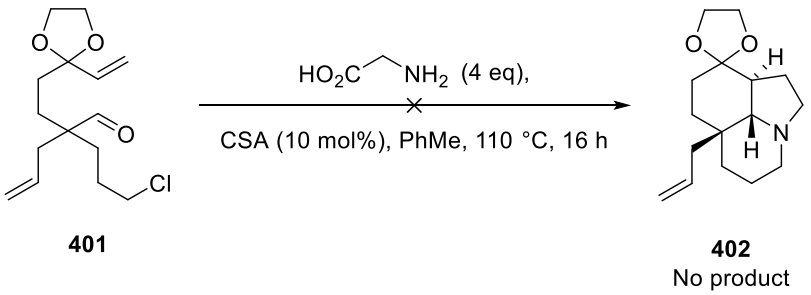
Scheme 174

Although nitrile **404** was commercially available it was decided to synthesise it from 4-bromobutene **407**. Heating with potassium cyanide gave the desired nitrile **404** in 62% yield (Scheme 175).[135] Having isolated nitrile **404** we could now carry on with the synthesis of aldehyde **401**. Alkylation of nitrile **404** with bromide **372** gave nitrile **405** in 39% yield. Subsequent alkylation with 1-bromo-3-chloropropane then gave nitrile **406** in a good yield of 82%. Reduction of the nitrile group using DIBAL-H gave the desired aldehyde **401** in 59% yield.



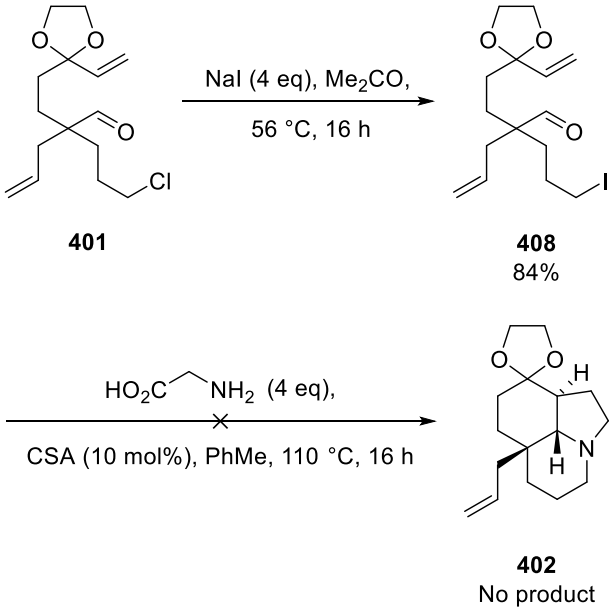
Scheme 175

Aldehyde **401** was then subjected to the original cycloaddition reaction conditions with glycine (Scheme 176). Unfortunately, no desired product **402** was isolated and TLC analysis of the crude reaction mixture indicated that aldehyde **401** may have decomposed during the reaction. LCMS analysis of the crude reaction mixture confirmed this and indicated no product had been formed as well.



Scheme 176

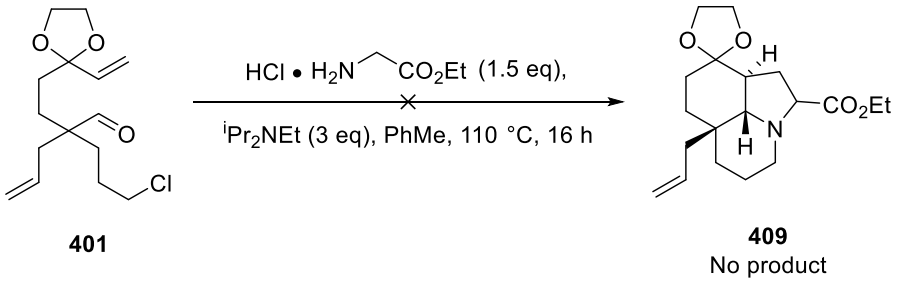
As aldehyde **401** was very similar in structure to aldehyde **286**, which was used to successfully synthesise aspidospermidine, it was surprising to see that the cycloaddition reaction with aldehyde **401** failed to give any of the desired product **402**. We potentially thought there may have been a problem with the cyclisation step, therefore aldehyde **401** was converted to aldehyde **408** using a Finkelstein reaction with sodium iodide.[128] Aldehyde **408** was isolated in a yield of 84%, however subjecting it to the same cycloaddition reaction conditions failed to give any of the desired cycloadduct **402** and starting aldehyde **408** was recovered (Scheme 177).



Scheme 177

In a final attempt to promote a cycloaddition reaction we decided to investigate forming a different azomethine ylide. Heating aldehyde **401** with glycine ethyl ester hydrochloride in the presence of Hünig's base and toluene failed to give the desired cycloadduct **409** (Scheme 178).[128] LCMS

analysis of the crude reaction mixture confirmed that no product had been formed and that the starting material had decomposed during the reaction.



401 **409** No product

Scheme 178

As a result of the unsuccessful results obtained throughout the multiple attempts of the cycloaddition reaction using various aldehyde substrates it was decided to stop work towards the synthesis of kopsinine.

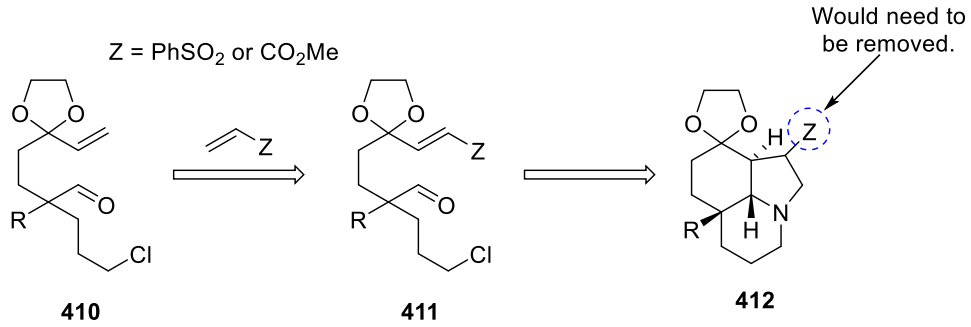
4.6 Conclusions and Future Work

Although we have managed to successfully synthesise three aldehyde precursor molecules in an attempt to access the main core of kopsinine, we were unable to achieve the desired cycloaddition reaction with glycine. Therefore we were not able to achieve our main goal of applying the cascade chemistry developed in the group towards the total synthesis of kopsinine.

We were unsure why none of the cycloaddition reactions were successful and due to the number of steps involved in the cascade reaction it was difficult to identify which step was not working in the reactions. However, as most reactions gave the aldehyde starting material back this was potentially an indication that either the imine formation or the cyclisation was problematic with these substrates. In particular, for substrates **366** and **381** the aldehyde group may have been too hindered by the presence of the phenyl sulfide group and TBDMS protected ethyl alcohol chain respectively. Presumably as a result, no imine formation could take place.

In the cases that led to decomposition, activation of the alkene function group may allow a cycloaddition reaction to take place. Previously in the group this has been achieved using a Grubbs metathesis reaction using alkenes such as phenyl vinyl sulfone and methyl acrylate. However, this

poses a new problem as if a cycloaddition reaction were to take place then the activating group would need to be removed, introducing another step into the synthetic route (Scheme 179).



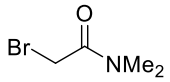
Scheme 179

Chapter 5 – Experimental

General Experimental Details

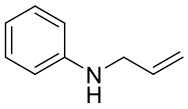
All reagents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Dry solvents were obtained from a Grubbs dry solvent system (model: SPS-200-6 or SPS-400-6). Diisopropylamine was freshly distilled from CaH_2. Thin layer chromatography (TLC) analysis was performed on Merck silica gel 60 F_{254} plates and visualised by UV irradiation at 254 nm or by staining with an alkaline $KMnO_4$ dip. Flash column chromatography was carried out on VWR silica gel (40-63 micron mesh). Petrol refers to petroleum ether, b.p. 40–60 °C. Furthermore, unless stated, the ^1H proton NMR spectra were recorded on a Bruker Avance 400, a Bruker Avance III 400, a Bruker Avance III HD 400 (all 400 MHz) or a Bruker Avance III HD 500 (500 MHz) instrument, at 30 °C in deuterochloroform, hexadeuterodimethyl-sulfoxide or deuterium oxide. All chemical shifts are expressed in parts-per-million (ppm) with respect to the residual solvent peaks. Coupling constants (*J*) are given in Hertz (Hz) to the nearest 0.5 Hz and were corrected. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. Diastereotopic protons are assigned as CH unless otherwise stated. ^{13}C NMR were recorded on the above instruments at 100 MHz. Low and high resolution (accurate mass) mass spectra were recorded on a Micromass Autospec for Electron Impact (EI) and on a Walter LCT instrument for electrospray (ES) with Time of Flight (TOF) analysis. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum RX Fourier Transform IR System. Only selected peaks are reported and absorption maxima are given in cm^{-1}. Melting points were recorded using a Gallenkamp hot stage and were uncorrected.

2-Bromo-*N,N*-dimethylacetamide (102)



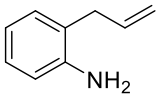
To a stirred solution of bromoacetyl bromide (2.2 mL, 25 mmol) in CH_2Cl_2 (90 mL) at 0 °C was added dimethylamine (15 mL, 30 mmol, 2 M in THF), followed by Et_3N (4.1 mL, 30 mmol). The reaction mixture was warmed to rt and left to stir for 1 h. The mixture was diluted with CH_2Cl_2 (100 mL) and aqueous HCl (100 mL, 2 M). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give bromide **102** (2.1 g, 50 %) as a brown oil; R_f 0.11 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.86 (2H, s, CH_2), 3.10 (3H, s, CH_3), 2.98 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.8 (C=O), 38.1 (CH_3), 36.0 (CH_3), 26.1 (CH_2). Data consistent with the literature.[136]

N-Allylaniline (91)



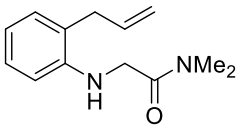
To a stirred solution of aniline (20.0 mL, 215 mmol) in THF (300 mL) was added K_2CO_3 (25 g, 179 mmol) followed by allyl bromide (16.0 mL, 179 mmol). The mixture was heated at 85 °C for 16 h then cooled to rt and filtered. The filtrate was diluted with water (300 mL) and EtOAc (200 mL). The aqueous layer was separated and washed further using EtOAc (2 x 200 mL). The organic extracts were combined and washed further with water (3 x 200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (99:1) to give the aniline **91** (9.3 g, 39%) as a pale yellow oil; R_f 0.59 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25–7.20 (2H, m, 2 × CH), 6.80–6.60 (3H, m, 3 × CH), 6.05–5.96 (1H, m, CH), 5.40–5.15 (2H, m, CH_2), 3.83–3.81 (3H, m, CH_2 & NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.2 (C), 135.5 (CH), 129.3 (CH), 117.6 (CH), 116.2 (CH_2), 113.0 (CH), 46.6 (CH_2). Data consistent with the literature.[137]

2-Allylaniline (92)



To a stirred solution of aniline **91** (1.0 g, 7.5 mmol) in *o*-xylene (5 mL) was added boron trifluoride etherate solution (3.1 mL, 11 mmol, 48% w/v). The mixture was heated at 185 °C in a sealed tube for 2 h. After cooling to rt, the mixture was poured onto aqueous NaOH (10 mL, 10% w/v) and left to stir for 30 min. The organic product was extracted using EtOAc (30 mL), washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a pale brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give the aniline **92** (723 mg, 72%) as an orange oil; R_f 0.14 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.15–7.10 (2H, m, 2 × CH), 6.82–6.70 (2H, m, 2 × CH), 6.07–5.97 (1H, m, CH), 5.22–5.14 (2H, m, 2 × CH), 3.71 (2H, br s, 2 x NH), 3.37 (2H, d, *J* = 6.0 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.9 (C), 136.0 (CH), 130.2 (CH), 127.6 (CH), 124.1 (C), 118.9 (CH), 116.1 (CH_2), 115.9 (CH), 36.5 (CH_2). Data consistent with the literature.[138]

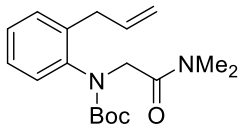
N,N-Dimethyl-2-{[2-(prop-2-en-1-yl)phenyl]amino}acetamide (104)



To a stirred solution of aniline **92** (3.1 g, 23 mmol) in DMF (18 mL) was added bromide **102** (1.9 g, 12 mmol) in DMF (6 mL), followed by dropwise addition of Et_3N (1.6 mL, 12 mmol) in DMF (6 mL). The mixture was stirred for 1.5 h at rt. The mixture was diluted with EtOAc (200 mL) and saturated aqueous $NaHCO_3$ (60 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) to give the amide **104** (1.2 g, 47%) as an orange oil; R_f 0.31 [petrol–EtOAc (1:1)]; FT-IR ν_{max}

(film)/cm^{-1} 3390, 2836, 2344, 1657 (C=O), 1498, 1394, 1125, 910, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 (1H, td, *J* = 7.5, 1.5 Hz, CH), 7.11 (1H, dd, *J* = 7.5, 1.5 Hz, CH), 6.74 (1H, br d, *J* = 7.5 Hz, CH), 6.55 (1H, d, *J* = 8.0 Hz, CH), 6.05–5.95 (1H, m, CH), 5.27–5.16 (2H, m, CH_2), 5.10 (1H, br s, NH), 3.90 (2H, s, CH_2), 3.40 (2H, d, *J* = 6.5 Hz, CH_2), 3.07 (3H, s, CH_3), 3.06 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.2 (C=O), 145.3 (C), 135.6 (CH), 129.8 (CH), 127.6 (CH), 124.3 (C), 117.2 (CH), 116.5 (CH_2), 110.3 (CH), 45.2 (CH_2), 36.4 (CH_2), 35.8 (CH_3), 35.7 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 219.1494. $C_{13}H_{19}N_2O$ requires MH$^+$ 219.1492; LRMS *m/z* (ES) 146 (15%), 219 (100%, MH$^+$).

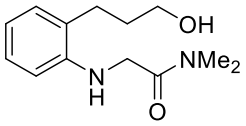
tert-Butyl *N*-[(Dimethylcarbamoyl)methyl]-*N*-[2-(prop-2-en-1-yl)phenyl]carbamate (96)



To a stirred solution of amide **104** (856 mg, 3.92 mmol) in dry THF (4.5 mL) at −78 °C was added *n*-BuLi (2.2 mL, 4.7 mmol, 2.1 M in hexanes). After 10 min, Boc_2O (1.3 g, 5.9 mmol) in dry THF (4.5 mL) was added and the mixture was allowed to warm to rt over 16 h. The reaction mixture was diluted with MeOH (10 mL) and was concentrated under reduced pressure to give a crude residue that was diluted with EtOAc (200 mL) and saturated aqueous $NaHCO_3$ (60 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (3:1) to give the amide **96** (425 mg, 34%) as a brown oil; R_f 0.17 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2919, 1701 (C=O), 1658 (C=O), 1383,1363, 1154, 1025, 726; ^{1}H NMR (400 MHz, $CDCl_3$, rotamer peaks present, asterisks denote minor rotamer peaks) δ = 7.60 (1H, d, *J* = 7.0 Hz, CH), 7.26–7.16 (3H, m, 3 × CH), 6.04–5.87 (1H, m, CH), 5.14–5.04 (2H, m, CH_2), 4.75 (0.7H, d, *J* = 16.5 Hz, CH), 4.59* (0.3H, d, *J* = 16.5 Hz, CH), 3.83–3.68 (1H, m, CH), 3.52–3.31 (2H, m, CH_2), 2.01−2.98 (6H, m, 2 × CH_3) 1.49* (2H, s, *t*-Bu), 1.37 (7H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamer peaks present, asterisks

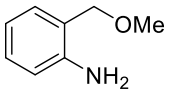
denote minor rotamer peaks) δ = 168.4* (C=O), 168.0 (C=O), 155.3 (C=O), 141.7* (C), 141.5 (C), 137.6* (C), 137.2* (CH), 137.1 (C), 136.9 (CH), 129.8* (CH), 129.7 (CH), 129.5 (CH), 129.2* (CH), 127.5* (CH), 127.4 (CH), 130.0 (CH), 116.1 (CH_2), 115.9* (CH_2), 80.4* (C), 80.3 (C), 52.2* (CH_2), 51.6 (CH_2), 36.2 (CH_3), 35.9 (CH_3), 35.8* (CH_2), 35.5 (CH_2), 28.2 (CH_3); HRMS *m/z* (ES) Found: MH^+, 319.2019. $C_{18}H_{27}N_2O_3$ requires MH^+ 319.2016; LRMS *m/z* (ES) 146 (10%), 219 (100%), 263 (15%), 319 (10%, MH^+), 341 (5%, MNa^+).

2-{[2-(3-Hydroxypropyl)phenyl]amino}-*N,N*-dimethylacetamide (106)



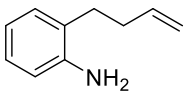
To a stirred solution of amide **104** (371 mg, 1.70 mmol) in dry THF (1.7 mL) at −10 °C was added BH_3•THF complex solution (1.7 mL, 1.7 mmol, 1 M). The mixture was allowed to stir for 2 h at rt and then was cooled to −10 °C. EOH (1 mL), aqueous NaOH (0.33 mL, 6 M) and H_2O_2 (0.66 mL, 30 % w/v) were added dropwise. The mixture was warmed slowly to rt and was heated at 50 °C for 1 h. After cooling to rt, aqueous potassium carbonate (20 mL, 2 M) was added and the organic product was extracted using EtOAc (50 mL). The organic product was washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a pale brown oil. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (99:1) to give the alcohol **106** (162 mg, 40%) as a yellow oil; R_f 0.12 [CH_2Cl_2–MeOH (97:3)]; FT-IR ν_{max} (film)/cm^{-1} 3410 (O-H), 2933, 2869, 1641 (C=O), 1504, 1453, 1396, 1132, 1051, 749, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19–7.08 (2H, m, 2 × CH), 6.73 (1H, t, *J* = 7.5 Hz, CH), 6.54 (1H, d, *J* = 7.5 Hz, CH), 5.09 (1H, br s, NH), 3.92 (2H, s, CH_2), 3.70 (2H, t, *J* = 6.0 Hz, CH_2), 3.07 (3H, s, CH_3), 3.06 (3H, s, CH_3), 2.73 (2H, t, *J* = 6.0 Hz, CH_2), 1.95–1.88 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.5 (C=O), 145.1 (C), 129.8 (CH), 127.2 (CH), 126.5 (C), 117.5 (CH), 110.4 (CH), 61.8 (CH_2), 45.2 (CH_2), 35.9 (CH_3), 35.8 (CH_3), 32.1 (CH_2), 28.0 (CH_2); HRMS *m/z* (ES) Found: MH^+, 237.1602. $C_{13}H_{21}N_2O_2$ requires MH^+ 237.1598; LRMS *m/z* (ES) 237 (100%, MH^+).

2-(Methoxymethyl)aniline (109)



To a stirred solution of 2-aminobenzyl alcohol (20 g, 162 mmol) in MeOH (160 mL) at 0 °C was added concentrated sulfuric acid (10 mL, 179 mmol, 95% w/w) slowly over a period of 5 min. The mixture was heated at 50 °C for 7 h and then was cooled to 0 °C. The mixture was neutralised with saturated aqueous $NaHCO_3$ solution and the organic product was extracted with CH_2Cl_2 (250 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) to give the ether **109** (17 g, 76%) as a yellow oil; R_f 0.37 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (1H, td, *J* = 7.5, 1.5 Hz, CH), 7.09 (1H, dd, *J* = 7.5, 1.5 Hz, CH), 6.76–6.70 (2H, m, 2 × CH), 4.51 (2H, s, CH_2), 4.17 (2H, br s, NH_2), 3.37 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.3 (C), 130.1 (CH), 129.4 (CH), 122.0 (C), 117.9 (CH), 115.7 (CH), 73.7 (CH_2), 57.4 (CH_3). Data consistent with the literature.[60]

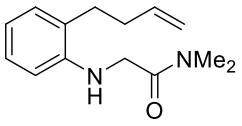
2-(But-3-en-1-yl)aniline (110)



To a stirred solution of ether **109** (9.4 g, 69 mmol) in Et_2O (70 mL) at 0 °C was added allylmagnesium bromide (150 mL, 150 mmol, 1 M in Et_2O) slowly over a period of 20 min. The mixture was warmed to rt over 16 h and then was cooled to 0 °C. Aqueous hydrochloric acid (50 mL, 2 M) was added dropwise to quench any excess Grignard reagent. The organic solvent was removed under reduced pressure and the remaining aqueous layer was adjusted to pH 7 using saturated aqueous $NaHCO_3$ (50 mL). The organic product was extracted using EtOAc (3 x 200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give the aniline **110** (5 g, 50%) as a yellow oil; R_f 0.33

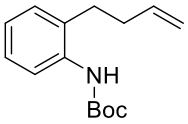
[petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26–7.07 (2H, m, 2 × CH), 6.88–6.71 (2H, m, 2 × CH), 6.01–5.85 (1H, m, CH), 5.17–5.00 (2H, m, CH_2), 3.66 (2H, br s, NH_2), 2.65–2.56 (2H, m, CH_2), 2.46–2.38 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.1 (C), 138.2 (CH), 129.4 (CH), 127.1 (CH), 126.5 (C), 118.8 (CH), 115.6 (CH_2), 115.1 (CH), 32.9 (CH_2), 30.8 (CH_2). Data consistent with the literature.[60]

2-{[2-(But-3-en-1-yl)phenyl]amino}-*N,N*-dimethylacetamide (111)



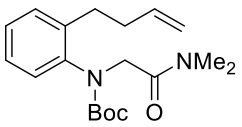
To a stirred solution of aniline **110** (5 g, 34 mmol) in DMF (45 mL) was added bromide **102** (5.6 g, 34 mmol) in DMF (10 mL), followed by dropwise addition of Et_3N (2.4 mL, 17 mmol) in DMF (10 mL). The mixture was stirred at rt for 1 h followed by further addition of bromide **102** (5.6 g, 34 mmol) in DMF (10 mL) and Et_3N (2.4 mL, 17 mmol) in DMF (10 mL). After stirring for a further 1 h at rt, saturated aqueous $NaHCO_3$ (200 mL) was added. The organic product was extracted using EtOAc (500 mL), washed with water (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) to give the amide **111** (4.5 g, 57%) as an amorphous white solid; m.p. 63–65 °C; R_f 0.37 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2934, 1640 (C=O), 1600, 1575, 1511, 1392, 1129, 907, 743; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (1H, td, *J* = 7.5, 1.0 Hz, CH), 7.11 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 6.73 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.55 (1H, d, *J* = 7.5 Hz, CH), 6.00–5.90 (1H, m, CH), 5.15–5.01 (3H, m, CH_2 & NH), 3.91 (2H, s, CH_2), 3.08 (6H, s, 2 × CH_3), 2.72–2.68 (2H, m, CH_2), 2.47–2.42 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.2 (C=O), 145.0 (C), 138.2 (CH), 129.4 (CH), 127.2 (CH), 126.0 (C), 117.1 (CH), 115.1 (CH_2), 110.2 (CH), 45.3 (CH_2), 35.7 (CH_3), 32.6 (CH_2), 30.8 (CH_2); HRMS *m/z* (ES) Found: MH^+, 233.1653. $C_{14}H_{21}N_2O$ requires MH^+ 233.1648; LRMS *m/z* (ES) 160 (5%), 233 (100%, MH^+).

tert-Butyl *N*-[2-(But-3-en-1-yl)phenyl]carbamate (113)



To a stirred solution of aniline **110** (5.8 g, 39 mmol) in THF (36 mL) was added Boc_2O (8.6 g, 39 mmol) and Et_3N (5.5 mL, 39 mmol). The reaction was heated under reflux for 24 h and cooled to rt. The solvent was removed under reduced pressure and the remaining residue was diluted with EtOAc (200 mL), washed with aqueous citric acid (3 x 70 mL, 1 M), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) to give the carbamate **113** (4.7 g, 48%) as a yellow oil; R_f 0.29 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 2980, 1698 (C=O), 1584, 1518, 1443, 1369, 1228, 1154, 1051, 1025, 907, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (1H, d, *J* = 7.5 Hz, CH), 7.25–7.06 (3H, m, 3 × CH), 6.32 (1H, br s, NH), 5.96–5.86 (1H, m, CH), 5.14–5.04 (2H, m, CH_2), 2.69 (2H, t, *J* = 8.0 Hz, CH_2), 2.42–2.36 (2H, m, CH_2), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.4 (C=O), 137.6 (CH), 135.7 (C), 131.9 (C), 129.4 (CH), 126.9 (CH), 124.3 (CH), 122.5 (CH), 115.6 (CH_2), 80.4 (C), 33.8 (CH_2), 30.8 (CH_2), 28.4 (CH_3); HRMS *m/z* (ES) Found: MNa^+, 270.1468. $C_{15}H_{21}NO_2Na$ requires MNa^+ 270.1465; LRMS *m/z* (ES) 132 (5%), 148 (10%), 192 (100%), 270 (5%, MNa^+).

2-{[2-(But-3-en-1-yl)phenyl]amino}-*N,N*-dimethylacetamide (112)



Method A:

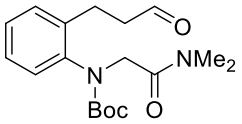
To a stirred solution of amide **111** (200 mg, 0.860 mmol) in dry THF (0.7 mL) at −40 °C was added *n*-BuLi (0.41 mL, 1.03 mmol, 2.5 M in hexanes). After 10 min, Boc_2O (282 mg, 1.29 mmol) in dry THF (1 mL) was added and the mixture was allowed to warm to rt over 16 h. The mixture was diluted with MeOH (5 mL). The solvent was removed under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (3:1) to give the amide **112** (72 mg, 25%) as a brown oil; R_f 0.20 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 3001, 2713, 1789, 1692 (C=O), 1660 (C=O), 1491, 1379, 1322, 1153, 1022, 915, 878, 736, 599; ^{1}H NMR (400 MHz, $CDCl_3$, rotamer peaks present, asterisks denote minor rotamer peaks) δ = 7.60 (1H, d, *J* = 8.0 Hz, CH), 7.27–7.12 (3H, m, 3 × CH), 5.95–5.79 (1H, m, CH), 5.12–4.95 (2H, m, CH_2), 4.80 (0.8H, d, *J* = 16.5 Hz, C*H*^{A}H^B), 4.64* (0.2H, d, *J* = 16.5 Hz, C*H*^{A}H^B), 3.73* (0.2H, d, *J* = 16.5 Hz, CH^A*H*^{B}), 3.67 (0.8H, d, *J* = 16.5 Hz, CH^A*H*^{B}), 3.01−2.97 (6H, m, 2 × CH_3), 2.77–2.58 (2H, m, CH_2), 2.48–2.27 (2H, m, CH_2), 1.47* (2H, s, *t*-Bu), 1.35 (7H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamer peaks present, asterisks denote minor rotamer peaks) δ = 168.3* (C=O), 167.8 (C=O), 155.4 (C=O), 154.6* (C=O), 141.7* (C), 141.4 (C), 139.2* (C), 138.6 (C), 138.5* (CH), 138.1 (CH), 129.6 (CH), 129.3* (CH), 129.2 (CH), 127.5* (CH), 127.4 (CH), 127.1* (CH), 126.7 (CH), 115.1 (CH_2), 114.8* (CH_2), 80.2 (C), 52.2* (CH_2), 51.6 (CH_2), 36.2* (CH_3), 35.9 (CH_3), 34.2 (CH_2), 30.7* (CH_2), 30.5 (CH_2), 28.3 (CH_3); HRMS *m/z* (ES) Found: MH^+, 333.2175. $C_{19}H_{29}N_2O_3$ requires MH^+ 333.2173; LRMS *m/z* (ES) 160 (10%), 233 (100%), 277 (30%), 333 (10%, MH^+).

Method B:

To a stirred suspension of NaH (97 mg, 4.0 mmol) in dry DMF (1 mL) at 0 °C was added carbamate **113** (1 g, 4.0 mmol) in dry DMF (1 mL) dropwise, followed by bromide **102** (0.9 g, 5.3 mmol) in

DMF (1 mL). The mixture was warmed to rt over 16 h. The reaction was quenched with water at 0 °C and diluted with EtOAc (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (4:1) to give the amide **112** (1.0 g, 74%) as an oil; data as above.

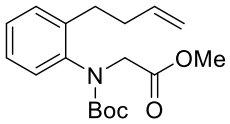
tert-Butyl *N*-[(Dimethylcarbamoyl)methyl]-*N*-[2-(3-oxopropyl)phenyl]carbamate (98)



To a stirred solution of amide **112** (939 mg, 2.82 mmol) in MeOH (14 mL) and water (3.5 mL) was added osmium tetroxide (72 mg, 0.28 mmol) and *N*-methylmorpholine *N*-oxide (2.1 mL, 7.1 mmol, 40% wt in water). The mixture was stirred at rt for 16 h and aqueous sodium sulfite (1 mL, 1 M) was added. The solvent was removed under reduced pressure and the resulting residue was dissolved in EtOAc (100 mL), washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude diol intermediate. The residue was dissolved in MeOH (11 mL) and water (3.3 mL) and cooled to 0 °C. Sodium periodate (905 mg, 4.23 mmol) was added and the mixture was stirred for 2 h at 0 °C. The mixture was filtered, and the solvent was removed under reduced pressure. The organic product was extracted using CH_2Cl_2 (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:1) to give the aldehyde **98** (530 mg, 56%) as a yellow oil; R_f 0.20 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2931, 1698 (C=O), 1658 (C=O), 1383, 1317, 1240, 1154, 1022, 870, 758, 595; ^{1}H NMR (400 MHz, $CDCl_3$, rotamer peaks present, asterisks denote minor rotamer peaks) δ = 9.82 (1H, s, CH), 7.60–7.58 (1H, m, CH), 7.26–7.18 (3H, m, 3 × CH), 4.72 (0.7H, d, J = 16.5 Hz, CH^AH^B), 4.60* (0.3H, d, J = 16.5 Hz, CH^AH^B), 3.89−3.80 (1H, m, CH^AH^B), 3.02–2.77 (10H, m, 2 × CH_3 & 2 × CH_2), 1.47* (3H, s, *t*-Bu), 1.37 (6H,

s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamer peaks present, asterisks denote minor rotamer peaks) δ = 202.2* (CHO), 201.6 (CHO), 168.3* (C=O), 167.7 (C=O), 155.3 (C=O), 154.7* (C=O), 141.7* (C), 141.6 (C), 138.2* (C), 137.5 (C), 129.6 (CH), 129.2* (CH), 129.2* (CH), 128.9 (CH), 127.8* (CH), 127.7 (CH), 127.6* (CH), 127.2 (CH), 80.6* (C), 80.5 (C), 52.2* (CH_2), 51.6 (CH_2), 44.4* (CH_2), 44.1 (CH_2), 36.2* (CH_3), 35.9 (CH_3), 28.3 (CH_3), 28.2* (CH_3), 23.5 (CH_2); HRMS *m/z* (ES) Found: MH^+, 335.1972. $C_{18}H_{27}N_2O_4$ requires MH^+ 335.1965; LRMS *m/z* (ES) 144 (5%), 187 (5%), 217 (100%), 279 (20%), 335 (55%, MH^+), 357 (20%, MNa^+).

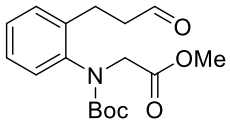
Methyl 2-{[2-(But-3-en-1-yl)phenyl][(*tert*-butoxy)carbonyl]amino}acetate (114)



To a stirred suspension of NaH (97 mg, 4.0 mmol) in dry DMF (1 mL) at 0 °C was added carbamate **113** (1 g, 4 mmol) in dry DMF (1 mL) dropwise, followed by methyl bromoacetate (0.8 g, 5.3 mmol) in DMF (1 mL). The mixture was warmed to rt over 16 h. The reaction was quenched with water at 0 °C and diluted with EtOAc (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) to give ester **114** (957 mg, 74%) as a yellow oil; R_f 0.18 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 2976, 1755 (C=O), 1693 (C=O), 1363, 1206, 1151, 1025, 990, 910, 756, 619; ^{1}H NMR (400 MHz, $CDCl_3$, rotamer peaks present, asterisks denote minor rotamer peaks) δ = 7.44–7.39 (1H, m, CH), 7.29–7.17 (3H, m, 3 × CH), 5.94–5.80 (1H, m, CH), 5.09–4.99 (2H, m, CH_2), 4.62 (0.7H, d, *J* = 17.5 Hz, C*H*^{A}H^B), 4.45* (0.3H, d, *J* = 17.5 Hz, C*H*^{A}H^B), 3.87–3.74 (4H, m, CH^A*H*^{B} & CH_3), 2.75–2.62 (2H, m, CH_2), 2.46–2.27 (2H, m, CH_2), 1.50* (3H, s, *t*-Bu), 1.37 (6H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, rotamer peaks present, asterisks denote minor rotamer peaks) δ = 170.4* (C=O), 170.1 (C=O), 155.2 (C=O), 154.2* (C=O), 141.3* (C), 141.1 (C), 139.5* (C), 138.9 (C), 138.3* (CH), 137.9 (CH), 129.7* (CH), 129.5 (CH), 128.8 (CH), 128.5* (CH), 127.9*

(CH), 127.6 (CH), 127.2* (CH), 126.7 (CH), 115.2 (CH_2), 114.9* (CH_2), 80.9* (C), 80.6 (C), 52.7* (CH_2), 52.1 (CH_3), 51.7 (CH_2), 34.2 (CH_2), 30.5* (CH_2), 30.3 (CH_2), 28.2 (CH_3); HRMS *m/z* (ES) Found: MNa^+, 342.1680. $C_{18}H_{25}NO_4Na$ requires MNa^+ 342.1676; LRMS *m/z* (ES) 160 (5%), 220 (100%), 264 (30%), 342 (10%, MNa^+).

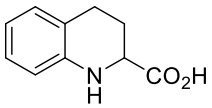
Methyl 2-{[(*tert*-Butoxy)carbonyl][2-(3-oxopropyl)phenyl]amino}acetate (83)



To a stirred solution of ester **114** (750 mg, 2.39 mmol) in MeOH (12 mL) and water (3 mL) was added osmium tetroxide (60 mg, 0.24 mmol) and *N*-methylmorpholine *N*-oxide (1.7 mL, 5.9 mmol, 40% wt in water). The mixture was stirred at rt for 16 h and aqueous sodium sulfite (1 mL, 1 M) was added. The solvent was removed under reduced pressure and the resulting residue was dissolved in EtOAc (100 mL), washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude diol intermediate. The residue was dissolved in MeOH (9.2 mL) and water (2.8 mL) and cooled to 0 °C. Sodium periodate (905 mg, 4.23 mmol) was added and the mixture was stirred for 2 h at 0 °C. The mixture was filtered, and the solvent was removed under reduced pressure. The organic product was extracted using CH_2Cl_2 (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (7:3) to give the aldehyde **83** (393 mg, 52%) as a white amorphous solid; m.p. 55–59 °C [petrol–EtOAc]; R_f 0.34 [petrol–EtOAc (7:3)]; FT-IR ν_{max} (film)/cm^{-1} 2814, 2717, 1745, 1698 (C=O), 1494, 1430, 1395, 1355, 1213, 1156, 1044, 739; ^{1}H NMR (400 MHz, $CDCl_3$, rotamer peaks present, asterisks denote minor rotamer peaks) δ = 9.82 (1H, s, CH), 7.47–7.34 (1H, m, CH), 7.28–7.18 (3H, m, 3 × CH), 4.52 (0.5H, d, *J* = 17.5 Hz, CH^AH^B), 4.40* (0.5H, d, *J* = 17.5 Hz, CH^AH^B), 3.97−3.88 (1H, m, CH^AH^B), 3.77* (1.5H, s, CH_3), 3.76 (1.5H, s, CH_3), 3.03–2.72 (4H, m, 2 × CH_2), 1.48* (4.5H, s, *t*-Bu), 1.37 (4.55H, s, *t*-Bu); ^{13}C NMR

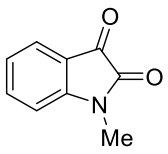
(100 MHz, $CDCl_3$, rotamer peaks present, asterisks denote minor rotamer peaks) δ = 201.8* (CHO), 201.4 (CHO), 170.3* (C=O), 170.0 (C=O), 155.0 (C=O), 154.3* (C=O), 141.3* (C), 141.1 (C), 138.4* (C), 137.8 (C), 129.5* (CH), 129.2 (CH), 128.7 (CH), 128.5* (CH), 128.1* (CH), 127.9 (CH), 127.6* (CH), 127.3 (CH), 81.2* (C), 80.9 (C) 52.6* (CH_2), 52.1 (CH_3), 51.7 (CH_2), 44.3* (CH_2), 44.1 (CH_2), 28.2 (CH_3), 28.1* (CH_3), 23.4 (CH_2); HRMS *m/z* (ES) Found: MNa^+, 344.1476. $C_{17}H_{23}NO_5Na$ requires MNa^+ 344.1468; LRMS *m/z* (ES) 204 (100%), 222 (10%), 344 (15%, MNa^+), 362 (5%, MK^+).

1,2,3,4-Tetrahydroquinoline-2-carboxylic acid (120)



To a stirred solution of quinaldic acid (2.0 g, 11 mmol) in dry MeOH (20 mL) was added PtO_2 (26 mg, 0.12 mmol). The resulting mixture was placed under a hydrogen gas atmosphere (1 atm) for 16 h. The mixture was filtered through a pad of celite, and the solvent was removed under reduced pressure to give the acid **120** (1.7 g, 83%) as a white gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.01–6.93 (2H, m, 2 × CH), 6.70–6.55 (2H, m, 2 × CH), 4.09 (1H, dd, *J* = 5.0, 3.5 Hz, CH), 2.88–2.65 (2H, m, 2 × CH), 2.31–2.05 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.5 (C=O), 142.1 (C), 129.3 (CH), 127.2 (CH), 121.3 (C), 118.2 (CH), 114.9 (CH), 53.2 (CH), 25.1 (CH_2), 24.2 (CH_2). Data consistent with the literature.[139]

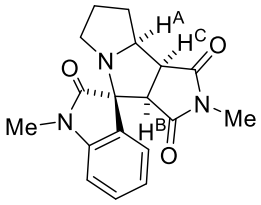
N-Methylisatin (122)



To a stirred solution of isatin (10 g, 68 mmol) in DMF (136 mL) was added methyl iodide (4.2 mL, 68 mmol), followed by potassium carbonate (10 g, 75 mmol). The mixture was left to stir at rt for 16 h. The mixture was diluted with CH_2Cl_2 (600 mL) and water (300 mL). The organic layer was separated and washed with water (2 x 300 mL), dried over anhydrous $MgSO_4$, filtered, and

concentrated under reduced pressure to give *N*-methylisatin **122** (8.5 g, 77%) as an orange amorphous solid; m.p. 122–124 °C [CH_2Cl_2] (lit.[140] 129–130 °C [no solvent]); R_f 0.33 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65–7.61 (2H, m, 2 × CH), 7.16 (1H, td, *J* = 7.5, 0.5 Hz, CH), 6.93–6.91 (1H, m, CH), 3.28 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 183.3 (C=O), 158.2 (C=O), 151.7 (C), 138.4 (CH), 125.3 (CH), 123.9 (CH), 117.5 (C), 109.9 (CH), 26.2 (CH_3). Data consistent with the literature.[141]

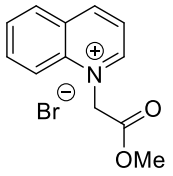
1,2'-Dimethyl-1,2,2',3',3a,3'a,6',7',7a,8',8'a,8'b-dodecahydro-1'H-spiro[indole-3,4'-pyrrolo[3,4-a]pyrrolizine]-1',2,3'-trione (127)



To a stirred solution of *N*-methylisatin **122** (200 mg, 1.24 mmol) in MeOH (3.8 mL) and water (1.3 mL) was added L-proline (143 mg, 1.24 mmol) followed by *N*-methylmaleimide (138 mg, 1.24 mmol). The mixture was heated under reflux at 90 °C for 1 h and cooled to rt. The mixture was poured onto a mixture of aqueous $NaHCO_3$ and ice and was stirred for 5 min. The organic product was extracted using EtOAc (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown solid. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:1) to give the lactam **127** (339 mg, 84%) as a white cubes; m.p. 179–182 °C [petrol–EtOAc]; R_f 0.16 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2961, 2504, 2167, 2037, 1686 (C=O), 1610 (C=O), 1465, 1367, 1121, 969, 766, 672, 498; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 (1H, t, *J* = 7.5 Hz, CH), 7.08 (1H, t, *J* = 7.5 Hz, CH), 6.97 (1H, d, *J* = 7.5 Hz, CH), 6.87 (1H, d, *J* = 7.5 Hz, CH), 4.44 (1H, q, *J* = 7.5 Hz, CH^A), 3.67 (1H, d, *J* = 7.5 Hz, CH^B), 3.51 (1H, t, *J* = 7.5 Hz, CH^C), 3.20 (3H, s, CH_3), 3.06 (3H, s, CH_3), 2.48–2.33 (2H, m, 2 × CH), 2.05–1.88 (4H, m, 4 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.8 (C=O), 176.6 (C=O), 175.5 (C=O), 144.1 (C), 130.0 (CH), 126.5 (CH), 124.3 (C), 122.4 (CH), 108.5 (CH), 68.5 (C), 64.7 (CH), 56.0 (CH), 45.7 (CH), 44.5 (CH_2), 26.1 (CH_2), 26.0

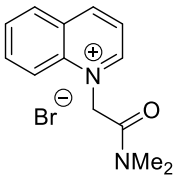
(CH_3), 25.1 (CH_3), 23.6 (CH_2); HRMS *m/z* (ES) Found: MH^+, 326.1505. $C_{18}H_{20}N_3O_2$ requires MH^+ 326.1499; LRMS *m/z* (ES) 121 (20%), 214 (10%), 326 (100%, MH^+); Found: C, 66.54; H, 5.63; N, 12.91. $C_{18}H_{19}N_3O_2$ requires C, 66.45; H, 5.89; N, 12.91.

1-(2-Methoxy-2-oxoethyl)quinolin-1-ium bromide (131)



To a stirred solution of quinoline (4.6 mL, 39 mmol) in PhMe (50 mL) was added methyl bromoacetate (4.0 mL, 43 mmol). The mixture was heated at 65 °C for 16 h and cooled to rt forming an orange suspension. The mixture was filtered, washed with Et_2O (200 mL), and dried to give ester **131** (4.7 g, 43 %) as an orange amorphous solid; m.p. 149–151 °C [Et_2O] (lit.[142] 152–153 °C [no solvent]); ^1H NMR (400 MHz, D_2O) δ = 9.13–9.09 (2H, m, 2 × CH), 8.26 (1H, d, *J* = 8.5 Hz, CH), 8.13–8.08 (2H, m, 2 × CH), 7.97 (1H, dd, *J* = 8.5, 6.0 Hz, CH), 7.91–7.87 (1H, m, CH), 5.89 (2H, s, CH_2), 3.72 (3H, s, CH_3); ^{13}C NMR (100 MHz, D_2O) δ = 167.7 (C=O), 150.2 (CH), 149.6 (CH), 138.6 (C), 136.7 (CH), 131.0 (CH), 130.3 (CH), 130.0 (C), 121.7 (CH), 117.7 (CH), 57.7 (CH_2), 53.9 (CH_3). Data consistent with the literature.[142]

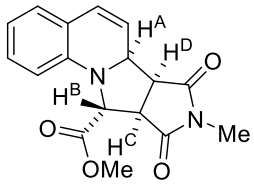
1-[(Dimethylcarbamoyl)methyl]quinolin-1-ium bromide (132)



To a stirred solution of quinoline (1.8 mL, 16 mmol) in PhMe (20 mL) was added bromide **102** (2.8 g, 17 mmol). The mixture was heated at 65 °C for 16 h and cooled to rt forming a light brown suspension. The mixture was filtered, washed with Et_2O (200 mL), and dried to give amide **132** (2.2 g, 47 %) as an off-white amorphous solid; m.p. 175–177 °C [Et_2O]; FT-IR ν_{max} (film)/cm^{-1} 3407,

2911, 1653 (C=O), 1586, 1528, 1405, 1369, 1147, 804, 771, 597, 507; ^{1}H NMR (400 MHz, D_2O) δ = 9.11–9.03 (2H, m, 2 × CH), 8.26 (1H, dd, *J* = 8.0, 1.0 Hz, CH), 8.10–7.86 (4H, m, 4 × CH), 6.02 (2H, s, CH_2), 3.18 (3H, s, CH_3), 2.89 (3H, s, CH_3); ^{13}C NMR (100 MHz, D_2O) δ = 165.5 (C=O), 150.0 (CH), 149.2 (CH), 138.9 (C), 136.4 (CH), 130.8 (CH), 130.2 (CH), 129.9 (C), 121.6 (CH), 117.9 (CH), 58.4 (CH_2), 36.4 (CH_3), 35.9 (CH_3); HRMS *m/z* (ES) Found: M^+−Br, 215.1181. $C_{13}H_{15}N_2OBr$ requires M^+−Br 215.1179; LRMS *m/z* (ES) 215 (100%, M^+−Br).

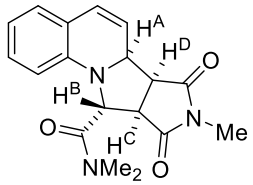
Methyl 13-Methyl-12,14-dioxo-1,13-diazatetracyclo[8.6.0.0²,⁷.0¹¹,¹⁵]hexadeca-2(7),3,5,8-tetraene-16-carboxylate (133)



To a stirred suspension of ester **131** (141 mg, 0.500 mmol) in MeOH (3 mL) was added *N*-methylmaleimide (56 mg, 0.50 mmol) followed by Et_3N (0.07 mL, 0.5 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product as an orange solid. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (3:1) to give ester **133** (120 mg, 77%) as pale yellow needles; m.p. 182–185 °C [petrol–EtOAc]; R_f 0.26 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2934, 1701 (C=O), 1638 (C=O), 1494, 1430, 1374, 1351, 1290, 1136, 1016, 753, 622; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.09 (1H, td, *J* = 7.5, 1.5 Hz, CH), 6.96 (1H, dd, *J* = 7.5, 1.5 Hz, CH), 6.73 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.48 (1H, br d, *J* = 8.0 Hz, CH), 6.39 (1H, dd, *J* = 10.0, 2.0 Hz, CH), 6.07 (1H, dd, *J* = 10.0, 2.0 Hz, CH), 5.13 (1H, dt, *J* = 7.5, 2.0 Hz, CH^A), 4.82 (1H, s, CH^B), 3.82 (3H, s, CH_3), 3.59–3.52 (2H, m, CH^C & CH^D), 2.98 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.6 (C=O), 175.8 (C=O), 170.5 (C=O), 141.1 (C), 129.2 (CH), 127.4 (CH), 126.5 (CH), 121.9 (C), 120.9 (CH), 119.0 (CH), 110.9 (CH), 60.8 (CH), 59.7 (CH), 52.7 (CH_3), 47.7 (CH), 47.0 (CH), 25.5 (CH_3); HRMS *m/z* (ES) Found: MH^+, 313.1188. $C_{17}H_{17}N_2O_4$ requires MH^+

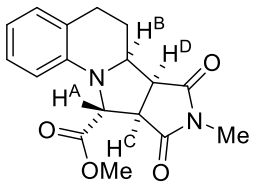
313.1183; LRMS *m/z* (ES) 313 (100%, MH^+), 335 (15%, MNa^+); Found: C, 65.04; H, 5.24; N, 8.58. $C_{17}H_{16}N_2O_4$ requires C, 65.38; H, 5.16; N, 8.97.

N,N,13-Trimethyl-12,14-dioxo-1,13-diazatetracyclo[8.6.0.0²,⁷.0¹¹,¹⁵]hexadeca-2(7),3,5,8-tetraene-16-carboxamide (134)



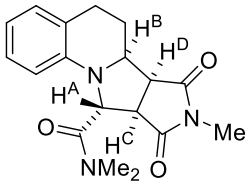
To a stirred suspension of amide **132** (295 mg, 1.00 mmol) in MeOH (6 mL) was added *N*-methylmaleimide (111 mg, 1.00 mmol) followed by Et_3N (0.14 mL, 1.0 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product as an orange solid. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:1) to give amide **134** (282 mg, 87%) as an off-white amorphous solid; m.p. 155–158 °C [petrol–EtOAc]; R_f 0.07 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2671, 1696 (C=O), 1655 (C=O), 1489, 1436, 1290, 1139, 1116, 753, 612; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.07–6.92 (2H, m, 2 × CH), 6.72–6.66 (1H, m, CH), 6.42–6.38 (1H, m, CH), 6.17–6.08 (2H, m, 2 × CH), 5.41 (1H, dt, *J* = 8.0, 2.0 Hz, CH^A), 4.96 (1H, s, CH^B), 3.52–3.49 (1H, m, CH^C), 3.42–3.39 (4H, m, CH^D & CH_3), 3.07 (3H, s, CH_3), 2.97 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.5 (C=O), 176.0 (C=O), 169.5 (C=O), 141.7 (C), 129.1 (CH), 127.4 (CH), 126.4 (CH), 122.4 (C), 121.4 (CH), 118.7 (CH), 110.1 (CH), 60.7 (CH), 59.3 (CH), 47.9 (CH), 47.5 (CH), 37.1 (CH_3), 35.9 (CH_3), 25.4 (CH_3); HRMS *m/z* (ES) Found: MH^+, 326.1506. $C_{18}H_{20}N_3O_3$ requires MH^+ 326.1499; LRMS *m/z* (ES) 229 (15%), 253 (5%), 326 (100%, MH^+).

Methyl 13-Methyl-12,14-dioxo-1,13-diazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5-triene-16-carboxylate (115)



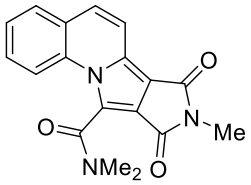
To a stirred solution of ester **133** (100 mg, 0.320 mmol) in EtOAc (6 mL) was added 10% Pd/C (17 mg, 0.016 mmol). The mixture was stirred at rt under a hydrogen gas atmosphere (1 atm) for 48 h. The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give the crude product as a yellow solid. The crude product was purified using a silica gel plug, eluting with petrol–EtOAc (1:1) to give ester **115** (85 mg, 85%) as an off-white amorphous solid; m.p. 163–165 °C [petrol–EtOAc]; R_f 0.26 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2929, 1701 (C=O), 1640 (C=O), 1499, 1436, 1282, 1142, 1006, 755, 617, 587; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.08–7.02 (2H, m, 2 × CH), 6.73 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.54 (1H, d, *J* = 7.5 Hz, CH), 4.91 (1H, s, CH^{A}), 4.17–4.09 (1H, m, CH^{B}), 3.77 (3H, s, CH_3), 3.53–3.49 (2H, m, CH^{C} & CH^{D}), 3.05–2.96 (4H, m, CH & CH_3), 2.88–2.81 (1H, m, CH), 2.47–2.41 (1H, m, CH), 1.63–1.52 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.8 (C=O), 175.6 (C=O), 171.2 (C=O), 142.3 (C), 129.3 (CH), 127.1 (CH), 122.5 (C), 118.7 (CH), 112.2 (CH), 61.0 (CH), 58.0 (CH), 52.4 (CH_3), 48.6 (CH), 47.2 (CH), 27.6 (CH_2), 25.3 (CH_3), 25.2 (CH_2); HRMS *m/z* (ES) Found: MH^{+}, 315.1344. $C_{17}H_{19}N_2O_4$ requires MH^{+} 315.1339; LRMS *m/z* (ES) 315 (100%, MH^{+}), 337 (15%, MNa^{+}).

N,N,13-Trimethyl-12,14-dioxo-1,13-diazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5-triene-16-carboxamide (116)



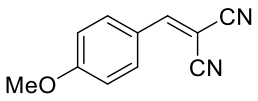
To a stirred solution of amide **134** (100 mg, 0.310 mmol) in EtOAc (6 mL) was added 10% Pd/C (17 mg, 0.016 mmol). The mixture was stirred at rt under a hydrogen gas atmosphere (1 atm) for 48 h. The mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure to give the crude product as a green solid. The crude product was purified using a silica gel plug, eluting with EtOAc to give amide **116** (73 mg, 73%) as a brown amorphous solid; m.p. 195–197 °C [petrol–EtOAc]; R_f 0.07 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2929, 1701 (C=O), 1640 (C=O), 1499, 1436, 1282, 1142, 1006, 755, 617, 587; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.05–6.99 (2H, m, 2 × CH), 6.68 (1H, t, *J* = 7.5 Hz, CH), 6.21 (1H, d, *J* = 7.5 Hz, CH), 5.10 (1H, s, CH^{A}), 4.49–4.43 (1H, m, CH^{B}), 3.51 (1H, t, *J* = 8.5 Hz, CH^{C}), 3.42 (3H, s, CH_3), 3.34 (1H, d, *J* = 8.5 Hz, CH^{D}), 3.11–2.97 (7H, m, CH & 2 × CH_3), 2.88–2.80 (1H, m, CH), 2.47–2.40 (1H, m, CH), 1.66–1.55 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.7 (C=O), 175.9 (C=O), 170.5 (C=O), 142.9 (C), 129.4 (CH), 127.0 (CH), 122.4 (C), 118.3 (CH), 111.1 (CH), 59.0 (CH), 58.8 (CH), 48.8 (CH), 47.5 (CH), 37.0 (CH_3), 35.8 (CH_3), 27.7 (CH_2), 25.4 (CH_2), 25.2 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 328.1661. $C_{18}H_{22}N_3O_3$ requires MH$^+$ 328.1656; LRMS *m/z* (ES) 328 (100%, MH$^+$).

N,N,13-Trimethyl-12,14-dioxo-1,13-diazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5,8,10,15-hexaene-16-carboxamide (135)



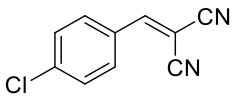
To a suspension of amide **134** (163 mg, 0.500 mmol) in dry THF (2 mL) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (227 mg, 1.00 mmol). The mixture was heated under reflux for 10 min and cooled to rt. The solvent was removed under reduced pressure and the mixture was diluted with CH_2Cl_2 (100 mL) and filtered. The filtrate was concentrated under reduced pressure to obtain the crude product that was purified by column chromatography on silica gel eluting with petrol–EtOAc (3:2) to give amide **135** (92 mg, 57%) as an yellow amorphous solid; m.p. 262–264 °C [petrol–EtOAc]; R_f 0.40 [petrol–EtOAc (1:4)]; FT-IR ν_{max} (film)/cm^{-1} 3054, 2933, 1752, 1693 (C=O), 1632 (C=O), 1567, 1427, 1392, 1348, 979, 958, 818, 757, 736; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (1H, d, *J* = 8.5 Hz, CH), 7.76 (1H, d, *J* = 8.0 Hz, CH), 7.66 (1H, d, *J* = 9.5 Hz, CH), 7.60 (1H, t, *J* = 8.0 Hz, CH), 7.54–7.46 (2H, m, 2 × CH), 3.34 (3H, s, CH_3), 3.29 (3H, s, CH_3), 3.12 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.2 (C=O), 164.0 (C=O), 162.1 (C=O), 133.6 (C), 129.8 (CH), 129.6 (C), 129.5 (CH), 127.8 (CH), 126.0 (CH), 125.0 (C), 124.4 (C), 118.4 (C), 117.3 (CH), 116.8 (CH), 110.9 (C), 38.5 (CH_3), 35.5 (CH_3), 24.2 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 322.1186. $C_{18}H_{16}N_3O_3$ requires MH$^+$ 315.1186; LRMS *m/z* (ES) 201 (25%), 221 (10%), 274 (40%), 322 (55%, MH$^+$), 344 (100%, MNa$^+$), 360 (20%).

2-[(4-Methoxyphenyl)methylidene]propanedinitrile (138a)



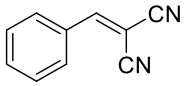
To a stirred solution of malononitrile (363 mg, 5.50 mmol) in absolute EtOH (12 mL) was added anisaldehyde (0.6 mL, 5 mmol) followed by saturated aqueous $NaHCO_3$ (1.5 mL). The mixture was stirred at rt for 1 h. The mixture was filtered to collect the crude product which was recrystallized in absolute EtOH to give arylidenemalononitrile **138a** (681 mg, 74%) as yellow needles; m.p. 111–113 °C [EtOH] (lit.[143] 116–118 °C [no solvent]); R_f 0.55 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95–7.92 (2H, m, 2 × CH), 7.68 (1H, s, CH), 7.06–7.02 (2H, m, 2 × CH), 3.94 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.9 (C), 158.9 (CH), 133.5 (CH), 124.1 (C), 115.2 (CH), 114.5 (CN), 113.4 (CN), 78.6 (C), 55.8 (CH_3). Data consistent with the literature.[143]

2-[(4-Chlorophenyl)methylidene]propanedinitrile (138b)



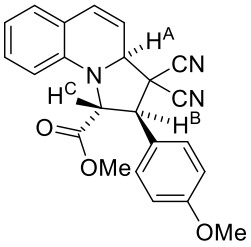
To a stirred solution of malononitrile (363 mg, 5.50 mmol) in absolute EtOH (12 mL) was added 4-chlorobenzaldehyde (0.7 g, 5 mmol) followed by saturated aqueous $NaHCO_3$ (1.5 mL). The mixture was stirred at rt for 1 h. The mixture was filtered to collect the crude product which was recrystallized in absolute EtOH to give arylidenemalononitrile **138b** (700 mg, 74%) as white needles; m.p. 156–158 °C [EtOH] (lit.[143] 167–168 °C [no solvent]); R_f 0.67 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90–7.86 (2H, m, 2 × CH), 7.76 (1H, s, CH), 7.56–7.53 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.3 (CH), 141.2 (C), 131.9 (CH), 130.1 (CH), 129.3 (C), 113.5 (CN), 112.4 (CN), 83.4 (C). Data consistent with the literature.[143]

2-(Phenylmethylidene)propanedinitrile (138c)



To a stirred solution of malononitrile (363 mg, 5.50 mmol) in absolute EtOH (12 mL) was added benzaldehyde (0.5 mL, 5 mmol) followed by saturated aqueous $NaHCO_3$ (1.5 mL). The mixture was stirred at rt for 1 h. The mixture was filtered to collect the crude product which was recrystallized in absolute EtOH to give arylidenemalononitrile **138c** (137 mg, 18%) as white needles; m.p. 83–85 °C [EtOH] (lit.[143] 84–85 °C [no solvent]); R_f 0.63 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95–7.92 (2H, m, 2 × CH), 7.81 (1H, s, CH), 7.69–7.64 (1H, m, CH), 7.59–7.55 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.0 (CH), 134.7 (CH), 130.9 (C), 130.8 (CH), 129.7 (CH), 113.7 (CN), 112.6 (CN), 82.9 (C). Data consistent with the literature.[143]

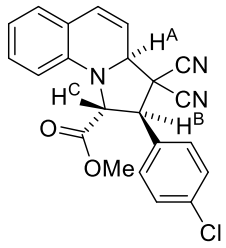
Methyl 3,3-dicyano-2-(4-methoxyphenyl)-1H,2H,3H,3aH-pyrrolo[1,2-a]quinoline-1-carboxylate (139)



To a stirred suspension of ester **131** (282 mg, 1.00 mmol) in MeOH (6 mL) was added arylidenemalononitrile **138a** (184 mg, 1.00 mmol) followed by Et_3N (0.14 mL, 1.0 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product that was purified by column chromatography on silica gel eluting with petrol–EtOAc (9:1) to give ester **139** (245 mg, 64%) as yellow needles; m.p. 130–133 °C [petrol–EtOAc]; R_f 0.59 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2944, 2221, 1737 (C=O), 1604 (C=C), 1571, 1510, 1257, 1177, 1021, 835, 755, 569, 525; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.57–7.54 (2H, m, 2 × CH), 7.21–7.19 (1H, m, CH), 7.07–7.03 (3H, m, 3 × CH), 6.79 (1H,

dd, *J* = 10.0, 2.0 Hz, CH), 6.73–6.69 (1H, m, CH), 6.39 (1H, d, *J* = 8.0 Hz, CH), 5.89 (1H, dd, *J* = 10.0, 2.5 Hz, CH), 5.62 (1H, dd, *J* = 2.5, 2.0 Hz, CH^A), 4.91 (1H, d, *J* = 8.5 Hz, CH^B), 4.57 (1H, d, *J* = 8.5 Hz, CH^C), 3.80 (3H, s, CH_3), 3.67 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, one CH missing/overlapping) δ = 171.0 (C=O), 160.4 (C), 141.5 (C), 130.7 (CH), 130.4 (CH), 128.2 (CH), 124.7 (C), 119.2 (C), 119.1 (CH), 116.3 (CH), 114.9 (CH), 112.9 (2 × CN), 110.7 (CH), 68.5 (CH), 63.0 (CH), 55.7 (CH), 53.6 (CH_3), 53.2 (CH_3), 49.3 (C); HRMS *m/z* (ES) Found: MH^+, 386.1502. $C_{23}H_{20}N_3O_3$ requires MH^+ 386.1499; LRMS *m/z* (ES) 386 (100%, MH^+).

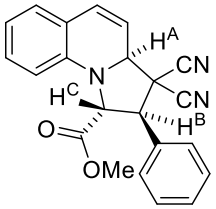
Methyl 2-(4-chlorophenyl)-3,3-dicyano-1H,2H,3H,3aH-pyrrolo[1,2-a]quinoline-1-carboxylate (140)



To a stirred suspension of ester **131** (282 mg, 1.00 mmol) in MeOH (6 mL) was added arylidenemalononitrile **138b** (189 mg, 1.00 mmol) followed by Et_3N (0.14 mL, 1.0 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product that was purified by column chromatography on silica gel eluting with petrol–EtOAc (9:1) to give ester **140** (260 mg, 67%) as a yellow amorphous solid; m.p. 95–98 °C [petrol–EtOAc]; R_f 0.67 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2954, 2489, 2162 (C≡N), 1740 (C=O, 1648 (C=C), 1594, 1453, 1254, 1198, 735, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49–7.47 (4H, m, 4 × CH), 7.16 (1H, td, *J* = 7.5, 1.5 Hz, CH), 7.02 (1H, dd, *J* = 7.5, 1.5 Hz, CH), 6.82–6.74 (2H, m, 2 × CH), 6.40 (1H, dd, *J* = 10.0, 1.5 Hz, CH), 5.81 (1H, dd, *J* = 10.0, 2.5 Hz, CH), 5.64 (1H, dd, *J* = 2.5, 1.5 Hz, CH^A), 4.70 (1H, d, *J* = 8.5 Hz, CH^B), 4.05 (1H, d, *J* = 8.5 Hz, CH^C), 3.81 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.4 (C=O), 141.0 (C), 136.3 (C), 131.3 (CH), 130.6 (CH), 129.8 (2 × CH), 129.7 (C), 128.5 (CH), 119.9 (CH), 119.3 (C), 114.8 (CH), 112.4 (CN), 111.3 (CN), 109.8 (CH), 69.9 (CH), 64.6 (CH), 55.7 (CH), 53.3 (CH_3), 48.5 (C); HRMS *m/z* (ES) Found: MH^+, 390.1007. $C_{22}H_{17}N_3O_2{}^{35}Cl$ requires MH^+ 390.1004; Found: MH^+, 392.0989.

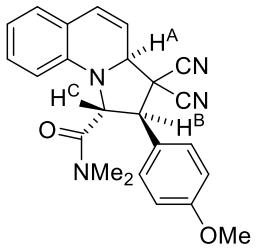
$C_{22}H_{17}N_3O_2{}^{37}Cl$ requires MH^+ 392.0974; LRMS *m/z* (ES) 390 (100%, MH^+ for ^{35}Cl), 392 (35%, MH^+ for ^{37}Cl).

Methyl 3,3-Dicyano-2-phenyl-1H,2H,3H,3aH-pyrrolo[1,2-a]quinoline-1-carboxylate (141)



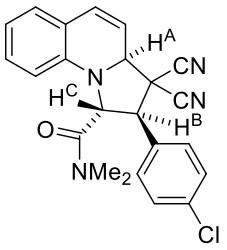
To a stirred suspension of ester **131** (282 mg, 1.00 mmol) in MeOH (6 mL) was added arylidenemalononitrile **138c** (154 mg, 1.00 mmol) followed by Et_3N (0.14 mL, 1.0 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product that was purified by column chromatography on silica gel eluting with petrol–EtOAc (9:1) to give ester **141** (274 mg, 77%) as a yellow amorphous solid; m.p. 111–113 °C [petrol–EtOAc]; R_f 0.63 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 3200, 2952, 2491, 2154 (C≡N), 1735 (C=O), 1647 (C=C), 1594, 1451, 1203, 727, 701; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.57–7.49 (5H, m, 5 × CH), 7.16 (1H, td, *J* = 7.5, 1.5 Hz, CH), 7.02 (1H, dd, *J* = 7.5, 1.5 Hz, CH), 6.82–6.74 (2H, m, 2 × CH), 6.42 (1H, dd, *J* = 8.0, 2.0 Hz, CH), 5.82 (1H, dd, *J* = 8.0, 2.5 Hz, CH), 5.66 (1H, dd, *J* = 2.5, 2.0 Hz, CH^A), 4.77 (1H, d, *J* = 8.5 Hz, CH^B), 4.08 (1H, d, *J* = 8.5 Hz, CH^C), 3.81 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.6 (C=O), 141.1 (C), 131.2 (C), 131.2 (CH), 130.5 (CH), 130.1 (CH), 129.5 (CH), 128.4 (CH), 128.4 (CH), 119.8 (CH), 119.3 (C), 114.9 (CH), 112.6 (CN), 111.4 (CN), 109.8 (CH), 69.9 (CH), 64.6 (CH), 56.3 (CH), 53.2 (CH_3), 48.6 (C); HRMS *m/z* (ES) Found: MH^+, 356.1399. $C_{22}H_{18}N_3O_2$ requires MH^+ 356.1394; LRMS *m/z* (ES) 356 (100%, MH^+).

3,3-Dicyano-2-(4-methoxyphenyl)-*N,N*-dimethyl-1H,2H,3H,3aH-pyrrolo[1,2-a]quinoline-1-carboxamide (142)



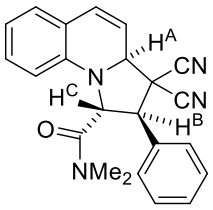
To a stirred suspension of amide **132** (295 mg, 1.00 mmol) in MeOH (6 mL) was added arylidenemalononitrile **138a** (184 mg, 1.00 mmol) followed by Et_3N (0.14 mL, 1.0 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product that was purified by column chromatography on silica gel eluting with petrol–EtOAc (9:1) to give amide **142** (140 mg, 35%) as a light brown amorphous solid; m.p. 133–135 °C [petrol–EtOAc]; R_f 0.32 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2936, 2498, 2156 (C≡N), 1643 (C=O), 1515, 1490, 1456, 1399, 1371, 1255, 1178, 1136, 1119, 1027, 829, 784, 743, 621, 542; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.70–7.67 (2H, m, 2 × CH), 7.11–7.02 (4H, m, 4 × CH), 6.75 (1H, dd, *J* = 10.0, 2.0 Hz, CH), 6.67 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.10 (1H, d, *J* = 7.5 Hz, CH), 5.89 (1H, dd, *J* = 10.0, 2.0 Hz, CH), 5.68 (1H, t, *J* = 2.0 Hz, CH^A), 5.27 (1H, d, *J* = 7.5 Hz, CH^B), 4.22 (1H, d, *J* = 7.5 Hz, CH^C), 3.81 (3H, s, CH_3), 2.83 (3H, s, CH_3), 2.71 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, one CH missing/overlapping) δ = 170.0 (C=O), 160.5 (C), 141.5 (C), 130.9 (CH), 130.5 (CH), 128.0 (CH), 124.6 (C), 119.7 (C), 118.6 (CH), 117.0 (CH), 114.9 (CH), 113.3 (2 × CN), 110.5 (CH), 69.6 (CH), 59.2 (CH), 55.7 (CH_3), 55.4 (CH), 48.8 (C), 37.1 (CH_3), 36.1 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 399.1825. $C_{24}H_{23}N_4O_2$ requires MH$^+$ 399.1816; LRMS *m/z* (ES) 399 (100%, MH$^+$).

2-(4-Chlorophenyl)-3,3-dicyano-*N,N*-dimethyl-1H,2H,3H,3aH-pyrrolo[1,2-a]quinoline-1-carboxamide (143)



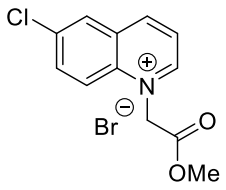
To a stirred suspension of amide **132** (295 mg, 1.00 mmol) in MeOH (6 mL) was added arylidenemalononitrile **138b** (189 mg, 1.00 mmol) followed by Et_3N (0.14 mL, 1.0 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product that was purified by column chromatography on silica gel eluting with petrol–EtOAc (9:1) to give amide **143** (245 mg, 61%) as a light brown amorphous solid; m.p. 120–123 °C; R_f 0.51 [40-60 petroleum ether/ethyl acetate (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 3054, 2936, 2489, 2162, 2026, 1645 (C=O), 1492, 1459, 1402, 1374, 1136, 1088, 1011, 830, 778, 742, 622, 507; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.83–7.80 (2H, m, 2 × CH), 7.61–7.57 (2H, m, 2 × CH), 7.11–7.03 (2H, m, 2 × CH), 6.76 (1H, dd, *J* = 10.0, 1.5 Hz, CH), 6.68 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.13 (1H, d, *J* = 8.0 Hz, CH), 5.91 (1H, dd, *J* = 10.0, 2.0 Hz, CH), 5.70 (1H, t, *J* = 2.0 Hz, CH^A), 5.34 (1H, d, *J* = 7.5 Hz, CH^B), 4.41 (1H, d, *J* = 7.5 Hz, CH^C), 2.84 (3H, s, CH_3), 2.71 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 169.6 (C=O), 141.4 (C), 134.9 (C), 132.3 (C), 131.5 (CH), 130.6 (CH), 130.5 (CH), 129.6 (CH), 128.0 (CH), 119.8 (C), 118.7 (CH), 116.9 (CH), 113.1 (2 × CN), 110.6 (CH), 69.7 (CH), 58.9 (CH), 54.7 (CH), 48.6 (C), 37.1 (CH_3), 36.1 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 403.1322. $C_{23}H_{20}N_4O^{35}Cl$ requires MH$^+$ 403.1320; Found: MH$^+$, 405.1310. $C_{23}H_{20}N_4O^{37}Cl$ requires MH$^+$ 405.1291; LRMS *m/z* (ES) 403 (100%, MH$^+$ for ^{35}Cl), 405 (35%, MH$^+$ for ^{37}Cl).

3,3-Dicyano-*N,N*-dimethyl-2-phenyl-1H,2H,3H,3aH-pyrrolo[1,2-a]quinoline-1-carboxamide (144)



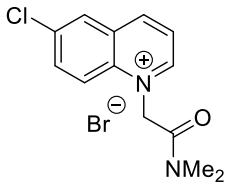
To a stirred suspension of amide **132** (295 mg, 1.00 mmol) in MeOH (6 mL) was added arylidenemalononitrile **138c** (154 mg, 1.00 mmol) followed by Et_3N (0.14 mL, 1.0 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product that was purified by column chromatography on silica gel eluting with petrol–EtOAc (9:1) to give amide **144** (243 mg, 66%) as a light brown amorphous solid; m.p. 87–90 °C [petrol–EtOAc]; R_f 0.28 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 3034, 2492, 2162 (C≡N), 1650 (C=O), 1571, 1597, 1489, 1464, 1400, 1374, 1236, 1134, 740, 699, 625; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.78–7.72 (2H, m, 2 × CH), 7.53–7.45 (3H, m, 3 × CH), 7.11–7.03 (2H, m, 2 × CH), 6.77 (1H, dd, *J* = 10.0, 2.0 Hz, CH), 6.68 (1H, td, *J* = 7.5, 0.5 Hz, CH), 6.14 (1H, d, *J* = 7.5 Hz, CH), 5.91 (1H, dd, *J* = 10.0, 2.0 Hz, CH), 5.71 (1H, t, *J* = 2.0 Hz, CH^A), 5.33 (1H, d, *J* = 7.5 Hz, CH^B), 4.29 (1H, d, *J* = 7.5 Hz, CH^C), 2.83 (3H, s, CH_3), 2.69 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 169.8 (C=O), 141.5 (C), 133.1 (C), 130.5 (CH), 130.5 (CH), 130.1 (CH), 129.6 (CH), 129.6 (CH), 128.1 (CH), 119.8 (C), 118.7 (CH), 116.9 (CH), 113.2 (2 × CN), 110.5 (CH), 69.7 (CH), 59.0 (CH), 55.7 (CH), 48.7 (C), 37.0 (CH_3), 36.1 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 369.1715. $C_{23}H_{21}N_4O$ requires MH$^+$ 369.1710; LRMS *m/z* (ES) 369 (100%, MH$^+$).

6-Chloro-1-(2-methoxy-2-oxoethyl)quinolin-1-ium bromide (146)



To a solution of 6-chloroquinoline (2.0 g, 12 mmol) in PhMe (16 mL) was added methyl bromoacetate (1.3 mL, 14 mmol). The mixture was heated at 65 °C for 16 h and cooled to rt. The mixture was filtered, washed with Et_2O (50 mL), and dried to give ester **146** (417 mg, 11%) as a red amorphous solid; m.p. 184–188 °C [Et_2O]; FT-IR ν_{max} (film)/cm^{-1}: 1744 (C=O), 1216 , 1201, 1170; ^{1}H NMR (400 MHz, D_2O) δ = 9.16−9.00 (2H, m, CH), 8.28 (1H, d, *J* = 2.4 Hz, CH), 8.08-7.98 (3H, m, CH), 5.90 (2H, s, CH_2), 3.72 (3H, s, CH_3); ^{13}C NMR (100 MHz, D_2O) δ = 167.3 (C=O), 150.6 (CH), 148.6 (CH), 137.1 (C), 136.8 (CH), 136.0 (C), 130.6 (C), 129.2 (CH), 122.8 (CH), 119.8 (CH), 57.9 (CH_2), 53.9 (CH_3); HRMS *m/z* (ES) Found: M^+−Br, 236.0475. $C_{12}H_{11}{}^{35}ClNO_2$ requires M^+−Br 236.0473; Found: M^+−Br, 238.0445. $C_{12}H_{11}{}^{37}ClNO_2$ requires M^+−Br 238.0473; LRMS *m/z* (ES) 236 (100%, M^+−Br for ^{35}Cl), 238 (30%, M^+−Br for ^{37}Cl).

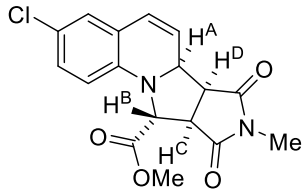
6-Chloro-1-[(dimethylcarbamoyl)methyl]quinolin-1-ium bromide (147)



To a solution of 6-chloroquinoline (714 mg, 4.36 mmol) in PhMe (6 mL) was added bromide **102** (0.52 mL, 4.8 mmol). The mixture was heated at 65 °C for 16 h and cooled to rt. The mixture was filtered, washed with Et_2O (50 mL), and dried to give amide **147** (368 mg, 26%) as a pale yellow powder; m.p. 238–240 °C [Et_2O]; FT-IR ν_{max} (film)/cm^{-1}: 3017 (C-H), 1643 (C=O), 1526, 1401, 1383, 1362, 1257, 1239, 1156, 1041, 900, 852, 798; ^{1}H NMR (400 MHz, D_2O) δ = 9.13−9.05 (2H, m, CH), 8.34 (1H, d, *J* = 6.0 Hz, CH), 8.08−8.03 (3H, m, CH), 6.07 (2H, s, CH_2), 3.23 (3H, s, CH_3),

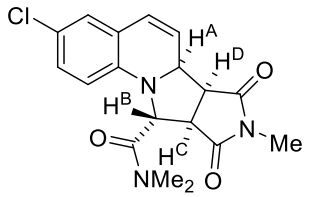
2.95 (3H, s, CH_3); ^{13}C NMR (100 MHz, D_2O) δ = 165.2 (C=O), 150.4 (CH), 148.3 (CH), 137.5 (C), 136.6 (CH), 135.9 (C), 130.6 (C), 129.2 (CH), 122.8 (CH), 120.0 (CH), 58.8 (CH_2), 36.4 (CH_3), 35.9 (CH_3); HRMS *m/z* (ES) Found: M^+−Br, 249.0789. $C_{13}H_{14}{}^{35}ClN_2O$ requires M^+−Br 249.0789; Found: M^+−Br, 251.0764. $C_{13}H_{14}{}^{37}ClN_2O$ requires M^+−Br 251.0760; LRMS *m/z* (ES) 249 (100%, M^+−Br for ^{35}Cl), 251 (30%, M^+−Br for ^{37}Cl).

Methyl 5-Chloro-13-methyl-12,14-dioxo-1,13-diazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5,8-tetraene-16-carboxylate (148)



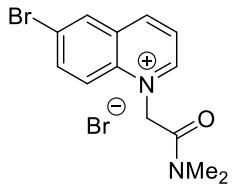
To a stirred suspension of ester **146** (200 mg, 0.630 mmol) in MeOH (4 mL) was added *N*-methylmaleimide (70 mg, 0.63 mmol) followed by Et_3N (0.08 mL, 0.6 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product that was purified by column chromatography on silica gel, eluting with pentane−EtOAc (3:1) to give ester **148** (125 mg, 57%) as a yellow powder; m.p. 158–161 °C [pentane−EtOAc]; R_f 0.38 [petrol−EtOAc (1:1)]; FT-IR ν_{max} /cm^{-1}: 2954 (C=O), 1781 (C=O), 1697 (C=O), 1596, 1489, 1431, 1380, 1285, 1209, 1176 (C-O), 1127, 807 (C-Cl), 759; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.05−6.97 (2H, m, 2 × CH), 6.50 (1H, d, *J* = 8.0 Hz, CH), 6.38 (1H, dd, *J* = 10.0, 2.5 Hz, CH), 6.04 (1H, dd, *J* = 10.0, 2.5 Hz, CH), 4.85 (1H, dt, *J* = 7.5, 2.5 Hz, CH^A), 4.76 (1H, s, CH^B), 3.72 (3H, s, CH_3), 3.71−3.59 (2H, m, CH^C & CH^D), 2.81 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 177.5 (C=O), 176.4 (C=O), 170.4 (C=O), 140.8 (C), 128.7 (CH), 126.7 (CH), 125.1 (CH), 123.8 (CH), 123.4 (C), 122.1 (C), 113.1 (CH), 60.6 (CH_3), 59.5 (CH_3) 53.0 (CH), 47.9 (CH), 47.3 (CH), 25.4 (CH); HRMS *m/z* (ES) Found: MH^+, 347.0789. $C_{17}H_{16}{}^{35}ClN_2O_4$ requires MH^+ 347.0793; Found: MH^+, 349.0771. $C_{17}H_{16}{}^{37}ClN_2O_4$ requires MH^+ 349.0764; LRMS *m/z* (ES) 347 (100%, MH^+ for ^{35}Cl), 349 (35%, MH^+ for ^{37}Cl).

5-Chloro-N,N,13-trimethyl-12,14-dioxo-1,13-diazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5,8-tetraene-16-carboxamide (149)



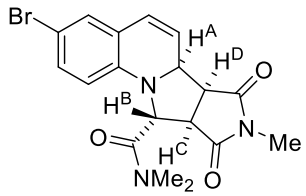
To a stirred suspension of amide **147** (200 mg, 0.600 mmol) in MeOH (4 mL) was added *N*-methylmaleimide (67 mg, 0.60 mmol) followed by Et_3N (0.08 mL, 0.6 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product that was purified by column chromatography on silica gel, eluting with pentane−EtOAc (1:1) to give amide **149** (143 mg, 66%) as a yellow powder; m.p. 182–184 °C [pentane−EtOAc]; R_f 0.17 [petrol−EtOAc (1:1)]; FT-IR ν_{max} /cm^{-1}: 2943, 2814, 1696 (C=O), 1653 (C=O), 1489, 1383, 1292, 1126, 1059, 870, 812, 759; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.00−6.94 (2H, m, 2 × CH), 6.35 (1H, dd, *J* = 10.0, 2.5 Hz, CH), 6.21 (1H, d, *J* = 8.5 Hz, CH), 6.06 (1H, dd, *J* = 10.0, 2.5 Hz, CH), 5.11 (1H, dt, *J* = 7.0, 2.5 Hz, CH^{A}), 4.87 (1H, s, CH^{B}), 3.65−3.52 (2H, m, CH^{C} & CH^{D}), 3.28 (3H, s, CH_3), 2.88 (3H, s, CH_3), 2.84 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 177.3 (C=O), 175.8 (C=O), 169.1 (C=O), 140.4 (C), 128.4 (CH), 126.9 (CH), 125.5 (CH), 123.9 (C), 121.5 (C), 123.0 (CH), 111.3 (CH), 60.6 (CH), 59.2 (CH), 47.5 (CH), 47.5 (CH), 37.1 (CH_3), 35.9 (CH_3), 25.5 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 360.1110. $C_{18}H_{19}{}^{35}ClN_3O_3$ requires MH$^+$ 360.1109; Found: MH$^+$, 362.1091. $C_{18}H_{19}{}^{37}ClN_3O_3$ requires MH$^+$ 362.1080; LRMS *m/z* (ES) 360 (100%, MH$^+$ for ^{35}Cl), 362 (30%, MH$^+$ for ^{37}Cl).

6-Bromo-1-[(dimethylcarbamoyl)methyl]quinolin-1-ium bromide (152)



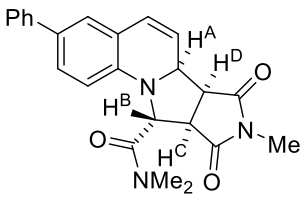
To a stirred solution of 6-bromoquinoline (2.0 mL, 14 mmol) in PhMe (18 mL) was added bromide **102** (2.6 g, 16 mmol). The mixture was heated at 65 °C for 16 h and cooled to rt forming an orange suspension. The mixture was filtered, washed with Et_2O (100 mL), and dried to give amide **152** (2.4 g, 45 %) as a pale orange amorphous solid; m.p. 248–250 °C [Et_2O]; FT-IR ν_{max} (film)/cm^{-1} 3072, 3013, 1642 (C=O), 1592, 1553, 1403, 1383, 1358, 1263, 1155, 887, 845, 798; ^{1}H NMR (400 MHz, D_2O) δ = 9.21 (1H, d, *J* = 6.0 Hz, CH), 9.16 (1H, d, *J* = 8.5 Hz, CH), 8.62 (1H, d, *J* = 2.0 Hz, CH), 8.30 (1H, dd, *J* = 9.5, 2.0 Hz, CH), 8.15 (1H, dd, *J* = 8.5, 6.0 Hz, CH), 8.07 (1H, d, *J* = 9.5 Hz, CH), 6.15 (2H, s, CH_2), 3.31 (3H, s, CH_3), 3.03 (3H, s, CH_3); ^{13}C NMR (100 MHz, D_2O) δ = 165.2 (C=O), 150.5 (CH), 148.2 (CH), 139.2 (CH), 137.8 (C), 132.6 (CH), 130.9 (C), 124.0 (C), 122.7 (CH), 119.8 (CH), 58.7 (CH_2), 36.4 (CH_3), 35.9 (CH_3); HRMS *m/z* (ES) Found: M^+−Br, 293.0. $C_{13}H_{14}{}^{79}BrN_2O$ requires M^+−Br 293.0284; Found: M^+−Br, 295.0. $C_{13}H_{14}{}^{81}BrN_2O$ requires M^+−Br 295.0264; LRMS *m/z* (ES) 293 (100%, M^+−Br for ^{79}Br), 294 (15%), 295 (100%, M^+−Br for ^{81}Br), 296 (15%).

5-Bromo-N,N,13-trimethyl-12,14-dioxo-1,13-diazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5,8-tetraene-16-carboxamide (153)



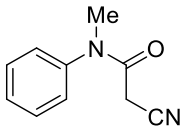
To a stirred suspension of amide **152** (200 mg, 0.538 mmol) in MeOH (3 mL) was added *N*-methylmaleimide (60 mg, 0.54 mmol) followed by Et_3N (0.08 mL, 0.5 mmol). The mixture was heated under reflux for 1 h and cooled to rt. The solvent was removed under reduced pressure to obtain the crude product as an orange solid. The crude product was purified by column chromatography on silica gel, eluting with EtOAc to give amide **153** (145 mg, 67%) as an off-white amorphous solid; m.p. 196–198 °C [EtOAc]; R_f 0.19 [EtOAc]; FT-IR ν_{max} (film)/cm^{-1} 3011, 2935, 1695 (C=O), 1645 (C=O), 1587, 1486, 1439, 1383, 1288, 1149, 817, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.08 (1H, dd, *J* = 8.5, 2.0 Hz, CH), 7.02 (1H, d, *J* = 2.0 Hz, CH), 6.29 (1H, dd, *J* = 10.0, 2.0 Hz, CH), 6.13 (1H, d, *J* = 10.0 Hz, CH), 5.96 (1H, d, *J* = 8.0 Hz, CH), 5.36 (1H, d, *J* = 8.0 Hz, CH^{A}), 4.85 (1H, s, CH^{B}), 3.48 (1H, t, *J* = 8.0 Hz, CH^{C}), 3.41–3.33 (4H, m, CH^{D} & CH_3), 3.03 (3H, s, CH_3), 2.97 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.2 (C=O), 175.7 (C=O), 169.0 (C=O), 140.8 (C), 131.3 (CH), 129.7 (CH), 125.4 (CH), 124.3 (C), 122.9 (CH), 111.7 (CH), 110.6 (C), 60.6 (CH), 59.2 (CH), 47.6 (CH), 47.5 (CH), 37.0 (CH_3), 35.9 (CH_3), 25.5 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 404.0593. $C_{18}H_{19}{}^{79}BrN_3O_3$ requires MH$^+$ 404.0604; Found: MH$^+$, 406.0584. $C_{18}H_{19}{}^{81}BrN_3O_3$ requires M$^+$ 406.0584; LRMS *m/z* (ES) 404 (100%, MH$^+$ for ^{79}Br), 405 (20%), 406 (100%, MH$^+$ for ^{81}Br), 407 (20%), 426 (30%, MNa$^+$ for ^{79}Br), 427 (10%), 428 (30%, MNa$^+$ for ^{81}Br), 429 (10%).

1,1'-Biphenyl; N,N,13-trimethyl-12,14-dioxo-1,13-diazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5,8-tetraene-16-carboxamide (150)



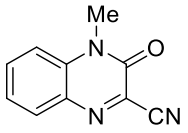
A mixture of amide **153** (91 mg, 0.23 mmol), phenyl boronic acid (36 mg, 0.30 mmol), tetrakis(triphenylphosphine)palladium(0) (14 mg, 0.012 mmol) and Na_2CO_3 (105 mg, 0.988 mmol) in PhMe (0.2 mL), H_2O (0.2 mL), and EtOH (0.1 mL) was heated at 75 °C for 16 h. After cooling to rt, the mixture was filtered through a pad of celite. The filtrate was diluted with water (10 mL) and CH_2Cl_2 (25 mL). The organic layer was separated and washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:4) to give amide **150** (55 mg, 61%) as an off-white amorphous solid; m.p. 200–202 °C [petrol–EtOAc]; R_f 0.17 [petrol−EtOAc (1:3)]; FT-IR ν_{max} (film)/cm^{-1} 3061, 2960, 2822, 1708 (C=O), 1642 (C=O), 1482, 1431, 1378, 1288, 1131, 769, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 (2H, dd, *J* = 8.0, 1.0 Hz, 2 × CH), 7.37 (2H, t, *J* = 7.5 Hz, 2 × CH), 7.30–7.23 (2H, m, 2 × CH), 7.17 (1H, d, *J* = 2.0 Hz, CH), 6.45 (1H, dd, *J* = 10.0, 2.5 Hz, CH), 6.21 (1H, d, *J* = 8.0 Hz, CH), 6.14 (1H, dd, *J* = 10.0, 2.0 Hz, CH), 5.42 (1H, dt, *J* = 8.0, 2.0 Hz, CH^{A}), 4.98 (1H, s, CH^{B}), 3.51 (1H, t, *J* = 8.0 Hz, CH^{C}), 3.43–3.37 (4H, m, CH^{D} & CH_3), 3.05 (3H, s, CH_3), 2.96 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, one CH missing/overlapping) δ = 177.4 (C=O), 175.9 (C=O), 169.4 (C=O), 141.2 (C), 141.0 (C), 131.9 (C), 128.7 (CH), 127.7 (CH), 126.42 (CH), 126.37 (CH), 126.1 (CH), 122.7 (C), 121.9 (CH), 110.5 (CH), 60.8 (CH), 59.4 (CH), 47.9 (CH), 47.6 (CH), 37.1 (CH_3), 35.9 (CH_3), 25.4 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 402.1821. $C_{24}H_{24}N_3O_3$ requires MH$^+$ 402.1812; LRMS *m/z* (ES) 241 (5%), 261 (15%), 402 (100%, MH$^+$), 424 (30%, MNa$^+$), 440 (10% MK$^+$).

2-Cyano-*N*-methyl-*N*-phenylacetamide (157)



To a stirred suspension of cyanoacetic acid (2.2 g, 26 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added oxalyl chloride (2.0 mL, 24 mmol), followed by DMF (12 drops). The mixture was warmed up to rt. After 3 h, *N*-methylaniline (2.2 mL, 20 mmol) in CH_2Cl_2 (80 mL) was added, followed by dropwise addition of Et_3N (7.0 mL, 70 mmol) at 0 °C. The mixture was warmed to rt and stirred for 17 h. Water (40 mL) was added, and the organic layer was separated and washed with aqueous HCl (40 mL, 1 M). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a pale orange solid. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:1) to give amide **157** (3.4 g, 98%) as an off-white amorphous solid; m.p. 74–76 °C [petrol–EtOAc] (lit.[144] 76–79 °C [EtOH]); R_f 0.24 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58–7.39 (3H, m, 3 × CH), 7.33–7.20 (2H, m, 2 × CH), 3.34 (3H, s, CH_3), 3.25 (2H, s, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.7 (C=O), 142.4 (C), 130.5 (CH), 129.1 (CH), 127.1 (CH), 114.1 (CN), 37.9 (CH_3), 25.4 (CH_2). Data consistent with the literature.[144]

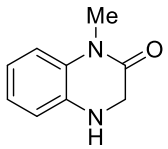
4-Methyl-3-oxo-3,4-dihydroquinoxaline-2-carbonitrile (158)



To a stirred solution of amide **157** (1 g, 6 mmol) in MeCN (29 mL) was added *tert*-butyl nitrite (3.5 mL, 29 mmol), Cs_2CO_3 (3.7 g, 12 mmol), glacial acetic acid (1.6 mL, 29 mmol) and 4 Å MS (2.9 g). The mixture was stirred at 100 °C for 6 h. $Na_2S_2O_4$ (3.5 g, 20 mmol) in a mixture of EtOH (57 mL) and water (115 mL) was added and the mixture was heated for a further 2 h at 90 °C. After cooling the mixture to rt the organic product was extracted using EtOAc (2 × 250 mL) and washed with aqueous $NaHCO_3$ (150 mL), brine (150 mL), dried over anhydrous $MgSO_4$, filtered, and

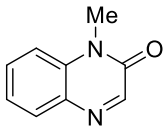
concentrated under reduced pressure to give the crude product as an orange solid. The crude product was flushed through a silica gel plug, eluting with petrol–EtOAc (3:2) to give crude nitrile **158** (0.8 g, 74%) as a yellow amorphous solid. The material was used without further purification.

1-Methyl-1,2,3,4-tetrahydroquinoxalin-2-one (159)



To a solution of crude nitrile **158** (567 mg, 3.06 mmol) in dry THF (12 mL) was added $NaBH_4$ (579 mg, 15.3 mmol). The reaction mixture was heated at 50 °C for 1 h. After cooling to rt the mixture was diluted with water (50 mL) and EtOAc (150 mL). The organic layer was separated and washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a red oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:1) to give amine **159** (370 mg, 75%) as orange oil which crystallised on standing to give an orange solid. m.p. 52–54 °C [petrol–EtOAc]; R_f 0.23 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.96 (1H, d, *J* = 8.5 Hz, CH), 6.90–6.81 (1H, m, CH), 6.78–6.68 (2H, m, 2 × CH), 6.05 (1H, br s, NH), 3.77 (2H, s, CH_2), 3.23 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.8 (C=O), 137.1 (C), 129.0 (C), 123.6 (CH), 118.6 (CH), 115.1 (CH), 114.0 (CH), 47.2 (CH_2), 28.6 (CH_3). Data consistent with the literature (no lit. m.p. given).[72]

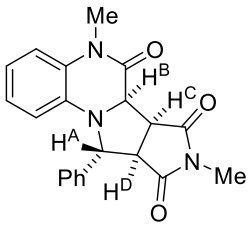
1-Methyl-1,2-dihydroquinoxalin-2-one (161)



To a solution of amine **159** (100 mg, 0.617 mmol) in dry PhMe (2.5 mL) was added CSA (14 mg, 0.060 mmol). The mixture was heated under reflux for 17 h under air. After cooling to rt, the mixture was diluted with EtOAc (150 mL) and water (50 mL). The organic layer was separated, washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow solid. The crude product was purified by column

chromatography on silica gel, eluting with petrol–EtOAc (1:1) to give a mixture (ratio 1:1.2) of amine **159** and imine **161** as an orange solid (24 mg, 24%). Data for imine **161**: ^{1}H NMR (400 MHz, DMSO-d^{6}) δ = 8.24 (1H, s, CH), 7.82 (1H, dd, *J* = 8.0, 1.5 Hz, CH), 7.71–7.63 (1H, m, CH), 7.62–7.55 (1H, m, CH), 7.44–7.35 (1H, m, CH), 3.60 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 154.8 (C=O), 150.6 (CH), 133.6 (C), 133.1 (C), 131.5 (CH), 130.0 (CH), 123.9 (CH), 115.4 (CH), 29.0 (CH_3). Data consistent with the literature.[145]

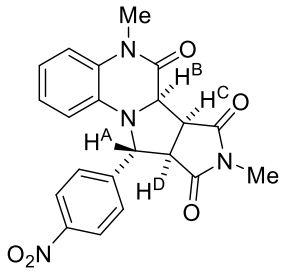
8,13-Dimethyl-16-phenyl-1,8,13-triazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5-triene-9,12,14-trione (160)



To a solution of amine **159** (75 mg, 0.46 mmol) in dry PhMe (2.5 mL) was added benzaldehyde (0.03 mL, 0.3 mmol), *N*-methylmaleimide (34 mg, 0.31 mmol), CSA (11 mg, 0.046 mmol) and 4 Å MS (200 mg). The mixture was heated under reflux for 16 h under an argon atmosphere and cooled to rt. The mixture was filtered and concentrated under reduced pressure. The organic product was extracted using EtOAc (150 mL) and washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (17:3) to give cycloadduct **160** (77 mg, 69%) as a pale yellow amorphous solid; m.p. 210–212 °C [petrol–EtOAc]; R_f 0.13 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 3072, 2955, 2163, 1982, 1698 (C=O), 1648 (C=O), 1592 (C=O), 1525, 1380, 1252, 1130, 1037, 996, 854, 739, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48–7.30 (5H, m, 5 × CH), 7.03–6.78 (3H, m, 3 × CH), 6.59 (1H, dd, *J* = 8.0, 1.0 Hz, CH), 5.57 (1H, d, *J* = 1.5 Hz, CH^{A}), 4.76 (1H, d, *J* = 7.0 Hz, CH^{B}), 3.81 (1H, t, *J* = 7.0 Hz, CH^{C}), 3.57 (1H, dd, *J* = 7.0, 1.5 Hz, CH^{D}), 3.49 (3H, s, CH_3), 2.80 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.0 (C=O), 174.8 (C=O), 162.8 (C=O), 138.1 (C), 132.5 (C), 129.3 (CH), 128.0 (CH), 127.6 (C), 125.9 (CH), 124.1 (CH), 119.6 (CH), 114.7 (CH), 111.8 (CH),

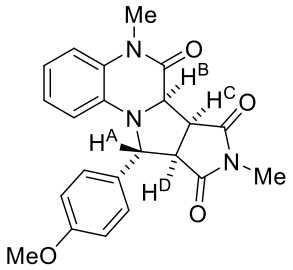
65.7 (CH), 61.5 (CH), 51.5 (CH), 48.9 (CH), 28.9 (CH_3), 25.3 (CH_3); HRMS *m/z* (ES) Found: MH^+, 362.1497 $C_{21}H_{20}N_3O_3$ requires MH^+ 362.1499; LRMS *m/z* (ES) 362 (100%, MH^+), 384 (50%, MNa^+).

8,13-Dimethyl-16-(4-nitrophenyl)-1,8,13-triazatetracyclo[8.6.0.0^{2,7}.0^{11,15}]hexadeca-2(7),3,5-triene-9,12,14-trione (164)



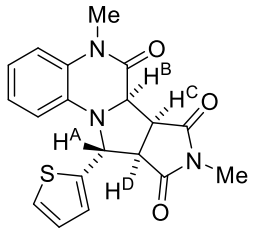
To a solution of amine **159** (75 mg, 0.46 mmol) in dry PhMe (2.5 mL) was added 4-nitrobenzaldehyde (47 mg, 0.31 mmol), *N*-methylmaleimide (34 mg, 0.31 mmol), CSA (11 mg, 0.046 mmol) and 4 Å MS (200 mg). The mixture was heated under reflux for 16 h under an argon atmosphere and cooled to rt. The mixture was filtered and concentrated under reduced pressure. The organic product was extracted using EtOAc (150 mL) and washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:1) to give cycloadduct **164** (58 mg, 46%) as a pale yellow amorphous solid; m.p. 248–250 °C [petrol–EtOAc]; R_f 0.09 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1}; 3076, 2984, 1705 (C=O), 1674 (C=O), 1592, 1432, 1392, 1381, 1287, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (2H, d, *J* = 8.5 Hz, 2 × CH), 7.62 (2H, d, *J* = 8.5 Hz, 2 × CH), 7.07–6.84 (3H, m, 3 × CH), 6.49 (1 H, d, *J* = 7.5 Hz, CH), 5.58 (1H, s, CH^A), 4.72 (1H, d, *J* = 7.0 Hz, CH^B), 3.86 (1 H, t, *J* = 7.0 Hz, CH^C), 3.59–3.47 (4H, m, CH^D & CH_3), 2.82 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.3 (C=O), 174.3 (C=O), 162.2 (C=O), 147.7 (C), 145.8 (C), 131.9 (C), 127.7 (C), 127.2 (CH), 124.6 (CH), 124.2 (CH), 120.4 (CH), 115.1 (CH), 111.8 (CH), 65.8 (CH), 61.7 (CH), 51.5 (CH), 48.8 (CH), 29.0 (CH_3), 25.5 (CH_3); HRMS *m/z* (ES) Found: MH^+, 407.1356. $C_{21}H_{19}N_4O_5$ requires MH^+ 407.1356; LRMS *m/z* (ES) 407 (100%, MH^+), 429 (95%, MNa^+).

16-(4-Methoxyphenyl)-8,13-dimethyl-1,8,13-triazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5-triene-9,12,14-trione (165)



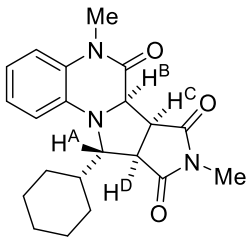
To a solution of amine **159** (75 mg, 0.46 mmol) in dry PhMe (2.5 mL) was added 4-methoxybenzaldehyde (0.04 mL, 0.3 mmol), *N*-methylmaleimide (34 mg, 0.31 mmol), CSA (11 mg, 0.046 mmol) and 4 Å MS (200 mg). The mixture was heated under reflux for 16 h under an argon atmosphere and cooled to rt. The mixture was filtered and concentrated under reduced pressure. The organic product was extracted using EtOAc (150 mL) and washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:1) to give cycloadduct **165** (32 mg, 27%) as an off-white amorphous solid; m.p. 198–200 °C [petrol–EtOAc]; R_f 0.13 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 3063, 2935, 2835, 1778, 1698 (C=O), 1670 (C=O), 1596, 1511, 1432, 1383, 1248, 1179, 1027, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (2H, d, *J* = 8.5 Hz, 2 × CH), 7.00–6.88 (4H, m, 4 × CH), 6.83 (1H, td, *J* = 8.0, 1.5 Hz, CH), 6.61 (1H, d, *J* = 8.0 Hz, CH), 5.53 (1H, br s, CH^{A}), 4.73 (1H, d, *J* = 7.0 Hz, CH^{B}), 3.83 (3H, s, CH_3), 3.80 (1H, t, *J* = 7.0 Hz, CH^{C}), 3.55 (1H, dd, *J* = 7.0, 2.0 Hz, CH^{D}), 3.48 (3H, s, CH_3), 2.78 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.0 (C=O), 174.8 (C=O), 162.8 (C=O), 159.3 (C), 132.6 (C), 129.9 (C), 127.6 (C), 127.2 (CH), 124.1 (CH), 119.6 (CH), 114.7 (CH), 114.6 (CH), 111.8 (CH), 65.4 (CH), 61.5 (CH), 55.4 (CH_3), 51.5 (CH), 48.8 (CH), 28.8 (CH_3), 25.2 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 392.1616. $C_{22}H_{22}N_3O_4$ requires MH$^+$ 392.1605; LRMS *m/z* (ES) 392 (100%, MH$^+$), 414 (30%, MNa$^+$).

8,13-Dimethyl-16-(thiophen-2-yl)-1,8,13-triazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5-triene-9,12,14-trione (166)



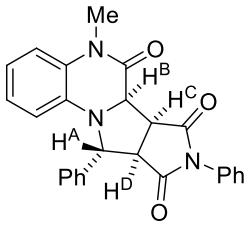
To a solution of amine **159** (75 mg, 0.46 mmol) in dry PhMe (2.5 mL) was added 2-thiophenecarbaldehyde (0.03 mL, 0.3 mmol), *N*-methylmaleimide (34 mg, 0.31 mmol), CSA (11 mg, 0.046 mmol) and 4 Å MS (200 mg). The mixture was heated under reflux for 16 h under an argon atmosphere and cooled to rt. The mixture was filtered and concentrated under reduced pressure. The organic product was extracted using EtOAc (150 mL) and washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:1) to give cycloadduct **166** (67 mg, 59%) as an off-white amorphous solid; m.p. 248–250 °C [petrol–EtOAc]; R_f 0.14 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 3103, 2945, 1780, 1698 (C=O), 1670 (C=O), 1593, 1471, 1418, 1282, 1093, 979, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 (1H, dd, *J* = 5.0, 1.0 Hz, CH), 7.09 (1H, dt, *J* = 3.5, 1.0 Hz, CH), 7.03 (1H, dd, *J* = 5.0, 3.5 Hz, CH), 6.99–6.94 (2H, m, 2 × CH), 6.90–6.81 (2H, m, 2 × CH), 5.85 (1H, br s, CH^{A}), 4.74 (1H, d, *J* = 7.5 Hz, CH^{B}), 3.84 (1H, t, *J* = 7.5 Hz, CH^{C}), 3.68 (1H, dd, *J* = 7.5, 1.0 Hz, CH^{D}), 3.45 (3H, s, CH_3), 2.72 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.3 (C=O), 174.5 (C=O), 162.8 (C=O), 141.9 (C), 132.1 (C), 128.1 (C), 127.3 (CH), 125.8 (CH), 125.7 (CH), 124.0 (CH), 121.0 (CH), 114.9 (CH), 112.3 (CH), 62.5 (CH), 61.4 (CH), 51.5 (CH), 48.0 (CH), 28.9 (CH_3), 25.2 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 368.1000. $C_{19}H_{18}N_3O_3S$ requires MH$^+$ 368.1063; LRMS *m/z* (ES) 368 (100%, MH$^+$), 390 (32%, MNa$^+$).

16-Cyclohexyl-8,13-dimethyl-1,8,13-triazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5-triene-9,12,14-trione (167)



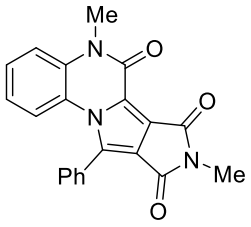
To a solution of amine **159** (75 mg, 0.46 mmol) in dry PhMe (2.5 mL) was added cyclohexanecarbaldehyde (0.04 mL, 0.3 mmol), *N*-methylmaleimide (34 mg, 0.31 mmol), CSA (11 mg, 0.046 mmol) and 4 Å MS (200 mg). The mixture was heated under reflux for 16 h under an argon atmosphere and cooled to rt. The mixture was filtered and concentrated under reduced pressure. The organic product was extracted using EtOAc (150 mL) and washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (17:3) to give cycloadduct **167** (35 mg, 31%) as an off-white amorphous solid; m.p. 248–250 °C [petrol–EtOAc]; R_f 0.21 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 2924, 2848, 1701 (C=O), 1670 (C=O), 1596, 1479, 1430, 1399, 1298, 1280, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.99–6.86 (2H, m, 2 × CH), 6.80–6.73 (2H, m, 2 × CH), 4.46 (1H, d, *J* = 7.0 Hz, CH^{B}), 4.22 (1H, d, *J* = 10.0 Hz, CH^{A}), 3.67 (1H, t, *J* = 7.0 Hz, CH^{C}), 3.45 (3H, s, CH_3), 3.27 (1H, d, *J* = 7.0 Hz, CH^{D}), 2.51 (3H, s, CH_3), 2.03–1.88 (3H, m, 3 × CH), 1.82–1.71 (2H, m, 2 × CH), 1.54–1.41 (1H, m, CH), 1.37–1.00 (5H, m, 5 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.7 (C=O), 175.4 (C=O), 162.4 (C=O), 134.1 (C), 127.0 (C), 124.2 (CH), 119.6 (CH), 114.9 (CH), 111.3 (CH), 70.7 (CH), 61.5 (CH), 49.0 (CH), 46.2 (CH), 39.7 (CH), 30.2 (CH_2), 30.0 (CH_2), 28.8 (CH_3), 26.2 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 24.9 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 368.1967. $C_{21}H_{25}N_3O_3$ requires MH$^+$ 368.1969; LRMS *m/z* (ES) 368 (100%, MH$^+$), 390 (45%, MNa$^+$).

8-Methyl-13,16-diphenyl-1,8,13-triazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5-triene-9,12,14-trione (169)



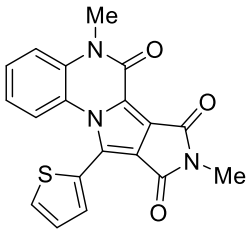
To a solution of amine **159** (75 mg, 0.46 mmol) in dry PhMe (2.5 mL) was added benzaldehyde (0.03 mL, 0.3 mmol), *N*-phenylmaleimide (53 mg, 0.31 mmol), CSA (11 mg, 0.046 mmol) and 4 Å MS (200 mg). The mixture was heated under reflux for 16 h under an argon atmosphere and cooled to rt. The mixture was filtered and concentrated under reduced pressure. The organic product was extracted using EtOAc (150 mL) and washed with water (2 x 20 mL), brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (17:3) to give cycloadduct **169** (51 mg, 39%) as an off-white amorphous solid; m.p. 248–250 °C [petrol–EtOAc]; R_f 0.33 [petrol–EtOAc (1:1)]; FT-IR ν_{max} (film)/cm^{-1} 3064, 2924, 1707 (C=O), 1670 (C=O), 1593, 1504, 1394, 1303, 1191, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56–7.31 (8H, m, 8 × CH), 7.05–6.88 (3H, m, 3 × CH), 6.84 (1H, d, *J* = 7.5 Hz, CH), 6.76–6.69 (2H, m, 2 × CH), 5.87 (1H, br s, CH^{A}), 4.71 (1H, d, *J* = 7.5 Hz, CH^{B}), 3.94 (1H, t, *J* = 7.5 Hz, CH^{C}), 3.81 (1H, dd, *J* = 7.5, 1.5 Hz, CH^{D}), 3.48 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.1 (C=O), 173.9 (C=O), 162.3 (C=O), 138.0 (C), 133.2 (C), 131.4 (C), 129.3 (CH), 129.0 (CH), 128.8 (CH), 128.2 (CH), 127.8 (C), 126.2 (CH), 125.9 (CH), 124.4 (CH), 120.3 (CH), 115.2 (CH), 112.0 (CH), 67.3 (CH), 62.1 (CH), 51.3 (CH), 49.3 (CH), 28.9 (CH_3); HRMS *m/z* (ES) Found: MH^{+}, 424.1659. $C_{26}H_{22}N_3O_3$ requires MH^{+} 424.1656; LRMS *m/z* (ES) 424 (100%, MH^{+}), 446 (100%, MNa^{+}).

8,13-Dimethyl-16-phenyl-1,8,13-triazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5,10,15-pentaene-9,12,14-trione (170)



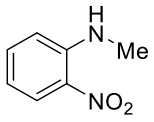
To a suspension of cycloadduct **160** (128 mg, 0.354 mmol) in THF (1.4 mL) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (161 mg, 0.708 mmol). The mixture was heated under reflux for 5 min and cooled to rt. The solvent was removed under reduced pressure and the mixture was diluted with CH_2Cl_2 (100 mL) and filtered. The filtrate was concentrated under reduced pressure to obtain the crude product as a brown solid. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:4) to give pyrroloquinoxalinone **170** (106 mg, 84%) as a white amorphous solid; m.p. 282–284 °C [petrol–EtOAc]; R_f 0.18 [petrol–EtOAc (1:4)]; FT-IR ν_{max} (film)/cm^{-1} 3062, 2931, 1766 (C=O), 1714 (C=O), 1665 (C=O), 1419, 1361, 983, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70–7.50 (5H, m, 5 × CH), 7.45–7.32 (3H, m, 3 × CH), 7.01–6.89 (1H, m, CH), 3.74 (3H, s, CH_3), 3.14 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon signal missing) δ = 163.7 (C=O), 162.0 (C=O), 153.6 (C=O), 131.5 (C), 130.3 (CH), 129.6 (CH), 129.2 (C), 129.2 (CH), 127.4 (CH), 124.2 (C), 124.1 (C), 122.4 (CH), 121.9 (C), 120.6 (C), 118.8 (CH), 116.0 (CH), 29.1 (CH_3), 24.4 (CH_3). HRMS *m/z* (ES) Found: MH$^+$, 358.1194. $C_{21}H_{16}N_3O_3$ requires MH$^+$ 358.1186; LRMS *m/z* (ES) 358 (100%, MH$^+$), 380 (50%, MNa$^+$).

8,13-Dimethyl-16-(thiophen-2-yl)-1,8,13-triazatetracyclo[8.6.0.0^{2},^{7}.0^{11},^{15}]hexadeca-2(7),3,5,10,15-pentaene-9,12,14-trione (171)



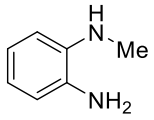
To a suspension of cycloadduct **166** (20 mg, 0.050 mmol) in THF (0.2 mL) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (23 mg, 0.10 mmol). The mixture was heated under reflux for 5 min and cooled to rt. The solvent was removed under reduced pressure and the mixture was diluted with CH_2Cl_2 (50 mL) and filtered. The filtrate was concentrated under reduced pressure to obtain the crude product as a brown solid. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (1:1) to give oxidised pyrroloquinoxalinone **171** (12 mg, 61%) as a white amorphous solid; m.p. 314–316 °C [petrol–EtOAc]; R_f 0.37 [petrol–EtOAc (1:4)]; FT-IR ν_{max} (film)/cm^{-1} 3094, 2914, 2850, 1762 (C=O), 1708 (C=O), 1665 (C=O), 1424, 1362, 979, 736; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (1H, dd, *J* = 5.0, 1.0 Hz, CH), 7.46 (1H, d, *J* = 9.0 Hz, CH), 7.44–7.38 (3H, m, 3 × CH), 7.27 (1H, dd, *J* = 5.0, 3.5 Hz, CH), 7.07–6.98 (1H, m, 1H), 3.74 (3H, s, CH_3), 3.15 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.4 (C=O), 161.9 (C=O), 153.4 (C=O), 131.5 (C), 131.0 (CH), 129.9 (CH), 129.0 (C), 128.1 (CH), 127.6 (CH), 125.8 (C), 124.3 (C), 122.7 (CH), 122.4 (C), 121.7 (C), 121.0 (C), 118.3 (CH), 116.0 (CH), 29.1 (CH_3), 24.5 (CH_3). HRMS *m/z* (ES) Found: MH$^+$, 364.0765. $C_{19}H_{14}N_3O_3S$ requires MH$^+$ 364.0750; LRMS *m/z* (ES) 364 (70%, MH$^+$), 386 (100%, MNa$^+$).

N-Methyl-2-nitroaniline (178)



To a stirred solution of 2-nitroaniline (5.0 g, 36 mmol) in DMF (36 mL) at 0 °C, was added sodium hydride (956 mg, 39.8 mmol) and the mixture was left to stir for 10 min. Methyl iodide (2.25 mL, 36.2 mmol) in DMF (18 mL) was added dropwise to the mixture and once addition was complete, the mixture was warmed up to rt over 16 h. The mixture was diluted with water (200 mL) and EtOAc (500 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give aniline **178** (4.3 g, 78%) as a pale orange oil; R_f 0.21 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (1H, dd, *J* = 8.5, 1.5 Hz, CH), 8.04 (1H, br s, NH), 7.47–7.43 (1H, m, CH), 6.83 (1H, d, *J* = 8.5 Hz, CH), 6.66–6.60 (1H, m, CH), 3.01 (3H, d, *J* = 5.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.4 (C), 136.3 (CH), 126.8 (CH), 125.4 (C), 115.2 (CH), 113.4 (CH), 29.7 (CH_3). Data consistent with the literature.[146]

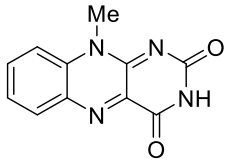
N-Methylbenzene-1,2-diamine (179)



To a stirred suspension of sodium borohydride (492 mg, 13.0 mmol) and 10% Pd/C (0.5 g, 0.5 mmol) in THF (20 mL) at 0 °C was added aniline **178** (989 mg, 6.50 mmol) in MeOH (10 mL) dropwise. The mixture was left to stir for 30 min at rt and filtered through a pad of celite. The solvent was removed under reduced pressure to give the crude product which was partitioned between EtOAc (200 mL) and water (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown oil. The crude product was then purified by column chromatography on silica gel, eluting with

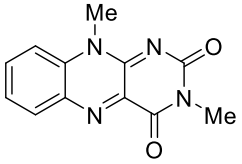
petrol–EtOAc (7:3) to give amine **179** (626 mg, 79%) as a pale brown oil; R_f 0.32 [petrol–EtOAc (3:2)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.97–6.90 (1H, m, CH), 6.78–6.72 (3H, m, 3 × CH), 3.40 (3H, br s, 3 x NH), 2.91 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.0 (C), 134.1 (C), 120.8 (CH), 118.5 (CH), 116.3 (CH), 111.0 (CH), 31.0 (CH_3). Data consistent with the literature.[147]

10-Methyl-2H,3H,4H,10H-benzo[g]pteridine-2,4-dione (180)



To a stirred solution of amine **179** (100 mg, 0.819 mmol) in glacial acetic acid (16 mL) was added alloxan monohydrate (131 mg, 0.819 mmol) followed by boric acid (51 mg, 0.82 mmol). The mixture was heated at 120 °C for 1 h and then cooled to rt. The acetic acid was removed under reduced pressure to give the crude product that was flushed through a silica gel plug, eluting with CH_2Cl_2–MeOH (97:3) to obtain the crude isoalloxazine **180** as an orange solid (101 mg). The material was used without further purification.

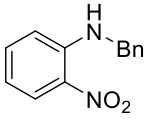
3,10-Dimethyl-2H,3H,4H,10H-benzo[g]pteridine-2,4-dione (181)



To a stirred suspension of crude isoalloxazine **180** (101 mg, 0.438 mmol) in DMF (12 mL) was added Cs_2CO_3 (228 mg, 0.701 mmol) followed by methyl iodide (0.08 mL, 1 mmol). The mixture was left to stir at rt for 1 h. The solvent was removed under reduced pressure to give the crude product which was partitioned between CH_2Cl_2 (50 mL) and water (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange solid. The crude product was purified by column chromatography on silica gel eluting with CH_2Cl_2–MeOH (97:3) to give isoalloxazine **181** (60 mg, 30%) as a yellow amorphous solid; m.p. >250 °C (decomposition); R_f 0.17 [CH_2Cl_2–MeOH (97:3)];

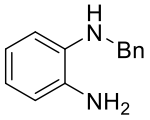
FT-IR ν_{max} (film)/cm^{-1} 3070, 2760, 1706, 1646 (C=O), 1609, 1586, 1549. 1460, 1420, 1271, 1204, 1181, 1044, 960, 766, 711, 634, 547; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.20–8.17 (1H, m, CH), 7.99–7.97 (2H, m, 2 × CH), 7.70–7.66 (1H, m, CH), 4.00 (3H, s, CH_3), 3.29 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 160.0 (C=O), 155.6 (C=O), 150.0 (C), 138.2 (C), 135.5 (CH), 135.3 (C), 133.7 (C), 132.1 (CH), 126.6 (CH), 121.8 (CH), 32.2 (CH_3), 28.5 (CH_3); HRMS *m/z* (ES) Found: MH$^+$, 243.0880. $C_{12}H_{11}N_4O_2$ requires MH$^+$ 243.0877; LRMS *m/z* (ES) 243 (100%, MH$^+$).

N-Benzyl-2-nitroaniline (182)



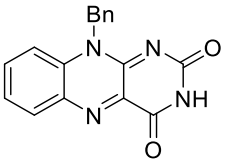
To a stirred solution of 2-nitroaniline (2.0 g, 15 mmol) in acetone (30 mL) at rt was added sodium hydroxide (0.72 g, 18 mmol). The mixture was heated under reflux for 15 min and benzyl bromide (2.1 mL, 18 mmol) was added dropwise over a period of 5 min. The mixture was heated under reflux for a further 1 h and then cooled to rt. The mixture was diluted with water (100 mL) and the organic product was extracted with EtOAc (150 mL), washed with brine (150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give amine **182** (1.4 g, 41%) as an orange amorphous solid; m.p. 63–65 °C [petrol–EtOAc] (lit.[148] 76–78 °C [no solvent]); R_f 0.29 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.47 (1H, br s, NH), 8.23 (1H, dd, *J* = 8.5, 1.5 Hz, CH), 7.43–7.31 (6H, m, 6 × CH), 6.84 (1H, dd, *J* = 8.5, 1.5 Hz), 6.72–6.67 (1H, m, CH), 4.58 (2H, d, *J* = 5.5 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon signal missing) δ = 145.3 (C), 137.4 (C), 136.2 (CH), 129.0 (CH), 127.7 (CH), 127.1 (CH), 126.9 (CH), 115.8 (CH), 114.2 (CH), 47.1 (CH_2). Data consistent with the literature.[148]

N1-Benzylbenzene-1,2-diamine (183)



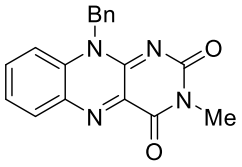
To a stirred suspension of sodium borohydride (331 mg, 8.76 mmol) and 10% Pd/C (0.2 g, 0.19 mmol) in THF (30 mL) at 0 °C was added amine **182** (1.0 g, 4.4 mmol) in MeOH (45 mL) and THF (15 mL) dropwise. Once addition was complete the mixture was left to stir for 30 min at rt and then filtered through a pad a celite. The solvent was removed under reduced pressure to give the crude product as a brown gum. The crude product was purified using a silica gel plug, eluting with petrol–EtOAc (1:1) to give amine **183** (837 mg, 79%) as a brown oil; R_f 0.58 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.28 (5H, m, 5 × CH), 6.87–6.70 (4H, m, 4 × CH), 4.35 (2H, s, CH_2), 3.73 (1H, br s, NH), 3.38 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.4 (C), 137.8 (C), 134.2 (C), 128.6 (CH), 127.8 (CH), 127.3 (CH), 120.8 (CH), 118.9 (CH), 116.6 (CH), 112.0 (CH), 48.7 (CH_2). Data consistent with the literature.[149]

10-Benzyl-2H,3H,4H,10H-benzo[g]pteridine-2,4-dione (184)



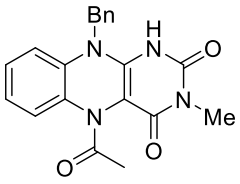
To a suspension of alloxan monohydrate (565 mg, 3.53 mmol) and boric acid (218 mg, 3.53 mmol) in glacial acetic acid (10 mL) at rt was added amine **183** (700 mg, 3.53 mmol) in glacial acetic acid (14 mL). The mixture was stirred at rt for 1 h and then heated at 50 °C for 16 h under an argon atmosphere. The mixture was cooled to rt and the acetic acid was removed under reduced pressure to give the isoalloxazine **184** as a yellow solid (2.5 g). The material was used without further purification.

10-Benzyl-3-methyl-2H,3H,4H,10H-benzo[g]pteridine-2,4-dione (185)



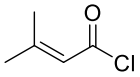
To a stirred suspension of crude isoalloxazine **184** (2.5 g, 3.5 mmol) in DMF (24 mL), was added potassium carbonate (1.7 g, 12 mmol) followed by methyl iodide (0.77 mL, 12 mmol). The mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure to give the crude product which was partitioned between CH_2Cl_2 (150 mL) and water (50 mL). The organic layer was separated and the aqueous layer was washed further with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow solid. The crude product was purified by using column chromatography on silica gel eluting with CH_2Cl_2–MeOH (97:3) to give isoalloxazine **185** (830 mg, 74%) as a yellow amorphous solid; m.p. >250 °C (decomposition); R_f 0.33 [CH_2Cl_2–MeOH (97:3)]; FT-IR ν_{max} (film)/cm^{-1} 3038, 1708, 1641 (C=O), 1547, 1514, 1491, 1465, 1445, 1271, 1221, 1176, 1144, 1042, 957, 788, 731; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.21 (1H, d, *J* = 8.0 Hz, CH), 7.85 (1H, t, *J* = 8.0 Hz, CH), 7.72 (1H, d, *J* = 8.0 Hz, CH), 7.63 (1H, t, *J* = 8.0 Hz, CH), 7.38–7.25 (5H, m, 5 × CH), 5.94 (2H, br s, CH_2), 3.31 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 160.1 (C=O), 155.8 (C=O), 150.2 (C), 138.9 (C), 135.6 (C), 135.3 (CH), 135.2 (C), 132.7 (C), 132.3 (CH), 129.1 (CH), 128.0 (CH), 127.3 (CH), 126.6 (CH), 117.2 (CH), 47.4 (CH_2), 28.5 (CH_3); HRMS *m/z* (ES) Found: MH^+, 319.1197. $C_{18}H_{15}N_4O_2$ requires MH^+ 319.1190; LRMS *m/z* (ES) 319 (100%, MH^+).

5-Acetyl-10-benzyl-3-methyl-1H,2H,3H,4H,5H,10H-benzo[g]pteridine-2,4-dione (190)



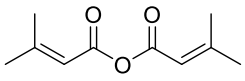
To a solution of isoalloxazine **185** (100 mg, 0.314 mmol) in acetic anhydride (5 mL) and glacial acetic acid (5 mL) under an argon atmosphere was added *c*H_2SO_4 (5 drops). Activated zinc (5.0 g, 77 mmol) was added slowly over 1 h and the mixture was left to stir for 16 h at rt. The mixture was filtered through a plug of cotton wool which was rinsed through with hot glacial acetic acid (25 mL) and the solvent was removed under reduced pressure. The residue obtained was diluted with NH_4OH (50 mL, 1 M) and cooled to 0 °C for 1 h. The mixture was filtered and the filtrate was neutralised with glacial acetic acid. The organic product was extracted using CH_2Cl_2 (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give isoalloxazine **190** (76 mg, 67%) as a pale green amorphous solid; m.p. >250 °C (decomposition); R_f 0.17 [CH_2Cl_2−MeOH (97:3)]; FT-IR ν_{max} (film)/cm^{-1} 3116, 3012, 2977, 1702, 1632 (C=O), 1486, 1392, 1352, 1329, 1269, 1057, 1007, 984, 757, 722, 689, 611; ^{1}H NMR (400 MHz, DMSO-d^6) = 11.70 (1H, s, NH), 7.41 (1H, d, *J* = 7.0 Hz, CH), 7.36–7.28 (2H, m, 2 × CH), 7.27–7.18 (3H, m, 3 × CH), 7.17–7.05 (3H, m, 3 × CH), 5.21 (2H, d, *J* = 6.0 Hz, CH_2), 3.16 (3H, s, CH_3), 2.06 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d^6, four quaternary carbon signals missing) δ = 158.7 (C=O), 151.0 (C), 136.9 (C), 129.1 (CH), 127.9 (CH), 127.0 (CH), 126.5 (CH), 126.3 (CH), 123.3 (CH), 116.2 (CH), 97.2 (C), 48.1 (CH_2), 27.6 (CH_3), 21.5 (CH_3); HRMS *m/z* (ES) Found: MH^+, 363.1456. $C_{20}H_{19}N_4O_3$ requires MH^+ 363.1452; LRMS *m/z* (ES) 363 (100%, MH^+).

3-Methylbut-2-enoyl chloride (193)



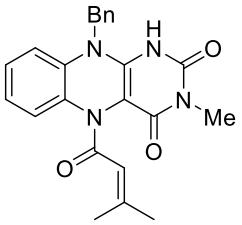
To a solution of 3,3-dimethylacrylic acid (3.0 g, 30 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added oxalyl chloride (2.8 mL, 33 mmol) dropwise. The mixture was warmed to rt and stirred for 1 h. The solvent was then removed under reduced pressure to give the crude product which was washed with $CHCl_3$ (3 × 100 mL). The washings were combined and the solvent was removed under reduced pressure to give the final crude acid chloride **193** as a pale yellow oil (3.5 g). The material was used without further purification.

3-Methylbut-2-enoyl 3-methylbut-2-enoate (194)



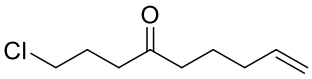
To a stirred suspension of NaH (0.3 g, 11 mmol) in THF (20 mL) at 0 °C was added 3,3-dimethylacrylic acid (1.0 g, 10 mmol) in THF (10 mL). The mixture was warmed to rt over 2 h and crude acid chloride **193** (1.2 g, 10 mmol) was added in THF (6 mL). After stirring for a further 1.5 h the solvent was removed under reduced pressure and diluted with Et_2O (50 mL). The mixture was filtered through a pad of celite and concentrated under reduced pressure to give anhydride **194** (1.2 g, 66%) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.73 (s, 2H), 2.24 (s, 6H), 1.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.8 (C=O), 162.1 (C), 115.3 (CH), 27.8 (CH_3), 20.8 (CH_3); Data consistent with the literature.[150]

10-Benzyl-3-methyl-5-(3-methylbut-2-enoyl)-1H,2H,3H,4H,5H,10H-benzo[g]pteridine-2,4-dione (195)



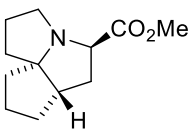
To a solution of isoalloxazine **185** (200 mg, 0.628 mmol) in glacial acetic acid (10 mL) under an argon atmosphere was added *c*H_2SO_4 (10 drops) followed by anhydride **194** (2.0 g, 11 mmol). Activated zinc (10.0 g, 153 mmol) was added slowly over 1 h and the mixture was left to stir for 16 h at rt. The mixture was filtered through a plug of cotton wool which was rinsed through with hot glacial acetic acid (100 mL) and the solvent was removed under reduced pressure. The residue obtained was diluted with NH_4OH (50 mL, 1 M) and cooled to 0 °C for 1 h. The mixture was filtered and the filtrate was neutralised with glacial acetic acid. The organic product was extracted using CH_2Cl_2 (200 mL), washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2−MeOH (19:1) to give isoalloxazine **195** (90 mg, 36%) as a yellow amorphous solid; m.p. 110-113 °C [CH_2Cl_2−MeOH]; R_f 0.23 [CH_2Cl_2−MeOH (97:3)]; FT-IR ν_{max} (film)/cm^{-1} 3199, 3063, 2959, 2516, 2158, 2029, 1703, 1627, 1576, 1486, 1445, 1383, 1359, 1262, 1151, 1048, 985, 847, 799; 1H NMR (400 MHz, $CDCl_3$) δ = 10.63 (1H, s, NH), 7.66–7.50 (1H, m, CH), 7.37–7.24 (3H, m, 3 × CH), 7.18–7.04 (4H, m, 4 × CH), 6.83 (1H, d, *J* = 8.0 Hz, CH), 5.95–5.87 (1H, s, CH), 5.16 (2H, s, CH_2), 3.27 (3H, s, CH_3), 2.15 (3H, s, CH_3), 1.85 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.0 (C=O), 158.2 (C=O), 153.6 (C=O), 151.6 (C), 147.2 (C), 137.7 (C), 134.6 (C), 131.0 (C), 129.2 (CH), 128.1 (CH), 126.8 (CH), 126.4 (CH), 126.0 (CH), 123.9 (CH), 115.7 (CH), 115.1 (CH), 97.8 (C), 48.5 (CH_2), 27.7 (CH_3), 27.5 (CH_3), 20.7 (CH_3); HRMS *m/z* (ES) Found: MH^+, 403.1768. $C_{23}H_{23}N_4O_3$ requires MH^+ 403.1765; LRMS *m/z* (ES) 403 (100%, MH^+).

1-Chloronon-8-en-4-one (219)



To a suspension of magnesium (0.66 g, 27 mmol) in THF (48 mL) under an argon atmosphere was added 5-bromo-1-pentene (3.0 mL, 25 mmol) dropwise. The mixture was heated under reflux for 3 h and cooled to rt. Upon cooling the mixture to −78 °C CuBr (3.7 g, 25 mmol) was added and the mixture was stirred for 10 min. 4-Chlorobutyryl chloride (3.0 mL, 27 mmol) was added dropwise and the mixture was warmed to rt over 17 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with Et_2O (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a pale green oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (49:1) to give ketone **219** (3.5 g, 79%) as a colourless oil; R_f 0.17 [petrol–EtOAc (19:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.85–5.71 (1H, m, CH), 5.07–4.96 (2H, m, CH_2), 3.59 (2H, t, *J* = 6.5 Hz, CH_2), 2.62 (2H, t, *J* = 7.0 Hz, CH_2), 2.45 (2H, t, *J* = 7.5 Hz, CH_2), 2.12–2.01 (4H, m, 2 × CH_2), 1.76–1.66 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 209.8 (C=O), 137.9 (CH), 115.3 (CH_2), 44.6 (CH_2), 42.1 (CH_2), 39.3 (CH_2), 33.1 (CH_2), 26.3 (CH_2), 22.8 (CH_2). Data consistent with the literature.[95]

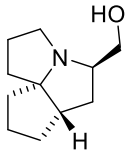
Methyl octahydro-1H-cyclopenta[h]pyrrolizine-5-carboxylate (232)



To a mixture of ketone **219** (200 mg, 1.15 mmol) in PhMe (14 mL) was added glycine methyl ester hydrochloride (216 mg, 1.72 mmol), *N*,*N*-diisopropylethylamine (0.60 mL, 3.44 mmol) and anhydrous $MgSO_4$ (1 g). The mixture was heated under reflux for 17 h and was cooled to rt. The solvent was removed under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–NH_3 (49:1:0.5) to give cycloadduct **232** (127 mg, 53%) as a brown oil; R_f 0.17 [CH_2Cl_2–MeOH–NH_3

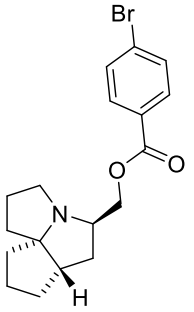
(49:1:0.3)]; FT-IR ν_{max} (film)/cm^{-1} 2949, 2864, 1738 (C=O), 1449, 1434, 1196, 1155, 1104, 917, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.90–3.84 (1H, m, CH), 3.74 (3H, s, CH_3), 3.01–2.93 (1H, m, CH), 2.61–2.52 (1H, m, CH), 2.30–2.19 (2H, m, 2 × CH), 1.93–1.63 (9H, m, 9 × CH), 1.52–1.40 (1H, m, CH), 1.35–1.23 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.9 (C=O), 82.3 (C), 64.6 (CH), 51.6 (CH_3), 49.6 (CH_2), 48.7 (CH), 41.7 (CH_2), 39.7 (CH_2), 34.7 (CH_2), 33.2 (CH_2), 26.3 (CH_2), 26.0 (CH_2); HRMS *m/z* (ES) Found: MH$^+$, 210.1495. $C_{12}H_{20}NO_2$ requires MH$^+$ 210.1489; LRMS *m/z* (ES) 210 (100%, MH$^+$).

{Octahydro-1H-cyclopenta[h]pyrrolizin-5-yl}methanol (238)



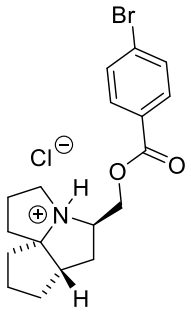
To a mixture of cycloadduct **232** (258 mg, 1.23 mmol) in THF (21 mL) at 0 °C was added $LiAlH_4$ (108 mg, 2.84 mmol). The mixture was stirred for 45 min at 0 °C and cooled further to −10 °C. After 5 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL) and water (3 mL) and was warmed to rt. The mixture was filtered through a pad of celite and rinsed with Et_2O (3 × 30 mL). The organic layer was separated, washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give alcohol **238** (159 mg, 71%) as a colourless oil; R_f 0.01 [CH_2Cl_2–MeOH–NH_3 (49:1:0.3)]; FT-IR ν_{max} (film)/cm^{-1} 3225 (O−H), 2943, 2862, 1449, 1045, 909, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.92 (1H, br s, OH), 3.81 (1H, dd, *J* = 11.0, 8.0 Hz, CH), 3.68 (1H, dd, *J* = 11.0, 5.5 Hz, 1H), 3.41–3.27 (1H, m, CH), 2.93–2.83 (1H, m, CH), 2.63–2.47 (1H, m, CH), 2.09 (1H, q, *J* = 8.0 Hz, 1H), 1.97–1.56 (9H, m, 9 × CH), 1.46–1.34 (2H, m, 2 × CH), 1.33–1.19 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 81.7 (C), 62.9 (CH), 62.8 (CH_2), 50.3 (CH), 47.0 (CH_2), 41.7 (CH_2), 40.8 (CH_2), 33.8 (CH_2), 33.3 (CH_2), 26.5 (CH_2), 25.9 (CH_2); HRMS *m/z* (ES) Found: MH$^+$, 182.1542. $C_{11}H_{20}NO$ requires MH$^+$ 182.1539; LRMS *m/z* (ES) 182 (100%, MH$^+$).

{Octahydro-1H-cyclopenta[h]pyrrolizin-5-yl}methyl 4-bromobenzoate (239)



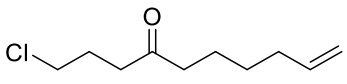
To a suspension of 4-bromobenzoic acid (455 mg, 2.26 mmol) in CH_2Cl_2 (4 mL) was added oxalyl chloride (0.21 mL, 2.5 mmol). The mixture was cooled to 0 °C and DMF (10 drops) was added. The mixture was warmed to rt and was stirred for 1 h. The solvent was removed under reduced pressure to give a residue that was dissolved in CH_2Cl_2 (13 mL). To the mixture was added alcohol **238** (205 mg, 1.13 mmol) and 4-(dimethylamino)pyridine (276 mg, 2.26 mmol) at 0 °C, followed by Et_3N (0.47 mL, 3.4 mmol). The mixture was stirred for 1 h at 0 °C and was diluted with saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a pale orange oil. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–NH_3 (97:3:1) to give ester **239** (243 mg, 59%) as a pale orange oil; R_f 0.23 [CH_2Cl_2–MeOH–NH_3 (49:1:0.3)]; FT-IR ν_{max} (film)/cm^{-1} 2948, 2858, 1718 (C=O), 1589, 1396, 1265, 1104, 1070, 1012, 846, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (2H, d, *J* = 8.5 Hz, 2 × CH), 7.60 (2H, d, *J* = 8.5 Hz, 2 × CH), 4.66–4.42 (2H, m, CH_2), 3.59 (1H, td, *J* = 12.0, 6.0 Hz, CH), 2.99–2.85 (1H, m, CH), 2.74–2.61 (1H, m, CH), 2.17 (1H, q, *J* = 7.5 Hz, CH), 2.03–1.60 (9H, m, 9 × CH), 1.58–1.23 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.0 (C=O), 131.7 (CH), 131.3 (CH), 129.0 (C), 128.1 (C), 82.0 (C), 65.3 (CH_2), 59.3 (CH), 50.1 (CH), 47.9 (CH_2), 42.0 (CH_2), 40.8 (CH_2), 33.9 (CH_2), 33.7 (CH_2), 26.4 (CH_2), 26.3 (CH_2); HRMS *m/z* (ES) Found: MH^+, 364.0908. $C_{18}H_{23}{}^{79}BrNO_2$ requires MH^+ 364.0907; Found: MH^+, 366.0893. $C_{18}H_{23}{}^{81}BrNO_2$ requires MH^+ 366.0886; LRMS *m/z* (ES) 364 (100%, MH^+ for ^{79}Br), 366 (100%, MH^+ for ^{81}Br).

5-[(4-Bromobenzoyloxy)methyl]-decahydrocyclopenta[h]pyrrolizin-4-ium chloride (240)



To a mixture of ester **239** (169 mg, 0.464 mmol) in CH_2Cl_2 (2 mL) was added HCl (2.3 mL, 4.6 mmol, 2 M in Et_2O) at rt. After 5 min, the mixture was concentrated under reduced pressure to give salt **240** (186 mg, quantitative yield) as a white amorphous solid; m.p. 215–218 °C [CH_2Cl_2]; FT-IR ν_{max} (film)/cm^{-1} 2953, 2394, 1710, 1590, 1397, 1274, 1119, 1011, 761, 683; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.46 (1H, br s, NH), 8.17 (2H, d, *J* = 8.5 Hz, 2 × CH), 7.73 (2H, d, *J* = 8.5 Hz, 2 × CH), 4.62 (1H, dd, *J* = 13.0, 3.5 Hz, CH), 4.45 (1H, dd, *J* = 13.0, 9.5 Hz, CH), 4.20–4.06 (1H, m, CH), 3.40–3.23 (2H, m, 2 × CH), 2.48–2.34 (2H, m, 2 × CH), 2.27–2.14 (1H, m, CH), 2.10–1.73 (8H, m, 8 × CH), 1.62–1.42 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.2 (C=O), 132.5 (CH), 132.2 (CH), 128.7 (C), 128.3 (C), 88.6 (C), 62.1 (CH_2), 60.7 (CH), 48.3 (CH), 48.0 (CH_2), 38.3 (CH_2), 38.1 (CH_2), 32.9 (CH_2), 31.3 (CH_2), 26.6 (CH_2), 25.5 (CH_2); HRMS *m/z* (ES) Found: M^+−Cl, 364.0922. $C_{18}H_{23}{}^{79}BrNO_2$ requires M^+−Cl 364.0907; Found: M^+−Cl, 366.0904. $C_{18}H_{23}{}^{81}BrNO_2$ requires M^+−Cl 366.0886; LRMS *m/z* (ES) 364 (100%, M^+−Cl for ^{79}Br), 366 (100%, M^+−Cl for ^{81}Br).

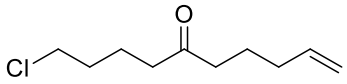
1-Chlorodec-9-en-4-one (222)



To a suspension of magnesium (0.26 g, 11 mmol) in THF (19 mL) under an argon atmosphere was added 6-bromo-1-hexene (1.3 mL, 10 mmol) dropwise. The mixture was heated under reflux for 3 h and cooled to rt. Upon cooling the mixture to −78 °C CuBr (1.4 g, 10 mmol) was added and the

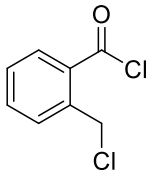
mixture was stirred for 10 min. 4-Chlorobutyryl chloride (1.2 mL, 11 mmol) was added dropwise and the mixture was warmed to rt over 17 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a pale green oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give ketone **222** (1.3 g, 69%) as a colourless oil; R_f 0.33 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.87–5.74 (1H, m, CH), 5.07–4.94 (2H, m, CH_2), 3.59 (2H, t, *J* = 6.5 Hz, CH_2), 2.62 (2H, t, *J* = 7.0 Hz, CH_2), 2.45 (2H, t, *J* = 7.5 Hz, CH_2), 2.12–2.02 (4H, m, 2 × CH_2), 1.66–1.57 (2H, m, CH_2), 1.45–1.35 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 209.9 (C=O), 138.4 (CH), 114.7 (CH_2), 44.6 (CH_2), 42.8 (CH_2), 39.2 (CH_2), 33.5 (CH_2), 28.4 (CH_2), 26.3 (CH_2), 23.3 (CH_2). Data consistent with the literature.[95]

1-Chlorodec-9-en-5-one (241)



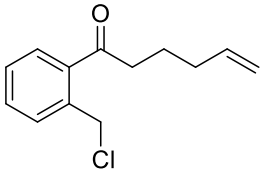
To a suspension of magnesium (0.26 g, 11 mmol) in THF (19 mL) under an argon atmosphere was added 5-bromo-1-pentene (1.2 mL, 10 mmol) dropwise. The mixture was heated under reflux for 3 h and cooled to rt. Upon cooling the mixture to −78 °C CuBr (1.4 g, 10 mmol) was added and the mixture was stirred for 10 min. 5-Chlorovaleroyl chloride (1.4 mL, 11 mmol) was added dropwise and the mixture was warmed to rt over 17 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a pale green oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give ketone **241** (1.5 g, 79%) as a colourless oil; R_f 0.27 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.85–5.72 (1H, m, CH), 5.07–4.96 (2H, m, CH_2), 3.55 (2H, t, *J* = 6.5 Hz, CH_2), 2.50–2.39 (4H, m, 2 × CH_2), 2.07 (2H, q, *J* = 7.0 Hz, CH_2), 1.85–1.67 (6H, m, 3 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 210.2 (C=O), 137.9 (CH), 115.2 (CH_2), 44.6 (CH_2), 41.9 (CH_2), 41.8 (CH_2), 33.1 (CH_2), 32.0 (CH_2), 22.8 (CH_2), 21.1 (CH_2). Data consistent with the literature.[95]

2-(Chloromethyl)benzoyl chloride (249)



A stirred mixture of phthalide (5.0 g, 37 mmol), benzyltriethylammonium chloride (0.9 g, 3.7 mmol) and H_3BO_3 (0.2 g, 4 mmol) was heated at 130 °C until all the phthalide had melted. To the mixture was added thionyl chloride (3.5 mL, 49 mmol) over a period of 4 h. Once addition was complete the mixture was heated for a further 5 h at 130 °C. After cooling to rt excess thionyl chloride was removed under reduced pressure to give the crude acid chloride **249** (6.3 g, 89%) as a yellow oil. The material was used without further purification.

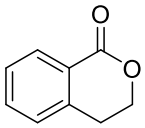
1-[2-(Chloromethyl)phenyl]hex-5-en-1-one (242)



To a suspension of magnesium (0.26 g, 11 mmol) in THF (19 mL) under an argon atmosphere was added 5-bromo-1-pentene (1.2 mL, 10 mmol) dropwise. The mixture was heated under reflux for 3 h and cooled to rt. Upon cooling the mixture to −78 °C CuBr (1.4 g, 10 mmol) was added and the mixture was stirred for 10 min. Crude acid chloride **249** (2.0 g, 11 mmol) was added dropwise and the mixture was warmed to rt over 17 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a pale green oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (97:3) to give ketone **242** (598 mg, 27%) as a yellow oil; R_f 0.38 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3070, 2975, 2936, 2865, 1686 (C=O), 1642, 1572, 1448, 1365, 1265, 1233, 994, 912, 753, 739, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (1H, d, *J* = 7.5 Hz, CH), 7.59–7.39 (3H, m, 3 × CH), 5.89–5.77 (1H, m, CH), 5.12–4.99 (2H, m, CH_2), 4.94 (2H, s, CH_2), 3.01–2.92

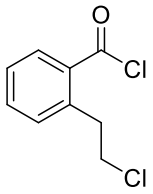
(2H, m, CH_2), 2.24–2.13 (2H, m, CH_2), 1.93–1.80 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.0 (C=O), 138.0 (CH), 137.9 (C), 137.0 (C), 131.6 (CH), 131.0 (CH), 128.6 (CH), 128.3 (CH), 115.4 (CH_2), 44.2 (CH_2), 40.6 (CH_2), 33.1 (CH_2), 23.2 (CH_2); HRMS *m/z* (ES) Found: M^+, 222.0814. $C_{13}H_{15}O^{35}Cl$ requires M^+ 222.0811; Found: M^+, 224.0788. $C_{13}H_{15}O^{37}Cl$ requires M^+ 224.0782; LRMS *m/z* (ES) 222 (100%, M^+ for ^{35}Cl), 224 (35%, M^+ for ^{37}Cl).

3,4-Dihydro-1H-2-benzopyran-1-one (253)



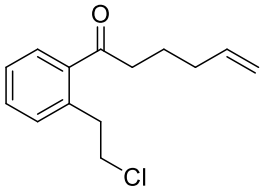
To a mixture of isochroman (3.8 mL, 30 mmol) in CH_2Cl_2 (300 mL) was added benzyltriethylammonium chloride (20 g, 90 mmol) and $KMnO_4$ (14 g, 90 mmol). The mixture was heated under reflux for 6 h and cooled to rt. Upon cooling the mixture to 0 °C aqueous $NaHSO_3$ (300 mL, 1M) was added, followed by CH_2Cl_2 (500 mL) and the organic layer was separated. Drying over anhydrous $MgSO_4$, filtering, and concentrating under reduced pressure gave the crude product as a pale yellow oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (7:3) to give lactone **253** (3.1 g, 70%) as a colourless oil; R_f 0.24 [petrol–EtOAc (7:3)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (1H, d, *J* = 7.5 Hz, CH), 7.54 (1H, t, *J* = 7.5 Hz, CH), 7.39 (1H, t, *J* = 7.5 Hz, CH), 7.27 (1H, d, *J* = 7.5 Hz, CH), 4.53 (2H, t, *J* = 6.0 Hz, CH_2), 3.06 (2H, t, *J* = 6.0 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.1 (C=O), 139.6 (C), 133.7 (CH), 130.4 (CH), 127.7 (CH), 127.3 (CH), 125.3 (C), 67.3 (CH_2), 27.8 (CH_2). Data consistent with the literature.[2]

2-(2-Chloroethyl)benzoyl chloride (250)



A mixture of lactone **253** (3.1 g, 21 mmol) and phosphorus pentachloride (8.7 g, 42 mmol) was heated at 100 °C for 16 h and was then cooled to rt. The mixture was filtered through a pad of cotton wool to give the crude acid chloride **250** (3.9 g, 92%) as a yellow oil. The material was used without further purification.

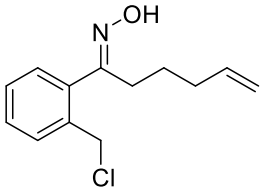
1-[2-(2-Chloroethyl)phenyl]hex-5-en-1-one (243)



To a suspension of magnesium (0.23 g, 9.3 mmol) in THF (16 mL) under an argon atmosphere was added 5-bromo-1-pentene (1.0 mL, 8.7 mmol) dropwise. The mixture was heated under reflux for 3 h and was cooled to rt. Upon cooling the mixture to −78 °C CuBr (1.3 g, 8.7 mmol) was added and the mixture was stirred for 10 min. Crude acid chloride **250** (1.9 g, 9.3 mmol) was added dropwise and the mixture was warmed to rt over 17 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (100 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (49:1) to give ketone **243** (186 mg, 9%) as a yellow oil; R_f 0.43 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3070, 2973, 2934, 2871, 1681 (C=O), 1639, 1571, 1444, 1279, 1230, 914, 753, 707, 651; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.71 (1H, d, *J* = 7.5 Hz, CH), 7.46 (1H, td, *J* = 7.5, 1.5 Hz, CH), 7.40–7.33 (2H, m, 2 × CH), 5.90–5.76 (1H, m, CH), 5.12–4.97 (2H, m, CH_2), 3.81 (2H, t, *J* = 7.0 Hz, CH_2), 3.27 (2H, t, *J* = 7.0 Hz, CH_2), 2.95 (2H, t, *J* = 7.0 Hz, CH_2),

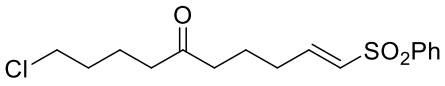
2.22–2.11 (2H, m, CH_2), 1.85 (quin, *J* = 7.5 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.0 (C=O), 138.2 (C), 137.9 (CH), 137.9 (C), 132.4 (CH), 131.4 (CH), 128.9 (CH), 127.0 (CH), 115.4 (CH_2), 45.3 (CH_2), 40.6 (CH_2), 37.5 (CH_2), 33.1 (CH_2), 23.3 (CH_2); HRMS *m/z* (ES) Found: MH^+, 237.1046. $C_{14}H_{18}O^{35}Cl$ requires MH^+ 237.1041; Found: MH^+, 239.1021. $C_{14}H_{18}O^{37}Cl$ requires MH^+ 239.1011; LRMS *m/z* (ES) 237 (100%, MH^+ for ^{35}Cl), 239 (35%, MH^+ for ^{37}Cl).

(*Z*)-*N*-{1-[2-(Chloromethyl)phenyl]hex-5-en-1-ylidene}hydroxylamine (260)



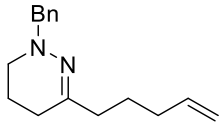
To a mixture of ketone **242** (255 mg, 1.15 mmol) in PhMe (14 mL) was added hydroxylamine hydrochloride (119 mg, 1.72 mmol) and *N*,*N*-diisopropylethylamine (0.6 mL, 3.44 mmol). The mixture was heated under reflux for 17 h and was cooled to rt. The solvent was removed under reduced pressure to give the crude product as a brown solid. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (49:1) to give oxime **260** (79 mg, 29%) as an orange solid; m.p. 52–54 °C [CH_2Cl_2–MeOH]; R_f 0.33 [CH_2Cl_2–MeOH (19:1)]; FT-IR ν_{max} (film)/cm^{-1} 3228 (O−H), 3065, 2936, 2865, 1640, 1435, 1301, 1201, 999, 958, 912, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.15 (1H, br s, OH), 7.53–7.33 (4H, m, 4 × CH), 5.92–5.70 (1H, m, CH), 5.11–4.92 (2H, m, CH_2), 4.57 (2H, s, CH_2), 2.96–2.81 (2H, m, CH_2), 2.13 (2H, q, *J* = 7.0 Hz, CH_2), 1.68 (2H, quin, *J* = 7.0 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.4 (C), 139.0 (C), 137.9 (CH), 136.2 (C), 131.2 (CH), 129.0 (CH), 128.3 (CH), 128.3 (CH), 115.2 (CH_2), 64.8 (CH_2), 33.8 (CH_2), 27.7 (CH_2), 25.4 (CH_2). Mass spectrometry results showed no peaks corresponding to correct mass of compound.

(9E)-10-(Benzenesulfonyl)-1-chlorodec-9-en-5-one (261)



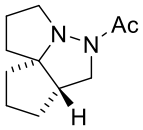
To a solution of ketone **241** (0.76 g, 4.0 mmol) in CH_2Cl_2 (200 mL) was added phenyl vinyl sulfone (1.4 g, 8.0 mmol). The mixture was degassed with argon and heated under reflux. Grubbs 2nd generation catalyst (170 mg, 0.200 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the mixture was left to stir for a further 24 h before being exposed to air and cooled to rt. DMSO (0.7 mL, 10 mmol) was added and the mixture was stirred for a further 24 h. The mixture was concentrated under reduced pressure to give the crude product as a dark brown residue. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (17:3) to give ketone **261** (1.0 g, 76%) as a pale brown oil; R_f 0.23 [petrol–EtOAc (3:2)]; FT-IR ν_{max} (film)/cm^{-1} 3059, 2942, 1710 (C=O), 1626, 1447, 1306, 1144, 1085, 815, 752, 688, 590, 550; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91–7.84 (2H, m, 2 × CH), 7.66–7.60 (1H, m, CH), 7.58–7.52 (2H, m, 2 × CH), 6.99–6.91 (1H, m, CH), 6.34 (1H, dt, *J* = 15.0, 1.5 Hz, CH), 3.53 (2H, t, *J* = 6.5 Hz, CH_2), 2.46–2.39 (4H, m, 2 × CH_2), 2.30–2.21 (2H, m, CH_2), 1.81–1.65 (6H, m, 3 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 209.2 (C=O), 145.9 (CH), 140.6 (C), 133.3 (CH), 131.1 (CH), 129.3 (CH), 127.6 (CH), 44.6 (CH_2), 41.8 (CH_2), 41.3 (CH_2), 31.9 (CH_2), 30.6 (CH_2), 21.4 (CH_2), 21.0 (CH_2); HRMS *m/z* (ES) Found: MH^+, 329.0987. $C_{16}H_{22}O_3S^{35}Cl$ requires MH^+ 329.0973; Found: MH^+, 331.0958. $C_{16}H_{22}O_3S^{37}Cl$ requires MH^+ 331.0943; LRMS *m/z* (ES) 329 (85%, MH^+ for ^{35}Cl), 331 (30%, MH^+ for ^{37}Cl), 346 (100%, MNH_4^+ for ^{35}Cl), 348 (40%, MNH_4^+ for ^{37}Cl), 351 (80%, MNa^+ for ^{35}Cl), 353 (25%, MNa^+ for ^{37}Cl).

1-Benzyl-3-(pent-4-en-1-yl)-1,4,5,6-tetrahydropyridazine (274)



To a mixture of ketone **219** (166 mg, 0.950 mmol) in PhMe (14 mL) was added benzylhydrazine dihydrochloride (222 mg, 1.14 mmol) and *N*,*N*-diisopropylethylamine (0.75 mL, 4.3 mmol). The mixture was heated under reflux for 17 h and was cooled to rt. The solvent was removed under reduced pressure to give the crude product as a brown solid. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (49:1) to give compound **274** (110 mg, 48%) as an orange oil; R_f 0.56 [CH_2Cl_2–MeOH (19:1)]; FT-IR ν_{max} (film)/cm^{-1} 3067, 2933, 2826, 1495, 1451, 1354, 913, 736, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.22 (5H, m, 5 × CH), 5.94–5.80 (1H, m, CH), 5.09–4.95 (2H, m, CH_2), 4.19 (2H, s, CH_2), 2.60 (2H, dd, *J* = 7.0, 4.0 Hz, CH_2), 2.22–2.01 (6H, m, 3 × CH_2), 1.95–1.84 (2H, m, CH_2), 1.71–1.59 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.4 (C), 138.7 (CH), 138.1 (C), 129.2 (CH), 128.1 (CH), 127.1 (CH), 114.6 (CH_2), 63.2 (CH_2), 46.3 (CH_2), 37.5 (CH_2), 33.5 (CH_2), 26.23 (CH_2), 24.0 (CH_2), 20.2 (CH_2); HRMS *m/z* (ES) Found: MH$^+$, 243.1865. $C_{16}H_{23}N_2$ requires MH$^+$ 243.1856; LRMS *m/z* (ES) 243 (100%, MH$^+$).

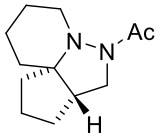
1-{5,6-Diazatricyclo[6.3.0.0^{1,5}]undecan-6-yl}ethan-1-one (275)



To a mixture of ketone **219** (168 mg, 0.960 mmol) in PhMe (14 mL) was added acetylhydrazine (142 mg, 1.92 mmol). The mixture was heated under reflux for 17 h and was cooled to rt. The solvent was removed under reduced pressure to give the crude product as a brown solid. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (49:1) to give cycloadduct **275** (114 mg, 61%) as a pale yellow oil; R_f 0.37 [CH_2Cl_2–MeOH (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3479, 2949, 2866, 1651, 1409, 1218, 1127, 949, 918, 618, 591; ^{1}H NMR

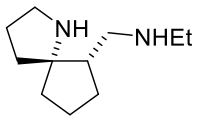
(400 MHz, $CDCl_3$) δ = 3.97 (1H, dd, *J* = 12.0, 2.0 Hz, CH), 3.39 (1H, dd, *J* = 12.0, 8.0 Hz, CH), 3.28 (1H, dt, *J* = 10.0, 6.0 Hz, CH), 2.65 (1H, dt, *J* = 10.0, 8.0 Hz, CH), 2.41–2.30 (1H, m, CH), 2.18 (3H, s, CH_3), 2.03–1.67 (7H, m, 7 × CH), 1.63–1.38 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8 (C=O), 82.0 (C), 55.9 (CH_2), 50.8 (CH), 49.2 (CH_2), 40.4 (CH_2), 37.4 (CH_2), 33.3 (CH_2), 26.0 (CH_2), 24.4 (CH_2), 21.3 (CH_3); HRMS *m/z* (ES) Found: MH^+, 195.1496. $C_{11}H_{19}N_2O$ requires MH^+ 195.1492; LRMS *m/z* (ES) 195 (100%, MH^+).

1-{7,8-Diazatricyclo[6.4.0.0^{1,5}]dodecan-7-yl}ethan-1-one (277)



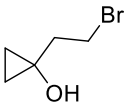
To a mixture of ketone **241** (181 mg, 0.960 mmol) in PhMe (14 mL) was added acetylhydrazine (142 mg, 1.92 mmol) and TBAI (37 mg, 0.10 mmol). The mixture was heated under reflux for 17 h and was cooled to rt. The solvent was removed under reduced pressure to give the crude product as a brown solid. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (49:1) to give cycloadduct **277** (90 mg, 45%) as a pale yellow oil; R_f 0.37 [CH_2Cl_2–MeOH (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3454, 2935, 2864, 1645, 1443, 1416, 1276, 1200, 902, 629, 595; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.70–3.55 (2H, m, 2 × CH), 2.99 (1H, d, *J* = 10.5 Hz, CH), 2.74–2.66 (1H, m, CH), 2.48–2.36 (1H, m, CH), 2.16 (3H, s, CH_3), 1.87–1.49 (11H, m, 11 × CH), 1.37–1.24 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.8 (C=O), 75.6 (C), 53.0 (CH_2), 48.0 (CH_2), 43.0 (CH), 39.5 (CH_2), 33.8 (CH_2), 30.3 (CH_2), 24.6 (CH_2), 21.6 (CH_2), 21.3 (CH_2), 21.0 (CH_3); HRMS *m/z* (ES) Found: MH^+, 209.1650. $C_{12}H_{21}N_2O$ requires MH^+ 209.1648; LRMS *m/z* (ES) 209 (100%, MH^+).

({1-Azaspiro[4.4]nonan-6-yl}methyl)(ethyl)amine (281)



To cycloadduct **275** (43 mg, 0.22 mmol) was added BH_3•THF complex solution (2.2 mL, 2.2 mmol, 1 M). The mixture was heated under reflux for 17 h and was cooled to rt. The reaction was quenched with MeOH (10 mL) and the mixture was concentrated under reduced pressure to give the crude product as a colourless. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH–NH_3 (9:1:0.5) to give diamine **281** (22 mg, 55%) as a pale yellow oil; R_f 0.11 [CH_2Cl_2–MeOH–NH_3 (9:1:0.5)]; FT-IR ν_{max} (film)/cm^{-1} 3391 (N-H), 3269, 2958, 2873, 1634, 1539, 1455, 1302, 1112, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.00 (2H, br s, 2 × NH), 3.26–3.12 (1H, m, CH), 3.03–2.83 (2H, m, 2 × CH), 2.83–2.69 (3H, m, 3 × CH), 2.09–1.96 (2H, m, 2 × CH), 1.92–1.83 (3H, m, 3 × CH), 1.82–1.69 (4H, m, 4 × CH), 1.64–1.53 (1H, m, CH), 1.50–1.41 (1H, m, CH), 1.18 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 73.5 (C), 50.6 (CH_2), 45.3 (CH_2), 43.4 (CH), 43.2 (CH_2), 38.4 (CH_2), 37.3 (CH_2), 28.4 (CH_2), 25.1 (CH_2), 21.6 (CH_2), 14.1 (CH_3); HRMS *m/z* (ES) Found: MH^+, 183.1860. $C_{11}H_{23}N_2$ requires MH^+ 183.1856; LRMS *m/z* (ES) 183 (100%, MH^+).

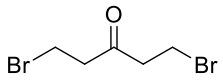
1-(2-Bromoethyl)cyclopropan-1-ol (376)



To a solution of ethyl 3-bromopropionate (4.6 mL, 36 mmol) in Et_2O (36 mL) was added $Ti(O^iPr)_4$ (1.1 mL, 3.6 mmol) and cooled to 0 °C. A solution of EtMgBr in Et_2O [prepared from magnesium (2.0 g, 81 mmol) and bromoethane (6.0 mL, 81 mmol) in Et_2O (39 mL), stirred at reflux for 1 h] was added dropwise. The mixture was warmed to rt and stirred for 16 h. The reaction was quenched with water (150 mL) and the mixture was diluted with 5% v/v aqueous H_2SO_4 (150 mL) and EtOAc (300 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown oil. The crude product

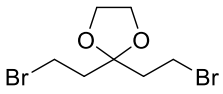
was purified by column chromatography on silica gel, eluting with petrol−EtOAc (4:1) to give cyclopropanol **376** (5 g, 84%) as a yellow oil; R_f 0.43 [petrol–EtOAc (7:3)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.64 (2H, t, *J* = 7.5 Hz, CH_2), 2.23–2.11 (3H, m, OH & CH_2), 0.86–0.81 (2H, m, CH_2), 0.59–0.54 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 55.0 (C), 41.3 (CH_2), 29.9 (CH_2), 13.6 (CH_2). Data consistent with the literature.[151]

1,5-Dibromopentan-3-one (377)



To a solution of cyclopropanol **376** (5.0 g, 30 mmol) in CH_2Cl_2 (60 mL) was added N-bromosuccinimide (5.4 g, 30 mmol) at 0 °C. The mixture was warmed to rt and stirred for 1 h. The solvent was removed under reduced pressure to give the crude product as an orange solid. The crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (7:3) to give ketone **377** (5.7 g, 78%) as an orange oil; R_f 0.52 [petrol–EtOAc (7:3)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.56 (4H, t, *J* = 6.5 Hz, 2 × CH_2), 3.05 (4H, t, *J* = 6.5 Hz, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 204.4 (C=O), 45.6 (CH_2), 24.7 (CH_2). Data consistent with the literature.[151]

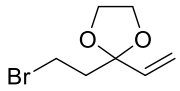
2,2-Bis(2-bromoethyl)-1,3-dioxolane (378)



To a solution of ketone **377** (4.4 g, 18 mmol) in benzene (160 mL) was added ethylene glycol (1.1 mL, 20 mmol) followed by TsOH.H_2O (169 mg, 0.888 mmol). The mixture was heated at reflux for 16 h with a Dean-Stark trap and cooled to rt. The solvent was removed under reduced pressure to give the crude product as a dark brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (49:1) to give ketal **378** (2.5 g, 49%) as a colourless oil which crystallised on standing to give a white solid; m.p. 48−50 °C [petrol−EtOAc] (lit.[112] 65 °C [no solvent]); R_f 0.60 [petrol–EtOAc (7:3)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.99 (4H,

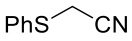
s, 2 × CH_2), 3.43–3.37 (4H, m, 2 × CH_2), 2.30–2.22 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 109.8 (C), 65.3 (CH_2), 41.1 (CH_2), 26.2 (CH_2). Data consistent with the literature.[112]

2-(2-Bromoethyl)-2-ethenyl-1,3-dioxolane (372)



To a solution of ketal **378** (8.2 g, 29 mmol) in PhMe (32 mL) was added KO^{t}Bu (3.8 g, 34 mmol) in THF (32 mL) at 0 °C using a syringe pump (0.2 mLmin^{-1}). Once addition was complete the mixture was allowed to warm up to rt and stirred for 1 h. The mixture was diluted with saturated aqueous NH_4Cl (80 mL) and EtOAc (300 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (19:1) to give bromide **372** (3 g, 51%) as a colourless oil; R_f 0.62 [petrol–EtOAc (7:3)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.71 (1H, dd, *J* = 17.0, 10.5 Hz, CH), 5.41 (1H, dd, *J* = 17.0, 1.5 Hz, C*H*^{A}H^B), 5.22 (1H, dd, *J* = 10.5, 1.5 Hz, CH^A*H*^{B}), 4.00–3.84 (4H, m, 2 × CH_2), 3.45–3.38 (2H, m, CH_2), 2.35–2.27 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.8 (CH), 116.4 (CH_2), 108.0 (C), 64.7 (CH_2), 41.5 (CH_2), 26.4 (CH_2). Data consistent with the literature.[112]

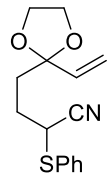
2-(Phenylsulfanyl)acetonitrile (371)



To a solution of bromoacetonitrile (7 mL, 0.1 mol) in DMF (227 mL) was added thiophenol (9.3 mL, 91 mmol) at 0 °C followed by K_2CO_3 (25 g, 0.18 mmol). The mixture was stirred for 2.5 h and warmed to rt. The mixture was filtered through a pad of celite and the filtrate was diluted with Et_2O (250 mL) and water (200 mL). The organic layer was separated, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give nitrile **371** (8.6 g, 64%) as a colourless oil; R_f 0.45 [petrol–EtOAc (7:3)]; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.53–7.48 (2H, m, 2 × CH), 7.47–7.39 (2H, m, 2 × H), 7.37–7.31 (1H, m, CH), 4.25 (2H, s, CH_2);

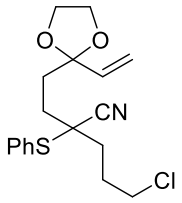
^{13}C NMR (100 MHz, DMSO-d_6) δ = 133.3 (C), 130.0 (CH), 129.9 (CH), 128.0 (CH), 118.4 (CN), 18.9 (CH_2). Data consistent with the literature.[152,153]

4-(2-Ethenyl-1,3-dioxolan-2-yl)-2-(phenylsulfanyl)butanenitrile (373)



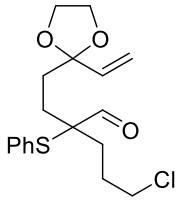
To a solution of diisopropylamine (0.15 mL, 1.0 mmol) in THF (0.5 mL) was added *n*-BuLi (0.4 mL, 1 mmol, 2.5 M in hexanes) at −78 °C. After 10 min, nitrile **371** (72 mg, 0.50 mmol) in THF (0.2 mL) was added. After 10 min, bromide **372** (100 mg, 0.483 mmol) in THF (0.2 mL) was added and the mixture was allowed to warm to rt over 1 h. The mixture was diluted with saturated aqueous NH_4Cl (5 mL) and Et_2O (50 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (19:1) to give nitrile **373** (61 mg, 46%) as a colourless oil; R_f 0.50 [petrol–EtOAc (7:3)]; FT-IR ν_{max} (film)/cm^{-1} 3061, 2951, 2887, 2232, 1477, 1436, 1196, 1042, 945, 746, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66–7.58 (2H m, 2 × CH), 7.45–7.37 (3H, m, 3 × CH), 5.71 (1H, dd, *J* = 17.0, 10.5 Hz, CH), 5.40 (1H, dd, *J* = 17.0, 1.5 Hz, C*H*^{A}H^B), 5.22 (1H, dd, *J* = 10.5, 1.5 Hz, CH^A*H*^{B}), 3.99–3.83 (5H, m, 2 × CH_2 & CH), 2.06–1.92 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.0 (CH), 134.7 (CH), 130.6 (C), 129.5 (CH), 129.4 (CH), 119.3 (CN), 116.4 (CH_2), 108.3 (C), 64.7 (CH_2), 64.6 (CH_2), 36.9 (CH), 34.5 (CH_2), 26.7 (CH_2); HRMS *m/z* (ES) Found: MH^+, 276.1054. $C_{15}H_{17}NO_2S$ requires MH^+ 276.1053; Found: MNa^+, 298.0872. $C_{15}H_{17}NO_2SNa$ requires MNa^+ 298.0872; LRMS *m/z* (ES) 276 (MH^+, 70%), 298 (100% MNa^+).

5-Chloro-2-[2-(2-ethenyl-1,3-dioxolan-2-yl)ethyl]-2-(phenylsulfanyl)pentanenitrile (374)



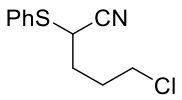
To a solution of diisopropylamine (0.07 mL, 0.5 mmol) in THF (0.5 mL) was added *n*-BuLi (0.19 mL, 0.48 mmol, 2.5 M in hexanes) at −78 °C. After 10 min, nitrile **373** (123 mg, 0.447 mmol) in THF (0.5 mL) was added dropwise. After 20 min, 1-bromo-3-chloropropane (0.05 mL, 0.5 mmol) was added and the mixture was stirred for a further 30 min at −78 °C. The mixture was allowed to warm to rt over 1 h and was diluted with saturated aqueous NH_4Cl (3 mL) and Et_2O (15 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as an orange oil. The crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (19:1) to give nitrile **374** (91 mg, 54%) as a colourless oil; R_f 0.47 [petrol–EtOAc (7:3)]; FT-IR ν_{max} (film)/cm^{-1} 3057, 2962, 2889, 2227, 1477, 1438, 1406, 1304, 1284, 1204, 1043, 992, 943, 914, 751, 697, 649; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.73–7.67 (2H, m, 2 × CH), 7.52–7.38 (3H, m, 3 × CH), 5.72 (1H, dd, *J* = 17.0, 10.5 Hz, CH), 5.40 (1H, dd, *J* = 17.0, 1.5 Hz, C*H*^{A}H^B), 5.21 (1H, dd, *J* = 10.5, 1.5 Hz, CH^A*H*^{B}), 3.99–3.85 (4H, m, 2 × CH_2), 3.64–3.53 (2H, m, CH_2), 2.20–1.81 (8H, m, 4 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.2 (CH), 137.1 (CH), 130.4 (CH), 129.3 (CH), 128.9 (C), 120.6 (CN), 116.2 (CH_2), 108.1 (C), 64.7 (CH_2), 64.68 (CH_2), 48.5 (C), 44.2 (CH_2), 34.2 (CH_2), 32.7 (CH_2), 30.5 (CH_2), 27.6 (CH_2); HRMS *m/z* (ES) Found: MH^+, 352.1144. $C_{18}H_{23}NO_2S^{35}Cl$ requires MH^+ 352.1133; Found: MH^+, 354.1128. $C_{18}H_{23}NO_2S^{37}Cl$ requires MH^+ 354.1103; LRMS *m/z* (ES) 352 (100%, MH^+ for ^{35}Cl), 354 (35%, MH^+ for ^{37}Cl).

5-Chloro-2-[2-(2-ethenyl-1,3-dioxolan-2-yl)ethyl]-2-(phenylsulfanyl)pentanal (366)



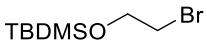
To a solution of nitrile **374** (99 mg, 0.28 mmol) in CH_2Cl_2 (3 mL) was added DIBAL-H (0.56 mL, 0.56 mmol, 1 M in hexanes) at −78 °C. The mixture was stirred for 1 h and aqueous oxalic acid (1 mL, 0.5 M) was added dropwise. After 20 min, the mixture was allowed to warm to rt before a further portion of aqueous oxalic acid (1 mL, 0.5 M) and Et_2O (20 mL) was added. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a colourless oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give aldehyde **366** (42 mg, 42%) as a colourless oil; R_f 0.38 [petrol–EtOAc (7:3)]; FT-IR ν_{max} (film)/cm^{-1} 3057, 2955, 2931, 2882, 1713 (C=O), 1472, 1440, 1277, 1184, 1038, 990, 948, 748, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.34 (1H, s, CHO), 7.54–7.23 (5H, m, 5 × CH), 5.77–5.66 (1H, m, CH), 5.39 (1H, dd, *J* = 17.0, 1.5 Hz, C*H*^{A}H^B), 5.24–5.17 (1H, m, CH^A*H*^{B}), 4.01–3.84 (4H, m, 2 × CH_2), 3.64–3.48 (2H, m, CH_2), 2.14–1.54 (8H, m, 4 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 194.8 (C=O), 137.2 (CH), 137.1 (CH), 129.8 (CH), 129.1 (CH), 128.7 (C), 116.1 (CH_2), 108.3 (C), 64.7 (CH_2), 48.5 (C), 44.8 (CH_2), 32.1 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 23.5 (CH_2); HRMS *m/z* (ES) Found: MH^+, 377.0955. $C_{18}H_{24}O_3S^{35}Cl$ requires MH^+ 377.0949; Found: MH^+, 379.0929. $C_{18}H_{24}O_3S^{37}Cl$ requires MH^+ 379.0919; LRMS *m/z* (ES) 377 (100%, MH^+ for ^{35}Cl), 379 (35%, MH^+ for ^{37}Cl).

5-Chloro-2-(phenylsulfanyl)pentanenitrile (380)



To a solution of diisopropylamine (0.65 mL, 4.6 mmol) in THF (3 mL) was added *n*-BuLi (1.7 mL, 4.2 mmol, 2.5 M in hexanes) at −78 °C. After 10 min, nitrile **371** (0.6 g, 4 mmol) in THF (1.5 mL) was added dropwise. After 10 min, 1-bromo-3-chloropropane (0.40 mL, 17 mmol) was added and the mixture was stirred for a further 10 min at −78 °C. The mixture was allowed to warm to rt over 1 h and was diluted with saturated aqueous NH_4Cl (15 mL) and Et_2O (200 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give nitrile **380** (505 mg, 56%) as a colourless oil; R_f 0.59 [petrol–EtOAc (7:3)]; FT-IR ν_{max} (film)/cm^{-1} 3059, 2957, 2917, 2867, 2235, 1580, 1476, 1441, 1304, 1284, 1065, 1025, 751, 691, 649; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66–7.62 (2H, m, 2 × CH), 7.45–7.40 (3H, m, 3 × CH), 3.80–3.72 (1H, m, CH), 3.63–3.58 (2H, m, CH_2), 2.16–1.97 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 134.8 (CH), 130.2 (C), 129.8 (CH), 129.6 (CH), 118.8 (CN), 43.6 (CH_2), 36.5 (CH), 29.8 (CH_2), 29.6 (CH_2). HRMS *m/z* (ES) Found: MNa^+, 248.0281. $C_{11}H_{12}NS^{35}ClNa$ requires MNa^+ 248.0271; Found: MNa^+, 250.0249. $C_{11}H_{12}NS^{37}ClNa$ requires MNa^+ 250.0242; LRMS *m/z* (ES) 248 (100%, MNa^+ for ^{35}Cl), 250 (35%, MNa^+ for ^{37}Cl).

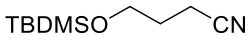
(2-Bromoethoxy)(tert-butyl)dimethylsilane (392)



To a solution of imidazole (3.7 g, 55 mmol) in DMF (7.5 mL) was added *tert*-butyldimethylsilyl chloride (6.4 g, 42 mmol) at rt and the mixture was stirred for 30 min. 2-bromoethanol (3.0 mL, 42 mmol) was added and the mixture was stirred for 16 h at rt. The mixture was diluted with Et_2O (150 mL) and water (50 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a colourless oil.

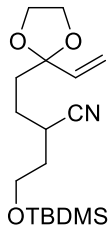
The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give compound **392** (7.8 g, 77%) as a colourless oil; R_f 0.68 [petrol–EtOAc (4:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.92 (2H, t, *J* = 6.5 Hz, CH_2), 3.42 (2H, t, *J* = 6.5 Hz, CH_2), 0.93 (9H, s, 3 × CH_3), 0.11 (6H, s, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 63.5 (CH_2), 33.2 (CH_2), 25.8 (CH_3), 18.3 (C), −5.3 (CH_3). Data consistent with the literature.[154]

4-[(tert-Butyldimethylsilyl)oxy]butanenitrile (388)



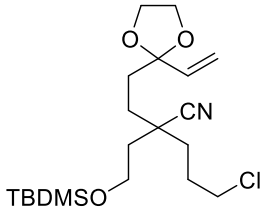
To a solution of diisopropylamine (6.2 mL, 44 mmol) in THF (42 mL) was added *n*-BuLi (17 mL, 42 mmol, 2.4 M in hexanes) at −78 °C. After 10 min, acetonitrile (4.4 mL, 84 mmol) was added dropwise. After 10 min, compound **392** (5 g, 21 mmol) was added and the mixture was stirred for a further 30 min at −78 °C. The mixture was allowed to warm to rt over 1 h and was diluted with saturated aqueous NH_4Cl (100 mL) and Et_2O (200 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a pale yellow oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give nitrile **388** (2.5 g, 60%) as a colourless oil; R_f 0.29 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.74 (2H, t, *J* = 5.5 Hz, CH_2), 2.47 (2H, t, *J* = 7.0 Hz, CH_2), 1.92–1.82 (2H, m, CH_2), 0.92 (9H, s, 3 × CH_3), 0.09 (6H, s, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 119.7 (CN), 60.6 (CH_2), 28.5 (CH_2), 25.8 (CH_3), 18.2 (C), 13.7 (CH_2), −5.5 (CH_3). Data consistent with the literature.[155]

4-[(tert-Butyldimethylsilyl)oxy]-2-[2-(2-ethenyl-1,3-dioxolan-2-yl)ethyl]butanenitrile (389)



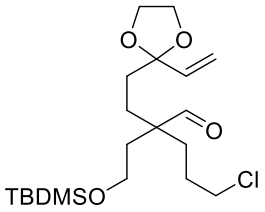
To a solution of diisopropylamine (3.0 mL, 21 mmol) in THF (15 mL) was added *n*-BuLi (10 mL, 21 mmol, 2.1 M in hexanes) at −78 °C. After 10 min, nitrile **388** (8.5 g, 42 mmol) in THF (3 mL) was added dropwise. After 10 min, bromide **372** (2.2 g, 11 mmol) in THF (3 mL) was added and the mixture was stirred for a further 30 min at −78 °C. The mixture was allowed to warm to rt over 1 h and was diluted with saturated aqueous NH_4Cl (100 mL) and Et_2O (200 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give nitrile **389** (2.7 g, 81%) as a colourless oil; R_f 0.39 [petrol–EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 2952, 2930, 2888, 2855, 1469, 1407, 1249, 1098, 1049, 933, 830, 777; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.73 (1H, dd, *J* = 17.0, 10.5 Hz, CH), 5.40 (1H, dd, *J* = 17.0, 1.5 Hz, C*H*^{A}H^B), 5.21 (1H, dd, *J* = 10.5, 1.5 Hz, CH^A*H*^{B}), 3.99–3.87 (4H, m, 2 × CH_2), 3.77 (2H, t, *J* = 6.0 Hz, CH_2), 2.92–2.83 (1H, m, CH), 2.02–1.69 (6H, m, 3 × CH_2), 0.91 (9H, s, 3 × CH_3), 0.09 (3H, s, CH_3), 0.08 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.2 (CH), 122.0 (CN), 116.1 (CH_2), 108.4 (C), 64.7 (CH_2), 64.5 (CH_2), 59.8 (CH_2), 35.3 (CH_2), 35.2 (CH_2), 27.9 (CH), 26.1 (CH_2), 25.9 (CH_3), 18.2 (C), -5.45 (CH_3), −5.47 (CH_3); HRMS *m/z* (ES) Found: MH^+, 326.2156. $C_{17}H_{32}NO_3Si$ requires MH^+ 326.2146; LRMS *m/z* (ES) 326 (100%, MH^+), 348 (30%, MNa^+).

2-{2-[(tert-Butyldimethylsilyl)oxy]ethyl}-5-chloro-2-[2-(2-ethenyl-1,3-dioxolan-2-yl)ethyl]pentanenitrile (390)



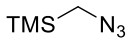
To a solution of diisopropylamine (2.4 mL, 17 mmol) in THF (15 mL) was added *n*-BuLi (7.9 mL, 17 mmol, 2.1 M in hexanes) at −78 °C. After 10 min, nitrile **389** (2.7 g, 8.3 mmol) in THF (2 mL) was added dropwise. After 20 min, 1-bromo-3-chloropropane (1.6 mL, 17 mmol) was added and the mixture was stirred for a further 30 min at −78 °C. The mixture was allowed to warm to rt over 1 h and was diluted with saturated aqueous NH_4Cl (60 mL) and Et_2O (150 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give nitrile **390** (2.3 g, 69%) as a colourless oil; R_f 0.43 [petrol–EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 2955, 2931, 2884, 2856, 1470, 1405, 1252, 1095, 1044, 940, 834, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.73 (1H, dd, *J* = 17.0, 10.5 Hz, CH), 5.40 (1H, dd, *J* = 17.0, 1.5 Hz, C*H*^{A}H^B), 5.22 (1H, dd, *J* = 10.5, 1.5 Hz, CH^A*H*^{B}), 4.00–3.87 (4H, m, 2 × CH_2), 3.82 (2H, t, *J* = 6.5 Hz, CH_2), 3.58 (2H, t, *J* = 6.5 Hz, CH_2), 2.00–1.69 (10H, m, 5 × CH_2), 0.92 (9H, s, 3 × CH_3), 0.09 (6H, s, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.2 (CH), 123.1 (CN), 116.2 (CH_2), 108.3 (C), 64.6 (CH_2), 59.3 (CH_2), 44.6 (CH_2), 38.6 (C), 38.3 (CH_2), 34.0 (CH_2), 32.6 (CH_2), 30.0 (CH_2), 27.6 (CH_2), 25.9 (CH_3), 18.2 (C), −5.4 (CH_3); HRMS *m/z* (ES) Found: MH^+, 402.2244. $C_{20}H_{37}NO_3Si^{35}Cl$ requires MH^+ 402.2226; Found: MH^+, 404.2224. $C_{20}H_{37}NO_3Si^{37}Cl$ requires MH^+ 404.2196; LRMS *m/z* (ES) 402 (100%, MH^+ for ^{35}Cl), 404 (35%, MH^+ for ^{37}Cl).

2-{2-[(tert-Butyldimethylsilyl)oxy]ethyl}-5-chloro-2-[2-(2-ethenyl-1,3-dioxolan-2-yl)ethyl]pentanal (381)



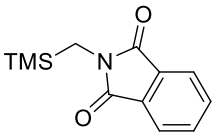
To a solution of nitrile **390** (350 mg, 0.871 mmol) in CH_2Cl_2 (8.7 mL) was added DIBAL-H (1.7 mL, 1.7 mmol, 1 M in hexanes) at −78 °C. The mixture was stirred for 1 h and aqueous oxalic acid (2 mL, 0.5 M) was added dropwise. After 20 min, the mixture was allowed to warm to rt before a further portion of aqueous oxalic acid (4 mL, 0.5 M) and Et_2O (100 mL) was added. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a colourless oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (19:1) to give aldehyde **381** (262 mg, 74%) as a colourless oil; R_f 0.46 [petrol–EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 2952, 2926, 2886, 2859, 1724 (C=O), 1471, 1459, 1257, 1092, 1045, 938, 834, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.42 (1H, s, CHO), 5.71 (1H, dd, *J* = 17.0, 10.5 Hz, CH), 5.38 (1H, dd, *J* = 17.0, 1.5 Hz, C*H*^{A}H^B), 5.20 (1H, dd, *J* = 10.5, 1.5 Hz, CH^A*H*^{B}), 4.01–3.84 (4H, m, 2 × CH_2), 3.61 (2H, t, *J* = 6.0 Hz, CH_2), 3.58–3.48 (2H, m, CH_2), 1.78 (2H, t, *J* = 6.0 Hz, CH_2), 1.74–1.51 (8H, m, 4 × CH_2), 0.88 (9H, s, 3 × CH_3), 0.03 (6H, s, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.1 (CH), 137.3 (CH), 116.0 (CH_2), 108.6 (C), 64.6 (CH_2), 58.7 (CH_2), 49.5 (C), 45.3 (CH_2), 36.7 (CH_2), 31.5 (CH_2), 28.1 (CH_2), 26.5 (CH_2), 25.9 (CH_3), 24.1 (CH_2), 18.2 (C), −5.6 (CH_3); HRMS *m/z* (ES) Found: MH^+, 405.2222. $C_{20}H_{38}O_4Si^{35}Cl$ requires MH^+ 405.2222; Found: MH^+, 407.2198. $C_{20}H_{38}O_4Si^{37}Cl$ requires MH^+ 407.2193; LRMS *m/z* (ES) 405 (100%, MH^+ for ^{35}Cl), 407 (35%, MH^+ for ^{37}Cl).

(Azidomethyl)trimethylsilane (399)



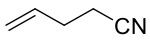
To a solution of chloromethyltrimethylsilane (3.4 mL, 25 mmol) in *N*,*N*-dimethylformamide (30 mL) was added sodium azide (4.8 g, 74 mmol) followed by potassium iodide (81 mg, 0.49 mmol). The mixture was stirred for 10 min at rt before being warmed to 60 °C. The mixture was stirred for 12 h and cooled to rt. The crude product was collected using vacuum distillation (vapour temperature 65 °C under house vacuum) and was diluted with Et_2O (10 mL), washed with water (2 × 5 mL), dried over anhydrous $MgSO_4$, and filtered. The solvent was removed through distillation to give azide **399** (2 g, 63%) as a colourless oil; FT-IR ν_{max} (film)/cm^{-1} 2958, 2893, 2088, 1685, 1293, 1253, 840; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.78 (2H, s, CH_2), 0.14 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 42.1 (CH_2), −2.6 (CH_3). Data consistent with the literature.[156]

2-[(Trimethylsilyl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione (400)



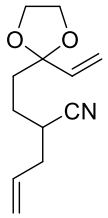
To a suspension of phthalimide potassium salt (7.8 g, 42 mmol) and TBAI (154 mg, 0.417 mmol) in DMF (50 mL) was added chloromethyltrimethylsilane (5.3 mL, 38 mmol). The mixture was heated at 70 °C for 4 h and cooled to rt. The mixture was diluted with Et_2O (200 mL) and water (50 mL). The organic layer was separated, washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product **400** (8.9 g, quantitative yield) as a yellow oil; R_f 0.25 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86–7.80 (4H, m, 2 × CH), 7.74–7.67 (2H, m, 2 × CH), 3.22 (2H, s, CH_2), 0.14 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.5 (C=O), 133.6 (CH), 132.3 (C), 122.9 (CH), 29.2 (CH_2), −1.8 (CH_3). Data consistent with the literature.[157]

Pent-4-enenitrile (404)



To a suspension of potassium cyanide (5.6 g, 85 mmol) in ethylene glycol (60 mL) was added 4-bromo-1-butene (8.0 mL, 78 mmol). The mixture was heated at 100 °C for 2 h and cooled to rt. The crude product was collected using vacuum distillation (vapour temperature 80 °C under house vacuum) and was diluted with Et_2O (20 mL), washed with water (2 × 10 mL), dried over anhydrous $MgSO_4$, and filtered. The solvent was removed using distillation to give nitrile **404** as a colourless oil; R_f 0.20 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.96–5.73 (1H, m, CH), 5.26–5.15 (2H, m, CH_2), 2.52–2.35 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 134.1 (CH), 119.2 (CN), 117.8 (CH_2), 29.3 (CH_2), 17.0 (CH_2). Data consistent with the literature.[158]

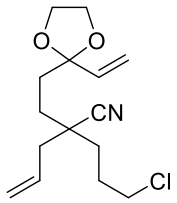
2-[2-(2-Ethenyl-1,3-dioxolan-2-yl)ethyl]pent-4-enenitrile (405)



To a solution of diisopropylamine (0.68 mL, 4.8 mmol) in THF (3 mL) was added *n*-BuLi (2.1 mL, 4.8 mmol, 2.3 M in hexanes) at −78 °C. After 10 min, nitrile **404** (784 mg, 9.66 mmol) in THF (1 mL) was added dropwise. After 10 min, bromide **372** (500 mg, 2.41 mmol) in THF (1 mL) was added and the mixture was stirred for a further 30 min at −78 °C. The mixture was allowed to warm to rt over 1 h and was diluted with saturated aqueous NH_4Cl (10 mL) and Et_2O (60 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) to give nitrile **405** (193 mg, 39%) as a colourless oil; R_f 0.17 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3085, 2948, 2889, 2241, 1645, 1454, 1408, 1207, 1189, 1043, 991, 927, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.90–5.78 (1H, m, CH), 5.73 (1H, dd, *J* = 17.0, 10.5 Hz, CH), 5.40 (1H, dd, *J* = 17.0, 1.5 Hz, C*H*^{A}H^B), 5.25–5.18 (3H, m, CH^A*H*^{B} & CH_2), 4.01–3.87 (4H, m, 2 × CH_2), 2.73–2.65 (1H, m, CH), 2.36 (2H, t, *J* = 7.0 Hz,

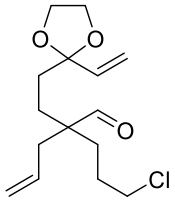
CH_2), 2.02–1.93 (1H, m, CH), 1.89–1.81 (1H, m, CH), 1.78–1.71 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.2 (CH), 133.1 (CH), 121.6 (CN), 118.9 (CH_2), 116.2 (CH_2), 108.3 (C), 64.7 (CH_2), 64.5 (CH_2), 36.3 (CH_2), 35.1 (CH_2), 31.4 (CH), 25.7 (CH_2); HRMS *m/z* (ES) Found: MH^+, 208.1333. $C_{12}H_{18}NO_2$ requires MH^+ 208.1332; LRMS *m/z* (ES) 208 (100%, MH^+).

2-(3-Chloropropyl)-2-[2-(2-ethenyl-1,3-dioxolan-2-yl)ethyl]pent-4-enenitrile (406)



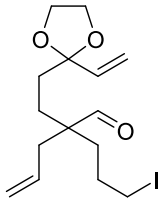
To a solution of diisopropylamine (0.22 mL, 1.6 mmol) in THF (1 mL) was added *n*-BuLi (0.66 mL, 1.5 mmol, 2.3 M in hexanes) at −78 °C. After 10 min, nitrile **405** (158 mg, 0.762 mmol) in THF (0.5 mL) was added dropwise. After 20 min, 1-bromo-3-chloropropane (0.15 mL, 1.5 mmol) was added and the mixture was stirred for a further 30 min at −78 °C. The mixture was allowed to warm to rt over 1 h and was diluted with saturated aqueous NH_4Cl (2 mL) and Et_2O (10 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) to give nitrile **406** (169 mg, 82%) as a colourless oil; R_f 0.69 [petrol–EtOAc (7:3)]; FT-IR ν_{max} (film)/cm^{-1} 3078, 2960, 2888, 2233, 1643, 1453, 1408, 1295, 1208, 1043, 993, 930, 655; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.89–5.77 (1H, m, CH), 5.73 (1H, dd, *J* = 17.0, 10.5 Hz, CH), 5.40 (1H, dd, *J* = 17.0, 1.5 Hz, CH^AH^B), 5.29–5.19 (3H, m, CH^AH^B & CH_2), 4.01–3.86 (4H, m, 2 × CH_2), 3.58 (2H, t, *J* = 6.0 Hz, CH_2), 2.41–2.31 (2H, m, CH_2), 2.00–1.90 (2H, m, CH_2), 1.90–1.83 (2H, m, CH_2), 1.81–1.65 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.1 (CH), 131.2 (CH), 122.9 (CN), 120.4 (CH_2), 116.2 (CH_2), 108.3 (C), 64.7 (CH_2), 44.6 (CH_2), 40.3 (CH_2), 39.7 (C), 33.4 (CH_2), 32.6 (CH_2), 29.5 (CH_2), 27.5 (CH_2); HRMS *m/z* (ES) Found: MH^+, 284.1418. $C_{15}H_{23}NO_2{}^{35}Cl$ requires MH^+ 284.1412; Found: MH^+, 286.1409. $C_{15}H_{23}NO_2{}^{37}Cl$ requires MH^+ 286.1382; LRMS *m/z* (ES) 284 (100%, MH^+ for ^{35}Cl), 286 (35%, MH^+ for ^{37}Cl).

2-(3-Chloropropyl)-2-[2-(2-ethenyl-1,3-dioxolan-2-yl)ethyl]pent-4-enal (401)



To a solution of nitrile **406** (130 mg, 0.458 mmol) in CH_2Cl_2 (5 mL) was added DIBAL-H (0.92 mL, 0.92 mmol, 1 M in hexanes) at −78 °C. The mixture was stirred for 1 h and aqueous oxalic acid (3 mL, 0.5 M) was added dropwise. After 20 min, the mixture was allowed to warm to rt before a further portion of aqueous oxalic acid (3 mL, 0.5 M) and Et_2O (20 mL) was added. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a colourless oil. The crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (19:1) to give aldehyde **401** (77 mg, 59%) as a colourless oil; R_f 0.47 [petrol–EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 3076, 2955, 2885, 2705, 1725 (C=O), 1640, 1460, 1408, 1298, 1203, 1043, 995, 943, 885; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.46 (1H, s, CHO), 5.77–5.60 (2H, m, 2 × CH), 5.38 (1H, dd, *J* = 17.0, 1.5 Hz, C*H*^{A}H^B), 5.25–5.07 (3H, m, CH^A*H*^{B} & CH_2), 4.00–3.85 (4H, m, 2 × CH_2), 3.52 (2H, t, *J* = 6.0 Hz, CH_2), 2.28 (2H, d, *J* = 6.0 Hz, CH_2), 1.73–1.55 (8H, m, 4 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.6 (CH), 137.3 (CH), 132.3 (CH), 118.8 (CH_2), 116.0 (CH_2), 108.6 (C), 64.6 (CH_2), 51.1 (C), 45.1 (CH_2), 36.4 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 26.6 (CH_2), 25.6 (CH_2); HRMS *m/z* (ES) Found: MH^+, 287.1418. $C_{15}H_{24}O_3{}^{35}Cl$ requires MH^+ 287.1408; Found: MH^+, 289.1396. $C_{15}H_{24}O_3{}^{37}Cl$ requires MH^+ 289.1379; LRMS *m/z* (ES) 287 (100%, MH^+ for ^{35}Cl), 289 (35%, MH^+ for ^{37}Cl).

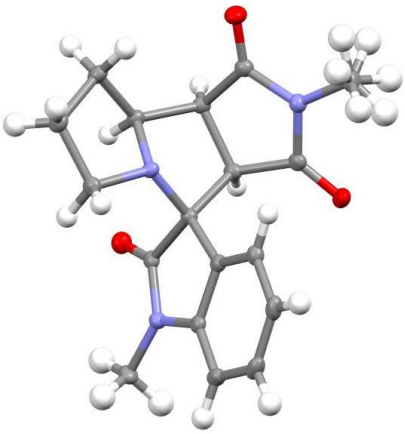
2-[2-(2-Ethenyl-1,3-dioxolan-2-yl)ethyl]-2-(3-iodopropyl)pent-4-enal (408)



To a solution of aldehyde **401** (133 mg, 0.464 mmol) in acetone (2.5 mL) was added sodium iodide (278 mg, 1.86 mmol). The mixture was heated at reflux for 16 h and cooled to rt. The mixture was diluted with Et_2O (10 mL) and 5% wt aqueous sodium thiosulfate (3 mL). The organic layer was separated, washed with water (2 × 3 mL), and brine (3 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give aldehyde **408** (148 mg, 84%) as a yellow oil; R_f 0.47 [petrol–EtOAc (4:1)]; FT-IR ν_{max} (film)/cm^{-1} 3076, 2952, 2887, 2701, 1722 (C=O), 1640, 1456, 1405, 1188, 1045, 992, 921; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.45 (1H, s, CHO), 5.79–5.60 (2H, m, 2 × CH), 5.38 (1H, dd, *J* = 17.0, 1.5 Hz, C*H*^{A}H^B), 5.23–5.09 (3H, m, CH^A*H*^{B} & CH_2), 3.99–3.86 (4H, m, 2 × CH_2), 3.16 (2H, t, *J* = 6.5 Hz, CH_2), 2.27 (2H, d, *J* = 7.5 Hz, CH_2), 1.76–1.57 (8H, m, 4 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.6 (CH), 137.3 (CH), 132.3 (CH), 118.8 (CH_2), 116.0 (CH_2), 108.6 (C), 64.6 (CH_2), 51.1 (C), 36.4 (CH_2), 32.9 (CH_2), 31.7 (CH_2), 27.4 (CH_2), 25.6 (CH_2), 6.47 (CH_2); HRMS *m/z* (ES) Found: MH^+, 379.0760. $C_{15}H_{24}O_3I$ requires MH^+ 379.0765; LRMS *m/z* (ES) 379 (100%, MH^+).

Appendices

Appendix 1: X-ray crystal structure data for compound **127**



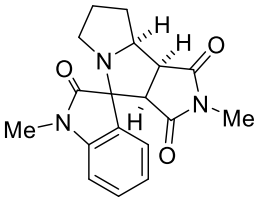
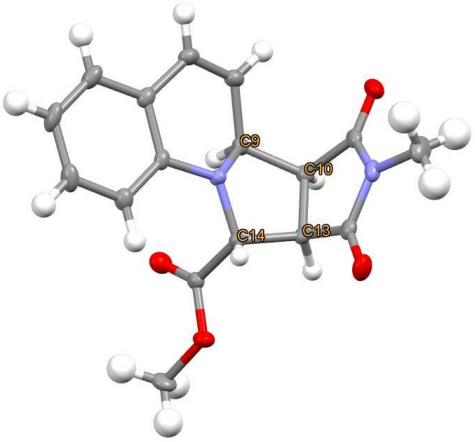


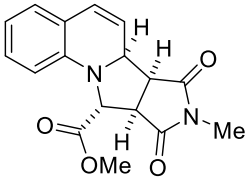
Table 1 Crystal data and structure refinement for oic278k_0m.

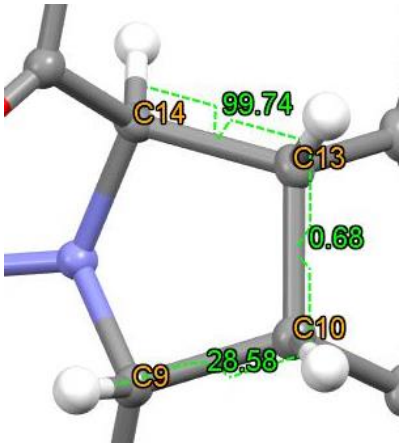
Identification code	oic278k_0m	
Empirical formula	$C_{18}H_{19}N_3O_3$	
Formula weight	325.36	
Temperature	100 K	
Crystal system	triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.1741(7) Å	α = 68.278(2)°
	b = 9.0755(8) Å	β = 87.555(3)°
	c = 11.7728(10) Å	γ = 72.855(2)°
Volume	773.11(12) $Å^3$	
Z	2	
Density (calculated)	1.398 g/cm^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	344	
Crystal size	0.32 × 0.28 × 0.21 mm^3	
Radiation	MoKα (λ = 0.71073)	
Theta range for data collection	3.734 to 55.246°	
Index ranges	-10 ≤ h ≤ 10, -11 ≤ k ≤ 11, -15 ≤ l ≤ 15	
Reflections collected	19731	
Independent reflections	3593 [R_{int} = 0.0247, R_{sigma} = 0.0181]	

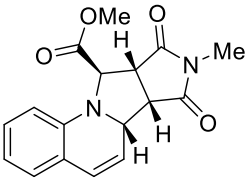
Data / restraints / parameters	3593 / 0 / 218
Goodness-of-fit on F^2	1.037
Final R indexes [I>=2σ (I)]	R_1 = 0.0354, wR_2 = 0.0873
Final R indexes (all data)	R_1 = 0.0432, wR_2 = 0.0928
Largest diff. peak and hole	0.31 and -0.23 e.Å^{-3}

Appendix 2: X-ray crystal structure data for compound **133** (key dihedral angles shown in green)









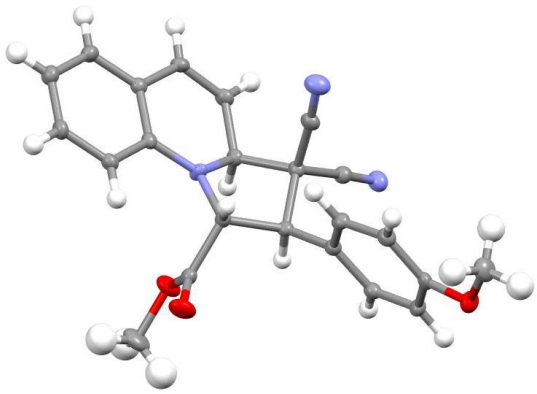
CCDC Deposition Number 1907019

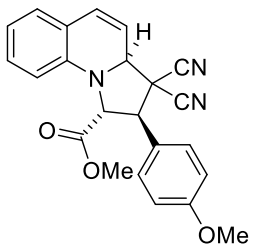
Table 1 Crystal data and structure refinement for oic292v_0m.

Identification code	oic292v_0m
Empirical formula	$C_{17}H_{16}N_2O_4$
Formula weight	312.32
Temperature	99.97 K
Crystal system	monoclinic
Space group	$P2_1/n$

Unit cell dimensions	a = 9.8029(10) Å	α = 90°
	b = 10.9827(10) Å	β = 108.944(4)°
	c = 14.4853(13) Å	γ = 90°
Volume	1475.1(2) $Å^3$	
Z	4	
Density (calculated)	1.406	
Absorption coefficient	0.841 mm^{-1}	
F(000)	656	
Crystal size	0.23 × 0.18 × 0.1 mm^3	
Radiation	CuKα (λ = 1.54178)	
Theta range for data collection	10.322 to 133.396°	
Index ranges	-11 ≤ h ≤ 11, -13 ≤ k ≤ 13, -17 ≤ l ≤ 17	
Reflections collected	18953	
Independent reflections	2596 [R_{int} = 0.0606, R_{sigma} = 0.0343]	
Data / restraints / parameters	2596 / 0 / 210	
Goodness-of-fit on F^2	1.242	
Final R indexes [I>=2σ (I)]	R_1 = 0.0412, wR_2 = 0.1397	
Final R indexes (all data)	R_1 = 0.0466, wR_2 = 0.1462	
Largest diff. peak and hole	0.31 and -0.25 e.$Å^{-3}$	

Appendix 3: X-ray crystal structure data for compound **139**



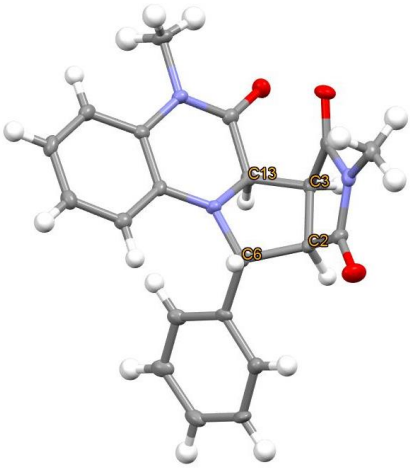


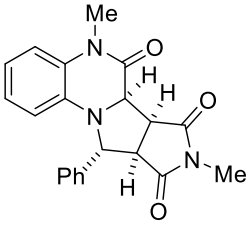
CCDC Deposition Number 1907018

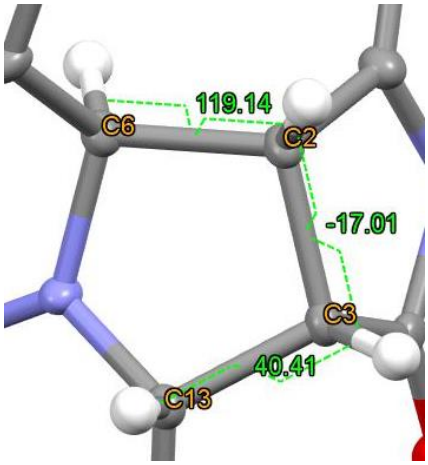
Table 1 Crystal data and structure refinement for oic289k_0m_a.

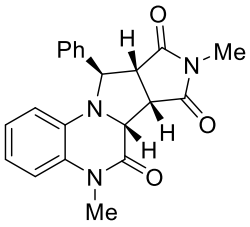
Identification code	oic289k_0m_a	
Empirical formula	$C_{23}H_{19}N_3O_3$	
Formula weight	385.41	
Temperature	100 K	
Crystal system	monoclinic	
Space group	Cc	
Unit cell dimensions	a = 12.810(3) Å	α = 90°
	b = 12.661(3) Å	β = 95.874(8)°
	c = 12.025(3) Å	γ = 90°
Volume	1940.1(8) $Å^3$	
Z	4	
Density (calculated)	1.319 g/cm^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	808.0	
Crystal size	0.379 × 0.267 × 0.211 mm^3	
Radiation	MoKα (λ = 0.71073)	
Theta range for data collection	4.536 to 55.28°	
Index ranges	-16 ≤ h ≤ 16, -16 ≤ k ≤ 16, -15 ≤ l ≤ 15	
Reflections collected	31377	
Independent reflections	4501 [R_{int} = 0.0533, R_{sigma} = 0.0369]	
Data / restraints / parameters	4501 / 2 / 264	
Goodness-of-fit on F^2	1.166	
Final R indexes [I>=2σ (I)]	R_1 = 0.0382, wR_2 = 0.1021	
Final R indexes (all data)	R_1 = 0.0493, wR_2 = 0.1210	
Largest diff. peak and hole	0.26 and -0.35 e.$Å^{-3}$	
Flack parameter	0.0(5)	

Appendix 4: X-ray crystal structure data for compound **160** (key dihedral angles shown in green)









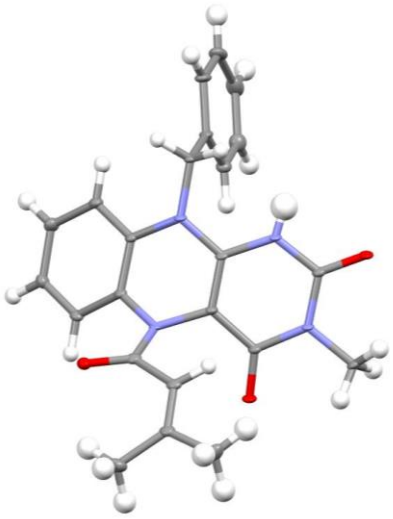
CCDC Deposition Number 1939356

Table 1 Crystal data and structure refinement for oic303k_0m.

Identification code	oic303k_0m	
Empirical formula	$C_{21}H_{19}N_3O_3$	
Formula weight	361.39	
Temperature	100 K	
Crystal system	monoclinic	
Space group	Cc	
Unit cell dimensions	a = 11.846(4) Å	α = 90°
	b = 18.586(7) Å	β = 124.369(9)°
	c = 9.443(3) Å	γ = 90°
Volume	1716.2(10) $Å^3$	
Z	4	

Density (calculated)	1.399 g/cm^3
Absorption coefficient	0.095 mm^{-1}
F(000)	760.0
Crystal size	0.36 × 0.28 × 0.26 mm^3
Radiation	MoKα (λ = 0.71073)
Theta range for data collection	4.382 to 55.102°
Index ranges	-15 ≤ h ≤ 15, -24 ≤ k ≤ 24, -12 ≤ l ≤ 12
Reflections collected	19109
Independent reflections	3965 [R_{int} = 0.0731, R_{sigma} = 0.0621]
Data / restraints / parameters	3965 / 2 / 246
Goodness-of-fit on F^2	0.869
Final R indexes [I>=2σ (I)]	R_1 = 0.0444, wR_2 = 0.1130
Final R indexes (all data)	R_1 = 0.0651, wR_2 = 0.1306
Largest diff. peak and hole	0.24 and -0.26 e.Å^{-3}
Flack parameter	0.0(8)

Appendix 5: X-ray crystal structure data for compound **195**



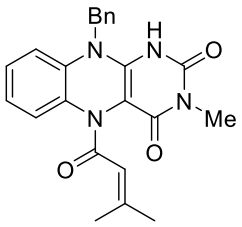


Table 1 Crystal data and structure refinement for oic299k_0m.

Identification code	oic299k_0m
Empirical formula	$C_{24}H_{24}Cl_2N_4O_3$
Formula weight	487.37

Temperature	100 K	
Crystal system	triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.6240(10) Å	α = 70.216(3)°
	b = 12.1397(14) Å	β = 77.391(3)°
	c = 12.1653(14) Å	γ = 74.423(3)°
Volume	1143.0(2) $Å^3$	
Z	2	
Density (calculated)	1.416 g/cm^3	
Absorption coefficient	0.319 mm^{-1}	
F(000)	508.0	
Crystal size	0.45 × 0.35 × 0.05 mm^3	
Radiation	MoKα (λ = 0.71073)	
Theta range for data collection	3.594 to 55.358°	
Index ranges	-11 ≤ h ≤ 11, -15 ≤ k ≤ 15, -15 ≤ l ≤ 15	
Reflections collected	33392	
Independent reflections	5297 [R_{int} = 0.0648, R_{sigma} = 0.0437]	
Data / restraints / parameters	5297 / 252 / 263	
Goodness-of-fit on F^2	1.042	
Final R indexes [I>=2σ (I)]	R_1 = 0.0550, wR_2 = 0.1474	
Final R indexes (all data)	R_1 = 0.0697, wR_2 = 0.1629	
Largest diff. peak and hole	1.07 and -0.93 e.$Å^{-3}$	

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