Novel (3+2) dipolar cycloadditions of pyridinium ylides



Tom Tongue

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Authorship

Declaration of Authorship

I declare that the work embodied in this thesis is the result of my own investigations. Where the work of other investigators has been used, this has been fully acknowledged in the text.

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Tom Tongue

Abstract

This thesis describes advances in novel (3+2) dipolar cycloadditions of pyridinium ylides, their reactions with electrophilic alkenes afford tetrahydroindolizines which can possess alkaloid-like scaffolds. Pyridinium ylides have been shown to be highly reactive intermediates that are able to rapidly generate molecular complexity with excellent regio and diastereoselectivity.

Chapter one reports an introduction on the chemistry of pyridinium ylides and introduces spirocyclic indolizidine containing natural products which could conceivably be synthesised through (3+2) dipolar cycloadditions.

The results and discussion section is divided into three chapters:

Chapter two describes the synthesis of indoxyl dipolarophiles including a novel approach towards the synthesis of 2-alkenylindol-3-ones. Details of the reactions of these dipolarophiles with pyridinium ylides to afford spirocyclic indoxyl cycloadducts follow. Subsequent modification of the 1,2-dihydropyridine moiety in the resulting cycloadducts is also demonstrated;

Chapter three describes the investigation towards an asymmetric (3+2) dipolar cycloaddition, using pyridinium ylides generated by the *in situ* decomposition of diazo compounds with transition metal catalysts;

Finally, chapter four describes attempts to synthesise spirocyclic indoxyl compounds which are structurally related to the opioid mitragynine pseudoindoxyl. Initially this is investigated *via* the methodology developed in chapter two, then subsequently using a magnesium iodide promoted ring expansion of a cyclopropane.

Acknowledgements

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List of abbreviations

9-BBN - 9-borabicyclo[3.3.1]nonane

Ac - acetyl

DBU - 1,8-diazabicyclo[5.4.0]undec-7-ene

DEPT - distortionless enhancement by polarization transfer

DIAD - diisopropyl azodicarboxylate

DMAD - dimethyl acetylenedicarboxylate

DMAP - dimethylaminopyridine

DMF - dimethylformamide

DMSO - dimethylsulfoxide

DOR - delta opioid receptor

e.e. - enantiomeric excess

EDG - electron-donating group

ESI - electrospray ionisation

EWG - electron-withdrawing group

GCMS - gas chromatography mass spectrometry

HOMO - highest occupied molecular orbital

HPLC - high performance liquid chromatography

HRMS - high resolution mass spectrometry

IR - infra-red

KOR - kappa opioid receptor

LDA - lithium diisopropylamide

LUMO - lowest unoccupied molecular orbital

m-CPBA - *meta*-chloroperoxybenzoic acid

MeCN - acetonitrile

Mesyl (Ms) - methanesulfonyl

MOR - mu opioid receptor

NMR - nuclear magnetic resonance

NOESY - nuclear Overhauser effect spectroscopy

Py - pyridine

TEMPO - 2,2,6,6-tetramethylpiperidine-1-oxyl

TFA - trifluoroacetic acid

THF - tetrahydrofuran

TLC - thin layer chromatography

Tosyl (Ts) - *p*-toluenesulfonyl

TPP - tetraphenylporphyrin

UV - ultra-violet

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Chapter 1. Introduction

1,3-Dipolar cycloadditions are a very efficient method of synthesising sp^3-rich heterocyclic scaffolds. The ability to rapidly generate molecular complexity from relatively simple starting materials using this reaction has long been attractive to synthetic chemists. Whilst there are many different 1,3-dipoles, we are interested in the use of pyridinium ylides **1** (Figure 1).

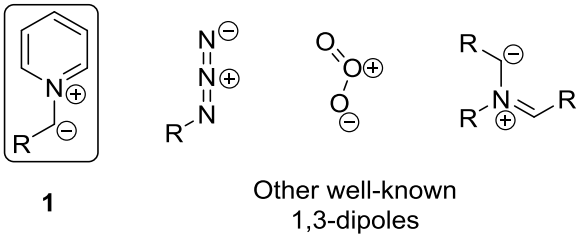
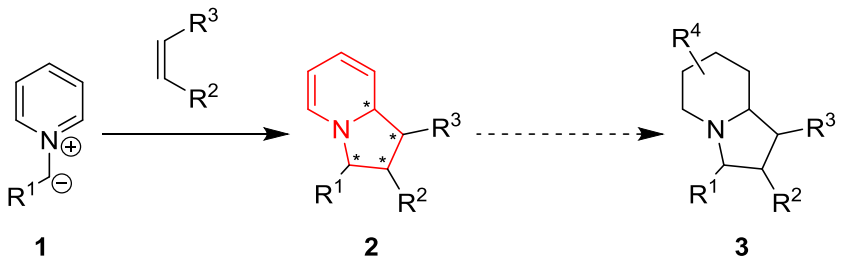


Figure 1 – 1,3-dipoles

As well as up to four new stereocenters (*), the resulting cycloadducts **2** feature a tetrahydroindolizine moiety (shown in red), which can be further functionalised to afford complex indolizidines **3** (Scheme 1).



Scheme 1 – Formation of indolizidine

Indolizidines are found in many biologically active alkaloids, as well as many pharmaceutical drugs.[1,2] Therefore, the development of

rapid synthesis of 'drug-like' structures with predictable regio and diastereoselectivity would be of significant value.

1.1 **Spirocyclic alkaloids**

Spirocyclic carbon centres are found within many indolizidine containing natural products. Indeed spirocyclic oxindoles are considered to be a privileged structure for drug discovery,[3] examples include strychnofoline **4** and ciliaphylline **5** (Figure 2).[4,5]

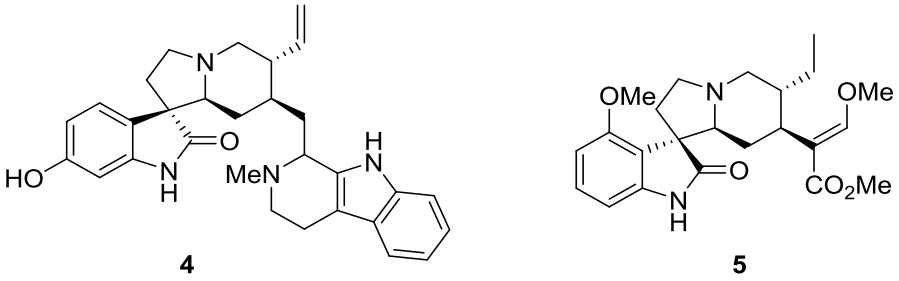


Figure 2 - Strychnofoline and ciliaphylline

The closely related family of spirocyclic indoxyl alkaloids is much smaller but they do exhibit some interesting biological activities. These include the alkaloids fluorocurine **6** and austamide **7** which are both spirocyclic indolones and exhibit high levels of toxicity in animals.[6,7]

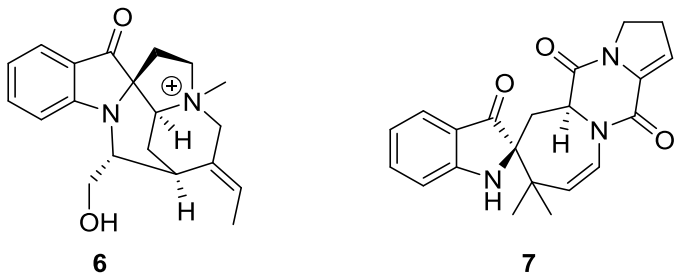
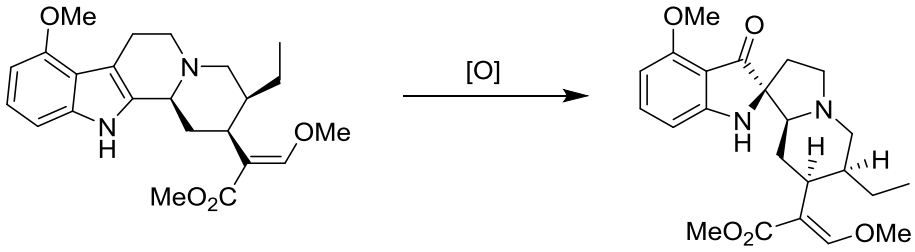


Figure 3 – Fluorocurine and austamide

Perhaps the most intriguing spirocyclic indoxyl is mitragynine pseudoindoxyl **9** which has been shown to possess 20-35 fold greater opioid agonistic activity than morphine.[8,9] It is an oxidative metabolite of the natural product mitragynine **8**, which is the most abundant alkaloid found in the *Mitragyna speciosa* tree, also known as kratom (Scheme 2).[10]



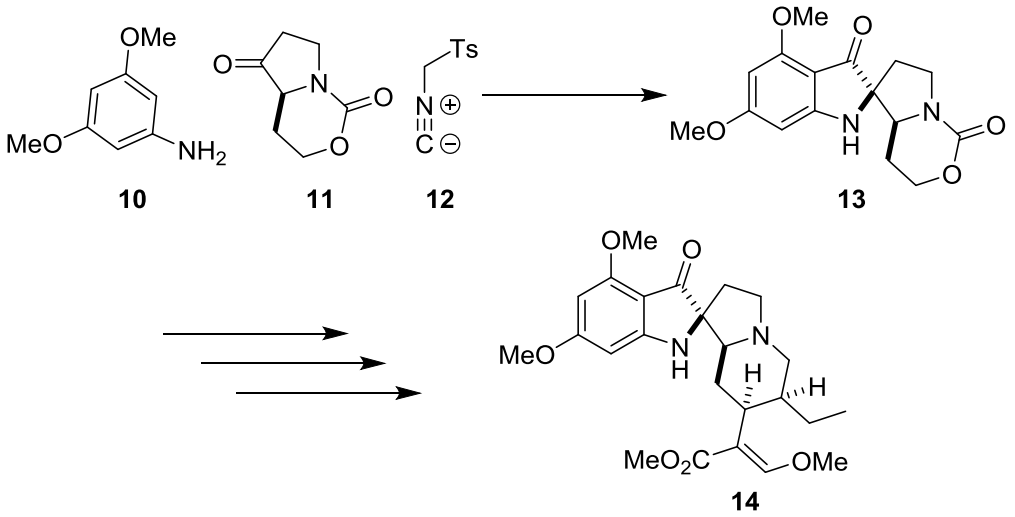
8 **9**

Scheme 2 – Mitragynine and mitragynine pseudoindoxyl

Mitragynine pseudoindoxyl **9** and ciliaphylline **5** are structural isomers of each other; and while there are several notable routes towards the synthesis of indolizidine containing spirocyclic oxindoles,[11,12,13] very few exist for spirocyclic indoxyls (*vide infra*). Cycloadditions between pyridinium ylides and suitable dipolarophiles may offer an expedient route towards the synthesis of such structures, though this chemistry remains largely unexplored to date. The following section will discuss the current methodologies towards the synthesis of spirocyclic indoxyls.

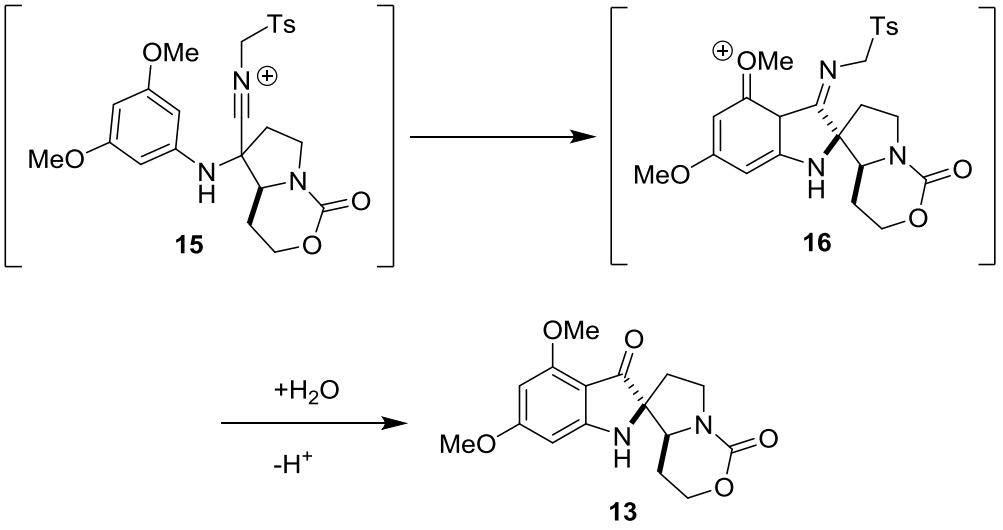
1.1.1 Synthesis of spirocyclic indoxyls

In the last few years the synthesis of spirocyclic indoxyls has received significant interest, in 2012 Sorensen *et al.* reported the synthesis of 11-methoxy mitragynine pseudoindoxyl **14** (Scheme 3).[14]



Scheme 3 – Synthesis of 11-methoxy mitragynine pseudoindoxyl

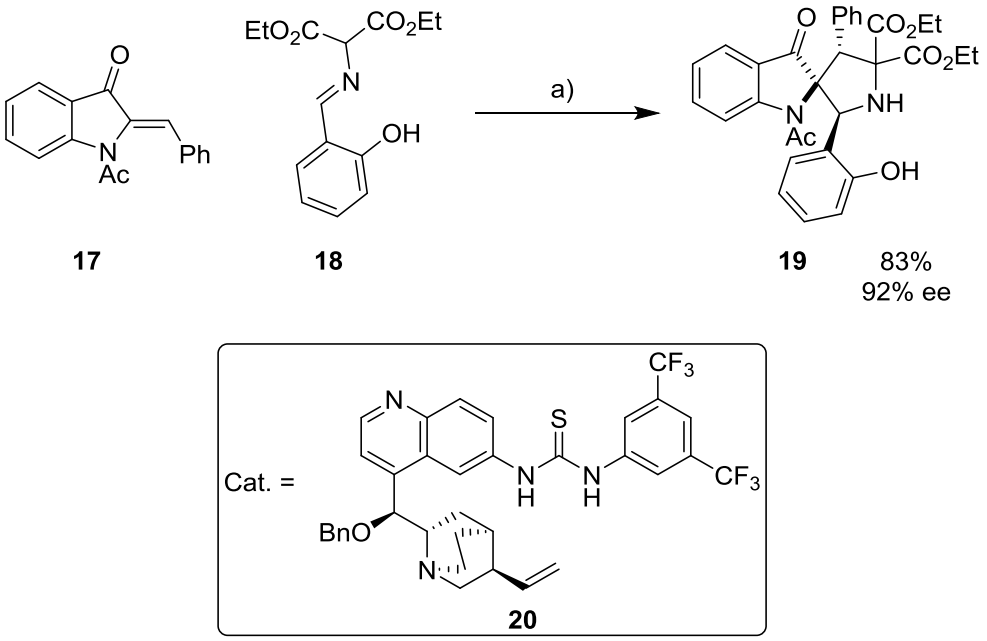
The key transformation in the synthesis was the formation of the indoxyl spirocenter, which was achieved through the use of an 'interrupted Ugi' reaction (Scheme 4). This 3 component reaction begins with the condensation of 3,5-dimethoxyaniline **10** with the cyclic carbamate **11**. The imine undergoes nucleophilic attack from the isocyanide **12** and subsequent cyclisation by means of electrophilic aromatic substitution of the electron rich aromatic ring. After rearomatization and imine hydrolysis the resulting product is the spirocyclic indoxyl **13**, and after subsequent steps affords 11-methoxy mitragynine pseudoindoxyl **14**.



Scheme 4 – 'Interrupted Ugi' reaction

The total synthesis was achieved in 19 steps but unfortunately, this route is not compatible with the synthesis of mitragynine pseudoindoxyl **9**. This is due to the 'interrupted Ugi' reaction proceeding *para* to the methoxy group which would afford the incorrect regioisomer for mitragynine pseudoindoxyl **9**.[15]

During the course of our studies Xu *et al.* reported the asymmetric synthesis of spirocyclic indoxyls *via* (3+2) dipolar cycloadditions of azomethine ylides.[16] This work was performed with imines rather than pyridinium salts leading to a range of spirocyclic pyrrolidines (Scheme 5).

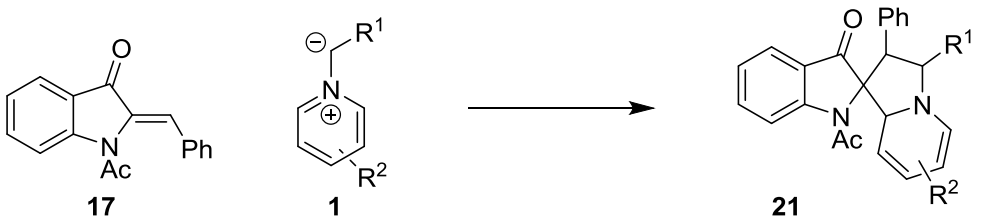


Scheme 5 - *Reagents and conditions* – a) cat. (10 mol%), DCE, 20 °C, 72 hr.

Through the use of a thiourea catalyst **20** a range of spirocyclic pyrrolidines were prepared in high yield and e.e. Deprotonation by the quinuclidine combined with activation of the imine through hydrogen bonding to the thiourea **20** generates the 1,3-dipole which performs the (3+2) dipolar cycloaddition. This approach does however have several limitations; firstly, it requires an acidic proton and secondly, it requires an alcohol on the aromatic ring to provide an intramolecular hydrogen bond to control the stereochemistry.

Performing (3+2) dipolar cycloadditions on dipolarophiles such as (*Z*)-1-acetyl-2-benzylideneindolin-3-one **17** is an efficient method of generating spirocyclic indoxyls. If the 1,3-dipole were a pyridinium ylide **1** then the resulting cycloadduct **21** would have the core

framework of the family of natural products including mitragynine pseudoindoxyl **9** and fluorocurine **6** (Scheme 6).



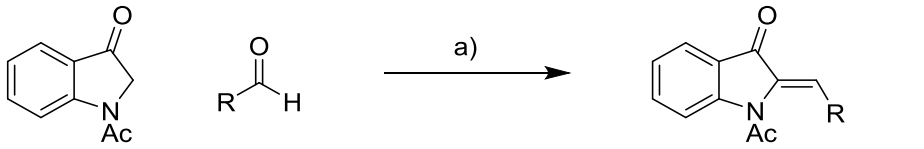
Scheme 6 – Dipolar cycloaddition of pyridinium ylide

The next section will discuss the current published approaches towards the synthesis of 2-alkenylindol-3-ones.

1.2 **Synthesis of 2-alkenylindol-3-ones**

There are several reported methodologies for the synthesis of 2-alkenylindol-3-ones, with each proceeding *via* different disconnections.

It is possible to perform an aldol condensation between 1-acetylindolin-3-one **22** and various aldehydes (Scheme 7). When this reaction is performed with benzaldehyde the product **17** is obtained in good yield, however, non-aromatic aldehydes such as ethyl glyoxylate result in poor yields.[17] One possible explanation for this could be due to the tendency for aliphatic aldehydes to form trimers, thus lowering the effective concentration of aldehyde in the reaction.

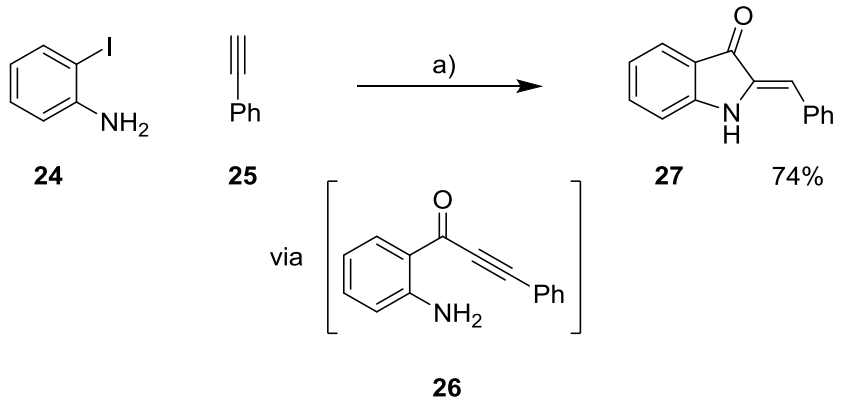


22

17 - 65% **-** R = Ph
23 - 10% **-** R = CO_2Et

Scheme 7 - *Reagents and conditions* – a) piperidine, toluene, 110 °C.

Another approach is intramolecular cyclisation, starting with an *ortho*-iodoaniline **24** (Scheme 8). This proceeds *via* a palladium catalysed carbonylation and reductive elimination with phenylacetylene **25** to afford the alkynone **26**. Subsequent intramolecular cyclisation generates (*Z*)-2-benzylideneindolin-3-one **27** in high yield.[18]



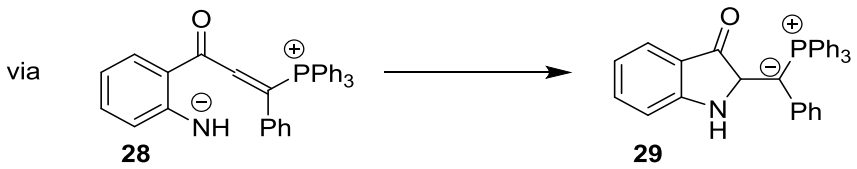
24 **25** **27** 74%

26

Scheme 8 - *Reagents and conditions* – a) $Pd(PPh_3)_4$ (0.2 mol%), PPh_3 (3.2 mol%), Et_3N, anisole, 80 °C, 5 bar carbon monoxide.

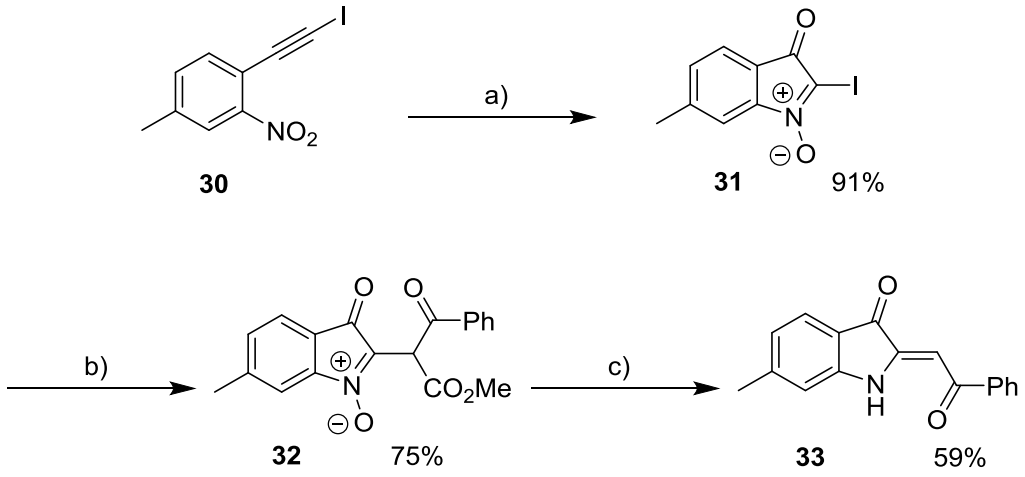
The authors propose that the intramolecular cyclisation is catalysed by triphenylphosphine (Scheme 9). When the catalyst was changed to [$PdCl_2$(dppf)], therefore excluding triphenylphosphine, the product was the 6-membered ring with an internal alkene, a result of palladium catalysed cyclisation. This approach suffers from limited

substrate scope, since generation of the 2-alkenylindol-3-ones requires an alkyne with an aromatic substituent.



Scheme 9 – Intramolecular cyclisation proposed by authors[18]

During this project a new methodology was published on the transformation of 2-iodoisatogens to 2-alkenylindol-3-ones.[19] The oxidative cyclisation of 1-(iodoethynyl)-4-methyl-2-nitrobenzene **30** generated the 2-iodoisatogen **31** in high yield (Scheme 10). Followed by iodide displacement with methyl 3-oxo-3-phenylpropanoate and subsequent Krapcho decarboxylation affords (*Z*)-6-methyl-2-(2-oxo-2-phenylethylidene)indolin-3-one **33**. There are no reported examples of non-aromatic alkenyl substituents by this approach. Though it is conceivable that if the iodide displacement were performed with dimethylmalonate, then the decarboxylation would proceed to afford the methylester.



Scheme 10 - *Reagents and conditions* – a) CuBr.DMS (25 mol%), THF, 66 °C 2 hr; b) methyl 3-oxo-3-phenylpropanoate, NaH, THF, 66 °C, 30 mins; c) NaI, DMF, 180 °C, 18 hr.

In summary, there are several reported methods to synthesise 2-alkenylindol-3-ones. However, substrate scope does seem to be a problem with this class of compound, with non-aromatic alkenes not tolerated or generated in very poor yields. This limits the variability of the dipolarophiles in the proposed (3+2) dipolar cycloaddition. The next section will discuss the reactivity and generation of pyridinium ylides.

1.3 **Synthesis of pyridinium ylides**

Pyridinium ylides are versatile reagents,[20] capable of performing several transformations. They have been shown to be highly reactive towards electrophiles. Work by Mayr *et al.* has compared the nucleophilicity of pyridinium ylides with other ylides (Table 1).[21,22,23]

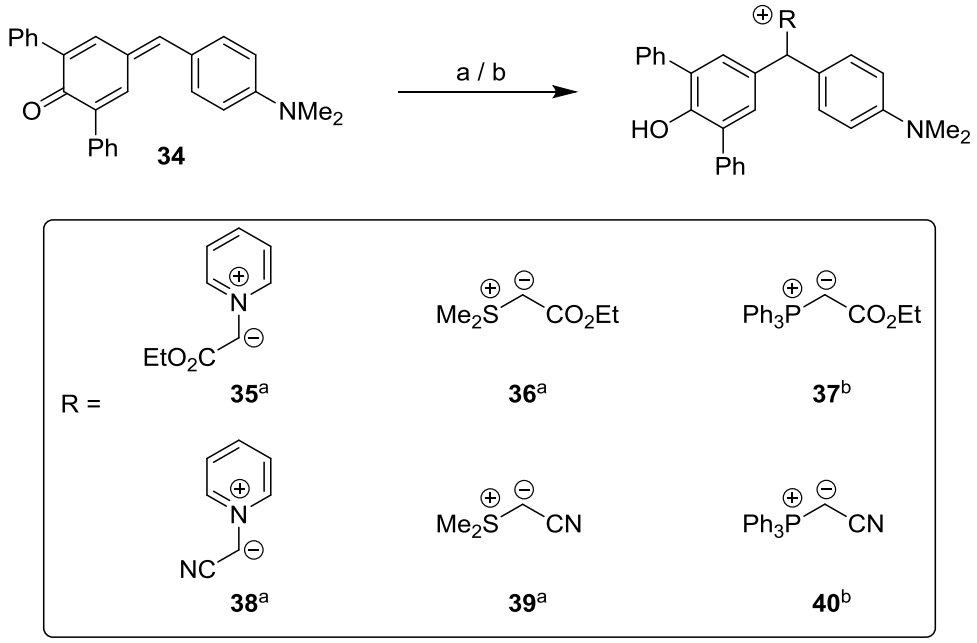


Table 1 - *Reagents and conditions* – a) DMSO, 20 °C; b) CH_2Cl_2, 20 °C.

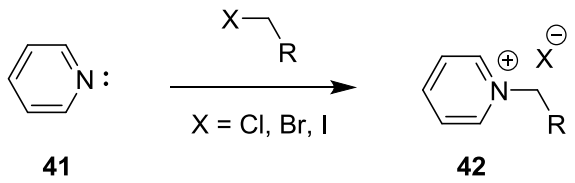
Entry	R	log k_2
1	**35**	4.95
2	**36**	1.49
3	**37**	-0.71
4	**38**	5.37
5	**39**	1.67
6	**40**	-0.82

The results show that pyridinium ylides are significantly more nucleophilic than the corresponding sulfonium and triphenylphosphonium ylides. For example, pyridinium ylide **35** is approximately a million times more reactive than the corresponding Wittig-type phosphonium ylide **37**. Though pKa is not directly related to nucleophilicity, the nucleophilicity of the ylide in each series can be rationalised by the pKa of the methylene proton, the lower the pKa the greater the relative nucleophilicity.

In this project pyridinium ylides will be generated in two ways; firstly, through deprotonation of a pyridinium salt, and secondly, through decomposition of diazo compounds.

1.3.1 From pyridinium salts

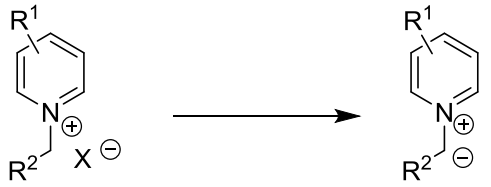
Pyridinium salts **42** can be synthesised in several ways, one of the simplest is by the addition of pyridine **41** to a primary alkyl halide (Scheme 11). The synthesis is generally straightforward and in many cases the product precipitates out of the reaction solvent with the halide as the counterion.[24]



41 **42**

Scheme 11 - *Reagents and conditions* - EtOAc, 70 °C, 12 hr.

Pyridinium ylides **1** can then be generated *via* deprotonation of pyridinium salts **42** with base (Table 2).



42 **1**

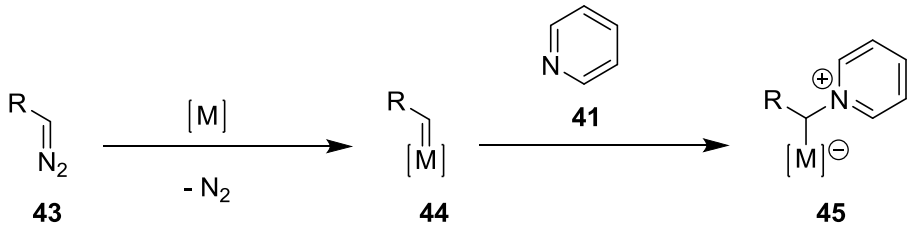
Table 2 - *Reagents and conditions* - Base, DMSO, 20 °C, 10 mins.

Entry	R^1	R^2	pK_a(DMSO)[25]
1	H	COPh	10.7
2	H	COMe	11.8
3	4-NMe_2	COPh	13.2
4	H	CO_2Et	14.1
5	H	CN	16.5

The pK_a of the methylene proton is dependent on both the functional group R^1 as well as the ylide stabilising group R^2. The greater the electron withdrawing effect of R_2 the lower the pK_a, while the addition of an electron donating group (Entries 1 and 3) increases the pK_a by over 2 log units. Reactions of the ethyl ester pyridinium salt (Entry 4, pKa 14.1) have been performed with triethylamine (pK_a 9.0 in DMSO)[26], suggesting that an equilibrium between salt and ylide can be sufficient in these cycloaddition reactions.[27]

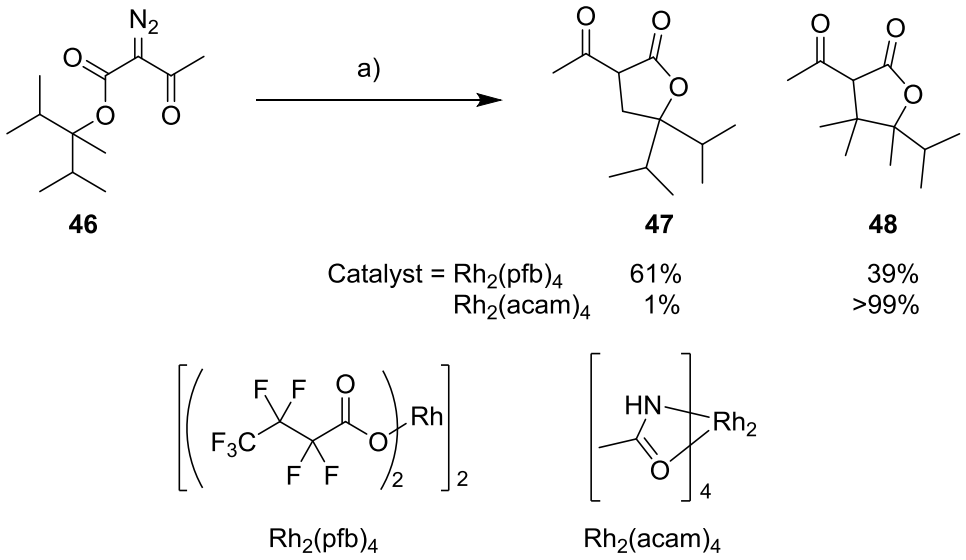
1.3.2 From diazo compounds

Pyridinium ylides **45** may also be generated from diazo compounds **43** *via* metallocarbenoids **44** (Scheme 12).[28]



Scheme 12 – Pyridinium ylide from diazo compound

The formation of metallocarbenoids from diazo compounds is well known.[20] These highly reactive intermediates are able to perform many different reactions such as: cyclopropanation,[29] C/X-H insertion[30,31] and heteroatom ylide formation[20] to name a few. Controlling selectivity with these reactive species can prove difficult, but it is possible to tune reactivity through both metal and ligand choice. For example, the selectivity of C-H insertion can be influenced by varying the ligands of the rhodium catalyst (Scheme 13).[32] The change from an electron-poor perfluorobutyrate ligand to an electron-rich acetamide ligand causes a significant change in the product ratio, arising from C-H insertion into the methyl **47** or isopropyl respectively **48**.



Scheme 13 – Selectivity of C-H insertion

The generation of pyridinium ylides *via* metallocarbenoids offers several potential benefits over deprotonation of pyridinium salts. It is base free, catalytic and can be performed in one-pot eliminating the need to synthesise the pyridinium salt. Although a sp^2 hybridised free-ylide is flat and so cannot preference one face; a nucleophilic C-M bond provides different opportunities towards asymmetric cycloadditions through the use of chiral ligands blocking one face of the ylide.

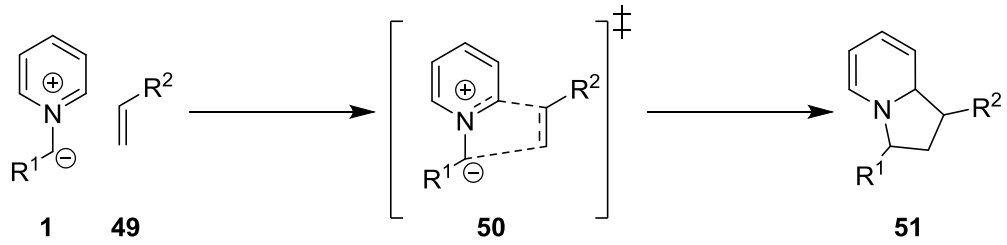
In summary, pyridinium ylides are highly reactive intermediates that can be generated either from the pyridinium salt or *via* metal catalysed diazo decomposition. The next section will discuss the possible reaction mechanisms for (3+2) dipolar cycloadditions.

1.4 **Mechanism of 1,3-dipolar cycloaddition**

There are two possible reaction pathways for 1,3-dipolar cycloadditions: the first is a concerted mechanism where both bonds are formed simultaneously; the second is a stepwise mechanism of conjugate addition followed by cyclisation.

1.4.1 Concerted mechanism

The concerted cycloaddition mechanism proceeds through a ring transition state **50** (Scheme 14). Which molecule acts as the nucleophile or electrophile is controlled by the energy levels of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO).



Scheme 14 - Cycloaddition transition state

Three types of concerted mechanism are possible; standard electron demand (Type 1) involves the HOMO of the ylide being close in energy to the LUMO of the dipolarophile. In this case the dipole is the nucleophile and is the case for the majority of 1,3-dipolar cycloadditions (Figure 4). Inverse electron demand (Type 3) is the reverse where the HOMO of the dipolarophile is close in energy to the LUMO of the 1,3-dipole, an example of this is ozonolysis. When both

molecules have HOMO's and LUMO's which are close in energy it is possible for the reaction to proceed *via* both pathways (Type 2).

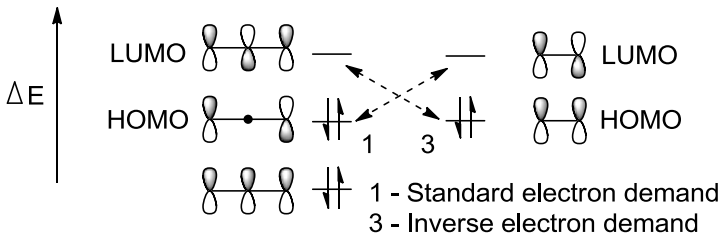


Figure 4 - HOMO - LUMO Energy diagram

1.4.1.1 Regioselectivity

In a concerted mechanism the transition state controls both the regio and stereoselectivity of the product. Regioselectivity is influenced by the size of the orbital coefficients, and thus the nature of the groups attached to the ylide or dipolarophile. Generally, the atom with the largest HOMO coefficient will have the strongest interaction with the atom with the largest LUMO coefficient. In a standard electron demand cycloaddition, the largest HOMO coefficient of the 1,3-dipole is the carbanion. Electron withdrawing groups increase the LUMO coefficients at specific carbons. This can be explained through resonance structures (Figure 5). The partial positive charge on the gamma carbon increases the orbital coefficient at this position therefore directing the regioselectivity of the reaction.[33]

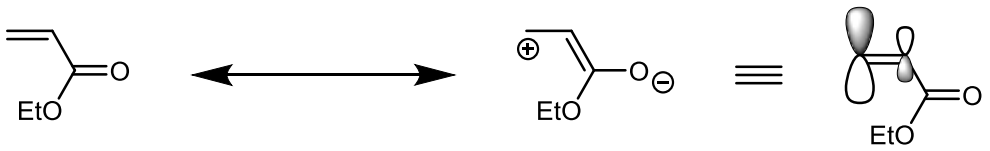


Figure 5 - Orbital Coefficients

1.4.1.2 Diastereoselectivity

The diastereoselectivity of the cycloadduct is determined by three factors: the stereochemistry of the starting materials, the transition state and the ylide shape in the transition state. The two possible transition states are *endo* and *exo*; an *endo* transition state is where the greatest units of unsaturation are closest in space, while in an *exo* transition state these are further apart (Figure 6).[34] Secondary orbital interactions of Π systems lower the energy of the *endo* transition state. Therefore, excluding any unfavourable steric interactions the *endo* transition state should be the favoured pathway generating *endo* the product **52**.

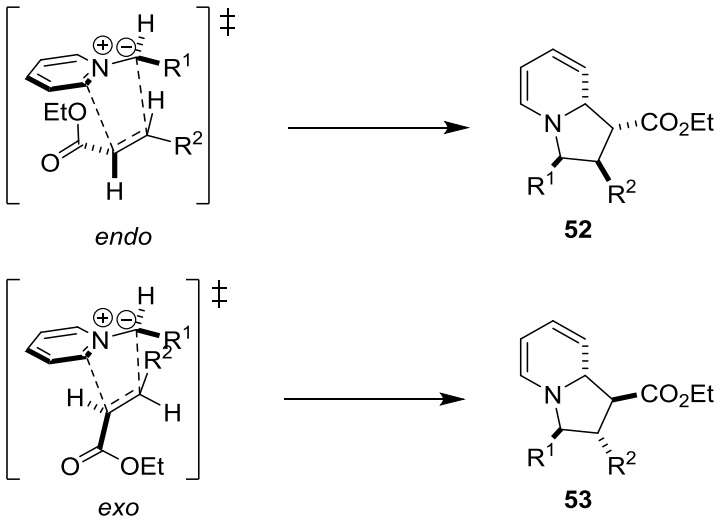
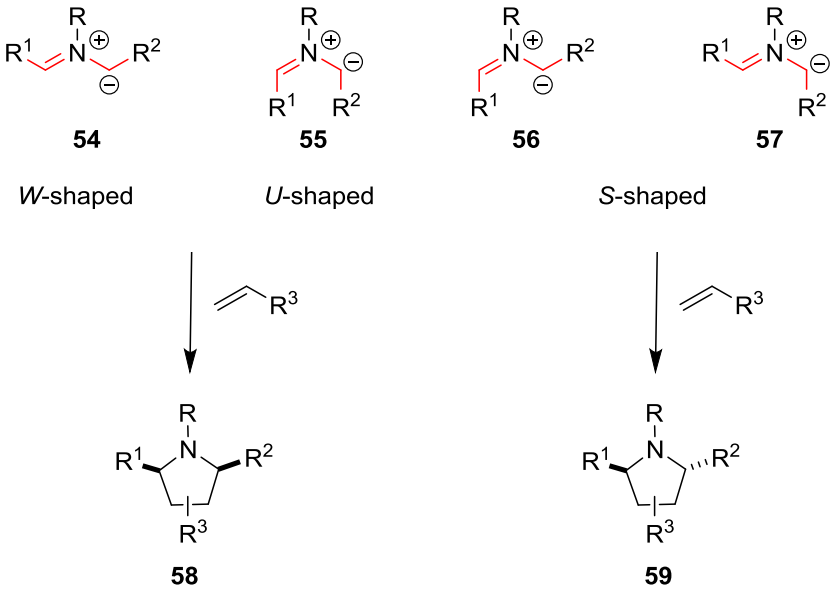


Figure 6 - *endo* and *exo* transition states

1.4.1.3 Ylide shape

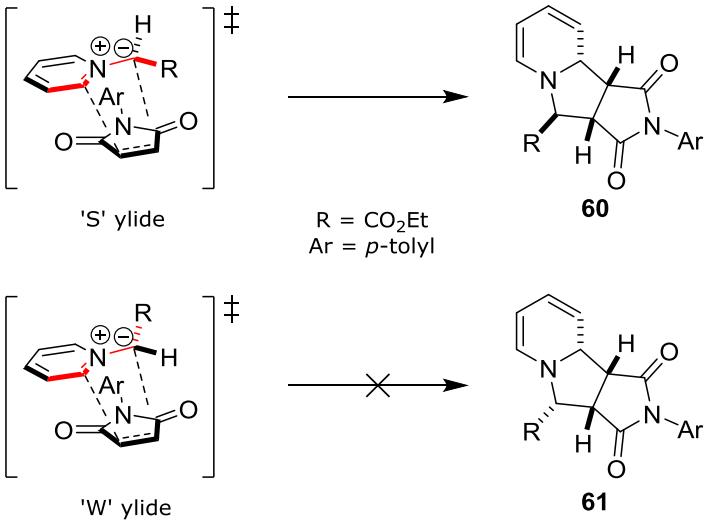
There are four possible conformations for azomethine ylides (shown in red), these are often referred to by shape: *W* **54**, *U* **55** and two different forms of *S* **56-57** (Scheme 15).[35] The *W* **55** and *U* **56**

conformations form the *syn* cycloadduct **58** with respect to R^1 and R^2 and *S* **56-57** conformations form the *anti* cycloadduct **59**.



Scheme 15 – Ylide shapes

Due to the ring, pyridinium ylides can only adopt two conformations in the transition state which are *W* **54** and *S* **57**. In the 1,3-dipolar cycloaddition between a pyridinium ylide and *N*-phenylmaleimide, the *W* ylide would lead to the *syn* cycloadduct **58**, while the *S* ylide would lead to the *anti* cycloadduct **59** (Scheme 16). The ylide shape is determined during the transition state when the σ-bonds are forming, therefore it is rationalised from the observed product. For the example in Scheme 16, reported by Tsuge, only the product derived for *S* ylide in an *endo* transition state **60** is observed.[36] Ylide shape affects the relative stereochemistry of the ylide stabilising group (R) observed in the product, with the preferred shape determined by the nature of the ylide stabilising group.

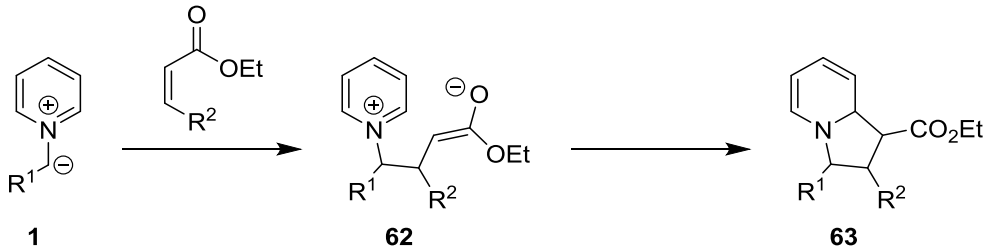


Scheme 16 - Ylide conformations in *endo* transition state

It has generally been observed that if R is a resonance stabilised group such as a carbonyl, then the *S* ylide product is preferred, whereas, for non-resonance stabilised groups the *W* is preferred.[37] One explanation for this observation is the minimisation of unfavourable dipole interactions. The *W* ylide places the lone pairs of electrons on the ylide and dipolarophile closer in space, thus disfavouring this transition state.

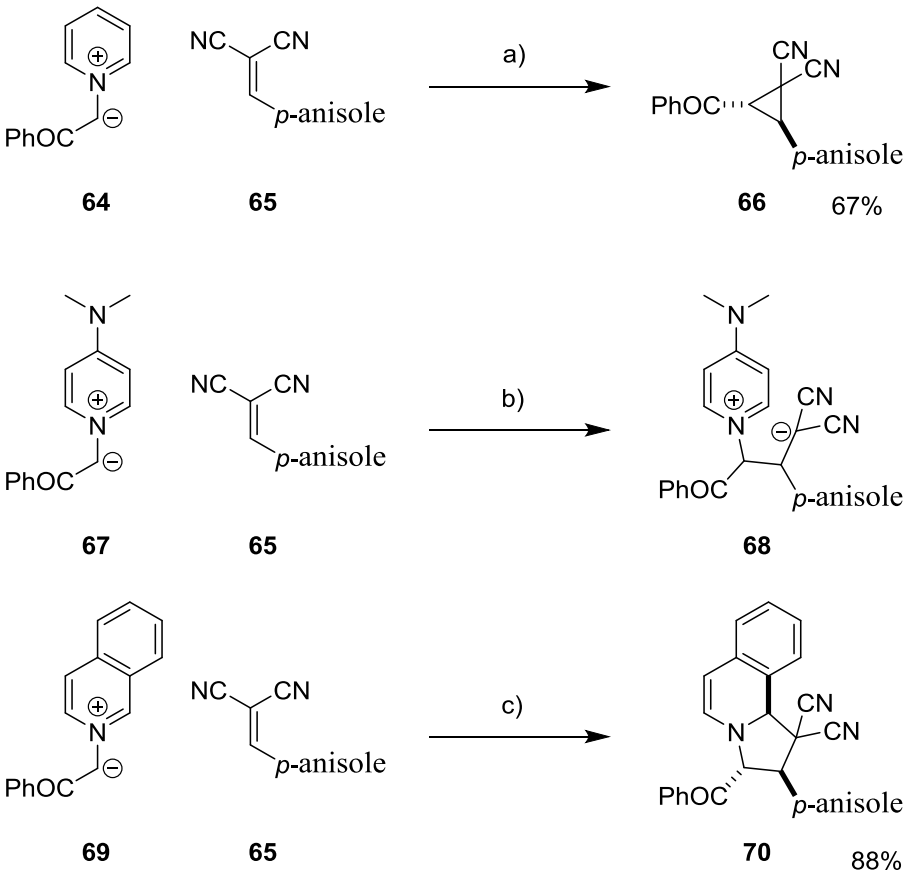
1.4.2 Stepwise mechanism

Recently Mayr *et al.* reported kinetic studies that confirmed 1,3-dipolar cycloadditions of pyridinium ylides **1** proceed *via* a step-wise addition to form a betaine intermediate **62** and subsequent cyclisation generating the cycloadduct **63** (Scheme 17).[21]



Scheme 17 - Conjugate addition mechanism

Possible products are influenced by small variations to either the pyridinium ylide or dipolarophile, these include: cycloadducts, cyclopropanes and betaines. Varying the pyridinium ylide in reactions with benzylidene malonitrile **65** has been shown to result in different products (Scheme 18). For example, the unsubstituted benzoyl pyridinium ylide **64** generates cyclopropane **66**, through elimination of pyridine from the betaine intermediate (not shown). While 4-*N,N*-dimethyl pyridinium ylide **67** leads to a stable betaine **68** which was characterised but not isolated. This betaine is presumably a result of the combination of having a highly stabilised anion as well as the electron donating group on the pyridinium. This reduces the nucleophilicity of the carbanion through resonance with the two nitrile substituents; whilst the dimethylamino group reduces the electrophilicity pyridinium again through resonance. By changing from a pyridinium ylide to an isoquinolinium ylide **69** the reaction proceeds to afford the cycloadduct **70**. The pyridinium ylide cycloadduct is thermodynamically disfavoured due to the complete loss of aromaticity in the formation of the dihydropyridine. Whilst this loss is reduced for the isoquinolinium as the phenyl ring remains with the enamine still in conjugation.



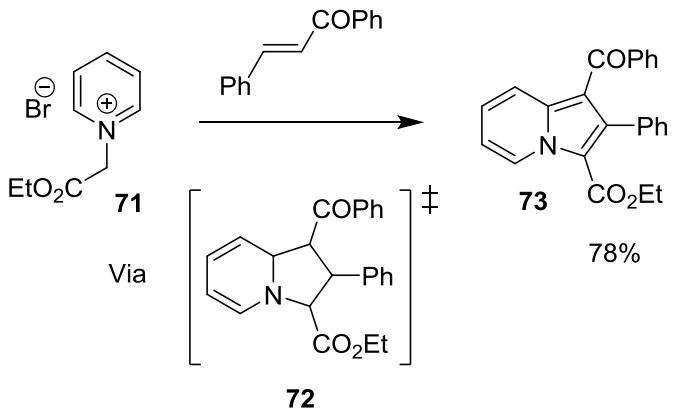
Scheme 18 - *Reagents and conditions* – a) Et_3N, DMSO, 20 °C, 1 hr; b) Triazabicyclodecene, DMSO-d_6, 20 °C, 5 mins; c) Et_3N, DMSO, 20 °C, 0.5 hr.

This shows the potential of pyridinium ylides to generate a range of products; stable betaines are rare and cyclopropanation is usually only observed when the betaine intermediate is highly stabilised. Indicating that the cycloadducts are kinetic products of pyridinium ylide reactions and cyclopropanes the thermodynamic products.

1.5 **Pyridinium ylide cycloadditions**

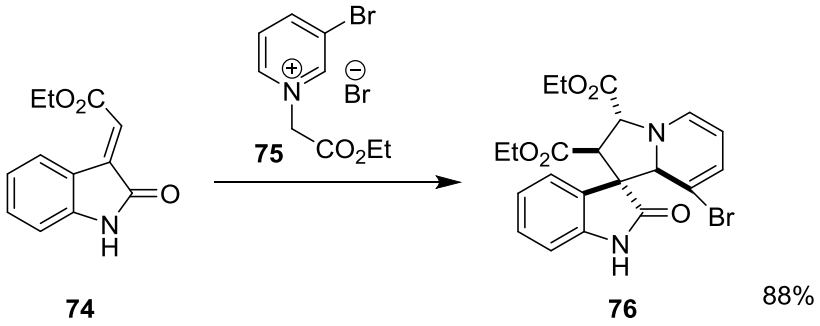
Cycloadducts generated through 1,3-dipolar cycloadditions of pyridinium ylides contain a 1,2-dihydropyridine moiety. This reactive group offers the potential for further functionalisation (*vide infra*), however, this reactivity can also limit cycloadduct stability. In many cases oxidation occurs to restore aromaticity resulting in decomposition of the cycloadduct.

Oxidation of cycloadduct **72** gives indolizine **73**, while this stabilises the product, it also decreases the utility of the reaction as valuable stereochemical information is lost (Scheme 19).[38]



Scheme 19 - *Reagents and conditions* – Et_3N, CrO_3, DMF, 90 °C, 4 hr.

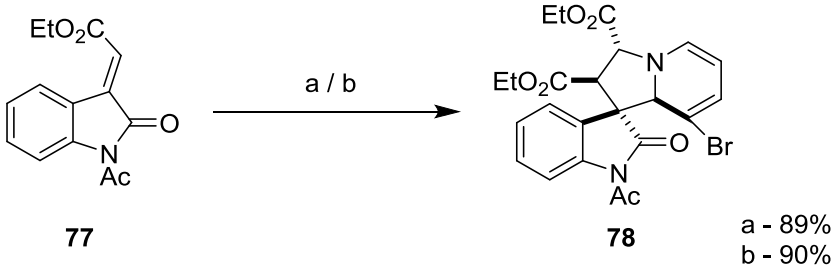
1,2-Dihydropyridine cycloadducts are isolable; however, an example from the Dowden group of a 1,3-dipolar cycloaddition between a pyridinium ylide and a 3-alkylidene oxindole **74** affords the cycloadduct **76** in high yield as a single diastereoisomer (Scheme 20).[11]



Scheme 20 - *Reagents and conditions* - Et_3N, CH_2Cl_2, 20 °C, 2 hr.

The stability of the oxindole cycloadducts depends greatly on the substituents on the dihydropyridine ring, electron withdrawing groups stabilise the cycloadducts by reducing the electron density of the 1,2-dihydropyridine. Subsequent functionalisation of the 1,2-dihydropyridine further stabilises the cycloadducts while also retaining the stereochemistry generated in the cycloaddition.

Recently, the Dowden group have developed an alternate methodology for performing 1,3-dipolar cycloadditions, in which pyridinium ylides are generated *via* metal catalysed decomposition of diazo compounds (Scheme 21).[39]



Scheme 21 - *Reagents and conditions* – a) 3-bromopyridine, ethyl diazoacetate, Fe(TPP)Cl (1 mol%), CH_2Cl_2, 20 °C, 2 hr; b) 3-bromopyridine, ethyl diazoacetate, $[(MeCN)_4Cu]PF_6$ (5 mol%), CH_2Cl_2, 20 °C, 2 hr.

Both an iron (III) porphyrin and a copper (I) catalyst were shown to facilitate the cycloaddition in high yield with excellent diastereoselectivity. The relative stereochemistry of the cycloadduct **78** was the same as when pyridinium salts were used to generate the pyridinium ylides. As seen previously with reactions of diazo compounds the catalyst choice plays a significant role in reaction outcome. Iron (III) and copper (I) produce the cycloadduct, while rhodium (II) acetate lead to the formation of the cyclopropane as the sole product (not shown). This suggests that the rhodium carbenoid is more nucleophilic than the iron or copper analogues resulting in direct reaction with the alkene over pyridinium ylide formation.

1.5.1 Asymmetric (3+2) dipolar cycloadditions

While there are many examples of asymmetric cycloadditions of various azomethine ylides, there are none thus far reported for pyridinium ylides. However, the asymmetric cycloaddition of the related isoquinolinium ylides with secondary amine catalysts has been reported.[40] This (3+2) dipolar cycloaddition was performed with the stable isoquinolinium ylide **79** and crotonaldehyde **80** (Table 3).

Whilst the reaction proceeds with no catalyst or additive (Entry 1), the use of secondary amine catalysis sufficiently increases the rate of reaction to obtain the cycloadduct **81** with high enantioselectivity. This approach shows that it is possible to perform asymmetric reactions of aromatic azomethine ylides. The highly stabilised ylide results in a slow uncatalyzed reaction, requiring the iminium formation to significantly activate the dipolarophile. However, the

method is not general and would not be suitable for the majority of 1,3-dipolar cycloadditions of pyridinium ylides.

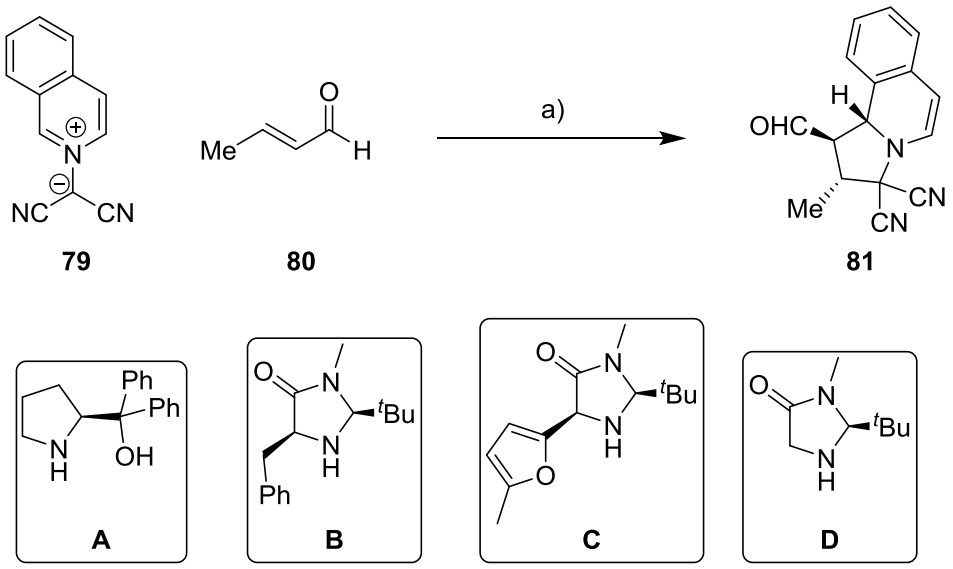


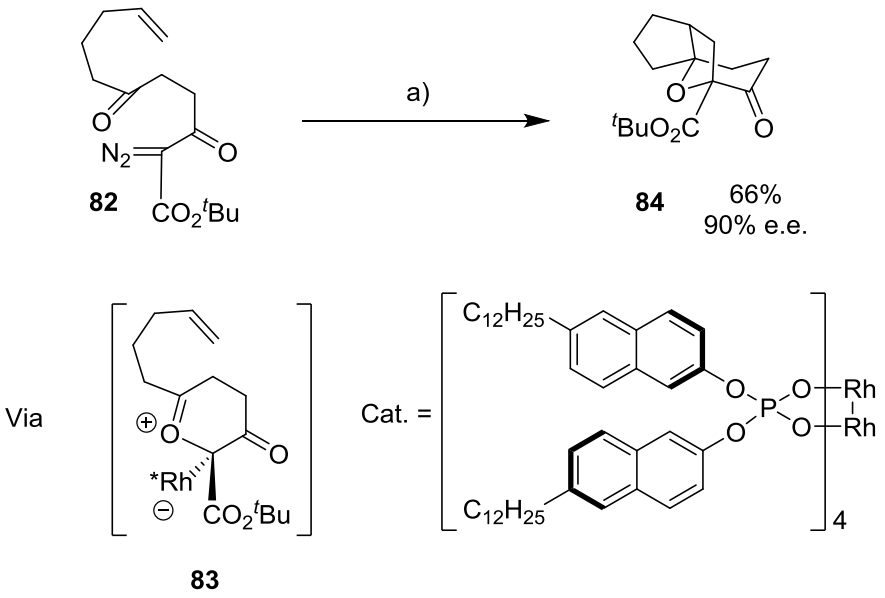
Table 3 - *Reagents and conditions* – a) Catalyst (20 mol%), Additive (20 mol%), THF, 20 °C.

Entry	Catalyst	Additive	Yield (%)	endo/exo	e.e. (%)[a]
1	---	---	40	5 : 95	---
2	A	---	52	47 : 53	82
3	B	TFA	87	88 : 12	88
4	C	TFA	32	71 : 28	46
5	D	TFA	33	95 : 5	44
6[b]	B	TFA	80	99 : 1	46
7[c]	B	TFA	53	94 : 6	88

[a] e.e. of endo diastereoisomer. [b] Reaction performed in EtOH. [c] Reaction performed at -30 °C.

Examples of asymmetric intramolecular (3+2) dipolar cycloadditions have been reported with oxonium ylides *via* metallocarbenoids (Scheme 22).[41] The rhodium carbenoid reacts with the Lewis basic carbonyl resulting in the formation of an oxonium ylide **83**. The

asymmetric rhodium complex restricts reaction to one face, allowing the intramolecular (3+2) cycloaddition to proceed in good yield and very high enantioselectivity.



Scheme 22 - *Reagents and conditions* – a) Cat., hexane, -15 °C.

This suggests that in at least some cases the ylide is sufficiently associated to the metal complex to impart stereoselectivity on the cycloadduct **84**. To date there are no reported examples of asymmetric cycloadducts generated through diazo generated pyridinium ylides. The use of chiral metal complexes to generate chiral pyridinium ylides is one of the key objectives of this project.

1.6 **Reactivity of 1,2-dihydropyridines**

1,2-Dihydropyridines feature two alkenes with potentially different reactivities (Figure 7). The enamine alkene is electron-rich and therefore can undergo reactions with electrophiles before the other

alkene. Therefore, it is possible to functionalise these molecules selectively.

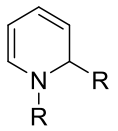
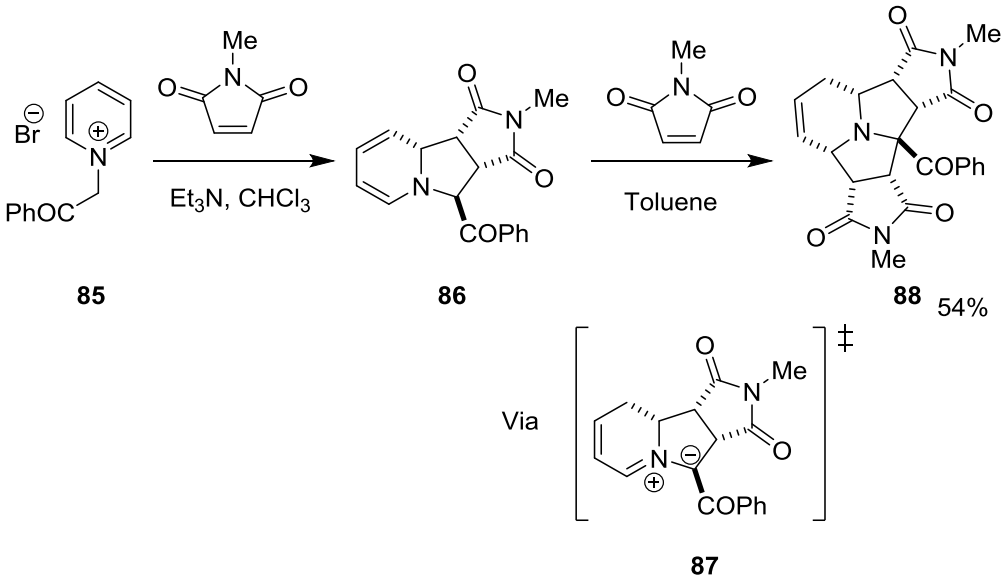


Figure 7 – 1,2-Dihydropyridine

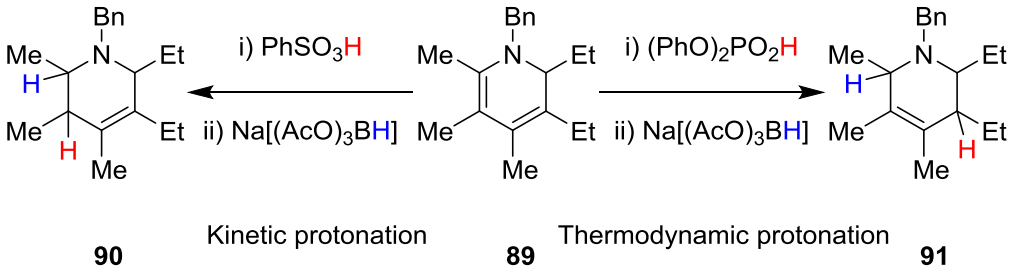
The inherent reactivity of dihydropyridines can be utilised to undergo many different transformations. These include but are not limited to: cycloadditions,[42,43] selective/complete reductions,[44] alkylation/additions[45] and epoxidation reactions.[46]

In 1989, Tsuge *et al.* demonstrated that the cycloadduct of a 1,3-dipolar cycloaddition of a pyridinium salt **85** and *N*-methylmaleimide can undergo further cycloadditions (Scheme 23).[42] The cycloadduct **86** was isolated and when heated under reflux in toluene the dihydropyridine tautomerised to generate an azomethine ylide **87**. This ylide was then able to react with another equivalent of *N*-methylmaleimide to form the *bis*-cycloadduct **88** as a single diastereoisomer.



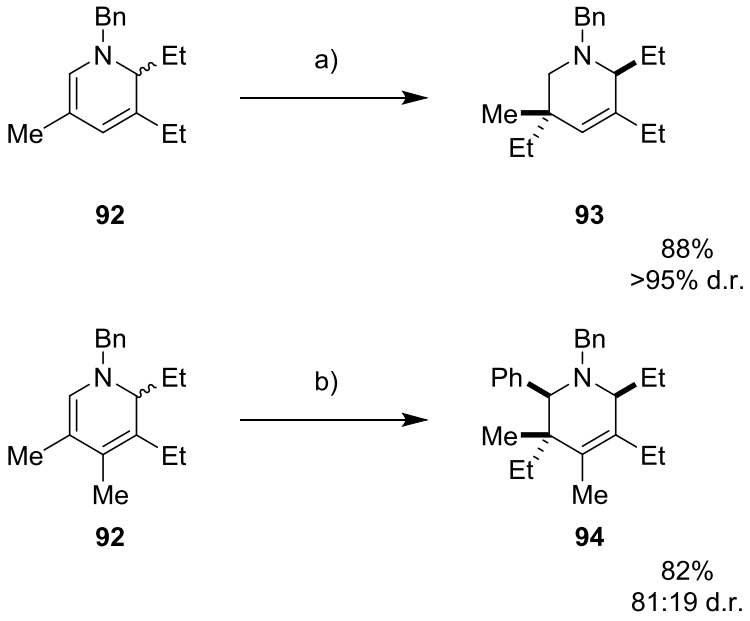
Scheme 23 - Tandem 1,3-dipolar cycloadditions

In 2013, Ellman *et al.* reported selective reductions of dihydropyridine **89** to either tetrahydropyridine **90** or **91** (Scheme 24).[44] Demonstrating that protonation can be achieved at different positions under either kinetic or thermodynamic control; stronger acids such as benzenesulfonic acid (pKa = -6.5 in DMSO)[47] produce the kinetic protonation product. While weaker acids such as diphenylphosphoric acid (pKa = 3.9 in DMSO)[48] generate the thermodynamic protonation product. Treatment with a mild reducing agent affords either the 1,2,3,6-tetrahydopyridine **91** or the 1,2,5,6-tetrahydropyridine **90** depending on the site of protonation.



Scheme 24 - Selective reductions of dihydropyridines

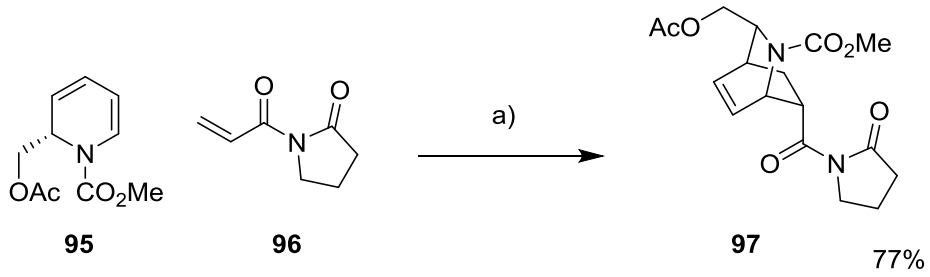
Further to this, Ellman has shown it is possible to alkylate 1,2-dihydropyridines with electrophiles (Scheme 25).[45] The enamine of the 1,2-dihydropyridine **92** reacts with ethyl triflate and the resulting iminium is reduced to afford the alkylated 1,2,5,6-tetrahydropyridine **93**. Highly reactive electrophiles were required for this work, alkyl iodides proved unreactive even at elevated temperatures. Both hydrides and Grignard reagents were demonstrated to react with the iminium allowing further functionalisation **94**.



Scheme 25 - *Reagents and conditions* – a) ethyl triflate, CH_2Cl_2, 20 °C, then $Me_4NBH(OAc)_3$, 0 °C; b) ethyl triflate, CH_2Cl_2, 20 °C, then PhMgBr, -78 °C.

In a review by Lavilla, transformations of dihydropyridines are discussed, in particular Diels-Alder and epoxidation reactions are demonstrated.[49] The Diels-Alder reaction was shown to proceed well in good yield as a single diastereoisomer, with the chiral

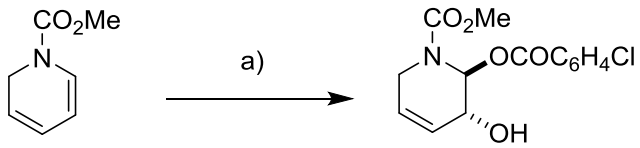
dihydropyridine **95** starting material directing the stereochemistry of the Diels-Alder adduct **97** (Scheme 26).[43]



95 **96** **97** 77%

Scheme 26 - *Reagents* and *conditions* – a) $AlCl_3$, CH_2Cl_2, 20 °C.

Selective epoxidation of the 1,2-dihydropyridine **98** was performed using *meta*-chloroperbenzoic acid (Scheme 27).[46] The resulting epoxide was opened by the resulting carboxylate affording the *trans*-tetrahydropyridine **99**. The observed selectivity is due to the higher reactivity of the electron-rich enamine double bond and the use of an electrophilic epoxidation reagent.



98 **99** 65%

Scheme 27 - *Reagents and conditions* – a) *m*-CPBA, CH_2Cl_2, 20 °C.

The variety of reactions possible with 1,2-dihydropyridines allows for the rapid development of further functionalisation of the cycloadducts. The modification of 1,2-dihydropyridines will be explored in this project as a way of rapidly developing molecular complexity and stabilising the cycloadducts.

1.7 Aims and objectives

This project has three main objectives; firstly, to generate spirocyclic indoxyl cycloadducts *via* (3+2) dipolar cycloadditions of pyridinium ylides. Secondly, to develop an asymmetric method for dipolar cycloadditions of pyridinium ylides. And thirdly, to use the developed methodologies to synthesise a range of 'drug-like' spirocyclic indoxyls related to mitragynine pseudoindoxyl **9**.

1.7.1 Synthesis of indoxyl cycloadducts

In order to achieve these goals, the synthesis of both pyridinium salts and 2-alkenylindol-3-ones will have to be performed. As previously discussed, the current methodology is largely limited to aromatic substituents on the alkene. Emphasis was placed on exploring alternative routes to the synthesis of non-aromatic substituted dipolarophiles.

The (3+2) dipolar cycloaddition will then be examined and the effects of varying the dipolarophile, pyridinium substituents and ylide stabilising group will be explored in pursuit of a predictable cycloaddition reaction. Subsequent modification of the 1,2-dihydropyridine will also be investigated to further diversify the cycloadducts increasing molecular complexity.

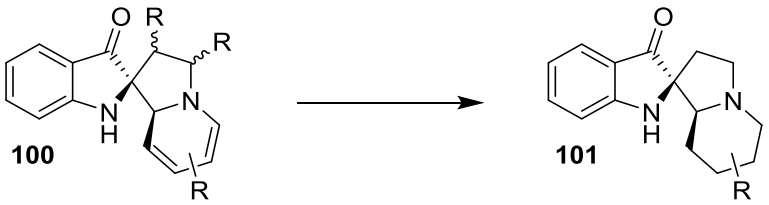
1.7.2 Development of an asymmetric methodology

The development of an asymmetric (3+2) dipolar cycloaddition will be investigated *via* the generation of pyridinium ylides from diazo compounds. A range of transition metal catalysts will be explored,

particular attention will be paid to differences in reactivity, diastereoselectivity and yield. Metals shown to achieve the desired cycloaddition will be followed up by the use of chiral ligands to explore the possibility of imparting stereoselectivity on the cycloadducts.

1.7.3 Synthesis of 'drug-like' spirocyclic indoxyls

As previously discussed, the cycloadducts contain the core of biologically active natural products. We are eager to use the developed chemistry to synthesise a range of related spirocyclic indoxyls which could in turn possess interesting biological activity (Scheme 28). The biological activity of mitragynine pseudoindoxyl **9** and analogues will be discussed in the context of this work at the start of that chapter.

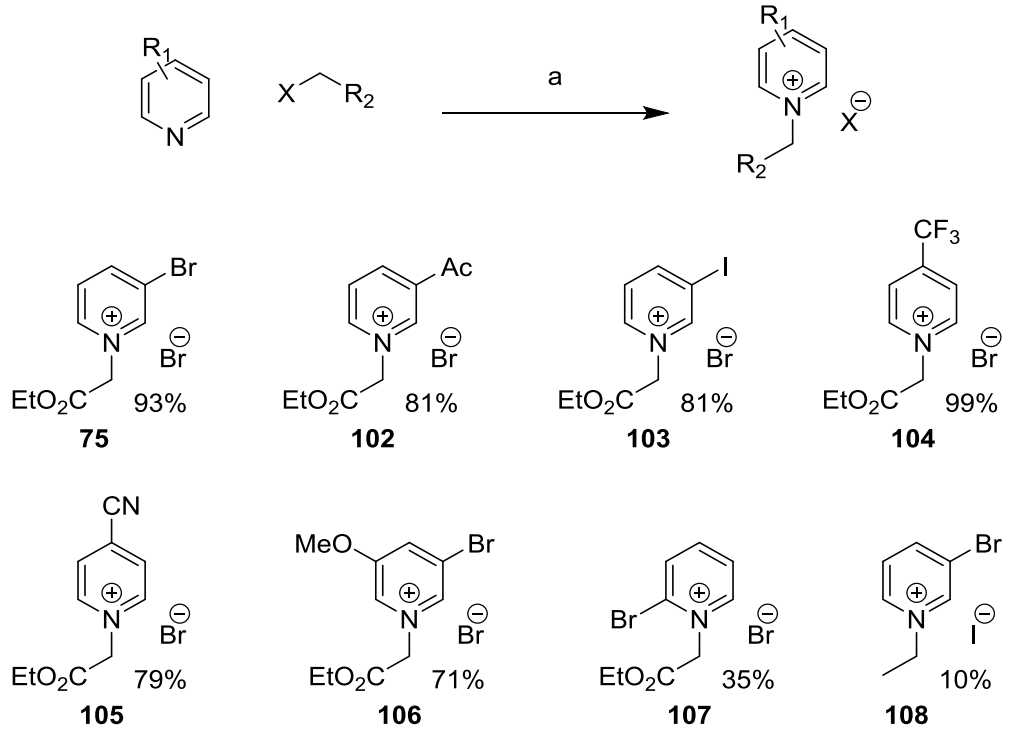


Scheme 28 – Desired cycloadduct transformation

Chapter 2. (3+2) Dipolar cycloadditions of 2-alkenylindoxyls

2.1 Synthesis of pyridinium salts

A variety of pyridinium salts were synthesised (Scheme 29) using substituted pyridines and primary alkyl halides, these generally proceeded in high yields with the exception of **107** and **108**.



Scheme 29 - *Reagents and conditions* - a) EtOAc, 77 °C, 16-72 hr.

The 2-bromo pyridinium salt **107** showed limited stability in solution reacting with residual water in the d_6-DMSO undergoing S_NAr displacement to form the pyridone **109** (Figure 8). However, it is stable for several months when stored as a solid under argon.

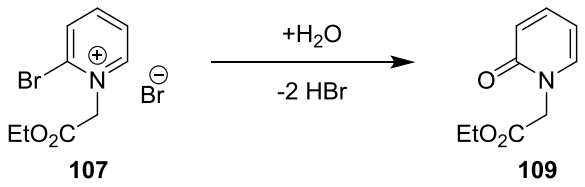
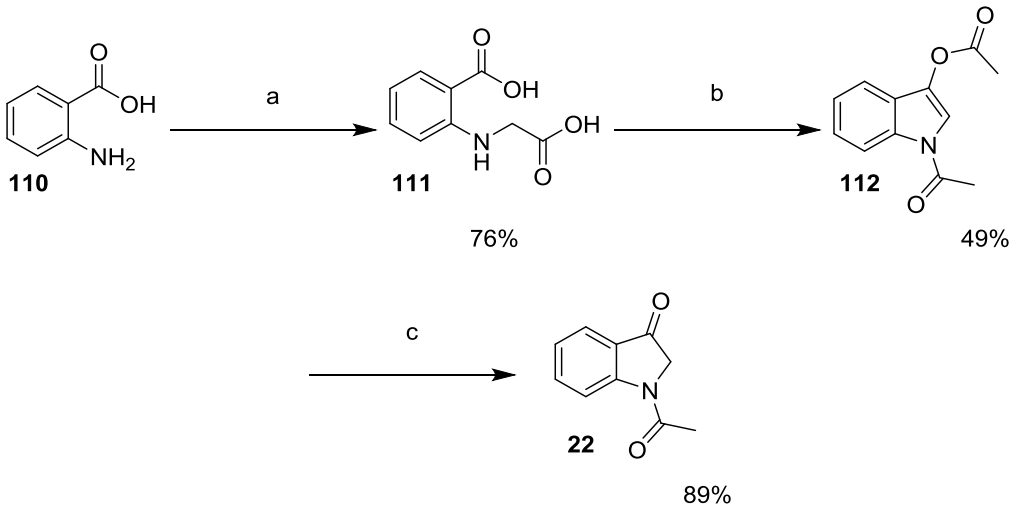


Figure 8 – Formation of 2-pyridone

2.1.1 Synthesis of aromatic substituted indoxyls

A literature route to 1-acetylindolin-3-one **22** was performed in order to synthesise a variety of indoxyl dipolarophiles (Scheme 30).[50]

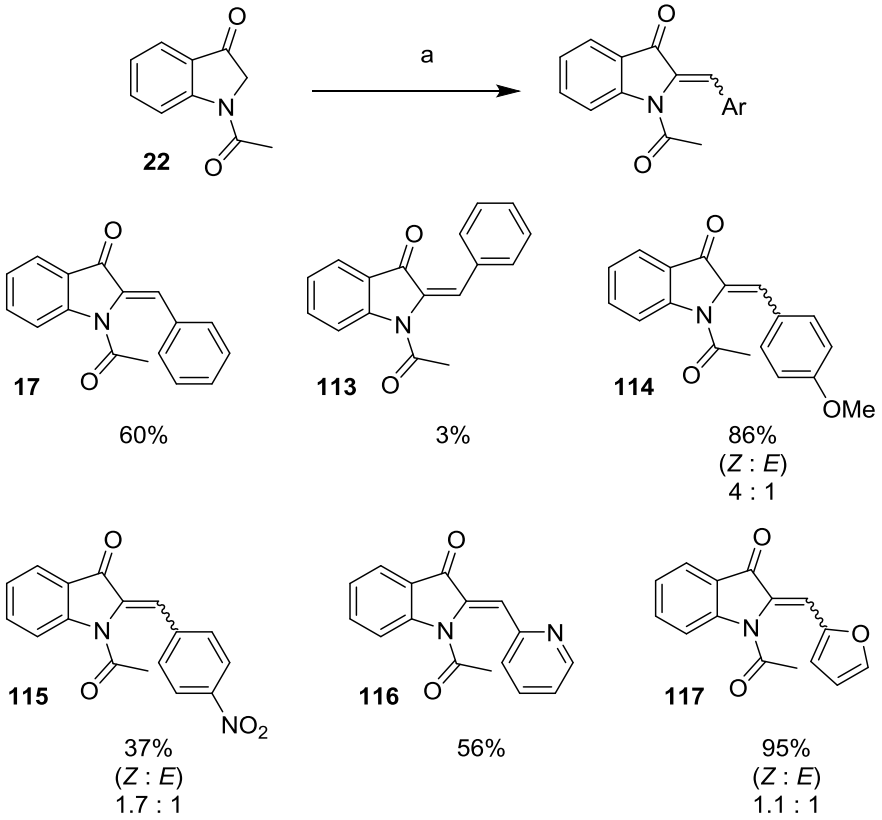


Scheme 30 - *Reagents and conditions* - a) bromoacetic acid, NaOH, $NaHCO_3$, H_2O, 110 °C, 15 hr; b) acetic anhydride, Na_2CO_3, 140 °C, 2 hr; c) Na_2SO_3, EtOH, H_2O, 60 °C, 15 hr.

The alkylation of anthranilic acid **110** required careful extraction from water maintaining the pH in the range of 3-4, but eventually gave the diacid **111** in high yield. Subsequent cyclisation and decarboxylation in acetic anhydride proceeded to generate 1-acetyl-1*H*-indol-3-yl acetate **112** in moderate yield. The next step was acetate hydrolysis to afford 1-acetylindolin-3-one **22** in high yield. However, attempts to deprotect both the *O*-acetyl and *N*-acetyl groups in the same

reaction produced a complex mixture and none of the desired product could be isolated. It is likely that this resulted in the formation of the homo-dimer of indolin-3-one (indigo), though this was never confirmed.

The final step to a range of aromatic indoxyl dipolarophiles was an aldol condensation (Scheme 31), this in every case, except for 2-pyridinecarboxaldehyde **116**, produced a mixture of *E* and *Z* alkenes.



Scheme 31 - *Reagents and conditions* - a) aromatic aldehyde, morpholine (20 mol%), toluene, 110 °C, 4 hr.

In the case of phenyl **17** and **113** they were separable by column chromatography, but generally these products were isolated as a mixture of isomers. The geometry of the alkene **17** was initially

assigned through ^{1}H NOESY NMR which showed a correlation between the acetyl methyl and an aromatic proton from the phenyl ring. An X-ray crystal structure confirmed the assignment of the major isomer (Figure 9). It is also worth noting that the *E*-alkene **113** isomerises over a few days at room temperature to the *Z*-alkene **17** indicating the latter to be the thermodynamic product.

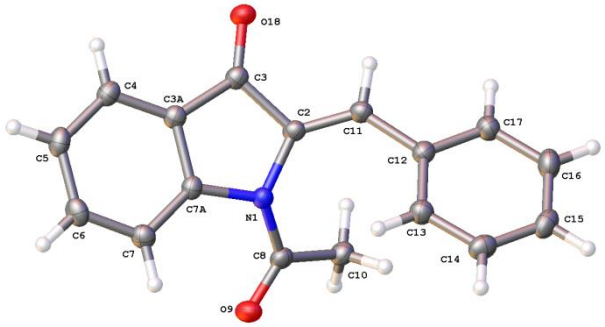
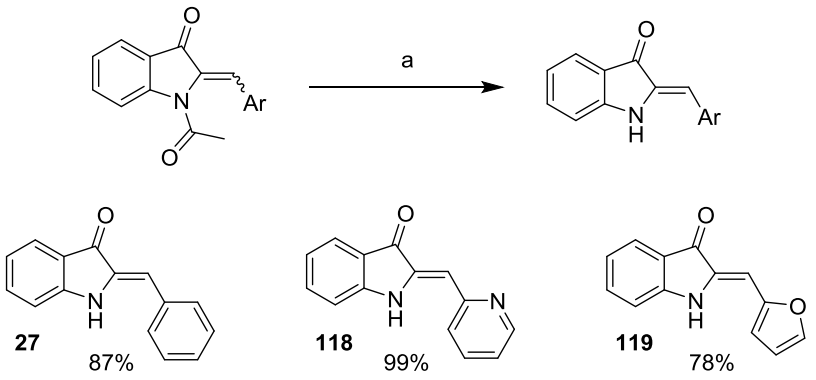


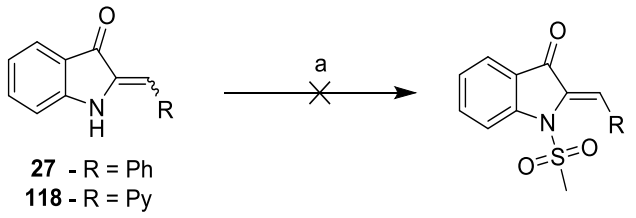
Figure 9 - Crystal structure of (*Z*)-1-acetyl-2-benzylideneindolin-3-one **17**

The acetyl group was removed from dipolarophiles **17**, **116** and **117** in order to directly compare the effect of this group on subsequent reactivity (Scheme 32). The deprotection proceeded well in all cases without requiring chromatography. Interestingly, regardless of the ratio of *E* and *Z* alkene in the starting material only the *Z* is observed in these products by ^{1}H NOESY NMR, again reinforcing this isomer as the thermodynamic product.



Scheme 32 - *Reagents and conditions* - a) K_2CO_3, MeOH, 20 °C, 1 hr.

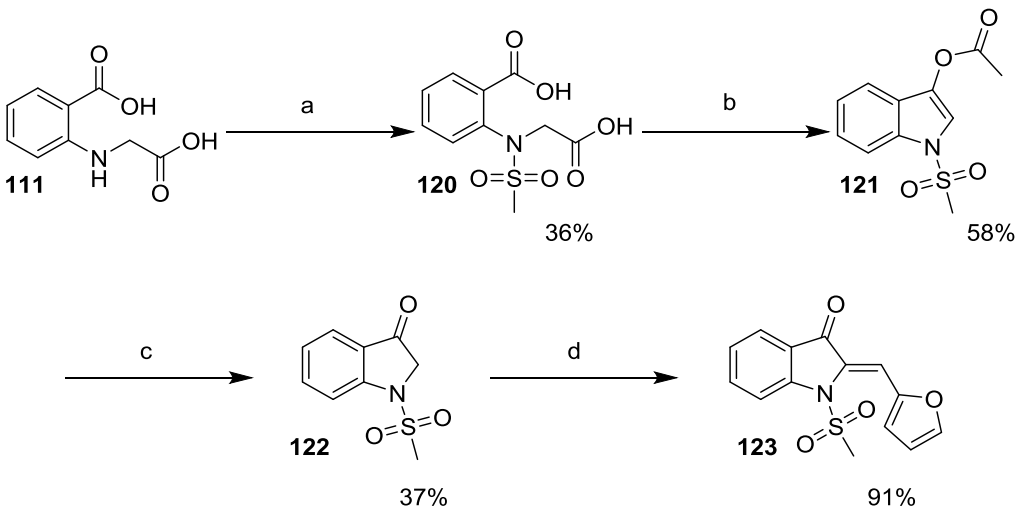
Initial cycloadditions performed with *N*-Ac dipolarophiles (See section 2.2) were present as a 1:1 mixture of compounds. To test the hypothesis these were rotamers resulting from the acetyl group it was decided to synthesise a dipolarophile with a symmetrical substituent on the nitrogen. Attempts to functionalise the nitrogen of dipolarophiles **27** and **118** as a sulfonamide were made (Scheme 33). In all cases these proved unreactive and resulted only in returned starting material.



Scheme 33 - *Reagents and conditions* - a) NaH, mesyl chloride, THF, 0 – 23 °C, 24 hr.

Sulfonamide functionalisation was thus installed earlier in the synthesis (Scheme 34). Alkylated anthranilic acid **111** was reacted with methanesulfonyl chloride to afford the mesylated product **120**

in modest yield and the remainder of the route proceeded as before, generating the desired *N*-mesyl dipolarophile **123** in 4 steps.



Scheme 34 - *Reagents and* conditions - a) Methanesulfonyl chloride, sat. aq. $NaHCO_3$, 0 °C, 2 hr; b) acetic anhydride, Na_2CO_3, 140 °C, 2 hr; c) Na_2SO_3, EtOH, H_2O, 60 °C, 15 hr; d) furfural, morpholine (20 mol%), toluene, 110 °C, 4 hr.

2.1.2 Synthesis of ester substituted indoxyls

When the aldol condensation was performed with ethyl glyoxylate only small amounts of the desired product were isolated (Table 4).

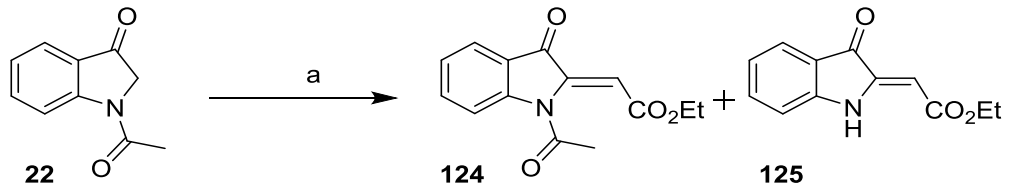
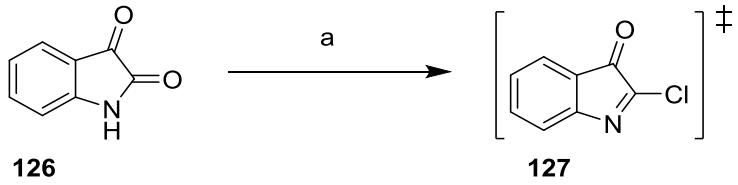


Table 4 - *Reagents and conditions* - a) ethyl glyoxylate, morpholine (20 mol%), 4 Å MS, toluene, temperature, 12 hr.

Entry	Temperature (°C)	Yield 124 (%)	Yield 125 (%)
1	110	16	25
2	50	19	0
		(3 : 2, *Z* : *E*)	

Heat is required to convert the trimeric form of ethyl glyoxylate to the aldehyde, however, at high temperatures (Entry 1) the major product is that of aldol condensation and deacetylation **125**.[17] By decreasing the temperature (Entry 2) this side reaction is slowed but low yields of the desired ethyl ester dipolarophile **124** are obtained. Also, at lower temperatures, a mixture of alkenes were isolated with a slight preference for the *Z* isomer; at higher temperatures gave the *Z* isomer as the exclusive product. With poor yields and a significant step count an alternative route was investigated towards synthesising non-aromatic 2-alkenylindolones.

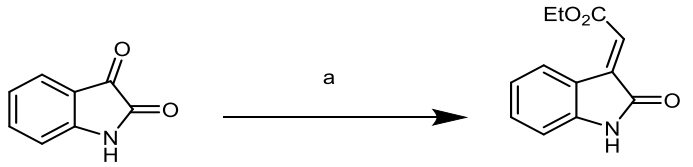
Katritzky had investigated reactions involving isatin **126** and PCl_5 (Scheme 35).[51] Although this product was too reactive to isolate subsequent reactions with *N* and *S* nucleophiles allowed the formation of 2-chloro-indol-3-one **127** to be inferred. We decided to investigate whether similar reactivity could be exploited for our purposes.



126 **127**

Scheme 35 - *Reagents and conditions* – a) PCl_5, benzene, 80 °C, 4 hr.

Enolate addition to this proposed intermediate was attempted, however, the product **128** resulted from addition to the carbonyl at the 3 position on the indole ring (Scheme 36).



126 **128** 10%

Scheme 36- *Reagents and conditions* – a) $POCl_3$, Et_3N, LiHMDS, ethyl acetate, THF, 40 - -78 °C, 2 hr.

Thus, we decided to protect this carbonyl with ethylene glycol which proceeded in good yield to afford the protected isatin **129** and reattempted the desired transformation (Table 5). Pleasingly, when protected isatin **129** reacted with $POCl_3$ and subsequently the enolate from ethyl acetate, the desired product **131** was generated albeit in very poor yield (Entry 1). As HCl is generated as a by-product of the reaction with $POCl_3$ it is likely the enolate was quenching upon addition to the reaction mixture. Addition of an amine base (Entry 2) showed a small increase in yield. However, as the proton is still present in the reaction as the triethylammonium the enolate is still able to act as a base or a nucleophile. Sodium hydride was examined (Entry 3) to remove the proton from the reaction as hydrogen before

the enolate addition, which afforded the desired product **131** in 24% yield. Further optimisation was achieved by increasing the equivalents of enolate (Entries 4 and 5) as this was likely also reacting with an electrophilic phosphorus species, using 3.8 equivalents the desired product **131** was generated in synthetically useful quantities.

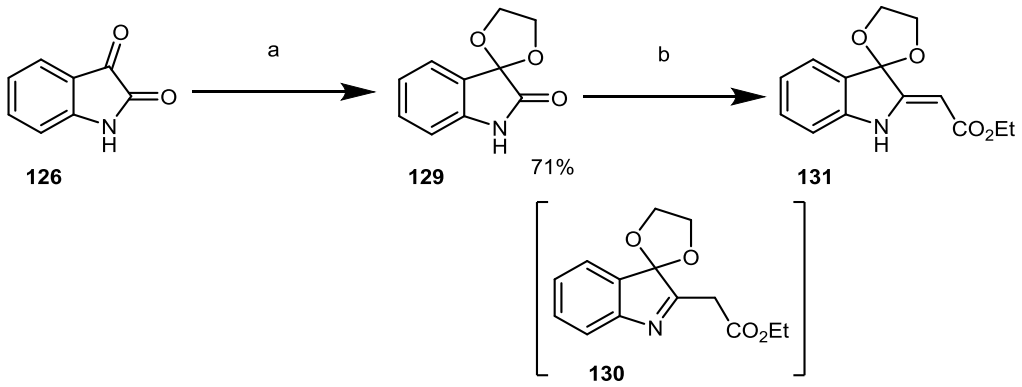
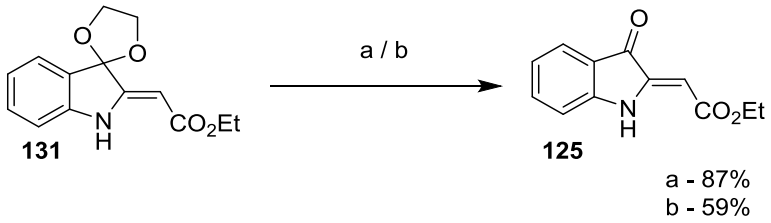


Table 5 - *Reagents and conditions* – a) ethylene glycol, *p*-toluenesulfonic acid monohydrate (10 mol%), toluene, 110 °C, 16 hr; b) $POCl_3$, Base, LDA, ethyl acetate, THF, 40 to -78 °C, 2 hr.

Entry	Base	Equiv. of enolate	Yield (%)
1	---	1.1	6
2	Proton Sponge	1.1	16
3	NaH	1.1	24
4	NaH	2.0	30
5	NaH	3.8	57

The acetal deprotection with *p*-toluenesulfonic acid proved capricious with generally poor yields isolated, so an alternate method using dilute aqueous HCl in dioxane was developed (Scheme 37). Although this required a prolonged reaction time it was found to provide consistent yields. This route demonstrates a novel expedient method

to generate substituted indoxyls in 35% over 3 steps, compared to the previous yield of 5% over 5 steps reported earlier.



Scheme 37 - *Reagents and conditions* - a) *p*-toluenesulfonic acid monohydrate, Na_2SO_4, acetone, 20 °C, 24 hr; b) HCl (0.02M) : dioxane (3 : 7), 30 °C, 96 hr.

In summary a wide variety of 2-alkenylindol-3-ones have been synthesised to be used as dipolarophiles for the subsequent cycloaddition investigation. A novel methodology was developed to synthesise non-aromatic substituted dipolarophiles, this was achieved *via* a concise route in good yield.

2.2 Spirocyclic tetrahydroindolizine indoxyls

2.2.1 Cycloadditions of substituted indoxyls with 3-bromopyridinium salt

A solvent study was performed with the phenyl dipolarophile **17** to determine the compatible solvents for these 1,3-dipolar cycloadditions (Table 6).

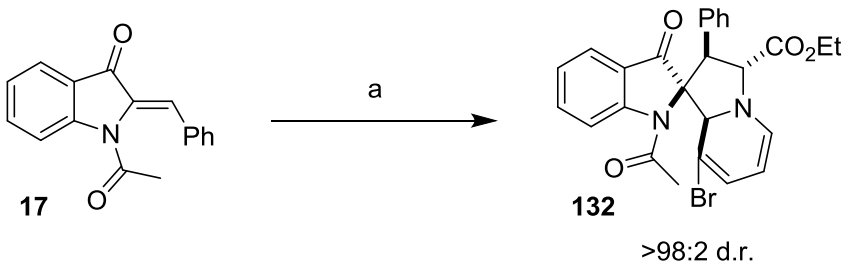


Table 6 - *Reagents and conditions* - a) 3-bromopyridinium salt (1.5 equiv.), Et_3N (1.5 equiv.), solvent, 20 °C, 4 hr.

Entry	Solvent	Polarity index[52]	Yield (%)
1	MeCN	5.8	97
2	EtOH	5.2	95
3	EtOAc	4.4	25[a]
4	CH_2Cl_2	3.1	95
5	TBME	2.5	6[a]
6	Toluene	2.4	5[a]

[a] average % conversion by crude ^1H NMR

Full conversion in 4 hours was observed in polar solvents (Entries 1,2 and 4) with the exception of ethyl acetate (Entry 3). Lower conversion observed in less polar solvents (Entries 5 and 6) can be explained through limited solubility of the pyridinium salt **75**, resulting in very slow ylide formation. The product in each case was produced as a single diastereomer, however, a mixture of rotamers is observed in the NMR spectrum due to the restricted rotation around the amide bond (*vide infra*).

A base study (Table 7) was performed with the three best solvents to ascertain ideal solvent and base combinations.

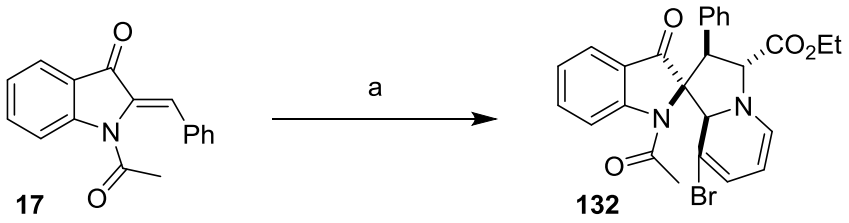


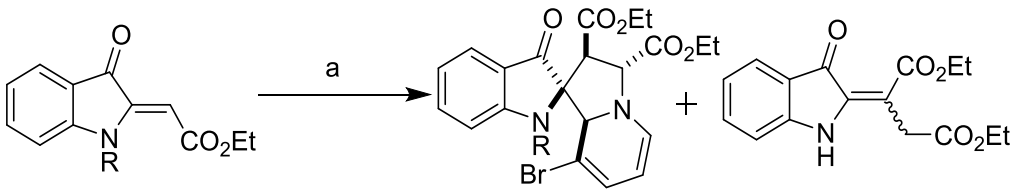
Table 7 - *Reagents and conditions* - a) 3-bromopyridinium salt (1.5 equiv.), Base (1.5 equiv.), solvent, 20 °C, 4 hr.

Entry	Base	Solvent	Yield (%)
1	Et_3N	CH_2Cl_2	95
2	^tBuOK	CH_2Cl_2	95
3	K_2CO_3	CH_2Cl_2	8[a]
4	K_2CO_3	MeCN	95
5	DBU	CH_2Cl_2	92
6	NaOAc	EtOH	50[a]
7	NaOAc	CH_2Cl_2	4[a]

[a] average % conversion by crude ^1H NMR

When performed in dichloromethane the reactions proceed well with homogenous bases (Entries 1, 2 and 5), however, only limited conversion was observed with inorganic bases (Entries 3 and 7). This again can be explained through lack of solubility with both potassium carbonate and sodium acetate performing significantly better in more polar solvents (Entries 4 and 6). Surprisingly sodium acetate (pKa ~5) in ethanol showed 50% conversion by ^1H NMR, with the pyridinium salt having a measured pKa of 14.10 in DMSO.[25] This suggests a fast rate of the cycloaddition reaction that proceeds with low concentrations of pyridinium ylide.

Several important findings were discovered when the cycloaddition was performed with the ethyl ester dipolarophiles **124** and **125** (Table 8). In acetonitrile with the acetyl group present (Entry 1) the desired cycloadduct **133** is observed as the sole product. However, with the free *NH* (Entry 2) the only isolated product is the result of elimination **135**. This alkene **135** is also observed within the product mixture when the reaction is carried out in dichloromethane. Initially it was thought that the elimination product **135** could be due to the decomposition of the cycloadduct **134**, but performing the reaction for varying time lengths always showed the same relative ratio of the two products. In dichloromethane this product distribution was found to be concentration dependent (Entries 3-7) with more elimination observed at higher concentrations up to 50% and only 5% at dilute concentration of 0.01 M.



124 - R = Ac
125 - R = H

133 - R = Ac
134 - R = H

135

Table 8 - *Reagents and conditions* - a) 3-bromopyridinium salt (1.5 equiv.), Et_3N (1.5 equiv.), solvent, 20 °C, 4 hr.

Entry	R	Solvent	Concentration	% of 133/134	% of 135
1	Ac	MeCN	0.05 M	94	0
2	H	MeCN	0.05 M	0	80
3	H	CH_2Cl_2	0.20 M	50[a]	50[a]
4	H	CH_2Cl_2	0.115 M	66[a]	33[a]
5	H	CH_2Cl_2	0.10 M	75[a]	25[a]
6	H	CH_2Cl_2	0.02 M	80[a]	20[a]
7	H	CH_2Cl_2	0.01 M	95[a]	5[a]

[a] – relative integration by ^1H NMR

These solvent effects may be explained by the reaction proceeding *via* a stepwise mechanism (Figure 10). Conjugate addition of the ylide into the alkene of the dipolarophile forms a betaine intermediate **136**. The betaine can either attack the pyridinium and generate the cycloadduct or eliminate 3-bromopyridine to form the alkene **135**. Elimination is more likely where the lifetime of the betaine intermediates **136** and **137** are extended, thus more polar solvents result in the elimination product **135**.

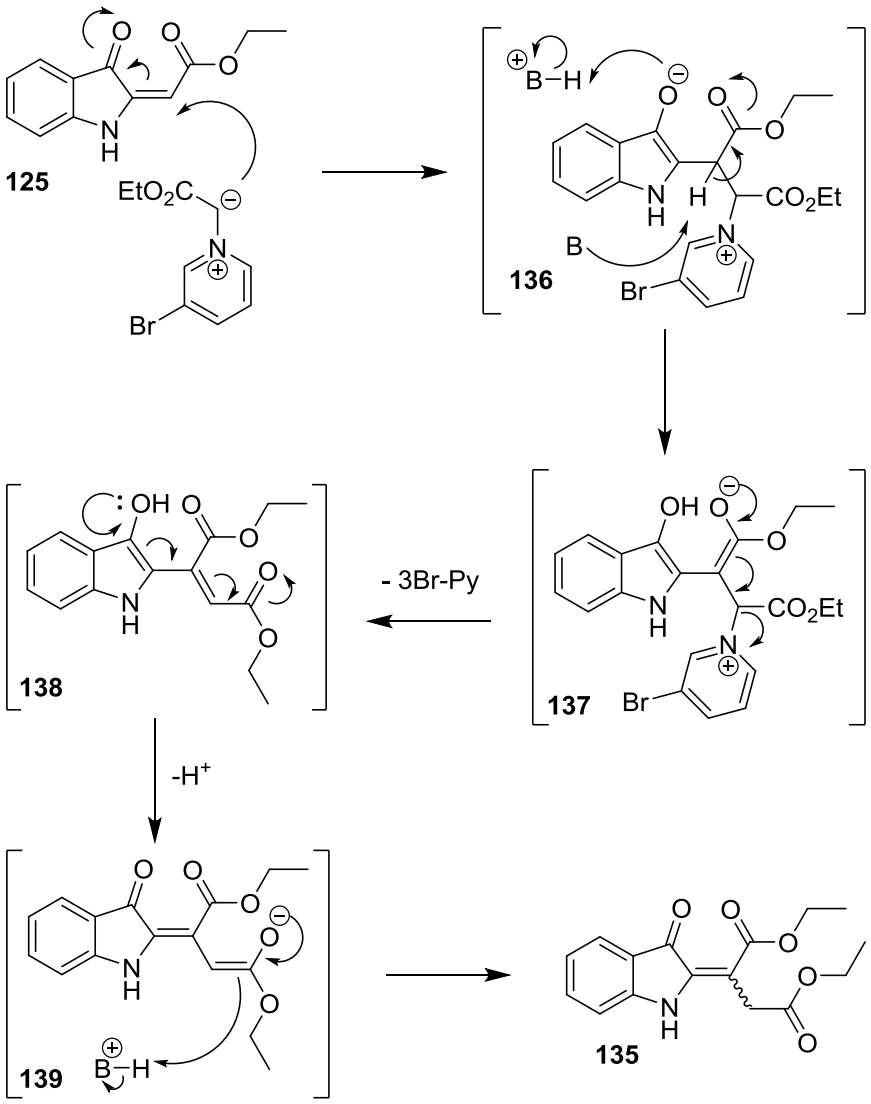


Figure 10 - Proposed elimination mechanism

Dichloromethane is a much poorer solvent for the stabilisation of the betaine intermediate **136**, we speculate that a dimeric interaction is able to form and increase the species lifetime (Figure 11).

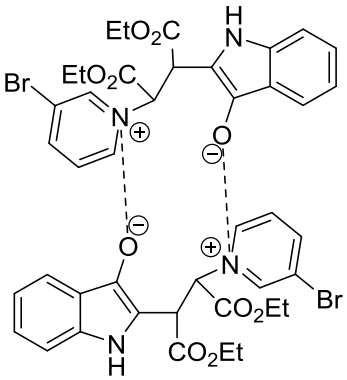


Figure 11 – Dimeric betaine stabilisation

At higher concentrations the molecules are more likely to be stabilised as dimers, while at much lower concentrations the unstable intermediate cyclises to generate the cycloadduct **134**.

2.2.2 Diastereoselectivity

The stereochemistry of the cycloadducts has been assigned through ^{1}H nOe NMR experiments with the key enhancements shown (Figure 12).

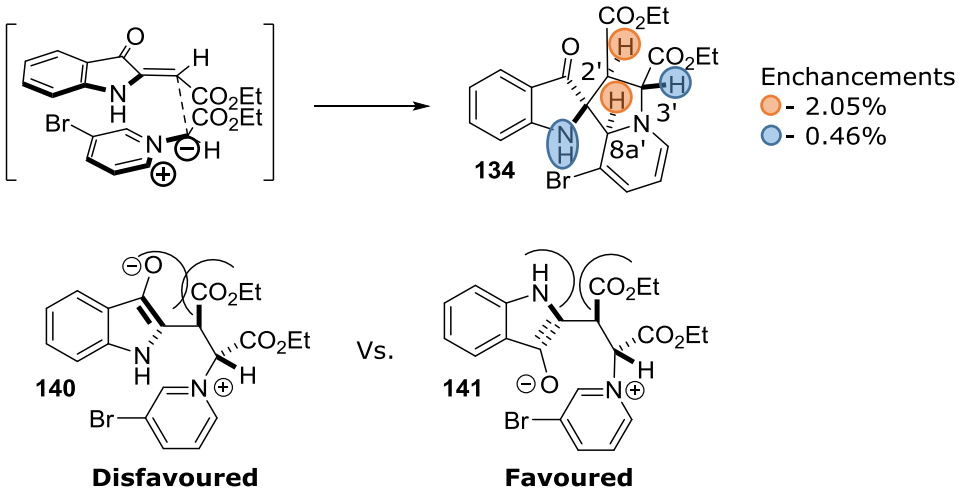
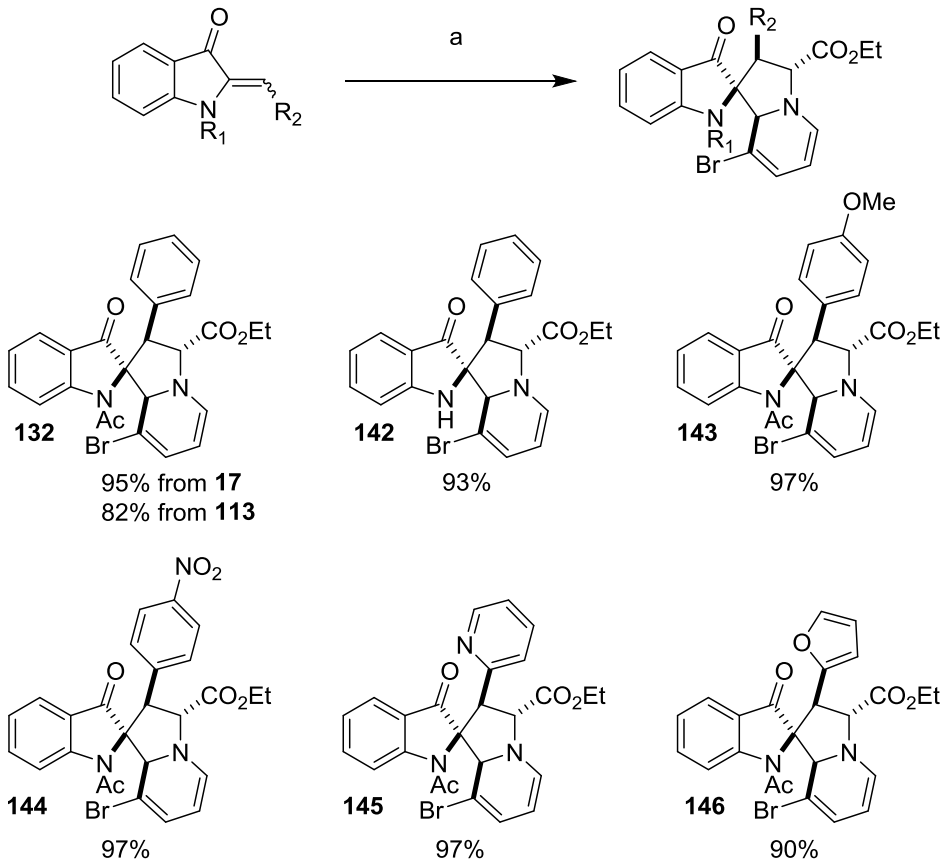


Figure 12 – Origin of stereochemistry

Enhancements between the 8a' and 2' protons (orange) and the NH and 3' proton (blue), along with the absence of enhancement between the NH and 8a', suggest the relative stereochemistry at the 4 new stereocenters of cycloadduct **134**. This stereochemistry can be rationalised through an 'endo' type approach due to a stabilising interaction between the electron rich indole ring and the electron deficient pyridinium ylide. The *trans* arrangement of the esters result from approaching on opposite faces to minimise dipole interactions. The spirocenter can be explained through steric repulsion within the resulting betaine intermediate with either the enolate **140** or the NH **141** on the same face as the adjacent ester, presumably the latter is more favourable, resulting in the observed relative stereochemistry. In this example, the observed regioselectivity is due bromine activating the carbon at the 2 position more than that at the 6 position on the pyridinium leading to only one observed regioisomer.

The cycloaddition was performed with a selection of dipolarophiles using the optimised conditions (Scheme 38). These all proceeded well with complete consumption of starting material. Interestingly, when the *E*-alkene **113** was used the resulting cycloadduct possessed the same relative stereochemistry as the *Z*-alkene **17**, reinforcing the proposed stepwise mechanism.



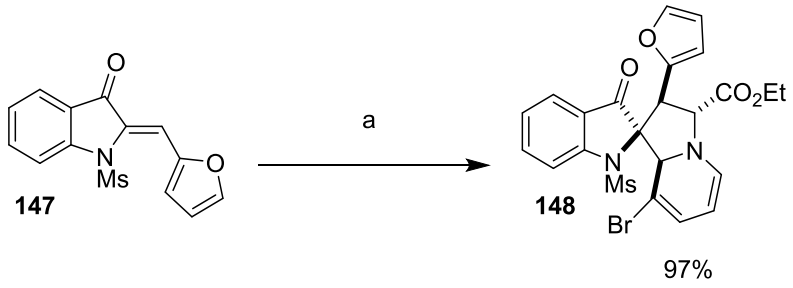
Scheme 38 - *Reagents and conditions* - a) 3-bromopyridinium salt (1.5 equiv.), Et_3N (1.5 equiv.), CH_2Cl_2, 20 °C, 4 hr.

It should be noted that the cycloadducts containing an electron withdrawing group on the indoxyl nitrogen were considerably more stable. The free *NH* cycloadducts were only stable in solution for a few hours before significant signs of decomposition was observed. This is presumably a result of the lone pair on the nitrogen participating in ring opening at the spirocenter.

The *NH* cycloadduct **142** only showed a single set of peaks in the NMR; while all cycloadducts containing the acetyl group **132** and **143-146** were present as the same mixture of rotamers previously observed. High temperature ^1H NMR experiments (70 °C and 90 °C)

was attempted to confirm the assignment of rotamers, however, this was unsuccessful as the cycloadduct **132** decomposed before there was any coalescence of the signals. Indicating the energy barrier to rotation is not accessible under these experimental conditions.

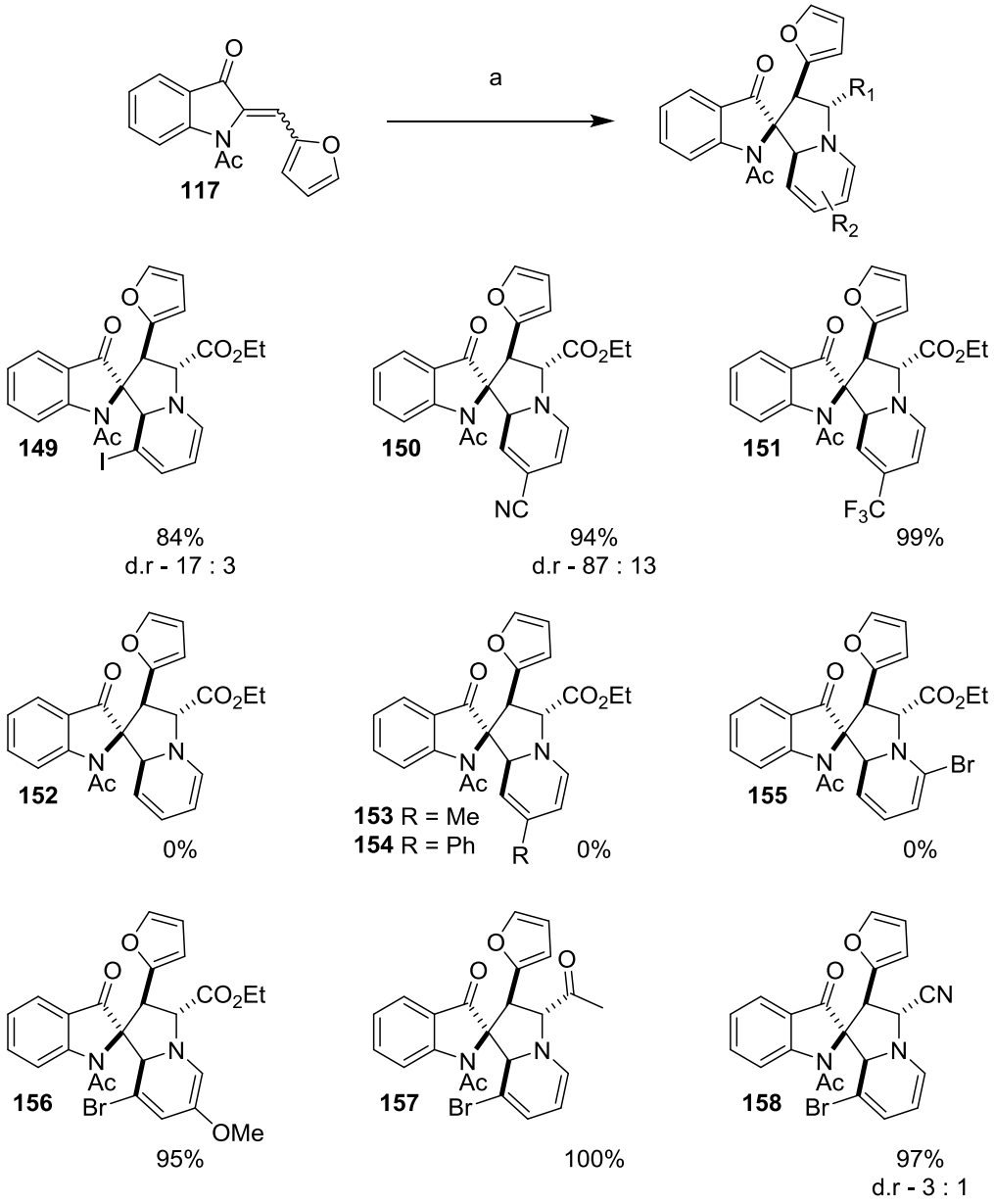
Further evidence for rotamers was found when a cycloaddition was carried out using the symmetrical mesyl nitrogen protecting group **147** which cannot produce rotamers (Scheme 39). This cycloadduct **148** as with the *NH* cycloadduct **142** showed only a single set of peaks in the NMR and was produced as the same single diastereoisomer.



Scheme 39 - *Reagents and conditions* - a) 3-bromopyridinium salt (1.5 equiv.), Et_3N (1.5 equiv.), CH_2Cl_2, 20 °C, 4 hr.

2.2.3 Variation of the pyridinium salt

The cycloaddition is tolerant to some variation of the pyridinium salt (Scheme 40). Electron withdrawing groups are tolerated in the 3 or 4 position as shown with 3-iodo **149**, 4-cyano **150** and 4-CF_3 **151** all proceeding in excellent yields.



Scheme 40 - *Reagents and conditions* - a) pyridinium salt (1.5 equiv.), Et_3N (1.5 equiv.), CH_2Cl_2, 20 °C, 4 hr.

However, unsubstituted dihydropyridine **152**, 4-Me **153** and 4-Ph **154** were all unsuccessful, with the resulting cycloadducts being too unstable to be isolated. This is presumably due to the dihydropyridine in the cycloadduct requiring electron withdrawing groups to stabilise the products. Formation of cycloadduct **155** using 2-bromopyridinium

salt **107** was also unsuccessful, in this case the ylide self-reacts and is therefore unable to undergo the cycloaddition.

Electron donating groups can be tolerated in the presence of an electron withdrawing group with 3-bromo-5-methoxy **156**. The regiochemistry of the cycloadduct is consistent with the other 3-bromo cycloadducts, as confirmed through HMBC correlations. A selection of ylide stabilising groups were tested to explore whether altering the pKa of the methylene proton influenced the products. The Methyl ketone **157** and nitrile **158** cycloadducts both worked well with the pyridinium salts still only requiring trimethylamine to generate the ylide. Cycloadducts **149**, **150** and **158** were isolated as a mixture of diastereoisomers. When a nitrile is used as the ylide stabilising group **158** a minor diastereoisomer arising from inversion at the 8a' position, as assigned through nOe NMR experiments was observed (Figure 13). We were unable to determine the stereochemistry of the other minor diastereoisomer for cycloadducts **149** and **150** due to the signals of interest overlapping with other peaks. Cycloadditions attempted using pyridinium salts with less acidic methylene protons such as N-ethyl **108** and N-benzyl required stronger bases LDA and sodium hydride respectively, however, these proved unsuccessful resulting in a complex mixture of products.

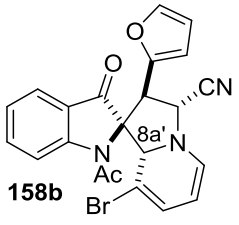
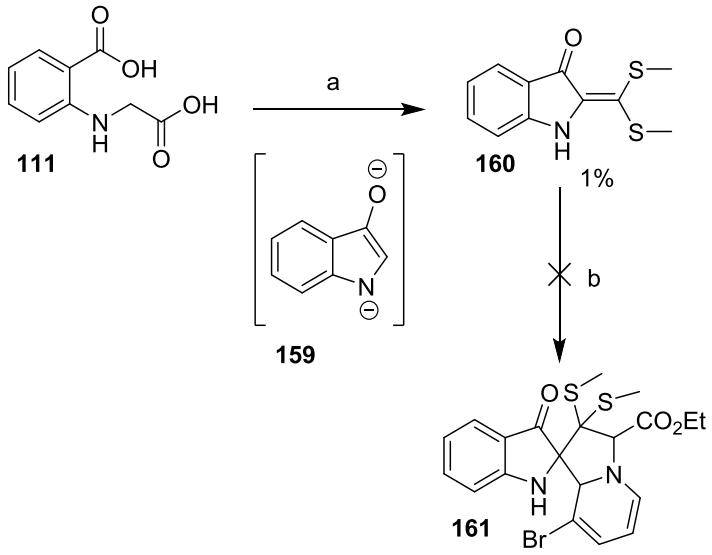


Figure 13 – Minor diastereoisomer of **158**

2.2.4 Tetra substituted dipolarophiles

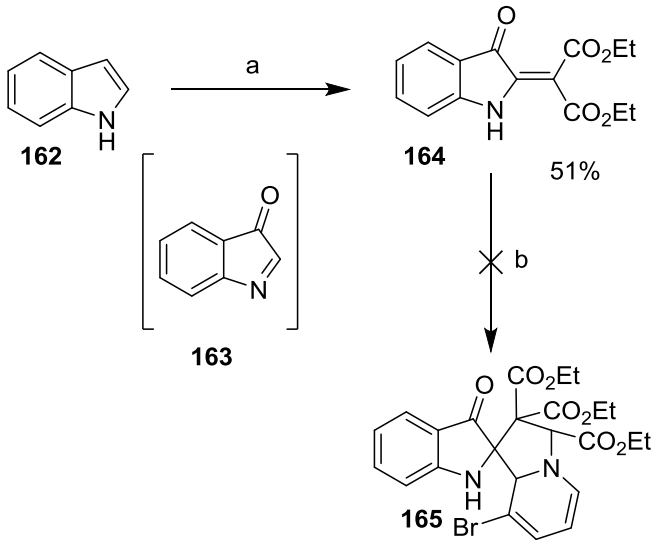
Two tetra substituted alkenes **160** and **164** were synthesised in order to evaluate if the 1,3-dipolar cycloaddition can be performed on such dipolarophiles; two short routes were selected generating dipolarophiles with very different properties in order to test this.

2-(Bis(methylthio)methylene)indolin-3-one **160** was synthesised from 2-((carboxymethyl)amino)benzoic acid **111** *via* a literature route, albeit in very low yield (Scheme 41).[53] This was likely due to the very harsh reaction conditions requiring decarboxylation and cyclisation to generate a proposed dianionic intermediate **159**. Despite this, sufficient 2-(bis(methylthio)methylene)indolin-3-one **160** was isolated to attempt a 1,3-dipolar cycloaddition; however no cycloadduct **161** was observed, even with heating and longer reaction times, resulting in recovered starting material.



Scheme 41 - *Reagents and conditions* - a) KOH, CS_2, MeI, H_2O, 220 – 0 °C, 16 hr; b) 3-bromopyridinium salt, Et_3N, MeCN, 40 °C, 24 hr.

A recent paper demonstrated that diethyl 2-(3-oxoindolin-2-ylidene)malonate **164** can be synthesised in one reaction from indole **162** and diethyl malonate (Scheme 42); this uses TEMPO and oxygen as oxidant to form 3*H*-indol-3-one **163** *in situ.*[54] This can then undergo an intramolecular nucleophilic addition and subsequent oxidation to generate diethyl 2-(3-oxoindolin-2-ylidene)malonate **164**. A 1,3-dipolar cycloaddition was then attempted and the desired mass ion was detected in the reaction mixture by mass spectrometry. Unfortunately work up gave a complex mixture and none of the desired cycloadduct **165** was detected.



Scheme 42 - *Reagents and conditions* - a) diethyl malonate, TEMPO, $CuSO_4.5H_2O$, toluene, 85 °C, 24 hr; b) 3-bromopyridinium salt, Et_3N, MeCN, 20 °C, 24 hr.

2.3 Dihydropyridine modification of indoxyl cycloadducts

Due to the highly reactive nature of 1,2-dihydropyridines the indoxyl cycloadducts only have a limited lifetime. If this reactivity can be harnessed, then further functionality may be added while also stabilising the products.

The pyridyl dipolarophile **118** was reacted with 4-CF_3 pyridinium salt **104** generating cycloadduct **166** in excellent yield as a 9 : 1 mixture of diastereomers. A range of hydrogenation conditions were evaluated in order to achieve selective reduction of the dihydropyridine to a spirocyclic indolizidine **167** (Table 9).

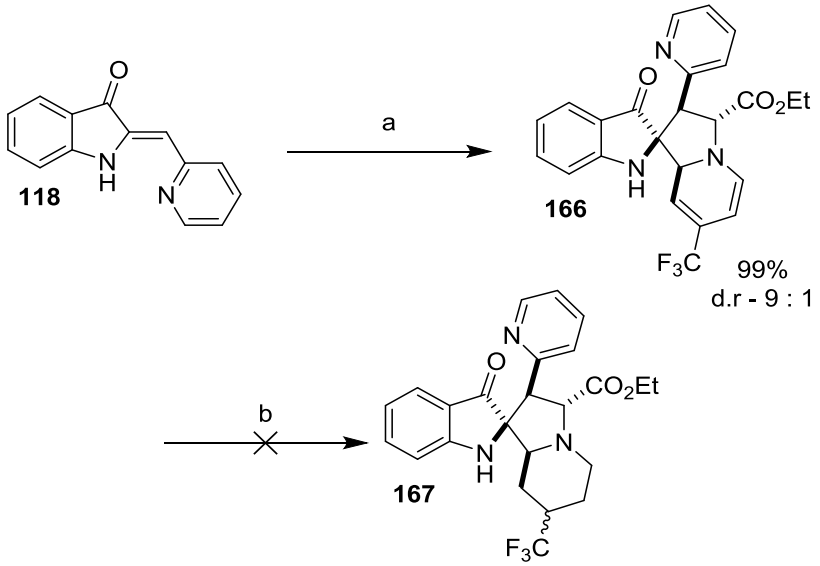


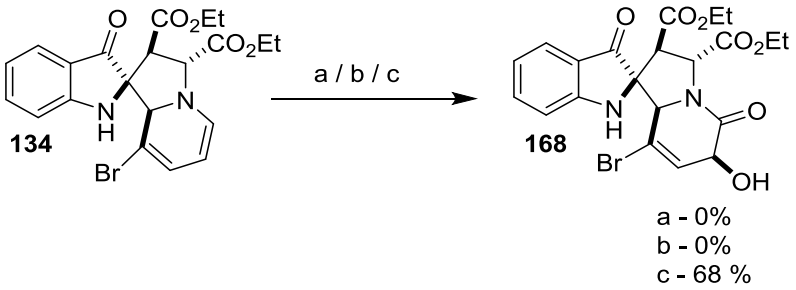
Table 9 - *Reagents and conditions* - a) 4-CF_3 pyridinium salt, Et_3N, CH_2Cl_2, 20 °C, 4 hr; b) catalyst, H_2, solvent, 20 °C, 4-24 hr.

Entry	Catalyst	Solvent	Time (hr)
1	$(Ph)_3RhCl$	(1:1) THF : ^{t}BuOH	24
2	$(Rh[COD]Cl)_2$	EtOH	24
3	Pd/C	EtOAc	16
4	Raney® nickel	EtOAc	16
5	Pt/C	EtOAc	4

Wilkinson's catalyst (Entry 1) and chloro(1,5-cyclooctadiene)rhodium(I) dimer (Entry 2) proved unreactive resulting in decomposition of the starting material. Palladium on carbon (Entry 3) and Raney® nickel (Entry 4) were highly reactive and non-selective, resulting in complex mixtures with no desired product isolated. Platinum on carbon (Entry 5) showed the most promise as a reductant; unfortunately, even shortened reaction times still gave over reduction (as observed by mass spectrometry of the crude mixture) that could not be controlled, likely due to reduction of

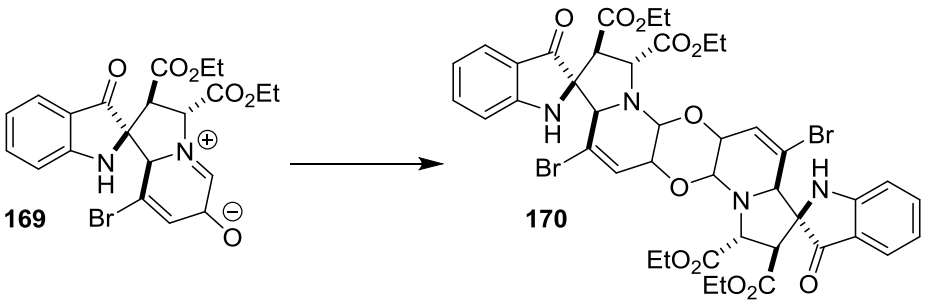
the carbonyl. Attempts to purify this reduced product were unsuccessful, only a complex mixture of presumed diastereomers and corresponding rotamers was observed.

Several different conditions for oxidation of cycloadduct **134** using *m*CPBA were next investigated (Scheme 43).



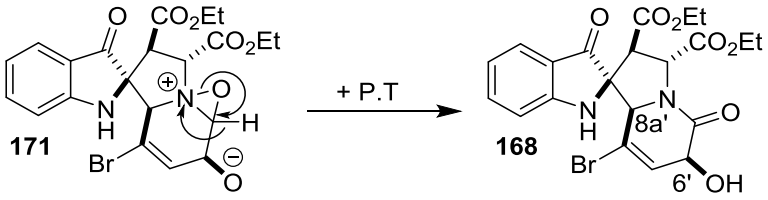
Scheme 43 - *Reagents and conditions* - a) *m*-CPBA, MeOH, 20 °C, 1 hr; b) *m*CPBA, MeOH, 0 °C, 1 hr; c) *m*-CPBA, MeOH, -78 °C, 1 hr.

Complex mixtures were isolated when the oxidations were performed at 0 ^{O}C or above. The *m/z* of the dimer **170** + sodium was observed in the mass spectrum of the reaction mixture; however, 2M+Na peaks in mass spectrometry are also possible and isobaric. This could be the result of dimerisation of the zwitterionic intermediate **169** formed, though this was never proved it has previously been reported with other enamines (Scheme 44).[55]



Scheme 44 – Proposed dimerisation of oxidation

At low temperature the oxidation proceeds to afford amide **168** as a single product, formed as a result of over oxidation. This can be rationalised through the same iminium species **169** generating the oxaziridine **171** which, following a 1,2-shift and proton transfer affords the amide **168** (Scheme 45). This transformation of imines to amides has been previously reported.[56]



Scheme 45 – Formation of amide

The relative stereochemistry of the alcohol of cycloadduct **168** was assigned through ^{1}H NOESY NMR with a correlation observed between the 6’ and 8a’ protons.

Selective mono-oxidation was achieved through the use of mild oxidants in the form of 3,3-dimethyldioxirane (DMDO) and oxaziridines (Table 10).

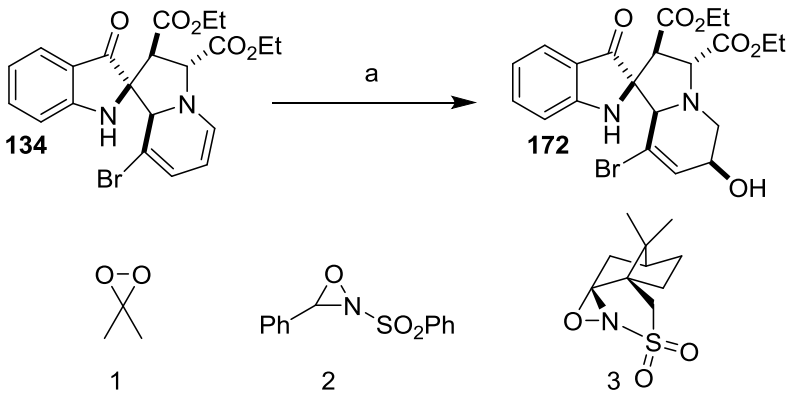


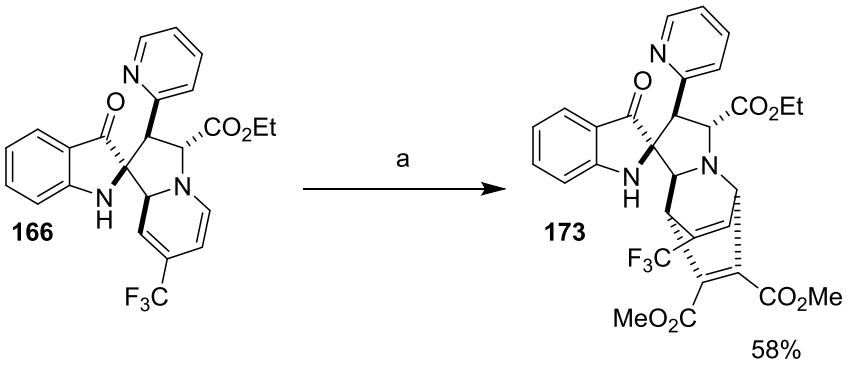
Table 10 - *Reagents and conditions* - a) oxidant, reductant, THF, -78 °C, 3 hr.

Entry	Oxidant	Reductant	Yield (%)	d.r
1	1	NMe_4 $BH(OAc)_3$	29	>19:1
2	2	$(Me_2SiH)_2O$	0	---
3	2	NMe_4 $BH(OAc)_3$	14	19:1
4	2	Na $BH(OAc)_3$	37	16:4
5	2	Na $NCBH_3$	52	18:2
6	3	NMe_4 $BH(OAc)_3$	58	>19:1

Reaction of cycloadduct **134** with DMDO (Entry 1) followed by iminium reduction with tetramethylammonium triacetoxyborohydride generated the desired alcohol **172** with excellent diastereoselectivity, but only modest yields were obtained. When the oxidation was performed with Davies' oxaziridine (Entries 3-5) an effect not seen with the other oxidants was observed; the reductant not only affected the yield but also the diastereoselectivity of the reaction. 1,1,3,3-Tetramethyldisiloxane (Entry 2) was evaluated as a mild reductant, however, this was not able to reduce the iminium. Tetramethylammonium triacetoxyborohydride showed excellent

diastereoselectivity as seen when used with all the oxidants, but gave low yields in combination with Davies' oxaziridine (Entry 3). Changing the counterion to sodium (Entry 4) saw a marked increase in yield but was accompanied by a significant drop in diastereoselectivity. That was also observed when sodium cyanoborohydride was used as reductant (Entry 5). Ultimately, conditions were found that resulted in good yield and very high diastereoselectivity when a combination of (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine and tetramethylammonium triacetoxyborohydride were used(Entry 6).

We also sought to evaluate the potential of the Diels-Alder reaction (Scheme 46). Reacting cycloadduct **166** with DMAD gave the corresponding Diels-Alder product **173** in good yield (77% over 2 steps) as a single diastereomer, the relative stereochemistry was assigned through ^{1}H NOESY analysis.



Scheme 46 - *Reagents and conditions* - b) dimethyl acetylenedicarboxylate, CH_2Cl_2, 20 °C, 16 hr.

Interestingly, the oxidation product **172** and the Diels-Alder cycloadduct **173** have the opposite relative stereochemistry of the newly formed bonds. A 3D model of cycloadduct **166** can be used to

rationalise the diastereoselectivity of the Diels-Alder cycloadduct **173**, showing the backface of the dihydropyridine to be more available resulting in the alkyne approaching from the less hindered face (Figure 14).[57]

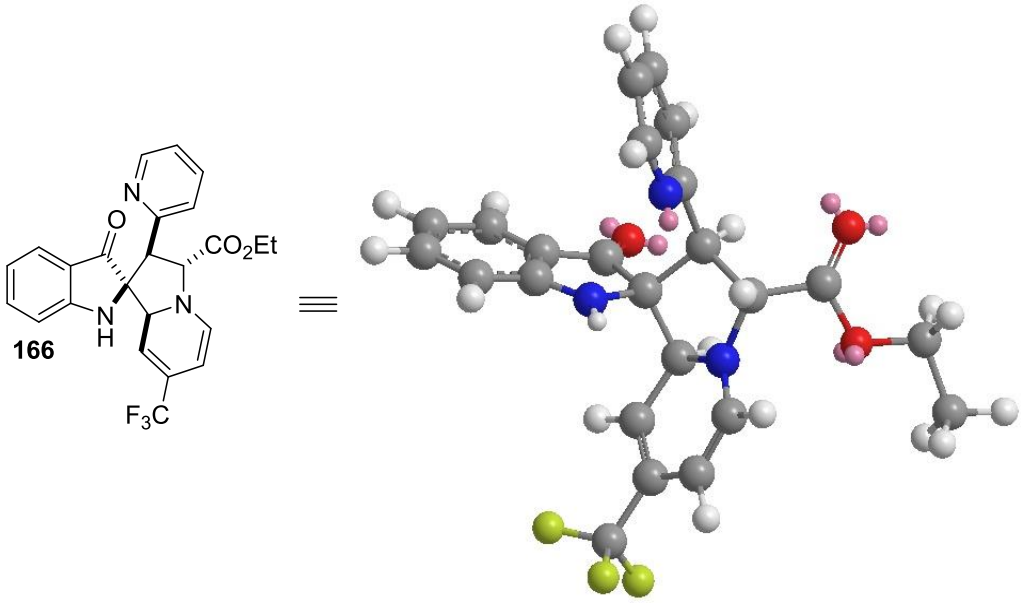


Figure 14 – 3D model of cycloadduct **166**

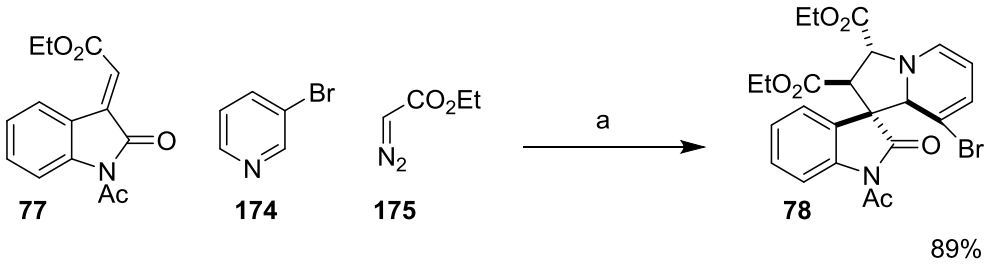
While reduction of these dihydropyridines proved difficult, we have been able to achieve both controlled oxidations and sequential cycloadditions. This reactivity can be explored further for adding molecular complexity in a few steps with good stereochemical control.

In summary the cycloaddition has been performed on many 2-alkenylindol-3-ones, the reaction proceeds very quickly with excellent diastereo and regioselectivity. The resulting cycloadducts have a limited lifetime but several transformations have been demonstrated to stabilise the cycloadducts while increasing molecular complexity

with excellent diastereoselectivity. Tetra-substituted alkenes have been synthesised and the cycloadditions attempted, however, these have proved unsuccessful in generating the desired cycloadducts.

Chapter 3. Investigation towards an asymmetric methodology

During this research a new methodology was developed in the group to perform (3+2) dipolar cycloadditions via the *in situ* generation of pyridinium ylides from diazo compounds (Scheme 47).[39]



Scheme 47 - *Reagents and conditions* - a) Fe(TPP)Cl (1 mol%), toluene, 20 °C, 4 hr.

Transition metal catalysts can decompose diazo compounds to afford metallocarbenoids. Addition of pyridine leads to an ylide that may or may not be associated or bound to the metal (Figure 15).

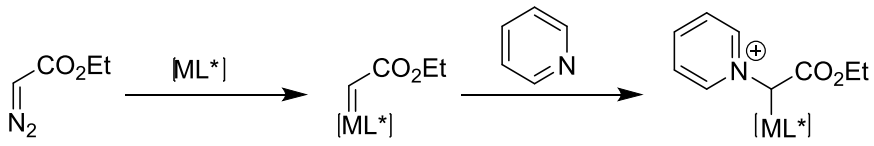


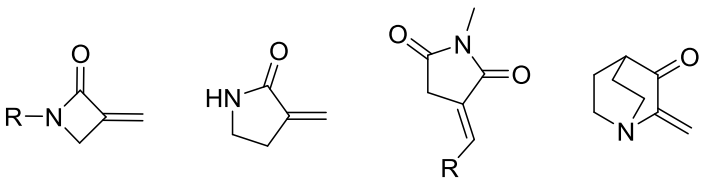
Figure 15 – Formation of pyridinium ylide

It was our hope that chiral ligands it may be possible to block one face of the pyridinium species and thus generate cycloadducts enantioselectively.

The best method for determining enantioselectivity is chiral HPLC. Unfortunately, the oxindole cycloadducts above, and the indoxyl cycloadducts synthesised in chapter two, proved unstable towards chiral HPLC. Therefore, we took the opportunity to investigate a range of dipolarophiles that might lead to interesting, potentially drug-like scaffolds, that we were able to resolve through chiral HPLC.

3.1 Synthesis and cycloadditions of other dipolarophiles

We were interested in the synthesis of sp^3 rich hetereocycles with exocyclic double bonds to be evaluated as dipolarophiles. Therefore, routes towards a range of dipolarophiles were performed (Figure 16).

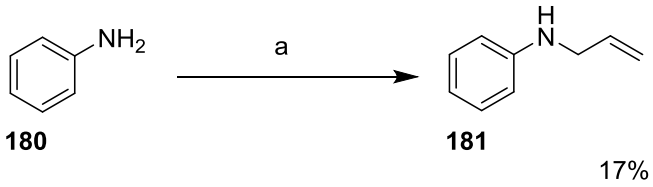


176 **177** **178** **179**

Figure 16 – Dipolarophiles synthesised

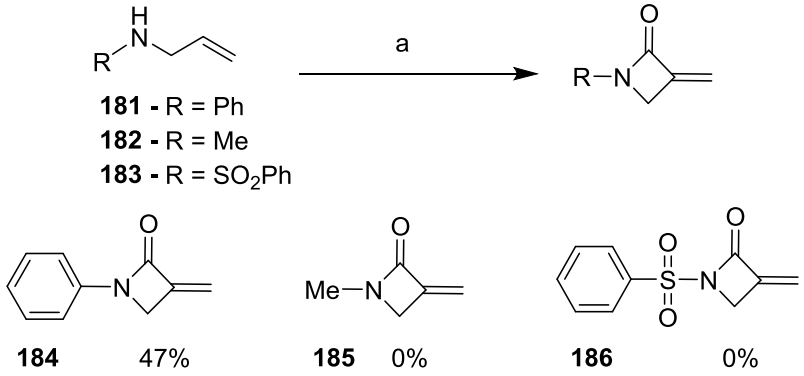
3.1.1 Beta-lactams

The synthesis of beta lactams through reactions of allyl amines and carbon monoxide have previously been reported.[58] The allylation of aniline **180** proceeded in poor yield due to the difficulty in separating the mono allylated product **181** from the *bis*-allylated side product (Scheme 48). However, sufficient material was obtained to attempt the lactam formation.



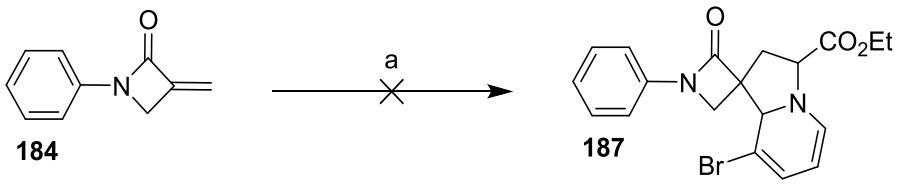
Scheme 48 - *Reagents and conditions* - a) allyl bromide, NaH, THF, 0 - 23 °C, 2 hr.

The cyclisation was attempted with a selection of allyl amines, **182** was commercially available and **183** was gifted[59] (Scheme 49). The literature example of *N*-allylaniline **181** proceeded well to afford the *N*-phenyl beta-lactam **184**. Both *N*-methyl **182** and *N*-sulfonamide **183** remained unreacted and resulted in the isolation of starting materials.



Scheme 49 - *Reagents and conditions* - a) carbon monoxide, $PdCl_2$, PCy_3, $Cu(OAc)_2$, PivOH THF, 100 °C, 24 hr.

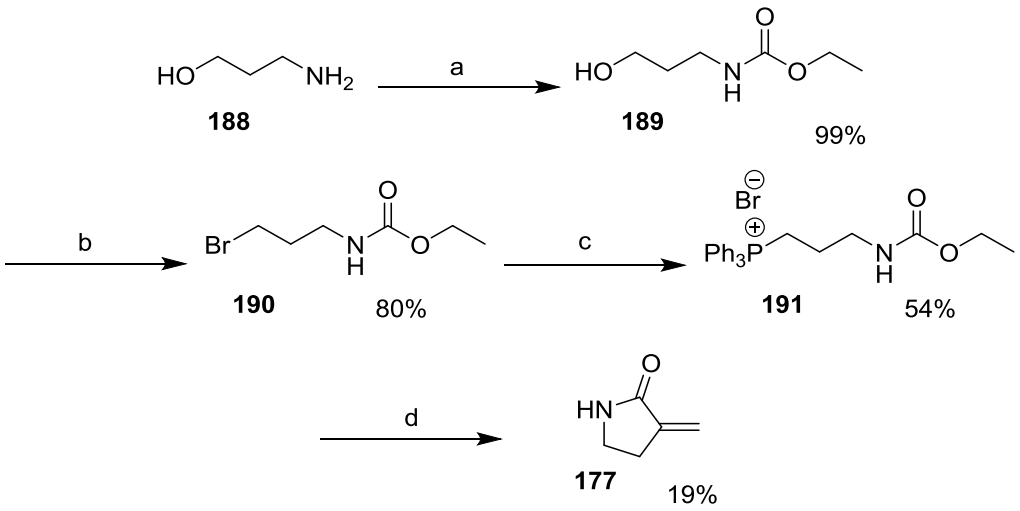
The cycloaddition was attempted with the beta lactam **184**, the 1,2-dihydropyridine peaks of the corresponding cycloadduct **187** were apparent in the crude ^1H NMR (Scheme 50). However, apparent decomposition of the cycloadduct on silica during the attempted purification prevented isolation of this product.



Scheme 50 - *Reagents and conditions* - a) 3-bromopyridinium salt, Et_3N, CH_2Cl_2, 20 °C, 4 hr.

3.1.2 Gamma lactams

Beta lactams showed promising reactivity but were unstable towards purification. It was thought that a five membered ring would be less strained and the cycloadducts may be more stable, so a literature route was performed to synthesise the gamma lactam **177** (Scheme 51).[60]

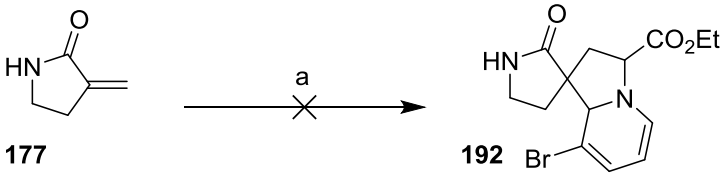


Scheme 51 - *Reagents and conditions* - a) ethyl chloroformate, K_2CO_3, H_2O, 0 °C, 2 hr; b) thionyl bromide, CH_2Cl_2, 23 °C, 16 hr; c) triphenyl phosphine, MeCN, 82 °C, 16 hr; d) ^tBuOK, paraformaldehyde, toluene, 23 – 50 °C, 2 hr.

The alkylation of 3-aminopropanol **188** proceeded quantitatively to afford the carbamate **189**, the alcohol was subsequently converted

into the alkyl bromide **190** in good yield. Reaction with triphenylphosphine generated the phosphonium salt **191** which was subject to intramolecular cyclisation and subsequent Wittig reaction with paraformaldehyde to afford the gamma lactam **177**. Though this final step gave a poor yield, enough material was produced so no attempt to optimise this reaction was undertaken.

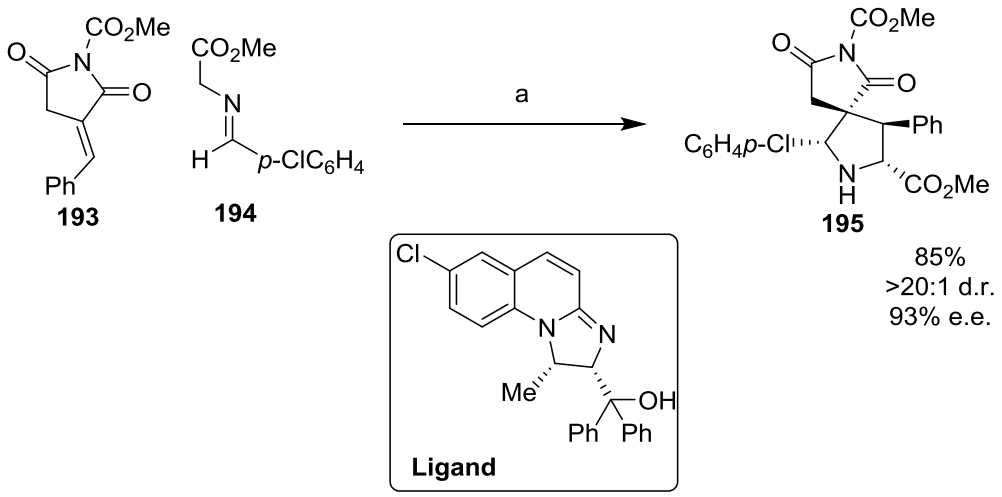
The cycloaddition was attempted, but as with the beta-lactams the desired cycloadduct **192** was observed by NMR as part of a complex mixture containing multiple 1,2-dihydropyridine peaks (Scheme 52). Unfortunately, this compound also proved unstable towards purification.



Scheme 52 - *Reagents and conditions* - a) 3-bromopyridinium salt, Et_3N, CH_2Cl_2, 20 °C, 4 hr.

3.1.3 α-alkylidene succinimides

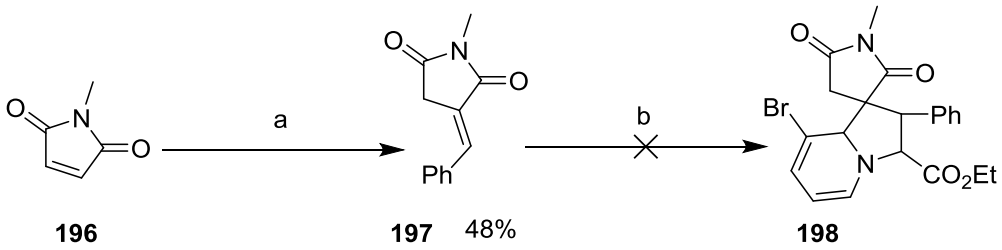
Recently work was published on 1,3-dipolar cycloadditions of azomethine ylides with α-alkylidene succinimides (Scheme 53).[61]



Scheme 53 - *Reagents and conditions* - a) $Cu(OAc)_2.H_2O$ (10 mol%), ligand (11 mol%), K_2CO_3, 4 Å MS, THF, 23 °C.

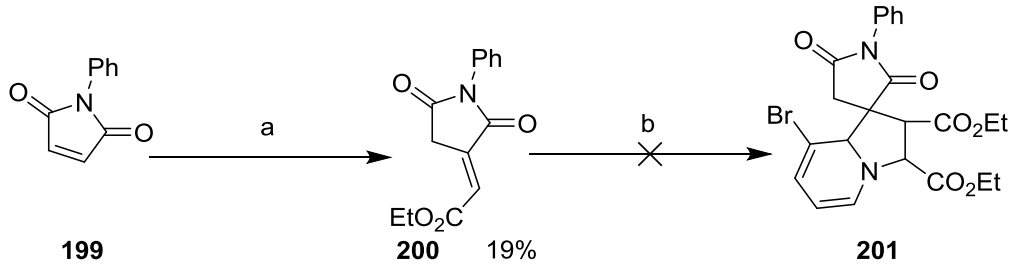
This reported cycloadduct **195** was generated with excellent diastereoselectivity and high levels of enantioselectivity. We decided to see if this dipolarophile could be subject to reactions with pyridinium ylides.

α-Alkylidene succinimide dipolarophile **197** was synthesised in a single step from *N*-methylmaleimide **196** and benzaldehyde in modest yield (Scheme 54). Unfortunately, reaction of this molecule with the 3-bromopyridinium salt **75** afforded the cycloadduct **198** as an inseparable mixture of several diastereoisomers.



Scheme 54 - *Reagents and conditions* - a) benzaldehyde, PPh_3, CH_2Cl_2, 20 °C, 24 hr; b) 3-bromopyridinium salt, Et_3N, CH_2Cl_2, 20 °C, 4 hr.

It was hoped that an aromatic substituent on the nitrogen of the succinimide would interact with the electron deficient pyridinium ylide; and thus could increase diastereoselectivity through our proposed mechanism (Figure 12) The dipolarophile **200** was synthesised using *N*-phenylmaleimide **199** and ethyl glyoxylate in modest yield (Scheme 55); when the cycloaddition was attempted the cycloadduct **201** was observed as an inseparable mixture of three diastereoisomers.



199 **200** 19% **201**

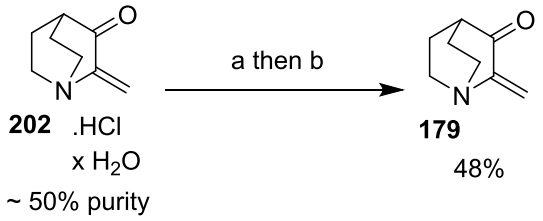
Scheme 55 - *Reagents and conditions* - a) ethyl glyoxylate, PPh_3, CH_2Cl_2, 20 °C, 24 hr; b) 3-bromopyridinium salt, Et_3N, CH_2Cl_2, 20 °C, 4 hr.

While the lactams and α-alkylidene succinimides did not fulfil the requirements for this investigation, they are interesting structures. Further investigation could provide conditions to improve the diastereoselectivity of these reactions, while *in situ* reduction may stabilise the products and enable purification and separation of the diastereoisomers.

3.1.4 Quinuclidinone

Commercially available 2-methylene-3-quinuclidinone hydrochloride hydrate **202** was found to only have a purity of ~ 50% by ^1H NMR. The free amine **179** was more desirable than the HCl salt, primarily

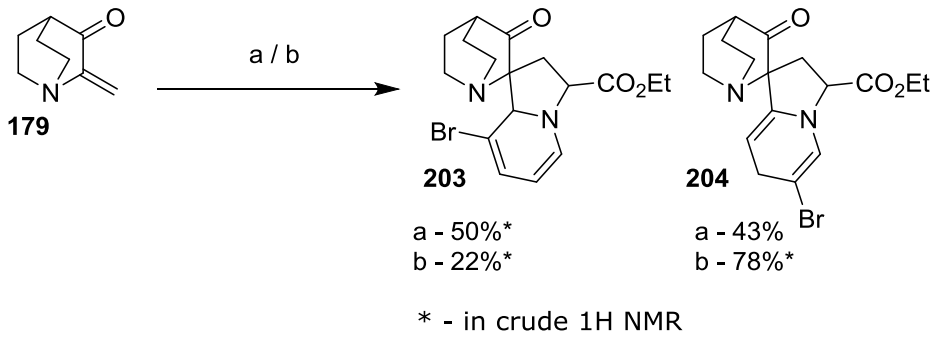
for solubility reasons, but also to reduce the amount of base required in the cycloaddition reaction. A hot filtration was performed with methanol followed by a biphasic reaction with potassium carbonate afforded the tertiary amine **179** in very good yield considering the starting purity (Scheme 56).



Scheme 56 - *Reagents and conditions* - a) MeOH, 65 °C, 10 mins; b) K_2CO_3, H_2O, CH_2Cl_2, 23 °C, 48 hr.

This reaction is surprisingly slow, if the reaction is worked up after 30 minutes no product is obtained and after 24 hours the product **179** is isolated in 25%.

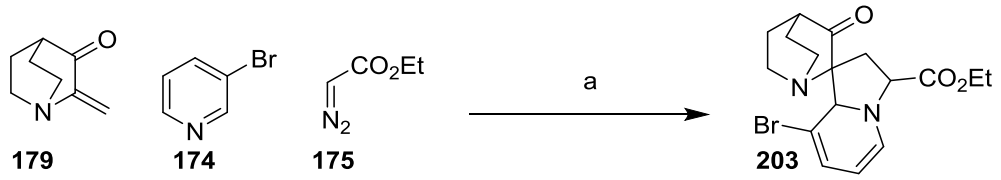
The cycloaddition was performed with the quinuclidinone **179** and the crude ^1H NMR spectroscopy showed two compounds were present in ~1:1 mixture (Scheme 57). The expected cycloadduct **203** was present in slight excess along with a related compound.



Scheme 57 - *Reagents and conditions* - a) 3-bromopyridinium salt, Et_3N, CH_2Cl_2, 20 °C, 4 hr; b) 3-bromopyridinium salt, Et_3N, CH_2Cl_2, 20 °C, 16 hr.

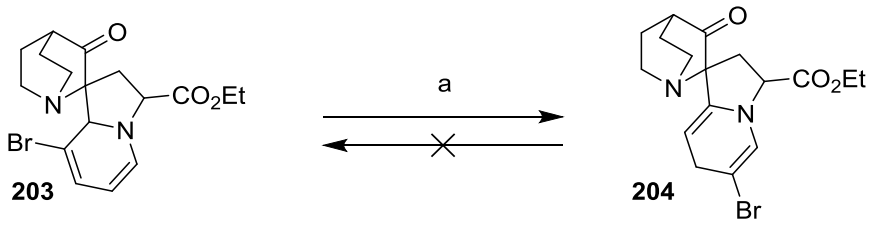
On workup cycloadduct **203** proved unstable on silica and was not isolated. However, the related compound was isolated and subsequently assigned as the 1,4-dihydropyridine with the opposite regiochemistry of the bromide than had ever previously been observed on any dipolarophile (i.e. corresponding to cyclisation at the 6 position of the pyridinium). According to NMR spectroscopic analysis of the reaction mixture, the 1,2-dihydropyridine **203** is first generated, then converts to the more stable 1,4-dihydropyridine **204**. Unfortunately, we were unable to obtain a crystal structure of this compound and so could not determine relative stereochemistry for this cycloadduct.

The reaction was performed *via* the diazo route to help determine the cause of this isomerisation (Scheme 58). Under these base free reaction conditions only the 1,2-dihydropyridine **203** was observed.



Scheme 58 - *Reagents and conditions* - a) Fe(TPP)Cl (1 mol%), toluene, 20 °C, 4 hr.

The role of base was investigated in two separate reactions. Firstly, by taking the crude mixture from the diazo experiment and adding triethylamine and secondly, starting with purified 1,4-dihydropyridine **204** and subjecting it to the same conditions (Scheme 59).



Scheme 59 - *Reagents and conditions* - a) Et_3N, CH_2Cl_2, 20 °C, 4 hr.

The results showed that the crude 1,2-dihydropyridine cycloadduct **203** could be converted to the 1,4-dihydropyridine **204** in the presence of base. However, the reverse transformation could not be effected under similar conditions. Indicating that the 1,2-dihydropyridine cycloadduct **203** is the kinetic product and that a base mediated pathway isomerises this to the more thermodynamically stable 1,4-dihydropyridine **204**. A proposed mechanism for this isomerisation is shown below (Figure 17).

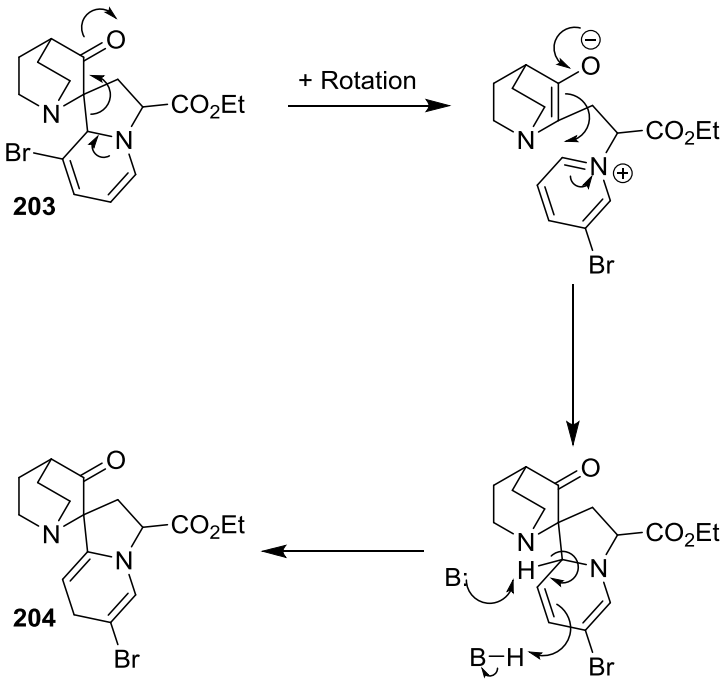


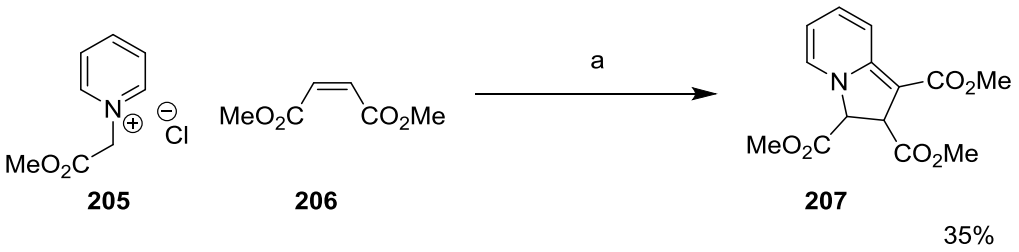
Figure 17 – Proposed mechanism for formation of **204**

In order to obtain the opposite regiochemistry the spirocenter must open allowing rotation of the pyridinium, then when this has reformed on the opposite side a base mediated 1,3-shift can occur to leave the more stable 1,4-dihydropyridine **204**.

A range of pyridinium salts were tested to determine if this 1,3-shift is a common feature with quinuclidinone cycloadducts. In many cases the 1,2-dihydropyridines were observed in the crude mixture. But unfortunately, these all proved unstable to purification. We never observed any other cycloadducts isomerising to the 1,4-dihydropyridine. Due to the significantly higher stability of the 1,4-dihydropyridine cycloadduct **204**, chiral HPLC was attempted. However, separation of the enantiomers could not be achieved, this is likely due to the molecule containing two basic nitrogen's.

3.1.5 Dihydroindolizine

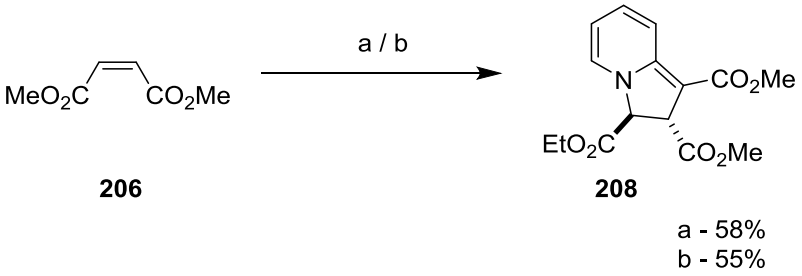
With many unsuccessful 'drug-like' dipolarophiles already evaluated it was decided to use a substrate that could act as a model for our asymmetric investigation. It had previously been reported that the reaction of a pyridinium salt **205** and dimethyl maleate **206** afforded the dihydroindolizine **207** (Scheme 60).[62]



Scheme 60 - *Reagents and conditions* - a) K_2CO_3, $CHCl_3$, 20 °C, 48 hr.

Though this product was isolated in poor yield, the air mediated oxidation of the tetrahydroindolizine to the dihydroindolizine **207** gave a stable product, whilst also maintaining two stereocenters formed by the cycloaddition. These products could potentially be used as a model substrate towards an enantioselective method if they could be separated by chiral HPLC.

The yield of the dihydroindolizine **208** was improved through changing the solvent and base combination (Scheme 61). Pleasingly, when the cycloaddition was performed using the diazo starting materials the reaction proceeded in almost identical yield to that obtained by deprotonation of the pyridinium salt. Furthermore, we were able to separate the enantiomers by chiral HPLC and so a catalyst screen was performed (Table 11).



Scheme 61 - *Reagents and conditions* - a) pyridinium salt, Et_3N, CH_2Cl_2, O_2, 20 °C, 16 hr; b) pyridine, ethyl diazoacetate, Fe(TPP)Cl (5 mol%), toluene, Argon → O_2, 20 °C, 16 hr.

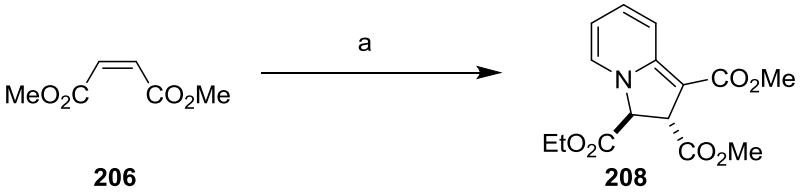
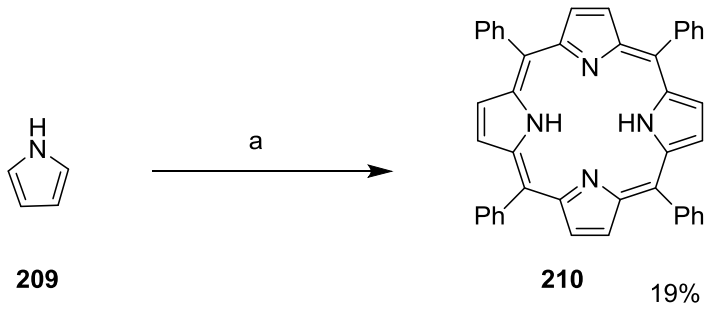


Table 11 - *Reagents and conditions* - a) pyridine, ethyl diazoacetate, catalyst (5 mol%), toluene, Argon → O_2, °C, 20 hr.

Entry	Catalyst	Yield (%)
1	$Rh_2(OAc)_4$	TRACE
2	$FeCl_2.4H_2O$	0
3	$FeCl_3.6H_2O$	0
4	$[(MeCN)_4CuPF_6]$	16
5	$Cu(OTf)_2$	0
6	$[(MeCN)_3RuCP^*PF_6]$	TRACE
7	$[(PPh_3)_2RuCP^*Cl]$	TRACE
8	$AgSbF_6$	0
9	$Pd(OAc)_2$	TRACE
10	$Pd(PhCN)_2Cl_2$	2

A selection of metal complexes known to decompose diazo compounds and support metal carbene chemistry were chosen. Rhodium acetate (Entry 1) showed trace cycloadduct, although complete consumption of starting material was observed. Iron (II) and (III) chloride (Entries 2 and 3) and silver hexafluoroantimonate (Entry 8) were ineffective as catalysts of this reaction. Pentamethylcyclopentadienyltris (acetonitrile)ruthenium(II) hexafluorophosphate (Entry 6), chlorocyclopentadienylbis(triphenylphosphine)ruthenium(II) (Entry 7), palladium acetate (Entry 9) and bis(benzonitrile)palladium chloride (Entry 10) all showed very low levels of catalytic activity, with the reaction mixture remaining largely unreacted starting material. Copper triflate (Entry 5) as catalyst was unsuccessful, however, tetrakis(acetonitrile)copper(I) hexafluorophosphate (Entry 4) was the best catalyst evaluated after the original Fe(TPP)Cl. It should be noted that this catalyst seems to degrade because batch to batch variation in cycloadduct yields were observed; this did not appear to be directly source or age related. As the iron porphyrin Fe(TPP)Cl had proved the best catalyst, a selection of other tetraphenylporphyrins were synthesised *via* literature routes.[63,64,65,66,67,68]

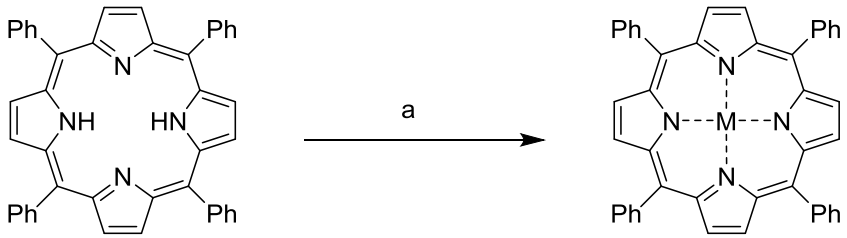
The condensation of pyrrole **209** and benzaldehyde proceeded well to afford the tetraphenylporphyrin **210** (Scheme 62).



209 **210** 19%

Scheme 62 - *Reagents and conditions* - a) Benzaldehyde, propionic acid, 140 °C, 0.5 hr.

All porphyrins were synthesised in good to excellent yields (Table 12).

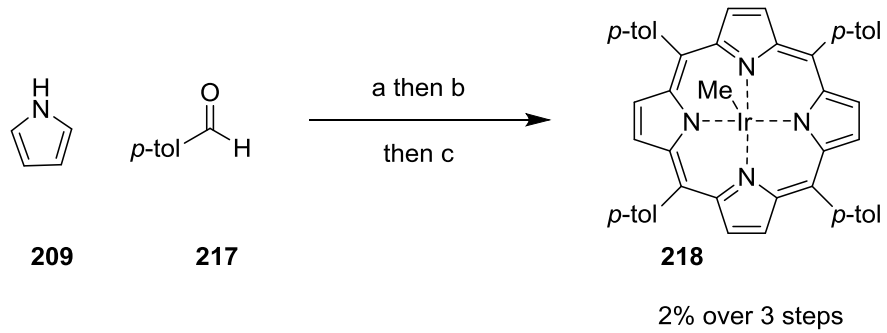


210

Table 12 - *Reagents and conditions* - a) Metal, Solvent, 150 °C, 6 hr.

Entry	Metal	Product	Yield (%)
1	$FeCl_3.6H_2O$	Fe(TPP)Cl **211**	71
2	$Cu(OAc)_2.H_2O$	Cu(TPP) **212**	56
3	$Zn(OAc)_2$	Zn(TPP) **213**	100
4	$CoCl_2.6H_2O$	Co(TPP)Cl **214**	49
5	$Ni(OAc)_2.H_2O$	Ni(TPP) **215**	59
6	$MnCl_2$	Mn(TPP)Cl **216**	81

An analogous iridium porphyrin was also synthesised *via* a literature route (Scheme 63).[69]



Scheme 63 - *Reagents and conditions* - a) Propionic acid, 140 °C, 1 hr; b) $[Ir(COD)Cl]_2$, xylene, 140 °C, 72 hr; c) $NaBH_4$, NaOH, MeI, THF : H_2O, 70 °C, 2 hr.

The cycloaddition was then performed with the synthesised porphyrins (Table 13).

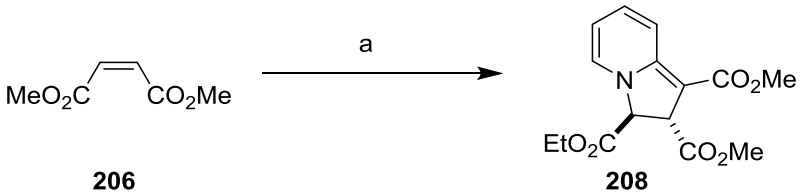


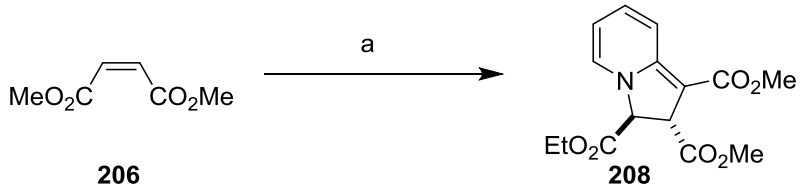
Table 13 - *Reagents and conditions* - a) pyridine, ethyl diazoacetate, catalyst (5 mol%), toluene, Argon → O_2, 20 °C, 20 hr.

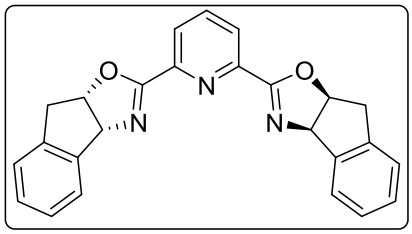
Entry	Catalyst	Yield (%)
1	Fe(TPP)Cl **211**	55
2	Ir(TTP)Me **218**	16
3	Cu(TPP) **212**	0
4	Zn(TPP) **213**	0
5	Co(TPP) **214**	0
6	Mn(TPP)Cl **216**	0

Other than Fe(TPP)Cl **211**, Ir(TTP)Me **218** (Entry 2) was the only metal tetraphenylporphyrin evaluated able to catalyse the cycloaddition, while all the other metal tetraphenylporphyrins showed no activity.

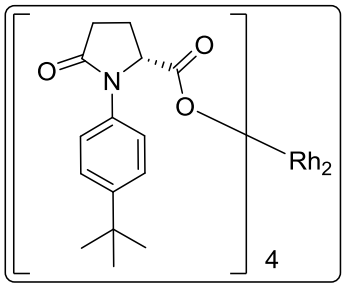
The metal, oxidation state and coordination of the ligand all have a significant effect on catalytic activity. For this substrate the metals that showed most promise were iron (III), rhodium (II) and copper (I). Many different chiral ligands were examined in combination with these metals, only the combinations which produced the desired cycloadduct **208** are shown (Table 14).

Four combinations produced the desired cycloadduct, tetrakis(acetonitrile)copper(I) hexafluorophosphate with the indenobox and Ph_4box ligands (Entries 1 and 4); along with tetrakis[1-[(4-*tert*-butylphenyl)sulfonyl]-(2*S*)-pyrrolidinecarboxylate]dirhodium(II) (Entry 2) and Doyle's catalyst (Entry 3). However, all of these failed to induce any enantioselectivity in the reaction, indicating that the metal is not associated with the ylide during these cycloadditions.

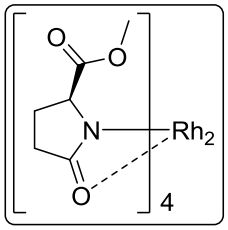




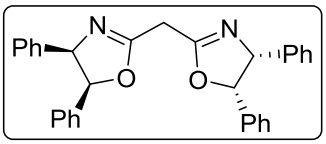
1



2



3



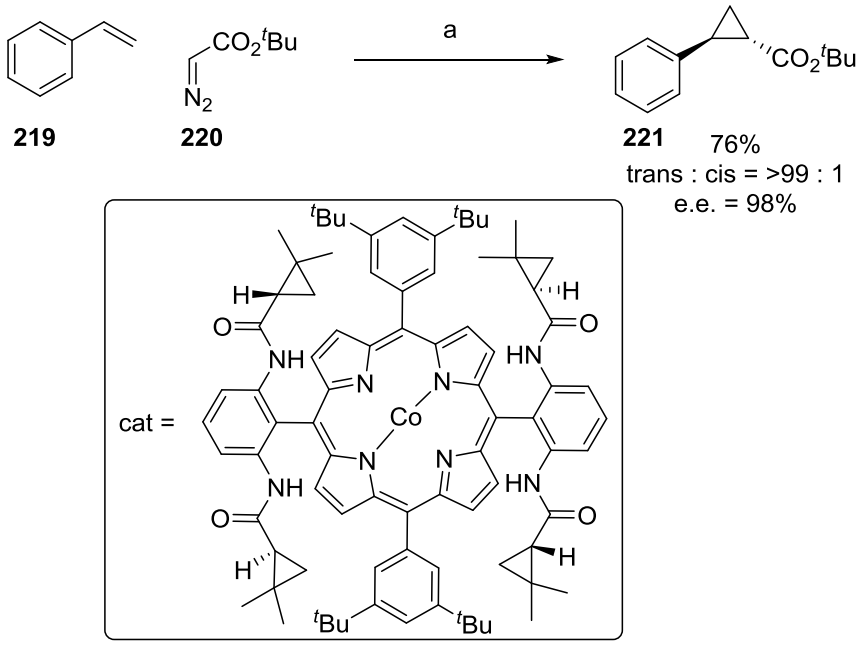
4

Table 14 - *Reagents and conditions* - a) pyridine, ethyl diazoacetate, catalyst, ligand, toluene, Argon → O_2, 20 °C, 20 hr.

Entry	Catalyst (mol %)	Ligand (mol %)	Yield (%)	e.e. (%)
1	$[(MeCN)_4CuPF_6]$ (5)	**1** (10)	15	0
2	**2** (10)	---	53	0
3	**3** (2)	---	11	0
4	$[(MeCN)_4CuPF_6]$ (5)	**4** (10)	17	0

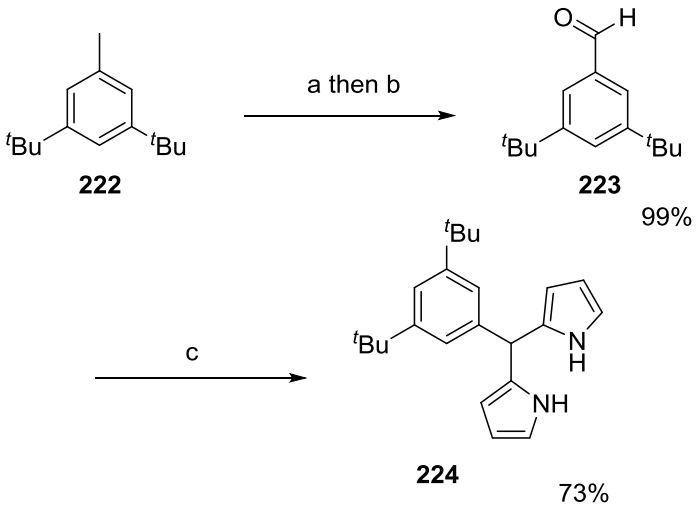
Chiral porphyrins have been shown to be very effective catalysts for enantioselective cyclopropanation of diazo compounds (Scheme 64).[70] Asymmetric cyclopropanation using the iron (III) analogue was

also been reported though with lower enantiomeric excess. Due to Co(TPP) **214** (Table 13, Entry 5) being unable to catalyse this cycloaddition it was decided to synthesise the iron (III) analogue **227** in search of asymmetric induction.



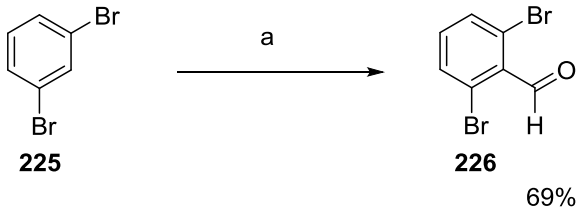
Scheme 64 - *Reagents and conditions* - a) catalyst (1 mol%), DMAP, toluene, -20 °C, 20 hr.

Bromination of 3,5-*tert*butyltoluene **222** followed by treatment with acid afforded the aldehyde **223** in quantitative yield (Scheme 65). Subsequent condensation with pyrrole generated the dipyrrin **224** in good yield.



Scheme 65 - *Reagents and conditions* - a) NBS, hexamine, hv, benzene, 80 °C, 16 hr; b) HCl, H_2O : EtOH, 90 °C, 5 hr; c) pyrrole, TFA, 20 °C, 0.5 hr.

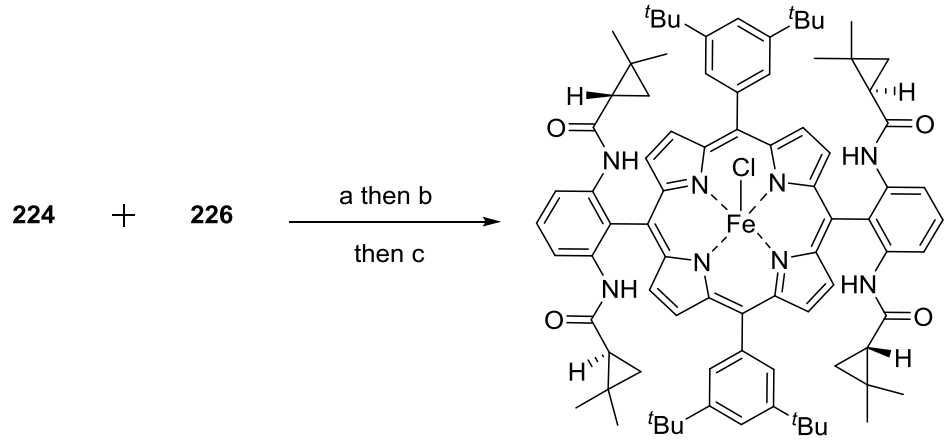
The other half of the porphyrin was prepared through the lithiation and formylation of 1,3-dibromobenzene **225** to afford the aldehyde **226** (Scheme 66).



Scheme 66 - *Reagents and conditions* - a) LDA, DMF, THF, -78 - 0 °C, 0.5 hr.

Reaction of the dipyrrin **224** and aldehyde **226** generated the tetrabromoporphyrin in a 57% yield (Scheme 67). The Buchwald-Hartwig amination proved difficult, requiring high temperature in a sealed tube along with a long reaction time to afford the chiral metal free porphyrin in only a 17% yield. Subsequent insertion of the iron

resulted in the chiral iron porphyrin **227** in a low yield over the 3 steps.

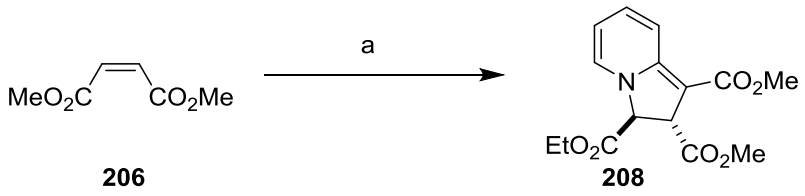


227

6% over 3 steps

Scheme 67 - *Reagents and conditions* - a) $BF_3.Et_2O$, Et_3N, DDQ, $CHCl_3$, 20 °C, 4 hr; b) chiral amide, $Pd(OAc)_2$, xantphos, Cs_2CO_3, THF, 100 °C, 72 hr; c) $FeCl_2$, 2,6-lutidine, DMF, 160 °C, 5 min.

The cycloaddition was performed using the chiral iron (III) porphyrin **227** and proved to be a highly active catalyst, generating the desired cycloadduct **208** in an 85% yield (Scheme 68). Unfortunately, no stereochemical induction was observed in the product **208**.



206 **208**

85%
0% e.e.

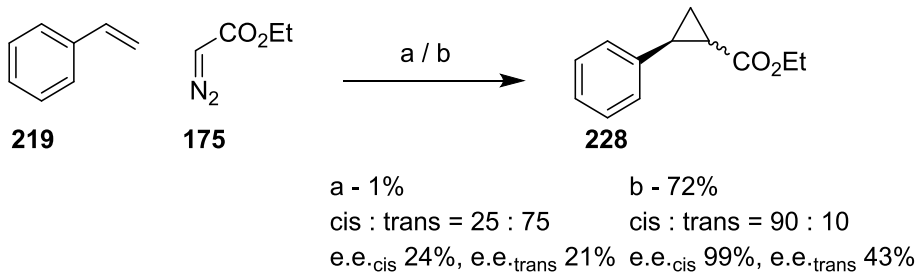
Scheme 68 - *Reagents and conditions* - a) pyridine, ethyl diazoacetate, chiral porphyrin (1 mol%), toluene, Argon → O_2, 20 °C, 20 hr.

3.1.6 Cytochrome P450

Cytochrome P450 proteins are members of the haemoprotein family, meaning they contain an iron-haem cofactor in the active site. In humans their main role is metabolism of drugs and harmful compounds, accounting for up to 75% of the total metabolism primarily through oxidation.[71] The term P450 is derived from the UV/VIS absorption maximum of the enzyme when complexed to carbon monoxide (450 nm).

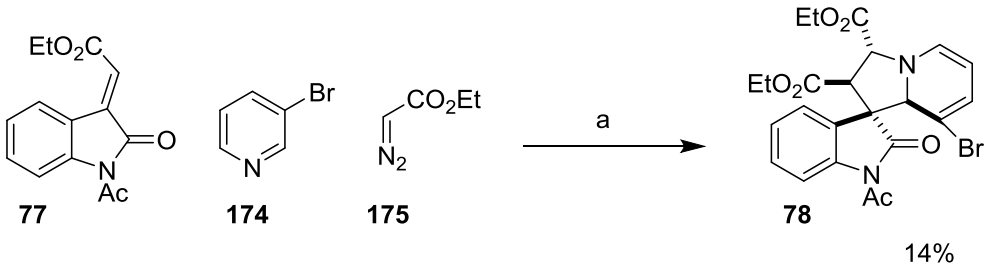
In order to metabolise drug molecules cytochrome P450's have evolved to be non-selective. This is appealing to chemists as it opens the possibility of using these proteins to catalyse a wide variety of substrates. Francis Arnold has done significant work showing cytochrome P450 proteins (wild type and mutants) to catalyse a large range of reactions using non-native substrates.[72] Of specific interest, their group has demonstrated that the iron-haem can catalyse a range of diazo reactions such as cyclopropanation, epoxidation and *NH* insertion (Scheme 69).[73,74,75,76] The cyclopropane was generated with the wild type protein albeit in low yield. While both *cis* and *trans* cyclopropanes were obtained enantioselectivity was observed for both products. Subsequently, Arnold has shown that mutation of the axial cysteine residue to a serine, along with 13 other mutations to change the shape of the binding site produced a highly active enzyme. The mutant protein has been named P411 due to the UV/VIS maximum changing to 411 nm. After mutation the *cis* cyclopropane

was generated in high yield with excellent diastereo and enantioselectivity.



Scheme 69 - *Reagents and conditions* - a) $P450_{BM3}$ (Wild type), phosphate buffer, $Na_2S_2O_4$, MeOH, 23 °C, 24 hr; b) $P411_{BM3}$-CIS (mutant), phosphate buffer, $Na_2S_2O_4$, 23 °C, 24 hr.

As the iron porphyrin Fe(TPP)Cl **211** has been so effective at catalysing the dipolar cycloaddition; it was our hope that the iron-haem in a P_{450} protein could also catalyse this reaction and perhaps give asymmetric induction. As part of a collaboration with Anca Pordea (Chemical Engineering) a small amount of wild type $P450_{BM3}$ was gifted and this reaction was examined (Scheme 70).



Scheme 70 - *Reagents and conditions* - a) $P450_{BM3}$ (0.15 mol%), $Na_2S_2O_4$, toluene : H_2O, 20 °C, 20 hr.

The cycloadduct **78** was isolated in 14% yield, which is a promising yield for an unoptimised reaction with a 'wild-type' protein.

Cyclopropanation was also observed as a minor component in around 5%. It should be noted that this work was performed before the development of HPLC-stable cycloadducts. As we did not have a means of chiral separation for this cycloadduct we were unable to determine if there was any enantioselectivity. Unfortunately, any remaining protein had degraded before the reaction could be performed on our model substrate. This work is now being investigated as a separate project by another member of the group, hopefully, initial results on asymmetric induction will be determined soon.

In summary, a wide variety of dipolarophiles searching for a HPLC stable cycloadduct were synthesised. This was achieved and a catalyst screen was performed showing several metal complexes were able to facilitate the reaction. A range of chiral metals complexes were tested with a few generating the cycloadduct, however, in all cases no enantioselectivity observed in the obtained products. As stated previously this may indicate that the metal complex is not bound to the ylide at the time of reaction. Further work needs to be performed with chiral complexes using other metals that have been shown to catalyse the cycloaddition, namely ruthenium (II), palladium (II) and iridium (II). Unfortunately, this work was not performed due to time constraints.

Chapter 4. Approaches towards opioid agonist targets

We were interested to see if we could use the developed methodology to synthesise the framework (shown in red) of several spirocyclic indoxyl natural products including mitragynine pseudoindoxyl **9** (Figure 18).

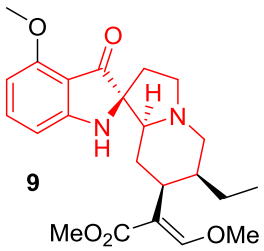


Figure 18 – mitragynine pseudoindoxyl **9**

4.1 Opioid receptors

Opioid receptors are a group of the G protein-coupled receptor family, which are transmembrane proteins. There are 3 subtypes of the opioid receptor: δ (delta), κ (kappa) and μ (mu) (DOR, KOR and MOR respectively). They are distributed widely in the brain and also found in the spinal cord and digestive tract.[77] All three receptors have been shown to produce an analgesic effect though strongest with MOR, other effects vary depending on receptor (Table 15).[78]

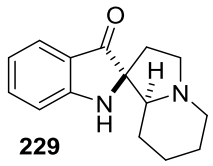
Receptor	Effects
DOR	Analgesia, convulsant effects, physical dependence
KOR	Analgesia, anticonvulsant effects, depression, hallucinations, sedation, stress
MOR	Analgesia, physical dependence, respiratory depression, reduced GI motility

Table 15 – Opioid receptor effects

The effects of MOR agonists have been shown to be ligand dependent, meaning some cause a single effect, while others produce a combination. Morphine is a DOR, KOR and MOR agonist and so while being very effective at pain relief it carries many side effects. The more notable of these being severe physical dependence, respiratory depression and reduced GI motility; as well as a natural tolerance development requiring ever increasing doses over prolonged usage.

Several studies in the biological activity of mitragynine pseudoindoxyl **9** and related analogues have been performed.[9,79] The latest of which performed by Majumdar *et al.* has shown mitragynine pseudoindoxyl **9** to be a very potent MOR agonist and DOR antagonist. It was shown to be 1.5-3 fold more potent towards pain relief compared to morphine; but did not show respiratory depression, physical dependence, tolerance development or significantly lower GI motility. The binding affinity of analogues were also screened, with *des*-4-methoxymitragynine pseudoindoxyl shown to be comparable to mitragynine pseudoindoxyl **9** implying the methoxy group to have little involvement in binding.

The implications of the biological assays lead us to believe the core of mitragynine pseudoindoxyl is a valuable synthetic target (Figure 19). If analogues could be synthesised and tested, it could lead to the development of novel non-opioid derived opioid agonists with significant therapeutic potential.



229

Figure 19 – Mitragynine pseudoindoxyl core **229**

4.2 **(3+2) Dipolar cycloaddition approach towards biologically active spirocyclic indoxyls**

All the indoxyl cycloadducts synthesised thus far (Chapter 2) have substitution at the 2' and 3' carbons. The synthesis of the unsubstituted core could be achieved in two ways, either: through the reaction between 2-methyleneindolin-3-one **231** and methyl pyridinium salt **232** or through incorporation of stabilising groups which could be removed after the cycloaddition (Figure 20).

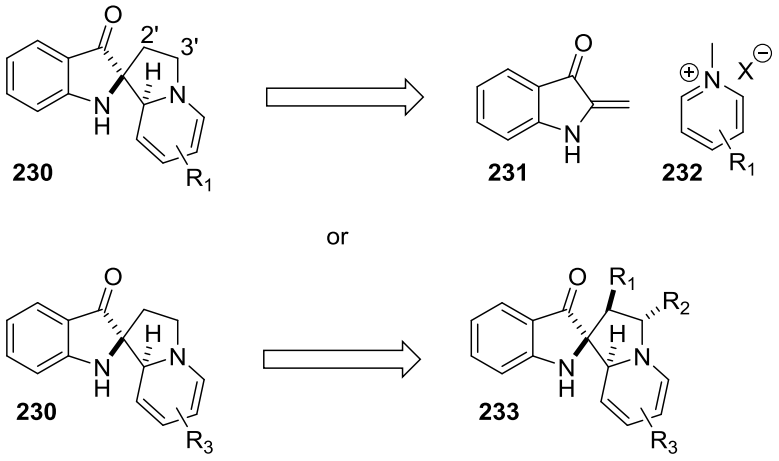
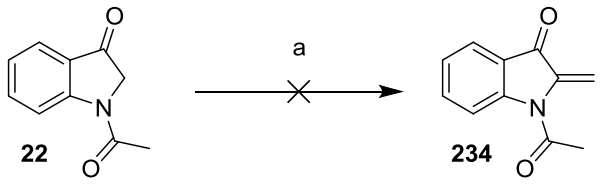


Figure 20 – Possible approaches

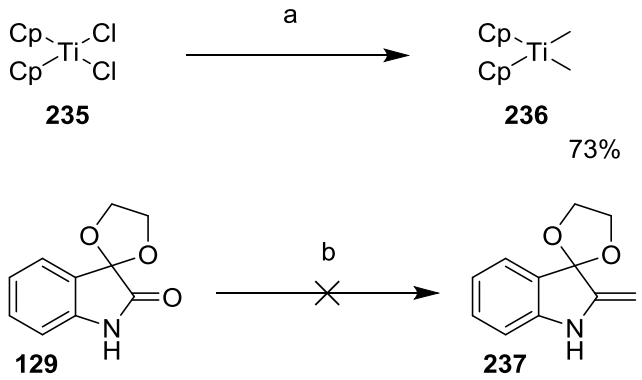
2-Methyleneindolin-3-one **231** would be the ideal dipolarophile for a concise synthesis of the mitragynine pseudoindoxyl core **229** as it would not require the removal of any functional groups. Before attempting this target there were concerns about the stability of the unsubstituted enamine moiety. With no literature precedence for this compound a variety of methods of synthesis were attempted.

An aldol condensation was attempted with the previously synthesised 1-acetylindolin-3-one **22** and paraformaldehyde, but this was unsuccessful resulting only in the recovery of starting material (Scheme 71).



Scheme 71 - *Reagents and conditions* - a) paraformaldehyde, morpholine (20 mol%), toluene, 110 °C, 24 hr.

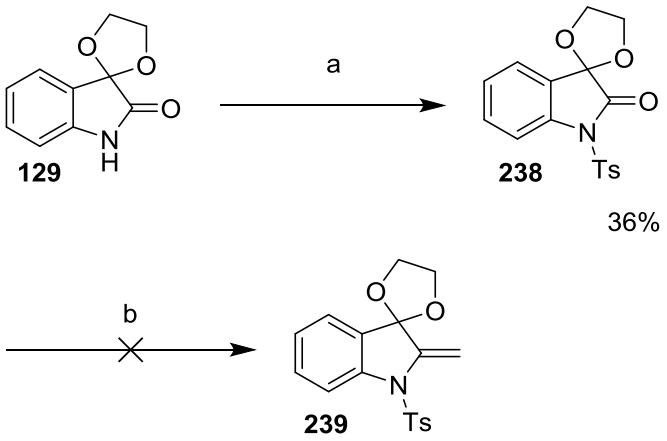
The next attempt was to use the Petasis reagent **236** which upon heating generates a titanium carbenoid with the loss of methane, this has been shown to transform amides to enamines in other systems.[80,81,82] As this would presumably react with the more electrophilic carbonyl in the 3-position, it was decided to use the previously synthesised spiro[indoline-3,2'-[1,3]dioxolan]-2-one **129**. The Petasis reagent **236** was freshly prepared from titanocene dichloride and methyl lithium, but unfortunately, reaction to form the desired 2-methylenespiro[indoline-3,2'-[1,3]dioxolane] **237** was not observed and only starting material was recovered (Scheme 72).



Scheme 72 - *Reagents and conditions* – a) Methyl lithium, Et_2O, 0 – 20 °C, 4 hr; b) Petasis reagent **236**, toluene, 110 °C, 3 hr.

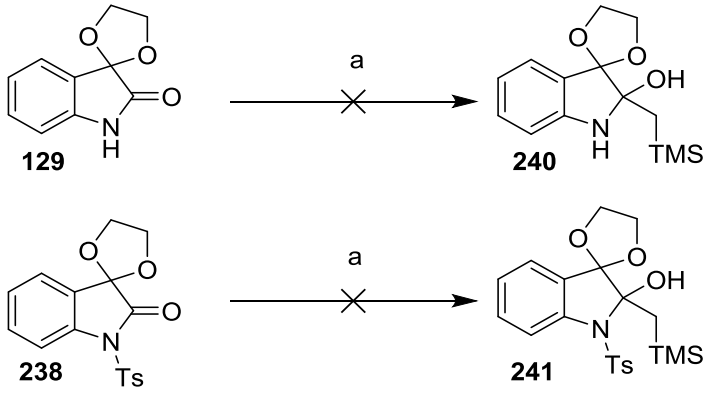
It was thought that an electron withdrawing group on the nitrogen would increase the reactivity of the carbonyl by reducing its amide character. The tosyl group was installed in moderate yield to afford 1-tosylspiro[indoline-3,2'-[1,3]dioxolan]-2-one **238** (Scheme 73). When this was reacted with the Petasis reagent **236**, the desired mass ion of 2-methylene-1-tosylspiro[indoline-3,2'-[1,3]dioxolane] **239** was observed by mass spectrometry. However, none was

isolated after workup, it is possible it was only ever present in small quantities or that it was unstable to column chromatography.



Scheme 73 - *Reagents and conditions* – a) tosyl chloride, sodium hydride, THF, 0 – 20 °C, 3 hr; b) Petasis reagent, toluene, 110 °C, 3 hr.

Addition of a Grignard reagent was attempted using ((trimethylsilyl)methyl)magnesium chloride with the intention of isolating 2-((trimethylsilyl)methyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-ol **240** and carrying out subsequent Peterson olefination (Scheme 74). Spiro[indoline-3,2'-[1,3]dioxolan]-2-one **129** was reacted with the Grignard reagent, however, only starting material was recovered. The reaction was also performed with 1-tosylspiro[indoline-3,2'-[1,3]dioxolan]-2-one **238** which did result in the consumption of starting material but the resulting product proved unstable to purification.



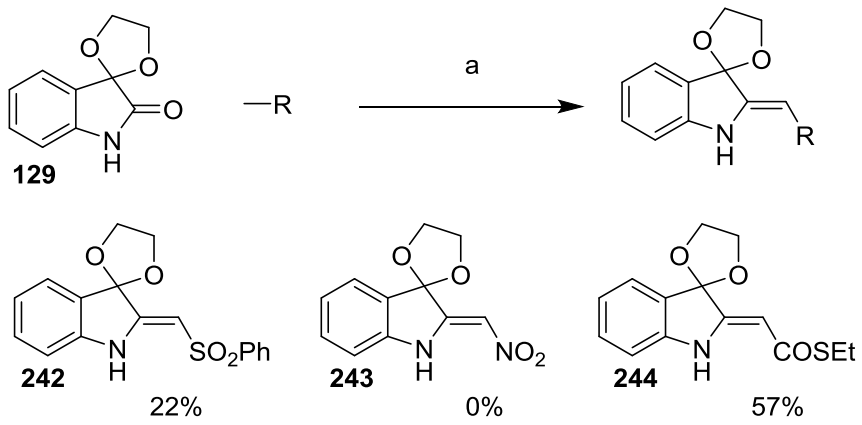
Scheme 74 - *Reagents and conditions* – a) (chloromethyl)trimethylsilane, magnesium, I_2, Et_2O, 20 °C, 4 hr.

In summary, several routes towards 2-methyleneindolin-3-one **231** were evaluated. In general, reactions of 1-tosylspiro[indoline-3,2'-[1,3]dioxolan]-2-one **238** showed more promise, but products could not be isolated its reactions.

The second proposed route to the synthesis of the mitragynine pseudoindoxyl core **229** was through removal of the 2′ and 3′ substituents after the cycloaddition. The substituents to be examined initially were a sulfone, nitro and thio ester, since removal of these groups after the cycloaddition could be envisaged.

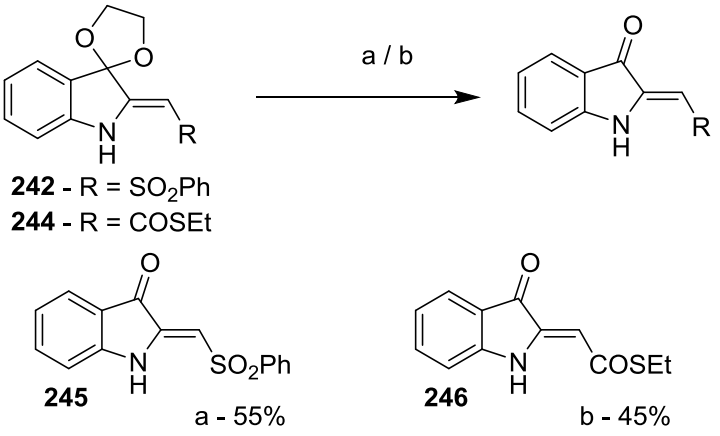
The previously developed phosphorus(V)oxychloride reaction used for the synthesis of the ethyl ester dipolarophile **125** was examined with a variety of stabilised carbon nucleophiles. (*Z*)-2-((phenylsulfonyl)methylene)spiro[indoline-3,2'-[1,3]dioxolane] **242** was obtained in low yield, presumably due to poor solubility of the methylphenylsulfone anion generated in the reaction mixture (Scheme 75). Reaction of nitromethane was unsuccessful with these reaction conditions, leading to recovery of starting material. Reaction

with ethyl thioacetate proceeded well affording *S*-ethyl (*Z*)-2-(spiro[indoline-3,2'-[1,3]dioxolan]-2-ylidene)ethanethioate **244** in good yield.



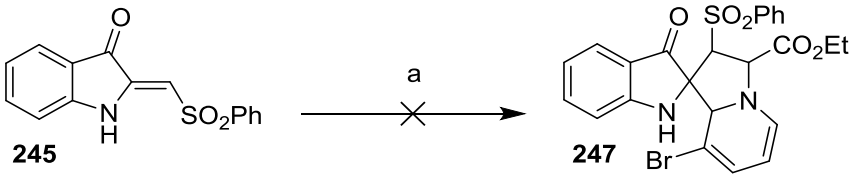
Scheme 75 - *Reagents and conditions* – a) $POCl_3$, Base, LDA, ethyl acetate, THF, 40 - -78 °C, 2 hr.

The 2-alkenylsulfoneindol-3-one **245** was synthesised *via* acetal deprotection using concentrated HCl in methanol (Scheme 76). The thioester analogue **244** was deprotected using the previously developed mild conditions affording *S*-ethyl (*Z*)-2-(3-oxoindolin-2-ylidene)ethanethioate **246**. Both of these reactions proceeded in moderate yield, however, sufficient material was obtained to examine the subsequent cycloaddition.



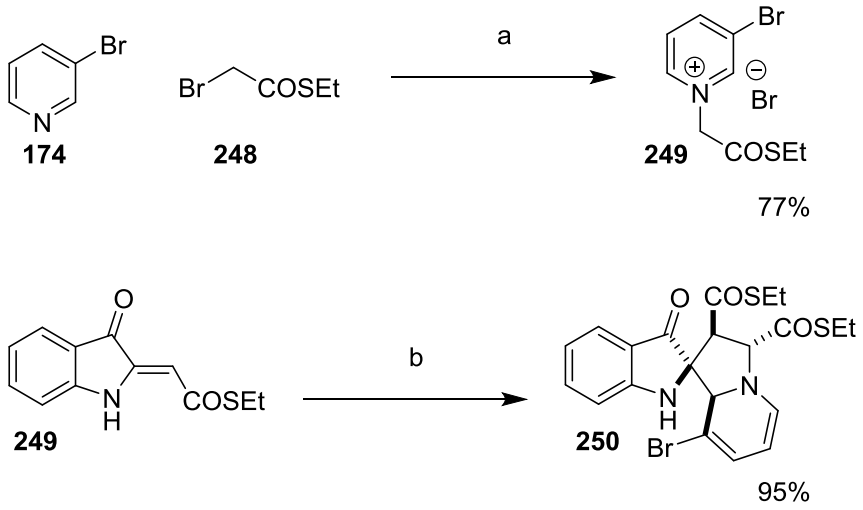
Scheme 76 - *Reagents and conditions* - a) HCl (conc.) MeOH, 20 °C, 0.5 hr; b) *p*-toluenesulfonic acid monohydrate, Na_2SO_4, acetone, 20 °C, 24 hr.

The cycloaddition was performed using (*Z*)-2-((phenylsulfonyl)methylene)indolin-3-one **245**, resulting in complete consumption of starting material (Scheme 77). However, only a complex mixture was observed upon workup, with none of the desired cycloadduct **247** detected. Therefore, this dipolarophile was not pursued further.



Scheme 77 - *Reagents and conditions* - a) 3-bromopyridinium salt, Et_3N, CH_2Cl_2, 20 °C, 4 hr.

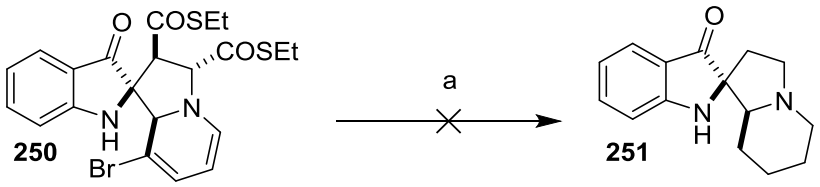
If the 2' and 3' substituents could be the same then these groups could be removed together in future steps. Thus it was decided to synthesise 3-bromo-1-(2-(ethylthio)-2-oxoethyl)pyridin-1-ium bromide **249**, which proceeded in good yield (Scheme 78).



Scheme 78 - *Reagents and conditions* - a) EtOAc, 78 °C, 16 hr; b) **249**, Et_3N, CH_2Cl_2, 20 °C, 4 hr.

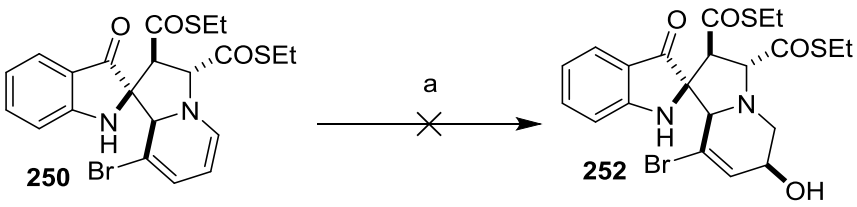
The subsequent cycloaddition afforded the desired bisthioester cycloadduct **250** in high yield. The same concentration effect was observed with this dipolarophile as the ethyl ester dipolarophile **125**, with the analogous elimination product isolated at higher concentrations.

Raney® nickel may facilitate the removal of thioesters, this presumably occurs through reduction of the carbon sulfur bond followed by deformylation.[83] Unfortunately, attempts towards a global reduction of the thioester cycloadduct **250** were unsuccessful (Scheme 79). The complex mixture isolated on workup is consistent with attempts to reduce the cycloadducts synthesised in Chapter two.



Scheme 79 - *Reagents and conditions* - a) Raney® nickel, H_2, EtOAc, 20 °C, 16 hr.

The instability of these cycloadducts was believed to arise from the highly reactive 1,2-dihydropyridine moiety. Therefore, it was thought that the thioester cycloadduct **250** could be stabilised *via* oxidation of the 1,2-dihydropyridine then the Raney® nickel reduction could be re-examined. Unfortunately, attempts to oxidise the thioester cycloadduct **250** were unsuccessful resulting in a complex mixture of products (Scheme 80).

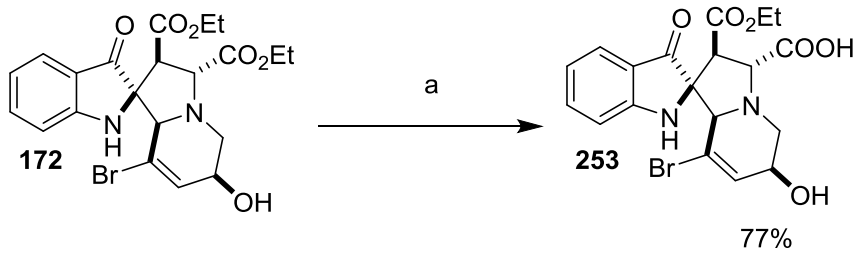


Scheme 80 - *Reagents and conditions* - a) Davies' oxaziridine, $NMe_4BH(OAc)_3$, THF, -78 °C, 3 hr.

In summary, the synthesis of cycloadducts with potentially removable substituents at the 2' and 3' carbons was examined. Thioester cycloadduct **250** was generated in good yield but we were unable to stabilise the dihydropyridine to attempt removal of the thioesters.

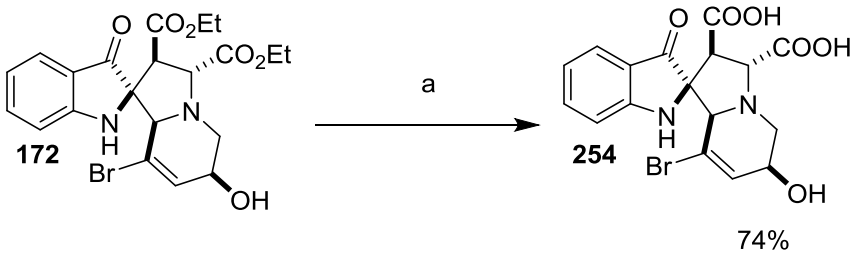
We next decided to attempt overall decarboxylation of the previously synthesised oxidised cycloadduct **172**, which had the potential benefit of a developed route.

Hydrolysis of the ethyl esters using aqueous sodium hydroxide performed at 0 °C to give the product corresponding to selective reaction at the 3' ester **253** (Scheme 81).



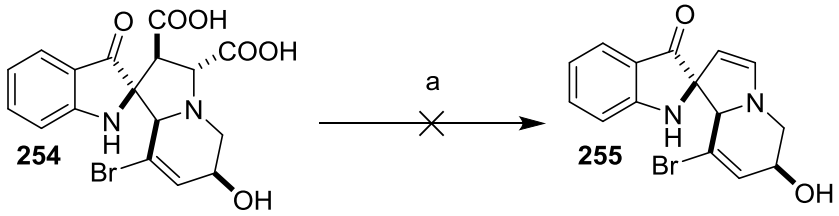
Scheme 81 - *Reagents and conditions* - a) NaOH, H_2O, THF, 0 °C, 20 mins.

Significant decomposition was observed if the reaction was performed at room temperature, however, if the reaction is started at 0 °C, then allowed to warm to room temperature overnight then the desired diacid **254** could be isolated in high yield (Scheme 82). Aqueous workup of this diacid **254** product proved difficult; presumably the product exists as a zwitterion. Ultimately, purification was achieved through trituration in acetone.



Scheme 82 - *Reagents and conditions* - a) NaOH, H_2O, THF, 0 - 20 °C, 16 hr.

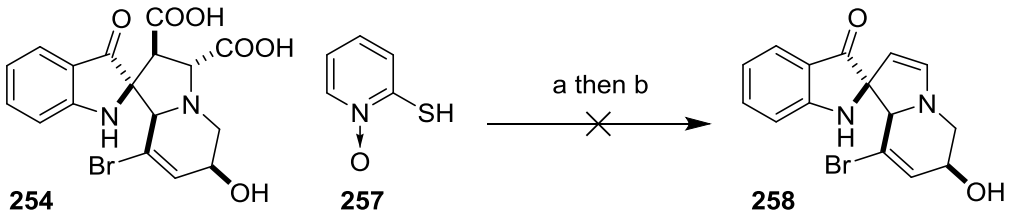
Following the synthesis of the 1,2-diacid **254** different radical decarboxylations were examined. The use of lead tetraacetate to oxidatively cleave 1,2-dicarboxylic acids has previously been reported.[84] However, when performed with our diacid **254** the reaction was unsuccessful, even with short reaction times only complex mixtures were observed (Scheme 83).



Scheme 83 - *Reagents and conditions* - a) $Pb(OAc)_4$, O_2, pyridine, 70 °C, 20 mins.

We next sought to investigate a route involving Barton decarboxylation. Reaction of diacid **254** with 2-mercaptopyridine N-oxide **257** and DCC appeared to proceed well but the *bis*-Barton ester intermediate was light sensitive and it was not possible to analyse the reaction other than by consumption of starting material by TLC (Scheme 84). Unfortunately, a one pot protocol involving the reaction

of this crude material with AIBN and tributyltin hydride was unsuccessful, instead producing a complex mixture of products.



Scheme 84 - *Reagents and conditions* - a) DCC, DMAP, CH_2Cl_2, 20 °C, 2 hr; b) AIBN, $(Bu)_3SnH$, benzene, 80 °C, 2 hr.

In summary, ester hydrolysis to afford the diacid cycloadduct **254** was achieved in high yield. But attempts to remove the 2' and 3' acids *via* radical decarboxylations were unsuccessful.

4.3 Other approaches to spirocyclic indoxyl core

We were unable to achieve our goal of synthesising the mitragynine pseudoindoxyl core **229** through the (3+2) dipolar cycloaddition methodology that we had previously developed. However, we were still interested in this structure and sought to develop a route to its synthesis.

4.3.1 Intramolecular route

Initial efforts were directed by our proposed cycloaddition reaction mechanism. If the reaction proceeds *via* a stepwise conjugate addition followed by cyclisation, then an appropriate pyridinium species might be expected to undergo cyclisation through deprotonation of the indolone **259** (Figure 21). This could generate a

spirocyclic indoxyl **230** with no substituents at the 2' and 3' carbons and subsequent reduction would afford the desired mitragynine pseudoindoxyl core **229**.

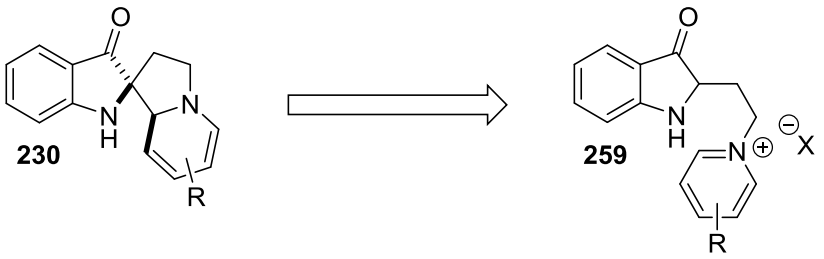


Figure 21 – Proposed intramolecular cyclisation

The target pyridinium salt **259**, could in turn be synthesised by alkylation using an appropriate electrophile **260** (Figure 22).

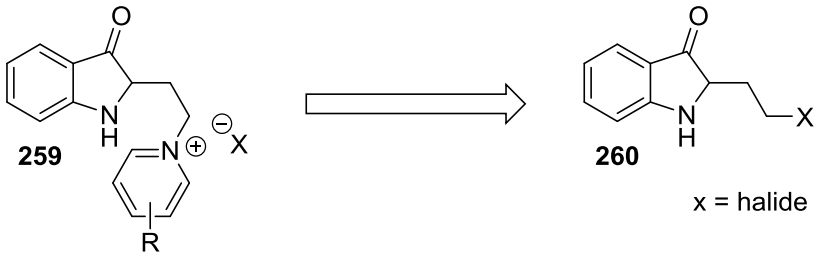
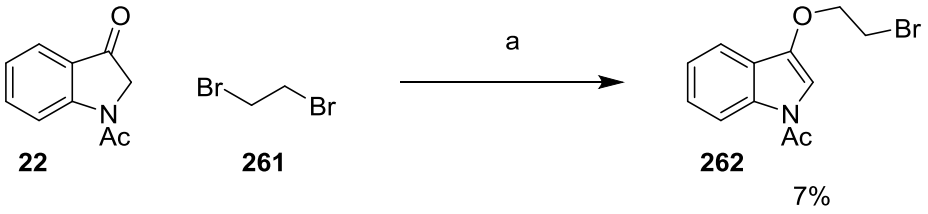


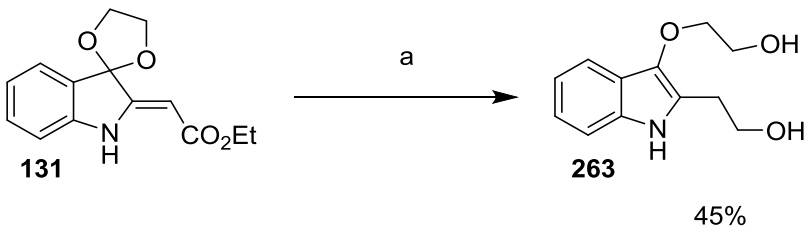
Figure 22 – proposed formation of pyridinium salt

Alkylation of 1-acetylindolin-3-one **22** with dibromoethane was attempted but the product was identified as the result of *O*-alkylation **262** (Scheme 85). This is likely driven by the aromaticity of the enolate reducing C-nucleophilicity.



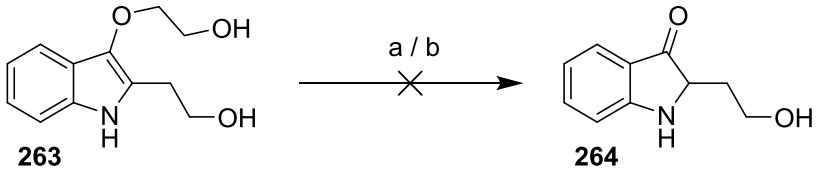
Scheme 85 - *Reagents and conditions* - a) NaH, DMF, -40 °C, 16 hr.

Sodium borohydride is able to reduce α,β-unsaturated esters to the corresponding saturated primary alcohols.[85] This transformation was attempted using previously synthesised ethyl (*Z*)-2-(spiro[indoline-3,2'-[1,3]dioxolan]-2-ylidene)acetate **131** (Scheme 86).



Scheme 86 - *Reagents and conditions* - a) $NaBH_4$, EtOH, 80 °C, 16 hr.

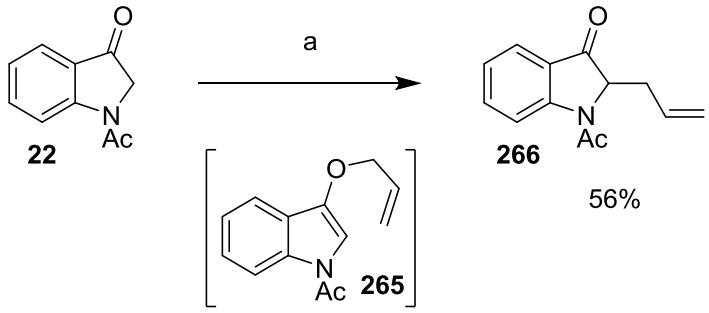
The desired reduction was achieved, but the isolated product was in fact the tautomer 2-(3-(2-hydroxyethoxy)-1H-indol-2-yl)ethan-1-ol **263** arising from ketal opening, again presumably driven by aromaticity. The planned conversion of the alcohol to a halide would not be possible with this molecule due to the presence of two primary alcohols. We therefore sought to hydrolyse the enol ether using Brønsted or Lewis acids (Scheme 87).



Scheme 87 - *Reagents and conditions* - a) HCl, dioxane, 20 °C, 16 hr; b) $BF_3.Et_2O$, MeOH, H_2O, 60 °C, 16 hr.

In both cases 2-(3-(2-hydroxyethoxy)-1H-indol-2-yl)ethan-1-ol **263** proved unreactive and resulted in recovered starting material. This route was not pursued further as a result of these problems.

1-Acetyl-2-allylindolin-3-one **266** has previously been synthesised from 1-acetylindolin-3-one **22**, by a reaction that proceeds *via* enol ether intermediate **265** and subsequent Claisen rearrangement (Scheme 88).[86] This generates the desired 2-alkylindol-3-one **266** in good yield, albeit as an allyl group rather than ethyl. Therefore, alkene oxidation would need to be explored to remove a carbon and install a functional group which could be converted into a leaving group.



Scheme 88 - *Reagents and conditions* - a) $MgSO_4$, camphorsulfonic acid, allyl alcohol, 130 °C, 3 hr.

Ozonolysis conditions were then examined and treatment of the resulting ozonide with different reductant and solvent combinations (Table 16).

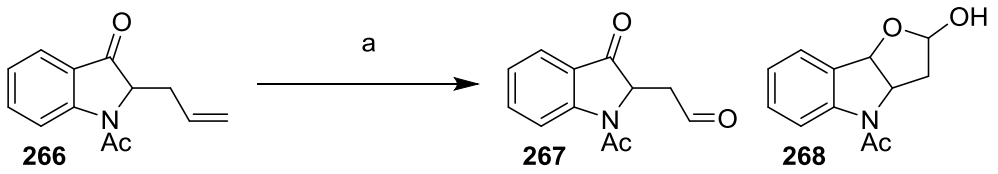


Table 16 - *Reagents and conditions* - a) Ozone, reductant, solvent, -78 °C, 30 mins.

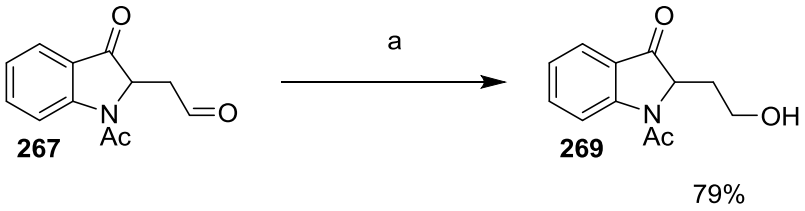
Entry	Reductant	Solvent	Yield 267 (%)	Yield 268 (%)
1	$NaBH_4$	EtOH:THF	56	0
2	$NaBH_4$	MeOH	0	33
3	SMe_2	CH_2Cl_2	32	0
4	PPh_3	CH_2Cl_2	71[a]	0
5	Polymer supported PPh_3	CH_2Cl_2	95	0

a- yield calculated from relative integration of **267** and O=PPh3 in 1H NMR after column chromatography

Sodium borohydride (Entries 1 and 2) gave varying products depending on the choice of solvent. In EtOH:THF the target aldehyde **267** was isolated in 56% yield but surprisingly hemiacetal **268** was obtained in methanol resulting from reduction of the ketone. This may be due to methanol temporarily forming the dimethylacetal from the aldehyde to prevent reduction at this position, prior to subsequent hydrolysis upon workup. Other reductants were examined in dichloromethane due to poor solubility of 1-acetyl-2-allylindolin-3-one **266** in alcohols. Dimethyl sulfide (Entry 3) produced a mixture of products but the desired aldehyde **267** was present as a minor

component. Treatment of the ozonide with triphenylphosphine (Entry 4) resulted in an improved yield. However, attempted separation of the desired aldehyde **267** from the triphenylphosphine oxide *via* column chromatography was unsuccessful, even after several attempts. Pleasingly, polymer supported triphenylphosphine (Entry 5) gave the desired aldehyde in near quantitative yield after filtration.

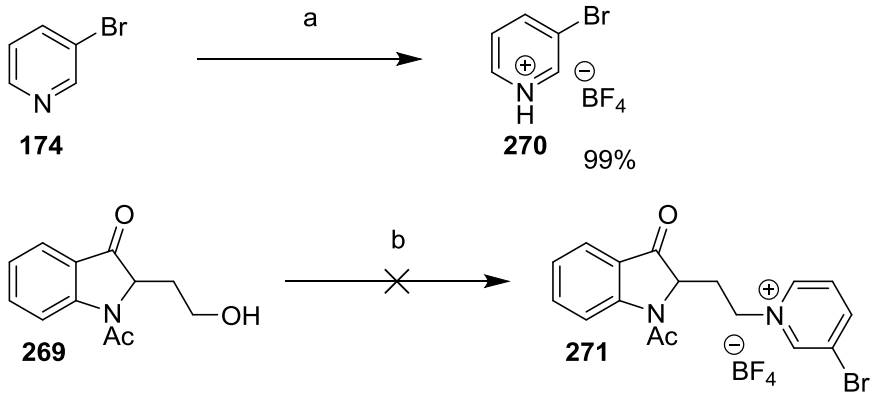
We had previously observed that sodium borohydride is capable of reducing both the aldehyde and ketone of 2-(1-acetyl-3-oxoindolin-2-yl)acetaldehyde **267** (Table 16, Entry 2). Tetramethylammonium triacetoxyborohydride was investigated as an alternative reductant but again poor selectivity was observed. Sterically hindered borane reducing agents are able to selectively reduce aldehydes in the presence of ketones.[87] Pleasingly, reduction of **267** with a borane reductant generated from 9-BBN proceeded with good selectivity, affording 1-acetyl-2-(2-hydroxyethyl)indolin-3-one **269** in high yield (Scheme 89).



Scheme 89 - *Reagents and conditions* - a) 9-BBN, 2-methylbut-2-ene, THF, 80 °C, 5 hr.

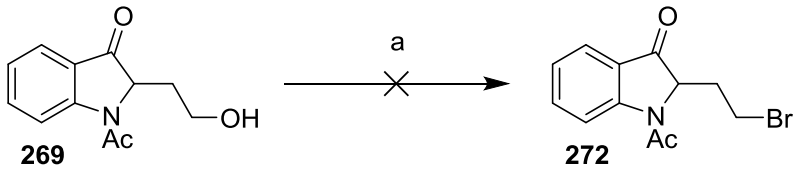
We were interested to see if it was possible to convert 1-acetyl-2-(2-hydroxyethyl)indolin-3-one **269** into the pyridinium salt **271** *via* a Mitsunobu type reaction with a preformed pyridinium salt. Recent

work has been published on this reaction for the formation of ionic liquids.[88] The authors conclude that the starting pyridinium salt requires a non-nucleophilic counterion ($^{-}BF_4$) to prevent subsequent displacement of the pyridinium from the product by the counterion. Thus, 3-bromopyridin-1-ium tetrafluoroborate **270** was synthesised quantitatively from tetrafluoroboric acid and 3-bromopyridine (Scheme 90). Subsequent Mitsunobu reaction of the indolone alcohol **269** was examined, but unfortunately, this was unsuccessful resulting in a complex mixture on workup.



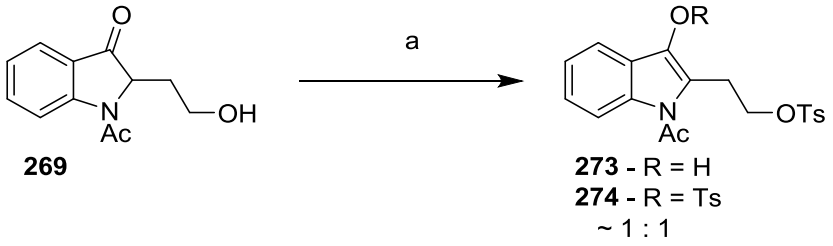
Scheme 90 - *Reagents and conditions* - a) $HBF_4.Et_2O$, Et_2O, 20 °C, 5 min; b) pyridinium salt **270**, PPh_3, DIAD, MeCN, 20 °C, 48 hr.

Conversion of 1-acetyl-2-(2-hydroxyethyl)indolin-3-one **269** to 1-acetyl-2-(2-bromoethyl)indolin-3-one **272** *via* the Appel reaction was attempted (Scheme 91). This reaction proceeded quickly and on workup, 70% of the desired bromide was isolated as identified by ^1H NMR and mass spectrometry of the crude. Unfortunately, this compound proved unstable and largely decomposed before full characterisation could be achieved.



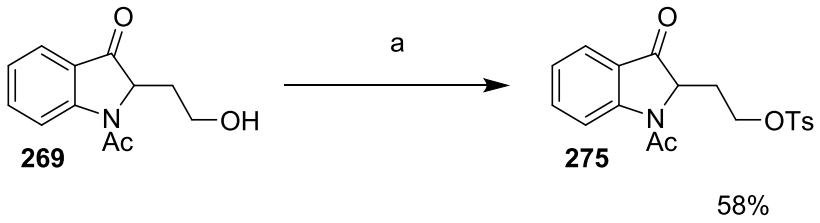
Scheme 91 - *Reagents and conditions* - a) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 2 hr.

It was therefore decided to convert the alcohol to a *p*-toluenesulfonyl which could undergo S_N2 displacement to form the pyridinium salt. When sulfonylation was performed with triethylamine, an inseparable mixture of two products in ~ 1 : 1 ratio was isolated (Scheme 92). The ketone had tautomerised to the enol and subsequently half of the material had further reacted with the remaining *p*-toluenesulfonyl chloride, leading to the formation of *bis*-tosylate **274**.



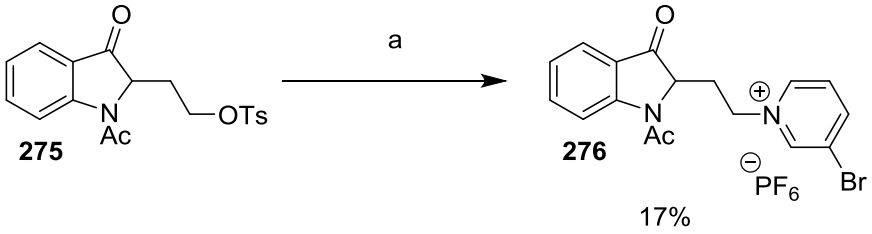
Scheme 92 - *Reagents and conditions* - a) *p*-Toluenesulfonyl chloride, Et_3N, DMAP, CH_2Cl_2, 20 °C, 16 hr.

Pyridine was examined as an alternative base, for this reaction it was hoped that due to the lower basicity, it would be unable to tautomerise the ketone of 1-acetyl-2-(2-hydroxyethyl)indolin-3-one **269**. Pleasingly, although this reaction was slower the desired 2-(1-acetyl-3-oxoindolin-2-yl)ethyl 4-methylbenzenesulfonate **275** was isolated in good yield (Scheme 93).



Scheme 93 - *Reagents and conditions* - a) *p*-Toluenesulfonyl chloride, pyridine, DMAP, CH_2Cl_2, 20 °C, 48 hr.

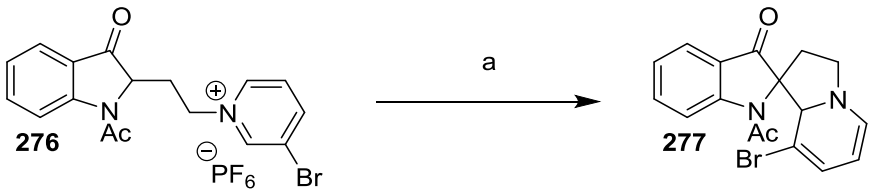
Subsequent displacement of the *p*-toluenesulfonyl with pyridine proved capricious. When performed on small scale in a sealed tube, complete consumption of starting material was observed (Scheme 94), but we were unable to separate the resulting *p*-toluenesulfonyl salt from other aqueous soluble by-products. However, counterion exchange with ammonium hexafluorophosphate provided an organic soluble salt **276** which could be purified *via* conventional column chromatography on silica gel.



Scheme 94 - *Reagents and conditions* - a) 3-bromopyridine, NH_4PF_6, EtOAc, 90 °C, 20 hr.

The intramolecular cyclisation of 1-(2-(1-acetyl-3-oxoindolin-2-yl)ethyl)-3-bromopyridin-1-ium hexafluorophosphate(V) **276** was performed with DBU (Scheme 95). Complete consumption of starting material was observed within 2 hours and ^{1}H NMR spectroscopy of the crude clearly showed the distinctive signals of the desired

dihydropyridine **277** were present, notably 6.33 (1H, d, *J* = 6.7 Hz), 6.24 (1H, d, *J* = 6.7 Hz) and 4.41 (1H, app. t, *J* = 6.7 Hz). Many attempts to purify and isolate **277** were made, however, this compound proved unstable towards column chromatography and so could not be isolated and fully characterised.

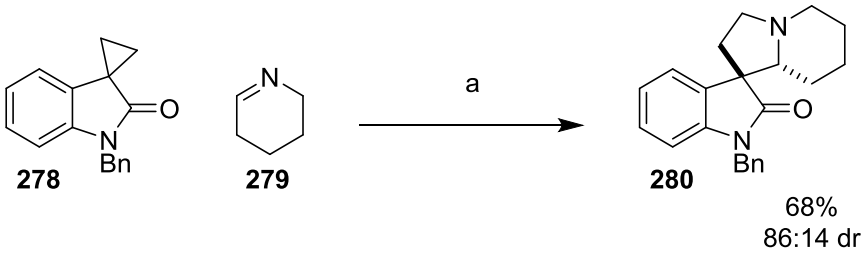


Scheme 95 - *Reagents and conditions* - a) DBU, CH_2Cl_2, 20 °C, 2 hr.

In summary, several different approaches were made to the synthesis of the desired indol-3-one pyridinium salt. This was achieved and we have preliminary evidence to suggest the cyclisation may proceed as predicted, but we were unable to isolate the desired 1-acetyl-8'-bromo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizin]-3-one **277**. Had time permitted, future work would involve attempted *in situ* reduction of the 1,2-dihydropyridine.

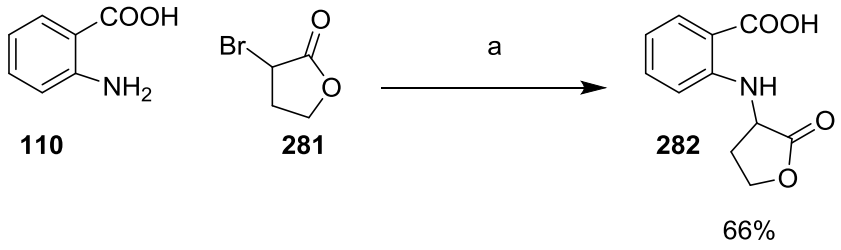
4.3.2 Cyclopropane ring expansion

During studies leading to the total synthesis of (±)-strychnofoline,[13] Carreira *et al.* published work on a novel ring expansion of cyclopropanes by aldimines.[89] The magnesium iodide promoted ring expansion was used to synthesise a variety of spirocyclic oxindoles including 1-benzyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizin]-2-one **280** in high yield and good diastereoselectivity (Scheme 96).



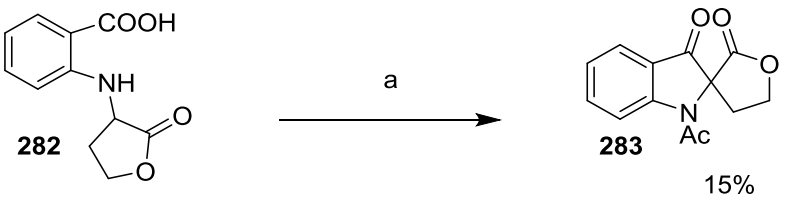
Scheme 96 - *Reagents and conditions* - a) MgI_2, THF, 125 °C, 12 hr.

In order to examine this reaction towards the synthesis of the mitragynine pseudoindoxyl core **229** the corresponding cyclopropane would need to be synthesised. This was achieved *via* a literature route to 1'-acetylspiro[cyclopropane-1,2'-indolin]-3'-one **284**.[90] The alkylation of anthranilic acid **110** with α-bromo-γ-butyrolactone **281** proceeded well, affording the desired 2-((2-oxotetrahydrofuran-3-yl)amino)benzoic acid **282** in good yield (Scheme 97).



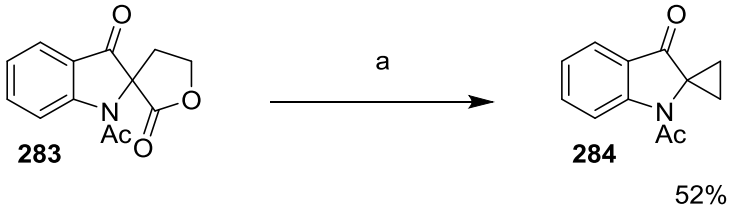
Scheme 97 - *Reagents and conditions* - a) Na_2CO_3, H_2O, 45 °C, 24 hr.

The intramolecular cyclisation of 2-((2-oxotetrahydrofuran-3-yl)amino)benzoic acid **282** generated the desired 1'-acetyl-4,5-dihydro-2H-spiro[furan-3,2'-indoline]-2,3'-dione **283**, though in poor yield (Scheme 98).



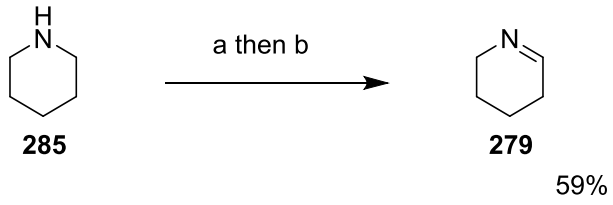
Scheme 98 - *Reagents and conditions* - a) Et_3N, acetic anhydride, 130 °C, 3 hr.

The subsequent Krapcho decarboxylation proceeded very cleanly, but the yield was lowered due to difficultly in removing residual DMSO during recrystallization (Scheme 99). However, sufficient 1'-acetylspiro[cyclopropane-1,2'-indolin]-3'-one **284** was isolated that further recovery was not pursued at this late stage in the project.



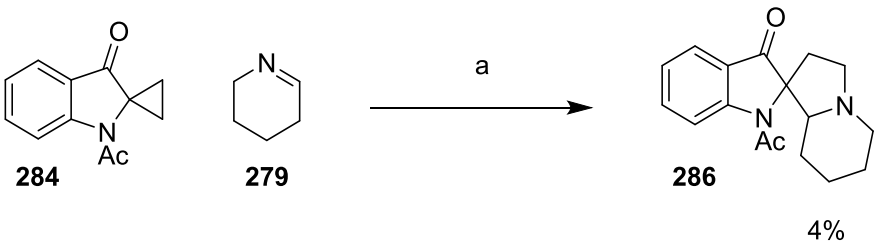
Scheme 99 - *Reagents and conditions* - a) NaCl, DMSO, 160 °C, 2 hr.

2,3,4,5-Tetrahydropyridine **279** was synthesised *via* a literature protocol of formation of the chloropiperidine followed by elimination with base (Scheme 100).[91] The imine **279** was isolated as a mixture of the monomer and trimer as is common for cyclic non-hindered imines.



Scheme 100 - *Reagents and conditions* - a) *N*-chlorosuccinimide, Et_2O, 20 °C, 3.5 hr; b) KOH, EtOH, Et_2O, 20 °C, 16 hr.

The cyclopropane ring expansion was attempted using the conditions optimised by Carreira *et al.* for the oxindole cyclopropanes (Scheme 101).



Scheme 101 - *Reagents and conditions* - a) MgI_2, THF, 125 °C, 24 hr.

These studies revealed that longer reaction times and higher catalyst loadings were required to achieve low levels of conversion. The product was isolated and separation of the apparent diastereoisomers proved very difficult. However, tentative NMR spectroscopy evidence is consistent with the proposed product **286**.[92] Unfortunately, this reaction could not be repeated due to time constraints. This work is being continued by other members of the group with the intention of performing a catalyst screen and examining functionalised cyclic imines.

In summary, the synthesis of the core **229** of this family of spirocyclic indoxyls was pursued, with many different routes examined. The intramolecular cyclisation and cyclopropane ring expansion approach shows most promise, with NMR evidence that this route was somewhat successful. Unfortunately, neither of these compounds could be isolated and fully characterised and this work is currently being explored by other members in the group.

Summary and future work

Summary

In this project a new route to synthesise 2-alkenylindol-3-ones has been reported, including the ability to access a range of non-aromatic substituted dipolarophiles which were only accessible in very poor yields from literature methods. A novel route to spirocyclic indoxyls *via* (3+2) dipolar cycloadditions of pyridinium ylides has been developed, with the resulting cycloadducts generated in high yields with very good regio and diastereoselectivity. These cycloadducts were further functionalised through reactions of the 1,2-dihydropyridine moiety, including Diels-Alder reactions and oxidations.

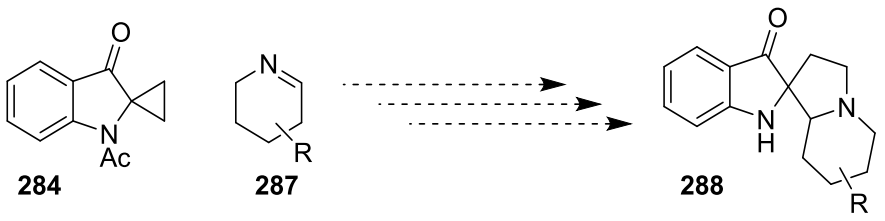
A variety of heterocyclic dipolarophiles were synthesised in the search of novel 'drug-like' cycloadducts which could be examined for the development of an asymmetric (3+2) dipolar cycloaddition reaction. While several interesting structures were generated, unfortunately, these failed to fulfil the requirements for the asymmetric investigation. Therefore, the asymmetric methodology was performed on a model system, with many different transition metal catalysts screened. The most promising of these were iron (III), rhodium (II) and copper (I) complexes; chiral ligands were explored through preforming chiral catalysts *in situ* and the synthesis of a chiral iron porphyrin. Several catalysts were able to generate the

desired cycloadduct, however, none were successful in imparting enantioselectivity.

Finally, we sought to synthesise spirocyclic indoxyls that resemble the highly active opioid mitragynine pseudoindoxyl **9**. First, this was attempted through the previously developed (3+2) dipolar cycloaddition chemistry in Chapter 2. Subsequently, it was explored through alternative approaches, culminating in the magnesium iodide promoted ring expansion, tentatively affording the desired target.

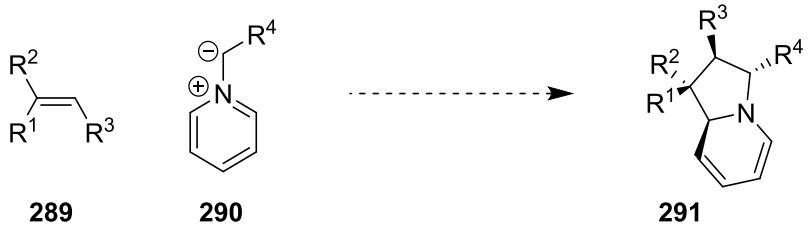
Future work

There remain several key areas for future work, several of which are currently being investigated within the group. Firstly, the synthesis of the core of mitragynine pseudoindoxyl **9**. Optimisation of the cyclopropane ring expansion is required to produce the product in sufficient quantity and confirm the current assignment. Once optimised this reaction could be used to create a library of compounds which could be screened for opioid activity (Scheme 102). With the compelling studies showing mitragynine pseudoindoxyl **9** to be a very effective opioid with very few of the side effects suffered with current drugs; this has the potential to offer significant therapeutic benefit.



Scheme 102 – Synthesis of mitragynine pseudoindoxyl analogues

Further work is also required for the development of an asymmetric methodology for (3+2) dipolar cycloadditions (Scheme 103). This is most likely to be achieved *via* the pyridinium ylide generated through diazo decomposition. There are many other transition metal complexes to be examined along with the development and optimisation of P450 proteins. This was the first reported example of using proteins for this transformation and to achieve such promising results from a 'wild-type' protein is encouraging.



Scheme 103 – Development of stereoselective cycloadduct

Chapter 5. Experimental

5.1 General experimental

Reagents obtained from commercial sources were used as received or purified according to C.L.L. Chai and W.L.F. Armarego 'Purification of Laboratory Chemicals' Elsevier Science PLC, 5th edition, 2003

Anhydrous THF was obtained by distillation from sodium/benzophenone, under dry nitrogen. Anhydrous dichloromethane was obtained by distillation from CaH_2, under dry nitrogen. Anhydrous Et_2O and toluene were obtained *via* filtration from a dry nitrogen pressurised, basic, activated 58 Å aluminium column. Reactions requiring anhydrous conditions were conducted in an inert atmosphere of dry argon in flame-dried apparatus. When conditions state reaction was performed at room temperature, this represents the ambient temperature in the laboratory which typically ranged from 18-22 °C.

Thin Layer Chromatography (TLC) was performed using Merck aluminium foil backed plates, pre-coated with silica gel 60 F_{254}. Visualisation carried out via U.V. fluorescence quenching (λ max = 254 nm) or staining with potassium permanganate solution, followed by heating. Flash column chromatography was performed using ICN Silica 32-73, 60 Å.

Melting points were measured on a Bibby™ Stuart Scientific SMP3 melting point apparatus. Melting points are recorded to the nearest °C and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR or Brüker Avatar 320 FTIR spectrometer as dilute solutions, in spectroscopic grade chloroform or using ATR (Attenuated total reflection) attachment. Absorption maxima (λ max) of major, significant peaks are reported in wavenumbers (cm^{-1}), quoted to the nearest integral wavenumber.

^1H Nuclear magnetic resonance spectra were recorded on either a: Brüker AV(III)800 (800 MHz), Brüker AV(III)600 (600 MHz), Brüker AV(III)500 (500 MHz), Brüker AV400 (400 MHz), Brüker AV(III)400 (400 MHz), Brüker AV(III)400HD (400 MHz), Brüker DPX400 (400 MHz) or Brüker DPX300 (300 MHz) spectrometer at ambient temperature unless otherwise stated. Proton magnetic resonance chemical shifts (δH) recorded in parts per million (ppm), are referenced relative to residual solvent peak, and recorded to two decimal places. Coupling constants (*J*), are reported to the nearest 0.1 Hz. Multiplicity of each signal is designated using a combination of the following abbreviations; s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet) and br (broad). Carbon magnetic resonance chemical shifts (δ_C), recorded in ppm, were referenced relative to the residual solvent peak and are recorded to one decimal place. Multiplicities were determined by DEPT analysis.

Mass spectra were recorded on a Brüker MicroTOF (ESI) mass spectrometer. All mass spectrometry data are high resolution.

Known porphyrins synthesised from literature procedures have been excluded: **211**,[63] **212**,[64] **213**,[65] **214**,[66] **215**,[67] **216**,[68] **218**[69] and **227**.[93]

5.1.1 Treatment of diastereoisomers and rotamers

When products are reported as a mixture of diastereoisomers, where possible relative stereochemistry is based upon nuclear Overhauser effect spectroscopy (NOESY). Where chemical shifts for different diastereoisomers can be distinguished, the label '*' indicates the minor diastereoisomer.

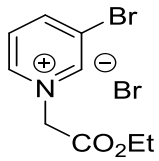
Cycloadducts present as a mixture of rotamers are often difficult to achieve absolute assignments due to coalescence of similar environments. Therefore, assignment of each rotamer is only reported in the ^{1}H NMR when the relative ratio of rotamers is not 1:1, where the minor rotamer is distinguished with the label '†'.

5.2 Synthesis of pyridinium salts

General Procedure A – Synthesis of pyridinium salts:

Pyridine (1 eq) was added to primary bromide (1.1 eq) in ethyl acetate (1M) and heated under reflux for 24-72 hours. The resulting precipitate was collected by filtration, washed with diethyl ether and dried to afford the desired pyridinium salt.

3-Bromo-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (75)[11]

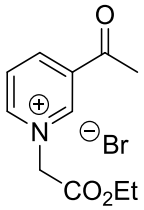


Prepared according to general procedure A:

Colourless solid (2.88 g, 93%); mp 177-179 °C (mp lit.[11] 178 °C); IR_{solid} (ν_{max}/cm^{-1}) 3124, 3052, 2992, 1767, 1628, 1236; NMR δ_H (400 MHz, DMSO-d_6) 9.53 (1H, br. s, Ar-*H*), 9.13 (1H, br. d, *J* = 6.1 Hz, Ar-*H*) 9.01 (1H, ddd, *J* = 8.5, 1.9, 1.1 Hz, Ar-*H*), 8.23 (1H, dd, *J*= 8.5, 6.1 Hz, Ar-*H*), 5.67 (2H, s, N-CH_2), 4.25 (2H, q, *J* = 7.1 Hz, CH_2CH$_3$), 1.26 (3H, t, *J* = 7.1 Hz, CH$_2$CH_3); NMR δ_C (100 MHz) 166.5 (C), 149.8 (CH), 147.9 (CH), 145.9 (CH), 129.2 (CH), 122.0 (C), 63.0 (CH_2), 60.8 (CH_2), 14.5 (CH_3); HRMS (ESI^+): calcd. $C_9NO_2{}^{79}BrH_{11}$ for ($[M]^+$) 243.9968, found 243.9973, calcd. $C_9NO_2{}^{81}BrH_{11}$ for ($[M]^+$) 245.9947, found 245.9951.

Data consistent with literature values.[11]

3-Acetyl-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (102)[11]

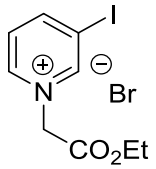


Prepared according to general procedure A:

Colourless solid (2.95 g, 75%); mp 118-120 °C (mp lit.[11] 123 °C); IR_{solid} (cm^{-1}) 2991, 1755, 1697, 1640, 1585, 1232, 1218, 1193, 641; NMR δ_H (400 MHz, DMSO-d_6) 9.76 (1H, br. s, Ar-*H*), 9.32 (1H, dt, *J* = 6.1, 1.4 Hz, Ar-*H*), 9.15 (1H, dt, *J* = 8.3, 1.4 Hz, Ar-*H*), 8.43 (1H, dd, *J* = 8.3, 6.1 Hz, Ar-*H*), 5.86 (2H, s, N-CH_2), 4.25 (2H, q, *J* = 7.2 Hz, CH_2CH$_3$), 2.75 (3H, s, O=C-CH_3), 1.27 (3H, t, *J* = 7.2, Hz, CH$_2$CH_3); NMR δ_C (100 MHz) 194.5 (C), 166.7 (C), 149.4 (CH), 147.3 (CH), 146.0 (CH), 135.4 (C), 128.4 (CH), 62.9 (CH_2), 61.0 (CH_2), 27.9 (CH_3), 14.4 (CH_3); HRMS (ESI^+): calcd. $C_{11}NO_3H_{14}$ for ($[M]^+$) 208.0968, found 208.0972.

Data consistent with literature values.[11]

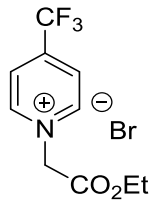
1-(2-Ethoxy-2-oxoethyl)-3-iodopyridin-1-ium bromide (103)



Prepared according to general procedure A:

Colourless solid (730 mg, 81%); mp 197-199 °C; IR_{solid} (ν_{max}/cm^{-1}) 3050, 2933, 1737, 1623, 1491, 1450, 1235, 1215, 1197, 1026, 823, 681; NMR δ_H (400 MHz, DMSO-*d*$_6$) 9.47 (1H, br. s, Ar-*H*), 9.09-9.07 (2H, m, Ar-*H*), 8.03 (1H, dd, *J* = 8.0, 6.4 Hz, Ar-*H*), 5.60 (2H, s, NC*H*$_2$), 4.25 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 1.26 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz) 166.6 (C), 154.7 (CH), 151.9 (CH), 145.7 (CH), 128.8 (CH), 96.2 (C), 62.9 (CH_2), 60.5 (CH_2), 14.4 (CH_3); HRMS (ESI^+): calcd. $C_9NO_2H_{11}I$ for ($[M]^+$) 291.9829 , found 291.9843.

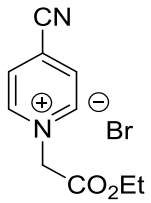
1-(2-Ethoxy-2-oxoethyl)-4-(trifluoromethyl)pyridin-1-ium bromide (104)



Prepared according to general procedure A:

Pale yellow solid (630 mg, 99%); mp 165-166 °C; IR_{solid} (ν_{max}/cm^{-1}) 2992, 2935, 2874, 1738, 1474, 1324, 1184, 1140, 1081, 1053, 1026, 892, 862; NMR δ_H (400 MHz, DMSO-d_6) 9.44 (2H, d, *J* = 6.7 Hz, Ar-*H*), 8.80 (2H, d, *J* = 6.7 Hz, Ar-*H*), 5.83 (2H, s, NCH_2), 4.27 (2H, q, *J* = 7.2 Hz, C$H_2$$CH_3$), 1.28 (3H, t, *J* = 7.2 Hz, CH_2CH_3); NMR δ_C (100 MHz) 166.4 (C), 149.2 (CH), 144.2 (CH, q, *J* = 35.9 Hz), 125.2 (CH, q, *J* = 3.3 Hz), 121.7 (C, q, *J* = 275.6 Hz), 63.1 (CH_2), 61.4 (CH_2), 14.5 (CH_3); HRMS (ESI^+): calcd. $C_{10}NO_2H_{11}F_3$ for ($[M]^+$) 234.0736, found 234.0747.

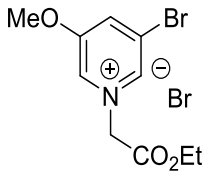
4-Cyano-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (105)



Prepared according to general procedure A:

Colourless solid (3.08 g, 79%); mp 210-212 °C; IR_{solid} (ν_{max}/cm^{-1}) 3103, 2983, 2925, 1735, 1644, 1566, 1520, 1472, 1343, 1295, 1222, 1193, 1022, 889, 858; NMR δ_H (400 MHz, DMSO-d_6) 9.34 (2H, d, *J* = 6.9 Hz, Ar-*H*), 6.78 (2H, d, *J* = 6.9 Hz, Ar-*H*), 5.76 (2H, s, NCH_2), 4.26 (2H, q, *J* = 7.1 Hz, CH_2CH$_3$), 1.28 (3H, t, *J* = 7.1 Hz, CH$_2$CH_3); NMR δ_C (100 MHz) 166.2 (C), 148.1 (CH), 131.2 (CH), 128.8 (C), 115.2 (C), 63.1 (CH_2), 61.6 (CH_2), 14.4 (CH_3); HRMS (ESI^+): calcd. $C_{10}N_2O_2H_{11}$ for ($[M]^+$) 191.0815, found 191.0829.

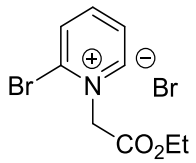
3-Bromo-1-(2-ethoxy-2-oxoethyl)-5-methoxypyridin-1-ium bromide (106)



Prepared according to general procedure A:

Colourless solid (1.33 g, 71%); mp 179-181 °C; IR_{solid} (ν_{max}/cm^{-1}) 2996, 2913, 2898, 1740, 1617, 1580, 1497, 1328, 1219, 1062, 965, 931, 896, 967, 744; NMR δ_H (400 MHz, DMSO-d_6) 9.08 (1H, t, *J* = 1.2 Hz, Ar-*H*), 9.04 (1H, dd, *J* = 2.3, 1.2 Hz, Ar-*H*), 8.75-8.73 (1H, m, Ar-*H*), 5.58 (2H, s, NCH_2), 4.26 (2H, q, *J* = 7.1 Hz, CH_2CH$_3$), 4.04 (3H, s, OCH_3), 1.27 (3H, t, *J* = 7.1 Hz, CH$_2$CH_3); NMR δ_C (100 MHz) 166.3 (C), 158.3 (C), 139.7 (CH), 135.0 (CH), 133.9 (CH), 122.2 (C), 63.0 (CH_2), 60.9 (CH_2), 58.5 (CH_3), 14.4 (CH_3); HRMS (ESI^+): calcd. $C_{10}NO_3H_{13}{}^{79}Br$ for ($[M]^+$) 274.0073, found 274.0070, calcd. $C_{10}NO_3H_{13}{}^{81}Br$ for ($[M]^+$) 276.0053, found 276.0051.

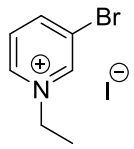
2-Bromo-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (107)



Prepared according to general procedure A:

Colourless solid (1.09 g, 35 %); mp 179-181 °C (decomp.); IR_{solid} (ν_{max}/cm^{-1}) 2992, 1741, 1610, 1442, 1220, 1197, 1020, 802; NMR δ_H (400 MHz, DMSO-d_6) 9.23 (1H, dt, *J* = 6.1, 1.1 Hz, Ar-*H*), 8.59 (1H, dd, *J* = 3.0, 1.1 Hz, Ar-*H*), 8.58 (1H, d, *J* = 1.1 Hz, Ar-*H*), 8.22 (1H, td, *J* = 6.1, 3.0 Hz, Ar-*H*), 5.82 (2H, s, NC*H*$_2$), 4.38 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 1.36 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz) 164.7 (C), 149.2 (CH), 147.6 (CH), 140.0 (C), 134.3 (CH), 126.9 (CH), 63.1 (CH_2), 62.4 (CH_2), 12.9 (CH_3); calcd. $C_9NO_2H_{11}{}^{79}Br$ for ($[M]^+$) 243.9968, found 243.9995, calcd. $C_9NO_2H_{11}{}^{81}Br$ for ($[M]^+$) 245.9947, found 245.9974.

3-Bromo-1-ethylpyridin-1-ium iodide (108)



Ethyliodide (0.51 mL, 6.34 mmol) was added to a stirring solution of 3-bromopyridine (0.31 mL, 3.17 mmol) in ethyl acetate (2 mL) and heated at 60 °C for 8 hours. The precipitate was collected by filtration, washed with diethyl ether and dried to afford the desired product as a yellow crystalline solid (141 mg, 10 %).

mp 128-130 °C; IR_{solid} (ν_{max}/cm^{-1}) 6055, 3032, 1625, 1489, 1479, 1450, 1314, 1198, 1172, 1102, 825, 814; NMR δ_H (400 MHz, DMSO-d_6) 9.52 (1H, br. s, Ar-*H*), 9.14 (1H, d, *J* = 6.2 Hz, Ar-*H*), 8.88 (1H, dd, *J* = 8.4, 1.0 Hz, Ar-*H*), 8.13 (1H, dd, *J* = 8.4, 6.2 Hz, Ar-*H*), 4.62 (2H, q, *J* = 7.3 Hz, C*H*$_2$CH$_3$), 1.56 (3H, t, *J* = 7.3 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz) 148.2 (CH), 146.4 (CH), 144.1 (CH), 129.3 (CH), 122.4 (C), 57.3 (CH_2), 16.6 (CH_3); calcd. $C_7NH_9{}^{79}Br$ for ($[M+H]^+$) 185.9913, found 185.9922, calcd. $C_7NH_9{}^{81}Br$ for ($[M]^+$) 187.9892, found 187.9899.

5.3 **Synthesis of Indoxyl cycloadducts**

General Procedure B - preparation of dipolarophiles:

1-Acetylindolin-3-one (1 eq) was added to a stirring solution of aldehyde (1.1 eq) in toluene (0.9 M) under argon. Morpholine (0.2 eq) was added and the reaction mixture was heated under reflux for 4 hours. The reaction was allowed to cool to room temperature and then concentrated *in vacuo* to afford the crude product, which was purified using column chromatography on silica gel using 4:1 (petrol : ethyl acetate) as eluent to afford the desired product.

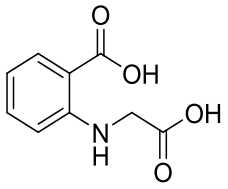
General Procedure C - deacylation of dipolarophiles:

Potassium carbonate (18 eq) was added to a stirring solution of dipolarophile (1 eq) in methanol (0.05 M) for 1.5 hours. Water was added and the solution was extracted with dichloromethane (3 times) the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the desired product.

General Procedure D - preparation of cycloadducts:

Base (1.5 equiv.) was added to pyridinium salt (1.5 equiv.) in dry solvent (2 mL) under argon and the mixture stirred at room temperature for 5 mins, followed by the addition of 2-alkenylindol-3-one (20 mg, 1 equiv.). The reaction mixture was stirred at room temperature for 4 hours. Water was added and was extracted with dichloromethane (3 times), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the desired cycloadduct.

2-((Carboxymethyl)amino)benzoic acid (111)[94]

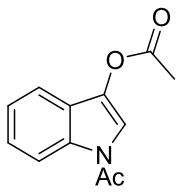


2-Aminobenzoic acid (25.0 g, 180 mmol) was added to a stirred solution of sodium hydroxide (18.3 g, 460 mmol) and sodium carbonate (3.00 g, 28.0 mmol) in water (110 mL) at 0 °C. The reaction was then heated under reflux for 24 hours then cooled to room temperature and acidified to pH 4 with conc. HCl. The precipitate was collected by filtration, washed with diethyl ether and dried to afford the desired product as an off white powder (27.5 g, 76%).

mp 180-182 °C (mp lit.[95] 185 °C); IR_{solid} (ν_{max}/cm^{-1}) 3378, 3038, 1721, 1655, 1572, 1519, 1458, 1434, 1395; NMR δ_H (400 MHz, DMSO-d_6) 7.80 (1H, dd, *J* = 8.0, 1.7 Hz, Ar-*H*), 7.36 (1H, ddd, *J* = 8.5, 7.2, 1.7 Hz, Ar-*H*), 6.61-6.58 (2H, m, Ar-*H*), 3.95 (1H, br. s, N*H*), 3.75 (2H, br. s, CH_2); NMR δ_C (100 MHz) 172.2 (C), 170.2 (C), 150.5 (C), 134.9 (CH), 132.1 (CH), 115.2 (CH), 112.0 (CH), 110.9 (C), 44.6 (CH_2); HRMS (ESI^+): calcd. $C_9NO_4H_{10}$ for ($[M+H]^+$) 196.0604, found 196.0631.

Data consistent with literature values.[94]

1-Acetyl-1H-indol-3-yl acetate (112)[96]

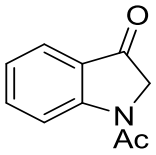


2-((Carboxymethyl)amino)benzoic acid (5.27 g, 27.0 mmol) was added to a stirred solution of sodium carbonate (7.16 g, 68.0 mmol) in acetic anhydride (50 mL, 0.53 mol). The reaction was heated under reflux for 3 hours then allowed to cool to room temperature, water (75 mL) was added and the mixture stirred for 1 hour. Aqueous work up was then performed using dichloromethane (3 x 80 mL), the organics were combined, then washed with saturated aq. sodium bicarbonate (3 x 80 mL). The organic layer was then separated, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the desired product as a brown oil (4.30 g, 73%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3201, 3007, 1759, 1707, 1601, 1574, 1452; NMR δ_H (400 MHz, $CDCl_3$) 8.48 (1H, d, *J* = 8.2 Hz, Ar-*H*), 7.73 (1H, s, C=C*H*), 7.55 (1H, d, *J* = 7.8 Hz, Ar-*H*), 7.40 (1H, m, Ar-*H*), 7.32 (1H, m, Ar-*H*), 2.62 (3H, s, O-C(O)CH_3), 2.40 (3H, s, N-C(O)CH_3); NMR δ_C (100 MHz) 168.7 (C) 167.9 (C), 134.7 (C), 132.9 (C), 126.2 (CH), 123.8 (CH), 123.6 (C), 117.5 (CH), 116.7 (CH), 113.3 (CH), 23.9 (CH_3), 21.1 (CH_3); HRMS (ESI^+): calcd. $C_{12}NO_3H_{12}$ for ($[M+H]^+$) 218.0812, found 218.0820.

Data consistent with literature values.[96]

1-Acetylindolin-3-one (22)[50]

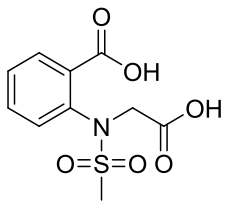


1-Acetyl-1H-indol-3-yl acetate (8.75 g, 40.0 mmol) was added to a stirred solution of sodium sulphite (7.62 g, 61.0 mmol) in water (80 mL) and ethanol (40 mL) under argon. The reaction was heated under reflux for 2 hours then cooled to room temperature, brine (100 mL) was added and the mixture was extracted with dichloromethane (3 x 100 mL). The organics were combined, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to afford the crude, which was purified using column chromatography on silica gel using 1:1 (petrol : ethyl acetate) as eluent to afford the desired compound as a brown solid (3.71 g, 53%).

mp 137-139 °C (mp lit.[97] 135 °C); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3008, 1722, 1683, 1608, 1496, 1391, 1354, 1281; NMR δ_H (400 MHz, $CDCl_3$) 8.58 (1H, d, *J* = 8.3 Hz, Ar-*H*), 7.76 (1H, d, *J* = 7.7 Hz, Ar-*H*), 7.68 (1H, m, Ar-*H*), 7.23 (1H, app. t, *J* = 7.7 Hz, Ar-*H*), 4.30 (2H, s, C*H*$_2$), 2.33 (3H, s, C*H*$_3$); NMR δ_C (100 MHz) 194.8 (C), 168.2 (C), 153.8 (C), 137.4 (CH), 124.9 (C), 124.3 (CH), 123.7 (CH), 118.7 (CH), 56.1 (CH_2), 24.3 (CH_3); HRMS (ESI^+): calcd. $C_{10}NO_2H_{10}$ for ($[M+H]^+$) 176.0706, found 176.0706.

Data consistent with literature values.[50]

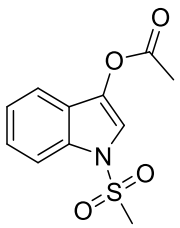
2-(*N*-(Carboxymethyl)methylsulfonamido)benzoic acid (120)



Methanesulfonyl chloride (5.72 mL, 0.07 mol) was added slowly to a stirred solution of 2-((carboxymethyl)amino)benzoic acid (9.66 g, 0.05 mol) in sat. sodium bicarbonate (100 mL) at 0 °C. The reaction mixture was stirred for 2 hours then conc. HCl (5 mL) and diethyl ether (150 mL) was added and stirred vigorously at room temperature for 1 hour. The organic layer was separated and the aqueous layer was extracted with diethyl ether (150 mL), the organics were combined, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to afford the desired product as a yellow gum (4.83 g, 36%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3043, 2934, 1704, 1494, 1409, 1321, 1175, 966; NMR δ_H (400 MHz, DMSO-d_6) 7.85 (1H, dd, *J* = 7.8, 1.5 Hz, Ar-*H*), 7.69 (1H, dd, *J* = 8.0, 1.1 Hz, Ar-*H*), 7.65-7.61 (1H, m, Ar-*H*), 7.53-7.48 (1H, m, Ar-*H*), 4.36 (2H, br. s, CH_2), 3.07 (3H, s, CH_3); NMR δ_C (100 MHz) 171.7 (C), 167.4 (C), 138.9 (C), 133.0 (CH), 132.7 (C), 132.4 (CH), 131.4 (CH), 129.4 (CH), 53.6 (CH_2), 40.7 (CH_3); HRMS (ESI^-): calcd. $C_{10}NO_6H_{10}S$ for ($[M-H]^-$) 272.0234, found 272.0228.

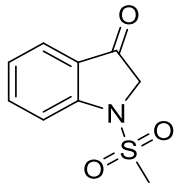
1-(Methylsulfonyl)-1H-indol-3-yl acetate (121)



2-(*N*-(carboxymethyl)methylsulfonamido)benzoic acid (4.83 g, 17.7 mmol) was added to a stirred solution of sodium carbonate (5.13 g, 44.2 mmol) in acetic anhydride (33 mL, 350 mmol) and heated under reflux for 3 hours, then allowed to cool to room temperature. Water (50 mL) was added and once cooled to room temperature the solution was extracted with dichloromethane (2 x 50 mL), the organics were combined and washed with saturated aq. sodium bicarbonate (3 x 50 mL), the organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the desired product as a brown solid (2.57 g, 58%).

mp 112-114 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3180, 3043, 2933, 1756, 1599, 1570, 1466, 1367, 1328, 1302, 1274, 1192, 1171, 1121, 1097, 985; NMR δ_H (400 MHz, $CDCl_3$) 7.96 (1H, d, *J* = 8.2 Hz, Ar-*H*), 7.73 (1H, s, N-C*H*), 7.61 (1H, br, d, *J* = 7.7 Hz, Ar-*H*), 7.46-7.41 (1H, m, Ar-*H*), 7.38-7.34 (1H, m, Ar-*H*), 3.09 (3H, s, S-CH_3), 2.40 (3H, s, OC(O)CH_3); NMR δ_C (100 MHz) 167.6 (C), 134.6 (C), 132.6 (C), 125.9 (CH), 124.1 (C), 123.7 (CH), 118.5 (CH), 114.5 (CH), 113.3 (CH), 40.4 (CH_3), 20.9 (CH_3); HRMS (ESI^+): calcd. $C_{11}NO_4H_{12}S$ for ($[M+H]^+$) 254.0482, found 254.0491.

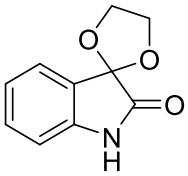
1-(Methylsulfonyl)indolin-3-one (122)



1-(methylsulfonyl)-1H-indol-3-yl acetate (2.57 g, 10.0 mmol) was added to a stirred solution of sodium sulphite (1.92 g, 15.0 mmol) in water (24 mL) and ethanol (12 mL). The reaction was heated to 60 °C for 1 hour then cooled to room temperature, brine (20 mL) was added and the mixture was extracted with dichloromethane (3 x 30 mL), the organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo* to afford the crude product. Which was purified using column chromatography on silica gel using 3:1 (petrol : ethyl acetate) as eluent to afford the desired product as a brown solid (790 mg, 37%).

mp 146-148 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3043, 1722, 1607, 1591, 1465, 1426, 1364, 1322, 1193, 1166, 1117, 1086, 974; NMR δ_H (300 MHz, $CDCl_3$) 7.82-7.77 (2H, m, Ar-*H*), 7.72-7.67 (1H, m, Ar-*H*), 7.28-7.23 (1H, m, Ar-*H*), 4.26 (2H, s, C*H*$_2$), 3.03 (3H, s, C*H*$_3$); NMR δ_C (75 MHz) 194.4 (C), 153.2 (C), 137.5 (CH), 124.8 (C), 124.7 (CH), 124.2 (CH), 115.0 (CH), 56.3 (CH_2), 37.0 (CH_3); HRMS (ESI^+): calcd. $C_9NO_3H_{10}S$ for ($[M+H]^+$) 212.0376, found 212.0392.

Spiro[[1,3]dioxolane-2,3'-indolin]-2'-one (129)[98]

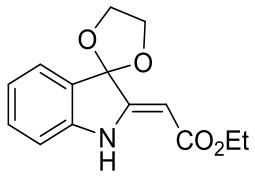


Isatin (10.0 g, 68.0 mmol) was added to a stirred solution of ethylene glycol (38.0 mL, 380 mmol) and tosic acid monohydrate (1.29 g, 6.80 mmol) in toluene (100 mL). The mixture was heated at 100 °C using Dean Stark apparatus under argon and stirred overnight. The reaction was cooled to room temperature, followed by the addition of water (75 mL) and potassium carbonate (4.50 g, 32.6 mmol) and stirred for 10 minutes. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the desired product as a yellow powder (9.17 g, 71%).

mp 121-123 °C (mp lit.[99] 134 °C); IR_{solid} (cm^{-1}) 3162, 2895, 1739, 1621, 1472, 756; NMR δ_H (400 MHz, $CDCl_3$) 8.14 (1H br. s, N*H*), 7.37 (1H, dd, *J* = 7.5, 0.6 Hz, Ar-*H*), 7.31 (1H, td, *J* = 7.8, 1.2 Hz, Ar-*H*), 7.07 (1H, td, *J* = 7.5, 0.6 Hz, Ar-*H*), 6.83 (1H, d, *J* = 7.8 Hz, Ar-*H*), 4.64-4.53 (2H, m, CH_2), 4.39-4.29 (2H, m, CH_2); NMR δ_C (100 MHz) 175.4 (C), 141.8 (C), 131.7 (CH), 125.2 (CH), 124.4 (C), 123.4 (CH), 110.7 (CH), 102.3 (C), 65.9 (CH_2); HRMS (ESI^+): calcd. $C_{10}NO_3H_{10}$ for ($[M+H]^+$) 192.0655, found 192.0659.

Data consistent with literature values.[98]

Ethyl (*Z*)-2-(spiro[indoline-3,2'-[1,3]dioxolan]-2-ylidene)acetate (131)

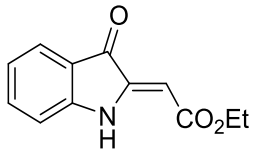


Phosphorus oxychloride (0.41 mL, 4.32 mmol) was added to a stirring solution of sodium hydride (188 mg, 4.71 mmol) and spiro[[1,3]dioxolane-2,3'-indolin]-2'-one (750 mg, 3.93 mmol) in tetrahydrofuran (20 mL) at -10 °C under argon. After 5 minutes the reaction was heated to 40 °C for 3 hours, then cooled to -78 °C. In a separate dry flask under argon LDA (15.7 mmol) was freshly prepared in tetrahydrofuran (10 mL) at -78 °C followed by the dropwise addition of ethyl acetate (1.46 mL, 14.9 mmol) and the mixture was stirred for 20 mins. The enolate was then transferred dropwise *via* cannula to the first flask at -78 °C and stirred for 1 hour. Then the reaction mixture was allowed to warm to 0 °C, water (60 mL) was added slowly, once the addition was complete, the mixture was extracted with dichloromethane (3 x 60 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the crude product. Purification by column chromatography on silica gel using 4:1 (petrol : ethyl acteate) as eluent afforded the desired product as an orange oil which solidified in the freezer to a yellow solid (580 mg, 57%).

mp 55-57 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3391, 2985, 2896, 1729, 1679, 1618, 1473, 1372, 1283, 1264, 1192, 1118, 1045; NMR δ_H (400 MHz,

$CDCl_3$) 9.11 (1H, br. s, N*H*), 7.34 (1H, br. d, *J* = 7.4 Hz, Ar-*H*), 7.28 (1H, ddd, *J* = 7.8, 7.6, 1.1 Hz, Ar-*H*), 6.95 (1H, ddd, *J* = 7.6, 7.4, 0.9 Hz, Ar-*H*), 6.80 (1H, br. d, *J* = 7.8 Hz, Ar-*H*), 5.19 (1H, s, C=C*H*), 4.40-4.32 (4H, m, O-CH_2-CH_2-O), 4.23 (2H, q, *J* = 7.1 Hz, O-C$H_2$$CH_3$), 1.33 (3H, t, *J* = 7.1 Hz, CH_2CH_3); NMR δ_C (100 MHz) 169.6 (C), 160.7 (C), 143.8 (C), 131.3 (CH), 127.3 (C), 124.2 (CH), 121.5 (CH), 110.3 (C), 110.0 (CH), 85.9 (CH), 65.73 (CH_2), 65.72 (CH_2), 59.7 (CH_2), 14.5 (CH_3); HRMS (ESI^+): calcd. $C_{14}NO_4H_{16}$ for ($[M+H]^+$) 262.1074, found 262.1068.

Ethyl (*Z*)-2-(3-oxoindolin-2-ylidene)acetate (125)

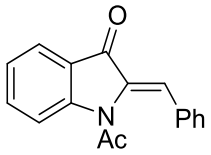


Ethyl (*Z*)-2-(spiro[indoline-3,2'-[1,3]dioxolan]-2-ylidene)ethanethioate (100 mg, 0.36 mmol) was added to a stirred solution of tosic acid monohydrate (21 mg, 0.11 mmol) and anhydrous sodium sulphate (256 mg, 1.81 mmol) in acetone (3 mL) under argon and heated to 50 °C for 24 hours. Ethyl acetate (25 mL) was added and then washed with saturated aq. sodium hydrogen carbonate (2 x 30 mL), the organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the desired product as an orange solid (73 mg, 87%).

mp 128-130 °C (mp lit.[17] 131 °C); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3416, 2928, 2360, 1716, 1678, 1615, 1469, 1287, 1192, 1148, 909; NMR δ_H (400 MHz, $CDCl_3$) 8.85 (1H, br. s, N-*H*), 7.67 (1H, br. d, *J* = 7.5, Ar-*H*), 7.48 (1H, ddd, *J* = 8.0, 7.5, 0.6 Hz, Ar-*H*), 6.97 (1H, td, *J* = 7.5, 0.8 Hz, Ar-*H*), 6.91 (1H, br. d, *J* = 8.0 Hz, Ar-*H*), 5.86 (1H, s, C=C*H*), 4.27 (2H, q, *J* = 7.2 Hz, CH_2), 1.34 (3H, t, *J* = 7.2 Hz, CH_3); NMR δ_C (100 MHz) 186.9 (C), 168.8 (C), 152.9 (C), 145.1 (C), 137.4 (CH), 125.5 (CH), 121.5 (CH), 120.6 (C), 111.6 (CH), 93.1 (CH), 60.7 (CH_2), 14.3 (CH_3); HRMS (ESI^+): calcd. $C_{12}NO_3H_{11}$ for ($[M+H]^+$) 218.0812, found 218.0812.

Data consistent with literature values.[17]

(*Z*)-1-Acetyl-2-benzylideneindolin-3-one (17)[17]

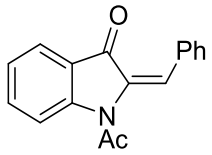


Prepared according to general procedure B:

Orange oil which crystallises on standing (450 mg, 60%); mp 124-126 °C (mp lit.[100] 132 °C); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3011, 1692, 1635, 1492, 1280; NMR δ_H (400 MHz, $CDCl_3$) 8.31 (1H, d, *J* = 8.3 Hz, Ar-*H*), 7.87 (1H, br. d, *J* = 7.7 Hz, Ar-*H*), 7.69 (1H, ddd, *J* = 8.5, 7.4, 1.4 Hz, Ar-*H*), 7.59-7.56 (2H, m, Ar-*H*), 7.48-7.43 (2H, m, Ar-*H*), 7.42-7.37 (1H, m, Ar-*H*), 7.35 (1H, s, C=C*H*), 7.32 (1H, td, *J* = 7.4, 0.8 Hz, Ar-*H*), 1.97 (3H, s, CH_3); NMR δ_C (100 MHz) 186.0 (C), 170.5 (C), 150.3 (C), 136.4 (CH), 135.1 (C), 134.0 (C), 130.2 (CH), 129.9 (CH), 129.3 (CH), 125.0 (CH), 124.2 (CH), 123.9 (C), 122.3 (CH), 117.9 (CH), 25.1 (CH_3); HRMS (ESI^+): calcd. $C_{17}NO_2H_{14}$ for ($[M+H]^+$) 264.1019, found 264.1012.

Data consistent with literature values.[17]

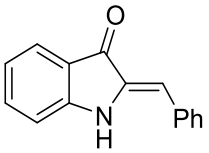
(*E*)-1-Acetyl-2-benzylideneindolin-3-one (113)[17]



Prepared according to general procedure B:

Green oil (22 mg, 3%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3003, 1691, 1635, 1430, 1281; NMR δ_H (400 MHz, $CDCl_3$) 8.14 (1H, d, *J* = 8.4 Hz, Ar-*H*), 7.91 - 7.85 (2H, m, Ar-*H*), 7.79 (1H, br. d, *J* = 7.5 Hz, Ar-*H*), 7.68 - 7.62 (1H, m, Ar-*H*), 7.58 (1H, s, C=C*H*), 7.49-7.41 (3H, m, Ar-*H*), 7.30-7.23 (1H, m, Ar-*H*), 2.66 (3H, s, CH_3); NMR δ_C (100 MHz) 186.0 (C), 170.5 (C), 150.3 (C), 136.0 (CH), 131.1 (C), 130.21 (CH), 130.16 (C), 130.10 (CH), 129.3 (CH), 128.0 (CH), 124.7 (CH), 124.2 (CH), 123.9 (C), 117.4 (CH), 26.4 (CH_3); HRMS (ESI^+): calcd. $C_{17}NO_2H_{14}$ for ($[M+H]^+$) 264.1019, found 264.1019.

(*Z*)-2-Benzylideneindolin-3-one (27)[101]

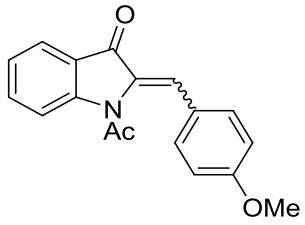


Prepared according to general procedure C:

Orange solid (12 mg, 48%); mp 150-152 °C (mp lit.[102] 164 °C); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3691, 3605, 3443, 3006, 1697, 1632, 0610, 1484, 1470, 1378, 1316, 1135; NMR δ_H (400 MHz, $CDCl_3$) 7.77 (1H, br. d, *J* = 7.7 Hz, Ar-*H*), 7.60-7.56 (2H, m, Ar-*H*), 7.52-7.44 (3H, m, 3xAr-*H*), 7.38-7.33 (1H, m, Ar-*H*), 7.05–6.97 (3H, m, Ar-*H,* N*H*), 6.89 (1H, s, C=C*H*); NMR δ_C (75 MHz) 186.6 (C), 153.2 (C), 136.2 (CH), 135.4 (C), 134.7 (C), 129.5 (CH), 129.2 (CH), 128.5 (CH), 125.0 (CH), 121.7 (C), 120.7 (CH), 112.0 (CH), 111.6 (CH); HRMS (ESI^+): calcd. $C_{15}NOH_{12}$ for ($[M+H]^+$) 222.0913, found 222.0914.

Data consistent with literature values.[101]

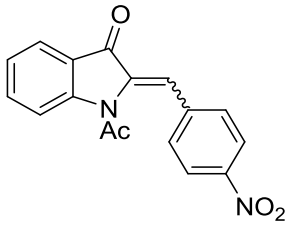
1-Acetyl-2-(4-methoxybenzylidene)indolin-3-one (114)



Prepared according to general procedure B:

Green oil solidified on standing (434 mg, 86%); mp 134-136 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3009, 2841, 1691, 1629, 1603, 1511, 1475, 1459, 1368, 1322, 1281, 1260, 1175, 1142, 1099, 1051, 1032; NMR δ_H (400 MHz, $CDCl_3$, 4 : 1 mixture of isomers, *indicates minor where different from major) 8.32 (1H, d, *J* = 8.3 Hz, Ar-*H*), 8.18 (1H, d, *J* = 8.4 Hz, Ar-*H**), 8.01 (2H, br. d, *J* = 8.7 Hz, 2xAr-*H**), 7.88 (1H, dd, *J* = 7.7, 0.8 Hz, Ar-*H*), 7.82 (1H, dd, *J* = 7.7, 0.8 Hz, Ar-*H**), 7.72-7.67 (1H, m, Ar-*H*), 7.66-7.63 (1H, m, Ar-*H**), 7.55 (2H, br. d, *J* = 8.8 Hz, 2xAr-*H*), 7.49 (1H, s, C=C*H**), 7.35 (1H, s, C=C*H*), 7.33-7.26 (2H, m, Ar-*H*, Ar-*H**), 7.01-6.97 (4H, m, 2xAr-*H*, 2xAr-*H**), 3.91 (3H, s, OCH_3*), 3.89 (3H, s, OCH_3), 2.66 (3H, s, COCH_3*), 2.08 (3H, s, COCH_3); NMR δ_C (100 MHz) 186.0 (C), 182.4 (C), 170.8 (C), 169.2 (C), 161.6 (C), 161.0 (C), 150.1 (C), 147.9 (C), 136.1 (CH), 135.6 (CH), 133.7 (C), 133.6 (CH), 132.4 (CH), 130.9 (CH), 126.0 (C), 124.9 (CH), 124.8 (C), 124.7 (C), 124.5 (CH), 124.3 (C), 124.04 (CH), 123.99 (CH), 122.9 (CH), 117.9 (CH), 117.3 (CH), 114.8 (C), 114.7 (CH), 113.5 (CH), 77.2 (C), 55.44 (CH_3), 55.43 (CH_3), 26.4 (CH_3), 25.2 (CH_3); HRMS (ESI^+): calcd. $C_{18}NO_3H_{16}$ for ($[M+H]^+$) 294.1125, found 294.1130.

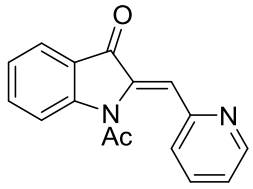
1-Acetyl-2-(4-nitrobenzylidene)indolin-3-one (115)



Prepared according to general procedure B:

Orange solid (183 mg, 37%); mp 157-159 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3008, 2934, 1706, 1640, 1596, 1522, 1347, 1282, 1141, 854; NMR δ_H (400 MHz, $CDCl_3$, 17 : 10 mixture of isomers, *indicates minor where different from major) 8.33 (2H, d, *J* = 8.8 Hz, 2xAr-*H**), 8.28 (2H, d, *J* = 8.8 Hz, 2xAr-*H*), 8.17 (1H, d, *J* = 8.4 Hz, Ar-*H**), 7.95-7.89 (5H, m, 2xAr-*H*, C=C*H*, 2xAr-*H**), 7.82 (1H, m, Ar-*H*), 7.78-7.68 (4H, m, 2xAr-*H*, 2xAr-*H**), 7.41-7.30 (3H, m, Ar-*H*, Ar-*H**, C=C*H**), 2.73 (3H, s, COCH_3), 2.12 (3H, s, COCH_3*); NMR δ_C (100 MHz) 185.5 (C), 183.0 (C), 169.23 (C), 169.16 (C), 150.3 (C), 148.3 (C), 141.0 (C), 139.4 (C), 136.9 (CH), 136.6 (CH), 136.5 (C), 136.1 (C), 132.6 (C), 131.2 (CH), 130.8 (CH), 126.4 (CH), 125.5 (CH), 125.0 (CH), 124.84 (CH), 124.75 (CH), 124.2 (CH), 123.8 (C), 123.1 (CH), 118.9 (CH), 117.8 (CH), 116.9 (CH), 77.2 (C), 76.0 (C), 26.9 (CH_3), 25.2 (CH_3); HRMS (ESI^+): calcd. $C_{17}N_2O_4H_{13}$ for ($[M+H]^+$) 309.0870, found 309.0860.

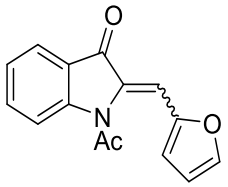
(*Z*)-1-Acetyl-2-(pyridin-2-ylmethylene)indolin-3-one (116)



Prepared according to general procedure B:

Orange solid (424 mg, 56%); mp 133-135 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3011, 1703, 1639, 1605, 1591, 1471, 1460, 1366, 1315, 1278, 1143; NMR δ_H (400 MHz, $CDCl_3$) 8.75 (1H, ddd, *J* = 4.8, 1.8, 0.9 Hz, Ar-*H*), 8.23 (1H, dt, *J* = 8.4, 0.7 Hz, Ar-*H*), 7.85 (1H, ddd, *J* = 7.7, 1.5, 0.7 Hz, Ar-*H*), 7.79 (1H, td, *J* = 7.7, 1.8 Hz, Ar-*H*), 7.66 (1H, ddd, *J* = 8.4, 7.3, 1.5 Hz, Ar-*H*), 7.55 (1H, dt, *J* = 7.8, 0.9 Hz, Ar-*H*), 7.29-7.22 (3H, m, 2xAr-*H*, C=C*H*), 2.10 (3H, s, COCH_3); NMR δ_C (100 MHz) 186.7 (C), 171.8 (C), 152.7 (C), 151.0 (C), 149.8 (CH), 136.9 (CH), 136.7 (CH), 136.1 (C), 127.6 (CH), 124.31 (CH), 124.28 (CH), 123.5 (CH), 122.6 (C), 118.5 (CH), 116.5 (CH), 25.4 (CH_3); HRMS (ESI^+): calcd. $C_{16}N_2O_2H_{13}$ for ($[M+H]^+$) 265.0972, found 265.0982.

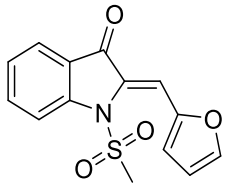
1-Acetyl-2-(furan-2-ylmethylene)indolin-3-one (117)



Prepared according to general procedure B:

Green oil solidified on standing (276 mg, 95%); mp 106-108 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3011, 1694, 1628, 1473, 1368, 1289, 1189, 1137, 1050; NMR δ_H (400 MHz, $CDCl_3$, 11 : 10 mixture of isomers, *indicates minor where different from major) 8.35 (1H, dt, *J* = 3.7, 0.7 Hz, Ar-*H**), 8.27 (1H, dt, *J* = 8.3, 0.7 Hz, Ar-*H*), 8.01 (1H, br. d, *J* = 8.4 Hz, Ar-*H**), 7.91-7.88 (2H, m, Ar-*H**, C=C*H**), 7.84 (1H, ddd, *J* = 7.5, 1.4, 0.6 Hz, Ar-*H*), 7.69-7.64 (4H, m, 2xAr-*H*, 2xAr-*H**), 7.22-7.27 (2H, m, Ar-*H*, Ar-*H**), 7.17 (1H, s, C=C*H*), 6.88 (1H, br. d, *J* = 3.5 Hz, Ar-*H*), 6.66 (1H, ddd, *J* = 3.6, 1.8, 0.6 Hz, Ar-*H**), 6.60 (1H, dd, *J* = 3.5, 0.9 Hz, Ar-*H*), 2.71 (3H, s, COCH_3*), 2.22 (3H, s, COCH_3); NMR δ_C (100 MHz) 185.8 (C), 182.6 (C), 171.5 (C), 169.1 (C), 150.1 (C), 149.7 (C), 148.8 (C), 147.5 (C), 146.0 (CH), 145.6 (CH), 136.3 (CH), 135.4 (CH), 132.2 (C), 131.7 (C), 124.7 (CH), 124.6 (C), 124.5 (CH), 124.1 (CH), 124.0 (CH), 123.7 (C), 119.2 (CH), 118.8 (CH), 117.1 (CH), 117.0 (CH), 116.5 (CH), 113.4 (CH), 113.2 (CH), 109.5 (CH), 27.0 (CH_3), 24.3 (CH_3); HRMS (ESI^+): calcd. $C_{15}NO_3H_{12}$ for ($[M+H]^+$) 254.0812, found 254.0827.

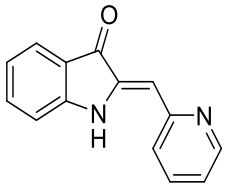
(*Z*)-2-(Furan-2-ylmethylene)-1-(methylsulfonyl)indolin-3-one (123)



Prepared according to general procedure B:

Yellow solid (248 mg, 91%); mp 164-166 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3043, 1694, 1611, 1580, 1468, 1354, 1322, 1297, 1187, 1171, 1100, 1086; NMR δ_H (400 MHz, $CDCl_3$) 8.43 (1H, d, *J* = 3.7 Hz, Ar-*H*), 8.03 (1H, dt, *J* = 8.5 , 0.7 Hz, Ar-*H*), 7.93-7.90 (2H, m, Ar-*H*, C=C*H*), 7.71-7.67 (2H, m, Ar-*H*), 7.40-7.36 (1H, m, Ar-*H*), 6.67 (1H, ddd, *J* = 3.7, 1.8, 0.7 Hz, Ar-*H*), 2.92 (3H, s, SO_2CH_3); NMR δ_C (100 MHz) 182.4 (C), 149.8 (C), 147.5 (C), 146.4 (CH), 135.9 (CH), 130.2 (C), 125.8 (C), 125.5 (CH), 124.3 (CH), 119.7 (CH), 117.5 (CH), 117.4 (CH), 113.5 (CH), 36.5 (CH_3); HRMS (ESI^+): calcd. $C_{14}NO_4H_{12}S$ for ($[M+H]^+$) 290.0482, found 290.0483.

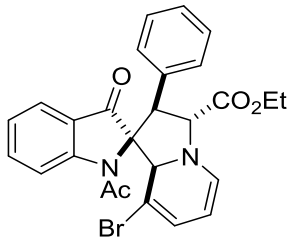
(*Z*)-2-(Pyridin-2-ylmethylene)indolin-3-one (118)



Prepared according to general procedure C:

Red solid (91 mg, 99%); mp 152-154 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3692, 3358, 3008, 1693, 1637, 1607, 1589, 1557, 1484, 1469, 1437, 1383, 1306, 1137, 1097; NMR δ_H (300 MHz, $CDCl_3$) 9.97 (1H, br. s, N-*H*), 8.69 (1H, dd, *J* = 4.9, 1.5 Hz, Ar-*H*), 7.74-7.67 (2H, m , Ar-*H*), 7.46 (1H, ddd, *J* = 8.4, 7.4, 1.5 Hz, Ar-*H*), 7.41 (1H, dd, *J* = 7.9, 1.1 Hz, Ar-*H*), 7.17 (1H, ddd, *J* = 7.4, 4.9, 1.1 Hz, Ar-*H*), 7.00 (1H, d, *J* = 7.9 Hz, Ar-*H*), 6.95-6.89 (1H, m, Ar-*H*), 6.63 (1H, s, C=C*H*); NMR δ_C (100 MHz) 187.8 (C), 156.0 (C), 153.2 (C), 149.3 (CH), 138.3 (C), 136.53 (CH), 136.47 (CH), 126.2 (CH), 125.0 (CH), 121.5 (CH), 120.7 (C), 120.0 (CH), 111.5 (CH), 105.2 (CH); HRMS (ESI^+): calcd. $C_{14}N_2OH_{11}$ for ($[M+H]^+$) 223.0866, found 223.0875.

(2S*,2'S*,3'R*,8a'R*)-Ethyl 1-acetyl-8'-bromo-3-oxo-2'-phenyl-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (132)

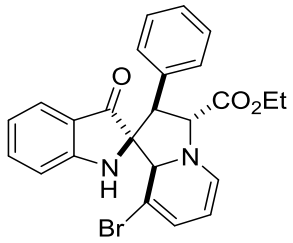


Prepared according to general procedure D:

Orange gum (37 mg, 95%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3006, 2940, 1734, 1674, 1610, 1499, 1372, 1306; NMR δ_H (400 MHz, $CDCl_3$, 1 : 1 mixture of rotamers) 7.79 (1H, dd, *J* = 6.8, 1.3 Hz, Ar-*H*), 7.62 (1H, dd, *J* = 7.0, 0.8 Hz, Ar*H*), 7.52-7.47 (2H, m, Ar-*H*), 7.36 (1H, m, Ar-*H*), 7.19-7.03 (13H, m, Ar-*H*), 6.37-6.32 (2H, m, NC*H*CBr, NC*H*=CH), 6.29 (1H, d, *J* = 7.0 Hz, NC*H*=CH), 6.15 (1H, br. d, *J* = 7.0 Hz, BrC=C*H*), 6.12 (1H, br. d, *J* = 7.0 Hz, BrC=C*H*), 5.76 (1H, br. s, NC*H*CBr), 5.10 (1H, d, *J* = 10.2 Hz, NC*H*(CO_2Et)), 5.02 (1H, br. d, *J* = 10.0 Hz, NC*H*(CO_2Et)), 4.97 (1H, d, *J* = 10.0 Hz, *CH*Ar), 4.63 (1H, app. t, *J* = 7.0 Hz, N-CH=C*H*), 4.57 (1H, app. t, *J* = 7.0 Hz, N-CH=C*H*), 4.30 (1H, d, *J* = 10.2 Hz, C*H*Ar), 4.23-4.12 (4H, m, C*H*$_2$CH$_3$, C*H*$_2$CH$_3$), 2.66 (3H, s, COC*H*$_3$), 2.42 (3H, s, COC*H*$_3$), 1.22 (3H, t, *J* = 7.2 Hz, CH$_2$C*H*$_3$), 1.17 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz) 197.7 (C), 195.8 (C), 171.9 (C), 171.2 (C), 169.4 (C), 169.1 (C), 152.7 (C), 152.4 (C), 136.44 (CH), 136.42 (CH), 135.8 (CH), 134.6 (CH), 132.84 (C), 132.76 (C), 128.7 (CH), 128.55 (CH), 128.46 (CH), 128.3 (CH), 128.14 (CH), 128.09 (CH), 127.9 (CH), 127.8 (CH),

124.9 (C), 124.6 (CH), 124.2 (C), 124.2 (CH), 123.6 (CH), 123.4 (CH), 115.3 (CH), 107.1 (C), 105.5 (C), 94.2 (CH), 93.1 (CH), 86.3 (C), 82.5 (C), 77.3 (C), 74.6 (CH), 71.0 (CH), 65.9 (C), 65.1 (CH), 64.6 (CH), 61.51 (CH_2), 61.46 (CH_2), 60.4 (C), 55.7 (CH), 46.2 (CH), 27.8 (CH_3), 26.2 (CH_3), 14.1 (CH_3), 14.0 (CH_3); HRMS (ESI^+): calcd. $C_{26}N_2O_4{}^{79}BrH_{24}$ for ($[M+H]^+$) 507.0914, found 507.0910, calcd. $C_{26}N_2O_4{}^{81}BrH_{24}$ for ($[M+H]^+$) 509.0893, found 509.0894.

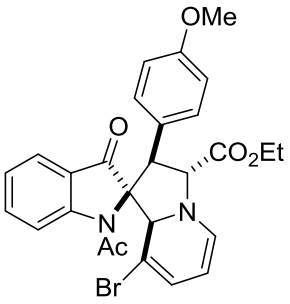
(2S*,2'S*,3'R*,8a'R*)-Ethyl 8'-bromo-3-oxo-2'-phenyl-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (142)



Prepared according to general procedure D:

Orange gum (39 mg, 93%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3420, 3011, 1740, 1700, 1619, 1485, 1470, 1429, 1193; NMR δ_H (500 MHz, $CDCl_3$) 7.48 (1H, br. d, *J* = 7.8 Hz, Ar-*H*), 7.31–7.28 (1H, m, Ar-*H*), 7.23–7.21 (2H, m, Ar-*H*), 7.18–7.13 (3H, m, Ar-*H*), 6.76–6.70 (2H, m, Ar-*H*), 6.30–6.26 (2H, m, Br-C=C*H*, N-C*H*=CH), 5.37 (1H, br. s, NC*H*CBr), 5.19 (1H, br. s, N*H*), 4.66 (1H, app. t, *J* = 6.8 Hz, N-CH=C*H*), 4.51 (1H, d, *J* = 9.0 Hz, NC*H*(CO_2Et)), 4.27-4.13 (2H, m, C*H*$_2$$CH_3$), 4.04 (1H, d, *J* = 9.0 Hz, C*H*Ar, 1.23 (3H, t, *J* = 7.1 Hz, CH_2C*H*$_3$); NMR δ_C (100 MHz) 197.9 (C), 171.0 (C), 160.8 (C), 136.7 (CH), 134.1 (CH), 133.5 (C), 128.7 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 124.2 (CH), 122.8 (C), 119.3 (CH), 112.3 (CH), 107.3 (C), 94.8 (CH), 80.1 (C), 73.0 (CH), 68.8 (CH), 61.8 (CH_2), 55.1 (CH), 14.1 (CH_3); HRMS (ESI^+): calcd. $C_{24}N_2O_3{}^{79}BrH_{22}$ for ($[M+H]^+$) 465.0808, found 465.0776, calcd. $C_{24}N_2O_3{}^{81}BrH_{22}$ for ($[M+H]^+$) 467.0788, found 467.0780.

(2S*,2'S*,3'R*,8a'R*)-Ethyl 1-acetyl-8'-bromo-2'-(4-methoxyphenyl)-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (143)

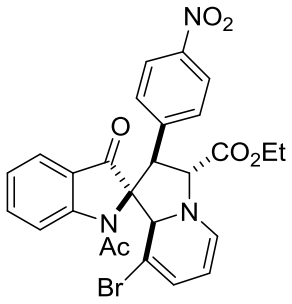


Prepared according to general procedure D:

Yellow foam (38 mg, 97%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3010, 2360, 1715, 1679, 1640, 1611, 1593, 1568, 1516, 1437, 1371; NMR δ_H (400 MHz, $CDCl_3$, 5 : 4 mixture of rotamers, † indicates minor where different from major) 7.76 (1H, dd, *J* = 7.6, 0.7 Hz, Ar-*H*†), 7.62 (1H, dd, *J* = 7.6, 0.6 Hz, Ar-*H*), 7.54-7.46 (3H, m, Ar-*H*, 2xAr-*H*†), 7.32 (1H, m, Ar-*H*), 7.14 (1H, d, *J* = 8.4 Hz, Ar-*H*), 7.13-6.96 (5H, m, 2xAr-*H*, 3xAr-*H*†), 6.63 (2H, d, *J* = 8.8 Hz, 2xAr-*H*), 6.60 (2H, d, *J* = 8.8 Hz, 2xAr-*H*†), 6.31-6.29 (2H, m, NC*H*CBr, NC*H*†=CH), 6.25 (1H, d, *J* = 7.2 Hz, NC*H*=CH), 6.12-6.08 (2H, m, BrC=C*H*, BrC=C*H*†), 5.73 (1H, d, *J* = 0.9 Hz, NC*H*†CBr), 5.00 (1H, d, *J* = 10.2 Hz, NC*H*†(CO-$_2$Et)), 4.95 (1H, br. d, *J* = 10.0 Hz, NC*H*(CO_2Et)), 4.89 (1H, d, *J* = 10.0 Hz, C*HAr*), 4.60 (1H, app. t, *J* = 6.8 Hz, N-CH=C*H*†), 4.53 (1H, app. t, *J* = 6.8 Hz, N-CH=C*H*), 4.23 (1H, d, *J* = 10.2 Hz, C*H*†Ar), 4.20-4.11 (4H, m, C$H_2$$CH_3$, C$H_2$†$CH_3$), 3.67 (3H, s, O-C$H_3$†), 3.66 (3H, s, O-C$H_3$), 2.63 (3H, s, COC$H_3$), 2.44 (3H, s, COC$H_3$†), 1.21 (3H, t, *J* = 7.1 Hz, CH_2CH_3†), 1.16 (3H, t, *J* = 7.2 Hz, CH_2CH_3); NMR δ_C (100 MHz) 197.9 (C), 195.9 (C), 171.9 (C), 171.2 (C), 169.3 (C),

169.1 (C), 159.1 (C), 159.0 (C), 152.8 (C), 136.43 (CH), 136.40 (CH), 135.7 (CH), 134.6 (CH), 129.7 (CH), 129.3 (CH), 128.6 (CH), 128.4 (CH), 124.9 (C), 124.6 (CH), 124.2 (CH), 123.6 (CH), 123.4 (CH), 115.3 (CH), 113.8 (CH), 113.5 (CH), 107.2 (C), 105.5 (C), 94.1 (CH), 93.0 (CH), 86.4 (C), 76.7 (C), 74.5 (CH), 71.4 (CH), 65.3 (CH), 64.6 (CH), 61.44 (CH_2), 61.42 (CH_2), 55.2 (CH), 55.1 (CH_3), 55.0 (CH_3), 45.6 (CH), 27.8 (CH_3), 26.2 (CH_3), 14.14 (CH_3), 14.11 (CH_3); HRMS (ESI^+): calcd. $C_{27}N_2O_5H_{26}{}^{79}Br$ for ($[M+H]^+$) 537.1020, found 537.1040, calcd. $C_{27}N_2O_5H_{26}{}^{81}Br$ for ($[M+H]^+$) 537.0999, found 539.1030.

(2S*,2'S*,3'R*,8a'R*)-Ethyl 1-acetyl-8'-bromo-2'-(4-nitrophenyl)-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (144)

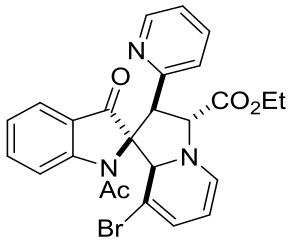


Prepared according to general procedure D:

Orange foam (35 mg, 97%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3009, 1716, 1679, 1641, 1609, 1569, 1525, 1498, 1473, 1371, 1349, 1305; NMR δ_H (400 MHz, $CDCl_3$, 4 : 3 mixture of rotamers, † indicates minor where different from major) 8.01 (2H, d, *J* = 8.8 Hz, Ar-*H*), 7.98 (2H, d, *J* = 8.8 Hz, Ar-*H*†), 7.81 (1H, d, *J* = 7.5 Hz, Ar-*H*†), 7.64 (1H, d, *J* = 7.7 Hz, Ar-*H*), 7.58-7.52 (2H, m, Ar-*H*, Ar-*H*†), 7.39 (2H, d, *J* = 8.8 Hz, Ar-*H*), 7.35-7.27 (4H, m, Ar-*H*, 3xAr-*H*†), 7.18-7.09 (2H, m, Ar-*H*, Ar-*H*†), 6.34-6.30 (3H, m, NC*H*CBr, NC*H*=CH, NC*H*†=CH), 6.19 (1H, d, *J* = 6.6 Hz, BrC=C*H*†), 6.15 (1H, d, *J* = 6.6 Hz, BrC=C*H*), 5.73 (1H, s, NC*H*†CBr), 5.18 (1H, d, *J* = 9.7 Hz, NC*H*(CO_2Et)), 5.13 (1H, d, *J* = 9.9 Hz, NC*H*†(CO_2Et)), 5.00 (1H, d, *J* = 9.7 Hz, C*H*Ar), 4.67 (1H, app. t, *J* = 6.6 Hz, NC=C*H*†), 4.61 (1H, app. t, *J* = 6.6 Hz, NC=C*H*), 4.38 (1H, d, *J* = 9.9 Hz, C*H*†Ar), 4.24-4.15 (4H, m, CH_2CH_3, CH_2†CH_3), 2.68 (3H, s, COCH_3), 2.48 (3H, s, COCH_3†), 1.24 (3H, t, *J* = 7.2 Hz, CH_2CH_3†), 1.19 (3H, t, *J* = 7.1 Hz, CH_2CH_3); NMR δ_C (100 MHz) 197.2 (C), 195.1 (C), 171.3 (C), 170.6 (C), 169.7 (C), 169.3 (C), 152.6 (C), 152.3 (C), 147.5 (C), 147.4 (C), 141.3 (C), 141.0 (C),

137.1 (CH), 137.0 (CH), 135.7 (CH), 134.6 (CH), 129.6 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 124.9 (CH), 124.5 (C), 124.4 (CH), 124.1 (CH), 123.95 (CH), 123.87 (C), 123.5 (CH), 123.4 (CH), 115.5 (CH), 115.3 (CH), 106.8 (C), 105.3 (C), 94.6 (CH), 93.5 (CH), 86.1 (C), 82.4 (C), 77.3 (C), 74.9 (CH), 71.2 (CH), 65.2 (CH), 64.8 (CH), 61.84 (CH_2), 61.80 (CH_2), 55.1 (CH), 45.7 (CH), 27.9 (CH_3), 26.1 (CH_3), 14.11 (CH_3), 14.07 (CH_3); HRMS (ESI^+): calcd. $C_{26}N_3O_6H_{23}{}^{79}Br$ for ($[M+H]^+$) 552.0765, found 552.0788, calcd. $C_{26}N_3O_6H_{23}{}^{81}Br$ for ($[M+H]^+$) 554.0744, found 554.0777.

(2S*,2'S*,3'R*,8a'R*)-Ethyl 1-acetyl-8'-bromo-3-oxo-2'-(pyridin-2-yl)-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (145)

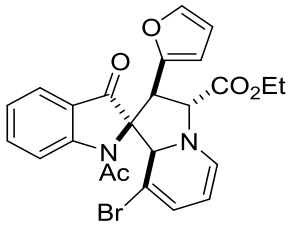


Prepared according to general procedure D:

Orange foam (37 mg, 97%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3010, 2460, 1723, 1676, 1641, 1612, 1592, 1571, 1473, 1436, 1371, 1305, 1191, 1023; NMR δ_H (400 MHz, $CDCl_3$, 5 : 4 mixture of rotamers, † indicates minor where different from major) 8.26 (1H, ddd, *J* = 4.9, 1.7, 0.9 Hz, Ar-*H*†), 8.21 (1H, ddd, *J* = 4.9, 1.6, 0.9 Hz, Ar-*H*), 7.91 (1H, ddd, *J* = 7.7, 1.6, 0.6 Hz, Ar-*H*), 7.66 (1H, ddd, *J* = 7.7, 1.7, 0.6 Hz, Ar-*H*†), 7.60-7.54 (2H, m, Ar-*H*, Ar-*H*†), 7.51, 7.43 (2H, m, Ar-*H*, Ar-*H*†), 7.28-7.19 (3H, m, 2xAr-*H*, Ar-*H*†), 7.14-6.98 (5H, m, 2xAr-*H*, 3xAr-*H*†), 6.35-6.33 (2H, m, NC*H*=CH, NC*H*†=CH), 6.28 (1H, br. s, NC*H*†CBr), 6.19 (1H, br. d, *J* = 6.5 Hz, BrC=C*H*), 6.13 (1H, br. d, *J* = 6.5, Hz, BrC=C*H*†), 5.62 (1H, s, NC*H*CBr), 5.38 (1H, d, *J* = 8.9 Hz, NC*H*(CO_2Et)), 5.26 (1H, d, *J* = 8.8 Hz, C*H*†Ar), 5.21 (1H, d, *J* = 8.8 Hz, NC*H*† (CO_2Et)), 4.61-4.57 (2H, m, NCH=C*H*, C*H*Ar), 4.52 (1H, app. t, *J* = 6.5 Hz, NCH=C*H*†), 4.31-4.22 (4H, m, C*H*$_2$$CH_3$, C*H*$_2$†$CH_3$), 2.66 (3H, s, COC*H*$_3$†), 2.24 (3H, s, COC*H*$_3$), 1.31 (3H, t, *J* = 7.2 Hz, CH_2C*H*$_3$), 1.27 (3H, t, *J* = 7.1 Hz, CH_2C*H*$_3$†); NMR δ_C (100 MHz) 197.0 (C), 195.6 (C), 172.3 (C), 171.6 (C), 169.5 (C), 168.5 (C), 154.6 (C),

154.5 (C), 152.9 (C), 148.8 (CH), 148.5 (CH), 136.6 (CH), 136.2 (CH), 136.1 (CH), 135.99 (CH), 135.96 (CH), 135.2 (CH), 129.1 (CH), 128.8 (CH), 125.3 (C), 124.8 (CH), 124.1 (CH), 123.5 (CH), 123.4 (CH), 122.8 (CH), 122.3 (CH), 121.9 (CH), 121.5 (CH), 115.5 (CH), 106.6 (C), 93.6 (CH), 92.3 (CH), 85.5 (C), 81.5 (C), 77.3 (CH), 75.9 (CH), 69.4 (CH), 65.0 (CH), 64.8 (CH), 61.7 (CH_2), 61.6 (CH_2), 56.2 (CH), 47.6 (CH), 27.8 (CH_3), 25.8 (CH_3), 14.2 (CH_3), 14.1 (CH_3); HRMS (ESI^+): calcd. $C_{25}N_3O_4H_{23}{}^{79}Br$ for ($[M+H]^+$) 508.0866, found 508.0853, calcd. $C_{25}N_3O_4H_{23}{}^{81}Br$ for ($[M+H]^+$) 510.0846, found 510.0839.

(2S*,2'S*,3'R*,8a'R*)-Ethyl 1-acetyl-8'-bromo-2'-(furan-2-yl)-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (146)

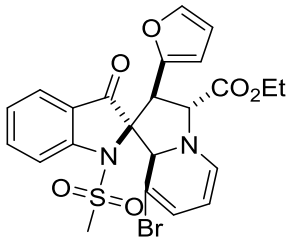


Prepared according to general procedure D:

Red oil (35 mg, 90%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3008, 1720, 1682, 1641, 1610, 1593, 1568, 1505, 1371, 1306, 1190, 1022; NMR δ_H (400 MHz, $CDCl_3$, 1 : 1 mixture of rotamers) 7.87 (1H, dd, *J* = 7.7, 0.5 Hz, Ar-*H*), 7.71 (1H, dd, *J* = 7.7, 0.5 Hz, Ar-*H*), 7.63-7.58 (2H, m, Ar-*H*), 7.47 (1H, br. d, *J* = 8.2 Hz, Ar-*H*), 7.29 (1H, m, Ar-*H*), 7.20 (1H, app. t, *J* = 7.5 Hz, Ar-*H*), 7.16 (1H, app. t, *J* = 7.5 Hz, Ar-*H*), 7.08 (1H, dd, *J* = 1.8, 0.9 Hz, Ar-*H*), 7.05 (1H, dd, *J* = 1.3, 0.5 Hz, Ar-*H*), 6.32 (1H, d, *J* = 7.1 Hz, N-C*H*=C), 6.26-6.24 (2H, m, NC*H*=CH, NC*H*CBr), 6.18-6.10 (6H, m, 4xAr-*H*, BrCC*H,* BrCC*H*), 5.64, (1H, d, *J* = 1.1 Hz, NC*H*CBr), 5.14 (1H, d, *J* = 9.4 Hz, NC*H*(CO_2Et)), 4.96 (1H, d, *J* = 9.5 Hz, NC*H*(CO_2Et)), 4.81 (1H, d, *J* = 9.4 Hz, C*H*Ar), 4.62 (1H, app. t, *J* = 7.1 Hz, NCH=C*H*), 4.54 (1H, app. t, *J* = 7.1 Hz, NCH=C*H*), 4.38 (1H, d, *J* = 9.5, C*H*Ar), 4.30-4.22 (4H, m, C*H*$_2$$CH_3$, C*H*$_2$$CH_3$), 2.67 (3H, s, O=C-C*H*$_3$), 2.43 (3H, s, O=C-C*H*$_3$), 1.31 (3H, t, *J* = 7.2 Hz, CH_2C*H*$_3$), 1.28 (3H, t, *J* = 7.1 Hz, CH_2C*H*$_3$); NMR δ_C (100 MHz) 197.0 (C), 195.2 (C), 171.5 (C), 170.9 (C), 169.3 (C), 168.6 (C), 152.7 (C), 148.7 (C), 148.5 (C), 142.3 (CH), 142.0 (CH), 136.5 (CH), 136.4 (CH), 135.8 (CH), 134.5 (CH), 128.7 (CH), 128.5 (CH), 125.0

(CH), 124.5 (C), 124.4 (CH), 124.0 (C), 123.7 (CH), 123.5 (CH), 115.6 (CH), 115.2 (CH), 110.2 (CH), 110.2 (CH), 108.2 (CH), 108.0 (CH), 106.8 (C), 105.5 (C), 94.1 (CH), 92.9 (CH), 85.1 (C), 81.1 (C), 77.2 (CH), 75.0 (CH), 70.6 (CH), 64.6 (CH), 64.4 (CH), 61.75 (CH_2), 61.71 (CH_2), 48.9 (CH), 40.1 (CH), 27.7 (CH_3), 26.2 (CH_3), 14.14 (CH_3), 14.11 (CH_3); HRMS (ESI^+): calcd. $C_{24}N_2O_5H_{22}{}^{79}Br$ for ($[M+H]^+$) 497.0707, found 497.0736, calcd. $C_{24}N_2O_5H_{22}{}^{81}Br$ for ($[M+H]^+$) 499.0686, found 499.0726.

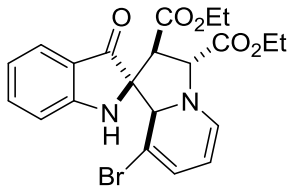
Ethyl (2S*,2'S*,3'R*,8a'R*)-8'-bromo-2'-(furan-2-yl)-1-(methylsulfonyl)-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (148)



Prepared according to general procedure D:

Yellow foam (36 mg, 97%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 2927, 2855, 1720, 1639, 1608, 1596, 1563, 1504, 1466, 1365, 1347, 1172, 971; NMR δ_H (400 MHz, $CDCl_3$) 7.68-7.58 (2H, m, Ar-*H*), 7.20 (1H, dd, *J* = 7.8, 7.2 Hz, Ar-*H*), 7.14-7.07 (2H, m, Ar-*H*), 6.30 (1H, br. d, *J* = 7.2 Hz, NC*H*=CH), 6.28-6.22 (2H, m, Ar-*H*, BrC=C*H*), 6.18-6.16 (1H, m, Ar-*H*), 6.05 (1H, d, *J* = 1.2 Hz, NC*H*C-Br), 4.91 (1H, br. d, *J* = 9.3 Hz, C*H*Ar), 4.76 (1H, br. d, *J* = 9.3 Hz, NC*H*(CO_2Et), 4.63-4.57 (1H, m, NCH=C*H*), 4.25 (1H, q, *J* = 7.1 Hz, C*H*$_2$$CH_3$), 3.34 (3H, s, S-C*H*$_3$), 1.31 (3H, t, *J* = 7.1 Hz, CH_2C*H*$_3$); NMR δ_C (100 MHz) 196.3 (C), 171.3 (C), 170.5 (C), 153.1 (C), 152.6 (C), 142.3 (CH), 137.1 (CH), 134.1 (CH), 129.1 (CH), 124.8 (CH), 124.2 (CH), 123.3 (CH), 123.0 (C), 114.1 (CH), 114.0 (CH), 110.7 (CH), 108.9 (CH), 95.0 (CH), 81.9 (C), 77.2 (CH), 61.9 (CH_2), 29.7 (CH_3), 14.1 (CH_3); HRMS (ESI^+): calcd. $C_{23}N_2O_6H_{22}S^{79}Br$ for ($[M+H]^+$) 533.0376, found 533.0375, calcd. $C_{23}N_2O_6H_{22}S^{81}Br$ for ($[M+H]^+$) 553.0356, found 535.0354.

(2S*,2'S*,3'R*,8a'R*)-Diethyl 8'-bromo-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-2',3'-dicarboxylate (134)

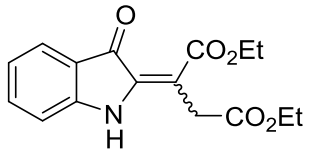


Triethylamine (2.40 mL, 17.3 mmol) was added to a stirring solution of ethyl (*Z*)-2-(3-oxoindolin-2-ylidene)acetate (2.50 g, 11.5 mmol) and 3-bromo-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (5.62 g, 17.3 mmol) in dichloromethane (1150 mL). The reaction was stirred for 4 hours at room temperature. Water (500 mL) was added and extracted with dichloromethane (2 x 200 mL), the organics were combined, dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford the desired product as a dark red gum (5.22 g, 98%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3692, 3394, 2985, 1736, 1708, 1619, 1604, 1484, 1469, 1327, 1193, 1025; NMR δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* = 7.8 Hz, Ar-*H*), 7.49-7.45 (1H, m, Ar-*H*), 6.93-6.89 (2H, m, Ar-*H*), 6.35 (1H, d, *J* = 6.4 Hz, NC*H*=CH), 6.32 (1H, d, *J* = 7.1 Hz, BrC=C*H*), 5.11 (1H, s, N*H*), 5.01 (1H, s, NC*H*CBr), 4.85 (1H, d, *J* = 6.4 Hz, NC*H*(CO_2Et)), 4.63 (1H, dd, *J* = 7.1, 6.4 Hz, NCH=C*H*), 4.33-4.27 (2H, q, *J* = 7.2 Hz, NCHCO_2C*H*$_2$), 4.07-3.99 & 3.86-3.78 (2H, m, NCHCH(CO_2C*H*$_2$), 3.75 (1H, d, *J* = 6.4 Hz, NCH(CO_2Et)C*H*), 1.34 (3H, t, *J* = 7.2 Hz, NCHCO_2CH_2C*H*$_3$), 0.69 (3H, t, *J* = 7.2 Hz, NCHCHCO_2CH_2C*H*$_3$); NMR δ_C (75 MHz) 196.9 (C), 170.5 (C), 168.4 (C), 160.7 (C), 136.8 (CH), 135.1 (CH), 129.4 (CH), 124.5 (CH),

123.1 (C), 119.9 (CH), 112.5 (CH), 105.9 (C), 94.2 (CH), 79.1 (C), 73.2 (CH), 65.3 (CH), 62.1 (CH_2), 61.6 (CH_2), 53.8 (CH), 14.2 (CH_3), 13.3 (CH_3); HRMS (ESI^+): calcd. $C_{21}N_2O_5H_{22}{}^{79}Br$ for ($[M+H]^+$) 461.0707, found 461.0708, calcd. $C_{21}N_2O_5H_{22}{}^{81}Br$ for ($[M+H]^+$) 463.0686, found 463.0694.

Diethyl 2-(3-oxoindolin-2-ylidene)succinate (135)

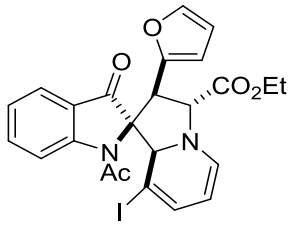


Triethylamine (18 µL, 0.13 mmol) was added to a stirring solution of 3-bromo-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (41 mg, 0.13 mmol) in dry acetonitrile (2 mL), under argon at room temperature. After 5 minutes 2-alkenylindol-3-one (18 mg, 0.08 mmol.) was added and the reaction was stirred for 4 hours. Water was added and the mixture was extracted with dichloromethane (3 x 5 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel using 4:1 (petrol : ethyl acetate) as eluent to afford the desired product as a red solid (13 mg, 80%).

mp 108-110 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3396, 1985, 1732, 1674, 1603, 1483, 1469, 1287, 1192, 1146; NMR δ_H (400 MHz, $CDCl_3$) 9.51 (1H, s, N*H*), 7.63 (1H, br. d, *J* = 7.7 Hz, Ar-*H*), 7.51-7.47 (1H, m, Ar-*H*), 6.93 (1H, td, *J* = 8.0, 0.8 Hz, Ar-*H*), 6.89 (1H, br. d, *J* = 8.0 Hz, Ar-*H*), 4.29 (2H, q, *J* = 7.2 Hz, C*H*$_2$CH$_3$), 4.17 (2H, q, *J* = 7.2 Hz, C*H*$_2$CH$_3$), 4.08 (2H, s, CC*H*$_2$), 1.33 (3H, t, *J* = 7.2 Hz, CH$_2$C*H*$_3$), 1.27 (3H, t, *J* = 7.2 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz) 188.3 (C), 171.4 (C), 169.1 (C), 151.9 (C), 141.5 (C), 137.2 (CH), 125.3 (CH), 121.0 (CH), 120.4 (C), 111.4 (CH), 104.1 (C), 61.3 (CH$_2$), 60.8 (CH$_2$), 29.9 (CH$_2$),

14.3 (CH_3), 14.2 (CH_3); HRMS (ESI^+): calcd. $C_{16}NO_5H_{17}$ for ($[M+H]^+$) 304.1179, found 304.1160.

(2S*,2'S*,3'R*,8a'R*)-Ethyl 1-acetyl-2'-(furan-2-yl)-8'-iodo-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (149)

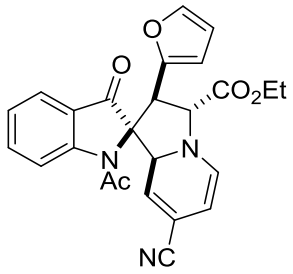


Prepared according to general procedure D:

Brown gum (36 mg, 84%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3008, 1719, 1682, 1633, 1611, 1593, 1557, 1505, 1473, 1436, 1371, 1190, 1015; NMR δ_H (500 MHz, $CDCl_3$, 1 : 1 mixture of rotamers, + 17 : 3 mixture of diastereoisomers. Only the assignments for the major diastereoisomer are reported)[103] 7.88-7.86 (1H, m, Ar-*H*), 7.71 (1H, dd, *J* = 7.7, 0.8 Hz, Ar-*H*), 7.63-7.59 (2H, m, Ar-*H*), 7.30-7.27 (2H, m, Ar-*H*), 7.20-7.14 (2H, m, Ar-*H*), 7.07-7.06 (1H, m, Ar-*H*), 7.03-7.02 (1H, m, Ar-*H*), 6.44 (1H, d, *J* = 6.8 Hz, IC=C*H*), 6.41 (1H, d, *J* = 6.9 Hz, IC=C*H*), 6.35 (1H, d, *J* = 6.8 Hz, NC*H*=CH), 6.27 (2H, m, NC*H*=CH, NC*H*CI), 6.19-6.08 (4H, m, Ar-*H*), 5.68 (1H, d, *J* = 1.3 Hz, NC*H*CI), 5.09 (1H, d, *J* = 9.3 Hz, C*H*Ar), 4.92 (1H, d, *J* = 9.7 Hz, NC*H*(CO_2Et)), 4.77 (1H, d, *J* = 9.3 Hz, NC*H*(CO_2Et)), 4.50 (1H, app. t, *J* = 6.8 Hz, NCH=C*H*), 4.41 (1H, app. t, *J* = 6.9 Hz, NCH=C*H*), 4.33 (1H, br. d, *J* = 9.7 Hz, C*H*Ar), 4.28-4.21 (4H, m, C*H*$_2$$CH_3$, C*H*$_2$$CH_3$), 2.68 (3H, s, O=C-C*H*$_3$), 2.44 (3H, s, O=C-C*H*$_3$), 1.31-1.21 (6H, m, CH_2C*H*$_3$, CH_2C*H*$_3$); NMR δ_C (125 MHz) 197.0 (C), 195.4 (C), 171.4 (C), 170.8 (C), 169.3 (C), 168.7 (C), 153.0 (C), 148.6 (C), 148.6 (C), 142.3 (CH), 142.0 (CH), 137.3 (CH), 137.2 (CH), 136.50 (CH),

136.46 (CH), 136.4 (CH), 135.6 (CH), 124.9 (CH), 124.7 (C), 124.7 (C), 124.4 (CH), 123.7 (CH), 123.5 (CH), 115.3 (CH), 110.19 (CH), 110.15 (CH), 108.2 (CH), 108.1 (CH), 95.2 (CH), 94.0 (CH), 85.5 (C), 77.6 (C), 77.2 (CH), 76.4 (C), 76.3 (CH), 70.3 (CH), 65.7 (CH), 64.4 (CH), 61.74 (CH_2), 61.70 (CH_2), 49.0 (CH), 39.7 (CH), 28.0 (CH_3), 26.3 (CH_3), 14.13 (CH_3), 14.12 (CH_3); HRMS (ESI^+): calcd. $C_{24}N_2O_5H_{22}I$ for ($[M+H]^+$) 545.0568, found 545.0599.

(2S*,2'S*,3'R*,8a'S*)-Ethyl 1-acetyl-7'-cyano-2'-(furan-2-yl)-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (150)

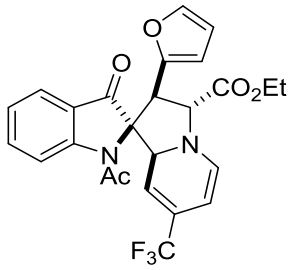


Triethylamine (17 µL, 0.12 mmol) was added to 3-bromo-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide (26 mg, 0.12 mmol) in dry dichloromethane (0.5 mL), under argon and the mixture stirred at room temperature. After 5 minutes 1-acetyl-2-(furan-2-ylmethylene)indolin-3-one (20 mg, 0.08 mmol) was added and the reaction was stirred at room temperature for 2 hours. Water was added and the organic layer was extracted with dichloromethane (3 x 3 mL), the organics were combined dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the desired product as an orange foam (33 mg, 94%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3011, 2986, 2230, 1722, 1683, 1634, 1609, 1472, 1371, 1304, 1020; NMR δ_H (400 MHz, $CDCl_3$, 1 : 1 mixture of rotamers, + 87 : 13 mixture of diastereoisomers. Only the assignments for the major diastereoisomer are reported)[103] 7.88 (1H, d, *J* = 7.7 Hz, Ar-*H*), 7.73-7.65 (3H, m, Ar-*H*), 7.53 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.41 (1H, d, *J* = 8.4 Hz, Ar-*H*), 7.30-7.26 (1H, m, Ar-*H*), 7.23 (1H, app. t, *J* = 7.4 Hz, Ar-*H*), 7.09-7.08 (2H, m, Ar-*H*), 6.34 (1H, d, *J* = 7.3 Hz, NC*H*=CH), 6.28 (1H, d, *J* = 7.4 Hz, NC*H*=CH),

6.21-6.10 (5H, m, 4xAr-*H*, NC*H*CH=C), 5.42 (1H, d, *J* = 2.9 Hz, NC*H*CH=C), 5.17 (1H, d, *J* = 9.4 Hz, NC*H*(CO_2Et)), 5.12-5.11 (1H, m, N≡CC=C*H*), 4.94 (1H, d, *J* = 9.4 Hz, NC*H*(CO_2Et)), 4.90-4.86 (2H, m, N≡CC=C*H*, C*H*Ar), 4.68 (1H, br. d, *J* = 7.3 Hz, NCH=C*H*), 7.58 (1H, br. d, *J* = 7.4 Hz, NCH=C*H*), 4.50 (1H, d, *J* = 9.4 Hz, C*H*Ar), 4.30-4.21 (4H, m, C$H_2$$CH_3$, C$H_2$$CH_3$), 2.67 (3H, s, O=C-C$H_3$), 2.39 (3H, s, O=C-C$H_3$), 1.32-1.24 (6H, m, CH_2CH_3, CH_2CH_3); NMR δ_C (100 MHz) 197.2 (C), 194.1 (C), 171.2 (C), 170.4 (C), 169.2 (C), 168.7 (C), 152.5 (C), 152.2 (C), 148.4 (C), 148.3 (C), 142.4 (CH), 142.2 (CH), 137.7 (CH), 137.1 (CH), 136.9 (CH), 125.4 (CH), 125.0 (CH), 124.5 (CH), 124.1 (CH), 123.3 (C), 122.9 (C), 120.9 (CH), 118.6 (CH), 117.8 (C), 117.6 (C), 115.5 (CH), 115.4 (CH), 113.4 (C), 113.2 (C), 110.32 (CH), 110.27 (CH), 108.1 (CH), 108.0 (CH), 92.1 (CH), 90.8 (CH), 84.5 (C), 79.9 (C), 77.3 (CH), 69.7 (CH), 69.5 (CH), 64.7 (CH), 62.0 (CH_2), 61.9 (CH_2), 61.3 (CH), 48.5 (CH), 39.5 (CH), 27.4 (CH_3), 26.2 (CH_3), 14.14 (CH_3), 14.10 (CH_3); HRMS (ESI^+): calcd. $C_{25}N_3O_5H_{22}$ for ($[M+H]^+$) 444.1544, found 444.1555.

(2S*,2'S*,3'R*,8a'S*)-Ethyl 1-acetyl-2'-(furan-2-yl)-3-oxo-7'-(trifluoromethyl)-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (151)

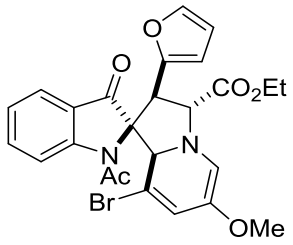


Prepared according to general procedure D:

Yellow foam (38 mg, 99%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3009, 2986, 2940, 1722, 1686, 1609, 1590, 1505, 1471, 1372, 1307, 1172, 1129, 1046; NMR δ_H (400 MHz, $CDCl_3$, 3 : 2 mixture of rotamers, † indicates minor where different from major) 7.90 (1H, dd, *J* = 7.7, 0.9 Hz, Ar-*H*), 7.73-7.64 (3H, m, Ar-*H*, 2xAr-*H*†), 7.55 (1H, br. d, *J* = 8.5 Hz, Ar-*H*†), 7.39 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.29-7.25 (1H, m, Ar-*H*), 7.21 (1H, app. t, *J* = 7.4 Hz, Ar-*H*†), 7.10-7.07 (2H, m, Ar-*H*, Ar-*H*†), 6.36 (1H, d, *J* = 7.5 Hz, NC*H*=CH), 6.32 (1H, d, *J* = 7.5 Hz, NC*H*†=CH), 6.21-6.09 (5H, m, 2xAr-*H*, 2xAr-*H*†, F_3CC=C*H*†), 5.44-5.42 (1H, m, NC*H*CH=C), 5.20 (1H, d, *J* = 9.4 Hz, NC*H*†(CO_2Et)), 4.98 (1H, d, *J* = 9.2 Hz NC*H*(CO_2Et)), 4.94-4.92 (1H, m, NC*H*†CH=C), 4.90 (1H, d, *J* = 9.4 Hz, C*H*†Ar), 4.77 (1H, dd, *J* = 7.5, 1.5 Hz, NCH=C*H*), 4.70-4.66 (2H, m, F_3CC=C*H*, NCH=C*H*†), 4.53 (1H, d, *J* = 9.2 Hz, C*H*Ar), 4.32-4.23 (4H, m, C$H_2$$CH_3$, C$H_2$†$CH_3$), 2.69 (3H, s, COC$H_3$†), 2.39 (3H, s, COC$H_3$), 1.34-1.27 (6H, m, CH_2CH_3, CH_2CH_3†); NMR δ_C (100 MHz) 197.2 (C), 194.4 (C), 171.5 (C), 170.8 (C), 169.1 (C), 168.3 (C), 152.6 (C), 152.2 (C), 148.8 (C, q, *J* = 8.8 Hz), 142.3 (CH), 142.0

(CH), 137.5 (CH), 137.4 (CH), 136.81 (CH), 136.78 (CH), 126.6 (CF_3, q, *J* = 271.5 Hz), 125.3 (CH), 124.7 (CH), 124.3 (CH), 123.8 (CH), 123.5 (C), 123.0 (C), 122.7 (CF_3, q, *J* = 272.2 Hz), 115.5 (CH), 115.4 (CH), 110.3 (CH), 110.2 (CH), 107.95 (CH), 107.88 (CH), 107.8 (CH), 107.6 (CH), 89.7 (C, q, J = 2.9 Hz), 88.1 (C, q, *J* = 2.2 Hz), 85.2 (C), 80.2 (C), 77.2 (CH), 70.2 (CH), 69.6 (CH), 65.0 (CH), 61.83 (CH_2), 61.79 (CH_2), 61.1 (CH), 48.5 (CH), 39.6 (CH), 27.4 (CH_3), 26.0 (CH_3), 14.14 (CH_3), 14.11 (CH_3); HRMS (ESI^+): calcd. $C_{25}N_2O_5H_{22}F_3$ for ($[M+H]^+$) 487.1475, found 487.1494.

(2S*,2'S*,3'R*,8a'R*)-Ethyl 1-acetyl-8'-bromo-2'-(furan-2-yl)-6'-methoxy-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (156)

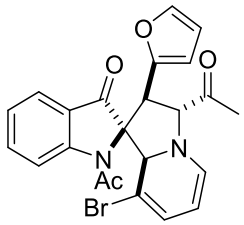


Prepared according to general procedure D:

Orange foam (40 mg, 95%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3011, 2908, 1720, 1672, 1644, 1609, 1504, 1372, 1306, 1240, 1023; NMR δ_H (400 MHz, $CDCl_3$, 3 : 2 mixture of rotamers, † indicates minor where different from major) 7.86 (1H, dd, *J* = 7.7, 0.8 Hz, Ar-*H*†), 7.65 (1H, br. d, *J* = 7.6 Hz, Ar-*H*), 7.61-7.57 (2H, m, Ar-*H*, Ar-*H*†), 7.29-7.27 (2H, m, Ar-*H*, Ar-*H*†), 7.20 (1H, app. t, *J* = 7.4 Hz, Ar-*H*†), 7.12 (1H, app. t, *J* = 7.6 Hz, Ar-*H*), 7.06-7.04 (2H, m, Ar-*H*, Ar-*H*†), 6.26 (1H, br. s, NC*H*†=CH), 6.19-6.15 (2H, m, Ar-*H*†, NC*H*=CH), 6.11-6.07 (3H, m, 2xAr-*H*, Ar-*H*†), 5.83 (1H, br. s, NC*H*CBr), 5.21 (1H, br. d, *J* = 10.0 Hz, C*H*Ar), 5.13 (1H, br. s, NC*H*†CBr), 5.04 (1H, br. s, BrC=C*H*†), 5.01 (1H, d, *J* = 9.5 Hz, NC*H*† (CO_2Et)), 4.99 (1H, br. s, BrC=C*H*), 4.83 (1H, d, *J* = 10.0 Hz, NC*H*(CO_2Et)), 4.50 (1H, d, *J* = 9.5 Hz, C*H*†Ar), 4.31-4.15 (4H, m, C*H*$_2$$CH_3$, C*H*$_2$†$CH_3$), 3.03 (3H, s, O-C*H*$_3$†), 3.01 (3H, s, O-C*H*$_3$), 2.65 (3H, s, COC*H*$_3$), 2.33 (3H, s, COC*H*$_3$†), 1.30 (3H, t, *J* = 7.1 Hz, CH_2C*H*$_3$†), 1.24 (3H, t, *J* = 7.2 Hz, CH_2C*H*$_3$); NMR δ_C (100 MHz) 196.4 (C), 194.9 (C), 171.8 (C), 170.8 (C), 168.9 (C), 167.9 (C), 152.3 (C), 149.0 (C), 148.2 (C), 146.7 (C),

145.8 (C), 142.2 (CH), 141.9 (CH), 136.2 (CH), 136.1 (CH), 129.0 (CH), 126.2 (CH), 125.0 (CH), 124.5 (CH), 123.8 (C), 123.7 (CH), 123.4 (CH), 123.3 (CH), 114.9 (CH), 110.2 (CH), 108.2 (CH), 107.7 (CH), 99.4 (CH), 98.9 (CH), 86.9 (C), 84.2 (C), 79.7 (C), 77.3 (CH), 71.2 (CH), 71.1 (CH), 65.2 (CH), 61.7 (CH_2), 61.6 (CH_2), 60.2 (CH), 54.7 (CH_3), 54.4 (CH_3), 48.8 (CH), 41.7 (C), 27.4 (CH_3), 26.0 (CH_3), 14.2 (CH_3), 14.1 (CH_3); HRMS (ESI^+): calcd. $C_{25}N_2O_6H_{24}{}^{79}Br$ for ($[M+H]^+$) 527.0812, found 527.0795, calcd. $C_{25}N_2O_6H_{24}{}^{81}Br$ for ($[M+H]^+$) 529.0792, found 529.0791.

1,1'-((2S*,2'S*,3'R*,8a'R*)-8'-Bromo-2'-(furan-2-yl)-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-1,3'-diyl)bis(ethan-1-one) (157)

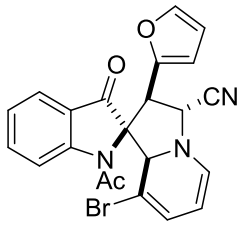


Prepared according to general procedure D:

Orange foam (37 mg, 100%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3055, 1717, 1672, 1642, 1612, 1473, 1371, 1306; NMR δ_H (500 MHz, $CDCl_3$, 3 : 2 mixture of rotamers, † indicates minor where different from major) 7.85 (1H, dd, *J* = 7.7, 1.0 Hz, Ar-*H*†), 7.69 (1H, d, *J* = 7.6, 1.0 Hz, Ar-*H*), 7.62-7.58 (2H, m, Ar-*H*, Ar-*H*†), 7.45 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.28-7.27 (1H, m, Ar-*H*†), 7.2 (1H, app. t, *J* = 7.4 Hz, Ar-*H*†), 7.15 (1H, app. t, *J* = 7.5 Hz, Ar-*H*), 7.08-7.03 (2H, m, Ar-*H*, Ar-*H*†), 6.28 (1H, s, NC*H*CBr), 6.18-6.10 (7H, m, 2xAr-*H*, 2xAr-*H*†, BrC=C*H*†, NC*H*CH, NC*H*†CH), 6.05 (1H, d, *J* = 7.1 Hz, BrC=C*H*), 5.60 (1H, d, *J* = 1.3 Hz, NC*H*†CBr), 4.93 (1H, d, *J* = 9.7 Hz, C*H*Ar), 4.88 (1H, d, *J* = 9.8 Hz, NC*H*†($COCH_3$), 4.67 (1H, d, *J* = 9.7 Hz, NC*H*($COCH_3$), 4.64 (1H, app. t, *J* = 7.0 Hz, NCH=C*H*†), 4.56 (1H, app. t, *J* = 7.1 Hz, NCH=C*H*), 4.05 (1H, d, *J* = 9.8 Hz, NCH($COCH_3$)C*H*†), 2.67 (3H, s, NCOCH_3), 2.41 (3H, s, NCOCH_3†), 2.30 (3H, s, NCHCOCH_3†), 2.27 (3H, s, NCHCOCH_3); NMR δ_C (125 MHz) 207.1 (C), 207.0 (C), 196.5 (C), 195.4 (C), 169.6 (C), 168.5 (C), 152.8 (C), 152.2 (C), 148.4 (C), 148.1 (C), 142.6 (CH), 142.2 (CH), 136.6 (CH), 136.5 (CH), 135.5 (CH), 134.0 (CH), 128.7 (CH),

128.4 (CH), 125.0 (CH), 124.6 (C), 124.4 (CH), 123.8 (CH), 123.6 (CH), 115.5 (CH), 115.2 (CH), 110.4 (CH), 110.3 (CH), 108.6 (CH), 108.5 (CH), 107.0 (C), 105.6 (C), 94.6 (CH), 93.3 (CH), 85.0 (C), 81.2 (C), 77.6 (CH), 77.3 (CH), 75.3 (CH), 71.7 (CH), 64.3 (CH), 48.4 (CH), 39.3 (CH), 27.7 (CH_3), 26.2 (CH_3), 26.0 (CH_3), 25.1 (CH_3); HRMS (ESI^+): calcd. $C_{23}N_2O_4H_{20}{}^{79}Br$ for ($[M+H]^+$) 467.0601, found 467.0605, calcd. $C_{23}N_2O_4H_{20}{}^{81}Br$ for ($[M+H]^+$) 469.0580, found 469.0589.

(2S*,2'S*,3'R*,8a'R*)-1-Acetyl-8'-bromo-2'-(furan-2-yl)-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carbonitrile (158)

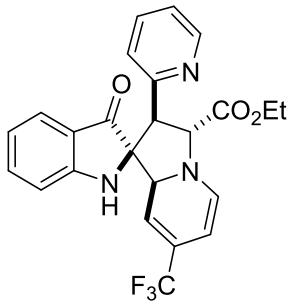


Prepared according to general procedure D:

Red foam (35 mg, 97%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3694, 3604, 2959, 2928, 2338, 1720, 1677, 1643, 1607, 1473, 1437, 1372, 1307, 909; NMR δ_H (500 MHz, $CDCl_3$, 1 : 1 mixture of rotamers + 0.3 minor diastereoisomer, *indicates minor where different from major) 7.90-7.86 (2H, m, Ar-*H*, Ar-*H**), 7.72 (1H, ddd, *J* = 7.7, 1.0, 0.5 Hz, Ar-*H*), 7.68-7.61 (4H, m, 2xAr-*H*, 2xAr-*H**), 7.44 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.34 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.24-7.16 (3H, m, 2xAr-*H*, Ar-*H**), 7.14-7.11 (3H, m, 2xAr-*H*, Ar-*H**), 6.67 (1H, d, *J* = 7.4 Hz, NC*H**=CH), 6.43 (1H, d, *J* = 6.5 Hz, BrC=C*H**), 6.27-6.11 (11H, m, 4xAr-*H*, 2xAr-*H**, NC*H*=CH, NC*H*=CH, BrC=C*H*, BrC=C*H*, NC*H*CBr), 5.74 (1H, s, NC*H**CBr), 5.64 (1H, d, *J* = 1.6 Hz, NC*H*CBr), 5.50 (1H, d, *J* = 10.7 Hz, NC*H**(CN)), 5.31 (1H, d, *J* = 10.3 Hz, NC*H*(CN)), 5.28 (1H, d, *J* = 10.4 Hz, NC*H*(CN)), 5.12 (1H, d, *J* = 10.4 Hz, C*H*Ar), 4.94 (1H, dd, *J* = 7.4, 6.5 Hz, NCH=C*H**), 4.75 (1H, dd, *J* = 7.1, 6.6 Hz, NCH=C*H*), 4.72 (1H, dd, *J* = 7.3, 6.4 Hz, NCH=C*H*), 4.35 (1H, d, *J* = 10.3 Hz, C*H*Ar), 3.73 (1H, d, *J* = 10.7 Hz, C*H**Ar), 2.67 (3H, s, CH_3), 2.47 (3H, s, CH_3), 2.38 (3H, s, CH_3*); NMR δ_C (125 MHz) 196.5 (C), 196.4 (C), 194.2 (C), 169.4 (C), 169.2 (C), 169.0 (C), 152.5 (C),

152.4 (C), 151.0 (C), 146.3 (C), 145.6 (C), 145.2 (C), 143.3 (CH), 143.0 (CH), 142.7 (CH), 136.97 (CH), 136.96 (CH), 136.8 (CH), 133.2 (CH), 131.9 (CH), 129.5 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 125.3 (CH), 124.9 (CH), 124.6 (C), 124.5 (CH), 124.3 (C), 124.2 (CH), 124.0 (CH), 123.9 (CH), 123.6 (C), 118.7 (C), 117.5 (C), 115.6 (CH), 115.2 (CH), 115.09 (C), 115.07 (CH), 110.5 (CH), 110.4 (CH), 109.6 (CH), 109.0 (CH), 108.6 (CH), 107.9 (C), 106.5 (C), 97.3 (CH), 97.1 (CH), 95.7 (CH), 83.9 (C), 83.4 (C), 79.2 (C), 77.2 (CH), 73.7 (CH), 69.7 (CH), 63.2 (CH), 59.3 (CH), 56.0 (CH), 53.1 (CH), 52.4 (CH), 50.5 (CH), 41.4 (CH), 27.6 (CH_3), 26.7 (CH_3), 26.2 (CH_3); HRMS (ESI^+): calcd. $C_{22}N_3O_3H_{17}{}^{79}Br$ for ($[M+H]^+$) 450.0448, found 450.0448, calcd. $C_{22}N_3O_3H_{17}{}^{81}Br$ for ($[M+H]^+$) 452.0427, found 452.0432.

Ethyl (2S*,2'S*,3'R*,8a'S*)-3-oxo-2'-(pyridin-2-yl)-7'-(trifluoromethyl)-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate (166)

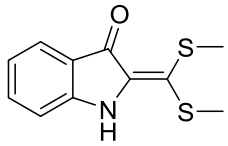


Prepared according to general procedure D:

Orange foam (110 mg, 97%); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3414, 3008, 2986, 1740, 1694, 1619, 1592, 1487, 1469, 1442, 1321, 1304, 1262, 1172, 1128, 1043; NMR δ_H (400 MHz, $CDCl_3$, isolated as a 9 : 1 mixture of diastereoisomers. Only the assignments for the major diastereoisomer are reported)[103] 8.51 (1H, ddd, *J* = 4.8, 1.7, 0.9 Hz, Ar-*H*), 7.50 (1H, br. d, *J* = 7.2 Hz, Ar-*H*), 7.43 (1H, td, *J* = 7.7, 1.7 Hz, Ar-*H*), 7.34-7.29 (1H, m, Ar-*H*), 7.10 (1H, ddd, *J* = 7.7, 4.8, 1.2 Hz, Ar-*H*), 6.97 (1H, ddd, *J* = 7.7, 1.2, 0.9 Hz, Ar-*H*), 6.75 (1H, app. t, *J* = 7.2 Hz, Ar-*H*), 6.71 (1H, br. d, *J* = 8.3 Hz, Ar-*H*), 6.42 (1H, d, *J* = 7.5 Hz, NC*H*=CH), 5.75 (1H, br. s, N*H*), 5.18-5.16 (1H, m, NC*H*CH=*C*), 5.11 (1H, d, *J* = 7.9 Hz, NC*H*(CO_2Et)), 5.04-5.01 (1H, m, F_3CC=C*H*), 4.81 (1H, dd, *J* = 7.5, 1.8 Hz, F_3CCC*H*), 4.28-4.18 (3H, m, C*H*$_2$$CH_3$, C*H*Ar), 1.24 (3H, t, *J* = 7.1 Hz, CH_2C*H*$_3$); NMR δ_C (100 MHz) 197.5 (C), 171.4 (C), 161.3 (C), 154.1 (C), 148.9 (CH), 137.6 (CH), 136.74 (CH), 136.66 (CH), 132.2 (C, q, *J* = 32.9 Hz), 124.4 (CH), 124.2 (CH), 122.8 (CH), 121.2 (C), 119.7 (CF_3, q, *J* = 273.0 Hz), 119.4 (CH), 112.7 (CH), 110.9 (CH, q, *J* = 5.9 Hz), 89.8 (CH, q,

J = 2.2 Hz), 80.7 (C), 68.5 (CH), 67.1 (CH), 61.8 (CH_2), 54.8 (CH), 14.1 (CH_3); HRMS (ESI^+): calcd. $C_{24}N_3O_3H_{21}F_3$ for ($[M+H]^+$) 456.1530, found 456.1534.

2-(Bis(methylthio)methylene)indolin-3-one (160)[53]



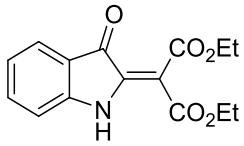
2-((Carboxymethyl)amino)benzoic acid (1.00 g, 5.10 mmol) was added to a stirring solution of potassium hydroxide (14.0 g, 250 mmol) in water (3 mL), the mixture was heated to 220 °C for 3 hours then cooled to 0 °C. Water (25 mL) and carbon disulphide (0.40 mL, 6.70 mmol) were added and the mixture was stirred for 2.5 hours and allowed to warm to room temperature. Methyl iodide (0.64 mL, 10.3 mmol) was added and the reaction was stirred for 16 hours. Saturated aq. ammonium chloride (60 mL) was added and the mixture was extracted with dichloromethane (3 x 50 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude material was purified using column chromatography on silica gel using 19:1 (petrol : ethyl acetate) as eluent to afford the desired compound as a dark red solid (11 mg, 1%).

mp 148-149 °C (mp lit.[53] 158 °C); IR_{sol} (cm^{-1}) 3691, 3435, 2927, 1670, 1621, 1542, 1484, 1465, 1372, 1319, 1193, 1146, 1099; NMR δ_H (400 MHz, $CDCl_3$) 7.71 (1H, br. d, *J* = 7.7 Hz, Ar-*H*), 7.43 (1H, ddd, *J* = 8.1, 7.2, 1.3 Hz, Ar-*H*), 7.03 (1H, br. s, N*H*), 7.01-6.89 (2H, m, Ar-*H*), 2.53 (3H, s, SCH_3), 2.49 (3H, s, SCH_3); NMR δ_C (100 MHz) 181.3 (C), 149.5 (C), 137.2 (C), 135.3 (CH), 127.5 (C), 124.9 (CH),

122.6 (C), 119.8 (CH), 111.1 (CH), 17.7 (CH_3), 17.4 (CH_3); HRMS (ESI^+): calcd. $C_{11}NOS_2H_{11}$ for ($[M+H]^+$) 238.0355, found 238.0352.

Data consistent with literature values.[53]

Diethyl 2-(3-oxoindolin-2-ylidene)malonate (164)[17]



Indole (0.30 g, 2.56 mmol) was added to a stirring solution of TEMPO (0.32 g, 2.05 mmol), copper sulphate pentahydrate (0.13 g, 0.51 mmol) and diethyl malonate (0.78 mL, 5.13 mmol) in toluene (2.5 mL). The reaction was heated to 85 °C for 20 hours, the solvent was removed *in vacuo* to afford a crude brown oil, which was purified using column chromatography on silica gel using 4:1 (petrol : ethyl acetate) as eluent to afford the desired compound as an orange solid (370 mg, 51%).

mp 106-108 °C (mp lit.[17] 114 °C); IR_{sol} (cm^{-1}) 3400, 2986, 2940, 2906, 1725, 1684, 1611, 1482, 1283, 1193; NMR δ_H (400 MHz, $CDCl_3$) 9.15 (1H, br. s, N*H*), 7.67 (1H, ddt, *J* = 7.5, 1.4, 0.7 Hz, Ar-*H*), 7.51 (1H, ddd, *J* = 8.0, 7.5, 1.4 Hz, Ar-*H*), 7.00 (1H, td, *J* = 7.5, 0.7 Hz, Ar-*H*), 6.93 (1H, dt, *J* = 8.0, 0.7 Hz, Ar-*H*), 4.42 (2H, q, *J* = 7.2, CH_2), 4.30 (2H, q, *J* = 7.2 Hz, CH_2), 1.39 (3H, t, *J* = 7.2 Hz, CH_3), 1.34 (3H, t, *J* = 7.2 Hz, CH_3); NMR δ_C (100 MHz) 185.7 (C), 166.1 (C), 164.7 (C), 152.2 (C), 142.5 (C), 137.5 (CH), 125.7 (CH), 122.1 (CH), 119.9 (C), 111.8 (CH), 111.8 (C), 62.0 (CH_2), 61.7 (CH_2), 14.1 (CH_3), 13.9 (CH_3); HRMS (ESI^+): calcd. $C_{15}NO_5H_{15}Na$ for ($[M+Na]^+$) 312.0842, found 312.0835.

Data consistent with literature values.[17]

Di(cyclopenta-1,3-dien-1-yl)dimethyltitanium (236)[104]

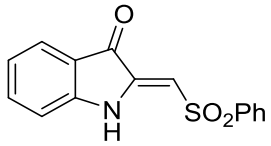


Methyl lithium (2.2M in Et_2O) (3.64 mL, 8.00 mmol) was added to a stirring solution of dichloro titanocene (1.00 g, 4.00 mmol) in dry diethyl ether (45 mL) at 0 °C under argon and stirred for 10 minutes, the reaction mixture was then allowed to warm to room temperature and stirred for a further 4 hours. Water (50 mL) was added and the mixture was extracted with diethyl ether (2 x 40 mL), the organics were combined, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to afford the desired product as an orange solid (0.61 g, 73%).

IR_{sol} (cm^{-1}) 3692, 3009, 2952, 2883, 1020, 821; NMR δ_H (400 MHz, $CDCl_3$) 6.07 (10H, s, 10xC*H*), -0.13 (6H, s, 2xCH_3); NMR δ_C (100 MHz) 113.1 (CH), 45.5 (CH_3); HRMS (ESI^+): calcd. $C_{12}H_{16}Ti$ for ($[M+H]^+$) 209.0804, found 209.0446.

Data consistent with literature values.[104]

(*Z*)-2-((Phenylsulfonyl)methylene)indolin-3-one (245)



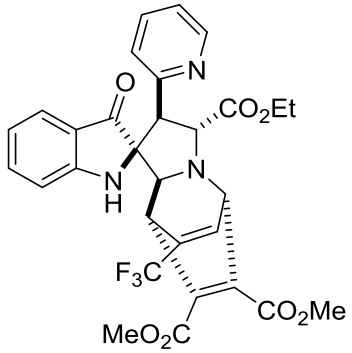
Phosphorus oxychloride (0.59 mL, 6.28 mmol) was added dropwise to a stirring solution of sodium hydride (262 mg, 6.55 mmol) and spiro[indoline-3,2'-[1,3]dioxolan]-2-one (1.00 g, 5.24 mmol) in dry THF (24 mL) under argon at 0 °C and allowed to warm to room temperature. The reaction was heated to 40 °C for 2 hours then cooled to -78 °C. In a separate flask LDA (20.9 mmol) was freshly prepared in dry THF (6 mL) at -78 °C under argon and (methylsulfonyl)benzene (3.10 g, 19.9 mmol) in dry THF (10 mL) was added dropwise and stirred for 10 minutes then the slurry was poured into the first flask. The mixture was stirred at -78 °C for 20 minutes, allowed to warm to 0 °C and water (20 mL) was added dropwise then allowed to warm to room temperature. Water (100 mL) and ethyl acetate (80 mL) was added, the organic was separated and the aqueous layer was washed with ethyl acetate (2 x 80 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude intermediate was partially purified using column chromatography on silica gel using 4:1 to 2:1 (petrol : ethyl acetate) as eluent to afford a colourless solid (1.62 g). The solid was dissolved in methanol (16 mL) followed by dropwise addition of HCl (12M) (2.32 mL, 27.8 mmol) under argon and stirred for 30 minutes then the reaction mixture was concentrated *in vacuo*. The crude product was purified column

chromatography using on silica gel using 4:1 (petrol : ethyl acetate) as eluent to afford the desired compound as an orange solid (180 mg, 12%).

mp 162-164 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3359, 1712, 1613, 1266, 1140, 1074, 575, 554; NMR δ_H (400 MHz, $CDCl_3$) 8.67 (1H, s, N-*H*), 8.01 – 7.94 (2H, m, Ar-*H*), 7.71–7.63 (2H, m, Ar-*H*), 7.63–7.51 (3H, m, Ar-*H*), 7.08 – 6.96 (2H, m, Ar-*H*), 6.15 (1H, s, SO_2-C*H*); NMR δ_C (100 MHz) 185.8 (C), 152.8 (C), 141.4 (C), 140.6 (C), 138.0 (CH), 133.8 (CH), 129.5 (CH), 127.1 (CH), 125.8 (CH), 122.2 (CH), 119.5 (C), 112.0 (CH), 102.0 (CH); HRMS (ESI^+): calcd. $C_{15}NO_3H_{12}S$ for ($[M+H]^+$) 286.0532, found 286.0530.

5.4 **1,2-Dihydromodification of cycloadducts**

3'-Ethyl 6',7'-dimethyl (2S*,2'S*,3'R*,5'S*,8'S*,8a'S*)-3-oxo-2'-(pyridin-2-yl)-9'-(trifluoromethyl)-2',3',8',8a'-tetrahydro-5'H-spiro[indoline-2,1'-[5,8]ethenoindolizine]-3',6',7'-tricarboxylate (173)

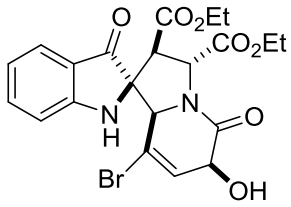


Dimethyl acetylenedicarboxylate (0.05 mL, 0.41 mmol) was added to a stirring solution of ethyl (2S*,2'S*,3'R*,8a'S*)-3-oxo-2'-(pyridin-2-yl)-7'-(trifluoromethyl)-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-3'-carboxylate **166** (0.12 g, 0.27 mmol) in dichloromethane (5 mL) under argon. The reaction was stirred for 48 hours then the reaction was concentrated *in vacuo*, the residue was purified using column chromatography using a gradient elution of 3:1 – 2:1 (petrol : ethyl acetate) to afford the desired product as an orange foam (57 mg, 39%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3691, 3011, 2953, 1724, 1706, 1437, 1323, 1303, 1248, 1188, 1137; NMR δ_H (600 MHz, C_6D_6) 8.07 (1H, br. d, *J* = 4.7 Hz, Ar-*H*), 8.00 (1H, s, NC*H*CH=CCF_3), 7.34 (1H, d, *J* = 7.6 Hz, Ar-*H*), 6.95 (1H, s, NCHC*H*=CCF_3), 6.92 (1H, d, *J* = 6.4 Hz, F_3CCC*H*), 6.75 (1H, dd, *J* = 8.2, 7.3 Hz, Ar-*H*), 6.52 (1H, dt, *J* =6.2, 1.6 Hz,

Ar-*H*), 6.47 (1H, d, *J* = 7.6 Hz, Ar-*H*), 6.27 (1H, dd, *J* = 6.2, 4.7 Hz, Ar-*H*), 6.25-6.20 (2H, m, Ar-*H*), 5.67 (1H, br. d, *J* = 6.4 Hz, NC*H*CCHCCF$_3$*)*, 5.38 (1H, br. s, N*H*), 5.03 (1H, d, *J* = 9.5 Hz, NC*H*CO$_2$Et), 4.36 (1H, d, *J* = 9.5 Hz, EtO$_2$CCHC*H*), 3.91-3.94 (2H, m, CH$_2$CH$_3$), 4.43-3.39 (6H, m, CO$_2$C*H*$_3$, CO$_2$C*H*$_3$), 0.93 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); NMR δ_C (150 MHz) 197.7 (C), 169.6 (C), 167.6 (C), 166.7 (C), 160.8 (C), 153.0 (C), 148.5 (CH), 144.8 (CH), 138.2 (C), 138.0 (C, q, *J* = 31.0 Hz), 137.5 (CH), 136.5 (CH), 131.0 (CH, q, *J* = 5.5 Hz), 129.2 (CH, q, *J* = 1.1 Hz), 124.7 (CH), 124.4 (CH), 122.8 (CF$_3$, q, *J* = 274.2 Hz), 122.7 (CH), 121.6 (C), 120.4 (CH), 112.9 (CH), 101.7 (C), 76.0 (C), 67.7 (CH), 65.7 (CH), 62.0 (CH$_2$), 55.6 (CH), 51.8 (CH$_3$), 51.1 (CH$_3$), 13.8 (CH$_3$); HRMS (ESI$^+$): calcd. $C_{30}N_3O_7H_{27}F_3$ for ([M+H]$^+$) 598.1796, found 598.1810.

Diethyl (2S*,2'R*,3'R*,6'S*,8a'R*)-8'-bromo-6'-hydroxy-3,5'-dioxo-2',3',6',8a'-tetrahydro-5'H-spiro[indoline-2,1'-indolizine]-2',3'-dicarboxylate (168)



*m*CPBA (115 mg, 0.50 mmol) was added to a stirring solution of (2S*,2'S*,3'R*,8a'R*)-diethyl 8'-bromo-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-2',3'-dicarboxylate **134** (115 mg, 0.25 mmol) in dry methanol (5 mL) under argon at -78 °C. After 1 hour the reaction mixture was concentrated *in vacuo* to afford the crude product, which was purified using column chromatography on silica gel using 1% methanol in dichloromethane as eluent to afford the desired compound as an orange oil (84 mg, 68%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3691, 3611, 3009, 2974, 2930, 1742, 1672, 1301, 946, 909; NMR δ_H (400 MHz, $CDCl_3$) 7.69 (1H, br. d, *J* = 7.4 Hz, Ar-*H*), 7.48 (1H, ddd, *J* = 8.4, 7.4, 1.2 Hz, Ar-*H*), 6.92-6.87 (2H, m, Ar-*H*), 6.41 (1H, dd, *J* = 2.8, 2.1 Hz, BrC=C*H*), 5.91 (1H, s, N*H*), 5.46 (1H, d, *J* = 8.8 Hz, NC*H*(CO_2Et), 4.93 (1H, dd, *J* = 5.3, 2.1 Hz, NC*H*CBr), 4.74 (1H, dd, *J* = 5.3, 2.8 Hz, HOC*H*), 4.28 (2H, q, *J* = 7.2 Hz, NCHCO_2CH_2), 3.69-3.80 (2H, m, NCHCHCO_2CH_2), 3.73 (1H, d, *J* = 8.8 Hz, NCHC*H*(CO_2Et), 2.0 (1H, br. s, O*H*), 1.30 (3H, t, *J* = 7.2 Hz, NCHCO_2CH_2CH_3), 0.67 (3H, t, *J* = 7.1 Hz, NCHCHCO_2CH_2CH_3); NMR δ_C (100 MHz) 196.4 (C), 169.0 (C), 167.0 (C), 166.8 (C), 160.4 (C), 137.6 (CH), 131.4 (CH), 124.6 (CH), 122.5 (C), 119.9 (CH),

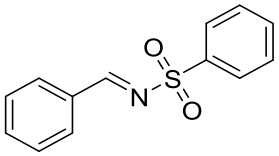
113.2 (C), 112.4 (CH), 73.9 (C), 69.7 (CH), 66.2 (CH), 62.4 (CH_2), 62.0 (CH_2), 57.1 (CH), 55.7 (CH), 14.1 (CH_3), 13.2 (CH_3); HRMS (ESI^+): calcd. $C_{21}N_2O_6H_{22}Br^{79}$ for ($[M+H]^+$) 493.0605, found 493.0613, calcd. $C_{21}N_2O_6H_{22}Br^{81}$ for ($[M+H]^+$) 495.0584, found 495.0601.

3,3-Dimethyldioxirane[105]



Oxone (25.0 g, 40.6 mmol) was added to a stirring solution of sodium bicarbonate (24.0 g, 0.29 mol) in acetone (30 mL) and water (20 mL) at 0 °C. After 15 minutes the stirrer bar was removed and the flask was placed on rotary evaporator with water bath at room temperature. An anti-splash adapter was cooled externally with dry ice / acetone and the pressure reduced to 207 mbar for 15 minutes then water bath heated to 40 °C over 10 minutes. The collected solution in the anti-splash adapter was then dried over anhydrous sodium sulphate and filtered to afford the desired product (0.067 M) in acetone. Concentration was determined by ^1H NMR analysis of 3 mL of solution added to premade 0.7 M solution of thioanisole in d6-acetone (0.6 mL) at 10 °C for 10 minutes. Analysing relative integration of sulfide and sulfoxide.

(*E*)-N-Benzylidenebenzenesulfonamide[106]

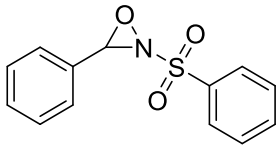


Dimethoxy benzaldehyde (5.25 mL, 35.0 mmol) was added to benzene sulfonamide (5.00 g, 31.9 mmol) in flask attached to short path distillation kit and heated to 170 °C for 16 hours. The hot flask was then transferred onto rotary evaporator for 1 hour, the resulting oil crystallised on standing and was recrystallised from toluene to afford the desired product as a colourless crystalline solid (5.35 g, 69%).

NMR δ_H (300 MHz, $CDCl_3$) 9.08 (1H, s, N=C*H*), 8.10–8.01 (2H, m, Ar-*H*), 7.99–7.90 (2H, m, Ar-*H*), 7.77–7.41 (6H, m, Ar-*H*); NMR δ_C (75 MHz) 170.6 (CH), 138.2 (C), 135.1 (CH), 133.6 (CH), 132.3 (C), 131.4 (CH), 129.18 (CH), 129.16 (CH), 128.0 (CH)

Data consistent with literature values.[106]

3-Phenyl-2-(phenylsulfonyl)-1,2-oxaziridine[106]

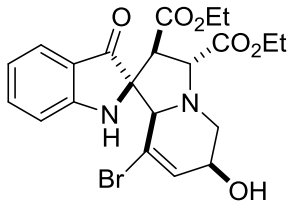


Oxone (7.52 g, 24.5 mmol) in water (37.5 mL) was added dropwise over 20 minutes to a vigorously stirring solution of potassium carbonate (11.8 g, 85.7 mmol) and (*E*)-N-benzylidenebenzenesulfonamide (3.00 g, 12.3 mmol) in toluene (120 mL) and water (8.4 mL). After 1.5 hours ^{1}H NMR of the crude mixture showed ~35% conversion, the aqueous layer was removed and oxone (15.0 g, 49.0 mmol) and potassium carbonate (23.7 g, 161 mmol) in water (90 mL) was added dropwise over 20 minutes and the reaction was stirred for a further hour. Organic layer was separated and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the desired product as a colourless solid (2.68 g, 84%).

+NMR δ_H (300 MHz, $CDCl_3$) 8.12–8.03 (2H, m, Ar-*H*), 7.85–7.73 (1H, m, Ar-*H*), 7.71–7.61 (2H, m, Ar-*H*), 7.56–7.40 (5H, m, Ar-*H*), 5.51 (1H, s, C*H*); NMR δ_C (75 MHz) 135.0 (CH), 134.7 (C), 131.4 (CH), 130.5 (C), 129.38 (CH), 129.36 (CH), 128.8 (CH), 128.2 (CH), 76.3 (CH); HRMS (ESI$^+$): calcd. $C_{13}NO_3H_{11}SNa$ for ([M+Na]$^+$) 284.0352, found 284.0336,

Data consistent with literature values.[106]

Diethyl (2S*,2'R*,3'R*,6'S*,8a'R*)-8'-bromo-6'-hydroxy-3-oxo-2',3',6',8a'-tetrahydro-5'H-spiro[indoline-2,1'-indolizine]-2',3'-dicarboxylate (172)

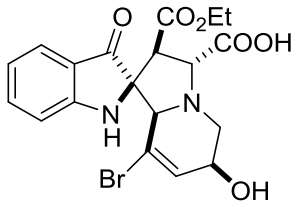


(2S*,2'S*,3'R*,8a'R*)-Diethyl 8'-bromo-3-oxo-2',3'-dihydro-8a'H-spiro[indoline-2,1'-indolizine]-2',3'-dicarboxylate **134** (92 mg, 0.20 mmol) in dry THF (3 mL) added dropwise to a stirred solution of (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (69 mg, 0.30 mmol) in dry THF (7 mL) at -78 °C under argon. The reaction was stirred for 1 hour then tetramethylammonium triacetoxyborohydride (158 mg, 0.60 mmol) added in one portion and reaction stirred at -78 °C for 1 hour then allowed to warm to room temperature. Reaction mixture was concentrated *in vacuo* to afford the crude product, which was purified using column chromatography on silica gel using 1% methanol in dichloromethane as eluent to afford the desired compound as an orange oil (52 mg, 54%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 2985, 1734, 1712, 1485, 1470, 1193; NMR δ_H (400 MHz, $CDCl_3$) 7.67 (1H, dd, *J* = 7.8, 0.5 Hz, Ar-*H*), 7.43 (1H, dt, *J* = 7.7, 0.5 Hz, Ar-*H*), 6.82 (1H, app. t, *J* = 7.8 Hz, Ar-*H*), 6.77 (1H, dd, *J* = 7.7, 0.5 Hz),6.38 (1H, dd, *J* = 5.9, 1.3 Hz, BrC=C*H*), 5.84 (1H, br. s, N*H*), 4.55 (1H, d, *J* = 5.6 Hz, NC*H*(CO_2Et), 4.37 (1H, d, *J* = 1.3 Hz, NC*H*CBr), 4.26 (2H, dq, *J* = 7.1, 2.8 Hz, NCHCO_2CH_2), 4.21 (1H, br. d, *J* = 5.9 Hz, HOC*H*), 3.98-3.77 (2H, m, NCHCHCO_2CH_2),

3.76 (1H, d, *J* = 5.6 Hz, NCHC*H*(CO_2Et), 3.27 (1H, ddd, *J* = 12.7, 2.3, 1.2 Hz, NC*H*$_A$H$_B$), 3.15 (1H, dd, *J* = 12.7, 1.3 Hz, NCH$_A$*H*$_B$), 1.33 (3H, t, *J* = 7.1 Hz, NCHCO$_2$CH$_2$C*H*$_3$), 0.65 (3H, t, *J* = 7.2 Hz, NCHCHCO$_2$CH$_2$C*H*$_3$); NMR δ_C (100 MHz) 198.8 (C), 171.6 (C), 169.0 (C), 160.8 (C), 137.0 (CH), 132.6 (CH), 124.5 (CH), 122.9 (C), 122.8 (C), 118.9 (CH), 111.7 (CH), 73.9 (C), 70.7 (CH), 66.2 (CH), 63.2 (CH), 61.5 (CH_2), 61.4 (CH_2), 57.0 (CH), 51.3 (CH_2), 14.3 (CH_3), 13.2 (CH_3); HRMS (ESI$^+$): calcd. $C_{21}N_2O_6H_{24}Br^{79}$ for ([M+H]$^+$) 479.0812, found 479.0800, calcd. $C_{21}N_2O_6H_{24}Br^{81}$ for ([M+H]$^+$) 481.0792, found 481.0806.

(2S*,2'S*,3'R*,6'S*,8a'R*)-8'-Bromo-2'-(ethoxycarbonyl)-6'-hydroxy-3-oxo-2',3',6',8a'-tetrahydro-5'H-spiro[indoline-2,1'-indolizine]-3'-carboxylic acid (253)

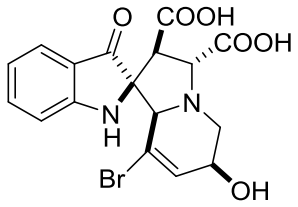


Diethyl (2S*,2'S*,3'R*,6'S*,8a'R*)-8'-bromo-6'-hydroxy-3-oxo-2',3',6',8a'-tetrahydro-5'H-spiro[indoline-2,1'-indolizine]-2',3'-dicarboxylate **172** (50 mg, 0.10 mmol) in THF (2 mL) added slowly to stirring solution of sodium hydroxide (21 mg, 0.52 mmol) in water (2 mL) at 0 °C for 20 minutes. 0.2M HCl (10 mL) was added the mixture was extracted with dichloromethane (3 x 10 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the desired product as a yellow foam (27 mg, 77%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 2963, 1736, 1712, 1620, 1485, 1470, 1323; NMR δ_H (400 MHz, Methanol-d_4) 7.59–7.52 (1H, m, Ar-*H*), 7.47 (1H, ddd, *J* = 8.3, 7.0, 1.4 Hz, Ar-*H*), 6.84 (1H, d, *J* = 8.3 Hz, Ar-*H*), 6.83–6.74 (1H, m, Ar-*H*), 6.32 (1H, dd, *J* = 5.5, 1.6 Hz, BrC=C*H*), 4.48 (1H, d, *J* = 5.8 Hz, NC*H*COOH), 4.22 (1H, d, *J* = 1.6 Hz, BrCC*H*), 4.19–4.13 (1H, m, NCH_2CHOH), 3.96–3.73 (2H, m, CH_2CH_3), 3.66 (1H, d, *J* = 5.8 Hz, NCHC*H*CO_2Et), 3.21 (1H, ddd, *J* = 12.4, 3.1, 1.2 Hz, NCH_AH_b), 3.08 (1H, dd, *J* = 12.4, 2.5 Hz, NCH_ACH_B), 0.67 (3H, t, *J* = 7.1 Hz, CH_2CH_3); NMR δ_C (100 MHz) 200.5 (C), 173.6 (C), 168.2 (C), 162.0 (C), 137.2 (CH), 132.7 (CH), 123.7 (CH), 122.2 (C), 121.1

(C), 117.8 (CH), 111.3 (CH), 74.2 (C), 70.6 (CH), 65.7 (CH), 63.2 (CH), 60.8 (CH_2), 57.4 (CH), 51.3 (CH_2), 12.3 (CH_3); HRMS (ESI^-): calcd. $C_{19}N_2O_6H_{18}Br^{79}$ for ($[M-H]^-$) 449.0354, found 449.0363, calcd. $C_{19}N_2O_6H_{18}Br^{81}$ for ($[M-H]^-$) 451.0333, found 451.0343.

(2S*,2'S*,3'R*,6'S*,8a'R*)-8'-Bromo-6'-hydroxy-3-oxo-2',3',6',8a'-tetrahydro-5'H-spiro[indoline-2,1'-indolizine]-2',3'-dicarboxylic acid (254)



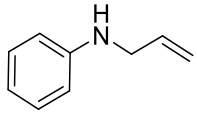
Diethyl (2S*,2'S*,3'R*,6'S*,8a'R*)-8'-bromo-6'-hydroxy-3-oxo-2',3',6',8a'-tetrahydro-5'H-spiro[indoline-2,1'-indolizine]-2',3'-dicarboxylate **172** (139 mg, 0.29 mmol) in THF (6 mL) added slowly to stirring solution of sodium hydroxide (58 mg, 1.45 mmol) in water (6 mL) at 0 °C for 2 hours. Then allowed to warm to room temperature and stirred for 16 hours. Reaction acidified with 0.5M HCl (10 mL) and washed with dichloromethane (10 mL), the aqueous layer was separated and concentrated *in vacuo*. The resulting solid was added to acetone (20 mL) and filtered, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the desired product as a golden brown foam (90 mg, 74%) (obtained in ~70% purity, data reported from crude NMR).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3244, 3067, 1710, 1618, 1469, 1326; NMR δ_H (400 MHz, Methanol-d_4) 7.51 (1H, ddd, *J* = 7.8, 1.4, 0.7 Hz, Ar-*H*), 7.38 (1H, ddd, *J* = 8.3, 7.1, 1.4 Hz, Ar-*H*), 6.82 (1H, dt, *J* = 8.3, 0.7 Hz, Ar-*H*), 6.68 (1H, ddd, *J* = 7.8, 7.1, 0.7 Hz, Ar-*H*), 6.21 (1H, d, *J* = 4.5 Hz, BrC=C*H*), 4.40 (1H, br. s, NC*H*CBr), 4.19 (1H, d, *J* = 5.8 Hz, NC*H*COOH), 4.12 (1H, m, NCH_2CHOH), 3.55 (1H, d, *J* = 5.8 Hz, NCHC*H*COOH), 3.20 (1H, d, *J* = 12.1 Hz, NCH_AH_B), 3.04 (1H, d, *J* =

12.1 Hz, NCH_AH_B); NMR δ_C (100 MHz) 200.6 (C), 173.8 (C), 169.6 (C), 162.2 (C), 137.0 (CH), 132.8 (CH), 123.7 (CH), 122.1 (C), 121.1 (C), 117.7 (CH), 111.3 (CH), 74.2 (C), 71.0 (CH), 65.7 (CH), 63.7 (CH), 57.3 (CH), 51.4 (CH_2); HRMS (ESI^-): calcd. $C_{17}N_2O_6H_{14}Br^{79}$ for ($[M-H]^-$) 421.0041, found 421.0041, calcd. $C_{17}N_2O_6H_{14}Br^{81}$ for ($[M-H]^-$) 423.0020, found 423.0014.

5.5 **Synthesis of other dipolarophiles**

***N*-Allylaniline (181)**



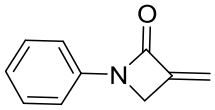
Aniline (2.94 mL, 32.0 mmol) was added slowly to a stirring solution of sodium hydride (1.42 g, 35.0 mmol) in dry THF at 0 °C under argon. The mixture was heated to 40 °C for 1 hour, cooled to 0 °C and allyl bromide (3.07 mL, 35.0 mmol) was added, the reaction was allowed to warm to room temperature and stirred for a further 2 hours. The reaction was quenched by the slow addition of water (50 mL), the mixture was then extracted with dichloromethane (3 x 100 mL) the organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel using 19:1 (petrol : ethyl acetate) as eluent to afford the desired product as an orange oil (741 mg, 17%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3445, 3085, 3056, 3008, 2918, 2846, 1645, 1603, 1505, 1467, 1432, 1315, 1253, 1181, 1155, 994, 925, 772; NMR δ_H (300 MHz, $CDCl_3$) 7.25-7.19 (2H, m, Ar-*H*), 6.75 (2H, dd, *J* = 7.3, 1.0 Hz, Ar-*H*), 6.69-6.65 (1H, m, Ar-*H*), 6.07-5.94 (1H, ddt, *J* = 17.2, 10.3, 5.2 Hz, H_2C=C*H*), 5.33 (1H, dd, *J* = 17.2, 1.6 Hz, CH=CH_AH_B), 5.21 (1H, dd, *J* = 10.3, 1.6 Hz, CH=CH_AH_B), 3.81 (3H, m, NCH_2, N*H*); NMR δ_C (75 MHz) 148.1 (C), 135.5 (CH), 129.2 (CH),

117.5 (CH), 116.2 (CH_2), 113.0 (CH), 46.6 (CH_2); HRMS (ESI^+): calcd. C_9NH_{12} for ($[M+H]^+$) 134.0964, found 134.0945.

Data consistent with literature values.[107]

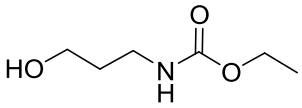
3-Methylene-1-phenylazetidin-2-one (184)[58]



N-Allylaniline (718 mg, 5.40 mmol) was added to a stirring solution of palladium dichloride (96 mg, 0.54 mmol), tricyclohexyl phosphine (301 mg, 1.08 mmol), copper (II) acetate (1.95 g, 10.8 mmol) and pivalic acid (1.24 mL, 10.8 mmol) in dimethyl formamide under a balloon of carbon monoxide. The reaction was heated to 100 °C for 22 hours, then the mixture was filtered through Celite and washed with ethyl acetate (25 mL), the mixture was neutralised with saturated aq. sodium bicarbonate (50 mL), the organic layer was separated and washed with water (3 x 50 mL). The organic layer was separated, dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel using 5:1 (petrol : ethyl acetate) as eluent to afford the desired product as an orange oil (403 mg, 47%). IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3677, 3009, 2956, 2886, 1821, 1743, 1600, 1503, 1462, 1379, 1132, 1053, 927; NMR δ_H (300 MHz, $CDCl_3$) 7.44-7.34 (4H, m, Ar-*H*), 7.15-7.10 (1H, m, Ar-*H*), 5.90 (1H, app. q, *J* = 1.5 Hz, C=C$H_A$$H_B$), 5.37 (1H, app. q, *J* = 1.5 Hz, C=C$H_A$$H_B$), 4.15 (2H, app. t, *J* = 1.5 Hz, NCH_2); NMR δ_C (75 MHz) 160.2 (C), 143.4 (C), 138.3 (C), 129.2 (CH), 124.1 (CH), 116.4 (CH), 111.3 (CH_2), 47.7 (CH_2); HRMS (ESI^+): calcd. $C_{10}NOH_{10}$ for ($[M+H]^+$) 160.0757, found 160.0756.

Data consistent with literature values.[58]

Ethyl (3-hydroxypropyl)carbamate (189)[108]

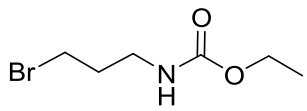


Ethyl chloroformate (5.71 mL, 60.0 mmol) was added to a stirring solution of 3-aminopropan-1-ol (3.05 mL, 40.0 mmol) and potassium carbonate (8.85 g, 64.0 mmol) in water (20 mL) at 0 °C for 2 hours. The reaction was allowed to warm to room temperature and the mixture was extracted with dichloromethane (3 x 30 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the crude product as a colourless oil (6.40 g, >100%) which was carried through to the next reaction.

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3625, 3456, 3006, 2947, 2885, 1699, 1518, 1479, 1446, 1431, 1385, 1351, 1257, 1173, 1141, 1094, 1072, 1044, 1006, 911; NMR δ_H (400 MHz, $CDCl_3$) 4.09 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 3.66 (2H, t, *J* = 5.8 Hz, NC*H*$_2$), 3.29 (3H, m, HOC*H*$_2$, N*H*), 1.69 (2H, quin, *J* = 5.8 Hz, NCH$_2$C*H*$_2$), 1.22 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz) 157.7 (C), 60.9 (CH_2), 59.4 (CH_2), 37.6 (CH_2), 32.5 (CH_2), 14.6 (CH_3); HRMS (ESI^+): calcd. $C_6NO_3H_{13}Na$ for ($[M+Na]^+$) 170.0788, found 170.0800.

Data consistent with literature values.[108]

Ethyl (3-bromopropyl)carbamate (190)[108]

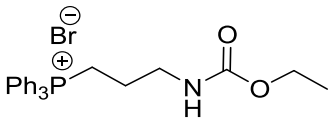


Thionyl bromide (4.05 mL, 52.2 mmol) was added slowly to a stirring solution of ethyl (3-hydroxypropyl)carbamate (6.40 g, 43.5 mmol) in dry dichloromethane (50 mL) under argon. The reaction was stirred at room temperature for 16 hours then poured onto saturated aqueous sodium carbonate (150 mL), the organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to the desired product as a pale yellow oil (7.27 g, 80%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3456, 2984, 1712, 1513, 1479, 1443, 1385, 1334, 1264, 1173, 1139, 1078, 1031; NMR δ_H (400 MHz, $CDCl_3$) 4.96 (1H, br. s, N*H*), 4.14-4.07 (2H, m, C*H*$_2$CH$_3$), 3.46 (2H, t, *J* = 6.4 Hz, BrC*H*$_2$), 3.34 (2H, app. q, *J* = 6.4 Hz, NC*H*$_2$), 2.08 (2H, app. quin, *J* = 6.4 Hz, NCH$_2$C*H*$_2$), 1.25 (3H, m, CH$_2$C*H*$_3$); NMR δ_C (100 MHz) 156.8 (C), 60.9 (CH_2), 39.3 (CH_2), 32.6 (CH_2), 30.8 (CH_2), 14.6 (CH_3); HRMS (ESI^+): calcd. $C_6NO_2H_{12}{}^{79}BrNa$ for ($[M+Na]^+$) 231.9944 , found 231.9950, calcd. $C_6NO_2H_{12}{}^{81}BrNa$ for ($[M+Na]^+$) 233.9923, found 233.9928.

Data consistent with literature values.[108]

(3-((Ethoxycarbonyl)amino)propyl)triphenylphosphonium bromide (191)[108]

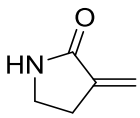


Ethyl (3-bromopropyl)carbamate (7.27 g, 34.6 mmol) in dry acetonitrile (20 mL) was added to a stirring solution of triphenylphosphine (9.52 g, 36.4 mmol) in dry acetonitrile (25 mL) under argon. The mixture was heated at reflux for 16 hours then allowed to cool to room temperature, the reaction was concentrated *in vacuo* to afford an orange oil. Ethyl acetate (100 mL) was added and stirred vigorously for 30 minutes, the resulting precipitate was collected by filtration, washed with diethyl ether (40 mL) and dried to afford the desired product as a colourless solid (8.81 g, 54%).

mp 168-170 °C (mp lit.[60] 178 °C); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 2869, 1696, 1511, 1439, 1385, 1284, 1247, 1138, 1114, 1049, 740; NMR δ_H (400 MHz, DMSO-d_6) 7.96-7.90 (3H, m, Ar-*H*), 7.86-7.77 (12H, m, Ar-*H*), 3.97 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 3.68-3.56 (2H, m, NC*H*$_2$), 3.20-3.12 (2H, m, PC*H*$_2$), 1.74-1.64 (2H, m, NCH$_2$C*H*$_2$), 1.15 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz) 156.7 (C), 135.48 (CH), 135.45 (CH) 134.1 (CH), 134.0 (CH), 130.8 (CH), 130.7 (CH), 119.3 (C), 118.4 (C), 60.2 (CH_2), 23.0 (CH_2), 19.0 (CH_2), 18.4 (CH_2), 15.1 (CH_3); HRMS (ESI^+): calcd. $C_{24}NO_2H_{27}P$ for ($[M]^+$) 392.1774, found 392.1781.

Data consistent with literature values.[108]

3-Methylenepyrrolidin-2-one (177)[108]

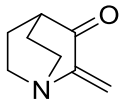


Potassium *tert*-butoxide (1.25g, 11.1 mmol) was added to a stirring solution of ((3-((ethoxycarbonyl)amino)propyl)phosphonium bromide (5.00 g, 10.6 mmol) in dry toluene (40 mL) under argon. The mixture was heated to 50 °C for 1 hour followed by the addition of para-formaldehyde (334 mg, 11.1 mmol), after a further 30 minutes the reaction was allowed to cool to room temperature. The mixture was filtered, concentrated *in vacuo* to afford the crude product, which was purified using column chromatography on silica gel using diethyl ether as eluent to afford the desired product as an off-white crystalline solid (200 mg, 19%).

mp 105-107 °C (mp lit.[109] 107 °C); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3444, 3008, 1702, 1663, 1442, 1421, 1300, 931; NMR δ_H (400 MHz, $CDCl_3$) 7.42 (1H, br. s, N*H*), 6.00 (1H, app. t, *J* = 2.9 Hz, C=C$H_A$$H_B$), 5.40-5.38 (1H, m, C=C$H_A$$H_B$), 3.49-3.45 (2H, m, NC$H_2$), 2.90-2.86 (2H, m, NC$H_2CH_2$); NMR δ_C (100 MHz) 171.5 (C), 139.3 (C), 115.7 (CH_2), 39.2 (CH_2), 26.2 (CH_2); HRMS (ESI^+): calcd. C_5NOH_8 for ($[M+H]^+$) 97.0528, found 97.0525.

Data consistent with literature values.[108]

2-Methylenequinuclidin-3-one (179)

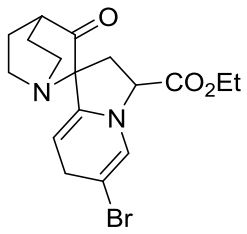


2-Methylene-3-quinuclidinone hydrochloride hydrate (1.37 g, 7.17 mmol) was added to methanol (20 mL) and heated at reflux for 1 minute, then filtered while hot. The precipitate collected was then added to potassium carbonate (1.48 g, 10.8 mmol) in water (25 mL) and dichloromethane (25 mL) and stirred for 48 hours. The organic layer was passed through a hydrophobic frit and concentrated *in vacuo* to afford the desired product as a yellow oil (472 mg, 48%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3009, 2950, 2876, 1715, 1643, 1471, 1457, 1376, 1337, 1321, 1254, 1172, 1056, 1022, 949, 957; NMR δ_H (400 MHz, $CDCl_3$) 5.84 (1H, s, C=C$H_A$$H_B$), 5.24 (1H, s, C=C$H_A$$H_B$), 3.19-3.12 (2H, m, NC$H_2$), 3.05-2.96 (2H, m, NC$H_2$), 2.61 (1H, m, C$H$), 2.00 (4H, dt, J = 7.9, 3.0 Hz, 2xCHCH_2); NMR δ_C 100 MHz) 204.4 (C), 152.5 (C), 113.6 (CH_2), 48.6 (CH_2), 40.4 (CH), 25.2 (CH_2); HRMS (ESI^+): calcd. C_8NOH_{12} for ($[M+H]^+$) 138.0913, found 138.0896.

Data consistent with literature values.[110]

Ethyl 6-bromo-3'-oxo-2,3-dihydro-7H-1'-azaspiro[indolizine-1,2'-quinuclidine]-3-carboxylate (204)

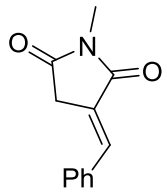


2-Methylenequinuclidin-3-one (50 mg, 0.37 mmol) in dry dichloromethane (0.5 mL) was added to a stirring solution of 3-bromopyridinium salt (181 mg, 0.56 mmol) and triethylamine (0.56 mmol) in dry dichloromethane (0.5 mL) under argon. The reaction was stirred for 4 hours at room temperature, water (5 mL) was added and the mixture was extracted with dichloromethane (3 x 5 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel using 1% (7M) ammonia solution in methanol in dichloromethane as eluent to afford the desired product as a pale yellow gum (107 mg, 70%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 2963, 2873, 2829, 2361, 1728, 1690, 1636, 1393, 1337, 1303, 1195, 909; NMR δ_H (400 MHz, $CDCl_3$) 6.35 (1H, t, *J* = 1.2 Hz, NC*H*), 4.23-4.15 (2H, m, C$H_2$$CH_3$), 4.10 (1H, app. t, *J* = 3.3 Hz, NC=C*H*), 3.92 (1H, dd, *J* = 8.7, 1.0 Hz, NC*H*(CO_2Et)), 3.53-3.45 (1H, m, NC$H_A$$H_B$), 3.35 (2H, dt, *J* = 3.3, 1.0 Hz, BrCCH_2), 3.21-3.12 (1H, m, NC$H_A$$H_B$), 2.85-2.76 (2H, m, 2xNC$H_A$$H_B$), 2.73 (1H, dd, *J* = 13.0, 1.0 Hz, NCH(CO_2Et)C$H_A$$H_B$), 2.46 (1H, quin, *J* = 3.0 Hz, O=CC*H*), 2.40 (1H, dd, *J* = 13.0, 8.7 Hz, NCH(CO_2Et)C$H_A$$H_B$), 2.06-

1.86 (4H, m, 2xNCH$_2$C*H*$_2$), 1.26 (3H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz) 219.1 (C), 171.2 (C), 141.0 (C), 129.2 (CH), 95.8 (C), 93.6 (CH), 74.4 (C), 61.3 (CH_2), 60.1 (CH), 44.0 (CH_2), 42.9 (CH_2), 40.5 (CH), 35.2 (CH_2), 33.5 (CH_2), 26.3 (CH_2), 24.4 (CH_2), 14.1 (CH_3); HRMS (ESI$^+$): calcd. $C_{17}N_2O_3H_{22}{}^{79}Br$ for ([M+H]$^+$) 381.0808, found 381.0822, calcd. $C_{17}N_2O_3H_{22}{}^{81}Br$ for ([M+H]$^+$) 383.0788, found 383.0805.

(*E*)-3-Benzylidene-1-methylpyrrolidine-2,5-dione (197)[61]

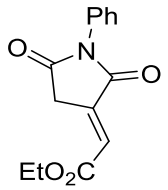


Triphenylphosphine (1.18 g, 4.50 mmol) was added to a stirring solution of *N*-methylmaleimide (500 mg, 4.50 mmol) and benzaldehyde (0.48 mL, 4.73 mmol) in dry dichloromethane (15 mL) under argon. After 24 hours the solvent was removed and the crude product was purified using column chromatography on silica gel using 3:1 to 2:1 (petrol : ethyl acetate) as eluent followed by recrystallization from ethyl acetate to afford the desired product as an colourless crystalline solid (351 mg, 48%).

mp 172-173 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 1763, 1694, 1655, 1433, 1383, 1153, 771, 690; NMR δ_H (400 MHz, $CDCl_3$) 7.66 (1H, t, *J* = 2.4 Hz, C=C*H*), 7.57–7.43 (5H, m, Ar-*H*), 3.61 (2H, d, *J* = 2.4 Hz, CH_2), 3.16 (3H, s, NCH_3); NMR δ_C (100 MHz) 174.2 (C), 171.2 (C), 134.3 (CH), 134.1 (C), 130.2 (CH), 130.2 (CH), 129.1 (CH), 123.5 (C), 34.1 (CH_2), 25.0 (CH_3); HRMS (ESI^+): calcd. $C_{12}NO_2H_{12}$ for ($[M+H]^+$) 202.0863, found 202.0871.

Data consistent with literature values.[111]

Ethyl (*E*)-2-(2,5-dioxo-1-phenylpyrrolidin-3-ylidene)acetate (200)



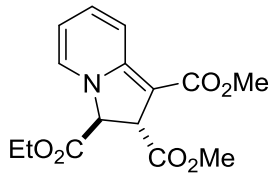
Triphenylphosphine (606 mg, 2.31 mmol) was added to a stirring solution of *N*-phenylmaleimide (400 mg, 2.31 mmol) and ethyl glyoxylate (0.47 mL, 2.31 mmol) in dry dichloromethane (8 mL) under argon. After 24 hours the solvent was removed and the crude product was purified using column chromatography on silica gel using 2:1 (petrol : ethyl acetate) as eluent to afford the desired product as an yellow crystalline solid (116 mg, 19%).

mp 115-117 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 1700, 1680, 1501, 1388, 1374, 1221, 1171, 1112, 691, 652; NMR δ_H (400 MHz, $CDCl_3$) 7.56 - 7.34 (5H, m, Ar-*H*), 6.96 (1H, t, *J* = 2.7 Hz, C=C*H*), 4.33 (2H, q, *J* = 7.2 Hz, C$H_2$$CH_3$), 3.90 (2H, d, *J* = 2.7 Hz, HC=CCH_2), 1.38 (3H, t, *J* = 7.2 Hz, CH_2CH_3); NMR δ_C (100 MHz) 172.6 (C), 168.0 (C), 164.8 (C), 139.7 (C), 131.5 (C), 129.2 (CH), 128.9 (CH), 126.3 (CH), 123.3 (CH), 61.5 (CH_2), 34.5 (CH_2), 14.2 (CH_3); HRMS (ESI^+): calcd. $C_{14}NO_4H_{13}Na$ for ($[M+Na]^+$) 282.0737, found 282.0736.

Data consistent with literature values.[112]

5.6 **Diazo generated cycloadducts**

3-Ethyl 1,2-dimethyl (2S*,3S*)-2,3-dihydroindolizine-1,2,3-tricarboxylate (208)

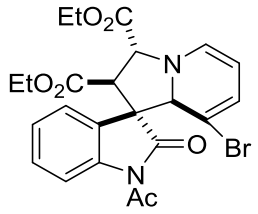


Ethyl diazoacetate (32 μL, 0.30 mmol) in toluene (0.6 mL) was added *via* syringe pump over 2 hours to a stirring solution of dimethyl maleate (20 μL, 0.20 mmol), pyridine (18 μL, 0.22 mmol) and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphin iron(III) chloride (1.4 mg, 0.002 mmol) in toluene (1.4 mL) under argon. After the addition the top was removed and nitrogen blown in to displace the argon and left open to air for 16 hours. The solvent was removed and the crude product was purified using column chromatography on silica gel using 2% methanol in dichloromethane as eluent to afford the desired compound as an orange gum (32 mg, 53%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 2949, 2361, 1737, 1657, 1621, 1514, 1437, 1206, 1014; NMR δ_H (400 MHz, $CDCl_3$) 7.39 (1H, br. s, NCC*H*=CH), 7.09 (1H, d, *J* = 6.8 Hz, NC*H*=CH), 7.03 (1H, dd, *J* = 8.7, 6.8 Hz, N-CCH=C*H*), 5.99 (1H, app. t, *J* = 6.8 Hz, NCH=C*H*), 5.01 (1H, d, *J* = 4.8 Hz, NC*H*(CO_2Et)), 4.33-4.23 (2H, m, C*H*$_2$$CH_3$), 4.20 (1H, d, *J* = 4.8 Hz, NCHC*H*), 3.77 (3H, s, CO_2C*H*$_3$), 3.69 (3H, s, CO_2C*H*$_3$), 1.32 (3H, t, *J* = 7.2 Hz, CH_2C*H*$_3$); NMR δ_C (100 MHz) 173.6 (C), 168.7 (C), 165.7 (C), 153.6* (C), 136.7 (CH), 135.1 (CH), 117.8 (CH), 106.9

(CH), 83.2* (C), 67.4 (CH), 62.8 (CH_2), 52.7 (CH_3), 50.1 (CH_3), 48.9 (CH), 14.1 (CH_3) (* = observed by HMBC); HRMS (ESI^+): calcd. $C_{15}NO_6H_{18}$ for ($[M+H]^+$) 308.1129, found 308.1151.

Diethyl (2'R*,3S*,3'R*,8a'R*)-1-acetyl-8'-bromo-2-oxo-2',3'-dihydro-8a'H-spiro[indoline-3,1'-indolizine]-2',3'-dicarboxylate (78)



Ethyl diazoacetate (31 µL, 0.29 mmol) in toluene (0.5 mL) was added *via* syringe pump over 16 hours to a stirring solution of ethyl (*E*)-2-(1-acetyl-2-oxoindolin-3-ylidene)acetate (50 mg, 0.19 mmol), 3-bromopyridine (56 µL, 0.58 mmol), $P450_{BM3}$ protein (for synthesis protocol of protein see appendix 3) (15 mg, 0.29 µmol) and sodium dithionite (2.5 mg, 0.02 mmol) in water (0.75 mL). Brine (20 mL) was added and the mixture was extracted with dichloromethane (3 x 15 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo.* The crude product was purified using column chromatography on silica gel using 9:1 (petrol : ethyl acetate) as eluent to afford the desired compound as a yellow film (14 mg, 14%).

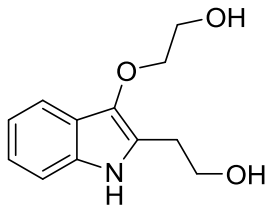
IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1744, 1710, 1636, 1561, 1466, 1370, 1308, 1272, 1191, 1023; NMR δ_H (400 MHz, d^6-acetone) 8.22 (1H, d, *J* = 8.2 Hz, Ar-*H*), 7.45-7.39 (2H, m, Ar-*H*), 7.21 (1H, td, *J* = 8.2, 1.4 Hz, Ar-*H*), 6.63 (1H, d, *J* = 7.1 Hz, NC*H*=CHCH), 6.11 (1H, d, *J* = 6.5 Hz, NCH=CHC*H*), 5.37 (1H, s, NC*H*), 5.05 (1H, d, *J* = 7.3 Hz, NC*H*(CO2Et)), 4.58 (1H, dd, *J* = 7.1, 6.5 Hz, NCH=C*H*CH), 4.29 (2H,

q, *J* = 7.1 Hz, NCHCO$_2$C*H*$_2$CH$_3$), 3.86 (1H, d, *J* = 7.3 Hz, CC*H*(CO2Et)), 3.69 (2H, q, *J* = 7.1 Hz, CCH(CO$_2$C*H*$_2$CH$_3$)), 2.66 (3H, s, NCOC*H*$_3$), 1.31 (3H, t, *J* = 7.1 Hz, NCHCOCH$_2$C*H*$_3$), 0.69 (3H, t, *J* = 7.1 Hz, CCH(CO$_2$CH$_2$C*H*$_3$)); NMR δ_C (100 MHz) 175.3 (C), 170.4 (C), 170.3 (C), 167.4 (C), 141.5 (C), 133.8 (CH), 129.4 (CH). 129.1 (CH), 125.4 (C), 124.7 (CH), 123.9 (CH), 115.9 (CH), 106.3 (C), 93.5 (CH), 74.3 (CH), 64.5 (CH), 63.8 (C), 61.7 (CH$_2$), 61.2 (CH$_2$), 53.6 (CH), 25.8 (CH$_3$), 13.5 (CH$_3$), 12.7 (CH$_3$); HRMS (ESI$^+$): calcd. $C_{23}N_2O_6H_{24}{}^{79}Br$ for ([M+H]$^+$) 503.0812, found 503.0802, calcd. $C_{23}N_2O_6H_{24}{}^{81}Br$ for ([M+H]$^+$) 505.0792, found 505.0788.

Data consistent with literature values.[11]

5.7 **Intramolecular approach**

2-(3-(2-Hydroxyethoxy)-1H-indol-2-yl)ethan-1-ol (263)

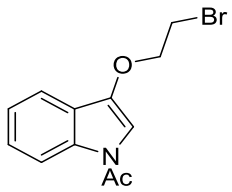


Sodium borohydride (29 mg, 0.77 mmol) added a stirring solution of ethyl (*Z*)-2-(spiro[indoline-3,2'-[1,3]dioxolan]-2-ylidene)acetate **125** (200 mg, 0.77 mmol) in THF (2 mL) and ethanol (447 µL) at 0 °C under argon. After 5 minutes the reaction was heated to reflux and sodium borohydride (58 mg, 1.44 mmol) was added after 3 hours. After 16 hours sodium borohydride (87 mg, 2.30 mmol) was added and after 21 hours the mixture was cooled to room temperature, saturated aq. ammonium chloride (10 mL) was added and the solution was extracted with dichloromethane (3 x 10 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel using step-gradient elution of 1:1 to 0:1 (petrol : ethyl acetate) as eluent to afford the desired compound as a colourless oil (52 mg, 31%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3463, 3016, 2936, 2883, 1709, 1619, 1337, 1072, 1032; NMR δ_H (400 MHz, $CDCl_3$) 8.22 (1H, br. d, N*H*), 7.56 (1H, d, *J* = 7.5 Hz, Ar-*H*), 7.22 (1H, d, *J* = 8.0 Hz, Ar-*H*), 7.16-7.05 (2H, m, Ar-*H*), 4.20-4.13 (2H, m, C=COC*H*$_2$), 3.87-3.83 (2H, m, C=COCH$_2$C*H*$_2$), 3.82 (2H, t, *J* = 5.9 Hz, C=C-C*H*$_2$), 3.26 (2H, br. s,

2xO*H*), 2.91 (2H, t, *J* = 5.9 Hz, C=C-CH_2-C*H_2*); NMR δ_C (100 MHz) 134.7 (C), 133.1 (C), 124.9 (C), 121.6 (CH), 121.2 (C), 119.3 (CH), 117.0 (CH), 111.2 (CH), 75.6 (CH_2), 61.8 (CH_2), 61.7 (CH_2), 27.9 (CH_2); HRMS (ESI^+): calcd. $C_{12}NO_3H_{15}Na$ for ($[M+Na]^+$) 244.0944, found 244.0942.

1-(3-(2-Bromoethoxy)-1H-indol-1-yl)ethan-1-one (262)

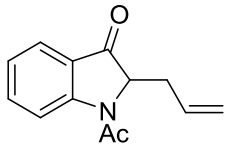


Sodium hydride (60% dispersion in mineral oil) (84 mg, 2.10 mmol) was added to a stirring solution of 1-acetylindolin-3-one (350 mg, 2.00 mmol) in DMF (20 mL) at 0 °C under argon. The mixture was cooled to -40 °C for 40 minutes followed by the addition of 1,2-dibromoethane (690 µL, 8.00 mmol) and the reaction was allowed to warm to room temperature and stirred for 16 hours. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL), the organics were combined then washed with brine (2 x 30 mL) then separated, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo.* The crude product was purified using column chromatography on silica gel using 4:1 (petrol : ethyl acetate) as eluent to afford the desired compound as a purple solid (42 mg, 7%).

mp 75-77 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3053, 2986, 2305, 2252, 1693, 1454, 1422, 1276, 1253; NMR δ_H (400 MHz, $CDCl_3$) 8.44 (1H, br. s, Ar-*H*), 7.65 (1H, d, *J* = 7.8 Hz, Ar-*H*), 7.42 (1H, dd, *J* = 8.3, 7.2 Hz, Ar-*H*), 7.32 (1H, dd, *J* = 7.8, 7.2 Hz, Ar-*H*), 6.86 (1H, br. s, NC*H*=C), 4.39 (2H, t, *J* = 6.3 Hz, OCH_2), 3.75 (2H, t, *J* = 6.3 Hz, BrCH_2), 2.62 (3H, br. s, COCH_3); NMR δ_C (100 MHz) 168.1 (C), 144.2 (C), 135.1 (CH), 134.1 (C), 126.4 (CH), 123.5 (CH), 118.15 (CH), 118.12 (C), 103.8 (CH), 70.2 (CH_2), 28.5 (CH_2), 16.9 (CH_3); GC-EIMS r.t = 12.25

min, exact mass $C_{12}NO_2H_{12}Br^{79}$ for ([M]) 281.0051, found 281.0046 exact mass $C_{12}NO_2H_{12}Br^{81}$ for ([M]) 283.0031, found 283.0025.

1-Acetyl-2-allylindolin-3-one (266)[86]



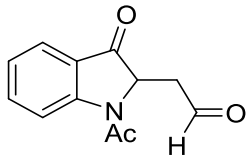
(1S)-(+)-10-Camphorsulfonic acid (23 mg, 0.10 mmol) was added to a stirring solution of 1-acetylindolin-3-one (175 mg, 1.00 mmol) and magnesium sulphate (444 mg, 3.70 mmol) in allyl alcohol (3.94 mL, 58.0 mmol) under argon. The reaction was sealed and heated to 130 °C for 2 hours, allowed to cool to room temperature then filtered and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel using 2:1 (petrol : ethyl acetate) as eluent to afford the desired compound as dark purple solid (119 mg, 55%).

mp 89-91 °C (mp lit.[113] 92 °C); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 1708, 1670, 1606, 1461, 1338, 1353, 1286, 753; NMR δ_H (400 MHz, DMSO-d_6, 70 °C) 8.32 (1H, d, J = 8.5 Hz, Ar-*H*), 7.72 (1H, ddd, *J* = 8.5, 7.2, 1.4 Hz, Ar-*H*), 7.68 (1H, ddd, *J* = 7.7, 1.4, 0.8 Hz, Ar-*H*), 7.26 (1H, ddd, *J* = 7.7, 7.2, 0.8 Hz, Ar-*H*), 5.46 (1H, dddd, *J* = 17.1, 10.1, 7.6, 6.8 Hz, C*H*=CH_AH_B), 5.09 (1H, ddt, *J* = 17.1, 2.0, 1.3 Hz, CH=C*H*$_A$H$_B$), 4.95 (1H, ddt, *J* = 10.1, 2.0, 1.1 Hz, CH=CH_AH_B), 4.68 (1H, dd, *J* = 6.6, 3.2 Hz, NC*H*), 2.88 (1H, dddt, *J* = 14.4, 7.6, 6.6, 1.1 Hz, NCHC*H*$_A$H$_B$), 2.76 (1H, dddt, *J* = 14.4, 6.8, 3.2, 1.3 Hz, NCHCH$_A$*H*$_B$), 2.38 (3H, s, COC*H*$_3$); NMR δ_C (100 MHz, 70 °C) 198.6 (C), 169.2 (C), 153.7 (C), 137.5 (CH), 131.1 (CH), 124.8 (C), 124.3 (CH), 123.6 (CH), 119.7 (CH_2), 118.2 (CH), 65.1 (CH), 36.0 (CH_2), 24.5 (CH_3);

GC-EIMS r.t = 12.83 min, exact mass $C_{13}NO_2H_{13}$ for ([M]) 215.0946, found 215.0941.

Data consistent with literature values.[86]

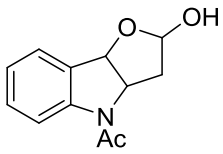
2-(1-Acetyl-3-oxoindolin-2-yl)acetaldehyde (267)



Ozone was bubbled through a stirring solution of 1-acetyl-2-allylindolin-3-one (1.00 g, 4.65 mmol) in dichloromethane (75 mL) at -78 °C for 20 minutes. TLC indicated no remaining starting material so reaction purged with argon for 10 minutes then polymer supported triphenylphosphine (1.60 mmol/g) (3.20 g, 5.12 mmol) was added in one portion and stirred for 5 minutes at -78 °C then allowed to warm to room temperature and stirred for 1 hour. The reaction was filtered and concentrated *in vacuo* to afford the desired product as an orange gum (954 mg, 95%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 2855, 1728, 1415, 1662, 1607, 1591, 1377, 1348, 1287, 774; NMR δ_H (400 MHz, $CDCl_3$) 9.74 (1H, s, *CH*O), 8.15-7.43 (1H, br. s, Ar-*H*), 7.84 (1H, dt, *J* = 7.6, 1.1 Hz, Ar-*H*), 7.29 (1H, m, Ar-*H*), 7.72 (1H, ddd, *J* = 8.6, 7.3, 1.5 Hz, Ar-*H*), 4.73 (1H, t, *J* = 4.9 Hz, NC*H*), 3.40 (1H, d, *J*=18.0 Hz, NCHCH_AH_B), 3.13 (1H, dd, *J* = 18.0, 4.9 Hz, NCHCH_AH_B), 2.51 (3H, s, COCH_3); NMR δ_C (100 MHz) 197.2 (CH), 197.1 (C), 168.5 (C), 137.2 (CH), 124.72 (CH), 124.71 (C), 124.3 (CH), 116.2 (CH), 60.9 (CH), 60.4 (C), 45.2 (CH_2), 25.3 (CH_3); HRMS (ESI^+): calcd. $C_{12}NO_3H_{11}Na$ for ($[M+Na]^+$) 240.0631, found 240.0637.

1-(2-Hydroxy-2,3,3a,8b-tetrahydro-4H-furo[3,2-b]indol-4-yl)ethan-1-one (268)

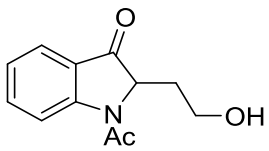


Ozone was bubbled through a stirring solution of 1-acetyl-2-allylindolin-3-one (215 mg, 1.00 mmol) in methanol (16 mL) at -78 °C for 5 minutes. TLC indicated no remaining starting material so reaction purged with argon for 10 minutes then sodium borohydride (38 mg, 1.00 mmol) was added, the reaction was stirred for 5 minutes then allowed to warm to room temperature. Saturated aqueous ammonium chloride (20 mL) was added and the mixture was extracted with dichloromethane (3 x 15 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel using 2% methanol in dichloromethane as eluent to afford the desired compound as colourless gum (71 mg, 33%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3008, 1658, 1604, 1481, 1397, 1049; NMR δ_H (400 MHz, $CDCl_3$) 8.26 (1H, d, *J* = 7.8 Hz, Ar-*H*), 7.43–7.29 (2H, m, Ar-*H*), 7.11 (1H, dtd, *J* = 16.1, 7.8, 1.0 Hz, Ar-*H*), 5.86 (1H, d, *J* = 7.8 Hz, NCHC*H*O), 5.63 (1H, d, *J* = 4.6 Hz, HO-C*H*), 5.03 (1H, app. q, *J* = 7.8 Hz, NC*H*), 3.68 (1H, br. s, O*H*), 2.71 (1H, dd, *J* = 12.9, 7.8 Hz, NCHCH_AH_B), 2.31 (3H, s, COCH_3), 2.14–2.00 (1H, m, NCHCH$_A$$H_B$); NMR δ_C (100 MHz) 168.8 (C), 142.4 (C), 130.3 (CH), 129.1 (C), 125.3

(CH), 124.4 (CH), 117.8 (CH), 98.3 (CH), 80.9 (CH), 63.1 (CH), 42.4 (CH_2), 24.0 (CH_3); HRMS (ESI^+): calcd. $C_{12}NO_3H_{13}Na$ for ($[M+Na]^+$) 242.0788, found 242.0783.

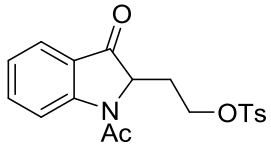
1-Acetyl-2-(2-hydroxyethyl)indolin-3-one (269)



2-Methylbut-2-ene (1.44 mL, 13.6 mmol) was added to a stirring solution of 9-borabicyclo[3.3.1]nonane (0.5 M in THF) (26.5 mL, 13.3 mmol) under argon and heated to reflux for 2 hours. 2-(1-Acetyl-3-oxoindolin-2-yl)acetaldehyde (720 mg, 3.32 mmol) in THF (8 mL) was added and after 2 hours the reaction was cooled to room temperature and the solvent removed. The crude product was was purified using column chromatography on silica gel using a step gradient of 1-2% methanol in dichloromethane as eluent to afford the desired compound as pale yellow gum (582 mg, 80%).

IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3213, 1719, 1674, 1609, 1466, 1382, 1301, 909; NMR δ_H (400 MHz, DMSO-d_6, 70 °C) 8.33 (1H, d, *J* = 8.4 Hz, Ar-*H*), 7.75–7.63 (2H, m, Ar-*H*), 7.25 (1H, ddd, *J* = 7.8, 7.2, 0.9 Hz, Ar-*H*), 4.62 (1H, dd, *J* = 7.8, 3.2 Hz, NC*H*), 4.11 (1H, br. s, O*H*), 3.51–3.42 (2H, m, HOCH_2), 2.35 (3H, s, NCOCH_3), 2.26–2.08 (2H, m, NCHCH_2); NMR δ_C (100 MHz, 70 °C) 199.1 (C), 169.2 (C), 153.3 (C), 137.0 (CH), 124.7 (C), 124.2 (CH), 123.6 (CH), 118.3 (CH), 63.5 (CH), 56.3 (CH_2), 35.0 (CH_2), 24.3 (CH_3); HRMS (ESI^+): calcd. $C_{12}NO_3H_{13}Na$ for ($[M+Na]^+$) 242.0788, found 242.0794.

2-(1-Acetyl-3-oxoindolin-2-yl)ethyl 4-methylbenzenesulfonate (275)

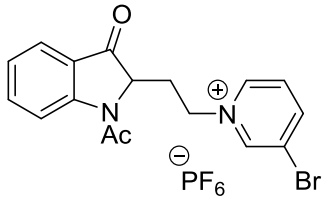


DMAP (6 mg, 0.05 mmol) was added to a stirring solution of 1-acetyl-2-(2-hydroxyethyl)indolin-3-one (110 mg, 0.50 mmol), 4-methylbenzenesulfonyl chloride (287 mg, 1.50 mmol) and pyridine (202 µL, 2.50 mmol) in dichloromethane (5 mL) under argon. After 24 hours 4-methylbenzenesulfonylchloride (287 mg, 1.50 mmol) and pyridine (202 µL, 2.50 mmol) was added and stirred for a further 24 hours. The solvent was removed *in vacuo* and the crude product was purified using column chromatography on silica gel using 0.5% methanol in dichloromethane as eluent to afford the desired compound as an orange solid (109 mg, 58%).

mp 142-144 °C; IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3042, 1719, 1678, 1466, 1378, 1177; NMR δ_H (400 MHz, DMSO-d_6) 8.29 (1H, br. s, Ar-*H*), 7.64 (1H, dt, *J* = 7.6, 1.1 Hz, Ar-*H*), 7.50 (2H, d, *J* = 8.4 Hz, Ar-*H*), 7.39 (2H, d, *J* = 8.4 Hz, Ar-*H*), 7.27 (1H, td, *J* = 7.6, 0.9 Hz), 4.70-4.61 (1H, m, NC*H*), 4.02 (2H, app. t, *J* = 5.6 Hz, SO_2OCH_2), 2.41 (3H, s, Ar-CH_3), 2.42-2.33 (2H, m, $NCHCH_2$), 2.29 (3H, br. s, $NCOCH_3$); NMR δ_C (100 MHz) 198.5 (C), 169.4 (C), 153.3 (C), 145.4 (C), 137.5 (CH), 132.2 (C), 130.6 (CH), 128.5 (C), 127.8 (CH), 124.5 (CH), 123.9 (CH), 118.5 (CH), 66.2 (CH_2), 62.5 (CH), 30.5 (CH_2), 24.5 (CH_3),

21.6 (CH_3); HRMS (ESI^+): calcd. $C_{19}NO_5H_{19}SNa$ for ($[M+Na]^+$) 396.0876, found 396.0872.

1-(2-(1-Acetyl-3-oxoindolin-2-yl)ethyl)-3-bromopyridin-1-ium hexafluorophosphate(V) (276)

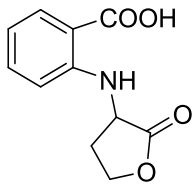


2-(1-Acetyl-3-oxoindolin-2-yl)ethyl 4-methylbenzenesulfonate (100 mg, 0.27 mmol) was added to a stirring solution of 3-bromopyridine (77 µL, 0.79 mmol) in ethyl acetate (2 mL) under argon, the tube was sealed, wrapped in foil and heated to 90 °C for 20 hours. The mixture was cooled to room temperature, water (5 mL) and diethyl ether (5 mL) were added and the aqueous layer was separated. Ammonium hexafluorophosphate (V) (1 g, 6.14 mmol) was added and the mixture was extracted with ethyl acetate (3 x 5 mL), the organics were combined, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel using 15% methanol in dichloromethane as eluent to afford the desired compound as a dark orange film (23 mg, 17%). (^{1}H NMR showed 0.6 equiv. 3-bromopyidine in mixture so mass of product = 20 mg, 15%. NMR data reported from this mixture)

NMR δ_H (400 MHz, DMSO-d_6) 9.42 (1H, dd, *J* = 2.0, 1.3 Hz, Ar-*H*), 9.08 (1H, dt, *J* = 6.2, 1.3 Hz, Ar-*H*), 8.83 (1H, ddd, *J* = 8.4, 2.0, 1.3 Hz, Ar-*H*), 8.33 (1H, br. s, Ar-*H*) 8.03 (1H, dd, *J* = 8.4, 6.2 Hz, Ar-*H*), 7.79 (1H, ddd, *J* = 8.0, 7.4, 1.5 Hz, Ar-*H*), 7.68 (1H, dt, *J* = 7.4, 1.1 Hz, Ar-*H*), 7.30 (1H, td, *J* = 8.0, 7.4, 1.1 Hz, Ar-*H*), 4.92–4.53

(3H, m, NC*H*, Py-C*H*$_2$), 2.84–2.60 (2H, m, NCHC*H*$_2$), 2.40 (3H, s, O=CC*H*$_3$); NMR δ_C (100 MHz) 198.3 (C), 169.6 (C), 153.4* (C), 148.7 (CH), 146.9 (CH), 144.6 (CH), 138.0 (CH), 129.0 (CH), 124.7 (CH), 124.1 (CH), 123.9 (C), 122.3 (C), 118.6 (br. CH), 63.1 (CH), 56.9 (br. CH_2), 32.1 (CH_2), 24.6 (br. CH_3) (* = observed by HMBC); HRMS (ESI$^+$): calcd. $C_{17}N_2O_2H_{16}Br^{79}$ for ([M]$^+$) 359.0390, found 359.0403. calcd. $C_{17}N_2O_2H_{16}Br^{81}$ for ([M]$^+$) 361.0369, found 361.0384.

2-((2-Oxotetrahydrofuran-3-yl)amino)benzoic acid (282)[90]

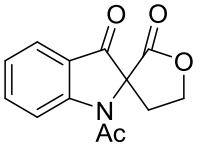


α-Bromo-γ-butyrolactone (8.43 mL, 91.2 mmol) was added to a stirring solution of anthranilic acid (10.0 g, 73.0 mmol) and sodium carbonate (19.1 g, 164 mmol) in water (58 mL) at 0 °C. After 5 hours the mixture was allowed to warm to room temperature and stirred for a further 24 hours then acidified to pH 1 with conc. HCl. The precipitate was collected by filtration, dried and the resulting solid was triturated with ether to afford the desired product as a pale yellow solid (10.7 g, 66%).

mp 92-94 °C (mp lit.[90] 198 °C); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 3347, 1665, 1573, 1240, 740; NMR δ_H (400 MHz, DMSO-d_6) 7.81 (1H, d, *J* = 7.7 Hz, Ar-*H*), 7.26 (1H, app. t, *J* = 8.3 Hz, Ar-*H*), 6.61 (1H, d, *J* = 8.3 Hz, Ar-*H*), 6.54 (1H, app. t, *J* = 7.7 Hz, Ar-*H*), 4.61 (2H, br. s, N*H*, O*H*), 4.08 (1H, app. t, *J* = 6.2 Hz, NC*H*), 3.56 (2H, app. d, *J* = 5.1 Hz, OCH_2), 1.98 (1H, m, $OCH_2CH_AH_B$), 1.84 (1H, m, $OCH_2CH_AH_B$); NMR δ_C (100 MHz) 175.9 (C), 171.0 (C), 150.3 (C), 134.1 (CH), 132.3 (CH), 114.6 (CH), 112.8 (C), 111.7 (CH), 58.1 (CH_2), 53.7 (CH), 36.0 (CH_2); HRMS (ESI^-): calcd. $C_{11}NO_4H_{10}$ for ($[M-H]^-$) 220.0615, found 220.0613.

Data excluding melting point consistent with literature values.[90]

1'-Acetyl-4,5-dihydro-2H-spiro[furan-3,2'-indoline]-2,3'-dione (283)[90]



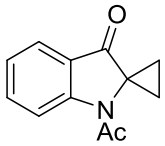
2-((2-Oxotetrahydrofuran-3-yl)amino)benzoic acid (5.00 g, 22.6 mmol) was added to a stirring solution of acetic anhydride (68 mL, 724 mmol) and triethylamine (135 mL, 973 mmol) under argon and heated to 130 °C for 3 hours. The reaction mixture was then concentrated *in vacuo*, water (100 mL) and dichloromethane (150 mL) was added, the organic layer was separated and washed with saturated aqueous sodium carbonate (3 x 100 mL). The organic layer was separated, dried with anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was stirred with diethyl ether (100 mL) for 30 minutes, the resulting solid was collected by filtration, dried and recrystallized from ethanol to afford the desired product as an off-white crystalline solid (495 mg, 9%).

mp 160-162 °C (mp lit.[90] 160 °C); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 1771, 1711, 1668, 1583, 1463, 1159, 960, 762; NMR δ_H (400 MHz, $CDCl_3$) 7.83 (1H, dd, *J* = 7.5, 1.5 Hz, Ar-*H*), 7.75 (1H, ddd, *J* = 8.5, 7.5, 1.5 Hz, Ar-*H*), 7.55 (1H, d, *J* = 8.5 Hz, Ar-*H*), 7.32–7.27 (1H, m, Ar-*H*), 4.73 (2H, m, $OCH_2CH_AH_B$), 2.96 (1H, dt, *J* = 12.9, 8.3 Hz, OCH_AH_B), 2.70–2.53 (4H, m, OCH_AH_B, $O{=}CCH_3$); NMR δ_C (100 MHz) 194.3 (C), 170.0 (C), 167.6 (C), 152.1 (C), 138.0 (CH), 126.0 (CH), 124.6 (CH), 123.0 (C), 114.9 (CH), 72.2 (C), 66.1 (CH_2), 30.7 (CH_2), 25.8 (CH_3);

HRMS (ESI^+): calcd. $C_{13}NO_4H_{11}Na$ for ($[M+Na]^+$) 268.0580, found 268.0582.

Data consistent with literature values.[90]

1'-Acetylspiro[cyclopropane-1,2'-indolin]-3'-one (284)[90]



1'-Acetyl-4,5-dihydro-2H-spiro[furan-3,2'-indoline]-2,3'-dione (450 mg, 1.84 mmol) was added to a stirring solution of sodium chloride (120 mg, 2.04 mmol) in dry DMSO (2 mL) under argon. The reaction was heated to 160 °C for 2 hours then allowed to cool to room temperature, then poured onto ice-water. The resulting precipitate was collected by filtration, dissolved in chloroform and activated charcoal was added. The mixture was then filtered through a pad of Celite, washed with chloroform and the filtrate was concentrated *in vacuo* then recrystallized from ethanol to afford the desired product as colourless crystalline solid (190 mg, 52%).

mp 157-159 °C (mp lit.[90] 157 °C); IR_{sol} (ν_{max}/cm^{-1}, $CHCl_3$) 1702, 1661, 1606, 1466, 1375, 1305, 763; NMR δ_H (400 MHz, $CDCl_3$) 7.87 (1H, dt, *J* = 7.7, 1.1 Hz, Ar-*H*), 7.74–7.64 (2H, m, Ar-*H*), 7.33–7.24 (1H, m, Ar-*H*), 2.56 (3H, s, O=CC*H*$_3$), 2.51 (2H, q, *J* = 4.0 Hz, C*H*$_2$), 1.49 (2H, q, *J* = 4.0 Hz, C*H*$_2$); NMR δ_C (100 MHz) 197.0 (C), 167.9 (C), 151.5 (C), 135.7 (CH), 124.2 (C), 124.0 (CH), 123.7 (CH), 116.1 (CH), 53.4 (C), 27.1 (CH_3), 16.9 (CH_2); HRMS (ESI^+): calcd. $C_{12}NO_2H_{11}Na$ for ($[M+Na]^+$) 224.0682, found 224.0680.

Data consistent with literature values.[90]

2,3,4,5-tetrahydropyridine (279)[91]



Piperidine (5.00 g, 58.8 mmol) was added to a stirring solution of *N*-chlorosuccinimide (8.12 g, 60.6 mmol) in diethyl ether (295 mL). After 3.5 hours the reaction mixture was filtered and concentrated *in vacuo* to ~40 mL (water bath maintained at 5 °C; due to the well-known thermal instability of chlorinated amines, the solvent must be removed without heating), then added to a premixed solution of potassium hydroxide (7.15 g, 128 mmol) in ethanol (120 mL) and stirred for 16 hours. The reaction mixture was concentrated *in vacuo* to ~15 mL, diethyl ether (100 mL) was added and then washed with water (2x50 mL). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated to afford the desired product as a clear oil (2.90 g, 59%). ^{1}H NMR spectroscopy showed the product as a mixture of monomer and trimer. The mixture was carried through without further purification.

; NMR δ_H (400 MHz, $CDCl_3$) 7.81 (1H, p, *J* = 2.5 Hz, N=C*H*, *monomeric form*), 3.56 (2H, dtt, *J* = 6.0, 5.0, 2.3 Hz, *monomeric form*), 3.13 (3H, dt, *J* = 10.5, 4.9 Hz, *trimeric form*), 2.86–2.75 (3H, m, *trimeric form*), 2.30–2.10 (2H, m, *monomeric form*), 2.11–1.86 (3H, m, *trimeric form*), 1.81–1.51 (20H, m, *trimeric form & monomeric form*), 1.37–1.27 (3H, m, *trimeric form*).

Data consistent with literature values.[91]

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Appendix 1. Crystal structure of (*Z*)-1-acetyl-2-benzylideneindolin-3-one (17)

TTWLLA

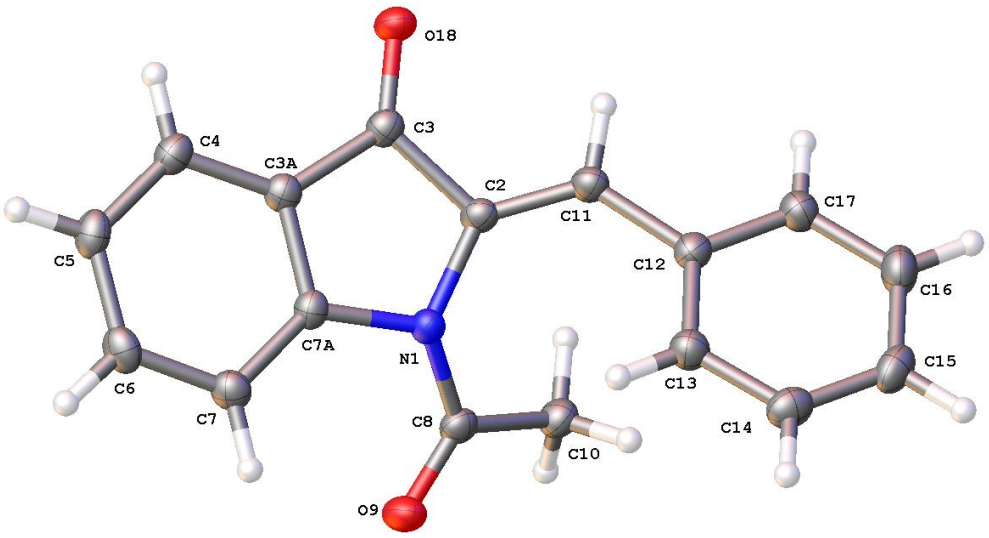


Table 1 Crystal data and structure refinement for TTWLLA.

Identification code	TTWLLA
Empirical formula	$C_{17}H_{13}NO_2$
Formula weight	263.28
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.7018(6)
b/Å	13.1984(6)
c/Å	8.2129(4)
α/°	90
β/°	92.344(5)
γ/°	90

Volume/Å^3	1267.38(11)
Z	4
ρ_{calc}mg/mm^3	1.380
m/mm^{-1}	0.732
F(000)	552.0
Crystal size/mm^3	0.49 × 0.3543 × 0.2473
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection	7.562 to 148.584°
Index ranges	-12 ≤ h ≤ 14, -13 ≤ k ≤ 16, -10 ≤ l ≤ 10
Reflections collected	5066
Independent reflections	2507 [R_{int} = 0.0195, R_{sigma} = 0.0214]
Data/restraints/parameters	2507/0/183
Goodness-of-fit on F^2	1.035
Final R indexes [I>=2σ (I)]	R_1 = 0.0376, wR_2 = 0.0994
Final R indexes [all data]	R_1 = 0.0412, wR_2 = 0.1022
Largest diff. peak/hole / e Å^{-3}	0.25/-0.20

Experimental

Single crystals of $C_{17}H_{13}NO_2$ **[TTWLLA]** were **[]**. A suitable crystal was selected and **[mounted in fomblin film on a micromount]** on a **GV1000, Atlas** diffractometer. The crystal was kept at 120(2) K during data collection. Using Olex2 [1], the structure was solved with the olex2.solve [2] structure solution program using Charge Flipping and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. (2013). in preparation.
3. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

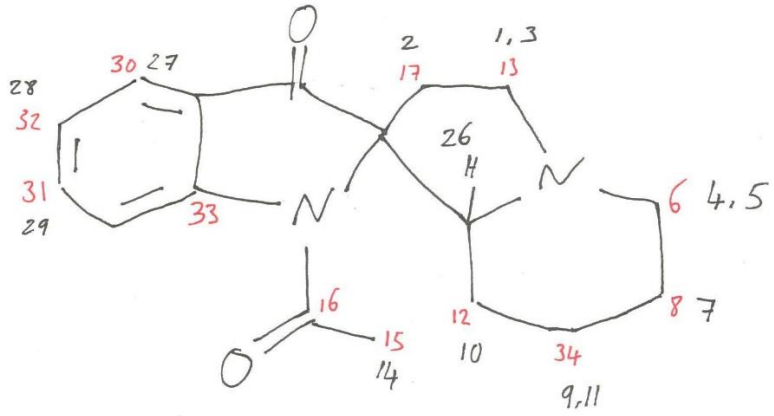
Appendix 2. Evidence for synthesis of 1-acetyl-2',3',6',7',8',8a'-hexahydro-*5'H*-spiro[indoline-2,1'-indolizin]-3-one (286)

Magnesium iodide (56 mg, 0.20 mmol) was added to a stirring solution of 1'-acetylspiro[cyclopropane-1,2'-indolin]-3'-one **284** (40 mg, 0.20 mmol) and 2,3,4,5-tetrahydropyridine (166 mg, 2.00 mmol) in dry THF (2 mL). The tube was sealed and heated to 125 °C for 24 hours then allowed to cool to room temperature. Water (15 mL) was added and the mixture was extracted with dichloromethane (3x15 mL) the combined organics were washed with brine (30 mL), then separated, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel using 2% methanol in dichloromethane as eluent to afford the desired compound as yellow film (2 mg, 4%).

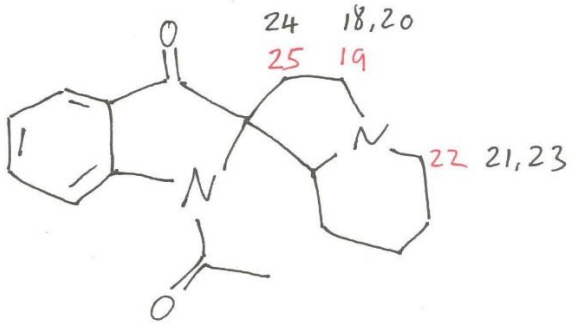
Major

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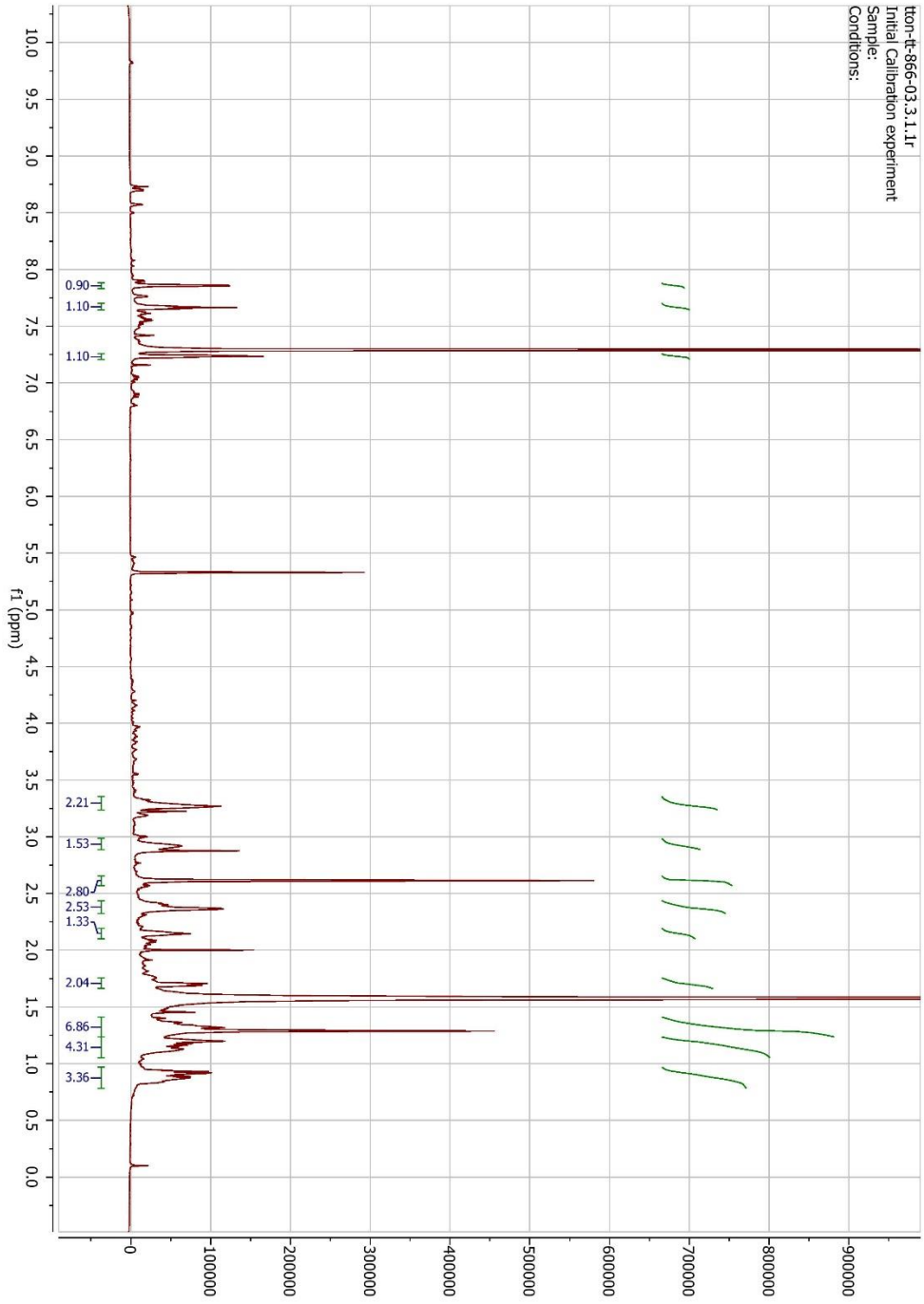
Red = ^{13}C

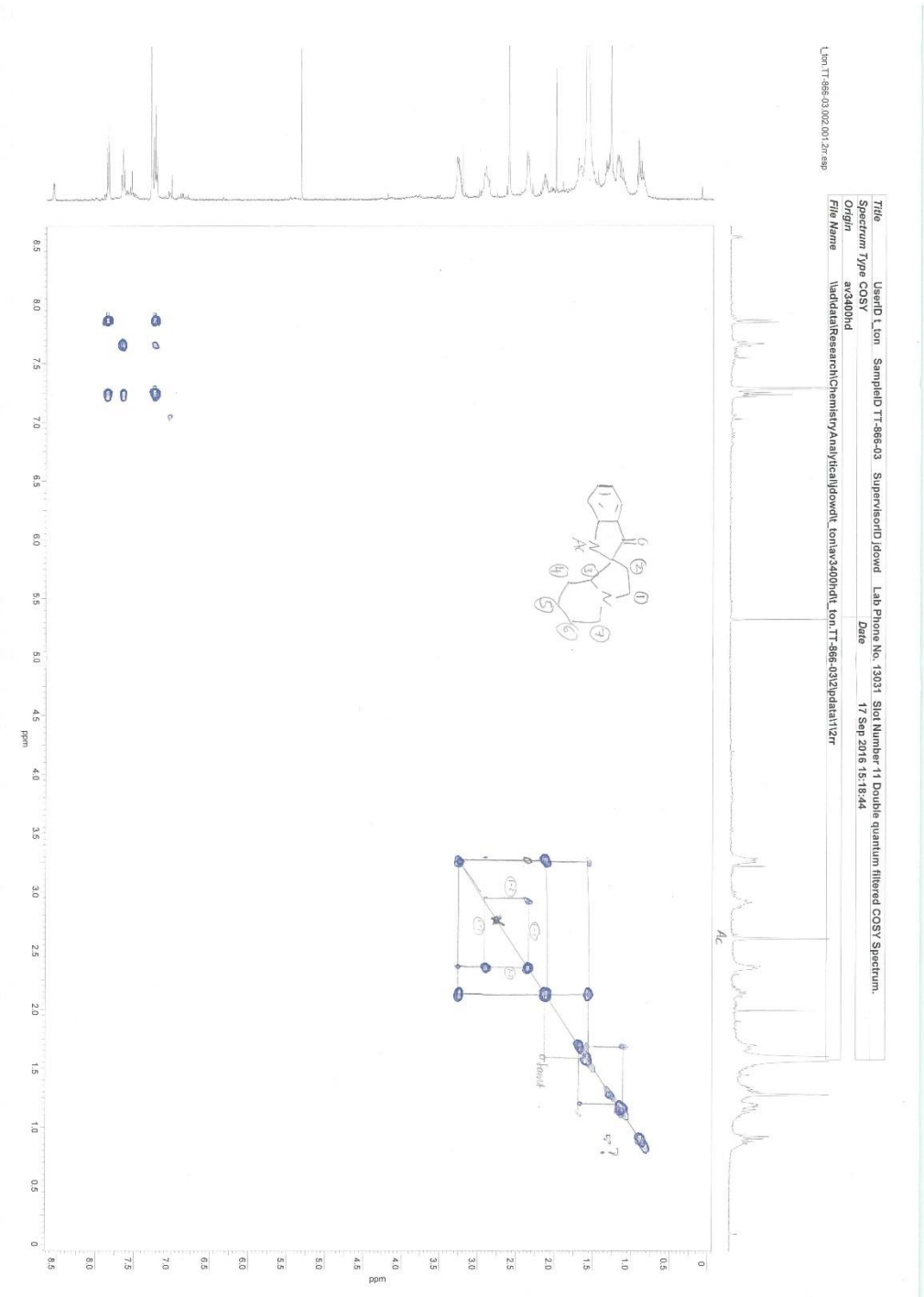


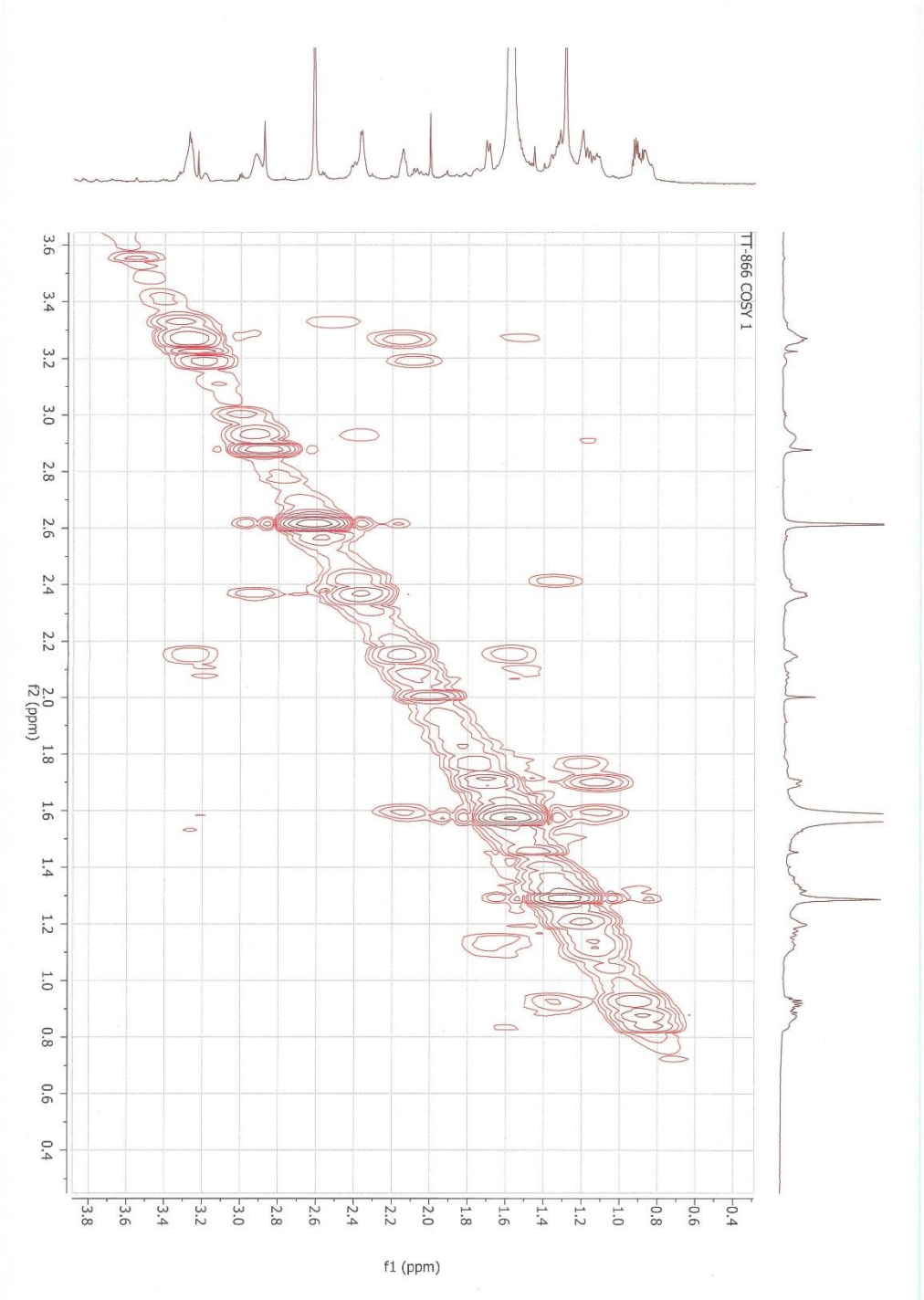
Minor

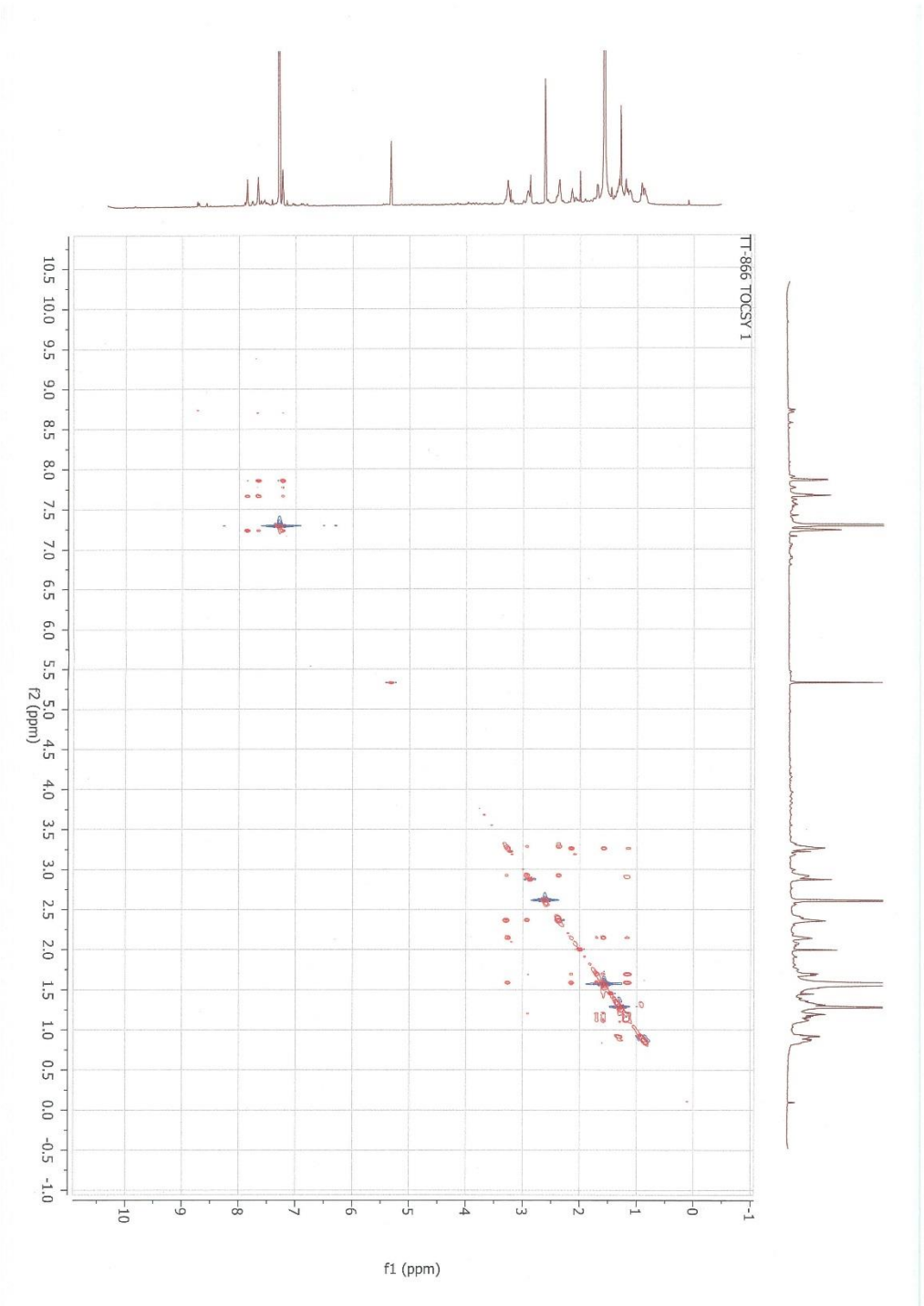


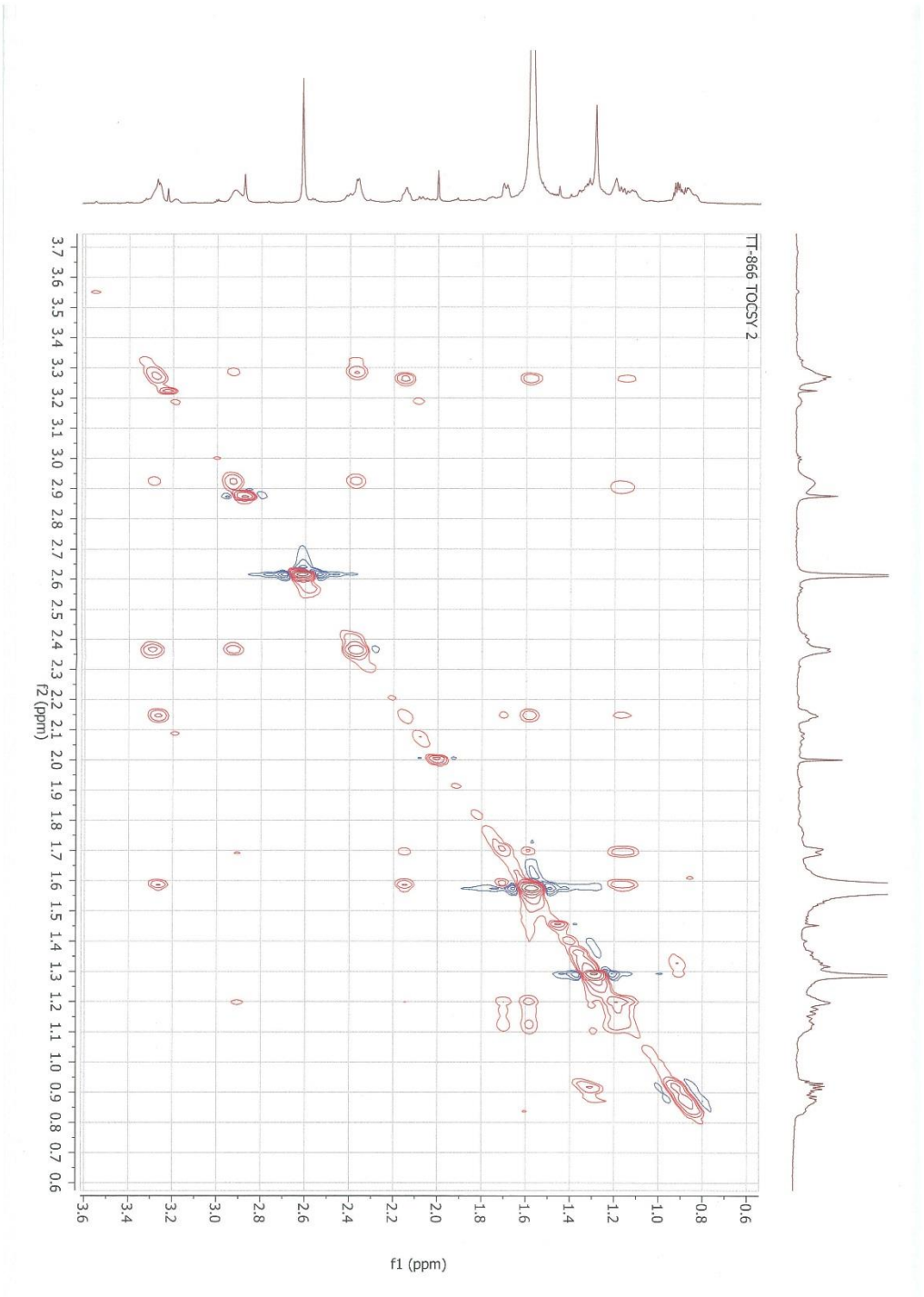
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3	3	3.28605	0.00145	[3]		1H
4	4	2.14905	0.00343	[4]		1H
5	5	3.26538	0.00285	[5]		1H
6	6	56.14848	0.02564	[6]		13C
7	7	1.58397	0.00439	[7]		1H
8	8	27.2626	0.05552	[8]		13C
9	9	1.19744	0.00494	[9]		1H
10	10	1.69904	0.00359	[10]		1H
11	11	1.12468	0.0032	[11]		1H
12	12	26.55551	0.07264	[12]		13C
13	13	56.8113	0.0069	[13]		13C
14	14	2.61018	0.00347	[14]		1H
15	15	29.87366	0	[15]		13C
16	16	170.3935	0	[16]		13C
17	17	34.77005	0	[17]		13C
18	18	3.32386	0.00242	[18]		1H
19	19	56.73016	0.02206	[19]		13C
20	20	2.56415	1.29E-04	[20]		1H
21	21	3.18546	0.00203	[21]		1H
22	22	55.85092	0.01306	[22]		13C
23	23	2.08228	0.0013	[23]		1H
24	24	2.36307	0	[24]		1H
25	25	34.64135	0	[25]		13C
26	26	2.9064	0.00103	[26]		1H
27	27	7.85951	0.00259	[27]		1H
28	28	7.23446	0.00239	[28]		1H
29	29	7.66716	0.00429	[29]		1H
30	30	127.4047	0.02442	[30]		13C
31	31	139.1629	0.06229	[31]		13C
32	32	126.5786	0	[32]		13C
33	33	154.4144	0.01455	[33]		13C
34	34	28.4543	0	[34]		13C

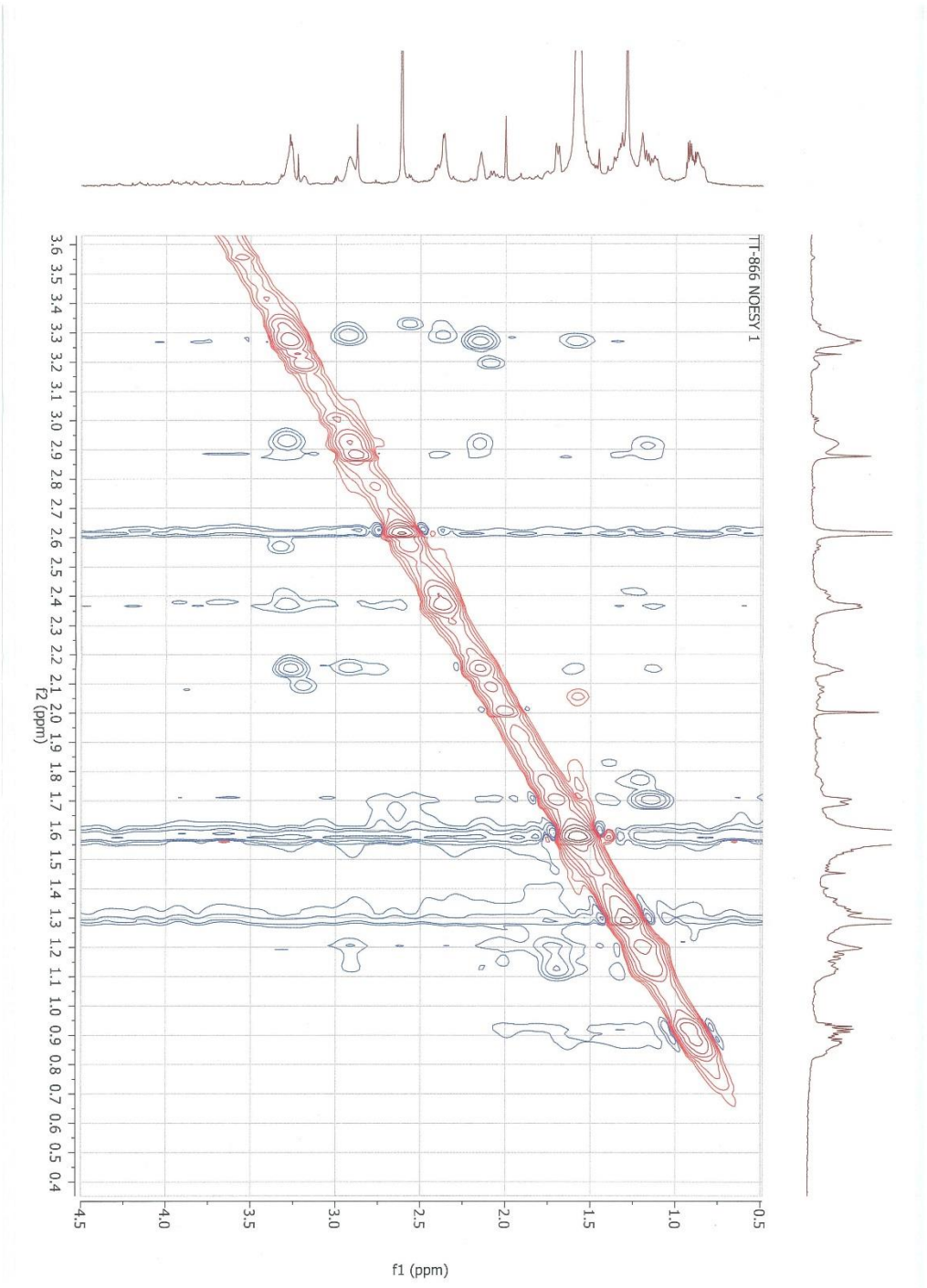

tton-tt-866-03.3.1.1r
Initial Calibration experiment
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1.53
2.80
2.53
1.33
2.04
6.86
4.31
3.36
f1 (ppm)

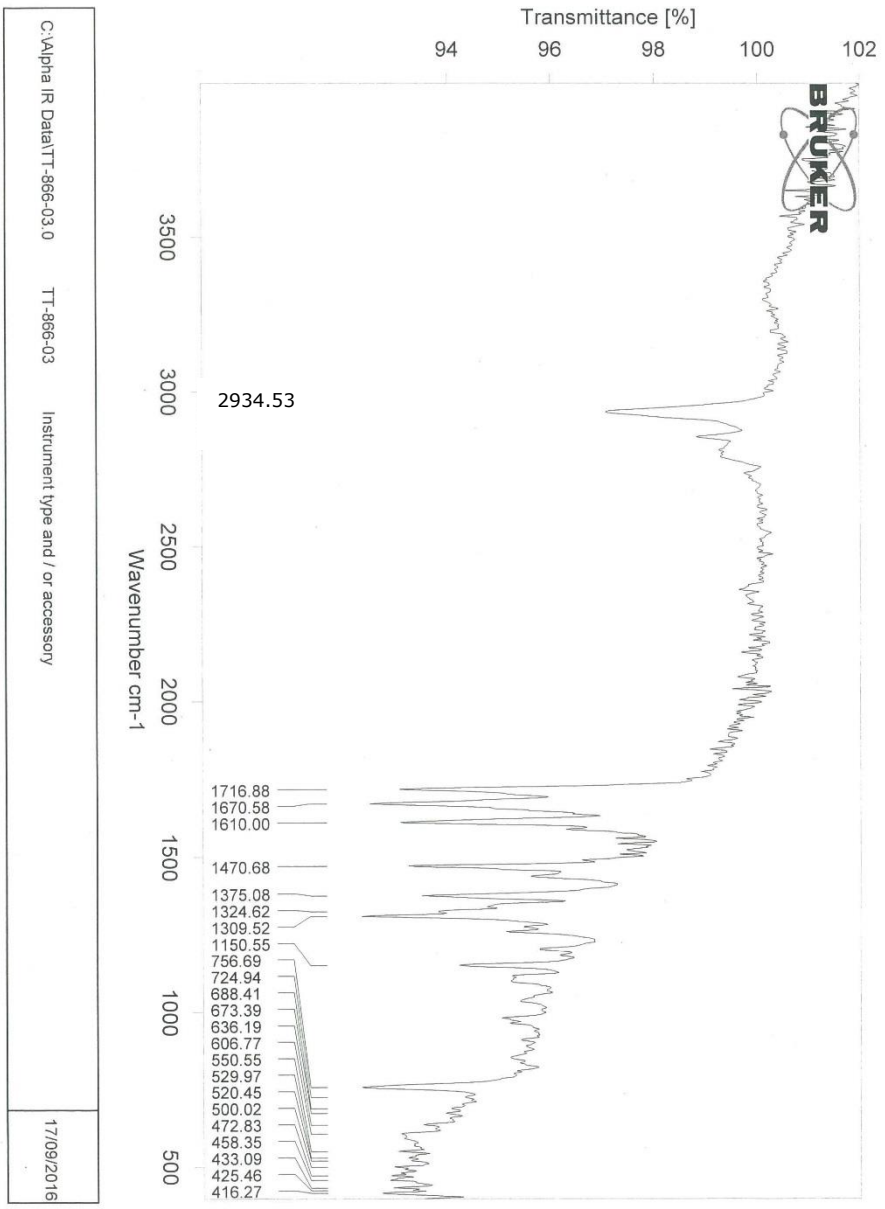

Title
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SampleID TT-868-03
SupervisorID jdowd
Lab Phone No. 13031
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Spectrum Type COSY
Date 17 Sep 2016 15:18:44
Origin av3400hd
File Name \\adhdata\Research\ChemistryAnalytical\jdowd\t_ton\av3400hd\t_ton.TT-868-0312\pdata\1\2rr
L.ton TT-868-03.002.001.2rr.esp
Ac
ppm
ppm


TT-866 COSY 1
f2 (ppm)
f1 (ppm)


TT-866 TOCSY 1
f2 (ppm)
f1 (ppm)


TT-866 TOCSY 2
f2 (ppm)
f1 (ppm)


TT-866 NOESY 1
f2 (ppm)
f1 (ppm)

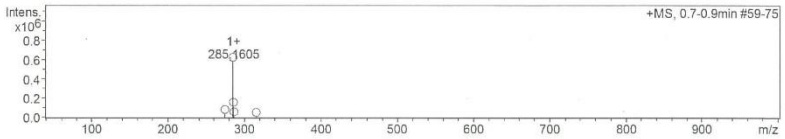

Transmittance [%]
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98
100
102
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2000
1500
1000
500
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1610.00
1470.68
1375.08
1324.62
1309.52
1150.55
756.69
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472.83
458.35
433.09
425.46
416.27
C:\Alpha IR Data\TT-866-03.0
TT-866-03
Instrument type and / or accessory
17/09/2016
Page 1/1

Mass Spectrometry
Analytical Services
School of Chemistry

The University of Nottingham

Sample-ID	t_ton_TT-866-F32	Lab	C13
Submitter	Tom Tongue	Supervisor	James Dowden
Analysis Name	t_ton_TT-866-F32_533213_4_01_30783.d	Acquisition Date	9/17/2016 2:51:10 PM
Ionisation Mode	ESI Positive	Instrument	Bruker MicroTOF

+MS, 0.7-0.9min #59-75



#	m/z	I %
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3	220.9382	0.3
4	221.2003	0.3
5	226.9517	0.3
6	229.1683	0.9
7	233.2000	0.3
8	243.1488	0.7
9	250.2277	0.4
10	275.1789	7.0
11	276.1834	1.3
12	285.1605	100.0
13	285.5653	0.3
14	286.1633	20.1
15	287.1679	2.7
16	288.1743	0.3
17	288.9233	0.2
18	307.1420	0.7
19	316.2746	1.9
20	317.2782	0.4

Generate Molecular Formula Parameters

No of Most Intense MS Peaks Analysed 5

Charge	Tolerance	sigma_limit	Calibration
+1	6 ppm	0.08	TRUE

Formula Min C 1 H 0 N 0 O 0 **Formula Max** C50 H100 N10 O10 H Na NH4 C3H5N2

#	meas. m/z	theo. m/z	|Err|[ppm]	Sigma	Formula
1	285.1605	285.1598	2.60	0.0047	C 17 H 21 N 2 O 2
		285.1614	3.10	0.0108	C 20 H 22 Na 1
2	286.1633	286.1622	3.90	0.0013	C 10 H 20 N 7 O 3
		286.1625	2.90	0.0026	C 12 H 25 N 1 Na 1 O 5
		286.1622	3.80	0.0073	C 11 H 26 O 8
		286.1636	0.80	0.0079	C 12 H 22 N 4 O 4
		286.1625	2.90	0.0093	C 11 H 19 N 8 Na 1

Appendix 3. Production and isolation data of cytochrome $P450_{BM3}$ protein

The P450 BM3 heme domain gene from *Bacillus megaterium* inserted into the pETM-11 expression vector was obtained as a gift from Dr Wong's group from the University of Sheffield. The protein was expressed and purified in Anca Pordea's laboratory (Faculty of Engineering, UoN), according to a published procedure.[1] Two variants were prepared: wild-type (WT) and the F87A mutant. The vector provides kanamycin resistance, and an N-terminal hexahistidine tag.

Briefly, pETM-11 vector containing P450 BM3 heme domain was transformed into *E.coli* BL21(DE3) competent cells. A single colony was used to prepare an overnight pre-culture in LB medium (100 mL) supplemented with kanamycin (25 μg/mL). The pre-culture was used to inoculate the expression culture to OD_{600} ~ 0.1. Cells were grown in 2L shake flasks (800 mL medium supplemented with trace elements and kanamycin, 37 °C, 250 rpm) to OD_{600} ~ 0.8. Trace elements were prepared as a 1000 times concentrate of the working concentration ($CaCl_2$*$2H_2O$ 3.4 mM; $ZnSO_4$ *$7H_2O$ 0.63 mM; $MnSO_4$ *$4H_2O$ 0.6 mM; Na_2-EDTA 54 mM; $FeCl_3$ *$6H_2O$ 62 mM; $CuSO_4$ *$5H_2O$ 0.64 mM; $CoCl_2$ *$6H_2O$ 0.76 mM). Expression was induced with IPTG at 30 °C (1 mM final concentration) and δ-aminolevulinic acid (δ-ALA, 0.5 mM) and the culture was continued for 15h (OD_{600} ~ 2.3). Post induction, cells were harvested by centrifugation (8000 rpm, 15 min, 4 °C). The cell pellet was purified using a HiTrap IMAC column (1 mL) precharged with Ni^{2+}, using an imidazole gradient elution. The pooled purified fractions were dialysed in 20 mM phosphate, pH 7.0 for 16 h. Protein concentration was determined using Lowry assay, collected fractions were concentrated to 19 mg/mL (WT) and 28 mg/mL (F87A), and the protein was stored at -20 °C.

Concentration of active heme was determined by CO-difference spectra, as reported by Omura and Sato,[2] using ε = 91 $mM^{-1}cm^{-1}$. Typically, the protein was diluted to 0.95 $mg.mL^{-1}$ (18 μM) in CO-saturated phosphate buffer (20mM, pH 7.0), then solid $Na_2S_2O_4$ was added in several portions (a few mg each). The

decrease in absorbance at 419 nm and the decrease in absorbance at 449 nm were monitored during the addition, until no change in spectrum was observed. The difference spectrum (in the presence and in the absence of $Na_2S_2O_4$) at 449 nm indicated the concentration of CO-bound heme. The calculated concentrations were 6.5 μM for WT and 7.6 μM for F87A.

1. Kuper, J.; Wong, T. S.; Roccatano, D.; Wilmanns, M.; Schwaneberg, U., Understanding a Mechanism of Organic Cosolvent Inactivation in Heme Monooxygenase P450 BM-3. *Journal of the American Chemical Society* **2007,** *129* (18), 5786-5787.

2. Omura, T.; Sato, R., The Carbon Monoxide-binding Pigment of Liver Microsomes: I. EVIDENCE FOR ITS HEMOPROTEIN NATURE. *Journal of Biological Chemistry* **1964,** *239* (7), 2370-2378.