Application of Direct Imine Acylation Methodology in the Synthesis of Nitrogen Heterocycles and Natural Products

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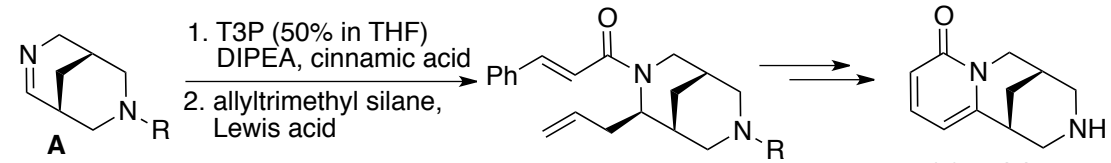
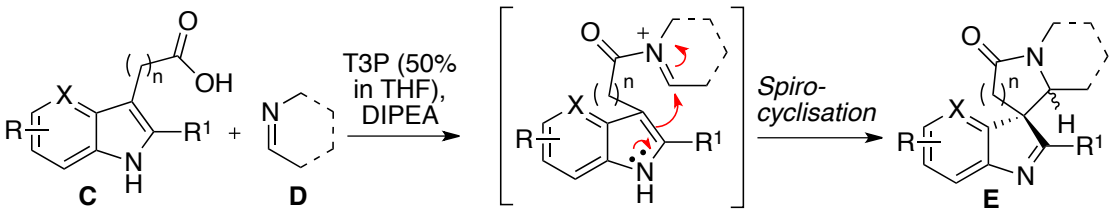
Abstract

This thesis describes the use of direct imine acylation (DIA) methodology in a range of different applications. Firstly, the attempted synthesis of (±)-cytisine is described (Chapter 2). The use of DIA methodology in the formation of the pyridone ring scaffold of (±)-cytisine has been explored. In the most advanced synthesis towards (±)-cytisine achieved in this project, the generation of *N*-acyliminium ions from imine **A** and subsequent nucleophilic addition of organometallic allyl reagents was developed to give diene **B**.



DIA methodology has also been utilised in the synthesis of spirocyclic products from simple indole acids **C** and imines **D** (Chapter 3). The reaction provides a broad range of products **E** in good yields and the indole acid starting materials **C** are readily synthesised using Fischer indole methodology. The stereoselectivity of the reaction, derivatisation of the products **E** and 3D shape analysis are also described.



Finally, work towards the synthesis of (±)-aspidospermidine, using the spirocyclisation methodology developed in this project, is introduced (Chapter 4). Two strategies are proposed utilising an intramolecular Heck reaction or a ring-closing metathesis to complete the polycyclic scaffold. A key DIA reaction between the synthesised acid **F** and imine **G** is reported and shows formation of the spirocyclic scaffold **H**.

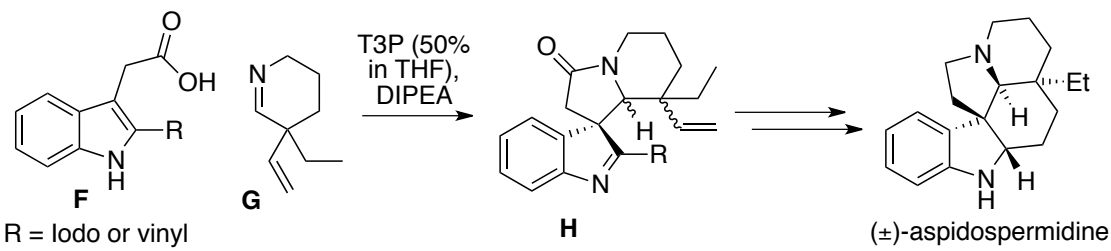


Table of Contents

List of Tables

List of Figures

Acknowledgements

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Finally, I would like to especially thank Joe for all of his love and encouragement throughout my PhD. Thank you for being by my side and reassuring me through the many failed reactions. A heartfelt thanks also goes to my family, in particular Mum and Dad, who have always provided endless support and motivation, for which I am extremely grateful.

Author's Declaration

The work presented in this thesis is my own and was carried out at the University of York between October 2012 and September 2016. The work is, to the best of my knowledge, original except where reference has been made to other workers. In Chapter 3, reference has been made to Dr Graeme Coulthard (Taylor group, University of York) who contributed to the synthesis of products. In Chapter 4, reference has been made to Dr Graeme Coulthard and Dr William Unsworth (Taylor group, University of York) who contributed to the synthesis of a starting material. In Section 3.3.10, the computational analysis was carried out in collaboration with Mary Wheldon (O'Brien group, University of York), Paul Bond and Professor Rod Hubbard (York Structural Biology Laboratory).

This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as references.

Part of this work has been reproduced in a published paper, a copy of which can be found in Appendix I:

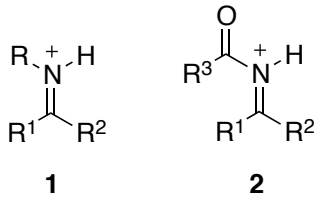
Chambers, S. J.; Coulthard, G.; Unsworth, W. P.; O'Brien, P.; Taylor, R. J. K.; From Heteroaromatic Acids and Imines to Azaspirocycles: Stereoselective Synthesis and 3D Shape Analysis; *Chem. Eur. J.* **2016**, *22*, 6496-6500.

1. Introduction

1.1. Introduction to *N*-Acyliminium Ions

1.1.1. Structure and Reactivity of *N*-Acyliminium Ions

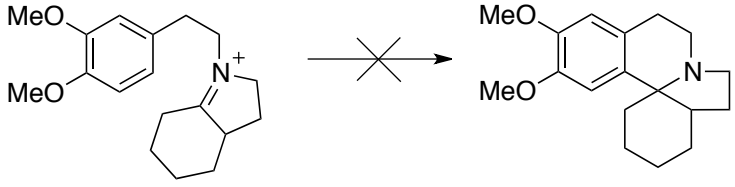
Iminium ions **1** and *N*-acyliminium ions **2** are important, reactive species in organic synthesis (Figure 1.1). They are very useful in the construction of carbon-carbon and carbon-heteroatom bonds.[1] *N*-acyliminium ions are particularly important due to their increased reactivity compared to iminium ions. The carbonyl group on the nitrogen is electron-withdrawing both inductively and mesomerically so that the iminium carbon atom is more electron deficient with more cationic character.[1]



1 **2**

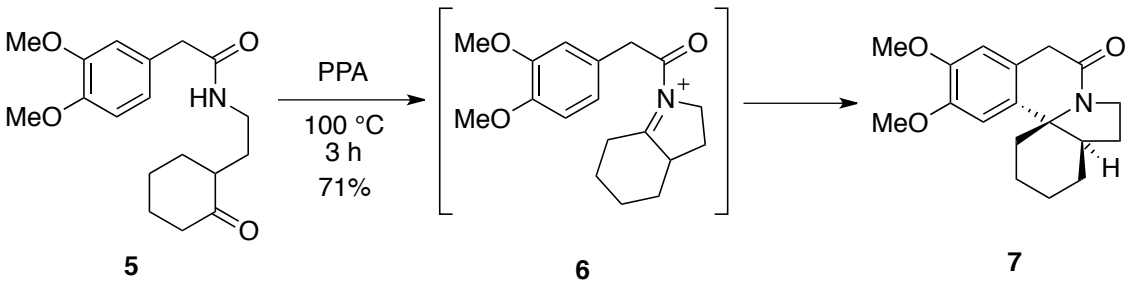
Figure 1.1 – Structure of iminium ion 1 and *N*-acyliminium ion 2

Nucleophiles that are relatively unreactive towards *N*-alkyliminium ions can be effectively used in the reaction with *N*-acyliminium ions.[1] This was exhibited in Belleau's early synthesis of the tetrahydroisoquinoline scaffolds of the *erythrina* alkaloids.[2,3] The poor reactivity of the iminium ion intermediates, used in the Pictet-Spengler approach to tetrahydroisoquinolines, was demonstrated by the failure of iminium ion **3** to cyclise to **4** under various conditions (Scheme 1.1).[3] Successful cyclisation of *N*-acyliminium ion **6** (prepared from **5**) to give the product **7** (Scheme 1.2) confirmed the expectation that the acyl component would increase electrophilic reactivity.[1,3]



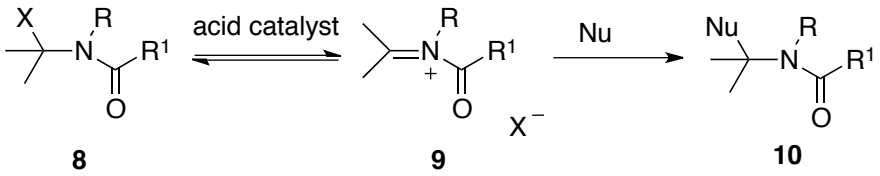
3 **4**

Scheme 1.1 – Unsuccessful nucleophilic addition onto iminium ion 3[3]



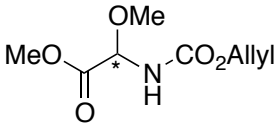
Scheme 1.2 – Successful cyclisation onto *N*-acyliminium ion 6[3]

The mechanistic scheme for the majority of amidoalkylation reactions is shown in Scheme 1.3. It has been observed that the intermediate *N*-acyliminium ion **9** is not generated stoichiometrically throughout the course of a reaction, as it can exist in equilibrium with a covalent adduct **8** (Scheme 1.3).[1] An irreversible nucleophilic reaction into the iminium carbon gives product **10**. In the synthesis of β-lactams, tertiary imines can be treated with acid chlorides to generate intermediate *N*-acyliminium species **9** with the ionic structure shown in Scheme 1.3 (where X = Cl). However, NMR spectroscopic studies have shown that the adducts of the reaction exist mainly as the α-chloroamides **8** (where X = Cl).[4] α-Alkoxycarbamates **8** (where X = OR) are a common precursor to *N*-acyliminium ions and have been shown to generate intermediate **9** on treatment with a Lewis acid. Yamamoto *et al.* have reported the existence of this type of equilibrium in solution and shown that the proportion of the ionic form **9** and covalent form **8** varies depending on the Lewis acid used.[5]



Scheme 1.3 – Mechanism for amidoalkylation reactions

The mechanistic pathway of a reaction involving an *N*-acyliminium ion will always go through a planar intermediate and therefore direct control of the stereochemistry is not possible. For example, the optically pure compound (+)-**11** (configuration unknown) formed racemic products when reacted with various nucleophiles (*e.g.* allyltrimethylsilane and furan) in the presence of a Lewis acid (Figure 1.2).[6] However, stereoselectivity can be induced in these reactions through the use of chiral auxiliaries,[7] or chiral acid catalysts as demonstrated by Muratore *et al*.[8]

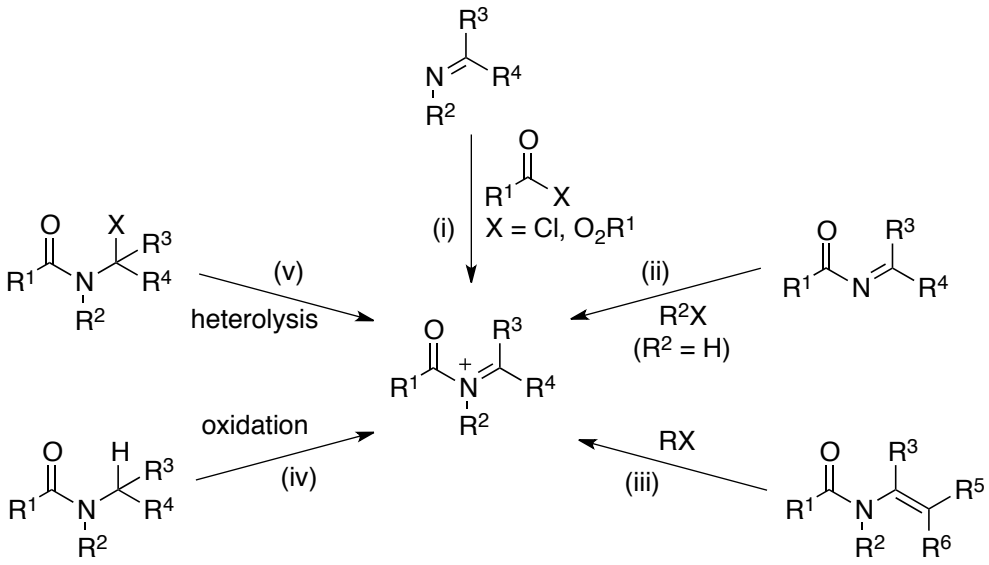


(+)-11

Figure 1.2 – Enantioenriched precursor of *N*-acyliminium ion

1.1.2. Synthesis of *N*-Acyliminium Ions

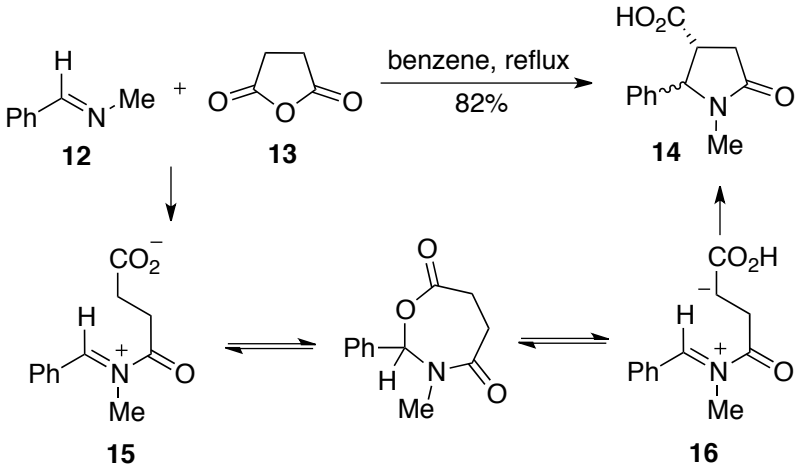
N-acyliminium ions can be generated in many different ways but owing to their reactivity they are almost always generated *in situ*.[1] The most common synthetic approaches to generate *N*-acyliminiums are shown in Scheme 1.4. These methods include: (i) acylation of imines, (ii) *N*-protonation of *N*-acylimines, (iii) electrophilic addition to enamides, (iv) oxidation of amides, and (v) heterolysis of amides bearing a leaving group 'X' on the carbon α to nitrogen.[5,9] These methods have been well documented but selected methods will be briefly discussed here.[9]



Scheme 1.4 – Methods for the synthesis of *N*-acyliminium ions

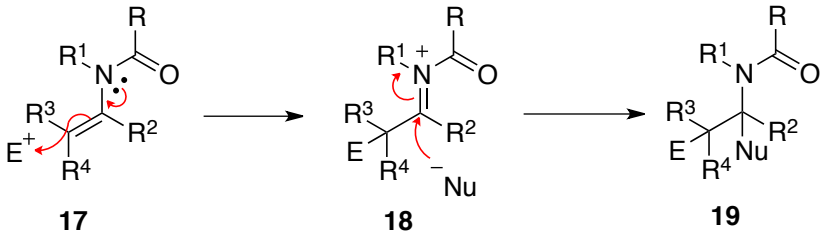
The preparation of *N*-acyliminium ions by the reaction of acid chlorides and imines (Scheme 1.4, (i)) was first reported in 1914 by James and Judd.[10] This methodology has since been used in a number of applications, such as the synthesis of β-lactams.[4] *N*-acyliminium ions can also be generated by the acylation of an imine with an anhydride. Castagnoli *et al.* demonstrated that use of a cyclic anhydride can enable subsequent

intramolecular nucleophilic trapping (Scheme 1.5).[11] Refluxing benzylidenemethylamine **12** and succinic anhydride **13** in benzene afforded an 82% yield of the stable pyrrolidone **14** *via* the two *N*-acyliminium ions **15** and **16** shown in Scheme 1.5. This methodology was then extended by other groups to include more complex imine and anhydride examples.[12]



Scheme 1.5 – Synthesis of lactam 14 *via* intramolecular trapping[11]

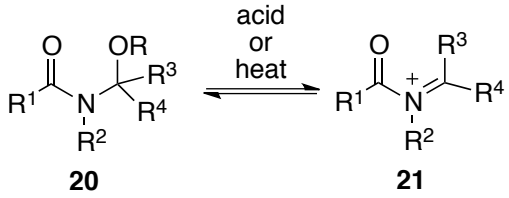
Electrophilic addition to enamides can also be used to access *N*-acyliminium ions (Scheme 1.4, (iii)). Enamides are easily accessible through the acylation of an imine with an acid chloride or anhydride, followed by elimination of HX. They are stable under neutral and basic conditions but under acidic conditions enamides **17** will be protonated or alkylated at the β-carbon to the nitrogen and form an *N*-acyliminium ion **18** (Scheme 1.6). These intermediates can be trapped with a nucleophile to form product **19**.[9] Generation of an *N*-acyliminium ion in this way has been exploited in the synthesis of the natural product nakadomarin A.[13]



Scheme 1.6 – Generation of *N*-acyliminium ions *via* enamides[13]

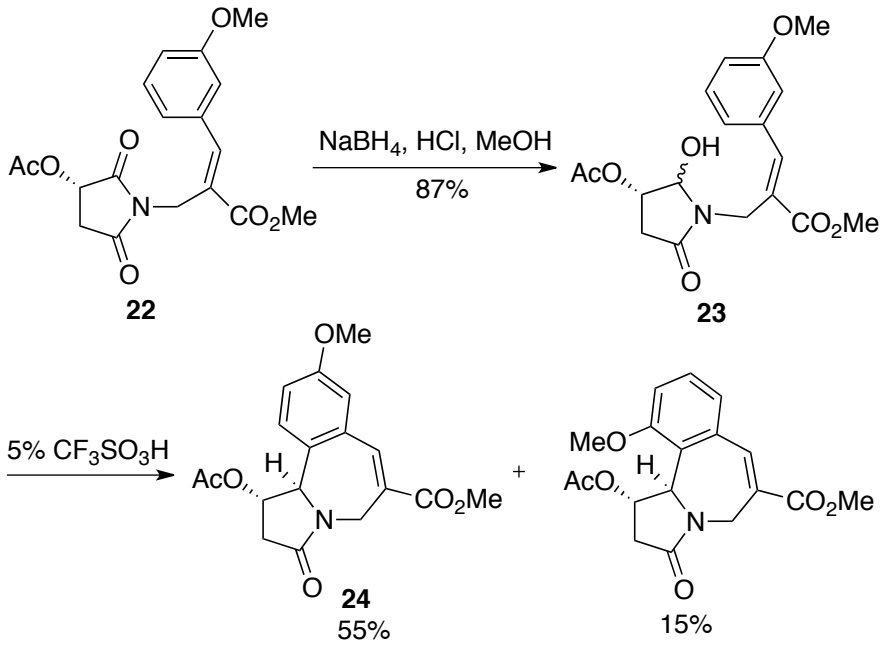
Of all the methods to generate *N*-acyliminium ions, the most frequently used is the heterolysis of α-substituted amides (Scheme 1.4, (v)). Most of the examples contain an oxygen substituent as the 'X' group, although nitrogen, sulfur and phosphorus can also

be used.[9] Where X = OR, Brönstead or Lewis acids are used to generate the *N*-acyliminium ion. If R is alkyl or hydrogen then an acid is required but when R is acetyl or methanesulfonyl heat is sufficient for the elimination (Scheme 1.7).[9]



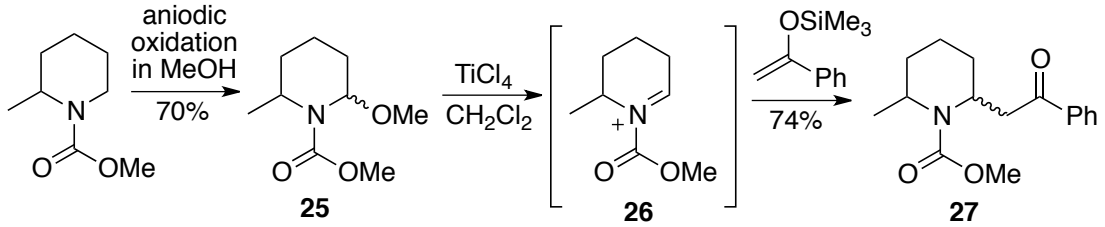
Scheme 1.7 – Generation of *N*-acyliminium ions *via* α-substituted amides

There are numerous ways to synthesise the precursor **20** that upon heterolysis will generate the *N*-acyliminium ion **21** *in situ.* Addition of oxygen nucleophiles to *N*-acyliminium ions, reaction of amides with aldehydes or ketones and addition of nucleophiles (*e.g.* organolithium and Grignard reagents) to cyclic imides have all been extensively documented as a route to *N*-acyliminium ion precursors.[1,9,14] The selective reduction of one carbonyl on a cyclic imide could be considered as the most successful and versatile technique.[1] This strategy has been demonstrated by Marson *et al.* in the enantioselective synthesis of a polycyclic 5,7,6-fused ring system **24** present in a number of biologically important compounds including the *cephalotaxus* alkaloids that exhibit anti-leukaemic activity.[15] Partial reduction of the cyclic imide **22** with $NaBH_4$ afforded the hemiaminal **23** (Scheme 1.8). Generation of the *N*-acyliminium ion was accomplished by reaction with triflic acid and cyclisation provided the tricyclic lactams as a mixture of diastereoisomers and regioisomers with the major isomer **24** isolated in 55% yield (Scheme 1.8).



Scheme 1.8 – Reduction of a cyclic imide and intramolecular cyclisation[15]

An alternative method for the synthesis of precursor **21** for use in the generation of an *N*-acyliminium ion is the α-oxidation of amides (Scheme 1.4, (iv)). Shono *et al.* demonstrated the first direct electrochemical oxidation of the α-methylene group of an amide.[16-18] The reaction proceeds *via* an aniodic oxidation and methoxylation step to give the precursor **25** (Scheme 1.9).[17] This key aniodic oxidation step is operationally simple and requires a standard electrochemical reaction set up.[16,19] Subsequent Lewis acid-catalysed heterolysis generated the *N*-acyliminium ion **26** *in situ* and trapping with a silyl enol ether gave the product **27** in 74% yield (Scheme 1.9).[18]

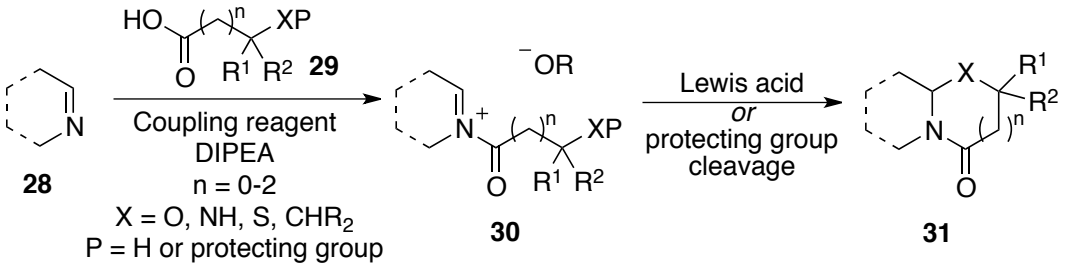


Scheme 1.9 – Generation of an *N*-acyliminium 26 *via* electrochemical oxidation[17]

1.1.3. Direct Imine Acylation

Direct Imine Acylation (DIA) is methodology developed by the Taylor group that has been shown to be useful in a number of interesting and novel cyclisation reactions.[20-22] The concept is built upon the direct acylation of imines using carboxylic acids rather than their activated derivatives.[21] Direct acylation onto imine structures using acid chlorides and anhydrides have previously been discussed and are well known methods to generate *N*-acyliminium ions, but acylation using carboxylic acids is much less common. The advantage of this method is that it allows the inclusion of an internal nucleophile, which would otherwise be incompatible with the activated carboxylic acid derivative, allowing subsequent trapping of the *N*-acyliminium ion intermediate to provide cyclised heterocyclic products.

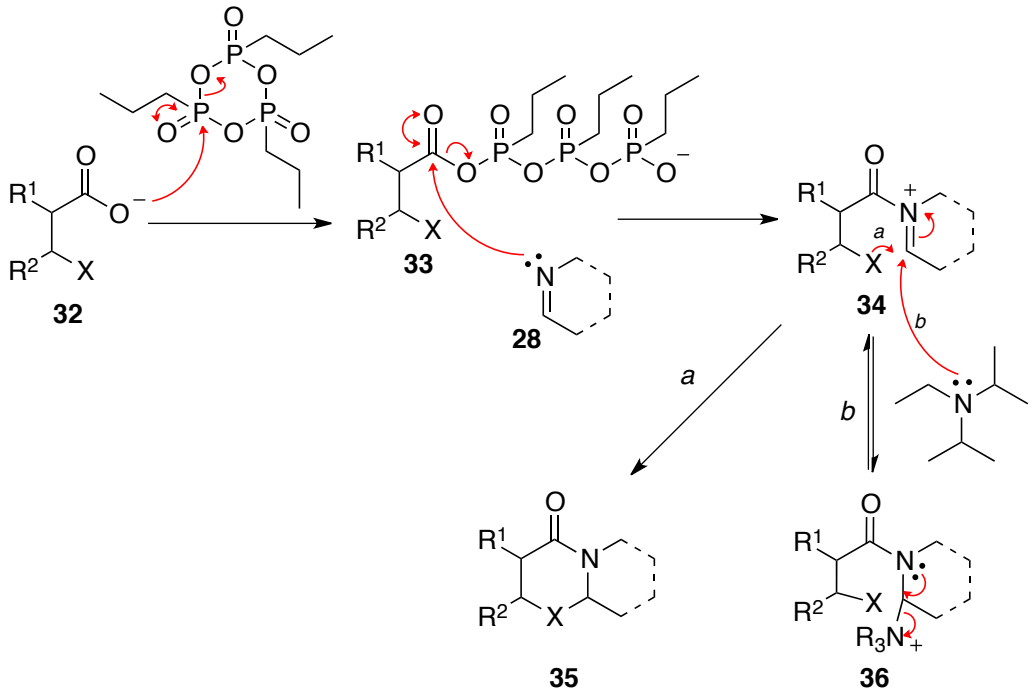
Scheme 1.10 shows the general conditions used the originally developed DIA reactions in the Taylor group. An imine **28** is directly acylated by a carboxylic acid **29**, containing an internal nucleophile, in the presence of a coupling agent and a base (DIPEA). This generates the *N*-acyliminium ion **30** that can undergo *in situ* cyclisation with the built-in nucleophile to give heterocycle **31**. Acid-promoted cyclisation or protecting group cleavage is sometimes required.



Scheme 1.10 – General scheme for a DIA reaction

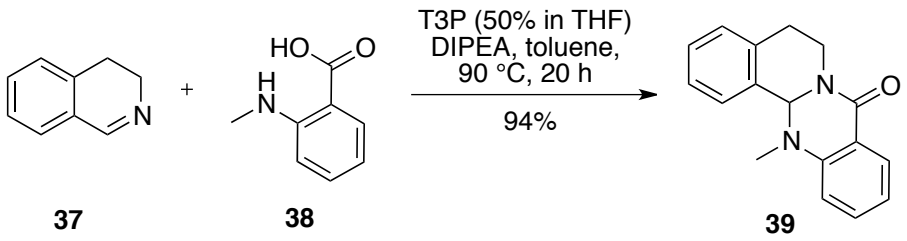
The mechanistic pathway for the formation of the *N*-acyliminium ion under DIA conditions is shown in Scheme 1.11. The reaction begins by activation of the carboxylate **32** with T3P to give coupling reagent **33**. On coupling with imine **28**, the T3P byproduct is released and has the advantage of being easily removed by aqueous extraction during the work-up. The *N*-acyliminium ion **34** formed undergoes cyclisation with the internal nucleophile to provide the cyclised product **35**. In theory, an alternative route where the nucleophile attacks the imine first and then intramolecular acylation

occurs would give the same product. Therefore, a mechanistic study using *in situ* ReactIR was carried out in the Taylor group to probe the reaction mechanism in detail and to confirm the mechanism.[21,23] The results confirmed that the *N*-acyliminium ion **34** is formed first. As expected, the *N*-acyliminium ion **34** was found to be short-lived and instead an alternative intermediate was observed. It was believed that this second intermediate was an ammonium salt **36**, formed from trapping with the excess DIPEA in the reaction mixture. However, this reaction would be reversible and it was observed that the *N*-acyliminium ion **34** was regenerated by elimination of the amine and intramolecular trapping of the nucleophile formed the product **35** (Scheme 1.11).[21,23]



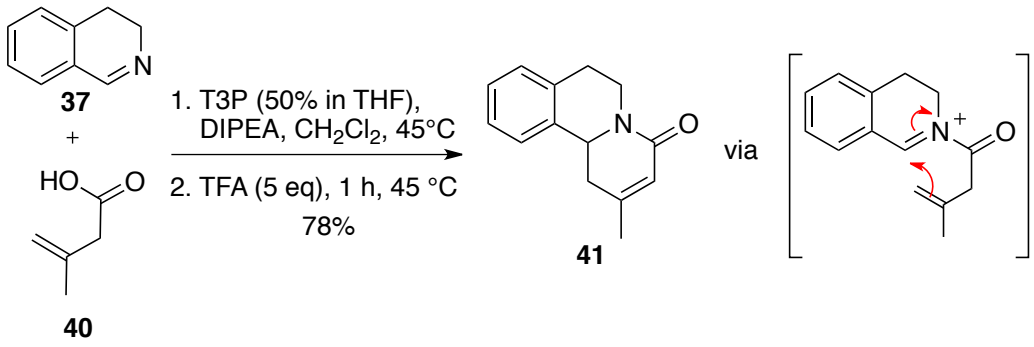
Scheme 1.11 – Mechanism for a DIA reaction

The initial publication from the Taylor group reporting this methodology showed DIA reactions of different functionalised benzoic acids and a variety of imines which highlighted the scope and potential of the method.[21] For example, the reaction of aromatic imine **37** and *N*-methylanthranilic acid **38** proceeded well under the DIA conditions shown to give the cyclised product **39** in 94% yield (Scheme 1.12). The methodology was shown to be a robust and useful technique with yields >90% for the majority of substrates, and a variety of internal nucleophiles were used.[21] A subsequent paper showcased the methodology with the synthesis of a natural product, Upenamide, where one of the key steps in the route was the efficient use of DIA methodology.[22]



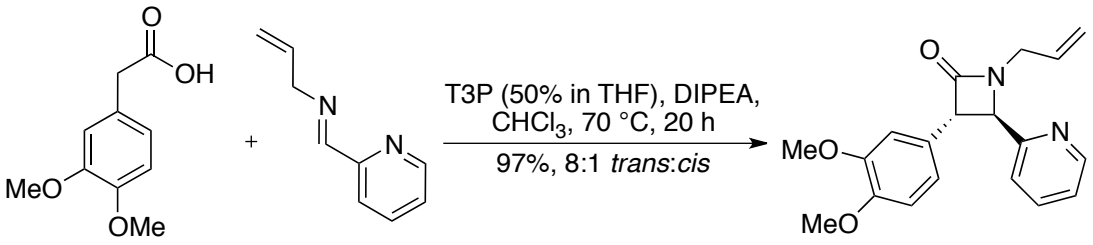
Scheme 1.12 – DIA reaction of *N*-methylanthranilic acid 38 and imine 37[21]

DIA methodology was then shown to be compatible with aliphatic carboxylic acids containing oxygen, nitrogen and sulfur nucleophiles.[20] A wide range of nucleophiles and imine substrates were showcased and demonstrated the wide scope of this methodology. Particularly noteworthy reactions in this report involved the use of acids containing carbon pro-nucleophiles such as aromatic groups and alkenes which allowed the formation of carbon-carbon bonds in the cylisation products.[20] An example of this is the reaction between aromatic imine **37** and 3-methyl-3-butenoic acid **40** under the conditions shown in Scheme 1.13 to provide the cyclised product **41** in 78% yield.



Scheme 1.13 – DIA reaction of 3-methyl-3-butenoic acid 40 and imine 37[20]

It was found that the methodology was also suitable for the synthesis of β-lactams, an example of which is shown in Scheme 1.14.[24] A good range of β-lactams were synthesised in high yield from acyclic imines and aryl-substituted acetic acids, with the *trans* isomer being the major product in most cases.[24] The lack of an acidic additive is important to avoid formation of the Friedel-Crafts type products seen when reacted with carbon pro-nucleophiles.[23]



Scheme 1.14 – Synthesis of β-lactams using DIA methodology[24]

1.2. Brief Outline of the Project

The overall aim of the work described in this thesis was to utilise DIA methodology in a range of different applications, and our three main target compounds are shown in Figure 1.3. It was hoped that development of a DIA cyclisation reaction would afford the pyridone ring scaffold present in the natural product (−)-cytisine (Chapter 2). DIA methodology would also be utilised in a novel route to spirocyclic scaffolds (Chapter 3). As an extension of this route to spirocycles, the DIA methodology would then be tested in an attempted synthesis of the natural product (±)-aspidospermidine (Chapter 4). The specific aims of each project will be discussed in more detail in each chapter, each accompanied with an associated introductory section.

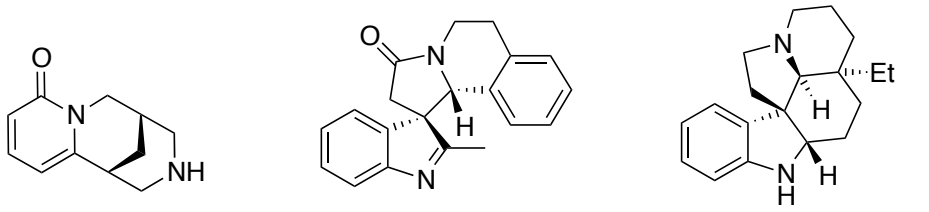


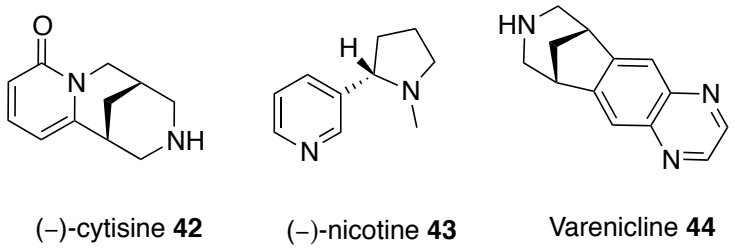
Figure 1.3 – Structure of target compounds of the projects in this thesis

2. Attempted Synthesis of (±)-Cytisine using Direct Imine Acylation Methodology

2.1. Introduction to Cytisine

2.1.1. Biological Activity and the Use of (−)-Cytisine

(−)-Cytisine **42** (Figure 2.1) is a naturally occurring lupin alkaloid prevalent in the plants and seeds of the *Leguminosae* family.[25] It shows significant biological activity at neuronal nicotinic acetylcholine receptors (nAChRs), which are found in the peripheral and central nervous systems.[26]



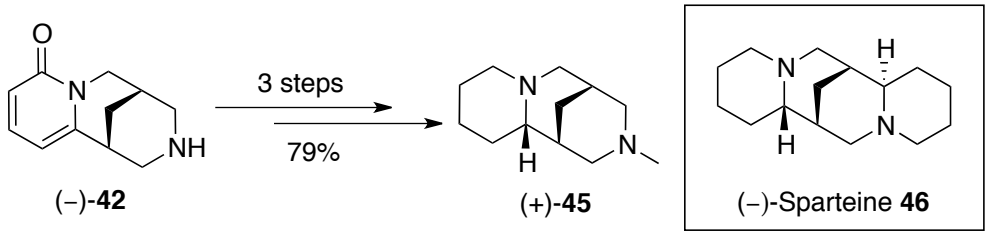
(–)-cytisine **42** (–)-nicotine **43** Varenicline **44**

Figure 2.1 – Structure of (–)-cytisine, (–)-nicotine and Varenicline

nAChRs are pentameric ligand-gated ion channels that consist of 17 known receptor subunits. Of these, the α4β2, α3β4 and α7 are the most important in the central nervous system.[26] It is known that the α4β2 nAChR subtype receptor plays a major role in reinforcing the addictive effects of (−)-nicotine **43** (Figure 2.1), through binding activation and the subsequent release of dopamine.[27] While (−)-nicotine **43** displays a full agonist profile at the α4β2 nAChR subtype receptor, (−)-cytisine **42** has also been shown to have a potent affinity for the receptor and acts as a partial agonist,[28] preventing (−)-nicotine **43** from binding and providing a reduced dopaminergic response comparatively. In this way, (−)-cytisine **42** can be used as a smoking cessation drug. This has been confirmed in a placebo controlled trial of (−)-cytisine **42** for smoking cessation[29] and it is a key ingredient in the smoking cessation drug Tabex® used since the 1960s throughout Eastern and Central Europe to treat nicotine addiction.[30] However, studies have shown that (−)-cytisine **42** has poor efficacy *in vivo* due to poor absorption and poor penetration at the blood brain barrier.[26,31,32] Due to the lack of bioavailability of (−)-cytisine **42**, recent work has revolved around developing analogues of (−)-cytisine **42** that maintain the significant *in vitro* activity but improve the *in vivo*

availability. Coe *et al.* at Pfizer developed Varenicline **44** (Figure 2.1) in 2005 using (−)-cytisine **42** as their starting point, which demonstrates the desired dopaminergic profile for the α4β2 nAChR receptor with high affinity.[26] It has since been approved as a smoking cessation drug, with studies highlighting its favourable pharmacokinetic profile.[33]

(−)-Cytisine **42** was first isolated in its pure form in 1862 by Husemann and Marmé.[34] It is commercially available but expensive. However, the naturally occurring compound can be extracted on a multigram scale from *Laburnum anagyroides* seeds.[31] Yields of isolation vary, but a reproducible process has been developed by the Rouden group and the O'Brien group, which usually provides up to 1.5 g of (−)-cytisine **42** for every 100 g of seeds used in the extraction.[35,36] This is put into synthetic use by the O'Brien group in the synthesis of a (+)-sparteine surrogate **45**, an analogue of the naturally occurring lupin alkaloid (−)-sparteine **46**, which is used as a chiral diamine ligand in the group's lithiation methodology.[37] The diamine surrogate **45** can be obtained *via* a simple, three-step procedure (Scheme 2.1) in 79% overall yield from the extracted (−)-cytisine **1**.[37]

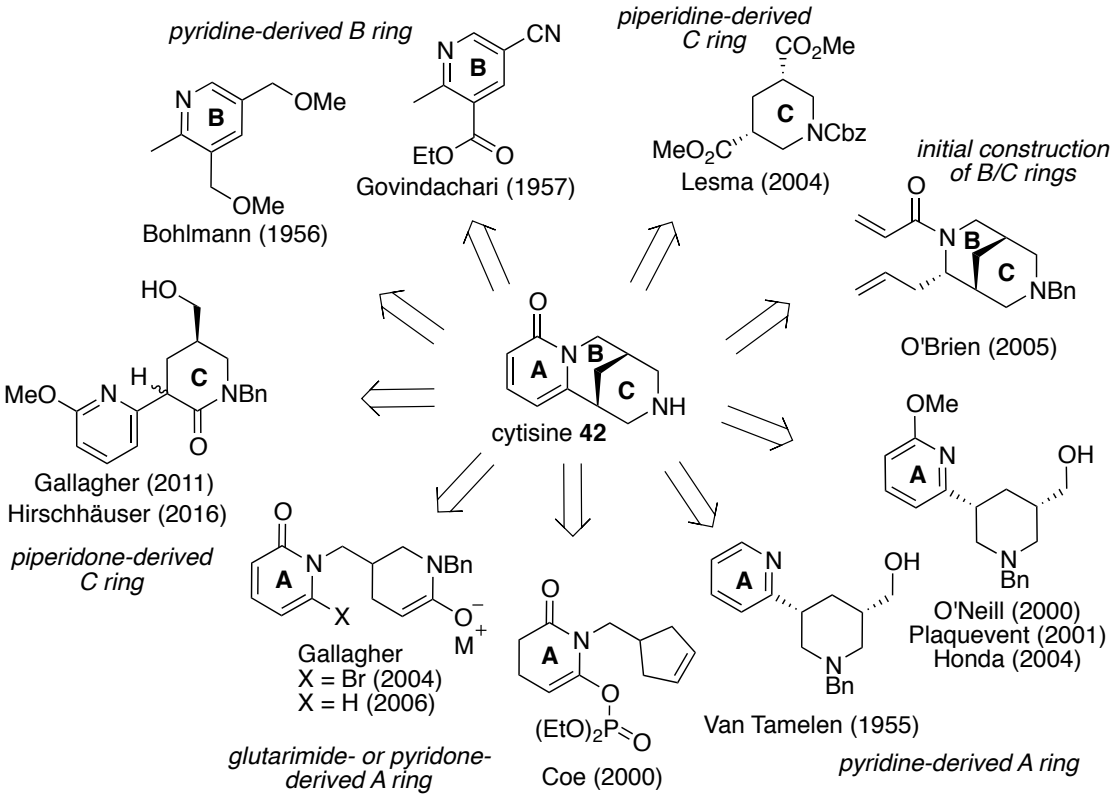


(−)-**42** (+)-**45** (−)-Sparteine **46**

Scheme 2.1 – Synthesis of the (+)-sparteine surrogate 45

2.1.2. Previous Syntheses of Cytisine

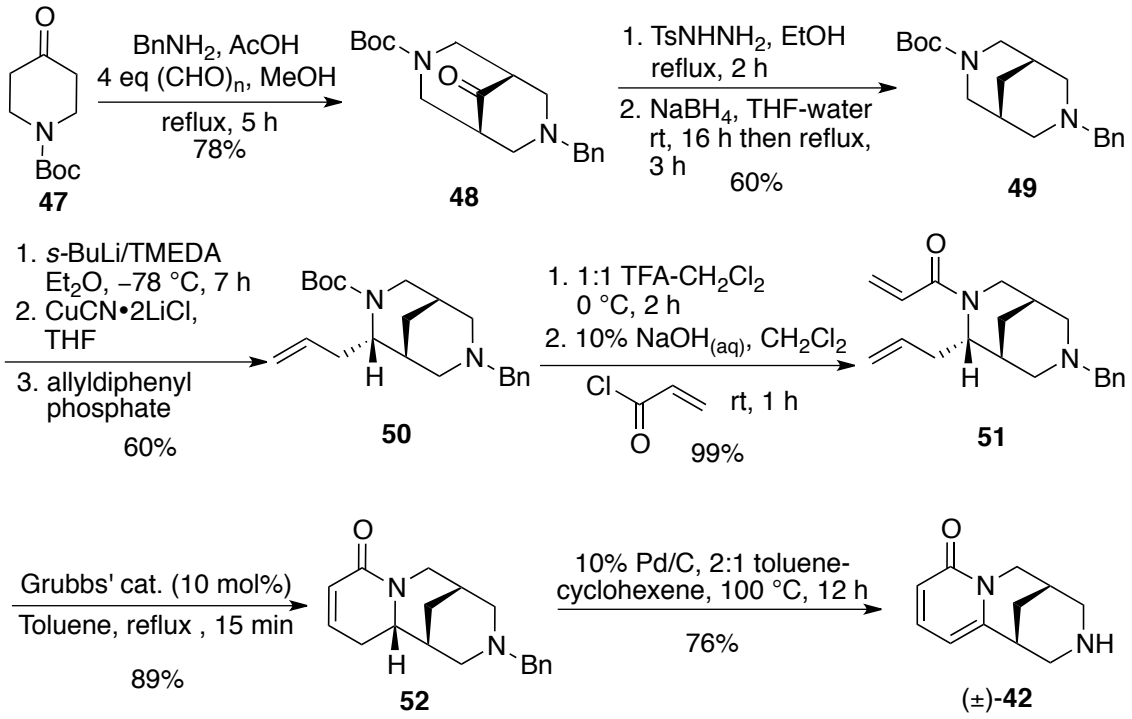
There have been numerous syntheses of cytisine **42** published.[25,31] The first total synthesis of (±)-cytisine **42** was completed in 1955 by van Tamelen,[38,39] and was followed by Bohlmann[40] and Govindachari[41] in 1956 and 1957 respectively. Following the recognition of the significant biological activity of the natural compound other syntheses were reported. A summary of the different approaches, with the key intermediates highlighted, is shown in Scheme 2.2. Syntheses of (±)-cytisine **42** are more common as asymmetric syntheses have proved to be more challenging.



Scheme 2.2 – Various approaches to cytisine 42 showing key intermediates

As shown in Scheme 2.2, cytisine **42** contains three connected rings, A, B, and C. The first route completed in 1955 by van Tamelen,[38,39] approached the synthesis using a pyridine-derived A ring and required a late-stage oxidation to obtain the desired pyridone ring. O'Neill revisited this approach in 2000,[42] a key difference being the introduction of the methoxy group on the A ring to remove the need for oxidation. This resulted in the shortest and highest yielding route to date (5 steps and 25% overall yield). Plaquevent reported a formal synthesis of (±)-cytisine **42**[43] using O'Neill's route but utilised a Negishi cross-coupling protocol to improve the yield of the key bis-pyridine intermediate. The combination of O'Neill's and Plaquevent's synthetic routes provided the most efficient synthesis of (±)-cytisine **42**. Coe[44] and Gallagher[45] used glutarimide- or pyridone-derived A rings as the key intermediates in their different approaches. Coe's synthesis was particularly attractive, as it avoided the need for any protecting groups.[44] Gallagher achieved a synthesis where the pyridone A-ring was intact throughout.[45]

One of the more recent syntheses of (±)-cytisine **42**, from the O'Brien group in 2005,[46] took a novel approach to the bispidine core structure compared to previous syntheses (Scheme 2.3). The B and C rings, i.e. the bispidine core, were initially constructed. Starting with a cheap commercially available starting material, *N*-Boc piperidone **47**, a double Mannich reaction was performed to give bispidone **48** followed by a Wolff-Kishner-style reduction providing protected bispidine **49** in 46% yield over the two steps. The pyridone A ring was then constructed, starting with allylation of the bispidine by lithiation and subsequent trapping to give substituted bispidine **50**. Highly efficient deprotection and acylation followed to give diene **51**, which underwent Grubbs ring-closing metathesis to give the dihydropyridone **52**. A simultaneous deprotection and aromatisation gave the desired product and this led to one of the most efficient syntheses of (±)-cytisine **42** to date, with 19% overall yield achieved in six steps.

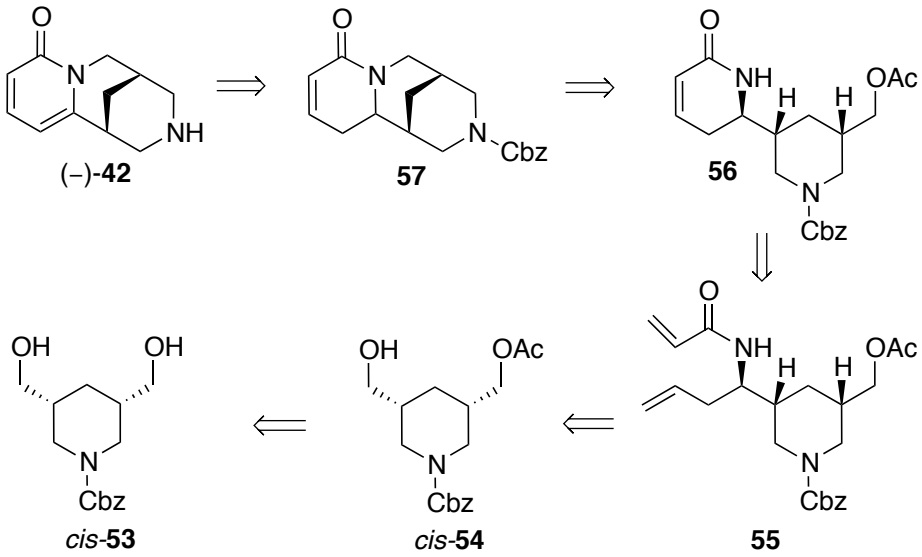


Scheme 2.3 – Synthesis of (±)-cytisine by initial construction of the B and C rings[46]

There have been relatively few asymmetric syntheses of cytisine **42**. The first asymmetric synthesis of (+)-cytisine **42** was accomplished by Honda in 2004, using an enantioenriched starting material and maintaining it through to the final product.[47] Gallagher developed a second-generation synthesis in 2006,[48] which utilised previous methodology of an intramolecular 1,6-addition of a lactam enolate to a pendant 2-pyridone, and incorporated enzymatic resolution of an early-stage intermediate to induce

enantioselectivity. This resulted in an 11-step synthesis of (+)-cytisine **42** in 4% overall yield.

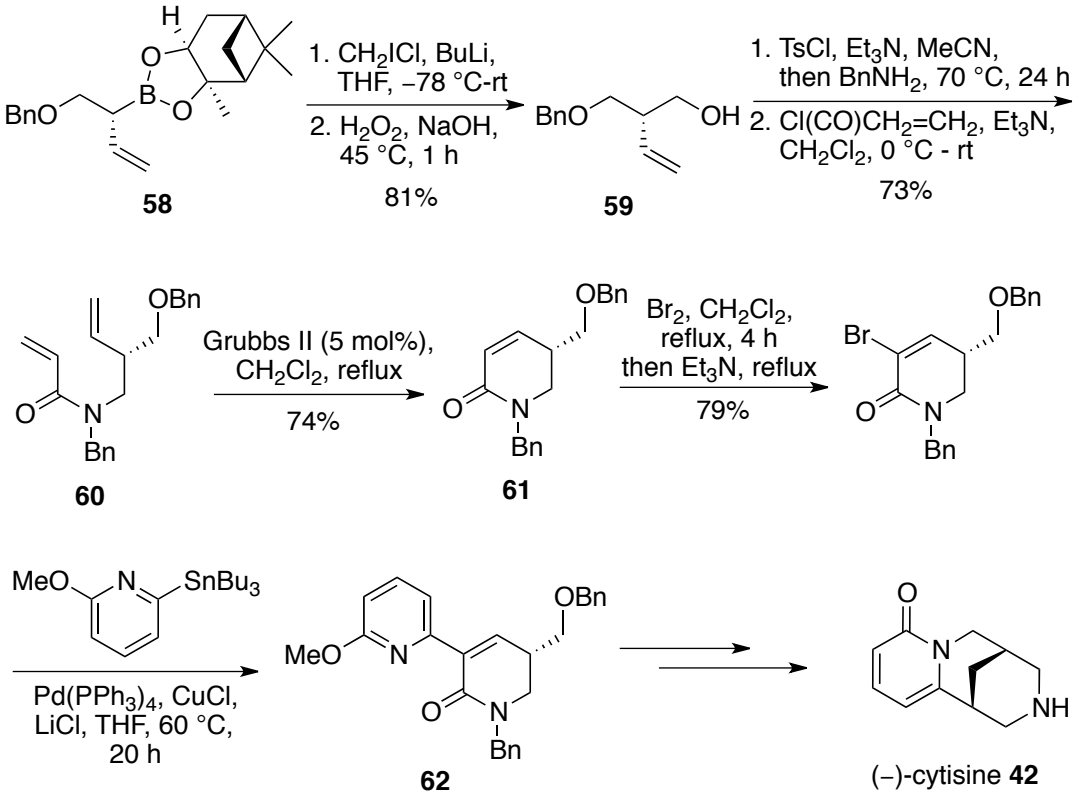
The first total synthesis of (−)-cytisine **42** was completed in 2004 by Lesma[49] and the retrosynthetic analysis is shown in Scheme 1.4. The approach relies on efficient enzymatic acetylation of diol *cis*-**53** using *Pseudomonas fluorescens lipase* (PFL) to piperidine 3,5-dimethanol monoacetate *cis*-**54**, which proceeds in 78% yield with >98% ee.[31] Following this, six steps were needed to access diene **55** and Grubbs ring-closing metathesis produced dihydropyridone **56**. The bispidine core **57** was then synthesised by acetate hydrolysis, mesylate activation and cyclisation using NaH. Aromatisation was achieved using DDQ, and deprotection gave the desired product (−)-cytisine **42** in 13 steps and 7% overall yield.



Scheme 2.4 – Retrosynthetic analysis of (−)-cytisine[49]

More recently, Hirschhäuser and Struth published an approach to (−)-cytisine **42** utilising methodology developed by Gallagher *et al.* in 2011.[50,51] The route focused on accessing the enantiomerically pure benzyl ether **63** and then utilised Gallagher's high yielding final steps to generate (−)-cytisine **42**. The chiral allylboronate **58** was accessed in 5 steps from a pinacol boronate and (−)-pinanediol. Alcohol **59** was obtained *via* reaction of the allylboronate **58** with a carbenoid and subsequent oxidation. Optimisation of this reaction to avoid the formation of stable borate ester side-products gave the desired product **59** in 81% yield. Conversion to the benzyl protected amine and

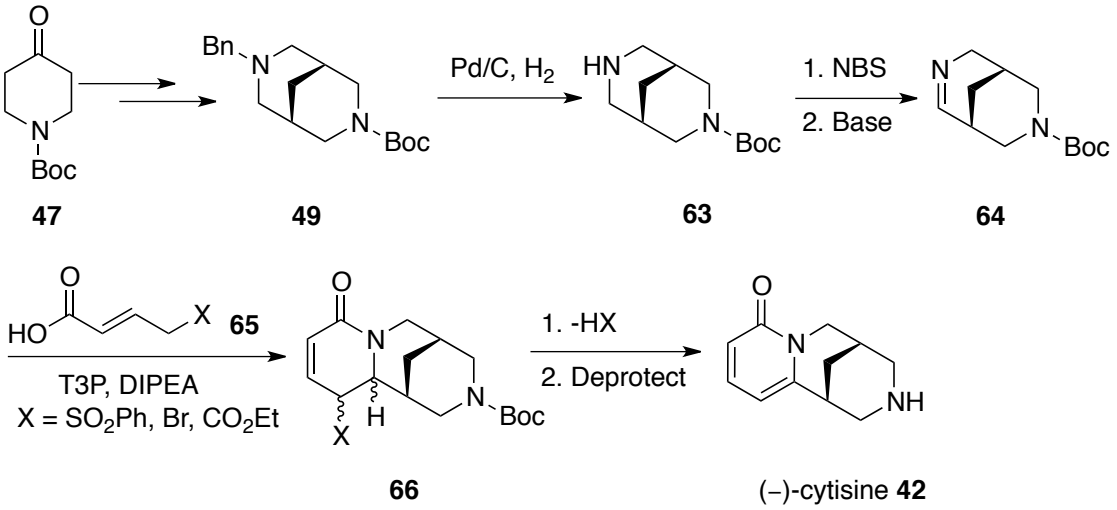
subsequent *N*-acylation gave diene **60** (73% yield), which was subjected to Grubbs' 2nd generation catalyst to effect ring-closing metathesis and give lactam **61** in 74% yield. α-Bromination and subsequent Stille coupling gave precursor **62**, which was converted into (−)-cytisine **42** using Gallagher's established route (Scheme 2.5).



Scheme 2.5 – Synthesis of (−)-cytisine *via* pyridine-derived C ring[51]

2.2. Project Outline

The aim of this part of the project was to utilise Taylor's direct imine acylation (DIA) methodology to develop a new synthesis of (±)-cytisine **42** that may also have potential for further modification to an asymmetric synthesis. The proposed route is shown in Scheme 2.6. The conversion of *N*-Boc piperidone **47** into bispidine **49** is known.[46] Following deprotection to mono-protected bispidine **63**, *N*-bromination and elimination should give bispidine imine **64**. The key novel step in the synthesis will utilise Taylor group DIA methodology[20,21] on imine **64**; this requires the development of unprecedented chemistry in this area, using an acid **65** containing a 'X' group that is electron-withdrawing or stabilising to the charge developed through the reaction. The DIA reaction of imine **64** with acid **65** should give **66**. Subsequent elimination of the 'X' group in **66** is required to form the pyridone ring observed in the desired scaffold. Following this, deprotection of the Boc protecting group would give (±)-cytisine **42**.



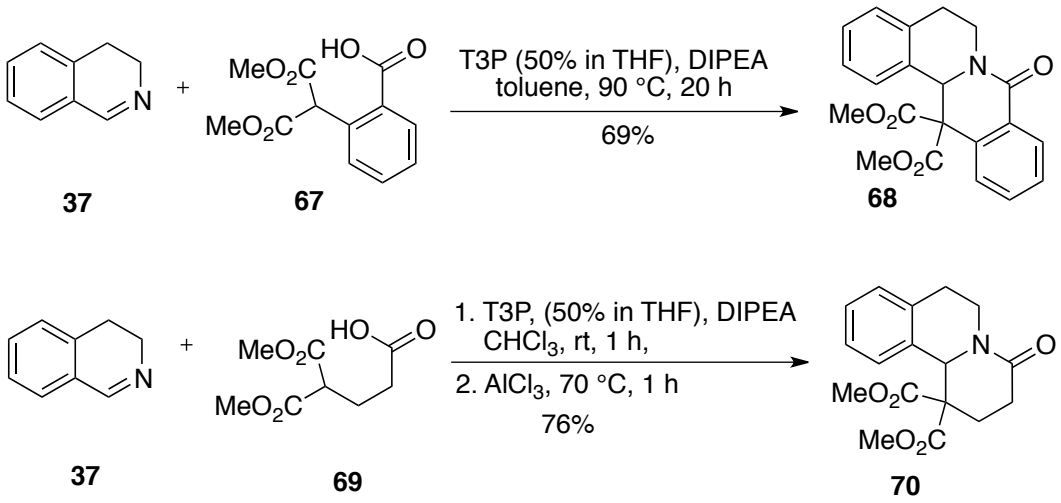
Scheme 2.6 – Proposed route towards (±)-cytisine

In this chapter, our efforts to implement the synthetic strategy shown in Scheme 2.6 (or variants thereof) are described.

2.3. Results and Discussion

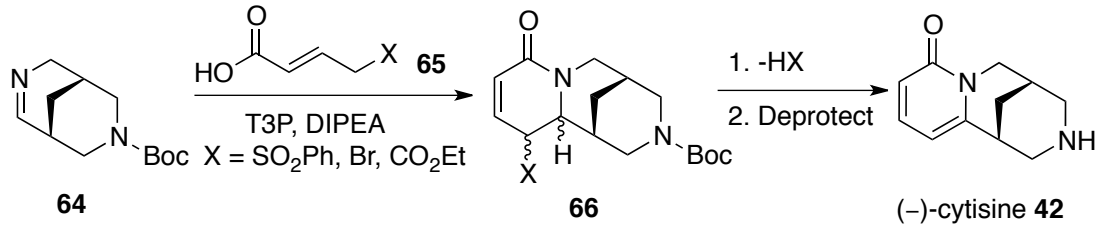
2.3.1. Direct Imine Acylation followed by Intramolecular Nucleophilic Addition of an Internal Carbon Nucleophile

The first priority was to develop an efficient annelation procedure for the synthesis of the pyridone scaffold present in (±)-cytisine **42** using DIA methodology. Previous examples of carbon nucleophiles in DIA methodology have involved a benzoic acid moiety, such as the reaction between benzoic acid **67** and imine **37** to give the cyclised product **68** in 69% yield (Scheme 2.7).[20,21] Aliphatic examples have also been demonstrated but the use of a Lewis acid was required to promote the cyclisation. Reaction of imine **37** and acid **69** in the presence of $AlCl_3$ gave lactam **70** in 76% yield (Scheme 2.7).[20] Investigations within the Taylor group showed that if only one ester group was present the reaction did not proceed.



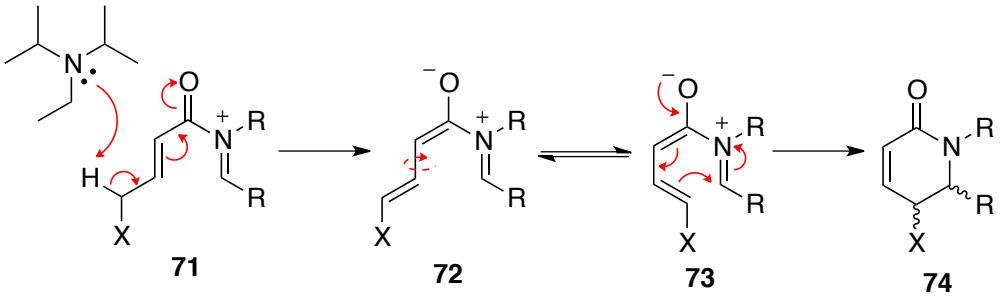
Scheme 2.7 – Examples of DIA reactions that form a carbon-carbon bond[20,21]

The original proposed route involved the use of a carboxylic acid **65** containing a stabilising 'X' group that could be eliminated in a subsequent step to give (±)-cytisine **42** (Scheme 2.8). Potential groups that could act as a stabilising group, but also allow for elimination to the pyridone, include a sulfone, halogen or ester.



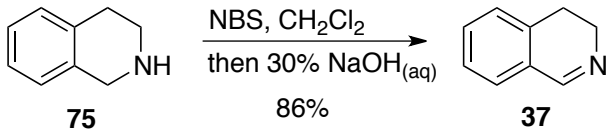
Scheme 2.8 – Key step in the proposed route to cytisine

The proposed mechanism for the DIA reaction can explain the required stabilising property of the 'X' group (Scheme 2.9). After formation of the *N*-acyliminium ion **71**, the most acidic position α to the stabilising 'X' group would be deprotonated to give intermediate enolate **72**. Rotation of the enolate **72** about the single bond provides the reactive cyclisation conformer **73**. The mechanism therefore suggests that the *cis*- or *trans*-alkene of the acid would work, as during the reaction the more reactive conformer can be accessed. Cyclisation of enolate **73** would then occur to provide the targeted ring system **74** (Scheme 2.9). The suggested formation of enolate **72** could mean that the cyclisation does not require the presence of a Lewis acid, which has been shown to be necessary in other DIA reactions containing an aliphatic carbon nucleophile.



Scheme 2.9 – Proposed mechanism for the DIA cyclisation reaction

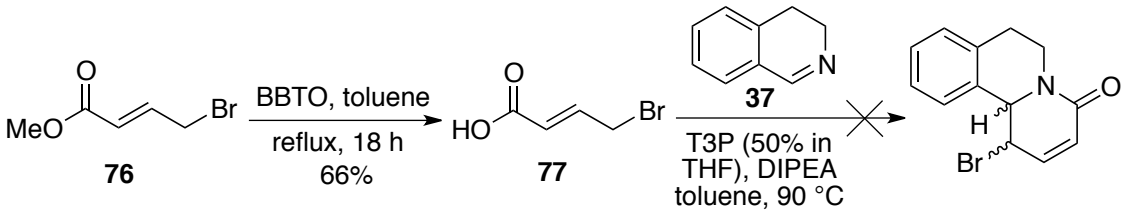
In order to investigate DIA methodology, an aromatic imine **37** was selected for our initial studies as this is a known stable imine, providing ease of handling, and had been successful in precedented DIA methodology.[21] In addition, this imine is unable to tautomerise to the enamine, which is known to improve the yield of DIA reactions.[23] Treatment of amine **75** with NBS and then base-mediated elimination gave imine **37** in 86% yield following a literature procedure (Scheme 2.10).[52]



Scheme 2.10 – Synthesis of aromatic imine 37

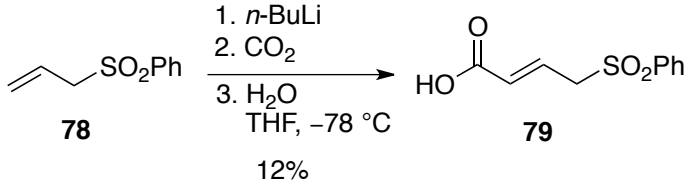
This imine was used in the following reactions as a model substrate. The plan was that once a successful annelation procedure was developed, the bispidine imine substrate could be synthesised and the reaction tested to generate the desired scaffold in cytisine **42**.

Bromine was first considered as a suitable 'X' group as it could stabilise the charge formed throughout the reaction and could be eliminated as HBr in the final step. Thus, 4-bromocrotonic acid **77** was synthesised in 66% yield *via* bis(tributyltin)oxide demethylation of the methyl ester **76** (Scheme 2.11).[53] However, reaction of the 4-bromocrotonic acid **77** with the aromatic imine **37** under non-acidic DIA conditions (refluxed in toluene with T3P and DIPEA) was unsuccessful and no product was isolated.



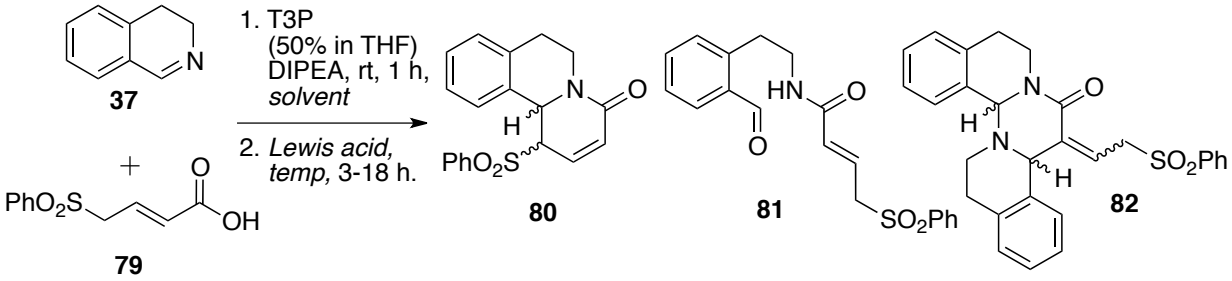
Scheme 2.11 – Synthesis and reaction of 4-bromocrotonic acid 77

Next, it was considered that a sulfone group may be suitable as both an anion stabilising group and a leaving group. Therefore, the sulfonyl acid **79** was synthesised using a literature procedure.[54] (Allylsufonyl)benzene **78** was treated with *n*-BuLi and trapped with CO_2 to give a 12% yield of 4-phenylsulfonylcrotonic acid **79** (Scheme 2.12). The (*E*)-alkene in **79** was confirmed using the ^{3}J-value (15.5 Hz).



Scheme 2.12 – Synthesis of sulfonyl acid 79 *via* lithiation of allyl phenyl sulfone 78

Initial studies on 4-phenylsulfonylcrotonic acid **79** under standard DIA conditions with imine **37** in toluene at 90 °C (T3P, DIPEA) were unsuccessful (Table 2.1, Entry 1). Instead of the desired cyclised product **80**, an interesting complex heterocyclic scaffold **82** was observed (31% yield) where a second molecule of imine has quenched the initial *N*-acyliminium ion followed by cyclisation from the internal nucleophile (full mechanism is discussed later). Other conditions were investigated in an attempt to form the desired product **80 (**Table 2.1**)**. Under DIA conditions at 70 °C with $AlCl_3$, the undesired product **82** was formed (Entry 2). A single diastereoisomer of product **82** with undefined relative stereochemistry was isolated following column chromatography. Other possible diastereoisomers were observed by ^{1}H NMR spectroscopy of the crude product but these were not isolated cleanly by column chromatography. A reaction was performed at rt with no Lewis acid to determine whether the suggested enolate pathway, shown in Scheme 2.9, would proceed. It was also suggested that if the *N*-acyliminium ion formed, but no cyclisation occurred, an aldehyde **81** would be observed following hydrolysis in the aqueous work-up (Entry 3). However, observation of **82** in the ^{1}H NMR spectrum of the crude product suggested that this product forms very readily, with no activation from temperature or Lewis acid being required. As a result, this substrate was not taken any further.

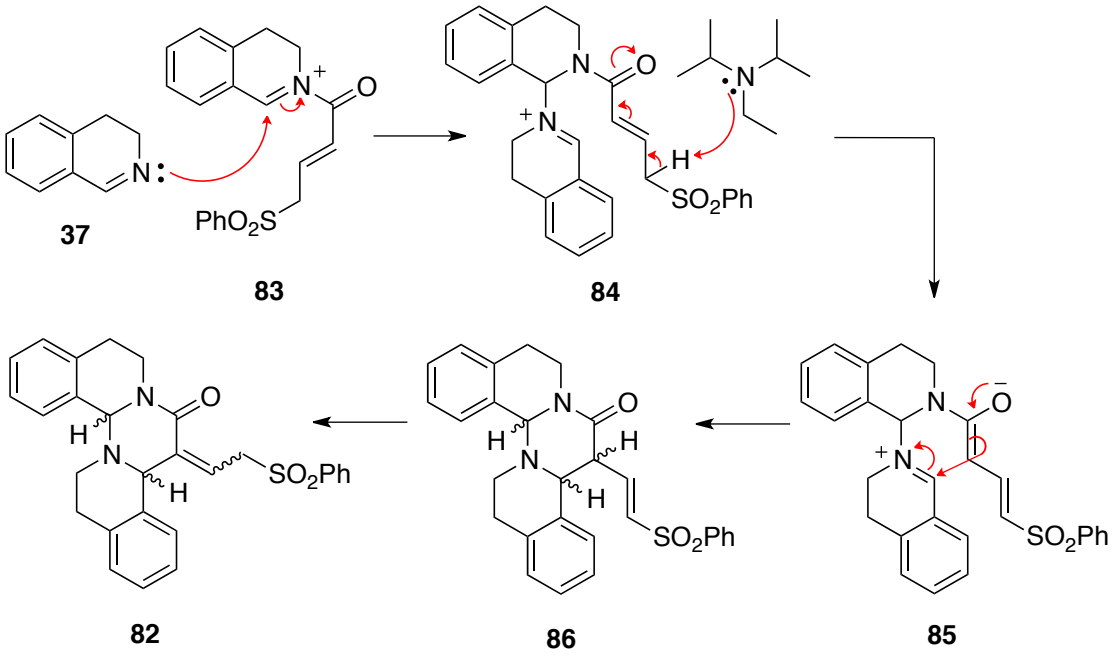


Entry	Solvent	Lewis acid	Temp	80 (%)	81 (%)	82 (%)
1	Toluene	-	90 °C	-	-	31
2	$CHCl_3$	$AlCl_3$	70 °C	-	-	29
3	CH_2Cl_2	-	rt	-	-	-[a]

[a] Analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture showed formation of **82** as the major product.

Table 2.1 – DIA reaction of imine 37 and acid 79

The proposed mechanism for the formation of the actual observed product **82** is shown in Scheme 2.13. It was believed that the desired *N*-acyliminium ion **83** did indeed form. However, rather than being deprotonated and cyclising (see Scheme 2.9), a second imine **37** added to give a different *N*-acyliminium ion intermediate **84**. Deprotonation of the allyl sulfone either at this point, or before addition of the second imine, would give enolate **85**. Next, addition to the *N*-acyliminium ion can occur through the carbon α to the carbonyl in order to form a six-membered ring and give product **86**. Finally, formation of product **82** is suggested to be as a result of tautomerisation of the vinylic sulfone to be in conjugation with the carbonyl bond of the central ring system (Scheme 2.13).

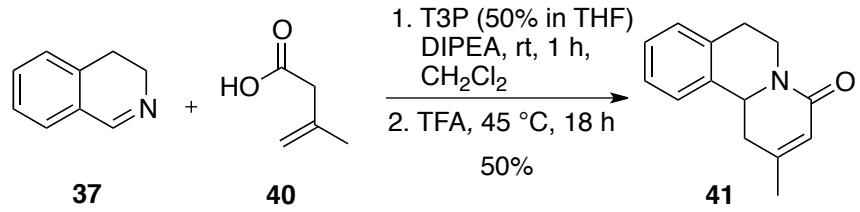


Scheme 2.13 – Proposed mechanism for the formation of 82

On inspection of the ^{1}H NMR and related 2D spectra of the product formed from the mechanism shown in Scheme 2.13, it was confirmed that the isolated product was not **86**. It became clear that the sulfone substituent was allylic and the structure of the product was **82**. Key signals in the ^{1}H NMR spectrum of **82** that suggested the allylic product structure were the two singlet peaks at 5.92 and 4.95 ppm for the NCHN proton and NCHC=C, rather than the expected single singlet that would be present in product **86**. Two signals at 5.02 and 4.57 ppm were more downfield than usually observed in this type of compound (for the NCH_2 peaks) and correlated to the CH_2 protons situated between the alkene and sulfone. This was confirmed by the ^{13}C/DEPT spectrum that

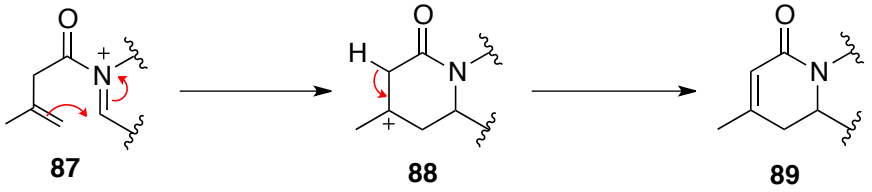
revealed five CH_2 peaks (four CH_2 peaks in **86**). These protons also showed a strong correlation by COSY NMR, providing sufficient evidence for the allylic sulfone tautomer **82** rather than the vinylic sulfone tautomer **86**.

Another approach was investigated, utilising an alkene as the nucleophile for attack onto the *N*-acyliminium ion intermediate. It had been shown in the Taylor group that reaction of 3-methyl-3-butenoic acid **40** and aromatic imine **37** under DIA conditions afforded the cyclised product **41** in 78% yield.[20] The reaction was repeated in our hands and confirmed that the cyclised product **41** could be formed and isolated in 50% yield (Scheme 2.14).



Scheme 2.14 – DIA reaction to give dihydropyridone 41

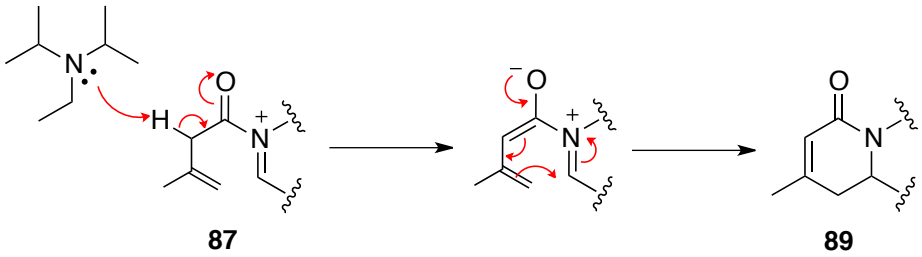
The suggested mechanism for this reaction is shown in Scheme 2.15. After formation of the *N*-acyliminium ion **87**, nucleophilic attack from the alkene would form the cyclised carbocation intermediate **88**. Deprotonation would give the cyclised product **89**. The presence of the methyl group in this reaction is the key to its success as it stabilises the carbocation formed *via* inductive effects. For example, reaction of 3-butenoic acid (which lacks the methyl group) did not give any cyclised product.



Scheme 2.15 – Mechanism for the cyclisation of *N*-acyliminium ion 87

An alternative mechanistic pathway can be envisaged for the cyclisation of *N*-acyliminium ion **87** involving an enolate intermediate (Scheme 2.16). This reaction pathway suggests that a Lewis acid is not needed for cylisation, but previous investigations within the Taylor group have confirmed that a Lewis acid is necessary for this substrate. In addition, if this reaction pathway was correct, the DIA reaction of 3-

butenoic acid (lacking the methyl group) may have been successful but no product was observed.



Scheme 2.16 – Alternative mechanism for cyclisation of *N*-acyliminium 87

Knowing that the cyclisation reaction of the alkene required functionality that could stabilise the carbocation formed in the reaction pathway, two iodo-substituted alkenes **90** and **91** were devised (Figure 2.2).

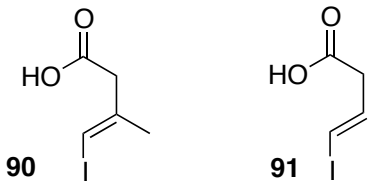
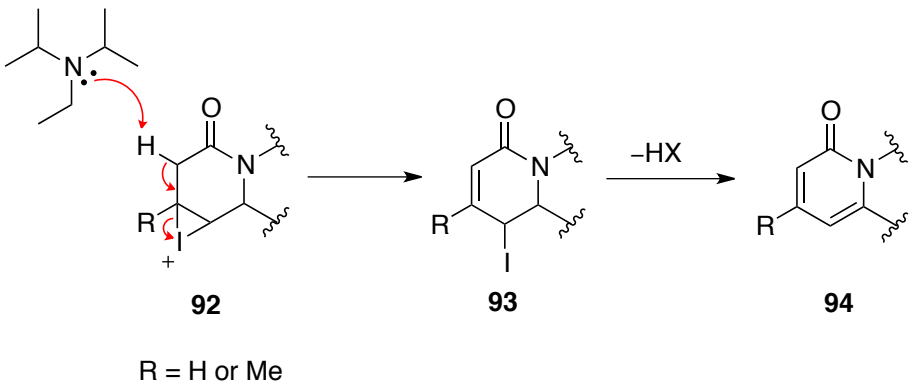


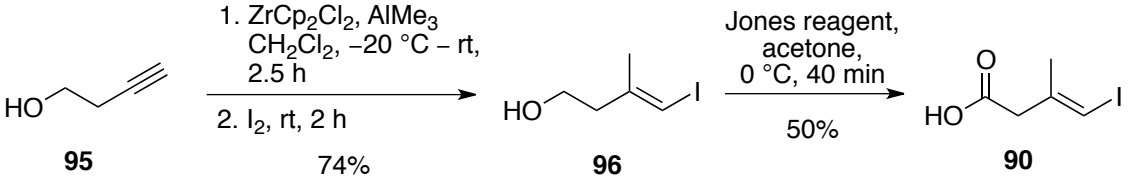
Figure 2.2 – Structure of iodo-substituted alkene substrates 90 and 91

It was thought that inclusion of an iodine substituent could provide suitable stabilisation for the generated carbocation *via* an iodonium ion **92**, and access to the cyclised product **93** (Scheme 2.17). Furthermore, subsequent elimination of HI would provide access to the pyridone ring scaffold and result in product **194**. The reaction of acid **90** would first be attempted to ensure that the presence of the iodine did not affect the cyclisation, then acid **91** would determine whether iodonium formation provided sufficient stabilisation for the carbocation intermediate.



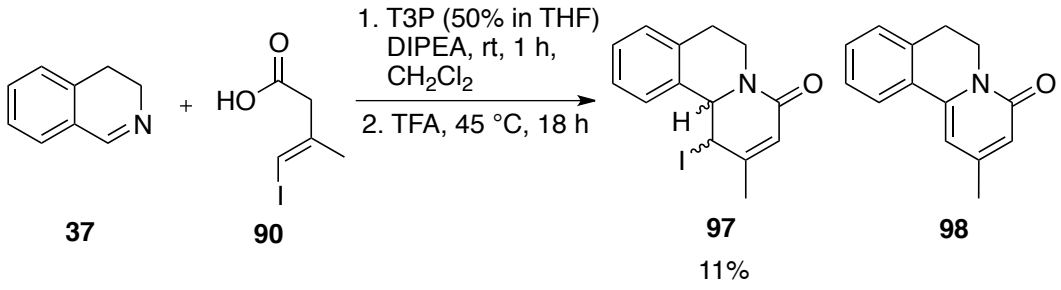
Scheme 2.17 – Stabilisation of carbocation intermediate by an iodonium ion

Acid **90** was synthesised using Negishi's Zr-catalysed carboalumination of 3-butyn-1-ol **95** to give alkene **96**,[55,56] followed by subsequent Jones oxidation (Scheme 2.18). The carboalumination reaction occurs by *syn*-addition of the C-Al species across the terminal alkyne, with the aluminium adding at the least sterically hindered end. Subsequent reaction with an electrophile, *e.g.* I_2, into the alkenylaluminium bond proceeds with retention of configuration and results in formation of the *(E)*-alkene product.[57]



Scheme 2.18 – Synthesis of iodo-substituted alkene acid 90

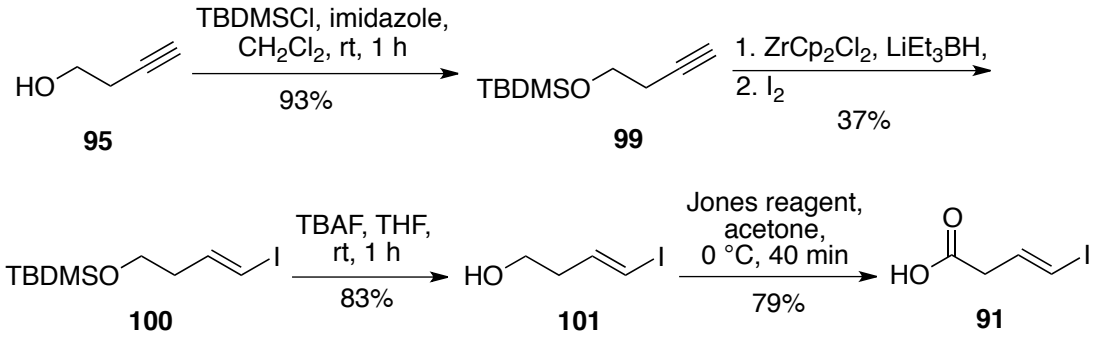
Subjecting acid **90** to the previously successful DIA conditions used for alkene addition, involving heating to 45 °C and addition of TFA, resulted in only an 11% yield of **97** after column chromatography (Scheme 2.22). A second compound was isolated but analysis of the ^{1}H NMR spectrum did not conclusively determine the structure. Mass spectrometry suggested that this was the pyridone **98**, formed by elimination of HI, although this result is not conclusive as this could be as a result of elimination within the mass spectrometer.



Scheme 2.19 – DIA reaction of imine 37 and iodo acid 90

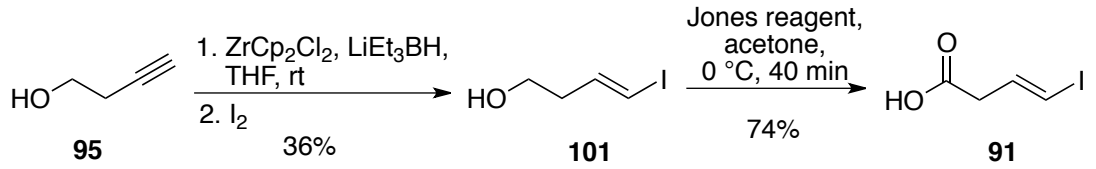
Despite only obtaining a poor yield of the cyclised product **97** using acid **90**, (*E*)-4-iodobut-3-enoic acid **91** was synthesised as the ideal annelation procedure would provide an unsubstituted pyridone ring scaffold. Synthesis of the iodo-substituted alkene **91** could be achieved using hydrozirconation chemistry originally developed by Schwartz in 1976.[58] Schwartz reagent, $HZrCp_2Cl$, is commercially available but has a short shelf-life and is expensive but can be generated *in situ* by treatment of $ZrCp_2Cl_2$ with a source of hydride. In order to synthesise *(E)*-4-iodobut-3-enoic acid **91**, 3-butyn-

1-ol **95** was initially protected to avoid deprotonation of the alcohol (Scheme 2.20).[59] Use of Lipshutz's mild *in situ* generation of $HZrCp_2Cl$, hydrozirconation and subsequent addition of iodine resulted in the formation of iodo-substituted alkene **100**.[60] Subsequent deprotection of the TBDMS group to the alcohol **101**, followed by Jones oxidation afforded the desired acid **91** in 22% yield over the four steps (Scheme 2.20).



Scheme 2.20 – Synthesis of iodo-substituted alkene acid 91

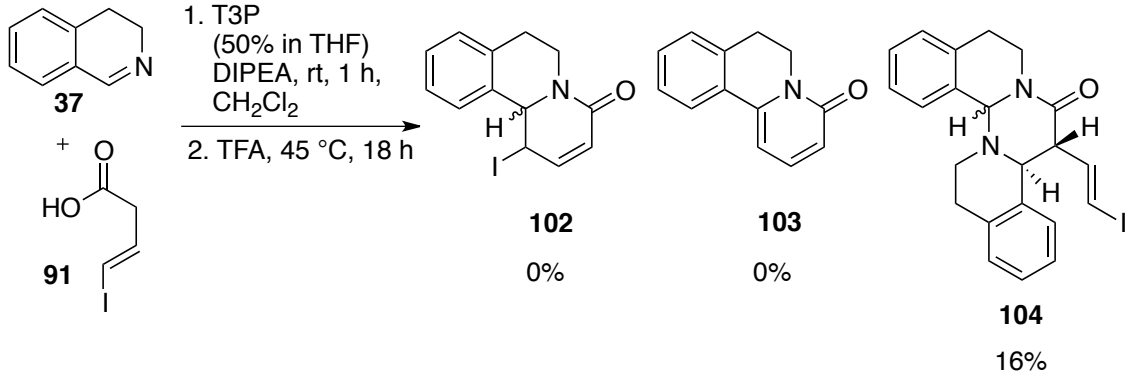
In a potentially shorter route, hydrozirconation was also carried out on the unprotected alcohol **95** (Scheme 2.21). Pretreating the alcohol with an equivalent of $LiEt_3BH$ was necessary for the reaction to proceed. Analysis of the ^1H NMR spectrum of the unpurified reaction mixture showed a more complex mixture of products compared with reaction on the TBDMS protected alcohol, presumably because of the deprotonated hydroxyl group initiating unwanted side reactions. This made purification more difficult and the desired alkene product **101** was isolated in 36% yield. Subsequent Jones oxidation provided the acid **91** in 26% overall yield (Scheme 2.21).



Scheme 2.21 – Synthesis of iodo alkene acid 91 without alcohol protection

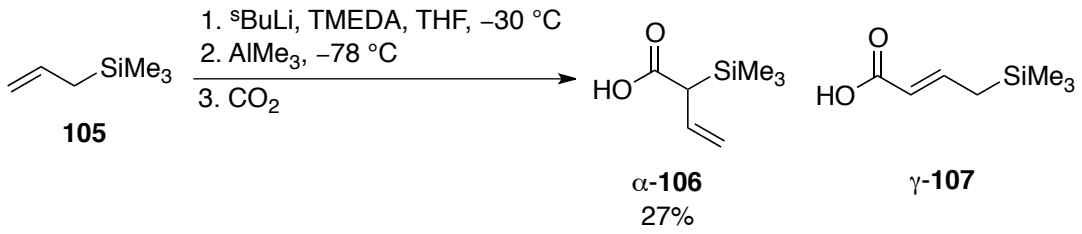
On reacting the iodo-alkenyl acid **91** under DIA conditions with imine **37** (Scheme 2.22), none of the desired cyclised product **102** or cyclised/eliminated product **103** was observed. Instead, a small amount of the fused pentacyclic product **104** was isolated. A single diastereoisomer of **104** (16% yield) was isolated after chromatography, with undefined relative stereochemistry. This reaction sequence is analogous to the pathway described in Scheme 2.13. Unlike the product formed when sulfone acid **79** was used,

the product **104** did not tautomerise to be in conjugation with the carbonyl of the central ring. The two hydrogens on the central ring have a ^{3}J coupling constant of 9.5 Hz. This suggests that they are positioned diaxially, making the ring and vinyl iodide substituents *trans* to each other. The result of this reaction suggests that, without the presence of the methyl group, the iodine substituent was not sufficiently stabilising of the carbocation that was formed during the reaction pathway. Therefore, the alkene did not attack and this allowed a second molecule of imine to be added into the *N*-acyliminium ion.



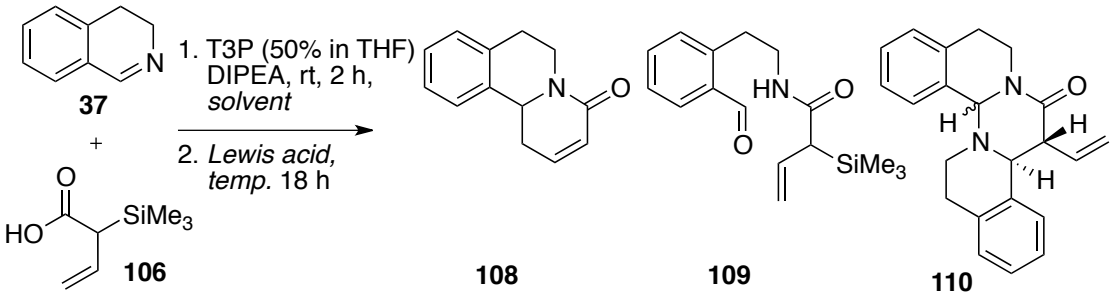
Scheme 2.22 – DIA reaction of imine 37 and iodo-substituted alkene acid 91

Finally, it was considered whether an appropriately placed trimethylsilyl group could stabilise the carbocation through the β-silicon effect.[61] Use of allyl trimethylsilane acid **106** may provide sufficient stabilisation of the intermediate carbocation formed on nucleophilic attack of the alkene into the *N*-acyliminium ion. This is analogous to the reaction pathway shown in Scheme 2.15, but the silicon group would be in the β-position to the carbocation that is formed. Allyl trimethylsilane acid **106** was synthesised by lithiation of allyl trimethylsilane **105** and subsequent *in situ* generation of an allylic aluminate complex, followed by trapping with CO_2.[62] Use of these conditions gave a 4:1 mixture of carboxylated products α-**106**:γ-**107** in the crude product mixture by ^{1}H NMR spectroscopy (Scheme 2.23). Purification by column chromatography gave a clean sample of α-**106** that was isolated in 27% yield and this sample was taken on to test under DIA conditions.



Scheme 2.23 – Synthesis of allyl trimethylsilane acid 106

Reaction of α-allyl trimethylsilane **106** with imine **37** under DIA conditions with BF_3•OEt_2 at rt resulted in none of the expected cyclised product **108** being observed (Table 2.2, Entry 1). As with other examples, a fused pentacyclic product **110** was isolated. The reaction was attempted with no acid activation at rt but product **110** was observed in the unpurified reaction mixture by ^{1}H NMR spectroscopy (Entry 2), showing that this product formed too readily to be prevented. The product **110** was isolated as a single diastereoisomer with undefined relative stereochemistry. The ^3J coupling constant for the hydrogens on the central ring system was 9.5 Hz indicating the *trans* stereochemistry of the ring and allyl substituents.



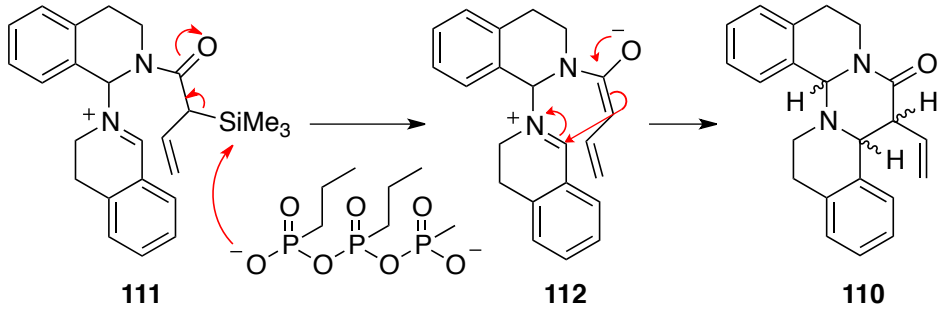
Entry	Solvent	Lewis acid	Temp	108 (%)	109 (%)	110 (%)
1	CH_2Cl_2	BF_3•OEt_2	rt	-	-	25
2	CH_2Cl_2	-	rt	-	-	-[a]

a) Analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture showed formation of **110** as the major product.

Table 2.2 – DIA reaction of allyl trimethylsilane acid 106 and imine 37

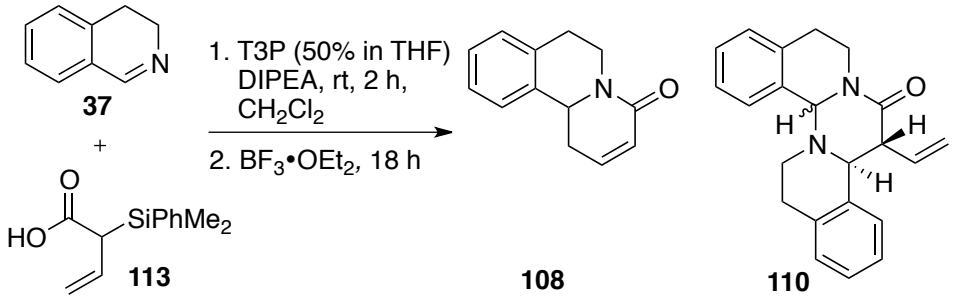
A mechanism for formation of product **110** is shown in Scheme 2.24. After formation of the *N*-acyliminium ion and attack by a second imine molecule, iminium ion **111** could form. Acid **107** has been shown to be unstable by loss of the TMS group, as reported by Uno *et al*.[63] Therefore, a suggested route could involve the removal of TMS (possibly

by the T3P byproduct) and enolate formation to give **112**. Subsequent cyclisation onto the *N*-acyliminium ion would provide the observed fused pentacyclic ring structure **110**.



Scheme 2.24 – Proposed reaction mechanism for the formation of product 110

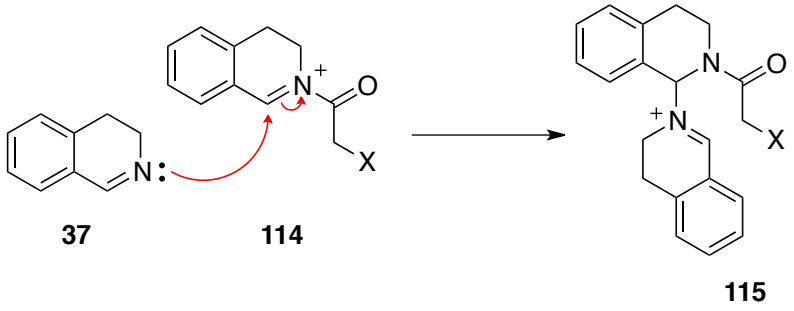
Use of a more stable α-silyl acid **113** that should not lose the silyl group so readily was also briefly explored. Dimethylphenylsilyl acid **113** was synthesised using Uno's conditions,[63] and was then reacted under DIA conditions with imine **37**. Initial reaction in CH_2Cl_2 at rt, followed by addition of BF_3•OEt_2 gave a complex mixture of products (Scheme 2.25). Attempted purification suggested that a small amount of the dihydropyridone **108** was isolated, but as a mixture with the polycyclic product **110**. Mass spectrometry confirmed that the dihydropyridone **108** was present. Increasing the temperature of the reaction resulted in a mixture where the dihydropyridone **108** was not observed. Reaction without addition of the Lewis acid gave the polycyclic product suggesting the preference for this product to form over the cyclisation of the alkene nucleophile. Following these results, this route was abandoned.



Scheme 2.25 – Attempted synthesis of dihydropyridone using a more stable silane

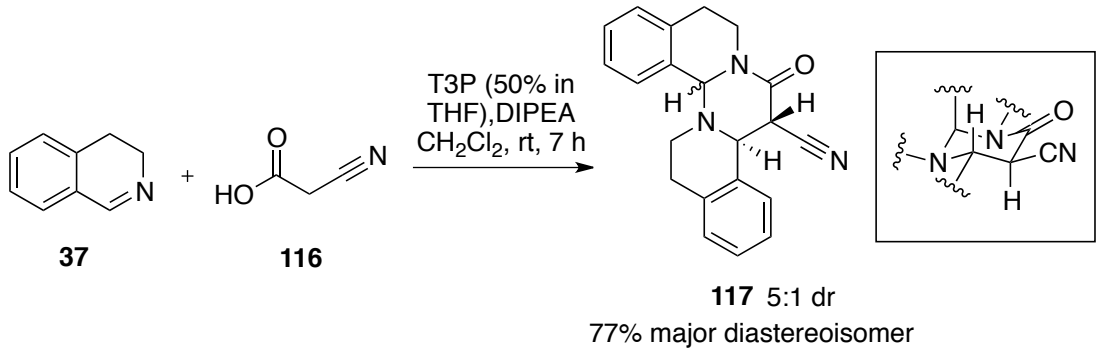
Unfortunately, attempts to initiate intramolecular nucleophilic addition of various carbon nucleophiles into *N*-acyliminium ions were unsuccessful. A fused pentacyclic ring scaffold was observed where a sulfone, alkene or iodo-substituted alkene was present. The electron-withdrawing nature of these substituents appears to lead to formation of the complex heterocyclic structure. As shown in Scheme 2.26, it was

proposed that if 'X' is electron-withdrawing then imine **37** attacks the *N*-acyliminium ion **114** first and forms iminium ion **115**. Once this has happened, the reaction goes on to form the pentacyclic product.



Scheme 2.26 – Nucleophilic addition of imine 37 into the *N*-acyliminium ion 114

Despite the pentacyclic ring structure not being the desired product that was wanted for a pyridone annelation procedure, it is a rapid and efficient way of building up a complex heterocyclic molecule. To demonstrate this, imine **37** (2 eq) and cyanoacetic acid **116** (1 eq) were subjected to standard DIA conditions and the pentacyclic product **117** was formed (Scheme 2.27). The ^{1}H NMR spectrum of the unpurified reaction mixture showed a 5:1 mixture of diastereoisomers and the major diastereoisomer was isolated in 77% yield following column chromatography. The ^{3}J-value for the hydrogens on the central ring was 10.5 Hz, indicating the *trans* stereochemistry of the ring and nitrile substitutents. It has been demonstrated within the Taylor group that the nature of the 'X' group is important, as a phenyl substituent results in formation of a β-lactam product, rather than the fused pentacyclic ring structure.[24] Interestingly, the formation of the *β*-lactam ring is not allowed by Baldwin's rules as it is defined as a 4-endo-trig cyclisation.[64] However, Baldwin followed up this publication with alternative rules for cyclisations involving an enolate intermediate,[65] which may explain the formation of the *β*-lactam products.

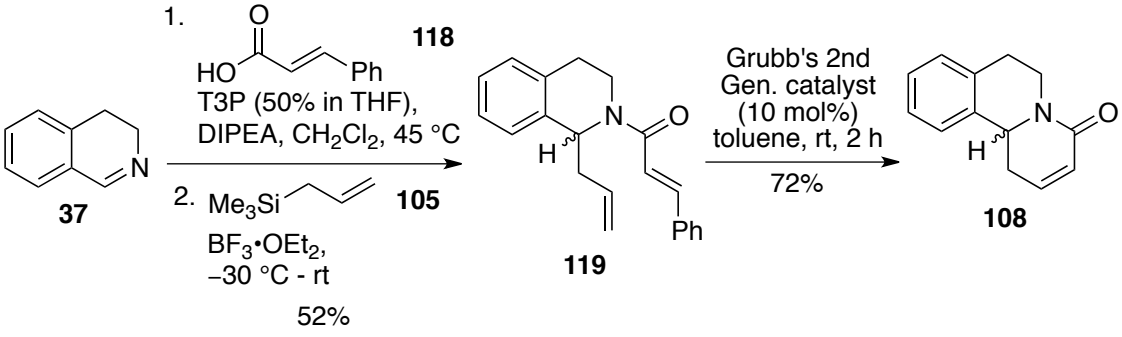


Scheme 2.27 – Selective formation of polycyclic product 117

2.3.2. Direct Imine Acylation followed by Intermolecular Nucleophilic Addition of an External Carbon Nucleophile

An alternative approach to the synthesis of cytisine using DIA methodology was needed to advance the project. In the O'Brien synthesis of (±)-cytisine **42**, the dihydropyridone ring structure was synthesised *via* formation of a diene, followed by Grubbs ring-closing metathesis (Scheme 2.3).[46] We envisaged that, using DIA methodology, a diene could be constructed using intermolecular nucleophilic addition. The *N*-acyliminium ion would be formed using the standard DIA conditions with an acid containing a suitable alkene substituent, and an external nucleophile would be added at a later stage in the reaction, to install the second alkene of the diene for subsequent ring-closing metathesis.

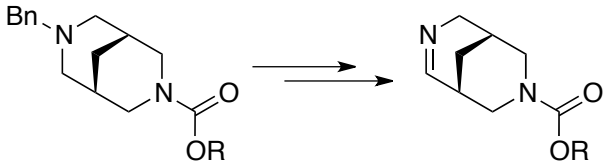
A DIA reaction between the aromatic imine **37** and *trans*-cinnamic acid **118** was carried out to form the *N*-acyliminium ion intermediate. The external nucleophile, allylsilane **105**, and BF_3•OEt_2 were introduced into the reaction for addition into the *N*-acyliminium ion. This intermolecular nucleophilic addition DIA approach was successful and provided diene **119** in 52% yield (Scheme 2.28). Subsequent ring-closing metathesis of diene **119** gave dihydropyridone **108** in 72% yield after 2 h at rt. This was a promising result as it gave a synthetically simple entry to an unsubstituted dihydropyridone scaffold, which upon oxidation would give the desired pyridone, as needed for a synthesis of (±)-cytisine **42**.



Scheme 2.28 – Synthesis of a dihydropyridone *via* direct imine acylation and addition of an external carbon nucleophile, followed by ring-closing metathesis

2.3.3. Synthesis and Reactions of Novel Bispidine Imines

Following the successful synthesis of a dihydropyridone scaffold *via* direct imine acylation and subsequent addition of an external carbon nucleophile (Scheme 2.28), it became a priority to synthesise a bispidine imine in order to trial this chemistry on the relevant scaffold. A known intermediate **48** (where R = *t*-Bu) from the O'Brien synthesis of (±)-cytisine **42** was used as a starting point for the synthesis of a bispidine imine. It was envisaged that deprotection of the benzyl group and oxidation would give the imines **64** and **121** (Scheme 2.29). The use of Boc- and ethyl carbamate-protecting groups would be explored as Boc is more acid-labile, whereas it was thought that the ethyl carbamate would be more stable to the acidic conditions used in DIA methodology.



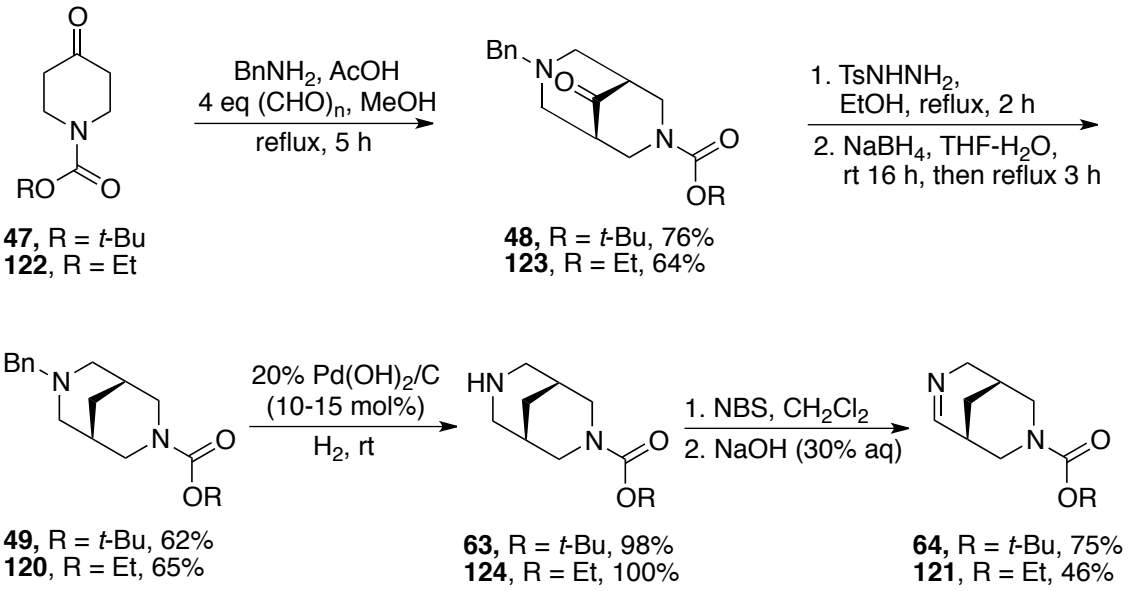
48, R = *t*-Bu
120, R = Et

64, R = *t*-Bu
121, R = Et

Scheme 2.29 – Planned synthesis of bispidine imines

The syntheses of the Boc- and ethyl carbamate-protected bisipidine imines **64** and **121** were completed in 4 steps (Scheme 2.30). The known protected bispidine **48** was first synthesised using a literature procedure previously used in the O'Brien synthesis of (±)-cytisine **1**.[46] Using the cheap, commercially available *N*-Boc piperidone **47** as starting material, a double Mannich reaction provided the protected bispidinone **48** in 76% yield. A milder version of the Wolff-Kishner reduction was then used to reduce the carbonyl and provide the protected bispidine **49** in 62% yield. This method was preferable as a mild hydride reduction of the hydrazide formed in the first step maintained the Boc protecting group for subsequent steps. Hydrogenation of the benzyl group was unsuccessful using 10% Pd/C, but was accomplished with Pearlmann's catalyst (20% $Pd(OH)_2/C$) to give the amine **63** in 98% yield. Oxidation conditions previously used to synthesise aromatic imine **37**,[52] using NBS bromination followed by base-mediated elimination, were also successful on the bispidine scaffold and imine **64** was isolated in 75% yield. This was a pleasing result as it was the most unexplored reaction and the DIA methodology relied on the successful isolation of a bispidine imine. The same

sequence of reactions was performed on the *N*-ethyl carbamate piperidone **122** to give ethyl carbamate-protected bispidine imine **121**, with similar yields achieved in each step (Scheme 2.30). Scaling up of the oxidation step to the imine **121** proved to be detrimental to the yield, which appeared to be due to poor conversion of the starting material.



47, R = *t*-Bu
122, R = Et

48, R = *t*-Bu, 76%
123, R = Et, 64%

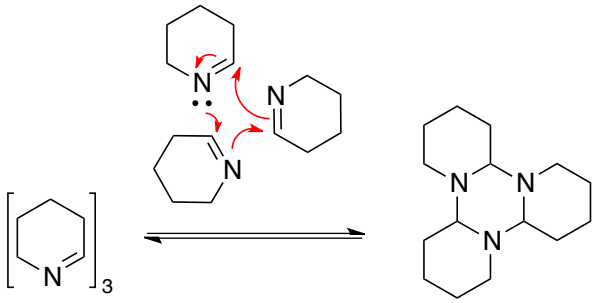
49, R = *t*-Bu, 62%
120, R = Et, 65%

63, R = *t*-Bu, 98%
124, R = Et, 100%

64, R = *t*-Bu, 75%
121, R = Et, 46%

Scheme 2.30 – Synthesis of bispidine imines 64 and 121

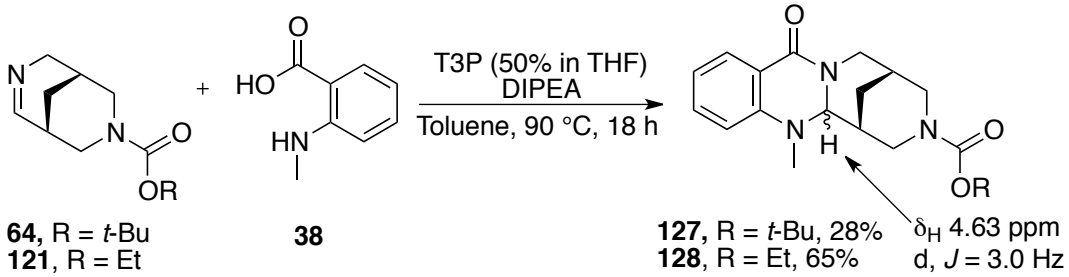
Some imines are known to form trimers,[66] particularly if they are not sterically hindered such as 2,3,4,5-tetrahydropyridine **125** (Scheme 2.31). Three of the monomer molecules **125** react to form a trimer **126** and this reaction is an equilibrium process. Analysis of the ^{1}H NMR spectrum of the ethyl carbamate-protected imine **121** suggested that it existed as a mixture of monomer and trimer. Integration of the signal at 7.84 ppm could be assigned to the monomer only for 1H (the imine proton), whereas other signals in the bispidine structure integrate for monomer and trimer, such as the CH_2CH_3 of the ethyl group. Using these signals, it was calculated that approximately 17% of trimer was present, although it is possible that the percentage of trimer depends on the concentration of the product in the NMR sample. In contrast, Boc imine **64** did not appear to trimerise.



125 **126**

Scheme 2.31 – Known trimerisation of imines[66]

Following the successful synthesis of bispidine imines **64** and **121**, a known DIA reaction using *N*-methyl anthranilic acid **38** was investigated.[21] The DIA reactions between *N*-methyl anthranilic acid **38** and imines **64** and **121** were completed in 28% and 65% yield respectively (Scheme 2.32). These results were pleasing as they indicated that the bispidine imines were able to undergo DIA reactions. ^{1}H NMR spectroscopy indicated that one diastereoisomer had been isolated in both examples, as only one signal (at 4.63 ppm in both products **127** and **128**) was observed for the bridgehead proton between the two nitrogen atoms.



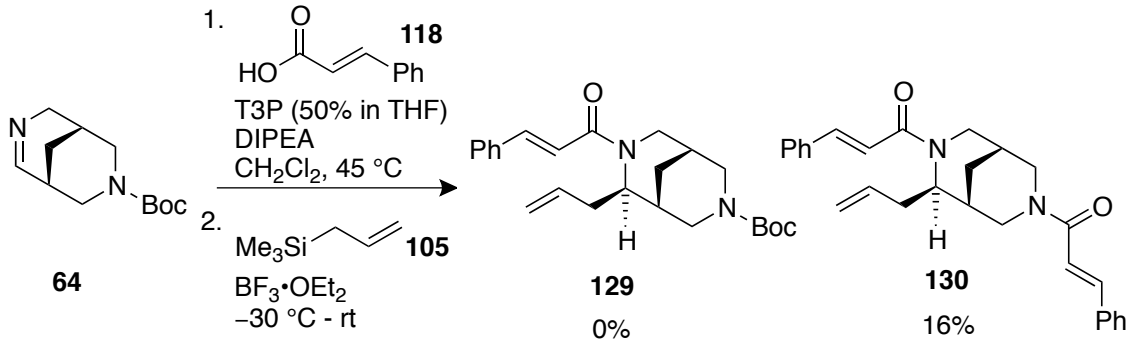
64, R = *t*-Bu
121, R = Et

38

127, R = *t*-Bu, 28%
128, R = Et, 65%

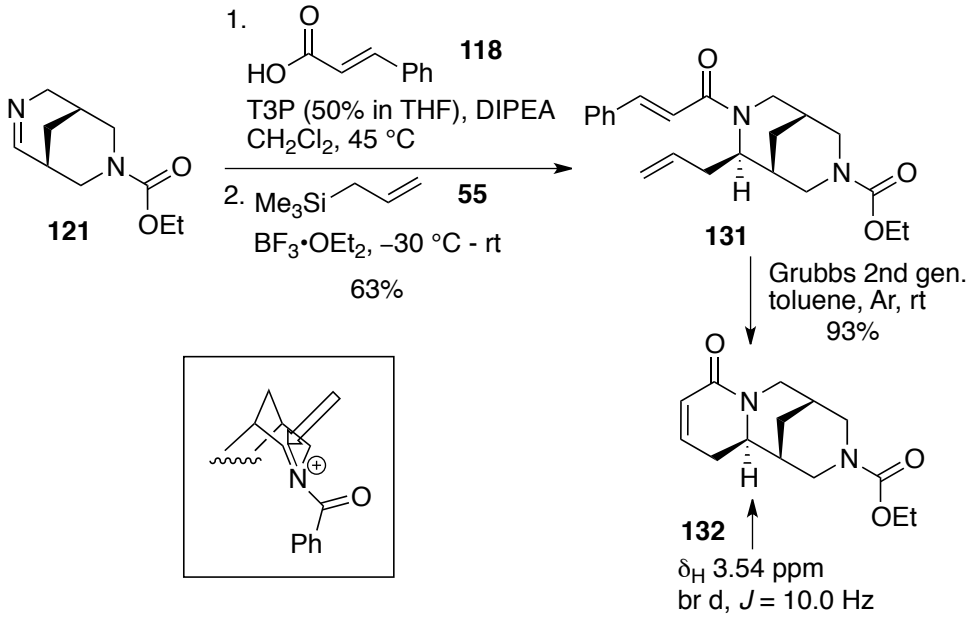
Scheme 2.32 – DIA reaction of bispidine imines 64 and 121 d

Trial of the intermolecular DIA methodology with *N*-Boc imine **64** provided an interesting result (Scheme 2.33). None of the desired product **129** was isolated but substituted bispidine **130** was isolated in 16% yield. ^{1}H NMR spectroscopy indicated that the Boc group had been removed and the mass spectrum clearly featured the corresponding $(M + H)^{+}$ peak for the product **130**. This suggested that the desired nucleophilic addition into the *N*-acyliminium ion had occurred. However, additional Boc deprotection and acylation of the second amine had also occurred. This was not an unexpected result as BF_3•OEt_2 has previously been shown to be effective and mild deprotection conditions for the Boc group.[67]



Scheme 2.33 – Direct imine acylation of bispidine imine 64

Pleasingly, the intermolecular nucleophilic addition approach on the ethyl carbamate bispidine imine **121** was successful (Scheme 2.34). Using DIA conditions to form the *N*-acyliminium ion, followed by introduction of the external nucleophile and Lewis acid, diene **131** was isolated in 63% yield. Grubbs ring-closing metathesis efficiently gave dihydropyridone **132** in 93% yield. Overall yields were reduced when crude diene was taken through so column chromatography of diene **131** is recommended.



Scheme 2.34 – Synthesis of dihydropyridone 132 *via* direct imine acylation

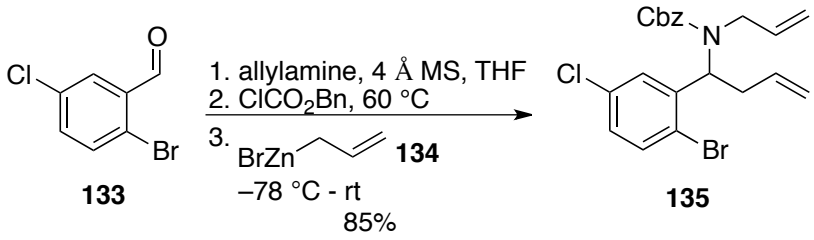
It was assumed that the product **132** had the stereochemistry shown in Scheme 2.34. This was based upon previous investigations of nucleophilic addition to *N*-acyliminium bispidine structures, which showed that attack proceeded through the more exposed *exo* face.[68,69,70] This assumption was confirmed and will be discussed later. ^{1}H NMR spectroscopy showed that one diastereoisomer of dihydropyridinone **132** was formed.

This was indicated by the single signal observed for the highlighted bridgehead proton (Scheme 2.34). This result confirmed that under the acidic conditions of this reaction the ethyl carbamate-protected imine **121** is a more suitable substrate than imine **64**.

2.3.4. Development of Lewis Acid-Free Conditions for the DIA Reaction with Addition of Intermolecular Nucleophile

In the DIA reactions with addition of an intermolecular nucleophile, the best results were obtained using the ethyl carbamate-protected bispidine imine **121**. However, the Boc protecting group is a more readily removed and more versatile protecting group, so an approach that could work with the *N*-Boc bispidine imine **64** was explored.

Addition of an organometallic nucleophile into *N*-acyliminium ions has previously been demonstrated in the synthesis of nitrogen heterocycles.[71] An example of this is shown in Scheme 2.35 where combination of the allyl amine and aromatic aldehyde **133** provided an allyl imine. Generation of the *N*-acyliminium intermediate by acylation with benzyl chloroformate was carried out at 60 °C to ensure complete formation of the intermediate *N*-acyliminium ion. Subsequent addition of the organometallic reagent facilitated nucleophilic attack into the *N*-acyliminium ion and afforded the product **135** in 85% yield (Scheme 2.35).[71]

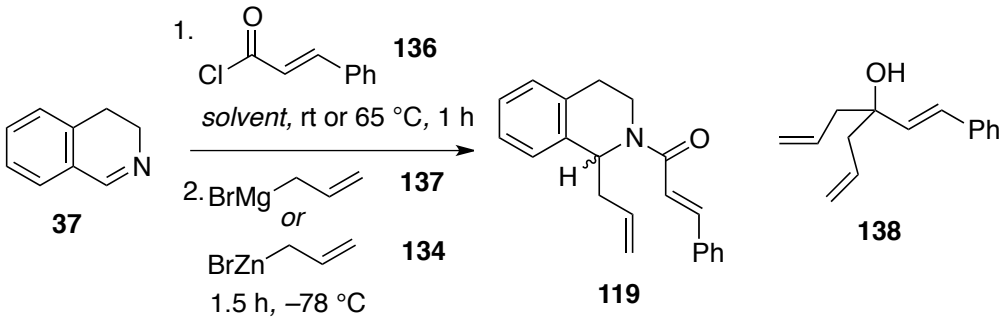


Scheme 2.35 – Synthesis of diene 135 *via* addition of an organometallic nucleophile[71]

It was envisaged that this methodology, consisting of nucleophilic addition into an iminium ion without the need for a Lewis acid, could be exploited in the synthesis of a Boc-protected diene as a key intermediate in the synthesis of (±)-cytisine **42**. In accordance with the literature, an acid chloride would be used to acylate the imine

precursor. Both allylzinc bromide **134** and allylmagnesium bromide **137** have been used in similar additions into *N*-acyliminium ions,[71,72] with allylzinc bromide having the advantage of better functional group tolerance. However, the Grignard reagent **137** is commercially available whereas the allylzinc bromide **134** reagent had to be freshly synthesised.[73]

Addition of the allylmagnesium bromide **137** into the *N*-acyliminium ion was attempted first (Table 2.3, Entries 1-3). Initially, the aromatic imine **37** and acid chloride **136** were reacted in either THF or CH_2Cl_2. Ethereal solvents are typically used in this type of addition reaction[71] but there is some precedent for CH_2Cl_2 increasing the yield of Grignard additions into similar imine derivatives.[72] In THF, the reaction of the acid chloride and imine required heating to solubilise the reaction mixture. Once the *N*-acyliminium ion had been generated, the reaction was cooled to −78 °C and the organometallic reagent was added. Addition of 2 equivalents of Grignard reagent resulted in no product (Entry 1). The byproduct **138** was observed but not isolated. Using only 1.2 equivalents of Grignard reagent in THF or CH_2Cl_2 resulted in a low yield of product **119** (Entries 2 and 3). In all cases where the Grignard reagent was used some of the unwanted byproduct **138** was observed, which suggested that the Grignard reagent preferred to react with the C=O of the *N*-acyliminium ion. Hence, a softer nucleophile, allylzinc bromide **134**, was tried instead and provided improved yields of diene **119** in THF at low temperature (Entries 4 and 5). Use of CH_2Cl_2 resulted in a 37% yield and a messier reaction profile (Entry 6). The best yield was achieved if the reaction was allowed to warm to rt following addition of the allylzinc bromide at −78 °C, providing the diene **119** in 76% yield (Entry 7).

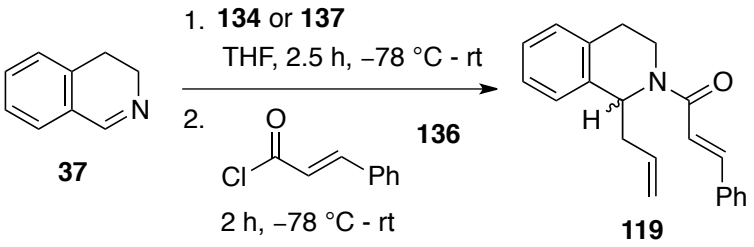


Entry	Solvent	Organometallic reagent	Scale (mmol)	Yield 119 (%)
1	THF	AllylMgBr **137** (2.0 eq)	0.76	0
2	THF	AllylMgBr **137** (1.2 eq)	0.84	17
3	CH_2Cl_2 [a]	AllylMgBr **137** (1.2 eq)	0.76	24
4	THF	AllylZnBr **134** (1.2 eq)	0.76	59
5	THF	AllylZnBr **134** (1.2 eq)	2.00	70
6	CH_2Cl_2 [a]	AllylZnBr **134** (1.2 eq)	2.00	37
7	**THF**	AllylZnBr **134** (1.2 eq)[b]	**1.52**	**76**

[a)] Reaction performed at rt in CH_2Cl_2. [b)] Reaction allowed to warm to rt after addition of organometallic at −78 °C.

Table 2.3 – Addition of organometallic reagents into an *N*-acyliminium ion

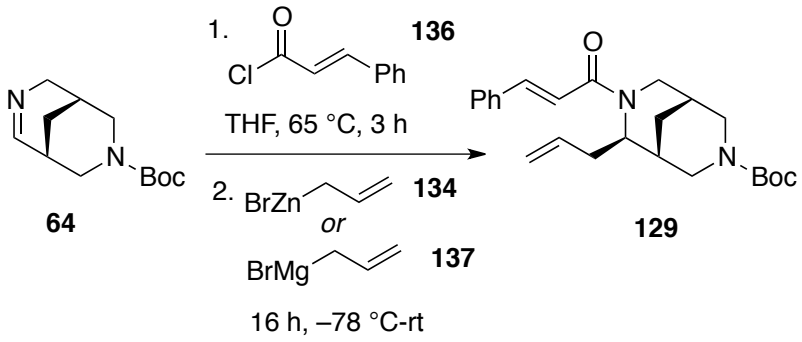
An alternative route to the same diene product **119** is by addition of the organometallic nucleophile first and subsequent trapping of the amine with the acid chloride **136**. The results of these reactions are shown in Table 2.4. Initial addition of the Grignard reagent **137** resulted in a 43% of diene **119** (Entry 1), which was higher than the yields obtained when the Grignard was added into the reaction mixture after formation of the *N*-acyliminium ion. This could be because the *N*-acyliminium ion carbonyl functionality is not present in the molecule, reducing the possibility of side reactions. Addition of the allylzinc bromide **134** reagent first resulted in a 64% yield of diene **119** (Entry 2). This was a slight decrease in yield compared to addition of the allylzinc bromide after formation of the *N*-acyliminium ion, and could possibly be due to the less electrophilic nature of the imine compared to the *N*-acyliminium ion.



Entry	Organometallic reagent	Scale (mmol)	119 Yield (%)
1	AllylMgBr **137**	0.76	43
2	AllylZnBr **134**	0.76	64

Table 2.4 – Synthesis of diene 119 *via* initial addition of organometallic reagent

The optimum conditions developed in this process were initial formation of the *N*-acyliminium ion and subsequent addition of the allylzinc bromide **134** at −78 °C, then allowing to warm to rt (Table 2.3, Entry 7). Therefore, these conditions were attempted on *N*-Boc bispidine imine **64** as a key step in the synthesis of (±)-cytisine **42** (Table 2.5). It was anticipated that these conditions would be compatible with the Boc protecting group. Following purification by column chromatography, the desired diene **129** was isolated. However, the isolated fractions contained a mixture of product **129** and a cinnamic acid impurity, formed from excess cinnamoyl chloride hydrolysed in the aqueous work-up. The cinnamic acid was removed by a basic wash with 10% $NaOH_{(aq)}$ to give the clean product **129** in 17% yield (Entry 1). The reaction was also tried using the Grignard reagent **137** but this was unsuccessful, likely due to the competing reaction with the carbonyl of the *N*-acyliminium ion intermediate (Entry 2). Initial addition of the Grignard reagent into the bispidine imine **64** in CH_2Cl_2, followed by trapping with the acid chloride was also attempted. It was thought that this would ensure all the Grignard had added to the imine prior to addition of the acid chloride, therefore avoiding the presence of the *N*-acyliminium ion carbonyl for side reactions to occur. However, the crude reaction mixture showed a complex mixture of products and upon purification by column chromatography none of the diene **129** was isolated.



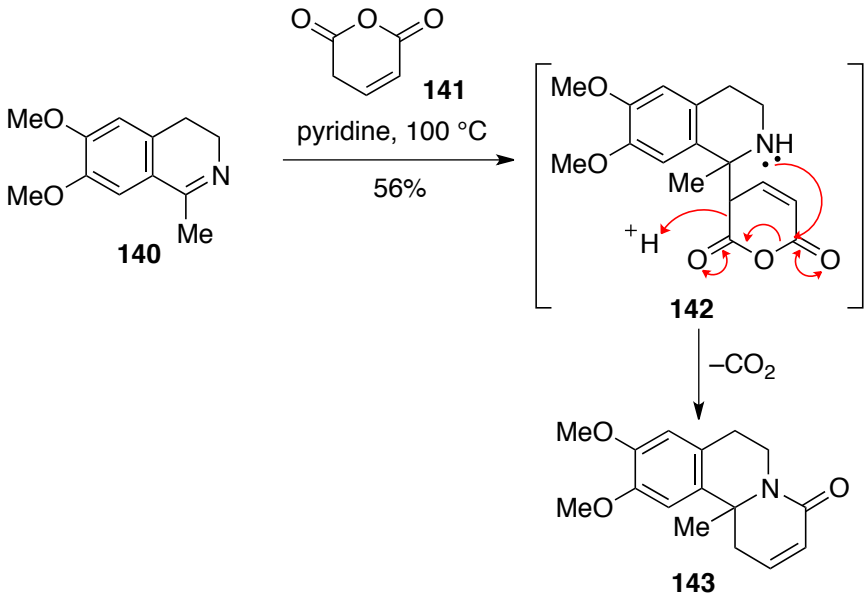
Entry	Organometallic	129 Yield (%)
1	AllylZnBr	17
2	AllylMgBr	0

Table 2.5 – DIA reaction and addition of intermolecular nucleophile

In summary, the DIA reaction involving addition of an intermolecular nucleophile was successfully developed on the aromatic imine **37** and ethyl carbamate-protected bispidine imine **121** but proved more challenging on the *N*-Boc bispidine imine **64**.

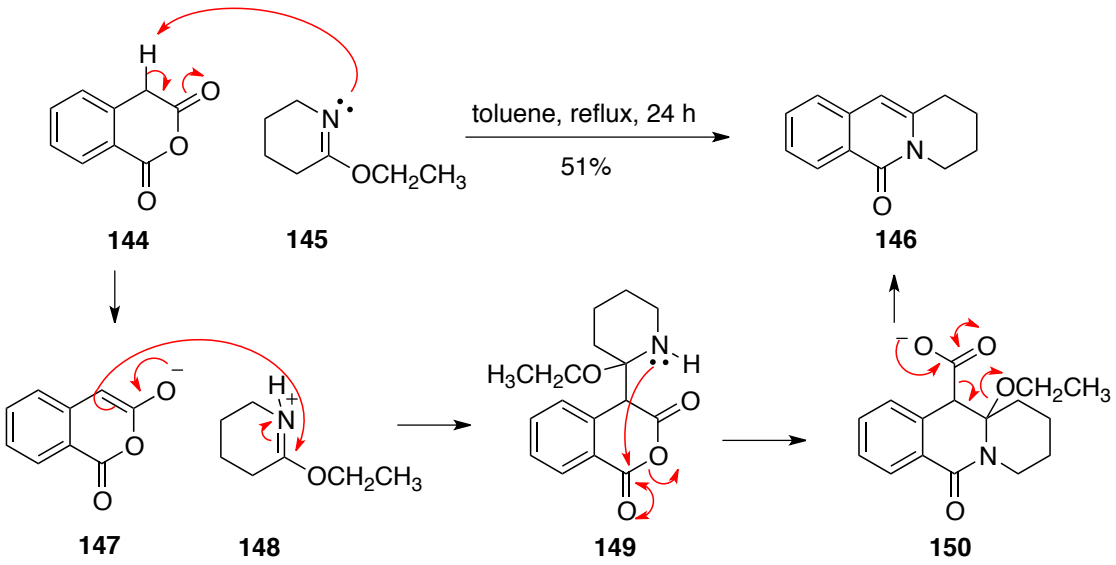
2.3.5. Reaction of Glutaconic Anhydride and Imidates as an Annelation Procedure

An alternative approach to the synthesis of the pyridone scaffold in (±)-cytisine **35** has also been explored. This very different approach was based on the reaction of cyclic anhydrides and imines to form various heterocylic molecules.[74] Early studies into new routes to benzo[α]quinolizines **143** in 1976, showed that the reaction of 3,4-dihydro-1-methylisoquinoline **140** with glutaconic anhydride **141** at 100 °C in pyridine formed the cyclised product **143** in 56% yield, *via* the intermediate shown in Scheme 2.36.[75] It was suggested that nucleophilic attack of the deprotonated methylene carbon in glutaconic anhydride **141** onto the imine would form **142**, which would be followed by cyclisation of the anhydride and decarboxylation to give the product **143** in 56% yield.



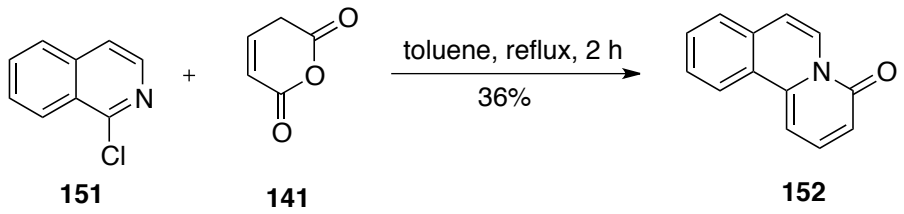
Scheme 2.36 – Reaction of glutaconic anhydride 141 and imine 140[75]

Following on from this preliminary work, Cushman[76] and Haimova[12] demonstrated the use of homophthalic anhydrides in formal cycloaddition reactions with cyclic imine substrates. Haimova[77] and Coppola[78] subsequently showed that chloroimine and alkyl imidates react readily with homophthalic anhydride and form unsaturated lactam products following spontaneous decarboxylation.[74] For example, reaction of homophthalic anhydride **144** with cyclic imidate **145** at high temperature provided the cyclised product **146** in 51% yield (Scheme 2.37). The proposed mechanistic pathway that Coppola suggested is given in Scheme 2.37. Deprotonation of the anhydride **144** by the imidate **145** forms an enolate **147** that attacks the resulting iminium ion **148** to generate intermediate **149**. Internal nucleophilic attack of the amine **149** onto the carbonyl may generate **150**, which could lose carbon dioxide and ethoxide to give the product **146**.[78] An alternative mechanism involving initial acylation of the imine, through nucleophilic attack onto the carbonyl of the anhydride, has also been suggested.[74]



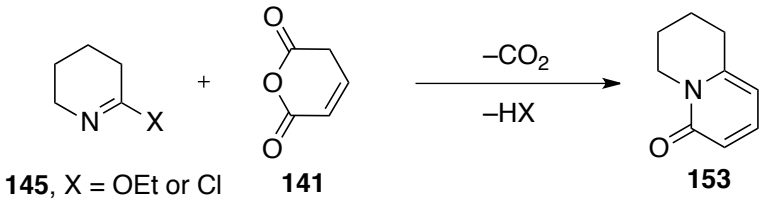
Scheme 2.37 – Reaction between anhydride 144 and imidate 145[78]

The product of the reaction of homophthalic anhydride **144** with the imidate **145** contained a pyridone ring-type scaffold, with additional aromatic functionality as a result of the anhydride used. If glutaconic anhydride **141** was used, it could be possible to form a pyridone ring with no additional substitution around it. Indeed, the reaction of 1-chloroisoquinoline **151** with glutaconic anhydride **141** has been shown to give the pyridone ring present in the product **152** (Scheme 2.38).[79]



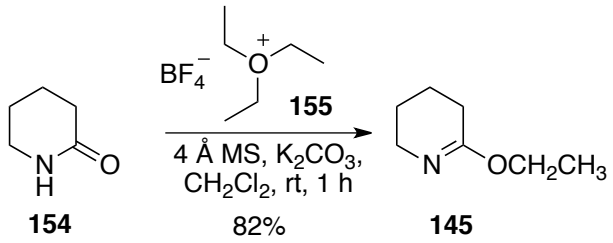
Scheme 2.38 – Synthesis of pyridone 152 by reaction of 1-chloroisoquinoline 151[79]

This precedent for the formation of pyridone scaffolds *via* cyclisation of cyclic anhydrides and imidate-type structures presented an interesting possibility for this project. It was envisaged that the reaction of glutaconic anhydride **141** and a cyclic imidate **145** (where X = OEt or Cl) might form a simple pyridone ring scaffold **153** (Scheme 2.39). Loss of carbon dioxide and elimination of 'X' might give a pyridone ring scaffold with no additional aromatic rings or substituents, and a synthetically simple procedure that could ultimately be used in synthesis of (±)-cytisine **42**.



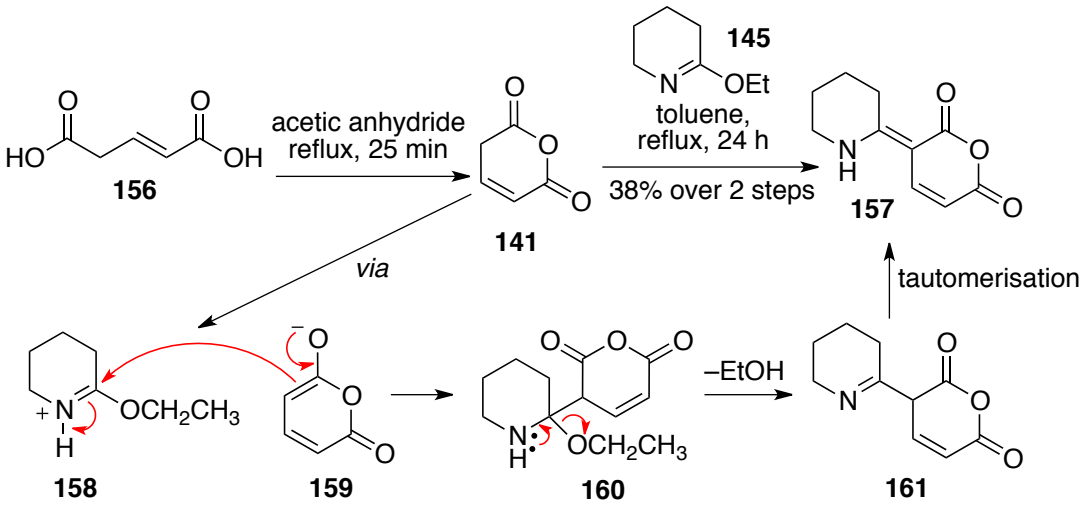
Scheme 2.39 – Proposed reaction for the synthesis of pyridone 153

In a model study, the synthesis of pyridone **153** was investigated. The cyclic imidate **145** (where X = OEt) was synthesised by alkylation of piperidin-2-one **154** using Meerwein's reagent **155** in 82% yield (Scheme 2.40).[22]



Scheme 2.40 – Synthesis of imidate 145

The glutaconic anhydride **141** starting material was synthesised by refluxing *trans*-glutaconic acid **156** in acetic anhydride following a literature procedure (Scheme 2.41).[80] Attempted purification of the crude glutaconic anhydride material by column chromatography resulted in decomposition. However, the ^{1}H NMR spectrum of the unpurified material suggested complete conversion to the glutaconic anhydride **141** and was clean enough to be carried straight through to the subsequent reaction (Scheme 2.41). Subjecting the glutaconic anhydride **141** and cyclic imidate **145** to the precedented conditions for this type of cycloaddition resulted in the α-condensation product **157** in 38% yield and none of the desired cyclised product **153** (Scheme 2.41). The suggested mechanistic pathway for formation of product **157** was generation of the anhydride enolate **159** and subsequent nucleophilic attack onto the iminium ion **158** (Scheme 2.41). Rather than the desired internal cyclisation by nucleophilic attack onto the carbonyl, loss of ethoxide from **160** would have formed enamine **161**. Tautomerisation to the product **157** creates a conformationally restricted compound that would be unlikely to cyclise due to steric hindrance.



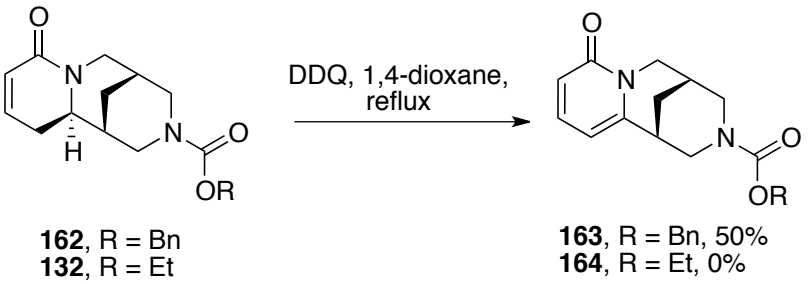
Scheme 2.41 – Synthesis of glutaconic anhydride and reaction with imidate 145

The product **157** was subjected to heating in the presence of catalytic DMAP in an attempt to facilitate cyclisation but only starting material was recovered. This type of α-condensation product had been observed in the literature and provides evidence for the reaction pathway shown in Scheme 2.41 rather than the alternative imine acylation pathway.[79] Conversion of these α-condensation products to the cyclised products had been shown to occur at high temperatures with acidic catalysts,[79] in particular heating in the presence of $POCl_3$.[81] However, due to the lack of literature precedent concerning this transformation and the fact that the specific reaction of glutaconic anhydride **141** and cyclic imidate **145** appeared to be novel, work on this annelation approach was stopped. At the time, this approach appeared to be the least promising and given that the cyclisation was unsuccessful on a model imine it was thought that there was less chance of success on the more complicated bispidine imine **64**.

2.3.6. Towards the Synthesis of (±)-Cytisine: Oxidation of the Dihydropyridone Ring

Development of the annelation procedure on the Boc-protected bispidine compound had proven challenging. The most advanced route in the synthesis of cytisine **42** could provide access to the ethyl-carbamate protected diyhydropyridone **132**. For a successful racemic synthesis of (±)-cytisine, oxidation conditions for transformation of the dihydropyridone to the pyridone **164** were required.

Lesma had successfully employed DDQ conditions to oxidise a Cbz protected bispidine **162** to give **163** in 50% yield (Scheme 2.42).[49] Previous attempts within the O'Brien group on a benzyl-protected dihydropyridone similar in structure to **162** had been unsuccessful. Subjecting dihydropyridone **132** to Lesma's DDQ conditions resulted in none of the desired pyridone **164** being isolated. Starting material was consistently observed using ^{1}H NMR spectroscopy of the crude reaction mixture after 18 h, despite the similarity of the bispidine structure used in Lesma's synthesis and the scaffold in this project (Scheme 2.42). Oxidation using MnO_2 was also attempted, using conditions previously used by Coe *et al.* in the syntheses of (±)-cytisine, but none of the desired pyridone **164** was isolated.[44,46]

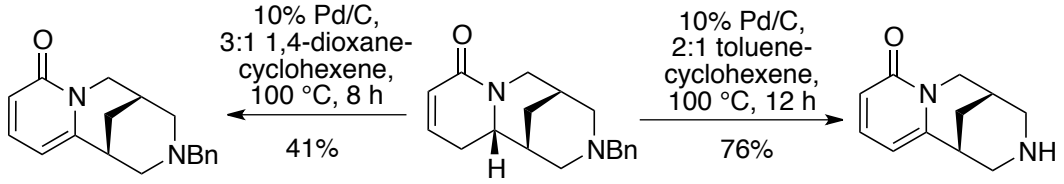


162, R = Bn
132, R = Et

163, R = Bn, 50%
164, R = Et, 0%

Scheme 2.42 – Lesma's oxidation of dihydropyridone

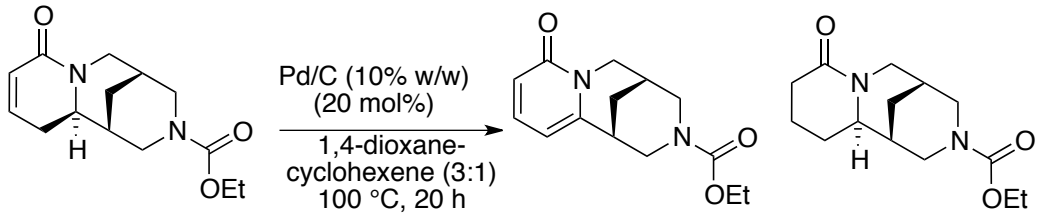
O'Brien has reported that reacting a benzyl-protected dihydropyridone **165** with 10% Pd/C in 3:1 1,4-dioxane-cyclohexene resulted in oxidation of the ring and left the benzyl group intact. Benzyl-protected cytisine **166** was obtained in 41% yield (Scheme 2.43).[46] The purpose of cyclohexene in this reaction is as a hydrogen acceptor to regenerate the catalyst, as the double bond of cyclohexene should be easily reduced. Following the reasonably low 41% yield, it was suggested that 1,4-dioxane could be acting as a hydrogen source and limiting how far the reaction could proceed. This problem was overcome by using toluene rather than 1,4-dioxane, which successfully gave the dihydropyridone and advantageously removed the benzyl group to give (±)-cytisine **42** in 76% yield (Scheme 2.43).[46]



166 **165** **(±)-42**

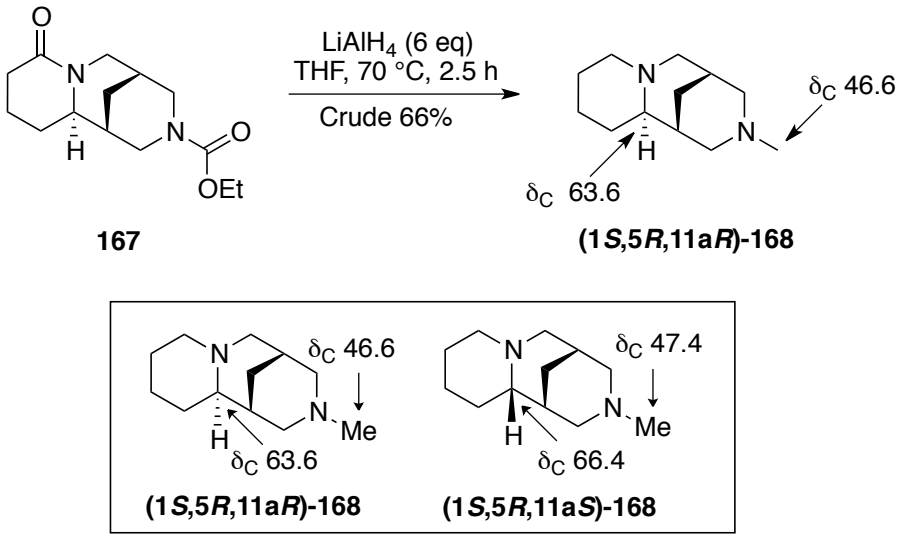
Scheme 2.43 – Precedented oxidation of dihydropyridone 165 using Pd/C[46]

Subjecting dihydropyridone **132** to 10% Pd/C in 1,4-dioxane and cyclohexene, in the hope that the ring would be oxidised, resulted in none of the desired protected cytisine **164**; instead a tetrahydropyridone **167** was isolated in 96% yield (Scheme 2.44). On swapping the solvent from 1,4-dioxane to toluene, the same undesired tetrahydropyridone **167** observed previously was isolated.



Scheme 2.44 – Attempted oxidation of dihydropyridine 132 using Pd/C

Although the oxidation conditions did not provide the desired pyridone product **164**, the tetrahydropyridone **167** was viewed as a useful tool for determining the stereochemistry observed when DIA reaction conditions were used. Following a $LiAlH_4$ reduction procedure previously used in the O'Brien synthesis of the sparteine surrogate **45**,[37] it was possible to convert the tetrahydropyridone **167** into a tricyclic diamine **168** (Scheme 2.45). Tricyclic diamines **(1*S*,5*R*,11a*S*)-168** and **(1*S*,5*R*,11a*R*)-168** had been previously synthesised within the O'Brien group (Scheme 2.45) and provided ^{13}C NMR spectroscopy data that allowed direct comparison with the data collected for the tricyclic diamine synthesised in this project.[69] The two diastereoisomers show different chemical shifts at the carbon groups indicated in Scheme 2.45. Analysis of the ^{13}C NMR spectrum of unpurified tricyclic diamine synthesised confirmed that the reduced product was tricyclic amine **(1*S*,5*R*,11a*R*)-168**. This showed that the earlier assumption that nucleophilic attack had occurred on the more exposed *exo* face during the intermolecular DIA nucleophilic addition was correct.



167 **(1*S*,5*R*,11a*R*)-168**

(1*S*,5*R*,11a*R*)-168 **(1*S*,5*R*,11a*S*)-168**

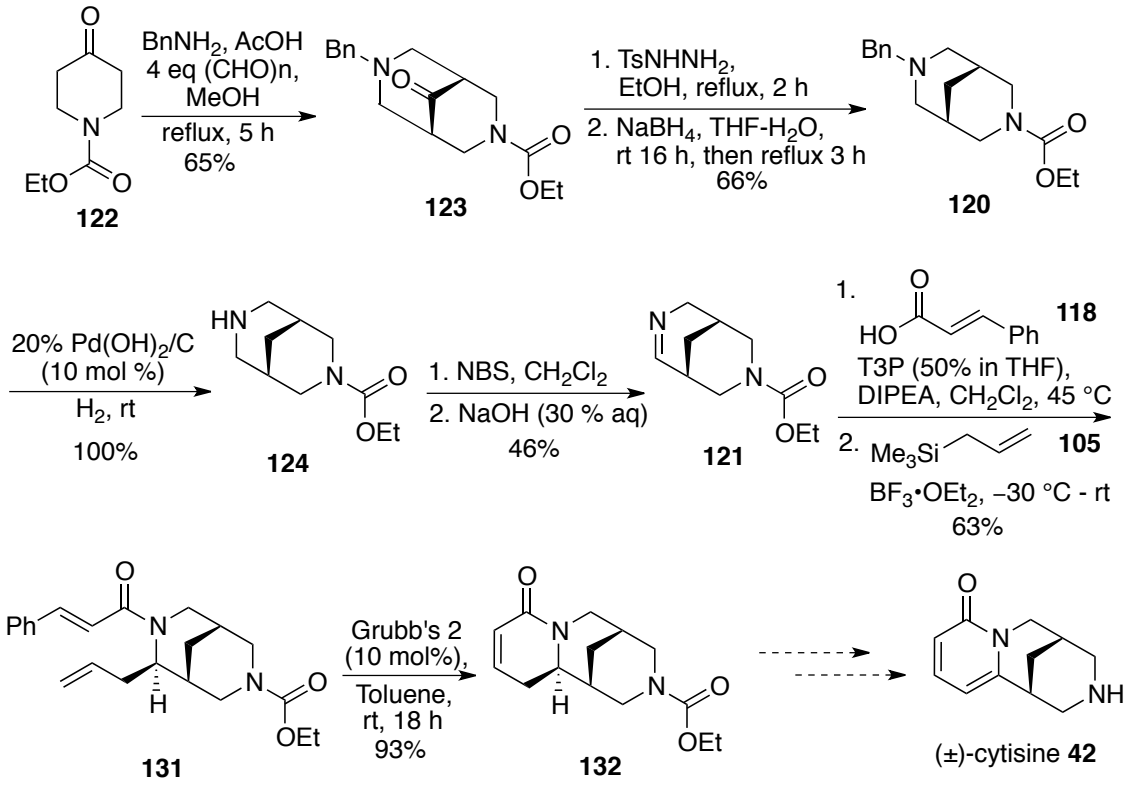
Scheme 2.45 – Reduction of tetrahydropyridone 167 and diagnostic ^{13}C NMR signals of tricyclic amine 168

Unfortunately, we were unable to progress ethyl carbamate imine **121** into (±)-cytisine **42**. All of our attempted oxidation conditions on dihydropyridone **132** were unsuccessful.

2.4. Conclusions and Future Work

The use of DIA methodology for the formation of a pyridone ring scaffold has proved unsuccessful in the route towards (±)-cytisine **42**. In the intramolecular DIA approach, none of the designed carboxylic acid substrates provided the desired cyclised dihydropyridone product. For a number of the substrates, an alternative fused pentacyclic product was observed and isolated as a single diastereoisomer of undefined relative stereochemistry in low yields. This product was a result of the addition of a second imine molecule into the initial *N*-acyliminium ion, followed by cyclisation as shown in Scheme 2.26. The selective and deliberate synthesis of this product using the appropriate reagent stoichiometry provided the fused pentacyclic product in high yield (Scheme 2.27).

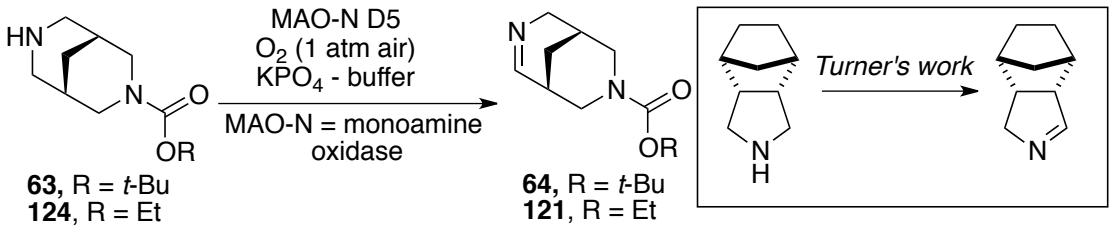
The most advanced route that was developed towards a racemic synthesis of (±)-cytisine **42** is shown in Scheme 2.46. An ethyl carbamate-protected dihydropyridone **132** was synthesised in 6 steps.



Scheme 2.46 – Most advanced route towards (±)-cytisine 42

Both the ethyl carbamate-protected bispidine imine **121** and the *N*-Boc-protected bispidine imine **64** were synthesised using the same routes with similar yields. However, during development of the subsequent key DIA reaction it was found that the *N*-Boc imine **64** was not suitable due to the instability of the Boc group under the acidic conditions. Attempts to develop an acid-free process were partially successful but inefficient and low yielding. The key step of the route involved the direct imine acylation of ethyl carbamate-protected bispidine imine **121** with *trans*-cinnamic acid **118** to form the *N*-acyliminium ion intermediate. Subsequent addition of an external nucleophile and Lewis acid resulted in intermolecular addition to the *N*-acyliminium ion and formation of the diene **131** (Scheme 2.46). Ring-closing metathesis was used to provide the dihydropyridone **132**. Various precedented oxidation techniques were attempted but none gave the desired pyridone scaffold **164**. Completion of this racemic synthesis requires development of a successful oxidation route from the dihydropyridone **132** to the corresponding pyridone and subsequent deprotection to give (±)-cytisine **42**.

Future work could focus on developing an asymmetric synthesis of (−)-cytisine **42**. Preliminary thoughts are to investigate enantioselective enzyme-catalysed desymmetrisation of the mono-protected bispidines **63** and **124** to imines **64** and **121** (Scheme 2.47), which would be the first chiral intermediates in the proposed route to (−)-cytisine **42**. Turner has demonstrated this chemistry on a range of unprotected pyrrolidines, with related scaffolds to the bispidine structure of cytisine (Scheme 2.47).[82]



Scheme 2.47 – Proposed enantioselective enzyme-catalysed desymmetrisation[82]

3. Synthesis of Spirocyclic Compounds using Direct Imine Acylation Methodology

3.1. Introduction

Recently, spirocyclic compounds have been attracting a significant amount of interest due to their three-dimensional, rigid scaffolds, which allow them to be used to probe areas of chemical space that are currently under-explored.[83,84] Access to new areas of chemical space could provide the opportunity to develop novel pharmaceutical compounds with interesting biological activities. Nitrogen-containing heterocycles are prevalent in medicinal chemistry and make up a significant proportion of FDA approved small molecule drugs.[85] Spirocyclic compounds containing nitrogen heterocycles are therefore attractive targets for synthesis as they have the potential to be interesting biologically active compounds which occupy undiscovered areas of chemical space.

3.1.1. Spirocyclic Scaffolds in Biologically Active Natural Products and Pharmaceutical Compounds

Spirocyclic scaffolds are important due to their presence in a large number of biologically active natural products and pharmaceutical compounds.[84] A number of alkaloid natural products contain a spirocyclic scaffold at their core. Examples include the *aspidosperma* and *strychnos* alkaloid families. The structures of aspidospermidine **169** and strychnine **170** (Figure 3.1) have been widely used to showcase synthetic methodologies aimed at rapidly assembling polycyclic structures.[86,87] Aspidospermidine **169** has been shown to possess some adrenergic receptor inhibitor activity but these natural products are more attractive as targets for total synthesis.[87,88] Some members of the *vinca* alkaloid family, vinblastine and vincristine, are clinically useful oncolytic agents whose structures are very closely related to the natural product vindoline **171** (Figure 3.1).[89,90] The spiroindolenine scaffold is present in a number of natural products including koumine **172** and spirobacillene **173**, with the former possessing analgesic and anti-cancer activity (Figure 3.1).[91-93] The spiroindoline scaffold occurs in pharmaceutically active compounds, such as the Sky kinase inhibitor **174**, further highlighting the importance of these spirocyclic motifs and their use as potential therapeutics (Figure 3.1).[94,95]

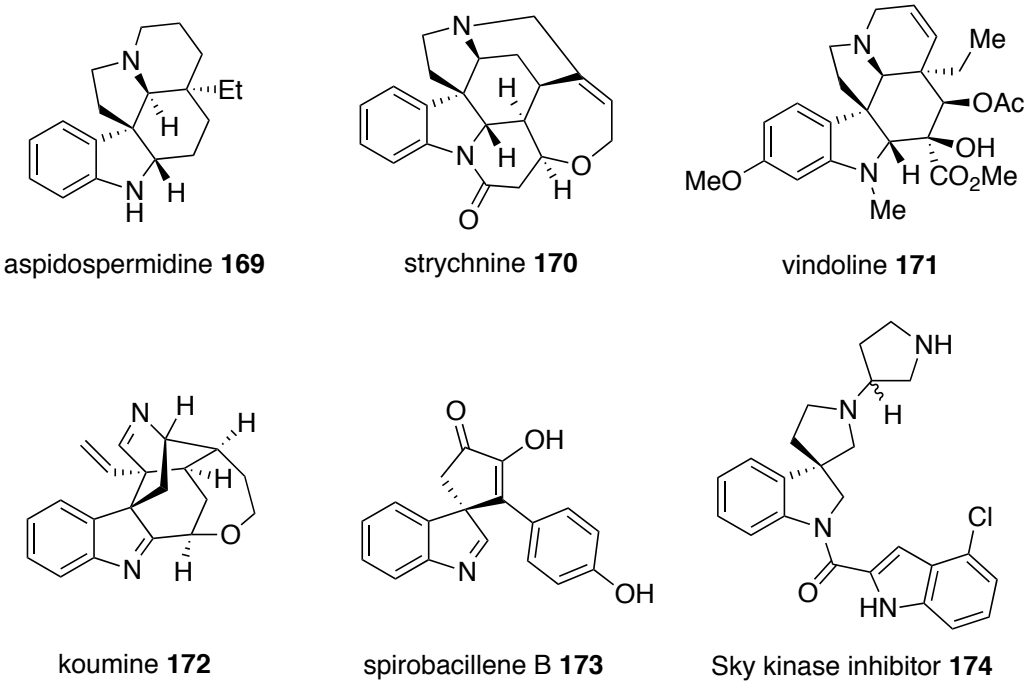


Figure 3.1 – Biologically active and naturally occurring spirocycles

A scaffold that shows a wide range of pharmacological activities is the spirooxindole scaffold.[96] The natural product (−)-horsifiline **175**, isolated from *Horsfieldia superba*, contains a simple spirooxindole scaffold and is used as an indigenous medicine (Figure 3.2).[96,97] Mitraphylline **176** was isolated from *Unicaria tomentosa* and shows anti-tumour activity against human brain cancer cell lines (Figure 3.2).[96,98] Spirotryprostatin A **177** and spirotryprostatin B **178** were both isolated from *Aspergillus fumigatus* and show powerful bioactivity in cell cycle modulation, with spirotryprostatin B **178** also showing cytotoxic activity on the growth of human leukemia cell lines.[99,100] In general, spirooxindole compounds display anti-tumour, anti-microbial, anti-proliferative and anti-fungal properties.[96] Due to the biological importance associated with the spirooxindole scaffold, there are many reports on the synthesis of such compounds. Transition-metal-mediated routes to 3,3-disubstituted oxindole compounds are widely used,[101,102] but other methodologies such as 1,3-dipolar cycloaddition of azomethine ylides have been developed to access these important compounds.[96]

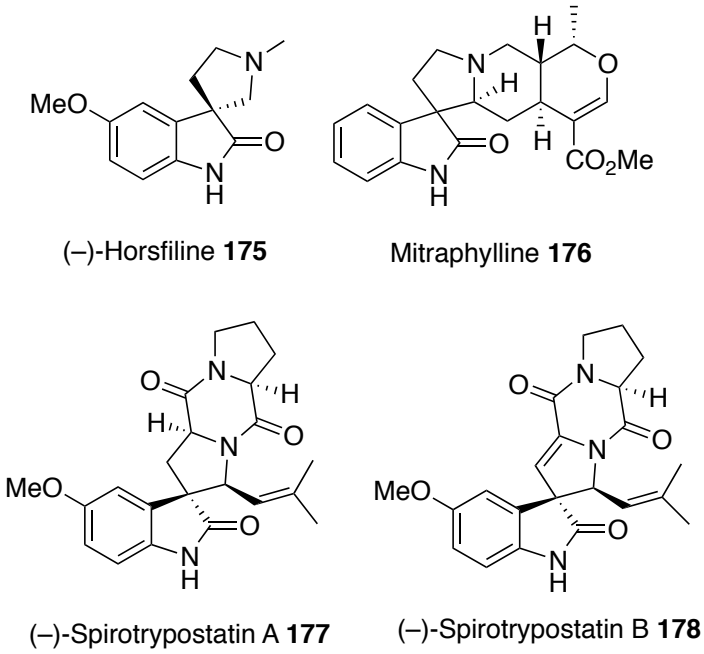
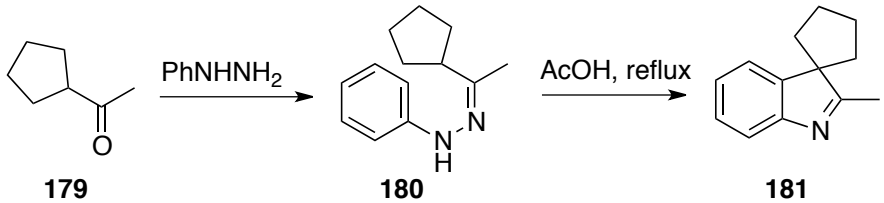


Figure 3.2 – Natural products with oxindole core scaffolds

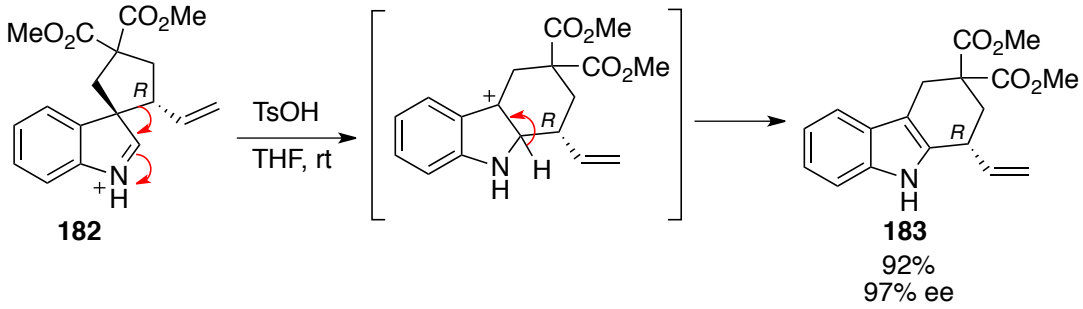
3.1.2. Synthesis of Spirocyclic Indolenines via Interrupted Fischer Indole Reactions

As outlined in a recent review from our group,[103] the synthesis of spirocyclic indolenine scaffolds can be separated into three main categories: interrupted Fischer indole reactions, condensation reactions and dearomatisation of indoles. The interrupted Fischer indole reaction is the oldest methodology for the synthesis of spirocyclic indolenines. In 1951, Wiktop and Patrick demonstrated the synthesis of simple cyclopentyl spirocyclic indolenines containing a group in the 2-position (Scheme 3.1).[104] The hydrazine intermediate **180** was generated by condensation of an aldehyde **179** and phenyl hydrazine, followed by an acid-catalysed interrupted Fischer indole reaction to give indole **181** (Scheme 3.1, no yields were given).



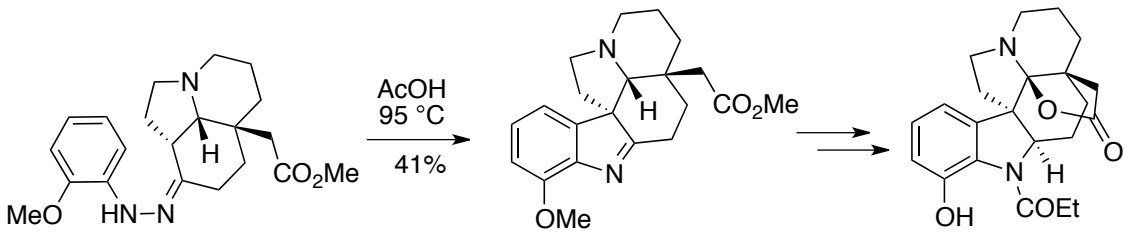
Scheme 3.1 – An interrupted Fischer indole reaction route to spiroindolenines[104]

The inclusion of a group in the 2-position of the spiroindolenine products is commonly used as a method to prevent a potential 1,2-migration reaction from occurring, which has been observed under acidic conditions.[105-107] This process was recently studied mechanistically by You *et al.* who reported the first selective migration of optically active chiral spiroindolenines (Scheme 3.2).[107] Previous work had demonstrated the synthesis of chiral spiroindolenines by an Ir-catalysed intramolecular asymmetric allylic dearomatisation reaction.[108] Upon treatment with catalytic TsOH, spiroindolenine **182** was converted into the tetrahydracarbazole **183** with the absolute configuration of the chiral centre at the allylic position conserved (Scheme 3.2).[107] It was shown that the migration reaction proceeded by a concerted mechanism, which involves a "three-centre-two-electron"-type transition state without formation of a free carbocation and therefore no racemisation occurs. The formation of the aromatic indole **183** can drive the rearrangement through formation of the more thermodynamically stable product (Scheme 3.2).[107]



Scheme 3.2 – Stereoselective 1,2-migration of chiral spiroindolenines[107]

Interrupted Fischer indole chemistry has been demonstrated as a powerful method in the synthesis of spirocyclic indolenines and has been showcased in the synthesis of natural products. Tokuyama *et al.* were able to utilise this methodology in the synthesis of (−)-aspidophytine and related alkaloids (+)-cimicidine and (+)-cimicine. Hydrazone **184** was treated with neat AcOH at 95 °C to afford the spiroindolenine **185** in 41% yield, which could be converted into (+)-cimicine **186** in subsequent steps (Scheme 3.3).[109]



Scheme 3.3 – Synthesis of (+)-cimicine *via* interrupted Fischer indole reaction[109]

3.1.3. Synthesis of Spirocyclic Indolenines via Dearomatisation of Indoles

The dearomatisation reaction of indoles is a popular method for the synthesis of spirocyclic indolenines.[103] The reaction provides a powerful method for the introduction of substituents onto aromatic compounds and leads to a variety of heterocyclic skeletons.[110] The generation of stereogenic quaternary centres is achievable and particularly useful in the synthesis of complex natural products.[111] In this broad synthetic field, there are many different variations of this dearomatisation process such as alkylation reactions, oxidative coupling reactions and conjugate additions as well as many more.[103,110,111] It is well known that the 3-position of an indole is the most reactive position with electrophiles. Electrophilic substitution at the 2-position of a 3-substituted indole is energetically unfavourable due to the formation of an intermediate **187** in which the aromatic ring system has been disturbed (Figure 3.3). In contrast, electrophilic substitution at the 3-position allows the aromatic ring to stay intact, forming an intermediate **188** (Figure 3.3).[112] This electronic character can be exploited to generate spirocyclic centres at the 3-position of an indole.

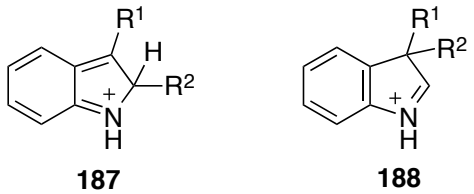
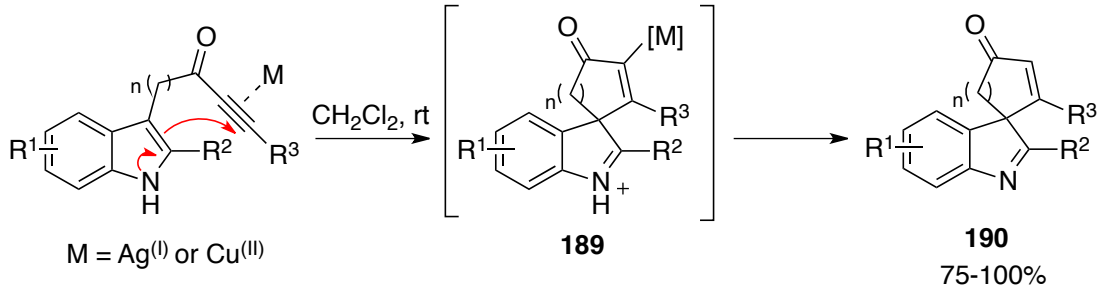


Figure 3.3 – Effects of electrophilic substitution at 2- and 3-position of indole

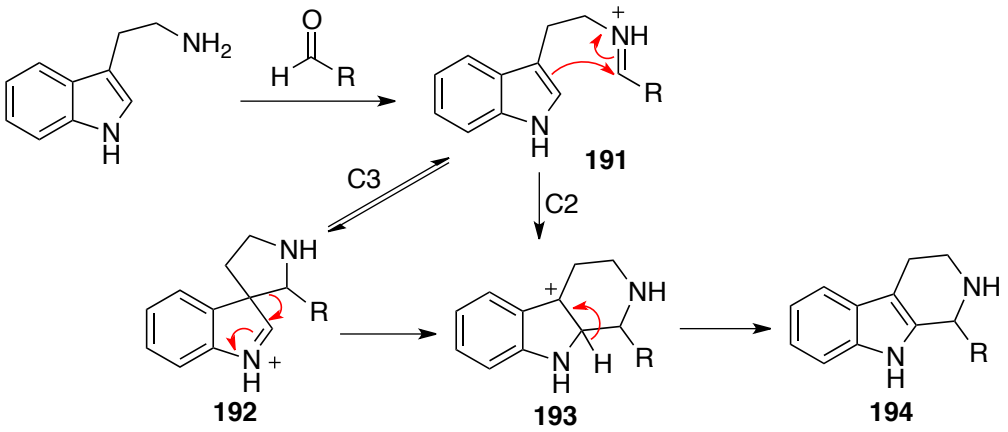
A recent example developed in the Taylor group focused on the electrophilic activation of alkynes using Ag(I) and Cu(II) catalysts to generate spirocyclic indolenine products

190 in 75-100% yield (Scheme 3.4).[113] The reaction proceeds through an intermediate **189**, which undergoes protodemetallation to give the spiroindolenine product **190**. It was noted that the ynone functionality was necessary as the carbonyl group reduces the migratory aptitude of the alkene and therefore prevents the possible 1,2-migration reaction. An asymmetric variant was also developed, through the use of Ag(I) salts of chiral phosphoric acids. Conducting the reaction at −10 °C gave a range of enantioenriched products between 75-100% yield and up to 86:14 er.[113]



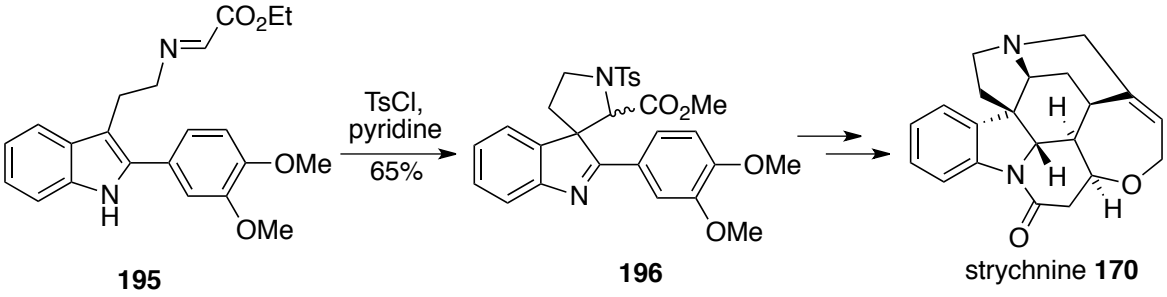
Scheme 3.4 – Synthesis of spiroindolenines *via* electrophilic activation of alkynes[113]

The dearomatisation of indoles involving nucleophilic addition into iminium ions most closely relates to the methodology developed in this project. The mechanism of this reaction is similar to that of the Pictet-Spengler reaction, which is often thought to proceed *via* a spirocyclic intermediate.[107] Following a condensation reaction to give the iminium ion intermediate **191**, nucleophilic attack can occur either through the 2- or 3-position of the indole (Scheme 3.5).[114,115] After formation of the spiroindolenine intermediate **192**, the tetrahydro-β-carboline product **194** can be formed either by a 1,2-migration reaction and rearomatisation of **193**, or ring-opening to reform the iminium ion **192** and direct attack through the 2-position (Scheme 3.5).[107] Therefore, in the synthesis of spirocyclic indolenine products *via* attack of an iminium ion, the potential 1,2-migration reaction should be prevented.



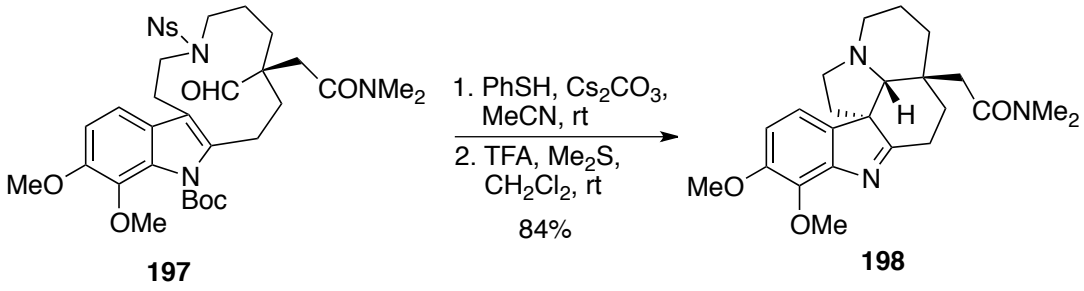
Scheme 3.5 – Possible reaction pathways in the Pictet-Spengler reaction

Woodward *et al.* demonstrated this dearomatisation strategy in their seminal work on the total synthesis of strychnine **170**.[116,117] In the dearomatisation process, the imine **195** was activated by TsCl to form an *N*-sulfonyliminium ion. The increased electrophilicity initiates subsequent attack of the indole through the 3-position to give the spiroindolenine product **196** in 65% yield (Scheme 3.6).[117]



Scheme 3.6 – Synthesis of a spirocyclic indolenine by nucleophilic attack[117]

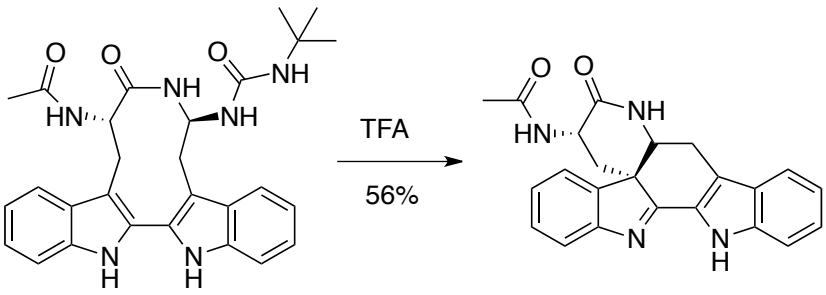
This method has commonly been used in transannular spirocyclisation reactions, where larger ring systems are converted into a polycyclic scaffold.[103] An elegant example of this is in the formation of an important precursor in the synthesis of (–)-aspidophytine by Fukuyama *et al.* (Scheme 3.7).[118] Initital deprotection of the nosyl group on indole **197** and subsequent TFA-catalysed condensation of the amine and aldehyde produced the reactive iminium ion intermediate. Following this, deprotection of the Boc group enabled attack through the 3-position to give the complex polycyclic scaffold **198** in 84% yield over two steps (Scheme 3.7).[118]



197 198

Scheme 3.7 – Synthesis of spirocyclic indolenine by transannular spirocyclisation[118]

Activation of the iminium ion can also be accomplished by acylation of the nitrogen to give an *N*-acyliminium ion with increased electrophilic character. Van Vranken *et al.* demonstrated an example of this in their synthesis of indolo[2,3-a]carbazoles.[119] Reaction of ditryptophan **199** with TFA afforded the spirocyclic indolenine **200** in 56% yield, through elimination of the carbamide and subsequent transannular spirocyclisation onto the reactive *N*-acyliminium species (Scheme 3.8).



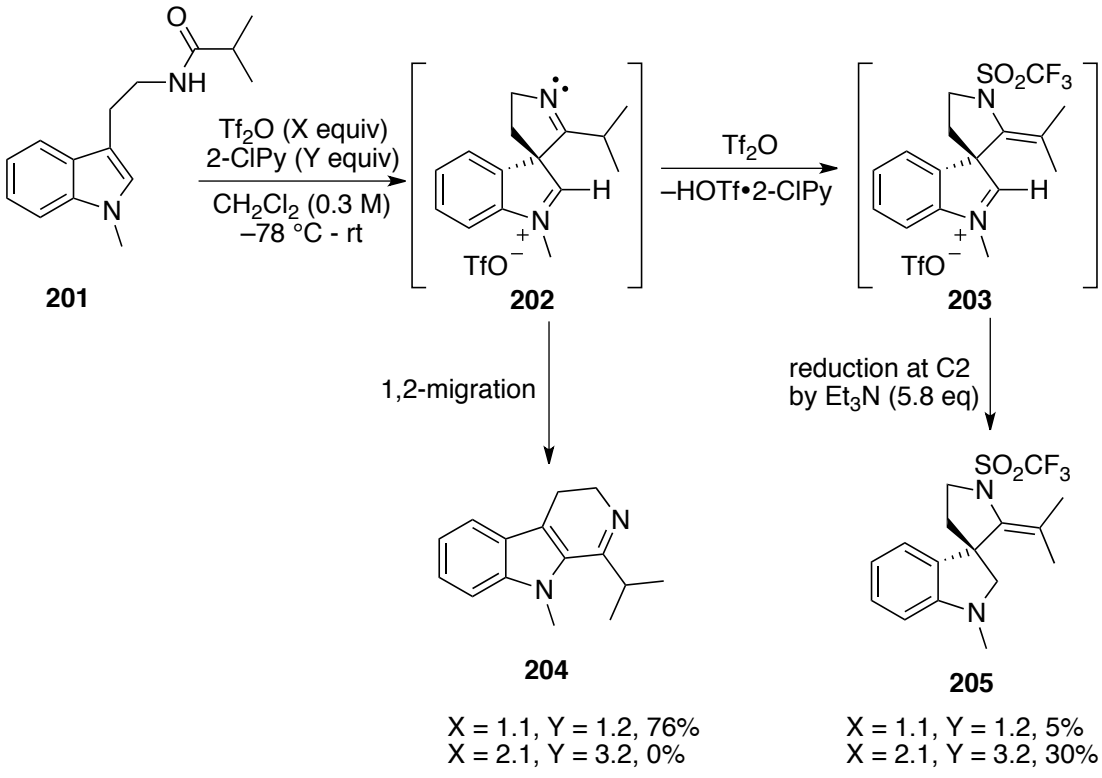
199 200

Scheme 3.8 - Synthesis of spirocyclic indolenine by transannular spirocyclisation[119]

3.1.4. Spirocyclic Indolenines as Precursors for Other Privileged Hetereocycles

Spirocyclic indolenine scaffolds are primed to undergo further transformations and they can therefore be useful precursors to other privileged heterocycles, such as oxindoles, indolines, indoles and polycyclic frameworks.[103,120] The formation of spirocyclic indoline products can be achieved through reduction of an indolenine intermediate. A recent synthesis of the spirocyclic indoline scaffolds found in the structures of the *aspidosperma* and *strychnos* alkaloid families demonstrates this, using an interrupted Bischler-Napieralski reaction.[94] Movassaghi *et al.* noted that spiropyrrolidino-

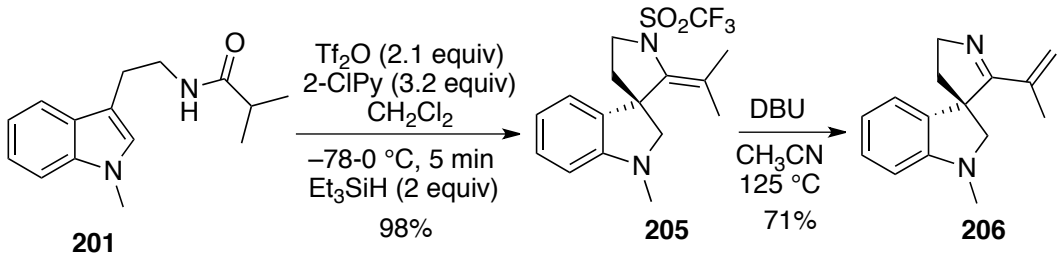
indoleninium intermediates **202** in the Bischler-Napieralski reaction underwent a 1,2-migration to give the fused cyclic product **204** (Scheme 3.9). This rearrangement occurs unless there is a strongly nucleophilic trap present in the reaction.[94] Using a reagent combination of Tf_2O and 2-ClPy to induce the Bischler-Napieralski reaction of secondary amides **201**, the product **204** was isolated in 76% yield and an unexpected spirocyclic side product **205** was isolated in 5% yield (Scheme 3.9). The yield of the spirocyclic product **205** could be increased to 30% by use of excess Tf_2O and 2-Cl-Py and was rationalised by interception of the expected spirocyclic indoleninium intermediate **202**. In comparison to the normal Bischler-Napieralski reaction, which goes *via* an iminium ion intermediate, formation of product **203** may go *via* a nitrilium ion instead to allow for trapping of the resulting imine with triflate (tautomerisation gives the enamine product **203**). Deuterium-labelling experiments demonstrated that the intermediate **203** was persisting until addition of an exogeneous hydride source, from the Et_3N added to the reaction, afforded reduction at the C-2 position (Scheme 3.9).[94]



Scheme 3.9 – Interruption of the Bischler-Napieralski reaction[94]

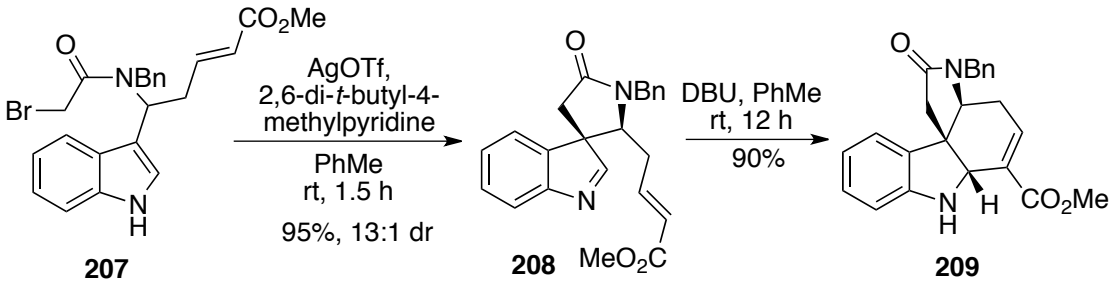
The group concluded that these results suggested that the *N*-trifluoromethanesulfonyl indoleninium **203** was electrophilic at C-2 but did not undergo the 1,2-migration due to deactivation of the trifluoromethane-sulfonamide nitrogen lone pair.[94] Optimisation of

the reaction conditions provided high yields of the spiropyrrolidinoindoline products, an example of which is shown in Scheme 3.10 using a less potent hydride source (Et_3SiH). Dehydrosulfination of **205** was achieved using DBU to afford the product **206** (Scheme 3.10).



Scheme 3.10 – Optimisation of the interrupted Bischler-Napieralski reaction[94]

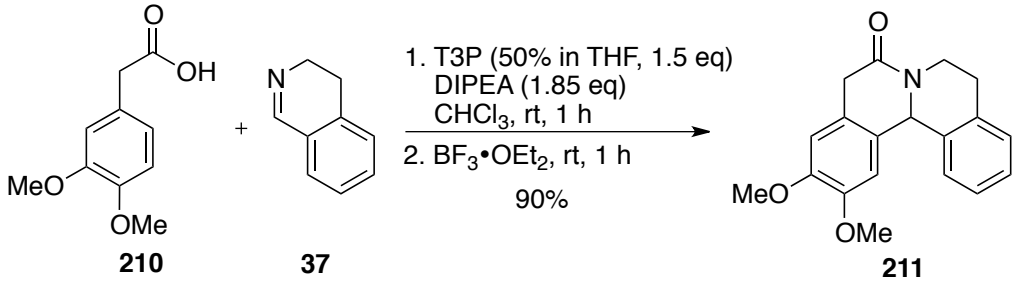
Polycyclic spirocyclic compounds can also be accessed *via* a spirocyclic indolenine intermediate. Many syntheses of compounds containing spirocyclic indole cores set the stereocentre of the spirocycle early in the synthesis, as Woodward did in his original synthesis of strychnine **170**.[116] A more recent report on the synthesis of tetracyclic frameworks present in the *Strychnos* alkaloids takes the same approach and the spirocyclic scaffold was constructed early on at the 3-position.[86] In the synthesis, the key spirocyclic scaffold **208** was afforded in high yield and stereoselectivity in the presence of AgOTf and base from the substituted indole **207** (Scheme 3.11). Subsequent intramolecular aza-Baylis-Hillman reaction with DBU gave the tetracyclic scaffold **209**. A one-pot spirocyclisation/intramolecular aza-Baylis-Hillman reaction was then carried out in 70% overall yield to demonstrate the efficiency with which these important tetracyclic scaffolds can be built (Scheme 3.11).[86]



Scheme 3.11 – Synthesis of tetracyclic frameworks present in *strychnos* alkaloids[86]

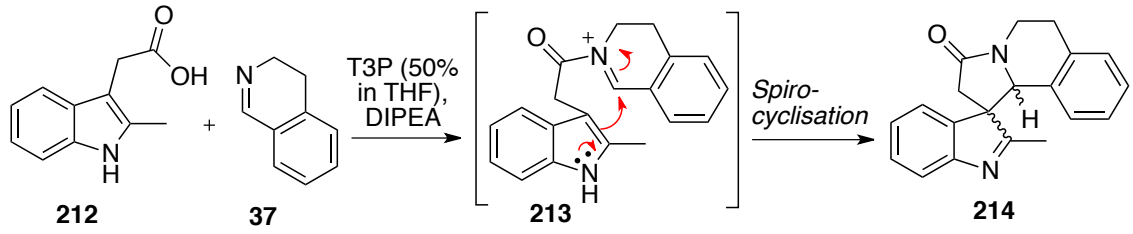
3.2. Project Outline

The aim of this part of the project was to develop new methodology to synthesise spirocyclic indolenine scaffolds in an efficient manner using DIA methodology developed in the Taylor group. As outlined in Chapter 1 (see Section 1.1.3), DIA methodology has previously been shown to be a quick and efficient way to build up the complexity in heterocyclic structures.[20,21] An example of this is shown in Scheme 3.12 where acid **210** and imine **37** are reacted in the presence of T3P and DIPEA to form the *N*-acyliminium ion intermediate. Lewis acid-promoted cyclisation afforded the fused polycyclic product **211** in 90% yield.



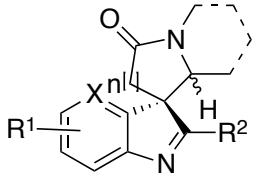
Scheme 3.12 – Synthesis of polycyclic heterocycles using DIA methodology[20]

It was envisaged that the appropriate acid starting materials and imine components could be combined under the standard DIA conditions of T3P and DIPEA to provide more complex 3D spirocyclic compounds. Our plan was that an indole acetic acid starting material **212** would be reacted with imine **37** in the presence of T3P and DIPEA in a DIA reaction to generate an *N*-acyliminium ion intermediate **213** (Scheme 3.13). The known nucleophilic reactivity of indoles would then be exploited to generate a spirocyclic scaffold in the 3-position of the indole to give an indolenine structure **214** (Scheme 3.13).



Scheme 3.13 – Synthesis of a spirocyclic indolenine using DIA methodology

The reaction conditions would then be optimised to determine the highest diastereoselectivity and yield possible. If successful, the project would then be extended to demonstrate the use of DIA methodology in the synthesis of various spirocyclic compounds by exploring the substrate scope of the indole acid and imine components. Substitution around the indole aromatic ring and in the 2-position would be explored, as well as varying the size of the spirocyclic ring formed. The imine substrate scope would be investigated to include other aromatic imine substrates with substitution around the aromatic ring and acyclic imine variants would also be explored (Figure 3.4).



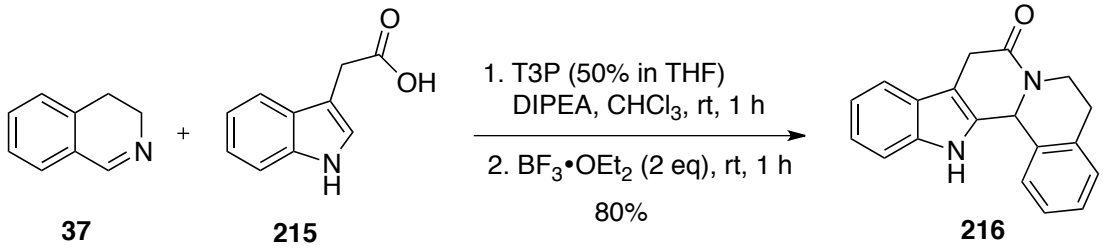
R^1 = OMe, halogen, alkyl
R^2 = alkyl, halide, aromatic
X = C or N
n = 1, 2

Figure 3.4 - Potential points for diversity around spirocyclic indolenine scaffold

3.3. Results and Discussion

3.3.1. Background and Initial Result

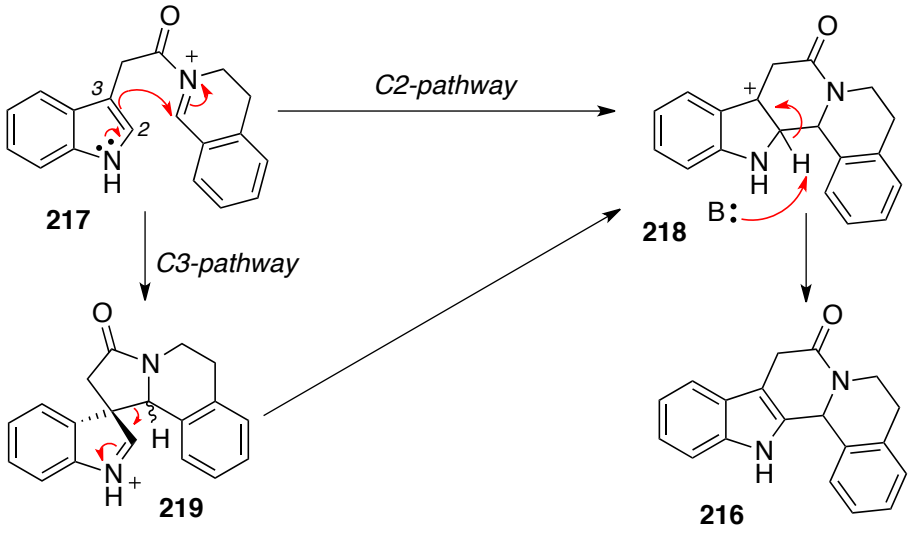
Previous work within the Taylor group on DIA methodology had focused on the acid-promoted cyclisation of various carbon nucleophiles onto *N*-acyliminium ions formed *in situ*.[20] The addition of a Lewis acid was found to be necessary for most carbon nucleophiles to react, presumably to increase the electrophilicity of the intermediate *N*-acyliminium ion.[20] For example, reaction of aromatic imine **37** with indole acid **215**, and addition of BF_3•OEt_2 after formation of the *N*-acyliminium ion, gave product **216** in 80% yield (Scheme 3.14).[20]



37 **215** **216**

Scheme 3.14 – Synthesis of pentacycle 216 using DIA methodology

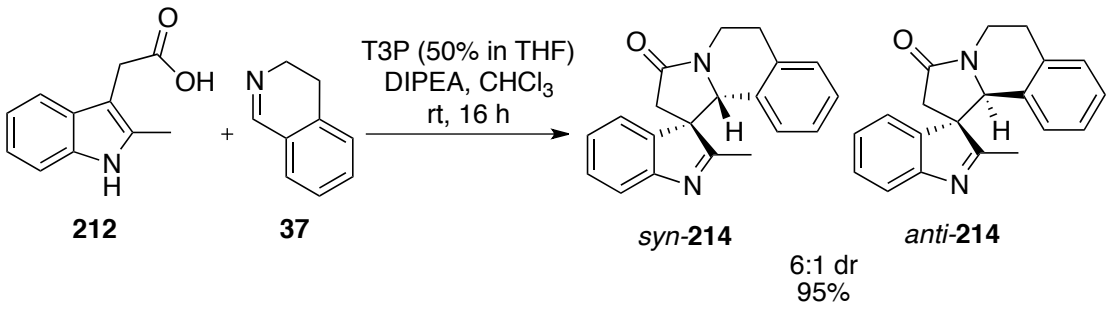
Mechanistically, this pentacyclic product **216** may have formed *via* initial *N*-acylation and direct cyclisation through the C2-position of the indole as shown in Scheme 3.15 (**217→218→216**). However, it is possible that the same product **216** could have formed *via* initial cyclisation through the C3-position of the indole to form a spirocyclic intermediate and a subsequent 1,2-migration reaction (**217→219→218→216**, Scheme 3.15); similar reactions are well precedented under acidic conditions.[107] Therefore, it was hypothesised that, in the above reaction (Scheme 3.14), product **216** could have been formed *via* a spirocyclic intermediate followed by a 1,2-migration promoted by the addition of BF_3•OEt_2. An investigation of this hypothesis was planned; it was believed that, due to the electron-rich nature of an indole, the spirocyclisation step might occur without the need for a Lewis acid and the reaction would end at the spirocyclic product.



Scheme 3.15 – Proposed mechanism for the formation of indole 216

Initial reaction investigations were carried out using an indole acid with a methyl group in the 2-position. This would increase the likelihood of a stable spirocyclic product being isolated and reduce the possibility of a 1,2-migration. The initial reaction used a commericially available indole acetic acid **212** and imine **37** in typical DIA conditions of T3P and DIPEA in $CHCl_3$ at rt for 16 h (Scheme 3.16).* Pleasingly, in our hands, the reaction proceeded very efficiently and the desired spirocyclic product was obtained as a 6:1 diastereomeric mixture of *syn*-**214**:*anti*-**214** determined by analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture. The diastereoisomers were separable by column chromatography to give clean *anti*-**214** and *syn*-**214** in 7% yield and 34% respectively and 54% yield of mixed diastereoisomers, resulting in an overall yield of 95%. An X-ray crystal structure of the major diastereoisomer was obtained (Figure 3.5),† and surprisingly revealed that the 2-position of the indolenine and the hydrogen (from the imine) were *syn* to each other. This was interesting as it might have been expected, from a steric hindrance perspective, that the most favoured diastereoisomer would be *anti*-**214**.

* The initial proof of concept was performed by Dr Graeme Coulthard in the Taylor group, but was repeated for the purpose of this project.
† X-ray obtained by Dr Graeme Coulthard.



Scheme 3.16 –DIA spirocyclisation of indole acid 212 and imine 37

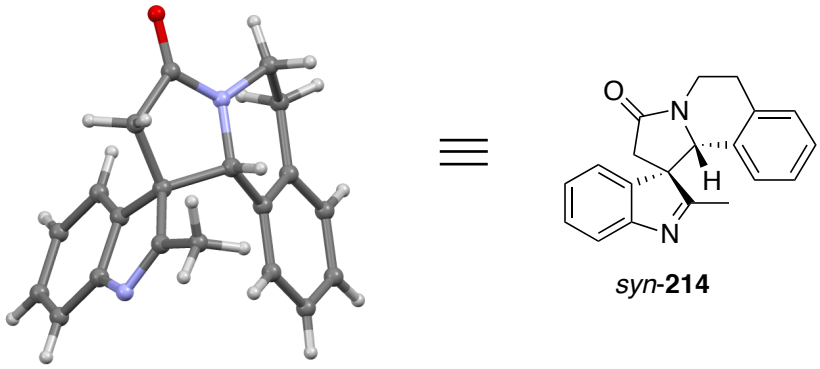
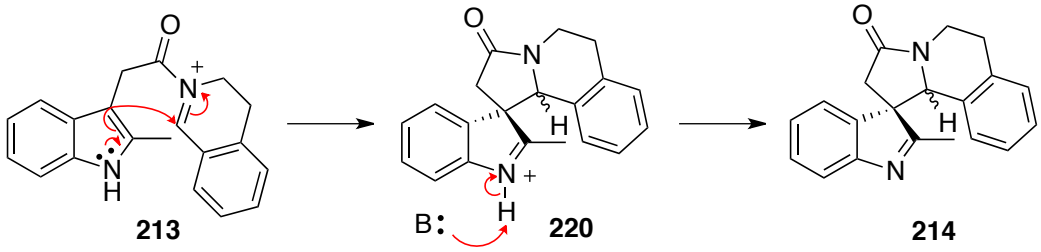


Figure 3.5 – X-ray crystal structure of *syn*-214 (CCDC: 1436464)

The likely mechanistic pathway is summarised below; following formation of the *N*-acyliminium ion **213**, the electron-rich nucleophilic indole would cyclise through the 3-position resulting in the spirocyclic intermediate **220**. Deprotonation by the base would give the spirocyclic product **214** (Scheme 3.17).



Scheme 3.17 – Proposed mechanism for the formation of spirocyclic indolenines

Assuming the reaction is irreversible, the diastereoselectivity of the reaction is determined by the facial selectivity of the nucleophilic addition into the *N*-acyliminium ion. The formation of *syn*-**214** as the major product could be attributed to a π-π stabilising interaction between the aromatic ring of the indole and imine, as depicted in **221** in Figure 3.6. Formation of the *anti*-**214** product would therefore be due to the *N*-

acyliminium ion **222** intermediate where there is a potentially destabilising clash between the methyl group and aromatic ring of the imine (Figure 3.6).

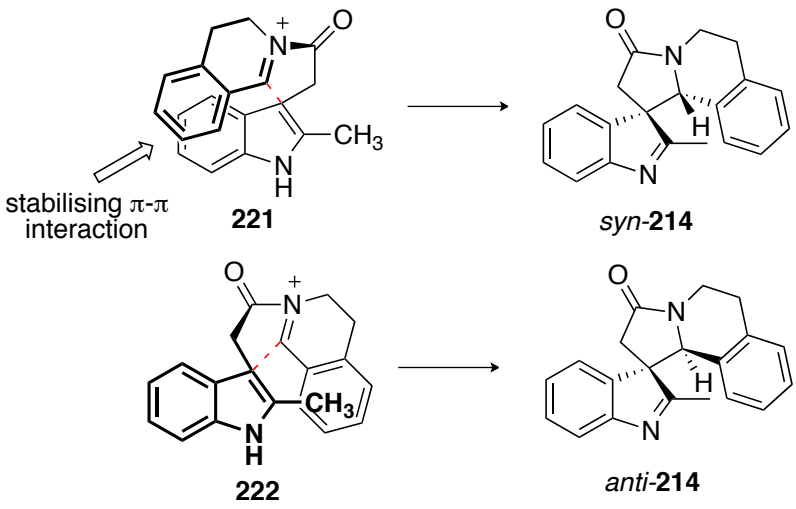
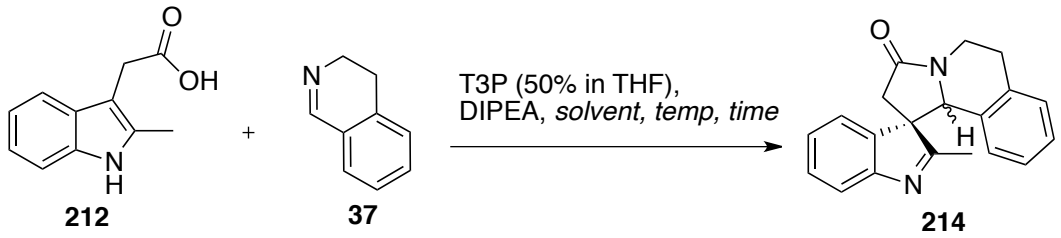


Figure 3.6 – Stereochemical model for the new spirocyclisation reaction

3.3.2. Optimisation of the Synthesis of Spirocyclic Compounds via N-Acyliminium Ions

Following the promising initial result observed for the 2-substituted spirocyclic product, an optimisation process was carried out using aromatic imine **37** and 2-methyl indole acetic acid **212**, using the established DIA conditions used previously (Table 3.1). The ratio of diastereoisomers was determined by analysis of the ^{1}H NMR spectra of the crude product mixtures. Entry 1 shows the initial promising result for the DIA spirocyclisation reaction. Various solvents were then screened and it was seen that the best diastereomeric ratio of 9:1 of *syn*-**214**:*anti*-**214** was observed when THF was used (Entry 2), also providing the product in good yield. Reactions carried out in 2-Me-THF, TBME and Et_2O showed very poor solubility (Entries 6, 7, 8 and 9) and generally lower diastereomeric ratios and yields. Scale-up of the reaction in THF (Entry 10) showed a reproducible diastereomeric ratio and excellent yield. A good yield could be obtained after only 1 h in THF at rt (Entry 11). Lowering the temperature to 0 °C did not affect the diastereomeric ratio but the yield was lower (Entry 12). Increasing the reaction temperature to 30 °C (Entry 13) appeared to have little effect, but increasing to 40 °C initially showed an interesting switch in diastereoselectivity (Entry 14). Similarly, a

switch in diastereoselectivity was seen at 60 °C (Entry 16) but analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture showed an unclean reaction mixture that was more difficult to purify. However, it turned out that these results at a higher temperature were not reproducible as the repeated reactions (Entries 15 and 17) showed only a slight decrease in diastereoselectivity compared to the results at rt. As described later, it was found that introduction of acidic conditions can have a great effect on the diastereomeric ratio observed so it was considered that these initial observations may be due to acidic contamination. Ultimately, it was determined that the optimum conditions to use for further investigations were THF at rt for 16 h.



Entry	Solvent	Temp (°C)	Time (h)	Scale (mmol imine)	Ratio of *syn*-214:*anti*-214	Yield (%)
1	$CHCl_3$	20	16	1.60	6:1	95
2	THF	20	16	0.38	9:1	82
3	Toluene	20	16	0.38	7:1	79
4	CH_2Cl_2	20	16	0.38	7.5:1	91
5	CH_3CN	20	16	0.38	5.5:1	61
6	2-MeTHF	20	16	0.38	7.8:1	74
7	TBME	20	16	0.38	1:1.1	51[a]
8	TBME	20	16	0.38	1.5:1	42[a]
9	Et_2O	20	16	0.38	1:1.4	40[a]
10	**THF**	**20**	**16**	**1.52**	**10.8:1**	**92**
11	THF	20	1	0.38	10:1	86
12	THF	0	3	0.38	10.3:1	44
13	THF	30	16	0.38	9.7:1	88
14	THF	40	16	0.38	1:1.5[b]	83
15	THF	40	16	0.38	8.5:1	91
16	THF	60	16	0.38	1:1.1[b]	49[a]
17	THF	60	16	0.38	7:1	82

[a.] Estimated yield of desired product; ^{1}H NMR spectra shows contamination by minor impuritities.

[b.] Observed ratios likely due to acidic contamination of the reaction mixture.

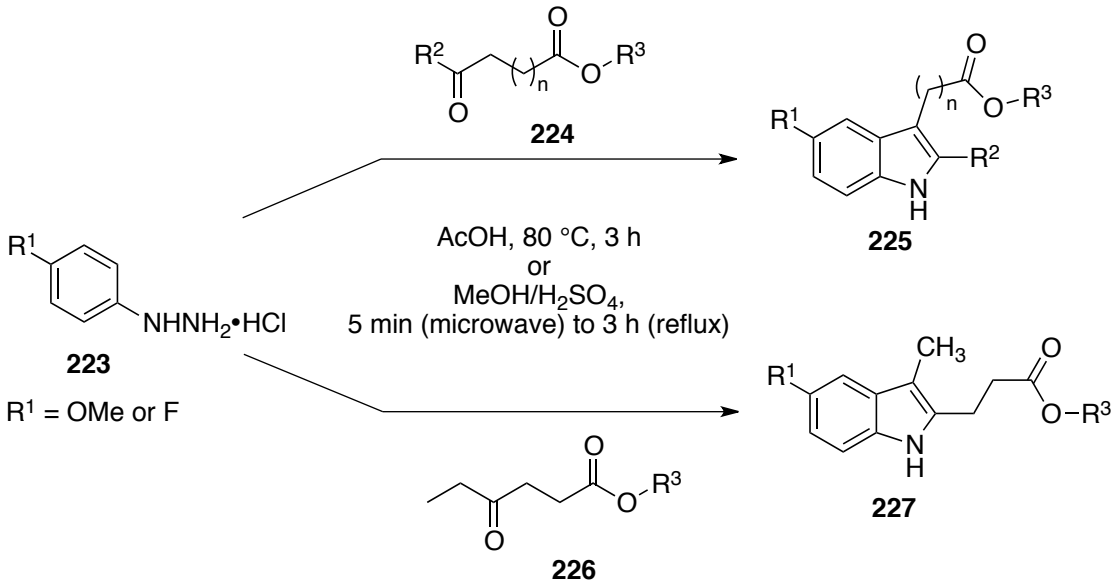
Table 3.1 – Solvent and temperature screen for the DIA spirocyclisation reaction

3.3.3. Broadening the Substrate Scope of the Spirocyclisation Reaction

A strategy for investigation into the substrate scope for the reaction was then envisaged. As discussed in the project outline (Figure 3.4), the indole acid substrate would be varied by substitution around the aromatic ring and in the 2-position. Additionally, the scope of the imine would be explored, as well as the size of the spirocyclic ring formed.

3.3.3.1 Fischer Indole Synthesis of 2-Methyl Substituted Indoles

The first point of diversity to be explored was substitution around the indole ring, keeping the 2-position substituent consistent as a methyl group. The required indole acids were unavailable commercially but could be synthesised using Fischer indole methodology. The Fischer indole reaction between arylhydrazones and ketones or aldehydes, in the presence of an acid catalyst, can be used to synthesise indole products.[121] One of the main features of the Fischer indole synthesis is the possible formation of two 2,3-disubstituted regioisomers when unsymmetrical ketones are used (Scheme 3.18).

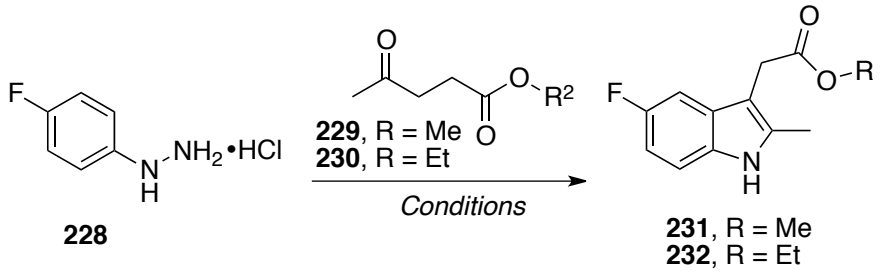


Scheme 3.18 – Formation of regioisomers in the Fischer indole reaction

The regioselectivity is generally dependent on the acidity of the medium, substitution of the hydrazine and steric effects in the ene-hydrazine intermediate formed.[122] In this project, initial investigations on the spirocycle synthesis require a methyl group in the 2-

position, with the acid functionality on the 3-position of the indole. Therefore, it was important that the chosen synthesis afforded the correct regioisomer. A literature procedure for the synthesis of a 5-fluoro indole ester **225** discussed the effect on the regioselectivity of using different ketone substrates. Liedtke *et al.* observed that when phenylhydrazine **223** was reacted under acidic conditions with substrate **224** (where R^2 = H or CH_3), the alkyl acid functionality was solely directed to the 3-position of the indole product **225**.[123] If substrate **226** was used under the same conditions (with an ethoxycarbonyl tail end), the alkyl acid was typically directed to the 2-position of the indole product **227** (Scheme 3.18). It was noted that elongation of the alkyl chain inbetween the two functional groups in substrate **224** was tolerated and did not affect regioselectivity, which would be useful for this project in varying the size of the spirocyclic ring formed. However, if the alkyl chain was extended in substrate **226** or the alkyl chain on the tail end was extended then different C^2/C^3 regioisomeric mixtures were obtained.

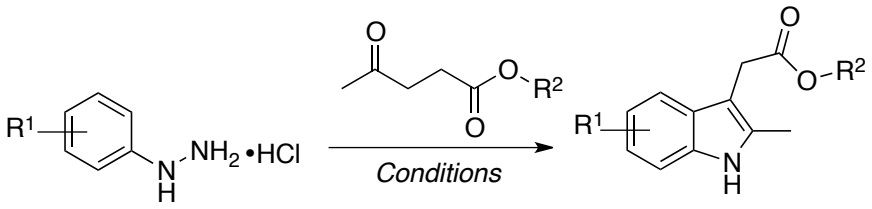
Due to this literature background, the synthesis of the 5-fluoro-substituted indole **231** was initially investigated and the results are shown in Table 3.2. The fluoro-phenylhydrazine hydrochloride salt **228** was used in the reaction as the free base form of these hydrazine-type starting materials are not very stable,[122] and the HCl salt is commercially available. Initially, synthesis of indole ester **231** was attempted by refluxing hydrazine **228** and ketone **229** in $MeOH/H_2SO_4$.[123] Purification by column chromatography provided a 3% yield of the pure substituted indole **231** (Entry 1) due to coelution of the rest with the remaining hydrazine intermediate. The Fischer indole reaction between fluorophenylhydrazine **228** and methyl 4-oxopentanoate **229** was significantly improved by microwave irradiation (MW) at 90 °C and the product was isolated in 87% yield (Entry 2).[123] Remaining methyl ester **229** was observed in the ^1H NMR spectrum of the unpurified reaction mixture; attempts to eliminate this by using an excess of the hydrazine **228** were unsuccessful so careful purification by column chromatography was required. Alternative reaction conditions were attempted in order to carry out this indole synthesis on a larger scale. Use of HCl in EtOH under reflux conditions provided the product **232** in 21% yield (Entry 3).[124]



Entry	Conditions	R group	Yield (%)
1	MeOH/H_2SO_4, reflux, 16 h	Me	3
2	MeOH/H_2SO_4, MW, 10 min, 120 °C	Me	87
3	2 M HCl/EtOH, reflux, 4.5 h	Et	21

Table 3.2 – Fischer Indole synthesis of 5-fluoro indole acetic ester 231 and 232

Following the successful synthesis of a 5-fluoro substituted indole ester **231**, the synthesis of other substituted indole substrates was focussed on. It was found that one set of Fischer indole conditions was not suitable for all the indole substrates, so a selection of conditions was used. This is due to the various substitution positions and groups that can affect the efficiency of the [3,3]-sigmatropic rearrangement reaction due to steric and electronic effects.[122] The conditions shown in Table 3.2 were attempted on other substrates, as well as refluxing in EtOH/H_2SO_4,[125] or initial formation of the hydrazone intermediate with acetic acid.[126,127] The best conditions for the synthesis of each indole ester substrate are shown in Table 3.3 and Table 3.4. The conditions in Table 3.4 use the γ- or δ-keto-acid starting material, which undergoes an *in situ* esterification to form the ester product.



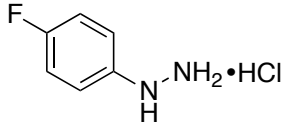
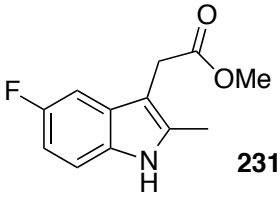
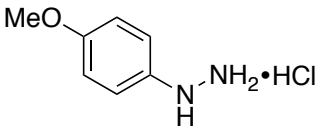
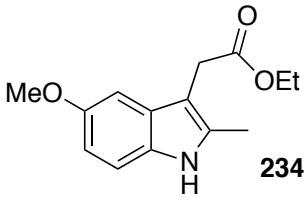
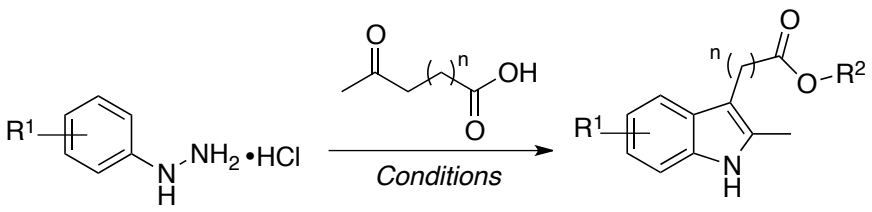
Hydrazine starting material	Reaction Conditions	Product	Yield (%)
 **228**	**R²** = Me $MeOH/H_2SO_4$, MW, 90 °C, 20 min	 **231**	87
 **233**	**R²** = Et 2M HCl/EtOH, reflux, 4-20 h	 **234**	57

Table 3.3 – Summary of Fischer Indole syntheses of indole ester substrates



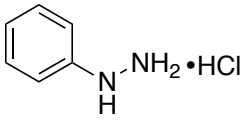
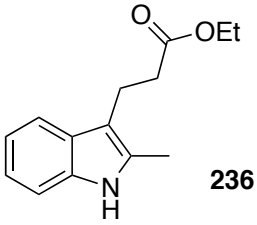
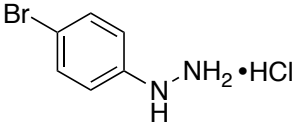
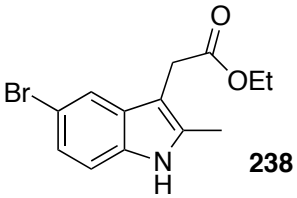
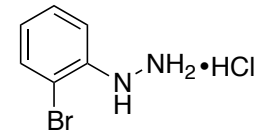
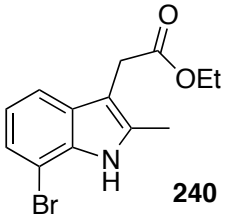
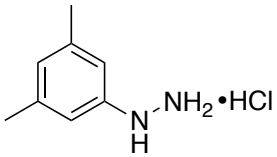
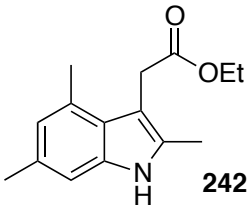
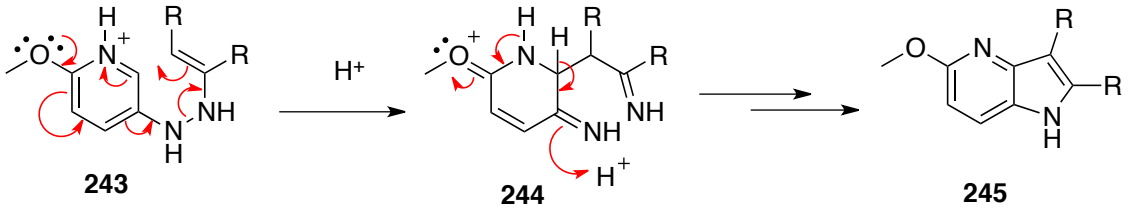
Hydrazine starting material	Reaction Conditions	Product	Yield (%)
 **235**	**n** = 2 2M HCl/EtOH, reflux, 4.5 h	 **236**	59
 **237**	**n** = 1 EtOH/H_2SO_4, reflux, 16-24 h	 **238**	63
 **239**		 **240**	42
 **241**		 **242**	72

Table 3.4 – Summary of Fischer Indole syntheses of indole ester substrates

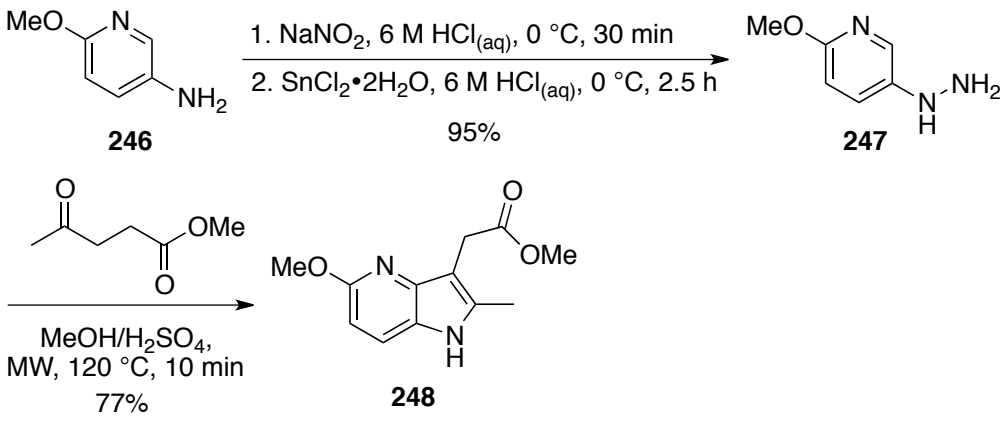
Azaindoles are very common structures in biologically active compounds and are important in medicinal chemistry so an azaindole substrate example was highly desired as part of our methodology.[85,128] Many classical indole syntheses have been used to synthesise azaindoles, such as the Reissert synthesis,[129,130] the Bartoli synthesis,[131] and the Larock synthesis[132] amongst others, with the various methods more suited to certain substitution patterns around the indole ring. The most well-known Fischer indole synthesis has rarely been applied to azaindole chemistry due to the unfavourable

electron withdrawing properties of the nitrogen which can affect the [3,3]-sigmatropic rearrangement step of the cyclisation.[128] Utilising the fact that Fischer indole cyclisations are more efficient when involving arylhydrazines with electron-donating groups,[35] Suzenet *et al*. were able to develop a synthesis of 4- and 6-azaindoles *via* the Fischer indole reaction.[128,133] Inclusion of a methoxy group in the *para*-position to the hydrazine function was shown to be essential for successful indole formation.[128] The postulated mechanism for the reaction included cleavage of the N-N bond in intermediate **243** assisted by the mesomeric effect of the methoxy group (Scheme 3.19). It should also be noted that the absence of symmetry in the hydrazine starting material could lead to the formation of two possible isomers but the suggested mechanism makes formation of the other regioisomer less likely.[128]



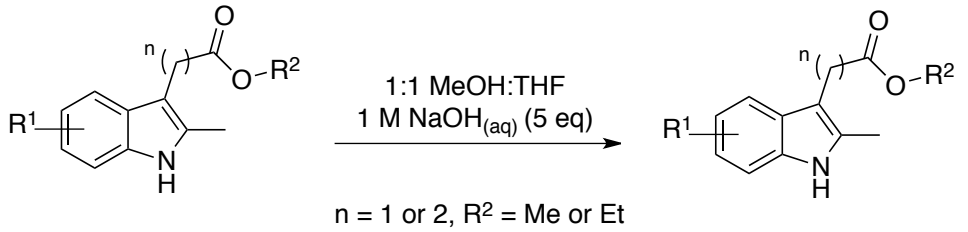
Scheme 3.19 – Fischer Indole mechanism for the synthesis of azaindoles

Synthesis of indole **248** was initially attempted using the literature conditions,[128] although the desired product **248** was not in the precedented substrate scope. First, the hydrazine **247** was synthesised from the amine **246** using the literature procedure.[128] Reaction of hydrazine **247** with levulinic acid in 4 wt% $H_2SO_{4(aq)}$ at 100 °C for 4 h resulted in an unclean reaction mixture which had no obvious product peaks by ^{1}H NMR spectroscopy. Reaction in 2 M HCl/EtOH at reflux, previously used successfully for other substrates, also resulted in a messy crude reaction mixture that was not purified. Pleasingly, indole **248** was successfully synthesised using the established microwave conditions and was isolated in 77% yield (Scheme 3.20).



Scheme 3.20 – Synthesis of azaindole ester *via* Fischer indole methodology

Hydrolysis of the indole ester substrates was then carried out to provide the required acid substrates. This could be achieved using the same conditions for all substrates and the results are shown in Table 3.5.



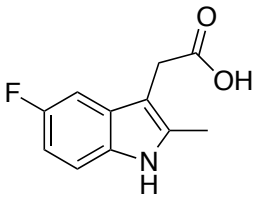
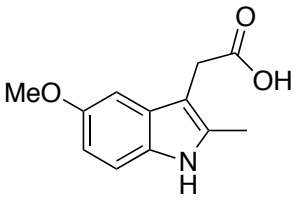
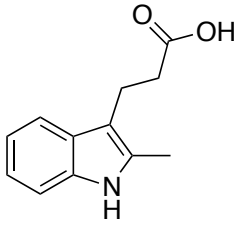
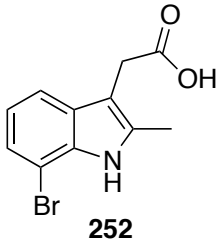
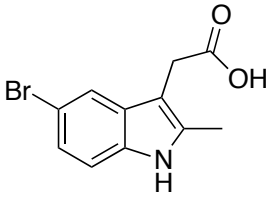
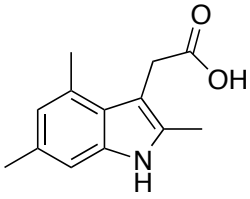
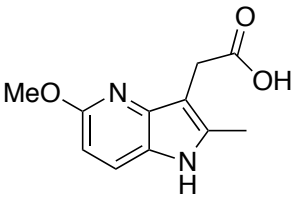
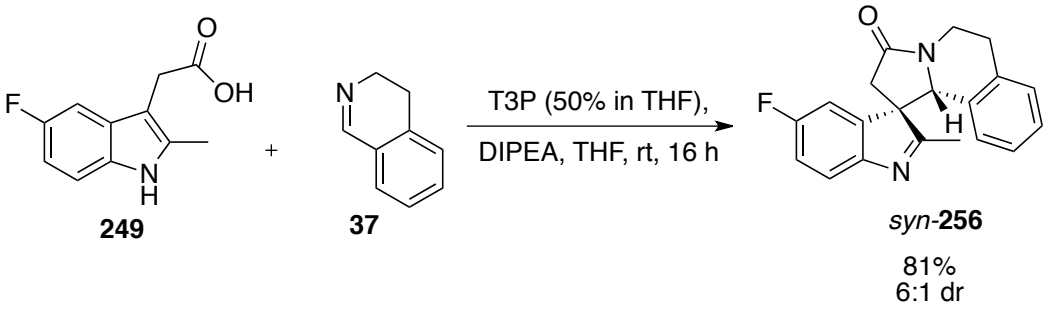
			
249 87%	**250** 96%	**251** 61%	**252** 86%
			
253 91%	**254** 79%	**255** 81%	

Table 3.5 - Hydrolysis conditions of indole esters to give indole acids

3.3.3.2 Reaction of 2-Methyl Indole Substrates in DIA Spirocyclisation and Assignment of Stereochemistry

The reaction of 5-fluoro substituted indole **249** and imine **37** was first attempted under the optimised conditions determined earlier (Table 3.1). The desired spirocyclic product **256** was formed in a 6:1 ratio of *syn*-**256**:*anti*-**256** diastereoisomers by ^{1}H NMR spectroscopy. The diastereomeric ratio obtained is lower than the 10:1 dr for the unsubstituted indole in THF at rt (see Table 3.1, Entry 10). The two diastereoisomers were separated by column chromatography and isolated with a combined yield of 81%.



Scheme 3.21 – DIA spirocyclisation reaction of 5-fluoro indole acid 256

Following this promising result, the remaining indole acid substrates **250**, **251**, **252**, **253**, **254** and **255** were reacted under the same conditions to give a range of spirocyclic products in good diastereoselectivity and 81-96% yield (Table 3.6). The major diastereoisomer formed in each reaction had *syn* relative stereochemistry. It each case, the diastereoselective ratio stated was determined by analysis of the unpurified reaction mixture using ^{1}H NMR spectroscopy. The isolated masses of the products can suggest an alternative ratio of *syn*:*anti* products, as seen in the Chapter 5.3.2. This could be due to equilibration of the diastereoisomers to the more thermodynamically stable product under the column conditions, which is an observed process under acidic conditions that will be discussed in section 3.3.8. Alternatively, the ratio of products could be affected during the selection of the column fractions, which is done to ensure the purity of the products.

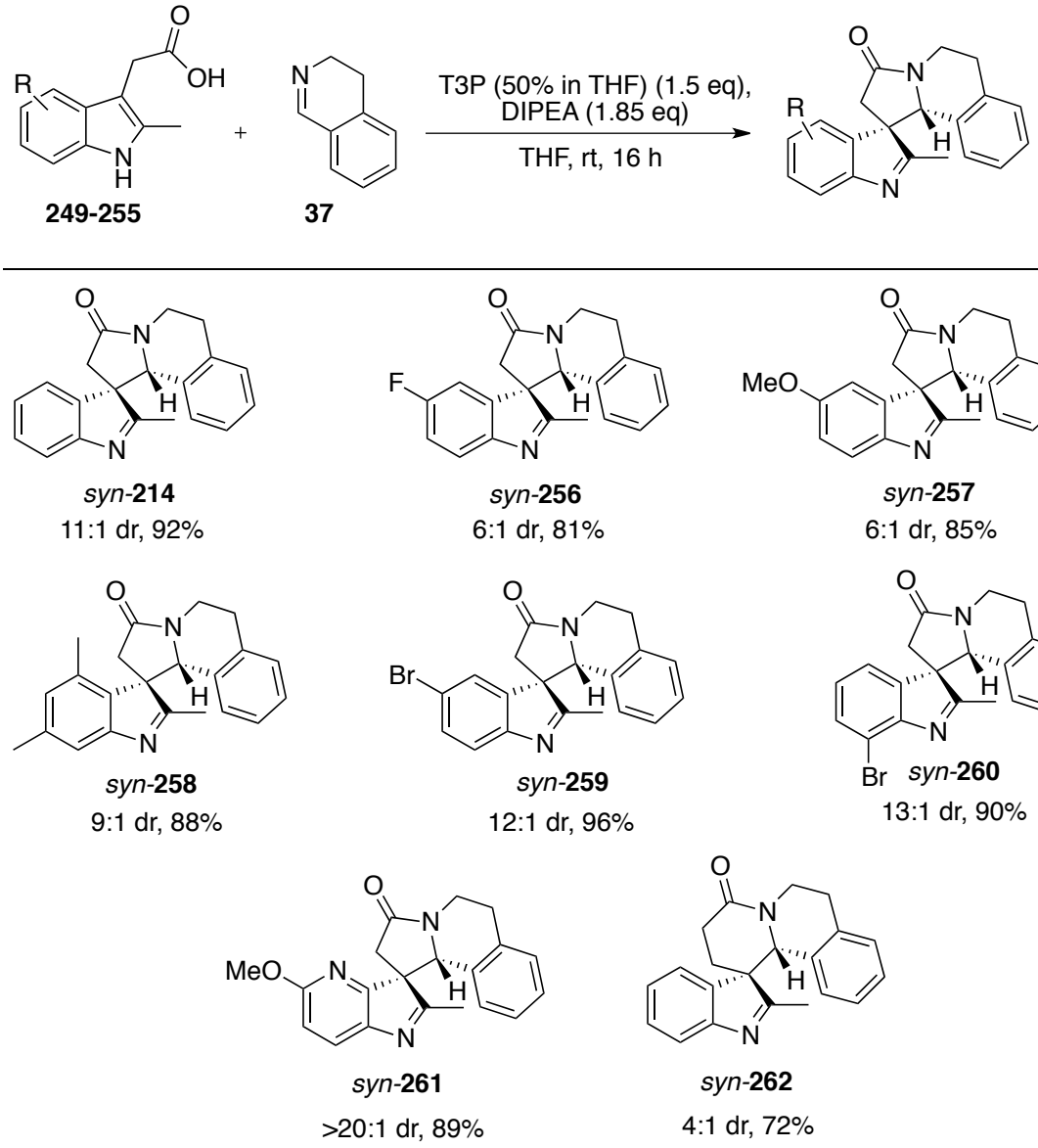


Table 3.6 – Spirocyclisation with 2-methyl 3-indole acetic acid derivatives

These results show that the spirocyclic reaction is not adversely affected by substitution on the indole scaffold of the product. Most of the diastereoisomers were separable or partially separable by column chromatography, and this allowed complete characterisation of both products. Throughout the process, diagnostic peaks were observed in the ^{1}H NMR spectra of the products and allowed the stereochemistry of the products to be assigned with some confidence, without the need for an X-ray crystal structure of each major isomer. The X-ray crystal structure of spirocyclic indolenine *syn*-**214** (Figure 3.7) was used to determine the stereochemistry of the related compounds shown in Table 3.6. The protons that gave diagnostic signals in the ^{1}H NMR spectra are shown in Figure 3.7. The aromatic proton (shown in red) was identified

unequivocally using HMBC analysis to confirm which aromatic proton was giving the diagnostic signal. The methyl group (shown in green) appears as a singlet, which is deshielded possibly due to anisotropic effects resulting from the neighbouring imine. The NCH proton (shown in blue) also appears as a singlet and shows diastereomeric character.

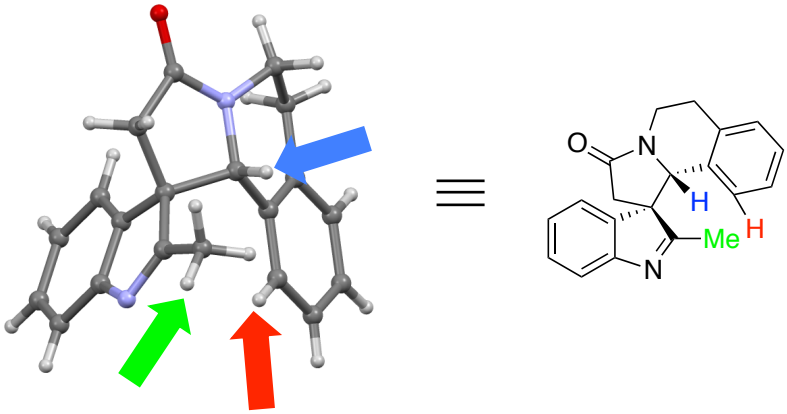


Figure 3.7 – X-ray crystal structure of spirocyclic indolenine 214

The diastereomeric ratios of the products were assigned from the ^{1}H NMR spectrum of the crude mixture using the signal corresponding to an aromatic proton shown in Figure 3.8. The ^{1}H NMR spectra of the major diastereoisomer *syn*-**214** and the minor diastereoisomer *anti*-**214** are shown in Figure 3.9 and Figure 3.10 respectively and the diagnostic signals from the aromatic and methyl signals can be observed.

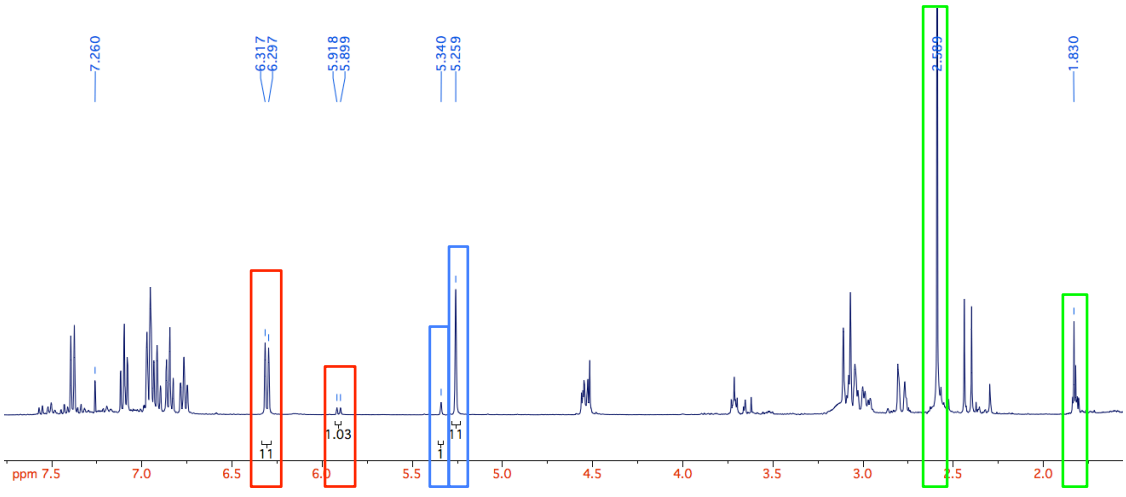


Figure 3.8 – ^{1}H NMR spectrum for crude mixture of spiroindolenine product *syn*-214 and *anti*-214

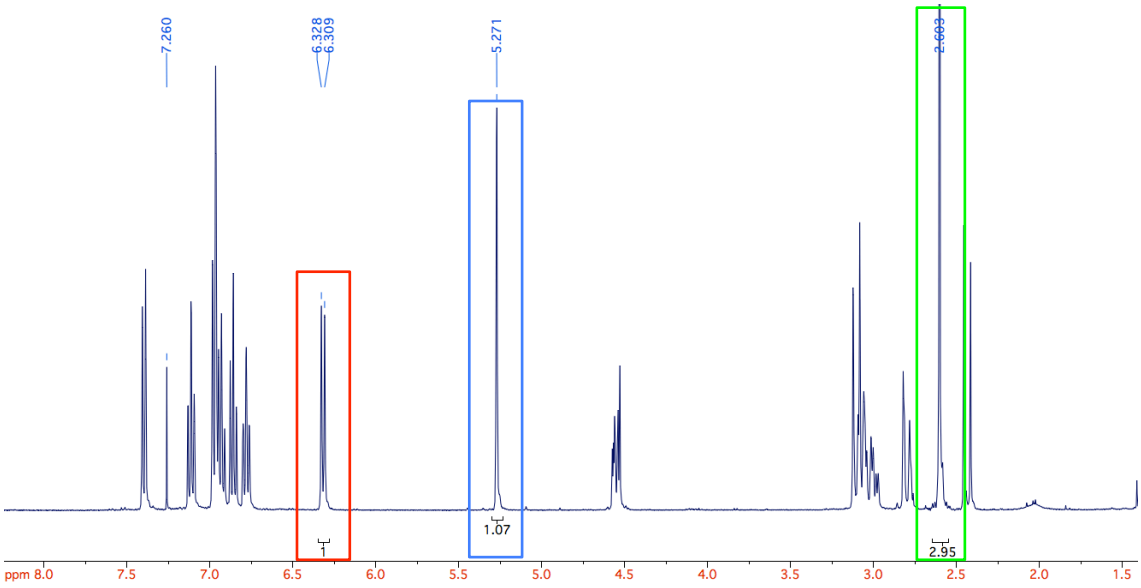


Figure 3.9 – ^{1}H NMR spectrum for the major spiroindolenine product *syn*-214

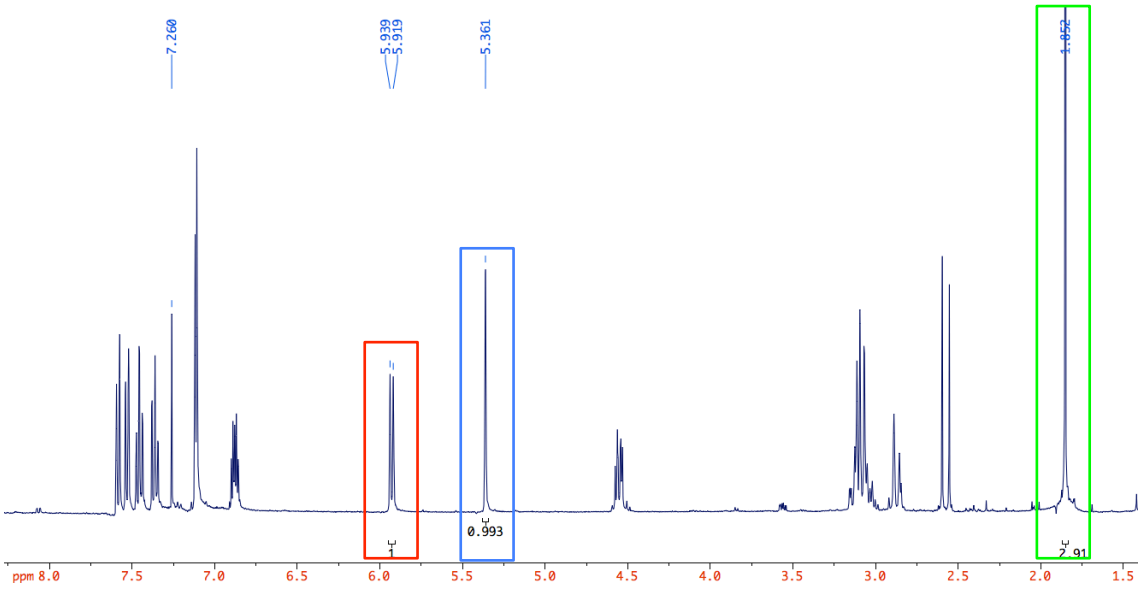


Figure 3.10 - ^{1}H NMR spectrum for the minor spiroindolenine product *anti*-214

The ^{1}H NMR spectra of the other compounds in Table 3.6 showed signals for the corresponding peaks at very similar chemical shift values to the values observed for *syn*-**214** and *anti*-**214**. The ^{1}H NMR spectra of the major *syn* diastereoisomers contain an aromatic proton signal between 6.54-6.32 ppm and/or a methyl signal between 2.65-2.54 ppm. The corresponding signals in the minor *anti* diastereoisomers appear at 5.99-5.81 ppm for the aromatic signal and 1.97-1.66 ppm for the methyl group. The signal for the NCH protons at the reaction centre also show some diastereomeric character, but the

ppm range for the major and minor diastereoisomer was much wider and less consistent so these were not used diagnostically to determine the stereochemistry (although these signals proved useful for determination of the diastereomeric ratio). The reason for the difference in ppm can be attributed to the anisotropic effects of the surrounding aromatic groups relative to the methyl group and aromatic proton. From the X-ray crystal structure of spiroindolenine **214** (Figure 3.7), it can be seen that the aromatic proton is very close in proximity to the indole aromatic ring, and the methyl group is mostly unaffected by the surrounding groups. The structure of *syn*-**214** and *anti*-**214** is depicted in Figure 3.11, highlighting the position of the diagnostic aromatic and methyl groups relative to the rest of the molecule.

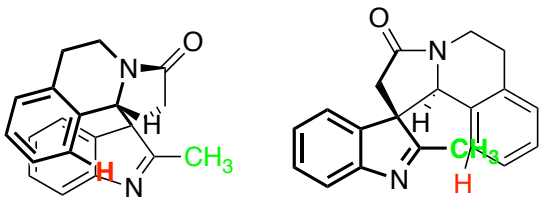


Figure 3.11 – Structure of *syn*-214 and *anti*-214 highlighting the position of the diagnostic aromatic and methyl protons

From Figure 3.11, it can be seen that in *syn*-**214** the methyl group is not in close proximity to other groups in the molecule so a chemical shift of 2.65-2.54 ppm is observed and is expected for a methyl group next to an imine functionality. However, in *anti*-**214** the methyl group is situated above the aromatic ring of the imine component and will be affected by the anisotropic effects of this group. As a result, the signal for the methyl group in *anti*-**214** is observed between 1.97-1.66 ppm due to the increased electron shielding from the delocalised ring of electrons in the aromatic π-system. The aromatic proton signal is observed between 5.99-5.81 ppm in *anti*-**214**, which is very shielded for an aromatic proton and can be attributed to the assumed proximity to the methyl group. In *syn*-**214**, the aromatic proton is a lot more deshielded than in *anti*-**214** by proximity to the electron-withdrawing nitrogen on the indole aromatic ring. These diagnostic signals proved to be a very useful tool in the characterisation of the two diastereoisomers. In addition, an X-ray crystal structure of the bromo-substituted spirocyclic product *syn*-**259** was also obtained to confirm that the ^{1}H NMR spectroscopy diagnostic signals were consistent for the same diastereoisomer (Figure 3.12).

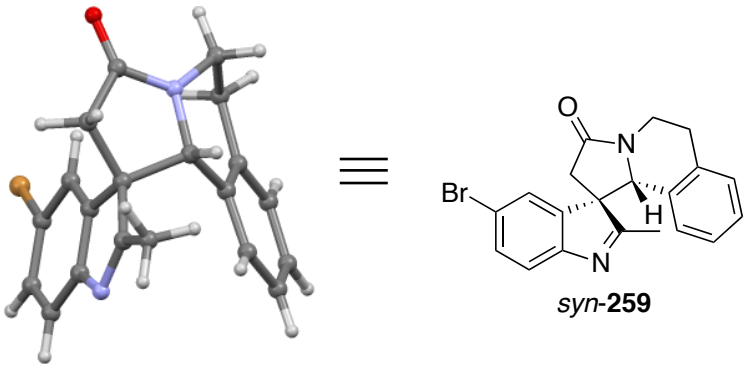
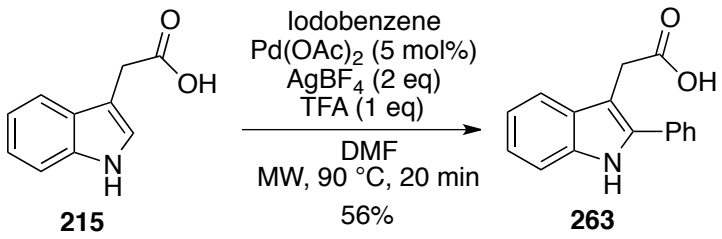


Figure 3.12 – X-ray crystal structure of *syn*-259 (CCDC: 1436468)

3.3.4. DIA Spirocyclisation with Variation in the 2-Position of the Indole

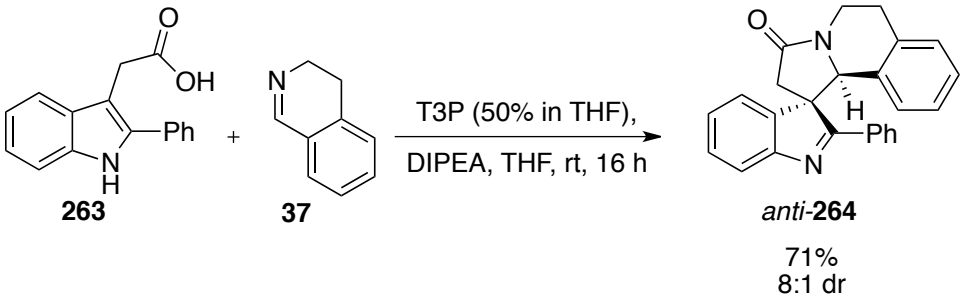
Following the successful reaction of 3-indole acetic acid **212** and imine **37**, variation of the group in the 2-position was investigated to determine the effect on diastereoselectivty and yield. Initially, an indole acid substrate containing a phenyl group in the 2-position was pursued. Lavilla *et al.* had previously developed an efficient C2 arylation of tryptophan carboxylic acids and had also demonstrated the transformation on indole carboxylic acids.[134] The literature conditions were therefore repeated on 3-indole acetic acid **215** to give 2-phenyl indole acid **263** in 56% yield (Scheme 3.22).



Scheme 3.22 – C-H arylation of 3-indole acetic acid 263

2-Phenyl-substituted indole **263** was then reacted in the subsequent DIA spirocyclisation reaction with imine **37** under the optimised conditions (Scheme 3.23) to give the spirocyclic product **264** in a 71% combined yield and 8:1 dr (by integration of the NCH proton signals in the ^{1}H NMR spectrum unpurified reaction mixtures). Analysis of the ^{1}H NMR spectrum of the crude mixture suggested that the diastereoselectivity of the

reaction was opposite to that observed with the 2-methyl substrates. This was based on the observation of an aromatic peak at 5.96 ppm for the major product and at 6.22 ppm for the minor product (see Figure 3.13); for the 2-methyl products the aromatic proton signal at the more downfield position is the major diastereoisomer. An X-ray crystal structure of the major diastereoisomer was thus obtained, confirming this switch in stereoselectivity (Figure 3.14).



Scheme 3.23 – DIA spirocyclisation reaction of 2-phenyl indole acid 263

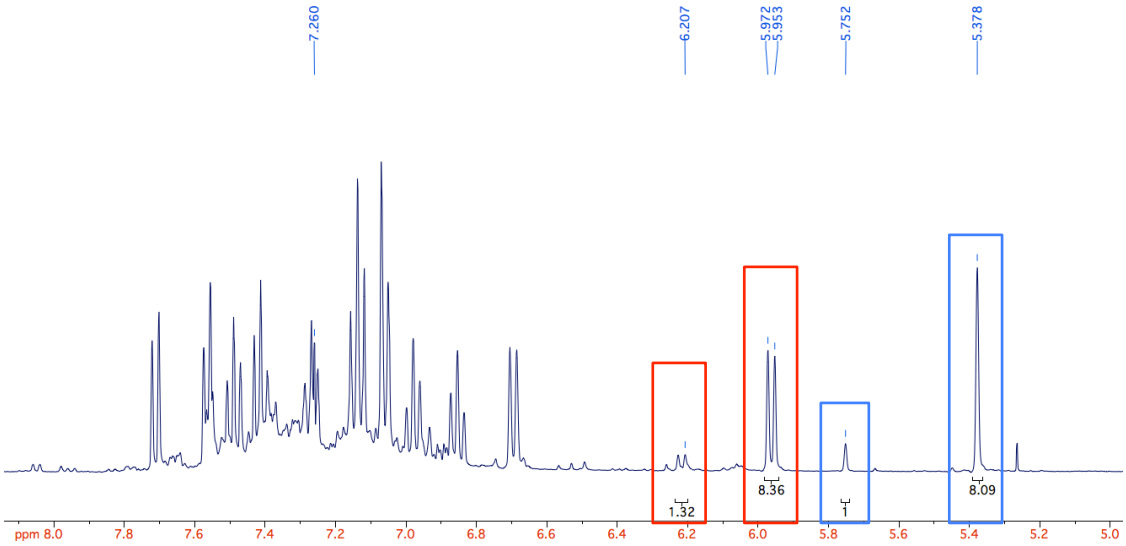


Figure 3.13 – ^{1}H NMR spectrum of the unpurified reaction mixture of spiroindolenine 264

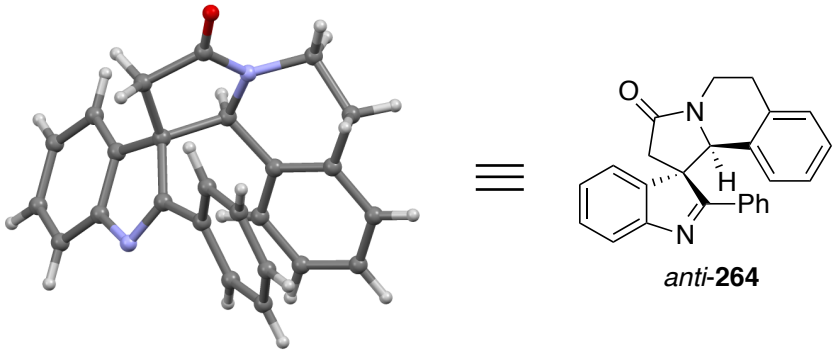


Figure 3.14 – X-ray crystal structure of *anti*-264 (CCDC: 1436405)

As discussed earlier (see Section 3.3.1), the facial selectivity of the nucleophilic attack of the indole onto the *N*-acyliminium ion establishes the diastereoselectivity of the reaction. The reactive conformation of the *N*-acylimiminium ion intermediate appears to be affected by the presence of either a methyl group or phenyl group in the 2-position. Figure 3.15 and Figure 3.16 show the 2 possible conformers of the 2-methyl *N*-acyliminium ion **265** and 2-phenyl *N*-acyliminium ion **266** respectively and how these relate to the major and minor diastereomeric products of **214** and **264**. As previously mentioned, it was thought that when there is a methyl group in the 2-position, the aromatic rings of the indole and imine can form a π-π stabilising interaction and upon formation of the spirocycle the major product *syn*-**214** is obtained (Figure 3.15). However, if there is a phenyl group in the 2-position then an alternative stronger π-π stabilising interaction between the 2-phenyl group and the aromatic ring of the imine is possible, which leads to the formation of the major diastereoisomer *anti*-**264**. In comparison to this stronger interaction, the possible π-π interaction between the aromatic rings of the indole and imine components is now less stabilising than the interaction in *N*-acyliminium ion **265** and *syn*-**264** is the minor product (Figure 3.16).

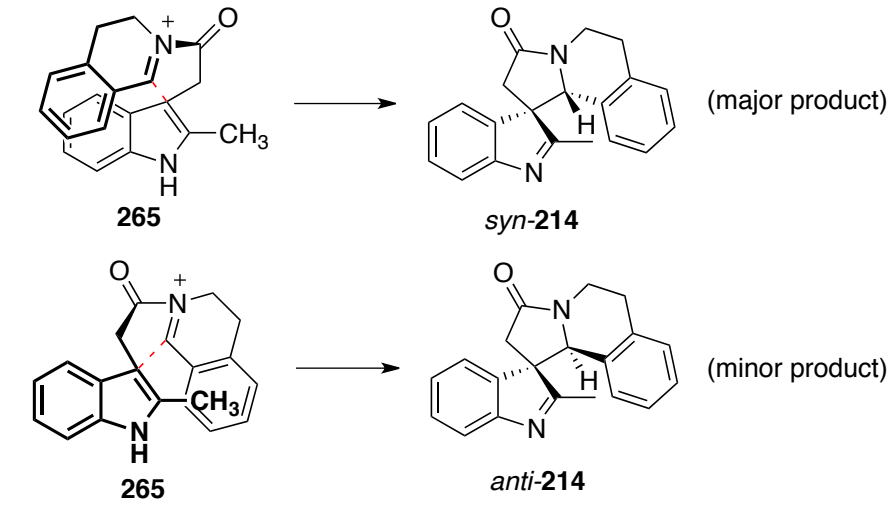


Figure 3.15 – Stereochemical model of the 2-methyl spirocyclisation reaction

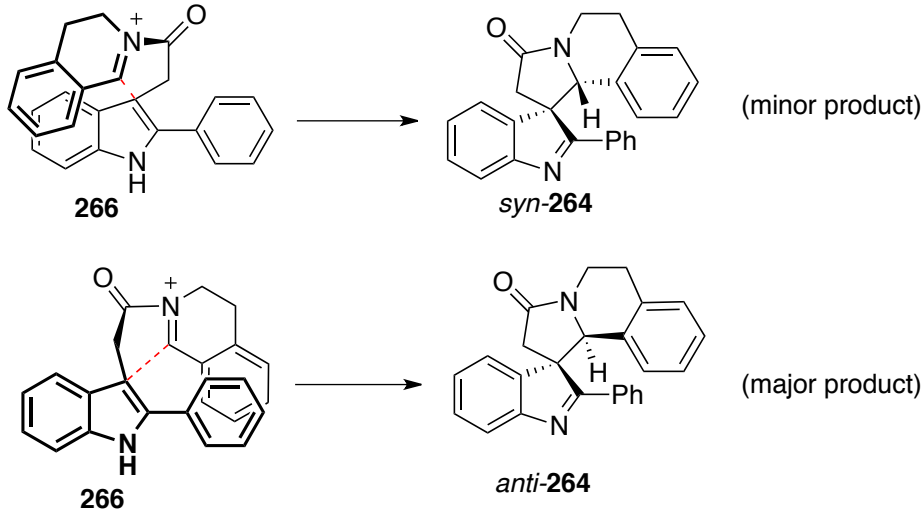
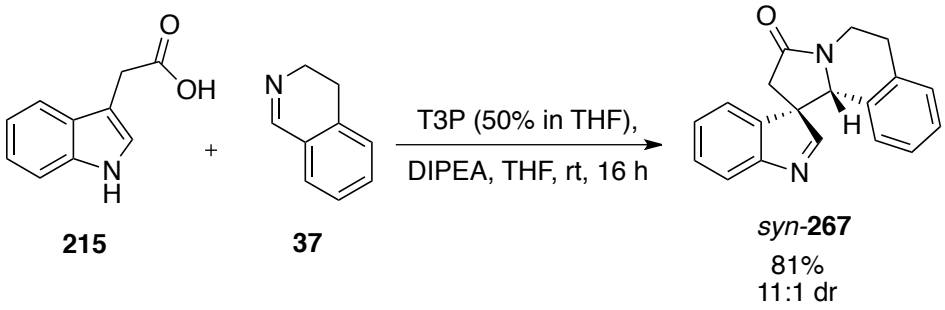


Figure 3.16 – Stereochemical model of the 2-phenyl spirocyclisation reaction

Variation of the group in the 2-position was targeted next to determine the effects of different groups on the diastereoselectivity and yield of the subsequent DIA spirocyclisation reaction. It was initially believed that having no group in the 2-position of the indole acid substrate would result in formation of a fused indole product, rather than a spirocycle.[107,135,136] However, upon subjecting 3-indole acetic acid **215** and imine **37** to the optimised reaction conditions for the DIA spirocyclisation, analysis of the ^{1}H NMR spectrum of the crude mixture revealed a good conversion to the spirocyclic product with an 11:1 dr of *syn*-**267**:*anti*-**267**. Upon column chromatography, the spirocyclic product was obtained in a combined yield of 81% (Scheme 3.24). An X-ray crystal structure of the major diastereoisomer, *syn*-**267**, was obtained to confirm the diastereoselectivity (Figure 3.17).



Scheme 3.24 – DIA spirocyclisation of 2-H indole acid 215 and imine 37

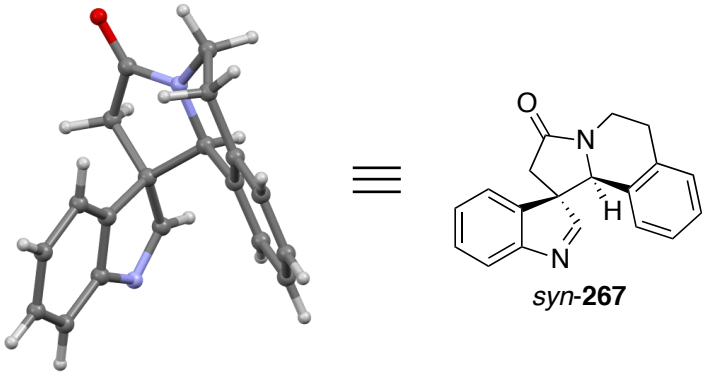
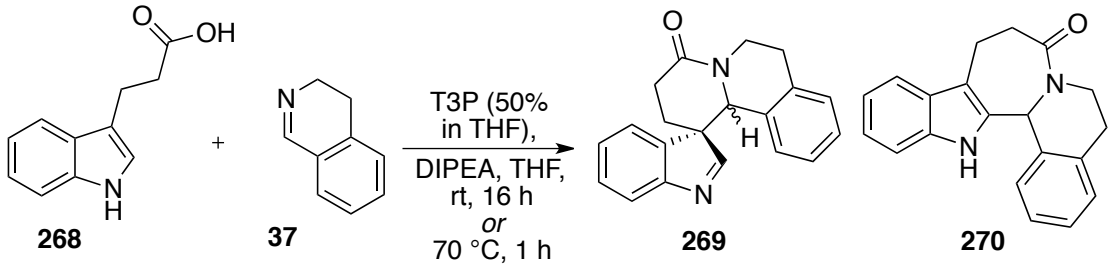


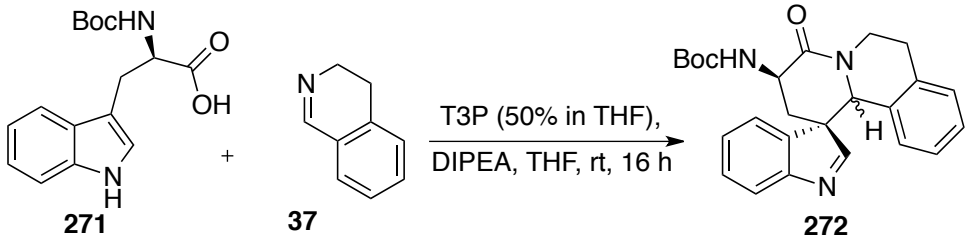
Figure 3.17 – X-ray crystal structure of *syn*-267 (CCDC: 1506360)

Following the successful synthesis of spiroindolenine **267**, synthesis of a 6-membered spirocycle with no substitution in the 2-position was attempted. Acid **268** and imine **37** were reacted under the optimised DIA conditions but the ^{1}H NMR spectrum of the unpurified reaction mixture appeared very broad making it challenging to determine the outcome of the reaction (Scheme 3.25). It was noted that the ^{1}H NMR spectrum lacked the distinctive signals between 4-5 ppm correlating to the NCH protons. However, mass spectrometry suggested that the product was present so purification by column chromatography was attempted, but the obtained fractions also did not show any clean product. It was thought that the lack of substitution on the 2-position of the resulting spiroindolenine **269** may lead to trimerisation in solution, as had previously been seen with analogous work within the Taylor group.[113] It was found that these trimers could be characterised by addition of TFA to break down the trimer to the monomer TFA salt. However, treatment of the reaction mixture with TFA appeared to show the presence of the rearranged product **270**, as seen in previous work in the Taylor group after addition of a Lewis acid (Scheme 3.25).[20] The reaction was not pursued as it had been anticipated that some of the 2-H spirocyclic targets could be a challenge due to potential migration and the presence of trimers.



Scheme 3.25 – DIA spirocyclisation reaction of 3-indole propanoic acid 268

The reaction of imine **37** and Boc-protected tryptophan **271** was also attempted under the optimised DIA conditions (Scheme 3.26). It should be noted that the inclusion of an additional chiral centre means that there are now four possible diastereomeric products, which could complicate the purification. Perhaps unsurprisingly, analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture showed a complex mixture of products by ^{1}H NMR spectroscopy but mass spectrometry showed an $[M + Na]^{+}$ peak for the product **272**. Upon thorough purification by column chromatography, many products were isolated but none looked clean by ^{1}H NMR spectroscopy. Suspecting the presence of trimers due to the lack of substitution on the 2-position, the most promising product sample was treated with TFA but this did not clarify the situation. It was suggested that Boc induced rotamers could have been present, further complicating the appearance of the ^{1}H NMR spectra. Therefore, it was decided that this product was not suitable and a potential tryptophan related product may need to contain a substituent in the 2-position with an alternative protecting group.



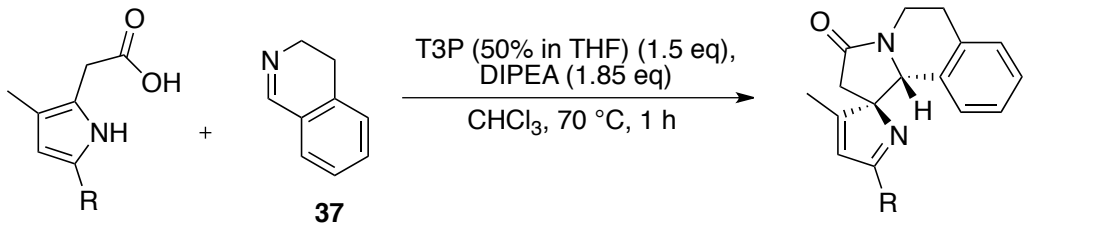
Scheme 3.26 – DIA spirocyclisation reaction of Boc-protected tryptophan 271

Complementary work on the DIA reaction of related tryptophan acid substrates containing an aromatic group at the 2-position of the indole with imine **37** has been successful, particularly when performed at higher temperatures.[*]

[*] Work carried out by MChem student, Jai Mistry.

3.3.5. Pyrrole-based Acid Substrates in the DIA Spirocyclisation Reaction

Pyrrole acetic acids were then investigated as potential substrates in the DIA spirocyclisation reaction. It has been shown that the dearomatisation of pyrroles *via* the 2-position is possible,[137-139] and another member of the Taylor group was able to demonstrate this using the DIA spirocyclisation methodology by reacting pyrroles **273** and **274** with indole **37** at 70 °C in $CHCl_3$ for 1 h to give spirocyclic products **275** and **276** in good yields (Scheme 3.27).* An elevated reaction temperature was necessary for the complete reaction of the pyrrole acid substrates. The phenyl substituted pyrrole spirocycle **276** was also crystalline so an X-ray crystal structure of the major diastereoisomer *syn*-**276** was obtained to determine the stereochemistry as pictured (Figure 3.18). These pyrrole examples showed the same stereoselectivity to the majority of indole substrates, where the nitrogen of the pyrrole is *syn* to the hydrogen of the NCH group.



Scheme 3.27 – DIA spirocyclisation of 2-pyrrole acetic acids 273 and 274*

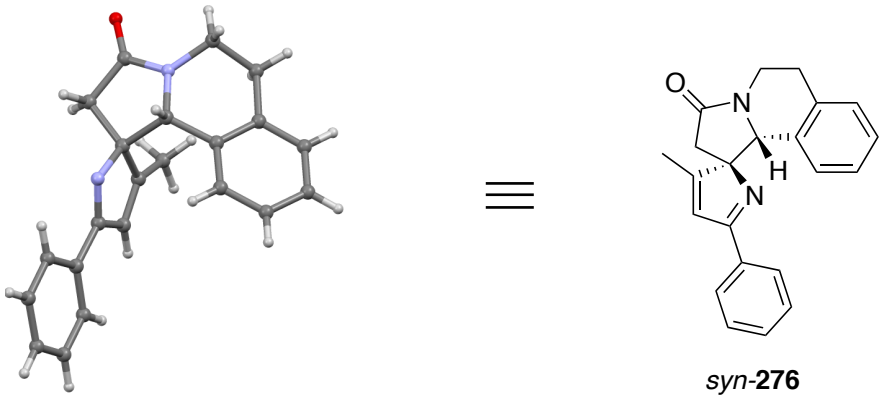
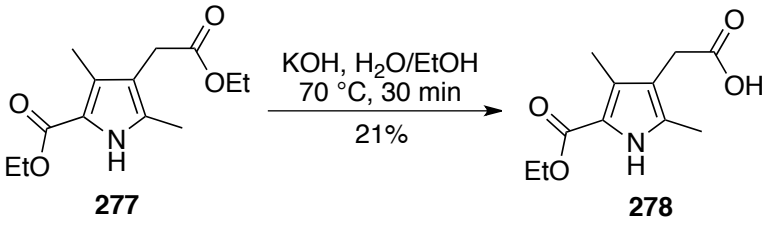


Figure 3.18 – X-ray crystal structure of *syn*-276 (CCDC: 1436465)*

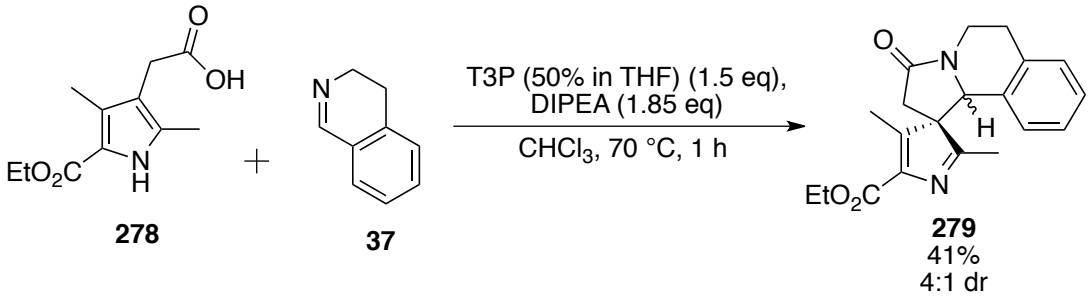
* Reaction carried out and X-ray crystal structure obtained by Dr. Graeme Coulthard in the Taylor group.

A more challenging pyrrole substrate **278** was then targeted for use in the DIA spirocyclisation reaction. Diester pyrrole **277** had been synthesised within the Taylor group using literature procedures.[140] Selective hydrolysis gave pyrrole acid **278** in a 21% yield (Scheme 3.28).



Scheme 3.28 – Selective hydrolysis of diester 277

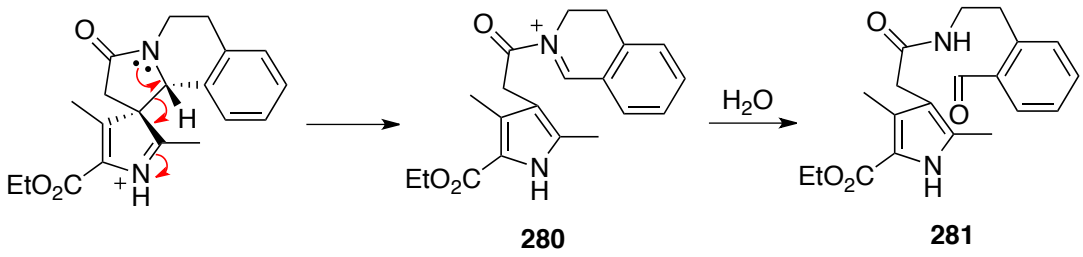
The pyrrole acid **278** was reacted with imine **37** in the DIA spirocyclisation using the same conditions as for the *2H*-pyrroles and the product **279** was obtained in a 41% yield (Scheme 3.29).* Unfortunately, product **279** was not crystalline so the relative stereochemistry could not be assigned.



Scheme 3.29 – DIA spirocyclisation of 3-pyrrole acetic acid 278

This example was particularly pleasing, as the synthesis of *3H*-pyrroles is a challenge due to their inherent instability.[141] Indeed, it was noted that during the process of obtaining NMR spectroscopic data for characterisation of **279** in $CDCl_3$, an aldehyde peak became present in the ^1H NMR spectra. This was thought to be due to the acidic $CDCl_3$ initiating a ring-opening process to give the *N*-acyliminium ion **280**, which could be hydrolysed to give aldehyde **281 (**Scheme 3.30).

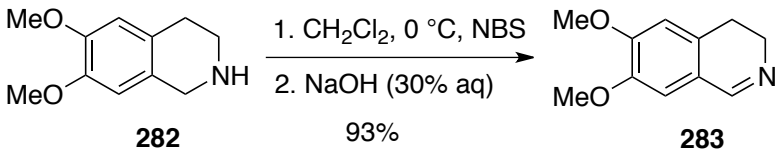
* Spiroindolenine **279** was obtained in 59% yield by Dr. Graeme Coulthard.



Scheme 3.30 – Possible ring-opening mechanism of *3H*-pyrrole spirocycle

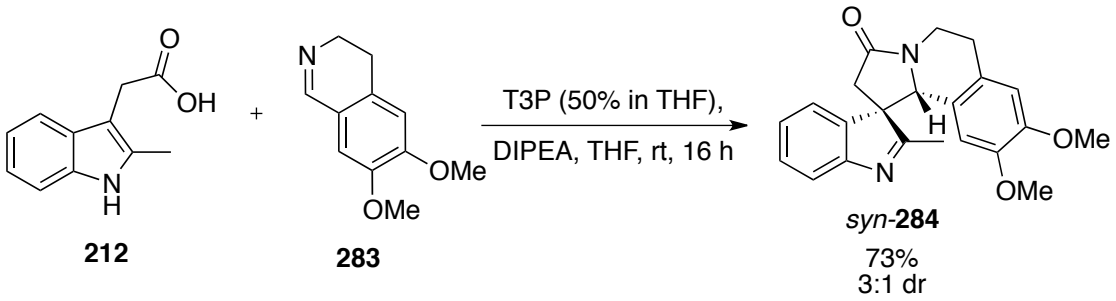
3.3.6. Preparation and Reaction of Different Imine Scaffolds in Spirocycle Synthesis

Having successfully broadened the substrate scope for the acid components in the spirocyclisation reaction, an investigation into the scope of the imine components was started. Use of the methoxy-substituted aromatic imine **283** was investigated first. 6,7-Dimethoxy-3,4-dihydroisoquinoline **283** was synthesised in 93% yield from the amine **282** using NBS oxidation (Scheme 3.31).[52]



Scheme 3.31 – Synthesis of methoxy-substituted aromatic imine 283

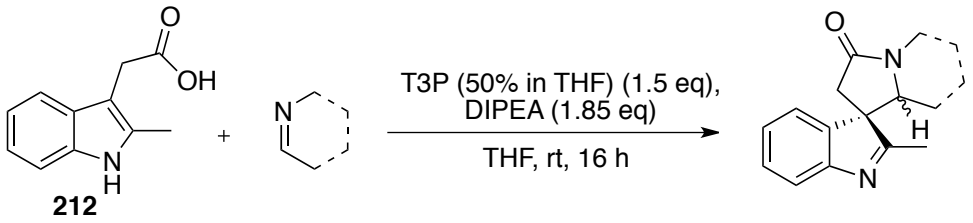
The DIA reaction of methoxy-substituted imine **283** and the unsubstituted indole acetic acid **212** successfully proceeded under the optimised conditions for spirocycle synthesis (Scheme 3.32). The product **284** was obtained as a 3:1 mixture of *syn*-**284**:*anti*-**284** by ^{1}H NMR spectroscopy and the diastereoisomers were partially separable by column chromatography. A combined yield of 73% indicated that variation of the imine scaffold was tolerated in the spirocycle synthesis. The diagnostic signals observed in the ^{1}H NMR spectra for the indolenine-methyl group confirmed that the major diastereoisomer was *syn*-**284** (singlet at 2.62 ppm for *syn*-**284** and 1.90 ppm for *anti*-**284**).



212 **283** *syn*-**284** 73% 3:1 dr

Scheme 3.32 – DIA spirocyclisation of methoxy-substituted aromatic imine 283

Other aromatic imine substrates were then reacted under the same conditions and the results are shown in Table 3.7. Tetra-substitution around the aromatic ring was shown not to hinder the reaction as spirocyclic product **285** was obtained in a 79% yield by performing the reaction at 70 °C in $CHCl_3$ for 1 h. Another member of the Taylor group was able to show that thiophene- and pyrrole-fused imines were also suitable substrates and obtained the spirocyclic products **286** and **287** in 81% and 75% respectively.*



212

285	**286***	**287***
79% [a]	81%	75%
9:1 dr	9:1 dr	5:1 dr

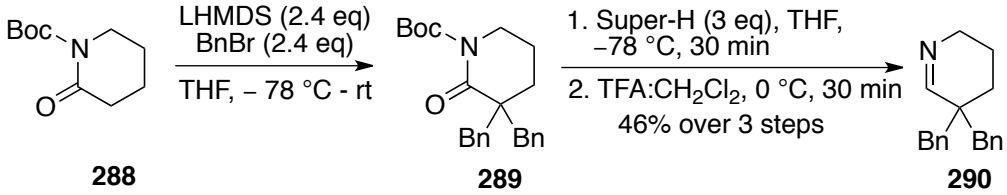
a) Reaction performed at 70 °C in $CHCl_3$ for 1 h.

Table 3.7 – DIA spirocyclisation reactions of various aromatic imines*

A dibenzylated imine **290** had previously been used as a model substrate in the development of DIA methodology to access a range of heterocycles.[21] It was hoped that this substrate would be tolerated in the DIA spirocyclisation reaction, despite the increased steric bulk of the dibenzyl groups. The imine **290** was synthesised by

* Thiophene- and pyrrole-fused imine examples carried out by Dr. Graeme Coulthard in the Taylor group.

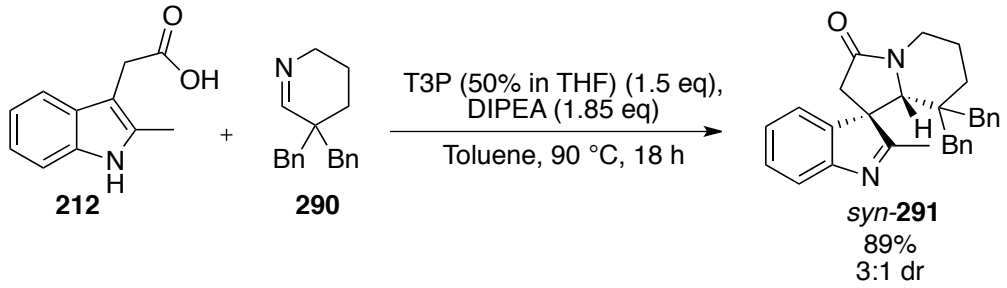
dialkylation of Boc-protected lactam **289** and subsequent reduction of the crude amide. The Boc group was then removed by addition of TFA which initiated *in situ* elimination of the hemiaminal to give the imine **289** in a 46% yield over 3 steps (Scheme 3.33).



288 **289** **290**

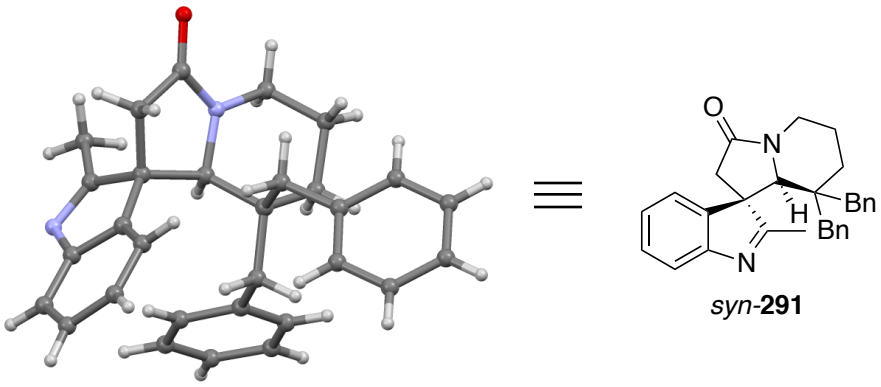
Scheme 3.33 – Synthesis of dibenzylated imine 290

Imine **290** had previously been reacted in other DIA reactions in toluene at 90 °C for 18 h,[21] and under these conditions the DIA spirocyclisation reaction proceeded to give product **291** in an 89% yield and 3:1 dr of *syn*-**291**:*anti*-**291**. An X-ray crystal structure was obtained for the major product and it was seen that the usual diastereoselectivity for the reaction of 2-methyl substituted indoles was observed, with the NCH proton and methyl group *syn* to each other (Figure 3.19).



212 **290** *syn*-**291**
89%
3:1 dr

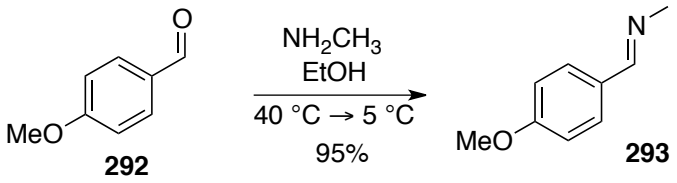
Scheme 3.34 – DIA spirocyclisation of dibenzylated imine 290



syn-**291**

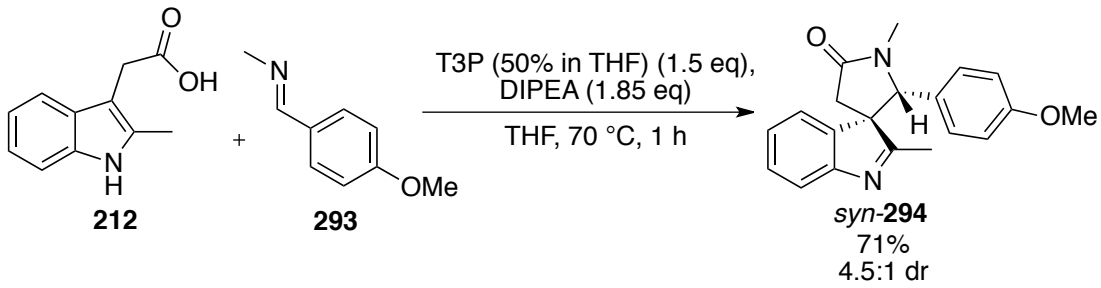
Figure 3.19 – X-ray crystal structure of *syn*-291 (CCDC: 1436396)

The next imine substrate of interest was an acyclic imine **293**. Acyclic imines are usually avoided in *N*-acyliminium chemistry because of their tendency to hydrolyse.[142] Imine **293** was synthesised following a literature procedure for the condensation of paramethoxybenzaldehyde **292** and methylamine to give the product in 95% with no further purification needed (Scheme 3.35).[143]



Scheme 3.35 – Synthesis of acylic imine 293

Subjecting this imine **293** and indole **212** to a range of DIA reaction conditions, varying the temperature and reaction time, showed that the optimum reaction conditions were in THF at 70 °C for 1 h. Using these conditions, the spirocyclic product **294** was isolated in a 71% yield with a 4.5:1 mixture of *syn*-**294**:*anti*-**294** diastereoisomers by ^{1}H NMR spectroscopy (Scheme 3.36). An amide byproduct resulting from hydrolysis of the intermediate *N*-acyliminium ion was also observed (but not isolated cleanly), indicating the increased tendency for acyclic *N*-acyliminium ions to undergo hydrolysis but pleasingly this was not the major product under the conditions used.



Scheme 3.36 – DIA spirocyclisation of acylic imine 293 and indole acetic acid 212

An X-ray crystal structure of the major diastereoisomer was also obtained to confirm the stereochemistry. It was observed that the diastereoisomer was *syn*-**294** but it can be seen from the X-ray structure that the untethered imine creates a distorted shape when compared to the cyclic imine examples (Figure 3.20).

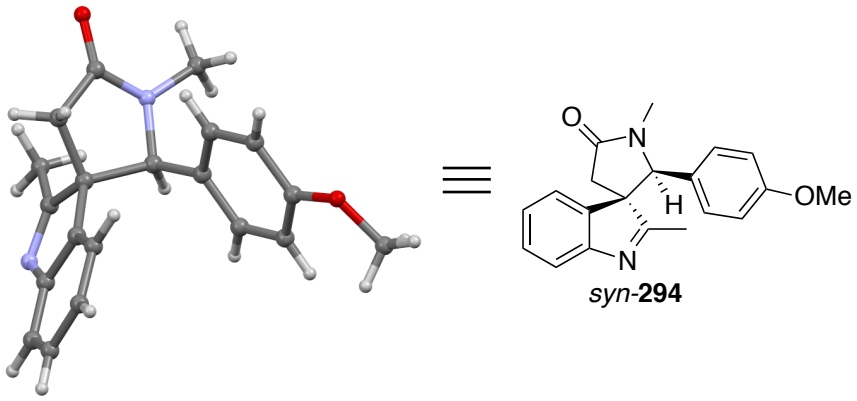
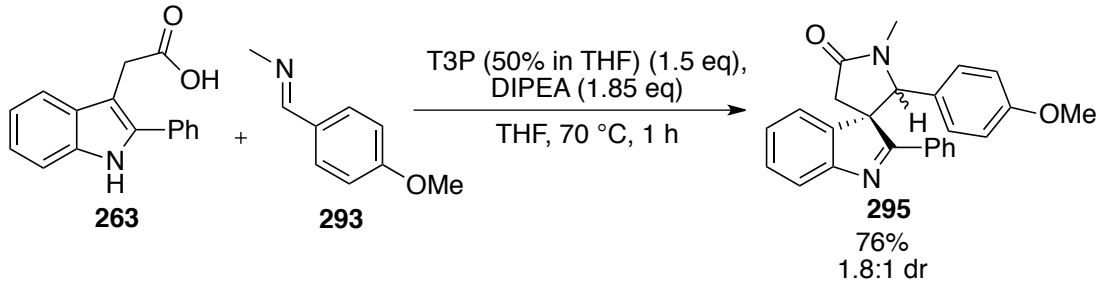


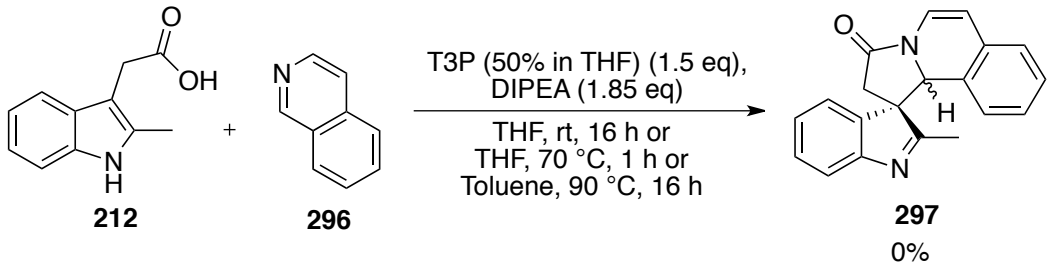
Figure 3.20 – X-ray crystal structure of *syn*-294 (CCDC: 1436400)

Imine **293** was also successfully used in the DIA reaction with 2-phenyl indole **263** to give the spirocyclic product **295** in a 76% yield and 1.8:1 dr, with unassigned stereochemistry (Scheme 3.37). Unfortunately, the diastereoisomers were not separable following column chromatography.



Scheme 3.37 – DIA spirocyclisation of 2-phenyl indole acid 263 and imine 193

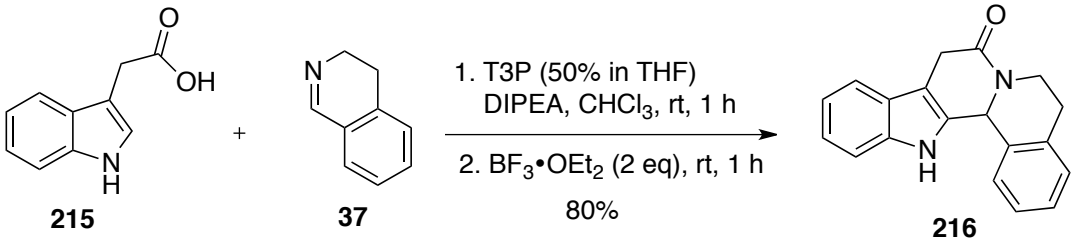
Next, isoquinoline **296** was employed in place of the imine substrate to determine whether cyclisation could occur and form a spirocyclic product **297** on this more difficult substrate; the main challenge is overcoming the loss of aromaticity upon cyclisation. The DIA reaction was attempted in THF at room temperature for 16 h and 70 °C for 1 h but both gave starting materials only. Conducting the reaction under more forceful conditions of toluene at 90 °C for 16 h also resulted in no product formation (Scheme 3.38).



Scheme 3.38 – Attempted DIA spirocyclisation reaction using isoquinoline

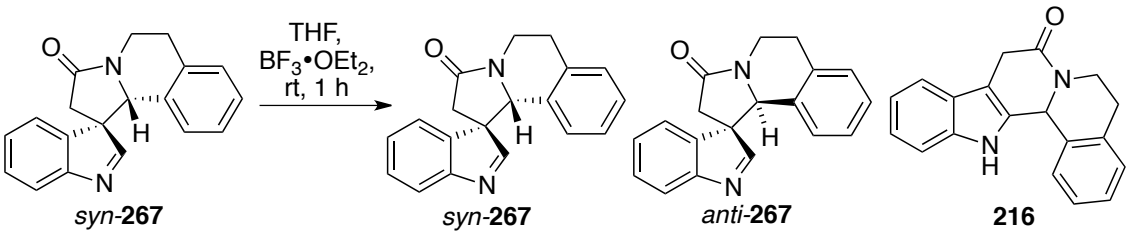
3.3.7. Addition of Lewis Acid to the Spirocyclisation Reaction

It was previously shown in the group that when a Lewis acid was added to the reaction of acid **215** and imine **37** under DIA conditions, a pentacyclic product **216** was formed (Scheme 3.39).[20] It was believed that the mechanism of the DIA reaction to give product **216** initially reacted through the 3-position of the indole, and then a 1,2-migration would give the planar product **216** (Scheme 3.15). Assuming this is correct, the spirocyclic product **267** should rearrange to the planar product **216** if subjected to a Lewis acid, as observed in other related reactions.[107]



Scheme 3.39 – DIA reaction of 3-indole acetic acid 215 and imine 37

Thus, the spirocycle *syn*-**267** was taken up in THF, then BF_3•OEt_2 was added and the reaction was stirred at rt for 1 h. On analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy, it could be seen that the spirocyclic products *syn*-**267**, *anti*-**267** and the fused product **216** were present 1:2.4:1.1 ratio of *syn*-**267**:*anti*-**267**:**216**. As the reaction had not gone to completion, it was repeated at 70 °C with a similar ratio of products observed.

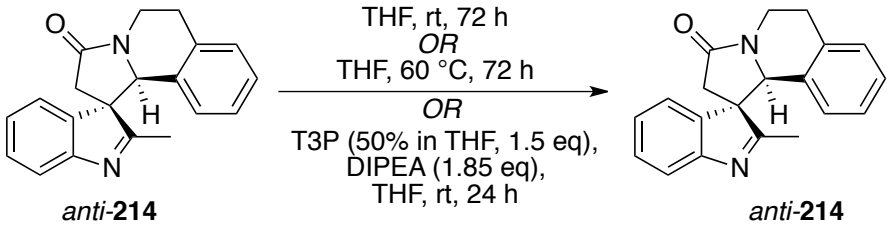


Scheme 3.40 – Attempted 1,2-migration of spiroindolenine 267

The migration reaction appears to be a lot more facile when the Lewis acid is added in the one-pot DIA reaction. However, observation of the pentacyclic product following addition of BF_3•OEt_2 to *syn*-**267** confirms that a 1,2-migration reaction is possible and suggests that this is how formation of the pentacyclic product proceeds. The fact that an epimerisation from *syn*-**267** to *anti*-**267** in the presence of the Lewis acid also occurs suggests that this could be an important factor in facilitating the 1,2-migration reaction to give product **216**.

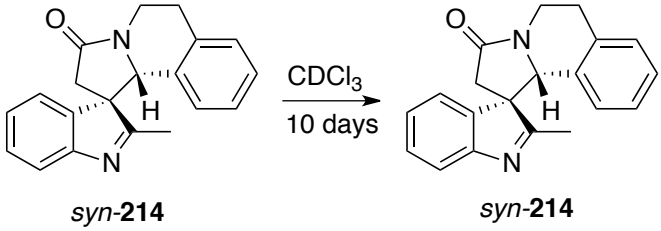
3.3.8. Equilibrium Studies on Spirocyclic Indolenines

Throughout the development of the DIA spirocyclisation epimerisation of the diastereostereoisomers was occasionally observed with some products, particularly in acidic conditions. As discussed earlier, subjecting *syn*-**267** to BF_3•OEt_2 resulted in some epimerisation to *anti*-**267** and rearrangement to give **216**. This epimerisation reaction had also been observed when samples were stored in $CDCl_3$ during ^{1}H NMR spectroscopy, most noticeably with spiroindolenines containing a *para*-methoxy substituent on the imine (**284** and **285**). Therefore, some equilibrium studies were undertaken to attempt to determine what might be causing this epimerisation. The stability of the spirocyclic indolenine *anti*-**214** was initially investigated by stirring the compound in THF at rt and 60 °C for 72 h, but no change in diastereomeric ratio was observed. *Anti*-**214** was then subjected to the DIA reaction conditions and no change was observed (Scheme 3.41).



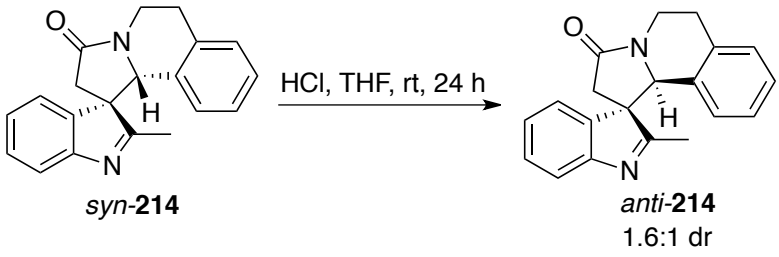
Scheme 3.41 – Reaction of *anti*-214 in THF and in DIA conditions

As epimerisation had been observed in $CDCl_3$ for the *para*-methoxy substituted spirocycles **284** and **285**, the same test was carried out on *syn*-**214**. A 0.02 mmol solution of spiroindolenine *syn*-**214** in $CDCl_3$ was analysed by ^1H NMR spectroscopy over 10 days, but no change in diastereomeric ratio was observed.



Scheme 3.42 – ^1H NMR spectroscopic equilibrium study on *syn*-214

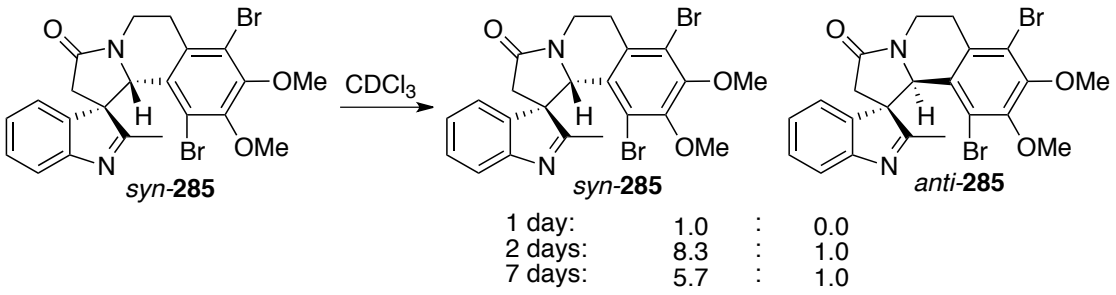
In earlier reactions where the reaction conditions had contained an acid (see Scheme 3.59) epimerisation of *syn*-**214** had been observed. Therefore, *syn*-**214** was subjected to a stoichiometric amount of HCl in THF for 24 h and analysis of the ^1H NMR spectrum of the unpurified reaction mixture showed a 1.6:1 dr of *anti*-**214**:*syn*-**214**, and after 72 h the dr was observed to be the same (Scheme 3.43).



Scheme 3.43 – Epimerisation of *syn*-214 in HCl

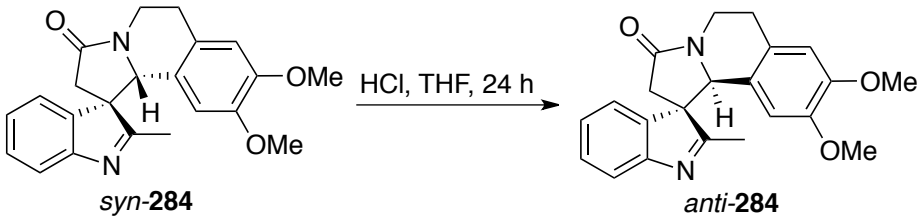
Therefore, it was concluded that epimerisation of the unfunctionalised spirocycle **214** was possible under strong acidic conditions but did not occur under the basic DIA reaction conditions. However, as mentioned earlier, spirocycles **284** and **285** containing a *para*-methoxy substituent on the imine component had been observed to readily undergo epimerisation if kept in $CDCl_3$. To investigate this, a 0.02 mmol solution of

syn-**285** in $CDCl_3$ was analysed by ^1H NMR spectroscopy at regular intervals over 10 days to observe any change in diastereomeric ratio. After one day, there was no change in diastereomeric ratio but by seven days a ~6:1 dr of *syn*-**285**:*anti*-**285** was observed (Scheme 3.44).



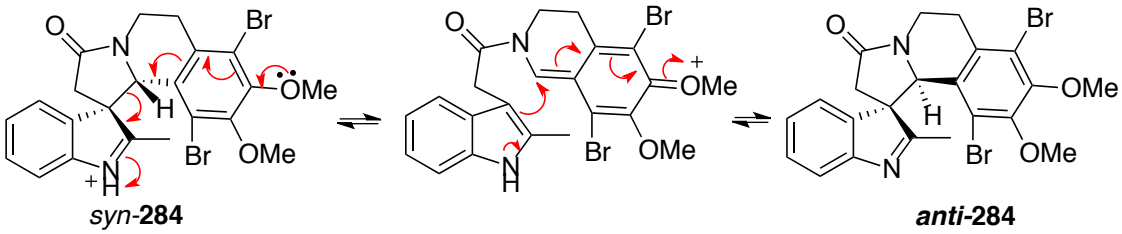
Scheme 3.44 – Epimerisation of *syn*-285 in $CDCl_3$

The spirocycle *syn*-**284** was also subjected to strongly acidic reaction conditions, and after stirring in THF with HCl for 24 h, a complete switch in stereochemistry to *anti*-**284** was observed by ^1H NMR spectroscopy (Scheme 3.45).



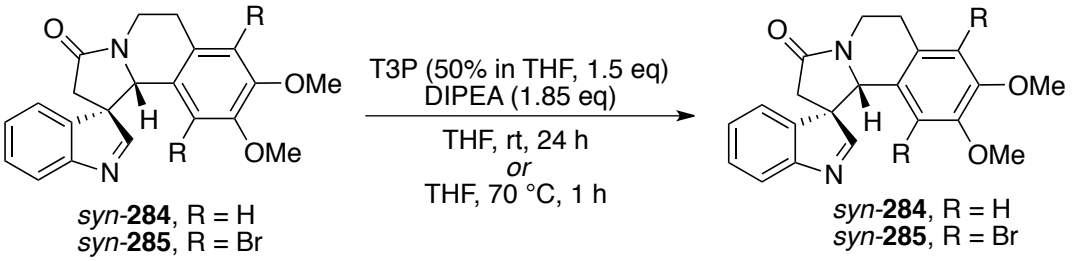
Scheme 3.45 – Epimerisation of *syn*-284 to *anti*-284 in HCl

A potential reason for the propensity of the methoxy-substituted spirocycle *syn*-**284** to undergo epimerisation could be that the mesomeric effect of the methoxy group provides an alternative epimerisation pathway (Scheme 3.46). Epimerisation of *syn*-**214** requires ring-opening *via* movement of electrons from the nitrogen lone pair, which are usually less available due to the amide.



Scheme 3.46 – Proposed mechanism for the epimerisation of *syn*-284

Spirocyclic indolenines *syn*-**284** and *syn*-**285** were also subjected to the DIA conditions but no change in diastereomeric ratio was observed by ^{1}H NMR spectroscopy (Scheme 3.47), showing that under the basic DIA reaction conditions no epimerisation occurs.



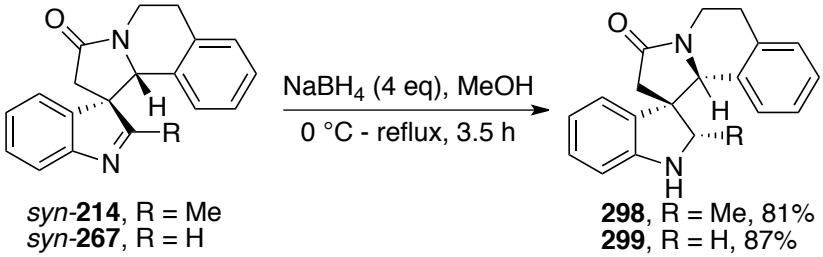
Scheme 3.47 – Reaction of *syn*-284 and *syn*-285 under DIA conditions

The conclusion from these experiments is that the diastereomeric ratios observed in the DIA spirocyclisation reactions must be kinetic ratios, formed as a result of the stabilising π-π stacking interaction between the aromatic rings of the indole and imine components. Subjecting the spiroindolenine products to the DIA reaction conditions confirmed that no epimerisation under these basic conditions occurred. However, it was shown that under strong acidic conditions, the spirocyclic products could undergo epimerisation to a presumably thermodynamic mixture of diastereoisomers. Spirocycles containing a *para*-methoxy substituent on the imine, such as *syn*-**284** were shown to epimerise more readily, thought to be due to the +M effect of the methoxy group that was believed to provide an alternative epimerisation pathway. The position of the equilibrium was also shown to be dependent on the acidic reaction conditions.

3.3.9. Derivatisation of Spirocyclic Products

The DIA spirocyclisation reactions provide access to a broad range of spirocyclic indolenine scaffolds, which contain a lot of functionality to allow for further transformations. This provides the opportunity to add further structural diversity or to tune the properties of the compounds. Initially, reduction of the imine functionality in spiroindolenine *syn*-**214** was investigated to afford a spirocyclic indoline product **298**. A few reduction conditions were attempted including reduction with sodium cyanoborohydride,[144] and reduction with a Hantzsch ester.[145] However, the best yield was achieved by refluxing in $NaBH_4$ to give the spiroindoline **298** in 81% yield (Scheme

3.48).[144] The same reduction conditions were used on the 2-H spirocyclic indolenine **267** and the spiroindoline **299** was produced in 87% yield (Scheme 3.48).



Scheme 3.48 – $NaBH_4$ reduction of spiroindolenines 214 and 267

The reduction of spiroindolenine **214** was completely diastereoselective and an X-ray crystal structure of the product **298** was obtained to confirm that the stereochemistry of the product is that shown in Scheme 3.48. The X-ray structure confirmed that the hydride source approached from the least sterically hindered face to give spirocycle indoline **298** (Figure 3.21).

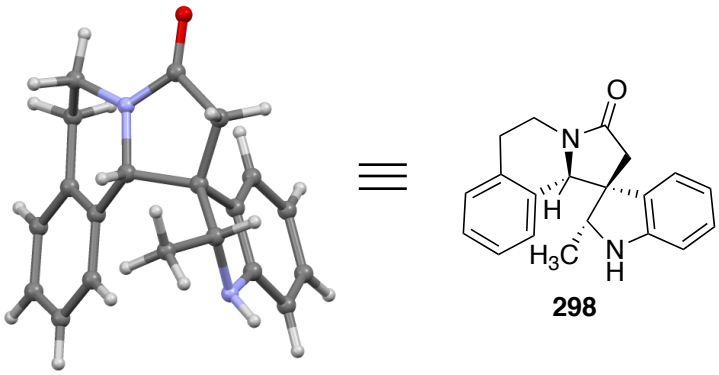
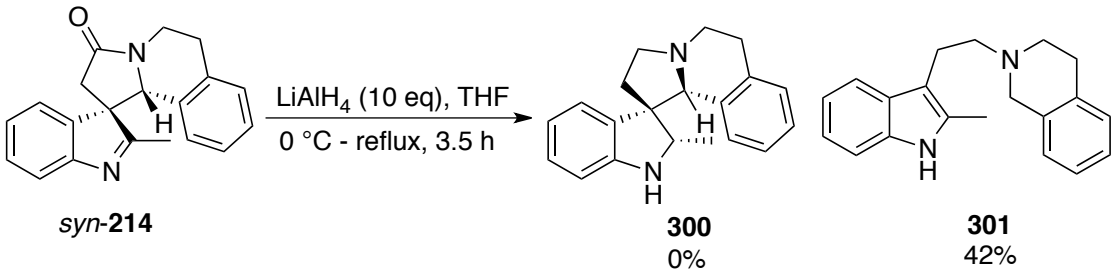


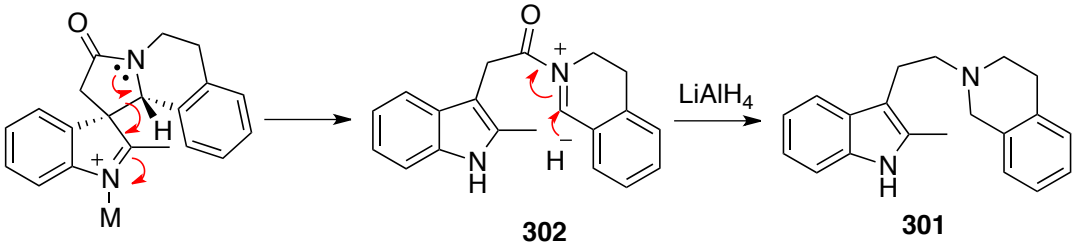
Figure 3.21 – X-ray crystal structure of spiroindoline 298 (CCDC: 1436401)

Reduction of the amide functionality within spirocyclic indolines **298** and **299** was then explored. Initially, $LiAlH_4$ reduction of spirocyclic indolenine **214** was carried out to determine whether the imine and amide functional groups could be reduced simultaneously. With an excess of $LiAlH_4$ and stirring at reflux for 3.5 h, none of the desired product **300** was isolated but indole **301** was isolated in 42% yield (Scheme 3.49).



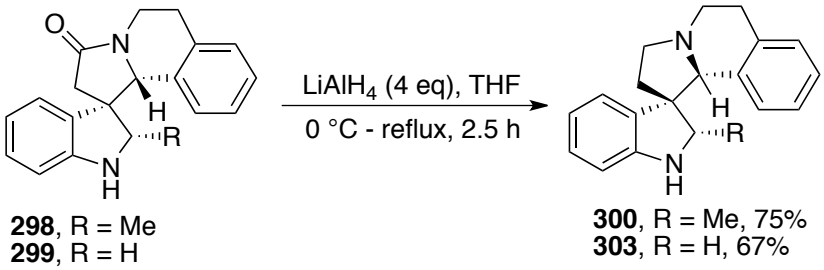
Scheme 3.49 – Attempted $LiAlH_4$ reduction of *syn*-214

It was thought that this indole product could form by coordination of a Lewis acidic metal species (Al or Li) to the imine and ring opening to give the intermediate *N*-acyliminium ion **302**. Nucleophilic addition of the hydride onto *N*-acyliminium ion **302** to give the amide and subsequent reduction of the amide would give the product **301** (Scheme 3.50). It was considered that the reduction of the amide should not occur before reduction of the imine, due to the lower electrophilicity but this cannot be ruled out as an alternative mechanism.



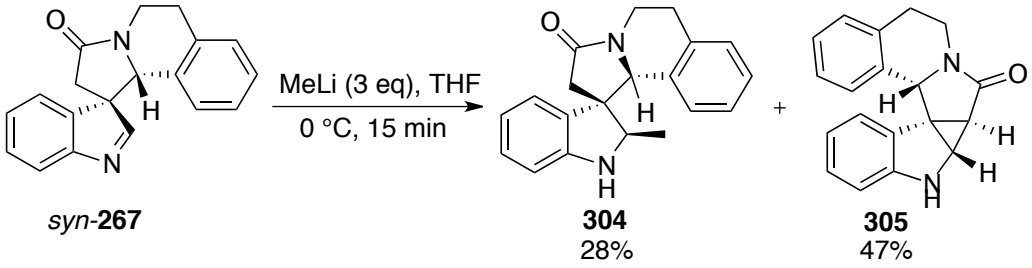
Scheme 3.50 – Proposed mechanism of $LiAlH_4$ reaction with *syn*-214

The undesired formation of product **301** demonstrated that the reduction of the imine has to be done first using $NaBH_4$ (as shown in Scheme 3.48), followed by reduction of the amide. Therefore, reduction of the spiroindolines **298** and **299** was carried out with $LiAlH_4$ to give the diamine spirocyclic products **300** and **303** in 75% and 67% respectively (Scheme 3.51).



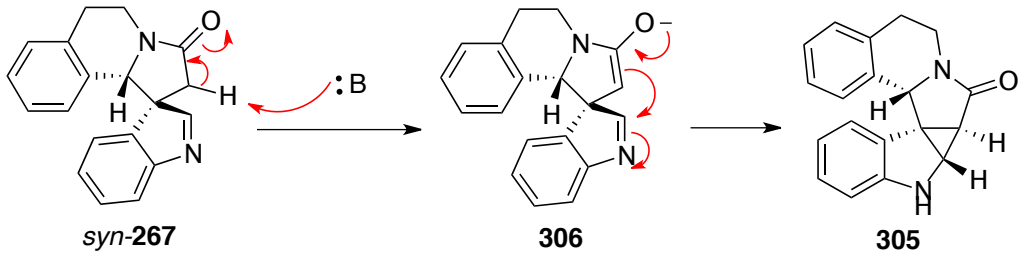
Scheme 3.51 – $LiAlH_4$ reduction of spiroindolines 298 and 299

Following the successful addition of a hydride nucleophile into the imine in spiroindolenines *syn*-**214** and *syn*-**267**, other nucleophiles were attempted. MeLi was initially chosen as a methyl nucleophile as it was thought that the opposite stereochemistry to spiroindoline **298** could be achieved by nucleophilic attack of MeLi onto the least sterically hindered face of spiroindolenine *syn*-**267**. Therefore, MeLi was reacted with spiroindolenine *syn*-**267** following literature conditions,[146] and following purification two products were isolated (Scheme 3.52). The desired product **304** was isolated in 28% yield and comparison of the ^{1}H NMR spectrum for the product **304** and spiroindoline **298** confirmed the opposite diastereoisomer was formed as expected.



Scheme 3.52 – Reaction of *syn*-267 with MeLi

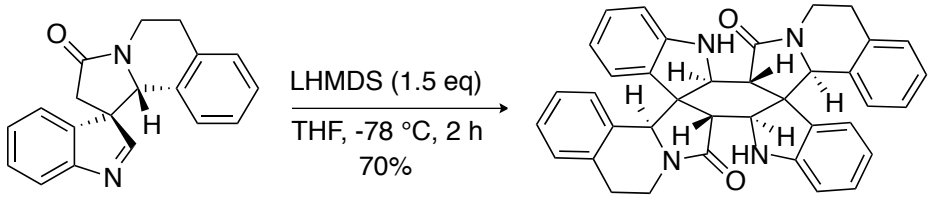
It was believed that the other isolated product **305** was a cyclopropane compound formed by the MeLi acting as a base, rather than a nucleophile, and forming the enolate **306** (Scheme 3.54). This could then add into the imine to form the cyclopropane **306**, which was observed as a single diastereoisomer. A believable model of this structure was also able to be made (where minimal ring strain was observed and all bonds looked feasible) and gave one possible diastereoisomer so it was thought that this was the product observed.



Scheme 3.53 – Suggested reaction mechanism for the possible formation of cyclopropane 305

All of the characterisation data matched up for cyclopropane **305** except for the mass spectrum which did not detect the $[M + H]^{+}$ ion. Therefore, it was thought that the

product should be deliberately formed by reaction with a base and an X-ray crystal of the product obtained to confirm the product. Reaction of spiroindolenine *syn*-**267** with LHMDS at −78 °C for 2 h resulted in isolation of the same product in 70% yield. Fortunately, the product was crystalline and observation of the X-ray crystal structure showed that, rather than a cyclopropane product **305**, a dimer **307** had formed (Scheme 3.54). The reaction was diastereoselective and the X-ray crystal structure showed the interesting shape of the product formed (Figure 3.22). It should be noted that the ^{1}H and ^{13}C NMR for the suspected product **305** and the dimer **307** matched, confirming that the dimer was formed in the MeLi reaction.



syn-**267** **307**

Scheme 3.54 – Synthesis of dimer 308 by enolate formation of spiroindolenine 267

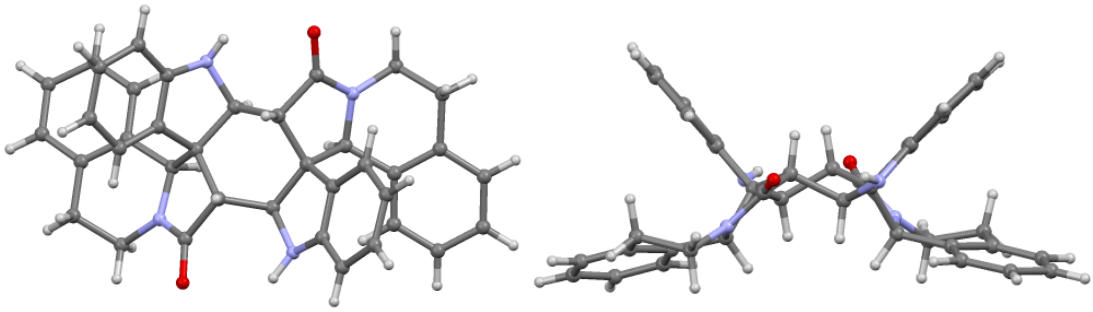
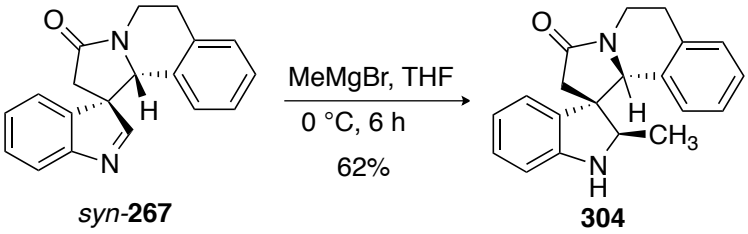


Figure 3.22 – Front and side view of X-ray crystal structure of 307 (CCDC:1506359)

The dimer product **307** would have formed *via* formation of the enolate and intermolecular addition into the imine, rather than the previously thought intramolecular reaction shown in Scheme 3.53. The reaction was repeated at 10 times the dilution to investigate whether the cyclopropane product **305** could be formed using a diluted reaction mixture to promote the intramolecular reaction between the enolate and imine. The reaction mixture was analysed by ^{1}H NMR spectroscopy and this confirmed that the product had formed selectively, but mass spectrometry was used to confirm the presence of dimer **307** by the observation of a $[M + Na]^{+}$ peak at 599.2438, which was the most intense peak in the spectrum.

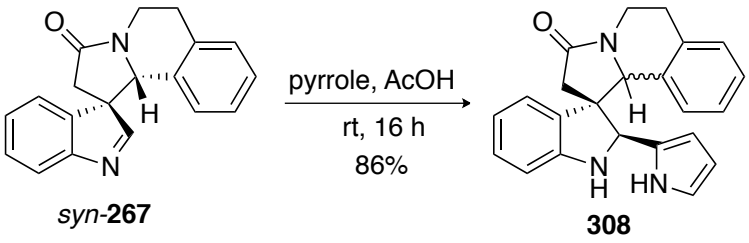
A Grignard reagent was then used as an alternative methyl nucleophile and the reaction conditions used were based on those used by Vincent *et al.* to add allylMgBr to a spiroindolenine (Scheme 3.55).[147] Stirring the reaction at rt resulted in decomposition and no product was isolated. Reaction at too low temperatures resulted in poor conversion of the starting material but, upon stirring at 0 °C for 6 h, the product **304** was isolated in 62% yield (Scheme 3.55). The reaction was diastereoselective from the methyl approaching the least sterically hindered face to give the product **304** with the opposite stereochemistry to spiroindoline **298** confirmed by ^{1}H NMR spectroscopy. It was assumed that the *syn* stereochemistry from the spiroindolenine starting material remained in tact in this reaction as there was no acidic additive or reagent in the reaction.



syn-**267** **304**

Scheme 3.55 – Grignard addition to spiroindolenine *syn*-267

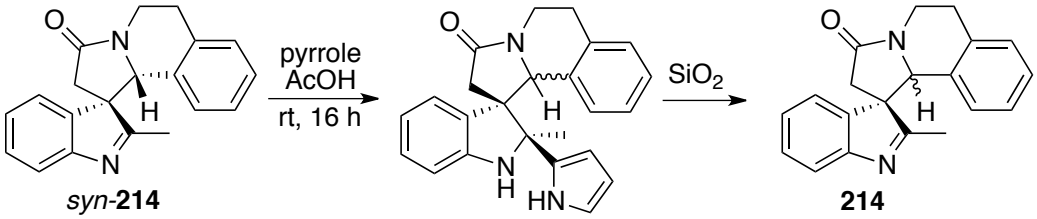
Smith *et al.* demonstrated the addition of pyrrole into a spiroindolenine by reaction in the presence of AcOH.[148] It was considered that in the presence of AcOH, a 1,2-migration may take place instead of the nucleophilic addition but pleasingly the nucleophilic addition occurred preferentially.[107] Subjecting *syn*-**267** to Smith's conditions and purification by column chromatography gave product **308** as one diastereoisomer in 86% yield (Scheme 3.56). The ^{1}H NMR spectrum of the unpurified reaction mixture suggested a >20:1 ratio of diastereoisomers. It was assumed that, like the methyl product **304**, the major diastereoisomer was as a result of nucleophilic attack on the least sterically hindered face. However, it cannot be assumed that the *syn* relationship of the starting material remained unchanged during the reaction. As discussed in section 3.8.8, under strongly acidic conditions *syn*-**267** can epimerise to *anti*-**267** and if this epimerisation occurred before addition of the pyrrole nucleophile the stereochemistry cannot be confidently assigned.



syn-**267** **308**

Scheme 3.56 – Addition of pyrrole to the spiroindolenine *syn*-267

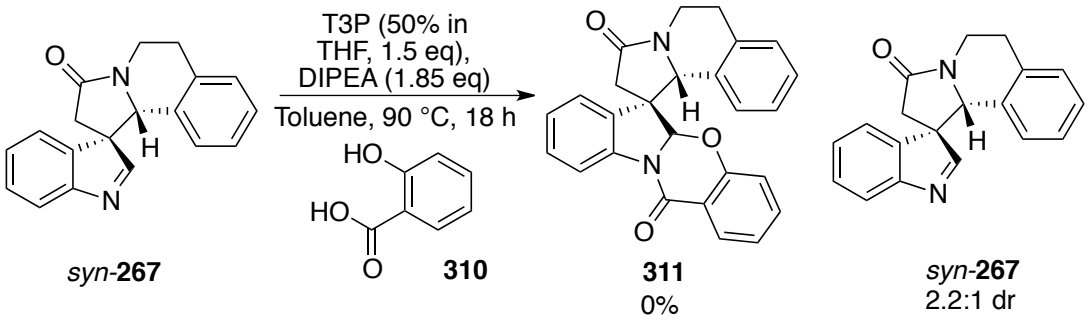
The nucleophilic addition of pyrrole was also carried out on the 2-methyl substituted spiroindolenine **214**. Surprisingly, analysis of the crude reaction mixture by ^{1}H NMR showed two diastereoisomers in a 1:1.1 ratio, suggesting that the pyrrole was as likely to attack from both sides of the imine despite one side being much more sterically hindered. However, following column chromatography, none of the pyrrole-substituted spiroindoline **309** was observed. Instead, *syn*-**214** and *anti*-**214** were isolated suggesting the addition of pyrrole is reversible when there is a substituent on the 2-position of the spiroindolenine (Scheme 3.57).



syn-**214** 1.1:1 dr **309** **214**

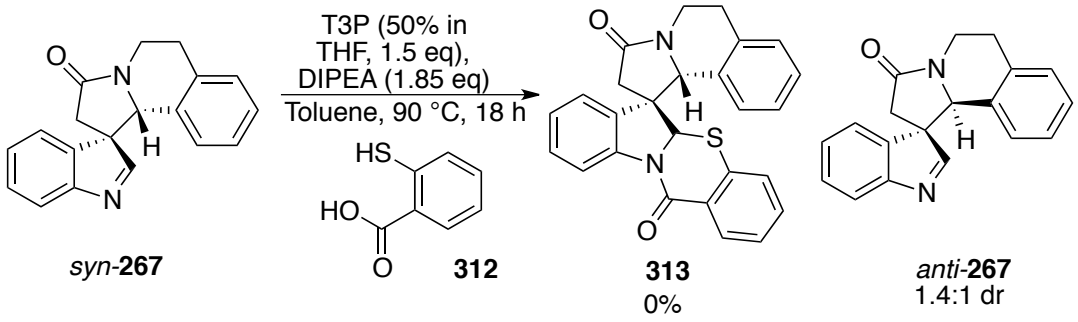
Scheme 3.57 – Attempted addition of pyrrole to spiroindolenine *syn*-214

The product of the DIA spirocyclisation reaction, spiroindolenine *syn*-**267**, contains an imine functionality that could potentially be used as the imine component in a second DIA reaction. To determine whether this was possible the spiroindolenine *syn*-**267** was reacted with salicylic acid **310** under standard DIA conditions.[21] Disappointingly, none of the desired product **311** was observed, perhaps because of the increased steric hindrance of this imine. Instead, the spiroindolenine *syn*-**267** had epimerised to a 2.2:1 dr of *syn*-**267**:*anti*-**267** (Scheme 3.58). Epimerisation of *syn*-**267** under acidic conditions has previously been discussed in Section 3.3.8.



Scheme 3.58 – Attempted DIA reaction of salicylic acid 310 with *syn*-267

The reaction was repeated using thiosalicylic acid **312** to see if this gave the desired product **313**. It has been previously suggested that when the acid component of a DIA reaction contains a thiol, the mechanism may proceed *via* initial nucleophilic attack of the sulfur into the imine, then intramolecular *N*-acylation.[23] Reaction of the spiroindolenine *syn*-**267** and thiosalicylic acid **312** under the standard DIA conditions resulted in none of the desired product **313**. The spiroindolenine had been epimerised to a 1.4:1 dr of *anti*-**267**:*syn*-**267** (Scheme 3.59).



Scheme 3.59 – Attempted DIA reaction of thiosalicylic acid 312 with *syn*-267

The derivatisation reactions shown highlight some of the possible transformations that can be done on the spiroindolenine products **214** and **267** obtained from the DIA spirocyclisation methodology. In addition, it is expected that these transformations would be possible on the other spirocyclic products described, and it should be noted that the transformations are not limited to the examples shown and that other reactions should be possible on these diverse scaffolds.

3.3.10. 3D Shape Analysis of Spirocycles

Recently, there has been a lot of interest in the exploration of rigid, 3D scaffolds that can access new and interesting areas of chemical space. Spirocycles are inherently 3D as a result of the tetrahedral carbon centre and are therefore attracting a lot of attention as they are currently poorly represented in drug and screening libraries.[83,149,150] Following the successful use of DIA methodology in the synthesis of spirocyclic indolenines, principal moments of inertia (PMI) plots were used to assess the 3D character of the synthesised compounds. Principal moments of inertia plots were introduced by Sauer and Schwarz,[151] and have been used in the O'Brien group to assess the 3D shape of a virtual lead-like library.[152] PMI plots are created by computationally generating the lowest energy 3D conformer of the molecule using a molecular mechanics analysis in Pipeline Pilot. The three principal moments of inertia are calculated from the 3D structure and sorted from lowest to highest value, I_1, I_2 and I_3. The PMI values are then normalised by dividing the two lowest values by the highest (I_1/I_3 and I_2/I_3) to give the normalised PMI ratios (NPR1 and NPR2), which can be plotted against each other to give a 2D triangular plot.[153] The triangular plot shows how rod-like, disc-like or sphere-like the compounds are depending on whether they are nearer the top-left, bottom or top right of the triangular plot respectively.

The PMI plot of 1439 FDA approved small molecule drugs was generated to visualise the 3D character of current drug compounds (Figure 3.23).[154] The blue triangle shown on the PMI plot indicates the under-populated area of chemical space where the molecules are more 3D/spherical, with the top right point of the plot representing a truly spherical compound (adamantane). The blue triangle contains compounds which have values of (NPR1 + NPR2) > 1.2 and is situated away from the rod-disk axis. The PMI analysis of the FDA approved small molecule drugs demonstrates that only 23% are found within this attractive area, and the majority of compounds are rod- and/or disc-like. This demonstrates the fact that 3D scaffolds are poorly represented in current drug libraries with most drug-screening libraries showing a similar shape distribution.[83,155]

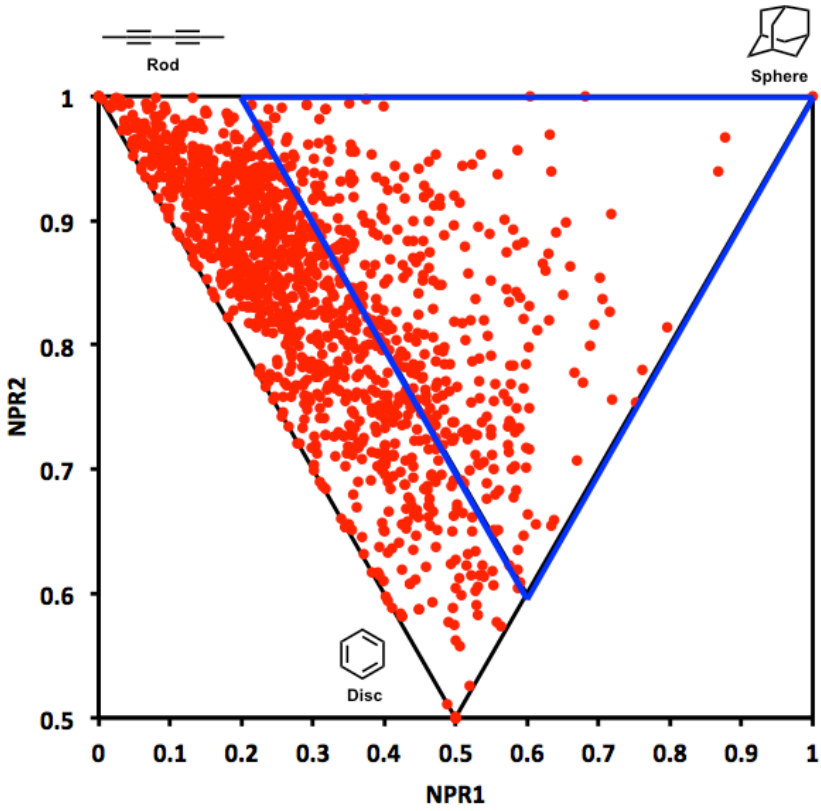


Figure 3.23 – PMI plot of FDA approved small molecule drugs[154]

The PMI plot of the lowest energy conformations of the major diastereomeric spirocycles synthesised was then generated,* as these were the compounds selectively formed in the highest yields throughout the development of the methodology (Figure 3.24). In contrast to the PMI plot for the FDA approved drug molecules (Figure 3.23), 88% of the major diastereoisomers are now in the (NPR1+NPR2)>1.2 region. The synthesised compounds can be seen to be very spherical, with spirocycles *syn*-**257**, *syn*-**261**, *syn*-**295**, *syn*-**259**, *syn*-**291**, *syn*-**256** and *anti*-**264** in particular populating the most spherical areas of the PMI plot and the structures of these compounds are shown in Figure 3.25. Small changes in the substituents or position of the substituents can be seen to make a large difference in how spherical the spirocycle is, e.g. 7-bromo *syn*-**260** is less spherical than 5-bromo *syn*-**259**.

* Method of analysis in Pipeline Pilot devised by Mary Wheldon (O'Brien group), Paul Bond and Rod Hubbard at the University of York (York Structural Biology Laboratory).

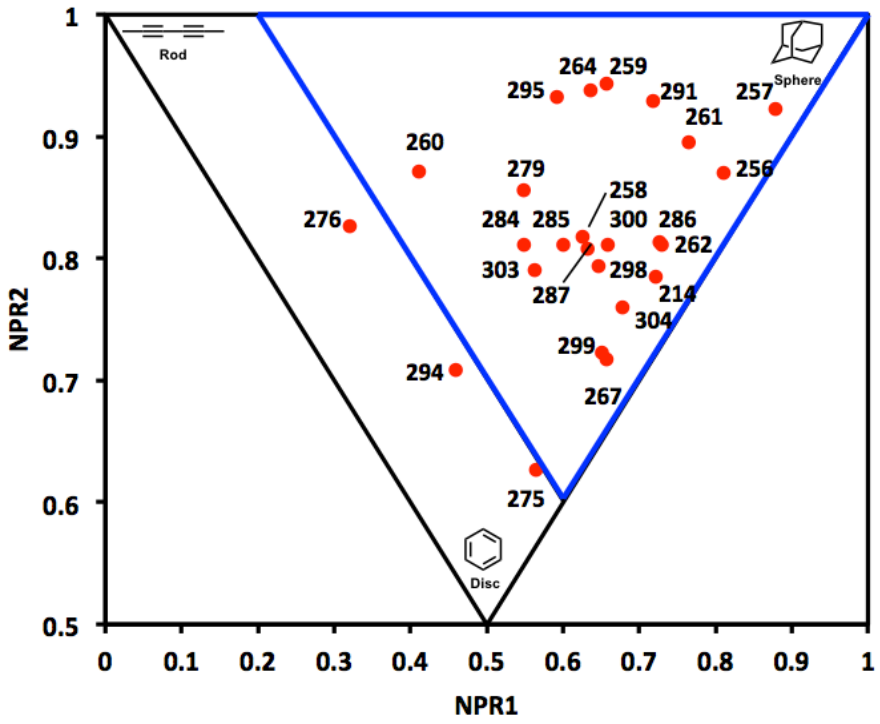


Figure 3.24 – PMI plot of lowest energy conformers of major spirocyclic products. (All compounds are *syn*-isomers, except for *anti*-264)

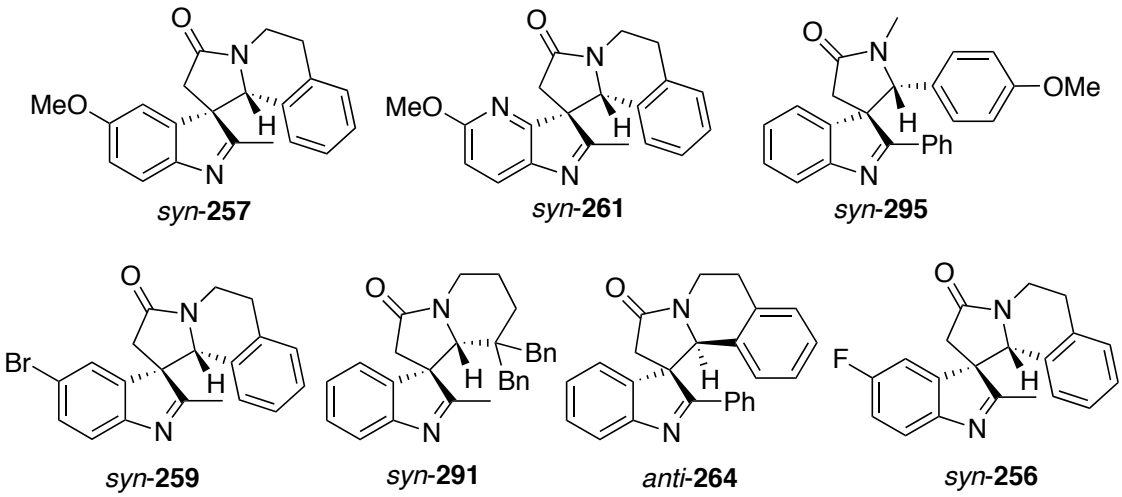


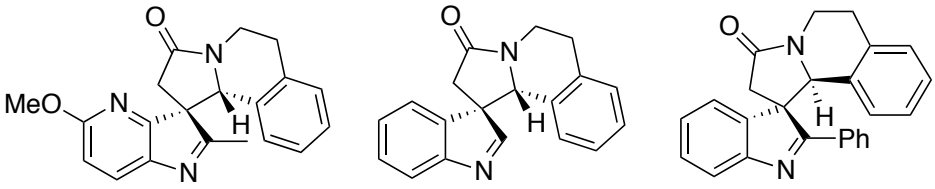
Figure 3.25 – Structure of the most spherical spiroindolenines

The PMI analysis of the spirocyclic scaffolds generated throughout the development of the DIA spirocyclisation methodology has shown that the isolated compounds are much more spherical in nature than the majority of current drug molecules. Some of the

spirocyclic products in particular have a very spherical shape and access areas of chemical space that are currently under-explored. Notably, the DIA spirocyclisation process takes simple, flat building blocks and quickly builds up molecular complexity and shape to give products that have highly desirable 3D scaffolds.

3.4. Conclusions and Future Work

DIA methodology was successfully applied in the synthesis of novel spirocyclic indolenine products. The method provides a new, metal-free dearomatisation reaction where simple 2D building blocks can be used to synthesise a broad range of 3D spirocyclic scaffolds in an efficient manner. The procedure uses mild conditions making it compatible with a wide range of functional groups, demonstrated by the broad substrate scope of the reaction. Interesting examples from the substrate scope are shown in Figure 3.26, including the azaspirocycle *syn*-**261**, the 2-H spirocycle *syn*-**267** and the 2-phenyl spirocycle *anti*-**264**. The observed diastereoselectivity favouring the *syn*-products for the 2-methyl spiroindolenines was rationalised by the presence of a stabilising π-π interaction between the aromatic rings of the indole and imine components, but this stereoselectivity was found to switch when a phenyl group was introduced to the 2-position. A number of X-ray crystal structures were obtained throughout the project to confirm the observed diastereoselectivity of the reaction. In addition, diagnostic signals in the ^{1}H NMR spectra of the products allowed confident assignment of the stereochemistry of related compounds, which proved to be a useful tool.



syn-**261** *syn*-**267** *anti*-**264**

Figure 3.26 – Structures of spiroindolenines synthesised using DIA methodology

The spirocyclic indolenine products formed through the DIA spirocyclisation methodology were primed for further functionalisation or derivatisation. This was successfully demonstrated with reduction of the imine and amide functionalities, and addition of nucleophiles into the imine. An interesting dimer product **307** was selectively formed by generation of the enolate and intermolecular addition into the spirocyclic imine.

The PMI analysis of the spirocyclic products indicated that the synthesised compounds were generally very spherical and occupy areas of chemical space that are currently

underexplored. Spirocyclic indolenines *syn*-**257**, *syn*-**261**, *syn*-**295**, *syn*-**259**, *syn*-**291**, *syn*-**256** and *anti*-**264** were all in a very spherical region of the PMI plot. Interestingly, small changes in the substituents were shown to dramatically change how spherical the products were. The structure of the spirocyclic indolenine products also allows further derivatisation (as demonstrated in the project) so that the properties of the products can be tuned further. The results of the 3D shape analysis highlight the efficiency of this methodology as a way of quickly building complex 3D scaffolds from simple 2D building blocks. The PMI analysis of the FDA approved small molecule drugs also emphasises the number of planar compounds that are currently used as drug compounds, so the development of methodology that can effectively produce 3D compounds would allow exploration of new and interesting chemical space.

A natural progression for this project would be to investigate an enantioselective route towards the spirocyclic indolenine products. The stereoselectivity of the reaction is determined by the facial selectivity of the nucleophilic attack onto the *N*-acyliminium ion intermediate. It was thought that enantioselectivity could be induced at this point by the introduction of a chiral phosphoric acid or a thiourea organocatalyst. Jacobsen *et al.* employed a thiourea organocatalyst in an enantioselective Pictet-Spengler reaction for the synthesis of a range of tetrahydrocarbazoles.[156] However, initial attempts within the Taylor group to employ such catalysts in the DIA reaction have proven unsuccessful and resulted in no enantiomeric enrichment of the spirocyclic products. Therefore, development of an asymmetric variant of the DIA spirocyclisation process could take a significant amount of work.

Initial attempts to use the DIA spirocyclisation methodology in the synthesis of aspidospermidine will be discussed in the next chapter. Future work for this project could focus on showcasing the methodology in the synthesis of other natural products containing a spirocyclic scaffold, to demonstrate the versatility of the methodology.

4. Attempted Synthesis of Aspidospermidine using Direct Imine Acylation Methodology

4.1. Introduction to Aspidospermidine

4.1.1. Classification and Biological Activity of the Aspidosperma Family

The *aspidosperma* family of indole alkaloids is a large subclass of natural products that are biosynthetically derived from tryptamine and a monoterpene unit.[157,158] They are classified based on the original terpene component and compounds that have a quaternary carbon centre as a feature of the terpene are part of the *aspidosperma* family, some examples of which are shown in Figure 4.1.[157,159]

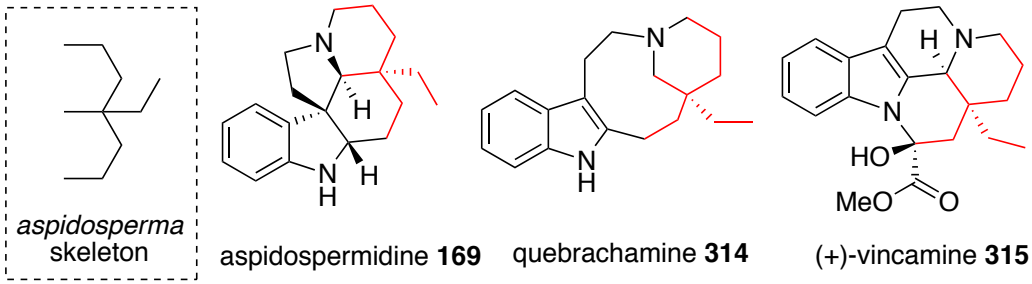
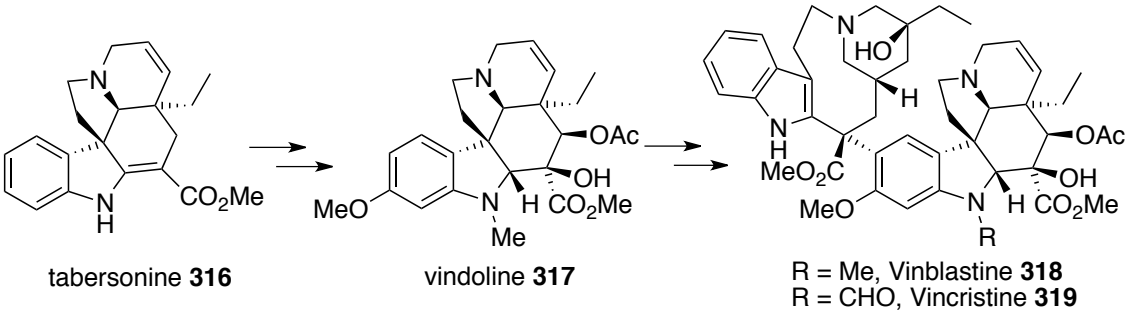


Figure 4.1 – Members of the aspidosperma family[157]

Aspidospermidine **169**, the parent compound of the *aspidosperma* family, has attracted a lot of attention from groups who wish to showcase new synthetic methodologies.[87] The scaffold is a desirable target to demonstrate the ability to build up spirocyclic centres, and aspidospermidine has also been shown to possess some adrenergic receptor activity.[88] Tabersonine **316** is an important member of the *aspidosperma* family due to its role in the biosynthesis and chemical synthesis of other important *aspidosperma* alkaloids. It is the precursor for the biologically active alkaloid vindoline **317** and biosynthetic and chemical pathways have been demonstrated for this transformation (Scheme 4.1).[160,161] The potent anti-cancer drugs Vinblastine **318** and Vincristine **319**, two biologically active *vinca* alkaloids, are derived from the dimerisation of vindoline **317** and catharanine (a member of the *iboga* family of alkaloids) and are used in the treatment of leukaemia, Hodgkin's lymphoma and other cancers (Scheme 4.1).[160] The

biological importance of these compounds highlights the necessity for new synthetic strategies towards these spirocyclic scaffolds.

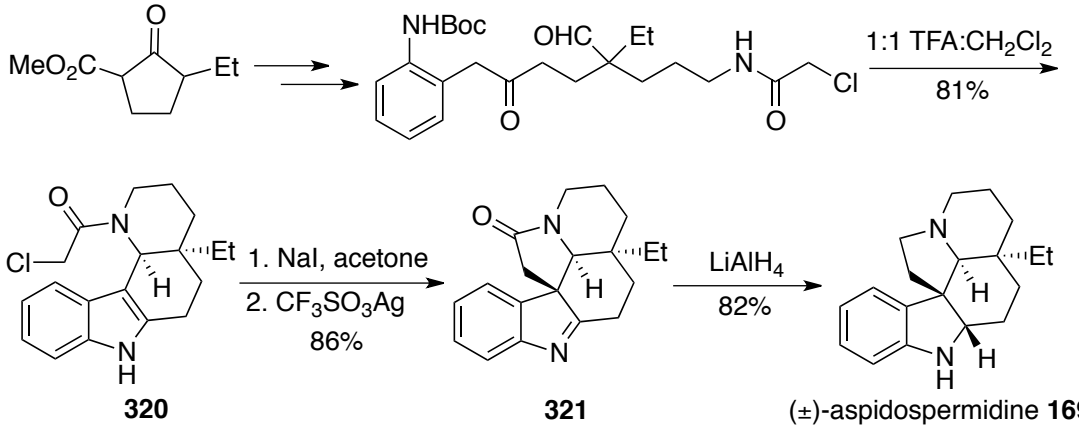


Scheme 4.1 – Generation of Vinblastine and Vincristine

4.1.2. Previous Syntheses of Aspidospermidine

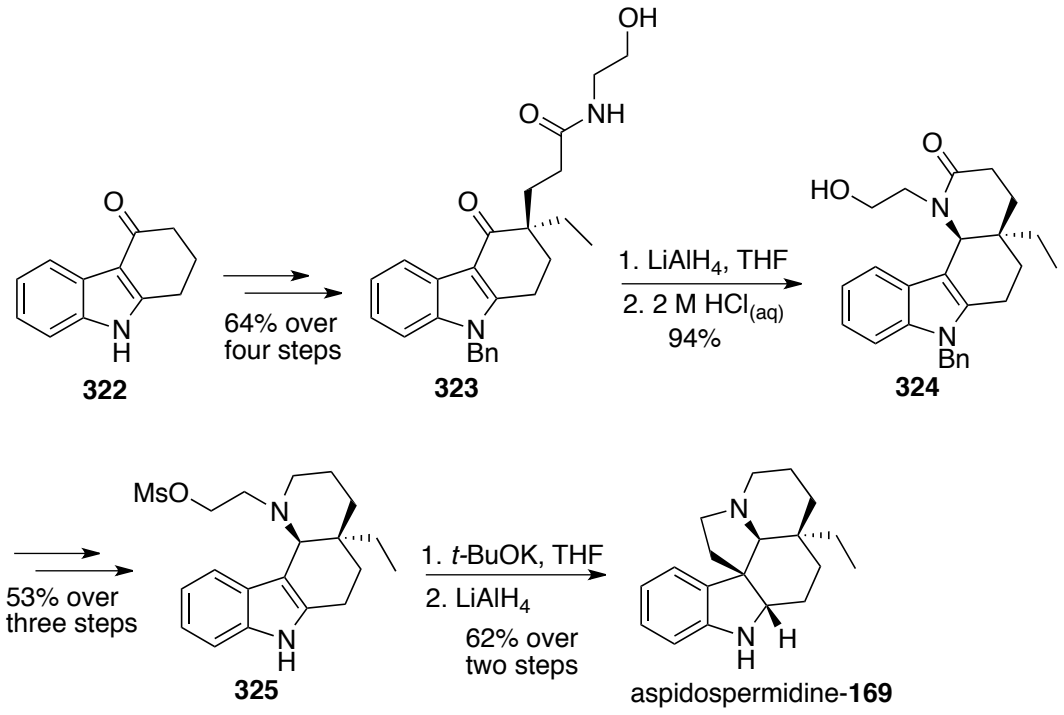
Groups wishing to demonstrate new methodology often choose aspidospermidine **169** as the synthetic target as it is a simple spirocyclic member of the *aspidosperma* family. Often, methodology aimed towards aspidospermidine can be applied to other examples through small modifications of the spirocyclic scaffold. One of the most common methods for the synthesis of aspidospermidine **169** involves the late stage construction of the indole moiety, first demonstrated by Stork and Dolfini.[162] Pictet-Spengler and Bischler-Napieralski based approaches are also popular methods due to their general applicability to other related alkaloids.[163]

The late-stage dearomatisation reaction of an indole to generate the final spirocyclic ring in the aspidospermidine scaffold is a common strategy.[87,164-166] Heathcock *et al.* demonstrated a facile method for the late-stage formation of the spirocyclic ring.[87] The haloacetamide functionality was chosen for the displacement reaction as it reduced the need to use protecting groups and the reactivity could be increased through the use of an iodo- rather than bromo- or chloro-acetamide. After halogen exchange on the chloroacetamide **320**, the iodoacetamide was treated with silver trifluoroacetate to give the spirocyclic indolenine **321** in 46% yield. This yield was dramatically improved to 86% through the use of silver triflate, as this modification prevents the formation of a trifluoroacetate-related side-product (Scheme 4.2).[87] Reduction of the spirocyclic indolenine gave (±)-aspidospermidine **169** in an overall yield of 5.9% over 13 steps.[87]



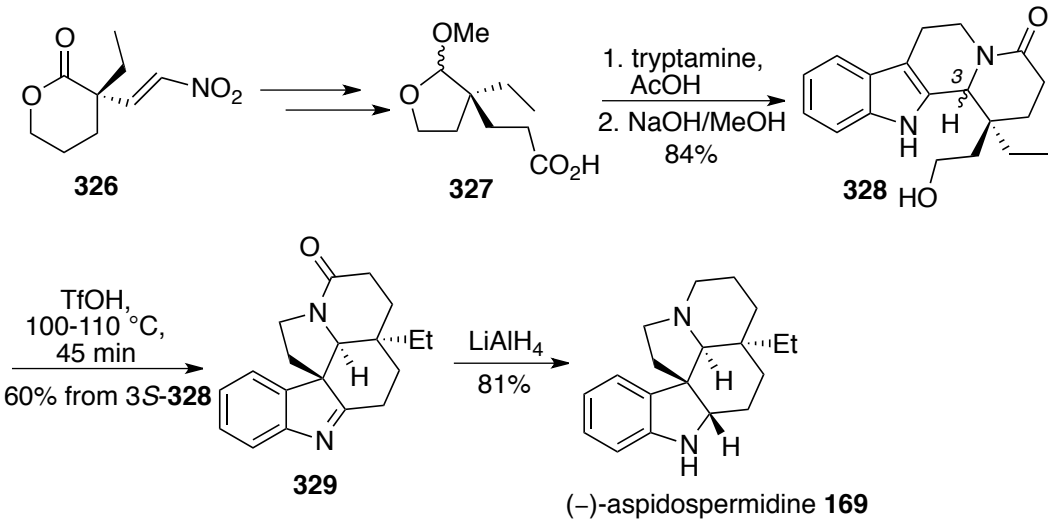
Scheme 4.2 – Synthesis of aspidospermidine 169 *via* a late-stage dearomatisation[87]

This effective strategy has also been used in an efficient synthesis of (±)-aspidospermidine **169** from the commercially available carbazole **322** (Scheme 4.3).[166] The substituted carbazole **323** was synthesised in 64% yield over four steps and then $LiAlH_4$ reduction of the ketone gave an intermediate alcohol. Addition of HCl to quench the reaction initiated a dehydration reaction to form an *α,β*-unsaturated iminium ion which was trapped intramolecularly by the amide to give the cyclised product **324** in 94% yield.[166] After a three-step sequence to the mesylated alcohol **325**, (±)-aspidospermidine **169** was generated in a one-pot alkylation/reduction reaction which gave the target compound in 20% overall yield over 10 steps (Scheme 4.3).[166]



Scheme 4.3 - Synthesis of aspidospermidine 169 *via* a late stage aromatisation[166]

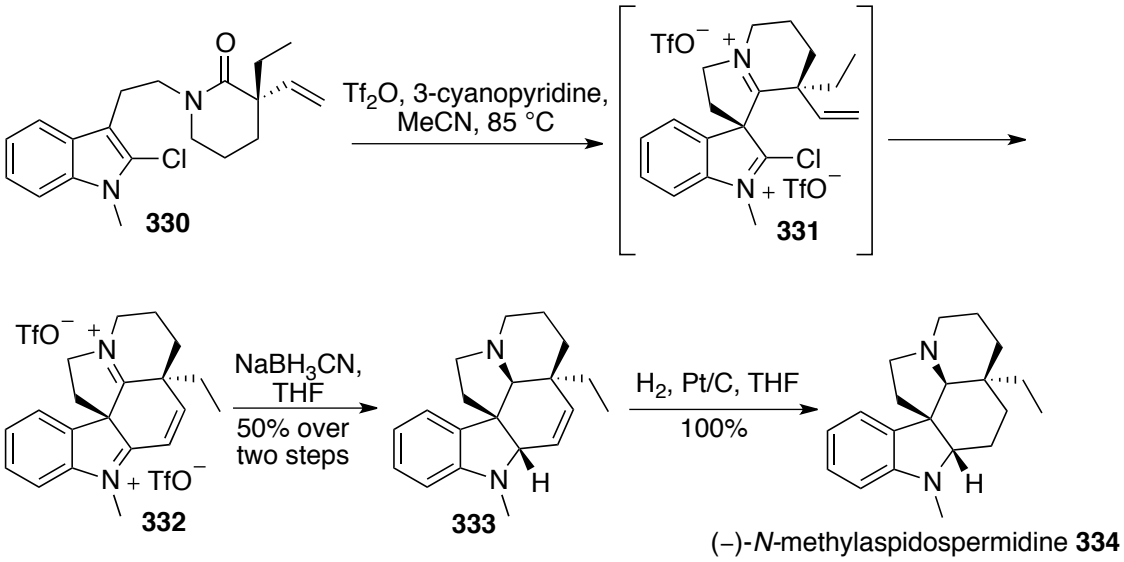
Fuji *et al*. demonstrated the first enantioselective synthesis of (–)-aspidospermidine **169** in 1987, based on the Pictet-Spengler approach.[163,167] The chiral lactone **326** contained the necessary C9 unit with the appropriate stereochemistry to form the monoterpene part of the target compound.[163] Indole **328** was obtained in a 1:1 ratio of diastereoisomers and 84% yield from a Pictet-Spengler reaction of acid **327** and tryptamine, and subsequent base hydrolysis (Scheme 4.4). Separation of the diastereoisomers gave only 3*S*-**328**, which cyclised upon treatment with TfOH to give the desired product **329** in 60% yield. Reduction of the spiroindolenine **329** and amide functionality provided (–)-aspidospermidine **169** (Scheme 4.4).[167] This transformation of alcohol **328** to spiroindolenine **329** was also demonstrated by Prasad *et al.* in a complementary synthesis of (–)-aspidospermidine **169** and other *aspidosperma* alkaloids from a common starting material.[168]



Scheme 4.4 – Synthesis of (–)-aspidospermidine 169 *via* a Pictet-Spengler reaction[167]

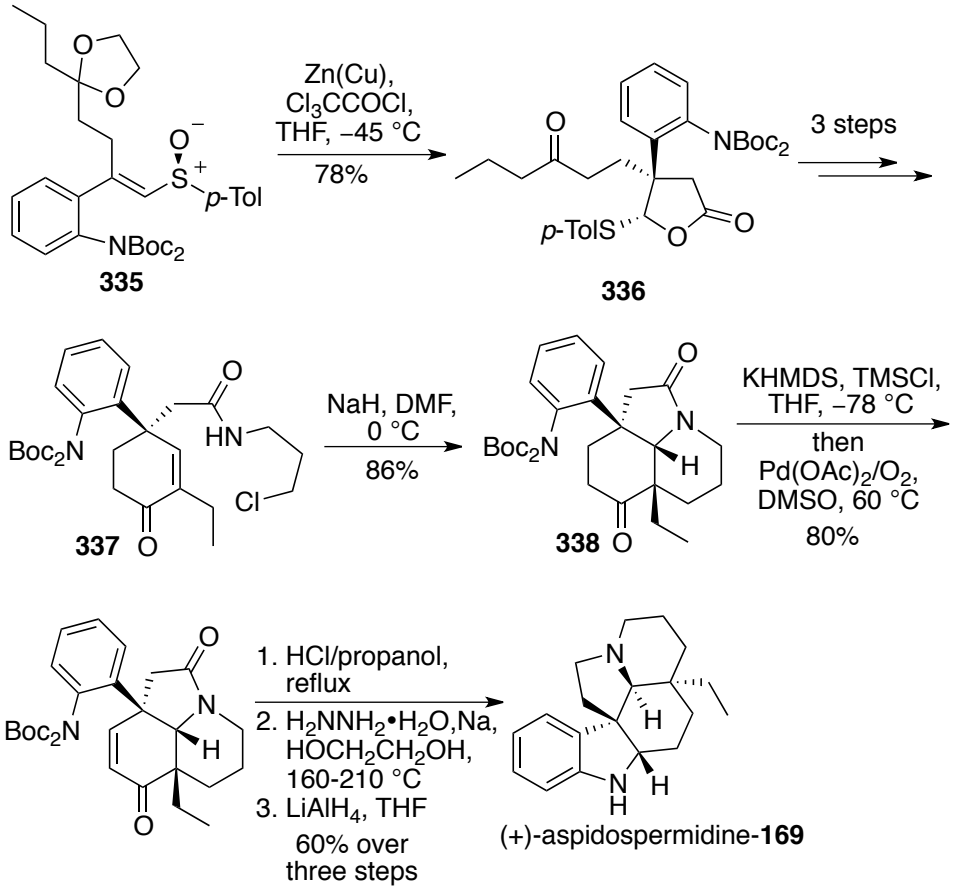
Movassaghi and Medley used a novel, stereoselective double cyclisation cascade in a concise synthesis of (–)-*N*-methylaspidospermidine.[169] Upon treatment with the mildly basic additive 3-cyanopyridine in acetonitrile, chiral lactam **330** underwent nucleophilic spirocyclisation onto the activated electrophilic carbonyl (Scheme 4.5). This resulted in the formation of 2-chlorospiroindoleninium intermediate **331**, which reacted further at its C2 position *via* attack of the tethered vinyl group with loss of HCl to give **332**. It was suggested that the second cyclisation occurs without the use of an activated alkene due to the presence of the chlorine on the 2-position and the resulting enhanced

electrophilicity.[169] The use of Tf_2O ensures the interruption of the Bischler-Napieralski reaction,[94] and subsequent reduction by sodium cyanoborohydride produced the indoline **333**. Hydrogenation of the alkene gave (–)-*N*-methylaspidospermidine **334** (Scheme 4.5).[169]



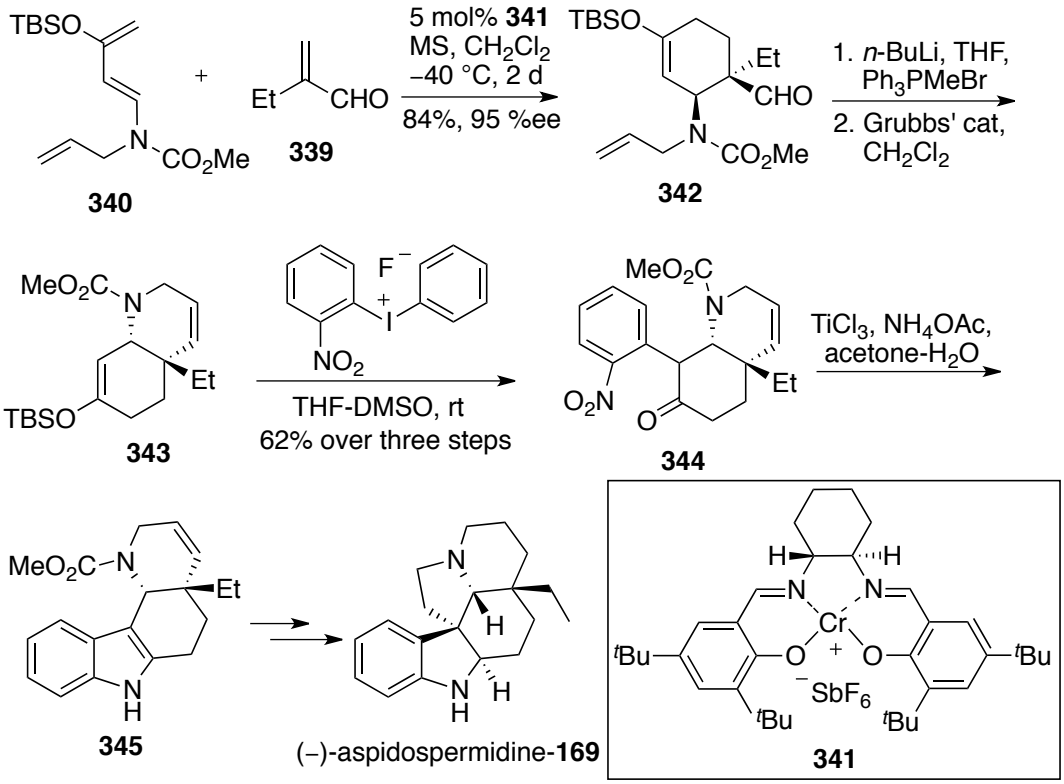
Scheme 4.5 – Synthesis of (–)-*N*-methylaspidospermidine 334 *via* an interrupted Bischler-Napieralski reaction[169]

Marino *et al.* employed a ketene lactonisation reaction, developed within their group,[170] to provide a novel approach to the enantiospecific synthesis of *aspidosperma* alkaloids.[171] The key reaction allows the chirality of the sulfoxide to be transferred through a novel [3,3]-sigmatropic rearrangement of a chiral vinyl sulfoxide **335** with a ketene (Scheme 4.6). The lactone **336** was then converted into cyclic enone **337** in three steps, which upon treatment with NaH forms the tricyclic core scaffold **338** through a tandem conjugate addition/intramolecular alkylation reaction (Scheme 4.6). The sequence was completed by Boc cleavage and subsequent conjugate addition, followed by Wolff-Kishner and $LiAlH_4$ reductions to provide (+)-aspidospermidine **169** (Scheme 4.6).[171] This unique approach to the synthesis of the *aspidosperma* alkaloids allows access to both enantiomeric series, and derivatisation of the intermediates can provide access to other *aspidosperma* alkaloids.[170]



Scheme 4.6 – Synthesis of (+)-aspidospermidine *via* a late stage indole formation[171]

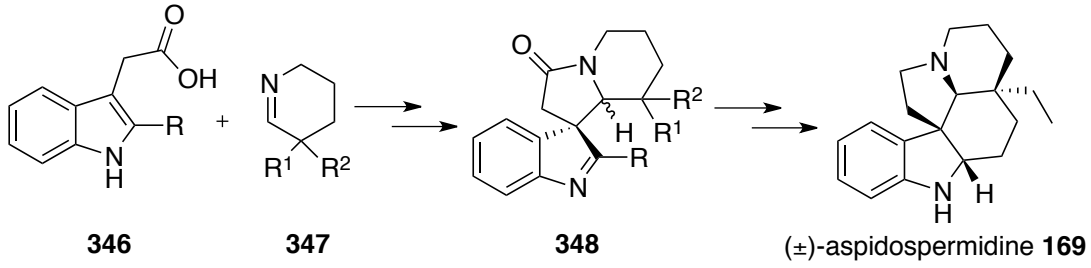
Rawal *et al.* described a highly regio- and stereocontrolled approach to the *aspidosperma* alkaloids *via* a [4+2] cycloaddition reaction.[172] This approach was then applied in the asymmetric synthesis of (+)-aspidospermidine and other related alkaloid natural products (Scheme 4.7). The strategy involved the enantioselective Diels-Alder reaction between 2-ethylacrolein **339** with 1-amino-3-siloxydiene **340** catalysed by a chiral Cr(III)-salen complex **341**. The cycloadduct **342** was obtained in an 84% yield with a 95% *ee*. A subsequent Wittig reaction and Grubbs ring-closing metathesis afforded the fused bicycle **343** which was arylated using the iodonium fluoride salt to give the enantiomerically enriched product **344** in 62% over three steps. Late-stage construction of the indole moiety *via* a $TiCl_3$ mediated reduction of the nitro group and subsequent condensation provided the indole **345**. Following this, removal of the carbamate and introduction of an alcohol group provided the necessary functionality to allow a displacement reaction to give the spirocyclic ring junction and the synthesis of (+)-aspidospermidine **169** was completed (Scheme 4.7).[172]



Scheme 4.7 – Synthesis of (−)-aspidospermidine 169 *via* a Diels-Alder reaction[172]

4.2. Project Outline

The biological importance of the spirocyclic scaffolds contained in the *aspidosperma* alkaloid core structures makes the development of new syntheses towards these structures desirable. It was envisaged that the DIA spirocyclisation methodology developed in this project could be applicable in the synthesis of these indole alkaloids. (±)-Aspidospermidine **169** was chosen as the target compound to explore the methodology as it has the simplest spirocyclic scaffold. The DIA spirocylisation reaction would provide efficient access to the spirocyclic core, and a concise synthesis of (±)-aspidospermidine should be possible (Scheme 4.8). Reaction of an indole **346** and imine **347** under the DIA spirocyclisation conditions would give a spirocyclic indolenine **348** and further steps would give access to (±)-aspidospermidine **169** (Scheme 4.8). This DIA approach also has the potential for further derivatisation, which could provide access to other *aspidosperma* alkaloids.

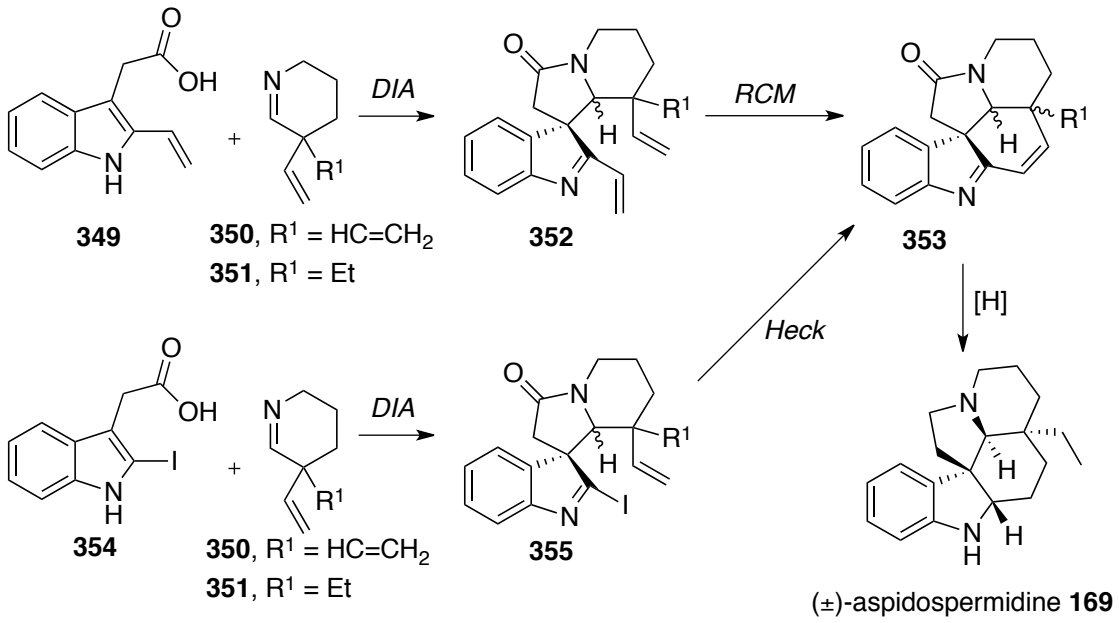


Scheme 4.8 – Overall strategy towards the synthesis of (±)-aspidospermidine 169

4.3. Results and Discussion

4.3.1. Proposed Routes Towards (±)-Aspidospermidine

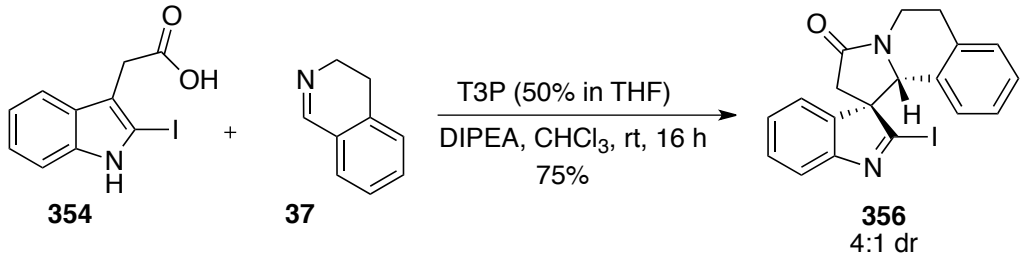
The aim of the project was to use the developed DIA spirocyclisation methodology in the synthesis of (±)-aspidospermidine **169**. The spirocyclic centre could be synthesised from the DIA reaction of an appropriate indole acid substrate (**349** or **354**) and imine substrate (**350** or **351**) (Scheme 4.9). Upon formation of the spirocyclic centre, the 6-membered ring would need to be synthesised to form the polycyclic scaffold **353** and a global reduction would then afford aspidospermidine **169** in an efficient manner.



Scheme 4.9 – Proposed route to (±)- aspidospermidine using DIA spirocyclisation

A number of methods can be imagined for the cyclisation to give the final 6-membered ring in the synthesis. Mukai *et al.* had previously demonstrated the use of an intermolecular cross metathesis reaction between two key components in the synthesis of another *aspidosperma* family alkaloid member, goniomitine.[173] We envisaged that if we also started with a 2-vinyl substituted indole acetic acid **349** and a vinyl substituted imine **350** or **351**, we could initially set the spirocyclic centre of the scaffold using DIA methodology and then carry out an intramolecular ring-closing metathesis to form the polycyclic product **353** (Scheme 4.9). Global reduction of this product would provide aspidospermidine **169**. Alternatively, a 2-iodo indole acid **354** could be used in a DIA spirocyclisation reaction with the vinyl-substituted imine **350** or **351** and a subsequent

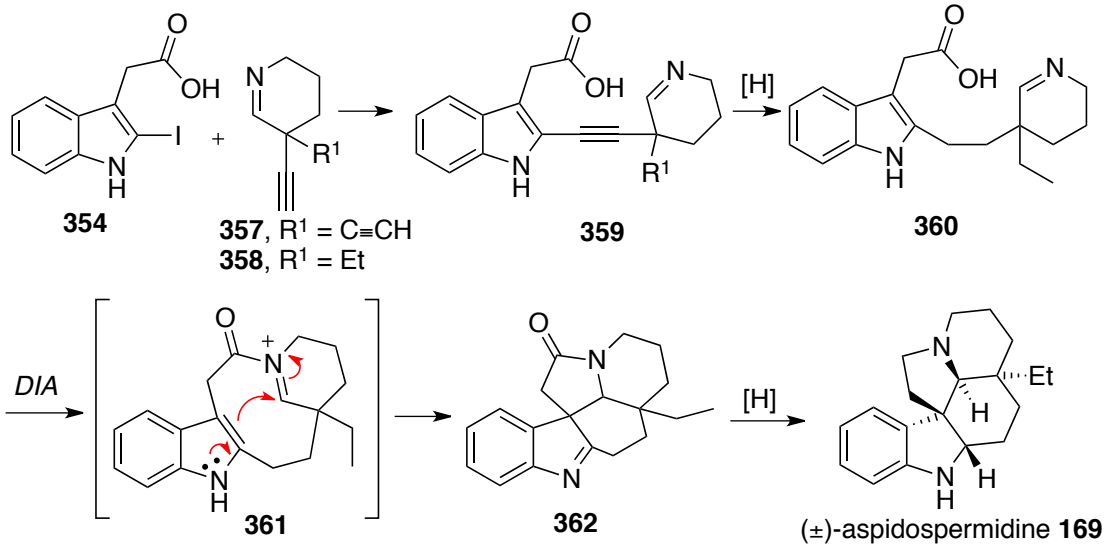
intramolecular Heck reaction could be could be performed to form the 6-membered ring (Scheme 4.9). In unpublished results* within the Taylor group, it was found that 2-iodo indole **354** could be reacted with imine **37** under DIA conditions to give spirocyclic product **356** in a 4:1 *dr* and 75% yield (Scheme 4.10). Therefore, it was reasoned that the proposed DIA reaction between iodo indole acid **354** and vinyl imine **351** should proceed.



Scheme 4.10 – DIA reaction of iodosubstituted indole 354 and imine 37*

An alternative use of the iodo indole acid **354** would be in a Sonogashira reaction with imine **357** or **358** (Scheme 4.11). This approach has been utilised in the synthesis of (±)-quebrachamine **314**, where the indole and piperidine components were joined by a Sonogashira reaction and lactamisation to afford the desired natural product.[174] In our proposed route, following the Sonogashira reaction, reduction of the alkyne **359** would give product **360**. A DIA reaction would provide the *N*-acyliminium intermediate **361**, which should undergo a transannular spirocyclisation reaction to give the spiroindolenine **362**. Reduction of the amide and imine would give aspidospermidine **169** (Scheme 4.11).

* Work carried out by Dr. Graeme Coulthard in the Taylor group.



Scheme 4.11 – Proposed route to aspidospermidine *via* a Sonogashira approach

Work was then focused on the synthesis of the necessary indole acid and imine components for testing the three proposed routes to aspidospermidine **169** (Figure 4.2). The 2-vinyl substituted indole acid **349** was required for use in the route containing a ring-closing metathesis step (Scheme 4.9). The 2-iodo indole acid **354** would be used in the route containing an intramolecular Heck reaction (Scheme 4.9), and also the route containing a Sonogashira reaction (Scheme 4.11). It was considered that in the planned DIA reactions, the number of possible diastereoisomers that could be formed would be reduced to 2 possible isomers if imine **350** was used (Scheme 4.9). However, it was found that there was limited literature precedent for six membered imines such as these and a disubstituted vinyl imine initially appeared more challenging to synthesise, so imine **351** was selected for synthesis. An analogous alkyne substituted imine **358** would also be required for the synthesis involving a Sonogashira reaction (Figure 4.2).

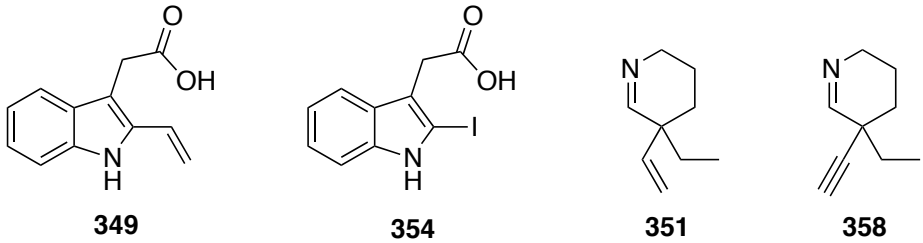
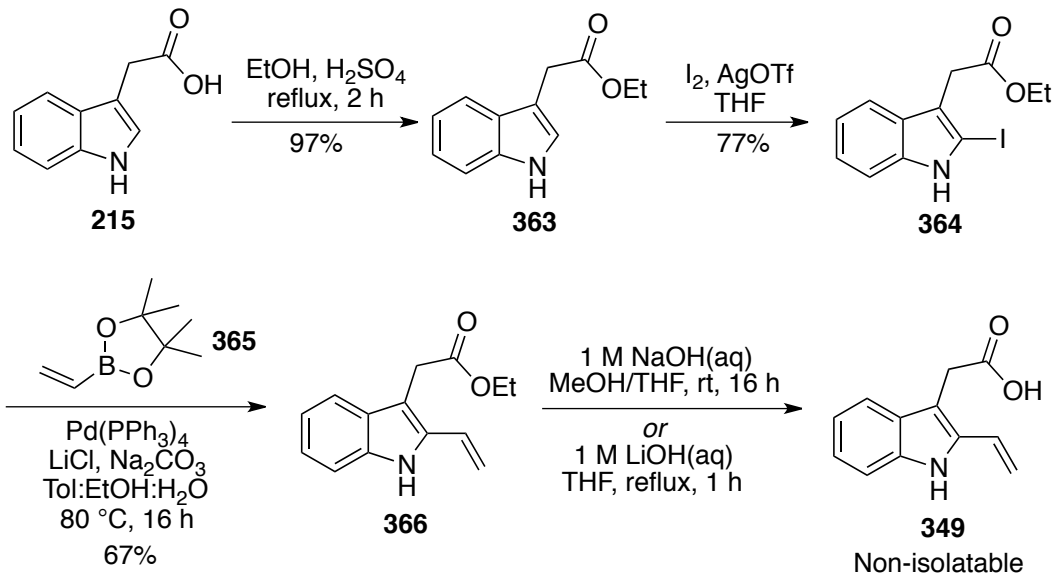


Figure 4.2 – Structure of target indole and imine compounds

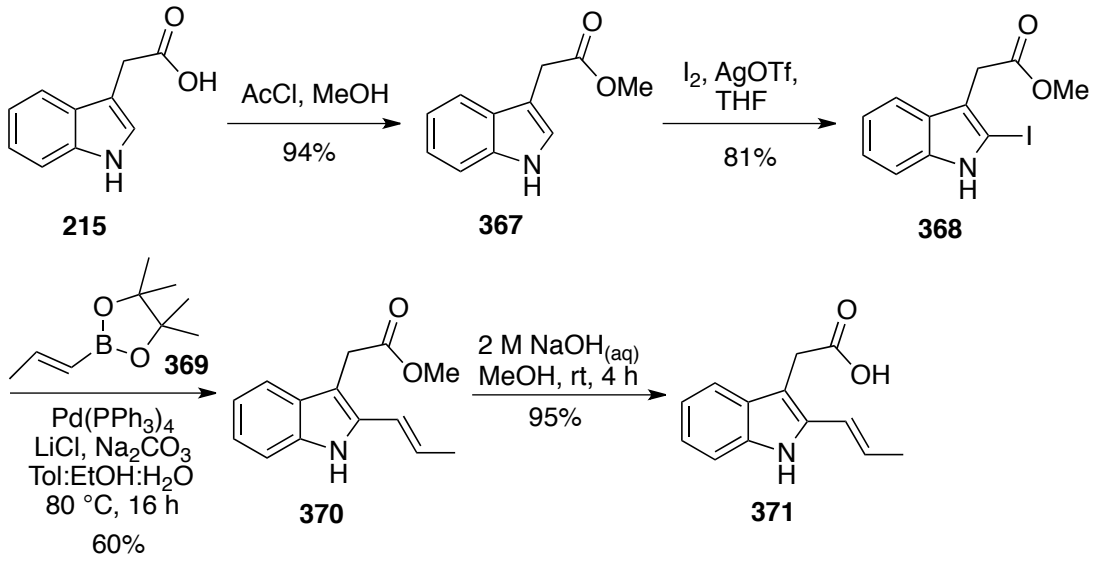
4.3.2. Synthesis of Indole Acid Components

Synthesis of the 2-vinyl substituted indole acid **349** began with the commercially available 3-indole acetic acid **215**, which was esterified to give indole **363** in 97% yield. An iodo group was introduced in the 2-position *via* an iodination procedure to give the 2-iodinated indole **364** in 77% yield.[174] A subsequent Suzuki reaction with vinyl boronic acid pinacol ester **365** installed the vinyl group at the 2-position to give product **366** in 67% yield.[113] Hydrolysis of this ester **366** proved more challenging than expected; difficulties in the purification and isolation of the product meant that the acid **349** could not be isolated. It was thought that polymerisation of this acid **349** was the main issue, as a plastic-like residue was often produced (Scheme 4.12).



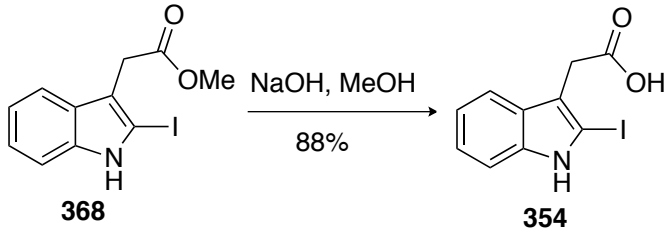
Scheme 4.12 – Attempted synthesis of vinyl substituted indole 349

It was thought that the synthesis of a methyl-substituted vinyl group in the 2-position could inhibit any polymerisation reactions and make isolation of the product easier and need not affect the planned ring-closing metathesis, as this group would be removed in the reaction. The synthesis of indole acid **371** began with esterification of the commericially available 3-indole acetic acid **215** to give the methyl ester **367**. A subsequent iodination reaction gave iodo indole **368** in 81% yield. The desired ester **370** was efficiently synthesised *via* a Suzuki reaction with iodinated methyl ester **368** and 1-propenyl boronic acid pinacol ester **369**. Pleasingly, a subsequent hydrolysis gave acid **371** in 95% yield as a stable solid product (Scheme 4.13).



Scheme 4.13 – Synthesis of a substituted alkene indole acid 371

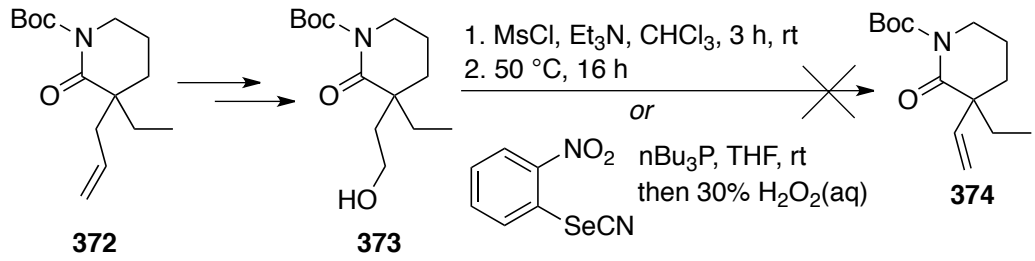
Iodo acid **254** was synthesised from the iodinated indole ester **368** (Scheme 4.14). It was found that ester **368** is unstable upon standing in air and it decomposed after ~72 h. Hydrolysis of ester **368** was achieved using 2 M NaOH in MeOH,[175] to give acid **254** in 88% yield, but careful acidification was required in the work-up. If the solution was taken to pH 1 formation of a brown oil was observed, which was believed to be the oxindole product from characteristic ^{1}H NMR spectroscopic signals. However, careful acidification to pH 4-5 resulted in formation of a white precipitate, which upon isolation was confirmed to be the desired product **354**. This acid was found to be very unstable and would decompose to the suspected oxindole product after ~24 h. Therefore, it is important that iodo acid **354** is synthesised fresh, just before use in the subsequent DIA reactions.



Scheme 4.14 – Synthesis of 2-iodo substituted indole acid 354

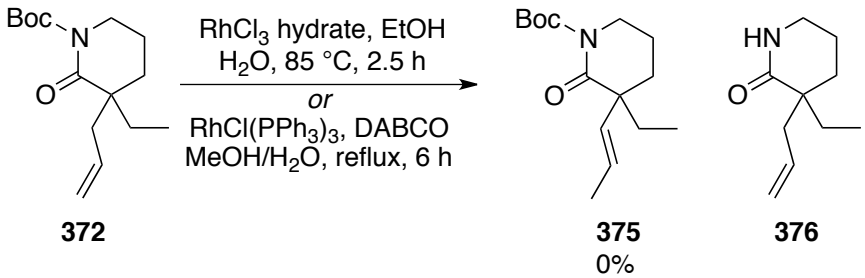
4.3.3. Work Towards Synthesis of the Imine Component

A route for the synthesis of vinyl-substituted imine **351** was investigated next. In a previous approach, the Taylor group synthesised allyl ethyl lactam **372**. The allyl group was then cleaved and converted into alcohol **373** *via* ozonolysis of the alkene and subsequent reduction.* With this alcohol available in the group, two elimination reactions to give vinyl lactam **374** were explored. Mesylation of alcohol **373**, followed by heating the reaction mixture at 50 °C overnight was unsuccessful; analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture clearly showed only starting material (Scheme 4.15). An alternative dehydration reaction was also attempted on the alcohol **373** using Grieco's conditions,[173,176] but only alcohol **373** and tributylphosphine were observed in the ^{1}H NMR spectrum of the unpurified reaction mixture (Scheme 4.15). Therefore, an alternative route towards the vinyl substituted imine **351** was considered.



Scheme 4.15 – Attempted elimination reactions of alcohol 373*

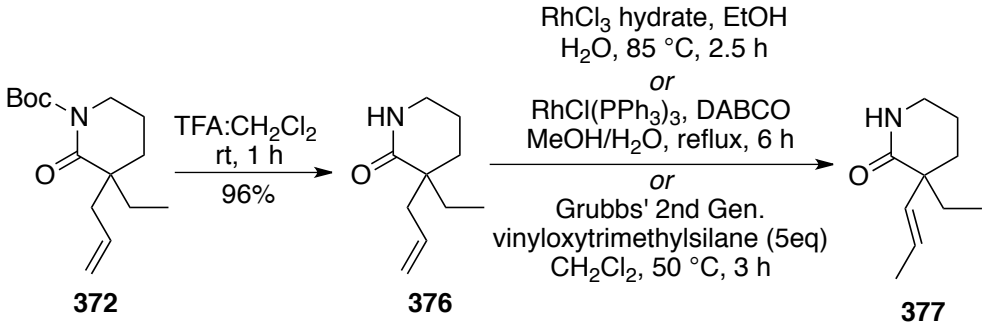
Next, we investigated whether it was possible to access the substituted alkene compound **375** *via* an isomerisation reaction. $RhCl_3$ hydrate and Wilkinson's catalyst (Scheme 4.16) were both attempted but the Boc-deprotected starting material **376** was observed in both cases.[177,178]



Scheme 4.16 – Attempted isomerisation of allyl 372

* Synthesis of **372** and **373** carried out by Dr. Graeme Coultard and Dr. William Unsworth in the Taylor group.

It was considered that the isomerisation reaction may proceed if the Boc group was removed, which was carried out with TFA in CH_2Cl_2 to give lactam **376** in 96% yield (Scheme 4.17). $RhCl_3$ hydrate[177] and Wilkinson's catalyst[178] were used again on the Boc-deprotected compound **376** but analysis of the ^1H NMR spectrum of the unpurified reaction mixture contained mainly starting material by ^1H NMR spectroscopy. Some potential product-like peaks were present at ~5.5 ppm which could be due to the internal alkene signals. The reactions were not purified as they were performed on a small scale and contained mainly starting material (Scheme 4.17).



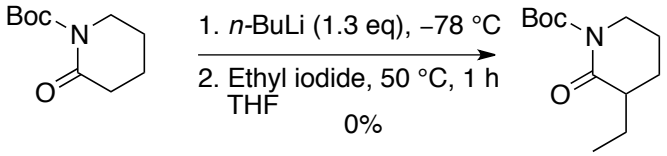
372 **376** **377**

Scheme 4.17 – Boc-deprotection of lactam 372 and attempted isomerisation

Nishida *et al.* had shown that the reaction of Grubbs' 2nd generation catalyst in the presence of vinyloxytrimethylsilane results in an isomerisation reaction of terminal alkenes to the corresponding internal alkene.[179] The group used varying equivalents of the vinyloxytrimethylsilane and showed that 10 equivalents were occasionally necessary for a quantitative reaction, but also showed that 1 equivalent was sufficient in some cases. In our case, 5 equivalents were used (Scheme 4.17) but analysis of the of the ^1H NMR spectrum of the unpurified reaction mixture showed mainly starting material with some very small potential product signals at ~5.5 ppm.

These results suggest that isomerisation is possible on the unprotected lactam **376**, and future work could involve reaction of the lactam **376** with $RhCl_3$ hydrate for a longer reaction time to determine if the reaction would proceed further. However, as more promising routes were being developed simultaneously, this strategy was not investigated any further in this project.

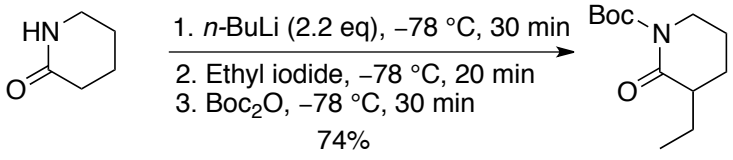
In the proposed routes, two imines **351** and **358** were targeted as substrates so a common intermediate for their synthesis was desired (Figure 4.2). Imine **351** contains an alkene and imine **358** contains an alkyne, so an aldehyde intermediate would be useful as this can be transformed into each of these functional groups in one step. Initially, efforts were focussed on the best way to introduce an ethyl group, beginning with enolate formation of lactam **288** with *n*-BuLi followed by alkylation with ethyl iodide (Scheme 4.18). However, analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture indicated a complex mixture of products and upon attempted purification by column chromatography none of the desired product **378** was obtained.



288 **378**

Scheme 4.18 – Attempted alkylation of lactam 288

The alkylation reaction was then attempted on the unprotected lactam **379** by formation of the dianion, followed by alkylation and subsequent protection of the amide.[180] Pleasingly, under the conditions shown in Scheme 4.19, the ethyl-substituted lactam **378** was isolated in 74% yield. It was found that the reaction yield decreased to 13% yield if the ethyl iodide was stirred for 2 h rather than 20 min.

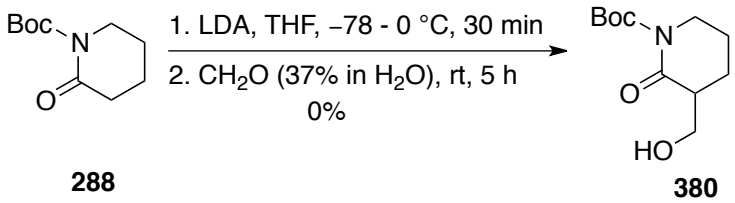


379 **378**

Scheme 4.19 – Ethyl alkylation of unprotected lactam 288

Investigations to determine the best way to generate the aldehyde group were then explored. Installation of an alcohol group was initially attempted by formation of the enolate with LDA (formed *in situ*) followed by addition of formaldehyde as reported in the literature (Scheme 4.20).[181] However, analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture showed a complex mixture of products that upon purification by column chromatography gave none of the desired product **380**. The reaction was attempted using paraformaldehyde as the electrophile, but the reaction was

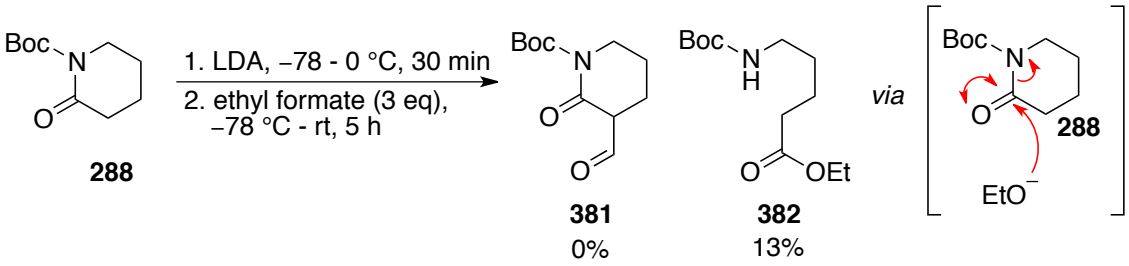
unsuccessful and analysis of the unpurified reaction mixture by mass spectrometry showed no signal for the $[M + H]^+$ ion.



288 **380**

Scheme 4.20 – Attempted addition of an alcohol group to lactam 288

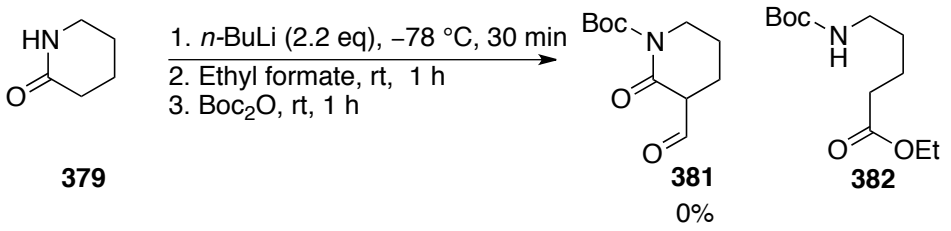
Ethyl formate was selected as an alternative electrophile, as it would allow the aldehyde to be installed directly. The lactam **288** was reacted with LDA to form the enolate and ethyl formate was added to the reaction mixture and stirred overnight (Scheme 4.21).[182] Purification by column chromatography gave **382** in 13% yield, which would most likely be formed by reaction of an ethoxide with the lactam **288** and ring-opening (Scheme 4.12). This suggested that alkylation with ethyl formate must have occurred in order to release the ethoxide, but none of the desired aldehyde **381** could be isolated. A mixture of other products were also observed but could not be identified, suggesting that this reaction is not selective for one product.



288 **381** 0% **382** 13%

Scheme 4.21 – Attempted direct installation of an aldehyde

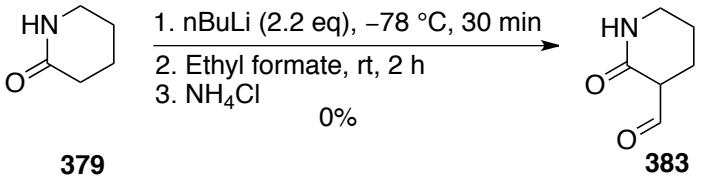
The ring-opening of **288** by ethoxide is made possible by the attached electron-withdrawing Boc group. Therefore, addition of the electrophile to the unprotected amide enolate was attempted. The commercially available lactam **379** was reacted with two equivalents of *n*-BuLi to generate the dianion, followed by addition of ethyl formate and then Boc_2O (Scheme 4.22). Unfortunately, ester **382** was observed in the crude reaction mixture by ^1H NMR spectroscopy and this was confirmed by mass spectrometry.



379 **381** 0% **382**

Scheme 4.22 – Attempted installation of an aldehyde to unprotected lactam 379

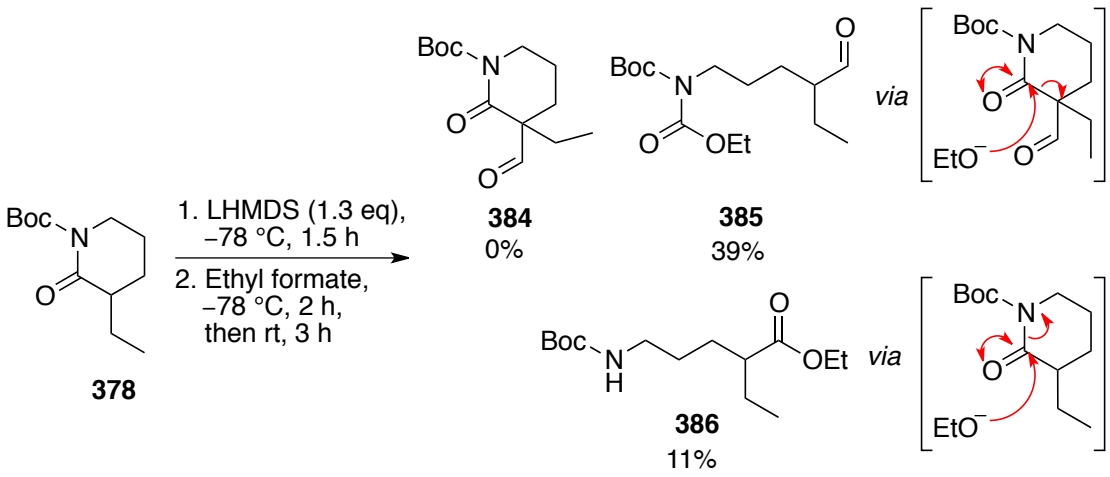
This result suggested that the remaining ethoxide needed to be quenched before protection of the amide to remove it from the reaction mixture and reduce reaction with the amide. Thus, lactam **379** was reacted with 2 equivalents of *n*-BuLi and then ethyl formate was added. Following this, the reaction was quenched with saturated $NH_4Cl_{(aq)}$. Analysis of the crude reaction mixture by ^1H NMR spectroscopy indicated that none of product **383** was present (Scheme 4.23).



379 **383**

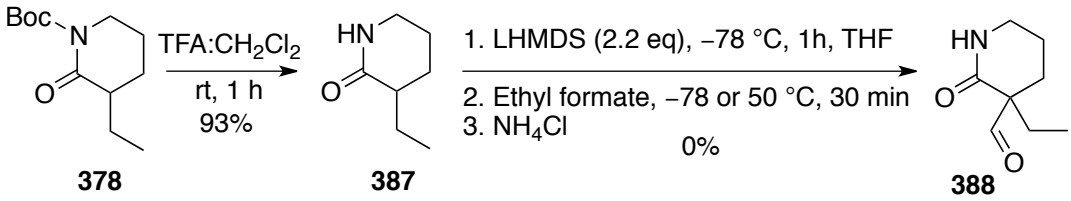
Scheme 4.23 – Attempted addition of aldehyde onto unprotected lactam 379

It was thought that the problems of introducing the alcohol or aldehyde into the α-position of the lactam ring were due to the mono-substitution at the α-position. Alcohol **380** could be susceptible to elimination reactions and aldehyde **381** could undergo tautomerisation, which would result in either the formation of incorrect products or difficulty in introducing a second group in this position. Therefore, the introduction of the aldehyde group was attempted after the ethyl group had been installed (Scheme 4.24). Following similar conditions (LHMDS) for reaction with ethyl formate, none of the desired product **384** was isolated after purification by column chromatography. Instead, a ring-opened product **385** was isolated in 39% yield, which would be made *via* formation of the desired product **384** followed by attack of the ethoxide into the amide carbonyl and ring-opening onto the α-carbon to form a stabilised anion that is quenched in the aqueous work-up. Another product **386** was also isolated in 11% yield, formed by attack of the ethoxide onto the starting material and ring-opening onto the nitrogen (Scheme 4.24).



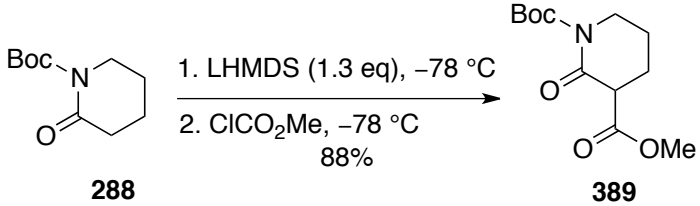
Scheme 4.24 – Reaction of ethyl-substituted lactam 378 with ethyl formate

The formation of product **385** shows that ethyl formate can install the aldehyde functional group (Scheme 4.24). To decrease the chance of ring-opening, a reaction with unprotected lactam **387** was undertaken. The Boc group was removed from the ethyl substituted lactam **378** by stirring in TFA:CH_2Cl_2 to give the lactam **387** in 93% yield (Scheme 4.25).[183] Formation of the enolate and addition of ethyl formate at −78 °C gave no product **388** (Scheme 4.25). The reaction was repeated at 50 °C but analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture indicated no product formation.



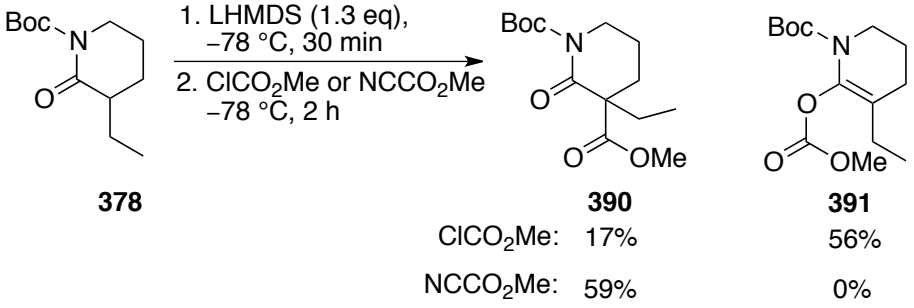
Scheme 4.25 – Attempted addition of aldehyde onto unprotected lactam 387

After these unsuccessful attempts to directly install the aldehyde using ethyl formate, an alternative route *via* an ester was attempted. Cossy *et al.* had shown that Boc-protected lactam **288** could be reacted with LHMDS to form the enolate, followed by addition of methylchloroformate. These conditions were repeated to obtain **389** in 88% yield.[184]



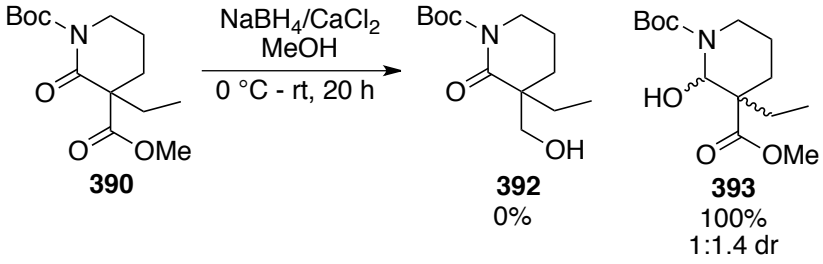
Scheme 4.26 – Synthesis of ester-substituted lactam 389

The same conditions were attempted on the ethyl-substituted lactam **378** and following purification by column chromatography, two products were isolated (Scheme 4.27). The desired product **390** was obtained in a 17% yield, but the major product of the reaction was the oxygen-acylated product **391** that was isolated in 56% yield. The reaction was repeated using Mander's reagent (methyl cyanoformate) and pleasingly the ester-substituted product **390** was isolated in a 59% yield (Scheme 4.27).



Scheme 4.27 – Synthesis of ester substituted lactam 390

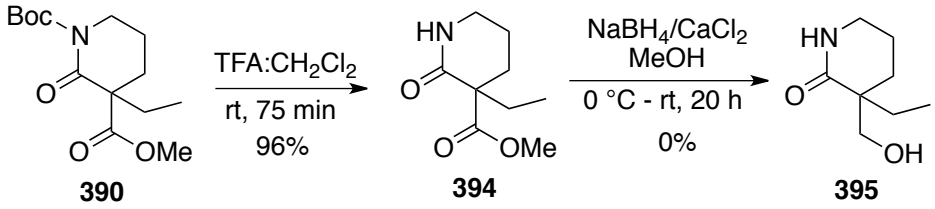
With the ester and ethyl groups successfully installed on the lactam ring, the conversion of the ester into an aldehyde became the next priority. Initially, it was thought that the ester could be reduced to an alcohol and subsequent oxidation would provide the aldehyde. Loreto had shown that an ester on an analogous lactam compound could be efficiently reduced using calcium tetrahydridoborate, prepared *in situ* by stirring $NaBH_4$ and $CaCl_2$ together.[185] Lactam **390** was subjected to these conditions but none of the desired reduced product **392** was observed (Scheme 4.28). Instead, the amide had been reduced to give the hemiaminal **393** in quantitative yield (1:1.4 dr), which required no purification following work-up.



Scheme 4.28 – Attempted reduction of ester 390

Presumably, the Boc group was promoting reduction of the amide rather than the ester. Therefore, it was hoped that if the Boc group was removed, the desired reduction of the ester would occur, as the $CaBH_4$ should not be reactive enough to reduce the amide.

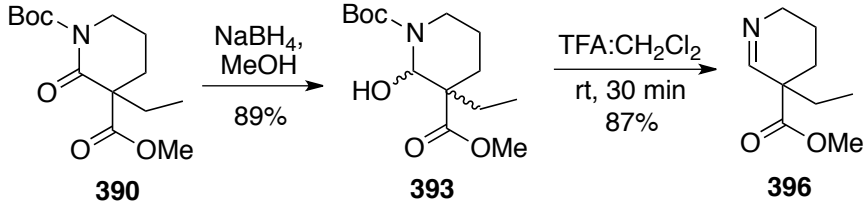
Removal of the Boc group proceeded efficiently to give lactam **394** in 96% yield, but subsequent reduction with the previously employed $CaBH_4$ conditions resulted in no reaction and starting material was observed (Scheme 4.29).



390 **394** **395**

Scheme 4.29 – Attempted reduction of the ester group on unprotected lactam 394

It was realised that it should be possible to convert hemiaminal **393** into imine **396** by reaction with TFA *via* removal of the Boc group and elimination. The reduction of lactam **390** to hemiaminal **393** was also attempted using $NaBH_4$, rather than $CaBH_4$, and hemiaminal was isolated in 89% yield (Scheme 4.30). The unpurified reaction mixture was sufficiently clean to be taken onto the subsequent reaction. Reaction of hemiaminal **393** in TFA:CH_2Cl_2 provided the imine **396** in 87% crude yield (Scheme 4.30). The product was sufficiently clean without additional purification but was seen to decompose over time. In a repeat reaction, purification by column chromatography gave imine **396** in a 47% yield. It was concluded that it is better to use these imines promptly after isolation without chromatography. It was planned that this imine could also be trialled in the DIA spirocyclisation step with indoles **354** and **371** to synthesise a different spirocyclic intermediate.

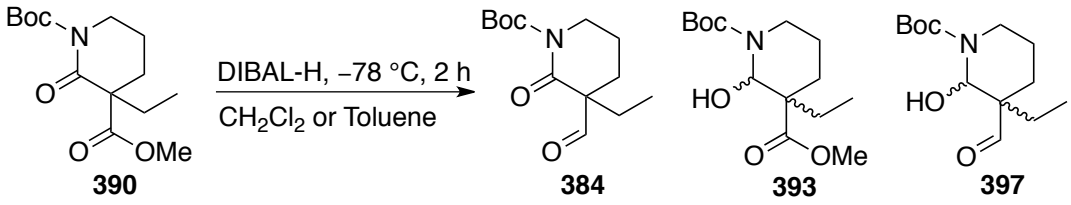


390 **393** **396**

Scheme 4.30 – Synthesis of ester-substituted cyclic imine 396

Alternative conditions were then investigated for the reduction of the ester-substituted lactam **390**. DIBAL reduction of the ester was attempted to determine if it could be directly reduced to the aldehyde (Scheme 4.31). Lactam **390** was reacted with DIBAL at −78 °C for 2 h in CH_2Cl_2 and the ^{1}H NMR spectrum of the unpurified reaction mixture indicated product-like signals in the aldehyde region. Attempted purification by column chromatography was unable to completely separate the products of the reaction but

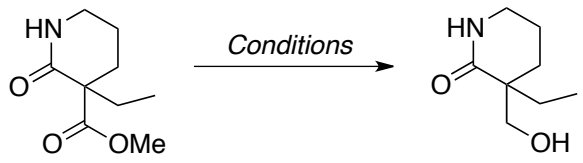
assisted in confirming that hemiaminal **393** was the main product of the reaction. The suggested aldehyde products **384** and **397** are possible structures that could explain the presence of aldehyde peaks in the ^{1}H NMR spectrum, but the open chain form of these structures could also be present providing an alternative explanation for the observed aldehyde signals. The reaction was repeated in toluene and a similar result was observed. Considering the capricious nature of DIBAL as a reducing reagent, these conditions were not explored further.



390 **384** **393** **397**

Scheme 4.31 – Attempted DIBAL reduction of ester 390

Other reduction conditions were carried out on the unprotected amide **394** to reduce the likelihood of the amide being reduced to the hemiaminal (Table 4.1). Reduction with $LiBH_4$ initially resulted in a 50% yield of alcohol **395** but this result was not reproducible and only 28% yield was achieved on a larger scale (Entry 1). Reduction with the bulkier base $LiAlH(O^tBu)_3$ required 4 equivalents of the base and heating to 60 °C to give a 45% yield of the alcohol **395** (Entries 2 and 3).[186] Kim *et al.* had shown that an analogous ester compound could be reduced under Luche conditions.[187,188] Ester **394** was initially heated with $NaBH_4$ and $CeCl_3$ but analysis of the crude reaction mixture by ^{1}H NMR spectroscopy and TLC showed formation of the product and other byproducts (Entry 4). Stirring the reaction at rt for 2.5 days resulted in much cleaner conversion but analysis of the crude reaction mixture showed a 1:2.2 ratio of ester **394** and alcohol **395** (Entry 5).[187]



394 **395**

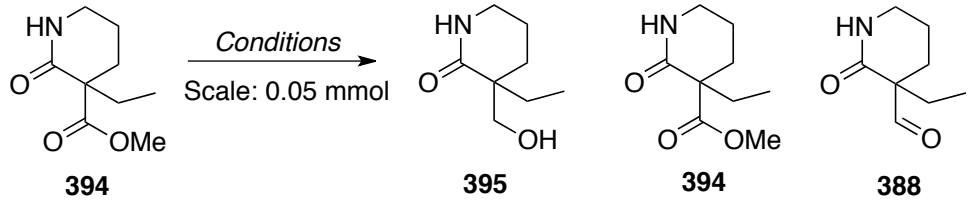
Entry	Conditions	Alcohol 395	Ester 394
1	$LiBH_4$, 0 °C-rt, 2 h	50% - 0.19 mmol 28% - 3.76 mmol	-
2	$LiAlH(O^tBu)_3$ (2 eq), THF, 0 °C-rt	-	-[a]
3	$LiAlH(O^tBu)_3$ (2 eq), THF, 60 °C, 20 h, then $LiAlH(O^tBu)_3$ (2 eq), 60 °C, 3 days	45%	-
4	$NaBH_4/CeCl_3$, EtOH, reflux, 3 h	-[a]	-
5	$NaBH_4/CeCl_3$, EtOH, rt, 2.5 days	2.2[b]	1[a]

[a)] Analysis of the ^1H NMR spectrum of the unpurified reaction mixture showed the product present. [b)] Ratio of products from ^1H NMR spectrum of crude reaction mixture.

Table 4.1 – Reduction of ester 394 to alcohol 395

$LiAlH_4$ was then explored at low temperature to avoid amide reduction. Initially, 3 equivalents of $LiAlH_4$ were added to ester **394** in THF at −78 °C and stirred for 1 h. Surprisingly, the ^1H NMR spectrum of the crude reaction mixture indicated that aldehyde **388** was the major product rather than the expected alcohol **395**. This reaction gave a 1:2.7:4.7 ratio of alcohol **395**, ester **394** and aldehyde **388** respectively (Table 4.2, Entry 1). The diagnostic peaks for the aldehyde **388**, ester **394** and alcohol **395** were a doublet at 9.62 ppm for the aldehyde proton, a singlet at 3.71 ppm for the methyl group of the ester and two doublets at 3.51 ppm for the diastereomeric CH_2 protons adjacent to the OH respectively. Formation of the aldehyde was thought to be due to a chelation effect between the oxygen on the amide and the oxygen of the aldehyde forming a stable tetrahedral intermediate that would be quenched upon work-up. Further experiments were conducted to determine if the ratio of starting material to product could be improved (Table 4.2). A solvent swap to Et_2O resulted in a better conversion of the starting material to the aldehyde (Entry 5). It was observed that increasing the reaction temperature to 0 °C resulted in significantly more alcohol **395** than aldehyde

388 (Entries 3 and 7). It was found that reaction at −40 °C in Et_2O gave a 10:1:9 ratio of alcohol **395** to ester **394** to aldehyde **388** (Entry 8).



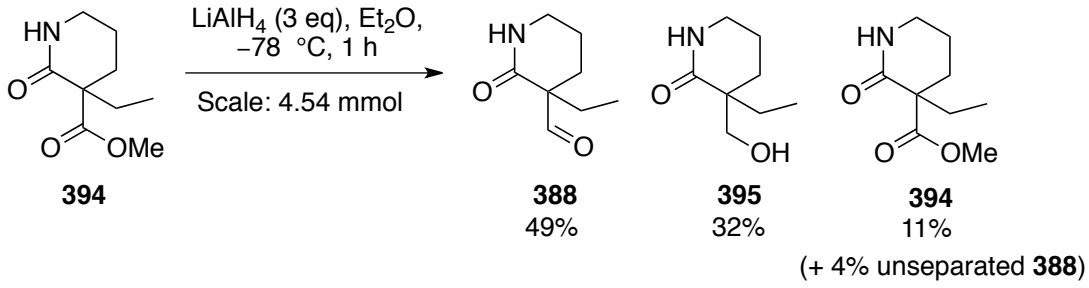
394 **395** **394** **388**

Entry	Conditions	Ratio of products[a]		
		Alcohol 395	Ester 394	Aldehyde 388
1	$LiAlH_4$ (3 eq), THF, -78 °C, 1 h	1	2.7	4.7
2	$LiAlH_4$ (3 eq), THF, -78 °C, 2 h	1	2.1	3.6
3	$LiAlH_4$ (3 eq), THF, 0 °C, 1 h	3.2	1	1.8
4	$LiAlH_4$ (6 eq), THF, -78 °C, 1 h	1	2.5	3.7
5	$LiAlH_4$ (3 eq), Et_2O, -78 °C, 1 h	1	1.2	4.1
6	$LiAlH_4$ (3 eq), Et_2O, - 78 °C, 3 h	1	2.9	4.4
7	$LiAlH_4$ (3 eq), Et_2O, 0 °C, 1 h	20	1	1.8
8	$LiAlH_4$ (3 eq), Et_2O, - 40 °C, 1 h	10	1	9

[a)] Ratio determined by ^1H NMR spectroscopy of the unpurified reaction mixture.

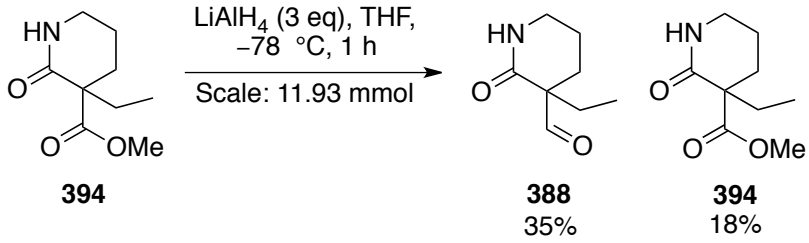
Table 4.2 – $LiAlH_4$ reduction of ester 394

It was initially thought that the best conditions to take forward were $LiAlH_4$ (3 eq) in Et_2O at −78 °C for 1 h (Entry 5), in order to get the most aldehyde **388** out of the reaction, and recycle the recovered starting material. These conditions were therefore repeated on a larger scale (4.54 mmol) and the crude mixture was purified by column chromatography to provide the aldehyde **388**, alcohol **395** and recovered ester **394** in 49%, 32% and 11% respectively (Scheme 4.32).



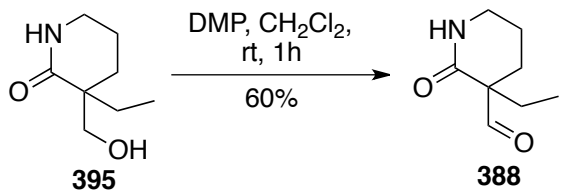
Scheme 4.32 – $LiAlH_4$ reduction of ester 394

Whilst isolating 49% of the aldehyde **388** was a useful result, a significant amount of alcohol **395** was also isolated possibly from the exotherm of the larger scale reaction increasing the reaction temperature and increasing the double reduction reaction. As a comparison with the reaction in Et_2O, the reaction was carried out in THF on a larger scale and 35% of aldehyde **388** was isolated (Scheme 4.33). However, the starting material was recovered in an 18% yield showing that this reaction was less efficient than in Et_2O. Poor recovery of the unpurified material was also a problem, indicating that a more efficient work-up procedure was required.



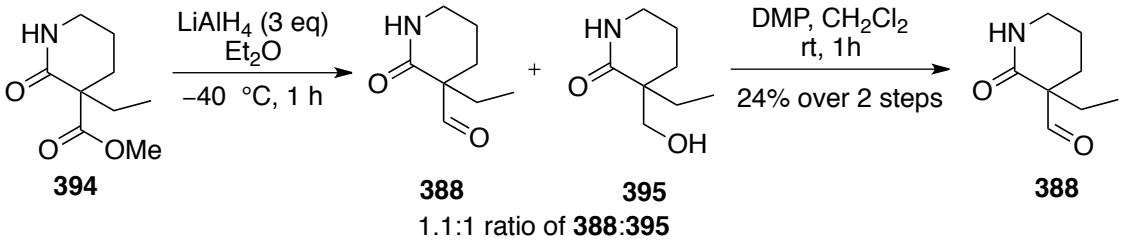
Scheme 4.33 – $LiAlH_4$ reduction of ester 394

It was then considered that better conditions to select would be reaction with $LiAlH_4$ (3 eq) in Et_2O at −40 °C for 1 h as this maximised conversion of the starting material to either aldehyde **388** or alcohol **395** but ensures that aldehyde **388** would be the main product. It was shown that the alcohol **395** could be directly oxidised to the aldehyde **388** in 60% yield using DMP (Scheme 4.34).[189]



Scheme 4.34 – Synthesis of aldehyde 388 *via* oxidation of alcohol 395

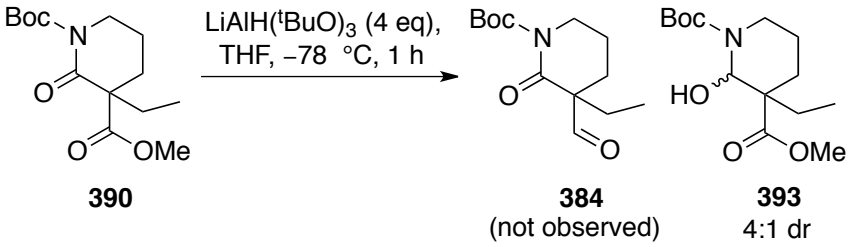
With this in mind, it was thought that the ester **394** could first be reduced to a mixture of aldehyde **388** and alcohol **395**, then separated by column chromatography and the alcohol **395** subsequently oxidised to give aldehyde **388**. Alternatively, following reduction of the ester **395**, the crude reaction mixture could be subjected to DMP oxidation conditions to convert the alcohol **395** into aldehyde **388** in a two-step process. Attempting to access the aldehyde **388** in this two-step process gave the product in a 24% yield, which was no improvement on partial reduction of the starting material using the conditions shown in Scheme 4.32 where the aldehyde was directly obtained in 49% yield.



Scheme 4.35 – Synthesis of the aldehyde 388 *via* reduction of the ester 394 and oxidation of the crude mixture

It should be noted that the inconsistency observed in the yields of the $LiAlH_4$ reduction reactions is likely to be due to the difficulties associated with the work-up, as the crude reaction mixtures were seen to be very clean by ^1H NMR spectroscopy. Use of Rochelle's salt to try and break down the metal-chelated products was attempted but recovery of the reaction material following aqueous work-up was variable. The ^1H NMR spectrum for the unpurified reaction mixture of the DMP oxidation also showed good conversion to the desired product, suggesting that this two-step process could be efficient if the work-up procedures were further optimised.

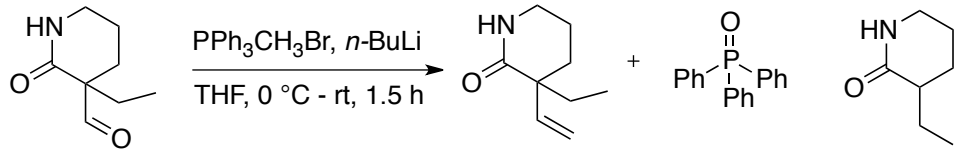
Reduction of the Boc-protected lactam **390** was also attempted using the bulkier base, $LiAlH(^tBuO)_3$, to determine if the added steric bulk would prevent reduction of the amide to the hemiaminal and give aldehyde **384** through the chelating effect observed with $LiAlH_4$. However, reaction of Boc-protected lactam **390** with $LiAlH(^tBuO)_3$ in THF at −78 °C for 1 h resulted in the formation of hemiaminal **393** in a 1:4 dr (Scheme 4.36), although the products were not isolated and so yields are not given. This confirmed the need for deprotection of the amide before reduction of the ester.



390 **384** (not observed) **393** 4:1 dr

Scheme 4.36 – Attempted reduction of the Boc-protected lactam 390

To progress the synthesis of the imine, conversion of the aldehyde to the alkene was achieved using Wittig conditions.[190] The ylide was initially formed *in situ* by adding *n*-BuLi to the phosphonium bromide salt, and the aldehyde was subsequently added. Upon column chromatography, the triphenylphosphine oxide byproduct **398** was inseparable from the alkene **397** so a yield was calculated from the ratios of the signals in the ^{1}H NMR spectrum and the masses of the known components. On a small scale, a 32% yield of alkene **397** was calculated (Table 4.3, Entry 1). Unfortunately, upon scaling up the reaction the yield of the alkene continued to decrease and the ethyl-substituted lactam **387** was isolated in 89% yield, which was likely formed as a result of a retro-Claisen condensation (Table 4.3).



388 **397** **398** **387**

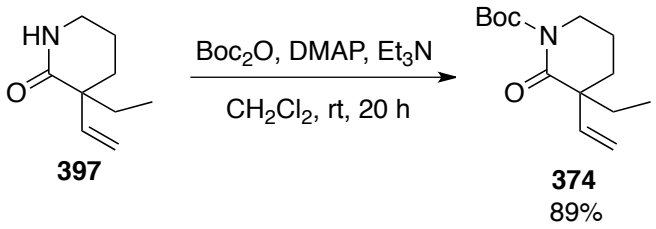
Entry	Scale	Yield 397 (%)[a]	Yield 387 (%)[a]
1	0.56 mmol	32	-
2	2.96 mmol	22	-
3	4.57 mmol	13	89

[a)] Yield based on ratio of signals of alkene **397** and triphenylphosphine oxide **398** in ^{1}H NMR spectrum of the isolated product.

Table 4.3 – Synthesis of alkene 397 *via* a Wittig reaction

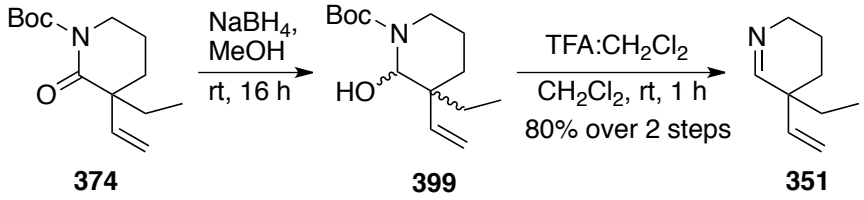
It was therefore decided to reintroduce the Boc group onto the amide as it was required in the imine formation step. Protection of the amide with a Boc group could be done with the triphenylphosphine oxide impurity present, and introduction of the protecting

group allowed separation by column chromatography giving the clean product **374**. Initially, the reaction conditions shown in Scheme 4.37 were carried out for 4 h and the product **374** was isolated in a 35% yield. A 47% yield of recovered starting material **397** was also isolated along with inseparable triphenylphosphine oxide. The reaction was difficult to monitor by TLC as the starting material and triphenylphosphine have the same R_F values so only product formation can be observed. Therefore the unreacted starting material was resubjected to the protection conditions and stirred overnight to give the product **374** in 89% yield (Scheme 4.37).[191]



Scheme 4.37 – Boc protection of lactam 397

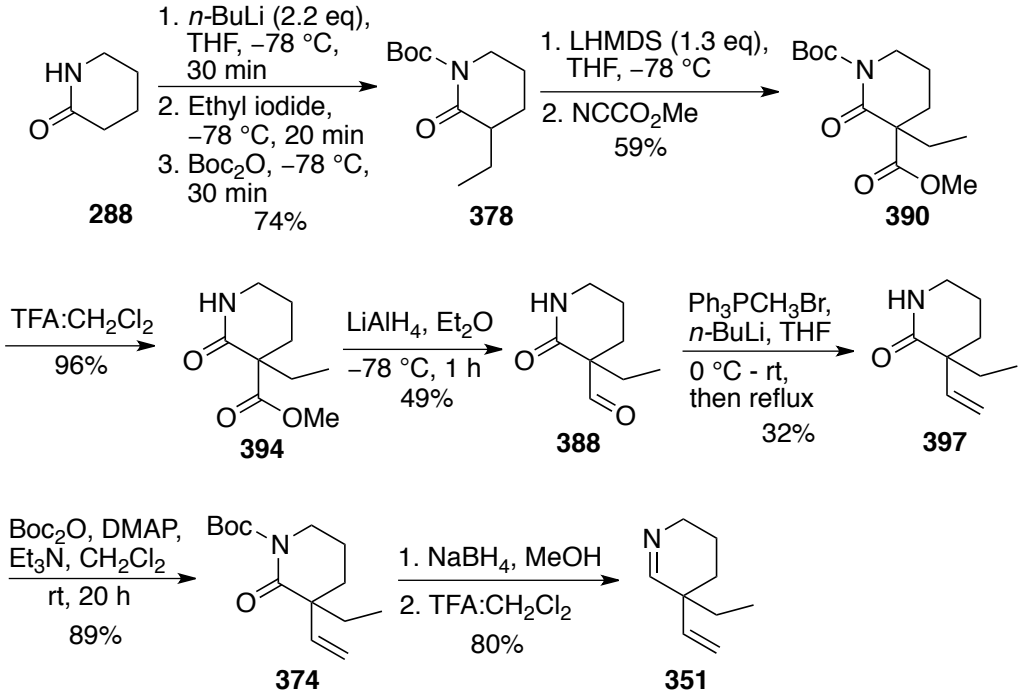
The same procedure as used previously (Scheme 4.30) was then used to convert Boc-protected amide **374** into imine **351**. Amide **374** was reduced to the hemiaminal with $NaBH_4$ and the unpurified reaction mixture was reacted with TFA in CH_2Cl_2 to deprotect the nitrogen and promote the elimination to the imine so that imine **351** was isolated in 80% yield over 2 steps (Scheme 4.38). The unpurified imine was sufficiently clean for use in the subsequent reaction, but was seen to decompose reasonably quickly. Upon attempted purification by column chromatography, the product could not be isolated and the product was suspected unstable on the silica and was also volatile.



Scheme 4.38 – Synthesis of vinyl substituted imine 399

The culmination of these studies towards the synthesis of imine **351** is shown in Scheme 4.39. This is currently the most advanced route towards this substrate and provides imine **351** in an overall yield of 4.7% in 7 steps. The starting lactam is commercially available and inexpensive. Alternatively, if a DIA reaction could be successfully performed using ester imine **396**, this will significantly reduce the number of steps

needed to access the imine substrate. However, this would require more functional group transformations to be performed on the spirocyclic compound, which could potentially be difficult due to the increased steric bulk.

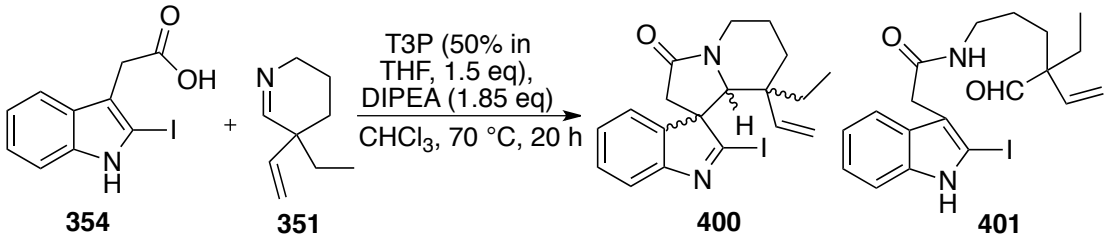


Scheme 4.39 – Synthesis of vinyl-substituted imine 351

4.3.4. Investigations into the DIA Spirocyclisation Step in the Synthesis of Aspidospermidine

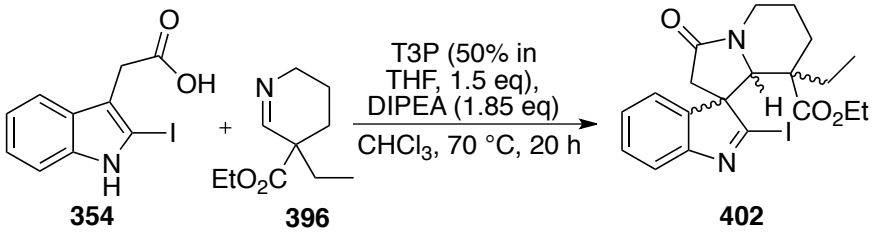
Having successfully synthesised iodo indole acid **354**, vinyl indole acid **371** and imines **351** and **396**, preliminary DIA spirocyclisation reactions were attempted. Initially, iodo indole acid **354** was reacted with imine **351** under the optimised DIA conditions (THF at rt) but the reaction did not go to completion. Reaction of the iodo indole **354** and imine **351** at 70 °C in $CHCl_3$ for 20 h (Scheme 4.40) was more promising. Analysis of the ^1H NMR spectrum of the unpurified reaction mixture indicated the presence of aldehyde **401** (singlet at 9.26 ppm), produced by hydrolysis of the *N*-acyliminium ion in the work-up, but some promising product-like peaks were also observed in the alkene region (e.g. multiplets at 5.64-5.56, 5.32-5.25 and 5.04-5.00 ppm). It was considered that the reaction could appear unclean due to the formation of four possible diastereoisomers. Purification by column chromatography was attempted but due to the small scale of the

reaction (0.10 mmol), analysis of the fractions was challenging. However, the $[M + Na]^+$ ion for the product **400** was observed in the mass spectrum suggesting successful formation of the product **400**.



Scheme 4.40 – DIA spirocyclisation reaction of indole 354 and imine 351

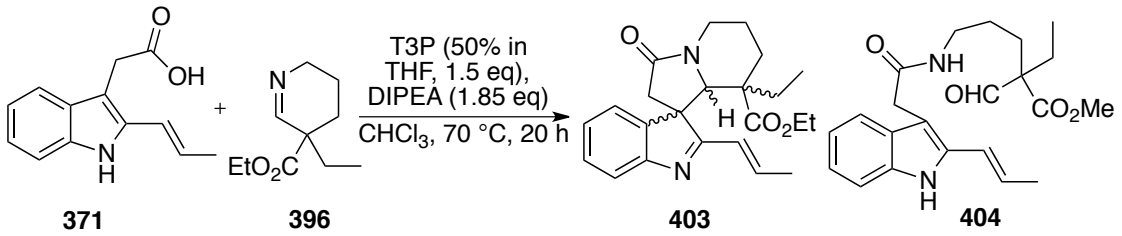
Synthesis of the ester imine **396** had proven much simpler and with more of this imine in hand the DIA spirocyclisation reactions were performed using this substrate. The iodo indole acid **354** was reacted with the ester-substituted imine **396** at 70 °C in $CHCl_3$ for 20 h (Scheme 4.41), which resulted in a cleaner ^1H NMR spectrum of the unpurified reaction mixture when compared to the reaction with vinyl-substituted imine **351**. Separation of the suspected diastereoisomers proved challenging by column chromatography and resulted in three different fractions that appeared to contain a mixture of diastereoisomers by ^1H NMR spectroscopy, but lack of material (~6 mg for the combined column fractions) made obtaining a routine ^{13}C NMR spectrum and 2D data difficult. Mass spectrometry analysis suggested the presence of the product **402** in each fraction, although a yield cannot be stated. The ester group in spirocyclic product **402** could in principle be converted into an alkene for a subsequent intramolecular Heck reaction.



Scheme 4.41 – DIA spirocyclisation reaction of indole 354 and imine 397

DIA spirocylisation of the ester imine **396** was also attempted with the methyl-substituted vinyl indole acid **354** in $CHCl_3$ in 70 °C for 20 h (Scheme 4.42). Analysis of the ^1H NMR spectrum of the unpurified reaction mixture suggested the product may have formed but also showed the presence of some aldehyde **404** (singlet at 9.67 ppm)

suggesting the need for more forceful reaction conditions to combat the added steric bulk of the ester and substituted alkene. Purification by column chromatography was attempted to determine if separation of the suspected diastereoisomers was possible. Unfortunately, separation of the individual diastereoisomers by column chromatography was challenging and the products could not be fully characterised, despite obtaining slightly more material for each fraction (~14 mg). Mass spectrometry analysis suggested the presence of the product **403** in each fraction, but a yield is not given. Conversion of the ester group into an alkene in the spirocyclic product **403** could provide the dialkene for a ring-closing metathesis reaction.



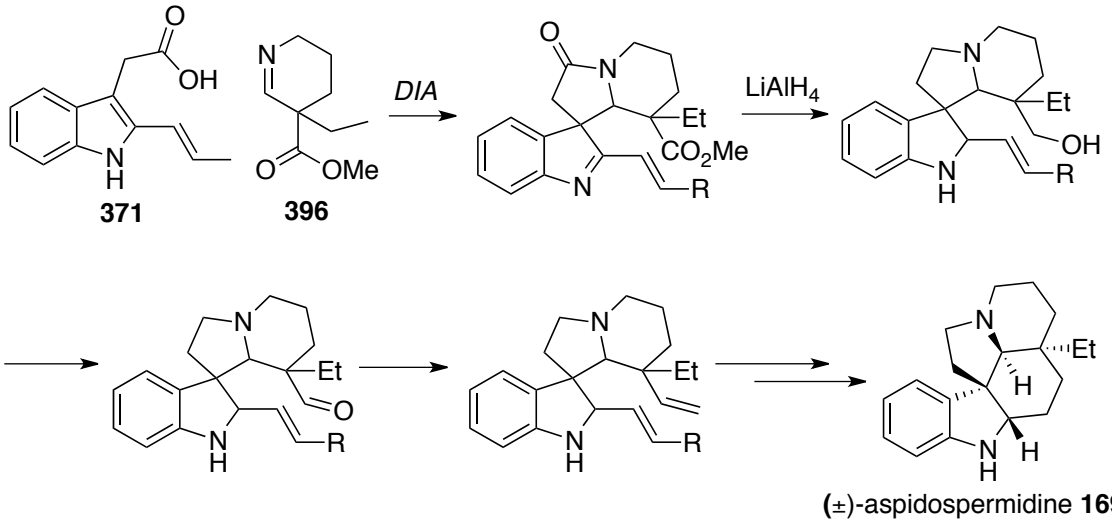
Scheme 4.42 – DIA spirocyclisation reaction of indole 371 and imine 396

Overall, the preliminary investigations into the key DIA spirocyclisation reactions were very promising. The reactions could only be conducted on a small scale (~0.10 mmol) due to the difficulty in synthesising the required imine substrates, but analysis of the reactions by mass spectrometry and ^{1}H NMR spectroscopy indicated the formation of products. It is anticipated that performing these reactions on a larger scale would result in successful formation of the desired spirocyclic products and allow separation of the diastereoisomers.

4.4. Conclusions and Future Work

Work towards the synthesis of (±)-aspidospermidine using DIA methodology was undertaken and two proposed routes were targeted, including an intramolecular Heck reaction and a ring-closing metathesis reaction. The synthesis of the required iodo indole acid **354** was successfully carried out to give the product in a 67% yield over three steps (Scheme 4.14). Isolation of the vinyl-substituted indole acid **349** was not possible, but this problem was solved by substitution of the vinyl group to prevent any polymerisation. As a result, the methyl-substituted vinyl indole acid **371** could be produced in 53% yield in 4 steps (Scheme 4.13).

Synthesis of the vinyl-substituted imine substrate **351** proved a lot more challenging, and future work should focus on optimisation of this route. An alternative ester imine **396** was also synthesised (Scheme 4.30), which could also be used in the DIA spirocyclisation reaction. Conversion of the ester to the alkene would be necessary to set up a ring-closing metathesis reaction for formation of the 6-membered ring (Scheme 4.43). The benefit of this would be a more efficient synthesis of the required imine.



Scheme 4.43 – Proposed use of imine 396 in the synthesis of aspidospermidine

Despite the challenging synthesis, sufficient amounts of the imines **351** and **396** were obtained to allow preliminary investigations into the key DIA spirocyclisation step. Figure 4.3 shows the structures of the spirocyclic scaffolds that were synthesised using DIA methodology. The test reactions were performed on a relatively small scale (~0.1

mmol), but analysis of the reaction by mass spectrometry and ^{1}H NMR spectroscopy suggested the successful formation of products. Optimisation of the DIA reactions is required, but the preliminary results are promising and suggest that this methodology could be successfully utilised in the synthesis of (±)-aspidospermidine **169**. Product **400** could be used in a subsequent intramolecular Heck reaction to generate the 6-membered ring in the natural product scaffold. Following conversion of the ester to the alkene, product **402** and **403** could be used in an intramolecular Heck or ring-closing metathesis respectively to produce the 6-membered ring.

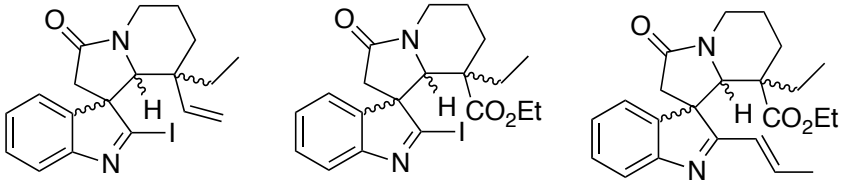


Figure 4.3 – Structures of the spirocycles made using DIA methodology

The DIA reactions also indicated that the ester-substituted imine **397** was a more suitable substrate than vinyl-substituted imine **351**. It was thought that this could be due to the suspected unstable and volatile nature of imine **351**. As with the vinyl-substituted indole acids **349** and **371**, the stability of the imine might be improved by substitution of a methyl group onto the vinyl to give imine **405** (Figure 4.4). As attempted in this project, the substituted vinyl functionality could be accessed by isomerisation of the easily installed allyl group. Further work on the isomerisation conditions could provide a feasible route to this compound.

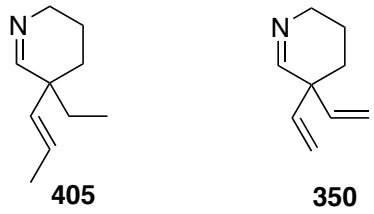


Figure 4.4 – Alternative imines for use in the DIA spirocyclisation reaction

A potential issue with the DIA spirocyclisation reaction was the generation of four possible diastereoisomers. Whilst this was not unexpected, the preliminary investigations of the DIA spirocyclisations suggested a lack of selectivity. A divinyl imine **350** (where R = $H_2C{=}CH_2$) would eliminate the possibility of four

diastereoisomers and could therefore improve the efficiency of the DIA spirocyclisation (Figure 4.4).

In summary, this project has successfully proven that the DIA spirocyclisation methodology can be applied to the synthesis of (±)-aspidospermidine **169**. Whilst the synthesis was not completed, the preliminary investigations into the key DIA reaction were promising and the desired spirocyclic scaffolds were formed. It is believed that with optimisation of the spirocyclisation step, and development of the subsequent reactions, the synthesis of (±)-aspidospermidine **169** could be completed.

5. Experimental

5.1. General Information

Except where stated, all reagents were purchased from commercial sources and used without further purification. Except where stated, all experimental procedures were carried out under an atmosphere of argon. Reactions carried out at room temperature (rt) includes temperatures between 20-25 °C. Anhydrous CH_2Cl_2 and toluene were obtained from an Innovative Inc. PureSolv® solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl immediately before use. Chloroform was used as supplied without additional drying. Petrol refers to the fraction of petroleum ether boiling in the range of 40-60 °C and was purchased in Winchester quantities. Brine refers to a saturated solution. Water is distilled water. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data were acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks, δ_H 7.26 and δ_C 77.0 for $CDCl_3$ and δ_H 2.50 and δ_C 39.5 for DMSO-d6 were used as a reference. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.5 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR two spectrometer as a thin film. Mass-spectra (low and high-resolution) were obtained by the University of York Mass Spectrometry Servive, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-TOF spectrometer. The melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with either basic aqueous potassium permanganate or ethanolic *p*-anisaldehyde as appropriate. Flash column chromatography was carried out using slurry packed silica gel (SiO_2), 35-75 μm particle size, 60 Å pore size, under a light positive pressure, eluting with the specified solvent system. Petrol refers to petroleum ether 40–60 °C. Microwave experiments were carried out using sealed vessels in a CEM Discover microwave reactor with variable power output (0-200 W). Pressure was recorded by the cavity lid, which resisted the deformation of the vial cap as pressure increased.

PMI shape analysis[154]

Computational analysis was carried out in collaboration with Mary Wheldon (O'Brien group), Paul Bond and Rod Hubbard (York Structural Biology Laboratory).

The following describes how a PMI plot was generated in the software package, Pipeline Pilot. A SMILES (simplified molecular input line entry specification) file containing the SMILES strings for all compounds was generated using ChemDraw 12.0, compiled in NotePad ++ and saved as a *.SMI file. This was input into the online Pipeline Pilot 8.5.0.200, 2011 protocol (described below). The generated conformations were used to generate the three Principal Moments of Inertia (I1, I2 and I3), which were then normalised by dividing the two lower values by the largest (I1/I3 and I2/I3) using Pipeline Pilot built-in components to generate NPR1 and NPR2.

Principal moments of inertia (PMI) about the principal axes of a molecule were calculated according to the following rules:

1. The moments of inertia are computed for a series of straight lines through the centre of mass.

2. Distances are established along each line proportional to the reciprocal of the square root of I on either side of the centre of mass. The locus of these distances forms an ellipsoidal surface. The principal moments are associated with the principal axes of the ellipsoid.

3. If all three moments are equal, the molecule is considered to be a symmetrical top. If no moments are equal, the molecule is considered to be an unsymmetrical top.

A file containing information for all conformations was generated and the *.csv file was saved in Excel 2013. The values for NPR1 and NPR2 for the lowest energy conformer were extracted from the generated data and a PMI plot was generated, whereby NPR1 was the *x*-axis and NPR2 was the *y*-axis.

Pipeline Pilot setup of workflow[154]

The following describes the settings for the protocol used in Pipeline Pilot. Prior to conformer generation a wash step was performed, which involved ionising the molecule

at pH 7.4, converting to the canonical tautomer and adding hydrogens. 3-dimensional coordinates were then generated using the built-in Conformation Generator component from the Discovery Studio Component Collection. Two copies of the molecule were generated, the original and mirror image. Conformers were generated using the BEST method in Catalyst using the rel option, run directly on the server and not through the built-in Conformation Generator component with a chosen maximum relative energy threshold of 20 kcal mol^{-1}, maximum of 255 conformers for each compound. Conformations were read and mirrored if the wrong enantiomer was generated. Duplicates were filtered with a chosen RMSD (root mean square deviation) threshold of 0.1. Minimisation was performed using the CHARMm (chemistry at Harvard macromolecular mechanics) forcefield with Momany-Rone partial charge estimation and a Generalised Born implicit solvent model. Duplicates were filtered again with a RMSD threshold of 0.1.

5.2. General Procedures

General Procedure A: Preparation of Jones reagent

Conc. H_2SO_4 (2.5 mL, 46.90 mmol, 1.88 eq) was added dropwise to a stirred solution of CrO_3 (2.5 g, 25.0 mmol, 1 eq) in water (7.5 mL, 416 mmol, 16.6 eq) at 0 °C. The resulting orange solution was stirred at 0 °C for 10 min to give a 2.5 M aqueous solution of Jones reagent.

General Procedure B: Jones oxidation of primary alcohol to carboxylic acid

The Jones reagent (prepared following general procedure A, 1.4 eq, 10.6 mL, 2.5 M) was added to a stirred solution of primary alcohol (1 eq, 1.88 mL, 18.85 mmol) in acetone (120 mL) at 0 °C until the reaction mixture remained orange in colour. The mixture was stirred at 0 °C for 40 min and then IPA (~50 mL) was added until the reaction mixture remained blue/green. Water was added until the solid was solubilised and the organic solvent was evaporated under reduced pressure. The remaining aqueous mixture was diluted with water (20 mL), Et_2O (50 mL) and 1 M $NaOH_{(aq)}$ (50 mL). The two layers were separated and the aqueous phase was acidified with 3 M $HCl_{(aq)}$ and extracted with Et_2O (3 x 100 mL). The combined organics were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the product.

General Procedure C: Activation of zinc powder and generation of allylzinc bromide

Zinc powder (1.2 eq, 170 mg, 2.6 mmol) was stirred in a solution of 1 M $HCl_{(aq)}$ for 1 min before the solvent was removed by pipette suction, leaving the zinc powder behind. The zinc was triturated with water (2 mL), EtOH (2 mL) and Et_2O (2 mL) and dried under reduced pressure to provide the activated zinc. Allyl bromide (1 eq, 207 µL, 2.4 mmol) was added to a stirred suspension of the activated zinc in dry THF (1 mL) at rt under Ar. The reaction mixture was stirred for 5 min to give the allylzinc bromide **134**.

General Procedure D: Nucleophilic addition of an allylmetal bromide into a *N*-acyliminium ion

Trans-cinnamoyl chloride (1.2 eq, 303 mg, 1.82 mmol) was added to a stirred solution of 3,4-dihydroisoquinoline **37** (1 eq, 200 mg, 1.52 mmol) in solvent (6 mL) and stirred at rt-65 °C for 1 h under Ar. The resulting solution was cooled to −78 °C and the allylmetal bromide (1.2 eq, 1.82 mmol) was added. The reaction was stirred at −78 °C or rt for 1.5-3 h under Ar. Sat. $NH_4Cl_{(aq)}$ (10 mL) was added and the reaction was extracted into Et_2O (20 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organics were dried ($MgSO_4$) and filtered, and the solvent removed under reduced pressure to give the crude product.

General Procedure E: Addition of an allylmetal bromide into an imine and subsequent trapping with an acid chloride

Allylmetal bromide (1.1 eq, 0.84 mmol) was slowly added to a stirred solution of imine (1 eq, 0.76 mmol) in THF (3 mL) at −78 °C under Ar. The reaction mixture was allowed to warm to rt and stirred for 2.5 h. After this time, the reaction was cooled to −78 °C and a solution of *trans*-cinnamoyl chloride (1.2 eq, 152 mg, 0.91 mmol) in THF (1 mL) was added. The reaction was allowed to warm to rt and the resulting solution was stirred for 2 h. Sat. $NH_4Cl_{(aq)}$ (5 mL) was added and the reaction was extracted into Et_2O (10 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organics were dried ($MgSO_4$) and filtered, and the solvent removed under reduced pressure to give the crude product.

General Procedure F: Synthesis of bispidones *via* a double Mannich reaction

A solution of *N*-protected piperidone (1 eq, 7.50 g, 37.64 mmol), acetic acid (1 eq, 2.16 mL, 37.64 mmol) and benzylamine (1 eq, 4.12 mL, 37.64 mmol) in MeOH (45 mL) was added dropwise over 20 min to a stirred suspension of paraformaldehyde (2.2 eq, 2.49 g, 82.81 mmol) in MeOH (75 mL) heated at reflux under Ar. The resulting mixture was stirred and heated at reflux for 1 h. Then paraformaldehyde (2.2 eq, 2.49 g, 82.81 mmol) was added in one portion. The resulting mixture was stirred and heated at reflux for 4 h. The mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O (150 mL) and washed with 1 M $KOH_{(aq)}$

(150 mL). The aqueous layer was extracted with Et_2O (5 x 150 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product.

General Procedure G: Reduction of bispidones

p-Toluenesulfonyl hydrazide (1.2 eq, 6.43 g, 34.54 mmol) was added in one portion to a stirred solution of *N*-protected bispidone (1 eq, 9.51 g, 28.78 mmol) in EtOH (250 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 3.5 h (TLC analysis indicated disappearance of bispidone). The reaction was allowed to cool to rt and the solvent was evaporated under reduced pressure. The residue was dissolved in THF:H_2O (4:1, 180 mL) and cooled to 0 $^{\circ}$C. $NaBH_4$ (9.15 g, 241.75 mmol) was added portionwise over 20 min (CARE – vigorous effervescence). The resulting mixture was stirred at rt for 18 h. The mixture was then stirred and heated at reflux for a specified time. The solution was allowed to cool to rt and water (150 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (4 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product.

General Procedure H: Hydrogenation of benzyl protecting group

20% (w/w) $Pd(OH)_2/C$ (10 mol %, 1.26 g, 1.80 mmol) was added to a stirred solution of *N*-benzyl bispidine (1 eq, 5.70 g, 18.01 mmol) in EtOH (170 mL) at rt under Ar. The flask was evacuated and back-filled with Ar three times and finally evacuated and back-filled with H_2. Then, the mixture was stirred at rt for 18 h, replacing the H_2 balloon as required. The solids were removed by filtration through a pad of Celite® and the solvent was evaporated under reduced pressure to give the product.

General Procedure I: Synthesis of imines using NBS

N-Bromosuccinimide (1.1 eq, 15.64 g, 87.87 mmol) was added portionwise to a stirred solution of tetrahydroisoquinoline (1 eq, 10 mL, 79.89 mmol) in CH_2Cl_2 (150 mL) at rt under Ar. The resulting mixture was stirred at rt for 3 h. $NaOH_{(aq)}$ (30% w/v, 50 mL) was added and the reaction mixture was stirred vigorously at rt for 16 h. The two layers

were separated and the organic layer was washed with water (150 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product.

General Procedure J: Synthesis of spirocycles by direct imine acylation

DIPEA (1.85 eq, 245 μL, 1.41 mmol) and T3P (1.5 eq, 725 mg of a 50% w/v solution in THF, 1.14 mmol) were added to a stirred solution of imine (1 eq, 0.762 mmol) and acid (1.2 eq, 0.909 mmol) in solvent (4 mL) at a specified temperature. The resulting solution was stirred in a sealed vessel for a specified time. The solution was diluted with CH_2Cl_2 (10 mL) and poured into sat. $NaHCO_{3(aq)}$ (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product.

General Procedure K: $NaBH_4$ reduction of spirocyclic indolenine

$NaBH_4$ (4 eq, 1.32 mmol) was added portionwise (CARE: effervescence) to a stirred solution of imine (1 eq, 0.33 mmol) in MeOH (5 mL) at 0 °C under Ar. The reaction mixture was heated to reflux and stirred for 3.5 h and then allowed to cool to rt. The solvent was evaporated under reduced pressure and the resulting residue taken up in H_2O (10 mL) and CH_2Cl_2 (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product.

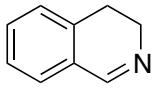
General Procedure L: $LiAlH_4$ reduction of spirocyclic indoline

$LiAlH_4$ (4 eq, 2.00 mmol) was added to a stirred solution of amide (1 eq, 0.50 mmol) in dry THF (15 mL) at 0 °C under Ar. The resulting suspension was heated to reflux and stirred for 2.5 h, then the reaction was allowed to cool to rt. The reaction was diluted with EtOAc (5 mL) and H_2O was carefully added until effervescence ceased. $NaSO_4$ was added and the resulting suspension stirred for 30 min, then the mixture was filtered and the solvent evaporated under reduced pressure to give the crude product.

5.3. Reaction Procedures and Compound Characterisation

5.3.1. Chapter 2

3,4-Dihydroisoquinoline 37

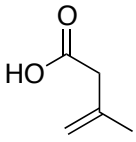


37

Using general procedure I, *N*-bromosuccinimide (15.64 g, 87.87 mmol) and tetrahydroisoquinoline (10 mL, 79.89 mmol) in CH_2Cl_2 (150 mL) at rt under Ar, then $NaOH_{(aq)}$ (30% w/v, 50 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (5:1) and then EtOAc as eluent gave 3,4-dihydroisoquinoline **37** (8.97 g, 86%) as an orange oil, R_F (1:1 petrol-EtOAc) 0.10; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H, CHN), 7.40-7.13 (m, 4H, Ar), 3.81-3.75 (m, 2H, CH_2), 2.79-2.61 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.2 (C=N), 136.1 (*ipso*-Ar), 130.9 (Ar), 128.3 (*ipso*-Ar), 127.3 (Ar), 127.0 (Ar), 126.9 (Ar), 47.2 (CH_2N), 24.9 (CH_2). HRMS (ESI) *m/z* calcd for C_9H_9N $(M + H)^+$ 132.0808, found 132.0812 (−3.8 ppm error). Spectroscopic data consistent with those reported in the literature.[192]

Lab Book Reference: SC2/6

3-Methylbut-3-enoic acid 40



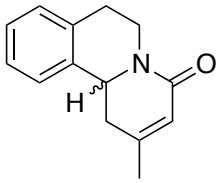
40

Using general procedure B, Jones reagent (10.6 mL of a 2.5 M solution, 26.39 mmol) and 3-methyl-3-buten-1-ol (1.88 mL, 18.85 mmol) in acetone (120 mL) at 0 °C gave the acid **40** (1.14 g, 61%) as a yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97-4.95 (m, 1H, C=CH_AH$_B$), 4.90-4.89 (m, 1H, C=CH$_A$$H_B$), 3.09 (d, J = 1.0 Hz, 2H, CH_2), 1.84 (t, J =

1.0 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.7 (C=O), 137.9 (*C*=CH_2), 115.4 (C=*C*H_2), 43.1 (CH_2), 22.4 (CH_3); Spectroscopic data consistent with those reported in the literature.[193]

Lab Book Reference: SC1/2

2-Methyl-6,7-dihydro-1*H*-pyrido[2,1-a]isoquinolin-4(11b*H*)-one 41

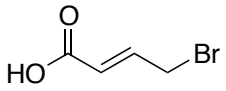


41

DIPEA (0.53 mL, 3.05 mmol) and T3P (1.46 g of a 50% w/v solution in THF, 2.29 mmol) were added to a stirred solution of 3,4-dihydroisoquinoline **37** (200 mg, 1.52 mmol) and 3-methyl-3-butenoic acid **40** (183 mg, 1.83 mmol) in CH_2Cl_2 (15 mL) under Ar at rt. The resulting solution was stirred and heated at reflux for 1.5 h. The solution was cooled to 0 °C and TFA (0.58 mL, 7.63 mmol) was added under Ar. The solution was stirred and heated at 45 °C for 18 h. The solution was cooled to rt, diluted with CH_2Cl_2 (20 mL) and poured into sat. $NaHCO_{3(aq)}$ (20 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (3:1) as eluent gave dihydropyridone **41** (150 mg, 46%) as a yellow oil, R_F (EtOAc) 0.20; IR (ATR) 2934, 1669 (C=O), 1624 (C=C), 1417, 1150, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.15 (m, 4H, Ar), 5.86 (dd, *J* = 2.5, 1.5 Hz, 1H, CHC(O)), 4.80-4.71 (m, 2H, CHN, C$H_A$$H_B$N), 2.97-2.76 (m, 3H, CH_AH_BN, CH_2), 2.58 (dd, *J* = 17.0, 5.0 Hz, 1H, C$H_A$$H_B$CMe=CH), 2.41-2.31 (m, 1H, CH_AH_BCMe=CH), 1.97 (dd, *J* = 1.0, 1.0 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.4 (C=O), 150.2 (*C*$(CH_3)_3$), 135.9 (*ipso*-Ar), 134.9 (*ipso*-Ar), 129.0 (Ar), 126.7 (Ar), 126.6 (Ar), 125.6 (Ar), 120.7 (*C*HC(O)), 54.3 (CHN), 38.6 (C=C*C*H_2), 37.7 (NCH_2), 29.5 (CH_2), 22.7 (CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{15}NO$ $(M + H)^+$ 214.1226, found 214.1218 (+4.0 ppm error). Spectroscopic data consistent with those reported in the literature.[20]

Lab Book Reference: SC1/3

(*E*)-4-Bromobut-2-enoic acid 77

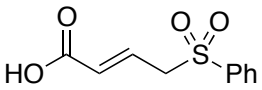


77

(*E*)-Methyl 4-bromobut-2-enoate **76** (0.35 mL, 3.0 mmol) was added to a stirred solution of bis(tributyltin) oxide (3.06 mL, 6.0 mmol) in toluene (30 mL) under Ar at rt. The resulting mixture was stirred and heated at reflux for 18 h. The mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (30 mL) and extracted with sat. $NaHCO_{3(aq)}$ (3 x 25 mL). The combined aqueous layers were acidified to pH 4-5 with 5 M $HCl_{(aq)}$ and extracted with EtOAc (3 x 25 mL). The combined organics were washed with brine (40 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Residual tin impurities were removed by partitioning the crude product in EtOAc (20 mL) and water (20 mL). The mixture was basified with sat. $NaHCO_{3(aq)}$ (20 mL) and the aqueous layer was washed with EtOAc (3 x 20 mL). The aqueous layer was acidified to pH 4-5 with 5 M $HCl_{(aq)}$ and extracted into EtOAc (3 x 20 mL). The combined organics were dried ($MgSO_4$) and the solvent evaporated reduced pressure to give the allylic acid **46** (283 mg, 57%) as an orange solid, mp 66-67 °C (lit,[53] 72-73 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (dt, *J* = 15.0, 7.5 Hz, 1H, C*H*=CHC(O)), 6.05 (dt, *J* = 15.0, 1.5 Hz, 1H, CH=C*H*C(O)), 4.03 (dd, *J* = 7.5, 1.5 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.0 (C=O), 144.4 (*C*H=CHC(O)), 123.7 (CH=*C*HC(O)), 28.7 (CH_2). Spectroscopic data consistent with those reported in the literature.[53]

Lab Book Reference: SC1/13

(*E*)-4-(Phenylsulfonyl)but-2-enoic acid 79

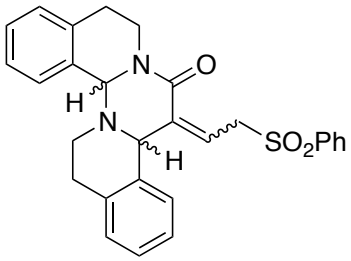


79

n-Butyllithium (3.44 mL of a 1.6 M solution in hexanes, 5.5 mmol) was added dropwise to a stirred solution of allylsulfonylbenzene **78** (0.76 mL, 5.0 mmol) in THF (10 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 1 h. Dry CO_2 (obtained by passing CO_2 gas through conc. H_2SO_4) was bubbled into the reaction flask and the reaction mixture was allowed to warm to rt. After 3 h, 2 M $HCl_{(aq)}$ (10 mL) was added. The mixture was basified with 2 M $NaOH_{(aq)}$ (until pH > 14) and the impurities were extracted with Et_2O (50 mL). The aqueous layer was acidified with 2 M $HCl_{(aq)}$ (10 mL) and extracted with Et_2O (3 x 50 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Trituration of the crude product by stirring in Et_2O (5 mL) gave a solid which was collected by filtration to give the 4-phenylsulfonylcrotonic acid **79** (136 mg, 12%) as a white solid, mp 141-142 °C (lit.,[54] 145 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.87 (m, 2H, Ph), 7.72-7.68 (m, 1H, Ph), 7.62-7.57 (m, 2H, Ph), 6.89 (dt, *J* = 15.5, 8.0 Hz, 1H, C(O)CH=C*H*), 5.86 (dt, *J* = 15.5, 1.5 Hz, 1H, C(O)C*H*=CH), 3.97 (dd, *J* = 8.0, 1.5 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.9 (C=O), 138.0 (*ipso*-Ph), 135.6 (C(O)CH=*C*H), 134.3 (Ph), 129.4 (Ph), 128.5 (C(O)*C*H=CH), 128.3 (Ph), 59.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{10}O_4S$ $(M + Na)^+$ 249.0192, found 249.0202 (−4.4 ppm error). Spectroscopic data consistent with those reported in the literature.[54]

Lab Book Reference: SC1/8

5-(2-(Phenylsulfonyl)ethylidene)-4b,5,8,9,15,16-hexahydropyrimido[2,1-*a*:4,3-*a′*]diisoquinolin-6(13b*H*)-one 82

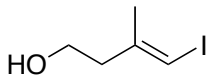


82

DIPEA (52 μL, 0.30 mmol) and T3P (146 mg of a 50% w/v solution in THF, 0.25 mmol) were added to a stirred solution of 3,4-dihydroisoquinoline **37** (20 mg, 0.15 mmol) and (*E*)-4-(phenylsulfonyl)but-2-enoic acid **73** (40 mg, 0.18 mmol) in toluene (2 mL) at rt under Ar. The resulting solution was stirred in a sealed vessel at rt for 3 h. The solution was diluted with CH_2Cl_2 (5 mL) and poured into sat. $NaHCO_{3(aq)}$ (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organics were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (3:2) as eluent gave a single diastereoisomer of **82** with undefined relative stereochemistry (11 mg, 31%) as a brown oil, R_F (3:2 petrol-EtOAc) 0.2; IR (ATR) 2928, 1696 (C=O), 1655 (C=C), 1604, 1426, 1305, 1142, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.63 (m, 2H, Ar), 7.56-7.52 (m, 1H, Ar), 7.50-7.47 (m, 1H, Ar), 7.44-7.40 (m, 2H, Ar), 7.30-7.14 (m, 6H, Ar), 7.00 (d, *J* = 7.0 Hz, 1H, Ar), 5.92 (s, 1H, NCHN), 5.49 (ddd, *J* = 8.5, 6.0, 2.0, 1H, C(O)C=CH), 5.02 (ddd, *J* = 15.5, 8.5, 1.0 Hz, 1H, $CH_AH_BSO_2Ph$), 4.95 (br s, 1H, NCHC=C), 4.80-4.76 (m, 1H, NCH), 4.57 (ddd, *J* = 15.5, 6.0, 2.0 Hz, 1H, $CH_AH_BSO_2Ph$), 2.95-2.81 (m, 3H, 3 x NCH), 2.75-2.70 (m, 1H, CH), 2.50 (dd, *J* = 16.5, 4.0 Hz, 1H, CH), 2.41 (dd, *J* = 12.0, 7.0 Hz, 1H, CH), 2.29 (ddd, *J* = 12.0, 12.0, 4.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.6 (C=O), 138.7 (*ipso*-Ar), 136.3 (*ipso*-Ar), 136.2 (*ipso*-Ar), 134.4 (*ipso*-Ar), 133.3 (Ar), 133.0 (*ipso*-Ar), 132.4 (C(O)*C*=C), 129.8 (Ar), 129.3 (C=*C*H), 129.1 (Ar), 128.9 (Ar), 128.8 (Ar), 128.2 (Ar), 127.9 (Ar), 127.8 (Ar), 127.0 (Ar), 126.9 (Ar), 125.4 (Ar), 74.8 (NCHN), 62.6 (N*C*HC=C), 56.3 (CH_2SO_2Ph), 37.9 (NCH_2), 36.3 (NCH_2), 28.6 (CH_2), 28.4 (CH_2); HRMS (ESI) *m/z* calcd for $C_{28}H_{26}N_2O_3S$ $(M + H)^+$ 471.1737, found 471.1727 (+0.9 ppm error). The ^1H and ^{13}C NMR spectra were assigned using the 2D COSY and HSQC spectra.

Lab Book Reference: SC1/14

(*E*)-4-Iodo-3-methylbut-3-en-1-ol 96

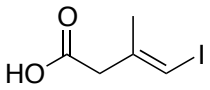


96

Trimethylaluminium (2 M in hexanes, 15.5 mL, 31.0 mmol) was added dropwise to a stirred solution of zirconocene dichloride (643 mg, 2.2 mmol) in CH_2Cl_2 (40 mL) at −20 °C under Ar. The reaction mixture was stirred for 10 min and then water (288 μL, 16.0 mmol) was added dropwise (caution: exothermic reaction). The reaction mixture was stirred for a further 15 min, and then 3-butyn-1-ol **95** (756 μL, 10 mmol) (pretreated with trimethyl aluminium (2 M in hexanes, 2 mL, 4.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C) was added slowly. The reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was then cooled to – 20 °C and a solution of I_2 (3.05 g, 12.0 mmol) in Et_2O (25 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction was cooled to 0 °C and quenched by careful addition of water (40 mL). The resulting biphasic mixture was filtered through a pad of Celite® and the layers were separated. The organic layer was washed with $Na_2S_2O_{3(aq)}$ (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-Et_2O (8:2) as eluent gave the iodo substituted alkene **96** (1.57 g, 74%) as a yellow liquid, R_F (8:2 hexane-Et_2O) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (tq, *J* = 1.0, 1.0 Hz, 1H, C(CH_3)=C*H*I), 3.72 (t, *J* = 6.5 Hz, 2H, CH_2OH), 2.48 (td, *J* = 6.5, 1.0 Hz, 2H, CH_2C=C), 1.88 (d, *J* = 1.0 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.5 (*C*(CH_3)=CHI), 76.9 (C=*C*HI), 60.1 (CH_2), 42.4 (CH_2), 23.8 (CH_3). Spectroscopic data consistent with those reported in the literature.[56]

Lab Book Reference: SC2/48

(*E*)-4-Iodo-3-methylbut-3-enoic acid 90

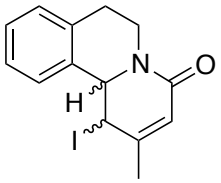


90

Using general procedure B, Jones reagent (synthesised using general procedure A, 3.7 mL of a 2.5 M aqueous solution, 9.25 mmol) and (*E*)-4-iodo-3-methylbut-3-en-1-ol **96** (1.37 g, 6.47 mmol) in acetone (20 mL) gave the acid product **90** (736 mg, 50%) as an orange solid, mp 55-58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (s, 1H, OH), 6.20 (d, *J* = 0.5 Hz, 1H, C=CHI), 3.24 (s, 2H, CH_2), 1.94 (d, *J* = 0.5 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.6 (C=O), 139.5 (*C*=CI), 80.4, (C=*C*I), 43.7 (CH_2), 23.9 (CH_3). Spectroscopic data consistent with those reported in the literature.[194]

Lab Book Reference: SC2/57

1-Iodo-2-methyl-6,7-dihydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one 97



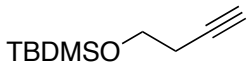
97

DIPEA (238 μL, 1.37 mmol) and T3P (706 mg of a 50% w/v solution in THF, 1.11 mmol) were added to a stirred solution of 3,4-dihydroisoquinoline **37** (97 mg, 0.74 mmol) (*E*)-4-iodo-3-methylbut-3-enoic acid **90** (200 mg, 0.88 mmol) in CH_2Cl_2 (3 mL) at rt under Ar. The resulting solution was stirred in a sealed vessel at rt for 1.5 h. TFA (113 μL, 1.48 mmol) was added and the reaction mixture was stirred and heated at 45 °C for 16 h. After being allowed to cool to rt, the solution was diluted with CH_2Cl_2 (10 mL) and poured into sat. $NaHCO_{3(aq)}$ (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with hexane-EtOAc (19:1 then 9:1) as eluent gave a single diastereoisomer of **97** with undefined relative stereochemistry (28 mg, 11%) as a yellow

oil, R_F (9:1 petrol-EtOAc) 0.3; IR (ATR) 3064, 2924, 1747, 1682 (C=O), 1639, 1152, 1014, 654, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.23 (m, 2H, Ar), 7.19-7.15 (m, 2H, Ar), 6.42-6.41 (m, 1H, CHC(O)), 4.46 (br s, 1H, NC*H*CHI), 3.99 (ddd, *J* = 12.5, 6.0, 4.0 Hz, 1H, NC$H_A$$H_B$), 3.77 (dd, *J* = 2.0, 1.0 Hz, 1H, CHI), 3.19-3.03 (m, 2H, NC$H_A$$H_B$, C$H_C$$H_D$), 2.80-2.74 (m, 1H, C$H_C$$H_D$), 2.05 (d, *J* = 1.0 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.0 (C=O), 141.0 (*C*(CH_3)), 134.6 (*ipso*-Ar), 133.9 (*ipso*-Ar), 129.6 (Ar), 127.6 (Ar), 127.1 (Ar), 125.9 (Ar), 80.3 (*C*HC(O)), 66.1 (ICH), 53.5 (NCH), 37.7 (NCH_2), 28.2 (CH_2), 22.1 (CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{14}INO$ $(M + H)^+$ 340.0193, found 340.0195 (−0.9 ppm error).

Lab Book Reference: SC2/60

(But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane 99

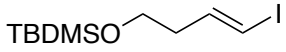


99

tert-Butyldimethylsilyl chloride (5.43 g, 36.0 mmol) and imidazole (3.68 g, 54 mmol) were added to a stirred solution of 3-butyn-1-ol **95** (2.27 mL, 30 mmol) in CH_2Cl_2 (100 mL) at rt under Ar. The reaction mixture was stirred for 1 h. Then, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 1 M $HCl_{(aq)}$ (100 mL) and brine (50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave the protected alkynol **99** (5.14 g, 93%) as a pale yellow liquid, R_F (EtOAc) 0.8; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (t, *J* = 7.0 Hz, 2H, OCH_2), 2.39 (td, *J* = 7.0, 2.5 Hz, 2H, CH_2C≡CH), 1.95 (t, *J* = 2.5 Hz, C≡CH), 0.89 (s, 9H, $Si(CH_3)_2C(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2C(CH_3)_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 81.5 (*C*≡CH), 69.3 (C≡*C*H), 61.7 (OCH_2), 25.9 ($Si(CH_3)_2C(CH_3)_3$), 22.8 (*C*H_2C≡CH), 18.3 ($Si(CH_3)_2C(CH_3)_3$), −5.3 ($Si(CH_3)_2C(CH_3)_3$). Spectroscopic data consistent with those reported in the literature.[195]

Lab Book Reference: SC2/49

(*E*)-*tert*-Butyl((4-iodobut-3-en-1-yl)oxy)dimethylsilane 100

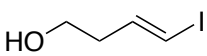


100

$ZrCp_2Cl_2$ (1.58 g, 5.4 mmol) was added to THF (20 mL) in a flame-dried flask and stirred at rt under Ar. The flask was shielded from light with an aluminium foil wrap. $LiEt_3BH$ (1 M in THF, 5.4 mL, 5.4 mmol) was added dropwise and the reaction was stirred for 1 h. (But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane **99** (500 mg, 2.7 mmol) was added to the reaction mixture and stirred for 10 min. I_2 (1.52 g, 6.00 mmol) was added and the resulting solution stirred at rt for 20 min. The resulting solution was poured into sat. $NaHCO_{3(aq)}$ (50 mL) and extracted with Et_2O (30 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organics were washed with $Na_2S_2O_{3(aq)}$ (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (19:1) as eluent gave iodo-substituted alkene **100** (354 mg, 36%) as a pale yellow oil, R_F (9:1 hexane:EtOAc) 0.90; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (dt, J = 14.5, 7.5 Hz, 1H, C*H*=CHI), 6.08 (dt, J = 14.5, 1.5 Hz, 1H, CH=C*H*I), 3.65 (t, J = 6.5 Hz, 2H, OCH_2), 2.26 (dtd, J = 7.5, 6.5, 1.5 Hz, 2H, CH_2C=C), 0.89 (s, 9H, $Si(CH_3)_2C(CH_3)_3$), 0.05 (s, 6H, $Si(CH_3)_2C(CH_3)_3$). Spectroscopic data consistent with those reported in the literature.[196]

Lab Book Reference: SC2/52

(*E*)-4-Iodobut-3-en-1-ol 101



101

$ZrCp_2Cl_2$ (2.92 g, 10 mmol) was added to THF (30 mL) in a flame-dried flask and stirred at rt under Ar. The flask was shielded from light with an aluminium foil wrap. $LiEt_3BH$ (1 M in THF, 10 mL, 10 mmol) was added dropwise and the reaction as stirred for 75 min. A solution of 3-butyn-1-ol **95** (378 μL, 5 mmol) in THF (pretreated with $LiEt_3BH$ (5.00 mL, 5.00 mmol) at rt under Ar) was added to the reaction mixture and

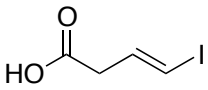
stirred for 10 min. I_2 (1.52 g, 6 mmol) was added and the resulting solution stirred at rt for 2 h. The solution was poured into sat. $NaHCO_{3(aq)}$ (50 mL) and extracted with Et_2O (30 mL). The two layers were separated and the organic layer was washed with $Na_2S_2O_{3(aq)}$ (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (3:1) as eluent gave iodo-substituted alkene **101** (354 mg, 36%) as a pale yellow oil.

Lab Book Reference: SC2/55

TBAF (1 M in THF, 1.26 mL, 1.26 mmol) was added to a stirred solution of (*E*)-*tert*-butyl((4-iodobut-3-en-1-yl)oxy)dimethylsilane **100** (263 mg, 0.84 mmol) in THF (20 mL) at rt under Ar. The resulting solution was stirred for 1 h. Sat. $NH_4Cl_{(aq)}$ (20 mL) was added and the mixture was extracted into Et_2O (20 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (3:1) as eluent gave iodo-substituted alkene **101** (137 mg, 83%) as a colourless oil, R_F (3:1 hexane-EtOAc) 0.15; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (dt, *J* = 14.5, 7.5 Hz, 1H, C*H*=CHI), 6.17 (dt, *J* = 14.5, 1.5 Hz, 1H, CH=C*H*I), 3.69 (t, *J* = 6.0 Hz, 2H, HOCH_2), 2.33 (dtd, *J* = 7.5, 6.0, 1.5 Hz, 2H, CH_2C=C), 1.44 (s, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.6 (*C*=CI), 77.3 (C=*C*I), 61.0 (CH_2OH), 39.2 (*C*H_2C=C). Spectroscopic data consistent with those reported in the literature.[196]

Lab Book Reference: SC2/56

(*E*)-4-Iodobut-3-enoic acid 91

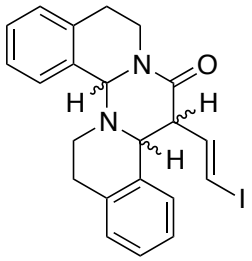


91

Using general procedure B, Jones reagent (synthesised using general procedure A, 0.3 mL of a 2.5 M aqueous solution, 0.75 mmol) and (*E*)-4-iodobut-3-en-1-ol **101** (106 mg, 0.54 mmol) in acetone gave acid **91** (97 mg, 79%) as an orange solid, mp 56-58 °C (lit.[194] 56-58 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (dt, *J* = 14.5, 7.5 Hz, 1H, C*H*=CHI), 6.31 (dd, *J* = 14.5, 1.5 Hz, 1H, CH=C*H*I), 3.14 (dd, *J* = 7.5, 1.5 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.0 (C=O), 136.3 (*C*=CI), 79.7, (C=*C*I), 40.4 (CH_2. Spectroscopic data consistent with those reported in the literature.[194]

Lab Book Reference: SC2/59

(*E*)-5-(2-Iodovinyl)-4b,5,8,9,15,16-hexahydropyrimido[2,1-*a*:4,3-*a′*]diisoquinolin-6(13b*H*)-one 104



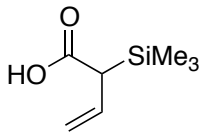
104

DIPEA (127 μL, 0.72 mmol) and T3P (380 mg of a 50% w/v solution in THF, 0.59 mmol) were added to a stirred solution of 3,4-dihydroisoquinoline **37** (51 mg, 0.39 mmol) and (*E*)-4-iodobut-3-enoic acid **91** (100 mg, 0.47 mmol) in CH_2Cl_2 (2 mL) at rt under Ar. The resulting solution was stirred in a sealed vessel at rt for 1 h. TFA (60 μL, 0.79 mmol) was added and the reaction was stirred and heated at 45 °C for 16 h. After being allowed to cool to rt, the solution was diluted with CH_2Cl_2 (10 mL) and poured into sat. $NaHCO_{3(aq)}$ (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure

to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (3:2) as eluent gave a single diastereoisomer of **104** with undefined relative stereochemistry (14.5 mg, 16%) as a yellow oil, R_F (9:1 petrol-EtOAc) 0.3; IR (ATR) 3061, 2924, 1687, 1639, 1604, 1425, 1149, 945, 657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.49 (m, 1H, Ar), 7.28-7.27 (m, 2H, Ar), 7.20-7.16 (m, 3H, Ar), 7.13-7.11 (m, 1H, Ar), 7.05-7.03 (m, 1H, Ar), 6.60 (dd, *J* = 14.5, 9.5 Hz, 1H, C*H*=CHI), 6.15 (d, *J* = 14.5 Hz, 1H, CH=C*H*I), 5.88 (s, 1H, NCHN), 4.72 (ddd, *J* = 13.0, 4.0, 4.0 Hz, 1H, NCH), 4.38 (d, *J* = 9.5 Hz, 1H, NC*H*CHC=C), 3.38 (dd, *J* = 9.5, 9.5 Hz, 1H, NCHC*H*C=C), 3.16-3.09 (m, 1H, NCH), 2.96-2.88 (m, 2H, 2 x NCH), 2.80-2.63 (m, 3H, 3 x CH), 2.56-2.51 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.1 (C=O), 141.4 (*C*H=CHI), 136.7 (*ipso*-Ar), 135.9 (*ipso*-Ar), 133.4 (*ipso*-Ar), 132.5 (*ipso*-Ar), 129.3 (Ar), 128.5 (Ar), 127.8 (Ar), 127.7 (Ar), 127.5 (Ar), 127.3 (Ar), 127.1 (Ar), 125.3 (Ar), 81.6 (CH=*C*HI), 74.2 (NCHN), 61.2 (N*C*HCHC=C), 53.2 (NCH*C*HC=C), 38.7 (NCH_2), 36.3 (NCH_2), 28.7 (CH_2), 28.6 (CH_2); HRMS (ESI) *m/z* calcd for $C_{22}H_{21}IN_2O$ $(M + H)^+$ 457.0771, found 457.0779 (−1.7 ppm error). The ^1H and ^{13}C NMR spectra were assigned using the 2D COSY and HSQC spectra.

Lab Book Reference: SC2/61

2-(Trimethylsilyl)but-3-enoic acid 106



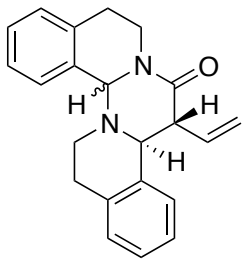
106

TMEDA (distilled over CaH_2, 389 μL, 2.60 mmol) was added to a solution of allyltrimethylsilane **105** (317 μL, 2.00 mmol) in THF (14 mL) in a flame-dried flask at rt under Ar. The resulting solution was cooled to −30 °C and *s*-BuLi (2.0 mL of a 1.3 M solution in hexane, 2.6 mmol) was added. The resulting yellow solution was stirred at −30 °C for 1 h. After cooling to −78 °C, trimethylaluminium (1.1 mL of a 2 M solution in hexanes, 2.2 mmol) was added and the mixture was stirred at −78 °C for 20 min. Dry CO_2 (obtained by passing CO_2 gas through $CaCl_2$ and into the reaction) was bubbled into the reaction mixture and stirred for 10 min. The resulting colourless solution was

quenched by slow addition of H_2O (10 mL). After being allowed to warm to rt, the reaction mixture was extracted with Et_2O (20 mL). The two layers were separated and the aqueous layer was acidified using 3 M $HCl_{(aq)}$ (10 mL) and extracted with Et_2O (2 x 20 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which contained an 80:20 mixture (by ^{1}H NMR spectroscopy) of α:γ substituted acid products. Purification by column chromatography using CH_2Cl_2 as eluent gave the α-substituted acid **106** (86 mg, 27%) as a white solid, R_F (CH_2Cl_2) 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (ddd, *J* = 17.0, 10.0, 10.0 Hz, 1H, C*H*=CH_AH_B), 4.98 (dd, *J* = 10.0, 1.0 Hz, 1H, CH=C*H*$_A$H$_B$), 4.91 (dd, *J* = 17.0, 1.0 Hz, 1H, CH=CH_AH_B), 2.94 (d, *J* = 10.0 Hz, CHC(O)), 0.13 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.4 (C=O), 132.5 (*C*H=CH_2), 113.8 (CH=*C*H$_2$), 45.3 (*C*HC(O)), −3.0 ($SiMe_3$). Diagnostic signals for the γ-substituted acid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (dt, *J* = 18.5, 6.5 Hz, 1H, =CH), 5.82 (dt, *J* = 18.5, 1.5 Hz, 1H, =CH), 3.17 (dd, *J* = 6.5, 1.5 Hz, 1H, CH_2C(O)), 0.06 (s, 9H, $SiMe_3$) Spectroscopic data consistent with those reported in the literature.[63]

Lab Book Reference: SC2/41

(4b*S,5*R**)-5-Vinyl-4b,5,8,9,15,16-hexahydropyrimido[2,1-*a*:4,3-*a*′]diisoquinolin-6(13b*H*)-one 110**



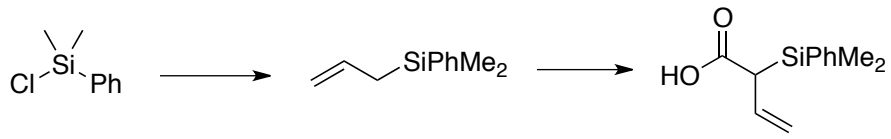
110

DIPEA (71 μL, 0.41 mmol) and T3P (209 mg of a 50% w/v solution in THF, 0.33 mmol) were added to a stirred solution of 3,4-dihydroisoquinoline **37** (29 mg, 0.22 mmol) and 2-(trimethylsilyl)but-3-enoic acid **106** (42 mg, 0.27 mmol) in CH_2Cl_2 (2 mL) at rt under Ar. The resulting solution was stirred in a sealed vessel at rt for 2 h. BF_3•OEt_2 (54 μL, 0.44 mmol) was added and the reaction mixture was stirred at rt for 16 h. The solution was diluted with CH_2Cl_2 (10 mL) and poured into sat. $NaHCO_{3(aq)}$

(10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (3:2) as eluent gave a single diastereoisomer of **110** with undefined relative stereochemistry (9 mg, 25%) as a yellow oil, R_F (2:1 hexane-EtOAc) 0.2; IR (ATR) 2923, 2853, 1642 (C=O), 1555, 1426, 1040, 920, 701, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 1H, Ar), 7.29-7.27 (m, 2H, Ar), 7.20-7.10 (m, 5H, Ar), 5.96 (ddd, *J* = 17.0, 10.0, 9.5 Hz, 1H, C*H*=CH_AH_B), 5.89 (s, 1H, NCHN), 5.40 (dd, *J* = 10.0, 1.0 Hz, 1H, CH=C*H*$_A$H$_B$), 5.18 (ddd, *J* = 17.0, 1.0, 1.0 Hz, 1H, CH=CH$_A$*H*$_B$), 4.71 (ddd, *J* = 13.0, 4.0, 4.0 Hz, 1H, NCH), 4.41 (d, *J* = 9.5 Hz, 1H, NC*H*CHC=C), 3.37 (dd, *J* = 9.5, 9.5 Hz, 1H, NCHC*H*C=C), 3.19-3.12 (m, 1H, NCH), 2.96-2.88 (m, 2H, 2 x NCH), 2.80-2.64 (m, 3H, 3 x CH), 2.56-2.51 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.8 (C=O), 136.9 (*ipso*-Ar), 136.6 (*ipso*-Ar), 134.9 (Ar), 133.4 (*ipso*-Ar), 132.8 (*ipso*-Ar), 129.2 (Ar), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 127.1 (*C*H=CH_2), 127.0 (Ar), 125.1 (Ar), 120.9 (CH=*C*H_2), 74.1 (NCHN), 61.7 (N*C*HCHC=C), 51.2 (NCH*C*HC=C), 38.6 (NCH_2), 36.4 (NCH_2), 29.7 (CH_2), 28.7 (CH_2); HRMS (ESI) *m/z* calcd for $C_{22}H_{21}N_2O$ $(M + Na)^+$ 353.1624, found 353.1607 (+4.8 ppm error). The ^1H and ^{13}C NMR spectra were assigned using the 2D COSY and HSQC spectra.

Lab Book Reference: SC2/46

2-(Dimethyl(phenyl)silyl)but-3-enoic acid 113



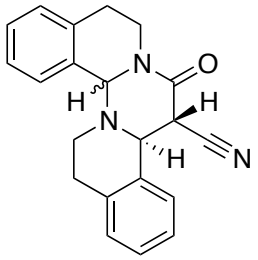
113

Chloro(dimethyl)phenylsilane (2.00 g, 11.75 mmol) was added to a solution of allylzinc bromide (synthesised using general procedure C, 2.35 M in THF, 10 mL, 23.51 mmol) and the resulting suspension was stirred at rt for 1.5 h. The reaction was cooled to 0 °C and sat. $NH_4Cl_{(aq)}$ (50 mL) was carefully added and the reaction mixture was extracted into Et_2O (50 mL). The two layers were separated and the aqueous layer was extracted

into Et_2O (2 x 50 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude allyl silane product; (^{1}H NMR (400 MHz, $CDCl_3$) 7.56-7.51 (m, 2H, Ar), 7.38-7.35 (m, 3H, Ar), 5.79 (ddt, J = 17.0, 10.0, 8.0 Hz, 1H, C*H*=CH_2), 4.88 (ddt, J = 11.5, 2.0, 1.0 Hz, 1H, CH=CH_A*H_B*), 4.85-4.84 (m, 1H, CH=C*H_A*H_B), 1.77 (ddd, J = 8.0, 1.0, 1.0 Hz, 2H, CH_2), 0.29 (s, 6H, 2 x CH_3)). TMEDA (distilled over CaH_2, 1.77 mL, 11.82 mmol) and *s*-BuLi (9.24 mL of a 1.28 M solution in hexane, 11.82 mmol) were added to a solution of allyl(dimethyl)phenylsilane (1.39 g, 7.88 mmol) in THF (23 mL) in a flame-dried flask at −78 °C under Ar. The resulting solution was stirred at for 1 h and then trimethylaluminium (5.12 mL of a 2 M solution in hexanes, 10.24 mmol) was added and the mixture was stirred at −78 °C for 20 min. Dry CO_2 (obtained by passing CO_2 gas through $CaCl_2$ and into the reaction) was bubbled into the reaction mixture and stirred for 10 min, then stirred at 0 °C for 10 min, The resulting colourless solution was quenched by slow addition of sat. $NH_4Cl_{(aq)}$ (20 mL). After being allowed to warm to rt, the reaction mixture was extracted with Et_2O (500 mL). The two layers were separated and the aqueous layer was acidified using 3 M $HCl_{(aq)}$ (30 mL) and extracted with Et_2O (2 x 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by column chromatography using hexane-EtOAc (8:2) as eluent gave the acid **113** (820 mg, 31%) as a colourless oil, R_F (hexane-EtOAc 8:2) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) 7.51-7.50 (m, 2H, Ar), 7.42-7.32 (m, 3H, Ar), 5.93 (dt, J = 17.0, 10.0 Hz, 1H, C*H*=CH_2), 4.94 (ddd, J = 10.0, 1.5, 0.5 Hz, 1H, CH=C*H_{cis}*H_{trans}), 4.79 (ddd, J = 17.0, 1.5, 0.5 Hz, 1H, CH_{cis}*H_{trans}*), 3.12 (d, J = 10.0 Hz, 1H, CH), 0.432 (s, 3H, CH_3), 0.429 (s, 3H, CH_3); HRMS (ESI) *m/z* calcd for $C_{12}H_{16}O_2Si$ $(M + Na)^+$ 243.0812, found 243.0815 (+1.4 ppm error). Spectroscopic data consistent with those reported in the literature.[63]

Lab Book Reference: SC6/25

(4b*S,5*S**)-6-Oxo-4b,5,6,8,9,13b,15,16-octahydropyrimido[2,1-*a*:4,3-*a*′]diisoquinoline-5-carbonitrile 117**



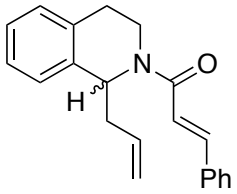
117

DIPEA (139 μL, 0.80 mmol) and T3P (362 mg of a 50% w/v solution in THF, 0.57 mmol) were added to a stirred solution of 3,4-dihydroisoquinoline **37** (100 mg, 0.76 mmol) and cyanoacetic acid **116** (39 mg, 0.46 mmol) in CH_2Cl_2 (4 mL) at rt under Ar. The resulting solution was stirred in a sealed vessel at rt for 7 h. The solution was diluted with CH_2Cl_2 (10 mL) and poured into sat. $NaHCO_{3(aq)}$ (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product which contained a 5:1 mixture of diastereoisomers by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with hexane-EtOAc (2:1) as eluent gave the major diastereoisomer of **117** (96 mg, 77%) as a cream solid, R_F (2:1 hexane-EtOAc) 0.20; mp 181-184 °C; IR (ATR) 3026, 2892, 2247 (C≡N), 1654 (C=O), 1427, 1285, 909, 726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.51 (m, 1H, Ar), 7.50-7.46 (m, 1H, Ar), 7.31-7.23 (m, 4H, Ar), 7.21-7.14 (m, 2H, Ar), 5.94 (s, 1H, NCHN), 4.86-4.82 (m, 1H, NCH), 4.80 (d, *J* = 10.5 Hz, 1H, C(O)CHCN), 3.84 (d, *J* = 10.5 Hz, 1H, NC*H*CHCN), 3.09 (ddd, *J* = 12.5, 12.5, 3.5 Hz, 1H, NCH), 2.99-2.88 (m, 2H, 2 x NCH), 2.79 (ddd, *J* = 16.0, 3.0, 3.0 Hz, 1H, CH), 2.69-2.64 (m, 1H, CH), 2.60-2.56 (m, 2H, 2 x CH);^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.6 (C=O), 136.2 (*ipso*-Ar), 134.1 (*ipso*-Ar), 133.1 (*ipso*-Ar), 131.3 (*ipso*-Ar), 129.4 (Ar), 128.8 (Ar), 128.2 (Ar), 128.1 (Ar) 127.3 (Ar), 127.2 (Ar), 127.2 (Ar), 126.4 (Ar), 117.6 (C ≡ N), 74.7 (NCHN), 59.6 (C(O)*C*HCN), 38.8 (NCH_2), 28.3 (*C*HCHCN), 35.9 (NCH_2), 28.3 (CH_2), 28.3 (CH_2); HRMS (ESI) *m/z* calcd for $C_{21}H_{19}N_3O$ $(M + Na)^+$ 352.1420, found 352.1416 (+1.0 ppm error) and the minor diastereoisomer of **117**, 80% clean by ^{1}H NMR spectroscopy, (18 mg, 11%) as a cream solid, R_F (2:1 hexane-EtOAc) 0.10; ^{1}H NMR (400 MHz, $CDCl_3$)

for **117**: δ 7.54 (d, *J* = 8.0 Hz, 1H, Ar), 7.38 (d, *J* = 8.0 Hz, 1H, Ar), 7.32-7.28 (m, 2H, Ar), 7.24-7.15 (m, 4H, Ar), 5.44 (s, 1H, NCHN), 4.85-4.80 (m, 1H, NCH), 4.34 (d, *J* = 11.0 Hz, 1H, C(O)CHCN), 3.83 (d, *J* = 11.0 Hz, 1H, NC*H*CHCN), 3.53-3.46 (m, 1H, NCH), 3.43-3.14 (m, 4H, 2 x NCH, 2 x CH), 2.97 (dd, *J* = 16.0, 3.5 Hz, 1H, CH), 2.77 (dd, *J* = 16.5, 4.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) for **117**: δ 159.8 (C=O), 135.7 (*ipso*-Ar), 135.0 (*ipso*-Ar), 133.1 (*ipso*-Ar), 132.6 (*ipso*-Ar), 129.5 (Ar), 129.3 (Ar), 128.7 (Ar), 128.4 (Ar) 128.3 (Ar), 126.9 (Ar), 126.2 (Ar), 124.9 (Ar), 116.7 (C≡N), 78.7 (NCHN), 53.9 (C(O)*C*HCN), 45.6 (NCH_2), 42.2 (NCH_2), 37.7 (*C*HCHCN), 29.2 (CH_2), 27.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{21}H_{19}N_3O$ $(M + Na)^+$ 352.1420, found 352.1407 (+3.2 ppm error). The ^{1}H and ^{13}C NMR spectra were assigned using the 2D COSY and HSQC spectra.

Lab Book Reference: SC3/4

(*E*)-1-(1-Allyl-3,4-dihydroisoquinolin-2(1*H*)-yl)-3-phenylprop-2-en-1-one 119



119

DIPEA (0.53 mL, 3.05 mmol) and T3P (1.45 g of a 50% solution in THF, 2.28 mmol) were added to a stirred solution of 3,4-dihydroisoquinoline **37** (200 mg, 1.52 mmol) and *trans*-cinnamic acid **118** (271 mg, 1.83 mmol) in CH_2Cl_2 (15 mL) under Ar at rt. The resulting solution was stirred and heated at 45 °C for 2.5 h. The solution was cooled to −30 °C and allyl trimethylsilane **105** (1.21 mL, 7.3 mmol) followed by BF_3•OEt_2 (0.56 mL, 4.56 mmol) were added. The mixture was allowed to warm to rt and stirred for 2 h. The mixture was diluted with CH_2Cl_2 (10 mL) and poured into sat. $NaHCO_{3(aq)}$ (20 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave substituted diene **119** (240 mg, 52%) as a yellow oil, R_F (1:1 petrol-EtOAc) 0.6 and 0.3, mixture of rotamers; IR (ATR) 2934, 1643 (C=O), 1597 (C=C), 1428, 1193,

908, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 55:45 mixture of rotamers δ; 7.72 (d, *J* = 15.5 Hz, 0.55H, CH=C*H*Ph), 7.71 (d, *J* = 15.5 Hz, 0.45H, CH=C*H*Ph), 7.46-7.52 (m, 2H, Ar), 7.41-7.33 (m, 3H, Ar), 7.22-7.12 (m, 4H, Ar), 6.99 (d, *J* = 15.5 Hz, 0.45H, C*H*=CHPh), 6.97 (d, *J* = 15.5 Hz, 0.55H, C*H*=CHPh), 5.95-5.82 (m, 1.45H, C*H*=CH_2, NCH), 5.22-5.03 (m, 2.55H, C=CH_2, NCH), 4.74 (ddd, *J* = 13.0, 5.5, 2.5 Hz, 0.45H, CH), 4.06 (ddd, *J* = 13.5, 5.0, 5.0 Hz, 0.55H, CH), 3.71 (ddd, *J* = 13.5, 10.0, 5.0 Hz, 0.55H, CH), 3.26 (ddd, *J* = 13.0, 11.5, 5.5 Hz, 0.45H, CH), 3.07-2.61 (m, 4H, 2 x CH, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 166.0 and 165.8 (C=O), 142.8 and 142.6 (CH=*C*HPh), 136.9 and 136.2 (*ipso*-Ar), 135.3 and 135.2 (*ipso*-Ar), 134.8 and 133.9 (*C*H=CH_2), 134.5 and 133.3 (*ipso*-Ar), 130.3, 129.5, 129.1, 128.8, 128.7, 128.5, 128.1, 127.7, 127.4, 127.0, 126.8, 126.6, 126.3 and 126.1 (9 x Ar), 118.7 and 117.2 (CH=*C*H_2), 118.0 and 117.4 (*C*H=CHPh), 56.6 and 52.6 (NCH), 41.6 and 41.1 (CH_2), 40.4 and 36.1 (CH_2), 29.3 and 28.1 (*C*H_2CH=CH_2); HRMS (ESI) *m/z* calcd for $C_{21}H_{21}NO$ $(M + H)^+$ 304.1696, found 304.1684 (+3.3 ppm error).

Lab Book Reference: SC1/15

(Table 2.3, Entry 2)

Using general procedure D, *trans*-cinnamoyl chloride **136** (167 mg, 1.01 mmol) and 3,4-dihydroisoquinoline **37** (110 mg, 0.84 mmol) in THF at 65 °C, then allylmagnesium bromide **137** (1 M in Et_2O, 0.92 mL, 0.92 mmol) at −78 °C for 1.5 h gave the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (8:1 then 4:1 then 1:1) as eluent gave the diene **119** (43 mg, 17%) as a yellow oil.

Lab Book Reference: SC2/64

(Table 2.3, Entry 3)

Using general procedure D, *trans*-cinnamoyl chloride **136** (152 mg, 0.91 mmol) and 3,4-dihydroisoquinoline **37** (100 mg, 0.76 mmol) in CH_2Cl_2 at rt, then allylmagnesium bromide **137** (1 M in Et_2O, 0.91 mL, 0.91 mmol) at −78 °C for 1.5 h gave the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (8:1 then 4:1 then 1:1) as eluent gave the diene **119** (55 mg, 24%) as a yellow oil.

Lab Book Reference: SC2/65

(Table 2.3, Entry 4)

Using general procedure D, *trans*-cinnamoyl chloride **136** (152 mg, 0.91 mmol) and 3,4-dihydroisoquinoline **37** (100 mg, 0.76 mmol) in THF at 65 °C, then allylzinc bromide **134** (synthesised using general procedure C, 0.91 M in THF, 1 mL, 0.91 mmol) at −78 °C for 2 h gave the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (3:1 then 1:1) as eluent gave the diene **119** (136 mg, 59%) as a yellow oil.

Lab Book Reference: SC2/62

(Table 2.3, Entry 5)

Using general procedure D, *trans*-cinnamoyl chloride **136** (400 mg, 2.4 mmol) and 3,4-dihydroisoquinoline **37** (262 mg, 2.0 mmol) in THF at 65 °C, then allylzinc bromide **134** (synthesised using general procedure C, 2.4 M in THF, 1 mL, 2.4 mmol) at −78 °C for 3 h gave the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (4:1 then 2:1 then 1:1) as eluent gave the diene **119** (430 mg, 70%) as a yellow oil.

Lab Book Reference: SC2/66

(Table 2.3, Entry 6)

Using general procedure D, *trans*-cinnamoyl chloride **136** (400 mg, 2.4 mmol) and 3,4-dihydroisoquinoline **37** (262 mg, 2.0 mmol) in CH_2Cl_2 at rt, then allylzinc bromide **134** (synthesised using general procedure C, 2.4 M in THF, 1 mL, 2.4 mmol) at −78 °C for 3 h gave the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (4:1 then 2:1 then 1:1) as eluent gave the diene **119** (220 mg, 37%) as a yellow oil.

Lab Book Reference: SC2/67

(Table 2.3, Entry 7)

Using general procedure D, *trans*-cinnamoyl chloride **136** (303 mg, 1.82 mmol) and 3,4-dihydroisoquinoline **37** (200 mg, 1.52 mmol) in THF at 65 °C, then allylzinc bromide **134** (synthesised using general procedure C, 1.82 M in THF, 1 mL, 1.82 mmol) added at −78 °C then allowed to warm to rt for 2 h gave the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (4:1 then 2:1 then 1:1) as eluent gave the diene **119** (351 mg, 76%) as a yellow oil.

Lab Book Reference: SC2/68

(Table 2.4, Entry 1)

Using general procedure E, 3,4-dihydroisoquinoline **37** (100 mg, 0.76 mmol) and allylmagnesium bromide **137** (1 M in Et_2O, 0.84 mL, 0.84 mmol), then *trans*-cinnamoyl chloride **136** (152 mg, 0.91 mmol) in THF (1 mL) gave the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (4:1 then 2:1 then 1:1) as eluent gave the diene **119** (100 mg, 43%) as a yellow oil.

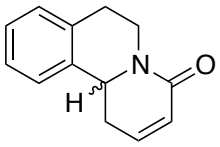
Lab Book Reference: SC2/69

(Table 2.4, Entry 2)

Using general procedure E, 3,4-dihydroisoquinoline **37** (100 mg, 0.76 mmol) and allylzinc bromide **134** (synthesised using general procedure C, 0.84 M in THF, 1 mL, 0.84 mmol), then *trans*-cinnamoyl chloride **136** (152 mg, 0.91 mmol) in THF (1 mL) gave the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (4:1 then 2:1 then 1:1) as eluent gave the diene **119** (150 mg, 65%) as a yellow oil.

Lab Book Reference: SC2/70

6,7-Dihydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one 108

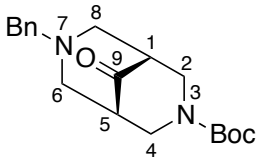


108

Grubbs' 2nd generation catalyst (19 mg, 0.022 mmol) was added in one portion to a stirred solution of diene **119** (82 mg, 0.27 mmol) in toluene (3 mL) at rt under Ar. The resulting solution was stirred at rt for 20 h and then the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave dihydropyridone **108** (38 mg, 72%) as a yellow oil, R_F (1:1 petrol-EtOAc) 0.2; IR (ATR) 2945, 1659 (C=O), 1606 (C=C), 1419, 1143, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.14 (m, 4H, Ar), 6.68 (ddd, *J* = 10.0, 6.5, 2.0 Hz, 1H, C*H*=CHC(O)), 6.08 (dd, *J* = 10.0, 3.0 Hz, 1H, CH=C*H*C(O)), 4.83-4.73 (m, 2H, CHN, NC$H_A$$CH_B$), 3.01-2.72 (m, 4H, NCH_AH_B, CH_2, C$H_C$$H_D$C=C), 2.34 (dddd, *J* = 17.0, 14.5, 3.0, 2.0 Hz, 1H, $CH_C$$H_D$C=C); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.6 (C=O), 139.0 (*C*H=CHC(O)), 135.7 (*ipso*-Ar), 134.7 (*ipso*-Ar), 128.9 (Ar), 126.7 (Ar), 126.6 (Ar), 125.6 (Ar), 125.3 (CH=*C*HC(O)), 54.4 (CHN), 37.8 (NCH_2), 33.3 (C=C*C*H_2), 29.4 (NCH_2*C*H_2); HRMS (ESI) *m/z* calcd for $C_{13}H_{13}NO$ $(M + H)^+$ 200.1070, found 200.1076 (−2.1 ppm error).

Lab Book Reference: SC1/20

(1*R,5*S**)-*tert*-Butyl 7-benzyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 48**



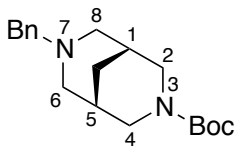
48

Using general procedure F, *tert*-butyl 4-oxopiperidine-1-carboxylate (7.50 g, 37.64 mmol), acetic acid (2.16 mL, 37.64 mmol), benzylamine (4.12 mL, 37.64 mmol) and paraformaldehyde (2 x (2.49 g, 82.81 mmol)) in MeOH (45 and 75 mL) at reflux under Ar gave the crude product. Purification by flash column chromatography on silica with

petrol-EtOAc (3:1) as eluent gave *N*-Boc bispidone **48** (9.51 g, 76%) as a yellow oil, R_F (3:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) 50:50 mixture of rotamers δ 7.36-7.24 (m, 5H, Ar), 4.58 (d, *J* = 13.5 Hz, 1H, C(O)NCH), 4.42 (d, *J* = 13.5 Hz, 1H, C(O)NCH), 3.54 (d, *J* = 13.0 Hz, 1H, CH_AH$_B$Ar), 3.48 (d, *J* = 13.0 Hz, 1H, CH$_A$$H_B$Ar), 3.36 (dd, *J* = 13.5, 2.0 Hz, 1H, C(O)NCH), 3.28 (dd, *J* = 13.5, 2.0 Hz, 1H, C(O)NCH), 3.20 (d, *J* = 11.5 Hz, 1H, NCH), 3.16 (d, *J* = 11.5 Hz, 1H, NCH), 2.72 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 2.66 (dd, *J* = 11.0, 3.5 Hz, 1H, NCH), 2.44 (br s, 1H, CH), 2.40 (br s, 1H, CH), 1.54 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 213.4 (C=O, ketone), 154.6 (C=O, Boc), 137.3 (*ipso*-Ar), 128.6 (Ar), 128.2 (Ar), 127.1 (Ar), 79.9 (*C*(CH$_3$)$_3$), 61.7 (CH$_2$Ar), 58.9 (NCH$_2$), 58.6 (NCH$_2$), 50.3 (C(O)N*C*H$_2$), 49.6 (C(O)N*C*H$_2$), 47.4 (2 x CH), 28.5 (C(*C*H$_3$)$_3$). Spectroscopic data consistent with those reported in the literature.[46]

Lab Book Reference: SC3/79

(1*R,5*S**)-*tert*-Butyl 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 49**



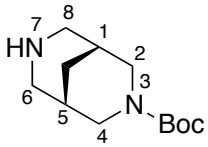
49

Using general procedure G, *p*-toluenesulfonyl hydrazide (6.43 g, 34.54 mmol), *N*-Boc bispidone **48** (9.51 g, 28.78 mmol) in EtOH (250 mL) at rt under Ar, then $NaBH_4$ (9.15 g, 241.75 mmol) at rt for 18 h and reflux for 4 h gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave *N*-Boc bispidine **49** (5.71 g, 62%) as a pale yellow oil, R_F (4:1 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) 50:50 mixture of rotamers δ 7.34-7.19 (m, 5H, Ar), 4.16 (br d, *J* = 13.0 Hz, 1H, C(O)NCH), 4.00 (br d, *J* = 13.0 Hz, 1H, C(O)NCH), 3.44 (d, *J* = 13.5 Hz, 1H, CH_AH$_B$Ar), 3.30 (d, *J* = 13.5 Hz, 1H, CH$_A$$H_B$Ar), 3.11-3.01 (m, 2H, C(O)NCH), 2.98 (br d, *J* = 11.0 Hz, 1H, NCH), 2.88 (br d, *J* = 11.0 Hz, 1H, NCH), 2.22 (br d, *J* = 11.0 Hz, 1H, NCH), 2.16 (br d, *J* = 11.0 Hz, 1H, NCH), 1.87 (br s, 1H, CH), 1.78 (br s, 1H, CH), 1.67-1.44 (m, 2H, CH$_2$), 1.52 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 155.0 (C=O), 138.9 (*ipso*-Ar), 128.5 (Ar), 128.0 (Ar), 126.5 (Ar),

78.6 ($C(CH_3)_3$), 63.4 (CH_2Ar), 58.9 (NCH_2), 58.6 (NCH_2), 48.3 (C(O)NCH_2), 47.5 (C(O)NCH_2), 31.1 (CH_2), 28.9 (2 x CH), 28.6 (C(CH_3)$_3$). Spectroscopic data consistent with those reported in the literature.[46]

Lab Book Reference: SC3/84

(1*R,5*S**)-*tert*-Butyl 3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 63**

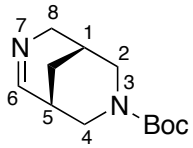


63

Using general procedure H, 20% (w/w) $Pd(OH)_2/C$ (1.26 g, 1.80 mmol) and bispidine **49** (5.70 g, 18.01 mmol) in EtOH (170 mL) at rt under Ar for 18 h gave amine **63** (3.97 g, 98%) as a yellow oil, IR (ATR) 3385 (N-H), 2919, 1681 (C=O), 1420, 1391, 1363, 1238, 1169, 1126, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.10 (d, J = 13.0 Hz, 2H, NCH), 3.21 (d, J = 13.5 Hz, 2H, NCH), 3.08 (dd, J = 13.0, 3.0 Hz, 4H, NCH), 1.93-1.89 (m, 1H, CH_AH$_B$), 1.81-1.75 (m, 3H, CH$_A$$H_B$, 2 x CH), 1.48 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6 (C=O), 80.2 ($C(CH_3)_3$), 50.4 (NCH_2), 48.8 (NCH_2), 30.6 (CH_2), 28.4 (C(CH_3)$_3$), 27.4 (CH); HRMS (ESI) *m/z* calcd for $C_{12}H_{22}N_2O_2$ $(M + H)^+$ 227.1754, found 2227.1751 (+1.5 ppm error).

Lab Book Reference: SC4/5

(1*R,5*R**)-*tert*-Butyl 3,7-diazabicyclo[3.3.1]non-7-ene-3-carboxylate 64**



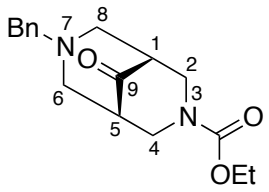
64

Using general procedure I, *N*-bromosuccinimide (77 mg, 0.43 mmol) and amine **63** (89 mg, 0.39 mmol) in CH_2Cl_2 (10 mL) at rt for 2 h, then 30% $NaOH_{(aq)}$ (3 mL) for 2 h gave

the crude product. Purification by column chromatography on silica with MeOH-CH_2Cl_2 (1:19) as eluent gave imine **64** (65 mg, 75%) as an orange oil, R_F (9:1 CH_2Cl_2-MeOH) 0.30; IR (ATR) 2930, 1681 (C=O), 1580 (C=N), 1423, 1365, 1264, 1239, 1167, 1136, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 50:50 mixture of rotamers δ 7.84 (br s, 1H, CH=N), 4.23 (br d, *J* = 13.0 Hz, 0.5H, C(O)NCH), 4.17 (br d, *J* = 13.0 Hz, 0.5H, C(O)NCH), 4.08 (br d, *J* = 13.0 Hz, 0.5H, C(O)NCH), 4.01 (br d, *J* = 13.0 Hz, 0.5H, C(O)NCH), 3.83-3.67 (m, 2H, CH=NC*H*$_2$), 2.96 (br d, *J* = 13.0 Hz, 0.5H, C(O)NCH), 2.87 (br d, *J* = 12.5 Hz, 0.5H, C(O)NCH), 2.84 (br d, *J* = 12.5 Hz, 0.5H, C(O)NCH), 2.76 (br d, *J* = 13.0 Hz, 0.5H, C(O)NCH), 2.42 (br s, 0.5H, CH), 2.32 (br s, 0.5H, CH), 1.94 (br s, 0.5H, CH), 1.90-1.84 (m, 1.5H, C*H*$_A$H$_B$, CH), 1.69-1.66 (m, 1H, CH$_A$*H*$_B$), 1.41 (s, 9H, C(CH$_3$)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 163.5 and 163.11 (CH=N), 154.9 (C=O), 79.7 (*C*(CH$_3$)$_3$), 55.3 and 55.2 (CH=N*C*H$_2$), 50.7 and 49.6 (C(O)N*C*H$_2$), 45.4 and 44.5 (C(O)N*C*H$_2$), 33.1 and 32.9 (N=CH*C*H), 28.7 (CH), 28.3 (C(*C*H$_3$)$_3$), 26.1 (CH$_2$); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}N_2O_2$ (M + H)$^+$ 225.1598, found 225.1601 (−1.3 ppm error).

Lab Book Reference: SC1/29

(1*R,5*S**)-Ethyl 7-benzyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 123**



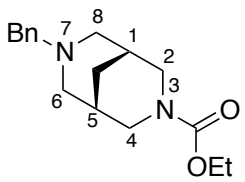
123

Using general procedure F, ethyl 4-oxopiperidine-1-carboxylate **122** (3.7 mL, 24.53 mmol), acetic acid (1.41 mL, 24.53 mmol), benzylamine (2.95 mL, 26.98 mmol) and paraformaldehyde (2 x (1.93 g, 53.97 mmol)) in MeOH (35 mL and 55 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (3:1) as eluent gave *N*-ethyl carbamate bispidone **123** (4.80 g, 64%) as a yellow oil, R_F (3:1 petrol-EtOAc) 0.20; IR (ATR) 2893, 2760, 1706 (C=O, ketone), 1671 (C=O, carbamate), 1412, 1208, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 50:50 mixture of rotamers δ 7.30-7.19 (m, 5H, Ar), 4.67 (ddd, *J* = 13.5, 2.0, 2.0 Hz, 1H, C(O)NCH), 4.44

(ddd, J = 13.5, 2.0, 2.0 Hz, 1H, C(O)NCH), 4.28-4.13 (m, 2H, OCH_2CH$_3$), 3.52 (d, J = 13.0 Hz, CH_AH$_B$Ar), 3.32-3.23 (m, 4H, CH$_A$$H_B$Ar, C(O)NCH, 2 x NCH), 3.14 (ddd, J = 11.0, 2.0, 2.0 Hz, 1H, C(O)NCH), 2.64 (dd, J = 11.0, 2.0 Hz, 1H, NCH), 2.56 (dd, J = 11.0, 2.0 Hz, 1H, NCH), 2.40 (br m, 1H, CH), 2.32 (br m, 1H, CH), 1.28-1.20 (m, 3H, OCH$_2$CH_3); ^{13}C NMR (100.6 MHz, CDCl$_3$) rotamers δ 213.0 (C=O, ketone), 155.5 (C=O, carbamate), 137.4 (*ipso*-Ar), 128.8 (Ar), 128.1 (Ar), 127.1 (Ar), 61.9 (CH$_2$Ar), 61.5 (O*C*H$_2$CH$_3$), 59.4 (NCH$_2$), 58.6 (NCH$_2$), 50.1 (C(O)N*C*H$_2$), 49.9 (C(O)N*C*H$_2$), 47.8 (CH), 47.5 (CH), 14.6 (OCH$_2$*C*H$_3$); HRMS (ESI) *m/z* calcd for C$_{17}$H$_{22}$N$_2$O$_3$ (M + H + MeOH)$^+$ 335.1965, found 335.1959.

Lab Book Reference: SC2/25

(1*R,5*S**)-Ethyl 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 120**



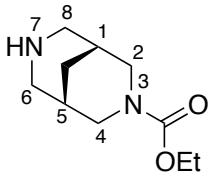
120

Using general procedure G, *p*-toluenesulfonyl hydrazide (4.49 g, 24.09 mmol) and *N*-ethyl carbamate bispidone **123** (6.07 g, 20.07 mmol) in EtOH (150 mL) at rt under Ar, then NaBH$_4$ (6.38 g, 168.59 mmol) at rt for 18 h, then reflux for 8 h gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave *N*-ethyl carbamate bispidine **120** (3.78 g, 65%) as a pale yellow oil, R_F (6:1 Petrol-EtOAc) 0.20; IR (ATR) 2871, 1668 (C=O), 1412, 1216, 1110 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) 50:50 mixture of rotamers δ 7.29-7.19 (m, 5H, Ar), 4.28 (br d, J = 13.0 Hz, 1H, C(O)NCH), 4.24-4.15 (m, 2H, OCH_2CH$_3$), 4.06 (br d, J = 13.0 Hz, 1H, C(O)NCH), 3.49 (d, J = 13.0 Hz, 1H, CH_AH$_B$Ar), 3.17 (d, J = 13.0 Hz, 1H, CH$_A$$H_B$Ar), 3.11-3.03 (m, 3H, 2 x C(O)NCH, NCH), 2.87 (br d, J = 11.0 Hz, 1H, NCH), 2.28 (ddd, J = 11.0, 2.0, 2.0 Hz, 1H, NCH), 2.12 (ddd, J = 11.0, 2.0, 2.0 Hz, 1H, NCH), 1.87 (br s, 1H, CH), 1.77 (br s, 1H, CH), 1.72-1.57 (m, 2H, CH$_2$), 1.28 (t, J = 7.0 Hz, OCH$_2$CH_3); ^{13}C NMR (100.6 MHz, CDCl$_3$) rotamers δ 155.7 (C=O), 138.9 (*ipso*-Ar), 128.7 (Ar), 127.9 (Ar), 126.6 (Ar), 63.7 (*C*H$_2$Ar), 60.8 (O*C*H$_2$CH$_3$), 59.2 (NCH$_2$), 58.1 (NCH$_2$),

48.1 (2 x C(O)NCH_2), 31.5 (CH_2), 29.1 (CH), 28.9 (CH), 14.8 (OCH_2CH_3); HRMS (ESI) *m/z* calcd for $C_{17}H_{24}N_2O_2$ $(M + H)^+$ 289.1911, found 289.1897 (+4.0 ppm error).

Lab Book Reference: SC1/58

(1*R,5*S**)-Ethyl 3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 124**

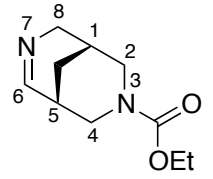


124

Using general procedure H, 20% (w/w) $Pd(OH)_2/C$ (721 mg, 1.03 mmol) and bispidine **120** (2.96 g, 10.26 mmol) in EtOH (80 mL) at rt under H_2 for 18 h gave amine **124** (2.04 g, 100%) as a pale brown oil, R_F (9:1 CH_2Cl_2-MeOH) 0.10; IR (ATR) 3470 (NH), 2912, 1690 (C=O), 1430, 1234, 1128, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23-3.97 (m, 2H, NCH), 4.10 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.11-3.05 (m, 4H, NCH), 2.94 (ddd, *J* = 13.5, 2.5, 2.5 Hz, 2H, NCH), 1.88-1.71 (m, 2H, CH_2), 1.66 (br s, 2H, CH), 1.22 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.1 (C=O), 61.2 (OCH_2CH_3), 51.2 (NCH_2), 48.8 (NCH_2), 31.1 (CH_2), 27.8 (CH), 14.6 (OCH_2CH_3); HRMS (ESI) *m/z* calcd for $C_{10}H_{18}N_2O_2$ $(M + H)^+$ 199.1441, found 199.1432 (+4.5 ppm error).

Lab Book Reference: SC2/31

(1*R,5*R**)-Ethyl 3,7-diazabicyclo[3.3.1]non-7-ene-3-carboxylate 121**



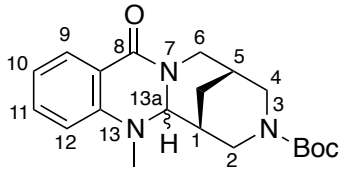
121

Using general procedure I, *N*-bromosuccinimide (2.30 g, 11.76 mmol) and amine **120** (2.33 g, 12.94 mmol) in CH_2Cl_2 (60 mL) at rt for 4 h, then 30% $NaOH_{(aq)}$ (30 mL) for

18 h gave the crude product. Purification by column chromatography on silica with MeOH-CH_2Cl_2 (1:19) as eluent gave imine **121** (1.07 g, 46%) as an orange oil, R_F (1:19 MeOH-CH_2Cl_2) 0.20; IR (ATR) 2927, 1683 (C=O), 1582 (C=N), 1432, 1263, 1230, 1129, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 50:50 mixture of rotamers for **121**, δ 7.84 (br s, 1H, CH=N), 4.26-4.01 (m, 2H, C(O)NCH), 4.05 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.81-3.67 (m, 2H, $CH{=}NCH_2$), 2.99 (br d, *J* = 13.0 Hz, 0.5H, C(O)NCH), 2.90 (br d, *J* = 13.0 Hz, 1H, C(O)NCH), 2.82 (br d, *J* = 13.0 Hz, 0.5H, C(O)NCH), 2.43 (br s, 0.5H, CH), 2.39 (br s, 0.5H, CH), 1.96 (br s, 0.5H, CH), 1.92 (br s, 0.5H, CH), 1.89-1.84 (m, 1H, CH_AH_B), 1.70-1.67 (m, 1H, CH_AH_B), 1.21 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers for **121** δ 163.4 and 163.1 (CH=N), 155.7 (C=O), 61.3 (OCH_2CH_3), 55.2 and 55.1 ($CH{=}NCH_2$), 50.2 and 50.1 ($C(O)NCH_2$), 44.9 ($C(O)NCH_2$), 32.8 and 32.7 (N=CHCH), 28.4 (CH), 25.9 (CH_2), 14.5 (OCH_2CH_3); ^1H NMR spectrum of the product indicates ~17% of the trimer as shown by broad signals at δ 4.26-4.02, 3.10-2.77 and 1.28-1.17 ppm. HRMS (ESI) *m/z* calcd for $C_{10}H_{16}N_2O_2$ $(M + H)^+$ 197.1285, found 197.1284 (+0.4 ppm error).

Lab Book Reference: SC1/76

(1*R,5*R**)-*tert*-Butyl 13-methyl-8-oxo-4,5,6,8,13,13a-hexahydro-1*H*-1,5-methano[1,5]diazocino[2,1-*b*]quinazoline-3(2*H*)-carboxylate 127**



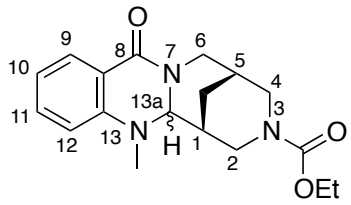
127

DIPEA (90 μL, 0.52 mmol) and T3P (267 mg of a 50% solution in THF, 0.42 mmol) were added to a stirred solution of imine **64** (63 mg, 0.28 mmol) and *N*-methylanthranilic acid **38** (52 mg, 0.34 mmol) in toluene (2 mL) at rt. The resulting solution was stirred and heated at 90 °C in a sealed vessel for 20 h. The solution was alloed to cool to rt. Then the solution was diluted with CH_2Cl_2 (10 mL) and poured into sat. $NaHCO_{3(aq)}$ (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by

flash column chromatography on silica with petrol-EtOAc (7:3) as eluent gave a gave a single diastereoisomer of **127** with undefined relative stereochemistry (28 mg, 28%) as a dark yellow oil, R_F (1:1 petrol-EtOAc) 0.20; IR (ATR) 2974, 1688 (C=O), 1651 (C=O), 1421, 1235, 1167, 1135, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (br d, *J* = 7.5 Hz, 1H, Ar), 7.35 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H, Ar), 6.80 (br dd, *J* = 7.5, 7.5 Hz, 1H, Ar), 6.58 (br d, *J* = 8.5 Hz, 1H, Ar), 4.91 (dd, *J* = 14.0, 10.5 Hz, 1H, NCH), 4.63 (d, *J* = 3.0 Hz, 1H, NC*H*NCH_3), 4.19-4.16 (m, 1H, NCH), 4.04-4.02 (m, 1H, NCH), 3.93-3.89 (m, 1H, NCH), 2.91 (s, 3H, NCH_3), 2.90-2.74 (m, 2H, NCH, C$H_A$$H_B$), 2.58 (dd, *J* = 14.0, 3.0 Hz, 1H, NCH), 2.23 (br s, 2H, 2 x CH), 1.64-1.61 (m, 1H, $CH_A$$H_B$), 1.48 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.4 (Ar(C=O)N), 156.7 (C=O, Boc), 146.6 (*ipso*-Ar), 133.8 (Ar), 128.9 (Ar), 118.1 (Ar), 115.4 (*ipso*-Ar), 112.1 (Ar), 80.2 ($C(CH_3)_3$), 75.5 (NCHN), 47.9 (NCH_2), 43.5 (NCH_2), 35.2 (CH), 34.5 (CH), 29.7 (CH_2), 28.4 (CH_3), 26.6 (C(CH_3)); HRMS (ESI) *m/z* calcd for $C_{20}H_{27}N_3O_3$ $(M + Na)^+$ 380.1945, found 380.1937 (+2.3 ppm error).

Lab Book Reference: SC1/35

(1*R,5*R**)-Ethyl 13-methyl-8-oxo-4,5,6,8,13,13a-hexahydro-1*H*-1,5-methano[1,5]diazocino[2,1-*b*]quinazoline-3(2*H*)-carboxylate 128**



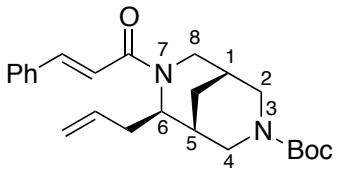
128

DIPEA (116 μL, 0.67 mmol) and T3P (343 mg of a 50% solution in THF, 0.54 mmol) were added to a stirred solution of imine **121** (71 mg, 0.36 mmol) and *N*-methylanthranilic acid **38** (65 mg, 0.43 mmol) in toluene (3 mL) under Ar at rt. The resulting solution was stirred and heated at 90 °C in a sealed vessel for 20 h. The solution was allowed to cool to rt. Then, the solution was diluted with CH_2Cl_2 (10 mL) and poured into sat. $NaHCO_{3(aq)}$ (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude

product. Purification by flash column chromatography on silica with petrol-EtOAc (2:1) as eluent gave a gave a single diastereoisomer of **128** with undefined relative stereochemistry (77 mg, 65%) as a pale yellow oil, R_F (EtOAc) 0.40; IR (ATR) 2923, 1690 (C=O), 1646 (C=O), 1605 (C=C), 1430, 1226, 1131, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar), 7.34 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H, Ar), 6.82-6.78 (m, 1H, Ar), 6.57 (dd, *J* = 8.5, 0.5 Hz, 1H, Ar), 4.92 (dd, *J* = 14.0, 10.5 Hz, 1H, NCH), 4.63 (d, *J* = 3.0 Hz, 1H, NC*H*NCH_3), 4.17 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 4.20-3.94 (m, 2H, NCH), 2.90 (s, 3H, CH_3), 2.92-2.81 (m, 2H, 2 x NCH), 2.58 (dd, *J* = 14.0, 2.5 Hz, 1H, NCH), 2.27-2.21(m, 2H, 2 x CH), 1.65-1.61 (m, 1H, OCH_AH_B), 1.44 (ddd, *J* = 13.5, 2.0, 2.0 Hz, 1H, CH_ACH_B), 1.28 (t, *J* = 7.0 Hz, CH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.3 (Ar(C=O)N), 156.8 (C=O, carbamate), 146.6 (*ipso*-Ar), 133.7 (Ar), 128.8 (Ar), 118.0 (Ar), 115.2 (*ipso*-Ar), 112.0 (Ar), 75.5 (NCHN), 61.7 (OCH_2CH_3), 48.8 (NCH_2), 48.4 (NCH_2), 43.4 (NCH_2), 35.0 (CH), 34.5 (CH), 27.8 (CH_2), 26.4 (CH_3), 14.6 (OCH_2CH_3); HRMS (ESI) *m/z* calcd for $C_{18}H_{23}N_3O_3$ $(M + H)^+$ 330.1812, found 330.1804 (+2.1 ppm error). Product **128** is a single diastereoisomer of unknown stereochemistry.

Lab Book Reference: SC1/48

(1*R,5*R**,6*R**)-*tert*-Butyl 6-allyl-7-cinnamoyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 129**



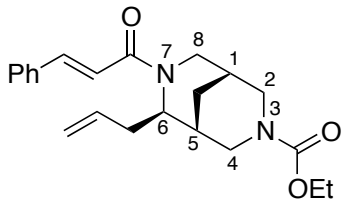
129

Using general procedure D, *trans*-cinnamoyl chloride **136** (83 mg, 0.50 mmol) and imine **64** (100 mg, 0.45 mmol) in THF at 65 °C for 2.5 h, then allylzinc bromide **134** (synthesised using general procedure C, 0.54 M in THF, 1 mL, 0.54 mmol) added at −78 °C then allowed to warm to rt for 16 h gave the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (2:1) as eluent gave the diene **129** (31 mg, 17%) as a colourless oil, R_F (2:1 hexane-EtOAc) 0.20; IR (ATR) 2975, 2855, 1682, 1644, 1600, 1424, 1364, 1239, 1169, 1135, 995, 761, 730 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) 50:50 mixture of rotamers δ 7.51-7.42 (m, 3H, CH=C*H*Ph, Ph), 7.37-7.30 (m, 3H, Ph), 6.93-6.84 (m, 1H, C*H*=CHPh), 5.88-5.76 (m, 0.5H, C*H*=CH_2), 5.74-5.64 (m, 0.5H, C*H*=CH_2), 5.13-5.03 (m, 2H, CH=CH_2), 4.93-4.72 (m, 0.5H, NC*H*CH_2), 4.63-4.60 (m, 0.5H, NCH), 4.48-4.35 (m, 0.5H, NCH), 4.27-4.05 (m, 2.5H, NC*H*CH_2, 2 x NCH), 3.49-3.40 (m, 0.5H, NCH), 3.14-2.94 (m, 2.5H, NCH), 2.48-2.28 (m, 2H, CH_2C=C), 2.10-2.07 (m, 1H, C$H_A$$H_B$), 1.87-1.84 (m, 2H, 2 x CH), 1.67-1.62 (m, 1H, $CH_A$$H_B$), 1.38 (s, 4.5H, C($CH_3$)$_3$), 1.36 (s, 4.5H, C($CH_3$)$_3$);^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 167.1 and 166.1 (C=O), 154.7 and 154.6 (C=O, carbamate), 141.5 and 141.2 (Ar), 135.7 (*ipso*-Ar), 135.1, 134.0, 129.1, 129.0, 128.7, 128.6, 128.5, (CH_2=*C*H, Ar), 127.7, 127.6, 119.1 and 119.0 (*C*H=CHPh, CH=*C*HPh), 118.3 and 117.1 (*C*H_2=CH), 79.7 (*C*(CH_3)$_3$), 57.7 and 53.5 (NCH), 50.0, 49.2, 48.9, 47.9, 46.9 and 43.4 (NCH_2), 37.2 and 35.1 (*C*H_2C=C), 29.8, 29.6 and 29.2 (CH), 28.3, 28.2 and 28.1 (C(*C*H_3)$_3$), 27.9 and 27.8 (CH), 26.2 and 26.0 (CH_2 bridge); HRMS (ESI) *m/z* calcd for $C_{24}H_{32}N_2O_3$ $(M + H)^+$ 397.2486, found 397.2491 (−1.5 ppm error).

Lab Book Reference: SC3/55

(1*R,5*R**,6*R**)-Ethyl 6-allyl-7-cinnamoyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate 131**



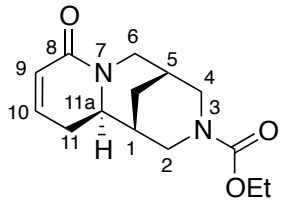
131

DIPEA (0.68 mL, 3.90 mmol) and T3P (2.02 g of a 50% solution in THF, 3.17 mmol) were added to a stirred solution of imine **121** (415 mg, 2.11 mmol) and *trans*-cinnamic acid (375 mg, 2.53 mmol) in CH_2Cl_2 (20 mL) under Ar at rt. The resulting solution was stirred and heated at 45 °C for 2.5 h. The solution was cooled to −30 °C and allyl trimethylsilane (1.68 mL, 10.55 mmol) followed by BF_3•OEt_2 (0.78 mL, 6.33 mmol) were added. The mixture was allowed to warm to rt and stirred for 2.5 h. Then, the solution was diluted with CH_2Cl_2 (20 mL) and poured into sat. $NaHCO_{3(aq)}$ (20 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10

mL). The combined organics were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with MeOH-CH_2Cl_2 (1:19) as eluent gave substituted diene **131** (489 mg, 63%) as a pale yellow oil, R_F (1:19 MeOH-CH_2Cl) 0.50; IR (ATR) 2932, 1687 (C=O), 1643 (C=O), 1599 (C=C), 1429, 1231, 1135, 995, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 50:50 mixture of rotamers δ 7.67-7.41 (m, 3H, CH=C*H*Ph, Ph), 7.38-7.28 (m, 3H, Ph), 6.93-6.84 (m, 1H, C*H*=CHPh), 5.88-5.76 (m, 0.5H, C*H*=CH_2), 5.76-5.64 (m, 0.5H, C*H*=CH_2), 5.14-4.94 (m, 2H, CH=CH_2), 4.86-4.78 (m, 0.5H, NC*H*CH_2), 4.67-4.64 (m, 0.5H, NCH), 4.43-4.30 (m, 1H, NCH), 4.29-3.81 (m, 4.5H, OC$H_2$$CH_3$, NC*H*$CH_2$, 2 x NCH), 3.51-3.41 (m, 0.5H, NCH), 3.17-2.97 (m, 2.5H, NCH), 2.47-2.29 (m, 2H, CH_2C=C), 2.13-2.07 (m, 1H, C$H_A$$H_B$), 1.94-1.79 (m, 2H, 2 x CH), 1.71-1.65 (m, 1H, $CH_A$$H_B$), 1.23-1.17 (m, 2H, OCH_2CH_3), 1.02-0.98 (m, 1H, OCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers δ 167.1, 166.2, 165.9 and 165.4 (C=O), 155.9 and 155.8 (C=O, carbamate), 142.1, 141.9, 141.4 and 141.0 (*C*HPh), 135.6 and 135.4 (*ipso*-Ar), 135.0, 134.5, 133.9 and 133.8 (CH_2=*C*H), 129.3, 129.1, 129.0, 128.7, 128.6, 128.5, 127.7, 127.6 and 128.5 (Ar), 119.1, 118.8, 118.5 and 118.4 (*C*H=CHPh), 118.3, 117.7, 117.5 and 117.1 (*C*H_2=CH), 61.4 and 61.2 (O*C*$H_2$$CH_3$), 57.8, 57.4, 53.2 and 53.0 (NCH), 49.7, 49.6, 48.9, 48.6 (NCH_2), 46.8 and 46.7 (NCH_2), 43.0 and 42.6 (NCH_2), 37.1, 36.8, 35.2 and 35.1 (*C*H_2C=C), 30.1 and 29.9 (CH), 27.9, 27.8 and 27.7 (CH), 26.3 and 26.1 (CH_2 bridge), 14.5 and 14.3 (OCH_2*C*H_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{28}N_2O_3$ $(M + H)^+$ 369.2173, found 369.2169 (+0.6 ppm error).

Lab Book Reference: SC1/62

(1*R,5*R**,11a*R**)-Ethyl 8-oxo-4,5,6,8,11,11a-hexahydro-1*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocine-3(2*H*)-carboxylate 132**

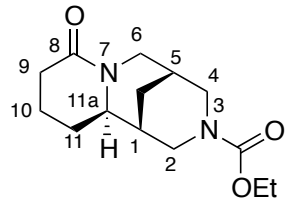


132

Grubbs' 2nd generation catalyst (22 mg, 0.026 mmol) was added in one portion to a stirred solution of diene **131** (114 mg, 0.31 mmol) in toluene (6 mL) at rt under Ar. The resulting solution was stirred at rt for 20 h and then the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave a single diastereoisomer (by ^{1}H NMR spectroscopy) of dihydropyridone **132** (76 mg, 93%) as a pale brown oil, R_F (EtOAc) 0.10; IR (ATR) 2867, 1691 (C=O), 1659 (C=O), 1610 (C=C), 1427, 1233, 1146, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (ddd, *J* = 9.5, 6.0, 2.5 Hz, 1H, C*H*=CHC(O)), 5.89 (dd, *J* = 9.5, 2.0 Hz, 1H, CH=C*H*C(O)), 4.37 (dd, *J* = 14.5, 10.5 Hz, 1H, NCH), 4.09 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 4.11-4.00 (m, 1H, NCH), 3.94 (br d, *J* = 11.5 Hz, 1H, NCH), 3.54 (br d, *J* = 10.0 Hz, 1H, NC*H*CH$_2$), 2.86-2.76 (m, 3H, NCH), 2.37-2.21 (m, 3H, CH=CHC*H*$_2$, CH), 1.89-1.83 (m, 1H, C*H*$_A$H$_B$), 1.76 (s, 1H, CH), 1.49 (ddd, *J* = 13.0, 2.5, 2.5 Hz, 1H, CH$_A$*H*$_B$), 1.21 (t, *J* = 7.0 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.2 (C=O, dihydropyridone), 156.4 (C=O, carbamate), 138.3 (*C*H=CHC(O)), 125.5 (CH=*C*HC(O)), 61.5 (O*C*H$_2$CH$_3$), 55.8 (NCH), 49.7 (NCH$_2$), 48.8 (NCH$_2$), 43.6 (NCH$_2$), 34.2 (CH), 32.6 (*C*H$_2$CH=CH), 25.5 (CH), 24.5 (CH$_2$), 14.6 (OCH$_2$*C*H$_3$); HRMS (ESI) *m/z* calcd for $C_{14}H_{20}N_2O_3$ $(M + H)^+$ 265.1547, found 265.1540 (+2.5 ppm error).

Lab Book Reference: SC1/59

(1*R,5*R**,11a*R**)-Ethyl 8-oxooctahydro-1*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocine-3(2*H*)-carboxylate 167**

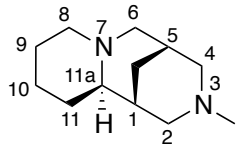


167

10% (w/w) Pd/C (42 mg, 0.04 mmol) was added to a stirred solution of dihydropyridone **132** (54 mg, 0.20 mmol) in a 3:1 mixture of 1,4-dioxane:cyclohexene (8 mL) at rt under N_2. The resulting suspension was stirred and heated at 100 °C for 20 h. The reaction was allowed to cool to rt. The solids were removed by filtration through a pad of Celite® and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent resulted in no product isolation. Flushing the column with MeOH gave tetrahydropyridone **167** (53 mg, 96%) as a yellow oil, IR (ATR) 2931, 2864, 1689 (C=O), 1632 (C=O), 1431, 1230, 1137, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (dd, *J* = 14.0, 11.0 Hz, 1H, NCH), 4.13 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 4.08-3.87 (m, 2H, 2 x NCH), 3.26-3.23 (m, 1H, NCH), 2.88-2.74 (m, 2H, 2 x NCH), 2.46-2.30 (m, 3H, NCH, 2 x CH), 2.20-2.17 (m, 1H, CH), 2.01-1.96 (m, 1H, CH), 1.82-1.53 (m, 5H, 2 x CH, CH_AH_B, 2 x CH), 1.38 (br d, *J* = 13.0 Hz, 1H, CH_AH_B), 1.25 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4 (C=O, dihydropyridone), 156.8 (C=O, carbamate), 61.5 (OCH_2CH_3), 57.4 (NCH), 49.1 (NCH_2), 48.2 (NCH_2), 42.3 (NCH_2), 35.5 (CH), 32.6 (CH_2), 26.1 (CH), 25.3 (CH_2 bridge), 19.7 (CH_2), 14.7 (OCH_2CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{22}N_2O_3$ $(M + H)^+$ 267.1703, found 267.1701 (+0.6 ppm error).

Lab Book Reference: SC1/66

(1*S,5*R**,11a*R**)-3-methyldecahydro-1*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocine 168**

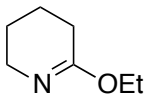


168

A solution of tetrahydropyridone **167** (47 mg, 0.18 mmol), in THF (2 mL) was added to a stirred suspension of lithium aluminium hydride (41 mg, 1.08 mmol), in THF (3 mL) at 0 °C. The resulting mixture was stirred and heated at reflux for 2.5 h. The reaction mixture was allowed to cool to rt before being cooled to 0 °C. H_2O (0.1 mL), 20% $NaOH_{(aq)}$ (0.1 mL) and H_2O (0.1 mL) were carefully added. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (10 mL). The filtrate was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude tricyclic amine product **168** (23 mg, 66%). Diagnostic peaks: ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 63.7 (CHN), 46.6 (NMe). Spectroscopic data consistent with those reported in the literature.[69]

Lab Book Reference: SC1/69

6-Ethoxy-2,3,4,5-tetrahydropyridine 145



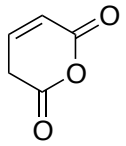
145

Triethyloxonium tetrafluoroborate **155** (2.28 g, 12 mmol) was added to a stirred solution of piperidin-2-one **154** (396 mg, 4 mmol) in CH_2Cl_2 (10 mL) at rt under Ar. 4 Å molecular sieves (2.2 g) and K_2CO_3 (2.21 g, 16 mmol) were added and the reaction mixture was stirred for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and the solids were removed by filtration through a pad of Celite®. The filtrate was washed with sat. $NaHCO_{3(aq)}$ (50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure (care: product is volatile) to give imidate **145** (414 mg, 82%) as a colourless liquid, ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$),

3.48-3.45 (m, 2H, NCH_2), 2.17-2.13 (m, 2H, $N{=}CCH_2$), 1.75-1.69 (m, 2H, CH_2), 1.59-1.53 (m, 2H, CH_2), 1.25 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3). Spectroscopic data consistent with those reported in the literature.[197]

Lab Book Reference: SC2/34

2*H*-Pyran-2,6(3*H*)-dione 141

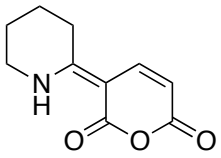


141

trans-Glutaconic acid **156** (1 g, 7.69 mmol) was taken up in acetic anhydride (2.91 mL, 30.75 mmol) and stirred and heated at reflux for 25 min. The reaction mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure to give the crude product **141** as a brown oily residue. Attempted purification by flash column chromatography using (1:9 MeOH-EtOAc) as eluent resulted in decomposition and no product isolated. The ^{1}H NMR spectrum of the crude reaction mixture contained a 75:25 mixture of **141** and acetic anhydride. ^{1}H NMR (400 MHz, $CDCl_3$) for **141** δ 6.96 (dt, *J* = 10.0, 3.5 Hz, 1H, CH=), 6.26 (dt, *J* = 10.0, 2.0 Hz, 1H, CH=), 3.54 (dd, *J* = 3.5, 2.0 Hz, 2H, CH_2); Diagnostic signal for acetic anhydride: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 6H, 2 x CH_3). Spectroscopic data consistent with those reported in the literature.[80]

Lab Book Reference: SC2/29

(*Z*)-3-(Piperidin-2-ylidene)-2*H*-pyran-2,6(3*H*)-dione 157



157

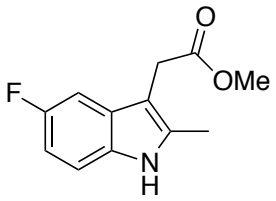
trans-Glutaconic acid **156** (186 mg, 1.43 mmol) was taken up in acetic anhydride (1.54 mL, 5.72 mmol) and stirred and heated at reflux for 25 min. The reaction mixture was

allowed to cool to rt and the solvent was evaporated under reduced pressure to give the crude product **141** as a brown oily residue. The residue was taken up in toluene (40 mL) and imidate **145** (200 mg, 1.57 mmol) was added to the stirred solution at rt under Ar. The reaction mixture was stirred and heated to reflux for 24 h. The reaction was allowed to cool to rt and the solvent was evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 (50 mL) and washed with sat. $NaHCO_{3(aq)}$. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organics were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc-petrol (1:1) as eluent gave the product **157** (104 mg, 38%) as a yellow solid, mp 170-172 °C; R_F (EtOAc) 0.20; IR (ATR) 3431, 3067, 2962, 2877, 1717 (C=O), 1684 (C=O), 1645, 1613, 1582, 1467, 1444, 1409, 1362, 1326, 1283, 955, 796 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.44 (br s, 1H, NH), 7.41 (d, *J* = 9.5 Hz, 1H, *H*C=CH), 5.53 (d, *J* = 9.5 Hz, 1H, HC=C*H*), 3.57-3.55 (m, 2H, NCH_2), 2.77-2.76 (m, 2H, CH_2), 1.92-1.86 (m, 4H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.9 (C=O), 165.5 (C=O), 162.7 (C), 143.1 (HC=), 100.9 (HC=), 91.7 (C), 42.4 (NCH_2), 25.3 (CH_2), 20.8 (CH_2), 18.3 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_{11}NO_3$ $(M + H)^+$ 194.0812, found 194.0812 (−0.3 ppm error).

Lab Book Reference: SC2/38

5.3.2. Chapter 3

Methyl 2-(5-fluoro-2-methyl-1*H*-indol-3-yl)acetate 231

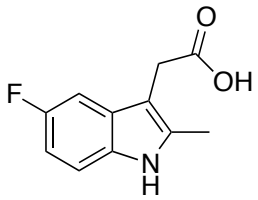


231

A mixture of methyl 4-oxopentanoate (136 μL, 1.10 mmol) and 4-fluorophenylhydrazine hydrochloride **228** (163 mg, 1.00 mmol) in MeOH (3 mL) and conc. H_2SO_4 (120 μL) was stirred under microwave irradiation at 120 °C for 10 min. After being allowed to cool to room temperature, H_2O (10 mL) was added and the reaction was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica using CH_2Cl_2 as eluent gave the substituted indole **231** (194 mg, 87%) as a pale yellow oil, R_F (CH_2Cl_2) 0.30; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H, NH), 7.22 (dd, J = 9.0, 4.5 Hz, 1H, Ar), 7.11 (dd, J = 10.0, 2.5 Hz, 1H, Ar), 6.82 (ddd, J = 9.0, 9.0, 2.5, 1H, Ar), 3.66 (s, 2H, $CH_2C(O)$), 3.58 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.9 (C=O), 156.8 (d, J = 230.5 Hz, *ipso*-Ar), 135.6 (C=*C*CH_3), 131.6 (*ipso*-Ar), 128.6 (d, J = 10.0 Hz, *ipso*-Ar), 111.2 (d, J = 10.0 Hz, Ar), 107.9 (d, J = 25.5 Hz, Ar), 103.7 (d, J = 4.5 Hz, *C*=CCH_3), 102.4 (d, J = 23.5 Hz, Ar), 51.5 (OCH_3), 29.8 (*C*$H_2C(O)$), 11.4 (CH_3); ^{19}F NMR (376 MHz, DMSO-d_6) δ −125.50 (ddd, J = 10.0, 10.0, 4.5); HRMS (ESI) *m/z* calcd for $C_{12}H_{12}FNO_2$ $(M + H)^+$ 222.0925, found 222.0932 (−3.3 ppm error). Spectroscopic data consistent with those reported in the literature.[123]

Lab Book Reference: SC3/42

2-(5-Fluoro-2-methyl-1*H*-indol-3-yl)acetic acid 249

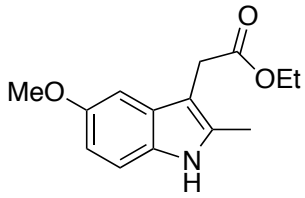


249

1 M $NaOH_{(aq)}$ (10 mL) was added to a stirred solution of methyl 2-(5-fluoro-2-methyl-1*H*-indol-3-yl)acetate **231** (448 mg, 2.03 mmol) in 1:1 THF/MeOH (40 mL). The resulting solution was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the resulting solid residue dissolved in water (5 mL). Conc. HCl was added dropwise until a solid precipitate was observed. The solid was isolated by vacuum filtration, washed with water (5 mL) and hexane (5 mL) and air dried to give the indole acetic acid **249** (369 mg, 87%) as a pale orange solid, mp 164–166 °C [lit.[198] 179–182 °C (from MeCN)]; IR (ATR) 3411 (NH), 2908 (OH), 2736, 2631, 1715 (C=O), 1587, 1481, 1241, 920, 840, 605 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H, OH), 10.94 (s, 1H, NH), 7.22 (dd, J = 9.0, 4.5 Hz, 1H, Ar), 7.12 (dd, J = 10.0, 2.5 Hz, 1H, Ar), 6.81 (ddd, J = 9.0, 9.0, 2.5, 1H, Ar), 3.54 (s, 2H, $CH_2C(O)$), 2.31 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.1 (C=O), 156.8 (d, J = 230.5 Hz, *ipso*-Ar), 135.3 (C=*C*CH_3), 131.6 (*ipso*-Ar), 128.7 (d, J = 10.0 Hz, *ipso*-Ar), 111.1 (d, J = 10.0 Hz, Ar), 107.8 (d, J = 26.0 Hz, Ar), 104.4 (d, J = 4.5 Hz, *C*=CCH_3), 102.5 (d, J = 23.0 Hz, Ar), 29.8 (*C*$H_2C(O)$), 11.4 (CH_3); ^{19}F NMR (376 MHz, DMSO-d_6) δ −125.70 (ddd, J = 10.0, 10.0, 4.5 Hz); HRMS (ESI) *m/z* calcd for $C_{11}H_{10}FNO_2$ $(M + H)^+$ 208.0768, found 208.0771 (−1.4 ppm error).

Lab Book Reference: SC3/24

Ethyl 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetate 234

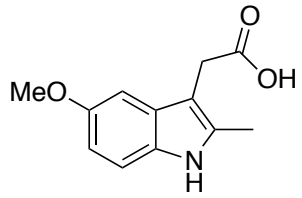


234

A mixture of methyl 4-oxopentanoate (354 μL, 2.86 mmol) and 4-methoxyphenylhydrazine hydrochloride **233** (500 mg, 2.86 mmol) in 2 M HCl/EtOH (20 mL) was stirred at 100 °C for 4 h. After cooling to room temperature the solvent was concentrated until a solid precipitate was observed. The precipitate was removed by filtration and the filtrate concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica with hexane-acetone (9:1 then 8:2) as eluent gave indole ethyl ester **234** (404 mg, 57%) as a brown oil, R_F (8:2 hexane-acetone) 0.10; IR (ATR) 3397 (NH), 2982, 1724 (C=O), 1627, 1592, 1485, 1216, 1174, 1031, 799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H, NH), 7.15 (d, J = 8.5 Hz, 1H, Ar), 7.00 (d, J = 2.5 Hz, 1H, Ar), 6.77 (dd, J = 8.5, 2.5 Hz, 1H, Ar), 4.13 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 3.86 (s, 3H, OCH_3), 3.64 (s, 2H, $CH_2C(O)$), 2.40 (s, 3H, CH_3), 1.24 (t, J = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.0 (C=O), 154.1 (*ipso*-Ar), 133.4 ($C=CCH_3$), 130.1 (*ipso*-Ar), 129.0 (*ipso*-Ar), 111.0 (Ar), 110.9 (Ar), 104.6 ($C=CCH_3$), 100.5 (Ar), 60.6 (OCH_2CH_3), 55.9 (OCH_3), 30.6 ($CH_2C(O)$), 14.3 (OCH_2CH_3), 11.8 (CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NO_3$ $(M + H)^+$ 248.1281, found 248.1274 (+3.0 ppm error). Spectroscopic data consistent with those reported in the literature.[199]

Lab Book Reference: SC3/35

2-(5-Methoxy-2-methyl-1*H*-indol-3-yl)acetic acid 250

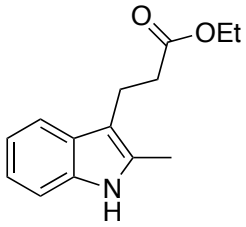


250

1 M NaOH (10 mL) was added to a stirred solution of ethyl 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetate **234** (395 mg, 1.60 mmol) in 1:1 THF/MeOH (40 mL). The reaction mixture was concentrated under reduced pressure and the resulting solid residue dissolved in water (5 mL). The solution was acidified (~pH 1) using conc. HCl resulting in the formation of an oily residue. CH_2Cl_2 (30 mL) and 1 M HCl (40 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the indole acetic acid **250** (331 mg, 95%) as a green/brown solid, mp 141–143 °C (lit.[200] 162 °C (from EtOH)); IR (ATR) 3353 (NH), 3104 (OH), 2903, 1723 (C=O), 1589, 1485, 1309, 1209, 1167, 1016, 804, 647 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H, OH), 10.65 (s, 1H, NH), 7.12 (d, J = 8.5 Hz, 1H, Ar), 6.88 (d, J = 2.5 Hz, 1H, Ar), 6.62 (dd, J = 8.5, 2.5, 1H, Ar), 3.72 (s, 3H, OCH_3) 3.52 (s, 2H, $CH_2C(O)$), 2.29 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.3 (C=O), 153.0 (*ipso*-Ar), 133.7 (C=*C*CH_3), 130.1 (*ipso*-Ar), 128.7 (*ipso*-Ar), 110.9 (Ar), 109.5 (Ar), 103.8 (*C*=CCH_3), 100.1 (Ar), 55.3 (OCH_3), 29.9 (*C*$H_2C(O)$), 11.4 (CH_3); HRMS (ESI) *m/z* calcd for $C_{12}H_{13}NO_3$ $(M + H)^+$ 220.0968, found 220.0967 (+0.6 ppm error). Spectroscopic data consistent with those reported in the literature.[200]

Lab Book Reference: SC3/36

Ethyl 3-(2-methyl-1*H*-indol-3-yl)propanoate 236

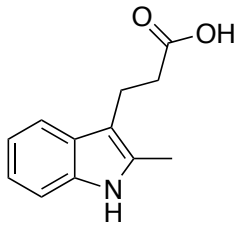


236

A mixture of 5-oxohexanoic acid (0.83 mL, 6.92 mmol) and phenylhydrazine hydrochloride **235** (1.0 g, 6.92 mmol) in a 2 M HCl/EtOH solution (6 mL) was stirred at 100 °C for 4.5 h. The reaction mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The resulting mixture was diluted with water (200 mL) and extracted into EtOAc (100 mL). The two layers were separated and the aqueous extracted with EtOAc (2 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using CH_2Cl_2 as eluent gave the indole ester **236** (948 mg, 59%) as an orange oil, R_F (CH_2Cl_2) 0.30; IR (ATR) 3398 (NH), 2980, 2919, 1712 (C=O), 1622, 1362, 1443, 1371, 1299, 1159, 1049, 859 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (br s, 1H, NH), 7.51 (d, J = 7.0 Hz, 1H, Ar), 7.27-7.25 (m, 1H, Ar), 7.14-7.06 (m, 2H, Ar), 4.12 (q, J = 7.0 Hz, 2H, OC$H_2$$CH_3$), 3.04 (t, J = 7.5 Hz, 2H, CH_2), 2.62 (t, J = 7.5 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 1.23 (t, J = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.5 (C=O), 135.1 (*ipso*-Ar), 131.3 (C=$C$$CH_3$), 128.1 (*ipso*-Ar), 120.8 (Ar), 119.0 (Ar), 117.7 (Ar), 110.2 (Ar), 109.9 (C=CCH_3), 60.3 (O$C$$H_2$$CH_3$), 35.1 ($CH_2$), 19.6 ($CH_2$), 14.1 ($OCH_2$$C$$H_3$), 11.3 ($CH_3$); HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NO_2$ $(M + H)^+$ 232.1332, found 232.1334 (−0.7 ppm error). Spectroscopic data consistent with those reported in the literature.[201]

Lab Book Reference: SC3/64

3-(2-Methyl-1*H*-indol-3-yl)propanoic acid 251

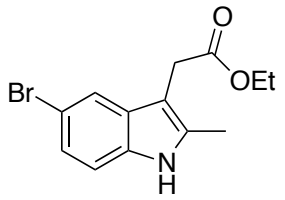


251

1 M $NaOH_{(aq)}$ (20 mL) was added to a stirred solution of the dimethyl-indole ester **236** (888 mg, 3.84 mmol) in 1:1 MeOH-THF (80 mL) at rt. The resulting solution was stirred at rt for 8 h and then the solvent was evaporated under reduced pressure. The resulting residue was taken up in a minimum amount of water (5 mL) and the resulting solution was taken to pH 1 with conc. $HCl_{(aq)}$ resulting in an oily residue. Water (40 mL) was added and the resulting mixture was extracted into CH_2Cl_2 (50 mL) and the two layers separated. The aqueous was extracted into CH_2Cl_2 (2 x 50 mL) and the combined organics dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc-AcOH (60:39.5:0.5) as eluent gave the indole acid **251** (476 mg, 61%) as a yellow solid, mp 121–123 °C (lit.[202] 132–134 °C); IR (ATR) 3384 (NH), 2929, 2634, 1692 (C=O), 1464, 1406, 1308, 1294, 1211, 920 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H, OH), 10.68 (s, 1H, NH), 7.39 (d, J = 7.5 Hz, 1H, Ar), 7.22-7.20 (m, 1H, Ar), 6.97 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.91 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, Ar), 2.87 (t, J = 7.5 Hz, 2H, CH_2), 2.45 (t, J = 7.5, 2H, CH_2), 2.31 (s, 3H, CH_3); ^{13} C NMR (100.6 MHz, DMSO-d_6) δ 174.2 (C=O), 135.2 (*ipso*-Ar), 131.7 (C=*C*CH_3), 127.9 (*ipso*-Ar), 119.9 (Ar), 118.1 (Ar), 117.3 (Ar), 110.4 (Ar), 108.9 (*ipso*-Ar), 35.1 (CH_2), 19.4 (CH_2), 11.2 (CH_3); HRMS (ESI) *m/z* calcd for $C_{12}H_{13}NO_2$ $(M + H)^+$ 204.1019, found 204.1014 (+2.5 ppm error).

Lab Book Reference: SC3/68

Ethyl 2-(5-bromo-2-methyl-1*H*-indol-3-yl)acetate 238

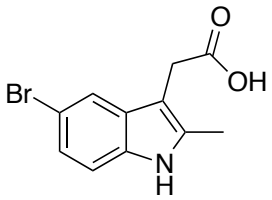


238

A mixture of 4-oxopentanoic acid (0.46 mL, 4.47 mmol) and 4-bromophenylhydrazine hydrochloride **237** (1.00 g, 4.47 mmol) in a solution of EtOH (6 mL) and conc. $H_2SO_{4\,(aq)}$ (0.45 mL) was stirred at reflux for 16 h. The reaction mixture was allowed to cool to room temperature, then water (20 mL) and EtOAc (20 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (1 × 10 mL). The combined organic phases were washed with 10% HCl (10 mL) and then sat. $NaHCO_3$ (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica using CH_2Cl_2 as eluent gave the indole ester **238** (834 mg, 63%) as an orange solid, mp 59–61 °C [lit.[203] 65–68 °C]; R_F (CH_2Cl_2) 0.30; IR (ATR) 3355 (NH), 2981, 2901, 1716 (C=O), 1578, 1469, 1434, 1368, 1304, 1260, 1162, 1030, 793 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H, NH), 7.64 (d, J = 2.0 Hz, 1H, Ar), 7.17 (dd, J = 8.5, 2.0 Hz, 1H, Ar), 7.07 (d, J = 8.5 Hz, 1H, Ar), 4.15 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 3.62 (s, 2H, CH_2C(O)), 2.35 (s, 3H, CH_3), 1.26 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.8 (C=O), 134.1 (C=*C*CH$_3$), 133.7 (*ipso*-Ar), 130.2 (*ipso*-Ar), 123.9 (Ar), 120.7 (Ar), 112.7 (*ipso*-Ar), 111.6 (Ar), 104.3 (*C*=CCH$_3$), 60.8 (O*C*H$_2$CH$_3$), 30.2 (*C*H$_2$C(O)), 14.2 (OCH$_2$*C*H$_3$), 11.7 (CH$_3$); HRMS (ESI) *m/z* calcd for $C_{13}H_{14}{}^{79}BrNO_2$ $(M + H)^+$ 296.0281, found 296.0279 (+0.7 ppm error). Spectroscopic data consistent with those reported in the literature.[204]

Lab Book Reference: SC3/65

2-(5-Bromo-2-methyl-1*H*-indol-3-yl)acetic acid 253

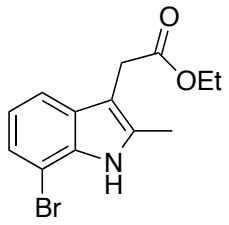


253

1 M $NaOH_{(aq)}$ (10 mL) was added to a stirred solution of bromo-substituted indole ester **238** (622 mg, 2.10 mmol) in 1:1 THF/MeOH (42 mL). The resulting solution was stirred at room temperature for 8 h. The reaction mixture was concentrated under reduced pressure and the residue dissolved in water (5 mL). The solution was made acidic (~pH 1) with conc. HCl resulting in the formation of a gummy precipitate. The resulting mixture was extracted into EtOAc (30 mL) and the two layers separated. The aqueous layer was extracted into EtOAc (2 x 20 mL) and the combined organics dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the indole acid **253** (513 mg, 91%) as a brown solid, mp 159–161 °C [lit.,[198] 189–191 °C]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (br s, 1H, OH), 11.08 (s, 1H, NH), 7.54 (d, J = 2.0 Hz, 1H, Ar), 7.21 (d, J = 8.5 Hz, 1H, Ar), 7.09 (dd, J = 8.5, 2.0 Hz, 1H, Ar), 3.56 (s, 2H, $CH_2C(O)$), 2.32 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.0 (C=O), 135.0 (C=*C*CH_3), 133.7 (*ipso*-Ar), 130.2 (*ipso*-Ar), 122.4 (Ar), 120.0 (Ar), 112.4 (Ar), 111.0 (*ipso*-Ar), 103.9 (*C*=CCH_3), 29.7 (*C*H_2C(O)), 11.3 (CH_3); HRMS (ESI) *m/z* calcd for $C_{11}H_{10}{}^{79}BrNO_2$ $(M + H)^+$ 267.9968, found 267.9982 (+0.7 ppm error). Spectroscopic data consistent with those reported in the literature.[205]

Lab Book Reference: SC3/70

Ethyl 2-(7-bromo-2-methyl-1*H*-indol-3-yl)acetate 240

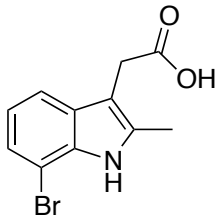


240

A mixture of 4-oxopentanoic acid (0.46 mL, 4.47 mmol) and 2-bromophenylhydrazine hydrochloride **239** (1.0 g, 4.47 mmol) in a solution of EtOH (6 mL) and conc. $H_2SO_{4\,(aq)}$ (0.45 mL) was stirred at reflux for 16 h. The reaction mixture was allowed to cool to rt and water (20 mL) was added. The resulting mixture was extracted into EtOAc (20 mL), the two layers separated and the aqueous extracted with EtOAc (10 mL). The combined organics were washed with 10% $HCl_{(aq)}$ (10 mL) and sat. $NaHCO_{3\,(aq)}$ (10 mL), then dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using CH_2Cl_2 as eluent gave the indole ester **240** (550 mg, 42%) as an orange solid, mp 64–66 °C; R_F (CH_2Cl_2) 0.45; IR (ATR) 3350 (NH), 2980, 2912, 1718 (C=O), 1623, 1583, 1491, 1446, 1368, 1304, 1296, 1151, 1030, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, NH), 7.47 (d, J = 8.0 Hz, 1H, Ar), 7.27-7.25 (m, 1H, Ar), 6.98 (dd, J = 8.0, 8.0 Hz, 1H, Ar), 4.13 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 3.66 (s, 2H, CH_2C(O)), 2.44 (s, 3H, CH_3), 1.24 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.7 (C=O), 133.7 (*C*=CMe), 133.5 (*ipso*-Ar), 129.6 (*ipso*-Ar), 123.5 (Ar), 120.7 (Ar), 117.4 (Ar), 106.0 (C=*C*Me), 103.9 (*ipso*-Ar), 60.8 (O*C*H$_2$CH$_3$), 30.6 (*C*H$_2$C(O)), 14.2 (OCH$_2$*C*H$_3$), 11.8 (CH$_3$); HRMS (ESI) *m/z* calcd for $C_{13}H_{14}{}^{79}BrNO_2$ $(M + H)^+$ 296.0281, found 296.0275 (+1.8 ppm error). Spectroscopic data consistent with those reported in the literature.[125]

Lab Book Reference: SC3/67

2-(7-Bromo-2-methyl-1*H*-indol-3-yl)acetic acid 252

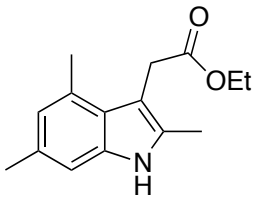


252

1 M $NaOH_{(aq)}$ (8 mL) was added to a stirred solution of the bromo-substituted indole ester **240** (459 mg, 1.55 mmol) in 1:1 MeOH-THF (30 mL) at rt. The resulting solution was stirred at rt for 8 h and then the solvent was evaporated under reduced pressure to give the crude product. The residue was taken up in a minimum amount of water (5 mL) and the resulting solution was taken to pH 1 with conc. $HCl_{(aq)}$ resulting in an oily mixture. The resulting mixture was extracted into CH_2Cl_2 (50 mL) and the two layers separated. The aqueous was extracted into CH_2Cl_2 (2 x 50 mL) and the combined organics dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the indole acid **252** (360 mg, 86%) as a brown solid, mp 128–131 °C (lit.[206] 160–161 °C); IR (ATR) 3380 (NH), 2902, 2634, 1690 (C=O), 1625, 1590, 1558, 1456, 1401, 1225, 1191, 768 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.13 (br s, 1H, OH), 11.02 (s, 1H, NH), 7.39 (d, J = 8.0 Hz, 1H, Ar), 7.21-7.19 (m, 1H, Ar), 6.89 (dd, J = 8.0, 8.0 Hz, 1H, Ar), 3.57 (s, 2H, $CH_2C(O)$), 2.35 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.0 (C=O), 135.0 (C=*C*CH_3), 133.4 (*ipso*-Ar), 130.0 (*ipso*-Ar), 122.6 (Ar), 119.8 (Ar), 117.1 (Ar), 105.5 (*C*=CCH_3), 103.3 (*ipso*-Ar), 29.9 (*C*$H_2C(O)$), 11.24 (CH_3); HRMS (ESI) *m/z* calcd for $C_{11}H_{10}{}^{79}BrNO_2$ $(M + H)^+$ 267.9968, found 267.9974 (−2.4 ppm error).

Lab Book Reference: SC3/69

Ethyl 2-(2,4,6-trimethyl-1*H*-indol-3-yl)acetate 242

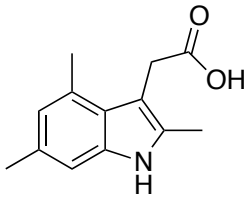


242

A mixture of 4-oxopentanoic acid (0.59 mL, 5.79 mmol) and 3,5-dimethylphenylhydrazine hydrochloride **241** (1.00 g, 5.79 mmol) in 2 M H_2SO_4/EtOH (40 mL) was stirred at 100 °C for 20 h. The reaction mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The resulting residue was diluted with water (20 mL) and extracted into EtOAc (50 mL). The two layers were separated and the aqueous extracted with EtOAc (2 x 50 mL). The combined organics were washed with sat. $NaHCO_{3\ (aq)}$ (10 mL), then dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using CH_2Cl_2 as eluent gave the indole ester **242** (1.035 g, 72%) as a pale yellow solid, mp 84–86 °C (lit.[207] 101–102 °C); R_F (CH_2Cl_2) 0.35; IR (ATR) 3353 (NH), 2978, 2909, 1710 (C=O), 1624, 1467, 1442, 1330, 1302, 1233, 1157, 1027, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H, NH), 6.85 (d, J = 1.0 Hz, 1H, Ar), 6.67 (s, 1H, Ar), 4.14 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 3.81 (s, 2H, $CH_2C(O)$), 2.64 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 1.25 (t, J = 7.0 Hz, 3H, OCH_2CH_3; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.7 (C=O), 135.7 (*ipso*-Ar), 132.0 ($C=CCH_3$), 130.7 (*ipso*-Ar), 129.1 (*ipso*-Ar), 124.6 (*ipso*-Ar), 123.1 (Ar), 108.3 (Ar), 104.7 ($C=CCH_3$), 60.6 (OCH_2CH_3), 31.7 ($CH_2C(O)$), 21.3 (CH_3), 19.8 (CH_3), 14.2 (OCH_2CH_3), 11.6 (CH_3); HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NO_2$ $(M + H)^+$ 246.1489, found 246.1494 (−2.1 ppm error).

Lab Book Reference: SC4/24

2-(2,4,6-Trimethyl-1*H*-indol-3-yl)acetic acid 254

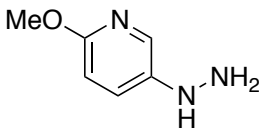


254

1 M $NaOH_{(aq)}$ (20 mL) was added to a stirred solution of the dimethyl-indole ester **242** (930 mg, 3.79 mmol) in 1:1 MeOH-THF (80 mL) at rt. The resulting solution was stirred at rt for 20 h and then the solvent was evaporated under reduced pressure to give the crude product. The residue was taken up in a minimum volume of water (5 mL) and conc. $HCl_{(aq)}$ was added dropwise until a solid precipitate was observed. The solid was isolated by vacuum filtration, washed with water (5 mL) and hexane (5 mL) and air dried to give the indole acetic acid **254** (651 mg, 79%) as a pale red solid, mp 190–192 °C (lit.[207] 203.5–204.5 °C); IR (ATR) 3398 (NH), 2918, 1706 (C=O), 1622, 1561, 1467, 1436, 1400, 1215, 843 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H, NH), 6.85 (s, 1H, Ar), 6.47 (s, 1H, Ar), 3.65 (s, 2H, $CH_2C(O)$), 2.49 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); ^{13} C NMR (100.6 MHz, $CDCl_3$) δ 174.1 (C=O), 135.6 (*ipso*-Ar), 132.2 (C=*C*CH_3), 128.7 (*ipso*-Ar), 128.0 (*ipso*-Ar), 124.6 (*ipso*-Ar), 121.9 (Ar), 108.4 (Ar), 104.2 (*C*=CCH_3), 31.2 (*C*$H_2C(O)$), 21.2 (CH_3), 19.5 (CH_3), 11.2 (CH_3); HRMS (ESI) *m/z* calcd for $C_{13}H_{15}NO_2$ $(M + H)^+$ 218.1176, found 218.1175 (+0.4 ppm error).

Lab Book Reference: SC4/29

5-Hydrazinyl-2-methoxypyridine 247



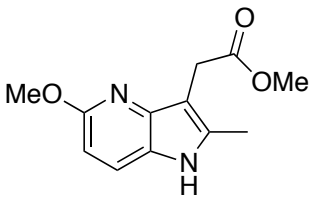
247

A solution of sodium nitrite **246** (278 mg, 4.03 mmol) in water (3 mL) was added dropwise to a solution of 5-amino-2-methoxypyridine (500 mg, 4.03 mmol) in 6 M $HCl_{(aq)}$ at 0 °C and the resulting solution was stirred for 30 min. A solution of

$SnCl_2 \bullet H_2O$ (2.28 g, 10.12 mmol) in 6 M $HCl_{(aq)}$ was added slowly to the reaction mixture at 0 °C. The mixture was stirred for 2.5 h at 0 °C, then $KOH_{(aq)}$ (40 % w/v) was added until the mixture reached pH 14. The reaction mixture was extracted into EtOAc (3 x 30 mL) and the combined organics were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the hydrazine **247** (532 mg, 95%) as a red solid (product stable for ~2 days if kept below 5°C but better to use straight away), mp 59-60 °C (lit. 64 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 3.0, 0.5 Hz, 1H, Ar), 7.20 (dd, *J* = 9.0, 3.0 Hz, 1H, Ar), 6.66 (dd, *J* = 9.0, 0.5 Hz, 1H, Ar), 4.93 (br s, 1H, NH), 3.87 (s, 3H, OCH_3), 3.61 (br s, 2H, NH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.8 (*ipso*-Ar), 141.8 (*ipso*-Ar), 130.4 (Ar), 125.8 (Ar), 110.8 (Ar), 53.4 (OCH_3). Spectroscopic data consistent with those reported in the literature.[128]

Lab Book Reference: SC4/17

Methyl 2-(5-methoxy-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)acetate 248



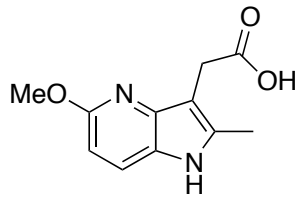
248

A mixture of methyl 4-oxopentanoate (136 μL, 1.08 mmol) and 5-hydrazinyl-2-methoxypyridine **247** in MeOH (3 mL) and conc. $H_2SO_{4(aq)}$ (120 μL) was placed in a suitable microwave vessel. The vessel was sealed and the mixture was stirred under microwave irradiation at 120 °C for 10 min. After being allowed to cool to rt, the mixture was diluted with EtOAc (20 mL) and washed with 10% aq. HCl (20 mL). The two layers were separated and the aqueous layer was taken to pH 7 with sat. $NaHCO_{3(aq)}$. The aqueous layer was extracted into EtOAc (3 x 20 mL) and the combined organics were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the indole ester **248** (181 mg, 77%) as a brown oil, IR (ATR) 3344 (NH), 2949, 1722 (C=O), 1619, 1579, 1475, 1436, 1288, 1241, 1166, 1100, 1023, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H, NH), 7.32 (d, *J* = 8.5 Hz, 1H, Ar), 6.42 (d, *J* = 8.5 Hz, 1H, Ar), 3.94 (s, 3H, OCH_3), 3.77 (s, 2H, $CH_2C(O)$), 3.69 (s, 3H, OCH_3),

2.31 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C=O), 159.6 (*ipso*-Ar), 142.4 (*ipso*-Ar), 135.9 (C=*C*CH_3), 123.6 (*ipso*-Ar), 120.8 (Ar), 104.6 (*C*=CCH_3), 103.4 (Ar), 53.3 (OCH_3), 51.9 (OCH_3), 28.4 (*C*H_2C(O)), 12.2 (CH_3); HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_2O_3$ $(M + H)^+$ 235.1077, found 235.1083 (−2.6 ppm error).

Lab Book Reference: SC4/25

2-(5-Methoxy-2-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)acetic acid 255

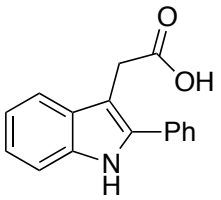


255

1 M $NaOH_{(aq)}$ (4 mL) was added to a stirred solution of the azaindole ester **248** (183 mg, 0.781 mmol) in 1:1 MeOH-THF (15 mL) at rt. The resulting solution was stirred at rt for 16 h and then the solvent was evaporated under reduced pressure. The resulting residue was taken up in a minimum amount of water (5 mL) and the resulting solution was taken to pH 7 with 5 M $HCl_{(aq)}$. The mixture was extracted into EtOAc (3 x 20 mL), the combined organics dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give azaindole acid **255** (140 mg, 81%) as a yellow solid, 191–193 °C; IR (ATR) 3192 (NH), 2968, 1697 (C=O), 1623, 1581, 1447, 1405, 1315, 1250, 1107, 1017, 818, 592 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.08 (s, 1H, OH), 10.91 (s, 1H, NH), 7.53 (d, *J* = 8.5 Hz, 1H, Ar), 6.42 (d, *J* = 8.5 Hz, 1H, Ar), 3.83 (s, 3H, OCH_3), 3.58 (s, 2H, $CH_2C(O)$), 2.32 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.1 (C=O), 158.6 (*ipso*-Ar), 142.3 (*ipso*-Ar), 136.3 (C=*C*CH_3), 123.3 (*ipso*-Ar), 121.0 (Ar), 104.3 (*C*=CCH_3), 102.7 (Ar), 52.4 (OCH_3), 28.3 (*C*H_2C(O)), 12.0 (CH_3); HRMS (ESI) *m/z* calcd for $C_{11}H_{12}N_2O_3$ $(M + H)^+$ 221.0921, found 221.0922 (−0.6 ppm error).

Lab Book Reference: SC4/22

2-(2-Phenyl-1*H*-indol-3-yl)acetic acid 263

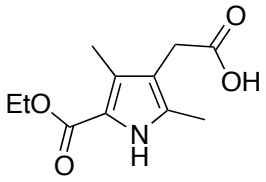


263

$Pd(OAc)_2$ (10.8 mg, 0.048 mmol), iodobenzene (164 μL, 1.44 mL), $AgBF_4$ (374 mg, 1.92 mmol) and TFA (74 μL, 0.96 mmol) were added to a solution of 3-indole acetic acid **215** (168 mg, 0.96 mmol) in DMF (4.8 mL) at rt in a suitable microwave vessel. The vessel was sealed and the reaction mixture was stirred under microwave irradiation at 90 °C for 20 min. The reaction was allowed to cool and filtered through a pad of Celite®. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with hexane-EtOAc (3:1 then 2:1) as eluent gave the indole acetic acid **263** (136 mg, 56%) as a pale brown solid, mp 163-165 °C (lit. 174-175 °C) R_F (3:1 hexane:EtOAc) 0.10; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br s, 1H, NH), 7.67 (d, *J* = 8.0 Hz, 1H, Ar), 7.65-7.62 (m, 2H, Ar), 7.51-7.47 (m, 2H, Ar), 7.43-7.39 (m, 2H, Ar), 7.26-7.22 (m, 1H, Ar), 7.18 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 3.88 (s, 2H, $CH_2C(O)$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.6 (C=O), 136.4 (*ipso*-Ar), 135.7 (*ipso*-Ar), 132.2 (*ipso*-Ar), 129.0 (Ar), 128.8 (*ipso*-Ar), 128.2 (Ar), 122.7 (Ar), 120.2 (Ar), 119.2 (Ar), 110.9 (Ar), 104.9 (*ipso*-Ar), 30.7 (CH_2); HRMS (ESI) *m/z* calcd for $C_{16}H_{13}NO_2$ $(M + H)^+$ 252.1019, found 252.1015 (1.5 ppm error). Spectroscopic data consistent with those reported in the literature.[134]

Lab Book Reference: SC4/44

2-(5-(Ethoxycarbonyl)-2,4-dimethyl-1*H*-pyrrol-3-yl)acetic acid 278

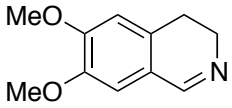


278

KOH (664 mg, 11.84 mmol) was added to a stirred solution of pyrrole diester **277** (1.00 g, 3.95 mmol) in water (8 mL) and EtOH (4 mL) and heated to 70 °C. The reaction was stirred for 30 min then allowed to cool to rt. The reaction was acidified with 10 % $HCl_{(aq)}$ (20 mL) and the reaction was extracted with EtOAc (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica using hexane-EtOAc-AcOH (75:23:2) as eluent gave the acid **278** (192 mg, 21%) as a brown solid, mp 160–162 °C (lit.[140] 194–196 °C); R_F (75:23:2 hexane-EtOAc-AcOH) 0.55; IR (ATR) 3304, 2985, 2917, 1706 (C=O), 1670 (C=O), 1444, 1274, 1218, 1172, 1091, 770, 722, 699, 623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 9.06 (br s, 1H, NH), 4.29 (q, J = 7.0 Hz, 2H, OC$H_2$$CH_3$), 3.41 (s, 2H, $CH_2C(O)$), 2.28 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.34 (t, J = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 177.2 (C=O), 162.0 (C=O), 131.2 (*ipso*-Ar), 127.6 (*ipso*-Ar), 117.2 (*ipso*-Ar), 113.9 (*ipso*-Ar), 59.9 (OCH_2CH_3), 29.8 ($CH_2C(O)$), 14.5 (CH_3), 11.5 (CH_3), 10.6 (CH_3); HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NO_4$ $(M + Na)^+$ 248.0893, found 248.0899 (–2.3 ppm error). Spectroscopic data consistent with those reported in the literature.[140]

Lab Book Reference: SC4/45

6,7-Dimethoxy-3,4-dihydroisoquinoline 283

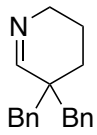


283

N-Bromosuccinimide (840 mg, 4.72 mmol) was added portionwise to a stirred solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **282** (830 mg, 4.30 mmol) in CH_2Cl_2 (20 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. $NaOH_{(aq)}$ (30% w/v, 9 mL) was added and the reaction was stirred at rt for 2 h. The two layers were separated and the organic layer was washed with water (50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc-MeOH (98:2) as eluent gave the imine **283** (766 mg, 93%) as a pale yellow oil, R_F (95:5 EtOAc-MeOH) 0.15; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H, HC=N), 6.81 (s, 1H, Ar), 6.67 (s, 1H, Ar), 3.91 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.75-3.70 (m, 2H, NCH_2), 2.70-2.66 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.6 (C=N), 151.1 (*ipso*-Ar), 147.8 (*ipso*-Ar), 129.8 (*ipso*-Ar), 121.5 (*ipso*-Ar), 110.3 (Ar), 110.3 (Ar), 56.1 (OCH_3), 56.0 (OCH_3), 47.3 (NCH_2), 24.7 (CH_2). Spectroscopic data consistent with those reported in the literature.[208]

Lab Book Reference: SC3/50

5,5-Dibenzyl-2,3,4,5-tetrahydropyridine 290



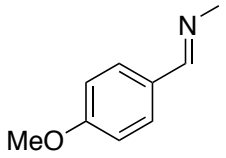
290

LHMDS (1 M in THF, 36.14 mL, 36.14 mmol) was added to a solution of *N*-Boc-piperidin-2-one **288** (3.00 g, 15.06 mmol) in THF (64 mL) and stirred at −78 °C for 1 h under Ar. Benzyl bromide (4.30 mL, 36.14 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 2 h. Sat. $NH_4Cl_{(aq)}$ (200 mL) was added and the reaction mixture was extracted with EtOAc (3 x 200 mL). The combined organics

were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude benzyl-substituted lactam **289**, which was used directly in the next step without further purification. The crude material was dissolved in THF (150 mL) and the resulting solution was cooled to −78 °C under Ar. Lithium triethylborohydride (1 M in THF, 45.18 mL, 45.18 mmol) was added carefully over 5 min and the reaction mixture was stirred for 30 min at −78 °C. A premixed solution of ethanol (136 mL) and conc. HCl (14 mL) was carefully added and the reaction mixture was diluted with CH_2Cl_2 (500 mL). The reaction mixture was washed with water (300 mL) and the organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product, which was used directly in the next step without further purification. A 1:1 mixture of CH_2Cl_2:TFA (32mL:32mL) that had been precooled to 0 °C was added to the crude product and the resulting mixture was stirred at 0 °C for 30 min. The reaction was allowed to warm to rt and the volatiles were removed under reduced pressure. The residue was taken up in CH_2Cl_2 (500 mL) and the resulting solution was washed with sat. $NaHCO_3$ (300 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica using hexane-EtOAc (1:1) as eluent gave imine **290** (1.84 g, 46%) as a white solid, mp 60-62 °C (lit.[21] 63-65 °C); R_F (hexane-EtOAc 1:1) 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H, N=CH), 7.31-7.22 (m, 6H, Ar), 7.17-7.15 (m, 4H, Ar), 3.21 (ddd, J = 5.5, 5.5, 2.5 Hz, 2H, NCH_2), 2.89 (d, J = 13.5 Hz, 2H, CH_AH_BPh), 2.67 (d, J = 13.5 Hz, 2H, CH_AH_BPh), 1.60-1.57 (m, 2H, CH_2), 1.32-1.26 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.0 (N=CH), 137.1 (Ar), 130.4 (Ar), 128.1 (Ar), 126.5 (Ar), 48.8 (NCH_2), 45.0 (CH_2Ph), 42.4 (C), 27.1 (CH_2), 18.7 (CH_2); HRMS (ESI) *m/z* calcd for $C_{19}H_{21}N$ $(M + H)^+$ 264.1747, found 264.1742 (+1.9 ppm error). Spectroscopic data consistent with those reported in the literature.[21]

Lab Book Reference: SC5/19

(*E*)-*N*-(4-Methoxybenzylidene)methanamine 293

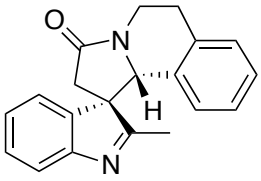


293

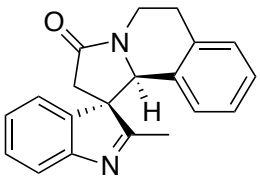
Methylamine (2 M in MeOH, 16.5 mL, 33.0 mmol) was added to a stirred solution of paramethoxybenzaldehyde **292** (3.64 mL, 30.0 mmol) in EtOH (15 mL) at 40 °C. The resulting solution was removed from the heat and stored in the fridge for 2.5 h. The solvent was evaporated under reduced pressure and the residue was taken up in CH_2Cl_2 (20 mL). The reaction mixture was washed with H_2O (10 mL) and the organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the imine **293** (4.47 g, 100%) as a yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.20 (m, 1H, HCN), 7.66-7.63 (m, 2H, Ar), 6.93-6.90 (m, 2H, Ar), 3.834-3.829 (m, 3H, OCH_3), 3.48-3.47 (m, 3H, NCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.8 (CH=N), 161.4 (*ipso*-Ar), 129.3 (Ar), 129.2 (*ipso*-Ar), 113.9 (Ar), 55.3 (OCH_3), 48.1 (NCH_3); HRMS (ESI) *m/z* calcd for $C_9H_{12}NO$ $(M + H)^+$ 150.0913, found 150.0909 (2.9 ppm error). Spectroscopic data consistent with those reported in the literature.[209]

Lab Book Reference: SC4/51

(1'*R,10b'*R**)-2-Methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *syn*-214 and (1'*R**,10b'*S**)-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *anti*-214**



syn-**214**



anti-**214**

Using general procedure J, DIPEA (245 μL, 1.41 mmol), T3P (725 mg of a 50% w/v solution in THF, 1.14 mmol), imine **37** (100 mg, 0.76 mmol) and 2-methyl-3-indole acetic acid **212** (172 mg, 0.91 mmol) in THF (4 mL) for 16 h at rt gave the crude product which contained a 11:1 mixture of spirocycles *syn*-**214** and *anti*-**214** based on

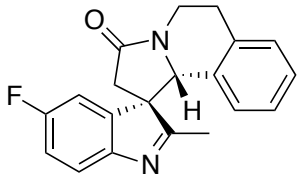
analysis by ^{1}H NMR spectroscopy: δ 6.32 (d, 11H, Ar) and 5.93 (d, 1H, Ar). Purification by flash column chromatography with EtOAc as eluent sequentially furnished *anti*-**214** (18 mg, 8%), a 1:3.3 mixture of *anti*-**214**:*syn*-**214** (27 mg, 12%) and *syn*-**214** (166 mg, 72%). Total combined yield of *syn*-**214** and *anti*-**214**: 211 mg, 92%. The isolated yields suggest a 7.7:1 ratio of *syn*-**214**:*anti*-**214**. *Syn*-**214** was recrystallised from EtOAc and an X-ray crystal structure obtained. CCDC 1436464 contains the supplementary crystallographic data.

Syn-**214**: Yellow solid, mp 177-179 °C; R_F (EtOAc) 0.15; IR (ATR) 3070, 2921, 1690 (C=O), 1577, 1458, 1429, 1414, 1305, 909, 726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 1H, Ar), 7.11 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.99-6.91 (m, 3H, Ar), 6.86 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.78 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar), 6.32 (d, *J* = 7.5 Hz, 1H, Ar), 5.27 (s, 1H, NCH), 4.58-4.53 (m, 1H, NCH_AH$_B$), 3.10 (d, *J* = 16.0 Hz, 1H, CH_CH$_D$C(O)), 3.09-2.97 (m, 2H, NCH$_A$$H_B$, C$H_EH_F$), 2.82-2.77 (m, 1H, CH$_E$$H_F$), 2.60 (s, 3H, CH_3), 2.44 (d, *J* = 16.0 Hz, 1H, CH$_C$$H_D$C(O)); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.4 (C=N), 170.4 (C=O), 153.7 (*ipso*-Ar), 140.3 (*ipso*-Ar), 133.3 (*ipso*-Ar), 132.0 (*ipso*-Ar), 129.0 (Ar), 128.4 (Ar), 127.1 (Ar), 126.6 (Ar), 125.5 (Ar), 123.5 (Ar), 120.9 (Ar), 120.1 (Ar), 63.3 (C), 60.4 (NCH), 39.9 (*C*H$_2$C(O)), 37.3 (NCH_2), 28.9 (CH_2), 16.4 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2O$ $(M + H)^+$ 303.1492, found 303.1496 (−1.4 ppm error).

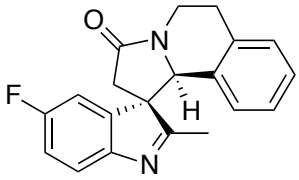
Anti-**214**: Yellow oil, R_F (EtOAc) 0.25; IR (ATR) 3070, 2920, 2855, 1690 (C=O), 1578, 1458, 1424, 1305, 925, 758, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.5 Hz, 1H, Ar), 7.53 (d, *J* = 7.5 Hz, 1H, Ar), 7.46 (ddd, *J* = 7.5, 7.5, 1.0 Hz, Ar), 7.36 (ddd, *J* = 7.5, 7.5, 1.0 Hz, Ar), 7.12-7.09 (m, 2H, Ar), 6.91-6.85 (m, 1H, Ar), 5.93 (d, *J* = 7.5 Hz, 1H, Ar), 5.36 (s, 1H, NCH), 4.58-4.53 (m, 1H, NCH_AH$_B$), 3.16-3.02 (m, 3H, NCH$_A$$H_B$, C$H_EH_F$, C$H_CH_D$C(O)), 2.89-2.85 (m, 1H, CH$_E$$H_F$), 2.58 (d, *J* = 17.0 Hz, 1H, CH$_C$$H_D$C(O)), 1.85 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 182.4 (C=N), 170.0 (C=O), 154.8 (*ipso*-Ar), 140.2 (*ipso*-Ar), 133.0 (*ipso*-Ar), 132.0 (*ipso*-Ar), 129.3 (Ar), 129.1 (Ar), 127.7 (Ar), 127.3 (Ar), 126.3 (Ar), 123.7 (Ar), 121.6 (Ar), 120.6 (Ar), 61.7 (C), 61.6 (NCH), 40.1 (*C*H$_2$C(O)), 37.1 (NCH_2), 28.5 (CH_2), 17.2 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2O$ $(M + H)^+$ 303.1492, found 303.1497 (−1.8 ppm error).

Lab Book Reference: SC4/82

(1'*R,10b'*R**)-5-Fluoro-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *syn*-256 and (1'*R**,10b'*S**)-5-fluoro-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *anti*-256**



syn-**256**



anti-**256**

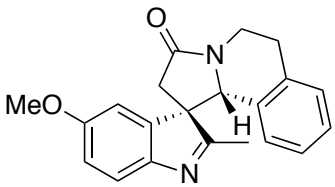
Using general procedure J, DIPEA (245 μL, 1.41 mmol), T3P (725 mg of a 50% w/v solution in THF, 1.14 mmol), imine **37** (100 mg, 0.76 mmol) and 2-(5-fluoro-2-methyl-1*H*-indol-3-yl)acetic acid **249** (188 mg, 0.91 mmol) in THF (4 mL) for 16 h at rt gave the crude product which contained 6:1 mixture of *syn*-**256**:*anti*-**256** based on analysis by ^{1}H NMR spectroscopy: δ 6.32 (d, 6H, Ar) and 5.96 (d, 1H, Ar). Purification by flash column chromatography with EtOAc as eluent sequentially furnished *anti*-**256** (21 mg, 9%) and *syn*-**256** (177 mg, 72%). Total combined yield of *syn*-**256** and *anti*-**256**: 198 mg, 81%. The isolated yields suggest a 8.4:1 ratio of *syn*-**256**:*anti*-**256**.

Syn-**256**: Yellow solid, mp 193-196 °C; R_F (EtOAc) 0.15; IR (ATR) 2924, 1694 (C=O), 1598, 1462, 1415, 1178, 920, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 8.5, 4.5 Hz, 1H, Ar), 7.02-6.95 (m, 2H, Ar), 6.83-6.78 (m, 2H, Ar), 6.68 (dd, J = 8.0, 2.5 Hz, 1H, Ar), 6.32 (d, J = 8.0 Hz, 1H, Ar), 5.26 (s, 1H, NCH), 4.56-4.52 (m, 1H, NCH_AH$_B$), 3.12-2.96 (m, 3H, CH_CH$_D$C(O)), NCH$_A$$H_B$, C$H_EH_F$), 2.84-2.79 (m, 1H, CH$_E$$H_F$), 2.58 (s, 3H, CH_3), 2.43 (d, J = 16.5 Hz, 1H, CH$_C$$H_D$C(O)); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.3 (C=N), 170.1 (C=O), 160.8 (d, J = 245.5 Hz, CF), 149.8 (d, J = 2.0 Hz, *ipso*-Ar), 142.1 (d, J = 9.0 Hz, *ipso*-Ar), 133.3 (*ipso*-Ar), 131.6 (*ipso*-Ar), 129.3 (Ar), 127.3 (Ar), 126.8 (Ar), 123.4 (Ar), 120.8 (d, J = 9.0 Hz, Ar), 115.1 (d, J = 23.5 Hz, Ar), 108.9 (d, J = 25.5 Hz, Ar), 63.8 (d, J = 2.0 Hz, C), 60.3 (NCH), 39.8 (*C*H$_2$C(O)), 37.3 (NCH$_2$), 28.9 (CH$_2$), 16.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.90 (ddd, J = 8.5, 8.5, 4.5 Hz); HRMS (ESI) *m/z* calcd for $C_{20}H_{17}FN_2O$ (M + H)$^+$ 321.1398, found 321.1384 (+4.3 ppm error).

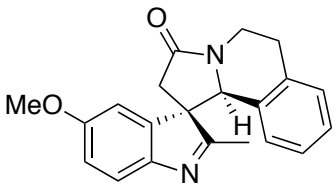
Anti-**256**: Yellow oil, R_F (EtOAc) 0.25; IR (ATR) 2925, 1696 (C=O), 1601, 1466, 1421, 1306, 1156, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.5, 4.5 Hz, 1H, Ar), 7.25 (dd, *J* = 7.5, 2.5 Hz, 1H, Ar), 7.17-7.12 (m, 3H, Ar), 6.93-6.89 (m, 1H, Ar), 5.96 (d, *J* = 8.0 Hz, 1H, Ar), 5.32 (s, 1H, NCH), 4.58-4.53 (m, 1H, NCH_AH_B), 3.16-3.02 (m, 3H, NCH_AH_B, CH_EH_F, $CH_CH_DC(O)$), 2.90-2.85 (m, 1H, CH_EH_F), 2.60 (d, *J* = 17.0 Hz, 1H, $CH_CH_DC(O)$), 1.84 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 182.3 (C=N), 169.7 (C=O), 161.6 (d, *J* = 245.5 Hz, CF), 150.7 (d, *J* = 2.0 Hz, *ipso*-Ar), 142.2 (d, *J* = 8.5 Hz, *ipso*-Ar), 133.1 (*ipso*-Ar), 131.8 (*ipso*-Ar), 129.4 (Ar), 127.9 (Ar), 127.4 (Ar), 123.6 (Ar), 121.5 (d, *J* = 8.5 Hz, Ar), 115.8 (d, *J* = 23.5 Hz, Ar), 109.5 (d, *J* = 25.0 Hz, Ar), 62.1 (d, *J* = 2.0 Hz, C), 61.6 (NCH), 40.1 ($CH_2C(O)$), 37.2 (NCH_2), 28.5 (CH_2), 17.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.00 (ddd, *J* = 8.5, 8.5, 4.5 Hz); HRMS (ESI) *m/z* calcd for $C_{20}H_{17}FN_2O$ $(M + H)^+$ 321.1398, found 321.1383 (+4.5 ppm error).

Lab Book Reference: SC3/28

(1'*R,10b'*R**)-5-Methoxy-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *syn*-257 and (1'*R**,10b'*S**)-5-methoxy-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *anti*-257**



syn-**257**



anti-**257**

Using general procedure J, DIPEA (245 μL, 1.41 mmol), T3P (725 mg of a 50% w/v solution in THF, 1.14 mmol), imine **37** (100 mg, 0.76 mmol) and 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid **250** (199 mg, 0.91 mmol) in THF (4 mL) for 16 h at rt gave the crude product which mixture contained 6:1 mixture of *syn*-**257**:*anti*-**257** based on analysis by ^1H NMR spectroscopy: δ 6.33 (d, 6H, Ar) and 5.99 (d, 1H, Ar). Purification by flash column chromatography with EtOAc as eluent sequentially furnished *anti*-**257** (38 mg, 15%), a 1:3 mixture of *anti*-**257**:*syn*-**257** (18 mg, 7%) and

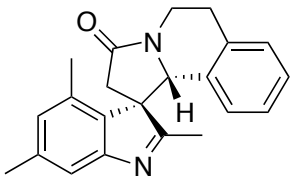
syn-**257** (160 mg, 63%). Total combined yield of *syn*-**257** and *anti*-**257**: 216 mg, 85%. The isolated yields suggest a 4.1:1 ratio of *syn*-**257**:*anti*-**257**.

Syn-**257**: Pale orange solid, mp 121-124 °C; R_F (EtOAc) 0.15; IR (ATR) 2934, 2836, 1689, 1610, 1579, 1470, 1431, 1305, 1178, 907, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 1H, Ar), 6.99-6.92 (m, 2H, Ar), 6.82-6.78 (m, 1H, Ar), 6.62 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar), 6.52 (d, *J* = 2.5 Hz, 1H, Ar), 6.33 (d, *J* = 8.0 Hz, 1H, Ar), 5.25 (s, 1H, NCH), 4.56-4.51 (m, 1H, NCH_AH_B), 3.57 (s, 3H, OCH_3), 3.11-2.95 (m, 3H, $CH_CH_DC(O)$, NCH_AH_B, CH_EH_F), 2.83-2.78 (m, 1H, CH_EH_F), 2.55 (s, 3H, CH_3), 2.43 (d, *J* = 16.5 Hz, 1H, $CH_CH_DC(O)$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.0 (C=N), 170.4 (C=O), 157.8 (*ipso*-Ar), 147.5 (*ipso*-Ar), 141.8 (*ipso*-Ar), 133.2 (*ipso*-Ar), 132.0 (*ipso*-Ar), 129.0 (Ar), 127.1 (Ar), 126.7 (Ar), 123.6 (Ar), 120.3 (Ar), 113.2 (Ar), 107.5 (Ar), 63.3 (C), 60.7 (NCH), 55.5 (OCH_3), 40.0 ($CH_2C(O)$), 37.3 (NCH_2), 29.0 (CH_2), 16.2 (CH_3); HRMS (ESI) *m/z* calcd for $C_{21}H_{20}N_2O_2$ $(M + H)^+$ 333.1598, found 333.1595 (+0.8 ppm error).

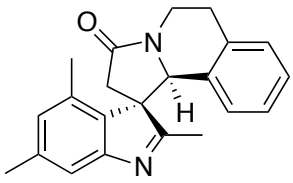
Anti-**257**: Pale orange solid, mp 168-171°C; R_F (EtOAc) 0.25; IR (ATR) 2923, 2836, 1690 (C=O), 1596, 1576, 1473, 1431, 1305, 1026, 909, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* 8.5 Hz, 1H, Ar), 7.12-7.10 (m, 2H, Ar), 7.08 (d, *J* = 2.5 Hz, 1H, Ar), 6.95 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar), 6.92-6.88 (m, 1H, Ar), 5.99 (d, *J* = 8.0 Hz, 1H, Ar), 5.30 (s, 1H, NCH), 4.56-4.52 (m, 1H, NCH_AH_B), 3.88 (s, 3H, OCH_3), 3.15-3.02 (m, 3H, $CH_CH_DC(O)$, NCH_AH_B, CH_EH_F), 2.92-2.84 (m, 1H, CH_EH_F), 2.59 (d, *J* = 17.0 Hz, 1H, $CH_CH_DC(O)$), 1.81 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.2 (C=N), 170.0 (C=O), 158.7 (*ipso*-Ar), 148.3 (*ipso*-Ar), 141.8 (*ipso*-Ar), 133.0 (*ipso*-Ar), 132.1 (*ipso*-Ar), 129.2 (Ar), 127.7 (Ar), 127.3 (Ar), 123.8 (Ar), 121.0 (Ar), 113.4 (Ar), 108.4 (Ar), 61.9 (C), 61.7 (NCH), 55.8 (OCH_3), 40.5 ($CH_2C(O)$), 37.1 (NCH_2), 28.5 (CH_2), 17.1 (CH_3); HRMS (ESI) *m/z* calcd for $C_{21}H_{20}N_2O_2$ $(M + H)^+$ 333.1598, found 333.1594 (+0.3 ppm error).

Lab Book Reference SC3/56

(1'*R,10b'*R**)-2,4,6-Trimethyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *syn*-258 and (1'*R**,10b'*S**)-2,4,6-trimethyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *anti*-258**



syn-**258**



anti-**258**

Using general procedure J, DIPEA (245 μL, 1.41 mmol), T3P (725 mg of a 50% w/v solution in THF, 1.14 mmol), imine **37** (100 mg, 0.76 mmol) and acid **254** (197 mg, 0.91 mmol) in THF (4 mL) for 16 h at rt gave the crude product which contained 9:1 mixture of *syn*-**258**:*anti*-**258** based on analysis by ^{1}H NMR spectroscopy: δ 5.21 (s, 9H, NCH) and 5.61 (s, 1H, NCH). Purification by flash column chromatography with EtOAc as eluent sequentially furnished a mixture of *anti*-**258** with minor contaminants (24 mg, 10%) and *syn*-**258** (198 mg, 78%). The isolated yields suggest a 8.2:1 ratio of *syn*-**258**:*anti*-**258**.

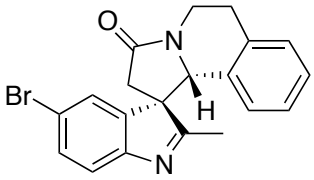
Syn-**258**: Pale orange solid, mp 128-130 °C; R_F (EtOAc) 0.10; IR (ATR) 3055, 2923, 1688 (C=O), 1626, 1593, 1459, 1433, 1305, 1264, 851, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H, Ar), 7.02-6.97 (m, 2H, Ar), 6.75-6.71 (m, 1H, Ar), 6.50 (s, 1H, Ar), 6.04 (d, J = 8.0 Hz, 1H, Ar), 5.21 (s, 1H, NCH), 4.59-4.54 (m, 1H, NCH_AH$_B$), 3.23-3.08 (m, 2H, NCH$_A$$H_B$, C$H_EH_F$), 2.99 (d, J = 17.5 Hz, 1H, CH_CH$_D$C(O)), 2.83-2.78 (m, 1H, CH$_E$$H_F$), 2.65 (d, J = 17.5 Hz, 1H, CH$_C$$H_D$C(O)), 2.52 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 1.83 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 182.5 (C=N), 170.6 (C=O), 154.9 (*ipso*-Ar), 138.3 (*ipso*-Ar), 136.1 (*ipso*-Ar), 133.2 (*ipso*-Ar), 132.8 (*ipso*-Ar), 132.7 (*ipso*-Ar), 128.9 (Ar), 128.8 (Ar), 127.1 (Ar), 126.2 (Ar), 125.0 (Ar), 118.7 (Ar), 61.3 (C), 59.7 (NCH), 37.9 (*C*H$_2$C(O), NCH$_2$), 27.6 (CH_2), 21.1 (CH_3), 19.2 (CH_3), 16.0 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{22}N_2O$ $(M + H)^+$ 331.1805, found 331.1800 (+1.4 ppm error).

Anti-**258**: Orange oil, R_F (EtOAc) 0.20; IR (ATR) 2923, 1688 (C=O), 1579, 1459, 1423, 1376, 1359, 1331, 1304, 1200, 923, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ

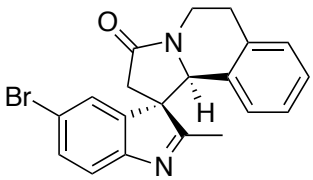
7.22 (s, 1H, Ar), 7.12-7.11 (m, 2H, Ar), 6.95-6.90 (m, 2H, Ar), 6.06 (d, J = 7.5 Hz, 1H, Ar), 5.61 (s, 1H, NCH), 4.59-4.55 (m, 1H, NCH_AH$_B$), 3.34 (dd, J = 17.5, 1.0 Hz, 1H, CH_CH$_D$C(O)), 3.17-2.99 (m, 2H, NCH$_A$$H_B$, C$H_EH_F$), 2.86 (dd, J = 16.0, 3.0 Hz, 1H, CH$_E$$H_F$), 2.51 (s, 3H, CH$_3$), 2.47 (d, J = 17.5 Hz, 1H, CH$_C$$H_D$C(O)), 2.42 (s, 3H, CH$_3$), 1.79 (s, 3H, CH$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 182.3 (C=N), 170.6 (C=O), 155.4 (*ipso*-Ar), 139.3 (*ipso*-Ar), 133.9 (*ipso*-Ar), 133.0 (*ipso*-Ar), 132.6 (*ipso*-Ar), 132.1 (*ipso*-Ar), 129.24 (Ar), 129.19 (Ar), 127.5 (Ar), 127.4 (Ar), 124.0 (Ar), 119.3 (Ar), 61.5 (C), 58.1 (NCH), 37.2 (NCH$_2$), 36.7 (*C*H$_2$C(O)), 28.4 (CH$_2$), 21.4 (CH$_3$), 18.4 (CH$_3$), 17.1 (CH$_3$); HRMS (ESI) *m/z* calcd for $C_{22}H_{22}N_2O$ $(M + H)^+$ 331.1805, found 331.1803 (+0.6 ppm error).

Lab Book Reference SC4/39

(1'*R,10b'*R**)-5-Bromo-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *syn*-259 and (1'*R**,10b'*S**)-5-bromo-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *anti*-259**



syn-**259**



anti-**259**

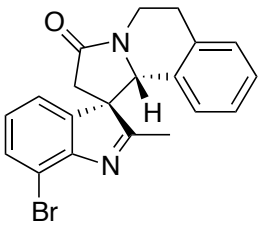
Using general procedure J, DIPEA (245 μL, 1.41 mmol), T3P (725 mg of a 50% w/v solution in THF, 1.14 mmol), imine **37** (100 mg, 0.76 mmol) and acid **253** (243 mg, 0.91 mmol) in THF (4 mL) for 16 h at rt gave the crude product which contained 12:1 mixture of *syn*-**259**:*anti*-**259** based on analysis by ^{1}H NMR spectroscopy: δ 6.33 (d, 12H, Ar) and 5.96 (d, 1H, Ar). Purification by flash column chromatography with EtOAc as eluent sequentially furnished *anti*-**259** (28 mg, 9%) and *syn*-**259** (250 mg, 87%). Total combined yield of *syn*-**259** and *anti*-**259**: 278 mg, 96%. *Syn*-**259** was recrystallised from EtOAc and an X-ray crystal structure obtained. CCDC 1436468 contains the supplementary crystallographic data.

Syn-**259**: Orange solid, mp 164-167 °C; R_F (EtOAc) 0.15; IR (ATR) 2918, 2852, 1695, 1648, 1604, 1572, 1449, 1423, 1410, 1302, 1246, 1193, 803, 760, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H, Ar), 7.13-7.12 (m, 1H, Ar), 7.05-6.98 (m, 2H, Ar), 6.83 (dd, J = 7.5, 7.5 Hz, 1H, Ar), 6.33 (d, J = 8.0 Hz, 1H, Ar), 5.27 (s, 1H, NCH), 4.59-4.54 (m, 1H, NCH_AH_B), 3.13-2.97 (m, 3H, $CH_CH_DC(O)$, NCH_AH_B, CH_EH_F), 2.86-2.81 (m, 1H, CH_EH_F), 2.60 (s, 3H, CH_3), 2.45 (d, J = 16.5 Hz, 1H, $CH_CH_DC(O)$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.8 (C=N), 170.0 (C=O), 152.7 (*ipso*-Ar), 142.3 (*ipso*-Ar), 133.3 (*ipso*-Ar), 131.5 (Ar), 131.4 (*ipso*-Ar), 129.3 (Ar), 127.5 (Ar), 126.8 (Ar), 124.3 (Ar), 123.3 (Ar), 121.4 (Ar), 119.2 (*ipso*-Ar), 63.9 (C), 60.4 (NCH), 39.7 ($CH_2C(O)$), 37.3 (NCH_2), 28.9 (CH_2), 16.5 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{17}BrN_2O$ $(M + H)^+$ 381.0597, found 381.0597 (−0.1 ppm error).

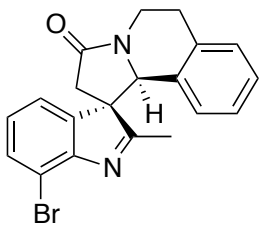
Anti-**259**: Orange oil, R_F (EtOAc) 0.25; IR (ATR) 2926, 2867, 1696 (C=O), 1604, 1578, 1455, 1423, 1305, 1186, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 2.0 Hz, 1H, Ar), 7.58 (dd, J = 8.0, 2.0 Hz, 1H, Ar), 7.45 (d, J = 8.0 Hz, 1H, Ar), 7.14-7.11 (m, 2H, Ar), 6.93-6.89 (m, 1H, Ar), 5.96 (d, J = 8.0 Hz, 1H, Ar), 5.34 (s, 1H, NCH), 4.57-4.52 (m, 1H, NCH_AH_B), 3.15-3.02 (m, 3H, $CH_CH_DC(O)$, NCH_AH_B, CH_EH_F), 2.89-2.85 (m, 1H, CH_EH_F), 2.58 (d, J = 17.0 Hz, 1H, $CH_CH_DC(O)$), 1.83 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 183.0 (C=N), 169.6 (C=O), 153.8 (*ipso*-Ar), 142.4 (*ipso*-Ar), 133.1 (*ipso*-Ar), 132.7 (Ar), 131.7 (*ipso*-Ar), 129.4 (Ar), 127.9 (Ar), 127.4 (Ar), 125.1 (Ar), 123.6 (Ar), 122.0 (Ar), 119.8 (*ipso*-Ar), 62.0 (C), 61.4 (NCH), 40.0 ($CH_2C(O)$), 37.1 (NCH_2), 28.4 (CH_2), 17.2 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{17}BrN_2O$ $(M + H)^+$ 381.0597 found 381.0598 (−0.1 ppm error).

Lab Book Reference SC3/73

(1'*R,10b'*R**)-7-Bromo-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *syn*-260 and (1'*R**,10b'*S**)-7-bromo-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *anti*-260**



syn-**260**



anti-**260**

Using general procedure J, DIPEA (245 μL, 1.41 mmol), T3P (725 mg of a 50% w/v solution in THF, 1.14 mmol), imine **37** (100 mg, 0.76 mmol) and acid **252** (243 mg, 0.91 mmol) in THF (4 mL) for 16 h at rt gave the crude product which contained 13:1 mixture of *syn*-**260**:*anti*-**260** based on analysis by ^{1}H NMR spectroscopy: δ 6.33 (d, 12H, Ar) and 5.96 (d, 1H, Ar). Purification by flash column chromatography with EtOAc as eluent sequentially furnished *anti*-**260** (24 mg, 8%), a 1:2.3 mixture of *anti*-**260**:*syn*-**260** (11 mg, 4%) and *syn*-**260** (227 mg, 78%). Total combined yield of *syn*-**260** and a*nti*-**260**: 262 mg, 90%. The isolated yields suggest a 8.6:1 ratio of *syn*-**260**:*anti*-**260**.

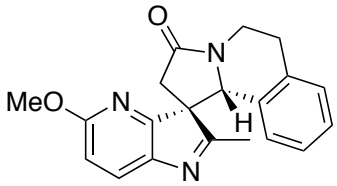
Syn-**260**: Orange solid, mp 190-192 °C; R_F (4:1 EtOAc-hexane) 0.15; IR (ATR) 2940, 2858, 1692, 1571, 1456, 1431, 1417, 1302, 1195, 803, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.0 Hz, 1H, Ar), 6.99-6.93 (m, 2H, Ar), 6.90 (d, J = 7.5 Hz, 1H, Ar), 6.82 (dd, J = 7.5, 7.5 Hz, 1H, Ar), 6.73 (dd, J = 7.5, 7.5 Hz, 1H, Ar), 6.32 (d, J = 8.0 Hz, 1H, Ar), 5.28 (s, 1H, NCH), 4.55-4.51 (m, 1H, NCH_AH$_B$), 3.11-2.95 (m, 3H, CH_CH$_D$C(O), NCH$_A$$H_B$, C$H_EH_F$), 2.82-2.78 (m, 1H, CH$_E$$H_F$), 2.65 (s, 3H, CH$_3$), 2.41 (d, J = 16.5 Hz, 1H, CH$_C$$H_D$C(O)); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 182.1 (C=N), 169.9 (C=O), 151.9 (*ipso*-Ar), 142.0 (*ipso*-Ar), 133.2 (*ipso*-Ar), 131.8 (Ar), 131.6 (*ipso*-Ar), 129.1 (Ar), 127.3 (Ar), 126.9 (Ar), 126.8 (Ar), 123.4 (Ar), 119.9 (Ar), 113.9 (*ipso*-Ar), 64.9 (C), 60.3 (NCH), 39.9 (*C*H$_2$C(O)), 37.3 (NCH$_2$), 28.8 (CH$_2$), 16.7 (CH$_3$); HRMS (ESI) *m/z* calcd for $C_{20}H_{17}{}^{79}BrN_2O$ $(M + H)^+$ 381.0597, found 381.0597 (0.0 ppm error).

Anti-**260**: Orange oil, R_F (4:1 EtOAc-hexane) 0.25; IR (ATR) 2933, 2861, 1690 (C=O), 1575, 1458, 1421, 1306, 1181, 783, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J

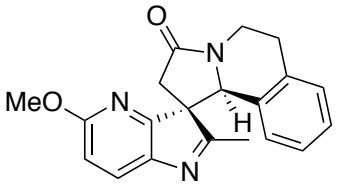
= 8.0 Hz, 1H, Ar), 7.47 (d, *J* = 7.5 Hz, 1H, Ar), 7.26-7.22 (m, 1H, Ar), 7.15-7.10 (m, 2H, Ar), 6.94-6.90 (m, 1H, Ar), 5.95 (d, *J* = 8.0 Hz, 1H, Ar), 5.35 (s, 1H, NCH), 4.57-4.52 (m, 1H, NCH_AH$_B$), 3.15-3.01 (m, 3H, CH_CH$_D$C(O), NCH$_A$$H_B$, C$H_EH_F$), 2.89-2.84 (m, 1H, CH$_E$$H_F$), 2.58 (d, *J* = 17.0 Hz, 1H, CH$_C$$H_D$C(O)), 1.89 (s, 3H, CH$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 184.0 (C=N), 169.6 (C=O), 153.1 (*ipso*-Ar), 142.0 (*ipso*-Ar), 133.0 (*ipso*-Ar), 132.6 (Ar), 131.7 (*ipso*-Ar), 129.4 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 123.5 (Ar), 120.6 (Ar), 114.5 (*ipso*-Ar), 63.4 (C), 61.5 (NCH), 40.2 (*C*H$_2$C(O)), 37.2 (NCH$_2$), 28.5 (CH$_2$), 17.5 (CH$_3$); HRMS (ESI) *m/z* calcd for $C_{20}H_{17}{}^{79}BrN_2O$ $(M + Na)^+$ 403.0416 found 403.0400 (+4.1 ppm error).

Lab Book Reference SC3/72

(1*S,10b*R**)-5'-Methoxy-2'-methyl-5,6-dihydro-2*H*-spiro[pyrrolo[2,1-*a*]isoquinoline-1,3'-pyrrolo[3,2-*b*]pyridin]-3(10b*H*)-one *syn*-261 and (1*S**,10b*S**)-5'-methoxy-2'-methyl-5,6-dihydro-2*H*-spiro[pyrrolo[2,1-*a*]isoquinoline-1,3'-pyrrolo[3,2-*b*]pyridin]-3(10b*H*)-one *anti*-261**



syn-**261**



anti-**261**

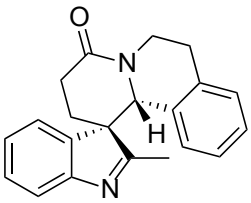
Using general procedure J, DIPEA (245 μL, 1.41 mmol), T3P (725 mg of a 50% w/v solution in THF, 1.14 mmol), imine **37** (100 mg, 0.76 mmol) and acid **255** (200 mg, 0.91 mmol) in THF (4 mL) for 16 h at rt gave the crude product which contained a >20:1 mixture of *syn*-**261**:*anti*-**261** based on analysis by ^{1}H NMR spectroscopy: δ 6.36 (d, Ar). Purification by flash column chromatography with EtOAc as eluent furnished *syn*-**261** (226 mg, 89%). The isolated yields suggest a >20:1 ratio of *syn*-**261**:*anti*-**261**.

Syn-**261**: Yellow solid, mp 139-141 °C; R_F (EtOAc) 0.10; IR (ATR) 2939, 1687 (C=O), 1594, 1472, 1407, 1307, 1222, 1145, 1022, 909, 829, 645 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 1H, Ar), 6.96-6.92 (m, 2H, Ar), 6.82-6.78 (m, 1H, Ar),

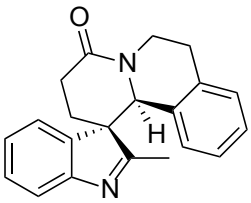
6.39 (d, J = 8.5 Hz, 1H, Ar), 6.36 (d, J = 8.0 Hz, 1H, Ar) 5.30 (s, 1H, NCH), 4.58-4.54 (m, 1H, NCH_AH$_B$), 3.70 (s, 3H, OCH$_3$), 3.20-3.11 (m, 1H, NCH$_A$$H_B$), 3.06-2.99 (m, 2H, C$H_EH_F$, C$H_CH_D$C(O)), 2.74-2.69 (m, 1H, CH$_E$$H_F$), 2.59 (s, 3H, CH$_3$), 2.46 (d, J = 16.0 Hz, 1H, CH$_C$$H_D$C(O)); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 178.2 (C=N), 170.3 (C=O), 162.2 (*ipso*-Ar), 159.2 (*ipso*-Ar), 140.9 (*ipso*-Ar), 134.6 (*ipso*-Ar), 131.7 (*ipso*-Ar), 129.4 (Ar), 128.8 (Ar), 127.1 (Ar), 126.5 (Ar), 123.3 (Ar), 109.5 (Ar), 62.1 (C), 60.0 (NCH), 53.5 (OCH$_3$), 38.0 (*C*H$_2$C(O)), 37.6 (NCH$_2$), 29.1 (CH$_2$), 16.8 (CH$_3$); HRMS (ESI) *m/z* calcd for C$_{20}$H$_{19}$N$_3$O$_2$ (M + H)$^+$ 334.1550, found 334.1550 (+0.1 ppm error).

Lab Book Reference SC4/32

(1'*R,11b'*R**)-2-Methyl-2',3',6',7'-tetrahydrospiro[indole-3,1'-pyrido[2,1-*a*]isoquinolin]-4'(11b'*H*)-one *syn*-262 and (1'*R**,11b'*S**)-2-methyl-2',3',6',7'-tetrahydrospiro[indole-3,1'-pyrido[2,1-*a*]isoquinolin]-4'(11b'*H*)-one *anti*-262**



syn-**262**



anti-**262**

Using general procedure J, DIPEA (245 μL, 1.41 mmol), T3P (725 mg of a 50% w/v solution in THF, 1.14 mmol), imine **37** (100 mg, 0.76 mmol) and acid **251** (184 mg, 0.91 mmol) in THF (4 mL) for 16 h at rt gave the crude product which contained 4:1 mixture of *syn*-**262**:*anti*-**262** based on analysis by ^{1}H NMR spectroscopy: δ 6.54 (d, 4H, Ar) and 5.81 (d, 1H, Ar). Purification by flash column chromatography with EtOAc-MeOH (98:2) as eluent sequentially furnished a 4.8:1 mixture of *syn*-**262**:*anti*-**262** (96 mg, 40%) and *syn*-**262** (77 mg, 32%). Total combined yield of *syn*-**262** and *anti*-**262**: 173 mg, 72%. The isolated yields suggest a 9.5:1 ratio of *syn*-**262**:*anti*-**262**.

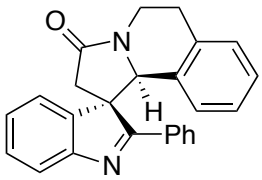
Syn-**262**: Yellow solid, mp 156-158 °C; R_F (98:2 EtOAc-MeOH) 0.20; IR (ATR) 2928, 2867, 1640 (C=O), 1577, 1455, 1432, 1410, 1247, 1047, 731 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 (d, J = 7.5 Hz, 1H, Ar), 7.14 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, Ar), 7.09 (d, J

= 7.5 Hz, 1H, Ar), 6.94 (dd, *J* = 8.0, 8.0 Hz, 1H, Ar), 6.90-6.86 (m, 2H, Ar), 6.82-6.78 (m, 1H, Ar), 6.54 (d, *J* = 8.0 Hz, 1H, Ar), 5.32 (s, 1H, NCH), 5.06-5.01 (m, 1H, NCH_AH_B), 2.94-2.74 (m, 4H, CH_EH_F, NCH_AH_B, $CH_CH_DC(O)$), 2.64-2.60 (m, 1H, $CH_CH_DC(O)$), 2.62 (s, 3H, CH_3), 2.44 (ddd, *J* = 13.5, 9.5, 8.0 Hz, 1H, $CH_EH_FCH_2C(O)$), 1.46 (dd, *J* = 13.5, 5.0, 5.0 Hz, 1H, $CH_EH_FCH_2C(O)$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 183.0 (C=N), 169.3 (C=O), 154.2 (*ipso*-Ar), 139.1 (*ipso*-Ar), 135.7 (*ipso*-Ar), 132.4 (*ipso*-Ar), 128.7 (Ar), 128.3 (Ar), 126.9 (Ar), 126.0 (Ar), 125.0 (Ar), 123.6 (Ar), 123.0 (Ar), 120.3 (Ar), 61.8 (C), 60.4 (NCH), 39.7 (NCH_2), 29.2 ($CH_2C(O)$, CH_2), 28.0 ($CH_2CH_2C(O)$), 17.1 (CH_3); HRMS (ESI) *m/z* calcd for $C_{21}H_{20}N_2O$ $(M + H)^+$ 317.1648 found 317.1646 (+1.1 ppm error).

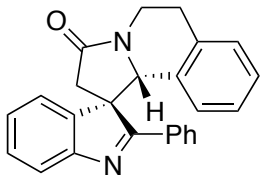
Diagnostic peaks for *anti*-**262**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (d, *J* = 8.0 Hz, 1H, Ar), 5.40 (s, 1H, NCH), 1.97 (s, 1H, CH_3) HRMS (ESI) *m/z* calcd for $C_{21}H_{20}N_2O$ $(M + H)^+$ 317.1648, found 317.1645 (+0.8 ppm error).

Lab Book Reference SC3/78

(1'*R,10b'*S**)-2-Phenyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *anti*-264 and (1'*R**,10b'*R**)-2-phenyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *syn*-264**



anti-**264**



syn-**264**

Using general procedure J, DIPEA (132 μL, 0.76 mmol), T3P (394 mg of a 50% w/v solution in THF, 0.62 mmol), imine **37** (53 mg, 0.41 mmol) and acid **263** (125 mg, 0.50 mmol) in THF (2 mL) for 16 h at rt gave the crude product which contained 8:1 mixture of *anti*-**264**:*syn*-**264** based on analysis by ^{1}H NMR spectroscopy: δ 5.40 (s, 8H, NCH) and 5.77 (s, 1H, NCH). Purification by flash column chromatography with EtOAc-hexane (1:1) as eluent sequentially furnished a 1:1.1 mixture of *syn*-**264**:*anti*-**264** (57 mg, 38%) and *anti*-**264** (49 mg, 33%). Total combined yield of *syn*-**264** and

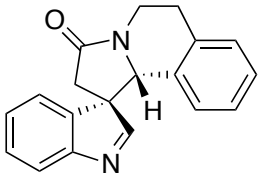
anti-**264**: 106 mg, 71%. The isolated yields suggest a 2.9:1 ratio of *syn*-**264**:*anti*-**264**. *Anti*-**264** was recrystallised from EtOAc and an X-ray crystal structure was obtained. CCDC 1436405 contains the supplementary crystallographic data.

Anti-**264**: Cream solid, mp 201-203 °C; R_F (EtOAc) 0.20; IR (ATR) 3062, 2931, 1689 (C=O), 1522, 1494, 1458, 1420, 1307, 910, 754, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 1H, Ar), 7.59 (d, *J* = 7.0 Hz, 1H, Ar), 7.51 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 7.45-7.41 (m, 1H, Ar), 7.31-7.27 (m, 1H, Ar), 7.16 (dd, *J* = 8.0, 8.0 Hz, 1H, Ar), 7.09-7.06 (m, 2H, Ar), 6.99 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar), 6.87 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar), 6.71 (d, *J* = 7.5 Hz, 1H, Ar), 5.98 (d, *J* = 8.0 Hz, 1H, Ar), 5.40 (s, 1H, NCH), 4.36-4.31 (m, 1H, NCH_AH_B), 3.30 (dd, *J* = 17.5, 1.0 Hz, 1H, $CH_CH_DC(O)$), 3.21 (d, *J* = 17.5 Hz, 1H, $CH_CH_DC(O)$), 2.91 (ddd, *J* = 13.0, 13.0 Hz, 3.0 Hz, 1H, NCH_AH_B), 2.36 (dd, *J* = 16.0, 3.0 Hz, 1H, CH_EH_F), 1.80 (ddd, *J* = 16.5, 13.0, 6.0 Hz, 1H, CH_EH_F); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 181.0 (C=N), 170.7 (C=O), 154.4 (*ipso*-Ar), 141.5 (*ipso*-Ar), 134.7 (*ipso*-Ar), 134.1 (*ipso*-Ar), 131.6 (*ipso*-Ar), 130.1 (Ar), 129.3 (Ar), 128.5 (Ar), 127.9 (Ar), 127.5 (Ar), 127.4 (Ar), 127.0 (Ar), 126.7 (Ar), 123.6 (Ar), 121.6 (Ar), 121.4 (Ar), 62.8 (C), 62.7 (NCH), 40.9 ($CH_2C(O)$), 37.0 (NCH_2), 27.6 (CH_2); HRMS (ESI) *m/z* calcd for $C_{25}H_{20}N_2O$ $(M + H)^+$ 365.1648, found 365.1646 (+0.6 ppm error).

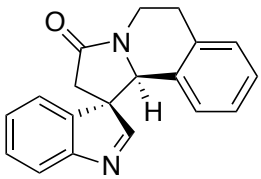
Diagnostic signals for *syn*-**264**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (d, *J* = 8.0 Hz, 1H, Ar), 5.77 (s, 1H, NCH), 4.68-4.64 (m, 1H, NCH).

Lab Book Reference: SC4/48

(1'*R,10b'*R**)-5',6'-Dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *syn*-267 and (1'*R**,10b'*S**)-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *anti*-267**



syn-**267**



anti-**267**

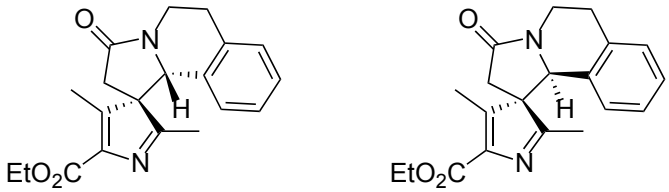
Using general procedure J, DIPEA (489 μL, 2.81 mmol), T3P (1.45 g of a 50% w/v solution in THF, 2.28 mmol), imine **37** (200 mg, 1.52 mmol) and 3-indole acetic acid (318 mg, 1.82 mmol) in THF (8 mL) for 16 h at rt gave the crude product which contained 11:1 mixture of *syn*-**267**:*anti*-**267** based on analysis by ^{1}H NMR spectroscopy: δ 6.44 (d, 11H, Ar) and 5.92 (d, 1H, Ar). Purification by flash column chromatography with EtOAc as eluent sequentially furnished a mixture of *anti*-**267** and a minor contaminant (18 mg, 8%) and *syn*-**267** (160 mg, 73%). Total combined yield of *syn*-**267** and *anti*-**267**: 178 mg, 81%. The isolated yields suggest a 8.9:1 ratio of *syn*-**267**:*anti*-**267**. *Syn*-**267** was recrystallised from EtOAc and an X-ray crystal structure was obtained. CCDC 1506360 contains the supplementary crystallographic data.

Syn-**267**: Pale yellow solid, mp 155-158 °C; R_F (EtOAc) 0.20; IR (ATR) 3026, 2925, 1687 (C=O), 1608, 1458, 1431, 1415, 1306, 923, 768, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H, N=CH), 7.52 (d, J = 8.0 Hz, 1H, Ar), 7.18 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H, Ar), 7.01-6.92 (m, 4H, Ar), 6.81-6.77 (m, 1H, Ar), 6.44 (d, J = 8.0 Hz, 1H, Ar), 5.50 (s, 1H, NCH), 4.58-4.54 (m, 1H, NCH_AH$_B$), 3.32 (dd, J = 16.5, 1.5 Hz, 1H, CH_CH$_D$C(O)), 3.14-2.99 (m, 2H, NCH$_A$$H_B$, C$H_EH_F$), 2.84-2.79 (m, 1H, CH$_E$$H_F$), 2.43 (d, J = 16.5 Hz, 1H, CH$_C$$H_D$C(O)); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.2 (C=N), 170.0 (C=O), 154.6 (*ipso*-Ar), 139.3 (*ipso*-Ar), 133.3 (*ipso*-Ar), 131.8 (*ipso*-Ar), 129.1 (Ar), 128.6 (Ar), 127.2 (Ar), 126.7 (Ar), 126.6 (Ar), 123.7 (Ar), 121.4 (Ar), 121.2 (Ar), 63.3 (C), 58.7 (NCH), 37.9 (*C*H$_2$C(O)), 37.4 (NCH$_2$), 29.1 (CH$_2$); HRMS (ESI) *m/z* calcd for $C_{19}H_{16}N_2O$ (M + H)$^+$ 289.1335, found 289.1333 (+0.9 ppm error).

Anti-**267**: Yellow oil, R_F (EtOAc) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H, N=CH), 7.68 (d, *J* = 7.5 Hz, 1H, Ar), 7.61 (d, *J* = 7.0 Hz, 1H, Ar), 7.52-7.43 (m, 2H, Ar), 7.12-7.10 (m, 2H, Ar), 6.85-6.81 (m, 1H, Ar), 5.92 (d, *J* = 7.5 Hz, 1H, Ar), 5.33 (s, 1H, NCH), 4.60-4.53 (m, 1H, NCH_AH_B), 3.13-2.99 (m, 3H, NCH_AH_B, CH_EH_F, $CH_CH_DC(O)$), 2.89-2.81 (m, 1H, CH_EH_F), 2.61 (d, *J* = 17.0 Hz, 1H, $CH_CH_DC(O)$); HRMS (ESI) *m/z* calcd for $C_{19}H_{16}N_2O$ $(M + H)^+$ 289.1335, found 289.1340 (−1.5 ppm error).

Lab Book Reference SC5/77

(1'*R,10b'*R**)-Ethyl 2,4-dimethyl-3'-oxo-3',5',6',10b'-tetrahydro-2'*H*-spiro[pyrrole-3,1'-pyrrolo[2,1-*a*]isoquinoline]-5-carboxylate and (1'*R**,10b'*S**)-ethyl 2,4-dimethyl-3'-oxo-3',5',6',10b'-tetrahydro-2'*H*-spiro[pyrrole-3,1'-pyrrolo[2,1-*a*]isoquinoline]-5-carboxylate 279**



279

Using general procedure J, DIPEA (141 μL, 0.81 mmol), T3P (419 mg of a 50% w/v solution in THF, 0.66 mmol), imine **37** (47 mg, 0.44 mmol) and acid **278** (120 mg, 0.53 mmol) in THF (3 mL) for 1 h at 70 °C gave the crude product which contained a 3.8:1 mixture of diastereoisomers **279-A** and **279-B** based on analysis by ^{1}H NMR spectroscopy: δ 5.15 (s, 3.8H, NCH) and 5.05 (s, 1H, NCH). Purification by flash column chromatography with EtOAc-MeOH (100:0 then 95:5) as eluent furnished **279-A** (55 mg, 37%) and **279-B** (7 mg, 4%). Total yield of **279-A** and **279-B**: 62 mg, 41%. The isolated yields suggest a 7.9:1 ratio of **279-A** and **279-B**.

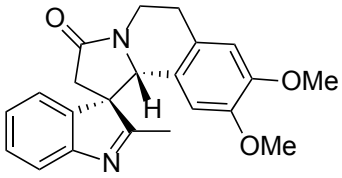
279-A: Yellow oil, R_f (9.5:0.5 EtOAc/MeOH) 0.20; IR (ATR) 3301, 2980, 2930, 1655, 1435, 1270, 1213, 1174, 1092, 910, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.10 (m, 2H, Ar), 7.07-7.03 (m, 1H, Ar), 6.42 (d, *J* = 7.5 Hz, 1H, Ar), 5.15 (s, 1H, NCH), 4.50–4.45 (m, 1H, NCH_AH_B), 4.36–4.25 (m, 2H, OCH_2), 3.12–2.98 (m, 2H,

NCH_AH_B, CH_EH_F), 2.93 (d, J = 16.5 Hz, 1H, $CH_CH_DC(O)$), 2.86-2.82 (m, 1H, CH_EH_F), 2.49 (s, 3H, CH_3), 2.35 (dd, J = 16.5, 2.0 Hz, 1H, $CH_CH_DC(O)$), 1.79 (s, 3H, CH_3), 1.33 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1 (C=N), 169.5 (C=O), 163.1 (C=O), 151.3 (*ipso*-Ar), 140.1 (*ipso*-Ar), 133.1 (*ipso*-Ar), 131.5 (*ipso*-Ar), 129.2 (Ar), 127.8 (Ar), 127.4 (Ar), 123.8 (Ar), 67.4 (C), 60.8 (OCH_2), 59.2 (NCH), 37.6 ($C(O)CH_2$), 37.4 (NCH_2), 28.3 (CH_2), 16.2 (CH_3), 14.3 (CH_3), 11.1 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_2O_3$ $[M + H]^+$ 339.1703, found 339.1688 (+4.4 ppm error).

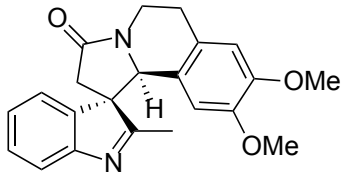
279-B: Yellow oil, R_F (9.5:0.5 EtOAc/MeOH) 0.30; IR (ATR) 3304, 2927, 1660, 1633, 1436, 1269, 1208, 1174, 1088, 1025, 919, 773, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.12 (m, 2H, Ar), 7.10–7.06 (m, 1H, Ar), 6.47 (d, J = 7.5 Hz, 1H, Ar), 5.05 (s, 1H, NCH), 4.51–4.36 (m, 3H, OCH_2, NCH_AH_B), 3.14–2.99 (m, 2H, NCH_AH_B, CH_EH_F), 2.91–2.79 (m, 1H, CH_EH_F), 2.86 (d, J = 16.5 Hz, 1H, $CH_CH_DC(O)$), 2.47 (s, 3H, CH_3), 2.29 (d, J = 16.5 Hz, 1H, $CH_CH_DC(O)$), 1.78 (s, 3H, CH_3), 1.42 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3 (C=N), 169.5 (C=O), 163.2 (C=O), 147.7 (*ipso*-Ar), 141.0 (*ipso*-Ar), 133.1 (*ipso*-Ar), 132.0 (*ipso*-Ar), 129.4 (Ar), 127.9 (Ar), 127.8 (Ar), 123.4 (Ar), 67.7 (C), 61.1 (OCH_2), 57.9 (NCH), 37.3 ($C(O)CH_2$), 36.9 (NCH_2), 28.3 (CH_2), 17.2 (CH_3), 14.3 (CH_3), 11.2 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_2O_3$ $[M + H]^+$ 339.1703, found 339.1698 (+1.5 ppm error).

Lab Book Reference: SC4/46

(1'*R,10b'*R**)-8',9'-Dimethoxy-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *syn*-284 and (1'*R**,10b'*S**)-8',9'-dimethoxy-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *anti*-284**



syn-**284**



anti-**284**

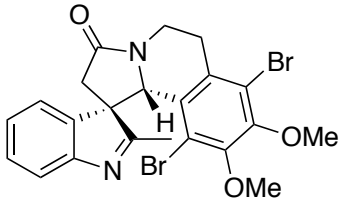
Using general procedure J, DIPEA (245 μL, 1.41 mmol), T3P (725 mg of a 50% w/v solution in THF, 1.14 mmol), 6,7-dimethoxy-3,4-dihydroisoquinoline **283** (145 mg, 0.76 mmol) and 2-(2-methyl-1*H*-indol-3-yl)acetic acid **212** (172 mg, 0.91 mmol) in THF (4 mL) for 16 h at rt gave the crude product which contained 3:1 mixture of *syn*-**284**:*anti*-**284** based on analysis by ^{1}H NMR spectroscopy: δ 6.43 (s, 3H, Ar) and 6.54 (s, 1H, Ar). Purification by flash column chromatography with EtOAc-MeOH (98:2) as eluent sequentially furnished *anti*-**284** (44 mg, 16%), a 1:3 mixture of *anti*-**284**:*syn*-**284** (15 mg, 5%) and *syn*-**284** (143 mg, 52%). Total combined yield of *syn*-**284** and *anti*-**284**: 202 mg, 73%. The isolated yields suggest a 3.2:1 ratio of *syn*-**284**:*anti*-**284**.

Syn-**284**: Yellow solid, mp 163-165 °C; R_F (EtOAc) 0.15; IR (ATR) 2933, 2835, 1693, 1518, 1457, 1256, 1124, 770, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.5 Hz, 1H, Ar), 7.17-7.13 (m, 1H, Ar), 6.94-6.87 (m, 2H, Ar), 6.43 (s, 1H, Ar), 5.72 (s, 1H, Ar), 5.21 (s, 1H, NCH), 4.53 (dd, J = 13.5, 5.0 Hz, 1H, NCH_AH$_B$), 3.73 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.12-3.08 (m, 2H, CH_CH$_D$C(O), NCH$_A$$H_B$), 2.95 (ddd, J = 13.5, 13.5, 5.0 Hz, 1H, CH_EH$_F$), 2.74-2.69 (m, 1H, CH$_E$$H_F$), 2.62 (s, 3H, CH_3), 2.47 (d, J = 16.5 Hz, 1H, CH$_C$$H_D$C(O)); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 181.0 (C=N), 170.4 (C=O), 153.8 (*ipso*-Ar), 147.7 (*ipso*-Ar), 147.6 (*ipso*-Ar), 140.5 (*ipso*-Ar), 128.6 (Ar), 125.8 (Ar), 125.5 (*ipso*-Ar), 124.0 (*ipso*-Ar), 121.4 (Ar), 120.1 (Ar), 111.1 (Ar), 105.9 (Ar), 63.1 (C), 60.2 (NCH), 55.6 (OCH_3 x 2), 39.8 (CH$_2$C(O)), 37.5 (NCH$_2$), 28.3 (CH_2), 16.4 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{22}N_2O_3$ $(M + H)^+$ 363.1703, found 363.1694 (+2.5 ppm error).

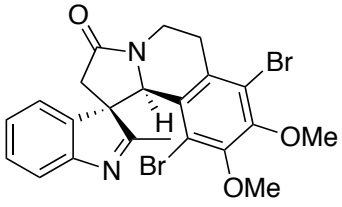
Anti-**284**: Yellow oil, R_F (EtOAc) 0.25; IR (ATR) 2932, 2853, 1692 (C=O), 1518, 1457, 1433, 1256, 1027, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.53 (m, 2H, Ar), 7.43 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H, Ar), 7.37 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.54 (s, 1H, Ar), 5.34 (s, 1H, Ar), 5.27 (s, 1H, NCH), 4.56-4.51 (m, 1H, NCH_AH_B), 3.80 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 3.13-2.91 (m, 3H, $CH_CH_DC(O)$, NCH_AH_B, CH_EH_F), 2.79-2.74 (m, 1H, CH_EH_F), 2.59 (d, *J* = 17.0 Hz, 1H, $CH_CH_DC(O)$), 1.90 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 182.9 (C=N), 170.1 (C=O), 155.0 (*ipso*-Ar), 148.3 (*ipso*-Ar), 147.3 (*ipso*-Ar), 140.0 (*ipso*-Ar), 129.2 (Ar), 126.3 (Ar), 124.9 (*ipso*-Ar), 123.5 (*ipso*-Ar), 121.8 (Ar), 120.4 (Ar), 111.3 (Ar), 105.7 (Ar), 61.9 (C), 61.8 (NCH), 55.8 (OCH_3), 55.0 (OCH_3), 39.7 ($CH_2C(O)$), 37.1 (NCH_2), 27.9 (CH_2), 17.4 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{22}N_2O_3$ $(M + H)^+$ 363.1703, found 363.1688 (+4.3 ppm error).

Lab Book Reference SC3/57

(1'*R,10b'*S**)-7',10'-Dibromo-8',9'-dimethoxy-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *syn*-285 and (1'*R**,10b'*R**)-7',10'-dibromo-8',9'-dimethoxy-2-methyl-5',6'-dihydro-2'*H*-spiro[indole-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one *anti*-285**



syn-**285**



anti-**285**

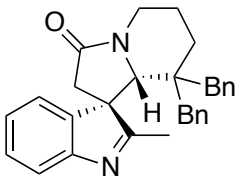
Using general procedure J, DIPEA (193 μL, 1.11 mmol), T3P (572 mg of a 50% w/v solution in THF, 0.90 mmol), 5,8-dibromo-6,7-dimethoxy-3,4-dihydroisoquinoline (210 mg, 0.60 mmol) and 2-methyl-3-indole acetic acid **212** (136 mg, 0.72 mmol) in THF (3.2 mL) for 1 h at 70 °C gave the crude product which contained 9:1 mixture of *syn*-**285**:*anti*-**285** based on analysis by ^1H NMR spectroscopy: δ 5.47 (s, 9H, NCH) and 5.63 (s, 1H, NCH). Purification by flash column chromatography with EtOAc as eluent sequentially furnished *anti*-**285** (27 mg, 8%) and *syn*-**285** (222 mg, 71%). Total combined yield of *syn*-**285** and *anti*-**285**: 249 mg, 79%. The isolated yields suggest a 8.2:1 ratio of *syn*-**214**:*anti*-**214**.

Syn-**285**: Yellow solid, mp 156-158 °C; R_F (EtOAc) 0.10; IR (ATR) 2936, 1693 (C=O), 1579, 1526, 1456, 1401, 1295, 1114, 1023, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 1H, Ar), 7.11 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.77 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar), 6.36 (d, *J* = 7.5, 7.5 Hz, 1H, Ar), 5.47 (s, 1H, NCH), 4.61-4.51 (m, 1H, NCH_AH_B), 3.73 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.01-2.84 (m, 4H, $CH_CH_DC(O)$, NCH_AH_B, CH_EH_F), 2.60 (s, 3H, CH_3), 2.36 (d, *J* = 17.5 Hz, 1H, $CH_CH_DC(O)$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 183.2 (C=N), 170.9 (C=O), 154.4 (*ipso*-Ar), 149.9 (*ipso*-Ar), 149.5 (*ipso*-Ar), 140.3 (*ipso*-Ar), 133.6 (*ipso*-Ar), 131.1 (*ipso*-Ar), 128.1 (Ar), 124.9 (Ar), 121.3 (Ar), 120.2 (Ar), 119.9 (*ipso*-Ar), 117.8 (*ipso*-Ar), 61.9 (C), 61.8 (NCH), 60.7 (OCH_3), 60.6 (OCH_3), 40.0 ($CH_2C(O)$), 37.7 (NCH_2), 30.9 (CH_2), 16.5 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{20}{}^{79}Br_2N_2O_3$ $(M + H)^+$ 518.9913, found 518.9937 (−4.6 ppm error).

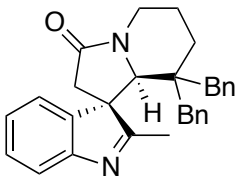
Anti-**285**: Yellow solid, mp 149-151 °C; R_F (EtOAc) 0.35; IR (ATR) 2927, 2854, 1698 (C=O), 1576, 1459, 1408, 1293, 1025, 979, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 1H, Ar), 7.46 (d, *J* = 7.5 Hz, 1H, Ar), 7.35 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 7.29 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 5.63 (s, 1H, NCH), 4.65-4.57 (m, 1H, NCH_AH_B), 3.87 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.05-2.97 (m, 2H, $CH_CH_DC(O)$, CH_EH_F), 2.92-2.84 (m, 2H, NCH_AH_B, CH_EH_F), 2.59 (d, *J* = 18.0 Hz, 1H, $CH_CH_DC(O)$), 1.66 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.5 (C=N), 170.7 (C=O), 154.3 (*ipso*-Ar), 150.4 (*ipso*-Ar), 150.1 (*ipso*-Ar), 144.4 (*ipso*-Ar), 134.0 (*ipso*-Ar), 131.3 (*ipso*-Ar), 128.6 (Ar), 126.2 (Ar), 121.5 (Ar), 120.4 (Ar), 120.2 (*ipso*-Ar), 117.1 (*ipso*-Ar), 63.4 (NCH), 61.8 (C), 60.9 (OCH_3), 60.7 (OCH_3), 40.8 ($CH_2C(O)$), 37.4 (NCH_2), 31.0 (CH_2), 16.7 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{20}{}^{79}Br_2N_2O_3$ $(M + H)^+$ 518.9913, found 518.9928 (−2.7 ppm error).

Lab Book Reference SC4/34

(1'*R,8a'*R**)-8',8'-Dibenzyl-2-methyl-6',7',8',8a'-tetrahydro-2'*H*-spiro[indole-3,1'-indolizin]-3'(5'*H*)-one *syn*-291 and (1'*R**,8a'*S**)-8',8'-dibenzyl-2-methyl-6',7',8',8a'-tetrahydro-2'*H*-spiro[indole-3,1'-indolizin]-3'(5'*H*)-one *anti*-291**



syn-**291**



anti-**291**

Using general procedure J, DIPEA (74 μL, 0.43 mmol), T3P (219 mg of a 50% w/v solution in THF, 0.35 mmol), imine **290** (60 mg, 0.23 mmol) and 2-methyl-3-indole acetic acid **212** (53 mg, 0.28 mmol) in toluene (1 mL) for 18 h at 90 °C gave the crude product which contained 3:1 mixture of *syn*-**291**:*anti*-**291** based on analysis by ^{1}H NMR spectroscopy: δ 6.33-6.31 (m, 6H, Ar) and 6.40 (d, 2H, Ar). Purification by flash column chromatography with EtOAc-Et_2O (10:90 then 20:80 then 50:50) as eluent sequentially furnished *anti*-**291** (26 mg, 26%) and *syn*-**291** (63 mg, 63%). Total combined yield of *syn*-**291** and *anti*-**291**: 89 mg, 89%. *Syn*-**291** was recrystallised from EtOAc to obtain an X-ray crystal structure. CCDC 1436396 contains the supplementary crystallographic data. The isolated yields suggest a 2.4:1 ratio of *syn*-**291**:*anti*-**291**.

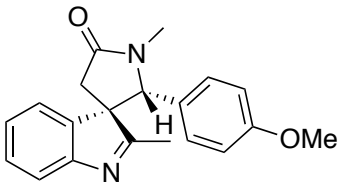
Syn-**291**: Brown solid, mp 225-227 °C; R_F (EtOAc) 0.35; IR (ATR) 3028, 2938, 1683, 1589, 1454, 1422, 1283, 908, 728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.5 Hz, 1H, Ar), 7.71 (d, J = 7.5 Hz, 1H, Ar), 7.48 (dd, J = 7.5, 7.5 Hz, 1H, Ar), 7.40 (dd, J = 7.5, 7.5 Hz, 1H, Ar), 7.36-7.28 (m, 3H, Ar), 7.24-7.22 (m, 2H, Ar), 7.09-7.07 (m, 3H, Ar), 6.33-6.31 (m, 2H, Ar), 4.41 (dd, J = 13.0, 5.5 Hz, 1H, NCH_AH$_B$), 3.47 (d, J = 13.5 Hz, 1H, CH_CH$_D$), 3.35-3.32 (m, 2H, NCH$_A$$H_B$, CH$_C$$H_D$), 3.13 (d, J = 17.5 Hz, 1H, CH_EH$_F$CO), 2.54 (ddd, J = 13.0, 13.0, 3.5 Hz, 1H, NCH), 2.45 (d, J = 13.5 Hz, 1H, CH_GH$_H$), 2.33 (d, J = 17.5 Hz, 1H, CH$_E$$H_F$CO), 2.19 (s, 3H, CH_3), 2.20-2.10 (m, 1H, CH), 2.09 (d, J = 13.5 Hz, 1H, CH$_G$$H_H$), 1.56-1.50 (m, 2H, 2 x CH), 1.24-1.17 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 185.1 (C=N), 170.6 (C=O), 156.1 (*ipso*-Ar), 137.6 (*ipso*-Ar), 136.6 (*ipso*-Ar), 135.9 (*ipso*-Ar), 130.84 (Ar), 130.75 (Ar), 129.5 (Ar), 128.3 (Ar), 127.8 (Ar), 126.7 (Ar), 126.7 (Ar), 126.2 (Ar), 125.9 (Ar), 125.4 (Ar), 121.2 (Ar), 64.8 (NCH), 60.0 (C), 43.3 (C), 40.4 (NCH_2), 40.0 (CH_2Ar), 38.7 (CH$_2$C(O)), 34.8

(CH_2Ar), 31.1 (CH_2), 20.2 (CH_2), 16.0 (CH_3); HRMS (ESI) *m/z* calcd for $C_{30}H_{30}N_2O$ (M + H)$^+$ 435.2431, found 435.2447 (−3.8 ppm error).

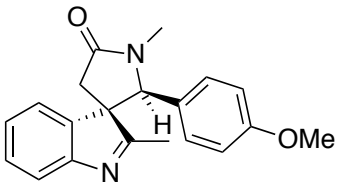
Anti-**291**: Yellow oil, R_F (EtOAc) 0.50; IR (ATR) 3029, 2932, 1686 (C=O), 1601, 1556, 1454, 1441, 1265, 732, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.5 Hz, 1H, Ar), 7.43 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar), 7.35-7.20 (m, 7H, Ar), 7.02- 6.98 (m, 1H, Ar), 6.90 (dd, *J* = 7.5, 7.5 Hz, 2H, Ar), 6.40 (d, *J* = 7.5 Hz, 2H, Ar), 4.39 (dd, *J* = 13.0, 5.0 Hz, 1H, NCH_AH$_B$), 3.77 (s, 1H, NCH), 3.30 (d, *J* = 13.5 Hz, 1H, CH_CH$_D$), 3.00 (d, *J* = 13.5 Hz, 1H, CH$_C$$H_D$), 2.93-2.88 (m, 4H, C$H_EH_F$CO, CH_3), 2.64 (ddd, *J* = 13.0, 13.0, 3.5 Hz, 1H, NCH$_A$$H_B$), 2.49 (d, *J* = 14.0 Hz, 1H, CH_GH$_H$), 2.46 (d, *J* = 14.0 Hz, 1H, CH$_G$$H_H$), 2.39 (d, *J* = 16.5 Hz, 1H, CH$_E$$H_F$CO), 2.19-2.04 (m, 1H, CH), 1.59-1.52 (m, 2H, 2 x CH), 1.09-1.01 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.1 (C=N), 171.3 (C=O), 152.4 (*ipso*-Ar), 145.3 (*ipso*-Ar), 136.8 (*ipso*-Ar), 135.8 (*ipso*-Ar), 131.0 (Ar), 130.8 (Ar), 128.9 (Ar), 128.3 (Ar), 127.6 (Ar), 126.82 (Ar), 126.79 (Ar), 126.2 (Ar), 120.7 (Ar), 120.4 (Ar), 71.4 (NCH), 61.2 (C), 42.5 (C), 40.9 (CH_2Ar), 40.8 (NCH_2), 39.7 (CH_2C(O)), 35.7 (CH_2Ar), 31.0 (CH_2), 21.9 (CH_3), 20.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_{30}H_{30}N_2O$ (M + H)$^+$ 435.2431, found 435.2445 (−3.3 ppm error).

Lab Book Reference: SC4/88

(2'*R,3*R**)-2'-(4-Methoxyphenyl)-1',2-dimethylspiro[indole-3,3'-pyrrolidin]-5'-one *syn*-294 and (2'*S**,3*R**)-2'-(4-methoxyphenyl)-1',2-dimethylspiro[indole-3,3'-pyrrolidin]-5'-one *anti*-294**



syn-**294**



anti-**294**

Using general procedure J, DIPEA (245 μL, 1.41 mmol), T3P (725 mg of a 50% w/v solution in THF, 1.14 mmol), imine **293** (113 mg, 0.76 mmol) and acid **212** (172 mg, 0.91 mmol) in THF (4 mL) for 1 h at 70 °C gave the crude product which contained 4:1 mixture of *syn*-**294**:*anti*-**294** based on analysis by ^{1}H NMR spectroscopy: δ 4.40 (s,

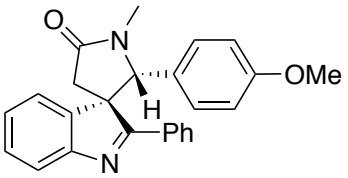
4H, NCH) and 4.66 (s, 1H, NCH). Purification by flash column chromatography with EtOAc as eluent sequentially furnished *anti*-**294** (32 mg, 13%) and *syn*-**294** (141 mg, 58%). Total combined yield of *syn*-**294** and *anti*-**294**: 173 mg, 71%. *Syn*-**294** was recrystallised from EtOAc to obtain an X-ray crystal structure. CCDC 1436400 contains the supplementary crystallographic data. The isolated yields suggest a 4.4:1 ratio of *syn*-**294**:*anti*-**294**.

Syn-**294**: Orange solid, mp 166-168 °C; R_F (EtOAc) 0.20; IR (ATR) 2910, 1682 (C=O), 1608, 1583, 1511, 1455, 1248, 1171, 1023, 843, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.5 Hz, 1H, Ar), 7.18 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.82-6.74 (m, 5H, Ar), 6.03 (d, J = 7.5 Hz, 1H, Ar), 4.40 (s, 1H, NCH), 3.78 (s, 3H, OCH_3), 2.97-2.92 (m, 4H, NCH_3, $CH_AH_BC(O)$), 2.44 (d, J = 17.0 Hz, 1H, $CH_AH_BC(O)$), 2.38 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 183.3 (C=N), 173.1 (C=O), 159.7 (*ipso*-Ar), 154.4 (*ipso*-Ar), 137.1 (*ipso*-Ar), 128.4 (Ar), 128.1 (Ar), 127.7 (*ipso*-Ar), 125.1 (Ar), 123.8 (Ar), 119.7 (Ar), 114.0 (Ar), 67.0 (NCH), 61.0 (C), 55.3 (OCH_3), 36.8 ($CH_2C(O)$), 29.0 (NCH_3), 16.1 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{20}N_2O_2$ $(M + H)^+$ 321.1598, found 321.1589 (+2.6 ppm error).

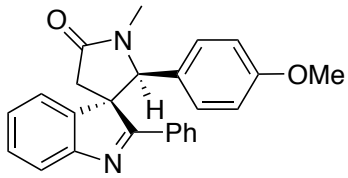
Anti-**294**: Orange oil, R_F (EtOAc) 0.40; IR (ATR) 2926, 1694 (C=O), 1612, 1573, 1513, 1459, 1396, 1250, 1176, 1031, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.5 Hz, 1H, Ar), 7.42-7.36 (m, 2H, Ar), 7.29-7.25 (m, 1H, Ar), 6.89-6.84 (m, 4H, Ar), 4.66 (s, 1H, NCH), 3.80 (s, 3H, OCH_3), 2.99-2.95 (m, 4H, NCH_3, $CH_AH_BC(O)$), 2.52 (d, J = 16.5 Hz, 1H, $CH_AH_BC(O)$), 1.62 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 181.4 (C=N), 173.3 (C=O), 160.0 (*ipso*-Ar), 143.8 (*ipso*-Ar), 128.8 (Ar), 128.2 (*ipso*-Ar), 127.4 (Ar), 127.1 (*ipso*-Ar), 126.3 (Ar), 120.4 (Ar), 120.2 (Ar), 114.5 (Ar), 70.4 (NCH), 61.8 (C), 55.3 (OCH_3), 36.8 ($CH_2C(O)$), 29.2 (NCH_3), 17.7 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{20}N_2O_2$ $(M + H)^+$ 321.1598, found 321.1594 (+1.0 ppm error).

Lab Book Reference: SC4/53

(2'*R,3*R**)-2'-(4-Methoxyphenyl)-1'-methyl-2-phenylspiro[indole-3,3'-pyrrolidin]-5'-one *syn*-295 and (2'*S**,3*R**)-2'-(4-methoxyphenyl)-1'-methyl-2-phenylspiro[indole-3,3'-pyrrolidin]-5'-one *anti*-295**



syn-**295**



anti-**295**

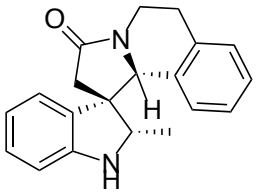
Using general procedure J, DIPEA (116 μL, 0.67 mmol), T3P (286 mg of a 50% w/v solution in THF, 0.45 mmol), imine **293** (45 mg, 0.30 mmol) acid **263** (90 mg, 0.36 mmol) in THF (1.5 mL) for 1 h at 70 °C gave the crude product which contained a 1.8:1 mixture of *syn*-**295**:*anti*-**295** based on analysis by ^{1}H NMR spectroscopy: δ 4.96 (s, 1.8H, NCH) and 4.92 (s, 1H, NCH). Purification by flash column chromatography with hexane-EtOAc (1:1) as eluent furnished an inseparable 1:1.2 mixture of diastereoisomers. Total yield of *syn*-**295** and *anti*-**295**: 73 mg, 76%.

Anti-**295** and *syn*-**295**: Pale brown solid, mp 169-171 °C; R_F (1:1 hexane-EtOAc) 0.20; IR (ATR) 3060, 2932, 1693, 1612, 1586, 1513, 1458, 1304, 1249, 1176, 1032, 911, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for a 1.2:1 mixture of diastereoisomers δ 7.99-7.97 (m, 2.4H, Ar), 7.61 (m, 1H, Ar), 7.56-7.48 (m, 7.8H, Ar), 7.46-7.42 (m, 1.2H, Ar), 7.39-7.34 (m, 2H, Ar), 7.27 (dd, *J* = 7.5, 7.5 Hz, 2H, Ar), 7.20-7.16 (m, 1.2H, Ar), 6.95-6.91 (m, 1.2H, Ar), 6.71-6.64 (m, 5.8H, Ar), 6.44-6.40 (m, 2H, Ar), 6.35-6.32 (m, 2H, Ar), 4.96 (s, 1H, NCH), 4.92 (s, 1.2H, NCH), 3.70 (s, 3.6H, OCH_3), 3.64 (s, 3H, OCH_3), 3.44 (d, *J* = 18.0 Hz, 1H, CH_AH$_B$C(O)), 3.23 (d, *J* = 18.0 Hz, 1.2H, CH_AH$_B$C(O)), 3.06 (d, *J* = 18.0 Hz, 1H, CH$_A$$H_B$C(O)), 3.05 (d, *J* = 18.0 Hz, 1.2H, CH$_A$$H_B$C(O)), 2.92 (s, 3H, CH_3), 2.84 (s, 3.6H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.6 (C=N), 179.0 (C=N), 174.4 (C=O), 173.8 (C=O), 159.4 (*ipso*-Ar), 159.3 (*ipso*-Ar), 153.6 (*ipso*-Ar), 153.4 (*ipso*-Ar), 140.6 (*ipso*-Ar), 134.6 (*ipso*-Ar), 132.4 (*ipso*-Ar), 131.1 (Ar), 130.3 (Ar), 129.0 (Ar), 128.96 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 127.89 (Ar), 127.88 (Ar), 127.4 (Ar), 127.3 (*ipso*-Ar), 126.9 (Ar), 125.7 (Ar), 125.4 (*ipso*-Ar), 123.5 (Ar), 121.1 (Ar), 120.8 (Ar), 120.7 (Ar), 113.6 (Ar), 113.3 (Ar), 71.8 (NCH), 68.4 (NCH), 61.7 (C), 61.1 (C), 55.2 (OCH_3), 55.1 (OCH_3), 39.4 (CH_2C(O)), 39.3 (CH_2C(O)), 29.7 (CH_3), 29.5 (CH_3);

HRMS (ESI) *m/z* calcd for $C_{25}H_{22}N_2O_2$ $(M + H)^+$ 383.1754, found 383.1743 (+3.0 ppm error).

Lab Book Reference: SC4/61

(1'*S,2*S**,10b'*R**)-2-Methyl-5',6'-dihydro-2'*H*-spiro[indoline-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one 298**

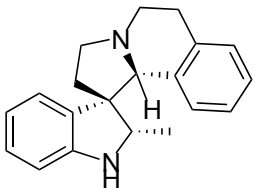


298

Using general procedure K, $NaBH_4$ (50 mg, 1.32 mmol) and imine *syn*-**214** (100 mg, 0.33 mmol) in MeOH (5 mL) at reflux for 3.5 h gave the crude product. Purification by flash column chromatography using EtOAc-hexane (9:1) as eluent gave spiroindoline **298** (81 mg, 81%) as a cream solid, mp 229-231 °C; R_F (EtOAc) 0.50; IR (ATR) IR (ATR) 3318 (NH), 3058, 2924, 1682 (C=O), 1606, 1578, 1459, 1305, 1143, 909, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.5 Hz, 1H, Ar), 6.97-6.89 (m, 3H, Ar), 6.83 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.80-6.78 (m, 1H, Ar), 6.46 (d, *J* = 8.0 Hz, 1H, Ar), 6.43 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 5.18 (s, 1H, NCH), 4.52-4.47 (m, 1H, NCH_AH_B), 4.05 (br s, 1H, NH), 4.01 (q, *J* = 7.0 Hz, 1H, $CHCH_3$), 2.97-2.81 (m, 3H, NCH_AH_B, CH_EH_F, $CH_CH_DC(O)$), 2.73 (dd, *J* = 16.5, 1.0 Hz, 1H, $CH_CH_DC(O)$), 2.69-2.65 (m, 1H, CH_EH_F), 1.64 (d, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.8 (C=O), 149.6 (*ipso*-Ar), 134.3 (*ipso*-Ar), 133.2 (*ipso*-Ar), 132.9 (*ipso*-Ar), 128.5 (Ar), 128.2 (Ar), 126.7 (Ar), 126.4 (Ar), 125.7 (Ar), 122.4 (Ar), 119.2 (Ar), 109.4 (Ar), 62.2 (NCH), 61.8 ($CHCH_3$), 53.9 (C), 44.8 ($CH_2C(O)$), 37.3 (NCH_2), 29.3 (CH_2), 15.7 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{20}N_2O$ $(M + H)^+$ 305.1648, found 305.1645 (+1.1 ppm error). **298** was recrystallised from EtOAc to obtain an X-ray crystal structure. CCDC 1436401 contains the supplementary crystallographic data.

Lab Book Reference: SC5/48

(1'*S,2*S**,10b'*R**)-2-Methyl-3',5',6',10b'-tetrahydro-2'*H*-spiro[indoline-3,1'-pyrrolo[2,1-*a*]isoquinoline] 300**

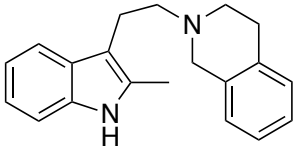


300

Using general procedure L, $LiAlH_4$ (76 mg, 2.00 mmol) and amide **298** (153 mg, 0.50 mmol) in dry THF (15 mL) under Ar at reflux for 2.5 h gave the crude product. Purification by flash column chromatography EtOAc as eluent gave spiroindoline **300** (110 mg, 75%) as a white solid, mp 141-143 °C; R_F (EtOAc) 0.45; IR (ATR) 3356 (NH), 2981, 2897, 2804, 1604, 1467, 1330, 935, 762, 556 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.5 Hz, 1H, Ar), 7.02 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar), 6.96-6.91 (m, 2H, Ar), 6.89-6.81 (m, 2H, Ar), 6.54 (d, *J* = 7.5 Hz, 1H, Ar), 6.49 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 4.02 (q, *J* = 7.0 Hz, 1H, C*H*CH_3), 3.64 (s, 1H, NCH), 3.30-3.22 (m, 2H, NCH), 3.14-3.06 (m, 1H, CH), 2.67 (dd, *J* = 16.0, 4.0 Hz, 1H, CH), 2.60-2.46 (m, 3H, 2 x NCH, CH), 1.98-1.92 (m, 1H, CH), 1.50 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.0 (*ipso*-Ar), 136.3 (*ipso*-Ar), 136.1 (*ipso*-Ar), 135.3 (*ipso*-Ar), 128.1 (Ar), 127.2 (Ar), 127.1 (Ar), 125.5 (Ar), 125.2 (Ar), 125.0 (Ar), 118.1 (Ar), 108.8 (Ar), 69.4 (NCH), 63.9 (*C*HCH_3), 56.7 (C), 52.2 (NCH_2), 49.9 (NCH_2), 41.6 (CH_2), 29.2 (CH_2), 16.1 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_2$ $(M + H)^+$ 291.1856, found 291.1860 (−1.6 ppm error).

Lab Book Reference: SC5/37

2-(2-(2-Methyl-1*H*-indol-3-yl)ethyl)-1,2,3,4-tetrahydroisoquinoline 301



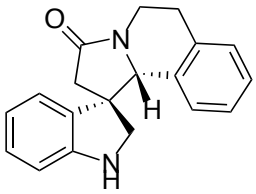
301

Using general procedure L, $LiAlH_4$ (27 mg, 0.70 mmol) and *syn*-**214** (20 mg, 0.07 mmol) in dry THF (3 mL) under Ar at reflux for 3.5 h gave the crude product.

Purification by flash column chromatography using hexane-EtOAc (1:1) as eluent gave indole **301** (9 mg, 42%) as a yellow oil, R_F (hexane-EtOAc 1:1) 0.10; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (br s, 1H, Ar), 7.55-7.53 (m, 1H, Ar), 7.29-7.26 (m, 2H, Ar), 7.16-7.05 (m, 5H, Ar), 3.82 (s, 2H, CH_2N), 3.06-2.98 (m, 4H, 2 x CH_2), 2.93-2.90 (m, 2H, CH_2), 2.81-2.77 (m, 2H, CH_2), 2.41 (s, 3H, CH_3); HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2O$ $(M + H)^+$ 291.1856, found 291.1848 (+1.9 ppm error).

Lab Book Reference: SC5/4

(1'*S,10b'*R**)-5',6'-Dihydro-2'*H*-spiro[indoline-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one 299**

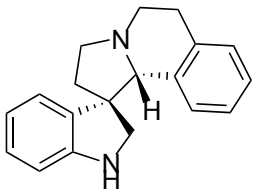


299

Using general procedure K, $NaBH_4$ (52 mg, 1.39 mmol) and imine *syn*-**267** (100 mg, 0.35 mmol) in MeOH (5 mL) at reflux for 3.5 h gave the crude product. Purification by flash column chromatography using EtOAc as eluent gave spiroindoline **299** (87 mg, 87%) as a cream solid, mp 211-213 °C; R_F (EtOAc) 0.30; IR (ATR) 3330 (NH), 2924, 2855, 1675 (C=O), 1606, 1487, 1459, 1415, 1306, 909, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.31 (m, 1H, Ar), 7.01-6.93 (m, 3H, Ar), 6.85 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.77-6.75 (m, 1H, Ar), 6.47 (d, *J* = 8.0 Hz, 1H, Ar), 6.44-6.40 (m, 1H, Ar), 5.04 (s, 1H, NCH), 4.51-4.47 (m, 1H, NCH_AH$_B$), 4.09 (d, *J* = 10.0 Hz, 1H, NHCH_AH$_B$), 3.35 (d, *J* = 10.0 Hz, 1H, NHCH$_A$$H_B$), 2.98-2.84 (m, 4H, NCH$_A$$H_B$, CH, CH$_AH_B$C(O)), 2.71-2.67 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.3 (C=O), 150.6 (*ipso*-Ar), 134.1 (*ipso*-Ar), 132.9 (*ipso*-Ar), 131.5 (*ipso*-Ar), 128.7 (Ar), 128.4 (Ar), 126.7 (Ar), 126.0 (Ar), 125.6 (Ar), 122.4 (Ar), 118.8 (Ar), 109.5 (Ar), 68.2 (NCH), 57.6 ($NHCH_2$), 52.4 (C), 46.2 (CH_2C(O)), 35.1 (NCH_2), 29.2 (CH_2); HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2O$ $(M + H)^+$ 291.1492, found 291.1486 (+1.9 ppm error).

Lab Book Reference: SC5/49

(1'*S,10b'*R**)-3',5',6',10b'-Tetrahydro-2'*H*-spiro[indoline-3,1'-pyrrolo[2,1-*a*]isoquinoline] 303**

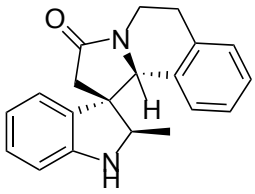


303

Using general procedure L, $LiAlH_4$ (78 mg, 2.04 mmol) and amide **299** (148 mg, 0.51 mmol) in dry THF (15 mL) under Ar at reflux for 2.5 h gave the crude product. Purification by flash column chromatography EtOAc as eluent gave spiroindoline **303** (94 mg, 67%) as a yellow oil, R_F (EtOAc) 0.10; IR (ATR) 3291 (NH), 2923, 2790, 1638, 1604, 1577, 1484, 1264, 1026, 731, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.0 Hz, 1H, Ar), 7.00-6.97 (m, 2H, Ar), 6.90 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.83 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar), 6.79-6.77 (m, 1H, Ar), 6.60 (d, *J* = 8.0 Hz, 1H, Ar), 6.47 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 4.01 (d, *J* = 9.5 Hz, 1H, $NHCH_AH_B$), 3.71 (d, *J* = 9.5 Hz, 1H, $NHCH_AH_B$), 3.54 (s, 1H, NCH), 3.31-3.12 (m, 3H, 2 x NCH, CH), 2.79-2.75 (m, 1H, CH), 2.65-2.56 (m, 2H, NCH), 2.29 (ddd, *J* = 13.0, 9.5, 8.0 Hz, 1H, CH), 2.17 (ddd, *J* = 13.0, 8.0, 2.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 150.9 (*ipso*-Ar), 135.7 (*ipso*-Ar), 135.4 (*ipso*-Ar), 135.0 (*ipso*-Ar), 128.4 (Ar), 127.2 (Ar), 126.0 (Ar), 125.7 (Ar), 125.2 (Ar), 125.0 (Ar), 118.8 (Ar), 109.1 (Ar), 73.1 (NCH), 60.7 ($NHCH_2$), 55.0 (C), 52.7 (NCH_2), 49.4 (NCH_2), 42.7 (CH_2), 29.4 (CH_2); HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_2$ $(M + H)^+$ 277.1699, found 277.1700 (−0.2 ppm error).

Lab Book Reference: SC5/38

(1'*S,2*R**,10b'*R**)-2-Methyl-5',6'-dihydro-2'*H*-spiro[indoline-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one 304**

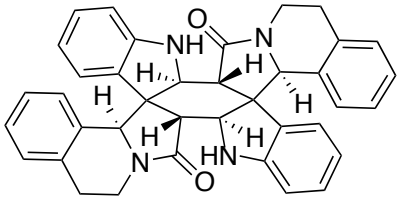


304

MeMgBr (3M in Et_2O, 0.59 mL, 1.77 mmol) was added to a stirred solution of spiroindolenine *syn*-**267** (170 mg, 0.59 mmol) in dry THF (7 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 6 h, then quenched with NH_4Cl (10 mL) and diluted with CH_2Cl_2 (10 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography using EtOAc-hexane (9:1) as eluent gave the spiroindoline **304** (112 mg, 62%) as an orange solid, mp 141-143 °C; R_F (EtOAc) 0.45; IR (ATR) 3319 (NH), 3051, 2926, 1676 (C=O), 1606, 1459, 1415, 1305, 1264, 730, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.36 (m, 1H, Ar), 7.02-6.95 (m, 2H, Ar), 6.93-6.91 (m, 1H, Ar), 6.83 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.76 (d, J = 7.5 Hz, 1H, Ar), 6.43-6.39 (m, 2H, Ar), 4.94 (s, 1H, NCH), 4.49-4.45 (m, 1H, NCH_AH_B), 4.32 (q, J = 6.5 Hz, 1H, $CHCH_3$), 3.05 (dd, J = 16.0, 1.0 Hz, 1H, $CH_CH_DC(O)$), 2.96-2.82 (m, 2H, NCH_AH_B, CH_EH_F), 2.71-2.64 (m, 1H, CH_EH_F), 2.52 (d, J = 16.0 Hz, 1H, $CH_CH_DC(O)$), 1.31 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.8 (C=O), 148.9 (*ipso*-Ar), 134.6 (*ipso*-Ar), 132.8 (*ipso*-Ar), 130.7 (*ipso*-Ar), 128.5 (Ar), 128.3 (Ar), 126.6 (Ar), 126.2 (Ar), 125.7 (Ar), 122.7 (Ar), 118.4 (Ar), 109.2 (Ar), 67.6 (NCH), 61.3 ($CHCH_3$), 56.7 (C), 40.4 ($CH_2C(O)$), 37.0 (NCH_2), 29.3 (CH_2), 19.5 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{20}N_2O$ $(M + H)^+$ 305.1648, found 305.1650 (−0.5 ppm error).

Lab Book Reference: SC5/46

(8a*R*,8b*S***,13c*S***,21a*R***,21b*S***,26c*S***)-5,6,8b,9,18,19,21a,21b,22,26c-Decahydrobenzo[7,8]indolizino[2,1-*a*]benzo[7,8]indolizino[2,1-*d*]indolo[3,2-*b*]carbazole-8,21(8a*H*,13c*H*)-dione 307**

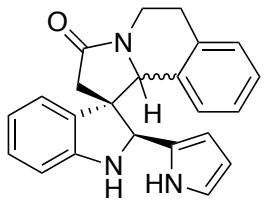


307

LHMDS (1 M in THF, 0.57 mL, 0.57 mmol) was added to a solution of spiroindolenine *syn*-**267** (110 mg, 0.38 mmol) in THF (5 mL) at −78 °C under Ar and the resulting mixture was stirred at 2.5 h. Sat. $NH_4Cl_{(aq)}$ (10 mL) was added and the reaction was extracted into Et_2O (3 x 10 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (1:1) as eluent gave the dimer **307** as an orange solid, mp 163-165 °C, R_F (1:1 Hex-EtOAc) 0.30; IR (ATR) 3346, 3051, 2927, 1672 (C=O), 1606, 1459, 1433, 1402, 1305, 1264, 1040, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.54 (m, 2H, Ar), 7.01-6.97 (m, 4H, Ar), 6.94-6.91 (m, 2H, Ar), 6.86-6.82 (m, 2H, Ar), 6.73 (d, *J* = 7.0 Hz, 2H, Ar), 6.55 (d, *J* = 8.0 Hz, 2H, Ar), 6.41-6.38 (m, 2H, Ar), 5.28 (s, 2H, NH), 5.22 (s, 2H, NCH), 4.60-4.56 (m, 2H, NCH), 4.29 (d, *J* = 11.5 Hz, 2H, CHCO), 3.04 (ddd, *J* = 12.5, 12.5, 3.5 Hz, 2H, NCH), 2.91-2.83 (m, 2H, CH), 2.75-2.70 (m, 2H, CH), 2.55 (d, *J* = 11.5 Hz, 2H, NHC*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C=O), 148.9 (*ipso*-Ar), 133.8 (*ipso*-Ar), 131.7 (*ipso*-Ar), 129.6 (*ipso*-Ar), 129.1 (Ar), 128.6 (Ar), 127.0 (Ar), 126.2 (Ar), 125.8 (Ar), 122.2 (Ar), 119.1 (Ar), 110.9 (Ar), 67.8 (NCH), 62.6 (*C*HCO), 55.4 (C), 51.8 (NHCH), 37.4 (NCH_2), 29.2 (CH_2); HRMS (ESI) *m/z* calcd for $C_{38}H_{32}N_4O_2$ $(M + H)^+$ 577.2598, found 577.2600 (−0.4 ppm error). **307** was recrystallised from EtOAc to obtain an X-ray crystal structure. CCDC 1506359 contains the supplementary crystallographic data.

Lab Book Reference: SC5/44

(1'*S,2*S**)-2-(1*H*-Pyrrol-2-yl)-5',6'-dihydro-2'*H*-spiro[indoline-3,1'-pyrrolo[2,1-*a*]isoquinolin]-3'(10b'*H*)-one 308**



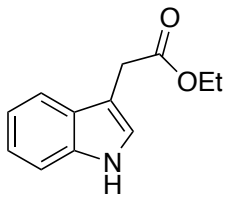
308

A flask was charged with spiroindolenine *syn*-**267** (100 mg, 0.35 mmol) and pyrrole (218 μL, 3.15 mmol). AcOH (2.5 mL) was added and the reaction was stirred for 16 h. Sat. $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were carefully added to the reaction and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave the spirocyclic product **308** (107 mg, 86%) as a yellow solid, mp 234-236 °C; R_F (EtOAc) 0.25; IR (ATR) 3326 (NH), 3180, 2927, 2851, 1655 (C=O), 1607, 1484, 1467, 1249, 969, 729 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H, NH), 7.32 (d, J = 7.5 Hz, 1H, Ar), 7.10-6.98 (m, 3H, Ar), 6.79 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.75-6.73 (m, 1H, Ar), 6.46 (d, J = 7.5 Hz, 1H, Ar), 6.43 (d, J = 7.5 Hz, 1H, Ar), 6.26 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.18 (d, J = 2.5 Hz, 1H, NH), 6.07-6.05 (m, 1H, Ar), 6.03-6.02 (m, 1H, Ar), 5.42 (d, J = 2.5 Hz, 1H, NHC*H*Ar), 5.08 (s, 1H, NCH), 4.15 (ddd, J = 12.5, 5.0, 2.5 Hz, 1H, NCH_AH_B, 3.00-2.93 (m, 1H, NCH_AH_B), 2.89-2.74 (m, 2H, CH_EH_F), 2.31 (d, J = 16.5 Hz, 1H, $CH_CH_DC(O)$), 1.88 (d, J = 16.5 Hz, 1H, $CH_CH_DC(O)$); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 170.1 (C=O), 150.2 (*ipso*-Ar), 134.9 (*ipso*-Ar), 134.0 (*ipso*-Ar), 131.3 (*ipso*-Ar), 130.6 (*ipso*-Ar), 128.9 (Ar), 127.7 (Ar), 126.3 (Ar), 126.2 (Ar), 125.8 (Ar), 122.3 (Ar), 117.6 (Ar), 117.1 (Ar), 108.4 (Ar), 107.5 (Ar), 106.3 (Ar), 64.0 (NH*C*HAr), 63.7 (NCH), 57.1 (C), 43.0 ($CH_2C(O)$), 36.5 (NCH_2), 29.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_{23}H_{21}N_3O$ $(M + H)^+$ 356.1757, found 356.1746 (3.3 ppm error).

Lab Book Reference: SC5/28

5.3.3. Chapter 4

Ethyl 2-(1*H*-indol-3-yl)acetate 363

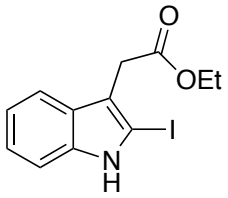


363

Acid **215** (3.00 g, 17.13 mmol) was added to a stirred solution of EtOH (150 mL) and conc. $H_2SO_{4(aq)}$ (3 mL) at rt and the resulting solution was heated and stirred at reflux for 3 h. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The residue was diluted with water (30 mL) and taken to pH 10 with 1 M $NaOH_{(aq)}$. The reaction mixture was extracted into CH_2Cl_2 (3 x 50 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the ester **363** (3.41 g, 97%) as a yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (br s, 1H, NH), 7.64 (d, *J* = 8.0 Hz, 1H, Ar), 7.35 (d, *J* = 8.0 Hz, 1H, Ar), 7.21 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H, Ar), 7.16-7.13 (m, 2H, Ar), 4.18 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 3.78 (d, *J* = 1.0 Hz, 2H, CH_2), 1.27 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.1 (C=O), 136.1 (*ipso*-Ar), 127.2 (*ipso*-Ar), 123.0 (Ar), 122.1 (Ar), 119.6 (Ar), 118.9 (Ar), 111.1 (Ar), 108.6 (*ipso*-Ar), 60.8 (OCH$_2$), 31.4 (*C*H$_2$C(O)), 14.2 (CH$_3$); HRMS (ESI) *m/z* calcd for $C_{12}H_{13}NO_2$ $(M + H)^+$ 204.1019, found 204.1022 (−1.5 ppm error). Spectroscopic data consistent with those reported in the literature.[210]

Lab Book Reference: SC5/67

Ethyl 2-(2-iodo-1*H*-indol-3-yl)acetate 364

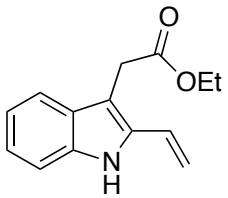


364

A solution of iodine (1.25 g, 4.92 mmol) in THF (10 mL) was carefully added to a solution of AgOTf (1.64 g, 6.40 mmol) and indole **363** (1.00 g, 4.92 mmol) in THF (24 mL) at rt. The resulting suspension was stirred at rt for 10 min and sat. $Na_2S_2O_{3(aq)}$ (10 mL) was added. The reaction mixture was extracted into EtOAc (3 x 50 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (8:1 then 6:1) gave the iodinated indole **364** (1.25 g, 77%) as an orange oil, R_F (6:1 hexane-EtOAc) 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (br s, 1H, NH), 7.56-7.54 (m, 1H, Ar), 7.28-7.25 (m, 1H, Ar), 7.15-7.08 (m, 2H, Ar), 4.17 (q, J = 7.0 Hz, 2H, OCH_2CH$_3$), 3.72 (s, 2H, CH_2), 1.27 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.1 (C=O), 138.7 (*ipso*-Ar), 127.4 (*ipso*-Ar), 122.4 (Ar), 120.1 (Ar), 118.2 (Ar), 115.2 (*ipso*-Ar), 110.4 (Ar), 79.8 (*ipso*-Ar), 61.0 (OCH_2CH$_3$), 33.1 (CH_2C(O)), 14.2 (CH_3). Spectroscopic data consistent with those reported in the literature.[174]

Lab Book Reference: SC6/9

Ethyl 2-(2-vinyl-1*H*-indol-3-yl)acetate 366



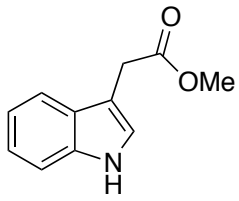
366

Vinyl boronic acid pinacol ester **365** (815 μL, 4.81 mmol), LiCl (313 mg, 7.40 mmol) and Na_2CO_3 (980 mg, 9.25 mmol) were added to a stirred solution of indole **364** (1.22 g,

3.70 mmol) in a mixture of toluene (8 mL), ethanol (8 mL) and water (5.7 mL) at rt. The reaction flask was purged three times with Ar and $Pd(PPh_3)_4$ (214 mg, 0.19 mmol) was added at rt. The reaction flask was purged again with Ar and the resulting suspension was heated and stirred at 80 °C for 18 h. The reaction was allowed to cool and was poured into water (50 mL). The reaction mixture was extracted into EtOAc (3 x 100 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (6:1 then 5:1) as eluent gave the vinyl substituted indole **366** (570 mg, 67%) as a yellow oil, R_F (6:1 hexane-EtOAc) 0.30; IR (ATR) 3341 (NH), 3056, 2980, 2932, 1714 (C=O), 1461, 1368, 1304, 1158, 1027, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (br s, 1H, NH), 7.69-7.66 (m, 1H, Ar), 7.28-7.22 (m, 2H, Ar), 7.18 (ddd, *J* = 8.0, 6.5, 1.5 Hz, 1H, Ar), 6.90 (dd, *J* = 17.5, 11.5 Hz, 1H, C*H*=CH_2), 5.54 (d, *J* = 17.5 Hz, 1H, CH=C$H_{trans}H_{cis}$), 5.31 (d, *J* = 11.5 Hz, 1H, CH=$CH_{trans}H_{cis}$), 4.22 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.87 (s, 2H, CH_2), 1.31 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.8 (C=O), 136.0 (*ipso*-Ar), 133.5 (*ipso*-Ar), 128.4 (*ipso*-Ar), 125.1 (*C*H=CH_2), 123.0 (Ar), 119.7 (Ar), 119.0 (Ar), 112.4 (CH=*C*H_2), 110.7 (Ar), 107.7 (*ipso*-Ar), 60.9 (O*C*H_2CH_3), 30.3 (*C*H_2C(O)), 14.1 (CH_3). Spectroscopic data consistent with those reported in the literature.[211]

Lab Book Reference: SC6/12

Methyl 2-(1*H*-indol-3-yl)acetate 367



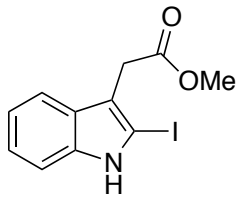
367

Acetyl chloride (10 mL, 140.6 mmol) was added to a solution of the indole acid **215** (3.00 g, 17.13 mmol) in MeOH (150 mL) at rt. The resulting solution was stirred for 20 h and the volatiles were removed under reduced pressure. Sat. $NaHCO_{3(aq)}$ (200 mL) was added to the residue and the mixture was extracted into CH_2Cl_2 (3 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure

to give the indole ester **367** (3.07 g, 94%) as an orange oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H, NH), 7.63 (d, *J* = 8.0 Hz, 1H, Ar), 7.35 (d, *J* = 8.0 Hz, 1H, Ar), 7.22 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 7.18-7.13 (m, 2H, Ar), 3.80 (d, *J* = 1.0 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C=O), 136.1 (*ipso*-Ar), 127.2 (*ipso*-Ar), 123.0 (Ar), 122.2 (Ar), 119.7 (Ar), 118.8 (Ar), 111.2 (Ar), 108.4 (*ipso*-Ar), 52.0 (OCH_3), 31.1 (CH_2C(O)); HRMS (ESI) *m/z* calcd for $C_{11}H_{11}NO_2$ $(M + Na)^+$ 212.0682, found 212.0692 (−4.8 ppm error). Spectroscopic data consistent with those reported in the literature.[212]

Lab Book Reference: SC7/59

Methyl 2-(2-iodo-1*H*-indol-3-yl)acetate 368

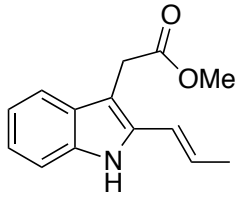


368

A solution of iodine (4.03 g, 15.86 mmol) in THF (34 mL) was carefully added to a solution of AgOTf (5.93 g, 20.62 mmol) and indole **367** (3.00 g, 15.86 mmol) in THF (78 mL) at rt. The resulting suspension was stirred at rt for 15 min and sat. $Na_2S_2O_{3(aq)}$ (100 mL) was added. The reaction mixture was extracted into EtOAc (3 x 100 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (8:1 then 6:1) gave the iodinated indole **368** (4.08 g, 81%) as a pale orange oil, R_F (6:1 hexane-EtOAc) 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (br s, 1H, NH), 7.55-7.53 (m, 1H, Ar), 7.31 (m, 1H, Ar), 7.16-7.08 (m, 2H, Ar), 3.74 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6 (C=O), 138.8 (*ipso*-Ar), 127.5 (*ipso*-Ar), 122.6 (Ar), 120.3 (Ar), 118.3 (Ar), 115.2 (*ipso*-Ar), 110.5 (Ar), 79.7 (*ipso*-Ar), 52.2 (OCH_3), 33.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_{11}H_{10}INO_2$ $(M + Na)^+$ 337.9648, found 337.9664 (–4.5 ppm error). Spectroscopic data consistent with those reported in the literature.[213]

Lab Book Reference: SC7/38

(*E*)-Methyl 2-(2-(prop-1-en-1-yl)-1*H*-indol-3-yl)acetate 370

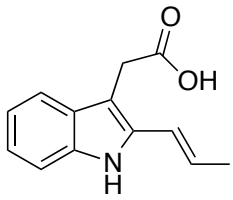


370

1-Propenyl boronic acid pinacol ester **369** (1.01 g, 6.00 mmol), LiCl (390 mg, 9.22 mmol) and Na_2CO_3 (1.22 g, 11.53 mmol) were added to a stirred solution of indole **368** (1.45 g, 4.61 mmol) in a mixture of toluene (10 mL), ethanol (10 mL) and water (7 mL) at rt. The reaction flask was purged three times with Ar and $Pd(PPh_3)_4$ (265 mg, 0.23 mmol) was added at rt. The reaction flask was purged again with Ar and the resulting suspension was heated and stirred at 80 °C for 18 h. The reaction was allowed to cool and was poured into water (100 mL). The reaction mixture was extracted into EtOAc (3 x 200 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (8:1) as eluent gave the 1-propenyl substituted indole **370** (643 mg, 60%) as a yellow solid, mp 100-102 °C (lit.[214] 115 °C); R_F (8:1 hexane-EtOAc) 0.20; IR (ATR) 3347 (NH), 3023, 2957, 2913, 1721, 1700, 1437, 1328, 1210, 1169, 947, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1H, NH), 7.56 (d, *J* = 8.0 Hz, 1H, Ar), 7.27 (d, *J* = 8.0 Hz, 1H, Ar), 7.16 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 7.10 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, Ar), 6.54 (dq, *J* = 16.0, 1.5 Hz, 1H, C*H*=CHCH$_3$), 6.04, (dq, *J* = 16.0, 6.5 Hz, 1H, CH=C*H*CH$_3$), 3.77 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 1.94 (dd, *J* = 6.5, 1.5 Hz, 3H, CH=CHC*H*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.2 (C=O), 135.8 (*ipso*-Ar), 133.7 (*ipso*-Ar), 128.7 (*ipso*-Ar), 125.4 (CH=*C*HCH$_3$), 122.6 (Ar), 119.78 (*C*H=CHCH$_3$), 119.75 (Ar), 118.7 (Ar), 110.4 (Ar), 105.9 (*ipso*-Ar), 52.0 (OCH_3), 30.1 (CH_2), 18.8 (CH=CH*C*H$_3$); HRMS (ESI) *m/z* calcd for $C_{14}H_{15}NO_2$ $(M + H)^+$ 230.1176, found 230.1172 (+1.4 ppm error). Spectroscopic data consistent with those reported in the literature.[214]

Lab Book Reference: SC7/78

(*E*)-2-(2-(Prop-1-en-1-yl)-1*H*-indol-3-yl)acetic acid 371

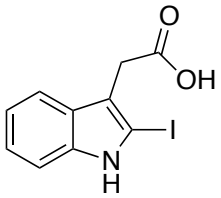


371

2 M $NaOH_{(aq)}$ (7 mL) was added to a stirred solution of indole ester **370** (320 mg, 1.40 mmol) in MeOH (14 mL) at rt. The reaction was stirred for 4 h and the solvent was evaporated under reduced pressure. The residue was diluted with water (5 mL) and the solution was acidified with 6 M $HCl_{(aq)}$ until an orange precipitate was observed. The precipitate was filtered to give the acid **371** (288 mg, 95%) as an orange solid, mp 145-147 °C; IR (ATR) 3424 (NH), 3039, 2913, 2676, 2571, 1695 (C=O), 1460, 1433, 1416, 1304, 1240, 950, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (br s, 1H, NH), 7.35 (dd, *J* = 7.5, 0.5 Hz, 1H, Ar), 7.28-7.26 (m, 1H, Ar), 7.16 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar), 7.09 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar), 6.51 (dq, *J* = 16.0, 1.5 Hz, 1H, C*H*=CHCH$_3$), 6.05 (dq, *J* = 16.0, 6.5 Hz, 1H, CH=C*H*CH$_3$), 3.77 (s, 2H, CH_2), 1.94 (dd, *J* = 6.5, 1.5 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.1 (C=O), 135.8 (*ipso*-Ar), 133.9 (*ipso*-Ar), 128.6 (*ipso*-Ar), 125.7 (CH=*C*HCH$_3$), 122.7 (Ar), 119.9 (Ar), 119.6 (*C*H=CHCH$_3$), 118.7 (Ar), 110.5 (Ar), 105.2 (*ipso*-Ar), 29.8 (CH_2), 18.8 (CH_3); HRMS (ESI) *m/z* calcd for $C_{13}H_{13}NO_2$ $(M + H)^+$ 216.1019, found 216.1025 (−2.6 ppm error).

Lab Book Reference: SC7/83

2-(2-Iodo-1*H*-indol-3-yl)acetic acid 354

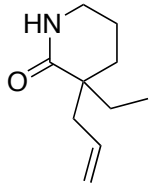


354

2 M $NaOH_{(aq)}$ (2.40 mL) was added to a stirred solution of indole ester **368** (150 mg, 0.48 mmol) in MeOH (4.8 mL) at rt. The reaction was stirred for 2 h and the solvent was evaporated under reduced pressure. The residue was diluted with water (5 mL) and the solution was taken to pH 4 by addition of 6 M $HCl_{(aq)}$ until a white precipitate was observed. The mixture was extracted into EtOAc (3 x 30 mL) and the combined organics dried ($MgSO_4$), filtered were evaporated under reduced pressure to give the acid **354** (127 mg, 88%) as an off-white solid, mp 81-85 °C; IR (ATR) 3397 (NH), 2896, 1691 (C=O), 1446, 1408, 1393, 1227, 1199, 742 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.27 (br s, 1H, OH), 11.55 (s, 1H, NH), 7.45 (d, J = 8.0 Hz, 1H, Ar), 7.29 (d, J = 8.0 Hz, 1H, Ar), 7.04 (td, J = 7.5, 7.5, 1.5 Hz, 1H, Ar), 6.97 (td, J = 7.5, 7.5, 1.0 Hz, 1H, Ar), 3.57 (s, 2H, CH_2); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 172.3 (C=O), 138.6 (*ipso*-Ar), 127.4 (*ipso*-Ar), 121.3 (Ar), 119.0 (Ar), 117.9 (Ar), 113.9 (*ipso*-Ar), 110.6 (Ar), 82.9 (*ipso*-Ar), 32.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{10}H_8INO_2$ $(M + Na)^+$ 323.9492, found 323.9488 (1.2 ppm error).

Lab Book Reference: SC7/43

3-Allyl-3-ethylpiperidin-2-one 376

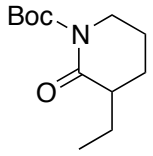


376

Trifluoroacetic acid (10 mL) was added to a stirred solution of Boc-protected lactam **372** (2.00 g, 7.48 mmol) in CH_2Cl_2 (10 mL) and the resulting solution was stirred at rt for 1 h. The volatiles were evaporated under reduced pressure and sat. $NaHCO_{3(aq)}$ (50 mL) was added. The mixture was extracted into CH_2Cl_2 (3 x 50 mL) and the combined organics were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the lactam **376** (1.20 g, 96%) as a yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (br s, 1H, NH), 5.81-5.71 (m, 1H, C*H*=CH_2), 5.07-5.02 (m, 2H, CH=C*H*$_2$), 3.23 (ddd, *J* = 6.0, 6.0, 2.5 Hz, 2H, NCH_2), 2.46 (dddd, *J* = 13.5, 6.5, 1.0, 1.0 Hz, 1H, C*H*$_A$H$_B$C=C), 2.16 (dd, *J* = 13.5, 8.0 Hz, 1H, CH$_A$*H*$_B$C=C), 1.78-1.65 (m, 5H, C*H*$_A$H$_B$$CH_3$, 2 x CH_2), 1.47 (dq, *J* = 14.0, 7.5 Hz, 1H, CH$_A$*H*$_B$$CH_3$), 0.87 (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.9 (C=O), 134.6 (*C*H=CH_2), 117.8 (CH=*C*H_2), 44.7 (NCH_2), 42.7 (C), 42.6 (*C*H_2C=C), 31.0 (*C*H_2CH_3), 28.5 (CH_2) 19.6 (CH_2), 8.6 (CH_3); HRMS (ESI) *m/z* calcd for $C_{10}H_{17}NO$ $(M + H)^+$ 168.1383, found 168.1384 (−0.6 ppm error). Spectroscopic data consistent with those reported in the literature.[215]

Lab Book Reference: SC7/36

***tert*-Butyl 3-ethyl-2-oxopiperidine-1-carboxylate 378**



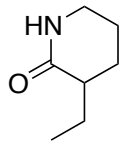
378

n-BuLi (2.5 M in hexanes, 26.6 mL, 66.66 mmol) was added to a stirred solution of δ-valerolactam **379** in THF (25 mL) at −78 °C under Ar. The resulting solution was stirred

at 0 °C for 30 min, then EtI (2.43 mL, 30.26 mmol) was slowly added and the resulting cloudy mixture was stirred for 20 min. Boc_2O (6.60 g, 30.26 mmol) was added and the resulting mixture was stirred for 30 min at 0 °C before sat. $NH_4Cl_{(aq)}$ (100 mL) was added and the reaction was allowed to warm to room temp. The reaction mixture was extracted with Et_2O (3 x 100 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (95:5 then 90:10) as eluent gave the ethyl substituted lactam **378** (5.09 g, 74%) as a pale yellow oil, R_F (9:1 hexane-EtOAc) 0.20; IR (ATR) 1968, 2941, 2875, 1769 (C=O), 1713 (C=O), 1458, 1367, 1296, 1252, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (ddd, J = 13.0, 7.5, 5.0 Hz, 1H, NCH), 3.62-3.55 (m, 1H, NCH), 2.35-2.27 (m, 1H, CH), 2.04-1.75 (m, 4H, 3 x CH, CH_AH$_B$), 1.52 (s, 9H, C(CH_3)$_3$), 1.52-1.46 (m, 2H, CH$_A$$H_B$, CH), 0.95 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.3 (C=O), 153.1 (C=O), 82.6 (C), 45.7 (CH), 45.1 (NCH_2), 28.0 (C(CH_3)$_3$), 25.4 (CH_2), 24.0 (CH_2), 21.7 (CH_2), 11.5 (CH_3); HRMS (ESI) *m/z* calcd for $C_{12}H_{21}NO_3$ $(M + Na)^+$ 250.1414, found 250.1419 (−2.1 ppm error).

Lab Book Reference: SC7/63

3-Ethylpiperidin-2-one 387



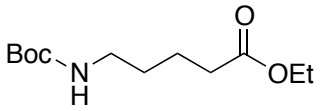
387

Lactam **378** (523 mg, 2.30 mmol) was added to a solution of trifluoroacetic acid (5 mL) and CH_2Cl_2 (5 mL) at rt and the resulting solution was stirred for 1 h. The volatiles were removed under reduced pressure and sat. $K_2CO_{3(aq)}$ (20 mL) was added to the resulting residue. The mixture was extracted into Et_2O (3 x 50 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the deprotected lactam **387** (273 mg, 93%) as a pale yellow oil, ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (br s, 1H, NH), 3.27-3.16 (m, 2H, NCH_2), 2.17-2.10 (m, 1H, CH), 1.92-1.75 (m, 3H, CH_AH$_B$, CH_2), 1.68-1.58 (m, 1H, CH), 1.52-1.41 (m, 2H, CH$_A$$H_B$, CH), 0.88 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.4 (C=O), 42.1

(NCH_2), 42.0 (CH), 25.2 (CH_2), 24.2 (CH_2), 21.1 (CH_2), 11.2 (CH_3); HRMS (ESI) *m/z* calcd for $C_7H_{14}NO$ $(M + H)^+$ 128.1070, found 128.1072 (−2.0 ppm error). Spectroscopic data consistent with those reported in the literature.[216]

Lab Book Reference: SC5/74

Ethyl 5-((*tert*-butoxycarbonyl)amino)pentanoate 382

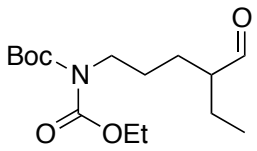


382

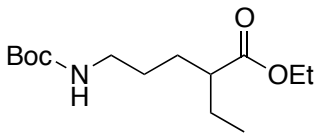
n-BuLi (2.04 M in hexanes, 0.27 mL, 0.55 mmol) was added to a solution of diisopropylamine (0.077 mL, 0.55 mmol) in THF at −78 °C under Ar. The resulting solution was stirred for 1 h at 0 °C and then cooled to −78 °C and N-Boc piperidone **288** (100 mg, 0.50 mmol) was added. The resulting solution was stirred at 0 °C for 30 min and ethyl formate (121 μL, 1.50 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 20 h. AcOH (2 mL) was added and the reaction was poured into sat. $NaHCO_{3(aq)}$ (10 mL). The reaction mixture was extracted into EtOAc (3 x 20 mL) and the combined organics were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica using hexane-EtOAc (4:1) as eluent gave the unwanted side-product **382** (16 mg, 13%) as a colourless oil, R_F (4:1 hexane-EtOAc) 0.30; IR (ATR) 3375 (NH), 2978, 2934, 1713 (C=O), 1694 (C=O), 1520, 1454, 1366, 1248, 2267, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.57 (br s, 1H, NH), 4.12 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.12 (td, *J* = 6.5, 6.5 Hz, 2H, NCH_2), 2.31 (t, *J* = 7.5 Hz, 2H, $C(O)CH_2$), 1.68-1.60 (m, 2H, CH_2), 1.54-1.45 (m, 2H, CH_2), 1.43 (s, 9H, $C(CH_3)_3$), 1.24 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.5 (C=O), 155.9 (C=O), 79.1 (C), 60.3 (OCH_2CH_3), 40.1 (NCH_2), 33.8 (CH_2), 29.5 (CH_2), 28.4 ($C(CH_3)_3$), 22.1 (CH_2), 14.2 (OCH_2CH_3); HRMS (ESI) *m/z* calcd for $C_{12}H_{23}NO_4$ $(M + Na)^+$ 268.1519, found 268.1512 (+2.7 ppm error).

Lab Book Reference: SC5/59

***N-tert*-Butoxycarbonyl(4-formylhexyl)-carbamic acid ethyl ester 385 and ethyl 5-((*tert*-butoxycarbonyl)amino)-2-ethylpentanoate 386**



385



386

LHMDS (1 M in THF, 1.14 mL, 1.14 mmol) was added to a stirred solution ethyl-susbstituted lactam **378** (200 mg, 0.88 mmol) in THF (10 mL) at −78 °C under Ar. The resulting mixture was stirred at −78 °C for 90 min and then ethyl formate (78 μL, 0.97 mmol) was added. The reaction mixture was stirred at −78 °C for 2 h and then allowed to warm to rt and stirred for 3 h. Sat. $NH_4Cl_{(aq)}$ (20 mL) was added and the reaction mixture was extracted into Et_2O (3 x 20 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (95:5 then 90:10 then 85:15) as eluent gave the unwanted byproducts **385** (104 mg, 39%) and **386** (27 mg, 11%).

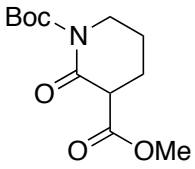
Aldehyde **385**, pale yellow oil; R_F (9:1 hexane-EtOAc) 0.20; IR (ATR) 2965, 2937, 1731 (C=O), 1705 (C=O), 1688 (C=O), 1459, 1396, 1340, 1140, 1029, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H, CHO), 4.12 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 3.55 (t, J = 7.0 Hz, 2H, NCH_2), 2.28-2.21 (m, 1H, CH), 1.65-1.36 (m, 8H, 4 x CH_2), 1.52 (s, 9H, $C(CH_3)_3$), 1.24 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.86 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.8 (C=O), 163.0 (CHO), 152.5 (C=O), 83.9 ($C(CH_3)_3$), 60.1 (OCH_2CH_3), 46.8 (CH), 40.3 (NCH_2), 29.0 (CH_2), 28.0 ($C(CH_3)_3$), 26.1 (CH_2), 25.3 (CH_2), 14.3 (OCH_2CH_3), 11.6 (CH_3); HRMS (ESI) *m/z* calcd for $C_{15}H_{27}NO_5$ $(M + Na)^+$ 324.1781, found 324.1769 (+3.9 ppm error).

Ester **386**, pale yellow oil; R_F (9:1 hexane-EtOAc) 0.10; IR (ATR) 3376 (NH), 2967, 2934, 2881, 1712 (C=O), 1694 (C=O), 1517, 1457, 1366, 1249, 1165, 1027, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.53 (br s, 1H, NH), 4.13 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 3.12-3.07 (m, 2H, NCH_2), 2.29-2.22 (m, 1H, CH), 1.67-1.36 (m, 8H, 4 x CH_2), 1.42 (s,

9H, $C(CH_3)_3$), 1.25 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.88 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.0 (C=O), 155.9 (C=O), 79.0 ($C(CH_3)_3$), 60.1 (OCH_2CH_3), 46.9 (CH), 40.3 (NCH_2), 29.0 (CH_2), 28.4 ($C(CH_3)_3$), 27.9 (CH_2), 25.5 (CH_2), 14.3 (OCH_2CH_3), 11.7 (CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{27}NO_4$ $(M + Na)^+$ 296.1832, found 296.1830 (+0.8 ppm error).

Lab Book Reference: SC5/66

1-*tert*-Butyl 3-methyl 2-oxopiperidine-1,3-dicarboxylate 389

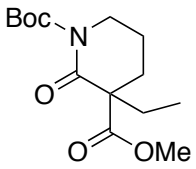


389

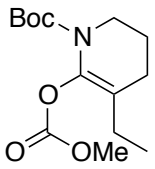
LHMDS (1 M in THF, 0.7 mL, 0.70 mmol) was added to a stirred solution of *N*-Boc piperidone **288** (108 mg, 0.54 mmol) in THF (5 mL) at −78 °C under Ar. The resulting mixture was stirred at −78 °C for 1 h and then methyl chloroformate (46 μL, 0.59 mmol) was added. The reaction mixture was stirred for 90 min and then sat. $NH_4Cl_{(aq)}$ (10 mL) was added. The reaction mixture was extracted into Et_2O (3 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (4:1) as eluent gave the ester substituted lactam **389** (123 mg, 88%) as a pale yellow oil, R_F (4:1 hexane-EtOAc) 0.30; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H, OCH_3), 3.69-3.66 (m, 2H, NCH_2), 3.52 (dd, J = 9.0, 7.0 Hz, 1H, CHC(O)), 2.22-2.04 (m, 2H, CH), 2.01-1.92 (m, 1H, CH), 1.87-1.76 (m, 1H, CH), 1.52 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.3 (C=O), 167.5 (C=O), 152.6 (C=O), 83.4 ($C(CH_3)_3$), 52.6 (OCH_3), 51.3 (CH), 45.8 (NCH_2), 27.9 ($C(CH_3)_3$), 24.1 (CH_2), 21.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_{12}H_{19}NO_5$ $(M + Na)^+$ 280.1155, found 280.1159 (−1.1 ppm error). Spectroscopic data consistent with those reported in the literature.[217]

Lab Book Reference: SC5/64

1-*tert*-Butyl 3-methyl 3-ethyl-2-oxopiperidine-1,3-dicarboxylate 390 and *tert*-butyl 5-ethyl-6-((methoxycarbonyl)oxy)-3,4-dihydropyridine-1(2*H*)-carboxylate 391



390



391

LHMDS (1 M in THF, 19.16 mL, 19.16 mmol) was slowly added to a stirred solution of lactam **378** (3.35 g, 14.8 mmol) in THF (30 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min and then methyl cyanoformate (1.17 mL, 14.74 mmol) was added. The resulting mixture was allowed to warm to rt and stirred for 16 h. Sat. $NaHCO_{3(aq)}$ (200 mL) was added and the reaction was extracted into CH_2Cl_2 (4 x 200 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (90:10) as eluent gave ester substituted lactam **390** (360 mg, 59%) as a colourless oil, R_F (9:1 Hexane-EtOAc) 0.10; IR (ATR) 2976, 2881, 1771 (C=O), 1718 (C=O), 1457, 1368, 1248, 1278, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H, OCH_3), 3.72-3.65 (m, 1H, NCH), 3.57-3.51 (m, 1H, NCH), 2.29 (dddd, J = 13.5, 6.0, 6.0, 0.5 Hz, 1H, CH), 1.98-1.92 (m, 2H, CH_2), 1.90-1.79 (m, 2H, CH), 1.76-1.69 (m, 1H, CH), 1.50 (s, 9H, $C(CH_3)_3$), 0.90 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.6 (C=O), 170.5 (C=O), 152.9 (C=O), 82.9 (C), 56.9 (C), 52.6 (OCH_3), 45.5 (NCH_2), 29.0 (CH_2), 28.7 (CH_2), 27.9 ($C(CH_3)_3$), 20.0 (CH_2), 8.9 (CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{23}NO_5$ $(M + Na)^+$ 308.1468, found 308.1460 (+2.7 ppm error).

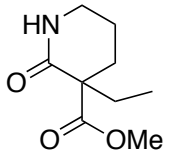
Lab Book Reference: SC7/14

LHMDS (1 M in THF, 2.86 mL, 2.86mmol) was slowly added to a stirred solution of lactam **378** (500 mg, 2.20 mmol) in THF (20 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 90 min and then methyl chloroformate (187 μL, 2.42 mmol) was added and the resulting mixture was stirred for 2 h. The reaction was allowed to warm to room temperature and sat. $NH_4Cl_{(aq)}$ (30 mL) was added. The reaction was extracted into Et_2O (3 x 50 mL) and the combined organics were dried

($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using hexane-EtOAc (90:10) as eluent gave lactam **390** (112 mg, 17%) as a colourless oil and unwanted byproduct **391** (355 mg, 56%) as a pale yellow oil, R_F (9:1 Hexane-EtOAc) 0.20; IR (ATR) 2976, 2941, 1768 (C=O), 1713 (C=O), 1442, 1368, 1256, 1235, 902 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 3.58-3.56 (m, 2H, NCH_2), 2.14 (dd, J = 7.0, 7.0 Hz, 2H, CH_2), 2.01 (q, J = 7.5 Hz, CH_2CH_3), 1.82 -1.76 (m, 2H, CH_2), 1.45 (s, 9H, $C(CH_3)_3$), 0.99 (t, J = 7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 153.2 (C=O), 152.9 (C=O), 135.3 (C), 115.0 (C), 81.2 ($C(CH_3)_3$), 55.1 (OCH_3), 45.1 (NCH_2), 28.1 ($C(CH_3)_3$), 25.3 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 12.1 (CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{23}NO_5$ $(M + Na)^+$ 308.1468, found 308.1466 (+0.9 ppm error).

Lab Book Reference: SC 5/65

Methyl 3-ethyl-2-oxopiperidine-3-carboxylate 394

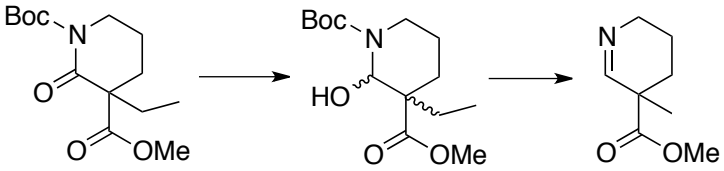


394

Lactam **390** (445 mg, 1.56 mmol) was added to a solution of trifluoroacetic acid (5 mL) and CH_2Cl_2 (5 mL) at rt and the resulting solution was stirred for 1 h. The volatiles were removed under reduced pressure and sat. $NaHCO_{3(aq)}$ (50 mL) was added to the resulting residue. The mixture was extracted into CH_2Cl_2 (3 x 50 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the deprotected lactam **394** (279 mg, 96%) as a pale yellow solid, mp 58-60 °C, R_F (EtOAc-hexane 2:1) 0.20; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (br s, 1H, NH), 3.72 (s, 3H, OCH_3), 3.38-3.25 (m, 2H, CH), 2.19-2.13 (m, 1H, CH), 2.05-1.89 (m, 2H, CH_2), 1.88-1.75 (m, 3H, CH), 0.93 (3H, t, J = 7.5 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.5 (C=O), 171.0 (C=O), 54.1 (C), 52.4 (OCH_3), 42.3 (NCH_2), 28.9 (CH_2), 28.4 (CH_2), 19.6 (CH_2), 8.9 (CH_3); HRMS (ESI) *m/z* calcd for $C_9H_{15}NO_3$ $(M + H)^+$ 186.1125, found 186.1122 (+1.6 ppm error). Spectroscopic data consistent with those reported in the literature.[191]

Lab Book Reference: SC6/20

Methyl 3-ethyl-3,4,5,6-tetrahydropyridine-3-carboxylate 396



390 **393** **396**

$NaBH_4$ (453 mg, 11.99 mmol) was added to a stirred solution of Boc-protected lactam **390** (1.71 g, 5.99 mmol) in MeOH (20 mL) at 0 °C and the resulting reaction mixture was stirred for 18 h at rt. The volatiles were removed under reduced pressure and the residue was taken up in water (100 mL) and the resulting solution was extracted into CH_2Cl_2 (3 x 100 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude hemiaminal **393** (1.54 g) as a pale yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) 1:2.3 ratio of diastereoisomers δ 6.00 (br s, 1H, C*H*OH), 5.74 (br s, 2.3H, C*H*OH), 3.85-3.81 (m, 3.3H, OH), 3.72 (s, 6.9H, CO_2CH_3), 3.6 (s, 3H, CO_2CH_3), 3.09-3.01 (m, 3.3H, NCH), 2.07-1.99 (m, 3.3H, NCH), 1.70-1.49 (m, 19.8H, 3 x CH_2), 1.46 (s, 29.7H, $C(CH_3)_3$), 0.82 (t, J = 7.5 Hz, 3H, CH_3), 0.77 (t, J = 7.5 Hz, 6.9H, CH_3). The crude hemiaminal **393** (1.54 g, 5.35 mmol) was taken up in a solution of TFA (7 mL) and CH_2Cl_2 (7 mL) and the resulting solution was stirred at rt for 1 h. The volatiles were evaporated under reduced pressure and sat. $NaHCO_{3(aq)}$ (100 mL) was added to the residue. The mixture was extracted into CH_2Cl_2 (100 mL) and the two layers were separated. The aqueous layer was extracted into CH_2Cl_2 (2 x 100 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave the imine **396** (427 mg, 47%) as a colourless oil.

Lab Book Reference: SC7/19

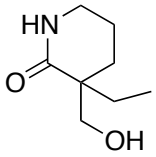
The crude hemiaminal **393** (170 mg, 0.59 mmol) was taken up in a solution of TFA (5 mL) and CH_2Cl_2 (5 mL) and the resulting solution was stirred at rt for 30 min. The volatiles were evaporated under reduced pressure and sat. $NaHCO_{3(aq)}$ (20 mL) was

added to the residue. The mixture was extracted into CH_2Cl_2 (3 x 20 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the imine **396** (87 mg, 87%) as a colourless oil.

Lab Book Reference: SC6/8

Colourless oil; R_F (EtOAc) 0.25; IR (ATR) 2936, 1858, 1729 (C=O), 1682, 1650 (C=N), 1448, 1434, 1239, 1169, 1197, 1131, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (br d, *J* = 1.0 Hz, 1H, N=CH), 3.72 (dd, *J* = 1.0, 1.0 Hz, 3H, CO_2CH_3), 3.71-3.63 (m, 1H, NCH), 3.49-3.41 (m, 1H, NCH), 2.48-2.22 (m, 1H, CH), 1.91-1.81 (m, 1H, CH), 1.70-1.61 (m, 2H, 2 x CH), 1.60-1.50 (m, 1H, CH), 1.48-1.41 (m, 1H, CH), 0.89 (tdd, *J* = 7.5, 1.0, 1.0 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.5 (C=O), 162.6 (N=CH), 52.1 (OCH_3), 49.5 (NCH_2), 49.0 (C), 30.5 (CH_2), 26.4 (CH_2), 8.5 (CH_3); HRMS (ESI) *m/z* calcd for $C_9H_{15}NO_2$ $(M + H)^+$ 170.1176, found 170.1172 (+2.3 ppm error).

3-Ethyl-3-(hydroxymethyl)piperidin-2-one 395



395

$LiBH_4$ (4 M in THF, 2.82 mL, 11.27 mmol) was added to a solution of lactam **394** (696 mg, 3.76 mmol) in THF (20 mL) at 0 °C under Ar and the reaction mixture was stirred at rt for 2 h. The reaction was cooled to 0 °C and NH_4Cl (100 mL) was carefully added. The reaction mixture was extracted into CH_2Cl_2 (3 x 10 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc-MeOH (90:10) as eluent gave the alcohol **395** (170 mg, 28%) as an off-white solid.

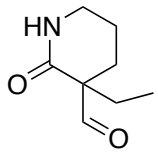
Lab Book Reference: SC6/28

Lithium tri-*tert*-butoxyaluminiumhydride (150 mg, 0.59 mmol) was added to a stirred solution of lactam **394** (50 mg, 0.27 mmol) in THF (3 mL) at rt under Ar. The reaction was heated and stirred at 60 °C for 16 h. Another portion of lithium tri-tert-butoxyaluminiumhydride (150 mg, 0.59 mmol) was added and the reaction was stirred at 60 °C for 72 h. The reaction was allowed to cool to rt and EtOAc (5 mL) was slowly added. Water (5 mL) was added and an excess of sat. $Na_2SO_{4(aq)}$ was added and stirred for 30 min. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc-MeOH (95:5) as eluent gave the alcohol **395** (19 mg, 45%) as an off white solid.

Lab Book Reference: SC7/34

Off-white solid, mp 64-66 °C (lit.[218] 91-93 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (br s, 1H, NH), 3.93 (dd, *J* = 8.5, 2.0 Hz, 1H, OH), 3.55-3.47 (m, 2H, C*H*$_2$OH), 3.26 (ddd, *J* = 7.0, 5.0, 2.0 Hz, 2H, NCH_2), 1.87-1.67 (m, 5H, C*H*$_2$$CH_3$, CH), 1.47 (ddd, *J* = 13.0, 10.0, 3.5 Hz, 1H, CH), 0.88 (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.5 (C=O), 67.3 (CH_2OH), 45.1 (C), 42.2 (NCH_2), 26.7 (CH_2), 26.4 (CH_2), 19.3 (CH_2), 7.8 (CH_3); HRMS (ESI) *m/z* calcd for $C_8H_{15}NO_2$ $(M + H)^+$ 158.1176, found 158.1174 (+0.7 ppm error). Spectroscopic data consistent with those reported in the literature.[191]

3-Ethyl-2-oxopiperidine-3-carbaldehyde 388



388

Dess-Martin periodinane (890 mg, 2.10 mmol) was added to a stirred solution of alcohol **395** (165 mg, 1.05 mmol) in CH_2Cl_2 (6 mL) at rt for 2.5 h. Sat. $Na_2SO_{4(aq)}$ (20 mL) and sat. $NaHCO_{3(aq)}$ (20 mL) were added and the resulting mixture was stirred for 30 min at rt. The reaction mixture was extracted into CH_2Cl_2 (3 x 20 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the

crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave aldehyde **388** (97 mg, 60%) as an off-white solid

Lab Book Reference: SC7/3

$LiAlH_4$ (516 mg, 13.61 mmol) was added to a stirred solution of lactam **394** (840 mg, 4.54 mmol) in Et_2O (50 mL) at −78 °C under Ar. The resulting mixture was stirred for 1 h and EtOAc (10 mL) was added, followed by water (5 mL) and dried by adding an excess of $MgSO_4$. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc-MeOH (100:0 then 95:5) as eluent gave the aldehyde **388** (350 mg, 49%) as an off-white solid, together with alcohol **395** as an off-white solid (230 mg, 32%) and an unseparated mixture of ester **394** (92 mg, 11%) and aldehyde **388** (28 mg, 4%).

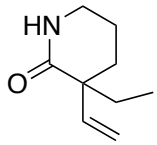
Lab Book Reference: SC7/56

$LiAlH_4$ (239 mg, 2.11 mmol) was added to a stirred solution of lactam **394** (390 mg, 2.11 mmol) in Et_2O (10 mL) at −40 °C under Ar. The resulting mixture was stirred for 1 h and EtOAc (100 mL) was added, followed by water (10 mL). A saturated solution of Rochelle salt was added and the reaction mixture stirred for 18 h. The reaction mixture was extracted into EtOAc (3 x 100 mL) and the combined organics were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product containing a 1:6.5:6.5 mixture of ester **394**, aldehyde **388** and alcohol **395**. The crude product was taken up in CH_2Cl_2 (9 mL) and Dess-Martin periodinane (594 mg, 2.80 mmol) was added at rt. The resulting mixture was stirred for 1 h and then sat. $NaHCO_{3(aq)}$ (50 mL) and $Na_2S_2O_{3(aq)}$ (50 mL) were added and the resulting mixture was stirred at rt for 30 min. The reaction mixture was extracted into CH_2Cl_2 (3 x 100 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc-hexane (3:1) as eluent gave the aldehyde **388** (80 mg, 24 %) over two steps, as an off-white solid.

Lab Book Reference: SC7/71 and SC7/72

Off-white solid, mp 59-61 °C (lit.[218] 63-65 °C); R_F (EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, *J* = 1.0 Hz, 1H, CHO), 7.08 (br s, 1H NH), 3.29-3.26 (m, 2H, NCH_2), 2.26 (ddd, *J* = 13.5, 6.0, 2.5 Hz, 1H, CH), 2.00 (dq, *J* = 14.0, 7.0 Hz, 1H, CH_AH$_B$), 1.83 (dq, *J* = 14.0, 7.0 Hz, 1H, CH$_A$$H_B$), 1.73-1.55 (m, 3H, CH), 0.88 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 201.3 (C=O), 171.2 (C=O), 58.8 (C), 42.3 (NCH_2), 27.1 (CH_2), 24.0 (CH_2), 20.1 (CH_2), 8.1 (CH_3); HRMS (ESI) *m/z* calcd for $C_8H_{13}NO_2$ $(M + H)^+$ 178.0838, found 178.0839 (−0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[218]

3-Ethyl-3-vinylpiperidin-2-one 397



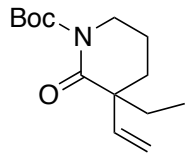
397

n-BuLi (2.5 M in hexanes, 0.34 mL, 0.84 mmol) was slowly added to a stirred solution of methyltriphenylphosphonium bromide (300 mg, 0.84 mmol) in THF (2 mL) at 0 °C and the resulting mixture was stirred for 20 min. A solution of aldehyde **388** (87 mg, 0.56 mmol) in THF (1 mL) was added dropwise to the ylide mixture and stirred for 20 min at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 30 min at rt, then heated and stirred at reflux for 1 h. The reaction mixture was allowed to cool to rt and sat. $NH_4Cl_{(aq)}$ (50 mL) was added. The mixture was extracted into CH_2Cl_2 (3 x 50 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using EtOAc as eluent gave an inseparable 1:1 mixture of alkene **397** (28 mg, 32% by ^{1}H NMR spectroscopy) and triphenylphosphine oxide as an off-white solid, R_F (EtOAc) 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (br s, 1H NH), 5.82 (dd, *J* = 17.5, 11.0 Hz, 1H, C*H*=CH$_A$H$_B$), 5.09 (dd, *J* = 11.0, 1.0 Hz, CH=CH_AH$_B$), 5.05 (dd, *J* = 17.5, 1.0 Hz, CH=CH$_A$$H_B$), 3.22-3.19 (m, 2H, NCH_2), 1.83-1.66 (m, 5H, 4 x CH, CH_AH$_B$), 1.57 (dq, *J* = 14.0, 7.5 Hz, 1H, CH$_A$$H_B$), 0.81 (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1 (C=O), 141.9 (*C*H=CH_2), 114.1 (CH=*C*H_2), 48.8 (C), 42.6 (NCH_2), 31.0 (CH_2), 28.4 (CH_2), 19.0 (CH_2), 8.3 (CH_3); HRMS (ESI) *m/z*

calcd for $C_9H_{15}NO$ $(M + H)^+$ 176.1046, found 176.1048 (−1.3 ppm error). The mixture was taken on crude to the subsequent step.

Lab Book Reference: SC7/7

***tert*-Butyl 3-ethyl-2-oxo-3-vinylpiperidine-1-carboxylate 374**

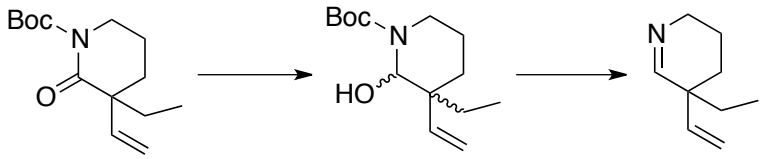


374

Boc_2O (412 mg, 1.89 mmol), DMAP (23 mg, 0.19 mmol) and Et_3N (263 μL, 1.89 mmol) were added to a mixture of triphenylphosphine oxide **398** and lactam **397** (62 mg, 0.40 mmol of lactam **397**) in CH_2Cl_2 (8 mL) at rt. The reaction mixture was stirred at rt for 18 h and then the volatiles were removed under reduced pressure. Purification by flash column chromatography on silica using EtOAc-hexane (9:1 then EtOAc) as eluent gave the Boc-protected lactam **374** (89 mg, 89%) as a yellow oil, R_F (9:1 hexane-EtOAc) 0.3; IR (ATR) 2922, 2855, 1717 (C=O), 1590, 1397, 1271, 1102, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 17.5, 11.0 Hz, 1H, C*H*=CH_2), 5.15 (d, *J* = 11.0 Hz, 1H, CH=C$H_A$$H_B$), 5.07 (d, *J* = 17.5 Hz, 1H, CH=$CH_A$$H_B$), 3.67-3.61 (m, 1H, NCH), 3.53-3.47 (m, 1H, NCH), 1.84-1.75 (m, 5H, C$H_A$$H_B$, 4 x CH), 1.64 (dq, *J* = 14.0, 7.5 Hz, 1H, $CH_A$$H_B$), 1.48 (s, 9H, $C(CH_3)_3$), 0.83 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.8 (C=O), 153.7 (C=O), 141.6 (C*H*=CH_2), 114.7 (CH=CH_2), 82.4 ($C(CH_3)_3$), 51.6 (C), 46.9 (NCH_2), 31.6 (CH_2), 29.2 (CH_2), 27.9 ($C(CH_3)_3$), 19.5 (CH_2), 8.3 (CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{23}NO_3$ $(M + Na)^+$ 276.1570, found 276.1562 (+2.9 ppm error).

Lab Book Reference: SC7/62

5-Ethyl-5-vinyl-2,3,4,5-tetrahydropyridine 351



374 **399** **351**

$NaBH_4$ (39 mg, 1.04 mmol) was added to a stirred solution of Boc-protected lactam **374** (66 mg, 0.26 mmol) in MeOH (3 mL) at 0 °C and the resulting reaction mixture was stirred for 18 h at rt. The volatiles were removed under reduced pressure and the residue was taken up in water (20 mL) and the resulting solution was extracted into CH_2Cl_2 (3 x 20 mL) and the combined organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the hemiaminal **399** with a 1:1 mixture of diastereoisomers (by ^1H NMR spectroscopy). Diagnostic signals for diastereoisomers: ^1H NMR (400 MHz, $CDCl_3$) 1:1 mixture of diastereoisomers δ 5.73 (dd, *J* = 17.5, 11.0 Hz, 1H, *H*C=CH_AH_B), 5.51 (dd, *J* = 18.0, 11.5 Hz, 1H, *H*C=CH_AH_B), 5.24 (d, *J* = 11.0 Hz, 1H, HC=C*H*$_A$$H_B$), 5.16 (d, *J* = 11.5 Hz, 1H, HC=C*H*$_A$$H_B$), 5.06 (d, *J* = 17.5 Hz, 1H, HC=CH_A*H*$_B$), 5.00 (dd, *J* = 18.0, 1.0 Hz, 1H, HC=CH_A*H*$_B$), 0.82 (t, *J* = 7.5 Hz, 3H, CH_3), 0.73 (t, *J* = 7.5 Hz, 3H, CH_3). The crude hemiaminal **399** was taken up in a solution of TFA (3 mL) and CH_2Cl_2 (3 mL) at rt and stirred for 1 h. The volatiles were removed under reduced pressure and sat. $NaHCO_{3(aq)}$ (20 mL) was added to the residue. The reaction mixture was extracted into CH_2Cl_2 (10 mL) and the two layers were separated. The aqueous layer was extracted into CH_2Cl_2 (2 x 10 mL) and the combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the imine **351** (30 mg, 80%) as a yellow oil; IR (ATR) 2961, 2925, 2864, 1779, 1731, 1668, 1448, 1199, 1173, 1136, 933, 797, 721, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H, C=NH), 5.71 (dd, *J* = 18.0, 11.0 Hz, 1H, C*H*=CH_2), 5.42 (d, *J* = 11.0 Hz, 1H, CH=C*H*$_A$$H_B$), 5.01 (d, *J* = 18.0 Hz, 1H, CH=CH_A*H*$_B$), 3.85 (dddd, *J* = 17.0, 3.5, 3.5, 1.5 Hz, 1H, NCH), 3.65 (dddd, *J* = 17.0, 9.5, 5.5, 2.5 Hz, 1H, NCH), 2.04-1.84 (m, 3H, CH), 1.80-1.70 (m, 3H, C*H*$_2$$CH_3$, CH), 1.00 (t, *J* = 7.5 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.7 (C=N), 137.0 (*C*H=CH_2), 119.4 (CH=*C*H_2), 45.1 (NCH_2), 44.9 (C), 30.6 (CH_2), 26.6 (CH_2), 16.6 (CH_2), 7.6 (CH_3); HRMS (ESI) *m/z* calcd for $C_9H_{15}N$ $(M + H)^+$ 138.1277, found 138.1284 (−4.6 ppm error).

Lab Book Reference: SC7/76 and 7/77

Appendices

Appendix I: *Chem. Eur. J.* 2016, *22*, 6496-6500

ChemPubSoc Europe

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CHEMISTRY
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Communication

Spirocycles

From Heteroaromatic Acids and Imines to Azaspirocycles: Stereoselective Synthesis and 3D Shape Analysis

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Abstract: Heteroaromatic carboxylic acids have been directly coupled with imines using propylphosphonic anhydride (T3P) and NEt(iPr)$_2$ to form azaspirocycles via intermediate *N*-acyliminium ions. Spirocyclic indolenines (3*H*-indoles), azaindolenines, 2*H*-pyrroles and 3*H*-pyrroles were all accessed using this metal-free approach. The reactions typically proceed with high diastereoselectivity and 3D shape analysis confirms that the products formed occupy areas of chemical space that are under-represented in existing drugs and high throughput screening libraries.

In recent years, the biological evaluation of under-explored regions of chemical space has attracted significant attention in the search for new pharmaceutical lead compounds. In particular, rigid, three-dimensional scaffolds have been targeted, as they are generally poorly represented in current drugs and screening libraries.[1] With this in mind, functionalised spirocycles are of much current interest and efficient methods to generate such compounds are of high value.[1,2]

In this paper, the formation and 3D shape analysis of spirocyclic indolenines and related azaspirocycles are described. Spirocyclic indolenines (also known as 3*H*-indoles)[3] are important scaffolds in their own right, being present in a number of bioactive natural products, and also since they serve as precursors to other privileged heterocycles including β-carbolines,[4] oxindoles[5] and indolines.[6] The most common synthetic strategies currently used to generate spirocyclic indolenines are shown in Figure 1 A. Interrupted Fisher-indole reactions (**1**→**4**)[7] and intramolecular imine condensation routes (**2**→**4**)[8] have each been well used over the years, whereas dearomatising spirocyclisation reactions (**3**→**4**)[9] are of particular current interest[10] and underpin the approach described herein.

Our new, connective method is based on the coupling of aromatic carboxylic acids **5** with imines **6** to form reactive *N*-acyliminium ions **7**[11,12] in situ, that can then be intercepted by intramolecular nucleophilic attack, exemplified in Figure 1 B by the formation of spirocyclic indolenines **8**.[13] The high electrophilicity of the *N*-acyliminium ion intermediate is a key design feature, as it means sufficiently mild conditions can be used to the allow the products to be isolated, without competing 1,2-migration and dimerisation/trimerisation reactions taking place.[3] Herein we report the successful implementation of this strategy, which allows indoles and other simple, electron-rich aromatics to be converted into complex azaspirocycles, in a one-pot, metal-free, stereoselective process. Furthermore, 3D shape analysis,[1b,14] using the principal moments of inertia (PMI) method,[15] shows that most of the products formed occupy interesting and under-exploited regions of "3D chemical space".

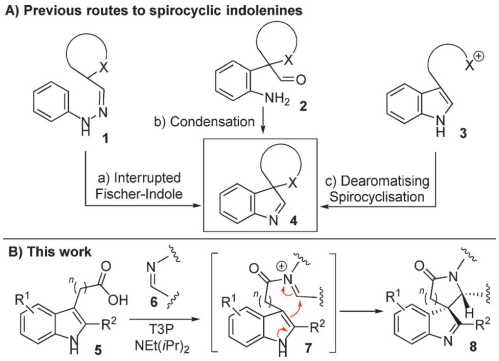

Figure 1. Previous and new strategies for spirocyclic indolenine synthesis.

To explore the viability of this new approach, the reaction between 2-methyl-3-indole acetic acid **5a** and imine **6a** was first examined (Scheme 1), by stirring these compounds in the presence of NEt(iPr)$_2$ and propylphosphonic anhydride (T3P) in THF at RT. Pleasingly, this led to the formation of the expected spirocycle as a mixture of diastereoisomers (**8a**:**9a**, 11:1), through a process that is conceptually similar to an interrupted Pictet–Spenger reaction.[16] The diastereomeric products were partially separable by column chromatography, and isolated in 92% overall yield (Scheme 1). The stereochemistry of the major diastereoisomer **8a** was confirmed by X-ray crystallography (Figure 2, see later).[17] Following a temperature and solvent screen (see the Supporting Information), a range of other 2-methyl indole acetic acid derivatives (**5b**–**5f**)[18] were also coupled with imine **6a** under the optimised conditions; substi-

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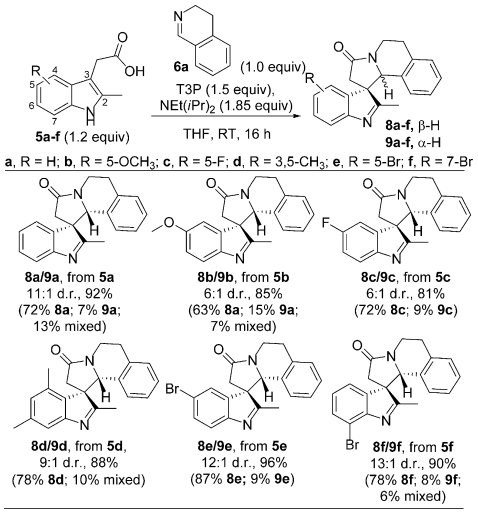
Supporting information and ORCID from the author for this article are available on the WWW under http://dx.doi.org/10.1002/chem.201600823.



Scheme 1. Spirocyclisation with 2-methyl 3-indole acetic acid derivatives. For full experimental details, see the Supporting Information; major diastereoisomer is shown, d.r. values based on ^{1}H NMR analysis before chromatography; yields obtained following column chromatography.

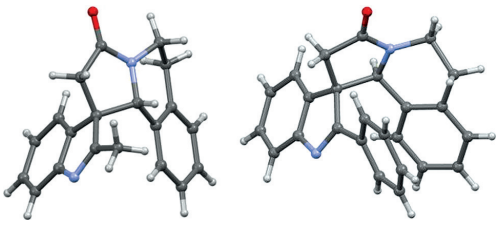
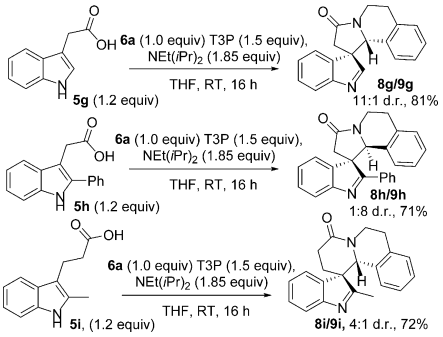


Figure 2. X-ray images for spirocycles **8a** (left) and **9h** (right).

tution on all positions of the indole ring was examined and the desired spirocyclic indolenines were formed in good to excellent overall yield (**8/9b–f**, 81–96%). The diastereoselectivity was universally high (d.r. 6:1–13:1), with the same major diastereoisomer being formed in all cases.[19]

Indole acetic acid itself (**5g**) was also compatible with the standard procedure, furnishing spirocycles **8g**/**9g** in good yield (Scheme 2), demonstrating that substitution on the indole 2-position is not a requirement, which is pleasing given the propensity for related compounds to undergo 1,2-migration reactions.[20] Phenyl substitution at the 2-position (acid **5h**) was also well-tolerated, with spirocycles **8h**/**9h** being formed in good yield, and interestingly the major product in this case was **9h** (confirmed by X-ray crystallography, Figure 2), which shows opposite diastereoselectivity to the previous examples.[17] Finally, six-membered ring spirocyclic lactams **8i**/**9i** were formed in good overall yield, using higher homologue **5i**.

A plausible explanation for the observed diastereoselectivities is depicted in Figure 3, using the reaction of indole **5a** and imine **6a** as an example. The reaction is thought to proceed



Scheme 2. Additional acid substrates in the spirocyclisation with imine **6a**; for full experimental details see the Supporting Information.

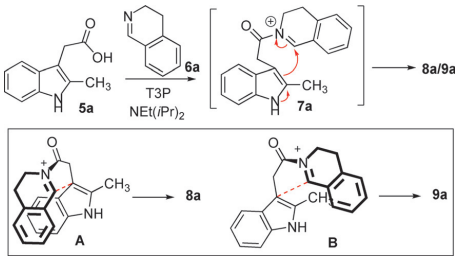


Figure 3. Stereochemical model for the spirocyclisation of indole acetic acid derivatives with imine **6a**.

through activation of the carboxylic acid with T3P, followed by *N*-acylation to generate a reactive *N*-acyliminium ion **7a**. Assuming that this is correct, the stereoselectivity is then determined by the facial selectivity of the nucleophilic attack onto the *N*-acyliminium ion (**7a**→**8a**/**9a**). In **A**, the benzenoid rings of the imine and indole components appear to be relatively close together in space and look well-suited to experience a stabilising π-stacking interaction, whereas in **B**, this interaction is absent, and replaced by a potentially destabilising steric clash between the imine and the indole 2-methyl group. These transition-state models also offer a plausible explanation for the switch in stereoselectivity in products **8h**/**9h**; in this case, as the indole 2-position is substituted with a phenyl group rather than a methyl, a stabilising π-stacking interaction now appears to be viable in model **B**. The reactions are believed to be under kinetic control, based on the fact that re-subjecting a purified sample of spirocycle **8a** to the optimised reaction conditions led to no change in the d.r., indicating that the spirocyclisation is not reversible in this case.

The scope of the reaction with respect to the imine coupling partner was examined next, with the imines used (**6b–6g**)[21] shown in Figure 4 and spirocyclisation results in Scheme 3. Dimethoxy-substituted imine **6b** successfully gave the expected products **8j** and **9j** in moderate diastereoselectivity. Tetra-substitution around the aromatic ring of the imine did not hinder the reaction as 2,5-dibromo-3,4-dimethoxy-substituted substrate **6c** gave products **8k** and **9k** in good yield and diaste-

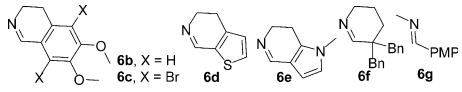
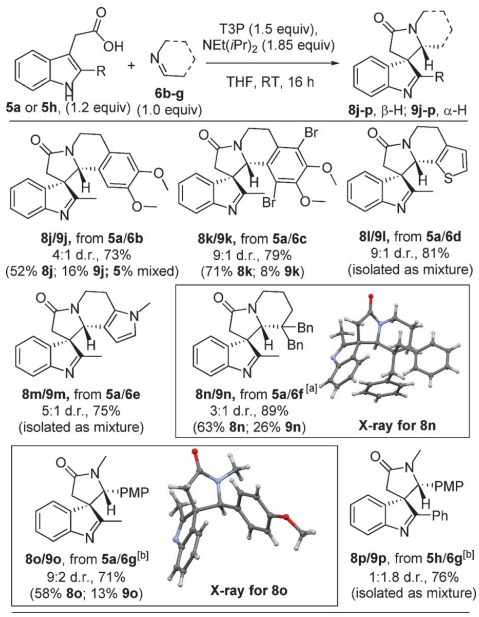


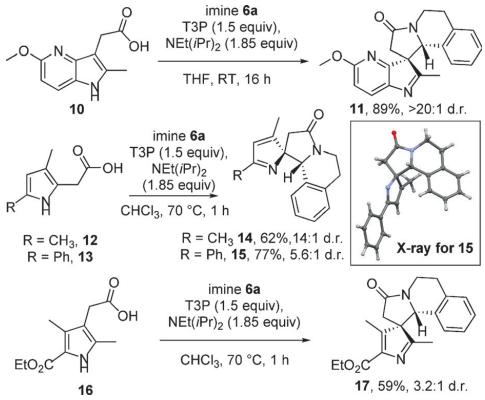
Figure 4. Imines **6b–6g**.



Scheme 3. Spirocyclisation with imines **6b–g**. For full experimental details, see the Supporting Information; major diastereoisomer shown, d.r. values based on ^{1}H NMR analysis before chromatography; yields obtained following column chromatography. [a] Reaction performed at 90 °C in toluene for 18 h; [b] reaction performed at 70 °C in THF for 1 h.

reoselectivity. Thiophene- and pyrrole-fused imines **6d** and **6e** were also suitable substrates, as was benzylated imine **6f**, all forming the expected spirocycles **8l/9l–8n/9n** with generally good diastereoselectivity and in good yield. Acyclic imines, which are often avoided in related methods based on *N*-acyliminium ion chemistry due to their tendency to hydrolyse,[22] are also well-tolerated, with spirocyclic products **8o/9o** and **8p/9p** each isolated in good overall yields. The major diastereoisomer formed in each case was assigned based on ^{1}H NMR spectroscopy,[19] and in the case of spirocycles **8n** and **8o**, confirmed by X-ray crystallography (Scheme 3).[17]

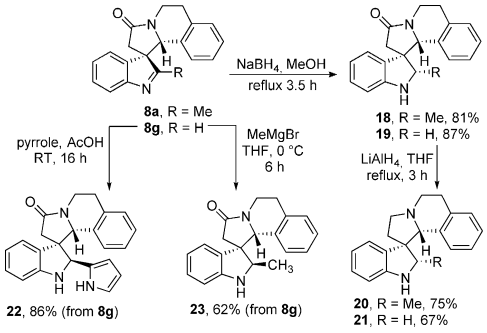
Preliminary work also confirms that this method can be extended to other heterocyclic systems. Aza-indoles are important structures in medicinal chemistry[23] and pleasingly we found that aza-indoleacetic acid **10**[18b] reacted with imine **6a** under the usual conditions to give the spirocyclic product **11** in excellent yield as a single diastereoisomer (Scheme 4), with the stereoselectivity seemingly being consistent with the analogous indole examples. Dearomatising via the 2-position of pyrroles **12** and **13**[24] is also possible;[25] on these systems, only a small amount of the desired product was formed when the



Scheme 4. Other heterocycles in the spirocyclisation; for full experimental details see the Supporting Information.

standard conditions were used, but by switching the reaction solvent to $CHCl_3$ and increasing the temperature to 70 °C, spirocycles **14** and **15** were each formed in good yield, with good to excellent diastereoselectivity. In the phenyl-substituted case, the major diastereoisomer **15** was separable by chromatography and X-ray crystallography was used to assign the configuration depicted.[17,26] Finally, this same modified set of conditions was used to form spirocycle **17** through the reaction of pyrrole **16** with imine **6a**; this example is noteworthy, given that 3*H*-pyrroles are known to be unstable and their synthesis is a considerable challenge using existing methods.[27]

The dearomatisation reactions described allow access to a diverse array of spirocyclic scaffolds, and the products formed are well primed to undergo further transformations, allowing additional structural diversity to be introduced or the properties of the compounds to be tuned. This is exemplified using spirocycles **8a** and **8g** (Scheme 5), and it is likely that similar processes (and many more) will be broadly applicable across the other spirocyclic products described in this paper. For example, indolenines **8a** and **8g** were both reduced to indolines **18** and **19** respectively by sodium borohydride in refluxing methanol. In the case of product **18**, the reduction was completely diastereoselective, with the hydride source approaching



Scheme 5. Modification of spirocycles **8a** and **8g**.

the indolenine from the less sterically hindered side (i.e., away from the two benzenoid rings, verified by X-ray crystallography).[17] Indolenines **18** and **19** could also be reduced further, forming products **20** and **21**, upon reaction with lithium aluminium hydride in refluxing THF. Products with complementary relative stereochemistry to indoline **18** could also be obtained through the addition of carbon-based nucleophiles; products **22** and **23** were formed, again with complete diastereoselectivity, through the addition of pyrrole and methyl magnesium bromide respectively to indolenine **8g**.[28]

Finally, the principal moments of inertia (PMI) method[1b,14] was used in order to characterise the 3D shape of the azaspirocycles produced.[29] The PMI method utilises the molecular mechanics-generated lowest-energy conformation and the normalized principal moments of inertia ratios, NPR1 and NPR2, are displayed on a triangular plot, with the three vertices corresponding to rod-, disc- and spherical-shaped molecules. A PMI plot containing the major diastereoisomeric forms of all of the azaspirocyclic products synthesised during the course of our study is shown in Figure 5. As this plot highlights, 88% (22 out of 25, compounds **8a–g**, **8i–p**, **9h**, **14**, **15**, **17–21**, **23**) of the new azaspirocycles occupy the highlighted '3D region' (blue triangle) and have values of (NPR1 + NPR2) > 1.2. These 3D shape properties are in stark contrast to the majority of current drugs, most of which lie close to the rod-disc axis. For example, PMI analysis of 1439 FDA-approved small molecule drugs[30] shows that just 23% are found within the (NPR1 + NPR2) > 1.2 area (see the Supporting Information), and most drug-screening libraries have a similar shape distribution.[31] Hence, these results are significant, in view of the current interest in the synthesis of compounds that populate under-explored regions of chemical space, especially spherical areas (e.g., azaspirocycles **8b**, **8c**, **8e**, **8n**, **8p**, **9h**, **11**), in pharmaceutical lead-identification programs.

In conclusion, a new, metal-free, connective method for the synthesis of a range of 3D spirocyclic scaffolds has been reported, starting from far simpler 2D building blocks. The reactions proceeded in moderate to excellent yields and are diastereoselective, with the major diastereoisomers isolable in good overall yield in the majority of cases. This study focused predominantly on the synthesis of spirocyclic indolenines, but the successful results obtained using azaindoleacetic acid, as well as 2- and 3-substituted pyrrole acetic acids, indicate that the process is much more general. 3D shape analysis indicates that a high percentage of the compounds generated in this study occupy underexplored regions of chemical space, and the ability to modify the scaffolds further has also been demonstrated, meaning that their desirable spatial and physicochemical properties can be further tuned. Future applications in the generation of medicinally relevant scaffolds/lead compounds and natural products are anticipated, and the development of asymmetric variants of these reactions will also be explored.[32]

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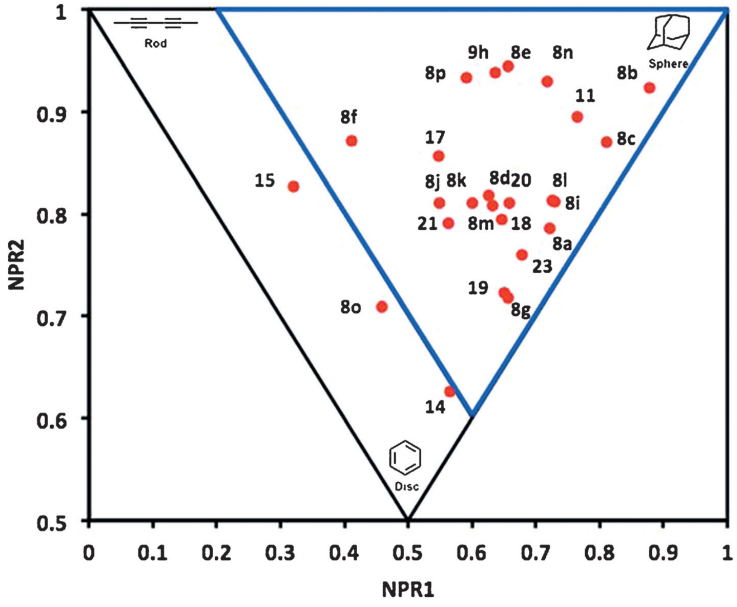

Figure 5. PMI analysis of spirocycles **8a–g**, **8i–p**, **9h**, **14**, **15**, **17–21** and **23**.

Keywords: 3D space · dearomatisation · lead identification · *N*-acyliminium ions · spirocycles

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Abbreviations

Ac	Acetyl
Ar	Argon
Ar (in NMR)	Aromatic proton signal
aq.	Aqueous
Boc	*t*-butoxycarbonyl
br	Broad
Bu	Butyl
CHARMm	Chemistry at Harvard macromolecular mechanics
COSY	Correlation spectroscopy
cm^{-1}	Wavenumber
δ	Chemical shift
d	Doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DEPT	Distortionless enhancement by polarisation transfer
DBU	1,8-Diazabicycloundec-7-ene
DIA	Direct Imine Acylation
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N,N*-Diisopropylethylamine
DMP	Dess-Martin periodinane
dr	Diastereomeric ratio
ee	Enantiomeric excess
eq.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
Et_2O	Diethyl ether
g	Gram(s)
h	Hour(s)
[H]	Reduction
HMBC	Heteronuclear multiple bond correlation
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz

IR	Infra-red
J	Coupling constant in Hz
LDA	Lithium diisopropylamide
LHMDS	Lithium bis(trimethylsilyl)amide
lit.	Literature
μL	Microlitres
m	Multiplet
M	Molar
M^+	Molecular ion
Me	Methyl
mg	Milligram(s)
MHz	Megahertz
min	Minutes(s)
mL	Millilitre(s)
mmol	Millimole(s)
mp	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves (4Å)
MW	Microwave irradiation
m/z	Mass to charge ratio
nAChRs	Nicotinic acetylcholine receptors
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
Petrol	Petroleum ether (fraction which boils at 40-60 °C)
Ph	Phenyl
PMI	Principle moment of inertia
ppm	Parts per million
q	Quartet
R_F	Retention factor
RMSD	Root mean square deviation
rt	Room temperature
s	Singlet
sat.	Saturated
SMILES	simplified molecular input line entry specification

t	Triplet
T3P	Propylphosphonic anhydride
TBAF	Tetrabutylammonium fluoride
TBME	*tert*-Butyl methyl ether
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	*N,N, N',N'*-tetramethylethylenediamine
Ts	*p*-Toluenesulfonyl
PPA	Polyphosphoric acid
Py	Pyridine

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