# A ‘top down’ approach to the synthesis of complex, diverse lead-like scaffolds

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# Declaration

The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference was made to the work of others.

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# Acknowledgements

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Finally, I want to appreciate my family and friends who stood by me through thick and thin in the course of the programme. I dedicate this thesis to them.

# Abstract

Lead-oriented synthesis (LOS) is a concept that seeks to underscore the usefulness of developing new methodologies suitable for making a diverse library of highly three-dimensional small organic molecules with controlled molecular properties that qualify them to most likely serve as lead compounds or be in the 'lead-like' space. The 'top down' approach to LOS seeks to gain rapid access to complex polycyclic assemblies which can then be deconstructed or modified through ring addition, cleavage and expansion to generate multiple, diverse lead-like scaffolds. This strategy hopes to solve the problem of high attrition rates in drug discovery. 14 diverse $sp^3$-rich scaffolds have been synthesized through this means from relatively cheap and simple materials using a novel oxidative dearomatisation reaction as the complexity-generating step. The scaffolds have been decorated along different vectors with exemplar medicinal chemistry capping groups to generate 52 final compounds, with their molecular properties assessed by LLAMA (Lead-likeness and Molecular Analysis) prior to the decoration, and shall be tested for biological activity against a wide range of targets.

Chapter 1 discusses the the general overview to small molecule drug discovery. Some of the issues touched are the high attrition rates of drug discovery, factors linked to such attrition rates and the importance of synthetic chemistry in the drug discovery process.

Chapter 2 discusses the key scaffold synthesis and the application of the ‘top down’ approach to generate complex and diverse molecular scaffolds.

Chapter 3 discusses the functionalisation of the diverse scaffolds along different vectors to generate final compounds for biological screening, as well as the LLAMA analysis of such compounds.

# Abbreviations

| | |
|---|---|
| 1D | One-dimensional |
| $^{1}$H-$^{1}$H COSY | Proton-proton correlation spectroscopy |
| 2D | Two-dimensional |
| 3D | Three-dimensional |
| ADMET | Absorption, distribution, metabolism, excretion and toxicity |
| All | Allyl |
| AlogP | Atom-based computed value of the logarithm of partition coefficient |
| ATP | Adenosine triphosphate |
| BCR | Benzoyl CoA reductase |
| BINAP | [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] |
| Bn | Benzyl |
| br.d | Broad doublet |
| br.s | Broad singlet |
| CAN | Cerium ammonium nitrate |
| Cbz | Benzyloxycarbonyl |
| clogP | Fragment-based computed value of the logarithm of partition coefficient |
| d | Doublet |
| Da | Dalton |
| DCM | Dichloromethane |
| dd | Doublet of doublet |
| ddd | Doublet of doublet of doublet |

| | |
|---|---|
| dddd | Doublet of doublet of doublet of doublet |
| ddt | Doublet of doublet of triplet |
| DIBAL | Diisobutylaluminium hydride |
| DIPEA | *N*,*N*-Diisopropylethylamine |
| DMAP | 4-Dimethylaminopyridine |
| DMF | Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| DNA | Deoxyribonucleic acid |
| DOS | Diversity-oriented synthesis |
| *dr* | Diastereomeric ratio |
| dt | Doublet of triplet |
| dtd | Doublet of triplet of doublet |
| EDC | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| $Et_3N$ | Triethylamine |
| FBDD | Fragment based drug discovery |
| FDA | Food and Drug Adminstration |
| $Fsp^3$ | Fraction of $sp^3$ carbon atoms |
| hept | Heptet |
| HFIP | Hexafluoroisopropanol |
| HMBC | Heteronuclear multiple bond correlation |
| HMQC | Heteronuclear multiple quantum coherence |
| HOBT | 1-Hydroxybenzotriazole |

| | |
|---|---|
| HRMS | High resolution mass spectrometry |
| HTS | High throughput screening |
| IND | Investigational New Drug |
| *i*-Pr | Isopropyl |
| IR | Infrared |
| *J* | Coupling constant |
| LCMS | Liquid chromatography-mass spectrometry |
| LLAMA | Lead-likeness and Molecular Analysis |
| LOS | Lead-oriented synthesis |
| m | Multiplet |
| Ms | Methanesulfonyl |
| NaDPH | Nicotine adenine dinucleotide phosphate |
| NDA | New Drug Application |
| NMR | Nuclear magnetic resonance |
| NOE | Nuclear overhauser effect |
| NOESY | Nuclear overhauser enhancement spectroscopy |
| PAINS | Pan assay interference compounds |
| PIFA | Phenyliodine bis(trifluoroacetate) |
| PMI | Principal moment of inertia |
| PMP | *Para*-Methoxyphenyl |
| PPA | Polyphosphoric acid |
| ppm | parts per million |

| | |
|---|---|
| q | Quartet |
| qd | Quartet of doublet |
| quint | Quintet |
| $R_f$ | Retention factor |
| RO3 | Rule of three |
| rt | Room temperature |
| s | Singlet |
| SBDD | Structure-based drug discovery |
| sext | Sextet |
| $S_NAr$ | Nucleophilic aromatic substitution |
| SPR | Surface plasmon resonance |
| t | Triplet |
| TBA | Tetrabutylammonium |
| TBS | *tert*-Butyldimethylsilyl |
| $^t$Bu | *tert*-Butyl |
| td | Triplet of doublet |
| tdd | Triplet of doublet of doublet |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMS | Trimethylsilyl |
| TosMIC | Toluenesulfonylmethyl isocyanide |
| Ts | *p*-Toluenesulfonyl |

| | |
|---|---|
| tt | Triplet of triplet |
| *Z*-Gly-OH | *N*-Carbobenzyloxy glycine |

# Contents

# 1.0 Introduction

## 1.1 A general overview of small molecule drug discovery

Drug discovery is a multidisciplinary and complex process which can take 12-15 years to complete and can cost in excess of $1 billion for the development of a new drug. The process usually begins as a result of a clinical condition with no suitable chemotherapy and this motivates researchers to seek a solution. The first step in a drug discovery program is the identification of a target to be modulated. The term target applies to a range of biological entities such as proteins, DNA and RNA. A good target has to be druggable, efficacious, safe and, meet both clinical and commercial needs. Once the target is identified, a hypothesis can be put forward predicting a therapeutic effect upon the inhibition or activation of the target. The target is then validated using a range of techniques from *in vitro* tools and using whole animal models, to the modulation of a desired target in patients of interest. Despite the fact that each target-validation technique may be right in its own context, a multi-validation approach of targets significantly increases the credibility of the observed outcome.[1]

After target identification and validation, the hit and lead discovery phase commences. It is at this stage that compound screening methodologies are developed. A hit can be defined as a molecule with a desired activity and whose activity can be confirmed after retesting. Different screening protocols exist for hit identification. An example is high throughput screening (HTS) which involves the screening of an entire compound library (which could be of the order of 1 million samples)[2] directly against the target; or in a more complex protocol, such as a cell-based assay, whose activity is dependent upon the target but which would require the confirmation of the site of action through secondary assays. Other screening paradigms which may be chosen from include focused screen, fragment screen, structure-aided drug design, virtual screening, physiological screening and NMR screening.[1,3] Apart from *de novo* and HTS methods of sourcing hits, scientists also turn to nature and biotechnology for biologics that may be progressed into vaccines and monoclonal antibodies.[4,5]

The next stage is the hit-to-lead phase where structure-activity relationship (SAR) investigations are carried out on each hit to measure the activity and selectivity of each compound. The aim is

to refine the hits to produce more potent and selective, but less toxic compounds. New binding sites on the target may be discovered in the process. Subsequently, absorption, distribution, metabolism, excretion and toxicological (ADMET) tests are carried out on the lead compounds to determine their pharmacokinetics. The final phase of drug discovery is the lead optimization phase. This is to increase the therapeutic index of the lead compound, maintaining its favourable properties and improving on undesirable features in its structure.[1,4]

An Investigational New Drug (IND) application is filed with the Food and Drug Administration (FDA) for the optimized lead compound(s) prior to clinical development. Clinical development is divided into phase I to phase IV clinical trials which will determine whether the drug candidate should be approved for the market or not.[5] Below is a diagrammatic representation of a typical small molecule drug discovery paradigm.

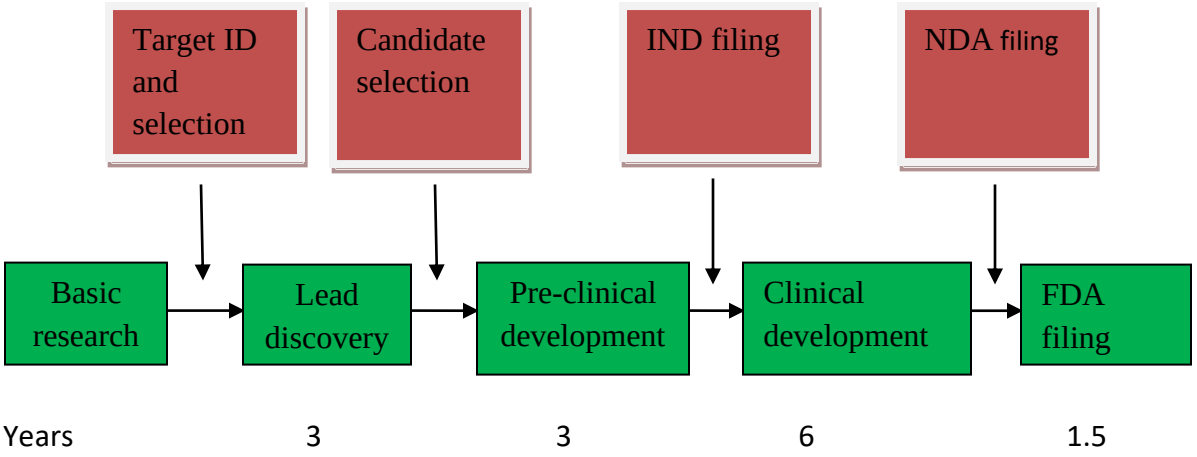



*Figure 1. Drug discovery process and the corresponding timescale for each stage. IND, Investigational New Drug; NDA, New Drug Application; FDA, Food and Drug Administration. Adapted from source.*[1]

## 1.2 Attrition rate in drug discovery

Although there has been a surge in the number of biologics approved as drug candidates in recent times by the FDA, small molecules are known to dominate the science of drug discovery.[6] However, the success rate of new chemical entity (NCE) drug discovery, from first-in-man clinical trial to approval by the FDA is very low (11% for all disease types). So, there is an

89% chance that a drug candidate will fail during clinical development. Some of the factors responsible for the undesirably high attrition rate are poor pharmacokinetic properties, lack of efficacy and safety considerations.[7] The conclusion above is drawn from a study that was carried out**,** for candidates subjected to clinical development from 1991 to 2000 by 10 big pharmaceutical companies in Europe and the United States. Even till 2019, drug discovery success rate is still not impressive considering the fact that only 32 small molecules were approved by the FDA in the same year.[8]

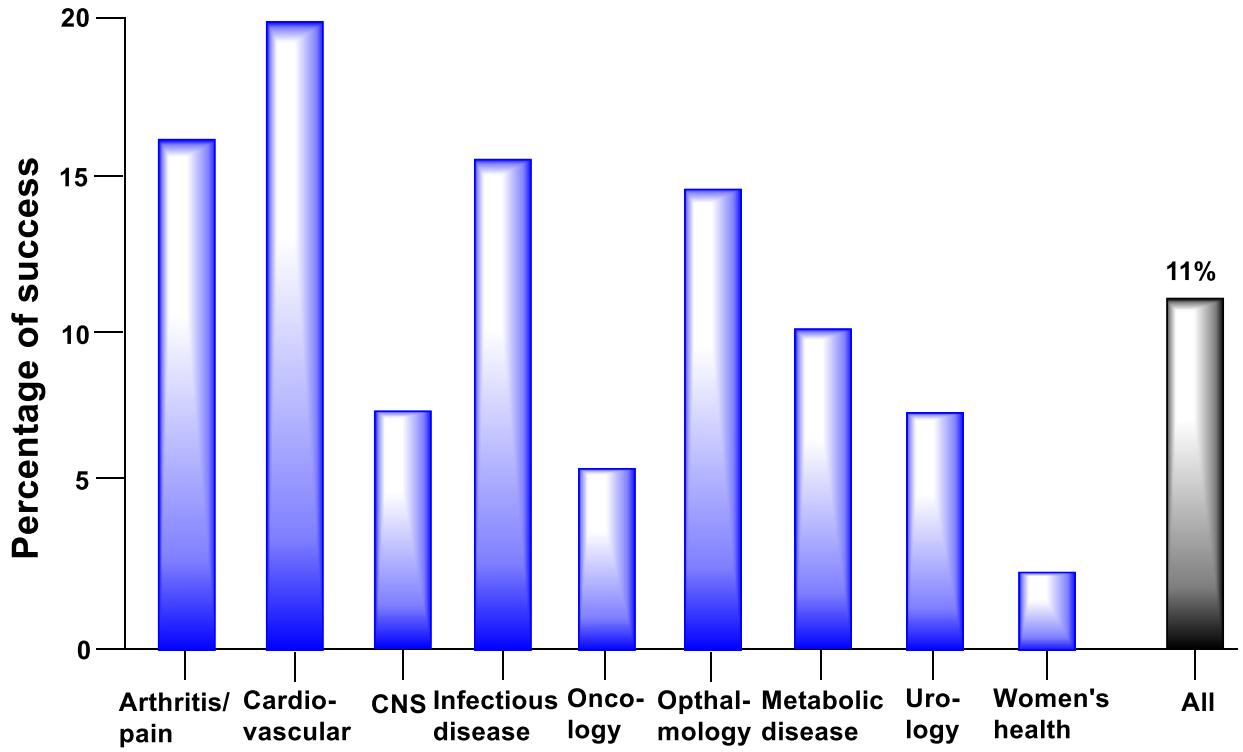



*Figure 2. Drug discovery success rate from phase I clinical trial to registration. Adapted from source.*[7]

### 1.2.1 Factors linked to attrition in drug discovery

Right from the time of Lipinski's introduction of the 'rule of five', synthetic chemists have become more aware of the importance of physicochemical properties in drug discovery. Some of the properties deemed to be important in this context are lipophilicity, number of aromatic rings, molecular weight, saturation and the number of chiral centres present in a drug candidate.[9–12]

Safety of candidates is very important in drug discovery. Therefore, toxicity related issues are a major cause of attrition at the preclinical stage. It has been observed that less polar or more lipophilic compounds have a higher probability of exhibiting increased toxicity.[10] Also, aromatic ring count is another factor that has been observed to be important in early stage drug discovery. Increasing the number of aromatic rings in a molecule leads to increased binding on biological targets. However, more than three aromatic rings in a molecule correlates with poor developabilty, decreased aqueous solubility and increased lipophilicity; and hence can increase the risk of attrition.[11]

On the other hand, an increase in the complexity of drug candidates has been observed to correlate well with success. It results in a better biological target/candidate complementarity which may lead to additional interactions inaccessible to flat molecules, and hence improving potency and selectivity. This is also supported by the fact that many drugs are offshoots of complex and diverse natural products. An attempt has been made to measure complexity using the carbon bond saturation and the number of chiral centres present in a molecule. Saturation can be measured as a fraction of $sp^3$ ($Fsp^3$) carbons present in a molecule with respect to the total carbon count. Increasing the $Fsp^3$ and number of chiral centres in a drug molecule increases its chances of success.[12]

## 1.3 The importance of synthesis in drug research and development

Small organic molecules play crucial roles in drug discovery. Of the 6000 potential drug targets in the human genome, only about 300 have been targeted by approved drugs. There are still many diseases with limited or no treatment options. Nevertheless, the impact of approved drugs on public health is outstanding.[13]

A number of approaches have been used to access complex and diverse scaffolds with the potential of targeting biologically relevant chemical space. A few of such approaches will be reviewed in this report. Below is a diagram that depicts the pharma space relevant to this project.

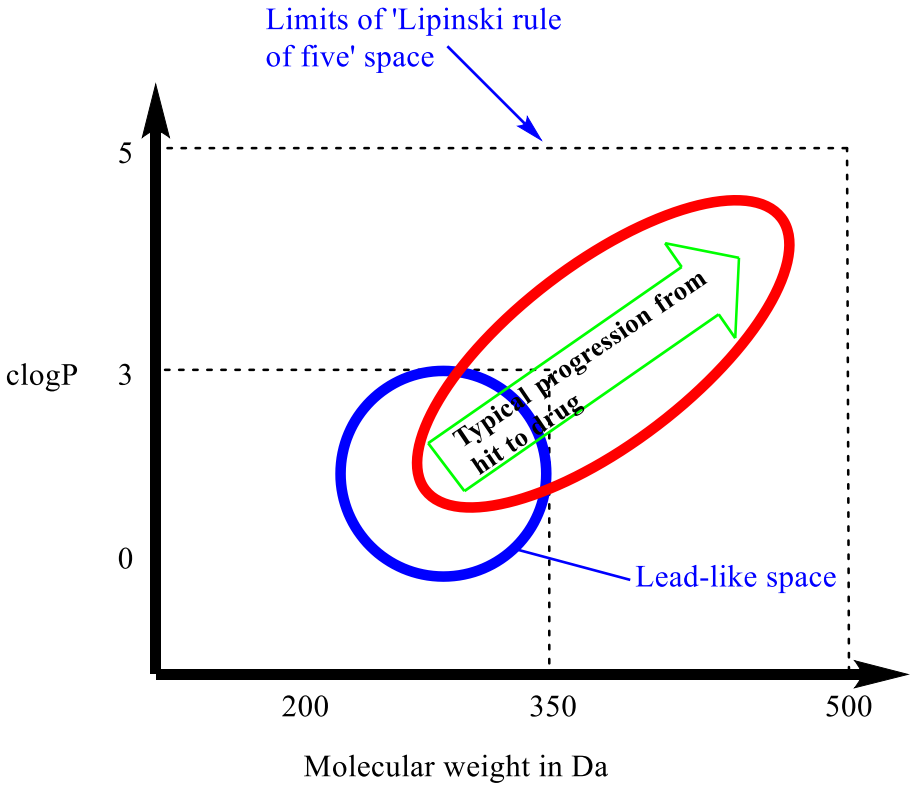


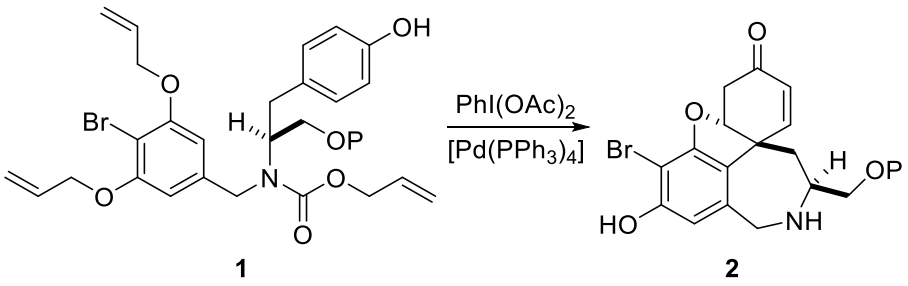

*Figure 3. A graph indicating lead-like space and optimal drug-like space. Adapted from source.*[14]

### 1.3.1 Diversity-oriented synthesis

In a study in 2008, it was discovered that 0.25% of molecular frameworks were found in 50% of known cyclic organic compounds.[15] It therefore means chemists tend to synthesise compounds based on already known frameworks. Diversity-oriented synthesis (DOS) – a term first introduced by Schreiber[16] - was intended to solve an important problem in chemical biology which is the design and synthesis of libraries that can modulate a wide range of biologically-relevant chemical space. The aim of DOS is to provide access to structurally complex and diverse molecules which combinatorial chemistry fails to achieve. In DOS, structural complexity is desired because many small molecules known to modulate protein-protein interactions are complex natural products. Equally, structural diversity is desired because diverse scaffolds are more likely to be successful in chemical genetic-like phenotypic screens which are cell- or organism based. DOS is therefore different from target-oriented synthesis where a preselected protein target is used for screens of structurally similar compound libraries.[15–18] Three different

pathways to diversity-oriented synthesis have been reviewed in the past and are discussed below.[19,20]

**Appendage or substitutional diversity:** This has been termed the simplest process for generating molecular diversity. It involves the functionalization of vectors inherent in a scaffold with different building blocks. In this way, many diverse compounds can be synthesized depending on the number of functional groups the molecular skeleton carries.[19] Shair and co-workers[21] demonstrated a biomimetic, solid-phase synthesis of a complex scaffold via oxidative dearomatization as shown below.

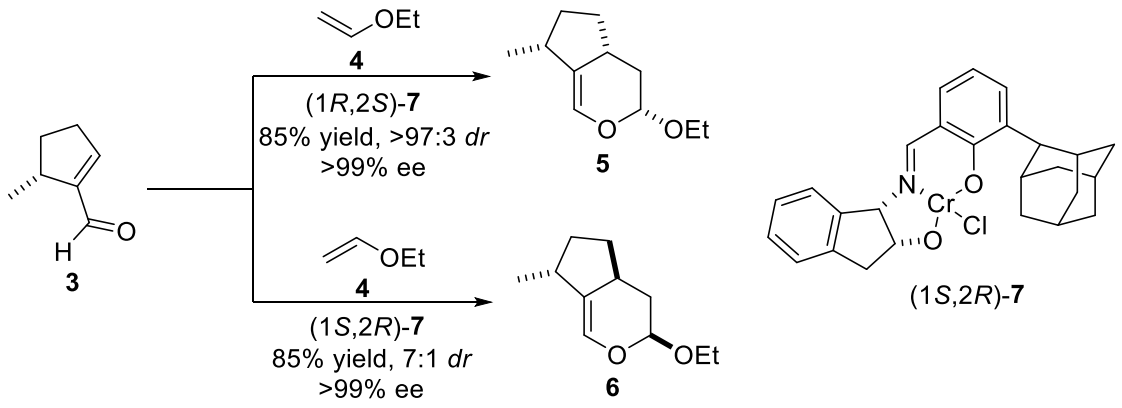



**1** **2**

*Scheme 1. Natural product inspired complexity-generating oxidative cyclisation.*[19,21]

The product **2** has six different points of possible orthogonal attachment to different building blocks, thereby having the potential to generate diversity.

**Sterochemical diversity:** Increasing the stereochemical diversity of a biologically active molecule increases its chance of modulating the target at different orientations. Therefore, methodologies that impart diastereo- or enantioselectivity on products of reactions are valuable in drug discovery.[19] An example is shown below in the work of Jacobsen and Chavez[22] using chiral catalysis to override substrate bias in a Diels-Alder reaction.

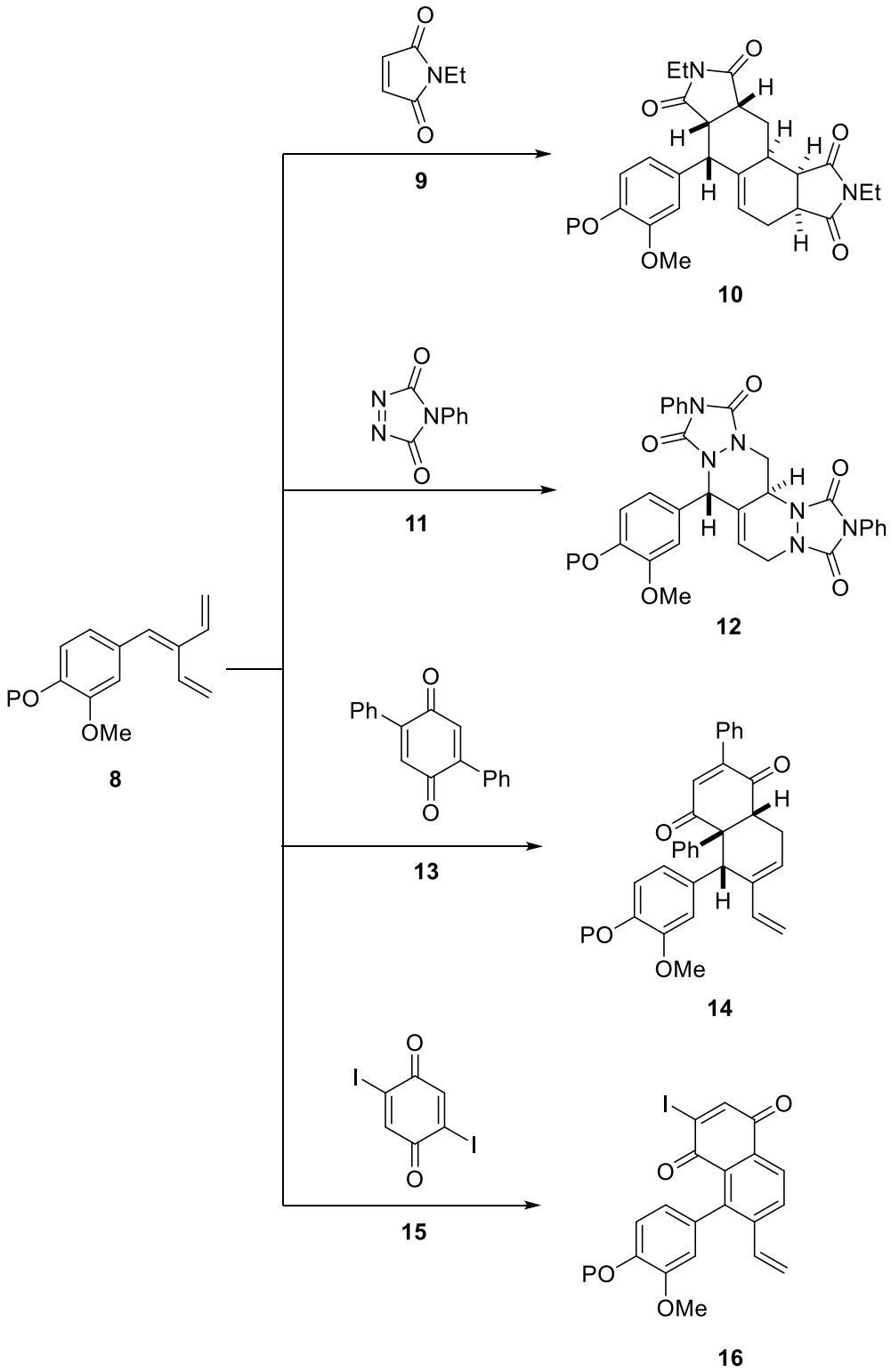



*Scheme 2. Demonstrating stereochemical diversity through chiral catalysis.*[19,22]

Using the catalyst (1*R*,2*S*)-**7**, the product **5** was obtained. This is also consistent with the stereochemical bias imparted on the reaction by the methyl group on the chiral centre of **3**. However, such bias can be overridden by using the enantiomer (1*S*,2*R*)-**7** instead, thereby yielding compound **6** as product.[19,22]

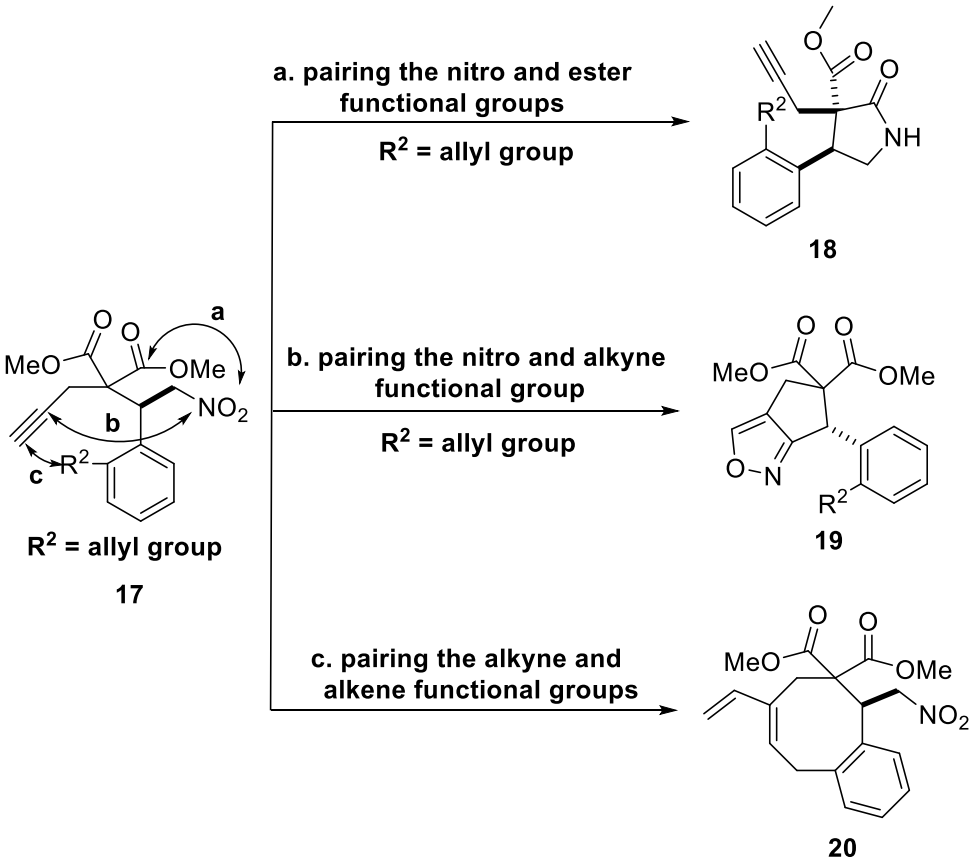
**Skeletal diversity:** Pathways that lead to diverse molecular skeletons are important in diversity-oriented synthesis. Three approaches have been described to achieve this objective. Therefore, skeletal diversity can be achieved by: one, reacting the same part of a molecule with different reagents to generate diverse scaffolds; two, using a molecule that is densely functionalized by orthogonally pairing the different functional groups present in the molecule to generate diverse scaffolds; and finally using different substrates - pre-encoded with different structural features subjected to the same type of reactions – to generate diverse scaffolds.[19,20]

Illustrating the first approach, Schreiber and co-workers[23] reacted the same part of the triene **8** with different dienophiles to generate diverse scaffolds as shown in *Scheme 3* below. Less reactive tri- and tetrasubstituted dienophiles such as **13** and **15** gave monocyclization products. However, using halogenated quinones such as **15**, led to products that spontaneously underwent dehydrohalogenation and aromatization to give benzene derivatives.



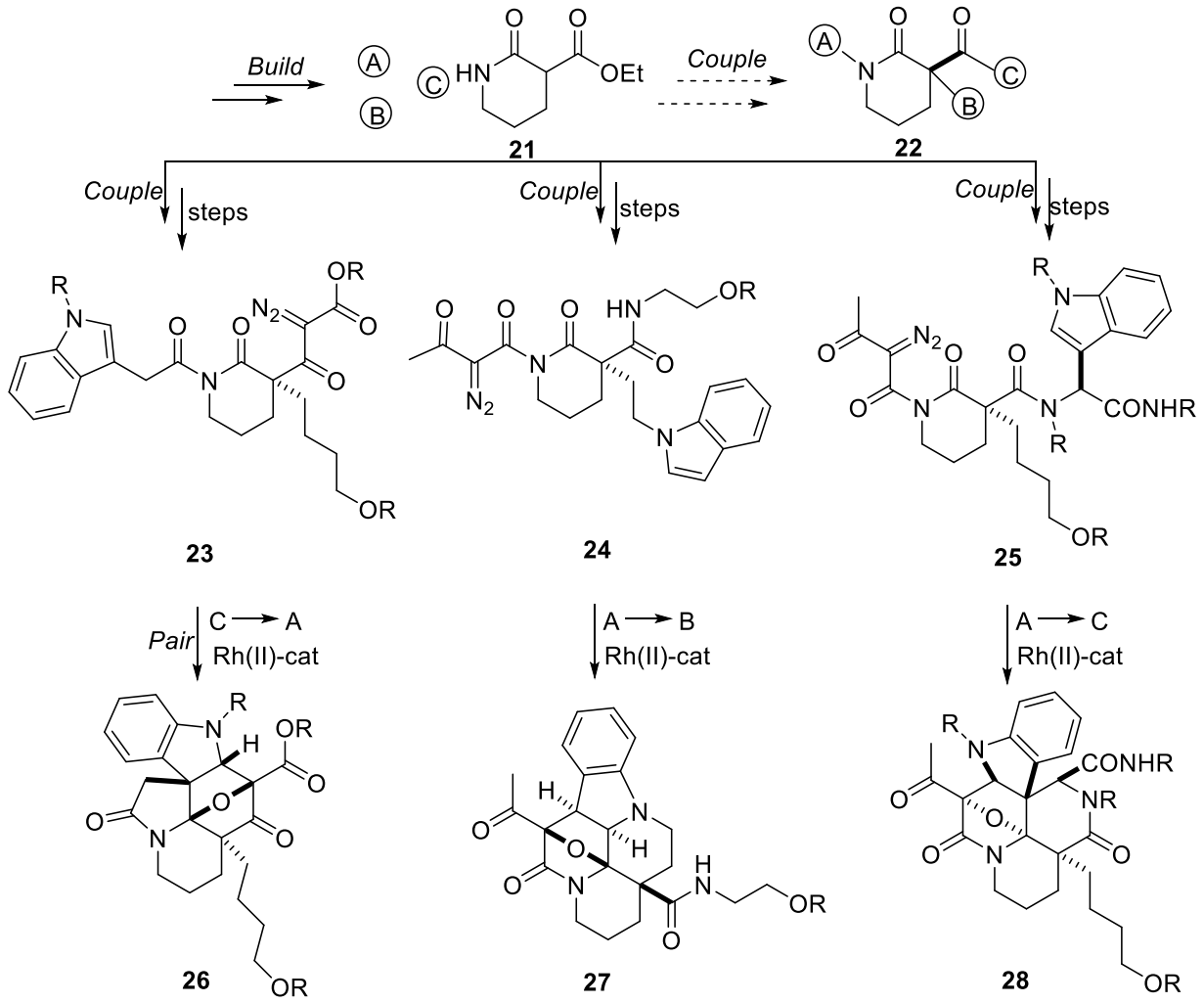

*Scheme 3. Syntheses of diverse scaffolds by reacting the same part of a molecule with different reagents.*[19]

For the second approach, Porco and co-workers[24] demonstrated the syntheses of diverse scaffolds by orthogonally pairing the different functional groups of a densely functionalised molecule as shown below.




*Scheme 4. Syntheses of diverse scaffolds through the orthogonal pairing of functional groups on the same substrate.*[20,24]

A classical example of the third approach to skeletal diversity is the work done by Oguri and Schreiber[25] inspired by the Mejia-Oneto and Padwa's[26] synthesis of indole alkaloids through the [3+2] cycloaddition of a carbonyl ylide with a pre-encoded indole ring on different substrates. Distinct molecular skeletons were therefore obtained as illustrated below.




*Scheme 5. Illustrating skeletal diversity using different substrates with pre-encoded structural features.*[27]

The Rh(II) catalyst interacts with the diazo groups of **23, 24** and **25** to form the respective Rh carbenoids. Each of the carbenoids then interacts with the neighbouring carbonyl group to form the ylide that undergoes a [3+2] cycloaddition with the 2,3-double bond of the indole ring to form the products.[25]

### 1.3.2 Lead-oriented synthesis

Lead-oriented synthesis[14] (LOS) is a concept that underscores the usefulness of developing new methodologies suitable for making small molecules in the 'lead-like space', thereby enhancing optimisation. It has been observed that there is an unintentional bias towards the synthesis of

non-lead-like small molecules due to the deficiencies of current synthetic methodologies. With respect to *Figure 3*, the lead-like space gives room for the optimisation of small molecules thereby improving the therapeutic indices of the final drug candidates.

As mentioned earlier, the Lipinski 'rule of five' for orally bioavailable drugs and other studies have continually stressed the importance of physicochemical descriptors to drug discovery.[9,14] The key descriptors that correlate strongly with success are molecular weight, lipophilicity and the fraction of $sp^3$-hybridised carbon.[28] The lead-like space has been defined as $-1 < \text{clog P} < 3$ for lipophilicity and $14 \leq \text{heavy atoms} \leq 26$ for molecular size (or a molecular weight range of 250 – 350 Da). Factors to consider in a lead-oriented synthesis programme include lipophilicity, molecular size and complexity, molecular shape and substructural considerations.[14]

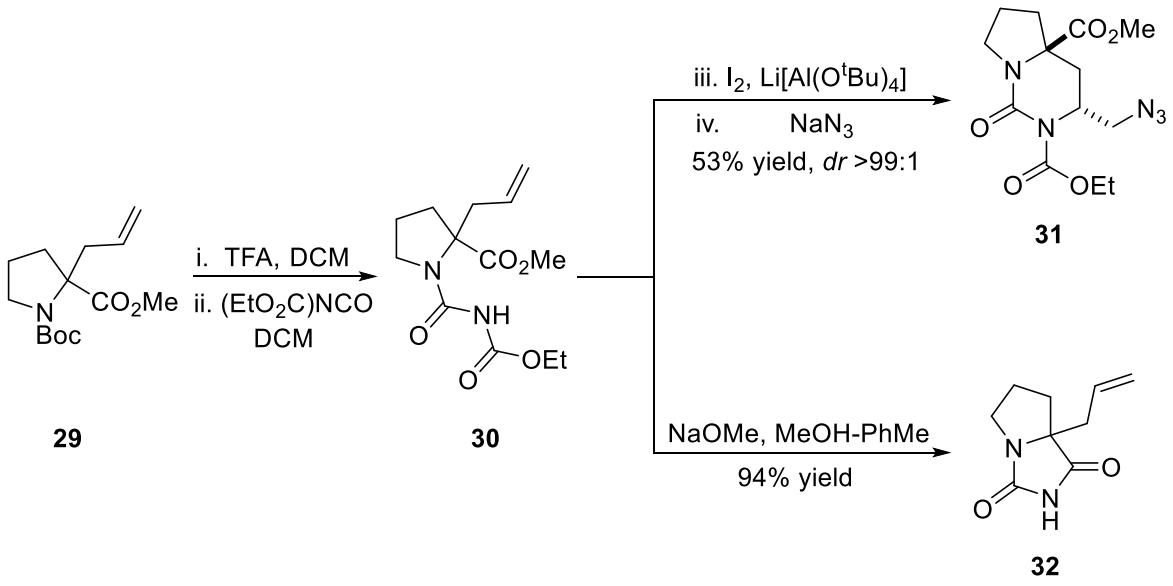
Lipophilicity is probably the most important of the factors listed above. A high logP usually favours the binding of small molecules to biological targets thereby enhancing potency. However, of concern is the resultant poor aqueous solubility and promiscuous binding to undesired targets which may lead to toxicity and side effects, and consequently, attrition. The advantage of starting a drug discovery programme with small molecules is that they more efficiently sample biologically relevant chemical space than bigger molecules and they have more utility for optimisation. The three-dimensional shape and aromatic character of small molecules are also becoming increasingly important. Increasing the number of aromatic rings decreases aqueous solubility, as well as the observation that highly aromatic molecules have high rates of attrition. Finally, there are undesirable functional groups and substructures that are problematic to drug discovery due to their ability to make a molecule unstable, electrophilic or have a potential for redox chemistry which should be avoided.[14]

The Marsden and Nelson groups have made significant strides towards making small molecules that fall within the lead-like space of which a few will be touched in this review. The groups have developed two approaches towards accessing lead-like scaffolds. They are the bottom-up and top-down approaches discussed below.

### 1.3.2.1 The bottom-up approach to lead-oriented synthesis

The bottom-up approach to LOS is a strategy developed in the Marsden and Nelson groups to make specific classes of small polyfunctionalised substrates that can be cyclised to afford complex and diverse molecular scaffolds using orthogonal reaction toolkits.[29]

Drawing inspiration from the work of Licini[30], Marsden and co-workers[31] demonstrated the bottom-up approach by using α-allyl α-amino acid derivatives as substrates. The amino end was armed with functional groups that can be tuned for cyclisation with either the adjacent ester or alkene functionality. Diversity was also introduced by the choice of the skeletal framework of the amino acid derivative itself. From four amino acids and six pairing reactions, 22 distinct scaffolds were synthesized. A typical example is illustrated below.




*Scheme 6. Illustrating the bottom-up approach to lead-oriented synthesis.*[31]

### 1.3.2.2 The top-down approach to lead-oriented synthesis

The top-down approach to LOS, also developed in the Marsden and Nelson groups, seeks to gain access to complex polycyclic assemblies which can then be broken apart or modified using a toolkit of synthetic methodologies to produce multiple diverse lead-like scaffolds. The complex polycyclic assembly is designed in such a way that it possesses bonds that can be

selectively cleaved and modified. The complexity-generating reaction also has to take place in a single step.[29]

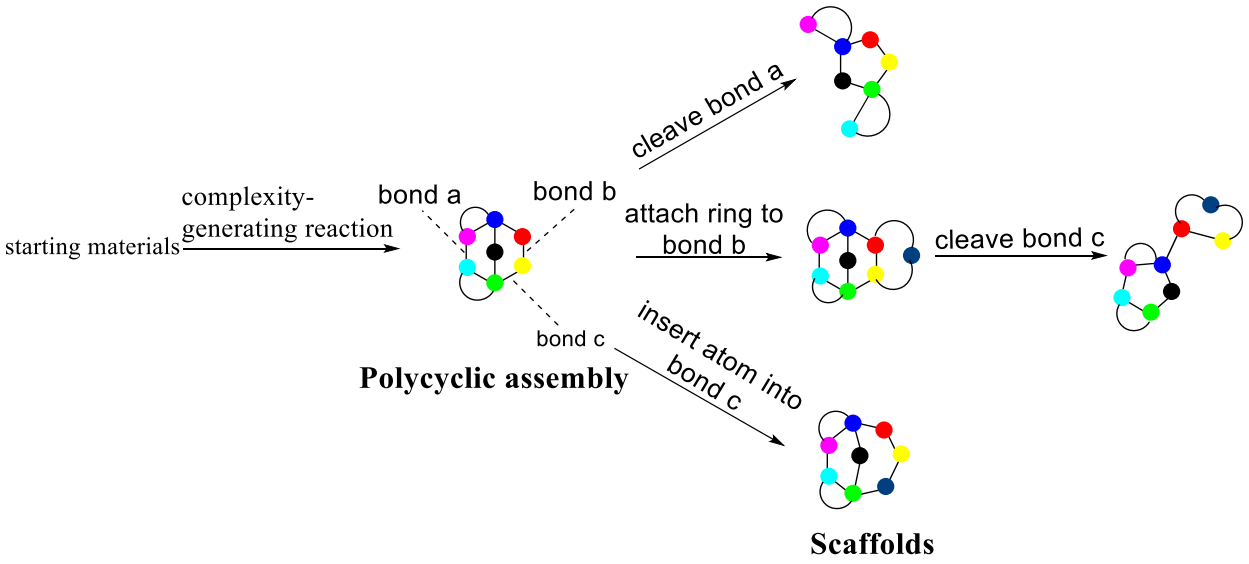
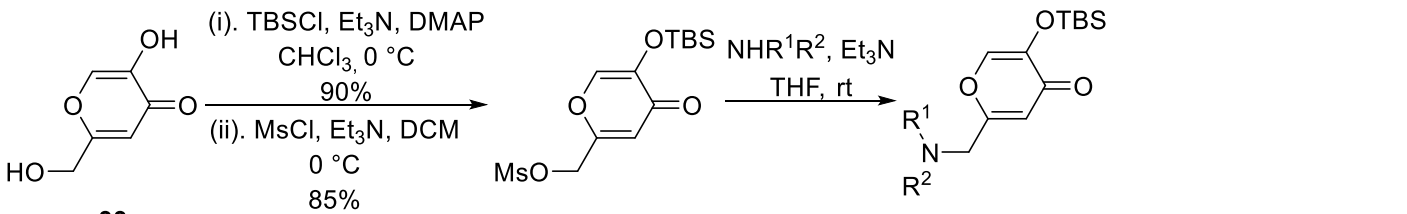



*Figure 4. An overview of the proposed strategy to make a complex polycyclic assembly and the complexity generating illustrations*[29]

Drawing inspiration from the work done by Mascarenas and co-workers[32]; Nelson, Marsden and co-workers[33] made β-alkoxy-γ-pyrones from kojic acid. The β-alkoxy-γ-pyrones were made to undergo [5+2] cycloaddition reactions to generate the scaffold to be used to demonstrate the top down approach to LOS.[29] This is illustrated in the scheme below.



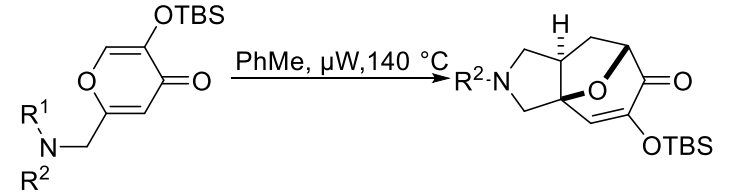

**33**
Kojic acid

**34**

**35** $R^1 = R^2$ = allyl 76%
**36** $R^1$ = allyl, $R^2$ = H 56%
**37** $R^1$ = allyl, $R^2$ = Cbz 29% over 4 steps
**38** $R^1$ = propargyl, $R^2$ = Cbz 18% over 4 steps

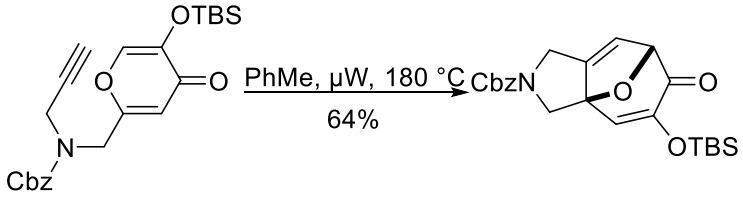
*Scheme 7. Preparation of β-alkoxy-γ-pyrones as starting materials for generating scaffolds to demonstrate the top-down approach to LOS.*[33]

As stated earlier, the intramolecular [5+2] cycloaddition of the β-alkoxy-γ-pyrones generated the scaffolds in good yields as shown in the scheme below.




**35** $R^1 = R^2$ = allyl
**36** $R^1$ = allyl, $R^2$ = H
**37** R1 = allyl, $R^2$ = Cbz

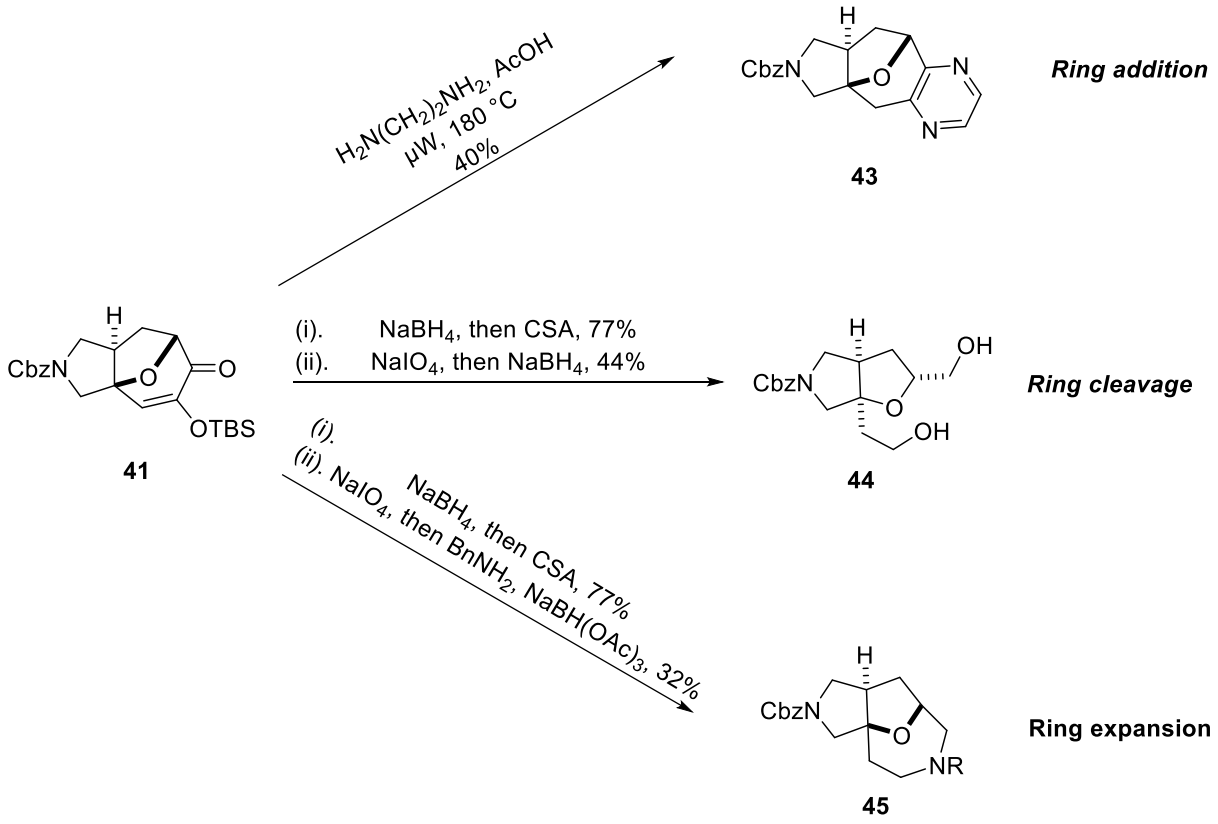
**39** 73%
**40** No reaction
**41** 89%




**38** **42**

*Scheme 8. Synthesis of scaffolds for the demonstration of the top-down approach to LOS*[33]

Demonstrating the top down approach on synthesised scaffolds via ring addition, cleavage and expansion; 52 fragments were made for biological screening.[33] An example of each class of scaffold elaboration is shown in the scheme below.




*Scheme 9. Illustrating the top-down approach using the ring addition, cleavage and expansion strategies*[33]

### 1.3.3 Fragment based drug discovery

Fragment-based drug discovery (FBDD) is an approach that makes use of lower molecular weight (typically 120-250 Da) screening libraries as compared to HTS compound libraries (probably from 250–600 Da).[34] Hits from fragment-based approaches are primarily detected by biophysical methods such as surface plasmon resonance (SPR), protein crystallography and NMR among others, rather than bioassays because of the typically weak inhibition (10 μM–mM) of such hits. Fragment hits are highly suitable for optimisation into drug-like compounds because they possess high ligand efficiency. However, compared to HTS hits, they are simpler, less functionalised and possess lower affinity.[34]

Theoretically, a high quality fragment library samples by far a greater proportion of biologically relevant chemical space than a high quality HTS library as there is an inverse relationship between the molecular complexity of a compound and its probability of possessing good

complementarity with a target protein.[35,36] Therefore fragments in a library will have a high likelihood to sample chemical space as thoroughly as possible thereby forming high quality interactions with the target even if the binding affinity is low. Due to the extensive exploration of chemical space, hit-rates from fragments can be used to determine the chemical tractability of a target.[37] Structure-based drug design (SBDD) is often used in conjunction to help in the design and synthesis of fragments with desirable properties. It also guides the control of molecular properties as fragments are grown into leads.[38,39]

Congreve and co-workers in 2003 proposed that on average, fragment hits obey a 'rule of three (RO3)' which are: molecular weight ≤ 300 Da, the number of hydrogen bond donors and acceptors ≤ 3 respectively and cLogP ≤ 3.[40] The RO3 is still very relevant today. However, other factors have come into play and these are to ensure that fragment libraries: contain pharmacophores that induce binding to biologically relevant chemical space; have appropriate size and shape distribution; contain synthetic handles or growth vectors to aid optimisation; and do not contain groups that are highly reactive or aggregate in solution, examples of which are, pan assay interference compounds (PAINS) and aggregators that constitute problems at high concentrations, during assays.[41–46]

A more elaborate guideline for the chemical characteristics of good fragments was published by Rees and Murray in 2016.[47] The properties highlighted are discussed below.

**Molecular recognition**: Fragments should contain diverse, usually polar groups, for binding to the target protein. It is desirable to express a given binding pharmacophore in different chemotypes. It is also important for fragments to possess multiple synthetically accessible vectors for fragment growth in three dimensions in order to investigate new binding interactions.[47]

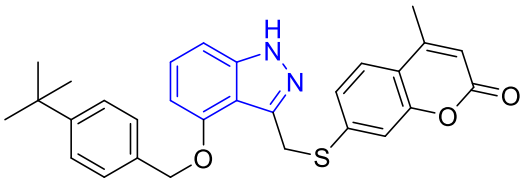
**Physicochemical properties**: The molecular weight of fragments should be between 140 – 230 $gmol^{-1}$, the non-hydrogen atoms should be between 10 – 16 and the lipophilicity (clogP) should be between 0.0 – 2.0. They also have to possess properties required for biophysical screening at high concentrations – the aqueous solubility should preferably be more than or equal to 5 mM

in 5% DMSO, or other screening co-solvents and should not possess highly reactive groups or groups that can aggregate in solution.[47]

**Synthetic tractability and shape**: Fragments should be synthetically tractable at 50 – 100 mg scale and can be made in not more than 4 steps from commercially available reagents. They should possess a variety of 3-dimensional shapes for each scaffold and pharmacophore; the number of freely rotatable bonds should be between 0 and 3 and the number of chiral centres should be between 0 and 1, sometimes 2.[47]

As a result of the size range of HTS hits, the hit-rates are often low and many of the hits do not progress to optimisation.[48,49] In the same vein, some of the initial drug-like properties of HTS hits may be lost or reduced when optimized, thereby reducing the scope of developability.[50–52] FBDD aims to solve the problem of poor hit-rates from HTS campaigns as well as improving optimisation to drug-like compounds. More than 26 protein targets have been investigated by fragments.[53,54] A typical example of the usefulness of FBDD is discussed below.

HTS screens to identify compounds that bind to the ATP site of the bacterial enzyme DNA gyrase proved unsuccessful.[55] However, over a dozen fragments were identified as needle-hits (or fragment hits) binding to the same target by using a high concentration bioassay screening technique. The screening methodology was validated by biophysical methods such as NMR, SPR and X-ray crystallography. Indazole, highlighted in blue in *Figure 5*, was one of the fragment hits. Selected needle hits binding to the same target were used to obtain 3-D structural information which proved to be a useful optimisation guide that gave the lead compound **46** that is more than 10,000 times as active as the indazole fragment.[34]




**46**

*Figure 5. Lead compound obtained from fragment-based methods with the starting fragment in blue*

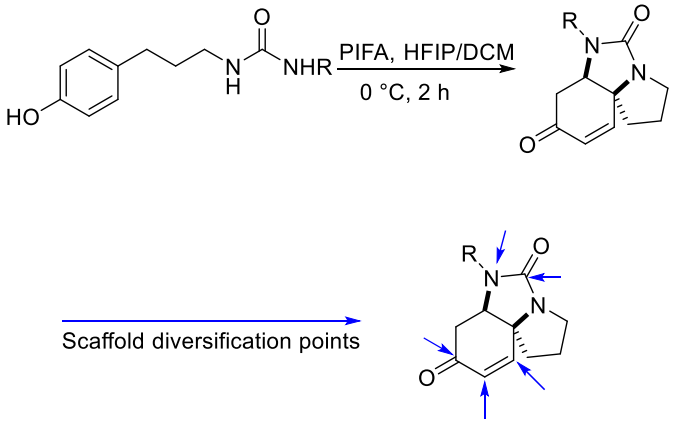
In recent times, it has been stated that FBDD has been used less systematically in academia. Therefore a call has been made for a deeper collaboration between players in industry and academia so that industrial discoveries will not be reinvented.[41]

## 1.4 Aim and objectives of the project

The aim of the project was to prepare and decorate complex and diverse molecular scaffolds for hit identification and optimisation through the top-down approach to lead-oriented synthesis.

The objectives of the project were:

i. To make the complex polycyclic assembly (primary scaffold) to be used as a starting point for the implementation of the top-down strategy to lead-oriented synthesis. The primary scaffold was to be made from a multistep sequence of which the final step is illustrated below. Also, some of the points of diversification for a potential demonstration of the top down approach to LOS are illustrated with the blue arrow.




*Scheme 10. Synthetic route for scaffold to be used to demonstrate the top-down approach to LOS*

ii. To modify the complex polycyclic assembly to generate multiple diverse lead-like scaffolds. The primary scaffold was to be used to generate secondary scaffolds through ring addition, cleavage and expansion as shown below.

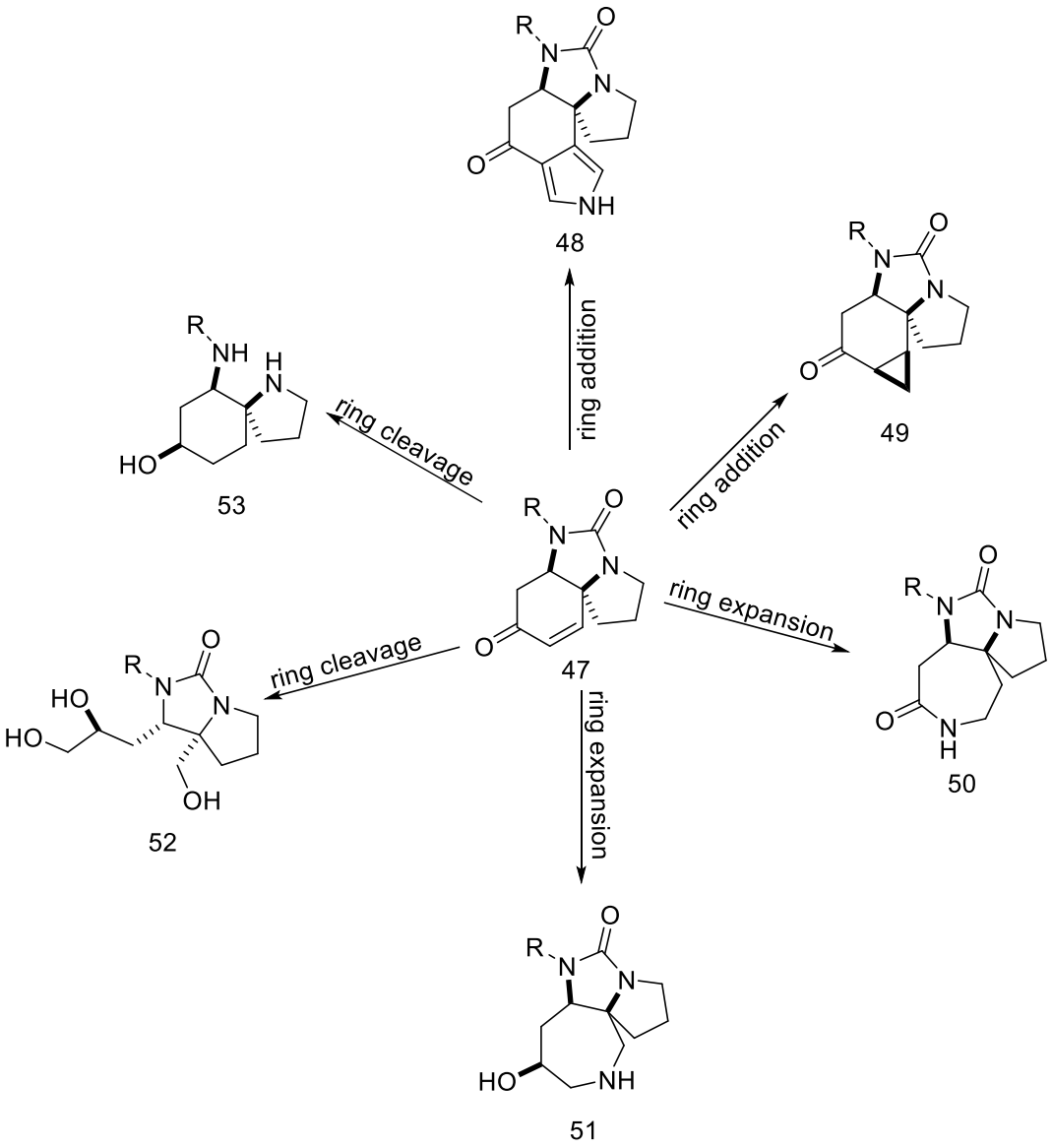
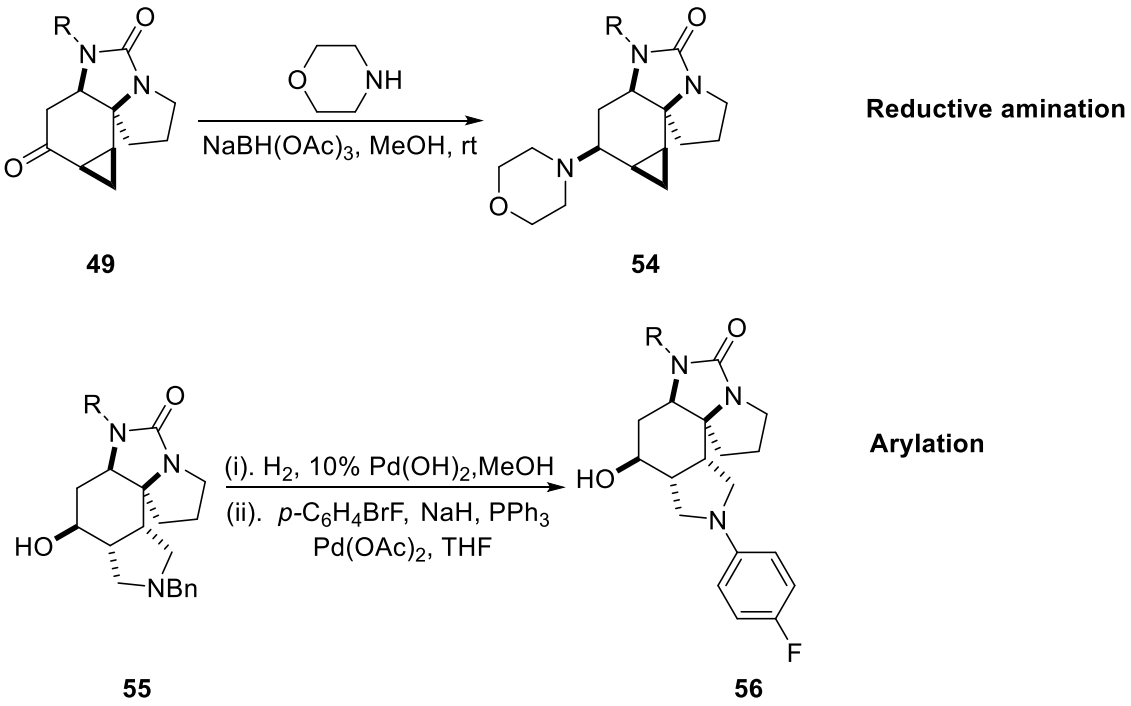



*Figure 6. Potential diversification reactions for demonstrating the top-down approach to LOS*

iii. To decorate the lead-like scaffolds prepared in (ii) with exemplar medicinal chemistry capping groups to give about 50 final compounds for biological screening. Some of the decoration reactions are alkylation, reductive amination and amidation among others.The molecular properties of these compounds will be assessed by LLAMA, a lead-likeness computational software developed within the Marsden and Nelson groups[56], to ensure they are in the lead-like space. Two examples are illustrated in the scheme below.



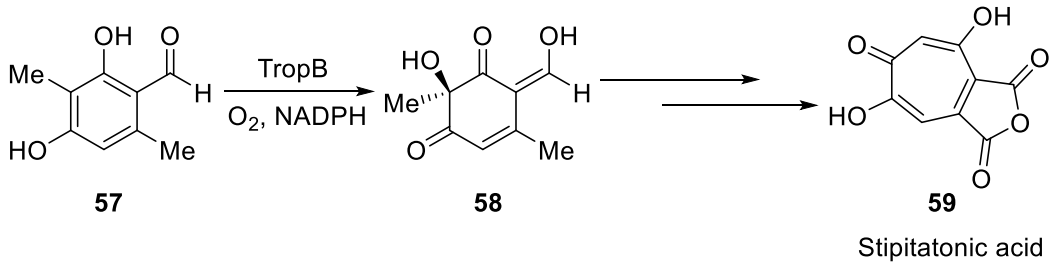

*Scheme 11. Exemplar decoration reactions for secondary scaffolds generated from the top-down approach to LOS*

# 2.0 Results and discussion 1

## 2.1 Dearomatisation

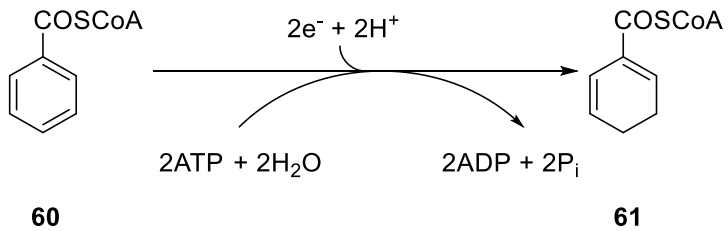
Enzymatic dearomatisation reactions are known in nature. They can either proceed via oxidative mechanism (by the use of oxygenases) or reductive mechanism (by the use of reductases).[57–60] However, there are chemoenzymatic[61] or completely chemical means of making arenes or their derivatives lose aromaticity.[57]

An example of a biocatalysed (regio- and stereoselective) oxidative dearomatisation by the use of the enzyme TropB is shown below. This step is important in the biosynthesis of the tropolone-based stipitatonic acid.[62–64]




*Scheme 12. Enzymatic oxidative dearomatisation towards the biosynthesis of stipitatonic acid*[62]

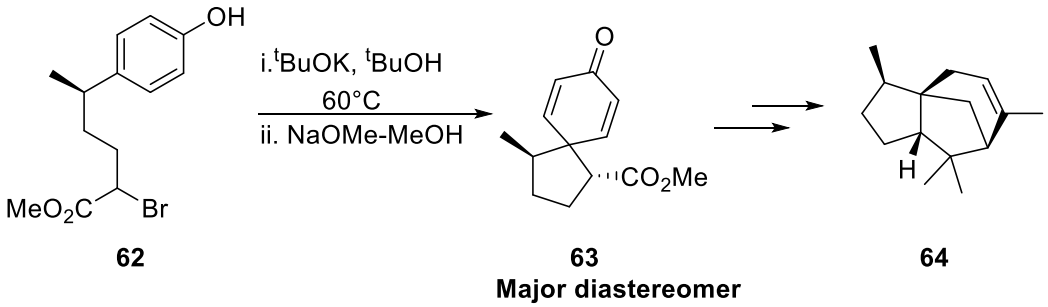
Also, under anaerobic conditions, benzoyl CoA redutase (BCR) found in the bacteria *T. aromatica* is known to catalyse the Birch-like dearomatisation of benzoyl CoA **60** to cyclohexa-1,5-diene-1-carbonyl-CoA **61.** Ferredoxin serves as the donor of the two electrons that are transferred to the aromatic ring as shown below**.**[65]




*Scheme 13. Enzymatic reductive dearomatisation of benzoyl CoA*[65]

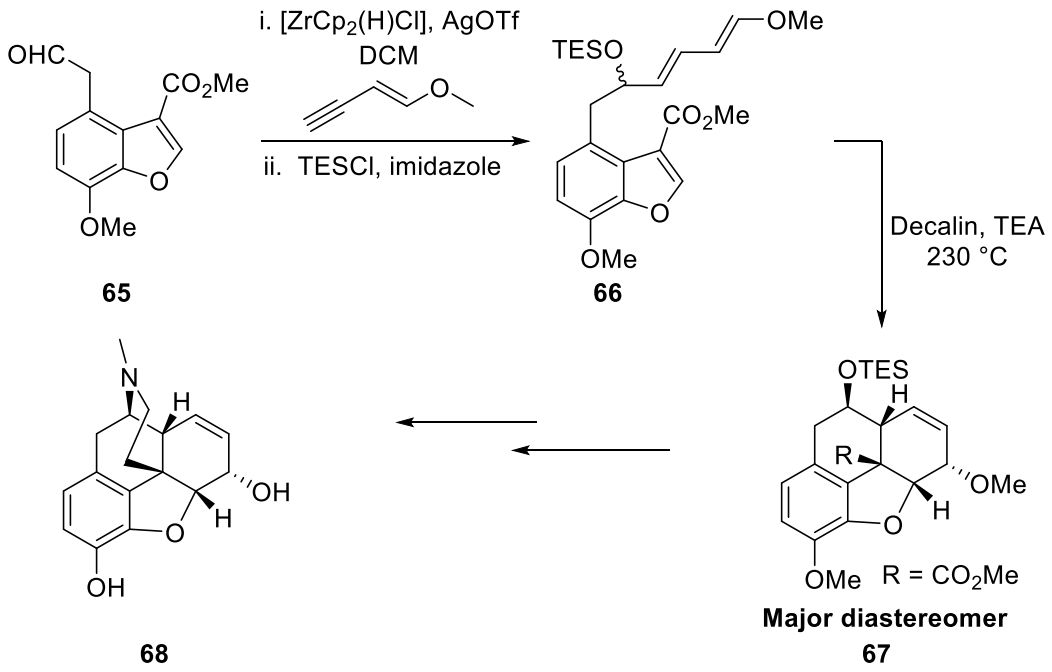
Dearomatisation leads to highly reactive intermediates which can spontaneously form carbon-carbon and carbon-heteroatom bonds; or result in cascade reactions, and cycloadditions.[57] Therefore, it is a powerful tool for accessing complexity and diversity from relatively simple aromatics or heteroaromatics. It has been recognised as a bridge between rich sources of aromatic hydrocarbons and the alicyclic skeletons frequently found in bioactives.[66–71] Two examples demonstrating the use of dearomatisation as a complexity-generating step in total synthesis are discussed below.

Subjecting the phenol **62** to deprotonation, Corey and co-workers[72] synthesised cedrene **64**, via alkylative dearomatization as a key complexity-generating step as shown in *Scheme 14*.




*Scheme 14. Illustration of dearomatisation towards the synthesis of cedrene*[57]

Schulte and co-workers[73] took advantage of the same concept in their synthesis of morphine **68**. Hydrozirconation of the alkyne followed by addition to the aldehyde **65**, and subsequent protection of the resulting alcohol, gave the silyl ether **66** which was then subjected to a crucial dearomatisation reaction (via an intramolecular 4+2 cycloaddition) to give the teracyclic compound **67** that was pertinent to the synthesis of the target molecule.

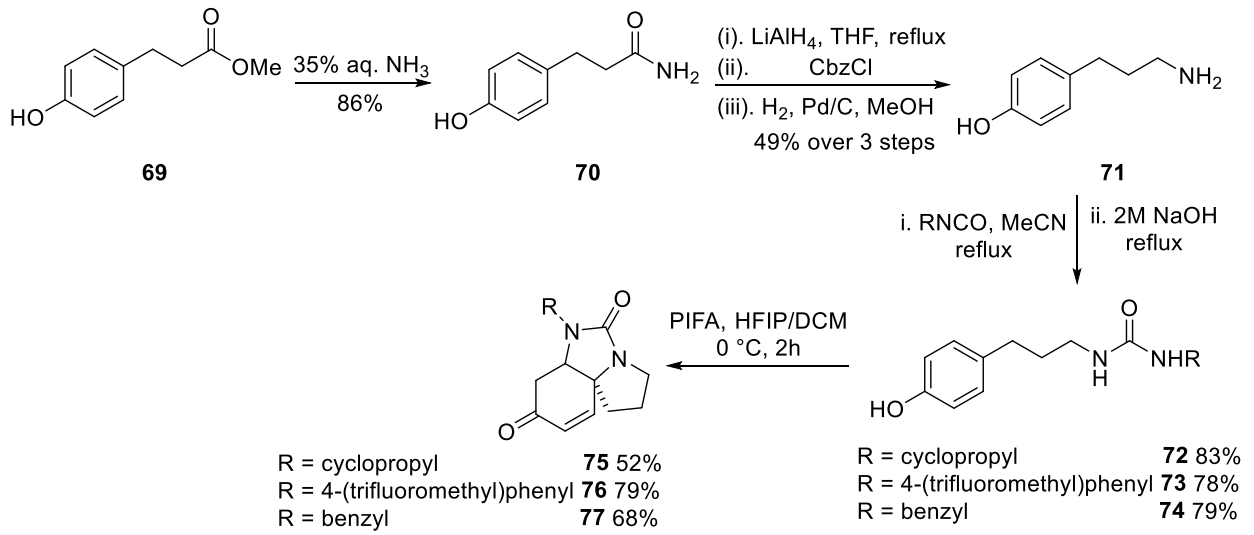



*Scheme 15. Illustration of dearomatisation towards the synthesis of morphine*[57]

Oxidative dearomatization, via a hypervalent iodine reagent, was employed for the complexity-generating step in the synthesis of the key scaffold used in this project to demonstrate the top-down approach to lead-oriented synthesis as shown in *Scheme 10*.

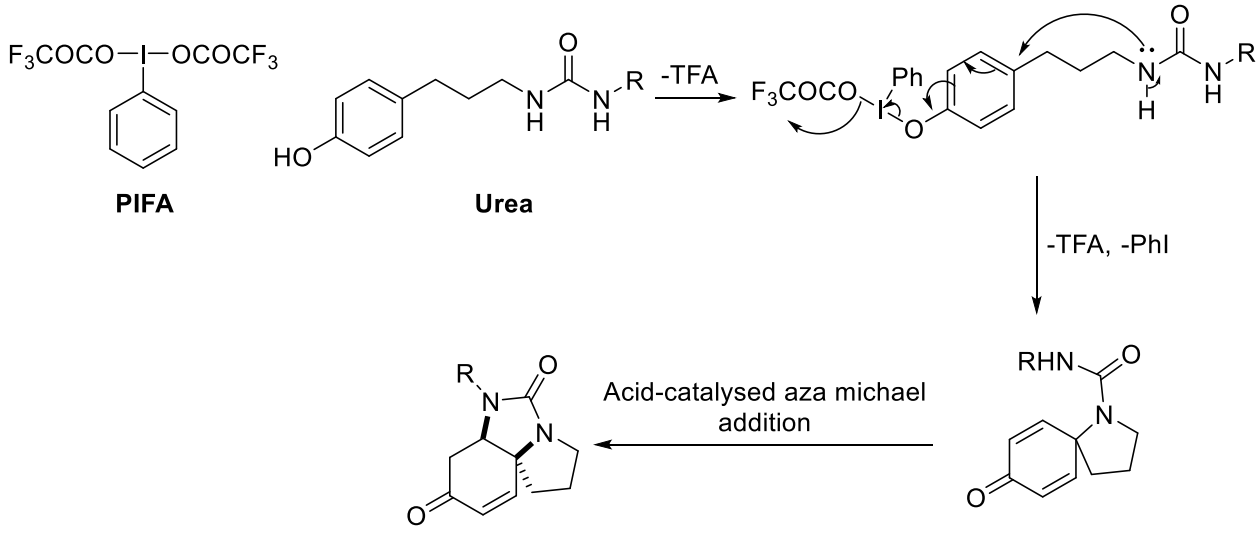
## 2.2 Complexity-generating reactions for the key scaffold for LOS

The primary scaffold used to demonstrate the top-down approach to lead-oriented synthesis in this work was made in the Marsden and Nelson groups and added to the European Lead Factory Joint Compound Library.[74] The route used to access the scaffold is shown below.




*Scheme 16. Discovery route for scaffold to be used to demonstrate the top-down approach to LOS*

Ammonolysis of the ester **69** gave the amide **70** which was then reduced with lithium aluminium hydride, protected and hydrogenated to afford the key amine **71** relevant to the synthesis of the scaffold. The amine **71** was reacted with different isocyanates to give ureas that were utilised in making variants of the scaffold (**75**-**77**) upon treatment with PIFA, as shown in the proposed mechanism below.




*Scheme 17. Proposed mechanism for the synthesis of key scaffold*

Some of the decorations that had been carried out on the scaffold (with the decoration points indicated in red) are shown below (unpublished results).

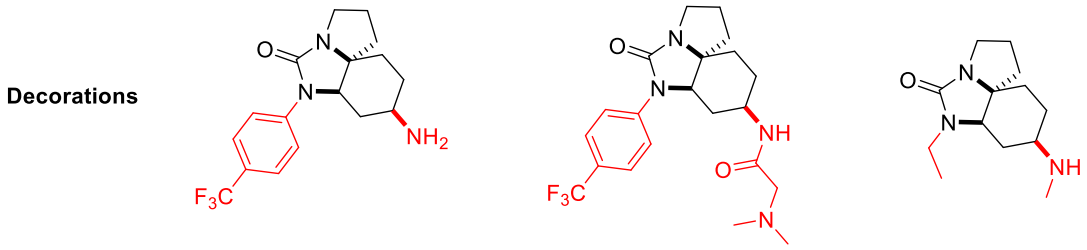
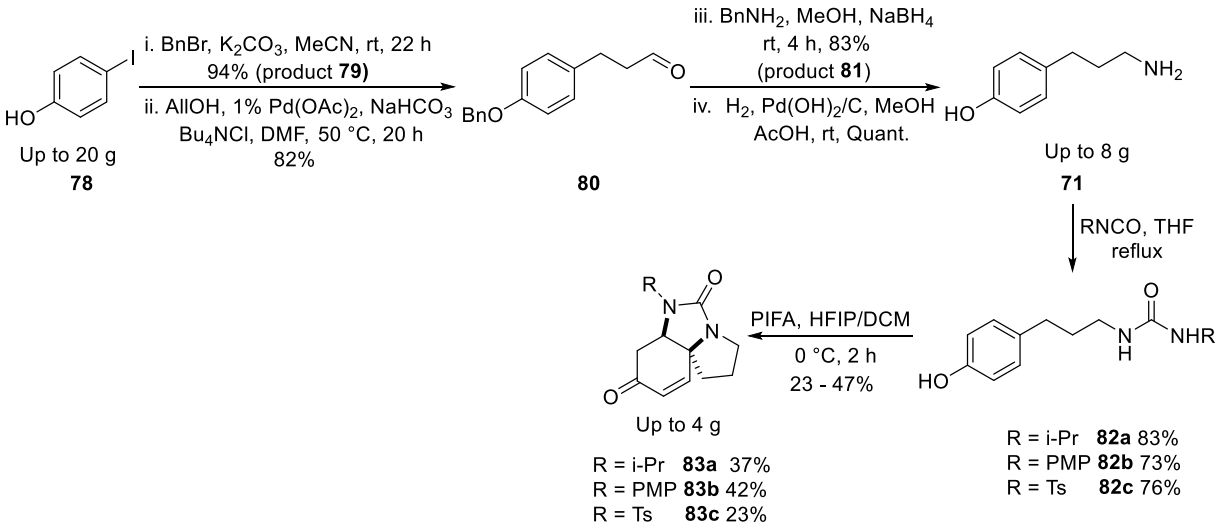



*Figure 7. Decorations carried out on the scaffold obtained via oxidative dearomatisation*

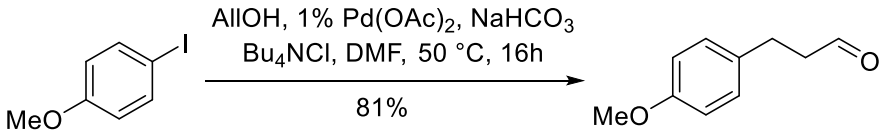
The scaffold has two fused rings, two spirocyclic rings, a cyclic urea, an enone functionality and two stereocentres. Hence, it is a starting point of good quality for lead-oriented synthesis. Accessing the key precursor of the scaffold in large amounts is crucial to the project. Therefore, we had to develop an alternative route to the key amine **71** via a key aldehyde **80.** Compound **80** was obtained through the Heck reaction of the aryl iodide **79** with allyl alcohol. We envisioned transforming **80** to **71** to avoid the risk of using lithium aluminium hydride in the synthesis of **71** on a large scale (see *Scheme* 16). The opted route to the amine **71** and the scaffold is depicted below.




*Scheme 18. Optimised synthesis of scaffold through a key Heck reaction*

Heck reaction[75] is a typical cross-coupling reaction that can allow the formation of carbon-carbon bonds between alkenes and; aryl, benzyl and styryl halides via palladium(0) catalysis. It works well with a wide range of substrates and it is known to give aldehydes and ketones as products when aryl halides are reacted with allyl alcohols under suitable conditions.[76,77] A known drawback of intermolecular Heck reactions is that it requires high temperatures (about 100 °C) to take place. Therefore, Jeffery developed a set of conditions[77,78] that would enable the formation of products at milder temperatures (room temperature to 30 °C), using tetrabutylammonium chloride as a solid-solution phase transfer agent. This extends the scope of the reaction to substrates that are thermally unstable such as methyl vinyl ketone and acrolein.

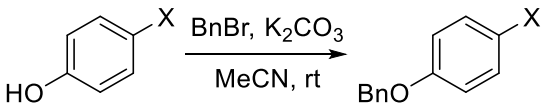
In their development of a catalyst system for alkyne metathesis and its application to the synthesis of natural products, Furstner and co-workers[79] took advantage of the 'Jeffery conditions' to make the aldehyde **85** after performing a Heck reaction between 4-iodoanisole **84** and allyl alcohol as shown below.




**84** **85**

*Scheme 19. Heck reaction of 4-iodoanisole with allyl alcohol*[79]

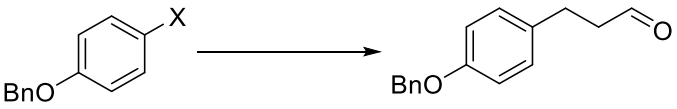
Based on the precedent above (*Scheme 19*), 4-iodophenol **78** and 4-bromophenol **86** were benzylated to give the ethers **79** and **87** respectively in preparation for Heck reaction with allyl alcohol.




X = I **78** X = I **79** 94%
X = Br **86** X = Br **87** 96%

*Scheme 20. Benzylation of 4-iodophenol and 4-bromophenol*

Attempts to make the key aldehyde **80** using the protected halophenols **79** and **87** are summarized in the table below.



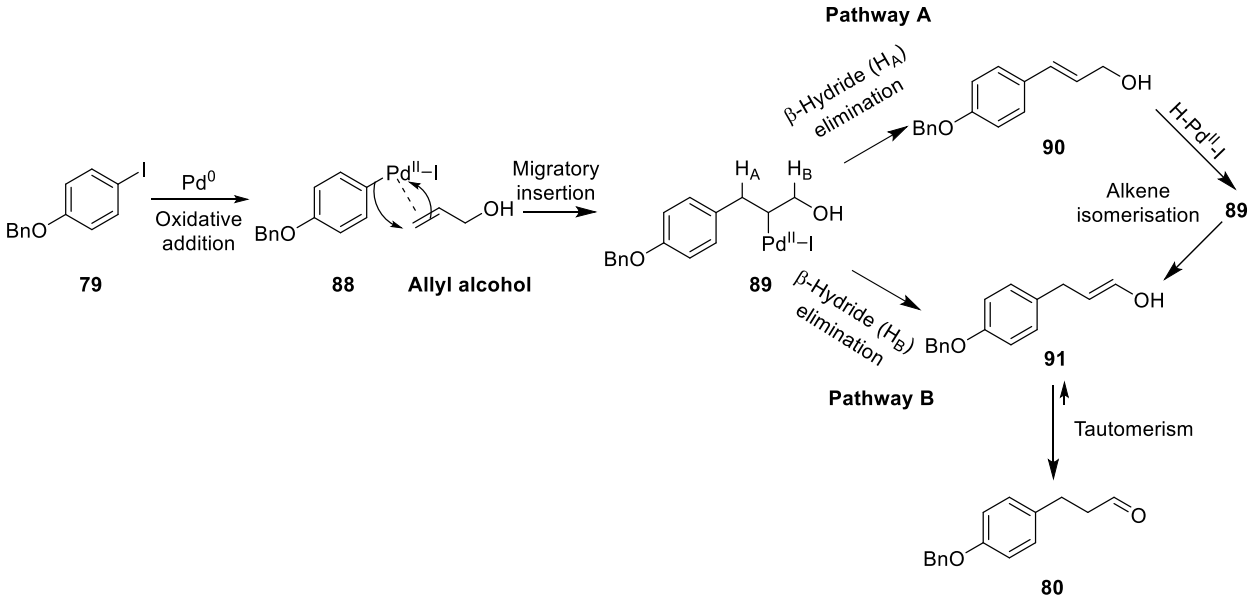

X = I **79**
X = Br **87**

**80**

| Entry | Compound | Reaction conditions | Outcome |
|---|---|---|---|
| **1** | **87** | AllOH (1.5 eq.), 1% $Pd(OAc)_2$, $Bu_4NCl$ (1.0 eq.), $NaHCO_3$ (2.0 eq.), DMF, 50 - 90°C, 43.5 h | No reaction. Starting material detected by TLC and proton NMR of the crude reaction mixture |
| **2** | **87** | AllOH (1.1 eq.), 5% $Pd(OAc)_2$, 10% P-(*o*-Tol)$_3$, $Et_3N$, 110 °C, 17 h | Unknown mixture monitored by TLC and proton NMR |
| **3** | **79** | AllOH (1.1 eq.), 5% $Pd(OAc)_2$, 10% P-(*o*-Tol)$_3$, $Et_3N$, 110 °C, 17 h | Unknown mixture monitored by TLC and proton NMR |
| **4** | **79** | AllOH (1.5 eq.), 1% $Pd(OAc)_2$, $Bu_4NCl$ (1.0 eq.), $NaHCO_3$ (2.0 eq.), DMF, 90 °C, 21 h | Unknown mixture as monitored by TLC and proton NMR |
| **5** | **79** | AllOH (1.5 eq.), 1% $Pd(OAc)_2$, $Bu_4NCl$ (1.0 eq.), $NaHCO_3$ (2.0 eq.), DMF, 50 °C, 20 h | 20:1 molar ratio of desired product to its branched isomer respectively as deduced from the proton NMR of the crude mixture. The aldehyde **80** was isolated in 82% yield. |

*Table 2. A table showing the results of the Pd-coupling between allyl alcohol and, compounds **87**and **79**respectively under different conditions*

The proposed mechanism for the Heck reaction between the protected 4-iodophenol and allyl alcohol under 'Jeffery conditions' is shown below.




*Scheme 21. Proposed mechanism for the Heck reaction between the aryl iodide **79** and allyl alcohol*

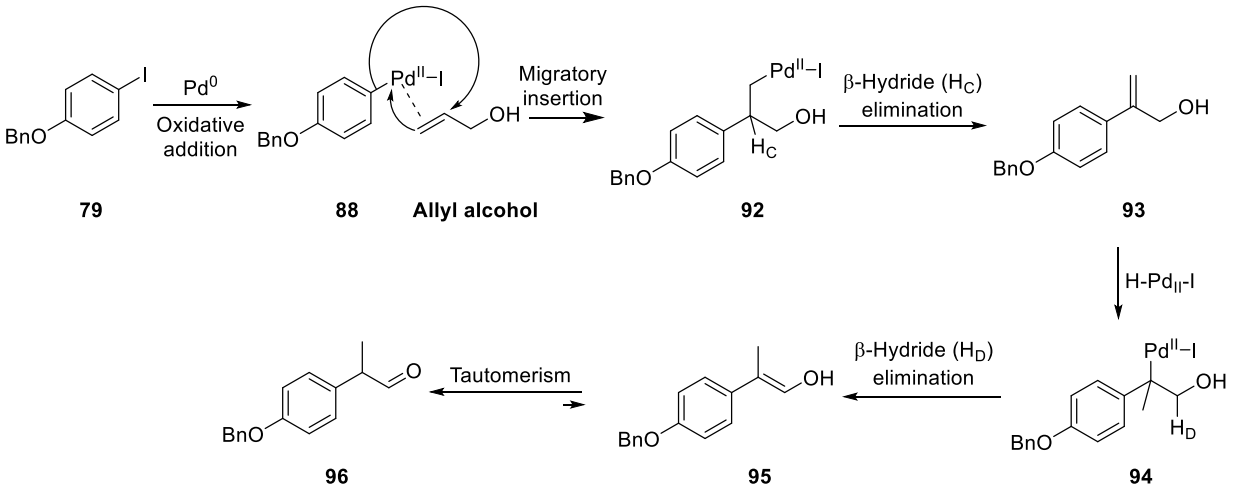
The palladium (0) undergoes oxidative addition to the aryl iodide **79** to form the σ-arylpalladium (II) complex **88** in the first step. The complex **88** then coordinates with the double bond of allyl alcohol for syn-insertion into the alkene to generate the σ-alkylpalladium(II) complex **89**.The complex **89** then undergoes β-hydride elimination to give either the allylic product **90** or the enol **91** in the third step. The enol **91** once formed, tautomerises to the more thermodynamically stable aldehyde **80**.[80–82]

Selectivity in this case can be determined by the hydricity of $H_A$ and $H_B$ (see *Scheme 21*). Since $H_A$ is in principle more hydridic than $H_B$, the major product obtained via β-hydride elimination, is expected to be the aryl-substituted allylic alcohol **90**. However, the β-hydride elimination step is a reversible process which can lead to the re-insertion of the eliminated H-$Pd^{II}$-I species into the allylic double bond of **90**, thereby enhancing isomerisation to the enol **91**. Another factor that favours the formation of the enol **91** is the fact that the lone pairs on the oxygen atom of the alcohol **89** stabilise the consequent partial positive charge on the neighbouring

carbon atom when $H_B$ is eliminated. Sodium bicarbonate is used for the reductive elimination of the H-$Pd^{II}$-I species in order to turn over the catalyst.[80,81]

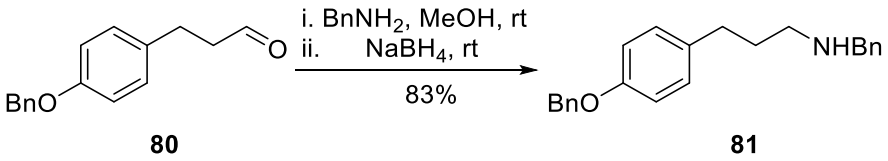
However, Jeffery developed another set of conditions[83] to achieve selectivity in obtaining the substituted allylic alcohol such as **90** as the major product instead of the aldehyde. This involves the use of silver carbonate or silver acetate instead of sodium bicarbonate for the reductive elimination step. Palladium acetate and triphenylphosphine are also needed in catalytic amounts. The silver ion ($Ag^+$) is known to be a good trap for hydrohalic acids.[84–87] Therefore, silver salts prevent the re-insertion of H-$Pd^{II}$-X (where X is a halogen) into an alkene such as **90** and this in turn prevents isomerisation.

Also, from the proton NMR of the crude product, the molar ratio of the aldehyde **80** and its branched isomer **96** is 20:1 respectively. This supports the alkene isomerisation mechanism and also shows that the migratory insertion step can pose problems to selectivity as shown below. The aldehyde **96** was isolated and characterized by both proton and carbon-13 NMR. Neither the allylic alcohol **90** nor **93** was detected in the proton NMR of the crude product.



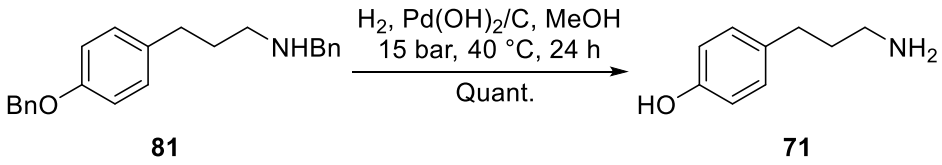

*Scheme 22. Proposed mechanism for the formation of the contaminant aldehyde **96** in the Heck reaction between the aryl iodide **79** and allyl alcohol*

Reductive amination of the aldehyde **80** with benzylamine to give the secondary amine **81** was facile as shown below.




*Scheme 23. Synthesis of the precursor to the key amine **71***

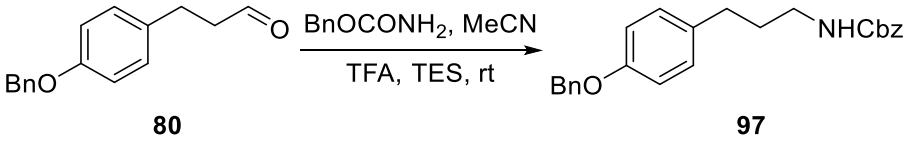
Subjecting **81** to double debenzylation via hydrogenation to give the key amine **71** using Pd/C as catalyst was sluggish. Only the mass of the mono-debenzylated product was detected by LCMS, even after adding acetic acid to the reaction system to prevent catalyst poisoning by the amino group.[88] Using $Pd(OH)_2/C$ as catalyst instead of Pd/C in the presence of AcOH, the desired product was obtained (see *Scheme 18*). As stated earlier, accessing the key amine **71** in large amounts was crucial to the project. However, the hydrogenation of the secondary amine **81** on an 800 mg to 3.8 g scale took two days to reach completion but it took five days on a 13 g scale when telescoped from **80** without purification of the intermediate **81**. This problem was solved by carrying out the hydrogenation step under pressure at 15 bar and 40 °C as shown below. The double debenzylation of 15 g of **81** was then accomplished in 24 h.




*Scheme 24. Accelerated synthesis of the key amine **71***

The primary amine **71** was then reacted with different isocyanates to give the different ureas **82a-c** (see *Scheme 18*).

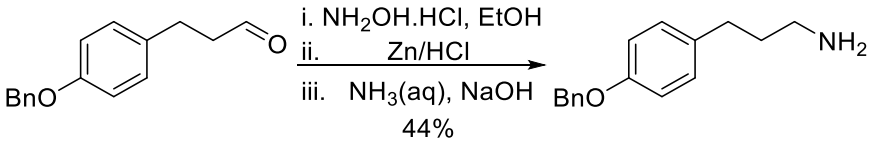
Other methods to synthesise key precursors of the primary scaffold were also investigated. One of such was the attempted reductive alkylation of carbamates and subsequent deprotection, as demonstrated by Dube and Scholte.[89] Benzyl carbamate was reacted with the aldehyde **80** as illustrated in the scheme below. The mass of the intended product **97** was detected by LCMS but was not successfully isolated.




**80** **97**

*Scheme 25. Attempted alkylation of benzyl carbamate with the key aldehyde **80**.*

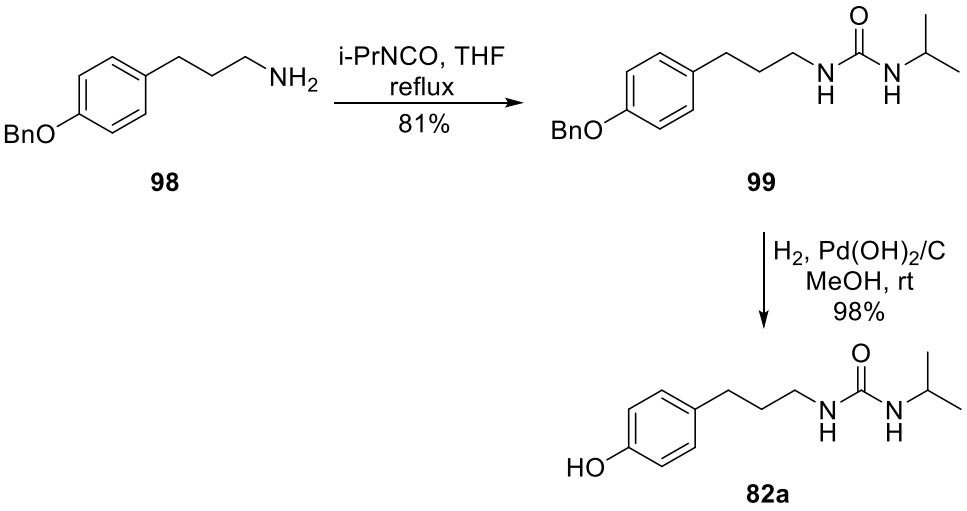
Another method considered was the synthesis of primary amines from one-pot reductive amination of aldehydes via oximes as demonstrated by Delmas and co-workers[90] As shown in *Scheme 26* below, oximation of the aldehyde **80** with hydroxylamine followed by metal-in-acid reduction afforded the amine **98** in 44% yield.




**80** **98**

*Scheme 26. Synthesis of an alternative primary amine as a key precursor of the primary scaffold*

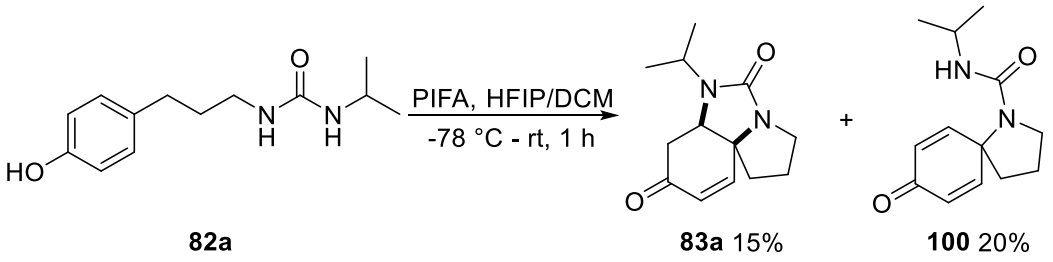
The amine **98** was then reacted with isopropyl isocyanate towards the synthesis of the urea **82a** as shown below.




**98** **99** **82a**

*Scheme 27. Alternative route to the synthesis of the urea **82a***

The ureas **82a-c** were then used for the oxidative dearomatisation step to make variants of the primary scaffold **83a-c** (see *Scheme**18***). In an attempt to optimise scaffold synthesis, PIFA dearomatisation was carried out with the urea **82a** at -78 °C. Only the mass of the starting material was observed by LCMS. However, upon allowing the reaction to warm up to room temperature for 1 h, both the scaffold **83a** and the intermediate **100** were isolated in 15% and 20% yields respectively. This supports the mechanism mentioned earlier (see *Scheme 17*).




**82a** **83a** 15% **100** 20%

*Scheme 28. Attempted optimisation of primary scaffold synthesis*

The expected stereochemical outcome for the primary scaffold is the *cis*-ring fusion based on previous work[74] and the likely energetic preference for this over a trans-fused 6,5-ring system. We confirmed this in the case of the tosyl derivative of the scaffold by x-ray crystallography as shown in *Figure 7*.

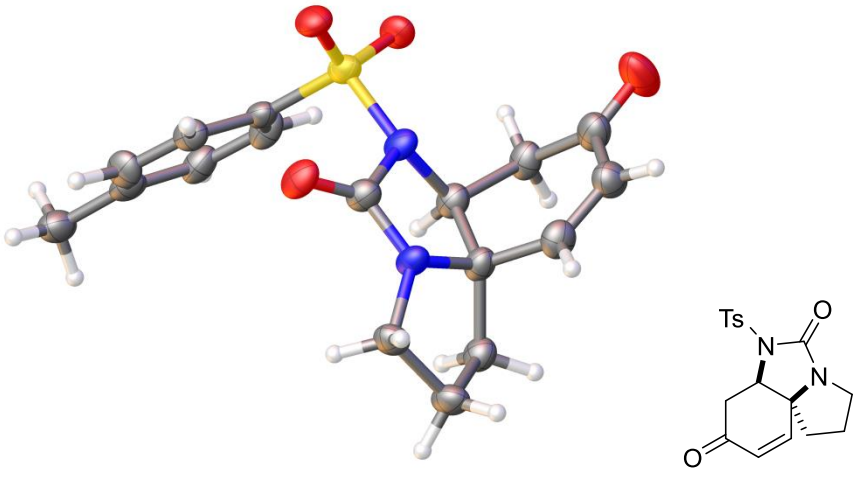
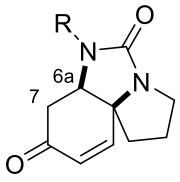



*Figure 7. X-ray crystal structure of the tosyl variant of the primary scaffold*

Comparatively, the PMP and isopropyl derivatives of the primary scaffold were obtained in higher yields than the tosyl derivative. This is presumably because amines are more nucleophilic than sulfonamides and therefore will serve as better Michael donors in the PIFA dearomatisation step (see *Scheme 17*).

In order to determine the solution conformation of the variants of the primary scaffold, *J* values were looked at as depicted in table 1 below. However, the values are not consistent with truly axial/axial and axial/equatorial couplings, and therefore cannot be used to deduce the solution conformation of the variants of the primary scaffold.



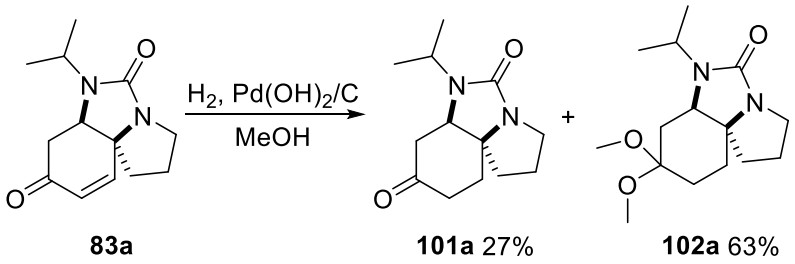

| **Entry** | **Multiplicity/*J*values in Hz for proton 6a** | **Multiplicity/*J*values in Hz for proton 7-$H_A$** | **Multiplicity/*J*values in Hz for proton 7-$H_B$** |
|---|---|---|---|
| **R = i-Pr** | dd, *J* = 6.9, 5.3 | dd, *J* = 16.1, 5.2 | dd, *J* = 16.1, 6.9 |
| **R = PMP** | t, *J* = 5.1 | dd, *J* = 16.6, 5.0 | dd, *J* = 16.6, 5.2 |
| **R = Ts** | dd, *J* = 8.8, 5.8 | dd, *J* = 15.9, 5.7 | dd, *J* = 15.9, 8.8 |

*Table 1. Multiplicities and coupling constants for key protons of the primary scaffolds for LOS*

## 2.3 Double bond reduction ofenone scaffolds

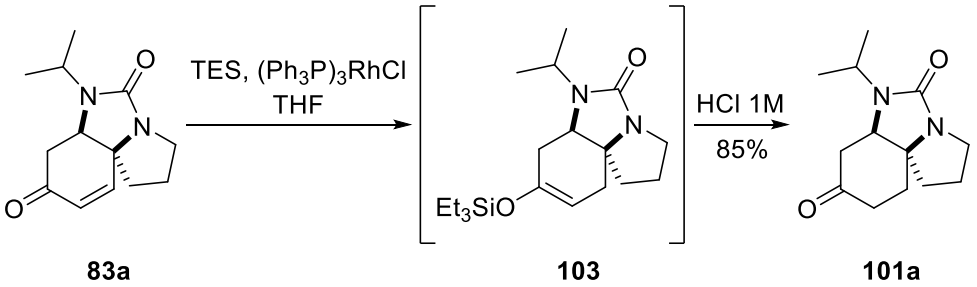
Reducing the double bonds of the scaffolds **83a-c** to the corresponding saturated ketones is desirable because they can either be utilised in making secondary scaffolds with distinct molecular skeletons, or making final compounds for biological screening.

Hydrogenation of the isopropyl derivative of the scaffold **83a** in methanol using $Pd(OH)_2/C$ as catalyst gave a mixture of the ketone **101a** and the acetal **102a** as shown below. Carrying out the same reaction in ethyl acetate instead of methanol, only the mass of the starting material was observed by LCMS.



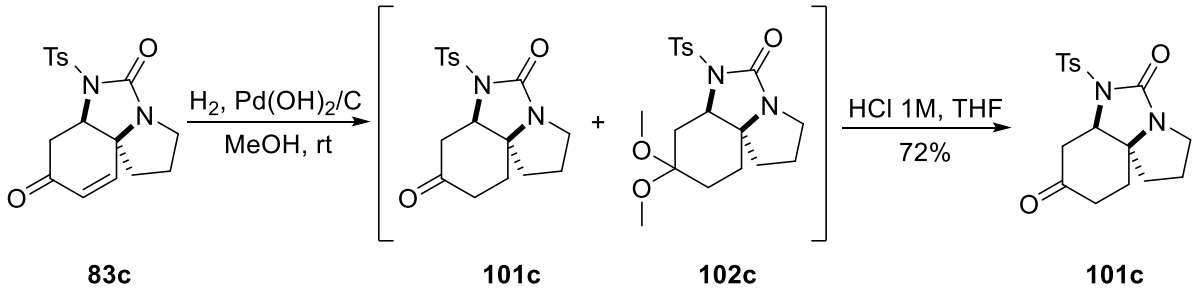

*Scheme 18. Hydrogenation of the isopropyl variant of the primary scaffold*

However, performing a metal-catalysed hydrosilylation and subsequently hydrolysing the resulting silyl enol ether **103** with 1M HCl afforded the ketone **101a** in 85% yield over two steps. The silyl enol ether **103** was isolated in 85% yield and characterised. However, in all cases, the reaction was telescoped, without further purification, to the ketone **101a**.




*Scheme 19. Synthesis of the ketone of the isopropyl variant of the primary scaffold via hydrosilylation*

In the same vein, hydrogenation of the tosyl variant of the primary scaffold **83c** in methanol gave a mixture of both the ketone **101c** and the acetal **102c** as deduced from the analysis of the proton NMR of the crude product. Subjecting the crude product to acid hydrolysis in THF gave the ketone **101c** in 72% yield over two steps. The crystal structure of **101c** is shown in *Figure 8*.




*Scheme 20. Synthesis of the ketone of the tosyl variant of the primary scaffold*

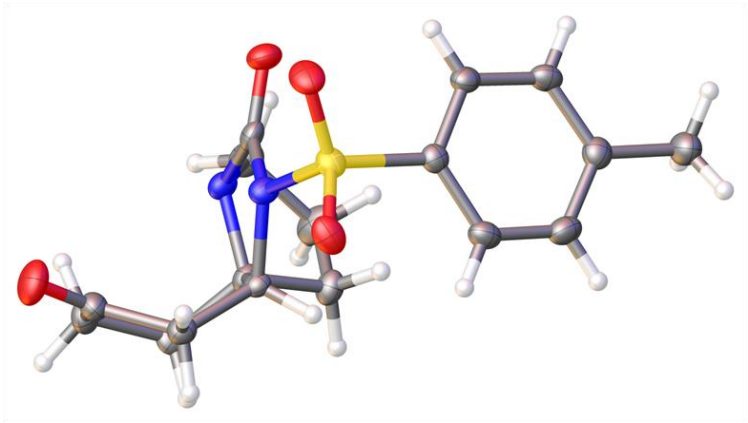
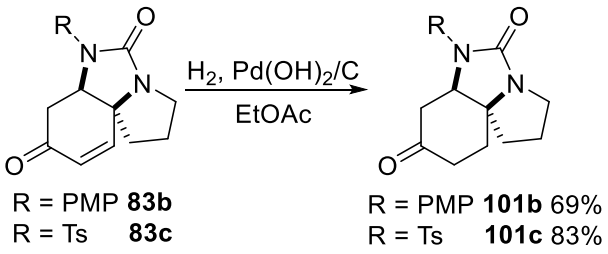


*Figure 8. X-ray crystal structure of theketone **101c***

The chair conformation is known to be more energetically stable for cyclohexane and cyclohexanone rings than the boat form. However, the carbonyl group in cyclohexanone rings is known to considerably lower the energy of the boat conformer with respect to the chair conformer.[91–94] In the crystalline state, the cyclohexanone ring of **101c** prefers the boat conformation as shown above.

Also, it was observed that hydrogenation of the PMP variant of the scaffold **83b** and the tosyl variant of the scaffold **83c** in ethyl acetate using $Pd(OH)_2/C$ as catalyst gave the corresponding ketones in 69% and 83% yields respectively. As stated earlier, hydrogenating the isopropyl variant of the scaffold **83a** under the same conditions was not successful. It could be that **83a** is not soluble enough in ethyl acetate to be hydrogenated in the same medium.

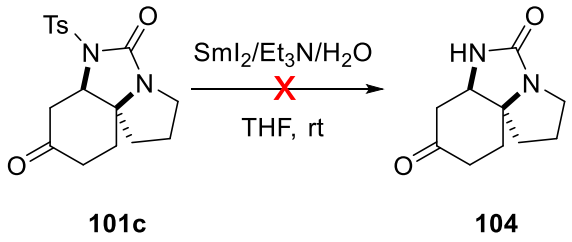



*Scheme 21. Hydrogenation of the PMP and Ts variants of the primary scaffold in ethyl acetate*

## 2.4 Attempted deprotection of the ketone of the tosyl and PMP variants of the primary scaffold

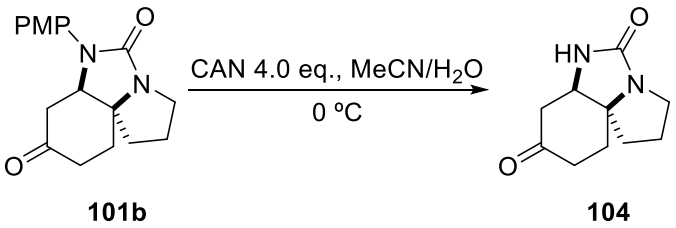
The ketones **101b** and **101c** were sought to be deprotected (removal of the –R group) to afford the secondary urea nitrogen for functionalization with exemplar medicinal chemistry capping groups.

Inspired by the work of Ankner and Hilmersson[95], **101c** was subjected to radical deprotection by exposing it to $SmI_2$ in the presence of triethylamine and water. Only the mass of the starting material was observed by LCMS.




*Scheme 22. Deprotection of the ketone of the tosyl variant of the key scaffold*

However, exposing **101b** to CAN gave the desired product **104** although there were difficulties with respect to reproducibility in terms of yield (14 – 95%) on a scale of 13 – 20 mg. The crystal structure of **104** is shown in *Figure 9.* The cyclohexanone ring of **104** adopts the boat conformation similar to that adopted by the cyclohexanone ring of **101c** (see *Figures 8* and *9*).




**101b** **104**

*Scheme 23. Deprotection of the ketone of the PMP variant of the key scaffold*

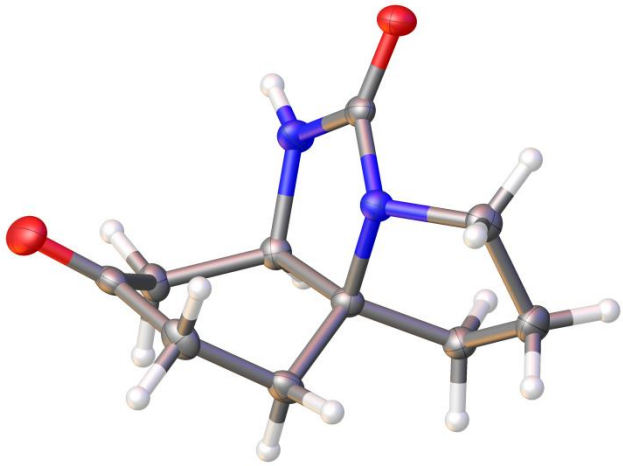


*Figure 9. X-ray crystal structure of deprotected PMP ketone of key scaffold*

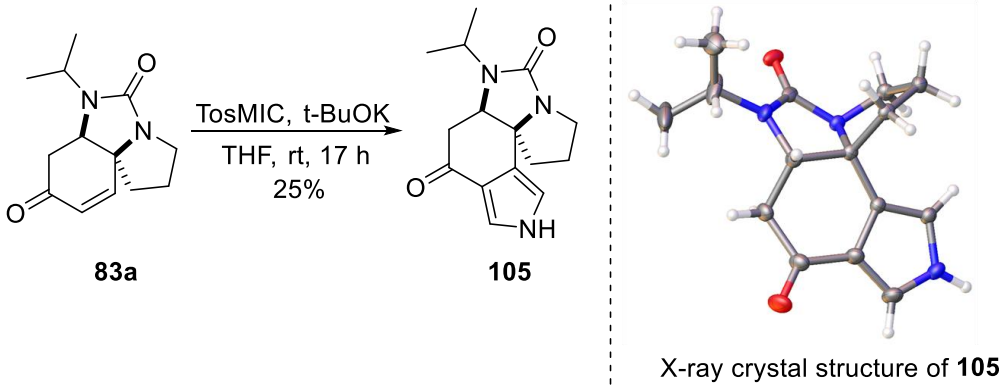
## 2.5 Generationof secondary scaffolds via ring addition

Ring addition or fusion to the 6-membered ring of the derivatives of the primary scaffold (**83a-c)** was one of the strategies used to generate secondary scaffolds.

### 2.5.1 Ring fusion to the enone functionality of the primary scaffold

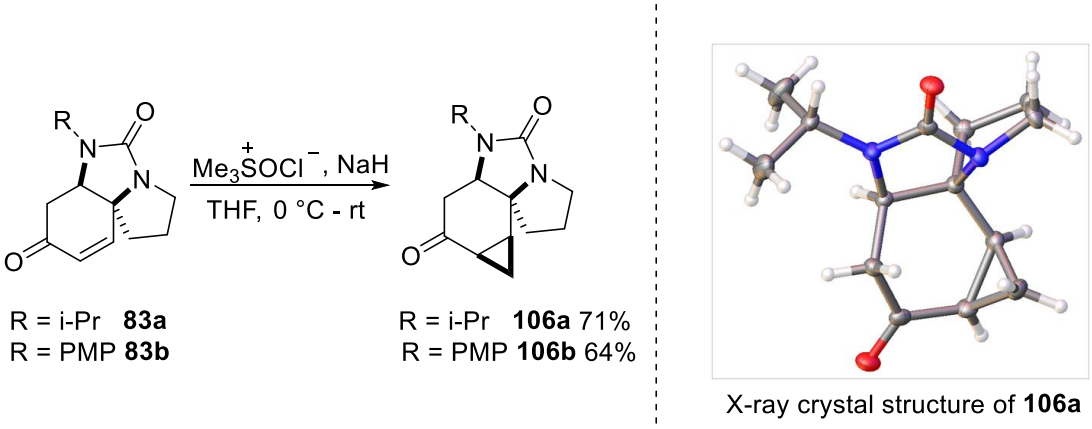
The enone functionality of the variants of the primary scaffold was utilized to generate secondary scaffolds by the addition of rings as discussed below.

Van Leusen reaction[96] was used to append a pyrrole to the double bond of the isopropyl derivative of the key scaffold **83a** as shown below.



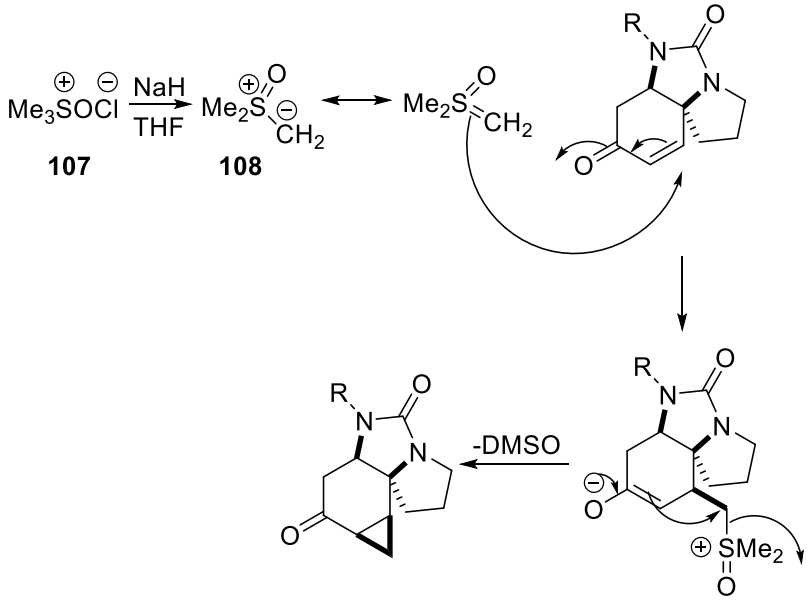

*Scheme 24. Pyrrole synthesis via Van Leusen reaction*

Also, Corey-Chaykovsky cyclopropanation[97] was carried out on the double bond of the isopropyl derivative of the primary scaffold **83a** to give **106a** in 71% yield. The same reaction was carried out on the PMP derivative of the key scaffold **83b** to give **106b** in 64% yield. From the proton NMR of the crude reaction mixtures, the diastereomeric ratio for the product of the cyclopropanation of **83a** is 13:2 while that of **83b** is 3:1. However, the products **106a** and **106b** were isolated as single diastereomers respectively. An attempt to determine the stereochemistry of **106a** by NOESY correlations was unsuccessful but this was solved by obtaining its x-ray crystal structure. For **106b**, the stereochemistry was assigned by knowledge of that of its derivative **191** (see *Scheme 88*).




*Scheme 25. Cyclopropanation of the isopropyl and PMP variants of the primary scaffold*

Selectivity in this case can be adduced to the fact that the ylide generated from trimethylsulfoxonium chloride is bulky. It therefore attacks from the face of the electrophilic double bond that is anti to the hindered pyrrolidine ring. The proposed mechanism is shown below.

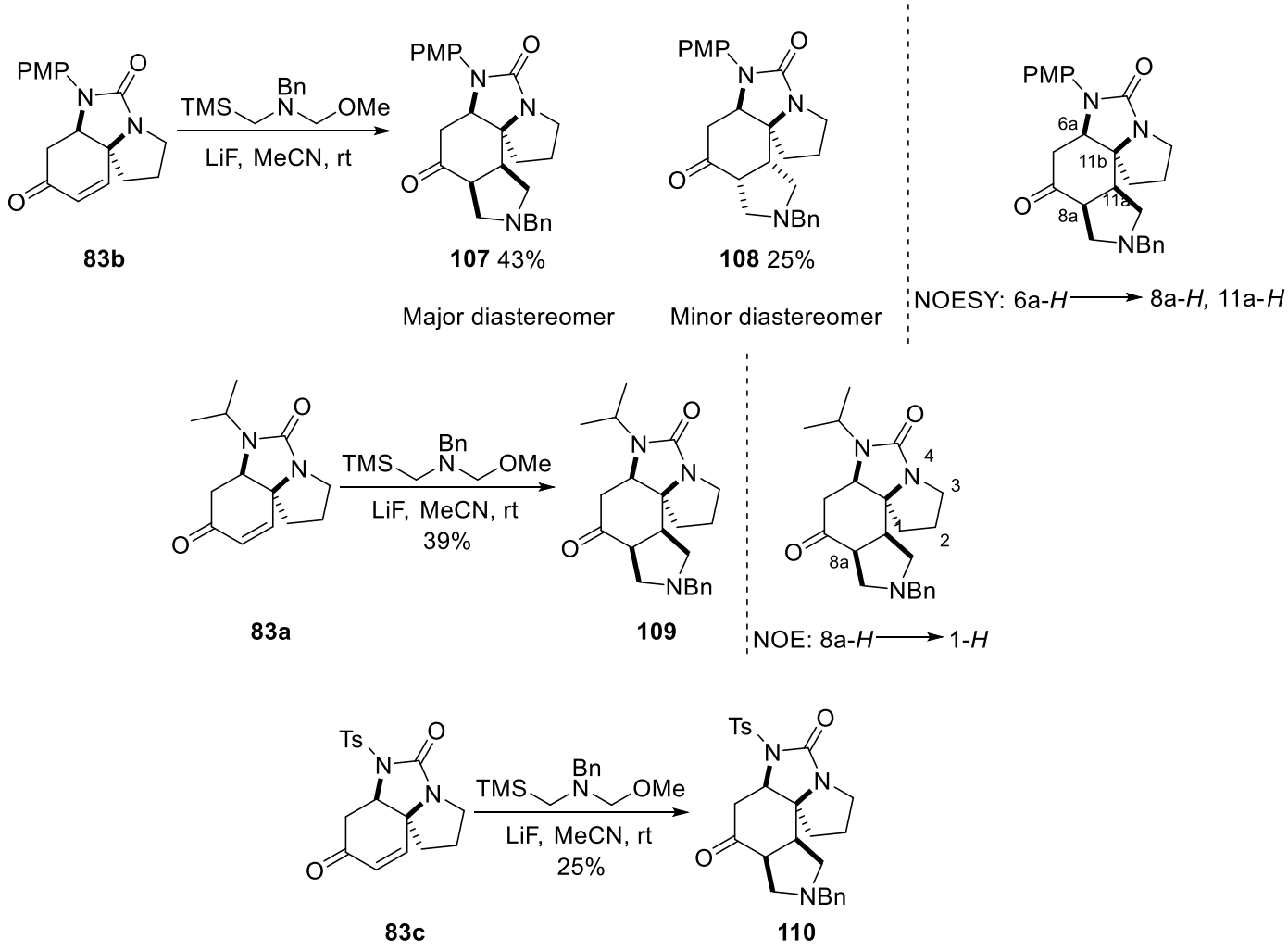



*Scheme 26. Proposed mechanism for the Corey-Chaykovsky cyclopropanation of the primary scaffold*

It is known that desoxybenzoin and $\Delta^4$-cholestenone are substrates that seem to be resistant to the Corey-Chaykovsky reaction probably because of an enhanced ability to transfer protons to the dimethylsulfoxonium methylide **108** via enolisation.[97] When the tosyl derivative of the primary scaffold **83c** was subjected to the same reaction, only the mass of the starting material was observed by LCMS. The tosyl group is electron withdrawing and could enhance the acidity of the enolisable protons of the primary scaffold **83c**.

The last ring addition strategy to the enone functionality was demonstrated via the syntheses of pyrrolidines as described by Fray and co-workers.[98] This ensued through the [3+2] cycloaddition of the derivatives of the primary scaffold **83a-c** to an azomethine ylide. From the proton NMR of the crude reaction mixture, the diastereomeric ratio for the products of the reaction of **83b** was 2:1. The two diastereomeric products (**107** and **108**) were isolated cleanly.

Deducing the diastereomeric ratios for the products of the reactions of **83a** and **83c** from the proton NMR of their respective crude mixtures proved difficult because of extensive signal overlap. However, single diastereomers (**109** and **110**) were isolated from each reaction after column chromatography. The stereochemistry of **107** was deduced from the NOESY correlation of the proton at position 6a (6a-*H*) and those at positions 8a and 11a (8a-*H* and 11a-*H*) while that of **109** was determined by the NOESY correlation between its 8a-*H* and 1-*H* as shown below. The stereochemistry of **110** was determined by the NOESY correlations of the derived alcohol **181** (see *Scheme 72*).

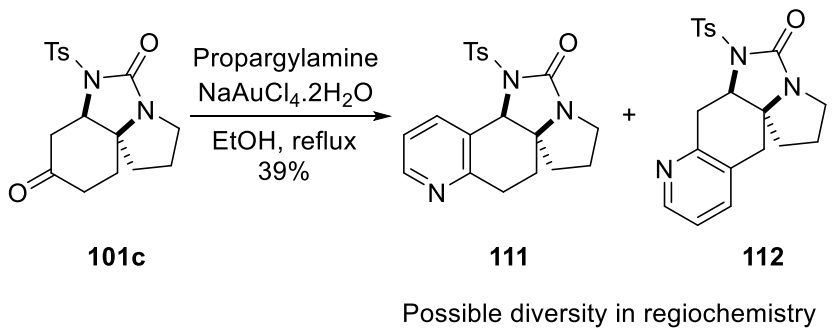



*Scheme 27. Synthesis of pyrrolidines via 1,3-dipolar cycloaddition of the variants of the primary scaffold to an azomethine ylide*

In principle, it was expected that the major diastereomers formed in the 1,3-dipolar cycloaddition reactions will have the pyrrolidine ring *syn* to the urea ring for the same reason as in the case of the Corey-Chaykovsky reaction shown in *Scheme 26*.

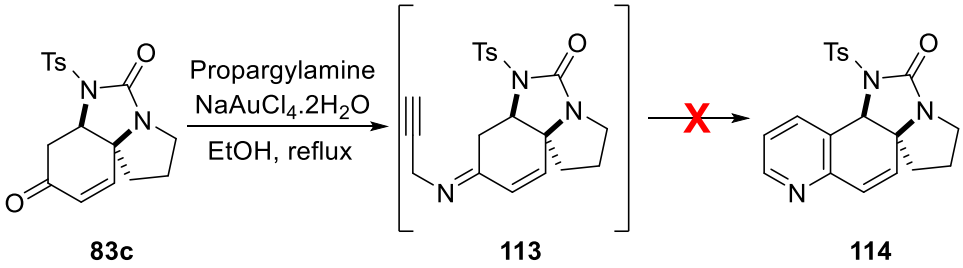
### 2.5.2 Pyridine synthesis

Arcadi and co-workers[99] developed a method for the synthesis of pyridines from ketones or aldehydes and propargylamine via gold catalysis. Therefore, refluxing the ketone **101c** with propargylamine in the presence of sodium tetrachloroaurate (III) dihydrate gave regiomeric pyridines (1:2 isomeric ratio from the proton NMR of the crude product) that were not separated cleanly.



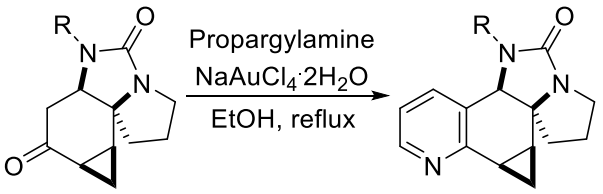

*Scheme 28. Pyridine synthesis from the ketone of the tosyl variant of the primary scaffold*

Therefore, the tosyl derivative of the primary scaffold **83c** was used for the same reaction to see if it would allow for regiocontrol. However, only the mass of the imine **113** was observed by LCMS.




*Scheme 29. Attempted pyridine synthesis from the tosyl derivative of the primary scaffold*

Using the cyclopropanes **106a** and **106b** for the same reaction, product formation was observed by both LCMS and the proton NMR of the crude reaction mixture. However, only the PMP variant **115b** could be isolated cleanly.

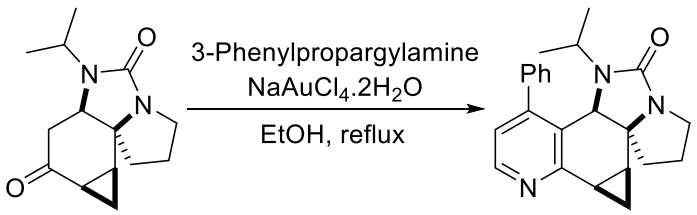



R = i-Pr **106a**
R = PMP **106b**

R = i-Pr **115a** (obtained with an unknown impurity)
R = PMP **115b** 40%

*Scheme 30. Pyridine synthesis from the cyclopropane-fused scaffolds*

An attempt was made to synthesize a substituted pyridine from the cyclopropane **106a** by using a substituted propargylamine. Therefore, **106a** was refluxed with 3-phenylpropargylamine hydrochloride under the same conditions but in the presence of DIPEA to release the free amine for condensation with the ketone, followed by cyclization and then aromatisation. Product formation was observed by both LCMS and the proton NMR of the crude reaction mixture. However, the product **116** was not isolated cleanly. It was obtained with an unknown impurity after column chromatography.



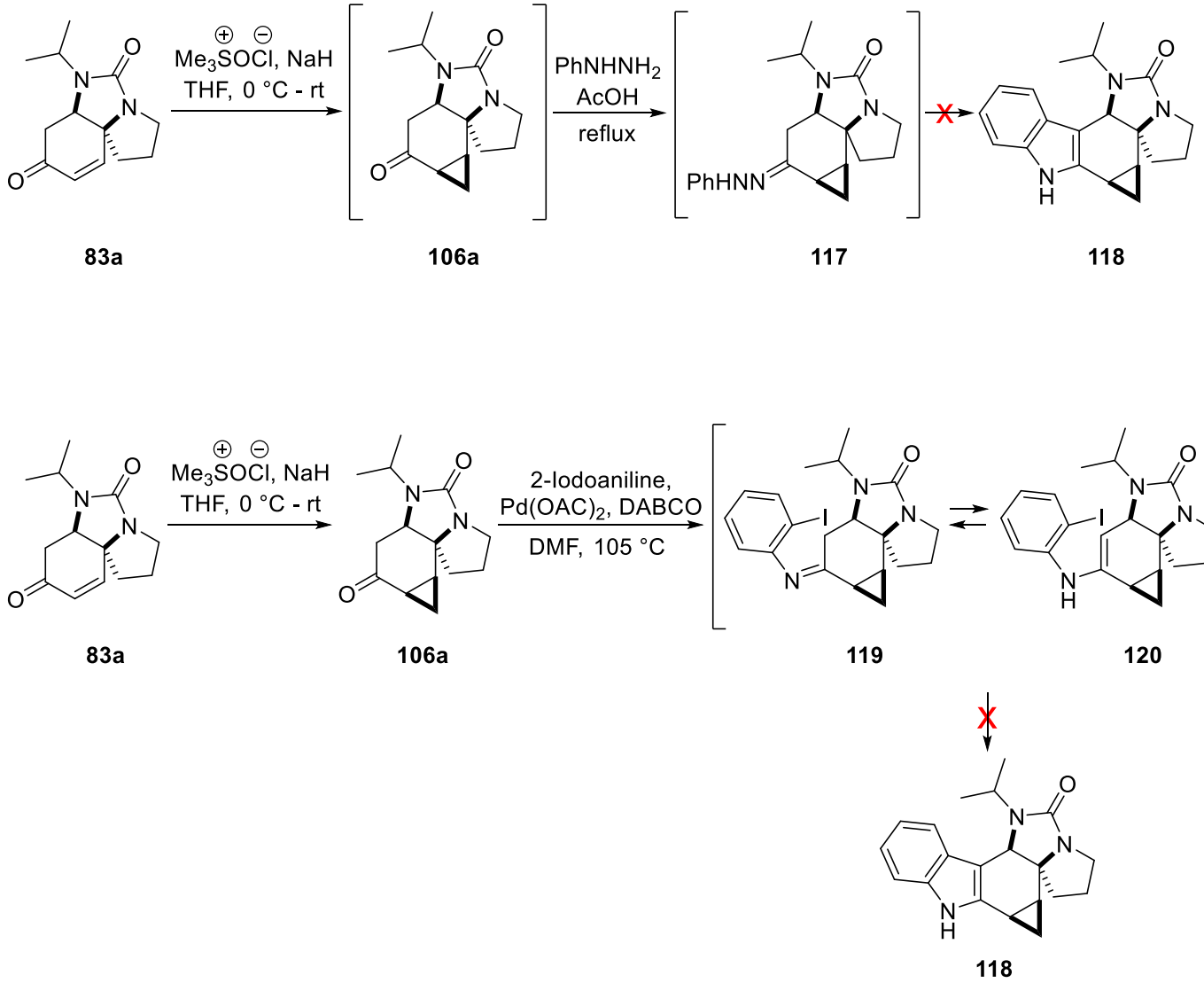

**106a** **116**

*Scheme 31. Attempted synthesis of a substituted pyridine*

### 2.5.3 Attempted Indole synthesis

Attempts were also made to use the cyclopropane **106a** to synthesise the indole **118** via the Fischer method[100] or via the annulation of *o*-iodoanilines to ketones developed by Chen and co-workers.[101] However, neither approach was successful. For the Fischer indole method, only the masses of the intermediate cyclopropane **106a** and the phenylhydrazone **117** were observed by

LCMS. Also, for the o-iodoaniline annulation method, the masses of the intermediate cyclopropane **106a** and the imine **119** (or its tautomeric enamine **120**) were detected by LCMS but not the product.



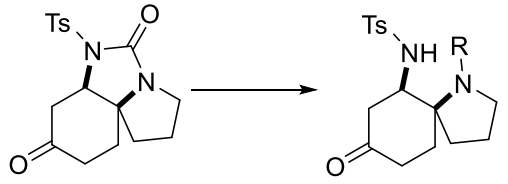

*Scheme 32. Attempted indole synthesis via the Fischer method, and the annulation of o-*iodoaniline to the cyclopropane **106a**

## 2.6 Secondary scaffolds generated via ring cleavage

Urea cleavage of **101a-c** and the cleavage of the double bond of the enone **83a** were investigated to generate ring-cleaved secondary scaffolds.

### 2.6.1 Urea cleavage of ketones of the primary scaffold

Attempts to cleave the urea functionality of **101c** under the conditions tabulated below were unsuccessful.

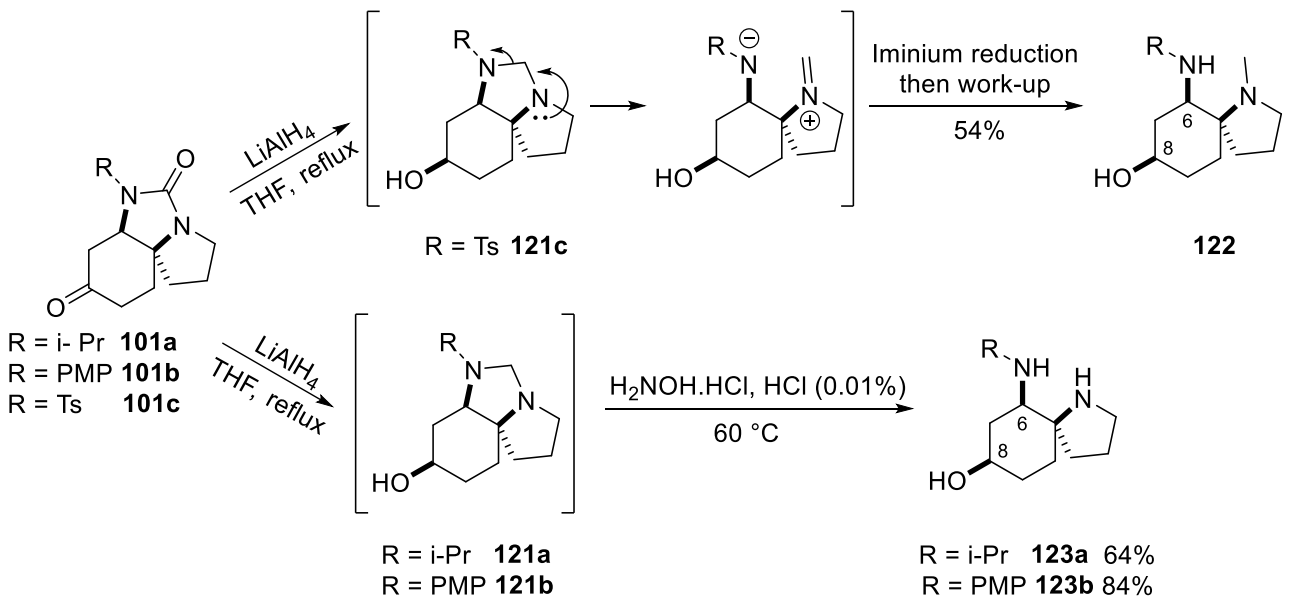



**101c** R = H or COMe

| Entry | Compound | Condition | Outcome |
|---|---|---|---|
| **1** | **101c** | $K_2CO_3$, MeOH, 70 °C, 5 h | Only the starting material was detected by LCMS |
| **2** | **101c** | $Ba(OH)_2{\cdot}8H_2O$, $EtOH/H_2O$, 100 °C, 6 h | Only the starting material was detected by LCMS |
| **3** | **101c** | NaOMe, PhMe, 80 °C, 1 h | Only the starting material was detected by LCMS |
| **4** | **101c** | NaOMe, PhMe, 80 °C, 4 h | Only the starting material was detected by LCMS |
| **5** | **101c** | NaOMe, PhMe/MeOH, 80 °C, 1 h | Only the starting material was detected by LCMS |

*Table 3. Attempted cleavage of the urea functional group of the ketone of the tosyl variant of the primary scaffold*

However, cyclic ureas are known to be deoxygenated by lithium aluminum hydride to form aminals which can then be subjected to acidic cleavage to afford diamines as demonstrated by Keyserlingk and Martens.[102] Carrying out the reaction with the tosyl-substituted urea **101c**, it was noticed that the second step was not needed because the compound had already spontaneously undergone a reductive cleavage with concomitant reduction of the ketone. This is presumably due to the toluenesulfonamide group acting as a nucleofugal leaving group after the formation of the aminal **121c** as shown below.




*Scheme 33. Urea cleavage via deoxygenation by lithium aluminium hydride*

Subjecting the isopropyl- and PMP-substituted ureas **101a** and **101b** to the same reaction did not result in spontaneous reductive cleavage. Instead, the intermediate aminals (**121a** and **121b**) were formed which were then used crude for the cleavage step. Cleaving the aminal **121a** with HCl proved difficult even at reflux. However, aminals are also known to be cleaved by hydroxylamine hydrochloride to give diamines as demonstrated by Trost and Fandrick.[103] Therefore subjecting **121a** and **121b** to cleavage by hydroxylamine hydrochloride afforded the diamines **123a** and **123b** in 64% and 84% yields respectively.The diamine **123b** can be of great synthetic utility for ring-swap reactions with different reagents. Therefore, the original urea ring can be swapped for other rings of the same size or larger. This is because **123b** has a secondary pyrrolidine, which in principle, will be more reactive than its secondary aniline. The stereochemistry of **122** and **123b** were determined by the NOE correlation between the 6-*H* and 8-*H* of the respective compounds. This was confirmed by x-ray crystallography. However, attempts to determine the stereochemistry of **123a** by NOE correlations were not successful but it was determined by the coupling constant analysis of its 6-*H* (t, *J* = 3.2 Hz) and 8-*H* (quint, *J*= 2.4 Hz) protons. Both protons are equatorial and therefore have to be on the same face of the cyclohexanol ring.

In an instant, after the cleavage step, residual PMP-substituted aminal **121b** was also isolated,

characterised and its structure confirmed by x-ray crystallography.

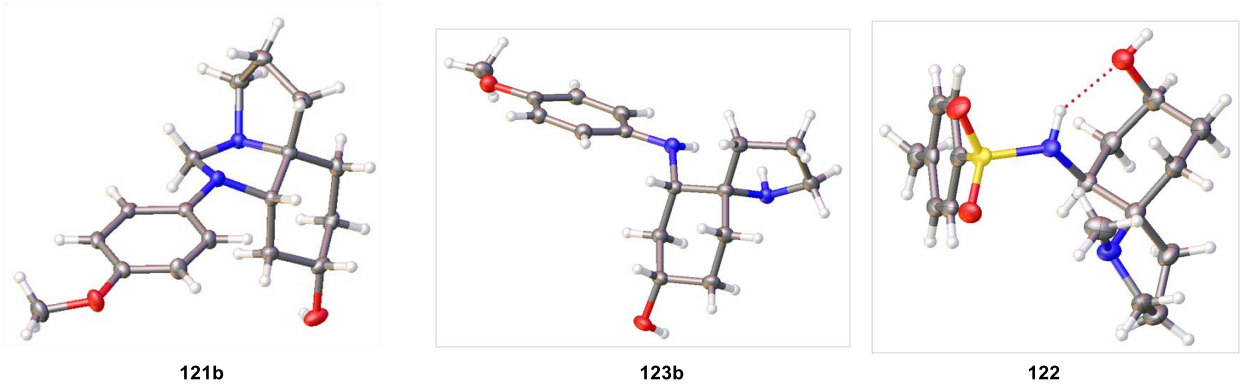
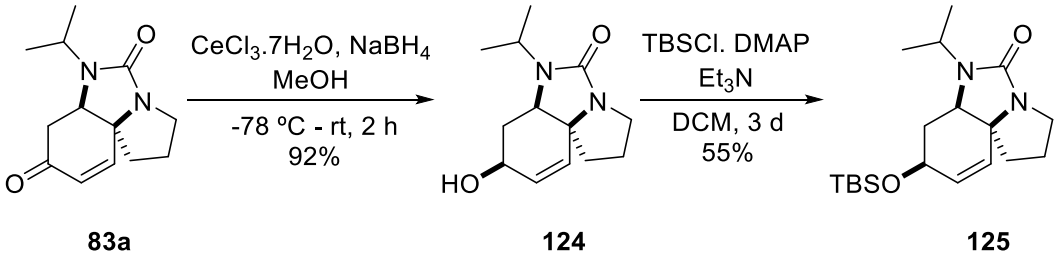



*Figure 10. X-ray crystal structures of PMP-substituted aminal **121b**, PMP-substituted diamine **123b** and tosyl-substituted diamine **122***

### 2.6.2 Cleavage of the double bond of the isopropyl derivative of the primary scaffold

The double bond functionality of the enone **83a** was investigated for oxidative cleavage. However **83a** itself was not used because enones are difficult to cleave oxidatively since they are electrophilic in character and most of the oxidising agents used to cleave alkenes are themselves electrophilic. Therefore, **83a** was reduced to the allylic alcohol **124** in 92% yield under Luche conditions.[104] The diastereomeric ratio from the proton NMR of the crude product is 13:1 but it was isolated as a single diastereomer. Protection of the alcohol functionality of **124** with TBSCl did not reach completion after 3 days. Proton NMR of the crude reaction mixture indicated a mixture of the allylic alcohol **124** and the product **125** in about 1:1 ratio from which the product **125** was isolated in 55% yield as shown below.




*Scheme 34. Synthesis of protected allylic alcohol for oxidative cleavage*

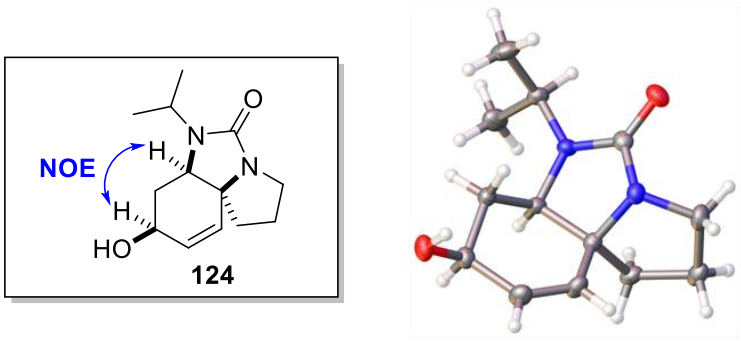
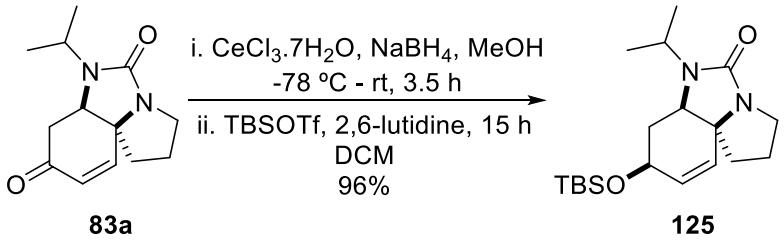


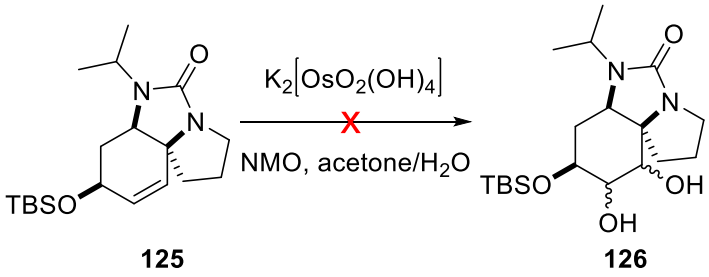

*Figure 11. NOE correlation and x-ray crystal structure of the allylic alcohol **124***

Using TBSOTf instead of TBSCl for the protection led to complete conversion of **124** to **125** in 96% yield over two steps.



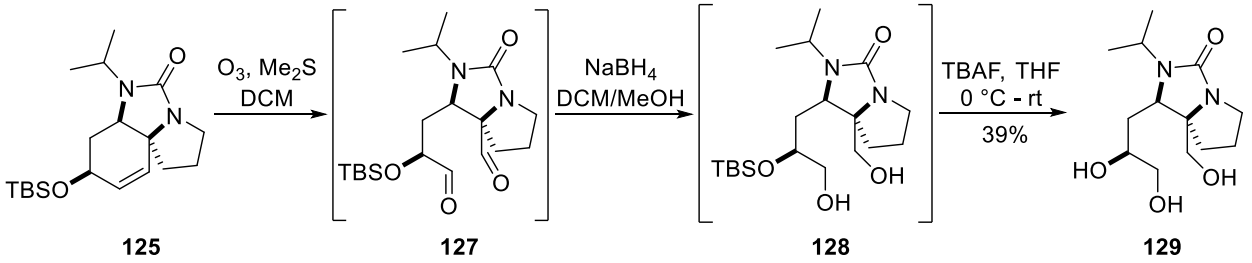

*Scheme 35. Alternative synthesis of protected allylic alcohol for oxidative cleavage*

Dihydroxylation of the double bond of **125** with potassium osmate and NMO prior to a proposed oxidative cleavage with sodium periodate was not successful. After two weeks, only the starting material was observed from the proton NMR of the crude reaction mixture.




*Scheme 36. Attempted dihydroxylation of the double bond of the protected allylic alcohol **126***

Therefore **125** was subjected to ozonolysis followed by reduction and TBAF deprotection to give the triol **129** (isolated with 4% TBAF contamination) as shown below.




*Scheme 37. Synthesis of triol **102** via oxidative cleavage*

## 2.7 Secondary scaffolds generated via ring expansion

The strategies investigated for the generation of secondary scaffolds via ring expansion are:

i. Post-ozonolysis nitrogen insertion into the 6-membered ring of the primary scaffold

ii. Cyclopropane ring opening

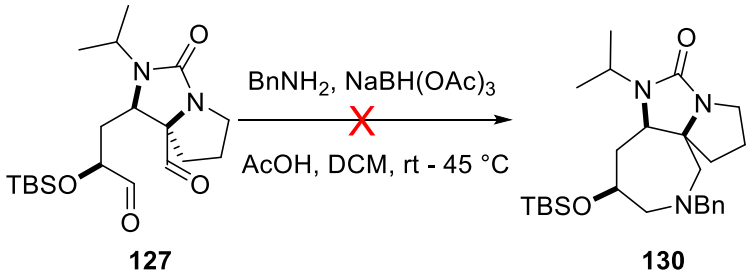
iii. A ring swap reaction of the 6,3-fused ring of **106a** for a cyclohexanol ring

iv. Ring swap reactions with the PMP-substituted diamine **123b**

v. Beckmann rearrangement

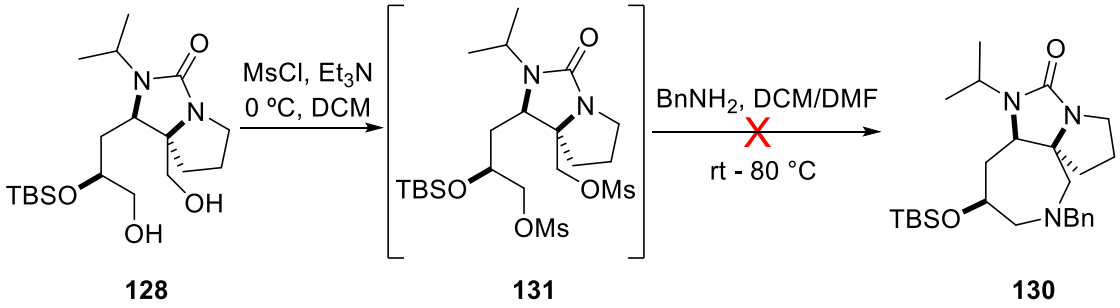
### 2.7.1 Attempted azepane synthesis

The dialdehyde **127** could be detected by LCMS after ozonolysis but it was not purified due to concerns about its stability. It was therefore subjected crude to double reductive amination with benzylamine in the presence of sodium triacetoxyborohydride (at room temperature) in an attempt to make the azepane **130** as shown below. However, only the masses of both the dialdehyde **127** and the imine from condensation with one equivalent of benzylamine were observed by LCMS, even upon heating.




*Scheme 38. Attempted ring expansion by post-ozonolysis nitrogen insertion via double reductive amination*

Therefore, a different approach to the desired azepane was investigated based upon nucleophilic substitution. The crude diol **128** was mesylated and subjected crude to a double $S_N2$ reaction with benzylamine in an attempt to make the azepane **130.** The mass of the the dimesylated compound **131** was observed by LCMS but not that of the desired azepane.



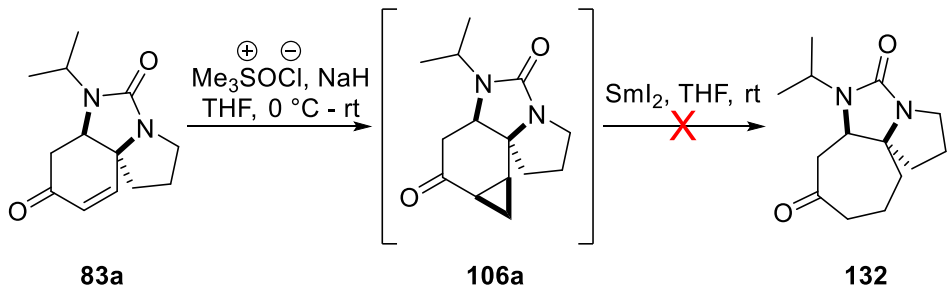

*Scheme 39. Attempted ring expansion by post-ozonolysis nitrogen insertion via a double $S_N2$ reaction*

### 2.7.2 Attempted cyclopropane ring opening

Two approaches towards ring expansion were investigated via a proposed opening of the cyclopropane ring of **106a**. The first approach investigated was an attempted radical-induced cyclopropane ring opening while the second was an attempt to open the cyclopropane ring via hydrogenation.

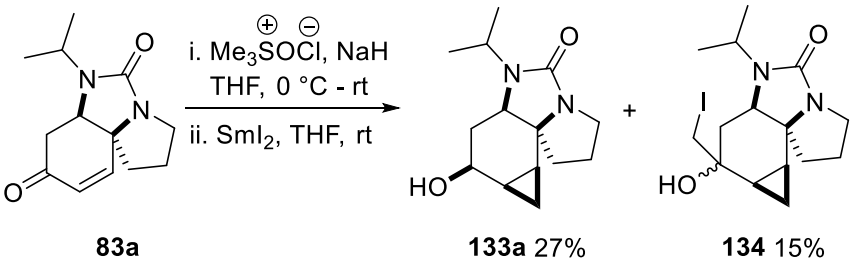
#### 2.7.2.1 Attempted radical-induced cyclopropane ring opening

The cyclopropane **106a** was subjected to radical ring opening using samarium iodide in THF at room temperature in an attempt to make the cycloheptanone **132** as shown below.




*Scheme 40. Attempted radical-induced cyclopropane ring opening*

Instead of the desired product **132**, the secondary and tertiary alcohols **133a** and **134** were formed in 27% and 15% yields respectively. Both **133a** and **134** were obtained as single diastereomers. The stereochemistry of **133a** was determined by comparison with an identical compound obtained from the sodium borohydride reduction of **106a** (see *Scheme 43*). The stereochemistry of **134** was not determined. The tertiary alcohol **134** may have been formed from a bis(iodomethyl)samarium contaminant which was most probably present in the commercial samarium iodide used.



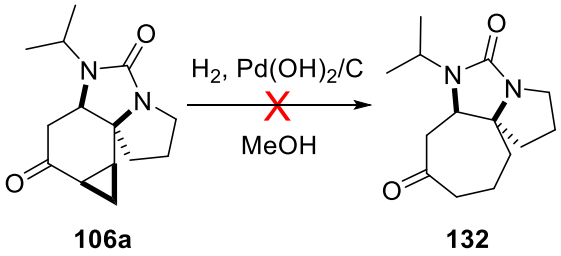

**83a** **133a** 27% **134** 15%

*Scheme 41. Samarium iodide reduction of the cyclopropane **106a***

Using tributyltin hydride and AIBN to open the cyclopropane ring of **106a** resulted in a complex mixture.

### 2.7.2.2 Attempted cyclopropane ring opening via hydogenation

The cyclopropane ring is known to possess the characteristics of a double bond.[105] Therefore, an attempt was made to open the cyclopropane ring of **106a** via hydrogenation to give the cycloheptanone **132**. This led to the partial conversion of **106a** to the alcohol **133a** as monitored by proton NMR.

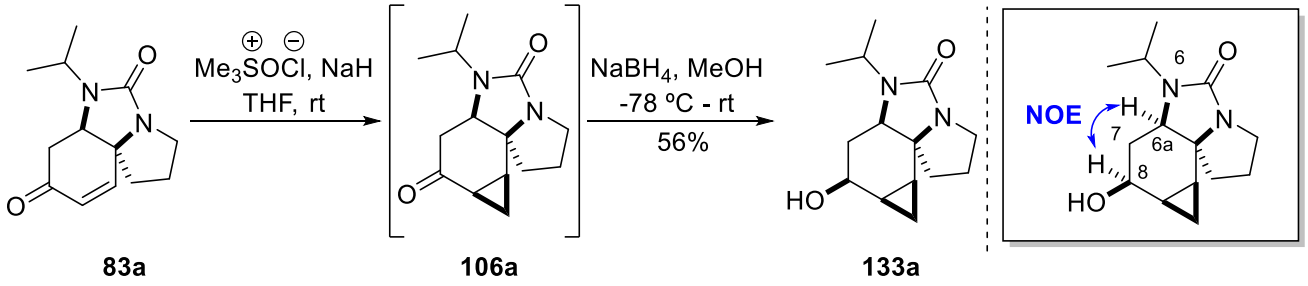



**106a** **132**

*Scheme 42. Attempted cyclopropane ring opening via hydrogenation*

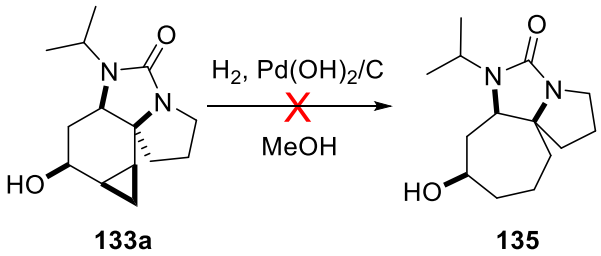
### 2.7.3 Attempted swap of the 6,3-fused ring of 106a for a cycloheptanol ring

Compound **106a** was reduced to the alcohol **133a** in an attempt to subsequently swap its 6,3-fused ring for a cycloheptanol ring as shown below. DIBAL gave a 1:2 mixture of diastereomers as deduced from the proton NMR of the crude reaction mixture, and the product was isolated in the same ratio in 29% yield. The major diastereomer is identical to the alcohol obtained from the samarium iodide/sodium borohydride reduction. Reduction of **106a** with sodium borohydride gave the corresponding alcohol isolated as a single diastereomer (*dr* from the proton NMR of the crude product is 92:8). The stereochemistry of the product **133a** was determined by the NOE correlation between its 6a-*H* and 8-*H*.




*Scheme 43. Cyclopropanation and subsequent reduction*

The alcohol **133a** was hydrogenated in an attempt to obtain the ring-expanded cycloheptanol **135**. However, only the mass of the starting material was detected by LCMS.

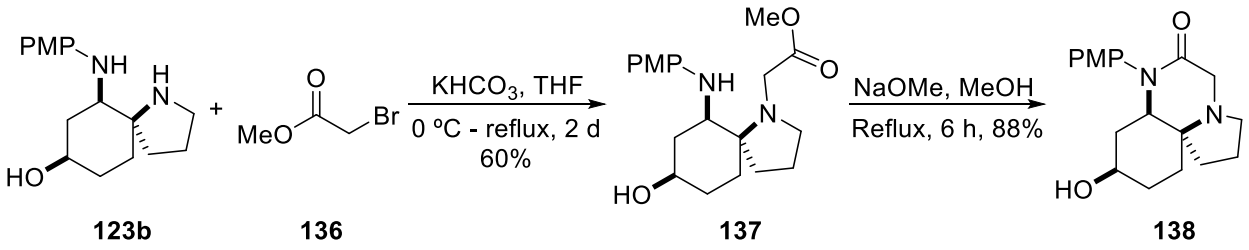



*Scheme 44. Attempted swap of the 6,3-fused ring of **106a** for a cycloheptanol ring*

### 2.7.4 Urea ring swap for isomeric piperazinone rings

As stated earlier, the PMP-substituted diamine **123b** can be of great synthetic utility for swapping the urea ring in **101b** for other ring forms. This is because the secondary pyrrolidine

of **123b** is expected to be more nucleophilic than its aniline. Therefore, the diamine **123b** was selectively alkylated with methyl bromoacetate **136** followed by base-mediated intramolecular amidation to swap the original urea ring of **101b** for a piperazinone ring. The regiochemistry of both the intermediate and final product were determined by NOE correlations. Telescoping the intermediate **137** without purification, the piperazinone **138** was isolated in 90% yield (over two steps).




*Scheme 45. Urea ring swap for a piperazinone via the diamine **123b***

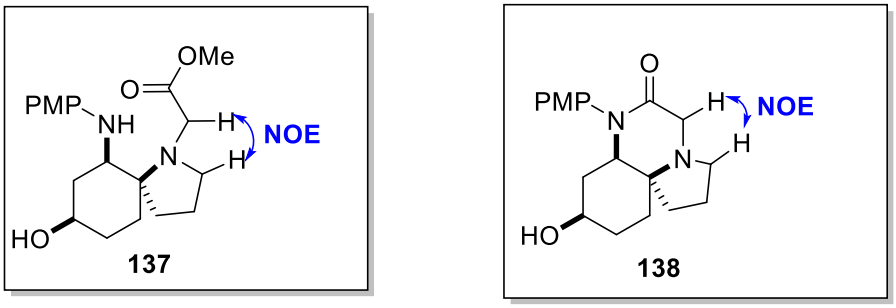
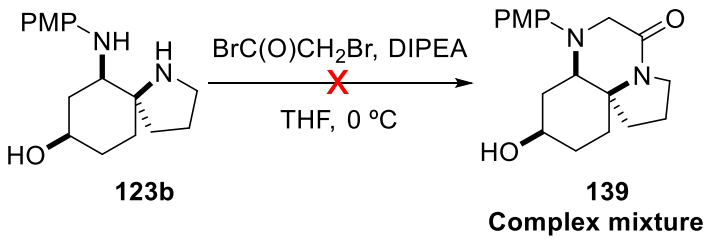


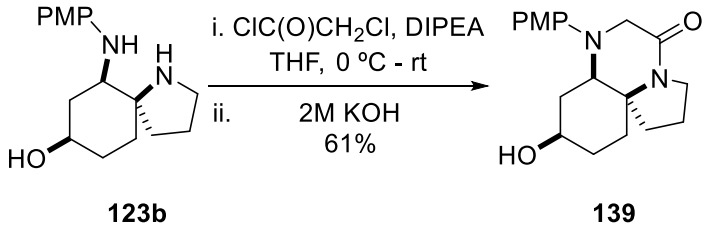

*Figure 12. Determination of regiochemistry through NOESY correlations*

The regioisomeric piperazinone **139** could be accessed by using bromoacetyl bromide as the electrophile, leading to the acylation of the more nucleophilic aliphatic amine, followed by internal nucleophilic substitution to give the desired product. For this reaction, a complex mixture was obtained even though the mass of the desired product was detected by LCMS.




*Scheme 46. Attempted ring swap reaction for the synthesis of the regioisomer of **138***

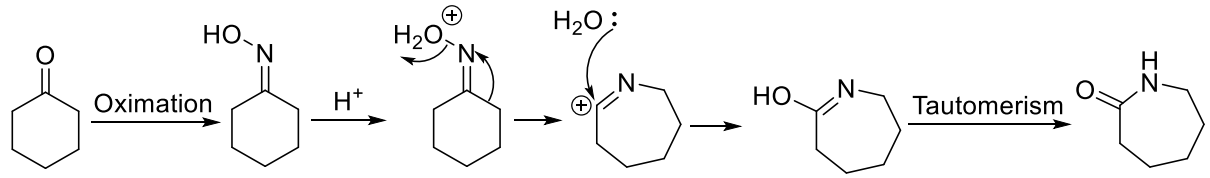
However, using chloroacetyl chloride and DIPEA, the desired product was obtained in one pot in 61% yield. The acylation of the hydroxyl group to give the chloromethyl ester was also observed, but this could be easily hydrolysed by 2M KOH.




*Scheme 47. Urea ring swap reaction for the synthesis of the regioisomer of **138***

### 2.7.5 Beckmann rearrangement

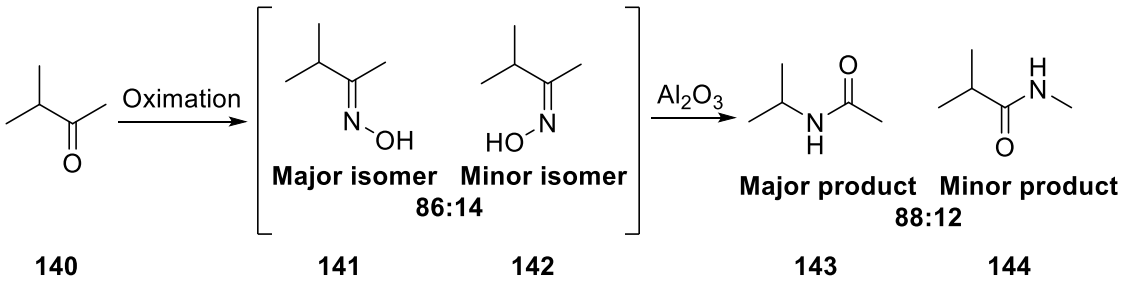
The last ring expansion strategy investigated was Beckmann rearrangement.[106–108] It involves the protic acid- or lewis acid-mediated rearrangement of aldoximes or ketoximes to give the corresponding amides or lactams. The mechanism of the reaction is shown below.




*Scheme 48. Mechanism for Beckmann rearrangement*[108]

For strong orbital overlap, only the group *anti* to the hydroxyl group of the oxime migrates to the nitrogen atom in Beckmann rearrangement. Therefore, when unsymmetrical cyclic ketones are subjected to this reaction, a mixture of isomeric lactams will be expected since ketoximes exhibit geometrical isomerism. However, when a branched migratory group competes with an

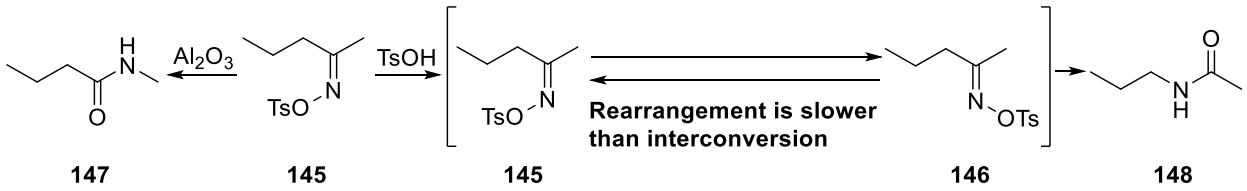
unbranched one, more of the oxime with the hydroxyl group anti to the branched group will be formed. This therefore determines regioselectivity.[108]




*Scheme 49. Depiction of selectivity in Beckmann rearrangement*[108]

In addition, when single isomers of unsymmetrical ketoximes are tosylated (as in the case of **145**) and rearranged in the presence of protic acids, they are known to convert to their corresponding geometric isomers, followed by equilibriation and rearrangement. An example is shown in *Scheme 50* below. Therefore, for **145**, either the n-propyl group or the methyl group can migrate to the nitrogen atom to make the corresponding amides after treatment with toluenesulfonic acid. However, the product formed will be determined by electronic factors. In the example below,the n-propyl group migrates faster under equilibrating conditions because it stabilises a positive charge better than the methyl group.[108]

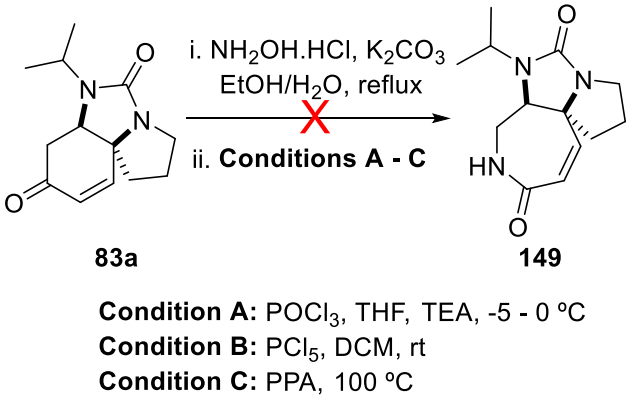
Rearrangement of **145** with alumina however results in the methyl group migrating because a Lewis acid does not permit isomeric interconversion.[108]




*Scheme 50. Comparison of Beckmann rearrangement under oxime-equilibriating and non-equilibriating conditions*[108]

### 2.7.5.1 Beckmann rearrangement of the isopropyl derivative of the primary scaffold

Attempts were made, albeit unsuccessfully, to expand the enone ring of **83a** by Beckmann rearrangement. The oxime synthesis was successful as monitored by LCMS but treatment of the crude with either polyphosphoric acid, phosphorus (V) oxychloride or phosphorus pentachloride failed to give the desired product. The crude oxime was observed by TLC.

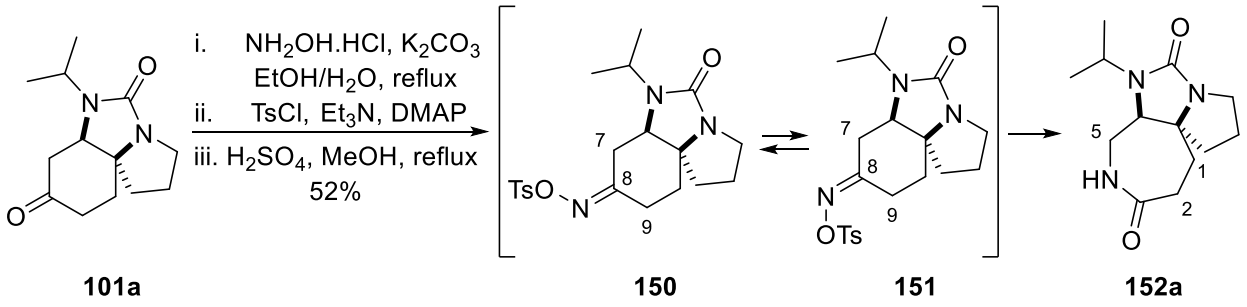



*Scheme 51. Attempted Beckmann rearrangement of the isopropyl variant of the primary scaffold*

### 2.7.5.2 Beckmann rearrangement of the isopropyl, PMP and tosyl variants of the ketone of the primary scaffold

The ketone **101a** was then chosen to investigate Beckmann rearrangement. Oxime synthesis as in *Scheme 51* was successful as monitored by LCMS. The crude oxime was then tosylated to improve selectivity via equilibriation upon treatment with protic acids (see *Scheme 52*). Therefore, treating the crude tosylated oxime with acetic acid at room temperature or reflux, only the mass of the tosylated oxime and the ketone **101a** could be detected by LCMS. However, using sulphuric acid instead of acetic acid surprisingly afforded the lactam **152a** in a highly regioselective manner as shown below. The isomeric ratio from the proton NMR of the crude reaction mixture is 93:7 but after purification by column chromatography, only **152a** was isolated cleanly. Although the reaction was expected to be regioselective, **152a** was not expected to be the major product under equilibriating conditions. This is because the carbon atom at position 9 (*C*-9) of the oximes (**150** and **151**) was expected to migrate faster than the

one at position 7 (*C*-7) since the primary alkyl group terminating at *C*-9 is expected to stabilise a positive charge better than the one terminating at *C*-7. The lactam **152a** may have been formed predominantly because the oxime **151** persisted as the major isomer in solution to avoid steric clashes between the tosylate and isopropyl groups. Hence *C*-7 of **151** migrated to the nitrogen atom preferentially. The structure of the isolated product **152a** was determined from the $^{1}$H-$^{1}$H COSY NMR correlation between its N-*H* proton and the two diasterotopic 5-*H* protons. This was confirmed by x-ray crystallography.




*Scheme 52. Beckmann rearrangement of the ketone **101a** to give the lactam **152a***

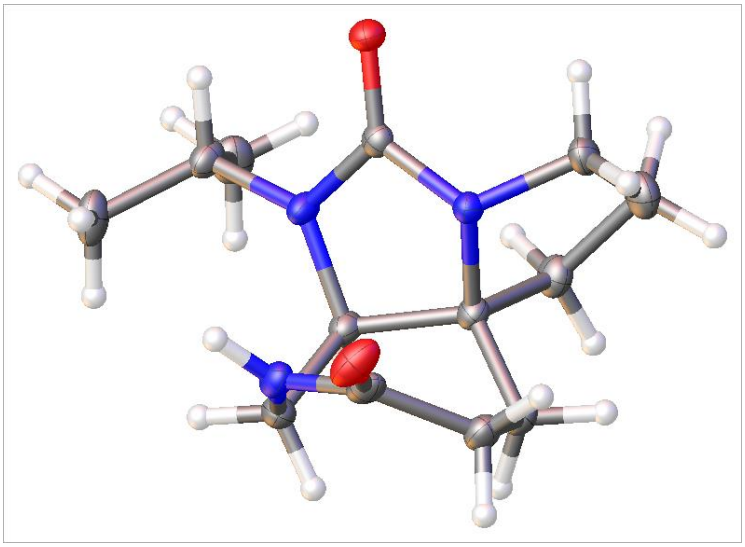
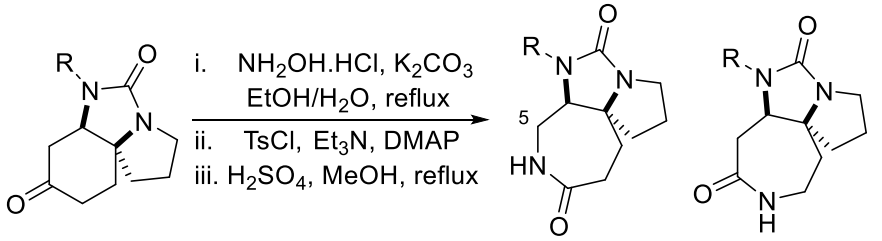


*Figure 13. X-ray crystal structure of the lactam **152a***

A similar observation was made for the PMP variant of the ketone of the primary scaffold **101b** as well as the tosyl variant **101c** when subjected to Beckmann rearrangement under the same conditions as **101a**. From the proton NMR of the crude reaction mixtures, the isomeric ratio for

the lactams obtained from the reaction of **101b** (isolated as a 93:7 mixture) is 3:1 while that for the lactams obtained from the reaction of **101c** (isolated as a 90:10 mixture) is 2:1. Regiochemistry was determined by the $^{1}$H-$^{1}$H COSY NMR correlations between the N-*H* protons and the diastereotopic 5-*H* protons of the major products **152b** and **152c** respectively.

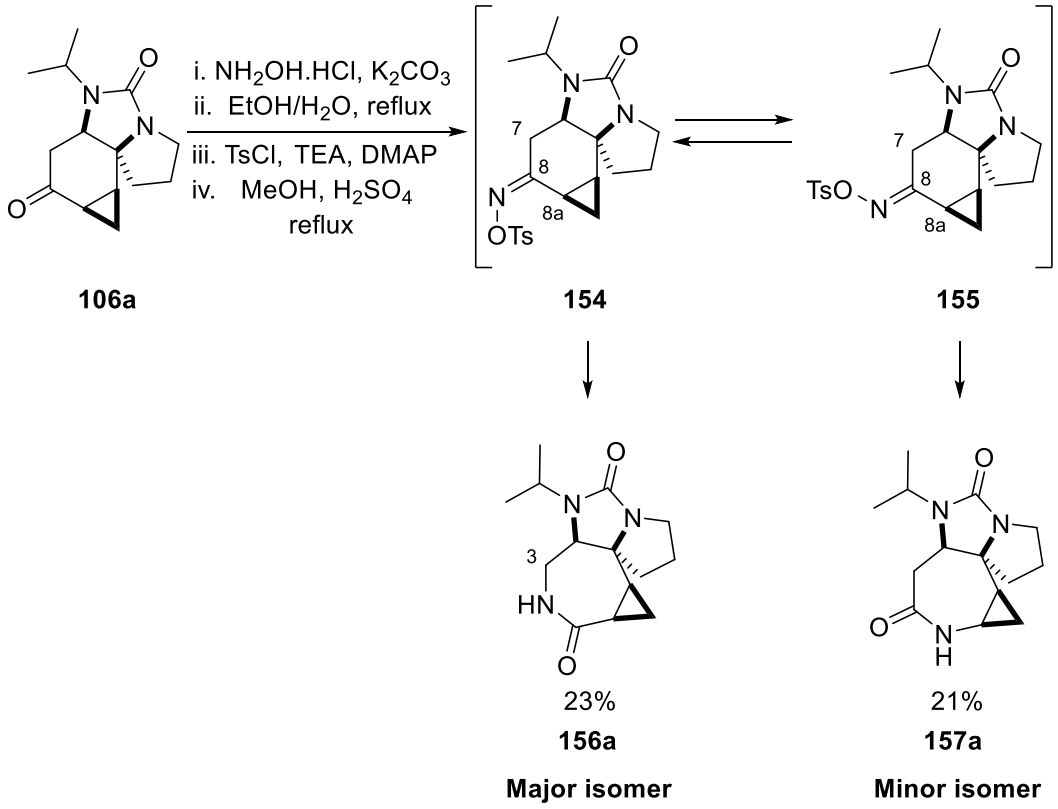



| | | | |
|---|---|---|---|
| R= PMP **101b** | **152b** | **153b** | Isolated as a 93:7 mixture (62%) |
| R = Ts **101c** | **152c** | **153c** | Isolated as a 90:10 mixture (40%) |

*Scheme 53. Beckmann rearrangement of the PMP and tosyl variants of the ketone of the primary scaffold*

### 2.7.5.3 Beckmann rearrangement of the isopropyl and PMP variants of the 6,3-fused cyclopropane scaffolds

The isopropyl variant of the cyclopropane scaffold **106a** was subjected to Beckmann rearrangement under oxime-equillibriating conditions. This was to see if more of the tosyl oxime **155** with the tosylate group anti to *C*-3 will persist in solution as compared to the reaction of **101a** discussed in *Section 2.7.5.2* (see *Scheme 52*). From the proton NMR of the crude mixture for the reaction of **106a**, the isomeric ratio of the formed lactams is 60:40 as compared to 93:7 for the reaction of **101a**. The lactams **156a** and **157a** were isolated in 23% and 21% yields respectively as shown below. The regiochemistry of **156a** was determined by the $^{1}$H-$^{1}$H COSY NMR between the N-H proton and the diastereotopic 3-*H* protons. This was confirmed by the x-ray crystal structure of both **156a** and **157a**.




*Scheme 54.Beckmann rearrangement of the isopropyl variant of the cyclopropane scaffold **106a***

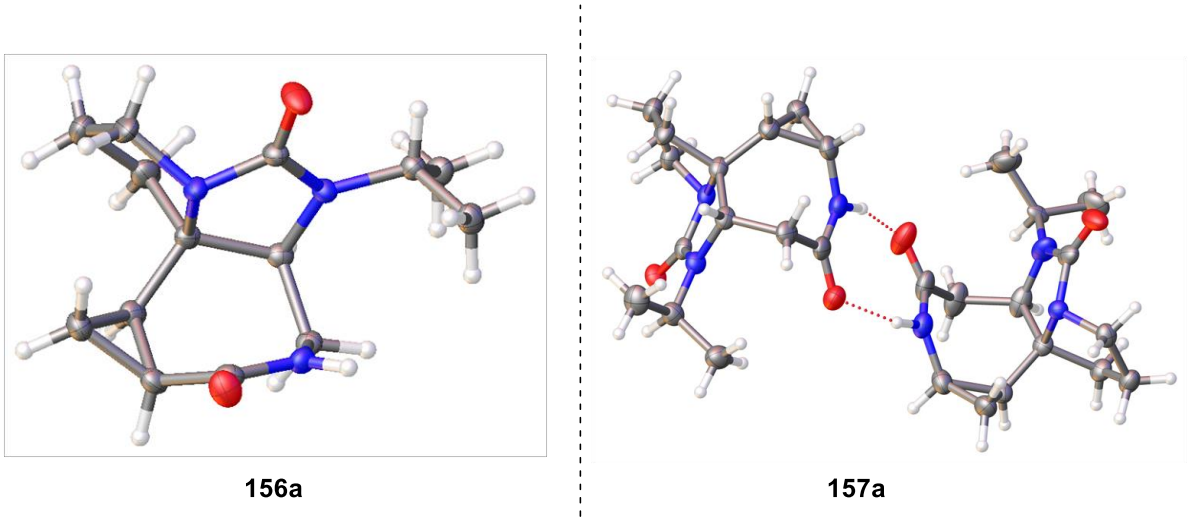
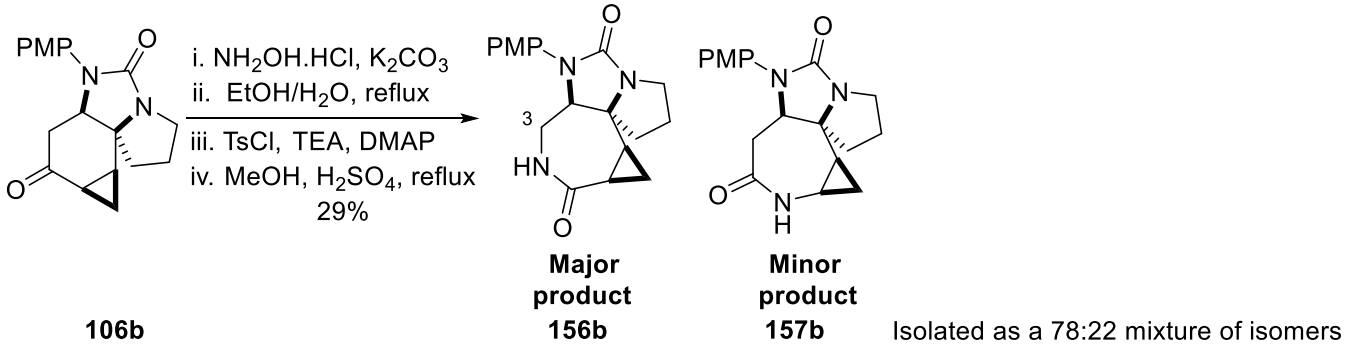



*Figure 14. X-ray crystal structures of the lactams from the Beckmann rearrangement of **106a***

The PMP variant of the cyclopropane scaffold **106b** was then subjected to the same rearrangement reaction conditions as **106a**. From the proton NMR of the crude reaction

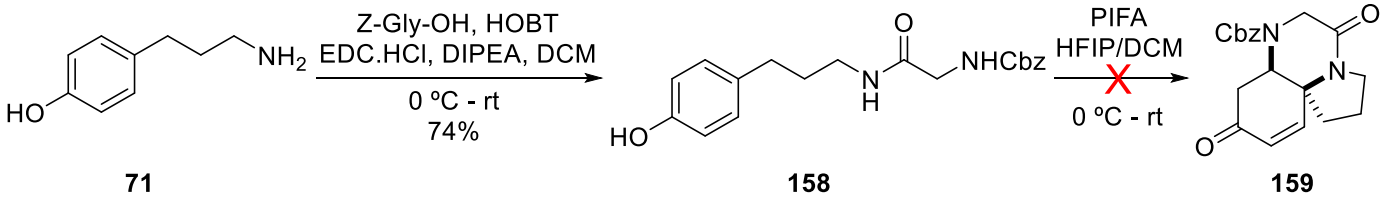
mixture, the isomeric ratio of the lactams formed is difficult to deduce. However, the product was isolated as a 78:22 mixture of the isomeric lactams **156b** and **157b** respectively. The regiochemistry of the major product **156b** was determined by the $^{1}$H-$^{1}$H COSY NMR correlation between its N-*H* proton and the diastereotopic 3-*H* protons.




*Scheme 55. Beckmann rearrangement of the PMP variant of the cyclopropane scaffold **106b***

## 2.8 Attempted PIFA dearomatisation of a pseudopeptide

The pseudopeptide **158** was made from the reaction between the key amine **71** and Z-Gly-OH as shown below. It was then subjected to PIFA dearomatisation to give direct access to piperazinone-containing skeleta such as **139** above. However, the complexity-generating step did not proceed as desired. The mass of the intended product was observed by LCMS in the course of the reaction but it decomposed into an unknown mixture upon work up.




*Scheme 56. Attempted synthesis of a key scaffold via PIFA deromatisation of a pseudopeptide*

## 2.8 Summary of scaffolds prepared

From the primary scaffold variants **83a-c** synthesised via PIFA dearomatisation, 14 diverse secondary scaffolds were obtained employing the ring addition, cleavage and expansion strategies to the top down approach to LOS as shown in the figure below.

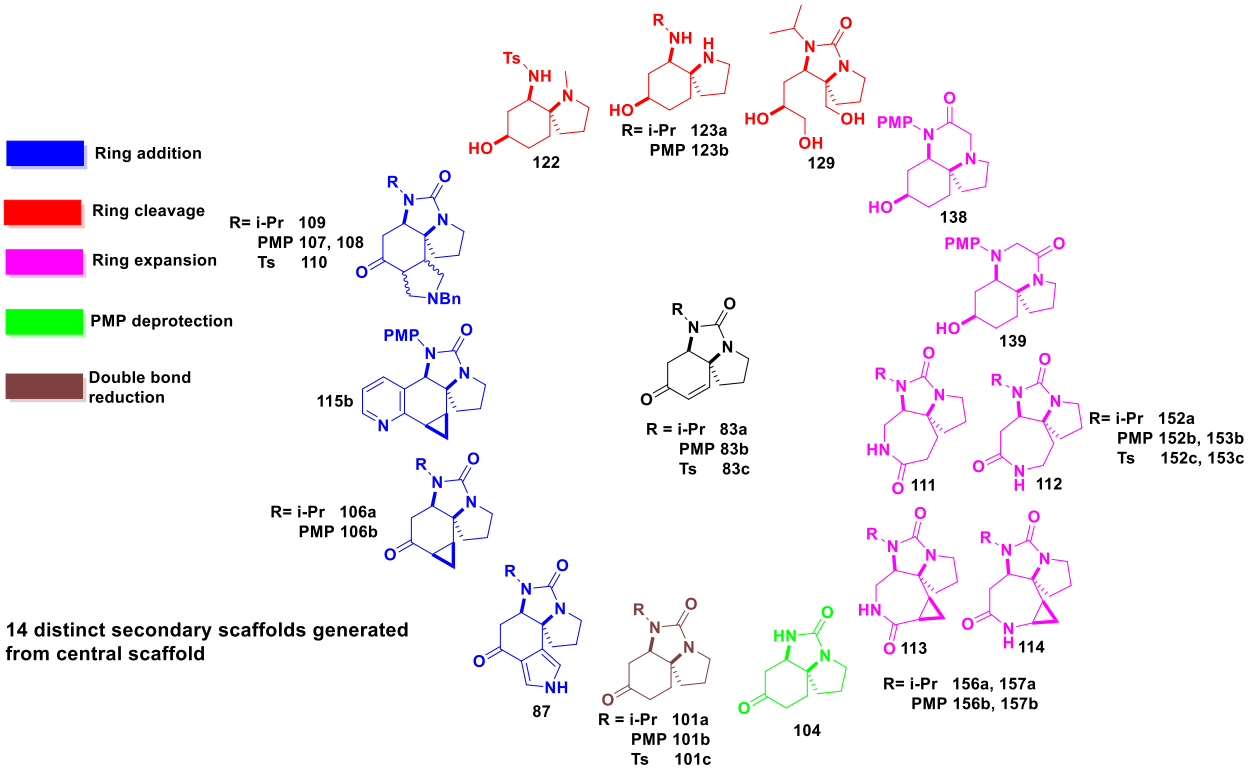



*Figure 15. Summary of secondary scaffolds obtained from variants of the key scaffold*

# 3.0 Results and discussion 2

## 3.1 Decoration of secondary scaffolds

Our plan for decoration of secondary scaffolds involves the functionalisation of such scaffolds along different vectors, with exemplar medicinal chemistry capping groups to furnish final compounds for biological screening. A typical decoration plan is shown in *Figure 16* below. The ketone **101a** can be reduced to the alcohol for carbamate synthesis or $S_NAr$ reactions. Direct reductive amination of **101a** with exemplar medicinal chemistry capping groups can also furnish final compounds. Alternatively, **101a** can be used for reductive amination with methylamine to keep the molecular weight of the product small enough (not more than +15 mass unit of the molecular weight of the ketone of the primary scaffold) for subsequent amidation, sulfonylation and Buchwald-Hartwig coupling among other possible decoration reactions.

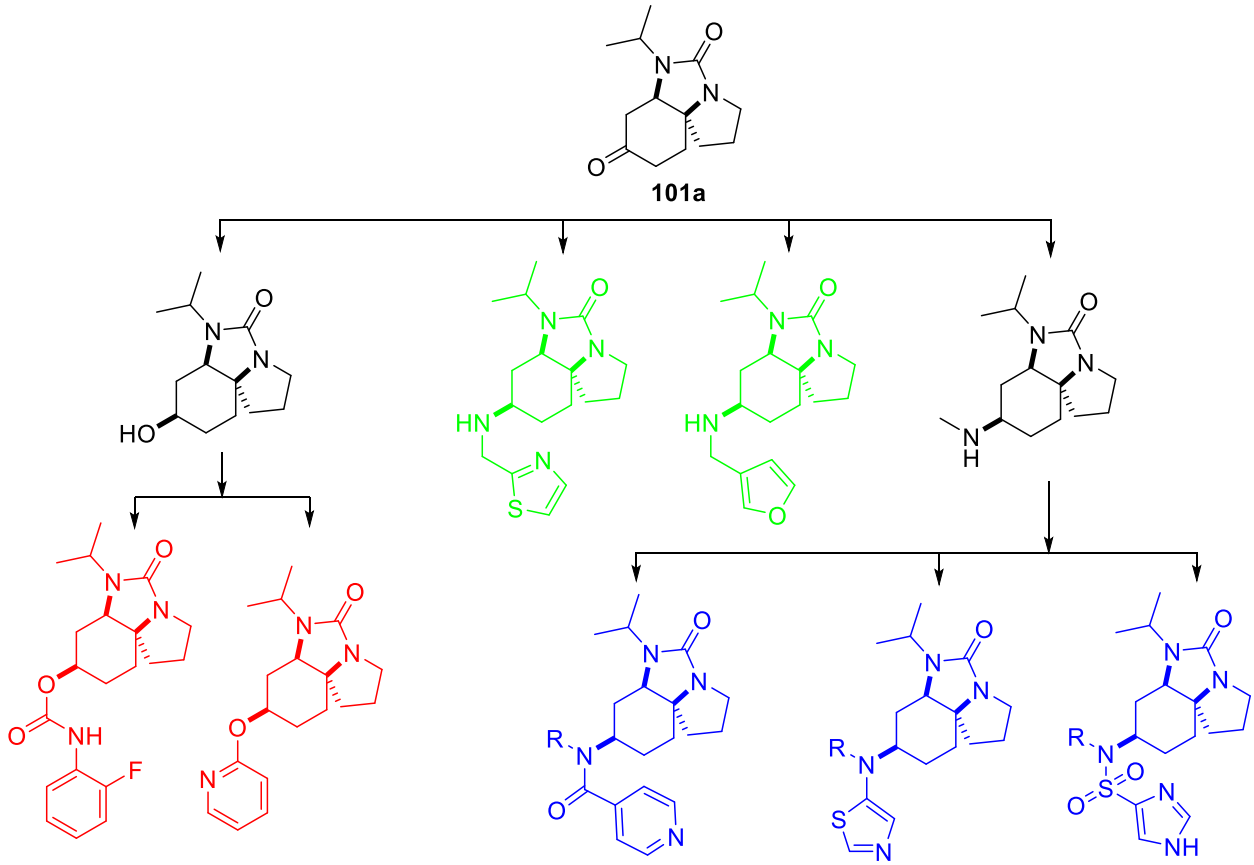



*Figure 16. A typical diversity-generating decoration plan for the synthesis of final compounds for biological screening*

The medicinal chemistry capping groups were selected on the basis that the final compounds would be in lead-like space after assessment by LLAMA. Therefore, with respect to molecular weight considerations, there is less flexibility for the design of final compounds for the PMP- and tosyl-substituted secondary scaffolds than for the isopropyl substituted ones.

The series of final compounds prepared by functionalisation of secondary scaffolds are discussed below.

### 3.1.1 Final compounds derived from the isopropyl variant of the ketone of the primary scaffold

The final compounds obtained from the ketone **101a** for biological screening are shown below.

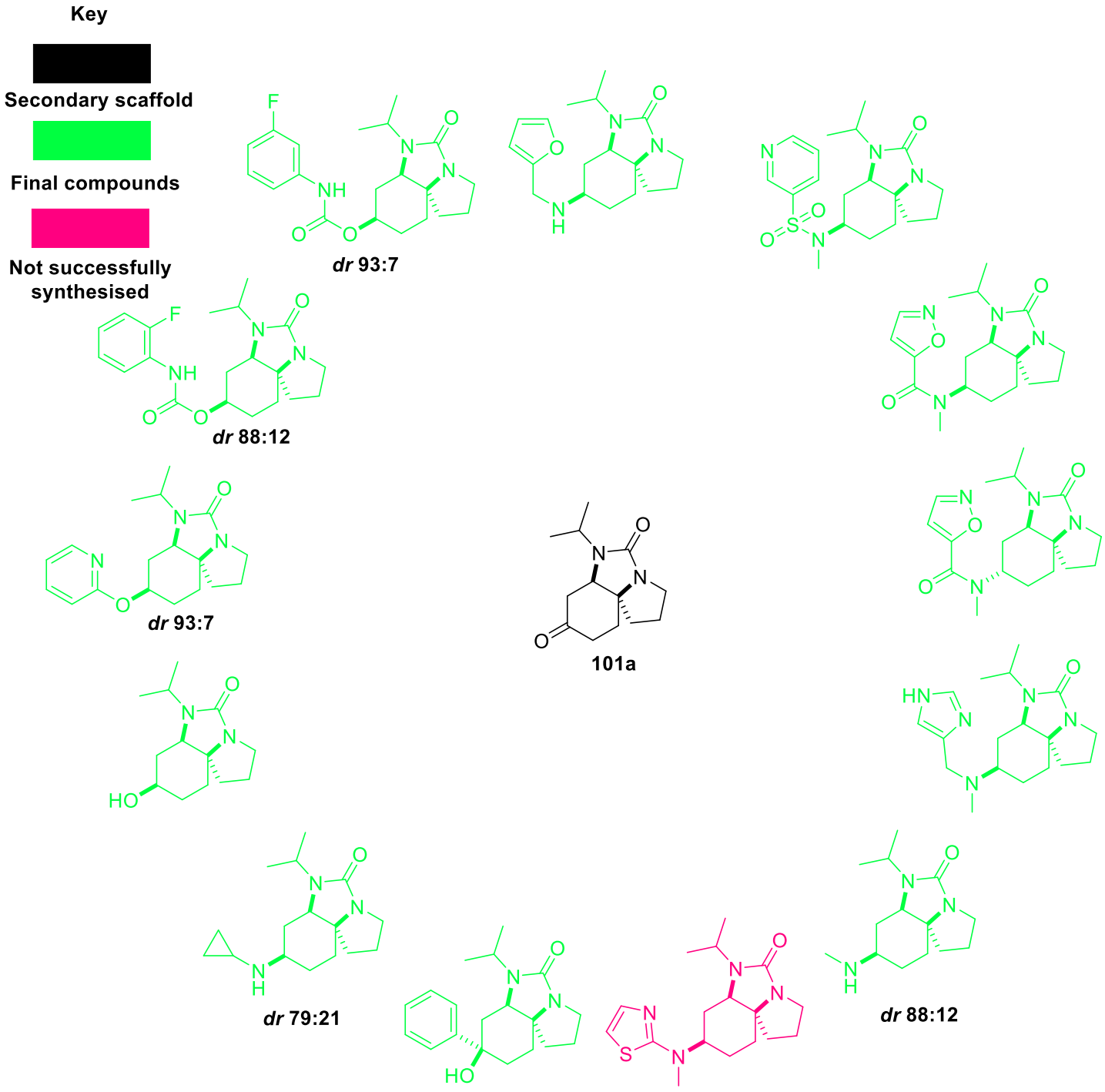
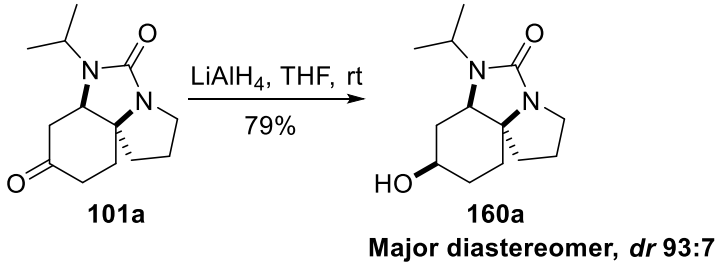


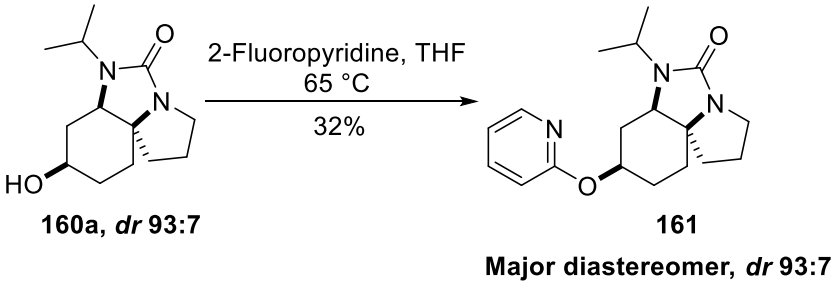

*Figure 18. Final compounds obtained from the ketone **101a***

The ketone **101a** was converted to the alcohol **160a** for $S_NAr$ and carbamate syntheses. Therefore, treatment of **101a** with $LiAlH_4$ at room temperature gave **160a** in 79% yield but the product was isolated as a mixture of diastereomers with a *dr* of 93:7 (proton NMR of the crude reaction mixture was not taken). The stereochemistry of the major diastereomer is the same as that of the product of the sodium borohydride reduction of **101a** (see *Scheme 60*).



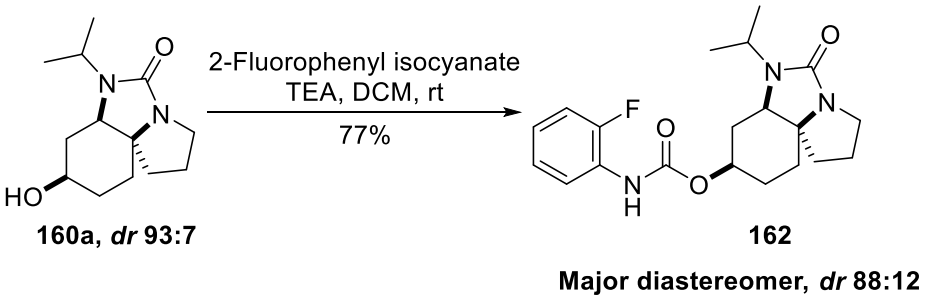

*Scheme 57. Lithium aluminium hydride reduction of the ketone**101a** to the alcohol **160a***

Compound **160a** was then used to carry out an $S_NAr$ reaction with 2-fluoropyridine to append the heteroaromatic ring to the oxygen atom of the alcohol functionality. From the proton NMR of the crude reaction mixture, the diastereomeric ratio of the pyridines formed was difficult to deduce but the product was isolated as a 93:7 mixture of diastereomers. Half of the starting alcohol was recovered.



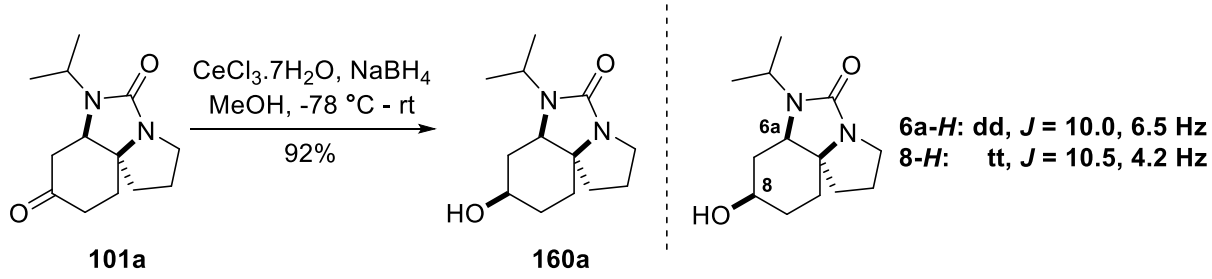

*Scheme 58. Functionalisation of the alcohol **160a** with 2-fluoropyridine*

The recovered alcohol **160a** was used to react with 2-fluorophenylisocyanate to obtain the corresponding carbamate **162**. From the proton NMR of the crude reaction mixture, the diastereomeric ratio of the product formed is 82:18 but was isolated as an 88:12 mixture of diastereomers as shown below.




*Scheme 59. Carbamate synthesis by reacting 2-fluorophenylisocyanate with the alcohol **160a***

In an attempt to improve diastereoselectivity, reduction of the ketone **101a**, under Luche conditions[104], was carried out to obtain a product with a diastereomeric ratio of 93:7 (from the proton NMR of the crude reaction mixture) but was isolated cleanly in 92% yield as a single diastereomer. The product is identical to the major diastereomer of the alcohol obtained via reduction with lithium aluminium hydride (see *Scheme 56*). Attempts to determine the stereochemistry of **160a** by NOE correlations was unsuccessful. However, it was determined from the analysis of the coupling constants of the protons at positions 6a (6a-*H*: dd, *J* = 10.0, 6.5 Hz) and 8 (8-*H*: tt, *J* = 10.5, 4.2 Hz). Both protons are axial and have to be on the same face of the cyclohexanol ring. This was confirmed by the x-ray crystal structure of the derived carbamate **163**.




*Scheme 60. Sodium borohydride reduction of the ketone functionality of **101a** to its corresponding alcohol*

Generally, nucleophilic attacks on the carbonyl groups of **101a-c** respectively gave products that indicate that such attacks were predominantly on the diasteretopic face of the carbonyl group that is *anti* to the urea ring. Theoretical and experimental results by Burgi, Dunitz and co-

workers[109,110] have shown that the angle of attack of a nucleophille towards a carbonyl carbon is 105 ± 5°. This is consistent with the stereochemical outcome of the attack of nucleophiles on the carbonyl function of the scaffolds **101a-c** as shown below, both for the boat conformation (as this seems to be favoured in the solid state, exemplified by the crystal structures of **101c** and **104**) and the chair conformation of the scaffolds. Similar stereochemical outcome was observed for the imines during reductive amination at the carbonyl function of the scaffold. Also, attack from the convex face (for the boat conformation) or the axial face (for the chair conformation) of the carbonyl group of **101a-c** by a nucleophile seems to be the path of less steric resistance as compared to a nucleophilic attack on the concave face (for the boat conformation) or equatorial face (for the chair conformation) respectively.

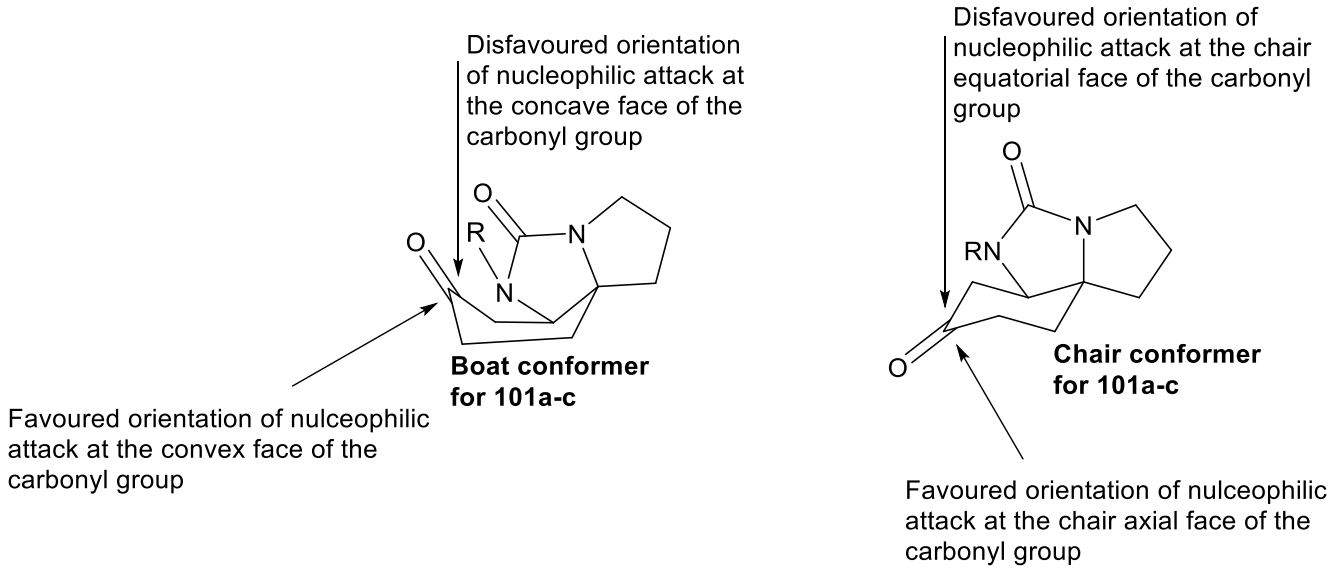
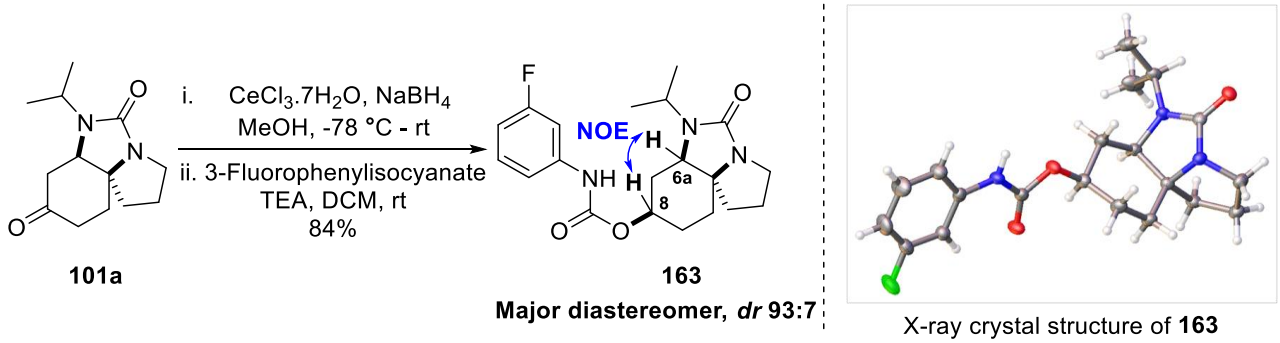



*Figure 17. Depiction of nucleophilic attack on the carbonyl group of **101a-c***

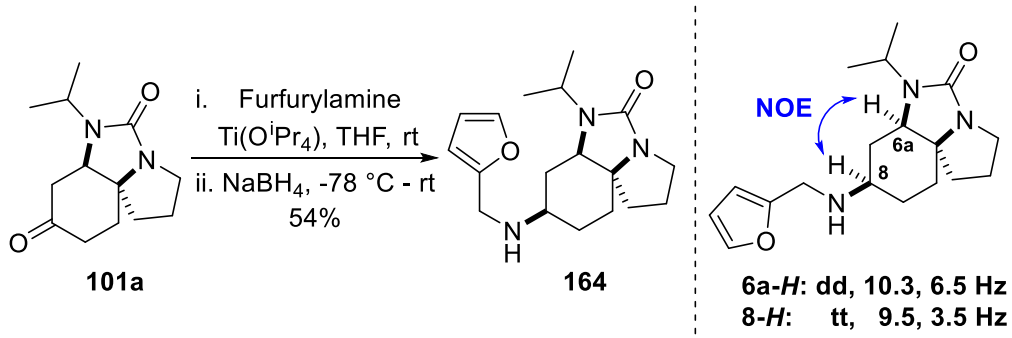
The alcohol **160a** was again obtained under Luche conditions and used crude to react with 3-fluorophenylisocyanate to obtain the corresponding carbamate as a 93:7 diastereomeric mixture in 84% yield. The stereochemistry of the major diastereomer was determined by the presence of an NOE correlation between the protons at positions 6a and 8, and was confirmed by x-ray crystallography.




*Scheme 61. Carbamate synthesis by reacting 3-fluorophenylisocyanate with the alcohol **160a***

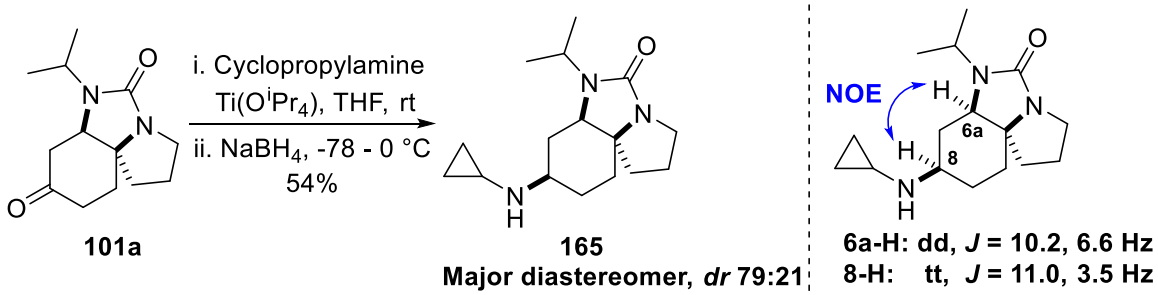
As indicated in *Scheme 61*, the aliphatic six-membered ring of **163** adopts the chair conformation in the crystalline state upon reduction of the carbonyl group of **101a**, followed by carbamate synthesis. This is in sharp contrast to what was observed for the x-ray crystal structures of **101c** and **104**. In all cases where the carbonyl and imino groups in the scaffolds were reduced to the alcohol or amine respectively, and the crystal structures of the products were obtained, the chair conformation is preferred in the solid state. Presumably, the cyclohexanone ring in the scaffolds **101a-c** shifts from the boat conformation to the chair conformation in the crystalline state upon reduction. As stated earlier, the doubly bonded oxygen in cyclohexanone rings is known to considerably lower the energy of the boat conformer with respect to that of the chair conformer.[91–94] (See *Section 2.3*).

The ketone **101a** was also utilised in making final compounds through reductive aminations. The reductive amination of **101a** with furfurylamine gave a single diastereomer of the amine **164** as product. The stereochemistry of the product was determined by an NOE correlation between the 6a-*H* (dd, *J* = 10.3, 6.5 Hz) and 8-*H* (dd, *J* = 9.5, 3.5 Hz) protons. The coupling constants of both protons indicate that they are axial and so have to be on the same face of the six-membered ring.




*Scheme 62. Reductive amination of the ketone **101a** with furfurylamine*

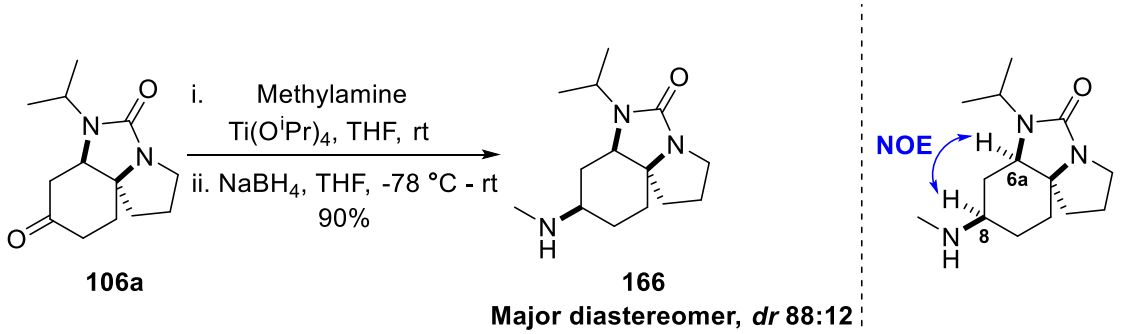
Cyclopropylamine was also used for reductive amination with the ketone **101a** to make the amine **165.** The diastereomeric ratio of the crude product is difficult to discern from the proton NMR but **165** was isolated as a 79:21 mixture of diastereomers in 73% yield. The stereochemistry of the major diastereomer was determined from an NOE correlation between 6a-*H* (dd, *J* = 10.2, 6.6 Hz) and 8-*H* (tt, *J* = 11.0, 3.5 Hz) as well as the analysis of their coupling constants. Both protons are axial and therefore have to be on the same face of the six-membered ring.




*Scheme 63. Reductive amination of the ketone **101a** with cyclopropylamine*

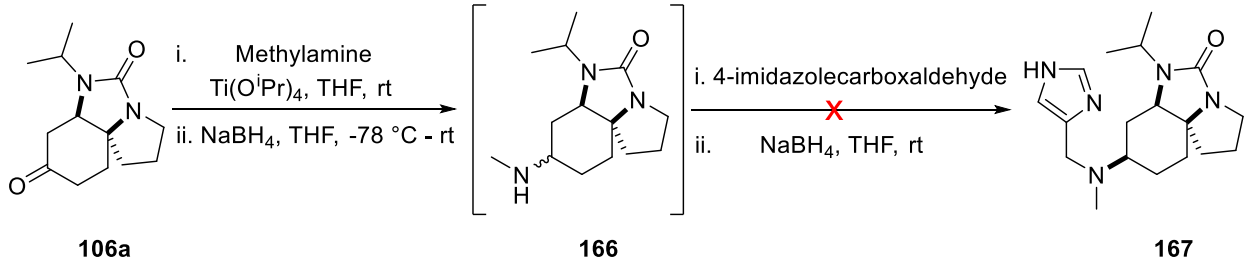
In the same vein, reductive amination of **101a** with methylamine was carried out to obtain a product with a diastereomeric ratio of 83:17 as analysed from the proton NMR of the crude reaction mixture. However, the product **166** was isolated as an 88:12 mixture of diatereomers in 90% yield. Compound **166** can be further utilised for final library syntheses by reductive amination with ketones and aldehydes or in making amides, sulfonamides and carbamates among others. The stereochemistry of the major diastereomer of **166** was determined by the

presence of an NOE correlation between its 6a-*H* and 8-*H* protons. This was confirmed by the x-ray crystal structure of the derived sulfonamide **168**.



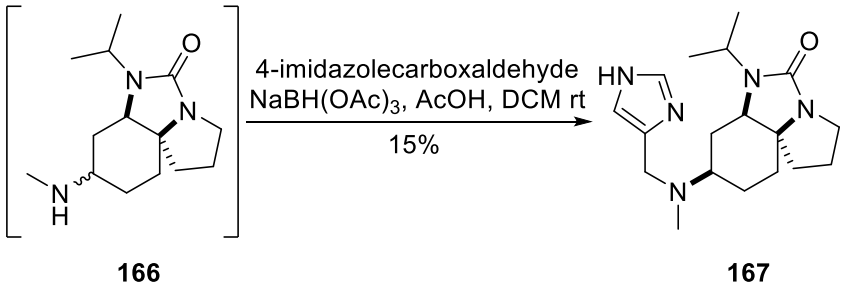

*Scheme 64. Reductive amination of the ketone **101a** with methylamine*

An attempt to perform a one-pot reductive amination on the crude methylamine **166** with 4-imidazolecarboxaldehyde using sodium borohydride failed as shown below. Only the mass of the amine **166** was detected by LCMS.



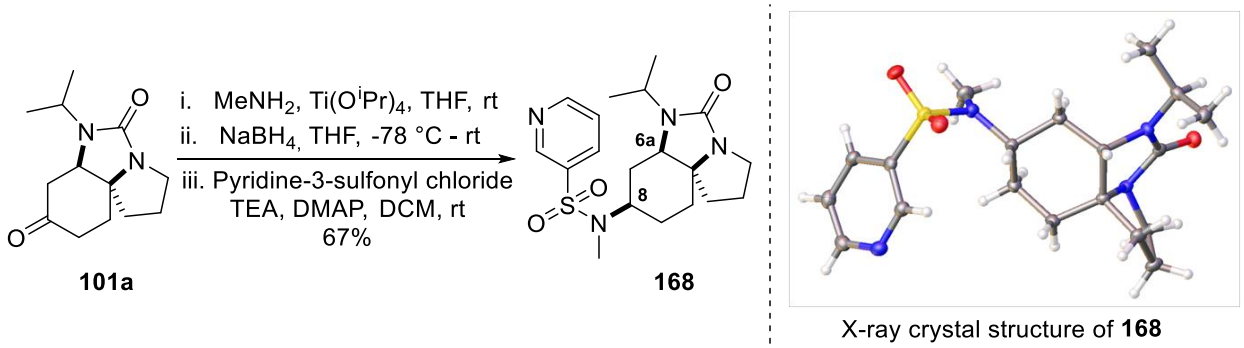

*Scheme 65. Attempted reductive amination of 4-imidazolecarboxaldehyde with the amine **166***

It was thought that the excess sodium borohydride from the first step might be reducing the 4-imidazolecarboxaldehyde to the corresponding alcohol thereby bringing the last step of the reaction to a halt. The crude amine **166** was therefore recovered and used for the same reaction using sodium triacetoxyborohydride to prevent the possible reduction of the aldehyde. The product **167** was then obtained in 15% yield as an 80:20 mixture of imidazole tautomers at 50% conversion after 3 days.



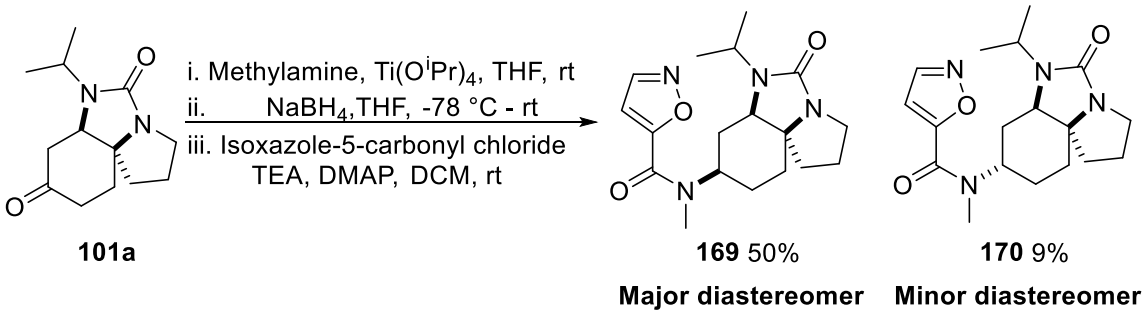

*Scheme 66. Reductive amination of 4-imidazolecarboxaldehyde with the amine **166***

The amine **166** was also used to make the sulfonamide **168** by reacting it with pyridine-3-sulfonyl chloride as shown below. A single diastereomer was isolated in 67% yield over three steps. The stereochemistry of **168** was determined by the presence of an NOE correlation between its 6a-*H* and 8-*H* protons and confirmed by X-ray crystallography.



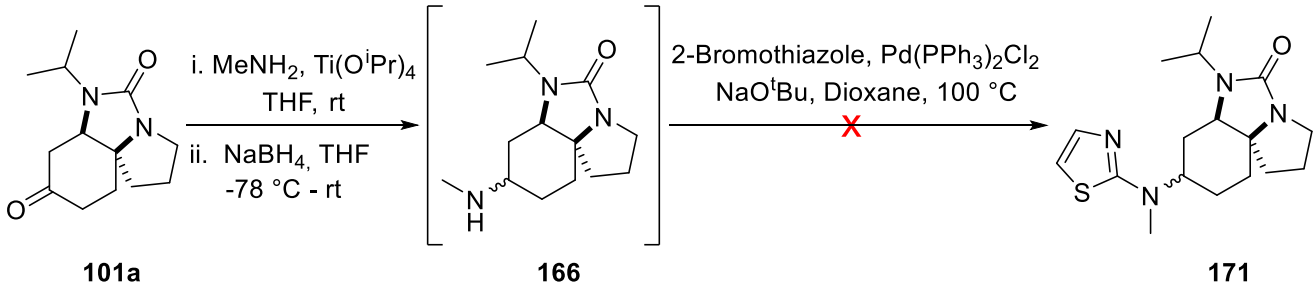

*Scheme 67. Sulfonamide synthesis from the amine **166***

Amides were also obtained from the amine **166** by reacting it with isoxazole-5-carbonyl chloride as shown below. The major diastereomer was obtained as a 63:37 mixture of rotamers while the minor diastereomer was obtained as a 50:50 mixture of rotamers as indicated by analysis of their proton NMR spectra.



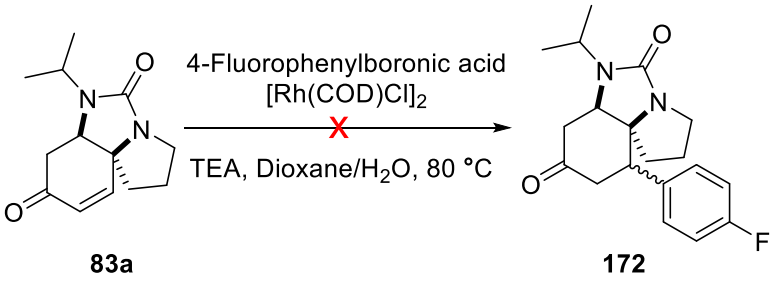

*Scheme 68. Amide synthesis from the amine **166***

The amine **166** was also used as a substrate for a Buchwald-Hartwig reaction[111,112] with 2-bromothiazole as shown below but only a trace amount of the product was detected by LCMS.



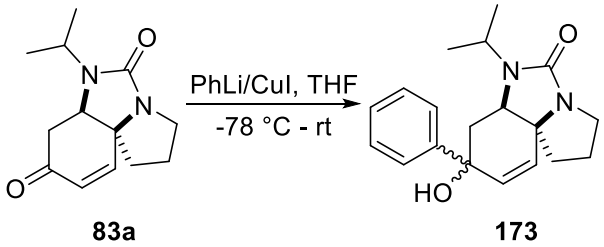

*Scheme 69. Attempted Buchwald-Hartwig coupling of the amine **166** with 2-bromothiazole*

Rhodium catalysed 1,4-addition of 4-fluorophenylboronic acid to the enone **83a** was attempted as shown below but only a trace amount of a product with the correct mass was detected by LCMS.




*Scheme 70. Attempted 1,4-addition of an arylboronic acid to the enone **83a***

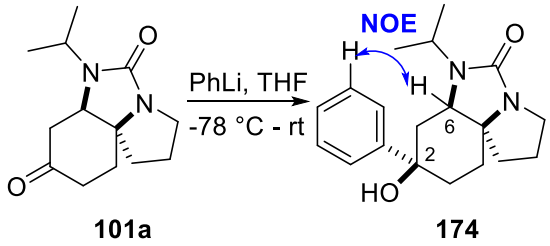
Using an organocopper as a soft organometallic nucleophile to effect the 1,4- addition to the enone **83a**[113] instead of an arylboronic acid, the 1,2-addition product was observed from the proton NMR of the crude product. This might be as a result of the fact that the desired site of attack is hindered.




**83a** **173**

*Scheme 71. Attempted 1,4-addition of an organocopper to the enone **83a***

Therefore 1,2-addition of organometallic reagents to the ketone **101a** became desirable. Adding 2-thienylmagnesium bromide to **101a** gave a complex mixture. However, using phenyllithium as the nucleophilic reagent, the desired product **174** was obtained as a single diastereomer arising from addition to the bottom face of the ketone as in the hydride reductions. The stereochemistry was determined by the presence of an NOE correlation between 6a-*H* and the aromatic ring protons.




**101a** **174**

*Scheme 72. 1,2-addition of phenyllithium to the ketone **101a***

### 3.1.2 Final compounds derived from the PMP and tosyl variants of the ketone of the primary scaffold

The final compounds obtained from the PMP-subtituted ketone **101b** and tosyl-substituted ketone **101c** are shown below. As stated earlier, there is less flexibility in the design of final compounds for **101b** and **101c** as compared to **101a** due to molecular weight limitations.

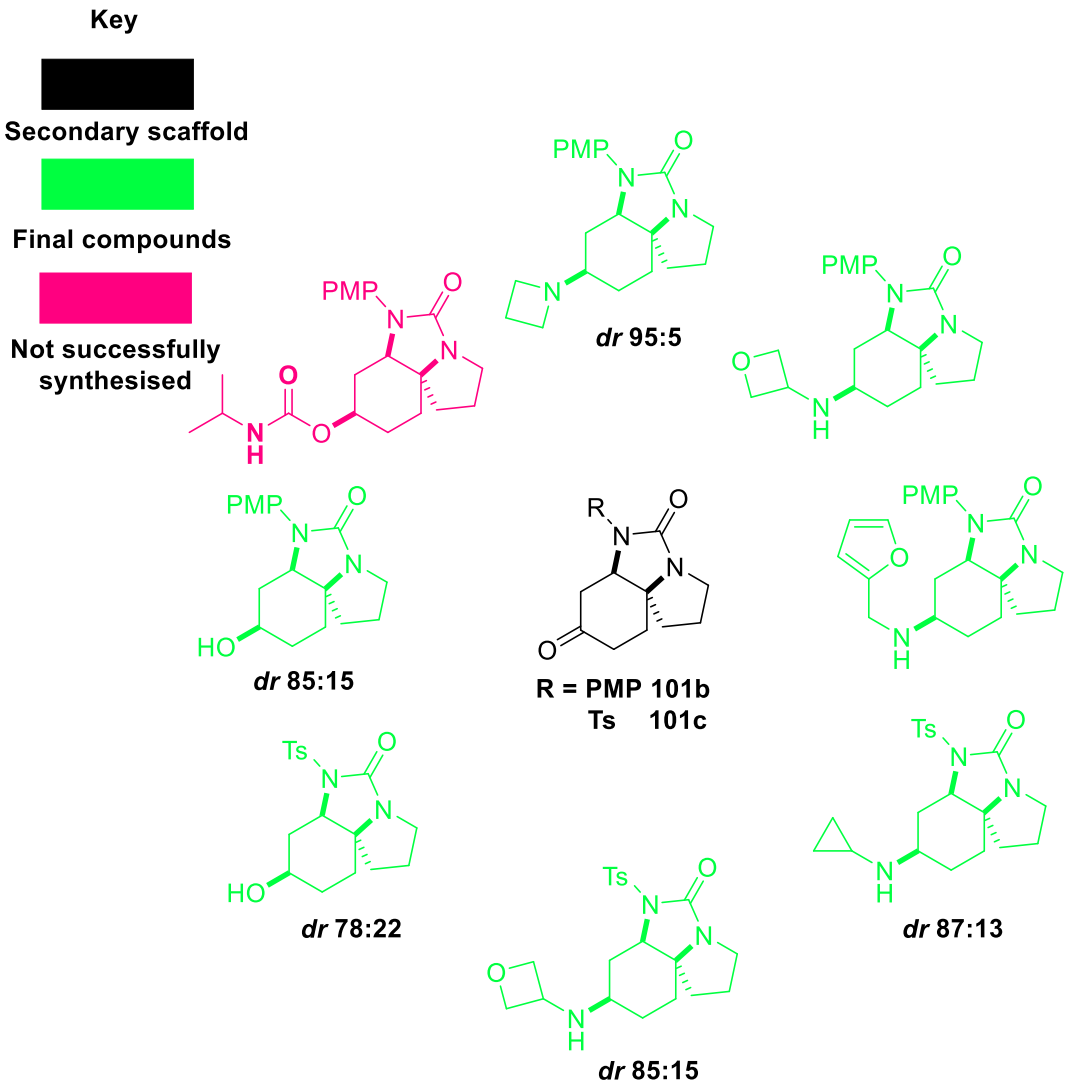
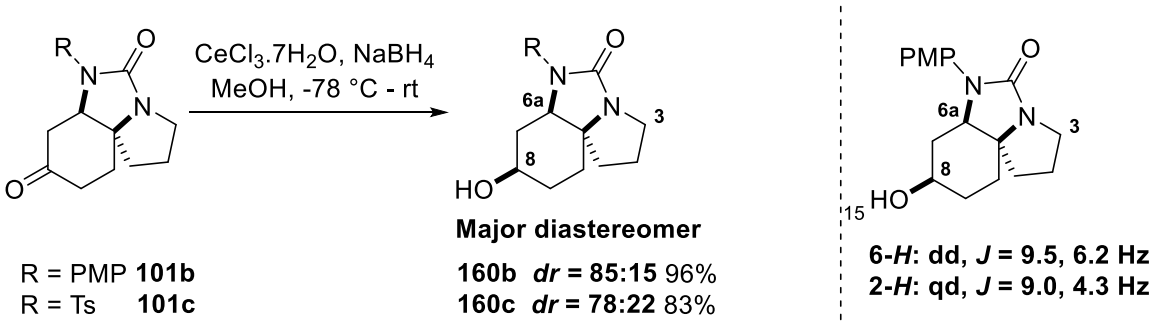



*Figure 19. Final compounds obtained from the ketones **101b** and **101c** respectively*

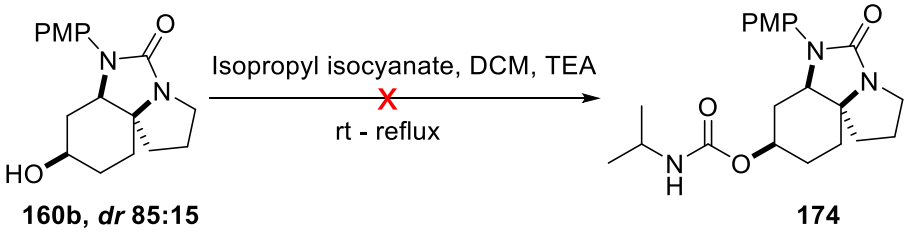
The PMP variant of the ketone of the primary scaffold **101b** and its tosyl analogue **101c** were subjected to sodium borohydride reduction, under Luche conditions, to obtain the corresponding alcohols **160b** (*dr* of 85:15 both in the crude and isolated product) and **160c** (*dr*

of 78:22 both in the crude and isolated product) respectively.The stereochemistry of the major diastereomer **160b** was determined via the coupling constants of its 6a-*H* (dd, *J* = 9.5, 6.2 Hz) and 8-*H* (qd, *J* =9.0, 4.3 Hz) confirming both protons are axial but that of **160c** was assigned by analogy to those of **160a** and **160b**. The NMR peak of the 8-*H* proton of **160c** overlaps with the NMR peak of one of its diastereotopic 3-*H* protons. Therefore, neither NOESY nor coupling constant analysis could be used to determine its stereochemistry.




*Scheme 73. Sodium borohydride reduction of the ketone functionality of **101b** and **101c** to their corresponding alcohols*

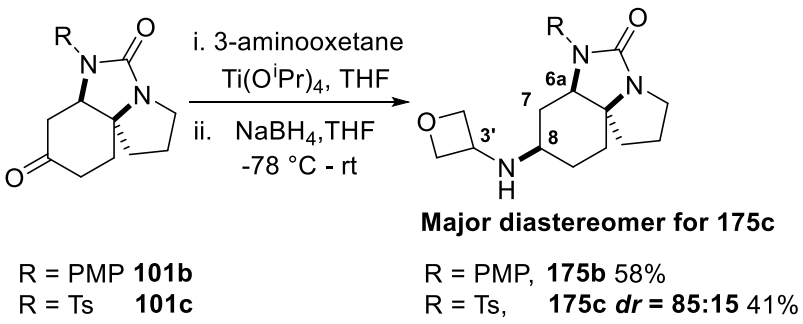
Reacting the alcohol **160b** with isopropyl isocyanate to make the corresponding carbamate, only the mass of the starting material was detected by LCMS. This is despite the fact that the alcohol **160a** was used in making carbamates with 2- and 3-fluorophenyl isocyanates (see *Schemes 59 and 61*).




*Scheme 74. Attempted carbamate synthesis by reacting isopropyl isocyanate with the alcohol **160b***

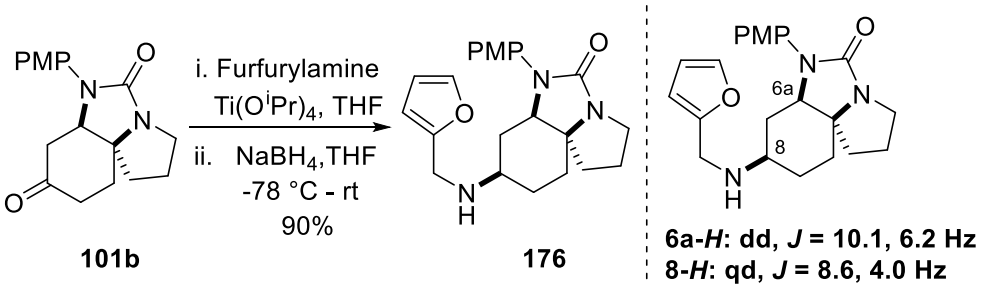
Reductive amination of **101b** and **101c** with 3-aminooxetane gave the desired products in 58% and 41% yields respectively. From the proton NMR of the crude product for the reaction of

**101b**, the diastereomeric ratio is 81:19 but it was isolated as a single diastereomer. Also, from the proton NMR analysis of the crude product for the reaction of **101c**, the diastereomeric ratio is 80:20 but it was isolated as an 85:15 mixture of diastereomers. The stereochemistry of **175b** and **175c** were assigned by analogy, to those of **164-166** (see *Section 3.1.1*), and also to those of **176** and **177** (see *Schemes 76* and *77*). From the proton NMR, the 6a-*H* peak of **175b** overlaps with the 3'-*H* peak (the numbering of the protons is shown below). Similarly, the 8-*H* peak of **175c** overlaps with the peak of one of the diastereotopic 7-*H* protons. Therefore, it is difficult to determine the stereochemistry of both **175b** and **175c** either by the presence of NOE correlations or coupling constant analyses.



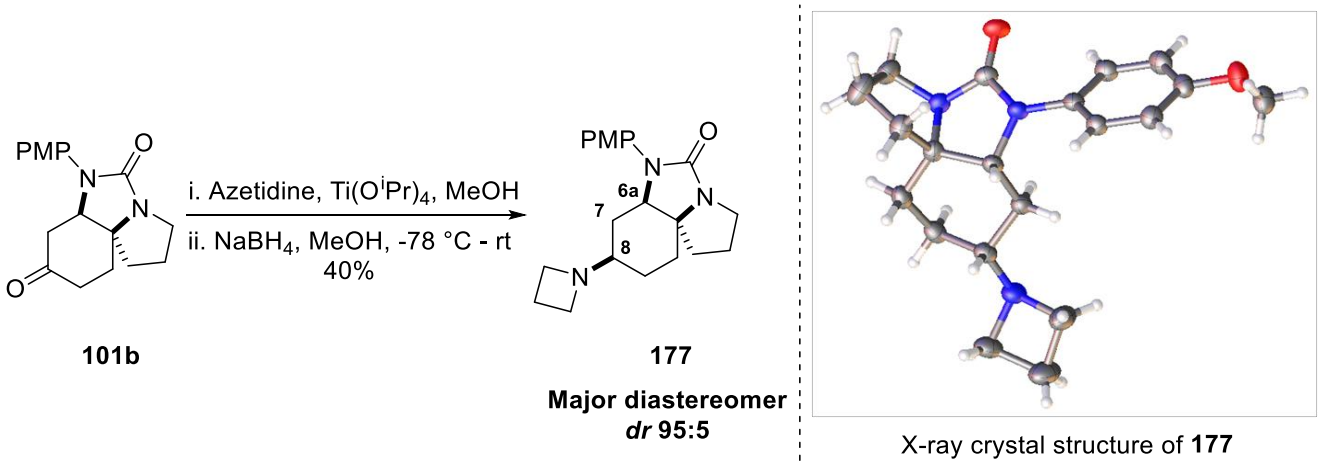

*Scheme 75. Reductive amination of the ketones **101b** and**101c** with 3-aminoxetane*

Similarly, subjecting the ketone **101b** to reductive amination with furfurylamine gave the desired product whose diastereomeric ratio is difficult to tell from the proton NMR of the crude reaction mixture. However, it was isolated as a 93:7 mixture of diastereomers in 90% yield as shown below. The stereochemistry of the product was determined from the coupling constants of its 6a-*H* (dd, *J* = 10.1, 6.2 Hz) and 8-*H* (qd, *J* = 8.6, 4.0 Hz) protons and by analogy with compound **164**. Even though the coupling constant of 8.6 Hz for 2-*H* is not typical for axial/axial coupling, 2-*H* is most probably an axial proton because such a coupling constant is way out of range for an equatorial proton.




*Scheme 76. Reductive amination of the ketone **101b** with furfurylamine*

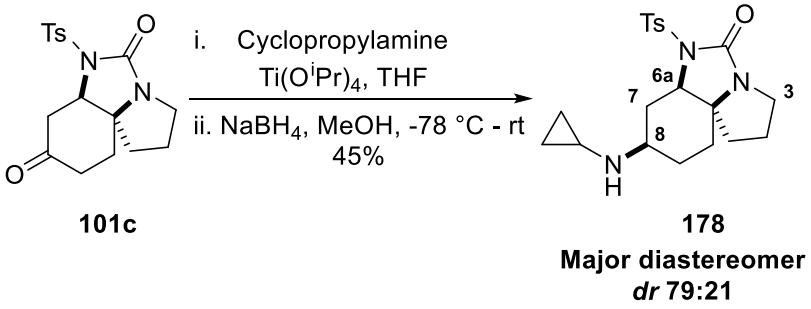
Using azetidine for reductive amination with **101b**, the desired product **177** was obtained as a 74:26 diastereomeric mixture from the proton NMR of the crude reaction mixture. However, the product was isolated as a 95:5 mixture of diastereomers in 44% yield. Analysis of the stereochemistry of the major product from the presence of NOE correlations or the coupling constants of its 6a-*H* and 8-*H* protons was difficult. This is because the 8-*H* signal (in the proton NMR) overlaps with the signal of one of the diastereotopic 7-*H* protons. However, the x-ray crystal structure was obtained and it shows that the azetidine is *syn* to the urea.




*Scheme 77. Reductive amination of the ketone **101b** with azetidine*

Also, using cyclopropylamine to carry out reductive amination with the ketone **101c**, the product was isolated as a 79:21 mixture of diastereomers. The diastereomeric ratio from the proton NMR of the crude product is difficult to deduce. The stereochemistry of the major diastereomer **177** was assigned by analogy to that of **165**. Determining the stereochemistry of

**177** by the presence of NOE correlations and/or coupling constant analysis between the 6a-*H* and 8-*H* protons proved difficult. This is because the 8-*H* peak (in the proton NMR) overlaps with the peak for one of the diastereotopic 7-*H* protons, and also overlaps with the peak of one of the diastereotopic 3-*H* protons.




**101c** **178**

**Major diastereomer**

***dr* 79:21**

*Scheme 78. Reductive amination of the ketone **101c** with cyclopropylamine*

### 3.1.3 Final compounds derived from the pyrrolidine-fused secondary scaffolds

The final compounds obtained from the pyrrolidine-fused secondary scaffolds are shown below.

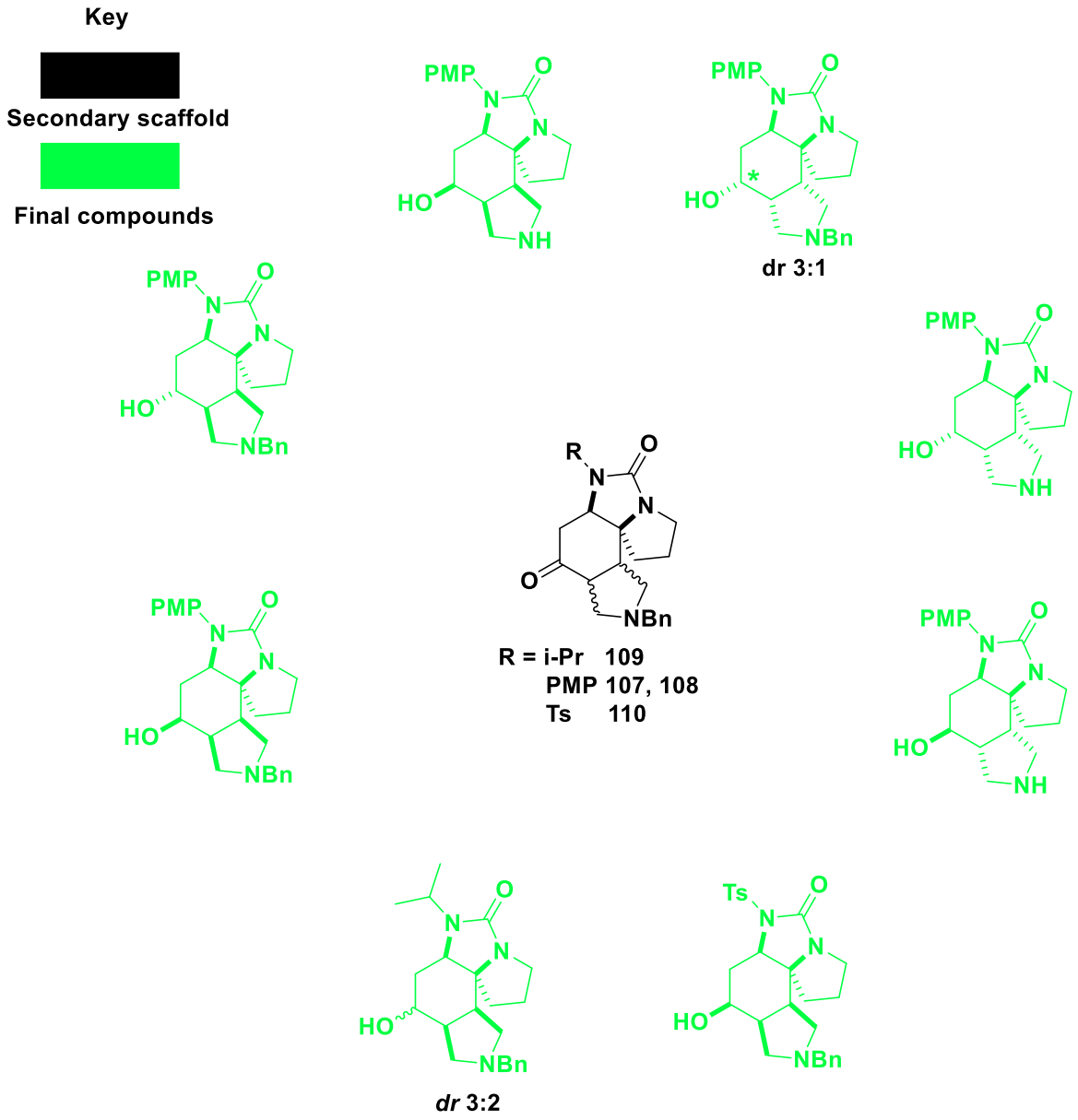
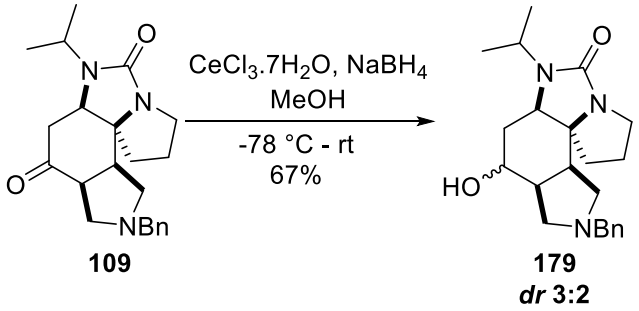



*Figure 20. Final compounds obtained from the pyrrolidine-fused secondary scaffolds*

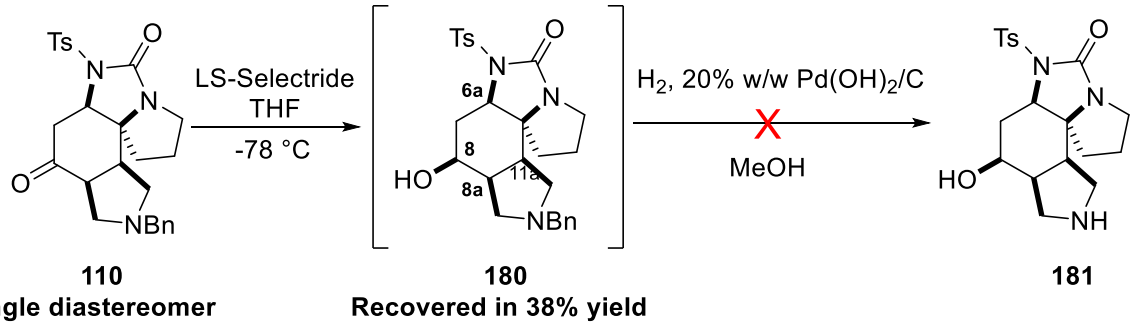
The carbonyl group of the pyrrolidine **109** was subjected to sodium borohydride reduction under Luche conditions to obtain a product whose diastereomeric ratio was difficult to deduce from the proton NMR of the crude product but was isolated as a 3:2 mixture of diastereomers

in 67% yield. The identities of the diastereomers were not able to be determined because of extensive signal overlap in the proton NMR of the mixture.




*Scheme 79. Sodium borohydride reduction of the ketone functionality of the pyrrolidine **109** to its corresponding alcohol*

In an attempt to improve diastereoselectivity, LS-selectride was used for the reduction of **110** instead of sodium borohydride. It is difficult to discern the diastereomeric ratio of the crude product from its proton NMR. The crude product was then subjected to debenzylation via hydrogenation, catalysed by 20% w/w $Pd(OH)_2/C$ as shown below. This was to access the secondary pyrrolidine for proposed decoration reactions. However, only the mass of the alcohol **180** was detected by LCMS. Compound **180** was then recovered from the column as a single diastereomer in 38% yield. The stereochemistry of the pyrrolidine ring was determined by the presence of NOE correlations of 6a-*H*, to 8a-*H* and 11a-*H* protons. Determination of the stereochemistry of the alcohol functionality from the presence of NOE correlations was not successful. However, it was analysed from the coupling constants of 6a-*H* (dd, *J* = 10.5, 5.4 Hz) and 8-*H* (dt, 9.3, 5.6 Hz). Both protons (6a-*H* and 8-*H*) are axial and have to be on the same face of the six-membered ring.



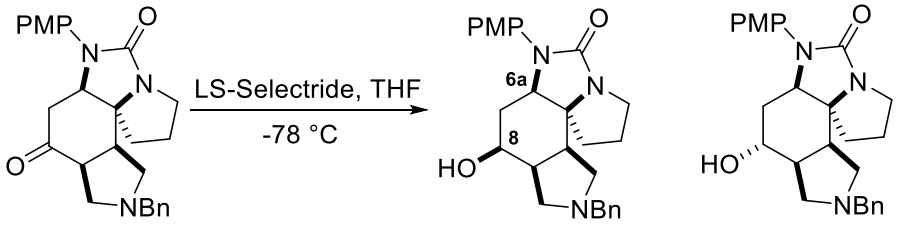

**110**
**Single diastereomer**

**180**
**Recovered in 38% yield**

**181**

*Scheme 80. LS-selectride reduction of **110** to its alcohol followed by attempted debenzylation*

In a similar vein, using LS-selectride to reduce the carbonyl group of **107** (26 mg scale), the alcohols **182** and **183** were obtained in 29% (7.6 mg) and 7% (1.7 mg) yields respectively. From the proton NMR of the crude product, the diastereomeric ratio is difficult to determine. The stereochemistry of **182** was determined by the presence of an NOE correlation between its 6-*H* and 8-*H* protons, meaning the stereochemistry of **183** can be assigned by inference.



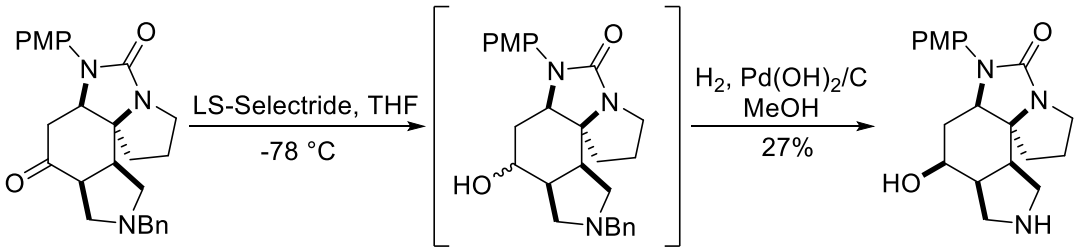

**107**

**182** 29%

**183** 7%

*Scheme 81. LS-selectride reduction of **107** to the corresponding alcohols*

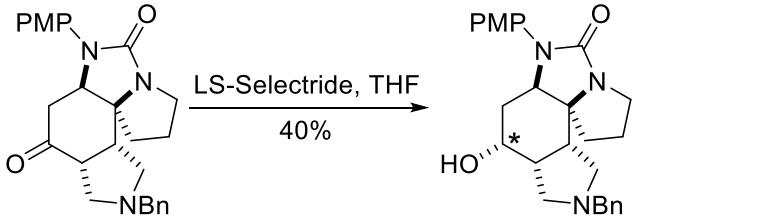
In a two-step process, the crude product of the LS-selectride reduction of **107** (52 mg scale) was then subjected to debenzylation via hydrogenation with a slurry of $Pd(OH)_2/C$ as catalyst as shown below. However, only one diastereomer **184** was isolated in 27% yield as determined from both LCMS and NMR spectral data. Compound **184** was taken to be the debenzylated product of **182** based on the yield.




**107** **184**

*Scheme 82. LS-selectride reduction of **107** followed by debenzylation*

The alternate pyrrolidine diastereomer **108** was subjected to LS-selectride reduction to give a product whose diastereomeric ratio is 3:1 as analysed from the proton NMR of the crude reaction mixture. The product was isolated in the same ratio in 40% yield as shown below. The stereochemistry of the major diastereomer was assigned by inference from that of **187** (See *Scheme 84*).

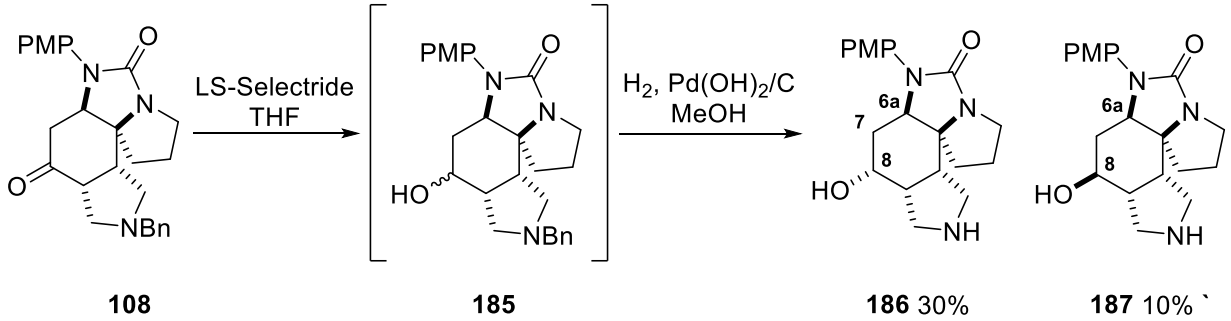



**108** **185**
**Major diastereomer, *dr* 3:1**

*Scheme 83. LS-selectride reduction of **108** to the corresponding alcohol*

In a two-step process, the crude product of the LS-selectride reduction of **108** was subjected to debenzylation via hydrogenation with a slurry of $Pd(OH)_2/C$ as catalyst as shown below. The two debenzylated products **186** and **187** were isolated in 30% and 10% yields respectively. Attempts to determine the stereochemistry of both **186** and **187** by NOESYexperiments were unsuccessful. However, the stereochemistry of the minor diastereomer **187** was determined from the analysis of the coupling constants of its 6a-*H* (dd, *J* = 9.0, 7.0 Hz) and 8-*H* (ddd, *J* = 11.5, 7.0, 3.0 Hz). The proton 6a-*H* is thought to be axial because a coupling constant of 9.0 Hz is out of range for an equatorial proton. Therefore, both the 6a-*H* and 8-*H* protons of **187** would have to be on the same face of the six-membered ring. The 6a-*H* proton of the major

diastereomer **186** is a triplet with a coupling constant of 4.7 Hz while the 8-*H* and the both of its 7-*H* protons appeared as unassignable multiplets in the proton NMR spectrum. Therefore, it is difficult to decipher the stereochemistry of the alcohol functionality of the major diastereomer from the analysis of coupling constants but it can be deduced from that of the minor diastereomer. In this instance, LS selectride seems to have preferentially attacked the face of the carbonyl group that is *anti* to the fused pyrrolidine ring of **108**.




**108** **185** **186** 30% **187** 10% `

*Scheme 84. LS-selectride reduction of **108** to the alcohol followed by debenzylation*

The tetracyclic pyrrolidines are complex and have vectors that can be differentially functionalised to access a range of lead-like compounds for biological screening.

### 3.1.4 Final compounds derived from the cyclopropane-fused secondary scaffolds

The final compounds obtained from the cyclopropane-fused secondary scaffolds are shown below.

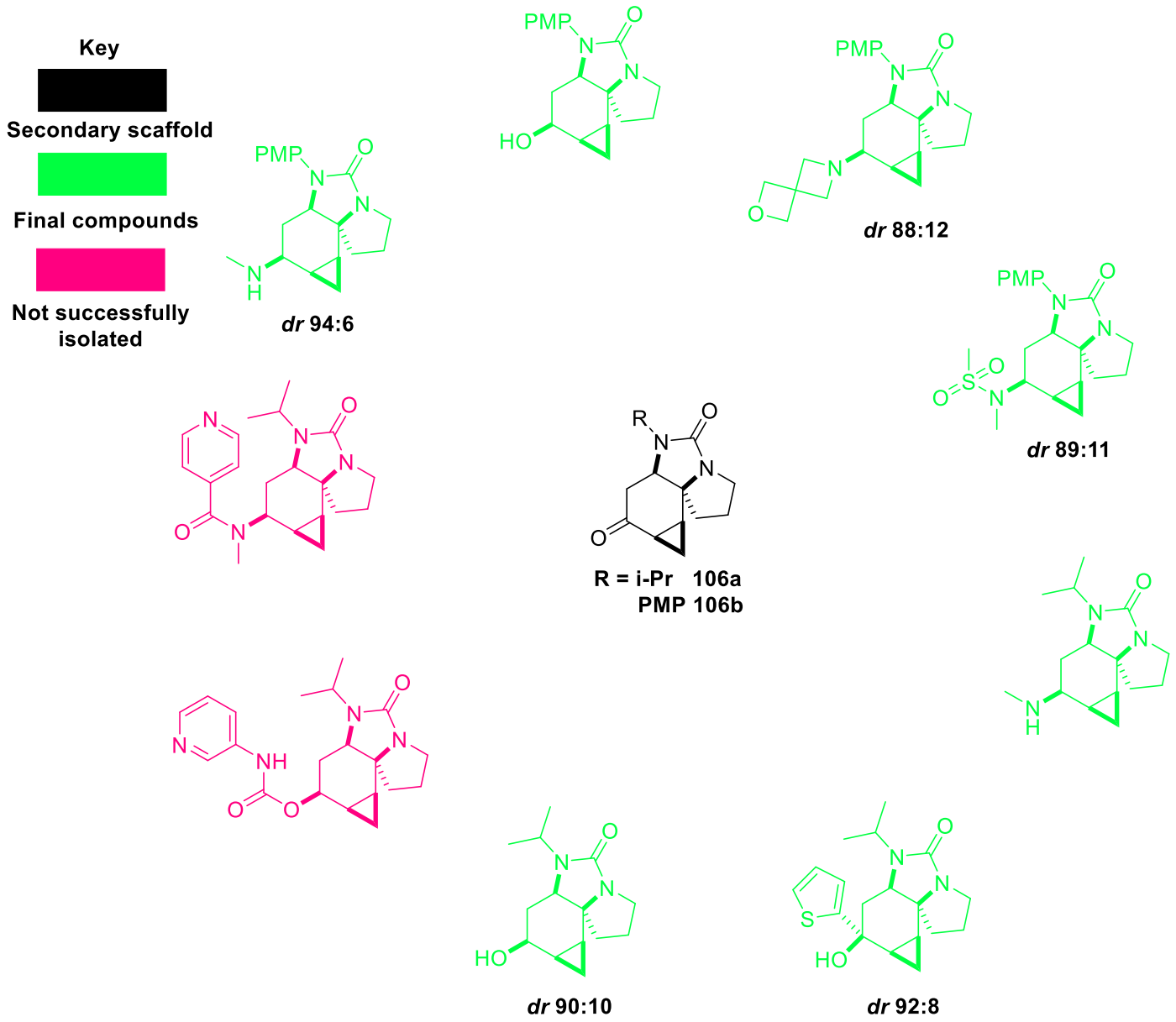
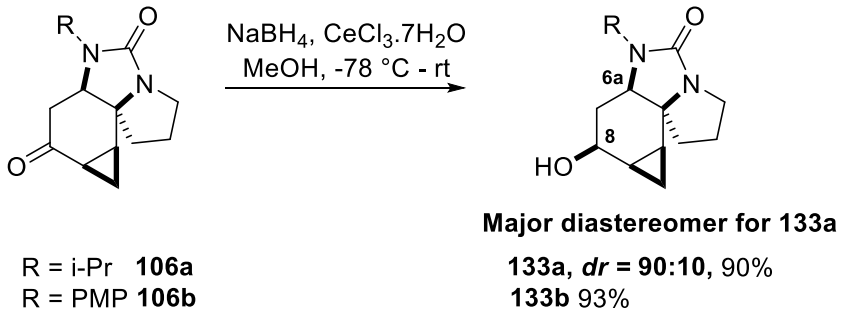



*Figure 21. Final compounds obtained from the cyclopropane-fused secondary scaffolds*

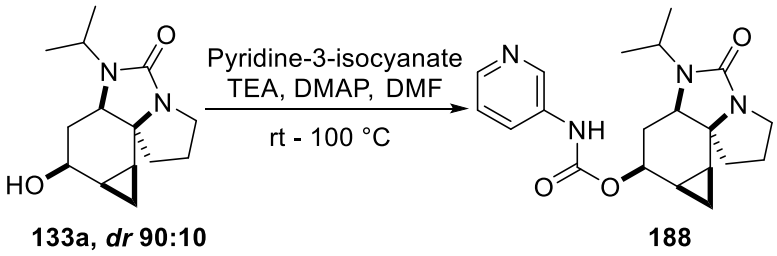
Sodium borohydride reduction of **106a** under Luche conditions gave the corresponding alcohol as an 86:14 mixture of diastereomers from the analysis of the proton NMR of the crude product

but was isolated as a 90:10 mixture of diastereomers. The stereochemistry of the major diastereomer **133a** was determined from the analysis of the coupling constants of its 6a-*H* (dd, *J* = 12.0, 5.5 Hz) and 8-*H* (dt, *J* = 12.0, 4.5 Hz) protons. Both protons are therefore axial and have to be on the same face of the cyclopropane-fused cyclohexanol ring. However, the sodium borohydride reduction of **106b** under Luche conditions gave a single diastereomer**133b** in 93% yield. The stereochemistry of **133b** was determined from the coupling constant of its 6a-*H* (dd, *J* = 12.5, 5.5 Hz) and 8-*H* (dt, *J* = 12.0, 4.5 Hz) protons. Both protons are therefore axial and the alcohol functionality is *syn* to the urea ring.




*Scheme 85. Sodium borohydride reduction of the ketone functionality of the cyclopropane-fused secondary scaffolds **106a** and **106b***

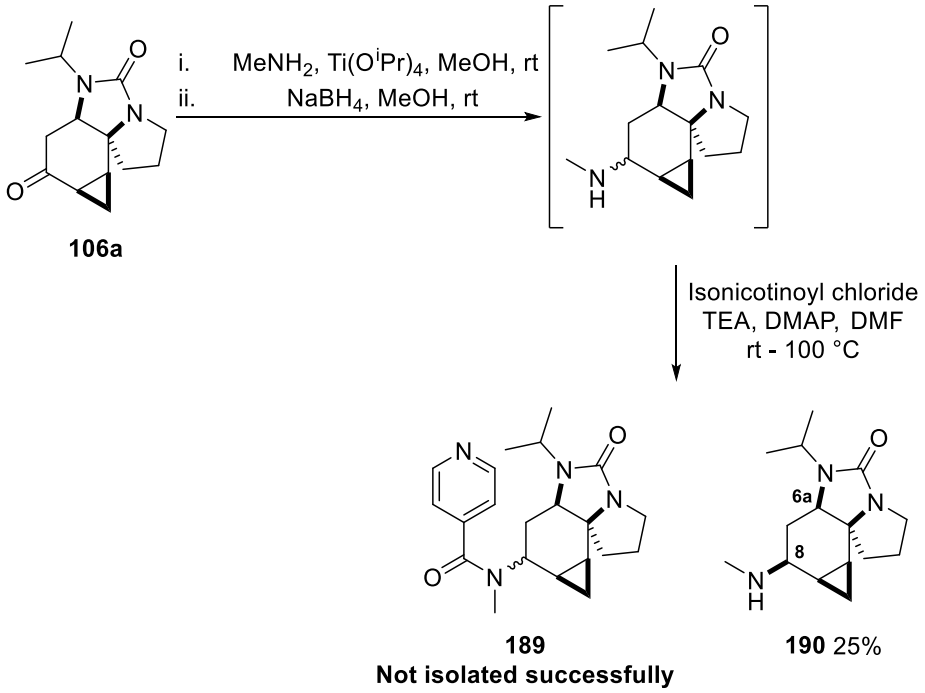
The alcohol **133a** (*dr* 90:10) was then reacted with excess pyridine-3-isocyanate to obtain the corresponding carbamate. Even though the mass of the desired product **188** was observed by LCMS, it was not isolated cleanly.




*Scheme 86: Attempted carbamate synthesis by reacting the alcohol **133a** (dr* 90:10*) with excess pyridine-3-isocyanate*

Reductive amination of **106a** with methylamine gave the desired product whose diastereomeric ratio was difficult to determine from the proton NMR of the crude reaction mixture. The

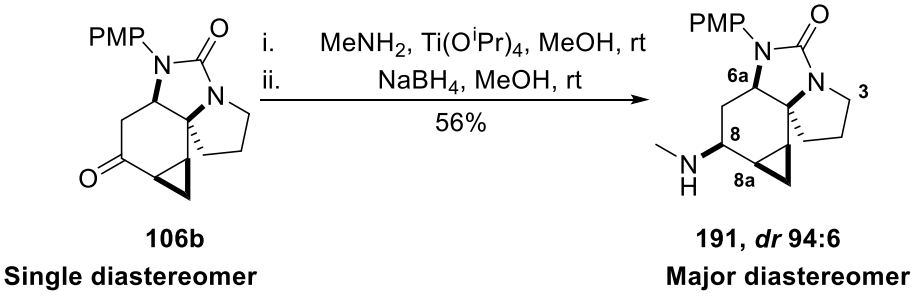
product was then subjected crude to amidation with isonicotinoyl chloride. Even though the mass of the desired amide **189** was observed by LCMS, it was not isolated cleanly. However, the intermediate **190** was recovered from the column as a single diastereomer in 25% yield. From the proton NMR of the crude reaction mixture, it is difficult to deduce the ratio of the intermediate **190** to that of the desired product **189**. The stereochemistry of **190** was determined from the analysis of the coupling constants of its 6-*H* (dd, *J* = 12.1, 5.2 Hz) and 8-*H* (dt, *J* = 12.5, 4.5 Hz). Both protons are therefore axial and have to be *cis* to each other on the 6-membered ring.




*Scheme 87: Attempted amide synthesis by reacting the crude of **190** with isonicotinoyl chloride*

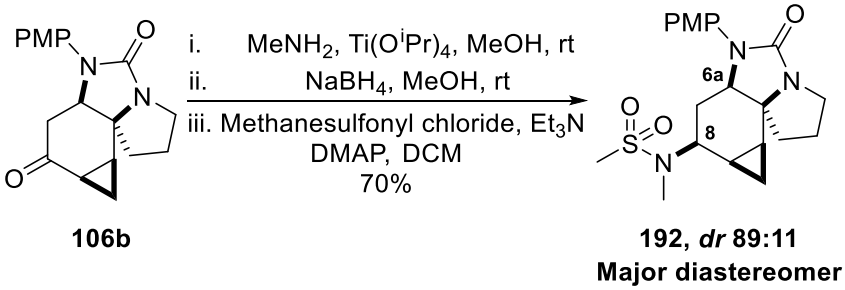
Similarly, subjecting **106b** to reductive amination with methylamine gave the desired product whose diastereomeric ratio is difficult to determine from the proton NMR of the crude reaction mixture but was isolated as a 94:6 mixture of diastereomers. The stereochemistry of the cyclopropane was assigned by the NOESY correlation between the 6a-*H* and 8a-*H* protons of the major diastereomer **191**. An attempt to determine the stereochemistry of the amino functionality of **191** by NOE correlations or coupling constant analysis was unsuccessful. The 8-*H* proton signal colludes with the signal of one of the 3-*H* protons and appears as an

unassignable multiplet in the proton NMR. However, the stereochemistry of the amino functionality was assigned by knowledge of the stereochemistry of its derived sulfonamide (see *Scheme 89*).




*Scheme 88. Reductive amination of the cyclopropane-fused scaffold **106b** with methylamine*

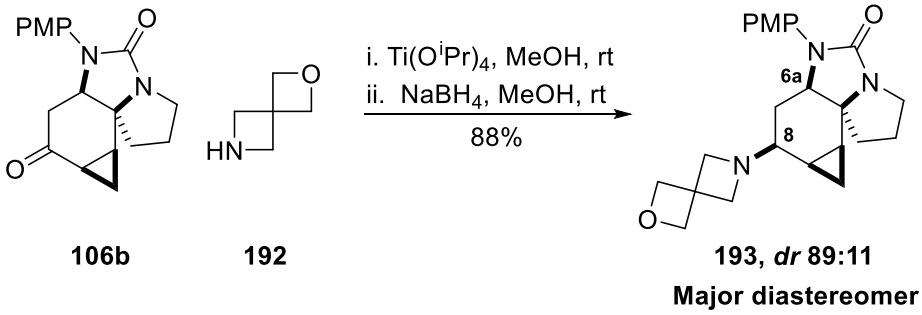
In a three-step process, the crude product of the reductive amination of **106b** with methylamine was reacted with methanesulfonyl chloride to obtain the desired sulfonamide.The diastereomeric ratio of the crude sulfonamide is difficult to deduce from its proton NMR but it was isolated as an 89:11 mixture of diastereomers. The stereochemistry of the major product was determined by the analysis of the coupling constant of its 6a-*H* (dd, *J* = 12.0, 5.0 Hz) and 8-*H* (dt, *J* = 13.0,4.0 Hz) protons. Both protons are therefore axial and have to be *cis* to each other on the six-membered ring.




*Scheme 89. Sulfonamide synthesis by reacting the crude amine **191** with methanesulfonyl chloride*

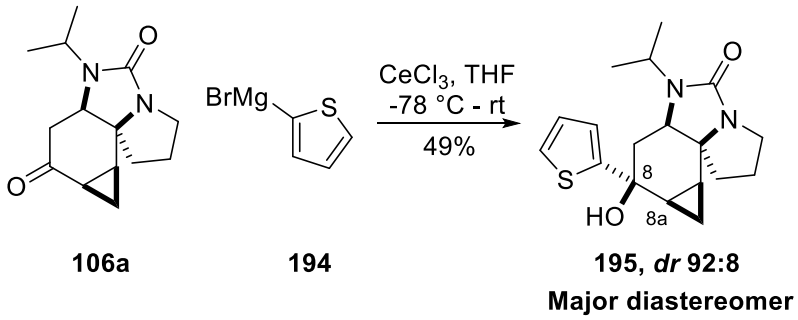
Reductive amination of **106b** with 2-oxa-6-aza-spiro[3.3]heptane **192** gave the desired product with a diastereomeric ratio of 88:12 as analysed from the proton NMR of the crude reaction mixture. The desired product was isolated in the same ratio. The stereochemistry of the major

diastereomer **193** was determined from the analysis of the coupling constants of its 6a-*H* (dd, *J* = 12.0, 5.0 Hz) and 8-*H* (br. d, *J* =12.5 Hz) protons. Both protons are axial and are therefore *cis* to each other on the six-membered ring.




*Scheme 90. Reductive amination of the cyclopropane-fused scaffold **106b** with the amine **192***

Finally, 1,2-addition of 2-thienylmagnesium bromide **194** to **106a** gave the desired product with a diastereomeric ratio that is difficult to determine from the proton NMR of the crude reaction mixture but was isolated as a 92:8 mixture of diastereomers. The stereochemistry of the major product **195** was determined by the NOESY correlation of its 8a-*H* proton to an aromatic proton.




*Scheme 91. 1,2-addition of 2-thienylmagnesium bromide to **106a***

### 3.1.5 Final compounds derived from the tosyl-substituted diamine 122

The final compounds obtained from the tosyl-substituted diamine are shown below.

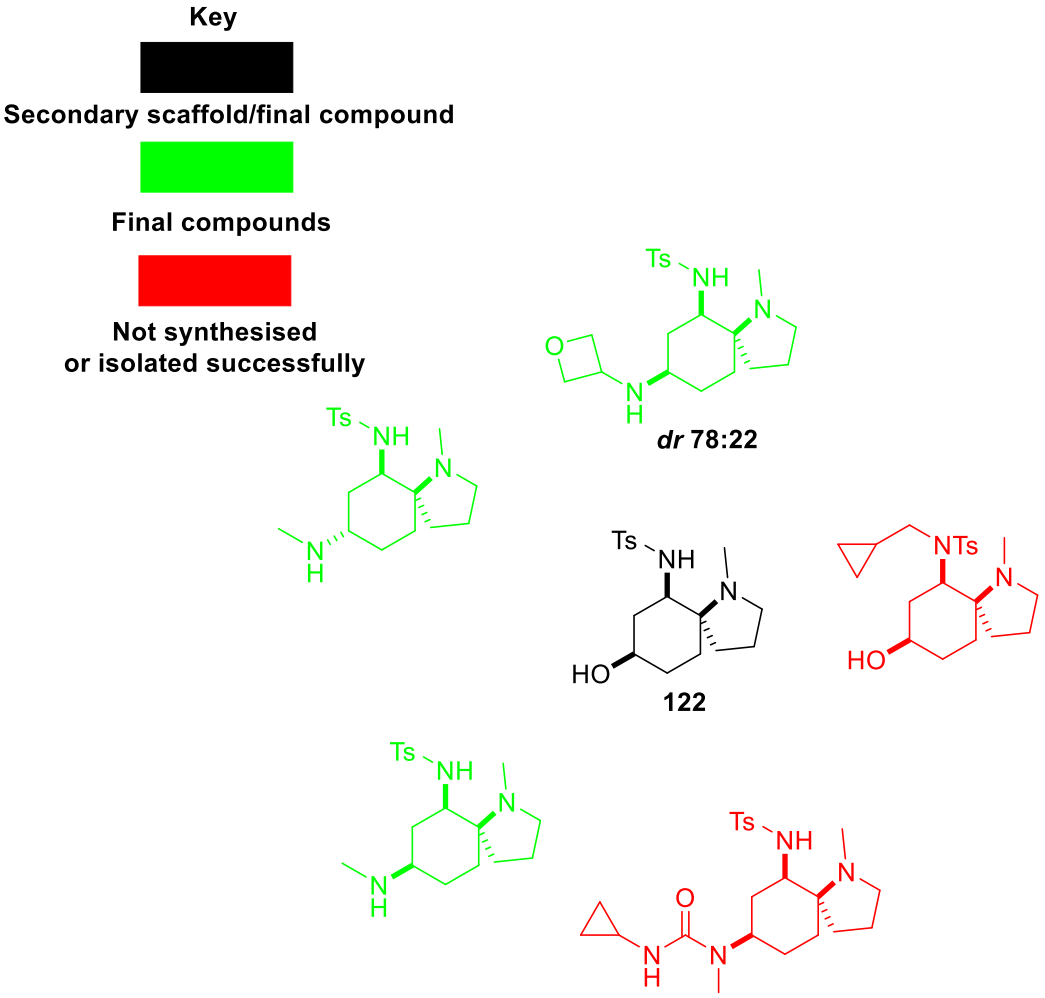
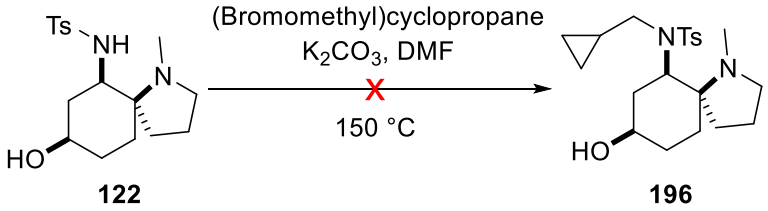



*Figure 22. Final compounds obtained from the tosyl-substituted diamine **122***

It was envisaged that the sulfonamide group of the tosyl-substituted diamine **122** could be preferentially alkylated over the alcohol. This is because toluenesulfonamide has a much lower *p*$K_a$ (10.17)[114] than isopropanol (17.1).[108] Therefore, the base-mediated alkylation of the sulfonamide group of **122** with (bromomethyl)cyclopropane was attempted in acetone by heating the reaction mixture at 56 °C in a pressure vial. There was no reaction as monitored by TLC. The acetone was removed and replaced with DMF. The reaction mixture was then heated to 150 °C. The mass of the desired product **196** was detected by LCMS. The proton NMR of the crude product, and observation by TLC indicated the starting material was used up. However,

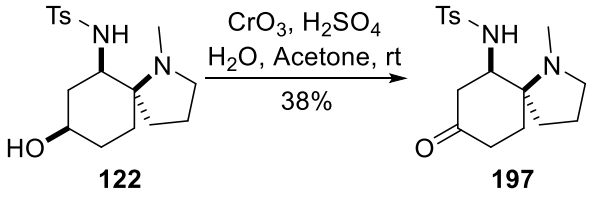
the product was not successfully isolated. Also, a possibly competing reaction could be the alkylation of the tertiary amino group of the pyrrolidine ring to give the quaternary ammonium salt.




**122** **196**

*Scheme 92. Attempted selective alkylation of the sulfonamide group of the diamine **122***

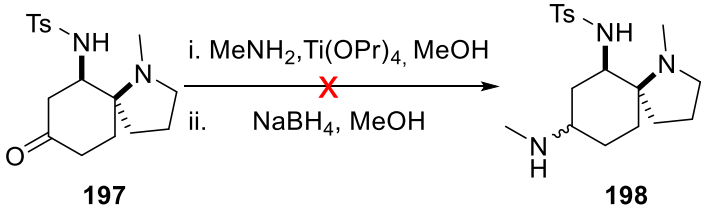
Therefore, it became desirable to convert the alcohol functionality of **122** to that of a ketone for onward functionalisation. Using Dess-Martin periodinane for this purpose, the reaction was sluggish and did not reach completion after three days as monitored by LCMS. However, using Jones' reagent instead, the desired ketone was obtained in 38% yield.




**122** **197**

*Scheme 93. Jones oxidation of the alcohol functionality of **122***

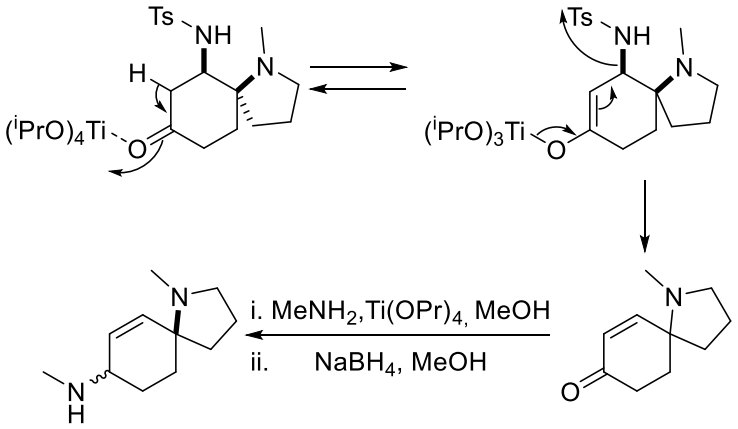
When **197** was subjected to Lewis acid-assisted reductive amination with methylamine, the desired product was not detected by LCMS but only toluenesulfonamide was isolated cleanly.



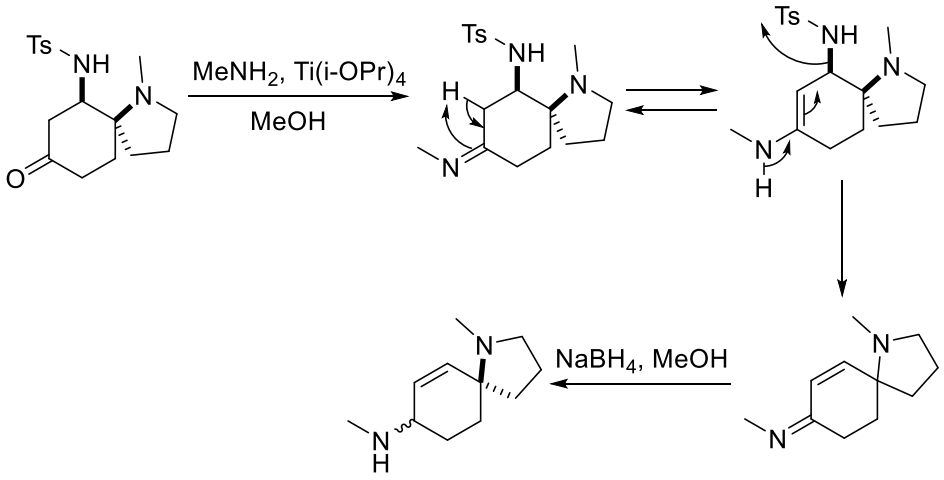

**197** **198**

*Scheme 94. Attempted titanium isopropoxide-catalysed reductive amination of the ketone **197** with methylamine*

The proton NMR spectrum of the crude product indicates a mixture of toluenesulfonamide and another compound with 2-methyl groups and two proton signals which appear to belong to alkene protons. The proposed sequence of events is shown below.



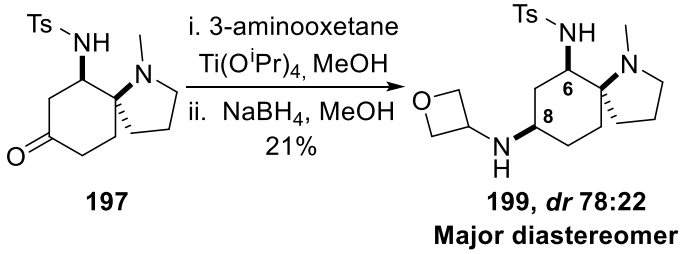

Toluenesulfonamide can also be displaced via the enamine as shown below.




*Scheme 95. Proposed mechanism for the titanium isopropoxide-catalysed reductive amination of **197** with methylamine*

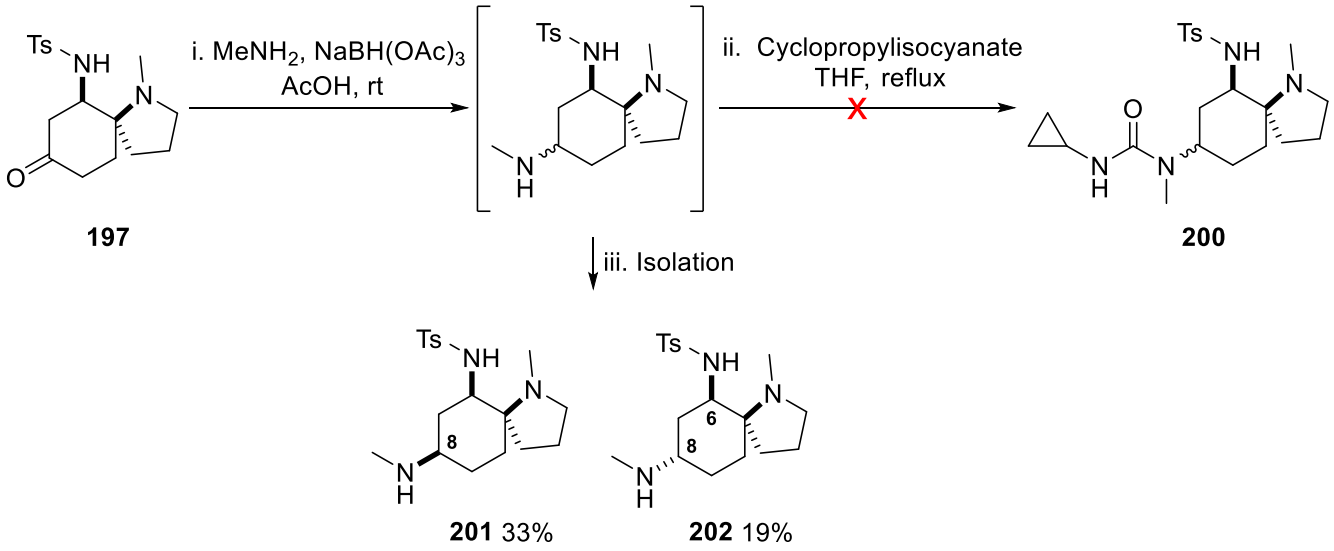
However, titanium isopropoxide-assisted reductive amination of **197** with 3-aminooxetane gave the desired product as a 64:36 mixture of diastereomers as analysed from the proton NMR of the crude reaction mixture but was isolated as a 78:22 mixture of diastereomers in 21% yield. Two proton signals corresponding to alkenes are present in the proton NMR spectrum of the crude product and this may suggest complications due to enolisation as in the case of the

reductive amination with methylamine (see *Scheme 95*). The stereochemistry of the major diastereomer **199** was determined from the analysis of the coupling constants of its 6-*H* (dd, *J* = 9.5, 4.5 Hz) and 8-*H* (tt, *J* = 12.5, 4.0 Hz). Both protons are considered to be axial and have to be *cis* to each other on the six-membered ring.




*Scheme 96. Reductive amination of the ketone **197** with 3-aminooxetane*

There was therefore a need to carry out reductive aminations with **197** without using titanium isopropoxide. The ketone **197** was then used for reductive amination with methylamine using sodium triacetoxyborohydride as the reducing agent and acetic acid as catalyst. The mass of the desired product was detected by LCMS in this case. From the proton NMR of the crude product, a 1:1 ratio of diastereomeric amines was obtained. However, the amines were directly subjected crude to urea synthesis by reacting them with cyclopropylisocyanate. The mass of the desired urea was however not detected by LCMS and the amines **201** and **202** were isolated in 33% and 19% yields respectively. The stereochemistry of **202** was determined from the analysis of the coupling constants of its 6-*H* (t, *J* = 3.0 Hz) and its 8-*H* (tt, 11.0, 4.0 Hz) protons. 6-*H* is an equatorial proton while 8-*H* is an axial proton. Therefore, both protons have to be *anti* to each other on the six-membered ring. The 8-*H* proton of **201** appears as an unassignable multiplet (overlaps with other peaks) in the proton NMR spectrum. Therefore, its stereochemistry as shown below was deduced from that of **202**.




*Scheme 97. Attempted urea synthesis via the reductive amination of **197** with methylamine*

### 3.1.6 Final compounds derived from the PMP-substituted diamine 123b

The final compounds whose syntheses were attempted from the PMP-substituted diamine **123b** are shown below.

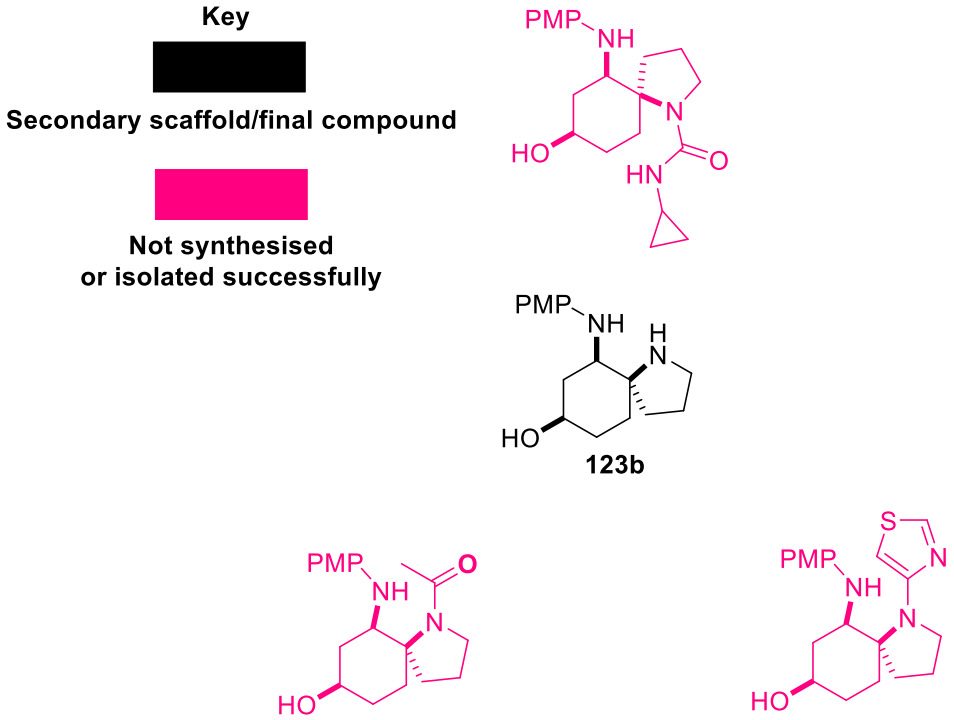
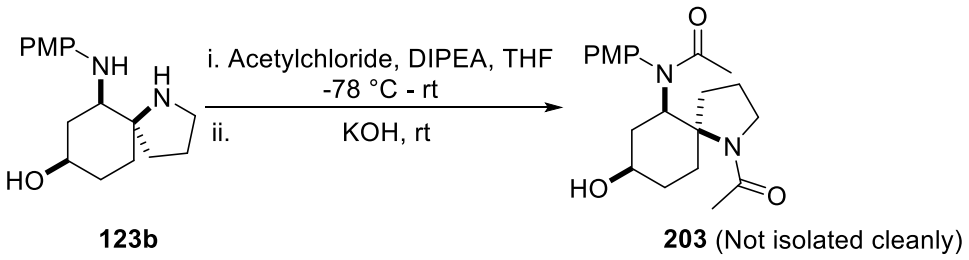



*Figure 23. Attempted synthesis of final compounds from the diamine **123***

It has been proven that the amino group of the secondary pyrrolidine of **123b** can be selectively functionalised (see Section 2.7.4, *Scheme 45*). Therefore an attempt was made to synthesise final compounds by reacting the amino group of the secondary pyrrolidine of **123b** with different electrophiles.

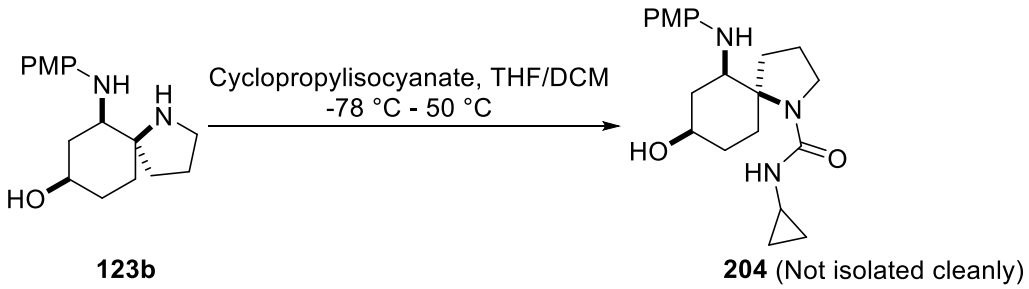
However, based on the scale (about 20 mg) the reactions were carried out, it was difficult to measure 1 eq. of the electrophile required to react with **123b**. Amidation of **123b** with acetyl chloride gave a mixture of the mono-, di-, and trisubstituted products as monitored by LCMS. The reaction was allowed to proceed to completion to the trisubstituted product. The ester of the trisubstituted product was then hydrolysed with 2M KOH in order to obtain the diamide **203** but it was not isolated cleanly.




**123b** **203** (Not isolated cleanly)

*Scheme 98. Attempted selective amidation of the secondary pyrrolidine of **123b***

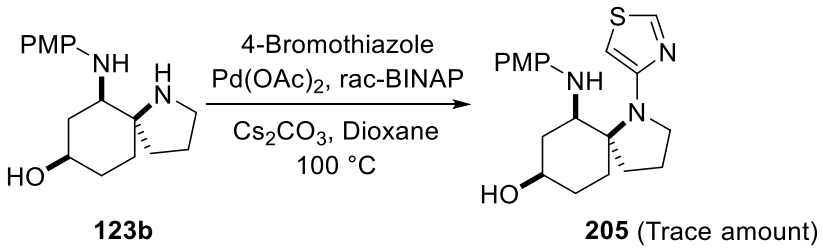
Also, an attempt was made to selectively synthesise the urea **204** by reacting the secondary pyrrolidine of **123b** with cyclopropylisocyanate. The reaction was sluggish and did not reach completion after 24 h even upon heating to 50 °C. From the proton NMR of the crude reaction mixture, it was difficult to deduce the percent conversion of the starting material. The desired product was not isolated cleanly.




**123b** **204** (Not isolated cleanly)

*Scheme 99. Attempted selective urea synthesis with the diamine **123b***

Attempted selective Buchwald-Hartwig coupling of 4-bromothiazole to the secondary pyrrolidine of **123b** was also sluggish. Only the mass of trace amounts of the desired product was detected by LCMS and observed by TLC after heating at 100 °C for 24 h. From the proton NMR of the crude reaction mixture, it is difficult to deduce the percent conversion of the starting material.




**123b** **205** (Trace amount)

*Scheme 100. Attempted Buchwald-Hartwig coupling with the diamine **123b***

Generally, to achieve success with the selective functionalisation of the pyrrolidine nitrogen of **123b** requires adding just an equivalent of the electrophile. This is evident in the triacylation of **123b** as described above (see *Scheme 98*). The urea synthesis described in *Scheme 99* might be successful if it is base-catalysed. Finally, the Buchwald-Hartwig reaction described in *Scheme 100* might become successful if different conditions are scoped.

### 3.1.7 Final compounds derived from the piperazinone-containing secondary scaffold 138

The final compounds obtained from the piperazinone-containing scaffold **138** are shown below.

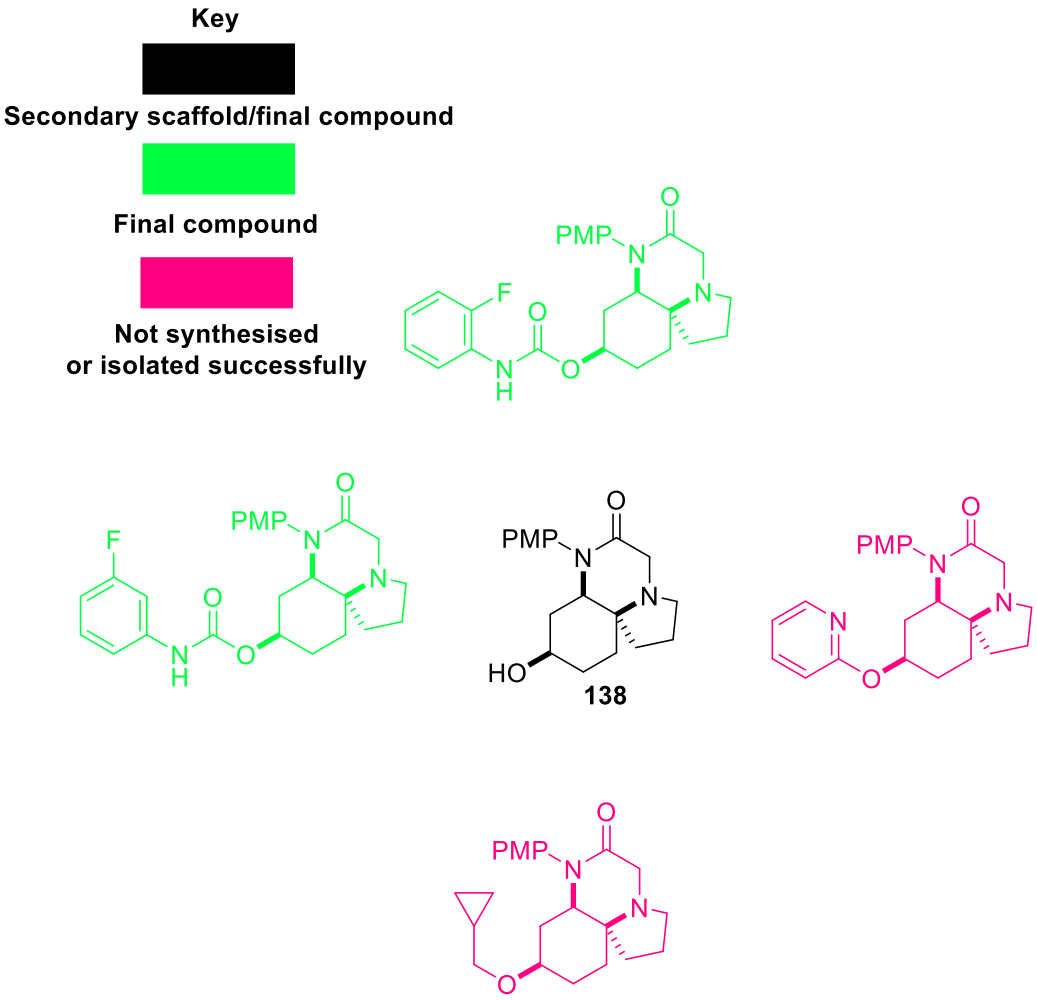
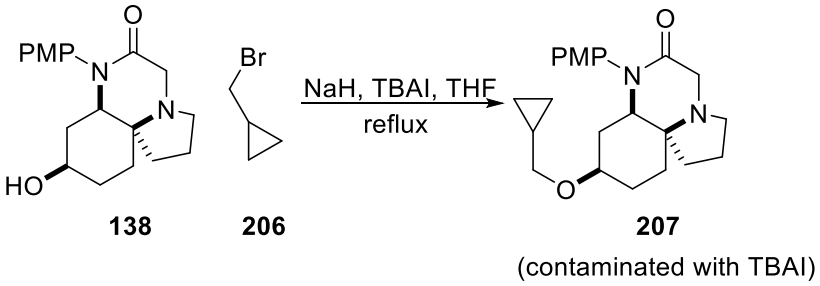


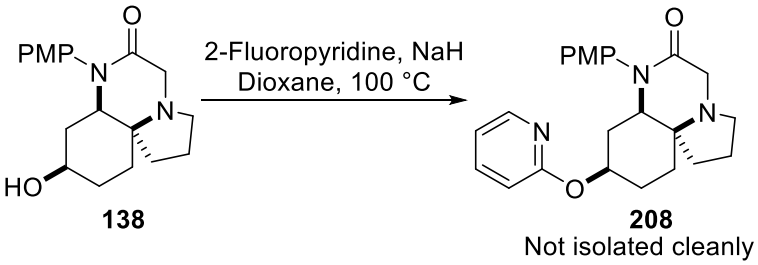

*Figure 24. Final compounds obtained from the piperazinone containing secondary scaffold **138***

Alkylation of the alcohol functionality of **138** with (bromomethyl)cyclopropane **206** under the conditions shown below gave a product with the desired mass as detected by LCMS but was not isolated cleanly. It was contaminated with 27% (molar percentage) of TBAI as deduced from the proton NMR spectrum. It was thought that TBAI undergoes Finkelstein reaction[115] with **206** in order to make the alkylation faster. Therefore, the reaction was repeated with sodium iodide instead of TBAI at 90 °C using dioxane as solvent. However, only trace amounts of the product was detected by LCMS, as well as the mass of the starting material.



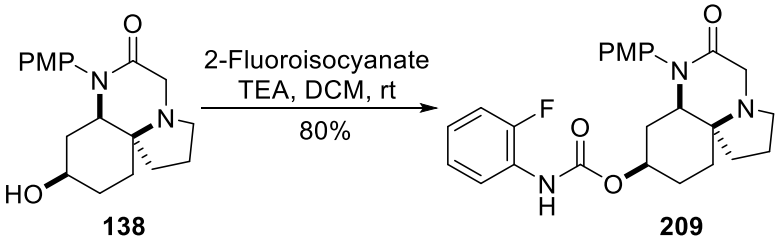

*Scheme 101. Alkylation of the alcohol functionality of **138** with (bromomethyl)cyclopropane*

Also, the lactam **138** was subjected to $S_NAr$ reacton with 2-fluoropyridine as shown below. The reaction did not reach completion after 48 h. From the proton NMR of the crude reaction mixture, it was difficult to deduce the percent conversion of the starting material. The product was not isolated cleanly.

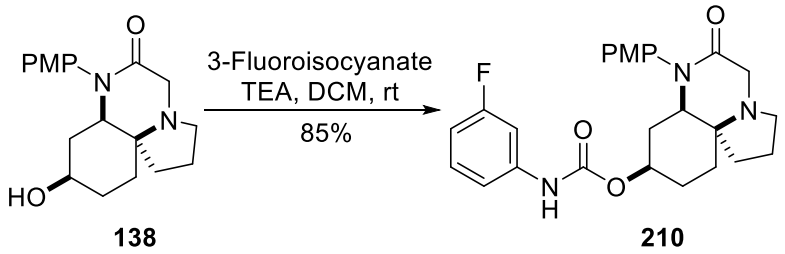



*Scheme 102. Attempted $S_NAr$ reaction of **138** with 2-fluoropyridine*

However, reacting **138** with 2-fluorophenylisocyanate and 3-fluorophenylisocyanate, the desired carbamates **209** and **210** were obtained in 80% and 85% yields respectively.




*Scheme 103. Carbamate synthesis by reacting **138** with 2-fluorophenylisocyanate*




*Scheme 104. Carbamate synthesis by reacting **138** with 3-fluorophenylisocyanate*

### 3.1.8 Compound series from the piperazinone-containing secondary scaffold 139

The final compounds whose syntheses were attempted from the piperazinone-containing scaffold **139** are shown below.

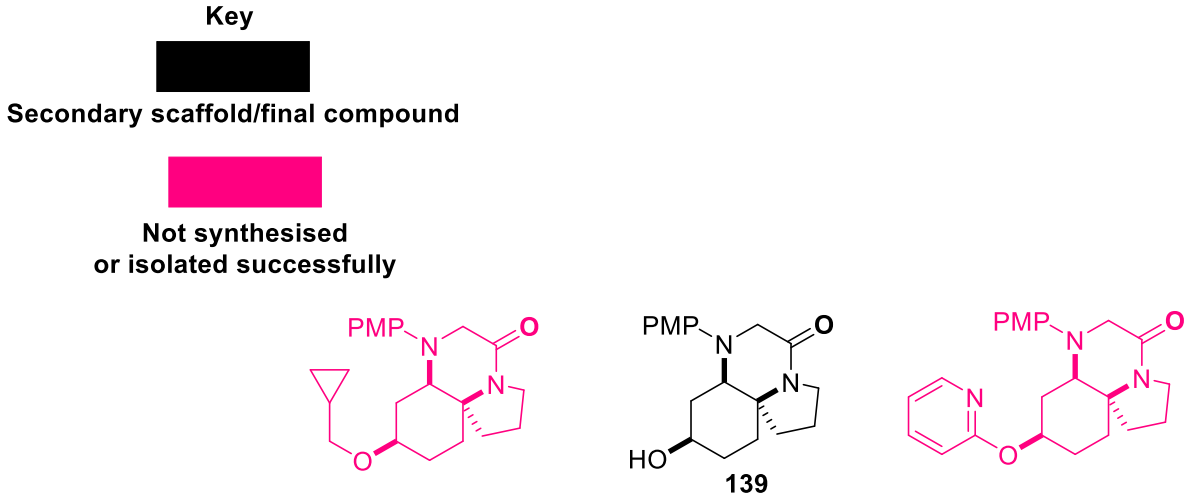
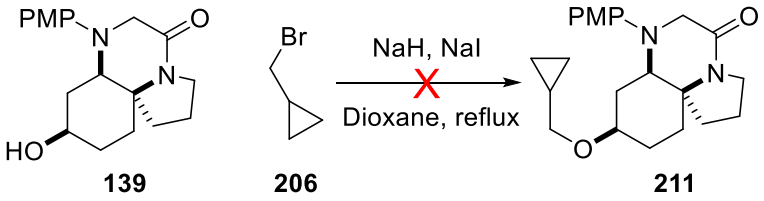


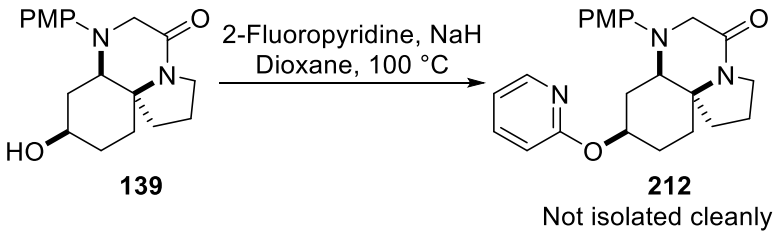

*Figure 25. Attempted synthesis of final compounds from the piperazinone-containing secondary scaffold **139***

Attempted alkylation of the alcohol functionality of **139** with (bromomethyl)cyclopropane **206** under the conditions shown below was not successful. Only the mass of the starting material was detected by LCMS. TBAI was then added to the reaction mixture (as in the case of **138,** see *Scheme 101*) which was heated at 90 °C but still, there was no reaction.




*Scheme 105. Attempted alkylation of the alcoholfunctionality of **108***

Subjecting **139** to $S_NAr$ reaction with 2-fluoropyridine, the desired product **212** was formed as observed by both LCMS and proton NMR. However, it was not isolated cleanly. The desired product was obtained with an unknown contaminant after column chromatography.




*Scheme 106. Attempted $S_NAr$ reaction of **139** with 2-fluoropyridine*

### 3.1.9 Final compound obtained from the PMP-deprotected urea

The final compound obtained from the PMP-deprotected urea **104** is shown below.

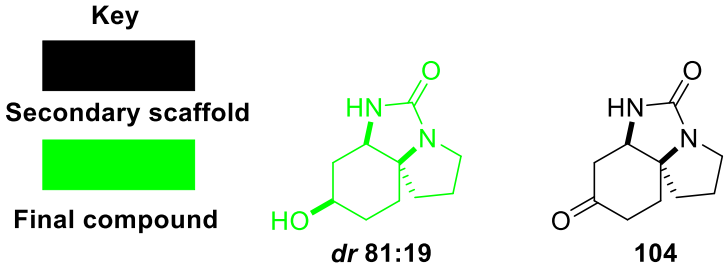
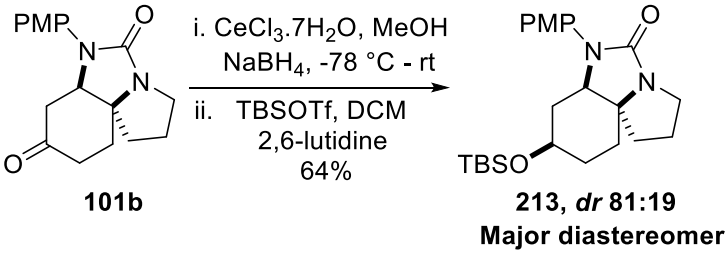


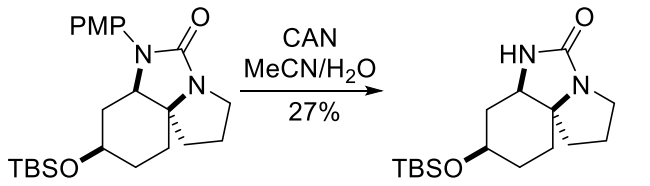

*Figure 26. Final compound obtained from the PMP-deprotected urea **104***

In a two-step process, the alcohol **160b** was converted to the silyl ether **213** prior to a proposed PMP-deprotection to afford the secondary urea for selective functionalisation as shown below.




*Scheme 107. Protection of the alcohol **160b** prior to a proposed PMP-deprotection.*

Reacting **213** with CAN, the PMP-deprotected product **214** was obtained in 27% yield as well as 11% of the alcohol **160b**. This approach was not investigated further due to the low yield of **214**.

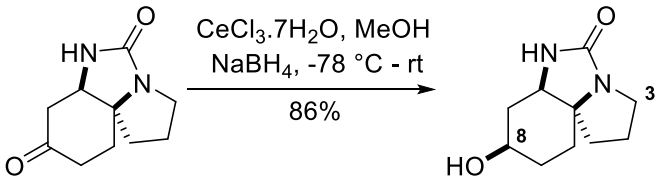



**213 *dr* 81:19**
**Major diastereomer**

**214 *dr* 80:20**
**Major diastereomer**

*Scheme 108. PMP-deprotection of the urea **213***

Therefore the PMP-deprotected urea **104** was subjected to sodium borohydride reduction, under Luche conditions, to give the desired alcohol as an 85:15 mixture of diastereomers as deduced from the proton NMR of the crude product and was isolated in the same ratio. The stereochemistry of the major diastereomer was assigned by analogy to that of **160a-c**. Both **101c** and **104** adopt the boat conformation in the solid state and may react in a similar manner when subjected to sodium borohydride reduction to give a major product whose alcohol functionality is *syn* to the urea ring. The 8-*H* proton appears as an unassignable multiplet overlapping with the 3-*H* proton in the NMR spectrum. Therefore, NOESY experiments as well as coupling constant analyses will not be helpful for stereochemical determination.




**104**

**215 *dr* 85:15**
**Major diastereomer**

*Scheme 109. Sodium borohydride reduction of the ketone functionality of the PMP-deprotected urea **104***

### 3.1.10 Lead-Likeness and Molecular Analysis

Lead-Likeness and Molecular Analysis (LLAMA) is a computational tool hosted at the University of Leeds.[56] It is used for the *in silico* assessment of the 'lead-likeness' of molecular scaffolds and derived compounds. The software has an in-built set of typical medicinal chemistry building blocks and reactions that can be used to virtually decorate molecular scaffolds along different

vectors. This will generate a library of final compounds for computational assessment. Penalty scores are assigned to compounds based on how close or far away they are from the lead-like space. Compounds with low penalty scores are generally more lead-like than those with higher scores. The scores are usually assigned to the individual properties that define the lead-like space for a molecule. The overall penalty score would then be the sum of all the individual scores assigned against any of the molecular properties enumerated below.[56]

**Heavy atom count:** Compounds with a heavy atom count of 17-24 have a penalty score of 0. The ones with 16 and 25 heavy atoms have a penalty score of 1, those with 14-15 and 26-27 heavy atoms have a penalty score of 2 while those with fewer than 14 or more than 27 heavy atoms have a penalty score of 3.[56]

**Lipophilicity:** Compounds with AlogP values between -1 and 3 have a penalty score of zero. The ones with AlogP values between -1.0 and -1.5 have a penalty score of 1. Also, compounds with AlogP values between 3.0 – 3.5 have a penalty score of 1. The ones with AlogP values between -1.5 and -2.0 have a penalty score of 2, as well as those with AlogP values between 3.5 – 4.0. Finally, compounds with AlogP values less than -2.0 or greater than 4.0 have a penalty score of 3.[56]

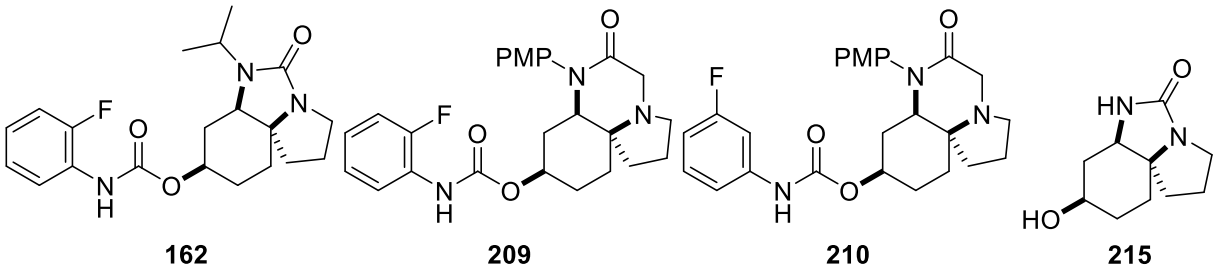
**Number of aromatic rings:** Compounds with one or two aromatic rings have a zero penalty score. The ones with no aromatic ring or three aromatic rings have a penalty score of 1, those with four to five aromatic rings have a penalty score of 2 while those with more than five aromatic rings have a penalty score of 3.[56]

**Undesirable functional groups:** Compounds with undesirable functional groups or substructural features as discussed earlier (see *Section 1.3.2*) have a penalty score of 5.[56]

Where a final compound was isolated as a mixture of two diastereomers, only the major diastereomer was subjected to LLAMA analysis. In the case of the isomeric lactams **152b**/**153b** and **152c**/**153c** (see *Section 2.7.5.2*), only the major isomers were subjected to LLAMA analysis. Also, for the isomeric lactams **156b**/**157b** (see *Section 2.7.5.3*), only the major isomer was subjected to LLAMA analysis.

#### 3.1.10.1 Penalty score distribution for final compounds

The lead-likeness penalty distribution obtained from the LLAMA analysis of the final compounds is shown in *Figure 27* below. Eighteen compounds have an overall penalty score of 0. Sixteen compounds have a score of 1. Two compounds have a score of 2. Thirteen compounds have a score of 3 while four compounds have a score of 4. The mean penalty score for all the compounds is 0.849.[116] Medicinal chemistry capping groups were carefully selected so that final compounds obtained from them will have good lead-like properties. An average penalty score of 1.57 has been interpreted to mean the compounds are in lead-like space. As stated earlier, compounds with low penalty scores are generally more lead-like than the ones with higher scores.[56] As shown in *Figure 27*, the compounds with the high penalty score of 4 are **162**, **209**, **210** and **215**. The high overall penalty score for **162**, **209** and **210** is due to their high molecular weights (out of the lead-like range - penalty score of 3) and lipophilicities (penalty score of 1). The PMP group of **209** and **210** could be viewed as a protecting group and when removed will improve the lead-like properties of both compounds. Compound **215** has a high overall penalty score because of its low molecular weight (penalty score of 3) and the absence of an aromatic ring (penalty score of 1). Even though the properties of **215** increase the scope of its developability into the drug-like space, such properties take it out of the lead-like space.



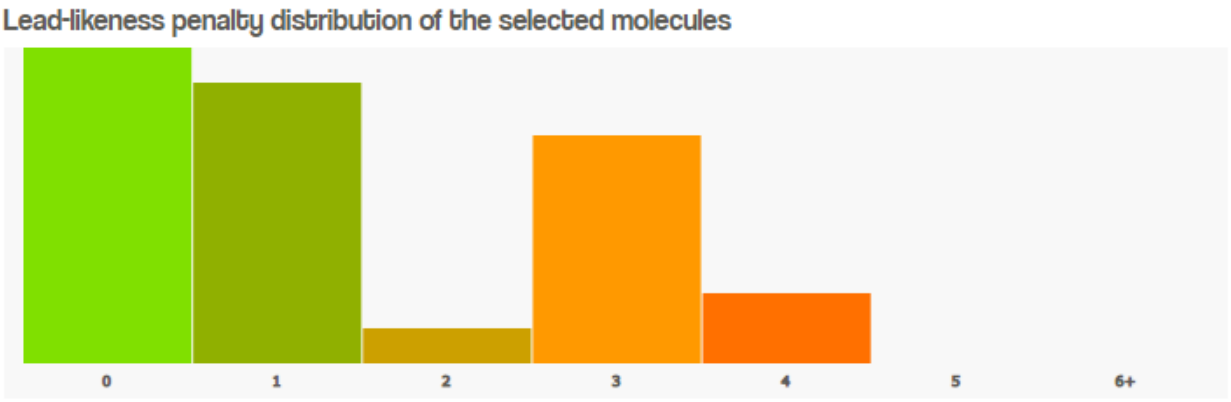




*Figure 27. Structures of four final compounds with a high penalty score and a plot showing the lead-likeness penalty distribution of all the final compounds for biological screening*

### 3.1.10.2 Mass distribution of final compounds for biological screening

The LLAMA plot of the mass distribution of the final compounds obtained from the secondary scaffolds is shown in *Figure 28* below. The molecular weight (MW) range for lead-oriented synthesis as given by Ian Churcher and co-workers[14] is 250 – 350 Da or with respect to heavy atom count, the range is 14 ≤ heavy atoms ≤ 26 (although the LLAMA filter is slightly different as discussed in *Section 3.1.10*). Some of the compounds that are way out of the lead-like space have protecting groups which when removed will lead to a decrease in their molecular weights. An example is the pyrrolidine **181** (MW = 481.61) that has both tosyl and benzyl groups in the molecule. The compound with the molecular weight of 196.25 is the derived alcohol of the PMP-deprotected urea **104**.[116]

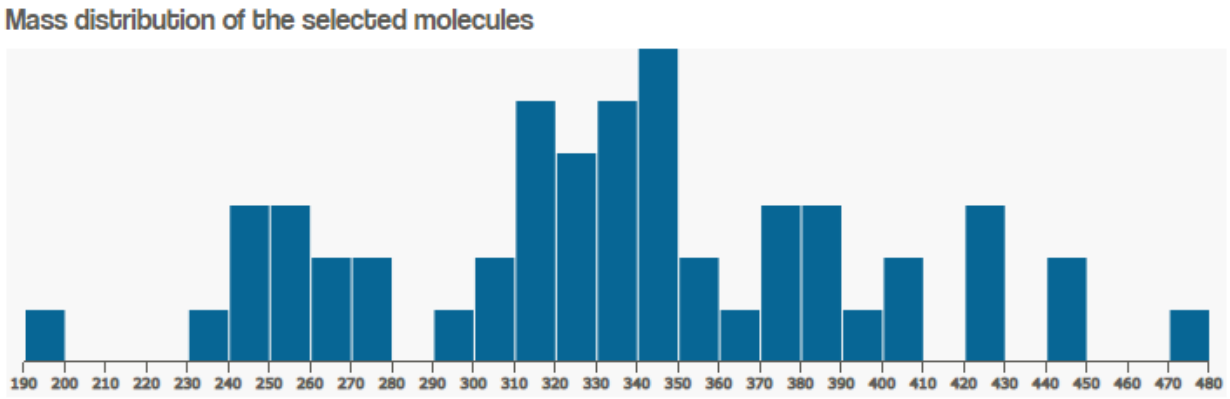



*Figure 28. Mass distribution of final compounds for screening*

### 3.1.10.3 Lipophilicity distribution of final compounds for biological screening

All the final compounds have the right lipophilicity values for lead-oriented synthesis except for three compounds that have their AlogP values above 3.0. The compounds are: **162** with an AlogP of 3.06, **209** with an AlogP of 3.22 and **210** with an AlogP of 3.33. The lipophilicity of **162** as calculated by LLAMA is 3.06 (slightly higher than the maximum value of 3.0 required for lead-oriented synthesis).[116] Deprotecting the PMP group of both **209** and **210** could increase their polarity and hence, enhance their lead-like properties (See *Section 3.1.10.1* and *Figure 27*).

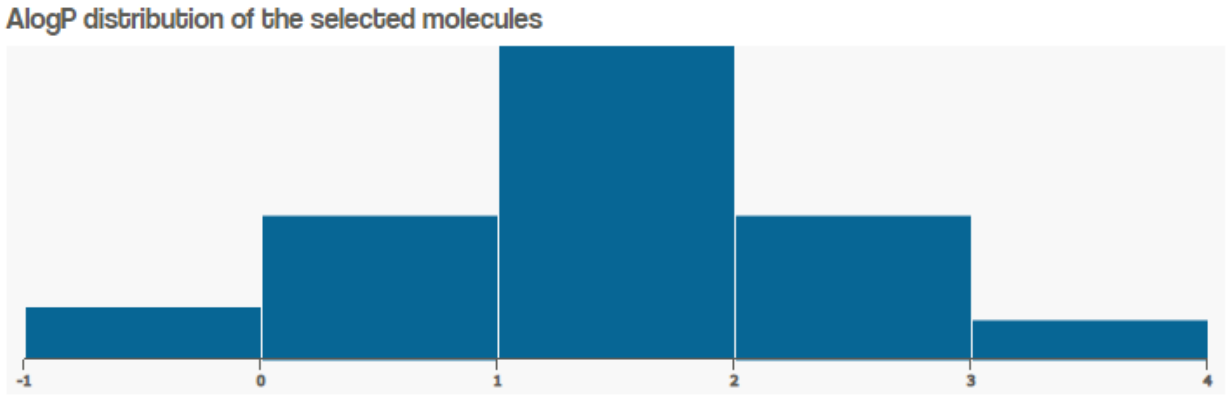



*Figure 29. AlogP distribution of final compounds for biological screening*

### 3.1.10.4 Overall assessment of the lead-likeness of final compounds by LLAMA

The final compounds can be subjected to lead-likeness assessment with respect to both molecular weight and lipophilicity as shown by the plot below. The compounds (indicated as

coloured dots based on their overall penalty score) within the dotted bounds of the rectangle can be said to be in the lead-like space. Therefore, with respect to *Figure 30*, 35 compounds (66%) are in lead-like space while 18 compounds (34%) are outside lead-like space mainly due to molecular weight considerations.

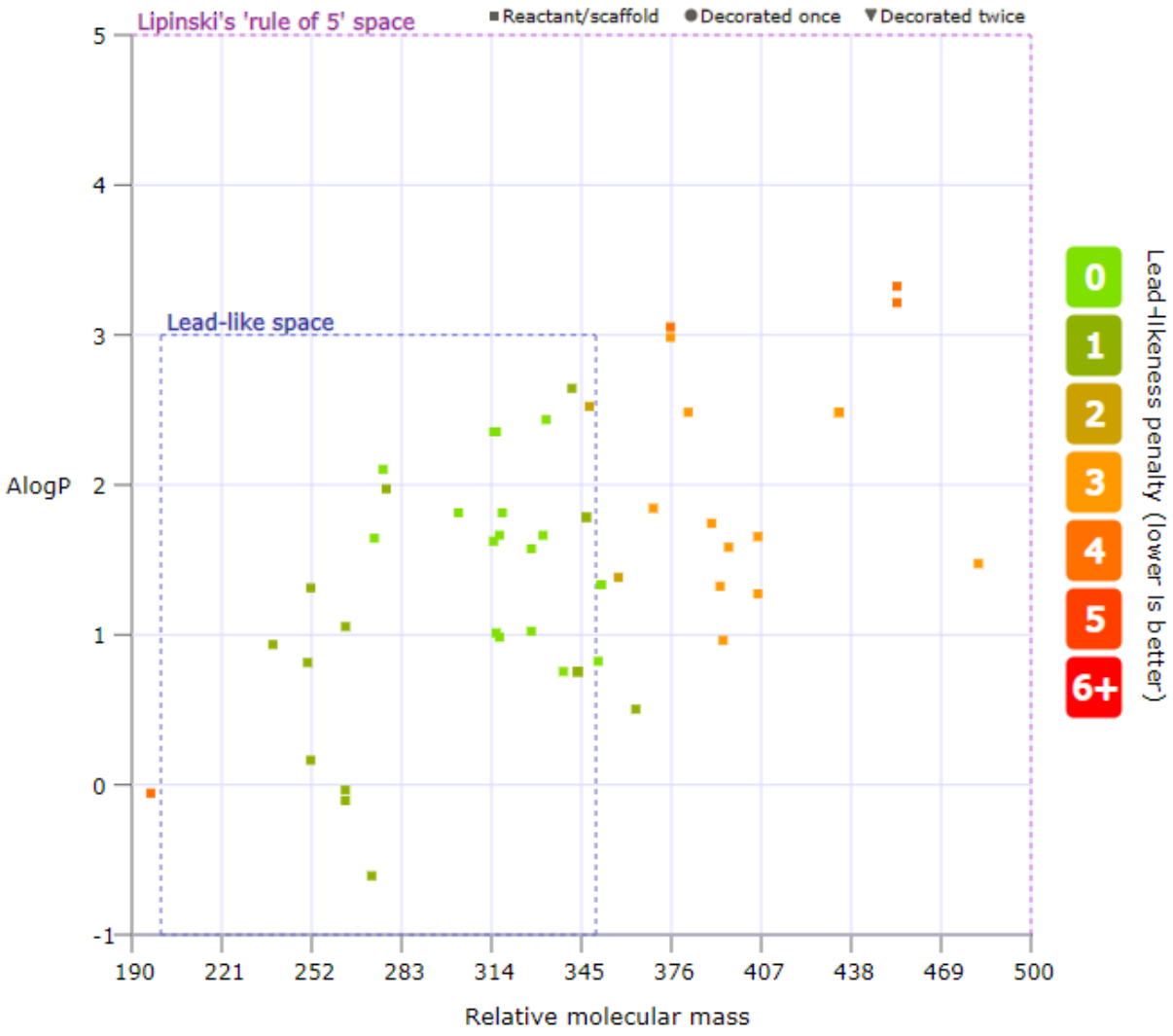



*Figure 30. Overall lead-likeness assessment of final compounds for biological screening*

However, the key statistic was obtained from LLAMA with respect to not just molecular weight and lipophilicity but also the number of aromatic ring(s) and bad functional group(s). It indicates that 58.5% of the final compounds are within the lead-like space. This is a good

outcome as considerably more than half of the final compounds have been analysed to perfectly be in lead-like space.

#### 3.1.10.5 Shape distribution of the final compounds for biological screening

The shape diversity or distribution of the final compounds can be represented by the principal moment of inertia (PMI) plot as shown in *Figure 32*. LLAMA produces PMI coordinates for every molecule by first minimizing the energy of a number of generated three-dimensional conformers. The conformer of lowest energy will then be selected and its moments of inertia along the *x*, *y* and *z* axes will be calculated. The plot is made up of a histogram of 20 bins. The compounds in the bins are shown as coloured dots (as in *Figure 30*) based on the overall penalty score. The higher the bin number, the higher the three-dimensionality of the compound(s) that are in it. In other words, as molecules spread from the vertex represented by the linear diacetylene to the disc-like benzene and finally adamantane, three-dimensionality increases.[116] Three-dimensionality is a measure of complexity and therefore making compounds with increased three-dimensionality is desirable for lead-oriented synthesis (see *Section 1.3.2*).

The ZINC database contains commercially available compounds that have been made available for virtual screening.[117,118] It has been shown by Young and co-workers[119] that deliberately synthesised 3D fragments have a better shape distribution on the PMI plot than a representative set of fragments from the ZINC database. Also, Cohen and coworkers[120] have also shown that intentionally synthesised 3D metallofragments have a better shape diversity on the PMI plot than a representative set of fragments from the ZINC database. The fragments from the ZINC database tend to occupy the axis between the linear diacetylene and the disc-like benzene portion of the PMI plot.

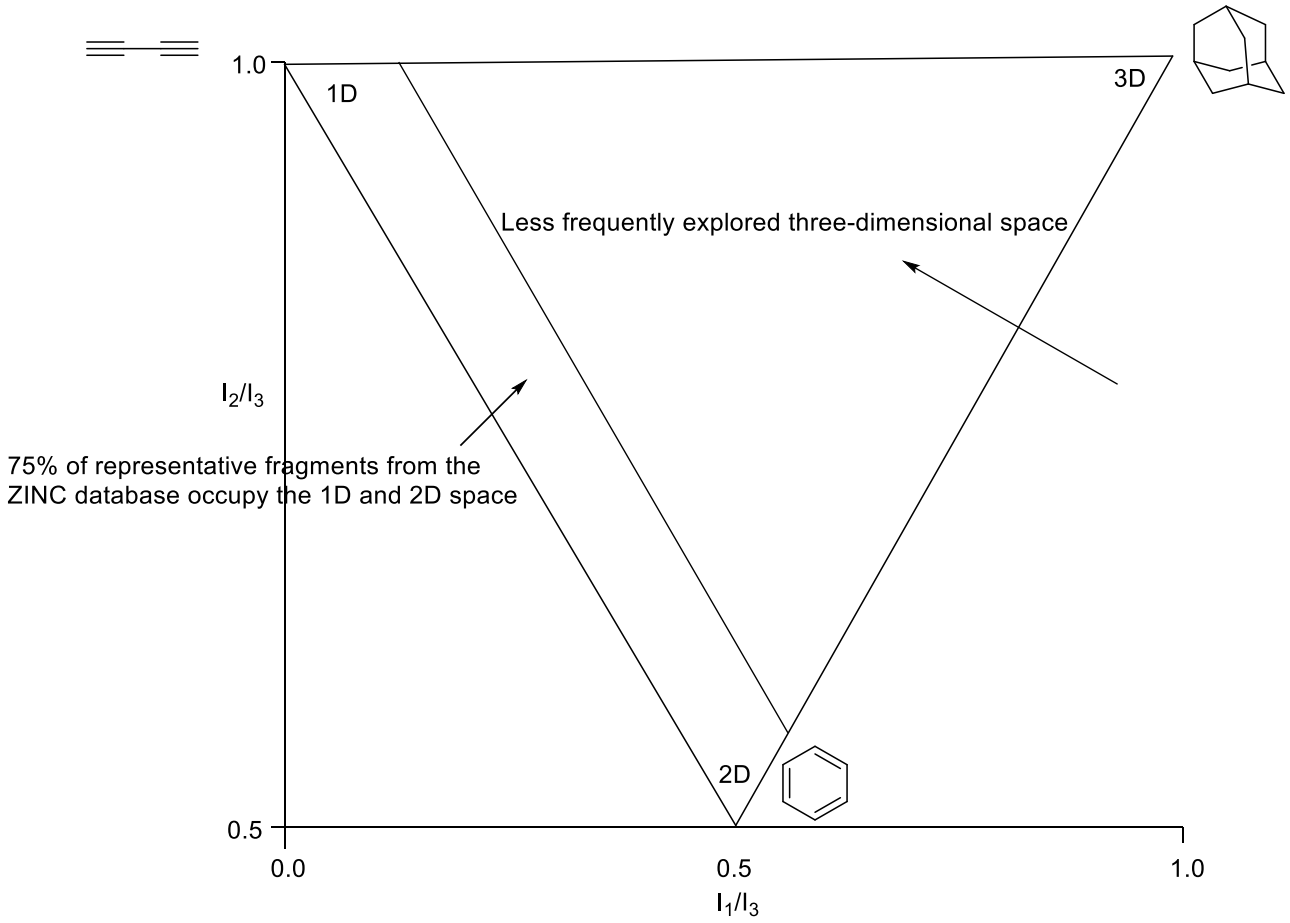



*Figure 31. Illustration of the low shape diversity of a representative set of fragments from the ZINC database*[119,120]

From the PMI plot shown in *Figure 32*, the final compounds we made for biological screening have a better spread than compounds from the ZINC database, and hence a better shape distribution.

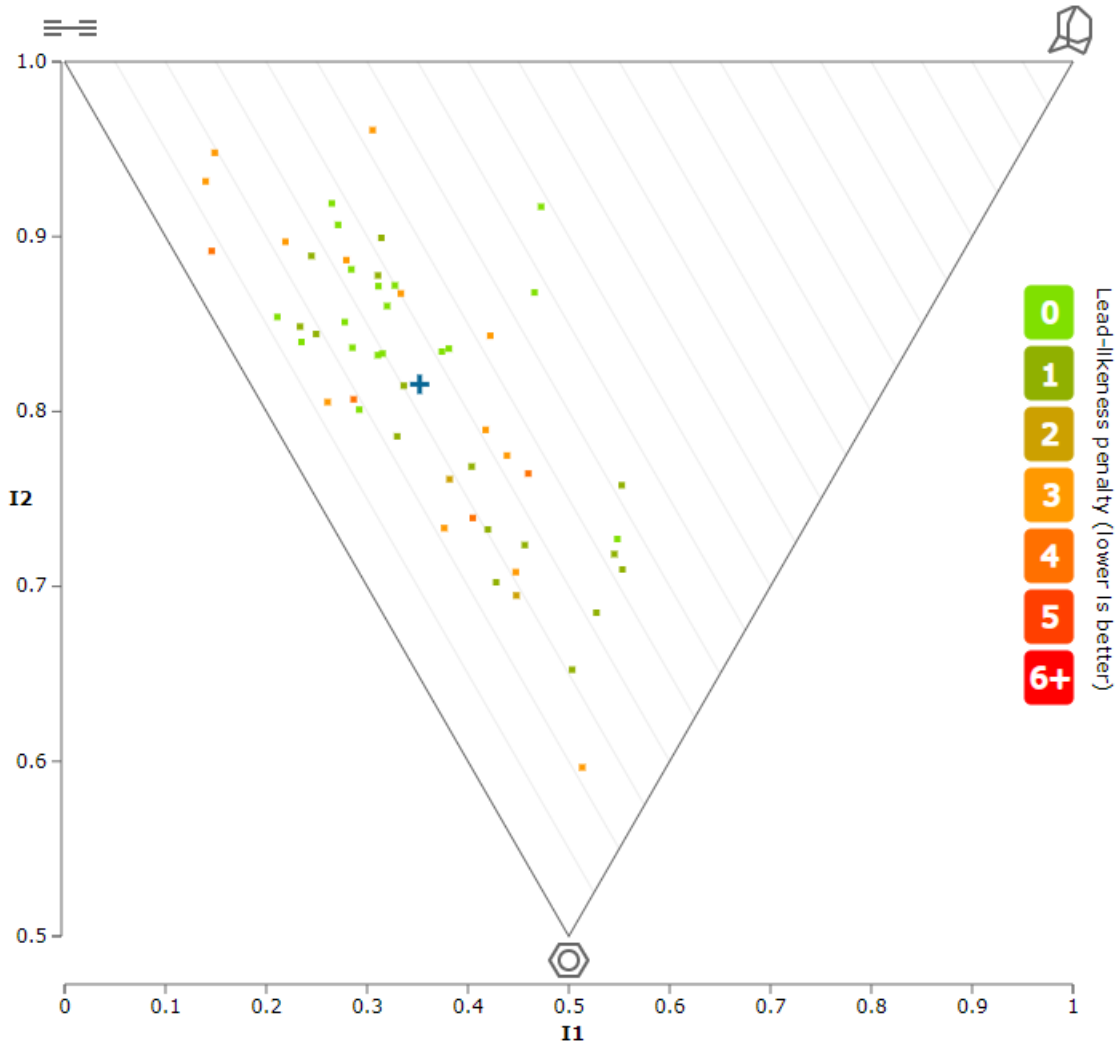



*Figure 32. Shape distribution of final compounds for biological screening*

### 3.1.10.6 Fraction of $sp^3$ distribution of final compounds for biological screening

The fraction of $sp^3$ carbon atoms ($Fsp^3$) of a molecule is a measure of the carbon bond saturation of the molecule (see *Section 1.2.1*). It can also be taken to be a measure of complexity because saturation allows synthetic chemists access more complex scaffolds. Increased $Fsp^3$ is known to correlate well with success during clinical development. The mean $Fsp^3$ for approved drugs, as indicated by a study carried out in 2009, is higher than the mean $Fsp^3$ for candidates at the earlier stages of drug discovery because those with lower $Fsp^3$ fail more often, as shown in *Figure 33* below.[12] Also, compounds with high $Fsp^3$ sample chemical space more efficiently than those with lower $Fsp^3$ without a significant corresponding increase

in molecular weight due to saturation. As indicated in *Figure 33* below, dimethylpyridine with an $Fsp^3$ of 0.29 has 5 isomers while dimethylpiperidine with a perfect $Fsp^3$ has 34 isomers.[12]

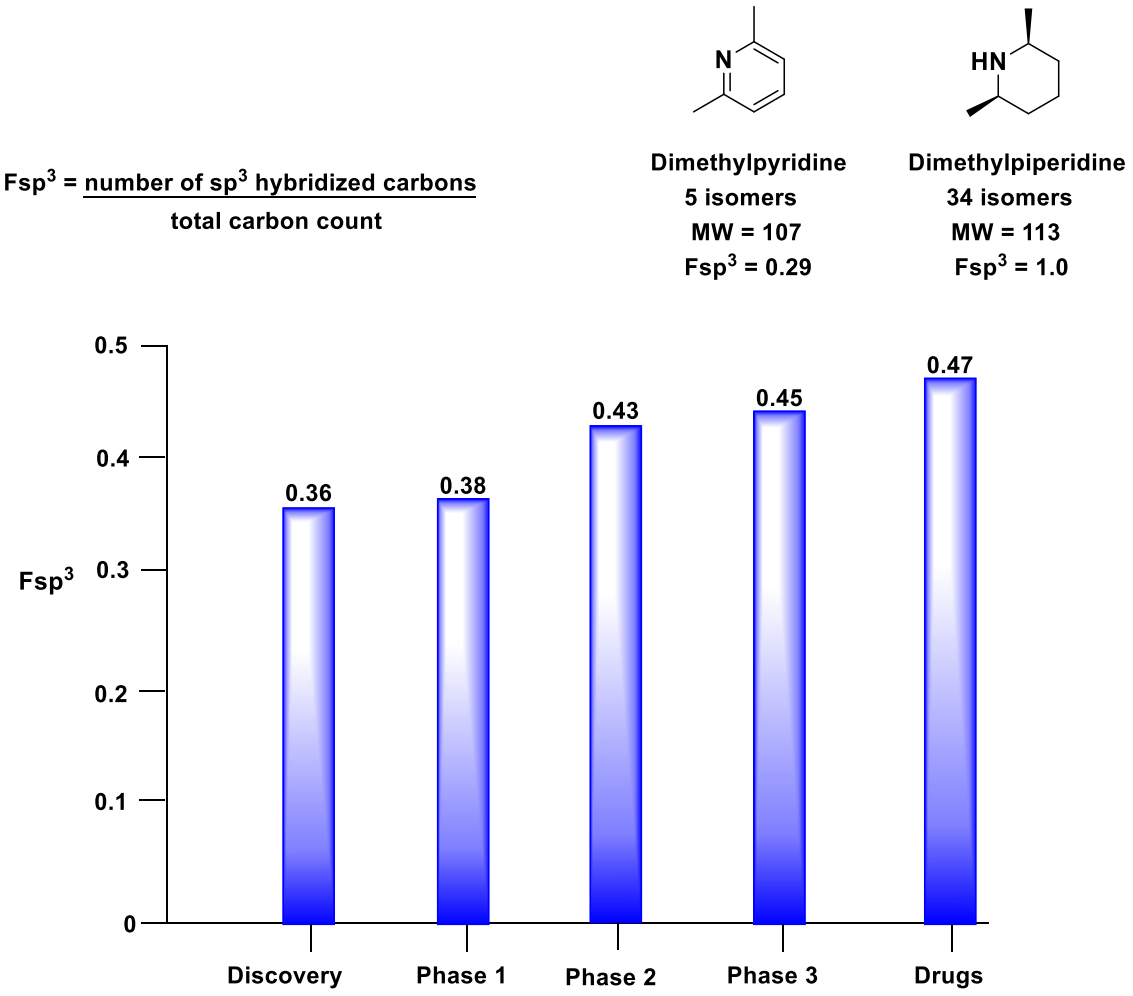



*Figure 33. Exhibition of the importance of $Fsp^3$ in drug discovery*[12]

The $Fsp^3$ distribution of the final compounds for biological screening as assessed by LLAMA[116] is shown in *Figure 34* below. The mean $Fsp^3$ is 0.68. This is higher than the mean $Fsp^3$ for approved drugs as indicated in *Figure 33*. This also means the final compounds have room for developability into drug molecules.

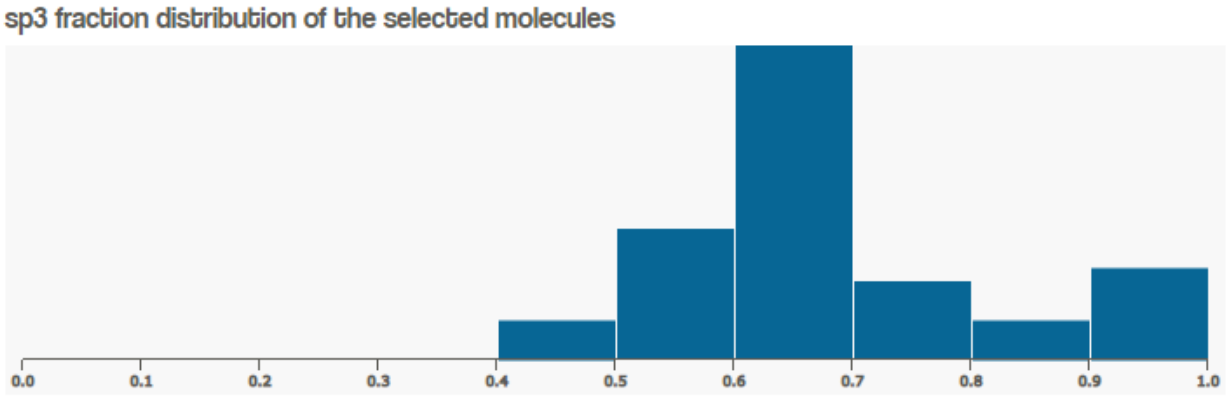
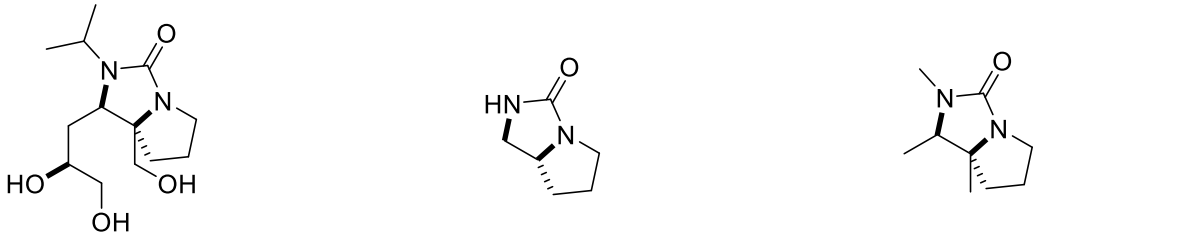



*Figure 34. $Fsp^3$ distribution of final compounds for biological screening*

### 3.1.10.7 Novelty assessment of final compounds for biological screening

The novelty of scaffolds could be assessed with respect to their Murcko or Murcko plus alpha frameworks. The Murcko framework of a molecule consists of the core scaffold without substitutions while the Murcko plus alpha framework includes not just the core scaffold but also the positions of alpha-substitutions on it.[121] With respect to the scaffold **129**, the Murcko and Murcko plus alpha frameworks are depicted below.




**129** **Murcko framework** **Murcko plus alpha framework**

*Figure 35. The triol **129**, its Murcko and Murcko plus alpha frameworks*

Each of the 53 final compounds for biological screening was analysed by LLAMA[116] for novelty with respect to an identical framework (using both the Murcko and Murcko plus alpha frameworks) or as a substructure (using both the Murcko and Murcko plus alpha frameworks). All the final compounds, except **129**, show no match in terms of the same framework or as a substructure when compared to a random 2% of the ZINC database of commercially available compounds. The triol **129** has 5 hits as a substructure with respect to the Murcko framework only. This indicates that the final compounds are highly novel.

### 3.1.10.8 Conclusion

In conclusion, the top down approach is a viable tool to demonstrate lead-oriented synthesis.

Comparatively, the bottom up approach to lead-oriented synthesis makes use of different precursors 'armed' with different functional groups which could be made to undergo mutually exclusive cyclisations to generate complex and diverse scaffolds. This approach might generate diverse scaffolds faster than the top down approach to lead-oriented synthesis, because in this case, the extent to which diversity could be generated depends on:

i. The type of precursor chosen (different precursors can be obtained for this purpose).
ii. The types of functional groups the precursors are 'armed' with.
iii. The type of pairing reactions the functional groups are made to undergo orthogonally. Generally, these reactions could be less difficult than the kind of reactions employed for the top down approach to lead-oriented synthesis as discussed below.

In contrast, the top down approach is a more convergent concept and it is meant to rapidly give access to complex and diverse scaffolds from a single key scaffold, while keeping a tight control of the molecular properties of the scaffolds generated in the process. Through this approach, a suitable key scaffold is deconstructed or modified via ring addition, cleavage and expansion to generate diversity. However, the diversity generating reactions in this case are intermolecular and may be more difficult as compared to the intramolecular pairing reactions employed by the bottom up approach to LOS. The ring cleavage and expansion reactions are generally more difficult than the ring addition reactions but can lead to compounds that occupy novel chemical space which may be more difficult to synthesise otherwise (especially where the key scaffold has considerable stereochemical complexity as in the case of compound **83**). The products of cleavage reactions open great synthetic possibilities and can be used as starting materials to generate compounds that have very little structural semblance to the key scaffold.

In this project, the ring addition reactions that worked are the Van Leusen pyrrole synthesis (*Scheme 24*), Corey-Chaykovsky cyclopropanation (*Scheme 25*), pyrrolidine synthesis via a 1,3-

dipolar cycloaddition reaction as described by Fray and coworkers (*Scheme 27*) and pyridine synthesis (*Scheme 31*). Corey-Chaykovsy cyclopropanation gave products in which the stereochemistry of the cyclopropane ring is *syn* to the urea. The pyrrolidines gave a mixture of diastereomers whose diastereomeric ratios could not be determined for the isopropyl- and tosyl-substituted urea-pyrrolidines due to extensive overlap in the proton NMR of the crude products. However single diastereomers were isolated with the stereochemistry of the pyrrolidine ring *syn* to the urea. For the PMP-substituted urea-pyrrolidines, the major diastereomer has its pyrrolidine ring *syn* to the urea while the minor diastereomer has its pyrrolidine ring *anti* to the urea. The ring addition reaction that did not work is the attempted indole synthesis through the Fischer method or via the method described by Chen and coworkers (*Scheme 32*).

The ring cleavage reactions that worked are the urea cleavage that employed lithium aluminium hydride only or lithium aluminium hydride followed by hydroxylamine hydrochloride-aided hydrolysis of aminals (*Scheme 33*), and the ozonolysis of the double bond of the key scaffold (*Scheme 37*). The attempted cleavage reactions that did not work are the base-catalysed solvolysis of the urea ring (*Table 3*) and the osmium tetroxide mediated cleavage of the double bond of the key scaffold. The diol precursor was not formed. (*Scheme 36*).

The ring expansion reactions that worked are the ring swap of the urea ring of the key scaffold for isomeric piperazinone rings (*Schemes 45* and *47*) and Beckmann rearrangements (*Schemes 52-55*). The ring expansion reactions that did not work are the attempted azepane synthesis via double reductive amination or double $S_N2$ reaction (Schemes 38 and 39) and attempted cyclopropane ring opening (Schemes 40, 42 and 44).

Fifty-two final compounds were synthesised, and prepared in 10 mM DMSO solutions for biological screening, by functionalising the diverse scaffolds along different vectors. With the exception of a few compounds whose stereochemistry were assigned by analogy, final compounds obtained via the reduction of the carbonyl group of the scaffolds or through reductive amination (via a pre-formed imine) have their alcohol and amino functionalities *syn*

to the urea except compound **186**. Compound **186** has its alcohol functionality *anti* to the urea but *syn* to the neighbouring pyrrolidine ring. Summarily, the structures of the final compounds synthesised for biological screening are shown in *Figure 36* below.

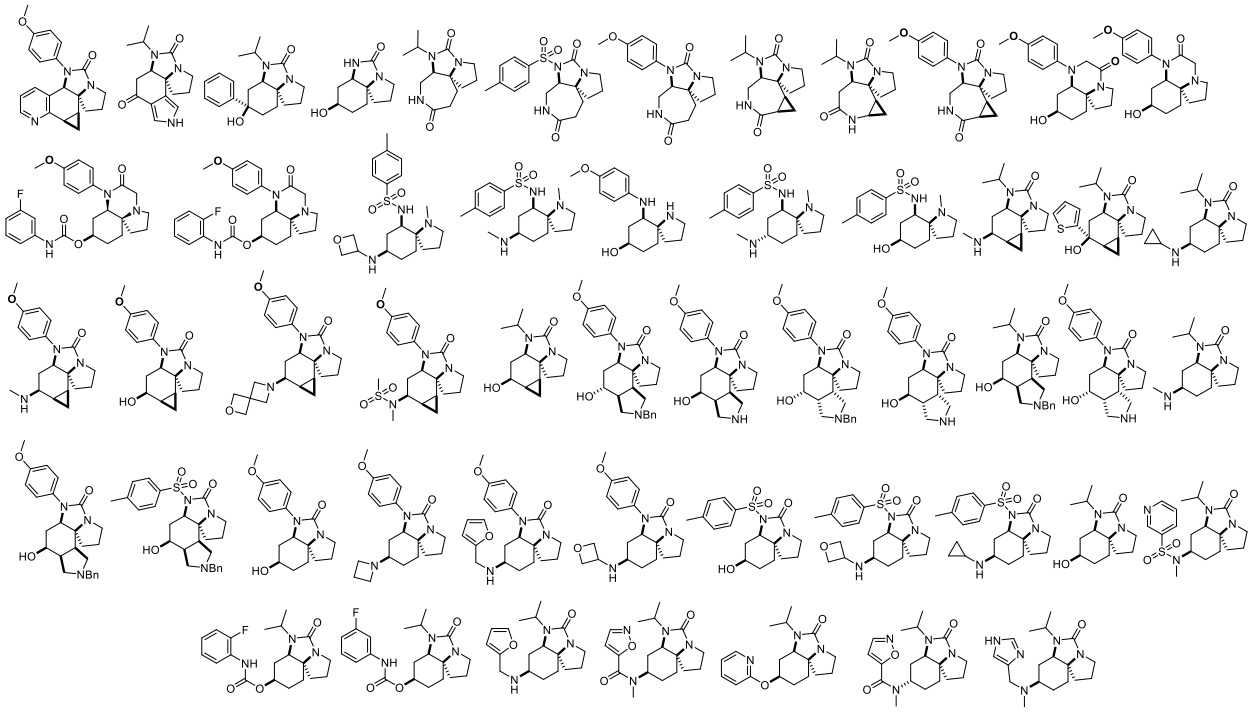


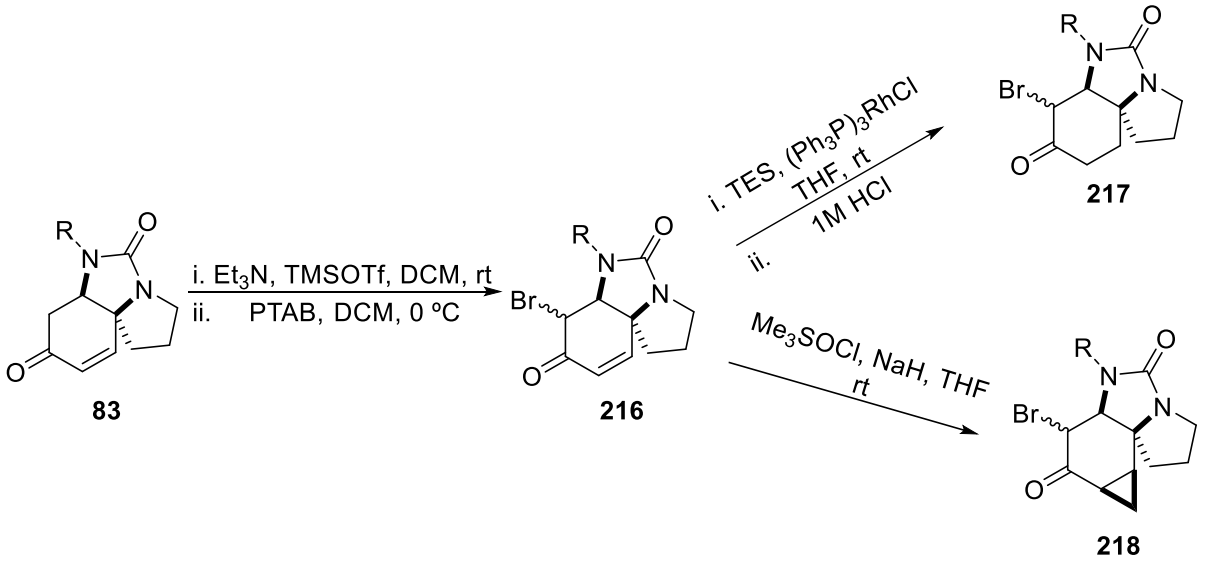
*Figure 36. Structures of final compounds for biological screening*

The final compounds shall be tested against the autophagy target and hedgehog osteogenesis target at the Max Planck Institute, Dortmund. They shall also be tested against DNA i-motif at the University of East Anglia and *Plasmodium falciparum* at the University of Cape Town.

### 3.1.10.9 Future work

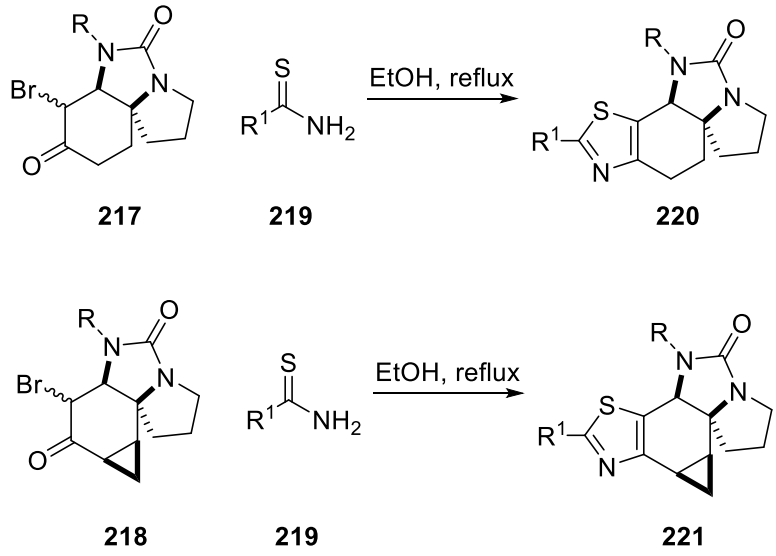
To mention a few, some future work could be done as an extension of this project as shown below.

Firstly, the enone scaffold **83** could be brominated and the double bond reduced or cyclopropanated so that the respective products **217** and **218** could become substrates for Hantzch synthesis and other related reactions, as shown below.




*Scheme 110. Potential syntheses of substrates for Hantzsch thiazole synthesis and other related reactions.*

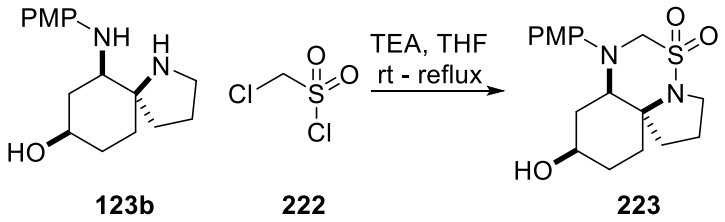
Refluxing **217** and **218** respectively with thioamides in ethanol could give thiazoles as shown below.




*Scheme 111. Potential Hantzsch synthesis using the α-bromoketones **217** and **218** as substrates*

Secondly, the diamine **123b** could be used for other ring swap reactions apart from the isomeric piperazinones shown in *Section 2.7.4* (see *Schemes 45 and 47*). An example, among others, is a

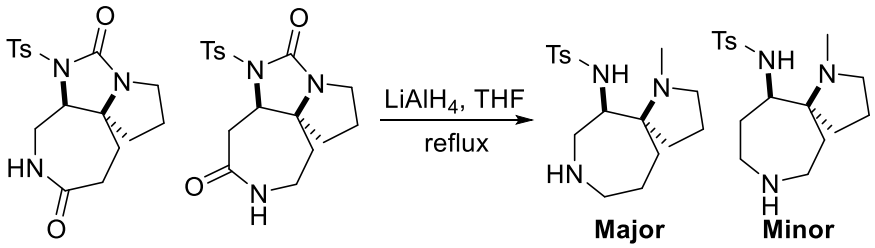
potential reaction between **123b** and chloromethanesulfonyl chloride **222** to give the cyclic sulfonamide **223** as shown below. There is literature precedence which suggests that sulfonylation at the pyrrolidine nitrogen could be faster than alkylation.[122]




**123b** **222** **223**

*Scheme 112. Potential ring swap of the original urea ring of **101b** for a cyclic sulfonamide*

Thirdly, a scaffold could be made to incorporate the three strategies of the top-down approach to lead-oriented synthesis, namely ring addition/cleavage/expansion, in a single molecule. The isomeric lactams **152c/153c** (90:10 mixture, see *Scheme 53*) could be subjected to urea cleavage with concomitant reduction of the amide to furnish the triamines **224** and **225** which could be differentially functionalised along its vectors.

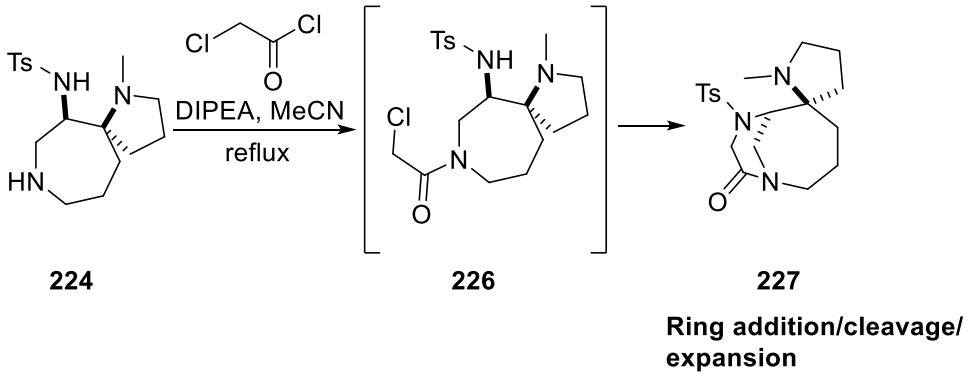



**152c** **153c** **224** **225**

**90:10 mixture** **Major** **Minor**

*Scheme 113. Potential synthesis of triamines for selective functionalisation*

Compound **224** can also be viewed as an alternating 1,2-diamine. Therefore, treating **224** with chloroacetyl chloride could lead to the formation of the lactam **227** which incorporates the ring addition/cleavage/expansion strategies in its structure.




*Scheme 114. Potential synthesis of a hybrid scaffold that incorporates the ring addition/cleavage/expansion strategies to lead-oriented synthesis in its structure*

The reaction in *Scheme 113* was actually attempted on a 26 mg scale. 13 mg of the major isomer **224** was isolated with 82% purity. The triamine **224** was then treated with chloroacetyl chloride as shown in *Scheme 114*. Both the masses of the intermediate **226** and that of the desired product were observed as monitored by LCMS. Less than 1 mg of product was isolated. Therefore, only the accurate mass was acquired [(M + $H^+$): calculated 378.1846, found 378.1857, 2.9 ppm error]. Therefore compounds **224, 225** and **227** could be isolated cleanly and in sufficient amounts (for full characterisation) in the future if the reactions generating them are scaled up.

# 4.0 Experimental

## 4.1 General experimental

All reactions were carried out under an atmosphere of nitrogen. Solvents used were of analytical grade and were dried where necessary by means of a Pure Solv MD solvent purification system (Innovative Technology Inc.). Starting materials were obtained from commercial sources and used without further purification.

Commercially available silica gel-coated aluminium plates (Merck silica Kiesel gel 60F254) were used for thin layer chromatography. Also, silica gel (35 – 70 µm) was used for solvent gradient column chromatography.

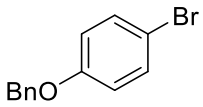
An Agilent 1200 series LC coupled to a Bruker HCT Ultra ion trap mass spectrometer was used for LCMS analysis. High resolution mass spectrometry (HRMS) was recorded on a Bruker HCT Ultra spectrometer. Both nominal and accurate mass spectral data were obtained using the Bruker Maxis Impact with electrospray ionisation (ESI) source.

$^{1}H$ and $^{13}C$ NMR spectral data were acquired using Bruker Avance DPX 300, AV-3 400, Avance 500, DRX 500 and JEOL ECA600II spectrometers. 2D NMR experiments such as $^{1}H$-$^{1}H$ COSY, HMQC, HMBC and NOESY were carried out to aid structural assignments. Coupling constants are in Hz. The Bruker Alpha FTIR spectrometer using 'platinum ATR' accessory was used to record the IR spectral data in wavenumbers.

Crystallographic studies were carried out to determine the conformation of molecules in their crystalline state as well as their stereochemistry. The X-ray crystallography experiments were carried out by Dr Christopher Pask.

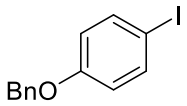
## 4.2 Experimental for the syntheses of compounds

1-(Benzyloxy)-4-bromobenzene **87**




To a mixture of 4-bromophenol **86** (11.8 g, 68.2 mmol, 1.01 eq.) and potassium carbonate (12.9 g, 93.3 mmol, 1.39 eq.) in HPLC grade acetonitrile (80 mL), benzyl bromide (8.0 mL, 67.3 mmol, 1.0 eq.) was added and the mixture was stirred at room temperature for 22 h. The reaction mixture was filtered through a sintered funnel washing with MeCN (300 mL) and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 0 - 10% EtOAc in hexane afforded a white solid **87** (17.1 g, 64.8 mmol, 96% yield); $\mathbf{R_f}$ **=** 0.54 (5% EtOAc in hexane). The NMR data is in agreement with the literature.[122] **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.46 – 7.34 (7H, m, Ar*H*), 6.90 (2H, d, *J* = 9.0, Ar*H*), 5.07 (2H, s, ArC*H*$_2$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ 157.9 (*Ar*), 136.6 (*Ar*H), 132.3 (*Ar*), 128.7 (*Ar*H), 128.1 (*Ar*H), 127.5 (*Ar*H), 116.7 (*Ar*H), 113.2 (*Ar*), 70.3 (Ar*C*H$_2$). **IR** $\nu_{max}$(neat)/cm$^{-1}$: 3060, 3031, 2887, 2852 (C-H), 1574, 1485, 1451 (C=C), 1245 (C-O).

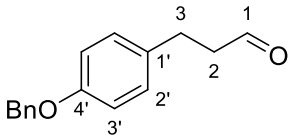
1-(Benzyloxy)-4-iodobenzene **79**




To a mixture of 4-iodophenol **78** (9.68 g, 44.0 mmol, 1.0 eq.) and potassium carbonate (7.91 g, 57.2 mmol, 1.3 eq.) in HPLC grade acetonitrile (20 mL), benzyl bromide (5.75 mL, 48.4 mmol, 1.1 eq.) was added and the mixture was stirred at room temperature for 20 h. The reaction mixture was filtered through a sintered funnel washing with 300 mL DCM and concentrated *in vacuo*. Recrystallisation from hexane afforded a brown solid **79** (12.8 g, 41.3 mmol, 94%); $\mathbf{R_f}$ = 0.54 (5% EtOAc in hexane). The NMR data is in agreement with the literature.[123] **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 7.59 (2H, d, *J* = 8.8, Ar*H*), 7.46 – 7.37 (5H, m, Ar*H*), 6.79 (2H, d, *J* = 8.8, Ar*H*), 5.07 (2H, s, ArC*H*$_2$). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 158.5 (*Ar*), 138.3 (*Ar*H), 136.7 (*Ar*), 128.5 (*Ar*H),

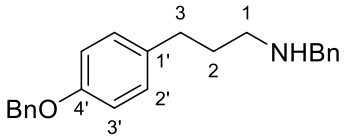
128.0 (*Ar*H), 127.5 (*Ar*H), 117.4 (*Ar*H) 83.1 (*Ar*I), 70.1 (Ar*C*$H_2$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3062, 3030, 2928, 2874 (C-H), 1579, 1481, 1378 (C=C), 1235 (C-O).

3-[(4-Benzyloxy)phenyl]propanal **80**



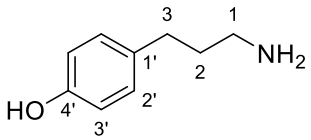

To a mixture of sodium bicarbonate (10.8 g, 129 mmol, 2.0 eq.), tetrabutylammonium chloride (17.9 g, 64.6 mmol, 1.0 eq.), palladium acetate (146 mg, 0.646 mmol, 1 mol%) and 1-(benzyloxy)-4-iodobenzene **79** (20.0 g, 64.6 mmol, 1.0 eq.) in anhydrous DMF (65.5 mL) was added allyl alcohol (6.59 mL, 96.8 mmol, 1.5 eq.) and the mixture was heated at 50 °C for 20 h. The reaction mixture was filtered through a plug of Celite eluting with EtOAc (400 mL) and evaporated *in vacuo*. The filtrate was extracted with EtOAc (5 × 100 mL) in water (50 mL), washed with brine (100 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Purification by flash chromatography on silica gel eluting with 10 – 20% EtOAc in hexane followed by recrystallisation from $Et_2O$ afforded a brown solid **80** (12.8 g, 53.1 mmol, 82% yield); $\mathbf{R_f}$ = 0.55 (20% EtOAc in hexane). The NMR data is in agreement with the literature.[124] **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 9.84 (1H, t, *J* = 1.3, 1-*H*), 7.51 – 7.35 (5H, m, Ar*H*), 7.17 (2H, d, *J* = 8.4, Ar*H*), 6.97 (2H, d, *J* = 8.8, Ar*H*), 5.09 (2H, s, ArC$H_2$O), 2.95 (2H, t, *J* = 7.5, 3-$H_{A,B}$), 2.77 (2H, td, *J* = 7.6, 1.2, 2-$H_{A,B}$). **$^{13}$C NMR** (100 .MHz, $CDCl_3$): δ 201.7 (1-*C*), 157.5 (*Ar*), 136.9 (*Ar*), 132.7 (*Ar*), 129.3 (*Ar*H), 128.5 (*Ar*H), 128.0 (*Ar*H), 127.2 (*Ar*H), 115.0 (*Ar*H), 70.1 (Ar*C*$H_2$O), 45.4 (3-*C*), 27.1 (2-*C*). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3067, 3033, 2925, 2859, 2733 (C-H), 1716 (C=O), 1608, 1579, 1510 (C=C), 1234 (C-O).

*N*-Benzyl-3-[4-(benzyloxy)phenyl]propan-1-amine **81**




To a solution of the aldehyde **80** (1.00 g, 4.16 mmol, 1.0 eq.) in anhydrous MeOH (8.40 ml), $BnNH_2$ (0.60 ml, 5.49 mmol, 1.3 eq.) was added and the mixture was allowed to stir for 1.5 h at room temperature. Sodium borohydride (79.4 mg, 2.10 mmol, 0.50 eq.) was then added and stirring continued at room temperature for 2.5 h. The reaction mixture was extracted with DCM (5 × 20 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography on silica gel eluting with 5 – 10% MeOH in DCM afforded a thick brown oil **81** (1.14 g, 3.44 mmol, 83%); $\mathbf{R_f}$ = 0.39 (100% EtOAc). **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 7.37 – 7.25 (5H, m, Ar*H*), 7.25 – 7.14 (5H, m, Ar*H*), 7.01 (2H, d, *J* = 8.4, Ar*H*), 6.81 (2H, d, *J* = 8.4, Ar*H*), 4.96 (2H, s, OC$H_2$Ar), 3.71 (2H, s, NHC$H_2$Ar), 2.59 (2H, t, *J* = 7.2 Hz, 1-$H_{A,B}$), 2.53(2H, t, *J* = 7.2, 3-$H_{A,B}$), 1.75 (2H, quint, *J* = 7.2, 2-$H_{A,B}$). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ ppm 157.1 (*Ar*), 139.9 (*Ar*), 137.3 (*Ar*), 134.5 (*Ar*), 129.3 (*Ar*H), 128.6 (*Ar*H), 128.5 (*Ar*H), 128.3 (*Ar*H), 127.9 (*Ar*H), 127.5 (*Ar*H), 127.1 (*Ar*H), 114.8 (*Ar*H), 70.1 (O*C*$H_2$Ar), 53.9 (NH*C*$H_2$Ar), 48.7 (1-*C*$H_2$), 32.7 (3-*C*$H_2$), 31.7 (2-*C*$H_2$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3407 (N-H), 3061, 3030, 2928, 2859, 2804 (C-H), 1609, 1509, 1452 (C=C), 1236 (C-O). **HRMS** (ESI): $C_{23}H_{26}NO$ [M + $H^+$]: calculated 332.2009, found 332.2006.

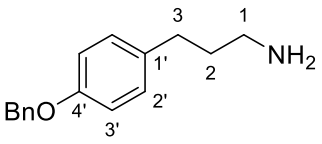
4-(3-Aminopropyl)phenol **71**




To $Pd(OH)_2$/C (3.03 g, 20% w/w) under an inert atmosphere in a round bottomed flask, 10 mL of MeOH was gently added. A solution of the amine **81** (15.1 g, 45.7mmol, 1.0 eq.) in MeOH (40 mL) was then added followed by 76.6 mL of AcOH. The reaction mixture was diluted (by adding 260 mL of MeOH) and transferred to the steel vessel of the PAT-instrumented batch reactor.

The mixture was degassed and nitrogen gas was bubbled into it. This procedure was repeated twice. Similarly, the reaction mixture was degassed and hydrogen gas was bubbled into it. This procedure was also repeated twice. From the control unit, the mixture was made to stir at 1000 rpm. The pressure and temperature were set at 15 bar and 40 °C respectively. After 24 h, the reaction mixture was filtered through a plug of celite with MeOH (400 mL) and evaporated *in vacuo*. Flash chromatography on silica gel eluting with 10% MeOH in DCM followed by 10% saturated $NH_3$/MeOH in DCM afforded a sticky brown oil **71** (6.90 g, 45.6 mmol, quant.); $\mathbf{R_f}$ = 0.19 (10% saturated $NH_3$/MeOH in DCM). The NMR data aligns with the literature.[125] **$^1$HNMR** (500 MHz, MeOD): δ ppm 6.90 (2H, d, *J* = 8.5, Ar*H*), 6.58 (2H, d, 8.5, Ar*H*), 2.53 (2H, t, *J* = 7.5, 1-$H_{A,B}$), 2.44 (2H, t, *J* = 7.5, 3-$H_{A,B}$), 1.63 (2H, quint, *J* = 7.5, 2-$H_{A,B}$). **$^{13}$CNMR** (125 MHz, MeOD): δ ppm 155.3 (*Ar*), 132.5 (*Ar*), 128.8 (*Ar*H), 114.8 (*Ar*H), 40.6 (1-*C*), 34.3 (2-*C*), 31.9 (3-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3348 (N-H), 3009, 2928, 2854, 2674, 2586 (C-H), 1592, 1513, 1452 (C=C), 1244 (C-O).

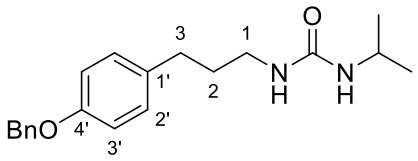
3-(4-(Benzyloxy)phenyl)propan-1-amine **98**




A mixture of the aldehyde **80** (300 mg, 1.25 mmol, 1.0 eq.) and hydroxylamine hydrochloride (104 mg, 1.50 mmol, 1.2 eq.) in 3 mL of anhydrous EtOH was allowed to stir for 1 h at room temperature. 12 M HCl (0.42 mL, 5.0 mmol, 4.0 eq.) was then added to the reaction mixture followed by zinc dust (205 mg, 3.13 mmol, 2.5 eq.) and the mixture was left to stir for 40 min, after which 0.36 mL of 30% aqueous ammonia and 0.77 mL of 6 M NaOH were added. The reaction mixture was extracted with DCM (5 × 20 mL), dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by silica gel chromatography eluting with 3 – 7% MeOH in DCM followed by 3 – 10% of saturated $NH_3$/MeOH in DCM, afforded a white solid **98** (132 mg, 0.55 mmol, 44% yield); $\mathbf{R_f}$ = 0.39 (6% $NH_3$/MeOH in DCM). **$^1$H NMR** (300 MHz, MeOD): δ ppm 7.34 – 7.14 (5H, m, Ar*H*), 7.00 (2H, d, *J* = 8.6, Ar*H*), 6.79 (2H, d, *J* = 8.7, Ar*H*), 4.93 (2H, s, ArOC$H_2$), 2.55 (2H, t, *J* = 7.4,

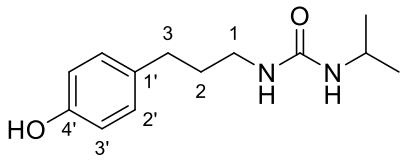
1-$H_{A,B}$), 2.49 (2H, t, *J* = 7.6, 3-$H_{A,B}$), 1.66 (2H, quint, *J* = 7.5, 2-$H_{A,B}$). **$^{13}$C NMR** (75 MHz, MeOD): δ ppm 158.4 (*Ar*), 138.8 (*Ar*), 135.3 (*Ar*), 130.2 (*Ar*H), 129.4 (*Ar*H), 128.7 (*Ar*H), 128.4 (*Ar*H), 115.9 (*Ar*H), 71.0 (ArO*C*H$_2$), 41.7 (1-*C*), 34.9 (3-*C*), 33.1 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3366 (N-H), 3061, 3032, 2927, 2857 (C-H), 1235 (C-O). **HRMS** (ESI): $C_{16}H_{20}NO$ [M + H$^+$]: calculated 242.1539, found 242.1538.

1-(3-(4-(Benzyloxy)phenyl)propyl)-3-isopropylurea **99**




Isopropyl isocyanate (0.63 mL, 6.45 mmol, 1.1 eq.) was added to a solution of the amine **98** (1.41 g, 5.86 mmol, 1.0 eq.) in anhydrous DCM and the mixture was refluxed for 5 h. The reaction mixture was then evaporated *in vacuo.* Flash chromatography with 50 – 100% EtOAc in hexane afforded the compound **99** as a white solid (1.71 g, 5.25 mmol, 90% yield); **$R_f$** = 0.75 (100% EtOAc). **$^1$H NMR** (300 MHz, MeOD): δ ppm 7.36 – 7.14 (5H, m, Ar*H*), 6.99 (2H, d, *J* = 8.4, Ar*H*), 6.79 (2H, d, *J* = 8.7, Ar*H*), 4.93 (2H, s, ArOC*H$_2$*), 3.70 (1H, hept, *J* = 6.5, isopropyl C*H*), 3.01 (2H, t, *J* = 7.0, 1-$H_{A,B}$), 2.47 (2H, t, *J* = 7.5, 3-$H_{A,B}$), 1.64 (2H, quint, *J* = 7.3, 2-$H_{A,B}$), 1.02 (6H, d, *J* = 6.5, isopropyl C*H$_3$*). **$^{13}$C NMR** (75 MHz, MeOD): δ ppm 160.5 (urea *C*=O), 158.4 (*Ar*), 138.9 (*Ar*), 135.4 (*Ar*), 130.3 (*Ar*H), 129.4 (*Ar*H), 128.7 (*Ar*H), 128.5 (*Ar*H), 115.8 (*Ar*H), 71.0 (ArO*C*H$_2$), 42.8 (isopropyl-*C*H), 40.4 (1-*C*), 33.3 (3-*C*), 33.2 (2-*C*), 23.5 (isopropyl C*H$_3$*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3328 (N-H), 2964, 2935, 2864 (C-H), 1726 (C=O), 1236 (C-O). **HRMS** (ESI): $C_{20}H_{27}N_2O_2$ [M + H$^+$]: calculated 327.2067, found 327.2065.

1-[3-(4-Hydroxyphenyl)propyl]-3-isopropylurea **82a**



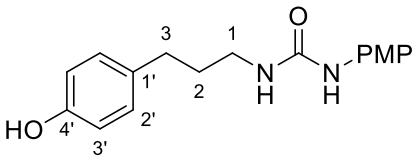

**Method A**

To a mixture of $Pd(OH)_2/C$ (10.1 mg, 10% w/w) and urea **99** (101 mg, 0.31 mmol, 1.0 eq.) under an atmosphere of nitrogen, 5 mL of MeOH was added gently. The reaction mixture was degassed and hydrogen gas was bubbled through it with the aid of a balloon, and this procedure was repeated twice. The mixture was then allowed to stir under a balloon of hydrogen for 23 h at room temperature. The reaction mixture was filtered through a plug of Celite washing with 100 mL MeOH. The filtrate was evaporated *in vacuo*. Flash chromatography eluting with 80 - 100% EtOAc in hexane afforded the product **82a** as a colourless oil (70 mg, 0.30 mmol, 92%).

**Method B**

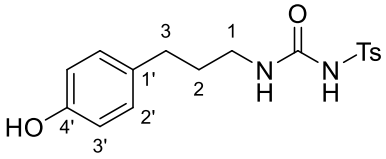
Isopropyl isocyanate (1.64 mL, 16.7 mmol, 1.01 eq.) was added to a solution of the amine **71** (2.50 g, 16.6 mmol, 1.0 eq.) in anhydrous THF and the mixture was refluxed for 1 h. The reaction mixture was evaporated *in vacuo.* Flash chromatography with 50 – 100% EtOAc in hexane afforded the product **82a** as a colourless oil (3.24 g, 13.6 mmol, 83% yield); $\mathbf{R_f}$ = 0.55 (100% EtOAc). **$^1$H NMR** (500 MHz, MeOD): δ ppm 7.02 (2H, d, *J* = 8.4, Ar*H*), 6.74 (2H, d, *J* = 8.4, Ar*H*), 3.82 (1H, hept, *J* = 6.5, isopropyl C*H*), 3.13 (2H, t, *J* = 7.0, 1-$H_{A,B}$), 2.53 (2H, t, *J* = 7.5, 3-$H_{A,B}$), 1.76 (2H, quint, *J* = 7.5, 2-$H_{A,B}$), 1.14 (6H, d, *J* =6.6, isopropyl C$H_3$). **$^{13}$C NMR** (125 MHz, MeOD): δ ppm 160.7 (urea *C*=O), 156.5 (*Ar*), 134.0 (*Ar*), 130.4 (*Ar*H), 116.3 (*Ar*H), 43.0 (isopropyl *C*H), 40.6 (1-*C*), 33.6 (3-*C*), 33.3 (2-*C*), 23.7 (isopropyl *C*$H_3$). **IR** $\nu_{max\ (neat)}/cm^{-1}$: 3334 (O-H, N-H), 3014, 2969, 2931, 2872 (C-H), 1558, 1514, 1455 (C=C), 1240 (C-O).**HRMS** (ESI): $C_{13}H_{21}N_2O_2$ [M + $H^+$]: calculated 237.1598, found 237.1592.

1-(3-(4-Hydroxyphenyl)propyl)-3-(4-methoxyphenyl)urea **82b**




4-Methoxyphenyl isocyanate (0.30 mL, 2.30 mmol, 1.01 eq.) was added to a solution of the amine **71** (345 mg, 2.28 mmol, 1.0 eq.) in anhydrous THF and the mixture was refluxed for 1 h. The reaction mixture was evaporated *in vacuo.* Flash chromatography with 50 – 100% EtOAc in hexane afforded the compound **82b** as a brown oil (497 mg, 1.66 mmol, 73% yield); $\mathbf{R_f}$ = 0.41 (70% EtOAc in hexane). **$^1$H NMR** (300 MHz, MeOD) δ ppm 7.10 (2H, d, *J* = 9.0, Ar*H*), 6.90 (2H, d, *J* = 8.4, Ar*H*), 6.72 (2H, d, *J* = 9.0, Ar*H*), 6.59 (2H, d, *J* = 8.7, Ar*H*), 3.63 (3H, s, ArOC$H_3$), 3.07 (2H, t, *J* = 6.9, 1-$H_{A,B}$), 2.45 (2H, t, *J* = 7.2, 3-$H_{A,B}$), 1.67 (2H, quint, *J* = 7.3, 2-$H_{A,B}$). **$^{13}$C NMR** (75 MHz, MeOD): δ ppm 158.8 (Urea *C*=O), 157.0 (*Ar*), 156.4 (*Ar*), 133.8 (*Ar*), 133.6 (*Ar*), 130.2 (*Ar*H), 122.8 (*Ar*H), 116.1 (*Ar*H), 115.0 (*Ar*H), 55.8 (ArO*C*H$_3$), 40.4 (1-*C*), 33.3 (3-*C*), 33.2 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3308 (O-H, N-H), 3053, 2935, 2837 (C-H), 1647 (C=O), 1554, 1509, 1441 (C=C), 1228 (C-O). **HRMS** (ESI): $C_{17}H_{21}N_2O_3$ [M + H$^+$]: calculated 301.1547, found 301.1543.

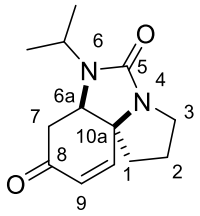
*N*-((3-(4-Hydroxyphenyl)propyl)carbamoyl)-4-methylbenzenesulfonamide **82c**




4-Toluenesulfonyl isocyanate (0.35 mL, 2.28 mmol, 1.01 eq.) was added to a solution of the amine **71** (341 mg, 2.26 mmol, 1.0 eq.) in anhydrous THF and the mixture was refluxed for 1 h. The reaction mixture was evaporated *in vacuo.* Flash chromatography with 30 – 90% EtOAc in hexane afforded the product **82c** as a brown oil (595 mg, 1.72 mmol, 76% yield); $\mathbf{R_f}$ = 0.48 (70% EtOAc in hexane). **$^1$H NMR** (300 MHz, MeOD): δ ppm 7.74 (2H, d, *J* = 8.4, Ar*H*), 7.26 (2H, d, *J* = 8.1, Ar*H*), 6.78 (2H, d, *J* = 8.7, Ar*H*), 6.56 (2H, d, *J* = 8.7, Ar*H*), 2.97 (2H, t, *J* = 6.9, 1-$H_{A,B}$), 2.29 (2H, t, *J* = 6.9, 3-$H_{A,B}$), 2.29 (3H, s, ArC$H_3$), 1.54 (2H, quint, *J* = 6.9, 2-$H_{A,B}$). **$^{13}$C NMR** (75 MHz, MeOD): δ ppm 156.4 (Urea *C*=O), 153.9 (*Ar*), 145.7 (*Ar*), 138.6 (*Ar*), 133.4 (*Ar*), 130.6 (*Ar*H),

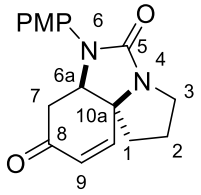
130.1 (*Ar*H), 128.5 (*Ar*H), 116.0 (*Ar*H), 40.3 (1-*C*), 32.8 (3-*C*), 32.6 (2-*C*), 21.4 (Ar*C*$H_3$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3352 (O-H, N-H), 2929, 2860 (C-H), 1668 (C=O), 1539,1514, 1444 (C=C), 1157 (C-O). **HRMS** (ESI): $C_{17}H_{21}N_2O_4S$ [M + $H^+$]: calculated 349.1217, found 349.1217.

(6a*R**, 10a*S**)-6-Isopropyl-2,3,6a,7-tetrahydro-1*H,*5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazole-5,8(6*H*)-dione **83a**



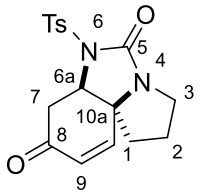

A solution of PIFA (1.21g, 2.81 mmol, 1.1 eq.) dissolved in DCM/HFIP (7ml, 50:50) was added to a solution of the urea **82a** (603 mg, 2.55 mmol, 1.0 eq.) in 7 mL of the same solvent system at 0 °C and the mixture was stirred for 2 h after which it was allowed to warm up to room temperature for 20 min. The reaction mixture was washed with 20 mL of 10% $Na_2CO_3$ solution and the aqueous layer was extracted with DCM (4 × 25 mL) and evaporated *in vacuo*. Flash chromatography on silica gel eluting with 1% MeOH in DCM gave a colourless oil **83a** (222 mg, 0.95 mmol, 37%); $\mathbf{R_f}$ **=** 0.36 (100% EtOAc). **$^1$H NMR** (300 MHz, MeOD): δ ppm 6.58 (1H, d, *J* = 10.2, 9-*H*), 5.96 (1H, d, *J* =10.2, 10-*H*), 4.04 (1H, dd, *J* = 6.9, 5.3, 6a-*H*), 3.82 (1H, hept, *J* = 6.9, isopropyl C*H*), 3.65 (1H, ddd, *J* = 15.6, 7.8, 3.9, 3-$H_A$), 3.02 (1H, m, 3-$H_B$), 2.81 (1H, dd, *J* = 16.1, 5.2, 7-$H_A$), 2.61 (1H, dd, *J* = 16.1, 6.9, 7-$H_B$), 2.05 - 1.90 (1H, m, 2-$H_A$), 1.90 – 1.82 (1H, m, 1-$H_A$), 1.82 – 1.72 (2H, m, 1-$H_B$, 2-$H_B$), 1.14 (3H, d, *J* = 6.9, isopropyl C$H_{3A}$), 1.11 (3H, d, *J* = 6.9, isopropyl $CH_{3B}$). **$^{13}$C NMR** (75 MHz, MeOD): δ ppm 198.2 (8-*C*), 164.2 (5-*C*), 147.8 (9-*C*), 128.2 (10-*C*), 64.7 (10a-*C*), 59.1 (6a-*C*), 46.7 (3-*C*), 46.0 (isopropyl *C*H), 41.9 (7-*C*), 35.8 (1-*C*), 25.5 (2-*C*), 21.4 (isopropyl *C*$H_{3B}$), 19.5 (isopropyl *C*$H_{3A}$). **IR** $\nu_{max\ (}$neat)/$cm^{-1}$: 2966, 2938, 2876 (C-H), 1681 (C=O), 1456 (C=C). **HRMS** (ESI): $C_{13}H_{19}N_2O_2$ [M + $H^+$]: calculated 235.1441, found 235.1437.

(6a*R**,10a*S**)-6-(4-Methoxyphenyl)-2,3,6a,7-tetrahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazole-5,8(6*H*)-dione **83b**



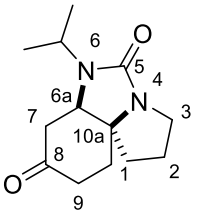

A solution of PIFA (361 mg, 0.84 mmol, 1.01 eq.) dissolved in DCM/HFIP (0.62 mL, 50:50) was added to a solution of the urea **82b** (250 mg, 0.83 mmol, 1.0 eq.) in 2.7 mL of the same solvent system at 0 °C and the mixture was stirred for 2 h after which it was allowed to warm up to room temperature in 20 min, and then evaporated *in vacuo*. Flash chromatography on silica gel eluting with 1% MeOH in DCM gave a white solid **83b** as product (104 mg, 0.35 mmol, 42%); $\mathbf{R_f}$ **=** 0.35 (100% EtOAc). **$^1$H NMR** (300 MHz, $CDCl_3$): δ ppm 7.13 (2H, d, *J* = 9.0, Ar*H*), 6.91 (2H, d, *J* = 9.0, Ar*H*), 6.56 (1H, d, *J* = 10.2, 9-*H*), 6.13 (1H, d, *J* = 10.3, 10-*H*), 4.36 (1H, t, *J* = 5.1, 6a-*H*), 3.99 – 3.88 (1H, m, 3-$H_A$), 3.80 (3H, s, ArOC$H_3$), 3.30 - 3.19 (1H, m, 3-$H_B$), 2.74 (1H, dd, *J* = 16.6, 5.0, 7-$H_A$), 2.66 (1H, dd, *J* = 16.6, 5.2, 7-$H_B$), 2.30 – 2.12 (1H, m, 1-$H_A$), 2.12 – 2.07 (1H, m, 1-$H_B$), 2.06 – 1.99 (2H, m, 2-$H_{A,B}$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ ppm 195.1 (8-*C*), 160.6 (5-*C*), 157.7 (*Ar*), 146.2 (9-*C*), 129.8 (*Ar*), 127.6 (10-*C*), 125.8 (*Ar*H), 114.6 (*Ar*H), 62.8 (10a-*C*), 61.7 (6a-*C*), 55.5 (ArO*C*$H_3$), 45.9 (3-*C*), 38.1 (7-*C*) 35.5 (1-*C*), 25.7 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2957, 2900, 2834 (C-H), 1686 (C=O), 1582, 1510, 1443, 1390 (C=C). **HRMS** (ESI): $C_{17}H_{19}N_2O_3$ [M + H$^+$]: calculated 299.1390, found 299.1390.

(6a*R**,10a*S**)-6-(4-Toluenesulfonyl)-2,3,6a,7-tetrahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazole-5,8(6*H*)-dione **83c**



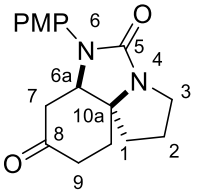

A solution of PIFA (645 mg, 1.50 mmol, 1.01 eq.) dissolved in DCM/HFIP (1.1 mL, 50:50) was added to a solution of the urea **82c** (518 mg, 1.49 mmol, 1.0 eq.) in 4.9 mL of the same solvent system at 0 °C and the mixture was stirred for 2 h after which it was allowed to warm up to room temperature in 20 min, and then evaporated *in vacuo*. Flash chromatography on silica gel eluting with 40% EtOAc in hexane gave a white solid **83c** (118 mg, 0.34 mmol, 23%) $\mathbf{R_f}$ **=** 0.57 (100% EtOAc). **$^1$H NMR** (300 MHz, $CDCl_3$): δ ppm 7.85 (2H, d, *J* = 8.3, Ar*H*), 7.26 (2H, d, *J* = 8.2, Ar*H*), 6.40 (1H, d, *J* = 10.3, 9-*H*), 6.05 (1H, d, *J* = 10.3, 10-*H*), 4.54 (1H, dd, *J* = 8.8, 5.8, 6a-*H*), 3.84 – 3.70 (1H, m, 3-$H_A$), 3.12 (1H, dd, *J* = 15.9, 5.7, 7-$H_A$), 3.05 (1H, ddd, *J* = 12.9, 5.7, 1.2, 3-$H_B$), 2.86 (1H, dd, *J* = 15.9, 8.8, 7-$H_B$), 2.36 (3H, s, ArC$H_3$), 2.04 – 1.82 (3H, m, 1-$H_A$, 2-$H_{A,B}$), 1.63 (1H, dt, *J* = 12.8, 9.5, 1-$H_B$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ ppm 194.5 (8-*C*), 156.3 (5-*C*), 145.2 (*Ar*), 142.8 (9-*C*), 135.5 (*Ar*), 129.7 (*Ar*H), 129.0 (10-*C*), 128.3 (*Ar*H), 63.2 (10a-*C*), 58.3 (6a-*C*), 44.7 (3-*C*), 41.3 (7-*C*) 35.1 (1-*C*), 23.5 (2-*C*), 21.7 (Ar*C*$H_3$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2958, 2930 (C-H), 1736, 1685 (C=O), 1597, 1494, 1458, 1369 (C=C). **HRMS** (ESI): $C_{17}H_{19}N_2O_4S$ [M + $H^+$]: calculated 347.1060, found 347.1060.

(6a*R**,10a*S**)-6-Isopropylhexahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazole-5,8(6*H*)-dione **101a**




To a solution of the enone **83a** (197 mg, 0.84 mmol, 1.0 eq.) and tris(triphenyl)rhodium(I) chloride (15.6 mg, 16.9 µmol, 2.0 mol%) in 5 mL THF, 6 mL of TES was added. The mixture was stirred at room temperature for 24 h. 0.05 mL of 1M HCl was then added and the mixture was stirred at room temperature for 1 h and evaporated *in vacuo*. Flash chromatography eluting with 50 – 100% EtOAc in hexane afforded the product **101a** (167 mg, 0.71 mmol, 85%); $\mathbf{R_f}$ = 0.43 (100% EtOAc). **$^1$H NMR** (300 MHz, MeOD) δ ppm 4.03 (1H, dd, *J* = 5.1, 3.2, 6a-*H*), 3.71 (1H, hept, *J* = 6.9, isopropyl C*H*), 3.53 (1H, ddd, *J* = 12.0, 6.0, 3.3, 3-$H_A$), 2.92 (1H, ddd, *J* = 12.0, 5.7, 3.6, 3-$H_B$), 2.83 (1H, dd, *J* = 15.5, 5.3, 7-$H_A$), 2.50 (1H, dd, *J* = 15.5, 3.1, 7-$H_B$), 2.31 – 2.22 (2H, m, 1-$H_A$, 9-$H_A$), 2.03 (1H, ddd, *J* = 14.5, 10.1, 6.5, 1-$H_B$), 1.95 – 1.78 (4H, m, 9-$H_B$, 10-$H_A$, 2-$H_{A,B}$), 1.65 – 1.52 (1H, m, 10-$H_B$), 1.14 (3H, d, *J* = 6.9, isopropyl C$H_{3A}$), 1.12 (3H, d, *J* = 6.9, isopropyl C$H_{3B}$). **$^{13}$C NMR** (75 MHz, MeOD) δ ppm 213.1 (8-*C*), 164.9 (5-*C*), 66.6 (10a-*C*), 60.0 (6a-*C*), 46.3 (isopropyl *C*H), 45.3 (3-*C*), 43.6 (7-*C*), 38.0 (10-*C*), 36.1 (1-*C*), 29.5 (9-*C*), 24.6 (2-*C*), 21.4 (isopropyl *C*$H_{3B}$), 19.5 (isopropyl *C*$H_{3A}$). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2967 (C-H), 1682 (C=O). **HRMS** (ESI): $C_{13}H_{21}N_2O_2$ [M + $H^+$]: calculated 237.1598, found 237.1595.

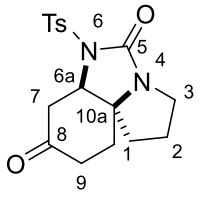
(6a*R**,10a*S**)-6-(4-Methoxyphenyl)hexahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazole-5,8(6*H*)-dione **101b**




To a mixture of $Pd(OH)_2$/C (20.8 mg, 20% w/w) and enone **83b** (104 mg, 0.35 mmol, 1.0 eq.) under an atmosphere of nitrogen, 10 mL of HPLC grade EtOAc was added gently. The reaction mixture was degassed and hydrogen gas was bubbled through it with the aid of a balloon, and this procedure was repeated twice. The mixture was then allowed to stir under a balloon of

hydrogen for 23 h at room temperature. The reaction mixture was filtered through a plug of Celite washing with 100 mL EtOAc. The filtrate was evaporated *in vacuo*. Flash chromatography eluting with 2 - 4% MeOH in DCM afforded the product **101b** as a brown solid (72 mg, 0.24 mmol, 69%); $\mathbf{R_f}$ = 0.41 (100% EtOAc). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.04 (2H, d, *J* = 9.0, Ar*H*), 6.81 (2H, d, *J* = 9.0, Ar*H*), 4.35 (1H, t, *J* = 4.0, 6a-*H*), 3.76 (1H, ddd, *J* = 11.5, 5.5, 3.5, 3-$H_A$), 3.71 (3H, s, ArOC$H_3$), 3.07 (1H, ddd, *J* = 11.5, 6.0, 3.5, 3-$H_B$), 2.60 – 2.54 (2H, m, 7-$H_{A,B}$), 2.54 -2.49 (1H, m, 1-$H_A$), 2.31 (1H, dt, *J* = 19.0, 3.9, 1-$H_B$), 2.03 – 1.89 (5H, m, 2-$H_{A,B}$; 9-$H_{A,B}$; 10-$H_A$), 1.80 (1H, ddd, *J* = 16.0, 9.5, 3.5, 10-$H_B$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 208.2 (8-*C*), 160.0 (5-*C*), 156.3 (*Ar*), 128.9 (*Ar*), 124.3 (*Ar*H), 113.6 (*Ar*H), 63.2 (10a-*C*), 60.0 (6a-*C*), 54.5 (ArO*C*$H_3$), 43.5 (3-*C*), 39.4 (7-*C*) 37.4 (10-*C*), 34.2 (1-*C*), 28.7 (9-*C*), 23.4 (2-*C*). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2998, 2953, 2891 (C-H), 1710 (C=O), 1617, 1586, 1516, 1406 (C=C). **HRMS** (ESI): $C_{17}H_{21}N_2O_3$ [M + $H^+$]: calculated 301.1547, found 301.1544.

(6a*R**,10a*S**)-6-(4-Toluenesulfonyl)hexahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazole-5,8(6*H*)-dione **38**




**Method C**

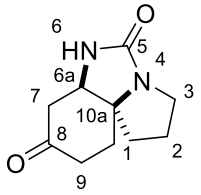
To a mixture of $Pd(OH)_2/C$ (20.0 mg, 20% w/w) and enone **83c** (98.0 mg, 0.28 mmol, 1.0 eq.) under an atmosphere of nitrogen, 10 mL of HPLC grade MeOH was added gently. The reaction mixture was degassed and hydrogen gas was bubbled through it with the aid of a balloon, and this procedure was repeated twice. The mixture was then allowed to stir under a balloon of hydrogen for 3 days at room temperature. The reaction mixture was filtered through a plug of Celite washing with 100 mL MeOH. The filtrate was evaporated *in vacuo*. To a solution of the crude in 2 mL of THF, 0.68 mL of 1 M HCl was added and stirred at room temperature for 6 h. 4 mL of a saturated solution of aqueous $NaHCO_3$ was then added. The reaction mixture was

extracted with EtOAc (5 × 20 mL), dried over $MgSO_4$, and evaporated *in vacuo*. Flash chromatography eluting with 30 - 90% EtOAc in hexane afforded the product **101c** as a white solid (70.0 mg, 0.20 mmol, 71%).

**Method D**

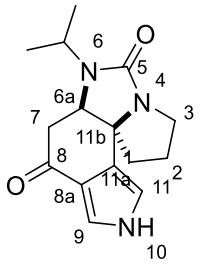
To a mixture of $Pd(OH)_2/C$ (27.0 mg, 20% w/w) and enone **83c** (133 mg, 0.38 mmol, 1.0 eq.) under an atmosphere of nitrogen, 10 mL of HPLC grade EtOAc was added gently. The reaction mixture was degassed and hydrogen gas was bubbled through it with the aid of a balloon, and this procedure was repeated twice. The mixture was then allowed to stir under a balloon of hydrogen for 27 h at room temperature. The reaction mixture was filtered through a plug of Celite washing with 100 mL EtOAc. The filtrate was evaporated *in vacuo*. Flash chromatography eluting with 50 - 90% EtOAc in hexane afforded the product **101c** as a white solid (111 mg, 0.32 mmol, 83%); **$R_f$ =** 0.61 (100% EtOAc). **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 7.83 (2H, d, *J* = 8.4, Ar*H*), 7.32 (2H, d, *J* = 8.8, Ar*H*), 4.56 (1H, dd, *J* = 5.2, 3.8, 6a-*H*), 3.66 (1H, ddd, *J* = 12.0, 5.6, 3.2, 3-$H_A$), 3.13 (1H, dd, *J* = 16.3, 3.7, 7-$H_A$), 2.94 (1H, ddd, *J* = 12.1, 9.2, 4.9, 3-$H_B$), 2.84 (1H, dd, *J* = 16.3, 5.3, 7-$H_B$), 2.35 (3H, s, ArC$H_3$), 2.34 - 2.18 (2H, m, 1-$H_{A,B}$), 2.03 – 1.79 (5H, m, 2-$H_{A,B}$; 9-$H_{A,B}$; 10-$H_A$), 1.59-1.50 (1H, m, 10-$H_B$). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ ppm 208.1 (8-*C*), 156.6 (5-*C*), 145.0 (*Ar*), 135.4 (*Ar*), 129.6 (*Ar*H), 128.4 (*Ar*H), 65.1 (10a-*C*), 59.4 (6a-*C*), 43.6 (3-*C*), 42.9 (7-*C*), 37.1 (10-*C*), 34.8 (1-*C*), 28.4 (9-*C*), 23.5 (2-*C*), 21.7 (Ar*C*$H_3$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2959 (C-H), 1718 (C=O), 1596, 1494, 1455, 1352 (C=C). **HRMS** (ESI): $C_{17}H_{21}N_2O_4S$ [M + $H^+$]: calculated 349.1217, found 349.1217.

(6a*R**,10a*S**)-Hexahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazole-5,8(6*H*)-dione **104**




To a mixure of the ketone **101b** (13 mg, 0.04 mmol, 1.0 eq.) and CAN (94 mg, 0.17, 4.0 eq.) in 0.43 mL of HPLC grade MeCN, 0.24 mL of $H_2O$ was added and the mixture was left to stir for 5 min. The reaction mixture was extracted with EtOAc (5 × 20 mL), dried over $MgSO_4$, and evaporated *in vacuo*. Flash chromatography with 2 – 4% MeOH in DCM afforded the product **104** as a pale yellow solid (8 mg, 0.04 mmol, 95% yield). **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 4.79 (1H, s, 6-*H*), 3.99 (1H, m, 6a-*H*), 3.65 (1H, ddd, *J* = 12.0, 5.6, 4.0, 3-$H_A$), 2.98 (1H, ddd, *J* = 12.0, 5.2, 2.0, 3-$H_B$), 2.64 (1H, dd, *J* = 16.3, 4.5, 7-$H_A$), 2.52 (1H, ddd, *J* = 18.8, 10.4, 1.6, 1-$H_A$), 2.45 (1H, dd, *J* = 16.4, 3.6, 7-$H_B$), 2.29 (1H, dt, *J* = 19.0, 3.9, 1-$H_B$), 1.99 – 1.83 (5H, m, 2-$H_{A,B}$; 10-$H_A$, 9-$H_{A,B}$), 1.81 – 1.71 (1H, m, 10-$H_B$). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ ppm 208.6 (8-*C*), 162.8 (5-*C*), 65.9 (10a-*C*), 55.1 (6a-*C*), 43.1 (3-*C*), 42.5 (7-*C*), 37.2 (10-*C*), 34.1 (1-*C*), 30.1 (9-*C*), 24.9 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3312 (N-H), 2969, 2938 (C-H), 1734, 1703 (C=O). **HRMS** (ESI): $C_{10}H_{14}N_2NaO_2$ [M + $Na^+$]: calculated 217.0947, found 217.0946.

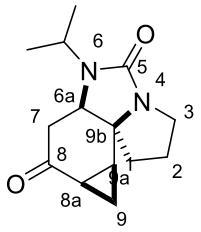
(6a*R**,11b*S**)-6-Isopropyl-2,3,6a,7-tetrahydro-1*H*-pyrrolo[1',2':3,4]imidazole[4,5-*e*]isoindole-5,8(6*H*, 10*H*)-dione **105**




To a mixture of potassium *tert*-butoxide (382 mg, 3.40 mmol, 5.0 eq.) and TosMIC (132.8 mg, 0.68 mmol, 1.0 eq.), a solution of the enone **83a** (160 mg, 0.68 mmol, 1.0 eq.) in 3.5 mL

anhydrous THF was added and the mixture was stirred for 17 h at room temperature. The reaction mixture was extracted with DCM (5 × 12 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography on silica gel eluting with 50 – 100% EtOAc in hexane afforded a brown oil **105** (32.0 mg, 0.12 mmol, 17%). $\mathbf{R_f}$ = 0.50 (100% EtOAc). **$^1$H NMR** (300 MHz, MeOD): δ ppm 7.25 (1H, d, *J* = 1.8, Ar*H*), 6.80 (1H, d, *J* = 1.8, Ar*H*), 4.15 (1H, dd, *J* = 9.5, 5.7, 6a-H), 3.92 (1H, hept, *J* = 6.9, isopropyl C*H*), 3.79 (1H, ddd, *J* = 12.0, 7.2, 3.4, 3-$H_A$), 3.02 (1H, ddd, *J* = 12.4, 8.8, 7.0, 3-$H_B$), 2.87 (1H, dd, *J* = 16.1, 5.7, 7-$H_A$), 2.61 (1H, dd, *J* = 16.2, 9.6, 7-$H_B$), 2.12 – 1.78 (4H, m, 1-$H_{A,B}$; 2-$H_{A,B}$), 1.18 (6H, d, *J* = 6.9, isopropyl C$H_{3A,B}$). **$^{13}$C NMR** (75 MHz, MeOD): δ ppm 194.0 (8-*C*), 165.0 (5-*C*), 127.8 (*Ar*), 120.4 (*Ar*H), 120.4 (*Ar*), 117.6 (*Ar*H), 64.9 (11b-*C*), 59.2 (6a-*C*), 46.2 (isopropyl *C*H), 45.6 (3-*C*), 45.2 (7-*C*), 37.4 (1-*C*), 24.5 (2-*C*), 22.0 (isopropyl-*C*$H_{3A}$), 19.8 (isopropyl-*C*$H_{3B}$). **IR** $\nu_{max\ (}$neat)/cm$^{-1}$: 3271 (N-H), 2968, 2931 (C-H), 1691, 1665 (C=O), 1521, 1474, 1456 (C=C). X-ray crystal structure: See *Scheme 24*.

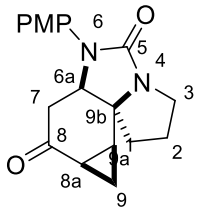
(6a*R**,8a*R**,9a*S**,9b*S**)-6-Isopropylhexahydro-1*H*-cyclopropa[5,6]benzo[1,2-*d*]pyrrolo[1,2-c]imidazole-5,8(6*H*, 8a*H*)-dione **106a**




To a mixture of trimethylsulfoxonium chloride (75.9 mg, 0.59 mmol, 1.1 eq.) and 60% sodium hydride in mineral oil (23.6 mg, 0.59 mmol, 1.1 eq.) at 0 °C, 2 mL of anhydrous THF was added and the mixture was left to stir for 15 min. The ice bath was removed and the chalky mixture was left to stir at room temperature for 30 min. 2 mL of anhydrous THF was then used to transfer the enone **83a** (126 mg, 0.54 mmol, 1.0 eq.) to the chalky mixture and was further left to stir for 2.5 h. The reaction mixture was extracted with DCM (5 × 15 mL) in 5 mL water, dried over $Na_2SO_4$ and concentrated *in vacuo*. Flash chromatography on silica gel eluting with 1% MeOH in DCM afforded the compound as a white solid **106a** (95 mg, 0.38 mmol, 71%). $\mathbf{R_f}$ = 0.36

(100% EtOAc). **$^1$H NMR** (300 MHz, MeOD): δ ppm 3.87 (1H, dd, *J* = 11.4, 6.3, 6a-H), 3.81 (1H, hept, *J* = 6.9, isopropyl C*H*), 3.68 (1H, ddd, 12.3, 8.8, 5.5, 3-$H_A$), 3.02 (1H, ddd,12.2, 8.8, 5.6, 3-$H_B$), 2.52 – 2.34 (2H, m, 7-$H_{A,B}$), 2.00 – 1.81 (4H, m, 9a-*H*, 1-$H_A$, 2-$H_{A,B}$), 1.70 – 1.61 (1H, m, 8a-*H*), 1.53 – 1.37 (2H, m, 1-$H_B$, 9-$H_A$), 1.27 (1H, td, *J* = 9.0, 5.4, 9-$H_B$), 1.11 (3H, d, 6.9, isopropyl C$H_{3A}$), 1.10 (3H, d, 6.6, isopropyl C$H_{3B}$). **$^{13}$C NMR** (75 MHz, MeOD): δ ppm 208.9 (8-*C*), 164.7 (5-*C*), 66.1 (9b-*C*), 60.6 (6a-*C*), 46.1 (isopropyl *C*H), 45.0 (3-C), 41.4 (7-C), 37.3 (1-C), 28.41 (8a-*C*), 28.37 (9a-*C*), 23.5 (2-C), 22.1 (isopropyl *C*$H_{3B}$), 19.7 (isopropyl *C*$H_{3A}$), 16.5 (9-*C*). **IR** $\nu_{max\ (}$neat)/cm$^{-1}$: 2972, 2938, 2892 (C-H), 1682 (C=O). **HRMS** (ESI): $C_{14}H_{21}N_2O_2$ [M + H$^+$]: calculated 249.1598, found 249.1598.

(6a*R**,8a*R**,9a*S**,9b*S**)-6-(4-Methoxyphenyl)hexahydro-1*H*-cyclopropa[5,6]benzo[1,2-*d*]pyrrolo[1,2-c]imidazole-5,8(6*H*, 8a*H*)-dione **106b**

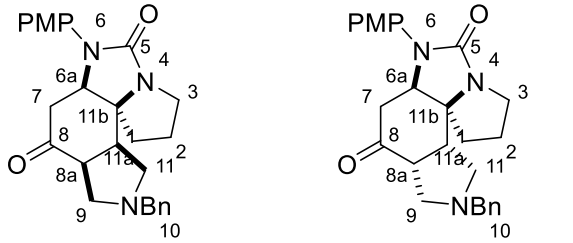



To a mixture of trimethylsulphoxonium chloride (240 mg, 1.87 mmol, 1.1 eq.) and 60% sodium hydride in mineral oil (74.9 mg, 1.87 mmol, 1.1 eq.) at 0 °C, 12.7 mL of anhydrous THF was added and the mixture was left to stir for 15 min. The ice bath was removed and the chalky mixture was left to stir at room temperature for 30 min. 3 mL of anhydrous DCM was then used to transfer the enone **83b** (508 mg, 0.54 mmol, 1.70 eq.) to the chalky mixture and was further left to stir overnight. The reaction mixture was extracted with DCM (5 × 20 mL) in 5 mL water, dried over sodium sulphate and concentrated *in vacuo*. Flash chromatography on silica gel eluting with 1% MeOH in DCM afforded the product **106b** (343 mg, 1.10 mmol, 64%). $\mathbf{R_f}$ = 0.56 (100% EtOAc). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.18 (2H, d, 9.5, Ar*H*), 6.80 (2H, d, 9.0, Ar*H*), 4.24 (1H, dd, *J* = 11.6, 5.9, 6a-H), 3.90 (1H, ddd, 12.0, 6.5, 3.5, 3-$H_A$), 3.71 (3H, s, ArOC$H_3$), 3.16 (1H, ddd,12.3, 9.3, 4.9, 3-$H_B$), 2.42 (1H, ddd, 14.1, 5.9, 1.3, 7-$H_A$), 2.28 (1H, dd, 14.0, 11.8, 7-$H_B$),

2.05 – 1.95 (3H, 1-$H_{A,B}$; 2-$H_A$), 1.96 – 1.91 (1H, m, 9a-*H*), 1.76 – 1.67 (1H, m, 2-$H_B$), 1.62 – 1.56 (1H, m, 8a-*H*), 1.45 (1H, q, *J* = 5.5, 9-$H_A$), 1.30 (1H, td, *J* = 8.9, 6.0, 9-$H_B$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 205.1 (8-*C*), 159.7 (5-*C*), 155.8 (*Ar*), 129.2 (*Ar*), 122.4 (*Ar*H), 113.5 (*Ar*H), 62.6 (9b-*C*), 61.0 (6a-*C*), 54.5 (ArO*C*$H_3$), 43.2 (3-C), 36.7 (7-C), 36.0 (1-C), 26.9 (8a-*C*), 26.6 (9a-*C*), 22.0 (2-C), 14.8 (9-*C*). **IR** $\nu_{max\ (neat)}/cm^{-1}$: 2960, 2837 (C-H), 1692 (C=O), 1611, 1512, 1460 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{18}H_{21}N_2O_3$ [M + $H^+$]: calculated 313.1547, found 313.1545.

(6a*R**,8a*S**,11a*R**,11b*S**)-10-Benzyl-6-(4-methoxyphenyl)octahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindole-5,8(6*H*,8a*H*)-dione **107**

(6a*R**,8a*R**,11a*S**,11b*S**)-10-Benzyl-6-(4-methoxyphenyl)octahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindole-5,8(6*H*,8a*H*)-dione **108**




**107**
**Major diastereomer**

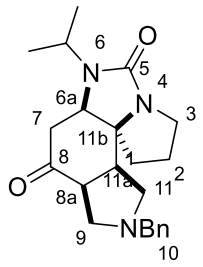



**108**
**Minor diastereomer**

To a mixture of lithium fluoride (22.1 mg, 0.85 mmol, 1.2 eq.) and the enone **83b** (211 mg, 0.71 mmol, 1.0 eq.) in dry MeCN (5.00 mL), *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (0.20 mL, 0.78 mmol, 1.1 eq.) was added and the mixture was left to stir overnight. The reaction mixture was evaporated *in vacuo* and taken up in 1 mL $H_2O$. 100 mL EtOAc was then added and the mixture was dried over sodium sulfate, and concentrated *in vacuo*. Flash chromatography on silica gel eluting with 2% MeOH in DCM afforded the two diastereomeric pyrrolidines **107** [**major product**, 131 mg, 0.30 mmol, 43%, $\mathbf{R_f}$ = 0.38 (4% MeOH in DCM)] and **108** [**minor product**, 72 mg, 0.17 mmol, 25%, $\mathbf{R_f}$ = 0.35 (4% MeOH in DCM)]. **$^1$H NMR** (**Major diastereomer**, 500 MHz, $CDCl_3$): δ ppm 7.26 - 7.16 (5H, m, Ar*H*), 7.14 (2H, d, *J* = 9.0, Ar*H*), 6.82 (2H, d, *J* = 9.0, Ar*H*), 4.50 (1H, br.d, *J* = 6.0, 6a-H), 3.81 (1H, ddd, *J* = 12.3, 9.2, 5.3, 3-$H_A$), 3.72 (3H, s, ArOC$H_3$),

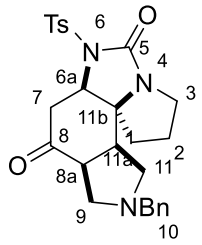
3.68 (1H, d, *J* = 13.0, ArC$H_{2A}$), 3.48 (1H, d, *J* = 13.0, ArC$H_{2B}$), 3.11 (1H, dd, *J* = 14.5, 6.5, 7-$H_A$), 3.00 (1H, ddd, *J* = 12.2, 8.7, 5.2, 3-$H_B$), 2.90 (1H, dd, *J* = 10.0, 1.5, 9-$H_A$), 2.84 – 2.81 (1H, m, 11-$H_A$), 2.81 – 2.77 (2H, m, 8a-*H*, 11a-*H*), 2.75 (1H, dd, 9.5, 6.0, 9-$H_B$), 2.65 (1H, t, 9.0, 11-$H_B$), 2.45 (1H, br.d, 14.5, 7-$H_B$), 1.97 – 1.62 (4H, m, 1-$H_{A,B}$; 2-$H_{A,B}$). **$^{13}$C NMR** (**Major diastereomer**, 125 MHz, $CDCl_3$): δ ppm 211.1 (8-*C*), 160.9 (5-*C*), 157.3 (*Ar*), 138.6 (*Ar*), 130.0 (*Ar*), 128.6 (*Ar*H), 128.6 (*Ar*H), 127.4 (*Ar*H), 125.4 (*Ar*H), 114.7 (*Ar*H), 66.2 (11b-*C*), 60.6 (6a-*C*), 59.8 (Ar*C*$H_2$), 59.1 (9-*C*), 55.7 (ArO*C*$H_3$), 54.1 (11-*C*), 49.0 (11a-*C*), 44.4 (3-*C*), 43.4 (8a-*C*), 41.3 (7-*C*), 35.1 (1-*C*), 23.6 (2-*C*). **IR** $\nu_{max\ (}$neat)/$cm^{-1}$: 2961, 2834, 2800 (C-H), 1697 (C=O), 1610, 1584, 1511 (C=C), 1245 (C-O). **HRMS** (ESI): $C_{26}H_{30}N_3O_3$ [M + $H^+$]: calculated 432.2282, found 432.2289. **$^1$H NMR** (**Minor diastereomer**, 500 MHz, $CDCl_3$): δ ppm 7.29 - 7.21 (5H, m, Ar*H*), 6.96 (2H, d, *J* = 9.0, Ar*H*), 6.81 (2H, d, *J* = 9.0, Ar*H*), 4.29 (1H, dd, *J* = 3.9, 2.2, 6a-*H*), 3.79 (1H, ddd, *J* = 11.5, 6.0, 2.0, 3-$H_A$), 3.71 (3H, s, ArOC$H_3$), 3.68 (1H, d, *J* = 13.0, ArC$H_{2A}$), 3.62 (1H, d, *J* = 13.0, ArC$H_{2B}$), 3.18 (1H, dd, *J* = 9.8, 7.2, 9-$H_A$), 3.10 (1H, ddd, *J* = 12.9, 9.9, 7.1, 8a-*H*), 3.03 (1H, dt, *J* = 11.7, 7.0, 3-$H_B$), 2.93 (1H, dd, *J* = 8.0, 5.5, 11-$H_A$), 2.64 – 2.49 (3H, m, 9-$H_B$, 7-$H_{A,B}$), 2.49 – 2.43 (1H, m, 11a-*H*), 2.38 (1H, dd, 10.3, 7.9, 11-$H_B$), 2.10 – 1.84 (4H, m, 1-$H_{A,B}$; 2-$H_{A,B}$). **$^{13}$C NMR** (**Minor diastereomer**, 125 MHz, $CDCl_3$): δ ppm 206.0 (8-*C*), 161.0 (5-*C*), 156.6 (*Ar*), 137.8 (*Ar*), 128.5 (*Ar*), 127.6 (*Ar*H), 127.4 (*Ar*H), 126.1 (*Ar*H), 124.7 (*Ar*H), 113.6 (*Ar*H), 64.2 (11b-*C*), 63.1 (6a-*C*), 59.7 (Ar*C*$H_2$), 54.5 (ArO*C*$H_3$), 52.4 (11-*C*), 49.0 (9-*C*), 48.1 (8a-*C*), 48.1 (11a-*C*), 46.4 (3-*C*), 37.8 (7-*C*), 37.7 (1-*C*), 24.8 (2-*C*). **IR** $\nu_{max\ (}$neat)/$cm^{-1}$: 2960, 2928, 2836 (C-H), 1697 (C=O), 1610, 1583, 1511 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{26}H_{30}N_3O_3$ [M + $H^+$]: calculated 432.2282, found 432.2292.

(6a*R**,8a*S**,11a*R**,11b*S**)-10-Benzyl-6-isopropyloctahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindole-5,8(6*H*,8a*H*)-dione **109**



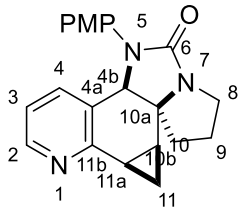

To a mixture of lithium fluoride (23.4 mg, 0.90 mmol, 1.2 eq.) and the enone **83a** (175 mg, 0.75 mmol, 1.0 eq.) in dry MeCN (1.60 mL), *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (0.22 mL, 0.83 mmol, 1.1 eq.) was added and the mixture was left to stir overnight. The reaction mixture was extracted with DCM (5 × 10 mL) in 10 mL of water, dried over sodium sulphate and evaporated *in vacuo*. Flash chromatography on silica gel eluting with 50 – 100% EtOAc in hexane afforded the product **109** (106 mg, 0.29 mmol, 39%). **$R_f$ =** 0.58 (10% MeOH in DCM).**$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.27 - 7.11 (5H, m, Ar*H*), 3.87 (1H, hept, 7.0, isopropyl C*H*), 3.83 (1H, dd, *J* = 6.0, 2.5, 6a-H), 3.74 – 3.68 (1H, m, 3-$H_A$), 3.64 (1H, d, *J* = 12.5, ArC$H_{2A}$), 3.59 (1H, d, *J* = 13.0, ArC$H_{2B}$), 3.15 (1H, dd, *J* = 10.0, 7.2, 9-$H_A$), 2.98 – 2.92 (1H, m, 8a-*H*), 2.91 – 2.85 (2H, m, 3-$H_B$, 11-$H_A$), 2.63 (2H, dd, *J* = 5.5, 2.5, 7-$H_{A,B}$), 2.54 (1H, t, *J* = 10.2, 9-$H_B$), 2.41 (1H, ddd, *J* = 13.0, 8.0, 3.0, 11a-*H*), 2.30 (1H, dd, *J* = 10.3, 8.0, 11-$H_B$), 1.98 – 1.89 (1H, m, 1-$H_A$), 1.78 – 1.69 (3H, m, 1-$H_B$; 2-$H_{A,B}$), 1.14 (3H, d, *J* = 7.0, isopropyl C$H_{3A}$), 1.09 (3H, d, *J* = 7.0, isopropyl C$H_{3B}$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 206.7 (8-*C*), 162.5 (5-*C*), 137.7 (*Ar*), 127.6 (*Ar*H), 127.4 (*Ar*H), 126.1 (*Ar*H), 64.0 (11b-*C*), 60.8 (6a-*C*), 59.7 (Ar*C*$H_2$), 52.5 (11-*C*), 49.1 (9-*C*), 48.2 (8a-*C*), 48.0 (11a-*C*), 46.6 (3-*C*), 43.6 (isopropyl *C*H), 39.9 (7-*C*), 37.5 (1-*C*), 24.6 (2-*C*), 20.2 (isopropyl *C*$H_{3B}$), 18.1 (isopropyl *C*$H_{3A}$). **IR** $\nu_{max\ (neat)}$/$cm^{-1}$: 2967, 2929, 2799 (C-H), 1685 (C=O), 1453, 1413, 1379 (C=C). **HRMS** (ESI): $C_{22}H_{30}N_3O_2$ [M + $H^+$]: calculated 368.2333, found 368.2330.

(6a*R**,8a*S**,11a*R**,11b*S**)-10-Benzyl-6-tosyloctahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindole-5,8(6*H*,8a*H*)-dione **110**



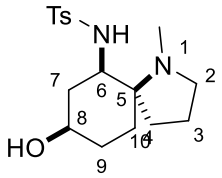

To a mixture of lithium fluoride (5.71 mg, 0.22 mmol, 1.2 eq.) and the enone **83c** (64.7 mg, 0.19 mmol, 1.0 eq.) in dry MeCN (5.00 mL), *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (0.05 mL, 0.78 mmol, 1.1 eq.) was added and the mixture was left to stir overnight. The reaction mixture was evaporated *in vacuo* and taken up in 1 mL $H_2O$. 100 mL EtOAc was then added and the mixture was dried over sodium sulfate, and concentrated *in vacuo*. Flash chromatography on silica gel eluting with 0.5 - 2% MeOH in DCM afforded the pyrrolidine **110** (22 mg, 0.05 mmol, 25%). $\mathbf{R_f}$ = 0.36 (3% MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.78 (2H, d, *J* = 8.4, Ar*H*), 7.25 - 7.14 (7H, m, Ar*H*), 4.43 (1H, dd, *J* = 4.2, 2.2, 6a-H), 3.64 (1H, ddd, *J* = 11.5, 8.0, 5.6, 3-$H_A$), 3.59 (1H, d, *J* = 13.0, ArC$H_{2A}$), 3.54 (1H, d, *J* = 13.0, ArC$H_{2B}$), 3.50 (1H, dd, *J* = 19.0, 2.0, 7-$H_A$), 3.14 (1H, dd, *J* = 10.1, 6.8, 9-$H_A$), 2.96 (1H, ddd, *J* = 11.5, 6.0, 4.0, 3-$H_B$), 2.86 (1H, dd, *J* = 8.0, 5.6, 11-$H_A$), 2.77 – 2.73 (1H, m, 8a-*H*), 2.73 – 2.69 (1H, m, 7-$H_B$), 2.45 (1H, t, 10.2, 9-$H_B$), 2.43 – 2.37 (1H, m, 11a-*H*), 2.35 (3H, s, ArC$H_3$), 2.13 (1H, dd, *J* = 10.3, 8.1, 11-$H_B$), 2.05 – 1.71 (4H, m, 1-$H_{A,B}$; 2-$H_{A,B}$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 205.3 (8-*C*), 156.5 (5-*C*), 144.2 (*Ar*), 137.5 (*Ar*), 134.1 (*Ar*), 128.6 (*Ar*H), 127.5 (*Ar*H), 127.4 (*Ar*H), 127.4 (*Ar*H) 126.2 (*Ar*H), 65.2 (11b-*C*), 62.5 (6a-*C*), 59.5 (Ar*C*$H_2$), 52.8 (11-*C*), 48.7 (9-*C*), 48.1 (8a-*C*), 47.9 (11a-*C*), 46.1 (3-*C*), 40.2 (7-*C*), 37.3 (1-*C*), 24.1 (2-*C*), 20.7 (Ar*C*$H_3$). **IR** $\nu_{max\ (neat)}$/cm$^{-1}$: 3029, 2922, 2801 (C-H), 1720 (C=O), 1596, 1513, 1458 (C=C). **HRMS** (ESI): $C_{26}H_{30}N_3O_4S$ [M + H$^+$]: calculated 480.1952, found 480.1964.

(4b*R**, 10a*S**, 10b*S**, 11a*R**)-5-(4-Methoxyphenyl)-4b,9,10,10b,11,11a-hexahydro-8*H*-cyclopropa[*h*]pyrrolo[1',2':1,5]imidazo [4,5-*f*]quinolin-6(5*H*)-one **115**



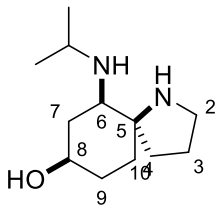

Anhydrous THF (1 mL) was added to a dry mixture of trimethylsulphoxonium chloride (11.6 mg, 0.09 mmol, 1.1 eq.) and 60% NaH in mineral oil (3.6 mg, 0.09 mmol, 1.1 eq.) and the mixture was stirred at 0 °C for 15 min after which it was allowed to warm up to room temperature for 30 min. 4 mL of anhydrous THF was then used to transfer the enone **83b** (24 mg, 0.08 mmol, 1.0 eq.) to the reaction mixture and it was stirred for 19 h at room temperature. The reaction mixture was then extracted with DCM (5 × 20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. A mixture of the crude, $NaAuCl_4.2H_2O$ (3.8 mg, 12 mol%) and propargylamine (10.2 µL, 0.16 mmol, 2.0) in HPLC grade EtOH was refluxed for 16 h. The reaction mixture was extracted with DCM (5 × 20 mL), dried over $Na_2SO_4$, and evaporated *in vacuo*. Flash chromatography eluting with 1 – 6 % MeOH in DCM afforded the product as a colourless oil (7 mg, 0.02 mmol, 25% yield over two steps). **$^1$H NMR** (600 MHz, $CDCl_3$) δ ppm 8.47 (1H, d, *J* = 4.8, Ar*H*), 7.29 (1H, t, *J* = 6.6, Ar*H*), 7.22 – 7.20 (1H, m, Ar*H*), 6.85 -6.80 (4H, m, Ar*H*), 4.73 (1H, s, 4b-*H*), 3.77 – 3.72 (4H, m, 8-$H_A$, *Ar*OC$H_3$), 3.46 – 3.39 (2H, m, 8-$H_B$, 11a-*H*), 2.34 – 2.23 (1H, m, 10-$H_A$), 2.22 - 2.09 (2H, m, 9-$H_{A,B}$), 2.06 (1H, q, *J* = 7.2, 10-$H_B$), 1.83 (1H, dt, *J* = 12.7, 7.9, 10b-*H*), 1.71 (1H, td, *J* = 8.4, 5.4, 11-$H_A$), 1.65 (1H, dd, *J* = 7.8, 5.4, 11-$H_B$). **$^{13}$C NMR** (150 MHz, $CDCl_3$) δ ppm 159.7 (6-*C*), 158.4 (*Ar*), 155.8 (*Ar*), 145.6 (*Ar*H), 139.2 (*Ar*H), 129.0 (*Ar*), 128.5 (*Ar*H), 127.4 (*Ar*), 120.9 (*Ar*H), 114.1 (*Ar*H), 67.0 (4b-*C*), 60.6 (10a-*C*), 54.5 (ArO*C*H$_3$), 43.8 (8-*C*), 37.7 (10-*C*), 26.7 (9-*C*), 26.1 (11a-*C*), 18.7 (10b-*C*), 16.4 (11-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2959, 2931 (C-H), 1700 (C=O), 1513, 1457, 1381 (C=C), 1248 (C-O). **HRMS** (ESI): $C_{21}H_{22}N_3O_2$ [M + H$^+$]: calculated 348.1707, found 348.1706.

*N*-(5*S**,6*R**,8*R**)-8-Hydroxy-1-methyl-1-azaspiro[4.5]decan-6-yl)-4-methylbenzenesulfonamide **122**




To a solution of the ketone **101c** (54 mg, 0.16 mmol, 1.0 eq.) in 4 mL of anhydrous THF, 1 M $LiAlH_4$ in THF (1.55 mL, 1.55 mmol, 10.0 eq.) was added and the mixture was refluxed for 6.5 h. The reaction mixture was quenched with 0.1 mL 10% KOH and and 0.1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$, and evaporated *in vacuo.* Flash chromatography eluting with 5% MeOH in DCM followed by 5% of a saturated solution of $NH_3$/MeOH in DCM afforded the product **122** as a pale yellow solid (28 mg, 0.08 mmol, 54% yield); **$R_f$ =** 0.42 (6% of saturated $NH_3$/MeOH in DCM). **$^1$H NMR** (300 MHz, $CDCl_3$): δ ppm 7.69 (2H, d, *J* = 8.1, Ar*H*), 7.22 (2H, d, *J* = 8.2, Ar*H*), 3.78 (1H, tt, *J* = 6.0, 3.6, 8-*H*), 2.91 (1H, dd, *J* = 6.6, 4.4, 6-*H*), 2.63 - 2.53 (1H, m, 2-$H_A$), 2.46 – 2.37 (1H, m, 2-$H_B$), 2.35 (3H, s, ArC$H_3$), 2.31 (3H, s, 1-C$H_3$), 1.99 (1H, ddd, *J* = 14.1, 9.3, 4.2, 9-$H_A$), 1.83 (1H, dt, *J* = 13.4, 6.6, 7-$H_A$), 1.73 – 1.62 (2H, m, 7-$H_B$, 10-$H_A$), 1.60 – 1.47 (3H, m, 9-$H_B$, 4-$H_A$, 3-$H_A$), 1.47 – 1.30 (2H, m, 3-$H_B$, 4-$H_B$), 1.16 (1H, ddd, 13.8, 7.2, 4.5, 10-$H_B$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): δ ppm 143.1 (*Ar*), 137.5 (*Ar*), 129.5 (*Ar*H), 127.2 (*Ar*H), 67.0 (8-*C*), 63.5 (5-*C*), 56.0 (6-*C*), 55.4 (2-*C*), 38.4 (1-*C*), 36.6 (4-*C*), 35.6 (7-*C*), 31.2 (9-*C*), 25.6 (10-*C*), 22.6 (3-*C*), 21.5 (Ar*C*$H_3$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3245 (O-H, N-H), 2929, 2871, 2787 (C-H), 1599, 1447, 1382 (C=C). **HRMS** (ESI): $C_{17}H_{27}N_2O_3S$ [M + $H^+$]: calculated 339.1737, found 339.1735.

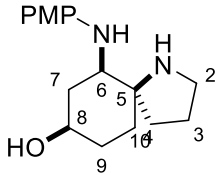
(5*S**,6*R**,8*R**)-6-(Isopropylamino)-1-methyl-1-azaspiro[4.5]decan-8-ol **123a**




To a solution of the ketone **101a** (59 mg, 0.25 mmol, 1.0 eq.) in 6.5 mL of anhydrous THF, 4 M $LiAlH_4$ in ether (0.63 mL, 2.52 mmol, 10.0 eq.) was added and refluxed for 12 h. The reaction

mixture was quenched with 0.1 mL 10% KOH and and 0.1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$, filtered and evaporated *in vacuo*. To a mixture of the crude and hydroxylamine hydrochloride (88 mg, 1.26 mmol, 5.0 eq.) was added 7 mL of 0.01% HCl and heated at 60 °C for 1 h. 29.3 mL of 0.5 M HCl was then added to the reaction mixture and washed with $CHCl_3$ (2 × 25 mL). The aqueous layer was carefully basified with copious amounts of solid $Na_2CO_3$, extracted with $CHCl_3$ (7 × 25 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography eluting with 3% of a saturated solution of $NH_3$/MeOH in DCM afforded a brown solid **123a** (34 mg, 0.16 mmol, 64% yield); $\mathbf{R_f}$ = 0.33 (6% $NH_3$/MeOH in DCM). **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 3.87 (1H, quint, *J* = 2.4, 8-*H*), 2.91 (1H, ddd, *J* = 11.8, 7.6, 4.2, 2-$H_A$), 2.83 (1H, hept, *J* = 6.4, isopropyl C*H*), 2.61 (1H, dt, *J* = 11.6, 4.0, 2-$H_B$), 2.51 (1H, t, *J* = 3.2, 6-*H*), 2.04 (1H, td, *J* = 13.4, 4.2, 10-$H_A$), 2.00 - 1.93 (1H, m, 7-$H_A$), 1.83 – 1.45 (7H, m, 9-$H_{A,B}$; 10-$H_B$; 3-$H_{A,B}$; 4-$H_{A,B}$), 1.31 (1H, dt, *J* = 14.4, 2.8, 7-$H_B$), 1.03 (3H, d, *J* = 6.4,isopropyl C$H_{3A}$), 0.95 (3H, d, *J* = 6.4, isopropyl C$H_{3B}$). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ ppm 66.9 (8-*C*), 64.9 (5-*C*), 56.0 (6-*C*), 45.5 (2-*C*), 45.4 (isopropyl *C*H), 35.2 (4-*C*), 31.8 (9-*C*), 29.9 (7-*C*), 28.1 (10-*C*), 27.2 (3-*C*), 24.5 (isopropyl *C*$H_{3A}$), 21.1 (isopropyl *C*$H_{3B}$). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3256 (O-H, N-H), 2958, 2928, 2865 (C-H), 1135 (C-O). **HRMS** (ESI): $C_{12}H_{25}N_2O$ [M + H$^+$]: calculated 213.1961, found 213.1960.

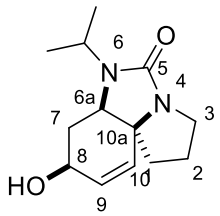
(5*S**,6*R**,8*R**)-6-(4-Methoxyphenyl)amino-1-azaspiro[4.5]decan-8-ol **123b**




To a solution of the ketone **101b** (798 mg, 2.66 mmol, 1.0 eq.) in 33 mL of anhydrous THF, 2 M $LiAlH_4$ in THF (7.98 mL, 16.0 mmol, 6.0 eq.) was added and refluxed for 11.5 h. The reaction mixture was quenched with 2 mL 10% KOH and and 2 mL $H_2O$, diluted with 300 mL EtOAc, dried over $Na_2SO_4$, filtered and evaporated *in vacuo*. To a mixture of the crude and hydroxylamine hydrochloride (924 mg, 13.3 mmol, 5.0 eq.), 74 mL of 0.01% HCl was added and heated at 60 °C overnight. The reaction mixture was washed with $CHCl_3$ (2 × 50 mL). The aqueous layer was carefully basified with copious amounts of solid $Na_2CO_3$, extracted with $CHCl_3$ (7 × 50 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography eluting with 8 – 10% MeOH in

DCM followed by 6 - 10% of a saturated solution of $NH_3$/MeOH in DCM afforded a pale yellow oil **123b** (620 mg, 2.24 mmol, 84% yield); $\mathbf{R_f}$ = 0.37 (6% $NH_3$/MeOH in DCM). **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 6.70 (2H, d, 8.8, Ar*H*), 6.58 (2H, d, 8.8, Ar*H*), 3.75 – 3.68 (1H, m, 8-*H*), 3.67 (3H, s, ArOC*H*$_3$), 3.00 (1H, dd, 8.3, 3.5, 6-*H*), 2.93 (1H, dt, *J* = 10.4, 6.7, 2-*H*$_A$), 2.81 (1H, dt, *J* = 10.4, 6.5, 2-*H*$_B$), 1.95 – 1.79 (3H, m, 7-*H*$_A$, 9-*H*$_{A,B}$), 1.76 – 1.35 (6H, m, 3-*H*$_{A,B}$; 4-*H*$_{A,B}$; 7-*H*$_B$; 10-*H*$_A$), 1.27 (1H, ddd, *J* = 13.6, 9.6, 4.0, 10-*H*$_B$). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ ppm 151.5 (*Ar*), 141.0 (*Ar*), 115.1 (*Ar*H), 113.9 (*Ar*H), 67.0 (8-*C*), 62.4 (5-*C*), 55.8 (6-*C*), 54.8 (ArO*C*H$_3$), 45.2 (2-*C*), 34.5 (9-*C*), 34.5 (4-*C*), 31.2 (10-*C*), 30.6 (7-*C*), 25.1 (3-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3346 (O-H, N-H), 2931, 2862, 2832 (C-H), 1509, 1464, 1441 (C=C), 1232 (C-O). **HRMS** (ESI): $C_{16}H_{25}N_2O_2$ [M + H$^+$]: calculated 277.1911, found 277.1909.

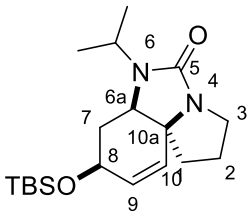
(6a*R**,8*S**,10*S**)-8-Hydroxy-6-isopropyl-2,3,6,6a,7,8-hexahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **124**




A mixture of enone **83a** (186 mg, 0.79 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (354 mg, 0.95 mmol, 1.2 eq.) in 4 mL of HPLC grade methanol was allowed to stir for 30 min at -78 °C after which $NaBH_4$ (35.9 mg, 0.95 mmol, 1.2 eq.) was added and the mixture was further stirred at the same temperature for 40 min. The reaction mixture was then allowed to warm up to room temperature for 1 h. It was extracted with EtOAc (5 × 20mL), dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel chromatography eluting with 70 – 90% EtOAc in hexane afforded the compound as a white solid (173 mg, 0.73 mmol, 92% yield); $\mathbf{R_f}$ = 0.42 (100% EtOAc). **$^1$H NMR** (300 MHz, MeOD): δ ppm 5.87 (1H, dt, *J* = 10.2, 1.3, 10-*H*), 5.67 (1H, dd, *J* = 10.2, 2.2, 9-*H*), 4.21 (1H, ddd, *J* = 10.8, 4.5, 2.4, 8-*H*), 3.96 (1H, hept, *J* = 6.9, isopropyl C*H*), 3.79 (1H, dd, *J* = 12.0, 5.1, 6a-*H*), 3.71 (1H, ddd, *J* = 12.3, 5.7, 3.0, 3-*H*$_A$), 3.04 (1H, ddd, *J* = 12.2, 9.2, 5.7, 3-*H*$_B$), 2.44 (1H, dtd, *J* = 11.2, 4.8, 1.4, 7-*H*$_A$), 2.04 – 1.79 (2H, m, 2-*H*$_{A,B}$), 1.69 (1H, ddd, *J* = 12.3, 7.8, 2.6, 1-*H*$_A$),

1.61 – 1.40 (2H, m, 1-$H_B$, 7-$H_B$), 1.28 (3H, d, *J* = 6.9, isopropyl C$H_{3A}$), 1.26 (3H, d, *J* = 6.6, isopropyl C$H_{3B}$). **$^{13}$C NMR** (75 MHz, MeOD): δ ppm 164.5 (5-*C*), 134.7 (10-*C*), 127.0 (9-*C*), 65.8 (10a-*C*), 65.5 (8-*C*), 56.0 (6-*C*), 46.1 (isopropyl *C*H), 45.3 (3-*C*), 39.8 (7-*C*), 36.3 (1-*C*), 23.6 (2-*C*), 22.4 (isopropyl *C*$H_{3A}$), 19.6 (isopropyl *C*$H_{3B}$). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3369 (O-H), 2971, 2937 (C-H), 1666 (C=O), 1416 (C=C), 1223 (C-O). **HRMS** (ESI): $C_{13}H_{21}N_2O_2$ [M + H$^+$]: calculated 237.1598, found 237.1598.

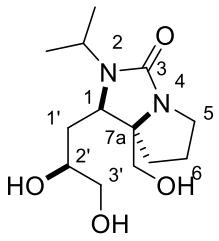
(6a*R**,8*S**,10a*S**)-8-((*tert*-Butyldimethylsilyl)oxy)-6-isopropyl-2,3,6,6a,7,8-hexahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **125**




A mixture of enone **83a** (57.0 mg, 0.24 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (108 mg, 0.29 mmol, 1.2 eq.) in 2 mL of HPLC grade methanol was allowed to stir for 30 min at -78 °C after which $NaBH_4$ (11.0 mg, 0.29 mmol, 1.2 eq.) was added and the mixture was further stirred at the same temperature for 40 min. The reaction mixture was then allowed to warm up to room temperature for 1 h. It was extracted with DCM (5 × 20mL), dried over $MgSO_4$ and evaporated *in vacuo*. To a solution of the crude in 2 mL of anhydrous DCM; 2,6-lutidine (0.06 mL, 0.48 mmol, 2.0 eq.) and TBSOTf (0.08 mL, 0.36 mmol, 1.5 eq.) were added. The mixture was allowed to stir at room temperature for 15 h. It was extracted with DCM (5 × 20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Flash chromatography with 70 – 90% EtOAc in hexane afforded the product as a white solid (82 mg, 0.23 mmol, 96% yield over two steps); $\mathbf{R_f}$ = 0.82 (100% EtOAc). **$^1$H NMR** (300 MHz, MeOD): δ ppm 5.67 (1H, dt, *J* = 10.2, 1.2, 10-*H*), 5.51 (1H, dd, *J* = 10.2, 2.1, 9-*H*), 4.27 – 4.17 (1H, m, 8-*H*), 3.83 (1H, hept, *J* = 6.9, isopropyl C*H*), 3.68 (1H, dd, *J* = 12.1, 4.9, 6a-*H*), 3.58 (1H, ddd, *J* = 12.2, 9.0, 5.8, 3-$H_A$), 2.91 (1H, ddd, *J* = 12.2, 9.2, 5.7, 3-$H_B$), 2.21 (1H, dtd, *J* = 11.3, 4.8, 1.4, 7-$H_A$), 1.91 – 1.66 (2H, m, 2-$H_{A,B}$), 1.55 (1H, ddd, *J* = 10.6, 7.9, 2.6, 1-$H_A$), 1.47 – 1.29 (2H, m, 1-$H_B$, 7-$H_B$), 1.14 (3H, d, *J* = 6.9, isopropyl C$H_{3A}$), 1.12 (3H, d, *J* = 6.6, isopropyl C$H_{3B}$),

0.79 (9H, s, tert-butyl C$H_3$), 0.00 (3H, s, SiC$H_{3A}$), -0.01 (3H, s, SiC$H_{3B}$). **$^{13}$C NMR** (300MHz, MeOD): δ ppm 164.6 (5-*C*), 135.3 (10-*C*), 126.7 (9-*C*), 67.0 (8-*C*), 65.7 (10a-*C*), 55.8 (6a-*C*), 46.1 (isopropyl *C*H), 45.3 (3-*C*), 40.6 (7-*C*), 36.2 (1-*C*), 26.2 (tert-butyl *C*$H_3$), 23.6 (2-*C*), 22.3 (isopropyl *C*$H_{3A}$), 19.7 (isopropyl *C*$H_{3B}$), 18.9 (tert-butyl *C*), 4.6 (Si*C*$H_{3A}$), 4.5 (Si*C*$H_{3B}$). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2956, 2930 (C-H), 1678 (C=O), 1508 (C=C), 1062 (C-O). **HRMS** (ESI): $C_{19}H_{34}N_2NaO_2Si$ [M + $Na^+$]: calculated 373.2282, found 373.2281.

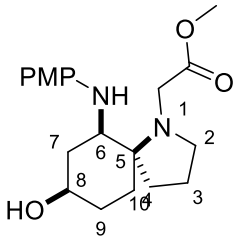
(1*R**, 7a*R**)-1-(2,3-Dihydoxypropyl)-7a-(hydroxymethyl)-2-isopropylhexahydro-3*H*-pyrrolo[1,2-*c*]imidazole-3-one **129**




Through a solution of the alkene **125** (40 mg, 0.11 mmol, 1.0 eq.) in 1 mL DCM, ozonized oxygen gas was passed at -78 °C until the solution turned blue in colour. Oxygen gas was then passed through the solution to get rid of the residual ozone (indicated by the disappearance of the blue colour). 8 mL of methanol was added followed by a careful addition of $NaBH_4$ (excess) at -78 °C, and left to stand for 30 min at the same temperature. The reaction mixture was then allowed to warm up to room temperature overnight and evaporated *in vacuo*. It was extracted with EtOAc (5×20 mL) in 5 mL water, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude in 4 mL THF, 0.10 mL of 1 M TBAF (in THF) was added and the mixture was allowed to stir overnight. The reaction mixture was evaporated *in vacuo* and taken up in 2 mL $H_2O$. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 4 – 10% MeOH in DCM afforded the product **129** with 4% TBAF contamination (12.0 mg, 0.04 mmol, 39%); $\mathbf{R_f}$ = 0.23 (10% MeOH in DCM). **$^1$H NMR** (500 MHz, MeOD): δ ppm 3.84 (1H, qd, *J* = 6.6, 3.0, 2'-*H*), 3.80 – 3.68 (3H, m, 1-*H,* 5-$H_A$, isopropyl C*H*), 3.63 – 3.54 (3H, m, 3'-$H_A$, 7a-C$H_{2A,B}$), 3.42 (1H, dd, *J* = 11.0, 7.0, 3'-$H_B$), 2.97 – 2.92 (4H, m, 5-$H_B$, 2'-CHO*H*, 3'- $CH_2$O*H*, 7a-

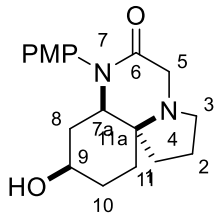
$CH_2OH$), 2.06 (1H, ddd, *J* = 14.5, 10.0, 2.5, 1'-$H_A$), 1.99 – 1.92 (1H, m, 7-$H_A$), 1.84 – 1.70 (3H, m, 1'-$H_B$, 6-$H_{A,B}$), 1.47 (1H, dt, *J* = 12.7, 8.8, 7-$H_B$), 1.24 (3H, d, *J* = 6.9, isopropyl C$H_{3A}$), 1.19 (3H, d, *J* = 6.8, isopropyl C$H_{3B}$). **$^{13}$C NMR** (125 MHz, MeOD): δ ppm 161.6 (3-*C*), 68.8 (7a-*C*), 68.3 (2'-*C*), 65.9 (3'-*C*), 60.8 (7a-$CH_2$OH), 58.2 (1-*C*), 45.1 (5-*C*), 44.5 (isopropyl *C*H), 32.7 (7-*C*), 31.7 (1'-*C*), 23.1 (6-*C*), 19.9 (isopropyl $CH_{3B}$), 18.6 (isopropyl $CH_{3A}$). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3385 (O-H), 2962, 2927, 2876 (C-H), 1670 (C=O), 1053 (C-O). **HRMS** (ESI): $C_{13}H_{25}N_2O_4$ [M + H$^+$]: calculated 273.1809, found 273.1801.

Methyl 2-((5*S**, 6*R**, 8*R**)-8-Hydroxy-6-((4-methoxyphenyl)amino)-1-azaspiro[4.5]decan-1-yl)acetate **137**



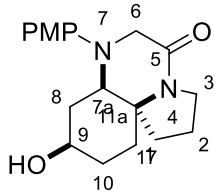

A mixture of the diamine **123b** (33 mg, 0.12 mmol, 1.0 eq), methyl bromoacetate (13.6 µL, 0.14 mmol, 1.2 eq.) and $KHCO_3$ (16 mg, 0.16 mmol, 1.3 eq.) in 2 mL of anhydrous THF was refluxed for 6 h, and evaporated *in vacuo*. Flash chromatography eluting with 1 – 2% MeOH in DCM afforded the product **137** as a brown oil (25 mg, 0.07 mmol, 60% yield); **$R_f$ =** 0.54 (6% MeOH in DCM). **$^1$H NMR** (400 MHz, $CDCl_3$) δ ppm 6.77 (2H, d, *J* = 9.2, Ar*H*), 6.72 (2H, d, *J* = 8.8, Ar*H*), 3.92 (1H, quint, *J* = 3.2, 8-*H*), 3.86 (1H, d, *J* = 16.8, pyrrolidine NC$H_{2A}$), 3.68 (3H, s, COOC$H_3$), 3.61 (3H, s, ArOC$H_3$), 3.21 (1H, d, *J* = 16.9, pyrrolidine NC$H_{2B}$), 3.11 (1H, ddd, *J* = 10.6, 7.7, 5.4, 2-$H_A$), 2.99 (1H, t, *J* = 3.3, 6-*H*), 2.64 (1H, dt, *J* = 10.5, 7.4, 2-$H_B$), 2.19 -2.07 (2H, m, 7-$H_{A,B}$), 1.92 – 1.80 (2H, m, 9-$H_{A,B}$), 1.79 – 1.70 (2H, m, 3-$H_{A,B}$), 1.64 – 1.50 (4H, m, NH, 10-$H_A$, 4-$H_{A,B}$), 1.26 (1H, dt, 12.8, 3.7, 10-$H_B$). **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ ppm 173.4 (ester *C*=O), 153.5 (*Ar*), 142.3 (*Ar*), 118.3 (*Ar*H), 114.6 (*Ar*H), 66.8 (8-*C*), 66.3 (5-*C*), 58.4 (6-*C*), 55.8 (COO*C*H$_3$), 53.9 (2-*C*), 52.8 (pyrrolidine N*C*H$_2$), 51.8 (ArO*C*H$_3$) 34.9 (4-*C*), 32.3 (7-*C*), 31.5 (9-*C*), 24.1 (10-*C*), 22.9 (3-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3368 (O-H, N-H), 2933 (C-H), 1734 (C=O), 1509, 1439, 1365 (C=C), 1232 (C-O). **HRMS** (ESI): $C_{19}H_{29}N_2O_4$ [M + H$^+$]: calculated 349.2122, found 349.2120.

(7a*R**,9*R**,11a*S**)-9-Hydroxy-7-(4-methoxyphenyl)octahydro-1H-pyrrolo[1,2-*d*]quinoxalin-6(5*H*)-one **138**



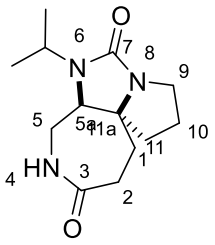

A solution of the diamine **137** (18 mg, 0.05 mmol, 1.0 eq.) and NaOMe (7.1 mg, 0.13 mmol, 1.1 eq.) in 2 mL of anhydrous MeOH was refluxed for 6 h. The reaction mixture was evaporated *in vacuo*. Flash chromatography eluting with 2 – 10% MeOH in DCM afforded the product **138** as a brown oil (14 mg, 0.04 mmol, 88%); $\mathbf{R_f}$ **=** 0.26 (6% MeOH in DCM) When the reaction was telescoped from the diamine **123b** without further purification of the intermediate **137,** the piperazinone **138** was isolated in 90% yield. **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 7.11 (2H, d, *J* = 9.2, Ar*H*), 6.85 (2H, d, *J* = 8.8, Ar*H*), 3.81 (1H, d, *J* = 17.6, 5-$H_A$), 3.73 (3H, s, ArOC$H_3$), 3.66 – 3.55 (2H, m, 9-*H*, 7a-*H*), 3.31 (1H, d, *J* = 17.6, 5-$H_B$), 3.05 (1H, ddd, *J* = 10.4, 6.4, 3.6, 3-$H_A$), 2.86 (1H, dt, 10.5, 6.8, 3-$H_B$), 2.05 (1H, dt, *J* = 13.4, 4.6, 8-$H_A$), 2.02 – 1.96 (1H, m, 10-$H_A$), 1.95 -1.89 (1H, m, 8-$H_B$), 1.85 – 1.82 (1H, m, 10-$H_B$), 1.82 – 1.77 (2H, m, 2-$H_{A,B}$), 1.77 – 1.60 (4H, m, 1-$H_A$; 11-$H_{A,B}$; 9-CHO*H*), 1.19 – 1.11 (1H, m, 1-$H_B$). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ ppm 169.7 (6-*C*), 158.3 (*Ar*), 133.9 (*Ar*), 127.9 (*Ar*H), 114.5 (*Ar*H), 67.6 (9-*C*), 62.2 (11a-*C*), 61.9 (7a-*C*), 55.6 (3-*C*), 55.5 (ArO*C*$H_3$), 54.5 (5-*C*), 36.9 (8-*C*), 36.5 (10-*C*), 30.7 (11-*C*), 30.2 (1-*C*), 23.3 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3378 (O-H), 2940, 2870 (C-H), 1642 (C=O), 1509, 1431, 1365 (C=C), 1242 (C-O). **HRMS** (ESI): $C_{18}H_{25}N_2O_3$ [M + H$^+$]: calculated 317.1860, found 317.1855.

(7a*R**, 9*R**, 11a*S**)-9-Hydroxy-7-(4-methoxyphenyl)octahydro-1*H*-pyrrolo[1,2-*d*]quinoxalin-5(6*H*)-one




To a solution of the diamine **123b** (100 mg, 0.36 mmol, 1.0 eq.) in 14 mL THF was added chloroacetyl chloride (0.03 mL, 0.40 mmol, 1.1 eq.) and DIPEA (0.15 mL, 0.87 mmol, 2.4 eq.) at -78 °C. The reaction mixture was left to warm up to room temperature overnight. 2 M KOH (2 mL) was then added and also left to stir at room temperature overnight. The reaction mixture was extracted with EtOAc (5 × 20 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography eluting with 1 – 4% MeOH in DCM afforded the product **139** as a colourless oil (70 mg, 0.22 mmol, 61% yield); **$R_f$ =** 0.38 (5% MeOH in DCM). **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 7.01 (2H, d, *J* = 8.8, Ar*H*), 6.83 (2H, d, *J* = 8.8, Ar*H*), 4.34 (1H, s, 9-CHO*H*), 3.96 (1H, d, *J* = 17.6, 6-$H_A$), 3.79 – 3.66 (5H, m, 9-*H*, 3-$H_A$, ArOC$H_3$), 3.58 – 3.47 (1H, m, 3-$H_B$), 3.32 (1H, d, *J* = 17.6, 6-$H_B$), 3.24 (1H, t, *J* = 3.2, 7a-*H*), 2.27 – 2.06 (3H, m, 1-$H_A$, 8-$H_A$, 11-$H_A$), 2.02 – 1.92 (2H, m, 2-$H_{A,B}$), 1.89 – 1.80 (1H, m, 10-$H_A$), 1.59 – 1.46 (3H, m, 1-$H_B$, 10-$H_B$, 11-$H_B$), 1.41 (1H, dt, *J* = 15.0, 3.0, 8-$H_B$). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ ppm 164.0 (5-*C*), 156.1 (*Ar*), 142.0 (*Ar*), 124.2 (*Ar*H), 114.1 (*Ar*H), 64.6 (9-*C*), 62.7 (11a-*C*), 60.0 (7a-*C*), 58.4 (6-*C*), 54.4 (ArO*C*$H_3$), 43.2 (3-*C*), 33.6 (11-*C*), 29.9 (10-*C*), 29.5 (8-*C*), 24.3 (1-*C*), 19.8 (2-*C*). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3434 (O-H), 2935, (C-H), 1642 (C=O), 1509, 1463, 1427 (C=C), 1242 (C-O). **HRMS** (ESI): $C_{18}H_{25}N_2O_3$ [M + $H^+$]: calculated 317.1860, found 317.1857.

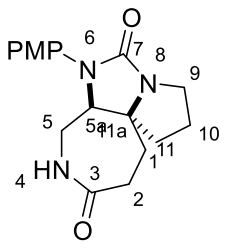
(5a*R**,11a*S**)-6-Isopropyloctahydro-9*H*-pyrrolo[1',2':1,5]imidazo[4,5-*c*]azepine-3,7-dione **152a**



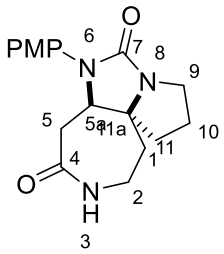

A solution of the ketone **101a** (51 mg, 0.22 mmol, 1.0 eq.), hydroxylamine hydrochloride (31 mg, 0.44 mmol, 2.0 eq.) and potassium carbonate (91.2 mg, 0.66 mmol, 3.0 eq.) in 3 mL EtOH/$H_2O$ (2:1 respectively) was refluxed for 2 h. The reaction mixture was extracted with DCM (5 × 20 mL), dried over $MgSO_4$ and evaporated *in vacuo*. To a solution of the crude, TsCl (63.0 mg, 0.33 mmol, 1.5 eq.) and DMAP (2.69 mg, 0.02 mmol, 10 mol%) in 14 mL of anhydrous DCM; $Et_3N$ (52 µL, 0.37 mmol, 1.7 eq.) was added and the mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was evaporated *in vacuo*. 1 mL of 98% sulphuric acid was then added to a solution of the crude in anhydrous MeOH and refluxed for 2 h. The reaction mixture was neutralized with copious amounts of solid $Na_2CO_3$ in 5 mL $H_2O$, extracted with DCM (5×40 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Flash chromatography with 3 – 4% MeOH in DCM afforded the product **152a** as a pale yellow oil (28 mg, 0.11 mmol, 52%). $\mathbf{R_f}$ = 0.20 (5% MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 6.37 (1H, s, 4-*H*), 3.94 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.79 (1H, ddd, *J* = 12.5, 4.5, 3.0, 9-$H_A$), 3.53 (1H, t, *J* = 5.5, 5a-*H*), 3.37 (2H, t, *J* = 6.0, 5-$H_{A,B}$), 2.84 (1H, ddd, *J* = 12.0, 5.5, 3.0, 9-$H_B$), 2.65 (1H, ddd, *J* = 17.3, 9.4, 4.4, 2-$H_A$), 2.39 (1H, ddd, *J* = 17.3, 7.5, 4.1, 2-$H_B$), 1.90 – 1.69 (5H, m, 1-$H_{A,B}$; 10-$H_{A,B}$; 11-$H_A$), 1.42 – 1.31 (1H, m, 11-$H_B$), 1.18 (3H, d, *J* = 6.9, isopropyl C$H_{3A}$), 1.16 (3H, d, *J* = 6.9, isopropyl C$H_{3B}$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 174.7 (3-*C*), 162.4 (7-*C*), 67.5 (11a-*C*), 58.8 (5a-*C*), 43.8 (isopropyl *C*H), 43.2 (9-*C*), 41.7 (5-*C*), 34.1 (11-*C*), 30.1 (2-*C*), 25.6 (1-*C*), 21.8 (10-*C*), 21.1 (isopropyl *C*$H_{3A}$), 18.6 (isopropyl *C*$H_{3B}$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3398 (N-H), 2976, 2945 (C-H), 1671, 1656 (C=O). **HRMS** (ESI): $C_{13}H_{22}N_3O_2$ [M + $H^+$]: calculated 252.1707, found 252.1707.

(5a*R**,11a*S**)-6-(4-Methoxyphenyl)octahydro-9*H*-pyrrolo[1',2':1,5]imidazo[4,5-*c*]azepine-3,7-dione **152b**

(5a*R**,11a*S**)-6-(4-Methoxyphenyl)hexahydro-9*H*-pyrrolo[1',2':1,5]imidazo[4,5-*d*]azepine-4,7(1*H*,5*H*)-dione **153b**




**152b**
**Major isomer**



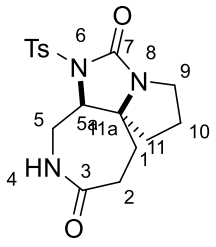

**153b**
**Minor isomer**

A solution of the ketone **101b** (127 mg, 0.42 mmol, 1.0 eq.), hydroxylamine hydrochloride (58.6 mg, 0.84 mmol, 2.0 eq.) and potassium carbonate (175 mg, 1.27 mmol, 3.0 eq.) in 8 mL EtOH/$H_2O$ (2:1 respectively) was refluxed for 2 h. The reaction mixture was evaporated *in vacuo* and taken up in 2 mL $H_2O$. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude, TsCl (121 mg, 0.63 mmol, 1.5 eq.), and DMAP (5.16 mg, 0.04 mmol, 10 mol%) in 14 mL of anhydrous DCM; $Et_3N$ (0.10 mL, 0.72 mmol, 1.7 eq.) was added and the mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was evaporated *in vacuo*. 2 mL of 98% sulphuric acid was then added to a solution of the crude in 7 mL of anhydrous MeOH and refluxed for 2 h. The reaction mixture was neutralized with copious amounts of solid $Na_2CO_3$ in 10 mL $H_2O$, extracted with EtOAc (5 × 50 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 6% MeOH in DCM afforded the product as an isomeric mixture in the ratio of 93:7 (83 mg, 0.26 mmol, 62%). $\mathbf{R_f}$ = 0.36 (6% MeOH in DCM). **$^1$H NMR** (Major isomer, 400 MHz, $CDCl_3$): δ ppm 7.20 (2H, d, *J* = 9.2, Ar*H*), 6.83 (2H, d, *J* = 8.8, Ar*H*), 6.26 (1H, s, 4-*H*), 4.08 (1H, t, *J* = 5.1, 5a-*H*), 3.84 (1H, ddd, *J* = 14.0, 9.6, 4.9, 9-$H_A$), 3.72 (3H, s, ArOC$H_3$), 3.30 (2H, t, *J* = 4.9, 5-$H_{A,B}$), 2.98 (1H, ddd, *J* = 14.4, 9.2, 5.6, 9-$H_B$), 2.69 (1H, ddd, *J* = 17.6, 8.8, 5.6, 2-$H_A$), 2.45 (1H, dt, *J* = 17.6, 5.6, 2-$H_B$), 1.98 – 1.77 (5H, m, 1-$H_{A,B}$; 10-$H_{A,B}$; 11-$H_A$), 1.71 – 1.61 (1H, m, 11-$H_B$). Signals for minor isomer visible at:

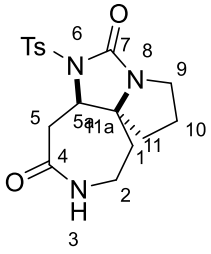
4.15 (0.07H, dd, *J* = 10.6, 2.9, 5a-*H*), 2.80 (0.08H, dd, *J* = 14.8, 10.6, 5-*H*). **$^{13}$C NMR** (Major isomer, 100 MHz, $CDCl_3$): δ ppm 175.3 (3-*C*), 161.5 (7-*C*), 157.1 (*Ar*), 130.3 (*Ar*), 124.4 (*Ar*H), 114.6 (*Ar*H), 67.4 (11a-*C*), 63.0 (5a-*C*), 55.6 (ArO*C*$H_3$), 44.4 (9-*C*), 40.4 (5-*C*), 36.0 (11-*C*), 31.3 (2-*C*), 26.9 (1-*C*), 23.1 (10-*C*). Signals for minor isomer visible at: ppm 124.8, 59.3, 50.8, 38.2, 35.4, 32.2, 23.5. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3291 (N-H), 3052, 2954, 2837 (C-H), 1693, 1659 (C=O), 1513, 1465, 1403 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{17}H_{22}N_3O_3$ [M + $H^+$]: calculated 316.1656, found 316.1657.

(5a*R**,11a*S**)-6-(4-Toluenesulfonyl)octahydro-9*H*-pyrrolo[1',2':1,5]imidazo[4,5-*c*]azepine-3,7-dione **152c**

(5a*R**,11a*S**)-6-(4-Toluenesulfonyl)hexahydro-9*H*-pyrrolo[1',2':1,5]imidazo[4,5-*d*]azepine-4,7(1*H*,5*H*)-dione **153c**




**152c**
**Major isomer**



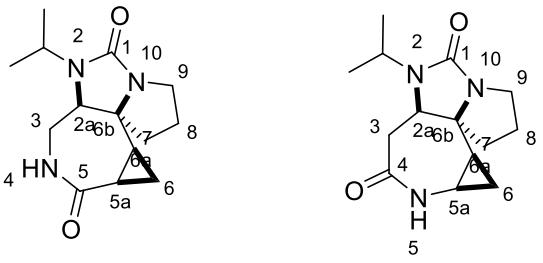

**153c**
**Minor isomer**

A solution of the ketone **101c** (110 mg, 0.32 mmol, 1.0 eq.), hydroxylamine hydrochloride (45.0 mg, 0.64 mmol, 2.0 eq.) and potassium carbonate (134 mg, 0.96 mmol, 3.0 eq.) in 6 mL EtOH/$H_2O$ (2:1 respectively) was refluxed for 2 h. The reaction mixture was evaporated *in vacuo* and taken up in 2 mL $H_2O$. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude, TsCl (93.0 mg, 0.48 mmol, 1.5 eq.), and DMAP (3.95 mg, 0.03 mmol, 10 mol%) in 12 mL of anhydrous DCM; $Et_3N$ (0.08 mL, 0.55 mmol, 1.7 eq.) was added and the mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was evaporated *in vacuo*. 1.5 mL of 98% sulphuric acid was then added to a solution of

the crude in 5 mL of anhydrous MeOH and refluxed for 2 h. The reaction mixture was neutralized with copious amounts of solid $Na_2CO_3$ in 10 mL $H_2O$, extracted with EtOAc (5 × 50 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 4% MeOH in DCM afforded the product as an isomeric mixture in the ratio of 90:10 (46 mg, 0.13 mmol, 40%). $\mathbf{R_f}$ = 0.41 (5% MeOH in DCM). **$^1$H NMR** (Major isomer, 400 MHz, $CDCl_3$): δ ppm 7.85 (2H, d, *J* = 8.3, Ar*H*), 7.27 (2H, d, *J* = 8.1, Ar*H*), 6.04 (1H, t, *J* = 7.2, 4-*H*), 4.16 (1H, dd, *J* = 6.8, 2.1, 5a-*H*), 3.75 (1H, ddd, 15.5, 6.2, 2.2, 9-$H_A$), 3.72 – 3.59 (2H, m, 5-$H_{A,B}$), 2.92 – 2.82 (1H, m, 9-$H_B$), 2.56 (1H, apdt, *J* = 18.0, 7.2, 2-$H_A$), 2.46 (1H, dt, *J* = 17.6, 5.5, 2-$H_B$), 2.37 (3H, s, ArC$H_3$), 1.86 – 1.69 (5H, m, 1-$H_{A,B}$; 10-$H_{A,B}$; 11-$H_A$), 1.25 – 1.09 (1H, m, 11-$H_B$). Signals for minor isomer visible at: 7.91 (0.23H, d, *J* = 8.3, Ar*H*), 6.33 (0.11H, s, 3-*H*), 4.43 (0.11H, dd, *J* = 7.6, 5.6, 5a-*H*). **$^{13}$C NMR** (Major isomer, 100 MHz, $CDCl_3$): δ ppm 173.3 (3-*C*), 156.6 (7-*C*), 144.2 (*Ar*), 134.4 (*Ar*), 128.8 (*Ar*H), 127.0 (*Ar*H), 67.1 (11a-*C*), 61.0 (5a-*C*), 43.0 (9-*C*), 41.4 (5-*C*), 34.7 (11-*C*), 29.8 (2-*C*), 24.9 (1-*C*), 21.5 (10-*C*), 20.7 (Ar*C*$H_3$). Signals for minor isomer visible at: 170.0, 128.6, 127.5, 57.4, 49.8, 37.6, 36.9, 34.7, 33.9, 21.9. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3228 (N-H), 3062, 2960 (C-H), 1726, 1657 (C=O), 1596, 1464, 1400 (C=C) **HRMS** (ESI): $C_{17}H_{22}N_3O_4S$ [M + $H^+$]: calculated 364.1326, found 364.1323.

(2a*R**,5a*R**,6a*S**,6b*S**)-2-Isopropyloctahydro-1*H*,*7H*-cyclopropa[*c*]pyrrolo[1',2':3,4]imidazo[4,5-*e*]azepine-1,5(5a*H*)-dione **156a**

(2a*R**,5a*R**,6a*S**,6b*S**)-2-Isopropyloctahydro-1*H*,*7H*-cyclopropa[*b*]pyrrolo[1',2':3,4]imidazo[4,5-*d*]azepine-1,4(2*H*)-dione **157a**



**156a**
**Major isomer**

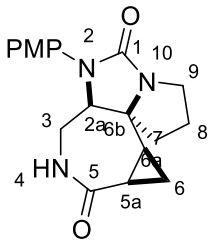
**157a**
**Minor isomer**

A solution of the cyclopropane scaffold **106a** (50.0 mg, 0.20 mmol, 1.0 eq.), hydroxylamine hydrochloride (28.0 mg, 0.40 mmol, 2.0 eq.) and potassium carbonate (83.5 mg, 0.60 mmol, 3.0 eq.) in 3 mL EtOH/$H_2O$ (2:1 respectively) was refluxed for 2 h. The reaction mixture was evaporated *in vacuo* and taken up in 2 mL $H_2O$. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude, TsCl (57.6 mg, 0.30 mmol, 1.5 eq.) and DMAP (2.46 mg, 0.02 mmol, 10 mol%) in 14 mL of anhydrous DCM; $Et_3N$ (47.0 µL, 0.34 mmol, 1.7 eq.) was added and the mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was evaporated *in vacuo*. 0.90 mL of 98% sulphuric acid was then added to a solution of the crude in 3 mL of anhydrous MeOH and refluxed for 2 h. The reaction mixture was neutralized with copious amounts of solid $Na_2CO_3$ in 5 mL $H_2O$, extracted with EtOAc (5×20 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 6% MeOH in DCM afforded the isomeric lactams **156a** [major isomer, 12 mg, 0.05 mmol, 23%, $\mathbf{R_f}$ = 0.31 (6% MeOH in DCM)] and **157a** [minor isomer, 11 mg, 0.04 mmol, 21%, $\mathbf{R_f}$ = 0.37 (6% MeOH in DCM)]. **$^1$H NMR** (Major isomer, 500 MHz, $CDCl_3$): δ ppm 5.71 (1H, s, 4-*H*), 4.02 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.93 (1H, dd, *J* = 15.2, 6.7, 3-$H_A$), 3.60 (1H, dt, *J* = 11.7, 7.8, 9-$H_A$), 3.54 (1H, br. s, 2a-*H*), 3.11 (1H, ddd, *J* = 15.4, 6.2, 2.5, 3-$H_B$), 2.97 – 2.87 (1H, m, 9-$H_B$), 1.87 – 1.79 (3H, m, 7-$H_A$, 8-$H_{A,B}$), 1.71 – 1.65 (1H, m, 5a-*H*), 1.52 – 1.43 (1H, m, 7-$H_B$), 1.18 (3H, d, *J* =

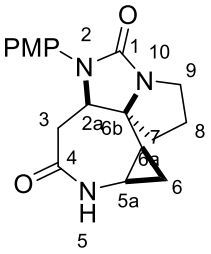
6.9, isopropyl C$H_{3A}$), 1.14 (3H, d, *J* = 6.9, isopropyl C$H_{3B}$), 1.02 – 0.96 (1H, m, 6-$H_A$). 0.90 (1H, td, *J* = 8.5, 5.6, 6a-*H*), 0.73 (1H, q, *J* = 5.5, 6-$H_B$). **$^{13}$C NMR** (Major isomer, 125 MHz, $CDCl_3$): δ ppm 170.5 (5-*C*), 163.0 (1-*C*), 66.5 (6b-*C*), 57.3 (2a-*C*), 46.4 (9-*C*), 43.5 (isopropyl *C*H), 42.7 (3-*C*), 37.5 (7-*C*), 22.2 (8-*C*), 21.3 (isopropyl *C*$H_{3A}$), 18.5 (isopropyl *C*$H_{3B}$), 15.7 (6a-*C*), 15.0 (5a-*C*), 7.1 (6-*C*). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3320 (N-H), 2968, 2904, 2878 (C-H), 1681 (C=O). **HRMS** (ESI): $C_{14}H_{22}N_3O_2$ [M + $H^+$]: calculated 264.1707, found 264.1701. **$^1$H NMR** (Minor isomer, 500 MHz, $CDCl_3$): δ ppm 5.52 (1H, s, 5-*H*), 3.83 (1H, t, *J* = 3.5, 2a-*H*), 3.78 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.68 – 3.61 (1H, m, 9-$H_A$), 3.12 (1H, dd, *J* = 13.5, 3.0, 3-$H_A$), 2.97 – 2.89 (1H, m, 9-$H_B$), 2.65 (1H, td, *J* = 7.2, 4.2, 5a-*H*), 2.47 (1H, ddd, *J* = 13.5, 3.9, 1.7, 3-$H_B$), 1.93 – 1.77 (3H, m, 7-$H_A$, 8-$H_{A,B}$), 1.48 (1H, td, *J* = 11.5, 9.2, 7-$H_B$), 1.25 (3H, d, *J* = 6.9, isopropyl C$H_{3A}$), 1.23 (3H, d, *J* = 6.9, isopropyl C$H_{3B}$), 1.00 (1H, ddd, *J* = 9.0, 7.3, 5.0, 6-$H_A$). 0.87 – 0.79 (1H, m, 6a-*H*), 0.73 (1H, dt, *J* = 6.5, 4.5, 6-$H_B$). **$^{13}$C NMR** (Minor isomer, 125 MHz, $CDCl_3$): δ ppm 171.2 (4-*C*), 162.1 (1-*C*), 66.3 (6b-*C*), 56.6 (2a-*C*), 45.3 (9-*C*), 44.5 (isopropyl *C*H), 39.0 (7-*C*), 36.8 (3-*C*), 25.4 (5a-*C*), 22.6 (8-*C*), 20.4 (isopropyl *C*$H_{3A}$), 19.1 (6a-*C*), 18.4 (isopropyl *C*$H_{3B}$), 12.1 (6-*C*). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3266 (N-H), 2968, 2930 (C-H), 1684 (C=O). **HRMS** (ESI): $C_{14}H_{22}N_3O_2$ [M + $H^+$]: calculated 264.1707, found 264.1704.

(2a*R**,5a*R**,6a*S**,6b*S**)-2-(4-Methoxyphenyl)octahydro-1*H*,*7H*-cyclopropa[*c*]pyrrolo[1',2':3,4]imidazo[4,5-*e*]azepine-1,5(5a*H*)-dione **156b**

(2a*R**,5a*R**,6a*S**,6b*S**)-2-Isopropyloctahydro-1*H*,*7H*-cyclopropa[*b*]pyrrolo[1',2':3,4]imidazo[4,5-*d*]azepine-1,4(2*H*)-dione **157b**




**156b**
**Major isomer**

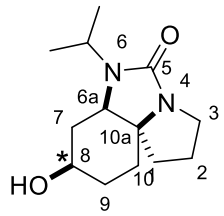



**157b**
**Minor isomer**

A solution of the cyclopropane scaffold **106b** (101 mg, 0.32 mmol, 1.0 eq.), hydroxylamine hydrochloride (45.2 mg, 0.65 mmol, 2.0 eq.) and potassium carbonate (134 mg, 0.97 mmol, 3.0 eq.) in 6 mL EtOH/$H_2O$ (2:1 respectively) was refluxed for 2 h. The reaction mixture was evaporated *in vacuo* and taken up in 2 mL $H_2O$. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude, TsCl (93.4 mg, 0.49 mmol, 1.5 eq.), and DMAP (3.95 mg, 0.03 mmol, 10 mol%) in 14 mL of anhydrous DCM; $Et_3N$ (0.08 mL, 0.55 mmol, 1.7 eq.) was added and allowed to stir at room temperature for 1.5 h. The reaction mixture was evaporated *in vacuo*. 1.5 mL of 98% sulphuric acid was then added to a solution of the crude in 5 mL of anhydrous MeOH and refluxed for 2 h. The reaction mixture was neutralized with copious amounts of solid $Na_2CO_3$ in 10 mL $H_2O$, extracted with EtOAc (5 × 50 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 6% MeOH in DCM afforded the product as an isomeric mixture in the ratio of 78:22 (83 mg, 0.26 mmol, 62%). $\mathbf{R_f}$ = 0.36 (6% MeOH in DCM). **$^1$H NMR** (Major isomer, 500 MHz, $CDCl_3$): δ ppm 7.22 (2H, d, *J* = 9.0, Ar*H*), 6.83 (2H, d, *J* = 9.0, Ar*H*), 5.62 (1H, s, 4-*H*), 4.34 (1H, t, *J* = 3.4, 2a-*H*), 3.82 – 3.73 (1H, m, 9-$H_A$), 3.72 (3H, s, ArOC$H_3$), 3.08 (1H, dt, 12.5, 3.5, 9-$H_B$), 3.03 (1H, dd, *J* = 13.5, 3.0, 3-$H_A$), 2.68 (1H, td, *J* = 7.0, 4.0, 5a-*H*), 2.47 (1H, ddd, *J* = 13.8, 3.4, 1.7, 3-$H_B$), 2.05 (1H, ddd, *J* = 11.5, 5.0, 1.5, 7-$H_A$), 1.97 – 1.92 (2H, m, 8-$H_{A,B}$), 1.81 (1H, dt, *J* = 11.0, 9.0, 7-$H_B$), 1.07 (1H, ddd,

9.5, 4.5, 2.0, 6-$H_A$), 0.97 – 0.91 (1H, m, 6a-*H*), 0.84 – 0.79 (1H, m, 6-$H_B$). Signal for minor isomer visible at: 5.50 (0.28H, t, *J* = 5.5, 5-*H*). **$^{13}$C NMR** (Major isomer, 125 MHz, $CDCl_3$): δ ppm 170.9 (5-*C*), 160.7 (1-*C*), 156.4 (*Ar*), 129.3 (*Ar*), 125.4 (*Ar*H), 113.4 (*Ar*H), 65.6 (6b-*C*), 59.7 (2a-*C*), 54.4 (ArO*C*$H_3$), 45.6 (9-*C*), 39.2 (7-*C*), 35.1 (3-*C*), 25.2 (5a-*C*), 22.8 (8-*C*), 19.4 (6a-*C*), 12.1 (6-*C*). Signals for minor isomer visible at: 155.9, 122.9, 113.7, 65.4, 61.0, 54.5, 46.4, 39.9, 38.3, 22.4, 16.2, 15.3, 7.1. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3300 (N-H), 2933 (C-H), 1691 (C=O), 1585, 1513, 1458 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{18}H_{22}N_3O_3$ [M + $H^+$]: calculated 328.1656, found 328.1653.

(6a*R**,8*R**,10a*S**)-8-Hydroxy-6-isopropyloctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **160a**




**Major diastereomer, *dr* 93:7 (Method E)**
**Single diastereomer (Method F)**

**Method E**

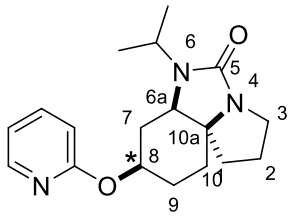
To a solution of the ketone **101a** (81.0 mg, 0.34 mmol, 1.0 eq.) in anhydrous THF (4 mL), 0.13 mL of $LiAlH_4$ (4 M in THF) was added at room temperature and the mixture was allowed to stir for 30 min. The reaction mixture was quenched with 0.1 mL 10% KOH and 0.1 mL $H_2O$, diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 4% MeOH in DCM afforded the product as a diastereomeric mixture in the ratio of 93:7 (65.0 mg, 0.27 mmol, 79% yield). **$R_f$** = 0.34 (5% MeOH in DCM). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 3.99 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.78 (1H, ddd, *J* = 12.4, 9.2, 5.2, 3-$H_A$), 3.57 (1H, tt, *J* = 10.5, 4.0, 8-*H*), 3.44 (1H, dd, *J* = 10.1, 6.5, 6a-*H*), 2.85 (1H, ddd, *J* =12.0, 6.0, 3.0, 3-$H_B$), 2.33 (1H, dddd, *J* = 12.7, 6.5, 4.3, 2.2, 7-$H_A$), 2.13 (1H, s, 8-CHO*H*), 1.85 (1H, dt, *J* = 14.5, 4.0, 10-$H_A$), 1.80 – 1.63 (3H, m, 2-$H_{A,B}$; 9-$H_A$), 1.50 – 1.34 (4H, m, 1-$H_{A,B}$; 7-$H_B$; 9-$H_B$), 1.31 – 1.23 (1H, m, 10-$H_B$), 1.14 (3H, d, *J* = 7.0, isopropyl C$H_{3A}$), 1.11 (3H, d, *J* = 6.5, isopropyl C$H_{3B}$). Signals

for minor isomer visible at: 3.72 (0.08H, ddd, *J* = 12.0, 6.0, 3.0, 3-$H_A$), 3.63 (0.07H, dd, *J* = 8.0, 6.0, 7-$H_A$). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 162.6 (5-*C*), 66.2 (8-*C*), 64.5 (10a-*C*), 53.6 (6a-*C*), 43.2 (isopropyl *C*H), 43.0 (3-*C*), 40.8 (7-*C*), 33.6 (1-*C*), 29.6 (10-*C*), 28.1 (9-*C*), 21.9 (2-*C*), 21.4 (isopropyl $CH_{3A}$), 18.8 (isopropyl $CH_{3B}$). Signals for minor isomer visible at: 64.7, 63.3, 52.3, 36.4, 34.3, 27.2, 24.6, 22.1, 21.2, 18.6. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3399 (O-H), 2937 (C-H), 1666 (C=O), 1056 (C-O). **HRMS** (ESI): $C_{13}H_{23}N_2O_2$ [M + $H^+$]: calculated 239.1754, found 239.1750.

**Method F**

A mixture of the ketone **101a** (24.0 mg, 0.10 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (45.5 mg, 0.12 mmol, 1.2 eq.) in 3 mL of HPLC grade MeOH and it was allowed to stir at –78 °C for 30 min. $NaBH_4$ (4.62 mg, 0.12 mmol, 1.2 eq.) was then added and the mixture was left to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 4% MeOH in DCM afforded the product **160a** as a single diastereomer (22.0 mg, 0.09 mmol, 92% yield) that is identical to the major diastereomer obtained from **Method E**.

(6a*R**,8*R**,10a*S**)-6-Isopropyl-8-(pyridine-2-yloxy)octahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **161**

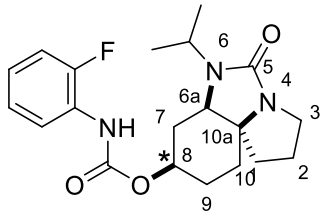



**Major diastereomer, *dr* 93:7**

To a mixture of the alcohol **160a** (28.0 mg, 0.12 mmol, 1.0 eq., obtained from **Method E**) and NaH (7.20 mg, 0.18 mmol, 1.5 eq.) in 4 mL THF, 2-fluoropyridine (0.02 mL, 0.18 mmol, 1.5 eq.)

was added and the mixture was heated at 65 °C for 24 h. The reaction mixture was evaporated *in vacuo* and taken up in 1 mL $H_2O$. It was then diluted with 50 mL DCM, dried over $MgSO_4$, and evaporated *in vacuo*. Flash chromatography with 1 – 5% MeOH in DCM afforded the product as a diastereomeric mixture in the ratio of 93:7 (12 mg, 0.04 mmol, 32% yield). $\mathbf{R_f}$ = 0.41 (5% MeOH in DCM). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 8.05 (1H, ddd, *J* = 5.1, 1.9, 0.6, Ar*H*), 7.49 (1H, ddd, *J* = 8.4, 7.1, 2.0, Ar*H*), 6.78 (1H, ddd, 7.0, 5.1, 0.9, Ar*H*), 6.62 (1H, dt, *J* = 8.5, 0.8, Ar*H*), 5.00 (1H, ddt, *J* = 11.4, 9.6, 4.2, 8-*H*), 3.99 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.81 (1H, ddd, *J* = 12.5, 7.0, 3.0, 3-$H_A$), 3.55 (1H, dd, *J* = 10.2, 6.4, 6a-*H*), 2.89 (1H, ddd, *J* =12.3, 9.3, 5.8, 3-$H_B$), 2.48 (1H, dddd, *J* = 12.6, 6.4, 4.5, 1.8, 7-$H_A$), 1.93 – 1.85 (2H, m, 9-$H_A$, 10-$H_A$), 1.82 – 1.58 (4H, m, 2-$H_{A,B}$; 7-$H_B$; 10-$H_B$), 1.51 – 1.38 (3H, m, 1-$H_{A,B}$; 9-$H_B$), 1.13 (3H, d, *J* = 7.0, isopropyl C$H_{3A}$), 1.12 (3H, d, *J* = 6.5, isopropyl C$H_{3B}$). Signals for minor isomer visible at: 3.70 (0.07H, dd, *J* = 12.0, 4.5, 6a-*H*), 2.99 (0.08H, ddd, *J* = 12.3, 8.8, 6.1, 3-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 162.5 (5-*C*), 162.0 (*Ar*), 145.7 (*Ar*H), 137.7 (*Ar*H), 115.6 (*Ar*H) 110.8 (*Ar*H), 68.7 (8-*C*), 64.6 (10a-*C*), 53.5 (6a-*C*), 43.2 (isopropyl *C*H), 43.0 (3-*C*), 36.8 (7-*C*), 33.8 (1-*C*), 27.9 (9-*C*), 26.0 (10-*C*), 21.9 (2-*C*), 21.4 (isopropyl *C*$H_{3A}$), 18.7 (isopropyl *C*$H_{3B}$). Signals for minor isomer visible at: 129.2, 126.4, 116.0, 110.4, 66.9, 63.9, 63.4, 53.1, 43.4, 21.4, 18.5. **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2964 (C-H), 1692 (C=O), 1594, 1569, 1470 (C=C), 1286 (C-O). **HRMS** (ESI): $C_{18}H_{26}N_3O_2$ [M + H$^+$]: calculated 316.2020, found 316.2020.

(6a*R**,8*R**,10a*S**)-6-Isopropyl-5-oxooctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-8-yl (2-fluorophenyl)carbamate **162**

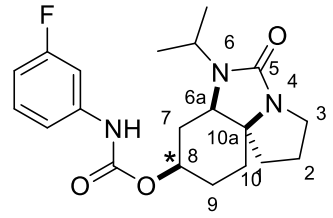



**Major diastereomer, *dr* 88:12**

To a solution of the alcohol **160a** (14.0 mg, 0.06 mmol, 1.0 eq., obtained from **Method E**) in 5 mL DCM, 2-fluorophenylisocyanate (0.01 mL, 0.07 mmol, 1.5 eq.) and TEA (0.03 mL, 0.18 mmol,

3.0 eq.) were added and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated *in vacuo*. Flash chromatography with 10 – 90% EtOAc in hexane afforded the product as a diastereomeric mixture in the ratio of 88:12 (17 mg, 0.05 mmol, 77% yield). $\mathbf{R_f}$ = 0.47 (80% EtOAc in hexane). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 8.00 (1H, br.s, Ar*H*), 7.06 (1H, t, *J* = 7.8, Ar*H*), 7.03 – 6.98 (1H, m, Ar*H*), 6.96 – 6.91 (1H, m, Ar*H*), 6.76 (1H, s, ArN*H*), 4.70 (1H, tt, *J* = 11.0, 4.0, 8-*H*), 4.00 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.81 (1H, ddd, *J* = 12.4, 9.2, 5.2, 3-$H_A$), 3.51 (1H, dd, *J* = 10.0, 6.5, 6a-*H*), 2.88 (1H, ddd, *J* =12.3, 9.4, 5.8, 3-$H_B$), 2.42 (1H, dddd, *J* = 10.5, 6.0, 4.5, 2.0, 7-$H_A$), 1.90 (1H, dt, *J* = 15.0, 4.5, 10-$H_A$), 1.86 – 1.71 (3H, m, 2-$H_{A,B}$; 9-$H_A$), 1.66 – 1.61 (1H, m, 9-$H_B$), 1.56 – 1.32 (4H, m, 1-$H_{A,B}$; 7-$H_B$, 10-$H_B$), 1.15 (3H, d, *J* = 7.0, isopropyl C$H_{3A}$), 1.12 (3H, d, *J* = 7.0, isopropyl C$H_{3B}$). Signals for minor isomer visible at: 5.07 (0.14H, quint, *J* = 5.0, 8-*H*), 3.70 (0.14H, dd, *J* = 8.5, 6.0, 6a-*H*), 2.19 (0.13H, dt, *J* = 10.7, 5.2, 10-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 162.4 (5-*C*), 151.6 (carbamate *C*=O), 151.1 (d, *J* = 241, *Ar*F), 125.3 (d, *J* =10.0, *Ar*), 123.6 (d, *J* = 3.63, *Ar*H), 122.5 (d, *J* = 7.25, *Ar*H), 119.1 (*Ar*H), 113.9 (d, *J* = 19.0, *Ar*H), 69.8 (8-*C*), 64.4 (10a-*C*), 53.2 (6a-*C*), 43.3 (isopropyl *C*H), 43.0 (3-*C*), 36.9 (7-*C*), 33.6 (1-*C*), 27.7 (10-*C*), 26.0 (9-*C*), 21.9 (2-*C*), 21.4 (isopropyl *C*$H_{3A}$), 18.7 (isopropyl *C*$H_{3B}$). Signals for minor isomer visible at: 68.4, 52.0, 34.3, 33.7, 25.0, 24.0, 22.1, 21.2, 18.6. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3246 (N-H); 2967 (C-H); 1724, 1682 (C=O); 1620, 1597, 1538 (C=C); 1258 (C-O). **HRMS** (ESI): $C_{20}H_{27}FN_3O_3$ [M + $H^+$]: calculated 376.2031, found 376.2027.

(6a*R**,8*R**,10a*S**)-6-Isopropyl-5-oxooctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-8-yl (3-fluorophenyl)carbamate **163**

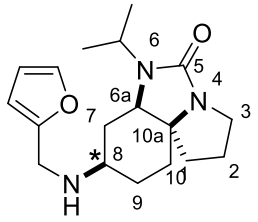



**Major diastereomer, *dr* 93:7**

A mixture of the ketone **101a** (27.0 mg, 0.11 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (51.0 mg, 0.14 mmol, 1.2 eq.) in 3 mL of HPLC grade MeOH was allowed to stir at – 78 °C for 30 min. $NaBH_4$ (5.18 mg, 0.14 mmol, 1.2 eq.) was then added and the mixture was left to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude product in 5 mL DCM, 3-fluorophenylisocyanate (13 µL, 0.11 mmol, 1.0 eq.) and TEA (0.05 mL, 0.34 mmol, 3.0 eq.) were added and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated *in vacuo*. Flash chromatography with 1 – 4% MeOH in DCM afforded the carbamate as a diastereomeric mixture in the ratio of 93:7 (36 mg, 0.10 mmol, 84% yield). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 7.30 (1H, d, *J* = 10.6, Ar*H*), 7.17 (1H, td, *J* = 8.2, 6.6, Ar*H*), 7.00 (1H, d, *J* = 8.0, Ar*H*), 6.68 (1H, td, *J* = 8.3, 2.3, Ar*H*), 4.69 (1H, tt, *J* = 10.8, 4.0, 8-*H*), 3.99 (1H, hept, *J* = 6.9, isopropyl C*H*), 3.79 (1H, ddd, *J* = 12.4, 9.3, 5.2, 3-$H_A$), 3.52 (1H, dd, *J* = 9.9, 6.5, 6a-*H*), 2.85 (1H, ddd, *J* =12.5, 7.0, 4.0, 3-$H_B$), 2.44 – 2.35 (1H, m, 7-$H_A$), 1.88 (1H, dt, *J* = 15.0, 4.0, 10-$H_A$), 1.85 – 1.80 (1H, m, 9-$H_A$), 1.77 (1H, ddd, *J* = 12.5, 6.0, 3.0, 1-$H_A$), 1.75 – 1.66 (1H, m, 2-$H_A$), 1.62 – 1.39 (4H, m, 1-$H_B$, 2-$H_B$, 7-$H_B$, 9-$H_B$), 1.36 (1H, ddd, *J* = 14.6, 10.8, 4.7, 10-$H_B$), 1.14 (3H, d, *J* = 6.9, isopropyl C$H_{3A}$), 1.12 (3H, d, *J* = 6.9, isopropyl C$H_{3B}$). Signals for minor isomer visible at: 5.06 (0.07H, quint, *J* = 4.5, 8-*H*), 3.70 (0.07H, dd, *J* = 8.2, 5.7, 6a-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 162.6 (5-*C*), 162.2 (d, *J* = 243, *Ar*F), 151.8 (carbamate *C*=O), 138.7 (d, *J* =13.2, *Ar*), 129.1 (d, *J* = 9.50, *Ar*H), 112.8 (*Ar*H), 108.9 (d, *J* = 21.3, *Ar*H), 104.9 (d, *J* = 26.8, *Ar*H), 69.3 (8-*C*), 64.4 (10a-*C*), 53.2 (6a-*C*), 43.3 (isopropyl *C*H), 43.0 (3-*C*), 36.9 (7-*C*), 33.6 (1-*C*), 27.6 (10-*C*), 26.0 (9-*C*), 21.9 (2-*C*), 21.4 (isopropyl *C*$H_{3A}$), 18.7 (isopropyl *C*$H_{3B}$). Signals for minor isomer visible at: 52.1, 34.4, 25.1, 24.1,

22.2, 21.2. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3254 (N-H); 3076, 2968 (C-H); 1723, 1671 (C=O); 1606, 1546, 1495 (C=C); 1221 (C-O). **HRMS** (ESI): $C_{20}H_{27}FN_3O_3$ [M + $H^+$]: calculated 376.2031, found 376.2028.

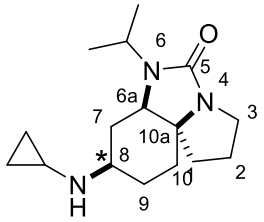
(6a*R**,8*R**,10a*S**)-8-[(Furan-2-ylmethyl)amino]-6-isopropyloctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **164**




To a solution of the ketone **101a** (39.0 mg, 0.17 mmol, 1.0 eq.) in 4 mL THF, furfurylamine (17.0 µL, 0.20 mmol, 1.2 eq.) and titanium isopropoxide (0.10 mL, 0.33 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (9.4 mg, 0.25 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo* and dissolved in 1 mL DMSO. Reverse phase chromatography by the use of a biotage machine (MeCN/1% HCOOH in $H_2O$) afforded the product **164** as a single diastereomer (28 mg, 0.09 mmol, 53% yield). $\mathbf{R_f}$ = 0.36 (6% MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.30 (1H, dd, *J* = 1.8, 0.7, Ar*H*), 6.26 (1H, dd, *J* = 3.1, 1.9, Ar*H*), 6.16 (1H, d, *J* = 3.0, Ar*H*), 3.98 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.88 – 3.69 (3H, m, 3-$H_A$, ArC$H_{2A,B}$), 3.39 (1H, dd, *J* = 10.3, 6.5, 6a-*H*), 2.85 (1H, ddd, *J* = 12.3, 9.4, 5.8, 3-$H_B$), 2.49 (1H, tt *J* = 9.5, 3.5, 8-*H*), 2.28 – 2.21 (1H, m, 7-$H_A$), 1.88 – 1.83 (1H, m, 9-$H_A$), 1.75 – 1.67 (3H, m, 2-$H_{A,B}$; 10-$H_A$,), 1.42 – 1.36 (2H, m, 1-$H_{A,B}$), 1.31 – 1.18 (4H, m, 7-$H_B$, 9-$H_B$, 10-$H_B$, ArC$H_2$N*H*), 1.13 (3H, d, *J* = 7.0, isopropyl C$H_{3A}$), 1.10 (3H, d, *J* = 7.0, isopropyl C$H_{3B}$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 162.5 (5-*C*), 152.1 (*Ar*), 141.0 (*Ar*H), 109.3 (*Ar*H), 106.4 (*Ar*H), 64.8 (10a-*C*), 53.6 (6a-*C*), 51.4 (8-*C*), 43.2 (isopropyl *C*H), 43.0 (3-*C*), 42.0 (Ar*C*$H_2$), 38.4 (7-*C*), 33.7 (1-*C*), 28.7 (9-*C*), 26.5 (10-*C*), 21.9 (2-*C*), 21.5 (isopropyl

*C*$H_{3A}$), 18.7 (isopropyl *C*$H_{3B}$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3304 (N-H); 2933 (C-H); 1687 (C=O); 1512, 1460 (C=C); 1246 (C-O). **HRMS** (ESI): $C_{18}H_{28}N_3O_2$ [M + $H^+$]: calculated 318.2176, found 318.2177.

(6a*R**,8*R**,10a*S**)-8-(Cyclopropylamino)-6-isopropyloctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **165**

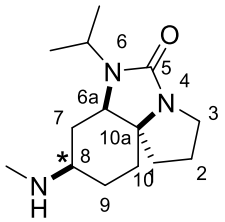



**Major diastereomer, *dr* 79:21**

To a solution of the ketone **101a** (18.0 mg, 0.08 mmol, 1.0 eq.) in 4 mL THF, cyclopropylamine (0.03 mL, 0.38 mmol, 5.0 eq.) and titanium isopropoxide (0.05 mL, 0.15 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (4.30 mg, 0.11 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in* vacuo. It was then taken up in 1 mL $H_2O$, diluted with 50 mL DCM, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 3.5% MeOH in DCM afforded the product as a diastereomeric mixture in the ratio of 79:21 (16.0 mg, 0.06 mmol, 76% yield). $\mathbf{R_f}$ = 0.47 (8% MeOH in DCM). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 3.99 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.78 (1H, ddd, *J* = 12.4, 9.1, 5.2, 3-$H_A$), 3.43 (1H, dd, *J* = 10.2, 6.6, 6a-*H*), 2.85 (1H, ddd, *J* = 12.4, 9.3, 5.9, 3-$H_B$), 2.58 (1H, tt, *J* =11.0, 3.5, 8-*H*), 2.35 – 2.30 (1H, m, 7-$H_A$), 2.12 (1H, ddd, *J* = 10.2, 6.8, 3.7, cyclopropyl C*H*), 1.89 – 1.84 (1H, m, 10-$H_A$), 1.81 – 1.70 (3H, m, 2-$H_{A,B}$; 9-$H_A$), 1.43 – 1.38 (2H, m, 1-$H_{A,B}$), 1.26 – 1.17 (3H, m, 7-$H_B$, 9-$H_B$, 10-$H_B$), 1.14 (3H, d, *J* = 7.0, isopropyl C$H_{3A}$), 1.12 (3H, d, *J* = 7.0, isopropyl C$H_{3B}$), 0.44 – 0.27 (4H, m, cyclopropyl C$H_{2A,B}$; cyclopropyl C$H_{2C,D}$). Signals for minor isomer visible at: 3.70 (0.33H, ddd, *J* = 11.9, 8.8, 5.9, 3-$H_A$), 3.60 (0.27H, t, 5.2, 6a-*H*), 2.65 (0.27H, ddd, *J* = 14.0, 7.5, 4.0, 8-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 162.6 (5-*C*), 64.9 (10a-*C*), 53.7 (6a-*C*), 52.8 (8-*C*), 43.2 (isopropyl *C*H), 43.0 (3-*C*), 39.0 (7-*C*), 33.8 (1-*C*), 28.9 (10-*C*), 27.1 (9-*C*), 26.7

(cyclopropyl *C*H), 21.9 (2-*C*), 21.5 (isopropyl *C*$H_{3A}$), 18.7 (isopropyl *C*$H_{3B}$), 5.5 (cyclopropyl *C*$H_{2A,B}$), 5.2 (cyclopropyl *C*$H_{2C,D}$). Signals for minor isomer visible at: 64.7, 57.8, 54.1, 48.9, 43.3, 43.0, 36.7, 35.0, 27.9, 25.4, 22.2, 21.2, 18.5, 4.6. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3288 (O-H), 2969, 2934 (C-H), 1687 (C=O). **HRMS** (ESI): $C_{16}H_{28}N_3O$ [M + $H^+$]: calculated 278.2227, found 278.2224.

(6a*R**,8*R**,10a*S**)-6-Isopropyl-8-(methylamino)octahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **166**

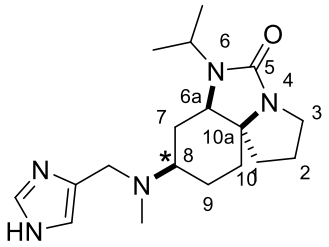



**Major diastereomer, *dr* 88:12**

To a solution of the ketone **101a** (22.0 mg, 0.09 mmol, 1.0 eq.) in 6 mL THF, 33 wt% methylamine in EtOH (0.10 mL, 0.93 mmol, 10.0 eq.) and titanium isopropoxide (0.06 mL, 0.19 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (5.30 mg, 0.14 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in* vacuo. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $MgSO_4$ and evaporated *in vacuo*. Flash chromatography with 5% MeOH in DCM, followed by 99:9:1 of DCM/MeOH/aq. $NH_3$ respectively, afforded the product as a diastereomeric mixture in the ratio of 88:12 (21.0 mg, 0.08 mmol, 90% yield). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 3.98 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.77 (1H, ddd, *J* = 12.4, 9.2, 5.3, 3-$H_A$), 3.41 (1H, dd, *J* = 10.4, 6.5, 6a-*H*), 2.84 (1H, ddd, *J* = 12.4, 9.3, 5.9, 3-$H_B$), 2.37 – 2.31 (4H, m, 8-*H*, NHC$H_3$), 2.26 (1H, dddd, *J* =12.5, 6.1, 3.7, 2.2, 9-$H_A$), 1.88 – 1.82 (1H, m, 7-$H_A$), 1.77 – 1.65 (4H, m, 2-$H_{A,B}$; 10-$H_A$; N*H*), 1.44 – 1.34 (2H, m, 1-$H_{A,B}$), 1.29 – 1.15 (3H, m, 7-$H_B$, 9-$H_B$, 10-$H_B$), 1.14 (3H, d, *J* = 7.0, isopropyl C$H_{3A}$), 1.11 (3H, d, *J* = 7.0, isopropyl C$H_{3B}$). Signals for minor isomer visible at: 3.69 (0.14H, ddd, *J* = 12.1, 8.8, 6.0, 3-$H_A$), 3.61 (0.13H, t, 5.5, 6a-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm

162.6 (5-*C*), 64.9 (10a-*C*), 54.0 (6a-*C*), 53.7 (8-*C*), 43.2 (isopropyl *C*H), 43.0 (3-*C*), 38.4 (7-*C*), 33.8 (1-*C*), 32.3 (NH*C*$H_3$), 28.8 (10-*C*), 26.4 (9-*C*), 21.9 (2-*C*), 21.5 (isopropyl *C*$H_{3A}$), 18.7 (isopropyl *C*$H_{3B}$). Signals for minor isomer visible at: 162.4, 64.8, 53.8, 43.3, 34.8, 32.8, 25.3, 24.4, 22.2, 21.2, 18.5. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3306 (N-H), 2966, 2936, 2791 (C-H), 1686 (C=O). **HRMS** (ESI): $C_{14}H_{26}N_3O$ [M + $H^+$]: calculated 252.2070, found 252.2079.

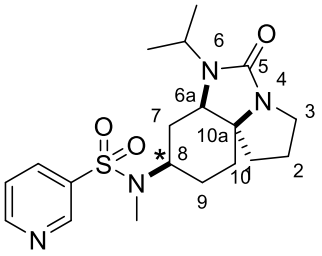
(6a*R**,8*R**,10a*S**)-8-(((1-*H*-Imidazol-4-yl)methyl)amino)-6-isopropyloctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **167**




To a solution of the ketone **101a** (28.0 mg, 0.12 mmol, 1.0 eq.) in 5 mL THF, 2 M methylamine in MeOH (0.60 mL, 1.20 mmol, 10.0 eq.) and titanium isopropoxide (0.07 mL, 0.24 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (6.80 mg, 0.18 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in* vacuo. It was then taken up in 1 mL $H_2O$, diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a mixture of the crude, 4-imidazolecarboxaldehyde (17.3 mg, 0.18 mmol, 1.5 eq.) and sodium triacetoxyborohydride (38.1 mg, 0.18 mmol, 1.5 eq.) in 5 mL DCM; 14.0 µL of acetic acid was added. The reaction mixture was allowed to stir at room temperature for 3 days after which 2 mL of saturated aqueous $Na_2CO_3$ was added. It was diluted with 100 mL DCM, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 5% MeOH in DCM followed by 2 - 4% of saturated $NH_3$/MeOH in DCM afforded the product as a single diastereomer but an 80:20 mixture of tautomers (8.00 mg, 0.03 mmol, 15% yield). $\mathbf{R_f}$ = 0.57 (8% of saturated $NH_3$/MeOH in DCM). **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 7.53 (0.75H, s, Ar*H*), 7.51 (0.20H, s, Ar*H*), 6.85 (0.72H,

s, Ar*H*), 6.83 (0.20H, s, Ar*H*), 3.99 (0.78H, hept, *J* = 6.8, isopropyl C*H*), 3.90 (0.20H, hept, *J* = 6.8, isopropyl C*H*), 3.77 (0.78H, ddd, *J* = 12.4, 7.2, 3.2, 3-$H_A$), 3.69 (0.15H, ddd, *J* = 12.4, 6.0, 3.6, 3-$H_A$), 3.65 (0.28H, m, 6a-*H*), 3.55 (1.44H, s, ArC$H_{2A,B}$), 3.52 (0.41H, s, ArC$H_{2A,B}$), 3.41 (0.86H, dd, *J* = 10.0, 6.4, 6a-*H*), 2.86 (1.21H, ddd, *J* = 12.4, 6.4, 3.2, 3-$H_B$), 2.48 (0.77H, t, *J* =11.2, 8-*H*), 2.20 – 2.04 (3.87H, s, NC$H_3$, 7-$H_A$), 1.88 (0.96H, dt, *J* = 14.4, 4,1, 10-$H_A$), 1.82 – 1.30 (8.09H, m, 1-$H_{A,B}$; 2-$H_{A,B}$; 7-$H_B$; 9-$H_{A,B}$; ArN*H*), 1.29 – 1.18 (1.23H, m, 10-$H_B$), 1.15 (3.21H, d, *J* = 6.8, isopropyl C$H_{3A}$), 1.12 (2.73H, d, *J* = 6.8, isopropyl C$H_{3B}$). **$^{13}$C NMR** (Major tautomer, 100 MHz, $CDCl_3$): δ ppm 163.6 (5-*C*), 153.6 (*Ar*), 152.7 (*Ar*), 134.9 (*Ar*H), 66.0 (10a-*C*), 57.7 (8-*C*), 55.5 (6a-*C*), 49.9 (Ar*C*$H_2$, **missing – found by HSQC**), 44.2 (isopropyl *C*H), 44.0 (3-*C*), 36.9 (N*C*$H_3$), 35.0 (7-*C*), 34.7 (9-*C*), 30.5 (10-*C*), 23.0 (1-*C*), 22.6 (isopropyl *C*$H_{3A}$), 22.4 (2-*C*), 19.8 (isopropyl *C*$H_{3B}$). Signals for minor tautomer visible at: 56.6, 44.4, 36.6, 27.2, 23.3, 22.1, 21.6, 19.5. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3049, 2967, 2937, 2794 (C-H), 1679 (C=O), 1459, 1412 (C=C). **HRMS** (ESI): $C_{18}H_{30}N_5O$ [M + $H^+$]: calculated 332.2445, found 332.2437.

(6a*R**,8*R**,10a*S**)-6-Isopropyl-5-oxooctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-8-yl)-*N*-methylpyridine-3-sulfonamide **168**

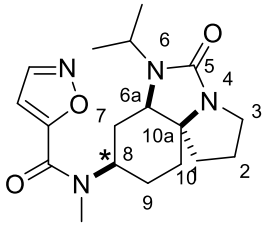



To a solution of the ketone **101a** (27.0 mg, 0.11 mmol, 1.0 eq.) in 5 mL THF, 2 M methylamine in MeOH (0.55 mL, 1.10 mmol, 10.0 eq.) and titanium isopropoxide (0.07 mL, 0.22 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (6.40 mg, 0.17 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in* vacuo. It was then taken up in 1 mL $H_2O$, diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude and

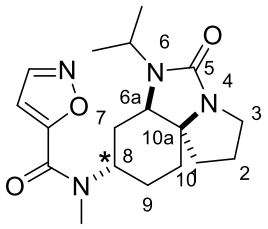
DMAP (1.00 mg, 2.75 µmol, 2.5 mol%) in 6 mL DCM, pyridine-3-sulfonyl chloride (14.0 µL, 0.12 mmol, 1.1 eq.) and TEA (23.0 µL, 0.17 mmol, 1.5 eq.) were added. The reaction mixture was allowed to stir at room temperature for 12 h after which 1 mL of saturated aqueous $Na_2CO_3$ was added. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 - 3% MeOH in DCM afforded the product **168** as a single diastereomer (30.0 mg, 0.08 mmol, 67% yield). $\mathbf{R_f}$ = 0.30 (5% MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 9.03 (1H, dd, *J* = 2.3, 0.6, Ar*H*), 8.80 (1H, dd, *J* = 4.8, 1.6, Ar*H*), 8.09 (1H, ddd, *J* = 8.0, 2.3, 1.7, Ar*H*), 7.47 (1H, ddd, *J* = 8.0, 4.8, 0.7, Ar*H*), 4.03 (1H, hept, *J* = 6.9, isopropyl C*H*), 3.89 (1H, tt, *J* = 12.0, 3.5, 8-*H*), 3.83 (1H, ddd, *J* = 12.5, 9.4, 5.0, 3-$H_A$), 3.55 (1H, dd, *J* = 9.9, 6.7, 6a-*H*), 2.84 (1H, ddd, *J* = 12.4, 9.5, 5.9, 3-$H_B$), 2.74 (3H, s, NC$H_3$), 2.00 (1H, dddd, *J* =12.5, 6.3, 3.5, 2.4, 7-$H_A$), 1.89 (1H, dt, *J* = 14.7, 3.8, 10-$H_A$), 1.85 – 1.72 (2H, m, 2-$H_{A,B}$), 1.60 – 1.49 (2H, m, 7-$H_B$, 9-$H_A$), 1.48 – 1.43 (2H, m, 1-$H_{A,B}$), 1.37 (1H, ddd, *J* = 14.7, 12.6, 3.9, 10-$H_B$), 1.28 - 1.22 (1H, m, 9-$H_B$), 1.13 (3H, d, *J* = 6.9, isopropyl C$H_{3A}$), 1.10 (3H, d, *J* = 6.8, isopropyl C$H_{3B}$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 163.4 (5-*C*), 153.2 (*Ar*H), 147.8 (*Ar*H), 136.5 (*Ar*), 134.5 (*Ar*H), 123.8 (*Ar*H), 65.2 (10a-*C*), 54.4 (6a-*C*), 53.2 (8-*C*), 44.2 (isopropyl *C*H), 44.0 (3-*C*), 37.0 (7-*C*), 34.4 (1-*C*), 30.1 (10-*C*), 28.6 (N*C*$H_3$), 24.8 (9-*C*), 22.8 (2-*C*), 22.4 (isopropyl *C*$H_{3B}$), 19.8 (isopropyl *C*$H_{3A}$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3054, 2966 (C-H), 1686 (C=O), 1572, 1463, 1438 (C=C). **HRMS** (ESI): $C_{19}H_{29}N_4O_3S$ [M + $H^+$]: calculated 393.1955, found 393.1952.

(6a*R**,8*R**,10a*S**)-6-Isopropyl-5-oxooctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-8-yl)-*N*-methylisoxazole-5-carboxamide **169**

(6a*R*,8*S*,10a*S*)-6-Isopropyl-5-oxooctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-8-yl)-*N*-methylisoxazole-5-carboxamide **170**




**169**
**Major diastereomer**

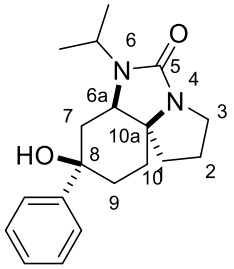



**170**
**Minor diastereomer**

To a solution of the ketone **101a** (30.0 mg, 0.13 mmol, 1.0 eq.) in 5 mL THF, 33 wt% methylamine in EtOH (0.16 mL, 1.30 mmol, 10.0 eq.) and titanium isopropoxide (0.08 mL, 0.26 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (7.40 mg, 0.20 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was further stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude and DMAP (1.00 mg, 8.19 µmol, 6.3 mol%) in 6 mL DCM, isoxazole-5-carbonyl chloride (14.0 µL, 0.14 mmol, 1.1 eq.) and TEA (27.0 µL, 0.20 mmol, 1.5 eq.) were added. The reaction mixture was allowed to stir at room temperature overnight after which 2 mL of saturated aqueous $Na_2CO_3$ was added. It was diluted with 100 mL DCM, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 - 2% MeOH in DCM afforded the products **169** [Major diastereomer, 22.0 mg, 0.06 mmol, 50% yield, 63:37 mixture of rotamers, $\mathbf{R_f}$ = 0.37 (5% MeOH in DCM)] and **170** [Minor diastereomer, 4.00 mg, 0.01 mmol, 9% yield, 50:50 mixture of rotamers, $\mathbf{R_f}$ = 0.41 (5% MeOH in DCM)]. **$^1$H NMR** (Major diastereomer, 400 MHz, $CDCl_3$): δ ppm 8.28 (0.3H, d, *J* = 1.7, Ar*H*), 8.25 (0.6H, d, *J* = 1.6, Ar*H*), 6.74 (0.3H, d, *J* = 1.6, Ar*H*), 6.71 (0.6H, d, *J* = 1.7, Ar*H*), 4.48 (0.6H, tt, 12.4, 3.2, 8-*H*), 4.02 (1.0H, m, isopropyl C*H*), 3.82 (1.4H, m, 3-$H_A$), 3.60 (0.6H, dd, *J* = 9.7, 6.8, 6a-*H*), 3.51 (0.3H, dd, *J* = 9.7, 6.7, 6a-*H*), 2.98 (1.9H,

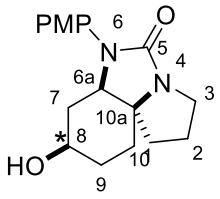
s, NC$H_3$), 2.91 (1.0H, s, NC$H_3$), 2.85 (1.1H, ddd, *J* = 15.0, 7.5, 4.0, 3-$H_B$), 2.22 (0.4H, m, 7-$H_A$), 2.15 (0.6H, m, 7-$H_A$), 1.95 (1.0H, tt, *J* = 14.5, 3.6, 2-$H_A$), 1.87 – 1.28 (8.0H, m, 1-$H_{A,B}$; 2-$H_B$; 7-$H_B$; 9-$H_{A,B}$; 10-$H_{A,B}$), 1.15 (2.9H, d, *J* = 6.8, isopropyl C$H_{3A}$), 1.12 (3.0H, d, *J* = 6.9, isopropyl C$H_{3A}$). **$^{13}$C NMR** (Major diastereomer, 100 MHz, $CDCl_3$): δ ppm 164.1 (amide *C*=O), 163.6 (5-*C*), 158.3/158.1 (*Ar*), 150.3/150.1 (*Ar*H), 107.7/107.4 (*Ar*H), 65.4/65.2 (10a-*C*), 54.4/54.0 (6a-*C*), 50.2 (8-*C*), 44.3 (isopropyl *C*H), 44.0 (3-*C*), 37.6/35.8 (7-*C*), 34.5/34.4 (1-*C*), 30.6/28.2 (N*C*$H_3$), 30.1 (10-*C*), 26.1 (9-*C*), 24.6/22.9 (2-*C*), 22.6/22.5 (isopropyl *C*$H_{3A}$), 19.9 (isopropyl *C*$H_{3B}$). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3104, 2965, 2935 (C-H), 1692, 1643 (C=O), 1576, 1512 (C=C), 1283 (C-O). **HRMS** (ESI): $C_{18}H_{27}N_4O_3$ [M + H$^+$]: calculated 347.2078, found 347.2072. **$^1$H NMR** (Minor diastereomer, 500 MHz, $CDCl_3$): δ ppm 8.23 (1.0H, s, Ar*H*), 6.71 (0.5H, s, Ar*H*), 6.54 (0.5H, s, Ar*H*), 4.46 (0.5H, s, 8-*H*), 4.23 (0.5H, s, 8-*H*), 3.94 (0.5H, hept, *J* = 6.6, isopropyl C*H*), 3.80 (0.5H, hept, *J* = 6.7, isopropyl C*H*), 3.74 (0.5H, s, 6a-*H*), 3.66 (1.4H, s, 6a-*H*, 3-$H_A$), 3.07 (1.5H, s, NC$H_3$), 2.93 (1.4H, s, NC$H_3$), 2.88 (0.9H, m, 3-$H_B$), 2.20 – 1.91 (2.2H, m, 2-$H_A$, 7-$H_A$), 1.85 – 1.55 (7.1H, m, 1-$H_A$; 2-$H_B$; 7-$H_B$; 9-$H_{A,B}$; 10-$H_{A,B}$), 1.46 – 1.30 (1.2H, m, 1-$H_B$), 1.21 (1.5H, d, *J* = 7.0, isopropyl C$H_{3A}$), 1.18 (1.5H, d, *J* = 7.0, isopropyl C$H_{3B}$), 1.07 (1.5H, d, *J* = 7.0, isopropyl C$H_{3B}$), 1.01 (1.5H, d, *J* = 7.0, isopropyl C$H_{3A}$). **$^{13}$C NMR** (Minor diastereomer, 125 MHz, $CDCl_3$): δ ppm 164.5 (amide *C*=O), 163.0/162.9 (5-*C*), 158.9/158.0 (*Ar*), 150.1/149.9 (*Ar*H), 107.5/105.6 (*Ar*H), 64.8/64.6 (10a-*C*), 57.5/57.1 (6a-*C*), 48.8/48.3 (8-*C*), 44.5 (isopropyl *C*H), 44.1 (3-*C*), 37.4/37.2 (1-*C*), 33.4/28.3 (N*C*$H_3$), 30.3/28.5 (7-*C*), 27.7/27.5 (10-*C*), 23.6/23.5 (9-*C*), 22.9 (2-*C*), 21.9/21.4 (isopropyl *C*$H_{3A}$), 19.3 (isopropyl *C*$H_{3B}$). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3100, 2927 (C-H), 1686, 1642 (C=O), 1576, 1460 (C=C), 1245 (C-O). **HRMS** (ESI): $C_{18}H_{27}N_4O_3$ [M + H$^+$]: calculated 347.2078, found 347.2072.

(6a*R**,8*R**,10a*S**)-8-Hydoxy-6-isopropyl-8-phenyloctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **174**




To a solution of the ketone **101a** (19.0 mg, 0.08 mmol, 1.0 eq.) in 4 mL THF at -78 °C, 1.9 M PhLi in diethyl ether (0.17 mL, 0.32 mmol, 4.0 eq.) was added and stirred at the same temperature for 4.5 h after which it was left to warm up to room temperature overnight. 0.10 mL of saturated aqueous ammonia and 0.9 mL of saturated aqueous ammonium chloride were added and allowed to stir for 20 min. The reaction mixture was diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 - 3% MeOH in DCM afforded the product **174** as a single diastereomer (15.0 mg, 0.05 mmol, 59% yield). $\mathbf{R_f}$ = 0.36 (5% MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.43 (2H, dt, *J* = 8.0, 2.0, Ar*H*), 7.33 (2H, tt, *J* = 7.5, 2.0, Ar*H*), 7.24 (1H, tt, *J* = 7.5, 2.0, Ar*H*), 3.96 (1H, hept, *J* = 6.9, isopropyl C*H*), 3.75 (1H, ddd, *J* = 12.2, 9.1, 5.7, 3-$H_A$), 3.55 (1H, dd, *J* = 8.9, 5.6, 6a-*H*), 2.92 (1H, ddd, *J* = 12.2, 9.2, 5.6, 3-$H_B$), 2.55 (1H, ddd, *J* = 14.0, 5.5, 1.3, 7-$H_A$), 2.26 (1H, s, 8-CO*H*), 2.11 – 2.03 (1H, m, 9-$H_A$), 1.99 – 1.91 (2H, m, 7-$H_B$, 9-$H_B$), 1.81 (1H, ddd, *J* = 14.5, 6.5, 3.5, 10-$H_A$), 1.79 – 1.67 (2H, m, 2-$H_{A,B}$), 1.46 (1H, ddd, *J* = 12.0, 8.0, 3.0, 1-$H_A$), 1.35 (1H, dt, *J* = 12.0, 10.0, 1-$H_B$), 1.28 (1H, ddd, *J* = 14.7, 9.2, 3.8, 10-$H_B$), 1.22 (3H, d, *J* = 6.8, isopropyl C$H_{3A}$), 1.18 (3H, d, *J* = 6.9, isopropyl C$H_{3B}$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 163.4 (5-*C*), 145.7 (*Ar*), 128.8 (*Ar*H), 127.6 (*Ar*H), 125.2 (*Ar*H), 72.2 (8-*C*), 65.4 (10a-*C*), 55.6 (6a-*C*), 44.7 (isopropyl *C*H), 44.0 (3-*C*), 42.7 (7-*C*), 35.2 (1-*C*), 35.1 (9-*C*), 28.6 (10-*C*), 23.2 (2-*C*), 22.0 (isopropyl *C*$H_{3A}$), 19.9 (isopropyl *C*$H_{3B}$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3388 (O-H), 2964 (C-H), 1673 (C=O), 1447 (C=C), 1052 (C-O). **HRMS** (ESI): $C_{19}H_{27}N_2O_2$ [M + $H^+$]: calculated 315.2067, found 315.2061.

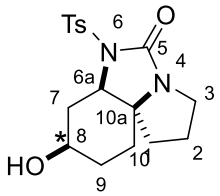
(6a*R**,8*R**,10a*S**)-8-Hydroxy-6-(4-methoxyphenyl)octahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **160b**




**Major diastereomer, *dr* 85:15**

A mixture of the ketone **101b** (30.0 mg, 0.10 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (44.7 mg, 0.12 mmol, 1.2 eq.) in 3 mL of HPLC grade MeOH was allowed to stir at –78 °C for 30 min. $NaBH_4$ (4.54 mg, 0.12 mmol, 1.2 eq.) was then added and the mixture was left to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 3% MeOH in DCM afforded the product **160b** as an 85:15 mixture of diastereomers (29.0 mg, 0.10 mmol, 96% yield). $\mathbf{R_f}$ = 0.37 (4% MeOH in DCM). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 7.27 (2H, d, *J* = 9.0, Ar*H*), 6.80 (2H, d, *J* = 9.5, Ar*H*), 3.96 (1H, dd, *J* = 9.5, 6.2, 6a-*H*), 3.85 (1H, ddd, *J* = 12.3, 9.0, 5.5, 3-$H_A$), 3.72 (3H, s, ArOC$H_3$), 3.65 (1H, qd, *J* = 9.0, 4.3, 8-*H*), 2.99 (1H, ddd, *J* =12.0, 6.0, 3.0, 3-$H_B$), 2.24 (1H, dddd, *J* = 12.7, 6.2, 4.5, 1.9, 7-$H_A$), 1.91 (1H, dt, *J* = 14.5, 4.0, 10-$H_A$), 1.89 – 1.73 (6H, m, 1-$H_{A,B}$; 2-$H_{A,B}$; 8-CHO*H*; 9-$H_A$), 1.49 (1H, tdd, *J* = 12.9, 9.4, 3.6, 9-$H_B$), 1.41 – 1.36 (1H, m, 7-$H_B$), 1.36 – 1.31 (1H, m, 10-$H_B$). Signals for minor isomer visible at: 4.15 (0.17H, dd, *J* = 6.5, 5.5, 6a-*H*), 4.03 (0.18H, quint, *J* = 5.5, 8-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 162.0 (5-*C*), 156.4 (*Ar*), 131.4 (*Ar*), 123.4 (*Ar*H), 114.4 (*Ar*H), 69.9 (8-*C*), 64.4 (10a-*C*), 58.4 (6a-*C*), 55.5 (ArOC$H_3$), 44.3 (3-*C*), 38.0 (7-*C*), 35.4 (1-*C*), 30.5 (9-*C*), 29.0 (10-*C*), 23.2 (2-*C*). Signals for minor isomer visible at: 64.6, 64.0, 57.7, 36.3, 33.9, 28.4, 26.6, 23.7. **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3398 (O-H), 2934 (C-H), 1674 (C=O), 1582, 1510, 1462 (C=C), 1244 (C-O). **HRMS** (ESI): $C_{17}H_{23}N_2O_3$ [M + H$^+$]: calculated 303.1703, found 303.1698.

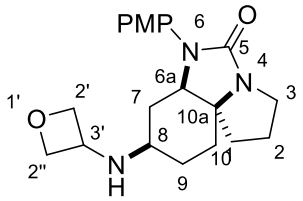
(6a*R**,8*R**,10a*S**)-8-Hydroxy-6-(4-toluenesulfonyl)octahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **160c**




**Major diastereomer, *dr* 78:22**

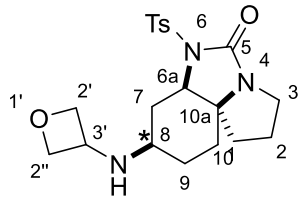
A mixture of the ketone **101c** (18.0 mg, 0.05 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (23.2 mg, 0.06 mmol, 1.2 eq.) in 3 mL of HPLC grade MeOH was allowed to stir at –78 °C for 30 min. $NaBH_4$ (2.40 mg, 0.06 mmol, 1.2 eq.) was then added and the mixture was left to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 2% MeOH in DCM afforded the product **160c** as a 78:22 mixture of diastereomers (15.0 mg, 0.04 mmol, 83% yield). $\mathbf{R_f}$ = 0.44 (4% MeOH in DCM). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 7.87 (2H, d, *J* = 8.5, Ar*H*), 7.24 (2H, d, *J* = 8.5, Ar*H*), 4.17 (1H, dd, *J* = 10.0, 6.4, 6a-*H*), 3.74 – 3.61 (2H, m, 8-*H*, 3-$H_A$), 2.89 (1H, ddd, *J* =12.1, 9.4, 5.7, 3-$H_B$), 2.67 (1H, dddd, *J* = 12.8, 6.4, 4.5, 1.9, 7-$H_A$), 2.35 (3H, s, ArC$H_3$), 1.86 – 1.70 (4H, m, 2-$H_{A,B}$; 9-$H_A$, 10-$H_A$), 1.60 – 1.24 (6H, m, 1-$H_{A,B}$; 7-$H_B$; 8-CHO*H*; 9-$H_B$; 10-$H_B$). Signals for minor isomer visible at: 4.29 (0.29H, dd, *J* = 8.0, 5.5, 6a-*H*), 4.09 (0.29H, quint, *J* = 5.0, 8-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 158.4 (5-*C*), 144.8 (*Ar*), 136.2 (*Ar*), 129.6 (*Ar*H), 128.2 (*Ar*H), 66.4 (8-*C*), 65.1 (10a-*C*), 57.7 (6a-*C*), 44.0 (3-*C*), 39.4 (7-*C*), 34.4 (1-*C*), 30.0 (9-*C*), 28.2 (10-*C*), 22.9 (2-*C*), 21.7 (ArC$H_3$). Signals for minor isomer visible at: 158.1, 144.7, 136.1, 129.5, 128.1, 65.4, 63.9, 57.3, 43.8, 36.7, 35.2, 27.6, 25.3, 23.0. **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3388 (O-H), 2922, 2852 (C-H), 1727 (C=O), 1658, 1597 (C=C), 1161 (C-O). **HRMS** (ESI): $C_{17}H_{23}N_2O_4S$ [M + H$^+$]: calculated 351.1373, found 351.1369.

(6a*R**,8*R**,10a*S**)-6-(4-Methoxyphenyl)-8-(oxetan-3-ylamino)octahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **175b**




To a solution of the ketone **101b** (19.0 mg, 0.06 mmol, 1.0 eq.) in 6 mL THF, 3-aminooxetane (5.30 µL, 0.08 mmol, 1.2 eq.) and titanium isopropoxide (0.04 mL, 0.13 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (2.88 mg, 0.08 mmol, 1.2 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 1 h. It was then allowed to warm up to room temperature for 4 h. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 2 - 4% MeOH in DCM afforded the product **175b** as a single diastereomer (13.0 mg, 0.04 mmol, 58% yield). $\mathbf{R_f}$ = 0.37. **$^1$H NMR** (400 MHz, $CDCl_3$): δ ppm 7.27 (2H, d, *J* = 8.8, Ar*H*), 6.81 (2H, d, *J* = 9.2, Ar*H*), 4.71 (1H, t, *J* = 6.4, 2'-$H_A$), 4.66 (1H, t, *J* = 6.8, 2''-$H_A$), 4.29 (1H, t, *J* = 6.4, 2'-$H_B$), 4.23 (1H, t, *J* = 6.4, 2''-$H_B$), 3.98 – 3.89 (2H, m, 6a-*H*, 3'-*H*), 3.85 (1H, ddd, *J* = 12.4, 9.0, 5.7, 3-$H_A$), 3.73 (3H, s, ArOC$H_3$), 2.98 (1H, ddd, *J* = 12.3, 9.1, 5.9, 3-$H_B$), 2.47 (1H, tt, *J* = 14.6, 4.0, 8-*H*), 2.09 (1H, dddd, *J* =10.1, 5.9, 4.0, 1.9, 7-$H_A$), 1.95 – 1.73 (3H, m, 2-$H_{A,B}$; 10-$H_A$), 1.70 – 1.54 (3H, m, 1-$H_{A,B}$; 9-$H_A$), 1.37 – 1.21 (2H, m, 9-$H_B$, 10-$H_B$), 1.21 – 1.13 (1H, m, 7-$H_B$). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ ppm 162.0 (5-*C*), 156.4 (*Ar*), 131.4 (*Ar*), 123.3 (*Ar*H), 114.4 (*Ar*H), 80.8 (2'-*C*), 80.3 (2''-*C*), 64.7 (10a-*C*), 58.2 (6a-*C*), 55.5 (ArO*C*$H_3$), 51.8 (8-*C*), 51.4 (3'-*C*), 44.3 (3-*C*), 36.6 (7-*C*), 35.4 (1-*C*), 29.8 (10-*C*), 28.8 (9-*C*), 23.2 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3296 (N-H), 2933, 2864 (C-H), 1691 (C=O), 1511, 1462, 1395 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{20}H_{28}N_3O_3$ [M + H$^+$]: calculated 358.2125, found 358.2128.

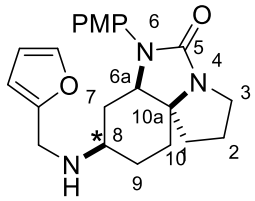
(6a*R**,8*R**,10a*S**)-8-(Oxetan-3-ylamino)-6-(4-toluenesulfonyl)octahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **175c**




**Major diastereomer, *dr* 85:15**

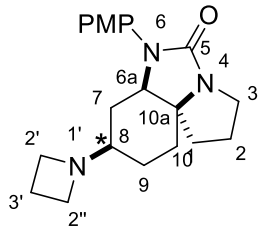
To a solution of the ketone **101c** (55.0 mg, 0.16 mmol, 1.0 eq.) in 6 mL THF, 3-aminooxetane (22.0 µL, 0.32 mmol, 2.0 eq.) and titanium isopropoxide (0.10 mL, 0.32 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (9.10 mg, 0.24 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 2 h. It was then allowed to warm up to room temperature for 1 h. The reaction mixture was evaporated *in vacuo*. It was then taken up in 2 mL $H_2O$, diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 - 2% MeOH in DCM afforded the product as an 85:15 mixture of diastereomers (26.0 mg, 0.06 mmol, 41% yield). $\mathbf{R_f}$ = 0.38. **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 7.86 (2H, d, *J* = 8.5, Ar*H*), 7.25 (2H, d, *J* = 8.0, Ar*H*), 4.77 (1H, t, *J* = 7.0, 2'-$H_A$), 4.74 (1H, t, *J* = 6.5, 2''-$H_A$), 4.32 (1H, t, *J* = 6.5, 2'-$H_B$), 4.30 (1H, t, *J* = 6.5, 2''-$H_B$), 4.15 (1H, dd, *J* = 10.3, 6.2, 6a-*H*), 3.97 (1H, quint, *J* = 6.7, 3'-*H*), 3.70 (1H, ddd, *J* = 12.4, 9.1, 5.6, 3-$H_A$), 2.86 (1H, ddd, *J* = 12.0, 6.5, 3.0, 3-$H_B$), 2.54 – 2.45 (2H, m, 7-$H_A$, 8-*H*), 2.36 (3H, s, ArC$H_3$), 1.81 (1H, dt, *J* =15.0, 4.0, 10-$H_A$), 1.78 – 1.70 (2H, m, 2-$H_{A,B}$), 1.59 – 1.08 (7H, m, 1-$H_{A,B}$; 7-$H_B$; 8-CHN*H*; 9-$H_{A,B}$; 10-$H_B$). Signals for minor isomer visible at: 4.21 (0.17H, t, *J* = 6.0, 6a-*H*), 3.88 (0.18H, quint, *J* = 6.5, 3'-*H*), 3.61 (0.20H, dt, *J* = 12.0, 7.6, 3-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 158.5 (5-*C*), 144.8 (*Ar*), 136.3 (*Ar*), 129.6 (*Ar*H), 128.1 (*Ar*H), 80.6 (2'-*C*), 80.5 (2''-*C*), 65.4 (10a-*C*), 57.6 (6a-*C*), 51.6 (8-*C*), 51.5 (3'-*C*), 44.0 (3-*C*), 38.3 (7-*C*), 34.4 (1-*C*), 29.0 (10-*C*), 28.2 (9-*C*), 22.8 (2-*C*), 21.7 (Ar*C*$H_3$). Signals for minor isomer visible at: 157.6, 144.7, 136.2, 128.0, 80.3, 80.0, 65.5, 58.5, 51.4, 47.0, 43.7, 35.5, 33.8, 26.0, 23.2. **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3303 (N-H), 2946, 2867 (C-H), 1727 (C=O), 1596, 1494, 1461 (C=C), 1168 (C-O). **HRMS** (ESI): $C_{20}H_{28}N_3O_4S$ [M + H$^+$]: calculated 405.1795, found 405.1802.

(6a*R**,8*R**,10a*S**)-8-[(Furan-2-ylmethyl)amino]-6-(4-methoxyphenyl)octahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **176**




To a solution of the ketone **101b** (40.0 mg, 0.13 mmol, 1.0 eq.) in 6 mL THF, 3-aminooxetane (14.1 µL, 0.16 mmol, 1.2 eq.) and titanium isopropoxide (0.08 mL, 0.27 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (6.05 mg, 0.16 mmol, 1.2 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 1 h. It was then allowed to warm up to room temperature overnight. The reaction mixture was evaporated *in vacuo*. It was then taken up in 2 mL $H_2O$, diluted with 100 mL DCM, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 - 3% MeOH in DCM afforded the product **176** as a single diastereomer (45.7 mg, 0.90 mmol, 90% yield). $\mathbf{R_f}$ = 0.42 (5% MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.27 (2H, d, *J* = 9.0, Ar*H*), 7.25 (1H, dd, *J* = 2.0, 0.5, Ar*H*), 6.80 (2H, d, *J* = 9.0, Ar*H*), 6.21 (1H, dd, *J* = 3.0, 2.0, Ar*H*), 6.04 (1H, dd, *J* = 3.0, 0.5, Ar*H*), 3.93 (1H, dd, *J* = 10.1, 6.2, 6a-*H*), 3.84 (1H, ddd, *J* = 12.3, 9.0, 5.5, 3-$H_A$), 3.72 (3H, s, ArOC$H_3$), 3.67 (2H, d, *J* = 1.5, ArC$H_{2A,B}$), 2.98 (1H, ddd, *J* = 12.3, 9.2, 5.8, 3-$H_B$), 2.51 (1H, qd, *J* = 8.6, 4.0, 8-*H*), 2.17 (1H, dddd, *J* = 12.5, 8.0, 6.0, 2.0, 7-$H_A$), 1.93 – 1.55 (6H, m, 1-$H_{A,B}$; 2-$H_{A,B}$; 9-$H_A$; 10-$H_A$), 1.37 – 1.25 (3H, m, 8-CHN*H*, 9-$H_B$; 10-$H_B$), 1.24 – 1.18 (1H, m, 7-$H_B$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 162.0 (5-*C*), 156.3 (*Ar*) 153.8 (*Ar*), 141.8 (*Ar*H), 131.6 (*Ar*), 123.4 (*Ar*H), 114.3 (*Ar*H), 110.1 (*Ar*H), 106.7 (*Ar*H), 64.9 (10a-*C*), 58.4 (6a-*C*), 55.5 (ArO*C*H$_3$), 51.9 (8-*C*), 44.3 (3-*C*), 43.3 (Ar*C*H$_2$) 36.0 (7-*C*), 35.4 (1-*C*), 29.7 (10-*C*), 28.0 (9-*C*), 23.2 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3315 (N-H), 2925, 2854 (C-H), 1692 (C=O), 1511, 1462, 1394 (C=C), 1245 (C-O). **HRMS** (ESI): $C_{22}H_{28}N_3O_3$ [M + H$^+$]: calculated 382.2125, found 382.2125.

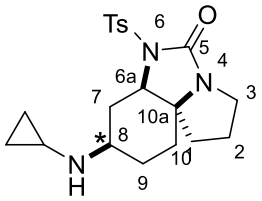
(6a*R**,8*R**,10a*S**)-8-(Azetidin-1-yl)-6-(4-methoxyphenyl)octahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **177**




**Major diastereomer, *dr* 95:5**

To a solution of the ketone **101b** (20.0 mg, 0.07 mmol, 1.0 eq.) in 6 mL THF, azetidine (14.1 µL, 0.21 mmol, 3.0 eq.) and titanium isopropoxide (0.04 mL, 0.14 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. Sodium triacetoxyborohydride (29.7 mg, 0.14 mmol, 2.0 eq.) was added to the reaction mixture at -78 °C and it was allowed to warm up to room temperature overnight. 1 mL of saturated aqueous $Na_2CO_3$ was added. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 3 - 10% MeOH in DCM afforded the product **177** as a 95:5 mixture of diastereomers (10.0 mg, 0.03 mmol, 44% yield). $\mathbf{R_f}$ = 0.14 (10% MeOH in DCM). **$^1$H NMR** ( Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 7.27 (2H, d, *J* = 9.0, Ar*H*), 6.81 (2H, d, *J* = 9.0, Ar*H*), 3.88 (1H, dd, *J* = 10.7, 6.2, 6a-*H*), 3.83 (1H, ddd, *J* = 12.0, 7.0, 3.5, 3-$H_A$), 3.72 (3H, s, ArOC$H_3$), 3.09 (4H, sext, *J* = 7.0, 2'-$H_{A,B}$; 2''-$H_{A,B}$), 2.97 (1H, ddd, *J* = 12.3, 9.3, 5.7, 3-$H_B$), 2.06 – 1.98 (2H, m, 7-$H_A$, 8-*H*), 1.94 (2H, t, *J* = 7.0, 3'-$H_{A,B}$), 1.92 – 1.74 (2H, m, 2-$H_{A,B}$), 1.66 – 1.49 (3H, m, 9-$H_A$, 10-$H_{A,B}$), 1.30 (1H, aptd, *J* = 11.5, 3.5, 1-$H_A$), 1.23 – 1.12 (2H, m, 1-$H_B$, 9-$H_B$), 1.05 (1H, q, *J* = 11.0, 7-$H_B$). Signal for minor isomer visible at: 4.15 (0.05H, t, *J* = 5.0, 6a-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 162.0 (5-*C*), 156.4 (*Ar*) 131.5 (*Ar*), 123.6 (*Ar*H), 114.3 (*Ar*H), 64.8 (10a-*C*), 62.5 (8-*C*), 58.0 (6a-*C*), 55.5 (ArO*C*$H_3$), 53.2 (2'/2''-*C*), 44.2 (3-*C*), 35.3 (10-*C*), 32.5 (7-*C*), 29.2 (1-*C*), 24.3 (9-*C*), 23.0 (2-*C*), 17.0 (3'-*C*). Signals for minor isomer visible at: δ ppm 62.3, 58.3, 32.9, 26.9, 23.7. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2932, 2833 (C-H), 1692 (C=O), 1511, 1462, 1441 (C=C), 1244 (C-O). **HRMS** (ESI): $C_{20}H_{28}N_3O_2$ [M + $H^+$]: calculated 342.2176, found 342.2173.

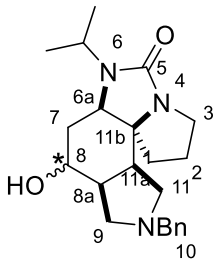
(6a*R**,8*R**,10a*S**)-8-(Cyclopropylamino)-6-tosyloctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazol-5-one **178**




**Major diastereomer, *dr* 87:13**

To a solution of the ketone **101c** (24.0 mg, 0.07 mmol, 1.0 eq.) in 4 mL THF, cyclopropylamine (24.0 µL, 0.34 mmol, 5.0 eq.) and titanium isopropoxide (0.04 mL, 0.14 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (3.90 mg, 0.10 mmol, 1.5 eq.) was then added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in* vacuo. It was then taken up in 1 mL $H_2O$, diluted with 50 mL DCM, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 4% MeOH in DCM afforded the product as a diastereomeric mixture in the ratio of 87:13 (12.0 mg, 0.03 mmol, 45% yield). $\mathbf{R_f}$ = 0.41 (6% MeOH in DCM). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 7.86 (2H, d, *J* = 8.5, Ar*H*), 7.24 (2H, d, *J* = 9.0, Ar*H*), 4.19 (1H, dd, *J* = 10.3, 6.4, 6a-*H*), 3.70 (1H, ddd, *J* = 12.5, 8.8, 6.0, 3-$H_A$), 2.91 – 2.73 (3H, m, 3-$H_B$, 7-$H_A$, 8-*H*), 2.35 (3H, s, ArC$H_3$), 2.15 (1H, quint, *J* = 5.0, cyclopropyl C*H*), 1.87 – 1.69 (5H, m, 2-$H_{A,B}$; 9-$H_A$; 10-$H_{A,B}$), 1.52 (1H, ddd, *J* = 12.0, 7.2, 2.6, 1-$H_A$), 1.38 – 1.29 (3H, m, 1-$H_B$, 7-$H_B$, 9-$H_B$), 0.65 – 0.40 (4H, m, cyclopropyl C$H_{2A,B,C,D}$). Signals for minor isomer visible at: 7.91 (0.32H, d, *J* = 8.5, Ar*H*), 4.36 (0.15H, t, 5.0, 6a-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 157.4 (5-*C*), 143.8 (*Ar*), 135.2 (*Ar*), 128.5 (*Ar*H), 127.2 (*Ar*H), 64.4 (10a-*C*), 56.6 (6a-*C*), 52.5 (8-*C*), 42.9 (3-*C*), 35.7 (7-*C*), 33.4 (1-*C*), 27.9 (9-*C*), 26.8 (cyclopropyl *C*H), 24.9 (10-*C*), 21.7 (2-*C*), 20.6 (Ar*C*$H_3$), 5.0 (cyclopropyl *C*$H_{2A,B}$), 4.6 (cyclopropyl *C*$H_{2C,D}$). Signals for minor isomer visible at: 64.0, 57.3, 52.4, 42.6, 34.6, 29.9, 28.6, 27.7. **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3274 (N-H), 2939, 2868 (C-H), 1726 (C=O), 1597, 1494, 1446 (C=C). **HRMS** (ESI): $C_{20}H_{28}N_3O_3S$ [M + H$^+$]: calculated 390.1846, found 390.1852.

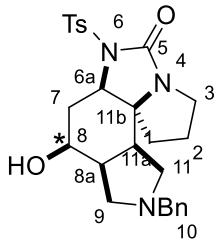
(6a*R**,8a*S**,11a*R**,11b*S**)-10-Benzyl-8-hydroxy-6-isopropyldecahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindol-5(6*H*)-one




***dr* 3:2**

A mixture of the pyrrolidine **109** (17.0 mg, 0.04 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (20.7 mg, 0.06 mmol, 1.2 eq.) in 3 mL of HPLC grade MeOH was allowed to stir at rt for 30 min. The temperature was lowered to –78 °C and $NaBH_4$ (2.10 mg, 0.06 mmol, 1.2 eq.) was then added and the mixture was left to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 5 – 10% MeOH in DCM afforded the product as a 3:2 mixture of diastereomers (10.0 mg, 0.03 mmol, 58% yield). $\mathbf{R_f}$ = 0.26 (10% MeOH in DCM). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 3.99 (1H, hept, *J* = 7.0, 17-*H*). **$^1$H NMR** (Minor diastereomer, 500 MHz, $CDCl_3$): δ ppm 3.89 (0.7H, hept, *J* = 7.0, 17'-*H*). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 163.2, 161.3, 128.3, 127.9, 127.9, 127.8, 127.5, 127.4, 127.3, 126.3, 65.6, 65.3, 63.1, 62.1, 59.5, 59.3, 59.1, 57.2, 56.7, 53.9, 53.3, 50.8, 47.3, 44.3, 43.8, 43.4, 43.3, 41.8, 40.2, 39.4, 37.5, 36.1, 35.7, 33.4, 23.9, 23.7, 21.0, 20.4, 18.2, 17.9. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3364 (O-H), 2965, 2923 (C-H), 1671 (C=O), 1453, 1418, 1380 (C=C), 1072 (C-O). **HRMS** (ESI): $C_{22}H_{32}N_3O_2$ [M + $H^+$]: calculated 370.2489, found 370.2485.

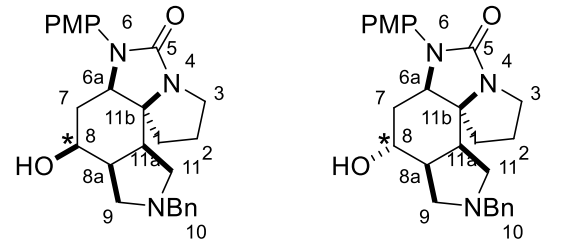
(6a*R**,8*S**,8a*S**,11a*R**,11b*S**)-10-Benzyl-8-hydroxy-6-isopropyldecahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindol-5(6*H*)-one **180**




To a solution of the pyrrolidine **110** (16.0 mg, 0.03 mmol, 1.0 eq.) in 4 mL THF at -78 °C, LS-selectride (37.0 µL, 0.04 mmol, 1.1 eq.) was added and the mixture was allowed to stir for 1 h. The reaction mixture was quenched with 0.01 mL of 10% KOH and 0.01 mL $H_2O$. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 3 – 7% MeOH in DCM afforded the product as a single diastereomer (6.0 mg, 0.01 mmol, 37% yield). $\mathbf{R_f}$ = 0.37 (8% MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.89 (2H, d, *J* = 8.3, Ar*H*), 7.29 – 7.20 (7H, m, Ar*H*), 4.09 (1H, dd, *J* = 10.5, 5.4, 6a-*H*), 3.77 (1H, dt, *J* = 9.3, 5.6, 8-*H*), 3.70 (1H, d, *J* = 13.5, ArC$H_{2A}$), 3.65 (1H, ddd, *J* = 12.5, 6.0, 2.5, 3-$H_A$), 3.62 (1H, d, *J* = 13.0, ArC$H_{2B}$), 2.96 – 2.89 (1H, m, 11-$H_A$), 2.88 – 2.78 (3H, m, 3-$H_B$, 9-$H_{A,B}$), 2.44 – 2.38 (1H, m, 7-$H_A$), 2.36 (3H, s, ArC$H_3$), 2.32 (1H, dd, *J* = 10.6, 8.5, 11-$H_B$), 2.18 (1H, ddd, *J* = 14.0, 9.5, 5.5, 7-$H_B$), 2.16 – 2.11 (1H, m, 8a-*H*), 1.95 – 1.88 (2H, m, 11a-*H*, 8-CHO*H*), 1.78 (1H, ddd, *J* = 12.2, 7.5, 4.6, 1-$H_A$), 1.72 – 1.64 (2H, m, 2-$H_{A,B}$), 1.55 (1H, ddd, *J* = 12.0, 4.5, 2.0, 1-$H_B$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 157.5 (5-*C*), 143.9 (*Ar*), 138.0 (*Ar*, **missing – observed through the HMBC of ArC$H_{2A,B}$**), 134.2 (*Ar*), 128.5 (*Ar*H), 127.8 (*Ar*H), 127.5 (*Ar*H), 127.4 (*Ar*H), 126.4 (*Ar*H), 69.5 (8-*C*), 65.8 (11b-*C*), 61.0 (6a-*C*), 59.8 (Ar*C*$H_2$), 55.0 (9-*C*), 53.0 (11-*C*), 46.9 (11a-*C*), 46.7 (3-*C*), 43.4 (8a-*C*), 36.3 (7-*C*), 35.5 (1-*C*), 23.5 (2-*C*), 20.7 (Ar*C*$H_3$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3399 (O-H), 3030, 2923 (C-H), 1729 (C=O), 1596, 1494, 1453 (C=C), 1169 (C-O). **HRMS** (ESI): $C_{26}H_{32}N_3O_4S$ [M + $H^+$]: calculated 482.2108, found 482.2108.

(6a*R**,8*S**,8a*S**,11a*R**,11b*S**)-10-Benzyl-8-hydroxy-6-(4-methoxyphenyl)decahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindol-5(6*H*)-one **182**

(6a*R**,8*R**,8a*S**,11a*R**,11b*S**)-10-Benzyl-8-hydroxy-6-(4-methoxyphenyl)decahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindol-5(6*H*)-one **183**



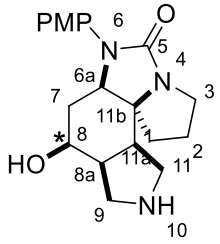

**182**
**Major diastereomer**

**183**
**Minor diastereomer**

To a solution of the pyrrolidine **107** (26.0 mg, 0.06 mmol, 1.0 eq.) in 4 mL THF at -78 °C, LS-selectride (66.0 µL, 0.07 mmol, 1.1 eq.) was added and the mixture was allowed to stir for 1 h. The reaction mixture was quenched with 0.01 mL of 10% KOH and 0.01 mL $H_2O$. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 7% MeOH in DCM afforded the products **182** [7.6 mg, 0.02 mmol, 29% yield, $\mathbf{R_f}$ = 0.39 (7% MeOH in DCM)] and **183** [1.7 mg, 3.92 µmol, 7% yield, $\mathbf{R_f}$ = 0.42 (7% MeOH in DCM)]. **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 7.36 (2H, d, *J* = 9.0, Ar*H*), 7.34 – 7.27 (5H, m, Ar*H*), 6.88 (2H, d, *J* = 9.0, Ar*H*), 4.30 (1H, t, *J* = 5.0, 6a-*H*), 4.24 (1H, ddd, *J* = 9.6, 5.2, 2.8, 8-*H*), 3.89 (1H, ddd, *J* = 12.4, 9.4, 5.7, 3-$H_A$), 3.79 (3H, s, ArOC$H_3$), 3.73 (1H, d, *J* = 13.0, ArC$H_{2A}$), 3.66 (1H, d, *J* = 12.5, ArC$H_{2B}$), 3.09 (1H, ddd, *J* = 12.5, 8.0, 3.0, 3-$H_B$), 3.00 – 2.81 (2H, m, 9-$H_{A,B}$), 2.79 (1H, t, *J* = 9.0, 11-$H_A$), 2.66 (1H, q, *J* = 9.0, 11a-*H*), 2.63 – 2.57 (1H, m, 8a-*H*), 2.49 – 2.39 (1H, m, 11-$H_B$), 2.19 (1H, ddd, *J* = 14.6, 9.8, 5.1, 7-$H_A$), 1.97 – 1.74 (4H, m, 1-$H_A$; 2-$H_{A,B}$; 8-CHO*H*), 1.64 – 1.62 (1H, m, 7-$H_B$), 1.57 – 1.53 (1H, m, 1-$H_B$). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 168.8 (5-*C*), 160.4 (*Ar*), 155.3 (*Ar*), 130.0 (*Ar*), 127.7 (*Ar*H), 127.5 (*Ar*H), 126.3 (*Ar*H), 122.2 (*Ar*H), 113.4 (*Ar*H), 64.6 (11b-*C*), 64.4 (8-*C*), 59.2 (Ar*C*H$_2$), 55.4 (11-*C*), 55.2 (9-*C*), 55.1 (6a-*C*), 54.5 (ArO*C*H$_3$), 43.2 (3-*C*), 39.0 (11a-*C*), 38.3 (8a-*C*), 32.9 (1-*C*), 31.1 (7-*C*), 22.2 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3399 (O-H), 2927, 2834, 2800 (C-H), 1688 (C=O), 1611, 1584, 1511 (C=C), 1245 (C-O). **HRMS** (ESI): $C_{26}H_{32}N_3O_3$ [M + H$^+$]: calculated 434.2438, found 434.2438. **$^1$H NMR** (Minor

diastereomer, 500 MHz, $CDCl_3$): δ ppm 7.29 -7.23 (7H, m, Ar*H*), 6.83 (2H, d, *J* = 9.0, Ar*H*), 4.12 (1H, dd, *J* = 5.8, 3.7, 6a-*H*), 3.87 (1H, ddd, *J* = 12.3, 9.2, 5.6, 3-$H_A$), 3.73 (3H, s, ArOC$H_3$), 3.66 – 3.46 (3H, m, 8-*H*, ArC$H_{2A,B}$), 3.10 – 3.01 (2H, m, 3-$H_B$, 9-$H_A$), 2.85 (1H, br.s, 8-CHO*H*), 2.77 (1H, t, *J* = 9.0, 11-$H_A$), 2.64 (1H, q, *J* = 9.0, 11a-*H*), 2.45 (1H, q, *J* = 9.0, 8a-*H*), 2.30 – 2.09 (2H, m, 9-$H_B$, 11-$H_B$), 1.98 – 1.71 (5H, m, 1-$H_A$; 2-$H_{A,B}$; 7-$H_{A,B}$;), 1.63 – 1.57 (1H, m, 1-$H_B$). **No good $^{13}$C NMR due to sample size but 183 was prepared for biology. IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3358 (O-H), 2956, 2922, 2851 (C-H), 1684 (C=O), 1585, 1513, 1454 (C=C), 1247 (C-O). **HRMS** (ESI): $C_{26}H_{31}N_3O_3$ [M + $H^+$]: calculated 434.2438, found 434.2435.

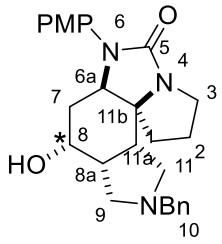
(6a*R**,8*S**,8a*S**,11a*R**,11b*S**)-8-Hydroxy-6-(4-methoxyphenyl)decahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindol-5(6*H*)-one **182**




To a solution of the pyrrolidine **107** (52.0 mg, 0.12 mmol, 1.0 eq.) in 4 mL THF at -78 °C, LS-selectride (0.13 mL, 0.13 mmol, 1.1 eq.) was added and the mixture was allowed to stir for 1 h. The reaction mixture was quenched with 0.01 mL of 10% KOH and 0.01 mL $H_2O$. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a mixture of the crude and $Pd(OH)_2$/C (in excess to form a slurry) under nitrogen, 10 mL of HPLC grade MeOH was added gently. The reaction mixture was degassed and hydrogen gas was bubbled through it with the aid of a balloon, and this procedure was repeated twice. The mixture was then allowed to stir under a balloon of hydrogen overnight at room temperature. The reaction mixture was then filtered through a plug of Celite washing with 100 mL MeOH and evaporated *in vacuo*. Flash chromatography eluting with 5 - 15% of saturated $NH_3$/MeOH in DCM afforded the product **184** as a single diastereomer (11 mg, 0.03 mmol, 27%). $\mathbf{R_f}$ = 0.44 (15% of saturated $NH_3$/MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.31 (2H, d, *J* = 9.0, Ar*H*), 6.82 (2H, d, *J* =

9.5, Ar*H*), 4.26 (1H, t, *J* = 5.3, 6a-*H*), 4.19 (1H, dt, *J* = 8.5, 4.5, 8-*H*), 3.86 (1H, ddd, *J* = 12.5, 9.5, 5.8, 3-$H_A$), 3.73 (3H, s, ArOC$H_3$), 3.27 – 3.13 (3H, m, 9-$H_{A,B}$; 11-$H_A$), 3.06 (1H, ddd, *J* = 12.0, 4.5, 3.0, 3-$H_B$), 2.75 (1H, t, *J* = 9.8, 11-$H_B$), 2.53 – 2.43 (3H, m, 8a-*H*, 11a-*H*, 8-CHO*H*), 2.05 (1H, ddd, *J* = 14.0, 8.5, 5.5, 7-$H_A$), 1.97 – 1.73 (4H, m, 1-$H_A$; 2-$H_{A,B}$; 10-N*H*), 1.61 – 1.53 (2H, m, 1-$H_B$, 7-$H_B$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 160.5 (5-*C*), 155.4 (*Ar*), 130.0 (*Ar*), 122.3 (*Ar*H), 113.4 (*Ar*H), 64.6 (8-*C*), 64.4 (11b-*C*), 54.8 (6a-*C*), 54.5 (ArO*C*$H_3$), 48.7 (9-*C*), 48.2 (11-*C*), 43.3 (3-*C*), 40.4 (8a-*C*), 38.8 (11a-*C*), 32.9 (1-*C*), 31.4 (7-*C*), 22.2 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3294 (O-H, N-H), 3051, 2927 (C-H), 1687 (C=O), 1611, 1512, 1461 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{19}H_{26}N_3O_3$ [M + H$^+$]: calculated 344.1969, found 344.1964.

(6a*R*,*8*R**,8a*R*,*11a*S**,11b*S**)-10-Benzyl-8-hydroxy-6-(4-methoxyphenyl)decahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindol-5(6*H*)-one **185**



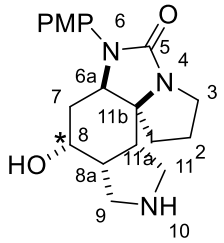

**Major diastereomer, *dr* 3:1**

To a solution of the pyrrolidine **107** (40.0 mg, 0.09 mmol, 1.0 eq.) in 4 mL THF at -78 °C, LS-selectride (0.10 mL, 0.10 mmol, 1.1 eq.) was added and the mixture was allowed to stir for 1 h. The reaction mixture was quenched with 0.01 mL of 10% KOH and 0.01 mL $H_2O$. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 3 – 10% MeOH in DCM afforded the product as a 3:1 mixture of diastereomers (16 mg, 0.04 mmol, 40% yield). **$R_f$** = 0.28 (8% MeOH in DCM). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 7.34 – 7.20 (5H, m, Ar*H*), 7.13 (2H, d, *J* = 9.0, Ar*H*), 6.83 (2H, d, *J* = 9.0, Ar*H*), 4.08 (1H, t, *J* = 4.3, 6a-*H*), 3.71 (3H, s, ArOC$H_3$), 3.65 (1H, d, *J* = 12.9, ArC$H_{2A}$) **No further characterisation because of extensive signal overlap**. Signal for minor isomer visible at: 4.13 (0.35H, t, *J* = 8.5, 6a-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 161.2, 159.3,

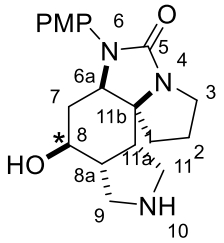
155.9, 155.6, 129.6, 127.8, 127.4, 123.3, 113.5, 69.8, 64.6, 62.0, 60.0, 55.9, 54.5, 52.7, 46.9, 46.8, 43.5, 36.8, 32.8, 24.4. Signals for minor isomer visible at: 155.6, 129.8, 128.0, 127.6, 126.2, 123.2, 113.3, 64.9, 63.2, 61.4, 59.4, 56.8, 54.5, 53.9, 44.6, 43.7, 40.3, 37.9, 31.1, 24.1. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3368 (O-H), 2924 (C-H), 1692 (C=O), 1513, 1454, 1427 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{26}H_{32}N_3O_3$ [M + $H^+$]: calculated 434.2438, found 434.2435.

(6a*R**,8*R**,8a*R**,11a*S**,11b*S**)-8-Hydroxy-6-(4-methoxyphenyl)decahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindol-5(6*H*)-one **186**

(6a*R**,8*S**,8a*R**,11a*S**,11b*S**)-8-Hydroxy-6-(4-methoxyphenyl)decahydro-1*H*-pyrrolo[1',2':3,4]imidazo[4,5-*e*]isoindol-5(6*H*)-one **187**




**186**
**Major diastereomer**

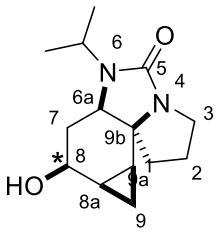



**187**
**Minor diastereomer**

To a solution of the pyrrolidine **108** (39.0 mg, 0.09 mmol, 1.0 eq.) in 4 mL THF at -78 °C, LS-selectride (0.10 mL, 0.10 mmol, 1.1 eq.) was added and allowed to stir for 1 h. The reaction mixture was quenched with 0.01 mL of 10% KOH and 0.01 mL $H_2O$. It was then diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a mixture of the crude and $Pd(OH)_2/C$ (in excess to form a slurry) under nitrogen, 10 mL of HPLC grade MeOH was added gently. The reaction mixture was degassed and hydrogen gas was bubbled through it with the aid of a balloon, and this procedure was repeated twice. The mixture was then allowed to stir under a balloon of hydrogen overnight at room temperature. The reaction mixture was then filtered through a plug of Celite washing with 100 mL MeOH and evaporated *in vacuo*. Flash chromatography eluting with 10 - 15% of saturated $NH_3$/MeOH in DCM afforded the products **186** [9.00 mg, 0.03 mmol, 30% yield, $\mathbf{R_f}$ = 0.24 (20% of saturated $NH_3$/MeOH in DCM)] and **187**

[3.0 mg, 0.01 μmol, 7% yield, $\mathbf{R_f}$ = 0.51 (20% of saturated $NH_3$/MeOH in DCM)]. **$^1$H NMR** (**Major diastereomer**, 500 MHz, $CDCl_3$): δ ppm 7.17 (2H, d, *J* = 9.0, Ar*H*), 6.83 (2H, d, *J* = 9.5, Ar*H*), 4.07 (1H, t, *J* = 4.7, 6a-*H*), 3.81 (1H, ddd, *J* = 10.5, 7.1, 3.4, 3-$H_A$), 3.72 (3H, s, ArOC$H_3$), 3.70 – 3.66 (1H, m, 8-*H*), 3.44 (1H, t, *J* = 10.0, 9-$H_A$), 3.17 – 3.13 (1H, m, 11-$H_A$), 3.04 – 2.92 (2H, m, 3-$H_B$, 8-CHO*H*), 2.81 (1H, t, *J* = 10.2, 11-$H_B$), 2.70 (1H, t, *J* = 10.5, 9-$H_B$), 2.21 – 2.13 (1H, m, 8a-*H*), 2.10 (1H, ddd, *J* = 15.2, 6.2, 4.5, 7-$H_A$), 1.89 – 1.76 (6H, m, 1-$H_{A,B}$; 2-$H_{A,B}$; 7-$H_B$; 11a-*H*). **$^{13}$C NMR** (**Major diastereomer**, 125 MHz, $CDCl_3$): δ ppm 161.6 (5-*C*), 156.0 (*Ar*), 129.6 (*Ar*), 123.6 (*Ar*H), 113.5 (*Ar*H), 68.9 (8-*C*), 64.8 (11b-*C*), 62.0 (6a-*C*), 54.5 (ArO*C*H$_3$), 49.2 (9-*C*), 47.7 (11a-*C*), 47.5 (3-*C*), 45.2 (11-*C*), 45.1 (8a-*C*), 36.8 (1-*C*), 33.7 (7-*C*), 24.2 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3294 (O-H, N-H), 3051, 2927 (C-H), 1687 (C=O), 1611, 1512, 1461 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{19}H_{26}N_3O_3$ [M + H$^+$]: calculated 344.1969, found 344.1964. **$^1$H NMR** (**Minor diastereomer**, 500 MHz, $CDCl_3$): δ ppm 7.31 (2H, d, *J* = 9.0, Ar*H*), 6.82 (2H, d, *J* = 9.5, Ar*H*), 4.26 (1H, t, *J* = 5.3, 6a-*H*), 4.19 (1H, dt, *J* = 8.5, 4.5, 8-*H*), 3.86 (1H, ddd, *J* = 12.5, 9.5, 5.8, 3-$H_A$), 3.73 (3H, s, ArOC$H_3$), 3.27 – 3.13 (3H, m, 9-$H_{A,B}$; 11-$H_A$), 3.06 (1H, ddd, *J* = 12.0, 4.5, 3.0, 3-$H_B$), 2.75 (1H, t, *J* = 9.8, 11-$H_B$), 2.53 – 2.43 (3H, m, 8a-*H*, 11a-*H*, 8-CHO*H*), 2.05 (1H, ddd, *J* = 14.0, 8.5, 5.5, 7-$H_A$), 1.97 – 1.73 (4H, m, 1-$H_A$; 2-$H_{A,B}$; 10-N*H*), 1.61 – 1.53 (2H, m, 1-$H_B$, 7-$H_B$). **$^{13}$C NMR** (**Minor diastereomer**, 125 MHz, $CDCl_3$): δ ppm 160.5 (5-*C*), 155.4 (*Ar*), 130.0 (*Ar*), 122.3 (*Ar*H), 113.4 (*Ar*H), 64.6 (8-*C*), 64.4 (11b-*C*), 54.8 (6a-*C*), 54.5 (ArO*C*H$_3$), 48.7 (9-*C*), 48.2 (11-*C*), 43.3 (3-*C*), 40.4 (8a-*C*), 38.8 (11a-*C*), 32.9 (1-*C*), 31.4 (7-*C*), 22.2 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3294 (O-H, N-H), 3051, 2927 (C-H), 1687 (C=O), 1611, 1512, 1461 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{19}H_{26}N_3O_3$ [M + H$^+$]: calculated 344.1969, found 344.1964.

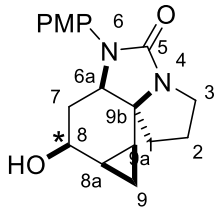
(6a*R**,8*S**,8a*R**,9a*S**, 9b*S**)-8-Hydroxy-6-isopropyloctahydro-1*H*-cyclopropa[5,6]benzo[1,2-*d*]pyrrolo[1,2-*c*]imidazol-5(6*H*)-one **133a**




**133a**
**Major diastereomer, *dr* 90:10**

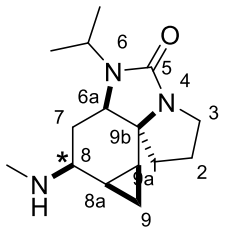
A mixture of the cyclopropane scaffold **106a** (30.0 mg, 0.12 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (54.0 mg, 0.14 mmol, 1.2 eq.) in 3 mL of HPLC grade MeOH was allowed to stir at –78 °C for 30 min. $NaBH_4$ (5.48 mg, 0.14 mmol, 1.2 eq.) was then added and the mixture was left to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 3% MeOH in DCM afforded the product **133a** as a 90:10 mixture of diastereomers (27.0 mg, 0.11 mmol, 90% yield). $\mathbf{R_f}$ = 0.29 (4% MeOH in DCM). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): 4.19 (1H, dt, *J* = 12.0, 4.5, 8-*H*), 3.92 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.73 (1H, ddd, *J* = 12.0, 6.0, 3.5, 3-$H_A$), 3.27 (1H, dd, *J* = 12.0, 5.5, 6a-*H*), 2.95 (1H, ddd, *J* =12.1, 8.9, 6.1, 3-$H_B$), 1.99 (1H, dtd, *J* = 12.5, 5.0, 1.0, 7-$H_A$), 1.88 – 1.81 (2H, m, 2-$H_{A,B}$), 1.74 – 1.70 (2H, m, 1-$H_A$, 8-CHO*H*), 1.45 (1H, tt, *J* = 8.5, 5.0, 8a-*H*), 1.37 (1H, q, *J* = 11.0, 1-$H_B$), 1.21 – 1.13 (1H, m, 7-$H_B$), 1.12 (3H, d, *J* = 6.5, isopropyl C$H_{3A}$), 1.10 (3H, d, *J* = 7.0, isopropyl C$H_{3B}$), 0.92 (1H, td, 8.9, 5.3, 9a-*H*), 0.75 (1H, q, *J* = 5.6, 9-$H_A$), 0.52 (1H, td, *J* = 8.6, 5.7, 9-$H_B$). Signal for minor isomer visible at: 4.33 (0.11H, dt, *J* = 4.0, 2.0, 8-*H*). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 162.9 (5-*C*), 65.6 (8-*C*), 64.3 (9b-*C*), 55.5 (6a-*C*), 44.2 (isopropyl *C*H), 43.7 (3-*C*), 36.8 (1-*C*), 34.0 (7-*C*), 22.8 (2-*C*), 22.4 (isopropyl $CH_{3A}$), 19.7 (isopropyl C$H_{3B}$), 19.5 (8a-*C*), 18.9 (9a-*C*), 4.4 (9-*C*). Signals for minor isomer visible at: 65.4, 64.5, 50.0, 43.6. **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3378 (O-H), 2967, 2880 (C-H), 1667 (C=O), 1221 (C-O). **HRMS** (ESI): $C_{14}H_{23}N_2O_2$ [M + H$^+$]: calculated 251.1754, found 251.1754.

(6a*R**,8*S**,8a*R**,9a*S**, 9b*S**)-8-Hydroxy-6-(4-methoxyphenyl)octahydro-1*H*-cyclopropa[5,6]benzo[1,2-*d*]pyrrolo[1,2-*c*]imidazol-5(6*H*)-one **133b**




A mixture of the cyclopropane scaffold **106b** (15.0 mg, 0.05 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (21.5 mg, 0.06 mmol, 1.2 eq.) in 3 mL of HPLC grade MeOH was allowed to stir at –78 °C for 30 min. $NaBH_4$ (2.20 mg, 0.06 mmol, 1.2 eq.) was then added and the mixture was left to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 4% MeOH in DCM afforded the product **133b** as a single diastereomer (14.0 mg, 0.04 mmol, 93% yield). $\mathbf{R_f}$ = 0.44 (100% EtOAc). **$^1$H NMR** (500 MHz, $CDCl_3$): 7.21 (2H, d, *J* = 9.0, Ar*H*), 6.79 (2H, d, *J* = 9.0, Ar*H*), 4.19 (1H, dt, *J* = 12.0, 4.5, 8-*H*), 3.83 (1H, ddd, *J* = 14.5, 8.0, 2.5, 3-$H_A$), 3.78 (1H, dd, *J* = 12.5, 5.5, 6a-*H*), 3.71 (3H, s, ArOC$H_3$), 3.08 (1H, ddd, *J* =14.5, 8.1, 4.3, 3-$H_B$), 1.99 – 1.96 (1H, m, 7-$H_A$), 1.95 – 1.90 (2H, m, 2-$H_{A,B}$), 1.90 – 1.84 (1H, m, 1-$H_A$), 1.63 (1H, q, *J* = 11.0, 1-$H_B$), 1.53 – 1.47 (2H, m, 8a-*H*, 8-CHO*H*), 1.04 (1H, q, *J* = 12.5, 7-$H_B$), 1.01 – 0.96 (1H, m, 9a-*H*), 0.80 (1H, q, *J* = 5.6, 9-$H_A$), 0.58 (1H, td, *J* = 8.7, 5.8, 9-$H_B$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 160.2 (5-*C*), 155.5 (*Ar*), 130.0 (*Ar*), 122.7 (*Ar*H), 113.3 (*Ar*H), 64.4 (8-*C*), 62.6 (9b-*C*), 57.6 (6a-*C*), 54.5 (ArO*C*$H_3$), 42.9 (3-*C*), 36.3 (1-*C*), 30.0 (7-*C*), 21.8 (2-*C*), 19.1 (8a-*C*), 18.`1 (9a-*C*), 3.5 (9-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3401 (O-H), 3010, 2954, 2836 (C-H), 1677 (C=O), 1611, 1511, 1462 (C=C), 1245 (C-O). **HRMS** (ESI): $C_{18}H_{23}N_2O_3$ [M + H$^+$]: calculated 315.1703, found 315.1699.

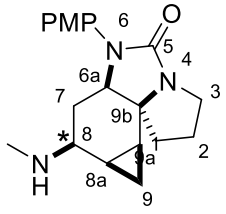
(6a*R**,8*S**,8a*R**,9a*S**, 9b*S**)-6-Isopropyl-8-(methylamino)octahydro-1*H*-cyclopropa[5,6]benzo[1,2-*d*]pyrrolo[1,2-*c*]imidazol-5(6*H*)-one **190**




To a solution of the cyclopropane scaffold **106a** (30.0 mg, 0.12 mmol, 1.0 eq.) in 6 mL THF, 2M methylamine in MeOH (0.60 mL, 1.21 mmol, 10.0 eq.) and titanium isopropoxide (0.06 mL, 0.24 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (6.90 mg, 0.18 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in* vacuo. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude, isonicotinoyl chloride (23.7 mg, 0.13 mmol, 1.1 eq.) and DMAP (14.8 mg, 0.12 mmol, 1.0 eq.) in 1 mL DMF; TEA (0.10 mL, 0.73 mmol,6.0 eq.) was added. The reaction mixture was stirred at room temperature for 16 h and then heated at 100 °C for 6 h. It was then evaporated *in vacuo*. Flash chromatography with 1 - 3% of saturated $NH_3$/MeOH in DCM afforded the intermediate amine **190** as a single diastereomer (8.0 mg, 0.030 mmol, 25% yield). $\mathbf{R_f}$ = 0.37 (6% of saturated $NH_3$/MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 3.92 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.77 (1H, ddd, *J* = 11.5, 6.5, 4.0, 3-$H_A$), 3.24 (1H, dd, *J* = 12.1, 5.2, 6a-*H*), 3.00 (1H, dt, *J* = 12.5, 4.5, 8-*H*), 2.94 (1H, ddd, *J* = 11.0, 6.5, 3.0, 3-$H_B$), 2.47 (3H, s, NHC$H_3$), 1.92 (1H, dt, *J* =12.5, 5.0, 7-$H_A$), 1.87 – 1.80 (2H, m, 2-$H_{A,B}$), 1.72 (1H, ddd, *J* = 12.0, 6.5, 3.5, 1-$H_A$), 1.65 (1H, s, N*H*), 1.47 – 1.41 (1H, m, 8a-*H*), 1.38 (1H, q, *J* = 11.5, 1-$H_B$), 1.12 (3H, d, *J* = 7.0, isopropyl C$H_{3A}$), 1.10 (3H, d, *J* = 7.0, isopropyl C$H_{3B}$), 0.97 (1H, q, *J* = 12.5, 7-$H_B$), 0.85 (1H, td, *J* = 8.9, 5.3, 9a-*H*), 0.60 (1H, q, *J* = 5.6, 9-$H_A$), 0.45 (1H, td, *J* = 8.7, 5.6, 9-$H_B$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 161.9 (5-*C*), 63.8 (9b-*C*), 54.5 (6a-*C*), 51.6 (8-*C*), 43.2 (isopropyl *C*H), 42.6 (3-*C*), 35.9 (1-*C*), 32.3 (NH*C*$H_3$), 30.6 (7-*C*), 21.7 (2-*C*), 21.4 (isopropyl *C*$H_{3A}$), 18.5 (isopropyl *C*$H_{3A}$), 16.7

(9a-*C*), 16.1 (8a-*C*), 3.1 (9-*C*). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3302 (N-H), 2964, 2933, 2790 (C-H), 1688 (C=O). **HRMS** (ESI): $C_{15}H_{26}N_3O$ [M + $H^+$]: calculated 264.2070, found 264.2063.

(6a*R**,8*S**,8a*R**,9a*S**, 9b*S**)-6-(4-Methoxyphenyl)-8-(methylamino)octahydro-1*H*-cyclopropa[5,6]benzo[1,2-*d*]pyrrolo[1,2-*c*]imidazol-5(6*H*)-one **191**

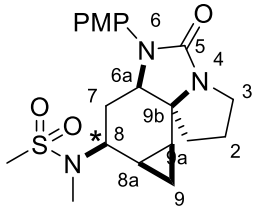



**191**
**Major diastereomer, *dr* 93:7**

To a solution of the cyclopropane scaffold **106b** (9.00 mg, 0.03 mmol, 1.0 eq.) in 4 mL THF, 2M methylamine in MeOH (0.15 mL, 0.29 mmol, 10.0 eq.) and titanium isopropoxide (0.02 mL, 0.06 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (1.60 mg, 0.04 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in* vacuo. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 2 - 3% of saturated $NH_3$/MeOH in DCM afforded the product **191** as a 93:7 mixture of diastereomers (5.3 mg, 0.020 mmol, 56% yield). **$^1$H NMR** (**Major diastereomer**, 500 MHz, $CDCl_3$): δ ppm 7.21 (2H, d, *J* = 9.0, Ar*H*), 6.79 (2H, d, *J* = 9.0, Ar*H*), 3.85 – 3.79 (1H, m, 3-$H_A$), 3.77 (1H, dd, *J* = 12.5, 5.5, 6a-*H*), 3.71 (3H, s, ArOC$H_3$), 3.12 -3.04 (2H, m, 3-$H_B$, 8-*H*), 2.40 (3H, s, NHC$H_3$), 1.97 -1.90 (3H, m, 2-$H_{A,B}$; 7-$H_A$), 1.89 – 1.84 (1H, m, 1-$H_A$), 1.63 (1H, q, *J* = 11.0, 1-$H_B$), 1.52 - 1.44 (1H, m, 8a-*H*), 0.99 – 0.88 (2H, m, 7-$H_B$, 9a-*H*), 0.71 (1H, q, *J* = 5.5, 9-$H_A$), 0.54 (1H, td, *J* = 8.7, 5.8, 9-$H_B$). Signal for minor isomer visible at: 3.38 (0.07H, dt, *J* = 12.7, 3.7, 3-*H*). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 160.2 (5-*C*), 155.4 (*Ar*), 130.1 (*Ar*), 122.6 (*Ar*H), 113.3 (*Ar*H), 63.0 (9b-*C*), 57.4 (6a-*C*), 54.5 (ArO*C*$H_3$), 51.6 (8-*C*), 42.8 (3-*C*), 36.4 (1-*C*), 31.7 (NH*C*$H_3$), 26.8 (7-*C*), 21.8 (2-*C*), 16.8 (9a-*C*), 16.2 (8a-*C*), 3.5 (9-*C*). Signals for minor isomer

visible at: 63.5, 62.4, 58.0, 57.6, 51.0, 46.6, 24.6, 15.7, 14.4. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3288 (N-H), 2953, 2790 (C-H), 1693 (C=O), 1512, 1460, 1427 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{19}H_{26}N_3O_2$ [M + $H^+$]: calculated 328.2020, found 328.2016.

*N*-[(6a*R**,8*S**,8a*R**,9a*S**,9b*S**)-6-(4-Methoxyphenyl)-5-oxodecahydro-1*H*-cyclopropa[5,6]benzo[1,2-*c*]imidazol-8-yl]methanesulfonamide **192**

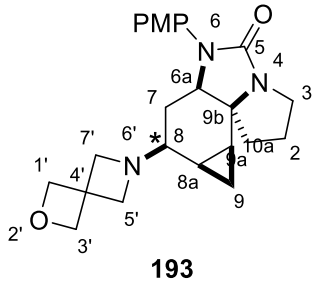



**192**
**Major diastereomer, *dr* 89:11**

To a solution of the cyclopropane scaffold **106b** (23.0 mg, 0.07 mmol, 1.0 eq.) in 4 mL THF, 2M methylamine in MeOH (0.37 mL, 0.74 mmol, 10.0 eq.) and titanium isopropoxide (0.04 mL, 0.15 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (4.18 mg, 0.11 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in* vacuo. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude and DMAP (1.00 mg, 0.12 mmol, 0.11 eq.) in 5 mL DCM; methanesulfonyl chloride (0.01 mL, 0.13 mmol, 1.7 eq.) and TEA (0.02 mL, 0.14 mmol, 1.9 eq.) were added. The reaction mixture was then stirred at room temperature overnight. It was evaporated *in vacuo*. Flash chromatography with 1 - 2% MeOH in DCM afforded the product as an 89:11 mixture of diastereomers (21.0 mg, 0.05 mmol, 73% yield). $\mathbf{R_f}$ = 0.56 (4% MeOH in DCM). **$^1$H NMR** (**Major diastereomer**, 500 MHz, $CDCl_3$): δ ppm 7.20 (2H, d, *J* = 9.0, Ar*H*), 6.80 (2H, d, *J* = 9.0, Ar*H*), 4.45 (1H, dt, *J* = 13.0, 4.0, 8-*H*), 3.93 (1H, dd, *J* = 12.0, 5.0, 6a-*H*), 3.81 (1H, ddd, *J* = 12.5, 6.5, 3.5, 3-$H_A$), 3.72 (3H, s, ArOC$H_3$), 3.06 (1H, ddd, *J* = 12.0, 5.5, 3.5, 3-$H_B$), 2.77 (3H, s, SC$H_3$), 2.74 (3H, s, NC$H_3$), 1.97 -1.88 (3H, m, 1-$H_A$, 2-$H_{A,B}$), 1.72 (1H, dt, *J* = 13.0, 4.5, 7-

$H_A$), 1.69 - 1.60 (1H, m, 1-$H_B$), 1.34 (1H, q, $J$ = 12.5, 7-$H_B$), 1.28 – 1.20 (1H, m, 8a-*H*), 0.94 – 0.86 (2H, m, 9-$H_A$, 9a-*H*), 0.80 -0.73 (1H, m, 9-$H_B$). Signal for minor isomer visible at: 4.36 (0.12H, br.d, $J$ = 11.2, 6a-*H*). **$^{13}$C NMR** (**Major diastereomer**,125 MHz, $CDCl_3$): δ ppm 159.9 (5-*C*), 155.6 (*Ar*), 129.7 (*Ar*), 122.6 (*Ar*H), 113.4 (*Ar*H), 62.4 (9b-*C*), 57.8 (6a-*C*), 54.5 (ArO*C*H$_3$), 49.8 (8-*C*), 42.9 (3-*C*), 37.8 (S*C*H$_3$), 36.5 (1-*C*), 27.9 (N*C*H$_3$), 25.4 (7-*C*), 21.8 (2-*C*), 15.2 (9a-*C*), 15.0 (8a-*C*), 5.4 (9-*C*). Signals for minor isomer visible at: 159.6, 155.3, 122.0, 113.3, 73.7, 70.0, 62.3, 55.9, 53.4, 49.3, 48.7, 27.0, 17.7, 15.8, 6.4. **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 2956 (C-H), 1695 (C=O), 1512, 1464, 1444 (C=C), 1246 (C-O). **HRMS** (ESI): $C_{20}H_{28}N_3O_4S$ [M + H$^+$]: calculated 406.1795, found 406.1794.

(6a*R**,8*S**,8a*R**,9a*S**,9b*S**)-6-(4-Methoxyphenyl)-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)octahydro-1*H*-cyclopropa[5,6]benzo[1,2-*d*]imidazol-5(6*H*)-one **193**

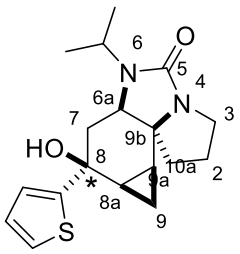



**193**
**Major diastereomer, *dr* 88:12**

To a solution of the cyclopropane scaffold **106b** (17.0 mg, 0.05 mmol, 1.0 eq.) in 4 mL THF, 2-oxa-6-aza-spiro[3.3]heptane (0.01 mL, 0.11 mmol, 2.0 eq.) and titanium isopropoxide (0.03 mL, 0.11 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (3.10 mg, 0.08 mmol, 1.5 eq.) was added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in* vacuo. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 - 6% MeOH in DCM afforded the product as an 88:12 mixture of diastereomers (19.0 mg, 0.05 mmol, 88% yield). **$R_f$** = 0.40 (4% MeOH in DCM). **$^1$H NMR** (**Major diastereomer**, 500 MHz, $CDCl_3$): δ ppm 7.19 (2H, d, $J$ = 9.0, Ar*H*), 6.80 (2H, d, $J$ = 9.5, Ar*H*), 4.65 (4H, s, 1'-$H_{A,B}$; 3'-$H_{A,B}$), 3.79 (1H, ddd, $J$ = 12.0, 7.5, 4.5, 3-$H_A$), 3.72 (3H, s, ArOC$H_3$), 3.70 (1H, dd,

*J* = 12.0, 5.0, 6a-*H*), 3.32 (4H, s, 5'-$H_{A,B}$; 7'-$H_{A,B}$), 3.06 (1H, dt, *J* = 12.2, 7.4, 3-$H_B$), 2.54 (1H, br.d, *J* = 12.5, 8-*H*), 1.96 -1.82 (3H, m, 1-$H_A$, 2-$H_{A,B}$), 1.66 – 1.56 (2H, m, 1-$H_B$, 7-$H_A$), 1.23 – 1.17 (1H, m, 8a-*H*), 0.87 (1H, td, *J* = 8.9, 5.3, 9a-*H*), 0.80 (1H, q, *J* = 12.5, 7-$H_B$), 0.72 (1H, q, *J* = 5.5, 9-$H_A$), 0.55 – 0.48 (1H, m, 9-$H_B$). Signal for minor isomer visible at: 4.15 (0.13H, dd, *J* = 11.2, 6.0, 6a-*H*). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 160.1 (5-*C*), 155.5 (*Ar*), 130.1 (*Ar*), 122.7 (*Ar*H), 113.4 (*Ar*H), 80.2 (1' or 3'-*C*), 63.0 (9b-*C*), 60.7 (5' or 7'-*C*), 59.2 (8-*C*), 57.1 (6a-*C*), 54.5 (ArO*C*$H_3$), 42.8 (3-*C*), 37.7 (4'-*C*), 36.5 (1-*C*), 24.2 (7-*C*), 21.8 (2-*C*), 16.0 (9a-*C*), 14.0 (8a-*C*), 3.8 (9-*C*). Signals for minor isomer visible at: 121.8, 113.2, 68.8, 65.3, 62.6, 53.6, 38.6, 36.2, 31.1, 28.6, 21.0, 6.4. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 2936, 2863, 2833 (C-H), 1692 (C=O), 1583, 1511, 1460 (C=C), 1245 (C-O). **HRMS** (ESI): $C_{23}H_{30}N_3O_3$ [M + $H^+$]: calculated 396.2282, found 396.2279.

(6a*R**,8*S**,8a*R**,9a*S**, 9b*S**)-8-Hydroxy-6-isopropyl-8-(thiophen-2-yl)octahydro-1*H*-cyclopropa[5,6]benzo[1,2-*d*]pyrrolo[1,2-*d*]imidazol-5(6*H*)-one **195**

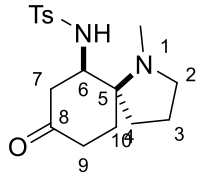



**195**
**Major diastereomer, *dr* 92:8**

To a mixture of the cyclopropane scaffold **106a** (20.0 mg, 0.08 mmol, 1.0 eq.) and $CeCl_3$ (39.7 mg, 0.16 mmol, 2.0 eq.) in 4 mL of anhydrous THF at -78 °C, 1M 2-thienylmagnesium bromide in THF (0.16 mL, 0.16 mmol, 2.0 eq.) was added and the mixture was stirred at the same temperature for 1 h. The reaction mixture was then allowed to warm up to room temperature overnight and it was quenched with 1 mL $H_2O$. It was evaporated *in vacuo*, taken up in 1 mL $H_2O$, diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography eluting with 0.5 – 3% MeOH in DCM afforded the product as a 92:8 mixture of diastereomers (13.0 mg, 0.04 mmol, 49% yield). **$^1$H NMR** (500 MHz, $CDCl_3$): 7.25 (1H, dd, *J* = 5.1,

1.1, Ar*H*), 7.09 (1H, dd, *J* = 3.5, 1.2, Ar*H*), 6.95 (1H, dd, *J* = 5.1, 3.6, Ar*H*), 3.82 (1H, hept, *J* = 7.0, isopropyl C*H*), 3.73 (1H, dt, *J* = 12.1, 7.7, 3-$H_A$), 3.03 – 2.95 (2H, m, 3-$H_B$, 6a-*H*), 2.22 (1H, s, 8-CHO*H*), 2.12 (1H, ddd, *J* = 13.0, 5.2, 1.4, 7-$H_A$), 1.89 – 1.81 (2H, m, 2-$H_{A,B}$), 1.80 – 1.71 (2H, m, 1-$H_A$, 8a-*H*), 1.63 (1H, t, *J* = 13.0, 7-$H_B$), 1.28 (1H, q, *J* = 10.5, 1-$H_B$), 1.22 – 1.19 (1H, m, 9a-*H*), 1.08 (3H, d, *J* = 6.8, isopropyl C$H_{3A}$), 0.94 (3H, d, *J* = 6.9, isopropyl C$H_{3B}$), 0.89 (1H, q, *J* = 5.7, 9-$H_A$), 0.74 (1H, td, *J* = 8.8, 6.0, 9-$H_B$). Signal for minor isomer visible at: 4.07 (0.09H, br.d, *J* = 3.2, 6a-*H*). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 161.7 (5-*C*), 150.3 (*Ar*), 125.7 (*Ar*H), 124.1 (*Ar*H), 122.7 (*Ar*H), 70.7 (8-*C*), 63.0 (9b-*C*), 53.9 (6a-*C*), 43.2 (isopropyl *C*H), 42.6 (3-*C*), 39.4 (7-*C*), 35.8 (1-*C*), 23.4 (8a-*C*), 21.8 (2-*C*), 21.3 (isopropyl *C*$H_{3A}$), 19.7 (9a-*C*), 18.3 (isopropyl *C*$H_{3B}$), 5.9 (9-*C*). Signals for minor isomer visible at: 126.5, 123.3, 122.4, 55.3, 43.5, 36.8, 23.1, 21.1, 18.6, 18.5, 16.6. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3355 (O-H), 2967, 2934 (C-H), 1673 (C=O), 1458, 1420, 1365 (C=C), 1232 (C-O). **HRMS** (ESI): $C_{18}H_{25}N_2O_2S$ [M + $H^+$]: calculated 333.1631, found 333.1624.

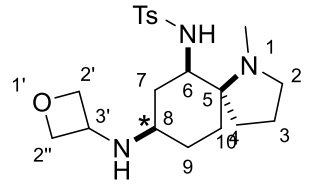
4-Methyl-*N*-[(5*S**,6*R**)-1-methyl-8-oxo-1-azaspiro[4.5]decan-6-yl)benzenesulfonamide **197**




To a solution of the alcohol **122 (**200 mg, 0.59 mmol, 1.0 eq.) in 10.5 mL of acetone; 3.3 M Jones reagent [0.31 mL, 1.18 mmol, 2.0 eq.; freshly prepared by slowly adding 0.26 mL of 98% sulfuric acid to a stirring solution of chromium (VI) oxide (300 mg, 3.00 mmol) in 0.60 mL of water at 0 °C and then leaving the mixture to warm up to room temperature for 30 min] was added and the mixture was stirred at room temperature for 1 h 20 min. 5 mL EtOH was added to the reaction mixture and it was basified with excess solid $Na_2CO_3$ to pH 8 as monitored by a strip of pH paper. It was then extracted with DCM (5 × 30 mL), dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 3% MeOH in DCM afforded the product **197** (60.0 mg, 0.18 mmol, 30% yield). $\mathbf{R_f}$ = 0.44 (10% MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.67 (2H, d, *J* = 8.3, Ar*H*), 7.23 (2H, d, *J* = 8.0, Ar*H*), 3.23 (1H, dd, *J* = 9.4, 4.9, 6-*H*), 2.82

(1H, ddd, *J* = 9.0, 7.0, 3.2, 2-$H_A$), 2.52 (1H, dd, *J* = 16.2, 9.4, 7-$H_A$), 2.49 – 2.43 (2H, m, 2-$H_B$, 7-$H_B$), 2.42 – 2.37 (1H, m, 9-$H_A$), 2.36 (3H, s, ArC$H_3$), 2.32 (3H, s, 1-C$H_3$), 2.18 (1H, ddd, *J* = 16.0, 10.5, 5.5, 9-$H_B$), 2.07 (1H, ddd, *J* = 15.5, 10.5, 5.0, 10-$H_A$), 1.69 – 1.61 (1H, m, 3-$H_A$), 1.59 – 1.52 (4H, m, 3-$H_B$; 4-$H_{A,B}$; 10-$H_B$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 207.8 (8-*C*), 142.4 (*Ar*), 136.3 (*Ar*), 128.6 (*Ar*H), 126.1 (*Ar*H), 62.4 (5-*C*), 54.4 (2-*C*), 54.2 (6-*C*), 43.0 (7-*C*), 36.9 (1-*C*), 36.6 (9-*C*), 35.7 (4-*C*), 25.2 (10-*C*), 21.0 (3-*C*), 20.5 (Ar*C*$H_3$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3261 (N-H), 2927, 2796 (C-H), 1672 (C=O), 1598, 1494, 1449 (C=C). **HRMS** (ESI): $C_{17}H_{25}N_2O_3S$ [M + $H^+$]: calculated 337.1580, found 337.1576.

4-Methyl-*N*-[(5*S**,6*R**,8*R**)-1-methyl-8-(oxoetan-3-ylamino)-1-azaspiro[4.5]decan-6-yl)benzenesulfonamide **199**



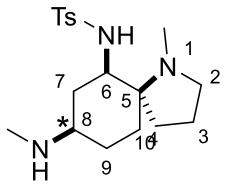

**199**
**Major diastereomer, *dr* 78:22**

To a solution of the ketone **197** (15.0 mg, 0.04 mmol, 1.0 eq.) in 3 mL MeOH, 3-aminooxetane (0.01 mL, 0.14 mmol, 3.2 eq.) and titanium isopropoxide (0.03 mL, 0.09 mmol, 2.0 eq.) were added and the mixture was left to stir at room temperature overnight. $NaBH_4$ (2.60 mg, 0.07 mmol, 1.5 eq.) was then added to the reaction mixture at -78 °C and it was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in* vacuo. It was then taken up in 1 mL $H_2O$, diluted with 100 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 1 – 4% MeOH in DCM afforded the product as a 78:22 mixture of diastereomers (3.60 mg, 0.01 mmol, 21% yield). $\mathbf{R_f}$ = 0.42 (5% MeOH in DCM). **$^1$H NMR** (Major diastereomer, 500 MHz, $CDCl_3$): δ ppm 7.69 (2H, d, *J* = 8.3, Ar*H*), 7.21 (2H, d, *J* = 8.1, Ar*H*), 4.71 (1H, t, *J* = 6.8, 2'-$H_A$), 4.67 (1H, t, *J* = 6.8, 2''-$H_A$), 4.31 – 4.26 (2H, m, 2'-$H_B$, 2''-$H_B$), 3.88 (1H, quint, *J* = 6.6, 3'-*H*), 3.06 (1H, dd, *J* = 9.5, 4.5, 6-*H*), 2.83 – 2.76 (1H, m, 2-$H_A$), 2.51 (1H, tt, *J* = 12.5, 4.0, 8-*H*), 2.44 (1H, dt, *J* = 16.0,

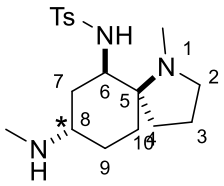
8.0, 2-$H_B$), 2.35 (3H, s, ArC$H_3$), 2.34 (3H, s, 1-C$H_3$), 2.15 (1H, s, 8-TsN*H*), 1.95 (1H, ddd, *J* = 14.6, 5.7, 4.3, 4-$H_A$), 1.69 – 1.66 (1H, m, 7-$H_A$), 1.54 – 1.49 (4H, m, 3-$H_A$, 9-$H_A$, 10-$H_{A,B}$), 1.40 – 1.38 (2H, m, 3-$H_B$, 7-$H_B$), 1.34 – 1.30 (1H, m, 9-$H_B$), 1.16 – 1.08 (1H, m, 4-$H_B$). Signal for minor isomer visible at: 3.81 (0.29H, quint, *J* = 6.5, 3'-H). **$^{13}$C NMR** (Major diastereomer, 125 MHz, $CDCl_3$): δ ppm 141.8 (*Ar*), 137.9 (*Ar*), 128.4 (*Ar*H), 125.8 (*Ar*H), 79.3 (2'-*C*), 79.1 (2''-*C*), 60.7 (5-*C*), 56.8 (6-*C*), 55.7 (2-*C*), 51.5 (8-*C*), 50.2 (3'-*C*), 39.0 (9-*C*), 37.8 (1-*C*), 29.9 (7-*C*), 29.1 (10-*C*), 27.5 (4-*C*), 22.0 (3-*C*), 20.5 (Ar*C*$H_3$). Signals for minor isomer visible at: 142.3, 140.2, 128.5, 126.4, 66.1, 31.1. **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3294 (N-H), 2951, 2868, 2794 (C-H), 1598, 1513, 1454 (C=C), 1160 (C-O). **HRMS** (ESI): $C_{20}H_{32}N_3O_3S$ [M + $H^+$]: calculated 394.2159, found 394.2139.

4-Methyl-*N*-[(5*S**,6*R**,8*R**)-1-methyl-8-(methylamino)-1-azaspiro[4.5]decan-6-yl)benzenesulfonamide **201**

4-Methyl-*N*-[(5*S**,6*R**,8*S**)-1-methyl-8-(methylamino)-1-azaspiro[4.5]decan-6-yl)benzenesulfonamide **202**




**201**

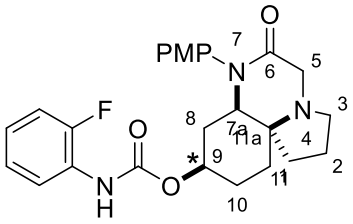



**202**

To a mixture of the ketone **197** (20.0 mg, 0.06 mmol, 1.0 eq.) and STAB (19.1 mg, 0.09 mmol, 1.5 eq.) in 5 mL THF, 2M $MeNH_2$ in MeOH (0.30 mL, 0.60 mmol, 10.0 eq.) and AcOH (0.01 mL, 0.17 mmol, 2.9 eq.) were added and the mixture was stirred at room temperature overnight. 2 mL of a saturated aqueous solution of $Na_2CO_3$ was then added to the reaction mixture and it was evaporated *in vacuo*. It was then taken up in 1 mL of $H_2O$, diluted with 100 mL DCM, dried over $Na_2SO_4$, and evaporated *in vacuo*. To a solution of the crude in 5 mL THF, cyclopropyl isocyanate (0.01 mL, 0.12 mmol, 2.0 eq.) was added and the mixture was refluxed for 30 h. The reaction mixture was evaporated *in vacuo*. Flash chromatography eluting with 2% MeOH in DCM followed by 2 – 10% MeOH in DCM afforded the intermediate amines **201** [7 mg, 0.02

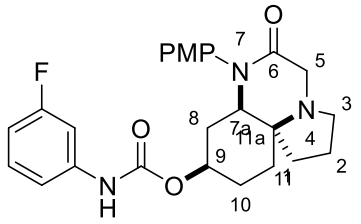
mmol, 33% yield, $\mathbf{R_f}$ = 0.50 (7% of saturated $NH_3$/MeOH in DCM)] and **202** [4 mg, 0.01 mmol, 19% yield, $\mathbf{R_f}$ = 0.41 (7% of saturated $NH_3$/MeOH in DCM)] as products. **$^1$H NMR** (**Compound 201**, 500 MHz, $CDCl_3$): δ ppm 7.71 (2H, d, *J* = 8.0, Ar*H*), 7.20 (2H, d, *J* = 8.0, Ar*H*), 3.14 (1H, dd, *J* = 7.6, 4.2, 6-*H*), 2.84 – 2.76 (1H, m, 2-$H_A$), 2.52 – 2.40 (2H, m, 2-$H_B$, 8-*H*), 2.35 (3H, s, ArC$H_3$), 2.33 (3H, s, 1-C$H_3$), 2.26 (3H, s, NHC$H_3$), 1.96 (1H, ddd, *J* = 13.0, 8.5, 4.0, 4-$H_A$), 1.68 – 1.35 (10H, m, TsN*H*, N*H*$CH_3$, 3-$H_{A,B}$; 7-$H_{A,B}$; 9-$H_{A,B}$; 10-$H_{A,B}$), 1.11 (1H, ddd, *J* = 13.5, 8.0, 4.5, 4-$H_B$). **$^{13}$C NMR** (**Compound 201**, 125 MHz, $CDCl_3$): δ ppm 142.6 (*Ar*), 139.0 (*Ar*), 129.3 (*Ar*H), 127.0 (*Ar*H), 62.2 (5-*C*), 58.4 (6-*C*), 56.3 (2-*C*), 55.5 (8-*C*), 38.8 (9-*C*, **missing but observed by HMQC**) 38.1 (1-*C*), 34.1 (7-*C*, **missing but observed by HMQC**), 33.9 (NH*C*$H_3$), 29.2 (10-*C*), 25.9 (4-*C*, **missing but observed by HMQC**), 22.6 (3-*C*), 21.5 (Ar*C*$H_3$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3324 (N-H), 2941, 2866, 2791 (C-H), 1598, 1541, 1450 (C=C). **HRMS** (ESI): $C_{18}H_{30}N_3O_2S$ [M + $H^+$]: calculated 352.2053, found 352.2054. **$^1$H NMR** (**Compound 202**, 500 MHz, $CDCl_3$): δ ppm 7.69 (2H, d, *J* = 8.5, Ar*H*), 7.23 (2H, d, *J* = 8.0, Ar*H*), 2.69 (1H, t, *J* = 3.0, 6-*H*), 2.59 (1H, tt, *J* = 11.0, 4.0, 8-*H*), 2.35 (3H, s, ArC$H_3$), 2.33 – 2.25 (3H, m, 2-$H_{A,B}$; 7-$H_A$), 2.23 (3H, s, NHC$H_3$), 2.17 (3H, s, 1-C$H_3$), 1.84 – 1.78 (1H, m, 9-$H_A$), 1.75 – 1.64 (3H, m, 3-$H_A$, 4-$H_A$, 10-$H_A$), 1.42 – 1.28 (4H, m, TsN*H*, 3-$H_B$, 4-$H_B$, 10-$H_B$), 1.16 (1H, ddd, *J* = 14.0, 11.0, 3.1, 7-$H_B$), 1.00 (1H, qd, *J* = 13.0, 3.5, 9-$H_B$). **$^{13}$C NMR** (**Compound 202**, 125 MHz, $CDCl_3$): δ ppm 143.1 (*Ar*), 136.6 (*Ar*), 129.5 (*Ar*H), 127.4 (*Ar*H), 67.1 (5-*C*), 54.0 (6-*C*), 53.8 (2-*C*), 52.2 (8-*C*), 38.5 (1-*C*), 33.6 (NH*C*$H_3$), 32.42 (7-*C*), 32.38 (10-*C*), 30.0 (9-*C*), 28.4 (4-*C*), 22.3 (3-*C*), 21.5 (Ar*C*$H_3$). **IR** $\nu_{max}$ (neat)/$cm^{-1}$: 3158 (N-H), 2939, 2862, 2792 (C-H), 1598, 1512, 1447 (C=C). **HRMS** (ESI): $C_{18}H_{30}N_3O_2S$ [M + $H^+$]: calculated 352.2053, found 352.2062.

(7a*R**,9*R**,11a*S**)-7-(4-Methoxyphenyl)-6-oxodecahydro-1H-pyrrolo[1,2-*d*]quinoxalin-9-yl (2-fluorophenyl)carbamate **209**



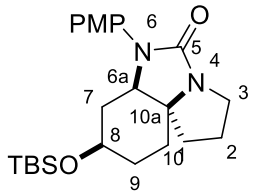

To a solution of the alcohol **138** (27.0 mg, 0.09 mmol, 1.0 eq.) in 4 mL DCM, 2-fluorophenylisocyanate (0.01 mL, 0.09 mmol, 1.1 eq.) and TEA (0.04 mL, 0.26 mmol, 3.0 eq.) were added and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated *in vacuo*. Flash chromatography with 1 – 8% MeOH in DCM afforded the product **210** (33.0 mg, 0.07 mmol, 86% yield) $\mathbf{R_f}$ = 0.29 (4% MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.93 (1H, t, *J* = 8.3, Ar*H*), 7.09 (2H, d, *J* = 9.0, Ar*H*), 7.07 – 6.99 (2H, m, Ar*H*), 6.96 – 6.91 (1H, m, Ar*H*), 6.80 (2H, d, *J* = 9.0, Ar*H*), 6.78 (1H, s, N*H*), 4.70 (1H, tt, *J* = 8.2, 4.2, 9-*H*), 3.85 (1H, d, *J* = 18.0, 5-$H_A$), 3.72 (1H, dd, *J* = 8.5, 5.6, 7a-*H*), 3.70 (3H, s, ArOC$H_3$), 3.38 (1H, d, *J* = 18.0, 5-$H_B$), 3.15 – 3.05 (1H, m, 3-$H_A$), 2.97 – 2.85 (1H, m, 3-$H_B$), 2.20 – 2.00 (2H, m, 1-$H_A$, 8-$H_A$), 2.00 – 1.67 (7H, m,2-$H_{A,B}$; 8-$H_B$; 10-$H_{A,B}$; 11-$H_{A,B}$), 1.30 – 1.20 (1H, m, 1-$H_B$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 168.3 (6-*C*), 157.3 (carbamate *C*=O), 151.5 (*Ar*), 151.2 (d, *J* = 242, *Ar*F), 132.3 (*Ar*), 126.6 (*Ar*H), 125.2 (d, *J* =9.75, *Ar*), 123.6 (d, *J* = 3.63, *Ar*H), 122.5 (d, *J* = 6.38, *Ar*H), 119.2 (*Ar*H), 113.9 (d, *J* = 18.8, *Ar*H), 113.5 (*Ar*H), 69.6 (9-*C*), 61.0 (11a-*C*), 60.0 (7a-*C*), 54.4 (ArO*C*$H_3$), 54.3 (3-*C*), 53.0 (5-*C*), 35.2 (10-*C*), 32.5 (8-*C*), 28.2 (1-*C*), 26.4 (11-*C*), 21.6 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3253 (N-H); 2955, 2836 (C-H); 1723, 1656 (C=O); 1619, 1536, 1510, 1456 (C=C); 1229 (C-O). **HRMS** (ESI): $C_{25}H_{29}FN_3O_4$ [M + H$^+$]: calculated 454.2137, found 454.2145.

(7a*R**,9*R**,11a*S**)-7-(4-Methoxyphenyl)-6-oxodecahydro-1H-pyrrolo[1,2-*d*]quinoxalin-9-yl (3-fluorophenyl)carbamate **210**




To a solution of the alcohol **138** (22.0 mg, 0.07 mmol, 1.0 eq.) in 5 mL DCM, 3-fluorophenylisocyanate (0.01 mL, 0.09 mmol, 1.3 eq.) and TEA (0.03 mL, 0.21 mmol, 3.0 eq.) were added and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated *in vacuo*. Flash chromatography with 1 – 4% MeOH in DCM afforded the product **209** (23.0 mg, 0.05 mmol, 73% yield). $\mathbf{R_f}$ = 0.37 (4% MeOH in DCM). **$^1$H NMR** (500 MHz, $CDCl_3$): δ ppm 7.33 (1H, br.s, Ar*H*), 7.15 (1H, dt, *J* = 11.0, 2.3, Ar*H*), 7.10 (2H, d, *J* = 9.5, Ar*H*), 6.86 (1H, dd, *J* = 8.0, 1.5, Ar*H*), 6.76 (2H, d, *J* = 9.0, Ar*H*), 6.65 (1H, td, *J* = 8.3, 2.4, Ar*H*), 4.73 (1H, tt, *J* = 7.0, 4.0, 9-*H*), 3.86 (1H, d, *J* = 18.0, 5-$H_A$), 3.75 (1H, dd, *J* = 8.0, 3.8, 7a-*H*), 3.66 (3H, s, ArOC$H_3$), 3.43 (1H, d, *J* = 17.5, 5-$H_B$), 3.14 – 3.04 (1H, m, 3-$H_A$), 3.00 – 2.90 (1H, m, 3-$H_B$), 2.14 – 2.08 (1H, m, 11-$H_A$), 2.07 – 1.84 (8H, m, 1-$H_{A,B}$; 2-$H_{A,B}$; 8-$H_{A,B}$; 10-$H_{A,B}$), 1.28 (1H, ddd, *J* = 14.0, 8.5, 3.5, 11-$H_B$). **$^{13}$C NMR** (125 MHz, $CDCl_3$): δ ppm 167.8 (6-*C*), 162.1 (d, *J* = 243, *Ar*F), 157.4 (*Ar*), 151.6 (carbamate *C*=O), 138.7 (d, *J* = 11.0, *Ar*), 113.9 (*Ar*), 129.0 (d, *J* = 1.88, *Ar*H), 126.8 (*Ar*H), 113.4 (*Ar*H), 112.9 (*Ar*H), 108.8 (d, *J* = 21.3, *Ar*H), 105.0 (d, *J* = 26.4, *Ar*H), 68.7 (9-*C*), 61.0 (11a-*C*), 59.5 (7a-*C*), 54.3 (ArO*C*H$_3$), 53.4 (3-*C*), 52.3 (5-*C*), 34.9 (10-*C*), 31.9 (8-*C*), 26.5 (1-*C*, 11-*C*, **confirmed from HMQC**), 21.3 (2-*C*). **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3268 (N-H); 2952 (C-H); 1723, 1642 (C=O); 1605, 1544, 1510 (C=C); 1223 (C-O). **HRMS** (ESI): $C_{25}H_{29}FN_3O_4$ [M + H$^+$]: calculated 454.2137, found 454.2141.

(6a*R**,8*R**,10a*S**)-8-[(*tert*-Butyldimethylsilyl)oxy]-6-(4-methoxyphenyl)octahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazole-5-one **213**



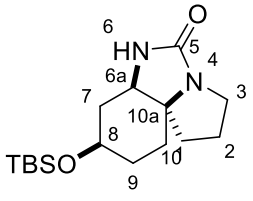

**213**

**Major diastereomer, *dr* 81:19**

A mixture of the ketone **101b** (36.0 mg, 0.12 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (53.7 mg, 0.14 mmol, 1.2 eq.) in 3 mL of HPLC grade MeOH was allowed to stir at –78 °C for 30 min. $NaBH_4$ (5.4 mg, 0.14 mmol, 1.2 eq.) was then added and the mixture was left to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. To a solution of the crude in 2 mL of anhydrous DCM; 2,6-lutidine (0.03 mL, 0.24 mmol, 2.0 eq.) and TBSOTf (0.04 mL, 0.18 mmol, 1.5 eq.) were added. The mixture was allowed to stir at room temperature overnight and evaporated *in vacuo*. Flash chromatography with 0 – 30% EtOAc in hexane afforded the product as an 81:19 mixture of diastereomers (32.0 mg, 0.23 mmol, 64% yield); $\mathbf{R_f}$ = 0.28 (30% EtOAc in hexane). **$^1$H NMR** (**Major diastereomer**, 500 MHz, MeOD): δ ppm 7.36 (2H, d, *J* = 9.0, Ar*H*), 6.89 (2H, d, *J* = 9.0, Ar*H*), 4.00 (1H, dd, *J* = 10.1, 6.3, 6a-*H*), 3.93 (1H, ddd, *J* = 12.0, 7.0, 3.5, 3-$H_A$), 3.80 (3H, s, ArOC$H_3$), 3.68 (1H, tt, *J* = 10.0, 4.5, 8-*H*), 3.06 (1H, ddd, *J* = 12.5, 6.5, 3.0, 3-$H_B$), 2.20 (1H, dddd, *J* = 12.9, 6.3, 4.6, 1.8, 7-$H_A$), 2.02 – 1.88 (3H, m, 2-$H_{A,B}$; 10-$H_A$), 1.76 – 1.62 (4H, m, 1-$H_{A,B}$; 9-$H_{A,B}$), 1.47 (1H, dt, *J* = 13.2, 10.4, 7-$H_B$), 1.39 (1H, ddd, *J* = 14.8, 12.3, 3.8, 10-$H_B$), 0.84 (9H, s, tert-butyl C$H_3$), 0.03 (3H, s, SiC$H_{3A}$), 0.00 (3H, s, SiC$H_{3B}$). Signal for minor isomer visible at: 4.20 (0.24H, dd, *J* = 7.6, 5.5, 6a-*H*). **$^{13}$C NMR** (**Major diastereomer**, 125 MHz, MeOD): δ ppm 161.0 (5-*C*), 155.2 (A*r*), 130.6 (A*r*), 122.3 (*Ar*H), 113.2 (*Ar*H), 66.6 (8-*C*), 63.4 (10a-*C*), 57.3 (6a-*C*), 54.4 (ArO*C*$H_3$), 43.2 (3-*C*), 37.6 (7-*C*), 34.3 (9-*C*), 29.9 (1-*C*), 28.1 (10-*C*), 24.8 (tert-butyl *C*$H_3$), 22.1 (2-*C*), 17.0 (tert-butyl *C*), -5.6 (Si*C*$H_{3A}$), -5.7 (Si*C*$H_{3B}$). Signals for minor isomer visible at: 122.0, 63.7, 63.6, 56.2, 35.1, 34.1, 27.9, 25.3, 22.5. **IR** $\nu_{max}$

(neat)/cm$^{-1}$: 2951, 2930, 2855 (C-H); 1698 (C=O); 1513, 1462, 1394 (C=C); 1247 (C-O). **HRMS** (ESI): $C_{23}H_{37}N_2O_3Si$ [M + H$^+$]: calculated 417.2568, found 417.2567.

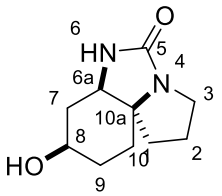
(6a*R**,8*R**,10a*S**)-8-[(*tert*-Butyldimethylsilyl)oxy]octahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazole-5-one **214**




**214**
**Major diastereomer, *dr* 80:20**

To a mixure of the urea **213** (20.0 mg, 0.05 mmol, 1.0 eq.) and CAN (105 mg, 0.19, 4.0 eq.) in 1.0 mL of HPLC grade MeCN, 0.50 mL of $H_2O$ was added and the mixture was left to stir for 5 min. The reaction mixture was extracted with EtOAc (5 × 20 mL). The combined organic layer was washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo*. Flash chromatography with 0.5 – 10% MeOH in DCM afforded the product as an 80:20 mixture of diastereomers. (4.00 mg, 0.01 mmol, 27% yield). **R$_f$** = 0.35 (1% MeOH in DCM). **$^1$H NMR** (**Major diastereomer**, 500 MHz, MeOD): δ ppm 4.68 (1H, s, N*H*), 3.73 (1H, ddd, *J* = 12.3, 9.1, 5.4, 3-*H$_A$*), 3.64 – 3.57 (1H, m, 8-*H*), 3.42 (1H, dd, *J* = 10.0, 6.0, 6a-*H*), 2.93 (1H, ddd, *J* = 12.0, 6.5, 3.0, 3-*H$_B$*), 2.12 (1H, dddd, *J* = 11.0, 6.0, 4.5, 2.0, 7-*H$_A$*), 1.89 – 1.80 (3H, m, 1-*H$_A$*, 2-*H$_{A,B}$*), 1.66 – 1.61 (2H, m, 9-*H$_A$*, 10-*H$_A$*), 1.52 – 1.45 (3H, m, 7-*H$_B$*, 9-*H$_B$*, 10-*H$_B$*), 1.27 (1H, ddd, *J* = 14.7, 12.2, 3.9, 1-*H$_B$*), 0.82 (9H, s, tert-butyl C*H$_3$*), 0.00 (3H, s, SiC*H$_{3A}$*), -0.003 (3H, s, SiC*H$_{3B}$*). Signal for minor isomer visible at: 4.04 (0.25H, ddd, *J* = 11.0, 5.5, 3.0, 3-*H*). **$^{13}$C NMR** (**Major diastereomer**, 125 MHz, MeOD): δ ppm 164.6 (5-*C*), 66.1 (8-*C*), 66.0 (10a-*C*), 51.7 (6a-*C*), 42.9 (3-*C*), 40.7 (7-*C*), 33.6 (9-*C*), 29.9 (10-*C*), 28.3 (1-*C*), 24.8 (tert-butyl *C*H$_3$), 22.6 (2-*C*), 17.1 (tert-butyl *C*), -5.6 (Si*C*H$_{3A}$), -5.7 (Si*C*H$_{3B}$). Signals for minor isomer visible at: 67.4, 67.1, 52.2, 38.7, 35.4, 29.0, 26.5, 24.1, -4.8, -4.9. **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3274 (N-H); 2951, 2929, 2856 (C-H); 1699 (C=O); 1086 (C-O). **HRMS** (ESI): $C_{16}H_{31}N_2O_2Si$ [M + H$^+$]: calculated 311.2149, found 311.2145.

(6a*R**,8*R**,10a*S**)-8-Hydroxyoctahydro-1*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*]imidazole-5-one **215**




**215**
**Major diastereomer, *dr* 85:15**

To a mixture of the ketone **104** (14.0 mg, 0.07 mmol, 1.0 eq.) and $CeCl_3.7H_2O$ (32.2 mg, 0.09 mmol, 1.2 eq.) in 3 mL of HPLC grade MeOH at –78 °C, $NaBH_4$ (3.30 mg, 0.09 mmol, 1.2 eq.) was added and the reaction mixture was stirred at the same temperature for 30 min. It was then allowed to warm up to room temperature for another 30 min. The reaction mixture was evaporated *in vacuo*. It was then taken up in 1 mL $H_2O$, diluted with 50 mL EtOAc, dried over $Na_2SO_4$ and evaporated *in vacuo*. Flash chromatography with 3 – 8% MeOH in DCM afforded the product as an 85:15 mixture of diastereomers (12.0 mg, 0.06 mmol, 85% yield). $\mathbf{R_f}$ = 0.34 (8% MeOH in DCM). **$^1$H NMR** (**Major diastereomer**, 500 MHz, MeOD): δ ppm 4.81 (1H, s, N*H*), 3.73 – 3.65 (2H, m, 3-$H_A$, 8-*H*), 3.49 (1H, dd, *J* = 8.5, 6.5, 6a-*H*), 2.94 (1H, ddd, *J* = 12.0, 8.8, 6.2, 3-$H_B$), 2.17 (1H, dt, *J* = 12.5, 6.5, 7-$H_A$), 1.90 – 1.80 (4H, m, 1-$H_A$; 2-$H_{A,B}$; 9-$H_A$), 1.66 – 1.61 (1H, m, 10-$H_A$), 1.56 – 1.45 (3H, m, 1-$H_B$, 7-$H_B$, 10-$H_B$), 1.31 (1H, qd, *J* = 11.5, 3.5, 9-$H_B$), 1.18 (1H, s, 8-CHO*H*). Signal for minor isomer visible at: 4.12 (0.18H, quint, *J* = 5.0, 8-*H*). **$^{13}$C NMR** (**Major diastereomer**, 125 MHz, MeOD): δ ppm 164.5 (5-*C*), 66.0 (10a-*C*), 65.4 (8-*C*), 52.5 (6a-*C*), 42.9 (3-*C*), 39.0 (7-*C*), 34.0 (10-*C*), 29.3 (1-*C*), 28.2 (9-*C*), 23.0 (2-*C*). Signals for minor isomer visible at: 63.1, 52.3, 36.3, 34.7, 27.6, 26.0, 23.3. **IR** $\nu_{max}$ (neat)/cm$^{-1}$: 3298 (N-H, O-H); 2931, 2855 (C-H); 1689 (C=O); 1049 (C-O). **HRMS** (ESI): $C_{10}H_{17}N_2O_2$ [M + H$^+$]: calculated 197.1285, found 197.1278.

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