New Methods for the Synthesis of Biologically Active Phenanthridine-Based Libraries

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DECLARATION

This thesis is submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Edinburgh. Unless otherwise stated the work in this thesis is original and has not been submitted previously in whole or in part for any degree or other qualification at this, or any other university. In accordance with the regulations this thesis does not exceed 70,000 words in length.

Lauren Rona Donaldson
For Mum, Dad, Neil and Finn.
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**ABSTRACT**

Small molecule libraries have become essential for the development of drug discovery campaigns and chemical genetics. The studies towards the synthesis of a small molecule library, based upon the *cis*-ring fused phenanthridine core I, will be described.

![Chemical Structure](image1)

The first section of this thesis examines the development and application of a novel intramolecular Heck cyclisation to the synthesis of core phenanthridine structure II, via precursor III (Chapter 2).

![Chemical Structure](image2)

The second section (Chapter 3) describes the extension of this methodology towards the development of a library of phenanthridines IV. This includes methodology designed to incorporate the key principles of diversity-oriented synthesis, namely appendage, stereochemical and skeletal diversity.

![Chemical Structure](image3)

The final part of this thesis (Chapter 4) describes the merging of these various methodologies to generate a small library of novel phenanthridine analogues. Preliminary biological evaluation of the phenanthridine library using whole organism zebrafish phenotyping, will also be discussed.
CONTENTS

DECLARATION I
DEDICATION II
ACKNOWLEDGEMENTS III
ABSTRACT IV

CHAPTER 1 INTRODUCTION 1

METHODS FOR THE SYNTHESIS OF BIOACTIVE SMALL MOLECULE LIBRARIES

1.1 Chemical libraries 1
1.2 Advances in combinatorial chemistry 3
1.3 Chemical space 4
1.4 Natural product based library synthesis 6

Libraries based on:
1.4.1 Core scaffolds of individual natural products 7
1.4.2 Specific substructures from classes of natural products 9
1.4.3 General characteristics of natural products 12
1.5 Diversity-oriented synthesis (DOS) 15
1.5.1 Forward-thinking synthetic analysis 15
1.5.2 Complexity generating reactions (simple → complex) 16
1.5.3 Diversity-generating processes (similar → diverse) 17
1.5.3.1 Appendage diversity 18
1.5.3.2 Stereochemical diversity 19
1.5.3.3 Skeletal diversity 20
1.5.4 Summary of DOS 24
1.6 Biologically-oriented synthesis (BIOS) 24
1.6.1 Protein structure similarity clustering (PSSC) 25
1.6.2 PSSC and SCONP 26
1.7 Conclusions 27
1.8 Proposed work 27
HECK CYCLISATION STUDIES

2.1 The Heck reaction

2.1.1 Recent developments in Heck chemistry

2.2 Proposed work

2.3 Catalyst screening studies

2.3.1 Precursor synthesis

2.3.2 Pd(OAc)$_2$

2.3.3 Microwave studies

2.3.4 Pd black

2.3.5 Herrmann-Beller palladacycle

2.3.6 Jeffery conditions

2.3.7 Pd(dppf)Cl$_2$

2.4 Neutral vs cationic

2.5 Product identification

2.5.1 Double bond isomers

2.5.2 Cis ring junction stereochemistry

2.6 Application of cationic conditions to protected amines

2.7 Application to a gem-dimethyl analogue

2.8 Diversity based applications

2.8.1 Herrmann-Beller neutral conditions

2.8.2 Low temperature alternative

2.8.2.1 Background information

2.8.2.2 Application to protected amine cyclisation precursors

2.8.2.3 Application to aryl iodides

2.8.3.4 Rationalising catalyst behaviour

2.8.3 Attempted cyclisation of an aryl chloride precursor

2.9 Mechanistic studies

2.9.1 Amine cyclisation precursors

2.9.2 Sulfonamide and carbamate substrates
2.9.3 Isomer variation with time 61
2.9.4 Resubmission experiments 63
2.9.5 Decomplexation vs hydro/dehydropalladation 65

2.10 Conclusions 66

CHAPTER 3 RESULTS AND DISCUSSION PART 2 67

DIVERSIFICATION METHODOLOGY

3.1 Introduction 67
3.2 Building block diversity 68
  3.2.1 Thiophene analogue 68
  3.2.2 Standard synthesis of aryl amines 70
  3.2.3 Synthesis of cyclisation precursors 72
  3.2.4 Piperonyl analogue 73
  3.2.5 Phenethyl substrate via Curtius rearrangement 77
  3.2.6 Issues with indoles 78
  3.2.7 Heck cyclisation of aryl/heteroaryl cyclisation precursors 81

3.3 Stereochemical diversity 84
  3.3.1 Cis-dihydroxylation 85
  3.3.2 Proof of stereochemistry 87
  3.3.3 Epoxidation using mCPBA or via a bromohydrin 88
  3.3.4 Epoxidation using DMDO (dimethyldioxirane) 90

3.4 Skeletal diversity 93
  3.4.1 Ring-rearrangement metathesis (RRM) 93
  3.4.2 ROM/RRM of unstrained cycloalkenes 94
  3.4.3 RRM in DOS 96
  3.4.4 Mechanism 96
  3.4.5 Proposed RRM of the phenanthridine core 98
  3.4.6 Synthesis of RRM precursors 99
    3.4.6.1 Heck cyclisation approach 99
    3.4.6.2 Attempted deprotection of N-Boc 99
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4.6.3 Flash vacuum pyrolysis (FVP) deprotection of N-Boc</td>
<td>101</td>
</tr>
<tr>
<td>3.4.6.4 RRM precursors via alkylation/acylation</td>
<td>102</td>
</tr>
<tr>
<td>3.4.7 RRM studies – Propargyl analogues</td>
<td>103</td>
</tr>
<tr>
<td>3.4.8 RRM of homopropargyl analogues</td>
<td>105</td>
</tr>
<tr>
<td>3.4.9 Other metathesis attempts</td>
<td>107</td>
</tr>
<tr>
<td>3.4.10 Conclusions for RRM</td>
<td>108</td>
</tr>
<tr>
<td>3.5 Conclusions</td>
<td>110</td>
</tr>
</tbody>
</table>

**CHAPTER 4**  
**RESULTS AND DISCUSSION PART 3**

**LIBRARY SYNTHESIS AND BIOLOGICAL EVALUATION**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Library synthesis</td>
<td>111</td>
</tr>
<tr>
<td>4.2 Screening of small molecule libraries</td>
<td>115</td>
</tr>
<tr>
<td>4.3 Zebrafish</td>
<td>116</td>
</tr>
<tr>
<td>4.3.1 Practicalities of high-throughput phenotyping in zebrafish</td>
<td>118</td>
</tr>
<tr>
<td>4.3.2 Developmental stages of zebrafish embryos</td>
<td>120</td>
</tr>
<tr>
<td>4.3.3 Biological evaluation of our library using zebrafish</td>
<td>121</td>
</tr>
<tr>
<td>4.4 Conclusion</td>
<td>125</td>
</tr>
</tbody>
</table>

**CHAPTER 5**  
**FUTURE WORK**

**CHAPTER 6**  
**EXPERIMENTAL PROCEDURES**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1 General experimental</td>
<td>128</td>
</tr>
<tr>
<td>6.2 Experimental for Chapter 2</td>
<td>131</td>
</tr>
<tr>
<td>6.3 Experimental for Chapter 3</td>
<td>166</td>
</tr>
<tr>
<td>6.4 Experimental for Chapter 4</td>
<td>239</td>
</tr>
</tbody>
</table>

**REFERENCES**

**ABBREVIATIONS**

**APPENDIX** Copy of Tetrahedron publication


**METHODS FOR THE SYNTHESIS OF BIOACTIVE SMALL MOLECULE LIBRARIES**

1.1 Chemical libraries

Modern drug discovery relies upon small molecule libraries to generate potential leads through the process of high-throughput screening.¹ These libraries are screened against a pre-validated biological target and any suitably active compounds (known as hits), are subjected to further development in lead optimisation (Figure 1.1).

![Figure 1.1](image)

**Figure 1.1 The process of modern drug discovery.**

More recently, compound libraries have been required to further the field of chemical genetics, an area that seeks to emulate the success of classical genetics by using small molecules to probe the function of proteins. This can be performed in a forward or reverse manner as depicted in Figure 1.2.²³ Forward chemical genetics involves identification of a phenotype in an organism or cell that is caused by a small molecule, in the example shown the mitotic spindle is in disarray. The protein target that has been modulated can then be identified, hence providing its function and a small molecule modulator from one process. Reverse chemical genetics involves the selection of a protein target (here a Lux-R type protein), against which small molecules are screened for candidates that affect the protein’s activity (here pigment production). In this reverse sense, by observance of the arising phenotype, the
function of a protein can be determined. This is akin to classical drug discovery, but in this case the function of the protein is not known beforehand.

A) Forward chemical genetics (Phenotype to Protein)

B) Reverse chemical genetics (Protein to Phenotype)

**Figure 1.2** A *Forward chemical genetics.* B *Reverse chemical genetics.*

A) A small molecule binds to the Eg5 motor protein causing disarray of the mitotic spindle (tubulin green, DNA blue). B) An agonist binds to a Lux-R type protein activating pigment production.

The ultimate goal of chemical genetics is to identify small molecules that perturb the function of every gene product, this is known as chemical genomics. Approximately 10% of the human genome (25,000 genes) is thought to encode proteins that will bind drug-like compounds, and of these only 1000 have a known small molecule chemical modulator. In addition, for all the approved therapeutic drugs, only 324 biological targets have been identified, therefore the potential for research in this area is huge.

Both chemical genetics and modern drug discovery processes put demands on the need for small molecule libraries. Library sources can be found in the form of in-house compound collections, commercially acquired libraries from combinatorial chemistry campaigns, or even virtual libraries. However, many such libraries suffer from a lack of diversity as a result of their origin. For example, pharmaceutical in-house compound collections can be biased as a result of the previous projects
undertaken in the company and by specific guidelines such as Lipinski’s rules.\textsuperscript{7} Therefore recently there has been renewed interest in compound libraries derived from natural products,\textsuperscript{5} and in libraries synthesised with the aim of maximising structural and skeletal diversity such as diversity-oriented synthesis (DOS) libraries,\textsuperscript{3} and biologically-oriented synthesis (BIOS) libraries.\textsuperscript{6} Approaches towards these different types of library synthesis will be addressed in this chapter.

1.2 Advances in combinatorial chemistry

Combinatorial chemistry enables the rapid assembly of collections of small molecules, usually using a solid support.\textsuperscript{7} Compared to target-oriented synthesis, combinatorial chemistry allows multiple reactions to be performed in parallel using different building blocks to access a diverse range of products (Figure 1.3). In combination with solid-phase split-pool chemistry, the rapid assembly of small molecule collections in high yield is possible.

\textbf{Figure 1.3} Single molecule (A), combinatorial (B) and (C) split-pool synthesis.\textsuperscript{7}

\textsuperscript{7} Lipinski’s analysis of the world drug index led to the ‘rule-of-five’, which identifies key properties considered appropriate for small molecules intended for oral administration. These properties are: molecular mass $<$500 Da, number of H-bond donors $<$5; number of H-bond acceptors $<$10; octanol-water partition coefficient $<$5.\textsuperscript{8}
These small molecules can then be screened as mixtures following cleavage from the solid-support, and any active hits can be deconvoluted and resynthesised individually using the existing route. More recently a wealth of technology has been developed to facilitate faster, cleaner and more robust synthesis, for example the use of automated microwave reactors to perform many reactions in sequence. Other areas include automated weighing devices, LCMS and NMR systems for automated sample analysis, and radio-frequency tagging or optical coding to track each specific compound throughout the synthesis process. Similarly, computer systems have been developed to manage the library and keep track of every compound synthesised, along with its purity and location, removing the need for human intervention to a large extent.

At its outset, combinatorial chemistry promised the synthesis of libraries comprising millions of compounds, which would rapidly accelerate the drug discovery hit to lead optimisation stage. However, more recently, questions have been raised as to whether this approach really fulfilled its promise, since some of the libraries produced few or no hits. Although the libraries created by combinatorial chemistry campaigns were large and structurally diverse from each other, compound members within a library were less so, as a result of the similar building blocks and reaction sequences used to construct them. As a result of this, the focus of library synthesis has shifted toward approaches that enable the introduction of greater structural diversity and wider population of chemical space.

1.3 Chemical space

Chemical space refers to the infinite number of chemical substances that in principle can be synthesised. Calculations have estimated this to represent approximately $10^{60}$ drug-like compounds, an unachievable number when considered there are only $10^{51}$ atoms on earth. Chemical space can be represented in 3D using different molecular descriptors as the three axis, where descriptors are characteristics of compounds such as molecular weight. The chemical space explored by three different approaches to complex molecule synthesis are illustrated by the axes shown in Figure 1.4.
Within chemical space there are voids where there are no molecules of biological interest, but likewise there are areas that correlate to excellent bioactivity. Several different approaches have been developed to try and identify the regions of chemical space for which the likelihood of obtaining biologically active compounds is given, or at least enhanced.

A recent principal component analysis, based on several molecular descriptors (number of chiral centers, rotatable bonds, C-N bonds, C-S bonds, C-O bonds, C-X bonds, degree of ring fusion, ratio of aromatic rings to ring atoms) showed that natural products and drug compounds occupied far greater areas of chemical space than combinatorial libraries (Figure 1.5). This suggests that the best chance of identifying bioactive molecules lies with a library that depends not on size, but on the quality and diversity of its components. The majority of approaches currently being investigated in the literature make use of natural products to varying degrees, as inspiration for the synthesis of high quality and diverse libraries.

Figure 1.4 Exploration of chemical space by Target-oriented synthesis (A), Focused library synthesis (B) and DOS (C).  

Figure 1.5 Principle component analysis of a) a random selection of combinatorial compounds; b) natural products; c) approved drugs.
1.4 Natural product based library synthesis

Despite the intrinsic bioactivity of natural products, their use in drug discovery libraries has been neglected over recent years. Much of this can be attributed to their structural complexity, which rendered them incompatible with high-throughput synthesis for many years, and difficult to modify into analogues. Natural products are also notoriously difficult to obtain and purify, and so are often screened as mixtures that are difficult and time-consuming to deconvolute. Additionally, despite natural products being used clinically to great success, they do not tend to lie within the parameters dictated by Lipinski’s rules, making them less favoured as potential drug leads.

However, despite these drawbacks, natural products still possess a higher hit-rate in drug discovery than any unspecific library. For example, between 1981 and 2002, 61% of the 877 new chemical entities approved by the FDA were natural product-based. Nature designed these molecules for a specific biological purpose and function, and given the close relationship shared by the genomes of all organisms, evolution selected natural products to bind to proteins similar to human proteins. Despite the recent lack of interest from mainstream pharmaceutical companies, natural product synthesis has formed the basis of much of the organic synthetic literature. As a result, many new pieces of methodology for manipulation and generation of these complex architectures have been reported, along with several reports of solid phase total synthesis. Additionally, advances in microbial genomics, and separation/purification technology have made the prediction, identification and isolation of natural products less challenging.

Natural products are unmatched in terms of their inherent bioactivity and their ability to probe chemical space. Therefore they offer excellent, biologically validated starting points upon which to base chemical library design. The three main ways in which this has been investigated will be discussed below.
1.4.1 Libraries based on the core scaffolds of individual natural products

Libraries based on the core scaffolds of individual natural products are a useful way of optimising the activity of a parent compound, and establishing structure-activity relationships.\textsuperscript{20} Fortunately, the combinatorial methods that caused the initial decline of natural product screening are now proving highly useful for this type of library synthesis. Typically, complex natural product skeletons (usually derived from total synthesis or semi-synthesis efforts) are immobilised on solid support, thus enabling relatively simple derivatisation.\textsuperscript{5,21} This method was used to prepare a library of analogues closely based on the anti-tubulin natural products sarcodictyin A and B (Scheme 1.1).\textsuperscript{22} In this example, immobilisation of advanced intermediate 5 on a solid support enabled the introduction of diversity at three points (R’, R” and R”’) on the core structure. A small library of 30 analogues was prepared, with several showing equal or better activity than the parent structures, including against taxol-resistant cancer strains.

\begin{center}
\textbf{Scheme 1.1} Solid phase synthesis of a 30-member focused library of sarcodictyin analogues.\textsuperscript{22}
\end{center}

An alternative approach to libraries of this type can be realised by making use of a synthetic route developed during the original natural product synthesis. If this pre-established chemistry is compatible with solid support, multi-component building
blocks can be used to rapidly build a focused library of analogues.\textsuperscript{21} This approach was successfully used for the generation of a 44-member library based on the natural products epothilone A and B (Scheme 1.2).\textsuperscript{23} The epothilones share their unusual anti-mitotic mode of action with paclitaxel, however they possess a more accessible core structure and have the advantage of being several-thousand times more active against paclitaxel resistant cell lines.\textsuperscript{24} The epothilone library was derived using radiofrequency tagged Merrifield resin that enabled sorting and tracking of intermediates throughout the split-pool synthesis. The key step involved simultaneous formation and release of the lactone macrocycle 11 by a ruthenium carbene-catalysed ring-closing metathesis reaction. Nine of the synthesised analogues showed cytotoxic activity against breast and ovarian cancer cells.

Scheme 1.2 Solid phase-SMART microreactor synthesis of a 44-member epothilone library:\textsuperscript{23}

a) i) NaHMDS (3 eq), THF:DMSO 1:1, 25 °C, 12 h; ii) A (2 eq), THF, 0 °C, 3 h; b) 0.2 M HCl in THF, 25 °C, 12 h; c) (COCl)\textsubscript{2} (4 eq), DMSO (8 eq), Et\textsubscript{3}N (12.5 eq), -78 → 25 °C; d) i) B (2 eq), LDA (2.2 eq), THF, -78 → -40 °C; ii) ZnCl\textsubscript{2} (2 eq), -78 → -40 °C, 2 h; e) C (5 eq), DCC (5 eq), DMAP (5 eq), 25 °C, 15 h; f) Grubbs I (0.2 eq), CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 48 h.
Individual natural products have also been the inspiration for libraries used to address a variety of biological targets. This approach works on the proposal that libraries based on a natural product that is known to bind one particular protein domain should be a rich source of compounds that bind selectively to other targets sharing the same protein fold. This is known as biologically oriented synthesis (BIOS) and is discussed in a separate section below (see section 1.6).

1.4.2 Libraries based on specific substructures from classes of natural products

Specific substructures of natural products can also be considered biologically validated, and libraries based on these foundations are becoming increasingly popular. The concept of a ‘scaffold tree’ was recently reported as a method for categorising natural product substructures. Stepwise deconstruction of complex structures into smaller parent structures was achieved using a set of rules derived from organic and medicinal chemistry. This maps the underlying scaffolds of natural products in a hierarchical manner based upon their cyclic frameworks and linkers (Figure 1.6). Within the scaffold tree, three scaffold classes are distinguished: carbocycles, N-heterocycles and O-heterocycles, with the most common scaffolds comprising of two to four rings.
The significance of this approach lies in its ability to enable correlation between different classes of scaffold, which is performed during BIOS (See section 1.6). It also enables the identification of biologically relevant core scaffolds for the design and synthesis of focused library collections. Such libraries are enhanced by their natural product origins, but also have the added benefit of increased structural diversity so that a wider range of biological targets might be addressed.

One of the earliest examples of this type of substructure-based focused library synthesis incorporated the 2,2-dimethylbenzopyran unit 12 (Scheme 1.3). This structural motif lies at the heart of many natural products including the flavenoids, stillbenoids, coumarins, rotenoids and the chromene glycosides, several of which have important medicinal applications. Initial efforts were concentrated on the combinatorial split-pool synthesis of six focused libraries, based around 2,2-dimethylbenzopyran targets of recent biological interest. This resulted in the development of novel solid-phase selenium-based cycloloading methodology for the
construction and elaboration of structures containing this template (Scheme 1.3). The selenyl bromide resin encompassed the essential features of both a solid-phase reagent and a traceless linker, eliminating the presence of any residual functionality in the product structure upon oxidative cleavage from the resin.

Scheme 1.3 Solid-phase synthesis strategy for the loading, elaboration and cleavage of 2,2-dimethylbenzopyrans.

This novel methodology was then applied in conjunction with the IRORI NanoKan optical encoding system, to synthesise a 10,000 member library containing approximately 1-2 mg of each small molecule. The library was then subjected to comprehensive biological screening, followed by parallel solution-phase optimisation to increase the number and diversity of library members, and aid identification of key structure activity relationships. As a result, several cyanostilbenes were identified which had low micromolar activity against MRSA, including compound 17 (Figure 1.7) which exhibited a 5 µM MIC (minimum inhibitory concentration) against six different MRSA strains. Another screen identified novel anti-steroidal agonists of the farnesoid X reporter gene, including compound 18, fexachloramide, which displayed an EC\textsubscript{50} value of 188 nM. While the active compounds are not potent enough to represent drug candidates, they do offer new avenues for lead optimisation and exploration.
1.4.3 Libraries based on the general characteristics of natural products

Libraries can also be synthesised using the general structural characteristics of natural products, rather than their specific structures or substructures. Natural products show bioactivity because their rigid structures are able to present functional groups in a favourable arrangement. Therefore mimicking the complex structures of natural products by the incorporation of dense stereochemical and functional diversity around a rigid molecular skeleton may lead to the identification of novel pharmacophores. Although this approach forgoes any direct connection to specific natural product structures, it does offer a unique opportunity for the synthesis of novel small molecules that may be able to address targets currently considered undruggable.

This type of library synthesis was applied to the 1,3-dioxane structure illustrated in Figure 1.8. The 1,3-dioxane was chosen due to its structural rigidity and its reproducible stereoselective synthesis in the presence of diverse ancillary groups. Initial efforts focused on the synthesis of a 1890-member pilot library using solid-phase split-pool chemistry in conjunction with various building blocks.
Introduction

From this library several bioactive compounds were identified including uretupamine B 19, a novel inhibitor of the yeast nutrient responsive signaling proteins Ure2p (Figure 1.9). Two selective inhibitors of the histone deacetylase (HDAC) family were also discovered, tubacin 20 and histacin 21. This led to the identification of a new potential antimetastatic and antiangiogenic therapeutic target, HDAC6.\textsuperscript{27}

More recently, this 1,3-dioxane library was expanded to 18,000 members through the incorporation of additional building blocks and stereochemical diversity. Principal component analysis assessed that the 18,000-member library explored an equivalent volume of chemical space to a known library of 2000 bioactive compounds (Figure 1.10 A).\textsuperscript{28} From the biological screening results, compound 22 (Figure 1.10, B) was shown to have a detrimental effect on cardiovascular development in embryonic
zebrafish, whereas its enantiomer, synthesised in the earlier library, did not. This illustrates the dividends of stereochemical library enrichment.

Figure 1.10 Stereochemical enrichment of a 1,3-dioxane library.\textsuperscript{28}

A: 1,3-dioxanes (red) and a known bioactive library (various colors) plotted in molecular diversity space. B: Compound 22 induces cardiac malfunction in zebrafish while its enantiomer does not.

Libraries constructed in this manner are termed by some to be diversity-oriented synthesis (DOS) around a privileged structure. Likewise, libraries synthesised around a natural product substructure could also technically earn this name. There is a fine line between these different approaches that tend to be described in different ways by different authors. However, for the purposes of this overview, DOS will refer to library synthesis governed by the specific rules and thought processes described in the next section (1.5).
1.5 Diversity-oriented synthesis (DOS)

It is clear from the natural product-based examples reported above (section 1.4) that the more complex and diverse a library is, the greater its chances are of producing a novel bioactive small molecule. The field of diversity-oriented synthesis was developed with the aim of creating structurally diverse libraries of architectures that mimic the overall complexity of natural products. The goals of DOS include the development of pathways that lead to the synthesis of collections of small molecules in three-to-five steps. These pathways must allow the incorporation of skeletal and stereochemical diversity by the use of complexity-generating reactions, and ideally lead to molecules with defined coordinates in chemical space. DOS methodology should also allow the incorporation of different building-blocks from the outset, and additionally create sites for the potential appendage of further building-blocks post-screening, so that active hits might be optimised.

1.5.1 Forward-thinking synthetic analysis

In contrast to target-oriented synthesis that employs retrosynthetic analysis, DOS makes use of forward synthetic planning to move in the direction of simple and similar structures to complex and diverse structures (Figure 1.11). The key subunits of retrosynthesis are the ‘retrons’ that must be identified before the application of a transformation. In contrast, the key subunit of forward-synthetic analysis is the transformation itself, which enables the conversion of a group of substrates into a group of products. The key element for the implementation of forward-synthetic analysis is the identification of reactive subunits common to a

![Figure 1.11 Retrosynthetic analysis versus forward-synthetic analysis.](image-url)
group of compounds, which enables them all to be potential substrates for the same reaction. DOS makes use of both complexity-generating reactions, and diversity-generating processes in its quest to populate chemical space, both methods can be considered independently, and will be discussed below.

1.5.2 Complexity generating reactions (simple $\rightarrow$ complex)

DOS requires reactions, or transformations, that promote its quest for the conversion of simple starting materials into complex products. Many multicomponent reactions are suitable for this purpose, including the asymmetric [3+2] azomethine ylide cycloaddition, and the Cu(II)-pybox catalysed Passerini reaction, both illustrated in Scheme 1.4. Both reactions proceed in excellent yield and in a highly stereoselective manner, generating complex products in just one step from relatively simple starting materials.

![Scheme 1.4](image)

Scheme 1.4 Highly stereoselective complexity-generating reactions.$^{29,30}$


Further complexity can be introduced by the identification of pairwise-relationships, where the product of one reaction is the substrate for another. These offer enormous potential for the generation of increasingly complex skeletons.$^{14}$ This was shown in an Ugi/Diels-Alder/ring-rearrangement metathesis sequence to the synthesis of complex polycycle 39 in just three steps (Scheme 1.5).$^{31}$
Scheme 1.5 *Three-step synthesis of a complex polycyclic 7-5-5-7 ring system.*

a) MeOH, THF, 48 h, 67%; b) KHMDS, allyl bromide, r.t., 18 h, 69%; c) Grubbs II, CH$_2$Cl$_2$, 40 °C, 36 h, 69%.

Careful choice and combination of transformations can therefore be a very powerful method for developing complex products in very few steps. Numerous examples of these types of reactions, and others, have been reported in the synthesis of DOS libraries.\textsuperscript{32-34}

**1.5.3 Diversity-generating processes (similar → diverse)**

In order to populate large areas of chemical space efficiently, DOS aims to move in the direction of similar structures to diverse structures. In order to do this, a series of products-equals-substrates relationships must be planned, where the products of one diversity-generating reaction share some common reactive functionality suitable for another reaction.\textsuperscript{14} Three different types of diversity can be identified in realising the goals of DOS, namely appendage (or building-block), stereochemical and skeletal diversity.
1.5.3.1 Appendage diversity

Combinatorial chemistry uses coupling reactions in conjunction with split-pool chemistry, to attach different building blocks to a molecular skeleton.\(^7\) In forward-synthetic analysis these are referred to as appending processes and tend to be performed using more sophisticated organic transformations than standard combinatorial synthesis. Multiple appending processes can be used on a common molecular skeleton to huge success, resulting in libraries of hundreds, thousands or even millions of members.\(^35\) One such example is illustrated in Scheme 1.6, where acyclic precursor 40 undergoes oxidative cyclisation to rigid skeleton 41, followed by four separate appending processes.\(^36\)

![Scheme 1.6 Appending processes for the elaboration of a molecular skeleton.\(^36\)](image)

\begin{itemize}
  \item a) i) Phl(OAc)$_2$, (CF$_3$)$_2$CHOH, CH$_2$Cl$_2$, 23 °C; ii) Pd(PPh$_3$)$_4$, morpholine-THF, 23 °C; b) R'$^1$OH, PPh$_3$, DIAD, THF, 0 °C; c) i) R'$^2$SH, 2,6-lutidine; ii) nBuLi, THF 0 → 40 °C; d) R'$^3$CHO, AcOH, MeOH-THF, then NaBH$_3$CN in MeOH, 23 °C or R'$^3$COCl, 2,6-lutidine, CH$_2$Cl$_2$, 23 °C or R'$^3$NCO, CH$_2$Cl$_2$, 23 °C; e) R'$^4$NH$_2$, AcOH, MeOH-CH$_2$Cl$_2$, 23 °C.
\end{itemize}
These processes encompass a Mitsunobu reaction to couple $R^1$; conjugate addition of thiols ($R^2$) to the cyclic enone; condensation or alkylation of the nucleophilic secondary amine to couple $R^3$; and finally reaction of the electrophilic ketone with hydroxylamines or hydrazines to couple $R^4$. As a result a library of 2527 molecules was submitted for biological screening, resulting in the identification of a novel compound that blocks protein transport from the Golgi apparatus to the cell membrane.\(^{36}\)

1.5.3.2 Stereochemical diversity

The incorporation of stereochemical diversity is essential to DOS-library synthesis in order that the orientations of macromolecule-interacting elements are maximised. This requires the use of enantio- or diastereoselective reactions that are also general, since they must be amenable to a collection of substrates.\(^{14}\) One such example is the diastereoselective intermolecular Diels-Alder transformation of chiral dialkenylboronic acid 46 into cycloadduct 47, with the selective formation of three stereocentres (Scheme 1.7).\(^{37}\) In this example, steric interactions with the TIPS-protected hydroxymethyl group direct cycloaddition to the less hindered face of the diene, giving rise to only one stereoisomer.

![Scheme 1.7 Stereoselective Diels-Alder reaction of a chiral dialkenylboronic acid.\(^{37}\)](image)

Although highly stereoselective reactions may increase the overall yields of DOS processes, they do have a disadvantage in that they limit the potential synthesis of the other possible stereoisomer products. In a situation where maximum diversity is required, the potential to tune particular reaction conditions in order to obtain any stereoisomer of choice, would prove highly useful.
For example, chiral catalyst 48 can be used in a hetero-Diels-Alder reaction to overcome the stereochemical bias of a chiral substrate 49 and generate diastereomeric products with high selectivity. (Scheme 1.8)\textsuperscript{4,38} The (1S,2R) catalyst shown leads to the formation of product 50, however selective use of the enantiomer of catalyst 48 leads to the formation of the diastereomeric product 51. The discovery of powerful reagents that are able to override stereochemical bias are essential to the further development of stereochemical diversity in DOS.

\textbf{Scheme 1.8} The use of a chiral reagent to override the stereochemical bias of a chiral substrate.\textsuperscript{14,38}

\subsection{1.5.3.3 Skeletal diversity}

The introduction of skeletal diversity to a small molecule library can be achieved using either a reagent–based approach (Figure 1.12, A), or a substrate-based approach (Figure 1.12, B).\textsuperscript{3} Reagent-based approaches encompass the use of a pluripotent functionality, where the same part of the molecule is subjected to different transformations induced by different reagents; or, the use of a multiple-group pairing strategy where different parts of the same densely functionalised molecule, are transformed by different reagents. Alternatively, a substrate-based approach called a folding process can be used, where different structurally encoding elements (σ elements), contained in different substrates, are subjected to the same reaction conditions.
An example of achieving skeletal diversity through the use of *pluripotent functionality* is illustrated in **Scheme 1.9**, using polyfluorocarbon tagged diazoacetate. The fluorous tag enables the use of various purification technologies, making the methodology compatible with high-throughput solution-phase combinatorial chemistry. The diazoacetate was utilised in various divergent reactions to give a wide variety of molecular skeletons including 54, 56 and 58. A small molecule collection of 223 compounds was synthesized in total, and found to occupy a greater area of chemical space than a focused library, or small pharmacological library, when assessed using molecular descriptors and PCA.

**Scheme 1.9** *Pluripotent functional group strategy using a fluorous-tagged diazoacetate.*

- a) C₆H₆, Rh₂(O₂CCF₃)₄, 70%; b) R≡CH, R₂(OAc)₃, [Bu≡CH, 57%]; c) RNH₂, NaOH then MeOH, H₂SO₄, [MeNH₂, 35%]; d) dienophile [dimethyl acetylenedicarboxylate, 59%]; e) C₅H₆, 92%. 

---

**Figure 1.12** *Generalised methods for achieving skeletal diversity.*
Multiple-group pairing strategies make use of densely functionalised molecules with pendant functionality. Different pairings of pendant functionalities give rise to multiple scaffolds using different reagents. For example, pairing the nitro and ester functionality of substrate 59 gives rise to lactam 60 under reductive cyclisation conditions (Scheme 1.10). Alternatively the nitro functionality of 59 could be activated towards reaction with the alkyne through intramolecular 1,3-cycloaddition of the derived nitrile-oxide, to afford bicyclic isoxazole 61. Finally, the alkyne could be subjected to microwave-promoted enyne metathesis conditions to afford diene 62, suitable for further elaboration under Diels-Alder conditions.

Scheme 1.10 Multiple-group pairing approach to skeletal diversity.

a) i) Zn, AcOH/THF; ii) Na$_2$CO$_3$ (aq), 92%; b) PhNCO, Et$_3$N, PhMe, r.t., 74%; c) Grubbs I, ethylene, µwave (150 W), 60 °C, CH$_2$Cl$_2$; d) N-phenylmaleamide, µwave (300 W), 160 °C, PhMe, 98%, 2 steps.

The folding process approach to DOS library synthesis makes use of substrates containing pre-encoded skeletal information (σ elements) that can be transformed into distinct molecular skeletons using common reaction conditions. Folding processes present a useful way to introduce new skeletons towards the end of a synthesis, whilst also enabling the generation of skeletons that might otherwise be difficult to access. Folding processes are also highly amenable to split-pool solid
phase synthesis, as a result of the structural similarity and therefore common reactivity, that is present until a later stage in the synthesis.

To plan such folding processes, a relatively unreactive core structure must first be identified, that can be transformed into a more reactive intermediate upon treatment with mild reagents. Various pre-encoded appendages (σ elements) having complementary reactivity to the reactive intermediate can then be attached to the common core. Finally, mild conditions are used to liberate the reactive intermediate, trigger reaction with the σ elements, and generate the different skeletons.

One such example of a relatively unreactive core is the aromatic furan ring that, upon treatment with a mild oxidant, can liberate a highly reactive cis-enedione intermediate (Scheme 1.11). By the appendage of three distinct two-carbon chains containing zero, one, or two hydroxyl groups to the furan core, it was possible to transform three similar substrates into three skeletally diverse products, using oxidative (NBS) then acidic (PPTS) conditions. Product 65 was formed via an oxidative ring opening followed by olefin isomerisation. Bicyclic ketal 67 was formed via NBS-mediated oxidative ring expansion followed by subsequent ketalisation. Finally, following oxidative ring expansion, substrate 68 underwent acid-catalysed dehydration to afford pyran-3-one 69.

\[ \text{Scheme 1.11 A skeletal diversity-generating folding process.}^{14} \]
M = macrobead.
1.5.4 Summary of DOS

Although the logic of DOS is still evolving, the information described above illustrates the clear guidelines and principles that are in place to promote its further development. The libraries that have been created so far using these principles of appendage, stereochemical, and skeletal diversity have shown great promise in both biological screens and PCA analysis, providing validation for the approach as a method for bioactive small molecule discovery.

An alternative approach to small molecule library synthesis is known as biologically oriented synthesis (BIOS).\(^6\) While DOS centres on libraries that are structurally diverse and complex, BIOS centres on libraries based around scaffolds of proven biological relevance. Although these approaches are conceptually different, they are not mutually exclusive since DOS libraries can be based around biologically privileged structures and BIOS libraries can be derived from hits generated in DOS campaigns. BIOS also significantly overlaps with the principles behind natural product libraries, however there are important differences that will be discussed below.

1.6 Biologically oriented synthesis (BIOS)

BIOS relies on principles derived from matching the complementary properties of bioactive small molecules, with their protein targets. If nature only explored a tiny amount of chemical space during evolution then it makes sense that there are huge untapped areas where great bioactivity may be discovered (this has been discussed previously, see section 1.3). The same is true for protein structures, nature only made use of a tiny fraction of all the possible amino acid combinations during evolution.\(^6\) Additionally, the three-dimensional folds of protein structures are highly conserved in structure, since similar fold structures can be formed by different amino acid sequences.

As a result of this, BIOS forges both natural products and proteins in its approach to library synthesis. Only scaffolds of proven biological relevance are chosen as starting points for library design, and the libraries generated are small, focused and limited in diversity. BIOS uses two concepts to aid its development, the scaffold tree (discussed previously, section 1.4.2) and protein structure similarity clustering (PSSC).\(^6\)
1.6.1 Protein structure similarity clustering (PSSC)

Proteins are built up from one or more domains that can be classified by their fold types (the spatial arrangement of secondary structure elements such as α-helices and β-sheets). It is estimated that the majority of proteins are built up from only 1000 fold types, although between 1000 and 10,000 different folds should exist in nature. As a consequence of this, and the limited number of natural product scaffolds, the prediction of small molecule scaffolds that might target whole groups of structurally similar proteins may be a feasible task (Figure 1.13).

![Diagram of Small Molecules, Proteins, Scaffolds, Folds](image)

**Figure 1.13** The principles of BIOS. Complementary binding between small molecules and proteins may lead to the identification of a similar complementary interaction between protein folds and small molecule core scaffolds.

PSSC uses computational algorithms to identify proteins in which the fold structure around the small molecule ligand-sensing core is similar. These structures are then assigned to the same protein similarity structure cluster. If a small molecule ligand is known for one member of the cluster, then it is rational to use the scaffold as the basis for a library that might target other members of the same cluster.
1.6.2 PSSC and Structural classification of natural products (SCONP)

The scaffold tree (Figure 1.6) is a method for the structural simplification of complex architectures that also enables links between scaffold types to be realised. The inner segment of the scaffold tree depicts less complex scaffolds, therefore moving inward along branches of the tree leads to the structural simplification of complex scaffolds. This can be used to identify suitable scaffolds for the basis of a library, following the identification of a small molecule during PSSC. This method was used to study the Cdc25A phosphatase protein cluster (Figure 1.14), which consists of Cdc25A phosphatase, AChE and 11β-hydroxysteroid dehydrogenase (11βHBD). Glycyrrhetinic acid 70 is known to be a ligand of 11βHBD, so its pentacyclic core was deconstructed using the scaffold tree to give several simpler scaffolds. One of these scaffolds, the dehydrodecaline 71 also formed the core structure of dysidiolide 72, whose natural receptor Cdc25A was also part of the cluster. This core structure was therefore considered to be a double-validated starting point for synthesis of a library of 11βHBD inhibitors, and indeed the resulting 500-member library produced 30 inhibitors with IC₅₀ values below 10 µM. This success clearly validates the principles of BIOS as a suitable approach for small molecule library design.

Figure 1.14 Merging PSSC and SCONP as a basis for library design.
1.7 Conclusions

Chemical genetics and drug discovery require small molecule libraries to further their development, and over the last decade or so, many approaches have been reported in the literature towards realising these demands. Many of these approaches are reliant upon solid-phase synthesis, and developments in this area have been fundamental to the advancement of library synthesis. Underpinning the majority of approaches is the use of natural products as a basis for library design. This can be in a very general sense (e.g. DOS), or more specifically (e.g. TOS, focused libraries, BIOS libraries). However, regardless of the approach that is used, the biological results clearly speak for themselves, fully justifying these methods for the successful discovery of novel bioactive small molecule ligands.

1.8 Proposed work

This thesis documents the work performed towards the synthesis of a small library of compounds based on the phenanthridine core 73 (Figure 1.15). The phenanthridine core forms an excellent basis for library design as it lies at the heart of numerous bioactive natural products including the antitumor antibiotic pancratistatin 74;\textsuperscript{45} antiviral lycorine 75;\textsuperscript{45,46} and the tubulin polymerization inhibitor chelidonine 76 (Figure 1.15).\textsuperscript{47,48}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure115.png}
\caption{The phenanthridine core and bioactive-phenanthridine based natural products.\textsuperscript{45-48}}
\end{figure}
We decided to focus our library around the cis-ring fused phenanthridine core (Figure 1.16) as the corresponding trans-analogues had already received significant attention in the literature.\textsuperscript{45,46} In realising our library, we developed novel Heck methodology for the synthesis of cis-ring fused phenanthridine core structures, which is described in Chapter 2.\textsuperscript{49} Additionally, methodology for the further elaboration of the phenanthridine core was developed, using the principles of DOS library synthesis (skeletal, stereochemical and appendage diversity) and natural product library design (Figure 1.16). This work is described in Chapter 3.

![Figure 1.16](image.png)

\textit{Figure 1.16} Phenanthridine library synthesis using the principles of DOS.

The methodology developed in Chapters 2 and 3 was then applied to the synthesis of a small library of phenanthridine analogues in Chapter 4. The biological assessment of the library was carried out using whole organism phenotype screening in zebrafish,\textsuperscript{50} which allows the simultaneous evaluation of all possible targets resulting from the protein domain similarities highlighted by PSSC.\textsuperscript{6}
RESULTS AND DISCUSSION PART 1
CHAPTER 2

HECK CYCLISATION STUDIES

A survey of conditions for the palladium catalysed intramolecular Heck cyclisation of protected benzylamines 77 to afford cis-ring fused phenanthridines 78 was conducted to determine the optimal conditions to carry out this transformation. This survey involved a catalyst screen, application of the optimal conditions to a range of protected benzylamines and a mechanistic study to probe the double bond isomers obtained as a result of the Heck cyclisation.

Scheme 2.1 Heck cyclisation studied in Chapter 2.
2.1 The Heck reaction

The Pd(0) catalysed vinylation of an aryl halide was reported over 30 years ago in independent studies by Mizoroki$^{51}$ and Heck.$^{52}$ The transformation is now generally referred to as the Heck reaction and is defined as the Pd(0) catalysed coupling of an aryl or vinyl halide $^{79}$ to an alkene $^{80}$ (Scheme 2.2).$^{53}$

![Scheme 2.2 The Heck reaction.](image)

Scheme 2.2 The Heck reaction.

$R = H, \text{alkyl, aryl, } \text{CN, CO}_2\text{R, OR, OAc, NHAc. } R' = \text{aryl, vinyl. } X = \text{I, Br, Cl, OTf.}$

The reaction proceeds via a catalytic cycle (Scheme 2.3) and involves oxidative addition of the Pd(0) to the C-X bond, migratory insertion of the Pd(II) into the alkene bond, $\beta$-hydride elimination to give the coupled alkene product, followed by reductive elimination to regenerate the catalytically active Pd(0) species.

![Scheme 2.3 Traditional mechanism of the Heck reaction.](image)

Scheme 2.3 Traditional mechanism of the Heck reaction.

$R, R'$ and $X$ as above. Ligands omitted for simplicity.
Since its discovery, the Heck reaction has been studied intensively, furthering the development of conditions to allow a huge range of couplings to take place efficiently. The first intramolecular Heck reaction was reported in 1977, by Mori and Ban and this was further developed into the asymmetric intramolecular Heck reaction, first reported independently by Shibasaki and Overman in 1989.

Scheme 2.4 First examples of an asymmetric Heck reaction. a) Pd(OAc)$_2$, (R)-BINAP, Ag$_2$CO$_3$, NMP, 60 °C; b) Pd(OAc)$_2$, (R,R)-DIOP, Et$_3$N, benzene, r.t.

Shibasaki’s work illustrated for the first time that an intramolecular Heck reaction could be used for the creation of a tertiary stereocentre. Overman illustrated that the intramolecular Heck reaction could be used to establish a quaternary stereocentre. Despite the modest enantioselectivities achieved with these initial examples, both studies illustrated the enormous potential of the asymmetric Heck cyclisation, and it has subsequently become the focus of many research groups worldwide and found successful application in many total syntheses.

Another area of Heck chemistry that has received a lot of attention is the development and study of new catalyst systems for more efficient Heck couplings. Traditionally, catalysts employed in the Heck reaction have a turnover number (TON) somewhere in the region of $10^2$ – $10^3$ (loadings 1 – 5 mol%). While this is more than acceptable for application in pharmaceutical and fine chemical synthesis, it is less so for plant scale synthesis where a TON of $>10^3$ (0.1 mol% loading) is desirable. To this end, extensive research has given rise to numerous catalytic
systems able to deliver such TONs, including palladacycles, coordinatively unsaturated Pd catalysts featuring bulky phosphanes [e.g. (tBu)3P2Pd], carbene ligands and even ligandless palladium. Catalysts like (tBu)3P2Pd have also proved to be particularly effective for the cross coupling of aryl chlorides and for room temperature cross-couplings.  

Like most organometallic cross-coupling reactions, the Heck reaction has been successfully carried out under microwave conditions. This rapid method of heating allows the elevated temperatures required for reaction to be reached in seconds, and in conjunction with the pressurised, sealed reaction vessels permits successful coupling in a matter of minutes. Generally microwave mediated cross-coupling reactions are found give less side products than conventional heating methods as the whole volume of the reaction solution can be heated simultaneously and uniformly. They are seen as a greener alternative to standard heating methods with regard to the amount of electricity employed, and the volume of water that is not wasted on condenser cooling.

One final area of Heck chemistry that has received much attention recently is the reaction mechanism. The sheer wealth of catalysts, ligands and results that have been generated in this area have led to some debate as to what the exact mechanism of the Heck reaction actually is. Recent reports have made claims for Pd(II)/(IV) catalytic cycles, and indeed some Pd(IV) species have been isolated. However generally, the standard neutral Pd(0)/Pd(II) cycle (Scheme 2.3) is accepted as the most accurate mechanism, although this can be diverted into the cationic manifold (see section 2.4) by the addition of Ag(I) or Tl(I) salts.
2.2 Proposed work

We were attracted to an intramolecular Heck cyclisation-based approach to the phenanthridine framework (Scheme 2.5) as there is good precedent for cis-stereocontrol in the formation of the 6,6-ring junction in related phenanthridone systems.

Scheme 2.5 Phenanthridine retrosynthesis.

P = protecting group.

For example, Grigg et al.\textsuperscript{70,71} reported the successful cyclisation of aryl iodide 86 to afford predominantly the cis-ring fused \( \Delta^{1,2} \) phenanthridone 87, along with some of the ring junction \( \Delta^{10b,1} \) double bond isomer 88, and Szmuzkovicz\textsuperscript{72} reported the formation of \( \Delta^{1,2} \) and \( \Delta^{2,3} \) cis-ring junction phenanthridones 90 and 91 from aryl iodide 89 (Scheme 2.6). The addition of \( \text{Tl}_2\text{CO}_3 \) permitted the reaction of 86 to be diverted into a cationic manifold and thus deliver solely cis \( \Delta^{1,2} \) isomer 87.

Scheme 2.6 Literature precedent for cis 6,6-ring junction.\textsuperscript{70-72}

a) \( \text{Pd(OAc)}_2 \) (0.1 eq), \( \text{PPh}_3 \) (0.2 eq), \( \text{K}_2\text{CO}_3 \) (2 eq), MeCN, 80 °C. i) with \( \text{Et}_3\text{NCl} \) (1 eq) 96 h, 78%. 87: 88 1.8:1. ii) with \( \text{Tl}_2\text{CO}_3 \), 22 h, 78% 87 only. b) \( \text{Pd(OAc)}_2 \) (0.1 eq), \( \text{PPh}_3 \) (0.2 eq), \( \text{Li}_2\text{CO}_3 \) (0.2 eq), DMF, 80 °C, 24 h, 72%. 90: 91 2:1.
Despite the literature precedent, we were concerned that the conditions reported were potentially limiting in a library-based approach to the phenanthridine core due to the lengthy reaction times (24-96 h) required for the cyclisation reaction, and the varying results with regard to the double bond isomer ratios obtained in the product.\textsuperscript{70-74} Our initial aims were thus two-fold: to develop conditions which might overcome these practical problems, whilst at the same time promoting the cyclisation of a range of functionalised amine precursors to allow access to a diverse library based upon the phenanthridine core.

2.3 Catalyst screening studies

2.3.1 Precursor synthesis

Our first task was to synthesise suitable cyclisation precursors to test in a catalyst screen. To this end, a range of sulfonamide, carbamate and amine cyclisation precursors 94a-e were found to be readily accessible through alkylation of commercially available 2-bromobenzylamine with 3-bromocyclohexene, followed by protection under the appropriate conditions (Scheme 2.7). Sulfonamide 94a provided an excellent substrate for catalyst screening studies due to its easy purification and characterisation (no amide rotamers).

\textbf{Scheme 2.7 Cyclisation precursor preparation.}

\begin{itemize}
\item P = 94a: SO\textsubscript{2}Me; 94b Boc; 94c Cbz; 94d Bn; 94e PMB.
\item a) \textsuperscript{1}Pr\textsubscript{2}NEt, 3-bromocyclohexene, MeCN, 16 h, r.t.; aii) HCl in Et\textsubscript{2}O, 99%; b) 94a MeSO\textsubscript{2}Cl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 16 h, 99%; 94b Boc\textsubscript{2}O, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 16 h, 90%; 94c NaH, DMF, 0 °C, 30 min, then benzylchloroformate, r.t., 16 h, 86%; 94d NaH, DMF, 0 °C, 30 min, then benzyl bromide, r.t., 16 h, 81%; 94e NaH, DMF, 0 °C, 30 min, then PMBBr, r.t., 16 h, 84%.
\end{itemize}
2.3.2 Pd(OAc)$_2$

We chose to use Pd(OAc)$_2$ as a starting point for our catalyst screening studies, as this was used in the corresponding phenanthridone synthesis (Scheme 2.6). The initial data for the Pd(OAc)$_2$ catalysed intramolecular Heck reaction of sulfonamide 94a are given in Table 2.1. In related intramolecular Heck cyclisation reactions of benzamides, a range of double bond isomers have been reported, including the bridgehead $\Delta^{10b,1}$ (95a), $\Delta^{1,2}$ (96a) and $\Delta^{2,3}$ (97a).$^{72-74}$ In this study, none of the bridgehead double bond isomer was formed, and the cis $\Delta^{1,2}$ isomer (96a) was observed as the major product, along with trace amounts of the cis $\Delta^{2,3}$ (97a) and cis $\Delta^{3,4}$ (98a) double bond isomers.$^6$

Table 2.1 Pd(OAc)$_2$ screening for the intramolecular Heck cyclisation of sulfonamide 94a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst$^a$</th>
<th>Base</th>
<th>T (°C)</th>
<th>t (min)</th>
<th>Solvent</th>
<th>Conversion (%)$^b$</th>
<th>Ratio 96a:97a:98a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$/PCy$_3$</td>
<td>MeNCy$_2$ (4 eq)</td>
<td>130</td>
<td>70</td>
<td>DMA</td>
<td>99</td>
<td>77:14:9</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$/PCy$_3$</td>
<td>MeNCy$_2$ (4 eq)</td>
<td>140</td>
<td>60</td>
<td>DMA</td>
<td>99</td>
<td>96:2:2</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$/PCy$_3$</td>
<td>MeNCy$_2$ (4 eq)</td>
<td>150</td>
<td>30</td>
<td>DMA</td>
<td>98</td>
<td>95:3:2</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$/PCy$_3$</td>
<td>Et$_3$N (4 eq)</td>
<td>140</td>
<td>70</td>
<td>DMA</td>
<td>58</td>
<td>90:2:8</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$/PCy$_3$</td>
<td>Py$_2$NEt (4 eq)</td>
<td>140</td>
<td>35</td>
<td>DMA</td>
<td>98</td>
<td>92:5:3</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$/PCy$_3$</td>
<td>K$_2$CO$_3$ (4 eq)</td>
<td>140</td>
<td>40</td>
<td>DMA</td>
<td>87</td>
<td>55:27:18</td>
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<tr>
<td>7</td>
<td>Pd(OAc)$_2$/PCy$_3$</td>
<td>2,6-lutidine (4 eq)</td>
<td>140</td>
<td>-</td>
<td>DMA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)$_2$/PCy$_3$</td>
<td>MeNCy$_2$ (4 eq)</td>
<td>140</td>
<td>35</td>
<td>DMF</td>
<td>95</td>
<td>94:5:1</td>
</tr>
</tbody>
</table>

$^a$ [5 mol% Pd(0) source] / [10 mol% ligand]$^b$ Conversion was determined through analysis of the $^1$H NMR of the crude reaction mixture.

Investigation of a range of bases at the optimum reaction temperature (140 °C) showed that Pr$_3$NEt gave comparable results to those obtained in presence of MeNCy$_2$, however Et$_3$N, K$_2$CO$_3$ and 2,6-lutidine gave lower conversion levels

$^6$ Unequivocal confirmation of the cis ring junction stereochemistry and the identity of the three double bond isomer products, is reported in section 2.5.
We observed that a switch in solvent from DMA to DMF (entry 8) resulted in similar or even enhanced reactivity with almost total conversion in only 35 minutes.

Unfortunately however, the results in Table 2.1 do not disclose the truth behind the reliability of our reaction. We discovered that regardless of the solvent, base or indeed the temperature (130-150 °C) employed, two apparently identical reactions, executed side by side, exhibited different colours (yellow vs black) and afforded contrasting product yields and ratios. In the reactions where the solution turned black, we either observed a significant amount (>50 %) of benzylamine 99a (Scheme 2.8) in addition to the desired cyclised products 96a-98a, or very little reaction at all. The presence of 99a was confirmed by comparison of the $^1$H and $^{13}$C NMR data of an authentic sample, synthesised in a similar manner to its bromide counterpart.

\begin{center}
\textbf{Scheme 2.8} Formation of benzylamine 99a.
\end{center}

\begin{equation}
a) \text{Pd(OAc)}_2, \text{MeNCy}_2, \text{DMA, 160 °C, 16 h, 99%}. \text{96a-98a: 99a 1:3.}
\end{equation}

\subsection*{2.3.3 Microwave studies}
As previously mentioned, microwave heating has been shown to accelerate many Pd-mediated cross-coupling reactions and can be effective at suppressing the formation of unwanted by-products, providing a generally cleaner reaction than traditional heating methods.\textsuperscript{64} We initially had concerns that the formation of unwanted benzylamine by-product 99a was occurring during the initial heating period (r.t.-140 °C) and we were interested to observe whether the rapid heating period utilised in microwave synthesis (typically <30 seconds) would eliminate this unwanted product.

Initial studies showed that a temperature of 180 °C was required to promote the Pd(OAc)$_2$ catalysed cyclisation. Performing the reaction in DMF, using either MeNCy$_2$ or iPr$_2$NEt led to significant amounts of benzylamine 99a being obtained (Table 2.2). However, using DMA as the solvent led to a significant reduction in this
unwanted by-product, with $\Delta^{1,2}$ isomer 96a being observed as the exclusive cyclised product (entries 3+4).

Table 2.2 *Microwave accelerated intramolecular Heck cyclisation of sulfonamide 94a.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>T (°C)</th>
<th>t (min)</th>
<th>Solvent</th>
<th>Conversion $^b$ (%) $^b$</th>
<th>Ratio 96a:97a:98a:99a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeNCy$_2$ (4 eq)</td>
<td>180</td>
<td>30</td>
<td>DMF</td>
<td>100</td>
<td>57:0:0:43</td>
</tr>
<tr>
<td>2</td>
<td>iPr$_2$NEt (4 eq)</td>
<td>180</td>
<td>30</td>
<td>DMF</td>
<td>100</td>
<td>70:0:0:30</td>
</tr>
<tr>
<td>3</td>
<td>MeNCy$_2$ (4 eq)</td>
<td>180</td>
<td>30</td>
<td>DMA</td>
<td>100</td>
<td>87:0:0:13</td>
</tr>
<tr>
<td>4</td>
<td>iPr$_2$NEt (4 eq)</td>
<td>180</td>
<td>30</td>
<td>DMA</td>
<td>100</td>
<td>86:0:0:14</td>
</tr>
<tr>
<td>5</td>
<td>MeNCy$_2$ (4 eq)</td>
<td>180</td>
<td>15</td>
<td>DMA</td>
<td>100</td>
<td>41:0:0:59</td>
</tr>
<tr>
<td>6</td>
<td>iPr$_2$NEt (4 eq)</td>
<td>180</td>
<td>15</td>
<td>DMA</td>
<td>100</td>
<td>66:0:0:34</td>
</tr>
<tr>
<td>7</td>
<td>MeNCy$_2$ (4 eq)</td>
<td>180</td>
<td>20</td>
<td>DMA</td>
<td>95</td>
<td>80:10:0:10</td>
</tr>
<tr>
<td>8</td>
<td>MeNCy$_2$ (4 eq)</td>
<td>180</td>
<td>20</td>
<td>DMA</td>
<td>100</td>
<td>85:12:0:3</td>
</tr>
</tbody>
</table>

$^a$ [5 mol % Pd(OAc)$_2$] / [10 mol% PCy$_3$] $^b$ Conversion was determined through analysis of the $^1$H NMR of the crude reaction mixture.

We investigated decreasing the reaction time to determine if this had any influence on the formation of by-product 99a, but this gave less favourable results at 15 mins (entries 5+6), and only comparable results at 20 mins, and with some loss in conversion (entry 7) and double bond isomerism (entry 8). Our optimal conditions therefore appeared those of entry 3 or entry 8, however again these results did not prove to be consistently reproducible, with variable amounts of 99a being formed.

We were led to conclude that regardless of the heating induction method employed, the catalyst itself was not reliable at the elevated temperatures required for reaction, using either heating approach. A survey of the literature led us to attribute this to the formation of Pd black.$^{75}$
2.3.4 Pd Black

Dehalogenated benzylamines such as 99a have been reported to form on the surface of Pd black, a colloidal species that is known to result from an excess of Pd(0) in the reaction medium (Scheme 2.9). In the Heck reaction of aryl bromides and chlorides the rate-determining step is the oxidative addition, which can result in a build up of Pd(0) in solution. Further Pd(0) build up can also occur when electron rich aryl substrates which are by nature less reactive toward oxidative addition, are employed. Additionally, it is plausible to propose that a catalyst that is rapidly converted from Pd(II) to Pd(0) can also lead to a build up of Pd(0) in the reaction medium. As a consequence, the formation of soluble nanoparticles of Pd(0) is highly likely, and if these grow beyond a certain size the formation of insoluble palladium black is observed (Scheme 2.9) giving the reaction a black colour and leading to catalyst deactivation and the formation of dehalogenated products such as 99a.

Scheme 2.9 Pd black formation.

It should be noted that the formation of Pd black is thought to be the eventual deactivation pathway for all standard Pd catalysed reactions, but that in some cases such as ours, a combination of the elevated temperature, catalyst and substrate can lead to an acceleration of this decomposition mechanism. The capricious nature of this particular catalyst system under both standard and microwave heating, led us to investigate other possible palladium sources.
2.3.5 Herrmann-Beller Palladacycle

We decided to examine the Herrmann-Beller palladacycle (100, Figure 2.1) as it is well known as a highly effective and stable source of Pd(0) for the arylation of alkenes at elevated temperatures. Its use also has precedent in intramolecular cyclisation reactions.

![Herrmann-Beller palladacycle](image)

**Figure 2.1** Herrmann-Beller palladacycle.

The reactivity of palladacycles is often attributed to high thermal stability, resulting in a slow-releasing source of Pd(0) and thus suppression of unwanted deactivation processes. While it is true that palladacycles are very thermally stable in the solid state, in solution they have actually been shown to be highly labile, undergoing facile transformations with and without fission of the palladacycle ring. Their ability to act as slow releasing reservoirs of Pd(0) is postulated to arise from their slow reaction with the other components of the reaction mixture, resulting in heterolytic cleavage of the Pd-C bond with subsequent reduction to Pd(0).
The application of 100 in conjunction with the MeNCy₂ (the optimum base from our Pd(OAc)₂ studies), gave relatively rapid cyclisation at a range of temperatures (130-150 °C), but led to diminished selectivity for the Δ¹,² double bond isomer (Table 2.3, entries 1-3).

**Table 2.3** Herrmann-Beller palladacycle screening for the intramolecular Heck cyclisation of sulfonamide 94a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst²</th>
<th>Base</th>
<th>T (°C)</th>
<th>t (min)</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Ratio 96a:97a:98a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Palladacycle 100</td>
<td>MeNCy₂ (4 eq)</td>
<td>130</td>
<td>360</td>
<td>DMF</td>
<td>85</td>
<td>39:38:23</td>
</tr>
<tr>
<td>2</td>
<td>Palladacycle 100</td>
<td>MeNCy₂ (4 eq)</td>
<td>140</td>
<td>180</td>
<td>DMF</td>
<td>98</td>
<td>44:31:25</td>
</tr>
<tr>
<td>3</td>
<td>Palladacycle 100</td>
<td>MeNCy₂ (4 eq)</td>
<td>150</td>
<td>110</td>
<td>DMF</td>
<td>88</td>
<td>52:16:32</td>
</tr>
<tr>
<td>4</td>
<td>Palladacycle 100</td>
<td>AgF (1 eq)</td>
<td>140</td>
<td>180</td>
<td>DMF</td>
<td>76</td>
<td>65:23:12</td>
</tr>
<tr>
<td>5</td>
<td>Palladacycle 100</td>
<td>Ag₃PO₄ (1 eq)</td>
<td>140</td>
<td>120</td>
<td>DMF</td>
<td>99</td>
<td>67:18:15</td>
</tr>
<tr>
<td>6</td>
<td>Palladacycle 100</td>
<td>Ag₂CO₃ (1 eq)</td>
<td>140</td>
<td>70</td>
<td>DMF</td>
<td>99</td>
<td>85:13:2</td>
</tr>
</tbody>
</table>

* [5 mol % Pd(0) source] * Conversion was determined through analysis of the ¹H NMR of the crude reaction mixture. † No significant change observed after 180 min, even on leaving reaction for 24 h.

With the aim of finding conditions that suppressed double bond migration through a cationic reaction pathway (see section 2.4),² we screened the use of a range of Ag(I) salts (entries 4-6) as additives.³ We were pleased to discover that the use of Ag₂CO₃ in conjunction with the Herrmann-Beller catalyst led to rapid conversion (70 min at 140 °C), good double bond isomer ratios and excellent reproducibility. We found that modifying the equivalents of Ag₂CO₃ salt used as the base made very little difference to the double bond isomer ratio or conversion, with one equivalent being optimal. The application of the optimal cationic (entry 6) reaction conditions to cyclisation precursors 94a-e is reported in section 2.6.
2.3.6 Jeffery conditions

Jeffery pioneered the application of the Heck reaction under aqueous conditions.\(^8^4\) Most recently these conditions have been successfully applied by Tietze in a double Heck reaction using the Herrmann-Beller palladacycle to establish two cis-annelated ring junctions (Scheme 2.10) in good yield.\(^8^5\)

![Scheme 2.10](image)

*Scheme 2.10 Application of Jeffery conditions to a double Heck reaction.*\(^8^5\)

a) Palladacycle 100, \(n\text{Bu}_4\text{NOAc}, \text{DMF/CH}_3\text{CN/H}_2\text{O 1:1:0.2, 130 – 140 °C, 1.5 h, 80%}.*

As we had achieved success with palladacycle 100 under organic phase conditions, we applied a slightly modified version of these aqueous conditions to the cyclisation of sulfonamide 94a (Table 2.4), generating the required \(n\text{Bu}_4\text{NOAc in situ}^\text{a} from \(n\text{Bu}_4\text{NBr and KOAc.}

![Table 2.4](image)

**Table 2.4 Application of modified Jeffery conditions to the cyclisation of sulfonamide 94a.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions(^a)</th>
<th>T (°C)</th>
<th>t (min)</th>
<th>Solvent(^b)</th>
<th>Conversion (%(^c))</th>
<th>Ratio 96a:97a:98a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Palladacycle 100, KOAc, (n\text{Bu}_4\text{NBr}</td>
<td>140</td>
<td>120</td>
<td>DMF: MeCN: H(_2)O 1:1:0.2</td>
<td>100</td>
<td>49:30:21</td>
</tr>
<tr>
<td>2</td>
<td>Palladacycle 100, KOAc, (n\text{Bu}_4\text{NBr}</td>
<td>150</td>
<td>40</td>
<td>DMF: MeCN: H(_2)O 1:1:0.2</td>
<td>100</td>
<td>37:49:14</td>
</tr>
<tr>
<td>3</td>
<td>Palladacycle 100, Ag(_2)CO(_3), (n\text{Bu}_4\text{NBr}</td>
<td>140</td>
<td>200</td>
<td>DMF: MeCN: H(_2)O 1:1:0.2</td>
<td>74</td>
<td>56:34:10</td>
</tr>
</tbody>
</table>

\(^a\) [5 mol % Pd(0) source] \(^b\) 1:1:0.2 ratio \(^c\) Conversion was determined through analysis of the \(^1\text{H NMR}\) of the crude reaction mixture.

We were pleased to discover that the aqueous conditions worked well using a neutral system (KOAc/\(n\text{Bu}_4\text{NBr}) to give a mixture of double bond isomers. In contrast to
the normal phase neutral cyclisation conditions reported in Table 2.3 that reach completion in 180 mins at 140 °C, these aqueous conditions take only 40 mins to give total conversion at the same temperature (entry 2), offering a significant improvement if a mixture of double-bond isomers was desired. However when we switched KOAc for Ag₂CO₃ to test the reaction under conditions that favoured a cationic pathway this led to incomplete conversion (entry 3) and a significant degree of double bond isomerism. As our initial aim was to obtain conditions for the cyclisation of sulfonamide 94a to afford predominantly one double bond isomer product, we did not pursue these aqueous conditions any longer.

2.3.7 Pd(dppf)Cl₂

We examined the use of one further catalyst, Pd(dppf)Cl₂ (Table 2.5). While this had been reported in the literature as a successful catalyst for Pd-catalysed cross-couplings at 80 °C,⁸⁶ we found that only low conversions were obtained under both neutral and cationic conditions at this temperature (22 - 50%). In addition we had no success in obtaining complete conversion of starting material in the presence of Ag₂CO₃ at any temperature (entries 3-5). However, complete conversion was achieved by employing Pd(dppf)Cl₂ under neutral conditions at 140 °C, leading to a mixture of double bond isomer products (entry 2).

Table 2.5 Pd(dppf)Cl₂ promoted Heck cyclisation of sulfonamide 94a.¹

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Solvent</th>
<th>Conversion (%) ¹</th>
<th>Ratio 96a:97a:98a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeNCy₂</td>
<td>80</td>
<td>2</td>
<td>DMF</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>MeNCy₂</td>
<td>140</td>
<td>2</td>
<td>DMF</td>
<td>100</td>
<td>37:49:14</td>
</tr>
<tr>
<td>3</td>
<td>Ag₂CO₃</td>
<td>80</td>
<td>16</td>
<td>DMF</td>
<td>50</td>
<td>47:34:19</td>
</tr>
<tr>
<td>4</td>
<td>Ag₂CO₃</td>
<td>140</td>
<td>16</td>
<td>DMF</td>
<td>53</td>
<td>69:21:10</td>
</tr>
<tr>
<td>5</td>
<td>Ag₂CO₃</td>
<td>160</td>
<td>16</td>
<td>DMF</td>
<td>59</td>
<td>85:9:6</td>
</tr>
</tbody>
</table>

¹ [5 mol% Pd(0) source] ⁸ Conversion was determined through analysis of the ¹H NMR of the crude reaction mixture.
As our optimum conditions for obtaining predominantly the $\Delta^{1,2}$ double bond isomer were obtained using palladacycle 100 under cationic conditions (Table 2.3, entry 6), these conditions were taken on and applied to the range of amine and carbamate substrates in hand (see section 2.6).

### 2.4 Neutral vs Cationic

A double catalytic cycle for the Heck reaction, documenting both a neutral and a cationic Heck reaction is shown in Scheme 2.11. Both cycles undergo similar oxidative addition steps to afford the Pd(II) intermediate 104 as shown. In the case of the cationic pathway, the Ag(I) ion abstracts the halide from the surface of 104, generating the cationic Pd(II) intermediate 105. Following migratory insertion and $\beta$–hydride elimination this affords cationic intermediate 106. It is thought this undergoes reductive elimination far faster than its neutral counterpart 107, resulting in rapid regeneration of Pd(0) and an increased rate of reaction (Table 2.3 entry 2 vs entry 6).\(^{82}\)

![Scheme 2.11](image)

**Scheme 2.11** *The Cationic and Neutral Heck catalytic cycles.*\(^{82}\)

The rapid reductive elimination step of the cationic cycle also results in decreased double bond isomerism. This is because such isomerism occurs via re-addition of the Pd(II) intermediate (106 or 107) to the alkene (108 or 109), followed by $\beta$-H elimination with an alternative proton. If the Pd(II) intermediate 106 rapidly
undergoes reductive elimination, as in the case of the cationic cycle, it is not able to participate greatly in the re-addition/β-H elimination sequence (Scheme 2.12), and thus double bond isomerism is reduced.

Scheme 2.12 Simplified illustration of double bond isomer formation (Neutral system).

2.5 Product identification
2.5.1 Double bond isomers

The identity of 96a-98a as double bond isomers was confirmed when a mixture of the compounds was treated under hydrogenation conditions to give a single saturated product 110 (Scheme 2.13). This process also told us that we had not made any of the bridgehead double bond isomer 95a, as hydrogenation could occur at either face of this phenanthridine giving rise to both the cis and trans ring junction saturated products.

Scheme 2.13 Double bond isomer conversion to a single product.

a) H₂, Pd/C, MeOH, r.t., 16 h, 60 %.

In order to determine the structure of each double bond isomer in the product mixture, they were first separated by HPLC, followed by full characterisation using 1D and 2D NMR techniques. We initially carried out COSY and HSQC NMR spectroscopy to identify the carbon backbone of each product. The COSY then enabled us to identify the Δ^2,3 isomer, as in keeping with its structure, this product did
not show any correlations between either of the ring junction protons and the alkene protons.

To distinguish between the $\Delta^{1,2}$ and $\Delta^{3,4}$ isomers we used 2D NOESY spectroscopy (Figure 2.2 and Figure 2.3). Key correlations for identifying the $\Delta^{1,2}$ product 96a include aromatics - alkene (Ar – a) and benzylic methylene - methylene of the cyclohexene ring - (g2 - d). In addition, the absence of the following correlations supported our structural assignment: (g – b), (h – d), (e – Ar), (d – Ar). Key correlations for identifying the $\Delta^{3,4}$ product 98a include benzylic methylene - alkene (g2 – d) and aromatics – cyclohexene ring methylene - (Ar – a1). As above, the absence of the following correlations supported our structural assignment: (g – a), (g – b), (e – b), (d – Ar), (e – Ar).

Figure 2.2. 2D NOESY spectrum for $\Delta^{1,2}$ isomer 96a.
Key correlations: (Ar – a), (g2 – d).
Figure 2.3. 2D NOESY spectrum for $\Delta^{3,4}$ isomer 98a.

Key correlations: (g2 – d), (Ar – a1).

Fortunately, each double bond isomer could be clearly identified in the $^1$H NMR spectrum, by the signal of its ring junction proton ‘h’ (Figure 2.4). This allowed quantification of the double bond isomer ratio for each reaction without undertaking HPLC purification.

Figure 2.4 Double bond isomer quantification for 96a-98a.
2.5.2 *Cis* ring junction stereochemistry

As suggested by the phenanthridone literature precedent, \(^{70-74}\) Heck cyclisation of precursor 94a gave the *cis*-ring fused phenanthridine product. Similar selectivity has also been reported for the Heck cyclisation of related carbocyclic systems.\(^{87a}\) Confirmation of the *cis*-ring junction stereochemistry was gained later in this study through the conversion of a mixture of 96b-98b to saturated phenanthridine 112 (Scheme 2.14), and comparison of its \(^1H\) and \(^{13}C\) NMR data with the *cis* \([\delta 2.60 (1H, m) \text{ and } 3.12 \text{ ppm (1H, m)})\] and *trans* \([\delta 2.36–2.49 \text{ ppm (2H, m)})\] ring junction phenanthridines reported in the literature.\(^{87b}\) This result was in good accord with the strong nOE observed across the ring junction in all the double bond isomer phenanthridine products (Figure 2.2 and Figure 2.3 protons h – e).

Scheme 2.14 *Cis* ring junction confirmation.

a) \(H_2, \text{Pd/C, MeOH, r.t., 16 h, 86%}\). b) TFA, \(\text{CH}_2\text{Cl}_2\), 10 mins, 98%.
2.6 Application of cationic conditions to protected amines

Our optimal cationic conditions, reported in section 2.3.5 were tested against our range of carbamate and amine cyclisation precursors to probe substrate scope.

Table 2.6 Application of optimal cationic conditions.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>P</th>
<th>t (min)</th>
<th>Yield (%)</th>
<th>Ratio (96:97:98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94a</td>
<td>SO(_2)Me</td>
<td>70</td>
<td>99</td>
<td>85:13:2</td>
</tr>
<tr>
<td>2</td>
<td>94b</td>
<td>Boc</td>
<td>120</td>
<td>99</td>
<td>83:16:2</td>
</tr>
<tr>
<td>3</td>
<td>94c</td>
<td>Cbz</td>
<td>120</td>
<td>99</td>
<td>92:6:2</td>
</tr>
<tr>
<td>4</td>
<td>94d</td>
<td>Bn</td>
<td>120</td>
<td>92</td>
<td>100:0:0</td>
</tr>
<tr>
<td>5</td>
<td>94e</td>
<td>PMB</td>
<td>160</td>
<td>76</td>
<td>97:3:0</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: aryl halide (1 eq), palladacycle 100 (5 mol%), Ag\(_2\)CO\(_3\) (1 eq), DMF, 140 °C. \(^b\) Minor isomer peaks could not be quantified.

In all cases our optimum conditions employing the Herrmann-Beller catalyst 100 gave excellent conversions to the phenanthridine core, strongly favouring the \(\Delta^{1,2}\) isomer (Table 2.6). With the exception of the PMB-protected amine precursor 94e, the reactions were complete in <2 h. The Bn and PMB protected analogues in particular showed excellent selectivity for the \(\Delta^{1,2}\) isomer.

The identity and ratios of the Boc and Cbz-protected products (96b-98b and 96c-98c respectively) were determined by direct correlation of their \(^1\)H NMR spectra with their sulfonamide counterparts (96a-98a); and the assignment of minor peaks was confirmed by TOCSY experiments. For the Bn and PMB products, extensive 2D NMR analysis confirmed that the major product in each of these two cases was the \(\Delta^{1,2}\) isomer (96d and 96e respectively), whilst the \(\Delta^{2,3}\) and \(\Delta^{3,4}\) minor products, where visible, were assigned by analogy with their sulfonamide counterparts.
2.7 Application to a gem dimethyl analogue

In order to assess the utility of these cationic conditions on a substrate biased towards the formation of a single double bond isomer, we chose to synthesise the gem dimethyl phenanthridine analogue, 114. The sulfonamide protected cyclisation precursor 115 was readily accessed (Scheme 2.15) through conversion of dimedone 116 to enol ether 117;\(^88\) conversion to known enone 118 via a reduction and subsequent rearrangement on silica;\(^89\) reduction of 118 to the corresponding enol 119 and conversion to allylic bromide 120 using CBr\(_4\);\(^90,91\) coupling of bromide 120 with 2-bromobenzylamine as described in section 2.3.1; and finally sulfonamide protection of the amine.

\[\text{Scheme 2.15 Synthesis and cyclisation of gem dimethyl analogue 114.}\]

\[\begin{array}{c}
\text{a) CAN, MeOH, r.t., 16 h, 73%; b i) LiAlH}_4, \text{Et}_2\text{O 0 }^\circ\text{C }\rightarrow \text{r.t., 1 h; b ii) silica, CH}_2\text{Cl}_2, \text{3 h, 91%; c) LiAlH}_4, \text{Et}_2\text{O, 0 }^\circ\text{C, 40 min, 72%; d) CBr}_4, \text{PPh}_3, \text{Et}_2\text{O, r.t., 2 h, 67%; e) o-BrPhCH}_2\text{NH}_2\text{HCl, }\text{iPr}_2\text{NEt, MeCN, r.t., 16 h, 63%; f) MeSO}_2\text{Cl, Et}_3\text{N, CH}_2\text{Cl}_2, \text{r.t., 3 h, 65%; g) 100 (5 mol%), Ag}_2\text{CO}_3, \text{DMF, 140 }^\circ\text{C, 2 h, 99%}.}\n\end{array}\]

Heck cyclisation of 115 employing the Herrmann-Beller catalyst resulted in quantitative conversion in 2 h to a colourless solid which was shown to be the desired \(\Delta^{1,2}\) 3,3-dimethyl-tetrahydrophenanthridine 114. This result clearly shows the efficiency of our cationic cyclisation conditions, and illustrates their potential utility in systems with additional functionality on the cyclohexenyl ring.
2.8 Diversity based applications of the phenanthridine cyclisation reaction

2.8.1 Herrmann-Beller neutral conditions

As reported in Chapter 1, the synthesis of natural-product-like libraries based on strategies which make use of the rapid introduction of stereochemical, structural and skeletal diversity,\textsuperscript{14} is one which has gained prominence in recent years as a means to efficiently cover chemical space.\textsuperscript{6,12} The initial results obtained for the cyclisation of sulfonamide 94a under neutral conditions in DMF or DMF:MeCN:H\textsubscript{2}O using the Herrmann-Beller catalyst (Table 2.3, entry 2 or Table 2.4 entry 2) offer considerable potential in this direction. In one step, the phenanthridine core unit is formed, whilst at the same time the potential for further diversification, through reaction of the newly-formed double bond at each of the three positions, $\Delta^{1,2}$, $\Delta^{2,3}$ and $\Delta^{3,4}$, is introduced. In combination with different amine precursors a large and diverse compound library based on the phenanthridine core might be rapidly assembled (Scheme 2.16).

![Scheme 2.16 Diversity oriented synthesis of a phenanthridine library.](image)

In order to determine the potential versatility of such an approach we screened the use of the Herrmann-Beller catalyst across the full range of precursors 94a-e (Table 2.7). Although our initial result for the neutral cyclisation of sulfonamide 94a under Jeffery conditions offered a more rapid cyclisation than that in DMF, we decided that the latter conditions had the advantage of giving a larger proportion of each isomer (37:49:14 Jeffery vs 44:31:25 in DMF) and thus used these in our screen.

We discovered that under these neutral conditions (Table 2.7) the Boc and Cbz protected substrates 94b and 94c behaved in a similar manner to 94a, giving a double bond isomer profile suitable for diversity-based applications. The Bn and PMB protected substrates 94d and 94e however, gave predominantly the $\Delta^{1,2}$ isomer.
rendering them unsuitable as protecting groups for the synthesis of a DOS library of phenanthridines.

Table 2.7 Application of neutral Herrmann-Beller conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>P</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>Ratio (96:97:98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94a</td>
<td>SO₂Me</td>
<td>3</td>
<td>98</td>
<td>44:31:25</td>
</tr>
<tr>
<td>2</td>
<td>94b</td>
<td>Boc</td>
<td>3</td>
<td>95</td>
<td>36:38:26</td>
</tr>
<tr>
<td>3</td>
<td>94c</td>
<td>Cbz</td>
<td>3</td>
<td>99</td>
<td>33:39:28</td>
</tr>
<tr>
<td>4</td>
<td>94d</td>
<td>Bn</td>
<td>5</td>
<td>93</td>
<td>83:8:9</td>
</tr>
<tr>
<td>5</td>
<td>94e</td>
<td>PMB</td>
<td>5</td>
<td>93</td>
<td>74:13:13</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: aryl halide (1 eq), MeNCy₂ (4 eq), palladacycle 100 (5 mol%), DMF, 140 °C.

2.8.2 Low temperature alternative

2.8.2.1 Background information

Although we were satisfied that the neutral conditions reported above would prove suitable for application in a DOS library, we examined one further catalyst system during our screening studies that offered an alternative set of low temperature conditions. As reported in section 2.1, the highly reactive catalyst \((\text{Bu}_3\text{P})_2\text{Pd}\) has been used to conduct intermolecular Heck coupling reactions at room temperature.\(^{62}\) It has limited precedent in intramolecular Heck cyclisations,\(^{92,93}\) with only one example of its use at low temperatures \((40 \, ^\circ\text{C}, \text{Scheme 2.17})\),\(^{94}\) and no examples of its application in a system similar to ours, but we were keen to examine if it could offer us a low temperature set of conditions for our cyclisation.

Scheme 2.17 Low temperature intramolecular Heck.\(^{94}\)

\(^a\) Pd\(_2\)(db)\(_3\) (1 mol%), \(\text{Bu}_3\text{PHBF}_{4}\) (4 mol%), DABCO (3 eq), 40 °C, dioxane, 60 h, 92%.
We were initially interested in the use of this particular catalyst system as a means of accessing predominantly the $\Delta^{1,2}$ double bond isomer. A recent literature report$^{95}$ examining the reductive elimination of HCl from $L_2$PdHCl stated that for $L = {^{\text{t}}\text{Bu}}_3\text{P}$ the process was very facile, suggesting to us that double bond isomerism might be disfavoured as in a cationic Heck reaction. Upon X-ray crystallographic analysis of the hydride species, this was attributed to the steric bulk of the ligands, (Figure 2.5). When compared to the corresponding PCy$_3$ hydride species, where the LL angle is 180°, it can be seen that the $^{\text{t}}\text{Bu}_3\text{P}$ ligands are forced away from the chlorine, with an LL angle of 161° at the cost of increased steric strain between the ligands and the hydride. This strain is relieved upon reductive elimination to generate Pd($^{\text{t}}\text{Bu}_3\text{P})_2$ thus providing a driving force for the process. We anticipated that an even greater relief of steric strain might be accomplished if the hydride species contained a bromine atom rather than a chlorine.

![Figure 2.5 Space-filling models based on the X-ray crystal structures of $L_2$PdHCl (left: $L = \text{PCy}_3$; right: $L = P(^{\text{t}}\text{Bu})_3$).$^{95}$](image)
2.8.2.2 Application to protected amine cyclisation precursors

With this in mind, we explored the use of this catalyst with cyclisation precursors 94a-e (Table 2.8). The intermolecular reactions are typically conducted in dioxane, but the use of this solvent in our system led to very low conversions. However, a simple solvent switch to MeCN gave much more promising results albeit to a roughly equal mixture of all three double bond isomers, not to predominantly the $\Delta^{1,2}$ isomer as predicted from the mechanistic precedent.

We observed complete conversion of sulfonamide 94a to products 96a-98a at room temperature, however, the Boc and Cbz protected precursors 94b and 94c required a slightly elevated temperature (50 °C) for the cyclisation reaction to proceed to completion. Intriguingly, the Bn and PMB-protected substrates 94d and 94e showed little or no reactivity at either temperature.

Table 2.8 Cyclisation under low-temperature conditions.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>P</th>
<th>Method</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>Ratio (96:97:98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94a</td>
<td>SO$_2$Me</td>
<td>A</td>
<td>9</td>
<td>99</td>
<td>12:65:23</td>
</tr>
<tr>
<td>2</td>
<td>94a</td>
<td>SO$_2$Me</td>
<td>B</td>
<td>4</td>
<td>99</td>
<td>55:41:4</td>
</tr>
<tr>
<td>3</td>
<td>94b</td>
<td>Boc</td>
<td>A</td>
<td>40</td>
<td>50</td>
<td>34:43:22</td>
</tr>
<tr>
<td>4</td>
<td>94b</td>
<td>Boc</td>
<td>B</td>
<td>7</td>
<td>95</td>
<td>34:37:29</td>
</tr>
<tr>
<td>5</td>
<td>94c</td>
<td>Cbz</td>
<td>A</td>
<td>40</td>
<td>64</td>
<td>53:34:13</td>
</tr>
<tr>
<td>6</td>
<td>94c</td>
<td>Cbz</td>
<td>B</td>
<td>7</td>
<td>85</td>
<td>36:5:59</td>
</tr>
<tr>
<td>7</td>
<td>94d</td>
<td>Bn</td>
<td>A</td>
<td>72</td>
<td>no reaction</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>94d</td>
<td>Bn</td>
<td>B</td>
<td>40</td>
<td>23</td>
<td>n.d.$^a$</td>
</tr>
<tr>
<td>9</td>
<td>94e</td>
<td>PMB</td>
<td>A</td>
<td>72</td>
<td>no reaction</td>
<td>--</td>
</tr>
<tr>
<td>10</td>
<td>94e</td>
<td>PMB</td>
<td>B</td>
<td>40</td>
<td>no reaction</td>
<td>--</td>
</tr>
</tbody>
</table>

| a | Conditions: Method A: Aryl halide (1 eq), Pd$_2$(dba)$_3$ (5 mol%), $^3$Bu$_3$PHBF$_4$ (10 mol%), MeNC$_2$ (4 eq), MeCN, r.t.; Method B: As Method A at 50 °C.$^b$ not determined |
2.8.2.3 Application to aryl iodides

Aryl iodides are known to undergo oxidative addition more rapidly than their bromo or chloro counterparts, so we decided to synthesise the Boc and Cbz aryl iodides to determine whether cyclisation could be facilitated at room temperature. As 2-iodobenzylamine is not commercially available, our synthesis of cyclisation precursors 124b and 124c started from 2-iodobenzoic acid 125 (Scheme 2.18). This was readily converted into the acid chloride, followed by treatment with aqueous ammonia to generate amide 126. Dehydration of amide 126 gave nitrile 127, which was converted into amine 128 by a LiAlH₄ mediated reduction. Conversion to the cyclisation precursors 124b and 124c proceeded in a similar manner to that previously shown.

Scheme 2.18 Synthesis of Boc and Cbz aryl iodide cyclisation precursors.
a) SOCl₂, 60 °C, 3 h; a ii) NH₄OH, r.t., 16 h, 61%; b) SOCl₂, 60 °C, 3 h, 99%; c) LiAlH₄, AlCl₃, Et₂O, 40 °C, 3 h, 52%; di) iPr₂NEt, 3-bromocyclohexene, MeCN, 16 h; ii) HCl in Et₂O, 99%; e) 124b P=Boc, Boc₂O, Et₃N, CH₂Cl₂, 16 h, 49%; f) 124c P=Cbz, NaH, DMF, 0 °C, 30 min, then benzylchloroformate, r.t., 16 h, 82%.

Surprisingly however, when we subjected aryl iodides 124b and 124c to the room temperature cyclisation conditions shown in Table 2.8, we only observed <20% conversion in each case after 16 h reaction. We were very surprised by these results and can only conclude that the additional steric bulk of the iodine on the Pd hindered the cyclisation from going to completion. Further evidence to support the incompatibility of (Bu₃P)₂Pd with bulky substrates comes from the failed cyclisation of our 3,3-dimethyl cyclisation precursor 115 at either r.t. or 50 °C using this catalyst.
2.8.2.4 Rationalising catalyst behaviour

While we were pleased to have an alternative set of mild conditions for our Heck cyclisation, we were puzzled as to the large degree of double bond isomerism observed, especially in light of the report illustrating the facile reductive elimination of HCl from (tBu₃P)₂PdHCl. Further examination of the literature suggested that when bulky phosphine ligands are employed, sterically-driven dissociation of one ligand occurs prior to the oxidative addition, giving rise to a mono-ligated Pd(0) (Scheme 2.19). If such a mono-ligated Pd(0) is the catalytically active species, then clearly the above arguments regarding steric-promoted reductive elimination are not valid, perhaps rationalising why double bond isomerism was not minimised.

![Scheme 2.19 Generation and reaction of a mono-ligated Pd(0).]

It is clear both from our results and from the literature precedent, that this mono-ligated Pd(0) species is also a highly reactive catalyst. It has long been proposed that high reactivity (TON) in the Heck reaction arises from coordinative unsaturation at Pd(II). Indeed, pre-dissociation of 16e-Pd(II) complexes to yield coordinatively unsaturated 14e-Pd(II) intermediates have been convincingly shown to offer a low free-energy pathway to transmetallation. It seems plausible therefore to suggest that weak σ-donor ligands as opposed to strong σ-donor ligands (such as the trialkylphosphines), would lead to more rapid ligand dissociation and coordinative unsaturation. However, contrary to this, trialkylphosphine ligands are able to rapidly generate mono-ligated Pd(0) species, but this arises not from their σ-donor capability but rather from their ability to create coordinative unsaturation by steric bulk. This creates a very powerful catalytic species that is further stabilised by the strong σ-donicity of the ligand.
The coordinatively unsaturated nature of the L-Pd(0) species renders it highly reactive toward oxidative addition. This permits the successful Pd-mediated cross-coupling of typically unreactive substrates e.g aryl chlorides, and electron-rich aromatics, and also permits the Heck reaction to be performed at non-elevated temperatures as we have observed.

Although we had initially employed the (tBu3P)2Pd catalyst system in an attempt to obtain one isomer product, we realised the potential our results offered toward our DOS library as complementary set of conditions for the cyclisation of thermally unstable and poorly reactive substrates.

2.8.3 Attempted cyclisation of an aryl chloride precursor

In light of the literature reports illustrating the low temperature (<50 °C) intermolecular Heck coupling of aryl chlorides using (tBu3P)2Pd,61,62 we were curious to examine what effect the catalyst system would have on an aryl chloride variant of our cyclisation precursor. Aryl chloride 130a was synthesised in a similar manner to its bromo and iodo counterparts, via alkylation of commercially available 2-chlorobenzylamine with 3-bromocyclohexene, followed by methylsulfonylation of the secondary amine 132.

![Scheme 2.20 Synthesis of an aryl chloride cyclisation precursor 130a.](image)

We first examined the cyclisation of aryl chloride 130a using dioxane as the solvent, but we observed no reaction (Table 2.9) at either r.t. or 120 °C. Switching the solvent for MeCN did little to improve the situation, giving only trace conversions (<1%) at both r.t. and 50 °C. We decided to employ our Herrmann-Beller palladacycle conditions since we had no success with the (tBu3P)2Pd catalyst. Under cationic conditions we observed only 8% conversion after 16 h, and using the neutral system...
we observed 15% conversion, although 11% of this was composed of the dehalogenated product 99a.

Table 2.9 *Study of Heck cyclisation conditions for aryl chloride 130a.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions(^a)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Solvent</th>
<th>Conversion ((%))(^b)</th>
<th>Ratio 96a:97a:98a:99a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Pd}<em>2\text{(dba)}<em>3) (\text{tBu}</em>{3} \text{PHBF}</em>{4}), (\text{MeNCy}_2) (\text{r.t})</td>
<td>16</td>
<td>dioxane</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Pd}<em>2\text{(dba)}<em>3) (\text{tBu}</em>{3} \text{PHBF}</em>{4}), (\text{MeNCy}_2)</td>
<td>120</td>
<td>16</td>
<td>dioxane</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Pd}<em>2\text{(dba)}<em>3) (\text{tBu}</em>{3} \text{PHBF}</em>{4}), (\text{MeNCy}_2) (\text{r.t})</td>
<td>16</td>
<td>MeCN</td>
<td>Trace</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Pd}<em>2\text{(dba)}<em>3) (\text{tBu}</em>{3} \text{PHBF}</em>{4}), (\text{MeNCy}_2), 50</td>
<td>16</td>
<td>MeCN</td>
<td>Trace</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Palladacycle 100, (\text{Ag}_2\text{CO}_3)</td>
<td>140</td>
<td>16</td>
<td>DMF</td>
<td>8</td>
<td>n.d</td>
</tr>
<tr>
<td>6</td>
<td>Palladacycle 100, (\text{MeNCy}_2)</td>
<td>140</td>
<td>16</td>
<td>DMF</td>
<td>15</td>
<td>27:0:0:14</td>
</tr>
<tr>
<td>7</td>
<td>Palladacycle 100, (\text{MeNCy}_2, \text{BuNBr})</td>
<td>140</td>
<td>16</td>
<td>DMF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>(\text{Pd}<em>2\text{(dba)}<em>3), (\text{tBu}</em>{3} \text{PHBF}</em>{4}, \text{NaOAc})</td>
<td>150</td>
<td>16</td>
<td>DMF</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) [5 mol\% Pd(0) source] / [10 mol\% ligand] \(^b\) Conversion was determined through analysis of the \(^1\text{H}\) NMR of the crude reaction mixture.

We examined the literature and discovered no reports of \((\text{tBuP})_2\text{Pd}\) being successfully employed in the intramolecular Heck reaction of an aryl chloride and only three examples of different catalyst systems being used for such a purpose.\(^98-100\) Two of these literature reports employed the use of one equivalent of tetra-\(n\)-butylammonium bromide or chloride to achieve poor to moderate conversions (28-70%), but when we tried this on our palladacycle catalysed neutral conditions we observed no trace of cyclisation (entry 7).\(^98\) The other report also used tetra-\(n\)-butylammonium bromide, but this time as the solvent.\(^99\) However, again we observed no conversion using this method (entry 8).

Therefore we were unable in our short investigation to generate reaction conditions for the cyclisation of aryl chloride 130a. The abundance of aryl chloride building blocks commercially available (as opposed to iodides and bromides) would make this area very worthwhile for further investigation, especially in light of the lack of successful conditions in the literature.
2.9 Mechanistic studies

2.9.1 Amine cyclisation precursors

The first mechanistic issue we wished to address was the minimal double bond isomerism observed upon the cyclisation of amine substrates 94d and 94e as opposed to sulfonamide and carbamate substrates 94a-c. Under cationic conditions both the amine cyclisations showed exceptional selectivity for the Δ1,2 isomer, well in excess of the amide substrates. Under the palladacycle catalysed neutral conditions, 94d and 94e both gave strong selectivity for the Δ1,2 isomer whereas the amide substrates gave a spread of the different isomer products. Additionally, they also showed minimal reactivity under the ('Bu3P)p2Pd catalysed conditions, as compared to the amide substrates.

We postulated that perhaps in the cyclisation of these amine precursors, the substrates themselves were acting as bases, capable of minimising isomerism. In order to test this theory we decided to synthesise dibenzylcyclohexylamine100 133, a simplified analogue of the benzyl protected cyclisation precursor 94d and use this instead of MeNCy2 as the base in one of our amide Heck cyclisations.

![Scheme 2.21 Synthesis of dibenzylcyclohexylamine 133.](a) Benzyl bromide, NaH, 16 h, r.t; a ii) H2, Pd/C, MeOH/EtOAc, 16 h, r.t., 63%; b) BnBr, NaH, 16 h, r.t., 82%.

We chose to test it on the cyclisation of sulfonamide analogue 94a as this gave rise to diverse range of double bond isomers under our standard neutral conditions and would provide a suitable comparison (Scheme 2.22). However, we discovered that while dibenzylcyclohexylamine100 proved to be an excellent base with regard to conversion (100%), it furnished significant quantities of each of double bond isomers 96a-98a.
The investigation shown in Scheme 2.22 dismisses the possibility of substrates 94d and 94e acting as bases intermolecularly, but not intramolecularly. Following β-hydride elimination, the Pd-H species ends up on the same face of the cyclohexene ring system as the amine nitrogen functionality. The close proximity of the amine nitrogen to the Pd-H species means that intramolecular reductive elimination could be facilitated rapidly, resulting in minimal double bond isomerism. This hypothesis could be examined by studying the cyclisation of substrates 94d or 94e in the absence of base.

2.9.2 Sulfonamide and carbamate substrates
We have shown very different results with regard to the double bond isomer ratio obtained for the sulfonamide and carbamate precursor cyclisations, using each of our optimised reaction conditions. In the case of the cationic cyclisation this can be easily rationalised as arising from the rapid reductive elimination step, as reported in section 2.4. However, under the neutral conditions, the double bond isomer profile obtained using different catalysts (Pd(OAc)$_2$, palladacycle 100, and (tBu$_3$P)$_2$Pd) shows dramatic variation, (e.g. from 92:6:2 to 33:39:28 for cyclisation of 94a), that cannot be so easily rationalised.

Beller has concluded that in the intermolecular Heck reaction of arylbromides with cyclohexene and cyclopentene, double bond migration is predominantly catalysed by the base used in the reaction, and not by a HPdX complex (Table 2.10). In this simple intermolecular study, the choice of solvent (entry 1 vs 3) and base (entries 1 vs 2 and 5 vs 6) was shown to have an important influence on the extent of C-C double bond migration, whilst different catalysts showed no significant changes in
selectivity (entries 1 vs 4 and 6 vs 7). It may be argued that the electron-withdrawing nature of the acetate group aids base-catalysed isomerism, however similar variation in the double bond isomer ratio was also observed for other aryl bromides ($m$-CF$_3$, $p$-OMe, phenyl).

**Table 2.10** *Base/Solvent catalysed double bond isomerism of cycloalkenes.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycloalkene</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Base</th>
<th>Conversion (%)</th>
<th>Ratio 139:140:141</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>137</td>
<td>DMA</td>
<td>Pd(OAc)$_2$/2PPh$_3$</td>
<td>NaOAc</td>
<td>96</td>
<td>4:17:79</td>
</tr>
<tr>
<td>2</td>
<td>137</td>
<td>DMA</td>
<td>Pd(OAc)$_2$/2PPh$_3$</td>
<td>p$_3$NEt</td>
<td>63</td>
<td>1:33:66</td>
</tr>
<tr>
<td>3</td>
<td>137</td>
<td>DMSO:DMA (4:1)</td>
<td>Pd(OAc)$_2$/2PPh$_3$</td>
<td>NaOAc</td>
<td>59</td>
<td>2:8:90</td>
</tr>
<tr>
<td>4</td>
<td>137</td>
<td>DMA</td>
<td>Pd$_2$(dba)$_2$/PCy$_3$</td>
<td>NaOAc</td>
<td>89</td>
<td>7:15:78</td>
</tr>
<tr>
<td>5</td>
<td>138</td>
<td>DMA</td>
<td>Pd$_2$(dba)$_2$/PCy$_3$</td>
<td>NaOAc</td>
<td>99</td>
<td>39:45:16</td>
</tr>
<tr>
<td>6</td>
<td>138</td>
<td>DMA</td>
<td>Pd$_2$(dba)$_2$/PCy$_3$</td>
<td>Na$_2$CO$_3$</td>
<td>99</td>
<td>91:7:2</td>
</tr>
<tr>
<td>7</td>
<td>138</td>
<td>DMA</td>
<td>Pd$_2$(OAc)$_2$/2PPh$_3$</td>
<td>Na$_2$CO$_3$</td>
<td>98</td>
<td>83:13:4</td>
</tr>
</tbody>
</table>

* [5 mol% Pd(0) source]; * 1 eq base, 120-140 °C.

In sharp contrast, our study demonstrates that in the intramolecular neutral Heck reaction where the two components are linked as the protected benzylamine, the palladium catalyst plays a pivotal role in double bond isomerism under otherwise identical conditions (Pd(OAc)$_2$ vs HB or (‘Bu$_3$P)$_2$Pd, with MeNCy$_2$ in DMF). To further probe why different catalysts were giving rise to such different results, we carried out a series of mechanistic studies.
2.9.3 Isomer variation with time

To determine at what point isomerism occurred, we monitored the double bond isomer ratio with time for each of our optimised reactions using sulfonamide cyclisation precursor 94a. Aliquots were taken from each reaction at the appropriate timepoint and the composition was analysed using $^1$H NMR spectroscopy. Integration of the three double bond isomer peaks highlighted in section 2.5, allowed us to plot the following graphs.

![Graph showing isomer variation for cationic cyclisation of 94a using palladacycle 100.](image)

**Figure 2.6** Isomer variation for cationic cyclisation of 94a using palladacycle 100.

Conditions: 94a (1 eq), palladacycle 100 (5 mol%), Ag$_2$CO$_3$ (1 eq), DMF, 140 °C

First of all we monitored the cationic cyclisation using the Herrmann-Beller palladacycle (Figure 2.6). The graph clearly shows that the $\Delta^{1,2}$ isomer is the major product at all times, holding true to the theory of rapid reductive elimination. With this reaction, no change in double bond isomer ratio is visible after the onset of the reaction, suggesting that once decomplexation of the catalyst occurs from the alkene, no recomplexation and subsequent isomerism occurs.

We next examined the Hermann-Beller palladacycle under neutral conditions (Figure 2.7). This graph illustrates an initial induction period (0-90 mins) where some variation in the $\Delta^{1,2}$ to $\Delta^{2,3}$ ratio occurs. After this point however, no significant variation in the ratio of the products is observed even though the reaction takes up to
180 minutes to reach completion (Table 2.3, entry 2). This again suggests that once the catalyst has decomplexed from the alkene, no further isomerism occurs.

![Graph](attachment:image.png)

**Figure 2.7** Isomer variation for neutral cyclisation of 94a using palladacycle 100. Conditions: ArBr (1 eq), MeNCy₂ (4 eq), palladacycle 100 (5 mol%), DMF, 140 °C.

Finally, we studied the (tBu₃P)₂Pd catalysed cyclisation (Figure 2.8) at room temperature, which clearly shows that the Δ₁,₂ isomer is the favoured product from the outset of the reaction and that there is essentially no change in double bond isomer ratio from the outset of the reaction.

![Graph](attachment:image.png)

**Figure 2.8** Isomer variation for neutral cyclisation of 94a using (tBu₃P)₂Pd. Conditions: ArBr (1 eq), Pd₂(db₃)₃ (5 mol%), tBu₃PHBF₄ (10 mol %), MeNCy₂ (4 eq), MeCN, r.t.
2.9.4 Resubmission experiments

The double bond isomer ratio monitoring experiments all suggest that further isomerism does not occur once the catalyst has decomplexed from the alkene. To test this hypothesis we decided to execute a series of experiments where the sulfonamide $\Delta^{2,3}$ isomer 97a was resubmitted to the optimised reaction conditions to observe if isomerism had occurred (Table 2.11). In addition to probing our decomplexation hypothesis, these studies also gave us the opportunity to observe whether double bond isomerism was base-catalysed.

Table 2.11 Resubmission experiments.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>$T$ ($^\circ$C)</th>
<th>$T$ (h)</th>
<th>Ratio (96a:97a:98a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Palladacycle 100, MeNCy$_2$, DMF</td>
<td>140</td>
<td>16</td>
<td>0: 100: 0</td>
</tr>
<tr>
<td>2</td>
<td>Palladacycle 100, Ag$_2$CO$_3$, DMF</td>
<td>140</td>
<td>16</td>
<td>0: 100: 0</td>
</tr>
<tr>
<td>3</td>
<td>Pd$_2$(dba)$_2$, Bu$_3$PHBF$_4$, MeNCy$_2$, MeCN</td>
<td>r.t</td>
<td>72</td>
<td>0: 100: 0</td>
</tr>
<tr>
<td>4</td>
<td>Palladacycle 100, MeNCy$_2$, DMF, HBr (1 eq)</td>
<td>140</td>
<td>72</td>
<td>4: 96: 0</td>
</tr>
<tr>
<td>5</td>
<td>CH$_3$COOH (excess), DMF</td>
<td>140</td>
<td>72</td>
<td>19: 78: 8</td>
</tr>
</tbody>
</table>

*Conversion was determined through analysis of the $^1$H NMR of the crude reaction mixture.*

Resubmission of sulfonamide $\Delta^{2,3}$ isomer 97a to each of the three optimised conditions (entries 1-3) resulted in no double bond isomerism. Each of these conditions should have permitted double bond migration to occur if, it were base-catalysed, so clearly in our case double bond isomerism results from other factors.

Although entries 1-3 suggest that no isomerism occurs following decomplexation, we had concerns that we had not taken into account the equivalent of HBr liberated during the reductive elimination process. We wondered if the catalyst system was able to turn over without this present, and whether our simple resubmission experiment was an accurate reflection of the environment faced by an alkene.
following reductive elimination. We repeated the resubmission of sulfonamide $\Delta^{2,3}$ isomer 97a to the neutral palladacycle catalysed conditions, this time including one equivalent of HBr. As indicated in Table 2.11 slight double bond isomerism was observed, but the extent of this did not explain the ratios observed under normal cyclisation circumstances, especially since the time period of the current experiment was significantly longer (72 h vs 6 h).

Out of interest, we examined the effect of acid on our phenanthridine system (entry 5) and the results clearly show that a significant proportion of the sulfonamide $\Delta^{2,3}$ isomer 97a undergoes conversion to the other isomers after 72 hours at elevated temperature. Although this has no bearing on our cyclisation reactions, it is an interesting result, which is in contrast to the previous report that isomerism in an intermolecular reactions is base-catalysed.\textsuperscript{101} In light of this result we propose that the minimal isomerism observed in the HBr resubmission experiment (entry 4) is actually a result of acid-catalysed migration.
2.9.5 Decomplexation vs hydro/dehydropalladation

From these results, it must therefore be concluded that the double bond isomer ratio is established at the outset of the reaction, and does not change following decomplexation of the catalyst from the alkene. The double bond isomer ratio obtained in these intramolecular Heck cyclisation reactions must therefore be a product of the differing rates of decomplexation of each catalyst as compared to the rate of hydro-palladation/dehydropalladation (Scheme 2.23 and Scheme 2.24).\(^\text{102}\)

**Scheme 2.23** Hydro-palladation/dehydro-palladation for the cationic reaction.

**Scheme 2.24** Hydro-palladation/dehydro-palladation for the neutral reaction.
2.10 Conclusions
We have successfully investigated and developed conditions for the Heck cyclisation of various sulfonamide, carbamate and amine precursors to give phenanthridines. If one double bond isomer is required, the reaction can be performed under cationic conditions using the Herrmann-Beller palladacycle 100 to give predominantly the $\Delta^{1,2}$ isomer. These conditions have been shown to achieve high yielding conversions (76-99%) to the Heck products in less than two hours, and have proved successful in a system with additional steric bulk on the cyclohexenyl ring.

We have also developed two sets of conditions for the synthesis of a mixture of phenanthridine double bond isomers using the Heck reaction, which we intend to utilise in the preparation of a DOS library (Chapters 3 and 4). Palladacycle 100 can be employed at elevated temperature using the sulfonamide and carbamate substrates to give the desired product mixture in less than 5 hours, with excellent yield (93-99%). Alternatively, the highly reactive Fu catalyst ($^3$Bu$_3$P)$_2$Pd can be used for the low temperature (r.t. or 50 °C) cyclisation of the sulfonamide and carbamate precursors, to give the double bond isomer mixture in less than 9 hours and with excellent conversions (85-99%).

We found that careful choice of the catalyst and reaction conditions employed had a significant effect on the outcome of the products, and our mechanistic investigations attribute this to either a cationic vs neutral pathway, or differing rates of decomplexation as compared to the rate of hydro-palladation/dehydropalladation for each catalyst, depending on the particular reaction in question.
3.1 Introduction
As discussed in Chapter 2, we realised the potential our two sets of neutral cyclisation conditions had toward the development of a DOS library. Each cyclisation performed under these conditions furnished three skeletons, each with an alkene handle suitable for further functionalisation. In addition to this, further incorporation of diversity could be accomplished by any of the three means outlined in Chapter 1, namely appendage (or building block) variation, introduction of stereochemistry, or by further skeletal diversification.

Building block variation of the A-ring was investigated through the synthesis (and subsequent cyclisation) of various aryl and heteroaryl Heck cyclisation precursors. We chose to investigate the introduction of stereochemical diversity by examining dihydroxylation protocols for the C-ring phenanthridine double-bond isomers. Finally, the introduction of skeletal diversity was examined using novel ring-rearrangement metathesis reactions of the phenanthridine C-ring (Figure 3.1).

Figure 3.1 Introducing diversity to the phenanthridine core.
P= Protecting group.
3.2 Building Block Diversity

We realised that the aromatic part of our phenanthridine core ring structure was an excellent component through which to investigate building block diversity. To this end we set about synthesising a range of suitable aromatic and heteroaromatic cyclisation precursors.

3.2.1 Thiophene analogue

Initial investigations in the area of building block diversity were based around the synthesis of a heteroaromatic thiophene equivalent of our standard sulfonamide protected phenanthridines 96a-98a. As a result we developed two synthetic routes to incorporate the heteroaromatic building block, both of which warrant discussion despite not being used in our final DOS library synthesis.

Our first synthetic strategy started with methylation of 3-bromothiophene 152 to afford 2-methylthiophene 153 in excellent yield.103 This was followed by a radical bromination using NBS/AIBN to afford thiophenemethyl bromide 154.104 Attempted monoalkylation of 3-aminocyclohexene105 with thiophenemethyl bromide 154 proceeded poorly giving the desired secondary amine in only 18% yield (Scheme 3.1). This poor yield, coupled with the undesirable use of CCl₄ earlier in the synthetic route, led us to investigate an alternative synthesis of amine 155.

![Scheme 3.1 First generation synthesis of a thiophene analogue.](image)

a) i) LDA, THF, 0 °C → -78 °C, 0.5 h; ii) MeI, -70 °C, 0.5 h, then r.t., 1 h, 99%; b) AIBN, NBS, CCl₄, 80 °C, 3 h, 53%; c) 3-aminocyclohexene, Pr₂NEt, MeCN, r.t., 16 h, 18%.
Our second generation synthesis also began using 3-bromothiophene 152, this time performing an α-lithiation followed by anion trapping with DMF to afford carbaldehyde 156 in excellent yield (Scheme 3.2). The initial lithiation step must be performed at 0 °C as the competitive formation of the 5-lithiated thiophene is known to occur at -78 °C. We next attempted a reductive amination using 3-aminocyclohexene 155 but as in the first generation synthesis, secondary amine 155 was obtained in very poor yield. The 3-aminocyclohexene used in both the coupling protocols was difficult to synthesise and purify, and we propose that this resulted in the poor conversions we observed in both cases.

Scheme 3.2 Second generation synthesis of a thiophene analogue.

Although neither route had proved to be particularly successful, we did manage to obtain sufficient quantities of amine 155 to take on in the synthetic sequence, and so sulfonamide 157 was synthesised in good yield using the previously reported conditions, giving us material to test our Heck cyclisation upon (Table 3.1).

Table 3.1 Heck cyclisation of thiophene analogues 158-160.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Ratio 158:159:160</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Palladacycle 100, Ag2CO3</td>
<td>140</td>
<td>2</td>
<td>DMF</td>
<td>91</td>
<td>77:16:7</td>
</tr>
<tr>
<td>2</td>
<td>Palladacycle 100, MeNCy2</td>
<td>140</td>
<td>4</td>
<td>DMF</td>
<td>74</td>
<td>32:41:27</td>
</tr>
<tr>
<td>3</td>
<td>Pd2(dba)3, BuPHBF3, MeNCy2</td>
<td>r.t.</td>
<td>18</td>
<td>MeCN</td>
<td>25</td>
<td>80:20:n.d.</td>
</tr>
<tr>
<td>4</td>
<td>Pd2(dba)3, BuPHBF3, MeNCy2</td>
<td>50</td>
<td>16</td>
<td>MeCN</td>
<td>55</td>
<td>76:15:9</td>
</tr>
</tbody>
</table>

*5 mol% Pd(0) source, 10 mol% ligand. *Conversion was determined through analysis of the 1H NMR of the crude reaction mixture. *n.d. not determined.
We were pleased to discover that both of our palladacycle-catalysed Heck cyclisation conditions proved to be robust for this heteroaromatic analogue, giving similar reactivities and double bond isomer ratios to the aromatic substrates studied previously. Interestingly, \((t\text{Bu}_3\text{P})_2\text{Pd}\) did not prove to be particularly reactive on heteroaromatic analogue 157, despite the success it had shown with the aromatic amides (see section 2.8.2), and unfortunately our best result was only 55% conversion at 50 °C (entry 4). Additionally, we were surprised to see that the double bond isomer ratio for this neutral cyclisation was in keeping with the cationic cyclisation, quite unexpected for \((t\text{Bu}_3\text{P})_2\text{Pd}\), given the precedent in the previous chapter.

Regardless of the \((t\text{Bu}_3\text{P})_2\text{Pd}\) results, we were confident that both our palladacycle catalysed conditions would prove successful across a range of aryl/heteroaryl analogues, so our next aim was to develop higher yielding route to the synthesis of such cyclisation precursors.

### 3.2.2 Standard synthesis of aryl amines

We had previously used several standard transformations to synthesise aryl iodides 124b and 124c from 2-iodobenzoic acid 125 (Scheme 2.18), so we took another look at this approach. In order for this to be viable we needed to identify a wide range of commercially available 2-bromobenzoic acid starting materials, and fortunately there were several available (Figure 3.2). In addition to benzoic acids, we identified two suitable heteroaromatic starting materials 161f and 161h, as well as 2-bromophenylacetic acid 161j that would potentially allow us to examine the synthesis of a 7-membered B–ring phenanthridine.

![Figure 3.2 Some commercially available benzoic acids.](image-url)
Application of the standard transformations developed in Chapter 2 proved compatible with the majority of the substrates (Table 3.2) although there were a few exceptions. Unfortunately the 5-NO$_2$ nitrile analogue 163g was not tolerant of the harsh LiAlH$_4$ reducing conditions so we did not pursue the synthesis of this analogue any further. Both the indole substrate and the phenethyl substrate required direct treatment of the amide substrate (162h or 162j) with LiAlH$_4$ to generate the desired amine. In the case of the phenethyl substrate this was poorly yielding (14%) and we performed the reaction in THF rather than Et$_2$O, to achieve a higher conversion (75%). An alternative approach to phenethyl substrate was developed later in this work (see section 3.2.5) and the problems associated with the synthesis of the indole analogue are addressed in section 3.2.6.

Table 3.2 Synthesis of amine building blocks.

<table>
<thead>
<tr>
<th>Entry</th>
<th>161</th>
<th>Substrate (R=)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>4-Me</td>
<td>95</td>
<td>73</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>4-F</td>
<td>94</td>
<td>97</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>5-MeO</td>
<td>73</td>
<td>99</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>4,5-MeO</td>
<td>99</td>
<td>88</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>[Naphthyl]$^3$</td>
<td>99</td>
<td>95</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>[Thiophene]$^3$</td>
<td>93</td>
<td>99</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>5-NO$_2$</td>
<td>99</td>
<td>99</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>[Indole]$^3$</td>
<td>98</td>
<td>-</td>
<td>55$^{aa}$</td>
</tr>
<tr>
<td>9</td>
<td>j</td>
<td>[Phenethyl]$^3$</td>
<td>74</td>
<td>-</td>
<td>75$^{ab}$</td>
</tr>
</tbody>
</table>

a) i) SOCl$_2$, 60 °C, 3 h; ii) NH$_4$OH, r.t., 16 h; b) SOCl$_2$, 60 °C, 3 h; c) i) LiAlH$_4$, AlCl$_3$, Et$_2$O, ∆, 16 h; ii) HCl in Et$_2$O. $^a$ By direct reduction of the amide. $^b$ 3.06:1 ratio amine:debrominated material (see section 3.2.6). $^c$ In THF, with no AlCl$_3$. $^S$ For simplicity, the scheme depicts a benzene ring substrate core, however where the substrate core is a hetero- or bicyclo-aromatic ring (cf Figure 3.2) this is signified by the parenthesised, italicised core name. This table and scheme should be read in conjunction with Figure 3.2.
3.2.3 Synthesis of cyclisation precursors.
With a range of amine hydrochlorides in hand we next examined construction of the cyclisation precursors. We decided to synthesise the Boc-protected analogues 165a-f since the parent Boc-cyclisation precursor 94b had proved reliable under both the cationic and neutral cyclisation conditions, and we envisaged easy removal of the Boc group to give the free amine phenanthridines. In the previous chapter, synthesis of the Boc-protected analogue was pursued via the secondary amine, so we proceeded to apply this to our range of amine substrates. Intriguingly, we observed approximately a 75:25 ratio of the mono-alkylated 166a-f to dialkylated product 167a-f (Table 3.3), something we had detected no trace of in the simple benzyl system. Alternative protocols for the selective mono-alkylation of primary amines have been reported, including CsOH promoted conditions,\textsuperscript{108} however such procedures were not pursued due to the success of an alternative strategy discussed below.

Table 3.3 Dialkylation of amines 164a-f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R=)</th>
<th>Ratio 166:167</th>
<th>Yield (%) Over 2 steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a 4-Me</td>
<td>84:16</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>b 4-F</td>
<td>75:25</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>c 5-MeO</td>
<td>75:25</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>d 4,5-MeO</td>
<td>75:25</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>e [Naphthyl]\textsuperscript{3}</td>
<td>70:30</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>f [Thiophene]\textsuperscript{3}</td>
<td>80:20</td>
<td>65</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Pr\textsubscript{2}NEt, 3-bromocyclohexene, MeCN, r.t., 16 h; \textsuperscript{b} Boc\textsubscript{2}O, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 16 h. \textsuperscript{3} See footnote to Table 3.2.
Although dialkylation material 167a-f could be separated from the Boc-protected material 165a-f, we realised that a Boc-protection then alkylation protocol, would allow us to circumvent the dialkylation problem. We found this to be a successful protocol across all our substrates 164a-f (Table 3.4) giving us higher conversions over the two steps in the majority of cases.

**Table 3.4 An alternative preparation of cyclisation precursors 165a-f.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R=)</th>
<th>Yield 168 (%)</th>
<th>Yield 165 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Me</td>
<td>99</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>4-F</td>
<td>88</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>5-MeO</td>
<td>85</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>4,5-MeO</td>
<td>99</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>[Naphthyl]</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>[Thiophene]</td>
<td>70</td>
<td>91</td>
</tr>
</tbody>
</table>

a) Boc₂O, Et₃N, CH₂Cl₂, 16 h; b) NaH, 3-bromocyclohexene, DMF, 0 °C - r.t., 16 h. See footnote to Table 3.2.

### 3.2.4 Piperonyl analogue

One additional cyclisation precursor that we were very interested in accessing was the piperonyl substrate 165k. Our interest in this target stemmed from the frequent observation of the piperonyl motif in biologically active natural products based on the phenanthridine core (Figure 1.15), and thus we were keen to include this in our DOS library. An alternative route to this substrate was developed as we initially had concerns over the stability of the piperonyl bridge toward the LiAlH₄ used in the standard amine synthesis (Table 3.2). We proposed to synthesise the cyclisation precursor 165k from Boc-protected piperonyl analogue 168k as previously shown, but this time synthesis of the latter substrate would be obtained directly from acid 169k via a Curtius rearrangement. (Scheme 3.3).

---

7 Subsequent to our investigation we have discovered two examples of the methylenedioxy bridge surviving both LiAlH₄ and DIBAL reductive conditions respectively.109,110
Scheme 3.3 Retrosynthetic analysis for piperonyl cyclisation precursor 165k.

The Curtius rearrangement in general involves three major steps, the first of which is diphenylphosphorylazide (dppa) 170 promoted conversion of an acid 171 into its corresponding acyl azide 173 (Scheme 3.4).\textsuperscript{111} The second step involves thermal decomposition of the azide, with release of N\textsubscript{2} to afford an isocyanate 176, via an acyl nitrene intermediate 177.\textsuperscript{112}

Scheme 3.4 The Curtius rearrangement.
The final step involves the highly electrophilic carbon of the isocyanate,\(^{112}\) that can be trapped with a nucleophile to afford a variety of products, both desired and undesired (Scheme 3.5). For our purposes, \(^1\)BuOH was used as the nucleophile as this permitted direct access to the desired Boc species 168k, but the reaction can be carried out in the presence of water to afford the corresponding amine 179.\(^{113}\) Commonly two side products are observed, namely the urea 180 or the carbamoyl azide 181, formed from nucleophillic attack of the isocyanate by the amine or residual \(\text{N}_3\) respectively.\(^{112}\)

![Scheme 3.5](image)

Scheme 3.5 Potential products from nucleophillic attack at the isocyanate.

Our first job was to synthesise the 2-bromo-homopiperonylic acid starting material in order that we could trial the Curtius rearrangement. We did this by treatment of commercially available homopiperonylic acid 182k with DBDMH (1,3-dibromo-5,5-dimethylhydantoin) under aqueous conditions which we found to be far superior to NBS under aqueous or DMF conditions (Scheme 3.6).\(^{114}\)

We had previously trialled some one-pot\(^{115,116}\) variants of the Curtius reaction on the homopiperonylic acid, resulting in low yields (<23%) and a significant amount of urea 180k and carbamoyl azide 181k side products being observed (Scheme 3.5, R=piperonyl). This led us to choose a two-pot modified Curtius reaction for the reaction of 2-bromo-homopiperonylic acid 169k, where the isocyanate intermediate was isolated.\(^{117}\)
Following these two-phase Curtius conditions we discovered that acyl azide 173k underwent partial conversion to isocyanate 176k upon purification through a silica plug. We could find no previous reports of this occurring in the literature where conversion to the isocyanate always requires heating conditions. However, one study examining the thermally-induced Curtius rearrangement of ortho-alkyl benzoyl azides, reported large rate-accelerations for these substrates as compared to their ortho-unsubstituted counterparts.118 The facile decomposition of acyl azide 173k to the corresponding isocyanate 176k on silica could therefore be due to a similar effect.

![Scheme 3.6](image)

**Scheme 3.6 Synthesis of piperonyl cyclisation precursor 165k.**

a) DBDMH, 4 M NaOH, H2O, r.t., 16 h, 91%; b) dppa, Et3N, CH2Cl2, 0 °C → r.t., 0.5 h; c) i) silica plug filtration (partial conversion); ii) PhMe, 110 °C, 1 h (total conversion); d) 'BuOH, 80 °C, 16 h, 50% over 3 steps; e) NaH, 3-bromocyclohexene, DMF, 0 °C- r.t., 16 h, 75%.

Total conversion to the isocyanate 176k was achieved after refluxing in toluene for 1 h, and subsequent treatment of the isocyanate with 'BuOH led to the formation of the desired Boc-analogue 168k in 50% yield over the three steps. Residual urea and carbamoyl azide by-products 180k and 181k were isolated from the product mixture, and identified by their carbonyl IR peaks (1579 cm⁻¹ and 2156 cm⁻¹ respectively). Subsequent alkylation of 168k under standard conditions afforded cyclisation precursor 165k in 75% yield.
This Curtius approach clearly offers a comparably yielding and milder route to the synthesis of the desired Boc-protected amine analogues, with the advantage of essentially two main steps as compared to four using the standard route (Table 3.2 and 3.4). While we were very pleased with its successful application to the piperonyl analogue, our alternative route to the other substrates was more than satisfactory, and a lack of commercial availability of other homo benzoic acid starting materials meant we did not apply the conditions to any of our other benzyl substrates.

3.2.5 Phenethyl substrate via Curtius rearrangement

However, we did apply the Curtius conditions to the synthesis of substrate 184j, since we had experienced problems accessing this analogue using the standard route, and the starting material 3-(2-bromophenyl)propionic acid 183j was commercially available (Scheme 3.7). We were delighted to discover that the desired carbamate product 184j was obtained in 77% yield, offering a marked improvement over the 3-step standard synthesis (see Chapter 6 for details).

\[183j\] (a) i) dppa, Et₃N, CH₂Cl₂, 0 °C – r.t., 0.5 h; ii) silica plug filtration (partial conversion); b) PhMe, 110 °C, 1 h (total conversion); c) tBuOH, 80 °C, 16 h, 77% over 3 steps; d) NaH, 3-bromocyclohexene, DMF, 0 °C- r.t., 16 h, 45%.

Unfortunately however, the final alkylation step to afford cyclisation precursor 185j only proceeded in 45% yield, and we were not able to improve upon this using the TBAI/Cs₂CO₃ protocol developed by Salvatore et al. for the N-alkylation of carbamates. The limitations of this step resulted in insufficient quantities of phenethyl analogue 185j for a satisfactory study of the Heck reaction. While it was clear from the initial studies that cyclisation occurred to a significant extent, identification of the complex mixture of isomeric products obtained, even under cationic conditions made the evaluation of this cyclisation a difficult task.
3.2.6 Issues with indoles

We experienced difficulty accessing the desired indole amine building block 164h. Following the LiAlH₄ reduction step in our standard synthetic sequence (Table 3.2), treatment of the free amine with HCl in Et₂O led to a complex mixture visible by ¹H NMR. Although we were confident that a significant proportion was the desired bromoindoleamine 164h, we were intrigued as to the identity of the minor product(s). We initially considered the formation of an indole-dimer species since 3-bromoindoles have been reported to undergo dimerisation under acidic conditions.¹²¹ The driving force for such a reaction is the loss of HBr which enables rearomatisation and formation of the 2,3-linked indole dimer (Scheme 3.8).

Scheme 3.8 Synthesis of dimeric indole species.¹²¹

R¹=H, Me; R²=H, Me, Bn; R³=H, Me, Ph.

However, this rearomatisation step was clearly not possible for our substrate due to the additional methylamine substituent at the 2-position of bromoindoleamine 164h. Additionally, no evidence for the presence of such a dimer was visible in the mass spectrum.

An extra singlet in the ¹H NMR spectrum at 6.26 ppm (in DMSO) led us to consider that one of the products was the debrominated indole amine 191 (Figure 3.3). Additionally, we observed the correct mass for this (m/z 146) in the mass spectrum of the mixture. Further evidence for the presence of this product was obtained when following a resynthesis, we purified the reaction mixture by flash chromatography on
silica, rather than by HCl salt formation. Although the majority of the reaction mixture appeared to decompose on the silica, the only isolated product was a trace amount of debrominated indole amine 191 (Figure 3.3), which we confirmed by comparison of its $^1$H NMR spectrum with that of the literature. We therefore proposed that 191 was formed during the LiAlH$_4$ reduction step, and that the hydrochloride salt of 191 was the minor contaminant in our product mixture. We propose that the remainder of the unassigned signals in the $^1$H NMR spectrum resulted from incomplete formation of the HCl salt of bromo-indole amine 164h.

![Figure 3.3 De-brominated indole 191](image)

We continued our studies towards indole cyclisation precursor 165h using the indole-amine hydrochloride mixture. After conversion of the amine hydrochloride salts to the free amines, coupling with 3-bromocyclohexene under standard conditions gave an inseparable mixture of products (Scheme 3.9), perhaps not surprising when mono- and dialkylation can occur for both the indole amine species.

![Scheme 3.9 Attempted synthesis of indole cyclisation precursor.](image)

*Scheme 3.9 Attempted synthesis of indole cyclisation precursor.*
a) Pr$_2$NEt, 3-bromocyclohexene, MeCN, 16 h, r.t.; b) Boc$_2$O, Et$_3$N, CH$_2$Cl$_2$, r.t., 16 h, 168h 49%, 192 24%; c) NaH, 3-bromocyclohexene, DMF, 0 °C → r.t., 16 h.

We therefore tried Boc-protecting the amine first, which had proved a successful method of circumventing the dialkylation issue previously. This gave excellent
conversion to a mixture of bromo-carbamate $168h$ and carbamate $192$, and permitted us to separate the two compounds. In contrast to an example in the literature, we observed no Boc-protection of the indole nitrogen, which we have attributed to using less equivalents of Boc$_2$O in our case (2 eq vs 5 eq).

Simple deprotonation of Boc-indole $168h$ with NaH, and attempted alkylation with 3-bromocyclohexene led, not surprisingly, to a complex mixture of products due to concomitant deprotonation/alkylation of the indole N-H. As a result we could not isolate any of the desired cyclisation precursor from the complex product mixture following the alkylation reaction. In light of the numerous setbacks we had encountered during the attempted synthesis of $165h$, we chose not to pursue the synthesis of this analogue any further. If the synthesis was to be repeated in future studies, it would be favourable to Boc-protect the indole nitrogen and the amine at the same time, or even Boc-protect the indole nitrogen at an earlier stage in the synthesis. Although Boc-indoles are less susceptible than Boc-amines to acidic deprotection conditions, they can be selectively removed under thermolysis at 130 °C in DMSO. The Heck cyclisation conditions at 140 °C would therefore most likely facilitate deprotection of the Boc-indole (Scheme 3.10).

![Scheme 3.10 Alternative synthesis of indole analogue.](image)

a) NaH, 3-bromocyclohexene, DMF, $0 \, ^{\circ}C \rightarrow \text{r.t.}$; b) Palladacycle 100 (5 mol%), Ag$_2$CO$_3$ (1 eq) or MeNCy$_2$ (4 eq), DMF, 140 °C.
3.2.7 Heck cyclisation of aryl/heteroaryl cyclisation precursors

With our cyclisation precursors 165a-f,k in hand we studied their reaction under both our cationic and neutral palladacycle 100 catalysed conditions.

Table 3.5 Cationic cyclisation of aryl/heteroaryl cyclisation precursors 165a-f,k.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R= )</th>
<th>t (h)</th>
<th>Yield 195-197 (%)</th>
<th>Ratio 195:196:197</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94b</td>
<td>H</td>
<td>2</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>4-Me</td>
<td>2</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>b</td>
<td>4-F</td>
<td>2.5</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>c</td>
<td>5-MeO</td>
<td>4</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>d</td>
<td>4,5-diMeO</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>e</td>
<td>[Naphthyl]$^\text{3}$</td>
<td>4</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>[Thiophene]$^\text{3}$</td>
<td>3</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>k</td>
<td>[Piperonyl]$^\text{3}$</td>
<td>2</td>
<td>70</td>
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</tbody>
</table>

$^a$ Conditions: aryl halide (1 eq), palladacycle 100 (5 mol%), Ag$_2$CO$_3$ (1 eq), DMF, 140 °C.

$c$ Ratio identified from $^1$H NMR of pure product mixture.

$^d$ Traces of minor diastereomer peaks visible in the $^1$H NMR.

$^*$ See footnote Table 3.2. * As in Scheme 3.6.

The cyclisation of all our substrates 165a-f,k was found to proceed rapidly and efficiently in all cases, although a slight loss in conversion was observed with the piperonyl analogue 165k which was surprising given the excellent reactivity of the 4,5-dimethoxy analogue. Identification of the isomer ratio was achieved by integration of the respective $^1$H NMR signals (as illustrated in Chapter 2.5.1). As expected, the $\Delta_1^2$ isomer was obtained as the major product from the cyclisation of all the analogues, with a comparable ratio to the cationic cyclisation of standard Boc substrate 94b (entry 1). Interestingly, three minor peaks were observed between 3.00 and 4.00 ppm in the $^1$H NMR spectra of the thiophene product mixture 195-197f where the NCHC=H proton is usually observed (proton ‘h’, Figure 2.4, Chapter 2). This suggests the possible formation of trace amounts of the trans-ring junction diastereomer, although reaction scale did not permit us to isolate any such product.
The application of our neutral Heck cyclisation conditions was also applied to substrates 165a-f,k as reported in Table 3.6.

Table 3.6 Neutral cyclisation of aryl/heteroaryl cyclisation precursors 165a-f,k.

<table>
<thead>
<tr>
<th>Entry</th>
<th>165</th>
<th>Substrate (R=)</th>
<th>t (h)</th>
<th>Yield 195-197 (%)</th>
<th>Ratio 195:196:197</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94b</td>
<td>H</td>
<td>3</td>
<td>95</td>
<td>36:38:26</td>
</tr>
<tr>
<td>2</td>
<td>a</td>
<td>4-Me</td>
<td>12</td>
<td>76</td>
<td>26:57:17</td>
</tr>
<tr>
<td>3</td>
<td>b</td>
<td>4-F</td>
<td>5</td>
<td>72</td>
<td>27:44:29</td>
</tr>
<tr>
<td>4</td>
<td>c</td>
<td>5-MeO</td>
<td>6</td>
<td>73</td>
<td>36:44:20</td>
</tr>
<tr>
<td>5</td>
<td>d</td>
<td>4,5-MeO</td>
<td>12</td>
<td>75</td>
<td>41:32:27</td>
</tr>
<tr>
<td>6</td>
<td>e</td>
<td>[Naphthyl]</td>
<td>5</td>
<td>74</td>
<td>42:42:16</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>[Thiophene]</td>
<td>5</td>
<td>79</td>
<td>18:34:30:18:18</td>
</tr>
<tr>
<td>8</td>
<td>k</td>
<td>[Piperonyl]</td>
<td>24</td>
<td>59 (32%)</td>
<td>41:26:33</td>
</tr>
<tr>
<td>9</td>
<td>k</td>
<td>[Piperonyl]</td>
<td>18</td>
<td>80 (11%)</td>
<td>18:46:36</td>
</tr>
<tr>
<td>10</td>
<td>k</td>
<td>[Piperonyl]</td>
<td>18</td>
<td>99</td>
<td>39:37:24</td>
</tr>
</tbody>
</table>

a Conditions: aryl halide (1 eq), MeNCy2 (4 eq), palladacycle 100 (5 mol%), DMF, 140 °C. b Ratio identified from 1H NMR of pure product mixture. c Quantifiable minor diastereomer peaks visible in the 1H NMR (7:11). d 32% dehalogenated product 198k recovered (see Chapter 6). e Pd2(dba)3 (5 mol%), tBuPHBF4 (10 mol%), MeNCy2 (4 eq), MeCN, r.t. f Starting material recovered. g as entry 9 but at 50 °C. h See footnote Table 3.2. * As in Scheme 3.6.

We found that for the majority of our substrates, the standard neutral palladacycle catalysed reaction conditions promoted cyclisation to the expected mixture of isomer products 195-197. However, conversions were lower in all cases than that exhibited by standard Boc substrate 94b (95% in 3 h), and reaction times were longer, especially with the electron rich aromatics (entries 2, 4, 5, 8) where clearly the oxidative addition step will be less favoured. For piperonyl substrate 165k (entry 8) a significant amount of the dehalogenated product 198k was recovered indicating the presence of Pd black (see section 2.3.4). This provides strong evidence for the reluctance of this substrate to undergo oxidative addition, since from our experience, Pd black is only formed from palladacycle 100 as a result of its standard deactivation.
pathway, i.e near the end of the catalyst’s lifetime. Fortunately, application of our low temperature (tBu₃P)₂Pd conditions (entry 9) enabled the recovery of the desired product mixture 195k-197k in 80% yield at r.t, and 99% yield at 50 °C (entry 10).

For the cyclisation of thiophene 165f we again observed traces of what we propose to be the trans-ring junction minor diastereomers. For the cyclisation of sulfonamide protected thiophene analogue 157 (section 3.2.1) under both neutral and cationic conditions, no trace of such a product was observed. Additionally, no similar product peaks have been observed in the ¹H NMR spectra for the cyclisation of any of the other Boc-protected analogues. The formation of such a product is therefore unique to the combination of the thiophene and the Boc-protecting group.

We propose that some form of chelation between the thiophene sulfur and the carbonyl of the Boc protecting group enables the cyclisation precursor to become locked in a conformation that allows subsequent formation of the trans-ring junction phenanthridine. However, due to the small scale of the reaction, we have not isolated any of the minor products and therefore do not have proof of this hypothesis. Additionally, a literature search for similar thiophene carbamates has not highlighted any similar reaction abnormalities.
3.3 Stereochemical Diversity

There are many bioactive phenanthridine natural products that have hydroxylated or polyhydroxylated C-rings (Figure 3.4). A sensible direction toward converting our aryl phenanthridine analogues into a DOS library would therefore be dihydroxylation or epoxidation of the alkene bond to introduce an element of stereochemical diversity.

Figure 3.4 Hydroxylated C-ring phenanthridine natural products.
3.3.1 *Cis*-dihydroxylation

Conditions for the *cis*-dihydroxylation of *trans*-ring junction phenanthridine 204, were reported in the literature, affording diastereomeric diol-products 205a and 206b in excellent yield (Scheme 3.11).\(^\text{126}\)

![Scheme 3.11 Literature conditions for cis-dihydroxylation.](image)

\(\text{a) OsO}_4, \text{NMO, THF/H}_2\text{O, r.t., 18 h, 84%, dr 1:1.}\)

*Trans*-ring junction phenanthridines sit in a flat conformation in 3D space, so the diasteromeric ratio of 1:1 is hardly surprising, since both faces of the C-ring are equally accessible by the OsO\(_4\) reagent (Figure 3.5). In contrast, *cis*-ring junction phenanthridines occupy a more cupped conformation, rendering the convex face more favourable for dihydroxylation, potentially resulting in high diastereomeric ratio (Figure 3.6).

![Figure 3.5 3D models of a typical trans ring junction phenanthridine.](image)

*Angle A* illustrating the full molecule. *Angle B* illustrating the lat planar conformation of molecule.
Figure 3.6 3D models of a typical cis ring junction phenanthridine.
Angle A illustrating the full molecule. Angle B illustrating the cupped conformation of molecule.

The reaction was tested on all three isolated double bond isomers 96-98b and we observed high conversions and diastereomeric ratios (>83:17) for the exo-syn product across all substrates (Table 3.7).

Table 3.7 Dihydroxylation test reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>dr&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>96b (Δ&lt;sup&gt;1,2&lt;/sup&gt;)</td>
<td>206m (Δ&lt;sup&gt;1,2&lt;/sup&gt;)</td>
<td>99</td>
<td>83:17</td>
</tr>
<tr>
<td>2</td>
<td>97b (Δ&lt;sup&gt;2,3&lt;/sup&gt;)</td>
<td>207m (Δ&lt;sup&gt;2,3&lt;/sup&gt;)</td>
<td>99</td>
<td>85:15</td>
</tr>
<tr>
<td>3</td>
<td>98b (Δ&lt;sup&gt;3,4&lt;/sup&gt;)</td>
<td>208m (Δ&lt;sup&gt;3,4&lt;/sup&gt;)</td>
<td>99</td>
<td>85:15</td>
</tr>
</tbody>
</table>

<sup>a</sup> Diastereomeric ratio determined by integration of the relevant peaks in the <sup>1</sup>H NMR spectrum.
3.3.2 Proof of stereochemistry

We were confident from the molecular models we had studied that the major product would have the hydroxyl groups on the exo-face, however confirmation was required. During the application of this methodology to the DOS library synthesis (Chapter 4) we isolated both the $\Delta^{2,3}$ piperonyl analogue $cis$-dihydroxyl products 207k and 209k and studied them using 2D nOESY NMR. For the major product, strong nOE’s were observed between the two ring junction protons, and between the two $CHOH$ protons, but there were no cross peaks between the two sets which is indicative of structure 207k (Figure 3.7). For the minor product, again strong nOE’s were observed between the two ring junction protons, and between the two $CHOH$ protons, but this time an additional cross peak was observed between one of the ring junction protons and one of the $CHOH$ protons (Figure 3.8). This would be true for the minor product where these two sets of protons are on the same face of the phenanthridine.

![Figure 3.7](image.png)

**Figure 3.7** 2D nOESY NMR for major exo-syn diol product 207k illustrating a lack of ring junction (rj) to $CHOH$ cross peaks.
3.3.3 Epoxidation using mCPBA or via a bromohydrin

With conditions for the cis-dihydroxylation of our phenanthridines safely in hand, we looked toward developing conditions for accessing the trans-diol, via the epoxide intermediate using mCPBA-promoted conditions reported in the literature (Scheme 3.12). Although a mixture of epoxides 210 was formed from the trans-ring-junction analogue 204, we expected exo-selectivity for epoxidation of the cis analogue, due to the aforementioned cupped conformation adopted by the substrate.

Scheme 3.12 Literature conditions for trans-diol formation via the epoxide.\textsuperscript{126}
a) mCPBA, CH\textsubscript{2}Cl\textsubscript{2}, r.t., 18 h, 73%; b) HClO\textsubscript{4}, H\textsubscript{2}O/THF, r.t., 1.5 h, 64%.

Figure 3.8 2D nOESY NMR for minor endo-syn diol product 209k illustrating a ring junction (rj) to CHOH cross peak.
Application of these conditions to alkene 96b led to the formation of desired epoxide 212, along with the corresponding phenanthridone epoxide 213 (Scheme 3.13). Lowering the temperature (0 °C) or reducing reaction time (3 h) offered no improvement. The benzylic position of the phenanthridine is known to be susceptible to oxidation under mCPBA conditions,¹²⁷ and a postulated mechanism involves H-atom abstraction, followed by benzylic radical trapping by air.¹²⁸

Scheme 3.13  Epoxidation using mCPBA.

\[ \text{Scheme 3.13} \quad \text{Epoxidation using mCPBA.} \]
\[ \text{a) mCPBA, CH}_2\text{Cl}_2, 16 \text{ h, r.t., 99\% 212:213 59:43; 0 \degree \text{C}, 16 \text{ h, 0\%; r.t., 3 h, 50\% 212:213 1:1.}} \]

An alternative approach for the epoxidation of alkenes involves a two-step sequence via an intermediate bromohydrin 215. This method was successfully applied in the synthesis of (+)-homochelidonine where prevention of benzylic oxidation was essential (Scheme 3.14).¹²⁹

Scheme 3.14  Bromohydrin formation in the synthesis of (+)-homochelidonine.¹²⁹

\[ \text{Scheme 3.14} \quad \text{Bromohydrin formation in the synthesis of (+)-homochelidonine.} \]
\[ \text{a) NBS, THF/H}_2\text{O, r.t., 1.5 h, 75\%; b) KO'Bu, THF, -78 \degree \text{C, 0.5 h, 99\%.}} \]

Unfortunately application of the bromohydrin formation conditions to our Boc alkene 96b resulted in the formation of multiple products along with considerable starting material. The formation of up to four bromohydrins was expected as the bromonium ion intermediate can form on either face of the alkene (although we would expect the \textit{exo} to be favoured), and can then open up in either direction. We propose that the cupped nature of the \textit{cis}-ring junction phenanthridine hindered both the formation of the bromohydrin on the concave face, and the opening of the \textit{exo-
bromohydrin by attack of H$_2$O from the concave face leading to the large amount of alkene 96b being recovered.

3.3.4 Epoxidation using DMDO (dimethyldioxirane)

Another alternative reagent for the preparation of epoxides from alkenes is DMDO 217 (Scheme 3.15), an oxidising agent derived from acetone. DMDO has been found to be both a mild and efficient reagent, with the added advantage that only acetone is produced as a by-product in the reaction. Although it is highly selective for alkenes, it is also capable of oxidising several other functional groups including primary amines to nitro compounds and sulfides to sulfoxides.

We were keen to explore the use DMDO for the epoxidation of our substrate after a recent report where the reagent was successfully applied to the synthesis of phenanthridine natural product fortucine 218. In this example DMDO was used to successfully oxidise sulphide 219 to sulfone 220, with no oxidation occurring at the benzylic position as we had observed with mCPBA.

Scheme 3.15 Application of DMDO in the synthesis of (+) Fortucine 218.

Although DMDO is a very well known reagent, it is very unstable and therefore not commercially available. To generate the reagent, a fresh solution must be prepared from oxone, sodium bicarbonate and acetone using a complex set-up of glassware under vacuum (Figure 3.9). The preparation of DMDO is known to be rather inefficient, typically yielding a solution of <0.15 M in acetone. Several factors account for this low concentration including a large number of possible side reactions, and inefficient collection of the dioxirane reagent in the cold trap.
In agreement with the literature precedent, we also found the preparation of DMDO to be extremely inefficient, even after careful repetition a number of times. Although the solution concentration was not measured, we found that the reaction of just $80 \mu$mol of alkene with 10 ml of DMDO solution, gave $<30\%$ conversion to the epoxide, suggesting a concentration of just 0.003 M. Although the conversion was poor, no trace of phenanthridone epoxide was observed in the product mixture suggesting a more efficient preparation of DMDO would provide the solution to achieving selective epoxidation.
Results and Discussion 2

There have been a number of reports of the \textit{in situ} generation of the reagent under phase-transfer conditions\textsuperscript{131,135}. We trialled these conditions for the epoxidation of styrene \textsuperscript{221} in order to determine if they would be successful (Scheme 3.16).

\textbf{Scheme 3.16} \textit{In situ generation of dioxirane.}\textsuperscript{131}

\begin{itemize}
  \item[a)] oxone, Me\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}, Na\textsubscript{2}HPO\textsubscript{4} aq. buffer, nBu\textsubscript{4}NHSO\textsubscript{4}, pH 7.5-8, 0 °C, 3 h, 20%;
  \item[b)] oxone, (CF\textsubscript{3})\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}, Na\textsubscript{2}HPO\textsubscript{4} aq. buffer, nBu\textsubscript{4}NHSO\textsubscript{4}, pH 7.5-8, r.t., 4 h, 20%;
\end{itemize}

The conditions for \textit{in situ} generation of the DMDO, though simpler than the traditional method, were still complex, requiring careful monitoring of the pH to avoid possible decomposition of the dioxirane at pH >8. Despite our care, we were not able to satisfactorily reproduce these conditions and only 20% conversion was observed at 0 °C. In an attempt to reduce the electron density of the O-O bond and therefore generate a more reactive dioxirane, we switched acetone for trifluoromethylacetone\textsuperscript{134}. However again, only a 20% epoxide was obtained, even after raising the reaction temperature from 0 °C to r.t.

Our studies into the application of DMDO showed that the reagent is selective for epoxidation without oxidation at the benzylic position to give the phenanthridone \textsuperscript{212}. However, we were not able to satisfactorily replicate the literature methods for traditional or \textit{in situ} generation of the dioxirane. After numerous unsuccessful attempts to obtain selective epoxidation, we stopped all investigations into the synthesis of epoxides to focus on other areas of the project.
3.4 Skeletal Diversity

3.4.1 Ring-rearrangement metathesis (RRM)

Olefin metathesis has now become a well-established tool in organic synthesis. Originally ring-closing metathesis (RCM) formed the basis of much of the research in this field, but more recent efforts have included the development of protocols to facilitate ring-opening metathesis (ROM) and cross-metathesis reactions. Domino metathesis or ring-rearrangement metathesis reactions (RRM), involving combinations of these metathesis protocols have also been reported, and implemented successfully in complex molecule synthesis. These reactions involve intramolecular metathesis between an endocyclic olefin and a tethered exocyclic C=\(\equiv\)C bond, in such a way that one ring is opening in a ROM process and another is formed in a RCM process (Scheme 3.17).^{138}

\begin{center}
\textbf{Scheme 3.17} RRM of 2-aminonorbornenes.\textsuperscript{138}
\end{center}

\begin{itemize}
  \item \textbf{a)} Grubbs I (10 mol%), ethylene, CH\textsubscript{2}Cl\textsubscript{2}, r.t., 16 h. R= Boc 90%; R= Cbz 90%; R= Ts 99%.
\end{itemize}

RRM has previously been used to prepare molecules with carbocyclic and oxocyclic skeletons,\textsuperscript{139} but there are far fewer reports of its successful implementation in the synthesis of nitrogen containing systems.\textsuperscript{140} Indeed, across the whole of metathesis chemistry, the presence of amino-functionality is rare (one example is illustrated above in Scheme 3.17).\textsuperscript{138} The reason behind this lies in the ability of the amino group to coordinate to the transition metal of the metathesis catalyst, thus leading to deactivation and poor reactivity. Successful approaches to counteracting this problem include the use of Lewis acids to coordinate the amine,\textsuperscript{141} the use of amines with strongly electron-withdrawing functionality (such as sulfonamides\textsuperscript{142} or carbamates, Scheme 3.17); and the use of ammonium salts.\textsuperscript{143}

In the above example (Scheme 3.17), the cycloalkene 223 that undergoes ROM is a very highly strained norbornene. The drive to achieve a lower energy structural conformation makes norbornene units highly effective for ROM, and indeed most of
the successful examples of the RRM of amino-containing substrates use norbornene as the cycloalkene unit. The majority of the other examples use cyclopentene or cyclobutene which both have more strained ring systems than cyclohexene and are thus pre-disposed to undergo ROM. To the best of our knowledge, only three successful examples of the ROM or RRM of unstrained cycloalkenes have been reported.

3.4.2 ROM/RRM of unstrained cycloalkenes

RRM of *bis*-propargyl-N-tosyl amine 225 was found to occur under Grubbs I or Grubbs II metathesis (Table 3.8). However in this example the RRM only proceeded with low yields (<22%) and 1,3-diene 227 was recovered as the major product along with significant starting material. Formation of the 1,3 diene 227 occurs from the cross metathesis of the alkyne with ethylene and has been attributed to steric hindrance of the ruthenium catalyst at the reaction site.

Table 3.8 Enyne metathesis of diyne 225.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Conversion (%)</th>
<th>226:227</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs I (5 mol%), CH₂Cl₂, CH₂=CH₂</td>
<td>25</td>
<td>20</td>
<td>63</td>
<td>1:5.3</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs I (10 mol%), CH₂Cl₂, CH₂=CH₂</td>
<td>25</td>
<td>20</td>
<td>79</td>
<td>1:3.9</td>
</tr>
<tr>
<td>3</td>
<td>Grubbs I (10 mol%), CH₂Cl₂, CH₂=CH₂</td>
<td>50</td>
<td>20</td>
<td>61</td>
<td>1:2.6</td>
</tr>
<tr>
<td>4</td>
<td>Grubbs II (10 mol%), PhMe, CH₂=CH₂</td>
<td>60</td>
<td>20</td>
<td>81</td>
<td>1:2.7</td>
</tr>
</tbody>
</table>
Interestingly, RRM of cycloalkyne-ynes 228a-c (Table 3.9),\(^{146}\) was reported to proceed under similar conditions to those reported in Table 3.8, but this time excellent conversions to the pyrrolidine products 229a-c was obtained in less than 4 hours at r.t. The 1,3-diene cross metathesis product was not observed though this could reasonably be attributed to the lack of steric congestion at the reaction site as opposed to bis-propargyl counterpart 225. To the best of our knowledge, this example remains the highest yielding RRM of an unstrained cyclohexene.

### Table 3.9 RRM of cycloalkyne-ynes.\(^{146}\)

<table>
<thead>
<tr>
<th>228</th>
<th>n</th>
<th>t (h)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>1</td>
<td>4</td>
<td>78</td>
</tr>
<tr>
<td>b</td>
<td>2</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>c</td>
<td>3</td>
<td>1</td>
<td>75</td>
</tr>
</tbody>
</table>

One final example illustrates how ROM can be used in an elegant manner to generate biologically active compounds.\(^{143}\) Exposure of the hydrochloride salt of Manzamine A 230 to Grubbs I under ethylene gave a 4:1 mixture of tetraene 231 and pentaene 232, formed from ROM of the 13-membered D ring or the 8-membered E ring respectively (Scheme 3.18). The high conversion obtained for the ROM of these large-ring cycloalkenes shows the power that a simple reaction such as ROM has to generate diversity from a common starting material.

### Scheme 3.18 ROM of manzamine A 230.\(^{143}\)

\(a\) i) HCl; ii) Grubbs I, ethylene, CH\(_2\)Cl\(_2\), r.t., 24 h, 71\%, 231:232 4:1.
3.4.3 RRM in DOS

Towards the end of our investigation into the RRM of our substrates, an example of the application of RRM to a DOS library was reported (Scheme 3.19). In this example the key step for the generation of molecular scaffold 233 required a RRM of highly strained norbornene derivative 234. This generated 1,3-diene 235 that was then converted to scaffold 233 using a Diels-Alder reaction. Variation of the N-alkyl group and the dienophile would enable the incorporation of further diversity. RRM is therefore clearly a powerful tool in DOS library synthesis, and the generation of methodology to enable unstrained cycloalkenes to be used for this purpose would be of great value.

![Scheme 3.19 Application of enyne metathesis in DOS library synthesis.](image)

a) Grubbs I (10 mol%), ethylene, MW, 60 °C, 1 h; b) Grubbs I (10 mol%), Grubbs II (10 mol%), ethylene, MW, 60 °C, 2 h; c) CN-CH$_2$CO$_2$K, MeOH, 1 h, 87% (over 3 steps); d) N-ethylmaleimide, PhMe, MW, 160 °C, 6 h. 99%.

3.4.4 Mechanism

It is postulated for all RRM reactions involving pendant alkynes, that the ruthenium catalyst first reacts with the more electron rich alkyne part, rather than facilitating the cycloalkene ring-opening immediately. The proposed mechanism for the RRM of a cycloalkene-yne has been briefly discussed in the literature, and is represented in Scheme 3.20 for the RRM of a substrate whose alkyne tether is connected to the C-3 position of the cycloalkene.
Scheme 3.20 Proposed mechanism for RRM. The alkyne part of substrate A reacts with the ruthenium complex to generate ruthenocyclobutene B. This gives rise to ruthenium-carbene complex C by ring-opening through cycloreversion. The carbene complex can then react intramolecularly with the cycloalkene part to generate the highly-strained ruthenium complex D, which then undergoes ring-opening to afford carbene complex E. The ruthenium-carbene E is unable to undergo further intramolecular reaction at this stage and as a result it will react with another molecule of A to afford a polymer (e.g. ROMP). However, if the reaction is carried out under an atmosphere of ethylene, ruthenium complex E would react with the gas to give RRM product G via ruthenacyclobutane F.
3.4.5 Proposed RRM of the phenanthridine core

We were aware from literature examples (section 3.4.2) that the RRM product varies depending on the size of the cycloalkene, the length of the alkyne tether, and the position of the alkene bond within the cycloalkene. We envisaged using this to our advantage in a RRM of our phenanthridine double bond isomer mixture. N-propargylation of our phenanthridine, followed by RRM would yield three skeletally different products using one common reaction (Scheme 3.21). In conjunction with aryl variation, a powerful and efficient approach to a DOS library may be realised.

![Scheme 3.21](Potential products from the RRM of propargyl phenanthridines 96-98f.)

In addition to the propargyl group, we also proposed to investigate the homopropargyl and Poc-protected analogues 96gh-98gh to potentially give us access to larger ring cycloalkene and cyclic carbamate products (Scheme 3.22).

![Scheme 3.22](Potential products from the RRM of homopropargyl and Poc phenanthridine derivatives 96-98g and 96-98h.)
3.4.6 Synthesis of RRM precursors

3.4.6.1 Heck cyclisation approach

In light of the generally poor yields reported in the literature, and to simplify analysis of the reaction, we decided to trial the RRM on single double bond isomers. We knew that our Heck cyclisation under cationic conditions gave predominantly the $\Delta^{1,2}$ double bond isomer and so we decided to generate cyclisation precursors with the appropriate $N$-functional groups. To this end we prepared propargyl$^{150}$ and Poc-protected$^{151}$ starting materials 94f and 94h (Scheme 3.23).

```
\textbf{Scheme 3.23 Synthesis and attempted cyclisation of propargyl precursors.}
\begin{align*}
a) & \quad P = \text{CH}_2\text{C}=\text{CH: propargyl bromide, K}_2\text{CO}_3, \text{DMF, r.t., 16 h, 99\%}; \\
b) & \quad P = \text{C(OCCH}_2\text{C}≡\text{CH: PocCl, Et}_3\text{N, CH}_2\text{Cl}_2, 0 ^\circ\text{C} \rightarrow \text{r.t., 16 h, 99\%}. \\
\end{align*}
```

Cationic cyclisation of both substrates gave none of the desired product, and in the case of the Poc analogue 94h, secondary amine 93 was recovered as the sole product. Application of our milder conditions using (‘Bu$_3$P)$_2$Pd at either r.t. or 50 °C gave similar results. Preparation and cyclisation of a homopropargyl analogue was not carried out due to these unsuccessful results.

3.4.6.2 Attempted deprotection of $N$-Boc

As the Heck cyclisation of propargyl precursors 94f and 94h had failed, we realised that to access the required propargyl phenanthridines we needed to perform a Boc-deprotection of the appropriate phenanthridine, followed by protection with the relevant propargyl reagent. As the desired propargyl and homopropargyl products were amines we presumed that separation of the Boc-protected double bond isomers would be easier. To this end HPLC separation of 96b-98b furnished us with sufficient quantities of the isolated double-bond isomers to take on to the next stage.
We had presumed that Boc-deprotection of 96b-98b would be a trivial step, indeed we had easily removed the Boc-group from saturated analogue 110b using TFA/CH$_2$Cl$_2$ when we proved the cis-ring junction stereochemistry of our phenanthridines (see section 2.5.2). However, in this case we had an alkene that was capable of unwanted isomerism under acid-catalysis conditions (see section 2.9.4), so we were forced to investigate alternative conditions by which to remove the Boc group from our phenanthridines (Table 3.10).

**Table 3.10 Conditions for the Boc-deprotection of $\Delta^{1,2}$ phenanthidine 96b.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions$^a$</th>
<th>T ($^\circ$C)</th>
<th>t (h)</th>
<th>Conversion (%)</th>
<th>Notes $\Delta^{1,2} \Delta^{2,3} \Delta^{3,4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA, CH$_2$Cl$_2$</td>
<td>r.t.</td>
<td>0.5</td>
<td>100</td>
<td>81:18:1 mixture of d.b. isomers</td>
</tr>
<tr>
<td>2</td>
<td>TFA, CH$_2$Cl$_2$</td>
<td>0</td>
<td>1</td>
<td>100</td>
<td>61:19:20 mixture of d.b. isomers</td>
</tr>
<tr>
<td>3</td>
<td>ZnBr$_2$ (2.7 eq), CH$_2$Cl$_2$</td>
<td>r.t.</td>
<td>16</td>
<td>100</td>
<td>77:0:23 mixture of d.b. isomers</td>
</tr>
<tr>
<td>4</td>
<td>CAN (0.2 eq), MeCN</td>
<td>80</td>
<td>16</td>
<td>100</td>
<td>Many products</td>
</tr>
<tr>
<td>5</td>
<td>CAN (2 eq), MeCN</td>
<td>80</td>
<td>16</td>
<td>100</td>
<td>Many products</td>
</tr>
<tr>
<td>6</td>
<td>SnCl$_4$ (4 eq), EtOAc</td>
<td>r.t.</td>
<td>16</td>
<td>n.d</td>
<td>S.M. + several products</td>
</tr>
<tr>
<td>7</td>
<td>TBAF (10 eq), THF</td>
<td>80</td>
<td>16</td>
<td>n.d</td>
<td>S.M. + several products</td>
</tr>
<tr>
<td>8</td>
<td>Na$_2$CO$_3$, DME/H$_2$O</td>
<td>80</td>
<td>72</td>
<td>0</td>
<td>S.M. recovered</td>
</tr>
<tr>
<td>9</td>
<td>FVP</td>
<td>500</td>
<td>0.5</td>
<td>n.d</td>
<td>Possible product formation</td>
</tr>
<tr>
<td>10</td>
<td>FVP</td>
<td>600</td>
<td>0.5</td>
<td>60</td>
<td>$\Delta^{1,2}$ isomer only</td>
</tr>
</tbody>
</table>

Entries 1 and 2 confirm that double bond isomerism occurred under standard TFA Boc-deprotection conditions, even at 0 $^\circ$C. Lewis acid mediated deprotection using ZnBr$_2^{152}$ gave a mixture of double bond isomers (entry 3) and incomplete deprotection/unidentifiable product formation using SnCl$_4^{153}$ (entry 6). Ceric ammonium nitrate (CAN) has been reported as a successful one-electron transfer catalyst for the removal of the Boc-group from a range of amines, alcohols and thiols.$^{154}$ However in our case, although complete removal of the Boc-group was observed, a mixture of unidentifiable products was obtained, rendering this approach
ineffective for our purposes (entries 4 and 5). TBAF has been shown to be an effective Boc-deprotecting agent for a range of aryl and heteroaryl substrates, however application of these conditions to Δ^{1,2} phenanthridine 96b led to incomplete conversion and a mixture of unidentifiable products. Na₂CO₃ in DME/H₂O has been used for the N-Boc deprotection of various heteroaryl amines, but no conversion was observed on our system. The conditions we finally used for selective deprotection of the Boc-group without double bond isomerism required flash vacuum pyrolysis at 600 °C (entry 10).

3.4.6.3 Flash vacuum pyrolysis (FVP) deprotection of N-Boc

Flash vacuum pyrolysis refers to the gas-phase pyrolysis of an organic material under low-pressure conditions. In its simplest form FVP involves vacuum distillation of an organic substrate through an empty hot pyrolysis tube, contained within a furnace (Figure 3.10). The products are simply collected afterwards in a U-tube contained within a cold trap, and generally require no work up and little purification.

FVP has significant advantages over condensed-phase methods because there are no solvent or reagent molecules present to interfere with the reactive intermediate. In addition to this, the ultra-high vacuum employed for FVP means that the molecules undergoing reaction spend mere milliseconds in the reaction zone (i.e the pyrolysis tube) before they are quenched. This means that even thermally unstable reactive intermediates usually survive FVP conditions.
The use of FVP to facilitate Boc-deprotection has been reported, and typically requires a furnace temperature of 600 °C. As reported in Table 3.10 we found that successful Boc-deprotection under these conditions was achieved for $\Delta^{1,2}$ phenanthridine 96b, and we were pleased to discover that this also held true for the $\Delta^{2,3}$ and $\Delta^{3,4}$ phenanthridines 97b and 98b (Scheme 3.24). Purification of the reaction products was achieved through subsequent Kugelrohr distillation.

**Scheme 3.24** FVP mediated Boc-deprotection of isolated phenanthridines 96b-98b.

\[ a) \text{i) FVP, } 600 ^\circ \text{C, } 0.5 \text{ h; ii) Kugelrohr distillation } 70 ^\circ \text{C, } \Delta^{1,2} 245 60\%, \Delta^{2,3} 246 81\%, \Delta^{3,4} 247 71\%. \]

3.4.6.4 RRM precursors via alkylation/acylation

With each of the three double-bond isomer amines 245-247 in hand, we set about synthesising the corresponding propargyl, homopropargyl and Poc-protected analogues. Unfortunately, the conditions we had used previously for the propargylation of secondary amine 93 (propargyl bromide, K$_2$CO$_3$, DMF, Scheme 3.23) did not prove to be successful on the phenanthridine substrates 245-247, furnishing the desired products in <10% yield. Our group had experience of N-propargylations, and it was suggested that the formation of side products was occurring due to the lengthy reaction time employed. The use of dry acetone and an elevated reaction temperature was suggested in order to increase the solubility of the K$_2$CO$_3$ and thus accelerate the reaction. After 2 h all three propargylated products 96f-98f were recovered in good yield (Table 3.11). Similar conditions were employed to access homopropargyl phenanthridines 96g-98g, although these reactions required heating for 16 h to achieve reasonable conversions. Finally, Poc-protected phenanthridines 96h-98h were obtained following reaction of a mixture of 245-247 with propargyl chloroformate as previously. Purification of mixture 96h-98h was easier as the substrates were carbamates and not amines and therefore less
polar. This enabled us to obtain sufficient isolated quantities of Poc-phenanthridines 96h-98h to use in our RRM studies.

Table 3.11 RRM precursor synthesis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Product</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>245</td>
<td>a</td>
<td>60</td>
<td>2</td>
<td>96f</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>246</td>
<td>a</td>
<td>60</td>
<td>2</td>
<td>97f</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>247</td>
<td>a</td>
<td>60</td>
<td>2</td>
<td>98f</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>245</td>
<td>b</td>
<td>60</td>
<td>16</td>
<td>96g</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>246</td>
<td>b</td>
<td>60</td>
<td>16</td>
<td>97g</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>247</td>
<td>b</td>
<td>60</td>
<td>16</td>
<td>98g</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>245-247</td>
<td>c</td>
<td>0 °C→r.t.</td>
<td>16</td>
<td>96h-98h</td>
<td>74</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Product</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>245</td>
<td>a</td>
<td>60</td>
<td>2</td>
<td>96f</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>246</td>
<td>a</td>
<td>60</td>
<td>2</td>
<td>97f</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>247</td>
<td>a</td>
<td>60</td>
<td>2</td>
<td>98f</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>245</td>
<td>b</td>
<td>60</td>
<td>16</td>
<td>96g</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>246</td>
<td>b</td>
<td>60</td>
<td>16</td>
<td>97g</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>247</td>
<td>b</td>
<td>60</td>
<td>16</td>
<td>98g</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>245-247</td>
<td>c</td>
<td>0 °C→r.t.</td>
<td>16</td>
<td>96h-98h</td>
<td>74</td>
</tr>
</tbody>
</table>

a) P=CH₂C≡CH: propargyl bromide (1.1 eq), K₂CO₃ (3 eq), acetone (dry); b) P=CH₂CH₂C≡CH: homopropargyl bromide (1.1 eq), K₂CO₃ (3 eq), acetone (dry); c) P=O(CH₂C≡CH: PocCl (4 eq), Et₃N (4 eq), CH₂Cl₂, 0 °C → r.t. a Mixture.

3.4.7 RRM studies – Propargyl analogues

The majority of recent Grubbs metathesis literature focuses on the use of four main catalysts: Grubbs I 248; Grubbs II 249; Hoveyda-Grubbs I 250; and Hoveyda-Grubbs II 251 (Figure 3.11). We initially decided to employ Hoveyda-Grubbs II 251 as our Ru source as this was the most recent generation catalyst and had precedent in ROM-polymerisation reactions.¹⁶¹

Figure 3.11 Commercially available Grubbs-metathesis catalysts.
We were delighted to observe that application of catalyst 251 to $\Delta^{2,3}$ propargyl phenanthridine 97f under an atmosphere of ethylene, led to formation of benzo[b]quinolizine product 237 in excellent yield (Scheme 3.25). We had presumed that this particular propargyl substrate would be most likely to undergo a successful RRM as it gave rise to a conformationally favoured 6,6,6-ring annulated product.

Scheme 3.25 RRM of $\Delta^{2,3}$ propargyl phenanthridine 97f.

a) Hoveyda-Grubbs II 251 (15 mol%), ethylene, CH$_2$Cl$_2$, r.t., 40 h, 71%.

Following the success of this result, we applied these conditions to other propargyl phenanthridines 96f and 98f. Disappointingly, we observed quantitative recovery of the starting material upon the attempted RRM of $\Delta^{1,2}$ propargyl-phenanthridine 96f. Presumably in this instance, the alkene was too far away for the propargyl tether to access it for the metathesis reaction. Performing this reaction at elevated temperature had no impact on the result. However, we were pleased to discover that $\Delta^{3,4}$ propargyl-phenanthridine 98f gave total conversion to the benzoindolizine product 238 (Scheme 3.26).

Scheme 3.26 RRM of $\Delta^{3,4}$ propargyl phenanthridine 98f.

a) Hoveyda-Grubbs II 251 (15 mol%), ethylene, CH$_2$Cl$_2$, r.t., 40 h, 80%.
3.4.8 RRM of homopropargyl analogues

The RRM of both $\Delta^{2,3}$ and $\Delta^{3,4}$ propargyl phenanthridines 97f and 98f were remarkable results given the lack of similar unstrained cycloalkene examples in the literature. However, in order for the reaction to be of use to us in a DOS library context, we required an RRM that was applicable to all three double bond isomers. We were hopeful that extension of the alkynyl chain by one or two atoms, would allow it to be long enough to undergo metathesis with the $\Delta^{1,2}$ alkene.

To this end, homopropargyl-phenanthridines 96g-98g were subjected to our RRM conditions (Table 3.12). Total conversion was observed in all cases, and the product exhibited the same mass and the correct number of $^1$H and $^{13}$C signals in the NMR as the desired RRM products 239-241. In addition to this, we observed the alkene quartet signal at 6.40 ppm that had been very distinctive in the $^1$H NMR spectrum of 237 and 238.

Table 3.12 Attempted RRM of isolated homopropargyl-phenanthridines 96g-98g.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>Product</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\Delta^{1,2}$</td>
<td>251</td>
<td>96j</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>$\Delta^{2,3}$</td>
<td>251</td>
<td>97j</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>$\Delta^{3,4}$</td>
<td>251</td>
<td>98j</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>$\Delta^{2,3}$</td>
<td>248</td>
<td>97j</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>$\Delta^{2,3}$</td>
<td>248</td>
<td>97j</td>
<td>89</td>
</tr>
</tbody>
</table>

a) Hoveyda-Grubbs II 251 or Grubbs I 248 (15 mol%), ethylene, CH$_2$Cl$_2$, r.t., 40 h at 45 °C.

However, in one of the literature examples illustrated (Table 3.8),146 two potential products from the treatment of an cycloalkene-yne with ethylene in the presence of a metathesis catalyst are identified. In addition to the desired RRM product (such as benzo[b]quinolizine 237 and benzoindolizine 238), the formation of a 1,3-diene can
occur from the metathesis of the alkyne with ethylene, without concommitant RRM. This would afford a product with the same mass, number of protons and number of carbons as the desired RRM product, leading to easy misinterpretation. We eventually assigned products 96j-98j as the undesired 1,3-dienes by careful analysis of the splitting pattern in the alkene region of the $^1$H NMR spectra.

For benzo[b]quinolizine RRM product 237 (Figure 3.12), each of the four terminal alkene signals (a+h) appear as doublets as a result of the proton (b or g) on the adjacent carbon. For the 1,3-diene product 97j (Figure 3.13), two of the terminal alkene signals appear as doublets (k1+k2) as a result of the proton (j) on the adjacent carbon, and the two remaining terminal alkenes appear as broad singlets (indicative of h). Proton b of the RRM product 237 is a high order multiplet, strongly indicative of its position adjacent to a and c. In addition to this, protons b and c of 1,3-diene 97j are positioned where we normally find the $\Delta^{2,3}$ isomer alkene signals of the phenanthridine. The two NMR examples given are typical of the other RRM and 1,3-diene products and further structural confirmation was obtained from 2D COSY NMR studies.

Figure 3.12 $^1$H NMR of benzo[b]quinolizine RRM product 237.
3.4.9 Other metathesis attempts

Similarly, the application of our standard metathesis conditions to Poc-phenanthridines 96h-98h also gave the corresponding 1,3-diene products 96k-98k (Table 3.13). Despite substrates 96h-98h failing to undergo RRM, we were pleased to observe that the carbamate functionality of the Poc-group had remained intact. As far as we know, this is the first report of such functionality surviving Grubbs-metathesis conditions, providing evidence to support its application in RCM studies.

Table 3.13 Attempted RRM of isolated Poc-phenanthridines 96h-98h.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\Delta^{12}$</td>
<td>96k</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>$\Delta^{23}$</td>
<td>97k</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>$\Delta^{34}$</td>
<td>98k</td>
<td>96</td>
</tr>
</tbody>
</table>

a) Hoveyda-Grubbs II 251 (15 mol%), ethylene, CH$_2$Cl$_2$, r.t., 40 h.
As suggested in section 3.4.2, the formation of 1,3-diene products has been proposed to occur as a result of steric congestion.\(^{146}\) In light of this, we were keen to observe what happened when we employed the less sterically hindered Grubbs I catalyst \(248\), which had found success in the literature precedent. However, application of this catalyst to the \(\Delta^{2,3}\) homopropargyl substrate \(97g\) at room temperature or \(45\,^\circ C\) in \(CH_2Cl_2\) (Table 3.12), gave quantitative conversion to the 1,3-diene product \(97j\), as we had previously observed using Hoveyda-Grubbs II \(251\).

One additional literature example reported the successful manipulation of a butenyl tether in the RRM of indolizidine alkaloids.\(^{162}\) As the homopropargyl and Poc-tethered phenanthridines had both formed the 1,3-diene under RRM conditions, we decided to synthesise butenyl-phenanthidine \(97m\). If this substrate were to undergo an alkene cross metathesis with ethylene, it would simply regenerate the starting material, thus we were hopeful that an RRM would be promoted under such circumstances. However, unfortunately when we attempted this reaction on the \(\Delta^{2,3}\) substrate \(97m\) using catalyst \(251\), all we recovered was the starting material in quantitative yield, suggesting that either a cross alkene metathesis with ethylene had occurred, or that the alkene tether was unreactive.

![Scheme 3.27](image)

**Scheme 3.27 Synthesis and attempted RRM of \(\Delta^{2,3}\) butenyl-phenanthidine \(97m\).**

a) Butenyl bromide (1.1 eq), \(K_2CO_3\) (3 eq), acetone (anhydrous); b) \(251\) (15 mol%), ethylene, \(CH_2Cl_2\), r.t., 40 h, 99%.

### 3.4.10 Conclusions for RRM

Several interesting points were raised from these preliminary investigations into the RRM of our phenanthidine substrates. Firstly, the reaction was clearly possible as exemplified by the successful synthesis of benzo[b]quinolizine \(237\) and benzooindolizine \(238\). As we have seen from the molecular model of a typical cis-phenanthidine (Figure 3.6), the molecule lies in a very cupped conformation as
compared to its flatter trans counterpart. Our working hypothesis as to the success of these RRM reactions, is that the relief of steric strain upon opening of the C-ring provides a strong driving force for the reaction. In order to test this hypothesis it would certainly be interesting to try the same RRM reaction on an analogous trans-phenanthridine. The formation of the conjugated diene in the RRM product, may also contribute to promotion of the RRM reaction.

The second interesting point is the formation of 1,3-dienes from the longer alkyne-tethered phenanthridines, rather than the desired RRM product. There are currently no reports in the literature comparing the relative abilities of propargyl and homopropargyl tethers to undergo RRM. However, instances of both being successfully manipulated in RRM are known, as are instances of both acting as precursors for formation of the 1,3-diene product.\textsuperscript{146} As we obtained no improvement using a less bulky catalyst (Grubbs I\textsuperscript{248}) we can only postulate that the reluctance of our long-chain alkynyl tethered phenanthridines to undergo RRM may be a result of the disfavoured formation of larger C-ring products. This may also have some bearing on the failed RRM of the propargyl $\Delta^{1,2}$ analogue as the product here would have had a 7-membered C-ring, however it is likely in this case that the tether was simply too short to allow the RRM reaction to take place.

In light of the time constraints for this project we had to be content with limiting our skeletal diversification to the successful generation of two RRM products. However, the work sets excellent precedent for further investigation into cis vs trans ring-fused cyclohexenes as substrates for RRM reactions.
3.5 Conclusions
Methodology for the synthesis of a DOS library of phenanthridines was explored from each of the three possible angles, namely building block diversity, stereochemical diversity and skeletal diversity.

i) Building block diversity
Conditions for the high yielding and efficient synthesis of various aromatic/heteroaromatic building blocks were developed, using standard transformations, or less standard Curtius methodology. These building blocks were readily converted to the corresponding cyclisation precursors 165a-f,k, and shown to undergo facile Heck cyclisation under cationic or neutral conditions, to afford the expected double bond isomer products 195-197a-f,k in excellent yield (72-99%).

ii) Stereochemical diversity
The synthesis of exo-syn dihydroxylated phenanthridines 206m-208m was shown to proceed with high dr (>83:17) and excellent yield (99%) across the range of double bond isomers. Attempts to introduce epoxide functionality to the C-ring were hampered by over-oxidation to the phenanthridone or failure to reproduce reported literature conditions. We were therefore unable to generate any trans-diol C-ring phenanthridines.

iii) Skeletal diversity
Methodology for the RRM of various propargyl-tethered phenanthridines was explored. High conversions were obtained for the RRM of Δ2,3 and Δ3,4 propargyl phenanthridines 97f and 98f giving a potential route to novel benzo[b]quinolizines and benzoindolizine products. Unfortunately the propargyl tether did not react with the Δ1,2 alkene, preventing this methodology from being applied to all members of the alkene library, and thus limiting its use in a DOS library context. Our attempts to lengthen the alkynyl tether led to the formation of unwanted 1,3-diene products 96jk-98jk.

Exploration of the amine building block diversity in conjunction with the cis-dihydroxylation protocol will be the two elements combined in Chapter 4 for the DOS library synthesis.
4.1 Library synthesis

We chose to synthesise a library based upon the phenanthridine core, using the building block and stereochemical diversity protocols developed in Chapter 3. To this end our aryl and heteroaryl double bond isomer phenanthridine mixtures 195-197a-f,k were treated under exo cis-dihydroxylation conditions (Table 4.1) to afford the corresponding diol mixtures 206-208a-f,k.

Table 4.1 Cis-dihydroxylation of aryl/heteroaryl phenanthridines 195-197a-f,k.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R=)</th>
<th>Yield 206-208 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield 206 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield 207 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield 208 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Me</td>
<td>78</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4-F</td>
<td>82</td>
<td>18</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>5-MeO</td>
<td>95</td>
<td>13</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>4,5-diMeO</td>
<td>70</td>
<td>6</td>
<td>19&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>[Naphthyl]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>87</td>
<td>14</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>[Thiophene]&lt;sup&gt;e&lt;/sup&gt;</td>
<td>64</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>[Piperonyl]&lt;sup&gt;f&lt;/sup&gt;</td>
<td>87</td>
<td>9</td>
<td>23 (3)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>70</td>
<td>13</td>
<td>11</td>
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</tbody>
</table>

<sup>a</sup> OsO₄, NMO, THF/H₂O, r.t., 18 h. <sup>b</sup> Isolated yield for mixture following flash chromatography. <sup>c</sup> Isolated yield of each isomer following flash chromatography or additional HPLC separation. <sup>d</sup> comprises approximately 1:1 mixture of $\Delta^{1,2}:\Delta^{2,3}$ diols. <sup>g</sup> $\Delta^{2,3}$ endo-syn diol product 209k isolated and characterised by 2D NMR studies (see section 3.3.2). <sup>g</sup> Reaction performed on parent phenanthridines 96b-98b. <sup>g</sup> See footnote Table 3.2. <sup>g</sup> As in Scheme 3.6.
In keeping with the high diasteromeric ratio we obtained for the \textit{cis}-dihydroxylation of carbamates 96b-98b in the previous chapter (Table 3.7), we observed the \textit{exo}-diols as the major products. Determination of the exact ratio was not possible due to the complex mixture of isomer products. Structural assignment was made by analogy with the parent diol analogues 206m-208m (R=H) that were synthesised as isolated products in the previous section (Table 3.7). The dihydroxylation of 96b-98b was repeated here using the mixture of double bond isomers to give a comparative result for the library synthesis (Table 4.1, entry 8). From the dihydroxylation of piperonyl phenanthridines 195k-197k (entry 7) we isolated a trace amount of the \(\Delta^{2,3}\) \textit{endo-syn} diol 209k that enabled us to confirm the major and minor product structures using 2D nOESY NMR (see section 3.3.2).

Following dihydroxylation, the three major products 206, 207 and 208 were isolated by silica-gel chromatography or HPLC separation, and in the majority of cases reasonable amounts of each were recovered (Table 4.1). However, unfortunately we were not able to separate the 4-methyl diol products 206a-208a despite repeated attempts. Similarly, the \(\Delta^{1,2}\) and \(\Delta^{2,3}\) dimethoxy analogue fractions 206d and 207d overlapped significantly in the HPLC separation and thus the \(\Delta^{2,3}\) sample had significant \(\Delta^{1,2}\) contamination. Additionally, due to the unselective Heck cyclisation of thiophene analogue 165f, we did not think it feasible to carry out HPLC separation of its diol counterparts. For these three substrates, mixtures of the appropriate compounds 206-208a,f,k were carried through to the biological testing stage.

For the last step in our library synthesis, we took the diol mixtures (with the exception of 206-208e,m) and isolated compounds and converted each into the hydrochloride salts, with yields as summarised in Table 4.2. In general, and where available, the diol mixtures were used in preliminary biological investigations, so that precious isolated material was not wasted.
Table 4.2 Boc deprotection to afford a phenanthridinium hydrochloride library.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>206-208</th>
<th>Substrate (R=)</th>
<th>Yield 252-254 (%)</th>
<th>Yield 252 (%)</th>
<th>Yield 253 (%)</th>
<th>Yield 254 (%)</th>
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<tr>
<td>1</td>
<td>a</td>
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<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
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<td>b</td>
<td>4-F</td>
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<td>74</td>
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<td>3</td>
<td>c</td>
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<td>88</td>
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<tr>
<td>4</td>
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<td>88</td>
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<td>60</td>
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<td>e</td>
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<td>f</td>
<td>[Thiophene]</td>
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<td>-</td>
<td>-</td>
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<td>7</td>
<td>k</td>
<td>[Piperonyl]</td>
<td>69</td>
<td>61</td>
<td>81 (60)</td>
<td>77</td>
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<tr>
<td>8</td>
<td>m</td>
<td>H</td>
<td>-</td>
<td>86</td>
<td>60</td>
<td>53</td>
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</table>

a) i) TFA, CH₂Cl₂, 1 h, r.t.; ii) NaOH, adjust to pH 9; iii) HCl in Et₂O, 0 °C. b) Performed on mixture. b) Approximately 1:1 mixture Δ₁,₂:Δ₂,₃. c) As reasonable quantities of the isolated isomers were available, no mixture of hydrochloride salts was synthesised for these analogues. d) Yield for deprotection of *endo-syn* piperonyl substrate 209k to afford diol hydrochloride 255k. e) See footnote Table 3.2. f) As in Scheme 3.6.

We also treated the sulfonamide protected thiophene mixture 158-160 to the *cis*-dihydroxylation conditions (Scheme 4.1). Purification by flash chromatography afforded isolated quantities of the three major *exo-syn* products, providing three additional compounds 256-258 for our library.

Scheme 4.1 Cis-dihydroxylation of thiophene sulfonamides 158-160.

a) OsO₄, NMO, THF/H₂O, r.t., 18 h, 73%. Isolated yields: Δ₁,₂ 256, 6%; Δ₂,₃ 257, 6%; Δ₃,₄ 258, 14%; mixture, 47%.
The structures of the 22 isolated compounds and 6 mixtures that were synthesised for biological testing are shown in full below (Figure 4.1).

Figure 4.1 Phenanthridine diol library members for biological testing.
4.2 Screening of small molecule libraries

As alluded to in Chapter 1, forward-chemical genetics describes a method of identifying small molecules that modulate the function of a biological pathway, resulting in an induction or reversion of a specific phenotype. The use of whole organisms to facilitate phenotypic screening of compound libraries, is an area that has received significant attention recently. In whole organisms the cells are not transformed, and are in their normal physiological environment offering significant advantages over traditional cell-based assays. Additionally, because the embryo contains many distinct cell-types, the identification of tissue-specific small molecules can be made. The use of whole organisms can also enable the screening of processes that are not easily replicated in vitro such as organ development. Finally, the metabolism of the organism permits the identification of compounds that become active as metabolites, something that is not possible in cell-based assays.

Carrying out in vivo screening right from the outset of a project can therefore save valuable time by providing a more accurate model in terms of toxicity, tissue-specificity and bioavailability. The validation of drug targets has traditionally been performed in mammalian models such as the mouse, however high-throughput validation of compound libraries requires smaller organisms that can be easily produced, studied and stored in great numbers. In light of this, interest has turned towards lower phylogenetic organisms such as Drosophila melanogaster (fruit fly), Caenorhabditis elegans (nematode worm) and Danio rerio (zebrafish).
4.3 Zebrafish

The zebrafish has been a popular pet for many years, but its use for research has increased dramatically over the last 15 years following the demonstration of its amenability to chemical genetics screens (Figure 4.2).

![Figure 4.2 Adult zebrafish - male (bottom) and female (top).](image)

There are many reasons for the suitability of zebrafish to high-throughput phenotyping. For example, following mating, the female adult zebrafish can produce up to 300 eggs. The breeding process is also very rapid, and a mating pair need only be set up the evening before the eggs are required. With multiple breeding pairs, sufficient eggs for the screening of large compound collections can be rapidly raised. Fertilisation occurs externally to the female’s body meaning that each stage of embryonic development can be easily examined, and importantly, the zebrafish embryo is transparent for the first five days of development, making it suitable for a wide range of optical analysis. This also means that the identification of phenotypes can be easily made without the need to kill or dissect the organism. As each embryo measures less than 1 mm in diameter they can be easily studied in microwell plates, and because the zebrafish is an aquatic organism, compounds can be directly aliquoted into the embryo medium.

One of the most valid reasons for high-throughput screening in zebrafish is their close evolutionary relationship to humans. There is a strong homology between the genes of mammalians and zebrafish, and phenotypes have been identified that closely resemble human diseases. In the past few years, several additional tools have been developed that greatly aid the use of the zebrafish as a model organism. For example, the zebrafish genome has now been fully sequenced, resulting in the availability of multiple DNA microarrays for expression-profiling experiments.
Antisense morpholino oligonucleotides can be utilised to knock-down proteins, permitting validation in circumstances where the small molecule in question may have multiple targets.\textsuperscript{166,167} Furthermore, transgenic lines\textsuperscript{168} (Figure 4.3) and targeted mutations\textsuperscript{169} can also be introduced, enabling forward-chemical genetics to be performed, where compounds are screened to observe a reversion of phenotype. Of additional interest is the ability of the zebrafish to regenerate fins, skin, the heart, and the brain in larval stages.\textsuperscript{164}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{transgenic_zebrafish.png}
\caption{A colourful example of transgenic zebrafish, genetically modified with sea anemone genes.\textsuperscript{170}}
\end{figure}

Despite the numerous advantages of performing high-throughput phenotypic screening in zebrafish, there are several drawbacks. For true high-throughput screening, the number of compounds is limited to a few thousand per week due to the number of embryos obtainable. The amount of labour involved is greater than that of cell-based assays due to fish husbandry and lower overall throughput. Additionally, certain compounds that have proven to be potent in cell lines showed no activity in zebrafish.\textsuperscript{171} The use of zebrafish assays should therefore be used as a complementary strategy to cell-based techniques, or as a secondary screening platform following a higher throughput primary screen.\textsuperscript{172}
4.3.1 Practicalities of high-throughput phenotyping in zebrafish

In order to set up a small molecule zebrafish screen, a pair of adult zebrafish must first be mated to allow the embryos to be collected (Figure 4.4, a).\textsuperscript{172} This is achieved by placing one male and one female in a small covered tank overnight, under darkness. When the lights are switched on the next morning the fish will mate and the embryos can be collected. Several clutches of embryos from different breeding pairs should be combined to minimise any unintended family effects from certain parents, or incorrectly genotyped fish. The embryos are washed with and stored in E3 medium that sustains their development.\textsuperscript{9} The embryos should be examined at this stage and any unfertilised eggs or dead embryos should be removed. Additionally, if dead embryos are noticed at any point during the screening process, they should be removed as they can be detrimental to the development and health of all the fish contained in their medium.

The embryos are incubated at 28.5 °C until they reach the appropriate age of development, this is usually between 4 and 24 hours post fertilisation (hpf). Typically, two to three embryos are transferred to each well of a 96-well plate using a wide-tipped plastic Pasteur pipette (Figure 4.4, b).\textsuperscript{172} The E3 medium is then decanted from the embryos using a Pasteur pipette and the appropriate small molecule is added at the relevant concentration in E3 (Figure 4.4, c&d). Drug concentrations tend to be in the range 1-100 µM for a preliminary screen, and it is standard to use up to 1% \textit{v/v} DMSO as a vehicle for transporting the small molecule across the cell membrane. Control experiments in E3 (plus up to 1% \textit{v/v} DMSO) are also performed so that the identification of phenotypes can be easily performed.

The development of the zebrafish embryos can then be carefully monitored over a period of five days, recording any phenotypes that arise (Figure 4.4, e). Any hits can then be traced back to the appropriate library member (Figure 4.4, f) and further assays carried out as appropriate.

\textsuperscript{9} E3 medium is comprised: 5 mM NaCl, 0.17 mM KCl, 0.4 mM CaCl\textsubscript{2}, and 0.16 mM MgSO\textsubscript{4}. To suppress the growth of mould the medium is supplemented with 10\textsuperscript{-5}% methylene blue.\textsuperscript{173}
Figure 4.4 *Zebrafish small-molecule screens.*

a) Adult zebrafish are mated, producing 200-300 embryos. b) Embryos are distributed to 96-well plates, 2-3 per well. c) A small molecule library is acquired or synthesised. d) Small molecules are added to the embryonic medium. e) After incubation at 28.5 °C, phenotypes are visually determined. f) Referral to the library database reveals the identity of bioactive small molecules.
4.3.2 Developmental stages of zebrafish embryos

The development of embryonic wild-type zebrafish (as used in our screens) is illustrated in Figure 4.5.\textsuperscript{174} At 48 hpf the embryo hatches from its chorion and becomes a free swimming larvae that is sensitive to the touch. Anatomical terminology for the zebrafish is given in Figure 4.6.\textsuperscript{173}

\textbf{Figure 4.5} Stages of embryo development in zebrafish.\textsuperscript{174}

\textbf{Figure 4.6} Anatomical terminology for zebrafish at 29 hpf, 48 hpf and 5 dpf.\textsuperscript{173}
4.3.3 Biological evaluation of our library using zebrafish phenotyping

In order to assess the applicability of our library to zebrafish screening, we proposed to carry out preliminary investigations using the diol hydrochloride mixtures 252-254. If any activity was apparent then the individual component compounds of the mixture could be screened individually. For the substrates where no mixture was in hand, the three isolated diols were screened separately (naphthyl analogues 252e-254e, parent analogues 252m-254m and thiophene sulfonamide 256-258). Using the procedure described in section 4.3.1, ‘high stage’ embryos (approximately 3-4 hpf) were treated with aliquots of the appropriate drug solution (all 0.5% v/v, DMSO in E3 medium), ranging in concentration from 10-100 µM for the mixtures, and 1-50 µM for the isolated compounds.

Several of the compounds/compound mixtures induced general symptoms of ill health in the fish. One such example was 5-methoxy compound mixture 252c-254c that induced the bent tail phenotype in 5 dpf larvae at 50 µM (Figure 4.7, a). When mixture 252c-254c was split out into its component compounds for a secondary assay, compound 254c (Δ3,4 isomer) was found to result in extended tail length in 5 dpf zebrafish, at a concentration of 100 µM (Figure 4.7, c).

Figure 4.7 Tail modification using 252c-254c at 5 dpf.

a) 50 µM 252c-254c. b) control; c) 100 µM 254c; d) control.
One other example of general toxicity was shown for parent compound 253m ($\Delta^{2,3}$ isomer) that was screened separately from the outset. This compound reproducibly induced oedema in the zebrafish at 50 µM, though no abnormal effects were shown above or below this concentration. Figure 4.8 illustrates the enlarged heart and hatching gland at 2 dpf (a), increasing to the grossly enlarged yolk sack and heart, visible at 5 dpf (c, e).

![Figure 4.8](image)

**Figure 4.8** *Generation of oedema by compound 253m.*

a) 50 µM 253m, 2 dpf; b) control, 2 dpf; c) 50 µM 253m, 5 dpf, side view; d) control, 5 dpf, side view; e) 50 µM 253m, 5 dpf, top view; f) control, 5 dpf, top view.

While these symptoms illustrated a level of toxicity associated with the appropriate compound/compounds, no dose dependence was shown and no tissue specificity was deduced since the general function of the organism was not altered overall. However, for fluorinated compound mixture 252b-254b we did observe more severe effects, with reproducible embryo death at 50 µM, after 1 dpf (Figure 4.9, a).
Although no effect was observed at the higher dose of 100 µM, the 50 µM results prompted us to screen compounds 252b, 253b and 254b individually. For compounds 253b and 254b we observed no abnormalities, however compound 252b (Δ1,2 isomer) appeared to slow down the development of the embryos significantly, and in a dose dependent manner (Figure 4.10).

At 5 dpf, the yolk sack of the fish treated with 100 µM 252b was significantly larger than that of the control, providing further evidence for delayed development. Additionally the positioning of the melanocytes (pigmentation) on the underside of
the yolk sack was noticeably different from that of the control (Figure 4.11, a&b). The fish treated with 50 μM 252b showed the bent tail phenotype reported previously (Figure 4.7), but no notable difference from the control was observed in the fish exposed to lower drug concentrations at 5 dpf.

![Figure 4.11 Delayed development of zebrafish embryos treated with 252b at 5 dpf.](image)

All photos at 5 dpf. a) 100 μM 252b, side view; b) control, side view; c) 100 μM 252b, top view; d) control, top view.

The results obtained for compound 252b are preliminary and require further investigation and replication on a larger scale to be of statistical significance. However, that being said, a decreased rate of embryo development and dose-dependence was clearly observed in our experiment. This suggests that compound 252b interferes in some way with the cell division process (mitosis). This would be in agreement with the activity of the benzophenantridine alkaloid chelidonine 76 that bears structural similarities to compound 252b (Figure 4.12). Chelidonine 76 is known to cause mitotic arrest and inhibition of tubulin polymerisation, as well as being the major component of Ukrain™ 259, a selectively toxic agent to malignant cells. Further studies of compound 252b using both zebrafish assays and cell-based techniques would enable a more probing identification of its specific mode of action.
The remaining compounds/compound mixtures showed no specific phenotype upon application to the zebrafish embryos. However, as previously mentioned, zebrafish assays should be used in conjunction with standard cell-based techniques to provide a more accurate assessment of any potential bioactivity.\(^{171}\)

### 4.4 Conclusion

The methodology developed in Chapters 2 and 3 was successfully applied to the synthesis of a small library of dihydroxylated phenanthridines. Biological evaluation was facilitated using whole organism phenotype screening with zebrafish embryos. Preliminary results suggest that 5-methoxy analogue 254c and phenyl analogue 253m induce signs of ill health in the developing embryos, but the phenotype they induce does not indicate any tissue specificity. 4-Fluoro analogue 252b was successfully shown to delay the zebrafish embryo development in a dose-dependent manner. Further evaluation of compound 252b using more advanced zebrafish assays and cell-based techniques would enable the specific mode of action to be probed.
The synthesis of a small library of phenanthridines was successfully achieved using the methodology described in Chapters 2, 3 and 4. This methodology could be extended to allow the incorporation of greater diversity, as illustrated in Scheme 5.1. The synthesis of oxygen and sulfur analogues such as 260 could be investigated using benzyl alcohol and benzyl thiol building blocks. Studies into the synthesis of a 7-membered B-ring derivative could be completed, and this methodology extended to incorporate 8- and 9-membered analogues such as 261. Alternatively, the synthesis of larger C-ring derivatives such as 262 might be realised by the use of larger cycloalkenyl bromide building blocks. Studies into the incorporation of heteroaryl building blocks would yield further skeletal variation. In particular, thiophene analogues 158-160 and 195f-197f are good precedent for the synthesis of pyrrole and furan equivalents such as 263. Finally, further optimisation of the epoxidation step would furnish 212 on a scale appropriate for the study a variety of nucleophile-promoted ring-opening reactions.

**Scheme 5.1** Further incorporation of diversity into the phenanthidine library.

*a* Only the $\Delta^{1,2}$-isomer epoxide isomer product is shown for simplicity.
The results obtained for the RRM studies (Chapter 3) also warrant further investigation. It would be interesting to examine the application of the RRM reaction to less strained ring systems, such as the equivalent trans-ring fused phenanthridines, or other trans-ring fused substrates. This would allow us to determine if the reactivity of our propargylated phenanthridines 97f and 98f was a result of their strained conformation. Additionally, application of the RRM reaction to other cis-ring fused systems would allow the evaluation of RRM as a general tool for the modification of cyclic systems of this type.

The preliminary results from the biological screening of our phenanthridine library using zebrafish are promising (Chapter 4). So far the screening has only been performed on a small scale using 2-3 fish per compound, per assay. A larger scale experiment using 20 fish would permit a more accurate assessment of the effect of our most active analogue 252b. Additionally, the effect of compound 252b could be examined using yeast cell assays, which may also allow us to tie down the specific biological pathway that the compound is acting upon.
6.1 General experimental

$^1$H nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock for the indicated reference at the stated temperature on Varian Gemini 200 (200 MHz), Bruker AC250 (250 MHz), Bruker DPX360 (360 MHz), Bruker DMX500 (500 MHz), Bruker AVA600 (600 MHz) and Bruker AVA800 (800 MHz) instruments. The data is presented as follows: chemical shift (in ppm on the $\delta$ scale relative to $\delta_{\text{TMS}} = 0$), integration, multiplicity ($s =$ singlet, $d =$ doublet, $t =$ triplet, $q =$ quartet, $m =$ multiplet, $td =$ triplet of doublets, $dd =$ doublet of doublets, $dt =$ doublet of triplets, $br =$ broad), coupling constants (in Hertz, Hz) and interpretation. $^{13}$C NMR spectra were recorded at the stated temperature on Bruker AC250 (62.9 MHz), Bruker DPX360 (90.6 MHz), Bruker DMX500 (125.7 MHz), Bruker AVA600 (151.1 Hz) and Bruker AVA800 (201.5 Hz) instruments. Assignments are made on the basis of DEPT 135, DEPT 90 and 2D HSQC experiments.

Infra-red spectra were recorded using a Biorad FTS-7 or Perkin-Elmer Paragon 1000 FT-IR spectrometer as thin films unless otherwise stated. The wavelengths of maximum absorbance ($\nu_{\text{max}}$) are quoted in cm$^{-1}$. Electron impact (EI) mass spectra were obtained using a Finnigan 4500 mass spectrometer, and electrospray (ESI) and fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS50TC mass spectrometer. The parent ion, or relevant fragments are quoted, followed by significant fragments and their relative intensities. Melting points were determined on a Gallenkamp Electrothermal Melting Point apparatus and are uncorrected. TLC was carried out using Merk silica gel 60F$_{254}$ foil-backed plates with visualisation by
ultraviolet and KMnO₄ (aq)⁵ and/or molybdate stain.⁹ Flash chromatography was carried out using Merck Kieselgel 60 (Merck 9385) under positive pressure by means of an airline or hand pump. Eluent compositions are quoted as v/v ratios. High performance liquid chromatography (HPLC) was carried out using a Gilson instrument using a Spherisorb column (internal diameter: 20 mm) and fitted with a Gilson refractive index detector. Flow rates are quoted for each separation in ml/min. All solvents used for HPLC were filtered prior to use and all HPLC samples were filtered through 0.45 µM nylon syringes prior to analysis.

All reactions non-aqueous were carried out under an atmosphere of nitrogen using flame- or oven-dried glassware that was cooled in a dessicator prior to use. Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without further purification. Dichloromethane (CH₂Cl₂), triethylamine (Et₃N) and diisopropylethylamine (Pr₂N) were distilled from calcium hydride and stored over calcium hydride under a nitrogen atmosphere. When used as a reagent, dimethylformamide (DMF) was also distilled from and stored over calcium hydride under a nitrogen atmosphere. Tetrahydrofuran (THF) was distilled from sodium/benzophenone and stored under a nitrogen atmosphere. Diethyl ether (Et₂O), toluene and methanol (MeOH) were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com. Anhydrous dimethylacetamide (DMA), DMF (when used as a solvent) and acetonitrile (MeCN) were used as supplied by BakerDRY. Extra dry acetone was used as supplied by Acros. Anhydrous 1,4-dioxane was used as supplied by Aldrich. Saturated aqueous solutions of inorganic salts are represented as (volume, sat. aq.)

⁵ Potassium permanganate dip prepared as follows: To water (1000 ml) was added KMnO₄ (10 g), K₂CO₃ (50 g) and NaOH (40 pellets). The mixture was stirred until the solid had dissolved.

⁹ Ammonium molybdate dip prepared as follows: To water (950 ml) was added concentrated sulphuric acid (50 ml), ammonium molybdate (50 g) and ceric sulfate (3 g). The mixture was stirred until all solid material had disappeared and a bright yellow solution remained.
The apparatus used for flash vacuum pyrolysis (FVP) is illustrated in Figure 3.10. The system was evacuated by use of an Edwards Model ED100 high capacity oil pump to maintain the pressure in the region of 0.030 Torr. A glass Büchi oven was used to heat the inlet tube in which the substrate was placed until it volatilises. The gaseous substrate passed through a silica tube (30 x 2.5 cm) heated by a Carbolite electronically controlled laboratory tube furnace (model number MTF 12/38/250). The estimated contact time in the hot zone is of the order of ten milliseconds and the gaseous phase of the substrate under vacuum ensures that intramolecular reactions are strongly favoured. The products are captured at the exit of the furnace in a U-shaped trap cooled in liquid nitrogen. Upon completion of the reaction the pump is isolated and the trap is allowed to warm to room temperature under a dry nitrogen atmosphere. Standard pyrolysis parameters used in this section are furnace temperature $T_f$, inlet temperature $T_i$, pressure $P$ and time of pyrolysis $t$.

Index for General Procedures.

<table>
<thead>
<tr>
<th>General Procedure A:</th>
<th>Secondary amine formation</th>
<th>131</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Procedure B:</td>
<td>Sulfonamide protection</td>
<td>131</td>
</tr>
<tr>
<td>General Procedure C:</td>
<td>Cationic protocol</td>
<td>138</td>
</tr>
<tr>
<td>General Procedure D:</td>
<td>Neutral protocol (140°C)</td>
<td>138</td>
</tr>
<tr>
<td>General Procedure E:</td>
<td>Neutral protocol (Low temp.)</td>
<td>138</td>
</tr>
<tr>
<td>General Procedure F:</td>
<td>Synthesis of aryl amide analogues</td>
<td>171</td>
</tr>
<tr>
<td>General Procedure G:</td>
<td>Reduction of aryl nitrile analogues</td>
<td>179</td>
</tr>
<tr>
<td>General Procedure H:</td>
<td>Boc protection of aryl analogues</td>
<td>186</td>
</tr>
<tr>
<td>General Procedure J:</td>
<td>Dialkylation</td>
<td>190</td>
</tr>
<tr>
<td>General Procedure K:</td>
<td>Monoalkylation</td>
<td>190</td>
</tr>
<tr>
<td>General Procedure L:</td>
<td>Propargylation</td>
<td>223</td>
</tr>
<tr>
<td>General Procedure M:</td>
<td>RRM reactions of amines</td>
<td>231</td>
</tr>
<tr>
<td>General Procedure N:</td>
<td>RRM reactions of Poc analogues</td>
<td>236</td>
</tr>
<tr>
<td>General Procedure P:</td>
<td>Dihydroxylation</td>
<td>239</td>
</tr>
<tr>
<td>General Procedure Q:</td>
<td>Hydrochloride salt formation</td>
<td>253</td>
</tr>
<tr>
<td>General Procedure R:</td>
<td>Zebrafish phenotype screening</td>
<td>267</td>
</tr>
</tbody>
</table>
6.2 Experimental for Chapter two

**General procedure A - Secondary amine formation**

To a suspension of the appropriate 2-halobenzylamine hydrochloride (1 eq) in MeCN at 0 °C was added iPr₂NEt (4 eq) and the reaction was stirred for 5 mins. 3-Bromocyclohexene (1 eq) was added and the reaction stirred for 16 h at r.t. The reaction was concentrated under reduced pressure and the residue taken up in CH₂Cl₂ (50 ml) and washed with NaCl (3 x 50 ml, sat. aq.). The organics were combined, dried (MgSO₄) and concentrated under reduced pressure. The residue was taken up in CH₂Cl₂, HCl (excess, 1.0 M in Et₂O) added and the resultant suspension filtered to afford the desired amine hydrochloride.

**General procedure B - Sulfonamide protection**

To a solution of the appropriate amine or amine hydrochloride (1 eq) in CH₂Cl₂ (10 ml) at 0 °C was added methanesulfonyl chloride (3 eq) and Et₃N (3 eq) and the reaction was warmed to r.t. and stirred for 16 h. The reaction was diluted with CH₂Cl₂ (20 ml), and washed with HCl (3 x 20 ml, 1 M aq.). The organics were dried (MgSO₄), concentrated under reduced pressure and purified by flash chromatography to afford the desired sulfonamide.
**N-(2-Bromo-benzyl)-cyclohex-2-enyl-amine hydrochloride 93**

General procedure A was followed using 2-bromobenzylamine hydrochloride (6.00 g, 27.0 mmol), MeCN (100 ml), tPr₂NEt (18.8 ml, 108 mmol), 3-bromocyclohexene (3.10 ml, 27.0 mmol), and HCl (30 ml, 1.0 M in Et₂O, 30.0 mmol) to afford amine hydrochloride 93 as a colourless solid (7.15 g, 99%).

**MP** 142 °C (Et₂O); **¹H NMR** δ (250 MHz, CD₃OD) 7.79 (1H, dd, /unimath 8.0, 1.3, ArH), 7.66 (1H, dd, J 7.6, ArH), 7.53 (1H, td, J 7.6, 1.3, ArH), 7.43 (1H, td, J 7.9, 1.7, ArH), 6.29-6.23 (1H, m, CH=CH), 5.91-5.87 (1H, m, CH=CH), 4.46 (2H, s, CH₂Ar), 4.06-4.03 (1H, m, CH₂N), 2.28-2.18 (3H, s, CH₃H₁B+CH₂), 1.94-1.87 (3H, m, CH₃H₁A+CH₂); **¹³C NMR** δ (250 MHz, CD₃OD) 135.4 (CH), 133.0 (CH), 131.6 (CH), 131.1 (CH), 130.9 (C), 128.0 (CH), 124.5 (C), 120.7 (CH), 54.3 (CH), 46.9 (CH₂), 24.8 (CH₂), 23.9 (CH₂), 18.8 (CH₂); **m/z** (FAB, THIOG) 266 ([⁸¹Br-M-H]⁺, 86 %), 264 ([⁷⁹Br-M-H]⁺, 70), 262 (27), 239 (25), 238 (28.5), 186 (91), 184 (88); **HRMS** (FAB, THIOG) Found: [⁸¹Br-M-H]⁺, 266.0372. C₁₃H₁₅N⁸¹Br requires 266.0369. Found: [⁷⁹Br-M-H]⁺, 264.0383. C₁₃H₁₅N⁷⁹Br requires 264.0388.

**Free Amine:** Rf [hexane:EtOAc, 3:1] = 0.90; vₑₓₘₐₓ (CH₂Cl₂)/cm⁻¹ 3361 (NH), 1466, 1436, 1010, 747; **¹H NMR** δ (250 MHz, CDCl₃) 7.68 (1H, dd, J 7.9, 1.3, ArH), 7.60 (1H, dd, J 7.7, 1.7, ArH), 7.43 (1H, td, J 7.4, 1.1, ArH), 7.26 (1H, td, J 7.6, 1.8, ArH), 5.97-5.87 (2H, m, CHCH=CH), 4.10 (1H, d, J 13.8, CH₂H₁YAr), 4.03 (1H, d, J 13.8, CH₂H₁YAr), 3.38 (1H, br s, CHN), 2.17-1.66 (6H, m, 3xCH₂); **¹³C NMR** δ (62.9 MHz, CDCl₃) 139.5 (C), 132.5 (CH), 130.0 (CH), 129.6 (CH), 128.9 (CH), 128.2 (CH), 127.2 (CH), 123.7 (C), 52.3 (CH), 50.8 (CH₂), 29.2 (CH₂), 25.1 (CH₂), 19.9 (CH₂).
**N-(2-Bromo-benzyl)-N-cyclohex-2-enyl-methanesulfonamide 94a**

General procedure B was followed using amine hydrochloride 93 (3.90 g, 14.6 mmol), CH$_2$Cl$_2$ (50 ml), Et$_3$N (6.20 ml, 43.8 mmol) and methanesulfonyl chloride (3.40 ml, 43.8 mmol). Flash chromatography (CH$_2$Cl$_2$-CH$_2$Cl$_2$:MeOH, 100:1) afforded sulfonamide 94a as a colourless solid (4.95 g, 99%).  

**Rf** [hexane:EtOAc, 3:1] = 0.46; **MP** 100 °C (Et$_2$O); **$\nu$**$_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1332 (SO$_2$), 1145 (SO$_2$); **$^1$H NMR** $\delta$ (250 MHz, CDCl$_3$) 7.67 (1H, dd, $J$ 7.8, 0.8, ArH), 7.49 (1H, dd, $J$ 7.9, 1.2, ArH), 7.33 (1H, td, $J$ 7.7, 1.2, ArH), 7.12 (1H, m, ArH), 5.98-5.93 (1H, m, NCHCH=CH), 5.53-5.47 (1H, m, NCHCH=CH), 4.66-4.57 (1H, m, NCH), 4.47 (1H, dd, $J$ 17.7, CH$_X$H$_Y$Ar), 4.33 (1H, d, $J$ 17.7, CH$_X$H$_Y$Ar), 2.97 (3H, s, CH$_3$), 1.99-1.92 (3H, m, CH$_A$H$_B$+CH$_2$), 1.70-1.34 (3H, m, CH$_A$H$_B$+CH$_2$); **$^{13}$C NMR** $\delta$ (62.9 MHz, CDCl$_3$) 137.7 (C), 133.7 (CH), 132.1 (CH), 129.2 (CH), 128.4 (CH), 127.3 (CH), 126.5 (CH), 121.9 (C), 55.6 (CH), 47.5 (CH$_2$), 39.4 (CH$_3$), 28.7 (CH$_2$), 24.2 (CH$_2$), 21.4 (CH$_2$); **m/z** (FAB, THIOG) 346 ($[^{81}$BrM+H]$^+$, 64 %), 344 ($[^{79}$BrM+H]$^+$, 68), 266 (80), 264 (85); **HRMS** (FAB, THIOG) Found: $[^{81}$BrM+H]$^+$, 346.0326. C$_{14}$H$_{19}$NO$_2$S$^{81}$Br requires 346.0301. Found: $[^{79}$BrM+H]$^+$ 344.0346. C$_{14}$H$_{19}$NO$_2$S$^{79}$Br requires 344.0320.
Experimental

To a suspension of amine 93 (500 mg, 1.87 mmol) in CH₂Cl₂ (20 ml) was added Et₃N (395 µl, 2.81 mmol). After 10 mins, the reaction was cooled to 0 °C, Boc₂O (613 mg, 2.81 mmol) in CH₂Cl₂ (5 ml) was added and the reaction was stirred for a further 10 mins. The reaction was warmed to r.t and stirred for 16 h. The reaction was diluted with CH₂Cl₂ (20 ml), extracted with NaCl (3 x 20 ml, sat. aq.), dried (MgSO₄) and concentrated under reduced pressure. Flash chromatography (hexane:EtOAc:Et₃N, 10:1:0.1) afforded Boc amine 94b as a colourless solid (685 mg, 90%).

R₉ [hexane:EtOAc, 3:1] = 0.8; MP 81 °C (hexane); νₘₐₓ (CHCl₃)/cm⁻¹ 3057, 3021, 1695 (C=O), 1274, 1253; ¹H NMR δ (360 MHz, 318 K, CDCl₃) 7.51 (1H, d, J 7.7, ArH), 7.29-7.26 (2H, m, 2xArH), 7.11-7.07 (1H, m, ArH), 5.83 (1H, br s, CH=CH), 5.50 (1H, d, J 10.1, CH=CH), 4.90 (1H, br s, NCH), 4.38 (2H, br s, CH₂Ar), 2.10-1.81 (3H, m, CH₂+CH₃), 1.81-1.70 (1H, m, CH₂), 1.35 (9H, s, 3CH₃); ¹³C NMR δ (90.6 MHz, 318 K, CDCl₃) 155.6 (C), 132.2 (CH), 131.7 (CH), 130.8 (C), 128.0 (CH), 127.7 (CH), 127.3 (CH), 126.9 (CH), 121.9 (C), 79.7 (C), 53.0 (CH), 52.6 (CH₂), 28.0 (3xCH₃), 27.3 (CH₂), 24.4 (CH₂), 21.2 (CH₂); m/z (FAB, THIOG) 368 ([¹⁸BrM+H]+, 12 %), 366 ([⁷⁹BrM+H]+, 15), 313 (33), 312 (68), 311 (39), 310 (70), 266 (28), 232 (57), 230 (51); HRMS (FAB, THIOG) Found: [¹⁸BrM+H]+ 368.1046. C₁₈H₂₅NO₂⁸¹Br requires 368.1050. Found: [⁷⁹BrM+H]+ 366.1067. C₁₈H₂₅NO₂⁷⁹Br requires 366.1069.
(2-Bromo-benzyl)-cyclohex-2-enyl-carbamic acid benzyl ester 94c

To a suspension of NaH (143 mg, 60% dispersion in mineral oil, 3.62 mmol) in DMF (10.0 ml) at 0 °C was added amine 93 (500 mg, 1.65 mmol) in DMF (10.0 ml). The solution was stirred for 30 mins then benzyl chloroformate (302 µl, 2.15 mmol) was added dropwise and the reaction was warmed to r.t. and stirred for 16 h. The reaction was diluted with Et₂O (20 ml), extracted with NaCl (3 x 20.0 ml, sat. aq.), dried (MgSO₄) and concentrated under reduced pressure to give the crude product. Flash chromatography (hexane:EtOAc:Et₃N, 100:1:0.1–100:5:0.1) afforded Cbz amide 94c as a colourless solid (570 mg, 86%).

Rₖ [hexane:EtOAc, 10:1] = 0.54; MP 48 °C (hexane); v_max (CHCl₃)/cm⁻¹ 3064, 3021, 1699, 1407, 1258; ¹H NMR δ (360 MHz, 323K, CDCl₃) 7.52 (1H, d, J 5.8, ArH), 7.40 – 7.22 (7H, m, 7xArH), 7.11-7.08 (1H, m, ArH), 5.87-5.85 (1H, m, CH=CH), 5.48 (1H, d, J 10.2, CH=CH), 5.16 (2H, br s, OCH₂Ar), 4.89 (1H, br s, CHN), 4.51 (1H, d, J 17.4, CHₓHᵧAr), 4.44 (1H, d, J 17.4, CHₓHᵧAr), 2.11-1.84 (3H, m, CH₂+CHₐHₖ), 1.80-1.70 (1H, m, CHₐHₖ), 1.70-1.47 (2H, m, CH₂); ¹³C NMR δ (90.6 MHz, 323K, CDCl₃) 156.4 (C), 138.4 (C), 136.7 (C), 132.4 (2xCH), 128.3 (CH), 127.9 (CH), 127.7 (3xCH), 127.6 (3xCH), 127.1 (CH), 122.1 (C), 67.3 (CH₂), 53.8 (CH), 47.7 (CH₂), 28.1 (CH₂), 24.5 (CH₂), 21.2 (CH₂); m/z (FAB, 3-NOBA) 402 ([¹⁸¹BrM+H]⁺, 35 %), 400 ([¹⁷¹BrM+H]⁺, 38), 310 (22), 308 (22), 171 (69), 169 (50); HRMS (FAB, THIOG) Found: [¹⁸¹BrM+H]⁺ 402.0821. C₂₁H₂₃O₂¹⁸¹BrN requires 402.0979. Found: [¹⁷¹BrM+H]⁺ 400.0918. C₂₁H₂₃O₂¹⁷¹BrN requires 400.0912.
Benzyl-(2-bromo-benzyl)-cyclohex-2-enyl-amine 94d

To a suspension of amine 93 (750 mg, 2.47 mmol) in DMF (20 ml) at 0 °C, was added NaH (217 mg, 60% dispersion in mineral oil, 5.43 mmol) and the reaction stirred for 30 mins. Benzyl bromide (382 µl, 3.21 mmol) was added dropwise and the reaction warmed to r.t and stirred for 16 h. Et₂O (20 ml) was added and the organics washed with NaCl (3 x 30 ml, sat. aq.), dried (MgSO₄), concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc:NH₃, 100:1:0.1) to afford benzylamine 94d as a colourless oil (712 mg, 81%).

R<sub>f</sub> [hexane] = 0.29; ν<sub>max</sub> (CHCl₃)/cm⁻¹ 3057, 3019, 1026; <sup>1</sup>H NMR δ (360 MHz, CDCl₃) 7.71 (1H, dd, J 7.7, 1.6, ArH), 7.49 (1H, dd, J 8.0, 1.2, ArH), 7.40 (2H, d, J 7.4, 2xArH), 7.31-7.27 (3H, m, 3xArH), 7.27-7.21 (1H, m, ArH), 7.07 (1H, td, J 7.9, 1.8, ArH), 5.89-5.84 (1H, m, CH=CH), 5.79 (1H, d, J 10.4, CH=CH), 3.81 (1H, d, J 15.3, CH₉HₚAr), 3.78 (1H, d, J 14.0, CHₓHᵧ), 3.75 (1H, d, J 15.3, CH₉HₚQ), 3.63 (1H, d, J 14.0, CHₓHᵧ), 3.39-3.36 (1H, m, NCH), 2.08-1.95 (3H, m, CH₂+CHₐHₜB), 1.85-1.76 (1H, m, CHₜHₚB), 1.64-1.42 (2H, m, CH₂); <sup>1</sup>3C NMR δ (90.6 MHz, CDCl₃) 140.3 (C), 139.5 (C), 132.3 (CH), 130.4 (CH), 130.3 (CH), 130.2 (CH), 128.4 (2xCH), 128.0 (2xCH), 127.8 (CH), 127.2 (CH), 126.6 (CH), 124.0 (C), 55.2 (CH), 54.0 (CH₂), 53.1 (CH₂), 25.2 (CH₂), 23.5 (CH₂), 21.7 (CH₂) ; m/z (FAB, THIOG) 356 ([<sup>81</sup>BrM+H]<sup>+</sup>, 52 %), 354 ([<sup>79</sup>BrM+H]<sup>+</sup>, 47 %), 329 (35), 327 (35), 276 (75), 274 (53), 184 (34), 171 (69), 169 (71); HRMS (FAB, THIOG) Found: [<sup>81</sup>BrM+H]<sup>+</sup> 356.0838. <sub>C₂₀H₂₃NO₂</sub><sup>8¹</sup>Br requires 356.0838. Found: [<sup>79</sup>BrM+H]<sup>+</sup> 354.0856. <sub>C₂₀H₂₃N</sub><sup>7⁹</sup>Br requires 354.0857.
Experimental

(2-Bromo-benzyl)-cyclohex-2-enyl-(4-methoxy-benzyl)-amine 94e

To a suspension of amine 93 (750 mg, 2.81 mmol) in DMF (20 ml) at 0 °C was added NaH (246 mg, 60% dispersion in mineral oil, 6.18 mmol) and the reaction was stirred until homogeneous. The reaction was warmed to r.t. and stirred for 30 mins, then cooled to 0 °C, p-methoxybenzyl bromide (614 µl, 4.21 mmol) was added and the reaction stirred for 15 mins. The reaction was warmed to r.t. and stirred for 16 h. Et₂O (30 ml) was added, the organics washed with NaCl (3 x 20 ml, sat. aq.), concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc:NH₃, 100:1.5:0.1) to afford PMB protected amine 94e as a colourless oil (912 mg, 84%).

R_f [hexane: EtOAc, 3:1] = 0.81; ν_max (CHCl₃)/cm⁻¹ 2857, 1541, 1508, 1457, 1248, 750; ¹H NMR δ (360 MHz, CDCl₃) 7.69 (1H, d, J 7.8, ArH), 7.47 (1H, dd, J 7.8, ArH), 7.31-7.25 (3H, m, 3xArH), 7.04 (1H, td, J 7.8, 1.7, ArH), 6.83 (2H, dd, J 6.7, 1.8, 2xArH), 5.85-5.82 (1H, m,CH=CH), 5.76 (1H, d, J 10.5, CH=CH), 3.76 (3H, s, OCH₃), 3.75 (2H, m, CH₂Ar), 3.70 (1H, d, J 13.8, CHₓHᵧAr), 3.55 (1H, d, J 13.8, CHₓHᵧAr), 3.34 (1H, br s, CHN), 2.04-1.93 (3H, m, CH₂CHₓHᵧB), 1.83-1.75 (1H, m, CHₓHᵧB), 1.58-1.48 (2H, m, CH₂); ¹³C NMR δ (90.6 MHz, CDCl₃) 158.3 (C), 139.6 (C), 132.2 (C), 132.1 (CH), 130.4 (CH), 130.1 (2xCH), 129.4 (2xCH), 127.7 (CH), 127.0 (CH), 123.9 (C), 113.4 (2xCH), 55.0 (CH₃), 54.9 (CH), 53.3 (CH₂), 52.9 (CH₂), 25.2 (CH₂), 23.4 (CH₂), 21.7 (CH₂); m/z (FAB, THIOG) 389 ([⁸¹BrM+H]⁺, 15 %), 387 ([⁷⁹BrM+H]⁺, 43), 359 (53), 357 (54), 306 (43.9), 304 (41.2), 280 (21.8), 278 (24.4), 216 (35.9), 214 (21.0); HRMS (FAB, THIOG) Found: [⁸¹BrM+H]⁺ 388.1068. C₂₁H₂₄NO⁸¹Br requires 388.1100. Found: [⁷⁹BrM+H]⁺ 386.1121. C₂₁H₂₄NO⁷⁹Br requires 386.1120).
General Procedures for Heck cyclisations

General procedure C

Cationic protocol: To a degassed solution of the aryl halide (1 eq) in DMF was added palladacycle 100 (5 mol%) and Ag$_2$CO$_3$ (1 eq), and the reaction was heated at 140 °C. At the conclusion of the reaction (as judged by TLC), the mixture was allowed to cool and then diluted with Et$_2$O (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.). The organics were combined, dried (MgSO$_4$) and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to give the stated mixture of double bond isomers.

General procedure D

Neutral protocol (140 °C): To a degassed solution of the aryl halide (1 eq) in DMF was added palladacycle 100 (5 mol%) and MeNCy$_2$ (4 eq), and the reaction was heated at 140 °C. At the conclusion of the reaction (as judged by TLC), the mixture was allowed to cool and then diluted with Et$_2$O (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.). The organics were combined, dried (MgSO$_4$) and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to give the stated mixture of double bond isomers.

General procedure E

Neutral protocol (Low temperature): To a degassed solution of the aryl halide (1 eq) and MeNCy$_2$ (4 eq) in MeCN was added Pd$_2$(dba)$_3$ (5 mol%) and t-Bu$_3$PHBF$_4$ (10 mol %), and the reaction mixture stirred at r.t. (Method A) or or 50 °C (Method B) for the indicated time. At the conclusion of the reaction (as judged by TLC), the mixture was allowed to cool and then diluted with Et$_2$O (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.). The organics were combined, dried (MgSO$_4$) and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to give the stated mixture of double bond isomers.
Application of optimised methods in Table 2.6, 2.7 and 2.8

Sulfonamide-functionalised phenanthridine 96a-98a

(Table 2.6, Entry 1) General procedure C was employed using sulfonamide 94a (50 mg, 0.144 mmol), palladacycle 100 (8.1 mg, 8.6 µmol) and Ag₂CO₃ (40 mg, 0.144 mmol) in DMF (3 ml). After 70 mins at 140 °C, work up and column chromatography (hexane:EtOAc, 10:1–4:1) afforded the phenanthridine as a colourless oil (38 mg, 99%). ¹H NMR of this oil showed it to be an 85:13:2 mixture of double bond isomers (96a:97a:98a).

(Table 2.7, Entry 1) General procedure D was employed using sulfonamide 94a (50 mg, 0.144 mmol), palladacycle 100 (8.1 mg, 8.6 µmol) and MeNCy₂ (122 µl, 0.576 mmol) in DMF (3 ml). After 3h at 140 °C, work up and column chromatography (hexane:EtOAc, 10:1–4:1) afforded the phenanthridine as a colourless oil (37 mg, 99%). ¹H NMR of this oil showed it to be an 44:31:25 mixture of double bond isomers (96a:97a:98a).

(Table 2.8, Entry 1) General procedure E (Method A) were employed using sulfonamide 94a (50 mg, 0.144 mmol), Pd₂dba₃ (6.6 mg, 7.2 µmol), ⁷Bu₃PHBF₄ (4.2 mg, 14.4 µmol) and MeNCy₂ (122 µl, 0.576 mmol) in MeCN (3 ml). After 9 h at r.t, work up and column chromatography (hexane:EtOAc, 10:1–5:1) afforded the phenanthridine as a colourless oil (38 mg, 99%). ¹H NMR of this oil showed it to be a 12:65:23 mixture of double bond isomers (96a:97a:98a).

(Table 2.8, Entry 2) General procedure E (Method B) was employed using sulfonamide 94a (50 mg, 0.144 mmol), Pd₂dba₃ (6.6 mg, 7.2 µmol), ⁷Bu₃PHBF₄ (4.2 mg, 14.4 µmol) and MeNCy₂ (122 µl, 0.576 mmol) in MeCN (3 ml). After 4 h at 50 °C, work up and column chromatography (hexane:EtOAc, 10:1–5:1) afforded the phenanthridine as a colourless oil (38 mg, 99%). ¹H NMR of this oil showed it to be a 54:41:4 mixture of double bond isomers (96a:97a:98a).
**Experimental**

**Boc-functionalised phenanthridine 96b-98b**

(Table 2.6, Entry 2) General procedure C was employed using amide 94b (96 mg, 0.26 mmol), palladacycle 100 (15 mg, 15.7 µmol) and Ag$_2$CO$_3$ (72 mg, 0.26 mmol) in DMF (6 ml). After 2 h at 140 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (74 mg, 99%). $^1$H NMR of this oil showed it to be an 83:15:2 mixture of double bond isomers (96b:97b:98b).

(Table 2.7, Entry 2) General procedure D was employed using amide 94b (53 mg, 0.144 mmol), palladacycle 100 (7 mg, 7.2 µmol) and MeNCy$_2$ (122 µl, 0.576 mmol) in DMF (3 ml). After 3 h at 140 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (39 mg, 95%). $^1$H NMR of this oil showed it to be an 38:36:28 mixture of double bond isomers (96b:97b:98b).

(Table 2.8, Entry 3) General procedure E (Method B) was employed using amide 94b (53 mg, 0.144 mmol), Pd$_2$(dba)$_3$ (6.6 mg, 7.2 µmol), $^t$Bu$_3$PHBF$_4$ (4.2 mg, 14.4 µmol) and MeNCy$_2$ (122 µl, 0.576 mmol) in MeCN (3 ml). After 7 h at 50 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (39 mg, 95%). $^1$H NMR of this oil showed it to be a 34:37:29 mixture of double bond isomers (96b:97b:98b).
Experimental

Cbz-functionalised phenanthridine 96c-98c

(Table 2.6, Entry 3) General procedure C was employed using amide 94c (100 mg, 0.25 mmol), palladacycle 100 (11.7 mg, 12.5 µmol) and Ag₂CO₃ (69 mg, 0.25 mmol) in DMF (6 ml). After 2 h at 140 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (86 mg, 99%). ¹H NMR of this oil showed it to be a 92:6:2 mixture of double bond isomers (96c:97c:98c).

(Table 2.7, Entry 3) General procedure D was employed using amide 94c (58 mg, 0.144 mmol), palladacycle 100 (7 mg, 7.2 µmol) and MeNCy₂ (122 µl, 0.576 mmol) in DMF (3 ml). After 3 h at 140 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (44 mg, 99%). ¹H NMR of this oil showed it to be a 33:29:28 mixture of double bond isomers (96c:97c:98c).

(Table 2.8, Entry 6) General procedure E (Method B) was employed using amide 94c (58 mg, 0.144 mmol), Pd₂(dba)₃ (6.6 mg, 7.2 µmol), 'Bu₃PHBF₄ (4.2 mg, 14.4 µmol) and MeNCy₂ (122 µl, 0.576 mmol) in MeCN (3 ml). After 7 h at 50 °C, work up and column chromatography (hexane:EtOAc, 25:1) afforded the phenanthridine as a colourless oil (39 mg, 85%). ¹H NMR of this oil showed it to be a 36:5:59 mixture of double bond isomers (96c:97c:98c).

Benzyl-functionalised phenanthridine 96d-98d

(Table 2.6, Entry 4) General procedure C was employed using amine 94d (100 mg, 0.29 mmol), palladacycle 100 (13.5 mg, 14.4 µmol) and Ag₂CO₃ (79 mg, 0.29 mmol) in DMF (6 ml). After 2 h at 140 °C, work up and column chromatography (hexane:EtOAc:Et₃N, 100:1:0–100:1:0.1) afforded the phenanthridine 96d as a colourless oil (73 mg, 92%).

(Table 2.7, Entry 4) General procedure D was employed using amine 94d (50 mg, 0.148 mmol), palladacycle 100 (7 mg, 7.4 µmol) and MeNCy₂ (126 µl, 0.592 mmol) in DMF (3 ml). After 5 h at 140 °C, work up and column chromatography (hexane:EtOAc:Et₃N, 100:1:0–100:1:0.1) afforded the phenanthridine as a colourless oil (37 mg, 93%). ¹H NMR of this oil showed it to be a 83:8:9 mixture of double bond isomers (96d:97d:98d).
PMB-protected phenanthridine 96e-98e

(Table 2.6, Entry 5) General procedure C was employed using amine 94e (112 mg, 0.29 mmol), palladacycle 100 (13.5 mg, 14.4 µmol) and Ag₂CO₃ (79 mg, 0.29 mmol) in DMF (6 ml). After 160 mins at 140 °C, work up and column chromatography (hexane:EtOAc, 50:1-10:1) afforded the phenanthridine as a colourless oil (67 mg, 76%). ¹H NMR of this oil showed it to be a 97:3:0 mixture of double bond isomers (96e:97e:98e).

(Table 2.7, Entry 5) General procedure D was employed using amine 94e (56 mg, 0.144 mmol), palladacycle 100 (7 mg, 7.2 µmol) and MeNCy₂ (122 µl, 0.576 mmol) in DMF (3 ml). After 5 h at 140 °C, work up and column chromatography (hexane:EtOAc, 50:1-10:1) afforded the phenanthridine as a colourless oil (41 mg, 93%). ¹H NMR of this oil showed it to be a 74:13:13 mixture of double bond isomers (96e:97e:98e).
(4aSR,10bSR)-5-Methanesulfonyl-3,4a,4,5,6,10b-hexahydro-phenanthridine

96a (Δ1,2 isomer)

\[ 
\begin{align*}
R_f & \text{ [hexane:EtoAc, 3:1] } = 0.38; \\
R_t & \text{ [hexane:EtoAc, 11:9] } 15.9 \\
\end{align*}
\]

mins; \( \nu_{\text{max}} \text{(CHCl}_3)/\text{cm}^{-1} \) 3029, 1671, 1328, 1152; \(^1\)H NMR \( \delta \) (360 MHz, CDCl\(_3\)) 7.31 (1H, d, \( J 7.5, \text{ArH} \)), 7.26 (1H, t, \( J 7.8, \text{ArH} \)), 7.19 (1H, t, \( J 7.3, \text{ArH} \)), 7.10 (1H, d, \( J 7.5, \text{ArH} \)), 5.58 (1H, ddt, \( J 10.0, 4.8, 1.9, \text{CHC} = \text{CH} \)), 5.86 (1H, dtd, \( J 10.0, 3.9, 1.7, \text{CH=CHCH}_2 \)), 4.59 (1H, d, \( J 16.2, \text{CHCH}_2 \)), 4.43 (1H, d, \( J 16.2, \text{CHXH} \)), 4.19 (1H, dt, \( J 8.4, 5.8, \text{NCHCH}_3 \)), 3.66 (1H, br s, \text{CCH=CH} \)); \(^{13}\)C NMR \( \delta \) (90.0 MHz, CDCl\(_3\)) 136.9 (C), 131.1 (C), 128.5 (CH), 127.7 (CH), 127.6 (CH), 126.7 (CH), 126.3 (CH), 125.9 (CH), 52.1 (CH), 44.1 (CH\(_2\)), 38.2 (CH\(_3\)), 37.4 (CH), 25.1 (CH\(_2\)), 24.0 (CH\(_2\)); \( m/z \) (FAB, THIOG) 264 ([M+H]+, 19 %), 217 (25), 130 (79), 109 (38); HRMS (FAB, THIOG) Found: [M+H]+ 264.1050. C\(_{14}\)H\(_{18}\)NO\(_2\)S requires 264.1058.

This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

(4aSR,10bSR)-5-Methanesulfonyl-1,4a,4,5,6,10b-hexahydro-phenanthridine

(97a) (Δ2,3 isomer)

\[ 
\begin{align*}
R_f & \text{ [hexane:EtoAc, 3:1] } = 0.32; \\
R_t & \text{ [hexane:EtoAc, 11:9] } 18.1 \\
\end{align*}
\]

mins; MP 140 °C (hexane); \(^1\)H NMR \( \delta \) (360 MHz, CDCl\(_3\)) 7.29-7.23 (3H, m, 3xArH)), 7.17 (1H, dd, \( J 6.5, 1.8, \text{ArH} \)), 5.69-5.66 (1H, m, CHCH\(_2\)CH=), 5.42(1H, ddt, \( J 10.0, 5.1, 2.3, \text{NCHCH}_2\text{CH=})\), 4.53 (2H, s, CH\(_2\)Ar), 4.29 (1H, ddd, \( J 10.4, 4.0, 2.4, \text{NCHCH}_2\)), 3.26-3.22 (1H, m, CHCH\(_2\)), 2.94 (3H, s, CH\(_3\)), 2.92-2.85 (1H, m, CH\(_A\)H\(_B\)), 2.69-2.58 (1H, m, CH\(_A\)H\(_B\)), 2.28-2.23 (1H, m, CH\(_C\)H\(_D\)), 1.80-1.71 (1H, m, CH\(_C\)H\(_D\)); \(^{13}\)C NMR \( \delta \) (90.0 MHz, CDCl\(_3\)) 135.6 (C), 128.5 (C), 127.3 (CH), 126.5 (CH), 126.4 (CH), 125.3 (CH), 124.9 (CH), 123.8 (CH), 51.7 (CH), 45.0 (CH\(_2\)), 37.7 (CH\(_3\)), 35.8 (CH), 27.9 (CH\(_2\)), 26.5 (CH\(_2\)). This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.
Experimental

(4aSR,10bSR)-5-Methanesulfonyl-1,2,4a,5,6,10b-hexahydro-phenanthridine (98a) (∆3,4 isomer)

\[
\text{Rf [hexane:EtOAc, 3:1] = 0.39; Rf [hexane:EtOAc, 11:9] 15.4 mins; ^1H NMR } \delta \ (360 \text{ MHz, CDCl}_3) 7.37 (1H, d, J 7.8, ArH), 7.26 (1H, t, J 7.2, ArH), 7.19 (1H, t, J 7.3, ArH), 7.07 (1H, d, J 7.4, ArH), 5.83-5.80 (1H, m, CH=CH), 5.61 (1H, dt, J 10.2, 1.0, CH=CHCH), 4.87-4.83 (1H, m, NCH), 4.59 (1H, d, J 16.5, CHXHYAr), 4.26 (1H, d, J 16.5, CHXHYAr), 3.39 (1H, br s, CHCH), 2.83 (3H, s, CH3), 2.43-2.38 (1H, m, CHAHB), 2.05-1.97 (1H, m, CHAHB), 1.94-1.76 (2H, m, CH2CH); ^13C NMR } \delta \ (90.6 \text{ MHz, CDCl}_3) 134.5 (C), 133.0 (C), 127.3 (CH), 126.9 (CH), 126.1 (2xCH), 125.8 (CH), 52.4 (CH), 43.3 (CH2), 39.8 (CH3), 34.1 (CH), 25.3 (CH2), 20.1 (CH3).
\]

This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

(4aSR,10bSR)-4,4a,6,10b-Tetrahydro-3H-phenanthridine-5-carboxylic acid tert-butyl ester 96b (∆1,2 isomer)

\[
\text{Rf [hexane:EtOAc, 10:1] = 0.42; Rf [hexane:EtOAc, 92:8] 17 min; } \nu_{\text{max}} \text{ (CHCl}_3)/\text{cm}^{-1} 3026, 1693 (\text{C}=\text{O}), 1258, 913, 745; \ ^1H \text{ NMR } \delta \ (360 \text{ MHz, CDCl}_3) 7.30 (1H, d, J 7.5, ArH), 7.25-7.17 (2H, m, 2xArH), 7.12 (1H, d, J 7.2, ArH), 6.17-6.13 (1H, m, CHCH=CH), 5.87-5.83 (1H, m, CH=CHCH), 4.71 (1H, d, J 16.5, CHXHYAr), 4.41 (1H, br s, NCHCH), 4.39 (1H, d, J 16.5, CHXHYAr), 3.57 (1H, br s, NCHCH), 2.31-2.27 (1H, m, CHAHB), 2.15-2.05 (1H, m, CHAHB), 1.79-1.69 (1H, m, CH2CHD), 1.61-1.40 (10H, m, 3 x CH3+CH=CH2); ^13C \text{ NMR } \delta \ (90.0 \text{ MHz, CDCl}_3) 155.0 (C), 137.8 (C), 132.5 (C), 128.3 (CH), 128.1 (C), 127.6 (CH), 127.3 (CH), 126.8 (CH), 126.1 (CH), 125.9 (CH), 79.6 (C), 43.5 (CH2), 37.3 (CH), 28.5 (3xCH3), 25.3 (CH2), 24.2 (CH2); m/z (FAB, THIOG) 284 ([M-H]+, 44 %), 228 (66), 184 (49), 130 (25); HRMS (FAB, THIOG) Found: [M-H]+ 284.1643. C_{18}H_{22}NO_2 requires 284.1650.
Experimental

(4aSR,10bSR)-4,4a,6,10b-Tetrahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 97b (Δ2,3 isomer)

$$R_f$$ [hexane:EtOAc, 10:1] = 0.39; $$R_f$$ [hexane:EtOAc, 92:8] 18 min; $$v_{max}$$ (CHCl3)/cm$$^{-1}$$ 3352, 1699 (C=O), 1392, 1367, 1167; $${}^1$$H NMR δ (250 MHz, CDCl3) 7.24-7.16 (4H, m, 4xArH), 5.70-5.66 (1H, m, CHCH2CH=), 5.45-5.37 (1H, m, NCHCH2CH=), 4.68-4.66 (3H, m, CH2Ar+NCHCH2), 3.32-3.18 (1H, m, CH2CH2), 2.86 (1H, dd, J 18.0, 4.5, CHAHz), 2.67-2.54 (1H, m, CHAHz), 2.28-2.16 (1H, m, CHC2D), 1.65-1.52 (10H, m, 3xCH3+CHC2D); $${}^{13}$$C NMR δ (62.9 MHz, CDCl3) 154.8 (C), 136.4 (C), 133.9 (C), 126.6 (CH), 126.4 (CH), 126.1 (CH), 125.4 (CH), 124.8 (CH), 123.7 (CH), 79.6 (C), 50.3 (CH), 44.6 (CH2), 35.5 (CH), 28.5 (3xCH3), 26.2 (CH2); m/z (EI) 285 ([M]+, 2 %), 231 (32), 175 (100), 130 (22); HRMS (EI) Found: [M]+ 285.1726. C18H23NO2 requires 285.1723.

(4aSR,10bSR)-2,4a,6,10b-Tetrahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 98b (Δ3,4 isomer)

$$R_f$$ [hexane:EtOAc, 10:1] = 0.44; $$R_f$$ [hexane:EtOAc, 92:8] 16 min; $$v_{max}$$ (CHCl3)/cm$$^{-1}$$ 3359, 1695 (C=O), 1400, 1367; $${}^1$$H NMR δ (250 MHz, CDCl3) 7.37 (1H, d, J 7.5, ArH), 7.26-7.13 (2H, m, 2xArH), 7.07 (1H, d, J 7.0, ArH), 5.72-5.65 (1H, m, CH2CH=CH), 5.52 (1H, d, J 11.0, CH=CHCH), 5.08 (1H, br s, NCH), 4.86 (1H, d, J 17.0, CHXH2Ar), 4.24 (1H, d, J 17.0, CHXH2Ar), 3.30 (1H, br s, CHCH2), 2.45-2.37 (1H, m, CHAHz), 2.08-1.94 (1H, m, CHAHz), 1.95-1.81 (2H, m, CH2), 1.50 (9H, s, 3xCH3); $${}^{13}$$C NMR δ (62.9 MHz, CDCl3) 154.8 (C), 135.1 (C), 133.9 (C), 130.8 (CH), 127.6 (CH), 126.5 (2xCH), 125.8 (CH), 125.6 (CH), 79.8 (C), 50.0 (CH), 42.6 (CH2), 34.5 (CH), 28.4 (3xCH3), 25.0 (CH2), 20.2 (CH2); m/z (EI) 285 ([M]+, 2 %), 229 (77), 228 (100), 184 (32), 175 (48); HRMS (EI) Found: [M]+ 285.1720. C18H23NO2 requires 285.1723.
Experimental

(4aSR,10bSR)-4a,6,10b-Tetrahydro-3H-phenanthridine-5-carboxylic acid benzyl ester 96c (\(\Delta^{1,2}\) isomer)

\[ R_t \] [hexane:EtOAc, 10:1] = 0.34; \( \nu_{\text{max}} \) (CHCl\(_3\))/cm\(^{-1}\) 3030, 1698 (C=O), 1410, 1263; \( ^1H \) NMR \( \delta \) (360 MHz, 323 K, CDCl\(_3\)) 7.29-7.22 (6H, m, 6xArH), 7.19-7.07 (2H, m, 2xArH), 7.01 (1H, d, J 6.1, ArH), 6.06-6.02 (1H, m, CH=CH), 5.77-5.73 (1H, m, CH=CH), 5.12 (2H, s, CH\(_2\)Ph), 4.72 (1H, d, J 16.6, CH\(_X\)H\(_Y\)Ar), 4.41 (1H, br s, NCHCH), 4.36 (1H, d, J 16.6, CH\(_X\)H\(_Y\)Ar), 3.49 (1H, br s, CHCH=CH), 2.24-2.09 (1H, m, CH\(_{AB}\)), 2.07-1.95 (1H, m, CH\(_{AB}\));

\( ^{13}C \) NMR \( \delta \) (90.6 MHz, 323 K, CDCl\(_3\)) 155.5 (C), 137.6 (C), 136.9 (C), 132.0 (C), 128.4 (2xCH), 128.3 (CH), 127.9 (CH), 127.8 (2xCH), 127.6 (CH), 127.1 (CH), 127.0 (CH), 126.0 (CH), 126.0 (CH), 67.1 (CH\(_2\)), 50.7 (CH), 43.6 (CH\(_2\)), 37.2 (CH), 25.1 (CH\(_2\)), 24.2 (CH\(_2\)); \( m/z \) (FAB, THIOG) 320 ([M+H]\(^+\), 24 %), 318 ([M-H]\(^+\), 51), 274 (37), 228 (26), 154 (61); HRMS (FAB, THIOG) Found: [M-H]\(^+\) 318.1483. C\(_{21}\)H\(_{20}\)NO\(_2\) requires 318.1494.

Diagnostic \( ^1H \) NMR data for 97c (\(\Delta^{2,3}\) isomer)

\( ^1H \) NMR \( \delta \) (360 MHz, 323 K, CDCl\(_3\)) 5.69-5.65 (1H, m, CH=CH), 5.41-5.37 (1H, m, CH=CH), 4.65 (1H, d, J 16.6, CH\(_X\)H\(_Y\)Ar), 4.59 (1H, d, J 16.6, CH\(_X\)H\(_Y\)Ar), 3.20 (1H, br s, CHCH\(_2\)), 2.88-2.81 (1H, m, CH\(_{AB}\)), 2.63-2.55 (1H, m, CH\(_{AB}\)).

Diagnostic \( ^1H \) NMR data for 98c (\(\Delta^{3,4}\) isomer)

\( ^1H \) NMR \( \delta \) (360 MHz, 323 K, CDCl\(_3\)) 5.75-5.71 (1H, m, CH=CH), 5.55 (1H, d, J 9.7, CH=CH), 4.95 (1H, d, J 16.6, CH\(_X\)H\(_Y\)Ar), 4.33 (1H, d, J 16.6, CH\(_X\)H\(_Y\)Ar), 3.33 (1H, br s, CHCH\(_2\)).
Experimental

(4aSR,10bSR)-5-(Benzyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine

96d (\(\Delta^{1,2}\) isomer)

\[ R_f \ [\text{hexane:EtOAc, 10:1}] = 0.44; \ \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3025, 1642, 1602, 1260; \ ^1H \ \text{NMR} \ \delta (360 \text{ MHz, CDCl}_3) 7.35 (2H, d, J 7.0, 2xArH), 7.29-7.20 (4H, m, 4xArH), 7.19 (1H, t, J 7.6, ArH), 7.10 (1H, t, J 7.6, ArH), 6.89 (1H, d, J 7.6, ArH), 6.06-6.02 (1H, ddt, J 9.8, 4.2, 1.8, CHCH=CH), 5.73-5.70 (1H, ddt, J 9.8, 5.5, 2.4, CH=CHCH), 3.89 (1H, d, 13.3, CHXHYAr), 3.75 (1H, d, J 15.6, CHpHQAr), 3.66 (1H, d, J 13.3, CHXHYAr), 3.58 (1H, br s, CHCH=CH), 3.54 (1H, d, J 15.6, CHpHQ), 3.14 (1H, ddd, J 10.6, 5.2, 2.5, CHpHQAr), 2.21-2.07 (2H, m, CHXHYAr), 1.86-1.77 (1H, m, CHpHQAr), 1.69-1.61 (1H, m, CHXHYAr); \ ^{13}C \ \text{NMR} \ \delta (90.0 \text{ MHz, CDCl}_3) 139.0 (C), 137.7 (C), 133.4 (C), 128.8 (CH), 128.7 (2xCH), 128.2 (2xCH), 127.7 (CH), 127.4 (CH), 126.9 (CH), 126.4 (2xCH), 125.2 (CH), 58.4 (CH2), 56.1 (CH), 50.9 (CH2), 37.8 (CH), 24.3 (CH2), 19.4 (CH2); \ m/z \ (\text{FAB, THIOG}) 276 ([M+H]^+), 76 \%); 200 (35), 184 (55), 154 (93), 136 (83); \ \text{HRMS (FAB, THIOG)} \ \text{Found: [M+H]^+ 276.1755. C}_{20}H_{22}N \ \text{requires 276.1754.}

This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

Diagnostic \(^1H \ \text{NMR data for 97d (\(\Delta^{2,3}\) isomer)}

\(^1H \ \text{NMR} \ \delta (360 \text{ MHz, CDCl}_3) 5.70-5.67 (1H, m), 5.58-5.55 (1H, m), 2.74-2.65 (1H, m).

Diagnostic \(^1H \ \text{NMR data for 98d (\(\Delta^{3,4}\) isomer)}

\(^1H \ \text{NMR} \ \delta (360 \text{ MHz, CDCl}_3) 5.96-5.92 (1H, m), 5.89-5.86 (1H, m).
(4aSR,10bSR)-5-(4-Methoxy-benzyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine

96e (Δ^{1,2} isomer)

R_f [hexane:EtOAc, 10:1] = 0.23; υ_{max} (CHCl$_3$)/cm$^{-1}$ 3024, 1647, 1609, 1511; $^1$H NMR δ (360 MHz, CDCl$_3$) 7.33-7.29 (3H, m, 3xArH), 7.18 (1H, t, J 7.3, ArH), 7.10 (1H, t, J 7.6, ArH), 6.96 (1H, d, J 7.6, ArH), 6.90-6.88 (2H, m, 2xArH), 6.12-6.08 (1H, m, CH=CH), 5.79-5.76 (1H, m, CH=CH$_2$), 3.89 (1H, d, J 13.0, CH$_3$Ar), 3.82 (3H, s, OCH$_3$), 3.80 (1H, d, J 16.1, CH$_3$Ar), 3.67 (1H, d, J 13.0, CH$_3$Ar), 3.62 (1H, br s, CH=CH=), 3.59 (1H, d, J 16.1, CH$_3$Q), 3.12 (1H, ddd, J 10.6, 5.4, 2.6, NCH), 2.20-2.00 (2H, m, CH$_2$), 1.90-1.63 (2H, m, CH$_2$); $^{13}$C NMR δ (90.0 MHz, CDCl$_3$) 158.6 (C), 137.7 (C), 133.4 (C), 130.9 (C), 129.9 (2xCH), 128.8 (CH), 127.6 (CH), 127.4 (CH), 126.4 (CH), 126.3 (CH), 125.2 (CH), 113.6 (2xCH), 57.7 (CH$_2$), 55.9 (CH), 55.1 (CH$_3$), 50.8 (CH$_2$), 37.8 (CH), 24.2 (CH$_2$), 19.2 (CH$_2$);

m/z (FAB, THIOG) 306 ([M+H]$^+$, 56 %), 305 ([M]$^+$, 58), 304 ([M-H]$^+$, 69), 251 (12.4), 184 (46.1); HRMS (FAB, 3-NOBA) Found: [M]$^+$ 305.1779. C$_{21}$H$_{23}$NO requires 305.1780. This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

Diagnostic $^1$H NMR data for 97e (Δ^{2,3} isomer)

$^1$H NMR δ (360 MHz, CDCl$_3$) 5.68-5.65 (1H, m), 5.56-5.53 (1H, m), 3.98 (1H, d, J 13.2), 3.18 (1H, br s), 2.71-2.65 (1H, m).

Diagnostic $^1$H NMR data for 98e (Δ^{3,4} isomer)

$^1$H NMR δ (360 MHz, CDCl$_3$) 5.96-5.91 (1H, m), 5.90-5.84 (1H, m), 4.05 (1H, J 13.3), 3.11 (1H, br s).
Experimental

**N-Benzyl-N-cyclohex-2-enyl-methanesulfonamide 99a**

General procedure B was followed using N-Benzyl-cyclohex-2-enyl amine (590 mg, 3.15 mmol), CH\textsubscript{2}Cl\textsubscript{2} (15 ml), Et\textsubscript{3}N (1.33 ml, 3.47 mmol) and methanesulfonyl chloride (0.73 ml, 9.45 mmol). Flash chromatography (hexane:EtOAc, 10:1–2:1) afforded colourless solid **99a** (300 mg, 63%).

\[ R_f \text{ [hexane:EtOAc, 3:1] = 0.47; MP 89 ^\circ C (Et}_2\text{O); } \nu_{\text{max}} \text{ (CHCl}_3)/\text{cm}^{-1}1334 \text{ (SO}}_2\text{), 1143 \text{ (SO}}_2; \] \[ ^1\text{H NMR } \delta \text{ (250 MHz, CDCl}_3) 7.40-7.25 \text{ (5H, m, 5xArH), 5.97-5.91} \text{ (1H, m, CHNCH=CH), 5.57-5.51} \text{ (1H, m, CHNCH=CH), 4.63-4.53} \text{ (1H, m, CHN),} \]

\[ 4.47 \text{ (1H, d, J 16.1, } CH}_XH_YPh\text{), 4.25} \text{ (1H, d, J 16.1, } CH}_XH_YPh\text{), 2.79 (3H, s, CH}_3\text{),} \]

\[ 1.98-1.93 (3H, m, } CH_AH_B+CH}_2\text{), 1.72-1.48 (3H, m, } CH_AH_B+CH}_2); ^13\text{C NMR } \delta \text{ (62.9 MHz, CDCl}_3) 138.4 \text{ (C), 132.8 (CH), 128.2 (2xCH), 127.7 (2xCH), 127.5} \text{ (CH), 127.1 (CH), 55.5 (CH), 47.2 (CH}_2\text{), 40.4 (CH}_3\text{), 28.9 (CH}_2\text{), 24.2 (CH}_2\text{), 21.5} \text{ (CH}_2\text{); } m/z \text{ (FAB, THIOG) ([2M+H]^+, 571, 21.3 %), ([M+H]^+ , 266, 70.1), 250} \text{ (33.2), 237 (35.6), 214 (49.5); HRMS (FAB, THIOG) Found: [M+H]^+, 266.1218.} \]

C\textsubscript{14}H\textsubscript{19}NO\textsubscript{2}S requires 266.1215.
Experimental

(4aSR,10bSR)-5-Methanesulfonyl-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine

To a solution of phenanthridines 96a-98a (316 mg, 1.18 mmol) in ethanol (10 ml) was added EtOAc (1 ml) and Pd/C (35 mg, 10% by weight). The reaction was stirred vigorously and exposed to an atmosphere of hydrogen for 12 h. The reaction was filtered through celite and concentrated under reduced pressure to afford phenanthidine 110 as a colourless solid (190 mg, 60%).

Rf [hexane:EtOAc, 3:1] = 0.33; MP 103 °C (EtOH); \( \nu_{\text{max}} \) (CHCl\(_3\))/cm\(^{-1}\) 3029, 1684, 1325 (SO\(_2\)), 1153 (SO\(_2\)); \( ^1\text{H NMR} \) δ (360 MHz, CDCl\(_3\)) 7.39 (1H, d, \( J \) 7.7, ArH), 7.25 (1H, t, \( J \) 6.0, ArH), 7.21 (1H, t, \( J \) 6.1, ArH), 7.11 (1H, d, \( J \) 6.7, ArH), 4.64 (1H, d, \( J \) 16.3, CH\(_X\)H\(_Y\)Ar), 4.42 (1H, d, \( J \) 16.3, CH\(_X\)H\(_Y\)Ar), 4.14-4.09 (1H, m, CHN), 3.26 (1H, br s, CH\(_\text{CHN}\)), 2.89 (3H, s, CH\(_3\)), 2.55-2.49 (1H, m, CH\(_A\)H\(_B\)), 1.83-1.65 (3H, m, CH\(_2\)+CH\(_A\)H\(_B\)), 1.48-1.42 (3H, m, CH\(_2\)+CH\(_C\)H\(_D\)), 1.26-1.15 (1H, m, CH\(_C\)H\(_D\)); \( ^{13}\text{C NMR} \) δ (90.6 MHz, CDCl\(_3\)) 134.7 (C), 131.8 (C), 127.1 (CH), 126.2 (CH), 126.1 (CH), 126.0 (CH), 54.0 (CH), 43.6 (CH\(_2\)), 38.8 (CH\(_3\)), 37.1 (CH), 27.6 (CH\(_2\)), 26.3 (CH\(_2\)), 25.0 (CH\(_2\)), 19.6 (CH\(_2\)); \( m/z \) (FAB, THIOG) 529 (2M+H\(^+\), 10 %), 266 ([M+H]\(^+\), 83), 264 (94), 262 (29), 234 (17), 222 (18); HRMS (FAB, THIOG) Found: [M+H]\(^+\) 266.1214. C\(_{14}\)H\(_{20}\)NO\(_2\)S requires 266.1215.
(4aSR,10bSR)-2,3,4,4a,6,10b-Hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 111

To a solution of phenanthridines 96b-98b (200 mg, 0.71 mmol) in methanol (20 ml) was added Pd/C (20 mg, 10% by weight). The reaction was stirred vigorously and exposed to an atmosphere of hydrogen for 16 h. The reaction was filtered through celite, concentrated under reduced pressure and purified by flash chromatography (CH$_2$Cl$_2$:EtOAc, 1:1) to afford phenanthridine 111 as a colourless oil (179 mg, 88%).

R$_f$ [hexane:EtOAc, 10:1] = 0.47; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 2927, 1693 (C=O), 1366, 1174; $^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 7.37 (1H, d, $J$ 7.6, ArH), 7.28-7.14 (2H, m, 2xArH), 7.13 (1H, d, $J$ 6.5, ArH), 4.72 (1H, d, $J$ 17.1, CH$_3$H$_2$Ar), 4.39 (1H, d, $J$ 17.1, CH$_3$H$_2$Ar), 4.32-4.29 (1H, m, NCHCH), 3.20 (1H, br s, NCHCH), 2.57-2.52 (1H, m, CH$_2$H$_2$B), 1.84-1.72 (1H, m, CH$_2$H$_2$B), 1.72-1.60 (2H, m, CH$_2$), 1.60-1.20 (13H, m, 3 x CH$_3$+CH$_2$CH$_2$); $^{13}$C NMR $\delta$ (90.6 MHz, 323 K, CDCl$_3$) 154.8 (C), 135.7 (C), 133.8 (C), 126.6 (CH), 126.3 (CH), 125.8 (CH), 125.7 (CH), 79.5 (C), 52.4 (CH), 43.8 (CH$_2$), 36.8 (CH), 28.5 (3xCH$_3$), 27.4 (CH$_2$), 26.5 (CH$_2$), 25.5 (CH$_2$), 19.9 (CH$_2$); m/z (FAB, THIOG) 286 ([M-H]$^+$, 31 %), 230 (75), 186 (55), 184 (18), 156 (12), 130 (17), 57 (100); HRMS (FAB, THIOG) Found: [M-H]$^+$ 286.1812. C$_{18}$H$_{24}$NO$_2$ requires 286.1807.
(4aSR,10bSR)-1,2,3,4,4a,5,6,10b-Octahydro-phenanthridinium; chloride 112

To a solution of Boc-protected amine 111 (154 mg, 0.54 mmol) in CH₂Cl₂ (10 ml) was added Trifluoroacetic acid (15.0 ml). After 10 minutes no starting material remained by TLC so the solution was adjusted to pH 9 using KOH pellets and extracted with CH₂Cl₂ (3 x 15 ml). The combined organics were dried (MgSO₄) and concentrated under reduced pressure. The residue was taken up in CH₂Cl₂ (1 ml), HCl added (1 ml, 1.0 M in Et₂O, 1 mmol) and the resultant suspension filtered to afford octahydrophenanthridinium chloride 112 as a pale yellow solid (106 mg, 88%).

MP 173 °C (Et₂O); ν_max (CHCl₃)/cm⁻¹ 3421 (NH); ¹H NMR δ (360 MHz, CD₃OD) 9.19 (1H, brs, NH), 7.97 (1H, d, J 7.5, ArH), 7.91 (1H, t, J 7.6, ArH), 7.63 (1H, d, J 7.6, ArH), 7.59 (1H, d, J 7.9, ArH), 4.90 (2H, s, CH₂Ar), 4.33 (1H, brs, NC₂CH), 3.30 (1H, m, NCH₂), 2.30-2.15 (1H, m, CH₆A₇B₀), 2.08-1.90 (1H, m, CH₆A₇B₀), 1.89-1.70 (2H, m, CH₂), 1.56 (2H, brs, CH₂); ¹³C NMR δ (90.0 MHz, CD₃OD) 142.9 (C), 138.0 (CH), 133.6 (CH), 127.7 (CH), 127.3 (CH), 122.8 (C), 53.4 (CH), 48.0 (CH₂), 36.0 (CH), 27.7 (CH₂), 25.9 (CH₂), 22.3 (CH₂), 20.0 (CH₂); m/z (FAB, THIOG) 188 ([M+H]^+), 156 (54), 144 (57), 130 (68); HRMS (FAB, THIOG) Found: [M+H]^+ 188.1436. C₁₃H₁₈N requires 188.1439.

Free Amine: Rf [EtOAc] = 0.29; ¹H NMR δ (360 MHz, CDCl₃) 7.02 (1H, d, J 6.5, ArH), 7.16-7.08 (3H, m, 3xArH), 4.16 (1H, d, J 16.2, CH₆H₁₄), 4.10 (1H, d, J 16.2 CH₆H₁₄), 3.16 (1H, d, J 3.3, NCH₂), 2.65-2.62 (1H, m, NCH₂), 2.16 (1H, br s, NH), 1.97-1.91 (1H, d, J 23.1, CH₆H₁₄), 1.86-1.69 (3H, m, CH₆H₁₄+CH₂), 1.65-1.36 (4H, m, CH₂+CH₂); ¹³C NMR δ (90.6 MHz, CDCl₃) 140.7 (C), 134.6 (C), 128.7 (CH), 126.9 (CH), 125.8 (CH), 125.7 (CH), 52.0 (CH), 48.7 (CH₂), 39.0 (CH), 31.7 (CH₂), 31.2 (CH₂), 25.8 (CH₂), 20.4 (CH₂).

¹H and ¹³C NMR data in good agreement with the literature.
3-Methoxy-5,5-dimethyl-cyclohex-2-enone 117

To a solution of dimedone (4.90 g, 34.9 mmol) in MeOH (100 ml) was added cerium(IV) ammonium nitrate (1.91 g, 3.49 mmol) and the reaction stirred for 16 h at r.t. The reaction was concentrated under reduced pressure and the organics taken up in Et₂O (200 ml) and washed with NaCl (3 x 100 ml, sat. aq.). The organics were dried (MgSO₄), concentrated under reduced pressure, and purified using flash chromatography (hexane:EtOAc, 10:1-2:1) to afford enol ether 117 as a pale yellow oil (3.90 g, 73%).

Rf [hexane:EtOAc, 3:1] = 0.15; υmax (CHCl₃)/cm⁻¹ 1656 (C=O), 1608, 1376, 1226, 1155; ¹H NMR δ (250 MHz, CDCl₃) 5.35 (1H, s, C=C), 3.67 (3H, s, OCH₃), 2.25 (2H, s, CH₂), 2.19 (2H, s, CH₂), 1.04 (6H, s, 2xCH₃); ¹³C NMR δ (62.9 MHz, CDCl₃) 199.4 (C), 176.9 (C), 100.9 (CH), 55.5 (CH₃), 50.5 (CH₂), 42.5 (CH₂), 32.3 (C), 28.1 (2xCH₃); m/z (FAB, THIOG) 155 ([M+H]+, 100%), 139 (28), 124 (12), 110 (16); HRMS (FAB, THIOG) Found: [M+H]+ 155.1073. C₉H₁₅O₂ requires 155.1072.

¹H and ¹³C NMR data in good agreement with the literature.
**5,5-Dimethyl-cyclohex-2-enone 118**

To a solution of enol ether 117 (900 mg, 5.84 mmol) in Et₂O (12 ml) at 0 °C was added LiAlH₄ (255 mg, 6.72 mmol) portionwise. The reaction was warmed to r.t. and stirred for 1 h. The LiAlH₄ was quenched by adding Na₂SO₄.5H₂O portionwise, then the reaction was filtered and the filtrate concentrated under reduced pressure. The residue was taken up in CH₂Cl₂ (10 ml) and stirred with silica (cat.) for 3 h to afford enone 118 as a colourless oil (661 mg, 91%).

\[ R_f \text{ [hexane:EtOAc, 3:1] = 0.55; } \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1678 (\text{C=O}), 1609, 1389, 1161; \]

\[^1H \text{ NMR } \delta \text{ (250 MHz, CDCl}_3) 6.75 \text{ (1H, dt, } J 10.1, 4.2, \text{ CH}2\text{CH}2\text{), 5.88 (1H, dt, } J 10.1, 2.1, \text{ CH}2\text{CH}2\text{), 2.14 (2H, s, CH}_2\text{), 2.13 (2H, dd, } J 4.2, 2.1, \text{ CH}_2\text{CH}2\text{), 0.89 (6H, s, } 2xCH}_3); \]

\[^{13}C \text{ NMR } \delta \text{ (62.9 MHz, CDCl}_3) 199.8 \text{ (C), 148.2 (CH), 128.9 (CH), 51.6 (CH}_2\text{), 39.8 (CH}_2\text{), 33.7 (C), 28.2 (2xCH}_3); m/z \text{ (FAB, THIOG) 125 ([M+H] }^+, 96 \%), 122 (43), 120 (35) 116 (33), 111 (73), 109 (92); HRMS \text{ (FAB, THIOG) Found: [M+H] }^+ 125.0968. C_8H_{13}O \text{ requires 125.0966.} \]

\[^1H \text{ and } ^{13}C \text{ NMR data in good agreement with the literature.} \]

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154
5,5-Dimethyl-cyclohex-2-enol 119

To a solution of enone 118 (661 mg, 5.32 mmol) in Et₂O (12 ml) at 0 °C was added portionwise LiAlH₄ (201 mg, 5.32 mmol). The reaction was stirred for at 0 °C for 40 mins then quenched by the addition of Na₂SO₄·5H₂O portionwise. The reaction was filtered and the filtrate vigorously stirred with potassium sodium tartate (50 ml, sat. aq.) for 1 h. The organic phase was separated and the aqueous phase washed with Et₂O (3 x 40 ml). The combined organics were dried (MgSO₄) and concentrated under reduced pressure to afford alcohol 119 as a colourless oil (525 mg, 72%).

Rₛ [hexane:EtOAc, 3:1] = 0.37; νₛₘₐₓ (CHCl₃)/cm⁻¹ 3336 (OH), 2952, 1650, 1454, 1089; ¹H NMR δ (250 MHz, CDCl₃) 5.71 (2H, s, CH=CH), 4.29-4.22 (1H, m, CHOH), 1.88-1.57 (3H, m, CH₂+CH₃), 1.31 (1H, dd, J 12.3, 8.7, CH₃), 1.00 (3H, s, CH₃), 0.92 (3H, s, CH₃); ¹³C NMR δ (62.9 MHz, CDCl₃) 129.1 (CH), 128.0 (CH), 66.2 (CH), 45.3 (CH₂), 38.9 (CH₂), 31.2 (CH₃), 30.7 (C), 26.0 (CH₃); m/z (FAB, THIOG) 149 ([M+Na]+, 33%), 127 ([M+H]+, 5), 125 ([M-H]+, 12), 124 (18), 111 (53); HRMS (FAB, THIOG) Found: [M-H]+ 125.0968. C₈H₁₃O requires 125.0966.

¹H and ¹³C NMR data in good agreement with the literature.
3-Bromo-5,5-Dimethyl-cyclohex-2-ene 120

To a stirred solution of alcohol 119 (2.00 g, 15.8 mmol) and CBr₄ (11.1 g, 33.3 mmol) in Et₂O (75 ml) at 0 °C was added PPh₃ (8.00 g, 33.3 mmol). The reaction was warmed to r.t. and stirred for 2 h. The reaction was filtered and the filtrate concentrated under reduced pressure to afford a colourless solid and a yellow oil. These were washed with pentane (2 x 100 ml) and the combined washings dried (MgSO₄) and concentrated under reduced pressure to afford bromide 120 as a pale yellow oil (2.00 g, 67%). This material was found to be unstable to flash chromatography and thus was used without further purification.

Rᵣ [hexane:EtOAc, 3:1] = 0.46; \( \nu_{\text{max}} \) (CHCl₃)/cm⁻¹ 1437, 1120, 723, 694; \(^{1}H\) NMR \( \delta \) (250 MHz, CDCl₃) 5.90-5.84 (1H, m, CH=CH), 5.75-5.71 (1H, m, CH=CH), 4.79-4.77 (1H, m, CHBr), 2.14-1.88 (3H, m, CH₃H₃+CH₂), 1.80-1.70 (1H, m, CH₃H₃), 1.02 (3H, s, CH₃), 0.96 (3H, s, CH₃); \(^{13}C\) NMR \( \delta \) (62.9 MHz, CDCl₃) 129.0 (CH), 128.2 (CH), 47.5 (CH), 46.7 (CH₂), 38.1 (CH₂), 31.9 (C), 30.7 (CH₃), 25.4 (CH₃).
**Experimental**

**N-(2-Bromo-benzyl)-5,5-dimethylocyclohex-2-enyl-amine 121**

![Chemical Structure]

To a suspension of 2-bromobenzylamine hydrochloride (412 mg, 1.85 mmol) in MeCN (20 ml) was added iPr<sub>2</sub>NEt (1.30 ml, 7.40 mmol) and the reaction stirred for 10 mins. Cyclohexenyl bromide 120 (700 µl, 3.70 mmol) was added dropwise and the reaction stirred at r.t. for 16 h. The reaction was concentrated under reduced pressure and the residue taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.). The combined organics were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to afford amine 121 as a brown oil (340 mg, 63%).

**R<sub>f</sub>** [hexane:EtOAc, 3:1] = 0.37; **ν**<sub>max</sub> (CHCl<sub>3</sub>)<sup>-1</sup> 3307 (NH), 1776, 1651, 1466; **<sup>1</sup>H** NMR δ (360 MHz, CDCl<sub>3</sub>) 7.53 (1H, dd, J 7.9, 1.2, ArH), 7.46 (1H, dd, J 6.1, 1.6, ArH), 7.28 (1H, t, J 7.4, 6.1, ArH), 7.11 (1H, td, J 7.8, 1.6, ArH), 5.76-5.70 (2H, m, CH=CH<sub>2</sub>), 3.92 (2H, s, CH<sub>2</sub>Ar), 3.31-3.24 (1H, m, CHN), 1.92 (1H, dd, J 17.8, 3.4, CH<sub>A</sub>H<sub>B</sub>), 1.79-1.71 (2H, m, CH<sub>A</sub>H<sub>B</sub>-CH<sub>C</sub>H<sub>D</sub>), 1.23 (1H, dd, CH<sub>C</sub>H<sub>D</sub>), 1.00 (3H, s, CH<sub>3</sub>), 0.92 (3H, s, CH<sub>3</sub>); **<sup>13</sup>C** NMR δ (90.6 MHz, CDCl<sub>3</sub>) 139.6 (C), 132.5 (CH), 130.0 (CH), 128.4 (CH), 128.3 (CH), 127.3 (CH), 127.2 (CH), 123.7 (C), 52.0 (CH), 50.7 (CH<sub>2</sub>), 43.2 (CH<sub>2</sub>), 39.0 (CH<sub>2</sub>), 31.8 (CH<sub>3</sub>), 30.2 (C), 25.4 (CH<sub>3</sub>); m/z (FAB, THIOG) 296 ([<sup>81</sup>BrM+H]<sup>+</sup>, 96 %), 294 ([<sup>79</sup>BrM+H]<sup>+</sup>, 100), 239 (25), 188 (33), 186 (51), 171 (42), 169 (48); **HRMS** (FAB, THIOG) Found: [<sup>81</sup>BrM+H]<sup>+</sup> 296.0845. C<sub>15</sub>H<sub>21</sub>N<sup>81</sup>Br requires 296.0837. Found: [<sup>79</sup>BrM+H]<sup>+</sup>, 294.0848. C<sub>15</sub>H<sub>21</sub>N<sup>79</sup>Br requires 294.0857.
**Experimental**

N-(2-Bromo-benzyl)-N-5,5-dimethylcyclohex-2-enyl-methanesulfonamide 115

General procedure B was followed using amine hydrochloride 121 (180 µl, 0.62 mmol), CH₂Cl₂ (5 ml), Et₃N (262 µl, 1.87 mmol) and methanesulfonyl chloride (214 µl, 1.87 mmol). Flash chromatography (hexane:EtOAc, 10:1–5:1) afforded sulfonamide 115 as a colourless oil (150 mg, 65%).

**Rf** [hexane:EtOAc, 3:1] = 0.77; **ν**\(_{\text{max}}\) (CHCl₃)/cm\(^{-1}\) 1335 (SO₂), 1159 (SO₂), 913, 745; **¹H NMR** \(\delta\) (360 MHz, CDCl₃) 7.66 (1H, d, \(J = 7.0\), ArH), 7.50 (1H, dd, \(J = 8.0, 1.2\), ArH), 7.32 (1H, td, \(J = 7.6, 0.7\), ArH), 7.11 (1H, J = 7.6, 1.8, ArH), 5.89-5.83 (1H, dddd, \(J = 10.3, 5.2, 2.7, 2.5\), CH=CH), 5.49 (1H, dd, \(J = 10.3, 1.3\), CH=CH), 4.63-4.47 (1H, m, CHN), 4.45 (1H, d, \(J = 17.6\), CHₓH₃), 4.31 (1H, d, \(J = 17.6\), CHₓH₃), 2.98 (3H, s, CH₃), 1.92-1.83 (1H, m, CHₓH₃), 1.75-1.68 (1H, m, CHₓH₃), 1.68-1.60 (1H, m, CHₓH₃), 1.30-1.25 (1H, m, CHₓHₓD), 0.95 (3H, s, CH₃), 0.91 (3H, s, CH₃); **¹³C NMR** \(\delta\) (90.6 MHz, CDCl₃) 137.7 (C), 132.1 (2xCH), 129.3 (CH), 128.5 (CH), 127.4 (CH), 125.1 (CH), 122.0 (C), 54.9 (CH), 47.7 (CH₂), 40.8 (CH₂), 39.5 (CH₃), 38.2 (CH₂), 31.7 (CH₃), 31.0 (C), 24.8 (CH₃); **m/z** (FAB, THIOG) 374 ([¹⁸¹BrM+H]⁺, 80 %), 372 ([¹⁷⁹BrM+H]⁺, 93), 294 (49), 292 (53), 264 (23), 262 (12), 171 (100), 169 (100);

Experimental

(4aSR,10bSR)-3,3-dimethyl-5-Methanesulfonyl-4,4a,5,6,10b-tetrahydrophenanthidine 114

General procedure C was employed using sulfonamide 115 (40 mg, 0.11 mmol), palladacycle 100 (5.0 mg, 5.4 µmol) and Ag₂CO₃ (30 mg, 0.11 mmol) in DMF (3 ml). After 2 h at 140 °C, work up and column chromatography (hexane:EtOAc, 10:1-5:1) afforded phenanthidine 114 as a colourless solid (31 mg, 99%).

R_f [hexane:EtOAc, 3:1] = 0.48; MP 104 °C (hexane); ν_max (CHCl₃)/cm⁻¹ 2957, 1332 (SO₂), 1153 (SO₂); ¹H NMR δ (360 MHz, CDCl₃) 7.32 (1H, d, J 7.5, ArH), 7.24 (1H, t, J 7.3, ArH), 7.20 (1H, t, J 7.9, ArH), 7.10 (1H, d, J 7.3, ArH), 6.03 (1H, dd, J 10.0, 5.6, CH=CH), 5.59 (1H, d, J 10.0, CH=CH), 4.60 (1H, d, J 16.2, CHₓHᵧ), 4.43 (1H, d, J 16.2, CHₓHᵧ), 4.41 (1H, dd, J 15.5, 6.2, CHN), 3.59 (1H, tr, J 5.6, CHCH=CH), 2.87 (3H, s, CH₃), 1.64-1.60 (2H, m, CH₂), 1.15 (3H, s, CH₃), 0.94 (3H, s, CH₃); ¹³C NMR δ (90.6 MHz, CDCl₃) 138.7 (CH), 136.3 (C), 130.3 (C), 127.9 (CH, C₁₀), 127.3 (CH), 126.1 (CH), 126.0 (CH, C₇), 123.7 (CH, C₁), 49.8 (CH, C₄a), 43.3 (CH₂, C₆), 39.0 (CH₃, SO₂Me), 38.2 (CH₂, C₄), 36.6 (CH), 34.0 (C, C₃), 30.3 (CH₃), 28.3 (CH₃); m/z (FAB, THIOG) 292 ([M+H]⁺, 100 %), 291 ([M]⁺, 82), 213 (44), 197 (40), 165 (12), 130 (15), 94 (89); HRMS (FAB, THIOG) Found: [M+H]⁺ 292.1371. C₁₆H₂₂NO₂S requires 292.1371.
Experimental

N-(2-Iodo-benzyl)-cyclohex-2-enyl-amine hydrochloride 129

General procedure A was followed using 2-iodobenzylamine hydrochloride (200 mg, 0.742 mmol), MeCN (5 ml) at 0 °C. iPr₂NEt (517 µl, 2.97 mmol), 3-bromocyclohexene (86.0 µl, 0.742 mmol) and HCl (2 ml, 1 M in Et₂O, 2.00 mmol) to afford amine hydrochloride 129 as a colourless solid (287 mg, 100%).

MP 241 °C; ¹H NMR δ (360 MHz, CD₃OD) 8.05 (1H, dd, J 8.0, 1.1, ArH), 7.65 (1H, dd, J 7.7, 1.6, ArH), 7.55 (1H, td, J 7.5, 1.1, ArH), 7.23 (1H, td, J 7.9, 1.6, ArH), 6.29 (1H, m, CH=H), 5.91 (1H, dd, J 9.6, 1.4, CH=CH), 4.45 (2H, s, CH₂Ar), 4.10-4.04 (1H, m, CHN), 2.29-2.18 (3H, m, CH₂+CH₂H₂B), 1.99-1.91 (2H, m, CH₂), 1.83-1.70 (1H, m, CH₂H₂B); ¹³C NMR δ (90.6 MHz, CD₃OD) 141.9 (C), 136.8 (CH), 135.9 (C), 132.6 (CH), 132.5 (CH), 130.4 (CH), 122.7 (CH), 101.9 (C), 55.8 (CH), 54.0 (CH₂), 26.6 (CH₂), 25.6 (CH₂), 20.6 (CH₂); m/z (FAB, 3-NOBA) 314 ([M+H]⁺, 99 %), 234 (51), 217 (53), 167 (39), 154 (63), 149 (100), 130 (92); HRMS (FAB, 3-NOBA) Found: [M+H]⁺ 314.0409. C₁₃H₁₇NI requires 314.0406.

Free Amine: Rf [hexane:EtOAc, 3:1] = 0.60; νmax (CH₂Cl₂)/cm⁻¹ 3361 (NH), 1562, 1437, 1011, 748.
Experimental

(2-Iodo-benzyl)-cyclohex-2-enyl-carbamic acid tert-butyl ester 124b

To a suspension of amine hydrochloride 129 (120 mg, 0.34 mmol) in CH₂Cl₂ (5 ml) was added Et₃N (72 µl, 0.52 mmol). After 10 mins, the reaction was cooled to 0 °C, Boc₂O (112 mg, 0.52 mmol) in CH₂Cl₂ (1 ml) was added and the reaction was stirred for a further 10 mins. The reaction was warmed to r.t. and stirred for 16 h. The reaction was diluted with CH₂Cl₂ (10 ml), extracted with NaCl (3 x 10 ml, sat. aq.), dried (MgSO₄) and concentrated under reduced pressure. Flash chromatography (hexane:EtOAc, 100:1) afforded Boc-protected amine 124b as a colourless oil (60 mg, 49%).

Rf [hexane:EtOAc, 3:1] = 0.82; νmax (CHCl₃)/cm⁻¹ 2930, 1694 (C=O), 1167; ¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.80 (1H, d, J 7.9, ArH), 7.31 (1H, tr, J 7.3, ArH), 7.22 (1H, d, J 7.6, ArH), 6.92 (1H, t, J 7.3, ArH), 5.83 (1H, br s, CH=CH), 5.48 (1H, d, J 10.0, CH=CH), 4.88 (1H, br s, NCH), 4.28 (2H, br s, CH₂Ar), 2.10-1.81 (3H, m, CH₂+CH₄H₅B), 1.81-1.70 (1H, m, CH₄H₅B), 1.55-1.46 (2H, m, CH₂), 1.35 (9H, s, 3CH₃); ¹³C NMR δ (90.6 MHz, 323 K, CDCl₃) 155.7 (C), 140.9 (C), 139.0 (2xCH), 128.1 (2xCH), 127.9 (CH), 127.1 (CH), 97.2 (C), 79.8 (C), 53.2 (CH), 52.9 (CH₂), 28.2 (3xCH₃), 24.5 (2xCH₂), 21.3 (CH₂); m/z (FAB, THIOG) 414 ([M+H]+, 20 %), 359 (100), 232 (22), 217 (41); HRMS (FAB, THIOG) Found: [M+H]+ 414.0929. C₁₈H₂₅NO₂I requires 414.0932.
(2-Iodo-benzyl)-cyclohex-2-enyl-carbamic acid benzyl ester 124c

To a suspension of NaH (15 mg, 60% dispersion in mineral oil, 0.37 mmol) in DMF (4 ml) at 0 °C was added amine hydrochloride 129 (58.0 mg, 0.17 mmol) in DMF (1 ml). The solution was stirred for 30 mins then benzyl chloroformate (31 µl, 0.22 mmol) was added dropwise and the reaction was warmed to r.t. and stirred for 16 h. The reaction was diluted with Et₂O (10 ml), extracted with NaCl (3 x 10 ml, sat. aq.), dried (MgSO₄) and concentrated under reduced pressure to give the crude product. Flash chromatography (hexane:EtOAc, 100:3) afforded Cbz protected amide 124c as a colourless oil (61 mg, 82%).

Rₚ [hexane:EtOAc, 10:1] = 0.78; νₘₐₓ (CHCl₃)/cm⁻¹ 1699 (C=O); ¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.80 (1H, d, J7.9, 1.5, ArH), 7.40 – 7.21 (7H, m, 7xArH), 7.18 (1H, td, J7.6, 1.5, ArH), 5.87-5.80 (1H, m, CH=CH), 5.47 (1H, d, J10.2, CH=CH), 5.15 (2H, br s, OCH₂Ar), 4.90 (1H, br s, CHN), 4.40 (1H, d, J16.9, CHₓHᵧAr), 4.33 (1H, d, J16.9, CHₓHᵧAr), 2.10-1.85 (3H, m, CH₂+CH₃Ar), 1.80-1.70 (1H, m, CH₃Ar), 1.70-1.42 (2H, m, CH₂); ¹³C NMR δ (90.6 MHz, 323 K, CDCl₃) 156.5 (C), 141.1 (C), 139.1 (2xCH), 131.8 (C), 129.9 (C), 128.2 (3xCH), 128.0 (CH), 127.7 (3xCH), 127.6 (CH), 127.2 (CH), 67.1 (CH₂), 53.8 (CH), 45.9 (CH₂), 28.1 (CH₂), 24.5 (CH₂), 21.2 (CH₂); m/z (FAB, THIOG) 448 ([M+H]⁺, 14 %), 217 (13), 171 (4), 94 (100); HRMS (FAB, 3-NOBA) Found [M+H]⁺ 448.0775. C₂₁H₂₃O₂IN requires 448.0774.
General procedure A was followed using 2-chlorobenzylamine (1.00 g, 8.28 mmol), MeCN (20 ml), iPr₂NEt (4.20 ml, 24.9 mmol), 3-bromocyclohexene (952 µl, 8.28 mmol) and HCl (10 ml, 1 M in Et₂O, 10 mmol) to afford amine hydrochloride 132 as a colourless solid (1.20 g, 66%).

**MP** 161 °C (Et₂O); **¹H NMR** δ (250 MHz, CD₃OD) 7.72-7.69 (1H, m, ArH), 7.62-7.47 (3H, m, 3xArH), 6.28-6.23 (1H, m, CH=CH), 5.90 (1H, dd, /J 10.3, 1.5, CH=CH), 4.45 (2H, s, CH₂Ar), 4.25-4.22 (1H, br s, CHN), 2.26-2.17 (3H, m, CH₂+CH₃Ar), 1.96-1.72 (3H, m, CH₂+CH₃H₃B); **¹³C NMR** δ (62.9 MHz, CD₃OD) 136.9 (CH), 136.0 (C), 133.4 (CH), 132.6 (CH), 131.2 (CH), 130.8 (C), 129.0 (CH), 122.4 (CH), 55.8 (CH), 46.6 (CH₂), 26.4 (CH₂), 25.5 (CH₂), 20.5 (CH₂); **m/z** (FAB, THIOG) 224 ([³⁷Cl-M+H]+, 39 %), 222 ([³⁵Cl-M+H]+, 100), 144 (11), 142 (34), 127 (16), 125 (47); **HRMS** (FAB, THIOG) Found: [³⁷Cl-M+H]+, 224.1026. C₁₃H₁₇N³⁷Cl requires 224.1020. Found: [³⁵Cl-M+H]+ 222.1057. C₁₃H₁₇N³⁵Cl requires 222.1050.

**Free amine:** R_f [hexane:EtOAc, 3:1] = 0.33; ν_max (MeOH/CH₂Cl₂)/cm⁻¹ 2937, 2707, 1573, 1445, 762.
**N-(2-Chloro-benzyl)-N-cyclohex-2-enyl-methanesulfonamide 130a**

General procedure B was followed using amine hydrochloride 132 (1.10 g, 4.96 mmol), CH₂Cl₂ (30 ml), Et₃N (2.10 ml, 14.9 mmol) and methanesulfonyl chloride (1.15 ml, 14.9 mmol). Flash chromatography (hexane:EtOAc, 10:1-3:1) afforded sulfonamide 130a as a colourless solid (890 mg, 60%).

**Rf** [hexane:EtOAc, 3:1] = 0.59; **MP** 89 °C (Et₂O); **ν**max (CHCl₃)/cm⁻¹ 2932, 1333 (SO₂), 1145 (SO₂); **¹H NMR** δ (250 MHz, CDCl₃) 7.68 (1H, dt, J 7.2, 1.7, ArH), 7.33-7.19 (3H, m, 3xArH), 5.99-5.93 (1H, m, CH=CH), 5.51 (1H, dt, J 10.1, 1.6, CH=CH₂), 4.66-4.59 (1H, m, NCH), 4.50 (1H, d, J 17.5, CH₃H₇Ar), 4.38 (1H, d, J 17.5, CH₃H₇Ar), 2.96 (3H, s, CH₃), 2.00-1.93 (3H, m, CH₃H₅+CH₂), 1.80-1.33 (3H, m, CH₃H₅+CH₂); **¹³C NMR** δ (62.9 MHz, CDCl₃) 137.0 (C), 133.7 (CH), 132.5 (C), 129.1 (CH), 128.9 (CH), 128.1 (CH), 126.8 (CH), 126.6 (CH), 55.6 (CH), 44.9 (CH₂), 39.4 (CH₃), 28.7 (CH₂), 24.2 (CH₂), 21.4 (CH₂); **m/z** (FAB, THIOG) 302 ([¹³⁷ClM+H]+, 5 %), 300 ([¹³⁵ClM+H]+), 220 (17), 127 (34), 125 (100), 109 (12); **HRMS** (FAB, THIOG) Found: [¹³⁷ClM+H]+, 302.0805. C₁₄H₁₉NO₂S¹³⁷Cl requires 302.0800. Found: [¹³⁵ClM+H]+, 300.0836. C₁₄H₁₉NO₂S²⁻Cl requires 300.0825.
**Experimental**

**Dibenzylcyclohexylamine 133**

To a suspension of amine 135 (4.62 g, 24.4 mmol) in DMF (100 ml) at 0 °C, was added NaH (2.14 g, 60% dispersion in mineral oil, 54.0 mmol) and the reaction stirred for 30 mins. Benzyl bromide (3.77 ml, 3.77 mmol) was added dropwise and the reaction warmed to r.t and stirred for 16 h. Et₂O (100 ml) was added and the organics washed with NaCl (3 x 100 ml, sat. aq.), dried (MgSO₄), concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 25:1). The resultant solid was recrystallised from EtOH (10 ml) to afford dibenzylamine 133 as a colourless solid (4.52 g, 61%).

**Rf** [hexane:EtOAc, 10:1] = 0.87; **MP** 63 °C (lit 62 °C)

**1H NMR** δ (360 MHz, CDCl₃) 7.41 (4H, d, J 6.9, 4xArH), 7.31 (4H, t, J 7.3, 4xArH), 7.23 (2H, t, J 7.3, 2xArH), 3.67 (4H, s, 2xC₄H₂), 2.51 (1H, tt, J 11.6, 3.4, NCH), 1.93 (2H, br d, J 12.6, CH₂), 1.81-1.78 (2H, m, CH₂), 1.64-1.62 (1H, m, CH₂H₈), 1.42-1.29 (2H, m, CH₂), 1.23-1.06 (3H, m, CH₂+CH₂H₈);

**13C NMR** δ (90.6 MHz, CDCl₃) 141.2 (2xC), 128.2 (4xCH), 127.9 (4xCH), 126.3 (2xCH), 57.6 (CH), 53.7 (2xCH₂), 28.5 (2xCH₂), 26.4 (CH₂), 26.1 (2xCH₂); **m/z** (EI) 279 ([M]+, 10%), 236 (18), 181 (7), 138 (11); **HRMS** (EI) Found: [M]+ 279.1979. C₂₀H₂₅N requires 279.1982.

**1H** Spectroscopic data in good agreement with the literature.}

165
6.3 Experimental for Chapter three

3-Bromo-2-methyl-thiophene 153

To a solution of diisopropylamine (6.00 ml, 42.6 mmol) in THF (20 ml) at 0 °C was added nBuLi (26.6 ml, 42.6 mmol, 1.6 M in hexanes). After addition was complete the reaction temperature was maintained at 0 °C for 30 mins. The flask was cooled to –78 °C, 3-bromothiophene (4.00 ml, 42.6 mmol) was added dropwise and the reaction warmed to 0 °C and stirred for 30 mins. The reaction was cooled again to –78 °C and methyl iodide (2.68 ml, 42.6 mmol) was added. After 30 mins the reaction was warmed to r.t. and stirred for 1 h. The reaction was diluted with Et₂O (100 ml) and washed with H₂O (3 x 50 ml). The organic phase was dried (MgSO₄) and concentrated under reduced pressure to afford methyl thiophene 153 as a grey oil (7.2 g, 99%).

R_f [hexane:EtOAc, 3:1] = 0.80; \nu_{max} (CHCl₃)/cm⁻¹ 3110, 2919, 2856, 1527, 1439, 1341; \textbf{¹H NMR} δ (360 MHz, CDCl₃) 7.08 (1H, d, J 5.4, HetH), 6.91 (1H, d, J 5.4, HetH), 2.43 (3H, s, CH₃); \textbf{¹³C NMR} δ (90.6 MHz, CDCl₃) 134.0 (C), 129.7 (CH), 127.4 (CH), 109.2 (C), 14.4 (CH₃).

\textsuperscript{¹}H and \textsuperscript{¹³}C NMR spectroscopic data in good agreement with the literature.

3-Bromo-2-bromomethyl-thiophene 154

To a solution of methyl thiophene 153 (600 mg, 2.82 mmol) in CCl₄ (15 ml) was added NBS (503 mg, 2.82 mmol) and AIBN (20 mg, cat.). The reaction was heated at 80 °C for 3 h and then cooled and filtered to remove the succinimide. The crude organics concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 100:2.5–100:5) to afford thiophenemethyl bromide 154 as a yellow oil (384 mg, 53%).

R_f [CH₂Cl₂:MeOH, 9:1] = 0.43; \nu_{max} (CHCl₃)/cm⁻¹ 2927, 1613, 1508; \textbf{¹H NMR} δ (250 MHz, CDCl₃) 7.32 (1H, d, J 5.4, HetH), 6.95 (1H, d, J 5.4, HetH), 4.69 (2H, s, CH₂); \textbf{¹³C NMR} δ (62.9 MHz, CDCl₃) 134.5 (C), 130.3 (CH), 126.6 (CH), 112.6 (C), 25.1 (CH₃).

\textsuperscript{¹}H and \textsuperscript{¹³}C NMR spectroscopic data in good agreement with the literature.
3-Bromothiophene-2-carbaldehyde 156

To a solution of diisopropylamine (7.03 ml, 50.0 mmol) in THF (80 ml) at 0 °C was added nBuLi (3.87 ml, 62.0 mmol, 1.6 M in hexanes) and the reaction stirred for 30 mins. 3-Bromothiophene (4.63 ml, 50.0 mmol) was added dropwise and the reaction was stirred for 30 mins. Freshly distilled DMF (3.87 ml, 50.0 mmol) was added dropwise and the reaction allowed to warm to r.t. and stirred for 2.5 h. The reaction was diluted with Et₂O (80 ml) and the organics washed with NH₄Cl (3 x 50 ml, sat. aq.), dried (MgSO₄), and concentrated under reduced pressure to afford aldehyde 156 as a yellow oil (8.85 g, 94%).

**Rf** [hexane:EtOAc, 3:1] = 0.64; **υmax (CHCl₃)/cm⁻¹** 1665 (C=O), 1498, 1416, 1213, 737; **¹H NMR δ (250 MHz, CDCl₃)** 9.99 (1H, d, J 1.4, COH), 7.75 (1H, dd, J 5.1, 1.4, HetH), 7.16 (1H, d, J 5.1, HetH); **¹³C NMR δ (62.9 MHz, CDCl₃)** 182.9 (C), 136.8 (C), 134.7 (CH), 131.9 (CH), 120.2 (C); **m/z** (FAB, THIOG) 283 (95), 281 (93), ([¹⁸¹BrM+H]+ 193, 96 %), ([¹⁷⁹BrM+H]+ 191, 100), 177 (19), 175 (18), 109 (17); **HRMS** (FAB, THIOG) (Found: [¹⁸¹BrM+H]+ 192.9147. C₅H₃N⁸¹BrOS requires 192.9147). (Found: [¹⁷⁹BrM+H]+ 190.9166. C₅H₃N⁷⁹BrOS requires 190.9166).

¹H and ¹³C NMR spectroscopic data in good agreement with the literature.¹⁰⁶
**Experimental**

**168**

**(3-Bromo-thiophen-2-ylmethyl)-cyclohex-2-enyl-amine 155**

*Alkylation:* To a suspension of 3-aminocyclohexene hydrochloride\(^{105}\) (53 mg, 0.39 mmol) in MeCN (5 ml) at 0 °C was added \(i\)Pr\(_2\)NEt (272 µl, 1.56 mmol), and the reaction was stirred for 5 mins. 3-Bromo-2-bromomethyl-thiophene \(154\) (100 mg, 0.39 mmol) was added and the reaction stirred for 16 h at r.t. The reaction was concentrated under reduced pressure and the residue taken up in CH\(_2\)Cl\(_2\) (5 ml) and washed with NaCl (3 x 5 ml, sat. aq.). The organics were combined, dried (MgSO\(_4\)), concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 10:1-5:1) to afford amine \(155\) as a brown oil (19 mg, 18%).

*Reductive amination:* To a suspension of 3-aminocyclohexene hydrochloride\(^{105}\) (5.64 g, 31.7 mmol) in toluene (150 ml) was added \(i\)Pr\(_2\)NEt (6.90 ml, 26.5 mmol) and the reaction was stirred for 10 mins. Aldehyde \(156\) (5.00 g, 26.5 mmol) and molecular sieves (5.00 g) were added and the reaction was heated at reflux for 16 h. The reaction was concentrated under reduced pressure, and the crude imine was dissolved in methanol (150 ml), cooled to 0 °C and Na(OAc)\(_3\)BH (33.6 g, 158.7 mmol) was added portionwise. The reaction was stirred at r.t. for 16 h then diluted with CH\(_2\)Cl\(_2\) (150 ml) and washed with NaCl (3 x 50 ml, sat. aq.). The organics were dried (MgSO\(_4\)), concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc:NH\(_3\), 100:10:0.1) to afford amine \(155\) as a brown oil (1.18 g, 16%).

\(R_f\) [hexane:EtOAc, 3:1] = 0.76; \(\nu_{max}\) (CHCl\(_3\))/cm\(^{-1}\) 3416 (NH), 1464, 1382, 1364; \(^1\)H NMR \(\delta\) (250 MHz, CDCl\(_3\)) 7.20 (1H, d, \(J=5.3\), Het\(\_\)H), 6.93 (1H, d, \(J=5.2\), Het\(\_\)H), 5.82-5.70 (2H, m, CH=CH), 4.02 (1H, d, \(J=15.1\), CH\_YHet), 3.96 (1H, d, \(J=15.1\), CH\_YHet), 3.24 (1H, br s, CHN), 2.13-1.84 (3H, m, CH\(_2\)+CH\(_3\)H\(_8\)), 1.82-1.72 (1H, m, CH\(_3\)H\(_8\)), 1.61-1.49 (2H, m, CH\(_2\)); \(^{13}\)C NMR \(\delta\) (62.9 MHz, CDCl\(_3\)) 139.3 (C), 129.9 (CH), 129.5 (CH), 129.2 (CH), 124.2 (CH), 107.9 (C), 52.0 (CH), 44.6 (CH\(_2\)), 29.3 (CH\(_2\)), 25.2 (CH\(_2\)), 20.0 (CH\(_2\)); \(m/z\) (FAB, 3-NOBA) 274 ([\(^{81}\)BrM+H]\(^+\), 63 %), 272 ([\(^{79}\)BrM+H]\(^+\), 69), 192 (78), 190 (46), 177 (80), 175 (78); \(\text{HRMS}\) (FAB, 3-NOBA) Found: [\(^{81}\)BrM+H]\(^+\), 274.0086. C\(_{11}\)H\(_{15}\)N\(^{81}\)BrS requires 274.0088.
**N-(3-Bromo-thiophen-2-ylmethyl)-N-cyclohex-2-enyl-methanesulfonamide 157**

General procedure B was followed using amine 155 (300 mg, 1.10 mmol), CH₂Cl₂ (10 ml), methanesulfonyl chloride (256 µl, 3.31 mmol) and Et₃N (465 µl, 3.31 mmol). Flash chromatography (hexane:EtOAc, 10:1–3:1) afforded sulfonamide 157 as a yellow oil (262 mg, 68%).

**S**

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**R**

Rf [hexane: EtOAc, 3:1] = 0.46; v_{max} (CHCl₃)/cm⁻¹: 1325, 1152, 745 ¹H NMR δ (360 MHz, CDCl₃) 7.26 (1H, d, J 5.4, HetH), 6.88 (1H, d, J 5.4, HetH), 6.01-5.95 (1H, m, CH=CH), 5.54-5.49 (1H, m, CH=CH), 4.56 (1H, d, J 16.8, CH₃H₃Het), 4.55-4.50 (1H, br s, CHN), 4.49 (1H, d, J 16.8, CH₃H₃Het), 2.94 (3H, s, CH₃), 2.94 (3H, s, CH), 2.06-1.94 (3H, m, CH₂+CH₃H₂B), 1.84-1.72 (1H, m, CH₂H₂B), 1.62-1.59 (2H, m, CH₂), 108.8 (C), 55.6 (CH), 42.2(CH₂), 40.3 (CH₃), 28.6 (CH₂), 24.3 (CH₂), 21.6 (CH₂); m/z (FAB, THIOG) 352[^81BrM+H]^+ (12 %), 350[^79BrM+H]^+ (15), 272 (25), 270 (37), 190 (34), 188 (56), 177 (73), 175 (74); HRMS (FAB, THIOG) Found:[^81BrM+H]^+ 349.9848. C₁₂H₁₇N[^81Br]O₂S₂ requires 349.9884.

**(5aSR,9aSR)-5-Methanesulfonyl-3a,4,5,5a,6,7,9a,9b-octahydro-thieno[2,3-c]quinoline 158 (Δ¹² isomer)**

**Cationic:** To a solution of cyclohexene 157 (50.0 mg, 0.14 mmol) in DMA (5 ml) was added Pd(OAc)₂ (1.6 mg, 7.0 μmol), PCy₃ (4.1 mg, 14.3 μmol) and MeNCY₂ (122 μl, 0.57 mmol) and the reaction was heated at 160 °C for 2 h. Flash chromatography (hexane:EtOAc, 10:1) afforded the quinoline as a colourless oil (23 mg, 60 %). ¹H NMR of this oil showed it to be 77:16:7 mixture of double bond isomers (158:159:160). **Neutral:** General procedure D was followed using cyclohexene 157 (30 mg, 0.090 mmol), palladacycle 100 (4.0 mg, 4.3 μmol) and MeNCY₂ (73 μl, 0.34 mmol). Flash chromatography (hexane:EtOAc, 100:1-10:1) afforded the quinoline as a colourless oil (17 mg, 74 %). ¹H NMR of this oil showed it to be 32:41:27 mixture of double bond isomers (158:159:160).
**Experimental**

$R_f$ [hexane:EtOAc, 3:1] = 0.41; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1447, 1325, 1151; $^1$H NMR $\delta$ (360 MHz, CDCl$_3$) 7.21 (1H, d, $J$ 5.1, HetH), 6.93 (1H, d, $J$ 5.1, HetH), 6.05-6.01 (1H, m, CH=CH), 5.83-7.78 (1H, m, CH=CH), 4.82 (1H, dd, $J$ 16.9, 0.9, CH$_X$H$_Y$Het), 4.42 (1H, dd, $J$ 16.8, 1.8, CH$_X$H$_Y$Het), 4.36-4.32 (1H, m, CHN), 3.56 (1H, br s, NCHCH), 2.86 (3H, s, CH$_3$), 2.38-2.26 (1H, m, CH$_2$H$_2$), 2.22-2.10 (1H, m, CH$_2$H$_2$), 1.84-1.78 (2H, m, CH$_2$); $^{13}$C NMR $\delta$ (90.6 MHz, CDCl$_3$) 135.8 (C), 127.8 (CH), 126.4 (CH), 125.9 (CH), 123.9 (CH), 111.28 (C), 51.4 (CH), 40.4 (CH$_2$), 39.9 (CH$_3$), 35.8 (CH), 25.2 (CH$_2$), 23.2 (CH$_2$); $m/z$ (FAB, THIOG) 270 ([M+H]$^+$, 50%), 268 (73), 214 (32), 190 (69), 188 (72), 175 (32), 163 (33); HRMS (FAB, 3-NOBA) Found: [M+H]$^+$, 270.0628. C$_{12}$H$_{16}$O$_2$NS$_2$ requires 270.0623.

Diagnostic $^1$H NMR data for 159 ($\Delta^{2,3}$ isomer)

$^1$H NMR $\delta$ (360 MHz, CDCl$_3$) 7.22 (1H, d, $J$ 5.2, HetH), 6.92 (1H, d, $J$ 5.2, HetH), 5.65-5.61 (1H, m, CH=CH), 5.52-5.48 (1H, m, CH=CH), 4.83 (1H, d, $J$ 16.3, CH$_X$H$_Y$Het), 4.51 (1H, dd, $J$ 16.3, 2.2, CH$_X$H$_Y$Het), 4.45-4.39 (1H, m, NCH), 3.29-3.25 (1H, m, NCHCH), 2.94 (3H, s, CH$_3$), 2.75-2.65 (2H, m, CH$_2$), 2.22-2.18 (2H, m, CH$_2$).

Diagnostic $^1$H NMR data for 160 ($\Delta^{3,4}$ isomer)

$^1$H NMR $\delta$ (360 MHz, CDCl$_3$) 5.87-5.80 (1H, m, CH=CH), 5.55-5.50 (1H, m, CH=CH), 4.86 (1H, br s, NCH), 4.73 (1H, d, $J$ 16.6, CH$_X$H$_Y$Het), 3.34 (1H, br s, NCHCH), 2.84 (3H, s, CH$_3$).
Experimental

General procedure F - Synthesis of aryl amide analogues

A mixture of the appropriate benzoic acid (approx. 1.00 g) and thionyl chloride (15 ml) was refluxed at 60 °C for 3 h. The thionyl chloride was removed under reduced pressure and the residue was dissolved in NH₄OH (15 ml, conc.) and stirred for 16 h at r.t. The reaction was filtered and the precipitate dried on the high vacuum line for several hours to afford the desired amide.

2-Bromo-4-methylbenzamide 162a

General procedure F was followed using 2-bromo-4-methyl benzoic acid (800 mg, 3.70 mmol) and thionyl chloride (12 ml) to afford amide 162a as a colourless solid (750 mg, 95%).

\[ \text{R} \text{f} [\text{CH}_2\text{Cl}_2:\text{MeOH, 95:5}] = 0.45; \text{MP} 171 \degree \text{C (H}_2\text{O)}, \text{lit 175} \degree \text{C}; \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3419 (\text{NH}), 1636 (\text{C}=\text{O}); {^1}\text{H NMR} \delta (250 \text{MHz, CD}_3\text{OD}) 7.46 (1\text{H}, \text{s, ArH}), 7.33 (1\text{H}, \text{d, } J 8.0, \text{ArH}), 7.19 (1\text{H, dd, } J 7.5, 0.8, \text{ArH}), 2.33 (3\text{H}, \text{s, CH}_3); {^{13}}\text{C NMR} \delta (62.9 \text{MHz, CD}_3\text{OD}) 173.4 (\text{C}), 143.1 (\text{C}), 136.6 (\text{C}), 134.7 (\text{CH}), 129.7 (\text{CH}), 129.2 (\text{CH}), 120.0 (\text{C}), 20.9 (\text{CH}_3); m/z (\text{FAB, 3-NOBA}) 216 ([^{81}\text{BrM}+\text{H}]^+, 75 \%), 214 ([^{79}\text{BrM}+\text{H}]^+, 77), 199 (10), 197 (10), 154 (100), 136 (100), 121 (27); HRMS (EI) Found: [^{81}\text{BrM}]^+, 214.9760. \text{C}_8\text{H}_8\text{ON}^{81}\text{Br requires 214.9763.}

Found: [^{79}\text{BrM}]^+, 212.9779. \text{C}_8\text{H}_8\text{ON}^{79}\text{Br requires 212.9784.}

2-Bromo-4-fluorobenzamide 162b

General procedure F was followed using 2-bromo-4-fluoro benzoic acid (1.00 g, 4.57 mmol) and thionyl chloride (15 ml) to afford amide 162b as a colourless solid (940 mg, 94%).

\[ \text{R} \text{f} [\text{CH}_2\text{Cl}_2:\text{MeOH, 95:5}] = 0.4; \text{MP} 155 \degree \text{C (H}_2\text{O}); \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3400 (\text{NH}), 1639 (\text{C}=\text{O}); {^1}\text{H NMR} \delta (360 \text{MHz, CD}_3\text{OD}) 7.50 (1\text{H, dd, } J 8.4, 5.8, \text{ArH}), 7.46 (1\text{H, dd, } J 8.6, 2.6, \text{ArH}), 7.22 (1\text{H, td, } J 8.4, 2.6, \text{ArH}); {^{13}}\text{C NMR} \delta (90.6 \text{MHz, CD}_3\text{OD}) 172.6 (\text{C}), 164.4 (1\text{C, d, } J 252.1, \text{C}), 136.5 (\text{C}), 131.7 (1\text{C, d, } J 9.0, \text{CH}), 121.7 (1\text{C, d, } J 25.1, \text{CH}), 121.2 (1\text{C, d, } J 9.9, \text{C}), 115.9 (1\text{C, d, } J 21.7, \text{CH}); m/z (\text{FAB, 3-NOBA}) 220 ([^{81}\text{BrM}+\text{H}]^+, 64 \%), 218 ([^{79}\text{BrM}+\text{H}]^+, 66), 167 (12), 165 (11), 136 (100); HRMS (EI) Found: [^{81}\text{BrM}]^+, 218.9511. \text{C}_7\text{H}_5\text{ON}^{81}\text{BrF requires 218.9513.}

Found: [^{79}\text{BrM}]^+, 216.9528. \text{C}_7\text{H}_5\text{ON}^{79}\text{BrF requires 216.9533.}
2-Bromo-5-methoxybenzamide 162c\textsuperscript{182}

General procedure F was followed using 2-bromo-5-methoxy benzoic acid (1.00 g, 4.53 mmol) and thionyl chloride (15 ml) to afford amide 162c as a colourless solid (650 mg, 65%).

R\textsubscript{f} [CH\textsubscript{2}Cl\textsubscript{2}:MeOH, 95:5] = 0.45; MP 154 °C, lit 157 °C\textsuperscript{182}; ν\textsubscript{max} (CHCl\textsubscript{3})/cm\textsuperscript{-1} 3415 (NH), 1635 (C=O); \textsuperscript{1}H NMR δ (250 MHz, CD\textsubscript{3}OD) 7.53 (1H, d, J 8.8, ArH), 7.04 (1H, d, J 3.3, ArH), 6.95 (1H, dd, J 8.8, 3.3, ArH), 3.84 (3H, s, CH\textsubscript{3}); \textsuperscript{13}C NMR δ (62.9 MHz, CD\textsubscript{3}OD) 160.1 (C), 150.8 (C), 134.7 (CH), 128.8 (C), 117.7 (CH), 115.0 (CH), 109.8 (C), 55.8 (CH\textsubscript{3}); m/z (FAB, 3-NOBA) 232 ([\textsuperscript{81}BrM+H]\textsuperscript{+}, 65 %), 230 ([\textsuperscript{79}BrM+H]\textsuperscript{+}, 67), 154 (100), 136 (100), 121 (26), 109 (42); HRMS (EI) Found: [\textsuperscript{81}BrM]\textsuperscript{+}, 230.9715. C\textsubscript{8}H\textsubscript{8}O\textsubscript{2}N\textsuperscript{81}Br requires 230.9713. Found: [\textsuperscript{79}BrM]\textsuperscript{+}, 228.9733. C\textsubscript{8}H\textsubscript{8}O\textsubscript{2}N\textsuperscript{79}Br requires 228.9733.

2-Bromo-4,5-methoxybenzamide 162d\textsuperscript{183}

General procedure F was followed using 2-bromo-4,5-methoxy benzoic acid (2.00 g, 7.66 mmol) and thionyl chloride (30 ml) to afford amide 162d as a colourless solid (1.45 g, 73%).

R\textsubscript{f} [CH\textsubscript{2}Cl\textsubscript{2}:MeOH, 95:5] = 0.49; MP 178 °C, lit 178 °C\textsuperscript{183}; ν\textsubscript{max} (CHCl\textsubscript{3})/cm\textsuperscript{-1} 3442 (NH), 1676 (C=O); \textsuperscript{1}H NMR δ (250 MHz, (CD\textsubscript{3})\textsubscript{2}SO) 7.73 (1H, br s, NH), 7.48 (1H, br s, NH), 7.14 (1H, s, ArH), 7.02 (1H, s, ArH), 3.80 (3H, s, CH\textsubscript{3}), 3.78 (3H, s, CH\textsubscript{3}); \textsuperscript{13}C NMR δ (62.9 MHz, (CD\textsubscript{3})\textsubscript{2}SO) 167.9 (C), 149.1 (C), 147.0 (C), 129.9 (C), 115.1 (CH), 111.4 (CH), 108.6 (C), 55.3 (CH\textsubscript{3}), 55.1 (CH\textsubscript{3}); m/z (FAB, 3-NOBA) 262 ([\textsuperscript{81}BrM+H]\textsuperscript{+}, 100 %), 260 ([\textsuperscript{79}BrM+H]\textsuperscript{+}, 83), 245 (100), 243 (71), 204 (23), 202 (34), 200 (24), 181 (37), 180 (26), 167 (27), 166 (30); HRMS (EI) Found: [\textsuperscript{81}BrM]\textsuperscript{+}, 260.9825. C\textsubscript{9}H\textsubscript{10}O\textsubscript{3}N\textsuperscript{79}Br requires 260.9818. Found: [\textsuperscript{79}BrM]\textsuperscript{+}, 258.9838. C\textsubscript{9}H\textsubscript{10}O\textsubscript{3}N\textsuperscript{79}Br requires 258.9839.
1-Bromo-naphthalene-2-carboxamide 162e\textsuperscript{184}

General procedure F was followed using 1-bromo-2-naphthoic acid (1.00 g, 3.98 mmol) and thionyl chloride (15 ml) to afford amide 162e as a colourless solid (995 mg, 99%).

R\textsubscript{f} [CH\textsubscript{2}Cl\textsubscript{2}:MeOH, 95:5] = 0.67; MP 202 °C (H\textsubscript{2}O); \( \nu_{\text{max}} \) \text{ (CHCl\textsubscript{3})/cm\textsuperscript{-1}} 3440 (NH), 1678 (C=O); \textsuperscript{1}H NMR \( \delta \) (250 MHz, (CD\textsubscript{3})\textsubscript{2}SO) 8.20 (1H, d, \( J \ 7.5, \text{ArH} \)), 8.17 (1H, br s, NH), 8.14 (2H, br s, 2xArH), 7.88 (1H, br s, NH), 7.84 (1H, td, \( J \ 6.8, 1.5, \text{ArH} \)), 7.79 (1H, td, \( J \ 6.8, 1.5, \text{ArH} \)), 7.62 (1H, d, \( J \ 6.8, \text{ArH} \)); \textsuperscript{13}C NMR \( \delta \) (62.9 MHz, (CD\textsubscript{3})\textsubscript{2}SO) 169.4 (C), 137.7 (C), 133.4 (C), 130.8 (C), 128.1 (2xCH), 127.7 (CH), 127.0 (CH), 126.4 (CH), 124.6 (CH), 117.8 (C); m/z (FAB, 3-NOBA) 252 ([\textsuperscript{81}BrM+H]\textsuperscript{+}, 76 %), 250 ([\textsuperscript{79}BrM+H]\textsuperscript{+}, 90), 235 (12), 233 (13), 154 (100), 149 (26), 138 (41), 136 (97), 107 (46); HRMS (EI +ve) Found: [\textsuperscript{81}BrM]\textsuperscript{+}, 250.9765. C\textsubscript{11}H\textsubscript{8}\textsuperscript{81}BrNO requires 250.9763. Found: [\textsuperscript{79}BrM]\textsuperscript{+}, 248.9782. C\textsubscript{11}H\textsubscript{8}\textsuperscript{79}BrNO requires 248.9784.

\textsuperscript{1}H and \textsuperscript{13}C NMR data in good agreement with the literature.\textsuperscript{184}

3-Bromothiophene-2-carboxamide 162f\textsuperscript{185}

General procedure F was followed using 3-bromothiophene-2-carboxylic acid (1.00 g, 4.88 mmol) and thionyl chloride (15 ml) to afford amide 162f as a beige solid (923 mg, 93%).

R\textsubscript{f} [CH\textsubscript{2}Cl\textsubscript{2}:MeOH, 95:5] = 0.59; MP 102 °C, lit 103 °C\textsuperscript{185}; \( \nu_{\text{max}} \) \text{ (CHCl\textsubscript{3})/cm\textsuperscript{-1}} 3432 (NH), 1642 (C=O), 1429; \textsuperscript{1}H NMR \( \delta \) (250 MHz, CD\textsubscript{3}OD) 7.71 (1H, d, \( J \ 5.5, \text{HetH} \)), 7.16 (1H, d, \( J \ 5.5, \text{HetH} \)); \textsuperscript{13}C NMR \( \delta \) (62.9 MHz, CD\textsubscript{3}OD) 167.0 (C), 143.0 (C), 134.1 (C), 132.7 (CH), 131.0 (CH); m/z (FAB, 3-NOBA) 208 ([\textsuperscript{81}BrM+H]\textsuperscript{+}, 66 %), 206 ([\textsuperscript{79}BrM+H]\textsuperscript{+}, 65), 154 (100), 138 (32), 137 (70), 136 (85); HRMS (EI) Found: [\textsuperscript{81}BrM]\textsuperscript{+}, 206.9169. C\textsubscript{5}H\textsubscript{4}ON\textsuperscript{81}BrS requires 206.9171. Found: [\textsuperscript{79}BrM]\textsuperscript{+}, 204.9190. C\textsubscript{5}H\textsubscript{4}ON\textsuperscript{79}BrS requires 204.9191.

\textsuperscript{1}H NMR data in good agreement with the literature.\textsuperscript{185}
2-Bromo-5-nitro-benzamide 162g

General procedure F was followed using 2-bromo-5-nitrobenzoic acid (2.00 g, 8.13 mmol) and thionyl chloride (30 ml) to afford amide 162g as a colourless solid (1.99 g, 99%).

R_f [CH_2Cl_2:MeOH, 95:5] = 0.63; MP 168 °C, lit 197-198 °C (EtOH); \( \nu_{\text{max}} \) (CHCl_3)/cm\(^{-1}\) 3420 (NH), 1654 (C=O); \(^1\)H NMR \( \delta \) (250 MHz, (CD_3)_2SO) 8.19 (1H, s, ArH), 8.17 (1H, dd, J 8.7, 2.8, ArH), 8.16 (1H, br s, NH), 7.98 (1H, td, J 8.8, 1.4, ArH), 7.88 (1H, br s, NH); \(^{13}\)C NMR \( \delta \) (62.9 MHz, (CD_3)_2SO) 167.5 (C), 146.8 (C), 140.6 (C), 134.9 (CH), 126.8 (C), 125.4 (CH), 123.4 (CH); m/z (FAB, 3-NOBA) 247 ([\(^{81}\)BrM+H]^+, 32 %), 245 ([\(^{79}\)BrM+H]^+, 33), 167 (22), 154 (100); HRMS (EI) Found: [\(^{81}\)BrM]^+, 245.9461. \( C_7H_5^{81}\)BrN_2O_3 \text{ requires} 245.9458. Found: [\(^{79}\)BrM]^+, 243.9485. \( C_7H_5^{79}\)BrN_2O_3 \text{ requires} 243.9478.

\(^1\)H and \(^{13}\)C spectroscopic data in agreement with literature.

3-Bromoindole-2-carboxylic acid amide 162h

General procedure F was followed using 3-bromo-2-carboxylic acid (1.00 g, 4.17 mmol) and thionyl chloride (15 ml) to afford amide 162h as a yellow solid (885 mg, 89%).

R_f [CH_2Cl_2:MeOH, 95:5] = 0.66; MP 173 °C; \( \nu_{\text{max}} \) ((CH_3)_2SO)/cm\(^{-1}\) 3452 (NH), 1672 (C=O), 1619 (C=O); \(^1\)H NMR \( \delta \) (250 MHz, (CD_3)_2SO) 12.0 (1H, br s, NH), 7.88 (1H, br s, NH), 7.46 (2H, t, J 7.8, 2xArH), 7.31 (1H, br s, NH), 7.33-7.27 (1H, m, ArH), 7.17 (1H, t, 8.1, ArH); \(^{13}\)C NMR \( \delta \) (62.9 MHz, (CD_3)_2SO) 161.2 (C), 134.9 (C), 128.3 (C), 126.6 (C), 124.8 (CH), 120.8 (CH), 119.5 (CH), 112.7 (CH), 90.7 (C); m/z (FAB, 3-NOBA) 241 ([\(^{81}\)BrM+H]^+, 61 %), 239 ([\(^{79}\)BrM+H]^+, 61), 223 (46), 221 (44), 165 (37), 152 (55), 138 (64), 125 (43), 109 (73); HRMS (ES, 3-NOBA) Found: [\(^{79}\)BrM]^+, 238.9814. \( C_9H_8^{79}\)BrN_2O requires 238.9815.
**Experimental**

2-(2'-bromophenyl)acetamide 162j\(^{187}\)

![Structural formula of 2-(2'-bromophenyl)acetamide 162j]

General procedure F was followed using 2-bromophenethyl carboxylic acid (3.00 g, 14.0 mmol) and thionyl chloride (30 ml) to afford amide 162j as a colourless solid (2.20 g, 74%).

**Rf** [CH\(_2\)Cl\(_2\): MeOH, 95:5] = 0.65; **MP** 184 °C (lit 184-186 °C\(^{187}\)); **v\(_{\text{max}}\)** ((CH\(_3\))\(_2\)SO)/cm\(^{-1}\) 3452 (NH), 1683 (C=O), 1635 (C=O); **\(^1\)H NMR** δ (250 MHz, (CD\(_3\))\(_2\)SO) 7.58 (1H, d, J 7.5, ArH), 7.47 (1H, br s, NH), 7.38-7.29 (2H, m, 2xArH), 7.19 (1H, dd, J 8.0, 2.8, ArH), 7.17 (1H, dd, J 7.8, 2.5, ArH), 7.00 (1H, br s, NH);

**13C NMR** δ (62.9 MHz, (CD\(_3\))\(_2\)SO) 170.2 (C), 135.4 (C), 131.5 (CH), 131.3 (CH), 127.8 (CH), 126.8 (CH), 123.8 (C), 41.4 (CH\(_2\)); **m/z** (FAB, 3-NOBA) 216 ([\(^{81}\)BrM+H]\(^+\), 72%), 214 ([\(^{79}\)BrM+H]\(^+\), 72%), 180 (21), 171 (52), 169 (61), 154 (77), 150 (41), 136 (79); **HRMS** (ESI+) Found: [\(^{79}\)BrM+NH\(_4\)]\(^+\), 231.0128. C\(_8\)H\(_{12}\)\(^{79}\)BrN\(_2\)O requires 231.0128.

2-Bromo-4-methyl benzonitrile 163a\(^{188}\)

![Structural formula of 2-Bromo-4-methyl benzonitrile 163a]

A mixture of amide 162a (750 mg, 3.50 mmol) and thionyl chloride (5 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile 163a as a colourless solid (500 mg, 73%).

**Rf** [hexane:EtOAc, 3:1] = 0.75; **MP** 55 °C, lit 56 °C\(^{188}\); **v\(_{\text{max}}\)** (CHCl\(_3\))/cm\(^{-1}\) 3408, 2230 (CN); **\(^1\)H NMR** δ (250 MHz, CD\(_3\)OD) 7.38-7.37 (2H, m, 2xArH), 7.34 (1H, dq, J 8.0, 1.5, ArH), 2.43 (3H, s, CH\(_3\)); **13C NMR** δ (62.9 MHz, CD\(_3\)OD) 146.8 (C), 134.6 (CH), 134.2 (CH), 129.3 (CH), 124.9 (C), 117.5 (C), 112.9 (C), 20.8 (CH\(_3\)); **m/z** (FAB, 3-NOBA) 198 ([\(^{81}\)BrM+H]\(^+\), 47%), 196 ([\(^{79}\)BrM+H]\(^+\), 48), 167 (13), 165 (12), 154 (100); **HRMS** (ES, 3-NOBA) Found: [\(^{81}\)BrM]\(^+\), 196.9656. C\(_8\)H\(_6\)\(^{81}\)BrN requires 196.9658. Found: [\(^{79}\)BrM]\(^+\), 194.9678. C\(_8\)H\(_6\)\(^{79}\)BrN requires 194.9678.
2-Bromo-4-fluorobenzonitrile 163b

A mixture of amide 162b (940 mg, 4.30 mmol) and thionyl chloride (6 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile 163b as a colourless solid (840 mg, 97%).

R<sub>f</sub> [hexane:EtOAc, 3:1] = 0.78; MP 76 °C (EtOH); <i>υ</i><sub>max</sub> (CHCl<sub>3</sub>)/cm<sup>-1</sup> 2228 (CN); <sup>1</sup>H NMR δ (360 MHz, CD<sub>3</sub>OD) 7.88 (1H, dd, 8.6, 5.4, ArH), 7.69 (1H, dd, J 8.3, 2.5, ArH), 7.35 (1H, td, J 8.6, 2.5, ArH); <sup>13</sup>C NMR δ (90.6 MHz, CD<sub>3</sub>OD) 166.4 (1C, d, J 259.3, C), 138.0 (1C, d, J 10.1, CH), 127.6 (1C, d, J 10.3, C), 122.5 (1C, d, J 26.1, CH), 117.6 (C), 117.3 (1C, d, J 22.9, CH), 113.5 (C); <i>m/z</i> (FAB, 3-NOBA) 202 ([<sup>81</sup>BrM+H]<sup>+</sup>, 3 %), 200 ([<sup>79</sup>BrM+H]<sup>+</sup>, 2), 154 (64), 121 (11); HRMS (EI) Found: [<sup>81</sup>BrM]<sup>+</sup>, 200.9407. C<sub>7</sub>H<sub>3</sub>81BrFN requires 200.9407. Found: [<sup>79</sup>BrM]<sup>+</sup>, 198.9422. C<sub>7</sub>H<sub>3</sub>79BrFN requires 198.9427.

2-Bromo-5-methoxybenzonitrile 163c<sup>189</sup>

A mixture of amide 162c (630 mg, 2.74 mmol) and thionyl chloride (3 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile 163c as a colourless solid (510 mg, 88%).

R<sub>f</sub> [hexane:EtOAc, 3:1] = 0.74; MP 95 °C, lit 98.5-99.5 °C<sup>189</sup>; <i>υ</i><sub>max</sub> (CHCl<sub>3</sub>)/cm<sup>-1</sup> 3420, 2229 (CN); <sup>1</sup>H NMR δ (250 MHz, CD<sub>3</sub>OD) 7.67 (1H, d, J 9.0, ArH), 7.38 (1H, d, J 3.1, ArH), 7.18 (1H, dd, J 9.0, 3.1, ArH), 3.89 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR δ (62.9 MHz, CD<sub>3</sub>OD) 161.3 (C), 134.9 (CH), 121.9 (CH), 120.0 (CH), 117.6 (C), 116.7 (C), 115.7 (C), 56.2 (CH<sub>3</sub>); <i>m/z</i> (FAB, 3-NOBA) 214 ([<sup>81</sup>BrM+H]<sup>+</sup>, 8 %), 212 ([<sup>79</sup>BrM+H]<sup>+</sup>, 8), 167 (20), 165 (26), 154 (100); HRMS (EI) Found: [<sup>81</sup>BrM]<sup>+</sup>, 212.9604. C<sub>8</sub>H<sub>6</sub>81BrNO requires 212.9607. Found: [<sup>79</sup>BrM]<sup>+</sup>, 210.9622. C<sub>8</sub>H<sub>6</sub>79BrNO requires 210.9627.
2-Bromo-4,5-methoxybenzonitrile 163d\textsuperscript{190}

A mixture of amide 162d (1.25 g, 4.81 mmol) and thionyl chloride (30 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile 163d as a colourless solid (1.15 g, 99%).

R_f [hexane:EtOAc, 3:1] = 0.5; MP 113 °C (EtOH), lit 117 °C\textsuperscript{190}; ν\textsubscript{max} (CHCl\textsubscript{3})/cm\textsuperscript{-1} 2229 (CN); \textsuperscript{1}H NMR δ (250 MHz, (CD\textsubscript{3})\textsubscript{2}SO) 7.49 (1H, s, ArH), 7.39 (1H, s, ArH), 3.87 (3H, s, C\textsubscript{H}\textsubscript{3}), 3.81 (3H, s, C\textsubscript{H}\textsubscript{3}); \textsuperscript{13}C NMR δ (90.6 MHz, (CD\textsubscript{3})\textsubscript{2}SO) 153.4 (C), 148.5 (C), 117.9 (C), 116.9 (C), 116.2 (CH), 115.9 (CH), 105.4 (C), 56.8 (CH\textsubscript{3}), 56.3 (CH\textsubscript{3}); m/z (FAB, 3-NOBA) 244 ([\textsuperscript{81}BrM+H]\textsuperscript{+}, 27 %), 242 ([\textsuperscript{79}BrM+H]\textsuperscript{+}, 42), 167 (16), 154 (98), 152 (17), 150 (15), 149 (49), 137 (82), 136 (74); HRMS (EI) Found: [\textsuperscript{81}BrM]\textsuperscript{+}, 242.9708. C\textsubscript{9}H\textsubscript{8}N\textsubscript{81}BrNO\textsubscript{2} requires 242.9713. Found: [\textsuperscript{79}BrM]\textsuperscript{+}, 240.9726. C\textsubscript{9}H\textsubscript{8}N\textsubscript{79}BrNO\textsubscript{2} requires 240.9733.

1-Bromo-2-naphthalene-2-carbonitrile 163e\textsuperscript{191}

A mixture of amide 162e (950 mg, 3.80 mmol) and thionyl chloride (6 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile 163e as a colourless solid (839 mg, 95%).

R_f [hexane:EtOAc, 3:1] = 0.83; MP 91 °C (EtOH), lit 93 °C\textsuperscript{191}; ν\textsubscript{max} (CHCl\textsubscript{3})/cm\textsuperscript{-1} 2226 (CN), 1580 (C=C), 1560 (C=C); \textsuperscript{1}H NMR δ (250 MHz, CD\textsubscript{2}OD) 8.33-8.29 (1H, m, ArH), 8.04-7.98 (2H, m, 2xArH), 7.80-7.72 (2H, m, 2xArH), 7.66 (1H, d, J 8.5, ArH); \textsuperscript{13}C NMR δ (62.9 MHz, CD\textsubscript{2}OD) 136.3 (C), 132.1 (C), 130.2 (CH), 129.6 (CH), 129.5 (CH), 129.2 (CH), 128.3 (CH), 128.2 (C), 127.9 (CH), 118.2 (C), 113.9 (C); m/z (FAB, 3-NOBA) 234 ([\textsuperscript{81}BrM+H]\textsuperscript{+}, 27 %), 232 ([\textsuperscript{79}BrM+H]\textsuperscript{+}, 27), 154 (99), 138 (48), 136 (100); HRMS (EI +ve) Found: [\textsuperscript{81}BrM]\textsuperscript{+}, 232.9656. C\textsubscript{11}H\textsubscript{6}N\textsubscript{81}Br requires 232.9658. Found: [\textsuperscript{79}BrM]\textsuperscript{+}, 230.9680. C\textsubscript{11}H\textsubscript{6}N\textsubscript{79}Br requires 230.9678.
Experimental

3-Bromothiophene-2-carbonitrile 163f

A mixture of amide 162f (920 mg, 4.48 mmol) and thionyl chloride (3 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile 163f as a brown oil (840 mg, 99%).

Rf [hexane:EtOAc, 3:1] = 0.52; v_max (CHCl_3)/cm^{-1} 3109, 2221 (CN); ^1H NMR δ (250 MHz, CDCl_3) 7.53 (1H, d, J 5.3, HetH), 7.07 (1H, d, J 5.3, HetH); ^13C NMR δ (62.9 MHz, CDCl_3) 132.7 (CH), 130.7 (CH), 121.7 (C), 112.6 (C), 108.5 (C); m/z (FAB, 3-NOBA) 189 ([^{81}BrM+H]^+, 3 %), 187 ([^{79}BrM+H]^+, 1), 165 (12), 154 (100), 149 (30), 138 (80), 137 (98), 136 (100), 125 (29); HRMS (FAB, 3-NOBA) Found: [^{81}BrM+H]^+, 188.9066. C_5H_2^{81}BrNS requires 188.9065. Found: [^{79}BrM+H]^+, 186.9086. C_5H_2^{79}BrNS requires 186.9086.

^1H NMR data in good agreement with the literature.

2-Bromo-5-nitro-benzonitrile 163g

A mixture of amide 162g (1.30 g, 5.29 mmol) and thionyl chloride (30 ml) was refluxed at 60 °C for 3 h. The reaction was concentrated under reduced pressure to afford nitrile 163g as a colourless solid (1.20 g, 99%).

Rf [CH_2Cl_2:MeOH, 95:5] = 0.91; MP 108 °C, lit 117 °C (H_2O); v_max (CHCl_3)/cm^{-1} 2253 (CN); ^1H NMR δ (250 MHz, (CD_3)_2SO) 8.85 (1H, d, J 2.7, ArH), 8.42 (1H, dd, J 8.9, 2.7, ArH), 8.20 (1H, d, J 8.9, ArH); ^13C NMR δ (90.6 MHz, (CD_3)_2SO) 147.8 (C), 135.6 (CH), 133.1 (C), 130.8 (CH), 130.1 (CH), 116.9 (C), 116.7 (C).
General procedure G - Reduction of aryl nitrile analogues

To a suspension of LiAlH$_4$ (2 eq) in Et$_2$O (10 ml) was added AlCl$_3$ (2 eq) and the reaction stirred for 10 mins at r.t. The mixture was cooled to 0 °C and the appropriate nitrile (1 eq) was added portionwise. The reaction was stirred at r.t for 30 mins then heated at 40 °C for 18 h. The reaction was quenched by the addition of Na$_2$SO$_4$.5H$_2$O portionwise, then it was filtered and the filtrate stirred vigorously with potassium sodium tartrate (100 ml, sat. aq.) for 1 h. The Et$_2$O layer was separated and the aqueous phase extracted with Et$_2$O (3 x 60 ml). The combined organic phases were dried (MgSO$_4$) and concentrated under reduced pressure. The residue was taken up in CH$_2$Cl$_2$ (1 ml), and HCl in Et$_2$O (20.0 ml, 1 M in Et$_2$O) added. The precipitate was removed by filtration and dried to afford the desired amine hydrochloride.

2-Bromo-4-methylbenzylamine hydrochloride 164a

General procedure G was followed using LiAlH$_4$ (186 mg, 4.90 mmol), Et$_2$O (5 ml), AlCl$_3$ (654 mg, 4.90 mmol) and nitrile 163a (480 mg, 2.45 mmol), to afford amine hydrochloride 164a as a colourless solid (465 mg, 80%).

MP 249 °C (Et$_2$O); $^1$H NMR δ (250 MHz, CD$_3$OD) 7.53 (1H, s, ArH), 7.43 (1H, d, J 8.0, ArH), 7.27 (1H, d, J 8.0, ArH), 4.23 (2H, s, CH$_2$), 2.35 (3H, s, CH$_3$); $^{13}$C NMR δ (62.9 MHz, CD$_3$OD) 142.8 (C), 134.4 (CH), 131.5 (CH), 130.5 (C), 129.9 (CH), 124.7 (C), 43.6 (CH$_2$), 20.5 (CH$_3$); m/z (FAB, 3-NOBA) 202 ([$^{81}$BrM+H]$^+$, 91 %), 200 ([$^{79}$BrM+H]+, 93), 185 (95), 183 (95),154 (51); HRMS (EI) Found: [$^{81}$BrM]$^+$, 200.9969. C$_8$H$_{10}^{81}$BrN requires 200.9971. Found: [$^{79}$BrM]$^+$, 198.9985 C$_8$H$_{10}^{79}$BrN requires 198.9991. Free Amine: R$_f$ [CH$_2$Cl$_2$;MeOH, 95:5] = 0.46; $\nu_{max}$ (CHCl$_3$)/cm$^{-1}$ 3371 (NH), 3304 (NH), 2922, 1605, 1488; $^1$H NMR δ (250 MHz, CDCl$_3$) 7.33 (1H, s, ArH), 7.19 (1H, d, J 7.7, ArH), 7.05 (1H, d, J 7.7, ArH), 3.81 (2H, s, CH$_2$), 2.27 (3H, s, CH$_3$); $^{13}$C NMR δ (62.9 MHz, CDCl$_3$) 138.4 (C), 137.6 (C), 132.4 (CH), 128.0 (CH), 127.6 (CH), 122.4 (C), 45.8 (CH$_3$), 19.8 (CH$_2$).
2-Bromo-4-fluorobenzylamine hydrochloride 164b

General procedure G was followed using LiAlH₄ (95 mg, 2.50 mmol), Et₂O (5 ml), AlCl₃ (334 mg, 2.50 mmol) and nitrile 163b (249 mg, 1.25 mmol) to afford amine hydrochloride 164b as a colourless solid (210 mg, 70%).

**MP** 251 °C (Et₂O); **¹H NMR** δ (250 MHz, CD₃OD) 7.63 (1H, dd, J 8.8, 6.0, ArH), 7.58 (1H, dd, J 8.3, 2.8, ArH), 7.28 (1H, td, J 8.5, 2.8, ArH), 4.29 (2H, s, CH₂); **¹³C NMR** δ (62.9 MHz, CD₃OD) 163.5 (1C, d, J 252.4, C), 133.1 (1C, d, J 9.0, CH), 129.6 (C), 125.3 (1C, d, J 10.3, C), 120.9 (1C, d, J 25.1, CH), 115.9 (1C, d, 21.6, CH), 42.8 (CH₂); **m/z** (FAB, 3-NOBA) 206 ([⁸¹BrM+H]+, 14 %), 204 ([⁷⁹BrM+H]+, 17), 189 (37), 187 (40), 149 (47); **HRMS** (ESI, +, CH₂Cl₂/MeOH/NH₄OAc) Found: [M+H]+, 203.9820. C₇H₈NF₂Br requires 203.9819.

Free Amine: **Rf** [CH₂Cl₂:MeOH, 95:5] = 0.46; **υmax** (CHCl₃)/cm⁻¹ 3285 (NH), 2926, 1597, 1484; **¹H NMR** δ (250 MHz, CDCl₃) 7.33 (1H, dd, J 8.5, 6.0, ArH), 7.26 (1H, dd, J 8.3, 2.5, ArH), 6.98 (1H, td, J 8.3, 2.5, ArH), 3.85 (2H, s, CH₂); **¹³C NMR** δ (62.9 MHz, CDCl₃) 160.6 (1C, d, J 249.3, C), 137.4 (C), 129.1 (1C, d, J 7.9, CH), 122.6 (1C, d, J 9.6, C), 119.1 (1C, d, J 24.8, CH), 113.9 (1C, d, J 20.8, CH), 45.4 (CH₂).
Experimental

2-Bromo-5-methoxybenzylamine hydrochloride 164c  

General procedure G was followed using LiAlH₄ (36.0 mg, 0.94 mmol), Et₂O (1.00 ml), AlCl₃ (432 mg, 0.94 mmol) and nitrile 163c (100 mg, 0.47 mmol), to afford amine hydrochloride 164c as a colourless solid (301 mg, 74%).

MP 201 °C; ¹H NMR δ (250 MHz, CD₃OD) 7.62 (1H, d, J 8.9, ArH), 7.19 (1H, d, J 3.0, ArH), 6.99 (1H, dd, J 8.9, 3.0, ArH), 4.27 (2H, s, CH₂), 3.87 (3H, s, CH₃), ¹³C NMR δ (62.9 MHz, CD₃OD) 160.6 (C), 146.3 (C), 134.7 (CH), 117.2 (CH), 117.1 (CH), 114.5 (C), 55.7 (CH₃), 43.7 (CH₂); m/z (FAB, 3-NOBA) 218 ([¹⁸¹BrM+H]⁺, 51 %), 216 ([¹⁷⁹BrM+H]⁺, 62), 201 (39), 199 (40), 154 (100), 149 (43), 137 (59); HRMS (EI) Found: [¹⁸¹BrM]⁺, 216.9915. C₈H₁₀ON¹⁸¹Br requires 216.9920. Found: [¹⁷⁹BrM]⁺, 214.9935. C₈H₁₀ON¹⁷⁹Br requires 214.9940. Free Amine: Rf [CH₂Cl₂:MeOH, 95:5] = 0.36; νmax (CHCl₃)/cm⁻¹ 3370 (NH), 1593, 1573, 1470, 1242; ¹H NMR δ (250 MHz, CDCl₃) 7.40 (1H, d, J 8.7, ArH), 6.93 (1H, d, J 3.0, ArH), 6.66 (1H, dd, J 8.7, 3.0, ArH), 3.84 (2H, s, CH₂), 3.78 (3H, s, CH₃), ¹³C NMR δ (62.9 MHz, CDCl₃) 158.8 (C), 142.7 (C), 132.9 (CH), 114.3 (CH), 113.4 (CH), 113.2 (C), 55.0 (CH₃), 46.6 (CH₂).
2-Bromo-4,5-methoxybenzylamine hydrochloride 164d

General procedure G was followed using LiAlH₄ (345 mg, 4.50 mmol), Et₂O (20 ml), AlCl₃ (1.21 g, 9.00 mmol) and nitrile 163d (1.10 g, 4.50 mmol), to afford amine hydrochloride 164d as a colourless solid (829 mg, 65%).

**MP** 194 °C; **¹H NMR** δ (250 MHz, CD₃OD) 7.25 (1H, s, ArH), 7.21 (1H, s, ArH), 4.25 (2H, s, CH₂), 3.90 (3H, s, CH₃), 3.88 (3H, s, CH₃); **¹³C NMR** δ (62.9 MHz, CD₃OD) 151.8 (C), 150.2 (C), 125.2 (C), 116.8 (CH), 115.4 (C), 114.9 (CH), 56.5 (2xCH₃), 43.7 (CH₂); **m/z** (FAB, 3-NOBA) 248 ([⁸¹BrM+H]+, 11 %), 246 ([⁷⁹BrM+H]+, 20), 231 (37), 229 (37), 154 (82), 149 (64), 136 (100); **HRMS (EI)** Found: [⁸¹BrM]+, 247.0016. C₉H₁₂O₂N⁸¹Br requires 247.0026. Found: [⁷⁹BrM]+, 245.0034. C₉H₁₂O₂N⁷⁹Br requires 245.0046. Free Amine: **Rf** [CH₂Cl₂:MeOH, 95: 5] = 0.54; **υmax** (CHCl₃)/cm⁻¹ 3368 (NH), 2935, 2841, 1602, 1505; **¹H NMR** δ (250 MHz, CDCl₃) 7.20 (1H, s, ArH), 7.11 (1H, s, ArH), 4.08 (3H, s, CH₃), 4.05 (3H, s, CH₃), 4.03 (2H, s, CH₂), 1.75 (2H, br s, NH₂); **¹³C NMR** δ (62.9 MHz, CDCl₃) 148.2 (C), 148.0 (C), 133.9 (C), 115.3 (CH), 112.8 (CH), 111.7 (CH), 55.8 (CH₃), 55.7 (CH₃), 46.2 (CH₂).

¹H and ¹³C NMR data in good agreement with the literature.
Experimental

(1-Bromo-2-naphthalen-2-yl) methyl amine hydrochloride 164e

General procedure G was followed using LiAlH$_4$ (261 mg, 6.89 mmol), Et$_2$O (10 ml), AlCl$_3$ (920 mg, 6.89 mmol) and nitrile 163e (800 mg, 3.45 mmol), to afford amine hydrochloride 164e as a colourless solid (504 mg, 55%).

MP 270 °C (Et$_2$O); $^1$H NMR $\delta$ (250 MHz, CD$_3$OD) 8.37 (1H, d, $J$ 9.3, ArH), 8.01 (1H, t, $J$ 8.5, ArH), 7.98 (1H, d, $J$ 9.5, ArH), 7.75-7.63 (3H, m, 3xArH), 4.54 (2H, s, CH$_2$); $^{13}$C NMR $\delta$ (62.9 MHz, CD$_3$OD) 136.5 (C), 133.9 (C), 132.3 (C), 130.4 (CH), 130.0 (CH), 129.9 (CH), 129.3 (CH), 128.8 (CH), 128.4 (CH), 126.4 (C) 45.7 (CH$_2$); m/z (FAB, 3-NOBA) 238 ([$^{81}$BrM+H]$^+$, 77 %), 236 ([$^{79}$BrM+H]$^+$, 43), 221 (97), 219 (97)167 (37), 165 (28), 154 (100); HRMS (EI +ve) Found: [$^{81}$BrM]$^+$, 236.9974. C$_{11}$H$_{10}$N$_{81}$Br requires 236.9971. Free Amine: $R_f$ [CH$_2$Cl$_2$:MeOH, 95:5] = 0.94; $\nu_{\max}$ (CHCl$_3$)/cm$^{-1}$ 3364 (NH), 1596 (NH$_2$); $^1$H NMR $\delta$ (250 MHz, CDCl$_3$) 8.15 (1H, d, $J$ 8.5, ArH), 7.62 (2H, t, $J$ 7.5, 2xArH), 7.42-7.29 (3H, m, 3xArH), 3.96 (2H, s, CH$_2$); $^{13}$C NMR $\delta$ (62.9 MHz, CDCl$_3$) 140.0 (C), 133.5 (C), 132.2 (C), 127.9 (CH), 127.8 (CH), 127.2 (CH), 126.9 (CH), 126.4 (CH), 126.0 (CH), 122.9 (C), 47.7 (CH$_2$).
Experimental

(3-Bromo-2-thiophen-2-yl) methylamine hydrochloride 164f

General procedure G was followed using LiAlH₄ (263 mg, 6.92 mmol), Et₂O (7 ml), AlCl₃ (924 mg, 6.92 mmol) and nitrile 163f (651 mg, 3.46 mmol) to afford amine hydrochloride 164f as a beige solid (700 mg, 89%).

MP 187 °C; ¹H NMR δ (250 MHz, CD₃OD) 7.68 (1H, d, J 5.3, HetH), 7.14 (1H, d, J 5.3, ArH), 4.36 (2H, s, CH₂); ¹³C NMR δ (62.9 MHz, CD₃OD) 130.9 (CH), 130.4 (C), 128.8 (CH), 113.7 (C), 37.2 (CH₂); m/z (FAB, 3-NOBA) 194 ([¹⁸¹BrM+H]⁺, 20 %), 192 ([¹⁷⁹BrM+H]⁺, 28), 177 (33), 175 (32), 154 (96), 138 (34), 137 (59), 136 (81); HRMS (EI) Found: [¹⁸¹BrM]⁺, 192.9376. C₅H₆¹¹BrNS requires 192.9378. Found: [¹⁷⁹BrM]⁺, 190.9393. C₅H₆¹⁷BrNS requires 190.9399. Free Amine: Rf [CH₂Cl₂:MeOH, 95:5] = 0.80; v_max (CHCl₃)/cm⁻¹ 3370 (NH), 1594, 1344; ¹H NMR δ (250 MHz, CDCl₃) 7.30 (1H, d, J 5.3, HetH), 7.06 (1H, d, J 5.3, HetH), 4.09 (2H, s, CH₂), 1.86 (2H, br s, NH₂); ¹³C NMR δ (62.9 MHz, CDCl₃) 140.7 (C), 129.5 (CH), 123.3 (CH), 106.9 (C), 39.9 (CH₂).
2-(2’-Bromophenyl) ethylamine hydrochloride 164j\[^{195}\]

To a suspension of LiAlH\(_4\) (709 mg, 18.7 mmol) in THF (15 ml) at 0 °C was added a solution of amide 162j in THF (2 ml) dropwise. The reaction was stirred at r.t. for 30 mins then heated at 70 °C for 18 h. The reaction was quenched by the addition of Na\(_2\)SO\(_4\).5H\(_2\)O portionwise, then it was filtered and the filtrate stirred vigorously with potassium sodium tartrate (50 ml, sat. aq.) for 1 h. The Et\(_2\)O layer was separated and the aqueous phase extracted with Et\(_2\)O (3 x 20 ml). The combined organic phases were dried (MgSO\(_4\)) and concentrated under reduced pressure. The residue was taken up in CH\(_2\)Cl\(_2\) (1 ml), and HCl in Et\(_2\)O (10.0 ml, 1 M in Et\(_2\)O) added. The precipitate was filtered and dried to afford amine hydrochloride 164j as a colourless solid (698 mg, 75%).

**MP** 203 °C; \(^1\)H NMR δ (360 MHz, CD\(_3\)OD) 7.66 (1H, dd, J 7.8, 0.6, ArH), 7.44-7.38 (2H, m, 2xArH), 7.24-7.23 (1H, m, ArH), 3.22-3.16 (4H, m, 2xC\(_2\)); \(^{13}\)C NMR δ (90.6 MHz, CD\(_3\)OD) 135.4 (C), 132.4 (CH), 130.3 (CH), 128.5 (CH), 127.5 (CH), 123.3 (C) 38.4 (CH\(_2\)), 33.0 (CH\(_2\)); m/z (FAB, 3-NOBA) 202 ([\(^{81}\)BrM+H]\(^+\), 85 %), 200 ([\(^{79}\)BrM+H]\(^+\), 91), 185 (33), 183 (34), 165 (47), 154 (100), 137 (100); HRMS (ESI+) Found: [\(^{79}\)BrM]\(^+\), 200.0070. C\(_8\)H\(_{11}\)N\(^{79}\)Br requires 200.0070.
General procedure H - Boc protection of aryl analogues

To a suspension of the appropriate amine hydrochloride (1 eq) in CH$_2$Cl$_2$ (10 ml) was added Et$_3$N (1.5 eq) and the reaction stirred for 10 mins. The reaction was cooled to 0 °C, Boc$_2$O (1.1 eq) added and the reaction allowed to warm to r.t. and stirred for 4 h. The reaction was diluted with CH$_2$Cl$_2$ (15 ml) and washed with NaCl (3 x 15 ml, sat. aq.). The organics were combined, dried (MgSO$_4$), concentrated under reduced pressure and purified by flash chromatography to afford the desired carbamate.

2-Bromo-4-methylbenzyl-tert-butylcarboxamide 168a

General procedure H was followed using amine hydrochloride 164a (170 mg, 0.72 mmol), CH$_2$Cl$_2$ (10 ml), Et$_3$N (222 µl, 1.58 mmol) and Boc$_2$O (173 mg, 0.79 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded carbamate 168a as a colourless oil (217 mg, 100%).

R$_f$ [3: 1 hexane: EtOAc] = 0.78; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 3346 (NH), 2978, 2928, 1700 (C=O), 1506, 1365, 1250, 1172; $^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 7.36 (1H, s, ArH), 7.25 (1H, d, J 7.8, ArH), 7.07 (1H, dd, J 7.8, 0.9, ArH), 4.98 (1H, br s, CHN), 4.34 (2H, d, J 6.2, CH$_2$Ar), 2.30 (3H, s, CH$_3$), 1.43 (9H, s, 3xCH$_3$); $^{13}$C NMR $\delta$ (90.6 MHz, 323 K, CDCl$_3$) 155.6 (C), 138.9 (C), 135.0 (C), 133.0 (CH), 129.4 (CH), 128.2 (CH), 123.2 (C), 79.3 (C), 44.6 (CH$_2$), 28.3 (3xCH$_3$), 20.4 (CH$_3$); $m/z$ (EI) 302 ([$^{81}$BrM+H]$^+$, 2 %), 300 ([$^{79}$BrM+H]$^+$, 2), 244 (7), 242 (7); HRMS (EI) Found: [$^{79}$BrM]$^+$, 299.0516. C$_{13}$H$_{18}^{79}$BrNO$_2$ requires 299.0515.
2-Bromo-4-fluorobenzyl tertbutylcarboxamide 168b

Experimental

General procedure H was followed using amine hydrochloride 164b (167 mg, 0.69 mmol), CH₂Cl₂ (8 ml), Et₃N (195 µl, 1.39 mmol) and Boc₂O (167 mg, 0.76 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded carbamate 168b as a colourless oil (184 mg, 88%).

Rf [hexane:EtOAc, 3:1] = 0.85; νmax (CHCl₃)/cm⁻¹ 3343 (NH), 1696 (C=O); ¹H NMR δ (250 MHz, CDCl₃) 7.35 (1H, dd, J 8.3, 6.0, ArH), 7.27 (1H, dd, J 8.3, 2.5, ArH), 6.99 (1H, dt, J 8.3, 2.5, ArH), 5.11 (1H, br s, CHN), 4.33 (2H, d, J 6.3, CH₂Ar), 1.44 (9H, s, 3xC₃H₃); ¹³C NMR δ (62.9 MHz, CDCl₃) 163.4 (C), 157.5 (1C, d, J 245.8, C), 133.8 (C), 130.5 (1C, d, J 7.8, CH), 123.2 (1C, d, J 9.6, C), 119.8 (1C, d, J 24.5, CH), 114.4 (1C, d, J 20.9, C), 79.6 (C), 44.0 (CH₂), 28.2 (3xCH₃); m/z (EI) 306 ([¹¹¹BrM+H]⁺, 1 %), 304 ([⁷⁹BrM+H]⁺, 1), 248 (14), 246 (13), 189 (17), 187 (18) 168 (100); HRMS (EI) Found: [⁷⁹BrM⁺], 303.0279. C₁₂H₁₅⁷⁹BrFNO₂ requires 303.0265.

2-Bromo-5-methoxybenzyl tertbutylcarboxamide 168c

General procedure H was followed using amine hydrochloride 164c (218 mg, 0.86 mmol), CH₂Cl₂ (10 ml), Et₃N (182 µl, 1.30 mmol) and Boc₂O (207 mg, 0.95 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded carbamate 168c as a colourless oil (230 mg, 85%).

Rf [hexane:EtOAc, 3:1] = 0.77; νmax (CHCl₃)/cm⁻¹ 3350 (NH), 2977, 1698 (C=O), 1506, 1471; ¹H NMR δ (360 MHz, CDCl₃) 7.40 (1H, d, J 8.7, ArH), 6.93 (1H, d, J 3.1, ArH), 6.68 (1H, dd, J 8.7, 3.1, ArH), 5.00 (1H, br s, NH), 4.33 (2H, d, J 6.3, CH₂Ar), 3.77 (3H, s, CH₃), 1.46 (9H, s, 3xCH₃); ¹³C NMR δ (90.6 MHz, CDCl₃) 159.2 (C), 155.6 (C), 139.0 (C), 133.1 (CH), 115.2 (CH), 114.6 (CH), 113.6 (C), 79.5 (C), 55.4 (CH₃), 45.0 (CH₂), 28.3 (3xCH₃); m/z (EI) 317 ([¹¹¹BrM⁺], 1 %), 315 ([⁷⁹BrM⁺], 1), 261 (3), 259 (3), 201 (9), 199 (10), 180 (100); HRMS (EI) Found: [⁷⁹BrM⁺], 315.0461. C₁₃H₁₈⁷⁹BrNO₃ requires 315.0465.
(2-Bromo-4,5-dimethoxy-benzyl)-carbamic acid tert-butyl ester 168d

General procedure H was followed using amine hydrochloride 164d (200 mg, 0.710 mmol), CH₂Cl₂ (10 ml), Et₃N (219 µl, 1.56 mmol) and Boc₂O (155 mg, 0.710 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded carbamate 168d as a colourless oil (267 mg, 100%).

Rᵥ [hexane:EtOAc, 3:1] = 0.63; νₑₓₑₐₓₑ (CHCl₃)/cm⁻¹ 3377 (NH), 1701 (C=O); ¹H NMR δ (360 MHz, CDCl₃) 6.93 (1H, s, ArH), 6.85 (1H, s, ArH), 5.07 (1H, br s, CHN), 4.24 (2H, d, J 6.0, CH₂Ar), 3.79 (6H, s, 2xCH₃), 1.39 (9H, s, 3xCH₃); ¹³C NMR δ (90.6 MHz, CDCl₃) 155.7 (C), 149.1 (C), 148.7 (C), 130.4 (CH), 115.9 (CH), 113.4 (C), 113.2 (C), 79.5 (C), 56.2 (CH₃), 56.1 (CH₃). 44.7 (CH₂), 28.3 (3xCH₃); m/z (EI) 347 ([¹⁸¹BrM]+, 4 %), 345 ([¹⁷⁹BrM]+, 4), 290 (27), 288 (27), 242 (13), 210 (100); HRMS (EI) Found: [¹⁷⁹BrM]+, 345.0570. C₁₄H₂₀¹⁷⁹BrNO₄ requires 345.0570.

(1-Bromo-naphthalen-2-ylmethyl) carbamic acid tert-butyl ester 168e

General procedure H was followed using amine hydrochloride 164e (200 mg, 0.73 mmol), CH₂Cl₂ (10 ml), Et₃N (155 µl, 1.10 mmol) and Boc₂O (176 mg, 0.81 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded carbamate 168e as a colourless solid (222 mg, 90%).

Rᵥ [hexane:EtOAc, 3:1] = 0.64; MP 96 °C; νₑₓₑₐₓₑ (CHCl₃)/cm⁻¹ 3346 (NH), 1699 (C=O), 1503, 1172; ¹H NMR δ (250 MHz, CDCl₃) 8.21 (1H, d, J 8.5, ArH), 7.72 (1H, d, J 7.3, ArH), 7.69 (1H, d, J 8.3, ArH), 7.53-7.39 (3H, m, 3xArH), 5.09 (1H, br s, NH), 4.54 (2H, d, J 6.3, CH₂), 1.37 (9H, s, 3xCH₃); ¹³C NMR δ (62.9 MHz, CDCl₃) 155.7 (C), 136.0 (C), 133.7 (C), 133.2 (C), 128.0 (CH), 127.8 (CH), 127.4 (CH), 127.0 (CH), 126.8 (CH), 126.3 (CH), 123.4 (C), 79.6 (C), 45.7 (CH₂), 28.3 (3xCH₃); m/z (EI) 337 ([¹⁸¹BrM]+, 1 %), 335 ([¹⁷⁹BrM]+, 1), 290 (27), 288 (27), 242 (13), 210 (100); HRMS (EI) Found: [¹⁷⁹BrM]+, 335.0506. C₁₄H₂₀¹⁷⁹BrNO₂ requires 335.0515.
Experimental

(3-Bromo-thiophen-2-ylmethyl)-carbamic acid tert-butyl ester 168f

General procedure H was followed using amine hydrochloride 164f (183 mg, 0.80 mmol), CH$_2$Cl$_2$ (10 ml), Et$_3$N (169 µl, 1.20 mmol) and Boc$_2$O (192 mg, 0.88 mmol). Flash chromatography (hexane:EtOAc, 20:1–10:1) afforded carbamate 168f as a colourless solid (164 mg, 70%).

R$_f$ [hexane:EtOAc, 3:1] = 0.85; $\nu$$_{max}$ (CHCl$_3$)/cm$^{-1}$ 3341 (NH), 2978, 1699 (C=O), 1505, 1167; $^1$H NMR $\delta$ (250 MHz, CDCl$_3$) 7.18 (1H, d, $\text{J }$5.4, HetH), 6.89 (1H, d, $\text{J }$5.4, HetH), 5.12 (1H, br s, NH), 4.41 (2H, d, $\text{J }$6.0, CH$_2$), 1.44 (9H, s, 3xCH$_3$); $^{13}$C NMR $\delta$ (62.9 MHz, CDCl$_3$) 155.3 (C), 136.3 (C), 129.7 (CH), 124.7 (CH), 109.0 (C), 79.7 (C), 38.5 (CH$_2$), 28.2 (3xCH$_3$); m/z (EI) 293 ([$^{81}$Br]M$^+$, 1 %), 291 ([$^{79}$Br]M$^+$, 1), 236 (26), 234 (24), 177 (28), 175 (27), 156 (100); HRMS (EI) Found: [79Br]M$^+$, 290.9917. C$_{10}$H$_{14}$BrNO$_2$S requires 290.9923.
**General procedure J - Dialkylation**

To a suspension of the appropriate amine hydrochloride (1 eq) in MeCN (5 ml) at 0 °C was added \( i\text{Pr}_2\text{NEt} \) (4 eq) and the reaction was stirred for 5 mins. 3-Bromocyclohexene (1 eq) was added and the reaction stirred for 16 h at r.t. The reaction was concentrated under reduced pressure and the residue taken up in CH\(_2\text{Cl}_2\) (5 ml) and washed with NaCl (3 x 5 ml, sat. aq.). The organics were combined, dried (MgSO\(_4\)) and concentrated under reduced pressure. The crude residue was taken up in CH\(_2\text{Cl}_2\) (10 ml), Et\(_3\)N (1 eq) was added, and the reaction was stirred for 10 mins. The reaction was cooled to 0 °C, Boc\(_2\text{O} \) (1.5 eq) was added and the reaction was stirred for a further 10 mins and then allowed to warm to r.t. and stirred for 16 h. The reaction was diluted with CH\(_2\text{Cl}_2\) (20 ml), extracted with NaCl (3 x 20 ml, sat. aq.), dried (MgSO\(_4\)) and concentrated under reduced pressure. Flash chromatography afforded the desired Boc amide.

**General procedure K – Monoalkylation**

To a solution of Boc carbamate (87 mg, 0.23 mmol) in DMF (1.5 ml) at 0 °C was added NaH (2 eq, 60% dispersion in mineral oil) and the reaction warmed to r.t. for 40 mins. The reaction was then cooled to 0 °C and 3-bromocyclohexene (2 eq) was added dropwise. The reaction allowed to warm to r.t. and stirred for 16 h. Et\(_2\)O (10 ml) was added and the organics washed with NaCl (3 x 15 ml, sat. aq.). The organics were dried (MgSO\(_4\)), concentrated under reduced pressure and purified by flash chromatography to afford the desired cyclohexenyl amine.
2-Bromo-4-methylbenzyl cyclohex-2-enyl-carbamic acid tert-butyl ester 165a

General procedure J was followed using amine hydrochloride 164a (150 mg, 0.63 mmol), MeCN (3 ml), \( \text{Pr}_2\text{NEt} \) (442 µl, 2.54 mmol), 3-Bromocyclohexene (73 µl, 0.63 mmol), \( \text{CH}_2\text{Cl}_2 \) (10 ml), \( \text{Et}_3\text{N} \) (134 µl, 0.95 mmol) and \( \text{Boc}_2\text{O} \) (208 mg, 0.95 mmol). Flash chromatography (hexane:EtoAc, 100:1) afforded Boc amide 165a as a colourless oil (140 mg, 59%).

General procedure K was followed using Boc carbamate 168a (198 mg, 0.659 mmol), DMF (5 ml), NaH (53 mg, 60% dispersion in mineral oil, 1.32 mmol) and 3-bromocyclohexene (153 µl, 1.32 mmol). Flash chromatography (hexane:hexane:EtoAc, 100:1) afforded cyclohexenyl amine 165a as a colourless oil (175 mg, 70%).

\[ R_f \text{ [hexane:EtoAc, 3:1] = 0.76; } \nu_{\max} (\text{CHCl}_3)/\text{cm}^{-1} \text{ 2978, 2927, 1640 (C=O), 1362, 1190}; \]

\[ ^1\text{H NMR } \delta (360 \text{ MHz, 323 K, CDCl}_3) 7.33 (1\text{H, s, ArH}), 7.14 (1\text{H, d, J 7.9, ArH}), 7.07 (1\text{H, d, J 7.9, ArH}), 5.82-5.80 (1\text{H, m, CH=CH}), 5.47 (1\text{H, d, J 10.2, CH=CH}), 4.84 (1\text{H, br s, CHN}), 4.39-4.34 (2\text{H, m, CH}_2\text{Ar}), 2.30 (3\text{H, s, CH}_3), 2.04-1.84 (3\text{H, m, CH}_2\text{CH}_3\text{H}_8), 1.80-1.68 (1\text{H, m, CH}_3\text{H}_8), 1.65-1.25 (11\text{H, m, CH}_2\text{+3xCH}_3); \]

\[ ^{13}\text{C NMR } \delta (90.6 \text{ MHz, 323 K, CDCl}_3) 155.7 (\text{C}), 137.6 (\text{C}), 135.9 (\text{C}), 132.6 (\text{CH}), 131.1 (\text{CH}), 128.2 (\text{CH}), 127.8 (\text{CH}), 127.3 (\text{CH}), 121.8 (\text{C}), 79.5 (\text{C}), 53.0 (\text{CH}), 47.3 (\text{CH}_2), 28.2 (3\text{xCH}_3), 28.1 (\text{CH}_2), 24.4 (\text{CH}_2), 21.3 (\text{CH}_2), 20.3 (\text{CH}_3); \]

\[ m/z \text{ (FAB, 3-NOBA) 382 ([}^{81}\text{Br}\text{M+H}^+]\text{, 12 }\% \), 380 ([}^{79}\text{Br}\text{M+H}^+]\text{, 15}), 326 (100), 324 (100), 185 (96), 183 (97); } \text{HRMS (EI) Found: } [^{79}\text{Br}\text{M}]^+, 379.1142. \text{C}_{19}\text{H}_{26}^{79}\text{BrNO}_2 \text{ requires 379.1141.} \]
2-Bromo-4-fluorobenzyl cyclohex-2-enyl-carbamic acid tert-butyl ester 165b

General procedure J was followed using amine hydrochloride 164b (150 mg, 0.62 mmol), MeCN (3 ml), iPr₂NEt (435 µl, 2.50 mmol), 3-Bromocyclohexene (72 µl, 0.62 mmol), CH₂Cl₂ (10 ml), Et₃N (132 µl, 0.94 mmol) and Boc₂O (205 mg, 0.94 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded Boc amide 165b as a colourless oil (161 mg, 67%).

General procedure K was followed using Boc carbamate 168b (175 mg, 0.56 mmol), DMF (4 ml), NaH (46 mg, 60% dispersion in mineral oil, 1.15 mmol) and 3-bromocyclohexene (133 µl, 1.15 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded cyclohexenyl amine 165b as a colourless oil (157 mg, 71%).

Rf [hexane:EtOAc, 3:1] = 0.75; 𝜈max (CHCl₃)/cm⁻¹ 2975, 2932, 1694 (C=O), 1485, 1169; ¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.29-7.22 (2H, m, 2xArH), 7.01 (1H, dt, J 8.4, 2.6, ArH), 5.86-5.84 (1H, m, CH=CH), 5.46 (1H, d, J 10.2, CH=CH), 4.83 (1H, br s, CHN), 4.30-4.26 (2H, m, CH₂Ar), 2.06-1.85 (3H, m, CH₂+CH₃H₈), 1.79-1.73 (1H, m, CH₃H₈), 1.70-1.55 (1H, m, CH₂H₉), 1.55-1.20 (10H, m, CH₃H₉+3xCH₃); ¹³C NMR δ (90.6 MHz, 323 K, CDCl₃) 161.0 (1C, d, J 249.0, C), 155.7 (C), 135.0 (C), 131.4 (CH), 128.5 (CH), 128.0 (CH), 121.7 (1C, d, J 9.5, C), 119.4 (1C, d, J 24.5, CH), 114.1 (1C, d, J 20.9, CH), 79.9 (C), 53.1 (CH), 47.0 (CH₂), 28.2 (3xCH₃), 28.1 (CH₂), 24.5 (CH₂), 21.3 (CH₃); m/z (FAB, 3-NOBA) 386 ([¹⁸⁷BrM+H]+, 86 %), 384 ([¹⁷⁹BrM+H]+, 95), 330 (98), 328 (98), 301 (47), 299 (49), 284 (96), 282 (97), 250 (96), 248 (97), 246 (94), 204 (77), 202 (87); HRMS (FAB, 3-NOBA) Found: [¹⁷⁹BrM]+, 384.0969. C₁₈H₂₄¹⁷⁹BrFNO₂ requires 384.0969.
Experimental

(2-Bromo-5-methoxybenzyl)-(cyclohex-2-enyl)-carbamic acid tert-butyl ester 165c

General procedure J was followed using amine hydrochloride 164c (200 mg, 0.79 mmol), MeCN (5 ml), iPr₂NEt (552 µl, 3.17 mmol), 3-Bromocyclohexene (92 µl, 0.79 mmol), CH₂Cl₂ (10 ml), Et₃N (167 µl, 1.19 mmol) and Boc₂O (260 mg, 1.19 mmol). Flash chromatography (hexane:EtOAc, 100:1–20:1) afforded Boc amide 165c as a colourless oil (181 mg, 58%).

General procedure K was followed using Boc carbamate 168c (222 mg, 0.703 mmol), DMF (5 ml), NaH (56 mg, 60% dispersion in mineral oil, 1.41 mmol) and 3-bromocyclohexene (163 µl, 1.41 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded cyclohexenyl amine 165c as a colourless oil (201 mg, 72%).

Rf [hexane:EtOAc, 3:1] = 0.74; υmax (CHCl₃)/cm⁻¹ 2975, 2929, 1694 (C=O), 1168; ¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.45 (1H, d, J 8.8, ArH), 6.85 (1H, d, J 3.1, ArH), 6.66 (1H, dd, J 8.8, 3.1, ArH), 5.89–5.80 (1H, m, CH=CH), 5.49 (1H, d, J 10.1, CH=CH), 4.88 (1H, br s, CHN), 4.37 (1H, d, J 17.4, CHₓHᵧAr), 4.30 (1H, d, J 17.4, CHₓHᵧAr), 3.77 (3H, s, OCH₃), 2.08–1.87 (3H, m, CHₓ+CHₓHᵧ), 1.80–1.71 (1H, m, CHₓHᵧ), 1.70–1.29 (11H, m, CHₓ+3xCH₃); ¹³C NMR δ (90.6 MHz, 323 K, CDCl₃) 159.1 (C), 155.7 (C), 132.8 (CH), 131.4 (C), 128.2 (2xCH), 113.8 (CH), 113.4 (CH), 112.5 (C), 79.8 (C), 55.3 (CH₃), 53.4 (CH), 47.7 (CH₂), 28.3 (CH₂), 28.2 (3xCH₃), 24.5 (CH₂), 21.3 (CH₂); m/z (EI) 398 ([⁸¹BrM+H]⁺, 7 %), 396 ([⁷⁹BrM+H]⁺, 9), 342 (100), 340 (100), 260 (100), 201 (41), 199 (42); HRMS (EI) Found: [⁷⁹BrM]⁺, 395.1090. C₁₉H₂₆⁷⁹BrNO₃ requires 395.1090.
Experimental

2-Bromo-4,5-dimethoxybenzyl-(cyclohex-2-enyl)-carbamic acid tert-butyl ester 165d

General procedure J was followed using amine hydrochloride 164d (200 mg, 0.710 mmol), MeCN (5 ml), \text{i}Pr\text{$_2$}NEt (493 µl, 2.83 mmol), 3-Bromocyclohexene (82 µl, 0.710 mmol), CH$_2$Cl$_2$ (10 ml), Et$_3$N (149 µl, 0.71 mmol) and Boc$_2$O (927 mg, 4.25 mmol). Flash chromatography (hexane:EtOAc:Et$_3$N, 100:5:0.5) afforded the Boc amide 165d as a colourless oil (170 mg, 56%).

General procedure K was followed using Boc carbamate 168d (87 mg, 0.23 mmol), DMF (1.5 ml), NaH (18 mg, 60% dispersion in mineral oil, 0.46 mmol) and 3-bromocyclohexene (53 µl, 0.46 mmol). Flash chromatography (hexane:EtOAc:Et$_3$N, 100:5:0.5) afforded cyclohexenyl amine 165d as a colourless oil (81 mg, 84%).

R$_f$ [hexane:EtOAc:3:1] = 0.49; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1640 (C=O), 1362, 1190, 1177; $^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 6.97 (1H, s, ArH), 6.82 (1H, s, ArH), 5.85-5.77 (1H, m, CH=CH), 5.44 (1H, d, $J$ 10.0, CH=CH), 4.80 (1H, br s, CHN), 4.35 (1H, d, $J$ 16.5, CH$_2$H$_A$Ar), 4.26 (1H, d, $J$ 16.5, CH$_2$H$_B$Ar), 3.83 (3H, s, CH$_3$), 3.81 (3H, s, CH$_3$), 2.05-1.92 (2H, m, CH$_2$), 1.91-1.80 (1H, m, CH$_A$H$_B$), 1.74-1.65 (1H, m, CH$_A$H$_B$), 1.65-1.30 (11H, m, CH$_2$+3xCH$_3$); $^{13}$C NMR $\delta$ (90.6 MHz, 323 K, CDCl$_3$) 155.7 (C), 148.6 (C), 148.3 (C), 131.3 (C), 131.1 (CH), 128.2 (CH), 115.6 (CH), 111.8 (C), 111.2 (CH), 79.6 (C), 56.1 (CH$_3$), 55.9 (CH$_3$), 53.1 (CH), 47.1 (CH$_2$), 28.2 (3xCH$_3$), 28.1 (CH$_2$), 24.4 (CH$_2$), 21.3 (CH$_2$); m/z (FAB, 3-NOA) 428 ([$^{81}$BrM+H]$^+$, 6 %), 426 ([$^{79}$BrM+H]$^+$, 9), 372 (34), 370 (40), 346 (16), 326 (10), 290 (100), 231 (100), 229 (100); HRMS (EI) Found: [$^{79}$BrM]$^+$, 426.1268. C$_{20}$H$_{29}$BrNO$_4$ requires 426.1275.
1-Bromo-naphthalen-2-ylmethyl-(cyclohex-2-enyl)-carbamic acid tert-butyl ester 165e

General procedure J was followed using amine hydrochloride 164e (150 mg, 0.55 mmol), MeCN (3 ml), iPr₂NEt (383 µl, 2.20 mmol), 3-Bromocyclohexene (64 µl, 0.55 mmol), CH₂Cl₂ (10 ml), Et₃N (116 µl, 0.83 mmol) and Boc₂O (180 mg, 0.83 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded the Boc amide 165e as a colourless oil (140 mg, 61%).

General procedure K was followed using Boc carbamate 168e (165 mg, 0.49 mmol), DMF (5 ml), NaH (40 mg, 60% dispersion in mineral oil, 0.982 mmol) and 3-bromocyclohexene (114 µl, 0.98 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded cyclohexenyl amine 165e as a colourless oil (175 mg, 86%).

Rₚ [hexane:EtOAc, 3:1] = 0.80; υₚₑₓₑ (CHCl₃)/cm⁻¹ 1652 (C=O); ¹H NMR δ (360 MHz, 323 K, CDCl₃) 8.33 (1H, d, J 8.7, ArH), 7.82 (1H, d, J 7.4, ArH), 7.80 (1H, d, J 8.4, ArH), 7.58 (1H, t, J 6.9, ArH), 7.48 (1H, ddd, J 8.3, 7.2, 1.1, ArH), 7.43 (1H, d, J 8.6, ArH), 5.83 (1H, br s, CH=CH), 5.52 (1H, d, J 10.0, CH=CH), 4.95 (1H, br s, CHN), 4.66 (2H, br s, CH₂Ar), 2.10-1.88 (3H, m, CH₂+CH₃H₈), 1.80-1.71 (1H, m, CH₃H₈), 1.70-1.30 (11H, m, CH₂+3xCH₃); ¹³C NMR δ (90.6 MHz, 323 K, CDCl₃) 155.9 (C), 137.3 (C), 133.6 (C), 132.2 (C), 131.3 (CH), 128.2 (CH), 127.9 (CH), 127.2 (2xCH), 126.7 (CH), 125.9 (CH), 125.0 (CH), 121.5 (C), 79.8 (C) 53.0 (CH), 48.6 (CH₂), 28.2 (3xCH₃), 28.1 (CH₂), 24.5 (CH₂), 21.3 (CH₂); m/z (FAB, 3-NOBA) 418 ([⁸¹BrM+H]⁺, 2 %), 416 ([⁷⁹BrM+H]⁺, 3), 362 (80), 360 (85), 221 (100), 219 (100), 200 (33), 141 (41), 139 (36); HRMS (EI) Found: [⁷⁹BrM]⁺, 415.1140. C₂₂H₂₆N⁷⁹BrNO₂ requires 415.1141.
Experimental

(3-Bromo-thiophen-2-ylmethyl)-(cyclohex-2-enyl)-carbamic acid tert-butyl ester 165f

General procedure J was followed using amine hydrochloride 164f (150 mg, 0.66 mmol), MeCN (3 ml), 1Pr₂NEt (457 µl, 2.62 mmol), 3-Bromocyclohexene (76 µl, 0.66 mmol), CH₂Cl₂ (10 ml), Et₃N (138 µl, 0.98 mmol) and Boc₂O (215 mg, 0.98 mmol). Flash chromatography (hexane:EtOAc, 100:1 – 100:2) afforded Boc amide 165f as a colourless oil (160 mg, 65%).

General procedure K was followed using Boc carbamate 168f (155 mg, 0.53 mmol), DMF (5 ml), NaH (42 mg, 60% dispersion in mineral oil, 1.06 mmol) and 3-bromocyclohexene (123 µl, 1.06 mmol). Flash chromatography (hexane:EtOAc, 100:1) afforded cyclohexenyl amine 165f as a yellow oil (180 mg, 91%).

Rf [hexane:EtOAc, 3:1] = 0.85; νmax (CHCl₃)/cm⁻¹ 1696 (C=O); ¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.17 (1H, d, J 5.3, HetH), 6.87 (1H, d, J 5.3, HetH), 5.91-5.84 (1H, m, CH=CH), 5.49 (1H, dt, J 10.2, 1.2, CH=CH), 4.74 (1H, s, CHN), 4.51-4.41 (2H, m, CH₂Ar), 2.16-1.99 (2H, m, CH₂), 1.91-1.81 (1H, m, CH₄H₅B), 1.80-1.68 (1H, m, CH₄H₅B), 1.68-1.50 (2H, m, CH₂), 1.46 (9H, s, 3xCH₃); ¹³C NMR δ (90.6 MHz, 323 K, CDCl₃) 155.3 (C), 139.4 (C), 131.4 (CH), 129.2 (CH), 128.3 (CH), 124.2 (CH), 107.7 (C), 80.2 (C), 53.3 (CH), 42.6 (CH₂), 28.3 (3xCH₃), 27.4 (CH₂), 24.6 (CH₂), 21.5 (CH₂); m/z (FAB, 3-NOBA) 374 ([¹⁸⁷Br⁺]+, 18 %), 372 ([¹⁷⁹Br⁺]+, 22), 318 (99), 316 (99), 236 (51), 234 (43), 177 (98), 175 (49), 154 (58), 140 (31), 138 (24), 136 (36); HRMS (EI) Found: [¹⁷⁹Br⁺]⁺, 371.0549. C₁₆H₂₂⁺BrNO₂S requires 371.0549.
**Experimental**

(6-Bromo-benzo[1,3]dioxol-5-yl)-acetic acid 169k

To a solution of 1,3-benzodioxole-5-acetic acid (700 mg, 3.89 mmol) and NaOH (1.0 ml, 5 M aq.) in H2O (7 ml) was added DBDMH (600 mg, 2.10 mmol) and the reaction stirred at r.t. under an air atmosphere for 48 h. The reaction was diluted with H2O (50 ml), acidified to pH 1 with HCl (6 M, aq.) and extracted into Et2O (3 x 30 ml). The organics were dried (MgSO4) and concentrated under reduced pressure to afford acid 169k as a colourless crystalline powder (909 mg, 91% yield).

**Rf** [CH2Cl2:MeOH, 95:5] = 0.23; **MP** 191 °C (EtOH), lit. 190 °C196; **ν<sub>max</sub>** (NUJOL)/cm<sup>-1</sup> 1699 (C=O); **¹H NMR** δ (250 MHz, DMSO) 7.21 (1H, s, ArH), 7.02 (1H, s, ArH), 6.07 (2H, s, OCH2O), 3.63 (2H, s, ArCH2); **¹³C NMR** δ (62.9 MHz, DMSO), 171.4 (C), 147.0 (C), 146.8 (C), 127.9 (C), 114.7 (C), 111.9 (CH), 111.4 (CH), 101.7 (CH2), 40.6 (CH2); **m/z** (EI) 260 ([¹⁸Br]<sup>M</sup>+ 49%), 258 ([¹⁸Br]<sup>M</sup>+ 48), 215 (97), 213 (100), 179 (92), 135 (38), 113 (27); **HRMS** (EI) Found: [⁷⁹Br]<sup>M</sup>+ 257.9522; C₉H₇O₄⁷⁹Br requires 257.9522.
6-Bromo-benzo[1,3]dioxol-5-ylmethyl)-carbamic acid tert-butyl ester 168k

To a suspension of acid 169k (1.72 g, 6.64 mmol) and Et₃N (1.31 ml, 9.40 mmol) in CH₂Cl₂ (50 ml) at 0 °C was added diphenylphosphoryl azide (2.00 ml, 9.30 mmol) and the reaction stirred at 0 °C for 30 mins. The reaction was warmed to r.t. and stirred for 30 mins before being filtered through a silica gel plug. The crude organics were concentrated under reduced pressure and refluxed in toluene (50 ml) at 80 °C for 1 h. The reaction was concentrated under reduced pressure and then refluxed at 80 °C in tBuOH (50 ml) for 19 h. The reaction was concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 100:2–100:8) to afford carbamate 168k as a colourless oil (1.09 g, 50%).

Rᶠ [hexane:EtOAc, 10:1] = 0.21; vₑₘₐₓ (CHCl₃)/cm⁻¹ 3346 (NH), 1694 (C=O), 1470; ¹H NMR δ (250 MHz, CDCl₃) 6.99 (1H, s, ArH), 6.95 (1H, s, ArH), 5.97 (2H, s, OCH₂O), 4.99 (1H, br s, NH), 4.28 (2H, d, J 6.2, CH₂Ar), 1.46 (9H, s, 3xCH₃); ¹³C NMR δ (90.6 MHz, CDCl₃), 155.6 (C), 147.4 (C), 147.3 (C), 131.1 (C), 113.6 (C), 112.5 (CH), 109.5 (CH), 101.6 (CH₂), 79.4 (C), 44.5 (CH₃), 28.2 (3xCH₃); m/z (EI) 331 ([⁸¹BrM]+, 1 %), 329 ([⁷⁹BrM]+, 1), 274 (1), 272 (1), 194 (7), 49 (100). HRMS (EI) Found: [⁷⁹BrM]+, 329.0258. C₁₃H₁₆O₄N⁷⁹Br requires 329.0257.
(4-Bromo-benzo[1,3]dioxol-5-ylmethyl)-(cyclohex-2-enyl)-carbamic acid tert-butyl ester 165k

General procedure K was followed using Boc carbamate 168k (140 mg, 0.42 mmol), DMF (4 ml), NaH (34 mg, 60% dispersion in mineral oil, 0.84 mmol) and 3-bromocyclohexene (100 µl, 0.84 mmol). Flash chromatography (hexane:EtOAc, 100:1–100:3) afforded cyclohexene 165k as a colourless oil (130 mg, 75%).

Rf [hexane:EtOAc, 3:1] = 0.69; νmax (CHCl3)/cm⁻¹ 1693 (C=O), 1479; ¹H NMR δ (360 MHz, 323 K, CDCl3) 6.95 (1H, s, ArH), 6.78 (1H, s, ArH), 5.93 (2H, s, OCH₂O), 5.83-5.81 (1H, m, CH=CH), 5.45 (1H, br d, J 10.2, CH=CH), 4.76 (1H, br s, CHN), 4.34-4.15 (2H, m, CH₂Ar), 2.01-1.97 (2H, m, CH₂), 1.90-1.88 (1H, m, CH₃H₉), 1.75-1.73 (1H, m, CH₃H₉), 1.63-1.59 (2H, m, CH₂), 1.44-1.41 (9H, s, 3xCH₃); ¹³C NMR δ (90.6 MHz, 323 K, CDCl₃), 155.7 (C), 147.4 (C), 146.8 (C), 132.6 (C), 131.0 (CH), 128.2 (CH), 112.3 (CH), 112.0 (C), 107.7 (CH), 101.4 (CH₂), 79.8 (C), 53.2 (CH), 47.5 (CH₂), 28.3 (3xCH₃), 28.0 (CH₂), 24.5 (CH₂), 21.3 (CH₂); m/z (EI) 411 ([⁸¹BrM]+, 1 %), 409 ([⁷⁹BrM]+, 1), 274 (92), 215 (65), 213 (69), 194 (100); HRMS (EI) Found: [⁷⁹BrM]+, 409.0889. C₁₅H₂₄O₄N⁷⁹Br requires 409.0883.
2-(2'-Bromophenyl) ethyl-tert-butyl ester 184j

General procedure H was followed using amine hydrochloride 164j (100 mg, 0.42 mmol), CH₂Cl₂ (5 ml), Et₃N (89 µl, 0.64 mmol) and Boc₂O (102 mg, 0.47 mmol). Flash chromatography (hexane:EtOAc, 25:1–5:1) afforded carbamate 184j as a colourless oil (71 mg, 56%).

Curtius: To a suspension of 3-(2-bromo-phenyl)-propionic acid (200 mg, 0.87 mmol) and Et₃N (172 µl, 1.22 mmol) in CH₂Cl₂ (10 ml) at 0 °C was added diphenylphosphoryl azide (263 µl, 1.22 mmol) and the reaction was stirred at 0 °C for 30 mins. The reaction was warmed to r.t. and stirred for 30 mins before being filtered through a silica gel plug. The crude organics were concentrated under reduced pressure and heated in toluene (10 ml) at 80 °C for 1 h. The reaction was concentrated under reduced pressure and then heated at 80 °C in 'BuOH (10 ml) for 19 h. The reaction was concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 25:1–5:1) to afford carbamate 184j as a colourless oil (201 mg, 77%).

Rf [3: 1 hexane: EtOAc] = 0.65; $\nu_{\text{max}}$ (CHCl₃)/cm⁻¹ 3300 (NH), 2977, 1700 (C=O), 1507, 1472, 1364; ¹H NMR $\delta$ (360 MHz, CDCl₃) 7.55 (1H, d, $\omega$ 7.7, ArH), 7.27-7.22 (2H, m, 2xArH), 7.10-7.06 (1H, m, ArH), 4.55 (1H, br s, NH), 3.41 (2H, q, $\omega$ 6.7, CH₂NH), 2.96 (2H, t, $\omega$ 7.1, CH₂Ar), 1.45 (9H, s, 3xCH₃); ¹³C NMR $\delta$ (90.6 MHz, CDCl₃) 155.7 (C), 138.4 (C), 132.9 (CH), 130.9 (CH), 128.0 (CH), 127.4 (CH), 124.6 (C), 79.2 (C), 40.4 (CH₂), 36.4 (CH₂), 28.3 (3xCH₃); m/z (EI) 301 ($^{79}\text{Br}M^+$, 2 %), 299 ($^{79}\text{Br}M^+$, 2), 286 (2), 284 (2), 245 (14), 243 (14), 172 (19), 170 (19), 164 (100); HRMS (EI) Found: $^{79}\text{Br}M^+$, 299.0512. C₁₃H₁₈⁷⁹BrNO₂ requires 299.0515.
Experimental

[2-(2'-Bromophenyl) ethyl]–cyclohex-2-enyl-carbamic acid tert-butyl ester 185j

General procedure K was followed using Boc carbamate 184j (67 mg, 0.223 mmol), DMF (2 ml), NaH (18 mg, 60% dispersion in mineral oil, 0.446 mmol) and 3-bromocyclohexene (52 µl, 0.446 mmol). Flash chromatography (hexane:EtOAc, 100:1–10:1) afforded cyclohexene 185j as a colourless oil (38 mg, 45%).

Rf [hexane:EtOAc, 3:1] = 0.79; v_max (CHCl_3)/cm^{-1} 2931, 1689 (C=O); $^1$H NMR δ (360 MHz, CDCl_3) 7.53 (1H, d, J 7.9, ArH), 7.27-7.21 (2H, m, 2xArH), 7.09-7.04 (1H, m, ArH), 5.84-5.82 (1H, m, CH=CH), 5.43 (1H, d, J 9.7, CH=CH), 4.66 (1H, br s, CHN), 3.30 (2H, dd, J 8.1, 6.2, CH_2), 3.04 (2H, m, CH_2), 2.10-1.93 (2H, m, CH_2), 1.85-1.78 (2H, m, CH_2), 1.63-1.58 (2H, m, CH_2), 1.52 (9H, s, 3xCH_3); $^{13}$C NMR δ (90.6 MHz, CDCl_3) 155.7 (C), 139.4 (C), 132.8 (CH), 131.0 (CH), 130.9 (CH), 129.0 (CH), 127.8 (CH), 127.4 (CH), 124.5 (C), 79.4 (C), 53.3 (CH), 44.1 (CH_2), 37.0 (CH_2), 28.5 (3xCH_3), 28.1 (CH_2), 24.6 (CH_2), 21.6 (CH_2); m/z (EI) 381 ([^{81}BrM]^+, 2 %), 379 ([^{79}BrM]^+, 2), 325 (9), 323 (9), 271 (6), 273 (6), 184 (22), 182 (22); HRMS (EI) Found: [^{79}BrM]^+, 379.1137. C_{19}H_{26}^{79}BrNO_2 requires 379.1141.
3-Bromoindole-2-methylamine hydrochloride 164h

To a suspension of LiAlH₄ (587 mg, 15.5 mmol) in THF (20 ml) at 0 °C was added dropwise a solution of amide 162h (920 mg, 3.87 mmol) in THF (2 ml). The reaction was allowed to warm to r.t. and then heated at 70 °C for 18 h. The reaction was quenched by the addition of Na₂SO₄,5H₂O portionwise, then it was filtered and the filtrate stirred vigorously with potassium sodium tartrate (100 ml, sat. aq.) for 1 h. The THF layer was separated and the aqueous phase extracted with Et₂O (3 x 60 ml). The combined organic phases were dried (MgSO₄) and concentrated under reduced pressure. The residue was taken up in CH₂Cl₂ (1 ml), and HCl in Et₂O (20.0 ml, 1 M in Et₂O) added. The brown precipitate was filtered and dried to afford a mixture of two products: amine hydrochloride 164h (528 mg, 52 %) and debrominated amine hydrochloride 191 (118 mg, 17%). The full reduction protocol above was also repeated and crude reaction mixture purified by flash chromatography (CH₂Cl₂:MeOH, 9:1) rather than HCl salt formation. This led to the recovery of a minor amount of the free amine of debrominated amine 191.

Rf [CH₂Cl₂:MeOH, 9:1] = 0.27; ¹H NMR δ (360 MHz, CD₃OD) 7.51 (1H, dt, J 7.9, 1.1, ArH), 7.47 (1H, dt, J 8.3, 1.1 ArH), 7.29 (1H, ddd, J 8.3, 7.2, 1.4, ArH), 7.19 (1H, ddd, J 7.9, 7.2, 1.1, ArH), 4.38 (2H, s, CH₂); ¹³C NMR δ (90.6 MHz, (CD₃OD) 135.5 (C), 126.4 (C), 126.2 (C), 123.2 (CH), 119.9 (CH), 118.1 (CH), 111.1 (CH), 91.9 (C), 33.9 (CH₂); m/z (EI) 226 ([⁸¹BrM(164h)]⁺, 62 %), 224 ([⁷⁹BrM(164h)]⁺, 64), 209 (91), 207 (86), 146 ([M(191)⁺, 76), 145 (59), 128 (100); HRMS (EI) Found: [⁷⁹BrM(164h)]⁺, 223.9947. C₉H₉⁷⁹BrN₂ requires 223.9944.
Data for Indole-2-methylamine hydrochloride 191.\textsuperscript{122}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{indole-2-methylamine-hydrochloride}
\end{figure}

$R_f$ [CH$_2$Cl$_2$:MeOH, 9:1] = 0.14; \textbf{\textsuperscript{1}H NMR} $\delta$ (360 MHz, CD$_3$OD) 7.56 (1H, dt, $J$ 7.9, 1.1, ArH), 7.41 (1H, dd, $J$ 7.6, 0.7, ArH), 7.17 (1H, ddd, $J$ 8.3, 7.2, 1.1, ArH), 7.06 (1H, ddd, $J$ 7.9, 7.2, 1.1, ArH), 6.60 (1H, s, =CH), 4.32 (2H, s, CH$_2$); \textbf{\textsuperscript{13}C NMR} $\delta$ (90.6 MHz, (CD$_3$OD) 121.6 (CH), 119.6 (CH), 118.9 (CH), 110.4 (CH), 101.6 (CH), 35.7 (CH$_2$). \textbf{Free amine:} \textbf{\textsuperscript{1}H NMR} $\delta$ (250 MHz, (CD$_3$)$_2$SO) 10.93 (1H, br s, NH), 7.44 (1H, dd, $J$ 7.1, 1.0, ArH), 7.32 (1H, dd, $J$ 8.0, 1.0, ArH), 7.03 (1H, td, $J$ 7.8, 1.3, ArH), 6.94 (1H, td, $J$ 7.1, 1.3, ArH), 6.26 (1H, s, =CH), 3.88 (2H, s, CH$_2$); \textbf{\textsuperscript{13}C NMR} $\delta$ (62.9 MHz, (CD$_3$)$_2$SO) 136.1 (C), 128.1 (C), 120.4 (CH), 119.5 (CH), 118.7 (CH), 110.9 (CH), 98.1 (CH), 48.6 (CH$_2$).

\textsuperscript{1}H NMR spectrum in agreement with the literature.\textsuperscript{122} \textsuperscript{13}C NMR data showed minor discrepancies.
(3-Bromo-1H-indol-2-ylmethyl)-carbamic acid tert-buty1 ester 168h

General procedure H was followed using 3.06:1 mixture of bromoindole 164h and debromoindole 191 (130 mg), CH₂Cl₂ (6 ml), Et₃N (141 µl, 1.00 mmol) and Boc₂O (218 mg, 1.00 mmol). Flash chromatography (hexane:EtOAc, 10:1) afforded bromoindole carbamate 168h as a yellow oil (87 mg, 49 %) and indole carbamate 192 as a colourless solid (32 mg, 24%).

R₇ [hexane:EtOAc, 3:1] = 0.57; ʋmax (CHCl₃)/cm⁻¹ 3401, 2979, 1696 (C=O), 1507, 1165; ¹H NMR δ (360 MHz, CDCl₃) 9.20 (1H, br s, NH), 7.57 (1H, d, J 7.8, ArH), 7.37 (1H, d, J 7.6, ArH), 7.30-7.19 (2H, m, 2xArH), 5.19 (1H, br s NH), 4.49 (2H, d, J 6.2, CH₂), 1.54 (9H, s, 3xCH₃); ¹³C NMR δ (90.6 MHz, (CDCl₃) 157.3 (C), 135.1 (C), 133.8 (C), 126.9 (C), 123.1 (CH), 120.4 (CH), 119.0 (CH), 111.3 (CH), 90.1 (C), 80.4 (C), 36.4 (CH₂), 28.3 (3xCH₃); m/z (EI) 326 ([¹⁸¹BrM(168h)]⁺, 25 %), 324 ([¹⁸⁰BrM(168h)]⁺, 25), 270 (25), 268 (26), 246 ([M(192)]⁺, 6), 210 (34), 208 (35), 189 (58), 145 (100); HRMS (EI) Found: [¹⁷⁹BrM(168h)]⁺, 324.0472. C₁₄H₁₇⁷⁹BrN₂O₂ requires 324.0468.

(1H-Indol-2-ylmethyl)-carbamic acid tert-buty1 ester 192 (Diagnostic data)

R₇ [hexane:EtOAc, 3:1] = 0.48; ¹H NMR δ (360 MHz, CDCl₃) 8.77 (1H, br s, NH), 7.57 (1H, dd, J 7.8, 1.1, ArH), 7.37 (1H, dd, J 8.0, 0.9, ArH), 7.18 (1H, td, J 7.1, 1.2, ArH), 7.10 (1H, td, J 7.9, 1.1, ArH), 6.34 (1H, s, =CH), 5.19 (1H, br s NH), 4.49 (2H, d, J 6.2, CH₂), 1.54 (9H, s, 3xCH₃).
Application of optimised methods in Table 3.5 and 3.6

9-Methyl phenanthridine 195a-197a

(Table 3.5, Entry 2) General procedure C was followed using cyclohexene 165a (20 mg, 53 µmol), palladacycle 100 (3 mg, 2.6 µmol) and Ag₂CO₃ (15 mg, 5.3 µmol). After 2 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1-100:2) afforded the phenanthridine as a colourless solid (18 mg, 99%). ¹H NMR of this oil showed it to be a 78: 17: 5 mixture of double bond isomers (195a:196a:197a).

(Table 3.6, Entry 2) General procedure D was followed using cyclohexene 165a (110 mg, 0.289 mmol), palladacycle 100 (14 mg, 14.5 µmol) and MeNCy₂ (245 µl, 1.16 mmol). After 12 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1-100:2) afforded the phenanthridine as a colourless solid (65 mg, 76%). ¹H NMR of this oil showed it to be 26: 57: 11 mixture of double bond isomers (195a:196a:197a).

9-Fluoro phenanthridine 195b-197b

(Table 3.5, Entry 3) General procedure C was followed using cyclohexene 165b (20 mg, 0.052 mmol), palladacycle 100 (2.5 mg, 2.6 µmol) and Ag₂CO₃ (14.5 mg, 0.052 mmol). After 2.5 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1-100:1) afforded the phenanthridine as a colourless oil (16 mg, 99%). ¹H NMR of this oil showed it to be an 81: 14: 5 mixture of double bond isomers. (195b:196b:197b).

(Table 3.6, Entry 3) General procedure D was followed using cyclohexene 165b (80 mg, 0.21 mmol), palladacycle 100 (10 mg, 10 µmol) and MeNCy₂ (175 µl, 0.84 mmol). After 5 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1-100:6) afforded the phenanthridine as a colourless oil (46 mg, 72%). ¹H NMR of this oil showed it to be a 27: 44: 29 mixture of double bond isomers (195b:196b:197b).
8-Methoxy phenanthridine 195c-197c

(Table 3.5, Entry 4) General procedure C was followed using cyclohexene 165c (23 mg, 0.058 mmol), palladacycle 100 (3 mg, 2.9 µmol) and Ag₂CO₃ (16 mg, 0.058 mmol). After 4 h at 140 °C, flash chromatography (hexane: EtOAc 100: 1) afforded the phenanthridine as a colourless oil (18 mg, 99%). ¹H NMR of this oil showed it to be a 77: 19: 4 mixture of double bond isomers (195c:196c:197c).

(Table 3.6, Entry 4) General procedure D was followed using cyclohexene 165c (110 mg, 0.278 mmol), palladacycle 100 (13 mg, 14.0 µmol) and MeNCy₂ (236 µl, 1.11 mmol). After 6 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1) afforded the phenanthridine as a colourless oil (64 mg, 73%). ¹H NMR of this oil showed it to be a 36: 44: 20 mixture of double bond isomers (195c:196c:197c).

8,9-Dimethoxy phenanthridine 195d-197d

(Table 3.5, Entry 5) General procedure C was followed using cyclohexene 165d (50 mg, 0.12 mmol), palladacycle 100 (6 mg, 5.9 µmol) and Ag₂CO₃ (33 mg, 0.12 mmol). After 1 h at 140 °C, flash chromatography (hexane:EtOAc, 100:15) afforded the phenanthridine as a colourless oil (40 mg, 99%). ¹H NMR of this oil showed it to be an 84: 13: 3 mixture of double bond isomers (195d:196d:197d).

(Table 3.6, Entry 5) General procedure D was followed using cyclohexene 165d (50 mg, 0.12 mmol), palladacycle 100 (6 mg, 5.9 µmol) and MeNCy₂ (100 µl, 0.47 mmol). After 12 h at 140 °C, flash chromatography (hexane:EtOAc, 100:5–100:15) afforded the phenanthridine as a colourless oil (30 mg, 75%). ¹H NMR of this oil showed it to be a 41: 32: 27 mixture of double bond isomers (195d:196d:197d).
**Benzo[k]phenanthridine 195e-197e**

(Table 3.5, Entry 6) General procedure C was followed using cyclohexene 165e (20 mg, 0.05 mmol), palladacycle 100 (2.3 mg, 2.4 µmol) and Ag$_2$CO$_3$ (14 mg, 0.05 mmol). After 4 h at 140 °C, flash chromatography (hexane: EtOAc 100:2 – 100: 4) afforded the phenanthridine as a colourless oil (14 mg, 88%). $^1$H NMR of this oil showed it to be an 81: 14: 5 mixture of double bond isomers (195e:196e:197e).

(Table 3.6, Entry 6) General procedure D was followed using cyclohexene 165e (110 mg, 0.26 mmol), palladacycle 100 (13 mg, 13 µmol) and MeNCy$_2$ (224 µl, 1.06 mmol). After 5 h at 140 °C, flash chromatography (hexane:EtOAc, 100:2–100:3) afforded the phenanthridine as a colourless oil (65 mg, 74%). $^1$H NMR of this oil showed it to be a 44: 42: 16 mixture of double bond isomers (195e:196e:197e).

**Thieno[2,3-c]quinoline 195f-197f**

(Table 3.5, Entry 7) General procedure C was followed using cyclohexene 165f (20 mg, 0.054 mmol), palladacycle 100 (3 mg, 2.7 µmol) and Ag$_2$CO$_3$ (15 mg, 0.054 mmol). After 3 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1–100:5) afforded the phenanthridine as a colourless oil (15 mg, 99%). $^1$H NMR of this oil showed it to be a 64:21:15 mixture of double bond isomers (195f:196f:197f), with unquantifiable possible traces of the corresponding trans-ring junction diastereomers.

(Table 3.6, Entry 7) General procedure D was followed using cyclohexene 165f (85 mg, 0.23 mmol), palladacycle 100 (11 mg, 11.4 µmol) and MeNCy$_2$ (194 µl, 0.913 mmol). After 5 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1) afforded the phenanthridine as a colourless oil (52 mg, 79%). $^1$H NMR of this oil showed it to be a 18:34:30 mixture of double bond isomers (195f:196f:197f), with possible traces of the corresponding trans-ring junction diastereomers (7:11:0).
[1,3]dioxolo[4,5-j]phenanthridine 195k-197k

(Table 3.5, Entry 8) General procedure C was followed using cyclohexene 165k (65 mg, 0.16 mmol), palladacycle 100 (8 mg, 8 µmol), Ag$_2$CO$_3$ (44 mg, 0.16 mmol) and DMF (2.5 ml). After 2 h at 140 °C, flash chromatography (hexane:EtOAc, 100:1–100:5) afforded the phenanthridine as a colourless oil (47 mg, 91%). $^1$H NMR of this oil showed it to be an 76:18:6 mixture of double bond isomers (195k:196k:197k).

(Table 3.6, Entry 8) General procedure D was followed using cyclohexene 165k (24 mg, 59 µmol), palladacycle 100 (3 mg, 3.0 µmol), MeNCy$_2$ (52 µl, 0.24 mmol) and DMF (2 ml). After 24 h at 140 °C, flash chromatography (hexane:EtOAc, 20:1) afforded the phenanthridine as a colourless oil (12 mg, 59%). $^1$H NMR of this oil showed it to be a 41:26:33 mixture of double bond isomers (195k:196k:197k). Additionally, 32% of the dehalogenated product 198k was recovered.

(Table 3.6, Entry 9) General procedure E (Method A) was followed using cyclohexene 165k (85 mg, 0.21 mmol), Pd$_2$(dba)$_3$ (9.6 mg, 11 µmol), P(Bu)$_3$HBF$_4$ (6.1 mg, 21 µmol) and MeNCy$_2$ (176 µl, 0.83 mmol). After 18 h at r.t., flash chromatography (hexane:EtOAc, 100:4) afforded the phenanthridine as a colourless oil (55 mg, 80%). $^1$H NMR of this oil showed it to be a 18:46:36 mixture of double bond isomers (195k:196k:197k). Additionally, 11% of the dehalogenated product 198k was recovered.

(Table 3.6, Entry 10) General procedure E (Method B) was followed using cyclohexene 165k (844 mg, 2.06 mmol), Pd$_2$(dba)$_3$ (94 mg, 0.10 mmol), P(Bu)$_3$HBF$_4$ (56 mg, 0.21 mmol) and MeNCy$_2$ (1.75 ml, 8.24 mmol). After 18 h at 50 °C, flash chromatography (hexane:EtOAc, 100:4) afforded the phenanthridine as a colourless oil (676 mg, 99%). $^1$H NMR of this oil showed it to be a 37:39:24 mixture of double bond isomers (195k:196k:197k).
Experimental

(4aSR,10bSR)-9-Methyl-4,4a,6,10b-tetrahydro-3H-phenanthridine-5-carboxylic acid tert-butyl ester 195a (Δ\(^{1,2}\) isomer)

R\(_f\) [hexane:EtOAc, 10:1] = 0.46; MP 105 °C; \(\nu_{\text{max}}\) (CHCl\(_3\))/cm\(^{-1}\) 2972, 1692 (C=O), 1398, 1364, 1169; \(^1H\) NMR \(\delta\) (360 MHz, 323 K, CDCl\(_3\)) 7.11 (1H, d, Ar\(H\)), 7.00 (2H, m, 2xAr\(H\)), 6.18-6.12 (1H, m, CH\(C=CH\)), 5.88-5.83 (1H, m, CH=CH\(CH_2\)), 4.68 (1H, d, \(J\) 16.3, CH\(X\)H\(Y\)Ar), 4.41 (1H, br s, NCH), 4.35 (1H, d, /uni0408\(16.3\), CH\(X\)H\(Y\)Ar), 3.54 (1H, br s, NCHC), 2.34 (3H, s, CH\(_3\)), 2.29-2.16 (1H, m, CH\(A\)H\(B\)), 2.15-2.05 (1H, m, CH\(_A\)H\(_B\)), 1.74-1.69 (1H, m, CH\(_C\)H\(_D\)), 1.61-1.50 (10H, m, 3 x CH\(_3\)+CH\(_C\)H\(_D\)); \(^{13}C\) NMR \(\delta\) (90.0 MHz, 323 K, CDCl\(_3\)) 155.0 (C), 137.6 (C), 136.3 (C), 128.2 (C), 128.1 (CH), 127.4 (CH), 126.6 (CH), 125.9 (CH), 123.8 (C), 79.6 (CH), 50.5 (CH), 43.3 (CH\(_2\)), 37.2 (CH), 28.5 (CH\(_2\)), 28.5 (3xCH\(_3\)), 25.3 (CH\(_2\)), 21.1 (CH\(_3\)); \textit{m/z} (EI) 299 ([M]\(^+\), 1 %), 242 (100), 198 (15), 189 (26), 144 (11); HRMS (EI) Found: [M]\(^+\) 299.1880. C\(_{19}\)H\(_{25}\)NO\(_2\) requires 299.1880.

Diagnostic \(^1H\) NMR data for 196a (Δ\(^{2,3}\) isomer)

\(^1H\) NMR \(\delta\) (360 MHz, 323 K, CDCl\(_3\)) 7.04 (3H, m, 3xAr\(H\)), 5.70-5.66 (1H, m, CH=CH), 5.45-5.40 (1H, m, CH=CH), 4.55 (1H, d, \(J\) 16.2, CH\(_X\)H\(_Y\)), 4.48 (1H, d, \(J\) 16.2, CH\(_X\)H\(_Y\)), 4.43 (1H, br s, NCH), 3.18 (1H, br s, NCHC), 2.63-2.56 (1H, m, CH\(_A\)H\(_B\)), 2.35 (3H, s, CH\(_3\)), 2.24-2.19 (1H, m, CH\(_C\)H\(_D\)), 1.57-1.48 (10H, m, CH\(_C\)H\(_D\)+3xCH\(_3\)).

Diagnostic \(^1H\) NMR data for 197a (Δ\(^{3,4}\) isomer)

\(^1H\) NMR \(\delta\) (360 MHz, 323 K, CDCl\(_3\)) 5.70-5.66 (1H, m, CH=CH), 5.53 (1H, dd, \(J\) 8.5, CH=CH), 5.06 (1H, br s, NCH), 4.82 (1H, d, \(J\) 16.7, CH\(_X\)H\(_Y\)), 4.21 (1H, d, \(J\) 16.7, CH\(_X\)H\(_Y\)), 3.26 (1H, br s, NCHCH), 2.10-1.95 (1H, m, CH\(_A\)H\(_B\)), 1.89-1.79 (1H, m, CH\(_A\)H\(_B\)).
Experimental

(4aSR,10bSR)-9-Fluoro-4,4a,6,10b-tetrahydro-3H-phenanthridine-5-carboxylic acid tert-butyl ester 195b (A\textsuperscript{1,2} isomer)

$R_f$ [hexane:EtOAc, 3:1] = 0.57; $\nu_{\text{max}}$ (CHCl\textsubscript{3})/cm\textsuperscript{-1} 2974, 2928, 1692 (C=O), 1498, 1400, 1365; \textsuperscript{1}H NMR $\delta$ (360 MHz, 323 K, CDCl\textsubscript{3}) 7.07 (1H, dd, $J$ 8.4, 5.7, ArH), 7.00 (1H, dd, $J$ 9.9, 2.6, ArH), 6.88 (1H, td, $J$ 8.4, 2.6, ArH), 6.12-6.06 (1H, m, CHC=CH), 5.89-5.87 (1H, m, CH=CHCH\textsubscript{2}), 4.65 (1H, d, $J$ 16.3, C\textsubscript{H}XH\textsubscript{Y}Ar), 4.40 (1H, br s, NCH), 4.36 (1H, d, $J$ 16.3, CH\textsubscript{3}H\textsubscript{Y}Ar), 3.53 (1H, br s, NCHC=O), 2.31-2.18 (1H, m, CH\textsubscript{A}H\textsubscript{B}), 2.17-2.08 (1H, m, CH\textsubscript{A}H\textsubscript{B}), 1.77-1.68 (1H, m, CH\textsubscript{C}H\textsubscript{D}), 1.53-1.46 (10H, m, 3xC\textsubscript{H}\textsubscript{3}+CH\textsubscript{C}H\textsubscript{D}); \textsuperscript{13}C NMR $\delta$ (90.0 MHz, 323 K, CDCl\textsubscript{3}) 161.9 (1C, d, $J$ 244.1, C), 154.6 (C), 140.0 (1C, d, $J$ 6.8, C), 129.0 (CH), 127.5 (1C, d, $J$ 8.0, CH), 126.5 (CH), 123.4 (C), 114.4 (1C, d, $J$ 22.1, CH), 113.0 (1C, d, $J$ 21.8, CH), 79.8 (C), 50.2 (CH), 43.0 (CH\textsubscript{2}), 37.3 (CH), 28.5 (3xCH\textsubscript{3}), 25.4 (CH\textsubscript{2}), 24.0 (CH\textsubscript{2}); $m/z$ (EI) 303 ([M]+, 8%), 247 (95), 246 (90), 202 (27), 193 (100), 148 (36); HRMS (EI) Found: [M]+ 303.1626. C\textsubscript{18}H\textsubscript{22}FNO\textsubscript{2} requires 303.1629.

Diagnostic \textsuperscript{1}H NMR data for 196b (A\textsuperscript{2,3} isomer)

\textsuperscript{1}H NMR $\delta$ (360 MHz, 323 K, CDCl\textsubscript{3}) 7.12 (1H, dd, $J$ 8.3, 5.7, ArH), 6.94 (1H, d, $J$ 10.5, ArH), 6.92-6.87 (1H, m, ArH), 5.69-5.66 (1H, m, CH=CH), 5.46-5.41 (1H, m, CH=CH\textsubscript{2}), 4.57 (1H, d, $J$ 16.2, CH\textsubscript{3}H\textsubscript{Y}), 4.46 (1H, br s, NCH), 4.45 (1H, d, $J$ 16.1, CH\textsubscript{3}H\textsubscript{Y}), 3.18 (1H, s, NCHC=O), 2.79-2.73 (1H, m, CH\textsubscript{A}H\textsubscript{B}), 2.67-2.60 (1H, m, CH\textsubscript{A}H\textsubscript{B}), 2.27-2.20 (1H, m, CH\textsubscript{C}H\textsubscript{D}), 1.53-1.45 (10H, m, CH\textsubscript{C}H\textsubscript{D}+3xCH\textsubscript{3})

Diagnostic \textsuperscript{1}H NMR data for 197b (A\textsuperscript{3,4} isomer)

\textsuperscript{1}H NMR $\delta$ (360 MHz, 323 K, CDCl\textsubscript{3}) 5.69-5.66 (1H, m, CH=CH), 5.52 (1H, d, $J$ 10.2, 1.0, CH=CH\textsubscript{2}), 5.08 (1H, br s, NCH), 4.84 (1H, d, $J$ 16.4, CH\textsubscript{3}H\textsubscript{Y}), 4.19 (1H, d, $J$ 16.4, CH\textsubscript{3}H\textsubscript{Y}), 3.28 (1H, br s, NCHC=O), 2.40-2.30 (1H, m, CH\textsubscript{A}H\textsubscript{B}), 2.12-2.00 (1H, m, CH\textsubscript{A}H\textsubscript{B}).
Experimental

(4aSR,10bSR)-8-Methoxy-4,4a,6,10b-tetrahydro-3H-phenanthridine-5-carboxylic acid tert-butyl ester 195c (Δ1,2 isomer)

Rf [hexane:EtOAc, 3:1] = 0.71; νmax (CHCl3)/cm⁻¹
2974, 1691 (C=O); ¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.19 (1H, d, J 8.5, ArH), 6.79 (1H, dd, J 8.5, 2.7, ArH), 6.66 (1H, d, J 2.7, ArH), 6.14-6.09 (1H, m, CHCH=CH), 5.84-5.80 (1H, m, CH=CHCH₂), 4.69 (1H, d, J 16.6, CHXHYAr), 4.34 (1H, br s, NCHCH), 4.30 (1H, d, J 16.6, CHXHYAr), 3.79 (3H, s, CH₃), 3.51 (1H, br s, NCHCH), 2.27-2.16 (1H, m, CH₃H₂B), 2.12-2.04 (1H, m, CH₃H₂B), 1.74-1.65 (1H, m, CH₃H₂D), 1.58-1.47 (10H, m, CH₃H₂D+3 x CH₃); ¹³C NMR δ (90.0 MHz, 323 K, CDCl₃) 157.9 (C), 154.9 (C), 130.0 (C), 128.5 (CH), 128.0 (CH), 127.6 (CH), 125.4 (CH), 113.0 (CH), 111.1 (CH), 79.6 (C), 55.2 (CH₂), 50.5 (CH), 43.7 (CH₂), 36.6 (CH), 28.6 (3xCH₃), 26.5 (CH₂), 25.3 (CH₂); m/z (EI) 315 ([M]+, 2 %), 259 (77), 242 (100), 205 (47); HRMS (EI) Found: [M]+ 315.1831. C₂₉H₂₅NO₃ requires 315.1829.

Diagnostic ¹H NMR data for 196c (Δ₂,₃ isomer)

¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.14 (1H, d, J 8.6, ArH), 6.73 (1H, d, J 2.3, ArH), 5.70-5.62 (1H, m, CH=CH), 5.44-5.40 (1H, m, CH=CH), 4.52 (2H, s, CH₂Ar), 3.15 (1H, br s, NCHCH), 2.81 (1H, dd, J 22.9, 4.7, CH₃H₂B), 2.62-2.54 (1H, m, CH₃H₂B).

Diagnostic ¹H NMR data for 197c (Δ₃,₄ isomer)

¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.26 (1H, d, J 8.6, ArH), 6.60 (1H, s, ArH), 5.51 (1H, d, J 10.2, CH=CH), 5.05 (1H, br s, NCH), 4.83 (1H, d, J 17.1, CH₃H₂Y), 4.22 (1H, d, J 17.1, CH₃H₂Y), 3.24 (1H, br s, NCHCH).
(4aSR,10bSR)-8,9-Dimethoxy-4,4a,6,10b-tetrahydro-3H-phenanthridine-5-carboxylic acid tert-butyl ester 195d (Δ^{1,2} isomer)

R_f [hexane:EtOAc, 3:1] = 0.44; MP 124 °C; ν_max (CHCl_3)/cm\(^{-1}\) 2973, 1692 (C=O); \(^1\)H NMR \(\delta\) (360 MHz, 323 K, CDCl_3) 6.77 (1H, s, ArH), 6.60 (1H, s, ArH), 6.12-6.07 (1H, m, CHCH=CH), 5.84-5.81 (1H, m, CH=CHCH_2), 4.62 (1H, d, \(J\) 16.3, CHXHYAr), 4.37 (1H, br s, NCHCH), 4.27 (1H, d, \(J\) 16.3, CHXHYAr), 3.85 (3H, s, CH_3), 3.83 (3H, s, CH_3), 3.47 (1H, br s, NCHCH), 2.25-2.20 (1H, m, CH_AH_B), 2.11-2.03 (1H, m, CH_AH_B), 1.69-1.65 (1H, m, CH_CH_D), 1.57 (1H, td, \(J\) 16.8, 5.8, CH_CH_D), 1.50-1.48 (1H, m, 3 x CH_3); \(^{13}\)C NMR \(\delta\) (90.0 MHz, 323 K, CDCl_3) 155.0 (CH), 148.2 (CH), 147.6 (C), 129.8 (C), 128.3 (CH), 127.2 (CH), 124.4 (C), 111.2 (CH), 109.5 (CH), 79.7 (C), 56.0 (2xCH_3), 50.2 (CH), 43.0 (CH), 36.6 (CH), 28.4 (3xCH_3), 25.3 (CH_2), 23.9 (CH_2); m/z (FAB, 3-NOBA) 346 ([M+H]^+), 26 %), 289 (100), 244 (82), 216 (36), 190 (52); HRMS (FAB, 3-NOBA) Found: [M+H]^+ 346.2017. C_{20}H_{28}NO_4 requires 346.2013.

Diagnostic \(^1\)H NMR data for 196d (Δ^{2,3} isomer)

\(^1\)H NMR \(\delta\) (360 MHz, 323 K, CDCl_3) 6.75 (1H, s, ArH), 6.66 (1H, s, ArH), 5.67-5.63 (1H, m, CH=CH), 5.44-5.40 (1H, m, CH=CH), 4.46 (2H, s, CH_2Ar), 3.13 (1H, br s, NCHCH), 2.77-2.73 (1H, m, CH_AH_B), 2.61-2.56 (1H, m, CH_AH_B).

Diagnostic \(^1\)H NMR data for 197d (Δ^{3,4} isomer)

\(^1\)H NMR \(\delta\) (360 MHz, 323 K, CDCl_3); 6.82 (1H, s, ArH), 6.53 (1H, s, ArH), 5.72-5.66 (1H, m, CH=CH), 5.48 (1H, dd, \(J\) 10.1, CH=CH), 5.03 (1H, br s, NCH), 4.75 (1H, d, \(J\) 16.5, CH_XHY), 4.13 (1H, d, \(J\) 16.5, CH_XHY), 3.21 (1H, br s, NCHCH).
Experimental

(4aSR,12cSR)-4,4a,6,12c-Tetrahydro-3H-benzo[k]phenanthridine-5-carboxylic acid tert-butyl ester 195e (Δ1,2 isomer)

$\text{R}_f$ [hexane:EtOAc, 3:1] = 0.80; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 2926, 1688 (C=O), 1400, 1166; $^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 8.08 (1H, d, $J$ 8.4, ArH), 7.87 (1H, dd, $J$ 8.1, 0.7, ArH), 7.71 (1H, d, $J$ 8.3, ArH), 7.55 (1H, ddd, $J$ 8.3, 6.8, 1.4, ArH), 7.48 (1H, ddd, $J$ 8.1, 6.8, 1.3, ArH), 7.29 (1H, d, $J$ 8.3, ArH), 5.97-5.92 (1H, m, C=CH), 5.43 (1H, ddd, $J$ 9.9, 1.6, 0.8, CH=CH), 5.11 (1H, d, $J$ 15.1, CH$_X$H$_Y$Ar), 4.62-4.59 (1H, m, CHCH=CH), 4.29-4.26 (1H, m, NCH), 4.23 (1H, d, $J$ 15.1, CH$_X$H$_Y$Ar), 2.56-2.21 (1H, m, CH$_C$H$_D$), 2.37-2.25 (1H, m, CH$_A$H$_B$), 2.17-2.07 (1H, m, CH$_A$H$_B$), 1.91-1.84 (1H, dddd, $J$ 13.6, 11.3, 5.2, 2.5, CH$_C$H$_D$), 1.49 (9H, m, 3xCH$_3$); $^{13}$C NMR $\delta$ (90.6 MHz, 323 K, CDCl$_3$) 155.2 (C), 133.7 (C), 133.4 (C), 130.6 (2xC), 129.2 (CH), 129.0 (CH), 126.8 (CH), 126.6 (CH), 126.2 (CH), 125.1 (CH), 124.7 (CH), 122.4 (CH), 79.6 (C) 49.8 (CH), 45.2 (CH$_2$), 35.2 (CH), 28.5 (3xCH$_3$), 26.9 (CH$_2$), 20.6 (CH$_2$); $m/z$ (EI) 335 ([M]$^+$, 4 %), 307 (30), 242 (35), 136 (100); HRMS (EI) Found: [M]$^+$,335.1880. C$_{22}$H$_{25}$NNO$_2$ requires 335.1880.

Diagnostic data for 196e (Δ2,3 isomer).

$^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 4.98 (1H, d, $J$ 16.1, CH$_X$H$_Y$Ar), 4.56 (1H, d, $J$ 16.1, CH$_X$H$_Y$Ar), 4.11 (1H, td, $J$ 5.7, 2.6, CHCH$_2$), 3.95-3.88 (1H, m, NCHCH$_2$), 2.97-2.92 (1H, m, CH$_A$H$_B$).

Diagnostic data for 197e (Δ3,4 isomer).

$^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 4.96 (1H, d, $J$ 16.0, CH$_X$H$_Y$Ar), 4.81-4.76 (1H, m, CHCH=CH), 4.35 (1H, d, $J$ 16.0, CH$_X$H$_Y$Ar), 4.03-3.97 (1H, m, NCHCH$_2$).
Experimental

(5aSR,9aSR)-5a,6,7,9a-Tetrahydro-4H-thieno[2,3-c]quinoline-5-carboxylic acid tert-butyl ester 195f (Δ\textsuperscript{1,2} isomer)

\[ R_f \text{ [hexane:EtOAc, 3:1]} = 0.79; \nu_{\max} \text{ (CHCl}_3)/cm\textsuperscript{-1} 3361, 2974, 2928, 1692 (C=O), 1400, 1365; ^1H NMR \delta (360 MHz, 323 K, CDCl}_3) 7.16 (1H, d, J 5.1, HetH), 6.90 (1H, d, J 5.1, HetH), 6.09-6.05 (1H, m, CH=CH), 5.80-5.76 (1H, m, CH=CH), 4.98 (1H, d, J 16.8, CH\textsubscript{X}H\textsubscript{Y}Ar), 4.60 (1H, br s, CHN), 4.24 (1H, d, J 16.8, 2.0, CH\textsubscript{X}H\textsubscript{Y}Ar), 3.48 (1H, br s, NCHCH), 2.33-2.20 (1H, m, CH\textsubscript{A}H\textsubscript{B}), 2.15-2.06 (1H, m, CH\textsubscript{A}H\textsubscript{B}), 1.75-1.60 (2H, m, CH\textsubscript{2}), 1.51 (9H, s, 3xCH\textsubscript{3}); ^13C NMR \delta (90.6 MHz, 323 K, CDCl}_3) 154.7 (C), 129.5 (C), 127.6 (CH), 127.3 (CH), 125.8 (CH), 123.9 (C), 123.1 (CH), 80.0 (C), 49.3 (CH), 39.9 (CH\textsubscript{2}), 35.9 (CH), 28.4 (3xCH\textsubscript{3}), 25.5 (CH\textsubscript{2}), 22.9 (CH\textsubscript{2}); m/z (El) 292 ([M+H]^+) 3 %, 236 (100), 234 (55), 177 (31), 175 (30); HRMS (El) Found: [M]^+ 291.1298. C\textsubscript{16}H\textsubscript{21}O\textsubscript{2}NS requires 291.1288.

Diagnostic ^1H NMR data for 196f (Δ\textsuperscript{2,3} isomer)

^1H NMR \delta (360 MHz, 323 K, CDCl}_3) 5.65-5.58 (1H, m, CH=CH), 5.52-5.45 (1H, m, CH=CH), 4.89 (1H, d, J 17.6, CH\textsubscript{X}H\textsubscript{Y}Ar), 4.40 (1H, d, J 17.2, CH\textsubscript{X}H\textsubscript{Y}Ar), 3.17 (1H, br s, NCHCH), 2.72-2.65 (2H, m CH\textsubscript{2}).

Diagnostic ^1H NMR data for 197f (Δ\textsuperscript{3,4} isomer)

^1H NMR \delta (360 MHz, 323 K, CDCl}_3) 5.90-5.81 (1H, m, CH=CH), 5.50-5.42 (1H, m, CH=CH), 4.88 (1H, d, J 17.3, CH\textsubscript{X}H\textsubscript{Y}Ar), 4.18 (1H, d, J 17.3, CH\textsubscript{X}H\textsubscript{Y}Ar), 3.24 (1H, br s, NCHCH).
Experimental

(4aSR,11bSR)-4,4a,6,11b-Tetrahydro-3H-[1,3]dioxolo[4,5-f]phenanthridine-5-carboxylic acid tert-butyl ester 195k ($\Delta^{1,2}$ isomer)

$\text{R}_f$ [hexane:EtOAc, 3:1] = 0.65; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 1692 (C=O), 1484, 1166; $^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 6.77 (1H, s, ArH), 6.59 (1H, s, ArH), 6.08-6.03 (1H, m, CH=CH), 5.92 (2H, s, OCH$_2$O), 5.86-5.83 (1H, m, CH=CH), 4.58 (1H, d, $\nu_{\text{uns}}$ 16.2, C$_X$H$_X$YAr), 4.36 (1H, br s, C$_H$CH=CH), 4.29 (1H, d, $\nu_{\text{uns}}$ 16.2, CH$_X$H$_Y$Ar), 3.46 (1H, m, NC$_H$), 2.26-2.19 (1H, m, CH$_A$H$_B$), 2.16-2.12 (1H, m, CH$_A$H$_B$), 2.72-1.68 (1H, m, CH$_C$H$_D$), 1.60-1.55 (1H, m, CH$_C$H$_D$), 1.51 (1H, s, 3xCH$_3$); $^{13}$C NMR $\delta$ (90.6 MHz, 323 K, CDCl$_3$) 154.9 (C), 146.7 (C), 145.8 (C), 131.0 (C), 128.5 (CH), 127.2 (CH), 125.7 (C), 107.7 (CH), 106.2 (CH), 100.7 (CH$_2$), 79.6 (C), 50.4 (CH), 43.6 (CH$_2$), 37.1 (CH), 28.5 (3xCH$_3$), 25.3 (CH$_2$), 24.1 (CH$_2$); m/z (EI) 329 ([M]$^+$, 1%), 272 (100); HRMS (EI) Found: [M]$^+$, 329.1621. C$_{19}$H$_{23}$O$_4$N requires 329.1622.

Diagnostic $^1$H NMR data for 196k ($\Delta^{2,3}$ isomer)

$^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 6.74 (1H, s, ArH), 6.65 (1H, s, ArH), 5.92 (2H, s, OCH$_2$O), 5.69-5.65 (1H, m, CH=CH), 5.47-5.42 (1H, m, CH=CH), 4.41 (2H, s, CH$_2$Ar), 3.10 (1H, br s, NCHCH), 2.72 (1H, dd, $\nu_{\text{uns}}$ 18.3, 4.9, CH$_A$H$_B$), 2.63-2.56 (1H, m, CH$_A$H$_B$), 2.25-2.20 (1H, m, CH$_C$H$_D$), 1.63-1.55 (1H, m, CH$_C$H$_D$), 1.52 (9H, s, 3xCH$_3$).

Diagnostic $^1$H NMR data for 197k ($\Delta^{3,4}$ isomer)

$^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 6.82 (1H, s, ArH), 6.52 (1H, s, ArH), 5.90 (2H, s, OCH$_2$O), 5.73-5.70 (1H, m, CH=CH), 5.52-5.48 (1H, m, CH=CH), 5.02 (1H, m, NCH), 4.74 (1H, d, $\nu_{\text{uns}}$ 16.5, ArCH$_X$H$_Y$), 4.13 (1H, d, $\nu_{\text{uns}}$ 16.5, ArCH$_X$H$_Y$), 3.20 (1H, m, NCHCH).
Experimental

(Benzo[1,3]dioxol-5-ylmethyl)-(cyclohex-2-enyl)-carbamic acid tert-butyl ester

$R_f$ [hexane:EtOAc, 3:1] = 0.69; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$: 1686 (C=O), 1490, 1245, 1166; $^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 6.77 (1H, br s, ArH), 6.73 (1H, d, $J$ 8.0, ArH), 6.69 (1H, br d, $J$ 8.6, ArH), 5.93 (2H, s, OCH$_2$O), 5.82-5.80 (1H, m, CH=CH), 5.49 (1H, d, $J$ 10.2, CH=CH), 4.71 (1H, br s, CHN), 4.34 (1H, d, $J$ 16.0, CH$_3$H$_2$Ar), 4.20 (1H, d, $J$ 16.0, CH$_3$H$_2$Ar), 1.99-1.97 (2H, m, CH$_2$), 1.90-1.82 (1H, m, CH$_3$H$_3$), 1.79-1.71 (1H, m, CH$_3$H$_3$), 1.66-1.43 (11H, m, CH$_2$+3xCH$_3$); $^{13}$C NMR $\delta$ (90.6 MHz, 323 K, CDCl$_3$), 155.9 (C), 147.6 (C), 146.1 (C), 134.6 (C), 130.5 (CH), 129.0 (CH), 119.8 (CH), 107.8 (CH), 107.5 (CH), 100.7 (CH$_2$), 79.6 (C), 53.3 (CH), 47.3 (CH$_2$), 28.4 (3xCH$_3$), 28.1 (CH$_2$), 24.6 (CH$_2$), 21.5 (CH$_2$); $m/z$ (EI) 331 ([M]$^+$, 13 %), 275 (38), 194 (100), 150 (14), 140 (14), 136 (28), 135 (46); HRMS (EI) Found: [M]$^+$, 331.1775. C$_{19}$H$_{25}$O$_4$N requires 331.1778.
(1aSR,3aSR,9bSR,9cRS)-1a,3a,5,9b,9c-Hexahydro-2H-1-oxa-4-aza-cyclopropa[c]phenanthrene-4-carboxylic acid tert-butyl ester 212

To a solution of mCPBA (42 mg, 0.22 mmol) in CH$_2$Cl$_2$ (4 ml) at r.t. was added dropwise 1,2-phenanthridine 96b (20 mg, 0.07 mmol) in CH$_2$Cl$_2$ (1 ml). The reaction was stirred for 2 h at r.t. then diluted with CH$_2$Cl$_2$ (15 ml) and washed with Na$_2$CO$_3$ (3 x 15 ml, sat. aq.). The organics were dried, concentrated under reduced pressure and purified by flash chromatography (hexane:EtOAc, 10:1) to afford epoxy phenanthridine 212 as a colourless oil (12 mg, 57%) and epoxy phenanthridone 213 as a colourless oil (8 mg, 36%).

R$_f$ [hexane:EtOAc, 3:1] = 0.54; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 2976, 1693 (C=O), 1234 (C-O);

$^1$H NMR $\delta$ (360 MHz, CDCl$_3$) 7.42 (1H, d, $J$ 6.9, ArH), 7.30-7.25 (2H, m, 2xArH), 7.19 (1H, d, $J$ 7.2, ArH), 4.77 (1H, d, $J$ 16.4, CH$_X$H$_Y$Ar), 4.29 (1H, br s, NCHCH$_2$), 4.26 (1H, d, $J$ 16.4, CH$_X$H$_Y$Ar), 3.60-3.57 (2H, m, CHOCH+CHCH$_2$), 3.23 (1H, t, $J$ 3.7, CHOCH), 2.12-2.03 (1H, m, CH$_A$H$_B$), 1.97-1.89 (1H, m, CH$_A$H$_B$), 1.51-1.40 (11H, m, CH$_2$+3xCH$_3$); $^{13}$C NMR $\delta$ (90.6 MHz, CDCl$_3$) 157.3 (C), 134.7 (C), 134.3 (C), 127.1 (CH), 126.7 (CH), 126.3 (CH), 126.1 (CH), 79.8 (C), 55.3 (CH), 51.8 (CH), 47.2 (CH), 43.9 (CH$_2$), 37.1 (CH), 28.4 (3xCH$_3$), 21.7 (CH$_2$), 21.6 (CH$_2$); m/z (El) 301 ([M]$^+$, 1 %), 244 ([M-1Bu]$^+$, 100), 228 (18), 172 (22); HRMS (El) Found: [M]$^+$, 301.1672. C$_{18}$H$_{23}$NO$_3$ requires 301.1673. This compound was also fully characterised by NOESY 2D NMR studies.
Experimental

(1aSR,3aSR,9bSR,9cRS)-5-Oxo-1a,3,3a,5,9b,9c-hexahydro-2H-1-oxa-4-aza-cyclopropa[c]phenanthrene-4-carboxylic acid tert-butyl ester 213

\[
\begin{align*}
R_f & \text{ [hexane:EtOAc, 3:1] } = 0.38; \ 
\upsilon_{\max} (\text{CHCl}_3)/\text{cm}^{-1} 2979, 1715 (\text{C}=\text{O}), 1691 (\text{C}=\text{O}), 1244 (\text{C}=-\text{O}); \ 
^1\text{H NMR} \ \delta (360 \text{ MHz, CDCl}_3) 8.21 (1\text{H}, \text{d}, J 7.8, 1.4, \text{ArH}), 7.58 (1\text{H}, \text{td}, J 7.5, 1.5, \text{ArH}), 7.73 (1\text{H}, \text{d}, J 7.7, \text{ArH}), 7.42 (1\text{H}, \text{t}, J 7.7, \text{ArH}), 4.56 (1\text{H}, \text{ddd}, J 12.2, 5.1, 3.2, \text{NCH}_2\text{CH}_2), 3.97-3.96 (1\text{H}, \text{m}, \text{CH}_2\text{CH}_2), 3.91 (1\text{H}, \text{t}, J 5.8, \text{CHOCH}), 3.27 (1\text{H}, \text{t}, J 4.1, \text{CHOCH}), 2.16-2.07 (1\text{H}, \text{m}, \text{CH}_A\text{H}_B), 1.98-1.89 (1\text{H}, \text{m}, \text{CH}_A\text{H}_B), 1.63-1.39 (1\text{H}, \text{m}, \text{CH}_2+3\text{xCH}_3); \ 
^{13}\text{C NMR} \ \delta (90.6 \text{ MHz, CDCl}_3) 162.9 (\text{C}), 152.7 (\text{C}), 136.9 (\text{C}), 133.2 (\text{CH}), 129.8 (\text{CH}), 128.9 (\text{C}), 127.5 (\text{CH}), 124.7 (\text{CH}), 83.4 (\text{C}), 77.1 (\text{CH}), 55.2 (\text{CH}), 51.2 (\text{CH}), 35.5 (\text{CH}), 27.9 (3\text{xCH}_3), 22.2 (\text{CH}_2), 21.6 (\text{CH}_2); \ 
\text{m/z (EI) } 315 ([M]^+, 7 \%), 260 (59), 216 (43), 146 (69), 57 (100); \ 
\text{HRMS (EI) Found: [M]^+}, 315.1467. \text{C}_{18}\text{H}_{21}\text{NO}_4 \text{ requires } 315.1465.
\end{align*}
\]
To a suspension of amine hydrochloride 93 (100 mg, 0.330 mmol) in DMF (5 ml) at r.t. was added K$_2$CO$_3$ (137 mg, 1.00 mmol) and the reaction stirred for 10 mins. Propargyl bromide (148 µl, 80 % by w/w in toluene, 1.66 mmol) was added dropwise and the reaction stirred for 16 h. The reaction was diluted with Et$_2$O (20 ml) and washed with NaCl (3 x 20 ml, sat. aq.), and the combined organics were dried (MgSO$_4$) and concentrated under reduced pressure. The resultant oil was purified using flash chromatography (hexane:EtOAc, 100:15) to afford propargyl amine 94f as a colourless oil (103 mg, 99%).

R$_f$ [hexane:EtOAc, 3: 1] = 0.89; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 3299(C≡C-H), 2931, 1439, 1025; $^1$H NMR $\delta$ (250 MHz, CDCl$_3$) 7.59 (1H, d, $J$ 7.6, ArH), 7.56 (1H, dd, $J$ 7.9, 1.2, ArH), 7.29 (1H, td, $J$ 7.4, 1.2, ArH), 7.10 (1H, td, $J$ 7.8, 1.4, ArH), 5.89-5.76 (2H, m, CH≡CCH), 3.91 (1H, d, $J$ 15.0, CH$_X$H$_Y$Ar), 3.82 (1H, d, $J$ 15.0, CH$_X$H$_Y$Ar), 3.56-3.53 (1H, m, CHN), 3.38 (2H, d, $J$ 2.4, CH$_2$C≡CH), 2.23 (1H, t, $J$ 2.4, $\equiv$CH), 2.03-1.84 (4H, m, 2xCH$_2$), 1.69-1.44 (2H, m, CH$_2$); $^{13}$C NMR $\delta$ (62.9 MHz, CDCl$_3$) 138.7 (C), 132.5 (CH), 130.6 (CH), 130.4 (CH), 129.7 (CH), 128.1 (C), 127.1 (CH), 124.2 (C), 81.4 (C), 72.2 (CH), 57.6 (CH), 52.9 (CH$_2$), 39.3 (CH$_2$), 25.2 (CH$_2$), 24.8 (CH$_2$), 21.2 (CH$_2$); m/z (EI) 305 ([81BrM]$^+$, 19 %), 303 ([79BrM]$^+$, 19), 277 (64), 275 (65), 251 (33), 249 (35), 213 (42), 171 (97), 169 (100), 106 (85); HRMS (EI) Found: [79BrM]$^+$, 303.0618. C$_{16}$H$_{18}$N$^{79}$Br requires 303.0617.
(2-Bromo-benzyl)-cyclohex-3-enyl-carbamic acid prop-2-ynyl ester 94h

To a suspension of amine hydrochloride 93 (100 mg, 0.33 mmol) in CH$_2$Cl$_2$ (10 ml) at 0 °C was added Et$_3$N (182 µl, 1.32 mmol) and propargyl chloroformate (130 µl, 1.32 mmol). The reaction was allowed to warm to r.t. and stirred for 16 h. The reaction was diluted with CH$_2$Cl$_2$ (10 ml) and washed with HCl (3 x 10 ml, 1 M aq.). The combined organics were concentrated under reduced pressure to afford Poc-amine 94h as a colourless oil (130 mg, 99%).

R$_f$ [hexane:EtOAc, 3:1] = 0.73; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 3298 (C≡C-H), 2937, 1703 (C=O), 1442, 1409; $^1$H NMR $\delta$ (360 MHz, 323 K, CDCl$_3$) 7.52 (1H, d, $J$ 7.7, ArH), 7.30-7.24 (2H, m, 2xArH), 7.10 (1H, td, $J$ 7.3, 2.2, ArH), 5.87-5.84 (1H, m, CH=C), 5.48-5.43 (1H, m, CH=CH), 4.86 (1H, br s, CHN), 4.77-4.71 (2H, m, CH$_2$C≡CH), 4.50 (1H, d, $J$ 17.3, CH$_2$Ar), 4.44 (1H, d, $J$ 17.3, CH$_2$YAr), 2.45-2.37 (1H, m, ≡CH), 2.02-1.90 (3H, m, CH$_2$ +CH$_2$), 1.80-1.70 (1H, m, CH$_2$), 1.70-1.49 (2H, m, CH$_2$); $^{13}$C NMR $\delta$ (90.6 MHz, 323 K, CDCl$_3$) 155.8 (C), 138.1 (C), 132.4 (CH), 131.9 (CH), 128.0 (CH), 127.7 (CH), 127.3 (CH), 127.2 (CH), 122.1 (C), 78.4 (C), 74.2 (CH), 54.0 (CH), 52.9 (CH$_2$), 47.6 (CH$_2$), 28.0 (CH$_2$), 24.4 (CH$_2$), 21.2 (CH$_2$); m/z (EI) 349 ($^{81}$Br$^+$, 13 %), 347 ($^{79}$Br$^+$, 14), 310 (99), 308 (100), 178 (57), 171 (88), 169 (93); HRMS (EI) Found: [$^{79}$Br$^+$], 347.0513. C$_{17}$H$_{18}$O$_2$N$^{79}$Br requires 347.0515.

220
(4aSR,10bSR)-3,4,4a,5,6,10b-Hexahydro-phenanthridine 245

Flash vacuum pyrolysis of Boc-protected Δ^{1,2} isomer phenanthridine 96b [500 mg, T_f 600 °C, T_i 140 °C, P 3.2 x 10^{-2} Torr, t 0.5 h], followed by Kugelrohr distillation (70 °C, 0.7 Torr) gave amine 245 as a yellow oil (193 mg, 60%).

R_f [CH_2Cl_2:MeOH, 9:1] = 0.36; \upsilon_{max} (CHCl_3)/cm^{-1} 3274 (NH), 3019, 2920, 1671 (C=C), 1449, 1260 (CN); ^1H NMR δ (360 MHz, CDCl_3) 7.22-7.21 (2H, m, 2xArH), 7.17-7.14 (1H, m, ArH), 7.03 (1H, d, J 7.5, ArH), 5.74-5.71 (1H, m, CH=CH), 5.66-5.62 (1H, m, CH=CH), 4.12 (1H, d, J 16.3, CH_XH_YAr), 4.04 (1H, d, J 16.3, CH_XH_YAr), 3.36 (1H, br s, NCHCH), 3.32-3.28 (1H, m, NCHC_H), 2.25-2.03 (2H, m, CH_2), 2.03-1.89 (2H, m, CH_2); ^13C NMR δ (90.6 MHz, CDCl_3) 138.4 (C), 135.7 (C), 130.2 (CH), 129.1 (CH), 126.4 (CH), 125.8 (CH), 125.7 (2xCH), 50.4 (CH), 48.3 (CH_2), 38.0 (CH), 27.4 (CH_2), 20.0 (CH_2); m/z (EI) 185 ([M]^+, 77 %), 170 (21), 168 (18), 131 (38), 130 (72), 128 (46); HRMS (EI) Found: [M]^+, 185.1196. C_{13}H_{15}N requires 185.1199.

(4aSR,10bSR)-1,4,4a,5,6,10b-Hexahydro-phenanthridine 246

Flash vacuum pyrolysis of Boc-protected Δ^{2,3} isomer phenanthridine 97b [900 mg, T_f 600 °C, T_i 140 °C, P 3.2 x 10^{-2} Torr, t 0.5 h], followed by Kugelrohr distillation (70 °C, 0.7 Torr) gave amine 246 as a yellow oil (500 mg, 81%).

R_f [CH_2Cl_2:MeOH, 9:1] = 0.34; \upsilon_{max} (CHCl_3)/cm^{-1} 3284 (NH), 3019, 2920, 1654 (C=C), 1453, 1260 (CN); ^1H NMR δ (360 MHz, CDCl_3) 7.17-7.13 (2H, m, 2xArH), 7.09-7.02 (2H, m, ArH), 5.73-5.66 (2H, m, CH=CH), 4.24 (1H, d, J 16.5, CH_XH_YAr), 4.15 (1H, d, J 16.5, CH_XH_YAr), 3.23 (1H, br s, NCHCH), 2.81 (1H, ddd, J 10.1, 6.4, 2.7, NCHCH), 2.65-2.59 (1H, m, CH_AH_B), 2.34-2.28 (1H, m, CH_AH_B), 2.15-2.10 (2H, m, CH_2); ^13C NMR δ (90.6 MHz, CDCl_3) 141.0 (C), 134.2 (C), 128.2 (CH), 126.0 (CH), 125.9 (CH), 125.8 (CH), 124.7 (CH), 124.1 (CH), 49.9 (CH), 48.5 (CH_2), 35.3 (CH), 31.9 (CH_2), 30.1 (CH_2); m/z (EI) 185 ([M]^+, 10 %), 130 (100); HRMS (EI) Found: [M]^+, 185.1202. C_{13}H_{15}N requires 185.1199.

221
Experimental

(4aSR,10bSR)-1,2,4a,5,6,10b-Hexahydro-phenanthridine 247

Flash vacuum pyrolysis of Boc-protected Δ³,4 isomer phenanthridine 98b [320 mg, Tᵣ 600 °C, Tᵢ 140 °C, P 3.2 x 10⁻² Torr, t 0.5 h], followed by Kugelrohr distillation (70 °C, 0.7 Torr) gave amine 247 as a yellow oil (190 mg, 71%).

Rᵣ [CH₂Cl₂:MeOH, 9:1] = 0.37; νₑₓₘₐₓ (CHCl₃)/cm⁻¹ 3283 (NH), 3020, 2902, 1654 (C=C), 1453, 1260 (CN); ¹H NMR δ (360 MHz, CDCl₃) 7.23-7.13 (3H, m, 3xArH), 7.03 (1H, d, J 7.2, ArH), 5.96-5.85 (2H, m, CH=CH), 4.05 (1H, d, J 16.6, CH₃Ar), 4.00 (1H, d, J 16.9, CH₃Ar), 3.46 (1H, br s, NCHCH), 2.74 (1H, dt, J 12.6, 3.6, NCHCH), 2.22-1.6 (4H, m, 2xCH₂); ¹³C NMR δ (90.6 MHz, CDCl₃) 139.3 (C), 135.8 (C), 130.0 (CH), 129.2 (CH), 128.3 (CH), 126.1 (CH), 125.7 (CH), 125.5 (CH), 50.7 (CH), 48.2 (CH₂), 36.5 (CH), 27.5 (CH₂), 25.8 (CH₂); m/z (EI) 185 ([M]+, 10 %), 130 (100); HRMS (EI) Found: [M]+, 185.1202. C₁₃H₁₅N requires 185.1199.
**General procedure L - Propargylation**

To a solution of the appropriate phenanthridine (1 eq) in acetone (5 ml) was added K$_2$CO$_3$ (3 eq) followed by relevant alkylating agent (1.1 eq). The reaction was heated at 60 °C for the stated time and then concentrated under reduced pressure. The crude product was purified by flash chromatography to the desired alkyl amine.

(4a$\text{SR}, 10b$SR)-5-(Prop-2'-ynyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine 96f

General procedure L was followed using amine 245 (150 mg, 0.81 mmol), acetone (5 ml), K$_2$CO$_3$ (368 mg, 2.67 mmol), and propargyl bromide (100 µl, 80 % w/w in toluene, 0.89 mmol). After 2 h, flash chromatography (CH$_2$Cl$_2$) afforded propargyl amine 96f as a yellow oil (103 mg, 57%).

$\text{R}_f$ [CH$_2$Cl$_2$:MeOH, 95:5] = 0.83; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 3290 (C≡C-H), 2925, 1696; $^1$H NMR $\delta$ (250 MHz, CDCl$_3$) 7.27-7.10 (3H, m, 3xArH), 7.10 (1H, d, J 7.2, ArH), 5.79 (2H, s, CH=CH), 4.01 (1H, d, J 15.0, CH$_2$H$_2$Ar), 3.83 (1H, dd, J 17.4, 2.4, CH$_2$H$_2$C≡CH), 3.81 (1H, d, J 15.0, CH$_2$H$_2$Ar), 3.56 (1H, dd, J 17.4, 2.4, CH$_2$H$_2$C≡CH), 3.56 (1H, br s, NCHCH), 3.16 (1H, br s, NCHCH), 2.28 (1H, t, J 2.4, C≡CH), 2.14-2.00 (3H, m, CH$_2$+CH$_2$H$_2$), 1.87-1.75 (1H, m, CH$_2$H$_2$B); $^{13}$C NMR $\delta$ (62.9 MHz, CDCl$_3$) 137.3 (C), 133.8 (C), 129.8 (CH), 128.0 (CH), 126.5 (CH), 126.4 (CH), 126.1 (CH), 125.6 (CH), 78.3 (C), 73.4 (CH), 53.8 (CH), 53.4 (CH$_2$), 42.3 (CH$_2$), 39.2 (CH), 23.2 (CH$_2$), 21.9 (CH$_2$); $m/z$ (EI) 223 ([M]$^+$, 59 %), 222 (100), 208 (16), 184 (17), 168 (36), 140 (34); HRMS (EI) Found: [M]$^+$, 223.1354. C$_{16}$H$_{17}$N requires 223.1356.
(4aSR,10bSR)-5-(Prop-2'-ynyl)-1,4,4a,5,6,10b-hexahydro-phenanthridine 97f

General procedure L was followed using amine 246 (50 mg, 0.27 mmol), acetone (2 ml), K$_2$CO$_3$ (112 mg, 0.81 mmol) and propargyl bromide (33 µl, 80 % w/w in toluene, 0.30 mmol). After 2 h, flash chromatography (CH$_2$Cl$_2$) afforded propargyl amine 97f as a colourless oil (45 mg, 75%).

R$_f$ [CH$_2$Cl$_2$:MeOH, 95:5] = 0.89; $\nu_{max}$ (CHCl$_3$)/cm$^{-1}$ 3292 (C≡C-H), 2925, 1663, 1604, 1430; $^1$H NMR $\delta$ (360 MHz, CDCl$_3$) 7.17-7.14 (2H, m, 2xArH), 7.12-7.08 (2H, m, 2xArH), 5.76-5.72 (1H, m, CH=CH), 5.67-5.63 (1H, m, CH=CH), 4.10 (1H, d, J 15.2, CH$_3$H=Ar), 3.88 (1H, d, J 15.2, CH$_3$H=Ar), 3.75 (1H, dd, J 15.3, 2.3, CH$_3$H=CH), 3.49 (1H, dd, J 15.3, 2.3, CH$_3$H=CH), 3.08-3.05 (1H, m, NCHCH), 2.99 (1H, td, J 7.9, 2.4, NCHCH), 2.53-2.43 (1H, m, CH$_3$H$_2$), 2.38-2.13 (3H, m, CH$_2$+CH$_3$H$_2$), 2.26 (1H, t, J 2.3, CH$_3$); $^{13}$C NMR $\delta$ (90.6 MHz, CDCl$_3$) 140.2 (C), 134.0 (C), 127.0 (CH), 126.5 (CH), 126.3 (CH), 125.8 (CH), 125.7 (CH), 122.9 (CH), 78.3 (C), 73.4 (CH), 54.4 (CH$_2$), 53.3 (CH), 42.2 (CH$_2$), 37.6 (CH), 31.4 (CH$_2$), 26.4 (CH$_2$); m/z (EI) 223 ([M]+, 6 %), 222 (6), 168 (100), 129 (25); HRMS (EI) Found: [M]$^+$, 223.1350. C$_{16}$H$_{17}$N requires 223.1356.
(4aSR,10bSR)-5-(Prop-2'-ynyl)-1,2,4a,5,6,10b-hexahydro-phenanthridine 98f

General procedure L was followed using amine 247 (52 mg, 0.18 mmol), acetone (5 ml), K₂CO₃ (76 mg, 0.55 mmol) and propargyl bromide (18 µl, 80% w/w in toluene, 0.20 mmol). After 2 h, flash chromatography (CH₂Cl₂) afforded propargyl amine 98f as a yellow oil (37 mg, 91%).

R.f [CH₂Cl₂:MeOH, 95:5] = 0.84; ν max (CHCl₃)/cm⁻¹ 3291 (C≡C-H), 3027, 2925, 1663; ¹H NMR δ (360 MHz, CDCl₃) 7.20-7.04 (3H, m, 3xAr H), 7.05 (1H, d, J 7.3, 2xArH), 6.02-5.93 (2H, m, CH=CH), 3.98 (1H, d, J 15.1, CHₓHyAr), 3.82 (1H, dd, J 17.2, 2.3, CHₓHₓQ≡CH), 3.78 (1H, d, J 15.1, CHₓHyAr), 3.51 (1H, dd, J 17.2, 2.4, CHₓHₓQ≡CH), 3.26 (1H, br s, NCHCH), 2.84 (1H, dt, J 11.2, 3.5, NCHCHH), 2.27 (1H, t, J 2.3, ≡CH), 2.16-2.04 (3H, m, CHₓ+CHₓHₓB), 1.85-1.76 (1H, m, CHₓHₓB); ¹³C NMR δ (90.6 MHz, CDCl₃) 138.8 (C), 134.5 (C), 132.1 (CH), 128.2 (CH), 126.2 (CH), 126.0 (CH), 125.6 (CH), 125.5 (CH), 78.5 (C), 73.1 (CH), 54.0 (CH₂), 54.0 (CH), 42.3 (CH₂), 38.0 (CH), 27.7 (CH₂), 25.7 (CH₂); m/z (EI) 223 ([M]+, 30 %), 222 (47), 194 (10), 169 (100), 129 (15).
Experimental

(4aSR,10bSR)-5-But-3-ynyl-3,4,4a,5,6,10b-hexahydro-phenanthridine 96g

General procedure L was followed using amine 245 (150 mg, 0.81 mmol), acetone (5 ml), K₂CO₃ (368 mg, 2.67 mmol) and 4-bromo-1-butyne (84 µl, 0.89 mmol). After 16 h flash chromatography (CH₂Cl₂) afforded homopropargyl amine 96g as a yellow oil (105 mg, 55%).

R₉ [CH₂Cl₂:MeOH, 9:1] = 0.9; υₘₐₓ (CHCl₃)/cm⁻¹ 3295 (C≡C-H), 3023, 2929; ¹H NMR δ (360 MHz, CDCl₃) 7.29 (1H, d, J 7.6, ArH), 7.19 (1H, t, J 7.5, ArH), 7.13 (1H, t, J 7.4, ArH), 7.03 (1H, d, J 7.5, ArH), 6.10-6.04 (1H, m, CH=CH), 5.82-5.77 (1H, m, CH=CH), 3.87 (1H, d, J 15.3, CHₓHᵧAr), 3.74 (1H, d, J 15.3, CHₓHᵧAr), 3.60 (1H, br s, NCH), 3.18-3.11 (1H, m, NCHCH), 2.97-2.92 (2H, m, CH₂), 2.52-2.47 (2H, m, CH₂), 2.17-2.10 (2H, m, CH₂), 2.01 (1H, t, J 2.6, =CHH), 1.83-1.75 (1H, m, CHₓHᵧ), 1.71-1.61 (1H, m, CHₓHᵧ); ¹³C NMR δ (90.6 MHz, CDCl₃) 137.4 (C), 133.1 (C), 128.7 (CH), 127.6 (CH), 127.4 (CH), 126.5 (CH), 126.3 (CH), 125.3 (CH), 82.8 (C), 69.0 (CH), 56.2 (CH), 52.9 (CH₂), 51.0 (CH₂), 37.8 (CH), 24.2 (CH₂), 20.0 (CH₂), 17.3 (CH₂); m/z (EI) 237 ([M]+, 5%), 198 (100), 141 (18), 128 (16); HRMS (EI) Found: [M]+, 237.1511. C₁₇H₁₉N requires 237.1512.
(4aSR,10bSR)-5-But-3-ynyl-1,4,4a,5,6,10b-hexahydro-phenanthridine 97g

General procedure L was followed using amine 246 (40 mg, 0.216 mmol), acetone (1.5 ml), K$_2$CO$_3$ (90 mg, 0.65 mmol) and 4-bromo-1-butyne (22 µl, 0.24 mmol). After 16 h flash chromatography (CH$_2$Cl$_2$–CH$_2$Cl$_2$:MeOH, 95:5) afforded homopropargyl amine 97g as a yellow oil (32 mg, 63%).

R$_f$ [CH$_2$Cl$_2$:MeOH, 9:1] = 0.65; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 3294 (C≡C-H), 2925, 1649 (C=C), 1452; $^1$H NMR $\delta$ (360 MHz, CDCl$_3$) 7.18-7.14 (3H, m, 3xAr $H$), 7.07-7.05 (1H, m, Ar$H$), 5.69-5.66 (1H, m, CH=CH), 5.60-5.56 (1H, m, CH=CH), 3.92 (2H, s, CH$_2$Ar), 3.16-3.12 (2H, m, 2xCH), 2.97-2.92 (2H, m, CH$_2$), 2.62-2.53 (1H, m, CH$_2$Ar), 2.49-2.42 (3H, m, CH$_2$+CH$_A$H$_B$), 2.21-2.19 (2H, m, CH$_2$), 2.00 (1H, t, J 2.7, ≡CH); $^{13}$C NMR $\delta$ (90.6 MHz, CDCl$_3$) 138.4 (C), 134.2 (C), 126.2 (2xCH), 126.0 (CH), 125.6 (CH), 125.5 (CH), 124.1 (CH), 82.8 (C), 69.0 (CH), 54.8 (CH), 52.9 (CH$_2$), 52.8 (CH$_2$), 36.8 (CH), 29.3 (CH$_2$), 24.0 (CH$_2$), 16.8 (CH$_2$); m/z (EI) 237 ([M]$^+$, 6 %), 198 (56), 182 (100), 144 (65), 128 (21); HRMS (EI) Found: [M]$^+$, 237.1509. C$_{17}$H$_{19}$N requires 237.1512.
Experimental

(4aSR,10bSR)-5-But-3-ynyl-1,2,4a,5,6,10b-hexahydro-phenanthridine 98g

General procedure L was followed using amine 247 (70 mg, 0.38 mmol), acetone (4 ml), K₂CO₃ (156 mg, 1.13 mmol) and 4-bromo-1-butyne (38 µl, 0.42 mmol). After 16 h flash chromatography (CH₂Cl₂) afforded homopropargyl amine 98g as a yellow oil (65 mg, 73 %).

Rᵣ [CH₂Cl₂:MeOH, 9:1] = 0.9; vₘₐₓ (CHCl₃)/cm⁻¹ 3294 (C≡C-H), 3022, 2925, 1648 (C=C); ¹H NMR δ (360 MHz, CDCl₃) 7.28 (1H, d, J 7.4, ArH), 7.19 (1H, t, J 7.3, ArH), 7.12 (1H, t, J 7.3, ArH), 7.01 (1H, d, J 7.4, ArH), 5.88 (1H, d, J 10.7, CH=CH), 5.82 (1H, d, J 11.9, CH=CH), 3.91 (1H, d, J 15.3, CHₓHₓAr), 3.69 (1H, d, J 15.3, CHₓHₓAr), 3.48 (1H, br s, NCHCH), 3.08-3.02 (1H, m, NCHCH), 3.00-2.89 (2H, m, CH₂), 2.46 (2H, t, J 7.1, CH₂), 2.24-2.18 (1H, m, CHₐH₈b), 2.01-1.93 (3H, m, CH₉+≡CH), 1.90-1.85 (1H, m, CHₐH₈b); ¹³C NMR δ (90.6 MHz, CDCl₃) 137.3 (C), 134.6 (C), 131.7 (CH), 127.3 (CH), 126.3 (CH), 126.2 (CH), 125.7 (CH), 125.4 (CH), 82.8 (C), 68.9 (CH), 56.3 (CH), 52.0 (2xCH₂), 35.9 (CH), 26.5 (CH₂), 23.4 (CH₂), 17.6 (CH₂); m/z (EI) 237 ([M⁺], 8 %), 199 (100), 169 (62), 167 (65), 164 (35), 141 (70); HRMS (EI) Found: [M⁺, 237.1515. C₁₁H₁₀N requires 237.1512.
Experimental

Tetrahydro-phenanthridine-5-carboxylic acid prop-2-ynyl ester 96h-98h

To a solution of amines 245-247 (271 mg, 1.46 mmol) at 0 °C in CH₂Cl₂ (15 ml) was added Et₃N (822 µl, 5.85 mmol) and propargyl chloroformate (573 µl, 5.85 mmol) dropwise. The reaction was allowed to warm to r.t. and stirred for 16 h. The reaction was diluted with CH₂Cl₂ (15 ml) and washed with HCl (3 x 15 ml, 1 M aq.). The combined organics were concentrated under reduced pressure to afford Poc-amide isomer mixture 96h-98h as a colourless oil (290 mg, 74 %). Flash chromatography (hexane:EtOAc, 100:5) afforded 96h (54 mg, 14%), 97h (48 mg, 12%), 98h (38 mg, 10%) and mixture 96h-98h (130 mg, 33%) all colourless oils.

(4aSR,10bSR)-4,4a,6,10b-Tetrahydro-3H-phenanthridine-5-carboxylic acid prop-2-ynyl ester 96h

Rᵣ [hexane:EtOAc, 3:1] = 0.64; vₓmax (CHCl₃)/cm⁻¹ 3291 (C≡C-H), 1700 (C=O); ¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.30 (1H, d, J 7.6, ArH), 7.24 (1H, td, J 7.2, 1.8, ArH), 7.18 (1H, tdd, J 7.2, 1.4, 0.7, ArH), 7.12 (1H, d, J 7.6, ArH), 6.16-6.11 (1H, m, CH=CH), 5.88-5.84 (1H, m, CH=CH), 4.81 (1H, d, J 16.5, CHXH₂YAr), 4.76 (2H, s, CH₂C=CH), 4.48 (1H, br s, NCHCH₂), 4.46 (1H, d, J 16.5, CHXH₂YAr), 3.60 (1H, br s, NCH), 2.46 (1H, t, J 1.2, =CH), 2.34-2.22 (1H, m, CH₁Ar₁), 2.17-2.07 (1H, m, CH₁Ar₂), 1.76-1.74 (1H, m, CH₁D₁), 1.67-1.55 (1H, m, CH₁D₂); ¹³C NMR δ (90.6 MHz, 323 K, CDCl₃) 154.6 (C), 137.4 (C), 131.7 (C), 128.3 (CH), 127.6 (CH), 127.0 (2xCH), 126.0 (2xCH), 78.5 (C), 74.3 (CH), 52.8 (CH₂), 50.7 (CH), 43.6 (CH₂), 37.1 (CH), 25.0 (CH₂), 24.0 (CH₂); m/z (El) 267 ([M]+, 34 %), 228 (100), 213 (50), 187 (37), 167 (59), 141 (21), 128 (30); HRMS (El) Found: [M]+, 267.1252. C₁₇H₁₇O₂N requires 237.1512.
Experimental

(4aSR,10bSR)-4,4a,6,10b-Tetrahydro-1H-phenanthridine-5-carboxylic acid prop-2-ynyl ester 97h

Rᵣ [hexane:EtOAc, 3:1] = 0.60; ν<sub>max</sub> (CHCl₃)/cm⁻¹ 3289 (C≡C-H), 1703 (C=O), 1695; <sup>1</sup>H NMR δ (360 MHz, 323 K, CDCl₃) 7.27-7.13 (4H, m, ArH), 5.71-5.68 (1H, m, CH=CH), 5.45-5.40 (1H, m, CH=CH), 4.84-4.80 (2H, m, CH₂), 4.66 (1H, d, J 16.2, CH₂H₀C≡CH), 4.59 (1H, d, J 16.2, CH₂H₀C≡CH), 4.51 (1H, br s, NCH), 3.23 (1H, t, J 4.8, NCH₂), 2.88 (1H, dd, J 18.3, 5.2, CH₃H₃B), 2.67-2.59 (1H, m, CH₃H₃B), 2.47 (1H, t, J 2.4, CH₃H₃D), 2.32-2.22 (1H, m, CH₃H₃D), 1.56-1.45 (1H, m, CH₃H₃D); <sup>13</sup>C NMR δ (90.6 MHz, 323 K, CDCl₃) 154.5 (C), 136.2 (C), 133.5 (C), 127.0 (CH), 126.4 (CH), 126.3 (CH), 125.2 (CH), 125.0 (CH), 123.8 (CH), 78.7 (C), 74.3 (CH), 52.8 (CH₂), 50.5 (CH), 45.0 (CH₂), 35.6 (CH), 27.1 (CH₂), 26.3 (CH₂); m/z (EI) 267 ([M⁺], 17 %), 228 (100), 184 (38), 167 (72); HRMS (EI) Found: [M⁺], 267.1252. C₁₇H₁₇O₂N requires 267.1254.

(4aSR,10bSR)-2,4a,6,10b-Tetrahydro-1H-phenanthridine-5-carboxylic acid prop-2-ynyl ester 98h

Rᵣ [hexane:EtOAc, 3:1] = 0.64; ν<sub>max</sub> (CHCl₃)/cm⁻¹ 3292 (C≡C-H), 1703 (C=O), 1433; <sup>1</sup>H NMR δ (360 MHz, 323 K, CDCl₃) 7.36 (1H, d, J 7.6, ArH), 7.28-7.15 (2H, m, 2xArH), 7.07 (1H, d, J 7.3, ArH), 5.75-5.72 (1H, m, CH=CH), 5.54 (1H, d, J 10.1, CH=CH), 5.17 (1H, br s, NCH₂), 4.92 (1H, d, J 16.6, CH₃H₃Ar), 4.78-4.77 (2H, m, CH₂C≡CH), 4.33 (1H, d, J 16.6, NCH₂), 3.35 (1H, br s, NCH), 2.47-2.40 (2H, m, CH₃C≡CH), 2.04-1.99 (1H, m, CH₃H₃B), 1.95-1.72 (2H, m, CH₂); <sup>13</sup>C NMR δ (90.6 MHz, 323 K, CDCl₃) 154.6 (C), 135.0 (C), 133.4 (C), 131.4 (CH), 127.0 (CH), 126.8 (CH), 126.6 (CH), 125.9 (CH), 125.8 (CH), 78.5 (C), 74.3 (CH), 53.0 (CH₂), 50.8 (CH), 42.8 (CH₂), 34.2 (CH), 25.1 (CH₂), 20.3 (CH₂); m/z (EI) 267 ([M⁺], 14 %), 228 (100), 184 (33), 167 (40); HRMS (EI) Found: [M⁺], 267.1254. C₁₇H₁₇O₂N requires 267.1254.
**General procedure M - RRM reactions of amines**

To a solution of the appropriate amine (1 eq) in CH$_2$Cl$_2$ (1 ml) was added HCl (1-2 ml, 1 M in Et$_2$O) and the solvent removed under reduced pressure. The resultant hydrochloride salt was dissolved in CH$_2$Cl$_2$ (10 ml) and degassed with ethylene for 10 mins. Hoveyda-Grubbs catalyst 2$^{nd}$ generation (0.15 eq) was added and the reaction stirred under an atmosphere of ethylene for 40 h at r.t. The crude product was washed with NaOH (3 x 20 ml, 1 M aq.) and the combined organics dried (MgSO$_4$), concentrated under reduced pressure and purified by flash chromatography to afford the appropriate product.

**General procedure M** was followed using propargyl amine 97f (50 mg, 0.22 mmol), CH$_2$Cl$_2$ (1 ml) and HCl (2 ml, 1 M in Et$_2$O), then CH$_2$Cl$_2$ (10 ml) and Hoveyda-Grubbs catalyst 2$^{nd}$ generation (21 mg, 33.6 µmol). Flash chromatography (CH$_2$Cl$_2$:MeOH, 100-100:1) afforded isoquinoline 237 as a colourless oil (40 mg, 71%).

R$_f$ [CH$_2$Cl$_2$:MeOH, 95:5] = 0.31; $\nu_{\text{max}}$ (CHCl$_3$)/cm$^{-1}$ 2925, 1655, 1636; $^1$H NMR $\delta$ (360 MHz, CDCl$_3$) 7.33 (1H, d, $J = 6.6$, ArH), 7.18-7.14 (2H, m, 2xArH), 7.04-7.02 (1H, m, ArH), 6.34 (1H, dd, $J = 17.8$, 10.9, CCH=CH$_2$), 6.00-5.88 (1H, dddd, $J = 17.1$, 10.3, 8.4, 5.6, CH$_2$CH=CH$_2$), 5.86-5.82 (1H, m, CH$_2$CH=C), 5.16 (1H, dq, $J = 17.1$, 1.2, CH$_2$CH=C=CH$_2$D), 5.12 (1H, br d, $J = 10.3$, CH$_2$CH=CH$_2$D), 5.06 (1H, d, $J = 17.8$, CCH=CH$_2$E), 4.97 (1H, d, $J = 10.9$, CCH=CH$_2$F), 4.07 (1H, d, $J = 15.8$, CCH=CH$_2$G), 3.78 (1H, d, $J = 15.8$, CH$_2$CH=CH$_2$H), 3.77 (1H, d, $J = 17.0$, NCH$_2$HO), 3.46 (1H, d, $J = 17.0$, NCH$_2$HO), 3.34-3.30 (2H, m, NCHCH), 2.91-2.84 (1H, m, CH$_2$=CHCH$_2$H)$_2$, 2.19-2.10 (1H, m, CH$_2$=CHCH$_2$H)$_2$, 2.06-1.94 (2H, m, CHCH$_2$)$_2$; $^{13}$C NMR $\delta$ (90.6 MHz, CDCl$_3$) 137.6 (CH), 136.8 (CH), 135.6 (C), 134.4 (C), 131.8 (C), 126.9 (CH), 126.3 (CH), 126.2 (CH), 126.0 (CH), 125.7 (CH), 116.4 (CH$_2$), 110.6 (CH$_2$), 53.8 (CH), 52.3 (CH$_2$), 50.0 (CH$_2$), 40.6 (CH), 34.2 (CH$_2$), 20.1 (CH$_2$); m/z (ESI+) 252 ([M+H]$^+$, 98 %), 211 (15), 172 (100), 145 (8), 131 (100); HRMS (El) Found: [M]$^+$, 251.1675. C$_{18}$H$_{21}$N requires 251.1669. This compound was also fully characterised by 2D COSY, NOESY and HSQC NMR experiments.
Experimental

(10SR,10aSR)-10-(But-3’-enyl)-2-vinyl-3,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline 238

General procedure M was followed using propargyl amine 98f (10 mg, 45 µmol), CH₂Cl₂ (1 ml) and HCl (1 ml, 1 M in Et₂O), then CH₂Cl₂ (5 ml) and Hoveyda-Grubbs catalyst 2nd generation (4.2 mg, 6.7 µmol). Flash chromatography (CH₂Cl₂:MeOH, 100-100:5) afforded isoquinoline 238 as a yellow oil (9 mg, 80%). This compound was not stable therefore full characterisation was not possible.

RF [CH₂Cl₂:MeOH, 95:5] = 0.36; ¹H NMR δ (360 MHz, CDCl₃) 7.18-7.16 (3H, m, 3xArH), 7.15-7.10 (1H, m, ArH), 6.52 (1H, dd, J 17.5, 10.9, CCH=CH₂), 5.89-5.77 (2H, m, CHCH=C+CH₂CH=CH₂), 5.14 (1H, br d, J 10.9, CCH=CHC₂H₇), 5.08 (1H, br d, J 17.5, CCH=CHC₂H₇), 5.03 (1H, dq, J 17.1, 1.5, CH₂CH=CHC₂H₇), 4.94 (1H, dq, J 11.2, 1.9, CH₂CH=CHC₂H₇), 4.08 (1H, d, J 14.6, CHXH₃Ar), 3.93-3.84 (4H, m, CHXH₃Ar+NCH₂+CH), 2.96-2.92 (1H, m, CH), 2.24-2.15 (2H, m, CH₂), 1.86-1.78 (2H, m, CH₂); ¹³C NMR δ (90.6 MHz, CDCl₃) 131.0 (CH), 128.9 (CH), 128.1 (2xCH), 126.6 (CH), 126.0 (CH), 125.6 (CH), 114.8 (CH₂), 114.2 (CH₂), 58.2 (CH), 55.5 (CH₂), 53.6 (CH₂), 41.3 (CH), 32.0 (CH₂), 30.7 (CH₂). ¹³C data was assigned using HSQC data, therefore four quaternary carbons remain unassigned.

This compound was also characterised by 2D COSY NMR.
(4aSR,10bSR)-5-(3’-Methylene-pent-4’-enyl)-3,4,4a,5,6,10b-hexahydro-phenanthridine 96j

**General procedure** M was followed using homopropargyl amine 96g (41 mg, 0.17 mmol), CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O) then CH₂Cl₂ (10 ml) and Hoveyda-Grubbs catalyst 2nd generation (16 mg, 26 µmol). Flash chromatography (CH₂Cl₂–CH₂Cl₂:MeOH, 100:0.5) afforded phenanthridine 96j as a colourless oil (31 mg, 69%).

R_f [CH₂Cl₂:MeOH, 95:5] = 0.48; ν_max (CHCl₃)/cm⁻¹ 3854, 3745, 2925, 1653, 1457; ¹H NMR δ (250 MHz, CDCl₃) 7.30 (1H, d, J 7.3, ArH), 7.20 (1H, td, J 7.0, 1.5, ArH), 7.13 (1H, td, J 6.3, 1.8, ArH), 7.05 (1H, d, J 7.3, ArH), 6.41 (1H, dd, J 17.6, 10.3, CCH=CH₂), 6.12-6.05 (1H, m, CHCH=CH), 5.85-5.77 (1H, m, CH=CH₂), 5.32 (1H, d, J 17.6, CH=CHHᵥ), 5.13-5.08 (3H, m, CH=CHHᵥ+CH₂), 3.91 (1H, d, J 15.5, CH₃HᵥAr), 3.77 (1H, d, J 15.3, CH₃HᵥAr), 3.62 (1H, br s, NCHCH), 3.16 (1H, ddd, J 10.0, 5.3, 2.8, NCHCH₂), 2.94-2.75 (2H, m, CH₂CH₂), 2.59-2.52 (2H, m, CH₂CH₂), 2.17-2.08 (2H, m, =CHCH₂), 1.86-1.76 (1H, m, CHNCH₄H₄B), 1.71-1.58 (1H, m, CHNCH₄H₄B); ¹³C NMR δ (62.9 MHz, CDCl₃) 144.6 (C), 138.7 (CH), 137.5 (C), 133.3 (C), 128.8 (CH), 127.6 (CH), 127.4 (CH), 126.4 (CH), 126.3 (CH), 125.3 (CH), 116.5 (CH₂), 113.3 (CH₂), 56.5 (CH), 53.4 (CH₂), 51.2 (CH₂), 37.8 (CH), 29.6 (CH₂), 29.4 (CH₂), 24.3 (CH₂); m/z (EI) 265 ([M]⁺, 6 %), 198 (100); HRMS (EI) Found: [M]⁺, 265.1827. C₁₉H₂₃N requires 265.1825. This compound was also characterised by 2D COSY NMR.
(4aSR,10bSR)-5-(3’-Methylene-pent-4'-enyl)-1,4,4a,5,6,10b-hexahydrophenanthridine 97j

General procedure M was followed using homopropargyl amine 97g (41 mg, 0.17 mmol), CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O), then CH₂Cl₂ (10 ml) Hoveyda-Grubbs catalyst 2nd generation (16 mg, 26 µmol). Flash chromatography (CH₂Cl₂–CH₂Cl₂:MeOH, 100:0.5) afforded phenanthridine 97j as a colourless oil (25 mg, 54%).

**Rf [CH₂Cl₂:MeOH, 95:5] = 0.51; v_max (CHCl₃)/cm⁻¹ 2907, 1646 (C=C); ¹H NMR δ (360 MHz, CDCl₃) 7.19-7.13 (3H, m, 3xArH), 7.09-7.07 (1H, m, ArH), 6.40 (1H, dd, J 17.5, 10.7, C CH=CH₂), 5.69-5.66 (1H, m, CH=CH), 5.58-5.55 (1H, m, CH=CH), 5.32 (1H, d, J 17.5, CH=CH(ν)), 5.31 (1H, br s, C=CH₂H₈), 5.11-5.07 (2H, m, CH=CH(ν)+C=CH₂H₈), 5.12 (2H, s, CH₂), 3.94 (2H, s, CH₂Ar), 3.20-3.10 (2H, m, NCHCH), 2.92-2.81 (2H, m, CH₂), 2.60-2.43 (4H, m, 2xCH₂), 2.22-2.18 (2H, m, CH₂); ¹³C NMR δ (90.6 MHz, CDCl₃) 144.7 (C), 138.8 (CH), 138.4 (C), 134.6 (C), 126.3 (CH), 126.1 (CH), 126.0 (CH), 125.6 (CH), 125.4 (CH), 124.5 (CH), 116.5 (CH₂), 113.3 (CH₂), 55.0 (CH), 53.3 (CH₂), 53.0 (CH₂), 36.8 (CH), 29.2 (CH₂), 28.8 (CH₂), 23.6 (CH₂); m/z (EI) 265 ([M]+, 7 %), 198 (16), 197 (100), 169 (12); HRMS (EI) Found: [M]+, 265.1827. C₁₉H₂₃N requires 265.1825.
(4aSR,10bSR)-5-(3'-Methylene-pent-4'-enyl)-1,2,4a,5,6,10b-hexahydrophenantridine 97j

General procedure M was followed using homopropargyl amine 98g (12 mg, 50.6 µmol), CH₂Cl₂ (1 ml) and HCl (1 ml, 1 M in Et₂O), then CH₂Cl₂ (10 ml) and Hoveyda-Grubbs catalyst 2nd generation (5 mg, 7.6 µmol). Flash chromatography (CH₂Cl₂–CH₂Cl₂:MeOH, 100:0.5) afforded phenanthridine 98j as a colourless oil (9 mg, 67%).

Rf [CH₂Cl₂:MeOH, 95:5] = 0.42; v_max (CHCl₃)/cm⁻¹ 3022, 2925, 1453; ¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.29 (1H, d, J 9.9, ArH), 7.21 (1H, t, J 7.5, ArH), 7.14 (1H, t, J 7.5, ArH), 7.03 (1H, d, J 7.5, ArH), 6.38 (1H, dd, J 17.6, 10.6, CCH=CH₂), 5.89 (2H, br s, CH=CH), 5.32 (1H, d, J 17.6, CH=CH₂), 5.12-5.07 (3H, m, CH₂+CH=CH₁H₂W), 4.01 (1H, d, J 15.2, CH₂H₂Ar), 3.76 (1H, d, J 15.5, CH₂H₂Ar), 3.63 (1H, br s, NCHCH), 3.14 (1H, br s, NCHCH), 2.99-2.94 (1H, m, CH₃H₈B), 2.91-2.83 (1H, m, CH₃H₇B), 2.62-2.50 (2H, m, CH₂), 2.36-2.26 (1H, m, CH₃H₇D), 1.99-1.90 (3H, m, CH₃H₈D+CH₂); ¹³C NMR δ (62.9 MHz, CDCl₃) 144.6 (C), 138.8 (CH), 137.2 (C), 134.9 (C), 131.4 (CH), 127.2 (CH), 126.3 (CH), 126.2 (CH), 125.7 (CH), 125.4 (CH), 116.4 (CH₂), 113.3 (CH₂), 56.5 (CH), 52.4 (CH₂), 52.0 (CH₂), 35.8 (CH), 29.5 (CH₂), 26.5 (CH₂), 23.2 (CH₂); m/z (El) 265 ([M]+, 8 %), 212 (70), 198 (100), 145 (30), 143 (46); HRMS (El) Found: [M]+, 265.1826. C₁₉H₂₃N requires 265.1825.
General procedure N - RRM reactions of Poc analogues

A solution of the appropriate amide (1 eq) in CH₂Cl₂ (10 ml) was degassed with ethylene for 10 mins. Hoveyda-Grubbs catalyst 2nd generation (0.15 eq) was added and the reaction stirred under an atmosphere of ethylene for 40 h at r.t. The crude product was concentrated under reduced pressure and purified by flash chromatography to afford the appropriate product.

(4aSR,10bSR)-4,4a,6,10b-Tetrahydro-3H-phenanthridine-5-carboxylic acid 2-methylene-but-3-enyl ester 96k

General procedure N was followed using Poc amide 96h (25 mg, 93.5 µmol), CH₂Cl₂ (5 ml) and Hoveyda-Grubbs catalyst 2nd generation (9 mg, 14.0 µmol). Flash chromatography (hexane:EtOAc, 20:1) afforded phenanthridine 96k as a colourless oil (20 mg, 73%).

Rf [hexane:EtOAc, 3:1] = 0.79; v_max (CHCl₃)/cm⁻¹ 2929, 1695 (C=O), 1418; H NMR δ (360 MHz, 323 K, CDCl₃) 7.30 (1H, d, J 7.4, ArH), 7.23 (1H, td, J 7.6, 1.4, ArH), 7.18 (1H, td, J 7.9, 1.1, ArH), 7.12 (1H, d, J 6.8, ArH), 6.41 (1H, dd, J 18.1, 11.1, CCH=CH₂), 6.11-6.11 (1H, m, CHCH=CH), 5.88-5.85 (1H, m, CH=CH₂), 5.33 (1H, d, J 18.1, CCH=CH₂), 5.29 (1H, br s, C=CH₃), 5.23 (1H, br s, C=CH₃), 5.15 (1H, d, J 11.1, CCH=CH₂), 4.87 (2H, s, OCH₂), 4.80 (1H, d, J 16.4, CH₂Ar), 4.48 (1H, br s, NCH), 4.46 (1H, d, J 16.4, CH₂Ar), 3.60 (1H, br s, NCH), 2.31-2.22 (1H, m, CHCH=CH), 2.15-2.08 (1H, m, CHCH=CH), 1.78-1.73 (1H, m, NCH₂), 1.66-1.64 (1H, m, NCH₂); C NMR δ (62.9 MHz, CDCl₃) 155.2 (C), 141.7 (C), 137.4 (C), 136.1 (2xCH), 131.9 (C), 128.3 (2xCH), 127.6 (CH), 126.9 (2xCH), 125.9 (CH), 117.3 (CH₂), 114.5 (CH₂), 64.5 (CH₂), 50.5 (CH), 43.6 (CH₂), 36.8 (CH), 25.1 (CH₂); m/z (EI) 295 ([M]+, 48 %), 268 (50), 228 (100), 184 (43), 167 (40); HRMS (EI) Found: [M]+, 295.1567. C₁₉H₂₁NO₂ requires 295.1567. This compound was also characterised by 2D COSY NMR.
Experimental

(4aSR,10bSR)-4,4a,6,10b-Tetrahydro-1H-phenanthridine-5-carboxylic acid 2-methylene-but-3-enyl ester 97k

General procedure N was followed using Poc amide 96h (24 mg, 89.9 µmol), CH₂Cl₂ (4 ml) and Hoveyda-Grubbs catalyst 2nd generation (8.5 mg, 13.5 µmol). Flash chromatography (hexane:EtOAc, 20:1) afforded phenanthridine 97k as a colourless oil (16 mg, 60%).

Rf [hexane:EtOAc, 3:1] = 0.66; νmax (CHCl₃)/cm⁻¹ 3026, 2929, 1699 (C=O), 1412; ¹H NMR δ (360 MHz, CDCl₃) 7.27-7.17 (4H, m, 4xArH), 6.42 (1H, dd, J 18.1, 11.1, CCH=CH₂), 5.71-5.67 (1H, m, CH=CH), 5.44-5.40 (1H, m, CH=CH), 5.34 (1H, d, J 18.1, CCH=CH₂H₆), 5.30 (1H, br s, C=CH₂R₃H₅), 5.25 (1H, br s, C=CH₂R₅H₇), 5.16 (1H, d, J 11.1, CCH=CH₂H₆W), 4.92 (1H, d, J 13.3, OCH₃H₃Q), 4.85 (1H, d, J 13.3, OCH₃H₃Q), 4.66 (1H, d, J 16.1, CHX₂H₇Ar), 4.60 (1H, d, J 16.1, CHX₂H₇Ar), 4.35 (1H, br s, NCH), 3.23 (1H, br s, NCHCH), 2.88 (1H, dd, J 18.2, 5.3, CHCH₃H₈B), 2.64-2.55 (1H, m, CHCH₃H₈B), 2.28-2.23 (1H, m, CHNCH₃H₈D), 1.61-1.49 (1H, m, CHNCH₃H₈D); ¹³C NMR δ (62.9 MHz, CDCl₃) 155.1 (C), 141.3 (C), 136.1 (C+CH), 133.4 (C), 126.8 (CH), 126.4 (CH), 126.2 (CH), 125.0 (CH), 124.9 (CH), 123.7 (CH), 117.3 (CH₂), 114.5 (CH₂), 64.4 (CH₂), 53.3 (CH), 50.2 (CH₂), 44.8 (CH₂), 35.5 (CH), 26.1 (CH₂); m/z (EI) 295 ([M]+, 12 %), 241 (100), 228 (13), 198 (13), 196 (25), 174 (12), 167 (10), 130 (69); HRMS (EI) Found: [M]+, 295.1567. C₁₉H₂₁NO₂ requires 295.1567. This compound was also characterised by 2D COSY NMR.
Experimental

(4aSR,10bSR)-2,4a,6,10b-Tetrahydro-1H-phenanthridine-5-carboxylic acid 2-methylene-but-3-enyl ester 98k

General procedure N was followed using Poc amide 98h (19 mg, 71.0 µmol), CH₂Cl₂ (4 ml) and Hoveyda-Grubbs catalyst 2nd generation (7 mg, 10.7 µmol). Flash chromatography (CH₂Cl₂) to afford phenanthridine 98k as a colourless oil (20 mg, 96%).

R_f [hexane:EtOAc, 3:1] = 0.63; υ_max (CHCl₃)/cm⁻¹ 3025, 2927, 1700 (C=O), 1430; ¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.36 (1H, d, J 7.5, ArH), 7.27-7.17 (2H, m, 2xArH), 7.06 (1H, d, J 7.3, ArH), 6.39 (1H, dd, J 17.8, 10.8, CCH=CH₂), 5.76-5.68 (1H, m, CH=CCH₂), 5.54 (1H, br d, J 10.8, NCHCH=CH), 5.31 (1H, d, J 17.8, CCH=CH₂Hᵥ), 5.26 (1H, s, C=CH₂Hₛ), 5.22 (1H, s, C=CH₂Hₛ), 5.14 (1H, d, J 10.5, CCH=CH₂Hᵥ), 5.13 (1H, br s, NCHCH), 4.93 (1H, d, J 16.8, CH₂HᵥAr), 4.86 (2H, s, OCH₂), 4.32 (1H, d, J 16.8, CH₂HᵥAr), 3.33 (1H, br s, NCHCH), 2.44-2.39 (1H, m, CHCH₂HᵥB), 2.04-1.99 (1H, m, CHCH₂HᵥB), 1.88-1.81 (2H, m, =CHCH₂); ¹³C NMR δ (90.6 MHz, 323 K, CDCl₃) 155.3 (C), 141.8 (C), 136.2 (CH), 135.1 (C), 133.7 (C), 131.3 (CH), 127.3 (CH), 126.7 (CH), 126.6 (CH), 125.8 (2xCH), 117.1 (CH₂), 114.5 (CH₂), 64.7 (CH₂), 50.7 (CH), 42.8 (CH₂), 34.2 (CH), 25.2 (CH₂), 20.3 (CH₂); m/z (EI) 295 ([M]⁺, 28 %), 228 (93), 199 (90), 184 (27), 167 (41); HRMS (EI) Found: [M]⁺, 295.1567. C₁₉H₂₁NO₂ requires 295.1567. This compound was also characterised by 2D COSY NMR.
Experimental

(4aSR,10bSR)-5-(But-3’-enyl)-1,4,4a,5,6,10b-hexahydro-phenanthridine 97m

General procedure L was followed using amine 246 (70 mg, 0.38 mmol), acetone (4 ml), K$_2$CO$_3$ (157 mg, 1.13 mmol) and 4-bromo-1-butene (46 µl, 0.45 mmol). After 16 h, flash chromatography (CH$_2$Cl$_2$) afforded butenyl amine 97m (84 mg, 93%) as a yellow oil.

$R_f$ [hexane:EtOAc, 3:1] = 0.68; $\nu_{max}$ (CHCl$_3$)/cm$^{-1}$ 3024, 2924, 1647, 1446; $^1$H NMR $\delta$ (250 MHz, CDCl$_3$) 7.22-7.11 (3H, m, 3xArH), 7.08-7.05 (1H, m, ArH), 5.87 (1H, ddt, J 17.1, 10.2, 6.8, CH=CH$_2$), 5.71-5.64 (1H, m, CH=CH), 5.61-5.54 (1H, m, CH=CH), 5.10 (1H, dq, J 17.1, 1.7, CH=CH$_2$H$_C$), 5.02 (1H, dq, J 10.2, 1.0, CH=CH$_2$H$_C$), 3.90 (2H, s, CH$_2$Ar), 3.18-3.11 (2H, m, NCHCH), 2.87-2.56 (3H, m, CH$_2$+CH$_A$H$_B$), 2.46-2.29 (3H, m, CH$_2$+CH$_A$H$_B$), 2.17 (2H, br s, CH$_2$); $^{13}$C NMR $\delta$ (69.2 MHz, CDCl$_3$) 138.4 (C), 136.7 (CH), 134.7 (C), 126.3 (CH), 126.1 (CH), 125.9 (CH), 125.5 (CH), 125.4 (CH), 124.4 (CH), 115.4 (CH$_2$), 54.8 (CH), 53.6 (CH$_2$), 52.9 (CH$_2$), 36.8 (CH), 31.3 (CH$_2$), 29.2 (CH$_2$), 23.5 (CH$_2$); $m/z$ (El) 239 ([M]$^+$, 2 %), 212 (10), 198 (100), 185 (36), 144 (37); HRMS (El) Found: [M]$^+$, 239.1671. C$_{17}$H$_{21}$N requires 239.1669.

6.4 Experimental for Chapter four

General procedure P - Dihydroxylation

To a solution of the appropriate phenanthridines (1 eq) in THF and H$_2$O at r.t was added OsO$_4$ (0.07 eq, 2.5% $w/w$ in tBuOH) and NMO (3 eq) and the reaction was stirred for 16 h. The reaction mixture was poured onto Na$_2$SO$_3$ (30 ml, sat. aq.) and extracted with EtOAc (3 x 30 ml). The combined organics were dried (MgSO$_4$), concentrated under reduced pressure and purified to afford the appropriate mixture of diols. Purification by flash chromatography afforded either a mixture of the isolated isomers/diol mixture, or purely the diol mixture. In cases where the isolated isomers were not obtained, further purification by HPLC afforded the corresponding isolated diols.
Dihydroxy-9-methyl-2,3,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 206a-208a ($\Delta^{1,2}$, $\Delta^{2,3}$, $\Delta^{3,4}$ isomer)

General procedure P was followed using phenanthridines 195a-197a (84 mg, 0.282 mmol), THF (165 µl), H$_2$O (820 µl), OsO$_4$ (247 µl, 2.5% w/w in tBuOH, 19.7 µmol) and NMO (132 mg, 0.846 mmol). Flash chromatography (CH$_2$Cl$_2$:CH$_2$Cl$_2$:MeOH, 100:2) afforded mixture of diols 206a-208a (73 mg, 78%). Further isolation of the individual diol products 206a-208a was not found to be possible by HPLC so these compounds were taken on as a mixture. 

$R_f$ [CH$_2$Cl$_2$:MeOH, 9:1] = 0.57; $\nu_{max}$ (CHCl$_3$)/cm$^{-1}$ 3421 (OH), 1664 (C=O); $m/z$ (EI) 319 ([M]$^+$, 2 %), 262 ([M-tBu]$^+$, 100), 218 ([M-Boc]$^+$, 22), 184 (75).

9-Fluoro-3,4-dihydroxy-2,3,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 206b-208b

General procedure P was followed using phenanthridines 195b-197b (50 mg, 0.165 mmol), THF (920 µl), H$_2$O (184 µl), OsO$_4$ (144 µl, 2.5% w/w in tBuOH, 11.5 µmol) and NMO (58 mg, 0.495 mmol). Flash chromatography (CH$_2$Cl$_2$:MeOH, 100:2) afforded mixture of diols 206b-208b (46 mg, 82%). HPLC (EtOAc:hexane, 3:1) of this mixture afforded $\Delta^{1,2}$ diol 206b (10 mg, 18%), $\Delta^{2,3}$ diol 207b (15.3 mg, 2 %), $\Delta^{3,4}$ diol 208b (11.4 mg, 20%), and mixed diol fractions (9 mg, 16%) giving an overall yield (45.7 mg, 82%), all colourless oils.
Experimental

(1RS,2SR,4aSR,10bSR)-9-Fluoro-1,2-dihydroxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 206b (Δ1,2 isomer)

\[
R_f [\text{CH}_2\text{Cl}_2:\text{MeOH, 9:1}] = 0.43; \quad R_t (\text{EtOAc:hexane, 3:1, flow rate: 10 ml/min}) = 15 \text{ min}; \quad \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3425 (\text{OH}), 2976, 2931, 1664 (\text{C}=\text{O}), 1367, 1167; \quad ^1\text{H NMR} \ \delta (360 \text{ MHz, 323 K, CDCl}_3) 7.13-7.04 (2\text{H, m, 2xArH}), 6.92 (1\text{H, td, } J 10.9, 2.6, \text{ ArH}), 4.70-4.62 (3\text{H, m, 2xCH+CH}_3\text{Ar}), 4.31 (1\text{H, d, } J 16.9, \text{CH}_3\text{Ar}), 3.73-3.68 (1\text{H, m, C}), 3.37 (1\text{H, br s, C}), 2.51 (1\text{H, br s, OH}), 1.92-1.84 (1\text{H, m, CH}_2\text{H}_2\text{B}), 1.70-1.52 (2\text{H, m, CH}_2\text{H}_2\text{CH}_2\text{H}_2\text{D}), 1.51 (9\text{H, s, 3xCH}_3), 1.91-1.82 (1\text{H, m, CH}_2\text{H}_2\text{D}); \quad ^{13}\text{C NMR} \ \delta (90.6 \text{ MHz, 323 K, CDCl}_3) 161.9 (1\text{C, d, } J 245.2, \text{C}), 154.8 (\text{C}), 135.3 (1\text{C, d, } J 6.9, \text{C}), 129.1 (\text{C}), 128.1 (1\text{C, d, } J 8.2, \text{CH}), 113.5 (1\text{C, d, } J 21.7, \text{CH}), 112.5 (1\text{C, d, } J 22.4, \text{CH}), 80.1 (\text{C}), 71.1 (\text{CH}), 67.4 (\text{CH}), 46.9 (\text{CH}), 43.0 (\text{CH}_2), 42.9 (\text{CH}), 28.4 (3\text{xCH}_3), 27.3 (\text{CH}_2), 24.2 (\text{CH}_2); \quad m/z (\text{EI}) 337 ([M]^+, 1 \%), 280 ([\text{M-}t\text{Bu}]^+, 100), 236 ([\text{M-Boc}]^+, 61), 192 (19), 162 (26).

(2RS,3SR,4aSR,10bSR)-9-Fluoro-2,3-dihydroxy-2,3,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 207b (Δ2,3 isomer)

\[
R_f [\text{CH}_2\text{Cl}_2:\text{MeOH, 9:1}] = 0.53; \quad R_t (\text{EtOAc:hexane, 3:1, flow rate: 10 ml/min}) = 20 \text{ min}; \quad \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3421 (\text{OH}), 2935, 1670 (\text{C}=\text{O}), 1412, 1167; \quad ^1\text{H NMR} \ \delta (360 \text{ MHz, 323 K, CDCl}_3) 7.17 (1\text{H, d, } J 10.1, \text{ArH}), 7.11-7.07 (1\text{H, m, ArH}), 6.91 (1\text{H, td, } J 8.3, 1.8, \text{ArH}), 4.80-4.72 (1\text{H, m, CH}), 4.66 (1\text{H, d, } J 17.1, \text{CH}_3\text{H}_2\text{Ar}), 4.31 (1\text{H, d, } J 17.0, \text{CH}_3\text{H}_2\text{Ar}), 3.93 (1\text{H, br s, CH}), 3.64-3.60 (1\text{H, m, CH}), 3.23 (1\text{H, br s, CH}), 2.40-2.23 (2\text{H, m, CH}_2), 1.92-1.89 (1\text{H, m, CH}_2\text{H}_2\text{B}), 1.52 (9\text{H, s, 3xCH}_3), 1.45-1.42 (1\text{H, m, CH}_2\text{H}_2\text{B}); \quad ^{13}\text{C NMR} \ \delta (62.9 \text{ MHz, CDCl}_3) 164.9 (1\text{C, d, } J 133.4, \text{C}), 154.7 (\text{C}), 136.8 (\text{C}), 128.6 (\text{C}), 127.9 (1\text{C, d, } J 8.3, \text{CH}), 113.4 (1\text{C, d, } J 21.6, \text{CH}), 112.5 (1\text{C, d, } J 21.9, \text{CH}), 80.2 (\text{C}), 69.1 (\text{CH}), 66.6 (\text{CH}), 46.3 (\text{CH}), 42.8 (\text{CH}_2), 36.4 (\text{CH}), 31.3 (\text{CH}_2), 29.1 (\text{CH}_2), 28.4 (3\text{xCH}_3); \quad m/z (\text{EI}) 337 ([M]^+, 1 \%), 280 ([\text{M-}t\text{Bu}]^+, 100), 236 ([\text{M-Boc}]^+, 27), 218 (19), 192 (35), 162 (34), 148 (24).

(3RS,4SR,4aRS,10bSR)-9-Fluoro-3,4-dihydroxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 208b (Δ3,4 isomer)

Experimental

Rf [CH2Cl2:MeOH, 9:1] = 0.47; Rf (EtOAc:hexane, 3:1, flow rate: 8 ml/min) = 17 min; vmax (CHCl3)/cm\(^{-1}\) 3404 (OH), 2937, 1670 (C=O), 1421, 1169; ¹H NMR δ (360 MHz, 323 K, CDCl₃) 7.11 (1H, dd, /uni0408 J 8.5, 5.7, ArH), 7.03 (1H, dd, J 10.0, 1.7, ArH), 6.92 (1H, m, ArH), 4.73-4.61 (2H, m, CH+CH₃H₂Ar), 4.41 (1H, d, /uni0408 J 16.4, CHXH₂YAr), 3.96 (1H, d, /uni0408 J 2.7, CH), 3.30-3.25 (2H, m, 2xCH), 2.85-2.72 (1H, m, CH₃H₂B), 2.17-2.12 (1H, m, CH₃H₂B), 1.87-1.82 (1H, m, CH₂CH₂), 1.60-1.50 (10H, m, CH₃H₂Ar+3xCH₃), ¹³C NMR δ (90.6 MHz, 323 K, CDCl₃) 162.1 (1C, d, /uni0408 J 245.1, C), 155.2 (C), 137.1 (1C, d, J 2.8, C), 128.9 (C), 128.0 (1C, d, J 8.2, CH), 113.4 (1C, d, J 21.7, CH), 112.3 (1C, d, J 22.1, CH), 81.0 (C), 69.5 (2xCH), 52.7 (CH), 42.1 (CH₂), 37.1 (CH), 28.4 (3xCH₃), 25.4 (CH₂), 20.1 (CH₂); m/z (EI) 337 ([M]+, 1 %), 281 (36), 280 ([M-¹Bu]+), 9), 236 ([M-Boc]+, 100), 218 (11), 206 (12), 192 (13), 162 (40).

Dihydroxy-8-methoxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 206c-208c

General procedure P was followed using phenanthridines 195c-197c (152 mg, 0.482 mmol), THF (2.70 ml), H₂O (541 µl), OsO₄ (423 µl, 2.5% w/w in ¹BuOH, 33.8 µmol) and NMO (226 mg, 1.93 mmol). Flash chromatography (CH₂Cl₂:MeOH, 100:1-10:1) afforded mixture of diols 195c-197c (159 mg, 95%).

HPLC (EtOAc:hexane, 4:1) of this mixture afforded Δ¹,² diol 206c (21 mg, 13%), Δ²,³ diol 207c (20 mg, 12%), Δ³,⁴ diol 208c (32 mg, 19%), and mixed diol fractions (32 mg, 19%), giving a total yield (105 mg, 63%), all colourless oils.
Experimental

(1RS,2SR,4aSR,10bSR)-1,2-Dihydroxy-8-methoxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 206c (Δ^{1,2} isomer)

\[ \text{R}_{f} [\text{CH}_2\text{Cl}_2:\text{MeOH}, 9:1] = 0.49; \text{R}_{t} (\text{EtOAc:hexane, 4:1, flow rate: 10 ml/min}) = 21 \text{ min}; \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3423 (\text{OH}), 2933, 1687 (\text{C}=\text{O}); \] 1\text{H NMR} \ \delta (360 \text{ MHz, CDCl}_3) 7.24 (1H, d, /uni0408 8.6, ArH), 6.79 (1H, dd, /uni0408 8.6, 2.7, ArH), 6.68 (1H, d, /uni0408 2.7, ArH), 4.72-4.63 (3H, m, 2×CH+CH₂H₂Ar), 4.30 (1H, d, /uni0408 17.1, CHXH₂YAr), 3.80 (3H, s, CH₃), 3.75-3.69 (1H, m, C-H), 3.35 (1H, br s, C-H), 2.60 (1H, br s, OH), 1.93-1.87 (1H, m, CH₃Ar), 1.69-1.64 (1H, m, CH₃H₂), 1.57-1.41 (11H, m, CH₂+3×CH₃); 13\text{C NMR} \ \delta (62.9 \text{ MHz, CDCl}_3) 157.9 (C), 154.8 (C), 134.6 (C), 126.5 (CH), 124.8 (C), 112.9 (CH), 111.5 (CH), 79.9 (C), 71.1 (CH), 67.3 (CH), 55.2 (CH₃), 46.8 (CH), 43.5 (CH₂), 42.0 (CH), 28.4 (3×CH₃), 27.3 (CH₂), 23.9 (CH₂); m/z (El) 349 ([M]+, 4%), 292 ([M-Boc]+, 27), 248 ([M-Boc]+, 21), 174 (22).

(2RS,3SR,4aSR,10bSR)-2,3-Dihydroxy-8-methoxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 207c (Δ^{2,3} isomer)

\[ \text{R}_{f} [\text{CH}_2\text{Cl}_2:\text{MeOH}, 9:1] = 0.49; \text{R}_{t} (\text{EtOAc:hexane, 4:1, flow rate: 10 ml/min}) = 24 \text{ min}; \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3392 (\text{OH}), 2935, 1672 (\text{C}=\text{O}); \] 1\text{H NMR} \ \delta (360 \text{ MHz, CDCl}_3) 7.37 (1H, d, /uni0408 8.5, ArH), 6.82 (1H, dd, /uni0408 8.5, 2.7, ArH), 6.67 (1H, d, /uni0408 2.6, ArH), 4.76-4.67 (2H, m, CH+CH₂H₂Ar), 4.31 (1H, d, /uni0408 3.1, C-H), 3.92 (1H, d, /uni0408 3.1, CH), 3.81 (3H, s, CH₃), 3.66-3.61 (1H, m, CH), 3.21 (1H, m, CH), 2.45-2.42 (1H, m, CH₃H₂), 2.26-2.17 (1H, m, CH₂H₂), 1.91-1.86 (1H, m, CH₂H₂), 1.52 (9H, s, 3×CH₃), 1.41 (1H, t, /uni0408 7.3, CH₂H₂); 13\text{C NMR} \ \delta (90.6 \text{ MHz, CDCl}_3) 158.2 (C), 154.7 (C), 134.5 (C), 126.8 (CH), 126.5 (C), 113.0 (CH), 111.5 (CH), 79.9 (C), 69.6 (CH), 66.7 (CH), 55.2 (CH₃), 46.5 (CH), 43.7 (CH₂), 35.7 (CH), 31.3 (CH₂), 29.5 (CH₂), 28.5 (3×CH₃); m/z (El) 349 ([M]+, 5%), 292 ([M-Boc]+, 38), 248 ([M-Boc]+, 37), 204 (35), 174 (40), 160 (33).
Experimental

(3RS,4SR,4aRS,10bSR)-3,4-Dihydroxy-8-methoxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 208c (Δ^{3,4} isomer)

\[ \text{Rf} \ [\text{CH}_2\text{Cl}_2:\text{MeOH}, 9:1] = 0.49; \text{Rf} \ (\text{EtOAc:hexane}, 4:1, \text{flow rate:} 10 \text{ ml/min}) = 17 \text{ min}; \nu_{\text{max}} \ (\text{CHCl}_3)/\text{cm}^{-1} 3492 \ (\text{OH}), 2935, 1668 \ (\text{C}=\text{O}); \]  

\[ ^1\text{H NMR} \ \delta \ (360 \text{ MHz, 323 K, CDCl}_3) 7.23 \ (1\text{H, d, J} 8.7, \text{ArH}), 6.82 \ (1\text{H, dd, J} 5.9, 2.7, \text{ArH}), 6.69 \ (1\text{H, d, J} 2.7, \text{ArH}), 4.80-4.62 \ (2\text{H, m, CH+CH}_3\text{H}_2\text{Ar}), 4.41 \ (1\text{H, d, J} 16.7, \text{CH}_2\text{H}_2\text{Ar}), 3.94 \ (1\text{H, d, J} 2.8, \text{CH}), 3.81 \ (3\text{H, s, CH}_3), 3.34-3.31 \ (1\text{H, m, CHF}), 3.24-3.22 \ (1\text{H, m, CHF}), 2.23-2.21 \ (1\text{H, m, CH}_2\text{H}_2\text{B}), 1.85-1.80 \ (1\text{H, m, CH}_2\text{H}_2\text{B}), 1.57-1.52 \ (10\text{H, s, CH}_2\text{H}_3\text{+}3\text{xCH}_3), 1.43-1.39 \ (1\text{H, m, CH}_2\text{H}_2\text{D}); \]  

\[ ^{13}\text{C NMR} \ \delta \ (90.6 \text{ MHz, 323 K, CDCl}_3) 158.2 \ (2\times\text{C}), 134.5 \ (\text{C}), 126.4 \ (\text{CH}), 123.4 \ (\text{CH}), 113.0 \ (\text{CH}), 111.6 \ (\text{CH}), 80.8 \ (\text{C}), 69.6 \ (2\times\text{CH}), 55.3 \ (\text{CH}_3), 53.3 \ (\text{CH}), 46.8 \ (\text{CH}_2), 36.2 \ (\text{CH}), 28.4 \ (3\times\text{CH}_3), 25.3 \ (\text{CH}_2), 20.1 \ (\text{CH}_2); \text{m/z} \ (\text{EI}) 349 \ ([\text{M}]^+, 21 \%), 292 \ ([\text{M-}^1\text{Bu}]^+, 100), 257 (56), 248 ([\text{M-Boc}]^+, 33), 230 (61), 204 (55). \]

Dihydroxy-8,9-dimethoxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 206d-208d

General procedure P was followed using phenanthridines 195d-197d (30 mg, 87 µmol), THF (488 µl), H_2O (98 µl), OsO_4 (76 µl, 2.5% w/w in tBuOH, 6.1 µmol) and NMO (31 mg, 0.26 mmol). Flash chromatography (CH_2Cl_2:MeOH, 100:5) afforded mixture of diols 206d-208d (23 mg, 70 %). HPLC (EtOAc:hexane, 84:16) afforded Δ^{1,2} diol 206d (2 mg, 6%), diol mixture 206d and 207d (6.2 mg, 19%) and Δ^{3,4} diol 208d (10 mg, 30%), giving an overall yield (18.2 mg, 55%), all colourless oils.
(1RS,2SR,4aSR,10bSR)-1,2-Dihydroxy-8,9-dimethoxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 206d (Δ1,2 isomer)

R_f [CH_2Cl_2:MeOH, 9:1] = 0.48; R_t (EtOAc:hexane, 84:16, flow rate: 10 ml/min) = 38 min; υ_max (CHCl_3/cm^{-1}) 3423 (OH), 2937, 1670 (C=O), 1520, 1406; 1H NMR δ (360 MHz, CDCl_3) 6.83 (1H, s, ArH), 6.61 (1H, s, ArH), 4.70-4.64 (3H, m, 2xC+CH+C), 4.24 (1H, d, CH), 3.87 (6H, s, 2xC), 3.70-3.67 (1H, m, CH), 3.34 (1H, br s, CH), 1.93-1.89 (1H, m, CH), 1.67-1.61 (2H, m, CH+CH), 1.53-1.45 (10H, m, CH+CH); 13C NMR δ (90.6 MHz, CDCl_3) 154.8 (C), 147.9 (C), 125.3 (C), 124.5 (C), 109.3 (CH), 108.6 (CH), 79.9 (C), 71.3 (CH), 67.5 (CH), 56.1 (CH), 46.7 (CH), 42.9 (CH), 28.4 (3xCH), 27.2 (CH), 23.8 (CH); m/z (EI) 379 ([M]+, 2 %), 322 (100), 278 (6), 234 (4).

(2RS,3SR,4aSR,10bSR)-2,3-Dihydroxy-8,9-dimethoxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 207d (Δ2,3 isomer)

NMR Data for Δ2,3 isomer 207d was deduced from 1H and 13C NMR of 206d and 207d mixture.

R_f [9: 1 CH_2Cl_2:MeOH] = 0.48; R_t (EtOAc:hexane, 84:16, flow rate: 10 ml/min) = 38 min; υ_max (CHCl_3/cm^{-1}) 3425 (OH), 2935, 1664 (C=O), 1520, 1259; 1H NMR δ (360 MHz, CDCl_3) 6.94 (1H, s, ArH), 6.60 (1H, s, ArH), 4.75-4.63 (2H, m, CH+CH), 3.89 (3H, s, CH), 3.87 (3H, s, CH), 3.63-3.60 (1H, m, CH), 3.20 (1H, br s, CH), 2.43-2.40 (1H, m, CH), 2.28-2.19 (1H, m, CH), 1.89-1.85 (1H, m, CH), 1.66-1.61 (1H, m, CH), 1.50 (9H, m, 3xCH); 13C NMR δ (90.6 MHz, CDCl_3) 154.7 (C), 148.1 (C), 147.6 (C), 128.5 (C), 126.1 (C), 109.2 (CH), 108.6 (CH), 79.9 (C), 69.3 (CH), 66.8 (CH), 56.1 (CH), 55.8 (CH), 45.8 (CH), 42.9 (CH), 35.7 (CH), 31.1 (CH), 29.6 (CH), 28.4 (3xCH); m/z (EI) 379 ([M]+, 2 %), 322 ([M-tBu]+, 100), 278 (38), 190 (10).
Experimental

(3RS,4SR,4aRS,10bSR)-3,4-Dihydroxy-8,9-dimethoxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 208d (Δ^3,4 isomer)

$$R_f \ [9: 1 \text{ CH}_2\text{Cl}_2:\text{MeOH}] = 0.51; \ R_t \ (\text{EtOAc}:\text{hexane}, 84:16, \text{flow rate: } 10 \text{ ml/min}) = 23 \text{ min; } \nu_{\max} (\text{CHCl}_3)/\text{cm}^{-1} \ 3404 \ (\text{OH}), 2931, 1668 \ (\text{C}=\text{O}), 1518, 1419; ^1\text{H NMR} \ \delta \ (250 \text{ MHz, CDCl}_3) \ 6.80 \ (1\text{H, s, ArH}), 6.63 \ (1\text{H, s, ArH}), 4.66-4.60 \ (2\text{H, m, CH}+\text{CH}_3\text{H}Y\text{Ar}), 4.37 \ (1\text{H, d, } J \ 16.8, \text{CH}X\text{H}Y\text{Ar}), 3.96 \ (1\text{H, br s, CH}), 3.88 \ (3\text{H, s, OCH}_3), 3.87 \ (3\text{H, s, OCH}_3), 3.35-3.31 \ (1\text{H, m, CH}), 3.22 \ (1\text{H, br s, CH}), 2.26-2.13 \ (2\text{H, m, CH}_2), 1.86-1.78 \ (1\text{H, m, CH}_AH_B), 1.53-1.42 \ (10\text{H, m, CH}_AH_B+3\text{CH}_3), ^{13}\text{C NMR} \ \delta \ (62.9 \text{ MHz, CDCl}_3) \ 157.7 \ (\text{C}), 148.0 \ (\text{C}), 147.6 \ (\text{C}), 127.6 \ (\text{C}), 125.2 \ (\text{C}), 109.4 \ (\text{CH}), 108.5 \ (\text{CH}), 80.8 \ (\text{CH}), 71.2 \ (\text{CH}), 69.4 \ (\text{CH}), 56.0 \ (\text{CH}_3), 55.9 \ (\text{CH}_3), 52.7 \ (\text{CH}), 43.9 \ (\text{CH}_3), 36.3 \ (\text{CH}), 28.4 \ (3\text{CH}_3), 25.4 \ (\text{CH}_2), 20.2 \ (\text{CH}_2); \ m/z \ (\text{EI}) \ 379 \ (\text{[M]}^+, \ 1\ %), 322 \ (\text{[M}^{-}\text{Bu}]^+, \ 2), 278 \ (\text{[M-Boc]}^+, \ 10) .

Dihydroxy-2,3,4,4a,6,12c-hexahydro-1H-benzo[k]phenanthridine-5-carboxylic acid tert-butyl ester 206e-208e

General procedure P was followed using phenanthridines 195e-197e (130 mg, 0.39 mmol), THF (2.17 ml), H$_2$O (434 µl), OsO$_4$ (338 µl, 2.5% w/w in tBuOH, 27.1 µmol) and NMO (136 mg, 1.16 mmol). Flash chromatography (CH$_2$Cl$_2$:MeOH, 100:0.5) afforded Δ$^{1,2}$ diol 206e (20 mg, 14%), Δ $^{2,3}$ diol 207e (40 mg, 28%), Δ $^{3,4}$ diol 208e (23 mg, 16%), and mixed diol (42 mg, 29%) giving a total yield (125 mg, 87%).
Experimental

(1RS,2SR,4aSR,12cSR)-1,2-Dihydroxy-2,3,4,4a,6,12c-hexahydro-1H-benzo[k]phenanthridine-5-carboxylic acid tert-butyl ester 206e (Δ^{1,2} isomer)

\[
\text{R}_f \ [\text{CH}_2\text{Cl}_2:\text{MeOH}, \ 9:1] = 0.65; \ \nu_{\max} (\text{CHCl}_3)/\text{cm}^{-1} \ 3418 \ (\text{OH}), \ 2932, \ 1668 \ (\text{C}=\text{O}), \ 1393, \ 1163; \ ^1\text{H NMR} \ \delta \ (360 \text{ MHz}, \ 323 \text{ K}, \ \text{CDCl}_3) \ 8.08 (1\text{H}, \text{ d}, J 8.5, \text{ ArH}), \ 7.85 (1\text{H}, \text{ d}, J 7.9, \text{ ArH}), \ 7.70 (1\text{H}, \text{ d}, J 8.3, \text{ ArH}), \ 7.54 (1\text{H}, \text{ t}, J 7.9, \text{ ArH}), \ 7.47 (1\text{H}, \text{ t}, J 7.9, \text{ ArH}), \ 7.26 (1\text{H}, \text{ d}, J 8.3, \text{ ArH}), \ 5.11 (1\text{H}, \text{ d}, J 15.9, \text{ CH}_3\text{H}_Y\text{Ar}), \ 4.41 (1\text{H}, \text{ m}, \text{ CH}), \ 4.30 (1\text{H}, \text{ d}, J 15.9, \text{ CH}_3\text{H}_Y\text{Ar}), \ 4.17-4.28 (2\text{H}, \text{ m}, 2\times\text{CH}), \ 3.98-3.95 (1\text{H}, \text{ m}, \text{ CH}), \ 2.79 (1\text{H}, \text{ br s}, \text{ OH}), \ 2.27 (1\text{H}, \text{ br s}, \text{ OH}), \ 2.01-1.93 (2\text{H}, \text{ m}, \text{ CH}_2), \ 1.75-1.69 (2\text{H}, \text{ m}, \text{ CH}_2), \ 1.49 (9\text{H}, \text{ m}, 3\times\text{CH}_3); \ ^{13}\text{C NMR} \ \delta \ (90.6 \text{ MHz}, \ 323 \text{ K}, \ \text{CDCl}_3) \ 156.0 \ (\text{C}), \ 134.8 \ (\text{C}), \ 133.3 \ (\text{C}), \ 132.6 \ (\text{C}), \ 130.6 \ (\text{C}), \ 128.8 \ (\text{CH}), \ 126.6 \ (\text{CH}), \ 126.2 \ (\text{CH}), \ 125.4 \ (\text{CH}), \ 124.6 \ (\text{CH}), \ 122.6 \ (\text{CH}), \ 80.6 \ (\text{C}), \ 71.2 \ (\text{CH}), \ 68.9 \ (\text{CH}), \ 56.7 \ (\text{CH}), \ 45.3 \ (\text{CH}), \ 30.9 \ (\text{CH}), \ 28.4 \ (3\times\text{CH}_2), \ 26.6 \ (\text{CH}_2), \ 26.5 \ (\text{CH}_2); \ m/z \ (\text{EI}) \ 369 ([\text{M}]^+, 4 \%), \ 313 \ (15), \ 312 ([\text{M}-\text{tBu}]^+, 100), \ 268 ([\text{M-Boc}]^+, 25), \ 250 \ (15), \ 180 \ (27).
\]

(2RS,3SR,4aSR,12cSR)-2,3-Dihydroxy-2,3,4,4a,6,12c-hexahydro-1H-benzo[k]phenanthridine-5-carboxylic acid tert-butyl ester 207e (Δ^{2,3} isomer)

\[
\text{R}_f \ [\text{CH}_2\text{Cl}_2:\text{MeOH}, \ 9:1] = 0.52; \ \nu_{\max} (\text{CHCl}_3)/\text{cm}^{-1} \ 3418 \ (\text{OH}), \ 2927, \ 1685 \ (\text{C}=\text{O}), \ 1393, \ 1163; \ ^1\text{H NMR} \ \delta \ (360 \text{ MHz}, \ 323 \text{ K}, \ \text{CDCl}_3) \ 8.11 (1\text{H}, \text{ d}, J 8.5, \text{ ArH}), \ 7.85 (1\text{H}, \text{ d}, J 8.1, \text{ ArH}), \ 7.71 (1\text{H}, \text{ d}, J 8.3, \text{ ArH}), \ 7.55 (1\text{H}, \text{ t}, J 8.4, \text{ ArH}), \ 7.48 (1\text{H}, \text{ t}, J 6.8, \text{ ArH}), \ 7.27 (1\text{H}, \text{ d}, J 8.3, \text{ ArH}), \ 5.10 (1\text{H}, \text{ d}, J 16.1, \text{ CH}_3\text{H}_Y\text{Ar}), \ 4.37 (1\text{H}, \text{ d}, J 16.1, \text{ CH}_3\text{H}_Y\text{Ar}), \ 4.17-4.02 (4\text{H}, \text{ m}, 4\times\text{CH}), \ 2.71-2.66 (1\text{H}, \text{ m}, \text{ CH}, \text{ CH}_2\text{H}_B), \ 2.44 (1\text{H}, \text{ br s}, \text{ OH}), \ 2.15-2.10 (2\text{H}, \text{ m}, \text{ CH}_2), \ 1.86-1.78 (1\text{H}, \text{ m}, \text{ CH}_2\text{H}_B), \ 1.60 (1\text{H}, \text{ br s}, \text{ OH}), \ 1.52 (9\text{H}, \text{ m}, 3\times\text{CH}_3); \ ^{13}\text{C NMR} \ \delta \ (90.6 \text{ MHz}, \ 323 \text{ K}, \ \text{CDCl}_3) \ 155.9 \ (\text{C}), \ 135.0 \ (\text{C}), \ 133.1 \ (\text{C}), \ 131.9 \ (\text{C}), \ 130.3 \ (\text{C}), \ 128.7 \ (\text{CH}), \ 126.7 \ (\text{CH}), \ 126.4 \ (\text{CH}), \ 125.4 \ (\text{CH}), \ 124.7 \ (\text{CH}), \ 122.4 \ (\text{CH}), \ 80.2 \ (\text{C}), \ 68.5 \ (\text{CH}), \ 67.9 \ (\text{CH}), \ 52.3 \ (\text{CH}), \ 46.6 \ (\text{CH}_2), \ 33.5 \ (\text{CH}_2), \ 31.9 \ (\text{CH}_2), \ 29.9 \ (\text{CH}), \ 28.5 \ (3\times\text{CH}_3); \ m/z \ (\text{EI}) \ 369 ([\text{M}]^+, 4 \%), \ 312 ([\text{M}-\text{tBu}]^+, 100), \ 268 ([\text{M-Boc}]^+, 25), \ 250 \ (15), \ 180 \ (27).
\]

247
Experimental

(3RS,4SR,4aSR,12cSR)-3,4-Dihydroxy-2,3,4,4a,6,12c-hexahydro-1H-benzo[k]phenanthridine-5-carboxylic acid tert-butyl ester 208e (Δ³,Δ⁴ isomer)

$R_f \ [\text{CH}_2\text{Cl}_2:\text{MeOH}, \ 9:1] = 0.66; \ \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3409 (\text{OH}), 2949, 1662 (\text{C}=\text{O}), 1393, 1033, 1017; \ ^1\text{H NMR} \ \delta (360 \text{ MHz}, 323 \text{ K}, \text{CDCl}_3) 8.20 (1\text{H}, \text{d}, J 8.5, \text{ArH}), 7.85 (1\text{H}, \text{d}, J 8.1, \text{ArH}), 7.76 (1\text{H}, \text{d}, J 8.3, \text{ArH}), 7.55 (1\text{H}, \text{t}, J 8.4, \text{ArH}), 7.48 (1\text{H}, \text{t}, J 8.1, \text{ArH}), 7.33 (1\text{H}, \text{d}, J 8.3, \text{ArH}), 5.23 (1\text{H}, \text{d}, J 16.0, \text{CH}_X\text{H}_Y\text{Ar}), 4.37 (1\text{H}, \text{d}, J 16.0, \text{CH}_X\text{H}_Y\text{Ar}), 4.18-4.09 (2\text{H}, \text{m}, 2\times \text{CH}), 4.01-4.00 (1\text{H}, \text{m}, \text{CH}), 3.90-3.86 (1\text{H}, \text{m}, \text{CH}), 2.52 (1\text{H}, \text{br s}, \text{OH}), 2.44-2.35 (1\text{H}, \text{m}, \text{CH}_A\text{H}_B), 2.16-2.04 (1\text{H}, \text{m}, \text{CH}_A\text{H}_B), 1.99-1.93 (1\text{H}, \text{m}, \text{CH}_C\text{H}_D), 1.83-1.79 (1\text{H}, \text{m}, \text{CH}_C\text{H}_D), 1.55 (1\text{H}, \text{br s}, \text{OH}), 1.48 (9\text{H}, \text{m}, 3\times \text{CH}_3); \ ^{13}\text{C NMR} \ \delta (90.6 \text{ MHz}, 323 \text{ K}, \text{CDCl}_3) 155.9 (\text{C}), 133.3 (\text{C}), 132.0 (\text{C}), 128.6 (\text{CH}), 127.2 (\text{CH}), 126.4 (\text{CH}), 125.5 (\text{CH}), 125.2 (\text{CH}), 123.3 (\text{CH}), 80.1 (\text{C}), 72.3 (\text{CH}), 68.1 (\text{CH}), 52.8 (\text{CH}), 47.2 (\text{CH}_2), 37.8 (\text{CH}), 28.4 (3\times \text{CH}_3), 25.6 (\text{CH}_2), 22.8 (\text{CH}_2); \ \text{m/z} (\text{EI}) 369 ([\text{M}]^+, 5 \%), 313 (26), 312 ([\text{M}-\text{tBu}]^+, 100), 268 ([\text{M-Boc}]^+, 12), 223 (27), 180 (29).

Dihydroxy-5a,6,7,8,9,9a-hexahydro-4H-thieno[2,3-c]quinoline-5-carboxylic acid tert-butyl ester 206f-208f (Δ⁸,⁹, Δ⁷,Δ⁸ and Δ⁶,Δ⁷ diol mixture)

General procedure P was followed using phenanthridines 195f-197f (15 mg, 53 µmol), THF (296 µl), H₂O (59 µl), OsO₄ (47 µl, 2.5% w/w in tBuOH, 3.7 µmol) and NMO (19 mg, 0.158 mmol). Flash chromatography (CH₂Cl₂:CH₂Cl₂:MeOH, 100:5) afforded mixture of diols 206f-208f (10 mg, 64%) as a yellow oil.

$\nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3421 (\text{OH}), 2929, 1676 (\text{C}=\text{O}), 1410, 1365, 1165; \ \text{m/z} (\text{EI}) 325 ([\text{M}]^+, 1 \%), 268 ([\text{M}-\text{tBu}]^+, 73), 224 (18), 152 (14).
Experimental

Dihydroxy-2,3,4,4a,6,11b-hexahydro-1H-[1,3]dioxolo[4,5-j]phenanthridine-5-carboxylic acid tert-butyl ester 206k-208k

General procedure P was followed using phenanthridines 195k-197k (125 mg, 0.38 mmol), THF (2.66 ml), H2O (531 µl), OsO4 (332 µl, 2.5% w/w in ‘BuOH, 26.6 µmol) and NMO (133 mg, 1.14 mmol). Flash chromatography (CH2Cl2:MeOH, 98:2) afforded Δ1,2 diol 206k (13 mg, 9%), Δ2,3 diol 207k (31 mg, 23%), Δ3,4 diol 208k (25 mg, 18%), minor diastereomer 209k (3 mg, 2%) and mixed diol (48 mg, 35%) giving a total yield (120 mg, 87%).

(1R,2S,4aSR,11bSR)-1,2-Dihydroxy-2,3,4,4a,6,11b-hexahydro-1H-[1,3]dioxolo[4,5-j]phenanthridine-5-carboxylic acid tert-butyl ester 206k (Δ1,2 isomer)

\[\text{R}_f \{\text{CH}_2\text{Cl}_2:\text{MeOH}, 9:1\} = 0.52; \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3392 (\text{OH}), 1685 (\text{C=O}); \] 1H NMR δ (360 MHz, 323 K, CDCl3) 6.83 (1H, s, ArH), 6.61 (1H, s, ArH), 5.94 (2H, dd, J 3.2, 1.4, OCH2O), 4.66-4.59 (3H, m, 2xCHOH+CH3H2Ar), 4.24 (1H, d, J 16.8, CHxH2Ar), 3.75-3.71 (1H, m, CH), 3.20 (1H, br s, CH), 2.41 (1H, br s, OH), 2.10-1.83 (3H, m, OH+CH2), 1.70-1.61 (2H, m, CH2), 1.52 (9H, s, 3xCH3); 13C NMR δ (90.6 MHz, 323 K, CDCl3) 154.8 (C), 147.0 (C), 146.2 (C), 126.8 (C), 126.1 (C), 106.7 (CH), 105.7 (CH), 100.9 (CH2), 79.9 (C), 71.4 (CH), 67.4 (CH), 47.2 (CH), 43.6 (CH2), 42.8 (CH), 28.9 (3xCH3), 27.3 (CH2), 24.0 (CH2); m/z (EI) 363 ([M]+, 6 %), 306 (53), 252 (22), 224 (30).
Experimental

(2R,3S,4aSR,11bSR)-2,3-Dihydroxy-2,3,4,4a,6,11b-hexahydro-1H-
[1,3]dioxolo[4,5-j]phenanthridine-5-carboxylic acid tert-butyl ester 207k (Δ2,3
isomer)

\[ \text{Rf} \left[ \text{CH}_2\text{Cl}_2: \text{MeOH}, 9:1 \right] = 0.59; \nu_{\text{max}} \left( \text{CHCl}_3 \right)/\text{cm}^{-1} 3391 \]

(2R,3S,4aSR,11bSR)-3,4-Dihydroxy-2,3,4,4a,6,11b-hexahydro-1H-
[1,3]dioxolo[4,5-j]phenanthridine-5-carboxylic acid tert-butyl ester 208k (Δ3,4
isomer)

\[ \text{Rf} \left[ \text{CH}_2\text{Cl}_2: \text{MeOH}, 9:1 \right] = 0.62; \nu_{\text{max}} \left( \text{CHCl}_3 \right)/\text{cm}^{-1} 3391 \]

250
Experimental

(2S,3R,4aSR,11bSR)-2,3-Dihydroxy-2,3,4,4a,6,11b-hexahydro-1H-[1,3]dioxolo[4,5-j]phenanthridine-5-carboxylic acid tert-butyl ester 209k (Δ\textsuperscript{2,3} isomer, minor diastereomer)

\[ \text{Rf} \ [\text{CH}_2\text{Cl}_2:\text{MeOH, 95:5}] = 0.37; \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3421 (\text{OH}), 2925, 1684 (\text{C}=\text{O}), 1236, 1165; ^1\text{H NMR} \ \delta (360 \text{ MHz, 323 K, CDCl}_3) 6.99 (1H, s, ArH), 6.57 (1H, s, ArH), 5.93 (2H, s, OCH\text{O}), 4.71 (1H, d, J 17.1, CH\text{XH}_2\text{YAr}), 4.38-4.32 (1H, m, CH), 4.27 (1H, d, J 16.7, CH\text{XH}_2\text{YAr}), 3.96 (1H, br s, CH), 3.71 (1H, br s, CH), 3.07 (1H, br s, CH), 2.76 (1H, dt, J 15.5, 3.3, CH\text{A}_2\text{B}), 2.02-2.00 (1H, m, CH\text{A}_2\text{B}), 1.80-1.72 (2H, m, CH\text{A}_2\text{B}), 1.51 (9H, s, 3xCH\text{A}_3), ^{13}\text{C NMR} \ \delta (90.6 MHz, 323 K, CDCl\text{	extsubscript{3}}) 154.5 (C), 146.7 (C), 146.3 (C), 128.5 (C), 125.7 (C), 106.9 (CH), 106.3 (CH), 100.9 (CH\text{A}_2\text{B}), 80.1 (C), 70.5 (CH), 69.0 (CH), 49.7 (CH), 43.2 (CH\text{A}_2\text{B}), 33.7 (CH), 30.8 (CH\text{A}_2\text{B}), 29.4 (CH\text{A}_2\text{B}), 28.4 (3xCH\text{A}_3);m/z (EI) 364 ([M+H]\textsuperscript{+}, 5 \%), 363 ([M]\textsuperscript{+}, 2), 306 (16), 262 (100), 218 (16).

Dihydroxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 206m-207m

General procedure P was followed using phenanthridines 96b-98b (200 mg, 0.70 mmol), THF (3.92 ml), H\text{2}O (785 µl), OsO\text{4} (613 µl, 2.5% w/w in tBuOH, 49.1 µmol) and NMO (329 mg, 2.81 mmol). Flash chromatography (CH\text{2}Cl\text{	extsubscript{2}}-CH\text{2}Cl\text{	extsubscript{2}}:MeOH, 100:3) afforded mixture of diols 206m-208m as a colourless oil (156 mg, 70%). HPLC (EtOAc:hexane, 3:1) of this mixture afforded Δ\textsuperscript{1,2} diol 206m (29 mg, 13%), Δ\textsuperscript{2,3} diol 207m (25 mg, 11%), Δ\textsuperscript{3,4} diol 208m (26 mg, 12%), and mixed diol fractions (44 mg, 20%), giving an overall yield (124 mg, 56%), all colourless oils.
Experimental

(1RS,2SR,4aSR,10bSR)-1,2-Dihydroxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 206m (Δ^{12} isomer)

Rt [CH2Cl2:MeOH, 9:1] = 0.57; Rt (EtOAc:hexane, 3:1, flow rate: 8 ml/min) = 23 min; vmax(CHCl3)/cm⁻¹ 3421 (OH), 1664 (C=O); 1H NMR δ (360 MHz, 323 K, CDCl3) 7.36-7.34 (1H, m, ArH), 7.24-7.18 (2H, m, 2xArH), 7.14-7.12 (1H, m, ArH), 4.74-4.66 (3H, m, CHO+CHNoc+CH3HAr), 4.35 (1H, d, J 17.1, CH3HAr), 3.95 (1H, br s, OH), 3.71 (1H, ddd, J 11.4, 4.7, 2.8, CHO), 3.40 (1H, br s, CHAr), 1.95-1.85 (1H, m, CHAHar), 1.70-1.60 (2H, m, CHAHar+CH2CH2), 1.51 (9H, s, 3xCH3), 1.40-1.33 (1H, m, CHCH2); 13C NMR δ (90.6 MHz, 323 K, CDCl3) 154.9 (C), 133.4 (C), 133.1 (C), 126.9 (CH), 126.6 (C), 126.3 (CH), 125.4 (CH), 79.9 (C), 71.1 (CH), 67.4 (CH), 47.1 (CH), 43.6 (CH2), 42.8 (CH), 28.4 (3xCH3), 27.4 (CH2), 24.2 (CH2); m/z (EI) 319 ([M]+, 2 %), 262 ([M-1Bu]+, 100), 218 ([M-Boc]+, 22), 184 (75). This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

(2RS,3SR,4aSR,10bSR)-2,3-Dihydroxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 207m (Δ^{23} isomer)

Rt [CH2Cl2:MeOH, 9:1] = 0.52; Rt (EtOAc:hexane, 3:1, flow rate: 8 ml/min) = 28 min; vmax(CHCl3)/cm⁻¹ 3414 (OH), 2930, 1671 (C=O), 1406, 1365; 1H NMR δ (360 MHz, 323 K, CDCl3) 7.47 (1H, d, J 7.6, ArH), 7.27-7.20 (2H, m, 2xArH), 7.12 (1H, d, J 6.8, ArH), 4.78-4.72 (1H, m, CHNoc), 4.71 (1H, d, J 17.3, CH3HAr), 4.36 (1H, d, J 17.3, CH3HAr), 3.92 (1H, m, CHOH), 3.64 (1H, dt, J 12.0, 3.9, CHOH), 3.26 (1H, br s, CHAr), 2.49 (1H, dt, J 13.6, 3.1, CHAHar), 2.25 (1H, ddd, J 13.6, 12.0, 4.8, CHAHar), 1.94-1.87 (1H, m, CH2CH2), 1.54-1.45 (10H, m, CHCH2+3xCH3); 13C NMR δ (90.6 MHz, 323 K, CDCl3) 154.8 (C), 134.5 (C), 133.2 (C), 126.9 (CH), 126.4 (CH), 126.2 (CH), 125.6 (CH), 80.0 (C), 69.4 (CH), 66.7 (CH), 46.3 (CH), 43.6 (CH2), 36.3 (CH), 31.5 (CH2), 29.3 (CH2), 28.4 (3xCH3); m/z (EI) 319 ([M]+, 1 %), 263 ([M-1Bu]+, 27), 262 (80), 218 ([M-Boc]+, 25), 200 (27), 174 (36), 146 (25), 144 (48); HRMS (EI) Found: [M]+, 319.1780. C18H25O4N requires 319.1778.
(3RS,4SR,4aRS,10bSR)-3,4-Dihydroxy-2,3,4,4a,6,10b-hexahydro-1H-phenanthridine-5-carboxylic acid tert-butyl ester 208m (Δ3,4 isomer)

\[ \text{Rf} [\text{CH}_2\text{Cl}_2:\text{MeOH}, 9:1] = 0.58; \text{Rf} (\text{EtOAc:hexane, 3:1, flow rate: 8 ml/min}) = 21 \text{ min}; \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3394 (\text{OH}), 2978, 2937, 1668 (\text{C}=\text{O}); ^1\text{H NMR} \delta (360 \text{ MHz, 323 K, CDCl}_3) 7.33 (1H, d, \text{J} 7.5, \text{ArH}), 7.27-7.19 (2H, m, 2\times\text{ArH}), 7.14 (1H, d, \text{J} 7.1, \text{ArH}), 4.80-4.66 (2H, m, \text{CHNBoc+CH}_3\text{HyAr}), 4.44 (1H, d, \text{J} 17.0, \text{CHxHyAr}), 3.94 (1H, dd, \text{J} 5.9, 2.9, \text{CHOH}), 3.31-3.29 (2H, m, \text{CHAr+CHOH}), 2.29-2.24 (2H, m, \text{CH}_2), 1.85-1.80 (1H, m, \text{CH}_A\text{H}_B), 1.58-1.52 (10H, m, \text{CH}_A\text{H}_B+3\times\text{CH}_3); ^{13}\text{C NMR} \delta (90.6 \text{ MHz, 323 K, CDCl}_3) 156.7 (\text{C}), 134.6 (\text{C}), 133.3 (\text{C}), 126.9 (\text{CH}), 126.5 (\text{CH}), 126.2 (\text{CH}), 125.3 (\text{CH}), 80.8 (\text{C}), 69.6 (2\times\text{CH}), 53.1 (\text{CH}), 43.9 (\text{CH}_2), 36.9 (\text{CH}), 28.4 (3\times\text{CH}_3), 25.4 (\text{CH}_2), 20.0 (\text{CH}_2); \text{m/z} (\text{EI}) 319 ([\text{M}]^+, 1 \%), 263 ([\text{M}-\text{Bu}]^+, 3), 233 (7), 218 ([\text{M-Boc}]^+, 6). \] This compound was also fully characterised by COSY, HSQC and NOESY 2D NMR studies.

**General procedure Q – Hydrochloride salt formation**

To a solution of the appropriate diol(s) 206-208 in CH$_2$Cl$_2$ (2 ml) was added TFA (5 ml) and the reaction was stirred at r.t. for 2 h. The reaction was diluted with H$_2$O (15 ml), adjusted to pH 8-9 by the addition of NaOH pellets, and then extracted with CH$_2$Cl$_2$ (3 x 15 ml). The combined organics were dried (MgSO$_4$) and concentrated under reduced pressure. The resultant oil was taken up in CH$_2$Cl$_2$ (1 ml), cooled to 0 °C and HCl (excess, 1 M in Et$_2$O) added. The resultant solid was washed with Et$_2$O and dried under vacuum to afford the desired amine hydrochloride(s) 252-254.
9-Methyl-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-diol hydrochloride 252a-254a (\(\Delta^{1,2}, \Delta^{2,3}, \Delta^{3,4}\) isomer mixture)

General procedure Q was followed using diols 206a-208a (16 mg, 48 \(\mu\)mol), CH\(_2\)Cl\(_2\) (2 ml) and TFA (5 ml), then CH\(_2\)Cl\(_2\) (1 ml) and HCl (2 ml, 1 M in Et\(_2\)O) to afford a amine hydrochlorides 252a-254a as a yellow oil (9 mg, 69%).

\[\text{m/z (ESI+)} \ 234 ([M+H]^+ , 100 \%), \ 232 (44); \ \text{HRMS (ESI+)} \ \text{Found [M+H]^+}, \ 234.1489. \ C_{14}H_{20}O_2N \text{ requires } 234.1489.\]

(1RS,2SR,4aSR,10bSR)-9-Fluoro-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-1,2-diol 252b (\(\Delta^{1,2}\) isomer)

General procedure Q was followed using diol 206b (10 mg, 30 \(\mu\)mol), CH\(_2\)Cl\(_2\) (2 ml), and TFA (5 ml), then CH\(_2\)Cl\(_2\) (1 ml) and HCl (2 ml, 1 M in Et\(_2\)O) to afford amine hydrochloride 252b as a colourless oil (9 mg, 99%).

\[\text{\(^1\)H NMR } \delta (360 \text{ MHz, D}_2\text{O}) 7.09 (1H, dd, J 8.6, 5.7, ArH), \ 7.03 (1H, dd, J 10.2, 2.6, ArH), \ 6.94 (1H, td, J 8.6, 2.7, ArH), \ 4.28 (1H, d, J 16.2, CH\text{H}\text{Ar}), \ 4.22 (1H, d, J 16.2, CH\text{H}\text{Ar}), \ 3.88 (1H, d, J 7.6, CH), \ 3.78-3.74 (2H, m, 2xCH), \ 3.19 (1H, dd, J 8.2, 4.4, CH), \ 2.01-1.91 (1H, m, CH\text{A}H\text{B}), \ 1.81-1.72 (1H, m,CH\text{A}H\text{B}), \ 1.68-1.60 (2H, m, CH\text{A}); \ \text{\(^{13}\)C NMR } \delta (90.6 \text{ MHz, D}_2\text{O}) 162.3 (1C, d, J 243.8, C), \ 135.0 (1C, d, J 7.7, C), \ 129.2 (1C, d, J 8.5, CH), \ 123.7 (C), \ 116.4 (1C, d, J 23.7, CH), \ 115.5 (1C, d, J 22.1, CH), \ 70.9 (CH), \ 68.2 (CH), \ 52.0 (CH), \ 43.4 (CH\text{A}), \ 39.5 (CH), \ 25.6 (CH\text{A}), \ 21.9 (CH\text{A}); \ \text{m/z (ESI+)} \ 238 ([M+H]^+, 100 \%), \ 236 (86); \ \text{HRMS (ESI+)} \ \text{Found [M+H]^+}, \ 238.1237. \ C_{13}H_{17}O_2NF \text{ requires } 238.1238.\]
Experimental

(2RS,3SR,4aSR,10bSR)-Fluoro-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-2,3-diol 253b (Δ$^{2,3}$ isomer)

General procedure Q was followed using diol 207b (10 mg, 30 µmol), CH$_2$Cl$_2$ (2 ml), and TFA (5 ml), then CH$_2$Cl$_2$ (1 ml) and HCl (2 ml, 1 M in Et$_2$O) to afford amine hydrochloride 253b as a colourless oil (7 mg, 86%).

$^1$H NMR δ (360 MHz, D$_2$O) 7.09-7.05 (1H, m, ArH), 6.98 (1H, dd, /uni0408/ 10.0, 2.1, ArH), 6.91 (1H, td, /uni0408/ 8.7, 2.6, ArH), 4.23 (1H, s, CH$_2$Ar), 3.81 (1H, dd, /uni0408/ 9.8, 4.7, CH), 3.77-3.75 (2H, m, 2xCH), 3.27-3.23 (1H, m, CH), 2.10-2.00 (2H, m, CH$_2$), 1.87-1.80 (1H, m, CH$_2$); $^{13}$C NMR δ (90.6 MHz, D$_2$O) 162.7 (1C, d, /uni0408/ 244.5, C), 137.2 (1C, d, /uni0408/ 7.6, C), 129.0 (1C, d, /uni0408/ 8.5, CH), 122.8 (C), 115.0 (1C, d, /uni0408/ 22.4, CH), 114.8 (1C, d, /uni0408/ 22.9, CH), 67.6 (CH), 66.5 (CH), 51.7 (CH), 43.9 (CH$_2$), 33.2 (CH), 31.6 (CH), 29.0 (CH$_2$); m/z (ESI+) 238 ([M+H]$^+$, 100 %), 211 (12), 179 (12); HRMS (ESI+) Found [M+H]$^+$, 238.1234. C$_{13}$H$_{17}$O$_2$NF requires 238.1238.

(3RS,4SR,4aRS,10bSR)-9-Fluoro-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-3,4-diol 254b (Δ$^{3,4}$ isomer)

General procedure Q was followed using diol 208b (15 mg, 46 µmol), CH$_2$Cl$_2$ (2 ml), and TFA (5 ml), then CH$_2$Cl$_2$ (1 ml) and HCl (2 ml, 1 M in Et$_2$O) to afford amine hydrochloride 254b as a yellow oil (9 mg, 74%).

$^1$H NMR δ (360 MHz, D$_2$O) 7.11-7.05 (2H, m, 2xArH), 6.91 (1H, dd, /uni0408/ 8.6, 2.7, ArH), 4.23 (1H, d, /uni0408/ 16.3, CH$_X$H$_Y$Ar), 4.17 (1H, d, /uni0408/ 16.3, CH$_X$H$_Y$Ar), 3.84-3.82 (1H, m6, CH), 3.77 (1H, dd, /uni0408/ 9.5, 5.3, CH), 3.59-3.57 (1H, m, CH), 3.32-3.30 (1H, m, CH), 2.02-1.92 (2H, m, CH$_2$), 1.64-1.57 (1H, m, CH$_A$H$_B$), 1.39-1.31 (1H, m, CH$_A$H$_B$); $^{13}$C NMR δ (90.6 MHz, D$_2$O) 163.1 (1C, d, /uni0408/ 245.1, C), 136.3 (C), 129.8 (1C, d, /uni0408/ 8.7, CH), 124.6 (C), 115.1 (1C, d, /uni0408/ 22.2, CH), 113.9 (1C, d, /uni0408/ 23.3, CH), 69.5 (CH), 66.7 (CH), 54.6 (CH), 49.5 (CH$_2$), 34.3 (CH), 26.3 (CH$_2$), 21.9 (CH$_2$); m/z (ESI+) 238 ([M+H]$^+$, 100 %), 225 (18), 211 (26), 210 (10), 197 (13), 179 (26); HRMS (ESI+) Found [M+H]$^+$, 238.1233. C$_{13}$H$_{17}$O$_2$NF requires 238.1238.
**Experimental**

(1RS,2SR,4aSR,10bSR)-8-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-1,2-diol 252c (Δ1,2 isomer)

General procedure Q was followed using diol 206c (21 mg, 60 µmol), CH₂Cl₂ (2 ml), and TFA (5 ml), then CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O) to afford amine hydrochloride 252c as a colourless oil (14 mg, 82%).

¹H NMR δ (800 MHz, D₂O) 7.17 (1H, d, J 8.8, ArH), 6.76 (1H, d, J 8.8, 2.4, ArH), 6.64 (1H, d, J 1.6, ArH), 4.23 (1H, d, J 16.6, CHₓHᵧAr), 4.18 (1H, d, J 16.6, CHₓHᵧAr), 3.85 (1H, br s, CH), 3.72-3.66 (2H, m, 2xCH), 3.61 (3H, s, CH₃), 3.12 (1H, m, CH), 1.92-1.89 (1H, m, CHₓHᵧ), 1.73-1.70 (1H, m, CHₓHᵧ), 1.63-1.52 (2H, m, CH₂); ¹³C NMR δ (200.0 MHz, D₂O) 158.6 (C), 131.1 (CH), 129.0 (C), 124.9 (C), 114.7 (CH), 111.9 (CH), 71.1 (CH), 68.1 (CH), 56.0 (CH₃), 52.2 (CH), 43.4 (CH₂), 38.7 (CH), 25.5 (CH₂), 21.8 (CH₂); m/z (ESI+) 250 ([M+H]⁺, 100 %), 248 (86), 246 (13); HRMS (ESI+) Found [M+H]⁺, 250.1435. C₁₄H₂₀O₃N requires 250.1438.

(2RS,3SR,4aSR,10bSR)-8-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-2,3-diol 253b (Δ2,3 isomer)

General procedure Q was followed using diol 207b (20 mg, 57 µmol), CH₂Cl₂ (2 ml), and TFA (5 ml), then CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O) to afford amine hydrochloride 253c as a yellow oil (15 mg, 92%).

¹H NMR δ (360 MHz, D₂O) 7.12 (1H, d, J 8.7, ArH), 6.79 (1H, dd, J 8.5, 2.2, ArH), 6.62 (1H, br s, ArH), 4.23-4.14 (2H, m, CH₂Ar), 3.75-3.64 (3H, m, 3xCH), 3.60 (3H, s, OCH₃), 3.18-3.13 (1H, m, CH), 2.06-1.94 (2H, m, CH₂), 1.85-1.72 (2H, m, CH₂); ¹³C NMR δ (90.6 MHz, D₂O) 158.1 (C), 129.8 (CH), 128.3 (C), 127.3 (C), 115.2 (CH), 111.5 (CH), 67.6 (CH), 66.4 (CH), 55.7 (CH₃), 52.3 (CH), 44.2 (CH₂), 32.4 (CH₂), 30.5 (CH), 29.0 (CH₂); m/z (ESI+) 250 ([M+H]⁺, 100 %), 249 (28), 248 (89); HRMS (ESI+) Found [M+H]⁺, 250.1438. C₁₄H₂₀O₃N requires 250.1438.
Experimental

(3RS,4SR,4aSR,10bSR)-8-Methoxy-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-3,4-diol 254c (Δ^{3,4} isomer)

General procedure Q was followed using diol 208c (2.1 mg, 6 µmol), CH₂Cl₂ (2 ml), and TFA (5 ml), then CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O) to afford amine hydrochloride 254c as a colourless oil (1.4 mg, 94%).

$^1$H NMR δ (800 MHz, D₂O) 7.22 (1H, d, J 8.0, ArH), 6.82 (1H, dd, J 8.8, 3.2, ArH), 6.67 (1H, d, J 2.4, ArH), 4.20 (1H, d, J 16.8, CHₓHᵧAr), 4.15 (1H, d, J 16.8, CHₓHᵧAr), 3.80 (1H, br s, CH), 3.70 (1H, m, CH), 3.64 (3H, s, CH₃), 3.60 (1H, m, CH), 3.23 (1H, br s, CH), 1.90-1.86 (2H, m, CH₂), 1.59-1.56 (1H, m, CH₃Ar), 1.35-1.31 (1H, m, CH₃Hₓ); $^{13}$C NMR δ (90.6 MHz, D₂O) 158.0 (C), 130.9 (CH), 130.0 (C), 128.6 (C), 114.9 (CH), 111.8 (CH), 70.1 (CH), 69.1 (CH), 55.8 (CH₃), 54.7 (CH), 41.6 (CH₂), 33.2 (CH), 26.9 (CH₂), 26.0 (CH₂); m/z (ESI+) 250 ([M+H]^+, 100 %), 248 (73), 239 (17), 233 (10), 211 (17), 209 (25), 197 (27), 185 (26); HRMS (ESI+) Found [M+H]^+, 250.1436. C₁₄H₂₀O₃N requires 250.1438.

(1RS,2SR,4aSR,10bSR)-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydro-phenanthridine-1,2-diol hydrochloride 252d (Δ^{1,2} isomer)

General procedure Q was followed using diol 206d (10 mg, 26 µmol), CH₂Cl₂ (2 ml), and TFA (5 ml), then CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O) to afford amine hydrochloride 252d as a yellow oil (9 mg, 88%).

$^1$H NMR δ (250 MHz, D₂O) 6.82 (1H, s, ArH), 6.68 (1H, s, ArH), 4.18 (2H, br s, CH₂Ar), 3.83-3.80 (1H, m, CH), 3.75-3.68 (2H, m, 2xCH₃), 3.66 (3H, s, CH₃), 3.64 (3H, s, CH₃), 3.09 (1H, q, J 4.4, CH), 2.04-1.87 (1H, m, CH₃Ar), 1.79-1.52 (3H, m, CH₂+CH₃Ar); $^{13}$C NMR δ (62.9 MHz, D₂O) 148.1 (C), 147.8 (C), 125.2 (C), 120.0 (C), 112.8 (CH), 109.9 (CH), 71.1 (CH), 68.1 (CH), 56.2 (2xCH₃), 52.2 (CH), 43.2 (CH₂), 38.5 (CH), 25.3 (CH₂), 21.6 (CH₂); m/z (ESI+) 280 ([M+H]^+, 61 %), 279 ([M]^+, 100); HRMS (ESI+) Found [M+H]^+, 280.1542. C₁₅H₂₂O₄N requires 280.1543.
Experimental

(2RS,3SR,4aSR,10bSR)-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine-2,3-diol hydrochloride 253d ($\Delta^{2,3}$ isomer)

General procedure Q was followed using diols 206d and 207d (6.2 mg, 16 µmol), CH$_2$Cl$_2$ (2 ml), and TFA (5 ml), then CH$_2$Cl$_2$ (1 ml) and HCl (2 ml, 1 M in Et$_2$O) to afford amine hydrochlorides 252d and 253d as a yellow oil (3 mg, 60%). Data for $\Delta^{2,3}$ isomer 253d was deduced from $^1$H, $^{13}$C and HSQC NMR data for the mixture of 252d and 253d.

$^1$H NMR $\delta$ (500 MHz, D$_2$O) 6.76 (1H, s, ArH), 6.66 (1H, s, ArH), 4.18-4.15 (2H, m, CH$_2$Ar), 3.75-3.71 (3H, m, 3xCH), 3.67 (3H, s, OCH$_3$), 3.64 (3H, s, OCH$_3$), 3.18-3.15 (1H, m, CH), 2.07-2.02 (2H, m, CH$_2$H$_B$CCH$_D$), 1.92-1.88 (1H, m, CH$_A$H$_B$), 1.83-1.78 (1H, m, CH$_C$H$_D$); $^{13}$C NMR $\delta$ (125.8 MHz, D$_2$O) 147.9 (C), 147.6 (C), 125.2 (C), 119.8 (C), 112.7 (CH), 111.1 (CH), 70.9 (CH), 67.5 (CH), 55.9 (2xCH$_3$), 53.3 (CH), 43.9 (CH$_2$), 33.6 (CH), 30.7 (CH$_2$), 28.9 (CH$_2$); $m/z$ (ESI+) 280 ([M+H]$^+$, 100%); 262 (6); HRMS (ESI+) Found [M+H]$^+$, 280.1542. C$_{15}$H$_{22}$O$_4$N requires 280.1543.

(3RS,4SR,4aRS,10bSR)-8,9-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrophenanthridine-3,4-diol hydrochloride 254d ($\Delta^{3,4}$ isomer)

General procedure Q was followed using diol 208d (10 mg, 26 µmol), CH$_2$Cl$_2$ (2 ml), and TFA (5 ml), then CH$_2$Cl$_2$ (1 ml) and HCl (2 ml, 1 M in Et$_2$O) to afford amine hydrochloride 254d as a yellow oil (5 mg, 60%).

$^1$H NMR $\delta$ (360 MHz, D$_2$O) 6.82 (1H, s, ArH), 6.67 (1H, s, ArH), 4.16 (1H, d, J 16.1, CH$_A$H$_Y$Ar), 4.09 (1H, d, J 16.1, CH$_X$H$_Y$Ar), 3.78 (1H, br s, CH), 3.72-3.65 (1H, m, CH), 3.65 (3H, s, OCH$_3$), 3.62 (3H, s, OCH$_3$), 3.23 (1H, br s, CH), 2.00-1.89 (2H, m, CH$_2$), 1.64-1.53 (1H, m, CH$_A$H$_B$), 1.38-1.29 (1H, m, CH$_A$H$_B$); $^{13}$C NMR $\delta$ (90.6 MHz, D$_2$O) 148.6 (C), 147.6 (C), 126.3 (C), 120.7 (C), 110.0 (2xCH), 71.7 (CH), 69.1 (CH), 56.1 (2xCH$_3$), 54.6 (CH), 41.0 (CH$_2$), 33.4 (CH), 26.0 (CH$_2$), 21.6 (CH$_2$); $m/z$ (ESI+) 280 ([M+H]$^+$, 100%); HRMS (ESI+) Found [M+H]$^+$, 280.1546. C$_{13}$H$_{22}$O$_4$N requires 280.1543.
(1RS,2SR,4aSR,12cSR)-1,2,3,4,4a,5,6,12c-Octahydro-benzo[k]phenanthridine-1,2-diol hydrochloride 252e (A<sup>1,2</sup> isomer)

General procedure Q was followed using diol 206e (20 mg, 54 µmol), CH₂Cl₂ (2 ml), and TFA (5 ml), then CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O) to afford amine hydrochloride 252e as a colourless oil (11 mg, 67%).

<sup>1</sup>H NMR δ (500 MHz, D₂O) 8.09 (1H, d, J = 8.5, ArH), 7.76 (1H, d, J = 8.5, ArH), 7.66 (1H, d, J = 8.5, ArH), 7.69 (1H, d, J = 8.5, ArH), 4.51 (1H, d, J = 16.5, CH₃HYAr), 4.47 (1H, d, J = 16.5, CH₃HYAr), 4.06 (2H, s, 2xCH₂), 3.67 (2H, s, 2xCH₂), 2.22-2.16 (1H, m, CH₂A), 2.19-2.12 (1H, m, CH₂B), 1.81 (2H, d, J = 2.5, CH₂); 13C NMR δ (125.9 MHz, D₂O) 135.0 (C), 134.7 (C), 132.6 (C), 130.8 (CH), 130.7 (CH), 128.7 (2xCH), 127.7 (C), 127.3 (CH), 126.5 (CH), 74.8 (CH), 71.3 (CH), 56.0 (CH), 46.9 (CH₂), 35.7 (CH), 27.8 (CH₂), 24.2 (CH₂); m/z (ESI+) 270 ([M+H]+, 38 %), 261 (13), 260 (15), 239 (36), 217 (15), 192 (22), 191 (44), 168 (100); HRMS (ESI+) Found [M+H]+, 270.1488. C₁₇H₂₀O₄N requires 270.1489.

(2RS,3SR,4aSR,12cSR)-1,2,3,4,4a,5,6,12c-Octahydro-benzo[k]phenanthridine-2,3-diol hydrochloride 253e (A<sup>2,3</sup> isomer)

General procedure Q was followed using diol 207e (40 mg, 66 µmol), CH₂Cl₂ (2 ml), and TFA (5 ml), then CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O) to afford amine hydrochloride 253e as a colourless oil (20 mg, 61%).

<sup>1</sup>H NMR δ (360 MHz, D₂O) 7.85 (1H, d, J = 8.4, ArH), 7.78 (1H, d, J = 8.2, ArH), 7.68 (1H, d, J = 8.6, ArH), 7.51 (1H, t, J = 7.0, ArH), 7.43 (1H, t, J = 7.0, ArH), 7.09 (1H, d, J = 8.6, ArH), 4.37 (2H, s, CH₂Ar), 3.95 (1H, br s, CH), 3.81-3.76 (2H, m, 2xCH₂), 3.67 (1H, br s, CH), 2.33-2.17 (2H, m, CH₂), 2.94-1.97 (1H, m, CH₂A), 1.67-1.52 (1H, m, CH₂B); 13C NMR δ (62.9 MHz, D₂O) 133.9 (C), 131.8 (C), 130.9 (CH), 129.1 (CH), 128.4 (CH), 127.6 (CH), 125.1 (CH), 125.0 (C), 123.7 (CH), 69.1 (CH), 66.5 (CH), 54.5 (CH), 46.5 (CH₂), 34.3 (CH), 30.5 (CH₂), 28.1 (CH₂); m/z (ESI+) 270 ([M+H]+, 100 %), 232 (15), 231 (12), 217 (16), 203 (16); HRMS (ESI+) Found [M+H]+, 270.1481. C₁₇H₂₀O₂N requires 270.1489.
(3RS,4SR,4aRS,12cSR)-1,2,3,4,4a,5,6,12c-Octahydro-benzo[k]phenanthridine-3,4-diol hydrochloride 254e (Δ¹⁴ isomer)

General procedure Q was followed using diol 208e (23 mg, 63 μmol), CH₂Cl₂ (2 ml), and TFA (5 ml), then CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O) to afford amine hydrochloride 254e as a colourless oil (13 mg, 69%).

¹H NMR δ (360 MHz, D₂O) 8.05 (1H, d, J 7.5, ArH), 7.77-7.73 (2H, m, 2xArH), 7.46-7.41 (2H, m, 2xArH), 7.16 (1H, d, J 8.5, ArH), 4.52 (1H, d, J 16.5, CHₓHᵧAr), 4.39 (1H, d, J 16.5, CHₓHᵧAr), 4.04-3.95 (2H, s, 2xCH), 3.64 (1H, d, J 11.4, CH), 3.54 (1H, br s, CH), 2.22-2.13 (1H, m, CHₓHᵧB), 1.93-1.89 (1H, m, CHₓHᵧB), 1.81-1.77 (2H, m, CH₂); ¹³C NMR δ (62.9 MHz, D₂O) 133.5 (C), 133.2 (C), 130.9 (C), 129.3 (CH), 129.2 (CH), 127.3 (2xC), 125.9 (CH), 125.7 (C), 125.0 (CH), 73.1 (CH), 69.6 (CH), 54.5 (CH), 45.2 (CH₂), 34.0 (CH), 26.2 (CH₂), 22.6 (CH₂); m/z (ESI+) 270 ([M+H]⁺, 71 %), 248 (12), 245 (14), 234 (15), 217 (21), 203 (16), 172 (27); HRMS (ESI+) Found [M+H]⁺, 270.1481. C₁₇H₂₀O₂N requires 270.1489.

4,5,5a,6,7,8,9,9a-Octahydro-thieno[2,3-c]quinoline-diol hydrochloride 252f-254f (Δ⁸,⁹, Δ⁷,⁸ and Δ⁶,⁷ diol mixture)

General procedure Q was followed using diol mixture 206f-208f (9 mg, 31 μmol), CH₂Cl₂ (2 ml) and TFA (3 ml), then CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O) to afford a mixture of amine hydrochlorides 252f-254f as a yellow oil (7 mg, 99%).

m/z (ESI+) 226 ([M+H]⁺, 20 %), 225 (11); HRMS (ESI+) Found [M+H]⁺, 226.0899. C₁₁H₁₆O₂NS requires 226.0896.
Experimental

(1RS,2SR,4aSR,11bSR)-1,2,3,4,4a,5,6,11b-Octahydro-[1,3]dioxolo[4,5-f]phenanthridine-1,2-diol hydrochloride 252k (A^{12} isomer)

General procedure \( Q \) was followed using diol 206k (18 mg, 50 \( \mu \)mol), \( \text{CH}_2\text{Cl}_2 \) (2 ml) and TFA (3 ml), then \( \text{CH}_2\text{Cl}_2 \) (1 ml) and HCl (2 ml, 1 M in Et\(_2\)O) to afford amine hydrochloride 252k as a yellow solid (9 mg, 61%).

\(^1\)H NMR \( \delta \) (360 MHz, D\(_2\)O) 6.76 (1H, s, Ar\( H \)), 6.57 (1H, s, Ar\( H \)), 5.80 (2H, s, OC\( H_2 \)), 4.21-4.12 (2H, m, C\( H_2 \)Ar), 3.95-3.85 (1H, m, C\( H \)), 3.83-3.75 (2H, m, 2xCH\( H \)), 3.11-3.05 (1H, m, C\( H \)), 2.04-1.59 (6H, m, 2xCH\( 2 \)+2xOH\( H \));

\(^{13}\)C NMR \( \delta \) (90.6 MHz, D\(_2\)O) 147.9 (C), 147.8 (C), 126.6 (C), 121.3 (C), 110.1 (CH), 107.3 (CH), 102.5 (CH\(_2\)), 71.7 (CH), 68.6 (CH), 52.6 (CH), 44.0 (CH\(_2\)), 39.6 (CH), 26.0 (CH\(_2\)), 22.2 (CH\(_2\)); \( m/z \) (ESI+) 264 ([M+H\(^+\)]\(^+\), 4 %), 150 (21), 149 (21);

HRMS (ESI+) Found [M+H\(^+\)]\(^+\), 264.1237. \( \text{C}_{14}\text{H}_{18}\text{O}_4\text{N} \) requires 264.1230.

(2RS,3SR,4aSR,11bSR)-1,2,3,4,4a,5,6,11b-Octahydro-[1,3]dioxolo[4,5-f]phenanthridine-2,3-diol hydrochloride 253k (A^{23} isomer)

General procedure \( Q \) was followed using diol 207k (10 mg, 28 \( \mu \)mol), \( \text{CH}_2\text{Cl}_2 \) (2 ml) and TFA (3 ml), then \( \text{CH}_2\text{Cl}_2 \) (1 ml) and HCl (2 ml, 1 M in Et\(_2\)O) to afford amine hydrochloride 253k as a yellow solid (7 mg, 81%).

\(^1\)H NMR \( \delta \) (360 MHz, D\(_2\)O) 6.69 (1H, s, Ar\( H \)), 6.54 (1H, s, Ar\( H \)), 5.80-5.79 (2H, m, OCH\( H \)), 4.17-4.09 (2H, m, CH\(_2\)Ar), 3.79-3.72 (3H, m, 3xCH\( H \)), 3.14-3.11 (1H, m, CH\( H \)), 2.09-1.98 (2H, m, CH\(_2\)), 1.88-1.72 (2H, m, CH\(_2\));

\(^{13}\)C NMR \( \delta \) (90.6 MHz, D\(_2\)O) 148.4 (C), 147.6 (C), 129.2 (C), 120.7 (C), 108.8 (CH), 107.3 (CH), 102.5 (CH\(_2\)), 68.3 (CH), 67.1 (CH), 52.9 (CH), 45.1 (CH\(_2\)), 34.4 (CH\(_2\)), 31.9 (CH), 29.8 (CH\(_2\)); \( m/z \) (ESI+) 264 ([M+H\(^+\)]\(^+\), 100 %), 262 (46);

HRMS (ESI+) Found [M+H\(^+\)]\(^+\), 264.1232. \( \text{C}_{14}\text{H}_{18}\text{O}_4\text{N} \) requires 264.1230.
Experimental

(3RS,4SR,4aRS,11bSR)-1,2,3,4,4a,5,6,11b-Octahydro-[1,3]dioxolo[4,5-
j]phenanthridine-3,4-diol hydrochloride 254k (Δ3,4 isomer)

General procedure Q was followed using diol 208k (5 mg, 14 µmol), CH₂Cl₂ (2 ml) and TFA (3 ml), then CH₂Cl₂ (1 ml) and HCl (2 ml, 1 M in Et₂O) to afford amine hydrochloride 254k as a colourless oil (3 mg, 73%).

¹H NMR δ (360 MHz, D₂O) 6.81 (1H, s, ArH), 6.58 (1H, s, ArH), 5.80 (2H, d, /uni0408 3.8, OC₂H₂O), 4.16 (1H, d, /uni0408 16.1, CHXH₂Y), 4.09 (1H, d, /uni0408 16.1, CHXH₂Y), 3.82-3.80 (1H, br s, CH₂O), 3.72 (1H, ddd, /uni0408 9.4, 4.5, CH), 3.62-3.59 (1H, m, CH), 3.22-3.21 (1H, br s, CH₂); ¹³C NMR δ (90.6 MHz, D₂O) 149.8 (C), 148.4 (C), 129.1 (C), 123.2 (C), 108.6 (2xCH), 102.1 (CH₂), 70.9 (CH), 68.6 (CH), 56.3 (CH), 42.8 (CH₂), 35.5 (CH), 27.7 (2xCH₂); m/z (ESI+) 264 ([M+H]+, 24 %), 225 (29), 211 (29), 179 (61); HRMS (ESI+) Found [M+H]+, 264.1234. C₁₄H₁₈O₄N requires 264.1230.

(2SR,3RS,4aSR,11bSR)-1,2,3,4,4a,5,6,11b-Octahydro-[1,3]dioxolo[4,5-
j]phenanthridine-2,3-diol 255k (Δ2,3 isomer, minor diastereomer)

General procedure Q was followed using endo-syn diol 209k (2.3 mg, 6 µmol), CH₂Cl₂ (2 ml) and TFA (3 ml), then CH₂Cl₂ (1 ml) and HCl (1 ml, 1M in Et₂O) to afford amine hydrochloride 255k as a colourless oil (1.0 mg, 60%).

¹H NMR δ (800 MHz, D₂O) 6.65 (1H, s, ArH), 6.51 (1H, s, ArH), 5.78 (2H, d, /uni0408 2.4, OCH₂O), 4.08 (2H, s, CH₂Ar), 3.91 (1H, d, /uni0408 2.4, CH), 3.72 (1H, ddd, /uni0408 11.2, 4.0, 2.4, CH), 3.49 (1H, s, CH), 2.98-2.97 (1H, m, CH), 2.14 (1H, dt, /uni0408 16.0, 3.2, CH₄H₅), 1.92-1.86 (2H, m, CH₄H₅+CH₃H₅), 1.67-1.62 (1H, m, CH₃H₅), 1.39-1.30 (2H, m, CH₂); ¹³C NMR δ (200.0 MHz, D₂O) 147.0 (C), 146.4 (C), 129.2 (C), 119.3 (C), 108.0 (CH), 105.9 (CH), 101.2 (CH₂), 69.3 (CH), 67.1 (CH), 51.3 (CH), 45.6 (CH₂), 35.4 (CH), 32.0 (CH₂), 31.7 (CH₂); m/z (ESI+) 264 ([M+H]+, 100 %), 209 (13); HRMS (ESI+) Found [M+H]+, 264.1232. C₁₄H₁₈O₄N requires 264.1230.
(1RS,2SR,4aSR,10bSR)-1,2,3,4,4a,5,6,10b-Octahydro-phenanthridine-1,2-diol

252m (Δ^{1,2} isomer)

General procedure Q was followed using diol 206m (29 mg, 91 µmol), CH₂Cl₂ (2 ml) and TFA (3 ml), then CH₂Cl₂ (1 ml) and HCl (1 ml, 1 M in Et₂O) to afford amine hydrochloride 252m as a colourless oil (20 mg, 86%).

^1H NMR δ (360 MHz, D₂O) 7.25-7.22 (1H, m, ArH), 7.17-7.13 (2H, m, 2xArH), 7.06-7.04 (1H, m, ArH), 4.28 (1H, J 16.2, CHₓHYAr), 4.21 (1H, d, J 16.2, CHₓHYAr), 3.90 (1H, br d, J 7.5, CH), 3.75-3.70 (2H, m, 2xCH), 3.17 (1H, dd, J 7.8, 4.4, CH), 1.92-1.85 (1H, m, CH₄H₅B), 1.76-1.70 (1H, m, CH₆H₅B), 1.63-1.56 (2H, m, CH₂); ^13C NMR δ (62.9 MHz, D₂O) 131.9 (C), 129.3 (CH), 129.0 (CH), 127.8 (CH), 127.2 (C), 126.9 (C), 125.1 (CH₂), 21.4 (CH₂); m/z (ESI+) 220 ([M+H]⁺, 77 %), 219 (29); HRMS (ESI+) Found [M+H]⁺, 220.1331. C₁₃H₁₈O₂N requires 220.1332.

(2RS,3SR,4aSR,10bSR)-1,2,3,4,4a,5,6,10b-Octahydro-phenanthridine-2,3-diol hydrochloride 253m (Δ^{2,3} isomer)

General procedure Q was followed using diol 207m (25 mg, 78 µmol), CH₂Cl₂ (2 ml) and TFA (3 ml), then CH₂Cl₂ (1 ml) and HCl (1 ml, 1 M in Et₂O) to afford amine hydrochloride 253m as a colourless oil (12 mg, 60%).

^1H NMR δ (360 MHz, D₂O) 7.18-7.17 (2H, m, 2xArH), 7.15-7.10 (1H, m, ArH), 7.02 (1H, d, J 7.4, ArH), 4.25-4.17 (2H, m, CH₂Ar), 3.78-3.70 (3H, m, 3xCH), 3.24-3.18 (1H, dt, J 10.5, 4.6, CHAr), 2.06-1.97 (2H, m, CH₂), 1.85-1.75 (2H, m, CH₂); ^13C NMR δ (150.8 MHz, D₂O) 131.1 (CH), 130.8 (C), 130.0 (CH), 129.4 (C), 129.4 (CH), 129.3 (CH), 70.1 (CH), 68.8 (CH), 54.7 (CH), 46.9 (CH₂), 36.1 (CH₂), 33.7 (CH), 31.6 (CH₂); m/z (ESI+) 220 ([M+H]⁺, 100 %), 219 (91), 211 (62), 179 (65); HRMS (ESI+) Found [M+H]⁺, 220.1331. C₁₃H₁₈O₂N requires 220.1332.
(3RS,4SR,4aRS,10bSR)-1,2,3,4,4a,5,6,10b-Octahydro-phenanthridine-3,4-diol hydrochloride 254m (Δ^{3,4} isomer)

General procedure Q was followed using diol 208m (26 mg, 82 µmol), CH₂Cl₂ (2 ml) and TFA (3 ml), then CH₂Cl₂ (1 ml) and HCl (1 ml, 1 M in Et₂O) to afford amine hydrochloride 254m as a colourless oil 11 mg, 53%.

¹H NMR δ (360 MHz, D₂O) 7.29 (1H, d, J 6.9, ArH), 7.20 (1H, t, J 7.1, ArH), 7.13 (1H, t, J 7.6, ArH), 7.05 (1H, d, J 7.5, ArH), 4.24 (1H, d, J 16.3, CHXH₂Ar), 4.18 (1H, d, J 16.3, CHXH₂Ar), 3.79-3.73 (2H, m, 2xCH), 3.56 (1H, br d, J 9.1, CH), 3.33-3.29 (1H, m, CH), 2.08-1.97 (1H, m, CHₐHₐ), 1.94-1.85 (1H, m, CHₐHₐ), 1.59-1.53 (1H, m, CHₐCHₐ), 1.34-1.26 (1H, m, CHₐCHₐ); ¹³C NMR δ (62.9 MHz, D₂O) 133.3 (C), 128.7 (CH), 128.1 (C), 127.4 (CH), 127.0 (CH), 126.8 (CH), 69.0 (CH), 66.7 (CH), 54.5 (CH), 41.3 (CH₂), 33.6 (CH), 25.9 (CH₂), 21.5 (CH₂); m/z (ESI+) 220 ([M+H]⁺, 100 %), 218 (21); HRMS (ESI+) Found [M+H]⁺, 220.1331. C₁₃H₁₈O₂N requires 220.1332.
5-Methanesulfonyl-4,5,5a,6,7,8,9,9a-octahydro-thieno[2,3-c]quinoline-diol 256-258

General procedure P was followed using phenanthridines 158-160 (15 mg, 56 µmol), THF (312 µl), H₂O (63 µl), OsO₄ (49 µl, 2.5% w/w in 'BuOH, 3.9 µmol) and NMO (20 mg, 0.16 mmol). Flash chromatography (CH₂Cl₂:CH₂Cl₂:MeOH, 100:2) afforded Δ₁,₂ diol 256 (1 mg, 6%), Δ₂,₃ diol 257 (1 mg, 6%), Δ₃,₄ diol 258 (2.4 mg, 14%), and mixed diol (8 mg, 47%) giving a total yield (12.4 mg, 73%).

(5aSR,8SR,9RS,9aSR)-5-Methanesulfonyl-4,5,5a,6,7,8,9,9a-octahydro-thieno[2,3-c]quinoline-8,9-diol 256 (Δ₁,₂ isomer)

R_t [CH₂Cl₂:MeOH, 9:1] = 0.09; ν_max (CHCl₃)/cm⁻¹ 3446 (OH), 2925, 1319, 1151; ¹H NMR δ (250 MHz, CDCl₃) 7.27 (1H, d, J 5.3, HetH), 6.95 (1H, d, J 5.3, HetH), 4.81 (1H, dd, J 16.8, 1.8, CHₓHᵧHet), 4.57-4.49 (2H, m, CHO₉NCH), 4.39 (1H, dd, J 17.0, 1.8, CHₓHᵧHet), 3.59-3.50 (1H, m, CH), 3.41 (1H, br s, CH), 2.90 (3H, s, CH₃), 1.99-1.92 (1H, m, CH₉H₈), 1.80-1.68 (3H, m, CH₂+CHₓHᵧ); ¹³C NMR δ (90.6 MHz, CDCl₃) 131.9 (C), 130.5 (C), 124.5 (CH), 124.4 (CH), 72.0 (CH), 67.6 (CH), 48.6 (CH), 42.1 (CH), 40.7 (CH₂), 39.8 (CH₃), 26.6 (CH₂), 23.4(CH₂); m/z (EI) 303 ([M]+, 2 %), 281 (5), 267 (8), 228 (41), 149 (33), 84 (100); HRMS (EI) Found: 303.0594. C₁₂H₁₇O₉NS₂ requires 303.0594.
Experimental

(5aSR,7SR,8RS,9aSR)-5-Methanesulfonyl-4,5,5a,6,7,8,9,9a-octahydrothieno[2,3-c]quinoline-7,8-diol 257 (A⁻³⁻⁻ isomer)

\[
\text{Rf} \ [\text{CH}_2\text{Cl}_2:\text{MeOH}, 9:1] = 0.09; \ \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3396 (\text{OH}), 2927, 1661, 1319, 1151; ^1\text{H NMR} \ \delta (250 \text{ MHz, CDCl}_3) 7.25 (1H, d, J 5.3, HetH), 7.01 (1H, d, J 5.0, HetH), 4.83 (1H, dt, J 17.0, 0.8, CH₃H₂Het), 4.43 (1H, dd, J 12.3, 4.8, NCH), 4.34 (1H, dd, J 16.8, 3.5, CH₂XH₂Het), 3.98 (1H, s, CHOH), 3.55-3.46 (1H, m, NCHCH), 3.27 (1H, br s, CHOH), 2.89 (3H, s, CH₃), 2.29-2.20 (2H, m, CH₂), 2.04-1.93 (1H, m, CH₃H₉), 1.87-1.75 (1H, m, CH₂H₂); ^13\text{C NMR} \ \delta (90.6 \text{ MHz, CDCl}_3) 134.7 (C), 129.8 (C), 125.0 (CH), 124.1 (CH), 69.2 (CH), 66.8 (CH), 47.8 (CH), 40.6 (CH₂), 39.7 (CH₃), 35.4 (CH), 30.5 (CH₂), 30.3 (CH₃); m/z (EI) 303 ([M]⁺, 5 %), 285 (18), 224 (67), 206 (36), 178 (23), 149 (32), 136 (100); HRMS (EI) Found: 303.0593. C₁₂H₁₇O₄NS₂ requires 303.0594.

(5aRS,6SR,7RS,9aSR)-5-Methanesulfonyl-4,5,5a,6,7,8,9,9a-octahydrothieno[2,3-c]quinoline-6,7-diol 258 (A⁻³⁻⁻ isomer)

\[
\text{Rf} \ [\text{CH}_2\text{Cl}_2:\text{MeOH}, 9:1] = 0.11; \ \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 3446 (\text{OH}), 2929, 1649, 1315, 1149; ^1\text{H NMR} \ \delta (360 \text{ MHz, CDCl}_3) 7.22 (1H, d, J 7.6, HetH), 6.90 (1H, d, J 7.2, HetH), 4.92 (1H, dd, J 24.5, 2.2, CH₃H₉Het), 4.43 (1H, dd, J 24.2, 2.9, CH₃H₉Het), 4.33 (1H, dd, J 14.8, 7.9, NCH), 4.06 (1H, d, J 4.0, CHOH), 3.55 (1H, dd, J 14.8, 4.3, NCHCH), 3.28 (1H, br s, CHOH), 2.98 (3H, s, CH₃), 2.26-2.16 (1H, m, CH₃H₉), 2.09-2.01 (1H, m, CH₃H₉), 1.83-1.75 (1H, m, CH₂H₂), 1.40-1.32 (1H, m, CH₂H₂); ^13\text{C NMR} \ \delta (90.6 \text{ MHz, CDCl}_3) 135.3 (C), 130.2 (C), 124.7 (CH), 124.0 (CH), 69.1 (CH), 67.4 (CH₂), 55.2 (CH), 40.7 (CH₂), 39.6 (CH₃), 36.1 (CH), 25.6 (CH₂), 21.7 (CH₂); m/z (EI) 303 ([M]⁺, 6 %), 285 (20), 228 (22), 224 (100), 206 (52); HRMS (EI) Found: 303.0588. C₁₂H₁₇O₄NS₂ requires 303.0594.
General Procedure R - Zebrafish phenotype screening

The following protocol was used for the preliminary wild-type screening of our compound library.172

1) Chemicals were diluted into the E3 screening medium. Aliquots of 200 µl (or multiples thereof) were prepared at concentrations ranging from 100 µM to 1 µM, all with 0.5% v/v DMSO. When not in use the aliquots were stored in the freezer.

2) Five small breeding tanks were set up in the evening, each containing one male zebrafish and one or two females. The tanks were kept in darkness until the next morning when the lights were switched on causing the fish to breed.

3) The embryos were collected, pooled and washed with E3 medium. Dead, delayed or unformed embryos were discarded, and the adult fish were returned to their main tank.

4) The embryos were divided into two petri dishes and stored in an incubator at 28.5 °C until required.

5) The chemical aliquots were placed in the same incubator to defrost.

6) Once the embryos had reached the desired age they were distributed in 96-well plates as appropriate to the screen, with two or three embryos per well.

7) The surrounding medium was removed from the embryos using a wide-tipped Pasteur pipette and then the appropriate 200 µl chemical aliquot was added to the well. Four control wells were used per plate, each containing E3 with 0.5% v/v DMSO.

8) The plates were incubated at 28.5 °C and examined periodically over the next five days using a microscope to assess any phenotypes. Photographs were taken where required using a digital camera coupled to a microscope.

9) At 5 dpf the embryos were disposed of.
REFERENCES

References

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References

184 Muller, P.; Bolea, C. Helvetica Chimica Acta 2001, 84, 1093-1111.
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APPENDIX