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Use of Novel Nitrones in the Synthesis of Piperidine Alkaloids

Glenn Philip Archibald

Abstract

The current study focused on development of a flexible synthetic strategy for the enantioselective preparation of 2-substituted-3-hydroxypiperidines utilising chiral 3-hydroxytetrahydropyridine N-oxides.

Initial studies into the regio- and stereoselectivity of the 1,3-dipolar cycloaddition reaction between O-benzyl protected 3-hydroxytetrahydropyridine N-oxide 208 and a range of alkenes, proceeded with excellent exo/endo selectivity and near perfect regioselectivity. However the anti/syn selectivity was only moderately in favour of the desired anti-compounds. Further development has led to the synthesis of a novel O-silyl protected 3-hydroxytetrahydropyridine N-oxide 198 which demonstrated enhanced reactivity towards nucleophilic attack by a wide range of Grignard and organolithium reagents. The reaction proceeded with high diastereoselectivity, affording trans-substituted hydroxylamines as the sole products except in the case of allylmagnesium bromide. Reductive cleavage of the hydroxylamines or isoxazolidine cycloadducts has generated a small library of 2-substituted-3-hydroxypiperidines which as well as possessing functional groups that are highly amenable to elaboration. Differentially N/O-protected derivatives of many of the formed compounds have been used as key intermediates in natural product synthesis.

The flexibility of the developed methodology was demonstrated by the concise synthesis of the L-rhamnosidase inhibitor (+)-swainsonine 397, which was accomplished in seven steps and 29.5% overall yield from nitrone 198. The C-2 stereocenter was installed with high diastereoselectivity, via addition of the C-lithiate of protected propargyl alcohol 491, affording trans-diastereoisomer 490 as the sole product. Extension of the developed methodology to the synthesis of quinolizidine alkaloids was realised via the substitution of protected but-3-yn-1-ol 533 as starting material with the formal synthesis of (-)-epiquinamide 529 being achieved in five steps and 20.7% overall yield from nitrone 198.

Finally, through efforts to synthesise cis-2,3-substituted piperidines, methodology has been developed for synthesis of the 2,6-disubstituted-3-hydroxypiperidine motif. Oxidation of 2,3-disubstituted-N-hydroxypiperidines unexpectedly provided access to the synthetically challenging aldonitrone. Nucleophilic addition and 1,3-dipolar cycloaddition have been shown to proceed with high selectivity giving access to highly substituted stereochemically defined piperidine scaffolds.
Acknowledgements

This thesis could not have been completed without the support and assistance from a number of persons whom I wish to acknowledge.

First and foremost, I would like to thank both of my supervisors, who without their inspiration, knowledge, guidance and motivation, none of this would be possible. Dr Vittorio Caprio, I have greatly appreciated your confidence in me and in this project. I am grateful for being given the opportunity to work in your group, thank you for four years of rewarding collaboration which I hope will continue in the future. Dr David Barker, thank you for your constant support and encouragement over the last three years, especially during the last few weeks of writing. I have enjoyed spending the second half of my studies as an unofficial member of your group.

A large amount of credit for my chemistry education should also go to Dr Yang. I am grateful for all that you taught me during the time we shared a lab together.

Thanks to all the staff members who have provided excellent advice and support; Dr Brett Copp, Dr George Clark, Dr Peter Boyd, Dr Michael Schmitz, Raisa Imatdieva, Tasdeeq Mohammed, Alistair Mead, Mike Wadsworth and Tania Groutso.

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To Kerri and Maree, thank you for just being yourselves and good friends to me throughout all of undergraduate and this project. Thank you for sharing in my excitement even when you may not know what I am talking about.

Last but certainly not least I wish to thank my family for their immense support and providing me with the financial means to undertake university studies. To my parents Stephen and Carole whom I admire so very much, thank you for always allowing me the freedom to pursue my own path. Without your love and support I could never have achieved all that I have.
# Table of Contents

Abstract ................................................................................................................................. ii

Acknowledgements ................................................................................................................ iii

Abbreviations and Acronyms ................................................................................................ viii

List of Figures ....................................................................................................................... xii

List of Tables ........................................................................................................................ xiv

1. Introduction .................................................................................................................... 16

1.1 Bioactive 3-Hydroxypiperidine Alkaloids ................................................................. 16

1.2 Methods for Synthesis of the 3-Hydroxypiperidine Core ........................................ 18

1.2.1 Intramolecular Nucleophilic Attack .................................................................... 18

1.2.2 Nucleophilic Addition to N-Acyliminium Ions .................................................... 26

1.2.3 Alkylation of Pyridinium Salts ............................................................................ 27

1.2.4 Cycloaddition Reactions ...................................................................................... 28

1.2.5 Ring-Closing Metathesis ...................................................................................... 30

1.2.6 Ring Expansion of Pyrrolidines .......................................................................... 33

1.2.7 Oxidation-Cyclisation of Furan Derivatives ....................................................... 34

1.2.8 Palladium Catalysed Cyclisation ........................................................................ 36

1.2.9 Rhodium-Catalysed Cyclohydrocarbonylation .................................................... 37

1.2.10 Cyclisation via Amidomercuration ................................................................... 38

1.2.11 Conclusion .......................................................................................................... 39

1.3 Overview of the Nitrone Reactivity Profile ................................................................. 40

1.4 1,3-Dipolar Cycloaddition Reaction to Nitrone ......................................................... 42

1.4.1 Selectivity of the 1,3-Dipolar Cycloaddition Reaction Between Alkenes and Nitrone ........................................................................................................... 44

1.5 Nucleophilic Addition to Nitrone .............................................................................. 47

1.6 Synthetic Applications of Enantiopure Cyclic Nitrone ............................................. 49

1.6.1 1,3-Dipolar Cycloaddition Reaction Between Alkenes and Cyclic Nitrone ...... 49
3.2 Previous Synthetic Studies Toward (+)-Swainsonine .......................................................... 121
   3.2.1 Synthesis of (+)-Swainsonine by Oishi et al. ............................................................... 121
   3.2.2 Syntheses of (+)-Swainsonine by Fleet and Co-workers ................................................ 123
   3.2.3 Synthesis of (+)-Swainsonine by Guo and O’Doherty .................................................... 125
   3.2.4 Synthesis of (+)-Swainsonine by Alam et al. ............................................................... 127
   3.2.5 Synthesis of (+)-Swainsonine by Chen et al. ............................................................... 128
   3.2.6 Synthesis of (+)-Swainsonine by Chooprayoon et al. .................................................... 129
3.3 Previous Syntheses of (-)-Swainsonine ................................................................................. 131
   3.3.1 Racemic Synthesis of Swainsonine by Mukai et al .......................................................... 131
   3.3.2 Synthesis of (-)-Swainsonine by Buschman et al ........................................................... 132
   3.3.3 Synthesis of (-)-Swainsonine by Lindsay and Pyne ......................................................... 133
3.4 Retrosynthesis ....................................................................................................................... 135
3.5 Total Synthesis of (+)-Swainsonine and (-)-1,2-Di-epi-swainsonine .................................... 136
   3.5.1 Nucleophilic Addition of Lithium Acetylide and Hydroxylamine Reduction ..................... 136
   3.5.2 Stereoselective Semi-Hydrogenation ................................................................................ 140
   3.5.3 Cyclisation to the Indolizidine Ring ................................................................................... 143
   3.5.4 Syn-Dihydroxylation of Indolizidine ................................................................................ 148
   3.5.5 Elaboration to (+)-Swainsonine and (-)-1,2-Di-epi-swainsonine ..................................... 151
3.6 A Brief Overview of (-)-Epiquinamide .................................................................................... 158
   3.6.1 Isolation and Biological Activity ....................................................................................... 158
3.7 Previous Synthetic Studies Towards (+)- and (-)-Epiquinamide ........................................ 159
   3.7.1 Synthesis of (+)-Epiquinamide by Tong et al. ................................................................. 159
   3.7.2 Synthesis of (-)-Epiquinamide by Huang et al. .............................................................. 160
3.8 Retrosynthesis ....................................................................................................................... 161
3.9 Formal Synthesis of (-)-Epiquinamide ................................................................................... 162
   3.9.1 Synthesis of the Cyclisation Precursor .............................................................................. 162
   3.9.2 Cyclisation to the Quinolizidine Ring .............................................................................. 162
3.9.3 Elaboration to (−)-Epiquinamide ...................................................... 165
3.10 Summary ............................................................................................. 167
3.11 A Serendipitous Entry into the 2,3,6-Substituted Piperidine System .................................................. 169
  3.11.1 Proposed Synthesis of the cis-3-Hydroxypiperidine Motif ...................... 169
  3.11.2 Attempted Enantiodivergent Synthesis of Advanced Precursor 549 .......... 171
  3.11.3 Nucleophilic Addition to Aldonitrone 557f ......................................... 173
  3.11.4 1,3-Dipolar Cycloaddition to Aldonitrone 557e ................................. 179
3.12 Overall Summary .................................................................................. 181
3.13 Future Work ......................................................................................... 183

4. Experimental ............................................................................................. 184
  4.1 General Experimental Details ................................................................. 184
  4.2 Synthesis of O-Benzyl Protected Nitrone .............................................. 185
  4.3 Model Studies Utilising O-Benzyl Nitrone ............................................. 190
  4.4 Synthesis of O-Silyl Protected Nitrone .................................................. 205
  4.5 Model Studies Utilising O-Silyl Protected Nitrone .................................. 209
  4.6 Total Synthesis of (+)-Swainsonine and (−)-1,2-Di-epi-swainsonine .......... 224
  4.7 Formal Synthesis of (−)-Epiquinamide ............................................... 238
  4.8 Synthesis of 2,6-Disubstituted-3-Hydroxypiperidines ......................... 244

5. References ................................................................................................. 257

6. Appendix .................................................................................................... 273
## Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
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<tr>
<td>[α]</td>
<td>specific optical rotation</td>
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<td>δ</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
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<td><em>O-terr</em>-butyl-S-(4,6-dimethyl-2-pyrimidinyl) thiocarbonate</td>
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<tr>
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<td>decomposition</td>
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<tr>
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<td>EDG</td>
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<td>electric eel acetylcholine esterase</td>
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<tr>
<td>K</td>
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<td>KHMDS</td>
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<td>LUMO</td>
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<td>Rf</td>
<td>retention factor</td>
</tr>
<tr>
<td>rt</td>
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<td>s</td>
<td>singlet (spectroscopic); second(s)</td>
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<td>Su</td>
<td>succinimide</td>
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<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl or tetramethylsilane</td>
</tr>
<tr>
<td>Tol</td>
<td>4-toluoyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>TPP</td>
<td>triphenylphosphine</td>
</tr>
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List of Figures

Figure 1.1.1. Representative 2-substituted 3-hydroxypiperidines. .........................................................16
Figure 1.1.2. Representative 2,6-substituted 3-hydroxypiperidines. ..........................................................16
Figure 1.1.3. Representative bi- and polycyclic alkaloids containing the 2-substituted 3-hydroxypiperidine. ..........................................................................................................................17
Figure 1.4.1. Classifications of 1,3-dipolar cycloaddition reaction with representative examples..............................................................................................................................................43
Figure 1.4.2 Possible stereoisomers resulting from approach of dipolarophile to a 3-substituted cyclic nitrone. ..............................................................................................................................................47
Figure 1.5.1. Mechanism of nucleophilic addition to nitrones. ........................................................................48
Figure 1.5.2. Nucleophilic addition to a facially-differentiated, cyclic nitrone. .............................................48
Figure 2.1.1. Representation of orbital interaction of the 3-substituent with the trans hydrogen.218 ............................................ ..........................................................67
Figure 2.2.1. Nitrogen inversion and chair inversion processes for isoxazolidines occurring at room or lower temperatures..................................................................................................................69
Figure 2.2.2. Expected NOESY interactions for exo-anti and endo-anti cycloadducts........70
Figure 2.2.3. Expected NOESY interactions for exo-syn and endo-syn cycloadducts. ........71
Figure 2.2.4. Observed NOESY interactions for exo-anti cycloadduct 296 . ........................71
Figure 2.2.5. Observed NOESY interactions for exo-syn cycloadduct 297 ........72
Figure 2.2.6. Observed NOESY interactions for piperidine 301 ..........................................................75
Figure 2.2.7. Observed NOESY interactions for piperidine 302 ..........................................................76
Figure 2.2.8. Observed NOESY interactions for piperidine 303 ..........................................................76
Figure 2.2.9. Observed NOESY interactions for exo-anti cycloadduct 306 ........................................78
Figure 2.2.10. Observed NOESY interactions for exo-syn cycloadduct 307 ...........................................79
Figure 2.2.11. Observed NOESY interactions for piperidine 308 ..........................................................80
Figure 2.2.12. Observed NOESY interactions for exo-anti cycloadduct 311 ...........................................81
Figure 2.2.13. Observed NOESY interactions for exo-syn cycloadduct 312 ...........................................82
Figure 2.2.14. Observed NOESY interactions for endo-anti cycloadduct 310 ........................................83
Figure 2.2.15. Observed NOESY interactions for piperidine 313 ..........................................................84
Figure 2.2.16. Observed NOESY interactions for exo-anti cycloadduct 316 ...........................................85
Figure 2.2.17. Observed NOESY interactions for exo-syn cycloadduct 317 ...........................................86
Figure 2.2.18. Observed NOESY interactions for endo-anti cycloadduct 315 ........................................87
Figure 2.2.19. Isoxazolidines present in the mixed fraction. .......................................................... 88
Figure 2.2.20. Alkene approach to nitro 208 to give 3-substituted cycloadducts. .................. 88
Figure 2.2.21. Observed NOESY interactions for indolizidinone 322 ........................................... 89
Figure 2.4.1 ORTEP representation of diol 341 as determined by X-ray diffraction .............. 99
Figure 2.6.1 Observed NOESY interactions for piperidine 346 .................................................. 103
Figure 2.6.2 Observed NOESY interactions for piperidine 362 .................................................. 106
Figure 2.8.1 Proposed model for the most reactive conformer of nitro 198 ......................... 115
Figure 3.1.1. Structures of (-)-swainsonine 11 and (+)-swainsonine 397 ............................ 118
Figure 3.1.2. Structural similarities between (+)-swainsonine 397 and L-rhamnose sugars. ................................................................. 119
Figure 3.1.3. Structural similarities between protonated (+)-swainsonine 400 and rhamnosyl cation 401 ................................................................. 119
Figure 3.1.4. Structure of the mycobacterial cell wall, emphasising the position and role of the linker region ................................................................. 120
Figure 3.3.1. Facial selectivity of OsO₄ attack caused by steric hindrance exerted by pseudo-axial hydrogens. .................................................................................. 134
Figure 3.5.1. Observed NOESY interactions for piperidine 498 .................................................. 138
Figure 3.5.2. Observed NOESY interactions for piperidine 489 .................................................. 141
Figure 3.5.3 ORTEP representation of piperidine 489 as determined by X-ray diffraction. 143
Figure 3.5.4. Observed NOESY interactions for indolizidine 488 .............................................. 144
Figure 3.5.5. Facial selectivity of OsO₄ attack .............................................................................. 148
Figure 3.5.6. Observed NOESY interactions for indolizidine 506 ............................................. 150
Figure 3.5.7. ORTEP representation of indolizidine 510 as determined by X-ray diffraction. 153
Figure 3.5.8. Observed NOESY (D₂O) interactions for (+)-swainsonine 397 ........................... 154
Figure 3.5.9. Observed NOESY (CD₃OD) interactions for (-)-1,2-di-epi-swainsonine 512. .................................................................................................................. 156
Figure 3.6.1. Structures of (+)-epiquinamide 514 and (+)-epibatidine 515 ............................ 158
Figure 3.9.1. Observed NOESY interactions for quinolizidine 537 ............................................ 163
Figure 3.11.1. Proposed ring flipped orientation of aldonitrones ............................................. 173
Figure 3.11.2. Observed NOESY interactions for piperidine 559 ............................................. 174
Figure 3.11.3. Observed NOESY interactions for piperidines 563 and 564 ............................. 176
Figure 3.11.4. Observed NOESY interactions for exo-anti cycloadduct 567 .......................... 180
List of Tables

Table 1.4.1. 1,3-Dipolar cycloaddition regioselectivity of N-methyl-C-phenyl and N-phenyl-C-phenyl nitrene. ................................................................. 44
Table 2.3.1. Summary of 1,3-dipolar cycloadditions with nitrone 208 ......................... 92
Table 2.4.1. Optimisation of diester reduction. ......................................................... 98
Table 2.4.2. Summary of methods of formation for the oxidation of hydroxylamine 343. .. 100
Table 2.7.1. Summary of addition of 3-lithiopyridine to nitrone 198 ......................... 111
Table 2.9.1. Summary of nucleophilic additions to nitrone 198 ................................. 116
Table 3.3.1. Summary of syn-dihydroxylation of literature indolizidines. .................. 134
Table 3.5.1. Summary of Lindlar reduction of alkyne 500 ...................................... 141
Table 3.5.2. Summary of ring closure to form indolizidine 488 ................................. 148
Table 3.5.3. Summary of syn-dihydroxylation of indolizidines .................................. 150
Table 3.5.4. Summary of physical data for swainsonine 397 .................................... 155
Table 3.5.5. Summary of physical data for (-)-1,2-di-epi-swainsonine 512 and (+)-1,2-di-epi-swainsonine ................................................................. 156
Table 3.5.6. Summary of physical data for triacetate 513 ...................................... 157
Table 3.9.1. Summary of ring closure to form quinolizidine 537 .............................. 165
Table 3.9.2. Summary of physical data for quinolizidine 530 .................................. 165
Table 3.11.1. Summary of oxidations to second generation nitrones. ....................... 172
Table 3.11.2. Summary of N-O reduction of 2,3,6-trisubstituted hydroxylamines. ....... 175
Table 4.8.1. Crystal data and structure refinement for 341 ...................................... 273
Table 4.8.2. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 341 ................................................................. 274
Table 4.8.3. Bond lengths [Å] and angles [°] for 341 ............................................ 275
Table 4.8.4. Anisotropic displacement parameters (Å^2 x 10^3) for 341 .................... 277
Table 4.8.5. Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 341 ................................................................. 278
Table 4.8.6. Crystal data and structure refinement for 489 ...................................... 280
Table 4.8.7. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 489 ................................................................. 281
Table 4.8.8. Bond lengths [Å] and angles [°] for 489 ............................................ 282
Table 4.8.9. Anisotropic displacement parameters (Å^2 x 10^3) for 489 .................... 284
Table 4.8.10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å² x 10^3) for 489 .......................................................... 285

Table 4.8.11. Crystal data and structure refinement for 510 .................................................. 287

Table 4.8.12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å² x 10^3) for 510 .......................................................... 288

Table 4.8.13. Bond lengths [Å] and angles [°] for 510 .................................................. 288

Table 4.8.14. Anisotropic displacement parameters (Å² x 10^3) for 510 ................................. 290

Table 4.8.15. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å² x 10^3) for 510 .......................................................... 291
1. Introduction

1.1 Bioactive 3-Hydroxypiperidine Alkaloids

The widespread occurrence of the 3-hydroxypiperidine moiety in a large number of structurally diverse alkaloids, displaying a broad spectrum of bioactivities, has led to it being designated as a privileged scaffold. \(^1\)

![Figure 1.1.1. Representative 2-substituted 3-hydroxypiperidines.](image)

For instance, \textit{trans}-2-substituted-3-hydroxypiperidines form the core structure of a diverse class of natural products such as the potent anti-malarial alkaloid (+)-febrifugine \(^1\), \(^2\), \(^3\) and a large family of naturally occurring polyhydroxylated azasugar glycosidases which are represented by (+)-deoxynojirimycin \(^2\). Although not naturally isolated, the conformationally restricted amino acid (2\(S\), 3\(S\))-3-hydroxypipecolic acid \(^3\) displays moderate inhibitory activity against \(\beta\)-N-acetylglucosaminidase as well as \textit{E. coli} \(\beta\)-glucuronidase. \(^4\)

The 2,6-disubstituted 3-hydroxypiperidine alkaloids 4-10 are a widely distributed class of compounds, commonly encountered in species of the plant genera \textit{Cassia} and \textit{Prosopis}. Possessing a 3-hydroxypiperidine core and a C-2 methyl or hydroxymethyl substituent, they can be distinguished by the configuration, length and functionality on the C-6 side chain.

![Figure 1.1.2. Representative 2,6-substituted 3-hydroxypiperidines.](image)
Representative examples of this family include the prosopis alkaloids, (-)-prosopinine 4 and the C-6 epimer (-)-prosophylline (not shown), isolated from the leaves of *Prosopis africana* Taub and exhibiting antibiotic, analgesic and anaesthetic properties.\(^5\)\(^6\) (+)-Spectaline 5, isolated from *Cassia spectabilis* is a potent antifungal agent,\(^7\) whilst structurally related (-)-cassine 6, isolated from *Cassia excels*,\(^8\) shows antimicrobial activity against *Staphylococcus aureus*.\(^9\) In addition to the glycosidase activity displayed by most of these compounds, members of this class have been reported to display a wide range of bioactivities, including analgesic and anti-inflammatory properties,\(^10\) inhibitory activity toward acetylcholine esterase,\(^11\) as well as cytotoxic,\(^12\) antibacterial,\(^9\)\(^,\)\(^13\) antimiycotic\(^9\) and DNA-binding activity.\(^14\) More recently the structurally related batzellaside B 8, isolated from the marine sponge *Batzella* sp. and representing the first example of a marine organism derived iminosugar, was shown to have antibacterial activity against *Staphylococcus epidermidis*.\(^15\)

Furthermore, this moiety is embedded within the structures of bicyclic alkaloids including the \(\alpha\)-mannosidase inhibitor (-)-swainsonine 11,\(^16\)\(^-\)\(^18\) (+)-castanospermine 12 and (+)-calystegine B\(_2\) 13\(^19\) which all exhibit inhibitory activity against sugar processing enzymes.

\[\text{Figure 1.1.3.} \text{ Representative bi- and polycyclic alkaloids containing the 2-substituted 3-hydroxypiperidine.}\]

(-)-Lepadin F 16, is a representative member of a family of decahydroquinolines, isolated from *Didemnum* sp.\(^20\) or *Clavelina lepadiformis*\(^21\) tunicates. Members of this family have been shown to exhibit significant in vitro cytotoxicity against several human cancer cell lines,\(^21\) as well as displaying antiplasmodial and antitrypanosomal activity.\(^20\) There are also recent reports these compounds act as potent blockers of neuronal nicotinic acetylcholine
receptors which are implicated in neurological disorders such as Parkinson’s and Alzheimer’s diseases. A structurally related compound, (+)-claveptic B \(14\), inhibits growth of murine leukemia and human solid tumour cell lines.\(^{23}\) Additionally, this moiety forms the core structure of complex polycyclic compounds such as the larvacidal stemocurtisine \(17\) as well as (-)-FR901483 \(15\) which has been isolated from the fermentation broth of \(Cladobotryum\) sp.\(^{24}\) and displays potent immunosuppressive activity with potential application as an organ transplant therapeutic.

Due to the scarcity and often poor therapeutic indices of natural products, the greatest potential of these compounds lies in their ability to serve as structural blueprints for the design of novel drug leads. Few candidates for a comprehensive SAR study can be accessed by modification of the parent compound, thus highly efficient and flexible methods are required for synthesis of the core structure and large libraries of related molecules.

1.2 Methods for Synthesis of the 3-Hydroxypiperidine Core

The presence of the 3-hydroxypiperidine moiety in an extensive number of biologically significant natural and non-natural products has led to the development of a large number of synthetic methods to obtain this core structure. A full discussion of all approaches is beyond the scope of this thesis and this area has been frequently reviewed in detail.\(^{1, 25-30}\) As such, selected routes for the enantioselective synthesis of the 2-substituted-3-hydroxypiperidine moiety will be presented, to give a general overview of the synthetic methodology available. This overview which focuses on the key step(s) is grouped in accordance to the strategies utilised for formation of the piperidine ring with appropriate substitution.

1.2.1 Intramolecular Nucleophilic Attack

The majority of examples concerning the synthesis of the piperidine ring take advantage of the nucleophilic nature of the nitrogen atom. Although the synthetic routes are highly varied, this typically involves cyclisation of a linear precursor which has been functionalised with the appropriate substituents for the target molecule. However this means that the stereochemistry needs to have already been established in previous steps which reduces synthetic flexibility.
1.2.1.1 Nucleophilic Displacement

Functionalised piperidines can be formed from appropriately substituted, linear intermediates by the intramolecular nucleophilic displacement of a good leaving group. Typically, alkyl halides, mesylates and tosylates are the most commonly used leaving groups although displacements of epoxides have found increased use.

Bodas and Kumar have developed an enantioselective synthetic route towards (2S, 3S)-3-hydroxyoxypipeolic acid 3 utilising asymmetric dihydroxylation and regioselective nucleophilic opening of a cyclic sulphate 20 to introduce chirality (Scheme 1.2.1).³¹

Mono-protection of diol 18 as a p-methoxybenzyl ether was followed by oxidation of the free alcohol to the aldehyde and subsequent elaboration using (ethoxycarbonylmethylene)-triphenylphosphorane gave Wittig product 19. Sharpless asymmetric dihydroxylation of the olefinic bond gave the respective cis-diol which was converted into the cyclic sulphate 20 by formation of a cyclic sulfite intermediate with SOCl₂ and Et₃N followed by oxidation. Nucleophilic ring opening of sulphate 20 with sodium azide occurred at the α-carbon to give anti-azido alcohol 21. Deprotection of the p-methoxybenzyl group followed by reduction of the azide under hydrogenation conditions in the presence of Boc₂O gave the amino diol 22. Conversion to the mesylate and treatment with triethylamine resulted in cyclisation to piperidine 23. Ester hydrolysis and subsequent Boc-deprotection afforded (2S, 3S)-3-hydroxyoxypipeolic acid 3 (Scheme 1.2.1).
Recently, a formal synthesis of (-)-swainsonine 11 was reported by Choi et al. utilising the readily available, enantiomerically pure 1-(R)-α-methylbenzylaziridine-2-carboxylic acid (-)-menthol ester 24 (Scheme 1.2.2).32

![Scheme 1.2.2. Reagents and conditions: (a) N,O-dimethylhydroxylamine hydrochloride, i-PrMgCl, THF, 0 °C to rt, 10 min, 95%; (b) (3-bromopropoxy)-tert-butyldimethylsilane, Mg, THF, reflux, 8 h, 67%; (c) NaBH₄, ZnCl₂, MeOH, -78 °C, 1.5 h, 94% (dr > 99:1); (d) TBSCl, DMAP, CH₂Cl₂, 0 °C to rt, 12 h, 99%; (e) AcOH, CH₂Cl₂, rt, overnight, 88%; (f) AcOH:H₂O:THF (3:1:1), rt, 2 d, 90%; (g) MsCl, Et₃N, CH₂Cl₂, 0 °C to rt, 1 d, 61%; (h) H₂, Pd(OH)₂/C, Boc₂O, MeOH, rt, 5 h; (i) KOH, MeOH, rt, 30 min; (j) (COCl)₂, DMSO, CH₂Cl₂, -78 °C, 30 min, then Et₃N, 0 °C, 30 min; (k) MePPh₃Br, LiHMDS, THF, 0 °C to rt, 1.5 h, 46% (over four steps).](image)

The reaction of aziridine 24 with N,O-dimethylhydroxylamine hydrochloride in the presence of i-PrMgCl gave the corresponding Weinreb amide which was followed by addition of 3-tert-butyldimethylsilyloxypropylmagnesium bromide to provide the ketone 25. Chelation-controlled reduction with *in situ* generated zinc borohydride was followed by protection of the newly formed secondary alcohol to give 26. Ring-opening of the aziridine ring with acetic acid proceeded regioselectively at the least sterically hindered C-3 position to give cyclisation precursor 27. Silyl deprotection and mesylation was followed by intramolecular cyclisation, furnishing piperidine 28 with the desired *trans*-stereochemistry. A series of functional group transformation gave the desired vinyl piperidine 29 which has been previously utilised by Bates *et al.* for the synthesis of (-)-swainsonine 11 (Scheme 1.2.2).33
Ham and co-workers have synthesised (-)-swainsonine 11 using a chiral oxazoline precursor\textsuperscript{34} which has been previously utilised in asymmetric syntheses of (+)-spectaline 5,\textsuperscript{35} (2S,3R)-3-hydroxy-pipeolic acid,\textsuperscript{36} and various azasugars (Scheme 1.2.3).\textsuperscript{37,38}

\begin{center}
\centering
\includegraphics[width=\textwidth]{Scheme_1.2.3.png}
\end{center}

\textbf{Scheme 1.2.3.} Reagents and conditions: (a) CbzCl, aq. NaHCO\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, H\textsubscript{2}O, 0 °C to rt, 8 h, 96%; (b) OsO\textsubscript{4}, NMO, acetone:H\textsubscript{2}O (10:1), 0 °C, 10 h, 89% (dr = 9:1); (c) (i) 2,2-dimethoxypropane, PPTS, acetone, 40 °C, 8 h; (ii) HF-Py, py, THF, 0 °C to rt, 3 h, 78%; (d) (i) Dess-Martin periodinane, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to rt, 1 h; (ii) TiCl\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, allyltrimethylsilane, -78 °C, 24 h, 83% (dr = 15:1); (e) (i) TBSOTf, 2,6-lutidine, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 3 h, 96%; (ii) BH\textsubscript{3}·SMe\textsubscript{2}, THF, -78 °C to rt, 16 h, then 1 M NaHCO\textsubscript{3}, 30% H\textsubscript{2}O\textsubscript{2}, 0 °C to rt, 3 h, 70%; (f) (i) MsCl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to rt, 1 h; (ii) NaH, THF, 0 °C, 3 h then 2 N NaOH, MeOH, rt, 2 h, 76%.

Treatment of trans-oxazoline \textbf{30} with benzyl chloroformate afforded carbamate \textbf{31} and was followed by diastereoselective Upjohn dihydroxylation, taking place from the least hindered site to give \textbf{32} as the predominant product after benzoyl migration. Diol protection and silyl deprotection of the major isomer to yield \textbf{33} was followed by oxidation to the corresponding aldehyde and titanium tetrachloride-mediated addition of allyltrimethylsilane to give the anti-amino alcohol \textbf{34} with high anti selectivity (dr = 15:1). Protection of the anti-isomer \textbf{34} as the silyl ether and oxidation of the alkene with borane-methyl sulfide gave the corresponding alcohol \textbf{35}. Conversion of alcohol \textbf{35} to the corresponding mesylate, was followed by base-mediated intramolecular cyclisation and ester hydrolysis to give piperidine \textbf{36}. A further three steps were used to afford (-)-swainsonine 11 (Scheme 1.2.3).\textsuperscript{34}
Liu and Wang have utilised a highly selective asymmetric pinacol-type reductive coupling of a chiral sulfinyl imine 38 in the synthesis of trans- and cis-3-hydroxyxypipeolic acids (Scheme 1.2.4). 39

Scheme 1.2.4. Reagents and conditions: (a) SmI₂, t-BuOH, THF, -78 °C, 6 h, 65% (ee > 98%); (b) (i) HCl, MeOH, rt, 4 h; (ii) Boc₂O, NaHCO₃, CH₂Cl₂, rt, overnight, 88%; (c) TBSCI, DMF, imid., rt, overnight, 93%; (d) (i) K₂CO₃, MeOH, reflux, 10 h; (ii) MsCl, Et₃N, CH₂Cl₂, 0 °C, 1 h; (iii) t-BuOK, THF, 0 °C to rt, 4 h, 79%.

Pinacol-type reductive coupling of 4-pivaloxybutanal 37 with α-benzyloxy-N-tert-butanesulfanyl imine 38 afforded 39 with excellent enantio- and diasterocontrol. The chiral auxiliary was removed under acidic conditions, and the resulting amine and secondary hydroxyl protected as the Boc ester and silyl ether respectively to give 40. Pivalate deprotection and mesylation of the terminal hydroxyl was followed by ring closure to furnish the trans-piperidine 41 which was converted into (2S, 3S)-3-hydroxyxypipeolic acid 3 in a further two steps (Scheme 1.2.4). 39 Liu et al. has utilised similar methodology to synthesise the human NK-1 SP receptor antagonists (+)-CP-99,994 and (+)-l-733,060. 40

1.2.1.2 Reductive Amination

Intramolecular reductive amination, either with or without isolation of the intermediate imine, constitutes one of the most popular methods for construction of the piperidine ring from linear precursors. Aldehydes and ketones have been extensively utilised for the synthesis of 2-substituted and 2,6-disubstituted 3-hydroxypiperidines respectively. 41-49

Jourdant and Zhu have demonstrated methodology for synthesis of the trans-2-substituted-3-piperidine moiety en route to their synthesis of (2R,3R)-3-hydroxyxypipeolic acid 45 utilising the L-serine derived serinol 42 (Scheme 1.2.5). 50
Swern oxidation of known serinol 42 to the corresponding aldehyde was followed by reaction with Büchi’s Grignard reagent to give amino alcohol 43 with high diastereoselectivity favouring the anti-stereoisomer. Hydrogenation under acidic conditions yielded the 2,3-disubstituted piperidine in one pot which was isolated as the corresponding Boc ester 44. Synthesis of (2R,3R)-3-hydroxypipecolic acid 45 was completed in a further five steps (Scheme 1.2.5). This methodology was further expanded in an asymmetric total synthesis of (-)-deoxoprosophylline 50.46

Vankar and co-workers have recently reported an efficient synthesis of (-)-deoxoprosophylline 50 using reductive amination as the key cyclisation step (Scheme 1.2.6).51

Chemoselective hydrogenation of the known Perlin aldehyde 46 furnished saturated 47. Addition of dodecylmagnesium bromide gave a diastereomeric mixture of alcohols which were oxidised to the corresponding ketone 48. Base-mediated acetate deprotection was followed by conversion to the mesylate and S_N2 displacement with sodium azide. Reductive ring closure of azido ketone 49 proceeded with debenzylation to give (-)-deoxoprosophylline 50 as a single isomer (Scheme 1.2.6).51
Chavan and Praveen have developed a simple entry into both enantiomers of desoxoprosophylline utilising highly selective Sharpless asymmetric dihydroxylation and reductive amination as key steps (Scheme 1.2.7).\(^5^3\)

\[
\begin{array}{c}
\text{Scheme 1.2.7. Reagents and conditions:} \\
a \quad \text{(a) CH}_3\text{C(OEt)}_3, \text{cat. propionic acid, 140 °C, 2 h, 94%}; \\
b \quad \text{(b) AD-mix-}\alpha, \text{MeSO}_2\text{NH}_2, \text{-BuOH}:\text{H}_2\text{O (1:1), 0 °C, 24 h, 95% (ee = 93%)}; \\
c \quad \text{(c) MsCl, Et}_3\text{N, CH}_2\text{Cl}_2, 92%}; \\
d \quad \text{(d) NaN}_3, \text{DMF, 90 °C, 89%}; \\
e \quad \text{(e) (i) TPP, H}_2\text{O, benzene, 8 h, (ii) CbzCl, Et}_3\text{N, DMAP, CH}_2\text{Cl}_2, 75%}; \\
f \quad \text{(f) C}_{12}\text{H}_{25}\text{SO}_2\text{Ph, }n\text{-BuLi, THF, -78 °C, 2 h, 94%}; \\
g \quad \text{(g) Na/Hg, Na}_2\text{HPO}_4, \text{MeOH, -10 °C, 95%}; \\
h \quad \text{(h) H}_2, \text{Pd(OH)}_2/C, \text{MeOH, rt, 24 h, 76%}. \\
\end{array}
\]

Johnson-Claisen rearrangement of allylic alcohol \(51\) with triethyl orthoacetate and catalytic propionic acid gave the \(\gamma,\delta\)-unsaturated ester \(52\). Sharpless asymmetric dihydroxylation with employing AD-mix-\(\alpha\) proceeded with in situ cyclisation to give the hydroxy lactone \(53\). Conversion to the mesylate, displacement with sodium azide and reduction furnished the corresponding amine with inversion of stereochemistry and was protected as its Cbz derivative to give lactone \(54\). Nucleophilic opening of the lactone and desulfonylation of \(55\) with sodium amalgam gave ketone \(56\). Deprotection and cyclisation of the ketone occurred in one pot, upon catalytic hydrogenation, affording (+)-deoxoprosophylline \(57\) (Scheme 1.2.7).

Similar approaches has been used by Kumar and co-workers for the synthesis of (-)-deoxocassine,\(^5^4\) Emmanuvel et al. in a synthesis of (+)-febrifugine \(1\)\(^5^5\) and Andrés et al. for the synthesis of enantiopure 2- and 2,6-substituted piperidin-3-ols.\(^5^6\)

1.2.1.3 Conjugate Addition

Takeuchi and co-workers utilised acid-catalysed intramolecular conjugate addition of an \(\alpha,\beta\)-unsaturated ketone and was applied to a total synthesis of (+)-febrifugine \(1\) (Scheme 1.2.8).\(^5^7\)
Asymmetric dihydroxylation of Cbz-protected tetrahydropiperidine 58 proceeded with moderate enantioselectivity. Wittig olefination of the N,O-acetal afforded the ring opened α,β-unsaturated ketone 59. Conjugate addition occurred selectively upon treatment with BF₃·OEt₂, to give the trans-piperidine as a single diastereoisomer due addition of the nitrogen to the less sterically hindered face of the α,β-unsaturated ketone, which was protected as the corresponding O-Cbz carbonate. Recrystallisation of piperidine 60 significantly improved the enantiopurity to above 99%. Synthesis of (+)-febrifugine 1 was completed in a further four steps (Scheme 1.2.8).

Evans and McLaughlin have recently reported an analogous synthesis directed towards both enantiomers of febrifugine as well as halofuginone, using Sharpless asymmetric dihydroxylation of a vinyl sulfone as the key step for the enantiodivergent synthesis of both enantiomers of the starting material.58

Carretero and co-workers have utilised conjugate addition of an α,β-unsaturated sulfone in a total synthesis of (-)-swainsonine 11 (Scheme 1.2.9).59
Racemic $\alpha,\beta$-unsaturated sulfone 62 was prepared by reaction of $p$-tolylsulfinylphenylsulfonylmethane with Boc protected 5-aminopentanal 61. After monodeprotection to reduce the steric hindrance, reaction with lipase-PS and vinyl acetate afforded a 1:1 mixture of (R)-acetate 64 and (S)-alcohol 63. Lipase-catalysed hydrolysis of acetate 64 and protection as the corresponding silyl-ether was followed by Boc-deprotection to afford cyclisation precursor 65. Cyclisation by intramolecular conjugate addition occurred upon treatment with base to provide a mixture of diastereoisomers ($dr = 95:5$), which were isolated as the alkyl ester derivatives 66. A further seven steps were used to convert trans-66 to (-)-swainsonine 11 (Scheme 1.2.9).

### 1.2.2 Nucleophilic Addition to N-Acyliminium Ions

Recently Liu et al. have reported the diastereoselective nucleophilic addition of various silyl enol ethers to a novel 3-hydroxy-piperidine N-acyliminium ion. The application of this methodology was demonstrated in an asymmetric synthesis of (+)-febrifugine 1 (Scheme 1.2.10).  

\[ \text{Scheme 1.2.10. Reagents and conditions:} \]  
\[(a) (i) \text{NaNO}_2, \text{AcOH}:\text{H}_2\text{O} (1:4), 0 \degree \text{C}, 3 \text{ h}; (ii) \text{NaHCO}_3, \text{MeI}, \text{DMF}, \text{rt}, 18 \text{ h}, 63\%; (b) (i) \text{TBSCl, imid.}, \text{DMAP, DMF, rt, overnight}, 85\%; (ii) \text{H}_2, \text{Pd/C, rt, 12 h, 83\%; (c} (i) \text{BH}_3\cdot\text{SMe}_2, \text{THF, 0 \degree \text{C to rt, 16 h; (ii) TsCl, py, DMAP, CH}_2\text{Cl}_2, \text{rt, 36 h; (iii) NaN}_3, \text{DMF, rt, 12 h, 68\%; (d) H}_2, \text{Pd/C, MeOH, rt, 36 h, 75\%; (e) n-BuLi, CbzCl, THF, -78 \degree \text{C, 1 h, 81\%; (f) (i) NaBH}_4, \text{MeOH, 0 \degree \text{C, 40 min; (ii) Ac}_2\text{O, Et}_3\text{N, DMAP, CH}_2\text{Cl}_2, \text{rt, overnight, 71\%; (g) 75, BF}_3\cdot\text{Et}_2\text{O, CH}_2\text{Cl}_2, -78 \degree \text{C, 4h, 78\% (}\text{dr = 96:4).}

Diazotisation of glutamic acid derivative 67 followed by in situ methanolysis afforded ester 68. Protection of the secondary alcohol as the silyl ether and deprotection of the benzyl ester furnished acid 69 which after reduction and tosylation, was treated with sodium azide to give azide 70. Hydrogenation was accompanied by lactam formation and was protected as the
corresponding Cbz ester to afford imide 71. Carbonyl reduction and subsequent reaction with acetic anhydride gave N,O-acetal 72. Treatment of acetal 72 with 2.0 equivalents of BF$_3$·Et$_2$O in the presence of silyl enol ether 75 proceeded through the N-acyliminium ion 73 to give piperidine 74, with excellent cis-selectivity (dr = 96:4). Three further steps were used to elaborate cis-piperidine 74 to (+)-febrifugine 1 (Scheme 1.2.10).

### 1.2.3 Alkylation of Pyridinium Salts

Substituted piperidines can be directly accessed by the regio- and diastereoselective addition of nucleophiles onto chiral N-alkyl- or N-acylpyridinium salts. Comins and co-workers have utilised this methodology for the synthesis of a range of bioactive alkaloids including deoxynojirimycin 2, FR901483 15, and (+)-deoxoprosopinine 57.

![Scheme 1.2.11. Reagents and conditions: (a) (-)-TCCOCOCl; (b) (i) BnOCH$_2$(2-thienyl)Cu(CN)Li$_2$, THF, -78 °C; (ii) 10% HCl, 70%; (c) (i) NaOMe, MeOH, reflux, 18 h; (ii) 6 N HCl, i-PrOH, 1.25 h, 100%; (d) n-BuLi, PhOCOCl, THF, -78 °C, 30 min, 94%; (e) Pb(OAc)$_4$, PhMe, reflux, 1 d, 57%; (f) HCO$_2$H, MeOH, reflux, 3.5 h, then NH$_3$, MeOH, 0 °C, 30 min, 73%; (g) (i) NaNH$_4$, CeCl$_3$·7H$_2$O, MeOH, -40 °C, 30 min; (ii) Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, 12 h, 98%; (h) (i) 82, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, -78 °C, 4 h; (ii) H$_2$, Pt/C, EtOH, rt, 5 h, 71%; (i) KOH, EtOH, sealed tube 140 °C, 12 h, 85%.

Treatment of the chiral acylpyridinium salt 77, prepared in situ by N-acetylation of the pyridine derivative 76, with a higher order cyanocuprate diastereoselectively furnished dihydropyridone 78. Reaction with sodium methoxide, which was followed by the addition of aqueous acid, resulted in removal of the TIPS and auxiliary groups and was followed by protection of the secondary nitrogen to give dihydropyridone 79. Treatment with lead(IV) acetate afforded trans-acetoxy carbamate derivative 80 with a de value in excess of 98%. Cyclisation of 80 to the oxazolidinone ring was followed by selective enone reduction and acetylation to give bicyclic 81. Lewis acid promoted addition of allylsilane 82 to the in situ
generated \(N\)-acyliminium was followed by catalytic hydrogenation of the diene intermediate and base-catalysed deprotection to give \((+)-\)deoxoprosopinine \(57\) (Scheme 1.2.11).

Charette and co-workers have exploited similar methodology in a highly efficient synthesis of \((+)-\)julifloridine \(7\) (Scheme 1.2.12).

Diastereoselective addition of a Grignard reagent to the chiral pyridinium salt prepared from amide \(84\) and pyridine \(83\) gave dihydropyridine \(85\). Chemoselective hydrogenation to afford the corresponding tetrahydropyridine was followed by a one pot epoxidation-methylation procedure, proceeding diastereoselectively, to yield \(86\) as a single product. Simultaneous removal of the chiral auxiliary and benzyl ether was achieved by Birch reduction, furnishing \((+)-\)julifloridine \(7\) (Scheme 1.2.12). This methodology has been further developed for the syntheses of a variety of substance P antagonists, \((2S,3S)-3\)-hydroxypipeolic acid as well as serving as a starting point for the synthesis of \((+)-\)lepadin B.

**1.2.4 Cycloaddition Reactions**

Cycloadditions are commonly used for the rapid synthesis of functionalised cyclic systems in a highly stereocontrolled manner. Substituted piperidine rings are typically obtained by 1,3-dipolar cycloaddition or hetero Diels-Alder reactions.

Kibayashi and co-workers have reported the use of an intramolecular hetero Diels-Alder reaction of a functionalised acylnitroso intermediate for the synthesis \((-)-\)swainsonine \(11\) (Scheme 1.2.13).
Scheme 1.2.13. Reagents and conditions: (a) BrPh,P^+CH_2CH≡CH_2, t-BuOK, THF, rt, 5 min 49% (E/Z = 1:4.3); (b) (i) DIBAL-H, CH_2Cl_2, rt, 1.5 h, 96%; (ii) hv, I_2, benzene, 30 min, 69%; (c) TsCl, py, 0 °C to rt, 4 h, 95%; (d) NaCN, DMSO, 60 °C, 1 h, 99%; (e) 25% aq. NaOH, MeOH, reflux, 9 h, 77%; (f) CH_3N_2, Et_2O, 0 °C, 15 min, 99%; (g) NH_2OH·HCl, KOH, MeOH, 0 °C, 30 min, 96%; (h) NaIO_4, H_2O, 0 °C, 10 min, 89% (dr = 1:4.1).

Enantiopure D-malic acid-derived, aldehyde 87 was used as starting material and Wittig olefination with allyltriphenylphosphonium bromide furnished diene 88 as an inseparable mixture of isomers (E/Z 1:4.3). Reduction of the acetal was followed by photoisomerisation to generate the geometrically pure (E)-diene 89. Tosylation, cyanide displacement, alkaline hydrolysis, and esterification afforded the ester 90 which was treated with hydroxylamine under alkaline conditions to produce the hydroxamic acid 91. Oxidation of acid 91, generated, in situ, acylnitroso intermediate 92 which underwent intramolecular hetero Diels-Alder reaction to afford a separable mixture of cis- and trans-1,2-oxazinolactams 93 and 94, proceeding with moderate selectivity. The synthesis of (-)-swainsonine 11 was completed in eight additional steps from trans-94 (Scheme 1.2.13).

This methodology has been further expanded by Kibayashi to the total synthesis of a number of compounds including (-)-lepadins A, B, and C, azimine and (+)-carpaine while Keck and Romer have used the OTBDPS protected derivative to synthesise swainsonine analogues.
Herdeis and co-workers developed a synthesis of (-)-cassine 6 utilising a cascade Horner-Wadsworth-Emmons/intramolecular 1,3-dipolar cycloaddition (Scheme 1.2.14).\textsuperscript{73}

Scheme 1.2.14. Reagents and conditions: (a) Ac₂O, HClO₄, 2 h; (b) PBr₃, H₂O, 15 °C, 2 h; (c) Zn, Cu, AcOH, NaOAc, -10 °C, 6 h; (d) HgSO₄, H₂O, acetone; (e) MSCl, Et₃N, CH₂Cl₂, -20 °C to 20 °C; (f) H₂, Lindlar catalyst, EtOAc; (g) NaN₃, DMSO, 60 °C, 12 h; (h) (i) 100, LiCl, DIPEA, MeCN, rt, 3 d, (ii) Rh₂(OAc)₄, rt, 12 h, 74% yield; (iii) crystallisation.

Conversion of (+)-rhamnose 95 to diacetylrhamnal 96 was achieved in a three-step, one-pot reaction according to literature procedures.\textsuperscript{74} A modified Perlin oxidation was followed by mesylation to give aldehyde 97. Chemoselective reduction of the double bond with Lindlar catalyst and azide displacement of the mesylate gave the aldehyde 98. Cyclisation occurred in a highly selective, one-pot procedure. Horner-Wadsworth-Emmons reaction with ketophosphonate 100 and concommitant 1,3-dipolar cycloaddition gave the triazoline intermediate, which isomerised to the diazoketone with base. Addition of rhodium acetate furnished the vinylogous amide 99 with evolution of nitrogen. Intermediate 99 was converted into (-)-cassine 6 in a further six steps (Scheme 1.2.14).\textsuperscript{73}

1.2.5 Ring-Closing Metathesis

Alkene metathesis has emerged as a powerful tool in organic synthesis for the rapid access of medium and large rings and provides a straightforward entrance to piperidines containing a double bond which can be easily reduced or further functionalised.\textsuperscript{75-80}

Riera and co-workers have developed an efficient procedure for the preparation of polyhydroxy piperidine and indolizine alkaloids using ring-closing metathesis (RCM) to form a synthetically flexible, bicyclic carbamate (Scheme 1.2.15).\textsuperscript{81}
Treatment of epoxide 101 with allyl isocyanate provided allyl carbamate 102 which was followed by intramolecular ring opening with sodium bis(trimethylsilyl)amide to selectively furnish oxazolidinone 103 as a single diastereoisomer. Ring-closing metathesis of bisolefin 103 gave oxazolidinylpiperidine 104 which was transformed into L-deoxymannojirimycin 105 in 5 steps. Alternatively, ent-104 was used to synthesise (-)-swainsonine 11 in 10 steps (Scheme 1.2.15).

Metathesis-induced molecular rearrangements have been utilised by Mariano and co-workers to synthesis (-)-swainsonine 11 (Scheme 1.2.16).82

Photoinduced transformation of the in situ generated pyridinium perchlorate furnished trans,trans-3,5-dihydroxy-4-aminocyclopentene which was isolated as the triacetyl derivative 106.83 Enzymic desymmetrisation of meso-compound 106 with EEACE (electric eel acetyl cholinesterase) gave monoalcohol 107, proceeding with moderate enantioselectivity (ee =
Silyl protection and $O$-acetyl deprotection gave known product 108, which was followed by Wipf inversion to produce the C1-epimer. Benzyl protection and $N$-allylation afforded cyclisation precursor 109. Tandem ring-opening/ring-closing metathesis of the cyclopentene 109 was conducted in an ethylene-saturated $\text{CH}_2\text{Cl}_2$ solution containing Grubbs II catalyst to furnish the desired trans-product 110 which was elaborated into (-)-swainsonine 11 (Scheme 1.2.16). This methodology has been further expanded by the same authors in syntheses of (+)-castanospermine 12 and the proposed structure of uniflorine-A. 85

Blechert and co-workers developed an efficient synthesis of unnatural, (+)-lepadin F 115 utilising a tandem ene-yne-ene RCM reaction (Scheme 1.2.17).

Scheme 1.2.17. Reagents and conditions: (a) benzyl propargyl ether, cis-4-hexenal, CuBr, PhMe, MS, rt, 3 d, 94% ($dr = 1:2$); (b) LiAlH$_4$, THF, -78 °C to rt, overnight, 86%; (c) oxalyl chloride, DMSO, $\text{CH}_2\text{Cl}_2$, -78 °C, 30 min, then Et$_3$N, 78 °C to rt, overnight, 99%; (d) vinylmagnesium bromide, THF, -78 °C, overnight, 63%; (e) Grubbs I catalyst (10 mol %), dichloroethane, 60 °C, 3 h, 90%.

L-Alanine was esterified and protected as the $N$-PMB ester to give amino-acid derivative 111. Condensation with cis-4-hexenal and copper-catalysed addition of benzyl propargyl ether gave a diastereomeric mixture of propargylamines in favour of 4-epi-112 ($dr = 1:2$). The isomers were able to be separated after reduction and the minor isomer was converted into allylic alcohol 113 by Swern oxidation and addition of vinylmagnesium bromide. Tandem ene-yne-ene RCM was carried out in the presence of Grubbs I catalyst, providing hexahydroquinoline 114. A stereoselective hydrogenation and a series of side chain modifications furnished (+)-lepadin F 115 (Scheme 1.2.17).
### 1.2.6 Ring Expansion of Pyrrolidines

Regioselective ring-expansion of pyrrolidines, represent a simple method of entry to substituted piperidine rings proceeding either *via* rearrangement of an aziridinium intermediate\(^{87-89}\) or a ring-opening/ring-closing expansion reaction.\(^{90}\)

Déchamps *et al.* have used enantioselective ring expansion in a formal synthesis of (\(-\))-swainsonine 11 using known prolinol 116 (Scheme 1.2.18).\(^{87, 88}\)

![Scheme 1.2.18. Reagents and conditions:](Image)

- (a) (i) 5 M HCl, Et\(_2\)O, rt, 24 h; (ii) allyl bromide, K\(_2\)CO\(_3\), n-Bu\(_4\)NBr, PhMe, rt, 24 h, 50%;
- (b) TFAA, Et\(_3\)N, THF, reflux, 15 h, then 2.5 M NaOH, rt, 2 h, 95%.

Deprotection of the trityl group and addition of allyl bromide gave \(N\)-allylprolinol 117. Proceeding through an aziridinium intermediate, treatment of prolinol 117 with trifluoroacetic anhydride and triethylamine under reflux, gave after saponification, 3-hydroxy-piperidine 118 with a de greater than 95%. An additional four steps completed the formal synthesis of (\(-\))-swainsonine 11 (Scheme 1.2.18).

Recently, Katoh and co-workers have synthesised (+)-febrifugine 1, employing the reductive deamination and simultaneous recyclisation of a proline derivative as a key step (Scheme 1.2.19).\(^{90}\)

![Scheme 1.2.19. Reagents and conditions:](Image)

- (a) cat. RuO\(_2\), NaIO\(_4\), EtOAc:H\(_2\)O, rt, 86%;
- (b) (i) LiEt\(_3\)BH, THF, -78 °C;
- (ii) (EtO\(_2\))\(_2\)P(O)CH\(_2\)CON(Me)OMe, NaH, THF, 83% from 120;
- (c) (i) MeMgBr, THF, 0 °C 88%;
- (ii) Tebbe’s reagent, THF, -40 °C to rt, 81%;
- (d) (i) ZnBr\(_2\), CH\(_2\)Cl\(_2\), rt; (ii) SmI\(_2\), THF:HMPA, MeOH, 0 °C to rt, 90%.
Commercially available (4R)-hydroxyproline was protected according to literature procedures to afford compound 119. Oxidation of the pyrrolidine ring with ruthenium(IV) oxide in the presence of sodium meta-periodate gave the desired lactam 120. Partial reduction of lactam 120 and Horner-Wadsworth-Emmons reaction of the resulting aminal furnished Weinreb amide 121 as a single product. Treatment of amide 121 with methylmagnesium bromide afforded the methyl ketone which underwent olefination using Tebbe’s reagent to give alkene 122. Boc-deprotection was followed by samarium diiodide-promoted reductive deamination to cleave the carbon-nitrogen bond, which proceeded with lactam formation, to furnish δ-lactam 123. Seven further steps were used to convert lactam 123 into (+)-febrifugine 1 (Scheme 1.2.19).

1.2.7 Oxidation-Cyclisation of Furan Derivatives

Several groups have utilised the aza-Achmatowicz oxidative rearrangement of α-furylamines for the synthesis of substituted piperidines. Early work by Zhou and co-workers has utilised this reaction for the synthesis of a number of alkaloids using chiral N-furfurylsulfonamides derived from Sharpless asymmetric dihydroxylation of vinyl furan or kinetic resolution of racemic α-furfurylamine derivatives using a modified Sharpless asymmetric epoxidation reagent.

A recent example from Haroutounian and co-workers is the application of this methodology to a highly enantioselective, formal synthesis of (+)-desoxoprosophylline 57 (Scheme 1.2.20).

![Scheme 1.2.20](image)

**Scheme 1.2.20. Reagents and conditions:** (a) HgSO₄, H₂SO₄, MeOH; (b) TBDPSCI, imid., DMAP, DMF, 92%; (c) DEAD, PPh₃, PhCO₂H, THF, rt, 1.5 h, 75%; (d) MeOH, 10% aq. NaOH, rt, 3 h, 80%; (e) DPPA, DBU, PhMe, 0 °C, 2 h, then rt, 20 h, 78%; (f) (i) H₂, Pd/C, EtOAc, rt, 40 min; (ii) TsCl, Et₃N, CH₂Cl₂, 0 °C to rt, 3 h, 94%; (g) m-CPBA, CH₂Cl₂, rt, 4 h, 87%; (h) HC(OMe)₃, BF₃·OEt₂, 4 Å MS, THF, 0 °C, 3 h, 88%; (i) NaBH₄, CeCl₃·7H₂O, MeOH, -30 °C, 40 min, 88%; (j) H₂, Pd/C, MeOH, rt, 2 h, 90%.
Reaction of D-glucal 124 with HgSO₄ was followed by silyl protection of the resulting primary hydroxyl group furnished substituted furan 125. A three step double inversion reaction sequence was used to introduce the azide functionality with retention of configuration and was followed by hydrogenation and tosylation of the resultant amine to afford N-furfurysulfonamide 126. Aza-Achmatowicz rearrangement was induced by exposure of 126 to an excess of m-CPBA, furnishing dihydropyridone 127. Treatment with trimethyl orthoformate furnished the N,O-acetal which under modified Luche reduction conditions, gave the corresponding allylic alcohol as a single diastereoisomer. Subsequent hydrogenation afforded cis-piperidine 128, which has served as a key intermediate in the total synthesis of (+)-desoxoprosophylline 57 (Scheme 1.2.20).²⁻³⁻ Previously, Haroutounian and co-workers have used similar methodology in an enantioselective synthesis of (-)-prosophylline.⁹⁻⁸⁻

This reaction has recently been applied to the synthesis of bicyclic alkaloids by Aggarwal and Bi who reported a concise synthesis of 8a-epi-swainsonine 137 (Scheme 1.2.21).⁹⁻⁹⁻

![Chemical Structure](image)

Scheme 1.2.21. Reagents and conditions: (a) (i) 138, KHMDS, CH₂Cl₂, -78 °C, 10-15 min; (ii) 129, CH₂Cl₂, -78 °C, 82%; (b) (i) aq. NH₃, MeOH, rt, 24 h; (ii) Na/Hg, K₂HPO₄, MeOH, rt, 20 min, 81%; (c) CbzCl, Na₂CO₃, CH₂Cl₂, 0 °C, 20 min, 98%; (d) m-CPBA, CH₂Cl₂, rt, 20 h, 72%; (e) PTSA, 4 Å MS, PhMe, rt, 1.5 h, 82%; (f) NaBH₄, CeCl₃·7H₂O, MeOH, 0 °C to rt, 10 min, 95%; (g) H₂, Pd/C, rt, 12 h, 67%.

Reaction of chiral aldehyde 129 with the ylide formed from sulfonyl substituted salt 138 furnished a mixture of epoxides (dr = 6:83:11) in which epoxide 131 predominated.
Direct aminolysis with aqueous ammonia, effected ring opening of 131, proceeding with inversion, to give the corresponding anti-amino alcohol. Subsequent removal of the sulfone group with sodium amalgam and protection of the amine gave Cbz-protected α-hydroxy amine 133 which was subjected to aza-Achmatowicz oxidation to furnish the ring expanded dihydropyridinone 134. The formed hemi-aminol was protected with the internal hydroxyl group by treatment of dihydropyridinone 134 with para-toluenesulfonic acid (PTSA) in the presence of 4 Å molecular sieves to give the anhydro-bicycle 135. This reaction also had the effect of blocking the Re-face of the enone, resulting in high diastereoselectivity in the subsequent reduction step. Luche reduction almost exclusively furnished a single diastereomer, which was subsequently hydrogenated to simultaneously reduce the alkene and cleave the N,O-acetal and Cbz groups to furnish the free amine 136. A further two steps were used to complete the synthesis of 8a-epi-swainsonine 137 (Scheme 1.2.1).99

1.2.8 Palladium Catalysed Cyclisation

Recently Makabe et al. have reported a synthesis of (-)-cassine 6 using a highly selective Pd(II)-catalysed cyclisation as a key step (Scheme 1.2.22).100

![Scheme 1.2.22. Reagents and conditions: (a) n-BuLi, (HCHO)_n, Et_2O, reflux, 2.25 h, 71%; (b) Na, NH_3, reflux, 2.5 h, 76%; (c) BnBr, NaH, n-Bu_3NI, 56%; (d) Ti(Oi-Pr)_4, TBHP, L-(+)-DET, CH_2Cl_2, -25 °C, 5 h, 90% (ee > 98%); (e) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 5 min; (ii) HClO_4, DMSO, 60 °C, 5 h, 90%; (f) K_2CO_3, MeOH, rt, 30 min, 89%; (g) MOMCl, DIPEA, CH_2Cl_2, rt, 2 d, 99%; (h) LiAlH_4, THF, 50 °C, 7 h, 96%; (i) TsCl, py, 0 °C to rt, 48 h, 96%; (j) NaH, DMF, 50 °C, 7 h, 47%; (k) PPh_3, THF, H_2O, rt, 1 d, 81%; (l) Boc_2O, Et_3N, CH_2Cl_2, rt, 12 h, 81%; (m) Na, NH_3, THF, -40 °C, 20 min, 90%; (n) PdCl_2, THF, rt, 12 h, 51% (dr > 49:1).](image)

Monobenzylation of the trans,trans-diene diol prepared from hexa-1,5-diyne 139,101 was followed by Sharpless asymmetric epoxidation with L-(+)-diethyl tartrate to give epoxide
with excellent enantiopurity (ee > 98%). Conversion into the terminal epoxide 141 was achieved in three steps by synthesis of the mesylate, opening of the epoxide ring and treatment with base. Protection of the secondary hydroxyl group as the MOM ether was followed by regioselective epoxide reduction to give 142, which was converted into azide 143 via the tosylate intermediate. Azide reduction, protection of the resultant amino group and debenzylation afforded cyclisation precursor 144. Allyl alcohol 144 was treated with catalytic PdCl₂ to regioselectively give the cyclised product with high diastereoselectivity (dr > 49:1). Conversion of cis-piperidine 145 to (-)-cassine 6 was achieved in five additional steps (Scheme 1.2.22).

1.2.9 Rhodium-Catalysed Cyclohydrocarbonylation

Ojima and Vidal reported a total syntheses of (+)-prosopinine 151 and (-)-deoxoprosophylline 50 by cyclohydrocarbonylation using a Rh-BIPHEPHOS complex (Scheme 1.2.23).²⁰²

![Scheme 1.2.23. Reagents and conditions: (a) vinylmagnesium bromide, THF, -30 °C to 0 °C, 1 h, 95% (dr = 1:6); (b) PTSA, MeOH, reflux, 1 h, 95%; (c) TBSCI, imid., DMF, 2 h, rt, 83%; (d) Rh(acac)(CO)₂ (1 mol %), BIPHEPHOS (2 mol %), H₂/CO (1:1, 4 atm), EtOH, 65 °C, 14 h, 92%; (e) Rh(acac)(CO)₂ (1 mol %), BIPHEPHOS (2 mol %), H₂/CO (1:1, 4 atm), THF, 65 °C, 14 h, 96%.

Stereoselective addition of vinylmagnesium bromide to (R)-serine-derived Garner’s aldehyde 146, afforded a 6:1 mixture of allylic alcohols in favour of the desired trans-isomer 148. Acetonide removal and protection as the bis-silyl-ether gave cyclisation precursor 149. Rh-BIPHEPHOS complex-catalysed cyclohydrocarbonylation under an atmosphere of CO and H₂ in ethanol afforded N-protected aminal 150 which was converted to (+)-prosopinine 151 in three steps via chelation-controlled addition of a complex alkylcopper(I) reagent to the in situ prepared acyliminium ion. Interestingly, substitution of an aprotic solvent for the
alcohol in the cyclohydrocarbonylation reaction furnished encarbamate 152, which was used in a second generation synthesis of (+)-prosopinine 151 (Scheme 1.2.23).102

This methodology has recently been utilised by Chiou et al. in the synthesis of enantiopure 3-hydroxypiperidine and 3-hydroxyptepicolic acid derivatives.103

1.2.10 Cyclisation via Amidomercuration

Finally, Han and co-workers have published a synthesis of (+)-iso-6-cassine 158 using stereoselective, Hg(II)-mediated intramolecular amidomercuration (Scheme 1.2.24).104

![Scheme 1.2.24. Reagents and conditions: (a) PMBCl, KH, DMF, 0 °C, 84%; (b) (i) 5% HCl, 86%; (ii) (EtO)₂P(O)CH₂CO₂Et, LiBr, DBU, THF, 78%; (c) DIBAL-H, THF, -40 °C to rt, 90%; (d) CCl₃CN, DBU, CH₂Cl₂, 0 °C, 92%; (e) 159, CH₂Cl₂, 40 °C, 80%; (f) (i) Hg(OTFA)₂, K₂CO₃, MeNO₂, 90% (dr = 20:1); (ii) Na/Hg, CbzCl, THF, 78%.](image_url)

Enantiopure allyl alcohol 153 formed via repetitive lipase-catalysed kinetic resolution of the corresponding racemic alcohol was protected as the PMB ether, before acetal hydrolysis and Horner-Wadsworth-Emmons olefination of the resulting aldehyde generated the α,β-unsaturated ester 154. Ester reduction and conversion of the allylic alcohol into a trichloroacetimidate 155 was followed by an enantioselective Overman rearrangement induced by a chiral cobalt oxazoline palladacycle 159, furnishing the cyclisation precursor, N-trichloroacetyl 156. Amidomercuration of 156 with Hg(OTFA)₂ in the presence of K₂CO₃ gave the desired trans-product with high diastereoselectivity (dr > 20:1), proceeding with trichloroacetyl deprotection. Reductive cleavage of the mercury was followed by N-Cbz protection to afford piperidine 157. A further two steps were used to synthesise (+)-iso-6-cassine 158 (Scheme 1.2.24).
Similar methodology has also been utilised by Raghavan and Mustafa for the stereoselective synthesis of (-)-deoxocassine and (+)-deoxoprosophylline 57 from chiral N-Cbz sulfilimines.\textsuperscript{105,106}

1.2.11 Conclusion

The abundance of natural products containing the 3-hydroxypiperidine moiety have meant that considerable synthetic attention has been directed towards the synthesis of this motif in enantiopure form. Despite the availability of a significant amount of number of synthetic routes for this class of compounds, few are sufficiently flexible for analogue synthesis and only allow limited modifications to be made to the C-2 functionality of the piperidine ring. The main strategy involved is \textit{via} cyclisation of linear precursors and although this method is generally high yielding it demonstrates a lack of convergence, and is specific for each target type, meaning access to other piperidines would require major revisions to be made early in the synthetic route.

There still exists a need to develop procedures that are more efficient than those currently in existence and the development of a single, readily obtainable key intermediate capable of acting as a synthetic gateway to a variety of 2,3-disubstituted piperidine alkaloids and their analogues in optically pure form would be an important advance in the field.

The nitrone functionality exhibits a broad reactivity profile making such compounds powerful intermediates for the construction of complex organic molecules. Thus an optically pure, six-membered cyclic nitro base building block that can be directly mapped onto the 2,3-disubstituted piperidine substructure and capable of undergoing stereoselective functionalisation represents an attractive synthetic intermediate of much potential.
1.3 Overview of the Nitrone Reactivity Profile

Nitrones exhibit a broad reactivity profile and are recognised as versatile synthetic intermediates due to their ability to undergo numerous useful reactions such as 1,3-dipolar cycloadditions, nucleophilic additions, and pinacol-type coupling reactions (Scheme 1.3.1). The chemistry of nitrones have been frequently reviewed, but it is ultimately dominated by their use as substrates for 1,3-dipolar cycloaddition and more recently, nucleophilic attack.

The wide breadth of reactivity is due to the structure of the nitrone functionality. Nitrones are isoelectronic with allyl anions and enolates, but the presence of the C=N moiety provides an iminium-type character which is responsible for its reactivity as an electrophile.

Accordingly, in addition to their 1,3-dipolar character, nitrones react with nucleophiles at the carbon atom and with electrophiles at the oxygen atom (Scheme 1.3.2). There are increasing reports of nucleophilic additions to nitrones to form α-substituted hydroxylamines. The electrophilic α-carbon of the dipole has been observed to react with a number of neutral...
and charged nucleophiles such as H₂O, HO⁻, RO⁻, RS⁻, R₃N, CN⁻, (R = alkyl, aryl),¹⁰⁸ and phosphonates.¹¹³-¹¹⁶ Conversely, there are several reports of electrophilic additions to nitrones. The negatively charged oxygen of the nitrone functionality behaves as a nucleophile, and reacts at oxygen with a variety of electrophiles including ketenes,¹¹⁷-¹¹⁹ isocyanates,¹²⁰ acetic anhydride,¹²¹ and various acid chlorides.¹²²-¹²⁴

Nitrones also serve as excellent scavengers for several types of radical, especially short-lived radicals.¹⁰⁸,¹²⁵ Forming more stable radical products, they act as spin traps which can be used in biology for evaluation of both in vivo and in situ systems for diagnostic purposes.¹²⁶,¹²⁷ They have also found use in chemical analysis, forming stable paramagnetic spin adducts that improve signal to noise ratios in electron spin resonance (ESR) spectroscopy and achieve high efficiency in spin trapping experiments¹²⁸-¹³⁰ as well as allowing the identification of intermediates in the study of radical mechanisms.¹³¹
1.4 1,3-Dipolar Cycloaddition Reaction to Nitrones

Nitrones undergo 1,3-dipolar cycloaddition reactions with a wide variety of dipolarophiles including alkenes, alkynes, cumulenes, thiocarbonyls, phosphoranes, isocyanates and nitriles. This powerful reaction can be utilised to create multiple chiral centres in a single step providing excellent synthetic routes to complex systems.

\[ R_1^+N^+R_2 + R_3 \rightleftharpoons R_4 \rightarrow R_1NOR_3O \]

Scheme 1.4.1. Isoxazolidine reaction products.

The 1,3-dipolar cycloaddition reaction with substituted alkenes to give isoxazolidines remains the single most studied reaction of nitrones. The isoxazolidine functionality; a saturated five-membered heterocycle containing adjacent nitrogen and oxygen atoms represents an important synthetic intermediate which can be manipulated by reductive cleavage of the relatively weak N-O bond to furnish 1,3-amino alcohols or by oxidation to give the corresponding nitrone (Scheme 1.4.1).

\[ R_1^+N^+R_2 + R_3 \rightleftharpoons R_4 \rightarrow R_1NOR_3O \]

Scheme 1.4.2. Proposed mechanisms of 1,3-dipolar cycloaddition.

Huisgen proposed the widely accepted concept of the 1,3-dipolar cycloaddition reaction proceeding via a concerted but not simultaneous process. An alternate mechanism, proposed by Firestone proceeds via a diradical intermediate. However this model does not explain the stereospecificity of the reaction (Scheme 1.4.2).
The transition state of the concerted 1,3-dipolar cycloaddition reaction is stabilised by interactions of the frontier molecular orbitals (FMOs). The dipolar components have been classified by Sustman into three categories on the basis of the relative FMO energies between the interacting reaction components (Figure 1.4.1).\textsuperscript{107, 109, 148-150}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.4.1}
\caption{Classifications of 1,3-dipolar cycloaddition reaction with representative examples.}
\end{figure}

In Type I reactions, typical of azomethine and carbonyl ylides, the dominant FMO interactions are between the HOMO\textsubscript{dipole} and the LUMO\textsubscript{dipolarophile}.\textsuperscript{107, 151} In contrast, type III processes, which include reactions of ozone and nitrous oxide, are controlled by FMO interactions between the LUMO\textsubscript{dipole} and HOMO\textsubscript{dipolarophile} (Figure 1.4.1).\textsuperscript{109}

The classification of the nitrone functionality as a type II dipole according to molecular perturbation theory means that the energy gaps between HOMO\textsubscript{dipole}-LUMO\textsubscript{dipolarophile} and LUMO\textsubscript{dipole}-HOMO\textsubscript{dipolarophile} are similar. This similarity of the FMO energies between both the dipole and dipolarophile indicates that both HOMO-LUMO interactions are important allowing nitrones to undergo both normal and inverse-demand cycloaddition reactions (Figure 1.4.1).\textsuperscript{107, 148, 149}
1.4.1 Selectivity of the 1,3-Dipolar Cycloaddition Reaction Between Alkenes and Nitrones

With the ability to form up to three new stereocenters in a single step, it is possible that up to eight isomers may arise from the cycloaddition reaction between the nitrone and alkenes. The preference for a particular product depends on diastereofacial selectivity, regioselectivity and whether the dipolarophile approaches the nitrone in an endo or exo fashion. This reaction generally proceeds in a predictable fashion, through a highly ordered transition state, allowing the regio- and stereochemical outcomes to be predicted.

1.4.1.1 Regioselectivity of Alkene Addition

The regioselectivities observed for the 1,3-dipolar cycloaddition with alkenes are controlled by a mixture of both steric and electronic effects and have been extensively studied. Steric factors favour the formation of 5-substituted isoxazolidines as the more sterically hindered functionality of the alkene tends to add to the oxygen atom of the 1,3-dipole.

Electronic factors may favour formation of either the 4- or 5-substituted isoxazolidine depending on the nature of the dipolarophile. The introduction of electron-donating or electron-withdrawing substituents on the dipole or dipolarophile can significantly change the relative FMO energies and hence the HOMO/LUMO interactions employed.

For instance, the reaction of N-methyl-C-phenyl nitrone with methyl acrylate is controlled by the HOMO-dipole-LUMO-dipolarophile interactions, whereas the reaction of the same nitrone with nitroethene is controlled by LUMO-dipole-HOMO-dipolarophile interactions (Table 1.4.1).

Table 1.4.1. 1,3-Dipolar cycloaddition regioselectivity of N-methyl-C-phenyl and N-phenyl-C-phenyl nitrone.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>5-isomer:4-isomer&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>NO₂</td>
<td>0:100</td>
<td>152</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>CO₂Me</td>
<td>100:0</td>
<td>152</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>CO₂Et</td>
<td>70:30</td>
<td>153</td>
</tr>
</tbody>
</table>

<sup>a</sup>Stereochemical outcome not shown, <sup>b</sup>Ratio determined by <sup>1</sup>H NMR analysis.

For instance, the reaction of N-methyl-C-phenyl nitrone with methyl acrylate is controlled by the HOMO<sub>dipole</sub>-LUMO<sub>dipolarophile</sub> interactions, whereas the reaction of the same nitrone with nitroethene is controlled by LUMO<sub>dipole</sub>-HOMO<sub>dipolarophile</sub> interactions (Table 1.4.1).
Selectivity of mono-substituted electron-rich or electron-neutral alkenes in 1,3-dipolar cycloadditions.

Generally, the reaction of terminal electron-rich ($R = \text{OEt}$) or electron-neutral alkenes ($R = \text{Ph}$) with nitrones proceeds to give the 5-substituted isomer. Regioselectivity is controlled predominantly by the $\text{LUMO}_{\text{nitrone}}-\text{HOMO}_{\text{alkene}}$ interactions where the largest coefficients are at the nitrone $\alpha$-carbon and the alkene terminal carbon, this reaction closely resembles a Type III process. This selectivity is further enhanced by steric factors. Thus, the nitrone and alkene combine in a regioselective manner to give the 5-substituted isoxazolidine (Scheme 1.4.3).\textsuperscript{107, 154}

Conversely, the reaction of terminal alkenes with electron-withdrawing groups ($R = \text{NO}_2, \text{CO}_2\text{Et}$) resembles a Type I process and is primarily controlled by the $\text{HOMO}_{\text{nitrone}}-\text{LUMO}_{\text{alkene}}$ interactions where the largest coefficients are at the nitrone oxygen and the alkene terminal carbon atom. This selectivity favours formation of the 4-substituted isomer. However, since steric factors oppose this selectivity, a mixture of regioisomers is often obtained (Scheme 1.4.4).\textsuperscript{107, 154}

Selectivity of 1,2-disubstituted electron-deficient alkenes in 1,3-dipolar cycloadditions.
However, in the reaction of nitrones with 1,2-disubstituted alkenes bearing an electron-withdrawing group the steric factor is eliminated, leading to FMO-controlled regioselectivity and the 4-substituted isomer is often obtained as a single product (Scheme 1.4.5).\textsuperscript{107, 154}

### 1.4.1.2 Diastereoselectivity and Enantioselectivity of the 1,3-Dipolar Cycloaddition Reaction with Alkenes

In the 1,3-dipolar cycloaddition reaction with alkenes, the nitrone can be approached in either an \textit{endo} or \textit{exo} fashion, as well as from the \(\alpha\)- or \(\beta\)-face.\textsuperscript{107} Prediction of the stereoselectivity is complicated by a number of factors including substrate structure, secondary orbital interactions, and nitrone isomerisation.

![Diels-Alder reaction endo transition state](image)

**Scheme 1.4.6:** Comparison of \textit{endo} selectivity of the Diels-Alder reaction and the \textit{endo}/\textit{exo} selectivity of the 1,3-dipolar cycloaddition reaction.\textsuperscript{109}

The unfavoured \textit{endo}-isomer of nitron cycloaddition arises from the transition state in which the nitrogen atom of the dipole points in the same direction as the substituent of the alkene. However, in comparison to the Diels-Alder reaction, in which the \textit{endo}-transition state is favoured due to stabilisation by secondary \(\pi\)-orbital interactions, the interaction is between the \(N\)-nitrone \(p_z\)-orbital and the vicinal \(p_z\)-orbital on the alkene, and thus the stabilisation is small (Scheme 1.4.6).\textsuperscript{107, 109} As a result the \textit{endo}/\textit{exo} selectivity in the 1,3-dipolar cycloaddition reaction is primarily controlled by the substituents on the alkene or nitrone or by a catalyst.\textsuperscript{107, 109}

![Diels-Alder reaction Z/E isomerisation](image)

**Scheme 1.4.7:** \(E/Z\) isomerisation of acyclic nitrones.
Acyclic nitrones exist in \((E)\)- and \((Z)\)- forms that may interconvert at high temperature, complicating the stereochemical prediction of reaction products and resulting in reduced diastereoselectivity (Scheme 1.4.7). A number of cyclic nitrones have been developed that avoid the issue of nitrone isomerisation by permitting only a single \((E)\)-geometry about the \(\text{C}=\text{N}\) double bond, reducing the number of possible cycloaddition products.\(^{110}\)

![Scheme 1.4.7](image)

**Figure 1.4.2** Possible stereoisomers resulting from approach of dipolarophile to a 3-substituted cyclic nitrone.

Substituted cyclic nitrones have become popular as facially differentiated reagents, allowing predictable asymmetric induction through their ability to force the cycloaddition reaction to proceed from one face of the 1,3-dipole. Approach of the dipolarophile \textit{anti} to the alkoxy group is by far the most preferred transition state over the \textit{syn} approach and the extent of diastereoselectivity is influenced by the bulkiness of the alkoxy group. This also favours the \textit{exo} approach of the dipolarophile due to steric interactions (Figure 1.4.2).

The enantioselectivity of 1,3-dipolar cycloadditions can be controlled by utilisation of a chiral non-racemic 1,3-dipole, alkene, or catalyst.\(^{107}\)

### 1.5 Nucleophilic Addition to Nitrones

The \(\alpha\)-carbon atom of the nitrone functionality is sufficiently electrophilic to react with a variety of nucleophiles, including organolithium, -magnesium,\(^{155, 156}\) -zinc, and -copper\(^{157-160}\) reagents to generate substituted \(N\)-hydroxylamines. The presence of the oxygen atom of
the azomethine-N-oxide group aids in the addition of organometallic reagents. Firstly, this atom acts as an additional chelation centre, allowing the formation of a five-membered cyclic transition state in the 1,3-addition of simple organometallic reagents such as Grignard and organolithium reagents, and secondly it significantly enhances the electrophilicity of the C=N double bond increasing reactivity in comparison to imines and other azomethines.

\[
\begin{align*}
\text{Figure 1.5.1.} & \quad \text{Mechanism of nucleophilic addition to nitrones.} \\
\text{The addition proceeds } \text{via} \text{ initial coordination of the metal centre to the negatively charged oxygen atom followed by intramolecular attack at the electrophilic carbon (Figure 1.5.1).}^{161} & \\
\text{Nucleophilic attack can potentially occur from either face of the nitrone yielding isomeric products. The selectivity can be greatly influenced by the presence of ligands or chiral auxiliaries to afford } N,N\text{-disubstituted hydroxylamines with excellent diastereo- and enantioselective control. Moreover the rate of reaction as well as the selectivity can be altered to a degree by precomplexation of the nitrone with various Lewis acids.}^{161} & \\
\text{The aforementioned facially-differentiated cyclic nitrones have found increased use providing asymmetric induction through their ability to force the nucleophile to approach } \text{anti} \text{ to the alkoxy group (Figure 1.5.2).}^{161}
\end{align*}
\]

\[
\begin{align*}
\text{Figure 1.5.2.} & \quad \text{Nucleophilic addition to a facially-differentiated, cyclic nitrone.}
\end{align*}
\]
1.6 Synthetic Applications of Enantiopure Cyclic Nitrones

Nitrones have found wide application in the total synthesis of a diverse range of target compounds including sugar and nucleoside analogues, β-lactams as well as polyhydroxylated alkaloids. A considerable volume of literature has been generated, meaning even a brief account of each synthesis would be well beyond the scope of this thesis. As such this thesis describes the chemistry of enantiopure, cyclic nitrones. A selection of recent syntheses, focusing on the use of derivatives of 3-hydroxypyrroline- and 3-hydroxypyridine N-oxides is presented to highlight the utility of nitrones as key synthetic intermediates.

1.6.1 1,3-Dipolar Cycloaddition Reaction Between Alkenes and Cyclic Nitrones

Enantiopure five-membered cyclic nitrones, bearing one or more hydroxy groups are excellent starting materials for the syntheses of naturally occurring pyrrolidine-containing alkaloids as well as their unnatural isomers and, consequently, have received the most synthetic attention.162-172

McCaig and co-workers synthesised both enantiomers of the indolizidine alkaloid lentiginosine 164 and related pyrrolizidines using the 1,3-dipolar cycloaddition reaction of a suitably functionalised cyclic nitrone with a terminal alkene (Scheme 1.6.1).173, 174

![Scheme 1.6.1](image)

Scheme 1.6.1. Reagents and conditions: (a) H₂C=CHCH₂CO₂Bn, PhMe, reflux, 4 d, 44%; (b) Zn, AcOH, 60 °C, 2 h, 83%; (c) BH₃·Me₂S, THF, rt, 4 h then EtOH, reflux, 3 h, 95%; (d) Im₂CS, DCE, reflux, 2 h then rt, overnight, 83%; (e) Bu₃SnH, AIBN, PhMe, reflux, 3 h, 53%; (f) 6 M HCl, rt, overnight, 60%.

1,3-Dipolar cycloaddition of L-tartrate-derived nitrone 160 with benzyl but-3-enolate yielded cycloadduct 161 as the sole product. Reductive N-O bond cleavage and simultaneous lactamisation with the pendant ester yielded lactam 162. Lactam reduction and conversion of the hydroxy group into the imidazolythiothiocabonyl derivative 163 was followed by radical
deoxygenation and acid-catalysed removal of the MOM protecting groups, affording (+)-lentiginosine 164 (Scheme 1.6.1).\textsuperscript{174}

Brandi and co-workers developed two separate syntheses of (+)-lentiginosine 164 from L-tartrate derived nitrones using either methylenecyclopropane or but-3-en-l-o1 as dipolarophiles (Scheme 1.6.2).\textsuperscript{175-177}

![Scheme 1.6.2. Reagents and conditions: (a) methylenecyclopropane, benzene, rt 7 d, 75\% (dr = 10:1); (b) xylene, 140 °C, 1.5 h, 167 45\%, 168 55\%; (c) (i) p-TsNHNH\textsubscript{2}, MeOH, 7 h; (ii) NaBH\textsubscript{4}, 65 °C 20 h, 45\%; (d) 40\% aq. HF, MeCN, rt, 2 d, 70\%; (e) but-3-en-l-o1, 60 °C, 2 d, 100\%; (f) MsCl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}; (g) H\textsubscript{2}, Pd/C, MeOH 24 h, 86\% over 2 steps; (h) Im\textsubscript{2}CS, THF, reflux, 2.5 h, 99\%; (i) Bu\textsubscript{3}SnH, PhMe, reflux, 16 h, 68\%; (j) TFA, 16 h, 93\%.](image)

Cycloaddition between nitrone 165 (R = TBDPS) and methylenecyclopropane afforded a 10:1 mixture of spirocyclopropylisoxazolidine 166 and its bridgehead epimer. Isoxazolidine 166 was heated in xylene whereupon rearrangement occurred to give a mixture of the desired indolizidinone 168 and the enaminone 167 byproduct. Reduction of the ketone via the tosylhydrazone and subsequent silyl deprotection gave lentiginosine 164. Due to the poor selectivity exhibited during the rearrangement of the isoxazolidine 166, an alternative route was developed. 1,3-Dipolar cycloaddition between but-3-en-l-o1 and nitrone 169 (R = t-Bu) yielded a separable mixture of three diastereomers in a ratio of 10:2:1. The major isomer 170 was converted to the corresponding mesylate which readily rearranged via the salt 171 to give hydroxyindolizidine 172. In analogous fashion to McCaig, (vide supra) deoxygenation of the thiocarbonylimidazolide and acid catalysed deprotection yielded (+)-lentiginosine 164 in excellent overall yield (Scheme 1.6.2).
Goti and co-workers synthesised the necine base (-)-rosmarinecine 179 using an intramolecular domino cycloreversion-intramolecular nitrone cycloaddition (Scheme 1.6.3).  

Scheme 1.6.3. Reagents and conditions: (a) styrene, PhMe, 80 °C, 11 h, 174 17%, 175 72%; (b) (i) PPTS, EtOH, reflux, 3 h; (ii) Ambersep 900-OH, MeOH, 3 h, 89%; (c) (Z)-4-methoxy-4-oxobut-2-enoic acid, DEAD, PPh₃, THF, 0 °C to rt, 2 d, 69%; (d) o-dichlorobenzene, reflux, 14 h, 70%; (e) H₂, Pd(OH)₂/C, MeOH, rt, 24 h, 56%; (f) Red-Al, THF, reflux, 3 h, 85%.

Cycloaddition between the L-malic acid derived nitrone 173 and styrene afforded a 1:4.2 mixture of cycloadducts 174 and 175. Deprotection of the hydroxyl group of the major isomer was followed by Mitsunobu reaction with (Z)-4-methoxy-4-oxobut-2-enoic acid to yield the requisite dipolarophile for the intramolecular cycloaddition while also effecting the required inversion at C-4. Upon reflux in o-dichlorobenzene, indolizidinone 176 underwent a domino cycloreversion-intramolecular nitrone cycloaddition to yield tricycle 177 as the sole isomer. Reductive ring opening of isoxazolidine 177, using Pearlman’s catalyst, proceeded with concomitant lactamisation, to furnish lactam 178 which was reduced with Red-Al to give (-)-rosmarinecine 179 (Scheme 1.6.3).
Cardona et al. have explored methodology for the novel addition of glycals to enantiopure cyclic nitrones which has been directed towards the synthesis of a new class of directly linked (1→3)-imino-C-disaccharides (Scheme 1.6.4).162, 172

Scheme 1.6.4. Reagents and conditions: (a) PhMe, rt, 1.5-2.5 h, 89%; (b) DIBAL-H, CH₂Cl₂, -78 °C, 4 h, 74%; (c) PTSA, reflux, 3.5 h; (d) H₂, Pd(OH)₂/C, MeOH, overnight; (e) TFFA, TFA, overnight, then MeOH, aq. NH₃, 10 min; (f) Ac₂O, py, overnight, 29% over 4 steps; (g) TFA, Ac₂O, 24 h, 93%.

Isolevoglucosenone 181 was reacted with nitrone 180 to afforded cycloadduct 182 as the sole regio- and stereoisomer. Stereoselective reduction of the carbonyl moiety exclusively yielded the D-gulo imino-C-disaccharide 183. Deprotection of the tert-butyl group gave diol 184. Hydrogenation of the N-O bond and subsequent protection of the amine as a trifluoroacetamide was followed by acetylation to furnish the fully protected triacetate 187. Acetolysis afforded imino-C-disaccharide 188 as a 1.4:1 mixture of the β- and α-isomers (Scheme 1.6.4).162
Whilst 3-hydroxypyrroline N-oxides and their polyhydroxylated derivatives have been shown to have much scope in the synthesis of pyrrolidine-based alkaloids of varying complexity, the corresponding six-membered 3-hydroxypyridine N-oxides have not been sufficiently investigated. To date most of the research in this area has been directed towards the synthesis of (+)-febrifugine 1 and the 1,3-dipolar cycloaddition of polyhydroxylated six-membered ring nitrones in the synthesis of various glycoprocessing inhibitors.\textsuperscript{179-182}

Duff \textit{et al.} synthesised anaza-C-disaccharide analogue of $\alpha_{\text{D}}$-Lyx(1→6)$\alpha_{\text{D}}$-Man and $\alpha_{\text{D}}$-Lyx(1→6)$\alpha_{\text{D}}$-Gal using the 1,3-dipolar cycloaddition of polyhydroxylated nitrone 189 and a substituted methyl $\alpha_{\text{D}}$-mannopyranoside derivative 190 (Scheme 1.6.5).\textsuperscript{181}

![Diagram](image)

**Scheme 1.6.5. Reagents and conditions:** (a) PhMe, reflux, 84%; (b) Ac$_2$O, DMAP, py; (c) Mo(CO)$_6$, MeCN: H$_2$O, reflux; (d) CbzCl, Na$_2$CO$_3$, acetone, 67% over 3 steps; (e) excess Im$_2$CS, CH$_2$Cl$_2$, reflux, 2 h, then Bu$_3$SnH, AIBN, PhMe, reflux, 81%; (f) NaOMe, MeOH; (g) H$_2$, Degussa Pd/C, MeOH; (h) HCl, MeOH, 80% over 3 steps.

1,3-Dipolar cycloaddition of nitrone 189 and mannopyranoside derivative 190 led to the isolation of the crystalline cycloadduct 191 as a sole product arising from an \textit{exo}-mode cycloaddition. Acetylation and reductive cleavage of isoxazolidine 191 was followed by protection of the resulting amine to give 192. Barton-McCombie deoxygenation was followed by global deprotection to yield the desired aza-C-disaccharide which was isolated as the hydrochloride salt 194 (Scheme 1.6.5).
A search of the literature reveals thus far only two examples of 3-hydroxypiperidine N-oxides that have found use in enantioselective syntheses of (+)-febrifugine 1.\textsuperscript{183-185}

Ooi \textit{et al.} have utilised a one pot nitrone formation/1,3-dipolar cycloaddition reaction in an enantioselective synthesis of (+)-febrifugine 1.\textsuperscript{183}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {$195$};
\node (b) at (1,0) {$196$};
\node (c) at (2,0) {$197$};
\node (d) at (3,0) {$198$};
\node (e) at (0,-1) {$199$};
\node (f) at (1,-1) {$200$};
\node (g) at (2,-1) {$201$};
\node (p) at (3,0) {$P = OTBDPS$};
\node (dr) at (1.5,2) {$dr = 10:64:26$};
\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);
\draw[->] (e) -- (f);
\draw[->] (f) -- (g);
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.6.6. Reagents and conditions:} (a) O\textsubscript{3} then Me\textsubscript{2}S, NaHCO\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C, 20 min; (b) allyl alcohol, NH\textsubscript{2}OH-HCl, Et\textsubscript{3}N, rt, 11 h, 74% over two steps ($dr = 10:64:26$).

Allyl alcohol was reacted directly with nitrone 198, which had been generated \textit{in situ} from aldehyde 196 \textit{via} oxime 197. Isoxazolidines 199, 200, and 201 were obtained in a ratio of 10:64:26 respectively and an overall yield of 74% yield from alkene 195 (Scheme 1.6.6).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {$202$};
\node (b) at (1,0) {$203$};
\node (c) at (2,0) {$204$};
\node (d) at (3,0) {$205$};
\node (e) at (4,0) {$206$};
\node (f) at (5,0) {$207$};
\node (p) at (0,-1) {$199$};
\node (q) at (1,-1) {$200$};
\node (r) at (2,-1) {$201$};
\node (beta) at (0,-2) {$\text{199, 200, 201 P = TBDPS}$};
\node (alpha) at (1,-2) {$\beta$-H; $\alpha$-H 78:22};
\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);
\draw[->] (d) -- (e);
\draw[->] (e) -- (f);
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.6.7. Reagents and conditions:} (a) (i) H\textsubscript{2}, PdCl\textsubscript{2}, MeOH, rt, 12 h; (ii) Boc\textsubscript{2}O, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, rt, 10 h, 94%; (b) N-tosylimidazole, NaH, THF, rt, 12 h, 92%; (c) 4-quinazolone, KH, DMF, 70 °C, 40 h, 77%; (d) Dess-Martin periodinane, CH\textsubscript{2}Cl\textsubscript{2}, rt, 3 h, 98%; (e) 6 M HCl, reflux, 6 h, 1 58%, 207 27%; (f) MeOH, reflux, 50%.

The diastereoisomeric mixture of isoxazolidines 199-201 was subjected to hydrogenolytic N-O bond cleavage and the resulting amine protected as the \textit{tert}-butyl ester. Reaction of diol 202 with N-tosylimidazole and sodium hydride afforded epoxide 203 which
was coupled with the potassium salt of 4-quinazolone to afford alcohol 204. Dess-Martin oxidation of the alcohol gave a separable mixture of epimers 205 and 206. The synthesis was completed by global deprotection by acid hydrolysis to give a separable mixture of (+)-febrifugine 1 and (+)-isofebrifugine 207 in a 67:33 ratio. (+)-Isofebrifugine 207 was then converted to (+)-febrifugine 1 by isomerisation, using conditions reported by Oshima and co-workers (Scheme 1.6.7).\textsuperscript{186}

Caprio and Ashoorzadeh have previously developed an efficient route to an isolatable 3-hydroxy-3,4,5,6-tetrahydropyridine N-oxide 208 and demonstrated the potential of this intermediate in the synthesis of (+)-febrifugine 1 (Scheme 1.6.8).\textsuperscript{184, 185}

\begin{equation}
\begin{align*}
\text{L-Glutamic acid-derived nitrone 208} & \quad \text{was heated under reflux with } \text{N-allylquinazoline 209 in toluene for 24 hours to give the resulting cycloaducts 210 and 211 as a separable mixture of two isomers favouring the desired product 218 in a ratio of 1:2.7. Reductive cleavage of isoxazolidine 211 using zinc in refluxing acetic acid was followed by Boc-protection of the resulting crude amine. Oxidation of the hydroxyl functionality by Dess-Martin periodinane yielded ketone 213 which was globally deprotected using boiling 6 M HCl to give (+)-febrifugine 1 (Scheme 1.6.8).}
\end{align*}
\end{equation}
1.6.2 Nucleophilic Additions to Cyclic Nitrones

While the behaviour of cyclic nitrones as 1,3-dipoles has been regularly exploited in synthesis, their reactivity as electrophiles in has been much less investigated. Although increasing attention has been given to nucleophilic addition to acyclic nitrones only sporadic examples of additions to cyclic nitrones have been reported and a detailed study is lacking.\textsuperscript{187} Work has largely focussed on the addition of Grignard reagents to pyrrolidine N-oxides, to access various pyrrolidine containing natural products and their isomers, and a number of biologically active tri- and tetrahydroxypyrrolidines.\textsuperscript{161,189-191}

Some of the earliest examples include the syntheses of (+)-lentiginosine \textsuperscript{164,192} and (-)-deacetylanisomycin \textsuperscript{219} by Petrini and co-workers, centred on highly selective nucleophilic addition of Grignard reagents to the L-tartaric acid derived nitrone \textsuperscript{160} (Scheme 1.6.9).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme1.6.9.png}
\caption{Reagents and conditions: (a) BnO(CH\textsubscript{2})\textsubscript{4}MgBr, THF, reflux, 82\% (de = 90\%); (b) (i) H\textsubscript{2}, Raney Ni, MeOH, rt; (ii) NH\textsubscript{2}COOH, Pd/C, EtOH, reflux 76\%; (c) PPh\textsubscript{3}, CCl\textsubscript{4}, Et\textsubscript{3}N, DMF, rt, 88\%; (d) HCl, MeOH, reflux, 91\%; (e) 4-methoxy-benzylmagnesium chloride, MgBr\textsubscript{2}-Et\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 30 min, \textsuperscript{216} 19\%, \textsuperscript{217} 42\%; (f) H\textsubscript{2}, Raney Ni, MeOH, rt, 6 h, 85\%; (g) 6 N HCl:MeOH (1:1), reflux, 24 h, 75\%.
\end{scheme}

Addition of 4-benzyloxybutylmagnesium bromide to nitrone \textsuperscript{160} afforded a 95:5 diastereomeric mixture of hydroxylamines favouring the desired \textit{trans}-product \textsuperscript{214}. Reduction of hydroxylamine \textsuperscript{214} by hydrogenation using Raney nickel, and hydrogenolysis of the benzyl ether afforded the amino-alcohol \textsuperscript{215} required for ring closure. A base-promoted intramolecular S\textsubscript{N}2 displacement and acid catalysed hydrolysis of the methoxymethyl protecting groups completed the synthesis of (+)-lentiginosine \textsuperscript{164} (Scheme 1.6.9).\textsuperscript{192}
A slight reversal in cis/trans selectivity was obtained in the reaction of 4-methoxybenzylmagnesium chloride in the presence of MgBr₂·Et₂O, yielding a separable mixture of diastereomers 216 and 217 in an approximate ratio of 3:7. Catalytic hydrogenation of the 2,3-cis isomer 217, in the presence of Raney nickel generated pyrrolidine 218, which was converted into (-)-deacetylanisomycin 219 on removal of the methoxymethyl protecting groups (Scheme 1.6.9).¹⁹³

This methodology has been expanded by various groups to provide access to 2,5-disubstituted hydroxypyrrolidines, primarily (-)-codonopsinine 233 and the radicamines.

Yu and Huang synthesised the proposed structures for radicamines A and B using the D-xylose derived nitrone 220 (Scheme 1.6.10).¹⁹⁴

\[ \text{Scheme 1.6.10. Reagents and conditions: (a) 4-benzyloxyphenylmagnesium bromide or 3-benzyloxy-4-methoxyphenylmagnesium bromide, THF, 0 °C to rt, 12 h, 221 89%, 222 80%; (b) H₂, Pd/C, MeOH, rt, 20 h, 223 87%, 224 93%}. \]

Reaction of nitrone 220 with 4-benzyloxyphenylmagnesium bromide afforded hydroxypyrrolidine 222 as the sole product. Debenzylation via catalytic hydrogenation proceeded, with concomitant N-O reductive cleavage, to produce ent-radicamine B 224 in excellent yield.¹⁹⁴ Use of 3-benzyloxy-4-methoxyphenylmagnesium bromide resulted in synthesis of ent-radicamine A 223 (Scheme 1.6.10). These products were determined to be the enantiomers of the natural products, on the basis of comparison of the optical rotations with those of the natural products. This discovery led to a revision of their stereochemical assignment.

Whilst a similar approach was undertaken by Gurjar et al., to also form ent-radicamine B 224, Merino et al. and Liu et al. have utilised D-arabinose and D-xylose, respectively, to synthesise the correct enantiomer.¹⁸⁹, ¹⁹⁵, ¹⁹⁶
While Toyao et al. have reported an approach towards the synthesis of (-)-codonopsinine 233 using similar methodology, Goti et al. have differentiated their route by accessing the 2,5-disubstituted hydroxypyrrolidine motif by functionalisation at both the 2- and 5-positions. (Scheme 1.6.11).

**Scheme 1.6.11.** Reagents and conditions: (a) MeMgBr, Et₂O, rt, 2 h, 100%; (b) MnO₂, CH₂Cl₂, 0 °C to rt, 18 h, 100% (dr = 2.3:1); (c) 4-methoxyphenylmagnesium bromide, Et₂O, rt, 2 h (dr = 2.3:1), 64%; (d) MeI, MeOH, 0 °C to rt, 20 h; (e) Zn, In, MeOH, sat. NH₄Cl, reflux, 1.5 h 76% over two steps; (f) (i) TFA, 0 °C to rt, 15 h; (ii) Ambersep 900 (OH⁻ form), MeOH, 15 h, 78%.

Methylmagnesium bromide underwent stereoselective addition to the D-tartrate derived nitron 225 to yield hydroxylamine 226 as the sole product. Subsequent oxidation furnished a mixture of regiosomeric nitrones 227 and 228 favouring the desired aldonitrone 227 with moderate selectivity. This mixture was reacted with 4-methoxyphenylmagnesium bromide, without purification, stereoselectively furnishing the 2,5-disubstituted 230 and 2,2-disubstituted 229 hydroxypyrrolidines. Methylation of 230 was followed by N-O reductive cleavage, with zinc and catalytic indium, and deprotection of the hydroxy groups to afford (-)-codonopsinine 233 as an enantiopure compound (Scheme 1.6.11).
Nucleophilic additions have also been used for the synthesis of a number of naturally occurring indolizidine and pyrrolizidine alkaloids.

Cardona et al. have recently reported a synthesis of (+)-lentiginosine 164 utilising a highly stereoselective organometallic addition to a cyclic nitrone followed by RCM to form the indolizidine ring. (Scheme 1.6.12).\(^{198}\)

Vinylmagnesium bromide underwent stereoselective addition to the L-tartrate derived nitrone 169 to yield hydroxylamine 234 as the sole product. Deoxygenation to the pyrrolidine was followed by acylation with but-3-enoic acid to give the requisite diene for ring closure 235. RCM, with first-generation Grubbs catalyst, effected formation of the bicyclic lactam core 236. Reduction of the lactam and alkene groups was followed by cleavage of the tert-butyl ethers to complete the synthesis of (+)-lentiginosine 164 (Scheme 1.6.12).\(^{198}\)

Similar methodology was used in a concise synthesis of the polyhydroxylated pyrrolizidine hyacinthacine A\(_2\) 241 (Scheme 1.6.13).\(^{199}\)

---

**Scheme 1.6.12. Reagents and conditions:** (a) vinylmagnesium bromide, Et\(_2\)O, 20 °C, 1.75 h, 96%; (b) Zn, In, sat. NH\(_4\)Cl, MeOH, reflux, overnight, 84%; (c) H\(_2\)C=CHCH\(_2\)CO\(_2\)H, HOBt, DCC, CH\(_2\)Cl\(_2\), 20 °C, 20 h, 71%; (d) Grubbs I catalyst (12 mol %), CH\(_2\)Cl\(_2\), reflux, 50 h, 60%; (e) LiAlH\(_4\), THF, reflux, 2 h, 62%; (f) H\(_2\), Pd/C, MeOH, overnight, 90%; (g) TFA, 20 °C, overnight, then Ambersep 900-OH, MeOH, 74%.

**Scheme 1.6.13. Reagents and conditions:** (a) vinylmagnesium bromide, Et\(_2\)O, 0 °C, 13 h, 98%; (b) Zn, AcOH:H\(_2\)O (1:1), rt, 40 min, quant; (c) allyl bromide, DMF, K\(_2\)CO\(_3\), Bu\(_4\)NI, rt, 12 h, 81%; (d) Grubbs II catalyst, PhMe, 80 °C, 14 h, 87%; (e) H\(_2\), Pd(OH)\(_2\)/C, MeOH, 1 M HCl, then Dowex 50WX8-200, 96%.
Nucleophilic addition of vinylmagnesium bromide, deoxygenation and N-allylation afforded the cyclisation precursor 239 as a single isomer. Ring-closing metathesis of diallylamine 239 yielded bicycle 240 which after catalytic hydrogenation and ion-exchange chromatography, gave hyacinthacine A$_2$ 241 (Scheme 1.6.13).$^{199}$

Using similar methodology, Kaliappan et al. have synthesised a small series of bicyclic calystegine analogues showing non-competitive inhibition against $\alpha$-mannosidase and $N$-acetyl-$\beta$-D glucosaminidase (Scheme 1.6.14).$^{200}$

Selective nucleophilic addition of allyl magnesium chloride to the mannose-derived nitrone 242 afforded hydroxylamine 243. Reductive cleavage of the N-O bond and protection of the resulting amine yielded compound 244. Selective removal of the 5,6-$O$-isopropylidene group, to expose the vicinal diol, was followed by Garegg-Samuelsson olefination$^{201}$ to give the desired RCM precursor diene 245. Ring-closing metathesis proceeded smoothly to afford 8-azabicyclo[3.2.1]octane 246, which was hydrogenated and deprotected under acidic conditions, to completed the synthesis. Metathesis product 246 was utilised as an advanced precursor for the syntheses of several more analogues of calystegine (Scheme 1.6.14).$^{200}$

Finally Hu et al. have synthesised indolizidine and pyrrolizidine alkaloids, with additional stereochemistry, on the formed ring allowing synthesis of the unnatural isomers of (-)-steviamine and (+)-hyacinthacine A$_3$.$^{202,203}$
Addition of Grignard reagent 249 to the D-ribose-derived nitrone 248 furnished hydroxylamine 250 with high diastereoselectivity (dr > 95%). Reduction of the resulting hydroxylamine gave the corresponding amine which was treated with Boc₂O to form the N-Boc derivative 251. The carbonyl group was exposed under mild acidic conditions to give ketone 252. The indolizidine ring was formed by an intramolecular reductive amination, after acidic deprotection of N-Boc ketone 252, furnishing a mixture epimers 253 and 254 with good diastereoselectivity favouring amine 254. Finally, the synthesis was completed by hydrogenolysis to give (+)-steviamine 255 (Scheme 1.6.15).²⁰²

Treatment of D-ribose-derived nitrone 227 with (3,3-dimethoxypropyl)magnesium bromide 256 and reductive N-O bond cleavage yielded amine 258 as a single isomer. Ring
closure of amino-acetal 258 was effected by treatment with potassium cyanide under acidic conditions to yield a mixture of pyrrolizidines, favouring α-amino nitrile 260. Bruylants reaction between the iminium salt equivalent 260 and methylmagnesium iodide in the presence of AgBF₄ yielded a mixture of pyrrolizidines ($dr = 8.6:1$) favouring 261. The synthesis was completed by catalytic hydrogenolysis of 261 to give (-)-hyacinthacine A₃ 262 (Scheme 1.6.16).

Kaliappan and Das utilised a highly selective Cope-House cyclisation to synthesise unnatural isomers of pyrrolizidine alkaloids hyacinthacine A₃ and hyacinthacine A₅.²⁰⁴

![Diagram](image)

**Scheme 1.6.17. Reagents and conditions:** (a) (i) 3-butenylmagnesium bromide, THF, -78 °C; (ii) CHCl₃, 24 h, 99%; (b) H₂, Pd/C, MeOH:THF (4:1), 6 N HCl, 3 d, 91%.

Addition of 3-butenylmagnesium bromide to the L-xylose-derived nitron 245 afforded hydroxylamine 263 as a single diastereomer. Cope-House cyclisation proceeded *via* a highly ordered planar five-membered transition state to give pyrrolizidine N-oxide 264 as a single diastereomer. Global hydrogenolysis of the benzyl protecting groups proceeded with N-O bond cleavage yielded 5-(+)-epi-hyacinthacine A₃ 265 (Scheme 1.6.17).²⁰⁴

Although a small amount of research has been directed towards nucleophilic additions to dihydroisoquinoline N-oxide derivatives,²⁰⁵-²⁰⁷ there have been only isolated reports of nucleophilic addition to simple 6-membered ring nitrones²⁰⁸-²¹³ and their polyhydroxylated derivatives which offers the potential for discovery in a relatively poorly explored field.

![Diagram](image)

**Scheme 1.6.18. Reagents and conditions:** (a) TMSCN, cat. AlMe₃Cl, CH₂Cl₂, 0 °C, 1.5 h; (b) PTSA, MeOH, rt, 20 min, 270 86%, 268 5%.
For example Peer and Vasella have demonstrated that the AlMe$_2$Cl-promoted addition of trimethylsilyl cyanide to the carbohydrate-derived cyclic nitrone 266 proceeds to give diastereoisomeric N-silyloxyamino nitriles, favouring the axial nitrile 270 (Scheme 1.6.18).\textsuperscript{180}

Berge \textit{et al.} synthesised four stereoisomeric analogues of the bacterial tyrosyl tRNA synthetase inhibitor SB-21938\textsuperscript{214} utilising addition of a glycine anion equivalent to arabinose derived nitrones (Scheme 1.6.19).\textsuperscript{215}

\textbf{Scheme 1.6.19. Reagents and conditions:} (a) 277, LiHMDS, PhMe, -78 °C; 271, -78 °C to 0 °C, 272: 35%, 273: 36%, 274: trace; (b) HCl, H$_2$O, dioxane, 25 °C; (c) (i) F$_3$CC(O)N(Me)TMS, DIPEA, py, 25 °C; BocTyrOSu, 60 °C; MeOH, H$_2$O, 25 °C; (ii) TFA, 25 °C (31% from 273).

Nucleophilic addition of the lithium enolate of glycine derivative 277 with the L-arabinose derived nitrone 271 proceeded with low diastereoselectivity to yield the diastereomeric isoxazolidines 272 and 273 as well as the uncyclised ester 274. Acidic hydrolysis of the acetal protection group and the O-acyl hydroxylamine of 273 yielded amino acid 275. Coupling of the L-tyrosine residue to amino acid 275 was achieved in two steps \textit{via} silylation using excess N-methyl-N-trimethylsilyl trifluoroacetamide followed by coupling to N-Boc-L-tyrosine. Global deprotection furnished depeptide 276 (Scheme 1.6.19). The equivalent isomer with D-configuration at the C-terminal amino acid was formed using compound 272 whereas the remaining two isomers with inverted chirality at the C-terminal amino acid were synthesised using a D-arabinose based nitrone.
1.7 Aim of the Current Project

The construction of versatile chiral building blocks for the efficient synthesis of biologically active natural products and their analogues is a topic of current interest. Current state of the art in this area does not meet these criteria with targets generally being prepared using separate, lengthy and inflexible synthetic strategies.

Hence work within the Caprio research group has focused on the development of methodology for the highly flexible, asymmetric synthesis of a diverse range of alkaloids containing the 3-hydroxypiperidine motif using chiral 3-hydroxy-3,4,5,6-tetrahydropyridine N-oxides. While Caprio and Ashoorzadeh have previously developed an efficient route to nitrone 208 and its synthetic utility verified by its use in a convergent approach to (+)-febrifugine 1 (Scheme 1.6.8), the reactivity of this compound has yet to be fully explored.

\[
\begin{align*}
\text{208} + \text{R}_1 & \rightarrow \text{278} \quad \text{R}_1 = \text{Ph}, \text{R}_2 = \text{H} \quad 98\% \quad dr = 65:35:0 \\
\text{279} & \quad \text{R}_1 = \text{OSiMe}_3, \text{R}_2 = \text{Me} \quad 55\% \quad dr = 49:29:22
\end{align*}
\]

Scheme 1.7.1. Reagents and conditions: (a) CHCl, 60 °C, 20 h, dr = 65:35:0, 98% overall; (b) PhMe, 110 °C, 48 h, dr = 49:29:22, 55% overall.

Due to the low reactivity observed in the nucleophilic addition to nitrone 208, previous work has been focused on examination of the 1,3-dipolar cycloaddition reaction with alkenes.\(^\text{184}\) However only limited examples aimed at determination of the regio- and stereochemical outcome have been performed which have shown that although the reaction proceeds with excellent exolendo selectivity and regioselectivity, the antisyn selectivity is only moderately in favour of the desired anti-compounds. (Scheme 1.7.1).\(^\text{184}\)

Therefore the initial aim of this work is to fully evaluate the synthetic scope of this chiral building block with the addition of further alkenes. Only electron-rich examples have been reported and in order to accurately determine the behaviour of nitrone 208, the addition of electron-deficient and electron-neutral alkenes is proposed.
The low reactivity towards nucleophilic addition currently limits the synthetic utility of nitrones of type 208. Direct attachment of functionality to the C-2 position of the piperidine ring can only be achieved by nucleophilic addition to the \( \alpha \)-carbon of the nitrone.

The major focus of this research is the further development of this methodology in order to permit the introduction of functionality by nucleophilic addition. It is proposed that synthesis of a differently protected nitrone may display better reactivity towards nucleophilic attack.

The ultimate aim is to apply the developed methodology to the synthesis of bioactive alkaloids such as (+)-swainsonine 397 using a chiral, (S)-3-hydroxytetrahydropyridine \( N \)-oxide as a key intermediate.
2. **Nitrone Synthesis and Model Studies**

2.1 **Synthesis and Configuration of \( O\)-Benzylnitrone 208

A chiral-pool based strategy developed within our research group by Ashoorzadeh and Caprio was utilised to prepare nitrone 208 in multi-gram quantities from L-glutamic acid 283 (Scheme 2.1.1).

![Scheme 2.1.1. Reagents and conditions:](image)

Lactone 284 was prepared according to the literature procedure, by treatment of commercially available L-glutamic acid 283 with sodium nitrite in aqueous hydrochloric acid. This proceeds via diazotisation of the amine functionality. Intramolecular attack of a neighboring carboxylate onto the diazo group followed by opening of the resulting 3-membered ring by the alternate carboxylate results in retention of configuration in the (S)-lactone product 284. Acid-catalysed esterification to give hydroxydiester 285 was followed by protection of the free hydroxyl as the corresponding benzyl ether 286 using benzyl bromide and freshly prepared silver(I) oxide. Reduction of the ester functionalities with lithium aluminium hydride afforded diol 287 which was subjected to standard tosylation conditions to give 1,5-ditosylate 288. Treatment of tosylate 288 with hydroxylamine hydrochloride under basic conditions gave the cyclic nitrone precursor, \( N\)-hydroxypiperidine 289, which was oxidised using activated manganese dioxide to give a readily separable...
regioisomeric mixture of nitrones 290 and 208 in a 1:2.8 ratio (Scheme 2.1.1). Unfortunately the ratio obtained was significantly lower than that obtained by Ashoorzadeh and Caprio and was not able to be improved.184

The oxidation of hydroxylamines is thought to be a two-step reaction, proceeding via oxidation of the N-hydroxylamine moiety 291 to give the intermediate nitrosonium ion 292, followed by rate determining hydrogen abstraction from the α-carbon, generating the regioisomeric nitrones (Scheme 2.1.2).168, 217-220

Scheme 2.1.2. Proposed mechanism for oxidation of the N-hydroxylamine moiety.

Independently, the research groups of Goti and Cicchi have investigated the mechanism of oxidation of N-hydroxypryrolidines with varying substituents at the C-3 and have shown a direct correlation between regioselectivity and the electronegativity of the substituent.168, 218 Although steric effects do play a minor role, the observed regioselectivity arises from polarisation of the C-H bond at C-2 which can be oriented in an antiperiplanar disposition with respect to the β-alkoxy group (Figure 2.1.1).168, 218

Figure 2.1.1. Representation of orbital interaction of the 3-substituent with the trans hydrogen.218

The electronegative substituent at the C-3 position stabilises the developing negative charge on the adjacent carbon by an electron-donating hyperconjugative effect (σC-H → σ* C-O) during the second deprotonation to yield the major nitrone 294 (Figure 2.1.1).168, 171, 218, 221 This effect results in removal of the proton anti to the alkoxy group being more kinetically favourable, limiting formation of the undesired nitrone, and generally a higher
regioselectivity will be obtained with C-3 substituents with a greater ability to stabilise the developing negative charge (Figure 2.1.1).\textsuperscript{218}

We are not certain that these effects apply in the case of a six-membered analogue as the substituent at C-3 could be in a pseudo-equatorial position.

The signal in the \textsuperscript{1}H NMR spectrum of compound \textit{208} at 7.22 ppm which was assigned to C-2, resonates as a doublet, \( J_{2,3} = 3.7 \text{ Hz} \). This coupling constant corresponds to a dihedral angle of \( 51^\circ \) which means the bulky benzyloxy group is not in the expected equatorial position. Instead it sits in a pseudo-axial orientation under the ring, effectively blocking one face. Thus, it is likely that any dipolarophiles will approach the nitrone from the face opposite the benzyloxy group to give \textit{trans}\textsuperscript{-2,3}-disubstituted products.

\textbf{2.2 1,3-Dipolar Cycloaddition of Alkenes with Nitrone 208}

One of the most comprehensive studies of the 1,3-dipolar cycloaddition reaction with cyclic nitrones was performed by Ali et al. examining the reaction between the unsubstituted 2,3,4,5-tetrahydropyridine 1-oxide and a variety of mono- and disubstituted alkenes.\textsuperscript{154, 222-224} The reactions proceeded with excellent regiocontrol and \textit{exo/endo}-selectivity, displaying a clear preference for the \textit{exo}-stereoisomer.

While it was expected that the results of our study would also reflect this, the presence of the bulky benzyloxy protection group at the C-3 position was expected to influence the approach of the dipolarophile to the nitrone functionality. Due to its orientation under the ring, this substituent was predicted to force the dipolarophile to approach from the opposite face yielding isoxazolidines with \textit{trans}-stereochemistry.

Although the regio- and stereochemical outcomes of the 1,3-dipolar cycloaddition reaction with styrene \textit{278} and 2-(trimethylsilyloxy)propene \textit{279} have been probed,\textsuperscript{184} more examples are required to develop a deeper understanding of the synthetic potential of nitrone \textit{208}. Both of these examples are electron rich alkenes and it was deemed prudent to examine the reaction of electron neutral and electron poor alkenes. Alkenes were chosen which, upon reductive cleavage of the formed isoxazolidine, would yield products with synthetic potential. Allyl alcohol \textit{209} and 3-butenol \textit{304} give cycloadducts of potential in the synthesis of indolizidine and quinolizidine ring systems respectively. Ethyl vinyl ether \textit{295}, ethyl acrylate
314, and 2-(trimethylsilyloxy)propene 279 would be expected to provide access to the aldehyde, ester and ketone moieties respectively which are all of synthetic utility.

2.2.1 Cycloaddition with Ethyl Vinyl Ether

The 1,3-dipolar cycloaddition reaction of nitrone 208 with the electron rich alkene, ethyl vinyl ether 295 was initially attempted in ethanol in accordance to the procedures outlined by Ali et al.154 This however led to the formation of an insoluble reaction mixture from which no products were observed.

![Scheme 2.2.1](image)

Scheme 2.2.1. Reagents and conditions: (a) PhMe, 45 °C, 12 h, dr 66:44, 80% overall.

The reaction of nitrone 208 with ten molar equivalents of ethyl vinyl ether 295 was performed in toluene under gentle heating for 12 h. This gave a separable mixture of diastereomeric isoxazolidines 296 and 297 in a ratio of 66:44 respectively and an overall yield of 80% (Scheme 2.2.1). High-resolution mass spectrometry of isoxazolidines 296 and 297 established that the molecular formulae of these products were identical indicating that they were isomeric.

The ¹H NMR spectra of the isoxazolidines were highly complex and required extensive 2D NMR experiments in order to assign all non-equivalent ring protons. However stereochemical determination of the resulting isoxazolidines was complicated by extensive line broadening of ¹H and ¹³C NMR spectra when recorded in CDCl₃ at room temperature.

![Figure 2.2.1](image)

Figure 2.2.1. Nitrogen inversion and chair inversion processes for isoxazolidines occurring at room or lower temperatures.
This phenomenon is observed in hydroxylamines, nitrones and isoxazolidines, arising from relatively slow nitrogen lone pair inversion caused by the presence of an adjacent heteroatom such as oxygen.\textsuperscript{219} The resultant isoxazolidine can in principle exist in three conformations, a \textit{cis}-conformer pair A and B and the \textit{trans}-conformer C. Although the \textit{cis}-pair are in rapid equilibrium \textit{via} chair inversion (C\textsubscript{i}), \textit{cis}-conformer B is converted into the \textit{trans}-conformer C by a relatively slow nitrogen inversion process (N\textsubscript{i}) (Figure 2.2.1).\textsuperscript{219, 225-227} This can be overcome either by cooling the sample, slowing inversion down to the point where the signals for both invertomers can be clearly observed, or heating to a elevated temperature so that the interconversion occurs at a sufficient rate and considerable line sharpening is observed.

Although recording the NMR spectrum at elevated temperatures resulted in sufficient reduction of signal line broadening, this makes some assignments ambiguous due to the fact an average signal is being analysed. There are however features that allow determination of the stereochemistry from $^1$H NMR, COSY and NOESY spectroscopic data.

The regiochemical outcome can be determined by the signal type observed for the $^1$H and $^{13}$C NMR resonances at the 2-position. Due to the deshielding effect of the isoxazolidine ring oxygen, the 2-substituted isomer would be expected to show a downfield methine signal whereas the 3-substituted isomer would be observed as a downfield methylene signal.

Considering only the 2-substituted isoxazolidines, which were expected to be favoured, there are four possible diastereomers arising from the \textit{exolendo} approach of the dipolarophile and also \textit{syn/anti} approach to the alkoxy group of the reacting nitrene.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig222.png}
\caption{Expected NOESY interactions for \textit{exo-anti} and \textit{endo-anti} cycloadducts.}
\end{figure}
For the 3a,4-trans isoxazolidines, NOE interactions of 3a-H with both 5ax-H and 7ax-H, and of 4-H with 6ax-H and 3-Hb are indicative of trans-geometry whilst interactions between 2-H and 3-Hb or 2-H and 3a-H/3-Ha are expected for exo- and endo-attack respectively (Figure 2.2.2).

Similarly, for the 3a,4-cis isoxazolidines, NOE interactions of 4-H with both 6ax-H and 3a-H, and of 5ax-H with 3-Ha are indicative of cis-geometry whilst interactions between 2-H and 7ax-H or 2-H and 3-Hb are expected for exo- and endo-attack respectively (Figure 2.2.3).

2.2.1.1 Stereochemical Determination of exo-anti Cycloadduct 296

The structure derived from the exo-anti approach of reactants was assigned to the major isoxazolidine 296 on the basis of an analysis of the 1H NMR, COSY and NOESY NMR spectroscopic data (Figure 2.2.4).

The regioselectivity was determined from the downfield methine signal attributed to the 2-position, appearing in the 1H NMR spectrum as a dd at 5.10 ppm, and the corresponding carbon resonance at 100.1 ppm. This confirmed formation of the 2-substituted cycloadduct. Strong NOE signals from 4-H to 6ax-H provided evidence that the 4-H was in an axial
position placing the bulky benzyloxy group in the sterically favoured equatorial position. Although the close proximity of the 3a-H and 7ax-H signals meant that the axial coupling could not be determined by an analysis of the NOESY spectrum, a strong NOE between 3a-H and 5ax-H indicated that 3a-H was in the axial position indicating the anti-stereochemistry. This was confirmed by analysis of the $^1$H NMR signal at 3.35 ppm which was attributed to the H-4 proton and observed as a ddd with coupling constants of $J = 4.3$, $8.1$ and $9.7$ Hz. This splitting pattern made up of one small and two larger coupling constants in a six-membered ring is consistent with two axial-axial couplings and one axial-equatorial coupling, indicative of a trans-diequatorial substituted ring. The 3-Hb proton showed a strong NOE interaction with 4-H as well as correlations to 2-H, indicating that this compound is the exo-isomer (Figure 2.2.4).

The stereochemistry of cycloadduct 296 was confirmed by reductive cleavage of the N-O bond and spectroscopic analysis of the resulting amino alcohol 301 (Scheme 2.2.3).

### 2.2.1.2 Stereochemical Determination of exo-syn Cycloadduct 297

The structure derived from the exo-syn approach of reactants was assigned to the minor isoxazolidine 297 on the basis of an analysis of the $^1$H NMR, COSY and NOESY NMR spectroscopic data (Figure 2.2.5).

![Figure 2.2.5. Observed NOESY interactions for exo-syn cycloadduct 297.](image)

The regiochemistry was assigned in the same fashion as the previous isomer. A downfield methine signal occurring in the $^1$H NMR spectrum as a dd at 5.29 ppm, and the corresponding carbon resonance at 101.5 ppm was assigned to the 2-position, confirming formation of the 2-substituted adduct. NOE correlations between the proton at 4-H and 6ax-H were consistent with 4-H having an axial orientation. NOE correlations between 3-Ha and both 5ax-H and 7ax-H as well as between 3a-H and 4-H both indicate syn-attack of the alkene. This is further supported by the $^1$H NMR signal at 3.82 ppm attributed to the H-4
proton. This was observed as a ddd but with coupling constants of $J = 4.3, 4.3$ and $8.5$ Hz. This splitting pattern, made up of one large and two smaller coupling constants is consistent with one axial-axial and two axial-equatorial couplings, indicative of a cis-orientation across the 4-3a bond where 4-H is in an axial position. Strong NOE correlations of 2-H with both 7ax-H and 3-Ha suggest that this compound is the endo-isomer (Figure 2.2.5).

These results indicate that the cycloaddition reaction occurred with 100:0 exo/endo-selectivity, 66:44 diastereofacial selectivity, and perfect regioselectivity.

### 2.2.1.3 Ring Opening of exo-anti Cycloadduct 296

Reductive cleavage of the N-O bond of the isoxazolidines to yield open-chain amine derivatives was also investigated in an effort to further probe the utility of nitrone 208 as an intermediate for the synthesis of substituted piperidines. Cleavage is typically performed in refluxing glacial acetic acid in the presence of excess zinc powder and catalytic copper(II) acetate.\(^\text{228, 229}\)

\[
\text{Scheme 2.2.2. Reagents and conditions: (a) Zn, Cu(OAc)\textsubscript{2}, AcOH, reflux, 1 h.}
\]

The major cycloadduct 296 was treated with zinc powder and catalytic copper(II) acetate and heated under reflux in glacial acetic acid for 1 h. Disappointingly, isoxazolidine 296 was not converted to the expected aldehyde 299 via the intermediate hemiacetal 298, instead yielding only a complex mixture of products (Scheme 2.2.2).

Attention then turned to alternative methods of conversion of isoxazolidines into the corresponding amino-alcohols. In addition to the previously described method, cleavage may be accomplished by hydrogenation over Raney Nickel, Pd/C,\(^\text{230}\) or Pd(OH)$_2$/C,\(^\text{231}\) or reaction with either Zn/H$^+$, In/Zn/NH$_4$Cl,\(^\text{232}\) TiCl$_3$/H$^+$,\(^\text{233, 234}\) Ni boride,\(^\text{235}\) Mo(CO)$_6$/H$_2$O,\(^\text{236}\) or SmI$_2$.\(^\text{237}\) Unfortunately, these reagents do not display a broad substrate generality,\(^\text{232}\) and methods such as hydrogenation and TiCl$_3$/H$^+$ or Zn/H$^+$, do not tolerate the presence of unsaturated and acid-sensitive functional groups, respectively.
The In/Zn/NH₄Cl system reported by Cicchi and co-workers appeared to be the most suitable reduction method, having demonstrated applicability to the reduction of hydroxylamines containing acid sensitive and unsaturated substituents. Although the described method has been shown to have utility in the reduction of hydroxylamines it had not been examined for the reductive cleavage of isoxazolidines.

Cycloadduct 296 was treated with a catalytic amount of indium and two molar equivalents of zinc powder in a solution of EtOH/NH₄Cl and stirred under reflux for six hours. Disappointingly, this yielded only a complex mixture of products where trace amounts of aldehyde 299 were detected in a ¹H NMR spectrum of crude material.

Caruthers et al. have reported similar problems with the cleavage of isoxazolidines synthesised from vinyl ethers. To avoid the possibility of a reverse Michael reaction of the formed aldehyde, isoxazolidines were converted to the N-benzyl ammonium salts and subsequently reduced with lithium aluminium hydride.²³⁸,²³⁹

Scheme 2.2.3. Reagents and conditions: (a) (i) BnBr, CH₂Cl₂, rt, 12 h; (ii) LiAlH₄, THF, reflux, 3 h, 59%; (b) H₂, Pd/C, MeOH, rt, 6 h, 100%.

Therefore isoxazolidine 296 was converted to the quaternary benzyl ammonium salt before reduction with LiAlH₄ to give the N-protected aminoalcohol 300 (Scheme 2.2.3). Unfortunately the observed coupling constants and NOE interactions were not consistent with the expected trans-stereochemistry. The signal at 3.44 ppm appearing as a ddd \((J = 6.6, 5.3, 3.5 \text{ Hz})\), was assigned to the C-3 proton. Also observed were NOE interactions from 5ax-H to 3-H and 3-H to 2-H. These observations were also not consistent with a ring flipped product where the C-2 and C-3 substituents are in the axial positions, indicating that the ring was likely to be in a twisted chair configuration.

Selective N-debenzylation, by hydrogenolysis, gave the free amine (Scheme 2.2.3). Coupling constants and NOE interactions were now consistent with the expected trans-stereochemistry. Signals at 2.75 ppm appearing as a td \((J = 8.7, 2.8 \text{ Hz})\), and at 3.08
ppm as a ddd \((J = 9.4, 8.7, 4.1\, \text{Hz})\), were assigned to the C-2 and C-3 protons respectively. A coupling constant of \(J_{2,3} = 8.7\, \text{Hz}\) corresponds to a dihedral angle of \(\sim 162^\circ\), indicating that the two protons are in a \textit{trans} diaxial orientation, and hence the substituents are in a \textit{trans} diequatorial arrangement (Figure 2.2.6).

![Diagram](image)

**Figure 2.2.6.** Observed NOESY interactions for piperidine 301.

This was further supported by analysis of the NOESY spectrum which showed interactions between 3-H and 5ax-H which was consistent with 3-H being in an axial orientation, and NOE interactions between 2-H, 4ax-H and 6ax-H, confirming the assignment of \textit{anti}-cycloadduct 296 (Figure 2.2.6).

In order to examine the effect of substitution on the amine group on the conformation of the six-membered ring, the quaternary methyl ammonium salt was formed before reducing with LiAlH\(_4\) to give the \(N\)-protected amino-alcohol 302 (Scheme 2.2.4).

![Scheme](image)

**Scheme 2.2.4.** Reagents and conditions: \(a\) (i) MeI, CH\(_2\)Cl\(_2\), rt, 6 h, (ii) LiAlH\(_4\), THF, reflux, 3 h, 56%.

Signals at 3.47 ppm appearing as a ddd \((J = 9.9, 8.6, 4.3\, \text{Hz})\), and at 2.17-2.33 ppm as a multiplet, were assigned to the C-3 and C-2 protons respectively. Although not being able to determine the proton splitting pattern at either the C-2 or C-4 positions meant that coupling constants were ambiguous, a previous discussion of this splitting pattern indicated a \textit{trans}-diequatorial substituted ring.
The NOESY spectrum showed NOE interactions between 3-H and 5ax-H as well as between 4ax-H and both 6ax-H and 2-H. These results are consistent with the H-2 and H-3 being in an axial orientation, and hence the substituents are in a trans-diequatorial arrangement, confirming the assignment of anti-cycloadduct 296 (Figure 2.2.7).

The minor exo-syn cycloadduct, isoxazolidine 297 was also converted to the quaternary benzyl ammonium salt before reduction with LiAlH₄ to give the N-protected amino-alcohol 303 (Scheme 2.2.5).

The NOESY spectrum showed interactions between 2’-H and 6ax-H showed 2-H was in an axial orientation, whilst NOE interactions between 2-H and 3-H indicated that the substituents are in a cis-orientation, confirming the assignment of syn-cycloadduct 297 (Figure 2.2.8).
2.2.2  Cycloaddition with (But-3-en-1-yloxy)(tert-butyl)dimethylsilane

Initially this was attempted with the electron neutral alkene, 3-buten-1-ol 304, however this resulted in low yields and extensive decomposition, observed as charring on the surface of the flask. Previous experience within the Caprio group had demonstrated that 1,3-dipolar cycloaddition of 3-buten-1-ol 304 proceeded poorly and the cycloadducts were often unstable to chromatography, but protection as the silyl ether had a large effect on increasing the yield.240,241

![Scheme 2.2.6. Reagents and conditions: (a) TBSCI, imid., CH₂Cl₂, rt, 24 h, 91%.](image)

Protection of 3-buten-1-ol 304 was carried out according to the literature procedure.242 3-Buten-1-ol, imidazole and tert-butyldimethylsilyl chloride were stirred in dichloromethane at room temperature for 24 h to furnish silyl ether 305 in an excellent yield of 91% (Scheme 2.2.6).

![Scheme 2.2.7. Reagents and conditions: (a) PhMe, 80 °C, 12 h, dr 72:28, 72% overall.](image)

The cycloaddition reaction of nitrone 208 with the silyl protected but-3-en-1-ol 305 was performed in toluene under gentle heating for 12 h. This gave a separable mixture of diastereomeric isoxazolidines 306 and 307 in a ratio of 72:28 respectively and an overall yield of 72% (Scheme 2.2.7). High-resolution mass spectrometry of isoxazolidines 306 and 307 established that the molecular formulae of these products were identical indicating that they were isomeric.

2.2.2.1 Stereochemical Determination of exo-anti Cycloadduct 306

The structure derived from the exo-anti approach of reactants was assigned to the major isoxazolidine 306 on the basis of an analysis of the ¹H NMR, COSY and NOESY NMR spectroscopic data (Figure 2.2.9).
Figure 2.2.9. Observed NOESY interactions for exo-anti cycloadduct 306.

A downfield methine signal attributed to the 2-position, appearing in the $^1$H NMR spectrum as a multiplet from 4.02-4.15 ppm, and the corresponding carbon resonance at 72.3 ppm. This confirmed formation of a 2-substituted cycloadduct, and hence the regiochemistry of the addition. NOE correlations between the proton at 4-H with both $6\text{ax}$-H and $5\text{eq}$-H were consistent with 4-H having an axial orientation. The severe closeness of the $3\text{a}$-H and $7\text{ax}$-H signals at 2.38-2.57 ppm meant that NOE correlations between themselves were masked by the diagonal and interactions with $5\text{ax}$-H were ambiguous for determination of the syn/anti stereochemistry. Fortuitously the $^1$H NMR signal at 3.40 ppm which was attributed to the 4-H proton, was observed as a ddd with coupling constants of $J = 9.0, 8.2, \text{and } 4.2$ Hz which as previously discussed is indicative of a trans-diequatorial substituted ring. Strong NOE correlations were observed between the overlapping signals of $6\text{eq}$-H/$1'$-H and $7\text{ax}$-H/$3\text{a}$-H. Although the interaction of $1'$-H with $3\text{a}$-H would be indicative of the exo-stereochemistry the interaction is equally as likely to be between $6\text{eq}$-H and $7\text{ax}$-H. Gratifyingly the proton at 3-Hb showed a strong NOE interaction with 4-H as well as correlations to 2-H, indicating that this compound is the exo-isomer (Figure 2.2.9).

The stereochemistry of cycloadduct 306 was confirmed by reductive cleavage of the N-O bond and spectroscopic analysis of the resulting amino alcohol 308 (Scheme 2.2.8).

2.2.2.2 Stereochemical Determination of exo-syn Cycloadduct 307

The structure derived from the exo-syn approach of reactants was assigned to the minor isoxazolidine 307 on the basis of an analysis of the $^1$H NMR, COSY and NOESY NMR spectroscopic data (Figure 2.2.10).
The regiochemistry was assigned in the same fashion as the previous isomer. A downfield methine signal appearing in the $^1$H NMR spectrum as a multiplet between 4.24 and 4.36 ppm, and the corresponding carbon resonance at 72.3 ppm was assigned to the 2-position, confirming formation of the 2-substituted adduct. Stereochemical analysis by NOESY was complicated by the overlapping signals of 3-Hb, 6eq-H, 5-H, and 1’-H between 1.45-1.80 ppm. NOE correlations between 4-H and 6ax-H were consistent with 4-H having an axial orientation. Correlations between 3-Ha and 5ax-H as well as 3a-H and 3-Hb which would be indicative of formation of the syn-isomer were not observed due to the signal overlap of 3-Hb and 5-H. Thankfully the 4-H proton showed a strong NOE interaction with 3a-H as well as 6ax-H indicating that this compound is the syn-isomer. Strong NOE correlations between 2-H and 7ax-H confirmed that this compound was the exo-isomer and was supported by interactions between 3-Ha and 2-H. Expected correlations between 1’-H and either 3-Hb or 3a-H were not observed due to overlapping signals of 1’-H (Figure 2.2.10).

These results indicate that the cycloaddition reaction occurred with 100:0 exo/endo-selectivity, 72:28 diastereofacial selectivity, and perfect regioselectivity.

2.2.2.3 Ring Opening of exo-anti Cycloadduct 306

The major cycloadduct 306 was treated with a catalytic amount of indium metal and two molar equivalents of zinc powder in EtOH/NH$_4$Cl under reflux for 12 h to provide adduct 308 in 53% yield, after purification by flash column chromatography (Scheme 2.2.8).

![Diagram of cycloadducts](image-url)
Signals at 2.89 ppm appearing as a ddd, and at 3.22-3.32 ppm as a multiplet, were assigned to the C-2 and C-3 protons respectively. Due to not being able to determine the proton splitting pattern at either the C-3 or C-3’ positions, coupling constants were ambiguous and could not be used for stereochemical determination.

![Diagram](image)

**Figure 2.2.11.** Observed NOESY interactions for piperidine 308.

The NOESY spectrum showed interactions between 3-H and 5ax-H which was consistent with 3-H being in an axial orientation, and NOE interactions between 2-H, 4ax-H and 6ax-H. These results indicate that the C-2 and C-3 protons are in a *trans*-diaxial orientation, and hence the substituents are in a *trans*-diequatorial arrangement, confirming the assignment of *anti*-cycloadduct 306 (Figure 2.2.11).

### 2.2.3 Cycloaddition with Allyl Alcohol

![Scheme](image)

**Scheme 2.2.9.** Reagents and conditions: (a) PhMe, 110 °C, 24 h, dr 12:70:18, 57% overall.

The cycloaddition reaction of nitrone 208 with the electron neutral alkene, allyl alcohol 309, was performed in toluene under reflux for 24 h (Scheme 2.2.9). The crude product was purified by flash column chromatography using CH$_2$Cl$_2$:MeOH (9:1) as eluent to give an isolated product which was visualised under UV irradiation as a single component by TLC. NMR analysis however indicated the presence of multiple products, indicating that a mixture of diastereomers had co-eluted during flash column chromatography. Use of a volatile solvent mixture containing MeOH:Et$_2$O was proved to provide satisfactory separation and gradient elution (0:100 to 1:99) gave a separable mixture of diastereomeric isoxazolidines 310, 311 and 312 in a ratio of 12:70:18 respectively and an overall yield of 57% (Scheme...
2.2.9). High-resolution mass spectrometry of isoxazolidines 310, 311 and 312 established that the molecular formulae of these products were identical indicating that they were isomeric.

2.2.3.1 Stereochemical Determination of exo-anti Cycloadduct 311

The structure derived from the exo-anti approach of reactants was assigned to the major isoxazolidine 311 on the basis of an analysis of the $^1$H NMR, COSY and NOESY NMR spectroscopic data (Figure 2.2.12).

![Diagram of exo-anti cycloadduct 311](image)

**Figure 2.2.12.** Observed NOESY interactions for exo-anti cycloadduct 311.

The regioselectivity was determined from the downfield methine signal attributed to the 2-position, appearing in the $^1$H NMR spectrum as a dq at 4.04 ppm, and the corresponding carbon resonance at 76.0 ppm. This confirmed formation of a 2-substituted cycloadduct. NOE correlations between the overlapping signals of 4-H/1’-H with both 5eq-H and 6ax-H were consistent with 4-H having an axial orientation. Although the 4-H signal is overlapping the proton at the 1’-position, H-1’ is not sufficiently close to both 5eq-H and 6ax-H in any of the expected configurations to be responsible for the NOE, which is therefore attributed to H-4. The overlapping 3a-H/7ax-H at 2.47-2.59 ppm meant that NOE correlations between themselves were masked by the diagonal and interactions with 5ax-H were ambiguous for determination of the syn/anti stereochemistry. The anti-stereochemistry of cycloadduct 311 was determined by reductive cleavage of the N-O bond and spectroscopic analysis of the resulting amino alcohol 313 (Scheme 2.2.10). The unusual grouping of 3-Ha and 3-Hb under the same peak meant that expected key correlations between 2-H and 3-Hb or 4-H to 3-Hb were not able to be clearly distinguished. A NOE interaction was observed between the overlapping signals of 4-H/1’-H and 3a-H/7ax-H and having determined the anti-stereochemistry, the only logical correlation was between 1’-H and 3a-H which is indicative of an exo-approach of the alkene (Figure 2.2.12).
2.2.3.2 Stereochemical Determination of \textit{exo-syn} Cycloadduct 312

The structure derived from the \textit{exo-syn} approach of reactants was assigned to isoxazolidine 312 on the basis of an analysis of the $^1$H NMR, COSY and NOESY NMR spectroscopic data (Figure 2.2.13).

![Diagram of 312]

\textbf{Figure 2.2.13.} Observed NOESY interactions for \textit{exo-syn} cycloadduct 312.

The regiochemistry was assigned in the same fashion as the previous isomer. A downfield multiplet in the $^1$H NMR spectrum between 4.19 and 4.30 ppm, and the corresponding carbon resonance at 76.2 ppm was assigned to the 2-position, confirming formation of the 2-substituted adduct. NOE correlations between the proton at 4-H with both 6ax-H and 5eq-H were consistent with 4-H having an axial orientation. Although the key 3a-H to 4-H interaction was unexpectedly not observed, NOE correlations between 3-Ha and both 5ax-H and 7ax-H indicated \textit{syn}-attack of the alkene. A strong NOE from 2-H to 7ax-H indicates \textit{exo} attack of the alkene as well as confirming the \textit{syn} geometry across the 3a-4 bond. The 3-Hb proton showed a strong NOE interaction with 3a-H as well as correlations to 1′-H, indicating that this compound is the \textit{exo}-isomer. This configuration is supported by the correlation between 3-Ha and 2-H (Figure 2.2.13).

2.2.3.3 Stereochemical Determination of \textit{endo-anti} Cycloadduct 310

The structure derived from the \textit{endo-anti} approach of reactants was assigned to the minor isoxazolidine 310 on the basis of an analysis of the $^1$H NMR, COSY and NOESY NMR spectroscopic data (Figure 2.2.14).
Figure 2.2.14. Observed NOESY interactions for endo-anti cycloadduct 310.

The regiochemistry was assigned in the same fashion as the previous isomer. A downfield multiplet in the $^1$H NMR spectrum between 3.95 and 4.06 ppm, and the corresponding carbon resonance at 76.5 ppm was assigned to the 2-position, confirming formation of the 2-substituted adduct. NOE correlations between the overlapping signals of 4-H/1'-H with both 5eq-H and 6ax-H was consistent with 4-H having an axial orientation. Although the 4-H signal is overlapping the proton at the 1'-position, H-1' is not sufficiently close to both 5eq-H and 6ax-H in any of the expected configurations to be responsible for the NOE, which is therefore attributed to H-4. The overlapping 3a-H/7ax-H meant that NOE correlations between themselves were masked by the diagonal and interactions with 5ax-H were ambiguous for determination of the syn/anti stereochemistry. The proton at 3-Hb showed a NOE interaction with 4-H as well as correlations to one of the protons at the 1'-position, indicating that this compound is the endo-isomer. This is further supported by the interaction between one of the top face protons 3a-H or 3-Ha and 2-H (Figure 2.2.14).

These results indicate that the cycloaddition reaction occurred with 88:12 exo-endoselectivity, 82:18 diastereofacial selectivity, and perfect regioselectivity.

The results closely resemble those obtained by Ooi et al. in their enantioselective synthesis of (+)-febrifugine 1 (Scheme 1.6.6).\(^{183}\) Interestingly the ratio of cycloadducts obtained in the reaction with allyl alcohol was similar regardless of the nitrone protection group. The combination of these results and the expected selectivity of the 1,3-dipolar cycloaddition lends credence to the proposed assignments.
2.2.3.4 Ring Opening of exo-anti Cycloadduct 311

The major cycloadduct 311 was treated with catalytic indium metal and two molar equivalents of zinc powder in EtOH/NH₄Cl under reflux for 12 h to provide adduct 313 in 45% yield, after purification by flash column chromatography (Scheme 2.2.10).

Scheme 2.2.10. Reagents and conditions: (a) In, Zn, EtOH, sat. NH₄Cl, reflux, 12 h, 45%.

Signals at 2.97 ppm appearing as a td, and at 3.30-3.40 ppm as a multiplet, were assigned to the C-2 and C-3 protons respectively. However, not being able to determine the proton splitting pattern at either the C-3 or C-3’ positions meant that the coupling constant at the C-2 position was ambiguous and could not be used for stereochemical determination.

Figure 2.2.15. Observed NOESY interactions for piperidine 313.

The NOESY spectrum showed interactions between 3-H and 5ax-H which was consistent with 3-H being in an axial orientation, and NOE interactions between 2-H, 4ax-H and 6ax-H. These results indicate that the C-2 and C-3 protons are in a trans-diaxial orientation, and hence the substituents are in a trans-diequatorial arrangement, confirming the assignment of anti-cycloadduct 311 (Figure 2.2.15).
2.2.4 Cycloaddition with Ethyl Acrylate

![Scheme 2.2.11 Reagents and conditions: (a) CH₂Cl₂, rt, 3 h, dr 9:60:26:2.5:2.5, 87% overall.]

The cycloaddition reaction of nitrone 208 with the electron poor alkene, ethyl acrylate 314, was performed in CH₂Cl₂ at room temperature for 3 h. This gave a separable mixture of isomeric isoxazolidines 315-319 in a ratio of 9:60:26:2.5:2.5 and an overall yield of 87% (Scheme 2.2.11). High-resolution mass spectrometry of isoxazolidines 315-319 established that the molecular formulae of these products were identical indicating that they were isomeric.

2.2.4.1 Stereochemical Determination of exo-anti Cycloadduct 316

The structure derived from the exo-anti approach of reactants was assigned to the major isoxazolidine 316 on the basis of an analysis of the ¹H NMR, COSY and NOESY NMR spectroscopic data (Figure 2.2.16).

![Figure 2.2.16 Observed NOESY interactions for exo-anti cycloadduct 316.]

The regioselectivity was determined from the downfield methine signal attributed to the 2-position, appearing in the ¹H NMR spectrum as a dd at 4.48 ppm, and the corresponding carbon resonance at 73.0 ppm. This confirmed formation of a 2-substituted cycloadduct. NOE correlations between the proton at 4-H with both 6ax-H and 5eq-H were consistent with
4-H having an axial orientation. The severe closeness of the 3a-H and 7ax-H signals at 2.60-2.71 ppm meant that NOE correlations between themselves were masked by the diagonal and interactions with 5ax-H were ambiguous for determination of the syn/anti stereochemistry. The $^1$H NMR signal at 3.46 ppm attributed to the 4-H proton, was observed as a ddd with coupling constants of $J = 9.1$, 7.8 and 4.2 Hz. As previously discussed this splitting pattern is indicative of a trans-diequatorial substituted ring. Unfortunately assignment of the endo/exo stereochemistry was not possible using coupling constants or 2D-NMR techniques. The unusual grouping of 3-Ha and 3-Hb under the same peak meant that expected key correlations between 2-H and 3-Hb or 4-H to 3-Hb could not to be clearly distinguished (Figure 2.2.16).

The exo-anti stereochemistry of cycloadduct 322 could be inferred by the structural assignments of the endo-anti 315 and exo-syn 317 cycloadducts and the expected selectivity for this cycloadduct. The structure was ultimately determined by reductive cleavage of the N-O bond and spectroscopic analysis of the resulting lactam 322 (Scheme 2.2.12).

### 2.2.4.2 Stereochemical Determination of exo-syn Cycloadduct 317

The structure derived from the exo-syn approach of reactants was assigned to isoxazolidine 317 on the basis of an analysis of the $^1$H NMR, COSY and NOESY NMR spectroscopic data (Figure 2.2.17).

![Figure 2.2.17. Observed NOESY interactions for exo-syn cycloadduct 317.](Image)

The regiochemistry was assigned in the same fashion as the previous isomer. A downfield methine signal occurring in the $^1$H NMR spectrum as a dd at 4.65 ppm, and the corresponding carbon resonance at 73.6 ppm was assigned to the 2-position, confirming formation of the 2-substituted adduct. NOE correlations between the proton at 4-H with both 6ax-H and 5eq-H were consistent with 4-H having an axial orientation. Although no signal was observed between the weak 3a-H resonance and 4-H strong NOE correlations between
3-Ha and 5ax-H indicate syn-attack of the alkene. Strong NOE correlations of 2-H with 7ax-H indicate that this compound is the endo-isomer as well as confirming the syn geometry across the 3a-4 bond (Figure 2.2.17).

2.2.4.3 Stereochemical Determination of endo-anti Cycloadduct 315

The structure derived from the endo-anti approach of reactants was assigned to isoxazolidine 315 on the basis of an analysis of the $^1$H NMR, COSY and NOESY NMR spectroscopic data (Figure 2.2.18).

![Figure 2.2.18. Observed NOESY interactions for endo-anti cycloadduct 315.](image)

The regiochemistry was assigned in the same fashion as the previous isomer. A downfield methine signal occurring in the $^1$H NMR spectrum as a dd at 4.45 ppm, and the corresponding carbon resonance at 73.0 ppm was assigned to the 2-position, confirming formation of the 2-substituted adduct. NOE correlations between the proton at 4-H with both 6ax-H and 5eq-H were consistent with 4-H having an axial orientation. Unfortunately the overlapping signals of the 3a-H and 7ax-H signals at 2.47-2.58 ppm, meant that the axial coupling could not be determined by an analysis of the NOSEY spectrum. The signal due to 5ax-H shows NOE correlations to the 3a-H/7ax-H peak so there possibly could be a correlation between 5ax-H and 3a-H indicating that 3a-H is in an axial position. However this is not unambiguous as the coupling could be purely due to the 5ax-H and 7ax-H. The $^1$H NMR signal at 3.43 ppm which was attributed to the 4-H proton, was observed as a ddd with coupling constants of $J = 9.6, 8.2$ and $4.3$ Hz. As previously discussed this splitting pattern is indicative of a trans-diequatorial substituted ring. An NOE from 4-H to only 3-Hb distinguishes the 3-Ha and 3-Hb signals whilst a strong NOE signal from 2-H to 3-Ha and a weaker one from 2-H to 3a-H indicates endo attack of the alkene (Figure 2.2.18).
2.2.4.4 Stereochemical Determination of 3-Substituted Cycloadducts 318 and 319

Compounds 318 and 319 were isolated as an inseparable 1:1 mixture as determined by integration of the $^1$H NMR spectrum (Figure 2.2.19).

![Figure 2.2.19. Isoxazolidines present in the mixed fraction.](image)

The regioselectivity was determined from the downfield two overlapping sets of non-equivalent methylene proton signals attributed to the 2-position, appearing in the $^1$H NMR spectrum as multiplets at 3.85-3.94 and 3.95-4.17 ppm and as the corresponding carbon resonances at 67.0 and 67.3 ppm. This indicated the formation of two different 3-substituted isomers. Although gross structural determination of the two compounds was possible via COSY and HSQC, the overlap of the majority of key resonances prevented stereochemical determination using NOE interactions. Fortuitously the 4-H proton signals for each product could be easily identified without overlap of other signals. Each compound was observed as a ddd with coupling constants of $J = 4.5, 9.8$ and $9.3$ Hz and $J = 4.1, 7.4$ and $8.3$ Hz respectively which as previously discussed is consistent with a trans-diequatorial substituted ring. The previous isolation of both 2-substituted anti-cycloadducts 315 and 316 confirmed the synthesis of the 3-substituted anti-cycloadducts.

![Figure 2.2.20. Alkene approach to nitrone 208 to give 3-substituted cycloadducts.](image)

Syn-attack of nitrone 208 is highly disfavoured due to steric interactions between the axial substituted benzyloxy side chain and the alkene substituents (Figure 2.2.20)
These results indicate that the cycloaddition reaction occurred with 88.5:11.5 exo/endo-selectivity, 74:26 diastereofacial selectivity, and almost perfect regioselectivity.

2.2.4.5 Ring Opening of exo-anti Cycloadduct 316

The major cycloadduct 316 was treated with catalytic Cu(OAc)$_2$ and 5.6 molar equivalents of zinc powder in acetic acid under reflux for 1 h to provide lactam 322 in 94% yield, after purification by flash column chromatography (Scheme 2.2.12).

Scheme 2.2.12. Reagents and conditions: (a) Zn, Cu(OAc)$_2$, AcOH, reflux, 1 h, 94%.

Reductive ring-opening of isoxazolidine 316 proceeded to give the expected indolizidinone 322 via ring cleavage and concomitant lactamisation. Unlike the previously described ring-opening reactions, the formed product has a rigid structure. The lack of freely rotatable bonds permits the definitive assignment of each of the stereocenters, finally allowing the determination of the stereochemistry of isoxazolidine 316.

Figure 2.2.21. Observed NOESY interactions for indolizidinone 322.

The stereochemistry of the 8-8a bond was determined by analysis of the multiplet at 3.11 ppm which was attributed to the 8-H proton. Observed as a ddd ($J = 3.9, 9.2$ and 10.2), this splitting pattern is consistent with two axial-axial and one axial-equatorial couplings, indicative of a trans-diequatorial substituted ring. This was confirmed by analysis of the NOESY spectra which showed interactions between 8-H and 6ax-H which was consistent with 8-H being in an axial orientation, and NOE interactions between 8a-H, 5ax-H and 7ax-H. These results indicate that the C-8 and C-8a protons are in a trans-diaxial orientation,
and hence the substituents are in a trans-diequatorial arrangement. A strong NOE was also observed between 8a-H and 2-H which due to cyclisation is now on the opposite face of the 5-membered ring, confirming the assignment of anti-cycloadduct 316 (Figure 2.2.21).

Next the reduction of lactam 322 was attempted with LiAlH₄ to give the O-protected dihydroxyindolizidine 324 of which the corresponding free diol has been reported to exhibit moderate inhibition of α-amylloglycosidase. Unexpectedly, this led to indolizidinone 323 being isolated as the sole product (Scheme 2.2.13).

Scheme 2.2.13. Reagents and conditions: (a) LiAlH₄, THF, 65 °C, 12 h, 50%.

Although successful reduction of the lactam was inferred by the appearance of signals in the ¹H and ¹³C NMR spectrum which was attributed to the newly formed C-3 methylene group, it was observed that the C-2 methine signal was now absent. Additionally a new highly downfield quaternary signal at 212.5 ppm had appeared in the ¹³C NMR spectrum. The presence of a ketone was confirmed by infrared analysis of the sample showing a strong absorption at 1759 cm⁻¹. The structure of the product was determined by 2D-COSY analysis which showed the newly formed C-3 methylene was isolated from the series of adjacent proton signals by a newly formed ketone.

Scheme 2.2.14. Proposed mechanism for synthesis of indolizidinone 323.

It is proposed that this product formed via the above mechanism. Electron donation from the nitrogen of the partially reduced lactam to the quaternary amine 325 would proceed with elimination of the chelated hydroxyl group. Base-mediated proton abstraction of 326
would give the enol intermediate 327 which would be in equilibrium with ketone 323 (Scheme 2.2.14).

Gratifyingly the carbonyl of lactam 322 could be converted into the desired methylene group by reduction with BH$_3$·SMe$_2$ (Scheme 2.2.15).

![Chemical Structure](image)

**Scheme 2.2.15. Reagents and conditions:** (a) BH$_3$·SMe$_2$, THF, -15 °C to 66 °C, 4 h; (b) H$_2$, Pd/C, MeOH, rt, 3 h, 89% over two steps.

Gentle reflux of 322 with at BH$_3$·SMe$_2$ in THF for 4 h was expected to give the desired reduction product (Scheme 2.2.15). Accomplishment of the reduction product was implicated by the appearance of signals attributed to the C-3 methylene group and the disappearance of the signal for the C=O group in the $^{13}$C NMR spectrum. However close examination of the $^1$H NMR spectrum showed a broad peak distorting the baseline which could not be attributed to residue water in the sample. Infrared analysis of the sample revealed absorptions at 2382, 2366 and 2274 cm$^{-1}$ which are indicative of B-H stretching indicating the formation of a quaternary borane salt 328 which have been known to not be observed in HRMS. Repetition of the reaction, with hydrogenation of the crude product, gave indolizidine 324 in excellent yield.

Further attempts at O-debenzylation using conventional hydrogenation techniques over Pd/C or Pd(OH)$_2$/C under an atmosphere of hydrogen were not successful and not examined further.

### 2.2.5 Cycloadditions with Acrolein and Acrylonitrile

The 1,3-dipolar cycloaddition of nitrone 208 with electron poor, acrolein and acrylonitrile was attempted in order to further examine the selectivity of electron-deficient alkenes. Although the reactions proceeded smoothly, the formed cycloadducts proved to be unstable to chromatography and these reactions were not examined further.
2.3 Summary of 1,3-Dipolar Cycloadditions

Table 2.3.1 summarises the regio- and stereochemical outcomes of the 1,3-dipolar cycloaddition reactions between nitrone 208 and a range of alkenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R$_1^a$</th>
<th>R$_2$</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Ratio A:B:C:D</th>
<th>Ratio E:F:G:H</th>
<th>Yield$^c$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>CHCl$_3$</td>
<td>20</td>
<td>60</td>
<td>0:65:35:0</td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>OSiMe$_3$</td>
<td>Me</td>
<td>PhMe</td>
<td>48</td>
<td>110</td>
<td>22:49:29:0</td>
<td>-</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>OEt$^b$</td>
<td>H</td>
<td>PhMe</td>
<td>12</td>
<td>45</td>
<td>0:66:44:0</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>(CH$_2$)$_2$OTBS</td>
<td>H</td>
<td>PhMe</td>
<td>12</td>
<td>80</td>
<td>0:72:28:0</td>
<td>-</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>CH$_2$OH</td>
<td>H</td>
<td>PhMe</td>
<td>24</td>
<td>110</td>
<td>12:70:18:0</td>
<td>2.5:2.5:0:0</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>CO$_2$Et</td>
<td>H</td>
<td>CH$_2$Cl$_2$</td>
<td>3</td>
<td>25</td>
<td>9:60:26:0</td>
<td>2.5:2.5:0:0</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>CN</td>
<td>H</td>
<td>CH$_2$Cl$_2$</td>
<td>12</td>
<td>25</td>
<td>Decomposed upon purification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CHO</td>
<td>H</td>
<td>CH$_2$Cl$_2$</td>
<td>12</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Unless otherwise stated cycloadditions were carried out using 3 equiv. of dipolarophile. $^b$Cycloaddition carried out using 10 equiv. of dipolarophile. $^c$Isolated, chromatographically pure products.

The cycloaddition reactions proceeded with excellent exo/endo selectivity ranging from 78:22 to 100:0 and with the exception of entry 6, perfect regioselectivity. The anti/syn selectivity is only moderately in favour of the desired anti-compounds, with diastereomeric ratios ranging from 1.5:1 (R = OEt) to 4.6:1 (R = CH$_2$OH). No trace of the fourth 2-substituted cycloadduct was detected which suggests that the endo-syn approach proceeds via a highly encumbered transition state.
The low stereoselectivity observed in the 1,3-dipolar cycloadditions of six-membered ring nitrones has previously been noted.\textsuperscript{180, 244, 245} Selectivity in these cases may be due to the sterically hindered nature of the sugar derived nitrones and the numerous substituents crowding one side of the ring.

Recently Stecko \textit{et al.} demonstrated that the 1,3-dipolar cycloaddition of nitrone 208 with \(\gamma\)-lactones proceeded with higher diastereoselectivity than that obtained in our study with terminal, acyclic alkenes (Scheme 2.3.1).\textsuperscript{246, 247} These results indicate that the addition of disubstituted or cyclic alkenes might proceed with higher selectivity due to increased steric interactions with the axial substituted benzyloxy side chain.

\begin{center}
\textbf{Scheme 2.3.1.} 1,3-dipolar cycloaddition of nitrone 208 with \(\gamma\)-lactones by Stecko \textit{et al.}
\end{center}

Isomerisation is observed for the reaction of \(\gamma\)-lactones with 5- or 6-membered nitrones under thermodynamic control. Reflux of the \textit{exo-anti} adduct 333 in a solution of toluene for four days yielded an equilibrium mixture of compounds 333 and 334 in a ratio of 2:1 as opposed to the 92:8 obtained under kinetic control.\textsuperscript{246}

Although it remains a possibility that the cycloadditions described in this thesis have proceeded to equilibrium under the thermodynamic conditions used this does not appear to be the case. Of the alkenes examined, only the ethyl acrylate and styrene adducts are recognised as undergoing cycloreversion reactions to regenerate the nitrone functionality. The 1,3-dipolar cycloaddition reaction with styrene has been performed under reflux in solutions of chloroform and toluene for 20 h and 48 h respectively.\textsuperscript{184} Use of the higher boiling solvent and longer reaction time led to an increase in selectivity from 2:1 to 3.3:1 which would not be expected if cycloreversion had occurred. If the reactions had undergone cycloreversion using the outlined conditions it is expected that there would also be evidence in the \textsuperscript{1}H NMR spectrum of the isolated isoxazolidines during sample heating. Close examination of the \textsuperscript{1}H NMR spectrum of the various isoxazolidines demonstrated that only the ethyl acrylate
cycloadducts showed signs of cycloreversion, which was at a temperature far above that at which the reaction was performed.

Additionally, similar selectivities were obtained for the reaction between allyl alcohol and either the O-benzyl 208 or O-silyl nitrene 198 which were performed at reflux and room temperature respectively. The O-benzyl nitrone 208 proceeded with 88:12 exo/endo-selectivity and 82:18 diastereofacial selectivity whilst O-silyl nitrene 198 proceeded with 90:10 exo/endo-selectivity and 74:26 diastereofacial selectivity (Scheme 1.6.6).
2.4 Synthesis and Configuration of O-Silyl Nitrone 198

Despite an increasing amount of literature devoted to the synthetic application of nucleophilic additions to five membered nitrones, use of the six membered analogues remains a relatively poorly explored field. The reactivity of nitrone 208 has previously been probed within the Caprio group by the addition of simple Grignard reagents.\textsuperscript{184} Although demonstrated to be highly \textit{trans}-selective, especially in comparison to the 1,3-dipolar cycloaddition reaction, disappointingly this reaction suffered from low yields and reproducibility.\textsuperscript{184} A possible explanation for the low yields obtained with the \textit{O}-benzyl protected nitrone 208 may be a competing deprotonation reaction occurring at the benzyl group.

Encouraged by the increased selectivity, it was decided to synthesise a differently protected analogue in an attempt to optimise this process. In order to minimise potential issues in the latter steps of any synthetic route, consideration must be given as to the compatibility with organometallic reagents and methods of deprotection. Bulky silyl reagents are particularly attractive due to their robustness to even highly basic reagents such as \textit{n}-butyllithium and the large number of deprotection reactions which may be performed under acidic or basic conditions.

Although five-membered nitrones with a silyloxy group at the C-3 position have been previously prepared, they have not found widespread use due to the scrambling of the silicon moiety to the newly formed hydroxyl groups during reduction of the diester precursor.\textsuperscript{218} The migration of silyl protecting groups between vicinal hydroxyl functionalities under basic conditions is well documented in the literature and is believed to occur \textit{via} an intermolecular process, probably involving formation of a five-membered ring intermediate containing a pentavalent silicon atom.\textsuperscript{248-256}

Goti \textit{et al.} have successfully prepared an enantiomerically pure \textit{O}-silyl protected five-membered cyclic nitrone 338 over four steps, using a deprotection/protection strategy to alter the oxygen substituent (Scheme 2.4.1).\textsuperscript{218}
Reagents and conditions: (a) CF₃COOH, rt, 1 h, 84%; (b) TBSCl, imid., DMF, rt, 1 d, 84%; (c) NH₂OH·HCl, Et₃N, reflux, 2 h; (d) HgO, CH₂Cl₂, rt, 2 h, 64% over two steps.

This was achieved by mesylation of the primary hydroxy groups of tert-butoxybutandiol to give dimesylate 334. Deprotection of dimesylate 334 with trifluoroacetic acid furnished the free secondary alcohol 335, which was subsequently protected as the corresponding silyl ether 336. Dimesylate 336 was then converted into a mixture of separable regioisomeric nitrones 338 and 339 by a one-pot, two step procedure via the formation of hydroxylamine 337 (Scheme 2.4.1).

Although application of this strategy was successful in providing access to a previously unavailable class of nitrone, it was not efficient, requiring two additional steps. To avoid the problems associated with silyl migration and in an effort to avoid the development of a lengthy synthetic route involving numerous protection/deprotection sequences, it was proposed to use a more bulky silyl protecting group which would be more resistant to migration, or a milder reducing agent.

Due to unsuccessful previous attempts within the Caprio group to utilise the tert-butylidimethyl (TBS) protecting group, the tert-butyldiphenylsilyl (TBDPS) protecting group was chosen and it was imagined that synthesis would proceed as previously described with minimal modification. It was also hoped that the increased steric bulk in comparison to the benzyl protection group would act to further block one face of the nitrone, increasing stereoselectivity. The increased lipophilicity of the TBDPS group would also be expected to be of assistance during isolation. Experience gained from the 1,3-dipolar cycloaddition model study had shown that the highly polar amines formed by cleavage of the isoxazolidine ring were difficult to purify by chromatography and may have suffered from poor recovery during extraction.
2.4.1 Silyl Protection and Diol Reduction

Accordingly, the alcohol functionality of hydroxydiester 285 was protected as the corresponding TBDPS ether. Initially, this was attempted in the presence of triethylamine and catalytic DMAP, however the desired product was only obtained in a relatively poor yield of 18%. Substitution for imidazole offered a significant improvement, affording silyl ether 340 in 95% yield (Scheme 2.4.2).

When reduction to diol 341 was attempted using LiAlH₄, none of the desired product was obtained (Scheme 2.4.2). TLC analysis of the reaction mixture indicated that two products had formed, although one was lost upon aqueous workup. It is proposed that the absence of diol 341 was the result of deprotection occurring during reduction. This was supported by analysis of the ¹H NMR spectrum of the sole isolated product which only showed the characteristic signals accounting for the TBDPS group and no signals which could be attributed to the expected diol. Alternate reduction conditions were attempted and the results summarised in Table 2.4.1.

To avoid silyl group migration during the reduction step, a milder reducing agent such as diisobutylaluminium hydride (DIBAL-H) can be used. This method has been investigated by Goti et al. for the synthesis of chiral N-hydroxypyrrolidines. In this approach TIPS protected diethyl malate 342 was reduced to diol 343 with no evidence of migration (Scheme 2.4.3).

Gratifyingly, the reaction of diester 340 with DIBAL-H proceeded to give the desired product in excellent yields, provided the temperature was maintained at -78 °C throughout and below -20 °C during workup. Unfortunately, the use of DIBAL-H for the reduction of
diesters is relatively expensive and not suitable for application on the desired scale owing to the large amounts of inorganic salts formed which make purification difficult.

Despite being the most recognised and frequently utilised hydride reagent, sodium borohydride is not regarded for its ability to reduce the ester functionality. This reactivity can be enhanced by the presence of additives in the reaction mixture. Commonly utilised additives include iodine, which reacts with sodium borohydride in THF to give the active $\text{H}_3\text{B-THF}$ complex,$^{257}$ and lithium, calcium or zinc halides, which act to form their respective saline borohydrides.$^{258,259}$ The use of lithium borohydride as a relatively mild reducing agent has been reported in the literature for the reduction of esters.$^{260}$ In ethereal solvents the reaction proceeded slowly, even under reflux conditions, resulting in decomposition at elevated temperatures. Soai and Ookawa reported that the addition of methanol to the reaction mixture was required to ensure rapid reduction of esters$^{261}$ however this resulted in total silyl migration. *In situ* generation of calcium borohydride using calcium chloride and sodium borohydride in methanol also resulted in migration.

Yamakawa *et al.* demonstrated a unique zinc chloride/sodium borohydride reagent system which showed a greatly enhanced activity towards the reduction of esters in the presence of a tertiary amine.$^{262}$ Use of this system in refluxing THF resulted in the formation of the required diol 341 in high yields with no evidence of migration.

![Reduction of diesters](image)

### Table 2.4.1. Optimisation of diester reduction.

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Solvent</th>
<th>Additive</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiAlH₄</td>
<td>THF</td>
<td>-</td>
<td>rt</td>
<td>12</td>
<td>0</td>
<td>silyl deprotection</td>
</tr>
<tr>
<td>LiAlH₄</td>
<td>Et₂O</td>
<td>-</td>
<td>rt</td>
<td>12</td>
<td>0</td>
<td>silyl deprotection</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>THF</td>
<td>-</td>
<td>-78</td>
<td>12</td>
<td>62-80</td>
<td>quenched &lt; -20 °C</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>THF</td>
<td>-</td>
<td>-78</td>
<td>12</td>
<td>62-80</td>
<td>silyl deprotection</td>
</tr>
<tr>
<td>LiBH₄</td>
<td>THF</td>
<td>-</td>
<td>rt</td>
<td>48</td>
<td>63</td>
<td>mixture of isomers</td>
</tr>
<tr>
<td>LiBH₄</td>
<td>Et₂O</td>
<td>-</td>
<td>rt</td>
<td>48</td>
<td>67</td>
<td>mixture of isomers</td>
</tr>
<tr>
<td>LiBH₄</td>
<td>Et₂O</td>
<td>MeOH</td>
<td>rt</td>
<td>12</td>
<td>90</td>
<td>total migration</td>
</tr>
<tr>
<td>Zn(BH₄)₂</td>
<td>THF</td>
<td>Et₃N</td>
<td>80</td>
<td>3</td>
<td>99</td>
<td>from ZnCl₂</td>
</tr>
</tbody>
</table>
Although the position of the protecting group could not be confirmed by NMR analysis, recrystallisation and analysis of the X-ray crystal structure of 341 provided unequivocal proof of the structure of the desired product (Figure 2.4.1).

2.4.2 Elaboration to Nitrone 198

![Figure 2.4.1 ORTEP representation of diol 341 as determined by X-ray diffraction.](image)

**Scheme 2.4.4. Reagents and conditions:** (a) TsCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, rt, 12 h, 97%; (b) NH$_2$OH·HCl, Et$_3$N, reflux, 4 h, 73%.

Synthesis of the cyclisation precursor was carried out as for O-benzyl protected nitrone 208. Standard tosylation conditions gave 1,5-ditosylate 342 which was followed by treatment with hydroxylamine hydrochloride under basic conditions to give the cyclic nitrone precursor, N-hydroxypiperidine 343 (Scheme 2.4.4).

The final step in the synthesis of nitrone 198 involved oxidation of the N-hydroxypiperidine 343 using an oxidant such as mercury(II) oxide or manganese(IV)
oxide, which have previously been used for the generation of five-membered cyclic nitrones.\textsuperscript{168, 221}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{343}};
\node at (1.5,0) {\textbf{344}};
\node at (3,0) {\textbf{198}};
\node at (0,-0.5) {OH};
\node at (1.5,-0.5) {O\textsuperscript{\prime}};
\node at (3,-0.5) {O\textsuperscript{\prime}};
\node at (0.25,0) {\textbullet{OTBDPS}};
\node at (1.75,0) {\textbullet{OTBDPS}};
\node at (3.25,0) {\textbullet{OTBDPS}};
\node at (1.5,-1) {\footnotesize{80\%}};
\node at (1.5,-1.5) {1:2.2};
\node at (-1,0) {a};
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.4.5. Reagents and conditions:} (a) MnO\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 2 h, 344 25\%, 198 55%.

Elaboration of \textit{N}-hydroxypiperidine 343 was carried out as previously demonstrated to give nitrones 344 and 198 as a mixture of regioisomers in a ratio of 1:2.2, slightly favouring the desired nitrone 198 (Scheme 2.4.5).

The nitrone was found to be unstable at room temperature and decomposes within a couple of days even when stored below -20 °C. At high concentrations, moderate heat caused rapid dimerisation e.g. solvent removal on rotary evaporation. Although this could be prevented by solvent removal at low temperatures (< 18 °C), this restricted the solvent choice to those with low boiling points such as dichloromethane.

Oxidation was also attempted using mercury(II) oxide in dichloromethane at 0 °C.\textsuperscript{155, 168, 221, 263} A similar ratio of the regioisomeric nitrones to that obtained with MnO\textsubscript{2} was observed, but with an inferior yield of 37%. Oxidation using \textit{N}-methylmorpholine-\textit{N}-oxide (NMO) and a catalytic amount of tetra-\textit{N}-propylammonium perruthenate (TPAP) in acetonitrile was also attempted.\textsuperscript{263} Although the reaction was observed to proceed well initially, extensive decomposition of the nitrone was observed, affording no product (Table 2.4.2).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Oxidant} & \textbf{Time (h)} & \textbf{Yield 344 (\%)} & \textbf{Yield 198 (\%)} \\
\hline
MnO\textsubscript{2} & 2 & 25 & 55 \\
HgO & 4 & 12 & 25 \\
NMO/TPAP & - & Decomposed during reaction \\
\hline
\end{tabular}
\caption{Summary of methods of formation for the oxidation of hydroxylamine 343.}
\end{table}
2.4.2.1 Conformation of Nitrone 198

The signal in the $^1$H NMR spectrum of compound 198 at 6.95 ppm which was assigned to C-2, resonates as a doublet, $J_{2,3} = 3.5$ Hz. This coupling constant is similar to that obtained for the $O$-benzyl protected nitrone 208 and indicates that the bulky silyloxy group is in a pseudo-axial orientation under the ring, effectively blocking one face. Thus, it is likely that nucleophilic attack will proceed from the face opposite the silyloxy group to give $\text{trans}$-2,3-disubstituted products.

Due to the similar selectivities obtained for the 1,3-dipolar cycloaddition reaction between allyl alcohol and either the $O$-benzyl 208 or $O$-silyl nitrone 198 (section 2.3) it was decided not to examine this reaction further as it was not believed that selectivity would show a significant improvement.
2.5 Nucleophilic Additions to Nitrone 198

The efficient total synthesis of piperidine-containing alkaloids requires that the products obtained en route to the target be formed in a highly predictable manner. In order for 3-hydroxypiperidine N-oxides to find use as key intermediates, a good knowledge of the stereochemistry of addition of reagents to this compound is necessary. This was initially achieved by probing its reactivity with a range of nucleophiles with varying electronic and steric dispositions.

A selection of 1º, 2º and 3º alkyl, aryl and heteroaryl organometallic species were chosen of which the majority possess functional groups which are able to be further elaborated, thus serving as a starting point for the synthesis of more complicated targets. Where possible, application of differently protected analogues of some of the products formed in this study are discussed in order to highlight the potential utility of this methodology in total synthesis.

2.6 Addition of Grignard Reagents

2.6.1 Addition of Saturated Grignard Reagents

![Scheme 2.6.1](image)

Scheme 2.6.1. Reagents and conditions: (a) MeMgBr, THF, 0 °C, 1 h, 81%; (b) Zn, In, EtOH, sat. NH₄Cl, reflux, 4 h, 81%.

Addition of methylmagnesium bromide to a solution of nitrone 198 in THF at 0 °C afforded the 2,3-trans adduct 345 as sole product in 81% yield (Scheme 2.6.1).

In a similar fashion to the previously described isoxazolidines, the ¹H and ¹³C NMR spectra of the N-hydroxypiperidines exhibited signal line broadening when recorded in CDCl₃ at room temperature, due to slow pyramidal inversion at nitrogen. However in comparison to the isoxazolidines, hydroxylamines were unstable and readily oxidised to nitrones when exposed to oxygen. Due to the difficulties in obtaining sufficient VT-NMR time, it was deemed prudent to reductively cleave the isolated hydroxylamine bond to give
the corresponding amine which displayed sharpened NMR signals and perform 2D-NOESY studies on these compounds.

Hydroxylamine 345 was treated with a catalytic amount of indium metal and five molar equivalents of zinc powder in EtOH/NH₄Cl under reflux for 4 h to provide the corresponding amine 346 in 81% yield (Scheme 2.6.1).

Analysis of the ¹H NMR spectrum of piperidine 346 revealed that the C-2 proton signal resonates at 2.59 ppm as a dq with coupling constants of \( J = 8.4 \) and \( 6.3 \) Hz, and the C-3 proton signal appears at 3.25 ppm as a ddd with coupling constants of \( J = 9.9, 8.4, \) and \( 4.1 \) Hz. These values are consistent with the trans-diaxial orientation of the protons in a six-membered ring.

![Figure 2.6.1. Observed NOESY interactions for piperidine 346.](image)

Analyses of the 2D NOESY spectrum results were also consistent with formation of the trans-diequatorial substituted ring system. Correlations between 2-H and both 4ax-H and 6ax-H as well as between 3-H and 5ax-H provided strong evidence that both the C-2 and C-3 hydrogens are in axial positions, confirming approach of the nucleophile from opposite the bulky OTBDPS group giving the desired trans-configuration across the C-2 to C-3 bond (Figure 2.6.1).

Subsequent additions of Grignard and organolithium reagents proceeded in a similar fashion and are only discussed in full in cases where the observed stereochemistry differed.

![Scheme 2.6.2. Synthetic applications of differentially protected piperidines 347 and 349.](image)
The differentially $N/O$-protected piperidine $347$ has found use in a synthesis of (-)-deoxocassine $348^{264}$ whilst piperidine $349$ has been used in total synthesis of (-)-clavepictine A $350$ and (+)-clavepictine B $14^{265}$ (Scheme 2.6.2).

![Scheme 2.6.3](image)

**Scheme 2.6.3. Reagents and conditions:** (a) EtMgBr, $i$-PrMgCl or PhCH$_2$MgBr, THF, 0 °C, 1 h, $R = $ Et 81%, $R = $ i-Pr 73%, $R = $ CH$_2$Ph 92%; (b) Zn, In, EtOH, sat. NH$_4$Cl, reflux, 4 h, $R = $ Et 84%, $R = $ i-Pr 82%, $R = $ CH$_2$Ph 99%.

Addition of ethyl-, isopropyl-, and benzyl Grignard reagents to a solution of nitrone $198$ in THF at 0 °C afforded 2,3-\textit{trans} adducts as the sole products and was followed by reductive cleavage of the N-O bond of the purified hydroxylamines with catalytic indium metal and zinc powder to afford the corresponding \textit{trans}-amines in excellent yields (Scheme 2.6.3).

### 2.6.2 Addition of Unsaturated Grignard Reagents

The unsaturated side chain introduced by the addition of a vinyl or allyl moiety offers a convenient handle for the introduction of additional functionality - e.g. oxidative cleavage, hydroboration, hydrometallation and chain extension using either Grubb’s RCM or olefination of the corresponding aldehyde.

Addition of a vinyl group was deemed important due to its ability to be readily converted to the hydroxymethyl functional group found in the prosopis alkaloids, \textit{via} oxidative cleavage of the alkene double bond.

![Scheme 2.6.4](image)

**Scheme 2.6.4. Reagents and conditions:** (a) vinylmagnesium bromide, THF, 0 °C, 1 h, 85%; (b) Zn, In, EtOH, sat. NH$_4$Cl, reflux, 4 h, 79%.
Addition of vinylmagnesium bromide to a solution of nitrone 198 in THF at 0 °C afforded the 2,3-trans adduct 357 as the sole product in 85% yield. Reductive cleavage of the N-O bond of the purified hydroxylamine with catalytic indium metal and zinc powder afforded the corresponding amine 358 in 79% yield (Scheme 2.6.4).

Hydroxylamines 359 and 360 were subjected to reductive cleavage of the N-O bond, affording the corresponding amines 361 and 362 in 91% and 81% yields respectively (Scheme 2.6.6).

In contrast to the results obtained thus far, addition of allylmagnesium bromide to a solution of nitrone 198 in THF at 0 °C afforded a separable mixture of the 2,3-trans-adduct 359 and 2,3-cis-adduct 360 as a 86:14 diastereomeric mixture in 81% yield (Scheme 2.6.6). Hydroxylamines 359 and 360 were subjected to reductive cleavage of the N-O bond, affording the corresponding amines 361 and 362 in 91% and 81% yields respectively (Scheme 2.6.6).

High-resolution mass spectrometry of isoxazolidines 361 and 362 established that the molecular formulae of these products were identical, indicating that they were isomeric.
Analysis of the 2D NOESY spectrum of the minor species revealed correlations between 2-H and 3-H which was consistent with formation of the cis-substituted ring system. However the lack of the expected 3-H to 5ax-H interaction and the NOE coupling of 3-H to both of the C-4 protons indicated that a ring flip had occurred and the O-silyl protecting group was now sitting in the axial position (Figure 2.6.2).

Although the lack of selectivity of organometallic reagents containing the allyl functionality cannot be explained, it has been observed both within the Caprio group\textsuperscript{269} and elsewhere in the literature.\textsuperscript{198, 270}

The differentially N/O-protected piperidine \textbf{363} have previously been used in two separate enantioselective synthesis of (+)-febrifugine \textbf{1} (Scheme 2.6.7).\textsuperscript{55, 80}

### 2.6.3 Addition of Aryl Grignard Reagents

An increasing variety of natural polyhydroxylated pyrrolidines possessing aromatic rings at the C-2 position have been reported which include the hypotensive and antibiotic (-)-codonopsine\textsuperscript{271} and the glycosidase inhibitor radicamine A.\textsuperscript{272, 273} Recently, small libraries of synthetic analogues of these compounds have been reported by Tsou \textit{et al.}\textsuperscript{274} and Merino \textit{et al.}\textsuperscript{189} A particular example is a synthetic analogue of radicamine A, containing a 3,4-dimethoxy substituent, which has shown to be a potent inhibitor of α-D-glucosidases (bacillus and yeast) with IC\textsubscript{50} values of 1.8 μM and 1.1 μM respectively.\textsuperscript{274}
Addition of (3,4-dimethoxyphenyl)magnesium bromide or phenylmagnesium chloride to a solution of nitrone 198 in THF at 0 °C afforded 2,3-trans adducts as the sole product in 73% and 80% yield respectively. Reductive cleavage of the N-O bond of the purified hydroxylamines with catalytic indium metal and zinc powder afforded the corresponding amines 365 and 367 in 76% and 97% yields respectively (Scheme 2.6.8).

The differentially N/O-protected piperidine 368 and its enantiomer have found increasing use in a number of syntheses of bioactive alkaloids.

3-Hydroxy-2-phenylpiperidine-1-carboxylate 368 is a powerful intermediate that can be regarded as an advanced precursor for a variety of non-peptide human NK-1 receptor antagonists of Substance P (Scheme 2.6.9). This biomolecule is involved in complex mechanisms related to the transmission of pain information in the central nervous system. Additionally, the enantiomer 549 has been used in the synthesis of the enantiomers of compounds 369-371 as well as (2R,3R)-3-hydroxypropecolic acid 45.66, 276
2.7 Addition of Organolithium Reagents

Next it was proposed to examine the behavior for the nucleophilic addition of organolithium reagents. Although, the addition of Grignard reagents had been demonstrated to proceed with excellent stereocontrol, the additions of certain functional groups such as acetylides and furan are more conveniently obtained as the corresponding lithiates.

2.7.1 Addition of Saturated Organolithium Reagents

Addition of methyl-, n-butyl-, and tert-butyllithium to solutions of nitrone 198 at -78 °C and subsequent reductive cleavage of the N-O bond afforded the 2,3-trans adducts as the sole products (Scheme 2.7.1). The obtained yields are significantly lower than those obtained for the additions of Grignard reagents and show a correlation with the pKa of the organometallic reagent. It was believed that addition of simple alkylolithiums were too highly basic and were most likely resulting in deprotonation of the nitrone at the β-position, forming hydroxylanamines.

2.7.2 Addition of Aromatic and Heteroaromatic Organolithium Reagents

Addition of nitrone 198 to a solution of (4-methoxyphenyl)lithium in THF at -78 °C afforded the 2,3-trans adduct 379 as the sole product in 69% yield. Reductive cleavage of the
N-O bond of the purified hydroxylamine with catalytic indium metal and zinc powder afforded the corresponding amine 380 in 92% yield (Scheme 2.7.2).

Compounds related to 380 have found use in the synthesis of 3-hydroxypipeolic acids 3 and the reduced analogue 2-hydroxymethylpiperidin-3-ol 381 (Scheme 2.7.3).\textsuperscript{77, 277}

\begin{center}
\[ \text{Scheme 2.7.3. Synthetic applications of differentially protected piperidine 382.} \]
\end{center}

\textit{trans}-3-Hydroxypipeolic acid 3 and its reduced analogue 381 have potential use in the preparation of other natural products such as (-)-swainsonine 1\textsuperscript{278} and various prosopis alkaloids.\textsuperscript{102, 279}

The furan and thiophene rings are also synthetic equivalents for the carboxylic acid functionality and the ruthenium-mediated oxidation of such heterocycles is well documented in the literature.\textsuperscript{280, 281} Reduction of the carboxylic acid to the hydroxymethyl group provides an alternate entry point to the synthesis of the prosopis alkaloids while partial reduction to the aldehyde has potential application in chain extension using Wittig olefination.

\begin{center}
\[ \text{Scheme 2.7.4. Reagents and conditions: (a) furan or thiophene, n-BuLi, THF, -78 °C, 1 h, X = O 72%, X = S 85%; (b) Zn, In, EtOH, sat. NH}_4\text{Cl, reflux, 4 h, X = O 94%, X = S 81%.} \]
\end{center}

Addition of nitrone 198 to a solution of 2-lithiofuran or 2-lithiothiophene in THF at -78 °C afforded the 2,3-\textit{trans} adducts as the sole products in 72% and 85% yield respectively. Reductive cleavage of the N-O bond of the purified hydroxylamines with catalytic indium metal and zinc powder afforded the corresponding amines 384 and 386 in 94% and 81% yield respectively (Scheme 2.7.4).
Additionally the furan moiety is present as a side chain in the insecticidal quinolizidine (+)-7-epi-deoxynupharidine. 282

The 3-substituted pyridine fragment is a common functionality in small molecules of biological importance and is found in piperidine and pyrrolidine alkaloids with demonstrated activity against nAChr receptors. Nicotine derivatives may be useful in the treatment of multiple human disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, migraines, depression, and pain. For example, (R)-epibatidine 515, isolated from the skin of an Ecuadorian frog acts as a powerful analgesic via neuronal nACh receptors.

Generation of lithiopyridine from bromopyridines via halogen lithium exchange is known to be difficult due to an extreme sensitivity to temperature. Side reactions include deprotonation, addition to the substrate, lithium bromide elimination to give pyridynes, bromine migration, and ring opening reactions. 283

![Scheme 2.7.5. Reagents and conditions: (a) n-BuLi, 3-bromopyridine, solvent, -78 °C.](image)

While the lithiation reaction has traditionally required extremely low temperatures, recent reports have indicated that the inverse addition of bromopyridine to a solution of n-butyl lithium helps minimise side reactions. 284

Initially the reaction was attempted by the addition of an ethereal solution of nitrone 198 to a solution of 3-pyridyl lithium at -78 °C. Although the lithiate could be successfully prepared, upon addition of the nitrone the solution turned dark green, which was indicative of decomposition of the 3-pyridyl lithium. Believing that the addition of what was a comparably warm solution of nitrone 198 to be the problem, the nitrone 198 was cooled to -78 °C and added dropwise to the lithiated pyridine. Unfortunately, no reaction was observed for these examples and only extensive decomposition occurred.

Cai et al. have reported that 3-pyridyl-lithium can be cleanly generated in a solution of toluene at relatively mild temperatures regardless of order of addition, forming a free flowing suspension of the organolithium which can be reacted as is or dissolved in a small amount of
Unfortunately addition of nitrone 198 as a solution in either THF or toluene was also not successful, resulting in extensive decomposition (Table 2.7.1).

Table 2.7.1. Summary of addition of 3-lithiopyridine to nitrone 198.

<table>
<thead>
<tr>
<th>3-lithiopyridine Solvent</th>
<th>Temp (°C)</th>
<th>Nitrone Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>-78</td>
<td>THF</td>
<td>rt</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>THF</td>
<td>-78</td>
<td>THF</td>
<td>-78</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Et₂O</td>
<td>-78</td>
<td>Et₂O</td>
<td>rt</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Et₂O</td>
<td>-78</td>
<td>Et₂O</td>
<td>-78</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Toluene</td>
<td>-78</td>
<td>Toluene</td>
<td>rt</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Toluene</td>
<td>-78</td>
<td>THF</td>
<td>rt</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Toluene</td>
<td>-78</td>
<td>Toluene</td>
<td>-78</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Toluene</td>
<td>-78</td>
<td>THF</td>
<td>-78</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

It was postulated that in a similar fashion to the simple alkyllithium reagents, 3-pyridyl lithium is too highly basic for addition to nitrone 198 and despite reports of low solubility and reactivity,\(^{284}\) it was decided to attempt formation of the corresponding Grignard reagent.

Scheme 2.7.6. Reagents and conditions: (a) (i) 3-bromopyridine, i-PrMgCl, THF, rt, 1 h; (ii) 198, 0 °C, 6 h, 62%; (b) Zn, In, EtOH, sat. NH₄Cl, reflux, 4 h, 71%.

In accordance with the procedures of Trécourt et al., isopropylmagnesium chloride was added to a solution of 3-bromopyridine in tetrahydrofuran to furnish the pyridylmagnesium chloride as a pale yellow suspension.\(^{283}\) The solution was cooled to 0 °C and a solution of nitrone 198 in tetrahydrofuran was added dropwise to give the 2,3-trans adduct 387 as the sole product in 62% yield. Reductive cleavage of the N-O bond of the purified hydroxylamine with catalytic indium metal and zinc powder afforded the corresponding amine 388 in 71% yield (Scheme 2.7.6).
2.7.3 Addition of Unsaturated Organolithium Reagents

The acetylene group provides a useful handle for the introduction of additional functionalisation - e.g. hydrometallation, carbometallation, and deprotonation/electrophile quench.

![Scheme 2.7.7](image)

**Scheme 2.7.7. Reagents and conditions:** (a) n-BuLi, ethynyltrimethylsilane, THF, -78 °C, 1 h, 81%; (b) Zn, In, EtOH, sat. NH₄Cl, reflux.

Addition of nitrone 198 to a solution of (trimethylsilylethynyl)lithium in THF at -78 °C afforded the 2,3-trans adduct 389 as the sole product in 81% yield (Scheme 2.7.7).

Disappointingly, reductive cleavage of the N-O bond of the purified hydroxylamine with catalytic indium metal and zinc powder proceeded slowly in comparison to the previously described reductions and after two days had not reached completion. Analysis of the NMR spectrum of the purified compounds indicated that N-O cleavage had been partially successful; affording a complex mixture of starting material 389 as well as the protected amine 390 and corresponding deprotected amine (Scheme 2.7.7). The use of stoichiometric indium was also not successful, yielding similar results.

![Scheme 2.7.8](image)

**Scheme 2.7.8. Reagents and conditions:** (a) In, 1% HCl, EtOH, reflux, 2 h, 70%.

Reduction of the N-O bond was finally achieved using conditions developed during the synthesis of (+)-swainsonine (Scheme 3.5.5). Stirring a solution of hydroxylamine 389 in ethanol in the presence of 1% aqueous hydrochloric acid and stoichiometric indium, under reflux, furnished amine 390. Interestingly it was observed that application of the typical workup procedure, by the addition of NaOH to the reaction mixture gave the desilylated
compound, and only by modification of the workup conditions by removal of ethanol and basification in ethyl acetate could we obtain the silylated compound 390 (Scheme 2.7.8).

Scheme 2.7.9. Synthetic applications of differentially protected piperidine 391.

The differentially N/O-protected racemate of piperidine 391 has been used in a racemic synthesis of swainsonine (±)-11 (Scheme 2.7.9). 285

Recently Reißig and co-workers have reported the highly diastereoselective addition of lithiated methoxyallene to chiral five-membered cyclic nitrones which upon a highly selective [3+3] cycloaddition, rearranges to form the 1,2-oxazine ring system. 163 This highly flexible intermediate has been demonstrated to be valuable for the synthesis of furan and pyran derivatives, 286 amino-alcohols 163, 287, 288 and pyrrolidines. 287, 288

Scheme 2.7.10. Reagents and conditions: (a) t-BuOK, 70 °C, 3 h, 69%.

1-Methoxypropa-1,2-diene 393 was prepared by isomerisation of methyl propargyl alcohol, according to literature procedures (Scheme 2.7.10). 289

Scheme 2.7.11. Reagents and conditions: (a) 393, n-BuLi, THF, -78 °C, 1 h, 50%; (b) CH₂Cl₂, rt, 5 d, 98%.

Addition of nitrone 198 to a solution of the lithiated methoxyallene in THF at -78 °C afforded the 2,3-trans adduct 394 as the sole product in 50% yield (Scheme 2.7.11).

In contrast to acyclic nitrones where 1,2-oxazines were isolated directly after reaction with alkoxyallenes, the addition of lithiated methoxyallene to cyclic nitrones permits the
isolation of the intermediate allenyl hydroxylamine.\textsuperscript{163} In this case, although hydroxylamine \textbf{394} was isolatable and an NMR spectrum obtained, the product was observed to be unstable, beginning to slowly cyclise to the 1,2-oxazine \textbf{395} in CDCl\textsubscript{3}. Therefore the crude product was left to stir in a dilute solution of dichloromethane for five days to form the stable cyclic product \textit{via} a [3+3] cycloaddition (Scheme 2.7.11). Initially, this reaction did not proceed cleanly and trace amounts of a second highly polar compound was observed by TLC analysis. This was presumed to be the indolizidine-\textit{N}-oxide which had previously been noted to form where more concentrated reaction mixtures were utilised.\textsuperscript{163} When the reaction was repeated with extra care taken to prevent evaporation the product was obtained as a single compound.

\textit{Dumez et al.} have proposed a reverse Cope elimination mechanism which proceeds through a transient aziridine \textit{N}-oxide intermediate \textbf{396} (Scheme 2.7.12).\textsuperscript{290, 291}

\textbf{Scheme 2.7.12.} Reverse Cope elimination of \textit{\textalpha{}}-allenylhydroxylamines into 1,2-oxazines.

There is still some conjecture as to the actual mechanism and at this time has it not been fully determined.\textsuperscript{292}
2.8 An Explanation of Selectivity

The preference for the obtained anti-stereoselectivity of nucleophilic addition even with small nucleophiles can be explained by stereoelectronic effects rather than being solely attributable to steric effects arising from the presence of the bulky TBDPS group (Figure 2.8.1).

![Figure 2.8.1. Proposed model for the most reactive conformer of nitrone 198.](image)

The reactive conformer of nitrone 198 can be rationalised by application of a Felkin-Anh-type transition state where the axial disposition of the C-O bond of the silyloxy group maximises $\pi^*_{(\text{nitrone})}\sigma^*_{(\text{C-O})}$ overlap (C≡N LUMO - C-O anti-bond), leading to a lowering in energy of the nitrone LUMO orbital. Thus, the nucleophile preferentially attacks this conformer. Approach of the nucleophile from the least hindered side, opposite the TBDPS group gives rise to the selectivity observed (Figure 2.8.1).
2.9 Summary of Nucleophilic Additions to Nitrone 198

Table 2.9.1 summarises the regio- and stereochemical outcome of the nucleophilic addition to nitrone 198.

Table 2.9.1. Summary of nucleophilic additions to nitrone 198.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Product</th>
<th>A (%)</th>
<th>B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me−MgBr</td>
<td><img src="image" alt="imidazole" /></td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Me−Li</td>
<td><img src="image" alt="imidazole" /></td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>MgBr</td>
<td><img src="image" alt="pipercidin" /></td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>MgCl</td>
<td><img src="image" alt="pipercidin" /></td>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>Ph-MgCl</td>
<td><img src="image" alt="pipercidin" /></td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>1-alkene-MgBr</td>
<td><img src="image" alt="imidazole" /></td>
<td>85</td>
<td>79</td>
</tr>
<tr>
<td>1,3-alkene-MgBr</td>
<td><img src="image" alt="imidazole" /></td>
<td>81</td>
<td>91</td>
</tr>
<tr>
<td>Ph-MgCl</td>
<td><img src="image" alt="pipercidin" /></td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>Br-Mg</td>
<td><img src="image" alt="pipercidin" /></td>
<td>73</td>
<td>97</td>
</tr>
</tbody>
</table>

Table continued:

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Product</th>
<th>A (%)</th>
<th>B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl-Mg</td>
<td><img src="image" alt="imidazole" /></td>
<td>62</td>
<td>71</td>
</tr>
<tr>
<td>1-alkene</td>
<td><img src="image" alt="imidazole" /></td>
<td>50</td>
<td>73</td>
</tr>
<tr>
<td>1,3-alkene</td>
<td><img src="image" alt="imidazole" /></td>
<td>31</td>
<td>93</td>
</tr>
<tr>
<td>Ph</td>
<td><img src="image" alt="pipercidin" /></td>
<td>69</td>
<td>92</td>
</tr>
<tr>
<td>1-alkene</td>
<td><img src="image" alt="imidazole" /></td>
<td>72</td>
<td>94</td>
</tr>
<tr>
<td>1,3-alkene</td>
<td><img src="image" alt="imidazole" /></td>
<td>85</td>
<td>81</td>
</tr>
<tr>
<td>Ph</td>
<td><img src="image" alt="pipercidin" /></td>
<td>81</td>
<td>70</td>
</tr>
<tr>
<td>1,3-alkene</td>
<td><img src="image" alt="imidazole" /></td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

*aAddition carried out at 0 °C in THF (M = MgBr/MgCl) or at -78 °C in THF (M = Li). *bStereochemistry determined by 2D-NOESY studies performed on piperidines. *cIsolated, chromatographically pure products. *dThe trans-product was exclusively obtained in all cases except allylMgBr (dr = 86:14).

We have demonstrated that 3-silyloxytetrahydropyridine N-oxide 198 undergoes highly diastereoselective nucleophilic addition with a wide range of Grignard reagents and
organolithium species, in good to excellent yield. Although the addition with allylmagnesium bromide proceeds with 86:14 trans:cis ratio, in all other cases the trans-isomer is the only product isolated (Table 2.9.1).
3. Application to Synthesis

In addition to the preparation of 3-hydroxypiperidine-based libraries, the developed methodology has potential utility in the synthesis of a number of bioactive alkaloids. This flexibility was demonstrated by the development of a total synthesis of the L-rhamnosidase inhibitor (+)-swainsonine 397 as well as a formal syntheses of the quinolizidine (-)-epiquinamide 529 and a variety of substance P antagonists from a single nitrone intermediate 198.

3.1 A Brief Overview of Swainsonine

Carbohydrate mimics, in which the ring oxygen of a sugar is replaced by nitrogen, have considerable therapeutic potential due to their inhibition of glycosidases and other sugar processing enzymes.\(^\text{293, 294}\)

\[
\begin{align*}
\text{(-)-swainsonine 11} & \quad \text{(+)-swainsonine 397}
\end{align*}
\]

\textbf{Figure 3.1.1.} Structures of (-)-swainsonine 11 and (+)-swainsonine 397.

(-)-Swainsonine 11 is a naturally occurring, trihydroxylated indolizidine alkaloid, which has been isolated from a variety of sources, including the fungi \textit{Rhizoctonia leguminicola}\(^\text{17, 18}\) and \textit{Metarhizium anisopliae},\(^\text{295-297}\) the legume of \textit{Swainsona canescens},\(^\text{298}\)\(^\text{299}\) plant cultures of normal and transformed roots of \textit{Swainsona galegifolia}\(^\text{300}\) and the spotted locoweed \textit{Astragalus lentiginosus} (Figure 3.1.1).\(^\text{301, 302}\) This potent mannosidase inhibitor has been found to be an effective inhibitor of lysosomal \(\alpha\)-mannosidase\(^\text{303-306}\) and Golgi \(\alpha\)-mannosidase II,\(^\text{307-309}\) which are involved in cellular degradation of polysaccharides and processing asparagine-linked glycoproteins respectively. Inhibition of these enzymes leads to disrupted polysaccharide metabolism and glycoprotein biosynthesis in the cell which is the basis for the potential antitumour-proliferative,\(^\text{310-315}\) anticancer,\(^\text{316-330}\) anti-metastatic\(^\text{331-339}\) and immuno-regulating activities\(^\text{340-342}\) exhibited by (-)-swainsonine 11.

By contrast, the unnatural isomer (+)-swainsonine 397 exhibits potent and specific inhibition of naringinase (an L-rhamnosidase),\(^\text{343}\) an enzyme which catalyses the hydrolytic cleavage of terminal \(\alpha\)-L-rhamnose from a large number of glycosides (Figure 3.1.1).\(^\text{344}\) The
inhibition potency and affinity of (+)-swainsonine was determined by competitive assays on naringinase isolated from *Penicillium decumbens*, which is known to possess both α-L-rhamnosidase and β-D-glucosidase activities.\(^{343, 345}\) (+)-Swainsonine \(397\) was demonstrated to be a highly specific, potent inhibitor of naringinase \((\text{IC}_{50} = 0.3 \, \mu\text{M}, \text{K}_i = 0.45 \, \mu\text{M})\) whereas (-)-swainsonine \(11\) showed no inhibitory activity toward this enzyme.\(^{343}\)

![Figure 3.1.2. Structural similarities between (+)-swainsonine 397 and L-rhamnose sugars.](image)

(+)-Swainsonine \(397\) owes its inhibitory effect on naringinase to its structure, which closely mimics L-rhamnose sugars (L-rhamnofuranose \(398\) and L-rhamnopyranose \(399\)) and the cis-diol configuration which has been demonstrated to be crucial in naringinase inhibition (Figure 3.1.2).\(^{343, 346}\)

![Figure 3.1.3. Structural similarities between protonated (+)-swainsonine 400 and rhamnosyl cation 401.](image)

This inhibitory activity is speculated to be due to protonated (+)-swainsonine \(400\) functioning as a transition state mimic for the rhamnosyl cation \(401\), a proposed intermediate for the enzymatic hydrolysis of L-rhamnose (Figure 3.1.3).\(^{18, 347}\)

It is believed that inhibition of cellular processes which utilise L-configured, non-mammalian sugars, may be effective in the treatment of diseases caused by mycobacteria such as tuberculosis and leprosy.\(^{348-350}\) Due to the absence of L-rhamnose sugars in human cells, it is widely regarded that imino sugar mimics would make desirable drug candidates exhibiting mycobacterium toxicity without affecting mammalian cells.\(^{351-353}\)

The cell wall of mycobacteria primarily consists of three covalently linked macromolecules: an outer lipid layer of mycolic acids, connected to an inner peptidoglycan via an arabinogalactan polysaccharide.\(^{354, 355}\) A key feature of this structure which ensures the integrity of the cell wall, making it essential for cell growth and survival, is the disaccharide
linker region between the arabinogalactan polysaccharide and peptidoglycan regions (Figure 3.1.4).\textsuperscript{355, 356}

![Diagram of mycobacterial cell wall components](image)

**Figure 3.1.4.** Structure of the mycobacterial cell wall, emphasising the position and role of the linker region.

The linker is a disaccharide phosphate unit, consisting of L-rhamnopyranose (highlighted) glycosidically bonded to an N-acetylated D-galactose (GalNAc) followed by a phosphate unit (Figure 3.1.4).\textsuperscript{352, 357} The L-rhamnopyranose unit is introduced into the mycobacterial cell wall \textit{via} the sugar nucleotide deoxythymidine diphosphorhamnose (dTDP-L-rhamnose) and it is possible that novel chemotherapeutic approaches could be developed based on either the inhibition of dTDP-L-rhamnose biosynthesis or its incorporation into the mycobacterial cell wall.

Biosynthesis of dTDP-L-rhamnose from dTDP-glucose-1-phosphate proceeds \textit{via} the multi enzyme, dTDP-L-rhamnose pathway,\textsuperscript{353, 355, 358} and is followed by attachment of GlcNAc and linking of arabinogalactan and peptidoglycan.\textsuperscript{351, 359} Studies into the inhibition of dTDP-L-rhamnose biosynthesis have demonstrated a possible correlation between naringinase inhibition and dTDP-L-rhamnose biosynthesis\textsuperscript{357} indicating that (+)-swainsonine \textsuperscript{397} has potential to disable the mycobacterial production of dTDP-rhamnose, resulting in malformation of the linker region between arabinogalactan and peptidoglycan, leading to a weakened cell wall and ultimately cell death.\textsuperscript{294}

Another therapeutic target for disabling mycobacterial cell wall biosynthesis is inhibition of rhamnosyltransferase (RhamT) which incorporates L-rhamnose into the mycobacterial cell wall by glycosylation of the GlcNAc-diphosphoprenyl acceptor by dTDP-rhamnose.\textsuperscript{358} It is speculated that (+)-swainsonine \textsuperscript{397} may possess the ability to inhibit this enzyme by mimicking the dTDP-rhamnose donor substrate or the transition state, achieving synergism with L-rhamnosidase inhibition, further weakening the integrity of the mycobacterial cell wall.\textsuperscript{359}
3.2 Previous Synthetic Studies Toward (+)-Swainsonine

The large number of both racemic and enantiopure syntheses that have been reported over the last two decades stand as testament to the attractiveness of (-)-swainsonine as a synthetic target. To date there have been over 35 syntheses and have been comprehensively reviewed by Nemr in 2000 and Pyne in 2005. However it is beyond the scope of this thesis to discuss these, and as such an overview of those with direct relevance to this body of work will be discussed.

Although a significant amount of research has been directed towards the synthesis of (-)-swainsonine and its analogues, only modest attention has been directed towards the unnatural isomer (+)-swainsonine. Since the first total synthesis by Hirama and co-workers in 1995, there have been six published syntheses which the following section covers in detail.

3.2.1 Synthesis of (+)-Swainsonine by Oishi et al.

The first total synthesis of (+)-swainsonine utilised chiral pool starting material and a highly stereoselective Upjohn dihydroxylation of an indolizidine double bond as key steps to introduce the required stereocenters.

![Scheme 3.2.1](image)

**Scheme 3.2.1.** Reagents and conditions: (a) NaH, PMBCl, THF, DMF, 76%; (b) NH₄OH, Et₂O, 0 °C, 79%; (c) TBSCI, imid., DMF, 91%; (d) KH, Boc-S, THF, -30 °C to 5 °C, 81%; (e) DDQ, CH₂Cl₂, H₂O, 94%; (f) DMSO, (COCl)₂, CH₂Cl₂, Et₃N, 81%; (g) (CF₃CH₂O)₂P(O)CH₂CO₂Me, 18-crown-6, KHMDS, PhMe, -78 °C, 85% (Z/E = 4.3:1); (h) TMSI, CHCl₃, 65%; (i) t-BuOK, THF, -55 °C, 80% (dr > 50:1).

Protection of L-glutamic acid-derived butyrolactone as the PMB ether and ring opening in the presence of ammonium hydroxide was followed by protection of the newly formed secondary alcohol to give amide 403. Boc-protection and PMB-deprotection to expose the primary alcohol was followed by oxidation to the corresponding aldehyde and Wadsworth-Emmons type olefination to give the cyclisation precursor, mainly as the desired (Z)-enoate. After separation of the isomers and Boc-deprotection, base-catalysed
intramolecular conjugate addition of (Z)-404 gave disubstituted lactam 405, predominantly as the trans-diastereomer (dr > 50:1) (Scheme 3.2.1).

Scheme 3.2.2. Reagents and conditions: (a) LiCHBr₂, THF, -90 °C, then n-BuLi, -90 °C, 59%; (b) K₂CO₃, MeOH, 92%; (c) MsCl, Et₃N, CH₂Cl₂, 94%; (d) KH, THF, 87%; (e) PTSA, acetone, 77%; (f) NaBH₄, MeOH, 0 °C, 98%; (g) NaH, THF, CS₂, then MeI, 98% (α:β = 1:6.7); (h) 180 °C, 68%; (i) cat. OsO₄, NMO, acetone, H₂O, rt, 82%; (j) CF₃CO₂H, THF, H₂O, then Ac₂O, py, CH₂Cl₂, 84% (β:α = 6.9:1); (k) BH₃·THF, reflux, K₂CO₃, MeOH, then 2 M HCl, reflux, 85%.

Homologation to bromoketone 406 was achieved using dibromomethyl lithium. The bromoketone 406 was then converted to the corresponding mesylate 407. Subsequent base-catalysed cyclisation and regeneration of the ketone afforded bicyclic lactam 408 which was stereoselectively reduced to give alcohol 409 (α:β = 1:6.7). Alkene 411 was accessed by treatment of alcohol 409 with carbon disulphide and methyl iodide to form xanthate 410, followed by heating to effect elimination. Upjohn dihydroxylation of 411 proceeded selectively from the β-face to yield a mixture of diastereomers in favour of the desired isomer 412 (β:α = 6.9:1). Finally, reduction of the β-isomer 413 and base mediated hydrolysis of the acetate groups to furnish (+)-swainsonine 397 (Scheme 3.2.2).
3.2.2 Syntheses of (+)-Swainsonine by Fleet and Co-workers.

Fleet and co-workers developed two separate syntheses of (+)-swainsonine 397, utilising chiral pool derived furanose sugar lactones as starting materials.\textsuperscript{343,362}

\textbf{Scheme 3.2.3. Reagents and conditions:} (a) (i) NaBH\textsubscript{4}, H\textsubscript{2}O; (ii) NaCN, H\textsubscript{2}O, rt, 68 h, then reflux, 23 h, 19%; (b) H\textsubscript{2}SO\textsubscript{4}, acetone, rt, 16 h, 73%; (c) (i) LiBH\textsubscript{4}, THF; (ii) MsCl, py, DMAP, 91%; (d) BnNH\textsubscript{2}, 110 °C, 2 d, 93%; (e) PTSA, MeOH, 68%; (f) MsCl, py, DMAP, 91%; (g) H\textsubscript{2}, Pd-black, EtOH, NaOAc, 62%; (h) AcOH:H\textsubscript{2}O (8:2), 85%; (i) Im\textsubscript{2}CS, PhMe, then TBSOTf, py, CH\textsubscript{2}Cl\textsubscript{2}, 72%; (j) (EtO)\textsubscript{3}P, reflux, 76%; (k) H\textsubscript{2}, Pd-black, EtOAc, 89%; (ii) CF\textsubscript{3}COOD:D\textsubscript{2}O (1:1), 74%.

Protected triacetonide lactone 415 was obtained by lactone reduction and one-carbon elongation of heptonolactone 414 using sodium cyanide followed by hydrolysis and acetonation.\textsuperscript{363} Reductive ring opening of glucoheptonolactone 415 and mesylation of the resultant diol gave 416. Reflux with benzylamine gave pyrrolidine 417. Removal of the terminal isopropylidene group and regioselective mesylation of the terminal hydroxyl group was followed by intramolecular cyclisation which occurred upon N-deprotection, yielding the bicyclic diacetonide 418.\textsuperscript{364} Regioselective hydrolysis of the six-membered ring acetonide was followed by treatment of the syn-diol with 1,1′-thiocarbonylidiimidazole and protection of the remaining hydroxyl group as a TBS ether to furnish thiocarbonate 420. Corey-Winter fragmentation of the thiocarbonate yielded unsaturated indolizidine 421 which was hydrogenated and globally deprotected to give (+)-swainsonine 397 (Scheme 3.2.3).
Fleet and co-workers developed a second, highly efficient synthetic route towards (+)-swainsonine 397 again by making use of a chiral pool derived key intermediate 422 as starting material.

Scheme 3.2.4. Reagents and conditions: (a) (i) NaIO₄, MeOH, H₂O; (ii) Bu₃P=CHCO₂Me, 81% over 2 steps; (b) H₂, Pd(OH)₂/C, dioxane:H₂O (6:1), 95%; (c) BH₃·THF, then TFA:H₂O (9:1), 82%.

Diol 423 was prepared from the readily available glucoheptonolactone 422 in three steps. Periodate cleavage of diol 423 gave the corresponding aldehyde which upon in situ Wittig olefination afforded the (E)-alkene 424. Hydrogenation/hydrogenolysis proceeded with concomitant lactamisation to give indolizidine 425 which upon subsequent lactam reduction and deprotection furnished (+)-swainsonine 397 (Scheme 3.2.4).
3.2.3 Synthesis of (+)-Swainsonine by Guo and O’Doherty

Contrary to the previous three syntheses, the approach developed by Guo and O’Doherty used commercially available achiral furan and γ-butyrolactone 427 as starting materials. Asymmetry was introduced by Upjohn dihydroxylation and a catalytic asymmetric reduction to enantiodivergently synthesise precursors to both (+)- and (-)-swainsonine.\textsuperscript{347, 369}

Scheme 3.2.5. Reagents and conditions: (a) 2-lithiofuran, THF, -78 °C, 5 h, 74%; (b) TBSCl, imid., DMF, 0 °C, 20 min, then rt, overnight, 98%; (c) (S,S)-Noyori’s catalyst 434 (5 mol %), HCO\textsubscript{2}H, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, rt, 24 h, 89%; (d) NBS, NaHCO\textsubscript{3}, NaOAc, THF:H\textsubscript{2}O (4:1), 0 °C, 30 min, 84%; (e) Boc\textsubscript{2}O, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C, 14 h, 85% (α/β = 8:1); (f) BnOH, Pd\textsubscript{2}(dba)\textsubscript{3}-CHCl\textsubscript{3} (2.5 mol %), PPh\textsubscript{3} (5 mol %), CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to rt, 2 h, 88%; (g) NaBH\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}:MeOH (1:1), -78 °C, 4 h, 94%; (h) MeCO\textsubscript{2}Cl, DMAP, py, CH\textsubscript{2}Cl\textsubscript{2}, rt, 24 h, 72%; (i) [Pd(allyl)Cl\textsubscript{2}]-dppb (1:4), TMSN\textsubscript{3}, THF, 50 °C, 24 h, 77%.

Treatment of γ-butyrolactone 426 with a solution of 2-lithiofuran afforded the furfuryl ketone which was protected as the corresponding TBS ether to give acylfuran 427. Asymmetric reduction of the ketone moiety was achieved via catalytic transfer hydrogenation in the presence of (S,S)-Noyori’s catalyst 434 to furnish (S)-alcohol 428 with excellent enantiopurity. Ring expansion of furyl alcohol 428 under Achmatowicz conditions gave pyranone 429 as a mixture of anomers. Diastereoselective protection of the anomeric alcohol was achieved via a two-step acylation/Pd-catalyzed glycosylation sequence. Treatment of hemiacetal 429 with Boc\textsubscript{2}O resulted in diastereoselective formation of Boc-protected pyranone 430 (α/β = 8:1). Benzylation of the α-pyranone proceeded under O’Doherty’s palladium glycosylation conditions to afford the benzyl-protected pyranone 431 as a single diastereomer. Diastereoselective reduction of ketone 431 to the equatorial allylic alcohol was followed by acylation with methyl chloroformate to give the corresponding mixed carbonate 432. Finally, carbonate 432 was converted to the allylic azide via a π-allylpalladium
intermediate, which was exposed to trimethylsilylazide to form azide 433 as a single regio- and stereoisomer (Scheme 3.2.5).  

Scheme 3.2.6. Reagents and conditions: (a) TBAF, THF, rt, 12 h, 99%; (b) MsCl, Et3N, CH2Cl2, 0 °C, 30 min, 99%; (c) OsO4 (1 mol %), NMO, t-BuOH:acetone (1:1), 0 °C, 24 h, 93%; (d) H2, Pd(OH)2/C, EtOH, rt, 3 d, 88%; (e) OsO4 (1 mol %), NMO, t-BuOH:acetone (1:1), 0 °C, 24 h, 92%; (f) Me2C(OMe)2, PTSA, acetone, 0 °C, 30 min, 97%; (g) TBAF, THF, rt, 12 h, 98%; (h) MsCl, Et3N, CH2Cl2, 0 °C, 30 min, 99%; (i) H2, Pd(OH)2/C, EtOH:THF (1:1), rt, 3 d, 85%; (j) 6 M HCl, THF, rt, overnight, then ion exchange (Dowex 1X8 200 OH\(^{-}\) form), 95%.

The synthesis was completed by silyl deprotection and subsequent mesylation to yield mesylate 435. The desired manno-stereochemistry was introduced by stereoselective Upjohn dihydroxylation of alkene 435 yielding syn-diol 436. An exhaustive global hydrogenolysis/alkylation/reductive amination sequence was utilised for the one pot synthesis of (+)-swainsonine 397 from azidosugar 436. Initial azide reduction and subsequent intramolecular alkylation gave compound 437 which underwent hydrogenolysis to form aldehyde 438 via the intermediate hemiacetal. Finally reductive amination of aldehyde 438 formed swainsonine via the imine intermediate. Alternatively, the incorporation of an acetonide protecting group meant that a protected form of (+)-swainsonine 397 could also be synthesised. Stereoselective Upjohn dihydroxylation of allylic azide 433 and diol protection as the acetonide gave protected azide 439. Conversion by means of an analogous end-game sequence (vide supra) afforded the ketal-protected intermediate 440 which was easily deprotected to furnish (+)-swainsonine 397 (Scheme 3.2.6). In similar fashion, the natural enantiomer was obtained from ent-428 by substitution for (R,R)-Noyori’s catalyst.  

126
3.2.4 Synthesis of (+)-Swainsonine by Alam et al.

Vankar and co-workers developed a synthesis making use of commercially available D-glucose 441 to synthesis key epoxide intermediate 443. The indolizidine core was accessed utilizing two successive intramolecular S$_N$2 cyclisations to build the bicyclic core.\(^{371}\)

Diol 442 was prepared from D-glucose in four steps according to literature procedures.\(^{372-375}\) Conversion of diol 442 into epoxide 443 was achieved in three steps with the required inversion of the C-5 stereocenter. Regiospecific ring opening of epoxide 443 with allylmagnesium chloride and subsequent protection of the free alcohol as the benzyl ether gave compound 444. Cleavage of the isopropylidene group proceeded with concomitant introduction of the anomeric methoxy group and was followed by benzyl protection of the free hydroxy group to give lactone 445. Acid-catalysed acetal hydrolysis and reduction of the subsequent hemiacetal was followed by conversion of the formed diol to the corresponding dimesylate 446. Alkene cleavage gave the corresponding aldehyde which was reduced to give hydroxy dimesylate 447. Heating of 447 with neat benzylamine furnished pyrrolidine 448 via an intramolecular S$_N$2 cyclisation. The second ring was formed by a second intramolecular
cyclisation which occurred upon hydrogenolysis to furnish (+)-swainsonine 397 (Scheme 3.2.7).

### 3.2.5 Synthesis of (+)-Swainsonine by Chen et al.

Chen and Tsai have utilised radical cyclisation of a chiral pool derived acylsilane 454 and a highly stereoselective Upjohn dihydroxylation of an indolizidine double bond as key steps.376

![Scheme 3.2.8](image)

**Scheme 3.2.8. Reagents and conditions:** (a) PPh₃, DIAD, phthalimide, THF, rt, 3 h, 95%; (b) (i) hydrazine, THF, 55 °C, 4 h; (ii) 2B4, (COCl)₂, DMF, CH₂Cl₂, 0 °C to rt, 2 h, then Et₃N, THF, -78 °C to rt, overnight, 65%; (c) t-BuOK, THF, -78 °C to -40 °C, 1.5 h, 91%; (d) (i) NaBH₄, MeOH:THF (7:1), -23 °C, 10 min; (ii) PTSA, PhSH, CH₂Cl₂, rt, overnight, 73%; (e) BzCl, DMAP, Et₃N, CH₂Cl₂, rt, 2 h, 95%; (f) Phi(OOCOCF₃)₂, NaHCO₃, H₂O, MeCN, rt, 23 min, 80%; (g) (i) Bu₃SnH, ACCN, PhMe, reflux, 1 h; (ii) TBAF, THF, rt, 35 min, 86%; (h) Martin sulfurane, THF, rt, overnight, 73%; (i) (i) OsO₄, NMO, acetone:H₂O (1:0.7), 0 °C, 2 h; (ii) Ac₂O, DMAP, Et₃N, CH₂Cl₂, 0 °C to rt, 5 h, 55% (dr = 10:1); (j) BH₃·Me₂, THF, rt, overnight, 80%; (k) NaOH, MeOH, rt, 1 h, 87%.

The required amine functionality was introduced via Mitsunobu coupling of alcohol 449 with phthalimide, affording imide 450. Deprotection and addition of the acid chloride, formed from L-glutamic acid-derived lactone 284, furnished lactone 451 which upon treatment with base, rearranged to glutarimide 452. Selective reduction of the C-2 carbonyl group was followed by reaction of the crude carbinol with thiophenol to give sulfide 453 as a mixture of diastereomers. Protection of the hydroxyl as the benzoyl-ether and hydrolysis of the dithiane moiety gave cyclisation precursor 454. Radical cyclisation of acylsilane 454 proceeded with high selectivity to give the desired trans-substituted indolizidine which was
desilylated to afford alcohol 455 as a pair of C-1 epimers. Dehydration with Martin sulfurane to olefin 456 was followed by diastereoselective Upjohn dihydroxylation and acetylation to give ester 457 as a mixture of two diastereomers. Reduction of the lactam to permit purification was followed by basic hydrolysis of the major isomer to give (+)-swainsonine 397 (Scheme 3.2.8).

### 3.2.6 Synthesis of (+)-Swainsonine by Chooprayoon et al.

Pohmakotr and co-workers developed a synthesis utilising a chiral pool starting material, chiral auxiliaries and a selective Upjohn dihydroxylation to introduce the required stereocenters. 377

![Chemical reaction diagram](image)

**Scheme 3.2.9. Reagents and conditions:** (a) (i) (COCl)₂, DMF, CH₂Cl₂, rt, 3 h; (ii) H₂N(CH₂)₃SPh, Et₃N, CH₂Cl₂, 0 °C to rt, 16 h, 67%; (b) t-BuOK, THF, -78 °C, 3 h, 72%; (c) TBSCl, imid., DMAP, CH₂Cl₂, rt, overnight, 87%; (d) NaIO₄, MeOH, H₂O, 0 °C to rt, 12 h, 90%; (e) (i) LiHMDS, -78 °C to rt, 16 h; (ii) PTSA, CH₂Cl₂, reflux, 16 h, 164 15%, 165 65%.

Derivatisation of the L-glutamic acid-derived lactone 284 as the acid chloride was followed by treatment with 3-phenylsulfanyl-1-aminopropane to afford amide 458. Lactone ring opening with potassium tert-butoxide and subsequent ring closure yielded the hydroxyimide which was protected as the TBS-ether. Oxidation of sulfide 459 furnished the chiral sulfanylylimide 460 as an inseparable mixture of two diastereomers. Cyclisation proceeded via intramolecular nucleophilic attack of the α-sulfenyl carbanion intermediate 462, formed by deprotonation of enolate 461, yielding hydroxyindolizidine amide 463 as a
mixture of diastereomers. This reaction took place chemoselectively at the C-2 carbonyl due to the temporary protection afforded by initial formation of the enolate from the C-6 carbonyl. Exposure of the crude amide 463 to PTSA in refluxing CH$_2$Cl$_2$ afforded a mixture of 464 and 465 in 15% and 65% yields, respectively (Scheme 3.2.9).

**Scheme 3.2.10. Reagents and conditions:** (a) NaCNBH$_3$, AcOH, TFA, 0 °C then 50 °C, 5 h, 68%; (b) PhMe, CaCO$_3$, reflux, 16 h, 85%; (c) (i) OsO$_4$, NMO, acetone:H$_2$O (3:1), rt, 3 h; (ii) LiAlH$_4$, THF, reflux, 16 h, 89%; (d) Dowex 50W-X8 (H$^+$ form), MeOH, rt, 24 h, 94%.

Reduction of unsaturated phenylsulfinyl 465 followed by heating at 50 °C furnished the saturated phenylsulfinyl 466 as a single isomer. Pyrolysis of the phenylsulfinyl group to alkene 411 was followed by a diastereoselective Upjohn dihydroxylation and reduction of the crude diol to give indolizidine 467 as a single isomer. The selectivity obtained was in contrast to the work by Hirama et al. and Chen et al. who obtained a mixture of diastereomers (Scheme 3.2.2). Treatment of indolizidine 467 with Dowex 50W-X8 (H$^+$ form) effected acidic desilylation to yield (+)-swainsonine 397 (Scheme 3.2.10).
3.3 Previous Syntheses of (-)-Swainsonine

There are many reported approaches to (-)-swainsonine 11 and a detailed discussion of this previous work is beyond the scope of this thesis. This short review will therefore present three syntheses with direct relevance to the synthetic strategy pursued in this research.

3.3.1 Racemic Synthesis of Swainsonine by Mukai et al.

Mukai et al. have developed a racemic approach involving endo-cyclisation of epoxide 468 which was derived from achiral (Z)-7-(trimethylsilyl)-hept-4-en-6-yn-1-ol in 5 steps. A key feature in this synthesis was the stereoselective dihydroxylation of a late-stage indolizidine intermediate 471.

![Scheme 3.3.1](image)

**Scheme 3.3.1. Reagents and conditions:** (a) (i) Co2(CO)8, CH2Cl2, rt, 15 min then -78 °C, 30 min; (ii) BF3·OEt2, -78 °C, 10 min; (iii) CAN, MeOH, 0 °C, 30 min, 85% (dr = 9:1); (b) TBSCI, imid., DMF, 70 °C, 1 h, 99%; (c) n-BuLi, -78 °C, 1 h, then (HCHO)n, rt, 1 h, 97%; (d) H2, Lindlar catalyst, EtOAc, 30 min, 99%; (e) (i) Na, naphthalene, THF, -78 °C, 20 min; (ii) CBr4, PPh3, Et3N, CH2Cl2, 0 °C to rt, 30 min, 57%; (f) (i) OsO4, NMO, acetone:H2O (3:1), rt, 3 h; (ii) TBAF, THF, rt, 2 h; (iii) Ac2O, py, DMAP, CH2Cl2, rt, 1 h 76% (472:473 = 12:88); (g) K2CO3, MeOH, rt, 1.5 h, 99%.

Successive treatment of key epoxide 468 with dicobalt octacarbonyl, catalytic boron trifluoride, and cerium (IV) ammonium nitrate furnished a mixture of trans-piperidine 391 and its cis-isomer (dr = 9:1). Protection of alcohol 391 as the corresponding silyl ether and homolation by treatment of the C-lithiate with paraformaldehyde gave alcohol 469, which was hydrogenated in the presence of Lindlar catalyst to exclusively afford cis-alkene 470. Removal of the N-tosyl group and intramolecular Appel reaction afforded indolizidine (±)-471. Stereoselective Upjohn dihydroxylation of olefin 471 furnished diastereomeric diols which were peracetylated to give a separable mixture of indolizidines 472 and 473 (dr = 12:88). Finally basic hydrolysis of the major isomer 473 furnished racemic swainsonine (±)-11 (Scheme 3.3.1).
3.3.2 Synthesis of (-)-Swainsonine by Buschman *et al.*

Buschman *et al.* has reported a synthesis using enantiopure oxazolidinone 474, as starting material, using ring closing metathesis and an intramolecular S_N2 reaction to synthesise the indolizidine core. 381

![Scheme 3.3.2](image)

**Scheme 3.3.2. Reagents and conditions:** (a) KOH, MeOH, 70 °C, 2 h, 98%; (b) allyl bromide, K_2CO_3, DMF, rt, 12 h, 99%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, overnight, 98%; (d) Grubbs I catalyst (5 mol %), H_2C=CH_2, CH_2Cl_2, 25 °C, 3 h, then Pb(OAc)_2, 14 h, 98%; (e) (i) 9-BBN, THF, 0 °C to 55 °C, 8 h, (ii) NaOH, H_2O, EtOH, reflux, 1 h, 83%; (f) (i) Na/Hg, K_2HPO_4·3H_2O, MeOH, reflux, 2 h, (ii) NaOH, H_2C=CHCH_2CO_2Cl, CH_2Cl_2/H_2O (1:1), rt, 1 h, 89%; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h, 98%; (h) Pd(PPh_3)_4, Et_3N, dimedone, THF, 3 h, rt, then 3 h 50 °C, 95%; (i) (i) AD-mix-α, MeSO_2NH_2, t-BuOH:H_2O (1:1), 3-6 °C, 1 week, (ii) TBAF, THF, rt, 24 h, (iii) Ac_2O, py, DMAP, CH_2Cl_2, rt, overnight, 68% (dr = 20:1); (j) Amberlite IRA-401 (OH^- form), MeOH, rt, 2 h, 96%.

Metathesis precursor 475 was synthesised in a three step reaction sequence involving carbamate hydrolysis, amide allylation, and protection of the secondary alcohol. Ruthenium-catalysed ring rearrangement of compound 475 selectively furnished dihydropyrrole 476 with a rearrangement driven by steric relief of the bulky TBS group. Selective hydroboration and oxidative workup provided the terminal alcohol was followed by removal of the N-tosyl group which was isolated as the corresponding allyl carbamate and mesylation of the terminal alcohol to give cyclisation precursor 477. Carbamate deprotection with polymer bound Pd(PPh_3)_4, proceeded with cyclisation to furnish indolizidine 471. Introduction of the cis-dihydroxy was initially attempted in accordance to the procedures of Mukai *et al.*, however no diastereoselectivity was observed. In an attempt to improve the facial selectivity of dihydroxylation reaction the bulkier AD-mix-α was used leading to a 20:1 mixture of diols favouring the desired diastereomer. The synthesis was completed by peracetylation and basic hydrolysis (*vide supra*) to afford (-)-swainsonine 11 (Scheme
3.3.2. Indolizidine 471 has since found use in three formal syntheses of (-)-swainsonine 11, 33, 266, 382, 383

3.3.3 Synthesis of (-)-Swainsonine by Lindsay and Pyne

Independently, Lindsay and Pyne developed a similar strategy of Sharpless dihydroxylation of a chiral indolizidine 483, utilising a trans-allylic alcohol 478, derived from commercially available 4-pentyn-1-ol as starting material. In a similar fashion to Buschman et al., ring closing metathesis and an intramolecular S_N2 reaction were used to synthesise the indolizidine core. 381, 384

Scheme 3.3.3. Reagents and conditions: (a) D-(-)-DIPT, Ti(Oi-Pr)_4, TBHP, 4 Å MS, CH_2Cl_2, -15 °C, 2.5 h, 52% (ee = 92%); (b) (i) DMSO, (COCl)_2, CH_2Cl_2, -60 °C, 1 h, then Et_3N, -60 °C, 5 min, (ii) Ph_3PMe^+Br^-, KHMDS, PhMe, 0 °C 1 h then rt 2 h, 63%; (c) allyl amine, PTSA, 105 °C (sealed tube), 3 d, 88%; (d) Boc_2O, Et_3N, THF, rt, 1 d, 98%; (e) Grubbs I catalyst (6 mol %), CH_2Cl_2, reflux, 20 h, 96%; (f) BnBr, NaH, Bu,Ni, THF, rt, 2 d, 74%; (g) anisole, TFA, CH_2Cl_2, rt, 1.5 h, 88%; (h) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0 °C, 1.5 h, 74%; (i) AD-mix-α, (DHQ)_2PHAL, MeSO_2NH_2, t-BuOH:H_2O (1.4:1), 4 °C, 7 d; (j) 2,2-dimethoxypropane, PTSA, CH_2Cl_2, rt, 3 h, 50% over two steps (dr = 98:2); (k) H_2, PdCl_2, MeOH, rt, 1 h; (l) 2 M HCl, THF, rt, 20 h, Dowex-1 (OH^- form), 94% over two steps.

Sharpless asymmetric epoxidation of the allylic alcohol 478 gave epoxide 479 in moderate yield and good enantioselectivity. Oxidation to the corresponding aldehyde and Wittig olefination gave vinyl epoxide 480 was followed by stereospecific aminolysis allylamine and protection to afford diene 481. Ring-closing metathesis to the corresponding pyrrolone was followed by protection of the secondary alcohol as the benzyl ether. Acidic treatment gave cyclisation precursor 482 which was converted to indolizidine 483 by an intramolecular Appel reaction. As with Buschman et al., Lindsay and Pyne found Upjohn dihydroxylation gave poor diastereoselectivity (dr = 2:1) and use of the bulkier osmium catalyst, AD-mix-α, proceeded with greater selectivity (dr = 98:2), ultimately furnishing a
separable mixture of acetonides favouring the desired indolizidine 484. Subsequent hydrogenolysis and acidic hydrolysis completed the synthesis of (−)-swainsonine 11 (Scheme 3.3.3).384

The stereoselectivity of osmium tetraoxide mediated-oxidation for these examples can be rationalised using the model depicted in Figure 3.3.1. Due to the steric hindrance exerted by the pseudoaxial H-8a and H-3β protons, OsO₄ predominantly oxidises the double bond from the bottom face (Figure 3.3.1).

![Figure 3.3.1. Facial selectivity of OsO₄ attack caused by steric hindrance exerted by pseudo-axial hydrogens.](image)

Introduction of the cis-diol to the racemic indolizidine (entry 2) was originally carried out by Mukai et al. who reported a selectivity of 88:12 in favour of the desired diastereomer 486 using osmium tetraoxide (entry 2).285 In contrast, Blechert and co-workers reported that utilisation of this methodology with enantiomerically pure indolizidine (entry 3) gave almost no diastereoselectivity,381 with similar results having been reported for the free hydroxyl (entry 1) and O-benzyl analogues (entry 5).59,384

![Image of chemical structures](image)

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</table>

Table 3.3.1. Summary of syn-dihydroxylation of literature indolizidines.
Unexpectedly, dihydroxylation of the TIPS protected analogue (entry 4), yielded a 20:80 mixture that favoured the undesired diastereomer 487.\textsuperscript{59} Independently, the groups of Pyne\textsuperscript{384} and Blechert\textsuperscript{381} demonstrated that the use of Sharpless asymmetric dihydroxylation reaction conditions favoured the desired diol. The higher diastereoselectivity observed with use of AD-mix-α or -β is presumably due to their bulkier nature and interestingly in the case of Pyne,\textsuperscript{384} use of either reagent gave the same major diastereomer suggesting that reaction is under substrate rather than catalyst control. Similar results were obtained by Cecon \textit{et al.} (entry 7).\textsuperscript{79}

Additionally, all three examples utilise intramolecular ring closures to form the indolizidine ring whilst the synthesis of Mukai \textit{et al.} demonstrates the partial reduction of an internal alkyne to a (Z)-alkene.

3.4 Retrosynthesis

It was envisaged that the developed nucleophilic addition-based methodology would be well suited to the synthesis of bioactive 2-substituted-3-hydroxypiperidine alkaloids due to the high yields and excellent diastereoselectivities obtained by addition of a wide variety of nucleophiles to nitrone 198.

Scheme 3.4.1. Retrosynthetic analysis of (+)-swainsonine 397.

Retrosynthetic analysis of (+)-swainsonine 397 focused on the use of indolizidine 488 as the key synthetic intermediate. It was proposed that treatment with AD-mix-α or -β would effect stereoselective dihydroxylation to give the target with the desired syn-stereochemistry.
The indolizidine core was planned to be formed *via* intramolecular cyclisation of *cis*-alkene 489, itself formed by stereoselective partial hydrogenation of the triple bond present in hydroxylamine 490. Compound 490 can be derived from the stereoselective addition of the C-lithiated *O*-silyl protected propargyl alcohol 491 to the L-glutamic acid-derived nitrone 198 (Scheme 3.4.1).

### 3.5 Total Synthesis of (+)-Swainsonine and (-)-1,2-Di-epi-swainsonine

#### 3.5.1 Nucleophilic Addition of Lithium Acetylide and Hydroxylamine Reduction

With multigram quantities of nitrone 198 having been synthesised, the first stage was the introduction of the propargyl moiety by reaction of a suitably substituted acetylide. The addition of terminal alkynes to nitrones has previously been achieved with lithium,165, 385-393 magnesium,270, 394-396 aluminium,397, 398 and zinc acetylides.399-405 Although commonly used for nucleophilic additions to acyclic nitrones, the use of zinc acetylides was not considered suitable due to the potential for alkyne 1,3-dipolar cycloaddition.401, 403 Alkynylalanes were also not considered due to low reported diastereoselectivities in the addition to cyclic 5-membered nitrones.398

Encouraged by the rapid reaction rate and high selectivity exhibited in the addition of lithiated ethynyltrimethylsilane to nitrone 198 (Scheme 2.7.7) it was decided to initially attempt addition of a lithium acetylide. Murahashi and co-workers had previously established that nucleophilic addition of various lithium acetylides to a chiral five-membered cyclic nitrone proceeded with high diastereoselectivities and good yields (Scheme 3.5.1).393

![Scheme 3.5.1. Addition of lithium acetylides by Murahashi and co-workers.](image)

Although the addition of the acetylide dianion 493, resulting from treatment of free alcohol with *n*-butyllithium, was also demonstrated, the yield and diastereoselectivity were comparatively lower than addition of protected acetylide 494 (Scheme 3.5.1).393 It was
therefore deemed necessary to protect the free alcohol of propargyl alcohol prior to addition. Consideration had to be given to the type of protecting group used and it was essential that it was compatible with both the lithiation and hydrogenation steps of the proposed retrosynthetic scheme and needed to be orthogonal to the protection group of nitrone 198 to ensure selective deprotection prior to cyclisation. Silyl protected propargyl ether 491 was a particularly attractive substrate having been previously shown to undergo rapid addition to nitrones\textsuperscript{393} and although not entirely orthogonal to the TBDPS group on the nitrone, a significant body of literature exists regarding the selective monodeprotection of bis-silyl ethers.\textsuperscript{406,407}

Accordingly, propargyl alcohol 497 was protected as the corresponding silyl ether 491, using literature procedures in a yield of 89\% (Scheme 3.5.2).

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {\text{\textsuperscript{\textbullet}OH}}; \node (b) at (1.5,0) {\text{\textsuperscript{\textbullet}OTBS}}; \node (c) at (3,0) {\text{\textsuperscript{\textbullet}N\textsuperscript{\textbullet}OH}};
\node (d) at (0,-0.5) {497}; \node (e) at (1.5,-0.5) {491}; \node (f) at (3,-0.5) {490};
\draw[->] (a) -- node[midway,above] {a\hspace{1cm}89\%} (b);
\draw[->] (b) -- node[midway,above] {b\hspace{1cm}90\%} (c);
\end{tikzpicture}
\end{center}

Scheme 3.5.2. Reagents and conditions: (a) TBSCl, imid., CH\textsubscript{2}Cl\textsubscript{2}, 12 h, 89\%; (b) (i) n-BuLi, 491, THF, -78 °C to 0 °C, (ii) 198, -78 °C to 0 °C, 1 h, 90\%.

Introduction of the propargyl moiety onto nitrone 198 was carried out using procedures described by Murahashi and co-workers.\textsuperscript{393} Treatment of silyl ether 491 with n-butyllithium in THF at -78 °C was followed by stirring at 0 °C for 30 min to ensure formation of the lithium acetylide. A solution of nitrone 198 dissolved in THF was then added at -78 °C and stirring continued at 0 °C for one hour before quenching with saturated aqueous ammonium chloride. This procedure gave hydroxylamine 490 in multi-gram quantities with 90\% yield (Scheme 3.5.2).

Successful addition was supported by mass spectrometry results. \textsuperscript{1}H and \textsuperscript{13}C NMR analyses of the products at normal temperature gave broad signals which made structural elucidation difficult. Although VT-NMR experiments were carried out to determine the gross structure, the instability of the compound at high temperatures made it more convenient to carry out stereochemical assignments after cleavage of the hydroxylamine.
Scheme 3.5.3. Reagents and conditions: (a) In, Zn, EtOH, sat. NH$_4$Cl, 100 °C, 4 h, 75%.

Hydroxylamine 490 was treated with a catalytic amount of indium metal and two molar equivalents of zinc powder in EtOH/NH$_4$Cl under reflux for 4 h to provide the corresponding amine 498 in 75% yield.

Figure 3.5.1. Observed NOESY interactions for piperidine 498

Analyses of the 2D NOESY spectrum results for piperidine 498 were consistent with formation of the *trans*-diequatorial substituted ring system. Correlations between 2-H and both 4ax-H and 6ax-H as well as between 3-H and 5ax-H provided strong evidence that both the C-2 and C-3 hydrogens are in axial positions, confirming approach of the nucleophile from opposite the bulky OTBDPS group giving the desired *trans*-configuration across the C-2 to C-3 bond (Figure 3.5.1).

Unfortunately efforts to repeat this reaction were not successful, resulting in variable yields, with the reaction often not proceeding to completion. It was also observed that partial deprotection of the TBS group had occurred; yielding a complex mixture of protected amine 498 and starting material 490 as well as the corresponding deprotected hydroxylamine and amine. The presence of the alkyne functionality limits the methods which can be used for cleavage of the hydroxylamine bond. Reduction of 490 using stoichiometric indium also proceeded slowly and in varying yields, due to the problems mentioned above.

From the results discussed above, it is apparent that reduction of the TBS-protected hydroxylamine 490, under the conditions investigated, was unreliable in terms of product yield, reaction duration and cleanliness. It was speculated that the weak acid, ammonium
chloride, used in the reduction procedure was responsible for the partial deprotection of the starting material as well as the amine product leading to an unclean reaction profile. Therefore it was first suggested to access hydroxylamine 499 via deprotection of hydroxylamine 490 which was available in multi-gram quantities (Scheme 3.5.4).

Scheme 3.5.4. Reagents and conditions: (a) 1% HCl, EtOH, rt.

Although it is well known that primary TBS-ethers can easily be hydrolysed by dilute acid solutions, this would involve the addition of an extra synthetic step and was therefore not desired. Attention then turned to the possibility of merging the two steps (deprotection and reduction) into a one-pot procedure. It was proposed to replace ammonium chloride with 1% aqueous hydrochloric acid which can act both as the deprotection reagent as well as the providing the acid source required for indium-mediated reduction. The use of zinc metal was avoided in this alternative procedure because the alkyne moiety in the substrate is known to be susceptible to hydration and reduction reactions by zinc metal in acidic conditions.387, 408, 409

Scheme 3.5.5. Reagents and conditions: (a) In, 1% HCl, EtOH, reflux, 2 h, 85%.

Stirring a solution of hydroxylamine 490 in ethanol in the presence of 1% aqueous hydrochloric acid and stoichiometric indium, under reflux, furnished amine 500 as a pale yellow oil in gram quantities in 85% yield. As opposed to the previous reactions this proceeded cleanly and, serendipitously, was rapid - reaching completion in two hours (Scheme 3.5.5).
3.5.2 Stereoselective Semi-Hydrogenation

The selective, semi-hydrogenation of internal alkynes to (Z)-alkenes is typically carried out using heterogeneous catalyst systems which includes the commercially available Lindlar catalyst (Pd/CaCO$_3$/Pb(OAc)$_2$).\textsuperscript{410,411}

Reduction of alkyne 500 to the corresponding (Z)-alkene 489 was initially attempted by Lindlar hydrogenation under an atmosphere of hydrogen (balloon). However, this led to significant over-reduction, yielding the undesired alkane 501.

In order to obtain good selectivity, the alkene product 489 must be desorbed rapidly from the catalyst to prevent further reduction or isomerisation. Typically, alkynes are more strongly adsorbed onto the catalyst than alkenes, competing for catalytic sites by either preventing re-adsorption of the alkene or displacing it. The addition of unreactive additives such as quinoline or 3,6-dithiaoctane-1,8-diol which function to compete with the alkene, but not the alkyne, for catalytic sites have been recommended to increase the selectivity of the reaction.\textsuperscript{410,411}

Although a reduction in the amount of alkane 501 was observed with the use of quinoline, it was not effective in preventing over-reduction. The use of 3,6-dithiaoctane-1,8-diol was also unsuccessful, proving to be too effective an additive, with no reaction observed after 12 hours.

It has been reported that the presence of an unprotected amino group accelerates over-reduction and reduces E/Z selectivity.\textsuperscript{412,413} Campos et al. reported that alkynes with a primary amine functionality were prone to over-reduction and that the addition of a single equivalent of ethylenediamine (EDA) to the hydrogenation mixture afforded the desired alkene with minimal isomerisation or over-reduction.\textsuperscript{412,413}

Alkyne 500 was converted to the corresponding (Z)-alkene 489 by stirring a catalytic amount of Lindlar catalyst and EDA in ethyl acetate under an atmosphere of hydrogen (balloon) for 12 hours, furnishing amine 489 in 65% yield.
The (Z)-olefin was obtained in high yield, exclusively as a single diastereoisomer. NOESY analysis of a purified sample of amine 489 was performed and major correlations are shown in Figure 3.5.2. Correlation between 3'-H and 2'-H confirmed that the cis-stereoisomer was formed.

The high polarity of amino-alcohol 500 appeared to cause significant problems. Low and inconsistent yields were obtained along with significant over-reduction. Difficulties were also encountered during separation of the alkene 489 and alkane by-product 501. In addition, isomerisation to the trans-alkene was occasionally observed.

It was thought that the low yields obtained were most likely caused by the product adhering to the catalyst. Possible solutions considered were to reduce the polarity by...
protection of the amine functionality or to perform the alkyne reduction at an earlier step in the synthesis.

Scheme 3.5.6. Stereoselective partial reduction of hydroxylamine 502 by Xu and Rozners.\textsuperscript{404}

A search of the literature demonstrated that alkyne reductions in the presence of the hydroxylamine moiety proceeded selectively both with and without additional poisons\textsuperscript{389, 404, 414}. Interestingly alkyne 502, which exhibited a high level of structural homology to hydroxylamine 490, underwent selective and high yielding partial reduction of the triple bond to yield (Z)-alkene 503 (Scheme 3.5.6).\textsuperscript{404}

Scheme 3.5.7. Reagents and conditions: (a) Lindlar catalyst, EtOAc, rt, 1h, 90%; (b) In, 1% HCl, EtOH, reflux, 2 h, 86%.

Alkyne 490 was converted to the corresponding (Z)-alkene 504 by stirring a catalytic amount of Lindlar catalyst in ethyl acetate under an atmosphere of hydrogen (balloon) for one hour (Scheme 3.5.7). Over-reduction was still observed; however in comparison to the reduction of amino-alcohol 500, this only became significant once the starting material had been consumed. Additionally the alkane, alkene and alkyne were all separable by TLC, allowing adequate monitoring of the reaction. Application of the N-O bond cleavage/deprotection reaction previously described gave cyclisation precursor, amine 489, in excellent yield in gram quantities (Scheme 3.5.7).
A crystal structure of piperidine 489 was obtained which confirmed the structural assignments made in the previous sections, clearly showing the desired 2,3-diequatorial substitution arising from diastereoselective nucleophilic addition (Figure 3.5.3).

3.5.3 Cyclisation to the Indolizidine Ring

Attention then turned to the use of mesyl chloride to affect cyclisation via formation of an O-mesylate. A solution of amino-alcohol 489 and triethylamine in dichloromethane was treated with mesyl chloride followed by stirring at room temperature for three hours.

Scheme 3.5.8. Reagents and conditions: (a) MsCl, Et₃N, CH₂Cl₂, 0 °C to rt, 3 h, 50%.

Spectroscopic analyses of the isolated products showed that the desired indolizidine product 488 had not formed, and instead the dimesylate 505 had been produced in 50% yield (Scheme 3.5.8).
Although, upon reflection, formation of the \( N \)-mesylate appeared likely, a review of the literature revealed that slow addition of a dilute solution of mesyl chloride in dichloromethane to the substrate could be used to suppress formation of the \( O \)-mesylate.\(^{415}\)

\[\text{Scheme 3.5.9. Reagents and conditions: (a) 0.1 M MsCl, Et}_3\text{N, CH}_2\text{Cl}_2, 0 ^\circ\text{C to rt, 4 h, then MeCN, reflux, 5 h, 38%}.\]

Therefore a 0.1 M solution of mesyl chloride in dichloromethane was added dropwise to a solution of amino-alcohol \( 489 \) in dichloromethane at 0 \(^\circ\)C followed by addition of triethylamine and the mixture was stirred at room temperature for four hours. Analysis of the \(^1\)H NMR spectrum of the crude product, resulting from the above treatment showed the presence of a mono-mesylated intermediate which was presumed to be the \( O \)-mesylate. The crude product was then dissolved in acetonitrile and stirred under reflux for five hours in an effort to effect cyclisation (Scheme 3.5.9). Isolation of the major product and subsequent spectroscopic analyses confirmed the successful synthesis of indolizidine \( 488 \) in 38\% yield. Encouragingly the \(^1\)H and \(^{13}\)C NMR spectrum were in strong agreement with that of differentially \( O \)-protected indolizidines of this type, which have found previous use in the synthesis of (-)-swainsonine \( 11 \).\(^{79,285}\)

\[\text{Figure 3.5.4. Observed NOESY interactions for indolizidine 488.}\]

Key NOESY correlations observed in indolizidine \( 488 \) are presented in Figure 3.5.4. Axial-axial correlations between 6ax-H and 8-H and between 5ax-H, 7ax-H, and 8a-H confirm the conformation of the bicyclic core. Axial-axial correlations between 3-H and 5-H, as well as between 3-H and 8a-H, suggest the hydrogens at C-3 and C-8a do indeed lie in
pseudo-axial positions - a crucial requirement for stereoselectivity in the next synthetic step (Figure 3.5.4).

Unfortunately it was observed during analysis of the $^{1}$H NMR spectrum that indolizidine 488 was beginning to decompose. Although the newly formed compound could not be isolated by chromatography it was postulated that this was due to aromatisation of the unstable pyrrolidine moiety to the corresponding pyrrole. The sensitivity to mildly acidic conditions such as silica gel has previously been noted with similar indolizidines$^{383}$ and could be minimised by purification on basic alumina and restricting the time that material is stored before the next step. Unfortunately, the inherent instability of this compound was deemed to not be compatible with the current method of cyclisation due to the extended period of reflux required.

Cyclisation of amino alcohols to form pyrrolidine and piperidine ring systems can be readily achieved with the use of phosphine based reactions such as the Appel or Mitsunobu reaction.

Mukai et al. have previously used an intramolecular Appel reaction to form the indolizidine core in a racemic synthesis of $(\pm)$-11 (Scheme 3.3.1).$^{285}$

Scheme 3.5.10. Reagents and conditions: (a) CBr$_4$, PPh$_3$, Et$_3$N, CH$_2$Cl$_2$, 0 °C to rt, 2 d, 39%.

The amino alcohol 489 was treated with triphenylphosphine and carbon tetrabromide in dichloromethane 0 °C before adding triethylamine to effect cyclisation of the indolizidine ring. Unexpectedly the reaction proceeded sluggishly and did not reach completion even after stirring for two days (Scheme 3.5.10). Substitution for carbon tetrachloride in order to form the chloride was also not successful, affording indolizidine 488 in a low 47% yield. This was in direct contrast to the observations of Mukai et al. who reported that the reaction proceeded to completion in 30 min.

Attention then shifted to the use of the Mitsunobu reaction, employing azodicarboxylate reagents such as diethyl azodicarboxylate (DEAD) or diisopropyl
azodicarboxylate (DIAD). Although DEAD was once the most commonly used Mitsunobu reagent, increased safety regulations regarding domestic shipping as a neat reagent has limited availability to a 40% solution in toluene. Due to the observed sensitivity of indolizidine 488, avoiding the use of high boiling solvents which would be difficult to remove was highly desired.

The major drawback of the Mitsunobu reaction is that it requires the use of at least stoichiometric quantities of two reagents, each of which produces a by-product. This means that even in high yielding reactions, the product can be difficult to isolate from the reaction mixture which can contain excess/unreacted reagents in addition to the two by-products. Although it was determined from thin layer chromatography that triphenylphosphine (TPP) and triphenylphosphine oxide (TPPO) had sufficiently different retention factors ($R_f$) compared to the cyclised product, neither DEAD nor DIAD were deemed to be suitable for the cyclisation reaction. The hydrazine by-products of each reagent were known to have $R_f$ values relatively close to that of the cyclised product and due to the lower degree of separation afforded by basic alumina it was not thought purification would be possible.  

Di-4-chlorobenzyl azodicarboxylate (DCAD) is a recently described alternative which can be easily prepared in three steps from 4-chlorobenzyl alcohol and 1,1’-carbonyldiimidazole.  

A comparative study has been performed with DCAD showing it to be an equally efficient reagent proceeding with comparable yields and reaction rate. This reagent has certain advantages over DEAD and DIAD that made it suitable for this reaction. Firstly DCAD is a stable crystalline solid at ambient temperatures making handling easier. More importantly the hydrazine by-product is distinctly different from that of DEAD or DIAD and can, for the most part, be removed from the reaction mixture simply by precipitation with dichloromethane and filtration.

The reaction was performed in dichloromethane which was chosen due to the limited solubility of hydrazine by-product in this solvent which was postulated to act as a reaction

Scheme 3.5.11. Reagents and conditions: (a) DCAD, PPh₃, Et₃N, CH₂Cl₂, 0 ºC, 1 h, 89%.
driving force. Dilution of the reaction mixture with additional dichloromethane followed by filtration through Celite allowed isolation of most of the hydrazine from the reaction mixture. Gratifyingly the target indolizidine 488 was obtained in high yield; proceeding to completion in one hour even when conducted at 0 °C (Scheme 3.5.11).

The mechanism of the Mitsunobu cyclisation reaction as applied to compound 489 is outlined in Scheme 3.5.12.

Scheme 3.5.12. Mechanism of the Mitsunobu Reaction.

Reaction of the zwitterionic adducts formed from the reaction of TPP and DCAD, is followed by deprotonation and activation of alcohol 489 by transformation into the alkoxytriphenylphosphine salt. Nucleophilic substitution furnishes indolizidine 488 along with the TPPO and the hydrazine by-products.
Table 3.5.2. Summary of ring closure to form indolizidine 488.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>via mesylation</td>
<td>MsCl</td>
<td>CH₂Cl₂</td>
<td>0 °C then reflux</td>
<td>9</td>
<td>38</td>
</tr>
<tr>
<td>Appel</td>
<td>CBr₄</td>
<td>CH₂Cl₂</td>
<td>0 °C to rt</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Appel</td>
<td>CCl₄</td>
<td>CH₂Cl₂</td>
<td>0 °C to rt</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>Mitsunobu</td>
<td>DCAD</td>
<td>CH₂Cl₂</td>
<td>0 °C</td>
<td>1</td>
<td>89</td>
</tr>
</tbody>
</table>

3.5.4 Syn-Dihydroxylation of Indolizidine

Significant literature precedent exists (Table 3.3.1) regarding the dihydroxylation of indolizidine 488, en route to (-)-swainsonine 11.

As depicted in Figure 3.5.5, dihydroxylation was predicted to predominantly occur from the α-face in order to avoid nonbonding interaction between the dihydroxylation reagent and the pseudoaxial allylic protons H-8α and H-3β resulting in preferential formation of the desired dihydroxylated product over its stereoisomer.

Despite the low selectivities previously obtained in the majority of dihydroxylation reactions using osmium tetroxide (OsO₄) it was still deemed worthwhile to test this reaction to determine the effect of the protecting group on selectivity.
**Scheme 3.5.13.** Reagents and conditions: (a) (i) OsO$_4$, NMO, acetone:H$_2$O (1:1), 0 °C to rt, 6 h, (ii) Ac$_2$O, py, DMAP, rt, 12 h, 42% (dr = 36:64).

Introduction of *cis*-dihydroxy functionality was carried out by treatment of a solution of alkene 488 in acetone:water with OsO$_4$ to give a mixture of the corresponding diol derivatives. The success of syn-dihydroxylation was inferred by the disappearance of the alkene signals at 5.77-5.84 and 6.03-6.09 ppm in the $^1$H NMR spectrum of indolizidine 488 and the loss of two alkene CH signals at 128.4 and 131.7 ppm in the $^{13}$C NMR spectrum. However, because the dihydroxylated products were not able to be isolated as pure compounds by column chromatography, the mixture was converted into the corresponding peracetylated derivatives by treatment with acetic anhydride. Column chromatography of the resulting mixture provided 506 and 507 in 15% and 27% yields respectively. The stereochemical outcome of dihydroxylation was not consistent with addition of the osmium reagent to the less hindered α-face of 488 (Scheme 3.5.13).

**Scheme 3.5.14.** Reagents and conditions: (a) (i) AD-mix-α, tert-BuOH:H$_2$O (1:1), MeSO$_2$NH$_2$, 0-4 °C, 4 d, (ii) Ac$_2$O, py, DMAP, rt, 12 h, 76%. (dr = 90:10).

Dihydroxylation of alkene 488 was also performed using commercially available AD-mix-α in the presence of methanesulfonamide in accordance with the procedures outlined by Lindsay and Pyne. After stirring alkene 488 in a solution of tert-butanol:water for 4 days at temperatures between 0-4 °C, the crude mixture of dihydroxylated compounds was converted into the corresponding peracetylated derivatives, furnishing a separable mixture of indolizidines 506 and 507 in 68% and 7.6% yields respectively. Gratifyingly the stereochemical outcome was now consistent with addition of the osmium reagent to the less hindered, α-face of alkene 488 (Scheme 3.5.14).
The stereochemistry of addition was best evaluated on indolizidine 506, arising from addition from the α-face of alkene 488 (Figure 3.5.6).

![Figure 3.5.6. Observed NOESY interactions for indolizidine 506.](image)

Analysis of the $^1$H NMR spectra of indolizidine 506 showed coupling constants of $J_{8a-8} = 8.8$ and $J_{8a-1} = 4.1$ Hz for 8a-H. The coupling constant of 8.8 Hz is consistent with the trans-diaxial orientation of the protons in a fused six-membered ring whilst the smaller coupling constant 4.1 Hz strongly supports the C-1 oxygen occupying the pseudo-axial position.

![Diagram](image)

Table 3.5.3. Summary of syn-dihydroxylation of indolizidines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Reagent</th>
<th>Ratio 486:487</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>OsO$_4$</td>
<td>60:40</td>
<td>45$^a$</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>TBS</td>
<td>OsO$_4$</td>
<td>88:12</td>
<td>76$^b$</td>
<td>285</td>
</tr>
<tr>
<td>3</td>
<td>TBS</td>
<td>OsO$_4$</td>
<td>50:50-42:58</td>
<td>-</td>
<td>381</td>
</tr>
<tr>
<td>4</td>
<td>TIPS</td>
<td>OsO$_4$</td>
<td>20:80</td>
<td>61$^a$</td>
<td>59</td>
</tr>
<tr>
<td>5$^d$</td>
<td>TBDPS</td>
<td>OsO$_4$</td>
<td>36:64</td>
<td>42$^a$</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>K$_2$OsO$_4$</td>
<td>66:34</td>
<td>56$^a$</td>
<td>384</td>
</tr>
<tr>
<td>7</td>
<td>TBS</td>
<td>AD-mix-α</td>
<td>95:5</td>
<td>68$^b$</td>
<td>381</td>
</tr>
<tr>
<td>8</td>
<td>TIPS</td>
<td>AD-mix-α</td>
<td>95:5</td>
<td>41$^c$</td>
<td>79</td>
</tr>
<tr>
<td>9$^d$</td>
<td>TBDPS</td>
<td>AD-mix-α</td>
<td>90:10</td>
<td>76$^a$</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Bn</td>
<td>AD-mix-α</td>
<td>98:2</td>
<td>44$^a$</td>
<td>384</td>
</tr>
<tr>
<td>11</td>
<td>Bn</td>
<td>AD-mix-β</td>
<td>95:5</td>
<td>49$^a$</td>
<td>384</td>
</tr>
</tbody>
</table>

$^a$Isolated as diacetate (two steps), $^b$Isolated as triacetate (three steps), $^c$Isolated as triacetate (four steps),
$^d$Enantiomeric indolizidine used as starting material.
Oxidation of alkene 488 using OsO$_4$ proceeded with similarly poor selectivity to that previously reported, with a slight reversal to that which was predicted, resembling results reported by de Vincente et al.$^{59}$ Although the ratio obtained for dihydroxylation using AD-mix-$\alpha$ was slightly lower than those previously reported, the yields were, in general, significantly higher, especially in comparison to that of Lindsay et al. (Table 3.5.3)$^{384}$

3.5.5 Elaboration to (+)-Swainsonine and (-)-1,2-Di-epi-swainsonine

Having successfully introduced the required diol with high diastereoselectivity, all that remained to complete the syntheses of (+)-swainsonine 397 and (-)-1,2-di-epi-swainsonine 512 was global deprotection of indolizidine 506 and 507 respectively.

It was observed that a sample of indolizidine 506 which had been left in non-neutralised deuterated chloroform had changed colour and was beginning to decompose. Owing to this acid sensitivity, the use of acid catalysed deprotection conditions was not considered further. The use of fluoride ion sources represented an alternate method of deprotection and a search of the literature revealed that Lindsay and Pyne had successfully performed a remarkably similar deprotection *en route* to an asymmetric synthesis of (-)-swainsonine 11 (Scheme 3.5.15).$^{418}$

![Scheme 3.5.15. Reagents and conditions: (a) TBAF, THF, rt, 5 d, 76%.

Although proceeding in good yield, it was noted that the reaction took 5 days and large equivalents of tetrabutylammonium fluoride (TBAF) was required in order to ensure completion, indicating that deprotection was likely to be difficult due to the increase in stability when placed at a secondary position.$^{418}$

Attempts to remove the secondary TBDPS group from substrate 506 utilising TBAF as a fluoride source gave disappointing results leading to the formation of complex mixtures.
Deprotection was initially attempted using the procedure described by Lindsay and Pyne.\textsuperscript{418} Treatment of indolizidine 506 with TBAF in anhydrous THF at 0 °C followed by stirring at room temperature resulted in decomposition of the starting material (Scheme 3.5.16). A significant problem with the use of esters as protecting groups is migration to neighbouring alcohols \textit{via} intramolecular transesterification\textsuperscript{419} and can be attributed to the basic nature of TBAF. Believing this to be the cause of the complex mixture obtained, suppression was attempted by buffering the reaction with excess or equimolar amount of acetic acid. However this was also not successful and again complex mixtures were obtained, possibly due to the sensitivity of indolizidine 506 to acidic conditions.

Although it remained a possibility that the reaction had proceeded with concomitant cleavage of the acetate protecting groups, it was deemed that even if the reaction could be optimised, highly polar, water soluble (+)-swainsonine 397 would not be compatible with aqueous workup procedures making it difficult to separate from the formed TBAF salts. Consideration was given to reversal of the deprotection steps, however this was also not deemed suitable due to the aforementioned purification problems.

Since the acetate protecting group is prone to cleavage/migration under basic conditions, use of an alternate fluoride source was considered. Hydrogen fluoride pyridine (HF-pyridine) and triethylamine trihydrofluoride (TREAT-HF) are mild reagents which have been employed in the desilylation of base sensitive compounds.\textsuperscript{420} The use of TREAT-HF is particularly attractive due to its almost neutral pH.\textsuperscript{421} Additionally the low corrosiveness in relation to other mixtures of HF with organic bases, allows reactions to be performed in borosilicate glassware, permitting the use of elevated temperatures.\textsuperscript{422, 423}
Deprotection was initially attempted using the procedure described by Matsumura et al. Indolizidine 506 was stirred for one week in a solution of TREAT-HF in acetonitrile that was buffered with excess triethylamine. Although no reaction was observed at room temperature it was gratifying to note that decomposition had not occurred and the starting material could be recovered. The reaction was repeated under reflux for 5 days to furnish the desired indolizidine 510 in excellent yield. It is important to note that even though the reaction required high equivalents of TREAT-HF, and long reaction times, no decomposition was observed and the reaction proceeded cleanly (Scheme 3.5.17).

![Figure 3.5.7. ORTEP representation of indolizidine 510 as determined by X-ray diffraction.](image)

A crystal structure was obtained which confirmed the assignment of the major indolizidine 510 arising from the dihydroxylation step (Figure 3.5.7). The enantiomer has previously been synthesised by partial acetylation of (-)-swainsonine 11. Although only partially characterised, a crystal structure was obtained which proved to be an excellent match for indolizidine 510.²⁹⁹,⁴²⁵

Finally, the synthesis of (+)-swainsonine 397 was completed by deprotection of indolizidine 510 by basic hydrolysis using a solution of sodium methoxide in methanol (Scheme 3.5.18).
**Scheme 3.5.18.** *Reagents and conditions: (a) NaOMe, MeOH, rt, 1 h, 80%.*

The crude product was purified by column chromatography using reverse phase C18 as the stationary phase to give (+)-swainsonine 397 in 80% yield as a white solid.

The spectroscopic data of (+)-swainsonine 397 made in both deuterated methanol (CD$_3$OD) and water (D$_2$O) were in agreement with those reported in the literature.$^{347, 369, 384}$ Analysis of the $^1$H NMR (CD$_3$OD) spectrum of indolizidine 397 showed coupling constants of $J_{8a-8} = 9.2$ and $J_{8a-1} = 3.3$ Hz for 8a-H. The coupling constant of 9.2 Hz is consistent with the *trans*-diaxial orientation of the protons in a fused six-membered ring whilst the smaller coupling constant of 3.3 Hz strongly supports the C-1 oxygen occupying the pseudo-axial position.

**Figure 3.5.8.** Observed NOESY (D$_2$O) interactions for (+)-swainsonine 397.

NOESY correlations were best determined from the spectrum collected in D$_2$O due the increased level of peak separation in comparison to that in CD$_3$OD. NOE correlations of 6ax-H with 8-H and of 7ax-H with both 8a-H and 5ax-H provided strong evidence that the 8-H and 8a-H are in an axial position, confirming the *trans*-configuration across the C-8 to C-8a bond. Furthermore NOE correlations between 8a-H and 1-H as well as between 3-H and 2-H support the stereochemistry of the C-1 to C-2 diol (Figure 3.5.8).

Table 3.5.4 shows the melting point and the optical rotation data for (+)-swainsonine 397. As illustrated, the melting point obtained and optical rotation are in close agreement with those reported by Guo and O’Doherty.$^{347, 369}$
Table 3.5.4. Summary of physical data for swainsonine 397.

<table>
<thead>
<tr>
<th>Physical data</th>
<th>Recorded data</th>
<th>Published data</th>
</tr>
</thead>
<tbody>
<tr>
<td>mp</td>
<td>143-144 °C</td>
<td>143-144 °C&lt;sup&gt;347, 369&lt;/sup&gt;</td>
</tr>
<tr>
<td>[α]&lt;sub&gt;D&lt;/sub&gt;</td>
<td>+79.9 (c 0.37, MeOH)</td>
<td>+80.0 (c 0.10, MeOH)&lt;sup&gt;347, 369&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

The deprotection reactions were repeated on the minor dihydroxylation product, indolizidine 507 to give (-)-1,2-di-epi-swainsonine 512.

![Chemical structure](image)

**Scheme 3.5.19. Reagents and conditions:** (a) Et₃N,3HF, MeCN, Et₃N, 80 °C, 4 d, 81%; (b) K₂CO₃, MeOH, rt, 1 h, 75%.

Using the previously described procedure, indolizidine 507 was heated at reflux for 4 days to give the desired indolizidine 511 in high yield. Acetate deprotection of indolizidine 511 was achieved by basic hydrolysis using potassium carbonate in methanol. The crude product was purified by column chromatography using reverse phase C18 as a stationary phase to give (-)-1,2-di-epi-swainsonine 512 in 75% yield as a white solid (Scheme 3.5.19).

In contrast to (+)-swainsonine 397 and its natural isomer 11, there are fewer examples of NMR spectra to make comparisons. Although the collected NMR spectra were in excellent agreement with the data reported by Kim et al.<sup>426</sup> it was often unclear what the spectra collected in D₂O had been referenced to. Additionally small variations were observed with minor disagreement between papers.
Variations were also observed in the magnitude of optical rotations and melting points reported for \((-\)-1,2-di-\textit{epi}-swainsonine 512 and its isomer (Table 3.5.5).

**Table 3.5.5.** Summary of physical data for \((-\)-1,2-di-\textit{epi}-swainsonine 512 and \((+\)-1,2-di-\textit{epi}-swainsonine.

<table>
<thead>
<tr>
<th>Physical data</th>
<th>Recorded data</th>
<th>Published data for ((-)-1,2-di-\textit{epi}-swainsonine</th>
<th>Published data for ((+)-1,2-di-\textit{epi}-swainsonine</th>
</tr>
</thead>
<tbody>
<tr>
<td>mp</td>
<td>127-128 °C</td>
<td>129-130 °C\textsuperscript{72} dec\textsuperscript{427}</td>
<td>104-106 °C\textsuperscript{384} dec\textsuperscript{428}</td>
</tr>
<tr>
<td>([\alpha]_D)</td>
<td>-17.7 (c 0.24, MeOH)</td>
<td>-18.7 (c 0.55, MeOH)\textsuperscript{72}</td>
<td>+16.1 (c 1.23, MeOH)\textsuperscript{428}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-14.0 (c 0.51, MeOH)\textsuperscript{426}</td>
<td>+17.0 (c 1.00, MeOH)\textsuperscript{59}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-21.2 (c 0.78, MeOH)\textsuperscript{427}</td>
<td>+4.0 (c 2.85, MeOH)\textsuperscript{384}</td>
</tr>
</tbody>
</table>

Similar inconsistencies have been observed in polyhydroxylated pyrrolizidines such as various isomers of hyacinthacine A\textsubscript{1},\textsuperscript{429} A\textsubscript{3},\textsuperscript{430} C\textsubscript{3},\textsuperscript{431} \((+\)-crotanecine,\textsuperscript{432} and \((-\)-rosmarinecine\textsuperscript{433} and it has been suggested that the spectroscopic data of polyhydroxylated alkaloids might be affected by pH,\textsuperscript{429} variations in the concentration of hydrates or \(N\)-complexes,\textsuperscript{432} and trace elements, such as the potassium cation.\textsuperscript{434}

These variations necessitated that a comprehensive structural study was undertaken in both CD\textsubscript{3}OD and D\textsubscript{2}O by means of both 1D- and 2D-NMR techniques to confirm the structure. Analysis of the NMR spectrum of indolizidine 512 revealed coupling constants of \(J_{8a-8} = 8.7\) and \(J_{8a-1} = 7.9\) Hz for 8a-H. The coupling constant of 8.7 Hz is consistent with the \textit{trans}-diorial orientation of the protons in a fused six-membered ring (Figure 3.5.9).

**Figure 3.5.9.** Observed NOESY (CD\textsubscript{3}OD) interactions for \((-\)-1,2-di-\textit{epi}-swainsonine 512.

Analysis of the 2D NOESY results indicated that the stereochemistries of the formed chiral centres were in accordance with those proposed for \((-\)-1,2-di-\textit{epi}-swainsonine 512. Correlations between 6ax-H and 8-H as well as 7ax-H and 8a-H provided strong evidence that the 8-H and 8a-H are in an axial position, confirming the \textit{trans}-configuration across the
C-8 to C-8a bond. Furthermore NOE correlations between 1-H and 8-H as well as between 1-H and 2-H support the stereochemistry of the C-1 to C-2 diol (Figure 3.5.9). All the NMR data indicated that our synthetic compound has the structure proposed for (−)-1,2-di-epi-swainsonine 512.

To further confirm the identity of the synthesised product, a solution of triol 512 in dichloromethane was treated with acetic anhydride in pyridine, affording the triacetate derivative 513 as a white solid in quantitative yield (Scheme 3.5.20).

![Scheme 3.5.20. Reagents and conditions: (a) Ac₂O, py, CH₂Cl₂, rt, 20 h, 100%.](image)

Gratifyingly the spectroscopic and physical data of indolizidine 513 were now in total agreement with that reported by Razavi et al. for the enantiomer 428 and Mukai et al. for the racemate 285 (Table 3.5.6).

<table>
<thead>
<tr>
<th>Physical data</th>
<th>Recorded data</th>
<th>Published data*</th>
</tr>
</thead>
<tbody>
<tr>
<td>mp</td>
<td>135-136 °C</td>
<td>132-134 °C 428</td>
</tr>
<tr>
<td>[α]D</td>
<td>-61.7 (c 0.30, MeOH)</td>
<td>+61.1 (c 2.11, MeOH) 428</td>
</tr>
</tbody>
</table>

*Published optical rotation is that of the enantiomer.
3.6 A Brief Overview of (-)-Epiquinamidie

3.6.1 Isolation and Biological Activity

The quinolizidine alkaloid (+)-epiquinamidie 514 was isolated in 2003, by Daly and co-workers, from the skin of the Ecuadorian poison dart frog *Epipedobates tricolour*.\(^{435}\) Initially reported as representing a new structural class of selective $\beta_2$-selective nicotinic acetylcholine receptor agonists, (+)-epiquinamidie represented an attractive synthetic target and a number of syntheses were published in rapid succession.\(^{436-442}\)

![Structures of (+)-epiquinamidie 514 and (+)-epibatidinie 515.](image)

Figure 3.6.1. Structures of (+)-epiquinamidie 514 and (+)-epibatidinie 515.

Through these synthetic efforts, the absolute structure of (+)-epiquinamidie 514 was determined by chiral GC analysis.\(^{437}\) Unexpectedly, recent biological studies performed on all four diastereoisomers, revealed that epiquinamidie does not exhibit nicotinic activity.\(^{440, 441, 443}\) Although re-evaluation of the natural extract still clearly indicated bioactivity, this was determined by gas chromatography-mass spectrometry (GC-MS) to be due to the presence of (+)-epibatidinie 515.\(^{443}\) Although only representing perhaps 0.1% of the sample, (+)-epibatidinie is an extraordinarily potent nicotinic agonist and was probably introduced to the sample by cross-contamination during isolation.\(^{443}\)
3.7 Previous Synthetic Studies Towards (+)- and (-)-Epiquinamide

Despite lacking biological activity, syntheses of (+)-epiquinamide 514 and its isomers continue to be reported, and to date fifteen papers have been published.376, 436-449 Two approaches with direct relevance to the proposed synthetic approach are presented.

3.7.1 Synthesis of (+)-Epiquinamide by Tong et al.

Barker and Tong synthesised (+)-epiquinamide 514 from the known aldehyde 516, which was synthesised in four steps from commercially available pipecolinic acid (Scheme 3.7.1).438

![Scheme 3.7.1: Reagents and conditions:](image)

Addition of acetylene 491 to aldehyde 516 proceeded with high diastereoselectivity favouring the desired erythro alkynol 517. Acetate protection of the free alcohol and alkyne reduction furnished cyclisation precursor 518. Formation of quinolizidine 519 was achieved in high yield over three steps; silyl deprotection, conversion to the mesylate and Boc deprotection, with cyclisation occurring upon neutralisation of the reaction mixture. After base-catalysed acetate hydrolysis, the free alcohol 520 was converted, via the mesylate, to the corresponding azide 521. This reaction proceeds with the required inversion of stereochemistry. Azide reduction and acetylation completed the synthesis to give (+)-epiquinamide 514 (Scheme 3.7.1).

Quinolizidine 520 and its enantiomer 530 have since found use in syntheses of (+)- and (-)-epiquinamide 529 respectively.444, 446
3.7.2 Synthesis of (-)-Epiquinamide by Huang et al.

Huang and co-workers utilised well developed methodology\textsuperscript{264, 450, 451} in an asymmetric synthesis of (-)-epiquinamide \textsuperscript{529} utilising a highly diastereoselective Grignard addition to (S)-3-benzyloxyglutarimide \textsuperscript{522} to introduce the desired stereochemistry (Scheme 3.7.2).\textsuperscript{439}

Scheme 3.7.2: Reagents and conditions: (a) (i) 4-tert-butyldimethylsilyloxybutylmagnesium bromide, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C, 3 h, 93%; (ii) Et\textsubscript{3}SiH, BF\textsubscript{3}·OEt\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C, rt, 2 d, 60% \textit{(dr = 96:4)}; (b) TsCl, py, CH\textsubscript{2}Cl\textsubscript{2}, -30 °C to -10 °C, overnight, 92%; (c) CAN, MeCN:H\textsubscript{2}O (9:1), 0 °C to rt, 1 h, 70%; (d) NaH, THF, -40 °C, 1 h, then 40 °C, 1 h, 100%; (e) H\textsubscript{2}, Pd/C, MeOH, rt, 1 d, 98%; (f) MsCl, Et\textsubscript{3}N, -10 °C, overnight, 100%; (g) NaN\textsubscript{3}, DMF, 65 °C, 40 h, 53%; (h) (i) LiAlH\textsubscript{4}, THF, 60 °C, 3 h; (ii) Ac\textsubscript{2}O, dioxane, 1 M NaOH, 6 h, rt, 78%.

Addition of the Grignard reagent to enantiopure glutarimide \textsuperscript{522} proceeded regioselectively at the C-2 position to give a diastereomeric mixture of \textsuperscript{523} and the open-chain keto-amide tautomer \textsuperscript{524}. Treatment of the reaction mixture with Et\textsubscript{3}SiH/BF\textsubscript{3}·OEt\textsubscript{2} proceeded via the N-acyliminium ion intermediate \textsuperscript{525} to give, in one pot, desilylated piperidinone \textsuperscript{526}. Tosylation of \textsuperscript{526} and oxidative N-deprotection gave the cyclisation precursor \textsuperscript{527}. Base-mediated cyclisation of piperidinone \textsuperscript{527} was followed by hydrogenolysis to furnish hydroxyquinolizidinone \textsuperscript{528}. The synthesis was completed by introduction of the N-acetyl functionality (\textit{vide supra}) proceeding with concomitant amide reduction to afford (-)-epiquinamide \textsuperscript{529} (Scheme 3.7.2).

Hydroxyquinolizidinone \textsuperscript{528} has featured as a key intermediate in three further syntheses of (-)-epiquinamide.\textsuperscript{376, 445, 448}
3.8 Retrosynthesis

Although displaying no known bioactivity, it was envisioned that a formal synthesis of epiquinamide would represent a good model for the formation of the quinolizidine ring system from nitrone 198.

Retrosynthetic analysis of (-)-epiquinamide 529 focused on the synthesis of the enantiomer of known hydroxyquinolizidine 530. This compound, along with its hydroxyquinolizidinone derivative, represents a popular intermediate for the synthesis of epiquinamide owing to the relative ease of conversion of the hydroxy moiety to the required cis-N-acetyl functionality.

The quinolizidine core was planned to be formed via intramolecular cyclisation of amino-diol 531, formed by N-O bond cleavage and hydrogenation of the triple bond present in hydroxylamine 534. Compound 534 can be derived by the stereoselective addition of the C-lithiated, O-silyl protected alcohol 533 to nitrone 198 (Scheme 3.8.1).
3.9  Formal Synthesis of (-)-Epiquinamide

3.9.1  Synthesis of the Cyclisation Precursor

Cyclisation precursor 531 was prepared by an analogous route to that developed for the synthesis of (+)-swainsonine 397. As a result of the extra carbon required for the six-membered ring, silyl protected but-3-yn-1-ol 533 was prepared from but-3-yn-1-ol 532 in a yield of 94%.

Addition of the lithium acetylide, formed by treatment of alkyne 533 with n-butyllithium, to a solution of nitrone 198 in THF at -78 °C proceeded diastereoselectively to furnish hydroxylamine 534 in 85% yield. Alkyne hydrogenation and application of the N-O bond cleavage/deprotection reaction previously described, gave cyclisation precursor, amine 531 in excellent yield (Scheme 3.9.1).

3.9.2  Cyclisation to the Quinolizidine Ring

Initially, cyclisation to the quinolizidine ring was attempted in accordance with the procedures of Tong et al.438 utilising intramolecular displacement of a mesylate group (Scheme 3.7.1).

Scheme 3.9.2: Reagents and conditions: (a) Boc₂O, Et₃N, CH₂Cl₂, rt, 1 h, 91%; (b) (i) MsCl, Et₃N, CH₂Cl₂, 0 °C, 1 h (ii) TFA, Et₃N, CH₂Cl₂, rt, 24 h, 63% over 2 steps.
Taking lessons from our attempts to synthesise (+)-swainsonine 397, the secondary amine of piperidine 531 was selectively protected as the N-Boc-ester 536. Elimination of DMAP from the reaction mixture prevented formation of the O-Boc-ester. A solution of alcohol 536 and triethylamine in dichloromethane was treated with mesyl chloride followed by stirring at room temperature for one hour. Cyclisation was achieved in one pot by reaction of the crude O-mesylate with trifluoroacetic acid to afford the intermediate TFA salt. Ring closure occurred upon neutralisation of the reaction mixture with excess base, furnishing quinolizidine 537 in good yield over two steps from piperidine 536 (Scheme 3.9.2).

![Figure 3.9.1. Observed NOESY interactions for quinolizidine 537.](image)

Analyses of the 2D NOESY spectrum results were consistent with formation of the quinolizidine ring system. Correlations between 1-H and both 3ax-H and 2eq-H as well as between 9a-H and both 6ax-H and 4ax-H provided strong evidence that the 1-H and 9a-H are in an axial position, confirming the trans-configuration across the C-8 to C-8a bond. Furthermore NOE correlations between 4eq-H and 6eq-H as well as between 6ax-H and 9a-H was further indicative that the desired ring system had been formed (Figure 3.9.1).

In an effort to shorten the synthesis of quinolizidine 537, application of the Mitsunobu reaction conditions developed in the synthesis of (+)-swainsonine 397 were used.

![Scheme 3.9.3: Reagents and conditions: (a) DCAD, PPh₃, Et₃N, CH₂Cl₂.](image)

Unfortunately, treatment of solution of amino-alcohol 531 with DCAD and PPh₃ using the previously described procedure was not successful, affording no product even after
stirring at room temperature overnight (Scheme 3.9.3). Substitution for DIAD was also not effective. However examination of the reaction mixture indicated that a reaction had occurred, and a second product which was inseparable from the starting material, had formed. Analysis of the $^1$H and $^{13}$C NMR spectrum of the reaction mixture showed slightly shifted peaks that were similar to the starting material.

Scheme 3.9.4: Formation of hydrazine derivative 540.

This side product was postulated to be the hydrazine derivative 540 which forms due to mono-anion 539 competing favourably as a nucleophile, in comparison to a relatively slow intramolecular attack of the amine functionality (Scheme 3.9.4). This unwanted reaction likely occurs due to the lower nucleophilicity of amine 531 in comparison to that used in the synthesis of (+)-swainsonine 397.

Scheme 3.9.5: Reagents and conditions: (a) CBr$_4$, PPh$_3$, Et$_3$N, CH$_2$Cl$_2$, 0 °C to rt, 7 h, 70%.

Cyclisation was next attempted using Appel conditions. Amino-alcohol 531 was treated with PPh$_3$ and CBr$_4$ in dichloromethane 0 °C before adding triethylamine to affect cyclisation (Scheme 3.9.5). Surprisingly, the Appel reaction proceeded quickly to furnish the desired bicycle 537 in good yield. The product obtained displayed identical spectroscopic and physical data to that obtained via mesylation.
Table 3.9.1. Summary of ring closure to form quinolizidine 537

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitsunobu</td>
<td>DCAD</td>
<td>CH₂Cl₂</td>
<td>0 to rt</td>
<td>48</td>
<td>NR</td>
</tr>
<tr>
<td>Mitsunobu</td>
<td>DIAD</td>
<td>THF</td>
<td>0 to rt</td>
<td>48</td>
<td>NR</td>
</tr>
<tr>
<td>Appel</td>
<td>CBr₄</td>
<td>CH₂Cl₂</td>
<td>0 to rt</td>
<td>7</td>
<td>70</td>
</tr>
</tbody>
</table>

3.9.3 Elaboration to (-)-Epiquinamidine

![Scheme 3.9.6: Reagents and conditions](image)

The formal synthesis of (-)-epiquinamide 529 was completed by silyl deprotection. Quinolizidine 537 was stirred overnight in a solution of TREAT-HF in acetonitrile, buffered with excess triethylamine. Although the reaction proceeded cleanly, the yield was significantly lower than what had been previously observed during the synthesis of (+)-swainsonine 397, possibly due to incomplete extraction from the aqueous phase.

Table 3.9.2 shows the melting point and the optical rotation data for quinolizidine 530 which were a good match for the reported literature values.

Table 3.9.2. Summary of physical data for quinolizidine 530.

| Physical data | Recorded data | Published data
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>mp</td>
<td>74-77 °C</td>
<td>71-72 °C⁴⁴⁶</td>
</tr>
<tr>
<td>[α]D</td>
<td>+23.0 (c 0.73, CHCl₃)</td>
<td>-21.7 (c 0.85, CHCl₃)⁴⁴⁶</td>
</tr>
</tbody>
</table>

*Published optical rotation is that of the enantiomer.

Although overlapping signals in the ¹H NMR spectrum made confirmation of the stereochemistry difficult by NOESY analysis, inspection of the ¹H NMR spectra of quinolizidine 530 revealed that the C-1 proton signal at 3.32 ppm was a ddd with coupling constants of 11.1, 8.8 and 4.6 Hz. These values are consistent with the trans-diaxial orientation of the protons in a fused decalin ring system. Additionally, the synthesised product was shown to have an identical ¹H and ¹³C NMR spectrum to a racemic sample provided by Dr David Barker.
Unfortunately, the obtained $^1$H NMR spectrum was not in agreement with that recently reported.\textsuperscript{444, 446} However neither paper had reported $^{13}$C spectrum which made comparisons difficult.

Nevertheless, earlier reports support the assignment of the products synthesised in the Caprio and Barker labs as being correct. Although full NMR data has not been published, the key C-1 proton signal has been reported by Arata \textit{et al.} who synthesised racemic quinolizidine \textbf{530} by Birch reduction of the quaternary salt \textbf{541} (Scheme 3.9.7).\textsuperscript{453}

![Scheme 3.9.7: Reagents and conditions: (a) Li, NH$_3$, 542 39\%, rac-530 24\%.](image)

The C-1 proton signal was reported as being observed at $\tau = 6.70$ (ppm = 10 – $\tau$) as a ddd with coupling constants of 11.0, 8.5 and 4.9 Hz. This value was a close match to the chemical shift and the coupling constants obtained for the C-1 proton. The melting point was also in close agreement to that reported by either Möhrle \textit{et al.}\textsuperscript{454} and Arata \textit{et al.}\textsuperscript{453} Interestingly neither Santos nor Srivastava have reported a melting point and at this time it is unclear as to the cause of the observed discrepancies. A possible explanation for the observed differences in the most recent papers could be due to the presence of the hydrochloride salt of quinolizidine \textbf{530}. This is supported by the acidic workup and reaction conditions used by both authors.\textsuperscript{444, 446}
3.10 Summary

The synthesis of (+)-swainsonine 397 was accomplished in seven steps and 29.5% overall yield from the nitrone 198. The C-2 stereocenter was installed with high selectivity, affording trans-diastereoisomer 490 as the sole product, demonstrating the utility of the nitrones of type 198 in synthesis. Partial reduction of the triple bond was followed by N-O bond reduction, proceeding with concomitant cleavage of the O-TBS group, furnishing alkenylpiperidine 489 (Scheme 3.10.1).

Scheme 3.10.1. Reagents and conditions: (a) n-BuLi, THF, -78 °C, 1 h, 90%; (b) H₂, Lindlar catalyst, EtOAc, rt, 1.25 h, 90%; (c) In, 1% HCl, EtOH, reflux, 2 h, 86%; (d) DCAD, PPh₃, CH₂Cl₂, 0 °C, 1 h, 89%; (e) (i) AD-mix-α, MeSO₂NH₂, t-BuOH:H₂O (1:1), 0-4 °C, 4 d; (ii) Ac₂O, py, DMAP, CH₂Cl₂, rt, overnight, 68% (dr = 9:1); (f) Et₃N·3HF, Et₃N, MeCN, 80 °C, 5 d, 88%; (g) NaOMe, MeOH, rt, 1 h, 80%; (h) Et₃N·3HF, Et₃N, MeCN, 80 °C, 6 d, 83%; (i) K₂CO₃, MeOH, rt 2 h, 81%.

Key bicycle 488 was then accessed by cyclisation under Mitsunobu conditions. Substrate-controlled dihydroxylation of the resultant indolizidine 488 proceeded with good selectivity (9:1) and was followed by acetylation of the resulting mixture of diols to give a separable 9:1 diastereomeric mixture of diacetates in favour of 506. Global deprotection of 506 and 507 yielded (+)-swainsonine 397 and (-)-1,2-di-epi-swainsonine 512 respectively (Scheme 3.10.1).

The extension of the developed methodology to the synthesis of quinolizidine alkaloids was realised with the formal synthesis of (-)-epiquinamide 529 in five steps and 20.7% overall yield (six steps 16.9%) from nitrone 198. Expanding on the methodology developed
for the synthesis of (+)-swainsonine, the C-2 stereocenter was installed with high selectivity, affording *trans*-diastereoisomer 534 as the sole product (Scheme 3.10.2).

Scheme 3.10.2: Reagents and conditions: (a) n-BuLi, THF, 0 °C, 1 h, 85%; (b) H₂, Pd/C, EtOAc, rt, 12 h, 91%; (c) In, EtOH, 1% HCl, reflux, 2 h, 91%; (d) Boc₂O, Et₃N, CH₂Cl₂, 1 h, 91%; (e) (i) MsCl, Et₃N, CH₂Cl₂, 0 °C, 1 h (ii) TFA, Et₃N, CH₂Cl₂, rt, 24 h, 63% over 2 steps; (f) CBr₄, PPh₃, Et₃N, CH₂Cl₂, 0 °C to rt, 7 h, 70%; (g) Et₃N·3HF, MeCN, Et₃N, 80 °C, 12 h, 42%.

Alkyne hydrogenation and cleavage of the N-O bond to alkylpiperidine 531 was followed by intramolecular cyclisation proceeding either via the mesylate or bromide. Deprotection of 537 yielded quinolizidine 530 which has previously been utilised in the synthesis of (-)-epiquinamide 529 (Scheme 3.10.2).
3.11 A Serendipitous Entry into the 2,3,6-Substituted Piperidine System

3.11.1 Proposed Synthesis of the cis-3-Hydroxypiperidine Motif

Due to the high prevalence of the cis-2,3-hydroxypiperidine moiety in nature, it was deemed that entry to this motif would be the next logical step in exploration of the synthetic potential of nitrones 198.

Although the use of metal complexes is an effective method for reversing the stereochemistry outcome of nucleophilic addition to acyclic α-alkoxy nitrones, cyclic nitrones do not share this behaviour and only poor reversal in facial selectivity has been observed.161,193,281,455 Instead a highly regio- and diastereoselective oxidation-reduction sequence has been utilised by different groups,281,455,456 taking advantage of the intermediate oxidation state of the hydroxylamine functionality.

Typically, the oxidation of 2-substituted-3-hydroxypyrrolidines proceeds regioselectively to give ketonitrone 545 as the sole product. The obtained nitrone can then be reduced diastereoselectivity, due to delivery of hydride to the less hindered face of the nitrone to furnish the corresponding cis-hydroxypyrrolidine 546 (Scheme 3.11.1). The presence of an electronegative atom such as oxygen at the C-3 position has a strong influence on selectivity of oxidation. The regioselectivity of oxidation has been determined to be dependent on the conformation of the substituents in the intermediate nitrosonium species, occurring preferentially on the side where the abstracted α-hydrogen can be oriented in an antiperiplanar disposition with respect to the β-alkoxy group. This orientation permits an electron-donating hyperconjugative effect (σC-H → σ*C·O) which specifically polarises the anti C-H bond of the α-hydrogen, favouring abstraction of the corresponding proton.168,189,218,456 Substitution at the C-2 position should further enhance this selectivity due to the general preference for the formation of the keto-nitrone.189,220,457
In contrast there have been no reports regarding the oxidation of the corresponding six-membered analogues of compound 543, and only limited examples using 2-substituted, 6-membered hydroxylamines.\textsuperscript{457-460}

The phenyl-substituted hydroxylamine 364 was considered to be an excellent model compound for the oxidation/reduction reaction. As previously discussed (Scheme 2.6.9) Boc piperidine 549 is a powerful intermediate that can be regarded as an advanced precursor for a variety of bioactive compounds.\textsuperscript{275}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme3.11.2}
\caption{Retrosynthetic analysis of (+)- and (-)-L-733,060.}
\end{figure}

(-)-L-733,060 547, a non-peptide human NK-1 receptor antagonist, can be synthesised from the ketone intermediate 548 which is readily available by oxidation of the known piperidine 549. As previously demonstrated, compound 364 can be derived from the stereoselective addition of phenylmagnesium chloride to the L-glutamic acid-derived nitrone 198. Reversal of the stereochemistry of the C-2 substituent would provide access to the diastereomer 552 from the same starting material. The obtained \textit{cis}-piperidine 552 could be used to form the enantiomeric ketone 551, which could be elaborated to (+)-L-733,060 550 (Scheme 3.11.2).
3.11.2 Attempted Enantiodivergent Synthesis of Advanced Precursor 549

Scheme 3.11.3. Reagents and conditions: (a) Boc₂O, CH₂Cl₂, Et₃N, rt, 12 h, 91%; (b) Et₃N.HF, Et₃N, MeCN, 80 °C, 12 h, 90%.

The synthesis of 3-hydroxy-2-phenylpiperidine-1-carboxylate 549 was completed in high yield over two steps using modified literature procedures (Scheme 3.11.3). Gratifyingly the spectroscopic and physical data were in agreement with those previously reported.²⁶⁴, ⁴⁶¹

Having completed the formal synthesis of (-)-L-733,060 547 attention was directed towards application of the oxidation-reduction sequence to invert the stereochemistry and access the enantiomer 550.

Scheme 3.11.4. Reagents and conditions: (a) MnO₂, CH₂Cl₂, 0 °C, 3 h; (b) (i) NaBH₄, MeOH, 0 °C, 2 h; (ii) Zn, In, EtOH, sat. NH₄Cl, reflux, 4 h, 75% over 3 steps.

The oxidation of hydroxylamine 364 and reduction of the crude nitrone 553 with NaBH₄ was carried out according to literature procedures.¹⁸⁹ Reductive cleavage of the N-O bond of the hydroxylamine surprisingly furnished amine 365 which had previously been synthesised in model studies (Scheme 3.11.4).

Two possibilities were considered in order to justify the outcome of this reaction. Firstly, presuming the desired ketonitrone 553 had formed, hydride attack could have proceeded from the opposite side to what was predicted. Alternatively the aldonitrone may have formed as the sole product and although this was deemed unlikely, owing to literature precedent,²⁸¹, ⁴⁵⁵, ⁴⁵⁶ reduction of this regioisomer would not result in alteration of the starting material stereochemistry.
To examine the reasoning behind the observed results, a small group of hydroxylamines, bearing substituents with different steric and electronic properties, were oxidised with manganese dioxide. The phenyl and vinyl substituents represent large and small groups that would be expected to form keto-nitrones due to stabilisation through conjugation. In contrast, the isopropyl, benzyl and methyl groups represent various sized, non-conjugated substituents.

![Table 3.11.1. Summary of oxidations to second generation nitrones.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>nitrone ratio 556:557</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>methyl</td>
<td>42:58</td>
<td>78</td>
</tr>
<tr>
<td>b</td>
<td>vinyl</td>
<td>unstable&lt;sup&gt;a&lt;/sup&gt;</td>
<td>71</td>
</tr>
<tr>
<td>c</td>
<td>allyl</td>
<td>22:78</td>
<td>74</td>
</tr>
<tr>
<td>d</td>
<td>benzyl</td>
<td>13:87</td>
<td>68</td>
</tr>
<tr>
<td>e</td>
<td>isopropyl</td>
<td>0:100</td>
<td>86</td>
</tr>
<tr>
<td>f</td>
<td>phenyl</td>
<td>0:100</td>
<td>89</td>
</tr>
</tbody>
</table>

<sup>a</sup>Product rapidly dimerised at rt; <sup>b</sup>ratio determined by <sup>1</sup>H NMR analysis of a crude sample

The results of the oxidation are summarised in Table 3.11.1. In all cases the aldonitrone 557 was isolated as the major product and a marked increase in regioselectivity was observed as the substituent size increased. The ratio of the vinyl substituted nitrone was not able to be determined owing to rapid dimerisation observed when analysis of the product by NMR spectroscopy was attempted.

Oxidation should occur preferentially by abstraction of the α-hydrogen, which must be oriented in an antiperiplanar conformation with respect to the β-alkoxy group in the intermediate nitrosonium species in order for the favourable electron-donating hyperconjugative effect to develop. It was postulated that this proton would be more likely to sit in the equatorial position when the C-2 substituent is bulky and would no longer be in the correct axial orientation for abstraction. Although the bulky C-2 substituent would be expected to be in the sterically favourable equatorial orientation, 1,3-allylic interactions with nitrosonium oxygen or steric interactions with the bulky β-alkoxy protecting group may force...
the substituent into the axial position. This would mean that, despite overwhelming electronic effects, abstraction would occur from the 6-position to give the aldonitrone. This is reflected in the increased favouring of the aldonitrone as the C-2 substituent gets larger, which may indicate that with the larger groups (Ph, \( i-Pr \)) the ring flip equilibrium lies more towards the diaxial substituted nitrosonium ion, whilst for the smaller substituents the ratio is much more even.

The formation of the more synthetically useful aldonitrones is interesting and has potential application in synthesis of 2,6-disubstituted-3-hydroxypiperidines. Current methodology is largely limited to the cyclisation of advanced linear precursors, and lacks synthetic flexibility, and direct introduction of substituents is only achieved via Beaks lithiation of Boc-protected piperidines.\(^{264, 463-466}\) A new method for the direct introduction of functionality to 3-hydroxypiperidines in a stereoselective manner would be an important advance in the state of the art in this field.

Due to the 3-hydroxypiperidine motif acting as a privileged scaffold, elaboration of this type of nitrone would provide a means of accessing novel, stereodefined triscaffolds for biological screening. A particular example would be to utilise a 3-hydroxypiperidinol with an anisole substituent, which as previously discussed is a synthetic equivalent of the hydroxymethyl group.\(^{77, 277}\) If the proposed sterics-dependent selectivity holds true, this compound would lead to selective formation of the desired aldonitrone which could be functionalised with a suitably substituted organometallic reagent or dipolarophile to provide rapid entry to the core structure of the Prosopis alkaloids.

3.11.3 Nucleophilic Addition to Aldonitrone 557f

![Figure 3.11.1](image-url) Proposed ring flipped orientation of aldonitrone.

Examination of the 2D-NOESY spectrum of the synthesised aldonitrones, indicated that the major conformer is one with 1,3-diaxial oriented substituents 557. It was initially postulated that the steric hindrance of the axial R-group would act to effect selectivity of nucleophilic attack or 1,3-dipolar cycloaddition (Figure 3.11.1).
Scheme 3.11.5. Reagents and conditions: (a) MeMgBr, THF, 0 °C, 1 h; (b) Zn, In, EtOH, sat. NH₄Cl, reflux, 4 h, 40% over two steps.

Addition of methylmagnesium bromide to nitrone 557f at 0 °C proceeded quickly to afford adduct 558 as the sole product (Scheme 3.11.5). Unfortunately, in contrast to the 2,3-disubstituted-N-hydroxypiperidines, the newly formed 2,3,6-disubstituted-N-hydroxypiperidines were observed to be highly unstable, undergoing oxidation to the corresponding nitrone within 30 minutes. Reductive cleavage of hydroxylamine 558 was then performed under standard conditions, yielding amine 559 in low yield over two steps (Scheme 3.11.5).

Analysis of the ¹H NMR spectrum of piperidine 559 revealed a coupling constant of $J_{2,3} 6.8$ Hz at 3.92 ppm for H-2. Although of smaller magnitude than previous examples, this was still consistent with a trans-disubstituted six-membered ring with axial-axial protons.

Figure 3.11.2. Observed NOESY interactions for piperidine 559.

Key NOESY correlations observed for piperidine 559 are presented in Figure 3.11.2. NOE correlations between the methyl protons and both 2-H and 4ax-H provided strong evidence that the methyl group was in an axial position, confirming the trans-configuration of the C-2 and C-6 substituents and attack from the side opposite to the bulky phenyl group.

Disappointingly, repeated attempts to duplicate the transformation of the N-hydroxylamine functional group were not successful, only resulting in extensive decomposition, requiring the examination of alternate reduction systems. The common Zn/AcOH/Cu(OAc)₂ system at either reflux²²⁸,²²⁹ or room temperature²⁰² and the TiCl₃/H⁺²³₃,²³⁴ were attempted. Once again rapid decomposition was observed, even with extensive
bubbling of nitrogen through the reaction mixture in an attempt to deoxygenate the solution (Table 3.11.2).

**Table 3.11.2. Summary of N-O reduction of 2,3,6-trisubstituted hydroxylamines.**

<table>
<thead>
<tr>
<th>Reducing System</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In/Zn</td>
<td>EtOH</td>
<td>100</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>Zn/Cu(OAc)₂</td>
<td>AcOH</td>
<td>100</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Zn/Cu(OAc)₂</td>
<td>AcOH/DCM</td>
<td>rt</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>TiCl₃/HCl</td>
<td>MeOH/H₂O</td>
<td>rt</td>
<td>12</td>
<td>-</td>
</tr>
</tbody>
</table>

![Scheme 3.11.6. Reagents and conditions: (a) (i) BnBr or MeI, CH₂Cl₂, rt; (ii) LiAlH₄, THF, reflux.](image)

Inspired by our work on the ethyl vinyl ether cycloadducts (Scheme 2.2.3), conversion of hydroxylamine 558 to the quaternary benzyl or methyl salt was attempted so that subsequent reduction with LiAlH₄ would directly give the corresponding N-protected amine (Scheme 3.11.6). Again, extensive decomposition of the starting material was observed, rendering determination of salt formation difficult owing to the number of polar compounds formed.

![Scheme 3.11.7. Reagents and conditions: (a) (i) MeMgBr, THF, 0 °C, 1 h; (ii) BzCl, DMAP, Et₃N, CH₂Cl₂, 0 °C, 30 min, 66%.](image)

Finally, protection of the hydroxylamine was considered, taking advantage of the reactivity of the hydroxylamine group towards acid chlorides. Addition of methylmagnesium bromide to nitrene 557f at 0 °C once again afforded adduct 558 as the sole product. After partial purification by flash column chromatography to remove polar impurities the hydroxylamine was stirred in a solution of benzoyl chloride, DMAP, triethylamine and
dichloromethane for 30 min affording protected hydroxylamine 562 in moderate yield over two steps (Scheme 3.11.7).

![Scheme 3.11.8. Reagents and conditions: (a) (i) BnMgCl, THF, 0 °C, 1 h; (ii) BzCl, Et₃N, DMAP, CH₂Cl₂. Products obtained as an inseparable mixture.](image)

The nucleophilic addition and protection reactions were repeated using benzylmagnesium chloride, affording a diastereomeric mixture of piperidines 563 and 564 in a 1:1.5 ratio as determined by ¹H NMR spectroscopy (Scheme 3.11.8). Stereochemical determination was not possible owing to the protected hydroxylamines being inseparable. Protection was repeated on purified samples of the corresponding hydroxylamines isolated from the nucleophilic addition step.

Analysis of the ¹H NMR spectrum showed J₂,₃ coupling constants of 9.2 Hz at 3.89 ppm and 9.0 Hz at 4.29 ppm for piperidines 563 and 564 respectively, confirming both compounds were trans-substituted around the C-2 to C-3 bond, and possessed diaxial orientated hydrogens.

![Figure 3.11.3. Observed NOESY interactions for piperidines 563 and 564.](image)

Key NOESY correlations for both piperidines are presented in Figure 3.11.3. Correlations between the methylene protons of the C-6 benzyl group and both 2-H and 4ax-H in compound 564, provided strong evidence that the benzyl group was in an axial position. This confirms the trans-configuration of the C-2 and C-6 substituents in piperidine 564 and attack of the nucleophile from the side opposite to the bulky phenyl group. Conversely, for
the minor isomer 563, correlations between 2-H and 6-H indicate that the C-6 substituent is in an equatorial orientation.

The differences in selectivity between the methyl and benzyl Grignard reagents were unexpected and cannot be rationalised solely in terms of steric hindrance.

Scheme 3.11.9. Conformers of the substituted aldonitrones.

Although the diaxial conformer 566 may show increased stabilisation, due to the eclipsing interactions between the nitrone oxygen and the R-group in the diequatorial conformer 565, consideration must be given as to which conformer actually participates in the reaction (Scheme 3.11.9).

Scheme 3.11.10. Competing modes for the attack on diaxial conformer 566.

Firstly, we considered the diaxial conformer 566 which has been observed by analysis of the NMR spectrum. On stereoelectronic grounds it would be expected that nucleophilic attack would proceed from “above” as this initially gives a chair-like product state, while attack from “below” gives the twist boat product state, which will in turn relax into the chair conformation. If the bulk of the R-group is the controlling factor in addition, small nucleophiles would be expected to attack from above, as stereoelectronic control are
dominant, but when larger nucleophiles are used, steric interactions with the R-group dominates and the reaction proceeds via the twist boat despite the higher energy of this conformer (Scheme 3.11.10).

This model does not correlate with the experimental observations, and although the observed selectivity could be due to pi-pi stacking of the benzyl Grignard with the phenyl group in the axial position of conformer 566 we must also consider the diequatorial conformer 565, where the bulky OTBDPS group is the dominating steric influence (Scheme 3.11.11).

![Scheme 3.11.11. Competing modes for the attack on diequatorial conformer 565.](image)

Utilisation of the arguments presented above, correlates with the experimental results. Attack from the same side as the C-3 protecting group only occurs for small nucleophiles as stereoelectronics dominate. Attack from the opposite side to the protecting group, via the twist boat, occurs when the nucleophile is large and steric effects dominate (Scheme 3.11.11).

Similar arguments have been proposed for the nucleophilic addition to polyhydroxylated, piperidine imines.⁴⁶⁷

If the proposed size dependent model for nucleophilic addition is correct, the benzyl Grignard reagent may represent a transitional point in selectivity between the cis- and trans-orientation of the C-2 and C-6 substituents. This implies that the selectivity of the reaction can be fine-tuned to access compounds with the desired orientation at the C-6 position. Stereoselective incorporation of functional groups that can easily be elaborated would be an important advance in the synthesis of piperidines.
3.11.4 1,3-Dipolar Cycloaddition to Aldonitrone 557e

The trapping of nitrones with reactive alkenes possessing electron-withdrawing groups has been shown to proceed rapidly with under mild conditions.\textsuperscript{468} Disubstituted alkenes such as dimethyl maleate were considered favourable due to the tendency for formation of regioisomers with monosubstituted, electron poor alkenes.

Accordingly, the 1,3-dipolar cycloaddition reaction was performed by stirring a room temperature solution of nitrone 557e in dichloromethane with dimethyl maleate overnight. However in this case, although the reaction proceeded quickly with little evidence of decomposition, no separation was possible between the formed cycloadduct(s) and dimethyl maleate.

![Scheme 3.11.12. Reagents and conditions: (a) CHCl$_3$, styrene, sealed tube 60 °C, 2 d, 77%.

The cycloaddition reaction of nitrone 557e with styrene was performed in chloroform under heating for 2 d in a sealed tube. This gave a mixture of isoxazolidine 567 and partially separable diastereomeric isoxazolidines 568 and 569 in a ratio of 40:1:1 respectively and an overall yield of 77% from the parent hydroxylamine (Scheme 3.11.12). High-resolution mass spectrometry of isoxazolidines 567, 568 and 569 established that the molecular formulae of these products were identical indicating that they were isomeric.

The regiochemistry of the major isomer 567 was determined from the downfield methine signal attributed to the 2-position, appearing in the $^1$H NMR spectrum as a dd at 5.29 ppm, and the corresponding carbon resonance at 77.9 ppm. This confirmed formation of the 2-substituted cycloadduct. The $^1$H NMR signal at 3.47 ppm was attributed to the H-6 proton and observed as a td with coupling constants of $J$ 9.6 and 4.6 Hz. This splitting pattern was consistent with two axial-axial and one axial-equatorial couplings, indicative of trans-diequatorial substitution across the C-7 to C-6 bond.
The key NOESY correlations observed for indolizidine 567 are presented in Figure 3.11.4. NOE correlations between 2-H and 7-H as well as 3-H and 5ax-H provided strong evidence that the reaction had proceeded selectively to give the expected exo-cycloadduct, approaching from opposite the bulky isopropyl group.

Although the mixed fraction of isoxazolidine 568 and 569 could be partially separated and the gross structure determined via COSY and HSQC, conflicting NOE interactions and small sample size meant that the stereochemistry could not be determined even with extensive NMR experiments.

Isoxazolidine 567 has the potential to act as an important intermediate for the synthesis of 2,6-disubstituted-3-hydroxypiperidine alkaloids. Styrene is known to act as a masking group for the nitrone functionality and can be cleaved relatively easily under mild conditions to regenerate the nitrone without decomposition. This temporary masking would permit access to alternatively substituted piperidines.

It was interesting to note the selectivity of the 1,3-dipolar cycloaddition reaction reflected the orientation of the nitrone as the diaxial conformer 566. As previously discussed, nucleophilic addition of more sterically demanding groups may proceed increasingly via the twist boat, preventing access to compounds with a trans-orientation between the C-2 and C-6 substituents. Therefore the high selectivity observed represents an alternate means of synthesising the 2,6-trans-compounds.
3.12 Overall Summary

The aim of this project was the development of a flexible synthetic strategy towards the enantioselective preparation of the 3-hydroxypiperidine substructure for application in the synthesis of bioactive alkaloids.

Initial studies into the regio- and stereoselectivity of the 1,3-dipolar cycloaddition reaction between O-benzyl protected 3-hydroxytetrahydropyridine N-oxide 208 has confirmed previous results obtained within the Caprio research group. The addition of a range of electron-rich, -neutral and -deficient alkenes proceeded with excellent exo/endo selectivity and near perfect regioselectivity. However the anti/syn selectivity was only moderately in favour of the desired anti-compounds.

Further development of the chiral pool based methodology has led to the gram scale synthesis of a novel O-silyl protected 3-hydroxytetrahydropyridine N-oxide 198 which demonstrated enhanced reactivity towards nucleophilic attack by a wide range of Grignard and organolithium reagents. The reaction proceeded with high diastereoselectivity, affording trans-substituted hydroxylamines as the sole products except in the case of allylmagnesium bromide.

Reductive cleavage of the formed hydroxylamines or isoxazolidine cycloadducts has generated a small library of 2-substituted-3-hydroxypiperidines which possess functional groups that are highly amenable to elaboration. The utility of the developed methodology is indicated by the prevalence of differentially N/O-protected derivatives of many model compounds as key intermediates in natural product synthesis.

Additionally we have demonstrated the nucleophilic addition of lithium acetylides with suitable chain length to be a versatile synthetic method for synthesis of the indolizidine and quinolizidine ring systems from a common nitrone intermediate.

The synthesis of (+)-swainsonine 397 was accomplished in seven steps and 29.5% overall yield from nitrone 198. The C-2 stereocenter was installed with high selectivity by the addition of the C-lithiate of protected propargyl alcohol 491 affording trans-diastereoisomer 490 as the sole product. Hydroxylamine 490 could be further elaborated to the advanced cyclisation intermediate 489 by partial reduction of the triple bond and reductive cleavage of the N-O bond. Key indolizidine bicycle 488 was accessed by cyclisation under Mitsunobu
conditions. The requisite diol of (+)-swainsonine 397 was introduced by substrate-controlled dihydroxylation of indolizidine 488, proceeding with excellent selectivity, which after peracetylation furnished a separable 9:1 diastereomeric mixture of diacetates in favour of 506. Global deprotection of polyhydroxylated indolizidines 506 and 507 yielded (+)-swainsonine 397 and (-)-1,2-di-epi-swainsonine 512 respectively.

Extension of the developed methodology to the synthesis of quinolizidine alkaloids was realised via the use of protected but-3-yn-1-ol 533 as starting material with the formal synthesis of (-)-epiquinamide 529 being achieved in five steps and 20.7% overall yield from nitrone 198. Alkyne hydrogenation and cleavage of the N-O bond to alkylpiperidine 535 was followed by intramolecular cyclisation proceeding via either the mesylate or bromide. Deprotection of 537 yielded quinolizidine 530 of which the enantiomer has previously been utilised in the synthesis of (+)-epiquinamide 529.

Finally, a proposed strategy for the synthesis of cis-2,3-substituted piperidines, has led to the development of methodology for entry into the 2,6-disubstituted-3-hydroxypiperidine motif. Oxidation of 2,3-disubstituted-N-hydroxypiperidines unexpectedly provided access to the synthetically challenging aldonitrone. Nucleophilic addition and 1,3-dipolar cycloaddition have been shown to proceed with high selectivity giving access to highly substituted stereochemically defined piperidine scaffolds.
3.13 Future Work

Although a considerable amount of progress has been accomplished, demonstrating that nitrone 198 has significant potential in the synthesis of bioactive alkaloids containing the 3-hydroxypiperidine substructure, significant scope remains for further research.

The synthetic utility of nitrones of this type has still not been fully explored and it is believed that the selectivity of the 1,3-dipolar cycloaddition reaction can still be optimised. Addition of alkenes with increased steric bulk is proposed in order to selectively furnish the desired trans-disubstituted products. The increased diastereoselectivity observed for the 1,3-dipolar cycloaddition with γ-lactones by Stecko et al.\textsuperscript{246, 247} indicates that disubstituted or cyclic alkenes might proceed with higher selectivity due to increased steric interactions with the axial substituted C-3 hydroxyl protecting group.

Extensive scope for further research also lies in the examination into the mechanism of formation of aldonitrones from 2,3-disubstituted hydroxylamines.

Initial work needs to be directed towards determination of the factors which influence the regioselectivity of oxidation. Oxidation of wider range of hydroxylamines with varying C-2 substituents displaying different steric and electronic properties needs to be examined. The effect of temperature and alternate oxidants, which have been demonstrated to influence the regioselectivity of oxidation also needs to be studied.\textsuperscript{189}

Once a number of differently substituted aldonitrones have been synthesised, a more thorough examination of the yield and stereoselectivities of 1,3-dipolar cycloadditions and nucleophilic additions can be conducted. A wider range of aromatic and non-aromatic substrates and reagents is required in order to develop an understanding of the reasons behind the observed selectivity of addition.
4. Experimental

4.1 General Experimental Details

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen using standard Schlenk-line techniques and oven dried glassware. All solvents were purified using the methods prescribed by Armarego and Chai. All reagents purchased from commercial suppliers were used as received unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) using aluminium plates pre-coated with Merck Kieselgel 60 F254. Compounds were visualised by ultraviolet irradiation (254 nm) or iodine vapour followed by staining with an acidic ethanolic solution of vanillin, ninhydrin or alkaline potassium permanganate solution and heating. Flash column chromatography was performed under pressure using Kieselgel S 63-100 μm (Riedel-de-Hahn) silica gel or reverse phase C18 chromatography as solid support with the indicated eluent. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials, unless otherwise stated. NMR spectra were recorded on either a Bruker DRX300 spectrometer operating at 300 MHz for 1H nuclei and 75 MHz for 13C nuclei or a Bruker DRX400 spectrophotometer operating at 400 MHz for 1H nuclei and 100 MHz for 13C nuclei. The chemical shifts are reported relative to TMS (1H 0.00 ppm), CDCl3 (1H 7.26 ppm, 13C 77.0 ppm), CD3OD (1H 3.31 ppm, 13C 49.15 ppm) or DMSO-d6 (1H 2.50 ppm, 13C 39.51 ppm). Chemical shifts are reported in parts per million (ppm) on the δ scale and coupling constants, J in hertz (Hz). Multiplicities are described as singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of doublets of doublets of doublets (dddd), triplet (t), doublet of triplets (dt), multiplet (m), broad (b). The symbols * and ** are used where possible to differentiate between the two isomers present in a mixed sample or to designate the presence of the rotamer signal of the specified carbon. Infrared (IR) spectra were recorded on a Spectrum One FT-IR ATR (Attenuated Total Reflectance) spectrometer from a thin film deposited on a zinc selenide and diamond crystal composite window. Melting points were determined on a Kofler hot-stage apparatus, and are uncorrected. Mass spectra and accurate mass data were obtained on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV for low resolution and at a nominal resolution of 5000 to 10000 as appropriate for high resolution. Optical rotations ([α]20D = 100(α_{obs}−α_{blank})/l.c) were measured by a Perkin-Elmer 341 polarimeter at 589 nm (sodium-D line). [α]20D values are reported in 10−1 deg cm2 g−1; concentration (c) is in g 100 mL−1.
4.2 Synthesis of O-Benzyl Protected Nitrone

(S)-5-Oxotetrahydrofuran-2-carboxylic acid (284)

(S)-5-Oxotetrahydrofuran-2-carboxylic acid 284 was prepared according to the literature procedure.216 A solution of sodium nitrite (16.8 g, 244 mmol) in deionised water (120 mL) was added over 3 h by syringe pump to a solution of L-glutamic acid 283 (30.0 g, 204 mmol) in dilute hydrochloric acid (1 mol L⁻¹, 320 mL) while maintaining an internal temperature below -2 °C. The solution was stirred at room temperature overnight and the aqueous phase removed under reduced pressure. The resulting residue was dissolved in ethyl acetate (250 mL) and stirred over anhydrous sodium sulphate (30 g, 249 mmol) for 2 h. The filtrate was concentrated under reduced pressure to give a pale yellow viscous oil which solidified upon standing overnight. The crude product was dissolved in anhydrous diethyl ether (100 mL), filtered and the solution stored in a freezer (-20 °C), to give the title compound (12.2 g, 46%) as a white crystalline solid. The spectroscopic data was in agreement with that reported in the literature.471

\[ \left[ \alpha \right]_{D}^{20} +15.9 \ (c \ 2.0, \ \text{EtOH}) \ \text{lit.} \left[ \alpha \right]_{D}^{20} +16.0 \ (c \ 2.0, \ \text{EtOH}); \delta_{H} \ (300 \ \text{MHz}; \ \text{CDCl}_3) \ 2.35-2.47 \ (1H, \ m, \ \text{CH}-3), \ 4.99-5.04 \ (1H, \ m, \ \text{CH}-2-H), \ 9.06 \ (1H, \ s, \ \text{CO}_2\text{H}). \]

(2S)-Dimethyl 2-hydroxypentanedioate (285)

(2S)-Dimethyl 2-hydroxypentanedioate 285 was prepared according to the literature procedure.472 Four drops of concentrated hydrochloric acid were added to a stirred solution of acid lactone 284 (6.0 g, 46.1 mmol) in methanol (60 mL). The reaction mixture was then stirred under reflux for 12 h, cooled to room temperature and sodium bicarbonate (1.0 g, 11.9 mmol) was added. The reaction mixture was stirred for a further 10 min, filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in dichloromethane (60 mL), and the solution dried with anhydrous magnesium sulphate and concentrated under
reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (4:1), to give the title compound (7.6 g, 93%) as a colourless oil. The spectroscopic data was in agreement with that reported in the literature.473

\([\alpha]_D^{20} -2.5 \text{ (c 0.9, EtOH)} \text{ lit. } [\alpha]_D^{20} -2.48 \text{ (neat)} ; \delta_H (300 MHz; CDCl}_3\) 1.91-2.00 (1H, m, CH\textsubscript{a}H\textsubscript{b}-3), 2.14-2.22 (1H, m, CH\textsubscript{a}H\textsubscript{b}-3), 2.24-2.58 (2H, m, H-4), 2.95 (1H, br s, OH), 3.68 (3H, s, C5-OMe), 3.80 (3H, s, C1-OMe), 4.25 (1H, dd, J\textsubscript{2-3a} 7.9, J\textsubscript{2-3b} 4.2 Hz, H-2); \delta_C (75 MHz; CDCl\textsubscript{3}) 29.1 (CH\textsubscript{2}, C-4), 29.3 (CH\textsubscript{2}, C-3), 51.6 (CH\textsubscript{3}, 5-OMe), 52.5 (CH\textsubscript{3}, 1-OMe), 69.4 (CH, C-2), 173.5 (C, C-1), 174.9 (C, C-5).

(2S)-Dimethyl 2-(benzyloxy)pentanedioate (286)

Silver(I) oxide was prepared from silver nitrate according to the literature procedure in a quantitative yield.474,475

A solution of hydroxydiester 285 (4.77 g, 27.1 mmol) in ethyl acetate (23 mL) was added dropwise to a suspension of freshly prepared silver(I) oxide (9.29 g, 40.1 mmol) in ethyl acetate (23 mL) at room temperature. The mixture was stirred for 10 min then benzyl bromide (4.74 mL, 40.1 mmol) was added. The reaction mixture was stirred at this temperature for 48 h then filtered through a short pad of Celite\textsuperscript{®} and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (1:4), to give the title compound (5.69 g, 79%) as a colourless oil.

\([\alpha]_D^{20} -71.6 \text{ (c 1.0, EtOH)} ; \nu_{\text{max}} \text{ (film) 3055, 2953 (C-H), 1735 (C=O), 1437 (C=C), 1206 cm}^{-1}; \delta_H (300 MHz; CDCl\textsubscript{3}) 2.06-2.18 (2H, m, H-3), 2.46 (2H, t, J\textsubscript{4,5} 7.4 Hz, H-4), 3.63 (3H, s, C1-OMe), 3.76 (3H, s, C5-OMe), 4.01 (1H, dd, J\textsubscript{2-3a} 8.2, J\textsubscript{2-3b} 4.5 Hz, H-2), 4.40 (1H, d, J\textsubscript{gem} 11.6 Hz, OCH\textsubscript{a}H\textsubscript{b}Ph), 4.72 (1H, d, J\textsubscript{gem} 11.6 Hz, OCH\textsubscript{a}H\textsubscript{b}Ph), 7.27-7.38 (5H, m, Ar-H); \delta_C (75 MHz; CDCl\textsubscript{3}) 27.9 (CH\textsubscript{2}, C-3), 29.6 (CH\textsubscript{2}, C-4), 51.6 (CH\textsubscript{3}, 5-OMe), 52.0 (CH\textsubscript{3}, 1-OMe), 72.4 (CH\textsubscript{2}, OCH\textsubscript{2}Ph), 76.5 (CH, C-2), 127.9 (CH, C-Ar), 128.1 (CH, C-Ar), 128.4 (CH, C-Ar), 137.2 (C, C-Ar), 172.7 (C, C-1), 173.3 (C, C-Ar); m/z (CI, NH\textsubscript{3}) 267 (93, MH\textsuperscript{+}), 235 (20), 198 (2), 181 (10), 176 (2), 160 (18), 145 (7), 108 (27), 91 (100%). HRMS (CI, NH\textsubscript{3}): MH\textsuperscript{+}, found C\textsubscript{14}H\textsubscript{19}O\textsubscript{5} requires 267.1233. C\textsubscript{14}H\textsubscript{19}O\textsubscript{5} requires 267.1233.
(2S)-2-(Benzyloxy)pentane-1,5-diol (287)

A solution of benzyloxydiester 286 (13.5 g, 50.7 mmol) in diethyl ether (270 mL) was added dropwise to a stirred solution of lithium aluminium hydride (3.86 g, 102 mmol) in diethyl ether (270 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 h then quenched by careful addition of ethyl acetate (270 mL) then water (24 mL) and aqueous sodium hydroxide (4 mol L⁻¹, 6 mL). The mixture was extracted with diethyl ether (3 × 200 mL) and the combined organic layers were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (2:1), to give the title compound (9.44 g, 88%) as a colourless oil.

[α]D²⁰ -19.7 (c 1.1, EtOH); νmax (film) 3369 (OH), 2942 (C-H), 1454 (C=C), 1062 cm⁻¹; δH (300 MHz; CDCl₃) 1.59-1.72 (4H, m, H-3, H-4), 1.96 (2H, br s, OH), 3.52-3.64 (4H, m, H-1, H-5), 3.69-3.73 (1H, m, H-2), 4.57 (1H, d, J_gem 11.5 Hz, OCH₃,H₆Ph), 4.62 (1H, d, J_gem 11.5 Hz, OCH₃,H₅Ph), 7.29-7.36 (5H, m, Ar-H); δC (75 MHz; CDCl₃) 27.3 (CH₂, C-3), 28.4 (CH₂, C-4), 62.7 (CH₂, C-5), 64.0 (CH₃, C-1), 71.6 (CH₂, OCH₃Ph), 79.4 (CH, C-2), 127.8 (2 x CH, C-Ar), 128.5 (CH, C-Ar), 138.2 (C, C-Ar), m/z (CI, NH₃) 211 (100, MH⁺), 193 (6), 108 (19), 101 (19), 91 (87), 85 (9), 71 (23%). HRMS (CI, NH₃): MH⁺, found 211.1337. C₁₂H₁₉O₃ requires 211.1334.

(2S)-(2-Benzyloxy)-1,5-bis(para-toluenesulfonyloxy)pentane (288)

A solution of para-toluenesulfonyl chloride (7.60 g, 39.9 mmol), in dichloromethane (50 mL) was added dropwise to a stirred solution of diol 287 (2.76 g, 13.1 mmol), triethylamine (5.3 mL, 38 mmol) and N,N-dimethyl-4-aminopyridine (0.32 g, 2.62 mmol) in dichloromethane (50 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h and then concentrated under reduced pressure. The residue was diluted with a solution of saturated aqueous brine and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over anhydrous magnesium sulphate and concentrated.
under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (1:2), to give the title compound (5.83 g, 86%) as a white solid.

\[ \alpha \]$_{D}^{20}$ -16.0 (c 0.9, CHCl$_3$); \( \nu_{\text{max}} \) (film) 3032, 2924 (C-H), 1597, 1453 (C=C), 1357, 1175 cm$^{-1}$; \( \delta_{\text{H}} \) (300 MHz; CDCl$_3$) 1.46-1.54 (2H, m, H-3), 1.60-1.72 (2H, m, H-4), 2.44 (6H, s, Ar-Me), 3.54 (1H, dq, \( J_{\text{gem}} \) 11.6 Hz, OCH$_{2}$Ph), 4.52 (1H, d, \( J_{\text{gem}} \) 11.6 Hz, OCH$_{2}$Ph), 7.20-7.22 (2H, m, Ar-H), 7.28-7.32 (3H, m, Ar-H), 7.32-7.34 (4H, m, Ar-H), 7.74-7.78 (4H, m, Ar-H); \( \delta_{C} \) (75 MHz; CDCl$_3$) 21.6 (CH$_3$, Ar-Me), 21.6 (CH$_3$, Ar-Me), 24.6 (CH$_2$, C-3), 27.5 (CH$_2$, C-4), 70.0 (CH$_2$, C-5), 70.8 (CH$_2$, C-1), 72.2 (CH$_2$, OCH$_2$Ph), 75.4 (CH, C-2), 127.8 (CH, C-Ar), 127.8 (CH, C-Ar), 127.8 (CH, C-Ar), 127.9 (CH, C-Ar), 128.4 (CH, C-Ar), 129.9 (CH, C-Ar), 132.8 (C, C-Ar), 133.1 (C, C-Ar), 137.7 (C, C-Ar), 144.8 (C, C-Ar), 145.0 (C, C-Ar); m/z (FAB) 519 (5, MH$^+$), 391(2), 347 (3) 341 (1), 257 (20), 219 (4), 165 (6), 91 (100), 85 (20%). HRMS (FAB): MH$^+$, found 519.1517. C$_{26}$H$_{31}$O$_7$S$_2$ requires 519.1511.

(35)-3-(Benzyloxy)-N-hydroxypiperidine (289)

\[ \begin{align*}
&\text{N} \\
&\text{O} \\
&\text{Bn} \\
&\text{OH}
\end{align*} \]

Ditosylate 288 (16.5 g, 31.9 mmol) was added to a stirred suspension of hydroxylamine hydrochloride (9.97 g, 144 mmol) in triethylamine (125 mL) at room temperature. The reaction mixture was stirred under reflux for 4 h and then cooled to room temperature. Diethyl ether (100 mL) was added and the suspension stirred for 1 h and filtered through Celite\textsuperscript{®}. The filtrate was dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (1:24), to give the title compound (5.10 g, 77%) as a colourless oil.

\[ \alpha \]$_{D}^{20}$ -9.6 (c 0.96, EtOH); \( \nu_{\text{max}} \) (film) 320 (OH), 3054, 2951 (C-H), 1454 (C=C) cm$^{-1}$; \( \delta_{\text{H}} \) (300 MHz; DMSO-$d_6$, 373.15 K) 1.17-1.33 (1H, m, CH$_3$H$_6$-4), 1.40-1.57 (1H, m, CH$_3$H$_6$-5), 1.64-1.76 (1H, m, CH$_3$H$_6$-5), 1.78-1.89 (1H, m, CH$_3$H$_6$-4), 2.42-2.53 (2H, m, CH$_3$H$_6$-2, CH$_3$H$_6$-6), 2.83-2.94 (1H, m, CH$_3$H$_6$-6), 3.11-3.22 (1H, m, CH$_3$H$_6$-2), 3.52-3.63 (1H, m, H-3), 4.54 (2H, s, OCH$_2$Ph), 7.21-7.36 (5H, m, Ar-H); \( \delta_{C} \) (75 MHz; DMSO-$d_6$, 353.15 K)
20.3 (CH$_2$, C-5), 28.7 (CH$_2$, C-4), 57.5 (CH$_2$, C-6), 62.3 (CH$_2$, C-2), 69.1 (CH$_2$, OCH$_2$Ph), 73.2 (CH, C-3), 126.5 (CH, C-Ar), 126.7 (CH, C-Ar), 127.5 (CH, C-Ar), 138.6 (C, C-Ar); $m/z$ (EI) 207 (M$^+$, 2%), 190 (1), 116 (16), 101 (3), 91 (100), 71 (22); HRMS (EI) C$_{12}$H$_{17}$NO$_2$ [M$^+$] requires 207.1259, found 207.1261.

(3S)-3-Benzylxoy-3,4,5,6-tetrahydropyridine N-oxide (208) and (5S)-5-benzylxoy-3,4,5,6-tetrahydropyridine N-oxide (290)

Hydroxypiperidine 289 (0.89 g, 4.3 mmol) in dichloromethane (10 mL) was added to a stirred suspension of activated manganese(IV) oxide (1.49 g, 17.1 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. The resulting suspension was filtered through a pad of magnesium sulphate/Celite® and the filtrate concentrated under reduced pressure, at a water bath temperature below 20 °C, to give a yellow oil. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (1:24), to give the title compounds 208 (0.45 g, 51%) and 290 (0.16 g, 18%) as yellow oils.

Data for 290: $R_f$ (5% MeOH/CH$_2$Cl$_2$) 0.17; [α]$_D^{20}$ +21.1 (c 1.0, CHCl$_3$); $\nu_{\text{max}}$ (film) 3053, 2985 (C-H), 1422 (C=C) cm$^{-1}$; $\delta_H$ (300 MHz; CDCl$_3$) 1.75-1.83 (1H, m, CH$_a$,H$_b$-4), 1.95-2.05 (1H, m, CH$_a$,H$_b$-4), 2.39-2.41 (1H, m, CH$_a$,H$_b$-3), 2.60-2.61 (1H, m, CH$_a$,H$_b$-3), 3.90 (2H, br s, H-6), 3.94-3.99 (1H, m, H-5), 4.56 (1H, d, $J_{\text{gem}}$ 12.0 Hz, OCH$_a$,H$_b$Ph), 4.61 (1H, d, $J_{\text{gem}}$ 12.0 Hz, OCH$_a$,H$_b$Ph), 7.16-7.27 (1H, m, H-2), 7.28-7.36 (5H, m, Ar-H); $\delta_C$ (75 MHz; CDCl$_3$) 127.5 (CH, C-5'), 127.9 (CH, C-3'), 128.5 (CH, C-4'), 136.0 (CH, C-2), 137.5 (C, C-2'); $m/z$ (EI) 205 (3, M$^+$), 184 (3), 109 (3), 99 (10), 91 (100), 83 (9%). HRMS (EI): M$^+$, found 205.1098. C$_{12}$H$_{17}$NO$_2$ requires 205.1103.

Data for 208: $R_f$ (5% MeOH/CH$_2$Cl$_2$) 0.11; [α]$_D^{20}$ -72.0 (c 1.2, EtOH); $\nu_{\text{max}}$ (film) 3031, 2949 (C-H), 1454 (C=C) cm$^{-1}$; $\delta_H$ (300 MHz; CDCl$_3$) 1.82-1.93 (3H, m, H-4, CH$_a$,H$_b$-5), 2.16-2.21 (1H, m, CH$_a$,H$_b$-5), 3.74-3.83 (2H, m, H-6), 4.15-4.18 (1H, m, H-3), 4.60 (2H, s, OCH$_2$Ph), 7.22 (1H, d, $J$ 3.7 Hz, H-2), 7.31-7.36 (5H, m, Ar-H); $\delta_C$ (75 MHz; CDCl$_3$) 19.0 (CH$_2$, C-5), 24.4 (CH$_2$, C-4), 58.7 (CH$_2$, C-6), 70.3 (CH, C-3), 71.0 (CH$_2$, OCH$_2$Ph), 127.6
(CH, C-5’), 128.0 (CH, C-3’), 128.5 (CH, C-4’), 135.1 (CH, C-2), 137.4 (C, C-2’); m/z (CI, NH₃) 206 (6, MH⁺), 192 (14), 190 (100), 188 (15), 174 (6), 100 (16), 98 (32), 91 (9), 84 (13%). HRMS (CI, NH₃): MH⁺, found 206.1182. C₁₂H₁₆NO₂ requires 206.1181.

4.3 Model Studies Utilising O-Benzyl Nitrone

General procedure for the synthesis of cycloadducts

A solution of dipolarophile in the solvent stated was added to a stirred solution of nitrone 208 in the same solvent at room temperature. The reaction mixture was then stirred at the temperature for the time specified. The solution was cooled to room temperature and filtered through a short pad of Celite® and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with the specified solvent.

(2R,3aR,4S)-2-Ethoxy-4-(benzyloxy)-hexahydrooxazolo[2,3-a]pyridine (296) and (2S,3aS,4S)-2-ethoxy-4-(benzyloxy)-hexahydrooxazolo[2,3-a]pyridine (297)

Following the general procedure, a solution of ethyl vinyl ether 295 (0.18 g, 2.4 mmol) in toluene (2 mL) was added to a solution of nitrone 208 (0.050 g, 0.24 mmol) in toluene (2 mL) and the mixture stirred at 45 °C for 3 h. Purification of the residue by flash column chromatography, eluting with ethyl acetate-hexanes (3:17), gave the title compounds 296 (0.036 g, 53%) and 297 (0.018 g, 27%) as yellow oils.

Data for 296: Rₛ (50% EtOAc/hexanes) 0.54; [α]D²⁰ -29.2 (c 1.1, CHCl₃); νₓ max (film) 2938, 2864 (C-H), 1454 (C=C), 1084, 989, 735, 697 cm⁻¹; δₓH (300 MHz; DMSO-d₆, 373.15 K) 1.12 (3H, t, J₂-₁ 7.0 Hz, H-2'), 1.22-1.35 (1H, m, H-5ax), 1.56-1.67 (2H, m, 6-H), 1.99-2.08 (1H, m, H-5eq), 2.12 (1H, ddd, J 2.3, 6.1, 12.7 Hz, 3-Ha), 2.22-2.34 (1H, m, 3-Hb), 2.67-2.80 (1H, m, H-7ax), 2.80-2.92 (1H, m, 3a-H), 3.12-3.21 (1H, m, H-7eq), 3.35 (1H, ddd, J 4.3, 8.1, 9.7 Hz, H-4), 3.44 (1H, dq, Jₓ gem 9.9, Jₓ-ₓ 7.0 Hz, CHₓaH₃b-1'), 3.62 (1H, dq, Jₓ gem 9.9, Jₓ-ₓ 7.0 Hz, CHₓaH₃bPh), 4.48 (1H, d, Jₓ gem 12.0 Hz, OCHₓaH₃bPh), 4.60 (1H, d, Jₓ gem 12.0 Hz, OCHₓaH₃bPh), 5.10 (1H, dd, J 2.3, 6.1 Hz, H-2), 7.23-7.39 (5H, m, Ar-H); δₓC (75 MHz; DMSO-d₆, 373.15 K) 14.5 (CH₃, C-2’), 19.7 (CH₂, C-6), 27.7 (CH₂, C-5), 39.2 (CH₂, C-3),

190
51.0 (CH2, C-7), 62.0 (CH2, C-1’), 64.4 (CH, C-3a), 69.6 (CH2, OCH2Ph), 75.6 (CH, C-4), 100.1 (CH, C-2), 126.7 (CH, C-Ar), 127.0 (CH, C-Ar), 127.6 (CH, C-Ar), 138.5 (C, C-Ar); m/z (EI) 277 (21, M+), 260 (65), 186 (38), 171 (6), 116 (10), 91 (100), 71 (57), 65 (6), 43 (14%). HRMS (EI): M+ found 277.1683. C16H23NO3 requires 277.1678.

Data for 297: Rf (50% EtOAc/hexanes) 0.37; [α]D20 +55.2 (c 1.1, CHCl3); νmax (film) 2926, 2868 (C-H), 1454 (C=C), 1108, 1078, 735, 696 cm⁻¹; δH (300 MHz; DMSO-d6, 353.15 K)
1.12 (3H, t, J2,1ʹ 7.0 Hz, H-2ʹ), 1.28-1.41 (1H, m, H-6ax), 1.48-1.61 (1H, m, H-5ax), 1.61–1.77 (2H, m, H-5eq, H-6eq), 1.89 (1H, ddd, J 1.2, 6.0, 12.7 Hz, 3-Hb), 2.42 (1H, ddd, J 6.0, 10.9, 12.7 Hz, 3-Ha), 2.67-2.79 (1H, m, H-7ax), 2.81-2.91 (1H, m, H-7eq), 3.45 (1H, dq, J 9.9, 7.0 Hz, OCHaHbCH3), 3.49 (1H, br s, 3a-H), 3.61 (1H, dq, J 9.9, 7.0 Hz, OCHaHbCH3), 3.82 (1H, ddd, J 4.3, 4.3, 8.5 Hz, H-4), 4.49 (1H, d, J gem 12.1 Hz, OCHaHbPh), 4.58 (1H, d, J gem 12.1 Hz, OCHaHbPh), 5.29 (1H, d, J 1.2, 6.0 Hz, H-2), 7.22-7.38 (5H, m, Ar-H); δC (75 MHz; DMSO-d6, 353.15 K) 14.6 (CH3, C-2ʹ), 19.1 (CH2, C-6), 24.3 (CH2, C-5), 33.9 (CH2, C-3), 51.3 (CH2, C-7), 61.5 (CH, C-3a), 61.9 (CH2, C-1ʹ), 69.9 (CH2, OCH2Ph), 73.7 (CH, C-4), 101.5 (CH, C-2), 126.7 (CH, C-Ar), 126.8 (CH, C-Ar), 127.6 (CH, C-Ar), 138.4 (C, C-Ar); m/z (EI) 277 (13, M+), 260 (49), 186 (31), 171 (7), 116 (10), 91 (100), 71 (54), 65 (9), 43 (13%). HRMS (EI): M+ found 277.1677. C16H23NO3 requires 277.1678.

2-[(2R,3S)-1-Benzyl-3-(benzyloxy)piperidin-2-yl]-ethan-1-ol (300)

Benzyl bromide (0.13 mL, 1.10 mmol) was added dropwise to a stirred solution of cycloadduct 296 (0.29 g, 1.05 mmol) in dichloromethane (12 mL) at room temperature. The reaction was then stirred overnight and concentrated under reduced pressure to give a yellow oil. The residue was diluted with tetrahydrofuran (15 mL) and lithium aluminium hydride (0.060 g, 1.58 mmol) was added portionwise. The mixture was then stirred under reflux for 3 h, cooled to 0 °C, and diluted with ethyl acetate (15 mL). The reaction was quenched by the addition of a saturated solution of Rochelle's salt (5 mL) and the mixture stirred for 30 min, filtered through Celite® and extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were concentrated under reduced pressure and the residue was purified by flash
column chromatography, eluting with methanol-dichloromethane (1:49), to give the title compound (0.20 g, 59% over two steps) as a yellow oil.

\[ [\alpha]_D^{20} +4.0 (c 0.80, \text{CHCl}_3); \nu_{\text{max}} (\text{film}) 3402 (\text{OH}), 2936, 2861 (\text{C-H}), 1452 (\text{C=C}), 1070, 732 \text{ cm}^{-1}; \delta_H (300 \text{ MHz}; \text{CDCl}_3) 1.24-1.38 (1H, m, CH\_a\_Hb\_5), 1.59-1.77 (2H, m, CH\_a\_Hb\_4, CH\_a\_Hb\_2'), 1.81-1.93 (1H, m, CH\_a\_Hb\_5), 1.93-2.05 (1H, m, CH\_a\_Hb\_4), 2.05-2.19 (1H, m, CH\_a\_Hb\_2'), 2.31 (1H, ddd, J 13.1, 7.1, 3.2, CH\_a\_Hb\_6), 2.84-2.92 (1H, m, H-2), 2.92-3.00 (1H, m, CH\_a\_Hb\_6), 3.44 (1H, ddd, J 6.6, 5.3, 3.5 Hz, H-3), 3.67 (1H, d, J\text{gem} 13.0 Hz, NCH\_a\_HbPh), 3.70-3.87 (2H, m, H-1'), 4.27 (1H, d, J\text{gem} 13.0 Hz, NCH\_a\_HbPh), 4.48 (1H, d, J\text{gem} 11.7 Hz, OCH\_a\_HbPh), 4.63 (1H, d, J\text{gem} 11.7 Hz, OCH\_a\_HbPh), 7.20-7.39 (10H, m, Ar-H); \delta_C (75 \text{ MHz}; \text{CDCl}_3) 17.9 (CH\_2), 127.6 (CH\_a\_Hb\_6), 127.1 (CH, C-Ar), 127.5 (CH, C-Ar), 127.6 (CH, C-Ar), 128.3 (CH, C-Ar), 128.4 (CH, C-Ar), 129.2 (CH, C-Ar), 138.6 (C, C-Ar), 138.7 (C, C-Ar); m/z (EI) 325 (0.3, M\text{+}), 280 (5), 234 (12), 91 (100), 65 (14), 41 (4%). HRMS (EI): M\text{+}, found 325.2048. C\text{21}H\text{27}NO\text{2} requires 325.2042.

2-[(2R,3S)-3-(Benzyloxy)piperidin-2-yl]-ethan-1-ol (301)

Palladium on carbon (4.5 mg) was added portionwise, to a solution of N-benzylpiperidine (0.045 g, 0.14 mmol) 300 in methanol (4.5 mL) and the mixture stirred under hydrogen for 6 h then filtered through Celite\textsuperscript{®}. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography, eluting with methanol-dichloromethane (9:1), to give the title compound (0.030 g, 100%) as a white solid.

m.p. 68.0-70.8 °C; [\alpha]_D^{20} +62.5 (c 0.56, CHCl\textsubscript{3}); \nu_{\text{max}} (solid) 3301 (NH), 3136 (OH), 2946, 2919, 2857, 2836 (C-H), 1454 (C=C), 1093, 1054 cm\textsuperscript{-1}; \delta_H (300 \text{ MHz}; \text{CDCl}_3) 1.35-1.45 (2H, m, H-4ax, H-5ax), 1.52-1.66 (1H, m, CH\_a\_Hb\_2'), 1.70-1.83 (1H, m, H-5eq), 1.94-2.05 (1H, m, CH\_a\_Hb\_2'), 2.18-2.27 (1H, m, H-4eq), 2.48-2.59 (1H, m, H-6ax), 2.75 (1H, td, J\text{J2,2'} = J\text{J2,2'} 8.7, J\text{J2,2'} 2.8 Hz, H-2), 2.89-2.99 (1H, m, H-6eq), 3.02 (2H, br s, O\_H, NH), 3.08 (1H, ddd, J\text{J3,4ax} 9.4, J\text{J3,4eq} 8.7, J\text{J3,4eq} 4.1 Hz, H-3), 3.76-3.83 (2H, m, H-1'), 4.43 (1H, d, J\text{gem} 11.5 Hz, OCH\_a\_HbPh), 4.64 (1H, d, J\text{gem} 11.5 Hz, OCH\_a\_HbPh), 7.23-7.38 (5H, m, Ar-H); \delta_C (75 MHz;
CDCl₃) 25.7 (CH₂, C-5), 29.3 (CH₂, C-4), 33.1 (CH₂, C-2'), 45.1 (CH₂, C-6), 62.1 (CH, C-2), 62.7 (CH₂, C-1'), 70.4 (CH₂, OCH₂Ph), 78.2 (CH, C-3), 127.6 (CH, C-Ar), 127.7 (CH, C-Ar), 128.3 (CH, C-Ar), 138.4 (C, C-Ar); m/z (FAB⁺, m-nitrobenzylalcohol) 236 (5, MH⁺), 154 (100), 136 (70), 124 (10), 120 (10), 107 (22), 89 (20%). HRMS (FAB⁺, m-nitrobenzylalcohol): MH⁺, found 236.1652. C₁₄H₂₂NO₂ requires 236.1651.

2-[(2S,3S)-1-Benzyl-3-(benzyloxy)piperidin-2-yl]-ethan-1-ol (303)

Benzyl bromide (0.074 mL, 0.62 mmol) was added dropwise to a stirred solution of cycloadduct 297 (0.16 g, 0.59 mmol) in dichloromethane (6 mL) at room temperature. The reaction was then stirred overnight and concentrated under reduced pressure to give a tan amorphous solid. The residue was diluted with tetrahydrofuran (10 mL) and lithium aluminium hydride (0.034 g, 0.89 mmol) was added portionwise. The mixture was then stirred under reflux for 3 h, cooled to 0 °C and diluted with ethyl acetate (10 mL). The reaction was quenched by the addition of a saturated solution of Rochelle's salt (5 mL) and the mixture stirred for 30 min, filtered through Celite® and extracted with ethyl acetate (4 × 25 mL). The combined organic extracts were concentrated under reduced pressure and the residue was purified by flash column chromatography, eluting with methanol-dichloromethane (1:49), to give the title compound (0.10 g, 52% over two steps) as a colourless oil.

[α]D₂₀ -7.0 (c 1.00, CHCl₃); νmax (film) 3379, 3028, 2930, 2856 (C-H), 1732, 1453 (C=C), 1091, 1072, 1026, 732, 696 cm⁻¹; δH (300 MHz; CDCl₃) 1.50-1.76 (4H, m, CH₂a, Hb-2', H-4ax, H-5), 1.86-1.96 (1H, m, H-4eq), 1.96-2.11 (1H, m, CHa₁Hb₂', 2.46-2.57 (1H, m, H-6eq), 2.78-2.91 (1H, m, H-6ax), 3.13-3.22 (1H, m, H-2), 3.63-3.81 (3H, m, H-3, H-1'), 3.81 (2H, s, NCH₂Ph), 4.47 (1H, d, Jgem 12.0 Hz, OCHa₁Hb₂Ph), 4.55 (1H, d, Jgem 12.0 Hz, OCHa₁Hb₂Ph), 7.20-7.38 (10H, m, Ar); δC (75 MHz; CDCl₃) 20.5 (CH₂a, Hb₂'), 25.9 (CH₂, C-4), 44.1 (CH₂, C-6), 57.7 (CH₂, NCH₂Ph), 61.1 (CH, C-2), 63.5 (CH₂, C-1'), 70.3 (CH₂, OCH₂Ph), 72.9 (CH, C-3), 127.3 (CH, C-Ar), 127.4 (CH, C-Ar), 127.6 (CH, C-Ar), 128.4 (CH, C-Ar), 128.8 (CH, C-Ar), 138.4 (C, C-Ar), 138.6 (C, C-Ar); m/z (EI) 325 (3, M⁺), 280 (22), 234 (52), 219 (15), 91 (100%). HRMS (EI): M⁺, found 325.2034. C₂₁H₂₇NO₂ requires 325.2042.
2-((2R,3S)-3-(Benzyloxy)-1-methylpiperidin-2-yl)ethanol (302)

Iodomethane (0.022 mL, 0.36 mmol) was added dropwise to a stirred solution of cycloadduct 296 (0.095 g, 0.32 mmol) in dichloromethane (5 mL) at room temperature. The reaction was then stirred for 6 h and concentrated under reduced pressure to give a yellow oil. The residue was diluted with tetrahydrofuran (10 mL) and lithium aluminium hydride (0.019 g, 0.51 mmol) was added portionwise. The mixture was then stirred under reflux for 3 h, cooled to 0 °C and diluted with ethyl acetate (10 mL). The reaction was quenched by the addition of a saturated solution of Rochelle's salt (5 mL) and the mixture stirred for 30 min, filtered through Celite® and extracted with ethyl acetate (4 × 25 mL). The combined organic extracts were concentrated under reduced pressure and the residue was purified by flash column chromatography, eluting with methanol-dichloromethane (5:95), to give the title compound (0.062 g, 56% over two steps) as a yellow oil.

[α]_D^{20} +53.3 (c 0.54, CHCl_3); \nu_{max} (film) 3365 (OH), 2936, 2860, 2789 (C–H), 1454 (C=C), 1125, 1091, 1073, 1027, 735, 697 cm\(^{-1}\); \delta_H (300 MHz; CDCl_3) 1.31 (1H, tdd, J_{gem} = J_{4ax-5ax} 12.1, J_{4ax-3} 9.9, J_{4ax-6eq} 4.0 Hz, H-4ax), 1.44-1.61 (1H, m, H-5’ax), 1.67-1.79 (1H, m, H-5eq), 1.92-2.05 (2H, m, H-2’), 2.11 (1H, ddd, J_{gem} 11.7, J_{6ax-5ax} 11.5, J_{6ax-5eq} 3.0 Hz, H-6ax), 2.17-2.33 (2H, m, H-2, H-4eq), 2.41 (3H, s, NCH_3), 2.86 (1H, dt, J 11.9, 3.8, 1.2 Hz, H-6eq), 3.47 (1H, ddd, J 9.9, 8.6, 4.3 Hz, H-3), 3.67 (1H, dt, J 11.0, 4.9 Hz, CH\textsubscript{a}H\textsubscript{b}1’), 3.81 (1H, ddd, J 5.3, 8.6, 11.0 Hz, CH\textsubscript{a}H\textsubscript{b}1’), 4.01 (1H, br s, OH), 4.44 (1H, d, J_{gem} 11.5 Hz, OCH\textsubscript{a}H\textsubscript{b}Ph), 4.66 (1H, d, J_{gem} 11.5 Hz, OCH\textsubscript{a}H\textsubscript{b}Ph), 7.23-7.38 (5H, m, Ar-H); \delta_C (75 MHz; CDCl_3) 21.7 (CH_2, C-5), 28.0 (CH_2, C-2’), 28.8 (CH_2, C-4), 43.2 (CH_3, NCH_3), 55.6 (CH_2, C-6), 60.9 (CH_2, C-1’), 67.2 (CH, C-2), 70.6 (CH_2, OCH_2Ph), 75.3 (CH, C-3), 127.6 (CH, C-1’), 127.7 (CH, C-1), 128.4 (CH, C-4), 138.3 (C, C-1); m/z (FAB\(^+\), m-nitrobenzylalcohol) 250 (100, MH\(^+\)), 248 (9), 158 (13), 154 (66), 142 (14), 136 (45), 120 (9), 107 (17), 91 (29%). HRMS (FAB\(^+\), m-nitrobenzylalcohol): MH\(^+\), found 250.1809. C_{15}H_{24}NO_2 requires 250.1807.
(But-3-en-1-yloxy)(tert-butyl)dimethylsilane (305)

(But-3-en-1-yloxy)(tert-butyl)dimethylsilane 305 was prepared according to the literature procedure.\textsuperscript{242} 3-Buten-1-ol 304 (2.0 g, 27.7 mmol) was added to a stirred solution of tert-butyl(dimethyl)silyl chloride (4.6 g, 30.5 mmol) and imidazole (2.1 g, 30.5 mmol) in dichloromethane (30 mL) and the mixture stirred at room temperature for 24 h. The reaction mixture was diluted with diethyl ether (50 mL) and washed with water (30 mL), aqueous hydrochloric acid (1 mol L\textsuperscript{-1}, 30 mL) and a solution of saturated brine (30 mL). The organic extract was dried over anhydrous magnesium sulphate and concentrated under reduced pressure to give a yellow oil. The residue was purified by flash column chromatography, eluting with diethyl ether-hexane (0.5:99.5), to give the title compound (4.7 g, 91%) as a colourless oil. The spectroscopic data was in agreement with that reported in the literature.\textsuperscript{242}

\[\delta_{\text{H}} (400 \text{ MHz}; \text{CDCl}_3) 0.04 (6\text{H}, \text{s}, \text{SiMe}_2), 0.88 (9\text{H}, \text{s}, \text{OSi}^\text{t}^\text{Bu}), 2.26 (2\text{H}, \text{app qt}, J_{3-4} \text{ 6.8, J}_{3,2} \text{ 1.3 Hz, H-3}), 3.64 (2\text{H}, \text{t}, J_{4-3} \text{ 6.8 Hz, H-4}), 4.97-5.09 (2\text{H}, \text{m}, \text{H-1}), 5.80 (1\text{H}, \text{ddt}, J_{2-1} \text{ 17.0, J}_{2,1} \text{ 10.2, J}_{2-3} \text{ 6.8 Hz, H-2}); \delta_{\text{C}} (100 \text{ MHz}; \text{CDCl}_3) -5.3 (\text{CH}_3, \text{SiMe}_2), 18.3 (\text{CH}_3, \text{OSi}^\text{t}^\text{Bu}), 25.9 (\text{C}, \text{OSi}^\text{t}^\text{Bu}), 37.5 (\text{CH}_2, \text{C-3}), 62.8 (\text{CH}_2, \text{C-4}), 116.3 (\text{CH}_2, \text{C-1}), 135.4 (\text{CH}, \text{C-2}).\]

(2R,3aR,4S)-2-[2′-(tert-Butyldimethylsilyloxy)ethyl]-4-(benzyloxy)-hexahydroisoxazolo[2,3-a]pyridine (306) and (2S,3aS,4S)-2-[2′-(tert-Butyldimethylsilyloxy)ethyl]-4-(benzyloxy)-hexahydroisoxazolo[2,3-a]pyridine (307)

Following the general procedure, a solution of alkene 305 in toluene (2 mL) was added to a solution of nitrone 208 (0.12 g, 0.58 mmol) in toluene (2 mL) and the mixture stirred at 80 °C for 12 h. Purification of the residue by flash column chromatography, eluting with ethyl acetate-hexanes (1:19), gave the title compounds 306 (0.12 g, 52%) and 307 (0.045 g, 20%) as yellow oils.
**Data for 306:** $R_f$ (50% EtOAc/hexanes) 0.63; $[\alpha]_D^{20} +56.4$ (c 1.0, CHCl$_3$); $\nu_{\text{max}}$ (film) 3422, 2949, 2856 (C-H), 1471 (C=C), 1255, 1098 cm$^{-1}$; $\delta_H$ (300 MHz; DMSO-$d_6$, 373.15 K) 0.05 (6H, s, OSiMe$_2$), 0.89 (9H, s, OSi'Bu), 1.16-1.35 (1H, m, H-5ax), 1.43-1.60 (1H, m, H-6ax), 1.60-1.81 (3H, m, H-6eq, H-1'), 1.95-2.07 (2H, m, 3-Ha, H-5ax), 2.16 (1H, dt, $J$ 11.8, 9.0 Hz, 3-Hb), 2.38-2.57 (2H, m, H-3a, H-7ax), 3.06-3.16 (1H, m, H-7eq), 3.40 (1H, ddd, $J_{4,5}$ax 9.0, $J_{4,3}$a 8.2, $J_{4,5}$eq 4.2 Hz, H-4), 3.67 (2H, td, $J$ 6.4, 1.2 Hz, H-2'), 4.02-4.15 (1H, m, H-2), 4.49 (1H, d, $J_{\text{gem}}$ 12.0 Hz, OCH$_{\text{a,a}}$Ph), 4.59 (1H, d, $J_{\text{gem}}$ 12.0 Hz, OCH$_{\text{a,b}}$Ph), 7.25-7.38 (5H, m, Ar-H); $\delta_C$ (75 MHz; DMSO-$d_6$, 353.15 K) -5.9 (CH$_3$, OSiMe$_2$), 17.3 (C, OSi'Bu), 20.4 (CH$_2$, C-6), 25.3 (CH$_3$, OSi'Bu), 28.1 (CH$_2$, C-5), 37.6 (CH$_2$, C-3), 37.7 (CH$_2$, C-1'), 51.8 (CH$_2$, C-7), 59.3 (CH$_2$, C-2'), 69.0 (CH, C-3a), 69.6 (CH$_2$, OCH$_2$Ph), 72.3 (CH, C-2), 76.8 (CH, C-4), 126.7 (CH, C-Ar), 126.8 (CH, C-Ar), 127.5 (CH, C-Ar), 138.5 C, C-Ar); $m/z$ (El) 391 (7, M$^+$), 300 (14), 142 (14), 131 (10), 101 (21), 97 (16), 91 (100), 75 (15), 71 (41), 65 (8), 57 (18), 41 (15%). HRMS (El): M$^+$, found 391.2537. C$_{22}$H$_{37}$NO$_3$Si requires 391.2543.

**Data for 307:** $R_f$ (50% EtOAc/hexanes) 0.54; $[\alpha]_D^{20}$ -20.9 (c 0.9, CHCl$_3$); $\nu_{\text{max}}$ (film) 3434, 2953, 2856 (C-H), 1471 (C=C), 1255, 1097 cm$^{-1}$; $\delta_H$ (300 MHz; DMSO-$d_6$, 368.15 K) 0.05 (6H, s, SiMe$_2$), 0.90 (9H, s, OSi'Bu), 1.31-1.45 (1H, m, H-6ax), 1.45-1.80 (6H, m, 3-Hb, 5-H, H-6eq, H-1'), 2.39 (1H, ddd, $J$ 9.2, 10.9, 12.0, 3-Ha), 2.61-2.72 (1H, m, H-7ax), 2.72-2.83 (1H, m, H-7eq), 3.25 (1H, br s, H-3a), 3.67 (2H, td, $J$ 6.5, 1.1 Hz, H-2'), 3.81-3.90 (1H, m, H-4), 4.24-4.36 (1H, m, H-2), 4.51 (1H, d, $J_{\text{gem}}$ 12.1 Hz, OCH$_{\text{a,a}}$Ph), 4.58 (1H, d, $J_{\text{gem}}$ 12.1 Hz, OCH$_{\text{a,b}}$Ph), 7.23-7.38 (5H, m, Ar-H); $\delta_C$ (75 MHz; DMSO-$d_6$, 368.15 K) -6.0 (CH$_3$, OSiMe$_2$), 17.2 (C, OSi'Bu), 19.6 (CH$_2$, C-6), 24.4 (CH$_2$, C-5), 25.2 (CH$_3$, OSi'Bu), 32.2 (CH$_2$, C-3), 37.8 (CH$_2$, C-1'), 49.8 (CH$_2$, C-7), 59.3 (CH$_2$, C-2'), 64.0 (CH, C-3a), 69.7 (CH$_2$, OCH$_2$Ph), 72.3 (CH, C-2), 73.8 (CH, C-4), 126.6 (CH, C-Ar), 126.7 (CH, C-Ar), 127.4 (CH, C-Ar), 138.4 (C, C-Ar); $m/z$ (El) 391 (25, M$^+$), 300 (27), 142 (10), 131 (21), 101 (21), 96 (12), 91 (100), 71 (55), 59 (10), 43 (12%). HRMS (El): M$^+$, found 391.2543. C$_{22}$H$_{37}$NO$_3$Si requires 391.2543.
(3'R)-4-[(2R,3S)-3-(Benzyloxy)piperidin-2-yl]-1-[(tert-butyldimethylsilyloxy)butan-3-ol (308)

Indium powder (0.002 g, 0.015 mmol) and zinc powder (0.02 g, 0.31 mmol) were added to a solution of cycloadduct 306 (0.060 g, 0.15 mmol) in ethanol/ saturated aqueous ammonium chloride (2:1, 1.5 mL) at room temperature. The reaction was then stirred under reflux for 12 h, cooled to room temperature and concentrated under reduced pressure. Saturated aqueous sodium carbonate (5 mL) and ethyl acetate (15 mL) were added and the layers separated. The aqueous layer was further extracted with ethyl acetate (2 × 15 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with methanol-dichloromethane (1:49), to give the title compound (0.032 g, 53%) as a yellow oil.

[α]D20 -29.2 (c 1.1, CHCl3); νmax (film) 3293 (OH), 2928, 2855 (C–H), 1455 (C=C), 1252, 1090, 833 cm⁻¹; δH (300 MHz; CDCl3) 0.06 (6H, s, OSiMe2), 0.90 (9H, s, OSiBu), 1.28-1.42 (1H, m, H-4ax), 1.42-1.55 (1H, m, H-5ax), 1.55-1.68 (1H, m, CH₃H₂-2'), 1.68-1.85 (4H, m, H-5eq, H-4', CH₃H₂-2'), 2.20-2.31 (1H, m, H-4eq), 2.57 (1H, td, Jgem = J₆ax-₅ax 11.7, J₆ax-₅eq 2.7 Hz, H-6ax), 2.89 (1H, ddd, J 8.9, 6.1, 4.1 Hz, H-2), 2.95-3.06 (1H, m, H-6eq), 3.22-3.32 (1H, m, H-3), 3.68-3.85 (4H, br m, NH, OH, H-1'), 3.97-4.08 (1H, m, H-3'), 4.44 (1H, d, Jgem 11.7 Hz, OCH₃H₂Ph), 4.64 (1H, d, Jgem 11.7 Hz, OCH₃H₂Ph), 7.23-7.38 (5H, m, Ar-H); δC (75 MHz; CDCl3) -5.4 (CH₃, OMe₂), 18.2 (C, OSiBu), 24.6 (CH₂, C-5), 25.9 (CH₃, OSiBu), 29.5 (CH₂, C-4), 37.8 (CH₂, C-4'), 39.9 (CH₂, C-2'), 45.4 (CH₂, C-6), 58.7 (CH, C-2), 61.3 (CH₂, C-1'), 67.6 (CH, C-3'), 70.5 (CH₂, OCH₂Ph), 77.3 (CH, C-3), 127.6 (CH, C-Ar), 127.7 (CH, C-Ar), 128.3 (CH, C-Ar), 138.5 (C, C-Ar); m/z (EI) 393 (0.6, M⁺), 336 (29), 302 (33), 287 (14), 284 (41), 228 (28), 189 (16), 131 (24), 114 (30), 101 (15), 91 (100), 89 (38), 75 (37), 73 (44), 56 (12), 43 (18%). HRMS (EI): M⁺, found 393.2696. C₂₂H₉₉NO₅Si requires 393.2699.
(2S,3aR,4S)-2-Hydroxymethyl-4-(benzoyloxy)-hexahydroisoxazolo[2,3-a]pyridine (310),
(2R,3aR,4S)-2-hydroxymethyl-4-(benzoyloxy)-hexahydroisoxazolo[2,3-a]pyridine (311)
and (2S,3aS,4S)-2-hydroxymethyl-4-(benzoyloxy)-hexahydroisoxazolo[2,3-a]pyridine
(312)

Following the general procedure, a solution of allyl alcohol 309 (1.39 g, 24.0 mmol) in
toluene (5 mL) was added to a solution of nitrone 208 (0.33 g, 1.60 mmol) in toluene (5 mL)
and the mixture stirred under reflux for 24 h. Purification of the residue by flash column
chromatography, eluting with methanol-diethyl ether (1:99), gave the title compounds
310 (0.030 g, 7%), 311 (0.17 g, 40%) and 312 (0.041 g, 10%) as yellow oils.

Data for 310: 

\[ R_f (5\% \text{ MeOH/Et}_2\text{O}) 0.53; \ [\alpha]^{20}_D +126.2 \ (c \ 0.57, \text{CHCl}_3); \nu_{\text{max}} \ (\text{film}) 3381 \ (\text{OH}),
2932, 2860 (\text{C-H}), 1454 (\text{C=C}), 1354, 1253, 1089, 1012, 736, 697 \ \text{cm}^{-1}; \delta_\text{H} \ (300 \ \text{MHz};
\text{DMSO-d}_6, 373.15 \ \text{K}) 1.22 (1H, tdd, J_{5ax-6ax} = J_{5ax-5eq} 12.6, J_{5ax-4} 10.1, J_{5ax-6eq} 4.8 Hz, H-5ax),
1.46-1.64 (1H, m, H-6ax), 1.67-1.86 (2H, m, 3-Hb, H-6eq), 2.01-2.11 (1H, m, H-5eq),
2.37-2.48 (3H, m, 3-Ha, C-3a, H-7ax), 3.16-3.24 (1H, m, H-7eq), 3.32-3.42 (2H, m,
CH_2OH, H-4), 3.44-3.54 (1H, m, CH_2OH), 3.95-4.06 (1H, m, H-2), 4.07 (1H, br s,
OH), 4.52 (1H, d, J_{gem} 12.1 Hz, OCH_3Ph), 4.60 (1H, d, J_{gem} 12.1 Hz, OCH_3Ph),
7.22-7.38 (5H, m, Ar-H); \delta_\text{C} \ (75 \ \text{MHz}; \text{DMSO-d}_6, 373.15 \ \text{K}) 20.4 (\text{CH}_2, C-6), 28.6
(\text{CH}_2, C-5), 35.1 (\text{CH}_2, C-3), 52.1 (\text{CH}_2, C-7), 63.8 (\text{CH}_2, C-1'), 68.6 (\text{CH}, C-3a), 69.6
(\text{CH}_2, OCH_3Ph), 76.5 (\text{CH}, C-2), 77.2 (\text{CH}, C-4), 126.5 (\text{CH}, C-Ar), 126.7 (\text{CH}, C-Ar), 127.4
(\text{CH}, C-Ar), 138.5 (C, C-Ar); m/z (EI) 263 (12, M^+), 232 (3), 172 (22), 126 (7), 116 (12), 91 (100),
84 (24), 71 (99), 66 (27), 43 (27), 41 (18%). HRMS (EI): M^+ found 263.1515. C_{15}H_{21}NO_3
requires 263.1521.

Data for 311: 

\[ R_f (5\% \text{ MeOH/Et}_2\text{O}) 0.47; \ [\alpha]^{20}_D +35.6 \ (c \ 0.92, \text{CHCl}_3); \nu_{\text{max}} \ (\text{film}) 3381 \ (\text{OH}),
2936, 2861 (\text{C-H}), 1454 (\text{C=C}), 1354, 1090, 1072, 736, 697 \ \text{cm}^{-1}; \delta_\text{H} \ (300 \ \text{MHz};
\text{DMSO-d}_6, 373.15 \ \text{K}) 1.28 (1H, dddd, J_{gem} 12.9, J_{5ax-6eq} 11.4, J_{5ax-4} 9.1, J_{5ax-6eq} 4.5 Hz,
H-5ax), 1.46-1.62 (1H, m, H-6ax), 1.68-1.80 (1H, m, H-6eq), 2.00 (1H, dq, J_{gem} 12.9, J_{5eq-4} =
J_{5eq-6eq} 4.3 Hz, H-5eq), 2.06-2.13 (2H, m, H-3), 2.47-2.59 (2H, m, H-3a, H-7ax),
3.07-3.16 (1H, m, H-7eq), 3.37-3.49 (3H, m, CH_2OH, H-4), 4.04 (1H, dq, J 7.8, 5.3 Hz, H-2),
4.52 (1H, d, $J_{\text{gem}}$ 12.0 Hz, OCH$_3$H$_b$Ph), 4.60 (1H, d, $J_{\text{gem}}$ 12.0 Hz, OCH$_3$H$_b$Ph), 7.24-7.36 (5H, m, Ar-H); $\delta_C$ (75 MHz; DMSO-$d_6$, 373.15 K) 20.1 (CH$_2$, C-6), 27.8 (CH$_2$, C-5), 34.3 (CH$_2$, C-3), 51.5 (CH$_2$, C-7), 62.8 (CH$_2$, C-1'), 67.3 (CH, C-3a), 69.5 (CH$_2$, OCH$_2$Ph), 76.0 (CH, C-2), 76.7 (CH, C-4), 126.5 (CH, C-Ar), 126.7 (CH, C-Ar), 127.4 (CH, C-Ar), 138.4 (C, C-Ar); m/z (EI) 263 (14, M$^+$), 232 (4), 172 (24), 126 (8), 116 (19), 91 (99), 71 (100), 65 (13), 43 (24%). HRMS (EI): M$^+$, found 263.1527. C$_{15}$H$_{21}$NO$_3$ requires 263.1521.

**Data for 312:** $R_f$ (5% MeOH/Et$_2$O) 0.41; $[\alpha]_{D}^{20}$ -1.4 (c 2.9, CHCl$_3$); $\nu_{\text{max}}$ (film) 3380 (OH), 2951, 2868 (C-H), 1453 (C=C), 1359, 1247, 1089, 1028, 735, 697 cm$^{-1}$; $\delta_H$ (300 MHz; DMSO-$d_6$, 373.15 K) 1.28-1.45 (1H, m, H-6ax), 1.47-1.60 (1H, m, H-5ax), 1.61-1.77 (2H, m, H-5eq, H-6eq), 1.87 (1H, ddd, J 12.1, 7.2, 3.9 Hz, 3-Hb), 2.32 (1H, ddd, $J_{\text{gem}}$ 12.1, 10.9, 9.4 Hz, 3-Ha), 2.68-2.80 (2H, m, H-7), 3.30 (1H, br s, H-3a), 3.39-3.46 (2H, m, CH$_2$OH), 3.80-3.90 (1H, m, H-4), 4.13 (1H, br s, OH), 4.19-4.30 (1H, m, H-2), 4.52 (1H, d, $J_{\text{gem}}$ 12.0 Hz, OCH$_3$H$_b$Ph), 4.59 (1H, d, $J_{\text{gem}}$ 12.0 Hz, OCH$_3$H$_a$Ph), 7.23-7.38 (5H, m, Ar-H); $\delta_C$ (75 MHz; DMSO-$d_6$, 373.15 K) 19.6 (CH$_2$, C-6), 24.3 (CH$_2$, C-5), 29.1 (CH$_2$, C-3), 49.8 (CH$_2$, C-7), 62.8 (CH$_2$, C-1'), 63.8 (CH, C-3a), 69.7 (CH$_2$, OCH$_2$Ph), 73.8 (CH, C-4), 76.2 (CH, C-2), 126.5 (CH, C-Ar), 126.6 (CH, C-Ar), 127.4 (CH, C-Ar), 138.4 (C, C-Ar); m/z (EI) 263 (14, M$^+$), 232 (4), 172 (22), 126 (8), 91 (99), 84 (10), 71 (100), 65 (13), 43 (25), 41 (15%). HRMS (EI): M$^+$, found 263.1512. C$_{15}$H$_{21}$NO$_3$ requires 263.1521.

(2'R)-3-[(2R,3S)-3-(Benzyloxy)piperidin-2-yl]propane-1,2-diol (313)

![313](image)

Indium powder (0.004 g, 0.036 mmol) and zinc powder (0.048 g, 0.73 mmol) were added to a solution of cycloadduct 311 (0.096 g, 0.37 mmol) in ethanol/saturated aqueous ammonium chloride (2:1, 2 mL) at room temperature. The reaction was then stirred under reflux for 12 h, cooled to room temperature and concentrated under reduced pressure. Saturated aqueous sodium carbonate (5 mL) and ethyl acetate (15 mL) were added and the layers separated. The aqueous layer was further extracted with ethyl acetate (2 × 15 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography eluting with methanol-dichloromethane (1:49), to give the title compound (0.043 g, 45%) as a yellow oil.
Following the general procedure, a solution of ethyl acrylate 314 (2.59 mL, 24.4 mmol) in dichloromethane (2 mL) was added to a solution of nitrone 208 (0.50 g, 2.44 mmol) in dichloromethane (11 mL) and the mixture stirred at room temperature for 3 h. Purification of the residue by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:19 to 1:17), gave the title compounds 315 (0.059 g, 8%), 316 (0.41 g, 55%) and 317 (0.18 g, 24%) as yellow oils as well as an inseparable mixture of 318 and 319 (0.031 g, 4%) as a yellow oil.

**Data for 315:**
- \( R_f (50\% \text{ EtOAc/hexanes}) 0.54; [\alpha]_D^{20} +99.0 (c 1.04, \text{CHCl}_3); \nu_{\text{max}} (\text{film}) 3292 (\text{OH}), 2930, 2858 (\text{C-H}), 1454 (\text{C=C}), 1200, 1175, 1075 \text{ cm}^{-1}; \delta_H (300\text{ MHz};

\begin{align*}
[\alpha]_D^{20} & +50.9 (c 0.79, \text{CHCl}_3); \\
\nu_{\text{max}} (\text{film}) & 3292 (\text{OH}), 2930, 2858 (\text{C-H}), 1454 (\text{C=C}), 1200, 1175, 1075 \text{ cm}^{-1}; \delta_H (300\text{ MHz};
\end{align*}
Data for 316: \( R_f \) (50% EtOAc/hexanes) 0.46; \([\alpha]_D^{20} +48.9 \) (c 0.95, CHCl<sub>3</sub>); \( \nu_{\text{max}} \) (film) 2938, 2860 (C-H), 1748, 1733 (C=O), 1454 (C=C), 1194, 1091, 1074 cm\(^{-1}\); \( \delta_H \) (300 MHz; DMSO-\( d_6 \), 373.15 K) 1.23 (3H, t, \( J_{2\cdots1'} \) 7.1 Hz, H-2'), 1.20-1.32 (1H, m, H-5ax), 1.47-1.64 (1H, m, H-6ax), 1.70-1.82 (1H, m, H-6eq), 1.99-2.10 (1H, m, H-5eq), 2.23 (1H, ddd, \( J_{\text{gem}} \) 11.8, 9.0, 6.6 Hz, 3-Hb), 2.47-2.58 (2H, m, H-7ax, H-3a), 2.69 (1H, ddd, \( J_{\text{gem}} \) 11.8, 8.9, 6.0 Hz, 3-Ha), 3.23 (1H, dt, \( J_{\text{gem}} \) 10.0, \( J_{\text{gem-6ax}} = J_{\text{gem-6eq}} \) 3.9 Hz, H-7eq), 3.43 (1H, ddd, J 9.6, 8.2, 4.3 Hz, H-4), 4.15 (2H, qd, J 7.1, 0.6 Hz, H-1'), 4.45 (1H, dd, J 8.9, 6.6 Hz, H-2'), 4.51 (1H, d, \( J_{\text{gem}} \) 12.1 Hz, OCH<sub>3</sub>H<sub>3</sub>Ph), 4.61 (1H, d, \( J_{\text{gem}} \) 12.1 Hz, OCH<sub>3</sub>H<sub>3</sub>Ph), 7.24-7.38 (5H, m, Ar-H); \( \delta_C \) (75 MHz; DMSO-\( d_6 \), 373.15 K) 13.2 (CH<sub>3</sub>, C-2'), 20.2 (CH<sub>2</sub>, C-6), 28.1 (CH<sub>2</sub>, C-5), 36.0 (CH<sub>2</sub>, C-3), 51.9 (CH<sub>2</sub>, C-7), 59.6 (CH<sub>2</sub>, C-1'), 67.9 (CH, C-3a), 69.6 (CH<sub>2</sub>, OCH<sub>3</sub>Ph), 73.0 (CH, C-2'), 76.6 (CH, C-4), 126.5 (CH, C-Ar), 126.7 (CH, C-Ar), 127.4 (CH, C-3a), 138.3 (C, C-Ar), 170.9 (C=O, CHO<sub>2</sub>Et); \( m/z \) (EI) 305 (11, M<sup>+</sup>), 126 (9), 91 (100), 71 (62), 65 (10), 43 (15%). HRMS (EI): M<sup>+</sup>, found 305.1632. C<sub>17</sub>H<sub>23</sub>NO<sub>4</sub> requires 305.1627.

Data for 317: \( R_f \) (50% EtOAc/hexanes) 0.34; \([\alpha]_D^{20} -4.6 \) (c 1.20, CHCl<sub>3</sub>); \( \nu_{\text{max}} \) (film) 2928, 2856 (C-H), 1734 (C=O), 1454 (C=C), 1193, 1094 cm\(^{-1}\); \( \delta_H \) (300 MHz; DMSO-\( d_6 \), 373.15 K) 1.23 (3H, t, \( J_{2\cdots1'} \) 7.1 Hz, H-2'), 1.34-1.48 (1H, m, H-6ax), 1.48-1.63 (1H, m, H-5ax), 1.63-1.80 (2H, m, H-5eq, H-6eq), 2.18 (1H, ddd, J 12.5, 6.8, 3.7 Hz, 3-Hb), 2.60 (1H, ddd, J 12.5, 10.8, 10.1 Hz, 3-Ha), 2.74-2.87 (2H, m, H-7), 3.40 (1H, br s, H-3a), 3.86-3.94 (1H, m, H-4), 4.16 (2H, q, J 1.1-2.1' 7.1 Hz, H-1'), 4.52 (1H, d, \( J_{\text{gem}} \) 12.1 Hz, OCH<sub>3</sub>H<sub>3</sub>Ph), 4.60 (1H, d, \( J_{\text{gem}} \) 12.1 Hz, OCH<sub>3</sub>H<sub>3</sub>Ph), 4.65 (1H, J 10.1, 3.7 Hz, H-2'), 7.24-7.38 (5H, m, Ar-H); \( \delta_C \) (75 MHz; DMSO-\( d_6 \), 373.15 K) 13.2 (CH<sub>3</sub>, C-2'), 19.3 (CH<sub>2</sub>, C-6), 24.2 (CH<sub>2</sub>, C-5), 31.2
(CH₂, C-3), 49.9 (CH₂, C-7), 59.8 (CH₂, C-1'), 63.5 (CH, C-3a), 69.8 (CH₂, OCH₂Ph), 73.6 (CH, C-2), 73.7 (CH, C-4), 126.6 (CH, C-Ar), 126.7 (CH, C-Ar), 127.4 (CH, C-Ar), 138.2 (C, C-Ar), 170.2 (C=O, CO₂Et); m/z (EI) 305 (5, M⁺), 232 (6) 126 (14), 91 (100), 71 (57), 65 (10), 43 (16%). HRMS (EI): M⁺, found 305.1630. C₁₇H₂₃NO₄ requires 305.1627.

**Data for 318 and 319:** Rf (50% EtOAc/hexanes) 0.60; νmax (film) 2935, 2862 (C-H), 1753, 1729 (C=O), 1454 (C=C), 1200, 1175, 1075 cm⁻¹; δH (300 MHz; DMSO-d₆, 373.15 K) 1.15 (3H, t, J 7.1 Hz, CO₂CH₂CH₃), 1.17 (3H, t, J 7.1 Hz, CO₂CH₂CH₃), 1.27-1. 46 (2H, m, CH₃H₆-5**, CH₃H₆-5*), 1.46-1.64 (2H, m, CH₃H₆-6**, CH₃H₆-6*), 1.68-1.83 (2H, m, CH₃H₆-6**, CH₃H₆-6*), 1.94-2.06 (1H, m, CH₃H₆-5*), 2.10-2.21 (1H, m, CH₃H₆-5**), 2.37-2.49 (1H, m, CH₃H₆-7**), 2.55-2.71 (2H, m, CH₃H₆-7*, H-3a), 2.92-3.02 (1H, m, H-3a*), 3.05-3.15 (1H, m, CH₃H₆-7*), 3.22-3.34 (2H, m, H-3*, CH₃H₆-7**), 3.46-3.55 (1H, m, H-3**), 3.55-3.63 (1H, ddd, J 4.1, 7.4, 8.3 Hz, H-4*), 3.71-3.81 (1H, ddd, J 4.5, 9.8, 9.3 Hz, H-4**), 3.85-3.94 (2H, m, CH₃H₆-2**, CH₃H₆-2*), 3.95-4.17 (6H, m, CH₃H₂-2**, CH₃H₂-2* CO₂CH₂CH₃**, CO₂CH₂CH₃*), 4.38 (1H, m, OCH₂CH₃Ph*), 4.48-4.64 (3H, m, OCH₂CH₃Ph**, OCH₂Ph*), 7.22-7.38 (10H, m, Ar-H**, Ar-H*); δC (75 MHz; DMSO-d₆, 373.15 K) 13.1 (CH₃ x 2, CO₂CH₂CH₃**, CO₂CH₂CH₃*), 19.7, 20.0 (CH₂, C-6* or C-6*), 26.9 (CH₂, C-5*), 28.4 (CH₂, C-5**), 48.0 (CH, C-3**), 49.8 (CH, C-3*), 50.8 (CH₂, C-7*), 52.3 (CH₂, C-7**), 59.3, 59.6 (CH₂, CO₂CH₂CH₃**, or CO₂CH₂CH₃*), 67.0, 67.3 (CH₂, C-2** or C-2*), 69.1 (CH₂, OCH₂Ph*), 69.4 (CH₂, OCH₂Ph*), 70.3 (CH, C-3a*), 70.7 (CH, C-3a**), 73.7 (CH, C-4**), 75.6 (CH, C-4*), 126.4 (CH, C-Ar), 126.5 (CH, C-Ar), 127.3 (CH, C-Ar), 127.3 (CH, C-Ar), 138.2 (C, C-Ar), 138.3 (C, C-Ar), 170.6, 171.3 (C=O, CO₂Et** or CO₂Et*); m/z (EI) 305 (16, M⁺), 214 (11), 96 (13), 91 (100), 71 (88), 65 (13), 43 (24%). HRMS (EI): M⁺, found 305.1633. C₁₇H₂₃NO₄ requires 305.1627.

**(2R,8S,8aR)-2-Hydroxy-8-benzyloxyoctahydroindolizin-3-one (322)**

![322](image)

A solution of cycloadduct 316 (0.050 g, 0.16 mmol) in glacial acetic acid (0.25 mL) was added to a suspension of copper(II) acetate (0.002 g, 0.011 mmol) and zinc powder (0.059 g, 0.92 mmol) in glacial acetic acid (0.25 mL) and one drop of deionised water at...
room temperature. The reaction mixture was then stirred under reflux for 1 h, cooled to room temperature and the pH adjusted to 9 by careful addition of a 6 M aqueous solution of sodium hydroxide. The mixture was then extracted with chloroform (3 x 10 mL) and the organic extract washed with a solution of saturated brine (10 mL), dried over anhydrous magnesium sulphate then concentrated under reduced pressure and purified by flash column chromatography, eluting with methanol-dichloromethane (1:19), gave the title compound (0.040 g, 94%) as a yellow oil.

\[ \alpha \] _D ^20 +172.3 (c 0.67, CHCl _3); \nu _{\text{max}} \text{(film)} 3292 (OH), 2989, 2962, 2925, 2866 (C-H), 1688 (C=O, lactam), 1485, 1435 (C=C), 1288, 1267, 1097, 734 cm \(^{-1}; \delta _{\text{H}} \text{(300 MHz; CDCl}_3) 1.23-1.52 (2H, m, H-6ax, H-7ax), 1.68 (1H, ddd, J_{\text{gem}} 13.1, J_{1-2} 8.6, J_{1-8a} 7.4 Hz, CH_3Hb-1), 1.75-1.87 (1H, m, H-6eq), 2.22-2.33 (1H, m, H-7eq), 2.50-2.64 (1H, m, H-5ax), 2.79 (1H, ddd, J_{\text{gem}} 13.1, J_{1-2} 8.6, J_{1-8a} 6.4 Hz, CH_3Hb-1), 3.11 (1H, ddd, J_{8-7eq} 3.9, J_{8-8a} 9.2, J_{8-7ax} 10.2 Hz, H-8), 3.16-3.26 (1H, m, H-8a), 3.98-4.08 (1H, m, H-5eq), 4.34 (1H, t, J_{2-1Ha} = J_{2-1Hb} 8.6 Hz, H-2), 4.50 (1H, d, J_{\text{gem}} 11.7 Hz, OCH(CH_3)Ph), 4.58 (1H, br s, OH), 4.67 (1H, d, J_{\text{gem}} 11.7 Hz, OCH(CH_3)Ph), 7.25-7.39 (5H, m, Ar-H); \delta _{\text{C}} \text{(75 MHz; CDCl}_3) 22.6 (CH_2, C-6), 29.4 (CH_2, C-7), 33.4 (CH_2, C-1), 39.4 (CH_2, C-5), 57.6 (CH, C-8a), 69.5 (CH, C-2), 71.0 (CH_2, OCH(CH_3)Ph), 80.6 (CH, C-8), 127.7 (CH, C-Ar), 127.8 (CH, C-Ar), 128.4 (CH, C-Ar), 137.9 (C, C-Ar), 173.9 (C=O, C-8); \text{m/z} \text{(EI)} 261 (5, M^+), 170 (94), 155 (71), 153 (6), 142 (33), 124 (13), 98 (31), 91 (100), 71 (71), 65 (16), 56 (6), 43 (27), 41 (17%). HRMS (EI): M^+, found 261.1362. C_{15}H_{19}NO_3 requires 261.1365.

(2R,8S,8aR)-8-(Benzyloxy)octahydroindolizin-2-ol (324)

Borane dimethyl sulfide (1.0 M in dichloromethane, 1.87 mL, 1.87 mmol) was added dropwise to a stirred solution of lactam 322 (0.065 g, 0.25 mmol) in tetrahydrofuran (4 mL) at -15 °C. The reaction mixture was stirred at -15 °C for 10 min, then at room temperature for 30 min and finally at 66 °C for 4 h. The mixture was then cooled to room temperature and water (5 mL) carefully added dropwise. The mixture was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. Palladium on carbon (7.5 mg) was added portionwise to
a solution of the residue in methanol (3 mL) and the mixture stirred under hydrogen for 5 h then filtered through Celite®. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography, eluting with methanol-dichloromethane (1:19), to give the title compound (0.055 g, 89%) as a yellow oil.

\[ [\alpha]_D^{20} +67.3 (c 0.69, \text{CHCl}_3); \nu_{\text{max}} \text{(film)} 3337 (\text{OH}), 2936 (\text{C-H}), 1454 (\text{C=C}), 1113 \text{ cm}^{-1}; \delta_H \text{(300 MHz; CDCl}_3) 1.14-1.31 (1H, m, H-7ax), 1.61-1.73 (1H, m, CH\text{\textsubscript{a}}H\text{\textsubscript{b}}-1), 1.73-1.83 (2H, m, H-6), 1.99-2.11 (2H, m, H-8a, H-5ax), 2.18-2.29 (1H, m, H-7eq), 2.45 (1H, dd, J 10.6, 5.9 Hz, CH\text{\textsubscript{a}}H\text{\textsubscript{b}}-3), 2.63-2.75 (1H, m, CH\text{\textsubscript{a}}H\text{\textsubscript{b}}-1), 3.05-3.16 (2H, m, C\text{\textsubscript{a}}H\text{\textsubscript{b}}-3, H-5eq), 3.49 (1H, ddd, J\textsubscript{8-7eq} 4.3, J\textsubscript{8-8a} 9.2, J\textsubscript{8-7ax} 10.5 Hz, H-8), 4.26-4.34 (1H, m, H-2), 4.52 (1H, d, J\textsubscript{gem} 11.7 Hz, OCH\text{\textsubscript{a}}H\text{\textsubscript{b}}Ph), 4.64 (1H, d, J\textsubscript{gem} 11.7 Hz, OCH\text{\textsubscript{a}}H\text{\textsubscript{b}}Ph), 7.23-7.38 (5H, m, Ar-H); \delta_C \text{(75 MHz; CDCl}_3) 23.3 (CH\text{\textsubscript{2}}, C-6), 30.0 (CH\text{\textsubscript{2}}, C-7), 40.2 (CH\text{\textsubscript{2}}, C-1), 51.3 (CH\text{\textsubscript{2}}, C-5), 3.7 (CH\text{\textsubscript{2}}, C-3), 68.4 (CH, C-8a), 68.8 (CH, C-2), 71.1 (CH\text{\textsubscript{2}}, OCH\text{\textsubscript{2}}Ph), 79.0 (CH, C-8), 127.6 (CH, C-Ar), 127.6 (CH, C-Ar), 128.3 (CH, C-Ar), 138.4 (C, C-Ar); m/z (CI, NH\textsubscript{3}) 248 (40, MH\textsuperscript{+}), 156 (100), 141 (39), 120 (19), 91 (32), 86 (20), 77 (12), 71 (47%). HRMS (CI, NH\textsubscript{3}): MH\textsuperscript{+}, found 248.1655. C\textsubscript{15}H\textsubscript{22}NO\textsubscript{2} requires 248.1651.

(8S,8aR)-8-(Benzyloxy)hexahydroindolizin-2(3H)-one (323)

Lithium aluminum hydride (0.015 g, 0.38 mmol) was added to a stirred solution of indolizidinone 322 (0.050 g, 0.19 mmol) of in tetrahydrofuran (5 mL) at 0 °C. The suspension was stirred at 65 °C for 12 h, cooled to 0 °C, and then quenched by careful addition of ethyl acetate (10 mL), followed by dropwise addition of deionised water (1 mL), and aqueous sodium hydroxide (6 mol L\textsuperscript{-1}, 2 mL). The mixture was extracted with ethyl acetate (3 x 10 mL), and the combined organic extracts dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (1:19), to give the title compound (0.023 g, 50%) as a brown oil.

\[ [\alpha]_D^{20} +109.7 (c 0.30, \text{CHCl}_3); \nu_{\text{max}} \text{(film)} 2927, 2854, 2781 (\text{C-H}), 1759 (\text{C=O}), 1454 (\text{C=C}), 1099, 1072, 696 \text{ cm}^{-1}; \delta_H \text{(300 MHz; CDCl}_3) 1.25-1.40 (1H, m, H-7ax), 1.57-1.76 (1H, m,
4.4 Synthesis of O-Silyl Protected Nitrone

(2S)-Dimethyl 2-(tert-butyldiphenylsilyloxy)pentanedioate (340)

[α]D20 -29.0 (c 1.09, CHCl3); νmax (film) 2952, 2932, 2858 (C-H), 1737 (C=O), 1427 (C=C), 1256, 1110 cm⁻¹; δH (300 MHz; CDCl3) 1.09 (9H, s, OSi′Bu), 1.98-2.13 (2H, m, H-3), 2.33-2.44 (1H, m, CH₂CH₅-4), 2.44-2.56 (1H, m, CH₅CH₂-4), 3.45 (3H, s, 1-OMe), 3.64 (3H, s, 5-OMe), 4.30 (1H, t, J2,3 5.4 Hz, H-2), 7.33-7.46 (6H, m, Ar-H), 7.60-7.68 (4H, m, Ar-H); δC (75 MHz; CDCl3) 19.3 (C, OSi′Bu), 26.8 (CH₃, OSi′Bu), 28.9 (CH₂, C-4), 29.9 (CH₂, C-3), 51.4 (CH₃, 1-OMe), 51.5 (CH₃, 5-OMe), 71.4 (CH, C-2), 127.5 (CH, C-Ar), 127.6 (CH, C-Ar), 129.8 (CH, C-Ar), 132.9 (C, C-Ar), 133.0 (C, C-Ar), 135.7 (CH, C-Ar), 135.9 (CH, C-Ar), 172.8 (C=O, C-1), 173.3 (C=O, C-5); m/z (CI, NH₃) 432 (6,
MNH₄⁺), 383 (7), 357 (100), 337 (94), 329 (14), 297 (61), 277 (8), 251 (15), 230 (8), 213 (74) 183 (18), 135 (9), 78 (10%). HRMS (EI): M⁺, found 432.2202. C₂₃H₃₄NO₅Si requires 432.2206.

(2S)-2-(tert-Butyldiphenylsilyloxy)pentane-1,5-diol (341)

A solution of silyloxydiester 340 (11.2 g, 27.0 mmol) in tetrahydrofuran (60 mL) was added slowly to a vigorously stirred suspension of zinc chloride (8.10 g, 59.4 mmol) and sodium borohydride (4.50 g, 119 mmol) in tetrahydrofuran (40 mL) at 0 °C. Triethylamine (8.24 mL, 59.4 mmol) was added and the mixture stirred at 0 °C for 10 min. The reaction mixture was warmed to 80 °C, stirred for a further 4 h, then cooled to 0 °C. Chloroform (100 mL) was added to the suspension and the mixture stirred for 10 min and then a saturated solution of ammonium chloride (100 mL) was added dropwise. The aqueous phase was extracted with chloroform (4 x 250 mL) and the combined organic extracts, washed with brine (100 mL), dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, using ethyl acetate-hexanes (gradient 1:3 to 1:1), to give the title compound (9.46 g, 98%) as a white solid. Recrystalisation from diethyl ether-hexanes (1:1) afforded colourless needles.

m.p. 75-77 °C; [α]D²⁰ +19.3 (c 1.18, CHCl₃); ν max (solid) 3289 (OH), 2957, 2927, 2876, 2876 (C-H), 1428 (C=C), 1365, 1108, 1080, 1054, 1018, 991 cm⁻¹; δ H (300 MHz; CDCl₃) 1.07 (9H, s, OSiᵗBu), 1.38-1.64 (4H, m, H-3, H-4), 2.53 (1H, br s, 2 x OH), 3.33-3.53 (4H, m, H-5, H-1), 3.74-3.82 (1H, m, H-2), 7.32-7.44 (6H, m, Ar-H), 7.63-7.72 (4H, m, Ar-H); δ C (75 MHz; CDCl₃) 19.2 (C, OSiᵗBu), 27.0 (CH₃, OSiᵗBu), 27.6 (CH₂, C-4), 29.6 (CH₂, C-3), 62.3 (CH₂, C-5), 65.4 (CH₂, C-1), 73.4 (CH, C-2), 127.6 (CH, C-Ar), 127.6 (CH, C-Ar), 129.7 (CH, C-Ar), 133.7 (C, C-Ar), 133.7 (C, C-Ar), 135.6 (CH, C-Ar), 135.8 (CH, C-Ar); m/z (CI, NH₃) 359 (4, MNH₄⁺), 283 (15), 281 (11), 223 (33), 203 (39), 199 (100), 181 (55), 161 (12), 145 (15), 135 (11), 91 (12), 85 (27), 78 (23%). HRMS (EI): M⁺, found 359.2038. C₂₁H₃₁NO₅Si requires 358.2043.
(2S)-2-(tert-Butyldiphenylsilyloxy)-1,5-bis(para-toluenedisulfonyloxy)pentane (342)

\[
\text{TsO} \quad \text{OTBDPS} \quad \text{OTs}
\]

\textit{para}-Toluenedisulfonyl chloride (5.49 g, 28.8 mmol) was added portion-wise to a solution of diol 341 (3.44 g, 9.60 mmol) in dichloromethane (80 mL) at 0 °C and the mixture stirred for 30 min. A solution of triethylamine (4.0 mL, 29.0 mmol) and \( N,N \)-dimethyl-4-aminopyridine (0.24 g, 1.92 mmol) in dichloromethane (20 mL) was added dropwise and the mixture warmed to room temperature and stirred overnight. Brine (80 mL) was added and the aqueous phase extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:19 to 3:17), to give the \textit{title compound} (6.20 g, 97%) as a colourless oil.

\[\alpha\] \text{D}^\circ -8.5 (c 2.0, CHCl_3); \nu_{\text{max}} \text{ (film)} 2931, 2857 (C-H), 1358 (C=C), 1188, 1174 cm\(^{-1}\); \delta_H (300 MHz; CDCl_3) 0.98 (9H, s, OSi\text{tBu}), 1.37-1.47 (2H, m, H-3), 1.47-1.57 (2H, m, H-4), 2.44 (6H, s, Ar-Me), 3.73-3.85 (5H, m, H-1, H-2, H-5), 7.24-7.36 (8H, m, Ar-H), 7.38-7.45 (2H, m, Ar-H), 7.50-7.56 (4H, m, Ar-H), 7.59-7.64 (2H, m, Ar-H), 7.70-7.74 (2H, m, Ar-H); \delta_C (100 MHz; CDCl_3) 19.2 (C, OSi\text{tBu}), 21.6 (CH_3, Ar-Me), 23.8 (CH_2, C-4), 26.8 (CH_3, OSi\text{tBu}), 29.5 (CH_2, C-3), 69.7 (CH, C-2), 70.1, 71.4 (CH_2, C-3, C-5), 127.6 (CH, C-Ar), 127.7 (CH, C-Ar), 128.8 (CH, C-Ar), 127.8 (CH, C-Ar), 129.8 (CH, C-Ar), 129.8 (CH, C-Ar), 129.9 (CH, C-Ar), 132.5 (CH, C-Ar), 133.0 (CH, C-Ar), 133.0 (C, C-Ar), 133.0 (C, C-Ar), 135.6 (CH, C-Ar), 135.7 (CH, C-Ar), 144.7 (C, C-Ar), 144.7 (C, C-Ar); HRMS (FAB+) C_{35}H_{43}O_7S_2Si [MH\text{+}] requires 667.2220, found 667.2222.

(3S)-3-(tert-Butyldiphenylsilyloxy)-N-hydroxypiperidine (343)

\[
\begin{align*}
\text{OH} & \\
\text{OTBDPS} & \\
\end{align*}
\]

Ditosylate 342 (11.6 g, 17.4 mmol) was added to a stirred suspension of hydroxylamine hydrochloride (5.44 g, 78.3 mmol) in triethylamine (100 mL) at room temperature. The reaction mixture was stirred under reflux for 4 h and then cooled to room temperature. Diethyl ether (100 mL) was added and the suspension stirred for 1 h and filtered through Celite\textsuperscript{®}. The filtrate was dried over anhydrous magnesium sulphate and concentrated under
reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 1:99 to 1:19), to give the title compound (4.46 g, 73%) as a colourless oil.

\[[\alpha]_D^{20}\] -24.2 (c 2.34, CHCl₃); \nu_{\text{max}} (film) 3070, 3048, 3028, 2948, 2930, 2855 (C-H), 1427 (C=C), 1103 cm⁻¹; \delta_H (300 MHz; DMSO-d₆, 393.15 K) 1.07 (9H, s, OSi-tBu), 1.18-1.48 (2H, m, \text{CH}_a\text{H}_b-4, \text{CH}_a\text{H}_b-5), 1.59-1.76 (2H, m, \text{CH}_a\text{H}_b-4, \text{CH}_a\text{H}_b-5), 2.35-2.50 (2H, m, \text{CH}_a\text{H}_b-2, \text{CH}_a\text{H}_b-6), 2.80-2.91 (1H, m, \text{CH}_a\text{H}_b-6), 3.04-3.14 (1H, m, CH\_a\text{H}_b-2), 3.87-4.00 (1H, m, 3-H), 7.61-7.70 (4H, m, Ar-H); \delta_C (75 MHz; DMSO-d₆, 120 °C) 18.0 (C, OSi-tBu), 19.9 (CH₂, C-4), 26.1 (CH₃, OSi-tBu), 31.9 (CH₂, C-5), 56.9 (CH₂, C-6), 64.8 (CH₂, C-2), 67.9 (CH, C-3), 126.8 (CH, C-Ar), 128.8 (CH, C-Ar), 132.6 (C, C-Ar), 134.4 (CH, C-Ar); \text{m/z} (CI, NH₃) 356 (100, MH⁺), 340 (18), 338 (15), 282 (12), 199 (15), 160 (21), 82 (38%). HRMS (CI): MH⁺, found 356.2049. C₂₁H₃₀NO₂Si requires 356.2046.

(S)-3-(tert-Butyldiphenylsilyloxy)-2,3,4,5-tetrahydropyridine 1-oxide (198) and (S)-5-(tert-butyldiphenylsilyloxy)-2,3,4,5-tetrahydropyridine 1-oxide (344)

**Method A: Oxidation Using Manganese(IV) oxide**

Activated manganese(IV) oxide (1.43 g, 16.5 mmol) was added portionwise to a solution of hydroxylamine 343 (2.34 g, 6.58 mmol) in dichloromethane (50 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The resulting suspension was filtered through a pad of magnesium sulphate/Celite® and the filtrate concentrated under reduced pressure, at a water bath temperature below 20 °C, to give a yellow oil. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 0:100 to 1:19), to give the title compounds 198 (1.29 g, 55%) and 344 (0.59 g, 25%) as colourless oils.

**Data for 344:** \( R_f \) (5% MeOH/CH₂Cl₂) 0.17; \[[\alpha]_D^{20}\] -9.8 (c 2.43, CHCl₃); \nu_{\text{max}} (film) 3340, 3071, 2931, 2892, 2835 (C-H), 1623, 1589 (C≡N), 1427 (C=C), 1104 cm⁻¹; \delta_H (400 MHz; CDCl₃) 1.07 (9H, s, OSi-tBu), 1.57-1.68 (1H, m, \text{CH}_a\text{H}_b-4), 1.67-1.78 (1H, m, \text{CH}_a\text{H}_b-4),
2.25-2.37 (1H, m, CH$_a$H$_b$-3), 2.63-2.76 (1H, m, CH$_a$H$_b$-3), 3.66-3.80 (2H, m, H-6), 4.18-4.24 (1H, m, H-5), 7.16-7.21 (1H, m, H-2), 7.36-7.49 (6H, m, Ar-H), 7.63-7.67 (4H, m, Ar-H); $\delta$ (100 MHz; CDCl$_3$) 19.2 (C, OSi$^t$Bu), 21.6 (CH$_2$, C-3), 25.1 (CH$_2$, C-4), 26.9 (CH$_3$, OSi$^t$Bu), 64.1 (CH$_2$, C-6), 65.5 (CH, C-5), 127.8 (CH, C-Ar), 127.9 (CH, C-Ar), 130.0 (CH, C-Ar), 130.1 (CH, C-Ar), 132.8 (C, C-Ar), 133.2 (C, C-Ar), 135.6 (CH, C-Ar), 135.9 (CH, C-2); HRMS (ESI+) C$_{21}$H$_{28}$NO$_2$Si [MH$^+$] requires 354.1884, found 354.1883.

Data for 198: $R_f$ (5% MeOH/CH$_2$Cl$_2$) 0.10; $[\alpha]_D^{20}$ -113.8 (c 2.53, CHCl$_3$); $\nu_{max}$ (film) 3071, 2931, 2858, 2892 (C-H), 1590 (C=N), 1427 (C=C), 1224, 1105, 1081 cm$^{-1}$; $\delta$ (400 MHz; CDCl$_3$) 1.07 (9H, s, OSi$^t$Bu), 1.69-1.85 (3H, m, H-4, CH$_a$, H$_b$-5), 2.11-2.23 (1H, m, CH$_a$H$_b$-5), 3.60-3.70 (1H, m, CH$_a$H$_b$-6), 3.74-3.84 (1H, m, CH$_a$H$_b$-6), 4.35-4.41 (1H, m, H-3), 6.93-6.97 (1H, m, H-2), 7.36-7.48 (6H, m, Ar-H), 7.62-7.67 (4H, m, Ar-H); $\delta$ (100 MHz; CDCl$_3$) 18.9 (CH$_2$, C-5), 19.0 (C, OSi$^t$Bu), 26.7 (CH$_3$, OSi$^t$Bu), 27.6 (CH$_2$, C-4), 58.4 (CH$_2$, C-6), 65.4 (CH, C-3), 127.8 (CH, C-Ar), 127.9 (CH, C-Ar), 130.0 (CH, C-Ar), 130.1 (CH, C-Ar), 132.8 (C, C-Ar), 133.0 (C, C-Ar), 135.6 (CH, C-Ar), 135.6 (CH, C-Ar), 137.4 (CH, C-2); HRMS (ESI+) C$_{21}$H$_{28}$NO$_2$Si [MH$^+$] requires 354.1884, found 354.1884.

4.5 Model Studies Utilising O-Silyl Protected Nitrone

General procedure 1: Synthesis of 2-substituted-3-silyloxy-1-hydroxypiperidines using Grignard reagents.

The Grignard reagent (1.5-3.0 equivalents) was added dropwise to a solution of nitrone 198 (1 equivalent) in tetrahydrofuran (10 mL) at 0 °C and the mixture stirred at this temperature for 1 h. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (10 mL) and the aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with the specified solvent to give trans-2,3-disubstituted piperidine-1-ols.

General procedure 2: Synthesis of 2-substituted-3-silyloxy-1-hydroxypiperidines using organolithium reagents.

A solution of nitrone 198 (1 equivalent) in tetrahydrofuran (3 mL) was added dropwise to a solution of organolithium (1.25-1.50 equivalents) in tetrahydrofuran (7 mL) at -78 °C and
the mixture stirred at this temperature for 1 h. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (10 mL) and the aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with the specified solvent to give trans-2,3-disubstituted piperidine-1-ols.

**General procedure 3: Reduction of N-hydroxypiperidines**

Zinc powder (5 equivalents) and indium powder (10 mol %) were added to a solution of hydroxylamine in ethanol/saturated aqueous ammonium chloride (2:1, 4.5 mL). The suspension was stirred under reflux for 4 h, cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated and saturated aqueous sodium carbonate (15 mL) was added. The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (1:99 to 9:91), to give the trans-2,3-disubstituted piperidines.

(2R,3S)-3-(tert-Butyldiphenylsilyloxy)-2-methylpiperidine (346)

Following general procedure 1, reaction of methylmagnesium bromide (3.0 M in diethyl ether, 0.17 mL, 0.50 mmol) and nitrone 198 (0.12 g, 0.33 mmol) followed by purification of the residue by column chromatography, using ethyl acetate-hexanes (1:4), gave the 2-methylpiperidin-1-ol 345 (0.10 g, 81%) as a yellow oil.

Following general procedure 3, reduction of 2-methylpiperidin-1-ol 345 (0.20 g, 0.53 mmol) gave the title compound (0.15 g, 81%) as a yellow oil.

$[\alpha]_{D}^{20} +26.0$ (c 2.16, CHCl$_{3}$); $\nu_{\text{max}}$ (film) 3048 (N-H), 2931, 2857 (C-H), 1427 (C=C), 1105, 1085 cm$^{-1}$; $\delta_{H}$ (300 MHz; CDCl$_{3}$) 1.05 (9H, s, OSi'tBu), 1.13 (3H, d, $J_{1\prime-2}$ 6.3 Hz, H-1'), 1.16-1.42 (2H, m, H-4ax, H-5ax), 1.47-1.57 (1H, m, H-5eq), 1.70-1.81 (1H, m, H-4eq), 1.97 (1H, br s, NH), 2.52 (1H, td, $J_{\text{gem}} = J_{6ax-5ax}$ 11.6, $J_{6ax-5eq}$ 3.1 Hz, H-6ax), 2.59 (1H, dq $J_{2-3}$ 8.4, $J_{2-1'}$ 6.3 Hz, H-2), 2.78-2.89 (1H, m, H-6eq), 3.25 (1H, ddd, $J_{3-4ax}$ 9.9, $J_{3-2}$ 8.4, $J_{3-4eq}$ 4.1 Hz,
H-3), 7.30-7.44 (6H, m, Ar-H), 7.65-7.74 (4H, m, Ar-H); δC (75 MHz; CDCl3) 19.3 (C, OSi’Bu), 19.4 (CH2, C-1’), 25.7 (CH2, C-5), 27.0 (CH3, OSi’Bu), 34.1 (CH2, C-4), 45.7 (CH2, C-6), 58.6 (CH, C-2), 75.7 (CH, C-3), 127.3 (CH, C-Ar), 127.5 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 133.9 (C, C-Ar), 134.8 (C, C-Ar), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar); m/z (EI) 353 (1, M+), 296 (100), 199 (23), 183 (10), 181 (10), 98 (10), 96 (10), 69 (11), 58 (45%). HRMS (EI+) C22H31NOSi [M+] requires 353.2175, found 353.2171.

(2R,3S)-3-(tert-Butyldiphenylsilyloxy)-2-ethylpiperidine (352)

Following general procedure 1, reaction of ethylmagnesium bromide (3.0 M in diethyl ether, 0.29 mL, 0.87 mmol) and nitrone 198 (0.21 g, 0.58 mmol) followed by purification of the residue by column chromatography, using ethyl acetate-hexanes (1:4), gave the 2-ethylpiperidin-1-ol 351 (0.18 g, 81%) as a yellow oil.

Following general procedure 3, reduction of 2-ethylpiperidin-1-ol 351 (0.15 g, 0.39 mmol) gave the title compound (0.12 g, 84%) as a yellow oil.

[α]D20 +30.4 (c 2.40, CHCl3); νmax (film) 2932, 2857 (C-H), 1427 (C=C), 1105, 1075 cm⁻¹; δH (400 MHz; CDCl3) 0.85 (3H, t, J1ʹ-2ʹ 7.5, H-1’), 1.05 (9H, s, OSi’Bu), 1.14-1.41 (3H, m, CHa,Hb,Ha-2’), 1.48-1.57 (1H, m, H-5eq), 1.70-1.78 (1H, m, H-4eq), 1.88-2.04 (2H, m, NH, CHa,Hb,Ha-2’), 2.41 (1H, td, J2,3 = J2,2’ 8.3, J2,2’ 3.3 Hz, H-2), 2.51 (1H, td, Jgem = J6ax-5ax 11.2, J6ax-5eq 3.0 Hz, H-6ax), 2.83-2.92 (1H, m, H-6eq), 3.34 (1H, dd, J3,4ax 9.6, J3,2 8.3, J3,4eq 4.1 Hz, H-3), 7.32-7.44 (6H, m, Ar-H), 7.65-7.72 (4H, m, Ar-H); δC (100 MHz; CDCl3) 10.0 (CH3, C-1’), 19.4 (C, OSi’Bu), 24.7 (CH2, C-2’), 25.4 (CH2, C-5), 27.0 (CH3, OSi’Bu), 34.0 (CH2, C-4), 45.7 (CH2, C-6), 64.2 (CH, C-2), 73.6 (CH, C-3), 127.3 (CH, C-Ar), 127.5 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 133.9 (C, C-Ar), 134.9 (C, C-Ar), 135.9 (CH, C-Ar), 135.9 (CH, C-Ar), HRMS (ESI+) C23H34NOSi [MH+] requires 368.2404, found 368.2411.
Following general procedure 1, reaction of isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 0.44 mL, 0.87 mmol) and nitrone 198 (0.21 g, 0.58 mmol) followed by purification of the residue by column chromatography, using methanol-dichloromethane (0.5:99.5), gave the 2-isopropylpiperidin-1-ol 353 (0.17 g, 73%) as a colourless oil.

Following general procedure 3, reduction of 2-isopropylpiperidin-1-ol 353 (0.097 g, 0.24 mmol) gave the title compound (0.076 g, 82%) as a yellow oil.

\[\alpha\]_D^{20} +24.9 (c 1.36, CHCl_3); \nu_{\text{max}} \text{(film)} 2932, 2857 (C-H), 1472, 1428 (C=C), 1105, 1079 cm\(^{-1}\); \delta_\text{H} (300 MHz; CDCl_3) 0.67 (3H, dd, J_{iPr-1'} 6.8 Hz, i-Pr), 0.94 (3H, dd, J_{iPr-1'} 6.8 Hz, i-Pr), 1.04 (9H, s, OSi'tBu), 1.09-1.28 (1H, m, H-5ax), 1.37 (1H, tdd, J_{ gem} = J_{4ax-5ax} 12.2, J_{4ax-3 9.8}, J_{4ax-5eq} 4.0 Hz, H-4ax), 1.45-1.57 (1H, m, H-5eq), 1.71-1.83 (1H, m, H-4eq), 2.29-2.42 (2H, m, H-2, H-1'), 2.48 (1H, td, J_{ gem} = J_{6ax-5a} 11.6, J_{6ax-5eq} 3.0 Hz, H-6ax), 2.84-2.94 (1H, m, H-6eq), 3.44 (1H, ddd, J_{3-4ax} 9.7, J_{3-2} 8.3, J_{3-4eq} 4.2 Hz, H-3), 7.31-7.46 (6H, m, Ar-H), 7.64-7.74 (4H, m, Ar-H); \delta_\text{C} (75 MHz; CDCl_3) 15.3 (CH_3, i-Pr), 19.3 (C, OSi'tBu), 20.5 (CH_3, i-Pr), 25.5 (CH_2, C-5), 26.0 (CH, C-1'), 27.0 (CH_3, OSi'tBu), 34.3 (CH_2, C-4), 45.9 (CH_2, C-6), 67.9 (CH, C-2), 71.3 (CH, C-3), 127.3 (CH, C-Ar), 127.6 (CH, C-Ar), 129.4 (CH, C-Ar), 129.6 (CH, C-Ar), 133.8 (C, C-Ar), 135.1 (C, C-Ar); HRMS (ESI+) C_{24}H_{36}NOSi [MH^+] requires 382.2572, found 382.2561.

Following general procedure 1, reaction of benzylmagnesium chloride (2.0 M in tetrahydrofuran, 0.45 mL, 0.89 mmol) and nitrone 198 (0.21 g, 0.59 mmol) followed by purification of the residue column chromatography using methanol-dichloromethane (0.5:99.5), gave the 2-benzylpiperidin-1-ol 355 (0.24 g, 92%) as a colourless oil.

(2R,3S)-3-(tert-Butyldiphenylsilyloxy)-2-isopropylpiperidine (354)

Following the general procedure 1, reaction of benzylmagnesium chloride (2.0 M in tetrahydrofuran, 0.45 mL, 0.89 mmol) and nitrone 198 (0.21 g, 0.59 mmol) followed by purification of the residue column chromatography using methanol-dichloromethane (0.5:99.5), gave the 2-benzylpiperidin-1-ol 355 (0.24 g, 92%) as a colourless oil.
Following general procedure 3, reduction of 2-benzylpiperidin-1-ol 355 (0.13 g, 0.31 mmol) gave the title compound (0.13 g, 99%) as a colourless oil.

[α]D^20 +6.8 (c 1.34, CHCl₃); ν_max (film) 2932, 2857 (C-H), 1453, 1427 (C=C), 1104, 1084 cm⁻¹; δ_H (300 MHz; CDCl₃) 1.09 (9H, s, OSi'tBu), 1.19-1.41 (2H, m, H-4ax, H-5ax), 1.41-1.54 (1H, m, H-5eq), 1.61 (1H, br s, NH), 1.79-1.89 (1H, m, H-4eq), 2.18 (1H, dd, J_{CH2Ph-2} 10.5, J_{gem} 3.3 Hz, CH₃H₂Ph), 2.34 (1H, td, J_{gem} = J_{6ax-5ax} 11.5, J_{6ax-5eq} 2.8 Hz, H-6ax), 2.52 (1H, m, H-6eq), 2.66 (2H, m, H-2), 2.84-2.93 (1H, m, H-6eq), 2.99-3.08 (1H, m, H-2), 3.44 (1H, ddd, J_{3-4ax} 9.7, J_{3-2} 8.4, J_{3-4eq} 4.1 Hz, H-3), 5.05-5.25 (2H, m, H-1'), 5.82-5.96 (1H, m, H-2'), 7.29-7.44 (6H, m, Ar-H); δ_C (75 MHz; CDCl₃) 19.3 (C, OSi'tBu), 25.1 (CH₂, C-5), 34.6 (CH₂, C-4), 39.2 (CH₂, C-Ph), 46.0 (CH₂, C-6), 64.9 (CH, C-2), 74.4 (CH, C-3), 126.2 (CH, C-Ph), 127.4 (CH, C-Ar), 127.6 (CH, C-Ar), 128.5 (CH, C-Ph), 129.3 (CH, C-Ph), 129.5 (CH, C-Ar), 129.6 (CH, C-Ar), 133.9 (C, C-Ar), 134.8 (C, C-Ar), 135.9 (CH, C-Ar), 136.0 (CH, C-Ar), 139.6 (C, C-Ph); HRMS (ESI) C_{28}H_{36}NOSi [MH⁺] requires 430.2561, found 430.2571.

(2R,3S)-3-(tert-Butyldiphenylsilyloxy)-2-vinylpiperidine (358)

Following general procedure 1, reaction of vinylmagnesium bromide (1.0 M in tetrahydrofuran, 0.93 mL, 0.93 mmol) and nitrone 198 (0.22 g, 0.62 mmol) followed by purification of the residue by column chromatography, using ethyl acetate-hexanes (1:9), gave the 2-vinylpiperidin-1-ol 357 (0.20 g, 85%) as a colourless oil.

Following general procedure 3, reduction of 2-vinylpiperidin-1-ol 357 (0.11 g, 0.30 mmol) gave the title compound (0.085 g, 79%) as a colourless oil.

[α]D^20 +12.5 (c 1.10, CHCl₃); ν_max (film) 3072, 2932, 2857 (C-H), 1453, 1427 (C=C), 1104 cm⁻¹; δ_H (300 MHz; CDCl₃) 1.03 (9H, m, OSi'Bu), 1.16-1.45 (2H, m, H-4ax, H-5ax), 1.48-1.59 (1H, m, H-5eq), 1.70-1.84 (2H, m, H-4eq, NH), 2.55 (1H, td, J_{gem} = J_{6ax-5ax} 11.5, J_{6ax-5eq} 2.9 Hz, H-6ax), 2.84-2.93 (1H, m, H-6eq), 2.99-3.08 (1H, m, H-2), 3.44 (1H, ddd, J_{3-4ax} 9.7, J_{3-2} 8.4, J_{3-4eq} 4.1 Hz, H-3), 5.05-5.25 (2H, m, H-1'), 5.82-5.96 (1H, m, H-2'), 7.29-7.44 (6H, m, Ar-H), 7.64-7.72 (4H, m, Ar-H); δ_C (75 MHz; CDCl₃) 19.3 (C, OSi'Bu), 25.1 (CH₂, C-5), 25.1 (CH₂, C-3), 27.1 (CH₃, OSi'Bu), 34.6 (CH₂, C-4), 39.2 (CH₂, C-Ph), 46.0 (CH₂, C-6), 64.9 (CH, C-2), 74.4 (CH, C-3), 126.2 (CH, C-Ph), 127.4 (CH, C-Ar), 127.6 (CH, C-Ar), 128.5 (CH, C-Ph), 129.3 (CH, C-Ph), 129.5 (CH, C-Ar), 129.6 (CH, C-Ar), 133.9 (C, C-Ar), 134.8 (C, C-Ar), 135.9 (CH, C-Ar), 136.0 (CH, C-Ar), 139.6 (C, C-Ph); HRMS (ESI) C_{28}H_{36}NOSi [MH⁺] requires 430.2561, found 430.2571.
Following the general procedure, reaction of allylmagnesium chloride (1.0 M in diethyl ether, 1.13 mL, 1.13 mmol) and nitrone 198 (0.27 g, 0.75 mmol) followed by purification of the residue by column chromatography, using methanol-dichloromethane (0.5:99.5), gave the trans-2-allylpiperidin-1-ol 359 (0.21 g, 70%) and cis-2-allylpiperidin-1-ol 360 (0.032 g, 11%) as a colourless oils.

Following general procedure 3, reduction of the first eluted compound, trans-2-allylpiperidin-1-ol 359 (0.11 g, 0.28 mmol) gave the title compound 361 (0.095 g, 91%) as a yellow oil.

\[
[a]_D^{20} +11.1 \ (c \ 1.88, \ CHCl_3); \ \nu_{\max} \ (\text{film}) \ 2932, 2857 \ (C-H), 1428 \ (C=C), 1105, 1083 \ cm^{-1}; \ \delta_H \ (400 \ MHz; \ CDCl_3) \ 1.05 \ (9H, \ s, \ OSiBu), \ 1.15-1.41 \ (2H, \ m, \ H-4ax, \ H-5ax), \ 1.45-1.54 \ (1H, \ m, \ H-5eq), \ 1.66-1.82 \ (2H, \ m, \ NH, \ H-4eq), \ 1.82-1.93 \ (1H, \ m, \ CH_aH_b-3'), \ 2.43-2.52 \ (2H, \ m, \ H-2, \ H-6ax), \ 2.77-2.89 \ (2H, \ m, \ H-6eq \ CH_aH_b-3'), \ 3.34 \ (1H, \ ddd, \ J_{3-4ax} 9.9, \ J_{3-2} \ 8.6, \ J_{3-4eq} \ 4.2 \ Hz, \ H-3), \ 5.02-5.12 \ (2H, \ m, \ H-1'), \ 5.71 \ (1H, \ dddd, \ J 16.9, \ 10.2, \ 8.8, \ 5.7 \ Hz, \ H-2'), \ 7.32-7.44 \ (6H, \ m, \ Ar-H), \ 7.65-7.72 \ (4H, \ m, \ Ar-H); \ \delta_C \ (100 \ MHz; \ CDCl_3) \ 19.4 \ (C, \ OSiBu), \ 25.4 \ (CH_2, \ C-5), \ 27.0 \ (CH_3, \ OSiBu), \ 34.5 \ (CH_2, \ C-4), \ 37.1 \ (CH_2, \ C-3'), \ 45.9 \ (CH_2, \ C-6), \ 62.1 \ (CH, \ C-2), \ 73.9 \ (CH, \ C-3), \ 117.7 \ (CH_2, \ C-1'), \ 127.3 \ (CH, \ C-Ar), \ 127.5 \ (CH, \ C-Ar), \ 129.4 \ (CH, \ C-Ar), \ 129.6 \ (CH, \ C-Ar), \ 133.8 \ (C, \ C-Ar), \ 134.8 \ (C, \ C-Ar), \ 135.8 \ (CH, \ C-2'), \ 135.8 \ (CH, \ C-Ar), \ 135.9 \ (CH, \ C-Ar); \ HRMS \ (EI) \ C_{24}H_{33}NOSi [M^+] \ requires \ 379.2331, \ found \ 379.2323.
\]

Following general procedure 3, reduction of the second eluted compound, cis-2-allylpiperidin-1-ol 360 (0.027 g, 0.068 mmol) gave the the title compound 362 (0.021 g, 81%) as an opaque oil.
\[ \alpha \]_D^{20} -13.1 (c 0.20, CHCl_3); \nu_\text{max} \text{ (film)} 3072, 2931, 2856 (C-H), 1427 (C=C), 1104 cm\(^{-1}\); \delta_H \text{ (300 MHz; CDCl}_3) 1.11 (9H, s, OSi'Bu), 1.27-1.46 (2H, m, H-4ax, H-5ax), 1.64-1.77 (1H, m, H-4eq), 1.79-1.97 (1H, m, H-5eq), 2.14-2.40 (2H, m, H-3'), 2.56-2.70 (2H, m, H-2, H-6ax), 2.86 (1H, br s, NH), 3.05-3.18 (1H, m, H-4eq), 1.64-1.77 (1H, m, H-1'), 5.55-5.71 (1H, m, H-2'), 7.33-7.47 (6H, m, Ar-H), 7.65-7.74 (4H, m, Ar-H); \delta_C \text{ (75 MHz; CDCl}_3) 19.5 (C, OSi'Bu), 21.1 (CH_2, C-5), 27.2 (CH_3, OSi'Bu), 31.0 (CH_2, C-4), 35.3 (CH_2, C-3'), 44.9 (CH_2, C-6), 60.1 (CH, C-2), 68.7 (CH, C-3), 117.0 (CH_2, C-1'), 127.5 (CH, C-Ar), 127.6 (CH, C-Ar), 129.7 (CH, C-Ar), 129.7 (CH, C-Ar), 133.7 (C, C-Ar), 134.2 (C, C-Ar), 135.5 (CH, C-2'), 136.0 (CH, C-Ar), 136.1 (CH, C-Ar); HRMS (ESI+) C_{24}H_{34}NO_{Si}[MH]^+ \text{ requires 380.2404, found 380.2395.}

\((2R,3S)-3\text-(\text{tert-Butyldiphenylsilyloxy})\text{-2-phenylpiperidine (365)}\)

Following general procedure 1, reaction of phenylmagnesium chloride (2.0 M in tetrahydrofuran, 0.42 mL, 0.86 mmol) and nitrone 198 (0.10 g, 0.28 mmol) followed by purification of the residue by column chromatography, using methanol-dichloromethane (0.5:99.5), gave the 2-phenylpiperidin-1-ol 364 (0.098 g, 80%) as a colourless oil.

Following general procedure 3, reduction of 2-phenylpiperidin-1-ol 364 (0.11 g 0.26 mmol) gave the title compound (0.080 g, 76%) as a colourless oil.

\[ \alpha \]_D^{20} -15.2 (c 1.60, CHCl_3); \nu_\text{max} \text{ (film)} 3070, 2931, 2855 (C-H), 1427 (C=C), 1103 cm\(^{-1}\); \delta_H \text{ (300 MHz; CDCl}_3) 0.75 (9H, s, OSi'Bu), 1.28-1.48 (2H, m, H-4ax, H-5ax), 1.48-1.56 (1H, m, H-5eq), 1.68-1.79 (1H, m, H-4eq), 1.80 (1H, br s, NH), 2.59-2.68 (1H, m, H-6ax), 2.91-2.99 (1H, m, H-6eq), 3.50 (1H, d, J_2,3 8.7 Hz, H-2), 3.62-7.70 (1H, m, H-3), 7.18-7.42 (13H, m, Ar-H), 7.55-7.61 (2H, m, Ar-H); \delta_C \text{ (75 MHz; CDCl}_3) 19.0 (C, OSi'Bu), 25.3 (CH_2, C-5), 26.6 (CH_3, OSi'Bu), 35.1 (CH_2, C-4), 46.7 (CH_2, C-6), 69.5 (CH, C-2), 74.5 (CH, C-3), 127.2 (CH, C-Ar), 127.4 (CH, C-Ar), 128.1 (CH, C-Ar), 128.5 (CH, C-Ar), 129.2 (CH, C-Ar), 129.3 (CH, C-Ar), 133.4 (C, C-Ar), 135.2 (C, C-Ar), 135.8 (CH, C-Ar), 142.5 (C, C-Ar); HRMS (EI+) C_{27}H_{34}NO_{Si}[M]^+ \text{ requires 415.2331, found 415.2324.}
(2R,3S)-3-(tert-Butyldiphenylsilyloxy)-2-(3,4-dimethoxyphenyl)piperidine (367)

Following general procedure 1, reaction of 3,4-dimethoxyphenylmagnesium bromide (0.5 M in tetrahydrofuran, 1.9 mL, 0.96 mmol) and nitrone 198 (0.11 g, 0.32 mmol) followed by purification of the residue by column chromatography, using ethyl acetate-hexanes (5:95), gave the 2-(3,4-dimethoxyphenyl)piperidin-1-ol 366 (0.12 g, 73%) as a colourless oil.

Following general procedure 3, reduction of 2-(3,4-dimethoxyphenyl)piperidin-1-ol 366 (0.11 g, 0.23 mmol) gave the title compound (0.10 g, 97%) as a colourless oil. 

\[ \alpha \] \text{D}_{20}^-17.4 \ (c \ 2.08, \ CHCl_3); \ \nu_{\text{max}} \ (\text{film}) \ 2933, 2856 \ (C-H), 1516, 1463 \ (C=C), 1262, 1104 \ cm^{-1}; \ \delta_H \ (300 \ \text{MHz}; \ CDCl_3) \ 0.80 \ (1H, \ s, \ OSi\text{Bu}), \ 1.48-1.30 \ (2H, \ m, \ H-4ax, \ H-5ax), \ 1.58-1.48 \ (1H, \ m, \ H-5eq), \ 1.84-1.74 \ (1H, \ m, \ H-4eq), \ 1.91 \ (1H, \ br \ s, \ NH), \ 2.63 \ (1H, \ td, \ J_{\text{gem}} = J_{6ax-5ax} 11.4, \ J_{6ax-5eq} 2.6 \ Hz, \ H-6ax), \ 2.99-2.89 \ (1H, \ m, \ H-6eq), \ 3.43 \ (1H, \ d, \ J_{2.3} 8.7 \ Hz, \ H-2), \ 3.67-3.56 \ (1H, \ m, \ H-3), \ 3.78 \ (3H, \ s, \ 3’-OMe), \ 3.87 \ (3H, \ s, \ 4’-OMe), \ 6.76 \ (1H, \ d, \ J_{5’-6’} 8.2 \ Hz, \ H-5’), \ 6.84 \ (1H, \ d, \ J_{2’-6’} 1.9 \ Hz, \ H-2’), \ 6.86 \ (1H, \ dd, \ J_{6’-5’} 8.2, \ J_{6’-2’} 1.9 \ Hz, \ H-6’), \ 7.27-7.17 \ (4H, \ m, \ Ar-H), \ 7.42-7.27 \ (4H, \ m, \ Ar-H), \ 7.59-7.53 \ (2H, \ m, \ Ar-H); \ \delta_C \ (75 \ \text{MHz}; \ CDCl_3) \ 18.9 \ (C, \ OSi\text{Bu}), \ 25.1 \ (CH_2, \ C-5), \ 26.6 \ (CH_3, \ OSi\text{Bu}), \ 35.1 \ (CH_2, \ C-4), \ 46.7 \ (CH_2, \ C-6), \ 55.7 \ (CH_3, \ C-3’), \ 55.9 \ (CH_3, \ C-4’), \ 69.3 \ (CH, \ C-2), \ 74.5 \ (CH, \ C-3), \ 110.8 \ (CH, \ C-5’), \ 111.1 \ (CH, \ C-2’), \ 121.0 \ (CH, \ C-6’), \ 127.1 \ (CH, \ C-Ar), \ 127.2 \ (CH, \ C-Ar), \ 129.2 \ (CH, \ C-Ar), \ 132.4 \ (C, \ C-Ar), \ 135.0 \ (C, \ C-Ar), \ 135.3 \ (C, \ C-1’), \ 135.8 \ (CH, \ C-Ar), \ 148.3 \ (C, \ C-4’), \ 148.8 \ (C, \ C-3’); \ HRMS \ (ESI+) \ C_{29}H_{39}NO_3Si \ [\text{MH}^+] \ requires \ 476.2615, \ found \ 476.2604.

3-(2R,3S)-3-(tert-Butyldiphenylsilyloxy)piperidin-2-yl)pyridine (388)

A solution of isopropylmagnesium chloride in tetrahydrofuran (2.0 M in tetrahydrofuran, 0.31 mL, 0.62 mmol) was added to a solution of 3-bromopyridine (0.11 mL, 0.67 mmol) in tetrahydrofuran (5 mL) and the mixture stirred at room temperature for 1 h. \textsuperscript{283}
The solution was cooled to 0 °C and nitrone (0.15 g, 0.42 mmol) in tetrahydrofuran (4 mL) was added dropwise and the mixture stirred for 6 h. Saturated aqueous ammonium chloride (10 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with methanol-dichloromethane (1:99), to give the 2-(3-pyridyl)piperidin-1-ol 387 (0.11 g, 62%) as a colourless oil.

Following general procedure 3, reduction of 2-(3-pyridyl)piperidin-1-ol 387 (0.11 g, 0.58 mmol) gave the title compound (0.077 g, 71%) as a colourless oil.

\[\alpha\]_D^20 -16.5 (c 1.54, CHCl_3); \nu_{max} (film) 2932, 2857 (C-H), 1426 (C=C), 1103 cm\(^{-1}\); \delta_H (300 MHz; CDCl_3) 0.76 (9H, s, OSi\(_{\text{tBu}}\)), 1.24-1.61 (3H, m, H-4ax, H-5), 1.70-2.00 (2H, m, H-4eq, NH), 2.65 (1H, td, \(J_{6ax:5ax} = J_{gem} \) 11.5, \(J_{6ax:5eq} \) 2.6 Hz, H-6ax), 2.90-3.00 (1H, m, H-6eq), 3.53 (1H, d, \(J_{6' \cdot 2'} \) 8.7 Hz, H-2), 3.57-3.68 (1H, m, H-3), 7.16 (1H, dd, \(J_{5':6'} \) 4.7, \(J_{5':4'} \) 7.7 Hz, H-5'), 7.20-7.30 (4H, m, Ar-H), 7.30-7.43 (4H, m, Ar-H), 7.53-7.61 (3H, m, Ar-H, H-4'), 8.50 (1H, dd, \(J_{6':2'} \) 1.4, \(J_{6':5'} \) 4.7 Hz, H-6'), 8.60 (1H, d, \(J_{2':6'} \) 1.6 Hz, H-2'); \delta_C (75 MHz; CDCl_3) 18.9 (C, OSi\(_{\text{tBu}}\)), 25.1 (CH_2, C-5), 26.5 (CH_3, OSi\(_{\text{tBu}}\)), 34.9 (CH_2, C-4), 46.6 (CH_2, C-6), 67.0 (CH, C-2), 74.4 (CH, C-3), 123.2 (CH, C-5'), 127.2 (CH, C-Ar), 127.4 (CH, C-Ar), 129.4 (CH, C-Ar), 129.4 (CH, C-Ar), 133.0 (C, C-Ar), 134.7 (C, C-Ar), 135.5 (CH, C-4'), 135.7 (CH, C-Ar), 135.8 (CH, C-Ar), 138.0 (C, C-3'), 148.8 (CH, C-6'), 150.3 (CH, C-2'); HRMS (ESI+) C_{26}H_{33}N_{2}OSi [MH\(^{+}\)] requires 417.2357, found 417.2366.

\((2R,3S)-2\text{-Butyl}-3\text{-}(\text{tert\text{-butyldiphenylsilyloxy})piperidine (376)}\)

Following general procedure 2, reaction of nitrone 198 (0.10 g, 0.28 mmol) and \textit{n}-butyllithium (1.6 M in hexanes, 0.27 mL, 0.42 mmol) followed by purification of the residue by column chromatography, using ethyl acetate-hexanes (1:9), gave the 2-butylpiperidin-1-ol 375 (0.070 g, 50%) as a colourless oil.

Following general procedure 3, reduction of 2-butylpiperidin-1-ol 375 (0.068 g, 0.17 mmol) gave the title compound (0.048 g, 73%) as a colourless oil.
[α]_D^{20} +22.5 (c 0.84, CHCl_3); ν_{max} (film) 2931, 2857 (C-H), 1428 (C=C), 1105, 1082 cm^{-1}; δ_H (300 MHz; CDCl_3) 0.86 (3H, t, J_{1\cdot 2} = 6.9, 1'-H), 1.05 (9H, s, OSi'Bu), 1.11-1.44 (7H, m, H-4ax, H-5ax, 2'-H, 3'-H, CH_3H_5-4'), 1.49-1.60 (1H, m, H-5eq), 1.70-1.82 (1H, m, H-4eq), 1.84-1.98 (1H, m, CH_3H_5-4'), 2.32 (1H, m, NH), 2.42-2.57 (2H, m, H-2, H-6ax), 2.83-2.92 (1H, m, H-6eq), 3.34 (1H, ddd, J_{3\cdot 4ax} = 9.6, J_{3\cdot 2} = 8.2, J_{3\cdot 4eq} = 4.1 Hz, H-3'), 7.30-7.45 (6H, m, Ar-H), 7.64-7.73 (4H, m, Ar-H); δ_C (75 MHz; CDCl_3) 14.0 (CH_3, C-1'), 19.4 (C, OSi'Bu), 22.8 (CH_2, C-2'), 25.2 (CH_2, C-5), 27.0 (CH_3, OSi'Bu), 27.8 (CH_2, C-3'), 31.6 (CH_2, C-4'), 33.9 (CH_2, C-4), 45.5 (CH_2, C-6), 62.8 (CH, C-2), 73.7 (CH, C-3), 127.3 (CH, C-Ar), 127.5 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 134.0 (C, C-Ar), 134.9 (C, C-Ar), 135.9 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (ESI+) C_{25}H_{38}NOSi [MH'] requires 396.2717, found 396.2719.

(2R,3S)-2-(tert-Butyl)-3-(tert-butyldiphenylsilyloxy)piperidine (378)

Following general procedure 2, reaction of nitrone 198 (0.26 g, 0.74 mmol) and tert-butyllithium (1.7 M in pentane, 0.65 mL, 1.10 mmol) followed by purification of the residue by column chromatography, using ethyl acetate-hexanes (1:9), gave the tert-butylpiperidin-1-ol 377 (0.099 g, 31%) as a colourless oil.

Following general procedure 3, reduction of tert-butylpiperidin-1-ol 377 (0.082 g, 0.20 mmol) gave the title compound (0.073 g, 93%) as a colourless oil.

[α]_D^{20} +46.0 (c 1.18, CHCl_3); ν_{max} (film) 2933, 2858 (C-H), 1474 (C=C), 1428, 1105, 1075 cm^{-1}; δ_H (300 MHz; CDCl_3) 1.01 (9H, s, OSi'Bu), 1.01-1.18 ((10H, m, H-5ax, CH'Bu), 1.20-1.45 (2H, m, H-4ax, H-5eq), 1.58-1.70 (1H, m, H-4eq), 1.87 (1H, br s, NH), 2.33 (1H, d, J_{2\cdot 3} = 7.8, H-2), 2.47 (1H, tld, J_{gem} = J_{6ax-5ax} = 11.6, J_{6ax-5eq} = 3.0 Hz, H-6ax), 2.82-2.93 (1H, m, H-6eq), 3.67 (1H, ddd, J_{3\cdot 4ax} = 9.4, J_{3\cdot 2} = 7.7, J_{3\cdot 4eq} = 3.7 Hz, H-3), 7.32-7.46 (6H, m, Ar-H), 7.70-7.82 (4H, m, Ar-H); δ_C (75 MHz; CDCl_3) 19.3 (C, OSi'Bu), 24.9 (CH_2, C-5), 27.0 (CH_3, OSi'Bu), 28.1 (CH_3, C'Bu), 33.8 (C, C'Bu), 35.0 (CH_2, C-4), 46.3 (CH_2, C-6), 70.7 (CH, C-2), 74.0 (CH, C-3), 127.2 (CH, C-Ar), 127.6 (CH, C-Ar), 129.2 (CH, C-Ar), 129.6 (CH, C-Ar), 133.7 (C, C-Ar), 135.5 (C, C-Ar), 135.7 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (ESI+) C_{25}H_{38}NOSi [MH'] requires 396.2717, found 396.2717.
(2R,3S)-3-(tert-Butyldiphenylsilyloxy)-2-(4-methoxyphenyl)piperidine (380)

Following general procedure 2, reaction of nitrone 198 (0.26 g 0.74 mmol) and (4-methoxyphenyl)lithium, prepared from n-butyllithium (1.6 M in hexanes, 0.69 mL, 1.11 mmol) and 4-bromoanisole (0.23 g, 1.26 mmol), followed by purification of the residue by column chromatography, using methanol-dichloromethane (0.5:99.5), gave the 2-(4-methoxyphenyl)piperidine-1-ol 379 (0.22 g, 69%) as a colourless oil.

Following general procedure 3, reduction of 2-(4′-methoxyphenyl)piperidine-1-ol 379 (0.13 g, 0.27 mmol) gave the title compound (0.11 g, 92%) as a colourless oil.

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\alpha_D^{20} -37.0 \ (c \ 1.76, \ CHCl_3); \ \nu_{\max} \ (film) \ 2932, \ 2856 \ (C-H), \ 1612, \ 1512, \ 1427 \ (C=C), \ 1249, \ 1239, \ 1104 \ cm^{-1}; \ \delta_H \ (300 \ MHz; \ CDCl_3) \ 0.79 \ (9H, \ s, \ OSi_tBu), \ 1.27-1.47 \ (2H, \ m, \ H-4ax, \ H-5ax), \ 1.48-1.56 \ (1H, \ m, \ H-5eq), \ 1.70-1.84 \ (2H, \ m, \ H-4eq, \ NH), \ 2.63 \ (1H, \ m, \ H-6ax), \ 2.89-2.96 \ (1H, \ m, \ H-6eq), \ 3.44 \ (1H, \ d, \ J_{2,3} \ 8.7 \ Hz, \ H-2), \ 3.57-3.65 \ (1H, \ m, \ H-3), \ 3.80 \ (3H, \ s, \ OMe), \ 6.79-6.84 \ (2H, \ m, \ H-3′, \ H-5′), \ 7.17-7.26 \ (6H, \ m, \ Ar-H, \ H-2′, \ H-6′), \ 7.29-7.42 \ (4H, \ m, \ Ar-H), \ 7.55-7.60 \ (2H, \ m, \ Ar-H); \ \delta_C \ (75 \ MHz; \ CDCl_3) \ 19.0 \ (C, \ OSi\_tBu), \ 25.3 \ (CH_2, \ C-5), \ 26.7 \ (CH_3, \ OSi\_tBu), \ 35.1 \ (CH_2, \ C-4), \ 46.8 \ (CH_2, \ C-6), \ 55.3 \ (CH_3, \ OMe), \ 68.8 \ (CH, \ C-3), \ 74.6 \ (CH, \ C-3), \ 113.5 \ (CH, \ C-3′,5′), \ 127.1 \ (CH, \ C-Ar), \ 127.2 \ (CH, \ C-Ar), \ 129.2 \ (CH, \ C-Ar), \ 129.2 \ (CH, \ C-Ar), \ 129.4 \ (CH, \ C-2′,6′), \ 133.5 \ (C, \ C-Ar), \ 134.9 \ (C, \ C-1′), \ 135.1 \ (C, \ C-Ar), \ 135.8 \ (CH, \ C-Ar), \ 135.8 \ (CH, \ C-Ar), \ 158.9 \ (C, \ C-4′); \ HRMS \ (ESI+) \ C_{28}H_{36}NO_2Si [MH^+] \ requires \ 446.2510, \ found \ 446.2522.
\]

(2S,3S)-3-(tert-Butyldiphenylsilyloxy)-2-(furan-2-yl)piperidine (384)

Following general procedure 2, reaction of nitrone 198 (0.20 g, 0.56 mmol) and 2-lithiofuran, prepared by reaction of n-butyllithium (1.6 M in hexanes, 0.53 mL, 0.84 mmol) and freshly distilled furan (0.065 g, 0.96 mmol), followed by purification of the residue by
column chromatography, using ethyl acetate-hexanes (1:9), gave the 2-(2'-furanyl)piperidine-1-ol 383 (0.17 g, 72%) as a yellow oil.

Following general procedure 3, reduction of 2-(2'-furanyl)piperidine-1-ol 383 (0.10 g, 0.24 mmol) gave the title compound (0.091 g, 94%) as a yellow oil.

\[ \alpha \] D 20 +4.5 (c 1.82, CHCl 3 ); \( \nu_{\text{max}} \) (film) 3071, 2930, 2856 (C-H), 1427 (C=C), 1104 cm\(^{-1}\); \( \delta \) H (300 MHz; CDCl 3 ) 0.88 (9H, m, OSi t Bu), 1.49-1.60 (1H, m, H-5eq), 1.71-1.83 (2H, m, H-4eq, NH), 2.59 (1H, td, \( J \text{gem} = J_{6ax-5ax} \) 11.5 Hz, \( J_{6ax-5eq} \) 2.9, H-6ax), 2.87-2.96 (1H, m, H-6eq), 3.67 (1H, d, \( J_{2-3} \) 8.6 Hz, H-2), 3.85 (1H, ddd, \( J_{3-2} \) 8.6, \( J_{3-4ax} \) 9.7, \( J_{3-5ax} \) 4.2 Hz, H-3'), 6.19 (1H, d, \( J_{3-4' \text{ax}} \) 3.2, \( J_{3-5' \text{ax}} \) 0.8 Hz, H-3'), 6.28 (1H, dd, \( J_{4'-3' \text{ax}} \) 3.2, \( J_{4'-5' \text{ax}} \) 1.9 Hz, H-4'), 7.24-7.48 (9H, m, Ar-H, H-5'), 7.59-7.65 (2H, m, Ar-H); \( \delta \) C (75 MHz; CDCl 3 ) 19.0 (C, OSi t Bu), 25.1 (CH 2 , C-5), 26.7 (CH 3 , OSi t Bu), 34.5 (CH 2 , C-4), 46.0 (CH 2 , C-6), 61.7 (CH, C-2), 72.4 (CH, C-3), 107.3 (CH, C-3'), 110.0 (CH, C-4'), 127.3 (CH, C-Ar), 127.3 (CH, C-Ar), 129.3 (CH, C-Ar), 139.3 (C, C-Ar), 133.5 (C, C-Ar), 134.9 (C, C-Ar), 135.8 (CH, C-Ar), 141.2 (CH, C-5'), 155.2 (C, C-2'); HRMS (ESI+) C 25 H 32 NO 2 Si [MH + ] requires 406.2197, found 406.2192.

(2S,3S)-3-(tert-Butyldiphenylsilyloxy)-2-(thiophen-2-yl)piperidine (386)

Following general procedure 2, reaction of nitrone 198 (0.22 g, 0.62 mmol) with 2-lithiothiophene, prepared by reaction of n-butyllithium (1.6 M in hexanes, 0.58 mL, 0.93 mmol) and thiophene (0.089 g, 1.06 mmol),\(^{476}\) followed by purification of the residue by column chromatography, using ethyl acetate-hexanes (1:9), gave the 2-(2'-thienyl)piperidine-1-ol 385 (0.23 g, 85%) as a colourless oil.

Following general procedure 3, reduction of 2-(2'-thienyl)piperidine-1-ol 385 (0.12 g, 0.26 mmol) gave the title compound (0.090 g, 81%) as a yellow oil.

\[ \alpha \] D 20 +2.7 (c 1.32, CHCl 3 ); \( \nu_{\text{max}} \) (film) 3072, 3048, 2934, 2856 (C-H), 1428 (C=C), 1106 cm\(^{-1}\); \( \delta \) H (300 MHz; CDCl 3 ) 0.85 (9H, s, OSi t Bu), 1.24-1.42 (2H, m, CH 3 H 5 -4ax, CH 3 H 5 -5ax), 1.42-1.55 (1H, m, H-5eq), 1.65-1.75 (1H, m, H-4eq), 1.87 (1H, br s, NH), 2.56-2.68 (1H, m, H-6ax), 2.87-2.97 (1H, m, H-6eq), 3.56-3.67 (1H, m, H-3), 3.84 (1H, d, \( J_{2-3} \)

220
δ 8.3 Hz, H-2), 6.93 (1H, dd, J_6,5′ 5.0, J_5,4′ 3.4 Hz, H-4′), 7.02 (1H, dd, J_{3,4′} 3.4, J_{3,5′} 1.0 Hz, H-3′), 7.18 (1H, dd, J_{6,5′} 5.0, J_{5,4′} 1.0 Hz, H-5′), 7.20-7.28 (2H, m, Ar-H), 7.28-7.43 (6H, m, Ar-H), 7.58-7.67 (2H, m, Ar-H); δ_C (75 MHz; CDCl_3) 19.0 (C, OSi(t-Bu)), 24.8 (CH_2, C-5), 25.7 (CH_3, OSi(Bu)), 34.6 (CH_2, C-4), 46.4 (CH_2, C-5), 64.3 (CH, C-2), 75.4 (CH, C-3), 123.9 (CH, C-5′), 125.5 (CH, C-3′), 126.1 (CH, C-4′), 127.3 (CH, C-Ar), 127.3 (CH, C-Ar), 129.3 (CH, C-Ar), 129.3 (CH, C-Ar), 133.4 (C, C-Ar), 135.0 (C, C-Ar), 135.8 (CH, C-Ar), 135.8 (CH, C-Ar), 146.3 (C, C-2′); HRMS (ESI+) C_{25}H_{32}NOSSi [MH^+] requires 422.1968, found 422.1977.

(2R,3S)-3-(tert-Butyldiphenylsilyloxy)-2-(trimethylsilylethynyl)piperidine (390)

Following general procedure 2, reaction of nitrone 198 (0.22 g, 0.62 mmol) with (trimethylsilylethynyl)lithium, prepared by reaction of n-butyllithium (1.6 M in hexanes, 0.48 mL, 0.77 mmol) and ethynyltrimethylsilane (0.091 g, 0.93 mmol), followed by purification of the residue by column chromatography, using ethyl acetate-hexanes (gradient 1:39 to 1:4), gave the 2-(trimethylsilylethynyl)piperidine-1-ol 389 (0.22 g, 80%) as a colourless oil.

Indium powder (0.070 g, 0.61 mmol) was added to a solution of 2-(trimethylsilylethynyl)piperidine-1-ol 389 (0.18 g, 0.31 mmol) in ethanol (3 mL) and the suspension heated to 80 °C. Aqueous hydrochloric acid (2 mol L^{-1}, 0.045 mL) was added and the suspension heated to 100 °C and stirred for 2 h. The reaction was concentrated under reduced pressure and the residue dissolved in ethyl acetate (20 mL). The pH was adjusted to 10 by the dropwise addition an aqueous solution of 2 M sodium hydroxide. The mixture was filtered through Celite® and the filtrate concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20 mL), washed with brine (20 mL) and the aqueous phase extracted with ethyl acetate (3 x 20mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (3:17), to give the title compound (0.093 g, 70%) as a colourless oil.

[α]_D^{20} -5.3 (c 1.66, CHCl_3); ν_{max} (film) 3071, 3051, 2932, 2895, 2857, 2175, 1590, 1428 (C=C), 1249, 1105, 1075, 840, 699 cm^{-1}; δ_H (300 MHz; CDCl_3) 0.12 (9H, s, OSi(Bu)), 1.08
1-Methoxypropa-1,2-diene (393)

1-methoxypropa-1,2-diene 393 was prepared according to the literature procedure.289 Potassium tert-butoxide (0.83 g, 7.41 mmol) was added portionwise to 3-methoxyprop-1-ynyl (5.00 g, 71.3 mmol) and the mixture gently heated in an oil bath at 70 °C for 3 h. The reaction mixture was allowed to cool to room temperature. Distillation of the reaction mixture under vacuum at room temperature gave a colourless oil that was dried over potassium hydroxide and stored in the refrigerator for 1 h. The crude product was then distilled under N2 (760 Torr, 50 °C), to give the title compound (3.44 g, 69%) as a colourless oil. The spectroscopic data was in agreement with that reported in the literature.289

\[ \delta^H (300 \text{ MHz; CDCl}_3) 3.42 (3H, s, OMe), 5.48 (2H, d, J_{3-1} 5.9 \text{ Hz, H-3}), 6.77 (1H, t, J_{1-3} 5.9 \text{ Hz, H-1}); \delta^C (75 \text{ MHz; CDCl}_3) 55.9 (\text{CH}_3, \text{OMe}), 91.3 (\text{CH}_2, C-3), 122.9 (\text{CH}, C-1), 201.1 (\text{C}, C-2). \]

(4aS,5S)-5-(tert-Butylphenylsilyloxy)-4-methoxy-2,4a,5,6,7,8-hexahydropyrido[1,2-b][1,2]oxazine (395)

Following general procedure 2, reaction of nitrone 198 (0.055 g, 0.17 mmol) with lithiated methoxyallene, prepared by reaction of n-butyllithium (1.6 M in hexanes, 0.15 mL,
0.23 mmol) and methoxyallene (0.018 g, 0.26 mmol), followed by purification of the residue by column chromatography, using ethyl acetate-hexamnes (1:4), gave the 2-(1′-methoxypropa-1,2-dien-1-yl)piperidine-1-ol \(394\) (0.036 g, 50%) as a colourless oil.

\[ R_f \, (25\% \, \text{EtOAc/hexanes}) \, 0.26; \, \delta_H \, (300 \, \text{MHz}; \, \text{CDCl}_3) \, 1.03 \, (9\, \text{H}, \, s, \, \text{OSi'Bu}), \, 1.19-1.34 \, (2\, \text{H}, \, m, \, \text{H}-4ax, \, \text{H}-5ax), \, 1.40-1.54 \, (1\, \text{H}, \, m, \, \text{H}-5eq), \, 1.58-1.68 \, (1\, \text{H}, \, m, \, \text{H}-4eq), \, 2.41-2.53 \, (1\, \text{H}, \, m, \, \text{H}-6ax), \, 3.00 \, (1\, \text{H}, \, d, \, J_{2-3} \, 9.1 \, \text{Hz}, \, \text{H}-2), \, 3.15-3.24 \, (1\, \text{H}, \, m, \, \text{H}-6eq), \, 3.36 \, (3\, \text{H}, \, s, \, \text{OMe}), \, 3.80-3.92 \, (1\, \text{H}, \, m, \, \text{H}-3), \, 5.45 \, (2\, \text{H}, \, m, \, \text{H}-3′), \, 5.89-6.02 \, (1\, \text{H}, \, br \, s, \, \text{OH}), \, 7.29-7.45 \, (6\, \text{H}, \, m, \, \text{Ar}-H), \, 7.64-7.72 \, (4\, \text{H}, \, m, \, \text{Ar}-H); \, \delta_C \, (75 \, \text{MHz}; \, \text{CDCl}_3) \, 19.2 \, (\text{C}, \, \text{OSi'Bu}), \, 20.7 \, (\text{CH}_2, \, \text{C}-5), \, 26.7 \, (\text{CH}_3, \, \text{OSi'Bu}), \, 33.2 \, (\text{CH}_2, \, \text{C}-4), \, 55.9 \, (\text{CH}_3, \, \text{OMe}), \, 57.8 \, (\text{CH}_2, \, \text{C}-6), \, 70.0 \, (\text{CH}, \, \text{C}-3), \, 77.3 \, (\text{CH}, \, \text{C}-2), \, 90.3 \, (\text{CH}_2, \, \text{C}-3′), \, 127.3 \, (\text{CH}, \, \text{C}-Ar), \, 127.3 \, (\text{CH}, \, \text{C}-Ar), \, 129.4 \, (\text{CH}, \, \text{C}-Ar), \, 129.5 \, (\text{CH}, \, \text{C}-Ar), \, 131.7 \, (\text{C}, \, \text{C}-1′), \, 133.6 \, (\text{C}, \, \text{C}-Ar), \, 134.6 \, (\text{C}, \, \text{C}-Ar), \, 135.8 \, (\text{CH}, \, \text{C}-Ar), \, 201.1 \, (\text{C}, \, \text{C}-2′); \, \text{HRMS} \, (\text{ESI+}) \, \text{C}_{25}\text{H}_{34}\text{NO}_3\text{Si} \, [\text{MH}^+] \, \text{requires} \, 424.2302, \, \text{found} \, 424.2316.\]

A solution of 2-(1′-methoxypropa-1,2-dien-1-yl)piperidine-1-ol \(394\) (0.033 g, 0.078 mmol) in dichloromethane (1.5 mL) was stirred at room temperature for five days. The solvent was removed under reduced pressure and the residue purified by flash column chromatography, eluting with ethyl acetate-hexamnes (1:9), to give the title compound (0.031 g, 95%) as a colourless oil.

\[ R_f \, (25\% \, \text{EtOAc/hexanes}) \, 0.54; \, [\alpha]_D^{20} \, +36.1 \, (c \, 0.62, \, \text{CHCl}_3); \, \nu_{\text{max}} \, (\text{film}) \, 3072, \, 2931, \, 2866 \, (\text{C}-\text{H}), \, 1669, \, 1428 \, (\text{C}=\text{C}); \, \delta_H \, (300 \, \text{MHz}; \, \text{CDCl}_3) \, 0.99\-1.11 \, (9\, \text{H}, \, m, \, \text{OSi'Bu}), \, 1.22\-1.42 \, (2\, \text{H}, \, m, \, \text{H}-6ax, \, \text{H}-7ax), \, 1.57\-1.80 \, (2\, \text{H}, \, m, \, \text{H}-6eq, \, \text{H}-7eq), \, 2.69\-2.87 \, (1\, \text{H}, \, m, \, \text{H}-8ax), \, 3.08\-3.19 \, (1\, \text{H}, \, d, \, J_{4a-5} \, 8.6 \, \text{Hz}, \, \text{H}-4a), \, 3.23\-3.47 \, (4\, \text{H}, \, m, \, \text{OMe}, \, \text{H}-8eq), \, 4.13\-4.51 \, (3\, \text{H}, \, m, \, \text{H}-2, \, \text{H}-5), \, 4.53 \, (1\, \text{H}, \, t, \, J_{3-2} \, 2.5 \, \text{Hz}, \, \text{H}-3), \, 7.29\-7.43 \, (6\, \text{H}, \, m, \, \text{Ar}-H), \, 7.65\-7.72 \, (4\, \text{H}, \, m, \, \text{Ar}-H); \, \delta_C \, (100 \, \text{MHz}; \, \text{CDCl}_3) \, 19.3 \, (\text{C}, \, \text{OSi'Bu}), \, 20.0 \, (\text{CH}_2, \, \text{C}-7), \, 26.8 \, (\text{CH}_3, \, \text{OSi'Bu}), \, 33.7 \, (\text{CH}_2, \, \text{C}-6), \, 53.1 \, (\text{CH}_2, \, \text{C}-8), \, 54.0 \, (\text{CH}_3, \, \text{OMe}), \, 65.8 \, (\text{CH}, \, \text{C}-4a), \, 66.7 \, (\text{CH}_2, \, \text{C}-2), \, 70.7 \, (\text{CH}, \, \text{C}-5), \, 91.0 \, (\text{CH}, \, \text{C}-3), \, 127.3 \, (\text{CH}, \, \text{C}-Ar), \, 127.3 \, (\text{CH}, \, \text{C}-Ar), \, 129.3 \, (\text{CH}, \, \text{C}-Ar), \, 129.3 \, (\text{CH}, \, \text{C}-Ar), \, 134.3 \, (\text{C}, \, \text{C}-Ar), \, 135.3 \, (\text{C}, \, \text{C}-Ar), \, 135.9 \, (\text{CH}, \, \text{C}-Ar), \, 156.2 \, (\text{C}, \, \text{C}-4); \, \text{HRMS} \, (\text{ESI+}) \, \text{C}_{25}\text{H}_{34}\text{NO}_3\text{Si} \, [\text{MH}^+] \, \text{requires} \, 424.2302, \, \text{found} \, 424.2315.\]
4.6 Total Synthesis of (+)-Swainsonine and (-)-1,2-Di-epi-swainsonine

3-(**tert**-Butyldimethylsilyloxy)prop-1-ynyl (491)

3-(**tert**-Butyldimethylsilyloxy)prop-1-ynyl 491 was prepared according to the literature procedure. A solution of **tert**-butyldimethylsilyl chloride (14.1 g, 93.6 mmol) in dichloromethane (20 mL) was added to a solution of propargyl alcohol 497 (5.00 g, 89.2 mmol) and imidazole (9.11 g, 134.0 mmol) in dichloromethane (30 mL) at 0 ºC. The reaction mixture was stirred at room temperature for 12 h then washed with an aqueous solution of hydrochloric acid (1 mol L⁻¹, 3 x 25 mL) and saturated sodium bicarbonate (3 x 25 mL). The organic extract was dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by distillation (25 mmHg, 57-63 ºC), to give the title compound (13.5 g, 89%) as a colourless oil. The spectroscopic data was in agreement with that reported in the literature.⁴⁷⁷

\[ \delta_H \ (300 \text{ MHz}; \text{CDCl}_3) \ 0.13 \ (6H, s, \text{OSi' Bu}), \ 0.91 \ (9H, s, \text{OSi' Bu}), \ 2.39 \ (1H, t, J_{3-1} \ 2.4 \ Hz, \ H-3), \ 4.31 \ (2H, d, J_{1-3} \ 2.4 \ Hz, \ H-1); \ \delta_C \ (75 \text{ MHz}; \text{CDCl}_3) \ -5.3 \ (\text{CH}_3, \text{ OSiMe}_2), \ 18.2 \ (C, \text{OSi' Bu}), \ 25.7 \ (\text{CH}_3, \text{OSi' Bu}), \ 51.5 \ (\text{CH}_2, C-1), \ 72.8 \ (\text{CH}, C-3), \ 82.4 \ (C, C-2). \]

(2R,3S)-2-(3-(**tert**-Butyldimethylsilyloxy)prop-1-ynyl)-3-(**tert**-butyldiphenylsilyloxy) piperidine-1-ol (490)

A solution of **n**-butyllithium (1.5 M in hexanes, 1.98 mL, 2.97 mmol) was added dropwise to a solution of 3-(**tert**-butyldimethylsilyloxy)prop-1-ynyl 491 (0.61 g, 3.56 mmol) in tetrahydrofuran (8 mL) at -78 ºC. The solution was stirred for 15 min then warming to 0 ºC and stirred for an additional 30 min. A solution of nitrone 198 (0.84 g, 2.38 mmol) in tetrahydrofuran (18 mL) was added at -78 ºC and the mixture warmed to 0 ºC and stirred for a further 1 h. Saturated aqueous ammonium chloride (10 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue
was purified by flash column chromatography, eluting with ethyl acetate-hexanes (1:19), to give the title compound (1.12 g, 90%) as a colourless oil.

\[ \alpha \rangle_{D}^{20} -23.0 \, (c \, 2.04, \text{CHCl}_3); \nu_{\text{max}} \, (\text{film}) \, 3222 \, (\text{OH}), \, 3073, \, 3054, \, 2953, \, 2930, \, 2895, \, 2857 \, (\text{C-H}), \, 1471 \, (\text{C=C}), \, 1253, \, 1104 \, \text{cm}^{-1}; \delta_{\text{H}} \, (300 \, \text{MHz}; \text{DMSO-d}_6, \, 373.15 \, \text{K}) \, 0.07 \, (6\text{H}, \, \text{s}, \, \text{OSiMe}_2), \, 0.88 \, (9\text{H}, \, \text{s}, \, \text{OSi}^\text{t} \text{Bu}), \, 1.07 \, (9\text{H}, \, \text{s}, \, \text{OSi}^\text{t} \text{Bu}), \, 1.24-1.46 \, (2\text{H}, \, \text{m}, \, \text{H-5ax}, \, \text{H-4ax}), \, 1.56-1.82 \, (2\text{H}, \, \text{m}, \, \text{H-5eq}, \, \text{H-4eq}), \, 2.57-2.69 \, (1\text{H}, \, \text{m}, \, \text{H-6ax}), \, 2.85-2.99 \, (1\text{H}, \, \text{m}, \, \text{H-6eq}), \, 3.53-3.62 \, (1\text{H}, \, \text{m}, \, \text{H-2}), \, 3.92-4.01 \, (1\text{H}, \, \text{m}, \, \text{H-3}), \, 4.20-4.26 \, (2\text{H}, \, \text{m}, \, \text{H-3'}), \, 7.35-7.49 \, (6\text{H}, \, \text{m}, \, \text{Ar-H}), \, 7.40-7.59 \, (1\text{H}, \, \text{m}, \, \text{NOH}), \, 7.61-7.75 \, (4\text{H}, \, \text{m}, \, \text{Ar-H}); \delta_{\text{C}} \, (75 \, \text{MHz}; \text{DMSO-d}_6, \, 100 \, ^\circ\text{C}) \, -5.9 \, (\text{CH}_3, \, \text{OSiMe}_2), \, 17.2 \, (\text{C}, \, \text{OSi}^\text{t} \text{Bu}), \, 18.3 \, (\text{C}, \, \text{OSi}^\text{t} \text{Bu}), \, 19.4 \, (\text{CH}_2, \, \text{C-5}), \, 25.1 \, (\text{CH}_3, \, \text{OSi}^\text{t} \text{Bu}), \, 26.3 \, (\text{CH}_3, \, \text{OSi}^\text{t} \text{Bu}), \, 29.1 \, (\text{CH}_2, \, \text{C-4}), \, 50.8 \, (\text{CH}_2, \, \text{C-3'}), \, 54.2 \, (\text{CH}_2, \, \text{C-6}), \, 63.9 \, (\text{CH}, \, \text{C-2}), \, 71.7 \, (\text{CH}, \, \text{C-3}), \, 82.3 \, (\text{C}, \, \text{C-2'}), \, 83.1 \, (\text{C}, \, \text{C-1'}), \, 126.9 \, (\text{CH}, \, \text{C-Ar}), \, 126.9 \, (\text{CH}, \, \text{C-Ar}), \, 128.9 \, (\text{CH}, \, \text{C-Ar}), \, 129.0 \, (\text{CH}, \, \text{C-Ar}), \, 133.2 \, (\text{C}, \, \text{C-Ar}), \, 133.4 \, (\text{C}, \, \text{C-Ar}), \, 134.7 \, (\text{CH}, \, \text{C-Ar}), \, 134.7 \, (\text{CH}, \, \text{C-Ar}); \text{HRMS (ESI)} \, \text{C}_{30}\text{H}_{46}\text{NO}_3\text{Si}_2 [\text{MH}^+] \, \text{requires} \, 524.3011, \, \text{found} \, 524.3012.

(2\text{R},3\text{S})-2-(3-(\text{tert-Butyldimethylsilyloxy})\text{prop-1-ynyl})-3-((\text{tert-butyldiphenylsilyl})\text{oxy})\text{piperididine (498)}

\[
\begin{array}{c}
\text{OTBDPS} \\
\text{498} \\
\text{OTBS}
\end{array}
\]

Zinc powder (0.094 g, 1.44 mmol) and indium powder (0.003 g, 0.029 mmol) were added to a solution of hydroxylamine 490 (0.15 g, 0.29 mmol) in ethanol/saturated aqueous ammonium chloride (2:1, 4.5 mL). The suspension was stirred under reflux for 4 h, cooled to room temperature and filtered through a short pad of Celite®. The filtrate was concentrated and saturated aqueous sodium carbonate (15 mL) was added. The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and the combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (1:19), to give the title compound (0.11 g, 75%) as an opaque oil.

\[ \alpha \rangle_{D}^{20} -0.8 \, (c \, 0.60, \text{CHCl}_3); \nu_{\text{max}} \, (\text{film}) \, 2930, \, 2857 \, (\text{C-H}), \, 1429 \, (\text{C=C}), \, 1253, \, 1105, \, 1083, \, 835, \, 702 \, \text{cm}^{-1}; \delta_{\text{H}} \, (300 \, \text{MHz}; \text{CDCl}_3) \, 0.07 \, (6\text{H}, \, \text{s}, \, \text{OSiMe}_2), \, 0.88 \, (9\text{H}, \, \text{s}, \, \text{OSi}^\text{t} \text{Bu}), \, 1.08 \, (9\text{H}, \, \text{s}, \, \text{OSi}^\text{t} \text{Bu}), \, 1.19-1.33 \, (1\text{H}, \, \text{m}, \, \text{H-5ax}), \, 1.35-1.48 \, (1\text{H}, \, \text{m}, \, \text{H-4ax}), \, 1.61-1.75 \, (1\text{H}, \, \text{m}, \, \text{H-5eq}), \, 1.75-1.87 \, (2\text{H}, \, \text{m}, \, \text{H-4eq}, \, \text{NH}), \, 2.57-2.68 \, (1\text{H}, \, \text{m}, \, \text{H-6ax}), \, 2.86-2.98 \, (1\text{H}, \, \text{m}, \, \text{H-6eq}),\]

225
226-3.54 (1H, m, H-2), 3.66-3.74 (1H, m, H-3), 4.21-4.24 (2H, d, J1-2 1.8 Hz, H-1’), 7.31-7.46 (6H, m, Ar-H), 7.65-7.74 (4H, m, Ar-H); δ (75 MHz; CDCl3) δ -5.2 (CH3, OSiMe2), 18.2 (C, OSi’Bu), 19.3 (C, OSi’Bu), 23.4 (CH2, C-5’), 25.8 (CH3, OSi’Bu), 27.0 (CH3, OSi’Bu), 31.2 (CH2, C-4’), 43.7 (CH2, C-6’), 51.8 (CH2, C-1), 54.1 (CH, C-2’), 71.4 (CH, C-3’), 82.8 (C, C-2), 84.3 (C, C-3), 127.5 (CH, C-Ar), 127.5 (CH, C-Ar), 129.5 (CH, C-Ar), 129.6 (CH, C-Ar), 133.8 (C, C-Ar), 134.3 (C, C-Ar), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar); m/z (EI) 507 (54, M+), 450 (93), 286 (10), 252 (15), 212 (18), 199 (100), 149 (16), 135 (50), 120 (20), 105 (11) 91 (8), 73 (46), 70 (50), 50 (22%). HRMS (EI): M+, found 507.2984. C30H45NO2Si2 requires 507.2989.

(2R,3S)-2-(3-Hydroxyprop-1-ynyl)-3-(tert-butyldiphenylsilyloxy)piperidine (500)

Indium powder (0.44 g, 3.80 mmol) was added to a solution of hydroxylamine 490 (0.99 g, 1.90 mmol) in ethanol (22 mL) and the suspension heated to 80 °C. Aqueous hydrochloric acid (1 mol L\(^{-1}\), 3.4 mL) was added and the suspension heated to 100 °C and stirred for 2 h. The reaction mixture was cooled to room temperature and the pH adjusted to 10 by the dropwise addition an aqueous solution of 2 M sodium hydroxide. The mixture was filtered through Celite\(^\circ\) and the filtrate concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), washed with a solution of saturated brine (20 mL) and the aqueous phase extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 5:95 to 9:91), to give the title compound (0.64 g, 85%) as a yellow oil.

[\(\alpha\)]\(_D\)\(^{20}\) -0.4 (c 1.08, CHCl3); v\(_{\text{max}}\) (film) 3285 (NH), 2932, 2892, 2856 (C-H), 1428 (C=C), 1105, 1027, 701 cm\(^{-1}\); δ\(_H\) (300 MHz; CDCl3) 1.08 (9H, s, OSi’Bu), 1.18-1.33 (1H, m, H-5ax), 1.35-1.47 (1H, m, H-4ax), 1.60-1.72 (1H, m, H-5eq), 1.79-1.89 (1H, m, H-4eq), 2.53-2.63 (1H, m, H-6ax), 2.86-2.96 (3H, m, H-6eq, NH, OH), 3.47-3.52 (1H, m, H-2), 3.62-3.70 (1H, m, H-3), 4.04 (2H, d, J1-2 1.5 Hz, H-1), 7.25-7.44 (6H, m, Ar-H), 7.66-7.71 (4H, m, Ar-H); δ\(_C\) (75 MHz; CDCl3) 19.3 (C, OSi’Bu), 23.4 (CH2, C-5’), 26.9 (CH3, OSi’Bu), 31.4 (CH2,
C-4'), 43.6 (CH₂, C-6'), 50.4 (CH₂, C-1), 54.1 (CH, C-2'), 71.5 (CH, C-3'), 83.6, (C, C-2), 84.2 (C, C-3), 127.5 (CH, C-Ar), 127.5 (CH, C-Ar), 129.6 (CH, C-Ar), 129.6 (CH, C-Ar), 133.8 (C, C-Ar), 133.9 (C, C-Ar), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar); m/z (EI) 393 (M⁺, 11), 337 (29), 336 (100), 199 (72), 198 (51), 197 (33), 181 (21), 137 (23), 135 (52), 120 (26), 105 (21), 98 (52), 91 (21), 41 (22%). HRMS (EI): M⁺, found 393.2119. C₂₄H₃₁NO₂Si requires 393.2124.

(2R,3S)-2-((Z)-3-(tert-Butyldimethylsilyloxy)prop-1-enyl)-3-(tert-butylidiphenylsilyloxy)piperidin-1-ol (504)

Lindlar catalyst (0.095 g) was added portionwise to a solution of hydroxylamine (0.38 g, 0.75 mmol) in ethyl acetate (10 mL). The mixture was stirred under a hydrogen atmosphere for 1.25 h, filtered through Celite® and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:19 to 3:17), to give the title compound (0.34 g, 90%) as a colourless oil.

[α]D²⁰ -38.8 (c 0.60, CHCl₃); νmax (film) 3228 (OH), 2928, 2856 (C-H), 1471, 1427 (C=C), 1253, 1090 cm⁻¹; δH (300 MHz; DMSO-d₆, 373.15 K) 0.06 (6H, s, Me₂), 0.91 (9H, s, OSi'Bu), 1.03 (9H, s, OSi'Bu), 1.15-1.36 (2H, m, H-4ax, H-5ax), 1.39-1.63 (2H, m, H-5eq, H-6eq), 2.36-2.49 (1H, m, H-6ax), 2.95-3.06 (1H, m, H-6eq), 3.08-3.19 (1H, m, H-2), 3.55-3.68 (1H, m, H-3), 4.24-4.43 (2H, m, H-3'), 5.25-5.37 (1H, m, H-1'), 5.53-5.65 (1H, m, H-2'), 7.15 (1H, br s, NOH), 7.34-7.49 (6H, m, Ar-H), 7.60-7.70 (4H, m, Ar-H); δC (75 MHz; DMSO-d₆, 100 °C) -5.8 (CH₃, SiMe₂), -5.9 (CH₃, SiMe₂), 17.2 (C, OSi'Bu), 18.2 (C, OSi'Bu), 19.8 (CH₂, C-5), 25.2 (CH₃, OSi'Bu), 26.3 (CH₃, OSi'Bu), 32.0 (CH₂, C-4), 56.3 (CH₂, C-6), 59.5 (CH₂, C-3'), 70.1 (CH, C-2), 72.1 (CH, C-3), 126.7 (CH, C-Ar), 126.8 (CH, C-Ar), 128.8 (CH, C-Ar), 128.9 (CH, C-Ar), 129.1 (CH, C-1'), 132.7 (CH, C-2'), 133.2 (C, C-Ar), 134.0 (C, C-Ar), 134.7 (CH, C-Ar), 134.8 (CH, C-Ar); HRMS (ESI): C₃₀H₄₈NO₆Si₂ [MH⁺] requires 526.3167, found 526.3163.
(2R,3S)-2-((Z)-3-Hydroxyprop-1-enyl)-3-(tert-butyldiphenylsilyloxy)piperidine (489)

**Method A: N-OH Bond Reduction of 504**

Indium powder (0.43 g, 3.70 mmol) was added to a solution of hydroxylamine 504 (0.97 g, 1.85 mmol) in ethanol (22 mL) and the suspension heated to 80 °C. Aqueous hydrochloric acid (1 mol L\(^{-1}\), 3.4 mL) was added and the suspension heated to 100 °C and stirred for 2 h. The reaction mixture was cooled to room temperature and the pH adjusted to 10 by the dropwise addition of a 2 M aqueous solution of sodium hydroxide. The mixture was filtered through Celite\(^{®}\) and the filtrate concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), washed with brine (20 mL) and the aqueous phase extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with using methanol-dichloromethane (gradient 3:97 to 9:91), to give the *title compound* (0.63 g, 86%) as a white solid. Recrystalisation from diethyl ether-hexanes (1:1) gave white needles.

m.p. 123.1-124.5 °C; \([\alpha]_D^{20} -19.7 (c 1.33, \text{CHCl}_3)\); \(v_{\text{max}}\) (solid) 3261, 3072, 3048, 2946, 2930, 2905, 2873, 2855 (C-H), 1427 (C=C), 1106, 1092 cm\(^{-1}\); \(\delta_H\) (300 MHz; CDCl\(_3\)) 1.04 (9H, s, OSi\text{tBu}), 1.14-1.30 (1H, m, H-5ax), 1.36-1.52 (1H, m, H-4ax), 1.57-1.70 (1H, m, H-5eq), 1.70-1.82 (1H, m, H-4eq), 2.59 (1H, ddd, \(J_{\text{gem}}\) 12.8, \(J_{6ax-5ax}\) 9.8, \(J_{6ax-5eq}\) 3.2 Hz, H-6ax), 2.83 (1H, dt, \(J_{\text{gem}}\) 12.8, \(J_{6eq-5eq} = J_{6eq-5ax}\) 4.3 Hz, H-6eq), 3.40-3.57 (2H, m, H-2, H-3), 3.74 (2H, br s, NH, OH), 4.08 (1H, ddt, \(J_{\text{gem}}\) 14.6, 5.1, 1.2 Hz, CH\(_{\text{a}}\)H\(_{\text{b}}\)-1′), 4.23 (1H, ddd, \(J_{\text{gem}}\) 14.6, 5.9, 1.2 Hz, CH\(_{\text{a}}\)H\(_{\text{b}}\)-1′), 5.46 (1H, ddt, \(J\) 11.5, 6.3, 1.2 Hz, H-3′), 5.74-5.85 (1H, m, H-2′), 7.32-7.46 (6H, m, Ar-H), 7.63-7.71 (4H, m, Ar-H); \(\delta_C\) (75 MHz; CDCl\(_3\)) \(\delta\) 19.3 (C, OSi\text{tBu}), 24.5 (CH\(_2\), C-5), 27.0 (CH\(_3\), OSi\text{tBu}), 32.3 (CH\(_2\), C-4), 43.8 (CH\(_2\), C-6), 59.1 (CH, C-2), 59.6 (CH\(_2\), C-1′), 72.9 (CH, C-3), 127.4 (CH, C-Ar), 127.6 (CH, C-Ar), 129.6 (CH, C-Ar), 129.7 (CH, C-Ar), 131.4 (CH, C-3′), 133.5 (CH, C-2′), 133.6 (C, C-Ar), 134.4 (C, C-Ar), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar); \(m/z\) (EI) 395 (3, M\(^+\)), 338 (12), 320 (17), 199 (12), 181 (21), 131 (21), 122 (26), 100 (20), 48 (100%). HRMS (EI): M\(^+\), found 395.2288. \(C_{24}H_{33}NO_2Si\) requires 395.2281.
Method B: Lindlar Reduction of 500

Lindlar catalyst (26 mg) was added portionwise to a solution of hydroxylamine 500 (0.26 g, 0.66 mmol) in methanol (10 mL). Ethylenediamine (0.053 mL, 0.79 mmol) was added and the suspension stirred for 10 min. The mixture was then stirred under a hydrogen atmosphere for 13 h, filtered through Celite \textsuperscript{®} and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 3:97 to 9:91), to give the title compound (0.17 g, 65% as a white solid. The spectroscopic data was in agreement with that reported using method A.

\((2R,3S)-2-((Z)-3\text{-Methanesulfonyloxyprop-1-etyl})-3\text{-}(\text{tert-butyldiphenylsilyloxy})\text{-1-methylosulfonylpiperidine (505)}\)

Amino alcohol 489 (0.080 g, 0.20 mmol) was dissolved in dichloromethane (4 mL) and cooled to 0 °C. Methanesulfonyl chloride (0.034 mL, 0.44 mmol) was added dropwise and the solution stirred for 10 min before triethylamine (0.17 mL, 1.21 mmol) was added. The reaction was stirred at room temperature for 3 h and then quenched by the addition of saturated aqueous sodium bicarbonate (5 mL). The mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:3 to 1:1), to give the title compound (0.055 g, 50%) as a yellow oil.

\([\alpha]_D^{20} -4.7 \text{ (c 1.70, CHCl}_3\); \(\nu_{\text{max}}\text{ (film) } 2932 \text{ (C-H), } 1427 \text{ (C=C), } 1337, 1322, 1175, 1154, 1111, 933, 716 \text{ cm}^{-1}; \delta_H \text{ (300 MHz; CDCl}_3\) 1.11 (9H, s, OSi’Bu), 1.50-1.62 (2H, m, CH<sub>a</sub>H<sub>b</sub>-4, CH<sub>a</sub>H<sub>b</sub>-5), 1.71-1.81 (1H, m, CH<sub>a</sub>H<sub>b</sub>-4), 2.15-2.32 (1H, m, CH<sub>a</sub>H<sub>b</sub>-5), 2.84 (3H, s, SO<sub>2</sub>CH<sub>3</sub>), 2.92 (3H, s, SO<sub>2</sub>CH<sub>3</sub>), 2.95-3.09 (1H, m, CH<sub>a</sub>H<sub>b</sub>-6), 3.66-3.71 (1H, m, CH<sub>a</sub>H<sub>b</sub>-6), 3.71-3.79 (1H, m, H-3), 4.10-4.20 (1H, m, CH<sub>a</sub>H<sub>b</sub>-1’), 4.29-4.39 (1H, m, CH<sub>a</sub>H<sub>b</sub>-1’), 4.47-4.53 (1H, m, H-2), 5.57-5.68 (1H, m, H-2’), 5.69-5.77 (1H, m, H-3’), 7.37-7.52 (6H, m, Si-Ar), 7.61-7.76 (4H, m, Si-Ar); \(\delta_C \text{ (75 MHz; CDCl}_3\) 19.0 (CH<sub>2</sub>, C-5), 19.2 (C, OSi’Bu), 26.5 (CH<sub>2</sub>, C-4), 27.0 (CH<sub>3</sub>, OSi’Bu), 37.4 (CH<sub>3</sub>, SO<sub>2</sub>CH<sub>3</sub>), 39.1 (CH<sub>3</sub>, SO<sub>2</sub>CH<sub>3</sub>), 40.7 (CH<sub>2</sub>, C-6), 56.1 (CH, C-2), 65.1 (CH<sub>2</sub>, C-1’), 68.6 (CH, C-3), 126.8 (CH,
C-2'), 127.8 (CH, C-3'), 127.9 (CH, C-Ar), 128.1 (CH, C-Ar), 130.0 (CH, C-Ar), 130.2 (CH, C-Ar), 133.3 (C, C-Ar), 133.4 (C, C-Ar), 135.7 (CH, C-Ar), 136.0 (CH, C-Ar); m/z (CI): 552 (MH+, 45), 494 (6), 378 (22), 89 (22%). Found MH+, 552.1900, C_{26}H_{38}NO_{6}S_{2}Si requires 552.1910.

(8S,8aR)-8-(tert-Butyldiphenylsilyloxy)-3,5,6,7,8,8a-hexahydroindolizine (488)

![Chemical structure of 488](attachment:image.png)

**Method A: Cyclisation via a Mitsunobu Reaction**

A solution of di-para-chlorobenzyl azodicarboxylate (0.34 g, 0.93 mmol) in dichloromethane (5 mL) was added to a stirred solution of amine alcohol 489 (0.30 g, 0.75 mmol) and triphenylphosphine (0.24 g, 0.93 mmol) in dichloromethane (20 mL) over a period of 10 min at 0 °C. The solution was stirred for 1 h at 0 °C then filtered through a short pad of Celite® and concentrated under reduced pressure. The residue was purified by column chromatography on basic alumina, eluting with ethyl acetate-hexanes (gradient 0:100 to 3:97), to give the title compound (0.25 g, 89%) as an opaque oil.

[α]_{D}^{20} +72.7 (c 0.48, CHCl_{3}); ν_{max} (film) 2932, 2889, 2856 (C-H), 1427 (C=C), 1110 cm⁻¹; δ_{H} (300 MHz; CDCl_{3}) 1.06 (9H, s, OSi_{t}Bu), 1.19-1.56 (3H, m, H-7ax, H-6), 1.73-1.83 (1H, m, H-7eq), 2.36 (1H, td, J_{gem} = J_{5ax-4ax} 11.2, J_{5ax-4eq} 3.2 Hz, H-5ax), 2.79-2.89 (1H, m, H-5eq), 2.97-3.07 (1H, m, H-8a), 3.14-3.25 (1H, m, CH_{a,b}-3), 3.51-3.66 (2H, m, CH_{a,b}-3, H-8), 5.77-5.84 (1H, m, H-1), 6.03-6.09 (1H, m, H-2), 7.30-7.44 (6H, m, Ar-H), 7.64-7.71 (4H, m, Ar-H); δ_{C} (75 MHz; CDCl_{3}) 19.3 (C, OSi′Bu), 24.3 (CH_{2}, C-6), 27.0 (CH_{3}, OSi′Bu), 34.2 (CH_{2}, C-7), 48.8 (CH_{2}, C-5), 57.8 (CH_{2}, C-3), 72.9 (CH, C-8), 74.0 (CH, C-8a), 127.4 (CH, C-Ar), 127.5 (CH, C-Ar), 128.4 (CH, C-1), 129.5 (CH, C-Ar), 129.5 (CH, C-Ar), 131.7 (CH, C-2), 134.1 (C, C-Ar), 134.7 (C, C-Ar), 135.8 (CH, C-Ar), 135.8 (CH, C-Ar); m/z (EI) 377 (M⁺, 6), 321 (29), 320 (100), 318 (20), 200 (21), 199 (100), 120 (69%). HRMS (EI): M⁺, found 377.2175. C_{24}H_{31}NOSi requires 377.2175.

**Method B: Cyclisation via an Appel Reaction**

Amino alcohol 489 (0.067 g, 0.17 mmol) was dissolved in dichloromethane (4 mL) and cooled to 0 °C. Carbon tetrabromide (0.044 g, 0.20 mmol) and triphenylphosphine (0.067 g,
0.25 mmol) were added portionwise and stirred for 1 h. Triethylamine (0.070 mL, 0.51 mmol) was added and the mixture stirred for 1 h at 0 °C and then a further 48 h at rt. The reaction was quenched with water (5 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to give a brown solid. The residue was purified by column chromatography on basic alumina, eluting with ethyl acetate/hexanes (gradient 0:100 to 3:97), to give the title compound (0.025 g, 39%) as a colourless oil. The spectroscopic data was in agreement with that reported using method A.

Method C: Cyclisation via formation of a methanesulfonate

A solution of methanesulfonyl chloride in dichloromethane (0.10 mol L\(^{-1}\), 1.41 mL, 0.141 mmol) was added, by syringe pump over a period of 30 min, to a stirred solution of amino alcohol 489 (0.053 g, 0.13 mmol) in dichloromethane (5 mL) at 0 °C. The solution was stirred for 10 min then triethylamine (0.093 mL, 0.67 mmol) was added, over a period of 10 min. The solution was allowed to warm to room temperature and stirred for 4 h. Diethyl ether (10 mL) was added and the organic phase was washed with a solution of saturated aqueous sodium bicarbonate (5 mL). The organic extract was dried over anhydrous magnesium sulphate and concentrated under reduced pressure to give the crude product as a yellow oil. The residue was dissolved in acetonitrile (5 mL) and the solution stirred under reflux for 5 h then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and washed with solutions of saturated aqueous sodium bicarbonate (5 mL) and saturated brine (5 mL). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography on basic alumina, eluting with ethyl acetate-hexanes (gradient 0:100 to 3:97), to give the title compound (0.019 g, 38%) as an opaque oil. The spectroscopic data was in agreement with that reported using method A.
(1R,2S,8S,8aR)-8-(tert-Butyldiphenylsilyloxy)octahydroindolizine-1,2-diyl diacetate (506) and (1S,2R,8S,8aR)-8-(tert-butylidiphenylsilyloxy)octahydro indolizine-1,2-diyl diacetate (507)

Method A: Using Sharpless Asymmetric Dihydroxylation

A solution of alkene 488 (0.25 g, 0.67 mmol) in tert-butyl alcohol (2.5 mL) was added to a solution of AD-mix-α (1.75 g) and methanesulfonamide (0.076 g, 0.80 mmol) in tert-butyl alcohol and water (1:2, 7.5 mL) at 0 °C. The suspension was stirred vigorously at 1-4 °C for 4 days. The reaction mixture was quenched by addition of saturated aqueous sodium sulfite (15 mL) and the mixture stirred for a further 2 h. The reaction mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was passed through a short pad of silica gel eluting with methanol-chloroform (9:91), to give a diastereomeric mixture of dihydroxylated products.

\[ R_f (25\% \text{ EtOAc/hexanes}) \text{ 0.14; } [\alpha]_D^{20} +63.4 \text{ (c 0.50, CHCl}_3\text{); } \nu_{\text{max}} \text{ (film) 2933, 2856 (C-H), 1743 (C=O), 1428 (C=C), 1371, 1243, 1223, 1079 cm}^{-1}; \delta_H (300 MHz; CDCl}_3\text{) 1.01 (9H, s, OSi}^t\text{Bu), 1.14-1.55 (3H, m, 6-H, CH}_a\text{H}_b\text{-7), 1.70-1.90 (5H, m, CH}_a\text{H}_b\text{-5, CH}_a\text{H}_b\text{-7, OAc), 1.98 (3H, s, OAc), 2.15 (1H, dd, }J\text{ 8.8, 4.1 Hz, 8a-H), 2.56 (1H, dd, }J\text{ 11.2, 7.7, CH}_a\text{H}_b\text{-3), 2.86-2.95 (1H, m, CH}_a\text{H}_b\text{-5), 2.98 (1H, dd, }J\text{ 11.2, 1.9, CH}_a\text{H}_b\text{-3), 3.96 (1H, ddd, }J\text{ 10.5, 8.8, 4.6 Hz, 8-H), 5.34-5.42 (1H, m, 2-H), 5.52 (1H, dd, }J\text{ 6.4, 4.1, 1-H),} \]

\[ \text{Data for 506: } R_f (25\% \text{ EtOAc/hexanes}) \text{ 0.14; } [\alpha]_D^{20} +63.4 \text{ (c 0.50, CHCl}_3\text{); } \nu_{\text{max}} \text{ (film) 2933, 2856 (C-H), 1743 (C=O), 1428 (C=C), 1371, 1243, 1223, 1079 cm}^{-1}; \delta_H (300 MHz; CDCl}_3\text{) 1.01 (9H, s, OSi}^t\text{Bu), 1.14-1.55 (3H, m, 6-H, CH}_a\text{H}_b\text{-7), 1.70-1.90 (5H, m, CH}_a\text{H}_b\text{-5, CH}_a\text{H}_b\text{-7, OAc), 1.98 (3H, s, OAc), 2.15 (1H, dd, }J\text{ 8.8, 4.1 Hz, 8a-H), 2.56 (1H, dd, }J\text{ 11.2, 7.7, CH}_a\text{H}_b\text{-3), 2.86-2.95 (1H, m, CH}_a\text{H}_b\text{-5), 2.98 (1H, dd, }J\text{ 11.2, 1.9, CH}_a\text{H}_b\text{-3), 3.96 (1H, ddd, }J\text{ 10.5, 8.8, 4.6 Hz, 8-H), 5.34-5.42 (1H, m, 2-H), 5.52 (1H, dd, }J\text{ 6.4, 4.1, 1-H),} \]

232
Method B: Upjohn Dihydroxylation

A solution of alkene 488 (0.063 g, 0.17 mmol) in acetone (1.40 mL) was added dropwise to a solution of N-methylmorpholine-N-oxide (0.039 g, 0.33 mmol) in acetone (0.70 mL) and water (0.70 mL) at 0 °C. Osmium tetroxide (4% in tert-butyl alcohol, 0.170 mL, 0.017 mmol) was added dropwise and the reaction stirred at room temperature for 6 h. The reaction mixture was quenched by addition of saturated aqueous sodium sulfite (10 mL), and stirred for 1 h. The reaction mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organic phases dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was passed through a short pad of silica gel eluting with methanol-chloroform (9:91), to give a diastereomeric mixture of dihydroxylated products.

N,N-Dimethyl-4-aminopyridine (0.002 mg, 0.017 mmol), pyridine (0.081 mL, 1.00 mmol) and acetic anhydride (0.063 mL, 0.66 mmol) were added to a solution of the crude
alcohols in dichloromethane (3 mL) at room temperature and the mixture stirred overnight at room temperature. The residue was dissolved in ethyl acetate (10 mL) and washed with a 10% solution of aqueous copper sulphate (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:9 to 3:7), to give the title compounds 068 (0.012 g, 15%) and 067 (0.022 g, 27%) as colourless oils. The spectroscopic data was in agreement with that reported using method A.

(1R,2S,8S,8aS)-8-Hydroxyoctahydroindolizine-1,2-diyl diacetate (510)

A solution of indolizidine 506 (0.40 g, 0.81 mmol), triethylamine (1.57 mL, 11.3 mmol) and triethylamine trihydrofluoride (1.32 mL, 8.07 mmol) in acetonitrile (25 mL) was stirred at 80 °C for 5 days. The reaction was cooled to room temperature and saturated aqueous sodium hydrogen carbonate (50 mL) added. The aqueous phase was extracted with ethyl acetate (3 x 80 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 1:99 to 3:97), to give the title compound (0.182 g, 88%) as a tan solid. Recrystallisation from diethyl ether-hexanes (1:1) yielded colourless needles.

m.p. 126-128 °C; [α]D20 -58.8 (c 1.04, CHCl3); vmax (solid) 3338, 2961, 2837, 2809 (C-H), 1727 (C=O, 2-OAc), 1719 (C=O, 1-OAc); δH (300 MHz; CDCl3) 1.23 (1H, tdd, J 12.5, 11.0, 5.3 Hz, CHaHb-7), 1.55-1.76 (2H, m, C-6), 1.85-1.98 (2H, m, H-8a, CHaHb-5), 2.02-2.13 (4H, m, 2-OAc, CHaHb-7), 2.17 (3H, s, 1-OAc), 2.60 (1H, dd, Jgem 11.0, 8.2 Hz, CHaHb-3), 2.98-3.07 (1H, m, CHaHb-5), 3.09 (1H, br s, OH), 3.20 (1H, dd, Jgem 11.0, 2.3 Hz, CHaHb-3), 3.49 (1H, ddd, J 10.8, 8.9, 4.7 Hz, H-8), 5.16 (1H, ddd, J 8.2, 6.3, 2.3 Hz, H-2), 5.47 (1H, dd, J 6.3, 3.6 Hz, H-1); δC (75 MHz; CDCl3) 20.5 (CH3, 2-OAc), 20.6 (CH3, 1-OAc), 23.2 (CH2, C-6), 31.5 (CH2, C-7), 51.8 (CH2, C-5), 58.5 (CH2, C-3), 65.9 (CH, C-8), 70.6 (CH, C-2), 71.8 (CH, C-1), 72.7 (CH, C-8a), 170.3 (C=O, 2-OAc), 171.9 (C=O, 1-OAc); HRMS (ESI) C12H20NO5 [MH+] requires 258.1336, found 258.1333.
A solution of sodium methoxide (1 mol L\(^{-1}\), 0.14 mL, 0.14 mmol) was added dropwise to a solution of diacetate 510 (0.073 g, 0.28 mmol) in methanol (10 mL) at room temperature and the mixture stirred for 1 h. The solution was concentrated under reduced pressure and the residue purified by reverse phase chromatography (C18), eluting with milli-Q water to give the *title compound* (0.039 g, 80%) as a white solid. The spectroscopic data was in agreement with that reported in the literature.\(^{343, 347, 365, 369}\)

\[\text{m.p. } 143-144 ^\circ\text{C}; \text{[lit. } 143-144 ^\circ\text{C},343, 365\text{]; } [\alpha]_D^{20} +79.9 \text{ (c 0.37, MeOH); [lit. } [\alpha]_D^{24} +83.3 \text{ (c 0.50, MeOH)}^{361}\text{]; } \nu_{\text{max}} \text{ (solid) 3364 (OH), 3051, 2941, 2882, 2800, 2726 (C-H), 1347, 1316, 1072 cm}^{-1}; \delta_1 \text{ (400 MHz; CD}_3\text{OD) 1.20 (1H, tdd, } J 12.7, 11.2, 4.9 \text{ Hz, CH}_a\text{H}_b\text{-7), 1.56-1.75 (2H, m, H-6), 1.72 (1H, dd, } J 9.2, 3.3 \text{ Hz, H-8a), 1.89 (1H, td, } J 11.6, 3.1 \text{ Hz, CH}_a\text{H}_b\text{-5), 2.07-1.98 (1H, m, CH}_a\text{H}_b\text{-7), 2.43 (1H, dd, } J 10.4, 6.8 \text{ Hz, CH}_a\text{H}_b\text{-3), 2.88-2.96 (2H, m, CH}_a\text{H}_b\text{-3, CH}_a\text{H}_b\text{-5), 3.79 (1H, ddd, } J 11.0, 9.2, 4.7 \text{ Hz, H-8), 4.17-4.26 (2H, m, H-1, H-2); } \delta_C \text{ (100 MHz; CD}_3\text{OD) 24.7 (CH}_2\text{, C-6), 34.2 (CH}_2\text{, C-7), 53.3 (CH}_2\text{, C-5), 63.3 (CH}_2\text{, C-3), 67.2 (CH, C-8), 70.0 (CH, C-2), 70.8 (CH, C-1), 75.4 (CH, C-8a); HRMS (ESI+) C}_8\text{H}_{16}\text{NO}_3 [\text{MH}^+] \text{ requires 174.1125, found 174.1120.}\]

\((1R,2S,8S,8aS)\)-Octahydroindolizine-1,2,8-triyl triacetate

\[\text{ (+-Swainsonine 397 (0.030 g, 0.17 mmol) was dissolved in pyridine (1 mL) and cooled to 0 } ^\circ\text{C. Acetic anhydride (1 mL) was added dropwise and the solution stirred at room temperature for 20 h. The reaction mixture was diluted with dichloromethane (20 mL) and washed with a saturated solution of sodium hydrogen carbonate (20 mL). The aqueous phase was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient...}^{146, 149, 151}\text{; HRMS (ESI+) C}_8\text{H}_8\text{O}_4 [\text{MH}^+] \text{ requires 124.0691, found 124.0691.}\]

\((+)-\text{Swainsonine 397\text{ (0.030 g, 0.17 mmol) was dissolved in pyridine (1 mL) and cooled to 0 } ^\circ\text{C. Acetic anhydride (1 mL) was added dropwise and the solution stirred at room temperature for 20 h. The reaction mixture was diluted with dichloromethane (20 mL) and washed with a saturated solution of sodium hydrogen carbonate (20 mL). The aqueous phase was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient...}^{146, 149, 151}\text{; HRMS (ESI+) C}_8\text{H}_8\text{O}_4 [\text{MH}^+] \text{ requires 124.0691, found 124.0691.}\]
1:5 to 1:1), to give the **title compound** (0.035 g, 68%) as a colourless oil. The spectroscopic data was in agreement with that reported in the literature for the enantiomer.  

\([\alpha]_D^{20} -8.2\ (c\ 0.30,\ MeOH);\ [\text{lit. ent.}\ [\alpha]_D^{26} +7.0\ (c\ 1.77,\ MeOH)];^{18} \nu_{\text{max}}\ (\text{film})\ 2955,\ 2802\ (C-H),\ 1730\ (C=O),\ 1370,\ 1235,\ 1225,\ 1065,\ 1044\ \text{cm}^{-1};\ \delta_H\ (400\ MHz;\ CDCl_3)\ 1.17-1.30\ (1H,\ m,\ H-7ax),\ 1.68-1.83\ (2H,\ m,\ H-6),\ 1.87-1.97\ (1H,\ m,\ H-5ax),\ 1.99\ (3H,\ m,\ OAc),\ 2.05\ (3H,\ s,\ OAc),\ 2.08\ (3H,\ s,\ OAc),\ 2.13\ (1H,\ dd,\ J_{8a-8} 9.6,\ J_{8a-1} 4.2\ Hz,\ H-8a),\ 2.10-2.18\ (1H,\ m,\ H-7eq),\ 2.58\ (1H,\ dd,\ J_{\text{gem}} 11.1,\ J_{3-2} 7.6\ Hz,\ CH_3,\ Hb-3),\ 3.05\ (1H,\ app.\ ddd,\ J_{7.7,6.6,1.9}\ Hz,\ H-2),\ 5.52\ (1H,\ dd,\ J_{8-7ax} 11.0,\ J_{8-8a} 9.5,\ J_{8-7eq} 4.7\ Hz,\ H-8),\ 5.22\ (1H,\ app.\ ddd,\ J_{7.7,6.6,1.9}\ Hz,\ H-2),\ 5.52\ (1H,\ dd,\ J_{6.5,1-8a} 4.3\ Hz,\ H-1);\ \delta_C\ (100\ MHz;\ CDCl_3)\ 20.4,\ 20.6,\ 21.0,\ 23.3,\ 29.8,\ 51.7,\ 59.2,\ 68.0,\ 69.2,\ 69.8,\ 70.2,\ 169.9,\ 170.2;\ \text{HRMS\ (ESI+)}\ C_{14}H_{22}NO_6\ [MH^+]\ requires\ 300.1442,\ found\ 300.1449.\)

**(1S,2R,8S,8aS)-8-Hydroxyoctahydroindolizine-1,2-diyl diacetate (511)**

A solution of indolizidine 507 (0.065 g, 0.13 mmol), triethylamine (0.26 mL, 1.84 mmol) and triethylamine trihydrofluoride (0.21 mL, 1.31 mmol) in acetonitrile (5 mL) was stirred at 80 °C for 6 days. The reaction was cooled to room temperature and saturated aqueous sodium hydrogen carbonate (10 mL) added. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 1:99 to 3:97), to give the **title compound** (0.028 g, 83%) as a tan solid.

m.p. 76-78 °C; \([\alpha]_D^{20} +60.0\ (c\ 0.40,\ CHCl_3);\ \nu_{\text{max}}\ (\text{solid})\ 3383\ (OH),\ 2940,\ 2802\ (C-H),\ 1739\ (C=O),\ 1374,\ 1221,\ 1128,\ 1063\ \text{cm}^{-1};\ \delta_H\ (300\ MHz;\ CDCl_3)\ 1.23\ (1H,\ tdd,\ J_{\text{gem}} = J_{7ax-6ax} 13.0,\ J_{7ax-8} 10.9,\ J_{7ax-6eq} 4.7\ Hz,\ H-7ax),\ 1.49-1.66\ (2H,\ m,\ H-6ax),\ 1.66-1.77\ (1H,\ m,\ H-6eq),\ 1.99-2.14\ (9H,\ m,\ H-5ax,\ H-7eq,\ 2xOAc),\ 2.41\ (1H,\ dd,\ J 9.4,\ 6.7\ Hz,\ H-3),\ 2.69\ (1H,\ br\ s,\ OH),\ 2.87-2.96\ (1H,\ m,\ H-5eq),\ 3.45\ (1H,\ dd,\ J 9.5,\ 6.8\ Hz,\ H-3),\ 3.54\ (1H,\ ddd,\ J_{8-7ax} 10.8,\ J_{8-8a} 8.8,\ J_{8-7eq} 4.5\ Hz,\ H-8),\ 5.02-5.19\ (2H,\ m,\ H-2,\ H-1);\ \delta_C\ (75\ MHz;\ CDCl_3)\ 20.5,\ 20.8
(CH₃, 2 x OAc), 23.8 (CH₂, C-6), 32.8 (CH₂, C-7), 51.2 (CH₂, C-5), 57.5 (CH₂, C-3), 68.8 (CH, C-2), 71.0 (CH, C-8), 72.2 (CH, C-8a), 73.8 (CH, C-1), 170.1 (C=O, 2-OAc), 171.2 (C=O, 1-OAc); HRMS (ESI) C₁₂H₂₀NO₅ [MH⁺] requires 258.1336, found 258.1331.

(-)-1,2-Di-epi-swainsonine (512)

Potassium carbonate (0.006 g, 0.043 mmol) was added to a solution of diacetate 511 (0.022 g, 0.086 mmol) in methanol (3 mL) at room temperature and the mixture stirred for 2 h. The solution was concentrated under reduced pressure and then triturated with methanol. The crude residue was purified by reverse phase chromatography (C18), eluting with milli-Q water to give the title compound (0.012 g, 81%) as a white solid. The spectroscopic data was in agreement with that reported in the literature.⁴²⁶

m.p. 127-128 °C; (lit. 129-130 °C); [α]_D²⁰ -17.7 (c 0.24, MeOH); [lit. [α]_D²⁰ -18.7 (c 0.55, MeOH)]; ν max (solid) 3273 (OH), 2932, 2855, 2805 (C-H) 1659, 1404, 1371, 1124, 1067 cm⁻¹; δ_H (400 MHz; CD₃OD) 1.25 (1H, tdd, J_gem = J₇ax-6ax 12.9, J₇ax-8 10.9, J₇ax-6eq 4.5 Hz, H-7ax), 1.48-1.62 (1H, m, H-6ax), 1.65-1.75 (1H, m, H-6eq), 1.82 (1H, dd, J₈a-8 8.7, J₈a-1 7.9 Hz, H-8a), 2.84-2.92 (1H, m, H-5eq), 3.32-3.36 (1H, m, CH₃a,Hb-3), 3.41 (1H, ddd, J₈-7ax 10.8, J₈-8a 9.0, J₈-7eq 4.4 Hz, H-8), 3.80-3.85 (1H, m, H-1), 4.05-4.12 (1H, m, H-2); δ_C (100 MHz; CD₃OD) 25.0 (CH₂, C-6), 34.9 (CH₂, C-7), 53.0 (CH₂, C-5), 62.2 (CH₂, C-3), 68.7 (CH, C-2), 72.8 (CH, C-8), 74.8 (CH, C-8a), 75.5; (CH, C-1); HRMS (ESI+) C₈H₁₆NO₃ [MH⁺] requires 174.1125, found 174.1129.

(1S,2R,8S,8aS)-Octahydroindolizine-1,2,8-triyl triacetate (513)

(-)-1,2-Di-epi-swainsonine 512 (0.012 g, 0.069 mmol) was dissolved in pyridine (1 mL) and the solution cooled to 0 °C. Acetic anhydride (1 mL) was added dropwise and the solution stirred at room temperature for 20 h. The reaction mixture was diluted with
dichloromethane (20 mL) and washed with a saturated solution of sodium hydrogen carbonate (20 mL). The aqueous phase was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:5 to 1:1), to give the title compound (0.015 g, 72%) as a white solid. The spectroscopic data was in agreement with that reported in the literature.  

m.p. 135-136 °C; (lit. ent. 132-134 °C); $[\alpha]_D^{20} -61.7 (c 0.30, CHCl_3)$; $[\alpha]_D^{23} +61.1 (c 2.11, CHCl_3)$; $\nu_{\max} (\text{solid}) 2946, 2802 (\text{C-H}), 1734 (\text{C=O}), 1373, 1236, 1043 \text{ cm}^{-1}$; $\delta_H (400 \text{ MHz}; CDCl_3) 1.22-1.35 (1H, m, H-7ax), 1.56-1.77 (2H, m, H-6), 2.00 (3H, s, OAc), 2.01-2.15 (8H, m, H-5ax, H-7eq, 2 x OAc), 2.29 (1H, app t, $J 8.6 \text{ Hz}$, H-8a), 2.33 (1H, dd, $J_{3,2} 5.6$, $J_{\text{gem}} 10.0 \text{ Hz}$, CH$_{\text{a}}$,H$_{\text{b}}$-3), 4.69 (1H, ddd, $J_{8,7\text{eq}} 4.5$, $J_{8,8a} 9.4$, $J_{8,7\text{ax}} 10.9 \text{ Hz}$ H-8), 5.01 (1H, t, $J 7.7 \text{ Hz}$-1), 5.16-5.24 (1H, m, H-2); $\delta_C (100 \text{ MHz}; CDCl_3) 20.4 (\text{CH}_3, \text{OAc}), 20.6 (\text{CH}_3, \text{OAc}), 21.0 (\text{CH}_3, \text{OAc}), 23.6 (\text{CH}_2, \text{C-6}), 30.1 (\text{CH}_2, \text{C-7}), 51.2 (\text{CH}_2, \text{C-5}), 58.5 (\text{CH}_2, \text{C-3}), 67.5 (\text{CH}, \text{C-8a}), 68.4 (\text{CH}, \text{C-2}), 72.9 (\text{CH}, \text{C-8}), 73.9 (\text{CH}, \text{C-1}), 169.2 (\text{C=O, OAc}), 169.9 (\text{C=O, OAc}), 170.0 (\text{C=O, OAc}); \text{HRMS (ESI+)} C_{14}H_{22}NO_6 [\text{MH}^+] \text{ requires } 300.1442, \text{ found } 300.1446.

4.7  Formal Synthesis of (-)-Epiquinamide

4-(tert-Butyldimethylsilyloxy)but-1-yne (533)

4-(tert-Butyldimethylsilyloxy)but-1-yne 533 was prepared according to the literature procedure. A solution of tert-butyldimethylsilylchloride (11.3 g, 74.9 mmol) in dichloromethane (20 mL) was added slowly to a solution of 3-buty1-1-ol (5.00 g, 71.3 mmol), triethylamine (14.9 mL, 107 mmol) and N,N-dimethyl-4-aminopyridine (0.87 g, 7.13 mmol) in dichloromethane (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h then washed with an aqueous solution of hydrochloric acid (1 mol L$^{-1}$, 2 x 50 mL) and saturated sodium bicarbonate (50 mL). The organic extract was dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was
purified by distillation (45 mmHg, 89 °C), to give the title compound (12.4 g, 94%) as a colourless oil. The spectroscopic data was in agreement with that reported in the literature.478

δ_H (300 MHz; CDCl_3) 0.08 (6H, s, OSiMe_2), 0.90 (9H, s, OSi’Bu), 1.96 (1H, t, J_a-2 2.6 Hz, H-4), 2.40 (2H, td, J_a-2, J_b-2 7.1, J_e-2 2.6 Hz, H-2), 3.74 (2H, t, J_a2 7.1 Hz, H-1); δ_C (75 MHz; CDCl_3) -5.3 (CH_3, OSiMe_2), 18.3 (C, OSi’Bu), 22.8 (CH_2, C-2), 25.9 (CH_3, OSi’Bu), 61.7 (CH_2, C-1), 69.3 (CH, C-4), 81.5 (C, C-3).

(2R,3S)-2-(4-(tert-Butyldimethylsilyloxy)but-1-ynyl)-3-(tert-butyldiphenylsilyloxy) piperidin-1-ol (534)

A solution of n-butyllithium (1.6 M in hexanes, 0.39 mL, 0.63 mmol) was added dropwise to a solution of 4-(tert-butyldimethylsilyloxy)but-1-yn-1-e 533 (0.14 g, 0.76 mmol) in tetrahydrofuran (7 mL) at -78 °C and the mixture stirred for 10 min. A solution of nitrene 198 (0.18 g, 0.50 mmol) in tetrahydrofuran (3 mL) was added at -78 °C and the mixture stirred for a further 1 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL) and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:19 to 1:9), to give the title compound (0.23 g, 85%) as a colourless oil.

[α]_D^20 -21.0 (c 1.06, CHCl_3); ν_max (film) 3205 (br, OH), 2952, 2929, 2856 (C-H), 1471, 1427 (C=C), 1102, 700 cm\(^{-1}\); δ_H (400 MHz; DMSO-d_6, 120 °C) 0.03 (6H, s, OSiMe_2), 0.87 (9H, s, OSi’Bu), 1.07 (9H, s, OSi’Bu), 1.23-1.43 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 1.60-1.78 (2H, m, CH_a,H_b-4, CH_a,H_b-5), 2.29 (2H, td, J_2-1 7.1, 1.9 Hz, H-2’), 2.54-2.64 (1H, m, CH_a,H_b-6), 2.89-2.98 (1H, m, CH_a,H_b-6), 3.49 (1H, br s, H-2), 3.61 (2H, t, J_1-2’ 7.1 Hz, H-1’), 3.88-3.99 (1H, m, H-3), 7.35-7.49 (7H, m, NOH, Ar-H), 7.63-7.75 (4H, m, Ar-H); δ_C (100 MHz; DMSO-d_6, 120 °C) -6.0 (CH_3, OSiMe_2), 17.2 (C, OSi’Bu), 18.3 (C, OSi’Bu), 19.5 (CH_2, C-5), 22.3 (CH_2, C-2’), 25.1 (CH_3, OSi’Bu), 26.3 (CH_3, OSi’Bu), 29.4 (CH_2, C-4), 54.3 (CH_2, C-6), 61.1 (CH_2, C-1’), 64.3 (CH, C-2), 71.9 (CH, C-3), 78.7 (C, C-2’), 81.6 (C, C-3’), 126.9 (CH, C-Ar), 126.9 (CH, C-Ar), 128.9 (CH, C-Ar), 129.0 (CH, C-Ar), 133.4 (C, C-Ar), 133.5 (C,
C-Ar), 134.7 (CH, C-Ar), 134.8 (CH, C-Ar); HRMS (ESI+) \( C_{31}H_{58}NO_3Si_2 [MH^+] \) requires 538.3167, found 538.3160.

\((2R,3S)-2-(4-(\text{tert-Butyldimethylsilyloxy})\text{butyl})-3-(\text{tert-butylidiphenylsilyloxy})\text{piperidin-1-ol (535)}\)

![Chemical Structure](image)

Palladium on carbon (17 mg) was added portionwise to a solution of alkyne 534 (0.17 g, 0.32 mmol) in ethyl acetate (10 mL) and the mixture stirred under an atmosphere of hydrogen for 12 h. The reaction mixture was filtered through Celite\textsuperscript{®} and the filtrate concentrated under reduced pressure to give a yellow oil. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:19 to 1:9), to give the title compound (0.16 g, 91%) as a colourless oil.

\([\alpha]_D^{20} -3.6 \, (c \; 0.90, \text{CHCl}_3)\); \(\nu_{\max} \, (\text{film}) \, 3312 \, (\text{OH}), \, 3072 \, (\text{NH}), \, 2930, \, 2857 \, (\text{C-H}), \, 1472 \, (\text{C=C}), \, 1102, \, 1094, \, 700 \, \text{cm}^{-1}; \delta_{\text{H}} \) (400 MHz; DMSO-\text{d}_6, 120 °C) 0.04 (6H, s, OSiMe\textsubscript{2}), 0.90 (9H, s, OSi'\text{Bu}), 1.04 (9H, s, OSi'\text{Bu}), 1.17-1.50 (7H, m, H-3', H-2', H-5, CH\textsubscript{2}H\textsubscript{5}-4), 1.56-1.71 (2H, m, CH\textsubscript{2}H\textsubscript{5}-4', CH\textsubscript{2}H\textsubscript{5}-4), 1.72-1.84 (1H, m, CH\textsubscript{2}H\textsubscript{5}-4'), 2.30-2.38 (1H, m, H-2), 2.44 (1H, td, \( J \) 11.2, 4.1 Hz, CH\textsubscript{2}H\textsubscript{5}-6), 2.94-3.03 (1H, m, CH\textsubscript{2}H\textsubscript{5}-6), 3.55 (2H, t, \( J \) 6.5 Hz, H-1'), 3.65-3.75 (1H, m, H-3), 7.03 (1H, s, NO\textsubscript{H}), 7.35-7.49 (6H, m, Ar-H), 7.60-7.70 (4H, m, Ar-H); \(\delta_{\text{C}} \) (100 MHz; DMSO-\text{d}_6, 120 °C) -5.9 (CH\textsubscript{3}, OSiMe\textsubscript{2}), 18.3 (C, OSi'\text{Bu}), 19.6, 21.3 (CH\textsubscript{2}, C-5, C-3'), 25.2 (CH\textsubscript{3}, OSi'\text{Bu}), 26.3 (CH\textsubscript{3}, OSi'\text{Bu}), 27.5 (CH\textsubscript{2}, C-4'), 32.5 (CH\textsubscript{2}, C-2'), 32.6 (CH\textsubscript{2}, C-4), 56.5 (CH\textsubscript{2}, C-6), 62.4 (CH\textsubscript{2}, C-1'), 70.8 (CH, C-3), 71.4 (CH, C-2), 126.8 (CH, C-Ar), 126.9 (CH, C-Ar), 128.9 (CH, C-Ar), 129.0 (CH, C-Ar), 133.4 (C, C-Ar), 134.1 (C, C-Ar), 134.7 (CH, C-Ar), 134.7 (CH, C-Ar); HRMS (ESI+) \( C_{31}H_{58}NO_3Si_2 [MH^+] \) requires 542.3480, found 542.3476.

\((2R,3S)-2-(4-\text{Hydroxybutyl})-3-(\text{tert-butylidiphenylsilyloxy})\text{piperidine (531)}\)

![Chemical Structure](image)

Indium powder (0.22 g, 1.93 mmol) was added to a solution of hydroxylamine 535 (0.53 g, 0.97 mmol) in ethanol (22 mL) and the suspension heated to 80 °C. Aqueous
hydrochloric acid (2 mol L$^{-1}$, 3 mL) was added and the suspension heated to 100 °C and stirred for 2 h. The reaction mixture was cooled to room temperature and the pH adjusted to 10 by the dropwise addition an aqueous solution of 2 M sodium hydroxide. The mixture was filtered through Celite® and the filtrate concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL), washed with a solution of saturated brine (20 mL) and the aqueous phase extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 1:19 to 1:17), to give the title compound (0.36 g, 91%) as a yellow oil.

[α]$_D^{20}$ +21.2 (c 0.92, CHCl$_3$); $\nu_{\text{max}}$ (film) 3252 (br, OH), 3071 (NH) 2930, 2857 (C-H), 1427 (C=C), 1104, 1074, 700 cm$^{-1}$; $\delta$H (400 MHz; CDCl$_3$) 1.05 (9H, s, OSi$_{\text{tBu}}$), 1.12-1.61 (8H, m, H-$3'$, H-$5$, H-$2'$, CH$_a$H$_b$-$4'$, H-4ax), 1.72-1.82 (1H, m, H-4eq), 1.85-1.96 (1H, m, CH$_a$H$_b$-$4'$), 2.44-2.54 (2H, m, H-2, H-6ax), 2.80-2.91 (1H, m, H-6eq), 2.97 (2H, m, NH, OH), 3.26-3.35 (1H, m, H-3), 3.47-3.59 (2H, m, H-1'), 7.33-7.45 (6H, m, Ar-H), 7.64-7.72 (4H, m, Ar-H); $\delta$C (100 MHz; CDCl$_3$) 19.3 (C, OSi$_{\text{tBu}}$), 21.5 (CH$_2$, C-2'), 25.1 (CH$_2$, C-5), 26.9 (CH$_3$, OSi$_{\text{tBu}}$), 31.3 (CH$_2$, C-1'), 32.4 (CH$_2$, C-3'), 33.6 (CH$_2$, C-4), 45.1 (CH$_2$, C-6), 61.9 (CH$_2$, C-4'), 62.2 (CH, C-2), 73.5 (CH, C-3), 127.3 (CH, Ar-H), 127.5 (CH, Ar-H), 129.4 (CH, Ar-H), 129.6 (CH, Ar-H), 133.6 (C, Ar-H), 134.5 (C, Ar-H), 135.8 (CH, Ar-H), 135.8 (CH, Ar-H); HRMS (ESI+) C$_{25}$H$_{38}$NO$_2$Si [MH$^+$] requires 412.2666, found 412.2663.

(2R,3S)-1-tert-Butoxycarbonyl-2-(4-Hydroxybutyl)-3-(tert-butylidiphenylsilyloxy) piperidine (536)

Triethylamine (0.11 g, 0.79 mmol) was added dropwise to a solution of amine 531 (0.15 g, 0.36 mmol) and di-tert-butyl dicarbonate (0.086 g, 0.40 mmol) in dichloromethane (4 mL) at room temperature and the mixture stirred for 3 h. Diethyl ether (10 mL) was added and the mixture stirred for a further 30 min then concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:9 to 3:7), to give the title compound (0.17 g, 94%) as a colourless oil.
[α]D 20\textsuperscript{−} -38.9 (c 1.66, CHCl\textsubscript{3}); ν\textsubscript{max} (film) 3414 (br, OH), 2930, 2857 (C-H), 1687, 1666, (C=O) 1426 (C=C), 1105, 700 cm\textsuperscript{−}1; δ\textsubscript{H} (300 MHz; CDCl\textsubscript{3}) 1.02 - 1.17 (12H, s, OSi\textsubscript{t}Bu, CH\textsubscript{a},H\textsubscript{b}-4\ Prime, H-3\ Prime), 1.24 - 1.64 (15H, m, CH\textsubscript{a},H\textsubscript{b}-5, CH\textsubscript{a},H\textsubscript{b}-4\ Prime, H-4, H-2\ Prime), 1.92 - 2.17 (1H, m, CH\textsubscript{a},H\textsubscript{b}-5), 2.70 (1H, br t, J 11.8 Hz, CH\textsubscript{a},H\textsubscript{b}-6), 3.50 (1H, t, J 6.5 Hz, H-1\ Prime), 3.72 (1H, app d, J 2.2 Hz, H-3), 4.09 (2H, br s, CH\textsubscript{a},H\textsubscript{b}-6, H-2). 7.29 - 7.47 (6H, m, Ar-H), 7.59 - 7.77 (4H, m, Ar-H); δ\textsubscript{C} (75 MHz; CDCl\textsubscript{3}) 19.2 (C, OSi\textsubscript{t}Bu), 19.4 (C, H\textsubscript{a},H\textsubscript{b}-5), 21.9 (CH\textsubscript{2}, C-3\ Prime), 26.6 (CH\textsubscript{2}, C-4), 26.9 (CH\textsubscript{3}, OSi\textsubscript{t}Bu), 28.4 (CH\textsubscript{3}, H\textsubscript{a},H\textsubscript{b}-6), 28.7 (CH\textsubscript{2}, C-4\ Prime), 32.2 (CH\textsubscript{2}, C-2\ Prime), 37.8 (CH\textsubscript{2}, C-6), 38.8 (CH\textsubscript{2}, C-6\ Prime), 56.1 (CH, C-2\ Prime), 57.3 (CH, C-2), 62.5 (CH\textsubscript{2}, C-1\ Prime), 68.8 (CH, C-3), 79.1 (C, H\textsubscript{a},H\textsubscript{b}-5), 127.5 (CH, C-Ar), 127.5 (CH, C-Ar), 129.5 (CH, C-Ar), 129.5 (CH, C-Ar), 134.0 (C, C-Ar), 134.3 (C, C-Ar), 135.7 (CH, C-Ar), 135.9 (CH, C-Ar), 155.7 (C, C=O); HRMS (ESI\textsuperscript{+}) C\textsubscript{30}H\textsubscript{46}NO\textsubscript{4}Si [MH\textsuperscript{+}] requires 512.3191, found 512.3194.

(1\textsubscript{S},9\textsubscript{a}R)-1-((tert-Butyldiphenylsilyl)oxy)octahydro-1H-quinolizine (537)

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\text{OTBDPS}
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Method A: Cyclisation via formation of a methanesulfonate

Triethylamine (0.11 mL, 0.80 mmol) was added to a solution of amino alcohol 536 (0.163, 0.318 mmol) in dichloromethane (8 mL) at 0 °C and the mixture stirred for 10 min. Methanesulfonyl chloride (0.037 mL, 0.48 mmol) was added dropwise and the solution stirred for 1 h. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (5 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure to give a colourless oil.

Trifluoroacetic acid (0.10 mL, 1.34 mmol) was added dropwise to a solution of the crude methanesulfonate in dichloromethane (10 mL) at 0 °C and the mixture stirred at room temperature for 12 h. The reaction mixture was cooled to 0 °C and triethylamine (0.37 mL, 2.69 mmol) was added dropwise. The mixture was stirred for a further 20 h at room temperature then extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure to give a yellow oil. The residue was purified by flash column chromatography, eluting with ethyl
acetate-hexanes (gradient 1:9 to 1:1), to give the title compound (0.079 g, 63% over two steps) as a yellow oil.

\[ \alpha \]$_{D}^{20}$ +25.4 (c 1.40, CHCl$_3$); \( \nu_{\text{max}} \) (film) 2931, 2856 (C-H), 1427 (C=C), 1110, 1084, 699 cm$^{-1}$; \( \delta_{\text{H}} \) (400 MHz; CDCl$_3$) 0.94-1.08 (10H, m, H-9ax, OSi$t$Bu), 1.17-1.33 (2H, m, H-2ax, H-8ax), 1.33-1.49 (2H, m, H-3), 1.49-1.63 (2H, m, H-7), 1.66-1.73 (1H, m, H-2eq), 1.73-1.82 (2H, m, H-9a, H-8eq), 1.95 (1H, td, \( J_{\text{gem}} = J_{\text{ax-3ax}} \) 11.6, \( J_{\text{ax-3eq}} \) 3.2, H-4ax), 2.02 (1H, td, \( J_{\text{gem}} = J_{\text{ax-7ax}} \) 11.8, 3.3, \( J_{\text{ax-7eq}} \) H-6ax), 2.28-2.37 (1H, m, H-9eq), 2.59-2.67 (1H, m, H-4eq), 2.76-2.85 (1H, m, H-6eq), 3.38-3.46 (1H, m, H-1), 7.31-7.43 (6H, m, Ar-H), 7.65-7.72 (4H, m, Ar-H); \( \delta_{\text{C}} \) (100 MHz; CDCl$_3$) 19.4 (C, OSi$t$Bu), 23.1 (CH$_2$, C-3), 24.3 (CH$_2$, C-8), 25.6 (CH$_2$, C-7), 27.1 (CH$_3$, OSi$t$Bu), 29.1 (CH$_2$, C-9), 34.3 (CH$_2$, C-2), 55.9 (CH$_2$, C-4), 56.2 (CH$_2$, C-6), 69.0 (CH, C-9a), 74.6 (CH, C-1), 127.3 (CH, C-Ar), 127.5 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 133.8 (C, C-Ar), 134.9 (C, C-Ar), 135.9 (CH, C-Ar), 135.9 (CH, C-Ar); HRMS (ESI+) C$_{25}$H$_{36}$NOSi [MH$^+$] requires 394.2561, found 394.2564.

**Method B: Cyclisation via Appel Reaction**

Carbon tetrabromide (0.092 g, 0.29 mmol) and triphenylphosphine (0.080 g, 0.37 mmol) were added portionwise to a solution of amino alcohol 531 (0.10 g, 0.25 mmol) dichloromethane (4 mL) at 0 ºC and the mixture stirred for 30 min. Triethylamine (0.10 mL, 0.74 mmol) was added and the mixture stirred for 1 h at 0 ºC and then a further 6 h at room temperature. The reaction was quenched with water (5 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure to give a brown solid. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:9 to 1:1), to give the title compound (0.068 g, 70%) as a yellow oil. The spectroscopic data was in agreement with that reported using method A.

(1S,9aR)-Octahydro-1H-quinolizin-1-ol (530)

![](image)

A solution of quinolizidine 537 (0.14 g, 0.36 mmol), triethylamine (0.70 mL, 5.05 mmol) and triethylamine trihydrofluoride (0.59 mL, 3.61 mmol) in acetonitrile (5 mL) was
stirred at 80 °C for 12 h. The reaction was cooled to room temperature and saturated aqueous sodium hydrogen carbonate (10 mL) added. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 1:19 to 9:91), to give the title compound (0.037 g, 66%) as a pale brown solid. The spectroscopic data was in agreement with that reported in the literature.

m.p. 74-77°C; (lit. ent. 71-72 °C, 85-83 °C); [α]D 20 +23.0 (c 0.73, CHCl3); [lit. ent. [α]D 28 -21.7 (c 0.85, CHCl3)]; νmax (solid) 3130 (OH), 2926, 2855, 2805, 2761 (C-H), 1441, 1106, 1047 cm⁻¹; δH (400 MHz; CDCl3) 1.13-1.34 (3H, m, H-2ax, H-8ax, H-9ax), 1.55-1.77 (5H, m, H-9a, H-3, H-7), 1.77-1.86 (1H, m, H-8eq), 1.97-2.10 (3H, m, H-2eq, H-4ax, H-6ax), 2.12-2.20 (1H, m, H-9eq), 2.72-2.80 (1H, m, H-4eq), 2.8-2.92 (1H, m, H-6eq), 3.32 (1H, ddd, J 11.1, 8.8, 4.6, H-1); δC (100 MHz; CDCl3) 23.1 (CH2, C-3), 24.0 (CH2, C-8), 25.5 (CH2, C-7), 28.5 (CH2, C-9), 33.9 (CH2, C-2), 55.8 (CH2, C-4), 56.1 (CH2, C-6), 68.8 (CH, C-9a), 72.3 (CH, C-1); HRMS (ESI+) C19H18NO [MH+] requires 156.1383, found 156.1386.

4.8 Synthesis of 2,6-Disubstituted-3-Hydroxypiperidines

(2R,3S)-1-tert-Butoxycarbonyl-3-(tert-butyldiphenylsiloxyl)-2-phenylpiperidine (554)

Triethylamine (0.19 mL, 0.79 mmol) was added dropwise to a stirred solution of amine 365 (0.15 g, 0.35 mmol) and di-tert-butyl dicarbonate (0.15 g, 0.70 mmol) in dichloromethane (10 mL) at room temperature and the mixture stirred overnight. Diethyl ether (10 mL) was added and the mixture stirred for 30 min then concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:99 to 1:19), to give the title compound (0.17 g, 91%) as a colourless oil.

[α]D 20 -25.3 (c 0.88, CHCl3); νmax (film) 2931, 2858 (C-H), 1690 (C=O), 1416 (C=C), 1365 cm⁻¹; δH (300 MHz; CDCl3) 1.13 (9H, s, OSi(tBu), 1.24-1.49 (11H, m, tBu, H-4ax, H-5eq), 1.53-1.68 (1H, m, H-4eq), 2.09-2.29 (1H, m, H-5ax), 2.92 (1H, td, J 13.1, 3.1 Hz, H-6ax),
4.19-4.31 (1H, m, H-6eq), 4.33-4.40 (1H, m, H-3), 5.27 (1H, br s, H-2), 6.70-6.80 (2H, m, Ar-H), 7.07-7.22 (3H, m, Ar-H), 7.34-7.50 (6H, m, Ar-H), 7.67-7.82 (4H, m, Ar-H); δC (75 MHz; CDCl₃) 18.8 (CH₂, C-5), 19.3 (C, OSi₂Bu), 26.4 (CH₂, C-4), 27.0 (CH₃, OSi₂Bu), 28.3 (CH₃, 'Bu), 40.1 (CH₂, C-6), 60.4 (CH, C-2), 69.3 (CH, C-3), 79.4 (C, 'Bu), 126.1 (CH, C-Ar), 126.4 (CH, C-Ar), 127.7 (CH, C-Ar), 127.8 (CH, C-Ar), 128.3 (CH, C-Ar), 129.7 (CH, C-Ar), 129.8 (CH, C-Ar), 133.8 (C, C-Ar), 134.2 (C, C-Ar), 135.8 (CH, C-Ar), 135.9 (CH, C-Ar), 138.9 (C, C-Ar), 156.2 (C, C=O); HRMS (ESI+) C₃₂H₄₂NO₃Si [MH⁺] requires 516.2928, found 516.2933.

(2R,3S)-1-tert-Butoxycarbonyl-3-hydroxy-2-phenylpiperidine (549)

A solution of piperidine 554 (0.12 g, 0.23 mmol), triethylamine (0.45 mL, 3.26 mmol) and triethylamine trihydrofluoride (0.38 mL, 2.33 mmol) in acetonitrile (8 mL) was stirred at 80 °C overnight. The reaction was cooled to room temperature and saturated aqueous sodium hydrogen carbonate (10 mL) added. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (1:4), to give the title compound (0.060 g, 93%) as a colourless oil. The spectroscopic data was in agreement with that reported in the literature.²⁶⁴

[α]D²⁰ -67.4 (c 0.64, CHCl₃); [lit. [α]D²⁰ -66.1 (c 0.9, CHCl₃)²⁶⁴]; νmax (film) 3436 (OH), 2932 (C-H), 1663 (C=O), 1415, 1365 (C=C), 984, 697 cm⁻¹; δH (400 MHz; CDCl₃) 1.35-1.43 (1H, m, H-6eq), 1.43-1.50 (9H, m, 'Bu), 1.56-1.66 (1H, m, H-4ax), 1.71-1.80 (1H, m, H-4eq), 1.86-2.01 (1H, m, H-5ax), 2.33 (1H, d, J 5.7 Hz, OH), 2.87 (1H, td, J 13.2, 3.4 Hz, H-6ax), 4.05-4.14 (1H, m, H-6eq), 4.48-4.54 (1H, m, H-3), 5.37 (1H, br s, H-2), 7.17-7.28 (3H, m, Ar-H), 7.31-7.38 (2H, m, Ar-H); δC (100 MHz; CDCl₃) 18.8 (CH₂, C-5), 25.9 (CH₂, C-4), 28.3 (CH₃, 'Bu), 35.9 (CH₂, C-6), 60.2 (CH, C-2), 67.4 (CH, C-3), 80.0 (C, 'Bu), 126.3 (CH, C-Ar), 126.8 (CH, C-Ar), 128.7 (CH, C-Ar), 138.2 (C, C-Ar), 156.7 (C, C=O); HRMS (ESI+) C₁₆H₂₄NO₃ [MH⁺] requires 278.1751, found 278.1751.
(2R,3S)-3-(tert-Butyldiphenylsilyloxy)-2-methyl-2,3,4,5-tetrahydropyridine 1-oxide (557a) and (S)-5-(tert-butyldiphenylsilyloxy)-6-methyl-2,3,4,5-tetrahydropyridine 1-oxide (556a)

Activated manganese(IV) oxide (0.084 g, 0.97 mmol) was added portionwise to a solution of hydroxylamine 345 (0.18 g, 0.48 mmol) in dichloromethane (10 mL) at 0 °C and the mixture stirred for 2 h. The resulting suspension was filtered through a pad of magnesium sulphate/Celite® and the filtrate concentrated under reduced pressure, at a water bath temperature below 20 °C. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 0.5:99.5 to 1:19), to give the title compounds 557a (0.081 g, 45%) and 556a (0.058 g, 33%) as colourless oils.

Data for 557a: Rf (5% MeOH/CH2Cl2) 0.29; δH (400 MHz; CDCl3) 1.07 (9H, s, OSi(tert-Bu)), 1.28 (3H, d, J1'-2 7.1 Hz, H-1'), 1.59-1.70 (2H, m, H-4), 2.28-2.40 (1H, m, H-5eq), 2.69-2.83 (1H, m, H-5ax), 3.71-3.80 (1H, m, H-2), 3.98-4.04 (1H, m, H-3), 7.16-7.21 (1H, m, H-6), 7.36-7.49 (6H, m, Ar-H), 7.61-7.69 (4H, m, Ar-H); δC (100 MHz; CDCl3) 17.9 (CH3, C-1'), 19.0 (C, OSi(tert-Bu)), 20.6 (CH2, C-4), 21.2 (CH2, C-5), 26.7 (CH3, OSi(tert-Bu)), 69.8 (CH, C-2), 70.0 (CH, C-3), 127.7 (CH, C-Ar), 127.8 (CH, C-Ar), 129.9 (CH, C-Ar), 130.0 (CH, C-Ar), 132.9 (C, C-Ar), 133.1 (C, C-Ar), 135.1 (CH, C-6), 135.4 (CH, C-Ar), 135.5 (CH, C-Ar); HRMS (ESI+) C22H30NO2Si [MH+] requires 368.2040, found 368.2047.

Data for 556a: Rf (5% MeOH/CH2Cl2) 0.32; δH (400 MHz; CDCl3) 1.06 (9H, s, OSi(tert-Bu)), 1.54-1.71 (1H, m, CHaHb-4), 1.71-1.88 (2H, m, CHaHb-4, CHaHb-3), 2.01 (3H, s, H-1'), 2.16-2.34 (1H, m, CHaHb-3), 3.64-3.80 (1H, m, CHaHb-2), 3.82-3.93 (1H, m, CHaHb-2), 4.24-4.33 (1H, m, H-5), 7.36-7.50 (6H, m, Ar-H), 7.61-7.72 (4H, m, Ar-H); δC (100 MHz; CDCl3) 16.5 (CH3, C-1'), 18.6 (CH2, C-3), 19.2 (C, OSi(tert-Bu)), 26.8 (CH3, OSi(tert-Bu)), 28.2 (CH2, C-4), 58.4 (CH2, C-2), 68.7 (CH, C-5), 127.7 (CH, C-Ar), 127.8 (CH, C-Ar), 130.0 (CH, C-Ar), 132.6 (C, C-Ar), 133.1 (C, C-Ar), 135.8 (CH, C-Ar), 146.4 (C, C-6); HRMS (ESI+) C22H30NO2Si [MH+] requires 368.2040, found 368.2047.
(2R,3S)-2-Allyl-3-(tert-butyldiphenylsilyloxy)-2,3,4,5-tetrahydropyridine 1-oxide (557c) and (S)-6-allyl-5-(tert-butyldiphenylsilyloxy)-2,3,4,5-tetrahydropyridine 1-oxide (556c)

Activated manganese(IV) oxide (0.055 g, 0.64 mmol) was added portionwise to a solution of hydroxylamine 359 (0.13 g, 0.32 mmol) in dichloromethane (10 mL) at 0 °C and the mixture stirred for 2 h. The resulting suspension was filtered through a pad of magnesium sulphate/Celite® and the filtrate concentrated under reduced pressure, at a water bath temperature below 20 °C. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 0.5:99.5 to 1:19), to give the title compounds 557c (0.074 g, 57%) and 556c (0.021 g, 16%) as colourless oils.

Data for 557c: \( R_f \) (5% MeOH/CH\(_2\)Cl\(_2\)) 0.34; \( \delta \)\(_{\text{H}} \) (400 MHz; CDCl\(_3\)) 1.06 (9H, s, OSi'Bu), 1.58-1.75 (2H, m, H-4), 1.99-2.10 (1H, m, CH\(_a\)H\(_b\)-3'), 2.29-2.40 (1H, m, CH\(_a\)H\(_b\)-5), 2.70-2.83 (1H, m, CH\(_a\)H\(_b\)-5), 2.92-3.00 (1H, m, CH\(_a\)H\(_b\)-3'), 3.62-3.69 (1H, m, H-2), 4.12-4.18 (1H, m, H-3), 4.81-4.90 (2H, m, H-1'), 5.16-5.29 (1H, m, H-2'), 7.18-7.22 (1H, m, H-6), 7.33-7.48 (6H, m, Ar-H), 7.59-7.66 (4H, m, Ar-H); \( \delta \)\(_{\text{C}} \) (100 MHz; CDCl\(_3\)) 19.1 (C, OSi'Bu), 20.5 (CH\(_2\), C-4), 21.2 (CH\(_2\), C-5), 26.9 (CH\(_3\), OSi'Bu), 36.4 (CH\(_2\), C-3'), 67.1 (CH, C-3), 73.3 (CH, C-2), 118.3 (CH\(_2\), C-1'), 127.8 (CH, C-Ar), 127.9 (CH, C-Ar), 129.9 (CH, C-Ar), 130.0 (CH, C-Ar), 132.8 (CH, C-2'), 133.3 (C, C-Ar), 135.6 (CH, C-6), 135.6 (CH, C-Ar), 135.8 (CH, C-Ar); HRMS (ESI+) \( C_{24}H_{32}NO_2Si \) [M\(^+\)] requires 394.2197, found 394.2206.

Data for 556c: \( R_f \) (5% MeOH/CH\(_2\)Cl\(_2\)) 0.37; \( \delta \)\(_{\text{H}} \) (400 MHz; CDCl\(_3\)) 1.06 (9H, s, OSi'Bu), 1.49-1.60 (1H, m, CH\(_a\)H\(_b\)-4), 1.72-1.82 (1H, m, CH\(_a\)H\(_b\)-3), 1.82-1.93 (1H, m, CH\(_a\)H\(_b\)-4), 2.24-2.37 (1H, m, CH\(_a\)H\(_b\)-3), 2.76-2.85 (1H, m, CH\(_a\)H\(_b\)-3'), 3.58-3.67 (1H, m, CH\(_a\)H\(_b\)-3'), 3.67-3.77(1H, m, CH\(_a\)H\(_b\)-2'), 3.86-3.94 (1H, m, CH\(_a\)H\(_b\)-2'), 4.31-4.37 (1H, m, H-5), 4.68-4.77 (1H, m, CH\(_a\)H\(_b\)-1'), 4.86-4.92 (1H, m, CH\(_a\)H\(_b\)-1'), 5.64-5.76 (1H, m, H-2'), 7.36-7.51 (6H, m, Ar-H), 7.62-7.72 (4H, m, Ar-H); \( \delta \)\(_{\text{C}} \) (75 MHz; CDCl\(_3\)) 18.5 (CH\(_2\), C-3), 19.3 (C, OSi'Bu), 26.9 (CH\(_3\), OSi'Bu), 28.2 (CH\(_2\), C-4), 33.4 (CH\(_2\), C-3'), 58.9 (CH\(_2\), C-2), 66.5 (CH, C-5), 117.6 (CH\(_2\), C-1'), 127.8 (CH, C-Ar), 127.8 (CH, C-Ar), 130.0 (CH, C-Ar), 130.1 (CH, C-Ar), 130.5 (CH, C-2'), 132.6 (C, C-Ar), 133.2 (C, C-Ar), 135.9 (CH, C-Ar), 146.7 (C, C-6); HRMS (ESI+) \( C_{24}H_{32}NO_2Si \) [M\(^+\)] requires 394.2197, found 394.2207.
(2R,3S)-2-Benzyl-3-(tert-butyldiphenylsilyloxy)-2,3,4,5-tetrahydropyridine 1-oxide (557d) and (S)-6-benzyl-5-(tert-butyldiphenylsilyloxy)-2,3,4,5-tetrahydropyridine 1-oxide (556d)

Activated manganese(IV) oxide (0.12 g, 1.35 mmol) was added portionwise to a solution of hydroxylamine 355 (0.30 g, 0.67 mmol) in dichloromethane (10 mL) at 0 °C and the mixture stirred for 2 h. The resulting suspension was filtered through a pad of magnesium sulphate/Celite® and the filtrate concentrated under reduced pressure, at a water bath temperature below 20 °C. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 0.5:99.5 to 1:19), to give the title compounds 557d (0.19 g, 62%) and 556d (0.028 g, 9%) as colourless oils.

Data for: 557d  
Rf (5% MeOH/CH2Cl2) 0.29; δH (400 MHz; CDCl3) 0.97 (9H, s, OSi′Bu), 1.49-1.56 (2H, m, H-4), 2.23-2.35 (1H, m, H-5), 2.62 (1H, dd, Jgem 13.8, J1,2 10.8 Hz, CH3,HbPh), 2.67-2.79 (1H, m, H-5), 3.58 (1H, dd, Jgem 13.8, J1,2 3.9 Hz, CHa,HbPh), 3.95-4.03 (1H, m, H-2), 4.03-4.08 (1H, m, H-3), 6.93-7.00 (2H, m, Ar-H), 7.11-7.19 (3H, m, Ar-H), 7.23-7.34 (5H, m, Ar-H, H-6), 7.36-7.49 (6H, m, Ar-H); δC (100 MHz; CDCl3) 19.0 (C, OSi′Bu), 20.4 (CH2, C-4), 21.2 (CH2, C-5), 26.8 (CH3, OSi′Bu), 37.9 (CH2, CH2Ph), 66.7 (CH, C-3), 75.0 (CH, C-2), 126.7 (CH, C-Ar), 127.7 (CH, C-Ar), 127.7 (CH, C-Ar), 127.7 (CH, C-Ar), 128.6 (CH, C-Ar), 128.9 (CH, C-Ar), 129.8 (CH, C-Ar), 132.7 (C, C-Ar), 133.2 (C, C-Ar), 135.4 (CH, C-Ar), 135.5 (CH, C-Ar), 135.8 (CH, C-6), 136.2 (C, C-Ar); HRMS (ESI+) C28H34NO2Si [MH+] requires 444.2353, found 444.2342.

Data for: 556d  
Rf (5% MeOH/CH2Cl2) 0.34; δH (400 MHz; CDCl3) 1.06 (9H, s, OSi′Bu), 1.42-1.54 (1H, m, CHa,Hb-4), 1.72-1.91 (2H, m, CHa,Hb-3, CHa,Hb-4), 2.29-2.43 (1H, m, CHa,Hb-3), 3.22 (1H, d, Jgem 13.7, CHa,HbPh), 3.68-3.79 (1H, m, CHa,Hb-2), 3.90-4.01 (1H, m, CHa,Hb-2), 4.34-4.39 (1H, app t, J 3.7, H-5), 4.43 (1H, d, Jgem 13.7, CHa,HbPh), 6.84-6.91(2H, m, Ar-H), 7.06-7.14 (3H, m, Ar-H), 7.33-7.51 (6H, m, Ar-H), 7.59-7.70 (4H, m, Ar-H); δC (100 MHz; CDCl3) 18.4 (CH2, C-3), 19.3 (C, OSi′Bu), 26.8 (CH3, OSi′Bu), 28.1 (CH2, C-4), 33.9 (CH2, CH2Ph), 59.1 (CH2, C-2), 66.3 (CH, C-5), 126.4 (CH, C-Ar), 127.8 (CH, C-Ar), 127.9 (CH, C-Ar), 128.3 (CH, C-Ar), 128.9 (CH, C-Ar), 130.0 (CH, C-Ar), 130.1 (CH, C-Ar), 132.7 (C, C-Ar), 133.1 (C, C-Ar), 135.9 (CH, C-Ar), 135.9 (CH, C-Ar), 135.9 (CH, C-Ar),
136.2 (C, C-Ar), 147.4 (C, C-6); HRMS (ESI+) C_{28}H_{34}NO_{2}Si [MH^+] requires 444.2353, found 444.2365.

(2R,3S)-3-(tert-Butyldiphenylsilyloxy)-2-isopropyl-2,3,4,5-tetrahydropyridine 1-oxide (557e)

![Structure of 557e]

Activated manganese(IV) oxide (0.11 g, 1.26 mmol) was added portionwise to a solution of hydroxylamine 353 (0.25 g, 0.63 mmol) in dichloromethane (10 mL) at 0 °C and the mixture stirred for 2 h. The resulting suspension was filtered through a pad of magnesium sulphate/Celite® and the filtrate concentrated under reduced pressure, at a water bath temperature below 20 °C. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 1:49 to 1:19), to give the title compound (0.21 g, 86%) as a colourless oil.

δ\textsubscript{H} (300 MHz; CDCl\textsubscript{3}) 0.71 (3H, d, J\textsubscript{7.0} i-Pr), 0.80 (3H, d, J\textsubscript{7.0} i-Pr), 1.07 (9H, s, OSi\textsubscript{t}Bu), 1.50-1.64 (1H, m, CH\textsubscript{a}H\textsubscript{b}-4), 1.64-1.76 (1H, m, CH\textsubscript{a}H\textsubscript{b}-4), 2.15-2.28 (1H, m, H-1'), 2.28-2.42 (1H, m, CH\textsubscript{a}H\textsubscript{b}-5), 2.66-2.82 (1H, m, CH\textsubscript{a}H\textsubscript{b}-5), 3.53 (1H, dd, J\textsubscript{5.8} 1.2 Hz, H-3), 4.14-4.19 (1H, m, H-2), 7.24 (1H, t, J\textsubscript{6.5} 4.0 Hz, H-6), 7.35-7.50 (6H, m, Ar-H), 7.60-7.70 (4H, m, Ar-H); δ\textsubscript{C} (75 MHz; CDCl\textsubscript{3}) 18.7 (CH\textsubscript{3}, i-Pr), 18.9 (C, OSi\textsubscript{t}Bu), 19.0 (CH\textsubscript{3}, i-Pr), 21.1 (CH\textsubscript{2}, C-5), 22.0 (CH\textsubscript{2}, C-4), 26.6 (CH\textsubscript{3}, OSi\textsubscript{t}Bu), 29.1 (CH, C-1'), 66.4 (CH, C-2), 78.6 (CH, C-3), 127.5 (CH, C-Ar), 127.6 (CH, C-Ar), 129.7 (CH, C-Ar), 129.8 (CH, C-Ar), 132.6 (C, C-Ar), 133.1 (C, C-Ar), 134.9 (CH, C-6), 135.3 (CH, C-Ar), 135.6 (CH, C-Ar).

(2R,3S)-3-(tert-Butyldiphenylsilyloxy)-2-phenyl-2,3,4,5-tetrahydropyridine 1-oxide (557f)

![Structure of 557f]

Activated manganese(IV) oxide (0.049 g 0.57 mmol) was added portionwise to a solution of hydroxylamine 364 (0.12 g 0.28 mmol) in dichloromethane (8 mL) at 0 °C and the mixture stirred for 4 h. The resulting suspension was filtered through a pad of magnesium...
sulphate/Celite® and the filtrate concentrated under reduced pressure, at a water bath temperature below 20 °C. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 1:49 to 1:19), to yield the title compound (0.12 g, 99%) as a colourless oil.

δH (300 MHz; CDCl3) 1.12 (9H, s, OSiBu), 1.48-1.64 (2H, m, H-4), 2.43-2.58 (1H, m, CHaHb-5), 2.81-2.98 (1H, m, CHaHb-5), 4.16-4.22 (1H, m, H-3), 4.85 (1H, br s, H-2), 6.69-6.78 (2H, m, Ar-H), 7.16-7.25 (3H, m, Ar-H), 7.36-7.56 (7H, m, Ar-H, H-6), 7.62-7.70 (2H, m, Ar-H), 7.70-7.78 (2H, m, Ar-H); δC (75 MHz; CDCl3) 19.2 (C, OSiBu), 19.3 (CH2, C-4), 21.6 (CH2, C-5), 27.0 (CH3, OSiBu), 71.8 (CH, C-3), 78.2 (CH, C-2), 126.1 (CH, C-Ar), 127.8 (CH, C-Ar), 127.9 (CH, C-Ar), 128.1 (CH, C-Ar), 128.7 (CH, C-Ar), 130.1 (CH, C-Ar), 130.3 (CH, C-Ar), 132.9 (C, C-Ar), 133.2 (C, C-Ar), 135.6 (CH, C-Ar), 135.8 (C, C-Ar), 135.9 (CH, C-Ar), 137.1 (CH, C-6); HRMS (ESI+) C27H32NO2Si [MH+] requires 430.2197, found 430.2187.

(2R,3S,6R)-3-(tert-Butyldiphenylsilyloxy)-6-methyl-2-phenylpiperidine (559)

Methylmagnesium bromide (3 M, 0.19 mL, 0.56 mmol) was added dropwise to a solution of nitrone 557f (0.12 g, 0.28 mmol) in tetrahydrofuran (10 mL) at 0 °C and the mixture stirred at this temperature for 1 h. Saturated aqueous ammonium chloride (10 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:99 to 8:92), to give the hydroxylamine (0.089 g) as a yellow oil.

Zinc powder (0.065 mmol, 1.0 mmol) and indium powder (0.002 g, 0.020 mmol) were added to a solution of the hydroxylamine in ethanol/saturated aqueous ammonium chloride (2:1, 3 mL). The suspension was stirred under reflux for 4 h, cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated and saturated aqueous sodium carbonate (10 mL) was added. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried over anhydrous magnesium sulphate and
concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (1:99 to 1:19), to give the title compound (0.048 g, 40% over two steps) as a colourless oil.

\[ \nu_{\text{max}} \text{ (film)}: 3070 (\text{N-H}), 2931, 2857 (\text{C-H}), 1428 (\text{C=C}), 1105, 1262, 1089 \text{ cm}^{-1}; \delta_{\text{H}} \text{ (400 MHz; CDCl}_3\text{): } 0.88 (9\text{H}, \text{s, OSi(tBu)}), 1.21 (3\text{H}, \text{d, } J = 6.7 \text{ Hz, CH}_3), 1.42-1.59 (3\text{H}, \text{m, H-5, CH}_a\text{H}_b\text{-4}), 1.60-1.72 (1\text{H}, \text{m, CH}_a\text{H}_b\text{-4}), 1.91 (1\text{H}, \text{br s, NH}), 3.05-3.17 (1\text{H}, \text{m, H-6}), 3.83-3.90 (1\text{H}, \text{m, H-3}), 3.92 (1\text{H}, \text{d, } J_{2,3} = 6.8 \text{ Hz, H-2}), 7.18-7.31 (7\text{H}, \text{m, Ar-H}), 7.31-7.44 (6\text{H}, \text{m, Ar-H}), 7.59-7.67 (2\text{H}, \text{m, Ar-H}); \delta_{\text{C}} \text{ (100 MHz; CDCl}_3\text{): } 19.1 (\text{C, OSi(tBu)}), 19.8 (\text{CH}_3, \text{CH}_3), 26.8 (\text{CH}_3, \text{OSi(tBu)}), 28.7 (\text{CH}_2, \text{C-4}), 29.2 (\text{CH}_2, \text{C-5}), 46.5 (\text{CH, C-6}), 61.3 (\text{CH, C-2}), 73.0 (\text{CH, C-3}), 126.9 (\text{CH, C-Ar}), 127.4 (\text{CH, C-Ar}), 127.4 (\text{CH, C-Ar}), 128.0 (\text{CH, C-Ar}), 128.1 (\text{CH, C-Ar}), 129.4 (\text{CH, C-Ar}), 133.6 (\text{C, C-Ar}), 134.9 (\text{C, C-Ar}), 135.8 (\text{CH, C-Ar}), 141.9 (\text{C, C-Ar}).

\((2R,3S,6R)-3-(\text{tert-Butyldiphenylsilyloxy})-6\text{-methyl-2-phenylpiperidin-1-yl benzoate} \quad (562)\)

Methylmagnesium bromide (3 M, 0.26 mL, 0.78 mmol) was added dropwise to a solution of nitrone 557f (0.11 g, 0.26 mmol) in tetrahydrofuran (10 mL) at 0 °C and the mixture stirred at this temperature for 1 h. Saturated aqueous ammonium chloride (10 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:99 to 8:92), to give the hydroxylamine (0.084 g) as a yellow oil.

Triethylamine (0.053 mL, 0.376 mmol) was added to a solution of hydroxylamine (0.084 g, 0.19 mmol) and \(N,N\text{-dimethyl-4-aminopyridine} \) (0.002 g, 0.019 mmol) in dichloromethane (8 mL) at 0 °C and the mixture stirred for 5 min. Benzoyl chloride (0.044 mL, 0.38 mmol) was added dropwise and the mixture stirred at 0 °C for 30 min. The reaction mixture was quenched by the addition of aqueous hydrochloric acid (1 mol L\(^{-1}\), 2 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed...
with a solution of saturated brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:99 to 9:91), to give the title compound (0.095 g, 66% over two steps) as a white solid.

m.p. 154-156 °C; [α]D20 -71.0 (c 0.54, CHCl3); νmax (solid) 2949, 2854 (C−H), 1734 (C=O), 1451, 1427 (C=C), 1262, 1089 cm−1; δH (400 MHz; CDCl3) 0.74 (9H, s, OSi-tBu), 1.27 (3H, d, J1′-6 6.6 Hz, H-1′), 1.42-1.56 (2H, m, CHa,Hb-4, CHa,Hb-5), 1.62-1.77 (1H, m, CHa,Hb-4), 1.79-1.92 (1H, m, CHa,Hb-5), 3.80-3.95 (2H, br s, H-3, H-6), 4.17 (1H, d, J2-3 9.1 Hz, H-2), 7.11-7.29 (9H, m, Ar-H), 7.30-7.47 (7H, m, Ar-H), 7.49-7.56 (2H, m, Ar-H), 7.57-7.65 (2H, m, Ar-H); δC (100 MHz; CDCl3) 10.5 (CH3, Me), 18.9 (C, OSi-tBu), 26.2 (CH2, C-5), 26.5 (CH3, OSi-tBu), 28.2 (CH2, C-4), 55.8 (CH, C-6), 70.3 (CH, C-2), 74.8 (CH, C-3), 127.3 (CH, C-Ar), 127.3 (CH, C-Ar), 127.4 (CH, C-Ar), 128.0 (CH, C-Ar), 128.0 (CH, C-Ar), 128.8 (CH, C-Ar), 129.0 (CH, C-Ar), 129.4 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 132.5 (CH, C-Ar), 132.7 (C, C-Ar), 134.8 (C, C-Ar), 135.9 (CH, C-Ar), 139.8 (C, C-Ar), 164.8 (C=O, O=Bz); HRMS (ESI+) C35H40NO3Si [MH+]* requires 550.2772, found 550.2774.

(2R,3S,6R)-6-Benzyl-3-(tert-butyldiphenylsilyloxy)-2-phenylpiperidin-1-yl benzoate (563) and (2R,3S,6S)-6-benzyl-3-(tert-butyldiphenylsilyloxy)-2-phenylpiperidin-1-yl benzoate (564)

Benzylmagnesium chloride (2 M, 0.55 mL, 1.10 mmol) was added dropwise to a solution of nitrone 557f (0.16 g) in tetrahydrofuran (10 mL) at 0 °C and the mixture stirred at this temperature for 1 h. Saturated aqueous ammonium chloride (10 mL) was added and the aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:99 to 8:92), to give the 6R-hydroxylamine (0.057 g, 30%) and 6S-hydroxylamine (0.096 g, 50%) as yellow oils.

6R-hydroxylamine: Triethylamine (0.030 mL, 0.22 mmol) was added to a solution of the first eluted compound, 6R-hydroxylamine (0.057 g, 0.109 mmol) and N,N-dimethyl-
aminopyridine (0.001 g, 0.011 mmol) in dichloromethane (8 mL) at 0°C and the mixture stirred for 5 min. Benzoyl chloride (0.025 mL, 0.21 mmol) was added dropwise and the mixture stirred at 0 °C for 30 min. The reaction mixture was quenched by the addition of aqueous hydrochloric acid (1 mol L⁻¹, 5 mL) and extracted with dichloromethane (3 x 20 mL). The organic extract was washed with a solution of saturated brine and dried over anhydrous sodium sulphate. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:99 to 1:19), to give the title compound (0.064 g, 94%) as a yellow oil.

**Data for 563:** [α]D²⁰ -37.5 (c 0.28, CHCl₃); νmax (film) 2957, 2855 (C-H), 1737 (C=O), 1451, 1428 (C=C), 1256, 1236, 1097 cm⁻¹; δH (400 MHz; CDCl₃) 0.70 (9H, s, OSi₄Bu), 1.19-1.45 (2H, m, CH₂-H₄-4, CH₂-H₅-5), 1.45-1.65 (2H, m, CH₃-H₅-4, CH₃-H₅-5), 2.57 (1H, dd, J gem 12.9, J1-6 9.6 Hz, CH₂-H₃-4, 1’), 2.94-3.13 (2H, m, H-6, CH₂-H₅-1’), 3.89 (1H, d, J2-3 9.2 Hz, H-2), 7.03-7.48 (2H, m, Ar-H), 7.51-7.58 (2H, m, Ar-H), 7.58-7.65 (2H, m, Ar-H), δC (100 MHz; CDCl₃) 18.9 (C, OSi₄Bu), 26.0 (CH₂, C-5), 26.4 (CH₃, OSi₄Bu), 33.6 (CH₂, C-4), 39.8 (CH₂, C-1’), 68.7 (CH, C-6), 73.8 (CH, C-3), 79.7 (CH, C-2), 126.1 (CH, C-Ar), 127.3 (CH, C-Ar), 127.4 (CH, C-Ar), 127.5 (CH, C-Ar), 127.8 (CH, C-Ar), 128.0 (CH, C-Ar), 128.2 (CH, C-Ar), 129.0 (CH, C-Ar), 129.1 (CH, C-Ar), 129.3 (CH, C-Ar), 129.4 (CH, C-Ar), 129.5 (CH, C-Ar), 132.5 (CH, C-Ar), 132.7 (C, C-Ar), 134.7 (C, C-Ar), 135.8 (CH, C-Ar), 138.6 (C, C-Ar), 139.1 (C, C-Ar), 165.3 (C=O, OBz); HRMS (ESI+) C₄₁H₄₃NO₃SiNa [MH⁺] requires 648.2904, found 648.2912.

6S-hydroxylamine: Triethylamine (0.078 mL, 0.37 mmol) was added to a solution of the second eluted compound, 6S-hydroxylamine (0.096 g, 0.18 mmol) and N,N-dimethyl-4-aminopyridine (0.002 g, 0.018 mmol) in dichloromethane (8 mL) at 0°C and the mixture stirred for 5 min. Benzoyl chloride (0.043 mL, 0.37 mmol) was added dropwise and the mixture stirred at 0 °C for 30 min. The reaction mixture was quenched by the addition of aqueous hydrochloric acid (1 mol L⁻¹, 5 mL) and extracted with dichloromethane (3 x 20 mL). The organic extract was washed with a solution of saturated brine and dried over anhydrous sodium sulphate. The residue was purified by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:99 to 9:91), to give the title compound (0.096 g, 83%) as a white solid.

**Data for 564:** m.p. 153-154 °C; [α]D²⁰ -11.3 (c 1.12, CHCl₃); νmax (solid) 2930, 2856 (C-H), 1748 (C=O), 1452, 1428 (C=C), 1243, 1104 cm⁻¹; δH (300 MHz; CDCl₃) 0.77 (9H, m,
OSiBu), 1.42-1.71 (3H, m, H-4eq, H-5), 1.71-1.89 (1H, m, H-4ax), 3.03 (1H, dd, J<sub>gem</sub> 13.1, J<sub>1-6</sub> 10.8 Hz, CH<sub>a</sub>H<sub>b</sub>-1'), 3.26 (1H, dd, J<sub>gem</sub> 3.1 Hz, CH<sub>a</sub>H<sub>b</sub>-1'), 3.81-4.02 (2H, m, H-3, H-6), 4.29 (1H, d, J<sub>2-3</sub> 9.0 Hz, H-2), 7.03-7.29 (14H, m, Ar-H), 7.30-7.48 (7H, m, Ar-H), 7.49-7.57 (2H, m, Ar-H), 7.58-7.66 (2H, m, Ar-H); δ<sub>C</sub> (75 MHz; CDCl<sub>3</sub>) 19.0 (C, OSiBu), 22.3 (CH<sub>2</sub>, C-5), 26.6 (CH<sub>3</sub>, OSiBu), 28.3 (CH<sub>2</sub>, C-4), 30.4 (CH<sub>2</sub>, C-1'), 63.1 (CH, C-6), 71.3 (CH, C-2), 74.7 (CH, C-3), 126.0 (CH, C-Ar), 127.4 (CH, C-Ar), 127.5 (CH, C-Ar), 128.0 (CH, C-Ar), 128.1 (CH, C-Ar), 128.4 (CH, C-Ar), 128.8 (CH, C-Ar), 129.1 (CH, C-Ar), 129.1 (CH, C-Ar), 129.3 (CH, C-Ar), 129.5 (CH, C-Ar), 129.5 (CH, C-Ar), 132.6 (CH, C-Ar), 132.8 (C, C-Ar), 134.8 (C, C-Ar), 135.9 (CH, C-Ar), 135.9 (C, C-Ar), 139.5 (C, C-Ar), 139.6 (C, C-Ar), 164.8 (C=O, OBz); HRMS (ESI+) C<sub>41</sub>H<sub>43</sub>NO<sub>3</sub>SiNa [MH]<sup>+</sup> requires 648.2904, found 648.2908.


Activated manganese(IV) oxide (0.056 g, 0.64 mmol) was added portionwise to a solution of hydroxylamine 353 (0.13 g, 0.33 mmol) in dichloromethane (10 mL) at 0 °C and the mixture stirred for 2 h. The resulting suspension was filtered through a pad of magnesium sulphate/Celite® and the filtrate concentrated under reduced pressure, at a water bath temperature below 20 °C. The residue was purified by flash column chromatography, eluting with methanol-dichloromethane (gradient 0.5:99.5 to 1:19), to yield nitrone 557e as a colourless oil. Styrene (0.10 g, 0.98 mmol) was added to a stirred solution of crude nitrone 557e in chloroform at room temperature and the reaction mixture stirred at 65 °C in a sealed tube for 2 days. The solution was cooled to room temperature and filtered through a short pad of Celite® and concentrated under reduced pressure. Purification of the residue by flash column chromatography, eluting with ethyl acetate-hexanes (gradient 1:99 to 1:9), gave the title compounds 567 (0.12 g, 73%), as well as a partially separable mixture of 568 and 569 (6 mg, 4%) as a yellow oils.

Data for 567: R<sub>f</sub> (10% EtOAc/hexanes) 0.71; [α]<sub>D</sub><sup>20</sup> -5.5 (c 2.42, CHCl<sub>3</sub>); ν<sub>max</sub> (film) 2953, 2932, 2892, 2859 (C-H), 1428 (C=C), 1106, 1088 cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 0.91 (3H, d, J
Data for 568: $R_f$ (10% EtOAc/hexanes) 0.74; $\delta_H$ (400 MHz; CDCl$_3$) 0.88 (3H, d, J 7.0 Hz, i-Pr), 0.95 (3H, d, J 7.0 Hz, i-Pr), 1.03 (9H, s, OSi’Bu), 1.39-1.59 (3H, m, CH$_3$-H$_b$-4, H-5), 1.83-1.93 (1H, m, CH$_3$-H$_b$-5), 2.16-2.29 (2H, m, CH$_3$-H$_b$-3, H-1’), 2.45 (1H, ddd, J 12.0, 7.5, 5.9 Hz, CH$_3$-H$_b$-3), 2.84 (1H, dd, J 7.1, 3.6 Hz, H-7), 3.51-3.65 (2H, m, H-6, H-3a), 4.99-5.07 (1H, m, H-2), 7.24-7.55 (11H, m, Ar-H), 7.65-7.76 (4H, m, Ar-H); $\delta_C$ (100 MHz; CDCl$_3$) 19.3 (C, OSi’Bu), 19.7 (CH$_3$, i-Pr), 20.2 (CH$_3$, i-Pr), 21.8 (CH$_2$, C-4), 27.0, (CH$_3$, OSi’Bu), 28.2 (CH, C-1’), 28.4 (CH$_2$, C-5), 40.5 (CH$_2$, C-3), 59.1 (CH, C-3a), 70.3 (CH, C-6), 70.7 (CH, C-7), 80.8 (CH, C-2), 126.6 (CH, C-Ar), 127.3 (CH, C-Ar), 127.4 (CH, C-Ar), 127.6 (CH, C-Ar), 133.2 (C, C-Ar), 133.7 (C, C-Ar), 135.9 (CH, C-Ar), 135.9 (CH, C-Ar), 141.2 (C, C-Ar); HRMS (ESI+) C$_{32}$H$_{42}$NO$_2$Si [MH$^+$] requires 500.2979, found 500.2984.

Data for 569: $R_f$ (10% EtOAc/hexanes) 0.74; $\delta_H$ (400 MHz; CDCl$_3$) 0.77 (3H, d, J 7.0 Hz, i-Pr), 1.05 (9H, s, OSi’Bu), 1.15 (3H, d, J 7.0 Hz, i-Pr), 1.09-1.20 (1H, m, CH$_3$-H$_b$-4), 1.39-1.52 (1H, m, CH$_3$-H$_b$-5), 1.64-1.76 (1H, m, CH$_3$-H$_b$-4), 1.76-1.85 (1H, m, CH$_3$-H$_b$-5), 1.96-2.07 (1H, m, CH$_3$-H$_b$-3), 2.21 (1H, dt, J 11.7, 9.7 Hz, CH$_3$-H$_b$-3), 2.42 (1H, dt, J 14.3, 7.2 Hz, H-1’), 2.52-2.72 (2H, m, H-7, H-3a), 3.61 (1H, br s, H-7), 4.94 (1H, dd, J 9.4, 4.9 Hz, H-2), 7.21-7.27 (1H, m, Ar-H), 7.28-7.46 (10H, m, Ar-H), 7.65-7.74 (4H, m, Ar-H); $\delta_C$ (100 MHz; CDCl$_3$) 15.7 (CH$_3$, i-Pr), 19.4 (C, OSi’Bu), 23.0 (CH$_3$, i-Pr), 25.3 (CH$_2$, C-5), 27.1 (CH$_3$, OSi’Bu), 27.3 (CH, C-1’), 34.1 (CH$_2$, C-5), 42.5 (CH$_2$, C-3), 65.7 (CH, C-3a), 71.1 (CH, C-6), 76.7 (CH, C-7), 77.8 (CH, C-2), 126.2 (CH, C-Ar), 127.2 (CH, C-Ar), 127.4 (CH, C-Ar), 127.6 (CH, C-Ar), 128.2 (CH, C-Ar), 129.5 (CH, C-Ar), 129.7 (CH, C-Ar), 133.5 (C, C-
C-Ar), 134.6 (C, C-Ar), 136.0 (CH, C-Ar), 136.0 (CH, C-Ar), 142.6 (C, C-Ar); HRMS (ESI+) C$_{32}$H$_{42}$NO$_2$Si [MH$^+$] requires 500.2979, found 500.2986.
5. References

59. de Vicente, J.; Arrayás, R. G.; Cañada, J.; Carretero, J. C., Synlett 2000, 1 (536).

263
310. Dennis, J. W., Cancer Res. 1986, 46 (10), 5131-5136.

270
6. Appendix

Crystallographic Data and Structure Refinement for Diol 341

Diagram derived from x-ray structure of diol 341 was created using ORTEP-III software.\textsuperscript{479}

Table 4.8.1. Crystal data and structure refinement for 341

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<td>Space group</td>
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<td></td>
<td>(b = 8.08870(10) \quad \text{Å} \quad \beta = 105.2230(10)^\circ)</td>
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R indices (all data) \[ R1 = 0.0406, \ wR2 = 0.0925 \]

Absolute structure parameter \[ -0.04(12) \]

Largest diff. peak and hole \[ 0.211 \text{ and } -0.281 \text{ e.Å}^{-3} \]

**Table 4.8.2.** Atomic coordinates (\( x \times 10^4 \)) and equivalent isotropic displacement parameters (\( Å^2 \times 10^3 \)) for 341

U(eq) is defined as one third of the trace of the orthogonalized \( U_{ij} \) tensor.

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Table 4.8.3. Bond lengths [Å] and angles [°] for 341

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<td>C(7)-C(6)-Si</td>
<td>119.52(16)</td>
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C(12)-C(17)-H(17A) 119.3  C(20)-C(18)-C(19) 108.9(2)
C(20)-C(18)-C(21) 109.3(2)  C(19)-C(18)-C(21) 108.5(2)
C(20)-C(18)-Si 110.27(16)  C(19)-C(18)-Si 113.01(15)
C(21)-C(18)-Si 106.73(15)  C(18)-C(19)-H(19A) 109.5
C(18)-C(19)-H(19B) 109.5  C(18)-C(19)-H(19C) 109.5
H(19B)-C(19)-H(19C) 109.5  C(18)-C(20)-H(20A) 109.5
C(18)-C(20)-H(20B) 109.5  C(18)-C(20)-H(20C) 109.5
H(20A)-C(20)-H(20B) 109.5  C(18)-C(21)-H(21A) 109.5
C(18)-C(21)-H(21B) 109.5  C(18)-C(21)-H(21B) 109.5
H(21A)-C(21)-H(21B) 109.5  C(18)-C(21)-H(21C) 109.5
H(21B)-C(21)-H(21C) 109.5

Symmetry transformations used to generate equivalent atoms:

Table 4.8.4. Anisotropic displacement parameters (Å² x 10^3) for 341

The anisotropic displacement factor exponent takes the form: -2π² [ h² a*²U11 + ... + 2 h k a* b* U12 ]

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Table 4.8.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 341

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</table>
Crystallographic Data and Structure Refinement for Piperidine 489

Diagram derived from x-ray structure of piperidine 489 was created using ORTEP-III software.479

Table 4.8.6. Crystal data and structure refinement for 489

<table>
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<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
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</tr>
<tr>
<td>Space group</td>
<td>C2</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
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</tr>
<tr>
<td></td>
<td>b = 7.3535(4) Å, beta = 100.394(4)°</td>
</tr>
<tr>
<td></td>
<td>c = 16.0097(10) Å, gamma = 90°</td>
</tr>
<tr>
<td>Volume</td>
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<tr>
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<tr>
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</tr>
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<td>Crystal size</td>
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<tr>
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<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
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<td>Refinement method</td>
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<tr>
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<td>R indices (all data)</td>
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Absolute structure parameter 0.06(8)
Largest diff. peak and hole 0.260 and -0.180 eÅ⁻³

Table 4.8.7. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å² x 10³) for 489

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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283
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Symmetry transformations used to generate equivalent atoms:

Table 4.8.9. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 489

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Table 4.8.10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 489
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Crystallographic Data and Structure Refinement for Indolizidine 510

Diagram derived from x-ray structure of indolizidine 510 was created using ORTEP-III software.\(^{479}\)

Table 4.8.11. Crystal data and structure refinement for 510

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<td>R indices (all data)</td>
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287
Largest diff. peak and hole 
0.224 and -0.288 e.Å⁻³

Table 4.8.12. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å² x 10³) for 510

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

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Table 4.8.13. Bond lengths [Å] and angles [°] for 510

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<td>Angle (°)</td>
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C(5)-C(6)-H(6B) 109.4  H(6A)-C(6)-H(6B) 108.0
C(6)-C(7)-C(8)  111.1(3)  C(6)-C(7)-H(7A)  109.4
C(8)-C(7)-H(7A) 109.4  C(6)-C(7)-H(7B)  109.4
C(8)-C(7)-H(7B) 109.4  H(7A)-C(7)-H(7B) 108.0
O(5)-C(8)-C(8A) 110.9(3)  O(5)-C(8)-C(7)  112.8(3)
C(8A)-C(8)-C(7) 108.8(3)  O(5)-C(8)-H(8)  108.1
C(8A)-C(8)-H(8) 108.1  C(7)-C(8)-H(8)  108.1
N(4)-C(8A)-C(1) 102.0(2)  N(4)-C(8A)-C(8)  112.5(3)
C(1)-C(8A)-C(8) 118.3(3)  N(4)-C(8A)-H(8A) 107.8
C(1)-C(8A)-H(8A) 107.8  C(8)-C(8A)-H(8A) 107.8
C(5)-N(4)-C(3)  114.1(2)  C(5)-N(4)-C(8A)  111.1(2)
C(3)-N(4)-C(8A) 103.2(2)  C(1")-O(1)-C(1)  116.7(3)
C(1")-C(2")-H(2"1) 109.5  C(1")-C(2")-H(2"2)  109.5
H(2"1)-C(2")-H(2"2) 109.5  C(1")-C(2")-H(2"3)  109.5
H(2"1)-C(2")-H(2"3) 109.5  H(2"2)-C(2")-H(2"3)  109.5
C(1')-O(3)-C(2)  117.4(3)  C(8)-O(5)-H(5)  109.5

Symmetry transformations used to generate equivalent atoms:

Table 4.8.14. Anisotropic displacement parameters (Å² x 10³) for 510

The anisotropic displacement factor exponent takes the form: -2π² [ h a* a* U11 + ... + 2 h k a* b* U12 ]

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Table 4.8.15. Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 510

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