A Biomimetic Total Synthesis of Clivonine

A Thesis Submitted in Partial Fulfilment of the Degree of PhD

Victoria L. Paddock

Department of Chemistry
Imperial College London
Acknowledgments

I first decided that I was going to undertake a PhD during my industrial placement year at Novartis. With the encouragement of my supervisor Catherine Howsham I applied to Imperial College and was fortunate enough to be offered a place within Professor Alan Spivey’s group.

I would like to thank Alan for his support as my supervisor over the past three years, he was always available to talk about my chemistry and offer ideas and guidance towards my work. I have learnt a lot during my time at Imperial, not only from Alan, but from all the members of the Spivey group, past and present, who made my time at Imperial most enjoyable. I would like to say a special thanks to Carles, who was always at the other end of an e-mail to help with difficult steps through the Clivonine synthesis.

Finally, I would like to thank my family and friends who have supported me, not only through my PhD but in all aspects of my life. My greatest thanks goes to Mum, Dad and Rachel whose love and support has helped me achieve everything that I have. I would also like to say a special thanks to Ed, who not only moved to London but has now moved to Paris for me, without his love, support, understanding and encouragement, none of this would have been possible.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcCl</td>
<td>Acetyl chloride</td>
</tr>
<tr>
<td>Ac₂O</td>
<td>Acetic anhydride</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>AgOAc</td>
<td>Silver acetate</td>
</tr>
<tr>
<td>AHA</td>
<td>Asymmetric Hydroamination</td>
</tr>
<tr>
<td>app</td>
<td>Apparent</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-Borabicyclo [3.3.1] nonane</td>
</tr>
<tr>
<td>BHT</td>
<td>Butylated hydroxytoluene</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>t-BuOOH</td>
<td>tert-Butyl hydperoxide</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>Butyllithium</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>tert-Butyllithium</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>m-CBA</td>
<td>meta-Chlorobenzoic acid</td>
</tr>
<tr>
<td>CBA</td>
<td>Carboxylic acid</td>
</tr>
<tr>
<td>cf.</td>
<td>Confer (Latin: 'compare')</td>
</tr>
<tr>
<td>cm</td>
<td>Centimetre</td>
</tr>
<tr>
<td>Conc</td>
<td>Concentration</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-Chloroperbenzoic acid</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0] undec-7-ene</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminiumhydride</td>
</tr>
<tr>
<td>DMAD</td>
<td>Dimethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethyl formamide</td>
</tr>
<tr>
<td>DMP</td>
<td>2,2-Dimethoxypropane</td>
</tr>
<tr>
<td>DMPU</td>
<td>1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>DPPE</td>
<td>1,2-Bis (diphenylphosphino)ethane</td>
</tr>
<tr>
<td>DIPA</td>
<td>Diisopropylamine</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>Et₃N</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Et₂O</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>Equiv.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>FC</td>
<td>Flash chromatography</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IBX</td>
<td>2-Iodoxybenzoic acid</td>
</tr>
<tr>
<td>im</td>
<td>Imidazole</td>
</tr>
<tr>
<td>IR</td>
<td>Infra red</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>LHS</td>
<td>Left hand side</td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>MeOTf</td>
<td>Methyl trifluoromethane-sulfonate</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>Min</td>
<td>Minute</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesyl</td>
</tr>
<tr>
<td>NaOAc</td>
<td>Sodium acetate</td>
</tr>
<tr>
<td>NMO</td>
<td>N-Methyl morpholine N-oxide</td>
</tr>
<tr>
<td>NMP</td>
<td>N-Methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>o</td>
<td>Ortho</td>
</tr>
<tr>
<td>p</td>
<td>Para</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>Pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-Methoxybenzyl ether</td>
</tr>
<tr>
<td>ppm</td>
<td>Part per million</td>
</tr>
<tr>
<td>i-PrOH</td>
<td>iso-Propanol</td>
</tr>
<tr>
<td>PS</td>
<td>Polystyrene</td>
</tr>
<tr>
<td>py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>quant.</td>
<td>Quantitative</td>
</tr>
<tr>
<td>RHS</td>
<td>Right hand side</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>SM</td>
<td>Starting material</td>
</tr>
<tr>
<td>Sol.</td>
<td>Solution</td>
</tr>
<tr>
<td>Sat.</td>
<td>Saturated</td>
</tr>
<tr>
<td>SCX</td>
<td>Strong cation exchange</td>
</tr>
<tr>
<td>TBAI</td>
<td>Tetrabutylammonium-iodide</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TBP</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMDS</td>
<td>1,1,4,4-Tetramethyldisiloxane</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TPP</td>
<td>5,10,15,20-Tetraphenylporphyrin</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>para-Toluenesulfonic acid</td>
</tr>
<tr>
<td>UV</td>
<td>Ultra violet</td>
</tr>
<tr>
<td>W</td>
<td>Watt</td>
</tr>
<tr>
<td>WCX</td>
<td>Weak cation exchange</td>
</tr>
</tbody>
</table>
Abstract

The first chapter of this thesis discusses the biomimetic total synthesis of clivonine. Clivonine is a member of the *Amaryllidaceae* family of alkaloids and was isolated from the plant *Clivia miniata* Regel by Wildman in 1956. Barton first proposed the biosynthesis of the *Amaryllidaceae* alkaloids in 1958, hypothesising that the key diversifying step in the biosynthesis was an intramolecular phenolic oxidati ve coupling of a common precursor, norbelladine. However, it was not until 2 years later, in 1960, that Barton was able to account for the biosynthesis of the lycorenine class of the *Amaryllidaceae* alkaloids, the class in which clivonine is a member. He proposed that a ‘ring-switch’ must occur after the initial intramolecular phenolic oxidative coupling from a lycorine type progenitor to that of a lycorenine type skeleton. Our synthesis of clivonine demonstrates for the first time the synthetic interconversion between these two classes of compounds in a manner that can be considered biomimetic.

The second chapter of this thesis details our synthesis of the acetonide protected derivative of cis-3,5-cyclohexadien-1,2-diol. The first section of this chapter highlights the importance of these types of molecules and reviews the previous syntheses of this compound. The second section then details the development of a five-step three-pot synthesis of this compound in an overall 50% yield starting from commercially available 1,3-cyclohexadiene.

The final chapter of this thesis discusses the studies towards the development of a catalytic asymmetric retro-Cope elimination reaction. This chapter will first highlight recent advances that have been made towards the asymmetric hydroamination (AHA) reaction before reviewing the recent progress made towards expanding the scope of the retro-Cope elimination reaction. Finally, our proposed method of developing an asymmetric retro-Cope reaction will be outlined, along with details of preliminary studies focussed on the development of a suitable system with which the asymmetric retro-Cope elimination can be studied.

Declaration

I declare that I have personally prepared this report, and the work described here is my own, carried out personally unless otherwise stated. All sources of information are acknowledged by means of reference.
# Contents

## Chapter 1 – The Biomimetic Total Synthesis of Clivonine

1.1. Introduction
   - 1.1.1. *Amaryllidaceae* Alkaloids 6
   - 1.1.2. Clivonine 7
   - 1.1.3. Irie’s Synthesis of Clivonine 11
   - 1.1.4. Biosynthesis of the *Amaryllidaceae* 13
   - 1.1.5. Synthetic Strategy and Project Aims 16
     - 1.1.5.1. The Ireland-Claisen Rearrangement 18
     - 1.1.5.2. The *retro*-Cope Elimination 20
     - 1.1.5.3. Biomimetic Ring-Switch 24

1.2. Results and Discussion
   - 1.2.1. Synthesis of (±) and (+)-Enone 40
   - 1.2.2. Synthesis of Oxime 46
   - 1.2.3. Synthesis of Iminium salt 38
   - 1.2.4. Purification of Iminium salt 38
   - 1.2.5. Biomimetic Ring-Switch 42

1.3. Conclusions and Future Work 48

## Chapter 2 – Synthesis of meso-Diol 74

2.1. Introduction
   - 2.1.1. Importance and Synthetic Utility of meso-Diol 74 49
   - 2.1.2. Previous Syntheses of meso-Diol 74 53
   - 2.1.3. Synthetic Strategy and Project Aims 55
     - 2.1.3.1. CoTPP Rearrangement of Endoperoxides 56

2.2. Results and Discussion
   - 2.2.1. Synthesis of Dibromo diol 134 62
   - 2.2.2. *bis*-Elimination of Dibromide 135 68

2.3. Conclusions 74

## Chapter 3 – Studies Towards an Asymmetric *retro*-Cope Elimination Reaction

3.1. Introduction
   - 3.1.1. Recent Advances in the Asymmetric Hydroamination Reaction 75
   - 3.1.2. Recent Advances in the *retro*-Cope Elimination Reaction 80
   - 3.1.3. Mechanistic Studies of the *retro*-Cope Elimination 86
   - 3.1.4. Project Aims 87

3.2. Results and Discussion
   - 3.2.1. Synthesis of Oximes 180a-180g 89
   - 3.2.2. *retro*-Cope Elimination Rate Studies 92
   - 3.2.3. Conclusions and Future Work 95

Overall Conclusions 96

## Chapter 4 - Experimental

4.1. General Directions 97

4.2. Experimental for Chapter 1 98

4.3. Experimental for Chapter 2 111

4.4. Experimental for Chapter 3 116

Appendices 130

References 139
1.1. Introduction

1.1.1. Amaryllidaceae Alkaloids

The Amaryllidaceae alkaloids are a large class of nitrogen containing compounds isolated from the Amaryllidaceae herbaceous perennials such as the daffodil. The plants of the Amaryllidaceae consist of approximately 85 genera and 1100 species and to date over 500 structurally diverse alkaloids have been isolated.\(^1\) These alkaloids can be categorised into 8 skeletally distinct subclasses (Figure 1).\(^2-3\)

![Figure 1: Subclasses of the Amaryllidaceae alkaloids.](image)

However with the large number of these alkaloids being isolated in the recent years the subgroups can now be extended up to 18.\(^1\) The structural classes relevant to this thesis have been highlighted above as the lycorenine and the lycorine classes. Clivonine is a member of the lycorenine class.

Many of the Amaryllidaceae alkaloids exhibit interesting biological and medicinal properties such as anticancer, anti-inflammatory, antifungal and antiviral activity, making them popular targets for synthesis.\(^4\) The last 15 years has seen a large number of total syntheses of these natural products, and the isolation of many new alkaloids in this class.\(^1,2,5-6\)
Clivonine (1) was first isolated by Wildman in 1956 from the plant *Clivia miniata* Regel (Figure 2).\(^7\)

Wildman found the molecular formula of clivonine (1) to be C\(_{14}H_{13}(O_2CH_2)(\text{NCH}_3)(\text{OH})(\text{COO})\) and proposed a structure for it based on homolycorine (2) (Figure 3). The presence of the lactone functionality was determined by the high solubility of clivonine (1) in a warm alkali solution. Treatment of the solution with acid allowed for relactonisation and the extraction of the hydrochloride salt into chloroform. The free base was then obtained upon neutralisation with sodium bicarbonate. A positive Labat test and IR absorptions at 2793 and 943 cm\(^{-1}\) provided evidence of the methylenedioxy group. It was placed in the 9, 10 position due to the very similar UV spectrum of the model compound 3 (Figure 3).

Clivonine (1) also appeared to be completely saturated as it absorbed no H\(_2\) unlike all the other lactonic alkaloids of the same family. After reduction of clivonine (1) with lithium aluminium hydride, tetrahydroclivonine (4) (Figure 3) was isolated. UV spectroscopy showed the disappearance of the carbonyl group and a titration with periodate confirmed the presence of a vicinal diol unit. From all this information Wildman was able to assign a tentative structure for clivonine which had the correct connectivity (i.e. cf. 1) but lacked stereochemical detail. It was not until 10 years later that Mehlis proposed the relative and absolute stereochemistry (Figure 4).\(^8\)
Mehlis correctly predicted the cis relationship between the C5 and C5a protons based on evidence that the product of lithium aluminium hydride reduction underwent a rapid periodate cleavage when compared to compounds known to be epimeric at C5. However, the stereochemistry he predicted at C11b and C11c in relation to C5a was based on comparisons made between clivonine and other lactones of the same family, and was soon proved to be incorrect by Döpke and Jeffs.

Döpke and Jeffs undertook mass spectrometric studies of various lactone alkaloids and were able to confirm the basic structure found by Wildman. This was followed by detailed ¹H NMR experiments on clivonine and its O-acetate derivative which led them to reassign the stereochemistry of clivonine. The spectra showed clear signals for the N-Me, methylenedioxy and the two aryl protons. By comparing the two spectra it was possible to assign the protons at δ 4.18 and 4.06 ppm as H5 and H5a respectively in clivonine (1) itself. This assignment was supported by a characteristic downfield shift of H5 to δ 5.35 ppm in the O-acetyl compound. The H5a signal in the O-acetyl compound shows as a doublet with coupling constants of 3.0 and 12.5 Hz. Irradiation of H5 at δ 5.35 ppm removes the smaller coupling to give the H5a signal as a doublet, confirming the coupling constants as $J_{5,5a} = 3.0$ Hz and $J_{5a,11b} = 12.5$ Hz. The coupling constant between H5 and H5a supports the cis relationship of the diol unit as proposed by Mehlis (cf. Figure 4). However, the large coupling constant between H5a and H11b suggests a trans diaxial relationship in contrast to the cis relationship previously suggested. From this data they proposed that there was a trans B:C ring fusion.

By studying the ¹H NMR spectrum of clivonine (1) the relationship of the H11b, H11c and H3a protons could also be assigned. The H11b signal at δ 3.23 ppm appears as a double doublet with coupling constants of 12.0 and 9.5 Hz. The coupling constant of 12.0 Hz is also observed for H5a at δ 4.09 ppm, which allowed the 9.5 Hz coupling constant to be assigned as $J_{11b,11c}$. The proton signal at δ 2.87 ppm assigned as the H11c proton showed apparent coupling constants of 9.5 and 5.8 Hz. The coupling constant of 9.5 Hz is reflected in the H11b signal which confirmed the trans H11b, H11c relationship. Following this, and
knowing H11c was axial, the coupling constant 5.8 Hz could be assigned as \( J_{11c,3a} \), indicating the cis relationship of these protons. This was further confirmed by looking at the spectra of \( O \)-acetyl clivonine where H5 had been irradiated to show the ABX splitting pattern of methylene protons H3a and H4. Coupling constants were found to be \( J_{4\alpha,4\beta} = 15.5 \) Hz, \( J_{4\alpha,3a} = 3.5 \) Hz and \( J_{4\beta,3a} = 6.5 \) Hz, supporting the equatorial orientation of H3a.

Döpke and Jeffs undertook chemical degradation studies on clivonine (1) to further confirm the stereochemical relationship assigned from the \(^1\)H NMR studies.\(^9\) Firstly a von Braun reaction on clivonine (1) was carried out by treatment with cyanogen bromide to give a single product assigned as bromide 5 by mass spectrometric and \(^1\)H spectroscopic NMR studies (Scheme 1).

![Scheme 1: Döpke and Jeffs' degradation of clivonine (1) by a von Braun reaction.\(^9\) Reagents and Conditions: i) CNBr, benzene, \( \Delta \).](image)

From studying the \(^1\)H NMR spectrum of bromide 5 the proton signal at \( \delta \) 4.70 ppm with coupling constants of 2.5 and 11.5 Hz and the signal at \( \delta \) 3.62 ppm with coupling constants of 3.5 and 11.5 Hz could be assigned as H5a and H11b respectively. The downfield shift of H5a could be attributed to the new 1,3-diaxial interaction it experiences with the axial bromine at C11c. Irradiation of the proton signal at \( \delta \) 4.82 ppm caused the collapse of the H11b signal to a doublet with a coupling constant of 11.5 Hz, allowing the signal at \( \delta \) 4.82 ppm to be assigned as H11c. The smaller coupling of H11b could be assigned to \( J_{11b,11c} \) supporting the new cis orientation of these two protons. However, attempts to confirm the relative stereochemistry of H5 and H3a with further chemical transformations on bromide 5 were unsuccessful. A second degradation pathway was also explored in which clivonine (1) was transformed into the known compound \( \alpha \)-dihydrohippeastrine (6) (Scheme 2).
Scheme 2: Döpke and Jeffs' degradation of clivonine (1) to dihydrohippeastrine (6). Reagents and Conditions: i) POCl₃, py, RT. ii) KOH, EtOH, Δ. iii) H₂SO₄, Δ. iv) NH₄OH.

Treatment of clivonine (1) with phosphorus oxychloride gave the chloride 7, which when heated in a basic solution formed the alkoxide 8. S_N2 displacement of the chlorine gave epoxide 9 which, under acidic conditions, afforded α-dihydrohippeastrine (6). As the relative and absolute stereochemistry of α-dihydrohippeastrine (6) had previously been assigned by the correlation of hippeastrine (10) with lycorine (11) (Figure 5), Döpke and Jeffs were able to confirm the absolute and relative stereochemistry of clivonine (1) as that depicted in Figure 2, page 7.

Figure 5: Structures of hippeastrine (10) and lycorine (11).

Shortly after Döpke and Jeffs had confirmed the relative and absolute stereochemistry of clivonine (1) its 13C NMR spectra was assigned by Gatti. In the lowfield region (> δ 90 ppm) the methylenedioxy peak showed a characteristic resonance at δ 130 ppm, and the carbonyl carbon of the lactone moiety was assigned as the resonance at ~ 160 ppm. The aryl carbons were firstly distinguished between CH and C' by looking at the off resonance multiplicity, and the positions of the signals assigned by comparisons with model systems. In
the highfield region the N-Me peak was easily assigned as the quartet at δ 42-46 ppm. The off resonance decoupling only gave a rough separation of the aliphatic CH and CH₂ groups and so single-frequency decoupled proton spectra were used. Firstly irradiation of H5, H5a and H11c resulted in the collapse of the ¹³C doublets at δ 68.5, 82.8, and 70.2 ppm respectively, allowing for the remaining two CH groups of C11b and C3a to be assigned as the strong signal at δ 34.0 ppm. Irradiation of the C4 CH₂ signal showed coalescence of the two triplets at δ 31, therefore one of these signals must be from C4, the other being assigned as C3. The final methylene group of C2 could therefore be assigned as the signal at δ 53.9, due to deshielding by nitrogen.

1.1.3. Irie’s Synthesis of Clivonine (1)

The first and only synthesis of (±)-clivonine (1) prior to the work described in this thesis was achieved by Irie in 1973.¹⁴ The synthesis consists of 17 steps with an overall yield of 0.43% starting from piperonal (Scheme 3).

![Scheme 3](image)

Scheme 3: Irie’s synthesis of clivonine (1) part 1. Reagents and conditions: i) Ac₂O, reflux, 4 h. ii) NaOH (aq). iii) Ac₂O, reflux, 12 h. iv) MeOH₂, benzene. v) SOCl₂, benzene, reflux, 1 h. vi) NaN₃, water, acetone, 1 h. vii) Benzene. viii) MeOH, reflux.

The synthesis starts with the cycloaddition of fumaric acid (12) and 3,4-methylenedioxyphenyl allyl carbinal (13) in boiling acetic anhydride, which gives a mixture of stereoisomeric anhydrides 14a and 14b and small amount of anhydride 14c. Both 14a and 14b were hydrolysed with NaOH followed by re-cyclisation to give the same trans-cis anhydride 14c. Treatment with methanol (1 equiv.) in benzene then gave the half esters 15a and 15b in a ratio of 7:3. Half ester 15a was converted to the acid chloride with thionyl chloride in benzene, which gave azide 16 after treatment with sodium azide. Curtius
rearrangement of azide 16 in refluxing benzene, followed by heating the resultant isocyanate in methanol gave urethane 17. The acid 18 obtained by hydrolysis of urethane 17 was subjected to the Arndt-Eistert homologation to form diazoketone 19 (Scheme 4).

Scheme 4: Irie’s synthesis of clivonine (1) part 2. Reagents and Conditions: i) HCl(10%)/AcOH. ii) SOCl₂, benzene, py, RT, 16 h then CH₂N₂ in ether, RT, 1 h. iii) Silver benzoate, Et₃N, MeOH, 40 °C, 4 h. iv) HCl(10%)/AcOH. v) Ac₂O, reflux, 2 h. vi) chloromethyl methyl ether, ZnCl₂, AcOH, RT, 16 h. vii) AgOAc, AcOH, Ac₂O, RT, 5 h. viii) LiAlH₄, ether. ix) OsO₄, py, ether, RT, 2 d. x) Na₂SO₃, 50% aq EtOH, reflux, 4 h. xi) 3% H₂SO₄, H₂O bath, 3 h. xii) MnO₂, CHCl₃, RT, 16 h.

The diazoketone 19 then underwent a Wolff rearrangement after treatment with silver benzoate and triethylamine. These conditions are those reported in the 1979 full paper on this synthesis; the Wolff rearrangement reported in the 1973 communication using just silver oxide apparently gave irreproducible results.¹⁵ The homoester 20 was hydrolysed with hydrochloric acid in acetic acid, and treatment of the resultant acid with acetic anhydride gave the imide 21. The imide 21 was treated with chloromethyl methyl ether in acetic acid in the presence of zinc chloride. The chloro methyl product was then treated with silver acetate in acetic acid and acetic anhydride to give benzylic acetate 22. Acetate 22 was reduced to the amino alcohol with lithium aluminium hydride in ether and then oxidised with osmium
tetroxide which, following work-up with sodium sulfite, gave a mixture of diastereomeric triols (±)-tetrahydroclivonine (4) and (±)-tetrahydroclividine (23) in a 1:1 ratio. (±)-Tetrahydroclividine (23) was crystallised from this mixture using acetone, whilst column chromatography on alumina of the mother liquor allowed for the separation of (±)-tetrahydroclivonine (4). Treatment of these triols with dilute sulfuric acid followed by oxidation with manganese dioxide gave (±)-clivonine (1) and (±)-clividine (24). Characterisation was based upon comparison with an authentic sample of isolated (+)-clivonine (1).

1.1.4. Biosynthesis of the Amaryllidaceae

Biosynthetically the Amaryllidaceae alkaloids are all derived from a common bis-phenol precursor, norbelladine (25) itself derived from tyrosine and phenylalanine (Scheme 5).

![Scheme 5: Biosynthesis of norbelladine (25).](image)

This concept was first proposed by Barton in 1957 when he hypothesised that the key diversifying step in the biosynthesis of many alkaloids arises from an intramolecular oxidative phenolic coupling. He used the alkaloids of the Amaryllidaceae to illustrate his ideas. Battersby subsequently showed the incorporation of both labelled tyrosine and phenylalanine into lycorine (11) (Scheme 6). When Narcissus plants were fed with DL-[2-14C]tyrosine or Nerine bowdenii plants fed with DL-[3-14C]tyrosine the lycorine (11) isolated was radioactive at the C2 and the C3 positions respectively. This gave proof that tyrosine made up one portion of the carbon skeleton and also showed that the remaining carbon skeleton was not derived from tyrosine. When Nerine bowdenii plants were fed DL-[3-14C]phenylalanine incorporation of the labelled atom was found solely at C7.
Scheme 6: Battersby’s feeding studies to show incorporation of tyrosine and phenylalanine during the biosynthesis of lycorine (11).\textsuperscript{17}

However, Barton’s theory was unable to account for the biosynthesis of the tazettine (26) and lycorenine (27) subclasses, which prompted him to originally suggest that an intermolecular phenolic coupling must occur for these classes of compounds.\textsuperscript{16} In 1960, however, Barton extended his hypothesis to include these structural classes, proposing that the key intramolecular coupling does occur, however, subsequently a bond must break in the haemanthamine (28) and lycorine type progenitor (29) to give the tazettine (26) and lycorenine type (30) carbon skeletons respectively following re-ring-closure (Scheme 7).\textsuperscript{18-19}

Scheme 7: Barton’s proposed ‘Ring-Switch’ from a lycorine progenitor 29 to lycorenine type product 30 and haemanthamine (28) to tazettine (26).\textsuperscript{18-19}

From norbelladine (25) o,p-phenolic coupling and subsequent processing leads to a lycorine type structure (29), whilst a p,p-phenolic coupling and subsequent processing gives haemanthamine (28). Benzylic oxidation of these precursors gives lactamol 31 and haemanthidine (32). For the lycorenine series, bond cleavage is followed by a 180° rotation, and finally a second benzylic oxidation affords the lycorenine type structure (30) (Scheme 7). For the tazettine (26) series, after bond cleavage a 90° rotation occurs to give pretazettine (33). At this point it is necessary to highlight that until 1968 tazettine (26) was thought to be a
natural product. However, whilst undertaking some isolation experiments Wildman
discovered that tazettine (26) was in fact the product of a intramolecular cross Cannizzaro
rearrangement of the natural product pretazettine (33) (see Section 1.1.5.3. Biomimetic Ring-
Switch).\textsuperscript{20}

The biosynthetic link between haemanthamine (28), and tazettine (26) was supported by
Wildman, when high yields of haemanthamine (28) were obtained from \textit{Sprekelia formosissima}
early in the flowering season, whilst yields of tazettine (26) where higher later in
the season.\textsuperscript{21} Wildman then went on to demonstrate that this biosynthetic sequence of
reactions leading from haemanthamine (28) to tazettine (26) via haemantidine (32) do
indeed occur \textit{in vivo} by injecting tritiated \textit{[8-\textsuperscript{3}H]}haemanthamine (34) into the stems of the
flowering plant \textit{Sprekelia formosissima}. Samples taken over 90 days confirmed the sequence
of events to give \textit{[8-\textsuperscript{3}H]}pretazettine, which upon isolation converted to \textit{[8-\textsuperscript{3}H]}tazettine (35)
(Scheme 8).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme8}
\caption{Wildman’s biosynthetic conversion of \textit{[8-\textsuperscript{3}H]}haemanthamine (34) to \textit{[8-\textsuperscript{3}H]}tazettine (35).\textsuperscript{21}}
\end{scheme}

Wildman also demonstrated the interconversion between the lycorine (11) and lycorenine
(27) class using isotopic labelling studies.\textsuperscript{22} Thus, King Alfred daffodils were fed with tritium
labelled \textit{[8-\textsuperscript{3}H]}norpluviine (36), and after 18 days the alkaloid \textit{[8-\textsuperscript{3}H]}lycorenine (37) was
isolated with 79\% of the specific molar activity of the original \textit{[8-\textsuperscript{3}H]}norpluviine (36)
(Scheme 9).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme9}
\caption{Wildman’s biosynthetic conversion of \textit{[8-\textsuperscript{3}H]}norpluviine (36) to \textit{[8-\textsuperscript{3}H]}lycorenine (37).\textsuperscript{22}}
\end{scheme}
1.1.5. Synthetic Strategy and Project Aims

The synthesis of our clivonine progenitor, lycorine-type iminium salt 38, is via a route analogous to that developed for the total synthesis of (+)-trianthine (39) by Oppolzer in 1994, utilising a retro-Cope elimination as a key step (Scheme 10).²³

![Scheme 10: Oppolzer’s synthesis of (+)-trianthine (39)²³. Reagents and Conditions: i) ArBr, Et₂O/THF (5:3), n-BuLi, -78 °C, 30 min, then 40, Et₂O, -78 °C → 0 °C, 3 h, then Ac₂O, 0 °C → RT, 30 min. ii) SME₂, THF, CuBr·SMe₂, vinyl magnesium chloride, -30 °C, 30 min, then, acetate 41. -30 °C → RT, 4 h. iii) 9-BBN, THF, 50 °C, 15 h, then H₂O, NaOH (20%aq. soln.), H₂O₂ (30%aq. soln.), RT, 3 h. iv) DMSO, oxalyl chloride, CH₂Cl₂, -50 °C, 5 min, then Et₃N, RT, 1.5 h. v) NH₃·HCl, NaOAc·3H₂O, Et₂O, 78 °C, 17 h. vi) NaCNBH₃, methyl orange, MeOH, MeOH/HCl conc. (10:1), 2 h. vii) benzene, 80 °C, 70 h. viii) Raney-Ni, Et₂O, RT, 5 h. ix) Eschenmoser’s salt, 40 °C, 15 h. x) AcCl, MeOH, RT, 11 h.

Oppolzer’s synthesis of (+)-trianthine (39) begins with a stereospecific 1,2-addition of 1-bromo-3,4-(methylenedioxy)benzene to enone 40, with concomitant trapping with acetic anhydride to give acetate 41. An anti $S_N2'$ elimination of acetate 41 with vinyl magnesium bromide gave the trans-vinylcyclohexene 42 with inversion of the stereochemistry set up from the 1,2-addition. Hydroboration, followed by Swern oxidation gave the corresponding aldehyde, which was converted to the oxime and reduced to hydroxylamine 43. retro-Cope elimination of hydroxylamine 43 was performed in refluxing, degassed benzene for 70 h to give N-hydroxyl pyrrolidine 44, setting up the two final stereogenic centres in (+)-trianthine (39). Hydrogenolysis with Raney-Ni gave the pyrrolidine then Pictet-Spengler cyclisation with Eschenmoser’s salt, and finally acetonide deprotection gave (+)-trianthine (39) in an overall 24% yield over 10 steps.
As with Oppolzer’s (+)-trianthine (39) synthesis our synthesis of (±)-clivonine (1) starts with a stereospecific 1,2-addition of 1-bromo-3,4-(methylenedioxy)benzene to enone 40 followed by trapping with acetic anhydride to give acetate 41 (Scheme 11).

Scheme 11: Retrosynthetic analysis for our clivonine (1) synthesis.

The second key step is a stereospecific Ireland-Claisen rearrangement of acetate 41 to give acid 45. This reaction takes place with retention of the stereochemistry set up from the 1,2-addition in contrast with the inversion of stereochemistry seen after the S<sub>N</sub>2’ elimination in the (+)-trianthine (39) synthesis (cf. Scheme 10). Functional group interconversions transform acid 45 into oxime 46 to which a Borch reduction is carried out to give
hydroxylamine 47. The retro-Cope elimination of hydroxylamine 47 to $N$-hydroxyl pyrrolidine 48, as with the (+)-trianthine (39) synthesis, is stereospecific and sets up the final two stereogenic centres in the natural product. After hydrogenolysis, a Bischler-Napieralski cyclisation is carried out on the corresponding formamide to give our clivonine progenitor iminium salt 38 [cf. a Pictet-Spengler cyclisation which is carried out in the (+)-trianthine (39) synthesis]. Finally a biomimetic ring-switch converts our lycorine type precursor, iminium salt 38, to that of a clivonine type product lactol 49 via lactamol 50.

At the outset of the work described in this thesis, the above described synthesis had already been successfully carried through to the biomimetic ring switch step by a previous PhD student, Carles Giró Mañas [Spivey Group 2004-2008]. The final steps had been attempted and tentatively deemed to have been successful but, unfortunately, there was not enough material for conclusive characterisation and in any case the yields through these last key steps were very poor. 24 Therefore the first aim of the project was to repeat the synthesis up to iminium salt 38, and to develop a robust method of purification of this key intermediate. Once purified the final steps were to be repeated in a reproducible manner to give (±)-clivonine (1) which could be characterised in full.

The following sections introduce some of the key reactions involved in this synthesis in order to place the work in correct context.

1.1.5.1. The Ireland-Claisen Rearrangement.

The Ireland-Claisen rearrangement was discovered by Ireland in 1972 and is a suprafacial, concerted [3,3]-sigmatropic rearrangement of a silyl ketene acetal derived from an allylic ester to give a 3,4-unsaturated acid. 25 Ireland found that ester enolates formed according to the method developed by Rathke in 1971 26 underwent a Claisen reaction on warming. 27 He found that when the lithium enolates were quenched with trimethylsilylchloride at −78 °C, the resultant silyl ketene acetals rearranged readily to give clean, stereocontrolled products with minimal competition from the competing aldol reactions. Although a small amount of C-silylated product was generated under these conditions (2-6%), it was later shown that the use of tert-butyldimethylchlorosilane to quench the enolate gave predominately O-silylation. 28

The Ireland-Claisen rearrangement is a widely used reaction due to the predictability of the new double bond geometry and the stereochemistry around the new carbon carbon sigma bond formed. These predications can be made as it is known that the reaction proceeds through a chair like transition state. Whilst researching the stereochemical outcome of the
enolate formation Ireland found that when THF is used as the solvent the kinetically favoured Z-enolate was formed (Scheme 12).\textsuperscript{29-30}

\begin{align*}
\text{Scheme 12: Formation of the kinetically favoured Z-lithium enolate leading to the E-silyl ketene acetyl.}
\end{align*}

However when 23% HMPA was used as a co-solvent with THF the thermodynamically favoured \textit{E}-enolate was found to be the major product. (Scheme 13).

\begin{align*}
\text{Scheme 13: Formation of the thermodynamically favoured E-enolate.}
\end{align*}

The formation of the \textit{E}-enolate when 23% HMPA is added is due to the solvation of the lithium ion of LDA with HMPA causing a breakdown of the 6 membered transition state. When the lithium is tightly coordinated to the ester carbonyl oxygen in the absence of HMPA the \textit{R} group clashes with the bulky isopropyl group of LDA when in the axial position (i.e. 1,3-diaxial strain) and so prefers to be positioned in the favoured equatorial position giving rise to the \textit{Z}-enolate (\textit{cf.} Scheme 12). Due to the breakdown in the interaction between lithium and the ester carbonyl oxygen in the presence of HMPA there is no unfavourable interaction between the \textit{R} group and the LDA. The \textit{R} group therefore prefers to be positioned in the axial position to avoid \textit{A}^{1,2} strain with the OR\textsuperscript{1} group giving rise to the \textit{E}-enolate. This predictable enolate geometry allows for the predication of the stereochemistry at the new carbon centre following Ireland-Claisen rearrangement (Scheme 14).

\begin{align*}
\text{Scheme 14: Prediction of the stereochemistry around the new sigma bond following an Ireland-Claisen rearrangement.}
\end{align*}
In addition, Ireland demonstrated that the ratio of \((E):(Z)\)-lithium enolates was not always directly related in the ratio of the resultant silyl ketene acycls, a kinetic resolution occurs. Ireland proved this, in the case of the reaction in THF/15% DMPU, by carrying out a series of competitive trapping experiments, showing that the \((Z)\)-lithium enolates and corresponding \((E)\)-silyl ketene acetals are significantly more reactive than the \((E)\)-lithium enolates and \((Z)\)-silyl ketene acetals. This suggests that the initial ratio of the \((E)\)- and \((Z)\)-lithium enolates arises from a kinetically controlled enolisation (as described above), to which a kinetic resolution occurs with addition of a trapping agent (such as DMSO or excess ester) to selectively react with the \((Z)\)-lithium enolate and increase the relative amount of the \((E)\)-lithium enolate formed.\(^{31}\)

Although the predictability of the reaction products is a useful tool, in our synthesis this aspect of stereocontrol is not important. The stereochemistry of the molecule is already set up from the 1,2-addition (cf. Scheme 11) and as the [3,3] sigmatropic rearrangement is suprafacial the stereochemistry at the new stereocentre must be retained. This reaction therefore sets up the correct stereochemistry for the subsequent retro-Cope elimination reaction (Scheme 15).

**Scheme 15:** Ireland-Claisen rearrangement of acetate 41 to acid 45.

### 1.1.5.2. The retro-Cope Elimination

The retro-Cope elimination was first discovered serendipitously by House in 1976 and later independently by Oppolzer in 1979 and can be described as a suprafacial concerted thermal cyclisation of an unsaturated hydroxylamine to its corresponding pyrrolidine or piperidine N-hydroxyl or N-oxide derivatives, although recently intermolecular variants have been developed, see later.\(^{32}\)

House first reported this type of reaction when during attempts to synthesise 1,3-dioximes 51 from the corresponding 1,3-diketones 52 a bicyclic side product of the structure 53 was isolated (Scheme 16).\(^{33}\)
Scheme 16: House’s serendipitous discovery of the retro-Cope elimination.\textsuperscript{33}

House extended his investigations by synthesising simpler hydroxylamines and found them to cyclise smoothly when allowed to stand overnight or when heated on a steam bath. House proposed that the reaction proceeded \textit{via} a radical mechanism (Scheme 17).

Scheme 17: House’s proposed retro-Cope elimination mechanism \textit{via} a radical process.\textsuperscript{33}

In 1978 Black and Doyle reported more examples of this reaction, demonstrating that terminally substituted alkenes failed to cyclise, even under forcing conditions (Scheme 18).\textsuperscript{34}

In this publication they also demonstrated that the addition of radical inhibitors such as hydroquinone, phenol and aniline did not affect the rate of cyclisation, casting doubt upon House’s predicated radical mechanism.

Scheme 18: Black and Doyle’s examples of the retro-Cope elimination.\textsuperscript{34}

Oppolzer first came across the reaction in 1979 when he found that a hydroxylamine intermediate for his studies towards [1,3]-dipolar cycloadditions was not stable and underwent a facile retro-Cope elimination to the cyclic hydroxylamine.\textsuperscript{35}
Although the discovery of the reaction was made in the mid 1970s it was not until the early 1990s that Ciganek and Oppolzer separately proved the mechanism and demonstrated the synthetic utility of the retro-Cope elimination.

Similarly to both House and Oppolzer, Ciganek first encountered the retro-Cope elimination serendipitously. When reacting 2,2-diphenyl-4-pentenal (54) with N-methylhydroxylamine the desired nitrene 55 was only isolated in 45% yield, the major product (51% yield) was found to be cyclised product N-hydroxyl pyrrolidine 56, the retro-Cope elimination product of hydroxylamine 57 (Scheme 19).36

Ciganek expanded on the scope of this reaction, firstly showing that both 5 and 6 membered N-oxides could be obtained from their corresponding hydroxylamines (Scheme 20).36-37

Following on from work carried out by Black and Doyle34 he also investigated the effect of substitution on the double bond, demonstrating that substrates with two distal substituents on the alkene cyclised very slowly. This suggested strongly that the radical mechanism originally proposed by House was incorrect, considering the radical intermediate should be stabilised by the two distal substituents. Ciganek proved that the reaction proceeded via a concerted mechanism by showing that O-deuterated hydroxylamine 58 gave a single, unassigned isomer of the corresponding product, N-oxide 59 (Scheme 21).36-37
Oppolzer finally provided definite proof of a concerted, suprafacial mechanism by reacting both (E)- and (Z)-isomers of an arylhydroxylamine 60 to give single, assigned epimeric products (Scheme 22).³³

Hydroxylamines 60a and 60b were heated in degassed benzene to yield the N-hydroxyl pyrrolidines 61a and 61b with no contamination by the opposite epimer. This supported Ciganek’s theory that the mechanism is concerted and proved it to be suprafacial.

Most recently, the group of Beauchemin has extended the scope of the retro-Cope elimination reaction significantly by showing that intermolecular variants are possible. Details of this work will be reviewed in Chapter 3.

As indicated previously, our synthetic strategy for the synthesis of clivonine (1) is closely related to the first total synthesis of (+)-trianthine (39) carried out by Oppolzer in 1994.³³ This synthesis constitutes a rare example of the synthetic utility of the retro-Cope elimination reaction (cf. Scheme 10). In our synthesis, attack of the hydroxylamine moiety must occur from the top face of the alkene, cis to the acetonide [unlike in the case of (+)-trianthine (39) where attack is anti to this group] to give the observed stereochemistry at the C11b and C11c centres (Scheme 23).
This facial selectivity is ensured by the two carbon chain linking the hydroxylamine to cyclohexene ring A which is sufficiently short to only allow attack to give a cis-fused indolizidine ring system. In other words, the stereocentre at C3a set up by the Ireland-Claisen rearrangement also dictates the two stereocentres established in the subsequent retro-Cope elimination. These two newly formed stereocentres are also set up with the correct stereochemistry required in clivonine (1) after the biomimetic ring-switch.

1.1.5.3. Biomimetic Ring-Switch

The biomimetic ring-switch is the final sequence of steps in our envisaged synthesis and allows for the conversion of the lycorine-type precursor lactamol 50 into the clivonine-type product lactol 49 (Scheme 24).

![Scheme 24: Biomimetic ring-switch of lactamol 50 to lactol 49.](image)

As discussed previously (Section 1.1.4, Biosynthesis of the Amaryllidaceae) this type of interconversion was first proposed by Barton in 1960, and since then biosynthetic interconversions between Amaryllidaceae alkaloid classes has been studied extensively.19,21-22

Biomimetically, the interconversion between the 6-hydroxy-5,10b-ethanophenthridine and the [2]benzopyrano[3,4-c]indole ring systems has already been documented.38-40 Wildman has demonstrated the biomimetic conversion of haemanthidine (32) to tazettine (26) by treatment with methyl iodide followed by dilute base. (Scheme 25).41

![Scheme 25: Wildman’s biomimetic conversion of haemanthidine (32) to tazettine (26).](image)  
Reagents and Conditions: i) Mel, aq. NaOH.
It was proposed by Wildman that the biomimetic ring-switch was followed immediately by an intramolecular hydride shift. This proved to be correct as determined by carrying out the interconversion of 6-hydroxycrinamine-6,11-\(d_2\) (62) to criwelline-8-\(d_2\) (63) (Scheme 26).\(^{42}\)

\[ \text{Scheme 26: Wildman's synthesis and interconversion of 6-hydroxycrinamine-6,11-\(d_2\) (62) to criwelline-8-\(d_2\) (63).} \]

Wildman synthesised the deuterated compound 62 by taking 6-hydroxycrinamine (64) and firstly oxidising the bridgehead hydroxyl group to the corresponding ketone with manganese dioxide, oxidising the lactamol to the corresponding lactam with acidic chromium trioxide in DMF containing a trace of sulfuric acid and then reducing this ketolactam with lithium aluminium deuteride. The resulting 6-hydroxycrinamine-6,11-\(d_2\) (62) was treated with methyl iodide to give the methiodide which underwent the ring switch on treatment with dilute base.

Further studies on the mechanism of the Cannizzaro-type rearrangement following ring-switch were carried out in the haemanthamine (28) to pretazettine (33) to tazettine (26) series.\(^\text{20}\) Wildman showed that the mechanism for the rearrangement of pretazettine (33) to tazettine (26) was that of an intramolecular Cannizzaro-type rearrangement (Scheme 27).

\[ \text{Scheme 27: Wildman's mechanism for the rearrangement of pretazettine (33) to tazettine (26).}\]
The driving force of the rearrangement is the release of the ring strain of the trans B-D fused ring system in pretazettine (33) to give the aldehyde intermediate 65. Hydride shift to give the ketone 66 followed by an intramolecular crossed-Cannizzaro reaction with subsequent hemiketal formation gives the less strained cis B-D fused ring system of tazettine (26). Wildman followed this up with synthetic studies to prove that pretazettine (33) is the original natural product and not tazettine (26).\textsuperscript{43}

Biosynthetically, the interconversion between the lycorine class (\textit{cf. 11}) and the lycorenine class (\textit{cf. 27}) has been demonstrated by Wildman (\textit{cf.} Scheme 9, Section 1.1.4). synthetically, Mizukami has achieved the overall conversion of a lycorine-type ring system to a clivonine-type one via a von Braun degradation. Thus, $\alpha$-dihydrocaranine (67) was converted to clivonine-type product 68 by treatment with cyanogen bromide in boiling benzene (Scheme 28).\textsuperscript{44}

![Scheme 28: Mizukami’s conversion of $\alpha$-dihydrocaranine (67) to clivonine-type product 68. Reagents and Conditions: i) CNBr, benzene, reflux, 3 h.](image)

Following on from Mizukami’s work Kotera achieved the synthetic conversion of diacetyl-lycorine (69) into hippeastrine (10) (Scheme 29).\textsuperscript{45}

![Scheme 29: Kotera’s conversion of diacetyl-lycorine (69) into hippeastrine (10). Reagents and conditions: i) CNBr, benzene, reflux, 3 h. ii) 5% EtOH/KOH, RT, 3 h. iii) 3% HCl (aq), reflux, 1 h. iv) 85% formic acid, 37% formalin, reflux, 6 h. v) Ac$_2$O, py. vi) CrO$_3$, py, RT, 24 h.](image)

Kotera used the same von Braun degradation conditions as Mizukami to give two ring opened products 70 and 71. Further synthetic manipulation of compounds 70 and 71 gave hippeastrine (10).
Wildman also attempted to effect the biomimetic interconversion of a lycorine derivative to a hippeastrine derivative. Thus, he converted diacetyl-lycorine (69) to diacetyl-7-oxolycorine (72) and then attempted a lactam half-reduction to give hemiacetal 73 which would was hoped to undergo the desired ring switch on treatment with methyl iodide. Wildman was however unable to find suitable conditions for the final reduction to access hemiacetal 73 or effect the ring-switch (Scheme 30).

Scheme 30: Wildman’s attempt to convert diacetyl-lycorine (69) to hemiacetal 73.²² Reagents and Conditions:
   i) KMnO₄.

Our synthesis of clivonine (1) shows for the first time the biomimetic interconversion between the lycorine (11) and lycocereine (27) classes of Amaryllidaceae alkaloids, supporting for the first time the biosynthetic hypothesis demonstrated by Barton 50 years ago.⁴⁶

1.2. Results and Discussion

1.2.1. Synthesis of (±)- and (+)-Enone 40

The first target molecule synthesised was enone 40 (Scheme 32), which was accomplished using two methods. The first route started from meso-diol 74 and furnished the racemic product whilst the second route started from halo-diol 75 or 76 to provide the enantiomerically pure product. Diols 74, 75 and 76 are obtained from the microbial oxidation of benzene or the respective halobenzene by the bacteria Pseudomonas putida (Scheme 31).

Scheme 31: Microbial oxidation of arenes.

The first stable cis-cyclohexadienediol was isolated by Gibson in 1968, and since then many compounds of these type have been obtained in this way.⁴⁷-⁴⁹
The first route explored was the synthesis of (+)-enone 40 via the Borchardt-Hudlicky route (Scheme 32).\textsuperscript{50-52}

Scheme 32: Synthesis of (+)-enone (40) via the Borchardt-Hudlicky route. Reagents and Conditions. i) DMP (6.0 equiv.), pTsOH-H\textsubscript{2}O (0.2 equiv.), CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 1 h, 77%. ii) m-CPBA (1.0 equiv.), CH\textsubscript{2}Cl\textsubscript{2}, 0 °C → RT, 16 h. iii) Pd\textsubscript{2}(dba)\textsubscript{3} (10 mol%), DPPE (20 mol%), m-CBA (~ 1.0 equiv.), THF, RT, 2.5 d, 64% (over two steps).

The first step was the protection of meso-diol 74 using DMP and p-tolyl sulfonic acid to give acetonide 77 in 77% yield. Epoxidation of one of the double bonds of diene 77 diastereoselectively on the face opposite to the acetonide was achieved using 1 equivalent of m-chloroperbenzoic acid (m-CPBA) to give epoxide 78. The subsequent palladium catalysed rearrangement gave (+)-enone 40 in 64% yield over the two steps from acetonide 77.

The palladium catalysed rearrangement was developed by Banwell and Hudlicky whilst studying different transformations that could be achieved with compounds such as epoxide 78. They found that when epoxide 78 was reacted with phthalimide in the presence of Pd(PPh\textsubscript{3})\textsubscript{4} two products were isolated, the expected syn-1,2-addition product, amino alcohol 79 in 38% yield and a second product assigned as enone 40 in 45% yield (Scheme 33).\textsuperscript{52}

Scheme 33: Banwell and Hudlicky’s reaction of epoxide 78 with phthalimide.\textsuperscript{52} Reagents and Conditions: i) phthalimide (1.0 equiv.), Pd(PPh\textsubscript{3})\textsubscript{4} (10 mol%), THF, 20 °C, 72 h.

The isolated yield of enone 40 could be increased up to 70% using [Pd(DPPE)\textsubscript{2}], however rearrangement would only occur in the presence of phthalimide or benzoic acid.\textsuperscript{52} Giró Mañas showed that the reaction proceeded in good yield when m-chlorobenzoic acid (m-CBA), the by product of the epoxidation, was used as the acid source.\textsuperscript{24} Therefore, the epoxide 78 was not isolated, and \textsuperscript{1}H NMR analysis was used to estimate the amount of m-CBA in the reaction mixture; 66% on this occasion. The crude material was therefore
submitted to the palladium rearrangement conditions. The proposed mechanism for this rearrangement is outlined below (Scheme 34).

![Scheme 34: Proposed mechanism for the palladium catalysed epoxide rearrangement.](image)

The mechanism proposed for this process starts with the diastereoselective nucleophilic addition of Pd(0) to the vinyl epoxide at the C2 position to give a \( \pi \)-allyl palladium species on the same face as the acetonide. Subsequent palladium mediated 1,4 hydride transfer would then give an \( \eta^2 \) Pd(II) ketone intermediate which upon reductive elimination would give (±)-enone 40.

The second route explored was the synthesis of (+)-enone 40 via a modified Oppolzer-Hudlicky route (Scheme 35).23,50,53

![Scheme 35: Synthesis of (+)-enone 40 via the modified Oppolzer-Hudlicky route.](image)

Similarly to the first route discussed, the first step of the synthesis was acetonide protection of the chloro and bromo-diols 75 and 76 with DMP and catalytic \( p \)-tolyl sulfonic acid to give acetonides 80 and 81 in 96% and 97% yields respectively. Photooxidation of acetonides 80 and 81 to give endoperoxides 82 and 83 was carried out in CCl₄, with TPP as the
photosensitiser and was complete within 2-2.5 h for both substrates. However, as reported by Hudlicky, we found that the chloro and bromo-acetonides 80 and 81 were very susceptible to dimerisation via a Diels-Alder cyclisation when neat at RT or upon standing in solution for prolonged periods of time (Scheme 36).

![Scheme 36: Diels-Alder dimerisation of acetonides 80 and 81.](image)

Due to this facile dimerisation the photooxidation had to be carried out at a relatively low concentration and kept at 0 °C throughout irradiation. It was found that the dimerisation of bromo acetonide 81 occurred more readily than chloro acetonide 80, therefore future reactions were only carried out on chloro acetonide 80. Due to the explosion hazard associated with endoperoxides, after irradiation the endoperoxide 82 was not isolated but was instead taken through to acetate 84 as a crude reaction mixture.

Hudlicky has reported the reduction of endoperoxide 82 to hydroxyenone 85 with thiourea to proceed in a good yield. However, previous members of the Spivey group working on this chemistry found hydroxyenone 85 to be very sensitive to the thiourea reaction side products and to chromatography on silica gel. Giró Mañas attempted to solve this problem by in situ protection of hydroxyenone 85 as its acetate 84, however, this was not successful due to the insoluble nature of thiourea in non-alcoholic solvents. The development of a solid supported thiourea resin however allowed for the reduction of endoperoxide 82 to hydroxyenone 85 to be carried out in CH₂Cl₂. After filtration of the resin the solution could be treated directly with acetic anhydride, triethylamine and catalytic DMAP to give the more stable acetate 84 in 85% yield from endoperoxide 82.

The thiourea resin was easily prepared by refluxing commercially available aminomethylated polystyrene 86 with isothiocyanate 87 in dry Et₂O to form the desired thiourea functionalised resin 88 as confirmed by IR spectroscopy (Scheme 37).
Once the photooxidation of acetonide 80 to endoperoxide 82 was complete the reaction mixture was concentrated in vacuo and immediately re-dissolved in CH₂Cl₂. This solution was then added to a pre-swelled suspension of thiourea resin 88 in CH₂Cl₂ at 0 °C and stirred vigorously for 45 min, during which time full consumption of endoperoxide 82 was observed by TLC analysis. The reaction mixture was filtered and treated with acetic anhydride to give acetate 84 in 65% yield from acetonide 80 after purification (cf. Scheme 35).

The final step towards (+)-enone 40 was the deacetoxylation of acetate 84, a reaction developed by Oppolzer for the total syntheses of (±)-α-lycorane and (+)-trianthine (39). Treatment of acetate 84 with 1,1,3,3-tetramethyldisiloxane in the presence of Pd(PPh₃)₄ in refluxing CH₂Cl₂ for 22 h saw complete consumption of acetate 84, followed by isomerisation of the resultant β,γ-ketone to give exclusively (+)-enone 40 in 43% yield. This yield was not as high as expected [Giró Mañas isolated (+)-enone 40 in 78%24] however all efforts to improve the yield for this reaction were unsuccessful.

The synthesis of clivonine (1) was attempted on both (+)- and (±)-enone 40. However, due to the limited amount of enantiomerically pure material obtained, the synthesis to give (+)-clivonine (1) could not be completed. As the route to (±)-enone 40 was shorter (3 steps vs. 4 steps) and higher yielding (50% from diol 74 vs. 27% from diol 75) in comparison to the route to (+)-enone the synthesis was completed using (±)-enone 40 to give (±)-clivonine (1).

1.2.2. Synthesis of Oxime 46

With (±)-enone 40 in hand, the first steps towards oxime 46 were to be 1,2-addition of lithiated aryl bromide 89 to give the Ireland-Claisen precursor, acetate 41. The Ireland-Claisen rearrangement would then give acid 45 which would be methylated with diazomethane to give the methyl ester 90 (Scheme 38). This chemistry had been previously optimised by Giró Mañas.24
Scheme 38: Synthesis of methyl ester 90. Reagents and Conditions: i) t-BuLi (1.5 M, 2.05 equiv.), THF, -78 °C, 1 h. ii) enone 40 (1.0 equiv.), THF, -78 °C, 2 h. iii) Ac₂O (2.5 equiv.), 0 °C → RT, 16 h. iv) DIPA (1.75 equiv.), n-BuLi (1.75 equiv.), THF, -78 °C, 30 min. v) TMSCl (3.0 equiv.), THF, -78 °C → 80 °C, 16 h. vi) Diazald (3.0 equiv.), KOH (3.5 equiv.), carbitol:water:Et₂O (3:1:1), Et₂O, 50 °C, 16 h, 44% (over three steps from enone 40).

Lithium halogen exchange on aryl bromide 89 with t-BuLi was carried out before adding (+)-enone 40. The resultant alcohol was quenched with acetic anhydride to give acetate 41 which was taken through crude to the Ireland-Claisen rearrangement. Enone formation was achieved using LDA made in situ with diisopropylamine and n-BuLi, followed by subsequent enone trapping with freshly distilled TMSCl to give the silyl ketene acetyl. The reaction mixture was heated to 80 °C to allow for the rearrangement to give acid 45. Methylation with diazomethane made in situ by treatment of Diazald® with potassium hydroxide was then carried out to give methyl ester 90, in an overall yield of 47% over the three steps.

The final steps of the synthesis of oxime 46 were the reduction of methyl ester 90 to aldehyde 91, followed by oxime formation with hydroxylamine hydrochloride. When Giró Mañas conducted these experiments the reduction of methyl ester 90 to aldehyde 91 was achieved in one step using DIBAL-H in 84% yield. Following these conditions the reaction was carried out at -78 °C and 1.1 equivalents of DIBAL-H (1 M solution in hexanes) were used in order to prevent the over reduction to alcohol 92. However, after 3 h the reaction mixture was found to contain both aldehyde 91 and alcohol 92 in 40% and 15% yields respectively (Scheme 39).
In order to prevent the formation of the alcohol the reaction was repeated with extra care being taken to ensure the reactants and reaction mixture were kept at -78 °C at all times. Unfortunately, after 2 h TLC analysis of the reaction mixture showed that starting material, aldehyde 91 and alcohol 92 were all present. As the DIBAL-H reduction was proving to be difficult to achieve selectively, it was decided that to save time and material, it would be more productive to reduce methyl ester 90 to alcohol 92, then oxidise to give aldehyde 91 (Scheme 40). Although this added one step to the synthesis it avoided the separation of the aldehyde from the alcohol by chromatography.

**Scheme 39:** Reduction of methyl ester 90 with DIBAL-H. *Reagents and Conditions:* i) DIBAL-H (1 M, 1.1 equiv), toluene, -78 °C, 3 h, 15% 92, 40% 91.

Reduction of methyl ester 90 to alcohol 92 was achieved by the addition of 7 equivalents of lithium borohydride (2.0 M solution in THF) to a solution of methyl ester 90 in THF over 40 h to afford alcohol 92 in 86% yield. The oxidation of alcohol 92 to aldehyde 91 was then explored.

**Scheme 40:** Reduction of methyl ester 90 to alcohol 92 followed by oxidation to aldehyde 91. *Reagents and conditions:* i) LiBH₄ (2.0 M, 7.0 equiv.), THF, RT, 40 h, 86%. ii) DMSO (2.0 equiv), oxalyl chloride (2.2 equiv.), NEt₃ (3.0 equiv.), THF, -78 °C. iii) Dess-Martin periodinane (3.0 equiv.), CH₂Cl₂, 0 °C → RT, 23.5 h.
material was recovered. It is unclear why this reaction was not successful; however it was not explored any further.

The Dess-Martin oxidation of alcohol 92 to aldehyde 91 was the second route investigated. Pleasingly, after just 1 h of stirring alcohol 92 with Dess-Martin periodinane in CH₂Cl₂ at RT 100% conversion to aldehyde 91 was observed by ¹H NMR. As aldehydes can be quite sensitive, aldehyde 91 was not purified at this stage and was taken onto the oxime formation step crude (Scheme 41).

![Scheme 41: Formation of oxime 46 from aldehyde 91. Reagents and conditions: i) NH₂OH·HCl (2.0 equiv.), NaOAc (2.5 equiv.), CH₂Cl₂, MeOH, RT, 1 h, 67% from methyl ester 90.]

Conversion of aldehyde 91 to oxime 46 was carried out by adding hydroxylamine hydrochloride and sodium acetate to a solution of aldehyde 91 in CH₂Cl₂. After 1 h of stirring the reaction showed no progress by TLC. When this reaction had been undertaken by Giró Mañas it was found that undesired products were formed when protic solvents such as methanol were used. However, these oxime forming reactions are normally carried out in such solvents due to the lack of solubility of NH₂OH·HCl in aprotic solvents such as CH₂Cl₂. When a small amount of MeOH was added to the reaction mixture the complete formation of the product was seen after just 1 h stirring at RT. This is most likely due to a small amount of reagent being dissolved by the MeOH allowing the reaction to occur, finally giving oxime 46 in 67% yield from methyl ester 90 after purification (1:1.2 cis:trans by ¹H NMR, the stereoisomers have been separated for characterisation, however separation was not carried out routinely throughout the synthesis and oxime 46 was taken through subsequent steps as a mixture of stereoisomers).
1.2.3. Synthesis of Iminium Salt 38

The next step towards synthesising our clivonine progenitor, iminium salt 38, was the Borch reduction of oxime 46 to give hydroxylamine 47. This was to be followed immediately by the retro-Cope elimination to give the N-hydroxyl pyrrolidine 48 (Scheme 42).

Scheme 42: Conversion of oxime 46 to N-hydroxyl pyrrolidine 48. Reagents and Conditions: i) NaCNBH₃ (2.0 equiv.), HCl/MeOH (1:10), MeOH, 0 °C → RT. ii) toluene, 80 °C, 14 h.

From work conducted previously by Giró Mañas it was anticipated that the Borch reduction of oxime 46 to hydroxylamine 47 would prove to be a delicate reaction. This reaction was attempted several times before a reproducible method was achieved (Table 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Purification of 47</th>
<th>Conc. of 47 in toluene</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCl/MeOH (1:10) slow addition</td>
<td>Flash Chromatography</td>
<td>0.016 M</td>
<td>Hydroxylamine 47 formed in 52% yield. N-hydroxyl pyrrolidine 48 formed. However, not detected until further analysis of the ¹H NMR was undertaken.</td>
</tr>
<tr>
<td>2</td>
<td>HCl/MeOH (1:10) slow addition</td>
<td>Flash Chromatography</td>
<td>0.012 M</td>
<td>Hydroxylamine 47 formed in 53% therefore N-hydroxyl pyrrolidine 48 formed. However, not detected until further analysis of the ¹H NMR was undertaken.</td>
</tr>
<tr>
<td>3</td>
<td>HCl/MeOH (1:10) fast addition</td>
<td>Flash Chromatography</td>
<td>0.012 M</td>
<td>No Product</td>
</tr>
<tr>
<td>4</td>
<td>HCl/MeOH (1:10) fast addition</td>
<td>Flash Chromatography</td>
<td>0.011 M</td>
<td>No Product</td>
</tr>
<tr>
<td>5</td>
<td>HCl/MeOH (1:10) slow addition</td>
<td>No Purification</td>
<td>0.015 M</td>
<td>Quantitative formation of hydroxylamine 47, therefore N-hydroxyl pyrrolidine 48 formed successfully.</td>
</tr>
</tbody>
</table>

Table 1: Borch reduction followed by retro-Cope elimination attempts.

Giró Mañas showed that the concentration of oxime 46 was very important to the success of the Borch reduction reaction and should be around 0.025 moldm⁻³. The reduction was carried out by dissolving oxime 46 and NaCNBH₃ in dry methanol. To this solution a few
drops of methyl orange indicator were added and the resulting bright yellow solution cooled to 0 °C. A solution of HCl in methanol (1:10 v/v) was added dropwise until an orange colour persisted and the reaction mixture stirred for 10 min at 0 °C. After this time the reaction mixture was stirred at RT for 5 min during which time the yellow colour returned. The solution was cooled back to 0 ºC and further acid was added to restore the orange colour and the reaction mixture allowed to stir for a further 10 min. The reaction mixture was then warmed to RT, and the yellow/orange solution was neutralised with 2 M NaOH. After work-up and purification by flash chromatography, $^1$H NMR analysis showed that hydroxylamine 47 had been formed in 52% yield (entry 1). The low yield was due to incomplete reduction of oxime 46 which was removed during purification. Hydroxylamine 47 was immediately dissolved in 10 mL toluene. The solution was degassed by a series of freeze-thaw cycles before being heated to 80 °C for 15 h. It was important that there was no water or oxygen present in the solution to prevent unwanted disproportionation and dimerisation reactions occurring. After this time the toluene was removed in vacuo and analysis of the resulting mixture by $^1$H NMR showed a 1:1.5 ratio of oxime 46 and a new product. The new product did not appear to be the desired N-hydroxyl pyrrolidine 48 by comparison with the $^1$H NMR spectra obtained by Giró Mañas, and it was assumed that the reaction had not been successful. It is proposed that oxime 46 arises through a disproportionation reaction between two molecules of hydroxylamine 47 to give oxime 46 and amine 93 (Scheme 43).

Scheme 43: Proposed disproportionation reaction between two hydroxylamine molecules.

The reaction was therefore repeated (Table 1, entry 2); this time more acid was added initially, in the hope that all oxime 46 would react. However, after work-up and purification hydroxylamine 47 was isolated in a comparable yield to the previous reaction. This product was subject to the retro-Cope elimination conditions. The $^1$H NMR spectrum of the crude
product mixture looked very similar to that of the previous reaction (entry 1) and it was again assumed the reaction had been unsuccessful.

The Borch reduction was attempted a couple more times in order to increase the yield by faster addition of the acid, unfortunately, with no success (entries 3 and 4). After work-up the $^1$H NMR spectra of the purified reactions did not correspond to the previous products of this reaction (entries 1 and 2). Both products were subject to the retro-Cope conditions, with addition of molecular sieves (entry 3) or degassing by purging with argon (entry 4). The $^1$H NMR analysis of the resultant mixtures after 16 h heating at 80 °C showed a mixture of compounds had formed, however column chromatography was not successful in isolating any expected product. The reaction was then attempted using neat acetic acid a procedure optimised within the Spivey group towards the total synthesis of lycorine. After work-up and submitting the crude reaction mixture to the retro-Cope elimination conditions, the outcome, as judged by inspection of the $^1$H NMR spectrum of the crude product mixture, was comparable to that of the previous reactions (entries 3 and 4). The results from these reactions suggested that too much acid was perhaps preventing the formation of hydroxylamine.

Whilst experiments were being undertaken to optimise the Borch reduction the combined products of the first 2 reactions (entries 1 and 2) were re-analysed by $^1$H NMR spectroscopy. It was concluded that the discrepancies with respect to the spectra of Giró Mañas might simply be an artefact of differences in the concentrations at which the spectra were recorded. It was also decided that purification of hydroxylamine after the Borch reduction might be the cause of the low yields obtained. The Borch reduction followed by the retro-Cope elimination was therefore repeated using conditions described for the first reaction (entry 5). Hydroxylamine was formed in essentially quantitative yield and the crude product submitted to the retro-Cope elimination. The reaction was successful giving N-hydroxyl pyrrolidine and a small amount of oxime (1:0.25 by $^1$H NMR spectroscopy), no purification was undertaken and N-hydroxyl pyrrolidine taken through the next steps crude.

With the Borch reduction and the retro-Cope elimination reactions working reproducibly the final steps towards iminium salt were carried out (Scheme 44).
Raney-Ni hydrogenolysis in wet ethanol gave pyrrolidine 94 in 90% yield, followed by formylation on the crude product with acetoformic anhydride to give formamide 95 in 65% yield prior to purification. This was a lower yield than anticipated and it was suspected that this could be due to deprotection of the acetonide group in the acidic reaction conditions. The resultant diol would have been water soluble and therefore lost during the work-up. Purification by flash chromatography proved to be more difficult than expected due to co-elution of the product with impurities on silica-gel and only a small amount of pure formamide 95 was eventually isolated in 34% yield.

Due to the low yield and problems of purification encountered during the synthesis of formamide 95 a different method of formylation was investigated. Pleasingly, when pyrrolidine 94 was refluxed in ethyl formate for 16 h, almost quantitative conversion to formamide 95 was observed. The side product of this reaction is ethanol and the boiling point of ethyl formate is just 54 °C, therefore the side product an excess reagent could be removed in vacuo. This avoided the need for an aqueous work-up and further purification by column chromatography. In addition the mild, non-acidic reaction conditions meant that no loss of product was seen by acetonide deprotection.

The final step in the synthesis of iminium salt 38 is the POCl₃ mediated Bischler-Napieralski cyclisation of formamide 95, followed by acetonide deprotection with HCl (Scheme 45).

**Scheme 44**: Conversion of N-hydroxyl pyrrolidine 48 to formamide 95. Reagents and conditions: i) Raney-Ni (excess), EtOH/H₂O (10:1), H₂, RT, 1-3 h, 90%. ii) acetoformic anhydride (3 equiv.), CH₂Cl₂, RT, 1-2 h, 31%. iii) Ethyl formate, 60 °C, 16 h, 99%.
To a solution of formamide 95 in MeCN was added POCl₃ dropwise and the resulting solution refluxed for 30 min. After this time, TLC showed consumption of all starting material and the reaction mixture was cooled to RT. Acetonide deprotection was then carried out in situ by the addition of aq. HCl (3 M) and allowing the solution to stir at RT for 1 h. Solvents were then removed in vacuo to yield iminium salt 38 as a dark orange oil. A ¹H NMR spectrum of the product was comparable to that obtained by Giró Mañas confirming that the iminium salt 38 had been formed. No yield could be reported for this step at this stage as the crude product contained unquantified and inseparable phosphorus impurities.

1.2.4. Purification of Iminium Salt 38.

As indicated above, the iminium salt 38 contained phosphorus impurities from the POCl₃ used in the Bischler-Napieralski cyclisation. As iminium salt 38 is water soluble an aqueous work-up to remove the impurities could not be carried out, and due to the very polar nature of the molecule, the use of normal phase silica flash chromatography was not viable. In order to save material it was deemed appropriate to trial some purification methods with model iminium salt 96. The model compound was synthesised in two steps from commercially available 3,4-dimethoxy-N-methylphenethylamine (97) (Scheme 46).

By simply refluxing 3,4-dimethoxy-N-methylphenethylamine (97) in ethyl formate, formamide 98 was formed in quantitative yield. The Bischler-Napieralski cyclisation was then carried out on formamide 98 and gave clean conversion to iminium salt 96 as judged by
analysis of its $^1$H NMR spectrum. With the model iminium salt 96 in hand, ion exchange chromatography was explored as a method for removing the phosphorus impurities. As the iminium salt is a positively charged molecule the ion exchange resin had to be negatively charged; this is known as cation exchange chromatography. A strong cation exchange (SCX) column was investigated first. These columns are available in pre-packed cartridges, and are made up of sulfonic acid groups bonded to silica (Figure 6).

![Diagram showing the interaction of a SCX column with iminium salt 96.](image)

The counter ion on the SCX column is replaced when a positively charged compound/ion of a higher affinity is passed down the column. Any uncharged molecules can be washed from the column with a suitable solvent. In our case it was envisaged that iminium salt 96 would stick to the column, replacing the $\text{H}^+$ ion, and the uncharged phosphorus salts would be washed away.

The crude iminium salt 96 was dissolved in methanol and loaded onto a 2 g SCX column. The column was then washed with copious amounts of methanol, and eluent fractions spotted on a TLC plate. The presence of compounds was monitored by viewing the plate under a UV lamp. Once no further impurities were seen to elute, aq. $\text{HCl} (1.0 \text{ M} \rightarrow 3.0 \text{ M})$ was passed down the column, and again the eluent was monitored by TLC. The desired product eluted very slowly with 3 M HCl and finally concentrated HCl was required to elute the entire product. All the eluted fractions were collected and concentrated in vacuo. The $^1$H NMR spectrum of the initial MeOH fractions did not contain the iminium salt 96 but rather a phosphorus-containing compound as evidenced by several peaks in the $^{31}$P NMR spectrum of this fraction. The expected product was found to elute in the HCl aqueous fraction, this was confirmed by $^1$H NMR spectroscopy and mass spectrometry; the $^{31}$P NMR spectrum of the aqueous fraction showed that it contained no phosphorus. This outcome demonstrated that the method of cation exchange chromatography could in principle remove the phosphorus impurities. However, the use of concentrated HCl to remove iminium salt 96 from the column was not ideal, as it is possible that under such acidic conditions silica and/or binding agents may be stripped from the column.
It was decided that a weak cation exchange (WCX) column might be better suited to the purification of our iminium salt 96, and allow for the use of a weaker acid for elution of the compound. The WCX resin selected for use was a carboxylic acid bound (CBA) pre-packed column (Figure 7).

Figure 7: Diagram showing the interaction of a CBA column with iminium salt 96.

Initial attempts at purification with the CBA column using conditions similar to those used with the SCX column were not successful. It was clear that iminium salt 96 was not sticking to the column and was seen to elute when the column was washed with water in order to remove the impurities. These initial results determined that the pH of both the column and the sample were key parameters for this purification method to be successful. A CBA column is completely ionised at pH 6.8 or above, however, in these initial attempts at purification the column was washed with deionised water with a pH of around 5-6. In order to exert greater control over the pH some buffers were tested.

After some research into different types of buffers it was decided that an ammonium carbonate (\(\text{NH}_4\text{HCO}_3\cdot\text{NH}_2\text{COONH}_4\)) buffer would be used. Ammonium carbonate is a volatile buffer that should avoid contaminating the purified product with any additional salts. A sample of iminium salt 96 was dissolved in a 0.01 M solution of the buffer previously basified to pH 8/9 with a 10% aqueous ammonia solution. After loading the sample onto the column (which had been pre washed with the buffer to ensure it was > pH 6.8) the column was washed with the buffer solution in order to remove the phosphorus impurities. The iminium salt 96 appeared to have stuck to the column and was eluted with 0.1 M HCl. This system proved to be successful, with the first fractions containing phosphorus but no iminium salt 96 by analysis of \(^1\text{H}\) and \(^{31}\text{P}\) NMR spectra. The later fractions contained iminium salt 96, free of phosphorus impurities.

Having optimised this method for the purification of the model iminium salt 96 the method was applied to iminium salt 38. It was found that the purification method was successful on a 20 mg scale, and that one column could be reused several times with complete removal of phosphorus impurities. This allowed for the purification of a sufficient quantity of iminium
Chapter 1  
Total Synthesis of Clivonine

salt 38 to allow investigations of the final steps of the synthesis. However, after removal of the aqueous media from iminium salt 38 by freeze drying it was clear that salts from the ammonium carbonate buffer where still present. These salts were therefore removed by reverse phase C18 chromatography, to give clean iminium salt 38. The yield for the final Bischler-Napieralski cyclisation could now be calculated as 42%.

In summary the synthesis of iminium salt 38 from oxime 46 could be completed in five steps in a 30% overall yield, with solid phase chromatography at the last step being the only purification method used throughout the five steps.

1.2.5. Biomimetic Ring-Switch.

The three final steps of the synthesis were the conversion of iminium salt 38 to lactamol 50, methylation to induce the biomimetic ring-switch and then benzylic oxidation of lactol 49 to give (±)-clivonine (1) (Scheme 47).

![Scheme 47: Final steps of the synthesis of clivonine (1). Reagents and Conditions: i) Cs2CO3 sat. aq. sol. (0.77 M, 1.3 equiv.), DMSO-d6/D2O (5:1), RT, 5-10 min. ii) Mel (2 equiv. sol. in DMSO-d6), RT, 5-10 min. iii) Fetizon’s (15 equiv.), toluene, 80 ºC, 1 h, 32% over the three steps.](image)

The first of these steps was conversion of iminium salt 38 to lactamol 50. Giró Mañas found that using chemistry developed by Rozwadowska59 and treating iminium salt 38 with NaOD in D2O/DMSO-d6 lead to the formation of lactamol 50 however, decomposition occurred very rapidly via a Cannizzaro type disproportionation under the reaction conditions. Successful conversion to lactamol 50 was achieved by using Dostal and Seckarova’s
conditions and treating iminium salt 38 with Na$_2$CO$_3$ in D$_2$O/DMSO-$d_6$\(^{60}\). Giró Mañas adapted these conditions and found that quantitative conversion to lactamol 50 could also be achieved using Cs$_2$CO$_3$ as the base.\(^{24}\)

The first challenge was to repeat the reaction using the conditions developed by Giró Mañas to obtain lactamol 50 from iminium salt 38. As expected, this was by no means trivial (Table 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conditions (In a NMR Tube)</th>
<th>Outcome ((^1)H NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO-$d_6$</td>
<td>i) 10 equiv. Na$_2$CO$_3$</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>DMSO-$d_6$</td>
<td>i) 10 equiv. Cs$_2$CO$_3$</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>DMSO-$d_6$/D$_2$O 2:1</td>
<td>i) Neutralisation (sat. aq. Na$_2$CO$_3$)</td>
<td>Decomposition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ii) 10 equiv. Na$_2$CO$_3$</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>DMSO-$d_6$/D$_2$O 2:1</td>
<td>i) Neutralisation (sat. aq. Na$_2$CO$_3$)</td>
<td>Decomposition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ii) 2 equiv. Na$_2$CO$_3$</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>DMSO-$d_6$/D$_2$O 2:1</td>
<td>i) Neutralisation (sat. aq. Cs$_2$CO$_3$)</td>
<td>Lactamol 50 observed (trace to clivonine (1))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ii) 2 equiv. Cs$_2$CO$_3$</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>DMSO-$d_6$/D$_2$O 5:1</td>
<td>Cs$_2$CO$_3$ aq. sol (0.77 M, 1.3 equiv.)</td>
<td>Quantitative conversion to lactamol 50 (13% to clivonine (1))</td>
</tr>
</tbody>
</table>

Table 2: Attempts at the conversion of iminium salt 38 to lactamol 50.

Initial attempts to convert iminium salt 38 to lactamol 50 with either Na$_2$CO$_3$ or Cs$_2$CO$_3$ were unsuccessful and only decomposition of lactamol 50 was observed (entries 1-4). It was decided that Cs$_2$CO$_3$ would be used as the base in future reactions, in the expectation that the higher solubility of Cs$_2$CO$_3$ in DMSO in comparison to Na$_2$CO$_3$ would increase the rate of lactamol 50 formation and allow for the use of less base (entry 5). After neutralisation of the sample with a saturated solution of Cs$_2$CO$_3$ in D$_2$O and the addition of 2 equivalents of solid Cs$_2$CO$_3$ followed by sonication the \(^1\)H NMR spectrum showed complete consumption of the iminium salt 38 and the presence of lactamol 50 (reactions were carried out in NMR tubes and conversion was monitored by the disappearance of the iminium methine proton at $\delta \sim$
9.07 ppm and the appearance of a new peak at δ ~ 4.92 ppm corresponding to the lactamol methine proton). This crude material was carried through the two final steps of the synthesis, methylation (~ 25 equiv. MeI), followed by a change in solvent to toluene and benzylic oxidation with Fetizon’s reagent.61 However, after work-up only a trace of clivonine (1) was observed in the 1H NMR spectrum of the crude reaction mixture. Although only a small amount of the target product had been obtained, this result demonstrated that lactamol 50 had been formed. Quantitative conversion to lactamol 50 was achieved when a neutral solution of iminium salt 38 was treated with an aqueous solution of Cs2CO3 (0.77 M, 1.3 equiv.) (entry 6). After methylation (~ 10 equiv. MeI) and oxidation (Fetizon’s reagent) clivonine (1) was isolated in 13% after purification by preparative TLC. This method could be carried out reproducibly to give a quantitative conversion of iminium salt 38 to lactamol 50 as judged by analysis of the 1H NMR spectra.

It was assumed that the low yield (13%, cf. Table 2, entry 6) obtained for the synthesis of clivonine (1) after methylation and oxidation was due to the inefficiency of the benzylic oxidation of lactol 49 using Fetizon’s reagent. Therefore in an effort to optimise this step some different oxidation conditions were investigated (Table 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO-d6</td>
<td>EtOAc, 1.2 equiv. IBX</td>
<td>No Product</td>
</tr>
<tr>
<td>2</td>
<td>DMSO-d6/D2O (5:1)</td>
<td>Fremy’s Salt, K2NO(SO3)2, 2 equiv.</td>
<td>Trace clivonine (1)</td>
</tr>
<tr>
<td>3</td>
<td>THF/0.1 M HCl (4:1)</td>
<td>MnO2, 2 equiv. then 1.1 equiv.</td>
<td>SM</td>
</tr>
</tbody>
</table>

Table 3: Alternative benzylic oxidation conditions.

Research carried out by Moorthy has shown that IBX can be used to oxidise lactols to lactones.62 In light of this work, formation of lactamol 50 was carried out in DMSO-d6, followed by methylation (~ 10 equiv. MeI). The reaction mixture was then diluted with EtOAc and 1.2 equivalents of IBX added (entry 1). The reaction mixture was then heated to 80 °C for 1 h, filtered and concentrated. Unfortunately, examination of the 1H NMR spectrum of the crude product showed no traces of clivonine (1). It was concluded that the desired
product was not isolated due to oxidation of the hydroxyl group as well as oxidation of lactol 49.

Fremy’s salt K₂NO(SO₃)₂ is a single electron oxidant and has been shown to chemoselectively oxidise benzylic alcohols over saturated alcohols.⁶³ Therefore after formation of lactamol 50 and methylation (~ 10 equiv. MeI) the crude reaction mixture was added to a solution of Fremy’s salt in a 5% aqueous Na₂CO₃ solution (entry 2). After 1 h stirring at room temperature a new spot had formed by TLC, however after work-up the ¹H NMR spectrum of the crude reaction mixture showed only a trace of clivonine (1) had formed.

Wildman has shown that solid MnO₂ can be used for the benzylic oxidation of lycorenine (27).⁶⁴ This oxidation was attempted on our substrate, however this time instead of forming lactamol 50 and treating with methyl iodide before oxidation, iminium salt 38 was treated directly with MnO₂ in an acidic media (entry 3). It was envisaged that the iminium salt 38 could undergo nucleophilic attack by water, and the resulting lactamol 50 would be protonated under the acid conditions. This would allow for the ring-switch to occur and with the presence of the MnO₂ benzylic oxidation of the corresponding lactol to lactone would give NH-clivonine, methylation of which could then afford clivonine (1). Unfortunately, the iminium salt 38 was not reactive under these conditions and only starting material was recovered after stirring for 6 h at RT.

As no improvement on the yield had been achieved by using different oxidants for the benzylic oxidation the methylation conditions were investigated next. Methylation had previously been carried out by the addition of an excess (10-25 equiv.) of methyl iodide directly into the solution of lactamol 50. As previously discussed, the quantitative formation of lactamol 50 was monitored by ¹H NMR spectroscopy. The ¹H NMR spectrum recorded after the addition of excess methyl iodide showed a complex mixture of products. At first it was assumed that this mixture was due to the labile nature of the lactamol 50, and that this compound was in equilibrium with aldehyde 99 and lactol 49 (see below). This notion was corroborated by the appearance of a singlet at δ ~ 10 ppm in the ¹H NMR spectrum which was assigned as the carbonyl proton of aldehyde 99. However, it was quite possible that over methylation could have been occurring in the presence of such a large excess of methyl iodide. Various reactions were therefore carried out in order to improve the methylation step, in the hope to improve the overall yield through to clivonine (1) (Table 4).
The use of alternative methylating reagents such as methyl triflate and dimethyl sulfate (entries 1 and 2) afforded no clivonine (1) after subsequent benzylic oxidation with Fetizon’s reagent. When 1.0 equivalent of a methyl iodide solution in DMSO-d$_6$ was added to a solution of lactamol 50 the $^1$H NMR spectrum showed complete consumption of lactamol 50 and the formation of a mixture of what appeared to be two compounds. One of the products was tentatively assigned as aldehyde 99 on the basis of the appearance of a singlet at $\delta \sim 9.5$-10 ppm and a $N$-methyl singlet at $\delta \sim 2.3$ ppm. Pleasingly after oxidation and purification by preparative TLC clivonine (1) was isolated in 27% yield. This was slightly improved when 2 equivalents of methyl iodide were added to lactamol 50 and clivonine (1) was isolated in 32% yield from iminium salt 38. Further improvement of the yield was not possible due to the formation of what appeared to be the quaternised salts after methyl iodide addition.

In conclusion, the biomimetic ring-switch of our lycorine type precursor, iminium salt 38 had been achieved to give (±)-clivonine (1) in 32% yield. This series of reactions was reproducible and allowed for the isolation of enough (±)-clivonine (1) for full characterisation. The spectroscopic data that we obtained for (±)-clivonine (1) matched what was reported for the natural material (Figure 8).$^9$,$^{13}$
Additionally a single-crystal X-ray structure determination was carried out on its hydrochloride salt, which confirmed the correct structure had been obtained after the biomimetic ring-switch (Figure 9).

Figure 8: $^1$H NMR spectrum of (±)-clivonine (1) (400 MHz, CDCl$_3$).

Figure 9: Molecular structure of the hydrochloride salt of (±)-clivonine (1) as determined by single-crystal X-ray crystallography.
1.3. Conclusions and Future Work

The main aim of this project was to complete the total synthesis of clivonine (1) via a biomimetic ring-switch from lycorine type precursor iminium salt 38. The initial challenge was to repeat the synthesis of iminium salt 38 which had been previously developed by Giró Mañas, and once completed to develop a method of purification. This was achieved by the use of a CBA weak cation exchange column followed by C18 reverse phase chromatography. This gave us access to clean iminium salt 38 which could be used for the optimisation of the final biomimetic ring-switch.

The second challenge was the optimisation of the biomimetic ring-switch, steps tentatively achieved by Giró Mañas. This challenge was successfully completed allowing for the isolation of clivonine in 32% over the three steps from iminium salt 38. This synthesis has shown experimentally for the first time the conversion of a lycorine-type structure to that of a clivonine type structure in a biomimetic fashion, confirming synthetically the biosynthetic pathway first proposed by Barton in 1960.

The total synthesis of lycorine (11) via a retro-Cope elimination is currently being undertaken within the Spivey group. Once this total synthesis has been completed, the conditions optimised for the biomimetic ring-switch will be used to then synthesise hippeastrine (10) directly from lycorine (11). This chemistry should also assist with planned investigations into the interconversion between these alkaloids during the life cycle of the Amaryllidaceae.
Chapter 2 – Synthesis of meso-Diol 74

2.1. Introduction

2.1.1. Importance and Synthetic Utility of meso-Diol 74 and Derivatives

The starting material for our total synthesis of clivonine was meso-diol 74, obtained from the microbial oxidation of benzene (cf. Chapter 1, Section 1.2.1).\(^{46}\) Gibson first proposed that meso-diol 74 was an intermediate in the oxidation of benzene to catechol by the bacterium *Pseudomonas putida* in 1968.\(^{47}\) He later showed that it was possible to isolate the meso-diol intermediates during the oxidation of benzene and toluene by a mutant strain of *Pseudomonas putida* (*P. Putida 39/D*).\(^{65}\) The area of microbial oxidation of arenes has been highly researched, with access to many monocyclic and fused aromatic diols having been established.\(^{48,66}\)

However, it was not until the 1980’s that the synthetic utility of such compounds was realised in industry and academia.\(^{67}\) The use of these types of compounds has been reviewed previously on several occasions.\(^{48,67-69}\) Therefore this section will only highlight some selected examples of the synthetic use of meso-diol 74 and its derivatives.

Imperial Chemical Industries (ICI) demonstrated the first industrial use of meso-diol 74, with their synthesis of poly(\(p\)-phenylene) (100) (Scheme 48).\(^{70-71}\)

\[
\begin{align*}
74 & \xrightarrow{n\text{RO}} \left[ \text{RO} \right]_n \xrightarrow{n\text{ROH}} \left[ \text{100} \right]_n + n\text{ROH} \\
\end{align*}
\]

Scheme 48: ICI’s synthesis of poly(\(p\)-phenylene) (100).\(^{70-71}\)

Polymerisation of protected meso-diol 74 in the presence of radical initiators gave the polymer 101, which was heated at high temperatures to affect aromatisation to give poly(\(p\)-phenylene) (100). It was found that the methyl carbonate protecting group was the most effective, due to the decomposition of the resulting methyl carbonic acid into methanol and carbon dioxide after aromatisation at high temperature.\(^{71}\) This chemistry has been developed further by Grubbs who has used transition metal catalysis to ensure 1,4-linked products are obtained selectively in high yields.\(^{72-73}\)
After ICI’s synthesis of poly(p-phenylene) (100) Ley was the first organic chemist to demonstrate the application of compounds such as meso-diol 74 in natural product synthesis, with his synthesis of (±)-pinitol (102) (Scheme 49).  

Scheme 49: Ley’s synthesis of pinitol (102).  
Reagents and Conditions: i) BzCl (2.2 equiv.), DMAP (1.8 mol%), py, 0 °C → RT, 16 h. ii) m-CPBA (90%, 1.2 equiv.), CH₂Cl₂, pH 8 phosphate buffer, RT, 22 h. iii) CSA·H₂O (14 mol%), CH₂Cl₂, MeOH, RT, 22.5 h. iv) Et₃NOAc·4H₂O (0.25 equiv.), BuOHH (70% aq. sol., 1.6 equiv.), OsO₄ (0.18 mol%), acetone, 0 °C → RT, 3 d. v) Et₃N/MeOH/H₂O (1:5:1), RT, 3 h.

The synthesis began with meso-diol 74 derivative dibenzoate 103. Epoxidation with m-CPBA gave predominately anti epoxide 104 (the syn epoxide was isolated in 17% yield). Regioselective ring opening of anti epoxide 104 with methanol gave dibenzoate 105. Finally, dihydroxylation with catalytic osmium tetroxide followed by hydrogenation gave (±)-pinitol (102) in an overall 61% yield. Ley went on to synthesise both (+)-pinitol (102) and (-)-pinitol (102) by separating the enantiomers of the menthoxyacetic ester of (±)-dibenzoate 105 before subsequent oxidation and hydrogenation.

Since Ley’s synthesis of pinitol (102) many groups have used meso-diol 74 and derivatives thereof for the synthesis of natural and biologically important products. One such group of compounds that are often synthesised starting from meso-diol 74 are the conduritols. The conduritols are an important class of compounds that possess interesting biological and medicinal properties such as antibiotic, antileukemic and glycosidase inhibitory effects (Figure 10).
Of this group of compounds only conduritol A and conduritol F have been isolated as natural products, making this group of compounds appealing synthetic targets. Over the last 20 years many racemic and asymmetric syntheses of the conduritols and conduramines (compounds where one of the hydroxyl groups of the corresponding conduritol has been replaced by an amine) and their analogues have been published.48,69,76-78

A recent example is Balci’s synthesis of bromo conduritol-C (106) (Scheme 50).79

Scheme 50: Balci’s synthesis of bromo conduritol-C (106).79 Reagents and Conditions: i) O2, TPP, hv, CH2Cl2, RT. ii) Br2 (1.1 equiv. in hexane), CHCl3, 0 °C, 1.5 h. iii) DMSO, 20 min. iv) NaBH4 (1.9 equiv.), THF, 0 °C, 4 h. v) Ac2O, H2SO4, RT, 12 h. vi) NH3 gas, MeOH, 30 min, RT, 2 h.

Photooxidation of meso-diol 74 derivative acetonide 77 was carried out to give endoperoxide 107 in 95% yield. Treatment of endoperoxide 107 with bromine gave dibromide 108 which underwent rearrangement in a solution of DMSO, followed by spontaneous HBr elimination.
to give bromoketone \textit{109}. Hydride reduction with NaBH$_4$, gave bromodiol \textit{110} which was subject to acetate protection in the presence of acid to give tetraacetate \textit{111}. Finally, deprotection with NH$_3$ in methanol afforded the desired bromo conduritol-C (\textit{106}) in an overall 48% yield.

Studer has also demonstrated the use of acetonide \textit{77} during the development of a Cu(I) catalysed enantioselective nitroso Diels-Alder reaction, and has employed this method for the asymmetric synthesis of (−)-peracetylated conduramine A-1 (\textit{112}) (Scheme 51).$^{80}$

\begin{center}

\textbf{Scheme 51:} Studer’s synthesis of (−)-peracetylated conduramine A-1 (\textit{112}).$^{80}$ \textit{Reagents and Conditions:} i) 2-nitrosopyridine (1 equiv.), [CuPF$_6$(MeCN)$_4$] (10 mol%), Walphos-CF$_3$ (10 mol%), CH$_2$Cl$_2$, -86 °C → -20 °C, 18 h. ii) [Mo(CO)$_6$] (1.2 equiv.), NaBH$_4$ (1.3 equiv.), MeOH/H$_2$O (10:1), 65 °C, 10 h. iii) DMF, TBSCl (1.4 equiv.), im (2.9 equiv.), RT, 24 h. iv) CH$_3$MgCl (1.2 equiv.), methyl chloroformate (3.0 equiv.), RT, 12 h. v) MeOTf (1.1 equiv.), 0 °C, 12 h. vi) NaOH (2 M, excess), MeOH, 50 °C, 6 h. vii) AcCl (15.0 equiv.), NaI (15.0 equiv.), MeCN, 65 °C, 40 h.

The enantioselective nitroso Diels-Alder reaction of acetonide \textit{77} with 2-nitrosopyridine was carried out using [CuPF$_6$(MeCN)$_4$]/Walphos-CF$_3$ as the catalyst to give the cycloadduct \textit{113} in 99% yield and 93% ee. Cleavage of the N-O bond with subsequent TBS protection of the resultant hydroxyl group gave the amino alcohol \textit{114} in 91% yield. Treatment of the amino alcohol \textit{114} with methyl magnesium chloride followed by methyl chloroformate gave the carbamate \textit{115}. Removal of the N-(2-pyridyl) group from carbamate \textit{115} was achieved by \textit{N}-methylolation of the pyridyl group with MeOTf followed by hydrolysis of the pyridinium salt with NaOH. Finally, cleavage of the acetonide and carbamate groups followed by acetyl protection gave (−)-peracetylated conduramine A-1 (\textit{112}) in an overall 40% yield.
Chapter 2  

Synthesis of meso-Diol

The groups of Pipersberg, Wood and Balci have also made use of the Diels-Alder reaction of acetonide 77 with a range of dienophiles towards the synthesis of natural or biologically active products.\(^{68,81-83}\) Burnell has also studied the Diels-Alder reaction of acetonide 77 with all carbon and azo dienophiles, investigating the facial selectivity observed in such reactions.\(^{84}\) There are many more instances in which derivatives of meso-diol 74 have been used in synthesis\(^{85-86}\) and to provide industrially relevant materials\(^{87}\), highlighting the importance of these types of compounds.

Meso-diol 74 is available to buy commercially, sourced from the microbial oxidation of benzene as described above. However, it is expensive, and due to its instability cannot be stored as a solid, even at temperatures below 0 °C.\(^{67}\) For this reason, non-enzymatic syntheses of meso-diol 74 have been developed.

### 2.1.2. Previous Syntheses of meso-Diol 74 Derivatives

Yang developed the first chemical synthesis of meso-diol 74 derivative acetonide 77 in 1982 starting from 1,4-cyclohexadiene (116) (Scheme 52).\(^{88-89}\)

![Scheme 52: Yang’s synthesis of acetonide 77. Reagents and Conditions: i) Br₂, CHCl₃, -78 °C. ii) aq. KMnO₄, buffered (MgSO₄) EtOH/H₂O, -5 °C for 5.5 h, then -15 °C for 15 h. iii) DMP (excess), H⁺ (catalytic). iv) DBU (3.6 equiv.), benzene, reflux, 6 h.](image)

1,4-Cyclohexadiene (116), available commercially or from the Birch reduction of benzene, was subject to a low temperature bromination forming dibromide 117, which precipitated out of solution preventing double bromination occurring. Dihydroxylation of the remaining double bond with potassium permanganate gave dibromo diol 118, which was treated with an excess of DMP and catalytic acid to give dibromo acetonide 119. Finally bis elimination of HBr using DBU as a base in refluxing benzene for 6 h gave acetonide 77 in an overall yield of 26% over 4 steps.

Johnson has reported that the dihydroxylation step of the above described synthesis can be improved by using osmium tetroxide and NMO instead of potassium permanganate to give acetonide 77 after acetonide protection and bis-elimination in an overall yield of 87% from benzene.\(^{90}\) Although interestingly, all subsequent reports of the use of this sequence of
reactions have cited Yang’s work and reported yields comparable to his original report, including Giró Mañas in our group (see below).

Mereyala has used myo-insitol (120) for the synthesis of meso-diol 74 derivative cyclohexylidene 121 (Scheme 53).\textsuperscript{91}

\textbf{Scheme 53:} Mereyala’s synthesis of cyclohexylidene 121.\textsuperscript{91} Reagents and Conditions: i) ethoxycyclohexene, \textit{p}TsOH (catalytic), DMF, 100 °C, 2 h. ii) PPh\textsubscript{3} (3.0 equiv.), I\textsubscript{2} (3.0 equiv.), im (3.0 equiv.), toluene, reflux, 6 h. iii) \textit{p}TsOH (catalytic), CH\textsubscript{2}Cl\textsubscript{2}, 0-5 °C, 4 h. iv) PPh\textsubscript{3} (3.0 equiv.), I\textsubscript{2} (3.0 equiv.), im (3.0 equiv.), toluene, reflux, 1 h.

The first step of the synthesis was treatment of myo-insitol (120) with ethoxycyclohexene to give a mixture of acetals 122, 123 and 124. Acetals 123 and 124 were taken forward and treated with triphenyl phosphine, iodide and imidazole in refluxing benzene which resulted in the elimination of the \textit{trans}-diol group to give the corresponding cyclohexane acetals 125 and 126. Deprotection of the \textit{trans}-cyclohexylidene group to furnish diols 127 and 128, followed by a second \textit{trans}-diol elimination under the same conditions gave cyclohexylidene 121 in an overall yield of 24% over 4 steps.
Fabris has also utilised myo-insitol (120), for the synthesis of meso-diol 74 derivative acetonide 77 (Scheme 54).  

![Scheme 54: Fabris synthesis of acetonide 77. Reagents and Conditions: i) DMP, pTsOH (catalytic), DMSO, 120 °C, ii) MsCl (5.0 equiv.), DMAP (5 mol%), py, 0 °C→RT, 16 h. iii) KI (7.7 equiv.), NMP, 120 °C, 10 Torr, 1 h. iv) Zn/Cu couple (12.0 equiv.), 120 °C, 24 h, then 20 Torr, 145 °C.](image)

Acetonide protection of the cis diol unit of myo-insitol (120) to give tetrol 129, followed by mesylation of the remaining hydroxyl groups provided tetramesylate 130. Elimination of the two mesylated trans-diol groups to give acetonide 77 was achieved using a zinc/copper couple at high temperature in NMP. Fabris found that the quality of the zinc/copper couple was important in order to obtain good yields of acetonide 77. The product was removed from the zinc salts by distillation at 145 °C at 20 Torr. Isolation of acetonide 77 was then achieved after work-up by careful distillation under reduced pressure to afford the desired product in yields between 48-60%. The overall synthesis of acetonide 77 was complete in 3 steps with an overall yield of 36%.

Due to problems that were encountered within the group when attempting to repeat the synthesis of acetonide 77 reported by Yang and modified by Johnson, and the seemingly difficult final step of the Fabris synthesis we have developed an alternative synthesis of acetonide 77 from 1,3-cyclohexadiene (131).

### 2.1.3. Synthetic Strategy and Project Aims

Our proposed synthesis of acetonide 77 starts with the photooxidation of 1,3-cyclohexadiene (131) to give endoperoxide 132. Rearrangement of endoperoxide 132 with CoTPP should then give the syn bis-epoxide 133. Bis ring opening of bis-epoxide 133 with a bromide source should then give dibromo diol 134 which upon acetonide protection, should furnish dibromide 135. Finally, bis-elimination of HBr from dibromide 135 would be expected to afford acetonide 77 (Scheme 55).
Photooxidation of dienes with singlet oxygen ($^{1}\text{O}_2$) is a reaction that has been carried out many times within the group and the formation of endoperoxide 132 from 1,3-cyclohexadiene (131) has previously been achieved in good yields. At the outset of this work, the rearrangement of endoperoxide 132 with CoTPP to give bis-epoxide 133 had also been carried out within the group and had been shown to be successful by analysis of the $^1\text{H}$ NMR spectrum of the product, however isolation of bis-epoxide 133 had suffered from low yields. Opening of the bis-epoxide 133 with CuBr$_2$ to give dibromodiol 134 had also been achieved on a small scale, however, as with the isolation of bis-epoxide 133, only low yields of the desired product had been obtained. The first aim of the project, therefore, was to develop a method of accessing scalable amounts of dibromodiol 134. The final step of our synthesis is bis-elimination of dibromide 135 to give acetonide 77. This step had been attempted within the group, but again with little success. The second aim of this project, therefore, was to optimise the bis-elimination conditions in order to isolated adequate quantities of acetonide 77 for future syntheses.

2.1.3.1. Co(II)TPP Rearrangement of Endoperoxides to syn bis-Epoxides

The chemistry of bicyclic endoperoxides (e.g. endoperoxide 132) has been studied comprehensively over the past 20 to 30 years. Thermolysis and photolysis of unsaturated endoperoxides, formed from the reaction of the corresponding diene with $^{1}\text{O}_2$, to give syn bis-epoxides (e.g. bis-epoxide 133) are common reactions for these types of compounds. An early example of this chemistry was shown by Masheshwari in 1970 with the photolysis of the natural product ascaridole (136) to the corresponding bis-epoxide 137 (Scheme 56).
However, it has been shown that the thermolysis and photolysis reactions of some unsaturated [n.2.2] bicyclic endoperoxides result in the formation of epoxyketones in addition to the expected bis-epoxides. The epoxyketone readily undergoes rearrangement to the corresponding hydroxyenone in the presence of acid, base or silica gel and is often not isolated. For example, both thermolysis and photolysis reactions of endoperoxide 132 results in the formation of both bis-epoxide 133 and epoxyketone 138 of which the latter readily rearranges to give hydroxyenone 139 (Scheme 57).

Scheme 57: Thermolysis or photolysis reactions of endoperoxide 132 to bis-epoxide 133 and hydroxyenone 139.

The mechanism for the formation of both bis-epoxide 133 and epoxyketone 138 start with the initial cleavage of the $O-O$ bond of endoperoxide 132 to give the diradical species 140, followed by the cyclisation of one of the oxygen radicals with the double bond to give the monoepoxide 141. At this point two different routes are followed, either monoepoxide 141 undergoes a second cyclisation to give bis-epoxide 133 (path A, Scheme 58) or a 1,2-hydrogen atom shift occurs to give the epoxyketone 138 (path B, Scheme 58).

Scheme 58: Mechanisms of bis-epoxide 133 and epoxyketone 138 formation.

Carless has shown that a number of endoperoxides undergo thermolysis and photolysis reactions to give a mixture of bis-epoxides and epoxyketones in varying ratios dependant on the substrate structure. An interesting example demonstrating this variation in product ratio involves the thermolysis and photolysis of tert-butyl substituted endoperoxides 142 and 143 (Scheme 59).
Scheme 59: Carless’ thermolysis and photolysis reaction of tert-butyl endoperoxides 142 and 143.\textsuperscript{96}

When \textit{cis} tert-butyl endoperoxide 142 was subject to thermolysis or photolysis reactions the major product was epoxyketone 144 and the ratio of this product to \textit{bis}-epoxide 145 was approximately 7:3. However, when \textit{trans} tert-butyl endoperoxide 143 underwent thermolysis or photolysis under identical conditions a complete switch in the ratio of the products was observed with \textit{bis}-epoxide 146 being the major product and with the ratio of \textit{bis}-epoxide 146 to epoxyketone 147 being approximately 8:2. Carless proposed that the difference in ratio of the products was due to conformational differences between the two substrates (Scheme 60).

Scheme 60: Carless’ rationale for the formation of epoxyketone 144 and \textit{bis}-epoxide 146 based on conformational analysis.\textsuperscript{96}

From the conformations depicted above it can been that in monoepoxide 148 the radical on the carbon atom is adequately aligned with the axial proton for the 1,2-hydrogen atom shift to occur to give epoxyketone 144. Whereas for monoepoxide 149 the oxygen radical is now in the axial position set up for the ring closure to give \textit{bis}-epoxide 146.\textsuperscript{96}

In 1980 Foote discovered that cobalt(II) tetrphenylporphyrin (CoTPP) could be used as a catalyst for the selective rearrangement of endoperoxides to \textit{bis}-epoxides at low temperature, circumventing the formation of epoxyketones.\textsuperscript{97} He showed that this is the case for a number of substrates, including unsaturated [n.2.2]bicyclic endoperoxides. For example, when
endoperoxide 132 was treated with CoTPP (1-5 mol%) at -10 °C bis-epoxide 133 was isolated in 74% yield in comparison to 39% yield for thermolysis and 27% yield for photolysis (Scheme 61).

\[ \text{Scheme 61: Foote’s rearrangement of endoperoxide 132 with CoTPP vs. photolysis and thermolysis.}^{97} \]

A mechanistic rationale for this selectivity has been postulated by Balci. He suggests that because CoTPP is capable of cleaving the O-O bond of the endoperoxide by electron transfer at low temperature, there is not sufficient energy for the 1,2-hydrogen atom shift to occur to give the epoxycetones, therefore bis-epoxides are the only products obtained.\(^98\) Balci has demonstrated that this is the case for a number of unsaturated [n.2.2]bicyclic endoperoxides (Scheme 62).\(^99\)

\[ \text{Scheme 62: Balci’s reactions of endoperoxides with CoTPP.}^{99} \]

The CoTPP rearrangement of endoperoxides to bis-epoxides has been applied to the synthesis of some interesting natural products that possess syn bis-epoxide moieties. For instance, the synthesis of (+)-crotexoxide (150) and (+)-boesenoxide (151) completed by Shing in 1998 (Scheme 63).\(^100\)
Scheme 63: Shing’s Synthesis of (+)-crotepoxide (150) and (+)-boesenoxide (151).\textsuperscript{100} \textbf{Reagents and Conditions:} i) O\textsubscript{2}, TPP (0.1 mol%), CCl\textsubscript{4}, hv, 5 h. ii) CoTPP (0.4 mol%), CHCl\textsubscript{3}, 0 °C, 3 h. iii) pyridinium fluoride (3 drops for a 0.1 mmol scale reaction), THF, RT, 12 h. iv) Et\textsubscript{3}N (2.0 equiv.), DMAP (catalytic), Ac\textsubscript{2}O (1.1 equiv.), CH\textsubscript{2}Cl\textsubscript{2}, RT, 12 h. v) Et\textsubscript{3}N (2.0 equiv.), DMAP (catalytic), BzCl (1.2 equiv.), CH\textsubscript{2}Cl\textsubscript{2}, RT, 12 h.

The key intermediate for the synthesis of (+)-crotepoxide (150) and (+)-boesenoxide (151) was diene 152. This compound was synthesised from (-)-quinic acid in 13 steps with an overall yield of 17%. Photooxidation of diene 152 with \textsuperscript{1}{O}_2 and TPP in CCl\textsubscript{4} gave endoperoxide 153 in 79% yield. Treatment of endoperoxide 153 with CoTPP gave the bis-epoxide 154 in a quantitative yield. The final steps were de-silylation to give alcohol 155 followed by protection of the hydroxyl group with acetic anhydride or benzoyl chloride to give (+)-crotepoxide (150) and (+)-boesenoxide (151) respectively.

The total synthesis of (+)-crotepoxide (150) described above follows a very similar route to that published by White in 1976 (Scheme 64).\textsuperscript{101}
During the synthesis, White found that when hydroxy endoperoxides 156 and 157, obtained from the photooxidation of diene 158, were subject to thermolysis or photolysis reactions only hydroxyenone 159 was formed, presumably via the corresponding epoxyketone (cf. Scheme 57). White also found, however, that the desired bis-epoxide 160 could be isolated from the thermolysis of diacetyl endoperoxide 161 in 24% yield [cf. Shing achieved a very similar transformation in 100% yield using CoTPP, Scheme 63], whereas diacetyl endoperoxide 162 gave only an aromatised product 163. Bis-epoxide 160 was then converted into (±)-crotepoxide (150) by hydrogenolysis of the benzyl group followed by benzoylation of the resultant hydroxyl group.

By comparing the syntheses of (±)- and (+)-crotepoxide (150) carried out by White and Shing respectively, the advantage of using CoTPP for the rearrangement of endoperoxides to bis-epoxides in synthesis over the traditional photolysis or thermolysis reactions is evident [27% yield vs. 100% yield].
Chapter 2

Synthesis of meso-Diol

Other transition metal complexes such as those based on Ru(II) and Pd(II) have also been shown to effect the rearrangement of endoperoxides to bis-epoxides. In particular, Noyori has demonstrated that RuCl$_2$(PPh$_3$)$_2$ and PdCl$_2$(PPh$_3$)$_4$ are efficient for this purpose: (Scheme 65).

![Scheme 65: Noyori’s rearrangement of endoperoxide 132 with Ru(II) and Pd(II) complexes.](image)

In light of this extensive precedent, we were confident that conditions could be found to achieve this transformation in our proposed synthesis.

2.2. Results and Discussion.

2.2.1 Synthesis of Dibromodiol 134

The first challenge of this project was the optimisation of the synthesis of dibromo diol 134 from 1,3-cyclohexadiene (131) (Scheme 66).

![Scheme 66: Synthesis of dibromo diol 134. Reagents and Conditions: i) O$_2$, TPP (2.0 mol%), CCl$_4$, hv, 0 °C, 2 h. ii) CoTPP (2.0 mol%), CCl$_4$, RT, 2.75 h. iii) O$_2$, PS-CoTPP (2.0 mol%), MeCN, 0 °C, 21 h. iv) LiBr (1.6 equiv.), CuBr$_2$ (3.2 equiv.), MeCN, RT, 1 h.](image)

It is well known that photosensitisers such as tetraphenylporphyrin (TPP), although necessary for the successful formation of singlet oxygen, can be hard to remove from the desired products after the reaction is complete. One option to overcome this problem is to use solid supported photosensitisers; these polymer supported photosensitisers can then be removed from the product by filtration after the reaction has come to completion. Griesbeck has developed a solvent-free process of photooxidation addressing this issue along with other problems associated with photooxidations. He has achieved this by adsorbing TPP non-covalently onto polystyrene beads cross-linked with divinylbenzene. This is done by swelling the polystyrene beads in an appropriate solvent, adding a catalytic amount of TPP (0.06
Chapter 2

Synthesis of *meso*-Diol

63 mol%) followed by evaporation of the excess solvent. The substrate is then added to the beads in a minimum amount of ethyl acetate and the solvent evaporated again. The resulting solid is then covered with a petri dish and irradiated with a sodium lamp or a halogen lamp with no cooling or addition of oxygen to the system. The desired product can then be washed off the polymer beads with ethanol. Griesbeck has shown that this method of photooxidation has been successful with a range of substrates with comparable yields to what was obtained upon photooxidation under conventional methods.  

As we had previously experienced issues with the removal of TPP from products after photooxidation during the synthesis of (+)-enone 40 (cf. Chapter 1, Section 1.2.1), Griesbeck’s method was an appealing option for our synthesis. We also envisaged that CoTPP could be used as the photosensitiser for our photooxidation of 1,3-cyclohexadiene (131) to endoperoxide 132, this would then allow for *in situ* rearrangement of endoperoxide 132 to *bis*-epoxide 133.

The PS-CoTPP was prepared following the method described by Griesbeck. CoTPP (0.06 mol%) in CH$_2$Cl$_2$ was added to a slurry of polystyrene beads in CH$_2$Cl$_2$. To this slurry was added 1,3-cyclohexadiene (131) and the slurry transferred to a petri dish and excess solvent allowed to evaporate. When the resin was dry it was covered loosely with a watch glass and irradiated with a 300 W lamp for 1.5 h. After this time analysis of the $^1$H NMR spectrum showed a 1:1 ratio of endoperoxide 132/*bis*-epoxide 133. The beads were therefore swollen in CH$_2$Cl$_2$ and stirred for a further 6 h, after this time complete conversion of endoperoxide 132 to *bis*-epoxide 133 was observed by TLC and $^1$H NMR analysis. However *bis*-epoxide 133 was isolated in just 15% yield. The boiling point of 1,3-cyclohexadiene (131) is 80 °C, therefore it is possible that evaporation of the starting material had occurred under the reaction conditions resulting in the low yield. It was also considered that *bis*-epoxide 133 could have a low boiling point, and therefore the product could have been lost on isolation. Notwithstanding the low yield obtained, this reaction did demonstrate that CoTPP could work as an effective photosensitiser.

In order to prevent loss of material during the reaction it was decided that the reaction should be run in solution. This would allow the temperature of the reaction to be lowered to 0 °C which would hopefully minimise the loss of the volatile starting material and intermediates. The ideal solvent was found to be MeCN, as the PS-CoTPP beads could be swollen in this solution without leaching of the CoTPP from the polystyrene. Thus, PS-CoTPP was prepared as previously described, this time without the addition of the 1,3-cyclohexadiene (131). The


dry resin was then swollen in MeCN and cooled to 0 °C before 1,3-cyclohexadiene (131) was added and the reaction mixture irradiated for 4 h with a constant flow of oxygen passing through the reaction mixture. After this time TLC analysis showed the reaction mixture contained both endoperoxide 132 and bis-epoxide 133 and the reaction mixture was allowed to stir at RT under N₂. After 17 h endoperoxide 132 was still present by TLC analysis and a further 0.12 mol % CoTPP and CH₂Cl₂ had to be added before complete conversion to bis-epoxide 133 was observed. Due to the expected low boiling point of bis-epoxide 133 the reaction mixture was filtered and the resin washed with MeCN and the solution treated directly with CuBr₂. After 4 h bis-epoxide 133 had been completely converted to dibromo diol 134 by TLC and ¹H NMR analysis. As we were unsure on the physical properties of dibromo diol 134, acetonide protection was carried out before isolation. Treatment of the crude solution of dibromo diol 134 with DMP and catalytic p-tolyl sulfonic acid gave dibromide 135 in 1 h by TLC analysis. Unfortunately, after attempted isolation by flash chromatography dibromide 135 could not be separated from unknown impurities and in any case the impure dibromide 135 was obtained in just a 20% yield.

The low yield was again attributed to loss of material during the photooxidation. Therefore the reaction was repeated and this time a Teflon cap fitted to the flask, no oxygen was passed through the reaction mixture and the irradiation time shortened to avoid loss of material. The catalyst loading of CoTPP adsorbed onto polystyrene was increased to 0.6 mol% to facilitate full conversion of endoperoxide 132 to bis-epoxide 133. After irradiation for 1 h the reaction mixture was stirred at RT for 17.5 h after which full conversion to bis-epoxide 133 was observed by TLC analysis. The reaction mixture was filtered, treated with CuBr₂ for 3.5 h to give dibromo diol 134, followed by acetonide protection with DMP and catalytic p-tolyl sulfonic acid. However, dibromide 135 was not isolated from the reaction mixture after purification by flash chromatography, instead dibromo diol 134 was isolated in 14% yield as a white crystalline solid, along with another crystalline side product in 44% yield. The structure of the side product was determined as dibromide 164 by comparison with literature data and as well as a single crystal X-ray structure determination that was carried out on the compound (Figure 11). ¹⁰⁶

![Figure 11: Molecular structure of bromide 164 as determined by single crystal X-ray crystallography.](image)
Originally it was suspected that the dibromide 164 had been formed by a reaction between dibromo diol 134 and Cu(I) or Cu(II). However, after some experimentation it was deduced that dibromide 164 was the product of the reaction of 1,3-cyclohexadiene (131) with CuBr₂. During these studies it was discovered that dilithium tetrabromocuprate (Li₂CuBr₄)₁⁰⁷, formed by premixing LiBr and CuBr₂ in MeCN at 0 °C and warming to RT before being added to a solution of bis-epoxide 133, could effect the ring opening of bis-epoxide 133 with slightly better yields than CuBr₂. This reagent also proved to be easier to remove by aqueous work-up in comparison to CuBr₂ and was therefore used in all future reactions. The large amount of dibromide 164 isolated from the reaction demonstrated that full conversion of 1,3-cyclohexadiene (131) to endoperoxide 132 had not been achieved. We now also knew that dibromo diol 134 was a solid and could be isolated before acetonide protection. Therefore, a series of reactions were carried out in order to monitor the conversion of 1,3-cyclohexadiene (131) to endoperoxide 132 and therefore increase the yield of dibromo diol 134 (Table 5).

![Conversion diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>PS-CoTPP</th>
<th>Conversion to endoperoxide 132</th>
<th>Conversion to bis-epoxide 133</th>
<th>Conversion to diol 134</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6 mol%</td>
<td>1.5 h, 100% a</td>
<td>84 h, 85% b</td>
<td>36%</td>
</tr>
<tr>
<td>2</td>
<td>0.6 mol%</td>
<td>12 h, 100% b</td>
<td>28 h, 54% b</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1.0 mol%</td>
<td>12 h, 100% b</td>
<td>37.5 h, 50% b</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2.0 mol%</td>
<td>6 h, 100% b</td>
<td>15 h, 100% b</td>
<td>67%</td>
</tr>
</tbody>
</table>

*Table 5: Conversion of 1,3-cyclohexadiene (131) to dibromo diol 134.* a monitored by GC. b monitored by ¹H NMR.

In order to minimise loss of starting material, all reactions were run in flasks sealed with suba seals. The Ps-CoTPP beads were swollen in MeCN and purged with O₂ for 10 min before the addition of 1,3-cyclohexadiene (131). In order to increase the yield by ensuring all of the starting material had been converted to endoperoxide 132 a reaction was run and monitored by GC (entry 1). After 1.5 h irradiation a peak corresponding to the endoperoxide 132 was present in the GC chromatogram, and no peaks were observed for 1,3-cyclohexadiene (131). The irradiation was therefore stopped and the reaction mixture allowed to stir at RT. After 84 h a maximum conversion of 85% to bis-epoxide 133 was observed by ¹H NMR analysis and
the reaction mixture was filtered. Bis-epoxide 133 was then treated with a solution of Li₂CuBr₄ in MeCN and dibromo diol 134 isolated by flash chromatography in 36% yield along with a small amount of dibromide 164. The low yield was attributed to incomplete conversion to endoperoxide 132, due to 1,3-cyclohexadiene (131) not being consistently detected by GC. It was therefore decided that ¹H NMR analysis would be a better method for monitoring the progress of the reaction. The reaction was repeated and complete conversion of starting material to endoperoxide 132 was achieved after 12 h irradiation (entry 2). However after irradiation was stopped the conversion of endoperoxide 132 to bis-epoxide 133 was not complete after 28 h, with a maximum of 54% conversion observed. In order to increase the conversion of endoperoxide 132 to bis-epoxide 133 a reaction was run using 1.0 mol% CoTPP adsorbed onto PS (entry 3). Endoperoxide 132 formation was achieved after 12 h, but again complete conversion to bis-epoxide 133 was not observed with a maximum of 50% conversion after 37.5 h. Finally the reaction was run using 2.0 mol% CoTPP adsorbed onto PS (entry 4), where conversion to endoperoxide 132 was seen after 6 h irradiation and 100% conversion to bis-epoxide 133 seen after 15 h stirring at RT. Filtration of the reaction mixture and treatment with a solution of Li₂CuBr₄ in MeCN gave dibromo diol 134 in 67% yield after purification.

Despite the good result obtained for the conversion of 1,3-cyclohexadiene (131) to dibromo diol 134 using 2.0 mol% PS-CoTPP this yield could not be reproduced: incomplete conversion to bis-epoxide 133 sometimes occurred. Due to the irreproducible results obtained using PS-CoTPP and the quantity of PS necessary (5-10 g PS for 14 mg CoTPP), the synthesis of dibromo diol 134 was carried out in solution (Table 6).
Chapter 2

Synthesis of meso-Diol

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Scale (mmol)</th>
<th>Conversion to endoperoxide 132</th>
<th>Conversion to bis-epoxide 133</th>
<th>Conversion to diol 134</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CoTPP (2 mol%), MeCN</td>
<td>1.05</td>
<td>8 h, 92%</td>
<td>23.5 h, 23%</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>CoTPP (2 mol%), CCl₄</td>
<td>1.05</td>
<td>Not observed</td>
<td>19 h, 85%</td>
<td>54%</td>
</tr>
<tr>
<td>3</td>
<td>CoTPP (2 mol%), CCl₄</td>
<td>5.25</td>
<td>Not observed</td>
<td>26 h, 70%</td>
<td>66%</td>
</tr>
<tr>
<td>4</td>
<td>TPP (2 mol%), CCl₄ then CoTPP (2 mol%)</td>
<td>5.25</td>
<td>5.5 h, 100%</td>
<td>2.5 h, 100%</td>
<td>68%</td>
</tr>
<tr>
<td>5</td>
<td>TPP (2 mol%), CCl₄ then CoTPP (2 mol%)</td>
<td>10.5</td>
<td>2 h, 100%</td>
<td>2.75 h, 100%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Table 6: Conversion of 1,3-cyclohexadiene (131) to dibromo diol 134.

Whilst the reaction run in MeCN was not successful (entry 1), the reaction run in CCl₄ saw 85% conversion to bis-epoxide 133 after 19 h irradiation (entry 2). It was noted that in this reaction the endoperoxide 132 was not observed at any point by ¹H NMR analysis during the reaction. After treatment with a solution of Li₂CuBr₄ in MeCN dibromo diol 134 was obtained in 54% yield as well as a trace of dibromide 164. In order to check if the yield was reproducible the reaction was repeated on a larger scale (5.25 mmol vs. 1.05 mmol, entry 3). After 26 h irradiation a maximum of 70% conversion of 1,3-cyclohexadiene (131) to bis-epoxide 133 was observed by ¹H NMR analysis. The reaction mixture was treated with a solution of Li₂CuBr₄ in MeCN to give dibromo diol 134 in 66% yield and dibromide 164 in 13% yield after purification. Due to the slow conversion of 1,3-cyclohexadiene (131) to bis-epoxide 133 using CoTPP as the photosensitiser it was decided that TPP would be used as the photosensitiser for the photooxidation to endoperoxide 132, CoTPP could then be added after photooxidation to form bis-epoxide 133. The photooxidation was therefore carried out with 2 mol% TPP in CCl₄ and pleasingly full conversion of starting material to endoperoxide 132 was observed after 5.5 h irradiation (entry 4). CoTPP (2 mol%) was then added to the reaction mixture and after 2.5 h complete conversion to bis-epoxide 133 had occurred by TLC analysis. Treatment of the crude bis-epoxide 133 with a solution of Li₂CuBr₄ in MeCN...
gave dibromo diol 134 in 68% yield after purification. Finally, the reaction was repeated on a larger scale (10.5 mmol vs. 5.25 mmol, entry 5). Full conversion to endoperoxide 132 was observed after 2 h irradiation, CoTPP (2 mol%) was added to give bis-epoxide 133 in a further 2.75 h. Treatment with a solution of Li₂CuBr₄ in MeCN then gave dibromo diol 134 in 64% yield after purification.

In conclusion, a quick, scalable, one pot approach has been optimised for the synthesis of dibromo diol 134 from 1,3-cyclohexadiene (131) in good yields.

2.2.2. Bis-Elimination of Dibromide 135

With a route optimised for the synthesis of dibromo diol 134 acetonide protection to give dibromide 135 could be carried out on a reasonable scale to access enough material for the bis-elimination reaction to be studied (Scheme 67).

![Scheme 67: Acetonide protection of dibromo diol 134. Reagents and Conditions: i) DMP (6.0 equiv.), pTsOH·H₂O (0.2 equiv.), CH₂Cl₂, 0 °C, 2 h, 88%.

A single crystal X-ray structure determination to was carried out on dibromide 135 to confirm the relative stereochemistry obtained after the opening of bis-epoxide 133 (Figure 12).

![Figure 12: Molecular structure of dibromide 135 as determined by single crystal X-ray crystallography.](image)

With plenty of dibromide 135 in hand work was carried out to optimise the bis-elimination to give acetonide 77 (Table 7).
The initial reaction was carried out in MeCN, using DBU as the base under microwave irradiation (entry 1). It was gratifying to see that all the starting material had been consumed by TLC analysis after just 6 min irradiation and acetonide 77 was present by analysis of the $^1$H NMR spectrum. However, there was a significant amount of an aromatic product. It was concluded that this aromatic product was due to the decomposition of the desired product, under the reaction conditions, to give phenol, seen in the $^1$H NMR spectrum as the DBU salt.

In order to prevent the formation of phenol the reaction was run under conventional heating (entry 2). After 16 h at 85 °C the $^1$H NMR spectrum of the crude reaction mixture was very
similar to that obtained from the previous reaction. This time, however, the ratio of phenol present was higher, suggesting that both temperature and reaction time were important parameters to be controlled in order to prevent decomposition of the desired product.

As elimination reactions are known to be solvent dependent it was deemed appropriate at this point in the optimisation process to conduct a small solvent screen (entries 3-7). The reaction time was shortened to 5 h and the conversion of starting material to product analysed by $^1$H NMR spectroscopy. The amount of TBAI was increased from 0.2 equivalents to 1.0 equivalents as it was thought that this might increase the rate of elimination allowing for shorter reaction times. The results show that little or no reaction occurred in toluene or Et$_2$O (entries 3 and 4), and a 15% conversion was observed after 5 h in CH$_2$Cl$_2$ (entry 5). MeCN and THF proved to be the best solvents with conversions of 31 and 35% respectively (entries 6 and 7). It was encouraging to see that the starting material was being converted to the product without the formation of phenol when the reactions were run at 45 °C. Therefore the reaction was repeated in MeCN and THF (entries 8 and 9), this time the reactions were monitored and allowed to heat for 20 h. After this time starting material remained and so a further 4 equivalents of DBU were added and the reactions allowed to heat for a further 4 h. After this time a 77% conversion was observed in MeCN and a 67% conversion in THF.

The optimal reaction conditions at this juncture appeared to be using MeCN as the solvent and >8 equivalents DBU at 45 °C. The reaction was repeated using these conditions, this time using 20 equivalents of DBU and 2 equivalents of TBAI (entry 10). After 4 h no starting material was present by GC analysis, however the product was only isolated in 58% yield. This was disappointing as by $^1$H NMR and TLC analysis full conversion to the product had occurred without the formation of any phenol. The reason for the low yield was concluded to be the low boiling point of acetonide 77 (70 °C, 5 Torr$^{108}$).

In order to overcome this problem it was thought that the use of different protecting groups on dibromo diol 134 could lead to products with higher boiling points after the bis-elimination, and therefore allow for a higher yield of the isolated product (Scheme 68).
Scheme 68: Synthesis of benzoyl and tert-butyldiphenylsilyl protected dibromides 166 and 167. 

Reagents and Conditions: i) BzCl (2.2 equiv.), DMAP (0.1 equiv.), py, 0 °C → RT, 17 h. ii) TBDDSICl (2.2 equiv.), im (4.4 equiv.), DMF, RT, 3.25 h. iii) (20 equiv.), TBAI (2 equiv.), MeCN, 45 °C, 4 h.

The alternative protecting groups chosen were the benzoyl and tert-butyldiphenylsilyl groups as these would give protected meso-diols 103 and 165 which are known solid compounds with melting points of 90.5-91.5 °C and 115-116 °C respectively.\textsuperscript{75} The benzoyl protection was successful giving dibenzoyl ester 166 in 77% yield after purification, however the silyl protection to give disilane 167 was not successful and only starting material was recovered. With dibenzoyl ester 166 in hand the \textit{bis}-elimination was attempted. After 17 h at 45 °C in MeCN the TLC of the crude reaction mixture showed no starting material was present. However, the \textsuperscript{1}H NMR spectrum of the crude reaction mixture showed no expected product. After separation of the major components in the crude reaction mixture by chromatography, mass spectrometric and \textsuperscript{1}H NMR analysis showed mainly aromatic products, suggesting the reaction had been successful but decomposition of the product had occurred. The reaction was repeated, however, after just 1 h of heating the \textsuperscript{1}H NMR spectrum of the crude reaction mixture showed only a mixture of starting material and aromatic products. This established that the benzoyl derivative 103 was even more sensitive to decomposition than the acetonide 77.

Another route explored in order to establish a yield for the \textit{bis}-elimination was to perform an \textit{in situ} Diels-Alder reaction on acetonide 77. These reactions were attempted with a previously synthesised batch of acetonide 77 (Scheme 69).
Scheme 69: Diels-Alder reactions of acetonide 77 with various dieneophiles. Reagents and conditions: i) H₂O, 25 °C, 21 h. ii) DBU (20 equiv.), TBAI (2.0 equiv.), MeCN, 45 °C, 17 h. iii) toluene, 25 °C, 21 h. iv) DBU (20 equiv.), TBAI (2.0 equiv.), MeCN, 45 °C, 17 h. v) toluene, 110 °C, 21 h. vi) DBU (20 equiv.), TBAI (2.0 equiv.), MeCN, 45 °C, 17 h.

The Diels-Alder reaction of DMAD, nitroso benzene and methyl acrylate with acetonide 77 were all successful in the absence of DBU and TBAI. However, when the reactions were carried out in MeCN at 45 °C in the presence of DBU and TBAI either starting material or no desired products were recovered from the reaction. This was most likely due to the fact that DBU also reacted with the dienophiles preventing the desired reaction occurring. As it was planned that the Diels-Alder reaction would take place in situ, this route was not explored any further due to the reactivity of DBU with the dienophiles.

As acetonide 77 had been synthesised previously from the protection of meso-diol obtained commercially from the microbial oxidation of benzene (cf. Chapter 1, Section 1.2.1) in good yield it was decided that issues with isolation of the desired product were due to the scale of the reaction being carried out (i.e. milligram scale vs. gram scale). Therefore the reaction was repeated on a larger scale (Table 8).
Table 8: Large scale *bis-*elimination of dibromide 135 to acetonide 77.

The first larger scale reaction was carried out with 10 equivalents of DBU and 2 equivalents TBAI in MeCN (*N.B.* 10 equivalents of DBU were used instead of 20 equivalents due to issues faced previously with incomplete removal of DBU after an aqueous work-up, entry 1). After 3 h at 45 °C the reaction was complete by TLC and GC analysis. After an aqueous work-up, Et₂O was removed by distillation at 45 °C. In order to remove the MeCN, MeOH was added to form an azeotrope with MeCN and distilled at 75 °C to give acetonide 77 in 56% yield. It was thought that the yield of isolation could be improved further by running the reaction in CH₂Cl₂ instead of MeCN, as it was found that some product was lost when the distillation temperature had to be increased in order to remove the MeCN. The reaction was repeated on a similar scale in CH₂Cl₂ (entry 2), and after 2 h at 45 °C GC analysis showed complete conversion to acetonide 77. After work-up and removal of CH₂Cl₂ by distillation at 55 °C acetonide 77 was isolated in 83% yield.
2.3. Conclusions

The first aim of this project was the synthesis of dibromo diol 134. The issue faced with this synthesis was the low boiling points of the starting material, 1,3-cyclohexadiene (131) and the intermediate bis-epoxide 133. This was overcome, firstly by ensuring the reaction vessel was purged with oxygen before the addition of 1,3-cyclohexadiene (131) and the photooxidation carried out at 0 °C in a sealed flask. Secondly, the procedure for converting 1,3-cyclohexadiene (131) to dibromo diol 134 via endoperoxide 132 and bis-epoxide 133 was achieved using a one-pot procedure, avoiding the need to isolate bis-epoxide 133. This one-pot procedure was accomplished in two ways, firstly by using CoTPP, adsorbed onto polystyrene or in solution, acting as the photosensitiser for the photooxidation of 1,3-cyclohexadiene (131) to endoperoxide 132 and as the catalyst for converting endoperoxide 132 to bis-epoxide 133. However, a quicker and more scalable approach was developed using TPP as the photosensitiser to convert 1,3-cyclohexadiene (131) to endoperoxide 132, followed by CoTPP addition to give bis-epoxide 133, and finally treatment with a preformed solution of Li₂CuBr₄ gave dibromo diol 134 in 64-68% yield in approximately 6 h.

The second aim of the project was to optimise the bis-elimination of dibromide 135 to give the desired acetonide 77. The main issue faced with this step was the low boiling point of the desired product, and the facile decomposition of the product at high temperatures to give phenol. These matters were overcome, firstly by running the reaction at 45 °C and secondly conducting the reaction on a reasonable scale in CH₂Cl₂ allowing the solvents to be removed by distillation. Acetonide 77 was isolated in 83% yield.

In conclusion, the synthesis of acetonide 77 from commercially available 1,3-cyclohexadiene (131) has been achieved in a 5 step, 3 pot synthesis with an overall yield of 50%.
3.1. Introduction

3.1.1. Recent Advances in the Asymmetric Hydroamination (AHA) Reaction

Amines are an extremely important class of compounds within all aspects of chemistry, with many biologically important and natural products containing amine functionalities. The hydroamination of alkenes and alkynes has become a very important reaction for the formation of \( C-N \) bonds and comprises the reaction between the \( N-H \) of an amine and an unsaturated \( C-C \) bond in an inter- or intramolecular fashion (Scheme 70).\(^ {112} \)

![Scheme 70: General inter- and intramolecular hydroamination reactions.\(^ {111} \)](image)

The hydroamination reaction is an atom economic process making it a very appealing reaction for the formation of nitrogen containing compounds. Although the hydroamination of alkenes is a thermodynamically allowed process most reactions require a catalyst for the reaction to occur, for the following reasons:\(^ {113} \)

- The electrostatic repulsion between the nitrogen lone pair and the electron rich \( \pi \) bond of the alkene as they come together to react results in a high activation barrier.
- A [2+2] addition between the \( N-H \) and the \( C=C \) double bond is orbital symmetry forbidden and is unfavourable due to the difference in energy between the alkene \( \pi \) bond and the \( N-H \) \( \sigma \) bond.
- Due to the negative enthalpy of the reaction, the activation barrier cannot be overcome by heating the reaction, as the equilibrium is then shifted towards the starting materials.

Over the last 10 years there has been a significant rise in the amount of research being conducted towards the development of efficient catalysts for the hydroamination reaction\(^ {112} \), with much focus being directed towards the development of asymmetric hydroamination (AHA) reactions.\(^ {113} \) A variety of different catalysts have been used to effect this
transformation, including ones based on rare earth metals, transition metals, and main group metals. The hydroamination reaction was reviewed comprehensively by Müller and Beller in 1998 and more recently by Müller and Hultzsch in 2008.\textsuperscript{112,114} Additionally, the AHA reaction has been reviewed by Hultzsch\textsuperscript{113,115} and more recently by Schulz\textsuperscript{116} and Chemler.\textsuperscript{117} This section will highlight some recent examples of intramolecular AHA reactions.

Hultzsch and Livinghouse have shown independently that rare earth metal binaphthalate complexes of lanthanum, scandium, yttrium and lutetium are efficient catalysts for the AHA reaction.\textsuperscript{118-119} Livinghouse’s yttrium bis(thiolate) complexes have catalysed the AHA reaction in good yields with enantioselectivities of up to 87% ee (Table 9).\textsuperscript{118}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & \(R^1, R^2, R^3\) & Time (h) & Yield (\(^{1}H\) NMR) & ee (%) \\
\hline
1 & H, H, H & 8 & > 95\% & 81 \\
2 & Me, H, H & 9 & > 95\% & 87 \\
3 & Me, Ph, H & 3 & > 95\% & 82 \\
4 & H, H, Me & 30 & > 95\% & 69 \\
\hline
\end{tabular}
\caption{Selected examples of Livinghouse’s AHA reaction.\textsuperscript{118}}
\end{table}

Using the yttrium catalyst shown, Livinghouse has reported that the reaction of \textit{gem} dimethyl containing substrates are complete within 3 and 9 h in 87\% and 82\% ee respectively (entries 2 and 3). He has also shown that \textit{N}‐alkylated substrates (entry 4) are successfully cyclised, albeit with a longer reaction time of 30 h and a slightly lower enantioselectivity of 69\% ee.

Hultzsch has reported that his 3-3’-\textit{bis}(trisarylsilyl)-substituted binaphthalate rare earth metal complexes can catalyse the AHA reaction in good yields and enantioselectivities (Table 10).\textsuperscript{119}
Hultsch’s scandium and lutetium complexes were able to catalyse the AHA reaction in high yields, within reasonable time scales and at moderate temperatures for most substrates studied. The highest enantioselectivities of 85-95% ee were obtained with substrates in the absence of terminal alkene or nitrogen substituents (entries 1, 3 and 4) with the exception of the gem dimethyl substrate, of which a lower, 69% ee was reported (entry 2). Substrates with terminally substituted alkenes underwent the reaction in good yields and enantioselectivities of up to of 72% ee, however the reaction temperature had to be increased up to 100 °C (entry 5). N-alkylated substrates gave the desired products in good yields, however with a lower enantioselectivity of 53% ee (entry 6).

As demonstrated by Livinghouse and Hultsch, rare earth metal complexes are effective catalysts for the AHA reaction. However, these complexes are often extremely air and moisture sensitive and consequently the use of a glove box is often required to set up and run these reactions. Therefore the development of catalysts based on more stable transition metal complexes has become an important area of research.

Group 4 metals have been studied and have been shown to act as efficient catalysts for the AHA reaction. Schafer has reported that impressive enantioselectivities of up to 93% ee can be obtained with her chiral neutral zirconium amidate complexes (Table 11).
Schafer’s zirconium complex can catalyse the AHA reaction of a simple test substrate in just 3 h with a 93% ee (entry 1), the highest ee value obtained for this particular substrate to date [cf. 87% ee for Livinghouse’s catalyst and 69% ee for Hultsch’s catalyst]. Other substrates bearing a gem dialkyl group have reacted successfully under these reaction conditions with good enantioselectivities of 74-88% ee being obtained (entries 2-4). However, no examples of substrates without a gem dialkyl group have been reported with this catalyst.

Taking a step towards expanding the substrate scope of this reaction, Buchwald has recently demonstrated the use of dialkylbiaryl phosphine ligands in the rhodium catalysed AHA reaction (Table 12).
Chapter 3 Asymmetric *retro*-Cope Elimination Reaction

![Chemical structure](image)

**Table 12:** Selected examples of Buchwald’s AHA reaction.\(^\text{121}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ar</th>
<th>L</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>C(_6)H(_5)</td>
<td>9</td>
<td>50</td>
<td>24</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>2-CH(_3)C(_6)H(_4)</td>
<td>9</td>
<td>50</td>
<td>24</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>2-CH(_3)C(_6)H(_4)</td>
<td>9</td>
<td>70</td>
<td>20</td>
<td>75</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>2-CH(_3)C(_6)H(_4)</td>
<td>8</td>
<td>70</td>
<td>20</td>
<td>50</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>4-ClC(_6)H(_4)</td>
<td>8</td>
<td>70</td>
<td>20</td>
<td>63</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>4-CO(_2)MeC(_6)H(_4)</td>
<td>8</td>
<td>70</td>
<td>20</td>
<td>61</td>
<td>83</td>
</tr>
</tbody>
</table>

Buchwald demonstrated that the AHA reaction would proceed in good yields and with good enantioselectivities at reasonable temperatures when using binaphthyl ligand L\(_9\) with *gem* diphenyl substituted substrates (entries 1 and 2). However, the enantioselectivity dropped to 62% ee when a *gem* dimethyl group replaced the *gem* diphenyl group (entry 3). He reported that L\(_8\) was a superior ligand with substrates in the absence of a *gem* dialkyl group and was able to obtain the desired products in 83-86% ee, albeit in slightly lower yields (entries 4-6). These examples also demonstrate that aryl chlorides (entry 5) and esters (entry 6) are stable to the reaction conditions, leading to products that are available to further modifications. Buchwald also showed that the protecting group on the nitrogen (*cf.* Ar = 2-CH\(_3\)C\(_6\)H\(_4\)) could be removed from the products of the AHA reaction by catalytic transfer hydrogenation in high yields (92%), to give the corresponding *N*-H pyrrolidines.

The examples described above demonstrate the high level of research being undertaken in the field of AHA, with a variety of different catalysts able to obtain the desired products in high yields and enantioselectivities. However, despite this recent progress the AHA reaction still requires the development a general catalyst that can provide high yields and enantioselectivities for a broad range of substrates.
3.1.2. Recent Advances in the retro-Cope Elimination Reaction

As discussed in Chapter 1, in the context of our use of this reaction as a key step in the synthesis of (±)-clivonine (1), the retro-Cope elimination is the suprafacial concerted thermal cyclisation of an unsaturated hydroxylamine to its corresponding pyrrolidine or piperidine N-oxide or N-hydroxyl derivative. It constitutes a possible alternative reaction to the direct hydroamination of alkenes, as described above, for the formation of new C-N bonds (Scheme 71, cf. Section 1.1.5.2)

![Scheme 71: A general retro-Cope elimination reaction.](image)

The retro-Cope elimination was reviewed comprehensively by Cooper and Knight in 2004, where they highlighted the scope and limitations of this reaction.\textsuperscript{32} Experimental evidence presented by Black and Doyle and independently by Ciganek has demonstrated that when the alkene is terminally substituted the cyclisation does not occur or is extremely slow (cf. Chapter 1, Section 1.1.5.2, Scheme 18).\textsuperscript{34,37} Ciganek also showed that whilst 6-membered N-oxides could be obtained from their corresponding hydroxylamines, 3-, 4- or 7-membered N-oxides could not be synthesised.\textsuperscript{37} There is also evidence that secondary hydroxylamines undergo cyclisation faster than that of the corresponding primary hydroxylamines.\textsuperscript{32,37}

Recently the group of Beauchemin have significantly expanded the scope of the retro-Cope elimination reaction and have developed an intermolecular variant. This section will review the work carried out by Beauchemin over the last 2-3 years.

Since many retro-Cope elimination reactions have been carried out using secondary hydroxylamines, the first intermolecular retro-Cope elimination reaction developed by Beauchemin was of alkynes with aqueous hydroxylamine (Table 13).\textsuperscript{122-123}
Chapter 3

Asymmetric retro-Cope Elimination Reaction

\[
\begin{array}{c}
\text{R}^1 \equiv - \text{R}^2 \\
\stackrel{\text{aq. NH}_2\text{OH}}{\text{113-140 °C}} \\
\text{NOH} \\
\end{array}
\]

Table 13: Selected examples of Beauchemin’s intermolecular retro-Cope elimination reaction with alkynes.\(^{122-123}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R^1 = Ph, R^2 = H</td>
<td>A</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>R^1 = 4-OMeC_6H_4, R^2 = H</td>
<td>A</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>R^1 = 4-FC_6H_4, R^2 = H</td>
<td>A^2</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>R^3 = 3-MeC_6H_4, R^2 = H</td>
<td>A</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>R^1 = n-C_6H_{13}, R^2 = H</td>
<td>B</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>R^1 = R^2 = Ph</td>
<td>C</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>R^1 = Ph, R^2 = Me</td>
<td>B</td>
<td>53</td>
</tr>
<tr>
<td>8</td>
<td>[\text{Alkene} ]</td>
<td>A^*</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>[\text{Alkene} ]</td>
<td>B</td>
<td>72</td>
</tr>
<tr>
<td>10</td>
<td>R^3 = H, Bn, Piv, PMB</td>
<td>B</td>
<td>91, 98, 90, 98</td>
</tr>
<tr>
<td>11</td>
<td>R^3 = H, Me, Ph</td>
<td>D, B, B</td>
<td>89, 75, 63</td>
</tr>
</tbody>
</table>

Table 13: Selected examples of Beauchemin’s intermolecular retro-Cope elimination reaction with alkynes.\(^{122-123}\)

After some experimentation Beauchemin found that by heating phenylacetylene and aqueous hydroxylamine in dioxane (1 M) at 113 °C in a sealed tube the desired oxime was obtained in 87% yield with only a 5% yield of the anti-Markovnikov product being isolated (entry 1). He then went onto show that these optimised conditions were successful with a range of alkynes containing various aryl substituents (entries 2-4). More challenging substrates such as 1-octyne (entry 5) and disubstituted alkynes (entries 6 and 7) reacted more efficiently when i-PrOH was used as the solvent and the reaction heated to 140 °C under conventional heating or microwave irradiation. Finally, Beauchemin demonstrated that the reaction was successful with alkynes bearing a pyridyl group (entry 8) and also free and protected hydroxyl groups (entries 10 and 11).
Having developed a successful procedure for the intermolecular retro-Cope elimination of alkynes with aqueous hydroxylamine, Beauchemin explored this new method with selected, activated alkenes (Table 14).\(^{122-123}\)

![Retro-Cope elimination reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>NH(_2)OH (equiv.)</th>
<th>Temp. (°C)</th>
<th>Yield (% A + B)</th>
<th>Ratio (A:B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Alkene 1" /></td>
<td>2</td>
<td>95</td>
<td>99</td>
<td>1:2.2</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Alkene 2" /></td>
<td>10</td>
<td>95</td>
<td>65</td>
<td>7.1:1</td>
</tr>
<tr>
<td>3a</td>
<td><img src="image" alt="Alkene 3a" /></td>
<td>2</td>
<td>95</td>
<td>98</td>
<td>1:1.5</td>
</tr>
<tr>
<td>3b</td>
<td><img src="image" alt="Alkene 3b" /></td>
<td>10</td>
<td>95</td>
<td>49</td>
<td>14:1</td>
</tr>
<tr>
<td>3c</td>
<td><img src="image" alt="Alkene 3c" /></td>
<td>2</td>
<td>95</td>
<td>95</td>
<td>1.9:1</td>
</tr>
<tr>
<td>3d</td>
<td><img src="image" alt="Alkene 3d" /></td>
<td>2</td>
<td>95</td>
<td>48</td>
<td>&gt; 20:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Alkene 4" /></td>
<td>2</td>
<td>95</td>
<td>55</td>
<td>&gt; 20:1</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Alkene 5" /></td>
<td>2</td>
<td>140</td>
<td>39</td>
<td>2:2:1</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Alkene 6" /></td>
<td>2</td>
<td>95</td>
<td>30</td>
<td>&gt; 20:1</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Alkene 7" /></td>
<td>2</td>
<td>115</td>
<td>13</td>
<td>&gt; 20:1</td>
</tr>
</tbody>
</table>

Table 14: Selected examples of Beauchemin’s intermolecular retro-Cope elimination reaction with alkenes.\(^{122-123}\)

\(^{123}\) aq. NH\(_2\)OH (x equiv.), alkene (1 equiv.), i-PrOH (5 M), sealed tube, blast screen, 24-48 h.

Initial experiments with norbornene and aqueous hydroxylamine demonstrated that the choice of solvent was very important for the success of this reaction. Whilst conditions used for the reaction of aryl alkynes (cf. Table 13, entries 1-4) resulted in almost no conversion of starting material, the reaction run in alcoholic solvents appeared to be more successful. After some optimisation it was found that heating norbornene and aqueous hydroxylamine in i-PrOH (5 M) at 95 °C in a sealed tube for 14 h gave a near quantitative yield of a mixture of primary and secondary hydroxylamines A and B (entry 1). Interestingly, Beauchemin reported that when 10 equivalents of aqueous hydroxylamine were used in the reaction compared to 2 equivalents the major product was the primary hydroxylamine A (entries 2 and 3b). Using his optimised conditions Beauchemin demonstrated that the intermolecular retro-Cope reaction...
elimination was successful with a range of alkenes. Strained and hindered bicyclic alkenes lead to the selective formation of the primary hydroxylamines (entries 3d and 4). Styrene and other vinylarenes lead to the desired hydroxylamine products under the reaction conditions, however, in lower yields (entries 5-7).

Beauchemin noted that since the reaction of aqueous hydroxylamine with alkenes gave a mixture of primary and secondary hydroxylamines A and B, the primary hydroxylamine A must be reactive under the optimised conditions to undergo a second retro-Cope elimination to form the secondary hydroxylamine B. Therefore, reactions were carried out in order to extended the intermolecular retro-Cope elimination of alkenes with N-alkylhydroxylamines (Table 15).

\[
\text{R}^1\text{N}=\text{O} + \text{HN}_{\text{R}_2}\xrightarrow{\text{Conditions}} \text{R}^1\text{N}^\circ\text{R}_2\text{O}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>(\text{R}_2)</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="norbornene" /></td>
<td>Cy</td>
<td>A</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="bicyclic alkene" /></td>
<td>Bn</td>
<td>A</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="bicyclic alkene" /></td>
<td>sec-butyl</td>
<td>A</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="bicyclic alkene" /></td>
<td>norbornane</td>
<td>A</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="n-propyl" /></td>
<td>Bn</td>
<td>B</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="styrene" /></td>
<td>Bn</td>
<td>B</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="n-propyl" /></td>
<td>Bn</td>
<td>B</td>
<td>36</td>
</tr>
</tbody>
</table>

**Table 15:** Selected examples of Beauchemin’s intermolecular retro-Cope elimination with N-alkylhydroxylamines and alkenes.\(^{123}\) A = alkene (2 equiv.), hydroxylamine (1 equiv.), NaCNBH\(_3\) (1 equiv.), \(n\)-PrOH (0.6 M), sealed tube, 110 °C, 18 h. B = alkene (2 equiv.), hydroxylamine (1 equiv.), NaCNBH\(_3\) (1 equiv.), \(n\)-PrOH (0.6 M), sealed tube, 140 °C, 14-18 h.

Initial attempts to react \(N\)-cyclohexylhydroxylamine with norbornene resulted in the isolation of the corresponding cyclohexanone oxime of \(N\)-cyclohexylhydroxylamine as the major product. However, after some experimentation Beauchemin found that \(n\)-PrOH was the optimal solvent for the reaction. He also conducted an additive screen and discovered that the
addition of 1 equivalent of NaCNBH3 in the reaction prevented the oxidation of the hydroxylamine to its corresponding oxime. He did, however, show with control experiments that the NaCNBH3 was inhibiting the oxidative process yielding the oxime, instead of simply reducing the oxime back to the hydroxylamine, as this process requires the presence of acid (cf. Borch reduction55, Chapter 1, Section 1.2.3). Under the optimised conditions the reaction of \( N \)-cyclohexylhydroxylamine with norbornene afforded the desired product in 83% yield (entry 1). These reaction conditions were then employed to study the reaction of norbornene with various \( N \)-alkylhydroxylamines, with good yields being obtained for different alkyl substituents (entries 2-4). Finally, the scope of the reaction with respect to the alkene was investigated and \( N \)-benzylhydroxylamine was reacted with a range of vinilarenes in reasonable yields (entries 5-7). Interestingly, when the vinilarenes were substituted with electron withdrawing groups (e.g. CF3) the anti-Markovnikov product was favoured.123

Beauchemin has also developed a tandem intermolecular retro-Cope elimination of \( N \)-alkylhydroxylamines with alkenes followed by a [2,3]-Meisenheimer rearrangement to effect the cyclisation of difficult substrates. He has used an intramolecular variant of this methodology to synthesise the alkaloids conine (168) and norreticuline (169) (Scheme 72).124

\[
\text{Scheme 72: Beauchemin’s synthesis of conine (168) and norreticuline (169) via an intramolecular retro-Cope elimination.124 Reagents and Conditions: i) benzene (0.01 M), H2O (10 equiv.), sealed tube, 140 °C, 47%. ii) AcOH (10 M), Zn dust (20 equiv.), 55 °C, 4 h. iii) benzene (0.01 M), H2O (10 equiv.), sealed tube, 120 °C, 54%. iv) AcOH/H2O (1:1), Zn dust (5.0 equiv.), RT, 1.5 h. v) BCl3 (4.4 equiv., 1.0 M soln. in CH2Cl2), CH2Cl2, -10 °C → 0 °C, 2 h, 45%.}
\]

In addition to the synthesis of the alkaloids conine (168) and norreticuline (169), Beauchemin has also synthesised the natural products pumiliotoxin C (170) and 2-epi-pumiliotoxin C (171) via an intramolecular retro-Cope elimination (Scheme 73).125
Scheme 73: Beauchemin’s synthesis of pumiliotoxin C (170) and 2-epi-pumiliotoxin C (171). Reagents and Conditions: i) n-PrOH (0.15 M), H₂O (10 equiv.), 180 °C, microwave irradiation, 5 h. ii) Zn/AcOH.

For this synthesis Beauchemin initially attempted the retro-Cope elimination of hydroxylamines 172 and 173 under the conditions reported by Oppolzer for his synthesis of lycorane [C₆H₆ (0.01 M), 180 °C][23], however, no cyclisation was observed. However, when the reaction was run in n-PrOH at 180 °C under microwave irradiation cyclisation of both C2 epimers was observed to give cyclised hydroxylamines 174 and 175. The reason for the dramatic change in reactivity was proposed to be due to the fact that n-PrOH assists the proton transfer step between the amine N-oxide intermediate and the hydroxylamine product. This possible explanation will be examined further in the next section (Section 3.1.3).

Following on from the intermolecular retro-Cope elimination of hydroxylamines with alkynes and alkenes, Beauchemin has also demonstrated that hydrazines can be used in the retro-Cope elimination with alkynes to give predominantly the anti-Markovnikov products.[126] He has also shown that hydrazines can be used in an intramolecular retro-Cope elimination with alkenes to give 5- and 6-membered rings (Scheme 74).[127]

Scheme 74: Beauchemin’s retro-Cope elimination reaction with hydrazines.[126-127]

Finally, Beauchemin has also demonstrated that ketonitrones can be synthesised via the intermolecular retro-Cope elimination reaction of alkenes with hydroxylamines (Scheme 75).[128-129]
Scheme 75: Beauchemin’s synthesis of ketonitrones via the retro-Cope elimination. 128-129

This section has highlighted how the scope of the retro-Cope elimination has been extended over the past few years, and demonstrated the need for more research to be undertaken to further increase the utility of this reaction.

3.1.3. Mechanistic Studies of the retro-Cope Elimination

Beauchemin has undertaken detailed density functional theory (DFT) calculations in order to probe the mechanism of the retro-Cope elimination reaction, studying the nature of the transition states of the initial cyclisation and the proton transfer step. 123 Beauchemin first mapped the potential energy characteristics of the reaction, determining the thermodynamic profiles of the reactions of alkenes and alkynes (Figure 13).

Figure 13: Beauchemin’s potential energy profiles for the reaction of alkynes (LHS) and alkenes (RHS). (Images taken from ref 122).

These results demonstrate that the activation barrier of the retro-Cope elimination reaction is very similar for both alkynes and alkenes. However, there is a large difference in the activation barriers for the proton transfer step. With alkynes the activation barrier of the proton transfer (PT) step is very similar to that of the initial cyclisation (IC) step ($\Delta G_{PT} = 30.1$ vs. $\Delta G_{IC} = 30.1$ kcal/mol for phenylacetylene). Whereas in the case of alkenes the intramolecular proton transfer step is rate limiting ($\Delta G_{PT} = 37.7$ vs. $\Delta G_{IC} = 32.0$ kcal/mol for norbornene). This provides an explanation as to why the retro-Cope elimination reaction of alkenes carried out by Beauchemin were solvent dependant and only successful in protic
Beauchemin postulated that similarly to the intramolecular reaction the intermolecular retro-Cope elimination would also be a concerted process (cf. Ciganek’s and Oppolzer’s mechanistic studies Chapter 1, Section 1.1.5.2). In order to gain more insight into the mechanism he determined the transition state structures for several different alkenes and alkynes and in all cases the results showed the involvement of 5-membered, coplanar transition states corresponding to concerted processes. He then studied the transition state of the proton transfer step from the $N$-oxide intermediate to the hydroxylamine product, in order to demonstrate the importance of this step and to determine the reason for the positive effect on rates observed in protic solvents. Three possible proton transfer transition states were studied (Figure 14).

![Figure 14: The three transition states A, B and C for the proton transfer in the retro-Cope elimination as studied by Beauchemin.](image)

The calculated energy of the intramolecular transition state A is high, due its 3-membered character. The bimolecular transition state B was calculated to have the lowest energy with the proton transfer occurring between the amine oxide and a protic species such as $i$-PrOH, explaining why some reactions react much better in protic solvents. An alternative transition state would be that of C, the $N$-oxide dimer. However, Beauchemin claimed that this transition state would be kinetically unlikely, it also did not account for the positive effects of the protic solvent.

### 3.1.4. Project Aims

The hydroamination of alkenes is an important reaction for the formation of new $C-N$ bonds, with many recent advances being made towards the AHA reaction. However, as previously discussed, this reaction requires the use of a catalyst, and there remains to be a general catalyst available for the AHA for a broad range of substrates. The retro-Cope elimination
could be used an alternative to the hydroamination reaction for the formation of C-N bonds, one advantage being that this reaction does not require the use of a catalyst to proceed. Beauchemin has recently expanded the scope of the retro-Cope elimination reaction, however, in order for the retro-Cope elimination to compete with the hydroamination reaction an asymmetric variant needs to be developed. The main aim of this project, therefore, was to develop an asymmetric retro-Cope elimination reaction.

The first step of the retro-Cope elimination is the reversible cyclisation to give the amine N-oxide intermediate. An irreversible proton transfer then occurs to give the N-hydroxyl pyrrolidine product (Scheme 76).

Scheme 76: Our proposed asymmetric retro-Cope elimination reaction.

Beauchemin has demonstrated by experiment and DFT calculations that the rate determining step of the reaction is the proton transfer step, and that this step is facilitated by protic solvents such as i-PrOH. Theoretically, if a chiral proton source could catalyse the proton transfer step, a dynamic kinetic resolution process could be set up in which only one enantiomer of the amine N-oxide intermediate undergoes the proton transfer leading to enantiomerically enriched products (Scheme 76).

The first aim of this project was to find a suitable system that could be used for the development of such an asymmetric retro-Cope elimination reaction. This system would be required to react at a reasonable rate, allowing for the reaction to be monitored by $^1$H NMR spectroscopy. To this end, the system would also require the starting material and product to have distinctive peaks in their $^1$H NMR spectra for simple, accurate analysis. Finally, the synthesis of suitable substrates needed to be designed so that analogues can be easily synthesised.
3.2. Results and Discussion

3.2.1. Synthesis of Oximes 180a-180g

In order to develop a suitable system to study the retro-Cope elimination reaction a robust route to a range of potential substrates of varying electronic demand needed to be established. The following route was developed for hydroxylamine 176a before being developed for the synthesis of other analogues (Scheme 77).

\[
\begin{align*}
178 & \xrightarrow{i) \; \text{Br} \rightarrow O_2N \rightarrow H_{177} \rightarrow O_2N \rightarrow H_{179a} \rightarrow OH_{176a} \\
\text{Scheme 77: Synthesis of hydroxylamine 176a. Reagents and Conditions: } & i) \text{NaNO}_2 \text{ (1.1 equiv.), DMF, 8 h, 32%}. \text{ii) styrene (7.2 equiv.), Grubbs II catalyst (7 mol%), CH}_2\text{Cl}_2, 45 ^\circ \text{C, 21 h, 65%}. \text{iii) } \text{SmI}_2 \text{ (4.0 equiv., 0.1 M in THF), THF/MeOH (2:1), 3 min.}
\end{align*}
\]

The first step of the synthesis was formation of 5-nitropent-1-ene (177) from commercially available 5-bromopent-1-ene (178) with sodium nitrite in DMF.\(^\text{130}\) The highest yield obtained for this reaction was just 32%, most likely due to the low boiling point of the product (82 °C, 32 mmHg\(^\text{131}\)). With 5-nitropent-1-ene (177) in hand the cross metathesis with styrene using Grubbs second generation catalyst was attempted following methodology developed by Parsons.\(^\text{130}\) Pleasingly, the reaction was successful to give nitroalkene 179a in 65% yield after purification (as an inseparable mixture of stereoisomers in a ratio of 0.14:1 cis/trans by \(^1\)H NMR analysis). The next step was the formation of hydroxylamine 176a from nitroalkene 179a. This was first attempted directly using SmI\(_2\) (Scheme 77).\(^\text{132}\) Thus, a solution of nitroalkene 179a in THF/MeOH (2:1) was cannulated into a solution of SmI\(_2\) (0.1 M in THF, 4.0 equiv.) to which the colour immediately changed from dark blue to yellow. This suggested that there was oxygen in the substrate solution, however, after the addition of a further 4 equivalents of SmI\(_2\) solution the reaction mixture retained the blue colour. After 3 min no starting material was present by TLC analysis and the reaction immediately quenched with a 10% aqueous sodium thiosulfate solution. The \(^1\)H NMR spectrum of the crude reaction mixture showed one major product had formed. A characteristic upfield shift, of the triplet of the CH\(_2\) group α to the nitrogen, from ~ δ 4.46 ppm to ~ δ 3.04 ppm was observed suggesting the reaction had been successful. However, it was not clear if reduction to hydroxylamine 176a or over reduction to the corresponding amine had occurred. Separation of the major product by flash chromatography followed by IR analysis showed the presence of an OH peak, again suggesting the formation of hydroxylamine 176a had been successful. However,
when the reaction was repeated the $^1$H NMR of the crude reaction mixture showed two major products had been formed. Unfortunately, attempts to isolate any of the expected product by flash chromatography were not successful.

As reactions with SmI$_2$ are known to be capricious and difficult to scale-up, an alternative route to hydroxylamine 176a via oxime 180a was explored (Scheme 78).

![Scheme 78: Synthesis of hydroxylamine 176a via oxime 180a. Reagents and Conditions: i) BnBr (1.1 equiv.), KOH (1.35 equiv.), TBAI (15 mol%), THF, 25 °C, 22 h, 61%. ii) NaCNBH$_3$ (2.0 equiv.), MeOH/HCl (10:1), methyl orange, MeOH, 0 °C, 40 min, 91%.](image)

Following Carreira’s procedure, nitroalkene 179a was treated with 1.1 equivalents of benzyl bromide, 1.05 equivalents of KOH and 15 mol% of TBAI in THF at RT. After 6 h, a 75% conversion of nitroalkene 179a to oxime 180a was observed by $^1$H NMR analysis, therefore a further 0.3 equivalents of KOH were added and the reaction mixture allowed to stir for a further 16 h. After this time complete consumption of the starting material had been observed by TLC analysis and oxime 180a was isolated in 61% yield after purification (1:0.9 cis/trans by $^1$H NMR spectroscopy, stereoisomers were not separated and taken through to the next step as a mixture). As hydroxylamines can be unstable upon storage the final Borch reduction$^{55}$ (cf. Chapter 1, Section 1.2.3) of oxime 180a to give hydroxylamine 176a was not carried out until immediately before the retro-Cope elimination reaction was to be run.

With a successful route to oxime 180a achieved oximes 180b-180f were successfully synthesised using the same pathway (Scheme 79).

![Scheme 79: Synthesis of oximes 180b-180f. Reagents and Conditions: i) styrene (3.6-7.2 equiv.), Grubbs II catalyst (5-7.5 mol%), CH$_2$Cl$_2$, 45 °C, 18.5-30.5 h, 35-59%. ii) BnBr (1.1 equiv.), KOH (1.35 equiv.),TBAI (15 mol%), THF, RT, 6-18.5 h, 44-68%.](image)
Cross metathesis of 5-nitropent-1-ene (177) with the appropriate styrene gave nitroalkenes 179b-179f in 35-57% yields. Treatment of the nitroalkenes 179b-179f with benzyl bromide, KOH and TBAI gave the oximes 180b-180f in 44-68% yields after purification (cis/trans ratios of the cross metathesis and the oxime formation reactions are detailed in the Experimental Section, Chapter 4). These substrates were selected for synthesis, as it was planned to investigate the influence of electron withdrawing and electron donating aryl substituents on the rate of the reaction, so as to identify a convenient substrate for catalyst development.

Additionally, oxime 180g was prepared in two steps from 4-pentenal (181) in order to assess the influence of a terminal alkyl group on the rate of the retro-Cope elimination (Scheme 80).

**Scheme 80:** Synthesis of oxime 180g. **Reagents and Conditions:** i) Grubbs II catalyst (4 mol%), CH₂Cl₂, 45 °C, 3.25 h, 18%. ii) NH₂OH·HCl (3.78 equiv.), NaOAc (4.7 equiv.), CH₂Cl₂, MeOH, RT, 1 h, 98%.

The cross metathesis of 5-nitropent-1-ene (177) with 4-phenylbut-1-ene (182) was attempted but no reaction was observed under conventional heating. Microwave irradiation lead to the formation of the desired product, however, homocoupled species of both coupling partners were also formed. Gratifyingly, the cross metathesis of 4-phenylbut-1-ene (182) with 4-pentenal (181) gave aldehyde 183, albeit in low yield. Treatment of aldehyde 183 with NH₂OH·HCl and NaOAc (cf. Chapter 1, Section 1.2.2.) gave oxime 180g in 98% yield after purification (cf. Scheme 80).
3.2.2. retro-Cope Elimination Rate Studies

With oximes 180a-180g in hand, studies of the rate of the retro-Cope elimination reaction could begin in order to find a suitable system to study the asymmetric retro-Cope elimination reaction. Firstly, the Borch reductions of oximes 180a-180d and 180g were carried out to give hydroxylamines 176a-176d and 176g in 86%-quantitative yields (Scheme 81).

Scheme 81: Borch reduction of oximes 180a-180d and 180g to hydroxylamines 176a-176d and 176g followed by the retro-Cope elimination reactions to N-hydroxyl pyrrolidines 184a-184d and 184g. Reagents and Conditions: i) NaCNBH₃ (2.0 equiv.), MeOH/HCl (10:1), Methyl orange, MeOH, 0 °C, 40 min, 86% - quant. ii) Solvent, RT → 40 °C → 60 °C.

The Borch reductions were performed the same day or the day before the rate reactions were to be run. Once the hydroxylamine had been formed it was divided into three batches and dissolved in methanol, chloroform or toluene at a concentration of 0.014 M. Each reaction mixture was then degassed (freeze-thaw × 3) and allowed to stir at RT. Analytical samples were taken after 1.5 h and 3 h (N.B. for hydroxylamines 176a and 176b no sample was taken after 3 h at RT) and the samples analysed by ¹H NMR spectroscopy. The reaction mixtures were then heated to 40 °C for 2.5 h before another sample was taken. Finally, the reaction mixtures were heated to 60 °C for 1 h and a final sample taken for analysis (Figure 15).
Figure 15: Graphs showing the rates of the retro-Cope elimination reaction of hydroxylamines 176a-d and g.

From the data collected it was clear that the rate of cyclisation of hydroxylamine 176a, having the unsubstituted phenyl ring, was very similar to that of the methyl substituted (i.e. 4-tolyl) analogue, hydroxylamine 176b, with 11-26% and 17-23% conversions to N-hydroxyl pyrrolidines 184a and 184b being observed respectively (graphs 1 and 2). Interestingly, when the phenyl group was substituted at the 4-position with an electron donating O-methyl substituent, hydroxylamine 176c, almost no reaction to give N-hydroxyl pyrrolidine 184c was observed in all three solvents (graph 3). However, a considerable amount of an unidentified side product did form when the reaction was run in methanol. Conversely, when the aryl 4-substituent was the electron withdrawing CF₃ group, hydroxylamine 176d, the reaction rates were significantly faster, with almost full conversion to N-hydroxyl pyrrolidine 184d being observed in all solvents (graph 4). Finally, the hydroxylamine 176g, having an alkyl
Asymmetric retro-Cope Elimination Reaction

substituent at the distal end of the alkene, was unreactive under the reaction conditions, with no \(N\)-hydroxyl pyrrolidine \(\text{184g}\) being observed in any solvent (graph 5). From these results it was decided that hydroxylamine \(\text{176c}\) bearing the \(O\)-methyl substituent would be a good substrate for our envisaged development of an asymmetric retro-Cope elimination reaction, as hydroxylamine \(\text{176c}\) was not reactive at low temperatures, but did start to cyclise 60 °C. This substrate would hopefully allow the screening of various additives without a background reaction interfering with possible catalyst activity.

Towards this end, and in order to assess if the addition of a proton source would accelerate the rate of reaction, a second rate study was conducted, using hydroxylamine \(\text{176c}\) as the substrate. This time the solvents used were methanol, toluene and toluene containing \(~ 5\) equivalents methanol. Reactions were started at 60 °C and monitored every 2 h for a total of 8 h (Figure 16).

As with the previous rate studies carried out on this substrate (cf. graph 3, Figure 15) a significant amount of a side product was formed alongside \(N\)-hydroxyl pyrrolidine \(\text{184c}\) when the reaction was run in methanol. This side product did not form when the solvent used was toluene, and pleasingly it was not observed in the presence of \(~ 5\) equivalents of methanol. The results show that there is a small increase in the rate of reaction when methanol was added to the reaction [60% conversion after 8 h vs. 74% with the addition of methanol, graph 6]. Finally, a reaction was carried out in toluene with \(~ 5\) equivalents of methanol following the same temperature profile as the first reaction rate study (graph 7, cf. graph 3, Figure 15). Disappointingly, there was no significant change in the reaction rate with the addition of methanol when compared to the results obtained in just toluene. Despite this result hydroxylamine \(\text{176c}\) will be used for future studies, in which many other additives will be screened.
3.3. Conclusions and Future Work

The first aim of this project was to synthesise and test substrates in order to establish a suitable system that could be used for the development of an asymmetric retro-Cope elimination reaction. This was achieved by synthesising a range of different hydroxylamines and studying the rate of reaction in different solvents at different temperatures. The results from these studies demonstrated that hydroxylamine 176c, containing an aryl group bearing an O-methyl substituent, was a suitable substrate for the purpose. We discovered that the retro-Cope elimination on this substrate would only occur at temperatures above 40 °C, this would allow us to screen various additives for catalytic activity without a background reaction occurring.

With a suitable system for the development of an asymmetric retro-Cope elimination reaction achieved, the next step for the project will be testing various additives to act as a proton source in order to catalyse the proton transfer step. After completing this screening, hopefully an additive will have been identified that will catalyse our reaction and therefore allow testing of chiral additives to be undertaken. A recent review written by Stoltz has outlined the latest advances in enantioselective protonation. Although many of the enantioselective protonation procedures that have been developed to date have been designed for enolate protonation, this review demonstrates that there a number of chiral proton sources that may be suitable for our system (Figure 17).

![Figure 17: Examples of chiral proton sources used for enantioselective protonation.](image)

The figure above shows some examples of chiral Brønsted acids that have been used successfully for the enantioselective enolate or decarboxylative protonation, that could be tested as possible enantioselective proton sources for our asymmetric retro-Cope elimination reaction.
Overall Conclusions

This thesis is comprised of three chapters, describing the research that has been undertaken within three different projects. The first of these chapters describes the biomimetic total synthesis of the *Amaryllidaceae* alkaloid clivonine. The key steps of the synthesis include an Ireland-Claisen rearrangement, a *retro*-Cope elimination and the biomimetic ring-switch of a lycorine type progenitor to that of a lycorenine type product. For the successful optimisation of the biomimetic ring switch step, a suitable method of purification of our key intermediate, iminium salt 38, was required. This was achieved with the use of solid phase, ion exchange chromatography, and allowed for the optimisation of the biomimetic ring-switch. Our synthesis of clivonine has shown for the first time a biomimetic interconversion of these two classes of compounds and has allowed for the corroboration of the biosynthetic pathway proposed for these alkaloids by Barton in 1960.

The second chapter describes the synthesis of the acetonide 77, an extremely important synthetic building block and the starting material for our clivonine synthesis. This was achieved, firstly, by the development of a high yielding, scalable three step one-pot procedure for the synthesis of dibromo diol 134 from 1,3-cyclohexadiene (131). The synthesis was completed by optimising the *bis*-elimination of dibromide 135, to give acetonide 77 in an overall yield of 50% from 1,3-cyclohexadiene (131).

Finally, the third chapter of this thesis describes the work carried out towards an asymmetric *retro*-Cope elimination reaction. The initial aim of this project was to establish a suitable system that could be used for the development of a catalytic asymmetric *retro*-Cope elimination reaction. This was achieved by synthesising a range of substrates and studying the effect of electron withdrawing and electron donating aryl substituents on the rate of the reaction. The results from this study revealed that hydroxylamine 176c bearing an O-methyl substituent would be the ideal substrate for the screening of additives for catalytic activity.
Chapter 4 – Experimental

4.1. General Directions

**Solvents and reagents:** Solvents were dried as follows: MeCN, CH$_2$Cl$_2$ and MeOH were distilled over CaH$_2$, CH$_3$Cl over MgSO$_4$, THF and Et$_2$O over Na-benzophenone ketyl and toluene over Na. Alternatively MeCN, CH$_2$Cl$_2$, THF, Et$_2$O and toluene were dried and deoxygenated with a Pure-Solv 400 solvent purification system by Innovative Inc., USA. The moisture content of the solvents was monitored by Karl Fischer coulometric titration (Mettler-Toledo DL39). CCl$_4$ was stirred over MgSO$_4$ for 1 h. Acetic anhydride was distilled from K$_2$CO$_3$ under N$_2$, $m$-CPBA was recrystallised from CH$_2$Cl$_2$ and stored in a plastic container at 4 °C and TMSCl was distilled from K$_2$CO$_3$ under N$_2$. All other reagents were used as commercially supplied unless otherwise stated and handled in accordance with COSHH regulations.** Photooxygenation:** These reactions were performed in standard pyrex® round-bottom flasks and direct irradiation from a 300 W sunlamp (General Electric TSP-56RB). **Chromatography:** Flash chromatography was performed on silica gel (Merck Kieselgel 60 F$_{254}$ 230-400 mesh) according to the method of W.C. Still.** Thin layer chromatography (TLC) was performed on either aluminium or glass backed plates pre-coated with silica (Merck 0.2 mm, 60 F$_{254}$) which were developed using standard visualising agents: ultra violet fluorescence (254 nm), KMnO$_4$/∆ or vanillin/∆. Solid Phase Extraction (SPE) was carried out on weak cation exchange (WCX) carboxylic acid (CBA) pre-packed columns (Bond Elut, 2 g) and reverse phase on C18 pre-packed columns (Varian Megabond Elute).

**$^1$H NMR spectra:** These were recorded at 400 or 500 MHz on a Bruker AV-400 or AV-500 instrument. Chemical shifts (δ$_H$) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak, with the abbreviations s, d, t, q, p and m denoting singlet, doublet, triplet, quartet, pentet and multiplet respectively. **$^{13}$C NMR spectra:** These were recorded at 100 or 125 MHz on a Bruker AV-400 or AV-500 instrument. Chemical shifts (δ$_C$) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak, with the abbreviations s, d, t, and q denoting C, CH, CH$_2$ and CH$_3$ respectively. **Infra red spectra:** These were recorded as thin films or as solids on PerkinElmer Spectrum 100 Series spectrometer. Only selected absorbencies (ν$_{max}$) are reported. **Mass spectra:** Low resolution and high resolution spectra were recorded on a VG Prospec spectrometer, with molecular ions and major peaks being reported. Intensities are given as percentages of the base peak. HRMS values are valid to 5 ppm.** Melting points:** Analyses were carried out using a Khofler hot stage and are uncorrected.
4.2. Experimental for Chapter 1

**cis-2,3-(Isopropylidenedioxy)cyclohexa-4,6-diene (77)**\(^{51}\)

![Chemical Structure](image_url)

To a stirred solution of meso-diol 74 (9.77 g, 87.3 mmol) in CH\(_2\)Cl\(_2\) (150 mL) at 0 °C was added DMP (64.4 mL, 523.8 mmol) and pTsOH·H\(_2\)O (0.83 g, 4.4 mmol) and the resultant mixture stirred at 0 °C for 1 h. After this time the reaction mixture was quenched with NaOH (1 M, 100 mL) and stirred at RT for 10 min, until two clear phases had formed. The phases were separated, the organic phase was washed with H\(_2\)O (2 × 100 mL) and the aqueous phase was extracted further with CH\(_2\)Cl\(_2\) (2 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated *in vacuo* to give acetonide 77 as a pale yellow oil (10.23 g, 77%); \(R\), 0.83 (petrol/EtOAc, 1:1); \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.38 (3H, s, CH\(_3\)), 1.40 (3H, s, CH\(_3\)), 4.64 (2H, m, C\(_2\)H and C\(_3\)H), 5.88 (2H, m, C\(_1\)H and C\(_4\)H), 5.98 (2H, m, C\(_3\)H and C\(_6\)H); \(^1^3^C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 24.69 (q), 26.70 (q), 70.32 (2 × d), 104.56 (s), 123.71 (2 × d), 125.26 (2 × d); IR \(v_{\text{max}}\) (neat): 694, 872, 1027, 1045, 1159, 1208, 1238, 1370, 1381, 1286, 2935, 2986, 3045 cm\(^{-1}\); \(\text{m/z (Cl}^+\}\) 322 [(2M+NH\(_4\))^+, 25%], 305 [(2M+H)^+, 10%], 170 [(MNH\(_4\))^+, 85%]; HRMS (Cl\(^+\}) calcd. for C\(_{18}\)H\(_{25}\)O\(_4\) [(2M+H)^+] 305.1753, found 305.1751 (Δ -0.6 ppm).

**(S\(^S\)*, 6S\(^S\)*)-Di-O-isopropylidene cyclohex-2-ene-1-one (40)**\(^{52}\)

![Chemical Structure](image_url)

To a stirred solution of acetonide 77 (9.16 g, 60.2 mmol) in CH\(_2\)Cl\(_2\) (25 mL) at 0 °C was added dropwise a solution of m-CPBA (10.4 g, 60.2 mmol) in CH\(_2\)Cl\(_2\) (100 mL). After stirring for 17 h at RT, the reaction mixture was concentrated *in vacuo* to yield a white solid which was re-dissolved in THF (50 mL). In a separate, dry flask wrapped in aluminium foil, Pd\(_2\)(dba)\(_3\) (5.5 g, 6.0 mmol) was added to a stirred solution of diphenylphosphino ethane (DPPE) (4.8 g, 12.1 mmol) in THF (50 mL). After stirring for 20 min at RT the solution
containing crude epoxide 78 was cannulated into that of the Pd(0). After stirring for 66 h at RT the reaction mixture was concentrated in vacuo to yield a dark brown solid which was partitioned between NaHCO$_3$ (sat. aq., 150 mL) and EtOAc (150 mL), the phases were separated and the aqueous phase extracted further with EtOAc (5 × 100 mL). The combined organic phases were dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude residue was purified by FC (SiO$_2$, petrol/Et$_2$O, 2:1→1:1→1:2) to give (±)-enone 40 as a pale yellow solid (6.5 g, 64%). m.p. 68-72 °C (Et$_2$O/pentane) [Lit., 87.0-88.0 °C (Et$_3$O/hexane)]$^{32}$; R$_f$ 0.4 (petrol/Et$_2$O, 1:2); $^1$H NMR (400 MHz, CDCl$_3$): δ 1.30 (3H, s, CH$_3$), 1.36 (3H, s, CH$_3$), 2.76 (1H, app ddt, J = 20.0, 5.2, 2.5, C$_4$H$_2$H), 2.85 (1H, app ddt, J = 20.0, 4.9, 1.5, C$_4$H$_2$H), 4.25 (1H, d, J = 5.0, C$_6$H), 4.59 (1H, app tt, J = 5.0, 1.5, C$_5$H), 6.08 (1H, ddd, J = 10.3, 2.5, 1.5, C$_2$H), 6.80 (1H, m, C$_5$H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 25.90 (q), 27.36 (q), 27.67 (t), 72.81 (d), 75.40 (d), 109.11 (s), 128.15 (d), 146.33 (d), 196.30 (s); IR ν$_{max}$ (neat): 1072, 1220, 1241, 1374, 1664, 2983 cm$^{-1}$; m/z (Cl$^+$) 186 [M+Cl$^+$], 100%; HRMS (Cl$^+$) calcd. for C$_9$H$_{13}$O$_2$ [(MH)$^+$] 169.0865, found 169.0863 (Δ -1.0 ppm).

(2S, 3S)-1-Chloro-2,3-di-O-isopropylcyclohex-4,6-diene (80)$^{138}$

$$\begin{align*}
\text{Chemical Formula: C}_9\text{H}_{13}\text{O}_2 \\
\text{Exact Mass: 186.04} \\
\text{Molecular Weight: 186.64}
\end{align*}$$

To a stirred solution of diol 75 (1.0 g, 6.85 mmol) in CH$_2$Cl$_2$ (30 mL) at 0 °C was added DMP (5.1 mL, 41.1 mmol) and pTsOH·H$_2$O (0.26 g, 1.37 mmol) and the resultant mixture stirred at 0 °C for 1.5 h. After this time the reaction mixture was quenched with NaOH (1 M, 15 mL) and the mixture allowed to stir for 10 min until two clear phases formed. The phases were separated, the organic phase was washed with H$_2$O (2 × 20 mL) and the aqueous phase was extracted further with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic phases were washed with brine (50 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give acetonide 80 as a pale yellow oil (1.22 g, 96%); $^1$H NMR (400 MHz, CDCl$_3$): δ 1.41 (3H, s, CH$_3$), 1.42 (3H, s, CH$_3$), 4.63 (1H, d, J = 8.8, C$_2$H), 4.76 (1H, dd, J = 8.8, 3.6, C$_3$H), 5.89 (1H, dd, J = 9.6, 3.6, C$_4$H), 5.94 (1H, d, J = 9.6, 5.8, C$_5$H), 6.09 (1H, d, J = 5.8, C$_6$H); m/z (Cl$^+$) 204 [M$(^{35}\text{Cl})$NH$_4^+$], 100%, 206 [M$(^{37}\text{Cl})$NH$_4^+$], 35%.

(2S, 3S)-1-Bromo-2,3-di-O-isopropylcyclohex-4,6-diene (81)$^{138}$
To a stirred solution of diol 76 (5.0 g, 26.18 mmol) in CH₂Cl₂ (80 mL) at 0 °C was added DMP (19.3 mL, 157.1 mmol) and pTsOH·H₂O (1.0 g, 5.2 mmol) and the resultant mixture stirred at 0 °C for 1 h. After this time the reaction mixture was quenched with NaOH (1 M, 75 mL) and the mixture allowed to stir for 10 min until two clear phases formed. The phases were separated, the organic phase was washed with H₂O (2 × 50 mL) and the aqueous phase was extracted further with CH₂Cl₂ (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give acetonide 81 as a pale yellow oil (5.84 g, 97%); ³¹H NMR (400 MHz, CDCl₃): δ 1.41 (3H, s, CH₃), 1.42 (3H, s, CH₃), 4.71 (2H, m, C₂H and C₃H), 5.85 (1H, dd, J = 9.6, 6.1, C₅H), 5.99 (1H, app d, J = 9.6, C₆H), 6.32 (1H, d, J = 6.1, C₆H); m/z (CI⁺) 231 [{M⁺BrH}⁺, 100 %], 233 [{M⁺¹¹BrH}⁺, 97 %].

(1R, 4R, 5R, 6S)-1-Chloro-7,8-dioxo-5,6-di-O-isopropylidenebicyclo[2.2.2]oct-2-ene (82)⁵⁰

A stirred solution of acetonide 80 (1.0 g, 5.38 mmol) and TPP (23 mg, 0.7 mol%) in CCl₄ (200 mL) was cooled to 0 °C and irradiated with a 300 W lamp whilst bubbling oxygen through the solution for 2 h. After this time the reaction mixture was concentrated in vacuo and the crude endoperoxide 82 taken onto the next step without any further purification. ³¹H NMR (400 MHz, CDCl₃): δ 1.32 (3H, s, CH₃), 1.34 (3H, s, CH₃), 4.44 (1H, d, J = 7.0, C₆H), 4.67 (1H, dd, J = 7.0, 4.6, C₅H), 4.89 (1H, app t, J = 5.1, C₄H), 6.46 (1H, d, J = 8.6, C₂H), 6.56 (1H, dd, J = 8.6, 6.0, C₃H).

(1R, 4R, 5R, 6S)-1-Bromo-7,8-dioxo-5,6-di-O-isopropylidenebicyclo[2.2.2]oct-2-ene (83)⁵⁰
A stirred solution of acetone 81 (4.5 g, 19.5 mmol) and TPP (84 mg, 0.7 mol%) in CCl₄ (50 mL) was cooled to 0 °C and irradiated with a 300 W lamp whilst bubbling oxygen through the solution for 2 h. After this time the reaction mixture was concentrated in vacuo and the crude endoperoxide 83 taken onto the next step without any further purification. ¹H NMR (400 MHz, CDCl₃): δ 1.33 (3H, s, CH₃), 1.36 (3H, s, CH₃), 4.60 (1H, dd, J = 7.2, 1.2, C₆H), 4.67 (1H, dd, J = 7.2, 4.3, C₃H), 4.96 (1H, ddd, J = 5.9, 4.3, 1.2, C₄H), 6.49 (1H, dd, J = 8.7, 5.9, C₂H), 6.62 (1H, app dt, J = 8.7, 1.3, C₃H).

Polystyrene-bound N-methyl-thiourea (88)²⁴

Aminomethylated resin 86 (25 g, 22.5 mmol, 0.9 mmol g⁻¹) was swelled in Et₂O (200 mL) for 20 min before a solution of isothiocyanate 87 (1.8 g, 24.8 mmol) in Et₂O (20 mL) was added via cannula. The resultant suspension was heated to 40 °C for 24 h. After this time the reaction mixture was cooled, filtered, washed with Et₂O (400 mL) and dried under high vacuum to yield thiourea resin 88 as a pale yellow solid (26 g, 97%, 0.84 mmol g⁻¹); IR νmax (KBr): 748, 1025, 1112, 1491, 1560, 2923, 3025, 3250, 3394. See Appendix 1 for loading level calculations.

(4R, 5S, 6S)-4-O-Acetoxy-5,6-di-O-isopropylidenecyclohex-2-ene-1-one (84)²³

A solution of endoperoxide 82 (0.88 g, 4.04 mmol) in CH₂Cl₂ was added via cannula to a pre-swelled suspension of thiourea resin 88 (7.2 g, 6.05 mmol, 0.84 mmol g⁻¹) in CH₂Cl₂ (100 mL) at 0 °C and the resultant suspension stirred for 30 min. After this time complete consumption of endoperoxide 82 was observed by TLC analysis. The reaction mixture was
filtered and the resin washed with CH$_2$Cl$_2$ (100 mL) and the resultant solution immediately sealed and put under an atmosphere of N$_2$. To this solution was added a solution of DMAP (45.3 mg, 0.40 mmol), Et$_3$N (0.85 mL, 6.06 mmol) and freshly distilled Ac$_2$O (0.54 mL, 5.66 mmol) in CH$_2$Cl$_2$ (5 mL) and the reaction mixture allowed to stir at RT for 1 h. After this time the reaction mixture was quenched with NaHCO$_3$ (sat. aq., 100 mL), and the phases separated. The aqueous phase was extracted further with CH$_2$Cl$_2$ (3 × 100 mL), the combined organic phases were washed with brine (100 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude residue was purified by FC (SiO$_2$, petrol/Et$_2$O, 7:1→5:1→4:1→3:1→2:1) to give acetate 84 as a pale yellow oil (597 mg, 65%); $^1$H NMR (400 MHz, CDCl$_3$): δ 1.38 (6H, s, 2 × CH$_3$), 2.11 (3H, s, OCH$_3$), 4.43 (1H, d, $J$ = 5.8, C$_6$H), 4.50 (1H, ddd, $J$ = 5.8, 3.3, 1.3, C$_5$H), 5.58 (1H, m, C$_4$H), 6.18 (1H, dd, $J$ = 10.3, 1.4, C$_2$H), 6.77 (1H, dd, $J$ = 10.3, 4.0, 1.3, C$_3$H); m/z (EI$^+$) 226 [(M$^+$)•, 10%].

(5S, 6S)-Di-O-isopropylidene-2-ene-1-one (40)$^{23}

A solution of acetate 84 (0.5 g, 2.2 mmol) in CH$_2$Cl$_2$ (25 mL) was degassed (freeze-thaw × 3). To this solution was added Pd(PPh$_3$)$_4$ (64 mg, 2.5 mol%) and TMDS (0.4 mL, 2.21 mmol) and the resultant mixture heated to 44 °C for 21 h in the dark. After this time Et$_3$N (0.32 mL, 2.32 mmol) was added and the mixture heated for a further 1 h at 44 °C. The reaction mixture was quenched with H$_2$O (50 mL), the phases were separated and the aqueous phase extracted further with CH$_2$Cl$_2$ (3 × 25 mL). The combined organic phases were washed with brine (50 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude residue was purified by FC (SiO$_2$, petrol/Et$_2$O, 4:1→3:1→2:1→1:1→1:2) to give (+)-enone 40 as a pale yellow solid (159 mg, 43%); Spectroscopic data as above but enantiomerically pure; [α]$_D^{20}$ + 93.4 (c = 1.000, MeOH), [Lit., [α]$_D^{20}$ + 107.5 (c = 1.000)]$^{23}$.

(3aS*,5S*,6R*)-5,6-Di-O-isopropylidene-3-[(methoxycarbonyl)methyl]-1-(3,4-methylenedioxyphenyl)cyclohex-1-ene (90)$^{46}$
To a solution of 1-bromo-3,4-(methylenedioxy)benzene 89 (4.49 mL, 37.46 mmol) in THF (85 mL) at -78 °C was added tert-BuLi (48.75 mL, 1.5 M solution in hexanes, 73.12 mmol) dropwise. After stirring for 30 min at -78 °C, a solution of enone 40 (6.0 g, 35.67 mmol) in THF (85 mL) was slowly added via cannula. The reaction mixture was stirred for 2 h at -78 °C, then allowed to warm to 0 °C over 45 min. Freshly distilled Ac₂O (8.40 mL, 89.18 mmol) was then added to the reaction mixture and the solution allowed to warm to RT over 14 h. The reaction mixture was partitioned between NaHCO₃ (sat. aq., 200 mL), the phases were separated and the aqueous phase extracted further with Et₂O (4 × 100 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo to give acetate 41 (~ 12 g); ¹H NMR (400 MHz, CDCl₃): δ 1.34 (3H, s, CH₃), 1.56 (3H, s, CH₃), 2.06 (3H, s, COCH₃), 2.38 (1H, ddd, J = 16.9, 7.5, 3.7, C₄H₃), 2.56 (1H, ddd, J = 16.9, 6.1, 5.5, 1.0, C₄H₃), 4.20 (1H, d, J = 7.5, C₆H), 4.39 (1H, app td, J = 7.5, 4.3, C₅H), 5.93 (2H, s, OCH₂O), 6.00 (1H, ddd, J = 9.5, 5.5, 3.7, C₃H), 6.40 (1H, ddd, J = 9.5, 2.5, 1.0, C₂H), 6.72-6.81 (3H, 3 × C₆H); m/z (EI⁺) 332 [(M)⁺, 29%]. To a solution of diisopropylamine (8.77 mL, 62.42 mmol) in THF (95 mL) was added n-BuLi (29.45 mL, 2.12 M in hexanes, 62.42 mmol) dropwise at -78 °C. The resultant solution was allowed to stir for 10 min at -78 °C and warmed to 0 °C for 10 min. This cooling and warming process was repeated 3 times to which the solution became a pale yellow colour. To a solution of crude acetate 41 (~ 12 g, ~ 35 mmol) in THF (100 mL) at -78 °C was added LDA (0.5 M in THF, as described above) dropwise via cannula and allowed to stir for 20 min. After this time freshly distilled TMSCl (13.68 mL, 107.01 mmol) was added and the reaction mixture stirred at -78 °C for 30 min. After this time the reaction mixture was warmed to 0 °C over 30 min before being allowed to reflux for 16 h. The reaction mixture was quenched with 10% citric acid solution until pH 4 was reached, brine (170 mL) was added, the phases separated and the aqueous phase extracted further with Et₂O (3 × 100 mL). The combined organic phases were washed with brine (25 mL), dried over Na₂SO₄ and concentrated in vacuo to give acid 45 (~ 12 g); ¹H NMR (400 MHz, CDCl₃): δ 1.46 (3H, s, CH₃), 1.50 (3H, s, CH₃), 1.55 (1H, m,
C₄H₄H), 2.04 (1H, ddd, J = 12.5, 4.9, 4.7, C₄HH), 2.54 (1H, dd, J = 15.9, 7.5, C₃HH), 2.59 (1H, dd, J = 15.9, 7.2, C₃HH), 2.76 (1H, m, C₃aH), 4.36 (1H, ddd, J = 10.1, 5.1, 4.9, C₃H), 4.86 (1H, d, J = 5.1, C₆H), 5.97 (2H, s, OCH₂O), 6.13 (1H, d, J = 2.6, C₂H). 6.80 (1H, d, J = 8.6, C₃aH), 7.06 (2H, m, 2 × C₄aH), OH (absent); m/z (EI⁺) 332 [(M⁺), 52%]. To a solution of Diazald® (22.93 g, 107.01 mmol) in Et₂O (240 mL), in diazomethane smooth-surface apparatus, was added a solution of KOH (7.0 g, 124.85 mmol) in carbitol/H₂O/Et₂O (135 mL, 3:1:1) dropwise at 50 °C. The resulting diazomethane that formed was condensed and dropped into a separate flask containing a solution of acid 45 (~ 12 g, ~ 35 mmol) in Et₂O (50 mL) cooled to 0 °C. The Diazald® solution was heated until no further diazomethane was seen to evolve and then cooled. The reaction mixture was allowed to stir at RT for 16 h. After this the reaction mixture was concentrated in vacuo and the crude residue purified by FC (SiO₂, petrol/Et₂O 4:1→3:1→2:1→1.5:1) to yield methylester 90 as a yellow oil (5.88 g, 47%); ¹H NMR (400 MHz, CDCl₃): δ 1.41 (3H, s, CH₃), 1.46 (3H, s, CH₃), 1.48 (1H, m, C₄H₄H), 1.96 (1H, app dt, J = 12.4, 6.7, C₄H₄H), 2.48 (2H, m, C₃H₂), 2.72 (1H, m, C₃aH), 3.70 (3H, s, OCH₃), 4.31 (1H, app p, J = 5.4, C₃H), 4.78 (1H, d, J = 5.4, C₆H), 5.93 (2H, s, OCH₂O), 6.06 (1H, d, J = 2.6, C₂H), 6.76 (1H, d, J = 8.9, C₃aH), 7.02-7.04 (2H, 2 × C₃aH); m/z (EI⁺) 346 [(M⁺), 55%].

(3aS*,5S*,6R*)-5,6-Di-O-isopropylidene-3-(2-oxoethyl)-1-(3,4-methylenedioxyphenyl)cyclohex-1-ene (91)⁴⁶

To a solution of methylester 90 (100 mg, 0.29 mmol) in toluene (4 mL) at -78 °C was added via cannula (wrapped in aluminium foil containing crushed dry ice) a cooled solution of DIBAL (1.0 M in hexanes, 0.32 mL, 0.32 mmol). After 3 h, MeOH (1.5 mL) cooled to -78 °C was added via cannula and the solution stirred for a further 30 min, before being warmed to RT. Solvents were removed in vacuo and the yellow/white solid was partitioned between sodium potassium tartrate (sat. aq., 6 mL) and EtOAc (6 mL). The phases were separated and the aqueous phase extracted further with EtOAc (5 × 6 mL). The combined organic phases were washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo. The crude residue was purified by FC (SiO₂, petrol/Et₂O, 3:1→1:1→1:3) to yield aldehyde 91 as a pale yellow oil (37 mg, 40%); ¹H NMR (400 MHz, CDCl₃): δ 1.41 (3H, s, CH₃), 1.45 (3H, s,
CH₃, 1.50 (1H, m, C₄H₅), 1.98 (1H, app dt, J = 12.6, 5.3, C₄H₅), 2.67 (2H, m, C₅H₂), 2.84 (1H, m, C₆H), 4.33 (1H, app p, J = 5.3, C₅H), 4.78 (1H, d, J = 5.3, C₆H), 5.93 (2H, s, OCH₂O), 6.06 (1H, d, J = 2.8, C₂H), 6.80 (1H, d, J = 8.7, C₆H), 7.00-7.03 (2H, 2 × C₆H), 9.83 (1H, s, CHO); m/z (E+) 316 [(M⁺), 76%].

\((E)\)- and \((Z)\)-(3aR\(^*\),5S\(^*\),6R\(^*\))-5,6-Di-O-isopropylidene-3-(2-hydroxyminoethyl)-1-(3,4-methylenedioxyphenyl)cyclohex-1-ene (46)\(^{46}\)

To a stirred solution of methyl ester 90 (6.73 g, 19.43 mmol) in THF (150 mL) at 0 °C was added LiBH₄ (68.01 mL, 2 M in THF, 136.01 mmol) over 41.5 h during which time the mixture warmed to RT. After stirring for a further 15 h the reaction mixture was quenched with H₂O (50 mL), the phases were separated and the aqueous phase extracted further with EtOAc (4 × 100 mL). The combined organic phases were washed with brine (200 mL), dried over Na₂SO₄ and concentrated in vacuo to give alcohol 92 as a yellow oil (5.34 g, 86%). \(^1\)H NMR (CDCl₃, 400 MHz): δ 1.44 (1H, m, C₄H₅), 1.47 (3H, s, CH₃), 1.52 (3H, m, CH₃), 1.61 (1H, br s, OH), 1.73 (1H, td, J = 13.9, 6.5, C₃H₅), 1.86 (1H, td, J = 13.5, 6.5, C₃H₅), 2.01 (1H, app dt, J = 12.1, 4.7, C₄H₅), 2.45 (1H, m, C₆H), 3.84 (2H, m, C₅H₂), 4.32 (1H, app dt, J = 10.5, 5.0, C₃H), 4.83 (1H, d, J = 5.0, C₆H), 5.98 (2H, s, OCH₂O), 6.17 (1H, d, J = 2.3, C₂H), 6.82 (1H, d, J = 8.3, C₆H), 7.07-7.10 (2H, 2 × C₆H); m/z (E+) 318 [(M⁺), 57%]. To a suspension of Dess-Martin periodinane (21.4 g, 50.4 mmol) in CH₂Cl₂ (60 mL) at RT was added a solution of alcohol 92 (5.34 g, 16.8 mmol) in CH₂Cl₂ (20 mL) dropwise via cannula. After stirring for 23.5 h the reaction mixture was filtered through Celite\(^®\) and the filtrate treated with NaHCO₃ (sat. aq., 100 mL). The phases were separated and the aqueous phase extracted further with CH₂Cl₂ (2 × 50 mL). The combined organic phases were washed with NaHCO₃ (sat. aq., 50 mL), dried over Na₂SO₄ and concentrated in vacuo to give aldehyde 91 as a dark red oil (5.04 g, 95%, \(^1\)H NMR yield); Spectroscopic data as above. To a solution of aldehyde 91 (5.04 g, 15.93 mmol) in CH₂Cl₂ (40 mL) was added hydroxylamine (2.21 g, 31.86 mmol), NaOAc (3.27 g, 39.83 mmol) and MeOH (7 mL) and the reaction mixture
allowed to stir open to the atmosphere at RT. After 2 h brine (50 mL) and EtOAc (200 mL) were added to the reaction mixture and the phases separated. The aqueous phase was extracted further with EtOAc (2 × 100 mL), the combined organic phases were washed with brine (100 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude residue was purified by FC (SiO$_2$, petrol/Et$_2$O, 2:1→1:1→1:2) to yield oxime $46$ as a yellow foam (4.3 g, E:Z, 1.2:1 by $^1$H NMR, 67% from methylester $90$). (NB. Protocol only with intermediate yields for alcohol $92$ and aldehyde $91$). Samples of the two isomers were isolated on an analytical scale by FC (SiO$_2$, petrol/Et$_2$O 1:1) to give:

$(E)$-oxime $46$ as a white solid; $^1$H NMR (400 MHz, CDCl$_3$): δ 1.40-1.46 (1H, C$_4$H), 1.42 (3H, s, CH$_3$), 1.46 (3H, s, CH$_3$), 1.96 (1H, app dt, $J = 12.4$, 4.5, C$_4$H), 2.36 (2H, m, C$_3$H$_2$), 2.43 (1H, m, C$_3$H), 4.28 (1H, app p, $J = 5.4$, C$_3$H), 4.78 (1H, d, $J = 5.4$, C$_6$H), 5.92 (2H, s, OCH$_2$O), 6.08 (1H, d, $J = 2.0$, C$_2$H), 6.76 (1H, d, $J = 8.0$, C$_A$H), 7.01-7.04 (2H, 2 × C$_A$H), 7.48 (1H, t, $J = 6.1$, NCH), 7.97 (1H, s, NOH); m/z (EI$^+$) 331 [(M$^+$)], 26%.

$(Z)$-oxime $46$ as a white solid; $^1$H NMR (400 MHz, CDCl$_3$): δ 1.41-1.47 (1H, C$_4$H), 1.42 (3H, s, CH$_3$), 1.47 (3H, s, CH$_3$), 1.96 (1H, app dt, $J = 12.5$, 4.3, C$_4$H), 2.48 (2H, m, C$_3$H$_2$), 2.64 (1H, m, C$_3$H), 4.28 (1H, app p, $J = 5.4$, C$_3$H), 4.78 (1H, d, $J = 5.4$, C$_6$H), 5.93 (2H, s, OCH$_2$O), 6.06 (1H, d, $J = 1.2$, C$_2$H), 6.77 (1H, d, $J = 8.8$, C$_A$H), 6.82 (1H, t, $J = 5.4$, NCH), 7.02-7.04 (2H, 2 × C$_A$H), 7.97 (1H, s, NOH); m/z (EI$^+$) 331 [(M$^+$)], 26%.

$(3aR^*,5S^*,5aR^*,11bS^*,11cR^*)$-5,5a-Di-O-isopropylidene-1-hydroxylamino-11b-(3, 4-methylenedioxyphenyl)-2, 3, 3a, 4, 5, 5a, 11b, 11c-octahydroindole (48)$^{46}$

A stirred solution of oxime $46$ (0.5 g, 1.51 mmol) and NaCNBH$_3$ (0.19 g, 3.02 mmol) in MeOH (58 mL) was cooled to 0 °C and 15 drops methyl orange added. MeOH/HCl (10:1) (1.1 mL over 10 min) was added dropwise to this bright yellow solution to give an orange solution. The reaction mixture was then warmed to RT for 5 min to which the solution returned to yellow colour and was cooled back down to 0 °C. MeOH/HCl was added
dropwise until the solution remained orange and the reaction mixture was again warmed to RT. After 5 min the yellow solution was concentrated to approximately 10 mL, partitioned between Et₂O (50 mL) and NaHCO₃ (sat. aq., 50 mL) and the phases separated. The aqueous phase was extracted further with Et₂O (5 × 50 mL), the combined organic phases were washed with brine (50 mL), dried over NaSO₄ and concentrated in vacuo to give hydroxylamine 47 as a yellow foam. The hydroxylamine was immediately redissolved in toluene (100 mL), the solution was degassed (freeze-thaw × 4) and heated to 80 °C. After 14 h the reaction mixture was concentrated in vacuo to give N/OH pyrrolidine 48 as a yellow solid (0.50 g, 94%); ¹H NMR (400 MHz, CDCl₃): δ 1.27 (3H, s, CH₃), 1.42 (3H, s, CH₃), 1.42-1.59 (2H, C₄H₂), 2.02-2.20 (4H, C₂H₂, C₃H₂, NH), 2.60 (1H, app t, J = 10.9, C₁₁bH), 2.66 (1H, ddd, J = 10.2, 9.9, 6.4, C₂HH), 2.98 (1H, ddd, J = 9.9, 6.8, 3.1, C₂HH), 3.13 (1H, dd, J = 10.9, 9.3, C₁₁cH), 4.15 (1H, dd, J = 10.9, 7.5, C₅aH), 4.29 (1H, ddd, J = 10.5, 7.5, 5.8, C₃H), 5.90 (2H, s, OCH₂O), 6.75 (2H, app s, 2 × C₃H), 6.78 (1H, app s, C₆H); m/z (EI) 318 [(MH⁺), 100%].

(3aR*,5S*,5aR*,11bS*,11cR*)-5,5a-Di-O-isopropylidene-11b-(3,4-methylenedioxyphenyl)-2, 3, 3a, 4, 5, 5a, 11b, 11c-octahydroindole (94)⁴⁶

To a solution of N-OH pyrrolidine 48 (500 mg 1.51 mmol) in EtOH/H₂O (10:1) (35 mL) was added an excess of Raney Ni (suspension in H₂O) and the reaction mixture allowed to stir at RT under an atmosphere of H₂. After 3 h the reaction mixture was filtered through Celite® and concentrated in vacuo to give pyrrolidine 94 as a yellow foamy solid (430 mg, 90%); ¹H NMR (400 MHz, CDCl₃): δ 1.27 (3H, s, CH₃), 1.42 (3H, s, CH₃), 1.42-1.59 (2H, C₄H₂), 2.02-2.20 (4H, C₂H₂, C₃H₂, NH), 2.60 (1H, app t, J = 10.9, C₁₁bH), 2.66 (1H, ddd, J = 10.2, 9.9, 6.4, C₂HH), 2.98 (1H, ddd, J = 9.9, 6.8, 3.1, C₂HH), 3.13 (1H, dd, J = 10.9, 9.3, C₁₁cH), 4.15 (1H, dd, J = 10.9, 7.5, C₅aH), 4.29 (1H, ddd, J = 10.5, 7.5, 5.8, C₃H), 5.90 (2H, s, OCH₂O), 6.75 (2H, app s, 2 × C₃H), 6.78 (1H, app s, C₆H); m/z (CI⁺) 318 [(MH⁺), 100%].

(3aR*,5S*,5aR*,11bS*,11cR*)-5,5a-Di-O-isopropylidene-1-formyl-11b-(3,4-methylenedioxyphenyl)-2, 3, 3a, 4, 5, 5a, 11b, 11c-octahydroindole (95)⁴⁶
Method 1:
A solution of acetoformic anhydride was prepared according to the method of Prosperi\textsuperscript{139} by heating a solution of acetic anhydride (2.0 mL) and formic acid (2.0 mL) at 60 °C for 2 h. To a solution of pyrrolidine 94 (0.43 g, 1.36 mmol) in CH₂Cl₂ (15 mL) was added a solution of acetoformic anhydride (0.36 g, 4.08 mmol) (prepared as described above) in CH₂Cl₂ (5 mL) and the reaction mixture allowed to stir at RT for 2 h. After this time the reaction mixture was quenched with NaHCO₃ (sat. aq., 20 mL), the phases were separated and the aqueous phase extracted further with CH₂Cl₂ (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over NaSO₄ and concentrated in vacuo. The crude residue was purified by FC (SiO₂, petrol:Et₂O, 1:2→1:4→100% Et₂O→2% MeOH in Et₂O→3% MeOH in Et₂O→5% MeOH in Et₂O→10% MeOH in Et₂O) to give formamide 95 as a white foam (160 mg, 34%); \textsuperscript{1}H NMR (400 MHz, CDCl₃): δ 1.27 (3H, s, CH₃), 1.43 (3H, s, CH₃), 1.79 (2H, m, C₄H₂), 2.09 (2H, m, C₃H₂), 2.46 (1H, m, C₃aH), 2.63 (1H, app t, J = 10.7, C₁₁bH), 3.23 (1H, app dt, J = 12.1, 7.7, C₁₁cH), 3.75 (2H, m, C₂H₂), 4.25 (1H, dd, J = 10.3, 6.8, C₃aH) 4.31 (1H, m, C₅H), 5.91 (2H, s, OCH₂O), 6.62 (1H, dd, J = 7.9, 1.5, C₇bH), 6.68 (1H, d, J = 1.7, C₈H), 6.79 (1H, d, J = 7.9, C₁₁H), 7.26 (1H, s, NCHO); m/z (Cl⁻) 346 [(MH⁻), 100%], 363 [(MNH₄)⁺, 52%].

Method 2:
A stirred solution of pyrrolidine 94 (121 mg, 0.38 mmol) in ethyl formate (20 mL) was heated to 60 °C and allowed to reflux for 16 h. After this time the reaction mixture was concentrated in vacuo to give formamide 95 as an off white foam (124 mg, 94%); Spectroscopic data as above.

(3aR\textsuperscript{*},5S\textsuperscript{*},5aR\textsuperscript{*},11bS\textsuperscript{*},11cR\textsuperscript{*})-5,5a-Dihydroxy-2,3,3a,4,5,5a,11b,11c-octahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridinium chloride (38)\textsuperscript{46}
To a solution of *formamide* 95 (361 mg, 1.05 mmol) in MeCN (20 mL) was added POCl₃ (0.15 mL, 1.58 mmol) dropwise and the reaction mixture refluxed for 30 min. After this time the reaction mixture was cooled to RT and treated with aqueous HCl (12 mL, 3 M). After 1 h the reaction mixture was concentrated *in vacuo* to give the crude product as a brown sticky oil. Purification by SPE using a WCX CBA ion exchange column followed by reverse phase C18 silica column gave the *iminium salt* 38 as a yellow oil (142 mg, 42 %). ¹H NMR (400 MHz, D₂O): δ 1.74 (1H, m, C₄H), 1.98 (1H, m, C₄H), 2.12 (1H, app qd, J = 12.6, 6.9, C₃H), 2.46 (1H, app dt, J = 12.6, 6.1, C₃H), 2.77 (1H, m, C₃H), 3.16 (1H, dd, J = 17.4, 8.5, C₁₁H), 3.88 (1H, m, C₃H), 4.04 (1H, m, C₁₁cH), 4.12 (1H, app dd, J = 17.7, 10.6, C₃H), 4.23 (1H, app dd, J = 12.7, 6.6, C₂H), 4.31 (1H, dd, J = 8.5, 5.3, C₅H), 6.19 (2H, s, OCH₂O), 7.22 (1H, s, C₈H), 7.33 (1H, s, C₁₁H), 8.76 (1H, s, N=CH), 2 × OH (absent); m/z (ESI) 288 [(M-Cl)⁺, 100%].

(±)-Clivonine (I)⁹,¹³,⁴⁶

To a solution of *iminium salt* 38 (5 mg, 0.015 mmol) in DMSO-δ₆/D₂O (0.5 mL:0.1 mL) in an NMR tube was added a solution of Cs₂CO₃ (25 μL, 0.77 M in D₂O) and the solution sonicated for 5 min. By ¹H NMR the iminium signal at δ 9.07 ppm had disappeared and the new benzylic proton signal of *lactamol* 50 at δ 4.92 ppm was observed. ¹H NMR (400 MHz, DMSO-δ₆): δ 1.62-1.78 (4H, C₂H₂ & C₄H₂), 1.88 (1H, m, C₃H), 2.11 (1H, m, C₃H), 2.58 (1H, dd, J = 15.8, 9.0, C₁₁bH), 2.80 (1H, app t, J = 9.0, C₁₁cH), 2.99 (1H, app dd, J = 15.8, 10.5, C₃aH), 3.65 (1H, m, C₃aH), 3.72 (1H, m, C₃H), 4.92 (1H, s, NCOH), 5.88 (2H, s, OCH₂O), 6.87 (1H, s, C₈H), 7.22 (1H, s, C₁₁H) 3 × OH (absent); Immediately, MeI (0.03 mmol dilute solution in DMSO-δ₆) was added and the reaction mixture sonicated for 5 min. Solvents were removed by freeze drying and the residue suspended in toluene (2.5 mL).
Freshly prepared Fetizon’s reagent (130 mg, 0.23 mmol) was added to the solution and the suspension was heated to 80 °C for 1 h. The reaction mixture was then cooled to RT, filtered through a pad of Celite®, washed with EtOAc (15 mL) and concentrated in vacuo. Purification by preparative TLC [pentane/Et₂O/MeOH (sat. NH₃), 50:45:5] gave (+)-clivonine 1 as a white solid (1.5 mg, 32%). m.p. 198-200 °C (CHCl₃) [Lit. 199-200 °C (EtOAc)]⁷; Rf 0.7 (CHCl₃/MeOH, 9:1); ¹H NMR (400 MHz, CDCl₃): δ 1.80 (1H, ddd, J = 15.3, 6.3, 3.9, C₄H₃H), 2.10 (1H, m, C₄H₃H), 2.26 (2H, m, C₂H₃H & C₃H₃H), 2.48-2.58 (5H, NCH₃, C₃H₃, C₃H₃), 2.89 (1H, dd, J = 10.0, 6.7, C₁₅H), 3.22 (1H, dd, J = 12.3, 10.0, C₁₅H), 3.29 (1H, m, C₂H₃H), 4.09 (1H, dd, J = 12.3, 2.7, C₃H₃), 4.24 (1H, dd, J = 6.3, 2.7, C₃H₃), 6.02 (2H, AB, J = 5.0, OCH₂O), 7.46 (1H, s, C₃H₃), 7.74 (1H, s, C₁₁H), OH (absent); ¹³C NMR (125 MHz, CDCl₃): δ 28.73 (t), 30.82 (t), 33.12 (d), 33.43 (d), 45.22 (q), 52.95 (t), 67.41 (d), 69.50 (d), 81.81 (d), 101.82 (t), 107.15 (d), 109.34 (d), 118.69 (s), 140.77 (s), 146.68 (s), 152.67 (s), 164.68 (s); IR νmax (neat): 1036, 1274, 1477, 1710, 2924, 3420 cm⁻¹; m/z (ESI⁺) 318 [(MH)⁺, 28%], 282 (70); HRMS (Cl⁺) calcd. for C₁₇H₂₀NO₅ [(MH)⁺] 318.1341, found 318.1345 (Δ 1.3 ppm). A single crystal X-ray structure determination was performed on the hydrochloride of this product (See Appendix 2).

**N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methylformamide (98)**⁴⁰

![Chemical structure of 98](image)

Ethyl formate (0.52 mL, 6.4 mmol) was added to 3,4-dimethoxyethylphenylamine (97) (0.47 mL, 2.7 mL) and the neat mixture refluxed at 60 °C for 16 h. After this time the reaction mixture was concentrated in vacuo to give the formamide 98 as a yellow oil (603 mg, 100%); ¹H NMR (400 MHz, CDCl₃): δ 2.83 (2H, m, NCH₂CH₂), 2.88 (3H, s, NCH₃) and 2.92 (3H, s, NCH₃), 3.47 (2H, t, J = 7.3, NCH₂CH₂) and 3.57 (2H, t, J = 7.3, NCH₂CH₂), 3.88-3.90 (6H, m, 2 × OCH₃), 6.66 (1H, d, J = 1.9, C₆H) and 6.69 (1H, d, J = 1.9, C₆H), 6.71 (1H, d, J = 1.9, C₆H) and 6.78 (1H, m, C₆H), 6.82 (1H, s, C₆H) and 6.84 (1H, s, C₆H), 7.85 (1H, s, CHO) and 8.05 (1H, s, CHO); m/z (EI⁺) 223 [(M)⁺, 27%].

**6,7-Dimethoxy-2-methyl-3,4-dihydroisoquinolinium (96)**

![Chemical structure of 96](image)
To a solution of formamide 98 (0.23 g, 1.03 mmol) in MeCN (4 mL) was added POCl₃ (0.15 mL, 1.65 mmol) dropwise and the reaction mixture allowed to reflux. After 1 h the reaction mixture was concentrated in vacuo to give the iminium salt 96 as a brown sticky oil/solid. ¹H NMR (500 MHz, CD₃OD): δ 3.27 (2H, t, J = 8.2, NCH₂CH₂), 3.77 (3H, s, NCH₃), 3.90 (3H, s, OCH₃), 3.99 (3H, s, OCH₃), 4.03 (2H, t, J = 8.2, NCH₂CH₂), 7.13 (1H, s, C₆H), 7.42 (1H, s, C₆H), 8.94 (1H, s, N=CH); ¹³C NMR (125 MHz, CD₃OD): δ 26.07 (t), 47.62 (q), 50.76 (t), 56.97 (q), 57.32 (q), 112.36 (d), 116.317 (d), 118.43 (s), 133.84 (s), 150.12 (s), 158.97 (s), 166.35 (d); IR νₚₙₐₓ (neat): 781, 986, 1010, 1124, 1158, 1242, 1339, 1395, 1520, 1603, 2286, 3033, 3449 cm⁻¹; m/z (ESI) 206 [(M-Cl)^+], 100%; HRMS (ESI): calcd. for C₁₂H₁₆NO₂ [(M-Cl)^+] 206.1181, found 206.1177 (Δ -1.9 ppm).

4.3. Experimental for Chapter 2

(1R*,2S*,4S*,7R*)-3,8-Dioxo-tricyclo[5.1.0.0²,₄]octane (133)

Method 1: Polystyrene CoTPP

Polystyrene CoTPP was prepared as according to the method of Griesbeck¹⁰⁵ by adding a solution of CoTPP (14 mg, 0.021 mmol) in CH₂Cl₂ to a slurry of polystyrene beads (5 g, 75-150 μm, 1% DVB cross-linked) in CH₂Cl₂. The dark pink/red slurry was poured onto a petri dish and the solvent allowed to evaporate. The dry resin was slurried in MeCN (10 mL) in a quick fit conical flask, sealed, cooled to 0 °C and purged with O₂ for 10 min. To this slurry was then added 1,3-cyclohexadiene (0.1 mL, 1.05 mmol) and the reaction mixture irradiated with a 300 W lamp for 6 h at 0 °C. After this time ¹H NMR analysis showed full conversion of starting material had occurred to give a mixture of endoperoxide 132 and bis-epoxide 133 (ratio of 1:0.3 endoperoxide/bis-epoxide). Endoperoxide 132: ¹H NMR (400 MHz, MeCN- d₃): δ 1.41 (2H, d, J = 9.2, CH₂), 2.10 (2H, m, CH₂), 4.57 (2H, m, 2 × CHO), 6.62 (2H, dd, J = 4.3, 3.3, CH=CH); The reaction mixture was allowed to stir at RT for 20 h. After this time the reaction was filtered and the resin was washed with MeCN (20 mL). This solution of the crude bis-epoxide 133 was sealed and used directly in the next step (see below). An aliquot of the solution was taken and purified by FC (SiO₂ 100% hexane → 95:5 hexane/Et₂O → 2:1 hexane/Et₂O); Rₗ 0.28 (Et₂O/hexane, 2:1); ¹H NMR (400 MHz, CDCl₃): δ 1.79 (4H, m, C₆H₂ and C₆H₃), 3.09 (2H, m, C₄H and C₇H), 3.31 (2H, dd, J = 3.1, 0.9, C₁H and C₂H); ¹³C NMR
HRMS (Cl⁺) calcd. for C₆H₁₂NO₂ [(MNH₄)⁺] 130.0868, found 130.0870 (Δ 1.5 ppm).

(1R⁺,2S⁺,3S⁺,6R⁺)-3,6-Dibromocyclohexane-1,2-diol (134)

A solution of dilithium tetrabromocuprate (Li₂CuBr₄) was prepared according to the method of Ciaccio¹⁰⁷ by dissolving CuBr₂ (375 mg, 1.68 mmol) and LiBr (292 mg, 3.36 mmol) in MeCN (5 mL) at 0 °C and warming to 25 °C. To this dark purple solution was added a solution of bis-epoxide 133 (~ 1 mmol) in MeCN (~ 30 mL) via cannula and the reaction mixture allowed to stir at RT for 1.5 h. After this time the solvent was removed in vacuo and the crude mixture partitioned between H₂O (40 mL) and Et₂O (40 mL). The phases were separated and the aqueous phase extracted further with Et₂O (3 × 40 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by FC (SiO₂, petrol/Et₂O, 2:1) to give diol 134 as a white solid (192 mg, 67%). m.p. 80-82 °C (hexane); Rf 0.42 (Et₂O/hexane, 2:1); ¹H NMR (400 MHz, CDCl₃): δ 2.10 (2H, unresolved m, CH₂), 2.24 (2H, m, CH₂), 3.06 (2H, s, 2 × OH), 4.21 (2H, m, C₁H and C₂H), 4.28 (2H, app br s, C₃H and C₄H); ¹³C (100 MHz, CDCl₃): δ 29.90 (2 × t), 52.59 (broad peak, 2 × d), 72.90 (2 × d); IR νₘₐₓ (neat): 675, 1040, 1077, 2946, 3395 cm⁻¹; m/z (EI⁺) 276 [(M⁺Br, ⁸¹Br)⁺⁺, 21%], 274 [(M⁺Br, ⁷⁹Br)⁺⁺, 45%], 272 [(M⁺Br, ⁷⁹Br)⁺⁺, 22%]; HRMS (EI⁺) calcd. for C₆H₁₀O₂Br₂ [(M)⁺⁺] 271.9048, found 271.9042 (Δ -2.0 ppm).

Method 2: CoTPP in Solution

A solution of CoTPP (71 mg, 0.11 mmol) in CCl₄ (20 mL) was purged with O₂ and 1,3-cyclohexadiene (0.5 mL, 5.25 mmol) added. The solution was cooled to 0 °C and irradiated with a 300 W lamp at this temperature for 26 h. After this time the reaction mixture was added to a preformed solution of Li₂CuBr₄ in MeCN (10 mL) [prepared as described above, CuBr₂ (1.88 g, 8.4 mmol), LiBr (1.46 g, 16.8 mmol)] and allowed to stir at 25 °C for 2 h. After this time solvent was removed in vacuo and the crude mixture partitioned between H₂O (40 mL) and Et₂O (40 mL). The phases were separated and the aqueous phase extracted further with Et₂O (2 × 40 mL), the combined organic phases were dried over MgSO₄, filtered...
and concentrated in vacuo. The residue was purified by FC (SiO₂, 100% hexane → hexane/Et₂O, 95:5 → hexane/Et₂O, 2:1 → hexane/Et₂O, 1:1 → hexane/Et₂O, 1:2) to give diol 134 as a white solid (944 mg, 66%); Spectroscopic data as above.

**Method 3: TPP then CoTPP in solution**

A solution of TPP (65 mg, 0.11 mmol) in CCl₄ (20 mL) was purged with O₂ and 1,3-cyclohexadiene (0.5 mL, 5.25 mmol) added. The solution was cooled to 0 °C and irradiated with a 300 W lamp at this temperature for 5.5 h. After this time full conversion to endoperoxide 132 was observed by ¹H NMR analysis. *Endoperoxide 132*: ¹H NMR (400 MHz, CDCl₃): δ 1.46 (2H, d, J = 9.4, CH₂), 2.27 (2H, d, J = 9.4, CH₂), 4.63 (2H, m, 2 × CHO), 6.66 (2H, dd, J = 4.4, 3.3, CH=CH); CoTPP (71 mg, 0.11 mmol) was added to the solution and the reaction mixture stirred at RT under an inert atmosphere. After 2.5 h full conversion to *bis-epoxide 133* was observed by TLC and the reaction mixture added via cannula to a preformed solution of Li₂CuBr₄ in MeCN (10 mL) [prepared as described above, CuBr₂ (1.88 g, 8.4 mmol), LiBr (1.46 g, 16.8 mmol)]. The flask was washed with MeCN (10 mL) and cannulated likewise and the reaction mixture allowed to stir at RT for 1 h. The solvent was then removed in vacuo and the crude mixture partitioned between H₂O (20 mL) and Et₂O (20 mL). The phases were separated and the aqueous phase extracted further with Et₂O (2 × 60 mL), the combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by FC (SiO₂, 100% hexane → hexane/Et₂O, 99:1 → hexane/Et₂O, 97:3 → hexane/Et₂O, 95:5 → hexane/Et₂O, 2:1 → hexane/Et₂O, 1:1 → hexane/Et₂O, 1:2) to give diol 134 as a white solid (983 mg, 68%); Spectroscopic data as above.

**(3S*,6S*)-3,6-Dibromocyclohexene (164)**

![Chemical Structure](image_url)

To a solution of CuBr₂ (375 mg, 1.68 mmol) and LiBr (292 mg, 3.36 mmol) in MeCN (20 mL) was added 1,3-cyclohexadiene (0.1 mL, 1.05 mmol) and the reaction mixture allowed to stir at 25 °C for 2 h. After this time solvent was removed in vacuo and the crude mixture partitioned between H₂O (20 mL) and Et₂O (20 mL). The phases were separated and the aqueous phase was extracted further with Et₂O (2 × 10 mL). The combined organic phases
were dried over Na₂SO₄ and concentrated in vacuo to give dibromide 164 as a white crystalline solid (151 mg, 60%). m.p. 82-88 °C (hexane); Rₛ 0.77 (hexane/Et₂O, 9:1); ¹H NMR (400 MHz, CDCl₃): δ 2.15 (2H, app d, J = 10.2, CH₂), 2.42 (2H, m, CH₂), 4.88 (2H, app s, C₂H and C₆H), 5.97 (2H, d, J = 2.9, C₁H and C₂H); ¹³C (100 MHz, CDCl₃): δ 27.74 (2 × t), 45.77 (2 × d), 130.35 (2 × d); IR νₘₚₓ (neat): 556, 793, 885, 994, 1078, 1199, 1396, 1424 cm⁻¹; m/z (EI) 242 [[M⁺], 20%], 240 [[M⁺, Br⁻], 45%], 238 [[M⁺, Br²⁻], 22%], 159 (35), 79 (100); HRMS (EI⁺) calcd. for C₈H₅Br₂ [[M⁺] 237.8993, found 237.8981 (Δ -0.4 ppm). A single crystal X-ray structure determination was performed on the product to confirm the relative stereochemistry (See Appendix 2).

(3aS*,4S*,7R*,7aR*)-4,7-Dibromo-2,2-dimethylhexahydro-1,3-benzodioxole (135)

![Chemical Structure](image)

To a solution of diol 134 (1.52 g, 5.55 mmol) in CH₂Cl₂ (60 mL) was added a solution of DMP (4.10 mL, 33.30 mmol) and pTsOH·H₂O (211 mg, 1.11 mmol) in CH₂Cl₂ (5 mL) at 0 °C and the resultant solution allowed to stir at this temperature for 2 h. After this time the reaction mixture was quenched with aqueous NaOH (100 mL, 1 M). The phases were separated and the aqueous phase extracted further with CH₂Cl₂ (2 × 50 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by FC (SiO₂, 100% hexane → hexane/Et₂O, 99:1 → hexane/Et₂O, 98:2 → hexane/Et₂O, 97:3 → hexane/Et₂O, 9:1) to give dibromide 135 as a white solid (1.53 g, 88%). m.p. 74-77 °C (hexane); Rₛ 0.42 (hexane/Et₂O, 9:1); ¹H NMR (400 MHz, CDCl₃): δ 1.34 (3H, s, CH₃), 1.47 (3H, s, CH₃), 2.13 (4H, m, C₃H₂ and C₆H₂), 4.21 (2H, m, C₄H and C₅H), 4.45 (2H, m, C₃H and C₇H); ¹³C (100 MHz, CDCl₃): δ 26.33 (q), 28.57 (q), 30.00 (2 × t), 49.98 (2 × d), 79.26 (2 × d), 110.13 (s); IR νₘₚₓ (neat): 864, 1050, 1063, 1220, 1211, 1382, 2986 cm⁻¹; m/z (CI⁻) 334 [[M⁺, Br⁻]Na₄⁺, 23%], 332 [[M⁺, Br⁻]Na₄⁺, 46%], 330 [[M⁺, Br⁻]Na₄⁺, 24%], 317 [[M⁺, Br⁻]H⁺, 48%], 315 [[M⁺, Br⁻]H⁺, 100%], 313 [[M⁺, Br⁻]H⁺, 50%]; HRMS (CI⁻) calcd. for C₉H₁₃O₂Br₂ [[M⁻] 312.9439, found 312.9449 (Δ 3.3 ppm). A single crystal X-ray structure determination was performed on the product to confirm the relative stereochemistry (see Appendix 2).

(1S*,2S*,3R*,4R*)-1,4-Dibromo-2,3-dibenzoylcyclohexane (166)
Following an adapted literature procedure by Ley\textsuperscript{75} benzoyl chloride (94 μL, 0.81 mmol) was added dropwise to a stirred solution of \textit{dial 134} (100 mg, 0.37 mmol) and DMAP (4.5 mg, 0.037 mmol) in pyridine (5 mL) at 0 °C. The resultant solution was allowed to stir at 0 °C for 0.5 h before being warmed to RT and stirred at this temperature for a further 17 h. After this time the reaction mixture was quenched with dilute aqueous CuSO\textsubscript{4} solution (5 mL) and allowed to stir for 15 min. Et\textsubscript{2}O (5 mL) was added, the phases were separated and the aqueous phase was extracted further with Et\textsubscript{2}O (3 × 5 mL). The combined organic phases were washed with a dilute aqueous CuSO\textsubscript{4} solution (2 × 5 mL), H\textsubscript{2}O (1 × 5 mL), brine (1 × 5 mL) and finally 0.1 M HCl (1 × 5 mL), dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The residue was purified by FC (SiO\textsubscript{2}, hexane/Et\textsubscript{2}O, 7:3) to give \textit{dibromide 166} as a foamy pale yellow solid (137 mg, 77%). m.p. 124-130 °C (hexane); R\textsubscript{f} 0.44 (hexane/Et\textsubscript{2}O, 2:1); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 2.25-2.45 (4H, C\textsubscript{2}H\textsubscript{2} and C\textsubscript{6}H\textsubscript{2}), 4.50 (2H, m, C\textsubscript{1}H and C\textsubscript{4}H), 5.88 (2H, d, J = 6.2, C\textsubscript{2}H and C\textsubscript{3}H), 7.40 (4H, \textit{app} t, J = 7.6, 4 × C\textsubscript{A}H), 7.55 (2H, \textit{app} t, J = 7.6, 2 × C\textsubscript{A}H), 7.96 (4H, dd, J = 1.2, 8.4, 4 × C\textsubscript{A}H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 30.49 (2 × t), 46.94 (2 × d), 72.77 (2 × d), 128.56 (4 × d), 129.26 (2 × s), 129.80 (4 × d), 133.53 (2 × d), 164.92 (2 × s); IR ν<sub>max</sub> (neat): 670, 685, 704, 755, 1025, 1067, 1088, 1257, 1601, 1722, 2957 cm<sup>-1</sup>; m/z (Cl<sup>+</sup>) 502 [\{M\textsuperscript{81}Br, \textsuperscript{81}Br\textsubscript{2}NH\textsubscript{4}\textsuperscript{+}, 65%\}], 500 [\{M\textsuperscript{79}Br, \textsuperscript{79}Br\textsubscript{2}NH\textsubscript{4}\textsuperscript{+}, 100%\}], 498 [\{M\textsuperscript{79}Br, \textsuperscript{79}Br\textsubscript{2}NH\textsubscript{4}\textsuperscript{+}, 65%\}; HRMS (Cl<sup>+</sup>) calcd. for C\textsubscript{20}H\textsubscript{12}NO\textsubscript{4}\textsuperscript{79}Br\textsubscript{2} [(MNH\textsubscript{4}\textsuperscript{+})] 497.9916, found 497.9928 (Δ 2.5 ppm).

\textit{cis-1,2-(Isopropylidenedioxy)cyclohexa-3,5-diene (77)}

\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}

Into a dry 2-necked flask containing TBAI (3.87 g, 9.75 mmol) was cannulated a solution of \textit{dibromide 135} (1.53 g, 4.87 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL), the flask was washed with CH\textsubscript{2}Cl\textsubscript{2} (3.6 mL) and cannulated likewise. To this solution was added DBU (7.28 mL, 48.70 mmol) and the solution heated to 45 °C. After 2 h the reaction mixture was quenched with a citric
acid monohydrate solution (15.40 g, 73.05 mmol in 20 mL H₂O) and allowed to stir for 10 min. The phases were separated and the aqueous phase extracted further with CH₂Cl₂ (3 × 15 mL). The combined organic phases were washed with brine (3 × 50 mL), H₂O (2 × 50 mL), dried over Na₂SO₄ and filtered. The crude product was isolated by distillation at 55 °C to give acetonide 77 as a yellow oil (617 mg, 83%). Spectroscopic data as described in Section 4.2, Chapter 1 Experimental.

4.4. Experimental for Chapter 3

5-Nitropent-1-ene (177)

To a solution of NaNO₂ (6.40 g, 92.85 mmol) in DMF (60 ml) was added 5-bromopent-1-ene (178) (10 mL, 84.4 mmol) and the resultant mixture allowed to stir at RT for 8 h. After this time the reaction mixture was quenched with ice cold H₂O (50 mL) and Et₂O (50 mL) added. The phases were separated and the aqueous phase extracted further with Et₂O (3 × 50 mL). The combined organic phases were washed with brine (5 × 100 mL), dried over Na₂SO₄ and concentrated by distillation. The crude residue was purified by FC (SiO₂, pentane/Et₂O, 9:1) and 5-nitropent-1-ene (177) isolated by distillation as pale yellow oil (3.12 g, 32%). Rf 0.49 (hexane/Et₂O, 9:1); ¹H NMR (400 MHz, CDCl₃): δ 2.12 (4H, m, C₃H₂ and C₄H₂), 4.37 (2H, t, J = 6.7, C₅H₂), 5.07 (2H, m, 2 × C₂H), 5.74 (1H, ddt, J = 17.0, 10.3, 6.5, C₃H); ¹³C NMR (100 MHz, CDCl₃): δ 26.35 (t), 30.18 (t), 74.77 (t), 116.87 (d), 135.75 (d); IR νmax (neat): 917, 995, 1381, 1435, 1547, 2930, 3081 cm⁻¹; m/z (Cl⁻) 133 [(MNH₄)⁺, 82%]; HRMS (Cl⁻) calcd. for C₅H₃N₂O₂ [(MNH₄)⁺] 133.0977, found 133.0973 (Δ -3.0 ppm).

[(1E)-5-Nitropent-1-en-1-yl]benzene (179a)

To a stirred solution of 5-nitropent-1-ene (177) (0.11 mL, 0.96 mmol) and styrene (0.4 mL, 3.46 mmol) in CH₂Cl₂ (15 mL) was added Grubbs 2nd generation catalyst (40 mg, 5 mol%) and the resultant mixture allowed to heat at 45 °C. After 17 h more styrene (0.4 mL, 3.46 mmol) and Grubbs catalyst (9 mg, 1.1 mol%) were added and the reaction mixture heated at 45 °C for a further 4 h. The reaction mixture was then concentrated in vacuo and the crude residue purified by FC (SiO₂, hexane 100% → hexane/Et₂O, 95:5) to give nitroalkene 179a.
as a pale yellow oil (119 mg, inseparable mixture of isomers, ratio Z/E 0.14:1 by $^1$H NMR, 65%, data reported on major isomer only). $R_f$ 0.24 (hexane/Et₂O, 9:1); $^1$H NMR (400 MHz, CDCl₃): δ 2.18 (2H, app p, $J = 7.0$, C₄H₂), 2.32 (2H, app q, $J = 7.1$, C₃H₂), 4.41 (2H, t, $J = 6.9$, C₂H₂), 6.12 (1H, dt, $J = 15.8$, 7.0, C₂H), 6.43 (1H, d, $J = 15.8$, C₁H), 7.21 (1H, m, C₆H), 7.27-7.34 (4H, 4 × C₆H); $^{13}$C NMR (100 MHz, CDCl₃): δ 26.91 (t), 29.53 (t), 74.80 (t), 126.10 (2 × d), 127.28 (d), 127.43 (d), 128.60 (2 × d), 132.18 (d), 137.00 (s); IR νₚₐₓ (neat): 695, 752, 1352, 1383, 1496, 1549, 2925, 3031 cm⁻¹; m/z (EI⁺) 191 [(M)⁺, 25%]; HRMS (EI⁺) calcld. for C₁₁H₁₃NO₂ [(M)⁺] 191.0946, found 191.0945 (Δ -0.7 ppm).

1-Methyl-4-[(1E)-5-nitropent-1-en-1-yl]benzene (179b)

![Chemical structure of 179b]

To a stirred solution of 5-nitropent-1-ene (177) (0.63 mL, 5.50 mmol) in CH₂Cl₂ (40 mL) was added Grubbs 2nd generation catalyst (233 mg, 5 mol%). To this solution was added 4-methylstyrene (2.6 mL, 19.76 mmol) in four portions over 6 h whilst being heated at 45 °C. After the complete addition of 4-methylstyrene the resultant mixture was allowed to stir at 45 °C for a further 15.5 h. After this time more 4-methylstyrene was added (2.60 mL, 19.76 mmol) in four portions over 6 h. The reaction mixture was then concentrated in vacuo and the crude residue purified by FC (SiO₂, 1% Et₂O in hexane → 3% Et₂O in hexane) to give nitroalkene 179b as a dark yellow oil (513 mg, inseparable mixture of isomers, ratio Z/E 0.22:1 by $^1$H NMR, 45%, data reported on major isomer only). $R_f$ 0.53 (hexane/Et₂O, 2:1); $^1$H NMR (400 MHz, CDCl₃): δ 2.22 (2H, app q, $J = 7.1$, C₄H₂), 2.33-2.39 (5H, C₃H₂ and CH₃), 4.46 (2H, t, $J = 7.0$, C₂H₂), 6.12 (1H, dt, $J = 15.8$, 6.9, C₂H), 6.45 (1H, d, $J = 15.8$, C₁H), 7.16 (2H, d, $J = 8.0$, 2 × C₆H), 7.28 (2H, d, $J = 8.0$, 2 × C₆H); $^{13}$C NMR (100 MHz, CDCl₃): δ 21.71 (q), 26.99 (t), 29.52 (t), 74.82 (t), 126.01 (2 × d), 126.26 (d), 129.31 (2 × d), 132.01 (d), 134.27 (s), 137.22 (s); IR νₚₐₓ (neat): 796, 967, 1379, 1432, 1512, 1547, 2922, 3024 cm⁻¹; m/z (EI⁺) 205 [(M)⁺, 74%]; HRMS (EI⁺) calcld. for C₁₃H₁₄NO₂ [(M)⁺] 205.1103, found 205.1100 (Δ -1.4 ppm).

1-Methoxy-4-[(1E)-5-nitropent-1-en-1-yl]benzene (179c)

![Chemical structure of 179c]

117
To a stirred solution of 5-nitropent-1-ene (177) (0.63 mL, 5.50 mmol) in CH₂Cl₂ (40 mL) was added Grubbs 2nd generation catalyst (233 mg, 5 mol%). To this solution was added 4-vinylanisole (2.63 mL, 19.78 mmol) in four portions over 6 h whilst being heated at 45 °C. After the complete addition of 4-vinylanisole the resultant mixture was allowed to stir at 45 °C for a further 15.5 h. After this time more 4-vinylanisole was added (1.47 mL, 11.05 mmol) in three portions over 6 h. The reaction mixture was then concentrated in vacuo and the crude residue purified by FC (SiO₂, 1% Et₂O in hexane → 3% Et₂O in hexane) to give nitroalkene 179c as a yellow oil (576 mg, inseparable mixture of isomers, ratio Z/E 0.20:1 by ¹H NMR, 47%, data reported on major isomer only). Rf 0.36 (hexane/Et₂O, 2:1); ¹H NMR (400 MHz, CDCl₃): δ 2.20 (2H, app p, J = 6.9, C₄H₂), 2.33 (2H, app q, J = 7.1, C₃H₂), 3.83 (3H, s, OCH₃), 4.45 (2H, t, J = 6.9, C₃H₂), 6.01 (1H, dt, J = 15.8, 7.0, C₂H), 6.40 (1H, d, J = 15.8, C₁H), 6.83 (2H, m, 2 × C₂H₃), 7.25 (2H, m, 2 × C₂H₃); ¹³C NMR (100 MHz, CDCl₃): δ 27.06 (t), 29.51 (t), 55.32 (q), 74.84 (t), 114.03 (2 × d), 125.07 (d), 127.24 (2 × d), 129.86 (s), 131.53 (d), 159.10 (s); IR νmax (neat): 805, 840, 967, 1174, 1243, 1379, 1463, 1509, 1547, 1606, 2837, 2955 cm⁻¹; m/z (EI⁺) 221 [(M)⁺⁺, 86%]; HRMS (EI⁺) calc. for C₁₂H₁₅NO₃ [(M)⁺⁺] 221.1052, found 221.1045 (Δ -3.1 ppm).

1-[(1E)-5-Nitropent-1-en-1-yl]-4-(trifluoromethyl)benzene (179d)

To a stirred solution of 5-nitropent-1-ene (177) (0.18 mL, 1.61 mmol) in CH₂Cl₂ (12 mL) was added Grubbs 2nd generation catalyst (68 mg, 5 mol%). To this solution was added 4-trifluoromethylstyrene (0.86 mL, 5.81 mmol) via syringe pump over 4 h whilst being heated at 45 °C. After complete addition of 4-trifluoromethylstyrene the resultant mixture was allowed to stir at 45 °C for a further 17 h. After this time more Grubbs catalyst was added (34 mg, 2.5 mol%) and the reaction mixture stirred at 45 °C for a further 7 h before being concentrated in vacuo. The crude residue was purified by FC (SiO₂, 1% Et₂O in hexane) to give nitroalkene 179d as a dark yellow oil (209 mg, inseparable mixture of isomers, ratio Z/E 0.04:1 by ¹H NMR, 50%, data reported on major isomer only). Rf 0.20 (hexane/Et₂O, 9:1); ¹H NMR (400 MHz, CDCl₃): δ 2.25 (2H, app p, J = 6.9, C₄H₂), 2.40 (2H, app q, J = 7.0, C₃H₂), 4.47 (2H, t, J = 6.8, C₃H₂), 6.28 (1H, dt, J = 15.8, 6.9, C₂H), 6.51 (1H, d, J = 15.8, C₁H), 7.46 (2H, d, J = 8.2, 2 × C₂H₂), 7.59 (2H, d, J = 8.2, 2 × C₂H₂); ¹³C NMR (100 MHz, CDCl₃): δ 26.66 (t), 29.59 (t), 74.74 (t), 120.46 (s) and 122.84 (s) and 125.37 (s) and 127.60 (s), 125.50 (2 × d) and 125.54 (2 × d) and 125.58 (2 × d) and 125.62 (2 × d), 126.25 (2 × d), 128.75 (s)
1-Chloro-4-[(1E)-5-nitropent-1-en-1-yl]benzene (179e)

To a stirred solution of 5-nitropent-1-ene (177) (0.60 mL, 5.25 mmol) in CH₂Cl₂ (40 mL) was added Grubbs 2nd generation catalyst (223 mg, 5 mol%). To this solution was added 4-chlorostyrene (2.27 mL, 18.90 mmol) via syringe pump over 6 h whilst being heated at 45 °C. After complete addition of 4-chlorostyrene the resultant mixture was allowed to stir at 45 °C for a further 14.5 h. After this time more Grubbs catalyst was added (112 mg, 2.5 mol%) and the reaction mixture stirred at 45 °C for a further 4 h before being concentrated in vacuo. The crude residue was purified by FC (SiO₂, 1% Et₂O in hexane → 2% Et₂O in hexane) to give nitroalkene 179e as a pale yellow oil (411 mg, inseparable mixture of isomers, ratio E/Z 0.05:1 by ¹H NMR, 35%, data reported on major isomer only). Rf 0.27 (hexane/Et₂O, 9:1); ¹H NMR (400 MHz, CDCl₃): δ 2.23 (2H, app p, J = 7.1, C₄H₂), 2.36 (2H, app q, J = 7.1, C₃H₂), 4.46 (2H, t, J = 6.9, C₅H₂), 6.15 (1H, dt, J = 15.7, 6.9, C₂H), 6.43 (1H, dt, J = 15.7, 1.3, C₁H), 7.30 (4H, app s, 4 × C₆H₆); ¹³C NMR (100 MHz, CDCl₃): δ 26.80 (t), 29.52 (t), 74.77 (t), 127.31 (2 × d), 128.03 (d), 128.74 (2 × d), 130.98 (d), 133.03 (s), 135.51 (s); IR νmax (neat): 802, 846, 966, 1011, 1089, 1379, 1432, 1489, 1546 2927, 3029 cm⁻¹; m/z (EI⁺) 227 [(M⁺Cl)⁺⁺, 15%], 225 [(M⁺Cl)⁺⁺, 45%]; HRMS (EI⁺) calcd. for C₁₁H₁₂ClNO₂ [(M⁺⁺) 225.67, found 225.0557, 225.0553 (Δ -0.6 ppm).

1-Fluoro-4-[(1E)-5-nitropent-1-en-1-yl]benzene (179f)

To a stirred solution of 5-nitropent-1-ene (177) (0.60 mL, 5.25 mmol) in CH₂Cl₂ (40 mL) was added Grubbs 2nd generation catalyst (223 mg, 5 mol%). To this solution was added 4-fluorostyrene (2.25 mL, 18.90 mmol) via syringe pump over 4 h whilst being heated at 45 °C. After complete addition of 4-fluorostyrene the resultant mixture was allowed to stir at 45 °C for a further 16 h. After this time more Grubbs catalyst (112 mg, 2.5 mol%) and 4-fluorostyrene (1.13 mL, 9.45 mmol) were added and the reaction mixture stirred at 45 °C for...
a further 3 h before being concentrated in vacuo. The crude residue was purified by FC (SiO₂, 1% Et₂O in hexane) to give nitroalkene 179f as a dark yellow oil (631 mg, inseparable mixture of isomers, ratio E/Z 0.15:1 by ¹H NMR, 57%, data reported on major isomer only). Rf 0.41 (hexane/Et₂O, 9:1); ¹H NMR (400 MHz, CDCl₃): δ 2.22 (2H, app p, J = 7.1, C₄H₂), 2.35 (2H, app q, J = 7.0, C₃H₂), 4.46 (2H, t, J = 6.9, C₂H₂), 6.08 (1H, dt, J = 15.8, 7.0, C₂H), 6.43 (1H, d, J = 15.8, C₁H), 6.98 (2H, m, 2 × C₆H₆), 7.28 (2H, m, 2 × C₆H₆); ¹³C NMR (100 MHz, CDCl₃): δ 26.88 (t), 29.49 (t), 74.79 (t), 115.37 (2 × d) and 115.59 (2 × d), 127.03 (d), 127.53 (2 × d) and 127.61 (2 × d), 130.97 (d), 132.91 (s) and 133.15 (s), 160.93 (s) and 163.42 (s); ¹⁹F NMR (376 MHz, CDCl₃): δ -114.8 (1F, s, ArF); IR νmax (neat): 807, 845, 967, 1158, 1223, 1380, 1433, 1506, 1547, 1601, 2933 cm⁻¹; m/z (EI⁺) 210 [{M(¹⁹F)}⁺⁺, 10%], 209 [{M(¹⁹F)}⁺⁺, 48%]; HRMS (EI⁺) calcd. for C₁₁H₁₂¹⁹FNO₂ [{M⁺}] 209.0852, found 209.0852 (Δ 0.00 ppm).

**General Method A:** To a stirred solution of nitroalkene 179a (288 mg, 1.51 mmol) in THF (10 mL) was added KOH (89 mg, 1.59 mmol) and TBAI (84 mg, 15 mol%) as solids. To this mixture was added benzylbromide (198 µL, 1.66 mmol) and the resultant suspension allowed to stir at RT. After 6 h a 75% conversion was observed by ¹H NMR analysis and more KOH (25 mg, 0.45 mmol) was added and the reaction mixture stirred at RT for a further 16 h. After this time full conversion was observed by TLC analysis and H₂O (10 mL) and Et₂O (10 mL) were added to the reaction mixture. The phases were separated and the aqueous phase was extracted further with Et₂O (4 × 10 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by FC (SiO₂, hexane/Et₂O, 9:1) to give oxime 180a as an off white solid (132 mg, inseparable mixture of isomers, ratio Z/E 1:0.9 by ¹H NMR, 50%, data reported on major isomer only). m.p. 82-88 °C, (Et₂O/pentane), [Lit., 104-106 °C, (Et₂O/pentane)]¹⁴²; Rf 0.37 (hexane/Et₂O, 2:1); ¹H NMR (400 MHz, CDCl₃): δ 2.47 (2H, app q, J = 7.1, C₃H₂), 2.63 (2H, app dd, J = 13.5, 5.9, C₂H₂), 6.25 (1H, dt, J = 15.8, 6.9, C₄H), 6.49 (1H, d, J = 15.8, C₂H), 6.84 (1H, t, J = 5.9, NCH), 7.27 (1H, app q, J = 7.1, C₆H₆), 7.36 (4H, m, 4 × C₆H₆), 9.24 (1H, br s, OH); ¹³C NMR (100 MHz, CDCl₃): δ 24.63 (t), 29.32 (t), 126.10 (2 × d), 127.19 (d), 128.55 (2 × d), 128.77 (d), 131.03 (d), 137.39 (s), 151.90 (d); IR νmax (neat): 741, 965, 1320, 1666, 1446,
2879, 3027, 3083, 3192 cm⁻¹, m/z (EI⁺) 175 [(M⁺)⁺, 22%]; HRMS (EI⁺) calcd. for C_{11}H_{13}NO [(M⁺)⁺] 175.0997, found 175.0999 (Δ 1.1 ppm).

(1Z,4E)-5-(4-methylphenyl)pent-4-enal oxime (180b)

Using general method A nitroalkene 179b (513 mg, 2.50 mmol), KOH (147 mg, 2.63 mmol), TBAI (140 mg, 15 mol%), benzylobromide (327 µL, 2.75 mmol) in THF (30 mL) after 14 h at RT gave a 78% conversion, more KOH (42 mg, 0.75 mmol) was added. After a further 3.5 h full conversion was observed. The crude residue was purified by FC (SiO₂, hexane/Et₂O, 4:1) to give oxime 180b as an off white crystalline solid (242 mg, inseparable mixture of isomers, ratio Z/E 1:0.42 by ¹H NMR, 52%, data reported on major isomer only). m.p. 110-117 °C (Et₂O/pentane); Rf 0.62 (hexane/Et₂O); ¹H NMR (400 MHz, CDCl₃): δ 2.31 (3H, s, CH₃), 2.38 (2H, app q, J = 7.1, C₃H₂), 2.54 (2H, app dd, J = 13.5, 7.1, C₂H₂), 6.13 (1H, dt, J = 15.9, 7.0, C₄H), 6.40 (1H, d, J = 15.9, C₃H), 6.76 (1H, t, J = 5.3, NCH), 7.09 (2H, d, J = 8.0, 2 × C₆H), 7.22 (2H, d, J = 8.0, 2 × C₆H), 7.71 (1H, br s, OH); ¹³C NMR (100 MHz, CDCl₃): δ 21.15 (q), 24.56 (t), 29.39 (t), 125.97 (2 × d), 127.52 (d), 129.22 (2 × d), 130.96 (d), 134.60 (s), 136.92 (s), 151.68 (d); IR ν̇max (neat): 795, 834, 916, 964, 1443, 1512, 1663, 2859, 3027, 3082, 3185 cm⁻¹; m/z (EI⁺) 189 [(M⁺)⁺, 28%]; HRMS (EI⁺) calcd. for C_{12}H_{15}NO [(M⁺)⁺] 189.1154, found 189.1154 (Δ 0.2 ppm).

(1Z,4E)-5-(4-Methoxyphenyl)pent-4-enal oxime (180c)

Using general method A nitroalkene 179c (576 mg, 2.60 mmol), KOH (153 mg, 2.73 mmol), TBAI (144 mg, 15 mol%), benzylobromide (340 µL, 2.86 mmol) in THF (30 mL) after 14 h at RT gave a 76% conversion, more KOH (44 mg, 0.78 mmol) was added. After a further 3.5 h full conversion was observed. The crude residue was purified by FC (SiO₂, hexane/Et₂O, 4:1 → 2:1) to give oxime 180c as an off white crystalline solid (233 mg, inseparable mixture of isomers, ratio Z/E 1:0.34 by ¹H NMR, 44%, data reported on major isomer only). m.p. 112-118 °C (Et₂O/hexane); Rf 0.36 (hexane/Et₂O, 2:1); ¹H NMR (400 MHz, CDCl₃): δ 2.43 (2H, app q, J = 7.1, C₃H₂), 2.59 (2H, m, C₂H₂), 3.83 (3H, s, CH₃), 6.09 (1H, dt, J = 6.8, 15.9, C₄H), 6.42 (1H, d, J = 15.9, C₃H), 6.81 (1H, t, J = 5.3, NCH), 6.87 (2H, m, 2 × C₆H), 7.31 (2H, m, 2 × C₆H), 7.68 (1H, br s, OH); ¹³C NMR (100 MHz, CDCl₃): δ 24.60 (t), 29.33 (t), 121
Using **general method A nitroalkene 179d** (209 mg, 0.81 mmol), KOH (48 mg, 0.85 mmol), TBAI (45 mg, 15 mol%), benzylbromide (106 μL, 0.89 mmol) in THF (15 mL) after 15.5 h at RT gave a 70% conversion, more KOH (14 mg, 0.24 mmol) was added. After a further 3 h full conversion was observed. The crude residue was purified by FC (SiO₂, hexane/Et₂O, 4:1) to give oxime 180d as an off white crystalline solid (90.5 mg, inseparable mixture of isomers, ratio Z/E 1:0.45 by ¹H NMR, 46%, data reported on the mixture of isomers). m.p. 91-94 °C (pentane/Et₂O); Rf 0.63 (Et₂O/hexane, 2:1); ¹H NMR (400 MHz, CDCl₃): δ 2.42-2.51 (2.62H, E C₃H₂, E C₃H₂ and Z C₃H₂), 2.63 (1.38H, app q, J = 7.0, Z C₂H₂), 6.34 (1H, dt, J = 15.9, 6.7, E and Z C₄H), 6.50 (0.31H, d, J = 15.9, E C₅H), 6.51 (0.69H, d, J = 15.9, Z C₅H), 6.81 (0.69H, t, J = 5.2, Z NCH), 7.46 (2H, d, J = 8.1, E and Z 2 × C₆H₅), 7.52 (0.31H, t, J = 5.5, E NCH), 7.58 (2H, d, J = 8.1, E and Z 2 × C₆H₅), 8.08 (0.31H, br s, E OH), 8.54 (1H, br s Z OH); ¹³C NMR (100 MHz, CDCl₃): δ 24.35 (Z t), 29.03 (Z t), 29.22 (E t), 29.83 (E t), 120.16 (s) and 122.86 (s) and 125.56 (s) and 128.26 (s), 125.37(2 × d) and 125.40 (2 × d) and 125.43 (2 × d) and 125.46 (2 × d), 126.16 (2 × d), 128.45 (s) and 128.77 (s) and 129.09 (s) and 129.41 (s), 129.74, (Z d), 129.92 (E d), 131.27 (Z d), 131.49 (E d), 140.75 (s), 151.14 (E d), 151.52 (Z d); ¹⁹F (376 MHz, CDCl₃): δ -62.46 (3F, s, CF₃); IR νmax (neat): 860, 1069, 1111, 1121, 1167, 1324, 1415, 1443, 1615, 2877, 3207 cm⁻¹; m/z (EI⁺) 244 [{M²⁰F}⁺, 3%], 243 [{M²¹F}⁺, 16%]; HRMS (EI⁺) calc. for C₁₂H₁₂F₃NO [(M⁺)⁺] 243.0871, found 243.0870 (Δ -0.4 ppm).

**Using general method A nitroalkene 179e** (411 mg, 1.82 mmol), KOH (107 mg, 1.91 mmol), TBAI (101 mg, 15 mol%), benzylbromide (238 μL, 2.00 mmol) in THF (30 mL) after 4 h at
RT gave a 64% conversion, more KOH (31 mg, 0.54 mmol) was added. After a further 11.5 h full conversion was observed. The crude residue was purified by FC (SiO₂, hexane/Et₂O, 4:1) to give oxime 180e as a white crystalline solid (222 mg, inseparable mixture of isomers, ratio Z/E 1:0.12 by ¹H NMR, 58%, data reported on major isomer only). m.p. 125-132 °C (Et₂O/pentane); Rf 0.22 (Et₂O/hexane, 2:1); ¹H NMR (400 MHz, CDCl₃): δ 2.45 (2H, app q, J = 7.1, C₃H₂), 2.60 (2H, m, C₂H₂), 6.21 (1H, dt, J = 15.9, 6.6, C₉H), 6.43 (1H, dt, J = 15.9, 1.4, C₃H), 6.80 (1H, t, J = 5.4, NCH), 7.29 (4H, app s, 4 × C₆H₅), 8.06 (1H, br s, OH); ¹³C NMR (100 MHz, CDCl₃): δ 24.39 (t), 29.30 (t), 127.28 (2 × d), 128.67 (2 × d), 129.48 (d), 129.83 (d), 132.75 (s), 135.86 (s), 151.90 (d); IR νmax (neat): 967, 1091, 1445, 1490, 1665, 2868, 3036, 3091, 3182 cm⁻¹; m/z (El⁺) 211 [{M(³⁷Cl)}⁺⁺, 8%], 210 [{M(³⁶Cl)}⁺⁺, 3%], 209 [{M(³⁵Cl)}⁺⁺, 28%]; HRMS (El⁺) calcd. for C₁₁H₁₂⁵ClNO [(M)⁺] 209.0607, found 209.0605 (Δ -1.2 ppm).

(1Z,4E)-5-(4-Fluorophenyl)pent-4-enal oxime (180f)

Using general method A nitroalkene 179f (631 mg, 3.02 mmol), KOH (178 mg, 3.17 mmol), TBAI (167 mg, 15 mol%), benzylbromide (395 µL, 3.32 mmol) in THF (30 mL) after 4 h at RT gave a 65% conversion, more KOH (51 mg, 0.91 mmol) was added. After a further 2 h full conversion was observed. The crude residue was purified by FC (SiO₂, hexane/Et₂O, 4:1) to give oxime 180f as a white crystalline solid (399 mg, inseparable mixture of isomers, ratio Z/E 1:0.23 by ¹H NMR, 68%, data reported on major isomer only). m.p. 96-102 °C (Et₂O/pentane); Rf 0.25 (pentane/Et₂O, 2:1); ¹H NMR (400 MHz, CDCl₃): δ 2.44 (2H, app q, J = 7.1, C₃H₂), 2.60 (2H, m, C₂H₂), 6.15 (1H, dt, J = 15.9, 6.7, C₉H), 6.44 (1H, d, J = 15.9, C₃H), 6.81 (1H, t, J = 5.3, NCH), 7.02 (2H, m, 2 × C₆H₅), 7.33 (2H, m, 2 × C₆H₅), 8.74 (1H, br s, OH); ¹³C NMR (100MHz, CDCl₃): δ 24.53 (t), 29.25 (t), 115.28 (2 × d) and 115.50 (2 × d), 127.48 (2 × d) and 127.55 (2 × d), 128.48 (d) and 128.49 (d), 129.84 (d), 133.51 (s) and 133.54 (s), 151.87 (d), 160.86 (s) and 163.31 (s); ¹⁹F NMR (376 MHz, CDCl₃): δ -115.23 (1F, s, ArF); IR νmax (neat): 969, 1226, 1319, 1446, 1507, 1599, 1666, 2868, 3085, 3190 cm⁻¹; m/z (El⁺) 194 [{M(²⁰F)}⁺⁺, 4%], 193 [{M(²¹F)}⁺⁺, 22%]; HRMS (El⁺) calcd. for C₁₁H₁₂¹⁹FNO [(M)⁺] 193.0903, found 193.0905 (Δ 1.1 ppm).

(4E)-7-Phenylhept-4-enal (183)¹³⁴
To a stirred solution of 4-pentenal (181) (587 µL, 5.94 mmol) and 4-phenylbut-1-ene (182) (3.2 mL, 21.38 mmol) in CH₂Cl₂ (15 mL) was added Grubbs 2\textsuperscript{nd} generation catalyst (204 mg, 4 mol%) and the resultant mixture heated to 45 °C for 3 h 15 min. After this time the solvent was removed under a stream of N₂ and the crude residue purified by FC (SiO₂, 1% Et₂O in hexane → 5% Et₂O in hexane) to give aldehyde 183 as a pale yellow oil (195 mg, 17%). R\textsubscript{f} 0.34 (hexane/Et₂O, 9:1); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta 2.30\) (4H, m, C₆H₂ and C₆H₂), 2.45 (2H, m, C₂H₂), 2.65 (2H, m, C₇H₂), 5.44 (2H, m, C₄H and C₅H), 7.13-7.18 (4H, 4 × C₆H), 7.26-7.29 (1H, C₆H), 9.72 (1H, t, \(J = 1.7\), CHO); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta 24.14\) (t), 34.29 (t), 35.86 (t), 43.42 (t), 125.79 (d), 128.27 (d), 28.48 (4 × d), 130.98 (d), 141.87 (s), 202.42 (s); IR \(\nu_{\text{max}}\) (neat): 697, 746, 968, 1453, 1495, 1722, 2853, 2926, 3027 cm\(^{-1}\); \(m/z\) (Cl\textsuperscript{+}) 206 [(MNH₄)\textsuperscript{+}, 100%]; HRMS (Cl\textsuperscript{+}) calcd. for C\textsubscript{13}H\textsubscript{26}NO [(MNH₄)\textsuperscript{+}] 206.1545, found 206.1551 (A 3.0 ppm).

(1Z,4E)-7-Phenylhept-4-enal oxime (180g) and (1E,4E)-7-phenylhept-4-enal oxime (180g)

To a stirred solution of aldehyde 183 (195 mg, 1.04 mmol) in CH₂Cl₂ (15 mL) was added NH₃OH·HCl (273 mg, 3.93 mmol) and NaOAc (404 mg, 4.93 mmol) as solids followed by MeOH (2.5 mL) and the resultant mixture allowed to stir at RT open to the atmosphere for 1 h. After this time brine (40 mL) was added and the reaction mixture and stirred until two clear phases had formed. The phases were separated and the aqueous phase extracted further with CH₂Cl₂ (2 × 40 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by FC (SiO₂, hexane/Et₂O, 4:1) to give oxime 180g as a colourless oil (207 mg, inseparable mixture of isomers, ratio Z/E 1:1.1 by \textsuperscript{1}H NMR, 98%, data reported on the mixture of isomers). R\textsubscript{f} 0.38 (hexane/Et₂O, 2:1); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta 2.26\) (2H, \textit{app} q, \(J = 6.8\), E and Z C₆H₂), 2.33 (0.94H, m, Z C₂H₂), 2.36-2.45 (2H, E and Z C₆H₂), 2.52 (1.06H, td, \(J = 7.3\), 5.4, E C₂H₂), 2.76 (2H, \textit{app} t, \(J = 7.6\), E and Z C₇H₂), 5.50 (1H, dt, \(J = 15.3\), 6.3, E and Z C₅H), 5.60 (1H, m, E and Z C₄H), 6.77 (0.47H, t, \(J = 5.3\), Z NCH), 7.24-7.29 (3H, 3 × C₆H), 7.36 (2H, m, 2 × C₆H), 7.49 (0.53H, t, \(J = 5.8\), E NCH), 9.24 (0.53H, br s, E OH), 9.66 (0.47H, br s, Z OH); \textsuperscript{13}C NMR (100 MHz,
CDCl$_3$: δ 24.75 (Z t), 29.50 (t), 29.64 (E t), 34.41 (t), 35.99 (t), 125.85 (d), 128.34 (2 × d), 128.54 (2 × d), 128.90 (Z d), 129.17 (E d), 130.93 (Z d), 131.07 (E d), 142.01 (s), 151.79 (E d), 152.23 (Z d); IR $\nu_{\text{max}}$ (neat): 698, 746, 968, 1076, 1335, 1453, 1495, 2853, 2917, 3027, 3236 cm$^{-1}$; m/z (EI$^+$) 203 [(M$^+$), 5%]; HRMS (EI$^+$) calcd. for C$_{13}$H$_{15}$NO [(M$^+$)] 203.1310, found 203.1302 (Δ -0.4 ppm).

(4E)-N-Hydroxy-5-phenylpent-4-en-1-amine (176a)$^{142}$

![Chemical Structure of 176a](https://example.com/structure.png)

**General Method B:** A solution of oxime 180a (47.2 mg, 0.27 mmol) and NaCNBH$_3$ (34 mg, 0.54 mmol) in MeOH (10.4 mL) was cooled to 0 °C and 14 drops methyl orange added. MeOH/HCl (10:1) (0.29 mL over 10 min) was added dropwise to this bright yellow solution to give an orange solution. The reaction mixture was then warmed to RT for 10 min to which the solution returned to yellow colour and was cooled back down to 0 °C. MeOH/HCl (10:1) (0.05 mL over 10 min) was added dropwise until the solution remained orange and the reaction mixture was again warmed to RT for 10 min. After this time the reaction mixture was quenched with NaOH (2 mL, 2 M) and allowed to stir for 10 min before Et$_2$O (10 mL) was added and the phases separated. The aqueous phase was extracted further with Et$_2$O (3 × 10 mL), the combined organic phases were washed with brine (20 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give hydroxylamine 176a as a yellow oil (43.4 mg, 91%). R$_f$ 0.57 (Et$_2$O/hexane, 9:1); $^1$H NMR (400 MHz, CDCl$_3$): δ 1.78 (2H, tt, J = 14.0, 7.1, C$_2$H$_2$), 2.31 (2H, app dd, J = 14.0, 6.8, C$_3$H$_2$), 3.04 (2H, t, J = 7.1, C$_4$H$_2$), 6.25 (1H, dt, J = 15.8, 6.8, C$_4$H), 6.45 (1H, d, J = 15.8, C$_3$H), 7.22-7.26 (1H, m, C$_A$H), 7.32-7.39 (4H, 4 × C$_A$H), NH and OH (absent); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 26.53 (t), 30.45 (t), 53.20 (t), 125.91 (2 × d), 126.89 (d), 128.43 (2 × d), 129.89 (d), 130.39 (d), 137.57 (s); IR $\nu_{\text{max}}$ (neat): 692, 745, 697, 1031, 1451, 1497, 1599, 2859, 2928, 3026, 3243 cm$^{-1}$; m/z (ESI) 178 [(MH)$^+$, 60 %]; HRMS (ESI) calcd. for C$_{11}$H$_{16}$NO [(MH)$^+$] 178.1232, found 178.1236 (Δ 2.2 ppm).

(4E)-N-Hydroxy-5-(4-methylphenyl)pent-4-en-1-amine (176b)

![Chemical Structure of 176b](https://example.com/structure.png)

Using *general method B* oxime 180b (50 mg, 0.26 mmol), NaCNBH$_3$ (33 mg, 0.53 mmol) in MeOH (10 mL) after the addition of MeOH/HCl (10:1) (0.32 mL over 10 min) then (0.4 mL over 10 min) gave hydroxylamine 176b as a white solid (47.5 mg, 96%). m.p. 54-62 °C; R$_f$
(4E)-N-Hydroxy-5-(4-methoxyphenyl)pent-4-en-1-amine (176c)

Using general method B oxime 180c (50 mg, 0.24 mmol), NaCNBH3 (31 mg, 0.49 mmol) in MeOH (9.2 mL) after the addition of MeOH/HCl (10:1) (0.31 mL over 10 min) then (0.1 mL over 10 min) gave hydroxylamine 176c as an off white solid (43 mg, 86%); m.p. 61-66 °C; Rf 0.57 (Et2O/hexane, 9:1); 1H NMR (400 MHz, CDCl3): δ 1.75 (2H, app q, J = 7.3, C2H2), 2.27 (2H, app q, J = 7.2, C2H2), 3.02 (2H, t, J = 7.2, C1H2), 3.82 (3H, s, CH3), 6.09 (1H, dt, J = 15.8, 6.9, C4H), 6.37 (1H, d, J = 15.8, C3H), 6.86 (2H, m, 2 × C4H), 7.30 (2H, m, 2 × C4H), NH and OH (absent); 13C NMR (125 MHz, CDCl3): δ 26.64 (t), 30.42 (t), 53.23 (t), 55.20 (q), 113.86 (2 × d), 126.97 (2 × d), 127.70 (d), 129.70 (d), 130.40 (s), 158.67 (s); IR νmax (neat): 840, 966, 1033, 1067, 1120, 1174, 1245, 1325, 1510, 1607, 2836, 2936, 3274 cm⁻¹; m/z (ESI) 208 [(MH)+, 100%]; HRMS (EI+) calcd. for C12H17NO [(MH)+] 207.1259, found 207.1253 (Δ -3.0 ppm).

(4E)-N-Hydroxy-5-[4-(trifluoromethyl)phenyl]pent-4-en-1-amine (176d)

Using general method B oxime 180d (48 mg, 0.20 mmol), NaCNBH3 (25 mg, 0.40 mmol) in MeOH (7.7 mL) after the addition of MeOH/HCl (10:1) (0.29 mL over 10 min) then (0.4 mL over 10 min) gave hydroxylamine 176d as a yellow semi-solid (49 mg, 100%). Rf 0.37 (Et2O/hexane, 9:1); 1H NMR (400 MHz, CDCl3): δ 1.79 (2H, app p, J = 7.3, C2H2), 2.32 (2H, app q, J = 7.1, C2H2), 3.02 (2H, t, J = 7.2, C1H2), 6.12 (1H, br s, OH), 6.33 (1H, dt, J = 15.9, 6.7, C4H), 6.45 (1H, d, J = 15.9, C3H), 7.42 (2H, d, J = 8.1, 2 × C4H), 7.55 (2H, d, J = 8.1, 2 × C4H), NH (absent); 13C NMR (125 MHz, CDCl3): δ 26.37 (t), 30.47 (t), 53.15 (t), 120.98 (s) and 123.14 (s) and 125.31 (s) and 127.46 (s), 125.34 (2 × d) and 125.37 (2 × d) and

126
125.40 (2 × d) and 125.43 (2 × d), 126.01 (2 × d), 128.35 (s) and 128.60 (s) and 128.86 (s) and 129.12 (s), 129.21 (s), 132.76 (d), 141.01 (s); $^{19}$F NMR (376 MHz, CDCl$_3$): δ = -62.38 (3F, s, CF$_3$); IR $\nu_{\text{max}}$ (neat): 855, 967, 1016, 1065, 1111, 1161, 1322, 1415, 1615, 2851, 2933, 3230 cm$^{-1}$; $m/z$ (ESI) 246 [(MH)$^+$, 54%]; HRMS (ESI) calcd. for C$_{12}$H$_{13}$F$_3$NO [(MH)$^+$] 246.1106, found 246.1106 (Δ 0.0 ppm).

(4E)-N-Hydroxy-7-phenylhept-4-en-1-amine (176g)

Using general method B oxime 180g (80 mg, 0.39 mmol), NaCNBH$_3$ (50 mg, 0.79 mmol) in MeOH (15 mL) after the addition of MeOH/HCl (10:1) (0.45 mL over 10 min) then (0.05 mL over 10 min) gave hydroxylamine 176g as a yellow oil (75.5 mg, 94%). R$_f$ 0.43 (Et$_2$O/hexane, 9:1); $^1$H NMR (400 MHz, CDCl$_3$): δ 1.65 (2H, app q, J = 7.3, C$_2$H$_2$), 2.10 (2H, m, C$_3$H$_2$), 2.38 (2H, m, C$_6$H$_2$), 2.73 (2H, app t, J = 7.8, C$_7$H$_2$), 2.95 (2H, t, J = 7.3, C$_1$H$_2$), 5.50 (2H, m, C$_4$H and C$_5$H), 7.24 (3H, app t, J = 7.2, 3 × ArH), 7.32 (2H, m, 2 × ArH), NH and OH (absent); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 26.63 (t), 30.07 (t), 34.43 (t), 36.06 (t), 53.21 (t), 125.77 (d), 128.29 (2 × d), 128.51 (2 × d), 130.14 (d), 130.21 (d), 142.06 (s); IR $\nu_{\text{max}}$ (neat): 697, 745, 967, 1030, 1453, 1495, 2850, 2918, 3026, 3251 cm$^{-1}$; $m/z$ (ESI) 206 [(MH)$^+$, 42%], 204 [(MH)$^+$ - H$_2$, 48%]; HRMS (ESI) calcd. for C$_{13}$H$_{20}$NO [(MH)$^+$] 206.1545, found 206.1549 (Δ 1.9 ppm), calcd. for C$_{13}$H$_{18}$NO [(MH)$^+$ - H$_2$] 204.1388, found 204.1388 (Δ 0.0 ppm).

(+)-2-Benzylpyrrolidin-1-ol (184a)

General Method C: Hydroxylamine 176a (10.85 mg, 0.06 mmol) in MeOH (4.3 mL) or CHCl$_3$ (4.3 mL) or toluene (4.3 mL) was degassed (3 × freeze/thaw) and then stirred at RT for 3 h before being heated to 40 °C for 2.5 h and then 60 °C for 16 h. After this time reactions were combined and the solvent removed in vacuo. The crude residue was purified by FC (SiO$_2$, hexane/Et$_2$O, 2:1) to give pyrrolidine 184a as an off white solid. m.p. 51-52 °C, [Lit., 67-68 °C, (hexane/ether)]; R$_f$ 0.26 (Et$_2$O/hexane, 2:1); $^1$H NMR (400 MHz, CDCl$_3$): δ 1.50 (1H, m, C$_3$HH), 1.73-1.87 (3H, C$_4$H$_2$ and C$_5$HH), 2.61 (1H, dd, J = 12.7, 9.7, PhCHH), 2.83 (1H, dd, J = 18.7, 9.7, C$_3$HH), 3.02 (1H, m, C$_3$H), 3.19 (1H, dd, J = 12.7, 4.9,
PhCHH), 3.34 (1H, app p, J = 5.3, C₅HH), 7.20-7.32 (5H, 5 × C₆H), OH (absent); ¹³C NMR (100 MHz, CDCl₃): δ 19.57 (t), 27.10 (t), 39.65 (t), 57.67 (t), 69.95 (d), 126.11 (d), 128.38 (2 × d), 129.07 (2 × d), 139.65 (s); IR vₘₐₓ (neat): 698, 745, 1029, 1365, 1453, 1495, 1603, 2856, 2925, 3216 cm⁻¹; m/z (ESI) 178 [(MH)⁺, 100%]; HRMS (ESI) calcd. for C₁₁H₁₆NO [(MH)⁺] 178.1232, found 178.1230 (Δ -1.1 ppm).

(±)-2-(4-Methylbenzyl)pyrrolidin-1-ol (184b)

Using general method C hydroxylamine 176b (11.9 mg, 0.062 mmol) in MeOH (4.3 mL) or CHCl₃ (4.3 mL) or toluene (4.3 mL) after 16 h at 60 °C gave pyrrolidine 184b as an off white solid. m.p. 50-57 °C; Rₛ 0.38 (Et₂O/hexane, 2:1); ¹H NMR (400 MHz, CDCl₃): δ 1.45 (1H, m, C₅HH), 1.75-1.89 (3H, C₄H₂ and C₅HH), 2.35 (3H, s, CH₃), 2.59 (1H, m, MePhCHH), 2.85 (1H, app q, J = 9.3, C₅HH), 3.03 (1H, m, C₂H), 3.17 (1H, dd, J = 13.2, 3.7, MePhCHH), 3.35 (1H, app p, J = 5.3, C₅HH), 7.13 (4H, app s, 4 × C₆H), OH (absent); ¹³C NMR (125 MHz, CDCl₃): δ 19.63 (t), 21.01 (q), 27.10 (t), 39.19 (t), 57.62 (t), 70.04 (d), 128.94 (2 × d), 129.06 (2 × d), 135.57 (s), 136.41 (s); IR vₘₐₓ (neat): 802, 1209, 1364, 1447, 1515, 1607, 2856, 2923, 3220 cm⁻¹; m/z (ESI) 192 [(MH)⁺, 100%]; HRMS (ESI) calcd. for C₁₂H₁₈NO [(MH)⁺] 192.1388, found 192.1384 (Δ -2.1 ppm).

(±)-2-(4-Methoxybenzyl)pyrrolidin-1-ol (184c)

Using general method C hydroxylamine 176c (10 mg, 0.048 mmol) toluene (3.4 mL) or toluene and MeOH (3.4 mL, 10 µL) after 8 h at 60 °C gave pyrrolidine 184c as an off white solid. m.p. 64-69 °C; Rₛ 0.19 (Et₂O/hexane, 2:1); ¹H NMR (400 MHz, CDCl₃): δ 1.43 (1H, m, C₅HH), 1.67-1.82 (3H, C₄H₂ and C₅HH), 2.52 (1H, m, O-MePhCHH), 2.79 (1H, app q, J = 9.2, C₅HH), 2.94 (1H, m, C₂H), 3.11 (1H, dd, J = 13.2, 4.8, O-MePhCHH), 3.30 (1H, app p, J = 5.3, C₅HH), 3.77 (3H, s, CH₃), 6.80 (2H, d, J = 8.6, 2 × C₆H), 7.11 (2H, d, J = 8.6, 2 × C₆H), OH (absent); ¹³C NMR (125 MHz, CDCl₃): δ 19.54 (t), 27.06 (t), 38.81 (t), 55.23 (q), 57.66 (t), 70.09 (d), 113.79 (2 × d), 129.93 (2 × d), 131.66 (s), 157.97 (s); IR vₘₐₓ (neat): 816,
Chapter 4

Experimental

HRMS (ESI) calcd. for C_{12}H_{18}NO_2 [(MH)^+] 208.1338, found 208.1325 (Δ -6.2 ppm).

(±)-2-[4-(Trifluoromethyl)benzyl]pyrrolidin-1-ol (184d)

Using general method C hydroxylamine 176d (13 mg, 0.053 mmol) in MeOH (3.8 mL) or CHCl_3 (3.8 mL) or toluene (3.8 mL) after 1 h at 60 °C gave pyrrolidine 184d as an off white solid. m.p. 67-70 °C; R_f 0.33 (Et_2O/hexane, 2:1); ^1H NMR (400 MHz, CDCl_3): δ 1.43 (1H, m, C_3H), 1.76-1.87 (3H, C_4H_2 and C_3H), 2.63 (1H, m, CF_3PhCH/H), 2.86 (1H, dd, J = 18.5, 9.5, C_3H), 2.99 (1H, m, C_2H), 3.26 (1H, dd, J = 13.2, 4.9, CF_3PhCH/H), 3.35 (1H, m, C_3H), 7.35 (2H, d, J = 8.1, 2 × C_1H), 7.57 (2H, d, J = 8.1, 2 × C_1H), OH (absent); ^13C NMR (125 MHz, CDCl_3): δ 19.66 (t), 27.01 (t), 39.40 (d), 57.66 (t), 69.51 (t), 121.05 (s) and 123.21 (s) and 125.37 (s) and 127.53 (s), 125.22 (2 × d) and 125.25 (2 × d) and 125.28 (2 × d) and 125.31 (2 × d), 128.12 (s) and 128.38 (s) and 128.64 (s) and 128.90 (s), 129.32 (2 × d), 143.70 (s); IR v_{max} (neat): 755, 818, 854, 1018, 1065, 1111, 1161, 1322, 1418, 1618, 2862, 2975, 3201 cm^{-1}; m/z (ESI) 246 [(MH)^+, 75%]; HRMS (ESI) calcd. for C_{12}H_{18}F_3NO [(MH)^+] 246.1106, found 246.1104 (Δ 0.4 ppm).
Appendices

Appendix 1

Loading Level (LL) Calculation.

- Start with 25 g of aminomethylated resin of which the LL = 0.9 \text{ mmolg}^{-1}, therefore, the mmol of the resin = 22.5 mmol

- Assume all available resin reacts with the isothiocyanate and so 1.8 g has been added to the overall mass.

- The total mass is now: 25 g + 1.8 g = 26.8 g and the mmol of the resin remains the same at 22.5 mmol. Therefore the LL = \text{ mmol/g} = \frac{22.5}{26.8} = 0.84 \text{ mmolg}^{-1}.
Appendix 2

Single Crystal X-Ray Structure Determinations

Clivonine·HCl (1)

Crystal data and structure refinement for compound 1

Identification code AS0906

Empirical formula (C17 H20 N O5)(Cl) . CHCl3

Formula weight 473.16

Temperature 173(2) K

Diffractometer, wavelength OD Xcalibur 3, 0.71073 Å

Crystal system, space group Monoclinic, P2(1)/n

Unit cell dimensions

\[
\begin{align*}
\text{a} &= 8.4338(2) \, \text{Å} & \alpha &= 90^\circ \\
\text{b} &= 22.7228(6) \, \text{Å} & \beta &= 97.729(2)^\circ \\
\text{c} &= 10.7268(3) \, \text{Å} & \gamma &= 90^\circ 
\end{align*}
\]

Volume, Z 2037.00(9) Å³, 4

Density (calculated) 1.543 Mg/m³

Absorption coefficient 0.612 mm⁻¹
<table>
<thead>
<tr>
<th>F(000)</th>
<th>976</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal colour / morphology</td>
<td>Colourless tablets</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.44 x 0.20 x 0.07 mm$^3$</td>
</tr>
<tr>
<td>$\theta$ range for data collection</td>
<td>2.89 to 32.18$^\circ$</td>
</tr>
<tr>
<td>Index ranges</td>
<td>$-12\leq h \leq 12$, $-33\leq k \leq 32$, $-15\leq l \leq 15$</td>
</tr>
<tr>
<td>Reflns collected / unique</td>
<td>18968 / 6530 [R(int) = 0.0232]</td>
</tr>
<tr>
<td>Reflns observed [F&gt;4\sigma(F)]</td>
<td>4519</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Analytical</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.957 and 0.831</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F$^2$</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>6530 / 33 / 294</td>
</tr>
<tr>
<td>Goodness-of-fit on F$^2$</td>
<td>1.008</td>
</tr>
<tr>
<td>Final R indices [F&gt;4\sigma(F)]</td>
<td>R1 = 0.0467, wR2 = 0.1111</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0781, wR2 = 0.1206</td>
</tr>
<tr>
<td>Largest diff. peak, hole</td>
<td>0.419, -0.186 eÅ$^{-3}$</td>
</tr>
<tr>
<td>Mean and maximum shift/error</td>
<td>0.000 and 0.001</td>
</tr>
</tbody>
</table>

Bond lengths [Å] and angles [°] for compound 1

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
<th>Angle [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(2)</td>
<td>1.350(2)</td>
<td>C(4)-C(5)</td>
</tr>
<tr>
<td>O(1)-C(20)</td>
<td>1.4534(19)</td>
<td>C(5)-O(6)</td>
</tr>
<tr>
<td>C(2)-O(2)</td>
<td>1.205(2)</td>
<td>C(5)-C(9)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.482(2)</td>
<td>O(6)-C(7)</td>
</tr>
<tr>
<td>C(3)-C(11)</td>
<td>1.394(2)</td>
<td>C(7)-O(8)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.408(2)</td>
<td>O(8)-C(9)</td>
</tr>
<tr>
<td>Bond</td>
<td>Distance (Å)</td>
<td>Bond</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.375(2)</td>
<td>C(5)-C(4)-C(3)</td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.410(2)</td>
<td>C(4)-C(5)-O(6)</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.5195(19)</td>
<td>C(4)-C(5)-C(9)</td>
</tr>
<tr>
<td>C(12)-C(20)</td>
<td>1.5193(19)</td>
<td>O(6)-C(5)-C(9)</td>
</tr>
<tr>
<td>C(12)-C(13)</td>
<td>1.538(2)</td>
<td>C(5)-O(6)-C(7)</td>
</tr>
<tr>
<td>C(13)-N(14)</td>
<td>1.5123(19)</td>
<td>O(6)-C(7)-O(8)</td>
</tr>
<tr>
<td>C(13)-C(17)</td>
<td>1.558(2)</td>
<td>C(9)-O(8)-C(7)</td>
</tr>
<tr>
<td>N(14)-C(21)</td>
<td>1.490(2)</td>
<td>O(8)-C(9)-C(10)</td>
</tr>
<tr>
<td>N(14)-C(15)</td>
<td>1.501(2)</td>
<td>O(8)-C(9)-C(5)</td>
</tr>
<tr>
<td>C(15)-C(16)</td>
<td>1.518(3)</td>
<td>C(10)-C(9)-C(5)</td>
</tr>
<tr>
<td>C(16)-C(17)</td>
<td>1.540(3)</td>
<td>C(9)-C(10)-C(11)</td>
</tr>
<tr>
<td>C(17)-C(18)</td>
<td>1.533(2)</td>
<td>C(3)-C(11)-C(10)</td>
</tr>
<tr>
<td>C(18)-C(19)</td>
<td>1.513(3)</td>
<td>C(3)-C(11)-C(12)</td>
</tr>
<tr>
<td>C(19)-O(22)</td>
<td>1.422(2)</td>
<td>C(10)-C(11)-C(12)</td>
</tr>
<tr>
<td>C(19)-C(20)</td>
<td>1.515(2)</td>
<td>C(20)-C(12)-C(11)</td>
</tr>
<tr>
<td>C(30)-Cl(3)</td>
<td>1.734(9)</td>
<td>C(20)-C(12)-C(13)</td>
</tr>
<tr>
<td>C(30)-Cl(2)</td>
<td>1.746(9)</td>
<td>C(11)-C(12)-C(13)</td>
</tr>
<tr>
<td>C(30)-Cl(4)</td>
<td>1.748(9)</td>
<td>N(14)-C(13)-C(12)</td>
</tr>
<tr>
<td>C(30')-Cl(2')</td>
<td>1.746(10)</td>
<td>N(14)-C(13)-C(17)</td>
</tr>
<tr>
<td>C(30')-Cl(3')</td>
<td>1.750(10)</td>
<td>C(12)-C(13)-C(17)</td>
</tr>
<tr>
<td>C(30')-Cl(4')</td>
<td>1.771(10)</td>
<td>C(21)-N(14)-C(15)</td>
</tr>
<tr>
<td>C(2)-O(1)-C(20)</td>
<td>119.75(12)</td>
<td>C(21)-N(14)-C(13)</td>
</tr>
<tr>
<td>O(2)-C(2)-O(1)</td>
<td>118.07(15)</td>
<td>C(15)-N(14)-C(13)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(3)</td>
<td>124.78(15)</td>
<td>N(14)-C(15)-C(16)</td>
</tr>
<tr>
<td>O(1)-C(2)-C(3)</td>
<td>117.14(14)</td>
<td>C(15)-C(16)-C(17)</td>
</tr>
<tr>
<td>C(11)-C(3)-C(4)</td>
<td>122.97(14)</td>
<td>C(18)-C(17)-C(16)</td>
</tr>
<tr>
<td>C(11)-C(3)-C(2)</td>
<td>120.98(14)</td>
<td>C(18)-C(17)-C(13)</td>
</tr>
<tr>
<td>C(4)-C(3)-C(2)</td>
<td>116.05(14)</td>
<td>C(16)-C(17)-C(13)</td>
</tr>
<tr>
<td>Bond</td>
<td>Angle (°)</td>
<td>Bond</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>C(19)-C(18)-C(17)</td>
<td>113.41(13)</td>
<td>Cl(3)-C(30)-Cl(2)</td>
</tr>
<tr>
<td>O(22)-C(19)-C(18)</td>
<td>113.30(15)</td>
<td>Cl(3)-C(30)-Cl(4)</td>
</tr>
<tr>
<td>O(22)-C(19)-C(20)</td>
<td>107.77(12)</td>
<td>Cl(2)-C(30)-Cl(4)</td>
</tr>
<tr>
<td>C(18)-C(19)-C(20)</td>
<td>107.24(14)</td>
<td>Cl(2')-C(30')-Cl(3')</td>
</tr>
<tr>
<td>O(1)-C(20)-C(19)</td>
<td>107.00(12)</td>
<td>Cl(2')-C(30')-Cl(4')</td>
</tr>
<tr>
<td>O(1)-C(20)-C(12)</td>
<td>110.43(12)</td>
<td>Cl(3')-C(30')-Cl(4')</td>
</tr>
<tr>
<td>C(19)-C(20)-C(12)</td>
<td>112.83(13)</td>
<td></td>
</tr>
</tbody>
</table>

(3S,6S)-3,6-Dibromocyclohexene (164)

[Diagram of the molecule]

Crystal data and structure refinement for compound 164

Identification code | AS0909
Empirical formula  | C₆H₈Br₂
Formula weight     | 239.94
Temperature        | 173(2) K
Diffractometer, wavelength | OD Xcalibur 3, 0.71073 Å
Crystal system, space group | Monoclinic, P2(1)/n
Unit cell dimensions | a = 6.9532(3) Å, α = 90°
                      | b = 5.63370(18) Å, β = 109.729(6)°
                      | c = 10.1488(5) Å, γ = 90°
Volume, Z            | 374.22(3) Å³, 2
Density (calculated) 2.129 Mg/m³
Absorption coefficient 10.729 mm⁻¹
F(000) 228
Crystal colour / morphology Colourless blocky needles
Crystal size 0.42 x 0.21 x 0.10 mm³
θ range for data collection 4.20 to 32.74°
Index ranges -5<=h<=10, -8<=k<=7, -15<=l<=15
Reflns collected / unique 3823 / 1268 [R(int) = 0.0247]
Reflns observed [F>4σ(F)] 851
Absorption correction Analytical
Max. and min. transmission 0.404 and 0.094
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 1268 / 0 / 55
Goodness-of-fit on F² 0.825
Final R indices [F>4σ(F)]
R1 = 0.0220, wR2 = 0.0406
R indices (all data) R1 = 0.0433, wR2 = 0.0424
Largest diff. peak, hole 0.612, -0.563 eÅ⁻³
Mean and maximum shift/error 0.001 and 0.002

Bond lengths [Å] and angles [°] for compound 164

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br(1)-C(1)</td>
<td>1.9928(18)</td>
<td>C(1)-C(2')</td>
<td>1.612(10)</td>
</tr>
<tr>
<td>C(1)-C(3)#1</td>
<td>1.366(10)</td>
<td>C(2)-C(3)</td>
<td>1.528(13)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.391(10)</td>
<td>C(3)-C(1)#1</td>
<td>1.366(10)</td>
</tr>
<tr>
<td>C(1)-C(3')#1</td>
<td>1.601(9)</td>
<td>C(2')-C(3')</td>
<td>1.295(16)</td>
</tr>
</tbody>
</table>
Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+1

\((3aS,4S,7R,7aR)-4,7\)-Dibromo-2,2-dimethylhexahydro-1,3-benzodioxole (135)

Crystal data and structure refinement for compound 135

Identification code: AS1001

Empirical formula: C9 H14 Br2 O2

Formula weight: 314.02

Temperature: 296(2) K

Diffractometer, wavelength: OD Xcalibur 3, 0.71073 Å

Crystal system, space group: Triclinic, P-1

Unit cell dimensions:

\[ a = 7.0842(10) \text{ Å} \quad \alpha = 95.640(8)^\circ \]
b = 9.0032(13) Å  \quad \beta = 97.798(9)^\circ

c = 9.5389(6) Å  \quad \beta = 110.869(13)^\circ

Volume, Z  
556.12(13) Å^3, 2

Density (calculated)  
1.875 Mg/m^3

Absorption coefficient  
7.256 mm^{-1}

F(000)  
308

Crystal colour / morphology  
Colourless blocks

Crystal size  
0.53 x 0.40 x 0.28 mm^3

\theta range for data collection  
3.01 to 32.83^\circ

Index ranges  
-10<=h<=10, -13<=k<=13, -11<=l<=14

Reflns collected / unique  
6459 / 3660 [R(int) = 0.0261]

Reflns observed [F>4\sigma(F)]  
1964

Absorption correction  
Analytical

Max. and min. transmission  
0.232 and 0.118

Refinement method  
Full-matrix least-squares on F^2

Data / restraints / parameters  
3660 / 0 / 119

Goodness-of-fit on F^2  
0.839

Final R indices [F>4\sigma(F)]  
R1 = 0.0315, wR2 = 0.0602

R indices (all data)  
R1 = 0.0727, wR2 = 0.0635

Extinction coefficient  
0.207(3)

Largest diff. peak, hole  
0.615, -0.597 eÅ^{-3}

Mean and maximum shift/error  
0.000 and 0.001
### Bond lengths [Å] and angles [°] for compound 135

<table>
<thead>
<tr>
<th>Bond Lengths</th>
<th>Angles</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(9) 1.429(2)</td>
<td>O(3)-C(2)-C(10) 110.7(2)</td>
</tr>
<tr>
<td>O(1)-C(2) 1.444(3)</td>
<td>O(1)-C(2)-C(10) 108.7(2)</td>
</tr>
<tr>
<td>C(2)-O(3) 1.431(3)</td>
<td>C(11)-C(2)-C(10) 113.0(2)</td>
</tr>
<tr>
<td>C(2)-C(11) 1.506(4)</td>
<td>C(4)-O(3)-C(2) 105.34(17)</td>
</tr>
<tr>
<td>C(2)-C(10) 1.514(3)</td>
<td>O(3)-C(4)-C(5) 108.71(18)</td>
</tr>
<tr>
<td>O(3)-C(4) 1.425(3)</td>
<td>O(3)-C(4)-C(9) 101.26(17)</td>
</tr>
<tr>
<td>C(4)-C(5) 1.517(3)</td>
<td>C(5)-C(4)-C(9) 116.66(18)</td>
</tr>
<tr>
<td>C(4)-C(9) 1.521(3)</td>
<td>C(6)-C(5)-C(4) 113.83(19)</td>
</tr>
<tr>
<td>C(5)-C(6) 1.505(3)</td>
<td>C(6)-C(5)-Br(5) 110.67(17)</td>
</tr>
<tr>
<td>C(5)-Br(5) 1.969(2)</td>
<td>C(4)-C(5)-Br(5) 106.86(16)</td>
</tr>
<tr>
<td>C(6)-C(7) 1.515(4)</td>
<td>C(5)-C(6)-C(7) 111.7(2)</td>
</tr>
<tr>
<td>C(7)-C(8) 1.513(3)</td>
<td>C(8)-C(7)-C(6) 108.7(2)</td>
</tr>
<tr>
<td>C(8)-C(9) 1.512(3)</td>
<td>C(9)-C(8)-C(7) 113.40(19)</td>
</tr>
<tr>
<td>C(8)-Br(8) 1.964(2)</td>
<td>C(9)-C(8)-Br(8) 109.48(15)</td>
</tr>
<tr>
<td>C(9)-O(1)-C(2) 108.65(15)</td>
<td>C(7)-C(8)-Br(8) 110.16(16)</td>
</tr>
<tr>
<td>O(3)-C(2)-O(1) 105.28(16)</td>
<td>O(1)-C(9)-C(8) 111.69(18)</td>
</tr>
<tr>
<td>O(3)-C(2)-C(11) 108.8(2)</td>
<td>O(1)-C(9)-C(4) 101.09(16)</td>
</tr>
<tr>
<td>O(1)-C(2)-C(11) 110.04(19)</td>
<td>C(8)-C(9)-C(4) 112.14(18)</td>
</tr>
</tbody>
</table>
References


(3) Bastida, J.; Lavilla, R.; Viladomat, F. The Alkaloids 2006, 63, 87-179, and previous reviews in this series.


(8) Mehlis, B. Naturwissenschaften 1965, 52, 33-34.


