Synthetic approach to the novel cholecystokinin (CCK)-B receptor antagonist tetronothiodin

This item was submitted to Loughborough University's Institutional Repository by the/an author.

Additional Information:


Metadata Record: [https://dspace.lboro.ac.uk/2134/34061](https://dspace.lboro.ac.uk/2134/34061)

Publisher: © Kevin John Batchelor

Rights: This work is made available according to the conditions of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) licence. Full details of this licence are available at: [https://creativecommons.org/licenses/by-nc-nd/4.0/](https://creativecommons.org/licenses/by-nc-nd/4.0/)

Please cite the published version.
Please note that fines are charged on ALL overdue items.
Synthetic Approach to the Novel Cholecystokinin (CCK)-B receptor Antagonist Tetronothiodin

By

Kevin John Batchelor

(A Doctoral Thesis Submitted in partial fulfilment for the award of Doctor of Philosophy of Loughborough University)
Acknowledgements

This thesis is dedicated to my parents for whom none of this would have been possible without their continuous support and encouragement over the years.

I would like to thank all the staff, friends and family who have given their help and support over the course of my Ph.D.
Abstract

The thesis consists first of an introduction discussing CCK-receptor antagonists and the role tetronothiodin plays. There is a section on the isolation and characterisation of the tetronothiodin structure. This leads to a retrosynthesis of the compound and the synthetic plan towards forming the oxaspirobicyclic moiety. The introduction includes the initial ideas for the construction of this subunit, with analogous subunits in the literature being discussed. A brief review of the likely chemistry is discussed.

The second chapter is the results and discussion section, beginning with the formation of the Diels-Alder precursors and the chemistry used to form a suitably functionalised cyclohexene rings with the aim of forming the cyclohexenone. The first successful reaction involves the repetition of previous research of the Diels-Alder reaction involving the hydroxy diene 9 and nitroethylene 13 as the dienophile. This resulted in the formation of the cyclohexene 14 with the probable stereochemistry shown. The formation of the cyclohexene was followed by attempts to achieve a Nef reaction to convert the nitro group to a ketone functionality.

This work resulted in the study of other dienophiles, including the use of phenyl vinyl sulfone which gave the Diels-Alder product 121 with its stereoisomer in a 3:1 ratio as shown. Attempted oxidative desulfonylation of the sulfone group to form the keto group was unsuccessful.
Another successful intermolecular Diels-Alder reaction involved the use of 2-chloroacrylonitrile to give 130 and its stereoisomer in a 2:1 ratio. A number of reactions were investigated with the Diels-Alder adduct in an attempt to access the keto group or the spiro tetronic acid, but without success.

The failure to form the cyclohexenone led to the use of other dienophiles and other methodology including the use of an intramolecular Diels-Alder reaction with a silicon tether. This gave the desired cycloadduct in high yields. The subsequent oxidations and protections provide the target cyclohexenone and allow further chemistry towards formation of the tetronic unit.
The final chapter is the experimental section with details of the procedures used and the relevant spectroscopic data for the compounds synthesized.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic</td>
</tr>
<tr>
<td>b.p.</td>
<td>boiling point</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-butyl</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>CCK</td>
<td>cholecystokinin</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionisation</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N'-dimethylpropyleneurea</td>
</tr>
<tr>
<td>DMS</td>
<td>dimethyl sulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>E+</td>
<td>electrophile</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>IMDA</td>
<td>intramolecular Diels-Alder</td>
</tr>
<tr>
<td>IR</td>
<td>infra red</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chlorobenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>ml</td>
<td>millilitres</td>
</tr>
<tr>
<td>mmol</td>
<td>millimoles</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrum</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>p-TSA</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>t-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>OTf</td>
<td>triflate</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetra-n-propylammonium perruthenate</td>
</tr>
<tr>
<td>UV</td>
<td>ultra violet</td>
</tr>
</tbody>
</table>
## Contents

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter One</td>
<td>1</td>
</tr>
<tr>
<td>1.0 Introduction</td>
<td>2</td>
</tr>
<tr>
<td>1.1 Tetronothiodin background</td>
<td>2</td>
</tr>
<tr>
<td>1.1.1 Cholecystokinin and its role</td>
<td>2</td>
</tr>
<tr>
<td>1.1.2 Biological activity of tetronothiodin</td>
<td>4</td>
</tr>
<tr>
<td>1.1.3 Structural elucidation</td>
<td>5</td>
</tr>
<tr>
<td>1.1.4 Stereochemistry</td>
<td>9</td>
</tr>
<tr>
<td>1.1.5 Summary</td>
<td>11</td>
</tr>
<tr>
<td>1.2 Different routes towards the synthesis of tetronothiodin</td>
<td>13</td>
</tr>
<tr>
<td>1.2.1 Retrosynthesis</td>
<td>13</td>
</tr>
<tr>
<td>1.2.2 Synthetic routes towards tetronothiodin</td>
<td>15</td>
</tr>
<tr>
<td>1.3 Spirocycles in other analogous natural products</td>
<td>26</td>
</tr>
<tr>
<td>1.3.1 Introduction</td>
<td>26</td>
</tr>
<tr>
<td>1.3.2 Oxaspirobicyclic moiety synthesis in kijanolide</td>
<td>26</td>
</tr>
<tr>
<td>1.3.3 Total synthesis of chlorothricolide</td>
<td>31</td>
</tr>
<tr>
<td>1.4 The Wittig and related reactions</td>
<td>34</td>
</tr>
<tr>
<td>1.4.1 Introduction</td>
<td>34</td>
</tr>
<tr>
<td>1.4.2 Stereochemistry in Wittig reactions</td>
<td>35</td>
</tr>
<tr>
<td>1.4.3 The Wittig reaction in synthetic applications</td>
<td>37</td>
</tr>
<tr>
<td>1.5 Analogous Wittig type reactions</td>
<td>39</td>
</tr>
<tr>
<td>1.5.1 The Horner-Wadsworth-Emmons reaction</td>
<td>39</td>
</tr>
<tr>
<td>1.5.2 The Peterson reaction</td>
<td>41</td>
</tr>
<tr>
<td>1.6 The Diels-Alder reaction</td>
<td>42</td>
</tr>
<tr>
<td>1.6.1 Introduction</td>
<td>42</td>
</tr>
</tbody>
</table>
2.4.3 Analysis of 1,6-dimethyl-3-(2-hydroxyethyl)-4-benzenesulfonyl-cyclohexene 121 and 122 and 1,6-dimethyl-3-(2-benzyloxyethyl)-4-benzenesulfonyl-cyclohexene 123

2.4.4 Oxidative desulfonylation of the cycloadduct using MoOPH 83

2.4.5 Addition of disulfides to the cycloadducts 84

2.4.6 Conclusion 87

2.5 Diels-Alder approach with 2-chloro-acrylonitrile 88

2.5.1 Introduction 88

2.5.2 Diels-Alder reactions 89

2.5.3 Analysis of 1,6-dimethyl-3-(2-benzyloxyethyl)-4-chloro-cyclohexene-4-carbonitrile 131

2.5.4 Hydrolysis of 1,6-dimethyl-3-(2-benzyloxy-ethyl)-4-chloro-cyclohexene-4-carbonitrile 131 92

2.5.5 Addition of dimethyl malonate to of 1,6-dimethyl-3-(2-benzyloxy-ethyl)-4-chloro-cyclohexene-4-carbonitrile 131 93

2.5.6 Conclusion 97

2.6 Diels-Alder reactions with other dienophiles 98

2.6.1 Introduction 98

2.6.2 Ethyl acrylate 98

2.6.3 Methyl α-acetoxyacrylate 102

2.6.4 2-Benzencesulfonyl-acrylic acid methyl ester 103

2.6.5 Acrylonitrile 105

2.7 Inverse-Electron-Demand Diels-Alder Reaction 106

2.7.1 Introduction 106

2.7.2 Synthesis of (E,E)-methyl-4-methyl-2,4-hexadienoate 155 107

2.7.3 Synthesis of 2-tert-butyl-5-methylene-1,3-dioxolan-4-one 163 108

2.7.4 Diels-Alder reaction 109

2.8 Intramolecular Diels-Alder reaction 111

2.8.1 Introduction 111
2.8.2 Synthesis of 5-methyl-hepta-3,5-dienyl propynoate 26 and IMDA reaction

2.9 Intramolecular Diels-Alder approach using silicon tethers

2.9.1 Introduction

2.9.2 Addition of silicon tethers and cyclisation

2.9.3 Tether cleavage by hydrogen peroxide oxidation

2.9.4 Analysis of 1,6-dimethyl-3-(2-hydroxyethyl)-cyclohexen-4-ol

34

2.10 Protection of the primary hydroxy group in 1,6-dimethyl-3-(2-hydroxyethyl)-cyclohexen-4-ol 34

2.10.1 Introduction

2.10.2 Protection of primary hydroxy group using pivaloyl chloride

2.10.3 Protection of primary hydroxy group using benzyl bromide

2.10.5 Protection of primary hydroxy group through O-silylation

2.10.5 Analysis of 1,6-dimethyl-3-(2-(tert-butyl-diphenyl-silanoxy)-ethyl) cyclohexen-4-ol

2.10.6 Conclusion

2.11 Oxidation of the secondary hydroxy group

2.11.1 Introduction

2.11.2 Pyridinium chlorochromate and dichromate

2.11.3 Swern oxidation

2.11.4 Dess-Martin periodinane

2.11.5 Tetra-n-propylammonium perruthenate (TPAP)

2.11.6 Analysis of 2-(2-(benzyloxy)-ethyl)-4,5-dimethyl-cyclohex-3-enone 192

2.11.7 Conclusion

2.12 Reactions of 2-[2-(tert-butyl-diphenyl-silanoxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone 194 and 2-(2-benzyloxyethyl)-4,5-dimethyl-cyclohex-3-enone 192 with trimethylcyanide (TMSCN)

2.12.1 Introduction
2.12.2 Treatment of cyclohexenone derivatives with TMSCN 140

2.12.3 Analysis of 1,6-dimethyl-3-(2-benzyloxyethyl)-4-trimethyl-silyloxy-cyclohexene-4-carbonitrile 207

2.12.4 Treatment of a cyclohexenone derivative using TMSCN and a Lewis acid catalyst 143

2.12.5 Conclusion 144

2.13 Reactions of 2-[2-(tert-butyl-diphenyl-silanoxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone 194 and 2-(2-benzyloxy-ethyl)-4,5-dimethyl-cyclohex-3-enone 192 with Wittig-like reagents 145

2.13.1 Introduction 145

2.13.2 Treatment of cyclohexenone derivatives with lithiated diphenyl-(methoxymethyl)-phosphide oxide 147

2.13.3 Wadsworth-Emmons approach 148

2.14 Reactions of 2-[2-(tert-butyl-diphenyl-silanoxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone 194 and 2-(2-benzyloxyethyl)-4,5-dimethyl-cyclohex-3-enone 192 with organometallic propynoate reagents 150

2.14.1 Introduction 150

2.14.2 Treatment of cyclohexenone derivatives with cerium methyl propynoate species 151

2.14.3 Treatment of cyclohexenone derivatives with lithiated methyl propynoate species 152

2.14.4 Conclusion 153

2.15 Final Conclusion 154

2.16 Future Work 156

Chapter Three

3.0 Experimental 157

3.1 General experimental 158

3.1.1 Preparation of glassware 158
3.1.2 Purification of chemicals
3.1.3 Purification methods
3.1.4 Spectroscopy
3.1.5 Other Data

3.2 Preparation of standard reagents
3.2.1 Purified meta-chloroperoxybenzoic acid (m-CPBA)
3.2.2 Oxodiperoxymolybdenum (pyridine)-1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (MoO₅.Py.DMPU)

3.3 Preparation of compounds

4.0 References
Chapter One
1.0 Introduction

1.1 Tetronothiodin background

1.1.1 Cholecystokinin and its role

Receptors are specific protein molecules, usually located within the cell membranes, which respond to endogenous chemicals or drugs in the body. These endogenous chemicals may be either transmitter substances released from nerve terminals, or hormones.1

Agonists are chemicals or drugs that bind to receptors and activate the receptors into a response. The function of the agonist depends on its affinity for the receptor, thus its ability to bind and form an agonist-receptor complex, and then its efficacy to initiate changes in the receptor to provide a response. Some chemicals can also bind to receptors but fail to activate the receptor’s response. These effectively reduce or block the agonist’s action and known as antagonists. Antagonists can be competitive, in which case they bind to the receptor reversibly or irreversibly, where they have a high affinity for the receptor but zero efficacy. The agonists or antagonists are attracted to the receptors by long range electrostatic forces. The affinity for the chemical on the receptor depends on the closeness of fit and the number of bonds that can be formed. These types of bonds are usually non-covalent hydrogen bonds or van der Waals attractions. Antagonists that are irreversible bind to the receptor normally by strong covalent bonds.1

Cholecystokinin (CCK) is a 33 amino acid peptide that was discovered in 1975.2 CCK has been discovered to interact with particular receptors. These are known as CCK receptors and act as hormonal regulators of pancreatic secretion as well as gall bladder contractions and gut motility.3-6 CCK has also been proposed as a neurotransmitter in the central nervous system (CNS).7,8 There have also been reports into the role CCK may have in schizophrenia.9,10 Studies with radioligands have enabled the identification of two subtypes of CCK receptor, known as CCK-A and CCK-B.11,12
CCK-A (alimentary) subtypes are found in the periphery and discrete regions of the CNS. CCK-A receptors have been found to mediate gall bladder contraction and pancreatic enzyme release, and appear responsible for the satiety actions of peripherally distributed CCK.\(^3\)–\(^6\) CCK-B (brain) receptors are widely distributed in the brain and thought to be associated with anxiety, pain and appetite.\(^13\)–\(^15\)

Sub-species of CCK have also been discovered which have different properties, such as CCK octapeptide (CCK\(_8\)), with a high affinity for both CCK-A and CCK-B receptors. CCK sub species such as CCK tetrapeptide (CCK\(_4\)), non-sulfated CCK\(_8\) (CCK-8NS) and gastrin I have also been identified and found to have higher affinities for CCK-B receptors than for CCK-A receptors.\(^15\),\(^16\)

CCK mediated mechanisms occurring at different sites in the brain can be blocked by non-peptide CCK receptor antagonists crossing the blood-brain barrier. This property relates to the CCK-B receptor antagonists increasing food intake and reducing anxiety. This has been proved further by anxiolytic effects through experiments using standard anxiety tests on rats.\(^9\),\(^10\) Reduction of analgesic effects of the \(\mu\)-opioid morphine and morphine tolerance through action on CCK receptors has given CCK an important role as a physiological modulator.\(^17\)–\(^21\)

The understanding of how the drug affects the receptors is essential for the development of drug treatment. A greater knowledge of CCK-B receptors would involve possible lucrative treatments for obesity, panic attacks and enhancing morphine analgesia. Physiological and pharmacological roles of CCK-B receptors are not yet fully understood due to a shortage of potent and specific CCK-B receptor antagonists. Structurally unique and specific CCK-B receptor antagonists are discovered through a screening process. This process involves microbial metabolites being screened through binding assays. In 1992 a binding assay method involving rat cerebral cortex membranes as receptors and \(^{125}\)I-labelled Bolton Hunter CCK\(_8\) (\([^{125}\text{I}]\)-CCK\(_8\)) as the radioligand found a novel CCK-B receptor antagonist called tetronothiodin 1. The screening process discovered tetronothiodin from a culture broth of \textit{Streptomyces} sp. NR0489.\(^22\)–\(^27\)

Tetronothiodin was isolated through a procedure that first uses fermentation of the strain NR0489. After cultivation for a period of ten days, centrifugation is carried out
to give a broth supernatant, and its pH is adjusted to allow column chromatography. Concentrating under reduced pressure, further re-extraction of aqueous layers and column chromatography give an active organic eluate. Final purification is achieved using reverse-phase preparative HPLC to give 1 as pale brown powder.\textsuperscript{25}

![Chemical Structure]

The structure has been determined by NMR spectroscopy and mass spectrometry and found to consist of an oxaspirobicyclic tetronic acid system, containing a tetronic acid moiety and cyclohexene unit. This is attached to an unsaturated macrocycle containing a functionalised tetrahydrothiopene unit bearing an $\alpha$-ketoacid. The structure contains 8 asymmetric centres, including 3 in the bicyclic unit. The stereochemistry of two of the asymmetric centres remain unassigned.

1.1.2 Biological Activity of tetronothiodin

The inhibitory activities of 1 against the binding of $[^{125}\text{I}]-\text{CCK}_8$ to CCK-A and CCK-B receptors were tested. The test procedure involves incubation of test samples at 23\textdegree C with $[^{125}\text{I}]-\text{CCK}_8$ containing either pancreatic membranes which have the CCK-A receptors or cerebral cortex membranes which contain the CCK-B receptors, both of which are in a buffer and bovine serum albumin solution. The samples reach equilibrium over a period of time, they are filtered and the radioactivity counted.

Tetronothiodin (1) was shown to inhibit the binding of $[^{125}\text{I}]-\text{CCK}_8$ to CCK-B receptors on rat cerebral cortex membranes in a concentration dependent manner. The affinity of 1 to CCK-B receptors was shown to be three to four times greater than...
known potent and selective CCK-B receptor antagonists, and only three times less potent than the natural ligand CCK$_8$. Tetronothiodin did not however inhibit the binding of [\textsuperscript{125}I]-CCK$_8$ to rat pancreatic membranes (CCK-A receptors). The ratio of affinity for CCK-A to CCK-B receptors of 1 was more than 27,000; it is thus a highly selective binding inhibitor for CCK-B receptors, with selectivity much greater than known antagonists.\textsuperscript{22,23,25}

The results were further corroborated by tests on GH3 cells (a rat anterior pituitary cell line) which also contain CCK-B receptors.\textsuperscript{28,29} These tests showed that 1 inhibited CCK$_8$ binding to GH3 cells with the same order of magnitude as that for brain CCK-B receptors. Tests with the same GH3 cells demonstrated that intracellular Ca$^{2+}$ was increased in a concentration-dependent manner and 1 inhibited this increase in the same dependent manner.

There are other known natural CCK-B receptor antagonists such as virginiamycin M$_1$ analogues\textsuperscript{30} and anthramycin,\textsuperscript{31} produced by \textit{Streptomyces} sp, which have different structures compared to tetronothiodin 1. It also differs from the CCK-A type receptor antagonist asperlicin\textsuperscript{32} produced by \textit{Aspergillus alliaceus}, which again is microbial in origin. It differs from the other CCK antagonists\textsuperscript{33} such as cyclic nucleotide dibutyryl cyclic GMP, amino acids proglumide and lorgumide and benzodiazepines such as devazepide. Tetronothiodin can be found to be structurally related to some antibiotics such as kijanimicin\textsuperscript{34}, tetrocarcins\textsuperscript{35} and MM46115\textsuperscript{36} in terms of a macrocyclic molecule containing an $\alpha$-acyltetronic acid. However, tetronothiodin showed no antibiotic activity against \textit{Bacillus subtilis} and \textit{Micrococcus luteus}.

\textbf{1.1.3 Structural elucidation}

The isolation procedure of tetronothiodin 1, which involves extraction with ethyl acetate at pH 2 and back extraction with water at pH 7.5, indicated its acidic nature. Tetronothiodin was found to be soluble in MeOH, THF, DMSO and alkaline water but insoluble in ether, chloroform, hexane and water. The free form of 1 was unstable in solution; it gradually decomposed during NMR experiments over two weeks in DMSO-\textit{d}$_6$ or CD$_3$OD. Its alkaline metal salts were stable for at least five months under the same experimental conditions. IR spectroscopy indicated the presence of a
γ-lactone with a clearly separate band at 1760 cm\(^{-1}\) as well as absorption bands at 3000–2300 and 1728 cm\(^{-1}\) suggesting a carboxylic acid. The UV spectrum in MeOH indicated absorption maxima at 233 and 273 nm which are attributable to an α-acyltetronic acid functionality. The molecular formula of 1 was found to be C\(_{31}\)H\(_{38}\)O\(_8\)S based on positive-ion FAB-MS (m/z 593 (M'Na)\(^+\)) and negative-ion high resolution FAB-MS data (569.2237, calculated for M-H, C\(_{31}\)H\(_{37}\)O\(_8\)S - 569.2210). This molecular formula was further supported by qualitative analysis for sulfur and analyses of the \(^1\)H NMR spectrum and the C\(^{13}\) NMR spectrum, which shows 31 carbon signals.\(^{26}\)

Structural elucidation was mainly carried out based on the NMR data obtained with the potassium salt of 1 in D\(_2\)O because all the carbon signals were observed in this solvent, compared to the use of DMSO-d\(_6\) which hides two carbon signals.

![Figure 1. Partial structures of tetronothiodin revealed by \(^1\)H-\(^1\)H COSY spectral data](image.png)

Interpretation of the \(^1\)H-\(^1\)H COSY spectra shows allylic coupling between 8-H and the methyl protons 28-H connecting the olefinic carbon C-8 and the quaternary carbon C-7. The fragments shown in figure 1 and the remaining quaternary carbons, C-4, C-26, C-30 and C-3 were connected to form the partial structure based on the analysis of the \(^{13}\)C-\(^1\)H long-range couplings (shown by the arrows in figure 2) obtained by HMBC experiments.\(^{22,26}\)
Figure 2. Partial structure of tetronothiodin elucidated by analysis of $^{13}$C-$^1$H long-range couplings.

$E$-stereochemistry was determined in all three double bonds in the macrocycle from the large coupling constants (15 Hz) associated with these olefinic proton signals. A hydroxy proton was located at C-16 through spin-spin coupling experiments with 16-H in DMSO-$d_6$.

Comparisons of the $^{13}$C NMR spectral data with a carolic acid derivative$^{37}$ 2 shown in figure 3 confirmed the presence of $\alpha$-acyltetronic acid$^{34}$ as suggested by UV and IR spectroscopy. The carbon signals assigned at C-2, C-1, C-26 and C-3 all correspond to a tetronic moiety respectively in tetronothiodin. This moiety was deemed to be attached to the cyclohexene ring at C-4 because of the $^{13}$C-$^1$H long-range coupling between 5-Ha and C-3.

Figure 3. $^{13}$C NMR data and a $^{13}$C-$^1$H long-range coupling for $\alpha$-acyltetronic acid moiety of tetronothiodin (1) comparable to data of carolic acid derivative.
$^{13}\text{C}-^1\text{H}$ long range coupling was observed between 23-H and C-24, suggesting the linkage of C-23 and C-24 through a heteroatom or quaternary carbon even though protons 23-H and 24-H were not coupled. This suggested either a sulfur atom or keto function inserted between C-23 and C-24. The cyclopentanone was eliminated as the possible structure through $^{13}\text{C}$ chemical shift and structural analysis of the reduced derivative. It was therefore reasonable to assume a sulfur between the two carbons, forming a tetrahydrothiophene ring. Comparisons with position 5 in dimethyl (2α,3β,4α)-2-(trimethylsilyl)tetrahydrothiophene-3,4-dicarboxylate 3,\textsuperscript{38} shown in figure 4, by chemical shift data further corroborated this structure.

![Figure 4](image)

**Figure 4.** Comparison of chemical shifts in tetronothiodin (1) with that of (2α,3β,4α)-2-(trimethylsilyl)tetrahydrothiophene-3,4-dicarboxylate (3).

Confirmation of the tetrahydrothiophene unit leaves two possible structures A and B for 1 seen in figure 5.

![Figure 5](image)

**Figure 5.** The two possible structures A and B for tetronothiodin (1).

Allocation of the only remaining carboxylic function to either the C-26 or C-30 position was achieved through reduction of 1 by NaBH$_4$ to give the epimeric alcohols 4 a, b seen in figure 6. The newly observed proton signal was assigned to 30-H by $^1\text{H}-^1\text{H}$ COSY experiments and shown to be spin coupled only to 23-H. This established
the structure to be represented by A in figure 5 and the gross structure to be established to be 1, shown in Figure 6.

Figure 6. Structures of tetronothiodin and its dihydro derivatives (4 a, 4 b).

1.1.4 Stereochemistry

The relative stereochemistry for six of the eight stereocentres has been determined through a series of nOe and long-range selective proton experiments (LSPD) carried out on the sodium salt of 1 in DMSO-d$_6$ as shown in figure 7. An nOe between 9-H and 5-Hb indicated the cis relationship between these protons. A small coupling constant ($J/2$ Hz) between 9-H and 8-H was determined by homodecoupling, supporting the pseudoaxial orientation of 9-H. The cis relationship between C-27 and 5-Ha was determined by a strong nOe between 5-Ha and 27-H and a weak nOe between 5-Hb and 27-H. The coupling constants between C-3 and proton signals 5-Hb and 9-H were determined to be less than 4 Hz using a long-range coupling experiment with a double irradiation technique. The coupling constant between an axial proton and axial carbon would be large due to a trans relation, thus these small coupling constants indicated a cis relationship between C-3 and 5-Hb or 9-H.$^{26}$
The cis relationship between 23-H and 25-H was established by the nOe between these protons for the tetrahydrothiophene ring shown in figure 8. Treatment of the free acid of 1 in CD$_3$OD resulted in the complete disappearance of the active hydrogen 25-H. Treatment of this sample with CH$_3$OH recovered tetronothiodin without epimerization at C-25 as revealed by the $^1$H NMR spectrum. This then showed that only one stable configuration exists in solution, and thus the less sterically hindered more thermodynamically stable trans relationship was assigned to the substituents C-22 and C-25, giving the partial structure shown in figure 8.

The stereochemistry for six of the eight stereocentres has thus been determined based on detailed spectroscopic analysis, although not supported by X-ray crystallography. The arrangement of the hydroxy and methyl group at positions C-16 and C-21 respectively, in the macrocyclic ring are unknown, thus tetronothiodin 1 is depicted as seen earlier, with these two stereocentres unassigned.
1.1.5 Summary

The discovery of CCK-B receptors and their role in appetite, pain and anxiety has led to interest in CCK-B antagonists, in particular in fully understanding their physiological and pharmacological roles. The clinical application of CCK-B receptor antagonists could provide increased food intake, anxiolytic activity and enhancement in morphine analgesia, as test studies in rats have shown. A novel CCK-B receptor antagonist tetronothiodin 1 was discovered and isolated from a fermentation broth of Streptomyces sp. NRO489. It was further revealed in numerous test studies to provide a high level of potency and selectivity. It can therefore provide a useful tool in the investigation of the roles in CCK-B receptors and clinical applications mentioned above. 22-26

The structure has been elucidated by detailed spectroscopic analysis and is not supported by X-ray crystallography. The molecular formula was determined to be C_{21}H_{39}O_{8}S based on positive-ion FAB-MS (m/z 593 M^+Na^+) and analysis by $^{13}$C NMR spectroscopy showed 31 signals. The presence of a tetronic acid unit was suggested by the UV and IR spectroscopy. Further structural interpretation was carried out through a number of NMR experiments which indicated a tetrahydrothiophene unit and detailed stereochemistry. At present the relative stereochemistry at six of the eight stereocentres is assigned, but the arrangement of the hydroxyl and methyl groups in the macrocyclic ring is unknown. 26

Synthetically, tetronothiodin has an interesting structure, the heart of which is an oxaspirobicyclic tetronic acid system, containing a tetronic acid moiety and a cyclohexene unit. This is attached to an unsaturated macrocycle containing a functionalised tetrahydrothiophene unit bearing an $\alpha$-ketoacid. The structure differs from already known CCK-B receptor antagonists such as virginiamycin M1 analogues 30 and anthramycin, 31 and CCK-A receptor antagonists such as asperlicin. 32 It is structurally related however to some antibiotics such as kijanimicin 34 in terms of being a macrocyclic molecule containing a tetronic acid moiety, although it has no antibiotic activity.
Tetronothiodin thus provides useful biological properties and is sufficiently structurally interesting to provide a challenge in devising a route towards its synthesis. The most interesting and most challenging part of the structure is the spirotetronic unit acid, and this is an ideal starting point for its synthesis.
1.2 Different routes towards the synthesis of tetronothiodin

1.2.1 Retrosynthesis

Retrosynthetic analysis of tetronothiodin provides a number of possible disconnections in the molecule. The original retrosynthesis in previous our research has provided three distant component molecules to provide the starting point towards the synthesis, as shown in scheme 1. These three components are the oxaspirobicyclic portion 5; the substituted tetrahydrothiophene unit\textsuperscript{38} 6 and the unsaturated haloalcohol 7.

The division of tetronothiodin into the three distinct parts enables the research to begin with the most interesting part of the molecule in from a synthetically challenging viewpoint, the oxaspirobicyclic subunit. The synthesis of this subunit will then be followed by the construction of the other units and then attempts to form tetronothiodin as discussed in the following sections.
Scheme 1. Retrosynthesis of tetronothiodin.

The synthesis of the oxaspirobicyclic unit may start with the synthesis of a suitably substituted cyclohexanone ring 8. Further retrosynthetic analysis provides a substituted diene 9 and a functionalised alkene 10; ideal candidates for a Diels-Alder\textsuperscript{39} approach towards the cyclohexanone ring.
Scheme 2. Retrosynthetic analysis of the cyclohexanone ring.

Previous research\textsuperscript{40} has utilized Wittig chemistry\textsuperscript{41} in the formation of the target substituted diene. Retrosynthetic analysis leads to \textit{trans}-2-methyl-2-butenal 11 which is commercially available and an appropriate Wittig salt such as 3-hydroxypropyl-1-triphenylphosphonium bromide 12 (Scheme 3). This non-stabilised phosphonium salt could cause problems in the formation of the desired \textit{E}-double bond stereochemistry. Work by Maryanoff has however found that olefins containing double bonds of high \textit{E}-stereoselectivities have been formed by reacting aldehydes with particular nonstabilised ylids bearing hydroxy groups.\textsuperscript{42}

Scheme 3. Retrosynthesis of the diene to give the \textit{trans}-methyl-butan-2-al and the hydroxy phosphonium salt.

1.2.2 Synthetic routes towards tetronothiodin

The formation of the diene enables the Diels-Alder approach to be established. The Diels-Alder reaction is extremely useful in organic synthetic chemistry, involving a [4 + 2] cycloaddition to yield a six membered ring. It provides remarkable stereoselectivity, a factor that has contributed to the formation of a number of natural products. It is a stereospecific reaction with a preferred transition state through which the relative stereochemistry of the substituents in both the dienophile and diene are retained. The believed transition state of the first proposed Diels-Alder reaction\textsuperscript{39}
between the hydroxy-diene 9 with nitroethylene\textsuperscript{43,44} 13 giving the cyclohexene unit 14 is shown in Scheme 4.

![Scheme 4. Diels-Alder transition state to give the desired cyclohexene unit 14.](image)

The Diels-Alder reaction would then be followed by protection of the hydroxy group 15 and a subsequent Nef reaction\textsuperscript{45} to yield substituted cyclohexenone 16 as shown in Scheme 5.

![Scheme 5. Diels-Alder reaction with nitroethylene and subsequent Nef reaction towards the formation of the substituted cyclohexenone (16).](image)

The use of other dienophiles such as phenyl vinyl sulfoxide can provide a number of routes towards the synthesis of the substituted cyclohexenone (Scheme 6). The use of phenyl vinyl sulfoxide\textsuperscript{46} or phenyl vinyl sulfone\textsuperscript{47} in Diels-Alder reactions has been well-documented and would give a cyclohexene unit such as 17. This functional group would enable the conversion to the desired keto function by first protecting the hydroxyl substituent as in 18, then a Pummerer rearrangement\textsuperscript{48,49} to give 19, and finally hydrolysis to give the substituted cyclohexenone.
Scheme 6. Diels-Alder reaction with phenyl vinyl sulfoxide and its Pummerer rearrangement to give the desired cyclohexenone.

Alternatively, the use of other dienophiles could be explored such as 2-chloroacrylonitrile, ethyl acrylate and acrylonitrile, all with the aim of providing a substituent that can be converted to the keto function in the cyclohexene unit. Following the formation of the desired substituted cyclohexenone 16, this must then be elaborated to furnish the spirotetronic acid. One proposal shown in Scheme 6 would start with the treatment of 16 with a nucleophile; for example treating with trimethylsilyl cyanide would give the cyanohydrin 20. The stereochemistry of the cyclohexene would allow the cyanide ion to attack the least hindered side giving the desired relative stereochemistry. The formation of the cyanohydrin would allow a subsequent DCC-DMAP mediated esterification, for example with methyl malonic acid 21.
Scheme 7. Nucleophilic addition of cyanide to the keto group would give the cyanohydrin (20) then esterification to acetoxyacetic acid (21) would form coupled species (22).

The treatment of species 22 with a suitable base would deprotonate the acidic position therefore inducing cyclisation in a manner similar to Dieckmann cyclisation, as shown in scheme 8. The final stage would then involve a deprotection reaction to give the free alcohol which could then be oxidised to form the oxaspirobicyclic portion 5.
Scheme 8. Deprotonation, induced cyclisation, deprotection and finally oxidation give the oxaspirobicyclic unit.

Another possible approach involves an intramolecular Diels-Alder reaction, used effectively in building the molecule. The intramolecular Diels-Alder (IMDA) reaction has advantages of being able to accelerate the rate of reaction compared to the intermolecular Diels-Alder reaction as the two components are joined and do not have to diffuse together. IMDA reactions also prevent regiochemical problems due to the ring constraints. A synthetic plan (Scheme 9) can first start with the coupling of the hydroxy diene with a suitable acid, in this example the use of propiolic acid 25 will form the ester Diels-Alder precursor with a suitable electron withdrawing group 26. The subsequent IMDA reaction produces the bicyclic structure with the expected relative stereochemistry 27. Epoxidation using hydrogen peroxide should provide the structure 28 which can then be reduced with a suitable bulky reducing agent to
give compound 29. Acidic conditions can then induce the lactone ring opening to give the suitably substituted cyclohexene 30 which, through further reactions outlined above, can give the spiro epimer intermediate 31 related to desired oxaspirobicyclic unit. The lack of literature precedent concerning the stereochemistry means the spiro epimer would be a useful intermediate to synthesise in characterising tetronothiodin and developing a synthetic route.

Scheme 9. The use of IMDA approach to give the desired oxaspirobicyclic unit.

The relative stereochemistry of the IMDA reaction to form 27 would be due to the ring constraints, which can be seen in the following transition state (Scheme 10).
Following from the use of an IMDA reaction as a possible route for the formation of the desired substituted cyclohexene, the use of tethers in IMDA reactions has been documented and can be developed for our synthesis. A temporary silicon containing connection was pioneered by Stork\textsuperscript{58} and proved versatile due to the silicon-carbon bond. An intramolecular Diels-Alder reaction would have a silicon atom connecting a diene and dienophile through, for example, an unsymmetrical silyl diether, or where silicon anchors the tether to the diene. A synthetic route (Scheme 11) can be adapted using this chemistry where the hydroxy diene would form an ether by reacting with a vinyl silane, and the resulting triene 32 could be then cyclised to give the bicyclic structure 33 as a mixture of the \textit{endo} isomer and the \textit{exo} isomer. The carbon-silicon bonds in the bicyclic product could be directly transformed into a carbon-oxygen bond with retention of stereochemistry through a Tamao oxidation\textsuperscript{59} to give the diol 34. Selective protection of the primary alcohol 35 and then oxidation of the secondary alcohol should give the desired substituted cyclohexenone 16.
The next stage would be to form the Wittig salt of the macrocyclic ring unit 7. A Wittig reaction of the salt 36 with the aldehyde functionality with the spirocycle 5 would combine the two units, as in 37. The obvious problem with this procedure lies in the potential stereochemistry complications due to a risk of poor control of E/Z ratio of the newly formed double bond. The required E-stereochemistry may be acquired by the use of a hydroxy-Wittig salt, which have been reported by Maryanoff as mentioned above to give E-stereochemistry in reactions with aldehydes (Scheme 12).
Scheme 12. The Wittig salt of the macrocycle (25) undergoes a Wittig reaction with the oxaspiro biscyclic unit (5) to combine the two units.

A second Wittig reaction could then be attempted to attach the substituted tetrahydrothiophene fragment to the macrocyclic end of the newly formed Wittig salt of 38 (Scheme 13). The stereocontrol would again be questionable but the presence of the hydroxy group would perhaps result in the desired stereochemistry as discussed above.
Scheme 13. Attachment of tetrahydrothiophene unit to (38).

The hydroxy group of 39 would then be protected to allow a selective reduction of the ester moiety to the aldehyde and then treating with a dithiol to give a thioacetal 40 (Scheme 14). The anion of the thioacetal can then be formed by treatment with a suitable base and this should lead to ring closure. The hydrolysis of the thioacetal should then give the ketone group and oxidation of the acetylene will provide the α-keto acid 60. The main problem associated with this procedure is the stereocontrol in the tetrahydrothiophene ring at C-22, C-23 and C-25. The more thermodynamically stable tetrahydrothiophene would result from equilibration at C-25, we believe giving the correct relative stereochemistry. The final stage would be to remove the protecting groups to give tetronothiodin.26
Scheme 14. Formation of the thioacetal allows treatment with a base to give ring closure and subsequent hydrolysis; oxidation of the acetylene and deprotection give tetraothiodin (1).
1.3 Spirocycles in other analogous natural products

1.3.1 Introduction

Related spirotetronate fragments to that found in tetronothiodin are found in several natural products including kijanolide 41, tetronolide 42 and chlorothricolide 43. These are aglycons of the spirotetronate antibiotics kijanimicin, tetricarcan A, and chlorothricin respectively and have attracted attention as synthetic targets for this reason. This section examines some developed synthetic routes to the spirotetronate fragments from the literature.

![Image of analogous natural products kijanolide (41), tetronolide (42) and chlorothricolide (43).]

Figure 9. Analogous natural products kijanolide (41), tetronolide (42) and chlorothricolide (43).

1.3.2 Oxaspirobicyclic moiety synthesis in kijanolide

Two approaches towards the upper fragment of kijanolide have been developed by Yoshii and involve Diels–Alder reactions of functionalised trienes with propynal and methyl-5-methylenetetronate.

The first synthesis starts with the preparation of (trimethylsilyl)oxy triene 45 prepared from the aldehyde 44 which then undergoes a Diels–Alder reaction with propargyl aldehyde 46 through refluxing in toluene to give a mixture of cycloadducts 47 and 48 as regioisomers in a 1:1.4 ratio (Scheme 15). The desired minor cycloadduct 47 then
had the carbonyl functionality reduced using DIBAL to give the alcohol which was subsequently silyl protected to give the cyclohexadienol silyl ether 49. This was then subjected to a selective desilylation under careful conditions to give the substituted cyclohexenone 50. The spirotetronate was finally synthesised by first reacting the carbonyl group with an organocerium reagent which performs a nucleophilic addition of the substituted alkyne group to give a acetylenic carbinol 51 as a single product. This was then heated with methanolic potassium methoxide to produce the desired cyclisation and give the product after a final silyl protection to give 52.
Scheme 15. Synthesis of upper fragment of kijanolide using a Diels-Alder approach with the functionalised triene and propynal.

The second route to the upper fragment of kijanolide\textsuperscript{61a} was the use of a direct construction of the functionalised spiro ring by using a Diels-Alder cyclisation with methyl-5-methylene tetronate 54 (Scheme 16). The dienophile 54 was prepared from methyl tetronate 53 through three steps: (dimethylamino)methylenation, reduction
with sodium cyanoborohydride and quaternization with methyl iodide, followed by treatment with aqueous sodium hydrogen carbonate. The Diels-Alder reaction took place upon heating in o-dichlorobenzene at 180 °C for seven hours with the appropriate triene and gave the cycloadducts as major 55 and minor isomers 56. Through detailed spectral analysis the minor cycloadduct was found to be the desired product.

Scheme 16. Diels-Alder approach using methyl-5-methyltetronate as a dienophile with a suitable triene.

Another highly diastereoselective synthesis of the spirotetronate moiety of kijanolide has been reported by Roush.\textsuperscript{61b} This involved a novel exo-selective Diels-Alder reaction between a triene 57 and a non-racemic dioxolane-4-one derivative 58 as the dienophile (Scheme 17). A mixture of cycloadducts 59 and 60 was formed in a 9:1 ratio in favour of major isomer 59. The next stage involved a reduction of the ester and keto groups of 59 using DIBAL to give the alcohol 61. This was then selectively silyl protected at the primary alcohol, so allowing oxidation of the secondary alcohol using a Swern procedure\textsuperscript{70} to give 62. Methanolysis then provides the hydroxy ester that can then be acylated to give 63. Treatment with a base generates an enolate producing Dieckman ring closure to give the MOM-protected spirotetronate 64.\textsuperscript{63b}
Scheme 17. Roush synthesis of top fragment of kijanolide.
1.3.3 Total synthesis of chlorothricolide

Roush reported the first total enantioselective synthesis of (-)-chlorothricolide 43, an aglycon of the antibiotic chlorothricin 64 and a member of the spirotetronate class of natural products. The total synthesis involved a route including tandem inter- and intramolecular Diels-Alder reactions between the diene 69 and the chiral dienophile, (2R)-2-tert-butyl-5-methylene-1,3-dioxolan-4-one 65. The Diels-Alder precursor 69 was synthesised through a ten step sequence from the acetylenic ketone 66 with the final step a Horner-Wadsworth-Emmons reaction however β-keto phosphonate 68 and compound 67 to give the desired product 69, as seen in scheme 18.

Scheme 18. The synthesis of the Diels-Alder precursor.
The tandem inter-intramolecular Diels-Alder reaction was performed by heating a mixture of 69 and two equivalents of the chiral dienophile 65. This class of dienophile has the tendency to be exo-selective and highly diastereofacially selective. This is reported to be due to steric factors and the endo transition state having a higher energy. The intermolecular Diels-Alder reaction is thus exo-selective while the intramolecular Diels-Alder reaction is endo-selective to give the desired product 70 in a 45 % yield as seen in scheme 19.

Scheme 19. The inter- intramolecular Diels-Alder reaction to give the desired cycloadduct (70).

The final steps involve a methanolysis followed by a DCC-DMAP mediated esterification with an α-hydroxy ester to give the triester 71. Dieckmann closure of the spiro tetronicate was achieved with the use of the base, trapping the enolate with the addition of MOM-Cl and removal of the allyl functionalities using Pd(PPh3)75 to give 72. Macrolactonisation was then achieved through the use of a base and BOP-Cl addition to furnish 73. The remaining steps involve the removal of protecting groups through standard procedures and the oxidation of the hydroxy group to the carboxylic acid to afford (-)-chlorothricolide 43 as seen in scheme 20.
Scheme 20. The final reactions towards the synthesis of (-)-chlorothricolide.
1.4 The Wittig and related reactions

1.4.1 Introduction

The reaction between a phosphorane or phosphonium ylid, and an aldehyde or ketone to form an alkene and a phosphine oxide as a by-product was first reported in 1953 by Georg Wittig and has proved a valuable preparative method for alkenes, the reaction requiring mild conditions and being very general.

Phosphonium ylids are generated through reacting an alkyl halide with trialkyl or triaryl phosphines (often using triphenylphosphine) to give a phosphonium salt. This is then converted to the ylid normally through treatment with a strong base such as butyl lithium, sodium amide and sodium hydride. When a base does not contain lithium the reaction for the formation of the ylid is said to be under “salt-free” conditions. The whole reaction is summarised in scheme 21.

Scheme 21. Formation of the phosphonium ylid and its subsequent reaction with a carbonyl compound to give an alkene.

The Wittig reaction gives rise to alkenes from an aldehyde or ketone which may be aliphatic, alicyclic or aromatic containing double or triple bonds. It may also contain a number of functional groups such as hydroxy, nitro, ester or halo groups with no
adverse effect on the overall process. Reactions with ketones tend to be much slower than with aldehydes for steric reasons.\textsuperscript{77-80}

1.4.2 Stereochemistry in Wittig reactions

An important attribute of the Wittig reaction apart from its simplicity and efficiency is the stereocontrol which can be achieved. The selectivity for Z-alkenes or E-alkenes depends on the type of ylid, carbonyl compound and reaction conditions.\textsuperscript{77b} Phosphonium ylids are often classified into three types: the non-stabilised ylid, stabilised ylid and the semi-stabilised ylid. Generally, non-stabilised ylids produce the thermodynamically less stable Z-alkene,\textsuperscript{87-91} while stabilised ylids, containing strong electron withdrawing groups on the \(\alpha\)-carbon, produce E-alkenes. Semi-stabilised ylids normally bear mildly conjugating substituents and have little preference for either Z-alkenes or E-alkenes.\textsuperscript{77b}

Mechanistic studies and the subsequent identification and behaviour of the reaction intermediates can explain these observations. Debate has occurred for a number of years in regard to whether zwitterionic phosphorus betaines X or 1,2-oxaphosphetanes Y or both are formed in the reaction sequence. The decomposition of these intermediates occurs to give the alkene and the phosphide oxide as seen in scheme 22.

\[
\begin{align*}
R_3P=CHR' + R'CHO & \rightarrow R_3P-O \quad \text{oxaphosphetane Y} \\
& \quad \text{betaine X} \\
& \quad R' \rightarrow R''
\end{align*}
\]

Scheme 22. Possible reactive intermediates formed during Wittig reaction.

Oxaphosphetanes were observed as intermediates through the use of \(^{31}\text{P}\) NMR spectroscopy on reactions of non-stabilised ylids at low temperatures.\textsuperscript{92} There is a lack
of evidence for uncomplexed betaines, and furthermore 1,2-oxaphosphetanes have been discovered in a variety of reactions of non-stabilised ylids with aldehydes and ketones. There is the possibility that betaines are formed before oxaphosphetanes and betaine-lithium halide precipitates\textsuperscript{93} have been isolated, and thus betaines are still of interest in Wittig chemistry.\textsuperscript{77b}

The orientation of this oxaphosphophetane dictates the stereochemistry in the Wittig reaction. The non-stabilised ylids generally form the cis oxaphosphetane through an early transition state which decomposes in a \textit{syn} manner to give Z-alkene.\textsuperscript{94,95} This preference for the cis-oxaphosphophetane is due to the steric crowding between the aryl ring attached to the phosphorus and other substituents present. A puckered four-membered transition state is favoured especially if R'\textsuperscript{'} is a bulky substituent, because this group can occupy a "pseudo-equatorial" position and the R' group, being "pseudo-axial," has no 1,3-diaxial interactions.\textsuperscript{96,81} The stabilised ylid reacts through late transition state to form the trans-oxaphosphetane which is thermodynamically more stable and decomposes to give the E-alkene.\textsuperscript{95,97} This alternative four membered transition state has a planar conformation with a degree of eclipsing and perhaps some unfavourable 1-3 diaxial interactions.\textsuperscript{77b,81} These transition states are shown in scheme 23.

\begin{center}
\textbf{Scheme 23. Orientation of oxaphosphophetanes and transition states dictating resulting stereochemistry.}
\end{center}
These are general stereochemical rules, and so there are a number of other factors, which can affect the overall stereochemical outcome of the reactions. The presence of lithium salt or salt-free trialkylphosphorus ylids in reactions affords lower levels of the cis oxaphosphaphetane.\textsuperscript{84,87,98} The effect of solvents, additives, concentration, and temperature on the stereochemistry also needs to be accounted for. Solvents such as THF, ethyl ether and dimethoxymethane have been found to give a higher yield and Z stereoselectivity.\textsuperscript{99}

The structural features of the carbonyl compound or ylid also play an important part in influencing the stereochemistry. When bulky aliphatic aldehydes such as pivaldehyde react under salt-free conditions they show enhanced Z-alkene stereoselectivity.\textsuperscript{87,88} Unsymmetrical ketones with similar substituents joined to the carbonyl group give poor stereochemistry, although bias for one alkene isomer can be achieved if one substituent is much bulkier.\textsuperscript{100} Aliphatic acylsilanes react under lithium salt conditions to give Z-vinylsilanes with high Z-stereoselectivity.\textsuperscript{101} Trifluoromethyl ketones can also give alkenes with high Z-stereoselectivity when reacted under certain conditions.\textsuperscript{77b,102}

1.4.3 The Wittig reaction in synthetic applications

There are numerous examples of the use of Wittig reactions in synthesis. They range from very simple reactions involving small unfunctionalised aldehydes and ketones with commonly used ylids to large complex compounds such as natural products with elaborate ylids.

The synthesis of (-)-anamarine \textsuperscript{76} from D-glucose involves a linkage between the ylid derived from \textsuperscript{74} and aldehyde \textsuperscript{75}.\textsuperscript{103} The ylid formation with \(\beta\)-alkoxy phosphonium salt is prone to elimination chemistry,\textsuperscript{104} however Lichtenthaler \textit{et al.}\textsuperscript{103} adapted a procedure from previous chemistry reported by Secrist and Wu \textsuperscript{104c} to give good yields of the Z-isomer, as shown in scheme 24.
Scheme 24. From the synthesis of (-)-anamarine from D-glucose.

There are few examples very relevant to the synthesis of tetrathiodin. In the synthesis of the spirotetronic acid portion of kijanolide, two Wittig reactions are reported as shown in scheme 25. The first reaction gave a Z/E ratio of 7:3 while the second is a Z-selective ketone olefination.

Scheme 25. Two Wittig reactions in the synthesis of the spirotetronic portion of kijanolide

The Wittig reaction has been carried out in an intramolecular fashion to give rings of 5 to 16 carbons by a single ring closure or a double ring closure as seen in scheme 26.
1.5 Analogous Wittig type reactions

1.5.1 The Horner-Wadsworth-Emmons reaction

A Wittig type reaction that uses phosphonates instead of ylids is known as the Horner-Wadsworth-Emmons reaction. It was first developed by Horner and later expanded by Wadsworth and Emmons. Phosphonate esters can be synthesised through a Michaelis-Arbusov reaction where a phosphite is treated with an alkyl halide to form an alkoxypophosphonium salt. This then reacts further to give the desired phosphonate ester. The reaction can then be carried out on aldehydes and ketones using the derived stabilised carbanions. A general example is shown in scheme 27.

Scheme 27. Horner-Wadsworth-Emmons reaction

The stabilisation is derived from the phosphonate ester group, although α-substituents such as nitrile, aryl, vinyl and sulfonyl can also provide stabilisation. The mechanism has been studied with the use of reaction rates and spectroscopic studies and is now generally understood. The phosphoryl-stabilised carbanion attacks the carbonyl group in a stepwise manner to give an oxyanion intermediate, which decomposes through a transient four-centred intermediate to yield an alkene.
The stereochemistry depends on the initial stereoselectivity in the carbon-carbon bond-forming step and the reversibility of the reaction steps. As with stabilised Wittig reagents, Horner-Wadsworth-Emmons reactions usually produce the $E$-alkene, although there are cases that differ. The threo-isomer intermediate formed is believed to be more thermodynamically stable than the erythro, and thus will predominate in thermodynamically-controlled reactions and result in the $E$-alkene, as shown in scheme 28.\textsuperscript{77b,114}

\begin{center}
\textbf{Scheme 28. Mechanistic view of the Horner-Wadsworth-Emmons reaction.}
\end{center}

A distinct advantage of a Horner-Wadsworth-Emmons reaction involves the separation of the phosphate anion. The Wittig reaction produces a phosphine oxide which is difficult to separate from the product, while the Horner-Wadsworth-Emmons reaction produces a water-soluble phosphate anion which can be easy to separate. The additional stabilisation provided by the electron withdrawing group in phosphonate anions make them ideal stabilised intermediates, often more reactive than stabilised phosphonium ylids. Therefore a number of aldehydes and ketones unreactive in the standard Wittig process are reactive in the Horner-Wadsworth-Emmons process.\textsuperscript{77b,78,114}
1.5.2 The Peterson reaction

Another alternative to the Wittig reaction uses anions derived from trialkyl silyl derivatives to react with carbonyl compounds; the intermediates formed decompose to give alkenes. This silicon version of the Wittig reaction was first reported by Peterson in 1968 and is therefore known as the Peterson reaction. The procedure normally requires a lithio or magnesio derivative of a trialkylsilane to add to the carbonyl compound to give a β-hydroxysilane alkoxide which eliminates trimethylsilanol in a stereospecific syn elimination to give the alkene, as seen in scheme 29.

![Scheme 29. General procedure for Peterson reaction.](image)

If the intermediate β-hydroxysilane is isolated, the stereochemistry can be controlled during the elimination step, where the use of a base generally gives stereospecific syn elimination while an acid generally gives anti elimination as shown in scheme 30.

![Scheme 30. Stereochemistry given when treated with either base or acid in Peterson reaction.](image)

An advantage the Peterson reaction as compared to the Wittig reaction is that it forms hexamethyldisiloxane as a by-product, which is volatile and therefore easier to
remove from the reaction product. It also has been known to work when the Wittig reaction has failed to give the desired alkene.\textsuperscript{79}

1.6 The Diels-Alder reaction

1.6.1 Introduction

The synthetic approach to tetronothiodin uses a Diels-Alder reaction as a key step in its synthesis, and it is therefore valuable to provide an account on this very useful synthetic reaction.

In 1928, Otto Diels and Kurt Alder\textsuperscript{39} carried out the first example of a Diels-Alder reaction,\textsuperscript{119} and it has since become one of the most important types of pericyclic reaction. The Diels-Alder reaction is essentially a [4 + 2] cycloaddition and in its simplest form involves the addition of butadiene 77, the conjugated diene, to ethene 78, the dienophile, to give cyclohexene\textsuperscript{119,\textsuperscript{120} 79}, as shown in the scheme 31. Ethene however is a poor dienophile and reacts very slowly under thermal conditions.\textsuperscript{121-\textsuperscript{125}}

\begin{equation}
\begin{array}{c}
\text{77} \\
\text{78} \\
\text{200 °C} \\
\text{20 %}
\end{array}
\end{equation}

Scheme 31. Diels-Alder Reaction between butadiene 77 and ethene 78 to give cyclohexene 79

These reactions can however occur in an easy and rapid manner and have a very important synthetic utility in the formation of carbon-carbon bonds. The Diels-Alder reaction has a broad scope due to the number of different dienes and dienophiles that may be used in the reaction. The reaction is promoted by the presence of electron-donating groups in the diene, such as a methyl or methoxy group at the C-1 or C-2 position. The dienophile also becomes more reactive with one or more electron-withdrawing groups, such as a nitro or sulfonyl group, as seen in scheme 32.\textsuperscript{121,\textsuperscript{122,\textsuperscript{125}}}
Scheme 32. Presence of electron withdrawing groups in dienes and electron donating groups in dienophiles.

The reaction is highly versatile in the degree of stereo- and regioselectivity it provides, giving one isomer exclusively or at least predominantly in most cases. The position of the substituents present in the diene and dienophile affects the outcome of the reaction, normally to give a preference for one isomer. The diene can perform a Diels-Alder reaction only when it is in a *cisoid* conformation rather than in the *transoid* conformation, explaining why cyclic dienes can be more reactive than open chained dienes. Another important principle concerns the relative stereochemistry of the substituents in the diene and dienophile, which is retained in the reaction. Thus, substituents that are *cis* in the dienophile remain *cis* in the product and *trans* substituents will remain *trans* in the product. The Diels-Alder reaction is therefore a stereospecific process. \(^{121,122,125}\)

![Diene Conformations](image)

Scheme 33. *Cisoid* and *transoid* conformation of the diene.

1.6.2 Frontier Molecular Orbital Theory

Diels-Alder reactions are not described adequately in terms of electrophilic-nucleophilic interactions or through radical pathways but considered mechanistically through the interactions of their frontier orbitals and are described as symmetry-controlled. Application of Woodward-Hoffmann\(^ {126}\) rules with regard to the conservation of orbital symmetry is used to explain the outcome of Diels-Alder
reactions. The orbitals considered in a Diels-Alder reaction are the Highest Occupied Molecular Orbital (HOMO) of one component and the Lowest Unoccupied Molecular Orbital (LUMO) of the other component. The necessary overlap between these orbitals permits bond formation and the cycloaddition is said to be symmetry-allowed.\textsuperscript{127,128}

![Diagram of HOMO and LUMO for dienes and dienophiles.](attachment:diene_dienophile_orbitals.png)

Scheme 34. The HOMO and LUMO for dienes and dienophiles.

HOMO-LUMO interactions gives \textit{syn} addition with respect to both the diene and dienophile, retaining the relative configuration in the product formed (Scheme 35). The electronic effects of substituents present in the diene and dienophile affect the formation of new bonds in the transition state during the reaction pathway. Electron-donating substituents in the diene increase the energy level of the HOMO, while electron-withdrawing groups in the dienophile decrease the energy level of the LUMO. This effect enhances the orbital overlap in the reaction and thus the reaction rate.\textsuperscript{127,128,129}

![Diagram of HOMO-LUMO overlap in a Diels-Alder reaction.](attachment:homo_lumo_overlap.png)

Scheme 35. HOMO-LUMO overlap between the diene and dienophile in a Diels-Alder reaction

Molecular orbital considerations can also be used to explain another important stereochemical characteristic of Diels-Alder reactions. The Diels-Alder reaction has a tendency to favour \textit{endo} orientation in the transition state under kinetic control of the reaction. This favoured \textit{endo} stereochemistry arises from the favourable "secondary
"orbital" interactions between the developing double bond in the diene and the unsaturated substituent groups of the dienophile. This observation is seen in a number of Diels-Alder reactions which follow an empirical rule known as the Alder endo rule. A good example of this stereoselectivity is the addition between maleic anhydride $80$ and 1,3-cyclopentadiene $81$. There are secondary orbital interactions between the LUMO lobes at the carbonyl groups and the HOMO lobes in the cyclopentadiene favouring endo approach.

Scheme 36. Endo-exo approach between maleic anhydride $80$ and cyclopentadiene $81$.

### 1.6.3 Inverse Electron-Demand Diels-Alder reactions

Diels-Alder reactions which have electron-withdrawing groups on the diene and electron-donating groups present on the dienophile are less common, yet occur and are described as "inverse electron-demand" reactions.

Molecular orbital theory can explain these reactions, where orbital overlap is increased, therefore facilitating the reaction. The presence of the electron-withdrawing group on the diene lowers the energy of the LUMO and the presence of the electron donating group raises the energy of the HOMO, as seen in scheme 37.

1.6.4 Catalysis of Diels-Alder reactions

Catalysts have been found to be of importance in the facilitation of Diels-Alder reactions. In some Diels-Alder reactions the use of catalysts may increase reaction rates and regio- and stereoselectivity compared to the use of the normal thermal conditions often employed.\(^{121,122,133}\) The most common catalysts used are Lewis acid-catalysts such as BF\(_3\), Et\(_2\)AlCl\(_2\), SnCl\(_2\), TiCl\(_4\), ZnBr\(_2\) and ZnCl\(_2\) (complexed with ethers).\(^{134,135}\) These Lewis-acid catalysts normally influence Diels-Alder reactions by complex formation with polar groups present in the dienophile. This is rationalised by the ability of the Lewis acid to lower the LUMO energy in the dienophile, reducing the energy difference between the orbitals and therefore inducing better overlap, resulting in a faster reaction.\(^{122}\) Other catalysts include organotransition metal complexes\(^{136}\) that can be used instead of more usual Lewis-acids, avoiding strong thermodynamic binding as well as being less water sensitive, and therefore requiring less catalyst loading.

For example, the use of 5 M LiClO\(_4\) in Et\(_2\)O as a solvent is a catalytic method reported to have accelerated Diels-Alder reactions.\(^ {137}\)

Numerous other methods have been reported for the acceleration of Diels-Alder reactions, such as use of water as a solvent, resulting from the formation of a tighter transition state.\(^ {138}\) Ultrasound and microwave irradiation\(^ {139}\) have been used to good effect in Diels-Alder cycloadditions. Diels-Alder reactions can be catalysed by the addition of a stable cation radical such as tris(4-bromophenyl)aminium hexachloroantimonate.\(^ {140}\) Biocatalysts such as protein, antibody and enzyme\(^ {141,142}\) have
been used in Diels-Alder cycloadditions. Finally, more recently, the use of polymer-bound dienophiles\textsuperscript{143} has attracted attention in Diels-Alder reactions.

**1.6.5 Intramolecular Diels-Alder reactions**

The intramolecular Diels-Alder (IMDA) reaction involves a diene and dienophile in which both are part of the same molecule to give a the formation of a two-ring fused system.\textsuperscript{144} This IMDA reaction was first reported in 1953,\textsuperscript{54} and is widely used in the synthesis of natural products such as alkaloids and steroids.

IMDA reactions have been shown to increase reaction rates, often under milder conditions than intermolecular Diels-Alder reactions. As two components do not have to diffuse together lower temperatures and ring constraints have been found to increase stereocontrol in intramolecular Diels-Alder reactions. The two possible regiochemical modes of addition can however occur, with the predominant formation of the fused product compared to the bridged product (Scheme 38).\textsuperscript{144a} The majority of fused ring systems formed reported in the literature are bicyclic 5-6 and 6-6 ring systems from trienes, with a few examples of 6,7-ring systems.\textsuperscript{122,145}

![Scheme 38. IMDA reactions resulting in the fused or bridge structure.](image)

The most valuable feature of IMDA reactions is the available control of stereoselectivity, where products frequently favour the \textit{endo} transition state, although these reactions may not follow the Alder \textit{endo} rule.\textsuperscript{146} Control arises in the conformational, non-bonding interactions of substituents and other steric effects in the transition state.

The IMDA reaction has already been used as a key step in the total synthesis of natural product (\textit{-})-chlorothricolide,\textsuperscript{63a} related structurally to tetronothiodin. Research
using an IMDA reaction as a synthetic approach to phorbol\textsuperscript{147} has also been used in our research group.

1.6.6 Disposable tethers in Diels-Alder reactions

The benefits of intramolecular Diels-Alder reactions have already been highlighted above, in which higher reaction rates under milder reaction conditions can be achieved compared to intermolecular reactions. The use of a temporary union of two reacting groups by a tether group would therefore prove beneficial by providing intramolecular reaction properties. Once the reaction has occurred the tether can then be removed.\textsuperscript{148}

A disposable tether has a number of requirements, for example it should be assembled readily through synthetic transformations and the precursor formed should then be stable to further purification and reactions. Once the reaction has occurred the temporary tether should then be easily and selectively removed. Tethers involving silicon groups have been used in several Diels-Alder reactions.\textsuperscript{149}

Reactions that require catalysts or elevated temperatures, are those that proceed with lower regioselectivity such as cycloadditions are ideal candidates for the use of tethers. Other reactions where tethers have been used include sigmatropic rearrangements, radical cyclisations, hydrosilylations, Ullman couplings and the formation of glycoside linkages.\textsuperscript{148}

One of the first examples of the use of a “disposable” tether to control regio- and stereochemistry in the Diels-Alder reaction was reported by Tamao and Ito (Scheme 39).\textsuperscript{150} The vinyl silane 83 was prepared by Ni(0) catalysed cyclisation of 1,7-octadiyne 82, and condensed with cinnamyl alcohol 84 to give the Diels-Alder precursor 85. The triene 85 was then cyclised to give siloxane 86 which was oxidatively cleaved to give the diol 87 as a single isomer.
Scheme 39. Disposable tether to control regio- and stereochemistry reported by Tamoa and Ito in Diels-Alder reaction.

The use of vinyl silane dienophiles has also been reported in silicon tethered Diels-Alder reactions. The cyclisation of vinylsilyloxy trienes 88 gives a mixture of exolendo isomers 89 after oxidative cleavage and has been reported by Stork.58

Scheme 40. Cyclisation of vinylsilyloxy trienes 88 and cleavage to diols 89.

Stork further elaborated this chemistry by cyclising similar trienes containing alkyl, aryl 90 and carboethoxy substituted 91 dienophiles with carboethoxy substituents, resulting in complete stereoselectivity (Scheme 41).58
Sieburth varied tether length and substituents on the silicon atom, affecting both the yields and the endo/exo selectivity. The trienes containing three or four atoms cyclise in good yields, although a tether length of five results in low yields. The alkyl substituent on silicon influences the endo/exo selectivity, which can be seen when reacting sorbyl alcohol with dimethylvinylsilane, diphenylvinylsilane and di-tert-butylvinylsilane. The dimethylsilyl group yields a 2:1 ratio of products with the endo isomer the major due to the steric influence of methyl silanes. Changing to the diphenylsilyl group gives a 1:1 ratio of products, while the di-tert-butyl group results in the formation of the exo derived product as the majority of a 4:1 isomeric ratio (Scheme 42).

Scheme 41. Effects of substituents on trienes in stereochmistry of Diels-Alder reactions.
1.7 Hydrogen peroxide oxidation of silicon-carbon bond in Organoalkoxysilanes

The first successful result on oxidative cleavage of the silicon-carbon bond used in Scheme 39 was reported by Tamao et al. The silicon-carbon bond was readily cleaved when treated with hydrogen peroxide under mild conditions to give the corresponding alcohols. The oxidation proceeds with retention of configuration at the carbon to be oxidised, thus oxygen functionality is introduced stereospecifically as well as regioselectively onto the original silicon-bearing carbon atom.

Some results are shown on table 1 below for the oxidative cleavage of n-octylmethyldiethoxysilane to n-octanol (Scheme 43) using a variety of conditions. The use of 30% hydrogen peroxide alone in DMF produces no reaction while the addition of potassium hydrogen difluoride increases the yield dramatically under these neutral conditions. The reaction also occurs with the use of methanol/THF as a solvent, with similar results. The use of this solvent with potassium hydrogen carbonate as an additive gives weak alkaline conditions with no fluoride ions being required, yet still produces good results. A more concentrated 90% hydrogen peroxide solution gave similar results to 30% hydrogen peroxide. m-CPBA is a
powerful oxidant, yet produces no real difference in the results achieved, while hydrogen peroxide has the advantage of being milder and cheaper.\textsuperscript{152}

\[
\text{[O]}
\]

\[
n\text{-C}_8\text{H}_{17}\text{-SiMe(OEt)}_2 \xrightarrow{[\text{O}]} n\text{-C}_8\text{H}_{17}\text{-OH}
\]

Scheme 43. Oxidative cleavage of \(n\)-octylmethyldiethoxysilane to \(n\)-octanol.

<table>
<thead>
<tr>
<th>Oxidant (eq.)</th>
<th>Additive (eq.)</th>
<th>Solvent</th>
<th>Temp, °C (Time, h)</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 % H\textsubscript{2}O\textsubscript{2} (12)</td>
<td>none</td>
<td>DMF</td>
<td>60 (7)</td>
<td>2 (67 % recovered)</td>
</tr>
<tr>
<td>30 % H\textsubscript{2}O\textsubscript{2} (12)</td>
<td>KHF\textsubscript{2} (2)</td>
<td>DMF</td>
<td>60 (7)</td>
<td>82</td>
</tr>
<tr>
<td>30 % H\textsubscript{2}O\textsubscript{2} (12)</td>
<td>KHF\textsubscript{2} (2)</td>
<td>MeOH/THF</td>
<td>60 (7)</td>
<td>83</td>
</tr>
<tr>
<td>30 % H\textsubscript{2}O\textsubscript{2} (12)</td>
<td>KHF\textsubscript{2} (2)</td>
<td>MeOH/THF</td>
<td>rt (3)</td>
<td>96</td>
</tr>
<tr>
<td>90 % H\textsubscript{2}O\textsubscript{2} (6)</td>
<td>KHF\textsubscript{2} (2)</td>
<td>DMF</td>
<td>60 (4)</td>
<td>88</td>
</tr>
<tr>
<td>MCPBA (2.5)</td>
<td>KHF\textsubscript{2} (2)</td>
<td>DMF</td>
<td>rt (2)</td>
<td>91</td>
</tr>
</tbody>
</table>

Table 1. Results of oxidative cleavage with various oxidants and conditions.

A likely mechanism for the reaction would first involve the nucleophilic attack of the hydrogen peroxide species with the silicon. This gives a silyl hydroperoxide species that undergoes intramolecular rearrangement to form a silane intermediate. The intermediate is hydrolysed to give the observed alcohol and a silanediol species that eventually should end in a mixture of inorganic silicic acid derivatives (Scheme 44). The role of fluoride ions in these processes can be described as a fluoride assisted rearrangement of silyl peroxide.\textsuperscript{59, 151, 152, 153}

\[
R' \quad \text{Alkyl, Aryl} \\
R'' \quad \text{Alkyl, Aryl}
\]

Scheme 44. Mechanism of oxidative cleavage using hydrogen peroxide.
1.8 Nef reaction

The Nef reaction can be described as the conversion of a primary or secondary nitroalkane into a carbonyl compound. J.U. Nef first reported the reaction in 1894. It is a useful synthetic tool given that nitroalkanes can generally be prepared readily, for example through the condensation of nitroalkanes with aldehydes (the Henry reaction), and thus lead easily towards a desired carbonyl compound (Scheme 45).^{154,155}

\[
\begin{align*}
R R' \quad \text{base} \quad & \quad \rightarrow \quad R' \quad R \\
& \quad \text{H}_2\text{SO}_4 \quad \rightarrow \quad R R'
\end{align*}
\]

Scheme 45. Nef reaction.

A number of mechanisms have been proposed.^{156} In its simplest form the Nef reaction involves the treatment of the conjugate base with sulfuric acid. The initial reaction of the nitro compound with a base gives a nitonate species 96. The next steps involve a protonation of this species on the oxygen atom followed by attack of water and decomposition of the intermediate to give the carbonyl species 97 (Scheme 46).

\[
\begin{align*}
\text{R} R' & \quad \text{H}^+ \\
\text{H}_2\text{O} & \quad \text{H}^+ \\
\text{R}' R & \quad \text{H}_2\text{O}, \text{H}^+ \\
\text{R} R' & \quad \text{H}^+ \\
\text{OH} & \quad \text{H}^+ \\
\text{R} R' & \quad \text{H}_2\text{O} + \text{N}_2\text{O}
\end{align*}
\]

Scheme 46. Mechanism of the Nef reaction.
This procedure of using a base then sulfuric acid can produce a number of unwanted side reactions, and thus a number of alternative methods have been developed, often with an increase in yield. Many of these modern approaches utilise oxidising agents such as potassium permanganate, for example on nitro compound 98 to give carbonyl compound 99,\textsuperscript{157} $m$-CPBA\textsuperscript{158} on nitronate ester 100 to give carbonyl compound 101, and TPAP\textsuperscript{159} for the formation of 103 from 102, as shown in scheme 47. Other oxidising agents include ceric ammonium nitrate (CAN),\textsuperscript{160} tert-butyl hydroperoxide,\textsuperscript{161} ozone,\textsuperscript{162} hydrogen peroxide\textsuperscript{163} and MoOPH.\textsuperscript{164}

![Scheme 47. Nitro compounds to carbonyl compounds using oxidising agents.](image)

A small number of reagents convert nitro compounds into aldehydes or ketones by reductive processes. The most widely used reductive modified Nef reaction uses aqueous titanium trichloride, as seen in the formation of 105 from 104 (Scheme 48). This reagent can be very acidic, and the reaction often uses an ammonium acetate or sodium acetate buffer to avoid any side reactions with sensitive compounds.\textsuperscript{154,155a,165}
Scheme 48. Nitro compound to carbonyl compound using TiCl₃ through a reductive process.

Other reagents include activated dry silica gel,¹⁶⁶ tin complexes in conjunction with sodium hydrogen sulfate,¹⁶⁷ and sodium nitrate.¹⁶⁸
1.9 Summary

The introduction provides a biological background to the discovery, isolation, biological properties and characterisation of tetronothiodin 1. The combination of useful biological properties and interesting structure that has never before been synthesised provides a significant research opportunity for the synthetic chemist.

The proposed synthetic pathway has developed from a retrosynthesis of tetronothiodin which has suggested three distinct components. These components are the oxaspirobicyclic portion 5; the substituted tetrahydrothiophene unit 6 and the unsaturated haloalcohol 7.

The oxaspirobicyclic portion 5 is the most obvious starting point to begin the synthesis in that it provides the most significant challenge to the chemist.

Investigation of analogous spirocyclic moieties in natural products has led to several synthetic routes towards kijanolide 41, tetronolide 42 and chlorothricolide 43. Previous research in this field and our own synthetic work has suggested a Diels-Alder approach towards the oxaspirobicyclic portion 5 in producing the cyclohexene ring. The precursors for the Diels-Alder reaction can be provided through the use of interesting Wittig chemistry. The Diels-Alder approach can also give numerous methods of providing the essential cyclohexene fragment through the use of either standard inter- or intramolecular Diels-Alder reactions or the use of silicon tethers as discussed above.

The requirement to form the carbonyl functionality in the cyclohexene ring also suggests a need for insight into the possible use of Nef reactions and oxidations as discussed briefly in this introduction.
Chapter Two
2.0 Results and Discussion

2.1 Introduction

As discussed above in the introduction the retrosynthesis of tetronothiodin suggested the formation of the oxaspirobicyclic portion 5. The synthesis of analogous natural products such as kijanolide\textsuperscript{61} and chlorothricolide\textsuperscript{63} has already established the use of Diels-Alder reactions in the formation of such cyclohexene units. The cyclohexene unit is required to be suitably functionalised to enable the preparation of the desired spirotetronic acid. Previous research established a possible route towards the synthesis of 5 using a similar Diels-Alder approach through the cyclohexenone unit 8 (Scheme 49).\textsuperscript{40}

Further retrosynthesis suggests the Diels-Alder precursors hydroxy diene 9 and dienophiles 10 containing functionalities that can be converted to the keto function. This gives a logical point for the research to begin, with the reproduction, and also possible improvement and extension of established protocols.

![Scheme 49. Retrosynthesis of oxaspirobicyclic portion to give the cyclohexenone unit.](image-url)
2.2 Diene synthesis

2.2.1 Wittig chemistry to diene synthesis

The synthesis of tetronothiodin begins with the synthesis of the Diels-Alder precursors which have previously been developed in our research group.\(^{40}\) The target diene necessary for the Diels-Alder reaction has been synthesised through the use of Wittig\(^{41}\) chemistry. Retrosynthesis of the hydroxy diene by a Wittig approach leads to a \textit{trans}-2-methyl-2-butenal 11 and the ylid 12 formed from 3-bromo-1-propanol act as the necessary starting materials (Scheme 50).

\begin{equation}
\text{HO} + \text{CHO} \rightarrow \text{HO} + \text{PPh}_3
\end{equation}

Scheme 50. Retrosynthesis of diene.

An important issue to be considered is the stereochemistry. Obviously the retrosynthesis indicates that the diene with the requires the \textit{E}-stereochemistry from the Wittig reaction. Literature searches found very significant work concerning the reaction between aldehydes and hydroxyphosphonium salts. Normally \textit{Z}-olefins are obtained by reacting non-stabilised ylids with aldehydes. However high \textit{E}-stereoselectivities have been observed when reacting aldehydes with non-stabilised ylids bearing hydroxy groups.\(^{42, 77b, 169, 170}\)

High \textit{E}-stereoselectivity was originally observed by a method which involves metallation of the Wittig intermediate at low temperatures to give a lithio \textit{\(\beta\)}-oxido intermediate then finally quenching with a proton source or other electrophile. This \textit{\(\beta\)}-oxido intermediate can be generated directly from \(\beta\)-hydroxyalkylphosphonium salts, and subsequently reacted with aldehydes to give \textit{E}-olefins. Further reports of stereoselectivity with \(\gamma\)-oxido intermediates have been made, and these have been used in further synthetic applications.\(^{42, 77b}\)
Mechanistically the \( E \)-stereoselectivity of \( \beta \)-oxido intermediates has been suggested to arise from the stereoselective formation of a \( \text{rac} \)-dioxido phosphonium adduct which has a preference for elimination to give \( E \)-alkenes.\(^{42,77b}\) A "lithium-bridging" mechanism has been suggested by Corey,\(^{171}\) where addition of the aldehyde to the oxido ylid 106 with minimal steric interaction gives the intermediate 107 which decomposes to generate the \( E \)-alkene (Scheme 51).

![Scheme 51. "Lithium bridging" mechanism by Corey.](image)

It has been proposed that the observed \( E \) stereoselectivity of \( \gamma \)-oxido ylids has an internal Schlosser\(^{170}\) type "\( \text{trans} \)-selective Wittig" mechanism involving proton exchange in an intermediate betaine/oxaphosphetane as illustrated for deuterium labelled Wittig reagent in Scheme 52.

![Scheme 52. "Trans-selective" Wittig mechanism suggested by Schlosser.](image)
A number of other explanations have been suggested for the formation of $E$-olefins from oxido ylids, and a number of factors affect this selectivity. The selectivity of Wittig reactions of oxido ylids has shown a great dependence on the cation used, where lithium gives the highest ratio of $E$-alkene. The chain length is also important in these reactions, where the longer the chain the less selectivity for the $E$-alkene. This chain length dependence may affect betaine formation as the basic oxygen is further away from the phosphorus atom. This would affect both the proposed mechanisms of lithium bridging or proton exchange where the oxygen atom is involved.$^{42,77b}$

This knowledge of the use of hydroxy phosphonium salts to give $E$-dienes desired led to the subsequent reactions being developed. The phosphonium salt, 3-(hydroxypropyl)-triphenylphosphonium bromide 12 was synthesised by refluxing 3-bromo-1-propanol with triphenyl phosphine in ethyl acetate for 48 hours to give 12 in a satisfactory yield of 56% (Scheme 53).

\[
\begin{align*}
\text{HO} - \text{Br} & \quad \xrightarrow{\text{PPh}_3(1 \text{ eq.})} \quad \text{HO} - \text{PPh}_3\text{Br}^{\ominus} \text{Br}^{\ominus} \\
\text{E.OAc,} & \quad \text{reflux, 48 hrs,} \\
& \quad 56 \%
\end{align*}
\]

Scheme 53. Synthesis of 3-Hydroxy-1-triphenylphosphonium bromide.

The phosphonium salt can then undergo a Wittig reaction through a standard procedure. The addition of two equivalents of $n$-butyl lithium as an effective strong base was required to deprotonate the hydroxy subunit and also form the ylid. The reaction was carried out initially with the phosphonium salt stirred at $0^\circ\text{C}$ with THF as the solvent for a period of an hour. The $trans$-2-methyl-2-butenal 11 was then slowly added and the reaction mixture was stirred for a further six and a half hours (Scheme 54).

\[
\begin{align*}
\text{HO} - \text{PPh}_3\text{Br}^{\ominus} & \quad \xrightarrow{(1 \text{ eq.})} \quad \text{OHC} - \\
& \quad n-\text{BuLi}(2 \text{ eq.}) \quad \text{THF, } 0^\circ\text{C, 6.5 hrs} \\
& \quad 73 \%
\end{align*}
\]

Scheme 54. Formation of the hydroxy diene.
Initial attempts at this reaction proved problematic with yields being unsatisfactory compared to the previous results. However, the necessity to use freshly distilled THF which was completely anhydrous gave expected yields of around 70% of the hydroxy diene (E,E)-5-methyl-3,5-heptadien-1-ol 9 identified through spectral analysis. The stereochemistry was established through the $^1$H NMR spectroscopy where the proton from the newly formed olefinic bond at 6.15 ppm possessed a coupling constant ($J$ 15 Hz) associated with trans-double bonds.

2.2.2 Hydroxy group protection in the diene

The reactivity of the hydroxy group in reactions subsequent to the Diels-Alder reaction led to the necessity for protecting the diene before the cycloaddition has taken place. There are numerous literature procedures for the protection of alcohols in synthesis. The protection of the diene before the cycloaddition readily allows the alcohol to be selectively protected before the compound contains more functionalities and is therefore more difficult to protect. It would also be useful to investigate the protected diene in a Diels-Alderasection to see if the group affects the transition state involving the dienophile during the reaction e.g. through steric hindrance or electron-donating effects.$^{172}$

The hydroxy diene was benzylated using a standard procedure.$^{40,173}$ Sodium hydride was used as the base, and the reaction mixture was stirred in DMF over a period of forty-five minutes (Scheme 55). This allowed deprotonation followed by the nucleophilic substitution on the benzyl bromide. The reaction was successfully repeated to obtain good yields of (E,E)-1-benzyloxy-5-methyl-3,5-heptadiene 108 which was identified by comparison of relevant spectra with previously reported spectra.

$$\text{(1) NaH (1.5 eq.), DMF, RT, 45 mins}$$

$$\text{(2) BuBr (1 eq.), 4 hrs, 63 \%}$$

Scheme 55. Benzylation of hydroxy diene.
Another standard procedure is the use of silylating agents for hydroxy group protection. The addition of imidazole to tert-butyl-dimethylsilyl chloride gives an intermediate which was reacted with the alcohol. The reaction mixture was stirred for two hours in DMF to give good yields of the desired product (Scheme 56).

\[
\begin{align*}
\text{HO} & \quad \text{Imidazole (2.5 eq.),} \\
& \quad \text{DMF} \\
& \quad \text{TBDMSO (1 eq.),} \\
& \quad 2 \text{ hrs, 71%}
\end{align*}
\]

Scheme 56. Silylation for protecting the hydroxy diene.

The (E,E)-1-tert-butyl-dimethylsiloxy-5-methyl-3,5-heptadiene 109 was fully characterised by \(^1\)H NMR, \(^{13}\)C NMR, and IR spectroscopy and MS.

2.3 Diels-Alder approach with nitroethylene

2.3.1 Introduction.

The formation of the diene enabled us to investigate at suitable dienophiles for a Diels-Alder reaction to give the desired cyclohexene subunit. The dienophile should contain a functionality that can be reacted further to provide the spirocycle subunit. Nitroethylene \(^4\) was used in the previous research and proved effective as a dienophile and with our hydroxy diene (Scheme 57). Nitroethylene has been shown to be a good dienophile in Diels-Alder reactions and has been used in Michael additions.

63
2.3.2 Synthesis of nitroethylene

Following a synthetic procedure by Ranganathan,$^4_3$ nitroethylene was produced through the dehydration of 2-nitroethanol using phthalic anhydride. A mixture of 2-nitroethanol was heated with phthalic anhydride to produce a liquid at around 145 °C. This was then heated further to 160 °C to distil off an orange liquid later characterised as the desired nitroethylene 13 (Scheme 58).

2.3.3 Diels-Alder reactions

The diene and dienophile could then be used in a Diels-Alder reaction. A mixture of hydroxy diene 9 and nitroethylene 13 in dry toluene was stirred at room temperature for three days under an inert atmosphere. This reaction gave the desired 1,6-dimethyl-3-(2-hydroxy-ethyl)-4-nitrocyclohex-1-ene 14 as a green oil with yields of around 50% after purification by flash column chromatography (Scheme 59). $^1$H NMR and IR spectra were compared with those from previous research.$^4_0$
2.3.4 Analysis of 1,6-dimethyl-3-(2-hydroxy-ethyl)-4-nitrocyclohex-1-ene (14) and 1,6-dimethyl-3-(2-benzyloxy-ethyl)-4-nitrocyclohex-1-ene (110)

This Diels-Alder reaction had previously been carried out with similar success to give 14 and the stereochemistry had already been determined. Previous research had fully characterised the product and thus its formation was established by comparison of
NMR spectroscopic data. An obvious important issue of this reaction is the regio- and stereochemistry. The products from this Diels-Alder reaction are likely to result from an *endo* transition state due to favourable secondary orbital overlap as discussed earlier in the introduction. There are two possible regioisomers; the desired isomer 14, and the undesired isomer 111 (Figure 10).

![Figure 10. Possible regioisomers formed by Diels-Alder reaction.](image)

The nitro group obviously has to be in the correct position to enable the formation of the keto group and further development. Previous research within the group had provided analysis by IR spectroscopy which showed the presence of the hydroxy functionality at 3404 cm\(^{-1}\) and nitro functionality at 1545 cm\(^{-1}\). Mass spectroscopy gave further proof by indicating a molecular ion of \(m/z\) 199, corresponding to the product. It is essential for the regiochemistry to be correct, and so detailed \(^1\)H NMR coupling experiments were performed.

A number of \(^1\)H NMR irradiation experiments were performed by the previous researcher.\(^{40}\) The first indication of the formation of the Diels-Alder product is the presence of the doublet signal at 5.50 ppm in the vinylic region which was assigned to 2-H. Irradiation of this signal changed the multiplet at 3.01-2.99 ppm assigned to 3-H. Correspondingly, irradiation of the 3-H signal collapsed the 2-H vinylic signal to a singlet. Both the methyl groups 7-H and 8-H are clearly assigned as a singlet and doublet respectively by \(^1\)H NMR spectroscopy.

A single ddd signal with a chemical shift at 4.67 ppm indicates the proton next to the nitro group. This proton signal at 4.67 ppm appears coupled to the multiplet signal of 3.01-2.99 ppm assigned above as the 3-H proton in the \(^1\)H NMR spectrum. This suggests that the proton at 4.67 ppm can be assigned as 4-H seen in 14. There is little
evidence of the proton at 4.67 ppm coupled to a signal relating to 6-H, which would indicate the nitro group at 5-H seen in II. Further effects were seen at the ddd signal corresponding to 4-H and the signal believed to be 1’-H. Irradiation of the 4-H signal changed the signal assigned to 5-Hb from a quartet to triplet signal. The 4-H signal was simplified to a double doublet signal on irradiation of the multiplet relating to the 5-Ha proton. The multiplet signal corresponding to 1’-H was simplified by irradiation by the 2’-H signal. The 6-H and 5-Hb protons are assigned as a multiplet at 2.26 ppm. The 1’-H gives a multiplet signal at 1.54-1.48 ppm coupled with the 2’-H signal at 3.70 ppm that is next to a hydroxy group.
The spectroscopic evidence suggested the formation of only one regioisomer. Comparison of $^1$H NMR spectrum to the NMR spectrum obtained by the previous researcher confirmed the formation of the same product. The $^{13}$C NMR spectrum which was obtained for the protected species 110 gave only one set of signals, thus confirming the formation of one isomer.
The stereochemistry is less important as the aim would be to convert the nitro group into a ketone group thereby losing the stereochemistry at this position. The two possible stereoisomers for both the Diels-Alder adducts are shown in Figure 11. The structure of the adduct is somewhat flexible, which makes it difficult to assign the stereochemistry from coupling constants, for example between the 3-H and 4-H position. Previous research has given coupling constants for the ddd signal at 4-H in compound 14 at 13.1, 5.8 and 2.9 Hz respectively.\(^{40}\) If the nitro group prefers the equatorial position in the conformation, the dihedral angles between the 4-H, 3-H and 5-H protons would give two small coupling constants and a large coupling constant using the Karplus curve.\(^{177}\) There is perhaps suggestion of one pseudo-ax-pseudo-ax coupling as the large constant at 13.1 Hz and two pseudo-ax-pseudo-eq couplings at 5.8 Hz and 2.9 Hz though further evidence would be required. This would suggest the endo product as the favoured stereoisomer. This can be supported by the theory that endo isomers are the more favoured due to secondary orbital overlap as discussed in the introduction and can be seen in Scheme 61. The \(^1\)H NMR spectra and other data obtained for 14 was compared to that obtained for 110 and established that 110 exhibits the same regio- and stereochemistry (Figure 11). This is due to similarities in the position of signals and their coupling constants.

![Scheme 61. Formation of the Diels-Alder adduct 14 via an endo transition state.](image-url)
2.3.5 Nef reactions

The formation of the cyclohexene ring with the nitro functionality can lead to the desired cyclohexenone through converting the nitro group into a ketone functionality. In the introduction we discussed this reaction the Nef reaction\(^{45}\) for the formation of the ketone group (as shown in Scheme 45).

![Scheme 45. Nef reaction.](image)

A number of alternative synthetic procedures have been devised using the principles developed by Nef yet using more reliable, milder reagents, with better results. Most Nef reactions involve either strongly acidic or strongly basic conditions which would obviously cause problems on a more complex or sensitive substrate rather than the simple nitro alkanes often used.\(^{154,155}\)

A procedure has been developed for the oxidative cleavage of nitronate anions under mild conditions by Palomo et al.\(^{158}\) The procedure initially involves the treatment of a nitroalkene with a suitable base and trialkylchlorosilane to give a trialkylsilylnitronate 114, followed by oxidative cleavage with \(m\)-CPBA resulting in nitroalkane (Scheme 62).

![Scheme 62. Palomo methodology for Nef reaction.](image)

This method was attempted using the unprotected nitro cyclohexene 14 under similar conditions to those given in the literature. However the starting material was treated
with excess base (DBU), TMSCl and m-CPBA due to the presence of the hydroxy group (Scheme 63).

![Scheme 63. Palomo conditions for the Nef reaction on 1,6-dimethyl-3-(2-hydroxy-ethyl)-4-nitrocyclohex-1-ene 14.]

The reaction failed to work, forming a complex mixture of unwanted material where product or starting material may have been present though only in trace amounts. It is possible that the hydroxy group present was reacting with the reagents, causing unwanted side reactions.

![Scheme 64. Palomo methodology for Nef reaction with 1,6-dimethyl-3-(2-benzyl ether)-4-nitrocyclohexene 110.]

The reaction was therefore attempted using the protected nitro cyclohexene substrate under the same conditions as stated in the literature (Scheme 64). However the reaction only gave starting material after work up. This suggested that more forcing conditions were perhaps required in the formation of the desired product. Changing the reaction conditions could enable the necessary reaction to proceed, for example by using a stronger base such as potassium tert-butoxide. However it was decided to attempt an alternative procedure which might provide the desired carbonyl species, as problems may occur upon deprotonation of 110 or 14.

A well documented procedure is the use of aqueous TiCl₃, first reported by McMurray et al.¹⁶⁵ A number of reports appear in the literature of primary and secondary nitro
compounds giving imines when treated with aqueous TiCl₃. Reduction occurs to give the imine which then hydrolyses to give the ketone or aldehyde. A variety of functional groups including ketone, ester, nitrile and hydroxyl have been shown to survive the reaction conditions. There has been some debate concerning the reaction mechanism, however the process probably proceeds via a nitroso intermediate 115 which then tautomerises to an oxime and is further reduced to the imine 116 (Scheme 65).

![Scheme 65. McMurry Nef type reaction using TiCl₃.](image)

The reaction was attempted using conditions stated in the literature on the unprotected nitro species 14. The compound was stirred in THF at room temperature under an inert atmosphere with aqueous TiCl₃ and left for a period of eighteen hours. The reaction provided a complex mixture after work up which contained some starting material yet failed to produce any desired product (Scheme 66).
Scheme 66. The use of TiCl₃ for the conversion of the nitro group to the carbonyl group in 1,6-dimethyl-3-(2-hydroxy-ethyl)-4-nitrocyclohexene 14.

The failure of this reaction may have been due to the acidic nature of the reaction conditions employed causing a variety of side reactions and decomposition. A vast amount of literature has been published on a number of different variants of the Nef reactions, and so another procedure was attempted.

Bartlett describes a procedure which involves the oxidative cleavage of nitronate anions under very mild conditions using tert-butyl hydroperoxide and VO(acac)₂ as a catalyst (Scheme 67).

Scheme 67. Bartlett mechanism for the formation of the carbonyl from the nitro group.

The general procedure in the literature was followed with 14 as substrate and with the use of two equivalents of base due to the hydroxy group (Scheme 68). Deprotonation was carried out in toluene by addition of potassium tert-butoxide as a base. After fifteen minutes a solution of tert-butyl hydroperoxide with VO(acac)₂ as a catalyst in toluene was added with stirring. The reaction was monitored by TLC over a period of three hours with little change to the starting material. This was confirmed when the reaction mixture only gave starting material when worked up and analysed.
1) t-BuOK (2.0 eq), Toluene, RT, 15 mins

2) t-BuOOH (3.5 eq), VO(acac)₂, Toluene, RT, 3 hrs

Scheme 68. Treatment of 1,6-dimethyl-3-(2-hydroxy-ethyl)-4-nitrocyclohexene 14 under Bartlett conditions.

The reaction conditions may have been too mild for the formation of the desired nitronate species.

A final attempt was carried out using an oxidative procedure on a protected nitro species 110 to see if the hydroxy group has any role in the failure of these reactions. A further number of reactions with previous conditions on both substrates 14 and 110 would eventually be required to give an overall conclusion to the effects of the hydroxy group. A procedure by Ihara was initially tried, which converts secondary nitro compounds to ketones by a catalytic amount of TPAP in the presence of NMO and 4 Å MS.\textsuperscript{178}

Following this procedure led only to the recovery of starting material 110, which may suggest that the conditions are again too mild for the conversion as noted in the literature (Scheme 69).

Scheme 69. Attempted conversion of the nitro group of 1,6-dimethyl-3-(2-benzyloxy-ethyl)-4-nitrocyclohexene 114 to ketone using TPAP.
2.3.6 Conclusions

The previous research and the further attempts to carry out the desired Nef type reaction have proved problematic, with numerous attempts and a variety of conditions examined. The complete lack of any of the desired product after work up has suggested a failure to form the nitronate anion necessary for subsequent transformation to the keto group. This may be due to the inability of the bases used to carry out deprotonation through possible steric hindrance. Changing the procedure has only produced conditions apparently too harsh, resulting in decomposition of the starting material, or too mild to allow the reaction to proceed. A vast amount of time could be spent investigating a number of different reactions with changes to the reaction conditions in the Nef reaction, however other possible routes towards the keto group can be examined. An obvious route would be to find other sources of functionality that could be converted into the desired keto function.
2.4 Diels-Alder approach with phenyl vinyl sulfone and phenyl vinyl sulfoxide

2.4.1 Introduction

A Diels-Alder reaction with phenyl vinyl sulfone\(^47\) or phenyl vinyl sulfoxide\(^46\) would provide a cyclohexene with a functionality that could be converted into the desired keto group (Scheme 70).

\[
\text{Dicls\textasciitildeAlder}\quad \begin{array}{c}
\text{HO} \\
\text{HO}
\end{array} \\
\begin{array}{c}
x \\
x
\end{array}
= \begin{array}{c}
\text{S(O)Ph} \\
\text{or} \\
\text{SO}_2\text{Ph}
\end{array}
\]

Scheme 70. Diels-Alder reaction of phenyl vinyl sulfoxide and phenyl sulfone with hydroxy diene.

These Diels-Alder reactions would require a different route for the desired synthetic intermediates. A reaction between the hydroxy diene with the phenyl vinyl sulfoxide should give the cycloadduct 17. Protection of the hydroxy group would be the next step to give 18. Whether protection of the hydroxy group were carried out before the cycloaddition or after the successful addition would have to be decided depending of the success of the respective routes to 18. A subsequent Pummerer reaction could afford 19, then hydrolysis could be attempted to give the desired cyclohexenone 16 (Scheme 71).

\[
\begin{array}{c}
\text{Protection} \\
\rightarrow 17
\end{array} \quad \begin{array}{c}
\text{Protection} \\
\rightarrow 18
\end{array} \\
\begin{array}{c}
\text{Hydrolysis} \\
\rightarrow 16
\end{array}
\]

Scheme 71. Pummerer rearrangement route to give the desired cyclohexenone 16.
If the phenyl vinyl sulfoxide failed as a suitable dienophile, the use of phenyl vinyl sulfone as the dienophile could provide intermediate 116, which could be converted to the sulfoxide through reduction to the sulphide and then oxidation to give the sulfoxide 17 (Scheme 72). However, there could be a difficulty in performing this procedure due to the stability of the sulfone to reducing agents.

Scheme 72. Reduction and the oxidation of sulfone to sulfoxide leading to cyclohexenone 16.

There are other possibilities to investigate including oxidative desulfonylation using MoOPh. This procedure has been shown in the literature to form the desired keto function directly (Scheme 73).

Scheme 73. Oxidation desulfonylation using MoOPh.

An alternative procedure would be to deprotonate the sulfone and carry out nucleophilic attack on species such as disulphides to form a derivative such as 117, which could act as a protected ketone and thus undergo hydrolysis to give the desired ketone (Scheme 74).
2.4.2 Diels-Alder reactions

The attempted reaction of diene 9 with the commercially available dienophiles phenyl vinyl sulfoxide and phenyl vinyl sulfone were first carried out by stirring in toluene under an inert atmosphere at room temperature for twenty-four hours. This resulted in the recovery of starting materials. It was then decided to increase the temperature and pressure in an attempt to force the reaction to take place. Thus the reaction mixtures were next reacted in sealed tubes with increasing temperatures over a period of days. At a temperature of 170 °C in toluene the phenyl vinyl sulfone reaction began to take place, giving product after four days. When the reaction proceeded no further the mixture was purified by flash column chromatography to remove any remaining starting material and unwanted products. The product was identified through IR, NMR and mass spectroscopy as a mixture of isomers, believed to be stereoisomers of 118 rather than regioisomers; this information will be discussed later. The crude reaction mixture still contained starting materials, however increasing the temperature and the length of reaction time further started to cause decomposition (Scheme 75).
Scheme 75. Diels-Alder reaction of hydroxy diene with phenyl vinyl sulphone.

Decomposition was also seen in the Diels-Alder reaction with phenyl vinyl sulfoxide which was attempted under the most forceful conditions of heating at temperatures of over 200 °C using xylene as a solvent in a sealed tube up to 14 days. The reaction gave no product during this reaction but unsurprisingly the starting materials decomposed during this period of time due to the extreme conditions (Scheme 76).

Scheme 76. Diels-Alder reaction of hydroxy diene with phenyl vinyl sulfoxide.

The success of the hydroxy diene in reacting with phenyl vinyl sulphone directed the study to the cycloaddition with the protected diene. The reaction was attempted with diene 108 under the same conditions through heating the starting materials in toluene in a sealed tube at around 170 °C. After 3 days a 40 % purified yield of cycloadduct was obtained. The product was purified by flash column chromatography and identified through IR, NMR and mass spectroscopy, and was believed at this stage to be one stereoisomer with the desired regiochemistry as discussed below (Scheme 77).

Scheme 77. Diels-Alder reaction of benzylxy diene 110 with phenyl vinyl sulphone.
Attempts to use Lewis acids as catalysts\textsuperscript{133, 134, 135} in these reactions proved unsuccessful. Only starting material was recovered after treatment with AlCl\textsubscript{3}\textsuperscript{135, 183} and ZnCl\textsubscript{2}\textsuperscript{135, 184} both commonly used for Diels-Alder reactions (Scheme 78). The reactions were more successful under the forceful thermal conditions.

![Scheme 78. Diels-Alder reaction using Lewis acid catalysts with phenyl vinyl sulfone as the dienophile.](image)

The major concern is obviously the formation of regioisomers that would complicate further reactions with unwanted products and reduce yields. Analysis of 118 by IR indicated the presence of the hydroxy group at 3512 cm\textsuperscript{-1} and a sulfonyle functionality at 1302 and 1142 cm\textsuperscript{-1}. A molecular ion of m/z 294 was observed by mass spectroscopy corresponding to the Diels-Alder product.

Analysis of 123 by IR indicated the presence of aromatic carbon-hydrogen bonds at 3087, 3062 and 3030 cm\textsuperscript{-1} and a sulfonyle functionality at 1365 and 1145 cm\textsuperscript{-1}. A molecular ion of m/z 385 was observed by mass spectroscopy corresponding to the Diels-Alder product.

\textbf{2.4.3 Analysis of 1,6-dimethyl-3-(2-hydroxy-ethyl)-4-benzenesulfonyl-cyclohexene (121 and 122).}

The use of detailed \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopy was necessary to determine the relative regiochemistry present in the compound formed. The \textsuperscript{1}H NMR spectrum suggested the presence of two products formed in a 3:1 ratio, for example by the presence of two signals in the vinylic region for (2-H) corresponding to the major and minor isomers. NMR techniques were then necessary to distinguish between the two possibilities of regioisomers 118 and 120 being product with the same stereochemistry (Figure 12), or \textit{exo/endo} stereoisomers of 118 being present.
The methyl group (8-H) with a doublet signal at 0.96 ppm for the major isomer was coupled to a single proton at 2.18 ppm (6-H). The methyl doublet of the minor isomer (8-H) at 1.03 ppm was coupled to a single proton (6-H) at 2.07 ppm. The proton (6-H) for both the major and minor should be each coupled to two protons 5-Ha and 5-Hb if the isomers are exo and endo diastereomers. This can be seen in the COSY spectrum of the major isomer where two signals at 1.85 ppm (5-Hb) and 1.67 ppm (5-Ha) are coupled to the 6-H signal. The 1H signals assigned to 5-Hb and 5-Ha are also correlated through HNQC data to a CH2 signal (DEPT) at 30.6 ppm. The minor isomer also has the 6-H proton coupled to two signals 5-Hb and 5-Ha at 1.9 and 1.7 ppm respectively. The 5-Ha and 5-Hb are also assigned as a CH2 group at 27.5 ppm in 13C NMR. The correct regiochemistry is proven further by both the major and minor 4-H protons being coupled to the two protons at 5-H and a single proton at 3-H again derived from COSY, DEPT and HNQC NMR analysis.

The next consideration is which of the isomers is endo or and which exo. This is difficult to establish due to the system being flexible, so we can only suggest the possible stereochemistry tentatively using the coupling constants from the NMR data. Comparisons with the NMR spectroscopy for the previous Diels-Alder reaction with nitroethylene to give 14 can act as a guide for the stereochemistry formed. Similarities can be seen between the data for the cycloadducts formed in this reaction. The coupling constants of the ddd signal for 4-H at 3.41 ppm in the major isomer are 10.8, 7.2, 3.6, which may suggest two pseudo ax-ax couplings and one pseudo-ax-pseudo-eq couplings corresponding to an exo conformation. The preferred conformation in which the sulfone and the alcohol functionality are equitorial, the dihedral angles may relate to the coupling constants seen according to the Karplus
The minor isomer has a ddd signal at 3.26 ppm with the coupling constants of 12.8, 4.4 and 2.4 Hz. This suggests one pseudo ax-ax coupling and two pseudo-ax-pseudo-eq couplings that would indicate an endo isomer 122. The conformations provide dihedral angles which possibly relate to the coupling constants according to the Karplus equation. The suggestion that the minor isomer may be the endo isomer 122 and the major isomer exo 121 would be surprising given our earlier results using nitroethylene. The preferential formation of endo isomers is generally the result of secondary orbital overlap as discussed in the introduction, and is we believe observed in our earlier results using nitroethylene. However Diels-Alder reactions at high temperature has a preference for exo stereochemistry, as exo is more thermodynamically stable than the kinetically preferred endo stereochemistry. The stereochemistry requires more investigation before the correct assignments could be determined correctly.

![Diagram of stereoisomers](image)

**Figure 13. The exo 121 and endo 122 stereoisomers.**

Analysis of 1,6-dimethyl-3-(2-benzyl-ox-ethyl)-4-benzenesulfonyl-cyclohexene (123)

NMR analysis including a single set of signals in the $^{13}$C NMR spectrum of the protected Diels-Alder adduct 123 (Figure 14) indicated that only one isomer was formed. Studying the NMR data as for 121/122, including comparisons to the set of signals with the unprotected adduct, would suggest the formation of the product with
the correct regiochemistry. There is a possibility of the stereochemistry being *exo* for the same reasons discussed above, but it still may be *endo* as more evidence would be required.

![Diagram of the exo stereoisomer 123 of the protected Diels-Alder adduct from phenyl vinyl sulfone.](exograph)

**Figure 14.** The *exo* stereoisomer 123 of the protected Diels-Alder adduct from phenyl vinyl sulfone.

### 2.4.4 Oxidative desulfonylation of the cycloadduct using MoOPD

The formation of the Diels-Alder product enabled us to attempt an oxidative desulfonylation as reported in the literature using a molybdenum complex to give the desired ketone functionality. MoOPH contains HMPA, a well known carcinogen, and thus an alternative reagent, called MoOPD, using DMPU instead of HMPA can be used in the same way for the procedure. The first step was to prepare MoOPD, achieved first through reacting molybdenum oxide 124 with hydrogen peroxide with the addition of DMPU, giving yellow crystals of the hydrated MoO₅·DMPU complex 125. Recrystallisation from methanol, dehydration under high vacuum over P₂O₅ then treatment of the resulting MoO₅·DMPU with one equivalent of pyridine in THF gave MoOPD 126 as fine yellow crystals in an overall 21% yield (Scheme 79).

\[
\begin{align*}
1) & \quad 30\% \text{ H}_2\text{O}_2 \text{ (aq)}, \text{ 40°C} \\
2) & \quad \text{DMPU (1 eq), 10°C, recrystallise (MeOH)} \\
3) & \quad 0.5 \text{ mmHg, P}_2\text{O}_5 \\
4) & \quad \text{pyridine (1 eq), THF}
\end{align*}
\]

**Scheme 79.** Synthesis of MoOPD.
The oxidative desulfonylation of 118 and 119 was then attempted following the literature procedure through first deprotonation with LDA at -78 °C in THF, then addition of the MoOPD complex in THF with further stirring. After a period of thirty minutes the mixture was quenched with aqueous sodium sulfite and worked up by pouring into water and extracting with diethyl ether; however only starting material was recovered in each case (Scheme 80).

Scheme 80. Reactions of 118 and its isomer and 119 with MoOPD.

2.4.5 Addition of disulfides to the cycloadducts

Again, the base may not be deprotonating the starting material or perhaps the molybdenum complex is not sufficiently reactive. The problems with this reaction led to attempted deprotonation and reaction with a disulfide to give an acetal species that could undergo subsequent hydrolysis to give a ketone functionality. A literature search provided a number of examples of the addition of disulfides as illustrated in scheme 81 with the formation of 127.\textsuperscript{185}

Scheme 81. Generation of sulfone anion and the reaction with a disulfide.
Thus, on the basis of this procedure the protected sulfonyl cyclohexene would be first treated with a suitable base, and the anion treated with a disulfide to give the acetal. The reaction was first attempted by the treatment of 119 in THF at -78 °C, with LDA. After a period of thirty minutes dimethyl disulfide was added and the reaction mixture was stirred for a further three hours before being left for eighteen hours to warm to room temperature (Scheme 82).

![Diagram](image)

Scheme 82. The attempted addition of dimethyldisulfide to the anion derived from 119.

The reaction failed to produce any desired product after work up, and purification through flash column chromatography only gave recovered starting material. This may again point to a difficulty in deprotonation.

The reaction was attempted again using n-butyl lithium as a base as used in the literature. The protected species 119 was again treated with base at -78 °C in THF and stirred for a period of thirty minutes before the addition of dimethyl disulfide. The reaction was left again for a period of eighteen hours with the reaction mixture warming to room temperature. The reaction again failed with only starting material being recovered. Further attempts were made with warmer conditions at 0 °C for the initial deprotonation, however, this gave similar results. A reaction was also attempted of diphenyl disulfide as the electrophile under the same conditions but with no success. Starting material only was recovered from a complex mixture (Scheme 83).
Scheme 83. Other conditions for the reaction of 119 with dimethyl- and diphenylsulfide species.

The problems may again be due to the formation of the anion and its stability and so the lack of success from trying LDA and n-BuLi at different temperatures and concentrations is not sufficient evidence to dismiss this reaction pathway. A complete run through of a number of bases and conditions to see whether there is a problem in deprotonation would be necessary. Also deprotonating the starting material and treatment with a good electrophile such as MeI could also be a method to prove problems with deprotonation. The problem may be due to steric difficulties and the reactivity of the electrophile used. A different electrophile, such as methanethiosulfonic acid-S-methyl ester, often used in the literature in these reactions, could be attempted. 186
2.4.6 Conclusion

The use of phenylvinyl sulfone as a dienophile has shown to give the desired cycloadduct. However, the yields are obviously lower than anticipated therefore making this route less viable towards the final synthesis of the desired cyclohexenone 16. Unfortunately, phenyl vinyl sulfoxide was unsuccessful as a dienophile which diverted interest away from the Pummerer rearrangement pathway. Attempts to functionalise the sulfone cycloadduct were unsuccessful for similar reasons to the nitro cycloadduct. It seems there may be a difficulty in deprotonation or in the stability of the anion and its subsequent reactivity. This could lead to a number of possible attempts with numerous bases under different conditions thus the scope for this area of research is endless. Also there could be the possibility of attempting a reduction and selective oxidation to give the sulfoxide however literature has often stated the difficulty in this reaction due to the stability of sulfones towards reducing reagents. The low yield of the Diels-Alder reaction and the problems involved in the subsequent functionalisation have meant that other synthetic routes were investigated rather than spending valuable time in an area which has a number of problems.
2.5 Diels-Alder approach with 2-chloroacrylonitrile

2.5.1 Introduction

Another dienophile is 2-chloroacrylonitrile 128, which can be used as a ketene equivalent. The formation of the cyclohexenone 8 from the cycloadduct 129 would then give a viable intermediate that could be converted to give the spirocycle as discussed earlier (Scheme 84).\textsuperscript{187}

Scheme 84. Diels-Alder reaction and hydrolysis using 2-chloroacrylonitrile as a dienophile.

2-Chloroacrylonitrile has been shown in the literature to act as a good dienophile under thermal conditions, reacting with cyclopentadienes and cyclohexadienes, and the cycloadducts have then been hydrolysed to give the desired ketone group (Scheme 85).\textsuperscript{188, 189, 190}

Scheme 85. 2-Chloroacrylonitrile as a dienophile in the literature.
The hydrolysis is usually carried out with either potassium hydroxide in DMSO\textsuperscript{188,191} or with sodium sulfide in refluxing ethanol\textsuperscript{192}.

2.5.2 Diels-Alder reactions

The Diels-Alder reaction was attempted following the literature procedure using thermal conditions by refluxing the hydroxydiene 9 in dry toluene with 2-chloroacrylonitrile under an inert atmosphere for a period of forty-eight hours. Purification of the mixture of starting materials and products gave the Diels-Alder cycloadduct 130 in a 40\% yield, characterised later by NMR and IR spectroscopy. Further attempts, through increasing the reaction times and temperatures including the use of a sealed tube, only caused further decomposition of the starting materials and reduced the yields (Scheme 86).

![Scheme 86. Diels-Alder reaction of hydroxydiene 9 with 2-chloroacrylonitrile to give cycloadduct 130.]

The reaction was attempted again with the protected diene 108 under the same thermal conditions. The reaction mixture was again purified by flash column chromatography to give the cycloadduct 131 in a 39\% yield (Scheme 87).

![Scheme 87. Diels-Alder reaction of benzyloxydiene 110 with 2-chloroacrylonitrile to give cycloadduct 131.]

89
2.5.3 Analysis of 1,6-dimethyl-3-(2-benzyloxy-ethyl)-4-chloro-cyclohexene-4-carbonitrile (131)

The relative success of the cycloaddition must then be determined in the regiochemistry of the isomers formed (Figure 15), as explained earlier, through spectroscopic analysis.

Early $^1$H NMR data suggested the formation of two isomers, which were either regioisomers or stereoisomers of 131. The diene 110 used in the reaction gave an unseparable mixture of cycloadducts in a 2:1 ratio by silica gel chromatography. $^1$H NMR spectroscopy showed the signal for the vinylic proton in the cycloadduct is clearly resolved. Analysis by IR spectroscopy showed the presence of an aromatic ring (3065 and 3032 cm$^{-1}$) and the nitrile group (2285 cm$^{-1}$) for the cycloadducts 131 and 134 (Figure 16). Mass spectroscopy provided a molecular ion at $m/z$ 303 that is consistent with the existence of a cycloadduct. The determination of the stereoisomers was provided through detailed $^1$H and $^{13}$C NMR coupling data. The methyl group 8-H signal was shown to be a clear doublet for the major isomer at 1.19 ppm and 1.09 ppm for the minor isomer. The COSY NMR data showed coupling to 8-H for the 6-H proton at the multiplet signal of 2.42-2.29 ppm for the major isomer and coupling at 2.56-2.46 ppm for the minor isomer. The 6-H signal would need to be coupled to the two protons at 5-H to give the desired regiochemistry. The two 5-H proton signals are the multiplets at 2.42-2.29 and 2.18-2.12 ppm. These signals also correlate through DEPT-135 and HNQC to a CH$_2$ group for the major isomer at 42.5 ppm. The minor isomer has the two 5-H proton signals as a multiplet and a dd at 2.42-2.29 ppm and 1.96 ppm respectively. These are further correlated through DEPT-135 and HNQC.
experiments as a CH$_2$ group at 41.5 ppm. The signals are seen to be coupled to the 5-H signal through COSY-45 NMR indicating the formation of the desired stereoisomers. This is further proven by the identification of the 3-H proton signals at 2.85 and 2.77 ppm for the minor and major isomers respectively which shows clear coupling to the 1'-H protons but no other protons through COSY-45 experiments. The actual configuration of the two isomers has not been completely determined in terms of the stereochemistry of the chloro and nitrile group. Previous literature using 2-chloroacrylonitrile as a dienophile indicated that the chloro group lies endo in the major isomer, though the reasons were not stated for this stereochemistry. However it may be due to possible steric reasons from the size of the chloro group compared to the nitrile group (Figure 16). $^{188,189}$

Through comparisons of the data collected for the protected example 131 and 134, the same regiochemistry was determined for the Diels-Alder adducts from the unprotected hydroxy diene 9. A ratio of 2:1 was observed for the stereoisomers 130 and 135. (Figure 17).

Figure 16. *Endo* 131 and *exo* 134 isomers for the cycloaddition of 2-chloroacrylonitrile and 108.
2.5.4 Hydrolysis of 1,6-dimethyl-3-(2-benzyloxy-ethyl)-4-chloro-cyclohexene-4-carbonitrile (131)

The success of the Diels-Alder reaction led the research to the attempted hydrolysis of the chloro-nitrile unit to give the carbonyl group. This was first attempted using the conditions employed by Evans et al. with sodium sulfide.\(^{190}\) The transformation has been suggested to proceed through a thioketone that is subsequently converted \textit{in situ} to the carbonyl group.

The reaction failed to yield any of the target ketone after purification with only a complex mixture of unidentified compounds being observed (Scheme 88). This may
be due to problems with the stability of the starting material under the conditions used causing unwanted side reactions.

This then led us to try the potassium hydroxide-mediated hydrolysis. This was again attempted on the protected Diels-Alder adduct 131 and was initially carried out at room temperature and heated up to 60 °C over a period of time (Scheme 89).

![Scheme 89. Attempted hydrolysis of 131 using potassium hydroxide.](image)

The reaction again failed to produce any desired product, although starting material was recovered after purification by flash column chromatography. The reaction was again heated at reflux for a period of eighteen hours, however, again only starting material was recovered from the reaction mixture, which also showed some decomposition.

### 2.5.5 Addition of dimethyl malonate to 1,6-dimethyl-3-(2-benzyloxy-ethyl)-4-chloro-cyclohexene-4-carbonitrile (131)

Difficulty in carrying out the hydrolysis, perhaps due to the harshness of the reaction conditions and the unreactivity of the functional group led to analysing the use of the chloro-cyano functionality for other possible routes towards the tetronic acid group. One idea was to perform nucleophilic attack using a dimethyl malonate species 136 onto the nitrile. 193, 194 A hydroxy group under a standard nucleophilic substitution reaction would then replace the chloro group. The aim of cyclising the malonate functionality through displacing the methoxy group to give the tetronic acid 137 could then be attempted (Scheme 90).
Initially attempts were carried out on the protected cyano cycloadduct using a base to deprotonate the dimethyl malonate 136 with the aim for this anion then to react with the nitrile group. The addition would then leave an enamine ready for the next series of reactions. The first attempt used sodium hydride as a base at a temperature of 0 °C to deprotonate the malonate species over forty-five minutes before addition of the nitrile compound. The reaction was kept at 0 °C for a period of two hours before allowing it to warm up to room temperature, and then left for a further eight hours (Scheme 91).
Scheme 91. Attempted addition of dimethyl malonate using sodium hydride as a base to 131.

Purification of the reaction mixture gave no target product with only some starting material recovered from a complex mixture of unwanted material. The reaction was attempted again with the use of a different base to see if deprotonation was a problem with the previous reaction. The dimethyl malonate was treated with LDA at -78 °C then reacted with the nitrile species over six hours, allowing the reaction to warm to 0 °C (Scheme 92).

Scheme 92. Attempted addition of dimethyl malonate using LDA as a base to 131.

The reaction failed to occur, and only starting material was recovered suggesting the difficulty in the nucleophilic attack by the anion on the stable and hindered nitrile group.

A literature search provided very few reports of similar chemistry involving malonates undergoing nucleophilic attack on nitrile groups. Trifluoro-, trichloro- and dichloroacetonitrile have been shown to react with malonic esters to give enamines using a catalytic amount of sodium or an aqueous solution of methanol in the presence of sodium acetate (Scheme 93).
A publication that showed more relevance to our own particular synthetic methodology reported the addition of malonates to simple nitriles under tin (IV) promoted conditions (Scheme 94).\textsuperscript{193}

These conditions were employed on our own nitrile compound to see whether addition could be achieved. One equivalent of the nitrile cycloadduct was reacted with dimethyl malonate in 1,2-dichloroethane and treated with two equivalents of tin (IV) chloride and heated to reflux for one hour under nitrogen. Further treatment with sodium carbonate then purification using flash column chromatography gave only a complex mixture of unidentified material (Scheme 95).

Scheme 93. Addition of malonates to trichloro-, trifluoro-, dichloroacetonitrile.

Scheme 94. Tin promoted addition of malonates to nitriles.

Scheme 95. Attempted tin-promoted addition of dimethyl malonate to 131.
The reaction was repeated with the shorter reaction time of fifteen minutes. Again, only decomposition was observed indicating that the conditions seem too harsh for the more sensitive nitrile compound as compared to the simple nitrile compounds used in the literature.

2.5.6 Conclusion

2-Chloroacrylonitrile again provided a suitable dienophile by reacting with the hydroxydiene 9 and protected diene 110 to give the cycloadducts 130 and 131 respectively, with the desired regiochemistry. The yields of the reactions were again low, suggesting the diene to be unreactive requiring the most forceful conditions with the reactive dienophile. The stability of the dienophile to these high temperatures however proved problematic. The use of Lewis acids as suggested in the literature, may overcome this problem however research was continued in other areas before this was attempted.

The formation of the cycloadduct does enable further functionalisation towards the formation of the cyclohexenone or another intermediate towards the synthesis of the oxaspirobicyclic tetronic acid substituent. The literature gave a clear indication of the potential of 2-chloroacrylonitrile as a ketene equivalent and the formation of ketones from the cycloaddition products has been successfully achieved by hydrolysis. Using these hydrolytic conditions for our substrate however proved unsuccessful due to reasons still not fully understood. Whether the functionalities present in the substrate were undergoing side reactions or sterically hindering the reacting centre would require further investigation.

A more ambitious route was also attempted involving addition of dimethyl malonate to the nitrile group. The reaction again failed, probably the result of the unreactivity of the nitrile group towards nucleophilic attack by the malonate species. Little literature precedence suggests that this is a difficult reaction to perform even on simple nitriles using harsh conditions.

The limited success of this route led to further work being stopped until other routes were thoroughly investigated.
2.6 Diels-Alder reactions with other dienophiles

2.6.1 Introduction

The limited success of nitroethylene, phenyl vinyl sulfone and 2-chloroacrylonitrile in reacting as dienophiles with the hydroxy diene and protected species led us to investigate the use of a number of other possible dienophiles. The aim is to create suitable functionality in the cyclohexene product which can be further reacted to give the tetronic acid substituent or at least act as a ketene equivalent to form the target cyclohexenone intermediate.

2.6.2 Ethyl acrylate

Ethyl acrylate has been proven to be successful dienophile in cycloadditions. The ester group would provide an ideal starting point from which the tetronic acid could be synthesised. A base should deprotonate the cyclohexene ring in the protected cycloadduct 138 at the 4-H position allowing addition to, say acetic anhydride to form intermediate 139. The formation of this intermediate would allow further transformation by hydrolysis to give the hydroxy acid, followed by esterification, then base induced cyclisation. The final steps would involve a deprotection and an oxidation to give the useful derivative of the desired oxaspirobicyclic compound however the control of stereochemistry could prove problematic (Scheme 96).
Scheme 96. Diels-Alder approach using ethyl acrylate as a dienophile.

Ethyl acrylate and diene 9 was thus used in a Diels-Alder reaction employing the same conditions that had proved successful in our previous chemistry. Heating the reaction mixture in a sealed tube in toluene at $170^\circ\text{C}$ for seventy-two hours led to the formation of the product as a mixture of stereo and regioisomers. Purification by flash column chromatography enabled separation of some of the cycloadduct isomers in a 40% yield (Scheme 97). The yield may be lower than anticipated due to polymerisation that occurs with ethyl acrylate at high temperatures.

Scheme 97. Diels-Alder reaction of ethyl acrylate with hydroxy diene 9.
Analysis of the crude mixture by NMR spectroscopy after an initial dry flash column indicated the formation of both the stereoisomers and regioisomers due to the presence of four proton signals in the vinylic region (Figure 18).

Figure 18. Stereo- and regioisomers formed by Diels-Alder reaction with ethyl acrylate.

Further separation by column chromatography gave a mixture of two isomers. Analysis through the use of detailed spectroscopy of the including NMR experiments with COSY and HNQC was necessary to determine the relative regiochemistry. The $^1$H NMR spectrum indicated the presence of two products in 5:2 ratio, e.g. from the presence of two vinylic signals (2-H) at 5.32 ppm and 5.24 ppm. The methyl group (8-H) with a doublet signal at 0.92 ppm for the major isomer is coupled to the multiplet signal for 6-H at 2.50-2.32 ppm. The signal at 6-H is coupled to a single ddd proton signal at 2.70-2.65 ppm. This proton signal correlates to the carbon signal at 44.78 ppm in the $^{13}$C NMR. The DEPT experiment shows this particular carbon to be a positive signal indicating a CH or CH$_3$ group and the higher frequency around 40-50 ppm also indicates a carbon next to an electronegative group such as an ester. This can therefore be assumed to be the 5-H proton next to the ester group. This then suggests the undesired regioisomer as the main product. The COSY spectrum further correlates the 5-H to be coupled to the two protons, 4-Ha and 4-Hb with multiplet signals at 1.99-1.85 ppm and 1.44-1.35 ppm. These $^1$H signals assigned to 4-Ha and 4-Hb are correlated through HNQC data to the CH$_2$ signal (DEPT) at 25.50 ppm. The minor isomer is more difficult to assign but the COSY data indicates the methyl doublet signal at 1.06 ppm coupled to the single proton 6-H within the multiplet signal at 2.56-2.36 ppm. The NMR suggests the 5-H signal also within the multiplet at 2.50-2.36 ppm coupled to two proton signals 4-Ha and 4-Hb at 1.99-1.85 ppm and 1.67-1.50 ppm. The correlation between the 5-H proton and the 6-H is difficult to determine due to both protons in the same multiplet signal at 2.50-2.36 ppm.
However no coupling from the 3-H signal at 2.30 ppm could be seen with a single proton next to the ester group if it was the desired regioisomer. Therefore the major isomer can be assigned as 1,6-dimethyl-3-[2-hydroxy-ethyl]-cyclohexene-5-carboxylic ethyl ester 141 while the minor isomer is assumed to be the stereoisomer though more evidence is required. The next consideration is whether the major isomer has an \textit{endo} or \textit{exo} conformation. This is difficult to establish due to the system being flexible so we can only suggest the possible stereochemistry from the coupling constants in the NMR data. The coupling constants for the ddd signal for the 5-H proton ddd are 13.2, 5.2 and 2.4 Hz. This suggests two pseudo-ax-pseudo-eq couplings and one pseudo ax-ax coupling through association of the coupling constants with the dihedral angles using the Karplus equation.\textsuperscript{177} Therefore we can suggest the \textit{endo} isomer as the major isomer which could be the result of secondary orbital interactions as explained in the introduction. More investigation would be required to assign the definite stereochemistry from this Diels-Alder reaction with certainty.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure19.png}
\caption{Regioisomers 143 and 144 of the Diels-Alder reaction using ethyl acylate as a dienophile.}
\end{figure}

Further attempts at purification using flash chromatography and short path distillation both proved unsuccessful on numerous attempts. Therefore no further chemistry was carried out due to the presence of the unwanted isomer in the reaction mixture.
2.6.3 Methyl α-acetoxyacrylate

The chemistry used earlier with ethyl acrylate suggests other potential dienophiles. Novak et al. describes the synthesis of methyl α-acetoxyacrylate 145 and its subsequent Diels-Alder reaction with butadiene in the presence of pyrogallol as a high boiling solvent. The adduct obtained is used to subsequently form quinic acid 146 (Scheme 98).\(^\text{195}\)

![Scheme 98. The use methyl α-acetoxyacrylate as a dienophile in the formation of quinic acid.](image)

The formation of methyl α-acetoxyacrylate was achieved through refluxing pyruvic acid 147 with acetic anhydride with a catalytic amount of p-toluenesulfonic acid (Scheme 99).

![Scheme 99. Synthesis of methyl α-acetoxyacrylate 145.](image)

The yields proved low due to the difficulty in purification through distillation however enough was produced to allow an attempted Diels-Alder reaction with \((E,E)\)-5-methyl-3,5-heptadien-1-ol 9. The same conditions were employed as suggested in the literature through heating the methyl α-acetoxyacrylate 144 with the hydroxy diene in pyrogallol at 160 °C over a period of days (Scheme 100).
Scheme 100. Attempted Diels-Alder reaction of hydroxy diene with methyl $\alpha$-acetoxyacrylate.

Purification gave only starting material suggesting the reaction should have been repeated at a higher temperature under pressure if there was sufficient time. Failure in this attempt however led us to look at the use of other potential dienophiles.

2.6.4 2-Benzene sulfonyl-acrylic acid methyl ester

The use of phenyl vinyl sulfone and phenyl vinyl sulfoxide as dienophile has been described and shown some success. The use of the same synthetic plan with a similar dienophile containing a sulfone group and an ester group would give the cycloadduct ideal in forming the tetronic acid through chemistry stated earlier (Scheme 101).

Scheme 101. Synthetic route to 5 using a dienophile with a sulfone and ester group.

The dienophile 2-benzenesulfonylacrylic acid methyl ester 153 was first synthesised through a literature procedure of Gipstein and Wilson. The reaction sequence started with the nucleophilic substitution reaction between the sodium salt 149 and methyl-2- chloro propionate 150. Heating the starting materials in ethanol under reflux gave the intermediate 2-benzenesulfonyl-propionic acid 151. This intermediate
was then deprotonated and treated with phenyl selenyl bromide to give the α-(phenylselenyl)-propionate 152, which proved difficult to isolate thus, reducing the yields. The next reaction involved a selenoxide elimination using hydrogen peroxide. Careful temperature control was necessary as the products readily polymerise. The dienophile 2-benzenesulfonylacrylic acid methyl ester 153 was isolated through flash column chromatography in a good yield of 76% and kept under cold conditions. It was used quickly in the subsequent reaction due to concern about its stability (Scheme 102).

Scheme 102. Synthesis of 2-benzenesulfonyl-acrylic acid methyl ester.

The successful synthesis of the dienophile enabled the Diels-Alder reaction to be attempted under the conditions employed earlier. Thus, heating of the (E,E)-5-methyl-3,5-heptadien-1-ol 9 and 2-benzenesulfonyl-acrylic acid methyl ester 153 in toluene in a sealed tube for a period of several days with temperatures ranging from 100 °C to 170 °C were employed. The work up and purification of the reaction mixture resulted only in the recovery of starting material (Scheme 103).
Scheme 103. Attempted Diels-Alder reaction between the hydroxy diene and 2-benzenesulfonyl-
acrylic acid methyl ester.

This evidence of the difficulty of carrying out Diels-Alder reactions with our
unreactive diene, even with potentially reactive dienophiles, has been noted in
previous research. The failure has led us to research into other dienophiles that could
give a useful cycloadduct.

2.6.5 Acrylonitrile

The use of 2-chloroacrylonitrile as a dienophile with its known ability to react with
the \((E,E)-5\)-methyl-3,5-heptadien-1-ol and the protected derivative led us to consider
the use of acrylonitrile 154 as a potential dienophile. Acrylonitrile has already been
shown to act as a ketene equivalent in previous research.\(^\text{188,189}\) This process involves
the chlorination of the nitrile precursor that can then undergo a similar hydrolysis,
indicated earlier (Scheme 104).

Scheme 104. Diels-Alder reaction using acrylonitrile as a dienophile.

The cycloaddition was carried out through the standard procedure of heating the
dienophile with \((E,E)-5\)-methyl-3,5-heptadien-1-ol 9 in a sealed tube in toluene at 170
\(^\circ\text{C}\) for 72 hours (Scheme 105).
Sea1ed Tube, Toluene, 170 °C, 72 hrs

STARTING MATERIAL

Scheme 105. Attempted Diels-Alder reaction of acrylonitrile with the hydroxy diene.

The reaction proved to be unsuccessful as only starting material was recovered. The diene is unreactive proved difficult probably due to the substituents present. The dienophile has to be very reactive and stable in the forceful conditions required to allow a Diels-Alder reaction to proceed.

2.7 Inverse Electron Demand Diels-Alder reaction

2.7.1 Introduction

Previous research led to the formation of an electron poor diene that could in principle undergo the required Diels-Alder reaction to give a cycloadduct with the potential to be converted to the oxaspirobicyclic tetronic acid. Our difficulties in inducing Diels-Alder reactions may be due to the low reactivity of the diene. As an alternative, an electron-poor diene may undergo an inverse electron demand Diels-Alder reaction with an electron-rich dienophile.121, 122, 125, 130

The previous researcher attempted this Diels-Alder reaction using a suitable electron poor diene 155 with the electron rich dienophile tert-butyl vinyl ether 156. However, this reaction failed to give the desired cycloadduct 157 (Scheme 106).40

Scheme 106. The use of tert-butyl vinyl ether with a electron poor diene.
The aim was now to attempt a Diels-Alder reaction using established chemistry by Roush which used a dioxolanone species 58 as the dienophile.\textsuperscript{61b} Chemistry has already been established, described in the introduction, that gives a clear pathway towards derivatives of tetronothiodin with the spirocycle present (Scheme 107). This chemistry can thus be applied with our diene through using the chemistry reported in the literature after the cycloadduct has been formed.

![Scheme 107. Roush synthesis of kijanolide using a dioxolane-4-one species 58 as a dienophile.](image)

2.7.2 Synthesis of diene (155)

The formation of the desired diene 155 was achieved through Wittig chemistry. The diene was obtained through reacting trans-2-methyl-butene with the stabilised ylid. This reaction occurs readily to give the desired diene in a 72\% yield (Scheme 108).\textsuperscript{42}
Scheme 108. Synthesis of \((E,E)\)-methyl-4-methyl-2,4-hexadienoate 155.

The diene was identified after purification using comparisons to previous spectral data. \(^1\)H NMR spectroscopy proved the desired trans-stereochemistry of the newly formed double bond; the signals for 2-H and 3-H each displayed coupling constants of 15 Hz, consistent with trans-stereochemistry.

2.7.3 Synthesis of the dienophile 2-tert-butyl-5-methylene-1,3-dioxolan-4-one (163)

Previous research in this group has successfully reproduced literature procedures for the stereoselective synthesis of \((2R)\)-2-tert-butyl-5-methylene-1,3-dioxolan-4-one 158 (Figure 20). Roush reported a six step reaction sequence to give the required (R)-enantiomer of the desired dioxolanone required for the subsequent Diels-Alder reaction. \(^{71a}\) However, it is only necessary for our research to determine if the reaction will proceed before undertaking a large scale stereoselective synthesis. A simpler synthetic route towards \((2S)\)-2-tert-butyl-5-methylene-1,3-dioxolan-4-one 159 (Figure 20) has been reported by Seebach et al.\(^{71c,197}\) and involved only three steps, giving the (S)-enantiomer or an enantiomeric mixture depending on the stereochemistry of the lactic acid used initially in the synthetic process.

Figure 20. \((2R)\) and \((2S)\) - 2-tert-butyl-5-methylene-1,3-dioxolan-4-one (158 and 159).
A reaction between the diene 155 and a racemic mixture of the dienophile 163 would allow us to determine whether the reaction can give the desired cycloadduct without carrying out any unnecessary reactions. The dioxolanone was synthesised from refluxing racemic lactic acid 160 with pivaldehyde using a catalytic amount of p-toluenesulfonic acid and the azeotropic removal of water, which gave a racemic mixture of 2-tert-butyl-5-methyl-[1,3]dioxolan-4-one 161. After distillation of the product and characterisation by comparisons to published literature data it was correctly identified as the desired product. It was then brominated to give 5-bromo-2-tert-butyl-5-methyl-[1,3]dioxolan-4-one 162. This was achieved through heating the product with NBS in chloroform under reflux and again distilling off the racemic product. Finally, elimination of HBr using triethylamine gave the target 2-tert-butyl-5-methylene-[1,3]dioxolan-4-one 163 in a 33 % yield after purification by silica gel chromatography (Scheme 109).

Scheme 109. Synthesis of racemic 2-tert-butyl-5-methylene-[1,3]dioxolan-4-one 163.

2.7.4 Diels-Alder reaction

Proton NMR spectroscopy confirmed the structure of the racemic mixture of 2-tert-butyl-5-methylene-[1,3]dioxolan-4-one 163, ready for the Diels-Alder reaction with diene 155. The Diels-Alder reaction was carried out under the same conditions used previously where the starting materials were heated, starting at 100 °C and increasing over a period of time to 170 °C in toluene (Scheme 110).
Scheme 110. Attempted Diels-Alder reaction of the diene 155 and the dienophile 163.

After seven days of careful monitoring by TLC no product was seen and this was confirmed when the reaction mixture was finally purified by flash chromatography, returning only starting material. As seen in previous research in our group, similar Diels-Alder reactions have proved difficult, probably due to steric interactions and a requirement for enhanced reactivity of both the starting materials for the reaction to proceed.
2.8 Intramolecular Diels-Alder reaction

2.8.1 Introduction

As mentioned in the introduction another possible route towards the oxaspirobicyclic unit involves an intramolecular Diels-Alder approach. An IMDA reaction has a number of advantages, discussed previously, over the intermolecular methodology, thus it is essential to investigate the possibilities of this route. A synthetic plan would first involve the coupling of the \((E,E)\)-5-methyl-3,5-heptadien-1-ol 9 with an acid derivative containing a suitable unsaturated group to allow an IMDA reaction to occur. This could be achieved for example using propiolic acid 25 to give ester 26, where the subsequent Diels-Alder reaction would provide the bicyclic structure 27 with the appropriate relative stereochemistry. Further functionalisation as discussed previously would lead towards the target molecule 24 (Scheme III).

\[
\begin{align*}
9 + & \text{COOH} & \text{Coupling} & \rightarrow & 26 \\
& \text{COOH} & & & 27 \\
\text{IMDA} & & & \rightarrow & 24
\end{align*}
\]

Scheme III. The use of an IMDA approach towards the target molecule 24.
2.8.2 Synthesis of 5-methyl-hepta-3,5-dienyl-propynoate and IMDA reaction

Utilising established methodology, the formation of the 5-methyl-hepta-3,5-dienyl-propynoate 26 was readily achieved. The hydroxy diene and propiolic acid were stirred at room temperature in dry dichloromethane with the addition of DCC and a catalytic amount of DMAP for sixteen hours (Scheme 112).40

\[
\begin{align*}
\text{9} & \quad \text{HO} \\
\text{1) } & \quad \text{OCC} \\
\text{2) } & \quad \text{DMAP, } \text{OCM, } \text{RT, } 16 \text{ hrs, } 63\% \\
\end{align*}
\]


Purification by flash column chromatography gave 26 in good yield (63%). The product was identified through IR and \(^1\)H NMR spectroscopic analysis and comparison of this data to previously obtained data in our research group.40

The next stage would be to carry out the IMDA reaction to give the bicyclic product. This had been attempted before by heating 26 in toluene under reflux, yet failed to give the desired product. The success of previous Diels-Alder reactions using harsher conditions of pressure and heat led to the reaction being attempted in a sealed tube using toluene as a solvent and heating to 170 °C for thirty six hours (Scheme 113).

\[
\begin{align*}
\text{26} & \quad \text{Sealed Tube, Toluene, } 170 \degree \text{C, } 36 \text{ hrs} \\
& \quad \text{DECOMPOSED} \\
\end{align*}
\]

Scheme 113. Attempted IMDA reaction of propionic acid-5-methyl-hepta-3,5-dienyl 26.

After 36 hours the starting material had failed to give any product. After purification and analysis of spectral data it was concluded that the starting material had decomposed. The 5-methyl-hepta-3,5-dienyl-propynoate 26 was unstable to the
extreme conditions, yet unreactive under less severe conditions. The problems of the stability of the starting material and the necessary chain length and rigidity to allow the necessary orbital overlap in the Diels-Alder reaction may be overcome by using a similar methodology utilising temporary silicon connections.

2.9 Intramolecular Diels-Alder approach using silicon tethers

2.9.1 Introduction

An IMDA approach towards a suitably functionalised bicyclic intermediate was shown earlier to be unsuccessful. One limitation is believed to be the high steric constraints in the transition state. The use of a temporary silicon connection has already shown its effectiveness in 4 + 2 cycloadditions, giving cycloadducts 166 and 167 from trienes formed from vinyl silanes 165 and dienol 164 as discussed earlier in the introduction (Scheme 114).58,148,149,151

\[
\begin{align*}
164 & \xrightarrow{\text{Heat}} 165 \xrightarrow{\text{SiR}_2X} 166 + 167 \\
R = \text{Me} & \quad 2:1 \\
R = \text{Ph} & \quad 1:1 \\
R = \text{t-Bu} & \quad 1:4
\end{align*}
\]

Scheme 114. Diels-Alder reaction of trienes to give the cycloadduct product as a mixture of *endo* 166 and *exo* 167 isomers.

Adaptation of this chemistry utilising the versatility of the silicon-carbon bond would allow the required flexibility in the Diels-Alder precursor to give the desired product 33. The silicon tether could be selectively removed by treatment of the mixture of cycloadducts with H$_2$O$_2$ to give the diol 34. This would provide a route the cyclohexene ring with ketone functionality 16 (Scheme 115).
2.9.2 Addition of silicon tether and cyclisation

The first reaction is the coupling of the diene with dimethylchlorovinyl silane. This was achieved by slow addition of dimethyl silane to triethylamine and the hydroxy diene in toluene. Following the procedure outlined by Sieburth et al. the reaction mixture was filtered, cooled and reduced in volume, and then heated to 190 °C in a sealed tube to allow cyclisation to give 16. The mixture was further cooled and concentrated to allow treatment with 30 % hydrogen peroxide to induce a Tamao oxidation to give the diol. Initial attempts proved unsuccessful, forming a mixture of starting material and low yields of the product, perhaps due to the impurity of the cycloadduct (Scheme 116).
Scheme 116. Attempted synthesis of silicon tethered cycloadducts and oxidation without isolating the intermediates.

It was decided the intermediates required purification after the initial coupling of the tether to allow a clean reaction to proceed. Purification of the reaction mixture through distillation proved unsuccessful, where triene and cycloadduct were unable to be separated.

Purification through the use of flash chromatography obviously proved difficult, as the compound was acid sensitive and hydrolysis could readily occur on the column, so reducing yields. However, using dry flash column techniques, the desired triene 169 was isolated and characterised through $^1$H NMR, $^{13}$C NMR, and IR spectroscopy, and MS (Scheme 117).

Scheme 117. Synthesis of dimethyl-(5-methylhepta-3,5-dienyloxy)-vinylsilane 169.

The pure triene was then cyclised through to the bicyclic product by again heating to 190 $^\circ$C in toluene for a period of twenty-four hours, although unreacted starting
material was still present by TLC analysis. The reaction proved successful in giving
the desired product but purification using flash chromatography reduced the yields
probably due to hydrolysis of the product. Hydrolysis would give the undesired
primary alcohol and oxidised silyl by-product rather than the desired diol. The actual
endo-exo selectivity for the Diels-Alder reaction has no importance as the final
desired cyclohexenone 16 as a keto function would remove the stereochemistry at this
centre. The IMDA reaction gave both endo and exo isomers 170 and 171 respectively
in which the endo isomer was favoured, as already seen in Sieburth's results where
the steric influence of the methyl silanes was small. The use of a sealed tube and
heating for a period of several days allowed the yields to be increased to 67% as the
harsher conditions enabled the unreactive triene to react further (Scheme 118).

Scheme 118. Synthesis of the bicyclic product as endo and exo isomers 170 and 171.

Purification after the cyclisation step seemed likely in reducing the amount of side
reactions such as hydrolysis and therefore proved an effective method in providing
suitable yields to proceed further with the synthesis.

The lower than expected yields of the triene and its bicyclic product when purified led
to the use of a more stable vinyl silane. The treatment of the hydroxy diene with
diphenylchlorovinyl silane 31 under the same conditions as before gave the product
32 which was more stable to the chromatographic conditions. The yields were
correspondingly to be higher in comparison to the dimethyl derivative (Scheme 119).
The triene was successfully isolated and characterised by full spectral analysis including $^1$H NMR, $^{13}$C NMR, MS and IR. The key features of the spectral data included the aromatic C-H signals at 7.62-7.59 ppm and 7.41-7.34 ppm and five signals in the vinylic region at 6.45 ppm, 6.26 ppm, 6.08 ppm, 5.89 ppm and 5.53-5.45 ppm in the proton NMR spectrum consistent with the product. Mass spectrometry provided a molecular ion at 334 that is consistent with the product. The cyclisation reaction was performed as before by heating in a sealed tube in toluene at a temperature of 190 $^\circ$C over several days to give the desired bicyclic product in a 95% yield (Scheme 120).

The main advantage of using an IMDA approach is the reaction works much faster with better yields compared to previous intermolecular Diels-Alder reactions tried earlier. Another advantage is the regiocontrol due to the fact that the desired ring system would be readily formed by constraints imposed by the silicon tether as discussed earlier. Interpretation of the $^1$H NMR and $^{13}$C NMR data suggests that
only two isomers are formed, which would correspond to the stereoisomers 172 and 173. Though the stereochemistry for the bicyclic products is not important for our chemistry, as the stereochemistry would be removed in the subsequent reaction when forming the keto group, it has been assumed be favour the endo product.

2.9.3 Tether cleavage by hydrogen peroxide oxidation

The formation of the bicyclic product with the silicon-carbon bond allowed us to investigate the next stage in the reaction sequence involving an oxidative cleavage to give the functionalised cyclohexene unit. A substantial amount of research has been published by Tamao et al. on this type of reaction. Using the established methodology the reaction was attempted on the bicyclic adducts. The reaction was carried out under a variety of conditions with the aim of producing the desired product with the highest yield (Scheme 121).

![Scheme 121. Oxidative cleavage of the bicyclic products to give 1,6-dimethyl-3-[2-(hydroxy)ethyl]-cyclohexen-4-ol.](image)

The reaction of 33 or 168 proved successful with the 1,6-dimethyl-3-[2-(hydroxy)ethyl]-cyclohexen-4-ol 34 isolated after purification using flash column chromatography. This product was fully characterised as two isomers by NMR and IR spectroscopy and MS; the analysis discussed below. A table of results (Table 2) clearly shows the variety of conditions employed including the oxidant, additive, solvent, temperature and reaction times.
<table>
<thead>
<tr>
<th>Starting material</th>
<th>Oxidant (eq.)</th>
<th>Additive (eq.)</th>
<th>Solvent</th>
<th>Temp, °C (Time, h)</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>MCPBA (2.5)</td>
<td>KHF₂ (2)</td>
<td>DMF</td>
<td>rt, (2)</td>
<td>0</td>
</tr>
<tr>
<td>168</td>
<td>MCPBA (3.5)</td>
<td>KHF₂ (2)</td>
<td>DMF</td>
<td>rt, (18)</td>
<td>0</td>
</tr>
<tr>
<td>33</td>
<td>30 % H₂O₂</td>
<td>KHF₂ (2)</td>
<td>DMF</td>
<td>60, (7)</td>
<td>52</td>
</tr>
<tr>
<td>33</td>
<td>30 % H₂O₂</td>
<td>KHCO₃ (1)</td>
<td>MeOH/THF</td>
<td>Reflux, (4)</td>
<td>78</td>
</tr>
<tr>
<td>168</td>
<td>30 % H₂O₂</td>
<td>KHCO₃ (1)</td>
<td>MeOH/THF</td>
<td>Reflux, (4)</td>
<td>57</td>
</tr>
<tr>
<td>33</td>
<td>30 % H₂O₂</td>
<td>KHCO₃ (1)</td>
<td>MeOH/THF</td>
<td>Reflux, (18)</td>
<td>0</td>
</tr>
<tr>
<td>168</td>
<td>30 % H₂O₂</td>
<td>NaHCO₃ (1)</td>
<td>MeOH/THF</td>
<td>Reflux, (4)</td>
<td>49</td>
</tr>
</tbody>
</table>

Table 2. Results of oxidative cleavage of 33 and 168 using different oxidants, additives, solvents and reaction times to give 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol 34.

The results show that the most effective procedure involved heating under reflux the silyl bicyclic starting material 33 in 30 % hydrogen peroxide, using a 50 % mixture of methanol and tetrahydrofuran with potassium carbonate as the additive. Heating was maintained for a period of four hours to give 34 in a yield of 78 % after purification. These harsh conditions gave the necessary cleavage and did not cause decomposition of the starting material, however, leaving the reaction for longer periods lead to significant amounts of decomposition. It was also seen that the diphenyl-silyl bicyclic adduct 33 proved more successful in providing higher yields of 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol 34. The m-CPBA oxidation proved ineffective for both the bicyclic substrates. Different additives and lower reaction temperatures in DMF only resulted in lower yields of the product.

2.9.4 Analysis of 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol (34)

The IMDA reaction allows the formation only of the desired regiochemistry, and therefore only the stereochemistry needs to be assigned for the mixture of products. Evidence for the formation of the product 34 was obtained using IR, ¹H NMR and ¹³C NMR spectroscopy and MS.

The IR spectrum contained signals at 3332 cm⁻¹ and 1660 cm⁻¹ assignable to the hydroxy stretch and the carbon double bond respectively. A molecular ion of m/z 171 was observed by mass spectrometry data corresponding to the desired 34.

This data closely correlated to the data for the previously described cycloadducts.
\(^1\)H NMR spectroscopy showed two signals present at 5.30 ppm and 5.05 ppm corresponding to the vinylic 2-H for the two isomers. The four vinylic carbons at 138.35, 137.53, 124.46 and 124.33 ppm were present in the \(^{13}\)C NMR spectrum for C-1 and C-2 for the two isomers. The cyclohexene was identified further by the presence of two doublet signals at 1.07 and 1.05 ppm in \(^1\)H NMR spectrum corresponding to 8-H methyl groups of each of the isomers.

The stereochemistry at C-4 has little relevance for our synthetic route though it can suggested using previous ideas discussed earlier when using the dienophiles nitroethylene and phenyl vinyl sulfone. The clear ddd signal at 4.00 ppm corresponding to the 4-H for the major isomer has coupling constants of 11.2, 5.6, and 3.6 Hz. This may suggest one pseudo-ax-ax coupling and two pseudo-ax-pseudo-eq couplings, which could correspond to an \textit{endo} isomer (Figure 21).

![Figure 21](image)

Figure 21. Analysis of 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol gives \textit{endo} 174 and \textit{exo} 175 isomers in a 5:4 ratio.

Integration of the \(^1\)H NMR signals established the isomer ratio as 5:4 favouring the major isomer, similar to the ratio of the starting material.
2.10 Protection of the primary hydroxy group in 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol

2.10.1 Introduction

The formation of 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol enables the synthesis to proceed towards the cyclohexenone target compound. It is therefore necessary to protect the primary hydroxy group to allow the secondary hydroxy group at C-4 to be oxidised and then functionalised further without any side reactions occurring at the other hydroxy position. There are numerous procedures documented for the protection of hydroxy groups however a selective protection would be required.

2.10.2 Protection of primary hydroxy group using pivaloyl chloride

A well documented procedure that gives protection to primary hydroxy groups in the presence of one or more secondary hydroxy groups is the acylation of the hydroxy group using pivaloyl chloride to give an ester. This can be seen in the following example in the selective protection of 176 to give 177 in high yield (Scheme 122).198

Following a literature procedure the 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol was stirred in dry pyridine and dry dichloromethane under nitrogen at 0 °C before the addition of the pivaloyl chloride and reacted for eighteen hours.198

After purification by flash chromatography the isomers 178 were isolated in a 48 % yield. Full characterisation was obtained through IR, 1H NMR and 13C NMR spectroscopy and MS, which identified the product as the two isomers of 178 in a 2:1 ratio favouring the major isomer (Scheme 123). The ratio of 2:1 of the product has
changed from the starting material as some product and starting material present in the reaction mixture was lost when purified.

Scheme 123. Protection of 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol using pivaloyl chloride.

The yield was disappointing for what was documented as an efficient protection method, and so other possible methods of protection of the hydroxy group were investigated. The formation of benzyl ethers has been often used as a form of protection for hydroxy groups. Benzyl ethers are stable under a variety of conditions including attack from a number of oxidising agents, and there are also a number of established procedures for their deprotection.\(^\text{40}\),\(^\text{173}\)

2.10.3 Protection of primary hydroxy group using benzyl bromide

Using known reaction conditions the 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol 34 was first treated with sodium hydride at \(0°C\) for a period of forty-five minutes in dry THF to induce deprotonation.\(^\text{173}\) The benzyl bromide was then carefully added and the reaction was stirred for a further four hours at room temperature (Scheme 124).

Scheme 124. Protection of 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol using benzyl bromide.
After purification by flash chromatography a yield of 72% was achieved for the isomers 179 of 1,6-dimethyl-5-[2-(benzyloxy)-ethyl]-cyclohexen-4-ol and characterised through $^1$H NMR, $^{13}$C NMR, IR and mass spectrometry. The yields proved variable and the purification of the desired product was often difficult due to the formation of other unwanted products. These unwanted side products were often the result of deprotonation on the secondary hydroxy group resulting in the protection of this group rather than the primary hydroxy group or deprotection of both the hydroxy groups. A number of alternative reaction conditions were attempted with the use of other bases, solvents, temperatures and reaction times. These still failed to give reaction conditions suitable to provide a selective protection of the primary hydroxy group without protection of the secondary group. These results suggested the ease of which the secondary hydroxy group can be deprotonated resulting in poor selectivity.

2.10.4 Protection of primary hydroxy group through O-silylation

The formation of silyl ethers, especially the more sterically demanding variants, is a standard method for protecting alcohols. Silyl ethers are useful for a number of reasons including being able to be synthesized under simpler conditions and stable to a number of reaction conditions. These reaction conditions include mild acids, base hydrolysis, organolithium and Grignard reagents, oxidations and reductions.

A popular bulky general purpose silyl protecting group is the tert-butyl dimethyl silyl group and it has been shown to react faster with primary than secondary alcohols as seen in the protection of 180 to give 181 in the above example (Scheme 125). In our case the protection was carried out by the addition of 2.5 equivalents of imidazole to 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol in dry DMF at room temperature. After stirring for a few minutes of 1.2 equivalents of $t$-
butyldimethylsilylchloride was carefully added and the mixture stirred for a further two hours before the reaction was quenched (Scheme 126).

Scheme 126. Protection of 1,6-dimethyl-3-[2-(hydroxy)ethyl]-cyclohexen-4-ol using TBDMSCI.

After purification by flash column chromatography compound 182 was isolated in a yield of 64% was isolated as a mixture isomers in a 10:9 ratio favouring the endo isomer. This was further established through spectroscopic analysis including $^1$H NMR, $^{13}$C NMR, and IR spectroscopy and MS. The key features include the two vinylic signals at 5.26 ppm and 5.02 ppm for the 2-H in both isomers in the $^1$H NMR spectrum. The t-butyl protons are present in the $^1$H NMR spectrum as a pair of signals at 0.92 ppm and 0.91 ppm correlating to the two protected isomers. The molecular ion of $m/z$ 284 by mass spectroscopy confirmed the product structure.

The results were promising, although the yield was lower than anticipated for such a standard procedure, known to give high yields for other alcohols. This may be the result of some loss through purification through flash chromatography with a suggestion that maybe the protecting group is more acid labile than anticipated. Therefore another acid stable protecting group was used to see if yields could be improved.

The next obvious choice for this would be to use tert-butyldiphenylsilyl protecting group first reported by Hanessian and Levalee which was proven to be more stable to acid hydrolysis. As a large bulky group it would be likely to provide the necessary selectivity to protect the primary alcohol in the presence of secondary alcohols, as seen for the reaction of 183 to give 184 as the product shown in the following example (Scheme 127).
The protection of 34 was achieved by addition of the imidazole (2.5 eq.) with the 1,2-dimethyl-5-[2-(hydroxy)-ethyl]-cyclohexen-4-ol in dry DMF with continued stirring at 0°C for thirty minutes. The tert-butyl diphenylsilyl chloride was then added and the reaction warmed to room temperature over sixteen hours before the reaction was quenched and purified by flash column chromatography. A yield of 86% was achieved for the formation of 185 as a mixture of isomers in a ratio of 10:9 ratio (Scheme 128).

This protection thus gives the necessary selectivity and yield required in the synthetic route. The product was fully characterised by spectroscopic analysis including ^1H NMR, ^13C NMR, IR and mass spectrometry.

2.10.5 Analysis of 1,6-dimethyl-3-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-cyclohexen-4-ol

It is essential that the protection has occurred on the primary hydroxy group rather than the secondary group or both hydroxy groups. Protection of 34 with tert-butyl diphenylsilyl chloride to give 1,6-dimethyl-5-[2-(hydroxy)-ethyl]-cyclohexen-4-
ol gave the best yields making it the obvious choice to give detailed spectroscopic analysis.

The IR spectrum contained signals at 3385 cm\(^{-1}\), 3070 cm\(^{-1}\), 1660 cm\(^{-1}\) and 1241 cm\(^{-1}\). Assignable to the hydroxy group, aromatic C-H, alkene double bond and silicon-carbon bond respectively. A molecular ion of m/z 409 was observed in the mass spectrum corresponding to the 1,6-dimethyl-3-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-cyclohexen-4-ol cation.

The spectra obtained were closely related to the previous cycloadduct spectroscopic data and enabled the characterisation of the mixture 185. \(^1\)H NMR spectroscopy identified the product, with the signals present at 5.15 ppm and 4.95 ppm corresponding to the vinylic 2-H for the two isomers. The four vinylic carbons at 138.76, 138.03, 124.69, 124.54 ppm were present in \(^{13}\)C NMR spectrum for C-1 and C-2 in both isomers. \(^1\)H NMR spectroscopy gave signals at 7.65-7.59 ppm and 7.38-7.27 ppm corresponding to the 10 aromatic C-H indicating the presence of the phenyl groups. This is also consistent with the signals at 1.00-96 ppm in the \(^1\)H NMR spectrum, corresponding to the tert-butyl group in both isomers. The \(^{13}\)C NMR analysis gave the signals at 69.41 ppm and 69.26 ppm for C-4 corresponding to the signals at 3.98 ppm and 3.82-3.69 ppm for H-4 in the \(^1\)H NMR spectrum for both isomers.

Comparisons of the 2'-H signal in the \(^1\)H NMR spectrum and the C-2' signal in the \(^{13}\)C NMR spectrum to the corresponding data of 174 and 175 show a chemical shift due to the protection of the primary hydroxy group. The 2'-H signals in the \(^1\)H NMR spectrum at 3.82-3.69 ppm relates to signals for 2'-C at 63.81 ppm and 63.62 ppm in the \(^{13}\)C NMR spectrum for both isomers 187 and 186 respectively. This differs from the signals 61.67 and 61.52 ppm in the \(^{13}\)C NMR spectrum for 174 and 175 respectively to suggest this protection of the primary hydroxy group. The integration of the signals and the relevant coupling constants compared to the previous analysis shows the mixture as a pair of endo 186 and exo 187 isomers in a 10:9 ratio (Figure 22).
Figure 22. Analysis of 1,6-dimethyl-3-[2-(tert-butyl-diphenyl-silanoxy)-ethyl]-cyclohexen-4-ol as endo 186 and exo 187 isomers.
2.10.6 Conclusion

There are numerous procedures to protect a hydroxy group published in the literature. The attempts used all proved successful in some degree with yield and selectivity obviously being the major concern. The use of pivaloyl chloride in forming the ester gives the correct selectivity in reacting with the primary hydroxy group rather than the secondary group, however the yield was lower than anticipated. The formation of benzyl ethers through the treatment of the alcohols with base and benzyl bromide again proves useful with some good yields, however selectivity often proved problematic. The protection can occur on the secondary hydroxy group instead of the primary hydroxy group giving a mixture of isomers that are difficult to separate. The best results proved to be with the formation of the silyl ethers using well established methods with both tert-butyldimethylsilyl chloride and tert-butyldiphenylsilyl chloride. The latter gave the best results with the highest yields and complete selectivity with the protection only occurring on the primary hydroxy group. This probably due to the fact the tert-Butyldiphenylsilyl protecting group is very stable under a number of conditions and very bulky making it very difficult for protection to occur on the secondary hydroxy group.
2.11 Oxidation of the secondary hydroxy group

2.11.1 Introduction

There are a number of possible methods for the oxidation of the secondary alcohols to give the ketone functionality. The reaction involves the loss of hydrogen and a number of reagents can be attempted to allow this oxidation to proceed even on unstable or unreactive molecules.\(^\text{201}\)

2.11.2 Pyridium chlorochromate and dichromate

Reagents that have proven to be successful in oxidising secondary alcohols to ketones in good yields are pyridinium chlorochromate\(^\text{202} 188\) and pyridinium dichromate\(^\text{203} 189\) that are commercially available or can be synthesised in the laboratory (Scheme 129).

\[
\text{Scheme 129. Synthesis of PCC and PDC.}
\]

The mechanism is related to that already established for the Jones reagent.\(^\text{204}\) This is a powerful oxidant that is made \textit{in situ} by the reaction of \(\text{H}_2\text{O}\) and chromic acid normally in the presence of sulfuric acid. The mechanism for a PCC oxidation involves the formation of a complex between the alcohol and the chromium (VI) reagent, known as a chromate ester 190. The ester then breaks down to give the carbonyl compound and a reduced chromium (IV) species 191 (Scheme 130).\(^\text{202b}\)

\[
\text{Scheme 130. Mechanism of oxidation using PCC.}
\]
The reaction was carried out on all the protected cycloadducts 35 with varied success using PCC or PDC as the oxidant (Scheme 131). Reaction with 1.5 eq. of PDC for sixteen hours gave the protected ketones 16 in fair to excellent yields ranging from 40-89%. PCC was unsuccessful for the oxidation of the pivaloyl-protected alcohol 168. These results are shown on the following table (Table 3) and explained in more detail in subsequent paragraphs.

Scheme 131. Oxidation of protected cyclohexen-4-ol using PCC or PDC.

<table>
<thead>
<tr>
<th>Alcohol 35 (No.)</th>
<th>Protecting Group (PG-)</th>
<th>Ratio (Isomers)</th>
<th>Oxidant (1.5 eq.)</th>
<th>Ketone 16 (No.)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>178</td>
<td>(CH₃)₂CO-</td>
<td>2:1</td>
<td>PCC</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>179</td>
<td>Bn-</td>
<td>10:8</td>
<td>PDC</td>
<td>192</td>
<td>55</td>
</tr>
<tr>
<td>182</td>
<td>TBDMS-</td>
<td>10:9</td>
<td>PDC</td>
<td>193</td>
<td>40</td>
</tr>
<tr>
<td>185</td>
<td>TBDPS-</td>
<td>10:9</td>
<td>PDC</td>
<td>194</td>
<td>89</td>
</tr>
</tbody>
</table>

Table 3. Oxidation results using various alcohols and oxidants.

The first attempted oxidation with 178 as the substrate using PCC resulted in decomposition of the starting material suggesting the conditions maybe too harsh for the protected alcohol 178.

Repeating the procedure on the other protected species provided better results. Treatment of 179 under the same conditions except using the non-acidic PDC gave a yield of desired product 192 of around 55%. Full characterisation of the cyclohexenone 192 was obtained by ¹H NMR, ¹³C NMR and IR and MS. The yield was lower than anticipated which may be due to purification problems, complicated by the inability to routinely prepare the starting alcohol free of impurities as discussed
above. Difficulties in the use of chromium reagents lie in the problematic and messy work up procedure where product could be easily lost during its isolation. Silyl protected species have been proven to be stable under PDC oxidation conditions, which led to the attempted oxidation of 182 and 185. The TBDMS protected alcohol was first reacted under the standard conditions with PDC and gave the desired cyclohexenone product 193 in a yield of 40% which again was lower than anticipated. The reasons for this may again be poor stability of the starting material or product toward the oxidation conditions, or problems in isolating the target ketone. The reaction was attempted using the more stable TBDPS-protected starting material 185. The same conditions were employed and found to give the desired product 194 with a very good yield of 89%. This suggests that the TBDPS ether is more stable to the reaction conditions. The number of other procedures noted in the literature for oxidations made it necessary to compare these to see if any improvements could be made to the overall yield.

2.11.3 Swern oxidation

The use of activated dimethyl sulphoxide (DMSO) as an oxidant was investigated by Swern et al.\textsuperscript{70a}. Swern showed that DMSO can be reacted with a number of electrophilic reagents such as trifluoroacetic anhydride,\textsuperscript{70b} thionyl chloride,\textsuperscript{70c} and oxalyl chloride\textsuperscript{70d} to activate the sulfur atom toward nucleophilic attack. The use of this activated DMSO was found to be effective in selective oxidations of various alcohols to the corresponding carbonyl compounds in good yields. An example is given in Scheme 132.\textsuperscript{201}

![Scheme 132. Oxidation of hydroxy group using Swern conditions.](image)

This mechanism initially involves the reaction between DMSO and, for example, oxalyl chloride 195 to give the activated species 196. The positively charged sulfur
can then undergo a nucleophilic attack from the alcohol. The TEA deprotonates the intermediate 197 which then leads to intramolecular proton abstraction 198 to give the carbonyl compound (Scheme 133).  

Scheme 133. Mechanism of the Swern oxidation.

Initial reaction of the oxalyl chloride and DMSO is normally carried out at −75 °C. The activated complex formed is unstable above −40 °C therefore the alcohol is normally added and allowed to react between −50 °C to −60 °C. Addition of TEA and raising the reaction temperature to 0 °C, then to room temperature, liberates the carbonyl product via the intermediate ylid species 198.

Scheme 134. Swern oxidation with 179 to give the cyclohexenone 192.

The Swern Oxidation gave the desired product 192 with a 50 % yield after purification by flash column chromatography. This yield proved comparable to previous yields using PDC for the alcohol 179. The yield again is lower than
expected, which may be related some impurity in the starting material as discussed earlier. There may also be a problem with the stability of the product to the reaction conditions and isolation.

2.11.4 Dess Martin periodinane

A mild and selective reagent called Dess-Martin periodinane 200 that will not oxidise sulfides and alkenes was first reported by Dess and Martin. Dess-Martin periodinane can be prepared readily from O-iodobenzoic acid 199, potassium bromate and acetic anhydride. It has been proven to be successful in the oxidation of a number of alcohols to aldehydes and ketones (Scheme 135) avoiding problems such as long reaction times, work up problems and the use of large excesses of oxidant as seen in other examples.

The mechanism is not fully understood but involves first an exchange of an acetate ligand on the iodine with the alcohol. The intermediate will then collapse to form the carbonyl compound, a reduced iodine compound and acetic acid.

The reaction was carried out following a procedure in the literature where by a solution of the 1,6-dimethyl-3-[2-(benzyloxy)-ethyl]-cyclohexen-4-ol in DCM was slowly added to a suspension of Dess-Martin periodinane in DCM at room temperature and stirred for an hour. After work-up and purification by flash column chromatography, 192 was obtained in a yield of 60 % (Scheme 136).
Scheme 136. Dess-Martin Periodinane oxidation with 1,6-dimethyl-3-[2-(benzyloxyl)-ethyl]-cyclohexen-4-ol to give 192.

The increased yield for alcohol 179 was promising compared to other oxidants with this substrate. However the yield was still much lower than the silyl protected alcohol 185 when using PDC. Further investigations with Dess-Martin periodinane were not undertaken.

2.11.5 Tetra-n-propylammonium perruthenate (TPAP)

The transformation of an alcohol to the carbonyl group may be carried out using a number of different procedures, as outlined above, but they still have problems such as unwanted side reactions and crude work up procedures, and thus modern developments have been established. A catalytic alternative was developed by Ley et al. 159 based on ruthenium catalysts that were proven to be reliable and easy to use.

The catalytic oxidants tetra-n-butylammonium perruthenate (TBAP) and tetra-n-propyl ammonium perruthenate (TPAP) with the addition of NMO as a co-oxidant will oxidise alcohols to carbonyl compounds. There is little known about the mechanism of the alcohol oxidation, but the structure of TPAP is shown below (Figure 23), where the ruthenium is at oxidation state 7. It is believed that the NMO re-oxidises the Ru $^+$ species back to oxidation state 7.

Figure 23. Structure of TPAP.
This methodology can give high yields of carbonyl compounds from a number of different alcohols, as shown in the following example (Scheme 137).

Scheme 137. The use of TPAP as an oxidant for the hydroxy group.

The use of the commercially available TPAP on both the 1,6-dimethyl-3-[2-(benzyloxy)-ethyl]-cyclohexen-4-ol 179 and 1,6-dimethyl-3-[2-((tert-butyl-diphenylsilanoyl)-ethyl]-cyclohexen-4-ol 185 was carried out under the standard conditions. A solution of the alcohol in dry DCM containing 4 Å molecular sieves and NMO (1.5 eq.) was stirred at room temperature under nitrogen. A catalytic amount of TPAP was added and stirred for a further 8 hours. The reaction was quenched, worked up and purified by flash column chromatography to give the desired cyclohexenones 192 and 194 from the respective alcohols (Scheme 138).

Scheme 138. Oxidation of alcohols 179 and 185 using TPAP to give cyclohexenones 192 and 194.

The benzyl protected species gave a yield of 50 %, which was comparable to previous results. The low yield problems may due to purity and stability of the initial starting
material as before. The use of the TBDPS-protected alcohol gives a much more favourable yield of 73%.

2.11.6 Analysis of 2-[2-(benzyloxy)-ethyl]- 4,5-dimethyl-cyclohex-3-enone (192)

The characterisation of 2-[2-(benzyloxy)-ethyl]- 4,5-dimethyl-cyclohex-3-enone 192 (Figure 24), which was the first cyclohexenone to be synthesised, is discussed below. Similar analysis of spectral data allowed the identification of 2-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]- 4,5-dimethyl-cyclohex-3-enone 193 and 2-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]- 4,5-dimethyl-cyclohex-3-enone 194. The analysis was carried out using NMR, and IR spectroscopy and MS. The first obvious identification for the formation of the desired product is the formation of one product from a mixture of isomers, as the stereochemistry is lost at the hydroxy group at C-4 position in both exo and endo isomers.

Analysis of IR indicated the presence of the aromatic C-H with signals at 3062 and 3029 cm⁻¹, a ketone signal at 1716 cm⁻¹, an alkene double bond signal at 1676 cm⁻¹ and carbon oxygen bond signal at 1100 cm⁻¹. A molecular ion of \( m/z \) 258 was observed by mass spectrometry, corresponding to the desired 2-[2-(benzyloxy)-ethyl]- 4,5-dimethyl-cyclohex-3-enone.

\(^1\)H NMR and \(^{13}\)C NMR spectra of 192 were compared to starting material data to establish positive identification of the formation of product and used further to compare the similar synthesised cyclohexenones 193 and 194. The first signal to be established was the signal at 5.35 ppm in the \(^1\)H NMR spectrum which correlated to the 3-H as a vinylic proton further proven by the \(^{13}\)C NMR signals at 139.58 and 123.65 ppm for the C-4 and C-3 alkene bond. The ketone C-1 can be seen clearly in the \(^{13}\)C NMR spectrum with a signal at 210.76 ppm.

The aromatic C-H signal at 7.33-7.28 ppm and the methylene doublet signal at 4.48 ppm further correlated to \(^{13}\)C NMR data give the presence of the protecting benzyl group. The ddd signal at 2.70 ppm with the coupling constants of 13.2, 6.4, 0.4 Hz and double doublet at 2.25 ppm with coupling constants 13.2 and 4.4 Hz correspond to the two 6-H protons. These protons are shown to be coupled to the multiplet signal for 5-H at 2.50 ppm by HMQC analysis. Further analysis by a DEPT -135 experiment confirms the presence of a CH₂ group at 46.49 ppm in the \(^{13}\)C NMR. The CH₂ group
for C-1' corresponds to the DEPT-135 at 31.66 ppm in the $^{13}$C NMR and proton signals of a double triplet at 2.08 ppm with coupling constants at 12.8 and 6.4 Hz and a multiplet at 1.70 ppm for 1'-H. This splitting of 1'-H occurs due to the adjacent protons of 2'-H, clearly seen as a double triplet at 3.55 ppm with coupling constants at 6.4 and 1.2 Hz and the other multiplet at 2.98 ppm for the 2-H proton. The methyl groups are identified at 1.75 ppm as a single signal for 7-H and a doublet at 1.01 ppm for 8-H. These signals are further correlated in the $^{13}$C NMR at 21.22 ppm and 19.95 ppm respectively for the C-7 and C-8 by the HMQC spectrum.

![Chemical structure](image)

Figure 24. Characterisation of 4,5-dimethyl-2-[2-(benzyloxy)-ethyl]-cyclohex-3-ene 192.
2.11.7 Conclusion

The final stage in the formation of the first target cyclohexenone species can be readily achieved through a number of standard procedures by oxidising the hydroxy groups on the selectively protected alcohols. The pivaloyl protected species proved to be unsuccessful using acidic conditions employed with PCC suggesting it to be a poor protecting group in acidic conditions for the necessary conversion of the secondary alcohol to the ketone. A number of other conditions were employed including the use of PDC, Swern, Dess Martin and TPAP were used with average to very good conversion of the secondary alcohol to the ketone group. The benzyl protected derivative proved consistently to give yields of around 50-60% in the above oxidation reactions which is lower than anticipated for these well documented procedures that include mild reaction conditions. This suggests a problem resulting from the starting material, which may be due to the stability though this is unlikely as it is well documented that the benzyl group is a stable protecting group for this transformation. Trace amounts of aldehyde were found after purification which suggested the presence of unprotected compound in the starting material. The selectively protected alcohol 179 was difficult to prepare in pure form which led to unacceptably low yields in the oxidation step. This then led to the use of the silyl protected cyclohexenols which proved the most successful substrates for oxidation. The tert-butyl dimethyl silyl species gave a good yield of 64% of the ketone with PDC as the oxidant while tert-butyl diphenyl silyl proved even more suitable with a yield of 87% of ketone using the same conditions. The use of TPAP with the tert-butyl diphenyl silyl cyclohexenol also gave good yields of around 70%. The ease with which the silyl protected starting materials, especially the diphenyl substrate, can be formed in pure form and their stability under the oxidation conditions make them ideal candidates for the formation of the cyclohexenone.
2.12 Reactions of 2-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone and 2-[2-(benzylxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone with trimethylsilyl cyanide

2.12.1 Introduction

The formation of the cyclohexenone allows the original proposal to be attempted by the reaction with trimethylsilyl cyanide to give a TMS cyanohydrin 20. Assuming the correct stereochemistry is achieved it would allow a DCC-DMAP mediated esterification with acetoxyacetic acid 21 to give an intermediate 22 ready to cyclise and give the desired tetronic acid (Scheme 139).

![Scheme 139. Synthetic route through cyanohydrin intermediate.](image)

The use of TMSCN has the distinct advantage compared to the use of hydrogen cyanide by forming trimethylsilyl cyanohydrin ethers with ketones, which are stable cyanohydrin equivalents. An example is shown in Scheme 140 where the TMS cyanohydrin of cyclohexenone is formed in an excellent yield. The procedure has also been shown to react well with hindered ketones in good yields.
Scheme 140. Treatment of cyclohexenone 201 with TMSCN to give a trimethyl cyanohydrin 202.

The addition of TMSCN to a conformationally locked ketone such as 4-tert-butylcyclohexenone 203 has been shown to be selective by giving a mixture of isomers in a ratio of 9:1 in a high yield. These are then reduced to form the amino alcohols. The major isomer 204 was proven by independent synthesis of the epoxide 206 with a known stereochemistry to give the amino alcohol 205 (Scheme 141).\textsuperscript{53} The isomer ratio favouring 204 is believed to be the result of kinetic rather than thermodynamic control. The literature shows the nitrile reacting at the hindered side favouring axial addition which would mean that the desired stereochemistry for my target TMS cyanohydrin would be the minor isomer. However the presence of the methyl group at the axial position at C-6 in the cyclohexenone substrates 192 and 194 may provide the desired stereochemistry in a higher ratio.

Scheme 141. Stereochemistry of the addition of TMSCN to 4-tert-butylcyclohexenone.

2.12.2 Treatment of cyclohexenone derivatives with TMSCN

Both 192 and 194 were subjected to standard reaction conditions. The starting material was stirred initially at room temperature in chloroform under nitrogen. The TMSCN (1.1 eq.) was then added slowly with catalytic amount of the zinc iodide and
stirred for a further hour before the reaction mixture was worked up and the product purified by flash column chromatography (Scheme 142).

Scheme 142. Addition of TMSCN to 2-[2-(benzyloxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone 192 and 2-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone 194.

The 2-[2-(benzyloxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone 192 reacted to give a yield of 45% of a product isolated as a mixture of isomers 207 in a 2:1 ratio, the minor isomer assumed to be of the desired conformation. The 2-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone reacted 194 to give the trimethylsilyl cyanohydrin product with a yield of 16% as two isomers 208 in a 2:1 ratio. Both products were fully characterised by $^1$H NMR, $^{13}$C NMR and IR spectroscopy and MS. Both the ketones used gave low yields due to the number of side reactions occurring to form a complex mixture. The mixture could only be purified by flash column chromatography which may have caused further decomposition of the product. Repeating the reaction under cooler reaction conditions at $0\, ^\circ\text{C}$ and reducing the reaction time failed to make any improvements to the overall yield.
2.12.3 Analysis of 1,6-dimethyl-3-(2-benzyloxy-ethyl)-4-trimethylsilanyloxy-cyclohexene-4-carbonitrile

An important issue in the formation of the cyanohydrin product is the resulting stereochemistry. A mixture of isomers are formed due to the attack of the nucleophile from either side of the conformationally locked ketone giving a preference for a particular isomer. A ratio of 2:1 isomers were formed for this reaction from both the ketones used, however the standard techniques of analysis used have been unable to establish the relative stereochemistry. It is therefore assumed that the stereochemistry for 207 consists of the major isomer 209 and minor isomer 210 is due to a preference for attack at the more hindered side (Figure 25).

![Figure 25. Possible major Isomer 209 and minor isomer 210 for 1,6-dimethyl-3-(2-benzyloxy-ethyl)-4-trimethylsilanyloxy-cyclohexene-4-carbonitrile.](image)

The full analysis of 207 is discussed below, and that similar analysis of spectral data allowed the identification of the TMS cyanohydrin 208.

IR spectroscopy indicated the loss of the carbonyl group and the presence of a nitrile signal at 2229 cm\(^{-1}\) as well as the presence of the aromatic C-H with signals at 3030 cm\(^{-1}\), an alkene signal at 1608 cm\(^{-1}\) and trimethylsilyl signal at 1253 cm\(^{-1}\), corresponding to the product. A molecular ion of \(m/z\) 357 was observed by mass spectrometry, corresponding to the desired product 207.

The \(^{13}\)C NMR spectrum shows the loss of the signal corresponding to the ketone carbon but the presence of nitrile carbon signals at 120.00 and 119.95 ppm, corresponding to the major and minor isomers respectively.

The \(^1\)H NMR spectrum indicated the presence of signals at 0.25 ppm and 0.24 ppm, corresponding to the TMS group for the major and minor isomers respectively, which is consistent with the formation of the product. Two signals for 2-H are seen in the
vinylic region at 5.60 ppm and 5.34 ppm, corresponding to the minor and major isomers respectively. The ratio of the isomers was also estimated by the integrals for the 2-H signal in the $^1$H NMR spectrum. Four alkene carbon signals are observed at 137.23, 137.16, 121.20, and 120.77 ppm for C-1 and C-2 for the minor and major isomers. The integrity of other functionalities such as the methyl groups and benzylic protecting groups for the isomers was estimated by the presence of relevant signals in the $^1$H NMR spectrum. These analogous signals are discussed in the relevant sections above.

2.12.4 Treatment of a cyclohexenone derivative using TMSCN and a Lewis acid catalyst

The low yield and selectivity of this reaction leads to the use of different literature conditions. A procedure by Trehan et al. $^{206}$ uses the trimethylsilylmethanesulfonate (TMSOTf) and other Lewis acid catalysts for the addition of TMSCN to carbonyl compounds. Following the reaction conditions provided in the literature, the addition of TMSCN (1.1 eq.) to the ketone at $-78 \degree C$ in DCM under nitrogen with the presence of 0.2 eq. of the TMSOTf catalyst was carried out. After a period of one hour the reaction was quenched, worked up and purified by flash column chromatography however no target product was isolated from the complex mixture (Scheme 143).

Scheme 143. Attempted addition of TMSCN to 194 using TMSOTf as a catalyst.
2.12.5 Conclusion

The formation of the trimethylsilyl cyanohydrin products was achieved, although with poor yields and as a mixture of isomers. The minor isomer 210 is believed to have the desired stereochemistry and therefore the reaction is not selective enough to provide adequate yields for subsequent reactions. The problems are probably due to the instability of the ketone substate or more likely the TMS cyanohydrin product to the reaction conditions. Purification through the use of flash column chromatography with silica gel was the only method used to purify the complex mixtures formed. However the acidic nature of this purification probably may have led to further decomposition through hydrolysis of the oxygen-silyl bond. If time and more product were available, purification with neutral alumina could have been attempted to see if silica was causing the problems through decomposition of the product. The reaction was attempted for shorter reaction times, with lower temperatures and the use of different catalysts, but with no success.

The problems in this methodology made it necessary to look at other possibilities in the formation of the spirotetronic acid species.
2.13 Reactions of 2-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]- 4,5-dimethyl-cyclohex-3-enone 192 and 2-[2-(benzyloxy)-ethyl]- 4,5-dimethyl-cyclohex-3-enone 194 with Wittig-like reagents

2.13.1 Introduction

The difficulties of producing good results with TMSCN and the ketones 192 and 194 to give TMS cyanohydrins and the subsequent methodology towards the target oxaspiro bicyclic target compound led to other routes. The formation of the cyclohexenone intermediates in good yields gives rise to the possibility of reacting this functionality in other ways with the aim of providing the target compound or similar derivatives.

One method would be to react the ketone using a Wittig reagent giving a vinyl ether product as a mixture of isomers 211, which could then be epoxidised through a standard procedure. The epoxide 212 would then be ring-opened by the use of the appropriate dimethyl malonate species. This species 213 would then cyclise by the hydroxy group reacting with the carboxylic group in a condensation type reaction. This would lead to the tetronic acid 214 following the chemistry described in the introduction (Scheme 144).

Although the epoxidation would be more likely to occur on the least hindered side of the intermediate, giving the wrong stereochemistry, the route would still be valuable in the synthesis of an oxaspirotetronic acid derivative. With very little literature precedence on the structure and stereochemistry of tetronothiodin, the formation of the oxaspirotetronic acid with the believed opposite stereochemistry at the spiro centre would still provide valuable information for research into the synthesis of tetronothiodin.
Scheme 144. Synthetic route to oxaspiro bicyclic derivative 214.

The synthesis of the lithiated derivative of diphenyl (methoxymethyl)phosphine oxides 215 and subsequent reaction with aldehydes and ketones to give vinyl ethers of the general type 216 was reported by Warren et al. (Scheme 145).²⁰⁷

Scheme 145. Synthesis of a vinyl ether using diphenyl(methoxymethyl)-phosphine oxide.

They successfully synthesised vinyl ethers as a mixture of diastereoisomers from a number of aldehydes and ketones. These methyl vinyl ethers have potential for further
reactions such as hydrolysis in aldehyde synthesis. Shlosser established cyclohexenone to be a successful substrate for this chemistry.

2.13.2 Treatment of cyclohexenone derivatives with lithiated diphenyl-(methoxymethyl)phosphine oxide

Using the literature procedure, diphenyl-(methoxymethyl)phosphine oxide (1.1 eq) was treated first with LDA at 0 °C in THF to give the lithium derivative. This was separately treated with each of the cyclohexenones 192 and 194 at -78 °C in THF with the aim of giving the respective diphenylphosphinoyl-1-methoxyalcohol intermediate (Scheme 146).

![Scheme 146. Reaction of 192 and 194 with the lithiated phosphine oxides.](image)

After working up the reaction, the crude product mixture was purified by flash column chromatography, however, only starting material was isolated from the mixture. The reaction was repeated at the higher temperature of 0 °C, with increased amounts of the lithiated diphenyl-1-(methoxymethyl) species and increased reaction times of over 24 hours, however, the ketone still proved unreactive. The crude product mixture was also treated with sodium hydride at room temperature in THF to see whether any hydroxy product was present to react further. However after work up, a complex mixture of unidentified material was obtained. The failure was not a
complete surprise, as ketones are known to be unreactive compared to aldehydes as they are less electrophilic and have steric constraints.

2.13.3 Wadsworth-Emmons approach

The problems with this reaction led to the use of other common Wittig-type reagents with the aim of seeing how reactive the ketones are towards these reagents and reaction conditions. A common procedure is the use of stabilised phosphonate esters known as the Wadsworth-Emmons procedure as discussed in the introduction (Scheme 147).

Scheme 147. Wadsworth-Emmons reaction.

Following standard procedures, 1.1 eq. of the base, either sodium hydride or potassium tert-butoxide, was used initially to deprotonate triethylphosphonate at 0 °C through stirring for 30 minutes in THF. The cyclohexenones 192 and 194 were then carefully added and the reaction was allowed to warm to room temperature and stirred for a further 18 hours. The reaction was quenched and worked up to give a complex mixture which was purified by flash column chromatography. Only starting material as well as a number of unknown products were isolated however (Scheme 148).
Again, the cyclohexenones seemed unreactive towards the reaction conditions. The starting material recovered from these reactions was often contaminated with unidentified material. There was some spectral evidence suggesting that this may have been small amount of the target olefin. However further purification and isolation of the products from the reaction mixture proved difficult to give suitable material for characterisation. There is also an indication that base mediated isomerisation of the double bond may occur as there was evidence of conjugated ketones being formed. This area of work again suggests the unreactivity of the ketone under Wittig type reactions. The use of more forceful conditions seems unfavourable as decomposition and unwanted side reactions occur. It would therefore be more useful to look at other potential reactions at the ketone which could lead towards the oxaspiro bicyclic tetronic acid.

Scheme 148. Reaction of 192 and 194 with phosphonate esters.
2.14 Reactions of 2-[(tert-butyl-diphenyl-silyloxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone 194 and 2-[(benzyloxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone 192 with organometallic propynoate reagents

2.14.1 Introduction

The synthesis of the upper fragment of kijanolide by Yoshii et al was described in the introduction. This made use of an organocerium reagent for the synthesis of intermediate 51 which was cyclized to a spirotetronate 52. Treatment of the ketone with a cerium reagent formed from lithiated methyl propynoate and cerium trichloride leads to the nucleophilic addition of the alkyne to the ketone 50. The intermediate obtained can be reacted with methanolic potassium methoxide to provide the transformation to the spirotetronate 52 (Scheme 149).

Scheme 149. Synthesis of spirotetronate in kijanolide synthesis using lithiated methyl propynoate.

The use of organocerium reagents for this nucleophilic addition has been established by extensive research by Imamoto for preparative formation of allyl alcohols from ketones. The organocerium reagents were synthesised by reacting organolithium reagents with anhydrous cerium chloride and reacted with a number of ketones at low temperatures to give high yields of the hydroxy products.
Other similar reactions have been performed using the lithiated propynoate species followed by organocuprate addition to give spirolactones 217 as seen in the following example (Scheme 150).209

\[ \text{Li} \quad \text{CO}_2\text{Me} \quad \text{THF, -100°C - 80°C, 30 mins} \quad \text{HO} \quad \text{Me} \quad \text{THF, -100°C - 80°C, 30 mins} \quad \text{H}^+ \quad \text{58%} \]

Scheme 150. Addition of lithiated propynoate to give a spirolactone 215.

2.14.2 Treatment of cyclohexenone derivatives with cerium propynoate species

Following the literature methodology209 the organocerium chemistry was attempted on the protected ketones 192 and 194. A solution of the organolithium reagent was prepared by the addition of \( n\)-BuLi (1.2 eq.) to methyl propynoate (1.2 eq.) at \(-78 \, ^\circ\text{C}\) in THF. This was then added to a solution of anhydrous cerium chloride in THF at the same temperature and stirred for 30 minutes. The ketone was then added to the resulting yellow solution and stirred for 3 hours, monitored by TLC before being quenched, worked up and purified by flash column chromatography (Scheme 151).

\[ \text{Cl}_2\text{Ce} \quad \text{CO}_2\text{Me} \quad \text{THF, -78°C, 3 hrs} \]

\[ \text{Cl}_2\text{Ce} \quad \text{CO}_2\text{Me} \quad \text{THF, -78°C, 3 hrs} \]

Scheme 151. Addition of cerium alkyne reagent to 192 and 194.
Both 192 and 194 failed to give any product, and only starting material was recovered from the reaction mixture. This suggests that either the cerium reagent may not have been synthesized in the reaction sequence or that ketone is unreactive under these conditions.

2.14.3 Treatment with cyclohexenone derivative with lithiated methyl propynoate species

The reaction was attempted on 192 using the lithiated methyl propynoate as outlined above at a temperature of -100 °C for a period of 1 hour. Following the reaction by TLC gave an indication of some product formed before the reaction was quenched, worked up and purified by flash column chromatography though mainly starting material was again recovered. Purification gave trace amounts of the product 218, which was isolated with a yield of approximately 5% and identified by 1H NMR and IR spectroscopic analysis. Decomposition of this material occurred before any further characterisation was obtained. Repetition of the reaction for longer periods and higher temperatures failed to give any target compound for the necessary characterisation (Scheme 152).

Scheme 152. Addition of lithiated methyl propynoate to 218.
2.14.4 Conclusion

The results suggest that the conditions are unsuccessful for the reaction of the alkynyl cerium and alkynyl lithium reagents with the ketone, where the stability of the reagents used are known to be problematic, thus none or little product was produced, although some spectral analysis suggested the formation of trace amounts of the product. Decomposition occurred before full characterisation was established. This suggests that the product formed may be unstable. Future efforts should therefore be concentrated on other routes towards the oxaspiro tetronic acid.
2.15 Final Conclusions

The formation of the hydroxy diene number with good yields and the desired E-stereoselectivity from previous research has enabled the continuation of research through the Diels-Alder approach towards the first cyclohexenone target compound.\textsuperscript{40}

The previous research led to cycloadditions using nitroethylene,\textsuperscript{43, 44} that successfully gave the Diels-Alder adduct. The research into the Nef reaction\textsuperscript{45} encountered a number of problems where conditions proved unsuccessful in forming the ketone group. The reasons could be the presence of the oxygen atom in the side chain or difficulties in initial deprotonation of the starting material.

The use of a number of other dienophiles was investigated with the same aim of forming the ketone group or other intermediates towards the oxaspiro bicyclic tetronic acid subunit. The use of phenyl vinyl sulfone\textsuperscript{47} under thermal conditions led to low yields of the cycloadduct and further functionalisation proved difficult, including oxidative desulfonylation.\textsuperscript{179, 180} This again was probably due to the same problems of stability of the anion and difficulties in deprotonation. The use of 2-chloroacrylonitrile provided the Diels-Alder adduct but with low yields. Attempted hydrolysis to give the ketone proved problematic, where the reaction conditions caused either decomposition or unreactive with the starting material.\textsuperscript{187-190}

The problems of low yields and the inability to further functionalise the Diels-Alder adducts from an intermolecular approach led to the use of an IMDA approach.\textsuperscript{56} The synthesis of the starting material was readily achieved, however the attempted cyclisation at high temperatures led to product decomposition. The problems in this area of research may be due to steric constraints. This required more forceful conditions, which led to the instability of the starting material. The problems of a constrained conformation have been known to be overcome by the versatility of a silicon-carbon bond, leading to the use of silicon tethers.\textsuperscript{149}

Temporary silicon connections can give trienes that successfully undergo Diels–Alder reactions: methodology studied by Stork\textsuperscript{58} and Sieburth.\textsuperscript{151} Following their
methodology, the hydroxy diene 9 was tethered by reacting with vinyl silanes to provide the trienes necessary for the cycloaddition. Successful cycloadditions occurred with yields of over 90% for one particular intermediate. The cycloadducts were then oxidatively cleaved using hydrogen peroxide59 with good yields to provide hydroxy cyclohexenols which are perfect intermediates for the formation of the cyclohexenone. The next stage was to perform a selective protection, then oxidation, of a secondary alcohol to give the ketone.

The use of silyl ethers gave the best results for selectively protecting the primary hydroxy group that enabled the secondary alcohol to undergo a clean oxidation using PDC.203 A route has thus been established for accessing the cyclohexenone target compound which is both selective and high yielding.

The next stage was to react the ketone group to provide the spiro tetronic acid, however initial attempts have proven difficult. The nucleophile addition of TMSCN has given poor results, where the reactive nucleophile may be reacting further, and difficulties have occurred with the isolation of the product.53 These problems have led to the use of Wittig type chemistry with the aim of providing a successful route towards an oxaspiro subunit. This has proven unsuccessful. Ketones are known to be unreactive towards Wittig reagents. The reactivity of the reagents used is also questionable for the intermediates used, and requires further investigation.

The use of the organocerium reagent used by Yoshii,61a and organolithium reagents proved unsuccessful in the formation of the spirotetronate species by a nucleophilic addition to the ketone group. These reagents can be difficult to handle and may be unstable which may be a factor in the difficulty of obtaining high yields of the hydroxy intermediates.
2.16 Future Work

The successful formation of the cyclohexenone derivatives in high yields means that efforts for future work should be concentrated on reacting the ketone group. The use of TMSCN provided the most promising results with the formation of the trimethylsilyl cyanohydrin intermediates. It would be first necessary to optimise these yields through attempting different reaction conditions and purification techniques. The trimethylsilyl cyanohydrin should be reacted with the methyl malonic acid through a DCC-DMAP esterification with the aim of seeing whether the route could be viable towards the target compound. Also trimethyl silyl cyanohydrins can be used in a Blaise reaction,\textsuperscript{210} where treatment with these Reformatsky type reagents has been shown to provide tetronic acids with good yields.\textsuperscript{211} Further investigation into the methodology in the formation of kijanolide\textsuperscript{61b,61c} and chlorothricolide\textsuperscript{63} may provide other ideas in the formation of the spirotetronic acid, however the use of organocerium reagents seen in the literature above failed to provide any product with the ketone.
Chapter Three
3.0 Experimental

3.1 General experimental procedure

3.1.1 Preparation of glassware

All reactions were carried out in round bottomed flasks which have previously been dried in an oven at 150 °C for a minimum of three hours. The flasks were left to cool in a vacuum desiccator over self indicating silica gel, then flushed with nitrogen before being stoppered with septum caps. All other apparatus used, such as needles, syringes, distillation apparatus, magnetic stirrers and cannulas were dried and cooled in a desiccator as above. Reactions carried out under a nitrogen atmosphere are described in the experimental procedure with the flask being sealed with a septum before the introduction of reagents and solvents via syringes and cannulas. High pressured Diels–Alder reactions were carried out in resealable Carius tubes carefully washed with potassium hydroxide solution and rinsed with copious amounts deionised water and acetone. The tubes were then dried in the same way as mentioned above.

3.1.2 Purification of chemicals

All chemicals used in all experiments were obtained from commercially available sources unless otherwise stated.

All solvents, unless otherwise stated were either obtained in an anhydrous form from commercially available sources or were dried and distilled in the laboratory. Dichloromethane was distilled over phosphorus pentoxide; ethyl acetate was distilled over calcium chloride; light petroleum (40 °C-60 °C) was distilled over calcium chloride; toluene was distilled over lithium aluminium hydride; diethyl ether distilled from the sodium-benzophenone ketyl radical and tetrahydrofuran was distilled from the sodium-benzophenone ketyl radical.
3.1.3 Purification methods

Compounds were purified through the use of flash chromatography, recrystallization and vacuum distillation.

Flash column chromatography was carried out using Kieselgel 60 (230-400 mesh) silica gel, using hand bellows for pressure.

Thin layer chromatography was carried out using aluminium-backed plates coated with a 0.25 mm layer of Merck Kieselgel 60 GF. The plates were visualised using ultra-violet light, and potassium permanganate and molybdate dips.

Purification by vacuum distillation was achieved using a buchi GKR-50 Kugelrohr as the heat source for bulb-to-bulb distillation. Condensation of the liquid product was achieved by covering the bulb in acetone soaked cotton wool.

3.1.4 Spectroscopy

All $^1$H NMR and $^{13}$C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 instruments. For data obtained using CDCl₃ as solvent, chemical shifts (d) are given in ppm downfield of tetramethylsilane (TMS); for data obtained using D₂O as solvent, chemical shifts are given in ppm downfield of trimethylsilylpropionic acid (TSP). Signals are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m) and coupling constants (J) are reported where possible in Hz.

Diastereomer ratios were obtained by integration of suitable peaks in the proton NMR spectrum.

Infrared spectra were recorded on Perkin-Elmer 883 spectrometer, in the range 4000-600 cm⁻¹ and calibrated against the 1602 cm⁻¹ absorption of polysterene. All samples were run on sodium chloride plates: liquid samples were run neat and solid samples were run as a nujol mull.

Electron ionisation (EI), chemical ionisation (CI) and fast atom bombardment (FAB) mass spectra were recorded on a Kratos MS spectrometer.

3.1.5 Other data

All microanalyses (C, H, N) were completed at Loughborough University using a PE 2400 elemental analyzer. Optical rotation measurements were run on a Optical
Activity Ltd. Polarimeter with a 100 cm cell and chloroform as solvent at 25 °C. Melting points were recorded on a Reichert-Kofler hot stage apparatus or with an Electrothermal digital melting point apparatus and are uncorrected.

3.2 Preparation of standard reagents

3.2.1 Purified meta-chloroper oxybenzoic acid (m-CPBA)

Commercial m-CPBA (50-55 %) was washed with a phosphate buffer solution prepared by dissolving potassium dihydrogenphosphate and disodium hydrogenphosphate in water (500 ml). The m-CPBA was collected by filtration and the process was repeated. The solid was then dissolved in dichloromethane (250 ml), with the separation of any remaining phosphate buffer and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo without heating to afford a white solid which was dried under vacuum in a desiccator over phosphorus pentoxide for twenty four hours to yield pure m-CPBA.

3.2.2 Oxodiperoxymolybdenum(pyridine)-1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (MoO₅.Py.DMPU)₁₈¹

30 % hydrogen peroxide (30 ml) was added to a flask containing MoO₃ (5 g, 35 mmol) and stirred vigorously, monitoring the internal temperature. The temperature was maintained between 35 °C and 40 °C for three and a half-hours. The reaction mixture was then cooled to 20 °C and the reaction mixture was filtered to remove solids and the yellow solution cooled to 10 °C. DMPU (4.2 ml, 35 mmol) was then added to the solution with stirring and the crystalline precipitate was collected and recrystalised from methanol to give MoO₅.H₂O.DMPU as a yellow crystalline solid (5.43 g, 51 %). The crystalline solid was then dried in a vacuum desiccator for twenty four hours over P₂O₅ to give MoO₅.DMPU. A solution of MoO₅.DMPU (5.21 g, 17 mmol) in dry THF (30 ml) was stirred and cooled to 20 °C while pyridine (1.37 ml, 17 mmol) was added dropwise. The yellow crystalline precipitate was collected, washed with dry THF (5 ml), dry diethyl ether (5 ml) and dried under vacuum to give MoO₅.Py.DMPU as a yellow finely divided solid (3.02 g, 28 %); m.p. 91-92 °C; νₘₚₙx
(nujol)/ cm⁻¹ 3158, 3105 (C-H aromatic), 2946, 2891 (sp³ C-H), 1631 (C=O), 960 (Mo=O) 856 (O-O); Analysis; found C 34.40, H 4.48, N 10.67 %. Calc. For C₁₁H₁₈MoN₃O₆, C 34.39; H 4.22, N, 10.94 %.

3.3 Preparation of compounds

3-Hydroxypropyl-1-triphenylphosphonium bromide⁴⁰ (12)

A solution of 3-bromo-propanol (10.00 g, 72 mmol), triphenylphoshine (18.88 g, 72 mmol) in ethyl acetate (50 ml) was refluxed for twenty four hours. The resultant white suspension was evaporated to dryness, washed with diethyl ether and recrystallised from ethanol to give a white solid (17.35 g, 60 %); m.p. 220-223 °C; νmax (nujol)/ cm⁻¹ 3200 (O-H), 2923 (sp³ C-H), 1437 (P-Ph) and 1044 (C-O); δH (250 MHz; D₂O) 7.69-7.61 (15 H, m, C₆H₅) 3.66 (2 H, t, J 6.0, 3-H) 3.35-3.23 (2 H, m, 1-H) and 1.90-1.81 (2 H, m, 2-H).

(E, E)-5-Methyl-3,5-heptadien-1-ol⁴⁰ (9)

3-Hydroxypropyl-1-triphenylphosphonium bromide (10.00 g, 24.9 mmol) in dry tetrahydrofuran (250 ml) was sonicated for one hour. The reaction mixture was then cooled to 0 °C and a 2.5 M solution of n-butyllithium in hexanes (20.00 ml, 49.9 mmol) was slowly added under a nitrogen atmosphere. The resultant dark red mixture was stirred for ten minutes before the addition of trans-2-methyl-butenal (2.45 ml, 24.94 mmol). The reaction mixture was left to stir for seven hours before being quenched with water (100 ml). The aqueous phase was extracted with dichloromethane (3 x 100 ml), dried over magnesium sulfate and the solvent was
removed in vacuo to give an orange liquid. Purification by flash column chromatography using silica gel as absorbent and ethyl acetate/ light petroleum (40 °C-60 °C) (1:3) as eluent gives a yellow oil (2.20 g, 70 %); \( \nu_{\text{max}} \) (film)/ cm\(^{-1} \) 3341 (O-H), 2922 (sp\(^3\) C-H) and 1651 (C=C); \( \delta_H \) (250 MHz; CDCl\(_3\)) 6.15 (1 H, d, J 15.6, 4-H), 5.56-5.46 (2 H, m, 3-H and 6-H), 3.67 (2 H, t, J 6.3, 1-H), 2.37 (2 H, q, J 6.2, 2-H) 1.74 (3 H, s, 8-H) and 1.73 (3 H, d, J 8, 7-H).

\((E, E)\)-Methyl-4-methyl-2,4-hexadienoate\(^{40} \) (155)

A solution of carbomethoxymethylenetriphenylphosphorane (5.00 g 15 mmol) was stirred in dry tetrahydrofuran (50 ml) with the addition of trans-2-methyl-butenal (1.44 ml, 15 mmol) at room temperature under a nitrogen atmosphere. The resultant mixture was stirred for a period of sixteen hours before being quenched with water (50 ml). The aqueous phase was extracted with dichloromethane (3 x 50 ml), dried over magnesium sulfate and evaporated to dryness. The product was purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/ light petroleum (40 °C-60 °C) (3:1) as an eluent to afford a yellow oil (1.49 g, 72 %); \( \nu_{\text{max}} \) (film)/ cm\(^{-1} \) 2950 (sp\(^3\) C-H), 1718 (C=O), and 1619 (C=C); \( \delta_H \) (250 MHz; CDCl\(_3\)) 7.27 (1 H, d, J 15.6, 2-H) 5.97 (1 H, m, 5-H), 5.78 (1 H, d, J 15.7, 3-H), 3.77 (3 H, s, CO\(_2\)CH\(_3\)) 1.76 (3 H, d, J 7.2, 6-H) and 1.74 (3 H, s, 7-H).
(E, E)-1-Benzylloxy-5-methyl-3,5-heptadiene (108)

To a stirred solution (E, E)-5-methyl-3,5-heptadien-1-ol (0.30 g, 2.4 mmol) in dry N,N-dimethylformamide (20 ml) was added sodium hydride (0.16 g, 4 mmol) and left under a nitrogen atmosphere at room temperature for forty-five minutes. Benzyl bromide (0.28 ml, 2.4 mmol) was added and the resultant mixture was left to stir for four hours. The reaction mixture was quenched with aqueous saturated ammonium chloride solution (50 ml). The aqueous phase was extracted with diethyl ether (5 x 50 ml) washed with water (3 x 50 ml), brine (3 x 50 ml), and dried with magnesium sulfate then evaporated to dryness. The product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/ light petroleum (40 °C- 60 °C) (5:95) as an eluent to afford a green oil (0.33 g, 63 %); \( \nu_{\text{max}} \) (film)/ cm\(^{-1} \) 2923 (sp\(^3\) C-H), 1651 (C=C) and 1099 (C-O); \( \delta_{\text{H}} \) (250 MHz; CDCl\(_3\) ) 7.34-7.25 (5 H, m, CH-aromatic), 6.10 (1 H, d, \( J = 15.5 \), 4-H), 5.61-5.45 (2 H, m, 3-H and 6-H), 4.51 (2 H, s, CH\(_2\)Ph) 3.54 (2 H, t, \( J = 6.9 \), I-H), 2.42 (2 H, q, \( J = 7.0 \), 2-H), 1.72 (3 H, s, 8-H) and 1.70 (3 H, d, \( J = 9 \), 7-H).

(E, E)-1-tert-Butyl-dimethylsiloxy-5-methyl-3,5-heptadiene (109)

5-Methyl-3,5-heptadien-1-ol (0.35 g, 2.8 mmol), imidazole (0.48 g, 7 mmol), tert-butyl-dimethylsilylchloride (0.51 g, 3.4 mmol) was stirred in dry DMF (10 ml) under nitrogen at room temperature for two hours. The reaction was quenched with water, extracted with diethyl ether (3 x 50 ml), dried with magnesium sulfate and evaporated to dryness. Flash column chromatography using silica gel as an absorbent and ethyl acetate/ light petroleum (40 °C-60 °C) (1:3) as an eluent afforded the desired product.
as a clear oil (0.42 g, 71 %); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 2926 (sp$^3$ C-H), 1652, 1630 (C=C), 1098 and 1006 (C-O); $\delta_{\text{H}}$ (CDCl$_3$, 250 MHz) 6.04 (1 H, d, $J$ 15.6, 4-H), 5.51-5.41 (2 H, m, 3-H and 6-H) 3.60 (2 H, t, $J$ 7.0, 1-H), 2.27 (2 H, q, $J$ 7.0, 2-H) 1.72 (3H, s, 8-H) 1.70 (3 H, d, $J$ 9, 8-H) 0.85 (9H, s, C(CH$_3$)$_3$) and 0.01 (6 H, s, Si-Me); $\delta_{\text{C}}$ (CDCl$_3$, 100 MHz) 136.55 (C-4), 134.38 (C-5), 125.01 (C-3), 123.08 (C-6), 63.39 (C-1), 36.49 (C-2), 25.96 (C(CH$_3$)$_3$), 18.39 (C(CH$_3$)$_3$), 13.71 (C-7), 11.99 (C-8) and -5.28 (Si(CH$_3$)$_2$); m/z (El) 240.19147 (M$^+$); C$_{14}$H$_{26}$OSi requires 240.190942.

Nitroethylene$^{43}$ (13)

\[\text{NO}_2\]

2-Nitroethanol (3 g, 33 mmol) and phthalic anhydride (7.3 g, 49 mmol) were mixed in a distillation unit equipped with a short fractionating column and ice-cooled receiver. The apparatus was heated and the oil bath temperature was maintained at 140°C-150°C until the mixture was homogenous and the temperature was then increased and held at 160°C to give a yellow oil (0.85 g, 80%); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 1534 (C-NO$_2$); $\delta_{\text{H}}$ (250 MHz; CDCl$_3$) 6.65 (1 H, dd, $J$ 7.3, $J'$ 14.9, 2-H), 5.93 (1 H, dd, $J$ 2.3, $J'$ 14.8, 1-H) and 5.22 (1 H, br d, 1-H).

Methyl $\alpha$-acetoxyacrylate$^{195}$ (145)

\[\begin{align*}
\text{MeO} & \\
\text{OAc} & \\
\end{align*}\]

A mixture of methyl pyruvate (4.42 ml, 49 mmol), acetic anhydride (9.25 ml, 98 mmol) and a catalytic amount of p-toluenesulfonic acid was heated at reflux for sixteen hours. Purification by fractional distillation under reduced pressure gave a clear oil (1.01 g, 16 %); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 1773 (OAc) 1736 (CO$_2$Me) and 1676 (C=C); $\delta_{\text{H}}$ (CDCl$_3$, 250 MHz) 6.05 (1H, s, C=CH), 5.48 (1H, s, C=CH), 3.87 (3H, s, OMe) and 2.25 (3H, s, COMe); $\delta_{\text{C}}$ (CDCl$_3$, 100 MHz) 225 (C=O), 168.9 (COO), 144.6 (C=CH$_2$), 114.9 (C=CH$_2$), 52.6 (OMe) and 20.7 (COMe).
1,6-Dimethyl-3-(2-hydroxyethyl)-4-nitrocyclohex-1-ene\textsuperscript{40} (14)

\[ \text{To a stirred mixture of nitroethylene (0.39 g, 5.3 mmol) in dry toluene (2 ml), was added } (E, E)-5-methyl-3,5-heptadien-1-ol (0.45 g, 3.6 mmol) \text{ at room temperature and left to stir for 36 hours under an atmosphere of nitrogen. The mixture was then evaporated to dryness and purified by flash chromatography eluting with ethyl acetate/ light petroleum (b.p. 40 °C - 60 °C) (I : 4) to give a green oil (0.35 g, 50 %); } \nu_{\text{max}} \text{ (film)/ cm}^{-1} 3404 (\text{O-H}), 2925 (\text{C-H}), 1545 \text{ and } 1376 (\text{C-NO}_2); \delta_{\text{H}} (\text{CDCl}_3, 250 \text{ MHz}) 5.50 (1 \text{ H, d, } J 5.8, 2\text{-H}), 4.67 (1 \text{ H, ddd, } J 13.1, J' 5.8, \text{ and } J'' 2.9, 4\text{-H}) 3.70 (2 \text{ H, t, } J 6.4, 2'\text{-H}) 3.01-2.99 (1 \text{ H, m, 3-H}), 2.27-2.24 (2 \text{ H, m, 5-H and 6-H}) 1.84 (1 \text{ H, dd, } J' 14.9, J'' 2.0, 5\text{-H}) 1.68 (3 \text{ H, s, 7-H}) 1.54-1.48 (2 \text{ H, m, 1'-H}) \text{ and } 1.11 (3 \text{ H, d, } J 6.6, 8\text{-H}). \]

1,6-Dimethyl-3-(2-benzylethyl)-4-nitrocyclohex-1-ene (110)

\[ \text{To a stirred solution of nitroethylene (0.13 g, 1.8 mmol) in dry toluene (2 ml), } (E, E)-1\text{-Benzyloxy-5-methyl-3,5-heptadiene (0.25 g, 1.2 mmol) was added at room temperature and left to stir under nitrogen for forty eight hours. The mixture was evaporated to dryness and purified by flash column chromatography eluting with ethyl acetate/light petroleum (40 °C-60 °C) (1:9) to give a pale green oil as the desired product (0.11 g, 35 %); } \nu_{\text{max}} \text{(film)/ cm}^{-1} 3063, 3030 (\text{aromatic C-H}), 2960, 2871 (\text{sp}^3) \]
C-H), 1545 and 1376 (-NO2); δ_H (CDCl3, 250 MHz) 7.36-7.28 (5H, m, CH-aromatic), 5.41 (1H, d, J 5.7, 2-H), 4.66 (1H, ddd, J 13.0, J' 5.8, J'' 2.8, 4-H), 4.47 (2H, d, J 8.3, CH2Ph), 3.51 (2H, t, J 7.3, 2'-H), 3.05-3.00 (1H, m, 3-H), 2.25-2.18 (2H, m, 5-H and 6-H), 1.84 (1H, dd, J' 12.8, J'' 2.1, 5-H), 1.68 (3H, s, 7-H), 1.62-1.44 (2H, m, 1'-H) and 1.09 (3H, d, J 6.6, 8-H); δ_C (CDCl3, 100 MHz) 138.56 (C-1), 138.26, 128.38, 127.68, 127.63 (Ph), 122.21 (C-2), 84.72 (C-4), 72.80 (CH2Ph), 67.32 (C-2'), 35.48 (C-6), 34.14 (C-3), 32.92 (C-1') 30.55 (C-5), 20.78 (C-7) and 19.40 (C-8); m/z (EI) 290.17561 (M+H); C17H23NO3 requires 289.16778.

1,6-Dimethyl-3-(2-hydroxy-ethyl)-4-chloro-cyclohexene-4-carbonitrile (130 and 135)

(E, E)-5-methyl-3,5-heptadien-1-ol (1.5 g, 11.9 mmol), 2-chloroacrylonitrile (1.04 ml, 13 mmol) was refluxed in dry toluene (5 ml) under nitrogen for forty eight hours. The brown mixture formed was evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography eluting with ethyl acetate/light petroleum (40-60 °C) (1:9) to give an oil as the product of (endo/ exo) isomers (2:1) (1.01 g, 40 %); ν_max (film)/ cm⁻¹ 3372 (O-H), 2964, 2880 (sp³ C-H), 2243 (-CN), 1693, 1682 (C=C), 1050 and 1029 (C-O); δ_H (CDCl3, 400 MHz) 5.48 (0.5 H, m, minor 2-H), 5.36 (1H, m, major 2-H), 3.88- 3.77 (3 H, m, major and minor 2'-H), 2.85-2.82 (0.5 H, m, minor 3-H), 2.77-2.74 (1 H, m, major 3-H), 2.56-2.48 (0.5 H, m, minor 6-H), 2.44-2.37 (1.5 H, m, major 6-H and minor 1'-H), 2.33-2.15 (3.5 H, m, major 1'-H, major 5-H and minor 5-H), 1.99 (0.5 H, dd, J 5.6, J' 9.6, minor 5-H) 1.73 (4.5 H, s, major 7-H and minor 7-H), 1.67-1.57 (1H, m, major 1'-H), 1.53-1.44 (0.5 H, m, minor 1'-H), 1.22 (3H, d, J 7.2, major 8-H) and 1.12 (1.5 H, d, J 7.2, minor 8-H); δ_C (CDCl3, 100 MHz) 138.54 (minor C-1), 138.05 (major C-1), 121.48 (minor C-2), 120.00 (minor nitrile) 119.66 (major C-2), 119.15 (major nitrile), 60.18 (minor C-2'), 59.85 (major C-2'), 59.65 (minor C-4), 59.20 (major C-4), 43.60 (major C-3),
42.69 (major C-5) 42.17 (minor C-3), 36.64 (major C-1'), 35.11 (minor C-1'), 34.34 (minor C-6), 32.15 (major C-6), 21.34 (major C-7), 21.08 (minor C-7), 18.82 (minor C-8) and 18.54 (major C-8); mlz (El) 213.09225 (M+);

C_{11}H_{16}ClON requires 213.09204.

1,6-Dimethyl-3-(2-benzylxy-ethyl)-4-chloro-cyclohexene-4-carbonitrile (131 and 134)

To a stirred solution of 2-Chloroacrylonitrile (1.2 g, 15 mmol) in dry toluene (5 ml), (E, E)-1-Benzylxy-5-methyl-3,5-heptadiene (0.65 g, 3 mmol) was added at room temperature then refluxed under nitrogen for forty eight hours. The mixture was evaporated to dryness and purified by flash column chromatography eluting with ethyl acetate/light petroleum (40 °C-60 °C) (1:9) to give an oil as the product of (endo/exo) isomers (2:1)(0.35 g, 39 %); ν_{max} (film)/ cm^{-1} 3065, 3032 (aromatic C-H), 2925, 2855 (sp^{3} C-H), 2285 (-CN), 1097 and 1071 (C-O); δ_{H} (CDCl_{3}, 250 MHz) 7.36-7.29 (7.5 H, m, CH-aromatic), 5.41-5.38 (0.5 H, m, minor 2-H), 5.30-5.28 (1 H, m, major 2-H), 4.58-4.48 (3 H, m, 2 x CH_{2}Ph), 3.66-3.55 (3 H, m, 2'-H), 2.85-2.83 (0.5 H, m, minor 3-H), 2.77 (1 H, m, major 3-H) 2.56-2.46 (0.5 H, m, minor 6-H) 2.42-2.29 (4 H, m, major 1'-H, minor 1'-H, major 5-H, minor 5-H and major 6-H) 2.18-2.12 (1 H, m, major 5-H) 1.96 (0.5 H, dd, J 6.4, J' 9.6, minor 5-H) 1.70 (3 H, s, major 7-H) 1.69 (1.5 H, s, minor 7-H) 1.63-1.54 (1 H, m, major 1'-H) 1.48-1.42 (0.5 H, m, minor 1'-H) 1.19 (3 H, d, J 6.8, major 8-H) and 1.09 (1.5 H, d, J 7.2, minor 8-H); δ_{C} (CDCl_{3}, 100 MHz) 138.61 (major C-1), 138.59 (minor C-1) 138.70, 138.20, 128.84, 128.82, 128.24, 128.24, 128.13, 128.07 (Ph), 122.05 (minor C-2), 120.44 (minor nitrile) 120.16 (major C-2), 119.54 (major nitrile) 73.41 (minor CH_{2}Ph) 73.73 (major CH_{2}Ph), 67.67 (minor C-2'), 67.31 (major C-2'), 60.11 (minor C-4), 59.66 (major C-4), 44.16 (major C-3), 42.54 (major C-5) 42.30 (minor C-3), 41.47 (minor C-5), 34.77 (minor C-6), 33.85 (major C-1'), 32.69 (minor C-1'), 32.53 (major C-6), 21.72 (major
C-7), 21.37 (minor C-7), 19.19 (minor C-8) and 18.93 (major C-8); m/z (EI) 303.13870 (M⁺); C₁₈H₂₂ClON requires 303.13898.

1,6-Dimethyl-3-(2-hydroxy-ethyl)-4-benzenesulfonyl-cyclohexene (121 and 122)

(E, E)-5-methyl-3,5-heptadien-1-ol (0.3 g, 2.4 mmol), phenyl vinyl sulfone (0.44 g, 2.6 mmol) in dry toluene (2 ml) was heated in a sealed tube at 170 °C for seventy two hours. The mixture was evaporated to dryness and purified by flash column chromatography eluting with ethyl acetate/light petroleum (40 °C-60 °C) (1:3) to give an oil as the product of (exo/endo) isomers (3:1)(0.25 g, 36 %); νmax (film)/ cm⁻¹ 3512 (O-H), 3063 (aromatic C-H), 2960 (sp³ C-H), 1654, 1648 (C=C), 1302 and 1142 (-SO₂-); δH (CDCl₃, 400 MHz) 7.91-7.89 (2.7 H, m, CH-aromatic), 7.66-7.64 (1.3 H, m, CH-aromatic), 7.59-7.55 (2.7 H, m, CH-aromatic) 5.55 (0.3 H, d, J₈, minor 2-H), 5.20-5.18 (1 H, m, major 2-H), 3.82 (0.3 H, m, minor 2’-H), 3.71 (2.3 H, m, major 2’-H and minor 2’-H), 3.45-3.38 (1 H, m, major 4-H), 3.26 (0.3 H, ddd, J₁₂.₈, J’ 4.₄, J” 2.₄, minor 4-H), 2.85-2.81 (0.3 H, m, minor 3-H), 2.80-2.78 (1 H, m, major 3-H), 2.39-2.35 (0.7 H, m, major 1’-H), 2.23-2.18 (1 H, m, major 6-H), 2.07-2.00 (0.3 H, m, minor 6-H), 1.96-1.88 (2.3 H, m, major 1’-H and minor 5-H), 1.85-1.80 (1H, m, major 5-H), 1.70-1.63 (4.3 H, m, minor 5-H, major 5-H and major 7-H) 1.62 (1 H, s, minor 7-H) 1.03 (1 H, d, J 6.₈, minor 8-H) and 0.96 (3H, d, J 7.₂, major 8-H); δC (CDCl₃, 100 MHz) 139.04 (minor C-1), 138.69 (major C-1), 138.82, 137.70, 133.63, 133.57, 129.20, 129.08, 128.95, 128.45 (Ph), 123.88 (minor C-2), 122.69 (major C-2), 63.76 (minor C-4), 60.82 (major C-4), 60.79 (minor C-2’), 60.22 (major C-2’), 37.37 (major C-1’), 34.79 (minor C-6), 34.66 (minor C-1’), 32.26 (major C-3) 31.71 (major C-6), 31.30 (minor C-3), 30.56 (major C-5), 27.49 (minor C-5), 21.68 (minor C-7), 21.02 (major C-7) 19.47 (minor C-8) and 18.94 (major C-8); m/z (EI) 294.12907 (M⁺); C₁₈H₂₂SO₃ requires 294.12897.
(E, E)-1-Benzylxy-5-methyl-3, 5-heptadiene (0.5 g, 2.3 mmol) phenyl vinyl sulfone (0.5 g, 3 mmol) in dry toluene (2 ml) was heated in a sealed tube at 170 °C for seventy two hours. The mixture was evaporated to dryness and purified by flash column chromatography eluting with ethyl acetate/light petroleum (40 °C-60 °C) (1:3) to give an oil as the product (0.31 g, 35%); νmax (film)/ cm⁻¹ 3087, 3062, 3030 (aromatic C-H), 2962, 2930, 2870 (sp³ C-H), 1670 (C=C), 1365 and 1145 (-SO₂-); δH (CDCl₃, 250 MHz) 7.90-7.29 (10 H, m, CH-aromatic), 5.20 (1 H, m, 2-H), 4.43 (2 H, d, J 1.5, CH₂Ph), 3.53-3.47 (1 H, m, 1'-H), 3.36 (1 H, ddd, J 10.5, J' 6.8, J'' 4.2, 4-H), 2.75-2.70 (1 H, m, 3-H), 2.25-2.20 (1 H, m, 6-H), 2.04-1.85 (3 H, m, 1'-H and 5-H), 1.72-1.67 (1 H, m, 5-H), 1.64 (3 H, s, 7-H) and 0.96 (3 H, d, J 7.1, 8-H); δC (100 MHz; CDCl₃) 138.48, 138.31 (Ph), 138.03 (C-1), 133.37, 129.04, 128.97, 128.34, 127.68, 127.51 (Ph), 122.38 (C-2), 72.92 (CH₂Ph), 67.82 (C-2'), 61.81 (C-4), 34.41 (C-1'), 32.54 (C-3), 31.53 (C-6), 30.03 (C-5), 21.68 (C-7) and 18.92 (C-8); m/z (FAB) 385.18350 (M⁺+H); C₂₃H₂₈SO₃ requires 384.17592.

1,6-Dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexene-5-carboxylic ethyl ester (143 and 144)

(E, E)-5-methyl-3,5-heptadien-1-ol (0.3 g, 2.4 mmol), ethyl acrylate (0.44 g, 2.6 mmol) in dry toluene (2 ml) was heated in a sealed tube at 170 °C for seventy two hours. The mixture was evaporated to dryness and purified by flash column chromatography eluting with ethyl acetate/light petroleum (40 °C-60 °C) (1:3) to give
an oil as the product of both stereoisomers (endo/exo) for the undesired regioisomer 1,6-dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexene-5-carboxylic ethyl ester (0.18 g, 40 %) in a ratio (5:2); \( \nu_{\text{max}} \) (film)/ cm\(^{-1} \) 3443 (O-H), 2967, 2936 (sp\(^3\) C-H), 1732, 1714 (-COO-), 1095 and 1036 (C-O); \( \delta_t \) (CDCl\(_3\), 400 MHz) 5.32 (0.4 H, m, minor 2-H), 5.24 (1 H, m, major 2-H) 4.21-4.12 (2.8 H, m, major CO\(_2\)CH\(_2\)CH\(_3\), minor CO\(_2\)CH\(_2\)CH\(_3\)), 3.79-3.71 (2.8 H, m, major 2'-H and minor 2'-H) 2.70-2.65 (1 H, ddd, \( J \) 13.2, \( J' \) 5.2, \( J'' \) 2.4, major 5-H) 2.50-2.36 (1.8 H, m, major 6-H, minor 6-H and minor 5-H), 2.30 (1.4 H, m, major 3-H and minor 3-H), 1.99-1.85 (1.4 H, m, major 4-H and minor 4-H) 1.71 (3 H, m, major 7-H) 1.69 (1.2 H, m, minor 7-H) 1.67-1.50 (3.2 H, m, major 1'-H, minor 1'-H and minor 4-H) 1.42-1.32 (1 H, m, major 4-H), 1.28 (4.2 H, t, \( J \) 7.2, major and minor CO\(_2\)CH\(_2\)CH\(_3\)) 1.06 (1.2 H, d, \( J \) 6.8, minor 8-H) 0.92 (3 H, d, \( J \) 6.8, major 8-H); \( \delta_c \) (100 MHz; CDCl\(_3\)) 176.01 (minor CO\(_2\)Et), 175.19 (major CO\(_2\)Et), 138.14 (major C-1) 137.22 (minor C-1) 126.00 (major C-2), 124.18 (minor C-2), 61.28 (minor CO\(_2\)CH\(_2\)CH\(_3\)), 61.00 (major CO\(_2\)CH\(_2\)CH\(_3\)), 60.67 (minor C-2'), 60.60 (major C-2') 45.45 (minor C-5), 44.78 (major C-5), 39.68 (major C-1'), 39.21 (minor C-1'), 35.83 (major C-6), 35.56 (minor C-6), 33.09 (major C-3), 30.40 (minor C-3), 28.80 (minor C-4), 25.50 (major C-4), 22.45 (major C-7), 22.37 (minor C-7), 19.19 (minor C-8), 15.22 (major C-8), 14.70 (major CO\(_2\)CH\(_2\)CH\(_3\)), 14.65 (minor CO\(_2\)CH\(_2\)CH\(_3\)); m/z (El) 226.15666 (M\(^+\)); C\(_{13}\)H\(_{22}\)O\(_3\) requires 226.15690.

**2-tert-Butyl-5-methyl-[1,3]dioxolan-4-one**\(^{197} \) (161)

![Diagram](attachment:image.png)

A mixture of lactic acid (6.22 g, 69 mmol), trimethylacetaldehyde (15 ml, 138 mmol), a catalytic amount of p-toluensulfonic acid (0.14 g) and conc. Sulfuric acid (1 drop) in pentane was refluxed with the azeotropic removal of water formed for sixteen hours. The resulting solution was washed with water (2 x 200 ml), dried (Magnesium sulphate) and concentrated under reduced pressure. A 4:1 (cis/trans) mixture was obtained through distillation as a clear liquid (10.25 g, 93 %); \( \nu_{\text{max}} \) (film)/ cm\(^{-1} \) 2978
(sp³ C-H), 1802 (C=O), 1736, 1702 (COO), 1086 and 1036 (C-O); δ_H (CDCl₃, 250 MHz) 5.20 (0.3 H, d, J 1.4, minor OCH(CH₃)₃) 5.05 (1 H, d, J 1.3, major OCH(CH₃)₃), 4.47 (0.3 H, dq, J 1.3, J' 7.0, minor CHCH₃), 4.36 (1 H, dq, J 1.2, J' 6.7, major CHCH₃), 1.48 (3 H, d, J 6.7, major CH₃) 1.44 (0.8 H, d, J 6.6, minor CH₃) 0.98 (9 H, s, major (CH₃)₂) and 0.96 (2.3 H, s, minor (CH₃)₂).

5-Bromo-2-tert-butyl-5-methyl-[1,3]dioxolan-4-one¹⁹⁷ (162)

2-tert-Butyl-5-methyl-[1,3]dioxolan-4-one (5 g, 32 mmol), NBS (5.63 g, 32 mmol) in chloroform (40 ml) was refluxed for three hours to give a deep red mixture. After filtration and then evaporation under reduced pressure a brown/red viscous liquid was obtained. The product was purified by distillation to give a pale yellow liquid (3.38 g, 45 %); v_max (film) cm⁻¹ 3444 (Br), 2970 (sp³ C-H), 1818 (C=O), 1136 and 1068 (C-O); δ_H (CDCl₃, 250 MHz) 5.22 (1 H, s, OCH(CH₃)₃), 2.21 (3H, s, CH₃) and 1.02 (9 H, s, (CH₃)₂).

5-Bromo-2-tert-butyl-5-methyl-[1,3]dioxolan-4-one(3.87g,1.6mmol) and triethylamine (3.39 ml, 2.45 mmol) was refluxed in chloroform (50 ml) for four hours. The reaction mixture was then filtered and evaporated to dryness under reduced pressure. Purification by flash column chromatography using ethyl acetate/light petroleum (b.p.
40 °C: 60 °C) on silica gel gave a clear oil as product (0.85 g, 33 %); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 2969, 2879 (sp$^3$ C-H), 1801 (C=O), 1669 (C=C), 1304 and 1128 (C-O); $\delta_{\text{H}}$ (CDCl$_3$, 250 MHz) 5.44 (1 H, s, OCH$_2$CH$_3$), 5.13 (1 H, d, J 2.7, C=CH), 4.86 (1 H, d, J 2.7, C=CH), 0.99 (9 H, s, (CH$_3$)$_3$).

2-Benzenesulfonyl-propionic acid methyl ester$^{196}$ (151)

[Chemical structure image]

Benzenesulfonic acid sodium salt (10 g, 61 mmol) and methyl-2-chloropropionate (7.47 g, 61 mmol) was refluxed in absolute ethanol (40 ml) for eighteen hours. The reaction mixture was then filtered and concentrated under reduced pressure to give a clear oil (8.51 g, 61 %); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 3065, 3003 (aromatic C-H), 2954, 2881 (sp$^3$ C-H), 1736 (-COO-), 1378, 1150 (-SO$_2$-) and 1084 (C-O); $\delta_{\text{H}}$ (CDCl$_3$, 250 MHz) 7.91-7.87 (2 H, m, CH-aromatic), 7.70-7.55 (3 H, m, CH-aromatic), 4.07 (1 H, q, J 7.2, CHCH$_3$), 3.68 (3 H, s, COOCH$_3$) and 1.58 (3 H, d, J 7.2, CHCH$_3$).

2-Benzenesulfonyl-2-phenylselanyl-propionic acid methyl ester (152)

[Chemical structure image]

To a stirred suspension of pentane-washed sodium hydride (0.35 g, 9 mmol) in dry tetrahydrofuran (20 ml), 2-benzenesulfonyl-propionic acid methyl ester (2 g, 9 mmol) in dry tetrahydrofuran (10 ml) was added at a temperature of −10 °C under a nitrogen atmosphere over fifteen minutes. After two hours the mixture was cooled further to −20 °C and phenylselenyl bromide (2.07 g, 9 mmol) in dry tetrahydrofuran (10 ml) was slowly added over fifteen minutes. After a further two hours the reaction mixture was allowed to warm to ambient temperature and was quenched with a saturated solution of ammonium chloride (10 ml). The tetrahydrofuran was removed under
reduced pressure and the residue was extracted with diethyl ether (3 x 100 ml) and washed with water (2 x 100 ml), brine (1 x 100 ml) and dried (Magnesium sulphate). The diethyl ether extracts were combined and evaporated under reduced pressure to give a yellow semi-solid. The product was further purified by flash column chromatography eluting with ethyl acetate/light petroleum (40 °C-60 °C) (1:9) on silica gel to give a yellow oil (1.16 g, 35 %); ν_max (film)/cm⁻¹ 3063 (aromatic C-H), 2953 (sp³ C-H), 1735 (COO-), 1324 and 1149 (-SO₂-); δ_H (CDCl₃, 250 MHz) 7.97 (2 H, dd, J 1.2, J' 8.4, CH-aromatic), 7.71-7.65 (3 H, m, CH-aromatic), 7.56-7.52 (2 H, m, CH-aromatic), 7.44-7.29 (3 H, m, CH-aromatic) 3.62 (3 H, s, COOCH₃) and 1.65 (3 H, s, CH₃); m/z (El) 383.99338 (M⁺); C₁₆H₁₆SO₄Se requires 383.99350.

2-Benzensulfonfyl-acrylic acid methyl ester (153)

2-Benzensulfonfyl-2-phenylselanyl-propionic acid methyl ester (1.12 g, 3 mmol) was stirred with the addition of 30 % hydrogen peroxide (0.23 ml, 7.5 mmol) in dichloromethane (30 ml) at 0 °C for one hour. The reaction vessel was momentarily taken out of the cold bath, and as the exothermic elimination started, it was cooled again to avoid polymerisation. The product was extracted with dichloromethane (50 ml), washed with sodium bicarbonate (50 ml), water (50 ml) and dried (sodium sulphate). The solvent was removed under vacuum without heating to give an oil as the product (0.55 g, 76 %); ν_max (film)/cm⁻¹ 2925, 2854 (sp³ C-H), 1740 (COO), 1648 (C=C), 1324 and 1146 (SO₂); δ_H (CDCl₃, 250 MHz) 8.00-7.97 (2 H, m, CH-aromatic) 7.68-7.52 (3 H, m, CH-aromatic), 7.16 (1 H, s, C=CH), 7.02 (1 H, s, C=CH) and 3.75 (3 H, s, CH₃); δ_C (100 MHz, CDCl₃) 147.0 (C=CH₂) 137.6 (C=CH₂), 133.8, 128.9, 128.8 (Ph) and 52.7 (Me); m/z (El) 226.02954 (M⁺); C₁₀H₁₀SO₄ requires 226.03000.
5-Methyl-hepta-3,5-dienyl propynoate\textsuperscript{40}(26)

\begin{center}
\includegraphics[width=0.2\textwidth]{5-Methyl-hepta-3,5-dienyl-propynoate.png}
\end{center}

\((E, E)-5\)-Methyl-3,5-heptadien-1-ol (0.34 g, 2.7 mmol) and propiolic acid (0.5 ml, 8 mmol) was stirred at room temperature in dry dichloromethane (15 ml) under a nitrogen atmosphere. After fifteen minutes 1,3-dicyclohexylcarbodiimide (1.65 g, 8 mmol) and 4-dimethylaminopyridine (catalytic amount) was added to the reaction mixture and left to stir for eighteen hours. The reaction mixture was then filtered, washed with dichloromethane and evaporated to dryness under reduced pressure. The product was purified by flash column chromatography using ethyl acetate/ light petroleum (40 \(^0\)C- 60 \(^0\)C) (1:3) as an eluent on silica gel absorbant to give an orange oil (0.3 g, 63 \%); \(\nu_{\text{max}}\) (film)/ cm\(^{-1}\) 3262 (alkyne), 2933, 2859 (sp\(^3\) C-H), 2120 (alkyne), 1718 (C=O), 1655 (C=C) and 1097 (C-O); \(\delta_H\) (CDCl\(_3\), 250 MHz) 6.15 (1 H, d, \(J 15.5, 4\)-H), 5.52-5.41 (2 H, m, 3-H and 6-H), 4.23 (2 H, t, \(J 6.9, 1\)-H), 2.87 (1 H, s, alkyne H), 2.47 (2 H, q, \(J 6.8, 2\)-H), 1.72 (3 H, s, 8-H), 1.71 (3H, d, \(J 5.2, 7\)-H).
Dimethyl-(5-methyl-hepta-3,5-dienyloxy)-vinyl-silane (169)

To a stirred solution of (E, E)-5-methyl-3,5-heptadien-1-ol (2g, 15.8 mmol) in dry dichloromethane (100ml), triethylamine (4.41 ml, 31.6 mmol) was added and left to stir for fifteen minutes at room temperature under a nitrogen atmosphere. Dimethylchlorovinylsilane (2.41 ml, 17.6 mmol) was then added dropwise to the reaction mixture and allowed to stir for sixteen hours before being reduced in volume and filtered to give a dark residue. This was further purified by flash column chromatography using ethyl acetate/light petroleum (40 °C - 60 °C) (2:98) as an eluent on silica gel absorbent to give a clear oil (2.15 g, 65 %); \( \nu_{\text{max}} \) (film)/ cm\(^{-1}\) 3031 (C=C-H), 2956, 2862 (sp\(^3\) C-H), 1650,1628, 1594 (C=C), 1251 (SiMe\(_2\)) and 1092 (C-O); \( \delta_{\text{H}} \) (CDCl\(_3\), 250 MHz) 6.20-5.96 (3 H, m, 4-H, SiCH=CH\(_2\) and SiCH=CH), 5.78 (1 H, dd, \( J 4.6, J' 19.3 \), SiCH=CH) 5.35-5.26 (2 H, m, 3-H and 6-H) 3.63 (2H, t, \( J 7.1 \), 1-H), 2.32 (2 H, q, \( J 7.1, 2-H \), 1.73 (3 H, s, 8-H), 1.70 (3 H, d, \( J 6.0, 7-H \)) and 0.18 (6 H, s, SiMe\(_2\)) ; \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 137.57 (C-4), 136.77 (CH=CH\(_2\)), 134.44 (C-5), 133.20 (CH=CH\(_2\)), 125.17 (C-3), 122.87 (C-6), 63.09 (C-1), 36.35 (C-2), 13.76 (C-7), 12.06 (C-8) and -2.02 (SiMe\(_2\)) ; \( m/z \) (EI) 210.14399 (M\(^+\)); \( \text{C}_{12}\text{H}_{22}\text{OSi} \) requires 210.14399.
Diphenyl-(5-methyl-hepta-3,5-dienyloxy)-vinyl-silane (32)

To a stirred solution of \((E, E)-5\text{-methyl-3,5-heptadien-1-ol}\) (2.85g, 22.6 mmol) in dry dichloromethane (100ml), triethylamine (6.35 ml, 45.2 mmol) was added at left to stir for fifteen minutes at room temperature under a nitrogen atmosphere. Diphenylchlorovinylsilane (4.99 ml, 22.6 mmol) was then added dropwise to the reaction mixture and allowed to stir for sixteen hours before being reduced in volume and filtered to give a dark residue. This was further purified by flash column chromatography using ethyl acetate/ light petroleum (40 \(^\circ\)C- 60 \(^\circ\)C) (2:98) as an eluent on silica gel absorbent to give a clear oil (6.19g, 82 %); \(\nu_{\text{max}}\) (film)/ cm\(^{-1}\) 3135, 3069 (C=C-H), 3051, 3024, 3001 (aromatic C-H), 2946, 2919, 2867 (sp\(^3\) C-H), 1591 (C=C) and 1118 (Si-O); \(\delta_h\) (CDCl\(_3\), 400 MHz) 7.62-7.59 (4 H, m, C-H aromatic), 7.41-7.34 (6 H, m, C-H aromatic), 6.45 (1 H, dd, \(J\) 14.9, \(J'\) 20.1, \(\text{CH}=\text{CH}_2\)), 6.26 (1 H, dd, \(J\) 4.2, \(J'\) 14.9, \(\text{CH}=\text{CH}_2\)), 6.08 (1 H, d, \(J\) 15.7, 4-H), 5.89 (1 H, dd, \(J\) 4.15, \(J'\) 20.1, \(\text{CH}=\text{CH}_2\)), 5.53-5.45 (2 H, m, 3-H and 6-H), 3.79 (2 H, t, \(J\) 6.9, 1-H), 2.38 (2 H, q, \(J\) 7.1, 2-H), 1.69 (3 H, s, 8-H) and 1.69 (3 H, d, \(J\) 5.3, 7-H); \(\delta_c\) (100 MHz, CDCl\(_3\)) 136.93 (CH=CH\(_2\)), 136.83 (C-4), 135.03 (Ph), 134.38 (C-5), 133.63 (CH=CH\(_2\)), 129.94, 128.68, 127.83 (Ph) 125.07 (C-3), 122.81 (C-6), 63.89 (C-1), 36.10 (C-2), 13.69 (C-7) and 11.99 (C-8); m/z (EI) 334.17529 (M\(^+\)); \(\text{C}_{22}\text{H}_{26}\text{OSi}\) requires 334.17529.
1,1,6,7-Tetramethyl-3,4,4a,7,8,8a-hexahydro-1H-benzo[c][1,2]oxasiline (170 and 171)

Dimethyl-(5-methyl-hepta-3, 5-dienyloxy)-vinyl-silane (2.15 g, 10.2 mmol), in dry toluene (2 ml) was heated in a sealed tube at 170 °C for ninety-six hours. The mixture was evaporated to dryness and purified by flash column chromatography eluting with ethyl acetate/light petroleum (40 °C-60 °C) (2:98) to give an oil as the product of (endo/ exo) isomers (5:4) (1.45 g, 67 %); ν<sub>max</sub> (film)/ cm<sup>-1</sup> 2958, 2849 (sp<sup>3</sup> C-H), 1663 (C=C), 1251 (SiMe₂), 1083 and 1048 (C-O); δ<sub>H</sub> (CDCl₃, 250 MHz) 5.41 (1 H, d, J 4, major 5-H), 5.22 (0.8 H, m, minor 5-H), 4.00-3.71 (3.6 H, m, major 2-H and minor 2-H), 2.34 (0.8 H, m, minor 7-H), 2.04 (0.8 H, m, minor 4-H), 2.00 (1H, m, major 7-H), 1.71 (1 H, m, major 4-H), 1.71 (5.4 H, s, major 10-H and minor 10-H), 1.70-1.25 (9 H, m, major 3-H, minor 3-H, major 8-H, minor 8-H, major 9-H and minor 9-H), 1.03 (3 H, d, J 7, major 11-H), 0.9788 (2.4 H, d, J 7, minor 11-H) and 0.19 (10.8 H, s, 2 x SiMe₂); δ<sub>C</sub> (400 MHz, CDCl₃) 141.11 (minor C-6), 140.62 (major C-6), 130.10 (minor C-5), 130.05 (major C-5), 67.51 (minor C-2), 66.90 (major C-2), 40.88 (minor C-7), 39.97 (minor C-3), 37.79 (major C-7), 37.47 (major C-4), 35.49 (major C-7), 35.47 (minor C-4), 32.59 (minor C-8), 31.66 (major C-8), 25.64 (minor C-9), 25.39 (major C-9), 24.96 (minor C-10), 23.98 (major C-10), 22.19 (minor C-11), 22.11 (major C-11), 0.04,0.00, -0.39, -3.26 (2 x SiMe₂); m/z (El) 210.14410 (M⁺); C₁₂H₂₂OSi requires 210.14399.
6,7-Dimethyl-1,1-diphenyl-3,4,4a,7,8,8a-hexahydro-1H-benzo[c][1,2]oxasiline (172 and 173)

Diphenyl-(5-Methyl-hepta-3,5-dienyloxy)-vinyl-silane (4.10 g, 12.2 mmol) was heated in a sealed tube at 170 °C for ninety-six hours. The mixture was evaporated to dryness and purified by flash column chromatography eluting with ethyl acetate/light petroleum (40 °C-60 °C) (2:98) to give an oil as the product of (endo/exo) isomers (5:4) (3.90 g, 95 %). νmax (film)/ cm⁻¹ 3069, 3050 (CH-aromatic), 2922, 2852, 1462 (sp³ C-H), 1118 (Si-O) and 1080 (C-O); δH (CDCl₃, 250 MHz) 7.70-7.48 (7.2 H, m, CH-aromatic), 7.42-7.25 (10.8 H, m, CH-aromatic), 5.41 (1 H, m, major 5-H), 5.22 (0.8 H, m, minor 5-H), 4.24-4.09 (2.8 H, m, major 2-H and minor 2-H), 3.87 (1 H, m major 2-H), 2.40 (1 H, m, major 4-H), 2.26 (1 H, m, minor 4-H), 2.03 (1 H, m, major 9-H), 1.90 (0.8 H, m, minor 9-H), 1.85-1.45 (9 H, m, major 7-H, minor 7-H, major 3-H, minor 3-H, major 8-H and minor 8-H), 1.65 (2.4 H, s, minor 10 H), 1.64 (3 H, s, 1 H), 1.08 (2.4 H, d, J=7, 11-H) and 0.93 (3 H, d, J=7, 11-H).

The endo isomer can be isolated by flash chromatography and crystalises on cooling to give a white crystalline solid (m.p. 39 °C- 41 °C); δH (CDCl₃, 400 MHz) (major isomer) 7.70-7.67 (2 H, m, CH-aromatic), 7.51-7.49 (2 H, m, CH-aromatic), 7.41-7.32 (6 H, m, C-H aromatic) 5.41 (1 H, m, 5-H), 4.11 (1 H, ddd, J=11, J'=14, J''=2, 2-H), 3.87 (1 H, dt, J=1, J'=13, 2-H), 2.40 (1 H, m, 4-H), 2.03 (1 H, m, 9-H), 1.80 (1 H, dq, J=4, J'=14, 7-H), 1.68 (1 H, m, 8-H), 1.64 (3 H, s, 10-H), 1.57-1.45 (3 H, m, 10-H and 3-H), 0.93 (3 H, d, J=7, 11-H); δC (100 MHz, CDCl₃) (major isomer) 138.24 (C-6), 134.88, 134.66, 134.57, 134.04, 129.87, 129.83, 128.03, 127.83 (Ph), 127.50 (C-5), 64.94 (C-2), 35.61 (C-7), 35.10 (C-4), 32.89 (C-3), 29.37 (C-8), 21.14 (C-9), 20.71 (C-10), 19.44 (C-11); CHN analysis C 78.59 %, H 7.85 %, N 0.03 %; C₂₄H₂₆OSi requires C
78.99 %, H 7.83 %, O 4.78 %, Si 8.40 %; m/z (El) 334.17487 (M+); C_{22}H_{26}O_{Si} requires 334.17529.

1,6-Dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol (174 and 175)

(Method A)

6,7-Dimethyl-1,1-diphenyl-3,4,4a,7,8,8a-hexahydro-1H-benzo[c][1,2]oxasiline (3.95 g, 11.8 mmol), potassium hydrogen carbonate (1.18 g 11.8 mmol) in 50:50 tetrahydrofuran/ methanol (100 ml) was stirred at room temperature for ten minutes. The 30 % hydrogen peroxide (4.74 ml, 153 mmol) was added to the reaction mixture and heated to reflux for four hours. The mixture was then poured into water and extracted with diethyl ether (5 x 100 ml). The combined extract was washed with 10 % sodium sulphite solution (200 ml), saturated sodium hydrogen carbonate (200 ml) and dried (sodium sulphate) then reduced in volume to give a clear oil. Further purification by flash column chromatography eluting with ethyl acetate/light petroleum (40 °C-60 °C) (1:3) to gives an oil as the product (1.57 g 78 %) of isomers (endo/exo) (5:4); 3332 (O-H), 2918 (sp³ C-H), 1660 (C=C), 1446 (sp³ C-H), 1063 and 1001 (C-O); δH (CDCl₃, 400 MHz) 5.30-5.28 (1 H, m, major 2-H), 5.05-5.04 (0.8 H, m, minor 2-H), 4.00 (1 H, ddd, J' 11.2, J' 5.6, J' 3.6, major 4-H), 3.84-3.69 (4.4 H, m, major 2'-H, minor 4-H and minor 2'-H), 2.40-2.37 (1 H, m, major 3-H), 2.20 (1.8 H, m, major 6-H and minor 3-H), 2.09-2.08 (0.8 H, m, minor 6-H) 1.87-1.64 (4.4 H, m, major 5-H, major 1'-H, minor 5-H and minor 1'-H) 1.67 (2.4 H, s, minor 7-H) 1.65 (3 H, s, major 7-H) 1.56-1.46 (2.6 H, m, major 5-H and minor 1'H and minor 5-H) 1.07 (3 H, d, J 7.2, minor 8-H) and 1.05 (3 H, d, J 7.2, major 8-H); δC (100 MHz, CDCl₃) 138.35 (minor C-1), 137.54 (major C-1) 124.46 (major C-2), 124.33 (minor C-2), 69.08 (major C-4) 69.08 (minor C-4) 61.67 (major C-2'), 61.52 (minor C-2'), 43.86 (minor C-3), 39.74 (major C-3), 38.57 (minor C-5), 38.39 (major C-5), 36.55 (major C-1'), 34.51 (major C-6), 33.98 (minor C-6), 33.51 (minor C-1'), 21.59 (minor C-7),
20.96 (major C-7), 19.93 (minor C-8) and 19.85 (major C-8); m/z (FAB) 171.13847 (M^+H); C_{10}H_{18}O + H requires 171.13851.

1,6-Dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol (174 and 175)

(Method B)

1,1,6,7-Tetramethyl-3,4,4a,7,8,8a-hexahydro-1H-benzo[c][1,2]oxasiline (1.3 g, 6.2 mmol), potassium hydrogen carbonate (0.62 g, 6.2 mmol) in 50:50 tetrahydrofuran/methanol (50 ml) was stirred at room temperature for ten minutes. The 30% hydrogen peroxide (2.48 ml, 80 mmol) was added to the reaction mixture and heated to reflux for four hours. The mixture was then poured into water and extracted with diethyl ether (5 x 50 ml). The combined extract was washed with 10% sodium sulphite solution (100 ml), saturated sodium hydrogen carbonate (100 ml) and dried (sodium sulphate) then reduced in volume to give a clear oil. Further purification by flash column chromatography eluting with ethyl acetate/light petroleum (40 °C-60 °C) (1:3) to give an oil as the product (0.60 g, 57%) of isomers (endo/ exo) (5:4).

For spectroscopic analysis see Method A.

1,6-Dimethyl-3-[2-(hydroxy)-ethyl]-cyclohexen-4-ol (174 and 175)

(Method C)

6,7-Dimethyl-1,1-diphenyl-3,4,4a,7,8,8a-hexahydro-1H-benzo[c][1,2]oxasiline (0.50 g, 1.5 mmol), potassium hydrogen difluoride (0.2 g, 3 mmol) in N,N-
dimethylformamide (30 ml) was stirred at room temperature for ten minutes. The 30% hydrogen peroxide (0.59 ml, 19 mmol) was added to the reaction mixture and heated to 60 °C for sixteen hours. The mixture was then poured into water and extracted with diethyl ether (5 x 100 ml). The combined extract was washed with 10% sodium sulphite solution (200 ml), saturated sodium hydrogen carbonate (200 ml) and dried (sodium sulphate) then reduced in volume to give a clear oil. Further purification by flash column chromatography eluting with ethyl acetate/light petroleum (endo/exo) (5:4).

For spectroscopic analysis see Method A.

1,6-Dimethyl-3-[2-(benzyloxy)-ethyl]-cyclohexen-4-ol (179)

To a stirred solution of 1,6-dimethyl-3-(2-hydroxy-ethyl)-cyclohexen-4-ol (0.45 g, 2.7 mmol) in dry tetrahydrofuran (20 ml) was added sodium hydride (0.11 g, 2.8 mmol) and left under a nitrogen atmosphere at 0 °C for forty five minutes. Benzyl bromide (0.31 ml, 2.7 mmol) was added and the resultant mixture was left to stir for four hours at room temperature. The reaction mixture was quenched with aqueous saturated ammonium chloride solution (50 ml). The aqueous phase was extracted with diethyl ether (5 x 50 ml) washed with water (3 x 50 ml), brine (3 x 50 ml), and dried with magnesium sulfate then evaporated to dryness. The product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/light petroleum (40 °C- 60 °C) (5:95) as an eluent to afford an oil (0.5 g, 72 %) of isomers (endo/exo) (5:4); νmax (film)/ cm⁻¹ 3408 (O-H), 3087, 3062 (C-H aromatic), 2930, 2869 (sp³ C-H), 1656, 1605 (C=C) and 1094 (C-O); δH (CDCl₃, 250 MHz) 7.35-7.25 (9 H, m, CH-aromatic) 5.36-5.34 (1 H, m, major 2-H), 5.22-5.20 (0.8 H, m, minor 2-H) 4.53-4.45 (3.6 H, m, CH₂Ph), 3.68-3.49 (4.6 H, m, major 4-H, major 2'-H and
minor 2'-H), 3.44-3.38 (0.8 H, m, minor 4-H) 2.58-2.50 (1 H, m, major 3-H), 2.31-2.05 (2.6 H, m, major 6-H, minor 3-H and minor 6-H), 1.92-1.84 (1.6 H, m, major 5-H and minor 5-H) 1.78-1.45 (5.4 H, m, major 1'-H, major 5-H, minor 1'-H and minor 5-H) 1.71 (2.4 H, s, minor 7-H), 1.64 (3 H, s, major 7-H) 1.05 (2.4 H, d, J 7.2, minor 8-H) and 1.04 (3 H, d, J 7.2, major 8-H); δc (100 MHz, CDCl3) 138.58 (Ph), 137.94 (minor C-1), 137.76 (Ph), 137.59 (major C-1), 128.49, 128.40, 127.87, 127.77, 127.62, 127.58 (Ph), 124.19 (minor C-2), 124.15 (major C-2), 73.54 (major CH2Ph), 73.11 (minor CH2Ph) 69.61 (minor C-4), 69.31 (major C-4), 63.46 (minor C-2'), 62.78 (major C-2'), 44.27 (minor C-3), 39.41 (major C-3), 37.93 (major C-1'), 36.64 (minor C-1'), 35.48 (major C-5), 34.10 (minor C-6) 33.66 (major C-6), 30.52 (minor C-5), 21.64 (major C-7), 21.14 (minor C-7), 19.98 (minor C-8) and 19.90 (major C-8); m/z (EI) 260.17761 (M+); C17H24O2 requires 260.17763.

2-(2-Benzylolxy-ethyl)-4,5-dimethyl-cyclohex-3-enone (192)

\[ \text{BnO} \]

\[ \text{O} \]

(Method A)

A solution of 3,4,5-trimethoxy benzyl alcohol (0.27 g, 0.63 mmol) in dichloromethane (10 ml) was slowly added to a solution of 1,6-dimethyl-3-[2-(benzyloxy)-ethyl]-cyclohexen-4-ol (0.15 g, 0.58 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for one hour under a nitrogen atmosphere before the addition of diethyl ether (40 ml). The resultant mixture was poured into saturated aqueous sodium hydrogen carbonate solution (50 ml) containing a sevenfold excess of sodium thiosulfate. The mixture was stirred to dissolve any solid and the layers separated. The diethyl ether extract was washed with saturated sodium hydrogen carbonate (50 ml), water (50 ml), dried (magnesium sulfate) and reduced in volume under reduced pressure. The product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/light petroleum (40
2-(2-Benzyloxy-ethyl)-4,5-dimethyl-cyclohex-3-enone (192)

\[
\begin{align*}
\text{BnO} & \quad \text{C}\text{O} \\
\text{2-(2-Benzyloxy-ethyl)-4,5-dimethyl-cyclohex-3-enone (192)}
\end{align*}
\]

(Method B)

To stirred solution of pyridinium dichlorochromate (1.21 g, 3.2 mmol) in dry dichloromethane (50 ml) under nitrogen, a solution of 1,6-dimethyl-5-[2-(benzyloxy)-ethyl]-cyclohexen-4-ol (0.56 g, 2.2 mmol) in dichloromethane (10 ml) was added at room temperature. The reaction mixture was stirred for a period of sixteen hours before the addition of diethyl ether (150 ml) and then the supernatant was decanted from the black gum. The insoluble residue was washed thoroughly with diethyl ether (3 x 50 ml) and the combined extracts were filtered through a pad of celite. The solvent was removed by reduced pressure and the product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/ light petroleum (40 °C- 60 °C) (1:9) as an eluent to afford a clear oil (0.31 g, 55%).

For spectroscopic analysis see Method A.
2-(2-Benzylxy-ethyl)-4,5-dimethyl-cyclohex-3-enone (192)

(Method C)
To a stirred solution of dichloromethane (15 ml) and oxaly chloride (0.07 ml, 0.76 mmol), dimethyl sulfoxide (0.1 ml, 1.4 mmol) was added slowly and stirred for five minutes. 1,6-Dimethyl-3-[2-(benzyloxy)-ethyl]-cyclohexen-4-ol (0.18 g, 0.69 mmol) in dichloromethane (5 ml) was then added over five minutes at a temperature between -50 °C and -60 °C. The reaction mixture was stirred for a further ten minutes before the addition of triethylamine (0.48 ml, 3.5 mmol) and stirred for ten minutes before allowing the reaction to warm to room temperature. The reaction was quenched with the addition of water (50 ml), then extracted with dichloromethane (3 x 50 ml), washed with brine (100 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by reduced pressure and the product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/light petroleum (40 °C- 60 °C) (1:9) as an eluent to afford a clear oil (0.09 g, 50 %). For spectroscopic analy

2-(2-Benzylxy-ethyl)-4,5-dimethyl-cyclohex-3-enone (192)

(Method D)
A solution of 1,6-dimethyl-3-[2-(benzyloxy)-ethyl]-cyclohexen-4-ol (0.25 g, 0.96 mmol) in dry dichloromethane (10 ml) containing 4 Å molecular sieves and 4-methylmorpholine-N-oxide (0.19 g, 1.4 mmol) was stirred at room temperature under
a nitrogen atmosphere. A catalytic amount of tetra-n-propylammonium peroxenate was then added and the reaction mixture was stirred for a further eight hours. The mixture was then diluted further with dichloromethane (30 ml) and washed with sodium sulfite solution (50 ml), brine (50 ml), saturated copper sulfite solution and dried with anhydrous magnesium sulfate. The solvent was removed by reduced pressure and the product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/light petroleum (40 °C-60 °C)(1:9) as an eluent to afford a clear oil (0.12 g, 50%).

For spectroscopic analysis see Method A.

1,6-Dimethyl-3-[2-(tert-butyldimethylsilanyloxy)-ethyl]-cyclohexen-4-ol (182)

$$\begin{align*}
\text{TBDMOSO} & \quad \text{OH} \\
\text{TBDMOSO} & \quad \text{OH}
\end{align*}$$

1,6-dimethyl-3-(2-hydroxy-ethyl)-cyclohexen-4-ol (0.3 g, 1.8 mmol), imidazole (0.3 g, 4.4 mmol), tert-butyl-dimethylsilylchloride (0.51 g, 1.8 mmol) was stirred in dry DMF (10 ml) under nitrogen at room temperature for 2 hrs. The reaction was quenched with water, extracted with diethyl ether (3 x 50 ml), dried with magnesium sulfate and evaporated to dryness. Flash column chromatography using silica gel as an absorbent and ethyl acetate/light petroleum (40 °C-60 °C)(1:9) as an eluent afforded the desired product as a clear oil (0.32 g, 64%) of isomers (endo/exo) (10:9); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3363 (O-H), 2929, 2857 (sp$^3$C-H) 1661 (C=C), 1255 (Si-Me$_2$), 1093 and 1005 (C-O); $\delta_H$ (CDCl$_3$, 400 MHz) 5.26 (1 H, dt, $J$ 4.8, $J'$ 1.6, major 2-H), 5.02-5.01 (0.9 H, m, minor 2-H), 3.95-3.90 (1 H, m, major 4-H), 3.85-3.55 (4.7 H, m, minor 4-H, minor 2"-H and major 2"-H), 2.38-2.35 (1 H, m, major 3-H), 2.21-2.16 (1.9 H, m, minor 3-H and major 6-H), 2.06-2.03 (0.9 H, m, minor 6-H), 1.86-1.81 (2 H, m, major 5-H and major 1'-H), 1.76-1.72 (1.8 H, m, minor 5-H and minor 1'-H), 1.67 (2.7 H, s, minor 7-H), 1.65 (3 H, s, major 7-H), 1.60-1.41 (3.8 H, m, major 5-H, major 1'-H, minor 5-H and minor 1'-H), 1.07 (2.7 H, d, J 7.2, minor 8-H), (3 H, d, J 7.2, major 8-H), 0.92 (8.1 H, s, minor C(CH$_3$)$_3$), 0.91 (9 H, s, major C(CH$_3$)$_3$), 0.09 (11.4 H, s, 2 x
SiMe$_2$; $\delta$ (CDCl$_3$, 400 MHz) 138.50 (minor C-1), 137.59 (major C-1), 124.61 (minor C-2), 124.51 (major C-2), 68.69 (minor C-4), 68.68 (major C-4), 62.87 (minor C-2'), 62.56 (major C-2'), 44.83 (minor C-3), 38.92 (major C-3), 38.93 (major C-1'), 37.95 (minor C-1'), 36.94 (major C-5), 34.18 (major C-6), 33.89 (minor C-6), 33.45 (minor C-5), 25.93 (major C(CH$_3$)$_3$), 25.89 (minor C(CH$_3$)$_3$), 21.63 (minor C-7), 21.09 (major C-7) 19.96 (major and minor C-8), 18.28 (major C(CH$_3$)$_3$), 18.00 (minor C(CH$_3$)$_3$), -5.42 and -5.46 (2 x SiMe$_2$); m/z (El) 284 (M$^+$).

1,6-Dimethyl-3-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-cyclohexen-4-ol (186 and 187)

1,6-Dimethyl-3-(2-hydroxy-ethyl)-cyclohexen-4-ol (3.0 g, 17.6 mmol) and imidazole (3.0 g, 44 mmol) was stirred in dry DMF (10 ml) under nitrogen at 0 °C for 30 minutes. This was followed by the addition of tert-butyl-diphenylsilylchloride (5.0 ml, 19.4 mmol) and allowed to warm to room temperature whilst stirring for sixteen hours. The reaction was quenched with water, extracted with diethyl ether (3 x 50 ml), dried with magnesium sulfate and evaporated to dryness. Flash column chromatography using silica gel as an absorbent and ethyl acetate/light petroleum (40 °C-60 °C) (1:9) as an eluent afforded the desired product as a clear oil (6.20 g 86%) of isomers (endo/ exo) (10:9); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 3385 (O-H), 3070 (aromatic C-H), 2931 (sp$^3$ C-H), 1589 (C=O), 1241 (Si-Ph$_2$) and 1111 (C-O); $\delta$(H) (CDCl$_3$, 400 MHz) 7.65-7.59 (7.6 H, m, CH-aromatic), 7.38-7.27 (11.4 H, m, CH-aromatic), 5.16-5.15 (1 H, m, major 2-H), 4.95-4.94 (0.9 H, m, minor 2-H), 3.90-3.88 (1 H, m, major 4-H), 3.82-3.69 (4.7 H, m, minor 4-H, minor 2'-H and major 2'-H), 2.35-2.32 (1 H, m, major 3-H), 2.17-2.05 (2.8 H, m, major 6-H and minor 6-H and minor 3-H), 1.80-1.78 (1.9 H, m, major 5-H and minor 5-H), 1.71-1.52 (3.8 H, m, major 1'-H and minor 1'-H), 1.58 (2.7 H, s, minor 7-H), 1.55 (3 H, s, major 7-H), 1.45-1.37 (1.9 H, m, major 5-H).
1,6-Dimethyl-3-[2-(2,2-dimethyl-propionic acid)-ethyl ester]-cyclohexen-4-ol (178)

1,6-Dimethyl-3-(2-hydroxy-ethyl)-cyclohexen-4-ol (0.78 g, 4.6 mmol) was stirred in dry pyridine (4.6 ml) and dry dichloromethane (10 ml) at a temperature of 0 °C under a nitrogen atmosphere. Pivaloyl chloride (0.56 ml, 4.6 mmol) was then added dropwise to the reaction mixture and the mixture was allowed to warm to room temperature and stirred for sixteen hours. The solvent was removed by reduced pressure and the product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/ light petroleum (40 °C- 60 °C) (1:3) as an eluent to afford a clear oil (0.56 g, 48 %) as endo/ exo isomers (2:1); ν_max (film)/ cm⁻¹ 3443 (O-H), 2963, 2933, 2872 (sp³ C-H), 1727 (COO), 1595 (C=C) and 1161 (C-O); δ_H (CDCl₃, 400 MHz) 5.31-5.30 (1 H, m, major 2-H), 5.19-5.18 (0.5 H, m, minor 2-H), 4.25-4.11 (3 H, m, major 3'-H and minor 2'-H), 4.02-3.97 (1 H, m, major 4-H) 3.75-3.66 (0.5 H, m, minor 4-H), 2.31-2.30 (1 H, m, major 3-H), 2.22-2.17 (1.5 H, m, major 6-H and minor 3-H), 2.12-2.09 (0.5 H, m, minor 6-H), 2.04-1.98 (1 H, m, major 5-H), 1.89-1.76 (2 H, m, major 1'-H, minor 5-H and 1'-H), 1.67 (1.5 H, s, minor 7-H), 1.65 (3 H, s, major 7-H), 1.63-1.59 (1 H, m, major 1'-H), 1.54-1.45 (2 H, m, major 5-
H, minor 5-H and 1'-H) 1.26 (4.5 H, s, minor C(CH$_3$)$_3$), 1.06 (1.5 H, d, $J$ 6.8, minor 8-H) and 1.05 (3 H, d, $J$ 7.2, major 8-H); ($\delta$$_C$ (CDCl$_3$, 100 MHz) 178.79 (minor C=O), 178.70 (major C=O), 138.66 (minor C-1), 137.31 (major C-1), 123.29 (major C-2), 122.49 (minor C-2), 69.17 (major C-4), 68.67 (minor C-4), 63.44 (major C-2'), 62.75 (minor C-2'), 41.79 (minor C-3), 38.75 (major C(CH$_3$)$_3$), 38.50 (minor C(CH$_3$)$_3$), 38.26 (minor C-1'), 37.80 (major C-3), 36.48 (major C-1'), 34.11 (major C-6), 32.91 (minor C-6), 32.50 (minor C-5), 29.34 (major C-5), 27.22 (minor C(CH$_3$)$_3$ and major C(CH$_3$)$_3$), 21.62 (minor C-7), 20.03 (major C-7) 19.91 (major C-8) and 19.82 (minor C-8). m/z (EI) 254.18777 (M$^+$); C$_{15}$H$_{26}$O$_3$ requires 254.18820.

2-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone (193)

To stirred solution of pyridinium dichlorochromate (0.40 g, 1.0 mmol) in dry dichloromethane (50 ml) under nitrogen, a solution of 1,6-dimethyl-3-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-cyclohexen-4-ol (0.20 g, 0.7 mmol) in dichloromethane (10 ml) was added at room temperature. The reaction mixture was stirred for a period of sixteen hours before the addition of diethyl ether (150 ml) and then the supernatant was decanted from the black gum. The insoluble residue was washed thoroughly with diethyl ether (3 x 50 ml) and the combined extracts were filtered through a pad of celite. The solvent was removed by reduced pressure and the product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/ light petroleum (40°C- 60°C) (1:9) as an eluent to afford a clear oil (0.08 g, 40 %); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 3057 (aromatic C-H), 2956, 2910, 2857 (sp$^3$ C-H), 1665 (C=O), 1556 (C=C), 1256 (Si-Me$_2$) and 1099 (C-O); $\delta$$_H$ (CDCl$_3$, 250 MHz) 5.35-5.33 (1 H, m, 3-H), 3.68 (2 H, t, $J$ 6.4, 2'-H), 2.96-2.93 (1 H, m, 2-H), 2.70 (1 H, dd, $J$ 6.4, $J'$ 13.1, 6-H), 2.52-2.49 (1 H, m, 5-H), 2.25 (1 H, dd, $J$ 4.4, $J'$ 13.1, 6-H), 2.05-2.00 (1 H, m, 1'-H), 1.77 (3 H, s, 7-H), 1.61-1.56 (1 H, m, 1'-H), 1.03 (3 H, d, $J$ 7.1, 8-H),

188
0.88 (9 H, s, C(CH$_3$)$_3$) and 0.44 (6 H, s, SiMe$_2$); $\delta$$_C$ (CDCl$_3$, 400 MHz) 211.83 (C-1), 139.96 (C-4), 123.16 (C-3), 60.74 (C-2'), 46.28 (C-2), 45.24 (C-6), 36.90 (C-5), 33.96 (C-1'), 25.94 (C(CH$_3$)$_3$) 22.70 (C-7), 20.80 (C-8) 17.50 (C(CH$_3$)$_3$) and 5.30 (SiMe$_2$) ; m/z (El) 282.20174 (M$^+$); C$_{16}$H$_{30}$O$_2$Si requires 282.20151.

2-[2-( tert-Butyl-diphenyl-silyloxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone (194)

![Image](image.png)

(Method A)

A solution of 1,6-dimethyl-3-[2-( tert-butyl-diphenyl-silyloxy)-ethyl]-cyclohexen-4-ol (3.25 g, 8 mmol) in dry dichloromethane (10 ml) containing 4 Å molecular sieves and 4-methylmorpholine-N-oxide (1.61 g, 12 mmol) was stirred at room temperature under a nitrogen atmosphere. A catalytic amount of tetra-$n$-propylammonium per­ruthenate was then added and the reaction mixture was stirred for a further eight hours. The mixture was then diluted further with dichloromethane (30 ml) and washed with sodium sulfite solution (50 ml), brine (50 ml), saturated copper sulfite solution (50 ml) and dried with anhydrous magnesium sulfate. The solvent was removed by reduced pressure and the product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/light petroleum (40°- 60°) (1:9) as an eluent to afford a clear oil (2.35 g, 73 %); $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 3070 (aromatic C-H), 2958 (sp$^3$ C-H), 1717 (C=O), 1589 (C=C), 1111 (C-O); $\delta$$_H$ (CDCl$_3$, 250 MHz) 7.68-7.33 (10 H, m, CH-aromatic) 5.32-5.28 (1 H, m, 3-H), 3.80-3.69 (2 H, m, 2'-H), 3.02-2.98 (1 H, m, 2-H), 2.68 (1 H, dd, $J$ 6.5, $J'$ 12.5, 6-H), 2.55-2.48 (1 H, m, 5-H), 2.24 (1 H, dd, $J$ 4.4, $J'$ 13.1, 6-H), 2.17-2.04 (1 H, m, 1'-H), 1.75 (3 H, s, 7-H), 1.65-1.49 (1 H, m, 1'-H), 1.04 (9 H, s, C(CH$_3$)$_3$) and 1.01 (3 H, d, $J$ 7.2, 8-H); $\delta$$_C$ (CDCl$_3$, 400 MHz) 211.72 (C-1), 138.94 (C-4), 135.59, 133.89, 129.58, 127.63 (Ph), 122.98 (C-3), 61.52 (C-2'), 46.23 (C-2), 45.17 (C-6), 36.84 (C-5), 33.91 (C-1'), 26.88 (C(CH$_3$)$_3$) 21.29 (C-7), 19.96 (C-8) and 19.21 (C(CH$_3$)$_3$); m/z (El) 406.23310 (M$^+$); C$_{26}$H$_{34}$O$_2$Si requires 406.23281.
To stirred solution of pyridinium dichlorochromate (0.62 g, 1.7 mmol) in dry 
dichloromethane (30 ml) under nitrogen, a solution of 1,6-dimethyl-3-[2-(tert-butyl-
diphenyl-silanyloxy)-ethyl]-cyclohexen-4-ol (0.45 g, 1.1 mmol) in dichloromethane 
(10 ml) was added at room temperature. The reaction mixture was stirred for a period 
of sixteen hours before the addition of diethyl ether (150 ml) and then the supernatant 
was decanted from the black gum. The insoluble residue was washed thoroughly with 
diethyl ether (3 x 50 ml) and the combined extracts were filtered through a pad of 
celite. The solvent was removed by reduced pressure and the product was then 
purified by flash column chromatography using silica gel as an absorbent and ethyl 
acetate/light petroleum (40 °C-60 °C) (1:9) as an eluent to afford a clear oil (0.40 g, 
89%).

For spectroscopic analysis see Method A.

1,6-Dimethyl-3-(2-benzyloxy-ethyl)-4-trimethylsilanyloxy-cyclohexene-4-
carbonitrile (209 and 210)

2-(2-benzyloxy-ethyl)-4,5-dimethyl-cyclohex-3-enone (0.1 g, 0.39 mmol) in dry 
chloroform (5 ml), trimethylsilyl cyanide (0.06 ml, 0.43 mmol), was carefully added 
at room temperature under dry conditions with an atmosphere of nitrogen. A catalytic
amount of zinc iodide was added after five minutes and the reaction mixture was stirred for a period of four hours. The solvent was then removed under reduced pressure and the product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/ light petroleum (40 °C- 60 °C) (1:9) as an eluent to afford a clear oil (0.07 g, 45 %) as a mixture of isomers (2:1); νmax (film)/cm⁻¹ 3030 (aromatic C-H), 2959, 2860 (sp³ C-H), 2229 (nitrile), 1608 (C=C), 1253 (SiMe₃) and 1123 (C-O); δH (CDCl₃, 400 MHz) 7.35-7.25 (7.5 H, m, major and minor CH-aromatic) 5.60-5.58 (0.5 H, m, minor 2-H), 5.34 (1 H, d, J 8, major 2-H), 4.55-4.47 (3 H, m, major CH₂Ph and minor CH₂Ph), 3.65-3.54 (3 H, m, major 2'-H and minor 2'-H), 2.65-2.60 (1 H, m, major 3-H), 2.50-2.40 (2 H, m, major 6-H, minor 3-H and minor 6-H), 2.30-2.00 (4.5 H, m, major 5-H, major 1'-H, minor 5-H and minor 1'-H), 1.65 (3 H, s, major 7-H), 1.64 (1.5 H, s, minor 7-H) 1.35-1.30 (1 H, m, major 5-H), 1.21-1.18 (0.5 H, m, minor 5-H), 1.05 (3 H, d, J 8, major 8-H), 1.03 (1.5 H, d, J 8, minor 8-H), 0.25 (9 H, s, major SiMe₃) and 0.24 (4.5 H, s, SiMe₃); δC (CDCl₃, 100 MHz) 137.23 (minor C-1), 137.16 (major C-1), 136.59, 136.49, 133.63, 127.06, 126.40, 126.35, 126.29, 126.22 (Ph), 121.20 (minor C-2), 120.77 (major C-2), 120.00 (major nitrile), 119.95 (minor nitrile), 71.67 (minor C-4), 71.62 (major CH₂Ph), 71.61 (minor CH₂Ph), 70.00 (major C-4) 66.86 (major C-2'), 66.74 (minor C-2'), 43.15 (minor C-3), 41.04 (major C-3), 39.00 (minor C-5), 38.54 (major C-5), 36.79 (minor C-6), 32.46 (major C-6), 29.86 (major C-1'), 28.50 (minor C-1'), 19.64 (major C-7), 19.34 (minor C-7), 17.79 (minor C-8), 17.75 (major C-8), 0.12 (minor SiMe₃) and 0.10 (major SiMe₃); m/z (El) 357.21308 (M⁺); C₂₁H₃₁O₂NSi requires 357.21241.
To a solution of 2-[2-(tert-butyl-diphenyl-silanyloxy)-ethyl]-4,5-dimethyl-cyclohex-3-enone (0.3 g, 0.74 mmol) in dry chloroform (5 ml), trimethylsilyl cyanide (0.15 ml, 1.1 mmol), was carefully added at room temperature under dry conditions with an atmosphere of nitrogen. A catalytic amount of zinc iodide was added after five minutes and the reaction mixture was stirred for a period of sixteen hours. The solvent was then removed under reduced pressure and the product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/ light petroleum (40 0C- 60 0C) (1:9) as an eluent to afford a clear oil (0.06 g, 16 %) as a mixture of isomers (2:1); v_max (film)/ cm\(^{-1}\) 3070, 3049 (aromatic C-H), 2959, 2858 (sp\(^3\) C-H), 2229 (nitrile), 1589 (C=C), 1253 (SiMe\(_3\)) and 1112 (C-O); \(\delta_H\) (CDCl\(_3\), 250 MHz) 7.69-7.66 (6 H, m, CH-aromatic), 7.40-7.38 (9 H, m, CH-aromatic), 5.65-5.64 (0.5 H, m, minor 2-H), 5.30-5.29 (1 H, m, major 2-H), 3.84-3.74 (3 H, m, major 2'-H and minor 2'-H), 2.68-2.60 (1 H, m, major 3-H), 2.48-2.40 ( 2 H, m, major 6-H, minor 3-H and minor 6-H), 2.18-1.53 (4.5 H, m, major 5-H, major 1'-H, minor 5-H and minor 1’-H), 1.65 (3 H, s, major 7-H) 1.64 (1.5 H, s, minor 7-H), 1.31-1.20 (1.5 H, m, major 5-H and minor 5-H), 1.05 (9 H, s, major C(CH\(_3\))\(_3\)), 1.04 (4.5 H, s, minor C(CH\(_3\))\(_3\)), 0.94 (1.5 H, d, J 6.6, minor 8-H), 0.82 (3 H, d, J 6.8, major 8-H), 0.24 (9 H, s, major SiMe\(_3\)) and 0.22 (4.5 H, s, minor SiMe\(_3\)); \(\delta_C\) (CDCl\(_3\), 100 MHz) 136.22 (major C-1), 134.32 (minor C-1), 134.31, 133.95, 128.36, 128.34, 128.26, 128.24, 126.39, 126.37 (Ph), 126.37 (major nitrile) 126.32 (minor nitrile) 121.31 (major C-2), 121.31 (major C-2), 120.96 (major C-2), 70.16 (minor C-4), 70.02 (major C-4), 61.91 (minor C-2’), 60.52 (major C-2’), 40.78 (major C-3), 39.01 (minor C-5), 38.65 (major C-5), 35.00 (minor C-5), 32.70 (major C-1’), 32.34 (major C-6), 32.28 (minor C-1’), 27.79 (minor C-6), 25.62 (major C(CH\(_3\))\(_3\)) 25.59 (minor C(CH\(_3\))\(_3\)), 19.65 (major C-7), 17.96 (minor C-7), 17.77 (major C-8), 16.94 (minor C-8) 13.20 (major
C(CH$_3$)$_3$, 13.00 (minor C(CH$_3$)$_3$), 0.11 (minor SiMe$_3$) and 0.07 (major SiMe$_3$); m/z (El) 448.21236 (M-‘Bu); C$_{26}$H$_{27}$NO$_2$Si$_2$ requires 448.21281.

[2-(2-Benzylxy-ethyl)-1-hydroxy-4,5-dimethyl-cyclohex-3-enyl]-propynoic acid methyl ester (218)

A solution of methyl propynoate (0.12 ml, 1.4 mmol) in of dry tetrahydrofuran (40 ml) was cooled to −100 °C, and n-Butyllithium (2.5 M solution in hexane) (0.56 ml, 1.4 mmol) was added dropwise over thirty minutes. After stirring for another ten minutes 2-(2-benzyloxy-ethyl)-4,5-dimethyl-cyclohex-3-enone (0.3 g, 1.2 mmol) was added in tetrahydrofuran (5 ml). The temperature was allowed to rise to −80 °C and the mixture was stirred for a further thirty minutes. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (5 ml), the mixture was warmed up to room temperature, the organic layer was decanted and the residue was washed with diethyl ether. The combined organic layers were dried with magnesium sulphate and the solvent was removed under reduced pressure. The product was then purified by flash column chromatography using silica gel as an absorbent and ethyl acetate/light petroleum (40 °C- 60 °C) (1:9) as an eluent to afford a clear oil (0.02 g, 5 %) as a single isomer. $\nu_{\text{max}}$ (film)/ cm$^{-1}$ 3323 (OH), 3298 (alkyne C-H), 3063, 3021 (aromatic C-H), 2963, 2872 (sp$^3$ C-H), 2126 (alkyne), 1589 (C=C), 1258 (SiMe$_3$) and 1118 (C-O); $\delta_{\text{H}}$ (CDCl$_3$, 250 MHz) 7.34-7.26 (5 H, m, CH-aromatic), 5.24 (1 H, m, 3-H), 4.59 (2 H, d, $J_{2.3}$, CH$_2$Ph), 3.77 (3 H, s, CO$_2$Me), 3.63-3.52 (2 H, m, 2'-H), 2.63 (1 H, m, 2-H), 2.35 (1 H, m, 5-H), 2.02-1.94 (2 H, m, 6-H and 1'-H), 1.68 (3 H, s, 7-H), 1.67-1.56 (2 H, m, 6-H and 1'-H) and 1.06 (3 H, d, $J_{7,8}$-H).
References


           (b) Pummerer, R. Chem. Ber. 1910, 43, 1401.
(57) (a) Payne, J. J. Am. Chem. Soc., 1959, 81, 4901


(b) Ireland, R. E.; Thompson, W. *J. Org. Chem.*, 1979, 44, 3041.
(c) Ireland, R. E.; Thompson, W. J.; Srouji, G. H.; Etter, R. *J. Org. Chem.*, 1981, 46, 4863.


200


(116) Reviews:
(a) Ager, D. J. *Org. React.*, 1990, 38, 1.
(b) Ager, D. J. *Synthesis*, 1984, 384.


(119) Reviews:
(b) Brieger, G.; Bennett, J. N. Chem. Rev., 1980, 80, 63.


(b) Oppolzer, W. *Synthesis*, 1978, 798.


    (b) Noland, W. E.; Freeman, H. I.; Baker, M. S. J. Am. Chem. Soc., 1956, 78, 188.


(208) Schlosser, M. S.; Thuong, H. S. *Chimia*, 1978, 30, 197.