Novel Routes to Substituted Dihydropyrans

Submitted by

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to the University of London as a thesis for the degree of

Doctor of Philosophy in Chemistry

September 2007

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Abstract

Dihydropyrans are important structural motifs that are found within many natural products and biologically active compounds. As such, a number of versatile methods have been developed for their construction. Chapter One provides several examples of interesting natural products which contain dihydropyran moieties and gives a brief summary of the existing methodology for the preparation of these heterocycles.

Chapter Two gives a detailed account of the silyl-Prins reaction and explains how the methodology may be expanded to encompass new types of substituted dihydropyran. The first strategy was to develop a route to dihydropyrans with an incorporated ester moiety in the 2-position. The second strategy involved the preparation of exo-methylene tetrahydropyrans using silyl-Prins methodology. Thirdly, an investigation into the Mukaiyama-Aldol silyl-Prins reaction, as a potential route to dihydropyrans with an incorporated hydroxyethyl moiety, was performed. The first step was the development of an expedient route to a vinyl ether precursor which was then used to investigate preliminary Mukaiyama-Aldol silyl-Prins reactions.

Chapter 3 provides a brief summary of the origin and pharmacology of (-)-centrolobine and kendomycin which both possess integral tetrahydropyran substructures making them attractive targets for synthesis using the silyl-Prins reaction. A literature overview of the existing methods for their syntheses is provided, with particular focus on the methodology used to construct the key tetrahydropyran core.

Chapter 4 discusses the retrosynthetic analysis of (±)-centrolobine and describes the development of synthetic pathways to (±)-centrolobine which enable the silyl-Prins reaction to be employed in the key cyclisation step. Kendomycin is also retrosynthetically analysed and a number of routes to the synthesis of its integral tetrahydropyran component using the silyl-Prins methodology are investigated.

Chapter 5 provides detailed experimental procedures and data for the compounds described in this thesis.
Contents

Abbreviations 9

Acknowledgements 12

Chapter 1: Introduction I: Historical Development of the Silyl-Prins Reaction 13

1.1 The Importance of the Dihydropyran Moiety in Nature 14
1.2 Family of Oxygenated Heterocycles 16
1.3 Methods for the Preparation of Dihydropyrans 16
1.3.1 Hetero-Diels-Alder Reactions 16
1.3.2 Ring-Closing Metathesis Reactions 18
1.3.3 Prins Cyclisations 22
1.3.4 Miscellaneous Reactions 24
1.3.5 The Silyl-Prins Reaction 27
1.4 Conclusion 28

Chapter 2: Results and Discussion I: Development of the Silyl-Prins Reaction 29

2.1 Overview of Research into the Silyl-Prins Reaction 30
2.2 Aims 35
2.3 Novel Applications of the Silyl-Prins Reaction 35
2.3.1 A Standard Silyl-Prins Reaction Procedure 35
2.3.2 Incorporation of an Ester Functionality 37
2.3.3 Exo-Methylene Tetrahydropyrans 45
2.4 Method Development: The Mukaiyama-Aldol Silyl-Prins Reaction

2.4.1 Background: The Mukaiyama-Aldol Reaction

2.5 Synthesis of the Vinyl Ether Precursor 117 for the MASP Reaction

2.6 Routes Involving Wittig Reaction Methodology

2.6.1 Wittig Approach: Route 1

2.6.2 Wittig Approach: Route 2

2.7 Nucleophilic Substitution-Based Route

2.8 Routes Involving Metathesis Methodology

2.8.1 Metathesis Approach: Route 1

2.8.2 Metathesis Approach: Route 2

2.9 Route Involving a Transesterification Reaction

2.9.1 Mercuric(II) Trifluoroacetate-Mediated Transesterification

2.9.2 Mercuric(II) Acetate-Mediated Transesterification

2.10 Preliminary Mukaiyama-Aldol Silyl-Prins Reactions

2.11 Conclusion

Chapter 3: Introduction II: The Natural Products, (-)-Centrolobine and Kendomycin and Existing Routes to their Synthesis

3.1 (-)-Centrolobine

3.1.1 Introduction

3.2 Literature Methods for the Preparation of (-)-Centrolobine

3.2.1 The Intramolecular Cyclisation of a Hydroxyketone

3.2.2 A Prins Cyclisation Strategy
### Contents

3.2.3 Stereoselective Construction of the Tetrahydropyran Ring via a Reductive Etherification

3.2.4 Two Successive One-Pot Reactions to Access Tetrahydropyran Core

3.2.5 Route Involving a Modified Maitland-Japp Reaction

3.2.6 Radical Cyclisation of a β-Alkoxyvinyl Ketone

3.2.7 Diastereoselective Ring-Rearrangement Metathesis-Isomerisation Sequence

3.2.8 Lewis Acid-Mediated Cyclisation of a 1,5-Diol to Prepare the Tetrahydropyran Core

3.3 Conclusion

3.4 Kendomycin

3.4.1 Introduction

3.5 Literature Methods for the Preparation of the Tetrahydropyran Core of Kendomycin

3.5.1 Route Involving a Lactonisation Step to Form the Tetrahydropyran Ring

3.5.2 A [4+2]-Annulation in the Preparation of the Tetrahydropyran Ring

3.5.3 A Petasis-Ferrier Union/Rearrangement Strategy

3.5.4 Route to Kendomycin Using a Prins Cyclisation

3.5.5 Route to Kendomycin using a Ag₂O-Mediated Oxidative Cyclisation

3.6 Conclusion

3.7 Aims
Chapter 4: Results and Discussion II: Application of the Silyl-Prins Reaction towards the Synthesis of Natural Products, (±)-Centrolobine and Kendomycin

4.1 Application of the Silyl-Prins Reaction to the Synthesis of (±)-Centrolobine

4.2 Route 1 - Preparation of Z-4-Trimethylsilyl-1-(4'-methoxy-phenyl)but-3-en-1-ol

4.2.1 Preparation of Vinyl anisole Oxide Using an Epoxidation Strategy

4.2.2 Methods for the Alkynylation of Vinyl anisole Oxide

4.2.3 Stereoselective Reduction of (±)-4-Trimethylsilyl-1-(4'-methoxy-phenyl)but-3-yn-1-ol

4.2.4 Preparation of 3-[4-(Benzyloxy)phenyl]-1-propanal

4.3 Preliminary Silyl-Prins Reactions to Generate Dihydropyran Fragment

4.4 Route 2 - An Alternative Route to (±)-Centrolobine

4.4.1 Future Work - Route to Z-6-Trimethylsilyl-1-[4'-benzyloxy]-hex-5-en-3-ol

4.5 Towards the Total Synthesis of Kendomycin Using the Silyl-Prins Reaction

4.5.1 Retrosynthetic Approach

4.6 Retrosynthetic Approach - Route 1

4.6.1 Preparation of the Aldehyde Precursor 246 - Approach 1a

4.6.2 Preparation of the Aldehyde Precursor 246 - Approach 1b

4.7 Retrosynthetic Approach – Route 2

4.7.1 Preparation of the Aldehyde Cyclisation Precursor 247
4.7.2 Model Studies of Potential Precursors 130
4.7.3 Preparation of the Disubstituted Silylated Homoallylic Precursor 274 134
4.7.4 Silyl-Prins Cyclisation Studies towards the Synthesis of Dihydropyran Fragment 264 139
4.8 Investigation of Cross-Coupling of Alkene-Terminated Alkyl Chain to Aromatic Ring 142
4.9 Conclusion 144
4.9.1 (±)-Centrolobine 144
4.9.2 Kendomycin 145

Chapter 5: Experimental 148

Chapter 6: References 217
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>act.</td>
<td>Activated</td>
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<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>Cat.</td>
<td>Catalyst</td>
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<tr>
<td>CI</td>
<td>Chemical ionisation</td>
</tr>
<tr>
<td>Cp</td>
<td>Cyclopentadienyl</td>
</tr>
<tr>
<td>CSA</td>
<td>10-Camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
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<td>2,6-DTBP</td>
<td>2,6-di-tert-butylpyridine</td>
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<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]nonene</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1'-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact</td>
</tr>
<tr>
<td>en.</td>
<td>Ethylenediamine</td>
</tr>
<tr>
<td>Eq.</td>
<td>Equivalent</td>
</tr>
<tr>
<td>ES</td>
<td>Electrospray</td>
</tr>
<tr>
<td>EVE</td>
<td>Ethyl vinyl ether</td>
</tr>
<tr>
<td>FG1</td>
<td>Functional group inversion</td>
</tr>
<tr>
<td>fod</td>
<td><em>Tris</em>(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)</td>
</tr>
<tr>
<td>GCMS</td>
<td>Gas chromatography-mass spectrometry</td>
</tr>
<tr>
<td>GI&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Concentration that causes 50% growth inhibition of a tumour</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
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<tr>
<td>HMTA</td>
<td>Hexamethylenetetramine</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>Definition</td>
</tr>
<tr>
<td>---------------</td>
<td>------------</td>
</tr>
<tr>
<td>IR</td>
<td>Infra red</td>
</tr>
<tr>
<td>ISMS</td>
<td>Intramolecular silyl-modified Sakurai reaction</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>LAED</td>
<td>Lithium acetylide-ethylenediamine complex</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>M</td>
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<tr>
<td>MAP</td>
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</tr>
<tr>
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</tr>
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</tr>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>nm</td>
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</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser effect</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium dichromate</td>
</tr>
<tr>
<td>PLA</td>
<td>Phospholipase A</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>R</td>
<td>Alkyl group</td>
</tr>
<tr>
<td>Ra-Ni</td>
<td>Raney nickel</td>
</tr>
<tr>
<td>RCM</td>
<td>Ring-closing metathesis</td>
</tr>
<tr>
<td>Rf</td>
<td>Retention factor</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>SN2</td>
<td>Substitution nucleophilic bimolecular</td>
</tr>
<tr>
<td>SPRIIX</td>
<td>Spiro bis(isoxazoline) ligand</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>TEA</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>(N,N,N',N'-\text{tetramethylenediamine})</td>
</tr>
<tr>
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<tr>
<td>Ts</td>
<td>(p)-Toluenesulfonyl</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
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Acknowledgements

I would like to thank Dr. Adrian P. Dobbs, my supervisor, for granting me the opportunity to work in an interesting and enjoyable research group over the last four years both at the University of Exeter and more recently at Queen Mary College, University of London. I could not have wished for a more supportive supervisor and am especially grateful to him for his enthusiasm, sense of humour, patience and encouragement.

I would like to thank the EPSRC for their invaluable funding of my project and also Queen Mary College for their additional funding. Thanks also to the EPSRC mass spectrometry centre in Swansea for their important contribution to my work.

The academic and technical staff at the now sadly closed University of Exeter Chemistry Department provided excellent assistance and support and I thank them for their help during my time there. While working in the laboratories in Exeter I met many nice people. In particular, I would like to thank Séb for all his help during my degree especially with interpreting NMR spectra. I would also like to thank Rob, Sabine, Kim, Joe, Ian, Levan, Marie, Irfan, Gavin, Jon, Vicky and all the other colleagues and post-docs from Lab 307, 302 and 411. I would also like to thank Saša for providing the foundation on which to build my project with her excellent work on the silyl-Prins reaction.

My special thanks to Mark for all his friendship, advice and support especially with the relocation to London. During my time at Queen Mary College, University of London I met many more kind people who provided invaluable help and advice. A big thank you to Julie, Jon, Sibanda and Diluar for their all their help and friendship. I would also like to thank Asma, Ester, Huy, Jay, Anna-Marie, Xi and all the other people from the 1st floor lab who have made me feel welcome. I am indebted to John, Alan, Jalal, and all the technical and academic staff at Queen Mary College for their hard work. Thanks also to Greg for helping me to run my NMRs.

A lot of thanks must go to my parents and sister for their love and support which I relied upon during my Ph.D. Finally, I would like to thank God for being a source of strength for me and providing me with guidance throughout my degree.
Chapter 1

Introduction I: Historical Development of the Silyl-Prins Reaction
1 Introduction I: Historical Development of the Silyl-Prins Reaction

1.1 The Importance of the Dihydropyran Moiety in Nature

Cyclic ethers occur frequently in nature with the 2,6-disubstituted dihydropyran ring system prevalent among these.\textsuperscript{1-5} In addition, dihydropyrans can serve as synthetically useful intermediates in the production of polysubstituted tetrahydropyran ring systems.

Martiriol (1, Figure 1) belongs to a family of active metabolites isolated from the red algae of the genus \textit{Laurencia}, a species located around the Canary Islands in Macronesia.\textsuperscript{6} It has shown some cytotoxicity against various tumour cell lines.\textsuperscript{7} Structurally, it is a squalene-derived triterpene which possesses four oxygenated heterocycles including a tetrahydropyran and two dihydropyran moieties, a 3,4-dihydro-2H-pyran and a 5,6-dihydro-2H-pyran.

Salinomycin (2, Figure 1) is a polyether ionophore antibiotic isolated from a culture broth of \textit{Streptomyces albicus} which has been shown to possess interesting antibacterial and anticoccidial properties.\textsuperscript{8,9} The molecular architecture of this natural product consists of a polyoxygenated backbone which includes a dihydropyran substructure in addition to tetrahydropyrans and a tetrahydrofuran.

![Figure 1 Bioactive marine metabolite martiriol 1 and antibiotic salinomycin 2](image)

Manoalide (3, Figure 2) is a novel anti-inflammatory sesterterpene isolated from the marine sponge \textit{Luffariella variabilis} collected in the Indo-Pacific.\textsuperscript{10} It has been shown
to act by inhibiting the phospholipase A2 which plays an important role in the inflammation process.\textsuperscript{11} As such it is now commercially available as a probe for PLA inhibition. Manoalide possesses a trisubstituted dihydropyran subunit within its overall structure.

The venturicidins A and B (4 and 5, Figure 2) are 20-membered macrolides isolated from several strains of *Streptomyces*.\textsuperscript{12-15} These glycosidic molecules contain two oxygenated heterocycles including a dihydropyran moiety in each case. Both are known to inhibit oxidative and mitochondrial ATPases and as such are used mainly in the study of mitochondrial function.\textsuperscript{16}

![Figure 2: Structures of manoalide 3 and venturicidins A 4 and venturicidin B 5](image-url)
Chapter 1

1.2 Family of Oxygenated Heterocycles

Closely related to their parent compound 2H-pyran 6, two isomeric dihydropyrans are known to exist; 3,4-dihydro-2H-pyran 7 and 5,6-dihydro-2H-pyran 8 (Figure 3). The primary focus of our investigation was on the preparation of 5,6-dihydro-2H-pyran 8 and future references to dihydropyrans can be assumed to be this variant.

![Figure 3](image_url) Figure 3 Family of oxygenated pyran structures

1.3 Methods for the Preparation of Dihydropyrans

Many versatile approaches towards dihydropyrans have been developed and a brief summary of the more important methods will be outlined. A particularly informative review of these procedures in relation to the preparation of tetrahydropyrans has been provided by Clarke.18

1.3.1 Hetero-Diels-Alder reactions

The vast synthetic utility of the Diels-Alder reaction for accessing functionalised cyclohexene structures with excellent regio- and stereoselectivity is well recognised.19 The analogous cycloaddition reactions between heterosubstituted dienes and dienophiles have since demonstrated their potential in the synthesis of 5,6-dihydro-2H-pyran.

Carreaux et al. have developed a strategy for the preparation of α-hydroxyalkyl dihydropyrans using an approach based on a tandem hetero[4+2]/allylboration reaction
The reaction begins with the [4+2] cycloaddition of (2E)-3-borylacrolein 9 with ethyl vinyl ether 10. This is followed by the addition of an aldehyde 11 to the allylboronate intermediate, thus providing the α-hydroxyalkyl dihydropyran 12 in one operation.

Scheme 1  Hetero-Diels-Alder reaction to prepare α-hydroxyalkyl dihydropyrans by Carreaux et al. 20

Recent research by Jacobsen et al. has led to the development of chiral chromium catalysts 15 for use in hetero-Diels-Alder reactions to prepare dihydropyrans. This methodology has been utilised in the total synthesis of an anti-tumour antibiotic known as FR901464 which forms part of a novel family of bacterially produced antibiotics (Scheme 2). 21,22

Scheme 2  Preparation of dihydropyran 16 using catalyst 15 by Jacobsen et al. 21,22
The chiral chromium catalyst 15, developed by Jacobsen et al. has also been employed by Paterson et al. in the synthesis of the cytostatic marine natural product phorboxazole A (Scheme 3). Hetero-Diels-Alder methodology is again used to generate the key dihydropyran substructure 19.

![Scheme 3](image)

**Scheme 3** Employment of the hetero-Diels-Alder reaction in the preparation of a key fragment of phorboxazole A by Paterson et al. 

### 1.3.2 Ring-Closing Metathesis Reactions

In recent years, olefin metathesis has developed into one of the most synthetically useful and widely used transformations in organic chemistry. In the presence of various metal carbene catalysts, alkenes may exchange groups around the double bond. The Grubbs 1\textsuperscript{st} 20 and 2\textsuperscript{nd} 21 generation catalysts and Schrock catalyst 22 have been at the forefront of this technology, allowing many novel synthetic routes to emerge (Figure 4).
The construction of cyclic structures using catalytic ring-closing metathesis has also emerged as a powerful synthetic tool allowing a wide range of cyclic structures including 5,6-dihydro-2H-pyrans to be prepared.27-30

Schmidt et al. have employed ring-closing metathesis in the preparation of dihydropyrans with orthogonally protected hydroxymethyl side chains (Scheme 4).31 Ring-closing metathesis of the diene 23, catalysed by Grubbs 1st generation catalyst, afforded the dihydropyran 24 in excellent yield (97%).

Sarkar and co-workers have used ring-closing metathesis to synthesise a variety of diastereomerically pure dihydropyrans 26 from various substituted diene precursors 25.
which were assembled on arene-tricarbonylchromium templates (Scheme 5). Ambient temperatures and good yields are attractive features of this strategy.

![Diagram](image)

**Scheme 5** The employment of RCM methodology to prepare dihydropyrans by Sarkar *et al.*

Enantiomerically-enriched (3-furyl)-2-pyran derivatives are key intermediates in the synthesis of the pharmacophoric pyranofuranone system of biologically active natural products such as cacospongionolide B 27, a sesterterpene isolated from soft sponge *Fasciospongia cavernosa*. Ring-closing metathesis has been employed by De Rosa *et al.* in the synthesis of these intermediates (Scheme 6). While good yields were obtained, the ring-closing metathesis reaction was particularly sensitive to steric factors and an increase in temperature (from 20 °C to 40 °C) and an increase in catalyst (from 2 mol% to 8 mol%) was required for the synthesis of the 5-methyl derivative.

![Diagram](image)

**Scheme 6** Synthesis of a key intermediate of cacospongionolide B using RCM by De Rosa *et al.*
Arylated dihydropyrans are a synthetic target for various pharmaceutical research laboratories as their potential applications encompass a wide range of biologically active molecules. Schmidt et al. have employed ring-closing metathesis for the synthesis of various arylated dihydropyrans 31 (Scheme 7).\textsuperscript{35}

\begin{center}
\begin{tikzpicture}

\begin{scope}[scale=0.4]

\node (a) at (0,0) {\includegraphics[width=1cm]{diagram1.png}};
\node (b) at (3,0) {\includegraphics[width=1cm]{diagram2.png}};
\node (c) at (1.5,-2) {\includegraphics[width=1cm]{diagram3.png}};
\node (d) at (4.5,-2) {\includegraphics[width=1cm]{diagram4.png}};
\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);
\end{scope}
\end{tikzpicture}
\end{center}

Scheme 7  Preparation of arylated dihydropyrans by Schmidt et al.\textsuperscript{35}
1.3.3 Prins Cyclisations

The Prins reaction involves an electrophilic addition of an aldehyde or ketone to an alkene in the presence of an acid catalyst followed by nucleophilic capture. The three possible products are dependent on the alkene and the reaction conditions (Scheme 8). In the presence of water and a protic acid, reaction of an alkene and formaldehyde produce a 1,3-diol. In the absence of water, dehydration occurs leading to the formation of an allylic alcohol. With a low reaction temperature and an excess of formaldehyde, a dioxane is formed.

Scheme 8 Potential outcomes of the Prins reaction

The related Prins cyclisation has also demonstrated its potential for the construction of various oxygenated heterocycles including substituted dihydropyrans. Rychnovsky et al. have employed this methodology in their preparation of brominated dihydropyrans (Scheme 9). Cyclisation of the α-acetoxy ether in the presence of SnBr₂ gave a mixture of two isomers in a 1:2.5 ratio. The major isomer was the tetrahydrofuran due to the preference for 5-endo-trig cyclisation while the dihydropyran was the minor isomer.
Chapter 1

Yadav et al. have developed a Prins cyclisation of silylmethyl-substituted cyclopropyl carbinols 38 to afford 2,4,6-trisubstituted dihydropyrans (Scheme 10).46 A mixture of isomeric 5,6-dihydro-2H-pyran 40 (48%) and 3,6-dihydro-2H-pyran 41 (32%) products were obtained. This lack of selectivity and the required rigorous reaction conditions limits the scope of this reaction as a route to dihydropyrans.

Scheme 10 Prins cyclisation of silicon-stabilised homoallylic cation from a cyclopropylcarbinol by Yadav et al.46

Tetra- and pentasubstituted halodihydropyrans have been synthesised in a Prins cyclisation using silylated secondary homopropargylic alcohols 42 and aldehydes 43 in the presence of stable iron(III) halides.47
1.3.4 Miscellaneous Reactions

De la Pradilla et al. have developed a highly selective base-promoted intramolecular cyclisation of 2-sulfinyl dienols \( 46 \) to afford allylic sulfinyl dihydropyran \( 47 \) (Scheme 12). \(^{48}\)

\[
\begin{align*}
\text{HO} & \quad \text{TMS} \\
\text{R} & \quad \text{OH} \quad \text{S} \quad \text{p-Tol} \\
\text{46} & \quad \text{LDA, THF} \quad -78^\circ\text{C to r.t.} \\
\text{47} & \quad R = n-\text{Bu} (94\%) \\
& \quad R = \text{Ph} (85\%)
\end{align*}
\]

Scheme 12 Sulfoxide-directed enantioselective synthesis of functionalised dihydropyran by de la Pradilla et al. \(^{48}\)

A novel sodium iodide-promoted ring expansion of cyclopropylidene alcohols has been developed to prepare dihydropyran (Scheme 13). \(^{49}\) A highly strained but accessible intermediate such as methylenecyclopropane \( 48 \) has been shown to ring-open in the presence of iodide ions (from NaI) to afford a homoallylic alcohol \( 49 \) which subsequently undergoes intramolecular cyclisation to afford the dihydropyran \( 50 \).
Scheme 13 Sodium iodide-promoted ring expansion of cyclopropylidene alcohols to dihydropyrans by Huang et al.\textsuperscript{49}

Toste et al. have developed a gold(I)-catalysed method for the stereocontrolled synthesis of 2-hydroxy-3,6-dihydropyrans 52 from propargyl vinyl ethers 51 (Scheme 14).\textsuperscript{50} Reaction of propargyl vinyl ethers 51 with [(Ph$_3$PAu)$_3$O]BF$_4$ (1 mol\%) and water (1 eq.) in dioxane at room temperature affords the expected dihydropyran products 52 in good yields (88\%-92\%).

Scheme 14 Gold(I)-catalysed synthesis of dihydropyrans by Toste et al.\textsuperscript{50}

Marson et al. have demonstrated the potential of 3-alkenamides 53 to condense with $s$-trioxane in the presence of 20\% v/v trifluoromethanesulfonic acid to afford dihydropyrans 54 in an oxo-ene type reaction (Scheme 15).\textsuperscript{51}
Chapter 1

Developed by Markó and co-workers, the intramolecular silyl-modified Sakurai reaction (ISMS) couples an aldehyde 56 to a silyl ether containing a strategically placed vinyl or silane moiety 55 to afford a 2,6-disubstituted dihydro-2H-pyran 57 (Scheme 16). The Lewis acid trimethylsilyl triflate is required to facilitate this reaction.

\[ \text{TMS} + \text{H} \rightarrow \text{R}_1 \rightarrow \text{R}_2 \rightarrow \text{CH}_2 \text{Cl}_2, -78^\circ \text{C} \rightarrow 20^\circ \text{C} \]

Scheme 15 Preparation of dihydropyrans using 3-alkenamides by Marson et al.\(^\text{51}\)

Scheme 16 The intramolecular silyl-modified Sakurai reaction to prepare dihydropyrans\(^\text{52-54}\)

A catalytic asymmetric Wacker-type cyclisation of alkenyl alcohols 58 promoted by chiral Pd(II)-spiro bis(isoxazoline) catalysts\(^\text{55}\) 59 has been developed to prepare dihydropyrans (Scheme 17).\(^\text{56}\) The dihydropyran products 60 are obtained in good yield (83%) and moderate enantiomeric excess (41%).

26
Scheme 17  Wacker-type cyclisation of alkenyl alcohols to prepare dihydropyrans by Sasai et al.\textsuperscript{56}

1.3.5 The Silyl-Prins Reaction

Hoffmann \textit{et al.} have employed silylated homoallylic alcohols 61 and aldehydes 62 in an ethylaluminium chloride-mediated reaction at -78 °C to afford trisubstituted dihydropyrans 63 in good yields.\textsuperscript{57}

Scheme 18  Preparation of dihydropyrans using silylated homoallylic alcohols by Hoffmann \textit{et al.}\textsuperscript{57}

Dobbs \textit{et al.} have demonstrated that dihydropyrans 62 can be prepared from silylated homoallylic alcohols 61 and aldehydes 43 using a mild Lewis acid reagent such
as indium(III) chloride in a silyl-Prins reaction.\textsuperscript{58} It is a rapid and high-yielding synthesis which requires only mild reaction conditions.

![Scheme 19](image)

Scheme 19  The silyl-Prins reaction by Dobbs \textit{et al.}\textsuperscript{58}

1.4 Conclusion

A literature survey of the existing methodology to access dihydropyrans reveals a range of efficient and selective pathways. While various routes possess their individual assets, a number of limiting issues recur throughout the literature. Many methods require the lengthy synthesis of a reaction precursor such as the ISMS reaction. Other routes afford complex mixtures of products that often require problematic separations. Furthermore, other reactions require rigorous or difficult to achieve reaction conditions or employ undesirable reagents such as those with toxicity issues. As such there is still much interest in the development of new methodologies to address the aforementioned issues in novel routes to dihydropyrans. The silyl-Prins reaction has demonstrated its potential to overcome many of the drawbacks of the existing methods and still has much scope to expand its range of applications. The aim of this research was to investigate new ways in which the silyl-Prins reaction could be employed to construct synthetically useful molecular structures and later to apply this methodology to the total synthesis of certain biologically interesting natural products.
Results and Discussion I: Development of the Silyl-Prins Reaction
2 Results and Discussion I: Development of the Silyl-Prins Reaction

2.1 Overview of Research into the Silyl-Prins Reaction

Recent research within the group has been concerned with the development of a novel methodology for the synthesis of various unsaturated heterocycles where the heteroatom may be oxygen (the silyl-Prins reaction)\textsuperscript{58}, sulfur (the thia-silyl-Prins reaction)\textsuperscript{59} or nitrogen (the aza-silyl-Prins reaction).\textsuperscript{60}

\textbf{Scheme 20}  Research by Dobbs \textit{et al.} into novel routes to heterocycles\textsuperscript{58-60}

The silyl-Prins reaction utilises compounds containing a 4-trimethylsilyl-3-buten-1-ol unit to react with aldehydes, epoxides or acetals under indium(III) chloride-mediated reaction conditions to afford 5,6-dihydro-2H-pyran in good yields from simple reaction precursors (Table 1).\textsuperscript{58} Indium(III) chloride was selected as the optimum Lewis acid promoter after an extensive Lewis acid screening programme in which it provided the best yields combined with mild reaction conditions.\textsuperscript{59} Further studies also determined that although employment of indium(III) chloride at sub-stoichiometric levels (minimum of 0.3 eq. required) produced good yields, they were lower than those observed in the stoichiometric reaction.\textsuperscript{59}
Table 1  Synthesis of heterocycles using the silyl-Prins reaction\textsuperscript{58,61}, the thia-silyl-Prins reaction\textsuperscript{59} and the aza-silyl-Prins reaction\textsuperscript{60}

\[
\begin{array}{cccc}
\text{Entry} & \text{X} & \text{R} & \text{R}^1 & \% \text{ Yield} \\
1 & \text{OH} & \text{H} & \text{PhCH}_2 & 88 \\
2 & \text{OH} & \text{H} & n-C_5H_{11} & 75 \\
3 & \text{OH} & \text{Me} & n-C_5H_{11} & 65 \\
4 & \text{OH} & \text{Me} & \text{Cyclohexyl} & 69 \\
5 & \text{OH} & \text{Et} & n-C_3H_{11} & 64 \\
6 & \text{OH} & \text{Ph} & n-C_3H_{11} & 57 \\
7 & \text{SH} & \text{Me} & \text{PhCH}_2\text{CH}_2 & 68 \\
8 & \text{NHBn} & \text{Me} & n-C_5H_{11} & 70 \\
\end{array}
\]

The reactions in Table 1 were performed with a 1:1:1 ratio of alcohol:aldehyde:indium(III) chloride. The solvent of choice was dry dichloromethane which had also been selected after careful screening of possible alternatives.\textsuperscript{58}

As Table 1 shows, 2-substituted 4-trimethylsilyl-3-butenols can be employed to prepare disubstituted 5,6-dihydro-2H-pyrans using the silyl-Prins reaction. These reactions were performed in good yields and have exhibited exclusive \textit{cis}-diastereoselectivity across the oxygen atom.\textsuperscript{58} This is in contrast to the analogous aza-silyl-Prins reaction in which \textit{trans} stereochemistry is observed across the nitrogen atom.\textsuperscript{60}

In addition, this methodology has shown the flexibility to enable incorporation of
different substituents in various positions on the heterocyclic ring including preparation of an aryl-substituted dihydropyran.\textsuperscript{61}

The silyl-Prins reaction has already demonstrated its potential for employment in the field of natural product synthesis.\textsuperscript{59} The civet cat constituent, (±)-(cis-6-methyltetrahydropyran-2-yl)acetic acid 66, is an important component of a commonly used fixative in the perfumery industry. Using the silyl-Prins reaction to generate the key dihydropyran adduct 69 facilitated the appropriate cis-stereochemistry in the final product. Subsequent hydrogenation and oxidation steps afforded the natural product 66 (Scheme 21).

![Scheme 21 Synthesis of civet component 66](image)

Mechanistically the silyl-Prins reaction is ultimately believed to be driven by the trimethylsilyl group attached to the double bond of a homoallylic alcohol 64. As the proposed mechanism shows (Scheme 22), the reaction is believed to proceed \textit{via} nucleophilic attack from the oxygen of the homoallylic alcohol 64 on to the Lewis acid
activated carbonyl group of the aldehyde. After proton transfer, cationic cyclisation occurs to produce a carbocation which is stabilised by the β-effect, forming the key intermediate of the reaction. The carbon-carbon π bond is then formed by the elimination of the silicon moiety which occurs at a faster rate than nucleophilic attack on the carbocation by the anion of the Lewis acid, the solvent or another equivalent of alcohol.

Scheme 22  Proposed mechanism for the silyl-Prins reaction

The importance of the silicon moiety in this reaction is shown by the stabilisation of the carbocation intermediate due to the β-effect, which is considered to be the driving force of this reaction. This effect is due to the overlap of the vacant p-orbital of the carbocation on the β-carbon atom and a polarised σ-orbital between the silicon atom and α-carbon (Figure 5). This stabilisation is due to hyperconjugation and maximum stabilisation only occurs if the vacant p-orbital of the carbocation and the polarised σ-orbital of the carbon-silicon bond are in the same plane. It should be noted that due to
rotation about the central bond, one of the C-Si bonds will always be approximately in line to overlap with the vacant p-orbital of the carbocation.

**Figure 5** Diagram to illustrate the β-effect

The cis-stereoselectivity observed in the silyl-Prins reaction can be explained by the formation of the initial (E)-oxocarbenium ion (Scheme 23). The two substituents adjacent to the oxygen atom take up pseudoequatorial positions in order to minimise 1,3-diaxial interactions. The trimethylsilyl moiety is oriented axially to allow greater stabilisation of the cation that develops β to the silane. Overman et al. have shown that this orientation provides more effective stabilisation than if the trimethylsilyl group were in the equatorial position. There is some evidence that a [3,3] oxonia-Cope rearrangement may occur to form a different oxocarbenium ion. Either of these intermediates, however, will undergo direct attack by the π-electrons of the double bond with the elimination of the TMS group occurring to form the same product.

**Scheme 23** Cis-stereoselectivity in the silyl-Prins reaction
Chapter 2

2.2 Aims

The development of the silyl-Prins reaction as a powerful synthetic tool to access 5,6-dihydro-2H-pyrans has created ample opportunities for further investigation in this area. Following the methodology established by our group, the aim was to expand further the scope of the silyl-Prins reaction, in particular investigating new avenues of research such as preparation of exo-methylene tetrahydroprans and incorporation of different substituents into the heterocyclic ring.

2.3 Novel Applications of the Silyl-Prins Reaction

2.3.1 A Standard Silyl-Prins Reaction Procedure

In order to ensure the correct procedures for all subsequent silyl-Prins reaction were followed, a repeat model silyl-Prins reaction was performed. The first step was preparation of the reaction precursor Z-4-trimethylsilylbut-3-en-1-ol. This was prepared first in two steps from commercially available 3-butyn-1-ol 71 (Scheme 24). Following the literature methods for the preparation of trimethylsilyl derivatives of acetylenic alcohols, 4-trimethylsilylbut-3-yn-1-ol 72 was prepared in 76% yield from but-3-yn-1-ol. Reduction of 4-trimethylsilylbut-3-yn-1-ol 72 was prepared in 76% yield from but-3-yn-1-ol. Reduction of 4-trimethylsilylbut-3-yn-1-ol using DIBAL-H afforded Z-4-trimethylsilylbut-3-en-1-ol 64 in 68% yield.

Scheme 24 Synthesis of precursor 64 for the silyl-Prins reaction\textsuperscript{58}
Commercially available phenylacetaldehyde 73 was used as the aldehyde precursor for the model silyl-Prins reaction (Scheme 25). This aldehyde (1 eq.) and indium(III) chloride (1 eq.) were stirred in dry dichloromethane at room temperature for 1 hour to allow activation of the aldehyde carbonyl group by Lewis acid to occur. After this time the alcohol precursor 64 was added under a nitrogen atmosphere and the reaction was allowed to stir for a further 20 hours at room temperature. The reaction was quenched by the addition of distilled water and the resultant mixture extracted into dichloromethane. Purification was performed using column chromatography (hexane:diethyl ether 10:1) to afford the dihydropyran 74 in excellent yield (83%). The aforementioned silyl-Prins reaction conditions and procedure are referenced in future descriptions of the silyl-Prins reaction where standard conditions and procedures are employed.

\[ \text{TMS-} + \text{H} \rightarrow \text{InCl}_3 \rightarrow \text{O} \]

\[ 64 \quad 73 \quad 74 \]

Scheme 25  The silyl-Prins reaction to prepare (±)-2-benzyl-5,6-dihydro-2H-pyran
2.3.2 Incorporation of an Ester Functionality

As previously described, the silyl-Prins reaction has demonstrated its ability to synthesise 5,6-dihydro-2H-pyrans with the stereocontrolled incorporation of various substituents in the 2-position. Dobbs et al. successfully achieved this by employing a range of aldehydes to incorporate various alkyl and aryl substituents.\textsuperscript{58,61} Our objective was to broaden the range of the silyl-Prins reaction in this area by the introduction of a different substituent in the 2-position with the use of a novel aldehyde precursor.

Pipecolic acid \textsuperscript{75}, a piperidine with incorporated acid functionality, is known to be an important intermediate in the catabolism of the essential amino acid L-lysine in yeast and other high fungi.\textsuperscript{70,71} Recent work by Dobbs et al. completed the synthesis of pipecolic acid and a range of its derivatives, successfully employing the aza-silyl-Prins reaction in the key tetrahydropyridine-forming step (Scheme 26).\textsuperscript{72} This reaction incorporates an ester functionality in the 2-position of the heterocycle which is subsequently converted into the desired natural product 75. It was envisioned that the silyl-Prins reaction could be employed in a similar manner to prepare oxygen analogues of these compounds.

\begin{center}
\begin{tabular}{c c c c}
| 76 | 77 | 78 |
\end{tabular}
\end{center}

\textbf{Scheme 26} Synthesis of pipecolic acid using the aza-silyl-Prins reaction\textsuperscript{72}

In addition to their structural similarity to pipecolic acid, dihydropyrans with an incorporated ester functionality form the structural backbone of a variety of natural products. The tetrahydropyran 79, known to be an attractant for cockroaches of the species \textit{Supella longipalpa} (brown banded cockroach) and \textit{Blatella germanica} (German...
cockroach) and possesses a THP core and incorporated ester group which is easily accessible from its dihydropyran analogue 80 (Figure 6). Furthermore the presence of an ester moiety provides a synthetically useful handle for further functionalisation of the dihydropyran and side chain functionalisation.

![Chemical structures of 79 and 80](image)

**Figure 6** The chemical structure of the cockroach attractant 79 and the closely related silyl-Prins reaction target molecule 80 and an image of a cockroach of the species *Supella longipalpa*

In order to apply the silyl-Prins methodology to the synthesis of 5,6-dihydro-2H-pyrans with an incorporated ester functionality, Z-4-trimethylsilylbut-3-en-1-ol was prepared first in two steps from commercially available 3-butyn-1-ol. This was achieved using the same methodology described in Scheme 24 with comparable yields.

Commercially available ethyl glyoxylate (50% in toluene) was employed as the aldehyde precursor to provide the dihydropyran 80 with incorporated ester functionality. Three Lewis acid promoters were investigated for their ability to promote this silyl-Prins reaction (Scheme 27).
Scheme 27 Use of the silyl-Prins reaction to prepare 5,6-dihydro-2H-pyran s with an incorporated ester moiety

Analysis of the crude product of the indium(III) chloride-mediated reaction using GCMS and $^1$H NMR techniques indicated the formation of a complex mixture (Figure 7). The formation of the desired cyclisation product 80 is suggested by GCMS analysis as an inseparable portion of the crude mixture (23%). The most abundant product, as indicated by $^1$H NMR data, appeared to be 3-buten-1-ol 71. According to GCMS analysis there was also the formation of two chlorinated diastereoisomeric tetrahydropyran derivatives 81 and 82 of the desired dihydropyran. There is also GCMS evidence for the alcohol 83 which may starting reagent alcohol 64 or its trans-isomer.

Figure 7 Products of InCl$_3$-mediated silyl-Prins reaction

The products that were observed in this reaction can be explained by a number of different processes some of which are interrelated (Scheme 28). After initial generation of the oxonium cation, an oxonia-Cope rearrangement can occur leading to either a β-stabilised carbocation or a reverse oxonia-Cope rearrangement product. Either of these species may lead to the desired dihydropyran 80. However, hydrolysis of the reverse oxonia-Cope product may also afford the alcohol 83 which can subsequently react with
an activated aldehyde precursor to afford either dihydropyran 80 or initiate a desilylation process. The resulting oxonium cation may then be protonating the vinylsilane moiety leading to desilylation by the proposed mechanism shown (Scheme 28). Once the 3-buten-1-ol product has been formed, a standard Prins reaction may occur to form the observed chlorinated derivatives 81 and 82. Similar processes have been observed by Dobbs et al. in their investigations of the aza-silyl-Prins reaction and they found the electrophilicity of the aldehyde precursor may control the rate of desilylation. The strong electrophilicity of the ethyl glyoxylate may therefore be promoting the desilylation in this case.
Scheme 28 Proposed mechanistic explanations for obtained products

A model Prins reaction was used to prepare the chlorinated diastereoisomers 81 and 82 in order to confirm that these compounds had been formed in the previous silyl-Prins reactions. Commercially available 3-buten-1-ol 71 was employed as the alcohol
precursor in these cases. GCMS data suggested the formation of the expected diastereoisomers and confirmed their presence in the previous reactions (Scheme 29).

\[
\text{\begin{align*}
\text{prop-1-ol} & \quad + \quad \text{H}^+\text{CO}_2\text{Et} \quad \xrightarrow{\text{InCl}_3/\text{CH}_2\text{Cl}_2} \quad \text{product 1} \\
71 & \quad 77 \\
\text{ratio: } 1.04 & \quad : \quad 1
\end{align*}}
\]

Scheme 29  Products of a Prins reaction between 3-buten-1-ol and ethyl glyoxylate

It was postulated that the ethyl glyoxylate may have polymerised and that heating immediately prior to addition to the reaction mixture may produce a more successful outcome for this silyl-Prins reaction. This new approach was investigated using a methyl-substituted version of the silylated homoallylic alcohol 67 and using indium(III) chloride as the Lewis acid promoter (Scheme 30) with standard silyl-Prins reaction conditions as shown in Scheme 25. In this case the most abundant product was recovered ethyl glyoxylate 77 and 4-penten-2-01. GCMS data suggests a small quantity of a chlorinated derivative of the target material may also be present.

\[
\text{\begin{align*}
\text{\text{TMS-prop-1-ol} } & \quad + \quad \text{H}^+\text{CO}_2\text{Et} \quad \xrightarrow{\text{InCl}_3/\text{CH}_2\text{Cl}_2} \quad \text{product 2} \\
67 & \quad 77 \\
\end{align*}}
\]

Scheme 30  Silyl-Prins reaction with prior heating of ethyl glyoxylate solution
Furthermore, the lack of success of this silyl-Prins reaction when compared to the aza-silyl-Prins version is believed to be due to the presence of the hydrogen (from InCl₂OH) in the intermediate 86 which is absent in the iminium ion 85 (Figure 8). This hydrogen can induce desilylation instead of cyclising to form the β-stabilised carbocation (Scheme 28). In the aza-silyl-Prins reaction the iminium ion 85 lacks a hydrogen to isomerise and the only option is for cyclisation to occur.

Figure 8 Iminium and oxonium cations in reactions to incorporate an ester moiety

The boron trifluoride etherate (1eq.) mediated cyclisation reaction was performed at room temperature and allowed to react for 18 hours under an atmosphere of nitrogen. The reaction was quenched with distilled water and extracted into dichloromethane. The major product obtained from the reaction was the homoallylic alcohol 71 (Figure 9). Trace quantities of the desired dihydropyran 80 are indicated by the GCMS data. The formation of fluorinated analogues of the target material 87 and 88, formed in an identical way to the previous reaction, were also observed.

Figure 9 Products of BF₃·OEt₂-mediated silyl-Prins reaction
Finally, trimethylsilyl triflate was investigated as the Lewis acid promoter for this reaction. Previous work by Penny has shown it can be employed as a catalyst in Prins cyclisations (Scheme 31).\(^7\)

\[
\begin{align*}
\text{\textit{O}} & + \text{H}_2\text{C}=\text{CH}-\text{R} & \text{TMS-OTf} \\
\text{CH}_2\text{Cl}_2 & \rightarrow & \text{O} \text{C}_2\text{H}_4\text{H}=\text{O} & \text{R} = \text{c-Hex, CH}_2\text{Ph} \\
\text{71} & & \text{89} & \text{90} & \text{91}
\end{align*}
\]

**Scheme 31** Use of TMS-OTf as Lewis acid mediator to prepare dihydropyran\(^7\)

Using trimethylsilyl triflate to promote our silyl-Prins reaction led to the homoallylic alcohol 71 being obtained as the major product (Figure 10). In addition, trace amounts of the desired dihydropyran 80 were again obtained in addition to various other inseparable reaction by-products such as 92 which were suggested by GCMS data. Product 92 may have formed from a reaction of the homoallylic precursor with ethyl glyoxylate which failed to cyclise.

**Figure 10** Products of TMSOTf-mediated silyl-Prins reaction
2.3.3 Exo-Methylene Tetrahydropyrans

The exo-methylene tetrahydropyran moiety is found in the molecular architecture of a wide range of natural products. Pederin (93, Figure 11), a vesicant, toxic compound found in the haemolymph of the Paederus and Staphylinidae families of beetle, possesses an exo-methylene tetrahydropyran substructure (Figure 6).\textsuperscript{77} Extracts from these beetles have long enjoyed use in herbal medicine and more recently studies have shown that pederin exhibits anti-cancer properties by blocking mitosis at levels as low as 1 ng/ml.\textsuperscript{78} It is thought to achieve this by inhibiting protein and DNA synthesis without affecting RNA synthesis. Further studies have shown that pederin extends the life of mice carrying a variety of tumours.\textsuperscript{79}

(+)-Dactyloolide (94, Figure 11) is a novel cytotoxic metabolite from the Vanuatu sponge Dactylospongia sp. which also contains an exo-methylene tetrahydropyran moiety.\textsuperscript{80} This natural product has shown cytotoxic activity against various tumour cell lines including L1210 (40%) and SK-OV-3 (63%).\textsuperscript{81} While these results may be less impressive than other more potent cytotoxic agents such as the phorboxazoles, they are still impressive due to the lack of complexity in the molecule.

![Figure 11](natural_products_exo-methylene_substructures.png)

Figure 11  Natural products possessing exo-methylene substructures

A number of procedures exist within the literature for the preparation of tetrahydropyrans with an exo-methylene double bond. Some of these introduce the exo-methylene moiety on to a preformed tetrahydropyran ring. For example, Kabat \textit{et al.}
in their preparation of a precursor of 1α,25-dihydroxy-vitamin D₃ used Wittig methodology to produce the exo-methylene tetrahydropyran 96 (Scheme 32). ²²

\[
\text{Scheme 32} \quad \text{The use of Wittig methodology to prepare exo-methylene tetrahydropyrans by Kabat et al.} \quad ²²
\]

Hoveyda et al. have developed a route to cis-2,6-disubstituted-4-methylene tetrahydropyrans using a Brønstead acid-catalysed reaction of enol ethers (Scheme 33). ³³ An enol ether 97 was reacted with a catalytic (0.01-0.1 mol%) quantity of TfOH to afford the desired tetrahydropyran 98 and its regioisomers 99 and 100.

\[
\text{Scheme 33} \quad \text{Diastereoselective TfOH-catalysed synthesis of cis-2,6-disubstituted-4-methylene tetrahydropyrans by Hoveyda et al.} \quad ³³
\]
Other procedures involve the simultaneous development of the tetrahydropyran ring system and its \textit{exo}-methylene portion. Loh \textit{et al.} have developed a method based on an In(OTf)$_3$-catalysed intramolecular 2,5-oxonium-ene cyclisation (Scheme 34).$^{84}$

![Scheme 34](image)

<table>
<thead>
<tr>
<th>R</th>
<th>R$^1$</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>80%</td>
</tr>
<tr>
<td>CO$_2$Me</td>
<td>c-hex</td>
<td>72%</td>
</tr>
<tr>
<td>TBDPSO(CH$_2$)$_2$</td>
<td>CH$_3$C=C(CH$_3$)$_2$</td>
<td>55%</td>
</tr>
</tbody>
</table>

$syn$ : $anti$

95 : 5
58 : 42
75 : 25

\textbf{Scheme 34} Preparation of \textit{exo}-methylene tetrahydropyrans by Loh \textit{et al.}$^{84}$

Previous vinylsilane-modified cyclisation reactions have demonstrated the importance of the position of the trimethylsilyl moiety on the $\beta$-stabilised carbocation in determining the double bond position of the resultant dihydropyran (Figure 12).$^{85,86}$ Panek \textit{et al.} have shown (1) how 3,6-dihydropyrans can be formed by reacting crotyl silanes with aldehydes in a Lewis acid-mediated reactions.$^{87}$ The silyl-Prins reaction has previously demonstrated the ability of the $\beta$-stabilised carbocation to generate a double bond to form 5,6-dihydro-$2H$-pyrans.$^{58}$ It occurred to us that a modification of the silyl-Prins reaction could be used in the synthesis of \textit{exo}-methylene tetrahydropyrans by the careful positioning of the trimethylsilyl moiety.
Mechanistically this reaction would be expected to proceed through a similar pathway to previous silyl-Prins reactions, with the key step being the generation of the β-stabilised carbocation (Scheme 35).

In order to explore the applicability of the silyl-Prins reaction to the synthesis of tetrahydropyrans with an exo-methylene group a suitable reaction precursor was first required. The precursor chosen for these reactions was 3-trimethylsilyl methyl-but-3-en-1-ol. This prerequisite alcohol 105 was prepared according to a literature method by the silylation of commercially available 3-methyl-3-buten-1-ol 107 using TMEDA (2 eq.).
butyllithium (2.5 M in hexane, 2 eq.), and trimethylsilyl chloride (3 eq.).\textsuperscript{88} The silylated alcohol 105 was obtained in 41\% yield (Scheme 36). The low yield obtained may be explained by the high volatility of this compound.

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\textbf{107}};
\node (B) at (3,0) {\textbf{105}};
\node (C) at (1.5,-1) {41\%};
\draw[->] (A) -- (B);
\draw[->] (A) -- (C);
\draw[->] (A) -- (1.5,0);
\draw[->] (A) -- (1.5,-1);
\node [above] at (0,-0.5) {1. n-BuLi, TMEDA};
\node [above] at (1.5,-0.5) {2. TMSCl};
\node [above] at (3,-0.5) {3. H\textsubscript{2}SO\textsubscript{4} (dil)};
\end{tikzpicture}
\end{center}

**Scheme 36** Synthesis of 3-(trimethylsilylmethyl)but-3-en-1-ol\textsuperscript{88}

To investigate the potential of this substrate in a silyl-Prins reaction, two commercially available aldehydes, phenylacetaldehyde and \textit{n}-hexanal, were investigated as co-reagents. Conditions for these reactions were the same as literature methods for standard silyl-Prins cyclisations with all reactions performed at room temperature using a stoichiometric quantity of Lewis acid catalyst indium (III) chloride.\textsuperscript{58}

Both of the reactions of alcohol 105 with phenylacetaldehyde and \textit{n}-hexanal produced a mixture of three regioisomeric olefins (Scheme 37). Although the desired \textit{exo}-methylene compound was produced in both reactions, the major product was the 3,6-dihydro-2\textit{H}-pyran regioisomer (65-75\%) with a much lower amount of the 5,6-dihydro-2\textit{H}-pyran regioisomer (16-30\%) also formed. These regioisomers were distinguished by differences in the \textit{^1}H NMR data.
The formation of these isomers can possibly be explained by the presence of acidic by-products of the indium(III) chloride in the reaction mixture which isomerises the \textit{exo}-methylene product to the more thermodynamically stable \textit{endo}-regioisomers (Scheme 38). Longer reactions times (40 h) increased the proportion of 2-benzyl-4-methyl-3,6-dihydro-2H-pyran 109 from 65% to 75% relative to its regioisomers including the \textit{exo}-methylene compound. In addition, the employment of an acidified work-up using sulfuric acid (2 M) to quench the reaction increased the proportion of the major regioisomer 109.

\begin{center}
\textbf{Scheme 38}  Protonation of \textit{exo}-methylene double bond
\end{center}
A work-up using ammonium chloride solution to quench the reaction was also investigated. This had a negligible effect on product distribution. Future work in this area should concentrate on reducing the temperature of the reaction and reducing the duration of the reaction. Furthermore, the addition of a buffer or basic species may also aid the formation of the exo-methylene moiety as previous work-ups involved acidic quenching of the reaction which may be causing the isomerisation.
2.4 Method Development: The Mukaiyama-Aldol Silyl-Prins Reaction

2.4.1 Background: The Mukaiyama-Aldol Prins Reaction

Recently developed by Rychnovsky, the Mukaiyama-Aldol Prins (MAP) reaction has demonstrated that unsaturated enol ethers 115 can be reacted with aldehydes 43 in the presence of TiBr4 in a Mukaiyama-Aldol-type reaction and then combined in a Prins reaction to afford 4-bromotetrahydropyran products 116 (Scheme 39).89 This reaction has proven to be high-yielding and leads to the creation of three new stereogenic centres. Furthermore, an additional hydroxyethyl group has been incorporated into the substituent of the tetrahydropyran ring.

\[
\begin{align*}
\text{Ph} & \quad \text{O} \quad \text{H} \\
+ & \quad \text{H} \quad \text{O} \\
\text{TiBr}_4 & \quad 2,6-	ext{DTBP} \\
\text{CH}_2\text{Cl}_2, -78^\circ \text{C} & \quad \text{Ph} \quad \text{H} \quad \text{O} \\
\text{Br} & \quad \text{OH} \\
\end{align*}
\]

Scheme 39 The Mukaiyama-Aldol Prins reaction

It occurred to us that the silyl-Prins methodology could be applied to the Mukaiyama-Aldol Prins reaction to prepare 5,6-dihydro-2H-pyrans with a hydroxyethyl moiety incorporated in the 2-position. Scheme 40 shows a generic version of this proposed cyclisation using a silylated vinyl ether precursor 117.

\[
\begin{align*}
\text{TMS} & \quad \text{O} \quad \text{O} \\
+ & \quad \text{H} \quad \text{O} \\
\text{InCl}_3 & \quad \text{CH}_2\text{Cl}_2 \\
\text{CH} & \quad \text{OH} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]

Scheme 40 Proposal for the Mukaiyama-Aldol silyl-Prins reaction
A postulated mechanism (Scheme 41) for this reaction involves initial activation of the aldehyde carbonyl group by a Lewis acid. The silyl vinyl ether 117 then attacks the aldehyde via Mukaiyama-Aldol addition. This generates an oxonium cation identical to that obtained in the silyl-Prins reaction. This would then be able to undergo a silyl-Prins cyclisation to afford a silicon-stabilised carbocation and subsequent desilylation furnishes the expected dihydropyran product 119.

Scheme 41  Proposed mechanism of the Mukaiyama-Aldol silyl-Prins reaction
2.5 Synthesis of the Vinyl Ether Precursor 117 for the MASP Reaction

In order for the proposed Mukaiyama-Aldol silyl-Prins reaction to be synthetically useful, it was necessary to develop a simple, efficient route to its integral precursor, Z-4-trimethylsilyl-1-vinlyoxybut-3-ene. Therefore initial studies were focussed on investigating a number of different pathways to this substrate 117 (Figure 13).

![Figure 13 Possible disconnections for the preparation of Z-4-trimethylsilyl-1-vinlyoxybut-3-ene 117](image)

2.6 Routes Involving the Application of Wittig Reaction Methodology

A number of attempts were made to prepare the precursor 120 with the employment of Wittig methodology. These investigations can be classified into two different approaches (Scheme 42). While the precursor 120 has a shorter carbon chain than the ideal vinyl ether 117, the compounds employed to generate the phosphonium salts 119 and 121 were commercially available whereas the desired ones were not, and so served as good model systems.

![Scheme 42 Retrosynthetic analysis of 120 to indicate Wittig pathways](image)
2.6.1 Wittig Approach: Route 1

The preparation of trimethylsilyl methanal 118 and triphenyl-(2-vinylxyethyl) phosphonium chloride 119 were the first two objectives in the overall aim of performing a Wittig reaction to afford the precursor 120 (Scheme 43).

\[
\begin{align*}
\text{TMS} & \quad + \quad \text{Ph}_3\text{P} & \quad \text{Cl} & \quad \text{CH} & \quad \text{CH} \\
118 & \quad 119 & \quad 120 \\
\end{align*}
\]

Scheme 43 Proposed Wittig reaction to prepare silylated vinyl ether 120

Generation of the phosphonium salt 119 was achieved using a literature method for the preparation of phosphonium salts with triphenylphosphine (1.5 eq.) added to 2-chloroethyl vinyl ether (2 eq.) (Scheme 44). IR data indicated the formation of triphenyl-(2-vinylxyethyl) phosphonium chloride 119 as white crystals (26%) while the \textsuperscript{1}H NMR data was not helpful in identification as the product was a salt. The low yield might be explained by the absence of solvent from the reaction mixture. Conclusive evidence for the formation of this compound was difficult to obtain due to the ionic nature of the product.

\[
\begin{align*}
\text{Ph}_3\text{P} & \quad + \quad \text{CH} & \quad \text{CH} & \quad \text{Cl} & \quad \text{Ph}_3\text{P} & \quad \text{CH} & \quad \text{CH} \\
123 & \quad 124 & \quad 119 \\
\end{align*}
\]

Scheme 44 Synthesis of triphenyl-(2-vinylxyethyl) phosphonium chloride 119
Two oxidation procedures were investigated for the preparation of trimethylsilyl methanal \textbf{118} from commercially available trimethylsilylmethanol \textbf{125} (Scheme 45).

\begin{center}
\begin{align*}
\text{TMS} & \overset{\text{Oxidation procedure I or II}}{\rightarrow} \text{TMS} \overset{\text{OH}}{\rightarrow} \\
\text{125} & \rightarrow \text{118}
\end{align*}
\end{center}

\textbf{Scheme 45} Oxidation reactions to generate trimethylsilyl methanal \textbf{118}

The first was a Swern oxidation\textsuperscript{91} which afforded the desired aldehyde \textbf{118} in low yield (10%). The low yield was due to the high volatility of the target material, much of which may have been lost during condensation \textit{in vacuo}. The reaction was repeated on a variety of scales but it was not possible to achieve a sufficient quantity of the aldehyde \textbf{118} by this method.

The employment of pyridinium chlorochromate was therefore investigated as an alternative oxidising agent. The reaction was performed according to literature methods for PCC oxidations.\textsuperscript{92} Trimethylsilylmethanol \textbf{125} was added to a flask containing pyridinium chlorochromate, silica gel (to aid in the removal of by-product chromium tars) and dry dichloromethane. Standard work-up was performed with filtration of the reaction mixture through Celite. Analysis of the crude mixture by $^1$H NMR spectroscopic techniques indicated the desired aldehyde \textbf{118} had been formed. Attempts to purify the crude product led to further loss of the product during evaporation.

In an attempt to circumvent the issues relating to the preparation of trimethylsilyl methanal \textbf{118} and its volatility, it was decided to perform a one-pot \textit{in situ} alcohol oxidation-Wittig reaction. There is much literature precedent for the employment of these types of reaction.\textsuperscript{93-95} In the case of an unactivated alcohol such trimethylsilylmethanol \textbf{125}, Taylor has demonstrated that an \textit{in situ} procedure involving activated manganese dioxide as the oxidising species could be employed successfully.\textsuperscript{96} Manganese dioxide
was considered to be a preferential choice as oxidant compared to barium permanganate which has toxicity issues and the Dess-Martin Periodinane where extreme care to exclude moisture is required.

Investigation of this reaction was first performed by the addition of activated manganese dioxide to a solution of trimethylsilylmethanol 125 (1 eq.), the previously prepared phosphonium salt 119 (1.1 eq.), guanidine base MTBD (2.2 eq.) and titanium isopropoxide (1 eq.) in dry THF (Scheme 46). After heating to reflux temperature for 1 hour, a second portion of manganese dioxide (5 eq.) was added and the reaction mixture was heated to reflux temperature for a further 72 hours. Analysis of the product mixture by $^1$H NMR spectroscopic techniques indicated only the presence of trimethysilylmethanol and unidentifiable compounds.

This reaction was repeated using a stronger base, n-butyllithium (2.5 M in hexane), in place of MTBD to deprotonate the phosphonium salt and form the required ylide. The reaction was performed in the previously employed reaction conditions with the duration of the reaction reduced to 45 hours. Analysis of the product mixture by GCMS and $^1$H NMR spectroscopic techniques indicated the presence of trimethylsilylmethanol 125 and unidentifiable products possessing aromatic moieties.

A series of model reactions were performed to investigate the results obtained in these in situ alcohol oxidation-Wittig reactions. First, a standard oxidation of trimethylsilylmethanol 125 to trimethylsilyl methanal 118 using manganese dioxide as the oxidant was attempted (Scheme 47). The manganese dioxide employed was extremely pure and, as in previous reactions, was heated to 100 °C for 24 hours in order
to ensure it was activated sufficiently. This reaction failed to produce any aldehyde 118 in the product mixture, indicating problems relating to the oxidation side of the \textit{in situ} synthesis.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {TMS$\text{-}$OH};
\node (b) at (2.5,0) {$\text{MnO}_2$ (act)};
\node (c) at (4.5,0) {THF};
\node (d) at (7,0) {TMS$\text{-}$H};
\node (e) at (0.5,1.5) {X};
\node (f) at (3.5,1.5) {X};
\end{tikzpicture}
\end{center}

\textbf{Scheme 47} Attempted oxidation of trimethylsilylmethanol 125 using manganese dioxide

Next, a series of test \textit{in situ} alcohol oxidation-Wittig reactions were performed using commercially available \textit{n}-heptanol 126 in place of trimethylsilylmethanol 125 (Scheme 48). The conditions of the reaction were kept the same as those previously described with first MTBD and then with \textit{n}-butyllithium (2.5 M solution in hexane) employed as the base. Both reactions were heated to reflux temperature whilst stirring for 48 hours. Analysis of the product mixtures from both reactions revealed the absence of the Wittig product 127 but there was some indication of \textit{n}-heptanal 128 present. This appears to indicate that the oxidation step may have been successful in this case but reaction failure occurred at the Wittig reaction stage.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {OH};
\node (b) at (2.5,0) {$\text{MnO}_2$, (act), Ti-(i-PrO)$_4$};
\node (c) at (4.5,0) {MTBD, THF};
\node (d) at (7,0) {$\text{Cl}$ Ph$_3$P$\text{-}$O$\text{-}$O$\text{-}$O$\text{-}$Cl$};
\node (e) at (0.5,1.5) {X};
\node (f) at (3.5,1.5) {X};
\end{tikzpicture}
\end{center}

\textbf{Scheme 48} Model study of an \textit{in situ} oxidation-Wittig reaction
Inability to access the required vinyl ether 120 was due to a number of factors. Firstly the high volatility of the aldehyde 118 made it difficult to prepare in sufficient quantities and purity using either the Swern or PCC oxidation. In the presence of manganese dioxide the trimethylsilyl methanal 118 did not form. The in situ reactions also encountered difficulties and the model studies indicate that the Wittig step may be part of the reason for this.

2.6.2 Wittig Approach: Route 2

An alternative Wittig reaction (Scheme 49) afforded an opportunity to prepare the desired vinyl ether precursor 120 from different starting reagents in an attempt to overcome some of the issues present in the first approach.

\[
\text{TMS-P}^+\text{Ph}_3\text{Br}^- + \text{HCO}_2\text{H} \xrightarrow{\text{Base}} \text{TMS-}120
\]

Scheme 49 Proposed Wittig reaction to prepare precursor 120

Preparation of the phosphonium salt 121 was performed according to literature procedure by the addition of triphenylphosphine (1.5 eq.) to a solution of bromomethyltrimethylsilane (2 eq.) in dry dichloromethane (Scheme 50).97a,b The phosphonium salt 121 was furnished in good yield (85 %) as a pale pink powder.

\[
\text{Ph}_3\text{P} + \text{TMS-Br} \xrightarrow{\text{CH}_2\text{Cl}_2} \text{TMS-P}^+\text{Ph}_3\text{Br}^- \xrightarrow{85\%}
\]

Scheme 50 Preparation of the phosphonium salt 121
It should be noted that preparation of the phosphonium ylide from phosphonium salt 121 would afford a silicon-stabilised carbanion which could perform either a Wittig reaction or a Peterson reaction (Scheme 51).\textsuperscript{97a,b}

\textbf{Scheme 51} Mechanisms of potential reactions using phosphonium salt 121

Therefore, in order to evaluate the applicability of the phosphonium salt 121 to the Wittig methodology, a test Wittig reaction was performed using the commercially available aldehyde \textit{n}-hexanal (Scheme 52). Analysis of the product mixture by GCMS indicated the formation of the desired product 130 in addition to a substantial quantity of triphenylphosphine oxide. The Peterson product 131 was not observed in the reaction mixture.
The required aldehyde precursor 122 for the Wittig reaction was to be obtained by oxidation of commercially available ethylene glycol vinyl ether 132. A variety of reagents were investigated for their capacity to oxidise ethylene glycol vinyl ether to 2-vinyloxyethanal (Scheme 53).

Analysis of the Swern oxidation by \(^1\)H NMR methods suggested the presence of trace amounts of aldehyde 122 in addition to unidentifiable compounds. The manganese dioxide oxidation gave only recovered starting reagent ethylene glycol vinyl ether (73%). In the case of the pyridinium dichromate oxidation the product mixture consisted of starting reagents, a small quantity of the desired aldehyde 122 and chromium reaction by-products. The pyridinium chlorochromate oxidation afforded mostly...
inseparable pyridinium by-products and unidentifiable compounds as indicated by the \(^1\)H NMR data.

One possible cause of the inability to form the desired aldehyde 122 could be due to its volatility. In an attempt to remedy this issue, an *in situ* alcohol oxidation-Wittig reaction was performed using the literature methodology employed in the first Wittig approach to the vinyl ether precursor 120 (Scheme 54).

\[ \text{HO} \xrightarrow{\text{MnO}_2, \text{Ti}(-\text{PrO})_4} \text{X} \xrightarrow{n-\text{BuLi, THF}} \text{TMS} \text{P}^\text{Ph}_3 \text{Br} \]

**Scheme 54**  *In situ* alcohol oxidation-Wittig reaction

The analysis of the product mixture did not indicate the formation of the target compound. There was, however, an inseparable aldehyde species present in the \(^1\)H NMR indicating that the oxidation step of the reaction may have occurred.
2.7 Nucleophilic Substitution-Based Route

Investigations were carried out into the use of a nucleophilic substitution reaction followed by DIBAL-H reduction to prepare the desired silyl vinyl ether 117 (Scheme 55).

Scheme 55 Potential route to the vinyl ether precursor 117

The first step was the *in situ* preparation of the lithiated alkyne from trimethylsilylacetylene (Scheme 56). Deprotonation was thus performed using *n*-butyllithium followed by reaction with a halo-ethyl vinyl ether. Initially, commercially available 2-chloroethyl vinyl ether 135 was investigated as the halo-ethyl vinyl ether for this reaction. The rapid formation of a yellow solution on the addition of the *n*-butyllithium suggests that the initial deprotonation to form the organolithium species had occurred. There was no indication of the desired vinyl ether 134 in the subsequent product mixture however.

Scheme 56 Attempted nucleophilic substitution using 2-chloroethyl vinyl ether
The major product was indicated by $^1$H NMR to be recovered 2-chloroethyl vinyl ether 135 and trimethylsilyl acetylene 133 (Figure 14). GCMS analysis suggested the possible formation of a small quantity of hydrolysed product 72.

![Figure 14 Products of nucleophilic substitution reaction](image)

In $\text{S}_2$ reactions iodide ions have long been recognised as superior leaving groups to chloride ions due to the decreased strength of the C-I bond (\(D\) values: CH$_3$-Cl = 85 kcal mol$^{-1}$, CH$_3$-I = 57 kcal mol$^{-1}$) and the anion stability of the iodide ions.\(^99\) Therefore conversion of the chlorine-containing precursor 135 to its iodo-derivative 136 using the Finkelstein methodology was investigated (Scheme 57).\(^100\) 2-Iodovinyl ether 136 was prepared according to literature methods (25%).

![Scheme 57 Finkelstein reaction to prepare 2-iodovinyl ether 136](image)
Repetition of the nucleophilic substitution reaction using 2-iodovinyl ether was performed but the vinyl ether 134 was not indicated by \textsuperscript{1}H NMR or GCMS analysis (Scheme 58).

\[ \text{TMS} \equiv \equiv \text{H} \xrightarrow{\text{n-BuLi, THF, } -78 \, ^\circ\text{C}} [\text{TMS} \equiv \equiv \text{Li}] \]

\[ \xrightarrow{\text{X, THF, } -78 \, ^\circ\text{C}} \text{TMS} \equiv \equiv \text{O} \equiv \equiv \text{O} \]

**Scheme 58** Attempted nucleophilic substitution using 2-iodovinyl ether

A number of other possible compounds were suggested by the GCMS data (Figure 15). One possibility is that residual acetone from the Finkelstein reaction may have preferentially quenched the deprotonated organolithium species instead of forming the desired alkyne 134.

\[ \text{TMS} \equiv \equiv \text{O} \equiv \equiv \text{O} \]

\[ \text{TMS} \equiv \equiv \text{OH} \]

**Figure 15** Products of the attempted S\textsubscript{N}2 nucleophilic substitution
2.8 Routes Involving Metathesis Methodology

Two varying approaches to the vinyl ether precursor 117, both employing olefin metathesis, were considered for investigation (Scheme 59).

\[
\begin{array}{c}
\text{TMS} + \begin{array}{c}
\text{Route 1} \\
\text{138} \begin{array}{c}
\text{139} \\
\text{117} \\
\text{64} \begin{array}{c}
\text{RCM} \\
\text{142} \\
\text{71} \\
\end{array}
\end{array}
\end{array}
\end{array}
\]

Scheme 59 Retrosynthetic analysis of \( \text{Z-4-trimethylsilyl-1-vinyloxybut-3-ene} \) 117 to obtain potential routes to its synthesis

2.8.1 Metathesis Approach: Route 1

Recent research by Langer et al. has shown that vinyltrimethylsilane can react with alkenyl epoxides in a cross-metathesis reaction using Grubbs I catalyst 20 (Scheme 60). While the desired product 144 was obtained, the reaction was low yielding and had a lack of olefin selectivity, with the formation of homocoupled products in most cases.
Despite these potential limitations, a selective cross-metathesis reaction using vinyltrimethyilsilane 138 was investigated as the achievement of a successful reaction to form the homoallylic alcohol 83 would greatly enhance the expediency of a potential route to the vinyl ether 117. A cross-metathesis reaction was attempted between commercially available 3-buten-1-ol (1 eq.), vinyltrimethyilsilane 138 (1.1 eq) and the metathesis catalyst (5 mol%) in dry dichloromethane (Scheme 61). Two catalysts were screened for their applicability to this reaction; Grubbs 2nd generation ruthenium catalyst and Schrock’s molybdenum catalyst. It should be noted that although an E-isomer may have resulted from this metathesis reaction, previous work within the group has shown that this would have no detrimental effect on the outcome of a subsequent silyl-Prins reaction. The stereochemistry of the double bond has no effect on the outcome of the silyl-Prins reaction when one or less substituents are present on the homoallylic alcohol precursor. When a second substituent is attached, steric effects alter the stereochemistry of the reaction product.

Scheme 60  Cross-metathesis of vinyltrimethylsilane 138 with an alkenyl epoxide 143 by Langer et al.\textsuperscript{101}

Scheme 61  Cross-metathesis route to vinyl ether 83
Reactions with both these catalysts afforded mostly recovered 3-buten-1-ol compounds. One possible explanation of this is that the hydroxyl group of 3-buten-1-ol is coordinating to the metal centre of the catalyst and thereby preventing a successful reaction. To test this hypothesis 3-buten-1-ol was protected using benzyl bromide\textsuperscript{102} and subsequently participated in the same metathesis reaction previously described (Scheme 62).

\begin{center}
\begin{tikzpicture}
    \node (a) at (0,0) {\ce{CH=CHCH2OH}};
    \node (b) at (2,0) {\ce{CH=CHCHCH3\text{Ph}}};
    \node (c) at (4,0) {\ce{CH=CHCH2CH=CH2\text{Ph}}};
    \draw (a) -- (b);
    \draw (b) -- (c);
    \draw (a) -- (b) node [midway, above] {\text{BnBr, KOH, THF}};
    \draw (b) -- (c) node [midway, above] {\text{Grubbs II, 21C2}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 62} Reaction to prepare vinylsilane 146 using cross-metathesis

The cross-metathesis product mixture, although containing mostly recovered starting material 145, contained also a small amount of the cross-metathesis product 146. This appears to indicate that protection of the hydroxyl group is having an impact on the metathesis reaction but the proportion of cross-metathesis product yielded is insufficient for further investigation of this strategy. Cross-metathesis reactions of this nature are known to be challenging as the lack of literature examples using vinyltrimethylsilane supports. In certain cases homo-coupled products may be obtained in preference to the desired product.\textsuperscript{101} As the research by Langer et al. has already indicated, there is some difficulty in achieving high yielding cross-metathesis reactions using vinylsilanes.\textsuperscript{101}

\subsection*{2.8.2 Metathesis Approach: Route 2}

An alternative approach to the preparation of the vinyl ether 117 was investigated involving a ring-closing metathesis step followed by nucleophilic ring-opening to afford 64. This could then be transetherified to produce the vinyl ether 117. The proposed route is shown in Scheme 63:
The diene 141 was prepared in good yield (77%) using literature methods from commercially available dimethylchlorovinylsilane 140 (1 eq.), imidazole (1.2 eq.) and 3-buten-1-ol 71 (1 eq.) in dry dichloromethane (Scheme 64).\textsuperscript{103}

The ring-closing metathesis step was attempted using Grubbs 2\textsuperscript{nd} generation catalyst 21 to facilitate the reaction. The product mixture indicated only recovered diene 141 by GCMS analysis (90%) (Scheme 65).
Denmark et al. have shown a similar reaction to this is possible using Schrock catalyst 22 and this catalyst may be more successful for these types of reaction than Grubbs II catalyst 21 (Scheme 66).  

\[
\text{Schrock cat. 22} \quad \text{benzene, r.t., 1h} \quad \text{95%}
\]

Scheme 66  Ring-closing metathesis by Denmark et al.\textsuperscript{104}

2.9 Route Involving a Transetherification Reaction

This pathway comprised 3 steps, the first two of which had previously been employed by Dobbs et al. in the preparation of silylated homoallylic alcohols for use in the silyl-Prins reaction.\textsuperscript{58} Following the standard route (Scheme 24), Z-4-trimethylsilylbut-3-en-1-ol 64 was prepared in 2 steps with comparable yields to those previously mentioned.

The final step involved the transetherification of the alcohol function.\textsuperscript{105,106} Ethyl vinyl ether (EVE) was used to perform the function of both the reactant and solvent for these transetherifications. DiPietro et al. have demonstrated previously several reactions of this type such as the example shown in Scheme 67.\textsuperscript{107}

\[
\text{EVE, Hg(OAc)}_2 \quad \text{r.t., 18 h} \quad \text{57%}
\]

Scheme 67  Hg(OAc)\textsubscript{2} catalysed transetherification reaction by DiPietro et al.\textsuperscript{107}
Two catalysts were investigated in the synthesis of the vinyl ethers; mercuric(II) trifluoroacetate and mercuric(II) acetate.

2.9.1 Mercuric(II) Trifluoroacetate-Mediated Transetherification

Prior to performing the transetherification on the homoallylic alcohol 64, a test mercuric(II) trifluoroacetate-mediated transetherification using commercially available 3-butyn-1-ol 71 was performed according to literature procedure (Scheme 68). Analysis by $^1$H NMR spectroscopic techniques indicated only the presence of recovered ethyl vinyl ether and 3-butyn-1-ol. This can be explained by the possible addition of mercury across the triple bond instead of the hydroxyl oxygen. Therefore further investigation into this transetherification strategy was continued as the desired silylated alcohols do not possess the problematic alkyne moiety.

![Chemical structure](image)

**Scheme 68** Transetherification of commercially available 3-butyn-1-ol 71

Mercuric(II) trifluoroacetate-mediated transetherification between Z-4-trimethylsilylbut-3-en-1-ol 64 and ethyl vinyl ether produced the desired product as indicated by $^1$H NMR and GCMS spectroscopic techniques as part of the crude mixture (Scheme 69). Difficulties regarding separation by column chromatography led to the implementation of various purification strategies including the basification of the silica stationary phase using triethylamine and the employment of a basic alumina stationary phase. Neither of these purification strategies proved successful.
2.9.2 Mercuric(II) Acetate-Mediated Transetherification

Mercuric(II) acetate-mediated transetherification\textsuperscript{107} was performed according to the literature procedure with the silylated alcohol \(64\) being stirred in ethyl vinyl ether for 23 hours at room temperature and then condensed \textit{in vacuo}. Another portion of EVE was added to the reaction mixture which was allowed to continue stirring for another 23 hours. This cycle was repeated once more and the reaction was quenched by the addition of triethylamine. After filtration through a small silica gel plug and purification by Kugelrohr distillation the vinyl ether \(117\) was obtained in a 4:1 ratio mixture with the starting reagent Z-4-trimethylsilylbut-3-en-1-ol (24%) (Scheme 70).

The presence of the unreacted alcohol \(64\) in the product mixture, while undesirable, did not preclude any attempts at the Mukaiyama-Aldol silyl-Prins cyclisation although its presence needs to be borne into consideration when analysing the results obtained.
Transetherification of commercially available 3-buten-1-ol promoted by mercuric(II) acetate was attempted but only starting reagents were recovered (Scheme 71). It was envisaged that if this reaction had been successful a cross-metathesis with vinyltrimethylsilane could have afforded the silyl-Prins precursor 117.

\[
\begin{align*}
\text{1. EVE, Hg(OAc)}_2 \text{, r.t.} & \quad \Rightarrow \quad \text{X}^- \\
\text{2. NaHCO}_3 & \\
\text{71} & \quad \text{152}
\end{align*}
\]

Scheme 71 Attempted transetherification of commercially available 3-buten-1-ol.

A future strategy for the addition of a vinyl group at hydroxyl oxygen may to employ acetylene gas as the vinylationing agent.\textsuperscript{109,110} The addition of this gas to the silylated homoallylic alcohol 64 could be used to afford the vinyl ether 117 (Scheme 72).

\[
\begin{align*}
\text{TMS} & \quad \equiv \quad \text{CsF-NaOH} \\
\text{64} & \quad \text{TMS} \quad \text{O} \quad \equiv \quad \text{117}
\end{align*}
\]

Scheme 72 Employment of acetylene gas in the preparation of vinyl ether 117\textsuperscript{109,110}
2.10 Preliminary Mukaiyama-Aldol Silyl-Prins (MASP) Cyclisations

Despite the issues relating to the preparation and purification of the vinyl ether precursor 117, it was possible to obtain a sufficient quantity of this compound using the transetherification procedure to investigate its potential in a series of preliminary Mukaiyama-Aldol silyl-Prins cyclisations with various Lewis acids (Scheme 73).

Scheme 73 The Mukaiyama-Aldol silyl-Prins reaction

Indium(III) chloride-mediated MASP cyclisation reactions were investigated initially due to its mild nature and its past compatibility with the silyl-Prins reactions. The commercially available aldehydes, phenylacetaldehyde and n-hexanal were reacted with Z-4-trimethylsilyl-1-vinyloxy-but-3-ene in the presence of indium(III) chloride and the results obtained are shown in Scheme 74. The general procedure involved addition of the chosen aldehyde to indium(III) chloride in dry dichloromethane under an atmosphere of nitrogen. After stirring for 1 hour the vinyl ether 117 was added and the reaction mixture was stirred for a further 16-17 hours. Purification of the reaction mixture was by column chromatography.

Scheme 74 Indium(III) chloride-mediated preliminary MASP cyclisations
In the phenylacetaldehyde reaction, \((\pm)-1-(5,6\text{-dihydro-2}\text{-pyran-1-yl})-3\text{-phenyl-propan-2-ol}\) (2%) was present in the crude mixture as suggested by the GCMS spectroscopic data, its gas chromatographic peak partially overlapping with that of the most abundant isolated product, \((\pm)-2\text{-benzyl-5,6\text{-dihydro-2}\text{-pyran}}\) (98%). This was formed when a standard silyl-Prins reaction occurred by the reaction of \(Z\)-4-\(\text{trimethylsilylbut-3-en-1-ol}\) with phenylacetaldehyde.

The presence of 20\% of \(Z\)-4-\(\text{trimethylsilylbut-3-en-1-ol}\) in the starting reagent mixture would undoubtedly account for a proportion of the silyl-Prins reaction product \(155\). There was, however, a greater quantity of \((\pm)-2\text{-benzyl-5,6\text{-dihydro-2}\text{-pyran}}\) obtained than the maximum yield that would have been obtained from \(Z\)-4-\(\text{trimethylsilylbut-3-en-1-ol}\) 64. This appears to indicate that an oxonia-Cope rearrangement of the oxonium cation (Scheme 75) leads to the formation of an isomeric trans-silylated homoallylic alcohol which takes part in a silyl-Prins reaction to form \((\pm)-2\text{-benzyl-5,6\text{-dihydro-2}\text{-pyran}}\). The aldol product \(157\) may also be formed as the presence of an extra aldehyde peak in the crude mixture in addition to the one from residual phenylacetaldehyde suggests.

Another possible factor contributing to the lack of desired dihydropyran formation may be the vinyl ether \(117\) becoming bound to the Lewis acid indium(III) chloride at the vinyl oxygen or protonation from the expected MASP by-product \(\text{InCl}_2\text{OH}\), both of which may prevent the Mukaiyama-Aldol step from occurring subsequently. This issue is referred to by Rychnovsky et al. and is combated by the employment of a pyridine base (DBTP) to suppress the protonation.\textsuperscript{111} Future work in this area may investigate the employment of this reagent.
With the employment of \( n \)-hexanal as the aldehyde substrate, a similar set of data was obtained. The desired dihydropyran 154 did appear to be present as a minor component of the GCMS mixture but the major product was 2-pentyl-5,6-dihydro-\( \text{2H} \)-pyran 156 (3\%). In a similar mode to the previous experiment the vinyl ether substrate appeared to be converting to its alcohol derivative and then performing a silyl-Prins cyclisation (Scheme 75).
Titanium(IV) chloride was investigated for its suitability as a catalyst for these reactions (Scheme 76). These reactions were performed at room temperature under an atmosphere of nitrogen. In the reaction with commercially available phenyl acetaldehyde, the main products were (±)-2-benzyl-5,6-dihydro-2H-pyran, (96%) and (±)-1-(5,6-dihydro-2H-pyran-1-yl)-3-phenyl-propan-2-ol (4%) as indicated by GCMS analysis. Characterisation of the minor product 153 was difficult due to overlap with similar species 155 in the $^1$H NMR spectra. The presence of residual titanium ions in the product mixture also made characterisation difficult. Employing $n$-hexanal as the aldehyde substrate in these reactions leads to the formation of (±)-1-(5,6-dihydro-2H-pyran-2-yl)-heptan-2-ol 154 and 2-pentyl-5,6-dihydro-2H-pyran 156, and unreacted $n$-hexanal.

Scheme 76  Titanium(IV) chloride-mediated preliminary MASP cyclisations

The results of these preliminary cyclisations reactions are very encouraging with the formation of a proportion of the desired dihydropryan in every reaction. The first issue to resolve is the preparation of greater quantities of pure vinyl ether precursor 117 which should increase the production of the desired products. Once this can be achieved, the employment of a basic species in the reaction mixture could aid the suppression of protonation in the MASP reactions. As mentioned in the previous case, the hindered pyridine base 2,6-di-tert butylpyridine (2,6-DTBP) may help prevent protonation of the vinyl ether 117. Of the two catalysts screened for use in this reaction, indium(III) chloride is preferred due to the formation of less unwanted reaction by-products. It also has the advantage of being a milder, more stable catalyst.
2.11 Conclusion

The development of the silyl-Prins reaction focused on three main areas. The first involved the preparation of a dihydropyran moiety with the incorporation of an ester functionality in the 2-position. While issues relating to the desilylation of the starting material prevented successful application of this methodology, there is scope to further explore this methodology. This possibility of polymerisation of the ethyl glyoxylate reagent is one area in particular which requires further investigation.

The second area of investigation involved the preparation of exo-methylene tetrahydropyrans using the silyl-Prins methodology. Data from these reactions indicated that the desired tetrahydropyran had formed in addition to two of its endocyclic regioisomers. Future work in this area should concentrate on modifying the reaction conditions in order to maximise the quantity of the regioisomer.

The Mukaiyama-Aldol Prins cyclisation provided an interesting example of the synthetic potential of cationic cyclisation reactions and afforded an opportunity to further develop the silyl-Prins reaction. Application of this methodology to the synthesis of dihydropyrans with a hydroxyethyl group in a proposed Mukaiyama-Aldol silyl-Prins reaction was therefore our chief objective.

Much of our early work was concerned with the development of a rapid, efficient and reliable route to the required vinyl ether precursor 117. Unfortunately, a satisfactory route to this precursor has not yet been achieved. A number of potential routes to this precursor are under consideration and future work in this area will concentrate on the investigation of these. One potential route involves the initial formation of a formate ester 158 which could then be reacted with Tebbe reagent to afford the desired vinyl ether (Scheme 77).
Another potential strategy could involve using commercially available vinyltrimethylsilane 138 which could be oxidised to form epoxide 159. This species could then undergo nucleophilic ring-opening to afford 160. After elimination using potassium hydride the product could then be silylated and stereoselectively reduced to afford the vinyl ether 117. (Scheme 78).

A further potential route to the vinyl ether 117 may involve performing a transesterification on commercially available 161 and subsequently using trimethylsilyl acetylene to react with in a nucleophilic substitution reaction (Scheme 79). The resultant product could then be stereoselectively reduced to afford the desired vinyl ether 117.
Another possibility is the repetition of the alcohol oxidation/Wittig reactions using a bulkier silicon group such as TBS to combat the volatility issues due to the aldehyde species 118.

Once the vinyl ether precursor 117 had been prepared, preliminary cyclisation studies demonstrate its potential as a substrate in the Mukaiyama-Aldol silyl-Prins reaction. The key issue to overcome regarding these cyclisations is suppression of protonation of the vinyl ether 117. On achievement of this objective, it is likely that this cyclisation can become a very synthetically useful transformation in organic synthesis.
Chapter 3

Introduction II: The Natural Products, (-)-Centrolobine and Kendomycin and Existing Routes to their Synthesis
3 Introduction II: The Natural Products, (-)-Centrolobine and Kendomycin and Existing Routes to their Synthesis

The structures of a vast array of natural products have been elucidated including many with tetrahydropyran and dihydropyran substructures. Our research has focused on routes towards the synthesis of two natural products (±)-centrolobine and kendomycin due to their molecular structures which possess key substituted tetrahydropyran subunits and interesting pharmacological profiles.

3.1 (-)-Centrolobine

3.1.1 Introduction

(-)-Centrolobine (163, Figure 16) is a natural product isolated from the heartwood of Centrolobium robustum\textsuperscript{112-114} and the stem of Brosinium potabile\textsuperscript{115} in the Amazon forest. It possesses a cis-2,6-disubstituted tetrahydropyran core structure. While the basic structure of (-)-centrolobine was first elucidated in 1964,\textsuperscript{112} its absolute configuration was only established in 2002 by an enantioselective total synthesis by Solladie \textit{et al}.\textsuperscript{116,117} It has been shown to act as an antileishmanial agent against \textit{Leishmania amazonensis} promastigotes, which is a significant health problem in Brazil.\textsuperscript{118}

![Figure 16](image_url)
There has been much recent interest in the synthesis of this natural product due to its biological activity and also its structure which provides a convenient testing ground to highlight new advances in the preparation of tetrahydropyran ring systems. A selection of the existing syntheses will be outlined with particular focus on the methods for the construction of the tetrahydropyran core.

3.2 Literature Methods for the Preparation of (±)- or (-)-Centrolobine

3.2.1 The Intramolecular Cyclisation of a Hydroxyketone

One of the earliest syntheses was by Solladié et al. which involved the intramolecular cyclisation of a hydroxyketone 164 with an excess of triethylsilane and trimethylsilyl triflate at 0 °C (Scheme 80). The tetrahydropyran 165 was obtained with complete syn stereoselectivity in good yield (81%). The presence of the sulfoxide moiety on this fragment 165 facilitates further functionalisation leading to (-)-centrolobine 163.

Scheme 80 Synthesis of (-)-centrolobine 163 using intramolecular cyclisation of a hydroxyketone by Solladié et al. 116,117
Overall, this asymmetric synthesis afforded (-)-centrolobine in nine steps with an overall 26% yield starting from commercially available glutaric anhydride.

### 3.2.2 A Prins Cyclisation Strategy

The Prins cyclisation has long been recognised as a powerful method for preparing tetrahydropyran rings. Rychnovsky et al., having conducted much work in this area, have developed a route to (-)-centrolobine using a segment-coupling Prins cyclisation (Scheme 81)\(^{120}\). A tin(IV) bromide-mediated intramolecular Prins cyclisation of \(\alpha\)-acetoxy ether 166 afforded the brominated species 167 which was subsequently converted to (-)-centrolobine in a further 4 steps.

\[
\begin{align*}
\text{TsO} & \quad \text{OAc} \\
\text{CHCl}_3 \quad & \quad -78^\circ C \\
\text{SnBr}_4 & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
\text{166} & \quad \text{167}
\end{align*}
\]

**Scheme 81** Synthesis of (-)-centrolobine using a Prins cyclisation to afford the tetrahydropyran core by Rychnovsky et al.\(^{120}\)
3.2.3 Stereoselective Construction of the Tetrahydropyran Ring via a Reductive Etherification

Recent research by Evans et al. has demonstrated that the stereoselective intramolecular reductive etherification of δ-trialkylsilyloxy-substituted ketones 168 with catalytic bismuth tribromide and triethylsilane affords cis-2,6-disubstituted tetrahydropyrans. This methodology was highlighted by its employment in the key tetrahydropyran-forming step of a total synthesis of (-)-centrolobine 163 (Scheme 82). Overall this total synthesis of (-)-centrolobine was accomplished in 5 steps with a 53% yield.

![Scheme 82](image)

Scheme 82  Stereoselective intramolecular etherification to afford (-)-centrolobine 163 by Evans et al.\textsuperscript{121}
3.2.4 Two Successive One-Pot Reactions to Access Tetrahydropyran Core

Cossy et al. have developed a route to (-)-centrolobine that involves a one-pot tandem cross-metathesis/hydrogenation to produce the lactone 171 (Scheme 83).\textsuperscript{122} From this lactone 171, a second successive one-pot reaction was performed with the addition of a Grignard reagent followed by addition at -78 °C of trimethylsilyl triflate and triethylsilane. By performing these successive one-pot reactions, purification of intermediates is avoided, making this a useful route for large scale preparations. This strategy provided a short (4 step) route to (-)-centrolobine 163 although the overall yield was low (7%).

\textbf{Scheme 83} Preparation of (-)-centrolobine using an \textit{in situ} cross-metathesis hydrogenation in the key ring-forming step by Cossy et al.\textsuperscript{122}
3.2.5 Route Involving a Modified Maitland-Japp Reaction

One of the most efficient approaches for the synthesis of (±)-centrolobine is provided by Clarke et al. with their use of a modified Maitland-Japp reaction in the key ring-forming reaction step (Scheme 84)\textsuperscript{123}. This one-pot, three-component reaction of the aldehyde 172, Chan’s diene 173 and anisaldehyde 174 (promoted by ytterbium(III) triflate) furnished a mixture of tetrahydropyran-4-ones 175 and 176 in excellent yield with an equilibrium ratio of 2:1. The yield of the desired isomer 175 was maximised by resubmission of 176 to the Lewis acidic reaction conditions which converted it with a 2:1 ratio of 175:176, thereby increasing the overall yield from 60% to 82%.

Scheme 84  Employment of a Maitland-Japp reaction in the ring-forming step of the (±)-centrolobine synthesis by Clarke et al.\textsuperscript{123}
3.2.6 Radical Cyclisation of a β-Alkoxyvinyl Ketone

Lee et al. have developed a stereoselective route to (-)-centrolobine which involves the radical cyclisation of a β-alkoxyvinyl ketone 178 in the presence of tris(trimethylsilyl)-silane and AIBN in benzene under reflux conditions to afford the tetrahydropyran 179 (Scheme 85).124

Scheme 85 Radical cyclisation to prepare tetrahydropyran fragment 179 by Lee et al.124

3.2.7 Diastereoselective Ring-Rearrangement Metathesis-Isomerisation Sequence

Ring-rearrangement metathesis has proven to be an important technique for the preparation of fused carbocycles, polycyclic ethers and various natural products. Stereo centres may be easily established in a ring and transferred to the side chain or vice versa. Blechert et al. have performed a one-pot ring-rearrangement metathesis-isomerisation reaction to access the tetrahydropyran fragment of (-)-centrolobine (Scheme 86).125 The metathesis precursor 180 was reacted with Grubbs II catalyst at 50 °C for 6 hours to afford the intermediate 181. The in situ reaction proceeded with isomerisation of the terminal double bond to the internal olefin which was achieved by...
the addition of sodium borohydride. Once the fragment 182 had been synthesised, two further steps were required to afford (-)-centrolobine 163 in moderate yield (50%).

\[
\text{180} \quad \xrightarrow[2 \times \text{Grubbs II 21 (5 mol\%)}]{\text{benzene-ethene, 50 °C, 8 h}} \quad \text{181}
\]

\[
\text{183} \quad \xrightarrow[1. \text{183, Hoveyda-Grubbs cat. 170 (10 mol\%)}; 2. \text{H}_2, \text{Pd/C (50% wt water)}]{\text{MeO}} \quad \text{182}
\]

Scheme 86 Diastereoselective ring-rearrangement metathesis to access key tetrahydropyran fragment 181 of (-)-centrolobine by Blechert et al.\textsuperscript{125}
3.2.8 Lewis Acid-Mediated Cyclisation of a 1,5-Diol to Prepare the Tetrahydropyran Core

Continuing research in the stereoselective synthesis of natural products from chiral pool materials, eg. L-(+)-tartaric acid, Prasad et al. have developed a stereoselective synthesis of (-)-centrolobine (Scheme 87). The key intermediate 1,5-diol 185 was prepared in 4 steps from the bis-amide 184, derived from L-tartaric acid. Reaction of the 1,5-diol 185 with iron(III) chloride produced a mixture of diastereoisomers 186 and 187 in a 7:1 ratio. After separation, reaction of 186 with lead(IV) acetate afforded the aldehyde 188 which led on to the formation of (-)-centrolobine 163.

Scheme 87 Synthesis of (-)-centrolobine using an iron(III) chloride-mediated cyclisation of a 1,5-diol by Prasad et al.126
3.3 Conclusion

The routes outlined provide an impressive array of pathways to (+)-centrolobine or (-)-centrolobine, showcasing much novel methodology in the generation of the 2,6-disubstituted tetrahydropyran moiety.

It occurred to us that the silyl-Prins reaction, which has previously demonstrated exclusive cis-diastereoselectivity, could also be applied to the synthesis of the key tetrahydropyran subunit in an overall total synthesis of (+)-centrolobine. Two potential routes, both employing the silyl-Prins reaction in the key cyclisation step are shown in Scheme 88.

**Route 1**

**Route 2**

**Scheme 88** Proposed silyl-Prins reactions for the preparation of the tetrahydropyran core of (+)-centrolobine
3.4 Kendomycin

3.4.1 Introduction

Kendomycin (193, Figure 17) is a structurally unique polyketide, first isolated in 1996 by Funahishi et al.\textsuperscript{127,128} and re-isolated for structural determination by Zeeck et al.\textsuperscript{129,130} in 2000, from the common soil bacteria \textit{Streptomyces violaceoruber}. It has demonstrated a range of interesting pharmacological properties such as impressive cytotoxicity against human breast, stomach, and liver carcinoma cell lines (GI\textsubscript{50} < 100 nM) with a potency comparable to that of clinically used drugs such as doxorubicin.\textsuperscript{130} Furthermore, kendomycin has displayed strong antibiotic activity against a range of bacteria including methicillin- and vancomycin-resistant \textit{Staphylococcus aureus}.\textsuperscript{130} In addition, the natural product is a potent antagonist of endothelin receptors and has exhibited anti-osteoporotic activity.\textsuperscript{131}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{kendomycin.png}
\caption{Structure of kendomycin 193 and an image of a slide culture of a \textit{Streptomyces sp.} grown on tap water agar.\textsuperscript{132}}
\end{figure}

In terms of its molecular architecture, kendomycin represents a novel \textit{ansa} system in which a densely substituted tetrahydropyran ring is directly attached to the quinone methide chromophore within a macrocyclic scaffold. The remarkable biological properties and unique chemical structure of kendomycin have rendered it an important synthetic target. In recent years there have been two total syntheses\textsuperscript{133,134} and several
chapter 3 damien gough

partial routes to kendomycin. These approaches will be outlined with the primary focus on the methods employed for the construction of the tetrahydropyran ring system.

3.5 Literature Methods for the Preparation of the Tetrahydropyran Core of Kendomycin

3.5.1 Route Involving a Lactonisation Step to Form the Tetrahydropyran Ring

Several methods for the preparation of kendomycin employ a lactonisation step to access the substituted tetrahydropyran portion of the molecule. Lee et al. constructed the THP fragment through a sequence that involved stereoselective aldolation, reduction and lactonisation (Scheme 89).

\[
\begin{align*}
\text{CHO} & \quad \rightarrow \quad \text{THP} \\
\text{194} & \quad \rightarrow \quad \text{195} \\
\text{195} & \quad \rightarrow \quad \text{196} \\
\text{196} & \quad \rightarrow \quad \text{THP} \\
\text{193} & \quad \rightarrow \quad \text{197}
\end{align*}
\]

**Scheme 89** Preparation of the tetrahydropyran core in kendomycin by Lee et al. \cite{Lee133}
Another lactonisation-based approach to an advanced kendomycin intermediate 200 is provided by Mulzer et al. (Scheme 90).\textsuperscript{135-139} This involved the stereoselective reduction of 198 to the β-hydroxy alcohol and the auxillary was cleaved with base. Subsequent acidification with 1 M hydrochloric acid gave the lactone 199.

Scheme 90  Preparation of kendomycin by Mulzer et al. using a lactonisation step\textsuperscript{135-139}

3.5.2 A [4+2]-Annulation in the Preparation of the Tetrahydropyran Ring

Panek has published the synthesis of a key fragment 204 of kendomycin and employs a chiral crotyl silane 202 in a Lewis acid promoted [4+2]-annulation to afford the functionalised dihydropyran 203 (Scheme 91).\textsuperscript{140} The dihydropyran 203 is obtained in good yield (85%) with excellent diastereoselectivity (dr >30:1) and four subsequent steps allow access to fragment 204 of kendomycin.

Scheme 91  Preparation of fragment 204 using a [4+2]-annulation by Panek et al.\textsuperscript{140}
3.5.3 A Petasis-Ferrier Union/Rearrangement Strategy

Smith et al. have developed a stereocontrolled total synthesis of kendomycin with a sequence consisting of 21 steps, starting from commercially available 2,4-dimethoxy-3-methylbenzaldehyde with an overall yield of 0.49%.\(^\text{134}\) In order to construct the polysubstituted tetrahydropyran ring, a Petasis-Ferrier union/rearrangement strategy\(^\text{144-153}\) was employed (Scheme 92). Initially a condensation of aldehyde 206 with β-hydroxy acid (+)-205 was performed using the Kurihara condensation protocol\(^\text{154}\), using \(i\)-PrOTMS and TMSOTf in order to effect in situ bis-silylation. This afforded the dioxanone 207 in good yield (77%) as a single stereoisomer. Next, a Petasis-Tebbe methylenation\(^\text{155}\) led to the formation of the unstable enol-acetal 208 which was immediately subjected to a Petasis-Ferrier rearrangement using diethylaluminium chloride to furnish the desired tetrahydropyran 209 (85%).

![Scheme 92 Petasis-Ferrier Union/rearrangement strategy by Smith et al.\(^\text{134}\)]
3.5.4 Route to Kendomycin Using a Prins Cyclisation

The Prins cyclisation has been employed by a number of research groups as a convergent and highly diastereoselective method to synthesise tetrahydropyranols.\textsuperscript{156-160} Rychnovsky used this approach in his preparation of a key fragment 213 of kendomycin (Scheme 93).\textsuperscript{141} Condensation of alcohol 210 with aldehyde 211 in the presence of boron trifluoride etherate and ethanol furnishes the desired tetrahydropyran 212 in moderate yield (50\%). A further two steps are required for the preparation of key kendomycin fragment 213.

\[ \text{210} + \text{211} \xrightarrow{\text{BF}_3\text{OEt}_2, \text{AcOH}} \text{212} \xrightarrow{\text{2 steps}} \text{213} \]

\textbf{Scheme 93} Preparation of a key kendomycin precursor 213 using a Prins cyclisation by Rychnovsky \textit{et al.}\textsuperscript{141}
3.5.5 Route to Kendomycin Using a Ag$_2$O-Mediated Oxidative Cyclisation

Uemura et al. have developed an approach to kendomycin using a Ag$_2$O-mediated oxidative cyclisation of the phenol 214 (Scheme 94). This reaction is believed to involve initial $o$-quinone methide formation followed by intramolecular attack of the secondary alcohol on the quinone methide, which occurs so that the bulky aromatic substituent is oriented as equatorial. A further seven steps are required to furnish the kendomycin fragment 216.

![Diagram of the reaction](image)

**Scheme 94** Preparation of a key fragment of kendomycin using a Ag$_2$O-mediated oxidative cyclisation

97
3.6 Conclusion

As this outline of recent research indicates, kendomycin presents a synthetically challenging target for total synthesis. The presence of the fully substituted C-aryl glycosidic core means an effective strategy for the synthesis of tetrahydropyrans needs to be employed. The chemical literature provides a range of options to achieve this objective including lactonisations, [4+2]-annulations and Prins reactions. The silyl-Prins reaction has the potential to provide a convenient and efficient route both to the required tetrahydropyran core of kendomycin and also various related analogues and this was the focus of our investigation.

3.7 Aims

The remainder of the work in this thesis will describe the application of the silyl-Prins reaction towards the total syntheses of the two natural products discussed in this chapter, (±)-centrolobine and kendomycin.
Chapter 4

Results and Discussion II: Application of the Silyl-Prins Reaction towards the Synthesis of Natural Products, (±)-Centrolobine and Kendomycin
Chapter 4 Damien Gough

4 Results and Discussion II: Application of the Silyl-Prins Reaction towards the Synthesis of Natural Products, (±)-Centrolobine and Kendomycin

4.1 Application of the Silyl-Prins Reaction to the Synthesis of (±)-Centrolobine

The silyl-Prins reaction has previously demonstrated its potential for application to the synthesis of natural products with the preparation of the civet constituent 66 by Dobbs et al. (Scheme 21). Given its tetrahydropyran core, (±)-centrolobine poses a slightly more challenging natural product target that could possibly be accessed via a silyl-Prins reaction. Retrosynthetic analysis was performed on (±)-centrolobine to determine the optimum pathway to this natural product and to decide upon the most appropriate reaction precursors for the key silyl-Prins cyclisation step (Scheme 95).
Our objective was to use the silyl-Prins reaction methodology to construct the cis-disubstituted dihydropyran adduct 191 which could then be hydrogenated to afford the tetrahydropyran core of (+)-centrolobine 163. The C-C and C-O disconnections between C(2) and C(3) and between C(2) and O(1) led to Z-4-trimethylsilyl-1-(4’-methoxyphenyl)but-3-en-1-ol 189 and 3-[4-(benzyloxy)phenyl]-1-propanal 190 which were the intended precursors for the silyl-Prins cyclisation step.

An alternative route to (+)-centrolobine 163 was also devised using a different retrosynthetic pathway but involving some of the same intermediates (Scheme 96).

![Scheme 96 Alternative retrosynthetic analysis of (+)-centrolobine – Route 2](image-url)
4.2 Route 1 - Preparation of Z-4-Trimethylsilyl-1-(4'-methoxyphenyl)but-3-en-1-ol

The development of an expedient route to Z-4-trimethylsilyl-1-(4-methoxyphenyl)but-3-en-1-ol 189 was integral to the overall synthesis of (±)-centrolobine. Two proposed pathways to this compound were postulated using procedures established by Dobbs et al. for simpler vinyl silanes58 (Scheme 97).

Scheme 97 Proposed routes to the silyl-Prins reaction precursor 189

4.2.1 Preparation of Vinylanisole Oxide Using an Epoxidation Strategy

The first step, the same in both pathways, was the epoxidation of commercially available vinylanisole. Two epoxidation procedures were investigated for their potential in this reaction.

An epoxidation procedure161 using meta-chloroperbenzoic acid (2 eq.), vinylanisole (1 eq.) and sodium hydrogen carbonate (4 eq.) in dry dichloromethane was first investigated (Scheme 98). The product mixture indicated the formation of the desired epoxide 218 but the presence of inseparable meta-chlorobenzoic acid 224 in the product mixture appeared to be coordinating to the oxygen atom of the epoxide causing a shift in certain peaks of the 1H NMR spectra. A number of purification strategies were
tried to remove the meta-chloroperbenzoic acid by-product, including repeated washings with sodium hydrogen carbonate but these were unable to isolate the epoxide 218.

\[ \text{MeO} \quad 217 \quad \text{mCPBA} \quad \text{NaHCO}_3, \text{CH}_2\text{Cl}_2 \quad 218 \quad \text{Cl} \quad \text{O} \quad \text{MeO} \quad 224 \]

**Scheme 98** Epoxidation of vinylanisole using mCPBA

In an effort to overcome the aforementioned issues, an alternative epoxidation procedure was investigated using commercially available Oxone® as the epoxidising agent (Scheme 99). Under biphasic water/dichloromethane conditions with excess acetone, a di-sodium hydrogen orthophosphate solution, tetra-n-butylammonium hydrogen sulfate (phase-transfer catalyst, 0.5 eq.) and vinylanisole (1 eq.), an Oxone® (4 eq.) solution in water was added dropwise at 0 °C over the period of 1 hour. The pH was monitored using universal indicator paper and maintained at pH 7-8 with the addition of 2 M potassium hydroxide solution.

\[ \text{MeO} \quad 217 \quad \text{Oxone}^\circ \quad \text{Acetone} \quad \text{NaHPO}_4 \quad n\text{-Bu}_4\text{N}^+\text{HSO}_4^- \quad \text{CH}_2\text{Cl}_2, \, 0 \, ^\circ\text{C} \quad 218 \quad 100\% \]

**Scheme 99** Epoxidation using Oxone®

This reaction works by the initial generation of dimethyldioxirane 226 from the nucleophilic attack of Oxone® (potassium monoperoxysulfate) on the carbonyl carbon of
acetone 225 with subsequent loss of potassium hydrogen sulphate (HSO$_4^-$) (Scheme 100). The oxygen is then transferred to the substrate and the acetone 225 regenerated. With the reformation of this acetone, it is then possible for more dimethyldioxirane 226 to be formed and the reaction can become catalytic. Owing to competitive peroxide decomposition, Oxone® was used in large excess (4 eq.) over the stoichiometric amount to produce sufficient dimethyldioxirane 226 to form the epoxide 218.

Pleasingly the target epoxide 218 was afforded in quantitative yield (100%) with no further purification required due to the facile removal by evaporation of most of the reaction by-products. The difference between the $^1$H NMR spectra peaks from those obtained from the reaction with mCPBA confirmed the effect the coordination of the meta-chlorobenzoic acid by-product was having in that previous case.
4.2.2 Methods for the Alkynylation of Vinylanisole Oxide

Having established an expedient route to the epoxide 218 using Oxone®, two potential pathways existed for the development of the synthetic route to (±)-centrolobine. The first pathway involved preparation of the alkyne 223 followed by silylation to generate 219 while the second pathway involved a one-step direct addition of trimethylsilylacetylene to prepare 219.

Despite their highly strained 3-membered ring structure, epoxides often require Brønstead or Lewis acid promotion and/or a powerful nucleophile to perform efficient alkynylation reactions.164-166 Issues regarding low yields and regioselectivity must also be addressed in certain cases. Whereas simple alkyl epoxides are usually attacked at the less hindered position, the regioselectivity of aryl epoxides relies on a balance between the steric and electronic effects at the benzylic carbon (Scheme 101). The regioselectivity also depends on a balance between the nucleophilicity of the acetylides and in the case of Lewis acid promoted reactions, the acidity of the metal promotor.167 When a mixture of isomeric products are obtained from these reactions they can be extremely difficult to separate. Therefore good regioselectivity is a very important factor in successful alkynylations of this type.

Scheme 101 Schematic of potential alkynylation products
Route A

The first route employed the use of commercially available lithium acetylide-ethylenediamine complex (1.4 eq.) in dry DMSO (Scheme 102). Only vinylanisole oxide 218 was recovered quantitatively. One possible explanation for this is that the organolithium species may be coordinating to the oxygen of the methoxy group and thus preventing the reaction from occurring. Repetition of this reaction in the future may find benefit in increasing the number of equivalents of lithium acetylide-ethylenediamine.

Scheme 102  Attempted alkynylation of 4-methoxystyrene oxide using LAED

An alternative route to compound 223, which did not involve 4-methoxystyrene oxide, was investigated with the use of a Grignard reagent as indicated in Scheme 102. This procedure aimed to first generate propargyl magnesium bromide from commercially available propargyl bromide (1 eq.) and subsequently react it with p-anisaldehyde (0.5 eq.) in dry diethyl ether to afford alkynic alcohol 223.

Scheme 103  Route to the alkynic alcohol 223 using a Grignard reagent
The most significant difficulties encountered with this reaction related to activation of the magnesium turnings. An iodine crystal was added to the reaction mixture in order to initiate this process. Some magnesium turnings may have dissolved at this stage and the subsequent steps in the reaction sequence were performed. Analysis of the reaction mixture indicated that only recovered starting material was present. There was also some unreacted magnesium turnings present in the flask.

Route B

At this stage, it was decided to investigate direct routes from the epoxide 218 to the silylated product 219 in order to circumvent the issues encountered during Route A. One important advantage of these reactions is that they have the potential to shorten the overall pathway to (±)-centrolobine by one step as a separate silylation stage would no longer be required.

Two different sets of reaction conditions were investigated for their ability to catalyse an alkynylation using commercially available trimethylsilylacetylene 133 (Scheme 104).

\[
\text{Conditions A or B}
\]

\[
\text{Conditions A. 1.2 eq. TMS-133, 1 eq. } n\text{-BuLi, 1.2 eq. BF}_3 \text{GEt}_2 \text{, THF}
\]

\[
\text{Conditions B. 2 eq. TMS-133, 2.2 eq. } n\text{-BuLi, 2.2 eq. Et}_2\text{AlCl, Tol}
\]

Scheme 104  Alkynylation to prepare silylated alkyne 219

In the first case (Conditions A), trimethylsilylacetylene (1.2 eq.) was deprotonated by addition of \( n\text{-butyllithium} \) (1 eq.) at -78 °C. After stirring at this temperature for 30 minutes, a solution of 4-methoxystyrene oxide 218 (1 eq.) in dry
THF was added, followed immediately by boron trifluoride etherate (1.2 eq.). The reaction was quenched by saturated ammonium chloride solution and extracted into diethyl ether. The crude product consisted of a mixture including 4-methoxystyrene oxide 218 and some unidentifiable material but which was not the desired product 219.

A test reaction was performed to determine the cause of failure of this particular ring opening reaction (Scheme 105). Commercially available styrene oxide 230 (1 eq.) was employed as the reaction substrate with identical reaction conditions to those previously used. The crude product contained an inseparable mixture (53:47) of the expected α- and β-alkynylated products.

\[
\text{Scheme 105 Model study of alkynylation reaction}
\]

Alternative reaction conditions for the preparation of silylated alkyne 219 involved the employment of a diethylaluminium chloride promoter.\(^{172}\) It was postulated that vinyl trimethylsilane could be deprotonated by \(n\)-butyllithium and then reacted with diethylaluminium chloride in a transmetallation process to give a dialkylalane reagent which would subsequently attack the epoxide 218 in a type of reaction with precedent for high regioselectivity.\(^{172}\) Employing Conditions B, trimethylsilylacetylene (2 eq.) was deprotonated by the addition of \(n\)-butyllithium (2.5 M in hexane, 2 eq.) in toluene at -30 °C (Scheme 104). After stirring at this temperature for 30 minutes, diethylaluminium chloride (1 M soln. in hexane, 2.2 eq.) was added while being allowed to warm to 0 °C over 1 hour. After recooling the reaction mixture to -30 °C, a solution of \(p\)-methoxystyrene oxide (1 eq.) in toluene was added. The reaction mixture was stirred for 20 hours and purification was performed by column chromatography. Gratifyingly the
desired compound 219 was isolated although the yield was poor (24%). The regioselectivity was not as high as expected and the formation of the α-alkynylated product (17%) was the chief cause of this low yield as clean separation by column chromatography was difficult due to close elution times. There was also material lost containing both products as only pure separation yields are given.

Recent work by Crotti et al. has shown the alkynylation of 4-methoxystyrene oxide using lithium acetylide in the presence of LiClO₄ affords predominantly β-alkynylated products (Scheme 106).\textsuperscript{172}

\begin{equation}
\text{Ph} \quad \text{MeO} \quad + \quad \text{Ph} \quad \text{Li} \quad \text{LiClO}_4 \quad \xrightarrow{\text{THF, 0 °C, 35%}} \quad \text{Ph} \quad \text{MeO} \quad \text{MeO} \quad + \quad \text{Ph} \quad \text{Ph}
\end{equation}

\begin{align*}
\text{Ratio} & \quad 75 & \quad 25
\end{align*}

\textbf{Scheme 106} Crotti employs lithium phenyl acetylide in presence of LiClO₄\textsuperscript{172}

The improvement in β-regioselectivity is due to chelating ability of Li\textsuperscript{+} which makes the epoxide react at the less hindered position. The nucleophilicity of the lithium acetylide is still present and thus affords the β-alkynylated products and the resonance effect does not contribute as much to the selectivity. It should be noted that although the β-alkynylated product is the major one, a potentially difficult separation must be performed to isolate this compound from the minor product.
4.2.3 Stereoselective Reduction of (±)-4-Trimethylsilyl-1-(4′-methoxy-phenyl)-but-3-yn-1-ol

The next step in this synthesis was the stereoselective reduction of the triple bond in 219 to the cis stereoisomer 189 (Scheme 107). This was performed using the standard DIBAL-H procedure developed by Dobbs et al. for reductions of silylated homoallylic alkynes. Diisobutylaluminium hydride (3 eq.) was added to a solution of the alkyne 219 (1 eq.) in dry diethyl ether at 0 °C. The reaction mixture was then heated to reflux temperature while stirring for 24 hours, followed by treatment with 2 M sulfuric acid at 0 °C. The alkene 189 was afforded in moderate yield (54%) but without the need for purification.

![Scheme 107 Stereoselective DIBAL-H reduction of alkyne 219](image)

This reduction step completed the synthesis of the silylated homoallylic alcohol precursor 189 required to perform the intended silyl-Prins reaction. While certain stages in this route to this precursor would benefit from optimisation to improve efficiency, a satisfactory quantity of this product could be obtained for evaluation in preliminary silyl-Prins cyclisations. The next step was to generate a sufficient quantity of the aldehyde precursor 190 to act as the complimentary reaction precursor in the silyl-Prins Reaction.

4.2.4 Preparation of 3-[4′-(Benzyloxy)phenyl]-1-propanal

3-[4′-(Benzyloxy)phenyl]-1-propanal 190 was prepared in two steps from commercially available 3-(4′-hydroxyphenyl)-1-propanol 221 using the literature
protocol for the preparation of this compound. The first step was a protection of the phenol hydroxyl group of 221 using benzyl bromide. This was required to prevent the presence of two hydroxyl groups within the silyl-Prins reaction which has the potential to hinder the reaction. Protection afforded 3-[4-(benzyloxy)phenyl]-1-propanol 220 in quantitative yield (100%). A standard Swern oxidation was performed next to afford the aldehyde 190 in good yield (78%). The aldehyde 190 is also a key intermediate in the second potential route to (±)-centrolobine (Scheme 108).

![Scheme 108 Preparation of the aldehyde precursor 190](image)

Having achieved a route to the required precursors it was now possible to investigate the silyl-Prins reaction as a route to the dihydropyran species 191 which is integral to the overall synthesis of (±)-centrolobine.
4.3 Preliminary Silyl-Prins Reactions to Generate Dihydropyran Fragment 191

A series of investigative reactions were then conducted to determine the optimum conditions for the silyl-Prins reaction required to prepare key (±)-centrolobine fragment 191. Variation of the Lewis acid catalyst has been previously proven to markedly affect the results of certain reactions, thus indium(III) chloride and trimethylsilyl triflate were investigated in these silyl-Prins reactions. Changing the equivalents of certain reagents could also alter the reaction outcome and this too was investigated (Table 3).

Table 3  Silyl-Prins reactions to prepare dihydropyran fragment 191

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde precursor 190</th>
<th>Lewis acid promoter</th>
<th>Temperature</th>
<th>%Yield 191</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 eq.</td>
<td>1 eq. InCl₃</td>
<td>r.t (91 h)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1 eq.</td>
<td>4 eq. InCl₃</td>
<td>r.t. (48 h), then reflux (60 h)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2 eq.</td>
<td>2 eq. InCl₃</td>
<td>r.t. (40 h)</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>1 eq.</td>
<td>2 eq. TMS-OTf</td>
<td>r.t. (19 h), then reflux (17 h)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>2 eq.</td>
<td>2 eq. TMS-OTf</td>
<td>r.t. (24 h)</td>
<td>-</td>
</tr>
</tbody>
</table>
In the cyclisation reactions promoted by indium(III) chloride the main product recovered was the aldehyde starting reagent 190. There may also be some dehydroxylated starting material 235 as indicated by GCMS analysis (M⁺ + H, 233) (Figure 18).

![191 and 235](image)

**Figure 18** Products obtained from indium(III) chloride-mediated reaction

One possible explanation for the presence of 235 in the product mixture is that the electron-donating capacity of the methoxy group and the position of the hydroxyl group in a benzylic position combine to cause this group to be lost (Scheme 109). Obviously loss of the hydroxyl moiety will prevent the formation of the oxocarbenium ion and the silyl-Prins cyclisation will not occur.

![Scheme 109](image)

**Scheme 109** Possible mechanism for loss of hydroxyl group

This reaction was repeated using two equivalents of the aldehyde precursor 190 as it was postulated that the first equivalent of Lewis acid promoter may be coordinating to the protected hydroxyl group instead of the carbonyl oxygen but this also failed to yield
any of the desired dihydropyran 191 (Entry No. 3). Increased quantities of indium(III) chloride were also used as it was again postulated that the methoxy group of the alcohol precursor 189 may be preferentially coordinating to the promoter metal centre preventing it from activating the aldehyde carbonyl group (Entry No.2). The presence of these extra equivalents of indium(III) chloride had a negligible effect on the reaction outcome.

In the cyclisation reactions using trimethylsilyl triflate as the Lewis acid promoter, the main products appeared to be starting reagents as indicated by $^1$H NMR analysis (Entry No. 4 and No. 5). Variation of the amount of aldehyde precursor from 1 eq. to 2 eq. and heating of the reaction mixture to reflux temperature was performed but no conclusive evidence of the desired dihydropyran 191 was obtained (Entry No. 5).

In order to understand the inability of this silyl-Prins reaction to produce the desired dihydropyran 191, model studies were performed to evaluate the reactivity of the reaction precursors. First, the vinylsilane precursor 189 was reacted with commercially available aldehyde $n$-hexanal 111. Standard silyl-Prins reaction conditions (Scheme 24) were employed and all reagents were used in a 1:1:1 ratio of equivalents. Analysis of the $^1$H NMR spectroscopic data indicated only the presence of precursor aldehyde 111 and unidentifiable compounds (Scheme 110).

![Scheme 110](image)

**Scheme 110** Investigation of the reactivity of reaction precursor 189 using a model silyl-Prins reaction

Dobbs *et al.* have previously demonstrated that aryl-substituted vinylsilane precursors 237 have been successfully employed in the silyl-Prins reaction (Scheme
This further supports the evidence that the methoxy moiety on the aromatic ring is having a detrimental effect on the silyl-Prins reaction.

\[
\begin{align*}
\text{TMS} & \quad + \quad \text{H} & \quad \text{InCl}_3 & \quad \text{CH}_2\text{Cl}_2 \\
\text{111} & & & & \text{238}
\end{align*}
\]

Scheme 111 Related aryl-substituted homoallylic alcohol in a silyl-Prins reaction

Secondly, in order to test the reactivity of the aldehyde, a model study was performed on the aldehyde precursor 190 to determine if there were problems relating to its employment in a Prins-type reaction. Mechanistically this indium(III) chloride-mediated Prins reaction proceeds through a β-stabilised carbocation as shown in Scheme 112. Commercially available 3-buten-1-ol 71 was selected as the alcohol precursor and reacted with the aldehyde 190 in an indium (III) chloride-mediated Prins cyclisation. The reaction was performed at room temperature with a 1:1:1 ratio of reactants in dry dichloromethane.

\[
\begin{align*}
\text{190} & \quad + \quad \text{InCl}_3 & \quad \text{CH}_2\text{Cl}_2 \\
\text{71} & & \text{239}
\end{align*}
\]

Scheme 112 Model study of aldehyde precursor 190
This cyclisation was successful in preparing the desired cyclised product (31%) and thus indicated that the aldehyde precursor 190 was amenable to Prins methodology and could be employed in the preparation of (±)-centrolobine. The result provided further evidence that the difficulties in the attempted silyl-Prins reactions were due to the vinylsilane precursor 189.

Repetition of this reaction using trimethylsilyl triflate as the Lewis acid promoter at -78 °C afforded only 3-buten-1-ol (34%) and unidentifiable compounds (66%) according to the interpreted $^1$H NMR spectroscopic data. This suggests that the milder Lewis acid indium(III) chloride is preferable as the promoter in these Prins-type reactions to generate (±)-centrolobine.

### 4.4 Route 2 – An Alternative Route to (±)-Centrolobine

Using the retrosynthetic pathway described in Scheme 2, an alternative route to (±)-centrolobine was developed (Scheme 113). The aldehyde portion 174 was found to be commercially available so the primary task is to develop an expedient route to the homoallylic precursor 192.

![Scheme 113 Route 2 – Postulated alternative approach to (±)-centrolobine](image)
4.4.1 Future Work - Route to Z-6-Trimethylsilyl-1-[4'-benzyloxy]-hex-5-en-3-ol

A proposed route (Scheme 114) to the alcohol precursor 192 involves the preparation of the aldehyde 190 which was previously prepared for the route 1 pathway as shown in Scheme 108. It is postulated that a Barbier-type reaction\textsuperscript{174} could be employed to generate the alkynic alcohol 240 which could then be silylated and stereoselectively reduced to afford the desired precursor 192. Research is ongoing within the group to develop this methodology towards an expedient route to (±)-centrolobine.

\begin{scheme}
\begin{align*}
\text{Br} & \quad \text{+} \quad \text{Zn. ultrasound} \quad \text{TMSCl} \quad \text{n-BuLi} \\
222 & \quad 190 & \quad 240 \\
\text{TMS} & \quad \text{DIBAL-H} \\
192 & \quad 241 \\
\end{align*}
\end{scheme}

\textbf{Scheme 114} Postulated route to homoallylic alcohol precursor 192
4.5 Towards the Total Synthesis of Kendomycin Using the Silyl-Prins Reaction

A programme towards the synthesis of a more complex natural product target to span several research projects was initiated. Kendomycin 193 presented an interesting target due to its molecular architecture and outstanding bioactive properties.\textsuperscript{129-131}

4.5.1 Retrosynthetic Approach

Retrosynthetic analysis was performed on kendomycin 193 to determine an expedient route to the synthesis of the key south-west fragment 244 of the molecule with the incorporation of the silyl-Prins reaction in the dihydropyran-forming step (Scheme 115).

Scheme 115 Outline of the retrosynthetic analysis of kendomycin 193
The aim of this approach was to develop the optimum route to the south-west portion of kendomycin utilising the stereocontrolled formation of the dihydropyran ring as a key step in this synthesis. Ring-closing metathesis could then be employed to complete the macrocyclic ring of the natural product 193. Two routes were investigated to examine their viability as potential pathways to the desired south-west fragment 244.

4.6 Retrosynthetic Approach - Route 1

The first pathway, derived from retrosynthetic analysis of the natural product 193, aimed to generate the reaction precursors 245 and 246 and subsequently employ them in a silyl-Prins reaction to afford the dihydropyran product 244 (Scheme 116).

Scheme 116 Proposed route to kendomycin fragment 244 using the silyl-Prins reaction
4.6.1 Preparation of the Aldehyde Precursor 246 - Approach 1a

Our attention first turned to the synthesis of the aldehyde portion 246 of the silyl-Prins reaction precursors and retrosynthetic analysis was performed which suggested that the desired aldehyde 246 could be obtained in 4 steps from commercially available 2.4-dimethoxy-3-methylbenzaldehyde (Scheme 117).

![Scheme 117 Retrosynthetic analysis of aldehyde precursor 246](image)

The proposed route (Scheme 118) involved an initial Baeyer-Villiger oxidation followed by base-catalysed hydrolysis could be used to generate the phenol 250. A Duff reaction could then be employed to produce the aldehyde moiety 251. Methylation of the phenol hydroxyl group followed by bromination could be employed to afford the desired precursor 246.
Thus 2,4-dimethoxy-3-methylphenol 250 was prepared from commercially available 2,4-dimethoxy-3-methylbenzaldehyde 249 according to literature procedure by Baeyer-Villiger oxidation followed by base-catalysed hydrolysis (Scheme 119). The phenol 250 was obtained in good yield (81%).
Formylation was then performed using Duff methodology with hexamethylenetetramine (HMTA) (6 eq.) added to a boiling solution of 2,4-dimethoxy-3-methylphenol 250 (1 eq.) in acetic acid (Scheme 120).\textsuperscript{176} After basic work-up and purification by column chromatography, 2-hydroxy-3,5-dimethoxy-4-methylbenzaldehyde 251 was afforded as a yellow solid (20%). The low yield is mainly due to difficulties relating to purification when the product had a propensity to disperse into the chromatographic elution solvent with a pre-column chromatography crude yield of 60% obtained.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {250};
  \node (b) at (2,0) {251};
  \draw [->] (a) -- (b) node[midway,above] {HMTA \text{CH}_3\text{CO}_2\text{H}, reflux};
\end{tikzpicture}
\end{center}

\textbf{Scheme 120} Preparation of 251 using Duff methodology\textsuperscript{176}

An alternative route to the aldehyde 251 was attempted using Fries methodology (Scheme 121).\textsuperscript{177, 178} The first step was to prepare formic acid 2,4-dimethoxy-3-methylphenyl ester 253 from commercially available 2,4-dimethoxy-3-methylbenzaldehyde 249 using \textit{meta}-chloroperbenzoic acid in a Baeyer-Villiger reaction. This was achieved in excellent yield (88%). A Fries reaction was then attempted using boron(III) chloride (1 M in dichloromethane) in dry dichloroethane which afforded only unidentifiable compounds.
Scheme 121  Attempted alternative route to aldehyde 251 using Fries methodology

Due to the lack of success of the Fries procedure, we returned to preparation of aldehyde 246 using Duff methodology (Scheme 119). The next step, was methylation of the hydroxyl group on the aromatic ring of aldehyde 246 (Scheme 122).\textsuperscript{175} This was achieved according to literature protocol using a basic solution of potassium hydroxide to deprotonate the hydroxyl group followed by reaction with an excess of methyl iodide (31 eq.). This afforded the trimethylated product 252 with moderate yield (60%).

Scheme 122  Methylation to prepare 252

The final step in the preparation of this reaction precursor involved the bromination of 252 using literature methods for general bromination (Scheme 123).\textsuperscript{134} A solution of 2,3,5-trimethoxy-4-methylbenzaldehyde 252 (1 eq.) in dichloromethane was treated with anhydrous potassium carbonate (\textit{ca.} 2 eq.) and bromine (2.2 eq.) at -10 °C. After warming to 0 °C, the reaction was stirred at this temperature for 2 hours followed by another 19 hours at room temperature. The product was purified by flash column
chromatography (petrol:diethyl ether 9:1) but only a small quantity of the desired compound 246 was shown to be present according to GCMS spectrometric techniques. The main compound was 2-bromo-6-hydroxy-3,5-dimethoxy-4-methyl-benzaldehyde 254 which formed because cleavage of one of the O-CH₃ bonds in one of the methoxy groups occurred. This can be explained by the duration of the reaction being too long and the temperature being higher than required. GCMS data of the reaction mixture after two hours, during which time the temperature was maintained at 0 °C, revealed 1/3 of the starting reagent remained and 2/3 had been converted into the desired product 246. It was only after allowing the reaction to warm to room temperature and continuing for a further 19 hours that compound 254 was indicated in the GCMS data.

Scheme 123  Bromination reaction to prepare precursor 246

Within the chemical literature, there is much precedent for the cleavage of methoxy groups using brominated species.¹⁷⁹-¹⁸¹ One example is provided by Rolla et al. who employed hydrogen bromide in the presence of phase transfer catalyst to cleave aryl alkyl ethers (Scheme 124).¹⁸² Future brominations using this methodology should ensure that the reaction temperature is maintained at 0 °C until the reaction has been completed.
Despite the failure to prepare the desired precursor, a test Prins reaction was performed using 2-bromo-6-hydroxy-3,5-dimethoxy-4-methylbenzaldehyde and the commercially available alcohol 3-buten-1-ol under standard silyl-Prins conditions (Scheme 125). This successfully afforded the cyclised product (18%) as a mixture of two diastereoisomers which were separated and characterised by comparison with known spectral data of related compounds. Recovered 3-buten-1-ol (60%) and 2-bromo-6-hydroxy-3,5-dimethoxy-4-methylbenzaldehyde (20%) accounted for the remainder of the crude material. There is still much scope for optimisation of this reaction.

The applicability of the aldehyde 254 to Prins reaction methodology was encouraging for future work in this area. Due to the low yields in certain steps, particularly the Duff reaction step, of the aldehyde 246 synthesis it was decided to investigate an alternative approach.
4.6.2 Preparation of the Aldehyde Precursor 246 - Approach 1b

An alternative route to this precursor 246 was investigated using a recently developed literature protocol\cite{cite} which was hoped would provide an improved route to compound 246. This involved a regioselective reductive alkylation step. The advantages of this route would include the avoidance of the problematic formylation step.

A second retrosynthetic analysis of the aldehyde precursor 246 was performed based upon an initial reductive alkylation of 259 to form aldehyde 261 followed by bromination and hydroxylation (Scheme 126).

![Scheme 126 Retrosynthetic analysis of precursor 246]

It was envisaged that by using a commercially available aldehyde 259 the low yielding formylation step could be avoided. The first two steps are part of a regioselective reductive alkylation developed by Azzena et al. (Scheme 127).\cite{cite}
Acetalisation of the commercially available aldehyde 259 was attempted using triethylorthoformate with a variety of equivalents and using a series of different reaction conditions found in the literature (Scheme 128)\textsuperscript{184-186}.

In the reactions of aldehyde 259 (1 eq.) with triethyl orthoformate (3.8 eq.) and ammonium chloride (0.06 eq.) in methanol (conditions A),\textsuperscript{184} only starting reagents were obtained from the product mixture. The presence of water in the methanol may have been detrimental to the success of this reaction. While this particular reaction was not repeated, it was ensured that similar reactions used only anhydrous methanol.

With reaction conditions B, \textit{p}-toluenesulfonic acid monohydrate (0.025 eq.) was employed as the acid catalyst in place of ammonium chloride and anhydrous methanol was employed.\textsuperscript{185} The desired product 260 was formed in low yield (35%). Despite the
low yield this result was encouraging and in addition to the new catalyst, this suggests the “dryness” of the methanol may also be having some impact on this reaction.

Investigation of camphorsulfonic acid (3.92 eq.) as acid catalyst (Conditions C) with triethyl orthoformate (6 eq.) in a mixed solvent system (MeOH/dichloromethane) was performed. These conditions afforded 3,4,5-trimethoxybenzaldehyde dimethylacetal in quantitative yield after recrystallisation from dichloromethane. The procedure became the preferred choice for preparation of the acetal 260. Conversion of the acetal 260 to the aldehyde 261 was performed according to the literature protocol using a dissolving metal reduction followed by methylation (Scheme 129).

![Scheme 129](image)

**Scheme 129** Preparation of aldehyde 261 by dissolving metal reduction

Addition of the acetal 260 (1 eq.) to a solution of the freshly cut sodium (3.06 eq.) in THF was followed by stirring for 24 hours. After this time the methyl iodide (1.47 eq.) was added and the reaction mixture was stirred for a further 48 hours at room temperature. The desired aldehyde 261 was afforded in low yield (16%). Possible explanations for this include the failure of the sodium to fully react in the reaction mixture. A significant quantity of acetal 260 was also recovered (60%) from the crude mixture.

In conclusion, the issues regarding optimisation of these reactions to generate sufficient quantities of reagent for a successful total synthesis meant that an alternative approach needed to be investigated. The successful Prins cyclisation using commercially available 3-buten-1-ol and aldehyde 254 was pleasing and demonstrated the potential of
this methodology once expedient routes to the precursors can be developed. At this stage, investigation of an alternative route to the kendomycin fragment 263 was initiated.

### 4.7 Retrosynthetic Approach - Route 2

A route to the kendomycin fragment 263 was investigated in order to develop a simpler, more efficient pathway to appropriate silyl-Prins reaction precursors to build the tetrahydropyran ring (Scheme 130).

![Scheme 130 Preparation of fragment 264 using the silyl-Prins reaction](image)

**Scheme 130** Preparation of fragment 264 using the silyl-Prins reaction

#### 4.7.1 Preparation of the Aldehyde Cyclisation Precursor 247

The aldehyde precursor 247 was prepared in two steps from commercially available (-)-β-citronellene 265 using a literature procedure. The first step was an epoxidation involving mCPBA which reacts preferentially at the more electron rich olefin group due to the inductive effect of the two methyl groups (Scheme 131). This reaction afforded the epoxide 266 in good crude yields (95-100%).
The crude epoxide 266 (1 eq.) was subsequently reacted with periodic acid (1.2 eq.) to afford the aldehyde 247 in moderate yield (53%) (Scheme 132). The moderate yield can be explained by the high volatility of this compound (79-81 °C at 25 Torr).

Scheme 132  Cleavage reaction using periodic acid to afford silyl-Prins precursor 247

4.7.2  Model Studies of Potential Precursors

With the aldehyde precursor 247 prepared, initial model studies to test the viability of this compound to the silyl-Prins methodology were performed. A substituted homoallylic alcohol 67 was selected as the alcohol substrate for the test silyl-Prins reaction shown in Scheme 132. The substrate 67 was prepared from 4-pentyn-2-ol 267 in
two steps using the method developed by Dobbs et al. to prepare these compounds and the observed yield was comparable with literature values.\textsuperscript{34}

\[
\begin{align*}
\text{H} & \rightarrow \text{H} \\
\text{OH} & \rightarrow \text{OH} \\
1.2 \text{ eq. } n-\text{BuLi, THF, } -78 \degree \text{C} & \rightarrow \\
2.2 \text{ eq. } \text{Me}_3\text{SiCl, } -78 \degree \text{C to } 20 \degree \text{C} & \rightarrow \\
3.0 \text{ M } \text{HCl} & \rightarrow \\
\rightarrow & \rightarrow \\
\rightarrow & \rightarrow \\
267 & \rightarrow 268 \\
\rightarrow & \rightarrow \\
\text{TMS} & \rightarrow \text{TMS} \\
\end{align*}
\]

\textbf{Scheme 133} Preparation of the methyl-substituted reaction precursor 67

A silyl-Prins reaction was then performed by reacting the methyl-substituted alcohol 67 with the aldehyde 247 in dry dichloromethane at room temperature in an indium(III) chloride-mediated reaction to afford a dihydropyran 269 similar to the desired kondenmycin fragment 264 (Scheme 133).

\[
\begin{align*}
\text{TMS} & \rightarrow \text{TMS} \\
\text{Me} & \rightarrow \text{Me} \\
\text{OH} & \rightarrow \text{OH} \\
+ & + \\
\rightarrow & \rightarrow \\
\rightarrow & \rightarrow \\
67 & \rightarrow 247 \\
\rightarrow & \rightarrow \\
\rightarrow & \rightarrow \\
\text{InCl}_3 & \rightarrow \\
\text{CH}_2\text{Cl}_2 & \rightarrow \\
\rightarrow & \rightarrow \\
\rightarrow & \rightarrow \\
\rightarrow & \rightarrow \\
20\% & \rightarrow \rightarrow \\
\rightarrow & \rightarrow \\
\end{align*}
\]

\textbf{Scheme 134} Model silyl-Prins study with aldehyde precursor 247

Gratifyingly the silyl-Prins cyclisation afforded the desired dihydropyran 269 and despite the unoptimised low yield (20\%), the aldehyde 247 had demonstrated its applicability to this methodology. The presence of only the cis-diastereoisomer was also encouraging for this reaction. There may also be a proportion of desilylated starting reagent alcohol in the product mixture as indicated by certain peaks in the \textsuperscript{1}H NMR data.

The next model study investigated whether the silyl-Prins reaction would be feasible for the preparation of 2,3,6-trisubstituted 5,6-dihydro-2H-pyran derivatives. A disubstituted silylated homoallylic alcohol 270 was first prepared according to literature
methods from commercially available 4-pentyn-2-ol 267. 5-Trimethylsilylpent-4-yn-2-ol 268 (1 eq.) was reduced stereoselectively with DIBAL-H (3 eq.) and after heating to reflux temperature for 24 hours, methyllithium (3 eq.) and methyl iodide (5 eq.) were added rather than quenching with dilute sulfuric acid as before (Scheme 135). After allowing the reaction to continue for a further 48 hours, the mixture was quenched with a dilute hydrochloric acid/ice mixture and filtered through Celite. This afforded (±)-Z-2-trimethylsilylhex-2-en-5-ol 270 in low yield (15%). There was also some unmethylated alkene product present in the reaction mixture.

Scheme 135 Preparation of disubstituted silyl-Prins precursor 270

A test silyl-Prins cyclisation was performed using commercially available n-butanal 271 as the aldehyde precursor to determine whether disubstituted precursors such as 270 are viable precursors in the silyl-Prins reaction (Scheme 136).

Scheme 136 Model silyl-Prins study of disubstituted precursor 270 with n-butyraldehyde 271
The desired dihydropyran 272 was obtained in low yield (11%). Despite the low yield, this result was encouraging but clearly optimisation would be necessary for some of these reactions.

A further model silyl-Prins reaction was performed to examine the potential of the disubstituted precursor 270 with the aldehyde 247 intended for use in the natural product synthesis (Scheme 137).

Pleasingly the dihydropyran product 273 was isolated (17%) and although the low yield leaves scope for improvement, the viability of the silyl-Prins reaction as a route to 2,3,6-trisubstituted 5,6-dihydro-2H-pyran derivatives is confirmed by this reaction. The incorporation of an alkene-terminated alkyl chain and the formation of the trisubstituted dihydropyran using silyl-Prins methodology were key objectives achieved with these model studies. While certain aforementioned reactions afforded yields that were unacceptably low for a long total synthesis, the main aim at this stage was to establish proof of concept with optimisation of these reactions to be performed later.
4.7.3 Preparation of the Disubstituted Silylated Homoallylic Precursor 274

Having demonstrated the potential of the silyl-Prins reaction to synthesise compounds with related components of the south-west fragment of kendomycin (Schemes 136-137), the next step was to prepare the appropriate silylated homoallylic precursor 274. This first route lacked the methoxy and methyl substituents on the aromatic ring and was intended as a starting point for further work in this area. As such, the route was not optimised as the fully substituted substrates were not being prepared. The bromo-substituent was intended as a handle for the coupling of the appropriate alkene-terminated alkyl chain necessary for preparation of the ring-closing metathesis generation of the macrocycle. Retrosynthetic analysis was performed in order to develop a viable route to the silyl-Prins precursor 274 (Scheme 138).

\[
\begin{align*}
274 & \quad \text{TMS} & \quad \text{TMS} & \quad \text{TMS} \\
\quad & \quad \text{OH} & \quad \text{OH} & \quad \text{OH} \\
\quad & \quad \text{Br} & \quad \text{Br} & \quad \text{Br} \\
\end{align*}
\]

Scheme 138 Retrosynthetic analysis of the alcohol precursor 274

Two epoxidation procedures were investigated to determine the optimum method for the preparation of 2-bromostyrene oxide 276 from commercially available 2-bromostyrene 275. Epoxidation using mCPBA was first investigated with sodium
hydrogen carbonate used to quench any by-product meta-chlorobenzoic acid (Scheme 139).\textsuperscript{161}

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{mCPBA, NaHCO}_3}\quad \text{Br} \\
\text{275} & \quad \xrightarrow{\text{CH}_2\text{Cl}_2}\quad \text{276} \\
\end{align*}
\]

Scheme 139 Epoxidation of 2-bromostyrene 275 using mCPBA

This procedure afforded the desired epoxide 276 in low yield (24%) with much product possibly lost during purification by column chromatography.

Epoxidation using Oxone\textsuperscript{®} as the epoxidising agent was investigated with the same procedure as that previously described (Scheme 140).\textsuperscript{162} A much improved crude yield (100%) of the epoxide 276 was obtained. The volatility of the by-products in this Oxone\textsuperscript{®} reaction meant that concentration \textit{in vacuo} afforded the product in sufficient purity to use in the next step without further purification.

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{\text{Oxone\textsuperscript{®}}}\quad \text{Br} \\
\text{275} & \quad \xrightarrow{\text{Acetone, CH}_2\text{Cl}_2}\quad \text{276} \\
\end{align*}
\]

Scheme 140 Epoxidation of 2-bromostyrene 275 using Oxone\textsuperscript{®}

Having achieved an excellent route to the epoxide 276, the next step was the introduction of an acetylene moiety by nucleophilic ring-opening. Lithium acetylide-ethylenediamine was investigated as a reagent to ring-open the epoxide 276 (Scheme 141).\textsuperscript{168} Attack on the less hindered position of the epoxide by the organometallic was
anticipated due to the strong nucleophilic presence of the lithium acetylide-ethylenediamine and for the reasons previously described.

\[ \text{Br} \quad \text{Li} \quad \text{==.en, DMSO} \quad \text{H}_2\text{O} \]

\[ \text{276} \quad \text{79%} \quad \text{277} \]

Scheme 141  Ring-opening of epoxide 276 using lithium acetylide-ethylenediamine

Pleasingly the alkynic alcohol 277 was afforded in good yield (79%) with no further purification necessary. There was no indication that any α-alkynylated product had formed.

The next step involved deprotonation of the alkyne 277 and subsequent addition of a trimethylsilyl moiety (Scheme 142). This was performed according to literature methods\(^{58}\) with n-butyllithium (2.5 M in hexane, 2 eq.) added to a solution of the acetylenic alcohol 277 in dry THF at -78 °C. After stirring for 1 hour, trimethylsilyl chloride (2 eq.) was added and the solution was allowed to warm slowly to room temperature. The reaction was quenched by the addition of dilute hydrochloric acid. Purification was performed by column chromatography to afford the desired compound 278 (38%). One possibility is that lithium-bromide exchange may be occurring which could account for this relatively low yield.
The monosubstituted homoallylic alcohol 279, while not the intended precursor for the kendomycin fragment, was considered a useful compound to act as a testing ground for this methodology. As such, both the monosubstituted 279 and disubstituted 274 derivatives were prepared using a stereoselective reduction (Figure 19).

In the preparation of the monosubstituted precursor 279, a standard stereoselective DIBAL-H reduction of the type previously used for simpler alcohols was performed (Scheme 143). Reduction using DIBAL-H (3 eq.) in dry diethyl ether afforded the desired reduced species in moderate yield (45%).
Scheme 143  Stereoselective reduction of silylated alkyne 278 using DIBAL-H

The trisubstituted alkene 274 was prepared according to the procedure previously used with an initial DIBAL-H reduction followed by subsequent methylation with methyllithium (1.6 M in Et₂O, 3 eq.) and methyl iodide (5 eq.) (Scheme 144). Purification by column chromatography (petrol:ethyl acetate 95:5) afforded the product 274 (9%).

Scheme 144  Stereoselective reduction/methylation of 278

One explanation for the low yield of this reaction was the formation of reaction by-product which is believed to be a di-silylated species. Evidence for this compound is provided by ¹H NMR data with two TMS peaks equal in integral size. A possible structure of this compound is shown in Figure 20. The methyllithium may be deprotonating the hydroxyl group which could then be binding to the trimethylsilyl group on unreacted starting material 278. In an attempt to covert this compound back to the alcohol it was washed with dilute hydrochloric acid (2 M) but the di-silylated species remained. Analysis by ¹H NMR spectroscopic techniques indicate that was also a
significant quantity of unmethylated alcohol 279 present which seems to indicate issues regarding the methylation step as seen in the previous case.

![Image](image1.png)

**Figure 20** Possible products obtained from DIBAL-H/methylation reduction of 278

### 4.7.4 Silyl-Prins Cyclisation Studies towards the Synthesis of Dihydropyran Fragment 264

Having developed a route to access the precursors in unoptimised yields, it was possible to investigate these precursors for their potential in preliminary cyclisation reactions. The monosubstituted homoallylic precursor 279 was examined first (Scheme 145). Following standard silyl-Prins methodology, indium (III) chloride (1 eq.) was added to a solution of the aldehyde 247 in dry dichloromethane which was stirred for 1 hour. After this time, the silylated homoallylic alcohol 279 (1 eq.) was added and the reaction was stirred for a further 20 hours at room temperature.

![Image](image2.png)

**Scheme 145** Silyl-Prins reaction to prepare disubstituted dihydropyran 281
Analysis of the product mixture by $^1\text{H}$ NMR spectroscopic techniques indicates that the desired dihydropyran 281 may be present but it is not conclusive. It was possible to isolate one of the many reaction by-products which appeared to be a desilylated derivative of the starting reagent alcohol 282 (Figure 21). This product appears to be forming according to a desilylation process similar to that shown in Scheme 28 and summarised again in Scheme 146.

![Figure 21 Main product identified from the silyl-Prins reaction](image)

![Scheme 146 Postulated desilylation mechanism of the homoallylic alcohol precursor 279](image)
Despite these un-promising results, investigation of the disubstituted homoallylic precursor 274 as a substrate for the preparation of the key kendomycin fragment 264 using silyl-Prins methodology was undertaken (Scheme 147). Using the established silyl-Prins protocol, the aldehyde 247 (1 eq.) was first activated with a stoichiometric quantity of Lewis acid indium (III) chloride (1 eq.). After 1 hour, the alcohol precursor 276 was added and the reaction mixture was stirred at room temperature for 24 hours while monitoring by TLC analysis. When no reaction was observed, the reaction mixture was heated to reflux temperature for a further 5 hours. Purification of the crude mixture was achieved using preparative thin-layer chromatography.

\[
\begin{align*}
276 & \quad 247 & \quad 264 \\
\text{TMS} & \quad \text{Me} & \quad \text{OH} & \quad \text{Br} & \quad \text{Me} & \quad \text{Br} & \quad \text{OH}
\end{align*}
\]

Scheme 147  Silyl-Prins reaction to prepare trisubstituted kendomycin fragment 264

Once again a complex mixture was formed, although pure samples could not be obtained. There was evidence that the desired product 264 was formed by mass-spectrometric analysis [(M') (\textsuperscript{79}Br) 334.0584]. While it was not possible to isolate 264 in pure form its presence in the product mixture is encouraging for future work in this area.
4.8 Investigation of Cross-Coupling of Alkene-Terminated Alkyl Chain to Aromatic Ring

Once an effective pathway to precursor 264 has been established, it will be necessary to attach an 8-membered carbon alkyl chain bearing a terminal alkene to the aromatic ring (Scheme 148). This alkene moiety will combine in an intramolecular fashion with the other alkene moiety in a ring-closing metathesis reaction to generate the macrocyclic kendomycin model compound 284.

![Scheme 148 Proposed pathway to a macrocyclic kendomycin derivative 284](image)

Having already developed a potential route, albeit in low yields, to a bromophenyl-substituted dihydropyran, an initial investigation was performed to determine an effective coupling reaction for the attachment of an alkene-terminated alkyl chain to the aromatic ring. Hayashi et al. have demonstrated that dichloro[1,1’-bis(diphenylphosphino)ferrocene]palladium (II) is an effective catalyst for the cross-coupling of organohalides with primary or secondary alkyl Grignard reagents. The coupling products were obtained selectively and with excellent yields. Therefore this methodology was examined for its suitability to our reaction.

Using a standard procedure for the formation of Grignard reagents, 8-bromo-1-octene 285 (1 eq.) was added at room temperature to a solution of magnesium turnings which had been pre-activated by vigorous dry stirring for 24 hours (Scheme 149).
The solution of 8-bromomagnesium-1-octene $286$ (2 eq.) in dry diethyl ether was added to a stirred solution of bromobenzene $287$ (1 eq.) and PdCl$_2$(dppf) (0.01 eq.) at -78 °C under an inert atmosphere of nitrogen (Scheme 150). The mixture was stirred at room temperature for 24 hours and quenched with dilute hydrochloric acid. Purification by column chromatography (petrol:ethyl acetate 99:1) afforded the desired compound $288$ in good yield (61%). This methodology has shown the potential to be applicable to the preparation of the required RCM precursor. Further development of this area is an ongoing investigation within our group.
4.9 Conclusion

The silyl-Prins reaction has previously shown its ability to synthesise substituted dihydropyrans in good yields with excellent diastereoselectivity. Furthermore its potential for use in total synthesis has been demonstrated by Dobbs et al. with the synthesis of the civet component (±)-(cis-6-methyltetrahydropyran-2-yl)acetic acid in 2003. The success of this total synthesis drove us to explore the application of the silyl-Prins methodology to the synthesis of other biologically interesting natural products.

4.9.1 (±)-Centrolobine

Centrolobine 163, a cis-2,6-disubstituted tetrahydropyran with antibiotic properties, possesses cis-stereochemistry across the oxygen atom and was therefore an attractive target for a racemic total synthesis using the silyl-Prins reaction. Two silyl-Prins reaction precursors were envisaged. The aldehyde precursor 190 was prepared in two steps from commercially available 3-(4'-hydroxyphenyl)-1-propanol 221 in 78% yield. The vinylsilane portion 189 was prepared in three steps from commercially available vinylanisole in 13% yield. These precursors were investigated in a series of silyl-Prins reactions with varying reaction conditions. These cyclisation reactions were unsuccessful and model studies were performed to determine possible causes. The results of these tests indicated that the methoxy group on the vinylsilane portion is the main factor behind the failure to cyclise. We postulate that the increased electron-donating effect of the methoxy group is conjugated through the aromatic ring to the benzylic position. This increases the favourability of loss of the hydroxyl group at this position and thereby prevents the silyl-Prins cyclisation occurring. This issue may be rectified in future work by the preparation of different precursors with the methoxy aromatic group forming part of the aldehyde portion.

The second proposed route to (±)-centrolobine, which is ongoing within the research group, may provide a more effective route to (±)-centrolobine (Scheme 151).
Scheme 151 Proposed future route to (±)-centrolobine employing silyl-Prins methodology

4.9.2 Kendomycin

Kendomycin 193 is a structurally unique polyketide isolated from various Streptomyces sp. with interesting biological properties.\textsuperscript{127-131} Due to possessing a polysubstituted tetrahydropyran core with 2,6-cis-diastereoselectivity, it provided an appealing target for synthesis using silyl-Prins methodology. Retrosynthetic analysis of kendomycin was performed to determine optimum strategies for the employment of the silyl-Prins reaction. Two potential routes to the synthesis of kendomycin analogues were postulated. Both involved using a ring-closing metathesis strategy to generate the macrocycle.

The first strategy involved the preparation of the aromatic aldehyde 246 which would contain much of the complexity required for the aromatic substituent of the dihydropyran ring. Two approaches to this aldehyde 246 were investigated. The first approach involved a four-step route but issues regarding the low yield of the formylation step and cleavage of a methoxy group during bromination led to the abandonment of this
strategy. The second strategy involved an unreliable regioselective reductive alkylation step which led to the discontinuation of this route.

The second strategy involved the preparation of an aromatic vinylsilane portion 263 which, in the initial studies, would possess only a monobrominated aromatic ring. The aldehyde precursor 247 was prepared in 53% yield over two steps from commercially available (-)-β-citronellene. A series of model reactions confirmed the viability of this aldehyde 247 in a silyl-Prins reaction. The vinylsilane precursor 263 was prepared from commercially available 2-bromostyrene in 3% yield over 4 steps. A potential future route to 263 could be provided by the employment of a Barbier type reaction followed by stereoselective reduction (Scheme 152).

![Scheme 152](image_url)

**Scheme 152** Proposed future strategy for the preparation of 263

A series of model reactions with a simpler disubstituted vinylsilane confirmed that these compounds can be used successfully in silyl-Prins reactions including with the employment of aldehyde precursor 247. Investigation of the reaction of the two precursors was performed using standard silyl-Prins conditions. This demonstrated that while only trace quantities of the desired dihydropyran 264 were detected using mass-spectrometric techniques, the presence of the desired dihydropyran 264 was encouraging and further work is ongoing to optimise these reactions.

The development of the RCM stage of the synthesis is also of particular importance to a successful total synthesis and potential model reactions are being performed within the research group to achieve this objective.
The present and future work can be summarised in Figure 22 including the macrocycle construction and coupling of the alkyl chain.

**Figure 22** Development of route to kendomycin including future strategies
Chapter 5

Experimental
Chapter 5

General Experimental Details

Instrumentation

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker ACF-300 ($^1$H NMR at 300 MHz and $^{13}$C NMR at 75 MHz) instrument, a Jeol EX270 ($^1$H NMR at 270 MHz, $^{13}$C NMR at 68 MHz) instrument, a Bruker Avance DRX ($^1$H NMR at 400 MHz and $^{13}$C NMR at 100 MHz) instrument and a Bruker Avance Ultrashield ACS-60 ($^1$H NMR at 400 MHz and $^{13}$C NMR at 100 MHz) instrument. $^1$H NMR spectra were reported in ppm relative to tetramethylsilane or residual solvent (CDCl$_3$ δ 7.26 ppm). Data is presented as follows: $^1$H NMR: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad), coupling constants in Hertz (Hz), and assignment. Multiplets (m) are reported over the range (ppm) at which they appear. $^{13}$C NMR data is presented as follows: chemical shift, assignment. $^1$H NMR and $^{13}$C NMR spectra assignments were made using COSY ($^1$H-$^1$H correlation), HMQC ($^1$H-$^{13}$C correlation), DEPT and NOESY NMR techniques.

High and low resolution mass spectral data was obtained on an Agilent 6890 Series GC System and a Thermoquest Trace GC 2000 Series/Agilent Technologies 1200 LC with Bruker Esquire 3000 plus MS. Conditions for Agilent 6890 Series GC: Heating ramp: 40 °C for 60 seconds, 40-50 °C for 60 seconds, then 50 °C for 60 seconds, followed by 10 °C rise per minute for 30 minutes; finish temp: 350 °C (1 μl injection volume).

Micromass Quattro II, Finnigan MAT 900 XLT, Masslab MD-800 and MAT95 instruments at the EPSRC National Mass Spectrometry Service, Swansea were also employed. GC conditions depend on those specified in the analysis request. The preferential stationary phase is polydimethylsiloxane (non-polar).

Infrared analysis was performed using an Avatar 360 FT-IR, a Perkin Elmer Spectrum instrument or a Shimadzu FT-IR 8300 instrument. Spectra were recorded as thin films between NaCl plates, in nujol mulls or as KBr discs, as indicated.
Melting point analysis was carried out using a Reichert instrument.

**Chromatography**

Column chromatography was carried out using Fluka silica gel 60 (220-440 mesh) (Brockmann 2-3). TLC analysis was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF\textsubscript{254}. Preparative TLC was carried out using glass-backed plates coated with Merck Kieselgel 60 GF\textsubscript{254}. Plates were visualised under UV-light (at 254 nm) or by staining with aqueous potassium permanganate solution followed by heating.

**Reagents**

Moisture sensitive reactions were carried out under an atmosphere of nitrogen using either flame or oven dried glassware and standard syringe/septa techniques. All other commercial reagents were used as received unless otherwise noted. Petrol refers to the fraction boiling between 40 °C and 60 °C. Dichloromethane was distilled over calcium hydride while diethyl ether, THF and toluene were distilled over sodium and benzophenone, which acted as an indicator. Stirring of reaction mixtures was by internal magnetic follower.
Chapter 5

Damien Gough

General Procedure for the Silylation of Homoallylic Alkynic Alcohols

To a stirred solution of the acetylenic alcohol (1 eq.) in dry THF (1.8 ml per mmol) under an inert nitrogen atmosphere was added dropwise n-butyllithium (2 eq., 2.5 M solution in hexane) at -78 °C and the resultant solution was stirred at -78 °C for 2 hours. After this time, trimethylsilyl chloride (2 eq.) was added and the solution was allowed to warm gradually to room temperature. Dilute hydrochloric acid (2 M, 20 ml) was added dropwise and the solution was stirred at room temperature for 30 minutes. The reaction mixture was extracted with diethyl ether (3 x 100 ml) and the combined organic extracts were washed with water (50 ml). The solution obtained was dried (MgSO₄), concentrated in vacuo and purified by either distillation or flash column chromatography to afford the desired trimethylsilyl-substituted alkynic alcohol. This reaction was repeated on several different scales between 2 mmol and 56 mmol with comparable yields.

4-Trimethylsilylbut-3-yn-1-ol (72)

Following the general silylation procedure, the title compound was prepared using 3-butyn-1-ol (4.04 g, 56 mmol), n-butyllithium (45.6 ml, 2.5 M in hexane, 112 mmol) and trimethylsilyl chloride (14.4 ml, 112 mmol) in dry THF (100 ml). After distillation under reduced pressure (60 °C, 3 mmHg) the title compound was isolated as a clear oil (6.21 g, 76%); Rf 0.28 (hexane:ethyl acetate 4:1); νmax/cm⁻¹ (neat) 3352 (O-H), 2185 (C≡C), 1272 (Si-C); δ_H (300 MHz; CDCl₃) 3.70 (2H, t, J 6.2, C(1)H₂OH), 2.50 (2H, t, J 6.2, C(2)H₂), 1.83 (1H, br s, OH). 0.11 (9H, s, 3 x CH₃). All other data in agreement with literature values.
Chapter 5

(±)-5-Trimethylsilylpent-4-yn-2-ol (268)

According to the general silylation procedure (p.151), the reaction of 4-pentyn-2-ol (2.39 g, 12 mmol, 1 eq.), n-butyllithium (22.5 ml, 2.5 M in hexane, 56 mmol, 2 eq.) and trimethylsilyl chloride (7.2 ml, 56 mmol, 2 eq.) in dry THF (50 ml) gave the title compound as a clear oil without further purification (3.34 g, 75 %); Rf 0.20 (petrol:ethyl acetate 9:1); δH (300 MHz; CDCl₃) 3.93 (1H, dd, J 6.0, 3.0, C(2)H), 2.23 (2H, dd, J 9.0, 3.0, C(3)H₂), 1.91 (1H, br s, OH), 1.26 (3H, d, J 9.0, C(1)H₃), 0.16 (9H, s, 3 x CH₃); m/z (Cl) 157.1 [(MH)+, 10%], 141 [(M)+ -OH, 100]. All other data is in agreement with the literature values.⁵³
General Procedure for the Reduction of Silylated Homoallylic Alcohols Using Diisobutylaluminium Hydride (DIBAL-H)\(^{53}\)

To a stirred solution of the trimethylsilylalkynic alcohol (1 eq.) in dry diethyl ether (2.8 ml per mmol) at 0 °C under an inert nitrogen atmosphere was slowly added diisobutylaluminium hydride (3 eq., 1 M solution in hexane). The reaction mixture was allowed to warm gradually to room temperature, after which time it was heated to reflux temperature for 24 hours. After cooling to room temperature and then to 0 °C, dilute sulfuric acid (2 M, excess) was added dropwise to the reaction mixture. The solution was allowed to warm to room temperature whilst being stirred for a further 45 minutes. After this time, the mixture was filtered through Celite, washing the residue with diethyl ether (20 ml). The two layers were separated, with the organic layer then extracted with water (250 ml) and the aqueous layer extracted with diethyl ether (250 ml). The combined organic layers were washed with ice cold water, dried (MgSO\(_4\)) and concentrated \textit{in vacuo}. The oil obtained was purified by distillation or flash column chromatography to afford the desired product. This reaction could be performed on scales between 1.19 mmol and 43.6 mmol with comparable yields.

\textit{Z-4-Trimethylsilylbut-3-en-1-ol (64)}\(^{190}\)

Following the general procedure for the reduction of trimethylsilylalkynes, the \textit{title compound} was prepared using 4-trimethylsilylbut-3-yn-1-ol 72 (6.20 g, 43.6 mmol) and DIBAL-H (129 ml, 1 M solution in hexane, 129 mmol, 3 eq.) in dry diethyl ether (120 ml). The oil obtained was distilled under reduced pressure (52 °C, 1.5 mmHg) to afford the \textit{title compound} as a clear oil (4.26 g, 68%); \(R_f\) 0.38 (hexane:ethyl acetate 4:1);
$v_{\text{max}}$/cm$^{-1}$ (neat) 3328 (O-H), 1608 (C=C), 1248 (Si-C); $\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 6.29 (1H, dt, $J$ 14.1, 7.4, C(3)H), 5.68 (1H, d, $J$ 14.1, C(4)H), 3.67 (2H, t, $J$ 6.2, C(1)H$_2$), 2.41 (2H, q, $J$ 6.2, C(2)H$_2$), 1.43 (1H, br s, C(1)OH), 0.13 (9H, s, 3 x CH$_3$); m/z (CI) 145 [(MH)$^+$, 3%], 129 [(MH)$^+$ -CH$_3$, 41], 103 [(MH)$^+$ -C$_2$H$_2$O, 100].

(±)-Z-5-Trimethylsilylpent-4-en-2-ol (67)

![Reaction Scheme]

According to the general procedure (p.153), the reaction of (±)-5-trimethylsilylpent-4-yn-2-ol 268 (3.34 g, 21.4 mmol, 1 eq.) with DIBAL-H (64 ml, 1 M solution in hexane, 64 mmol, 3 eq.) gave the title compound without further purification (3.11 g, 92%); $R_f$ 0.20 (petrol:ethyl acetate 9:1); $v_{\text{max}}$/cm$^{-1}$ (neat) 3354 (O-H) 1608 (C=C), 1247 (Si-C); $\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 6.32 (1H, m, C(4)H), 5.68 (1H, dt, $J$ 15.0, 3.0, C(5)H), 3.87 (1H, m, C(2)H), 2.30 (2H, t, $J$ 6.0, C(3)H$_2$), 1.21 (3H, d, $J$ 6.0, C(1)H$_3$), 0.13 (9H, s, 3 x CH$_3$). All other data is in agreement with the literature values.$^{53}$
Chapter 5

Damien Gough

**General Procedure for the Silyl-Prins Reaction**

To a stirred solution of aldehyde (1 eq.) in dry dichloromethane (9 ml per mmol) under an inert atmosphere of nitrogen was added indium(III) chloride (1 eq.). After stirring the solution for 1 hour at room temperature, the vinylsilyl alcohol (1 eq.) was added and the reaction mixture was stirred for a further 16-24 hours. The reaction mixture was then quenched with distilled water (10 ml) and the aqueous layer was extracted with dichloromethane (40 ml). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo to afford a residue which was purified by flash column chromatography to give the desired product.

(±)-2-Benzyl-5,6-dihydro-2H-pyran (74)

\[
\begin{align*}
\text{C}_{12}H_{14}O & \quad \text{Mol. Wt.: 174.24} \\
\text{74} & \quad \text{73}
\end{align*}
\]

To a solution of phenylacetaldehyde (0.5 g, 3.4 mmol, 1 eq.) in dry dichloromethane (30 ml) under an inert atmosphere of nitrogen was added indium(III) chloride (0.76 g, 3.4 mmol, 1 eq.). After stirring this solution for 1 hour at room temperature, Z-4-trimethylsilylbut-3-en-1-ol 64 (0.5 g, 3.4 mmol, 1 eq.) was added and the reaction mixture was stirred for a further 16 hours. The reaction was then quenched with the addition of distilled water (10 ml) and the aqueous layer was extracted with dichloromethane (40 ml). The combined organic extracts were dried (MgSO₄) and the solution was concentrated in vacuo. Purification by flash column chromatography (hexane:diethyl ether 10:1) afforded the **title compound** as a colourless oil (0.39 g, 83%): Rf 0.51 (hexane:diethyl ether 10:1); δH (300 MHz; CDCl₃) 7.31-7.70 (5H, m, Ar-H), 5.96 (1H, m, C(3)H), 5.78 (1H, dt, J 8.2. 2.2, C(4)H), 4.45 (1H, m, C(2)H). 4.11 (1H, m,
C(6)H₆, 3.79 (1H, ddd, J 9.6, 4.6, 3.9, C(6)H₆), 2.99 (1H, dd, J 13.6, 7.4, PhCH₂), 2.80 (1H, dd, J 13.6, 7.4, PhCH₂), 2.01 (1H, m, C(5)H₆), 1.88 (1H, m, C(5)H₆). All other data is in agreement with the literature values.⁵⁸

Synthesis of 5,6-Dihydro-2H-pyrans with Ester Functionality

Attempted preparation of (±)-5,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester (80)

![Chemical structure](image)

To a solution of indium(III) chloride (0.76 g, 3.46 mmol, 1 eq.) in dry dichloromethane (30 ml) was added ethyl glyoxylate (0.71 g, 3.46 mmol, 1 eq.) under an atmosphere of nitrogen. After stirring this solution for 1 hour at room temperature, Z-4-trimethylsilylbut-3-en-1-01 64 (0.64 g, 3.46 mmol, 1 eq.) was added and the reaction mixture was stirred for a further 17 hours. The reaction was then quenched with the addition of distilled water (10 ml) and the aqueous layer extracted with dichloromethane (40 ml). The combined organic extracts were dried (MgSO₄) and the solution was concentrated in vacuo. Purification by flash column chromatography (petrol:ethyl acetate 88:12) was unable to isolate the desired species from a number of other compounds although its presence is suggested by GCMS analysis; m/z (Cl) 157.0 [(MH)⁺, 74%]. GCMS analysis also indicates significant amounts of (±)-4-Chlorotetrahydropyran-2-carboxylic acid ethyl ester; m/z (Cl) 195 [M(³⁷Cl)⁺, 58%], 193 [M(³⁵Cl)⁺, 100%]. 157 [(MH)⁺, Cl³⁷, 20%].
b. Boron trifluoride etherate

To a solution of boron trifluoride etherate (0.44 ml, 3.46 mmol, 1 eq.) in dry dichloromethane (30 ml) was added ethyl glyoxylate (0.74 ml, 50% in toluene, 3.46 mmol, 1 eq.) at room temperature under an atmosphere of nitrogen. After stirring for 1 hour, Z-4-trimethylsilylbut-3-en-1-ol 64 (0.64 g, 3.46 mmol, 1 eq.) was added and the reaction mixture was stirred at room temperature for a further 17 hours. The reaction was quenched with the addition of distilled water (10 ml) and the aqueous layer was extracted with dichloromethane (40 ml). The combined organic extracts were dried (MgSO₄), concentrated in vacuo and purified by flash column chromatography (petrol:ethyl acetate 88:12). These purification techniques were unable to separate 5,6-dihydro-2H-pyran-2-carboxylic acid ethyl ester 80 from the mixture of products indicated by GCMS analysis.

c. Trimethylsilyl triflate

To a solution of trimethylsilyl triflate (0.44 ml, 3.46 mmol, 1 eq.) in dry dichloromethane (30 ml) was added ethyl glyoxylate (0.74 ml, 3.46 mmol, 1 eq.) at room temperature under an atmosphere of nitrogen. After stirring for 1 hour, Z-4-trimethylsilylbut-3-en-1-ol 64 (0.64 g, 3.46 mmol, 1 eq.) was added and the reaction mixture was stirred at room temperature for a further 18 hours. The reaction was quenched by the addition of distilled water (10 ml) and the aqueous layer was extracted with dichloromethane (40 ml). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. Analysis of the crude material by GCMS analysis indicated that in addition to the formation of the desired compound 80 there were a number of unidentifiable by-products.
To a solution of indium(III) chloride (0.28 g, 1.26 mmol, 1 eq.) in dry dichloromethane (30 ml) was added ethyl glyoxylate (0.29 g, 1.26 mmol, 1 eq.) under an atmosphere of nitrogen. After stirring this solution for 1 hour at room temperature, (±)-Z-5-trimethylsilylpent-4-en-2-ol 67 (0.20 g, 1.26 mmol, 1 eq.) was added and the reaction mixture was stirred for a further 24 hours. The reaction was then quenched with the addition of distilled water (10 ml) and the aqueous layer extracted with dichloromethane (40 ml). The combined organic extracts were dried (MgSO₄) and the solution was concentrated in vacuo. Analysis of the product mixture by ¹H NMR spectroscopic techniques indicates the major products were desilylated starting reagent and recovered ethyl glyoxylate.
To a solution of indium(III) chloride (1.53 g, 6.92 mmol, 2 eq.) in dry dichloromethane (25 ml) was added ethyl glyoxylate (1.03 ml, 5.19 mmol, 1.5 eq.) at room temperature under an atmosphere of nitrogen. After stirring for 1 hour, 3-buten-1-ol (0.30 ml, 3.46 mmol, 1 eq.) was added and the solution was stirred for a further 22 hours at room temperature. The reaction was quenched by the addition of distilled water (10 ml) and the aqueous layer was extracted with dichloromethane (20 ml). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo to afford a mixture containing the two inseparable diastereomeric versions of title compound and starting reagent 3-buten-1-ol (0.41 g). The following data is for the mixture of chlorinated diastereoisomers; Rf 0.13 (petrol:ethyl acetate 7:3); (+) or (-) 4-Chlorotetrahydropyran-2-carboxylic acid ethyl ester; m/z (Cl): 193 [(MH)⁺, 96%], 157 [(MH)⁺-Cl, 21]; (+) or (-) 4-Chlorotetrahydropyran-2-carboxylic acid ethyl ester; m/z (Cl)193 [(M)⁺, 100%], 157 [(M)⁺-Cl, 58]. ¹H NMR spectra indicate a mixture of products consisting primarily of 3-buten-1-ol.
To a solution of N,N,N,N-tetramethylenediamine (4.94 g, 42.5 mmol, 2 eq.) in hexane (25 ml) at -78 °C was slowly added a solution of n-butyllithium (26.7 ml, 2.5 M in hexane, 42.5 mmol, 2 eq.), followed by 3-methyl-3-buten-1-ol (1.83 g, 21.3 mmol, 1 eq.) under an atmosphere of nitrogen. The reaction mixture was vigorously stirred at 60 °C for 6 hours. The resulting solution was cooled to -78 °C and treated with trimethylsilyl chloride (6.92 g, 8.09 ml, 63.7 mmol, 3 eq.). The reaction mixture was warmed to room temperature and stirred for a further 16 hours. After this time ice (10 g) was added to the reaction mixture and after separation of the layers, the aqueous layer was extracted with diethyl ether (100 ml). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. This residue was treated with H₂SO₄ (2 M, 1 ml) in THF (5 ml) at 0 °C for 20 minutes. Subsequently the mixture was extracted with diethyl ether (50 ml), dried (MgSO₄) and concentrated in vacuo. The crude material was purified by flash column chromatography (hexane:ethyl acetate 9:1) to afford the title compound as a colourless oil (1.37 g, 41%); This reaction was repeated many times on several different scales (up to 21.3 mmol) with comparable yields; Rf 0.94 (hexane:ethyl acetate 9:1); Found [M+H]+ 159.1205; C₈H₁₅OSi [M+H]+ requires 159.1209; vₕ max/cm⁻¹ (neat) 3351 (O-H), 1650 (C=C), 1251 (Si-C); δH (300 MHz; CDCl₃) 4.77 (1H, s, C(4)Ha), 4.71 (2H, t, J 6.0, C(1)H₂), 3.69 (2H, t, J 6.0, C(2)H₂), 2.26 (2H, t, J 6.0, C(2)H₂), 1.74 (2H, s, (TMS)CH₂). 143.4 (C(2)H₂), 113.0 (C(4)H₂), 61.9 (C(1)H₂).
[(MH)\(^+\)- CH\(_4\), 37 %], 103 [(MH –C\(_3\)H\(_4\)O)\(^+\),100]. All other data in agreement with literature values.\(^\text{88}\)

2-Benzyl-4-methylenetetrahydropyran (108)

![Chemical Structure](image)

To a solution of indium(III) chloride (0.52 g, 2.34 mmol, 1 eq.) in dry dichloromethane (25 ml) was added phenylacetaldehyde (0.28 g, 2.34 mmol, 1 eq.) under an atmosphere of nitrogen. The resultant solution was stirred for 1 hour at room temperature. 3-Trimethylsilylmethylbut-3-en-1-ol 105 (0.37 g, 2.34 mmol, 1 eq.) was then added and the solution was stirred for a further 16 hours at room temperature. After this time the reaction was quenched with the addition of distilled water (10 ml) and the aqueous layer was extracted with dichloromethane (40 ml). The solution was then dried (MgSO\(_4\)) and concentrated in vacuo. GCMS analysis of the oil obtained indicated the presence of the desired exocyclic dihydropyran 108 (5%) in addition to two regioisomers, 2-benzyl-4-methyl-3,6-dihydro-2H-pyran 109 (65%) and 2-benzyl-4-methyl-5,6-dihydro-2H-pyran 110 (30%). The most abundant isomer, as indicated by \(^1\)H NMR spectroscopic techniques was 2-benzyl-4-methyl-3,6-dihydro-2H-pyran 109 and the following data applies to this compound; \(R_f\) 0.57 (hexane:diethyl ether 10:1); Found [M+H]\(^+\) 189.1255; C\(_{13}\)H\(_{17}\)O [M+H]\(^+\) requires 188.1279; \(n\text{max}/\text{cm}^{-1}\) (neat) 1604 (C=C), 1122 (C-O); \(\delta\)\(_H\) (400 MHz; CDCl\(_3\)) 7.18-7.32 (5H, m, Ar-H), 5.40 (1H, t, \(J\) 1.6, C(5)H), 4.14 (2H, m, C(6)H\(_2\)), 3.72 (1H, m, C(2)H), 2.97 (1H, dd, \(J\) 13.7, 6.8, PhCHH), 2.73 (1H, dd, \(J\) 13.7, 6.8, PhCHH), 1.99 (1H, m, C(3)H\(_2\)), 1.77 (1H, m, C(3)H\(_b\)), 1.66 (3H, s, C(4)CH\(_3\)); \(\delta\)\(_C\) (100 MHz; CDCl\(_3\)) 138.4 (Cipso), 126.0-131.5 [4 x C(Ar)], 119.5 (C(5)H), 74.5 (C(2)H), 65.8
(C(6)H₄), 42.2 (PhCH₂), 35.2 (C(3)H₂), 22.8 (CH₃); m/z (Cl) 189 [(MH)⁺, 39%], 171 [(MH)⁺-H₂O, 100].

The second most abundant isomer was 2-benzyl-4-methyl-5,6-dihydro-2H-pyran 110 and the following data applies to this compound; δH (400 MHz; CDCl₃) 7.32-7.19 (5H, m, Ar-H), 5.35 (1H, t, J 1.5, C(3)H), 4.28 (1H, m, C(2)H), 4.02 (1H, m, C(6)H₃), 3.64 (1H, ddd, J 9.0, 6.0, 3.0, C(6)H₆), 2.93 (1H, dd, J 12.0, 6.0, PhCHH), 2.26 (1H, dd, J 12.0, 6.0, PhCHH), 1.68 (1H, m, C(5)H₆), 1.60 (1H, m, C(5)H₆), 1.53 (3H, s, C(4)H₃); m/z (Cl) 189 [(MH)⁺, 32%], 171 [(MH)⁺-H₂O, 38].

The presence of title compound 2-benzyl-4-methylene tetrahydropyran 108 was indicated by its GCMS data: m/z (Cl) 189 [(MH)⁺, 4%], 171 [(MH)⁺-H₂O, 3].

4-Methylene-2-pentyltetrahydropyran (112)

To a solution of indium(III) chloride (0.23 g, 1.02 mmol, 1 eq.) in dry dichloromethane (10 ml) was added n-hexanal (0.10 g, 1.02 mmol, 1 eq.) under an atmosphere of nitrogen. The resultant solution was stirred for 1 hour at room temperature. After this time 3-trimethylsilylmethyl-but-3-en-1-ol 105 (0.16 g, 1.02 mmol, 1 eq.) was added and the mixture was stirred for a further 21 hours at room temperature. The reaction was quenched with the addition of distilled water (5 ml) and the aqueous layer was extracted with dichloromethane (20 ml). The solution was dried (MgSO₄) and concentrated in vacuo. The oil obtained was purified by flash column chromatography (hexane:diethyl ether 10:1) but it was not possible to isolate 4-methylene-2-pentyltetrahydropyran 112 (16%) from two regioisomeric products, 4-methyl-2-pentyl-3,6-dihydro-2H-pyran 113.
and 4-methyl-2-pentyl-5,6-dihydro-2H-pyran 114 (9%). The most abundant isomer, as indicated by ^1H NMR spectroscopic techniques was 4-methyl-2-pentyl-3,6-dihydro-2H-pyran 113 and the following data applies to this compound; R_f 0.57 (hexane:diethyl ether 10:1); Found [M+H]^+ 169.1592; C_{11}H_{21}O [M+H]^+ requires 169.1314;  v_{max} / cm^{-1} (neat) 1639 (C=C), 1139 (C-O); δ_H (300 MHz; CDCl_3) 5.40 (1H, m, C(5)H), 4.20 (2H, m, C(6)H_2), 3.47 (1H, m, C(2)H), 1.92 (1H, m, C(3)H_a), 1.82 (1H, m, C(3)H_b), 1.69 (3H, s, C(4)CH_3), 1.62 (2H, s, C(7)H_2), 1.47- 1.10 (overlapping 3 x CH_2), 0.89 (3H, t, J 6.0, C(11)H_3); δ_C (100 MHz; CDCl_3) 132.3 (C ipso), 120.1 (C(5)H), 74.2 (C(2)H), 66.3 (C(6)H_2), 36.3 (C(4)H_2), 32.3 (C(7)H_2), 23.1-25.6 (3 x CH_2), 14.5 (C(11)H_3); m/z (CI) 169 [(MH)^+, 100%], 151 [(MH)^+-H_2O, 16].

The second most abundant isomer, which was not separated from the other regioisomers, was 4-methyl-2-pentyl-5,6-dihydro-2H-pyran 114 and the following data applies to this compound; δ_H (300 MHz; CDCl_3) 5.33 (1H, m, C(3)H), 4.16 (C(2)H), 3.98 (C(6)H_a), 3.62 (C(6)H_b), 1.75 (C(5)H_a), 1.27-1.68 (9H, overlapping C(5)H_b and 4 x CH_2), 0.89 (3H, m, CH_3); m/z (CI) 169 [(MH)^+, 35%].

The presence of the title compound 4-methylene-2-pentyl-tetrahydropyran 112 is indicated by its GCMS data; m/z 169 [(MH)^+, 5%].
Development of the Mukaiyama-Aldol Silyl-Prins Reaction

Synthesis of the Vinyl Ether Precursor

Wittig approach: Route 1

Triphenyl-(2-vinylxyethyl)phosphonium chloride (119)

To a round bottom flask containing 2-chloroethyl vinyl ether (0.2 mol, 21.31 g, 2 eq.) under an inert nitrogen atmosphere was added triphenylphosphine (26.2 g, 0.1 mol, 1 eq.). This mixture was heated to 100-105 °C and stirred for 2 hours under an atmosphere of nitrogen. After this time, the reaction mixture was allowed to cool to room temperature and then 0 °C whereupon the walls of the flask were scratched to induce crystallisation. The resultant precipitate was filtered and the residue was washed with toluene (50 ml) and petrol (2 x 25 ml). The crystals obtained were spread out on a watch glass and allowed to dry in a desiccator which afforded the title compound as a white powder (9.6 g, 26%); νmax/cm⁻¹ (KBr) 3065 (C-H), 1474 (C=C), 1088 (C-O); M.p. 83-87 °C. ¹H NMR analysis could not be used to characterise this product due to its ionic structure and thus its insolubility in the chosen solvent.
Trimethylsilyl methanal (118)\textsuperscript{191}

\[ \text{TMS} \begin{array}{c} \text{OH} \\ \text{C}_4\text{H}_{10}\text{OSi} \\ \text{Mol. Wt.: 104.22} \end{array} \]

\text{Oxidation procedure a, b or c}

\[
\begin{array}{ccc}
\text{118} & \text{TMS} & \text{H} \\
\text{a. 1.1 eq. DMSO, 1.05 eq. (COCl)_2, Et}_2\text{O} \\
b. 1.5 eq. PCC, silica gel, CH}_2\text{Cl}_2 \\
c. 10 eq. MnO}_2', \text{THF} \\
\end{array}
\]

a. Swern oxidation

To a solution of oxalyl chloride (0.66 g, 5.25 mmol, 1.05 eq.) in anhydrous diethyl ether (15 ml) at -78 °C was added dropwise dimethyl sulfoxide (0.43 g, 5.50 mmol, 1.10 eq.) under an atmosphere of nitrogen. After slowly warming to -35 °C, the reaction was maintained at this temperature for a further 30 minutes whilst stirring, then re-cooled to -78 °C. Trimethylsilylmethanol (0.52 g, 5.00 mmol, 1 eq.) was then added dropwise to the reaction mixture. This solution was warmed up to -40 °C, maintained at this temperature for 1 hour and subsequently re-cooled to -78 °C. Triethylamine (3.3 ml, 23.68 mmol, 5 eq.) was added and the solution was stirred for a further 1 hour at this temperature. The reaction mixture was warmed up to 0 °C for 2 hours after which the solvent was removed by evaporation to afford a yellow oil. An attempt to purify the product by Kugelrohr distillation was unable to adequately isolate the title compound although \textsuperscript{1}H NMR spectroscopic techniques indicated it had been formed; (0.05 g, 10%); \(\delta\textsubscript{H} (300 \text{ MHz; CDCl}_3) 8.06 (1\text{H, s, CHO}), 0.08 (9\text{H, s, 3 x CH}_3); m/z (Cl) 103 [(MH\textsuperscript{+}, 100%),\textsuperscript{191}

b. Pyridinium chlorochromate oxidation

To a solution of pyridinium chlorochromate (6.57 g, 30 mmol, 1.5 eq.) in dry dichloromethane (60 ml) was added silica gel (10 g) under an inert nitrogen atmosphere. A solution of trimethylsilylmethanol (2.58 ml, 20 mmol, 1 eq.) in dry dichloromethane (20 ml) was added to the mixture which was stirred at room temperature for 1 hour. After
this time, the reaction mixture was diluted with dry diethyl ether (50 ml) and filtered through Celite, washing the residue with diethyl ether (3 x 10 ml). After careful concentration in vacuo, purification was attempted using column chromatography (petrol:ethyl acetate 84:16). Adequate purification was not achieved but the presence of the title compound is suggested by the following data; \( \delta_H \) (300 MHz; CDCl\(_3\)) 8.11 (1H, s, CHO), 0.06 (9H, s, 3 x CH\(_3\)); \( m/z \) (CI) 103 [(MH\(^+\), 55%].

c. Manganese dioxide oxidation

To a solution of trimethylsilylmethanol (0.06 ml, 0.5 mmol, 1 eq.) in dry THF (10 ml) was added activated (heated in oven at 100 °C) manganese dioxide (0.5 g, 5.0 mmol, 10 eq.) under a nitrogen atmosphere. The reaction mixture was heated to reflux temperature whilst being stirred for 16 hours. Monitoring of the progress of this reaction at this point by thin layer chromatography indicated that the trimethylsilylmethanol had not reacted.

**Attempted preparation of Z-3-trimethylsilyl-1-vinyloxyprop-2-ene (120)**

To a solution of trimethylsilylmethanol (0.06 ml, 0.55 mmol, 1 eq.), triphenyl-(2-vinyloxyethyl)phosphonium chloride 119 (0.20 g, 0.55 mmol, 1 eq.), \( n \)-butyllithium (0.22 ml, 0.55 mmol, 1 eq.) and titanium(IV) isopropoxide (0.15 ml, 0.55 mmol, 1 eq.) in dry THF (12 ml) was added activated (oven-heated for 24 hours at 100 °C) manganese dioxide (0.25 g, 2.5 mmol, 5 eq.) under a nitrogen atmosphere. The reaction mixture was heated at reflux temperature for 1 hour whilst being stirred vigorously. A second portion of manganese dioxide (0.25 g, 2.5 mmol, 5 eq.) was then added and the reaction was allowed to continue heating at reflux temperature for a further 45 hours. After this time,
the reaction mixture was allowed to cool to room temperature and was filtered through Celite washing the residue with diethyl ether (2 x 10 ml). The organic washings were neutralised with aqueous ammonium chloride solution, the layers separated and the aqueous layer extracted with diethyl ether (3 x 20 ml). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. Analysis of the crude product by ¹H NMR spectroscopic techniques indicated that the desired compound had not been formed.

**Attempted preparation of non-2-enyl vinyl ether (127)**

![Diagram]

a. Using n-butyllithium as a base

To a solution of n-heptanol (0.07 ml, 0.5 mmol, 1 eq.), triphenyl-(2-vinyloxyethyl)phosphonium chloride 119 (0.20 g, 0.55 mmol, 1.1 eq.), n-butyllithium (2.5 M in hexane, 0.2 ml, 0.55 mmol, 1 eq.) and titanium(IV) isopropoxide (0.15 ml, 0.5 mmol, 1 eq.) in dry THF (12 ml) was added activated (dried in 70 °C oven) manganese dioxide (0.25g, 2.5 mmol, 5 eq.) under an inert atmosphere of nitrogen. The solution was heated to reflux temperature and stirred for 1 hour. After this time, another portion of activated manganese dioxide (0.25g, 2.5 mmol, 5 eq.) was added and the reaction mixture was continually stirred under reflux conditions for a further 49 hours. The reaction mixture was filtered through Celite followed by quenching with ammonium chloride solution (20 ml). After extracting the mixture with diethyl ether (3 x 15 ml), the organic washings were dried (MgSO₄) and concentrated in vacuo. Analysis of the product mixture by ¹H NMR and GCMS spectroscopic techniques indicated a mixture of n-heptanol, n-heptanal, and triphenylphosphine oxide.
b. Using MTBD as base

To a solution of \( n \)-heptanol (0.07 ml, 0.5 mmol, 1 eq.), triphenyl-(2-vinyloxyethyl)phosphonium chloride \( \text{119} \) (0.20 g, 0.55 mmol, 1.1 eq.), MTBD (0.16 ml, 1.1 mmol, 2.2 eq.) and titanium(IV) isopropoxide (0.15 ml, 0.5 mmol, 1 eq.) in dry THF (12 ml) was added activated manganese dioxide (dried in 70 °C oven) (0.25 g, 2.5 mmol, 5 eq.) under an inert atmosphere of nitrogen. The solution was heated to reflux temperature and stirred for 1 hour. After this time, another portion of activated manganese dioxide (0.25 g, 2.5 mmol, 5 eq.) was added and the reaction mixture was continually stirred under reflux conditions for a further 20 hours. The reaction mixture was filtered through Celite followed by quenching with ammonium chloride solution (20 ml). After extracting the mixture with diethyl ether (3 x 15 ml), the organic washings were dried (MgSO\(_4\)) and concentrated \textit{in vacuo}. Analysis of the product mixture by \(^1\)H NMR spectroscopic techniques indicated a mixture containing primarily \( n \)-heptanol, \( n \)-heptanal and unidentifiable compounds.

\textbf{Wittig Approach: Route 2}

\textbf{1-Trimethylsilylmethyltriphenylphosphonium bromide (121)}

\( \text{TMS} \xrightarrow{\text{Br}} \xrightarrow{\text{Ph}_3\text{P}} \text{121} \)

\( \text{C}_4\text{H}_{11}\text{BrSi} \)

\text{Mol. Wt.: 167.12}  

\( \text{TMS} \xrightarrow{\text{P}^+\text{Ph}_3\text{Br}^-} \)

\( \text{C}_{22}\text{H}_{26}\text{BrPSi} \)

\text{Mol. Wt.: 429.41}

To a solution of triphenylphosphine (4.72 g, 18 mmol, 1.5 eq.) in dry dichloromethane (10 ml) was added bromomethyltrimethylsilane (1.76 ml, 12 mmol, 1 eq.) at room temperature. The reaction mixture was stirred while heating at reflux temperature for 17 hours. After this time, the solution was concentrated \textit{in vacuo} to yield a yellow precipitate which was washed with diethyl ether (2 x 20 ml) on a Buchner funnel. The product was
allowed to dry in a desiccator to afford the title compound as a pale pink powder (4.38 g, 85%). M.p. 79.5-102 °C. All other data is in agreement with the literature values. 192

1-Trimethylsilylhept-2-ene (130)\textsuperscript{193}

\[
\begin{align*}
\text{\textit{C}_{10}\text{H}_{22}\text{Si}} & \quad \text{Mol. Wt.: 170.37} \\
\text{\textit{C}_{6}\text{H}_{12}} & \quad \text{Mol. Wt.: 100.16}
\end{align*}
\]

To a solution of 1-trimethylsilylmethyltriphenylphosphonium bromide 121 (0.47 g, 1.1 mmol, 1.1 eq.) in dry THF (24 ml) was added \(n\)-butyllithium (0.88 ml, 2.5 M in hexane, 2.2 mmol) at -78 °C under an inert atmosphere of nitrogen. After 10 minutes, \(n\)-hexanal (0.12 g, 1 mmol, 1 eq.) was added to the reaction mixture. After stirring for 4 hours, the reaction was allowed to warm to room temperature and was quenched by the addition of ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 15 ml). The combined organic layers were then dried (MgSO\(_4\)) and concentrated \textit{in vacuo}. The residue was then filtered through a plug of silica washing with diethyl ether (100 ml). Analysis of the product mixture by GCMS techniques indicated the formation of the title compound as part of a mixture; m/z (Cl) 171.2 [(MH\(^+\)], 100%].
2-Vinyloxyethanal (122)

\[
\text{HO} \quad \text{O} \quad \text{O} \quad \text{HO} \\
\text{C}_4\text{H}_6\text{O}_2 \\
\text{Mol. Wt.: 86.09}
\]

\[
\text{O} \quad \text{O} \\
\text{C}_4\text{H}_6\text{O}_2 \\
\text{Mol. Wt.: 88.11}
\]

**Oxidation procedure**

- a. PCC, alumina, CH₂Cl₂
- b. MnO₂, THF
- c. PDC, mol sieves, CH₂Cl₂
- d. DMSO, COCl₂, Et₂O

a. Pyridinium chlorochromate oxidation

To a stirred solution of pyridinium chlorochromate (6.58 g, 30 mmol, 1.5 eq.) in dry dichloromethane (40 ml) was added a solution of ethylene glycol vinyl ether (1.82 ml, 20 mmol, 1 eq.) in dry dichloromethane (10 ml) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 2 hours. After this time the solution was diluted with diethyl ether (50 ml) and was filtered using a Buchner funnel to remove the chromium by-products. The filtrate was concentrated in vacuo but ¹H NMR analysis indicated only the presence of ethylene glycol vinyl ether and pyridinium chlorochromate.

b. Manganese dioxide oxidation

To a stirred solution of ethylene glycol vinyl ether (0.09 ml, 1 mmol, 1 eq.) in dry THF was added manganese dioxide (0.99 g, 10 mmol, 10 eq.) under an atmosphere of nitrogen. The reaction mixture was heated to reflux temperature whilst stirring for 94 hours. After this time the mixture was filtered through Celite and the residue was washed with diethyl ether (2 x 20 ml). The organic extracts were neutralised with aqueous ammonium chloride solution, the layers separated and the aqueous layer extracted with diethyl ether (20 ml). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The product was analysed by ¹H NMR spectroscopic methods which indicated only the recovery of ethylene glycol vinyl ether.
c. Pyridinium dichromate oxidation

To a solution of ethylene glycol vinyl ether (1.79 ml, 20 mmol, 1 eq.) in dry dichloromethane (50 ml) was added pyridinium dichromate (11.51 g, 30 mmol, 1.5 eq.) and activated (heated in 120 °C oven for 48 hours) molecular sieves (4Å, 15 g) at room temperature. The reaction mixture was stirred for 64 hours at room temperature under an atmosphere of nitrogen. After this time the mixture was filtered through a plug of MgSO₄ to remove any by-product chromium tars. The residue was washed with petrol (3 x 20 ml). Analysis by ¹H NMR spectroscopic techniques indicated that in addition to starting reagents, a trace amount of desired aldehyde 122 had formed but it was insufficient for purification.

d. Swern oxidation

To a stirred solution of oxalyl chloride (0.46 ml, 5.25 mmol, 1.05 eq.) in diethyl ether (15 ml) at -78 °C was added dropwise dimethyl sulfoxide (0.39 ml, 5.50 mmol, 1.10 eq.). After warming to -35 °C, the reaction mixture was maintained at this temperature for 30 minutes then re-cooled to -78 °C. Ethylene glycol vinyl ether (0.45 ml, 5.0 mmol, 1 eq.) was added dropwise and the mixture was warmed up to -40 °C, maintained at this temperature for 1 hour and then re-cooled to -78 °C. Triethylamine (3.3 ml, 23.68 mmol, 4.7 eq.) was added dropwise and the solution was stirred for a further 1 hour at this temperature. The reaction mixture was warmed to 0 °C for 2 hours and the solvent was removed by evaporation. The product mixture was analysed by ¹H NMR spectroscopic techniques and although a minute quantity of 2-vinylxoyethanal 122 appeared to have formed, it was of insufficient quantity to achieve successful purification.
Attempted preparation of Z-3-trimethylsilyl-1-vinyloxy-prop-2-ene (120)

\[
\begin{align*}
\text{HO} & \text{O} \\
\text{C}_4\text{H}_9\text{O}_2 & \text{Mol. Wt.: 88.11} \\
\text{132}
\end{align*}
\]

\[
\begin{align*}
\text{MnO}_2, \text{Ti(PrO)}_4 & \text{, n-BuLi, THF} \\
\text{TMS} & \text{P}^+\text{Ph}_3\text{Br} \\
\text{121}
\end{align*}
\]

\[
\begin{align*}
\text{TMS} & \text{O} \\
\text{C}_8\text{H}_{16}\text{OSi} & \text{Mol. Wt.: 156.30} \\
\text{120}
\end{align*}
\]

To a solution of ethylene glycol vinyl ether (0.45 ml, 0.5 mmol, 1 eq.) and titanium(IV) isopropoxide (0.15 ml, 0.55 mmol, 1.1 eq.) in dry THF (10 ml) was added manganese dioxide (0.25 g, 2.5 mmol, 5 eq.). In a separate round bottom flask, n-butyllithium (0.44 ml, 2.5 M in hexane, 1.1 mmol, 2.2 eq.) was added to a solution of 1-trimethylsilylmethyltriphenylphosphonium bromide 121 (0.24 g, 0.5 mmol, 1 eq.) in dry THF (5 ml) at -78 °C under an inert atmosphere of nitrogen. After stirring for 10 minutes, this solution was slowly added to the first solution at -78 °C under an inert atmosphere of nitrogen. The resultant mixture was allowed to slowly warm to room temperature and was then heated to reflux temperature whilst stirring for 16 hours. At this stage, another portion of manganese dioxide (0.25 g, 2.5 mmol, 5 eq.) was added. After stirring for a further 4 hours, the reaction was quenched by the addition of ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 15 ml). The combined organic layers were then dried (MgSO₄) and concentrated \textit{in vacuo}. The product mixture was analysed by \textsuperscript{1}H NMR spectroscopic techniques but the presence of the \textit{title compound} was not indicated.
Nucleophilic Substitution-Based Route

2-Iodoethyl vinyl ether (136)

To a solution of 2-chloroethyl vinyl ether (1.02 ml, 10 mmol, 1 eq.) in dry acetone (50 ml) was added sodium iodide in excess under a nitrogen atmosphere. The reaction mixture was heated to reflux temperature for 15 minutes. After this time, distilled water (50 ml) was added to quench the reaction and the aqueous layer was extracted with diethyl ether (20 ml). The solution was dried (MgSO₄) and the solvent was removed by evaporation to afford the **title compound** as a colourless oil (0.46 g, 25%). δH (300 MHz; CDCl₃) 6.48 (1H, dd, J 15.0, 6.0, C(3)H), 4.22 (1H, dd, J 15.0, 3.0, C(4)H₃), 4.07 (1H, dd, J 6.0, 3.0, C(4)H₂), 3.95 (2H, t, J 6.0, C(1)H₂), 3.71 (2H, t, J 6.0, C(2)H₂); m/z (Cl) 198 [(M)⁺, 25%], 171 [(M)⁺-C₂H₃, 17], 155 [(M)⁺-C₂H₄O, 100]. All other data in agreement with the literature values.¹⁹⁴
Attempted preparation of 1-trimethylsilyl-4-vinylxy-but-1-yne (134)

To a stirred solution of trimethylsilylacetylene (0.23 g, 2.34 mmol, 1 eq.) in dry THF (20 ml) was added dropwise n-butyllithium (0.94 ml, 2.5 M in hexane, 2.34 mmol, 1 eq.) at -78 °C under an atmosphere of nitrogen. This mixture was stirred for 1 hour under an inert atmosphere of nitrogen. After this time 2-iodoethyl vinyl ether 136 (0.46 g, 2.34 mmol, 1 eq.) was added slowly. The reaction mixture was stirred for a further 21 hours at room temperature. Ammonium chloride solution (20 ml) was added to quench the reaction and the aqueous layer was extracted with diethyl ether (2 x 20 ml). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. Analysis of the product using ¹H-NMR and GCMS did not indicate the presence of the title compound while GCMS data suggests the presence of 4-trimethylsilylbut-3-yn-1-ol: m/z (Cl) 141 [(M-H)⁺, 52%], 139 [(M-3H)⁺, 100], 123 [(M)⁺-H₂O, 6].
Chapter 5

Metathesis Approach - Route 1

 Attempted preparation of \( E-4 \)-trimethylsilylbut-3-en-1-ol (83)

\[
\begin{align*}
\text{71} & \quad \overset{\text{Cat. a or Cat. b}}{\text{CH}_2\text{Cl}_2} \quad \rightarrow \quad \overset{\text{138}}{\text{TMS}} \\
\text{83} & \quad \overset{\text{TMS}}{\text{OH}} \\
\end{align*}
\]

Cat. a: Grubbs II catalyst
Cat. b: Schrock catalyst

To a solution of 3-buten-1-ol (0.07 g, 1.0 mmol, 1 eq.) and either Grubbs 2nd generation catalyst or Schrock catalyst (5 mol%) in degassed dry dichloromethane (7 ml) was added trimethylvinylsilane (0.11 g, 1.1 mmol, 1.1 eq.) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred for 17 hours. After this time the solvent was removed by rotary evaporation and the mixture was filtered through a short plug of silica gel washing through with hexane (50 ml). The filtrate was dried (MgSO\(_4\)) and concentrated in vacuo. Analysis of the product by \(^1\)H NMR spectroscopic and GCMS techniques indicated only the presence of the starting reagents from reactions with both catalysts.

4-Benzyloxybut-1-ene (145)

\[
\begin{align*}
\text{71} & \quad \overset{\text{BnBr, KOH}}{\text{THF, r.t.}} \quad \rightarrow \quad \overset{145}{\text{2}} \\
\text{145} & \quad \overset{3}{\text{4}} \quad \overset{\text{Ph}}{\text{O}} \\
\end{align*}
\]

To a solution of 3-buten-1-ol (2.38 g, 33 mmol, 1 eq.) in THF/DMSO (9:1, 120 ml) was added finely powdered potassium hydroxide (1.84 g, 33 mmol, 1 eq.). After 5 minutes benzyl bromide (3.9 ml, 33 mmol, 1 eq.) was added under a nitrogen atmosphere while the reaction was kept at 0 °C. The reaction mixture was stirred at room temperature for
24 hours. The reaction was then quenched by the addition of water and diethyl ether (1:1. 250 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 200 ml) and ethyl acetate (2 x 200 ml). The organic extracts were combined, dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash column chromatography (petrol:ethyl acetate 9:1) to afford the title compound as colourless oil (5.35 g, 100%); Found [M+H]+ 163.1086; C₁₁H₁₅O [M+H]+ requires 163.1123; \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2856 [Ar(CH)], 1641 (C=C), 1100 (C-O); \( \delta_{\text{H}} \) (300 MHz; CDCl₃) 7.26-7.36 (5H, m, Ar-H), 5.86 (1H, ddt, \( J 18.0, 12.0, 6.0 \), C(2)H), 5.14 (2H, dt, \( J 9.0, 3.0 \), C(1)H₂), 4.52 (2H, s, PhCH₂), 3.53 (2H, t, \( J 6.0 \), C(4)H₂), 2.38 (2H, q, \( J 6.0 \), C(3)H₂); \( \delta_{\text{C}} \) (75 MHz; CDCl₃) 135.7 (C(2)H), 129.4-127.8 [overlapping 5 x C(Ar)], 116.8 (C(1)H₂), 73.3 (C(5)H₂), 70.0 (C(4)H₂), 34.7 (C(3)H₂); \( m/z \) (Cl) 163 [(MH)⁺, 15%], 145 [(MH⁻-H₂O, 100]. All other data is in agreement with the literature values.¹⁹⁵

Attempted preparation of E-4-trimethylsilyl-1-benzyloxy-but-4-ene (146)

![Chemical structure](image)

To a solution of the 4-benzyloxybut-1-ene 145 (0.16 g, 1.0 mmol, 1 eq.) and Grubbs 2nd generation catalyst (0.043 g, 0.5 mol%) in 7 ml of dry degassed dichloromethane was added trimethylvinyl silane (0.16 ml, 1.1 mmol, 1.1 eq) in dry degassed dichloromethane (8 ml) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred for 17 hours at room temperature. After this time the solvent was removed by rotary evaporation and the residue was filtered through a short plug of silica eluted with hexane/ethyl acetate (49:1). The filtrate was concentrated in vacuo to give a yellow oil. Analysis of this product by GCMS techniques indicated that the desired compound had formed: \( m/z \) (Cl) 235 [(MH)⁺, 11%], 145 [(MH⁻-C₇H₆, 100]. This product was present in the reaction mixture but in insufficient quantity to purify.
Metathesis Approach - Route 2

But-2-enyloxy-dimethylvinylsilane (141)

![Chemical structure](image)

To a solution of imidazole (0.21 g, 3 mmol, 1.2 eq.) in dry dichloromethane (8 ml) at 0 °C was added dimethylchlorovinylsilane (0.3 g, 2.5 mmol, 1 eq.) over a period of 5 minutes under an atmosphere of nitrogen. 3-Buten-1-ol (0.18 g, 2.5 mmol, 1 eq.) was slowly added to the solution over 30 minutes. The reaction mixture was warmed to room temperature and stirred for a further 3 hours. After this time the solution was concentrated in vacuo and then dissolved in petrol (20 ml). This mixture was dried (MgSO₄) and concentrated in vacuo to afford the title compound as a colourless oil (0.33 g, 77%); Rf 0.90 (petrol:ethyl acetate 9:1); δ_H (300 MHz; CDCl₃) 6.01 (1H, m, C(6)H₆), 5.79 (1H, m, C(5)H), 5.75 (1H, m, C(2)H), 5.08 (1H, m, C(1)H₆), 5.03 (2H, m, C(1)H₆), 3.64 (2H, t, J 6.0, C(4)H₂), 2.29 (2H, q, J 6.0, C(3)H₂), 0.19 (6H, s, 2 x CH₃); δ_C (75 MHz; CDCl₃) 139 (C(2)H), 137 (C(5)H), 135 (C(6)H₂), 119 (C(1)H₂), 65 (C(4)H₂), 39 (C(3)H₂), 0.0 (2 x CH₃); m/z (CI) 157 (MH⁺ 80%), 115 [(MH⁺ - C₂H₂O), 100]. All other data is in agreement with the literature values.¹⁰³
To a solution of dimethylchlorovinylsilane 141 (0.16 g, 1 mmol, 1 eq.) in degassed dry dichloromethane (10 ml) was added at solution of Grubbs II catalyst (0.04 g, 5 mol%) in degassed dry dichloromethane (5 ml) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred for 3 hours while being heated at reflux temperature. After this time the reaction was stirred for a further 17 hours at room temperature. Analysis of product mixture indicated only starting reagent 141.
Route Involving a Transetherification Strategy

**Attempted preparation of 4-vinyloxy-but-1-yne (151)**

\[ \text{71} \xrightarrow{1. \text{EVE, Hg(CF}_3\text{CO}_2)_2, \text{2. NaHCO}_3} \text{151} \]

\[
\begin{array}{c}
\text{C}_4\text{H}_8\text{O} \\
\text{Mol. Wt.: 70.09}
\end{array}
\]

To a solution of 3-butyn-1-ol (0.29 g, 4.18 mmol, 1 eq.) in ethyl vinyl ether (31.25 ml) was added mercuric(II) trifluoroacetate (0.18 g, 0.41 mmol, 0.1 eq.). The mixture was stirred at room temperature under an inert nitrogen atmosphere for 18 hours. After this time, the mixture was concentrated *in vacuo* to one third its volume and a solution of saturated sodium hydrogen carbonate solution (17.5 ml) was added. The aqueous layer was extracted with diethyl ether (3 x 30 ml) and the organic layers combined. After washing with deionised water (40 ml), the solution was dried (MgSO₄) and the solvent was removed by evaporation. Analysis of the product mixture by $^1$H NMR techniques indicated only the recovery of ethyl vinyl ether and unidentifiable compounds.

**Attempted preparation of 4-vinyloxybut-1-ene (152)**

\[ \text{71} \xrightarrow{1. \text{EVE}, (\text{CH}_3\text{CO}_2\text{)}_2\text{Hg}, \text{r.t.}, 2. \text{NaHCO}_3} \text{152} \]

\[
\begin{array}{c}
\text{C}_6\text{H}_{10}\text{O} \\
\text{Mol. Wt.: 98.14}
\end{array}
\]

To a solution of but-3-en-1-ol (0.43 g, 6 mmol, 1 eq.) in ethyl vinyl ether (10 ml, 0.6 mmol per 1 ml) was added mercuric(II) acetate (0.13 g, 0.4 mmol, 0.2 eq.) at room temperature under an atmosphere of nitrogen. The reaction mixture was stirred for 18
hours at room temperature. After this time the mixture was concentrated in vacuo and another portion of ethyl vinyl ether (10 ml) was added to the reaction vessel. After stirring the resultant solution for a further 20 hours, the solvent was again evaporated and another portion of ethyl vinyl ether (10 ml) was added. This cycle was repeated once more and then the reaction was quenched by the dropwise addition of triethylamine (3 ml). The mixture was partitioned between diethyl ether (20 ml) and dilute aqueous sodium hydrogen carbonate solution (20 ml). The organic layer was separated and washed with saturated sodium chloride solution (20 ml), dried (MgSO₄) and concentrated in vacuo. Analysis of the product by ¹H NMR spectroscopic techniques indicated only recovered 3-buten-1-ol and mercuric (II) acetate.

Z-4-Trimethylsilyl-1-vinylxybut-3-ene (117)

\[
\text{TMS-CH=CHCH=CH}_2\text{OH} \quad \begin{array}{c}1. \text{EVE, Catalyst a or b} \\ 2. \text{NaHCO}_3 \end{array} \quad \text{TMS-CH=CHCH=CH}_2\text{OSi} \\
\text{C}_7\text{H}_{16}\text{O} \quad \text{Mol. Wt.: 144.29} \\
\]

\[
\text{a. Hg(CF}_3\text{CO}_2\text{H} \\
b. Hg(CH}_3\text{CO}_2\text{H} \\
\]

To a solution of Z-trimethylsilylbut-3-en-1-ol (0.46 g, 3 mmol, 1 eq.) and ethyl vinyl ether (22.5 ml) at room temperature was added mercuric(II) trifluoroacetate (0.13 g, 0.6 mmol, 0.2 eq.). The reaction mixture was stirred under an inert nitrogen atmosphere for 18 hours at room temperature. After this time, the mixture was concentrated in vacuo to one third its volume and a solution of saturated sodium hydrogen carbonate solution (12.6 ml) was added. The aqueous layer was extracted with diethyl ether (3 x 30 ml) and the organic layers combined. After washing with deionised water (40 ml), the solution was dried (MgSO₄) and the solvent was removed by evaporation. Analysis of the product mixture by ¹H NMR and GCMS spectroscopic techniques indicated the formation of the title compound but separation was not achievable due to issues regarding the stability of
the vinyl group on silica. The following data is for the \textit{title compound} as a component of the product mixture with included some recovered starting materials; $\delta_{\text{H}}$ (300 MHz; CDCl$_3$) 6.46 (1H, dd, $J$ 14.3, 6.8, C(5)H), 6.30 (1H, dt, $J$ 14.1, 7.3, C(3)H), 5.64 (1H, d, $J$ 14.1, C(4)H), 4.20 (1H, dd, $J$ 14.3, 2.0, C(6)H$_a$), 3.99 (1H, dd, $J$ 6.8, 2.0, C(6)H$_b$), 3.70 (2H, t, $J$ 6.8, C(1)H$_2$), 2.50 (2H, q, $J$ 6.8, C(2)H$_2$), 0.15 (9H, s, 3 x CH$_3$); $m/z$ (CI) 171.2 [(MH)$^+$, 16%], 129.1 [(MH)$^+$-C$_2$H$_2$O], 103.1 [(MH)$^+$-C$_4$H$_4$O].

b. Using mercuric(II) acetate

To a solution of Z-trimethylsilylbut-3-en-1-0l (0.43 g, 3 mmol, 1 eq.) and ethyl vinyl ether (4.83 ml, 1.6 mmol per 1 ml) at room temperature was added mercuric(II) acetate (0.63 g, 0.2 mmol, 0.2 eq.). The reaction mixture was stirred vigorously for 23 hours at room temperature under an atmosphere of nitrogen. After this time the solution was concentrated \textit{in vacuo} and another portion of ethyl vinyl ether (4.12 ml) was added to the reaction mixture which was stirred for a further 23 hours. This cycle was repeated once more, after which the reaction was quenched by the dropwise addition of triethylamine (3 ml). Diethyl ether (20 ml) was added to the reaction mixture which was then washed with sodium hydrogen carbonate solution (20 ml), dried (MgSO$_4$) and concentrated \textit{in vacuo}. The product was filtered through a silica plug eluted with a dichloromethane:cyclohexane (3:1) system to give a clear oil which was purified by Kugelrohr distillation (65 °C, 10 mmHg) to give a mixture of 6-trimethylsilyl-3-vinyloxy-but-5-ene and unreacted Z-trimethylsilylbut-3-en-1-0l in a 4:1 ratio as a pale yellow oil (0.16 g, 24%); $R_f$ 0.48 (petrol:ethyl acetate 9:1); Found [M+H]$^+$ 171.1206; C$_9$H$_{19}$OSi [M+H]$^+$ requires 171.1205; $\nu_{\text{max}}$/cm$^{-1}$ (neat) 1602, 1640 (C=C), 1247 (Si-C); $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 6.46 (1H, dd, $J$ 14.4, 6.8, C(5)H), 6.29 (1H, dt, $J$ 14.0, 7.1, C(3)H), 5.65 (1H, d, $J$ 14.0, C(4)H), 4.18 (1H, dd, $J$ 14.4, 2.0, C(6)H$_a$), 3.99 (1H, dd, $J$ 6.8, 2.0, C(6)H$_b$), 3.71 (2H, t, $J$ 6.8, C(1)H$_2$), 2.50 (2H, q, $J$ 6.8, C(2)H$_2$), 0.15 (9H, s, 3 x CH$_3$); $\delta_{\text{C}}$ (100 MHz; CDCl$_3$) 151.8 (C(5)H), 143.7 (C(3)H), 132.6 (C(4)H), 86.5 (C(6)H$_2$), 67.4 (C(1)H$_2$), 33.0 (C(2)H$_2$), 0.1 (3 x CH$_3$); $m/z$ (CI) 171.1 [(MH)$^+$, 14%], 127.1 [(M)$^+$-C$_2$H$_2$O, 25].
Preliminary Mukaiyama-Aldol Silyl-Prins Reactions

Attempted preparation of (±)-1-(5,6-dihydro-2H-pyran-1-yl)-3-phenylpropan-2-ol (153)

\[
\begin{align*}
\text{Ph} & \quad \text{CHO} \\
\text{TMS} & \quad 73 \\
\text{Lewis acid a or b, CH}_2\text{Cl}_2, \text{r.t.} \\
\text{117} & \quad \text{153} \\
\end{align*}
\]

a. Using indium(III) chloride

To a solution of indium(III) chloride (0.33 g, 1.47 mmol, 1 eq.) in dry dichloromethane (15 ml) was added phenylacetaldehyde (0.19 ml, 1.47 mmol, 1 eq.). The reaction mixture was stirred for 1 hour at room temperature under an atmosphere of nitrogen. After this time (±)-Z-4-trimethylsilyl-1-vinyloxybut-3-ene 117 (0.25 g, 1.47 mmol, 1 eq.) was added and the mixture was stirred for a further 48 hours at room temperature. The reaction was subsequently quenched with the addition of distilled water (5 ml) and the aqueous layer was extracted with dichloromethane (40 ml). The combined organic extracts were dried (MgSO₄) and the solvent was removed by evaporation. The residue was purified by flash column chromatography (petrol:ethyl acetate 92:8). It was not possible to isolate the title compound, however GCMS analysis indicated its presence in the crude mixture: m/z (Cl) 218.13 [(MH⁺, 5%). The main compound isolated was (±)-2-benzyl-5,6-dihydro-2H-pyran (0.07 g, 36%) and the following data applies to this compound; Rf 0.58 (petrol:ethyl acetate 92:8); δH (300 MHz; CDCl₃) 7.18-7.30 (5H, m, Ar-H), 5.88 (1H, m, C(3)H), 5.67 (1H, dd, J 10.3, 1.7, C(4)H), 4.35 (1H, m, C(2)H), 4.03 (1H, m, C(6)H₆), 3.66 (1H, ddd, J 9.6, 5.6, 3.9, C(6)H₆), 2.97 (1H, dd, J 12.0, 6.0, PhCH₃), 2.78 (1H, dd, J 12.0, 6.0, PhCH₃), 2.28 (1H, m, C(5)H₆), 1.98 (1H, m, C(5)H₆); δC (100 MHz; CDCl₃) 129.0 – 127.7 (4 x Ar-H), 126.7 (C(3)H), 125.5 (C(4)H), 74.3
(C(2)H), 63.7 (C(6)H₂), 41.3 (PhCH₂), 24.7 (C(5)H₂); m/z (Cl) 175 [(MH)⁺, 100%], 157 [(MH)⁺-H₂O, 95].

b. Using titanium(IV) chloride

To a stirred solution of titanium(IV) chloride (0.15 ml, 1 M in toluene, 1.07 mmol, 1 eq.) in dry dichloromethane (9 ml) at -78 °C was added phenylacetaldehyde (1.36 ml, 1.07 mmol, 1 eq.). The solution was stirred for 1 hour under an atmosphere of nitrogen. After this time (±)-Z-4-trimethylsilyl-1-vinylbut-3-ene 117 (0.18 g, 1.07 mmol, 1 eq.) was added and the mixture was stirred at room temperature for a further 19 hours. The reaction was quenched with distilled water (5 ml) and the aqueous layer was extracted with dichloromethane (15 ml). The combined organic extracts were dried (MgSO₄) and the concentrated in vacuo. The residue was purified by flash column chromatography (petrol:ethyl acetate 92:8). In a similar way to the previous reaction, GCMS analysis indicated the presence of the desired compound; m/z (Cl) 220 [(MH₂)⁺, 3%]. The most abundant product appeared to be (±)-2-benzyl-5,6-dihydro-2H-pyran and the following data applies to that compound; m/z (Cl) 175 [(MH)⁺, 100%]. Analysis by ¹H NMR spectroscopic techniques also indicate the presence of this product supported by the data previously given.
Attempted preparation of (±)-1-(5,6-dihydro-2H-pyran-2-yl)-heptan-2-ol (154)

\[
\text{117} \xrightarrow{\text{Lewis acid a or b, } \text{CH}_2\text{Cl}_2, \text{r.t.}} \text{154}
\]

a. Using indium(III) chloride

To a solution of indium(III) chloride (0.36 g, 1.63 mmol, 1 eq.) in dry dichloromethane (20 ml) was added n-hexanal (0.20 ml, 1.63 mmol, 1 eq.) at room temperature under an atmosphere of nitrogen. The resultant solution was stirred for 1 hour after which time (±)-Z-4-trimethylsilyl-1-vinlyoxybut-3-ene 117 (0.18 g, 1.63 mmol, 1 eq.) was added. The reaction mixture was stirred at room temperature for 29 hours under a nitrogen atmosphere. After this time the reaction mixture was quenched with distilled water (5 ml) and the aqueous layer was extracted with dichloromethane (20 ml). The organic extracts were dried (MgSO₄) and concentrated in vacuo. The oil obtained was purified by flash column chromatography [gradient elution petrol:ethyl acetate (99:1)–(95:5)]. It was not possible to isolate the title compound 154, however GCMS analysis indicated its presence in the crude mixture: \( m/z \) (CI) 197 [(M-H)+, 10%]. The most abundant product was 2-pentyl-5,6-dihydro-2H-pyran 156 (0.01 g, 6%) and the following data applies to this compound: \( R_f \) 0.52 (petrol:ethyl acetate 97:3); \( \delta_H \) (400 MHz; CDCl₃) 5.82 (1H, m, C(3)H), 5.63 (1H, dt, \( J \) 10.2, 1.7, C(4)H), 4.05 (1H, m, C(2)H), 3.97 (1H, m, C(6)H₆), 3.65 (1H, dd, \( J \) 9.8, 5.2, 3.9, C(6)H₇), 2.27 (1H, m, C(7)H₆), 1.94 (2H, m, C(7)H₂), 1.29-1.54 (8H, overlapping 4 x CH₂), 0.87 (3H, m, CH₃); \( \delta_C \) (100 MHz; CDCl₃) 130.6 (C(3)H), 124.5 (C(4)H), 74.9 (C(2)H), 63.5 (C(6)H₂), 35.4, 31.9, 25.4, 24.9, 22.6 (4 x CH₂), 14.0 (CH₃); \( m/z \) (CI) 155 [(M+H)+, 100%], 137 [(M+H)+ -H₂O, 93]. There was also a significant amount of unreacted n-hexanal in the product mixture.
b. Using titanium(IV) chloride

To a stirred solution of titanium(IV) chloride (1.08 ml, 1 M solution in toluene, 1.08 mmol, 1 eq.) in dry dichloromethane (20 ml) at -78 °C was added n-hexanal (0.13 ml, 1.08 mmol, 1 eq.) under an atmosphere of nitrogen. The resultant solution was stirred for 1 hour at room temperature. After this time Z-4-trimethylsilyl-1-vinylxybut-3-ene 117 (0.18 g, 1.08 mmol, 1 eq.) was added and the reaction mixture was stirred for a further 19 hours at room temperature under an atmosphere of nitrogen. The reaction was quenched by the addition of distilled water (5 ml) and the aqueous layer was extracted with dichloromethane (20 ml). The organic extracts were dried (MgSO₄) and the solvent was removed by evaporation. GCMS analysis of the crude mixture indicated the presence of 1-(5,6-dihydro-2H-pyran-2-yl)-heptan-2-ol 154 but further purification was unable to isolate this product; m/z (CI) 197 [(M-H)⁺, 15%].
Synthesis of (±)-Centrolobine

**General Procedure for the Preparation of Epoxides Using Oxone®**

To a solution of acetone (40 ml), dichloromethane (30 ml), tetra-n-butylammonium hydrogen sulphate (0.06 eq.), aqueous di-sodium hydrogen orthophosphate (30 ml) and the alkene (1 eq.) at 0 °C was added Oxone® (4 eq.) in water (90 ml) over a period of 1 hour. During this time the pH was monitored using universal indicator paper and kept constant at pH 7.5-8.0 by the addition of potassium hydroxide solution (2 M). Upon completion of the addition the reaction mixture was stirred for 3 hours at 0 °C. The dichloromethane layer was separated and the aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo* to afford the epoxide, often with no further purification necessary.

4-Methoxystyrene oxide (218)

Following the general procedure for alkene epoxidation using Oxone®, the *title compound* was prepared using vinylanisole (0.50 g, 3.73 mmol), acetone (40 ml), dichloromethane (30 ml), tetra-n-butylammonium hydrogen sulfate (0.08 g, 0.22 mmol) di-sodium hydrogen orthophosphate solution (2 g in 30 ml distilled water) and Oxone® (9.142 g, 14.92 mmol). The *title compound* was isolated, without further purification as a pale yellow oil (0.60 g, 100%); Rₚ 0.16 (petrol:ethyl acetate 1:1); Found [M+H]^+ 151.0750; C₉H₁₀O₂ [M+H]^+ requires 151.0759; δH (300MHz; CDCl₃) 7.21 (2H, d, J 9.0, Ar-H), 6.91 (2H, d, J 9.0, Ar-H), 3.82 [overlapping (3H, s, (O)CH₃) and (1H, s, C(2)H)].
3.13 (1H, t, J 3.0 , C(1)H₆), 2.81 (1H, m, C(2)H₆); δC (75 MHz; CDCl₃) 160.1 [C(OCH₃)], 129.8 [C(C2)], 127.3 [2 x C(Ar)], 114.4 [2 x C(Ar)], 55.7 (OCH₃), 52.6 (C(2)H), 51.4 (C(1)H); m/z (CI) 151 [(M+H⁺), 100%], 121 [(MH⁺-OCH₃, 35]. All other data is in agreement with the literature values.¹⁹⁶

**Attempted preparation of 1-(4’-methoxyphenyl)-but-3-yn-1-ol (223)**

To a suspension of lithium acetylide-ethylenediamine complex (0.94 g, 9.31 mmol, 1.4 eq.) in dry DMSO (10 ml) at 0 °C was added a solution of 4-methoxystyrene oxide 218 (1.0 g, 6.65 mmol, 1 eq.) in dry DMSO (2 ml). The reaction was stirred at room temperature for 21 hours. After this time the reaction mixture was poured into water (50 ml). This mixture was separated into two layers and the aqueous layer was extracted with diethyl ether (4 x 20 ml). The combined organic extracts were washed with sodium chloride solution (50 ml), dried and concentrated *in vacuo*. Analysis of the crude residue indicated only recovered 4-methoxystyrene oxide 218 (91%).
n-Butyllithium (3.73 ml, 2.5 M in hexane, 9.32 mmol, 2.2 eq.) was added dropwise to a solution of trimethylsilylacetylene (1.17 ml, 8.4 mmol, 2 eq.) in toluene (30 ml) at -30 °C and stirred at this temperature for 30 minutes. After this time diethylaluminium chloride (9.33 ml, 1 M solution in hexane, 9.32 mmol, 2.2 eq.) was added and the solution was stirred for a further hour while being allowed to warm to 0 °C. The reaction was then cooled to -30 °C before a solution of 4-methoxystyrene oxide \( \text{218} \) (0.64 g, 4.42 mmol, 1 eq.) in toluene (10 ml) was added. The reaction was allowed to warm gradually to room temperature and was stirred for a further 19 hours. After this time the reaction was quenched by the addition of dilute sulfuric acid (10 ml) and stirred for a further 30 minutes at room temperature. The reaction mixture was then diluted by the addition of water (100 ml) and diethyl ether (100 ml), filtered through Celite and its layers separated. The aqueous layer was further extracted with diethyl ether (2 x 100 ml) and the combined organic layers were washed with brine (100 ml) and water (100 ml). The resultant extracts were then dried (MgSO₄), filtered and the solvent was removed \textit{in vacuo} to give a brown oil which was purified by flash column chromatography (petrol:diethyl ether 2:1) to afford the \textit{title compound} as a yellow oil (0.43 g, 24%); \( R_f \) 0.37 (petrol:diethyl ether 2:1): Found \([M]^+ \) 248.1226; \( C_{14}H_{20}O_2Si \) \([M]^+ \) requires 248.1233; \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) \( 3401 \) (O-H), 2172 (C=C); \( \delta_H \) (400 MHz; CDCl₃) 7.19 (2H, d, \( J 9.0 \), Ar-H), 6.85 (2H, d, \( J 9.0 \), Ar-H), 4.51 (1H, m, C(1)H), 3.79 (3H, s, OCH₃), 2.93 (2H, m, C(2)H₂), 1.81 (1H, d, \( J 6.0 \), OH), 0.16 (9H, s, 3 CH₃); \( \delta_C \) (75 MHz; CDCl₃) 159. (C\textsubscript{ipso} Ar(OCH₃), 131.1
Chapter 5

[overlapping 2 x C(Ar)], 131.1 (Cipso), 114.0 [overlapping 2 x C(Ar)], 63.7 (C(1)H), 55.5 (C(OCH3), 43.3 (C(2)H2), 0.1 (3 x CH3); m/z (CI) 249 [(MH)+, 3%], 231 [(MH)+ - H2O, 32], 151 [(MH)+ - C5H5Si, 100].

(±)-4-Trimethylsilyl-1-phenylbut-3-yn-1-ol (231)\(^{197}\)

\[
\begin{array}{c}
\text{TMS} \rightarrow \text{C} = \text{C} \rightarrow \text{TMS} \\
\text{OH} \\
\end{array}
\]

\(230\)

\(C_{13}H_{18}O\)

\(\text{Mol. Wt.: } 218.37\)

\[
\begin{array}{c}
\text{TMS} \rightarrow \text{C} = \text{C} \rightarrow \text{TMS} \\
\text{OH} \\
\end{array}
\]

\(231\)

\(C_{13}H_{18}OSi\)

\(\text{Mol. Wt.: } 218.37\)

\[
\begin{array}{c}
\text{TMS} \rightarrow \text{C} = \text{C} \rightarrow \text{TMS} \\
\text{OH} \\
\end{array}
\]

\(232\)

\(C_{13}H_{18}O\)

\(\text{Mol. Wt.: } 218.37\)

\(n\)-Butyllithium (4.07 ml, 2.5 M in hexane, 10.18 mmol, 2.2 eq.) was added dropwise to a solution of trimethylsilylacetylene (0.74 ml, 5.23 mmol, 1.2 eq.) in dry THF (31 ml) at -78 °C under an inert atmosphere of nitrogen. After stirring the solution for 30 minutes, a solution of styrene oxide (0.53 g, 4.36 mmol, 1 eq.) in dry THF (5 ml), followed by boron trifluoride etherate (0.76 g, 5.23 mmol, 1.2 eq.) was added at a rate which ensured the internal temperature of the flask did not rise above -65 °C. The resultant solution was stirred at -78 °C for 1 hour and then poured on to a saturated ammonium chloride solution (64 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 100 ml). The combined organic extracts were dried (MgSO\(_4\)) and concentrated in vacuo to afford the title compound and its regioisomer 232 in a 53:47 ratio which could not be separated: (±)-4-Trimethylsilyl-1-phenylbut-3-yn-1-ol: m/z (CI) 219 [(MH)+, 3%], 201 [(MH)+ - H2O, 100].

(±)-4-Trimethylsilyl-2-phenylbut-3-yn-1-ol: m/z (CI) 219 [(MH)+, 6%], 201 [(MH)+ - H2O, 29], 129 [(MH)+ - CH3SiOH, 100].

189
Following the general procedure for the reduction of trimethylsilylalkynes (p. 153), the title compound was prepared using 4-trimethylsilyl-1-(4-methoxyphenyl)-but-3-yn-1-ol 219 (0.435 g, 1.75 mmol) and DIBAL-H (5.26 ml, 1 M solution in hexane, 5.26 mmol). Without further purification, the title compound was isolated as a yellow oil (0.238 g, 54%); Rf 0.56 (petrol:diethyl ether 1:1); Found [M+NH₄]⁺ 268.1730; C₁₄H₂₂O₂Si [M+NH₄]⁺ requires 268.1727; νmax/cm⁻¹ (neat) 3412 (O-H), 1612 (C=C), 1248 (Si-C); δH (400 MHz; CDCl₃) 7.15 (2H, d, J 9.0, Ar-H), 6.85 (2H, d, J 9.0, Ar-H), 6.30 (1H, dt, J 14.2, 8.7, C(3)H), 5.68 (1H, d, J 14.2, C(4)H), 4.40 (1H, m, C(1)OH), 3.79 (3H, s, OCH₃), 2.76 (2H, m, C(2)H₂), 0.10 (9H, s, 3 x CH₃); δC (100 MHz; CDCl₃) 158.4 [Cipso(OCH₃)], 148.9 (C(3)H), 132.1 (C(4)H), 130.5 [overlapping 2 x C(Ar)], 129.58 (Cipso) 114.0 [overlapping 2 x C(Ar)], 73.3 (C(1)H), 55.3 (OCH₃), 43.0 (C(2)H₂), 0.3 (3 x CH₃); m/z (Cl) 251 [(MH)⁺, 2%], 233 [(MH)⁺-H₂O, 100].
3-[4-(Benzyloxy)phenyl]-1-propanol (220)

\[
\text{\begin{align*}
\text{C}_9\text{H}_{12}\text{O}_2 & \quad \text{Mol. Wt.: 152.19} \\
\text{C}_{16}\text{H}_{18}\text{O}_2 & \quad \text{Mol. Wt.: 242.31}
\end{align*}}
\]

A solution of 3-(4-hydroxyphenyl)-1-propanol (0.5 g, 3.29 mmol, 1 eq.) in DMF (5 ml) was added dropwise over 30 minutes to a stirred suspension of sodium hydride (0.18 g, 60% by weight, 4.93 mmol, 1.5 eq.) in DMF (5 ml) under nitrogen at room temperature. The resulting solution was stirred until gas evolution ceased and was then heated to 80 °C. After 20 minutes benzyl bromide (0.56 g, 3.29 mmol, 1 eq.) was added and the reaction mixture was heated to reflux temperature for 20 hours. The solution was then cooled, poured into distilled water (50 ml) and extracted with diethyl ether (3 x 25 ml). The combined organic phases were washed with two portions of sodium hydroxide solution (2 M), followed by extraction with brine (20 ml). The organic extracts were then dried (MgSO₄), filtered and concentrated in vacuo. After drying in a desiccator the title compound was isolated as a white solid (0.79 g, 100%); Rₚ 0.12 (petrol:diethyl ether 1:1); M.p. 59.5-61.5 °C; \( \delta_H \) (300 MHz; CDCl₃) 7.31-7.45 (5H, s, OCH₂Ph-H), 7.14 (2H, d, J 6.0, Ar-H), 6.90 (2H, d, J 6.0, Ar-H), 5.06 (2H, s, PhCH₂O), 3.67 (2H, m, ArCH₂CH₂OH), 2.66 (2H, t, J 6.0, ArCH₂), 1.87 (2H, m, ArCH₂CH₂), 1.23 (1H, m, OH). All other data is in agreement with literature values.¹⁷³
Dimethyl sulfoxide (0.457 g, 5.85 mmol, 2.2 eq.) was added to a solution of oxalyl chloride (0.25 ml, 2.93 mmol, 1.1 eq.) in dry dichloromethane (50 ml) at -78 °C under an atmosphere of nitrogen. The reaction mixture was stirred at this temperature for 10 minutes. After this time a solution of 3-[4-(benzyloxy)phenyl]-1-propanol 220 (0.645 g, 2.66 mmol, 1 eq.) in dry dichloromethane (5 ml) was added dropwise. The reaction mixture was then stirred for a further 15 minutes at -78 °C whereupon triethylamine (1.85 ml, 13.3 mmol, 5 eq.) was slowly added and the reaction was allowed to warm to room temperature over 30 minutes. The reaction was then quenched by the addition of saturated ammonium chloride solution (15 ml) and the aqueous phase washed with dichloromethane (2 x 40 ml). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (2 x 20 ml) and sodium chloride solution (2 x 20 ml). The resulting extracts were dried (MgSO₄), filtered and the filtrate was evaporated in vacuo to give a light brown oil. Filtration of this oil through silica gel, washing with dichloromethane (40 ml) yielded the title compound as a clear oil (0.496 g, 78%) which solidified on standing; R_f 0.28 (petrol:ethyl acetate); δ_H (300 MHz; CDCl₃) 9.82 (1H, s, CHO), 7.34-7.44 (5H, m, OCH₂Ph-H), 7.09 (2H, d, J 6.0, Ar-H), 6.92 (2H, d, J 6.0, Ar-H), 5.04 (2H, s, Ph-CH₂O), 2.91 (2H, t, J 9.0, Ar-CH₂), 2.76 (2H, t, J 9.0, Ar-CH₂CH₂); m/z (Cl) 240 [(M)+, 49%], 197 [(MH)⁺-CH₂=CHOH⁺, 100]. All other data is in agreement with the literature values.¹⁷³
Attempted preparation of 2-[2-(4-benzyloxyphenyl)-ethyl]-6-(4'-methoxyphenyl)-5,6-dihydro-2H-pyran (191)

An attempt was made to prepare the title compound using the general procedure for the silyl-Prins cyclisation (p. 155) using 3-[(benzyloxy)phenyl]-1-propanal 190 (0.15 g, 0.64 mmol, 2 eq.), indium(III) chloride (0.14 g, 0.64 mmol, 2 eq.) and Z-4-trimethylsilyl-1-(4'-methoxyphenyl)-but-3-en-1-ol 189 (0.08 g, 0.32 mmol, 1 eq.) in dry dichloromethane (10 ml). The crude mixture was purified by flash column chromatography (petrol:diethyl ether 7:3) but although a small quantity of 2-[2-(4-benzyloxyphenyl)-ethyl]-6-(4'-methoxyphenyl)-5,6-dihydro-2H-pyran may have been present according to $^1$H NMR analysis it was not possible to isolate it from other reaction by-products.
Attempted preparation of 2-pentyl-6-(4'-methoxyphenyl)-5,6-dihydro-2H-pyran (236)

An attempt was made to prepare the title compound using the general procedure for the silyl-Prins cyclisation (p. 155) using n-hexanal (0.04 g, 0.40 mmol, 1 eq.), indium(III) chloride (0.08 g, 0.40 mmol, 1 eq.) and Z-4-trimethylsilyl-1-(4'-methoxyphenyl)-but-3-en-1-ol 189 (0.10 g, 0.40 mmol, 1 eq.) in dry dichloromethane (6 ml). Analysis of the product mixture by $^1$H NMR spectroscopic techniques indicates only the presence of starting reagents and unidentifiable compounds.

2-[2-(4'-Benzyloxy-phenyl)ethyl]-4-chlorotetrahydropyran (239)

Indium(III) chloride (0.14 g, 0.63 mmol, 1 eq) was added to a solution of 3-[benzyloxy)phenyl]-1-propanal 190 (0.15 g, 0.63 mmol, 1 eq.) dissolved in dry dichloromethane (10 ml) under an atmosphere of nitrogen and the resulting solution was stirred for 1 hour. After this time, 3-buten-1-ol (0.05 g, 0.63 mmol, 1 eq.) was added and
the reaction mixture was stirred vigorously at room temperature for 57 hours. The reaction mixture was then quenched with distilled water (10 ml) and the water layer extracted with dichloromethane (40 ml). The combined organic extracts were dried (MgSO₄) and the solvent was removed in vacuo. The product was purified by flash column chromatography (petrol:diethyl ether 6:4) to afford the title compound as a mixture of diastereoisomers (cis:trans 95:5) as a yellow oil (0.06 g, 31%). The following data applies to the cis diastereoisomer; Rf 0.81 (petrol:diethyl ether 6:4); Found [M+NH₄]⁺ 348.1725; C₂₀H₂₃ClO₂ [M+NH₄]⁺ requires 348.1726; νmax/cm⁻¹ (neat) 3031 [Ar(C-H)], 2953, 2854 (OCH₃), 1240 (C-O), 738 (C-Cl); δH (300 MHz; CDCl₃) 7.34-7.47 (5H, m, Ar-H), 7.11 (2H, d, J 9.0, Ar-H), 6.93 (2H, d, J 9.0, Ar-H), 5.06 (2H, s, PhCH₂OCH₂), 4.02 (2H, m, C(6)H₂), 3.45 (1H, m, C(4)H), 3.26 (1H, m, C(2)H), 2.68 (2H, m, ArCH₂), 2.12 (2H, m, C(5)H₂), 1.88 (2H, m, ArCH₂CH₂), 1.66 (2H, m, C(3)H); δC (100 MHz; CDCl₃) 157.5 (CipsoOBn), 134.5 (CipsoCH₂), 129.8 [2 x C(Ar)], 129.0 [2 x C(Ar)], 128.3 [C(Ar)], 127.9 [2 x C(Ar)], 115.2 [2 x C(Ar)], 77.6 (ArCH₂O), 70.4 (C(2)H), 67.4 (C(6)H), 56.2 (C(4)H), 43.2 (C(3)H), 38.2 (ArCH₂CH₂), 37.5 (C(5)H), 31.0 (ArCH₂CH₂); m/z (Cl) 333 [M(³⁷Cl)⁺, 30%], 331 [M(³⁵Cl)⁺, 100%], 241 [MH(³⁷Cl)⁺, -C₇H₈, 9] 241 [MH(³⁵Cl)⁺-C₇H₈, 41].

The trans diastereoisomer was indicated in trace amounts by GCMS analysis but could not be isolated.
Towards the Synthesis of Kendomycin - Approach 1a

2,4-Dimethoxy-3-methylphenol (250)

\[
\begin{align*}
\text{249} & \quad \text{C}_{10}\text{H}_{12}\text{O}_3 \\
\text{Mol. Wt.:} & \quad 180.20
\end{align*}
\]

\[
\begin{align*}
\text{250} & \quad \text{C}_{9}\text{H}_{12}\text{O}_3 \\
\text{Mol. Wt.:} & \quad 168.19
\end{align*}
\]

*meta*-Chloroperbenzoic acid (2.53 g, 15 mmol, 1 eq.) was added to a solution of 2,4-dimethoxy-3-methylbenzaldehyde (1.80 g, 10 mmol, 1 eq.) in dry dichloromethane (50 ml) under an inert atmosphere of nitrogen. The resulting solution was stirred vigorously for 42 hours at room temperature. After this time the reaction was quenched with the addition of dilute sodium sulfite solution (100 ml). The layers were separated and the organic layer was washed with sodium hydrogen carbonate (50 ml). The organic extracts were then dried (MgSO\(_4\)), filtered and the solvent was removed *in vacuo* to afford formic acid 2,4-dimethoxy-3-methyl-phenyl ester (1.72 g, 88%) which was used in the next step without further purification. \(\delta\)\(_H\) (300 MHz; CDCl\(_3\)) 8.28 (1H, s, CHO), 6.92 (1H, d, \(J\) 9.0, Ar-H), 6.62 (1H, d, \(J\) 9.0, Ar-H), 3.83 (3H, s, OCH\(_3\)), 3.74 (3H, s, OCH\(_3\)). 2.17 (3H, s, CH\(_3\)). Formic acid 2,4-dimethoxy-3-methyl-phenyl ester (1.72 g, 8.77 mmol) was dissolved in methanol (10 ml) and added to a 10% solution of aqueous potassium hydroxide (10 ml) at room temperature. The resulting solution was acidified with 2 M H\(_2\)SO\(_4\) (50 ml) and extracted with dichloromethane (3 x 50 ml). The organic extracts were then washed with sodium hydrogen carbonate solution (100ml), dried (MgSO\(_4\)) and concentrated *in vacuo* to afford a yellow oil (1.36 g, 81%); R\(_f\) 0.38 (petrol:ethyl acetate 9:1); \(\delta\)\(_H\) (300 MHz; CDCl\(_3\)) 6.75 (1H, d, \(J\) 9.0, Ar-H), 6.55 (1H, d, \(J\) 9.0, Ar-H), 3.87 (6H, s, 2 x OCH\(_3\)), 2.17 (3H, s, CH\(_3\)); \(m/z\) (CI) 168 [(MH\(^+\), 100%), 153 [(MH\(^+\)-CH\(_3\), 91]. All other data is in agreement with the literature values.\(^{198}\)
2-Hydroxy-3,5-dimethoxy-4-methylbenzaldehyde (251)

Hexamethylenetetramine (HMTA) (9.34 g, 66.6 mmol, 6.1 eq.) was added to a boiling solution of 2,4-dimethoxy-3-methylphenol 250 (1.82 g, 10.8 mmol, 1 eq.) in acetic acid (65 ml). The reaction mixture was heated to reflux temperature whilst stirring for 19 hours. The solution was diluted with distilled water (150 ml) and extracted with dichloromethane (3 x 100 ml). The organic extracts were then washed with 5% aqueous sodium hydrogen carbonate solution (100 ml) and water (100 ml). The mixture was dried (MgSO₄), filtered and concentrated in vacuo. The solid product was purified by flash column chromatography (dichloromethane:hexane 9:1) to isolate the title compound as a yellow solid (0.42 g, 20%); Rf 0.35 (petrol:ethyl acetate 9:1); δH (300 MHz; CDCl3) 10.87 (1H, s, OH), 9.82 (1H, s, CHO), 6.70 (1H, s, Ar-H), 3.88 (3H, s, OCH₃), 3.84 (3H, s, OCH₃), 2.22 (3H, s, CH₃); δC (75 MHz, CDCl3) 196.1 (CHO), 151.6 (CipsO), 150.4 (CipsO), 147.2 (CipsO), 131.7 (CipsO), 118.5 (CipsO), 107.4 [C(Ar)], 60.7 (ArOCH₃), 56.31 (ArOCH₃), 10.3 (Ar-CH₃); m/z (CI) 196 [(M)+, 54%], 181 [(M)+ -CH₃, 100]. All other data is in agreement with the literature values.¹\(^\text{175}\)
**Formic acid 2,4-dimethoxy-3-methylphenyl ester (253)**

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{OMe} & \quad \text{Me} \\
\text{249} & \quad \text{C}_{10}\text{H}_{12}\text{O}_{3} \\
\text{Mol. Wt.: 180.20} \\
\text{mCPBA} & \quad \text{CH}_2\text{Cl}_2, \text{r.t.} \\
\text{253} & \quad \text{C}_{10}\text{H}_{12}\text{O}_{4} \\
\text{Mol. Wt.: 196.20}
\end{align*}
\]

Meta-Chloroperbenzoic acid (5.06 g, 30 mmol, 1.5 eq.) was added to a solution of 2,4-dimethoxy-3-methylbenzaldehyde (3.60 g, 20 mmol, 1 eq.) in dry dichloromethane (100 ml) under an atmosphere of nitrogen. The resulting solution was stirred vigorously for 48 hours at room temperature. After this time the reaction was quenched with the addition of dilute sodium sulfite solution (100 ml). The layers were separated and the organic layer was washed with sodium hydrogen carbonate (100 ml). The combined organic extracts were then dried (MgSO₄), filtered and the solvent was removed in vacuo to afford the title compound as a yellow oil (3.76 g, 96%); δ₉ (300 MHz; CDCl₃) 8.28 (1H, s, CHO), 6.92 (1H, d, J 9.0, Ar-H), 6.62 (1H, d, J 9.0, Ar-H), 3.83 (3H, s, OCH₃), 3.74 (3H, s, OCH₃), 2.17 (3H, s, CH₃); m/z (Cl) 197 [(MH⁺, 74%)], 168 [(MH⁺ - CHO, 100)]. All other data is in agreement with literature values.¹³⁴

**Attempted preparation of 2-hydroxy-3,5-dimethoxy-4-methylbenzaldehyde (251)**

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{OMe} & \quad \text{Me} \\
\text{253} & \quad \text{C}_{10}\text{H}_{12}\text{O}_{4} \\
\text{Mol. Wt.: 196.20} \\
\text{BCl₃} & \quad \text{DCE} \\
\text{251} & \quad \text{C}_{10}\text{H}_{12}\text{O}_{4} \\
\text{Mol. Wt.: 196.20}
\end{align*}
\]

To a stirred solution of formic acid 2,4-dimethoxy-3-methylphenyl ester 253 (1.00 g, 5.10 mmol, 1 eq.) in dry dichloroethane at 0 °C was added boron (III) chloride (6.4 ml, 1 M
solution in dichloromethane, 6.38 mmol, 1.2 eq.). The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 4 hours. After this time the reaction was heated to reflux temperature and stirred for a further 42 hours. The reaction was quenched by the dropwise addition of distilled water (15 ml), the solution filtered through Celite and the aqueous layer was separated from the organic layer. The aqueous layer was extracted with dichloromethane (10 ml), the organic extracts dried (MgSO₄) and concentrated in vacuo. Analysis of the product by ¹H NMR spectroscopic techniques indicated only the presence of unidentifiable compounds.

2,3,5-Trimethoxy-4-methylbenzaldehyde (252)

Methyl iodide (9.41 g, 66.3 mmol, 31 eq.) was added to a solution of 2-hydroxy-3,5-dimethoxy-4-benzaldehyde 251 (0.42 g, 2.14 mmol, 1 eq.) in 15% KOH solution (4 ml). The reaction mixture was heated at reflux temperature for 138 hours. After this time the mixture was cooled to room temperature and extracted with dichloromethane (2 x 15 ml). The organic extracts were then washed with 15% KOH solution, dried (MgSO₄), filtered and concentrated in vacuo to afford a yellow oil (0.27 g, 60%). The product was used in the next step without further purification; Rf 0.36 (petrol:ethyl acetate 9:1). δH (300 MHz; CDCl₃) 10.33 (1 H, s, ArCHO), 7.02 (1H, s, Ar-H), 3.94 (3H, s, ArOCH₃), 3.84 (3H, s, ArOCH₃), 3.83 (3H, s, ArOCH₃), 2.18 (3H, s, ArCH₃); m/z (Cl) 210 [(M)+, 32%], 195 [(M)+-CH₃, 100]. All other data is in agreement with the literature values.¹⁹⁹
A solution of 2,3,5-trimethoxy-4-methylbenzaldehyde 252 (0.27 g, 1.28 mmol, 1 eq.) in dichloromethane (5 ml) was treated with anhydrous potassium carbonate (0.29 g, mmol, 2 eq.) and then cooled to -10 °C. Bromine (0.13 ml, 2.56 mmol, 2.2 eq.) was slowly added and the reaction mixture was warmed to 0 °C and stirred for 2 hours. After this time the reaction was stirred for another 19 hours at room temperature. The reaction mixture was cooled to 0 °C and quenched with the addition of a 1:1 (v/v) mixture of 10% Na₂S₂O₃ and 10% NaHCO₃ aqueous solutions (10 ml). After warming to room temperature, the aqueous phase was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petrol: diethyl ether 9:1). GCMS data indicates the presence of some of the title compound; m/z (Cl) 291.1 [(MH)⁺(Br 81), 40%], 289.1 [(MH)⁺(Br 79), 42].

The most abundant product, as indicated by literature precedent, appeared to be 2-bromo-6-hydroxy-3,5-dimethoxy-4-methyl-benzaldehyde 253 which was isolated as a yellow solid (0.24 g, 65%) and the following data applies to this compound; Rf 0.50 (petrol:diethyl ether 9:1); M.p. 94-96 °C (Lit., mp 95-96 °C); δH (300 MHz; CDCl₃) 10.31 (1H, s, CHO), 3.88 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 2.31 (3H, s, CH₃); δC (75 MHz; CDCl₃) 198.2 (CHO), 155.6-115.8 [6 x C(Ar)], 61.1 (OCH₃), 60.6 (OCH₃), 11.5 (CH₃); m/z (Cl) 277 [(M-H)⁺(Br 81), 41%], 274 [(M-H)⁺(Br 79), 100%], 232.8 [(M-H)⁺-C₃H₇, 60], 230.8 [(M-H)⁺-C₃H₇, 65] 195.9 [(M)⁺-Br, 52].
Indium(III) chloride (0.48 g, 2.04 mmol, 4 eq.) was added to a solution of 2-bromo-6-hydroxy-3,5-dimethoxy-4-methylbenzaldehyde 254 (0.15 g, 0.52 mmol, 1 eq.) dissolved in dry dichloromethane (5 ml). The resulting solution was stirred at room temperature for 1 hour. After this time the 3-buten-1-ol (0.04 g, 0.52 mmol, 1 eq.) was added and the reaction was allowed to proceed for 65 hours. The reaction was quenched with the addition of distilled water (10 ml). This mixture was then extracted with dichloromethane (3 x 10 ml). The organic extracts were dried (MgSO₄) and concentrated in vacuo to afford a brown residue which was purified by column chromatography (1:1 petrol:diethyl ether) to afford the title compound as two diastereoisomers: cis:trans = 1:1.2 (18%). The remainder of the product mixture was recovered starting materials.

**Cis:** (0.015 g, 8%); δH (300 MHz; CDCl₃) 8.40 (1H, s, OH), 5.02 (1H, d, J 12.0, C(2)H), 4.28 (1H, m, C(6)H₃), 4.15 (1H, m, C(4)H), 3.84 (3H, s, ArOCH₃), 3.72 (3H, s, ArOCH₃), 3.62 (1H, d, J 12.0, C(6)H₆), 2.38 (1H, dd, J 12.0, 3.0, C(3)H₂), 2.23 (3H, s, ArCH₃), 2.23 (1H, m, C(3)H₆), 2.02 (2H, q, J 9.0, C(5)H₂); δC (75 MHz; CDCl₃) 111.1-148.8 (6 x Cipso), 81.7 (C(2)H), 68.3 (C(6)H₆), 60.8 (OCH₃), 60.5 (OCH₃), 54.4 (C(4)H), 41.0 (C(3)H₂), 36.9 (C(5)H₂), 10.6 (ArCH₃); m/z (Cl) 366 [(MH)⁺, 100%].

**Trans:** (0.02 g, 10%); Rf 0.23 (hexane:ethyl acetate 9:1); Found [M]⁺ 365.0155: C₁₄H₁₄BrClO₄ [M]⁺ requires 365.0150; νmax/cm⁻¹ (neat) 3301 (OH), 1450, 1419 (C=C), 1095 (C-O); δH (300 MHz; CDCl₃) 8.59 (1H, s, OH), 5.57 (1H, m, C(2)H), 4.65 (1H, m, C(4)H), 4.18 (2H, m, C(6)H), 3.81 (3H, s, ArOCH₃), 3.71 (3H, s, ArOCH₃), 2.24 (3H, s, ArCH₃), 2.24 (2H, m, C(3)H), 2.24 (1H, m, C(5)H₃), 1.94 (1H, d, J 15.0, C(5)H₆); δC (75
MHz; CDCl₃) 148.8 (C ipso), 146.9 (overlapping C ipso), 126.6 (C ipso), 122.8 (C ipso), 111.2 (C ipso), 76.8 (C(2)H), 63.9 (C(6)H₂), 60.8 (OCH₃), 60.5 (OCH₃), 55.6 (C(4)H), 37.6 (C(3)H₂), 33.6 (C(5)H₂), 10.5 (ArCH₃); m/z (Cl) 366 [(MH)⁺, 31%], 285 [(MH)⁺-Br, 95].

Towards the Synthesis of Kendomycin - Approach 1b

3,4,5-Trimethoxybenzaldehyde dimethylacetal (260)

To a solution of 3,4,5-trimethoxybenzaldehyde (2.34 g, 12 mmol, 1 eq.) in anhydrous methanol (30 ml) and dry dichloromethane (30 ml) was added trimethyl orthoformate (7.8 ml, 72 mmol, 6 eq.) and camphorsulfonic acid (0.74 g, 3.92 mmol, 3.92 eq.) under an atmosphere of nitrogen. After stirring for 48 hours at room temperature the reaction was quenched by the addition of triethylamine (2.7 ml) and concentrated in vacuo. The residue was recrystallised from dichloromethane to afford the title compound as white crystals (2.88 g, 100%); Rf 0.28 (hexane: ethyl acetate 9:1); M.p. 47-48 °C (No lit. mp recorded). Found [M⁺] 242.1147; C₁₂H₁₆O₅ [M⁺] requires 242.1149; ν max/cm⁻¹ (nujol) 1603 (C=C), 1132 (C-O); δH (300 MHz; CDCl₃) 6.67 (2H, s, 2 x Ar-H), 5.28 (1H, s, ArCH(OCH₃)₂), 3.85 (6H, s, 2 x ArOCH₃), 3.83 (3H, s, ArOCH₃), 3.35 (6H, s, 2 x ArCH(OCH₃)₂); δC (100 MHz, CDCl₃) 153.6 [2 x C(Ar)], 134.2 (2 x C ipso), 103.9 [C(OCH₃)₂], 103.6 [2 x C(Ar)] 61.2 (ArOCH₃), 56.5 (2 x ArOCH₃) 53.3 [2 x C(OCH₃)₂]; m/z 242 [(M⁺, 17%], 211 [(M⁺- OCH₃]. All other data is agreement with the literature values.¹⁸³
3,5-Dimethoxy-4-methylbenzaldehyde (262)

A solution of 3,4,5-trimethoxybenzaldeyde dimethylacetal 261 (0.43 g, 1.76 mmol, 1 eq.) in anhydrous THF (2.2 ml) was added to a mixture of freshly cut sodium (0.13 g, 5.38 mmol, 3.06 eq.) in THF (7 ml) chilled at 0 °C under an atmosphere of nitrogen. The reaction was stirred vigorously at room temperature for 20 hours. After this time the reaction mixture was cooled to 0 °C and methyl iodide (0.37 g, 2.58 mmol, 1.47 eq.) added. The reaction was allowed to continue for a further 48 hours. The reaction was then quenched by the dropwise addition of distilled water (5 ml). This was followed by the addition of diethyl ether (10 ml) and the layers separated. The organic layer was washed with water (10 ml) and the solvent was removed by evaporation. The resultant product was dissolved in a 1:1 solution of THF/1 M HCl (10 ml) and stirred at room temperature for 4 hours. The mixture was then extracted with diethyl ether (3 x 10 ml) and the organic extracts washed with water (2 x 20 ml), dried (MgSO₄) and concentrated in vacuo. The crude product was purified by flash column chromatography (petrol:ethyl acetate 8:2) to afford the title compound as a white solid (0.02 g, 5%); Rₓ 0.24 (hexane:ethyl acetate 9:1); M.p. 67-70 °C (from petrol:ethyl acetate) (lit.,¹⁸³ mp 93-94°C); δₓ (300 MHz; CDCl₃) 9.90 (1H, s, CHO), 7.03 (2H, s, 2 x Ar-H), 3.89 (6H, s, 2 x ArOCH₃), 2.15 (3H, s. ArCH₃); δₓ (100.6 MHz, CDCl₃) 190.6 (CHO), 103.3 [2 x C(Ar)], 54.2 (2 x ArOCH₃), 7.6 (ArCH₃). All other data is in agreement with literature values.¹⁸³
A solution of (-)-β-citronellene (1.31 ml, 7.23 mmol, 1 eq.) in dry dichloromethane (5 ml) was added dropwise to a vigorously stirred solution of meta-chloroperbenzoic acid (1.78 g, 8.67 mmol, 1.2 eq.) and sodium hydrogen carbonate (1.21 g, 14.4 mmol, 2 eq.) in dry dichloromethane (38 ml) under nitrogen at 0 °C. After 45 minutes the reaction was stopped with the addition of sodium hydrogen carbonate solution (50 ml). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 50 ml). The combined organic extracts were washed with sodium hydrogen carbonate solution (2 x 50 ml) and water (50 ml). The extracts were dried (MgSO₄) and concentrated in vacuo to afford a clear oil which was used in the next step without further purification. (1.20 g, 100%); Rf 0.13 (petrol:ethyl acetate 9:1); δH (270 MHz; CDCl₃) 5.66 (1H, m, C(2)H), 4.93 (2H, m, C(1)H), 2.68 (1H, t, J 5.4, C(6)H), 2.13 (1H, m, C(3)H), 1.49 (2H, m, C(5)H₂), 1.31(2H, m, C(4)H₂), 1.29 (3H, s, C(7)CH₃), 1.24 (3H, s, C(7)CH₃), 1.00 (3H, d, J 7.6, C(3)CH₃); δc (100 MHz; CDCl₃) 144.1 (C(1)H₂), 113.6 (C(2)H), 64.2 (C(6)H), 37.9 (C(3)H), 33.5 (C(4)H₂), 26.8 (C(5)H₂), 25.5 (2 x CH₃), 20.1 (CH₃). All other data is in agreement with the literature values.188
(R)-4-Methyl-5-hexenal (247)

To a solution of 1,1-dimethyl-2(3-(R)-3-methyl-pent-4-enyl)oxirane 266 (1.93 g, 12.5 mmol, 1 eq.) in dry diethyl ether (50 ml) was added periodic acid (3.42 g, 15 mmol, 1.2 eq.) under a nitrogen atmosphere. The reaction mixture was stirred vigorously for 19 hours at room temperature. After this time the colourless mixture was filtered through Celite and washed with saturated sodium hydrogen carbonate (50 ml) and sodium thiosulfate solutions (50 ml). The combined ethereal extracts were extracted with diethyl ether (30 ml), dried (MgSO₄) and filtered. The diethyl ether was then carefully removed using a controlled pressure rotary evaporator (25 °C, 300 mmHg) to afford the title compound as a clear oil (0.74 g, 53%); Rf 0.19 (petrol:ethyl acetate 9:1); δH (270 MHz; CDCl₃) 9.75 (1H, t, J 2.7, CHO), 5.60 (1H, m, C(5)H), 4.94 (1H, d, J 5.4, C(6)H₆), 4.92 (1H, s, C(6)H₆), 2.40 (2H, t, J 1.7, C(2)H₂), 2.14 (1H, m, C(4)H), 1.64 (2H, m, C(3)H₂). 0.99 (3H, d, J 5.4, CH₃); δC (100 MHz; CDCl₃) 202.6 (CHO), 143.3 (C(5)H), 113.9 (C(6)H₂), 41.9 (C(2)H₂), 37.5 (C(4)H), 28.2 (C(3)H₂), 20.2 (CH₃). All other data is in agreement with the literature values.¹⁸⁸
The title compound was prepared according to the general procedure for the silyl-Prins cyclisation (p. 155), using (R)-4-methyl-5-hexenal 247 (0.09 g, 0.84 mmol), indium(III) chloride (0.19 g, 0.84 mmol) and (±)-Z-5-trimethylsilylpent-4-en-2-ol 67 (0.13 g, 0.84 mmol) in dry dichloromethane (10 ml), and isolated by flash column chromatography (petrol:ethyl acetate 85:15) as a yellow oil (0.03 g, 20%); Rf 0.95 (petrol:ethyl acetate 85:15) δH (300 MHz; CDCl₃) 5.74 (1H, m, C(3)H), 5.65 (1H, m, C(10)H), 5.61 (1H, m, C(4)H), 4.91 (2H, m, C(11)H₂), 4.07 (1H, m, C(2)H), 3.64 (1H, m, C(6)H), 2.12 (1H, m, C(9)H), 1.93 (2H, m, C(5)H₂), 1.48 (2H, m, C(7)H₂), 1.22 (2H, m, C(8)H₂), 1.20 (3H, d, J 6.0, C(6)CH₃), 0.98 (3H, d, J 6.0, C(9)CH₃); δC (100 MHz; CDCl₃) 144.7 (C(10)H), 130.2 (C(3)H), 124.7 (C(4)H), 112.6 (C(11)H₂), 77.23 (C(2)H), 75.0 (C(6)H), 38.0 (C(9)H), 31.7-33.4 (overlapping 3 x CH₂), 21.7 (C(9)CH₃), 20.4 (C(6)CH₃); m/z (CI) 181 [(MH)⁺, 12%], 180 [(M)⁺, 100]. No ions observed by HRMS and due to all material being consumed it was not possible to perform IR analysis. Some (R)-4-methyl-5-hexenal was also recovered.
Chapter 5

(±)-Z-2-Trimethylsilylhex-2-en-5-ol (270)

To a solution of 5-trimethylsilylpent-4-yn-2-01 268 (0.5 g, 3.21 mmol, 1 eq.) in dry diethyl ether (5 ml) was added diisobutylaluminium hydride (9.6 ml, 1 M in hexane, 9.6 mmol, 3 eq.) at 0 °C under an atmosphere of nitrogen. After slowly warming to room temperature the reaction mixture was heated at reflux temperature for 24 hours. It was subsequently cooled to 0 °C and methyllithium (6.01 ml, 1.6 M in diethyl ether, 9.63 mmol, 3 eq.) was added. After stirring at room temperature for 30 minutes, methyl iodide (2.27 g, 16 mmol, 5 eq.) was introduced to the reaction mixture which was stirred vigorously for another 48 hours. The reaction mixture was cooled to 0 °C and poured onto a mixture of 0.5 M HCl/ice (10 ml/10 g). After filtration through Celite, the mixture was washed with diethyl ether (30 ml) and the aqueous phase extracted with diethyl ether (3 x 10 ml). The combined organic extracts were dried (MgSO₄) and the solvent was removed by evaporation to afford the title compound as a yellow oil (0.08 g, 15%): Rf 0.41 (petrol:ethyl acetate 9:1); νmax/cm⁻¹ (neat) 3336 (O-H), 1608 (C=C), 1248 (Si-C); δH (270 MHz; CDCl₃) 5.98 (1H, m, C(3)H), 3.81 (1H, m, C(5)H), 2.25 (2H, m, C(4)H), 1.78 (3H, d, J 1.2, C(1)H₃), 1.55 (1H, br s, OH), 1.20 (3H, d, J 6.1, C(6)H₃), 0.13 (9H, s, 3 x CH₃); All other data is in agreement with the literature values.⁵³
(±)-3,6-Dimethyl-6-propyl-5,6-dihydro-2H-pyran (272)

According to the general procedure for the silyl-Prins cyclisation (p. 155) using butyraldehyde (0.03 g, 0.46 mmol), indium(III) chloride (0.10 g, 0.46 mmol) and Z-2-trimethylsilyl-hex-2-en-5-01 270 (0.08 g, 0.46 mmol) in dry dichloromethane (5 ml), (±)-3,6-dimethyl-6-propyl-5,6-dihydro-2H-pyran 272 was formed as the main component of the product mixture which was a yellow oil (0.02 g, 11%); Rf 0.61 (hexane:ethyl acetate 9:1); v_{max}/cm^{-1} (neat) 3433 (O-H), 1458 (C=C), 1119 (C-O); δH (270 MHz; CDCl₃) 5.50 (1H, m, C(4)H), 4.06 (1H, m, C(2)H), 3.57 (1H, m, C(6)H), 1.89 (2H, m, C(5)H), 1.57-1.20 (6H, m, overlapping 3 x CH₂), 0.92-0.82 (9H, m, 3 x CH₃). Other components of the reaction mixture consisted chiefly of unreacted starting materials. Further characterisation was not performed due to insufficient material.

(±)-3,6-Dimethyl-6-[(R)-3-methylpent-4-enyl]-5,6-dihydro-2H-pyran (273)

The title compound was prepared according to the general procedure for the silyl-Prins cyclisation (p. 155), using (R)-4-methyl-5-hexenal 247 (0.05 g, 0.41 mmol), indium(III) chloride (0.09 g, 0.41 mmol) and Z-trimethylsilyl-hex-2-en-5-01 270 (0.07 g, 0.41 mmol).
in dry dichloromethane (5 ml), and isolated by preparative thin-layer chromatography (petrol:ethyl acetate 95:5) as a mixture of two diastereoisomers (0.02 g, 17%)(It was not possible to obtain a ratio of isomers since the only peak to indicate diastereoisomers at δ 5.49 was not fully resolved and hence integration could not be used to obtain a ratio): Rf 0.96 (petrol:ethyl acetate 95:5); No ions observed by HRMS. ν\textsuperscript{max}/cm\textsuperscript{-1} (neat) 3387 (OH), 1454 (C=C), 1259 (C-O); δ\textsubscript{H} (300 MHz; CDCl\textsubscript{3}) 5.70 (1H, m, C(10)H), 5.48 (1H, m, C(4)H), 4.90 (2H, m, C(11)H\textsubscript{2}), 4.05 (1H, m, C(2)H), 3.57 (1H, m, C(6)H), 2.10 (1H, m, C(9)H), 1.85 (2H, m, C(5)H\textsubscript{2}), 1.62-1.42 (4H, m, 2 x CH\textsubscript{2}), 1.18 (3H, d, J 9.0, C(6)CH\textsubscript{3}), 0.98 (3H, d, J 6.0, C(9)CH\textsubscript{3}); δ\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 144.0 (C(10)H), 143.8 (C\textsubscript{ipso}(3)) 119.7 (C(4)H), 111.5 (C(11)H\textsubscript{2}), 76.3 (C(2)H), 68.5 (C(6)H), 36.9 (C(9)H), 32.2 (C(5)H\textsubscript{2}), 29.9-28.3 (overlapping 3 x CH\textsubscript{2}), 20.5-17.9 (overlapping 2 x CH\textsubscript{3}); m/z (Cl) 195 [(MH\textsuperscript{+}, 57%], 177 [(MH -H\textsubscript{2}O)\textsuperscript{+}, 100].

**2-Bromostyrene oxide (276)**

![2-Bromostyrene oxide (276)](image)

Following the general procedure for alkene epoxidation using Oxone® (p. 186), the *title compound* was prepared using 2-bromostyrene (2.00 g, 10.9 mmol) and Oxone® (25.9 g, 43.7 mmol), and isolated without further purification as a yellow oil (2.34 g, 100%); Rf 0.55 (petrol:ethyl acetate 9:1); ν\textsuperscript{max}/cm\textsuperscript{-1} 2965 (C-H), 1473, 1436 (C=C), 754 (C-Br); δ\textsubscript{H} (300 MHz; CDCl\textsubscript{3}) 7.53 (1H, d, J 9.0, Ar-H), 7.12-7.45 (3H, m, Ar-H). 4.14 (1H, s, C(1)H), 3.17 (1H, m, C(2)Ha), 2.64 (1H, m, C(2)Hb). All other data is in agreement with the literature values.

209
(±)-1-(2-Bromophenyl)but-3-yn-l-ol (277)

To a solution of lithium acetylide ethylenediamine complex (2.47 g, 23.3 mmol, 2 eq.) in anhydrous DMSO (2 ml) was added a solution of 2-bromostryene oxide 276 (2.32 g, 11.6 mmol, 1 eq.) in anhydrous DMSO (20 ml) under an atmosphere of nitrogen. The reaction mixture was allowed to stir for 24 hours at room temperature. After this time the mixture was poured into water (20 ml) and extracted with diethyl ether (4 x 20 ml). The combined ether extracts were washed with brine (30 ml), dried (MgSO₄) and concentrated in vacuo to afford the title compound as a brown oil which was used in the next step without further purification (1.71 g, 79%); Rf 0.18 (petrol:ethyl acetate 9:1); νmax/cm⁻¹ (neat) 3350 (OH), 3299 (C-H), 2119 (C=C), 1466, 1439 (C=C), 755 (C-Br); δH (270 MHz; CDCl₃) 7.61 (1H, d, J 12.5, Ar-H), 7.51 (1H, d, J 7.9, Ar-H), 7.34 (1H, m, Ar-H), 7.15 (1H, m, Ar-H), 5.22 1H, m, CH(OH), 2.80 (1H, m, OH), 2.51 (2H, m, CH₂), 2.10 (1H, m, C=CH). All other data is in agreement with the literature values.²⁰¹
(±)-4-Trimethylsilyl-1-(2-bromophenyl)but-3-yn-1-ol (278)

Following the general silylation procedure (p. 151), reaction of 1-(2-bromophenyl)-but-3-yn-1-ol 277 (2.09 g, 9.28 mmol), n-butyllithium (8.16 ml, 2.5 M solution in hexane, 20.4 mmol, 2.2 eq) and trimethylsilyl chloride (2.60 ml, 20.4 mmol, 2.2 eq.) in dry THF (25 ml), gave the title compound after purification by flash column chromatography (petrol:ethyl acetate 9:1) as a yellow oil (1.06 g, 38%); Rf 0.61 (petrol:ethyl acetate 9:1): Found [M+NH₄]⁺ 314.0569; C₁₃H₁₇BrOSi [M+NH₄]⁺ requires 314.0570; ν_max cm⁻¹ (neat) 3418 (O-H), 2176 (C=C), 1465, 1438, (C=C), 1249 (Si-C); δ_H (270 MHz; CDCl₃) 7.59 (1H, d, J 6.7, Ar-H), 7.50 (1H, d, J 7.9, Ar-H), 7.33 (1H, t, J 7.9, Ar-H), 7.14 (1H, t, J 7.9, Ar-H), 5.19 (1H, m, C(1)H), 2.85 (1H, m, OH), 2.56 (2H, m, C(2)H₂), 0.15 (9H, s, 3 x CH₃); δ_C (100 MHz; CDCl₃) 132.6 [C(Ar)], 129.2 [C(Ar)], 127 [overlapping 2 x C(Ar)], 70.7 (C(1)H), 32.3 (C(2)H₂), 0.0 (C(4)TMS); m/z (Cl) 314[(M+NH₄)⁺, 7%]. 219 [(M)⁺-C₆H₅, 5].
Following the general procedure for the reduction of trimethylsilylalkynes (p. 153), the title compound was prepared using (±)-4-trimethylsilyl-1-(2-bromophenyl)but-3-yn-l-ol 278 (0.35 g, 1.19 mmol, 1 eq.) and diisobutylaluminium hydride (4.16 ml, 1M solution in hexane, 4.16 mmol, 3.5 eq.). After filtering through Celite, the title compound was isolated as a yellow oil (0.16 g, 45%); \( R_f \) 0.46 (petrol:ethyl acetate 9:1); Found [M+NH\(_4\)]\(^+\) 316.0723; \( C_{13}H_{19}BrOSi \) [M+NH\(_4\)]\(^+\) requires 316.0727; \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3379 (O-H), 1604 (C=C), 1247 (Si-C); \( \delta_H \) (270 MHz; CDCl\(_3\)) 7.56 (1H, d, J 7.6 Hz, C(Ar)), 7.51 (1H, d, J 7.9 Hz, C(Ar)), 7.34 (1H, m, C(Ar)), 7.12 (1H, m, C(Ar)), 6.36 (1H, m, C(3)H), 5.74 (1H, d, J 14Hz, C(4)H), 5.12 (1H, m, C(4)H), 2.66 (1H, m, C(2)H\(_b\)), 2.45 (1H, m, C(2)H\(_a\)), 2.08 (1H, br s, OH), 0.11 (9H, s, (3 x CH\(_3\))) \( \delta_C \) (100 MHz; CDCl\(_3\)) 143.1 (C(3)H), 133.6 (C(4)H), 132.4-127.0 [4 x C(Ar)], 71.7 (C(1)H), 41.1(C(2)H\(_2\)), 0.0 (3 x CH\(_3\)); \( m/z \) (ES) 299 [(M\(^+\), 51%], 221 [(M-Br\(^+\), 33%].
Chapter 5

Damien Gough

Attempted preparation of (±)-6-(2-bromophenyl)-2-[(R)-methylpent-4-enyl]-5,6-dihydro-2H-pyran (281)

![Chemical Structure](image)

The *title compound* was prepared according to the general procedure for the silyl-Prins cyclisation (p. 155) using (R)-4-methyl-5-hexenal 247 (0.06 g, 0.49 mmol, 1 eq.), indium(III) chloride (0.11 g, 0.49 mmol, 1 eq.) and (±)-Z-4-trimethylsilyl-1-(2-bromophenyl)but-3-en-1-ol 279 (0.15 g, 0.49 mmol, 1 eq.) in dry dichloromethane (5 ml) and purified by column chromatography (petrol:ethyl acetate 95:5). Analysis by $^1$H NMR spectroscopic techniques indicated that the main product was 2-bromophenyl-but-3-en-1-ol. A small amount of the *title compound* is suggested by $^1$H NMR spectroscopic techniques.

(±)-Z-4-Trimethylsilyl-1-(2-bromophenyl)-pent-3-en-1-ol (274)

![Chemical Structure](image)

To a solution of 4-trimethylsilyl-1-(2-bromophenyl)-but-3-yn-1-ol 278 (1.06 g, 3.56 mmol, 1 eq.) in dry diethyl ether (15 ml) was added diisobutylaluminium hydride (14.24...
ml. 1 M in hexane, 14.24 mmol, 4 eq.) at 0 °C under an atmosphere of nitrogen. After slowly warming to room temperature, the reaction mixture was heated to reflux temperature for 24 hours. The solution was subsequently cooled to 0 °C and methyllithium (6.68 ml, 1.6 M in diethyl ether, 10.68 mmol, 3 eq.) was added. After stirring at room temperature for 30 minutes, methyl iodide (1.108 ml, 17.8 mmol, 5 eq.) was introduced to the reaction mixture which was stirred vigorously for a further 45 hours. The cold (0 °C) reaction mixture was poured onto 0.5 M HCl/ice (10ml/10g), filtered through Celite, washed with diethyl ether (30 ml) and the aqueous phase extracted with diethyl ether (3 x 10 ml). The combined organic extracts were dried (MgSO4) and the solvent was removed by evaporation to leave a yellow oil which was purified by flash column chromatography (petrol:ethyl acetate 95:5) to afford the title compound as a clear oil (0.10 g, 9%); Rf 0.45 (petrol:ethyl acetate); Found [M+NH4]+ 330.0880; C14H21BrOSi [M+NH4]+ requires 330.0883; νmax/cm⁻¹ (neat) 3385 (O-H), 1441 (C=C), 1278 (Si-C); δH (270 MHz; CDCl3), 7.55 (2H, m, Ar-H), 7.33 (1H, m, Ar-H), 7.12 (1H, m, Ar-H), 6.06 (1H, m, C(3)H), 5.06 (1H, m, C(1)H), 2.62 (1H, m, C(2)H₆), 2.45 (1H, m, C(2)H₆), 2.09 (1H, s, OH), 1.81 (3H, s, C(5)H₃), 0.13 (9H, s, 3 x CH₃); δC (68 MHz; CDCl3) 137.0 (C(3)H), 125.5-134.4 [4 x C(Ar)], 73.0 (C(1)H), 41.4 (C(2)H₂), 25.0 (CH₃), 0.28 (3 x CH₃); m/z (Cl) 330 [(M+NH₄)⁺, 22%], 314 [(M+H)⁺, 36].
The *title compound* was prepared according to the general procedure for the silyl-Prins cyclisation (p. 155) using \((R)-4\)-methyl-5-hexenal 247 (0.04 g, 0.33 mmol, 1 eq.), indium(III) chloride (0.07 g, 0.33 mmol, 1 eq.) and \((\pm)-Z-4\)-trimethylsilyl-1-(2-bromophenyl)pent-3-en-1-ol 276 (0.10 g, 0.33 mmol, 1 eq.) in dry dichloromethane (10 ml). The crude product was purified by preparative thin layer chromatography (petrol:ethyl acetate 98:2). Analysis of several fractions of the product mixture by GCMS suggests the formation of the *title compound* in an inseparable mixture; \(m/z\) (Cl) 336 \([M(\text{HBr})^+ , 17\%], 334 [M(79\text{Br})^+ , 18], 312 [M(81\text{Br})^+ -24, 38], 310 [M(79\text{Br})^+ -24, 100].\) Analysis by \(^1\text{H}\) NMR spectroscopic techniques indicates the presence of the desilylated analogue of 276.
Modelling of the Macroyclic Ring

8-Phenyl-oct-1-ene (288)

To a stirred solution of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium-(II) (0.03 g, 0.04 mmol, 0.01 eq.) and bromobenzene (0.63 g, 4 mmol, 1 eq.) in dry diethyl ether (5 ml) was added 8-bromomagnesium-1-octene 286 (1.72 g, 8 mmol, 2 eq.) in dry diethyl ether (5 ml) at -78 °C under an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 24 hours and then hydrolysed with a solution of 10% hydrochloric acid (10 ml). The layers of the mixture were separated and the aqueous layer washed with diethyl ether (2 x 10 ml). The combined organic extracts were washed with sodium hydrogen carbonate solution (20 ml), water (20 ml) and dried (MgSO₄). After evaporation of solvent, the product was purified by flash column chromatography (petrol:ethyl acetate 99:1) to afford the title compound as a yellow oil (0.46 g, 61%); Rᵢ 0.85 (petrol:ethyl acetate 99:1); δₜ (270 MHz; CDCl₃) 7.25 (2H, m, 2 x Ar-H), 7.17 (2H, m, 2 x Ar-H), 7.15 (1H, m, Ar-H), 5.79 (1H, m, C(2)H), 4.93 (2H, d, J 12.3, C(1)H₂), 2.58 (2H, t, J 7.6, C(8)H₂), 2.03 (2H, m, C(3)H₂), 1.62 (2H, m, C(7)H₂), 1.24-1.52 (6H, m, overlapping 3 x CH₂); δₐ (68 MHz; CDCl₃) 139.2 (C(2)H), 125.6-128.4 [overlapping 5 x C(Ar)], 114.2 (C(1)H₂), 36.0 (C(8)H₂), 33.8 (C(3)H₂), 31.4 (C(7)H₂), 28.9-29.2 (overlapping 3 x CH₂). All other data is in agreement with the literature values.²⁰²
Chapter 6

References
References


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