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Synthetic Studies Towards
Antibiotics Containing
Phthalide Moieties

A thesis presented to the
University of Auckland
for the degree of

Doctor of Philosophy

By
Matthew Sidford

Department of Chemistry
University of Auckland.  December 2004
Abstract

An investigation into the synthesis of several analogues of antifungal agents related to the papulacandins was undertaken. Retrosynthetic analysis of these analogues identified phthalide (261) and allylstannane (278) as key intermediates in the synthesis of analogues of type (284).

The key step in the synthesis of phthalide (261) was the ortho formylation via ortholithiation of amide (255). The synthesis of phthalide (261) was carried out over five steps in 35% overall yield from (255).

Synthesis of the allylstannane intermediate from alcohol (351) proved problematic thus preventing further progress in this area of research.

Synthetic studies toward the anti-helicobactericidal phthalides CJ-12,954 (56), CJ-13,014 (57), CJ-13,015 (58), CJ-13,0102 (59), CJ-13,103 (60), CJ-13,104 (61), and CJ-13,108 (62) were undertaken. CJ-12,954 (56) and CJ-13,108 (62) were chosen as initial targets. Retrosynthetic analysis identified phthalide (288), spiroketal ylide (297) and ylide (468) as key intermediates for the synthesis of the natural products (56) and (62). The synthesis of spiroketal epoxide (300) was successfully achieved in fifteen steps starting from materials (386) and (381) in an overall yield of 8%. Unfortunately all attempts to effect ring opening of epoxide (300) were unsuccessful. The racemic synthesis of phthalide (288) was carried out in six steps starting from material 2,4-dimethoxybenzoic acid (296) in 33% overall yield. Wittig coupling of ylide (468) with phthalide (288) allowed complete total synthesis of racemic CJ-13,108 (62) from (288) in 42% overall yield.
<p>| Ac | = Acetyl |
| Ac₂O | = Acetic anhydride |
| 9-BBN | = 9-Borabicyclononane |
| Bn | = Benzyl |
| BH₃-DMS/BMS | = Borane-dimethyl sulphide complex |
| CAN | = Ceric ammonium nitrate |
| CSA | = Camphorsulphonic acid |
| DCM | = Dichloromethane |
| DDQ | = 2,3-Dichloro-5,6-dicyano-1,4-benzoquione |
| DIBAL-H | = Diisobutylaluminium hydride |
| DMAP | = 4-Dimethylaminopyridine |
| DMDO | = 2,2-Dimethyldioxirane |
| DMF | = N,N-Dimethylformamide |
| DMPU | = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone |
| DMSO | = Dimethylsulphoxide |
| DNA | = Deoxyribonucleic acid |
| Et₂AlCl | = Diethyl aluminium chloride |
| EtOAc | = Ethyl acetate |
| EtOH | = Ethanol |
| Et₃N | = Triethylamine |
| HMPA | = Hexamethyldiphosphoramidate |
| LDA | = Lithium diisopropylamide |
| LTMDA | = N,N,N′-Trimethylethylenediamine |
| mCPBA | = meta-chloroperoxybenzoic acid |
| MMPP | = Magnesium monoperoxyphthalate |
| MOM | = Methoxymethyl |
| MsCl | = Methanesulphonyl chloride |</p>
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>N-Methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>Piv</td>
<td>Pivaloyl, 2,2-dimethylacetyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-Methoxybenzyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium p-toluenesulphonate</td>
</tr>
<tr>
<td>Py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFO</td>
<td>Trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TFAA</td>
<td>Trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyranyl</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TIPS</td>
<td>Trisopropylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetrabutylammonium perruthenate</td>
</tr>
</tbody>
</table>
Contents

Abstract i
Abbreviations ii

Chapter 1 Introduction 1

1 Naturally occurring spiroketals 2

1.1 Steroidal saponins and sapogenins 3
1.2 Spiroketal enol ethers from Asteraceae species 3
1.3 Naturally occurring polyether ionophores 4
1.4 Insect pheromones 5
1.5 Phyllanthocin and phyllanthoside 6
1.6 The milbemycins and avermectins 7
1.7 Spiroketalts from marine origins 9
1.8 Trioxadispiroketal containing natural products 10
1.9 Aromatic spiroketals 12

1.9.1 Type 1 Aromatic spiroketals 13

1.9.1.1 The Rubromycins 13
1.9.1.2 The Griseusins 16
1.9.1.3 The Papulacandins 16

1.9.2 Type 2 Aromatic spiroketals: Phthalide containing spiroketals 18

1.9.3 Mode of action of aromatic spiroketals 20

2 Synthesis of spiroketals 22

2.1 Conformational effects 22
2.2 General methods 27
2.3 Synthesis of aromatic spiroketals

2.3.1 Synthesis of type 1 aromatic spiroketals

2.3.2.1 Synthesis of the Rubromycins and Heliquinomycin

2.3.2.2 Synthesis of the Griseusins

2.3.2.3 Synthesis of the Papulacandins

3 The present investigation

3.1 Synthetic studies toward type 1 aromatic spiroketals: Synthesis of analogues of the papulacandins

3.2 Synthetic studies towards type 2 aromatic spiroketals: Synthesis of phthalide-containing spiroketals

3.2.1 Retrosynthesis of CJ-13,108 (62)

3.2.2 Retrosynthesis of the phthalide unit of CJ-13,108 (62)

3.2.3 Retrosynthesis of CJ-12,954 (56)

3.2.4 [4.4] Spiroketal moiety (301)

Chapter 2 Discussion

The Papulacandins

1 Ortholithiation chemistry

1.1 Introduction

1.2 Mechanism

1.3 Classes of directing group

2 Synthesis of analogues of the papulacandins: Synthesis of aryl spiroketal (281)

2.1 Synthesis of phthalide (260)
2.1.1 Synthesis of amide (254) 102
2.1.2 Synthesis of aldehyde (256) 103
2.2 Synthesis of phthalide (261) 105
2.2.1 Synthesis of amide (255) 105
2.2.2 Synthesis of aldehyde (257) 106
2.3 Synthesis of allyl stannane (278) 114

Chapter 3 Discussion 122

Anti-ulcer compounds 122
1 Ulcers 122
1.1 Introduction 122
1.2 Helicobacter pylori: Structure and morphology 122
1.3 Helicobacter pylori: Habitat 123
1.4 Pathogenesis of Helicobacter pylori 124
1.5 Helicobacter pylori: Epidemiology 126
1.6 Helicobacter pylori: Treatments 127
2 Synthetic studies towards phthalide-containing spiroketals 129
2.1 Introduction 129
  2.1.1 Synthesis of intermediate acetylene (394) 139
  2.1.1.1 Asymmetric induction in preparation of (394) 140
  2.1.2 Synthesis of intermediate aldehyde (399) 142
  2.1.3 Coupling of acetylene (394) to aldehyde (399) 144
2.2 Synthetic studies towards spiroketal ylide (297) from ketone (403) 145
  2.2.1 Functionalisation of the terminal olefin 146
2.3 Coupling of acetylene (411) to aldehyde (399)

2.4 Synthetic studies towards spiroketal ylide (297) from ketone (414)

2.5 Attempted synthesis of spiroketal ylide (297) using a conjugate reduction step

2.6 Attempted synthesis of spiroketal ylide (297) from methyl acetal (431)

2.7 Investigations into ring opening of epoxide (300) with zinc borohydride (435)

2.8 Synthetic studies towards phthalide (288)

2.8.1 Synthetic studies towards hydroxyphthalide (370) using Borchardt’s route

2.8.2 Synthetic studies towards hydroxyphthalide (370) using Comins methodology

2.8.3 Synthetic studies towards hydroxyphthalide (370) using Napolitano methodology

2.8.4 Attempted synthesis of hydroxyphthalide (370) via ortho formylation

2.9 Synthetic studies towards CJ-13,108 (62) and CJ-12,957 (56)

2.9.1 Overall strategy

2.9.2 Union of aldehyde (288) with bromide (290)

2.9.3 Grignard addition of bromide (290) to aldehyde (288)

2.9.4 Addition of ylide (289) to aldehyde (288)
3 Towards an asymmetric synthesis of CJ-13,108 (62) 210
3.1 Introduction 210
3.2 Chiral allylation and crotylation reactions 212
   3.2.1 Introduction 212
   3.2.2 Stereochemistry 212
   3.2.3 Mechanism of the addition of allylmetal reagents to aldehydes 214
      3.2.3.1 Type 1 additions 215
   3.2.4 Asymmetric allylation of aldehyde (294) 222
3.3 Summary and future work 225

Chapter 4 Experimental 233
1 General 234

Chapter 5 References 293
Chapter 1. Introduction
1. Naturally occurring spiroketals

The spiroketal subunit is widely represented in natural products from many sources including insects, microbes, plants, fungi and marine organisms.\(^1\) The increased biological importance placed on compounds containing spiroketal moieties has been the catalyst for interest in both their synthesis and chemical reactivity. The vast majority of work conducted in this area focuses on spiro[5.5]undecane, spiro[5.4]decane and spiro[4.4]nonane ring systems (1), (2) and (3), because most natural products fall into one of these structural categories (Figure 1).

![Diagram of spiroketal structures](image)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,7-Dioxaspiro[5.5]undecane</td>
<td>Milbemycins, Avermectins, Insect pheromones, Aplysia toxin, Taleromycins, Okadaic acid, Sapogenins</td>
</tr>
<tr>
<td>1,6-Dioxaspiro[4.5]decane</td>
<td>Phyllanthocin, Monensin, Insect pheromones</td>
</tr>
<tr>
<td>1,6-Dioxaspiro[4.4]nonane</td>
<td>Chalogran, Asteracine metabolites, Insect pheromones</td>
</tr>
</tbody>
</table>

Figure 1 Structural categories of spiroketals
1.1 Steroidal saponins and sapogenins

These compounds represent some of the earliest isolated naturally occurring spiroketal structures. They were isolated from plants in the southwestern United States and Mexico in the 1930's and 1940's. Their structure consists of a steroidal nucleus containing a spiroketal fused to the D-ring. Two of the most common spiroketal structures are (4) and (5) below (Figure 2).

![Hecogenin (4)]

![Sarsapogenin (5)]

Figure 2 Hecogenin (4) and Sarsapogenin (5).

1.2 Spiroketal enol ethers from Asteraceae species

Enol ether spiroketal structures of the [4.5] and [5.5] type have been isolated from the plant family Asteraceae. Most examples contain functionality on one or both rings often comprising one or more acetylene units (Figure 3).

![Enol ether spiroketal from Asteraceae (6)]

Figure 3 Enol ether spiroketal from Asteraceae.
1.3 Naturally occurring polyether ionophores

The polyketide derived polyether antibiotics are produced by filamentous branching bacteria. The structural elucidation of one example monensin A (7)\(^2\) in 1967 and the discovery of its ionophoric properties initiated great interest in polyether compounds. The common spiroketal backbone of the polyether compounds is the 1,6-dioxaspiro[4.5]decane unit shared by all three examples below (Figure 4).

![Monensin A (7)](image)

![Ionomycin A (8)](image)

![Nigericin (9)](image)

**Figure 4** Monensin A (7), Ionomycin A (8), Nigericin (9).
1.4 Insect pheromones

Many insects utilise simple spiroketals as pheromone components. These spiroketals are usually contained within simple branched carbon skeletons, and more than one stereo- or structural isomer may be produced by the same organism. Some examples are illustrated below (Table 1).

Table 1 Table of insect pheromones

<table>
<thead>
<tr>
<th>Spiroketal</th>
<th>Name</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="10" alt="Spiroketal" /></td>
<td>1,7-dioxaspiro[5.5]undecane</td>
<td><em>Dacus oleae, Dacus cacuminatus</em></td>
</tr>
<tr>
<td><img src="11" alt="Spiroketal" /></td>
<td>(Z,Z)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane</td>
<td><em>Dacus cucumis</em></td>
</tr>
<tr>
<td><img src="12" alt="Spiroketal" /></td>
<td>Chalcogran, or (Z)-2-ethyl-1,6-dioxaspiro[4.4]nonane</td>
<td><em>Pityogenes chalcographus</em></td>
</tr>
<tr>
<td><img src="13" alt="Spiroketal" /></td>
<td>2-butyl-7-ethyl-1,6-dioxaspiro[4.4]nonane</td>
<td><em>Andrena wilkella</em> (all diastereomers)</td>
</tr>
<tr>
<td><img src="14" alt="Spiroketal" /></td>
<td>(E)-7-methyl-1,6-dioxaspiro[4.5]decane</td>
<td><em>Paravespula vulgaris</em></td>
</tr>
</tbody>
</table>
Chapter 1.

Introduction

<table>
<thead>
<tr>
<th>Molecular Structure</th>
<th>Chemical Formula</th>
<th>Insect Species</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Molecular Structure 1" /></td>
<td>(Z)-2-methyl-1,6-dioxaspiro[4.5]decane</td>
<td>Paravespula vulgaris</td>
</tr>
<tr>
<td><img src="image2" alt="Molecular Structure 2" /></td>
<td>2,7-dimethyl-1,6-dioxaspiro[4.6]undecane</td>
<td>Andrena haemorrhhoa</td>
</tr>
<tr>
<td><img src="image3" alt="Molecular Structure 3" /></td>
<td>(E)-2-methyl-1,7-dioxaspiro[5.6]decane</td>
<td>Andrena haemorrhhoa</td>
</tr>
</tbody>
</table>

The insect pheromones that have received most synthetic attention are 1,7-dioxaspiro[5.5]undecane (11) and chalcogran (12), the major components of the sex pheromones of *Dacus oleae* (olive fruit fly)⁴ and the beetle *Pityogenes chalcographus* respectively. The synthetic interest in these compounds stems from their structural simplicity and the extensive damage caused by these insects.

### 1.5 Phyllanthocin and phyllanthoside

Phyllanthocin (18) is the aglycone of the antileukemic compound phyllanthoside (19) which was isolated from *Phyllanthus acuminathus* by Kupchan *et al.*⁵ in 1977 (Figure 5). Five syntheses of (18)⁶,⁷,⁸,⁹,¹⁰ have been described as well as a synthesis of (19) by Smith *et al.*¹¹
Chapter 1. Introduction

Figure 5 Phyllanthocin (18) and phyllanthoside (19)

1.6 The milbemycins and avermectins

The milbemycins and avermectins are structurally related 16-membered macrocyclic lactones bridging one ring of a 1,7-dioxaspiro[5.5]undecane unit. They were first isolated from various species of *streptomycetes*. The major difference between the two classes is the absence of an additional glycoside moiety in the milbemycins (Figure 6).
## Chapter 1. Introduction

### Avermectins and milbemycins

<table>
<thead>
<tr>
<th></th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$X-Y$</th>
<th>$Z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avermectin $A_{1a}$ (20)</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>CH=CH</td>
<td>H</td>
</tr>
<tr>
<td>Avermectin $A_{1b}$ (21)</td>
<td>CH$_3$</td>
<td>H</td>
<td>CH=CH</td>
<td>H</td>
</tr>
<tr>
<td>Avermectin $A_{2a}$ (22)</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>CH$_2$-CH</td>
<td>OH</td>
</tr>
<tr>
<td>Avermectin $A_{2b}$ (23)</td>
<td>CH$_3$</td>
<td>H</td>
<td>CH$_2$-CH</td>
<td>OH</td>
</tr>
<tr>
<td>Avermectin $B_{1a}$ (24)</td>
<td>H</td>
<td>CH$_3$</td>
<td>CH=CH</td>
<td>H</td>
</tr>
<tr>
<td>Avermectin $B_{1b}$ (25)</td>
<td>H</td>
<td>H</td>
<td>CH=CH</td>
<td>H</td>
</tr>
<tr>
<td>Avermectin $B_{2a}$ (26)</td>
<td>H</td>
<td>CH$_3$</td>
<td>CH$_2$-CH</td>
<td>OH</td>
</tr>
<tr>
<td>Avermectin $B_{2b}$ (27)</td>
<td>H</td>
<td>H</td>
<td>CH$_2$-CH</td>
<td>OH</td>
</tr>
</tbody>
</table>

![Milbemycin $\beta_1$ (28)](image1)

![Milbemycin $\beta_3$ (29)](image2)

**Figure 6** Avermectins and milbemycins

The biological significance of these two classes stems from their antihelmintic properties in that they exhibit insecticidal and acaricidal activity, while maintaining low mammalian toxicity, making a potential treatment of parasitic infections. To date there have been two syntheses reported in the avermectin series by Danishefsky et al.
Chapter 1. Introduction

1.12 and Hanessian et al.13. Milbemycin β₃ has received most synthetic attention of all the milbemycins as it is the most simple structure in the series.14,15,16,17,18

1.7 Spiroketals from marine origins

A potent antitumour agent okadaic acid (30)19 was one of the first polyether carboxylic acid-containing spiroketals to be isolated from sponges of the genus *Halichondria* (Figure 7). The episulfide analogue, acanthafolicin (31) has been isolated from other organisms including dinoflagellates.20

![Okadaic acid (30)](image)

![Acanthafolicin (31)](image)

**Figure 7** Okadaic acid (30) and acanthafolicin (31)

More recent additions to the family of natural products containing a spiroketal moiety of marine origin are the spongiostatins (Figure 8).21 Spongiostatin 1 (32) was isolated from an East Indian ocean sponge of the genus *Spongia*. It was found to
Chapter 1. Introduction

exhibit potent cytotoxic and antineoplastic activity against cancer cells in the United States. Spongiostatins 8 (33) and 9 (34) were recently isolated from the southwest African marine sponge *Spirastrella spinispirulifera* and were found to potentially inhibit glutamine induced polymerisation of tubulin.  

![Spongiostatins](image)

**Figure 8** The Spongiostatins

### 1.8 Trioxadispiroketal containing natural products

A small number of polyether macrocyclic natural products contain trioxadispiroketal ring systems, a unique arrangement of three rings linked in a spiro fashion via two acetal carbons. To date several members of this family have been synthesized, namely narasin (35), salinomycin (36) and pinnatoxin A (37) (Figure 9).
Chapter 1.

Introduction

Narasin (35) \( R = \text{CH}_3 \), Salinomycin (36) \( R = \text{H} \)

Pinnatoxin A (37) \( R = \text{CO}_2\text{H} \)

**Figure 9** Narasin (35), Salinomycin (36) and Pinnatoxin A (37)

Recently isolated from digestive glands of both mussels (*Mytilus edulis*) and scallops (*Placopectin magellanicus*) are new members of the trioxadispiroketal class, namely the spirolides B (38) and D (39) (**Figure 10**).\(^{26}\) These macrocycles contain a novel spirolinked tricyclic ether system and an unusual 7-membered spiro-linked iminium moiety. They have been found to be weak type L calcium channel activators.
1.9. Aromatic spiroketals

Aromatic spiroketals are compounds which contain both aromatic and spiroketal rings, and are of particular relevance to this thesis. The known aromatic spiroketals can be classified into two classes. The first comprises compounds in which the aromatic ring and spiroketal rings are fused (Type 1, 40) and the second class comprises compounds in which the aromatic and spiroketal rings are separated via a carbon chain (Type 2, 41) (Figure 11).
1.9.1. Type 1 Aromatic spiroketals

1.9.1.1 The Rubromycins

The rubromycins are a family of structurally related antibiotic pigments consisting of naphthazin and isocoumarin ring structures linked through a [5,6]-spiroketal. Aromatic spiroketals of this family include γ-rubromycin (42), purpuromycin (43), heliquinomycin (44), griseorhodin C (46), and griseorhodin G (47) (Figure 12).
The rubromycins were isolated from various *Streptomyces* and are active against Gram-positive bacteria and act as inhibitors of human telomerase,\(^{31}\) however several of the members show other interesting biological activities. \(\gamma\)-Rubromycin (42) was isolated from *Staphylococcus aureus, Staphylococcus albus, Streptococcus pyogenes, Streptococcus viridans, Enterococcus* and *Diplococcus pneumoniae*.\(^{32}\) It has also been shown to be active against the reverse transcriptase of the human immunodeficiency virus-1.\(^{33}\)

Purpuromycin (43) is a purple crystalline antibiotic isolated from *Actinoplanes ianthinogenes*\(^{28a,28b}\) and is an hydroxy analogue of \(\gamma\)-rubromycin (42). It is active
against both Gram-positive and Gram-negative bacteria and is a potential topical agent for vaginal infections.\textsuperscript{34}

Heliquinomycin (44) is the most recent addition to the family and was isolated from \textit{Streptomyces} sp. MJ929-SF2. It contains one major structural difference to the other members in that it contains a sugar moiety cymarose, at the 3' position. Heliquinomycin (44) has been shown to inhibit DNA helicase,\textsuperscript{29} an essential process of DNA replication, repair, recombination and transcription, by unwinding of double-stranded DNA to its reactive single strand form. Other activity includes growth inhibition on several tumour cell lines including L1210 leukaemia, IMC carcinoma and FS-3 fibrosarcoma.

The importance of the spiroketal subunit on the biological activity of the rubromycins is illustrated by the significant difference in human telomerase inhibition properties exhibited by \(\gamma\)-rubromycin (42) and \(\alpha\)-rubromycin (45) (\textbf{Table 2}). \(\alpha\)-Rubromycin (44) does not contain a spiroketal unit, and is less active by two orders of magnitude than its spiroketal containing counterpart \(\gamma\)-rubromycin (42).\textsuperscript{31}

\textbf{Table 2} Inhibition of Telomerase by Rubromycins and their Analogues

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC(_{50}) ((\mu\text{M})) at Telomerase substrate primer concentration of 0.2 (\mu\text{M})</th>
<th>IC(_{50}) ((\mu\text{M})) at Telomerase substrate primer concentration of 2.0 (\mu\text{M})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)-Rubromycin (45)</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>(\gamma)-Rubromycin (42)</td>
<td>2.64 ± 0.09</td>
<td>17.8 ± 2.0</td>
</tr>
<tr>
<td>Purpuromycin (43)</td>
<td>3.19 ± 0.45</td>
<td>15.9 ± 2.1</td>
</tr>
<tr>
<td>Griscorhodin C (46)</td>
<td>5.87 ± 0.44</td>
<td>25.8 ± 1.7</td>
</tr>
</tbody>
</table>
1.9.1.2 The Griseusins

Griseusin A (48) and B (49) (Figure 13) were isolated from a soil sample collected in Peru which had been inoculated with *Streptomyces griseus* K-63. They are unique members of the pyranonaphthoquinone family of antibiotics and both contain a 1,7-dioxaspiro[5.5]undecane ring system.

![Griseusin A (48)](image1)

![Griseusin B (49)](image2)

**Figure 13** Griseusin A (48) and B (49)

The two structures differ by the presence of a lactone group in griseusin A (48) which is unmasked as a carboxylate group in griseusin B (49). Interest in these compounds arose due to their inhibitory activity against Gram-positive bacteria, pathogenic fungi and yeast, together with their proposed bioreductive alkylation properties.

1.9.1.3 The Papulacandins

The papulacandins A (50), B (51), C (52), D (53), E (Figure 14) are a group of C-arylglycosyl [5,6]-spiroketals isolated from *Papularia sphaerosperma* while more recent members Mer-WF3010 (54) and L-687,781 (55) (Figure 14) were isolated from the mycelia of *Monochaetia dimorphosporam* and *Phialophora cyclaminis*, and the cultivation of *Dictyochaeta simplex* ATCC 20960, respectively. The chemical
structures of all the papulacandins, with the exception of papulacandin E have been elucidated.\textsuperscript{41}

![Chemical structures of papulacandins](image)

**Figure 14** Papulacandins A (50), B (51), C (52), D (53), Mer-WF3010 (54) and L-687,781 (55)
Screening tests revealed that papulacandin A (50), B (51), C (52), D (53), and E exhibited potent in vitro activity against Candida albicans and related microorganisms\textsuperscript{40,42} while Mer-WF3010 (54) and L-687,781 (55) were found to overcome Pneumocystis carinii pneumonia, the common opportunistic infection in AIDS patients.\textsuperscript{42} The antifungal activity has been attributed to the ability of these compounds to inhibit 1,3-β-D-glucan synthase enzyme which is responsible for the biosynthesis of cell walls in fungi, but not in humans.\textsuperscript{42}

1.9.2 Type 2: Aromatic spiroketals: Phthalide containing spiroketals

In 1997 Dekker and co-workers isolated seven phthalides CJ-12,954 (56), CJ-13,014 (57), CJ-13,015 (58), CJ-13,0102 (59), CJ-13,103 (60), CJ-13,104 (61), and CJ-13,108 (62), from the basidiomycete Phanerochaete velutina CL6387 (Figure 15).\textsuperscript{43}
General screening tests against a wide range viral infections and diseases revealed that all of these phthalides exhibited anti *Helicobacter pylori* activity. CJ-12,954 (56) and CJ-13,014 (57) were the most potent with MICs of 5 ng/ml establishing that the
presence of a spiroketal moiety in addition to a phthalide unit enhances biological activity. The phthalide compounds (56)-(62) were specific for Helicobacter pylori in that they did not show antibacterial activity when tested against a panel of other micro-organisms.

1.9.3. Mode of action of aromatic spiroketals

Several aromatic spiroketals have been proposed to act as bioreductive alkylating agents.\(^{37}\) Lin et al.\(^{44}\) proposed a mechanism for griseusin A (48) proposing that its hydroquinone (63) formed upon bioreduction acts as a alkylating agent via quinone methide (64) as illustrated below (Scheme 1). In this class of compounds, lactone ring in hydroquinone (63) serves as a leaving group at the benzylic position. Subsequent opening of the pyran ring then generates a second quinone methide. It is possible then for bisalkylation of quinone methide (66) to occur, forming bis-adduct (67). A similar pathway can be used to explain the mechanism of action of griseorhodin C (46), G (47) and heliquinomycin (44) (Scheme 1).
Chapter 1.

Introduction

Scheme 1 Proposed bioreductive alkylation mechanism for Griseusin A (48)
2. Synthesis of spiroketals

2.1 Conformational effects

Studies carried out by Deslongchamps et al., on 1,7-dioxa[5,5]undecane systems (similar arguments can also be applied to [5,4] and [4,4] systems) identified three factors determining the preferred structural conformation:

1. steric influences
2. anomic and related effects
3. intramolecular hydrogen bonding and chelation effects.

To minimize unfavourable 1,3-diaxial steric interactions, there is a preference for sterically large substituents to be in equatorial positions.

Stereoelectronic effects are described in terms of the anomic and exo-anomic effects. The anomic effect is the strong preference for the carbon-oxygen bond at the 2-position in the tetrahydropyran to be in the axial position rather than the equatorial position despite unfavourable 1,3-diaxial steric interactions (Scheme 3).
There are two ways to explain the anomeric effect. The first explanation considers the dipolar effects to be destabilizing due to repulsion by lone-pair-lone-pair interactions in the β-anomer (69) hence making the α-anomer (68) more stable (Figure 16).

Alternatively, the effect may be stabilizing when an oxygen atoms lone pairs are orientated antiperiplanar to a polar carbon-X (X= OR, NR₂, or halogen, R= alkyl, vinyl, arene) bond, as occurs in the α-anomer (68). The stabilization occurs by partial transfer of an electron pair of one heteroatom to another (Scheme 4).
Scheme 4 Partial transfer of an electron pair in the stabilizing anomeric effect

This process can be illustrated using Frontier Molecular Orbital theory by considering the electronic interaction between the non-bonding electron pair on oxygen and the vacant \( \sigma^* \)-orbital of the adjacent C-O or C-X (X= halogen) bond (thus \( n_o-\sigma^* \) C-O or \( n_o-\sigma^* \) C-X). The oxygen lone pairs are the HOMO in these systems, the antibonding orbital of the \( \sigma \)-bond to the most electronegative substituent is the LUMO, and the antiperiplanar geometry allows optimal overlap (Figure 17).

![Figure 17 n-\( \sigma^* \) overlap as represented by the arrows](image)

The exo-anomeric effect refers to the preference for the gauche conformation about the OR (R= alkyl, vinyl, arene etc) bond of the substituent group. Three staggered conformations are possible for rotation around this bond in both the axial equatorial forms of a 2-alkoxytetrahydropyran, (73)-(78). In (75) and (77), there is a 1,3-diaxial repulsion with the axial H on C-4 in (75) and C-3 in (77). In order to minimize this interaction the choice is between the gauche (73), (76) and antiperiplanar (74), (78)
conformations. Since there is a stereoelectronic preference for conformations in which the best donor lone pair or bond is antiperiplanar to the best acceptor bond, the gauche effect predicts (73) and (76) are the preferred conformers (Figure 18).

![Diagram showing gauche and anti conformations](image)

**Figure 18** Conformations of the O-R (R= alkyl, vinyl, arene etc) bond

As a result of these factors Deslongchamps *et al.*\(^{45}\) came to the conclusion that the spiroketal 1,7-dioxaspiro[5.5]undecane (79), can exist in one of three possible conformations, namely (80), (81) or (82) (Figure 19).
In conformer (80), two oxygens have an electron pair (shaded lobe) antiperiplanar to a C-O bond, (81) has only one such oxygen, whereas (82) has none. This means (81) has two anomeric effects, (81) has one and (82) has none. Since anomeric effects are considered to be additive the relative stabilities of each conformer were calculated in terms of relative energies and the result was that (80) is the preferred conformation.

Intramolecular hydrogen bonding and related chelation effects can also have an important effect on the observed conformation. Ireland\textsuperscript{49} observed hydrogen bonding between axial hydroxy groups and 1,3-diaxial C-O spiro bonds when all four isomers of (83) isomerised upon hydrogenolysis of the benzyl group to give, only one of two possible compounds (84) which had the same configuration at the spiro centre but were epimeric at the ethoxycarbonyl-bearing carbon (Scheme 5).
Chapter 1.

Introduction

2.2 General methods

Over the past few decades there have been a number of strategies designed for the synthesis of spiroketa ls. These strategies have been extensively reviewed by several authors.\textsuperscript{1,50} By far the most commonly used approach involves the cyclisation of a dihydroxy ketone precursor (Scheme 6).

\begin{align*}
\text{Scheme 6} & \quad \text{Cyclisation of a pre-spiroketal}
\end{align*}

This method is most useful when the target spiroketal possesses the trans-diaxial conformation (85) in which the carbon-oxygen bond of each ring can adopt an axial position on the neighbouring ring thereby gaining maximum stabilization from the anomeric effect.\textsuperscript{45}
Chapter 1.

Introduction

There are four main strategies for the construction of dihydroxyketone precursors to spiroketals, (a) nucleophilic attack onto a carbonyl group that then becomes the spiroketal carbon\textsuperscript{56}, (b) alpha-alkylation of a carbonyl group that is then converted to a spiroketal\textsuperscript{57}, (c) aldol reaction involving the spiroketal carbonyl as an enolate\textsuperscript{58} and (d) use of acyl anion equivalents\textsuperscript{59} e.g. dithianes, nitro groups. These strategies are illustrated in the figure below (Figure 20).

Figure 20 Strategies used to construct spiroketals via a dihydroxyketone precursor

The remaining alternative methods to prepare spiroketals are listed below and are summarized in Scheme 7:

(i) **Intramolecular ring closure reactions**: additions to lactones\textsuperscript{60}
(ii) Intramolecular additions to unsaturated C-C bonds:
   (a) cyclisations of cyclic enol ethers\textsuperscript{61}
   (b) intramolecular conjugate additions\textsuperscript{62}

(iii) Carbonyl cascade processes\textsuperscript{63}

(iv) Hetero Diels-Alder cycloadditions\textsuperscript{64}

(v) Olefination processes\textsuperscript{65}

(vi) Electrophilic cyclisation\textsuperscript{66}

(vii) Radical cyclisation\textsuperscript{67}

(viii) Ring closing olefin metathesis\textsuperscript{68}

\textbf{Scheme 7} General methods for the synthesis of spiroketals
Chapter 1. Introduction

Later in the chapter the relevant methods chosen for spiroketal synthesis in the present investigation will be discussed in more detail using appropriate examples from the literature.

2.3 Synthesis of Aromatic spiroketals

As previously mentioned (section 1.9) aromatic spiroketals can be classified into two categories (Type 1: fused, Type 2: isolated) based on their chemical structure. The most common aromatic spiroketals are of type 1 which is reflected in the number of synthetic methods to prepare them. These synthetic endeavours are not only fuelled by the observed biological activity of aromatic spiroketals but also by their rich and challenging structures. Synthetic approaches to aromatic spiroketals of both classes will be discussed in this section.

2.3.1 Synthesis of Type 1 Aromatic spiroketals

2.3.2.1 Synthesis of the Rubromycins and Heliquinomycin

A total synthesis of the rubromycins has yet to be achieved, however syntheses of both the naphtharazin (88) and isoucomarin (89) moieties of the rubromycins have been achieved (Scheme 8). An efficient synthesis of the skeletal core of the rubromycins has also been reported.
Chapter 1. 

Introduction

Scheme 8 Retrosynthesis of the rubromycins to afford naphtharazin (88) and isocoumarin (89) building blocks

\[ \gamma\text{-Rubromycin (R = H, R}_1\text{ = H, R}_2\text{ = H) (42)} \]

\[ \text{Purpuromycin (R = H, R}_1\text{ = H, R}_2\text{ = OH) (43)} \]

\[ \text{Heliquinomycin (R = O-cymarose, R}_1\text{ = OH, R}_2\text{ = H) (44)} \]

\[ \text{MeO} \quad \text{OMe} \]

\[ \text{P = protecting group} \]

\[ \text{reduced naphtharazin (88)} \quad \text{isocoumarin (89)} \]

de Koning and co-workers\(^\text{72}\) developed a strategy to prepare an arylspiroketal core of \(\gamma\text{-rubromycin (42)}\) through the use of a Henry condensation and a novel Nef-type reaction mediated by Pearlman’s catalyst. The synthesis initially required preparation of a substituted benzaldehyde (90) (Scheme 9) and nitro alkane (91) (Scheme 10).
Chapter 1. Introduction

Conditions: (i) (a) MMPP, MeOH; (b) Silica, 94%; (ii) MOMCl, Pr$_2$NH, CH$_2$Cl$_2$, 0 °C, 88%; (iii) (a) n-BuLi, THF, TMEDA, -78 °C; (b) (CH$_2$O)$_n$, 87%; (iv) PCC, Celite, CH$_2$Cl$_2$, 86%; (v) p-TsOH, dioxane-H$_2$O, 55 °C, 96%; (vi) BnBr, K$_2$CO$_3$, DMF, 70 °C, 97%.

Scheme 9

Conditions: (i) CH$_2$=CHCH$_2$Br, K$_2$CO$_3$, 99%; (ii) 180 °C, 91%; (iii) BnBr, K$_2$CO$_3$, Me$_2$CO, 86%; (iv) O$_3$, MeOH, -40 °C; (v) Zn, AcOH, 84%; (vi) MeNO$_2$, cetyltrimethylammonium bromide, 0.025 Mol L$^{-1}$ NaOH, 100%; (vii) MsCl, Pr$_2$NEt, CH$_2$Cl$_2$, 96%; (viii) NaBH$_4$, MeOH/THF, 70%.

Scheme 10
Coupling of (90) and (91) *via* a Henry condensation using ammonium acetate in acetic acid in a microwave\(^73\) afforded the desired nitro olefin (103) in 58\% yield (Scheme 11). Exposure to Pearlman's catalyst [Pd(OH)\(_2\)/C in 96\% ethanol with a drop of concentrated HCl in cyclohexene] under an atmosphere of hydrogen afforded the desired spiroketal (106) in 62\% yield together with 17\% yield of the nitro compound (104).
Behar et al.\textsuperscript{69} synthesised a fully functionalised isocoumarin (109) of the DNA helicase inhibitor heliquinomycin (44). Isocoumarin (109) then provided an ideal precursor for a convergent total synthesis of heliquinomycin (44) (Scheme 12).
Chapter 1. Introduction

The synthesis involved treatment of the phthaldehydic acid (111) with a slight excess sodium hydride in DMPU, followed by addition of diethyl bromomalonate, which provides the cyclic compound (112) in 90% yield (Scheme 13). The excess hydride is presumed to facilitate the base catalysed aldol ring closure to (112) via the malonate ester of (111). Decarboxylative elimination affords (113) in 81% yield, which was then subjected to Fisher esterification to give (114) in 85% yield. Removal of the methyl ethers using BBr₃ provides an unstable isocoumarin catechol (115) in 98% yield which was then selectively allylated using sodium hydride and allyl bromide at -20 °C. The resultant allyl ether (116) was subjected to a thermal Claisen rearrangement without purification. The unstable catechol (117) was protected as its bis-(p-methoxybenzyl) ether derivative (109) in 70% overall yield from (116) (Scheme 13).
Kozlowski and Waters\textsuperscript{70} developed a route to the isocoumarin (89) present in the rubromycins (Scheme 8). Their strategy involved construction of a diester (121) from catechol (118) by the addition of CO$_2$ at high pressure followed by Fisher esterification (Scheme 14) and methylation. Monoiodination of diester (120) afforded iodide (121) that underwent selective hydrolysis to carboxylic acid (122).
The carboxylate group was then reduced using BH$_3$ in THF and the resultant alcohol protected as a tert butyldimethylsilyl ether (123) in 87% overall from (122) (Scheme 14). Heck coupling of (123) with methyl enol ether (124) provided 71% yield of (125) which upon exposure to 5% HCl/MeOH effected acid catalysed formation of isocoumarin (89) in 83% yield (Scheme 14).
Kozlowski and Xie\textsuperscript{71} also developed a strategy to a reduced version of the naphthazin ring (88) present in the rubromycins (Scheme 8). The synthesis involved construction of a chromium carbene (128)\textsuperscript{75} from vanillin (126) which then underwent a Dotz cyclisation with acetylene (129) to give the protected naphthol (130) in 53% yield (Scheme 15). Protection of the naphthol with benzyl bromide provided (131) in which the two \textit{tert}-butyldimethylsilyl ether groups now possess different oxidation potentials. DDQ oxidation gave aldehyde (132), which was then reduced to an alcohol using sodium borohydride and protected as a MOM ether (133). Removal of the \textit{tert}-butyldimethylsilyl ether with TBAF followed by oxidation of the resulting alcohol using Dess-Martin periodinane\textsuperscript{76} afforded aldehyde (134). Baeyer-Villiger oxidation buffered by \textit{m}CPBA provided a formate ester, which underwent hydrolysis with ammonia in ethanol to generate the unstable phenol (135). Phenol (135) was therefore immediately protected as a benzyl ether (136) in 55% yield from (134) (Scheme 15).
Chapter 1.

Introduction

Scheme 15

Conditions: (i) (a) Br₂, AcOH, (b) NaH, BnBr, 86%; (ii) (a) mCPBA, (b) KOH, (c) NaH, BnBr, 61%; (iii) (a) n-BuLi, (b) Cr(CO)₆, (c) Me₃OBF₄, 60-90%; (iv) THF, Ac₂O, 53%; (v) BnBr, K₂CO₃, 81%; (vi) DDQ, CH₂Cl₂/H₂O, 80%; (vii) (a) NaBH₄, (b) MOMCl, 85%; (viii) (a) TBAF, (b) Dess-Martin, 90%; (ix) (a) mCPBA, NaHCO₃, CH₂Cl₂, (b) NH₃, EtOH; (x) BnBr, K₂CO₃, 55% from (134).
2.3.2.2 Synthesis of the Griseusins

One of the few aromatic spiroketals to have succumbed to total synthesis are the pyranonaphthaquinone antibiotics Griseusin A (48) and B (49). These were prepared by Yoshii in 1983. The tetrahydropyran portion of the spiroketal was constructed from enantiopure aldehyde (137) that in turn was prepared in 30% overall yield from a carbohydrate sugar precursor (138) (Scheme 16).

The key step involved coupling the enantiopure aldehyde (137) with a 3-bromojuglone derivative (139) via halogen-metal exchange to yield a mixture of alcohols, which were oxidized to ketone (142) without purification. Addition of HOBr across the alkene, followed by in situ spirocyclization formed a mixture of spiroketals (143a) and (143b), the major isomer being the undesired axial isomer (143a). This mixture was converted into a mixture of nitriles, which upon hydrolysis by aqueous base afforded a single spiroketal (144). Acetylation, followed by acetal deprotection and oxidation to the quinone using silver oxide and nitric acid, yielded (+)-griseusin B (49) (Scheme 17).
Griseusin A (48) was synthesized from griseusin B (49) by stirring the latter in pyridine overnight allowing conversion to occur via a quinone methide intermediate.
(Scheme 18). Intramolecular conjugate addition of the carboxylic acid to the quinone methide forms a hydroquinone, which oxidizes in air to (48) (Scheme 18).

\[ \text{Griseusin B (49)} \]

\[ \text{(i)} \rightarrow \]

\[ \text{Griseusin A (48)} \]

**Conditions:** (i) pyridine, air, 25 °C, 15h, 63%.

**Scheme 18**

Brimble and Nairn\(^{79,80}\) developed strategies to the basic pentacyclic framework of griseusin A (48). The approach involved reaction of naphthoquinone (147) with 2-trimethylsilyloxyfuran (148) to yield the corresponding furan[3,2-b]naphtho[2,1-d]furans (149a, 149b) which upon oxidative rearrangement to lactols (150). Subsequent cyclisation with camphorsulfonic acid in dichloromethane then provided analogues (151a) and (151b) of griseusin A (48) (Scheme 19).
Chapter 1.

Introduction

\[
\text{(146)} \rightarrow \begin{cases} 
\text{(147)} + \text{(148)} 
\end{cases}
\]

\[
\begin{array}{c}
\text{(149a)} \\
\text{(149b)} \\
\text{(150a)} \\
\text{(150b)} \\
\text{(151a)} \\
\text{(151b)}
\end{array}
\]

Conditions: (i) CAN, CH$_3$CN, H$_2$O; then (148), 42%; (ii) CAN, CH$_3$CN, H$_2$O, then 5% HF 48%; (iii) CSA, CH$_2$Cl$_2$, reflux, 52%.

Scheme 19
2.3.2.3 Synthesis of the Papulacandins

Successful synthetic approaches to the C-aryl glycosidic spiroketal ring system present in the papulacandins have been reported and are divided into the following sections.

(a) Coupling of an aryl lithium with a protected gluconolactone.
(b) Palladium (0) catalysed coupling of an aryl halide with a stannyl glucal.
(c) Hetero-Diels-Alder reaction.
(d) Recent syntheses of the papulcandins

The principal features of these three approaches are discussed below.

(a) Coupling of an aryl lithium with a gluconolactone

Coupling of an appropriately substituted aryl lithium (152) with a protected gluconolactone (153) followed by spirocyclization would result in the construction of the tricyclic spiroketal nucleus of the papulacandins (Scheme 20).
Scheme 20 Coupling of an aryl lithium with a gluconolactone

Adapting this strategy, Schmidt and Frick\textsuperscript{81} found that the coupling between lithiated derivative (157) of 5-(hydroxymethyl)resorcinol and 2,3,4,6-tetra-O-benzyl-D-glucuronolactone (158) resulted in only low yields of lactol intermediate (159) (Scheme 21).

Scheme 21
The same researchers then examined the use of D-glucose aldehyde derivative (160) as well as its ester derivative, methyl gluconate (161) and found that these two compounds acted as better electrophiles with the organolithium (157) than gluconolactone (158) (Scheme 22).

Scheme 22

Rosenblum and Bihovsky\textsuperscript{82} also reported the use of 2,3,4,6-tetra-O-benzyl-D-gluconolactone (158) and MOM protected lithiated derivative (165) of 5-
(hydroxymethyl)resorcinol in their synthesis of the spiroketal nucleus of papulacandin D (52) (Scheme 23). Like Schmidt and Frick, Rosenblum and Bihovsky obtained low yields (14% each) of the two resultant spiroketal epimers (166) and (167). Significantly, conjugated lactone (168) was recovered in 50% yield. Attempted equilibration of the two epimers (166) and (167) with camphorsulfonic acid (8 h, 45 °C) or Dowex® 50 resin (3 days, 22 °C) did not alter the ratio.

It was postulated that conjugated lactone (168) was the major product because the basic alkoxide (165) encouraged enolate formation from gluconolactone (158) and thus the subsequent β-elimination of its benzyloxy group. The benzyl alcohol of (165) was therefore protected as a tert-butylidimethylsilyl ether (Scheme 24).
organolithium (169) with gluconolactone (158) afforded acyclic hydroxy ketone (170) in 42% yield while conjugated lactone (168) was formed in only 20% yield.

The silyl protecting group in (169) was removed using tetrabutylammonium fluoride to afford (171) in near quantitative yield. Subsequent hydrogenolysis of the benzyl groups induced cyclisation of (171) to spiroketal (172), formed exclusively as the β-anomer in 82% yield. Removal of the MOM protecting groups using Dowex® 50 resin then provided the tricyclic C-arylglycosyl spiroketal nucleus of the papulacandins (173) in 77% yield.
Czernecki and Perlat\textsuperscript{83} employed a similar approach to construct the tricyclic nucleus of papulacandin D (53). Lithiated derivative (174) of triphenylmethyl 2-bromobenzyl ether was reacted with 2,3,4,6-tetra-\textit{O}-benzyl-\textit{D}-gluconolactone (158) to give a mixture of hemiketals (175) in 19\% yield (Scheme 25), with the major product being unsaturated lactone (168) as experienced by Schmidt and Frick. The crude mixture of hemiketals (175) was then treated boron trifluoride etherate and triethylsilane to afford aryl spiroketal (176) exclusively as the β-anomer in 74\% yield. Spiroketal (176) was subsequently debenzylated by palladium-catalysed hydrogenolysis to give (177) in 98\% yield (Scheme 25).
Barrett and co-workers\textsuperscript{84} also used a similar approach in their total synthesis of papulacandin D (53). The lithiated species (178) was reacted with 2,3,4,6-tetra-\text{O-}
(trimethylsilyl)-\text{D-}glucosonolactone (179), affording hemiketal intermediate (180)
(Scheme 26). Treatment of (180) with Amberlite\textsuperscript{\textregistered} IR-120 followed by methanol provided the partially desilylated spiroketal (181) exclusively as the $\beta$-anomer in 29\% yield. Treatment of (181) with di(\textit{tert}-butyl)silyldi(trifluoromethanesulfonate)\textsuperscript{85} gave the silylene derivative (182) in good yield.
The unsaturated ester (183)\textsuperscript{84} was cleanly hydrolysed to acid (184) using potassium trimethylsilanolate,\textsuperscript{86} and converted to the mixed anhydride (185) with 2,4,6-trichlorobenzoyl chloride.\textsuperscript{87} Addition of (185) to a mixture of spiroketal (182) and 4-(dimethylamino)pyridine (DMAP) resulted in selective $O$-3 esterification to give the protected papulacandin D (187) in 57\% and the $O$-2 ester (186) in 14\% yield. Global deprotection of (187) was accomplished by treatment with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)\textsuperscript{88} to yield synthetic papulacandin D (53) in 64\% yield (Scheme 26).
Chapter 1. Introduction

Scheme 26

Conditions: (i) Et₂O, -78 °C; (ii) Amberlite IR-120, (b) MeOH, 29% overall; (iii) (Bu)₂Si(O Tf)₂, 2,6-lutidine, CH₂Cl₂, 85%; (iv) Me₂SiOK, THF; (v) Et₃N, 2,4,6-trichlorobenzoyl chloride, THF; (vi) (182), DMAP, DMF, 70% overall, 4 : 1 (3 esters); (vii) TASF, THF, 64%.

Papulacandin D (53)
(b) Palladium-catalysed coupling of an aryl halide with a stannyl glucal

The synthesis of the spiroketal nucleus of the papulacandins has also been achieved using palladium(0) catalysed Stille\textsuperscript{99} coupling of an aryl bromide with a stannyl glucal, followed by epoxidation of the enol ether double bond and subsequent spirocyclisation. Friesen and Sturino\textsuperscript{99} reported the coupling between 3,4,6-tri-O-(tert-butyldimethylsilyl)-1-(tributylstannyl)-D-glucal (188) and 3,5-bis(benzyloxy)-2-bromobenzyl acetate (189) in the presence of a palladium catalyst, affording C-arylglucal (190) as well as dimer (192) (Scheme 27). The yield of C-arylglucal (190) was maximised by using an excess of glucal (188) and allowing aryl bromide (189) to be the limiting reagent. In this manner, C-arylglucal (190) was obtained in 85\% yield. Reductive deprotection of (190) by lithium aluminium hydride provided benzyl alcohol (191) in 96\% yield.
Chapter 1. Introduction

Glycal (191) underwent epoxidation with dimethyldioxirane (DMDO), and following rapid intramolecular trapping of the initially formed α-epoxide by the benzylic hydroxyl group, the two anomic spiroketalts (193) and (194) were obtained in a
combined yield of 84% ((193):(194) 1:5) (Scheme 25). Isomerization of (193) to (194) was effected by a catalytic quantity of pyridinium para-toluenesulfonate (PPTS) at room temperature to provide the desired epimer in 80% yield. Deprotection of (194) was achieved by hydrogenolysis and treatment with tetrabutylammonium fluoride (TBAF) to afford (173), the papulacandin nucleus.

(c) Hetero Diels-Alder reaction

Danishefsky and co-workers\textsuperscript{91} utilised hetero Diels-Alder methodology to construct the spiroketal core of the papulacandins. As demonstrated below (Scheme 28) diene (195) was added with benzaldehyde derivative (196) via a hetero Diels-Alder reaction catalysed by Yb(fod)_3 to afford pyrone (197) in 92% yield. Treatment of pyrone (197) with vinyl magnesium bromide in the presence of cuprous iodide afforded tetrahydropyronene (198) in 70% yield. Oxidation of (198) using osmium tetroxide-sodium metaperiodate produced unstable ketoaldehyde (199), which was immediately treated with a tris(3-ethyl-3-pentyloxylaluminium) hydride reagent to give keto alcohol (200). Benzoylation of this keto alcohol using acetic anhydride then afforded (201) in 59% yield from (199).
In order to introduce oxygen function onto the pyrone, (201) was treated with hexamethyldisilazaine in the presence of iodonitromethylsilane to give a mixture of enol ethers (202) that were then treated with m-chloroperbenzoic acid, followed by methanol and benzyl chloride in pyridine to afford the desired keto benzoate (203), in 17% yield after purification by HPLC (Scheme 29). The next step involved the installation of an oxygenated substituent at C1 of pyrone (203) via an enone intermediate in order to set the stage for the construction of the spiroketal moiety. Treatment of (203) with lithium hexamethyldisilazaine, followed by quenching of the
reaction with chlorotrimethylsilane, gave a crude silyl enol ether which was subjected to palladium (II) acetate in acetonitrile to give enone (204) in 78% yield (Scheme 29).

Conditions: (i) (Me₃Si)₂NH, Me₃SiI; (ii) (a) mCPBA, (b) CH₃OH, (c) BzCl in py, 17% from (201); (iii) (a) LiN(SiMe₃)₂, (b) Me₃SiCl, (c) Pd(OAc)₂, 78% from (203); (iv) (a) (′Bu)₂AlH, -78 °C, (b) Ac₂O, 56%; (v) mCPBA in CH₃OH, 82%.

Scheme 29

Reduction, followed by acetylation of enone (204) afforded pseudoequatorial acetate (205) in 56% yield, which was then oxidised with m-chloroperoxybenzoic acid in methanol to give a mixture of methyl glycosides (206) in 82% yield (Scheme 29).

The final phase of the synthesis began with the cleavage of all the esters groups of (206) using sodium hydroxide in methanol to afford (207) (Scheme 30). Treatment of (207) with hydrochloric acid in methanol effected spirocyclisation. The resultant
product was dissolved in ethyl acetate and subjected to hydrogenolysis to afford the debenzyalted product. Acetylation using acetic anhydride afforded hexaacetate (208) in 38% yield from (207) (Scheme 30).

![Scheme 30]

(d) Other synthetic strategies to the papulacandins

(i) Use of α-sulfonyldihyfuran

More recently the [4,5]-spiroketal moiety of the papulacandins has been assembled by Carretero et al.\(^9\) using condensation of a D-arabino-1,4-lactone with a α-lithiated carbanion of a β-phenylsulfonyldihydrofuran (211) (Scheme 31).

![Scheme 31]

The required β-phenylsulfonyldihydrofuran (215) was readily prepared from dihydrofuran by sulfonylation at the β-position with phenyl methyl sulfoxide in the
presence of trifluoroacetic anhydride and subsequent \(m\)-chloroperoxybenzoic acid oxidation to give (215) in 88% overall yield (Scheme 32).

![Scheme 32](image)

The protected D-arabino-1,4-lactone was prepared in gram quantities in two steps from D-arabino-1,4-lactone (217)\(^9\) (available from D-glucose (216)) by reaction with di-\textit{tert}-butylsilyl-\textit{bis}(trifluoromethanesulfonate) and 2,6-lutidine giving (218) and further quantitatively silylated with trimethylsilyl chloride and imidazole to give (218) in 78% yield from (217) (Scheme 33).

![Scheme 33](image)

\(\alpha\)-Deprotonation of the \(\beta\)-phenylsulfonyldihydrofuran (215) with \(n\)-BuLi in THF at \(-78\ \degree\)C followed by reaction with (218) afforded spiroketal (219) as a single isomer in 40% yield after purification\(^9\) (Scheme 34).
Reduction of the carbonyl with sodium borohydride in methanol was fully stereoselective leading to the desired equatorial alcohol (220) in 94% yield. Finally, reductive elimination of the sulfonyl group was achieved via reaction with a sodium mercury amalgam in methanol affording the dihydroxy spiroketal (221) in 41% yield (Scheme 34).

(e) Use of Achmatowicz oxidative rearrangement of a furan

O’Doherty et al. made use of the Sharpless enantioselective catalytic asymmetric dihydroxylation of 5-aryl-2-vinylfurans to provide diols which underwent functional group manipulations to provide precursors to the spiroketal ring present in the papulacandins (Scheme 35). The spiroketal ring itself was formed using an Achmatowicz oxidative rearrangement of a furan.
Chapter 1. Introduction

Scheme 35 Retrosynthesis of papulacandin D (53) using the Achmatowicz oxidative rearrangement of a furan

The appropriate 5-aryl-2-vinylfurans were prepared from furfural and an appropriate aryl halide in a three-step Stille coupling route (Scheme 36). After protection of furfural (224) with tert-butyl-dimethylsilyl chloride, Wittig methylenation provided a quantitative yield of a terminal alkene that underwent Sharpless catalytic asymmetric dihydroxylation to diol (225). Pivaloylation of the primary alcohol group then gave (226) in 69% overall yield from (224). Exposure of (226) to Achmatowicz spiroketalization conditions (NBS, NaHCO₃, then 1 Molar L⁻¹ HCl) then provided enone (227) as a 4:1 mixture of anomers in 47% yield (Scheme 36). Treatment of (227) with sodium borohydride provided (228) as a single diasteromer of the
spiroallylic alcohol in 88% yield after purification (Scheme 36). The allylic alcohol (228) was then protected as a tert-butyl-dimethylsilyl ether (229), which upon dihydroxylation of the double bond with osmium tetroxide gave the tricyclic C-aryl mannopyranoside nucleus of papulacandin D (53) as the major isomer (230) in 69% yield. The stereochemistry of (230) was confirmed by X-ray crystallography and the unprotected sugar was then obtained in a two-step procedure to give (232) (Scheme 36).
Conditions: (i) (a) TBSCI, (b) Ph₂P=CH₂, (c) AD mix α; (ii) PivCl, 69%; (iii) NBS, NaHCO₃ then 1 Mol L⁻¹ HCl, 47%; (iv) NaBH₄, 88%; (v) TBSCI, DMF, 64%; (vi) OsO₄, t-BuOH/H₂O, 69%; (vii) DIBAL-H, 93%; (viii) TBAF, 93%.

Scheme 36
(f) Addition of a lithiated glycal to a quinone

As described above one of the main techniques used to synthesize C-aryl glycosides involves coupling of an aryl lithium species with a protected gluconolactone. Recently Parker et al.\textsuperscript{97} developed an umpolung approach involving nucleophilic 1,2-addition of a lithiated glycal to a functionalised quinone which after reductive aromatisation provides the C-arylglycoside. This approach afforded access to either the papulacandin or chaetiacandin nucleus (Scheme 37).

![Scheme 37: Access to the papulacandin nucleus through the use of lithiated glycals](image)

Addition of the lithiated glycal (234) to the quinone (233) was achieved in a modest 33% yield and was regioselective to the carbonyl flanked by the two oxygenated protecting groups which presumably aided in chelation control. The synthesis of the lithiated glycal (234) and quinone (233) are summarised below (Scheme 38).
Chapter 1.

Introduction

Oxidation of (235) with $m$CPBA cleanly to the $\alpha$-face provided the $\alpha$-epoxide in 84% which upon deprotection of the benzyl groups with hydrogen and palladium on carbon allowed spiroketalization to (243). Finally protection of the aromatic hydroxyl groups with tri-isopropylsilyl chloride gave the desired papulacandin nucleus (Scheme 38).
Chapter 1: Introduction

**Scheme 38**

Conditions: (i) BnBr, NaH, THF, 73%; (ii) NaBH₄, MeOH, 98%; (iii) BnBr, NaH, DMSO, 68%; (iv) O₂, salcomine, DMF, 72h, 64%; (v) (a) K₂CO₃, MeOH, 98%, (b) (r-Bu)₂Si(OTf)₂, 2,6-lutidine, DMF, -50 °C, 10h, 91%, (c) TIPSCI, imidazole, 45 °C, 24h, 96%; (vi) 2eq. r-BuLi, THF, -78 °C - 0 °C, 2h; (vii) addition of (233), BF₃·Et₂O, THF, -78 °C, 8h, 33%; (viii) (a) 5 eq. Na₂S₂O₄, THF/H₂O (5:2), 8h, (b) BnBr, NaH, THF, 85% over 2 steps; (ix) (a) mCPBA, 10:1 MeOH/THF, 2 days, 84%, (b) H₂, Pd/C, EtOAc/MeOH, (c) TIPSCI, 2.2 eq. Et₃N, CH₂Cl₂, 86% over 2 steps; (x) BH₃·THF, H₂O₂, aq. NaOH 81%.
Chapter 1.

3. The present investigation

3.1 Synthetic studies towards Type 1 aromatic spiroketalts:

Synthesis of analogues of the papulacandins

The advent of Acquired Immune Deficient Syndrome (AIDS) has highlighted the existence of an increasing number of serious opportunistic fungal infections in the last decade. This increase is due to a proliferation of immune deficiency syndromes. Dermatophyte fungal infections like *tinea pedis* and *candidiasis* although rarely fatal are widespread throughout the world. There are fungal diseases that are far darker in reputation and significance. Pathogens such as *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis carinii* and *Aspergillus fumigatus* cause considerable morbidity and mortality in immuno-compromised patients. Many of the current antifungal therapies such as the gold standard Amphotericin B (245) or the more recent Sulfamethoxazole (246) (*Figure 21*) are toxic to the host, experience resistance problems or are ineffective against new fungal diseases. Clearly there is a pressing need for development of new antifungal agents that combine high selectivity with low toxicity to the host and overcome drug resistance problems.
With such encouraging anti-fungal properties, the papulacandin family of antibiotics may provide the panacea required. These compounds and their synthesis have been the focus of attention in the Brimble research group who initially concentrated on a two step synthesis of a range of aryl spiroketals related to the papulacandins, via the addition of ortho-lithiated tertiary benzamides to lactones followed by acid-catalysed cyclization of the resultant keto alcohols (Scheme 39).
Difficulties were encountered when this methodology was applied to the synthesis of aryl spiroketals containing a similar oxygenation pattern to that present in the papulacandins owing to steric hindrance by the neighbouring methoxy group in the starting amide (251), which hindered addition of the bulky lactone electrophile to the ortho position of amide (251) (Scheme 40).
These difficulties were overcome through work by Brimble and Johnston\textsuperscript{101} who utilized phthalide acetates prepared from mono- or di-methoxy \(N,N\)-diethylbenzamides, as masked oxycarbenium ions (Scheme \textbf{41}). These oxycarbenium ions were then reacted with a range of allyl stannanes in the presence of Lewis acid trimethylsilyl triflate at -78 °C to give the appropriate allyl phthalides (Scheme \textbf{42}). Hydroboration of the double bond provided primary alcohols which then underwent oxidative cyclisation using iodobenzene diacetate to give aryl spiroketal analogues of the papulacandin.

Reaction of phthalide (261) with allylstannane (278) was of particular interest as it provided aryl spiroketal (281) with the required [5,6] spiroketal present in the papuacandins. (Scheme \textbf{43}). In this case the allylated adduct (279) underwent
deprotection with tetrabutylammonium fluoride to alcohol (280) that then underwent hypoiodite induced oxidative cyclisation to the [5,6] spiroketal (281).

\[
\begin{align*}
\text{R} &= \text{H (254), OMe (255)} & \text{R} &= \text{H (256), OMe (257)} & \text{R} &= \text{H (258), OMe (259)} \\
\text{(i)} & \rightarrow & \text{(ii)} & \rightarrow & \text{(iii)} & \rightarrow \\
\text{(262) Oxycarbenium ion} & \rightarrow & \text{Lewis Acid} & \rightarrow & \text{R} &= \text{H (260), OMe (261)}
\end{align*}
\]

Conditions: (i) (a) t-BuLi, TMEDA, THF, -78 °C, (b) DMF; (ii) HOAc, aq HCl, R = H (258) 67%, R = OMe (259) 63%; (iii) Ac₂O, Et₃N, DMAP, CH₂Cl₂, R = H (260) 90%, R = OMe (261) 98%.

Scheme 41
Chapter 1.

Introduction

R₁ = H (260), OMe (261)
R₂ = H, R₃ = H (263)
R₂ = Me, R₃ = H (264)
R₂ = H, R₃ = Me (265)
R₁ = OMe
R₂ = H, R₃ = H (266), 71%
R₂ = Me, R₃ = H (267), 98%
R₂ = Me, R₃ = Me (268), 43%
R₂ = H, R₃ = Me (269), 72%

R₁ = H
R₂ = H, R₃ = H (274), 31%
R₁ = OMe
R₂ = H, R₃ = H (275), 83%
R₂ = Me, R₃ = H (276), 72%
R₂ = H, R₃ = Me (277), 83%
R₁ = OMe
R₂ = H, R₃ = H (271), 50%
R₂ = Me, R₃ = H (272), 51%
R₂ = H, R₃ = Me (273), 54%

Conditions: (i) Me₃SiOTf, CH₂Cl₂, -78 °C; (ii) (a) BH₃-THF, 0 °C, (b) 3 mol L⁻¹ NaOH, 30% H₂O₂; (iii) Phl(OAc)₂, I₂, hv.

Scheme 42
The aim of the present investigation was to extend the work of Johnston by optimising the yields in the steps to aryl spiroketal (281) (Scheme 43) and then prepare analogues of the papulacandin as illustrated below (Figure 22). The compounds thus prepared would be sent for biological evaluation as antifungal agents.
A series of papulcandin analogues could be prepared with a range of different fatty acid side chains attached to C4' of the basic spiroketal ring. The synthesis would follow similar methodology to that outlined in Scheme 43, where the double bond on the pyran ring of spiroketal (281) acts as a handle upon which to attach too. Conceivably, ozonolysis of alkene (281) would afford ketone (287) that upon reduction would provide alcohol (285). Esterification of alcohol (285) with a range of fatty acids would hopefully provide a range of lipophilic aryl spiroketal (284) (Scheme 44).
3.2 Synthetic studies towards Type 2 aromatic spiroketalts:

Synthesis of phthalide-containing spiroketalts

As noted earlier the seven aromatic spiroketal compounds isolated by Dekker et al.\textsuperscript{43} were shown to exhibit selective anti-*Helicobacter pylori* activity when tested against a wide range micro-organisms (Figure 15). To date only one synthesis of one of the seven anti-ulcer phthalide compounds has been reported. Argade et al.\textsuperscript{183} synthesized racemic CJ-13,015 (58) in a six step sequence from 5-methylfurfural (363) in 65% overall yield (Scheme 75). The synthesis is discussed later chapter 3. These compounds have been the focus of a synthetic programme in the Brimble research group especially CJ-12,954 (56) and CJ-13,014 (57) since they contain spiroketal moieties that are of particular interest to this group. CJ-13,108 (62), CJ-13,014 (57) and CJ-12,954 (56) were the initial synthetic targets in this thesis. All three
compounds contain a phthalide moiety, however whereas CJ-13,108 (62) contains a simple straight chain ketone, CJ-12,954 (56) and CJ-13,014 (57) also contain a [4,4]-spiroketal ring system. Details of the configurations at the stereogenic centres in these synthetic targets are illustrated below (Figure 23).

**Figure 23** structures of CJ-13,108 (62), CJ-12,954 (56) and CJ-13,014 (57)
Both CJ-12,954 (55) and CJ-13,014 (56) contain the same configuration at C7' and C13' but differing in their configuration at the spiroketal carbon. The stereochemistry at C2 in the phthalide ring has not been determined for any of the compounds (56)-(62).

3.2.1 Retrosynthesis of CJ-13,108 (62)

Using a Wittig transform, retrosynthetic disconnection between C3' and C4' of CJ-13,108 (62) affords two fragments, namely phthalide (288) and ylide (289) (Scheme 45). The olefin in ylide (289) can be later transformed into a methyl ketone using a Wacker oxidation after union of the ylide (289) with aldehyde (288). This obviates the need to otherwise protect the methyl ketone in the key Wittig step.
3.2.2 Retrosynthesis of the phthalide unit (288) of CJ-13,108 (62)

The phthalide moiety of CJ-13,108 (62) is a regioisomer of a similar phthalide (261, p70) used earlier by Brimble et al. for the synthesis of analogues of the papulacandin. Synthetic pathways to phthalides are therefore well known in this research group thereby providing further impetus for the synthesis of the anti-ulcer compounds CJ-12,954 (56) and CJ-13,014 (57) (Scheme 46). Retrosynthetic disconnections for phthalide aldehyde (288) as required for the synthesis of CJ-12,954 (56) are outlined below (Scheme 43).
Scheme 46 Retrosynthesis of the phthalide (288)
3.2.3 Retrosynthesis of CJ-12,954 (56)

Using the same disconnection as that used above for the retrosynthesis of CJ-13,108 (62), namely disconnection between C3' and C4', affords phthalide (288) and a [4.4] spiroketal (297) as two key intermediates (Scheme 47).
Scheme 47 Retrosynthesis of CJ-12,954 (56)
3.2.4 [4.4] Spiroketal moiety (301)

It was envisaged that the phthalide and spiroketal moieties could be prepared separately then combined at a later stage using similar Wittig chemistry that was outlined above for the synthesis of CJ-13,108 (62). As previously discussed there are many strategies for the synthesis of spiroketals. The strategy chosen in the present work involved construction of a spiroketal precursor using strategy A (nucleophilic attack onto a carbonyl group that then becomes the spiroketal carbon). The nucleophile used in the present case was chosen to be an acetylide anion (Scheme 48).

The use of acetylide ions to prepare precursors to spiroketal construction is well established as illustrated by Marshall et al. in the synthesis of the C1-C21 subunit (311) of tautomycin (312) (Scheme 49). The target structure (311) was elaborated from spiroketal (310), which in turn was formed via cyclisation of the acyclic
protected dihydroxy ketone precursor (309). Transmetallation of lithium acetylide (305) with cerium trichloride gave the corresponding cerium acetylide (306), which was then added to aldehyde (307) to provide alcohol (308) in moderate yield. The resultant alcohol (308) was then oxidized to a ketone and subsequent reduction of the alkyne to an alkane facilitated spirocyclisation to spiroketal (310) upon exposure to methanolic HCl (Scheme 49).
Conditions: (i) CeCl₃; (ii) n-BuLi, THF,-78 °C, 88%; (iii) TPAP, NMO, CH₂Cl₂, 85%; (iv) H₂, Lindlar catalyst, EtOAc, 95%; (v) MeOH, HCl.

Scheme 49
Nakata et al.\textsuperscript{103} prepared the [5.5]-spiroketal fragment of reveromycin A (262) via addition of lithium acetylide (313) to Weinreb amide (314) (Scheme 50). The coupling proceeded in 97% yield affording ketone (315) and after hydrogenation of the triple bond. Selective cleavage of the acetonide using methanol and pyridinium \textit{p}-toluenesulfonate then gave bicyclic ketal (316). The \textit{tert}-butyldiphenylsilyl groups were removed using tetrabutylammonium fluoride to afford bicyclic ketal (317), which was then smoothly converted to a 1:1 mixture of the [5.5]-spiroketal (318) and bicyclic ketal (317) upon standing in CDCl\textsubscript{3} solution at room temperature.
Conditions: (i) n-BuLi, THF, -78 °C, 97%; (ii) H₂, Pd/C, AcOEt, 97%; (iii) PPTS, MeOH, 34%; (iv) TBAF, THF, 80%; (v) CDCl₃, 100%, 1:1 (317):(318).

Scheme 50
The Papulacandins

1. Ortholithiation chemistry

1.1 Introduction

Many modern synthetic targets, in particular those of interest for pharmaceutical and agrochemical preparations incorporate key aromatic or heteroaromatic components. Given the normal aromatic electrophilic substitution rules, regiospecific preparation of poly-substituted aromatic systems (1,2-, 1,2,3-, 1,2,3,4-) is a demanding synthetic challenge in both industrial and academic laboratories. To aid the synthetic chemist in the task of constructing poly-substituted aromatic ring a range of methods have evolved: (Figure 24)

(a) electrophilic substitution via para protection-deprotection
(b) ortho substitution via metal chelation
(c) \( \sigma \)-transition-metal complexes
(d) nucleophilic aromatic substitution S\(_{RN1}\)
(e) nucleophilic substitution of \( \pi \)-arene metal (Cr, Mn) tricarbonyl complexes
(f) sigmatropic rearrangements
(g) carbanionic \textit{de novo} ring construction
(h) cycloaddition with or without small molecule extrusion
(i) transformation of heterocycles
(j) dearomatization-rearomatization tactics
Chapter 2. Discussion

a. electrophilic substitution

\[ \text{E}^+ \rightarrow \text{E}^+ \]

\[ \text{E}^+ = \text{hal}^+, \text{NO}_2^+, \text{RCO}^+ \]

\[ Z = \text{carbon or heteroatom substituent} \]

b. ortho substitution via metal chelation

\[ \text{Y} = \text{NR, O} \]

\[ \text{M} = \text{B, Zn} \]

c. \( \sigma \)-transition metal complexes

\[ \text{M} = \text{Pd, Mn, Rh, Ni} \]

\[ \text{L} = \text{ligand} \]

\[ \text{Y} = \text{NHR, NHCOR, (CH}_2)_n\text{NR}_2, \text{CH}_2\text{OH, CH}=\text{NR, CO}_2\text{H} \]

d. nucleophilic aromatic substitution \( S_{RN1} \)

\[ \text{X} = \text{hal, } ^+\text{NR}_3, ^+\text{SR}_2 \]

\[ \text{Y} = \text{C-, N- substituent} \]

\[ \text{Nu}^- = \text{carbanion, heteroatom anion} \]

e. nucleophilic substitution of \( \pi \)-arene metal tricarbonyl complexes

\[ \text{(CO)}_3\text{Cr} \]

\[ X = \text{Cl, F} \]

\[ \text{Nu}^- = \text{reactive carbanions} \]

f. Sigmatropic rearrangements

\[ Y = Z = \text{carbon, heteroatom substituent} \]

g. de novo aromatic ring construction

h. small molecule extrusion

Figure 24 Synthetic approaches to substituted aromatic compounds
Ortholithiation, the directed metallation of an aromatic ring adjacent to a heteroatom containing functional group, has arguably overtaken classical electrophilic aromatic substitution as a principal means of making regiospecifically substituted aromatic rings. Landmarks in the development of ortholithiation since the first metallations of anisole by Gilman\textsuperscript{120} and Wittig,\textsuperscript{121} have included publication of an extensive review of the area by Gschwend and Rodriguez,\textsuperscript{122} and more recently the introduction and development of amide and oxazoline based directing groups by Beak,\textsuperscript{123} Meyers\textsuperscript{124}, Snieckus\textsuperscript{125,126} and Clayden.\textsuperscript{127}

Ortholithiations typically involve the deprotonation of a substituted aromatic ring by an organolithium, usually \textit{n}-, \textit{s}-, or \textit{t}-butyllithium or (for more electron deficient aromatic rings) LDA. Given that benzene is ten times more acidic than butane, thermodynamics pose no barrier to the removal of any aromatic proton by butyllithium. However, the kinetics of these reactions impede their usefulness, for example \textit{n}-butyllithium deprotonates benzene in hexane negligibly after 3 h at room temperature.\textsuperscript{128,129} The problem is that the reaction of aggregates such as hexameric \textit{n}-butyllithium that form in hydrocarbon solvents are extremely slow,\textsuperscript{130} and only after a lithium coordinating reagent such as monomeric binding THF, bidentate binding TMEDA, or tridentate binding HMPA has broken up the BuLi aggregates, can lithiation proceed at a reasonable rate (Scheme 51).\textsuperscript{129}

\begin{align*}
\text{Conditions: (i) BuLi, TMEDA, 25 °C, 92%}. \\
\text{Scheme 51}
\end{align*}
All hydrocarbon solvents tend to suffer to some extent from the tendency to react with organolithiums, precluding their use at temperatures above ambient and in some cases limiting to their use at 0 °C or below.

$s$-BuLi and $t$-BuLi are well known to decompose ethereal solvents far more rapidly than $n$-BuLi\textsuperscript{131,132} and it wise to avoid THF for extended reactions of $t$-BuLi or reactions conducted above 0 °C. THF readily decomposes by various mechanisms (Scheme 52) at room temperature\textsuperscript{133,134} by reverse cycloaddition of the anion derived from (323).\textsuperscript{135} The products from the decomposition (324) and (325) can be trapped.\textsuperscript{135,136} Occasionally THF decomposes by an alternative mechanism to give but-3-en-1-oxide (326) first observed in solution by Fleming (Scheme 52).\textsuperscript{137}
Usual decomposition pathway for THF

\[
\begin{align*}
\text{(322)} & \quad \xrightarrow{\alpha\text{-elimination}} \quad \text{(323)} \\
\text{(322)} & \quad \xrightarrow{\text{reverse [3+2]}} \quad \text{(324)} + \\
\end{align*}
\]

Alternative decomposition pathway for THF

Scheme 52

1.2 Mechanism

The directed ortholithiation reaction is considered to proceed by providing an alkyllithium with a point of coordination on the substrate, increasing the reactivity near the coordination site (usually via a basic heteroatom, directing metallation group) hence directing the regioselectivity (Scheme 53).\textsuperscript{138}
Infrared and kinetic evidence have shown a "substrate-organolithium" complex formed en route to α-lithiations of functional groups. It can be assumed for strong ortholithiation directing functional groups e.g. OCONEt₂ (not weak such as OMe, Cl) that a coordination between substrate and the organolithium takes place and that deaggregation of the organolithium marks the first step toward lithiation.

The use of intermolecular and intramolecular kinetic isotope effects to identify a complexation step during ortholithiation have been inconclusive. Detailed NMR and theoretical studies identified and characterised a number of complexes along the reaction path of anisole, 1,2-dimethoxybenzene and N,N-dimethylaniline. For example, anisole deaggregates the n-butyllithium hexamer to form a tetramer n-butyllithium-anisole complex (331). Addition of TMEDA displaces the anisole from the tetramer and breaks it down further to a n-butyllithium-TMEDA dimer (332), which deprotonates anisole at temperatures greater than 0 °C yielding (333) (Scheme 54).
Acidity is the only factor directing lithiation when coordination to the heteroatom is electronically or geometrically impossible. An example is the lithiation of fluorobenzene by n-BuLi-TMEDA which occurs slowly at -50 °C, despite the unlikelihood of a strong F-Li complex forming (no PhF-BuLi complex by NMR\textsuperscript{145}). As far as synthetic utility goes, it is clear that rings bearing electron withdrawing substituents which acidify nearby protons \textit{(via inductive effect)} are usually (not always) lithiated more rapidly than those protons which are not. Steric effects are undoubtedly involved, but the following lithiations carried out on 1-substituted naphthalenes\textsuperscript{147,148} \textbf{(Scheme 55)} illustrate the increasing importance of acidity as substituents become more inductively withdrawing \textbf{(Table 3)}. 


\textbf{Scheme 54}
This proton not acidified by X but close to RLi

\[
\begin{align*}
\text{component} & \\
\text{acidified by } X \quad \text{and also close to } RLi
\end{align*}
\]

\[
\begin{align*}
\text{perilithiation (336)} & \\
\text{ortholithiation (337)}
\end{align*}
\]

Scheme 55

Table 3 Ortho- and perilithiation of 1-substituted naphthalenes$^{148,149}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>X=</th>
<th>Conditions</th>
<th>E⁺</th>
<th>% Yield peri (338)</th>
<th>% Yield ortho (339)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{148}$</td>
<td>CH₂NMe₂</td>
<td>BuLi, Et₂O, hexane, 20 °C</td>
<td>Ph₂CO</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>2$^{150}$</td>
<td>NH₂</td>
<td>BuLi, Et₂O, heat</td>
<td>CO₂</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>3$^{151,152}$</td>
<td>NMe₂</td>
<td>BuLi, Et₂O, 20 °C</td>
<td>DMF</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>4$^{153}$</td>
<td>OH</td>
<td>n-BuLi, THP, 50 °C</td>
<td>Me₂S₂</td>
<td>50</td>
<td>19</td>
</tr>
<tr>
<td>5$^{154}$</td>
<td>OMe</td>
<td>t-BuLi, cyclohexane, 20 °C</td>
<td>CO₂</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>6$^{155}$</td>
<td>OMOM</td>
<td>n-BuLi, TMEDA</td>
<td>RCHO</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>7$^{156}$</td>
<td>OCONR₂</td>
<td>s-BuLi, TMEDA, THF, -78 °C</td>
<td>Mel</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>8$^{147,156}$</td>
<td>CONR₂</td>
<td>s-BuLi, TMEDA, THF, -78 °C</td>
<td>various</td>
<td>0</td>
<td>76-93</td>
</tr>
</tbody>
</table>

95
The amino substituted compounds in entries 1-3 are lithiated in the *peri* position, presumably because this is a purely coordination driven lithiation, and the geometry for *peri* lithiation by the amine-complexed BuLi is more favourable than the geometry required for ortholithiation. The presence of oxygenated substituents (entries 4-6) see acidity becoming more prevalent with the inductively electron withdrawing oxygen substituents, while the presence of an amide (entry 7) show exclusive ortholithiation due to its strong electron withdrawing nature.

The relative importance of coordination and acidity can also depend on the base employed during lithiation. Once coordinated to a basic solvent (e.g. THF or TMEDA) organolithiums become less Lewis-acidic: they have a decreased tendency to be directed by coordination and hence acidity becomes the dominant factor as illustrated below (Figure 25).

- **BuLi/TMEDA** deprotonates here
- **BuLi** alone deprotonates here

**Figure 25**

In the absence of TMEDA, deprotonation occurs *ortho* to the more Lewis-basic amino group, while in the presence of TMEDA, deprotonation occurs *ortho* to the more electronegative more acidifying methoxy group.¹⁵⁷
In summary ortholithiation is a reaction that proceeds in two steps, (i) complex formation and (ii) deprotonation. The rate and regioselectivity of lithiation are controlled by coordination between the organolithium and the heteroatom and the acidity of the proton to be removed.

1.3 Classes of directing group

In his 1990 review, Snieckus divided ortholithiation-directing groups into classes according to the ease with which they may be lithiated and the practicalities of their application in synthesis. The list was designed as a rough estimation of the powers of the ortholithiation directing groups (Figure 26).

![Decreasing ability to direct ortholithiation](image)

Typical conditions required for lithiation: RLi in THF or Et₂O at

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symbol</th>
<th>N+O class</th>
<th>O class</th>
</tr>
</thead>
<tbody>
<tr>
<td>-78 °C</td>
<td>-78 °C</td>
<td>-78 °C</td>
<td>0 °C</td>
</tr>
<tr>
<td>-78 °C</td>
<td>-78 °C</td>
<td>-78 °C</td>
<td>0 °C</td>
</tr>
<tr>
<td>-78 °C</td>
<td>-78 °C</td>
<td>-50 °C</td>
<td>&gt;0 °C</td>
</tr>
<tr>
<td>-20 °C</td>
<td>-20 °C</td>
<td>0 °C</td>
<td>&gt;0 °C</td>
</tr>
<tr>
<td>-78 °C</td>
<td>-78 °C</td>
<td>&gt;20 °C</td>
<td>-50 °C</td>
</tr>
</tbody>
</table>

Figure 26 Classes of directing group
The N+O class is by far the most powerful for several reasons. The first stems from their “amphoteric” nature: they all have functional groups with basic heteroatoms (oxygen in carbonyl amide is among the most basic of neutral oxygen atoms in organic chemistry) and many are strongly electron withdrawing and acidify aromatic ring protons. Secondly, they are functional groups that can be transformed to useful targets. The only drawback for the N+O class is that the carbonyl can sometimes suffer nucleophilic attack by the organolithium.

Sulfones and sulfonamides are members of the powerful S+O class. Occasionally they suffer nucleophilic attack on the aromatic ring but never suffer electrophilic attack at sulfur.\(^{158,159}\) The biggest drawback of the S+O class is their limited synthetic applications.\(^{159,160}\)

Less powerful with regard to directing ability (less basic and acidic) but of high synthetic value are functional groups containing only oxygen, the O class. Given that they do not suffer from nucleophilic attack by organolithium reagents, the best O class functional groups have two oxygen’s (e.g. MOM ethers), one attached to the aromatic ring to acidify nearby protons and the other to coordinate the incoming organolithium reagent.

Coordination is the strength of the N class which use their lone pair on nitrogen to lure the organolithium reagents. The drawback with the O and N classes is that they react slower and at higher temperatures than the N+O and S+O classes.

Halogens predominate in the X class which direct by the inductive acidifying effect alone. These functional groups work best when there are additional factors favouring deprotonation, for example if the aromatic ring is an electron deficient heterocycle. The drawback is that halogens are susceptible to attack by organolithiums, and
ortholithiated haloarenes are prone to elimination to give benzyneR, so conditions must be carefully controlled.

2. Synthesis of analogues of the papulacandins:

Synthesis of aryl spiroketal (281)

During the present investigation (section 3.1), it was mentioned the aim was to extend the work of Johnston, by optimising the yields in the steps to aryl spiroketal (281) (Scheme 43) then prepare analogues of the papulacandins as illustrated in Figure 22. The compounds thus prepared would be sent for biological evaluation as antifungal agents.
Chapter 2.

Discussion

Scheme 43

Conditions: (i) Me$_3$SiOTf, CH$_2$Cl$_2$, -78 °C; (ii) Bu$_4$NF, THF, 0 °C; (iii) PhI(OAc)$_2$, I$_2$, hv.

Figure 22: Examples of analogues of the papulacandins
The synthesis of aryl spiroketal (281) requires the initial preparation of phthalide (261). Johnston\textsuperscript{101} synthesized phthalide (261), which contained the same regiochemical arrangement of the methoxy groups as that present in the papulacandins as well as phthalide (260) which lacked a methoxy group at C5 (Scheme 41). Phthalides (260) and (261) were both initially prepared in the present work in order to provide two series of papulacandin analogues. The synthesis of these key materials involved ortholithation of amides (254) and (255) with \textit{tert}-butyl lithium followed by quenching with DMF to afford hydroxy-phthalides (258) and (259) respectively after hydrolysis of the initial formyl derivatives (256) and (257). Conversion of the hydroxy-phthalides (258) and (259) to the acetoxy phthalides (260) and (261) provides the precursors required to generate oxycarbenium ions that react with the nucleophilic allyl stannane (278).
Chapter 2.

Discussion

\[
\begin{align*}
& \text{R} = \text{H} (254), \text{OMe} (255) & \rightarrow & \text{R} = \text{H} (256), \text{OMe} (257) & \rightarrow & \text{R} = \text{H} (258), \text{OMe} (259) \\
& \text{(i)} & \rightarrow & \text{(ii)} & \rightarrow & \text{(iii)} \\
& \text{(262) oxycarbenium ion} & \rightarrow & \text{R} = \text{H} (260), \text{OMe} (261) & \\
\end{align*}
\]

Conditions: (i) (a) t-BuLi, TMEDA, THF, -78 °C, (b) DMF; (ii) HOAc, aq HCl, R = H (258) 67%, R = OMe (259) 63%; (iii) Ac₂O, Et₃N, DMAP, CH₂Cl₂, R = H (260) 90%, R = OMe (261) 98%.

Scheme 41

2.1 Synthesis of phthalide (260)

2.1.1 Synthesis of amide (254)

Preparation of the \(N, N\)-diethyl-3-methoxybenzamide (254) was achieved by heating 3-methoxybenzoic acid (342) under reflux with SOCl₂ under nitrogen (Scheme 56). The resultant residue was treated with diethylamine in dichloromethane at 0 °C to afford a pale yellow oil in 98% yield for which the boiling point compared favourably with the literature.\(^{161}\)
2.1.2 Synthesis of aldehyde (256)

The next step involved the use of hydrogen-lithium ortholithiation chemistry to generate an aromatic anion which on quenching with DMF provides the intermediate aldehyde (256) (Scheme 41). Without purification this aldehyde (256) undergoes cyclisation upon treatment with aqueous acid according to Baldwins\textsuperscript{162} rules (5-exo-trig) to provide the required phthalide (258). Swenton\textsuperscript{163} obtained phthalide (258) in 63\% yield from \(N,N\)-diethyl-3-methoxybenzamide (254) using sec-butyl lithium instead of tert-butyl lithium using a method similar to that used by Johnston\textsuperscript{101} who obtained phthalide (258) in 67\% yield (Scheme 41).

In the present work several attempts to repeat the work of Swenton or Johnston failed to yield any phthalide (258). Considerable colour change was observed in the reaction upon addition of tert-butyl lithium (from clear to bright yellow, a colour indicative of aromatic anions) and upon quenching with DMF (from bright yellow to colourless). However after treatment with aqueous acid to induce cyclisation no product was obtained. TLC analysis of the crude reaction mixture indicated the presence of a less polar spot along with starting material. Work up of the reaction involved extraction of the phthalide (258) with saturated sodium bicarbonate followed by acidification of the combined basic phases. Phthalide (258) should precipitate out
of solution, however this was not observed. Examination of the acidified solution did not reveal the presence of any phthalide (258).

It was therefore decided to modify the procedure, by firstly isolating and purifying the intermediate aldehyde (256) then proceeding with the cyclisation using aqueous acid. Work up for the cyclisation step simply involved removal of the aqueous acid under reduced pressure. The crude residue could then be extracted with dichloromethane and dried over magnesium sulphate providing clean phthalide (258) after purification by chromatography on flash silica gel.

Following this modified procedure, intermediate aldehyde (256) was obtained after purification as a yellow oil albeit in a low 23% yield. The $R_f$ observed upon TLC analysis of (256) was similar to that observed for the less polar product formed in earlier attempts to prepare phthalide (258) in one step thus supporting the decision to isolate (256) before attempting the cyclisation step.

The $^1$H NMR spectrum supported the presence of an aldehyde with a resonance observed at $\delta_H 10.47$ ppm that compared favourably with the literature. Cyclisation of the intermediate aldehyde (256) was successfully completed in glacial acetic acid and 10% HCl providing phthalide (258) in 96% yield as a white solid whose melting point and $^1$H NMR spectrum also compared favourably with the literature data (Scheme 57). The final step in the sequence required acetylation of phthalide (258) with acetic anhydride, Et$_3$N and DMAP in dichloromethane. After 2 hours TLC analysis revealed the conversion to a less polar product which upon work up gave (260) as a white solid in 80% yield. The characteristic signal at $\delta_H 2.17$ ppm (s, 3H, CH$_3$CO) in the $^1$H NMR spectrum indicated the presence of the required methyl group of the acetate and
the melting point and $^1$H NMR compared favourably with the literature (Scheme 57).\textsuperscript{101}

\begin{center}
(256) \quad \xrightarrow{(i), (ii)} \quad (258) \quad \xrightarrow{(iii)} \quad (260)
\end{center}

Conditions: (i) HOAc, aq HCl, 96%; (ii) Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, 80%.

\textbf{Scheme 57}

2.2 Synthesis of phthalide (261)

2.2.1 Synthesis of amide (255)

Preparation of the $N,N$-diethyl-3,5-dimethoxybenzamide (255) was achieved by heating 3,5-dimethoxybenzoic acid (343) under reflux with SOCl$_2$ under nitrogen (Scheme 58). The resultant residue was treated with diethylamine in dichloromethane at 0 °C to afford a pale yellow oil in 73\% yield for which the boiling point compared favourably with the literature data.\textsuperscript{166}

\begin{center}
(343) \quad \xrightarrow{(i), (ii)} \quad (255)
\end{center}

Conditions: (i) SOCl$_2$, 2h, reflux; (ii) Et$_2$HN, CH$_2$CH$_2$, 0 °C, 73\%.

\textbf{Scheme 58}
2.2.2 Synthesis of aldehyde (257)

As described for the previous preparation of aldehyde (256), the next step involved ortholithiation chemistry to prepare intermediate aldehyde (257), which undergoes by a S-exo-trig cyclisation upon treatment with aqueous acid to provide phthalide (259). Watanabe et al.\textsuperscript{167} obtained aldehyde (257) in 71\% yield using a similar procedure to that of Johnston.\textsuperscript{101} Differences in the reaction conditions were that Watanabe used sec-butyl lithium instead of tert-butyl lithium and the aromatic anion was left at -78 °C for 1 h instead of 45 min. Also the DMF was added as a solution in THF rather than neat (Scheme 59).

\[
\begin{align*}
\text{MeO} & \quad \text{NMe}_2 \\
\text{OMe} & \\
(255) & \quad \rightarrow \\
\text{MeO} & \quad \text{NMe}_2 \\
\text{OMe} & \\
(257) & \\
\end{align*}
\]

Conditions: (i) sec-BuLi, THF, -78 °C; (ii) DMF in THF, -78 °C to rt, 71%.

Scheme 59

The procedure reported by Watanabe et al.\textsuperscript{167} using sec-butyl lithium as the base successfully afforded aldehyde (257) as a yellow oil albeit in 20\% yield. The \textsuperscript{1}H NMR spectra was in agreement with the literature and revealed a signal at \(\delta_{\text{H}} 10.30\) ppm corresponding to the aldehyde proton, and the rest of the proton spectra was in good accordance with the literature.\textsuperscript{167} The \textsuperscript{1}H NMR of the crude product indicated at least 80\% of the starting amide (255) was recovered suggesting that the aromatic anion was not forming or was being protonated in solution.
In an effort to obtain a higher yield for this reaction attention turned to Johnston's procedure, who had managed to obtain phthalide (261) in 57% yield from N,N-diethyl-3,5-dimethoxybenzamide (255) using tert-butyl lithium. It was decided to isolate the intermediate aldehyde (257) before proceeding with the 5-exo-trig aqueous acid cyclisation in order to compare the yield obtained with that obtained using the Watanabe procedure. Towards this end several attempts using the Johnston procedure were carried out. Unfortunately $^1$H NMR and TLC analysis of the crude reaction mixture revealed only the presence of the starting amide (255) that was recovered in nearly quantitative yield. Visual observation of the reaction noted considerable colour change in the reaction solution upon addition of tert-butyl lithium (from colourless to bright yellow, a colour indicative of aromatic anion), however upon DMF quenching there was no decolourisation that had been seen in the earlier the mono-methoxy series.

It is known that reactive aromatic anions can be protonated by solvent especially in the case of THF which is known to decompose in the presence of strong basic conditions (Section 1.1). When protonation of the anion occurs no reaction is observed (Scheme 60). Therefore it is often preferable to use a solvent such as diethyl ether which is less likely to decompose under strong basic conditions.

![Scheme 60](image)

\[\text{Scheme 60}\]
It was decided at this point to undertake a series of hydrogen-lithium and halogen-
lithium ortholithiations reactions varying the amount (equivalents) of tert-butyl lithium and the time (min) after which the aromatic anion was quenched by DMF and the solvent in order to improve the outcome of the key formylation reaction.

(i) **Hydrogen-lithium exchange**

The first series of experiments varied the life of anion (min) from 1.0 min to 45 min and compared the use of diethyl ether versus THF as the solvent. Reactions carried out in THF as well as diethyl ether with the quantity of tert-butyl lithium added being kept constant at 1.1 equivalents (Scheme 61) and the lifetime of the anion before quenching with DMF was varied. The optimum results obtained are recorded in the table below and plotted graphically (Figure 27).

\[ \text{Conditions: (i) 1.1 t-BuLi, THF, -78 °C; (ii) DMF, -78 °C to rt.} \]

<table>
<thead>
<tr>
<th>Time (min) elapsed before DMF addition</th>
<th>1.0</th>
<th>5.0</th>
<th>6.0</th>
<th>7.5</th>
<th>10</th>
<th>15</th>
<th>30</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>% yield of aldehyde (257)</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>19</td>
<td>25</td>
<td>32</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Optimum solvent THF or Et₂O</td>
<td>-</td>
<td>-</td>
<td>THF</td>
<td>THF</td>
<td>THF</td>
<td>THF</td>
<td>THF</td>
<td>-</td>
</tr>
</tbody>
</table>

Scheme 61
The experiments revealed the best yield of (257) obtained was 32%, that was achieved when the aromatic anion was quenched 15 min after the tert-butyl lithium was added. Although the yield was still low it was an increase of 12% over the best yield obtained when using the conditions reported by Watanabe et al.\textsuperscript{167}

The second series of experiments was next carried out varying the life of the anion (min) and the solvent, with the quantity of tert-butyl lithium added increased to 2.2 equivalents (Scheme 64). Using an extra equivalent of tert-butyl lithium could give rise to the problem of dianion formation (Scheme 62). However Hauser \textit{et al}.\textsuperscript{169} had shown in his total synthesis of (±)-7-\textit{con}-O-Methylnogarol even the use of 5 equivalents of sec-butyl lithium, ortholithiation of amide (346) followed by quenching with DMF afforded aldehyde (347) in 75% yield (Scheme 63).
The results of this series of experiments using 2.2 equivalents of tert-butyl lithium are summarized in Scheme 64 and Figure 28.
Conditions: (i) 2.2 t-BuLi, THF, -78 °C; (ii) DMF, -78 °C to rt.

<table>
<thead>
<tr>
<th>Time (min) elapsed before DMF addition</th>
<th>2.5</th>
<th>5.0</th>
<th>7.5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>30</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>% yield of aldehyde (257)</td>
<td>0</td>
<td>5</td>
<td>51</td>
<td>50</td>
<td>58</td>
<td>55</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Optimum solvent</td>
<td>-</td>
<td>THF</td>
<td>THF</td>
<td>THF</td>
<td>THF</td>
<td>THF</td>
<td>THF</td>
<td>-</td>
</tr>
<tr>
<td>THF or Et₂O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scheme 64

Graph of ortholithiation using 2.2 equivalents of tert-butyl lithium

Figure 28
The best yield obtained in this case was 58\%, that was achieved when the aromatic anion was quenched 15 min after the addition of the tert-butyl lithium.

(ii) **Halogen-lithium exchange**

In a final attempt to increase the yield of aldehyde (257) our attention turned to the possibility of utilizing a more facile halogen-lithium exchange rather than a hydrogen-lithium exchange to generate the aryl-lithium species. It was hoped that the use of a more facile exchange would afford less opportunity for the aromatic anion to be protonated by the solvent THF before DMF addition. In order to investigate this reaction amide (255) needed to be converted to the bromo-amide (348). *Ortho* bromination of amide (255) was achieved by heating amide (255) with *N*-bromosuccinimide (375) in carbon tetrachloride under reflux and nitrogen for 2 days (Scheme 65) affording (348) in 99\% yield as a colourless oil.

\[
\begin{align*}
\text{(255)} & \quad \text{(348)} \\
\end{align*}
\]

**Scheme 65**

The high resolution mass spectrum for bromide (348) exhibited molecular ions at \(m/z\)
315.0468/317.0453 consistent with the molecular formulae

\[
\text{C}_{13}\text{H}_{18}^{79}\text{BrNO}_{2}/\text{C}_{13}\text{H}_{18}^{81}\text{BrNO}_{3}
\]

The \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra exhibited resonances
consistent with the addition of a bromine at C2, with only two doublets at $\delta_H$ 6.41 ppm (d, 1H, $J=2.6$ Hz, H4) and $\delta_H$ 6.47 ppm (d, 1H, $J=2.6$ Hz, H6) being observed as expected for a 1,2,3,5-tetra-substituted aromatic ring.

The halogen–lithium exchange reaction was carried out in a similar manner to the previous ortholithiation reactions with the exception that butyl lithium was used rather than tert-butyl lithium and the resulting anion was used within 5 minutes as halogen-lithium exchanges tend to be fairly facile (Scheme 66).

![Scheme 66](image)

Upon addition of butyl lithium to bromo-amide (348) at -78 °C, a considerable colour change was observed (clear to bright yellow) and the resultant anion was left at -78 °C for 5 minutes. Upon addition of neat DMF no decolourisation of the reaction was observed and TLC and $^1$H NMR analysis of the reaction mixture revealed a complex mixture unidentified products together with aldehyde (257) in a 10% yield.

It was therefore decided at this stage, that the optimum procedure to prepare aldehyde (257) involved the use of hydrogen-lithium exchange for the ortholithiation chemistry and that time was better spent making further progress toward the synthesis of the phthalide (261).

Cyclisation of the intermediate aldehyde (257) was successfully completed by heating in glacial acetic acid, and 10% HCl under reflux for 6h providing phthalide (259) in
95% yield as a white solid. The melting point and $^1$H NMR of phthalide (259) thus obtained, compared favourably with the literature data (Scheme 67).\(^{170}\) Finally acetylation of phthalide (259) was effected in 86% yield by stirring hydroxy phthalide (259) with acetic anhydride, Et$_3$N and DMAP in dichloromethane for 2 hours. The characteristic three proton singlet at $\delta_H$ 2.17 ppm indicated the presence of the required methyl group of the acetate and the melting point and $^1$H NMR compared favourably with the literature (Scheme 67).\(^{101}\)

![Chemical Structures](image)

**Scheme 67**

2.3 Synthesis of allyl stannane (278)

As illustrated in Scheme 43, allyl stannane (278) is a key intermediate reagent for the synthesis of the papulacandin analogues, (282) and (283). The synthesis of (278) and the manner in which it is coupled to phthalide (261) were pivotal to the success of the proposed synthetic route. The literature preparation of (278) involved protection of 3-methylbut-2-en-1-ol as a tert-butylidiphenylsilyl ether, epoxidation of the double bond, based induced ring opening of the epoxide and finally stannylation of the alcohol group (Scheme 68).\(^{171}\) Johnston\(^{101}\) had carried out the literature synthesis of the desired allyl stannane (278) with limited success and this work needed to be repeated to provide more material for the present investigation.
To freshly distilled 3-methylbut-3-en-1-ol (349) in dry THF was added tert-butyl diphenylsilyl chloride and imidazole. The reaction was stirred under nitrogen for 2 h providing the desired protected alcohol (350) as a colourless oil in 96% yield for which the $^1$H NMR spectrum compared favourably with the literature data (Scheme 68).\(^{171}\)

The protected alcohol (350) was next stirred with mCPBA buffered with sodium bicarbonate in dichloromethane at 0 °C for 3 h effecting epoxidation of the double bond. Epoxide (351) thus formed was isolated as a colourless oil in 90% yield. The $^1$H NMR spectrum revealed the absence of any vinylic protons consistent with epoxidation having taken place and the remaining spectrum compared favourably with the literature data (Scheme 68).\(^{171}\)

Epoxide (351) then underwent ring opening upon binding to the 2,2,6,6-tetramethylpiperidine-diethylaluminium complex that was prepared in situ. The procedure allowed the desired regioselective ring opening to occur in which the protons of the less hindered methyl group were removed, thus providing alcohol (352)
in 86% yield as a yellow oil (Figure 29). The $^1$H NMR compared favourably with the literature data (Scheme 68).

![Figure 29](image)

**Figure 29** 2,2,6,6-tetramethylpiperidine-diethylaluminium complex binding epoxide (351)

The final reaction in the preparation of the desired stannane (278) required stannylation of the protected allylic alcohol (352). The procedure involved mesylation of the alcohol group *in situ*, followed by nucleophilic displacement by tributylstannyl lithium to afford the desired allyl stannane (278) (Scheme 68). It was decided to initially test these reaction conditions using the methallyl alcohol (354) before attempting reaction with (354). Freshly distilled methallyl alcohol (354) was cooled to -78 °C and stirred with *n*-butyl lithium for 20 min (Scheme 69). Mesyl chloride was added and it was noticeable the clear reaction solution became cloudy and the dry ice bath began to melt indicating the reaction had become exothermic and the LiCl by-product was being formed (Scheme 69). After 35 min the solution was
treated with tributylstannyl lithium and the reaction solution stirred at -78 °C for 2 h then warmed to room temperature. Upon standard aqueous work-up allyl stannane (355) was obtained in 75% yield as a colourless oil that carried a pungent smell. The \(^1\)H NMR spectrum obtained for allyl stannane (355) was in good agreement with the literature.\(^{171}\)

\[
\begin{align*}
\text{(354)} & \xrightarrow{(i)} \text{(355)} + \text{LiCl} \\
\text{(355)} & \rightarrow \text{SnBu}_3
\end{align*}
\]

Conditions: (i) (a) \(n\)-BuLi, THF, -78 °C, 20-30 min, (b) MsCl, 25-30 min, Bu\(_3\)SnLi, 3 h, then r.t., 2-12 h, 70%.

\[\text{Scheme 69}\]

Having successfully effected conversion of methallyl alcohol to methallyltributyl stannane (355), it was hoped that use of a similar procedure be effective using the more complex allylic alcohol (352). Attempts to effect stannylation of alcohol (352) using this procedure were tried many times, however without success. Close inspection of the failed reactions noted similar findings to the reaction using methallyl alcohol in that the clear solution became cloudy and the dry ice bath heated up when the mesyl chloride was added.

In order to establish where the reaction was going wrong it was decided to isolate the mesylate (357). On work-up the \(^1\)H NMR spectrum of the crude mixture confirmed that the mesylation reaction had taken place, however TLC analysis indicated that mesylate (357) was unstable and rapidly decomposed back to allylic alcohol (352). It was next decided to focus on the formation of tributylstannyl lithium\(^{171}\) and the source of tributyl tin hydride (358). Fresh bottles of tributyl tin hydride were obtained from Sigma-Aldrich and their \(^1\)H NMR spectroscopy compared with the literature.\(^{172}\)
Preparation of tributylstannyl lithium by stirring tributyl tin hydride with LDA at 0 °C in solution for 30 mins followed by quenching with D₂O afforded the deuterated product in > 99% yield (Scheme 70). Thus the lack of success with the stannylation of alcohol (352) was puzzling.

\[
\text{SnBu}_3\text{H} \xrightarrow{(i)} \text{SnBu}_3\text{D}
\]

\[
(358) \quad (359)
\]

Conditions: (i) LDA, THF, 0 °C, 30 mins, 99%.

Scheme 70

In an attempt to simplify the reaction, it was decided to prepare and isolate a tosylate (360) of allylic alcohol (352) and transfer a solution of this tosylate via cannula into a flask containing tributylstannyl lithium (Scheme 71). The tosylate (360) was prepared by adding a solution of p-toluenesulfonyl chloride in THF into a solution of the allylic alcohol and n-butyl lithium at -78 °C. The mixture was left to stir at -78 °C for 1 h at which time TLC indicated the reaction was complete (Scheme 71).

\[
\text{OH}
\]

\[
\text{OTBDPS}
\]

\[
(352)
\]

\[
\text{OTs}
\]

\[
\text{OTBDPS}
\]

\[
(352)
\]

\[
(360)
\]

\[
(278)
\]

Conditions: (a) n-BuLi, THF, -78 °C, 20-30 min, (b) TsCl, 25-30 min, then r.t., 2-12 h, 69%; (ii) Bu₃SnLi, THF, -78 °C, 30 min.

Scheme 71

Tosylate (360) was obtained as a colourless oil in 69% yield after work-up and purification by chromatography on flash silica gel. The high resolution mass
spectrum for tosylate (360) exhibited a molecular ion at m/z 495.2017 consistent with the molecular formula C_{28}H_{35}SiSO_{4}. The \textsuperscript{1}H NMR spectrum exhibited resonances consistent with the addition of a tosylate group in that two doublets at \(\delta_H\) 7.27 ppm (d, 2H, \(J=8.2\) Hz, H3'-Ar) and \(\delta_H\) 7.74 ppm (d, 2H, \(J=8.2\) Hz, H2'-Ar) were observed for the two aromatic protons. The resonance for H1 at \(\delta_H\) 4.45 ppm (s, 2H, H1) was deshielded downfield resonating further than the analogues protons in alcohol (352) that resonated at \(\delta_H\) 4.08 ppm (s, 2H, H1). This observation is consistent with addition of an electron withdrawing tosylate group. Similarly the \textsuperscript{13}C NMR resonance for C1 \(\delta_C\) 72.7 ppm resonated further downfield than C1 in the starting alcohol (352), that resonated at \(\delta_C\) 65.8 ppm.

A solution of the tosylate (360) in THF at -78 °C was transferred via cannula to a solution of tributylstannyl lithium. The reaction mixture was left to stir at -78 °C for 30 mins after which time TLC analysis indicated that no reaction had taken place. Work up of the reaction afforded a near quantitative yield of the starting tosylate (360).

The lack of success using tosylate (360) prompted an alternative approach to the desired allyl stannane (278). Thus far the stannyl lithium species had been used as a nucleophile. It was therefore decided to attempt to reverse the role of the tin reagent and convert the allylic alcohol to an allylic bromide which could be converted to a Grigard reagent then reacted with tributyl tin chloride as an electrophile (Scheme 72).
Allylic bromide (361) was prepared by stirring alcohol (352) with phosphorus tribromide in ether at 0 °C for 10 mins. TLC analysis indicated all the starting material had been consumed. Subsequent work-up and purification by chromatography on flash silica gel afforded allylic bromide (361) as a colourless oil in 80% yield (Scheme 73).

The high resolution mass spectrum exhibited molecular ions at \( m/z \) 403.159/405.1087 consistent with the molecular formulae \( \text{C}_{21}\text{H}_{28}^{79}\text{BrSiSO} \) \( \text{C}_{21}\text{H}_{28}^{81}\text{BrSiSO} \). The \(^1\text{H} \) NMR spectrum was consistent with the addition of a bromine atom noticeably by the upfield shift observed for \( \text{H}1' \) at \( \delta_\text{H} \) 3.93 ppm (s, 2H, \( \text{H}1' \)) compared with allylic alcohol (352) where \( \text{H}1' \) resonated at \( \delta_\text{H} \) 4.08 ppm (s, 2H, \( \text{H}1' \)). Similarly the \(^{13}\text{C} \) NMR spectrum showed a considerable upfield shift for \( \text{C}1 \) at \( \delta_\text{C} \) 37.0 ppm compared with allylic alcohol (352) where \( \text{C}1 \) resonated at \( \delta_\text{C} \) 65.8 ppm. Stirring bromide (361)
in dry diethyl ether with magnesium powder and a drop of iodine under nitrogen failed to initiate formation of the Grignard reagent. The procedure was tried again using magnesium turnings, but the same result was obtained and no further variations of the Grignard reaction were tried.

Having exhausted many avenues for the synthesis of the desired allyl stannane (278), the limited time available for the pursuit of this research, prompted a major re-evaluation of the research undertaken to date. It was therefore decided to pursue another avenue of research to the synthesis of the antiulcer compounds CJ-12,954 (56) and CJ-13,014 (57) that have similarity to the papulacandins in that they contain a phthalide unit joined through a hydrocarbon chain to a spiroketal unit.
3. Anti-ulcer compounds

1 Ulcers

1.1 Introduction

Gastric and duodenal ulcers affect a significant portion of the human population worldwide. Prior to 1983, it was believed gastric acid served as the stomach’s barrier to colonisation by bacteria and other micro-organisms. Peptic ulcer disease was thought to be caused by dietary indiscretions like smoking, alcohol, stress and hyperacidity of the stomach. In 1983 Warren and Marshall\textsuperscript{173} isolated a spiral shaped organism \textit{Helicobacter Pylori} from between the gastric epithelial cell surface and the overlying mucus gel of a patient suffering chronic gastritis and peptic ulceration. This important discovery prompted research into \textit{Helicobacter pylori} and its association with gastritis as the underlying condition that causes ulcers and other stomach complaints.

1.2 \textit{Helicobacter pylori}: Structure and morphology

\textit{Helicobacter pylori} is a Gram-negative micro-aerophilic bacterium shaped like a curved rod. It is 2.5-1.0 \textmu m long and 0.5-1.0 \textmu m wide (\textbf{Figure 30}).

\textbf{Figure 30} \textit{Helicobacter pylori}
The organism has 4-6 unipolar flagellae (Figure 30) which are important to its motility and ability to penetrate the gastric mucus gel.\textsuperscript{174} When conditions for growth are unfavourable the organisms defence mechanism allows it to enter a coccoid form or dormant state for survival.

1.3 \textit{Helicobacter pylori}: Habitat

Gastric juices produced inside the stomach contain digestive enzymes and approximately 0.17 mol L\textsuperscript{-1} hydrochloric acid which kill non-acid tolerant proteins and bacteria. The stomach lining is protected from its own gastric juice \textit{via} a thick layer of mucus. It is beneath this mucus layer that \textit{Helicobacter pylori} seeks refuge. Once safely ensconced, the bacteria are able to neutralize the surrounding stomach acid for survival with an enzyme it produces called \textit{urease}. \textit{Urease} brakes down the abundant supply of urea in the stomach into strong bases, bicarbonate and ammonia (Scheme 74).

\[
\text{H}_2\text{N}\text{CONH}_2 + \text{H}^+ + 2\text{H}_2\text{O} \xrightarrow{\text{Urease}} \text{HCO}_3^- + 2(\text{NH}_4^+)
\]

\text{Scheme 74}

A diagram demonstrating the pH gradient generated near \textit{Helicobacter pylori} by \textit{urease} is depicted below (Figure 31)
Figure 31 Diagram of pH gradient generated near *Helicobacter pylori* by urease action.

*Helicobacter pylori* can survive a pH range from 5.5-8.5, but optimal growth is achieved at pH 6.5-8.5.\(^{175}\)

### 1.4 Pathogenesis of *Helicobacter pylori*

*Helicobacter pylori* colonises the stomach for years even decades. Patients either suffer continuous inflammation known as chronic superficial gastritis, or are lucky and remain asymptomatic. Between 30-40\% of the chronic superficial gastritis sufferers will eventually develop lymphoproliferative disease or gastric and duodenal ulceration, a condition known as peptic ulceration disease.\(^{176}\) The progression of chronic superficial gastritis into atrophic gastritis has been linked to the development of gastric cancer, in particular intestinal adenocarcinoma.\(^{177,178,179}\) (Figure 32)
Figure 32 Model of *Helicobacter pylori* infection and gastroduodenal pathology.

These findings led the International Agency for Research on Cancer of the World Health Organization to declare the bacterium a class 1 carcinogen. Gastric cancer is the second most common type of cancer worldwide and is most prevalent in countries like Brazil, Korea, China and Japan where *Helicobacter pylori* affects about half the populations.\(^{176}\)

Upon infection with *Helicobacter pylori* the body's immune system responds by sending killer T and white cells to eradicate the bacteria. However these cells are unable to penetrate the stomach lining and thus it is proposed inflammation caused by
Chapter 3.

Discussion

*Helicobacter pylori* causes peptic ulcer disease.\(^{180}\) Responsibility for the inflammation has been attributed to the toxic components produced by the bacteria. These components are summarized in the table below (Table 4).

**Table 4** Toxic components produced by *Helicobacter pylori*.

<table>
<thead>
<tr>
<th>Component</th>
<th>Origin</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>Produced by urea hydrolysis (scheme 74)</td>
<td>Eukaryotic cells</td>
</tr>
<tr>
<td><em>Urease</em></td>
<td>Enzyme</td>
<td>Gastric mucosa cells</td>
</tr>
<tr>
<td>Superficial antigens e.g. lipopolysaccharides</td>
<td><em>Helicobacter pylori</em>, overproduced outer membranes</td>
<td>Inflammatory mediators</td>
</tr>
<tr>
<td>Cytotoxins VacA and CagA</td>
<td>Produced by <em>Helicobacter pylori</em></td>
<td>Absorb into surrounding tissue and cause inflammation</td>
</tr>
</tbody>
</table>

1.5 *Helicobacter pylori*: Epidemiology

The infection with *Helicobacter pylori* has a worldwide distribution. Prevalence of the infection correlates best socio-economic status rather than race. In developing countries, more than 50% of the population is infected by the age of 10 years and this increases to 60-90% for adults.\(^{181}\) In Western countries, *Helicobacter pylori* affects about 20% of people below the age of 40, and 50% of those over the age of 60 years. *Helicobacter pylori* is an acid sensitive bacteria and colonisation of the stomach is more easily achieved when it is hypochlorohydric (acid deficient) making infant’s stomachs ideal targets. In developing countries this is possibly one of the
explanations for the high infection rates in young people, however there is a definite link with poor sanitary conditions like overcrowding and the sharing of beds leading to intrafamilial infection.\textsuperscript{181}

1.6 \textit{Helicobacter pylori}: Treatments

The current treatment plan for \textit{Helicobacter pylori} is aimed at eradication rather than temporary suppression of the bacteria. Initially treatments focussed on \textit{Urease} inhibitors, however these are toxic and have since been stopped.\textsuperscript{176} Current treatments are summarised in the table below (Table 5).

\textbf{Table 5} Current treatments for \textit{Helicobacter pylori}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Action</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid pump inhibitors</td>
<td>Decrease stomach acid secretion</td>
<td>Omeprazole, Lansoprazole</td>
</tr>
<tr>
<td>Histamine H2 receptor blockers</td>
<td>Prevents stomach acid secretion</td>
<td>Cimetidine (Tagamet), Ranitidine (Zantac), Famotidine (Pepcid)</td>
</tr>
<tr>
<td>Mucosal protective agents</td>
<td>Protection for stomach tissue</td>
<td>Misoprostol (Cytotec), Sucralfate (Carafate)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Antimicrobial agents</td>
<td>Amoxicillin, Tetracycline, Metronidazole, Clarithomycin</td>
</tr>
</tbody>
</table>

Successful treatments to date use a three-drug combination called a “triple treatment” or “triple therapy” where a proton pump inhibitor is used with one or more antibiotics,
and a bismuth salt. The bismuth salts aid the antibiotics in reaching *Helicobacter pylori* by releasing the bacteria from its niche beneath the mucosal layer.\(^\text{176}\) Examples of bismuth containing compounds used are colloidal bismuth subcitrate and bismuth subsalicylate.\(^\text{182}\)

Side effects from the multiple treatments include malaise, nausea, diarrhoea, sore mouth and fungal infections. The trouble with *Helicobacter pylori* is that it can acquire resistance to the current antibiotics and hence new drug combinations are still under investigation for increases success in eradication. Ideal drugs for eradication should have the following properties:\(^\text{183}\):

- Rapid dissolution and good dispersion in the stomach
- Stability and activity over a wide range of pH, especially in acidic solutions
- Absorption *via* the gastric mucosa
- Small molecular size to increase mucus penetration
- Low susceptibility to acquired resistance
- Activity against the slowly diving coccoid forms of *Helicobacter pylori*
- Low incidence of side effects
- Absence of systemic toxicity

Before a safe vaccine for *Helicobacter pylori* is available, scientists need to look for new, more effective and cheaper medicines for the treatment and prevention of *Helicobacter pylori* considering the high percentage of infection worldwide especially in developing countries.
2. Synthetic studies towards phthalide-containing spiroketales

2.1 Introduction

The discovery of the anti-ulcer compounds, phthalides CJ-12,954 (56), CJ-13,014 (57), CJ-13,015 (58), CJ-13,0102 (59), CJ-13,103 (60), CJ-13,104 (61), and CJ-13,108 (62) by Dekker et al.\textsuperscript{43} (Figure 15) has prompted their chemical synthesis to be undertaken by the Brimble research group. As noted earlier phthalides CJ-12,954 (56) and CJ-13,014 (57) were chosen as the initial synthetic targets since they contain spiroketal moieties that are of particular interest to this research group. To date only one synthesis of one of the seven anti-ulcer phthalide compounds has been reported. Argade et al.\textsuperscript{183} synthesized racemic CJ-13,015 (58) in a six step sequence from 5-methylfurfural (363) in 65\% overall yield (Scheme 75).

Treatment of (363) with the ylide generated by treatment of (8-hydroxyoctyl)triphenylphosphonium bromide and sodium methylsulfinylmethanide afforded (364) in 82\% yield as a mixture of E and Z isomers. Catalytic hydrogenation of the double bond over palladium on charcoal was effected and gave (365) in near quantitative yield. Tosylation of the primary alcohol followed by displacement with LiBr afforded (367) in 91\% overall yield. $S_N2$ substitution of the halide (367) with the anion of 3,5-dimethoxyphthalide afforded the coupled product in 90\% yield. Finally chemoselective hydrolysis of the furan ring with acetic acid and water gave the diketone CJ-13,015 (58) in quantitative yield.
Figure 15 Phthalides isolated from the basidiomycete Phanerochaete velutina

CL6387
Gorsuch and Brimble\textsuperscript{184} formulated a strategy for the synthesis of CJ-12,954 (56) that involved Wittig reaction of phthalide (288) with spiroketal ylide (297) (Scheme 76).
It was also proposed that phthalide (288) could be obtained from hydroxyphthalide (370) which had been prepared by Borchardt et al.\textsuperscript{185} from 3,5-dimethoxybenzoic acid (374) (Scheme 77).
The synthesis of hydroxyphthalide \((370)\) carried out by Borchart\(^{185}\) started with lithium aluminium hydride reduction of 3,5-dimethoxybenzoic acid \((374)\) to primary alcohol \((373)\) in 93% yield (Scheme 78). Bromination \textit{ortho} to the hydroxymethyl group was then achieved by heating the alcohol \((373)\) under reflux with NBS \((375)\) in \(\text{CCl}_4\) for 40 min under an atmosphere of nitrogen. Bromide \((372)\) was obtained in near quantitative yield. Despite \(\text{C}4\) on the aromatic ring of \((373)\) being the most electron rich site due to the electron donation from the two methoxy groups, the bromine was directed to the position \textit{ortho} to the hydroxymethyl group \(\text{C}2\). The reason for this outcome is that the strong hydrogen bonds can form between alcohol \((373)\) and the reagent NBS \((375)\), directing the bromine to \(\text{C}2\) (Figure 33).
Oxidation of the alcohol (372) with pyridinium chlorochromate (PCC) in dichloromethane provided the aldehyde (371) in 98\% yield (Scheme 78). The most important steps in the synthesis of hydroxyphthalide (370) from aldehyde (371) were then carried out using a three step procedure. Firstly, treatment of aldehyde (371) with lithium morpholide in THF at -50 °C for 15 min provided the morpholide alkoxide (376). n-BuLi was then added at -78 °C resulting in a halogen-lithium exchange reaction. The reaction was then left for 35 min and the anion quenched with solid CO₂ affording hydroxyphthalide (370) in 74\% yield upon aqueous acidic work-up (Scheme 78).
Chapter 3.

Discussion

Following the work of Borchart,\textsuperscript{185} Gorsuch\textsuperscript{184} effected the synthesis of the bromoaldehyde (371) in 48\% overall yield from 3,5-dimethoxybenzoic acid (374), however he was unable to convert this compound to the desired hydroxyphthalide (370).

While contemplating an alternative strategy his focus shifted to the synthesis of the spiroketal ylide (297). Utilizing method (a) "nucleophilic attack onto a carbonyl group that then becomes the spiroketal carbon"\textsuperscript{66} (Introduction, section 2.2), Gorsuch\textsuperscript{184} chose to construct spiroketal ylide (297) via the addition of acetylene (379) to aldehyde (303) affording ynone (302) (Scheme 79). Ynone (302) could then be

\textbf{Scheme 78}

\begin{align*}
\begin{array}{c}
\text{OMe} \\
\text{MeO} \\
\text{OH} \\
(374) \xrightarrow{(i)} \text{OMe} \\
\text{MeO} \\
\text{OH} \\
(373) \xrightarrow{(ii)} \text{OMe} \\
\text{MeO} \\
\text{Br} \\
(372) \\
\end{array}
\end{align*}

\textbf{Conditions:} (i) LiAlH}_4, \text{THF}, 93\%\; ; \; (ii) \text{NBS}, \text{CCl}_4, 40 \text{ min}, 98\%\; ; \; (iii) \text{PCC}, \text{CH}_2\text{Cl}_2, 98\%\; ; \; (iv) (a) \text{n-BuLi}, \text{morpholine}, \text{THF}, -50 \text{ to } -78 \text{ \degree C}, 15 \text{ min}\; ; \; (b) \text{n-BuLi}, -78 \text{ \degree C}, 35 \text{ min}\; ; \; (c) \text{solid CO}_2, 1\text{ h}, 74\%.

\begin{align*}
\begin{array}{c}
\text{OMe} \\
\text{MeO} \text{Br} \text{O} \text{Li} \\
\text{OMe} \\
(377) \xrightarrow{(ivb)} \text{OMe} \text{Li} \text{O} \text{Li} \\
\text{MeO} \\
(376) \xrightarrow{(iva)} \text{OMe} \\
\text{MeO} \\
\text{H} \\
(371) \\
\end{array}
\end{align*}

\begin{align*}
\begin{array}{c}
\text{OMe} \\
\text{MeO} \text{Br} \text{O} \text{Li} \\
\text{OMe} \text{Li} \text{O} \text{Li} \\
\text{OMe} \\
(370) \\
\end{array}
\end{align*}

\begin{align*}
\begin{array}{c}
\text{OMe} \\
\text{MeO} \\
(370)
\end{array}
\end{align*}
converted to protected dihydroxyketone (378) and then to the spiroketal (298) the precursor to the desired ylide (297).

![Diagram of chemical reactions]

In turn, it was envisaged the key intermediate acetylene (379) could be prepared from trimethylsilyl protected propargyl alcohol (382) (Scheme 80). The key step in the synthesis used a Wittig [2,3]-sigmatropic rearrangement of anion (381) to afford (380). The reaction was chosen with a view to using chiral bases such as (−)-sparteine to effect an asymmetric Wittig rearrangement to provide the required stereogenic centre at carbon (*) which is later transformed into C7' of the natural product CJ-12,954 (56).
The aldehyde (303) partner could be obtained from ethyl levulinate (387) in a five step procedure. Reduction of ethyl levulinate (387) to diol (386), chemoselective protection, and oxidation to the primary alcohol affords the desired aldehyde (303) (Scheme 81).
The proposed synthesis of aldehyde (303) was attractive in that it could be easily modified to introduce the required stereochemistry at carbon (*) that was later transferred to C13' in the natural product CJ-12,954 (56) by incorporating an enantioselective reduction into the synthetic sequence (Scheme 82).
2.1.1 Synthesis of intermediate acetylene (394)

The C-trimethylsilyl protected propargyl alcohol (382) was prepared by generating the dianion of (392) using two equivalents of n-BuLi at -78 °C in THF followed by quenching the reaction with trimethylsilyl chloride (TMSCl). The reaction mixture was then allowed to warm to room temperature and treated with 1 mol L⁻¹ HCl affording C-trimethylsilyl derivative (382) in 70% yield (Scheme 83). Allylation of (382) was carried out following the literature procedure using EtMgBr, and allyl bromide in THF/HMPA under reflux providing the allyloxyacetylene (381) in 67% yield. Gorsuch tried a number of alternative procedures to allylate (382) (sodium hydride/allyl bromide, n-BuLi/allyl bromide and EtMgBr/allyl bromide)
trying to avoid the use of the highly toxic reagent HMPA, however these alternative procedures were not successful. Wittig [2,3]-sigmatropic rearrangement\textsuperscript{186} of (381) initiated by treatment with \( n \)-BuLi at -78 °C in THF afforded racemic alcohol (380) in near quantitative yield. Protection of the alcohol (380) as a tert-butylimidethylsilyl ether (393) and removal of the trimethylsilyl group with sodium methoxide in methanol gave the desired acetylene (394) in 57% overall yield from (381) (Scheme 83).

\[
\begin{align*}
\text{(392)} & \quad \text{(i)} \quad \text{(392)} \quad \text{(382)} \quad \text{(ii)} \quad \text{(381)} \\
& \quad \text{(iii)} \quad \text{(394)} \quad \text{(380)}
\end{align*}
\]

Conditions: (i) (a) \( n \)-BuLi, THF, -78 °C, 30 min, (b) TMSCl, THF, -78 °C to rt, (c) 1 mol L\(^{-1}\) HCl, 30 min, 70%; (ii) (a) 1.2 Mol L\(^{-1}\) EtMgBr, HMPA, THF, 0 °C, 5 min, (b) allyl bromide, reflux, 4h, 67%; (iii) \( n \)-BuLi, THF, -78 °C, 10 min, 100%; (iv) TBDPSCI, imidazole, DMAP, DCM, rt, 1h; (v) NaOMe, MeOH, 40 min, 57% from (iii).

Scheme 83

### 2.1.1.1 Asymmetric induction in preparation of (394)

As mentioned in the introduction (section 2.1 scheme 81) it is possible to prepare acetylene (394) enantioselectively through the use of an asymmetric Wittig rearrangement.\textsuperscript{187} It was hoped to introduce the correct stereochemical configuration at C3 prior to coupling with aldehyde (393) and carry this configuration through to the conclusion of the synthesis of the spiroketal ylide (297). To this end, a series of chiral
bases were chosen to effect the asymmetric deprotonation of (381) and hence initiate a stereocontrolled Wittig rearrangement (Scheme 84). The crude Wittig rearrangement product was subjected to Mosher ester conditions [(R)-Mosher chloride, Et₃N, DMAP, 40 °C)] to allow the formation of the Mosher ester derivative that was analysed by ¹H NMR spectroscopy.

The slight enrichment of one diastereomer over the other when using (1R, 2S)-(-)-norephedrine could have been due to experimental error. The chiral bases used did
not effect any stereocontrol on the Wittig rearrangement, hence this avenue of investigation was not pursued.

2.1.2 Synthesis of intermediate aldehyde (399)

With the synthesis of acetylene (394) in hand, attention next turned to the synthesis of aldehyde (399) from ethyl levulinate (387) (Scheme 81). Starting from ethyl levulinate (387), reduction with lithium aluminium hydride in THF at 0 °C afforded pentane-1,4-diol (386) in 97% yield (Scheme 85). Adopting the method reported by Yamada et al.,\textsuperscript{192} pentane-1,4-diol (386) was acetylated regioselectively at C1 using sodium hydride and 3-acetylthetrahydrothiazole-2-thione in THF at room temperature. Protection of the remaining secondary hydroxyl group as a tert-butyldimethylsilyl ether followed by deacetylation with potassium carbonate in methanol gave alcohol (398) in 71% overall yield from diol (386). Oxidation with Dess-Martin periodinane\textsuperscript{76} afforded the desired racemic aldehyde (399) in 94% yield (Scheme 85).
Gorsuch\textsuperscript{183} also investigated an alternative synthesis of aldehyde (399) \textit{(Scheme 86)}, starting with the selective reduction of the ketone functionality in ethyl levulinate (387) using sodium borohydride. The resultant alcohol was protected as a \textit{tert-}butyldimethylsilyl ether and the crude mixture then subjected to DIBAL-H reduction to yield the desired aldehyde (399). The overall yields obtained via this route varied from 50-85\%. Problems with over reduction to the alcohol (398) and extraction of the product (399) from aluminium salts were believed to be factors affecting the yield \textit{(Scheme 86)}. 

\begin{scheme}
\begin{center}
\begin{tikzpicture}
\tikzstyle{process}=[rectangle, draw, rounded corners, minimum height=1em]
\tikzstyle{arrow}=[thick,->,>=stealth]
\tikzstyle{box}=[rectangle, draw, rounded corners, minimum height=1em]
\node[process, text width=5cm] (A) {LiAlH$_4$, THF, 0 °C to rt, 1h, 97\%};
\node[process, text width=5cm, below=of A] (B) {NaH, 3-acetyltetrahydrothiazole-2-thione, THF, rt, 2h};
\node[process, text width=5cm, below=of B] (C) {TBSCI, Imidazole, DMAP, DMF, rt, 4h};
\node[process, text width=5cm, below=of C] (D) {K$_2$CO$_3$, MeOH, rt, 18h, 71\% from (386)};
\node[process, text width=5cm, below=of D] (E) {Dess-Martin periodinane, CH$_2$Cl$_2$, rt, 1h, 94\%}.
\end{tikzpicture}
\end{center}
\end{scheme}

\textbf{Scheme 85}
Chapter 3. Discussion

**Conditions:**

(i) NaBH₄, MeOH, rt, 2h; (ii) TBSCI, Imidazole, DMAP, DMF, rt, 18h; (iii) DIBAL-H, CH₂Cl₂, -78 °C, 50-85%.

Scheme 86

It was decided to use the method outlined in (Scheme 85) on a routine basis for synthesis of (393).

### 2.1.3 Coupling of acetylene (394) to aldehyde (399)

With substantial quantities of both the acetylene (394) and aldehyde (399) in hand, attention turned to their union via formation of the lithium acetylide (Scheme 87). Treatment of (394) with a range of different bases including n-BuLi, t-BuLi and Schlosser's base¹⁹⁺ failed to yield an acceptable yield of the coupled product (402) upon reaction with aldehyde (399). Finally the use of TMEDA as co-solvent and n-BuLi as the base afforded the coupled product (402) in 85% yield as a mixture of diastereomers (Scheme 87). Subsequent oxidation of (402) with Dess-Martin periodinane⁷⁶ gave the ketone (403) in 83% yield as a mixture of diastereomers (Scheme 87).
2.2 Synthetic studies towards spiroketal ylide (297) from ketone (403)

Having established the conditions required for the union of acetylene (394) with aldehyde (399), the focus shifted to functionalising the terminal olefin of (403). Gorsuch\textsuperscript{184} envisaged introduction of an alcohol group via hydroboration as there was good precedent in the literature for the selective hydroboration of terminal olefins in the presence of acetylenes using 9-BBN.\textsuperscript{194} However after many attempts at effecting hydroboration of both (402) and ketone (403) using BH$_3$-DMS, 9-BBN and catecholborane, plans to continue the synthesis of spiroketal (297) along these lines were thwarted as chemoselective hydroboration proved problematic (Scheme 87).
The final steps in the synthesis of the spiroketal ylide (297) and phthalide (288) were carried out as part of this thesis.

2.2.1 Functionalisation of the terminal olefin

In view of the fact that Gorsuch\(^{184}\) had established a synthetic route to (403), it was decided to repeat the hydroboration of both (402) and (403) using fresh bottles of BH\(_3\).SMe\(_2\), 9-BBN and catechol borane. Compounds (402) and (403) were dissolved in dry THF in flame-dried flasks and up to four equivalents of the borane reagents
were added and the reactions stirred for 4 h at 0 °C (Scheme 88). Subsequent treatment with 3 mol L\(^{-1}\) sodium hydroxide and 30% hydrogen peroxide afforded none of the desired product (405) or (406).

\[
\begin{align*}
&\text{OH} \quad \text{(i), (ii)} \quad \text{(402)} \\
&\text{OTBDPS} \\
&\text{TBS}
\end{align*}
\]

\[
\begin{align*}
&(\text{i), (ii)} \quad \text{O} \\
&\text{OTBDPS} \\
&\text{TBS}
\end{align*}
\]

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

\[
\begin{align*}
&(\text{i), (ii)} \\
&\text{OTBDPS} \\
&\text{TBS}
\end{align*}
\]

Conditions: (i) Borane (3-4) equiv, THF, 4h, (ii) 3 mol L\(^{-1}\) NaOH, 30% H\(_2\)O\(_2\).

**Scheme 88**

It was decided at this point to seek an alternative approach to alcohol (406) via epoxidation of the double bond in (403) to give epoxide (407) followed by ring opening with zinc borohydride (435).\(^{195}\)

To a solution of (403) in dichloromethane was added meta-chloroperoxybenzoic acid and sodium acetate. The mixture was stirred at room temperature for five days (Scheme 89).
Epoxide (407) was obtained as a colourless oil and mixture of diastereomers in 79% yield after work up and purification by chromatography on flash silica gel. The high resolution mass spectrum for epoxide (407) exhibited a molecular ion at \( m/z \) 565.3183 consistent with the molecular formula \( C_{33}H_{49}Si_2O_4 \). The \(^1\)H NMR spectrum exhibited resonances at \( \delta_H \) 2.36-2.47 ppm (m, 1H, H11a), \( \delta_H \) 2.72-2.79 ppm (m, 1H, H11b) and \( \delta_H \) 3.08-3.17 ppm (m, 1H, H10) consistent with epoxidation of the double bond. The \(^{13}\)C NMR resonances for C10 at \( \delta_C \) 48.6 ppm and C11 at \( \delta_C \) 41.3 ppm resonated considerably further upfield than the vinylic carbons in the starting material (403) that resonated at \( \delta_C \) 132.6 ppm and \( \delta_C \) 118.6 ppm respectively.

The fact that it had taken five days to epoxidise the terminal olefin of (403), suggested it was a sterically hindered double bond and hence the use of longer reaction times for the previously unsuccessful hydroboration reactions may prove to be more fruitful in future.

Due to the presence of the carbonyl group at C5 in (407), it was decided to first hydrogenate and effect cyclisation to the spiroketal before opening the epoxide with zinc borohydride (412).\(^{195}\) Stirring (407) with 10% palladium on charcoal in ethyl acetate at room temperature for 2 hours under an atmosphere of hydrogen provided
(408) as a colourless oil and mixture of diastereomers in 98% yield after purification by chromatography on flash silica gel (Scheme 90).

\[
\begin{align*}
\text{(407)} & \quad \xrightarrow{(i)} \quad \text{(408)} \\
\end{align*}
\]

| Conditions: (i) Pd/C, H₂, EtOAc, rt, 2h, 98%. |

Scheme 90

The high resolution mass spectrum for (408) exhibited a molecular ion at \( m/z \) 569.3471 consistent with the molecular formula \( \text{C}_{33}\text{H}_{53}\text{Si}_{2}\text{O}_{4} \). The \(^{13}\text{C} \) NMR resonances for C6 at \( \delta_{C} \) 37.9, 38.7 ppm and C7 at \( \delta_{C} \) 33.1 ppm resonated considerably further upfield than the acetylene carbons in the starting material (407) that resonated at \( \delta_{C} \) 84.2 ppm and \( \delta_{C} \) 90.9 ppm respectively thus providing strong evidence for the saturation of the triple bond.

The next step was the global deprotection of the silyl groups to afford diol (409) that should undergo thermodynamically controlled spirocyclization to epoxy spiroketal (300). Attempts to carry out this reaction with tert-butyl ammonium fluoride and hydrogen fluoride/pyridine failed to yield (300). TLC analysis of the reactions mixture suggested removal of the silicon protecting groups had taken place with an intense baseline spot (\( R_{f} =0 \)) being observed using 50% diethyl ether/hexane as eluent. It was assumed the diol (409) resulting from deprotection would instantly cyclise to a spiroketal upon workup and the baseline spot should disappear. TLC analysis after work up revealed up to four non UV active spots running at higher \( R_{f} \) (Scheme 91).
Examination of the $^1$H NMR spectrum of each of the products isolated by chromatography on flash silica gel did not suggest the formation of epoxy spiroketal (300).

\[
\begin{align*}
\text{(408)} & \quad \xrightarrow{(i)} \quad \text{(409)} \\
\text{Intense Blue spot by TLC (409)}
\end{align*}
\]

Conditions: (i) tert-butyl ammonium fluoride or HF, py, N$_2$, THF, $0^\circ$C, 1h.

**Scheme 91**

The lack of success with the deprotection/cyclisation step may have been due to the length of time (1 hour) that (408) was left in the basic fluoride solution. TLC analysis of the reaction suggested that the tert-butyldiphenylsilyl (TBDPS) protecting group was more difficult to remove than the tert-butyldimethylsilyl (TBS) which was removed within 10 minutes. It was therefore decided to repeat the synthesis of (408) again, replacing the tert-butyldiphenylsilyl (TBDPS) protecting groups with more labile tert-butyldimethylsilyl (TBS) groups. It was necessary to repeat the work reported in section 2.1.1 with the necessary change in the protection step (**Scheme 92**).
2.3 Coupling of acetylene (411) to aldehyde (399)

With quantities of both acetylene (411) and aldehyde (399) in hand, attention turned to their union via formation of the lithium acetylide. Beginning with conditions that had been established by Gorsuch\textsuperscript{184} (section 2.1.3), the acetylene (411) and freshly distilled TMEDA were dissolved in dry THF in a flame-dried flask flushed with nitrogen and cooled to -78 °C. n-BuLi was added dropwise over 1 min and the mixture allowed to stir at -78 °C for 1 hour, then treated with a solution of aldehyde (399) in THF. Stirring was continued for 30 minutes, then the reaction mixture quenched with sodium bicarbonate and warmed to room temperature. After work up TLC indicated the presence of both starting materials (411) and (399) along with a new spot at lower R\textsubscript{f}. The ynol (414) was obtained as a colourless oil and mixture of diastereomers in a low 15% yield after purification by chromatography on flash silica gel (Scheme 93).
The high resolution mass spectrum for ynol (414) exhibited a molecular ion at $m/z$ 427.3062 consistent with the molecular formula $C_{23}H_{47}Si_2O_3$. The $^1H$ NMR spectrum exhibited resonances consistent with the formation of ynol (414) with multiplets observed at $\delta_H$ 1.55-1.77 ppm (m, 4H, H3, H4) and $\delta_H$ 3.80-3.89 ppm (m, 1H, H5). Notably the H4 protons were shifted upfield from $\delta_H$ 1.55-1.77 ppm (m, 4H, H3, H4) in the product (414) compared to $\delta_H$ 2.46-2.49 ppm (m, 2H, H4) in the starting material (399). The $^{13}C$ NMR resonances for C5 at $\delta_C$ 62.1 ppm and C6 at $\delta_C$ 85.5 ppm were consistent with the formation of a carbon attached to an alcohol group and a quaternary acetylene carbon (DEPT spectroscopy) which resonates considerably further downfield from the quaternary acetylenic carbon in the starting acetylene (410) at $\delta_C$ 72.4 ppm.

Having at best only isolated (414) in 15% yield, it was decided to investigate three variations to the reaction conditions in order to obtain a better yields. Firstly, acetylide ion (413) was warmed to -30 °C for 1 hour before being cooled to -78 °C and adding a solution of the aldehyde (399). It was hoped that use of a higher temperature would lead to the formation of more acetylide ion. Secondly the base was changed to the more reactive $t$-BuLi/TMEDA. Finally, the order of addition was reversed by adding the acetylide ion (413) to the aldehyde (399) thereby avoiding any possibility of enolization hampering reaction of the acetylide with aldehyde (399) (Scheme 93).
As depicted in Scheme 86 the best yield was obtained using a reverse addition procedure. When this procedure was repeated on larger scales the yield of product obtained were comparable. The reverse addition procedure was therefore adopted on a routine basis.
2.4 Synthetic studies towards spiroketal ylide (297) from ketone (414)

Having obtained the desired bis-tert-butylidemethylsilyl (TBS) protected ynol (413) attention turned to the synthetic pathway outlined in Schemes 89-91. Ynol (413) was firstly oxidised with Dess-Martin periodinane to afford ynone (415) as a colourless oil and mixture of diastereomers in 98% yield (Scheme 94).

\[
\begin{align*}
\text{(413)} & \quad \xrightarrow{(i)} \quad \text{(414)} \\
\text{Conditions: (i) Dess-Martin periodinane, py, CH}_2\text{Cl}_2, 30 \text{ min, 98%}.
\end{align*}
\]

Scheme 94

The high resolution mass spectrum for ynone (414) exhibited a molecular ion at \text{m/z} 425.2907 consistent with the molecular formula \( \text{C}_{23}\text{H}_{45}\text{Si}_2\text{O}_3 \). The \(^{13}\text{C}\) NMR resonances assigned to C4 at \( \delta_{\text{C}} \) 85.5 ppm, C5 at \( \delta_{\text{C}} \) 187.5 ppm and C7 at \( \delta_{\text{C}} \) 92.3 ppm, were consistent with the formation of a ketone at C5.

Epoxidation of (414) was then conducted by the addition of meta-chloroperoxybenzoic acid and sodium acetate in dichloromethane. The mixture was stirred at room temperature for five days affording epoxide (415) (Scheme 95).
Epoxide (415) was obtained as a colourless oil and as a mixture of diastereomers in 75% yield after work-up and purification by chromatography on flash silica gel. The high resolution mass spectrum for epoxide (415) exhibited a molecular ion at \( m/z \) 441.2284 consistent with the molecular formula \( \text{C}_{23}\text{H}_{45}\text{Si}_2\text{O}_4 \). The \(^1\text{H} \) NMR spectrum exhibited resonances consistent with formation of an epoxide [multiplets at \( \delta_\text{H} \) 2.62-2.65 ppm (m, 1H, H11a), \( \delta_\text{H} \) 2.77-2.80 ppm (m, 1H, H11b), \( \delta_\text{H} \) 3.06-3.09 ppm (m, 1H, H10)]. The \(^{13}\text{C} \) NMR resonances assigned to C10 at \( \delta_\text{C} \) 48.6 ppm and C11 at \( \delta_\text{C} \) 47.5 ppm resonated considerably further upfield than the vinylic carbons in the starting material (414) that resonated at \( \delta_\text{C} \) 132.9 ppm and \( \delta_\text{C} \) 118.4 ppm, respectively.

Despite the change of protection group from a tert-butyldiphenylsilyl (TBDPS) to a less bulky tert-butyldimethylsilyl (TBS) group, the terminal double bond of (414) still remained reasonably unreactive requiring 5 days for epoxidation to take place. Reduction of the triple bond in (416) was carried out by stirring over 10% palladium
on charcoal in ethyl acetate under an atmosphere of hydrogen for 2 hours. Ketone (416) was isolated as a colourless oil and as a mixture of diastereomers in 74% yield after purification by flash chromatography (Scheme 96).

The high resolution mass spectrum for (416) exhibited a molecular ion at $m/z$ 445.3180 consistent with the molecular formula $C_{23}H_{49}Si_2O_4$. The $^1H$ NMR spectrum exhibited resonances consistent with reduction of the triple bond with multiplets observed at $\delta_H$ 1.61-1.69 ppm ($m$, 4H, H3, H7) and $\delta_H$ 2.41-2.53 ($m$, 5H, H4, H6, H11a). The $^{13}C$ NMR resonances for C6 at $\delta_C$ 40.1, 40.2 ppm and C7 at $\delta_C$ 33.2 ppm resonated considerably further upfield than those in the starting material (415) (acetylenic carbons at $\delta_C$ 83.3, 83.8 ppm and $\delta_C$ 91.3, 91.8 ppm respectively).

The final step in the synthesis of spiroketal epoxide (300) required removal of the silyl protecting groups to afford diol (409). It was hoped that by changing to a more labile tert-butyldimethylsilyl (TBS) group at C8 that shorter reaction times would be required for the deprotection step and that spiroketal epoxide (300) would be afforded upon work up. Attempts to effect this desired reaction using tert-butyl ammonium fluoride and hydrogen fluoride/pyridine failed to yield spiroketal (300).
Chapter 3.

Discussion

(i) - Intense Blue spot by TLC

Conditions: (i) tert-butyl ammonium fluoride or HF, py, N₂, THF, 0°C, 1h.

Scheme 96

At this stage, an alternative approach was sought for synthesis of the desired spiroketal epoxide (300).

2.5 Attempted synthesis of spiroketal ylide (297) using a conjugate reduction step

Due to the lack of success in preparing spiroketal (300) by functionalising the terminal olefin of (403), an alternative synthetic pathway was proposed. The alternative route involved use of a Lindlar\textsuperscript{196} hydrogenation of (403) followed by conjugate hydride reduction of (418). Deprotection of the silyl groups would then allow the formation of the spiroketal (301), which could then be further functionalised at the terminal olefin (Scheme 97).
Partial hydrogenation of (403) was effected using Lindlar$^{196}$ catalyst in ethyl acetate containing a trace of quinoline until TLC analysis indicated the reaction was complete. Enone (417) was obtained as a colourless oil and as a mixture of diastereomers in 74% yield after work up and purification by chromatography on flash silica gel. The high resolution mass spectrum for enone (417) exhibited a molecular ion at $m/z$ 550.3305 consistent with the molecular formula $\text{C}_{33}\text{H}_{50}\text{Si}_{2}\text{O}_{5}$. The $^1\text{H}$ NMR spectrum exhibited a multiplet observed at $\delta_{\text{H}}$ 5.78-6.01 ppm (m, 3H, H6, H7, H10) consistent with partial hydrogenation. The $^{13}\text{C}$ NMR resonances for C6 at $\delta_{\text{C}}$ 129.6, 129.9 ppm and C7 at $\delta_{\text{C}}$ 150.2, 150.3 ppm resonated considerably further downfield than the acetylenic carbons in the starting material (403) that resonated at $\delta_{\text{C}}$ 83.9 ppm and $\delta_{\text{C}}$ 91.9 ppm, respectively.

In order to selectively remove the internal double bond leaving the terminal olefin intact, it was decided to try a number of hydride reagents that effect conjugate reduction of enones namely, copper hydride,$^{197}$ Raney$^{198}$ nickel and lithium triethoxy...
borohydride. These reagents however only effected reduction of the carbonyl group at C5 (419) or recovered starting material (417) (Scheme 98).

![Scheme 98](image)

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Conditions</th>
<th>Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CuH</td>
<td>CuI, LiAlH₄, THF, 0 °C</td>
<td>(417, 26%), (419, 15%)</td>
</tr>
<tr>
<td>Raney Ni²⁰⁰</td>
<td>Raney Ni, THF, 0 °C</td>
<td>(417, 100%)</td>
</tr>
<tr>
<td>LiBH(OE)₃</td>
<td>LiAlH(OE), THF, -78 °C</td>
<td>(419, 40%)</td>
</tr>
</tbody>
</table>

It was noted by Yamamoto et al.²⁰⁰ that steric ally hindered aluminium aryl oxides (Figure 34) have been successfully used as Lewis acids that effectively block the carbonyl functionality thus facilitating conjugate addition of organolithium reagents to α,β-unsaturated ketones and the selective reduction of more hindered ketones (Scheme 99).
R= Me, Methylaluminium bis(2,6-di-phenylphenoxide), (MAH) (420)

R= Br Methylaluminium bis(4-bromo-2,6-di-tert-butyl-4-methylphenoxide), (MABr) (422)

Aluminium tris(2,6-di-phenylphenoxide), (ATPH) (423)
Of particular interest is aluminium tris(2,6-diphenylphenoxide) (421) as it reported to be an efficient conjugate reducing reagent of α,β-unsaturated ketones when used with diisobutylaluminium hydride-"n"-butyllithium ate complex (DIBAL-"n"-BuLi) (Scheme 100). Using these reagents enone (428) underwent selective reduction to saturated ketone (429) with no reduction of the carbonyl group being observed.

Future work towards the synthesis of spiroketal ylide (297) using a conjugate reduction step should focus on using the reagents reported by Yamamoto, however this was not attempted in the present study.
2.6 Attempted synthesis of spiroketal ylide (297) from methyl acetal (431)

Due to the lack of reactivity of both the internal triple bond in (403) toward conjugate reduction and the terminal olefin toward hydroboration, it was decided to convert (414) to methyl acetal (431) (Scheme 101). The reason behind this decision was that methyl acetal (431) contains half of the desired spiroketal ring system and it was hoped that removal of the bulky tert-butyldimethylsilyl protecting group might allow functionalization of the olefin. To a solution of ynone (414) in methanol was added camphorsulfonic acid and the mixture stirred at room temperature for 2 hours. Methyl acetal (431) was obtained as a colourless oil and mixture of diastereomers in 97% yield after work up and purification by chromatography on flash silica gel.

\[
\begin{align*}
\text{(414)} & \quad \xrightarrow{(i)} \quad \text{(431)} \\
\text{Conditions: (i) Camphorsulfonic acid, MeOH, reflux, 2 h, 97%.} \\
\end{align*}
\]

Scheme 101

The high resolution mass spectrum for methyl acetal (431) exhibited a molecular ion at \( m/z \) 211.1335 consistent with the molecular formula \( C_{12}H_{19}O_3 \). The infrared spectrum showed a broad stretch at 3429 cm\(^{-1}\) consistent with the presence of an alcohol group. The \(^1\)H NMR spectrum exhibited resonances consistent with the formation of a methyl acetal with signals observed at \( \delta_H \) 4.48 ppm (s, 1H, OH), \( \delta_H \)
3.35, 3.36, 3.37, 3.38 ppm (s, 3H, OMe) and δ<sub>H</sub> 4.31-4.39 ppm (m, 1H, H3). This latter proton resonated at higher field than the same proton in the starting material that resonated at δ<sub>H</sub> 4.50 ppm (t, 1H, J=6.4 Hz, H8). The 13C NMR spectrum exhibited resonances for C2' at δ<sub>C</sub> 101.5, 101.8 ppm and the methoxy carbon (OCH<sub>3</sub>) resonated at δ<sub>C</sub> 61.4 ppm thus supporting the successive formation of the methyl acetal (431).

It now remained to effect hydroboration of the terminal double bond in (431) as outlined in Scheme 102.

![Scheme 102](image-url)
Alkene (431) was treated separately with fresh BH$_3$SMe$_2$, 9-BBN and catechol borane in dry THF (Scheme 103). The amount of borane reagent added was varied from three to four equivalents, and the reactions stirred for 4 h at 0 °C after addition of the borane. Disappointingly none of the hydroboration agents effected the desired formation of diol (432) from (431).

![Diagram of hydroboration reaction](image)

<table>
<thead>
<tr>
<th>Conditions: (i) Borane (3-4) equiv, THF, 4h, (ii) 3 mol L$^{-1}$ NaOH, 30% H$_2$O$_2$.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BH$_3$-DMS</td>
</tr>
<tr>
<td>(431)</td>
</tr>
</tbody>
</table>

Scheme 103

Having successfully effected epoxidation of (403) and (416) earlier (Sections 2.1.4 and 2.1.7) it was decided to epoxidize the alkene in methyl acetal (432) before proceeding with cyclisation to spiroketal epoxide (300). Ring opening of the epoxide (404) could be achieved later by reaction with zinc borohydride (435) (Scheme 104).
Alkene (431) was treated with *meta*-chloroperoxybenzoic acid and sodium acetate in dichloromethane at room temperature for two days (Scheme 105).

**Scheme 105**

Conditions: (i) *m*CBPA, NaOAc, CH₂Cl₂, rt, 2 days, 89%.
Epoxide (436) was obtained as a colourless oil and as a mixture of diastereomers in 89% yield after work up and purification by chromatography on flash silica gel. The high resolution mass spectrum for epoxide (436) exhibited an ion at \textit{m/z} 195.1012 consistent with the molecular formula C_{11}H_{18}O_{4}, assigned to M-OMe. The \textsuperscript{1}H NMR spectrum exhibited resonances consistent with epoxidation in that multiplets were observed at $\delta_H$ 2.49-2.52 ppm (m, 1H, H3), $\delta_H$ 2.80-2.85 ppm (m, 1H, H6b) and $\delta_H$ 3.10-3.20 ppm (m, 1H, H5) and were assigned to the epoxide ring protons. The \textsuperscript{13}C NMR resonances for C5 at $\delta_C$ 49.1 ppm and C6 at $\delta_C$ 46.9 ppm resonated considerably further upfield than those in the starting material (431), where they resonated at $\delta_C$ 132.9 ppm and $\delta_C$ 118.9 ppm respectively.

The fact that it had taken only two days to effect epoxidation of (431) compared with five days to effect epoxidation of (403) and (414), suggested that removal of the sterically bulky tert-butyldimethylsilyl protecting groups did indeed increase the reactivity of the terminal olefin of (431).

The next step involved reduction of the triple bond which then allows formation of the spiroketal epoxide (300) upon work-up. Acetylene (436) was stirred with 10% palladium on charcoal and sodium bicarbonate in ethyl acetate under a hydrogen atmosphere. After 2 hours (300) was afforded as a colourless oil and as a mixture of diastereomers in 63% yield after work-up and purification by chromatography on flash silica gel (Scheme 106).
The high resolution mass spectrum for spiroketal epoxide (300) exhibited an ion at \( m/z \) 197.3122 consistent with the molecular formula \( \text{C}_{11}\text{H}_{18}\text{O}_3 \) and assigned to M-H. The \( ^1\text{H} \) NMR spectrum exhibited resonances consistent with formation of the spiroketal epoxide (300) in that multiplets were observed at \( \delta_{\text{H}} 2.49-2.52 \text{ ppm} \) (m, 1H, H3'b), \( \delta_{\text{H}} 2.75-2.82 \text{ ppm} \) (m, 1H, H3'a) and \( \delta_{\text{H}} 3.00-3.10 \text{ ppm} \) (m, 1H, H2') and were assigned to the epoxide ring protons. The multiplets observed at \( \delta_{\text{H}} 1.57-1.70 \text{ ppm} \) (m, 4H, H3, H8) and \( \delta_{\text{H}} 2.15-2.21 \text{ ppm} \) (m, 4H, H4, H9) were consistent with the formation of the spiroketal ring structure. The \( ^{13}\text{C} \) NMR spectrum exhibited resonances for C3' at \( \delta_{\text{C}} 47.4, 47.5 \text{ ppm} \), C2' at \( \delta_{\text{C}} 49.5, 49.7, 49.8, 49.9 \text{ ppm} \) and the spiro carbon C5 at \( \delta_{\text{C}} 102.9, 103.9 \text{ ppm} \) were also consistent with the formation of (300).

2.7 Investigations into ring opening of epoxide (300) with zinc borohydride (435)

Good evidence for reductive cleavage of unsymmetrical alkyl-substituted epoxides to less substituted alcohols has been achieved using zinc borohydride (435) supported on silica gel.\textsuperscript{195} In general other nucleophilic hydrides like lithium aluminium hydride, sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) and
lithium triethylborohydride (super base) provide more substituted alcohols and hence access to the less substituted alcohols is not as simple.\textsuperscript{202} The ability of zinc borohydride (435) to provide the less substituted alcohol is attributed to its ability to coordinate to the oxygen of the epoxide and allow delivery of the hydride to the more substituted carbon of the epoxide (\textbf{Figure 35}).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure35.png}
\caption{Figure 35}
\end{figure}

Fresh batches of silica gel supported zinc borohydride (435) were prepared in order to effect reduction of spiroketal epoxide (300) (\textbf{Scheme 107}). Use of non-supported zinc borohydride (435) was also investigated. In both cases none of the desired alcohol (437) was furnished.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{scheme107.png}
\caption{Scheme 107}
\end{figure}

\textbf{Conditions:} (i) $\text{Zn(BH}_4\text{)}_2$/SiO$_2$, or Zn(BH$_4$)$_2$, THF, 24h, rt.
Chapter 3.

Discussion

It was next decided to examine the zinc borohydride (435) reduction of the spiroketal precursors (408), (416) and (436) (Scheme 108).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Zn(BH₄)₂ on silica</th>
<th>Zn(BH₄)₂</th>
<th>Product yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(408)</td>
<td>THF, 24h, rt</td>
<td>Zn(BH₄)₂</td>
<td>(438) 13%</td>
</tr>
<tr>
<td>(408)</td>
<td>THF, 24h, rt</td>
<td>(438) 23%</td>
<td></td>
</tr>
</tbody>
</table>
Given that no epoxide ring opened products were obtained and that only (438), (440) and (432) were formed by reduction of the ketone it was decided to discontinue synthetic work toward spiroketal ylide (297) following this procedure. Alternative strategies would need to be developed to overcome the lack of reactivity of the terminal olefins in ketones (403) and (414) toward hydroboration. Epoxidation followed by reductive ring opening offered an alternative to hydroboration, however reaction of spiroketal epoxide (300) and various precursors with zinc borohydride (435) did not yield the desired ring-opened product. Due to time constraints, the focus of the present work was shifted to the synthesis of the phthalide portion (288) of CJ-12,954 (56).

2.8 Synthetic studies towards phthalide (288)

As noted in the introduction (section 2.1), it was proposed that phthalide (288) could be obtained from hydroxyphthalide (370) which had been prepared by Borchardt et al.\textsuperscript{185} from 3,5-dimethoxybenzoic acid (374) (Scheme 77). Gorsuch\textsuperscript{184} had been unable to synthesize hydroxyphthalide (370) using this synthetic route (Scheme 78) and it was decided to initially to give the procedure one final try before seeking alternative pathways of synthesis.
2.8.1 Synthetic studies towards hydroxyphthalide (370) using Borchardt's$^{185}$ route

Lithium aluminium hydride reduction of 3,5-dimethoxybenzoic acid (374) to the primary alcohol (373) was carried out in THF at 0 $^\circ$C under an atmosphere of nitrogen. (373) was obtained as a yellow oil in near quantitative yield for which the $^1$H NMR spectrum compared favourably with the literature data (Scheme 109).$^{185}$

\[ \text{(374)} \xrightarrow{\text{(i)}} \text{(373)} \xrightarrow{\text{(ii)}} \text{(372)} \]

Conditions: (i) LiAlH$_4$, THF, 99%; (ii) NBS, CCl$_4$, 40 min, 94%; (iii) PCC, CH$_2$Cl$_2$, 81%; (iv) (a) n-BuLi, morpholine, THF, -50 to -78 $^\circ$C, 15 min; (b) n-BuLi, -78$^\circ$C, 35 min; (c) solid CO$_2$, 1h.

Scheme 109
Chapter 3. Discussion

Bromination ortho to the hydroxymethyl group was then achieved by heating alcohol (373) under reflux with NBS in CCl₄ for 40 min under an atmosphere of nitrogen. Bromide (372) was obtained as a colourless oil in 94% yield for which the ¹H NMR spectrum compared favourably with the literature data (Scheme 109).¹⁸⁵ Oxidation of the alcohol (372) with pyridinium chlorochromate (PCC) in dichloromethane provided aldehyde (371) as an orange oil in 81% yield (Scheme 109). The ¹H NMR spectrum compared favourably with the literature data.¹⁸⁵

The key step in Borchardt’s¹⁸⁵ synthesis of the hydroxyphthalide (370) involved the reversible reaction of morpholide ion with aldehyde (371), facile halogen lithium exchange and subsequent trapping of the anion with carbon dioxide. Attempts to effect this were not successful in the present work.

2.8.2 Synthetic studies towards hydroxyphthalide (370) using Comins²⁰³ methodology

It had been noted by Comins²⁰³ that lithium morpholide (as used by Borchardt¹⁸⁵ in 2.8.1) was limited as a reagent for the protection of aldehyde due to its strongly basic and nucleophilic properties. Use of the lithium amide of N,N,N'-trimethylethylenediamine (LTMDA), a relatively weak base, that does not deprotonate or attack aliphatic esters can be used to effect intramolecular TMEDA-like assisted metalations (Scheme 110).
Chapter 3.

Discussion

Conditions: (i) LTMDA, THF, -20 °C, 30 min; (ii) n-BuLi, -20 °C, 15 min; (iii) CO$_2$(g), or CO$_2$(s); (iv) 6 mol L$^{-1}$ HCl.

Scheme 110

It was envisaged that reaction of (443) prepared using Comins$^{203}$ methodology with carbon dioxide (gas or solid) would afford the desired hydroxyphthalide (370) on aqueous acid work-up. The lithium amide base prepared via reaction of n-BuLi with $N,N,N'$-trimethylethylenediamine (LTMDA) was reacted with aldehyde (371). After thirty minutes n-BuLi was added and the mixture left for a further fifteen minutes. The reaction was then quenched with carbon dioxide (both gaseous and solid state were tried) and acidified with aqueous acid. After work-up TLC analysis revealed only starting material and a spot of higher $R_F$ when run in 50% ethyl acetate/hexane. $^1$H NMR spectrum of the crude mixture identified this higher running spot to be 3,5-dimethoxybenzaldehyde (445) presumably formed from lithium-halogen exchange (Scheme 111).
Conditions: (i) $n$-BuLi, $-20^\circ$C, THF; (ii) 6 mol L$^{-1}$ HCl, 56% + 36% (371).

**Scheme 111**

### 2.8.3 Synthetic studies towards hydroxyphthalide (370) using Napolitano$^{204}$ methodology

Napolitano et al.$^{204}$ reported a synthesis of 3-hydroxy-7-methoxyphthalide (446) by reaction of 2-(3-methoxyphenyl)-1,3-dimethylimidazolidine (447) with $n$-BuLi in ether at $0^\circ$C followed by trapping with solid carbon dioxide at $-78^\circ$C (**Scheme 112**).
It was envisaged that the conditions of Napolitano et al.\textsuperscript{204} that had been used successfully to prepare mono-methoxy phthalide (446) could be applied to 2-(3,5-dimethoxyphenyl)-1,3-dimethylimidazolidine (450) which would lead to the desired dimethoxyphthalide (370) (Scheme 113).

To a solution of 3,5-dimethoxybenzaldehyde (445) in dry benzene was added \textit{N},\textit{N}'-dimethylethlenediamine and the mixture was heated under nitrogen for 5 hours using
Chapter 3.

Discussion

Dean-Stark apparatus. The imidazolidine (450) was obtained as a pale yellow oil in 98% yield (Scheme 114). The $^1$H NMR compared favourably with the literature data.\textsuperscript{205}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.4\textwidth]{example.png}};
\end{tikzpicture}
\end{center}

**Conditions:** $N,N'$-dimethylethylenediamine, benzene, Dean-Stark, 5h, 98%.

*Scheme 114*

$n$-BuLi was added to a solution of imidazolidine (450) in dry ether and stirred under an atmosphere of nitrogen for two hours (Scheme 115). The reaction mixture was then cooled to -78 °C and quenched with solid carbon dioxide. It was noticeable a visual change in the reaction solution's colour from bright to pale yellow occurred.
Chapter 3. Discussion

After work-up with aqueous HCl, $^1$H NMR spectrum of the crude reaction mixture established that the reaction had been unsuccessful with only 3,5-dimethoxybenzaldehyde (445) being recovered. Presumably aldehyde (445) was formed by acid hydrolysis of imidazolidine (450). Despite extensive use of alternative conditions, no phthalide (370) was obtained (Scheme 115). It was postulated that the anion being formed ortho to the imidazolidine was undergoing protonation at a faster rate than its reaction with carbon dioxide.

<table>
<thead>
<tr>
<th>RLi (equiv)</th>
<th>Temp (°C)</th>
<th>Time elapsed before $E^+$ addition (min)</th>
<th>$E^+$</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$-BuLi (1.2)$^{294}$</td>
<td>0</td>
<td>120</td>
<td>CO$_2$ (s)</td>
<td>(445)</td>
</tr>
<tr>
<td>$n$-BuLi (1.2)</td>
<td>0</td>
<td>120</td>
<td>CO$_2$ (g)</td>
<td>(445)</td>
</tr>
<tr>
<td>$n$-BuLi (1.2)</td>
<td>-78</td>
<td>30</td>
<td>CO$_2$ (g)</td>
<td>(445)</td>
</tr>
<tr>
<td>(1.2)/TMEDA (3)</td>
<td>-78</td>
<td>15</td>
<td>CO$_2$ (g)</td>
<td>(445)</td>
</tr>
<tr>
<td>$t$-BuLi (1.2)/TMEDA (3)</td>
<td>-78</td>
<td>20</td>
<td>TMSCl</td>
<td>(445)</td>
</tr>
<tr>
<td>$t$-BuLi (1.2)/TMEDA (3)</td>
<td>-78</td>
<td>45</td>
<td>TMSCl</td>
<td>(445)</td>
</tr>
</tbody>
</table>

Scheme 115
Chapter 3.

Discussion

Frustrated by the lack of success it was decided to attempt the literature reaction to validate the reaction conditions.

To a solution of 3-dimethoxybenzaldehyde (451) in dry benzene was added N,N'-dimethylethylenediamine and the mixture was heated under nitrogen for 5 hours using a Dean-Stark apparatus. The imidazolidine (447) was obtained as a pale yellow oil in 98% yield (Scheme 116). The \(^1\)H NMR spectrum compared favourably with the literature data.\(^{204}\)

\[
\begin{align*}
\text{(451)} & \quad \text{(i)} \quad \text{(447)} \\
\text{OMe} & \quad \text{OMe} \\
\text{H} & \quad \text{N} \\
\end{align*}
\]

Conditions: N,N'-dimethylethylenediamine, benzene, Dean-Stark, 5h, 98%.

Scheme 116

Attempting the subsequent lithiation/carboxylation procedures reported by Napolitano \textit{et al.}\(^{204}\) did not afford the desired phthalide (446) rather 3-dimethoxybenzaldehyde (451) was recovered from the reaction. It was noted again that quenching the anion (448) with carbon dioxide resulted in a visible colour change in the reaction solution from bright yellow to pale yellow, however the desired phthalide (446) was not accessed in this manner despite varying the nature of the base and the reaction time used (Scheme 117).
2.8.4 Attempted synthesis of hydroxyphthalide (370) via ortho formylation

(i) Synthetic strategies

As noted previously (section 2 of the papulacandins) synthesis of hydroxyphthalide (259) is possible via ortho-formylation of amide (255) to (257) followed by acid catalysed cyclization (Scheme 41).
Chapter 3.

Discussion

Scheme 41

It was envisaged that the above methodology could be extended to the synthesis of hydroxyphthalide (370) despite the fact that methoxy groups on the aromatic ring had a different regiochemical arrangement to those on hydroxyphthalide (259) (Scheme 118). This strategy was therefore adopted and required initial synthesis of amide (295)

Scheme 118

180
(ii) Synthesis of amide (295)

Amide (295) was prepared from 2,4-dimethoxybenzoic acid (296) that in turn is obtained by oxidation of 2,4-dimethoxybenzaldehyde (452). To a vigorously stirred suspension of KMnO$_4$ in water was added tetrabutylammonium bromide followed by a solution of 2,4-dimethoxybenzaldehyde (452) in benzene at 0 °C. After 30 min the “purple benzene” solution turned brown and Na$_2$S$_2$O$_5$ was added before the reaction mixture was acidified. After work-up, benzoic acid (296) was obtained as a white solid in 84% yield. The melting point and $^1$H NMR compared favourably with the literature data (Scheme 119).

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

(452) \quad \text{(i)} \quad \text{(ii), (iii)} \quad \text{MeO} \quad \text{OMe} \quad \text{NEt$_2$}

(295)

Conditions: (i) KMnO$_4$, Na$_2$S$_2$O$_5$, H$_2$O, Benzene, 0 °C, 84%; (ii) SOCl$_2$, 2h, reflux; (iii) Et$_2$NH, CH$_2$Cl$_2$, 0 °C, 98%.

Scheme 119

Preparation of the $N,N$-diethyl-2,4-dimethoxybenzamide (295) was achieved by heating 2,4-dimethoxybenzoic acid (296) at reflux with SOCl$_2$ under an atmosphere of nitrogen (Scheme 119). Treatment of the resultant residue with diethylamine in dichloromethane at 0 °C gave the desired amide (295) as a pale yellow oil in 99% yield after work-up and purification by chromatography on flash silica gel. The $^1$H NMR data compared favourably with the literature data.
(iii) *Synthesis of aldehyde (294)*

Having established conditions for the synthesis of aldehyde (256) from amide (255) as described earlier (section 2.1.2 papulacandin discussion), it was decided to adopt those conditions for synthesis of (294). In a flame-dried flask flushed with nitrogen, a vigorously stirred solution of amide (295) and TMEDA in dry THF were cooled to -78 °C. t-BuLi was added dropwise over 1 min and the resulting deep orange solution was left for 15 min. Anhydrous DMF was then added and the mixture was stirred at -78 °C for 1 h, then warmed to room temperature (Scheme 120).

![Chemical structure](image)

**Scheme 120**

TLC analysis of the reaction mixture revealed a mixture of two polar spots and unreacted starting material. After work up and purification by chromatography on flash silica gel, aldehyde (294) was obtained as a yellow oil in 12% yield. Alcohol (453) was also obtained as a yellow oil in 28% yield. The high resolution mass spectrum for aldehyde (294) exhibited a molecular ion at *m/z* 265.1314 consistent with the molecular formula C_{14}H_{19}NO_4. The $^1$H NMR spectrum exhibited a resonance at δH 9.96 ppm (s, 1H, CHO) consistent with formation of an aldehyde. The $^{13}$C NMR spectrum exhibited a resonance for CHO at δC 190.2 ppm also consistent with the formation of an aldehyde.
The presence of alcohol (453) in the product mixture suggested that $t$-BuLi was possibly acting not only as a base but also as a reducing agent (Figure 36). The first equivalent of $t$-BuLi would act as the base and the second equivalent reduces the aldehyde side chain.

**Figure 36**

Kawalaki et al.\textsuperscript{208} noted that certain enolizable $\alpha$-halo and $\alpha$-methoxy-substituted ketones undergo rapid reaction with LDA to give reduction products via formal hydride transfer to the carbonyl in competition with enolization (Scheme 121).

\begin{align*}
\text{Conditions:} & \quad \text{(i)} \ (a) \text{ LDA, } \text{Et}_2\text{O} ; \ (b) \text{ TMSCI, } R= \text{Cl}, (455) \ 17\% ; \ R= \text{OMe}, (456) \ 85\%. \\
\text{Scheme 121}
\end{align*}
Chapter 3.  

Discussion

One plausible mechanism that accounts for reduction of carbonyl groups by LDA is the nitrogen analogue of the Meerwein-Ponndorf-Verley reduction (Scheme 122).

![Diagram of Scheme 122](image)

The driving force for the reaction is the transfer of negative charge from nitrogen to oxygen and there is precedent for reduction proceeding via this pathway in the reaction of benzophenone with N-benzylanilide. With this in mind the amount of t-BuLi was reduced from 2.2 to 1.1 equivalents in order to avoid reduction of the aldehyde however in this case, the product mixture still consisted of a 1:5 mixture of aldehyde (294):alcohol (453) (Scheme 124). This experiment demonstrated that the extra equivalent of t-BuLi used may not be responsible for the formation of alcohol (453) and the DMF leaving group (NMe₂) may well be the reducing agent (Scheme 123).
With a best yield of aldehyde (294) obtained being only 12% and the competitive formation of alcohol (453), it was decided to investigate changes to the reaction conditions to improve the yield of the desired aldehyde (294) (Scheme 124).
Reducing the amount of $t$-BuLi did not prevent the formation of alcohol (453), however it was found that when the reaction was conducted on larger scales, the optimum procedure involved leaving the anion for 15 minutes (highlighted).

(iv) Synthesis of hydroxyphthalide (370)

With aldehyde (294) in hand, attention turned to the subsequent cyclization to provide the required hydroxyphthalide (370). To a stirred solution of aldehyde (294) in glacial acetic acid was added an aqueous solution of HCl. The solution was heated at reflux under an atmosphere of nitrogen for 6 h, then the solvent removed under reduced pressure. Purification by chromatography on flash silica gel afforded the hydroxyphthalide (370) in 92% yield as a colourless oil (Scheme 125). The $^1$H NMR spectrum compared favourably with the literature data.\textsuperscript{185}

(v) Synthesis of phthalide (288)

As outlined previously (section 2.1) (Scheme 77), synthesis of phthalide (288) from (370) required addition of an allyl group to acetate (369), followed by hydroboration and oxidation of the resulting primary alcohol. Having already had
success using a procedure involving trimethylsilyl triflate catalysed allyltributylstannane coupling on regioisomeric phthalide (261), it was hoped the same conditions could be used for acetate (369).  

\[
\text{Scheme 77}
\]

To a stirred solution of hydroxyphthalide (370) in dichloromethane was added Et\textsubscript{3}N, acetic anhydride and 4-(dimethylamino)pyridine (DMAP). The mixture was stirred for 2 h at room temperature at which time TLC analysis indicated the reaction was complete. After work-up and purification by chromatography on flash silica gel acetate (369) was obtained as a colourless in 92\% yield (Scheme 125).

The high resolution mass spectrum for acetate (369) exhibited a molecular ion at \(m/z\) at 252.0636 consistent with the molecular formula \(\text{C}_{12}\text{H}_{12}\text{O}_6\). The \(^1\text{H}\) NMR spectrum
Chapter 3.

Discussion

exhibited a resonance consistent with formation of an acetate in the characteristic singlet observed at $\delta_H \, 2.19 \, \text{ppm}$ (s, 3H, COCH$_3$). The $^{13}$C NMR spectrum exhibited the corresponding carbon resonance for the carbonyl group (COCH$_3$) of the acetate at $\delta_C \, 169.5 \, \text{ppm}$.

Treatment of acetate (369) in dichloromethane $-78 \, ^\circ \text{C}$ with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and allyltributylstannane and then warming the reaction to room temperature over 16 hours afforded only recovered starting material (369) (Scheme 126).

![Scheme 126](image)

Conditions: (i) TMSOTf or SnCl$_4$, allyl tributylstannane, CH$_2$Cl$_2$, $-78 \, ^\circ \text{C}$ to rt.

When the reaction was tried using SnCl$_4$ as the Lewis acid instead of TMSOTf unfortunately no allyl phthalide (292) was obtained. As noted in Scheme 41 addition of the Lewis acid results in the formation of an oxycarbenium ion (455) which then reacts with the allyltributylstannane to give the product. The oxycarbenium ion (262) thus generated from acetate (369) is stabilized by the two electron donating methoxy groups at C4 and C6 on the aromatic ring. However, the two methoxy groups on regioisomeric phthalide (363) cannot stabilize the oxycarbenium ion (462) generated in this case (Figure 37).
At this point it was decided to return to aldehyde (294) and attempt the selective addition reaction with the Grignard of allyl magnesium bromide to the aldehyde group. It was then envisaged that the resulting alcohol (293) would undergo cyclization with acid to give the desired allyl phthalide (292) (Scheme 127).

In a flame dried flask flushed with nitrogen, a vigorously stirred solution of aldehyde (294) in dry Et₂O was cooled to -40 °C. Allylmagnesium bromide was added dropwise over one min and the mixture allowed to warm slowly to room temperature.
Chapter 3.

Discussion

over 12 h. TLC analysis of the crude mixture revealed all of the starting material had been consumed and a more polar spot had formed. After work-up and purification by chromatography on flash silica, alcohol (293) was obtained as a colourless oil in 95% yield (Scheme 128).

The high resolution mass spectrum for alcohol (293) exhibited a molecular ion at m/z at 307.1786 consistent with the molecular formula C_{17}H_{25}NO_4. The ^1H NMR spectrum exhibited resonances consistent with formation of an allyl alcohol in the signals observed at δ_H 2.54-2.71 (m, 2H, H1'), δ_H 3.01 ppm (s, 1H, OH), δ_H 2.27-2.68 ppm (m, 2H, H2'), δ_H 5.18-5.75 ppm (m, 2H, H4') and δ_H 5.75-5.89 ppm (m, 1H, H3'). The ^13C NMR spectrum exhibited the corresponding carbon resonances for the allyl alcohol with C2' at δ_C 38.8, 38.6 ppm, C1' at δ_C 70.1, 71.5 ppm, C4' at 117.2, 118.3
and C3' at 134.8. Due to the presence of rotamers some carbon signals exhibited than one resonance.

Alcohol (293) then underwent cyclization upon heating under reflux in glacial acetic acid and 10% HCl for six hours. Removal of the solvent under reduced pressure and purification by chromatography on flash silica afforded allyl phthalide (292) as a colourless oil in 92% yield (Scheme 128). The high resolution mass spectrum for allyl phthalide (292) exhibited a molecular ion at m/z at 234.0892 consistent with the molecular formula C_{13}H_{14}O_{4}. The $^{13}$C NMR spectrum exhibited resonances consistent with the formation of allyl phthalide (292) with a resonance at δC 78.8 ppm assigned to C3 and resonances assigned to the allyl group C1' at 38.7 ppm, C3' at 119.4 ppm and C2' at 131.3 ppm.

Hydroboration of (292) was next achieved by treatment with BH$_3$.SMe$_2$ in THF under nitrogen at 0 °C. After five hours aqueous NaOH followed by H$_2$O$_2$ were added and the mixture was stirred at 0 °C for a further 30 min. After work-up and purification by chromatography on flash silica alcohol (291) was obtained as a white solid in 60% yield (Scheme 128).

The high resolution mass spectrum for alcohol (291) exhibited a molecular ion at m/z at 252.0994 consistent with the molecular formula C_{13}H_{16}O_{5}. The $^1$H NMR spectrum exhibited resonances consistent with formation of an alcohol in the signals observed at δ$_H$ 2.47 ppm (s, 1H, OH) and δ$_H$ 3.68-3.75 ppm (m, 2H, H3'). The $^{13}$C NMR spectrum exhibited a resonance for the C3' at δC 62.1 ppm consistent with a carbon attached to an alcohol group.

The final step in the sequence required an oxidation of alcohol (291) to phthalide aldehyde (288). Oxidation was conducted by stirring alcohol (291) in dichloromethane with tetrapropylammonium persruthenate, NMO and 4 Å molecular
The mixture was stirred at room temperature for 2 hours then poured through a short pad of silica and washed with water. Purification by chromatography on flash silica gel afforded phthalide aldehyde (288) as a colourless oil in 64% yield which was immediately stored under nitrogen (Scheme 128). The high resolution mass spectrum for phthalide aldehyde (288) exhibited a molecular ion at \( m/z \) at 250.0839 consistent with the molecular formula \( \text{C}_{13}\text{H}_{14}\text{O}_{5} \). The \( ^1\text{H} \) NMR spectrum exhibited a resonance consistent with formation of an aldehyde with a characteristic signal at \( \delta_{\text{H}} \) 9.81 ppm (s, br, 1H, CHO) being assigned to the aldehyde proton. The \( ^{13}\text{C} \) NMR spectrum exhibited the corresponding carbon resonance for C3’ at \( \delta_{\text{C}} \) 200.6 ppm consistent with presence of an aldehyde carbon.

2.9 Synthetic studies towards CJ-13,108 (62) and CJ-12,954 (56)

2.9.1 Overall strategy

With phthalide aldehyde (288) in hand, attention returned to the synthesis of antibiotics CJ-13,108 (62) and CJ-12,954 (56). In order to effect a synthesis of (62) and (56) a method of coupling aldehyde (288) to Grignard reagent (463) or ylide (289) respectively, must be demonstrated (Scheme 129, Scheme 47).
Scheme 129 Retrosynthesis of CJ-13,108 (62)
Scheme 47 Retrosynthesis of CJ-12,954 (56)
As noted in section 2.8 above, problems encountered during the attempted ring opening of spiroketal epoxide (300) meant the initial focus of our work was on the synthesis of CJ-13,108 (62).

2.9.2 Union of aldehyde (288) with bromide (290)

As demonstrated previously (Scheme 129) one method by which the required side chain in CJ-13,108 (62) can be coupled to aldehyde (288) involves addition of a Grignard\textsuperscript{215} reagent (463) derived from bromide (290) (Scheme 130). The resulting alcohol (464) can then be deoxygenated at C3' followed by Wacker\textsuperscript{222,223} oxidation at C13' to give CJ-13,108 (62).
Scheme 130
Scheme 131
2.9.3 Grignard addition of bromide (290) to aldehyde (288)

Undec-1-en-11-ylmagnesium bromide (463) was added dropwise over 1 minute to phthalide aldehyde (288) in dry diethyl ether at -40 °C and the mixture was allowed to warm to room temperature over 12 hours. TLC analysis revealed the presence of a less polar UV active spot. After work-up and repeated purification by chromatography on flash silica, alcohol (464) was obtained as a colourless greasy oil in 29% yield as a mixture of diastereomers (Scheme 132).

![Scheme 132](image)

Conditions: (i) Undec-1-en-11-ylmagnesium bromide, Et₂O, -40 °C to rt, 12h, 29%.

The high resolution mass spectrum for alcohol (464) exhibited a molecular ion at m/z at 404.2557 consistent with the molecular formula C₂₄H₃₆O₅. The ¹H NMR spectrum exhibited resonances consistent with formation of alcohol (464) in the signals observed at δ_H 3.61-3.66 ppm (m, 1H, H₃'), δ_H 4.91-5.02 ppm (m, 2H, H₁₄'a, H₁₄'b) and δ_H 5.75-5.87 ppm (m, 1H, H₁₃'). The ¹³C NMR spectrum exhibited the corresponding carbon resonances for the alcohol (464) with C₃' at δ_C 71.2, 71.7 ppm, C₁₄' at δ_C 114.1 ppm and C₁₃' at 139.2 ppm.

When the reaction was repeated, again only low yields of (464) were recovered. The low yields were not helped by the fact that the product alcohol (464) and aldehyde
(288) exhibited a similar $R_F$ in many eluents thus rendering chromatography on flash silica gel difficult. It was therefore decided not to pursue this Grignard addition strategy but rather focus on the Wittig method.

### 2.9.4 Addition of ylide (289) to aldehyde (288)

In order to obtain the required ylide (289) for attempted union with aldehyde (288) (Scheme 131), initial preparation of phosphonium salt (468) was required. Bromide (290) and triphenylphosphine in dry benzene were heated at reflux for 24 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure leaving a cloudy thick oil which was triturated with dry diethyl ether then dried under high vacuum to afford (468) as a thick colourless oil in 96% (Scheme 133). The $^{31}$P NMR data compared favourably with the literature data.\(^{221}\)

![Scheme 133](image)

**Conditions:** (i) PPh$_3$, benzene, reflux, 24 h, 96%.

In a flame-dried flask equipped with a reflux condenser and flushed with nitrogen, a vigorously stirred solution of the phosphonium bromide salt (468) in dry THF was cooled to -78 °C. $n$-BuLi was added dropwise over 1 min and the resulting deep orange/red solution was left for 25 min then transferred via cannula to a solution of phthalide aldehyde (288) in dry THF at -78 °C. The solution was left for 20 min,
allowed to warm to room temperature, then heated to reflux under nitrogen for 1 h. TLC analysis revealed the presence of a less polar UV product. After work-up and purification by chromatography on flash silica diene (466) was obtained as a colourless greasy oil in 68% yield (Scheme 134). The ratio of E:Z isomers of (466) was not determined and was not considered relevant in that the olefin at C3' would be hydrogenated in subsequent steps.

![Scheme 134](image)

Conditions: (i) (468), THF, -78 °C, n-BuLi, 25 min; (ii) cannula (i) into (288) in THF, -78 °C, 20 min, reflux, 1h, 68%.

The high resolution mass spectrum for diene (466) exhibited a molecular ion at m/z at 386.2451 consistent with the molecular formula C_{24}H_{34}O_{4}. The $^1$H NMR spectrum exhibited resonances consistent with formation of diene (459). Characteristic resonances were observed at $\delta_H$ 4.90-5.01 ppm (m, 2H, H14'a, H14'b), $\delta_H$ 5.27-5.48 ppm (m, 3H, H3, H3', H4') and $\delta_H$ 5.73-5.87 ppm (m, 1H, H13'). The $^1$H NMR spectrum was complex in the olefinic region at 4.90-5.90 ppm hence the E/Z ratio was not resolved. The $^{13}$C NMR spectrum exhibited the corresponding carbon resonances for diene (459) with C3' resonating at $\delta_C$ 127.4 ppm, C4' at $\delta_C$ 131.6 ppm, C14' at 113.9 ppm and C13' at 139.0 ppm.

The next reaction involved the selective Wacker$^{222,223}$ oxidation of the terminal olefin. It was conceived that this could be achieved using a variant of the commercially
important Wacker process. The mechanism of the Wacker process is outlined below (Scheme 135).

The process is believed to involve the formation of an initial palladium-olefin complex (469) followed by replacement of a co-ordinated chloride ligand trans to the olefin by water to the hydroxo complex (470). Nucleophilic attack by water onto the activated olefin at the more substituted end gives (471), which decomposes via a fast irreversible, 1,2-hydride shift to give the methyl ketone product and a Pd(0) species.
Reoxidation of the Pd(0) species to Pd(II) by Cu(II) with concomitant oxidation by elemental oxygen of the Cu(I) thus formed establishes a true homogeneous catalytic process with only oxygen and the alkene being consumed (Scheme 136).

\[
\begin{align*}
4\text{Cl}^- + \text{Pd(0)} + 2\text{Cu}^{2+} & \rightarrow [\text{PdCl}_4]^{2-} + 2\text{Cu}^+ \\
4\text{Cu}^+ + \text{O}_2 + 4\text{H}^+ & \rightarrow 4\text{Cu}^{2+} + 2\text{H}_2\text{O}
\end{align*}
\]

Scheme 136

Recent improvements to the Wacker oxidation by Tsuji et al.\textsuperscript{226,227} have enabled this reaction to be performed on a laboratory scale. In a procedure reported by Tsuji\textsuperscript{227} homoallyl keto-ester (473) was oxidised to methyl ketone (474) in 58% yield using palladium(II) chloride in a mixture of DMF and water (Scheme 137).

Conditions: (i) PdCl\textsubscript{2}, CuCl\textsubscript{2}, O\textsubscript{2}, DMF-H\textsubscript{2}O 8:1, 20h, 58%.

Scheme 137
McQuillen and Parker\textsuperscript{228} showed that the Wacker oxidation can be kinetically selective for terminal double bonds in the presence of internal double bonds (Scheme 138).

\begin{center}
\begin{tikzpicture}
\t\node (A) at (0,0) {\textbf{(475)}};
\t\node (B) at (2,0) {\textbf{(476)}};
\t\node (C) at (1,0) {\textbf{(i)}};
\end{tikzpicture}
\end{center}

Conditions: (i) PdCl\textsubscript{2}, CuCl, DMF-H\textsubscript{2}O, O\textsubscript{2}, 2h, 83%.

\textbf{Scheme 138}

Diene (466) was therefore treated with PdCl\textsubscript{2} and copper(I) chloride in DMF:H\textsubscript{2}O (8:1) and the mixture stirred under an atmosphere of oxygen at room temperature for three hours. TLC analysis indicated the presence of two more polar products. After work-up and purification by chromatography on flash silica ketone (467) was obtained as a colourless greasy oil in 63\% yield. The $E:Z$ ratio of the product was not determined (Scheme 139).
Conditions: (i) PdCl₂, CuCl, DMF-H₂O 8:1, O₂, 2h, 63% (467), 10% (477), 9% (466).

Scheme 139

The high resolution mass spectrum for ketone (467) exhibited a molecular ion at \( m/z \) at 402.2403 consistent with the molecular formula \( \text{C}_{24}\text{H}_{34}\text{O}_5 \).

The minor more polar product was established to be diketone (477) for which the mass spectrum exhibited characteristic fragmentation due to the McLafferty rearrangement\(^{229} \) (Scheme 140).
The high resolution mass spectrum for diketone (477) exhibited ions at $m/z$ 220 and $m/z$ 278 arising from the McLafferty rearrangements depicted by pathways a and b.

The $^1$H NMR spectrum exhibited resonances consistent with formation of the ketone (467) with characteristic resonances being at $\delta_H$ 2.13 (s, 3H, H14'), $\delta_H$ 2.41 (t, 2H, $J=$
7.4 Hz, H12') and $\delta_H$ 5.33-5.48 ppm (m, 2H, H3', H4'). The $^{13}$C NMR spectrum exhibited the corresponding carbon resonances for C3' at $\delta_C$ 127.5 ppm, C4' at $\delta_C$ 131.6 ppm, C13' at 209.2 ppm and C14' at 29.7 ppm.

The final step in the synthesis of racemic CJ-13,108 (62) required reduction of the internal double bond of (467) by hydrogenation. Reduction was carried out by stirring alkene (467) under hydrogen over 10% palladium on charcoal in ethyl acetate for one hour. TLC analysis established the formation of a slightly less polar product. After work-up and purification by chromatography on flash silica antibiotic CJ-13,108 (62) was obtained as a colourless greasy oil in 99% yield (Scheme 141).

The high resolution mass spectrum for CJ-13,108 (62) exhibited a molecular ion at $m/z$ at 404.2559 consistent with the molecular formula C$_{24}$H$_{36}$O$_5$. Comparison of the high resolution mass spectrum data obtained with that reported$^{43}$ is shown below (Table 6).
Table 6 Comparison of the high resolution mass spectrum between (62) and the literature\textsuperscript{43}

<table>
<thead>
<tr>
<th>m/z</th>
<th>% Relative intensities literature\textsuperscript{43}</th>
<th>% Relative intensities observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>404</td>
<td>58.7</td>
<td>32</td>
</tr>
<tr>
<td>347</td>
<td>81.5</td>
<td>65</td>
</tr>
<tr>
<td>207</td>
<td>43.8</td>
<td>57</td>
</tr>
<tr>
<td>194</td>
<td>31.1</td>
<td>32</td>
</tr>
<tr>
<td>193</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>165</td>
<td>13.4</td>
<td>15</td>
</tr>
<tr>
<td>58</td>
<td>15.5</td>
<td>10</td>
</tr>
<tr>
<td>43</td>
<td>42.8</td>
<td>19</td>
</tr>
</tbody>
</table>

Similarly, the $^1$H and $^{13}$C NMR spectra obtained from the material prepared (62) in the present work compared favourably with the literature data (Table 7).\textsuperscript{43}
Table 7 Comparison of $^1$H NMR and $^{13}$C NMR between (62) and the literature$^{43}$

<table>
<thead>
<tr>
<th>$^{13}$C NMR</th>
<th>Literature$^{43}$</th>
<th>(62)</th>
<th>$^1$H NMR data for (62)</th>
<th>(62) prepared herin</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>168.4</td>
<td>168.5</td>
<td>H3</td>
<td>5.27</td>
</tr>
<tr>
<td>C3</td>
<td>79.9</td>
<td>79.9</td>
<td>H4</td>
<td>6.39</td>
</tr>
<tr>
<td>C3a</td>
<td>155.1</td>
<td>155.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4</td>
<td>97.4</td>
<td>98.6</td>
<td>H6</td>
<td>6.38</td>
</tr>
<tr>
<td>C5</td>
<td>166.6</td>
<td>166.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C6</td>
<td>98.5</td>
<td>97.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C7</td>
<td>159.5</td>
<td>159.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C7a</td>
<td>106.8</td>
<td>106.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1'</td>
<td>34.7</td>
<td>34.8</td>
<td>H1'</td>
<td>1.91</td>
</tr>
<tr>
<td>C2'</td>
<td>24.5</td>
<td>24.6</td>
<td>H2'</td>
<td>1.26-1.70</td>
</tr>
<tr>
<td>C3'</td>
<td>29.2</td>
<td>29.9</td>
<td>H3'</td>
<td>1.26-1.70</td>
</tr>
<tr>
<td>C4'</td>
<td>29.3</td>
<td>29.7</td>
<td>H4'</td>
<td>1.26-1.70</td>
</tr>
<tr>
<td>C5'</td>
<td>29.3</td>
<td>29.5</td>
<td>H5'</td>
<td>1.26-1.70</td>
</tr>
<tr>
<td>C6'</td>
<td>29.3</td>
<td>29.4</td>
<td>H6'</td>
<td>1.26-1.70</td>
</tr>
<tr>
<td>C7'</td>
<td>29.4</td>
<td>29.4</td>
<td>H7'</td>
<td>1.26-1.70</td>
</tr>
<tr>
<td>C8'</td>
<td>29.4</td>
<td>29.4</td>
<td>H8'</td>
<td>1.26-1.70</td>
</tr>
<tr>
<td>C9'</td>
<td>29.4</td>
<td>29.3</td>
<td>H9'</td>
<td>1.26-1.70</td>
</tr>
<tr>
<td>C10'</td>
<td>29.0</td>
<td>29.1</td>
<td>H10'</td>
<td>1.26-1.70</td>
</tr>
<tr>
<td>C11'</td>
<td>23.7</td>
<td>23.8</td>
<td>H11'</td>
<td>1.50</td>
</tr>
<tr>
<td>C12'</td>
<td>43.7</td>
<td>43.8</td>
<td>H12'</td>
<td>2.36</td>
</tr>
<tr>
<td>C13'</td>
<td>209.3</td>
<td>209.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C14'</td>
<td>29.7</td>
<td>29.8</td>
<td>H14'</td>
<td>2.07</td>
</tr>
<tr>
<td>C5-OCH$_3$</td>
<td>55.8</td>
<td>55.9</td>
<td>C5-OCH$_3$</td>
<td>3.90</td>
</tr>
<tr>
<td>C7-OCH$_3$</td>
<td>55.9</td>
<td>55.9</td>
<td>C7-OCH$_3$</td>
<td>3.93</td>
</tr>
</tbody>
</table>
3. Towards an asymmetric synthesis of CJ-13,108 (62)

3.1 Introduction

Having successfully developed a racemic synthesis of CJ-13,108 (62), our attention next focussed on the synthesis of (62) as a single enantiomer. Dekker et al. had not defined the absolute stereochemistry at C3 on the phthalide ring in any of the seven phthalides CJ-12,954 (56), CJ-13,014 (57), CJ-13,015 (58), CJ-13,0102 (59), CJ-13,103 (60), CJ-13,104 (61), and CJ-13,108 (62) (Figure 15); however the specific rotation ([α]D) for (62) was reported to be +44.8°. It was envisaged that asymmetric addition of a chiral allyl metal reagent to aldehyde (294) would provide asymmetric induction in the construction of C3 in the phthalide unit (Scheme 142). Selection of an appropriate chiral allyl metal reagent would lead to the formation of benzylic alcohol (293a) with either (R) or (S) stereochemistry as required for the synthesis of (R)-CJ-13,108 (62a) or (S)-CJ-13,108 (62b). A discussion of methods available to effect the asymmetric allylation reaction is included in the following section.
Scheme 142
3.2 Chiral allylation and crotylation reactions

3.2.1 Introduction

The enantioselective addition of allylmetal reagents to aldehydes is well established as a powerful and general method for stereoselective carbon-carbon bond formation. Both enantiomers (483) and (484) are available when allylmetal reagents are used. If $Si$ attack of the allylmetal regent on the aldehyde takes place, (483) is obtained, while if attack occurs from the $Re$ face, (484) is formed (Scheme 143).

$$
\begin{align*}
\text{Si face} & \quad \text{attack} \\
\text{Scheme 143}
\end{align*}
$$

3.2.2 Stereochemistry

Allylmetal compounds can exist as either monohapto ($\eta^1$) or trihapto ($\eta^3$) bound forms (Scheme 144).
Isomerization is possible for the monohapto ($\eta^1$) compounds via metallotropic rearrangement of the intermediate ($\eta^1$)-allylmetal (485) and the transition state for the rearrangement can be represented by the trihapto ($\eta^3$)-allylmetal. A good example is the allyl rearrangement of $\beta$-allyl-9-BBN with a Gibbs free energy ($\Delta G^\circ$) of 13.3 kcal/mol (Scheme 145).^232

Allyllithiums also undergo rapid isomerization and usually exist as slightly distorted complexes which rearrange via the monohapto ($\eta^1$) intermediate (485), while allylmagnesium compounds exist as configurationally unstable monohapto ($\eta^1$) structures^233,234. Therefore in order to successfully effect stereoselective formation of carbon-carbon bonds, only the allylmetal compounds in which the rearrangement is suppressed are useful. Monohapto ($\eta^1$) allylmetal compounds which show the lowest tendency for metallotropic isomerization are the allyl silanes, but these are less
reactive than the corresponding lithium and magnesium counterparts. Alkyl tin compounds are less stable and sometimes undergo isomerization at temperatures of less than 100 °C or in the presence of Lewis bases.

The most commonly used allylmetal compounds of the third group elements are those of boron. The tendency for allyl boron compounds to undergo metallotropic rearrangement can be controlled to an extent by the choice of substituents on boron. Although dialkyl(allyl)boranes rearrange rapidly at room temperature, they are stable below -78 °C. Placement of π donor atoms such as oxygen and nitrogen on boron raise the energy of the vacant boron p orbital to an extent that the trihapto (η^3) structure does not readily form thus suppressing the rearrangement. Allyl boron compounds with two oxygen atoms on boron (boronate esters) are stable enough to be handled at room temperature without isomerization. Monohapto (η^1) allylchromium and titanium compounds are also stable and useful in stereoselective additions to aldehydes.

3.2.3 Mechanism of the addition of allylmetal reagents to aldehydes

The addition of allylmetal reagents to aldehydes can be classified into three main mechanistic types (1, 2, or 3) depending on the type of metal and the conditions of the reaction.

In type 1 metallation reactions the stereochemical outcome (syn:anti ratio) is dependent on the (E):(Z) ratio in the allyl/crotyl moiety. For type 2 and 3 metallation reactions the stereochemical outcome is independent of the allyl/crotyl geometry, however the syn products are favoured for type 2 while the anti product is favoured by type 3. Since the present work is only concerned with chiral allylmetal reagents of
type 1 where the problem of syn and anti product mixtures does not arise, only type 1 will be discussed.

3.2.3.1 Type I additions

Type 1 addition reactions are usually observed for boron, aluminium and tin based reagents and go through a Zimmerman-Traxler cyclic six-membered transition state where the Lewis acidic metal atom can coordinate to the carbonyl oxygen to form an ate-complex. For example the four transition states for reaction of an allylmethyl reagent with an aldehyde proceeding via a chair or boat transition state are shown below (Scheme 146).
Of the four possible transition states $C_1$ and $C_2$ are the preferred states. Both transition states $B_1$ and $B_2$ contain unfavourable 1,3-diaxial steric interactions between $R\leftrightarrow L$ and it is generally considered that boat-like transition states are less stable than chairs, as is the case for aldol reactions.246
Examples of Type I

As noted in section 3.1, it was envisaged that asymmetric induction could be introduced into the synthesis of CJ-13,108 (62) by reaction of achiral aldehyde (294) with a chiral allyl reagent (Scheme 142). Hence the use of chiral allyl boron reagents to react with achiral aldehydes was initially investigated in the present work.

Allyl boron reagents deliver high stereoselectivities and the ability to introduce chiral groups on the boron makes them the metal of choice. Early examples of chiral boronate esters are those derived from camphor by Hoffmann et al.\textsuperscript{247,248,249} as illustrated by the reaction of boronate (490) with acetaldehyde (491) to provide 4-penten-2-ol (492) in 86\% e.e. (Scheme 147).

\begin{center}
\begin{tikzpicture}

\node at (0,0) {\includegraphics[width=0.5\textwidth]{reaction.png}};

\node at (-2,0) {\textbf{Conditions: (i) triethanolamine, 86\% e.e..}};

\end{tikzpicture}
\end{center}

Later Reetz and Ziehe\textsuperscript{250} reported that the related allylborane (493) reacted with a range of aldehydes including acetaldehyde (491) to give products with e.e. values between 88-96\% (Scheme 148).
The \( R, \ R \)-tartrate allyl ester (496) described by Roush et al.\(^{251,252,253,254} \) is also effective in obtaining good levels enanatiocontrol when reacted with achiral aldehydes. The ester is easily prepared in either enanatiomeric form and can be stored at -10 °C without decomposition (Scheme 149).

Conditions: (i) \( R, \ R \)-tartrate; (ii) (482), toluene, -78 °C, 4 Å molecular sieves.

The origins of asymmetric induction with tartrate ester boronates such as (496) cannot be explained by steric interactions alone and two interconverting transition states (498) and (499) have been proposed to account for the selectivity observed (Figure 3E1.zst:ss).\(^{251,255} \)
Boron-oxygen bond rotation to form transition state (498) is preferred over (499) due to the destabilising electronic interaction that occurs between the lone pairs in (499). This proposal is supported by the substantially improved enantioselectivities observed for (502) which contains a rigid tartramide auxiliary, relative to (496) (Scheme 150).\textsuperscript{256}
Some of the most synthetically useful chiral allylmetal reagents are the dialkylboranes reported by Brown.\textsuperscript{257,258,259,260,261,262} Although alkylboranes are less stable than their boronate counterparts, they are configurationally stable at low temperatures and are more reactive. Unlike most of the chiral boronate esters, chiral centres in the dialkylboranes can be directly attached to the boron atom, leading to high enantioselectivities. Preparation of the dialkylboranes is simple, short and economical and the most common are those derived from the chiral terpene α-pinene which is available in both (+) and (-) forms (Scheme 151).
Chapter 3. Discussion

Reaction of (+)-allyldiisopinocampheylborane (Ipc₂B-allyl) (506) with a range of aldehydes at -78 °C afforded allylated products with good enantioselection (Scheme 152).

![Scheme 151](image)

<table>
<thead>
<tr>
<th>R</th>
<th>yield (%)</th>
<th>% e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>74</td>
<td>93</td>
</tr>
<tr>
<td>CH₃CH₂</td>
<td>71</td>
<td>86</td>
</tr>
<tr>
<td>Ph</td>
<td>81</td>
<td>98</td>
</tr>
</tbody>
</table>

Scheme 152

The exact nature of the stereoselection of the diisopinocampheylboranes is not fully understood, but it has been proposed that they react by a cyclic type 1 transition state (507) and (509) (Scheme 153).
Transition state (507) is preferred due to the developing steric interactions between the chiral boron ligands and the allyl group in (509).

### 3.2.4 Asymmetric allylation of aldehyde (294)

Reaction of achiral aldehydes with type I dialkylboranes (-) and (+)-allyldiisopinocampheylborane (Ipc₂B-allyl) had already been successfully used by the Brimble group in the synthesis of the spirolides.\(^{263}\) It was therefore decided to react aldehyde (294) with both (-) and (+)-allyldiisopinocampheylborane (Ipc₂B-allyl) to see whether any asymmetric induction would occur.

In a flame-dried flask equipped with a reflux condenser and flushed with nitrogen, a vigorously stirred solution (+)-B-methoxy-diisopinocampheylborane (Ipc₂B-OMe) in freshly distilled diethyl ether was cooled to -78 °C. Allylmagnesium bromide was then added and the cloudy mixture was stirred for one hour. Addition of the aldehyde
(294) brought about a visual change in the reaction solution to a viscous pale yellow colour. The reaction was left at -78 °C for 3 hours then warmed to room temperature. Oxidative work up with sodium hydroxide and hydrogen peroxide followed by reflux for two hours caused the reaction solution to become colourless. TLC analysis revealed the presence of a two less polar products. Purification of the crude reaction mixture by repeated chromatography on flash silica gel afforded alcohol (512) in 57% yield as a colourless oil (Scheme 154). The product was later shown to be enantioenriched by subsequent conversion of the alcohol (512) to its Mosher ester derivative.
Chapter 3

Discussion

Conditions: (i) Allylmagnesium bromide, Et$_2$O, -78 °C, 1 h; (ii) (294) in Et$_2$O, -78 °C, 3 h, warm to rt; (iii) NaOH, H$_2$O$_2$, reflux 2 h, 57%; (iv) (R)-Mosher chloride, Et$_2$N, DMAP, 40 °C, 8 h, 53%

Scheme 154
Reaction of (512) and (513) with (R)-Mosher chloride (α-methoxy-α-trifluoromethylphenylacetyl chloride), DMAP, Et₃N in dichloromethane gave the Mosher esters (514) and (515) in 57% yield after purification by chromatography on flash silica gel. Inspection of both the ¹H NMR and ¹⁹F NMR indicated a diastereomeric excess (d.e.) of only 22%. When the reaction (Scheme 154) was repeated using (-)-allylidiisopinocampheylborane (Ipc₂B-allyl) only 15% d.e. was obtained (Table 8).

**Table 8 Results of asymmetric induction of aldehyde (294)**

<table>
<thead>
<tr>
<th></th>
<th>% yield</th>
<th>(R)-Mosher ester</th>
<th>d.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-(Ipc₂B-allyl)</td>
<td>57</td>
<td>53</td>
<td>22</td>
</tr>
<tr>
<td>(-)-(Ipc₂B-allyl)</td>
<td>62</td>
<td>49</td>
<td>15</td>
</tr>
</tbody>
</table>

Having prepared alcohol (512) in low enantiomeric excess from reaction (294) with both (+)-(Ipc₂B-allyl) and (-)-(Ipc₂B-allyl), it was decided that future endeavours should focus on the use of an alternative type 1 chiral allylmetal reagent such as the tartrate ester boronates.

### 3.3 Summary and future work

To date the synthetic studies undertaken towards CJ-12,954 (56) has resulted in the synthesis of phthalide aldehyde (288) and spiroketal epoxide (300) (Scheme 155).
Undefined

CJ-12,954 (56)

* = racemic centre

Scheme 155
The synthesis of phthalide aldehyde (288) as a racemic mixture has been carried out in six steps starting from (296) in an overall yield of 33% (Scheme 156).

\[
\begin{align*}
(296) & \xrightarrow{(i)} (295) \\
(294) & \xrightarrow{(ii)} (291) \\
(292) & \xrightarrow{(iii)} (293) \\
(293) & \xrightarrow{(iv)} (292) \\
(294) & \xrightarrow{(v)} (294) \\
(294) & \xrightarrow{(vi)} (298)
\end{align*}
\]

Conditions: (i) (a) SOCl\textsubscript{2}, 2h, reflux; (b) Et\textsubscript{2}NH, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 98%; (ii) t-BuLi (1.1 eq.), THF, -78 °C, DMF, 99%; (iii) Allylmagnesium bromide, Et\textsubscript{2}O, -40 °C to rt, 95%; (iv) Glacial acetic acid, 10% HCl, reflux, 6h, 92%; (v) (a) BH\textsubscript{3},SMe\textsubscript{2}, THF, 0 °C, 5h, (b) NaOH, H\textsubscript{2}O\textsubscript{2}, 0 °C, 30 min, 60%; (vi) TPAP, NMO, CH\textsubscript{2}Cl\textsubscript{2}, 2h, 64%.

Scheme 156

Investigations aimed at developing an asymmetric variant of the above synthesis by controlling the stereochemistry at C1' in alcohol (293) and hence the stereochemistry at C3 in phthalide (288) using an asymmetric allylboration strategy have only been achieved in 22% e.e.. Future work should focus on using alternative chiral allylmetal reagents (see section 3.2.3.1) in an effort to increase the e.e. of the required alcohol
Alternatively oxidation of alcohol (293) to (516), followed by selective asymmetric reduction of the ketone functionality could also be investigated (Scheme 157).

The synthesis of spiroketal epoxide (300) has also been carried out in fifteen steps starting from (386) and (393) in an overall yield of 8% (Scheme 158-159). Unfortunately attempts to effect an asymmetric variant of the synthesis by executing an asymmetric Wittig rearrangement of (375) were not successful.
Discussion

Conditions: (i) (a) n-BuLi, THF, -78 °C, 30 min, (b) TMSCl, THF, -78 °C to rt, (c) 1 mol L⁻¹ HCl, 30 min, 70%; (ii) (a) 1.2 Mol L⁻¹ EtMgBr, HMPA, THF, 0 °C, 5 min, (b) allyl bromide, reflux, 4h, 67%; (iii) n-BuLi, THF, -78 °C, 10 min, 100%; (iv) TBScI, imidazole, DMAP, DCM, rt, 1h, 98%; (v) NaOMe, MeOH, 40 min, 96%.

Scheme 158
Chapter 3. Discussion

As mentioned earlier (section 2.8) all attempts to effect ring opening of epoxide (300) proved fruitless. An alternative enantioselective synthesis of spiroketal ylide (297) has since been carried out by Christina Funnell in this research group. The successful synthesis of (427) has been carried out in over ten steps from (557) in 11% overall yield (Scheme 160). The required (C7' S) stereochemistry in CJ-12,954 (56) was introduced by reaction of aldehyde (561) with the chiral allylborane (+)-(Ipc2B-allyl) (517). Reaction of chiral aldehyde (564) with the acetylide formed from the chiral acetylene (565) afforded (563) which contained the required stereochemistry for CJ-12,954 (56) at C13'. Subsequent hydrogenation, oxidation then cyclization afforded
spiroketal (569) with the required C7' S, C13' S stereochemistry present in CJ-12,954 (56) (Scheme 160).
Discussion

Conditions: (i) (a) NaH, THF, TBDPSCI, 0 °C to rt, 99%; (ii) PCC, CH₂Cl₂, 72%; (iii) (a) allyl bromide, Mg, Et₂O, (+)-B-diisopinocampheylmethoxyborane, 2h, -78 °C; (b) H₂O₂, NaOH, 23h, rt to reflux, 82%; (iv) TBSCI, imidazole, DMAP, CH₂Cl₂, 92%; (v) 2-methyl-2-butene, BH₃-SMe₂, THF, 0 °C to rt, 78%; (vi) Dess-Martin periodinane, py, CH₂Cl₂, 78%; (vii) n-BuLi (1 eq.), THF, 15 min, then (521), -100 °C, 6h, 61%; (viii) H₂, Pd/C, NaHCO₃, EtOAc, 92%; (ix) Dess-Martin periodinane, py, CH₂Cl₂, 62%; (x) PPTS, EtOH, 60 °C, 99%.

Scheme 160
Chapter 4.

Experimental
1 General

1. All new (i.e. unlisted in chemical abstracts) compounds have been written in italics where first reported with spectral data.

2. Melting points were determined on a Reichart-Kofler block and are uncorrected.

3. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer. Unless otherwise indicated, spectra were recorded as films on sodium chloride plates.

4. Ultraviolet spectra were recorded from dichloromethane solutions on a Varian DMS 100 spectrometer.

5. $^1$H and $^{13}$C NMR spectra were recorded on Bruker DRX-400, Bruker AVANCE-300 or AC-200 spectrometers operating at 400.13, 300.13 or 200.13 MHz for $^1$H and 100.62, 75.47 or 50.32 MHz for $^{13}$C nuclei. $^{19}$F NMR spectra were obtained in chloroform-\textit{d} on a Bruker DRX-400 operating at 376.5 MHz and were referenced to fluorotrichloromethane. $^1$H and $^{13}$C NMR spectra were normally obtained in chloroform-\textit{d} and were referenced to chloroform or tetramethylsilane (TMS). The $^1$H NMR data is quoted as chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, app.p = apparent pentet, app.sex = apparent sextet, m = multiplet, b = broad and unres. = unresolved), integration, coupling constant $J$ in HZ and assignment. Where the coupling constants of two mutually coupled resonances differed slightly, the mean is reported. The $^{13}$C NMR spectral data are quoted as chemical shift (ppm) and assignment. Multiplicities were normally determined using DEPT-135 and DEPT-90 spectra.
6. Low resolution mass spectra were recorded on a VG7070 spectrometer operating at a normal accelerating velocity of 70 eV. High resolution spectra were recorded at a nominal resolution of 5000 or 10000 as appropriate. Spectra were usually obtained under electron impact (EI) conditions using perfluorokerosene as an indicated standard. Where chemical ionisation (CI) was used this has been indicated.

7. Analytical thin layer chromatography (TLC) was carried out using 0.2 mm plates of Kieselgel F$_{24}$ (Merck). Visualisation was by UV light or by vanillin spray. Column chromatography was typically carried out on Kieselgel S 0.032-0.063 mm (Ridel-de-Haën).

8. Ether refers to diethyl ether, hexanes refers to a commercially available hydrocarbon solvent boiling at 65-69 °C. Dilute hydrochloric acid refers to a concentration of 1 mol L$^{-1}$ and dilute sulphuric acid refers to a concentration of 2 mol L$^{-1}$. Tetrahydrofuran (THF) and diethyl ether was distilled over sodium and acetophenone was used as an indicator of quality. All bulk solvents were distilled prior to use. Reagents were purified, where necessary, using methods given in Perrin, D.D.; Amerago, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd Ed. Pergamon Press, 1981.

9. Reaction temperatures were controlled using dry ice/hexanes (-100 °C), dry ice/acetone (-78 °C), ice/sodium chloride (-10 °C) or ice/water (0 °C) for short reaction times.

10. $t$-Butyllithium ($t$-BuLi), $s$-butyllithium ($s$-BuLi) and $n$-butyllithium ($n$-BuLi) were standardised using the method of Shapiro et. al.$^{272}$
Chapter 4.

Experimental

*N,N*-Diethyl-3-methoxybenzamide (254)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{OMe} & \quad \text{OMe} \\
\text{(342)} & \quad \text{(254)}
\end{align*}
\]

3-Methoxybenzoic acid (30.0 g, 197.6 mmol) was heated at reflux under nitrogen for 2 h with SOCl\(_2\) (51.7 g, 434 mmol). Benzene (100 mL) was added and the excess SOCl\(_2\) removed under reduced pressure. This procedure was repeated with additional benzene (2 × 30 mL). The residue was dissolved in CH\(_2\)Cl\(_2\) (100 mL), cooled to 0 °C and a solution of diethylamine (40.7 mL, 394.0 mmol) in CH\(_2\)Cl\(_2\) (100 mL) was slowly added. The mixture was stirred for 12 h under nitrogen at room temperature, then poured into CH\(_2\)Cl\(_2\) (500 mL), washed with 10% aq NaHCO\(_3\) (3 × 100 mL) and brine (3 × 50 mL). The organic extract was dried over MgSO\(_4\) and purified by distillation under reduced pressure to afford *N,N*-diethyl-3-methoxybenzamide (40.1 g, 98%) as a pale yellow oil. B.p. 176-178 °C/760 Torr (Lit.\(^\text{161}\) b.p. 177 °C/760 Torr).
Chapter 4.

Experimental

\textit{N,N-Diethyl-3,5-dimethoxybenzamide (255)}

\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{OMe} & \quad \text{OMe} \\
\text{(343)} & \quad \text{(255)}
\end{align*}

3,5-Dimethoxybenzoic acid (20.0 g, 109.8 mmol) was heated at reflux under nitrogen for 2 h with SOCl\textsubscript{2} (17.6 mL, 241.5 mmol). Benzene (100 mL) was added and the excess SOCl\textsubscript{2} removed under reduced pressure. This procedure was repeated with additional benzene (2 \times 30 mL). The residue was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (100 mL), cooled to 0 °C and a solution of diethylamine (22.7 mL, 219 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (70 mL) was slowly added. The mixture was stirred for 12 h under nitrogen at room temperature, then poured into CH\textsubscript{2}Cl\textsubscript{2} (500 mL), washed with 10% aq NaHCO\textsubscript{3} (3 \times 100 mL) and brine (3 \times 50 mL). The organic extract was dried over MgSO\textsubscript{4} and purified by distillation under reduced pressure to afford \textit{N,N-diethyl-3,5-dimethoxybenzamide (255)} (19.0 g, 73%) as a pale yellow oil. B.p. 163-167 °C/760 Torr (Lit.\textsuperscript{166} b.p. 165-167 °C/760 Torr).
In a flame-dried flask flushed with nitrogen, a vigorously stirred solution of N,N-diethyl-3-dimethoxybenzamide (254) (2.6 g, 12.5 mmol) in dry THF (40 mL) was cooled to -78 °C. t-BuLi (11.5 mL, 1.31 mol L⁻¹ in hexanes, 15.0 mmol) and freshly distilled anhydrous TMEDA (2.06 mL, 13.7 mmol) were added dropwise over 1 min to the centre of the solution while stirring was continued. The resulting bright yellow solution was left for 45 min. Anhydrous DMF (3.25 mL, 41.0 mmol) was then added and the mixture was stirred at -78 °C for 1 h, then warmed to room temperature over 12 h. The solvent was removed under reduced pressure, and the residue was dissolved into CH₂Cl₂ (30 mL), washed with brine (3 × 10 mL) and dried over MgSO₄. Chromatography on flash silica gel (50%, Et₂O : hexanes) afforded N,N-diethyl-2-formyl-3-methoxybenzamide (256) (0.69 g, 23%) as a yellow oil. The ¹H NMR data compared favourably with the literature data.¹⁶⁴
**N,N-Diethyl-2-formyl-3,5-methoxybenzamide (257)**

![Chemical structure](image)

In a flame-dried flask flushed with nitrogen, a vigorously stirred solution of N,N-diethyl-3,5-dimethoxybenzamide (255) (100 mg, 0.42 mmol) in dry THF (10 mL) was cooled to -78 °C. t-BuLi (0.71 mL, 1.31 mol L\(^{-1}\) in hexanes, 0.93 mmol) and freshly distilled anhydrous TMEDA (0.09 mL, 0.6 mmol) were added dropwise over 1 min to the centre of the solution while stirring was continued. The resulting bright yellow solution was left for 15 min. Anhydrous DMF (0.16 mL, 2.11 mmol) was then added and the mixture stirred at -78 °C for 1 h, then warmed to room temperature over 12 h. The solvent was removed under reduced pressure, and the residue was dissolved into CH\(_2\)Cl\(_2\) (10 mL), washed with brine (3 × 5 mL) and dried over MgSO\(_4\). Chromatography on flash silica gel (50%, Et\(_2\)O : hexanes) afforded N,N-diethyl-2-formyl-3,5-dimethoxybenzamide (257) (0.064 g, 58%) as a yellow oil. The \(^1\)H NMR data compared favourably with the literature data.\(^{167}\)
Optimisation of reaction conditions for preparation of \textit{N,N-diethyl-2-formyl-3,5-dimethoxybenzamide} (257)

<table>
<thead>
<tr>
<th>(t)-BuLi (equiv)</th>
<th>TMEDA (equiv)</th>
<th>TEMP (°C)</th>
<th>Anion Life (min)</th>
<th>DMF (equiv)</th>
<th>(257) (%)</th>
<th>(255) (%)</th>
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<td>5</td>
<td>48</td>
<td>52</td>
</tr>
</tbody>
</table>

\textbf{Note:} The conditions highlighted were found to be the best on any reaction scale.
Chapter 4.

Experimental

3-Hydroxy-4-methoxy-(3H)-isobenzofuran-1-one (258)

To a stirred solution of \( N,N\)-diethyl-2-formyl-3-methoxybenzamide (256) (690 mg, 2.93 mmol) in glacial acetic acid (5 mL) was added a 10\% aqueous HCl (5 mL). The solution was heated to reflux under nitrogen for 6 h then the solvent was removed under reduced pressure. Chromatography on flash silica gel (Et\(_2\)O) afforded 3-hydroxy-4-methoxy-(3H)-isobenzofuran-1-one (258) (510 mg, 96\%) as a white solid, mp 155-157 °C (Lit.\(^{165}\) mp 155-156 °C). The \(^1\)H NMR data compared favourably with the literature data.\(^{165}\)

4,6-Dimethoxy-3-hydroxy-(3H)-isobenzofuran-1-one (259)

To a stirred solution of \( N,N\)-diethyl-2-formyl-3,5-dimethoxybenzamide (257) (104 mg, 0.39 mmol) in glacial acetic acid (20 mL) was added 10\% aqueous HCl (20 mL). The solution was heated to reflux under nitrogen for 6 h and the solvent then removed under reduced pressure. Chromatography on flash silica gel (Et\(_2\)O) afforded
4,6-dimethoxy-3-hydroxy-(3H)-isobenzofuran-1-one (259) (78 mg, 95%) as a white solid, mp 162-164 °C (Lit.\textsuperscript{170} mp 165 °C). The \textsuperscript{1}H NMR data compared favourably with the literature data.\textsuperscript{170}

3-Acetoxy-4-methoxy-(3H)-isobenzofuran-1-one (260)

![](image)

(258) \rightarrow (260)

To a stirred solution of 3-hydroxy-4-methoxy-(3H)-isobenzofuran-1-one (258) (450 mg, 2.50 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (30 mL) was added Et\textsubscript{3}N (760 mg, 7.50 mmol), Ac\textsubscript{2}O (510 mg, 5.0 mmol) and 4-dimethylaminopyridine (5.0 mg). The reaction was allowed to stir for 2 h at room temperature, quenched with H\textsubscript{2}O (2 mL), extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 × 5 mL) and dried over MgSO\textsubscript{4}. Removal of the solvent under reduced pressure gave a pale pink solid which was purified by chromatography on flash silica gel (50%, EtOAc : hexanes) to afford 3-acetoxy-4-methoxy-(3H)-isobenzofuran-1-one (260) (450 mg, 80%) as a white solid, mp 157-159 °C (Lit.\textsuperscript{101} mp 158-159 °C). The \textsuperscript{1}H NMR data compared favourably with the literature data.\textsuperscript{101}
Chapter 4. Experimental

3-Acetoxy-4,6-dimethoxy-(3H)-isobenzofuran-1-one (261)

To a stirred solution of 3-hydroxy-4,6-dimethoxy-(3H)-isobenzofuran-1-one (259) (88 mg, 0.42 mmol) in CH$_2$Cl$_2$ (20 mL) was added Et$_3$N (127 mg; 1.26 mmol), Ac$_2$O (85 mg, 0.84 mmol) and 4-dimethylaminopyridine (5.0 mg). The reaction was allowed to stir for 2 h at room temperature, quenched with H$_2$O (2 mL), extracted with CH$_2$Cl$_2$ (2 × 5 mL) and dried over MgSO$_4$. Removal of the solvent under reduced pressure gave a pale pink solid which was purified by chromatography on flash silica gel (50%, EtOAc : hexanes) to afford 3-acetoxy-4,6-dimethoxy-(3H)-isobenzofuran-1-one (261) (91 mg, 86%) as a white solid, mp 154-156 °C (Lit.\textsuperscript{101} mp 154-155 °C). The $^1$H NMR data compared favourably with the literature data.\textsuperscript{101}
4-Methoxy-3-(2'-propenyl)-(3H)-isobenzofuran-1-one (527)

In a flame-dried flask flushed with nitrogen, a vigorously stirred solution of 3-acetoxy-4-methoxy-(3H)-isobenzofuran-1-one (260) (130 mg, 0.59 mmol) in dry CH₂Cl₂ (20 mL) was cooled to -78 °C. Allyltributylstannane (0.91 mL, 2.93 mmol) and trimethylsilyl trifluoromethanesulfonate (0.21 mL, 1.17 mmol) were added dropwise over 1 min to the centre of the solution. The reaction was allowed to warm to room temperature over 16 h, quenched with saturated aqueous NH₄Cl (2 mL), extracted with CH₂Cl₂ (2 × 10 mL) and dried over MgSO₄. Removal of the solvent under reduced pressure gave a white solid that was purified by chromatography on flash silica gel (50%, EtOAc : hexanes) to afford 4-methoxy-3-(2'-propenyl)-(3H)-isobenzofuran-1-one (527) (80 mg, 67%) as a white solid, mp 77-78 °C (Lit.¹⁰¹ mp 79-80 °C). The ¹H NMR data compared favourably with the literature data.¹⁰¹
1-(tert-Butyldiphenylsilyloxy)-3-methylbut-3-ene (350)

\[
\text{\begin{align*}
\text{OH} & \rightarrow \text{OTBDPS} \\
(349) & \rightarrow (350)
\end{align*}}
\]

To a solution 3-methylbut-3-en-1-ol (1.0 g, 11.6 mmol) (349) in dry THF (20 mL) was added imidazole (0.87 g, 12.8 mmol) and tert-butyldiphenylsilyl chloride (3.2 mL, 12.3 mmol). The mixture was stirred at room temperature for 2 h, filtered and the solvent removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (20 mL), washed with brine (2 × 10 mL) and dried over MgSO₄. Chromatography on flash silica gel (25%, EtOAc : hexanes) afforded 1-(tert-butyldiphenylsilyloxy)-3-methylbut-3-ene (350) (3.62 g, 96%) as a colourless oil. The ¹H NMR data compared favourably with the literature data.¹⁷¹

4-(tert-Butyldiphenylsilyloxy)-1,2-epoxy-2-methylbutane (351)

\[
\text{\begin{align*}
\text{OTBDPS} & \rightarrow \text{O} \\
(350) & \rightarrow (351)
\end{align*}}
\]

To a solution of 4-(tert-Butyldiphenylsilyloxy)-2-methylbut-1-ene (350) (2.00 g, 6.16 mmol) in CH₂Cl₂ (30 mL) was added meta-chlороperoxybenzoic acid (2.13 g, 12.3 mmol) and sodium bicarbonate (1.04 g, 12.3 mmol). The reaction mixture was stirred for 3 h at 0 °C then quenched with water (10 mL). The organic layer was washed with brine (2 × 10 mL), dried over MgSO₄ and the solvent evaporated in vacuo. Chromatography on flash silica gel (5%, Et₂O : hexanes) afforded 4-(tert-
butyldiphenylsilyloxy)-1,2-epoxy-2-methylbutane (351) (1.90 g, 90%) as a colourless oil. The \( ^1H \) NMR data compared favourably with the literature data.\textsuperscript{171}

### 2-[(2-tert-Butyldiphenylsilyloxy)ethyl]prop-2-en-1-ol (352)

\[
\begin{align*}
\text{OTBDPS} & \quad \text{OH} \\
(351) & \quad \text{OTBDPS}
\end{align*}
\]

In a flame dried flask flushed with nitrogen, a vigorously stirred solution of 2,2,6,6-tetramethylpiperidine (0.11 mL, 0.68 mmol) in dry toluene (10 mL) was cooled to 0 °C. \( n \)-BuLi (0.56 mL, 1.16 mol L\(^{-1} \) in hexanes, 0.65 mmol) was added dropwise over 1 min to the centre of the solution. The resulting yellow solution was left for 30 min at 0 °C. Diethylaluminium chloride (0.36 mL, 1.80 mol L\(^{-1} \) in toluene, 0.65 mmol) was added and the mixture stirred at 0 °C for a further 30 min. A solution of 4-(tert-butylidiphenylsilyloxy)-1,2-epoxy-2-methylbutane (351) (100 mg, 0.29 mmol) in dry toluene (5 mL) was added \textit{via} cannula and the mixture allowed to stir at 0 °C for 3 h. The solvent was removed under reduced pressure, the residue protonated with aqueous HCl (20%, 20 mL) and the resultant mixture extracted with CH\(_2\)Cl\(_2\) (30 mL), washed with brine (3 \times 10 mL) and dried over MgSO\(_4\). Chromatography on flash silica gel (10%, Et\(_2\)O : hexanes) afforded 2-[(2-tert-butylidiphenylsilyloxy)ethyl]prop-2-en-1-ol (352) (86 mg, 86%) as a yellow oil. The \( ^1H \) NMR data compared favourably with the literature data.\textsuperscript{171}
Chapter 4.

Experimental

2-[2-(tert-Butyldiphenylsilyloxy)ethyl]prop-2-en-1-yl p-toluenesulfonate (360)

In a flame-dried flask flushed with nitrogen, a vigorously stirred solution of 2-[2-(tert-butyldiphenylsilyloxy)ethyl]prop-2-en-1-ol (352) (310 mg, 0.91 mmol) in dry THF (20 mL) was cooled to -78 °C. n-BuLi (0.78 mL, 1.16 mol L⁻¹ in hexanes, 0.91 mmol) was added dropwise over 1 min to the centre of the solution. The resulting solution was left for 30 min then treated with a solution of p-toluenesulfonyl chloride (450 mg, 0.91 mmol) in dry THF (5 mL). The mixture was left at -78 °C for 1 h then warmed to room temperature over 12 h. The solvent was removed under reduced pressure, the residue taken up into CH₂Cl₂ (10 mL), washed with brine (3 x 10 mL) and dried over MgSO₄. Chromatography on flash silica gel (5%, Et₂O : hexanes) afforded 2-[2-(tert-butyldiphenylsilyloxy)ethyl]prop-2-en-1-yl p-toluenesulfonate (360) (310 mg, 69%) as a colourless oil. IR (CH₂Cl₂) 2931, 2857, 1598, 1428, 1363, 1177, 1189, 1111, 997, 937, 822, 738, 703 cm⁻¹; MS (C.I.) m/z 495 (MH⁺, 1.8), 353 (80), 333 (65), 323 (61), 173 (100); ¹H NMR (CDCl₃) δ 1.04 [s, 9H, C(CH₃)₃], 2.24 (t, 2H, J=6.3 Hz, H₁'), 2.39 (s, 3H, H₄'Ar-CH₃), 3.67 (t, 2H, J=6.3 Hz, H₂'), 4.45 (s, 2H, H₁), 4.97 (s, br, 1H, H₃a), 5.10 (s, br, 1H, H₃b), 7.27 (d, 2H, J=8.2 Hz, H₃'-Ar), 7.36-7.62 (m, 10H, Ar), 7.74 (d, 2H, J=8.2 Hz, H₂'-Ar); ¹³C NMR (CDCl₃) δ 19.0 [C(CH₃)₃], 21.5 (CH₃-Ar), 26.7 [C(CH₃)₃], 35.7 (C₁'), 62.2 (C₂'), 72.7, (C₁), 116.5 (C3), 127.8
(C2'), 129.6 (C3'), 133.1 (C1'), 127.6, 129.7, 135.4, 133.5 (2 × Ar), 139.4 (C4'), 144.6 (C2); HRMS for C28H35SiSO+: 495.2025 (calcd), 495.2017 (found).

3-Bromomethyl-1-(tert-butyldiphenylsilyloxy)-but-3-ene (361)

\[
\text{HO} \quad \text{Br}
\]

(352) \rightarrow (361)

To a solution of 2-[(2-tert-butyldiphenylsilyloxy)ethyl]prop-2-en-1-ol (352) (110 mg, 0.33 mmol) in dry Et2O (5 mL) at 0 °C was added phosphorus tribromide (45 mg, 0.16 mmol). The reaction mixture was left for 10 min then treated carefully with methanol (0.25 mL) and diluted with Et2O (30 mL). The mixture was poured onto water (10 mL), the organic layer washed with brine (2 × 10 mL) and dried over MgSO4. Chromatography on flash silica gel (50%, Et2O : hexanes) afforded 3-bromomethyl-1-(tert-butyldiphenylsilyloxy)-but-3-ene (361) (120 mg, 80%) as a colourless oil. IR (CH2Cl2) 2957, 2930, 1471, 1427, 1112, 1007, 910, 822, 738, 701, 608 cm⁻¹; MS (C.I.) m/z 403/405 (MH⁺, <1), 347/345 (13/12.5), 265 (28), 213 (27), 199 (100), 91 (27), 99 (58); ¹H NMR (CDCl3) δ 1.04 [s, 9H, C(CH₃)₃], 2.45 (dt, 2H, J=0.8 and 6.3 Hz, H2), 3.79 (t, 2H, J=6.4 Hz, H1), 3.93 (s, 2H, H1'), 4.97 (dd, 1H, J=1.1 and 2.3 Hz, H4b), 5.19 (s, br, 1H, H4a), 7.35-7.39 (m, 6H, Ar), 7.65-7.71 (m, 4H, Ar); ¹³C NMR (CDCl3) δ 19.1 [C(CH₃)₃], 26.8 [C(CH₃)₃], 36.3 (C2), 37.0 (C1'), 65.5 (C1), 116.0 (C4), 127.6, 127.7, 129.6, 129.7, 133.7, 134.8, 135.2, 135.5, 135.6 (2 × Ar), 143.0 (C3); HRMS for C21H28½BrSiO/C21H28 ⁸¹BrSiO: 403.1093/405.1072 (calcd), 403.1059/405.1087 (found).
2-Bromo-\(N,N\)-diethyl-3,5-dimethoxybenzamide (348)

![Structure](image)

To a solution of \(N,N\)-diethyl-3,5-dimethoxybenzamide (255) (1.00 g, 4.21 mmol) in dry \(CCl_4\) (30 mL) was added \(N\)-bromosuccinimide (375) (0.83 g, 4.64 mmol). The reaction mixture was heated to reflux under nitrogen for 48 h, then cooled and filtered and the solvent removed from the filtrate under reduced pressure. The residue was dissolved into \(CH_2Cl_2\) (20 mL), washed with brine (2 \(\times\) 10 mL) and dried over \(MgSO_4\). Chromatography on flash silica gel (70\%, \(Et_2O\) : hexanes) afforded 2-bromo-\(N,N\)-diethyl-3,5-dimethoxybenzamide (348) (1.32 g, 99\%) as a colourless oil. IR (\(CH_2Cl_2\)) 2975, 2936, 1633, 1584, 1458, 1429, 1332, 1220, 1199, 1054, 948, 829 cm\(^{-1}\); MS (E.I.) \(m/z\) 315/317 (M\(^+\), 46/48), 300/302 (17), 243/245 (91), 236 (48), 165 (100), 137 (24), 99 (58), 56 (50), 43 (36); \(^1\)H NMR (\(CDCl_3\)) \(\delta\) 1.08 (t, 3H, \(J=7.1\ Hz, NCH_2CH_3\)), 1.23 (t, 3H, \(J=7.1\ Hz, NCH_2CH_3\)), 3.17 (q, 2H, \(J=7.1\ Hz, NCH_2CH_3\)), 3.33 (d, 2H, \(J=7.1\ Hz, NCH_2CH_3\)), 3.80 (s, 3H, 3-OCH3), 3.87 (s, 3H, 5-OCH3), 6.41 (d, 1H, \(J=2.6\ Hz, H_4\)), 6.47 (d, 1H, \(J=2.6\ Hz, H_6\)); \(^13\)C NMR (\(CDCl_3\)) \(\delta\) 12.4 (NCH2CH3), 13.9 (NCH2CH3), 38.8 (NCH2CH3), 42.6 (NCH2CH3), 55.6 (3-OCH3), 56.3 (5-OCH3), 99.6 (C2), 99.7 (C6), 103.4 (C4), 140.3 (C1), 156.8 (C5), 160.2 (C3), 168.3 (C=O); HRMS for \(C_{13}H_{18}^{79}BrNO_3/C_{13}H_{18}^{81}BrNO_3\): 315.0470/317.0449 (calcd), 315.0468/317.0453 (found).
3-(Trimethylsilyl)prop-2-yn-1-ol (382)

To a stirred solution of propargyl alcohol (392) (5.0 g, 89.0 mmol) in dry THF (190 mL) cooled to -78 °C under nitrogen, was added n-BuLi (21.4 mL, 10 mol L⁻¹ in hexanes, 214 mmol). After 30 min trimethylsilyl chloride (28.0 mL, 223.3 mmol) was added and the mixture was warmed to room temperature and stirred for 1 h. Freshly prepared aqueous HCl (1.0 mol L⁻¹, 50 mL) was added, the mixture was stirred vigorously for 30 min and then extracted with Et₂O (50 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and evaporated in vacuo. Distillation of the residue under reduced pressure afforded 3-(trimethylsilyl)prop-2-yn-1-ol (382) (8.0 g, 70%) as a colourless mobile liquid, b.p. 100-110 °C/20 mmHg (lit. b.p. 120 °C/20 mmHg).²⁶⁵
Chapter 4.

Experimental

1-(2-Propenyloxy)-3-(trimethylsilyl)prop-2-yn-1-ol (381)

A stock solution of ethylmagnesium bromide was prepared as follows. Magnesium powder (0.30 g, 12.5 mmol) and a magnetic stirrer were placed into a three-necked round bottom flask with reflux condenser attached. The flask and its contents were flame dried under vacuum and then flushed with nitrogen. Dry THF (8 mL) was added, along with a crystal of iodine. Bromoethane (1.03 mL, 13.9 mmol) in dry THF (2 mL) was added via cannula dropwise to the centre of the solution. Assuming 100% conversion, the concentration of the Grignard solution was estimated to be 1.20 mol L⁻¹. In a flame-dried flask flushed with nitrogen, a vigorously stirred solution of 3-(trimethylsilyl)prop-2-yn-1-ol (382) (0.25 g, 1.95 mmol) in dry THF (10 mL) and freshly distilled HMPA (1.36 mL, 7.8 mmol) were cooled to 0 °C. Ethylmagnesium bromide (1.75 mL, 1.20 mol L⁻¹ in diethyl ether, 2.15 mmol) was added dropwise over 1 min to the centre of the solution. The mixture was stirred for 10 min, treated with 3-bromo-1-propene (0.35 g, 2.9 mmol) then heated under reflux for 4 h. The mixture was cooled to room temperature, quenched with water (3 mL) and 1 mol L⁻¹ HCl (5 mL), then extracted with Et₂O (25 mL). The organic phase was washed with water (2 x 10 mL) and brine (10 mL) then dried over MgSO₄. Evaporation of the solvent in vacuo followed by flash silica chromatography (2% Et₂O : hexane) afforded 1-(2-propenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (381) (0.22 g, 67%) as a colourless oil. The ¹H NMR data compared favourably with the literature data.¹⁹⁰
1-(Trimethylsilyl)hex-5-en-1-yn-3-ol (380)

To a stirred solution of 1-(2-propenyl)-3-(trimethylsilyl)prop-2-yn (381) (1.0 g, 4.0 mmol) in dry THF (40 mL) at -78 °C under nitrogen was added n-BuLi (2.5 mL, 1.6 mol L⁻¹ in hexanes, 4.0 mmol). The reaction was stirred for 20 min, warmed to -30 °C, then quenched by the addition of aqueous ammonium chloride (10%, 5 mL). The mixture was warmed to room temperature, diluted with Et₂O (30 mL) then washed with water (3 × 10mL) and brine (10 mL). The organic extract was dried over MgSO₄ and the solvent removed under reduced pressure to afford 1-trimethylsilylhex-5-en-1-yn-3-ol (380) (0.97 g, 97%) as a light yellow oil. The ¹H NMR data compared favourably with the literature data.²⁶⁶

3-(tert-Butyldiphenylsilyloxy)-1-(trimethylsilyl)-hex-5-en-1-yne (393)

To a stirred solution of 1-(trimethylsilyl)hex-5-en-1-yn-3-ol (380) (250 mg, 1.48 mmol), imidazole (120 mg, 1.78 mmol) and 4-dimethylaminopyridine (18 mg, 0.15 mmol) in CH₂Cl₂ (10 mL) at room temperature was added dropwise tert-butyldiphenylsilyl chloride (0.49 g, 1.78 mmol). After 1 h the reaction was quenched.
by the addition NaHCO₃ (2 mL) and water (10 mL) and the resultant mixture extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried over MgSO₄ and the solvent was evaporated in vacuo to afford 3-(tert-butyldiphenylsilyloxy)-1-(trimethylsilyl)-hex-5-en-1-yne (393) (580 mg, 98%) as a yellow oil. The ¹H NMR data compared favourably with the literature data.²⁶⁷

3-(tert-Butyldimethylsilyloxy)-1-(trimethylsilyl)-hex-5-en-1-yne (410)

To a solution of 1-(trimethylsilyl)hex-5-en-1-yn-3-ol (380) (6.64 g, 0.039 mol), imidazole (2.95 g, 0.043 mol) and 4-dimethylaminopyridine (0.5 g, 0.004 mmol) in CH₂Cl₂ (80 mL) at room temperature was added tert-butyldimethylsilyl chloride (6.23 g, 0.041 mol). After 1 h the reaction was quenched by the addition of aqueous NaHCO₃ (10%, 20 mL) and water (50 mL) and the mixture was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over MgSO₄ and the solvent was evaporated in vacuo to afford 3-(tert-butyldimethylsilyloxy)-1-(trimethylsilyl)-hex-5-en-1-yne (410) (10.9 g, 98%) as a light yellow oil. The ¹H NMR data compared favourably with the literature data.²⁶⁸
3-(tert-Butyldiphenylsilyloxy)hex-5-en-1-yne (394)

To a stirred solution of 3-(tert-butyldiphenylsilyloxy)hex-5-en-1-yne (393) (70 mg, 0.17 mmol) in methanol (1 mL) at room temperature was added a freshly prepared solution of sodium methoxide (12 mg sodium in 5 mL methanol). The mixture was heated at 45 °C for 20 min, cooled to room temperature, and then concentrated in vacuo to a volume of ca 1 mL. The residue was diluted with water (5 mL), extracted with CH$_2$Cl$_2$ (3 × 10 mL) and dried over MgSO$_4$. Evaporation of the solvent in vacuo afforded 3-(tert-butyldiphenylsilyloxy)hex-5-en-1-yne (394) (50 mg, 88%) as a colourless oil. IR (CH$_2$Cl$_2$) 3000, 1728, 1473, 1112, 1083, 701 cm$^{-1}$; MS (C.I.) m/z 334 (M$^+$, 6), 277 (100), 207 (60), 199 (45); $^1$H NMR (CDCl$_3$) $\delta$ 1.08 [s, 9H, C(CH$_3$)$_3$], 2.33 (d, 1H, J=2.1 Hz, H1), 2.31-2.39 (m, 1H, H4a); 2.44 (ddt, 1H, J=1.3, 7.0, and 12.7, Hz, 1H, H4b), 4.37 (ddd, 1H, J=2.1, 5.5, and 7.0 Hz, 1H, H3), 5.03-5.08 (m, 2H, H6), 5.80-5.87 (m, 1H, H5), 7.35-7.70 (m, 10H, 2 × Ar); $^{13}$C NMR (CDCl$_3$) $\delta$ 19.3 [C(CH$_3$)$_3$], 26.9 [C(CH$_3$)$_3$], 42.7 (C4), 63.4 (C3), 72.9 (C1), 84.4 (C2), 117.9 (C6), 127.4, 127.6, 129.7, 129.8, 135.9, 136.0 (Ar), 133.3 (C5); HRMS for C$_{22}$H$_{26}$OSi: 334.1753 (calcd), 334.1744 (found).
3-(tert-Butyldimethylsilyloxy)hex-5-en-1-yne (411)

To a stirred solution of 3-(tert-butyldimethylsilyloxy)-1-(trimethylsilyl)-hex-5-en-1-yne (410) (11.0 g, 39.0 mmol) in methanol (20 mL) at room temperature was added a freshly prepared solution of sodium methoxide in methanol (2.7 g sodium in 112 mL methanol). The mixture was then heated to 45 °C for 20 min, cooled to room temperature and then concentrated in vacuo to a volume of ca 5 mL. The residue was diluted with water (5 mL), extracted with CH2Cl2 (4 × 10 mL) and dried over MgSO4. Evaporation of the solvent in vacuo afforded 3-(tert-butyldimethylsilyloxy)hex-5-en-1-yne (411) (7.86 g, 96%) as a colourless oil. The 1H NMR data compared favourably with the literature data.269

3-Acetyltetrahydrothiazole-2-thione (529)

To a vigorously stirred solution of 2-mercapto-1,3-thiazoline (528) (3.0 g, 26 mmol) and triethylamine (3.26 g, 33 mmol) in THF (60 mL) at room temperature was added acetyl chloride (2.28 ml, 33 mmol). An intense yellow colour was immediately observed. After 18 h the mixture was diluted with water (30 mL) and the resultant mixture extracted with CH2Cl2 (3 × 40 mL). The combined extracts were washed
with brine (30 mL), dried over MgSO₄ and evaporated in vacuo. Chromatography on flash silica gel (50%, Et₂O : hexanes) afforded 3-acetyltetrahydrothiazole-2-thione (529) (4.1 g, 98%) as a luminous yellow oil. The ¹H NMR data compared favourably with the literature data.¹⁹²

4-Hydroxypent-1-yl acetate (396)

To a stirred solution of pentan-1,4-diol (386) (1.0 g, 9.6 mmol) and 3-acetyltetrahydrothiazole-2-thione (1.6 g, 10.1 mmol) in THF (60 mL) at room temperature was added portionwise sodium hydride (240 mg, 10.1 mmol). After 2 h the reaction was quenched by the addition of aqueous ammonium chloride (10%, 30 mL) and the mixture extracted with CH₂Cl₂ (2 × 50 mL). The combined extracts were washed with brine (30 mL) and dried over MgSO₄. Removal of the solvent under reduced pressure afforded 4-hydroxypent-1-yl acetate (396) (1.15 g, 82%) as a pale yellow oil. The ¹H NMR data compared favourably with the literature data.¹⁹²
4-(tert-Butyldimethylsilyloxy)pent-1-yl acetate (396)

\[
\begin{align*}
\text{AcO} & \quad \text{OH} \\
& \quad \text{OTBS}
\end{align*}
\]

To a stirred solution of 4-hydroxypent-1-yl acetate (396) (1.15 g, 7.9 mmol), imidazole (0.72 g, 10.6 mmol) and 4-dimethylaminopyridine (117 mg, 0.96 mmol) in DMF (20 mL) at room temperature was added tert-butyldimethylsilyl chloride (1.44 g, 9.6 mmol) in small portions. After 4 h the reaction was quenched by the addition of saturated aqueous ammonium chloride (15 mL) and water (10 mL), and the mixture was diluted with Et₂O (30 mL). The organic phase was separated, washed with water (2 x 10 mL), brine (5 mL) then dried over MgSO₄. Chromatography on flash silica gel (20%, Et₂O : hexanes) afforded 4-(tert-butyldimethylsilyloxy)pent-1-yl acetate (397) (1.93 g, 95%) as a light yellow oil. The \(^1\)H NMR data compared favourably with the literature data.²⁷⁰

4-(tert-Butyldimethylsilyloxy)pentan-1-ol (398)

\[
\begin{align*}
\text{AcO} & \quad \text{OTBS} \\
& \quad \text{OTBS}
\end{align*}
\]

To a stirred solution of 4-(tert-butyldimethylsilyloxy)pent-1-yl acetate (397) (1.93 g, 7.4 mmol) in methanol (35 mL) at room temperature was added K₂CO₃ (2.0 g, 14.6 mmol) in small portions. The mixture was stirred for 18 h, filtered through a
short pad of Celite™ the solvent removed *in vacuo*. Chromatography on flash silica gel (40%, Et₂O : hexanes) afforded 4-(*tert*-butyldimethylsilyloxy)pentan-1-ol (398) (1.5 g, 92%) as a colourless oil. The \(^1\)H NMR data compared favourably with the literature data.\(^{270}\)

### 4-(*tert*-Butyldimethylsilyloxy)pentanal (399)

\[
\begin{align*}
\text{HO} &\quad \text{OTBS} \\
\downarrow &\quad \quad \\
\text{H} &\quad \text{OTBS}
\end{align*}
\]

Dess-Martin periodinane\(^{76}\) (2.1 g, 4.97 mmol) was added portionwise to a mixture of 4-(*tert*-butyldimethylsilyloxy)pentan-1-ol (540 mg, 2.48 mmol) and pyridine (0.2 mL) in CH₂Cl₂ (35 mL) at room temperature. After 1 h the suspension was filtered through a short pad of Celite (2 cm x 0.4 cm) and the filtrate diluted with aqueous NaOH (1.3 molL\(^{-1}\), 10 mL). The mixture was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic extracts dried over MgSO₄. Chromatography on flash silica gel (5%, Et₂O : hexanes) afforded 4-(*tert*-butyldimethylsilyloxy)pentanal (500 mg, 94%) as a mobile colourless oil which was immediately stored under nitrogen. The \(^1\)H NMR data compared favourably with the literature data.\(^{271}\)
2-(tert-Butyldimethylsilyloxy)-8-(tert-butylidiphenylsilyloxy)undec-10-en-6-yn-5-ol (402)

In a flame-dried flask flushed with nitrogen, a vigorously stirred solution of 3-(tert-butyldiphenylsilyloxy)hex-5-en-1-yne (394) (0.2 mg, 0.60 mmol) and TMEDA (0.27 mL, 1.81 mmol) in dry THF (10 mL) was cooled to -78 °C. n-BuLi (0.36 mL, 1.6 mol L⁻¹ in hexane, 0.72 mmol) was added dropwise over 1 min to the centre of the solution. The solution was warmed to -30 °C for 40 min then cooled again to -78 °C and treated with a solution of 4-(tert-butyldimethylsilyloxy)pentanal (399) (0.16 g, 0.72 mmol) in dry THF (5 mL). Stirring was continued for a further 1 h then the reaction was quenched by the addition of NaHCO₃ (10%, 5 mL) and water (10 mL). The mixture was warmed to room temperature and extracted with Et₂O (3 x 15 mL). The combined organic extracts were washed with brine (10 ml), dried over MgSO₄ and evaporated in vacuo. Chromatography on flash silica gel (10%, Et₂O : hexanes) afforded 2-(tert-butyldimethylsilyloxy)-8-(tert-butylidiphenylsilyloxy)undec-10-en-6-yn-5-ol (402) (0.18 g, 54%) as a colourless oil. IR (CH₂Cl₂) 3429, 3000-2800, 1472, 1428, 1361, 1255, 1112, 835 cm⁻¹; MS (C.L) m/z 551 (MH⁺, 0.5), 361 (30), 199 (90), 159 (50), 75 (100). ¹H NMR (CDCl₃) δ 0.04 [2 x s, 6H, Si(CH₃)₂], 0.87 [s, 9H, C(CH₃)₃], 1.06 [s, 9H, C(CH₃)₃], 1.10 (d, 3H, J=6.1 Hz, H1), 1.40-1.62 (m, 4H, H3, H4), 2.39-2.46 (m, 2H, H9), 3.75-3.83 (m, 1H, H2), 4.17-4.19 (m, 1H, H5), 4.41-4.47 (m, 1H, H8), 5.00-5.10 (m, 2H, H11), 5.78-5.92 (m, 1H, H10), 7.26-7.70 (m, 10H, 2 x
Ph); 13C NMR (CDCl₃) δ -4.75, -4.44 (SiCH₃), 18.1, 19.2 [C(CH₃)₃], 23.3, 23.5, 23.6 (C1), 25.8 [C(CH₃)₃], 26.9 [C(CH₃)₃], 33.1, 33.2, 33.5, 33.6 (C3), 34.5, 34.9 (C4), 42.9 (C9), 62.1, 62.4 (C5), 63.5 (C8), 68.1, 68.2 (C2), 85.5, 85.7 (C7), 86.1, 86.4 (C6), 117.8 (C11), 133.5, 133.7, 134.1 (C10), 127.3, 127.6, 129.6, 129.7, 135.9, 136.1 (Ar). HRMS for C₃₃H₅₅Si₂O₃: 551.3377 (calcd), 551.3375 (found).

**2,8-Bis(tert-butyldimethylsilyloxy)undec-10-en-6-yn-5-ol (413)**

In a flame-dried flask flushed with nitrogen, a vigorously stirred solution of 3-(tert-butyldimethylsilyloxy)hex-5-en-1-yne (411) (570 mg, 2.7 mmol) and TMEDA (1.21 mL, 8.1 mmol) in dry THF (10 mL) was cooled to -78 °C. n-BuLi (2 mL, 1.6 M L⁻¹ in hexane, 3.24 mmol) was added dropwise over 1 min to the centre of the solution. After 50 min the mixture was transferred via cannula to a solution of 4-(tert-butyldimethylsilyloxy)pentanal (399) (700 mg, 3.24 mmol) in dry THF (10 mL) at -78 °C. Stirring was continued for 30 min and the reaction was quenched by the addition of aqueous NaHCO₃ (10%, 5 mL) and water (10 mL). The mixture was warmed to room temperature and extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄ and evaporated in vacuo. Chromatography on flash silica gel (10%, Et₂O : hexanes) afforded 2,8-bis(tert-butyldimethylsilyloxy)undec-10-en-6-yn-5-ol (413) (600 mg, 52%) as a colourless oil. IR (CH₂Cl₂) 3392, 2929, 1472, 1255, 1089, 836 cm⁻¹; MS (C.I.) m/z 427 (MH⁺, 24),
217 (100), 159 (64), 85 (75); \(^1\)H NMR (CDCl\(_3\), \(\delta\) 0.04, 0.05, 0.09, 0.10 (s, 12H, SiCH\(_3\), 0.88 [s, 9H, C(CH\(_3\)\(_3\)], 0.89 [s, 9H, C(CH\(_3\)\(_3\)], 1.13 (d, 3H, \(J=6.1\) Hz, H1), 1.55-1.77 (m, 4H, H3, H4), 2.37-2.41 (m, 2H, H9), 3.80-3.89 (m, 1H, H5), 4.35-4.41 m, 2H, H2, H8), 5.05-5.10 (m, 2H, H11), 5.78-5.87 (m, 1H, H10); \(^1\)C NMR (CDCl\(_3\), \(\delta\) -5.0, -4.8, -4.5, -4.4 (SiCH\(_3\)), 18.1 [C(CH\(_3\)\(_3\)], 18.2 [C(CH\(_3\)\(_3\)], 23.1, 23.2, 23.4 (C1), 25.8 [C(CH\(_3\)\(_3\)], 25.9 [C(CH\(_3\)\(_3\)], 33.1, 33.4, 33.8, 33.9 (C3), 34.4, 34.5 (C4), 43.2 (C9), 62.1 (C5), 62.5, 62.8 (C8), 68.1, 68.3 (C2), 85.5 (C6), 85.8 (C7), 117.6 (C11), 134.0 (C10); HRMS for C\(_{37}\)H\(_{47}\)Si\(_2\)O\(_3\): 427.3064 (calcd), 427.3062 (found).

2-(tert-Butyldimethylsilyloxy)-8-(tert-butyldiphenylsilyloxy)undec-10-en-6-yn-5-one (403)

![Chemical structure]

To a stirred solution of 2-(tert-butyldimethylsilyloxy)-8-(tert-butyldiphenylsilyloxy)undec-10-en-6-yn-5-ol (402) (0.12 g, 0.22 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at room temperature was added Dess-Martin periodinane\(^{26}\) (133 mg, 0.32 mmol) and pyridine (0.2 mL). After 2 h the suspension was filtered through a short pad of Celite (1 cm \(\times\) 0.2 cm) and the filtrate was diluted with NaOH (1.3 molL\(^{-1}\), 5 mL). The resultant mixture was extracted with CH\(_2\)Cl\(_2\) (3 \(\times\) 10mL) and the combined extracts dried over MgSO\(_4\) then concentrated under reduced pressure. Chromatography on flash silica gel (10\%, Et\(_2\)O : hexanes) afforded 2-(tert-butyldimethylsilyloxy)-8-(tert-butyldiphenylsilyloxy)undec-10-en-6-yn-5-one (403)
(99 mg, 83%) as a colourless oil. IR (CH₂Cl₂) 2958, 2213, 1687, 1471, 1245, 1091, 836 cm⁻¹; MS (E.I.) m/z 548 (M⁺, 2), 491 (28), 450 (65), 359 (65), 281 (40), 197 (100), 73 (75); ¹H NMR (CDCl₃) δ 0.03 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃), 0.88 [s, 9H, C(CH₃)₃], 1.08 [s, 9H, C(CH₃)₃], 1.10 (d, 3H, J=6.1 Hz, H1), 1.54-1.75 (m, 2H, H3), 2.37-2.54 (m, 4H, H4, H9), 3.77-3.86 (m, 1H, H2), 4.50 (t, 1H, J=6.1 Hz, H8), 5.06-5.11 (m, 2H, H11), 5.73-5.85 (m, 1H, H10), 7.36-7.70 (m, 10H, 2×Ar); ¹³C NMR (CDCl₃) δ -4.8 (SiCH₃), -4.4 (SiCH₃), 18.0 [C(CH₃)₃], 19.3 [C(CH₃)₃], 23.6 (C1), 25.8 [C(CH₃)₃], 26.8 [C(CH₃)₃], 33.1 (C3), 41.4 (C9), 42.1 (C4), 63.4 (C8), 67.2 (C2), 83.9 (C6), 91.9 (C7), 118.6 (C11), 132.6 (C10), 127.6-135.9 (Ar); 187.5 (C5); HRMS for C₃₃H₄₈Si₂O₅: 548.3142 (calcd), 548.3102 (found).

(Z)-2-(tert-Butyldimethylsilyloxy)-8-(tert-butylidiphenylsilyloxy)undeca-6,10-dien-5-one (417)

To a solution of 2-(tert-butyldimethylsilyloxy)-8-(tert-butylidiphenylsilyloxy)undec-10-en-6-yn-5-one (403) (130 mg, 0.24 mmol) in EtOAc (15 mL) was added Lindlar catalyst (1 mg, 0.024 mmol) and one drop of quinoline. The mixture was stirred at room temperature under an atmosphere of hydrogen until TLC analysis indicated that the starting material had been consumed. The reaction was then quenched with water (10 mL). The organic extract was washed with brine (2 × 10 mL), dried over MgSO₄ and the solvent evaporated in vacuo.
Chapter 4.

Experimental

Chromatography on flash silica gel (20%, Et₂O : hexanes) afforded (Z)-8-(tert-butyldimethylsilyloxy)-2-(tert-butyldiphenylsilyloxy)undeca-6,10-dien-5-one (417) (96 mg, 74%) as a colourless oil. IR (CH₂Cl₂) 2930, 1693, 1255, 1112, 1078, 912, 835, 774, 700 cm⁻¹; MS (E.I.) m/z 548 (M⁺, 1), 361 (30), 215 (26), 199 (100), 135 (20), 75 (25); ¹H NMR (CDCl₃) δ 0.03 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃), 0.88 [s, 9H, C(CH₃)₃], 1.06 [s, 9H, C(CH₃)₃], 1.00 (d, 3H, J=5.9 Hz, H1), 1.42-1.61 (m, 2H, H3), 2.19-2.63 (m, 4H, H4, H9), 3.72-3.78 (m, 1H, H2), 5.00-5.04 (m, 2H, H11), 5.23-5.37 (m, 1H, H8), 5.78-6.01 (m, 3H, H6, H7, H10), 7.21-7.70 (m, 10H, 2×Ar); ¹³C NMR (CDCl₃) δ -4.8 (SiCH₃), -4.4 (SiCH₃), 18.0 [C(CH₃)₃], 19.3 [C(CH₃)₃], 23.6, 23.8 (C1), 25.8 [C(CH₃)₃], 26.9 [C(CH₃)₃], 33.0, 33.1 (C3), 39.9, 40.0 (C4), 41.8 (C9), 67.6 (C2), 69.9 (C8), 117.1 (C11), 129.6, 129.9 (C6), 134.4 (C10), 127.6-135.9 (Ar), 150.2, 150.3 (C7), 200.4 (C5); HRMS for C₃₃H₅₀Si₂O₃: 550.3299 (calcd), 550.3305 (found).

2,8-Bis(tert-butyldimethylsilyloxy)undec-10-en-6-yn-5-one (414)

To a solution of 2,8-bis(tert-butyldimethylsilyloxy)undec-10-en-6-yn-5-ol (413) (400 mg, 0.94 mmol) in CH₂Cl₂ (10 mL) was added tetrabutylammonium perruthenate (16 mg, 0.0468 mmol), NMO (0.16 g, 1.4 mmol), and 4 Å molecular sieves (0.47 g, 500 mg/1 mmol compound). The mixture was stirred at room temperature for 30 min then filtered through a Celite pad and the solvent evaporated from the filtrate in vacuo. Chromatography on flash silica gel (10%, Et₂O : hexanes)
afforded 2,8-bis(tert-butyldimethylsilyloxy)undec-10-en-6-yn-5-one (414) (385 mg, 98%) as a colourless oil. IR (CH$_2$Cl$_2$) 2956, 2212, 1682, 1472, 1255, 1136, 1088, 836 cm$^{-1}$; MS (C.I.) m/z 425 (MH$^+$, 60), 293 (40), 141 (38), 75 (100); $^1$H NMR (CDCl$_3$) δ 0.01, 0.02, 0.03, 0.13 (s, 12H, SiCH$_3$), 0.87 [s, 9H, C(CH$_3$)$_3$], 0.89 [s, 9H, C(CH$_3$)$_3$], 1.12 (d, 3H, J=6.1 Hz, H1), 1.67-1.78 (m, 4H, H3, H9), 2.45 (t, 2H, J=6.7 Hz, H4), 2.58-2.63 (m, 2H, H9), 3.79-3.84 (m, 1H, H2), 4.50 (t, 1H, J=6.4 Hz, H8), 5.10-5.15 (m, 2H, H11), 5.76-5.86 (m, 1H, H10); $^{13}$C NMR (CDCl$_3$) δ -5.1, -4.8, -4.6, -4.4 (SiCH$_3$), 18.0 [C(CH$_3$)$_3$], 18.2 [C(CH$_3$)$_3$], 23.7 (C1), 25.7 [C(CH$_3$)$_3$], 25.8 [C(CH$_3$)$_3$], 33.2 (C3), 41.9 (C9), 42.3 (C4), 62.7 (C2), 67.2 (C8), 83.4 (C6), 92.3 (C7), 118.4 (C11), 132.9 (C10), 187.5 (C5); HRMS for C$_{23}$H$_{48}$Si$_2$O$_3$: 425.2907 (calcd), 425.2907 (found).

8-(tert-Butyldimethylsilyloxy)-2-(tert-butyldiphenylsilyloxy)-10,11-epoxy-undec-6-yn-5-one (407)

$$\text{OTBDPS} \quad \rightarrow \quad \text{OTBDPS}$$

To a solution of 2-(tert-butyldimethylsilyloxy)-8-(tert-butyldiphenylsilyloxy)undec-10-en-6-yn-5-one (403) (200 mg, 0.36 mmol) in CH$_2$Cl$_2$ (20 mL) was added meta-chloroperoxybenzoic acid (250 mg, 1.46 mmol) and sodium acetate (0.12 g, 1.46 mmol). The mixture was stirred at room temperature for five days then water (10 mL) was added. The organic layer was washed with brine (2×10 mL), dried over MgSO$_4$ and the solvent was evaporated in vacuo. Chromatography
on flash silica gel (20%, Et₂O : hexanes) afforded 8-(tert-butyldimethylsilyloxy)-2-(tert-butyldiphenylsilyloxy)-10,11-epoxyundec-6-yn-5-one (407) (160 mg, 79%) as a colourless oil. IR (CH₂Cl₂) 2930, 2214, 1681, 1472, 1428, 1255, 1120, 836 cm⁻¹; MS (FAB⁺) m/z 565 (MH⁺, 5), 195 (35), 135 (68), 73 (100); ¹H NMR (CDCl₃) δ 0.02 (s, 3H, SiCH₃), 0.03 (s, 3H, SiCH₃), 0.88 [s, 9H, C(CH₃)₃], 1.08 [s, 9H, C(CH₃)₃], 1.09 (d, 3H, J=6.1 Hz, H1), 1.59-1.71 (m, 2H, H3), 1.90-1.99 (m, 2H, H9), 2.36-2.47 (m, 1H, H11a), 2.36-2.47 (m, 2H, H4), 2.72-2.79 (m, 1H, H11b), 3.08-3.17 (m, 1H, H10), 3.75-3.79 (m, 1H, H2), 4.67-4.71 (m, 1H, H8), 7.37-7.73 (m, 10H, 2x Ph); ¹³C NMR (CDCl₃) δ -4.8 (SiCH₃), -4.5 (SiCH₃), 18.0 [C(CH₃)₃], 19.2 [C(CH₃)₃], 23.6 (C1), 25.8 [C(CH₃)₃], 26.8 [C(CH₃)₃], 32.9 (C3), 40.9 (C9), 40.9, 41.0, 41.2, 41.3 (C11), 47.3 (C4), 48.6 (C10), 61.5 (C8), 67.2 (C2), 84.2 (C6), 90.9 (C7), 127.2-135.4 (Ar), 187.2 (C5); HRMS for C₃₅H₄₅Si₂O₄: 565.3169 (calcd), 565.3183 (found).

2,8-Bis(tert-butyldimethylsilyloxy)-10,11-epoxyundec-6-yn-5-one (415)

![Chemical structure diagram](image)

To a solution of 2,8-bis(tert-butyldimethylsilyloxy)undec-10-en-6-yn-5-one (414) (70 mg, 0.16 mmol) in CH₂Cl₂ (20 mL) was added meta-chloroperoxybenzoic acid (170 mg, 0.99 mmol) and sodium acetate (81 mg, 0.99 mmol). The mixture was stirred at room temperature for five days then water (10 mL) was added. The organic layer was washed with brine (2 × 10 mL), dried over MgSO₄ and the solvent
evaporated in vacuo. Chromatography on flash silica gel (50%, Et_2O : hexanes) afforded \(2,8\)-bis(tert-butyldimethylsilyloxy)-10,11-epoxyundec-6-yn-5-one (415) (55 mg, 75%) as a colourless oil. IR (CH_2Cl_2) 2929, 2213, 1682, 1472, 1255, 1097, 837 cm\(^{-1}\); MS (C.I.) \(m/z\) 441 (MH\(^+\), 100), 309 (70), 92 (40), 74 (82); \(^1\)H NMR (CDCl_3) \(\delta\) 0.12, 0.14, 0.15, 0.17 (each s, 12H, SiCH_3), 0.86 [s, 9H, C(CH_3)_3], 0.90 [s, 9H, C(CH_3)_3], 1.10 (d, 3H, \(J=6.0\) Hz, H1), 1.66-1.78 (m, 2H, H3), 1.91-1.96 (m, 2H, H9), 2.49-2.55 (m, 2H, H4), 2.62-2.65 (m, 1H, H11a), 2.77-2.80 (m, 1H, H11b), 3.06-3.09 (m, 1H, H10), 3.78-3.86 (m, 1H, H2), 4.68-4.71 (m, 1H, H8); \(^{13}\)C NMR (CDCl_3) \(\delta\) -5.2, -4.9, -4.6, -4.4 (SiCH_3), 18.0 [C(CH_3)_3], 18.1 [C(CH_3)_3], 23.7 (C1), 25.5 [C(CH_3)_3], 25.7 [C(CH_3)_3], 33.1 (C3), 41.1, 41.2 (C9), 41.5 (C4), 46.7, 47.5 (C11), 48.6 (C10), 60.3, 60.8 (C8), 67.2 (C2), 83.3, 83.8 (C6), 91.3, 91.8 (C7), 187.3 (C5); HRMS for C_{23}H_{45}Si_{2}O_4: 441.2856 (calcd), 441.2284 (found).
8-(tert-Butyldiphenylsilyloxy)-2-(tert-butyldimethylsilyloxy)-10,11-epoxyundecan-5-one (408)

To a solution of 8-(tert-butyldimethylsilyloxy)-2-(tert-butyldiphenylsilyloxy)-10,11-epoxyundec-6-yn-5-one (407) (160 mg, 0.29 mmol) in EtOAc (10 mL) was added sodium bicarbonate (50 mg, 0.57 mmol) and 10% palladium on charcoal (5 mg). The reaction mixture was stirred at room temperature under an atmosphere of hydrogen. After 2 h the suspension was filtered through a short pad of Celite and the solvent removed from the filtrate under reduced pressure. Chromatography on flash silica gel (50%, EtO : hexanes) afforded 8-(tert-butyldiphenylsilyloxy)-2-(tert-butyldimethylsilyloxy)-10,11-epoxyundecan-5-one (408) (160 mg, 98%) as a colourless oil. IR (CH₂Cl₂) 2929, 1714, 1427, 1256, 1111 cm⁻¹; MS (C.l.) m/z 568 (M⁺, 0.16), 379 (94), 255 (100), 199 (93), 75 (89); ¹H NMR (CDCl₃) δ 0.01 (s, 3H, SiCH₃), 0.03 (s, 3H, SiCH₃), 0.88 [s, 9H, C(CH₃)₃], 1.06 [s, 9H, C(CH₃)₃], 1.09 (d, 3H, J=6.2 Hz, H1), 1.51-1.60 (m, 2H, H3), 1.61-1.86 (m, 2H, H7), 1.61-1.86 (m, 2H, H9), 2.26-2.40 (m, 4H, H4, H6), 2.26-2.40 (m, 1H, H11a), 2.61-2.65 (m, 1H, H11b), 2.84-2.95 (m, 1H, H10), 3.74-3.81 (m, 1H, H2), 3.93-3.99 (m, 1H, H8), 6.94-7.22 (m, 10H, Ph); ¹³C NMR (CDCl₃) δ -4.8 (SiCH₃), -4.4 (SiCH₃), 18.1 [C(CH₃)₃], 19.2 [C(CH₃)₃], 23.7 (C1), 25.9 [C(CH₃)₃], 26.5 [C(CH₃)₃], 30.4, 30.7 (C9), 33.1 (C3, C7), 37.9, 38.7, 39.4, 39.9 (C4, C6), 46.8, 47.2 (C11), 49.0, 49.4 (C10), 67.2 (C2), 70.5,
Experimental

70.8 (C8), 127.6-135.8 (Ph), 210.6 (C5); HRMS for C$_{33}$H$_{52}$Si$_2$O$_4$: 569.3482 (calcd), 569.3471 (found).

2,8-Bis(tert-butyldimethylsilyloxy)-10,11-epoxyundecan-5-one (416)

To a solution of 2,8-bis(tert-butyldimethylsilyloxy)-10,11-epoxyundec-6-yn-5-one (415) (50 mg, 0.12 mmol) in EtOAc (10 mL) was added sodium bicarbonate (21 mg, 0.25 mmol) and 10% palladium on charcoal (2 mg). The mixture was stirred at room temperature under an atmosphere of hydrogen. After 2 h the suspension was filtered through a short pad of Celite$^{\text{TM}}$ and the solvent removed from the filtrate under reduced pressure. Chromatography on flash silica gel (50%, Et$_2$O : hexanes) afforded 2,8-bis(tert-butyldimethylsilyloxy)-10,11-epoxyundecan-5-one (416) (41 mg, 74%) as a colourless oil. IR (CH$_2$Cl$_2$) 2929, 1716, 1472, 1236, 1072, 836 cm$^{-1}$. MS (C.I.) m/z: 445 (MH$^+$, 65), 313 (73), 255 (100), 181 (90), 75 (58); $^1$H NMR (CDCl$_3$) $\delta$ -0.02, -0.03, 0.01, 0.05 (each s, 12H, SiCH$_3$), 0.86 [s, 9H, C(CH$_3$)$_3$], 0.87 [s, 9H, C(CH$_3$)$_3$], 1.10 (d, 3H, J=6.0 Hz, H1), 1.61-1.69 (m, 4H, H3, H7), 1.71-1.75 (m, 2H, H9), 2.41-2.53 (m, 5H, H4, H6, H11a), 2.71-2.77 (m, 1H, H11b), 2.95-3.03 (m, 1H, H10), 3.77-3.84 (m, 1H, H2), 3.87-3.96 (m, 1H, H8); $^{13}$C NMR (CDCl$_3$) $\delta$ -4.77, -4.71, -4.54, -4.38 (SiCH$_3$), 17.99 [C(CH$_3$)$_3$], 18.0 [C(CH$_3$)$_3$], 23.7 (C1), 25.8 [C(CH$_3$)$_3$], 25.9 [C(CH$_3$)$_3$], 30.6, 31.2 (C9), 33.2 (C3, C7), 37.8, 38.3, 38.8 (C4), 40.1, 40.2 (C6), 46.8,
47.6 (C11), 49.2, 49.6 (C10), 67.5 (C2), 69.1, 69.3 (C8), 210.7 (C5); HRMS for
C_{23}H_{49}Si_2O_4: 445.3169 (calcd), 445.3180 (found).

1-(2-Methoxy-5-methyltetrahydrofuran-2-yl)hex-5-en-1-yn-3-ol (431)

To a solution of 2,8-bis(tert-butyldimethylsilyloxy)undec-10-en-6-yn-5-one (415) (100 mg, 0.236 mmol) in methanol (10 mL) was added camphorsulfonic acid (12 mg, 0.047 mmol) and the mixture was stirred at room temperature for 2 h. The methanol was removed under reduced pressure and the organic residue was washed with water (2 × 2 mL) and brine (2 × 1 mL) then extracted with Et₂O (5 mL). The organic extract was dried over MgSO₄ and concentrated under reduced pressure. Chromatography on flash silica gel (50%, Et₂O : hexanes) afforded 1-(2-methoxy-5-methyltetrahydrofuran-2-yl)hex-5-en-1-yn-3-ol (431) (491 mg, 97%) as a colourless oil. IR (CH₂Cl₂) 3429, 2973, 2243, 1444, 1381, 1315, 1235, 1145, 1089, 1048, 916 cm⁻¹; MS (C.I.) m/z 211 (MH⁺, 6), 179 (100), 169 (40), 137 (38), 91 (25); ¹H NMR (CDCl₃) δ 1.29 (d, 3H, J=6.2 Hz, CH₃), 1.51-1.70 (m, 2H, H₄'), 2.15-2.21 (m, 2H, H₃'), 2.47-2.51 (m, 2H, H₄), 3.35, 3.36, 3.37, 3.38 (s, 3H, OCH₃), 4.14-4.22 (m, 1H, H₅'), 4.31-4.39 (m, 1H, H₃), 4.48 (s, 1H, OH), 5.16-5.26 (m, 2H, H₆), 5.85-5.92 (m, 1H, H₅); ¹³C NMR (CDCl₃) δ 22.4 (CH₃), 31.5, 31.8 (C₄'), 40.0, 40.1 (C₃'), 41.8 (C₄), 61.4 (OCH₃), 75.3 (C₃), 77.7 (C₅'), 82.0 (C₁), 84.5, 84.7 (C₂), 101.5, 101.8
Experimental

(C2'), 118.9 (C6), 132.9 (C5); HRMS for C_{12}H_{19}O_{3}: 211.1334 (calcd), 211.1335 (found).

**5,6-Epoxy-1-(2-methoxy-5-methyltetrahydrofuran-2-yl)hex-1-yn-3-ol (436)**

To a solution of 1-(2-methoxy-5-methyltetrahydrofuran-2-yl)hex-5-en-1-yn-3-ol (431) (270 mg, 1.3 mmol) in CH_{2}Cl_{2} (20 mL) was added *meta*-chloroperoxybenzoic acid (450 mg, 2.6 mmol) and sodium acetate (210 mg, 2.6 mmol). The reaction mixture was stirred at room temperature for two days then quenched with water (10 mL). The organic layer was washed with brine (2 × 5 mL), dried over MgSO_{4}, and the solvent was evaporated in vacuo. Chromatography on flash silica gel (50%, Et_{2}O : hexanes) afforded **5,6-epoxy-1-(2-methoxy-5-methyltetrahydrofuran-2-yl)hex-1-yn-3-ol (436)** (260 mg, 89%) as a colourless oil. IR (CH_{2}Cl_{2}) 3429, 2973, 2242, 1444, 1381, 1315, 1235, 1145, 1089, 1048, 916 cm^{-1}; MS (E.I.) m/z 195 (M^{+}-OCH_{3}, 100), 137 (40), 55 (68), 43 (72), 41 (94); \(^1\)H NMR (CDCl_{3}) δ 1.29 (d, 3H, J=6.2 Hz, CH_{3}), 1.57-1.70 (m, 2H, H4'), 2.15-2.21 (m, 2H, H3'), 2.22-2.29 (m, 2H, H4), 2.55-2.61 (m, 1H, H6a), 2.80-2.85 (m, 1H, H6b), 3.10-3.20 (m, 1H, H5), 3.35, 3.36 (s, 3H, OCH_{3}), 4.14-4.22 (m, 1H, H5'), 4.66-4.70 (m, 1H, H3); \(^1\)C NMR (CDCl_{3}) δ 20.9 (CH_{3}), 31.6, 31.8 (C4'), 39.9, 40.1 (C3'), 41.1 (C4), 46.9 (C6), 49.1 (C5), 60.0, 60.3 (OCH_{3}), 75.4
Chapter 4.

Experimental

(C3), 77.2 (C5'), 77.9 (C1), 80.0 (C2), 103.9 (C2'); HRMS for M'\textsuperscript{+}-OMe C\textsubscript{11}H\textsubscript{18}O\textsubscript{4}: 195.1021 (calcd), M'\textsuperscript{+}-OMe 195.1012 (found).

2-(2,3-epoxyprop-1-yl)-7-methyl-1,6-dioxaspiro[4.4]nonane (300)

![Chemical structure](image)

To a solution of 5,6-epoxy-1-(2-methoxy-5-methyltetrahydrofuran-2-yl)hex-1-yn-3-ol (436) (20 mg, 0.090 mmol) in EtOAc (10 mL) was added sodium bicarbonate (24 mg, 0.17 mmol) and 10% palladium on charcoal (2 mg). The mixture was stirred at room temperature under a hydrogen atmosphere. After 2 h the suspension was filtered through a short pad of Celite and the solvent was removed from the filtrate under reduced pressure. Chromatography on flash silica gel (50%, Et\textsubscript{2}O : hexanes) afforded 2-(2,3-epoxyprop-1-yl)-7-methyl-1,6-dioxaspiro[4.4]nonane (300) (11 mg, 63%) as a colourless oil. IR (CH\textsubscript{2}Cl\textsubscript{2}) 2973, 1646, 1458, 1378, 1078, 861 cm\textsuperscript{-1}; MS (C.I.) \textit{m/z} 197 (M'\textsuperscript{+}-H, 7), 43 (100); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta 1.28 (d, 3H, \textit{J}=6.3 Hz, CH\textsubscript{3}), 1.57-1.70 (m, 4H, H3, H8), 2.03-2.10 (m, 2H, H1'), 2.15-2.21 (m, 4H, H4, H9), 2.49-2.52 (m, 1H, H3'b), 2.75-2.82 (m, 1H, H3'a), 3.00-3.10 (m 1H, H2'), 3.61-3.89 (m, 1H, H7), 4.13-4.36, m (1H, H2); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \delta 21.1, 21.3 (CH\textsubscript{3}), 30.5, 31.6, 31.9 (C8), 32.2, 32.6 (C3), 35.1, 35.4 (C4), 36.0, 36.2, 36.7 (C9), 40.7 (C1'), 47.4, 47.5 (C3'), 49.5, 49.7, 49.8, 49.9 (C2'), 73.9, 74.2 (C2), 75.9, 76.1 (C7), 102.9, 103.9 (C5); HRMS for M'\textsuperscript{+}-H C\textsubscript{11}H\textsubscript{18}O\textsubscript{3}: 197.3145 (calcd), M'\textsuperscript{+}-H 197.3122 (found).
3,5-Dimethoxybenzyl alcohol (373)

![Chemical structures](image)

To a vigorously stirred solution of 3,5-dimethoxybenzoic acid (374) (10.0 g, 55.0 mmol) in dry THF (100 mL) under nitrogen was added LiAlH₄ (4.2 g, 110.0 mmol) portion-wise over 1 h. The reaction was left until the analysis showed that on starting material remained. Triethanolamine (10 mL) was added and the mixture was allowed to stir for a further 30 min at room temperature. The mixture was filtered and the solvent was removed from the filtrate under reduced pressure. The extract was washed with brine (10 mL) and dried over MgSO₄. Chromatography on flash silica gel (Et₂O) afforded 3,5-dimethoxybenzylalcohol (373) (9.2 g, 99%) as a yellow oil. The \(^1\)H NMR data compared favourably with the literature data.\(^{185}\)
2-Bromo-3,5-dimethoxybenzyl alcohol (372)

![Chemical Structure](image)

To a stirred solution of 3,5-dimethoxybenzyl alcohol (373) (3.4 g, 20.3 mmol) in freshly distilled CCl₄ (140 mL) was added NBS (3.6 g, 20.3 mmol). The reaction mixture was heated to reflux under nitrogen for 24 h, cooled and filtered, and the filtrate was washed with water (10 mL) and dried over MgSO₄. Chromatography on flash silica gel (75%, Et₂O : hexanes) afforded 2-bromo-3,5-dimethoxybenzylalcohol (372) (4.7 g, 94%) as a clear oil. The 'H NMR data compared favourably with the literature data.¹⁸⁵

2-Bromo-3,5-dimethoxybenzylaldehyde (371)

![Chemical Structure](image)

To a solution of 2-bromo-3,5-dimethoxybenzylalcohol (372) (2.0 g, 8.1 mmol) in CH₂Cl₂ (30 mL) was added PCC (3.5 g, 16.2 mmol) and the mixture was stirred for 2 h at room temperature. The solution was decanted and the residue washed with CH₂Cl₂ (3 × 10 mL). To the combined organic phases was added Et₂O (10 mL), and
the solution was filtered through a silica pad. Evaporation of the solvents in vacuo afforded 2-bromo-3,5-dimethoxybenzylaldehyde (371) (1.6 g, 81%) as an orange oil. The $^1$H NMR data compared favourably with the literature data.$^{185}$

1,3-dimethyl-2-(3-methoxyphenyl)-imidazolidine (447)

![Chemical Structure](attachment:image.png)

To a solution of 3-methoxybenzaldehyde (451) (1.5 g, 11.0 mmol) in dry benzene (40 mL) was added $N,N$-dimethylethylenediamine (1.2 mL, 11.3 mmol) and the mixture was heated under nitrogen for 5 h using Dean-Stark apparatus. Evaporation of the solvent in vacuo afforded 1,3-dimethyl-2-(3-methoxyphenyl)-imidazolidine (447) (2.2 g, 98%) as a pale yellow oil. The $^1$H NMR data compared favourably with the literature data.$^{204}$

274
1,3-dimethyl-2-(3,5-dimethoxyphenyl)imidazolidine (450)

To a solution of 3,5-dimethoxybenzaldehyde (445) (1.7 g, 10.3 mmol) in dry benzene (40 mL) was added N,N-diethylethylenediamine (1.1 mL, 10.7 mmol) and the mixture was heated under nitrogen for 5 h using Dean-Stark apparatus. Evaporation of the solvent in vacuo afforded 1,3-dimethyl-2-(3,5-dimethoxyphenyl)imidazolidine (450) (2.4 g, 98%) as a pale yellow oil. The $^1$H NMR data compared favourably with the literature data.\(^{205}\)

2,4-Dimethoxybenzoic acid (296)

To a vigorously stirred suspension of KMnO$_4$ (5.7 g, 36.0 mmol) in water (50 mL) was added tetrabutylammonium bromide (0.5 g, 1.5 mmol) and then a solution of 2,4-dimethoxybenzaldehyde (452) (2.0 g, 12.0 mmol) in benzene (30 mL) at 0 °C. After 30 min and the "purple benzene" went brown. Na$_2$S$_2$O$_5$ (8.0 g) was added before the reaction mixture was acidified. The organic layer was dried over MgSO$_4$ and evaporation of the solvent in vacuo afforded 2,4-dimethoxybenzoic acid (296)
(1.8 g, 84%) as a white solid mp 108-109 °C (Lit\textsuperscript{206} mp 108-110 °C). The \textsuperscript{1}H NMR data compared favourably with the literature data.\textsuperscript{206}

\textbf{\textit{N,N-Diethyl-2,4-dimethoxybenzamide (295)}}

\begin{align*}
\text{OMe} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO}
\end{align*}

\begin{align*}
\text{OH} & \quad \rightarrow \quad \text{NET}_2 \\
(296) & \quad \text{MeO} \\
(295) & \quad \text{MeO}
\end{align*}

2,4-Dimethoxybenzoic acid (296) (7.0 g, 38.0 mmol) was heated to reflux under an atmosphere of nitrogen for 2 h with SOCl\textsubscript{2} (30 mL). Benzene (30 mL) was added and the excess SOCl\textsubscript{2} was removed under reduced pressure. This procedure was repeated with additional benzene (2 \times 20 mL). The residue was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (40 mL), cooled to 0 °C, and a solution of diethylamine (11.9 mL, 115.0 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) was slowly added. The mixture was stirred for 12 h under nitrogen at room temperature, then poured into CH\textsubscript{2}Cl\textsubscript{2} (50 mL), washed with aqueous NaHCO\textsubscript{3} solution (10\%, 3 \times 10 mL) and brine (3 \times 10 mL). The organic extract was dried over MgSO\textsubscript{4}. Chromatography on flash silica gel (75\%, Et\textsubscript{2}O : hexanes) afforded \textit{N,N-diethyl-2,4-dimethoxybenzamide (295)} (9.0 g, 99\%) as a pale yellow oil. The \textsuperscript{1}H NMR data compared favourably with the literature data.\textsuperscript{207}
**Chapter 4. Experimental**

*N,N-Diethyl-4,6-dimethoxy-2-formylbenzamide (294)*

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

(295) \quad (294) \quad (453)

In a flame-dried flask flushed with nitrogen, a vigorously stirred solution of *N,N*-diethyl-2,4-dimethoxybenzamide (295) (5.2 g, 21.7 mmol) in dry THF (193 mL) was cooled to -78 °C. *t*-BuLi (23 mL, 1.05 mol L\(^{-1}\) solution in hexanes, 23.9 mmol) was added dropwise over 1 min to the centre of the solution. The resulting deep orange solution was left for 15 min. Anhydrous DMF (6.7 mL, 87.0 mmol) was then added and the mixture was stirred at -78 °C for 1 h, then warmed to room temperature over 12 h. The solvent was removed under reduced pressure, the residue was dissolved in CH\(_2\)Cl\(_2\) (30 mL), washed with brine (3 x 10 mL) and dried over MgSO\(_4\). Chromatography on flash silica gel (Et\(_2\)O) afforded *N,N*-diethyl-4,6-dimethoxy-2-formylbenzamide (294) (5.71 g, 99%) as a yellow oil. IR (CH\(_2\)Cl\(_2\)) 3435, 1700, 1626, 1459, 1334, 1290, 1223, 1155, 1098, 1045, 936 cm\(^{-1}\); MS (E.I.) m/z 265 (M\(^+\), 3), 236 (57), 193 (100), 165 (34), 72 (16); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.02 (t, 3H, \(J=7.1\) Hz, NCH\(_2\)CH\(_3\)), 1.28 (t, 3H, \(J=7.1\) Hz, NCH\(_2\)CH\(_3\)), 3.13 (q, 2H, \(J=7.1\) Hz NCH\(_2\)), 3.45-3.76 (m, 2H, NCH\(_2\)), 3.84 (s, 3H, OCH\(_3\)), 3.87 (s, 3H, OCH\(_3\)), 6.70 (d, 1H, \(J=2.3\) Hz, H5), 7.03 (d, 1H, \(J=2.3\) Hz, H3), 9.96 (s, 1H, CHO); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 12.7 (NCH\(_2\)CH\(_3\)), 13.7 (NCH\(_2\)CH\(_3\)), 39.1 (NCH\(_2\)), 42.9 (NCH\(_2\)), 55.7 (OCH\(_3\)), 55.9 (OCH\(_3\)), 102.3 (C5), 104.8 (C3), 123.5 (C1), 134.3 (C2), 156.9 (C6), 160.9 (C4), 165.7 (C=O, amide), 190.2 (CHO); HRMS for C\(_{14}\)H\(_{19}\)NO\(_4\): 265.1314 (calcd), 265.1314 (found).
**N,N-Diethyl-4,6-dimethoxy-2-hydroxymethylbenzamide (453)**

![Diagram of the reaction](image)

IR (CH$_2$Cl$_2$) 3400, 1793, 1606, 1460, 1380, 1323, 1288, 1216, 1200, 1154, 1099, 1049, 735 cm$^{-1}$; MS (E.I.) $m/z$ 267 (M$^+$, 16), 236 (10), 195 (100), 74 (32), 58 (42); $^1$H NMR (CDCl$_3$) $\delta$ 1.03 (t, 3H, $J=5.3$ Hz, NCH$_2$CH$_3$), 1.24 (t, 3H, $J=5.3$ Hz, NCH$_2$CH$_3$), 3.11-3.19 (m, 2H, NCH$_2$), 3.26 (s, 1H, OH), 3.52-3.60 (m, 2H, NCH$_2$), 3.78 (s, 3H, OCH$_3$), 3.82 (s, 3H, OCH$_3$), 4.32 (d, 1H, $J=9.3$ Hz, CH$_3$OH), 4.54 (d, 1H, $J=9.3$ Hz, CH$_3$OH), 6.39 (d, 1H, $J=1.6$ Hz, H$_5$), 6.59 (d, 1H, $J=1.6$ Hz, H$_3$); $^{13}$C NMR (CDCl$_3$) $\delta$ 12.6 (NCH$_2$CH$_3$), 13.7 (NCH$_2$CH$_3$), 39.0 (NCH$_2$), 42.9 (NCH$_2$), 55.3 (OCH$_3$), 55.5 (OCH$_3$), 63.5 (CH$_2$OH), 97.7 (C$_5$), 105.1 (C$_3$), 118.1 (C$_1$), 140.8 (C$_2$), 156.2 (C$_6$), 161.1 (C$_4$), 168.5 (C=O); HRMS for C$_{14}$H$_{21}$NO$_4$: 267.1471 (calcd), 267.1469 (found).
Optimisation of reaction conditions for preparations of \(N,N\)-diethyl-4,6-dimethoxy-2-formylbenzamide using \(t\)-BuLi

<table>
<thead>
<tr>
<th>(t)-BuLi (equiv)</th>
<th>TMEDA (equiv)</th>
<th>Temp (^{\circ}\text{C})</th>
<th>Anion Life (Min)</th>
<th>DMF (equiv)</th>
<th>Ratio or % Isolated Yield Product (294)</th>
<th>Ratio or % Isolated Yield By Product (453)</th>
<th>S.M. (%)</th>
</tr>
</thead>
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<td>1.2</td>
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<td>5</td>
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<td>100</td>
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<td>-100</td>
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<td>5</td>
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<td>100</td>
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<tr>
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<tr>
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<td>Not isolated</td>
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</tr>
<tr>
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<td>-</td>
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<td>7.5</td>
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<td>4</td>
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Optimisation of reaction conditions for preparations of \(N,N\)-diethyl-4,6-dimethoxy-2-formylbenzamide using \(n\)-BuLi

<table>
<thead>
<tr>
<th>(n)-BuLi (equiv)</th>
<th>TMEDA (equiv)</th>
<th>Temp (^{\circ}\text{C})</th>
<th>Anion Life (Min)</th>
<th>DMF (equiv)</th>
<th>Ratio or % Isolated Yield Product (294)</th>
<th>Ratio or % Isolated Yield By Product (453)</th>
<th>S.M. (%)</th>
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<td>5</td>
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<td>2.5</td>
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<tr>
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<td>30</td>
<td>5</td>
<td>1</td>
<td>3.2</td>
<td>Not isolated</td>
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</table>

Note. When the reaction was conducted on more than 0.75 g of the starting amide, the optimum procedure involved leaving the anion for 15 minutes.
Chapter 4.

Experimental

\(N,N\)-Diethyl-4,6-dimethoxy-2-(1-hydroxy-but-3-enyl)benzamide (293)

\[
\begin{align*}
\text{OMe} & \quad \text{OMe} \\
\text{MeO} & \quad \text{MeO} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{MeO} & \quad \text{MeO} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

(294) \quad \rightarrow \quad (293)

A stock solution of allylmagnesium bromide was prepared as follows. Magnesium powder (2.0 g, 83.3 mmol) and a magnetic stirrer were placed into a 3-necked round bottom flask with a reflux condenser attached. The glassware was flame-dried under vacuum then flushed with nitrogen. Dry Et₂O (40 mL) was added along with a crystal of iodine. Allyl bromide (3.6 mL, 41.6 mmol) in dry Et₂O (10 mL) was then added via cannula dropwise to the centre of the solution. Assuming 100% conversion, the concentration of the Grignard solution was estimated to be 0.83 mol L⁻¹.

In a flame dried flask flushed with nitrogen, a vigorously stirred solution of \(N,N\)-diethyl-2-formyl-4,6-dimethoxybenzamide (294) (3.3 g, 12.0 mmol) in dry Et₂O (40 mL) was cooled to -40 °C. Allylmagnesium bromide (33.0 mL, 0.83 mol in Et₂O, 27.5 mmol) was added dropwise over 1 min to the centre of the solution. The mixture was allowed to warm slowly to room temperature over 12 h, then washed with brine (3 x 10 mL) and the organic layer dried over MgSO₄. Chromatography on flash silica gel (75% Et₂O : hexanes) afforded \(N,N\)-diethyl-4,6-dimethoxy-2-(1-hydroxy-but-3-enyl)benzamide (293) (3.49 g, 95%) as a colourless oil. IR (\(\text{CHCl}_3\)) 3251, 2975, 1606, 1455, 1434, 1351, 1318, 1287, 1220, 1152, 914, 735, 635 cm⁻¹; MS (E.I.) \(m/z\) 307 (M⁺, 8), 266 (24), 217 (20), 193 (100), 74 (8); \(^1\)H NMR (\(\text{CDCl}_3\)) \(\delta\) 1.01-1.07 (m, 3H, NCH₂CH₃), 1.19-1.26 (m, 3H, NCH₂CH₃), 2.27-2.68 (m, 2H, H²'), 3.11-3.20
(m, 2H, NCH\textsubscript{2}), 3.01 (s, 1H, OH), 3.38-3.71 (m, 2H, NCH\textsubscript{2}), 3.77 (s, 3H, OCH\textsubscript{3}), 3.84 (s, 3H, OCH\textsubscript{3}), 4.56-4.65 (m, 1H, H1'), 5.18-5.75 (m, 2H, H4'), 5.75-5.89 (m, 1H, H3'), 6.37-6.38 (m, 1H, H5), 6.64-6.67 (m, 1H, H3); \textsuperscript{13}C NMR # (CDCl\textsubscript{3}) \delta 12.6, 12.5 (NCH\textsubscript{2}CH\textsubscript{3}), 13.6, 13.5 (NCH\textsubscript{2}CH\textsubscript{3}), 38.8, 38.6 (C2'), 39.9 (NCH\textsubscript{2}), 42.9, 43.3 (NCH\textsubscript{2}), 55.4 (OCH\textsubscript{3}), 55.5 (OCH\textsubscript{3}), 70.1, 71.5 (C1'), 97.5, 97.6 (C5), 102.2, 102.6 (C3), 117.0, 117.1 (C1), 117.2, 118.3 (C4'), 134.8 (C3'), 143.1, 143.5 (C2), 156.1, 156.4 (C6), 160.0, 161.1 (C4), 167.9, 168.5 (C=O); HRMS for C\textsubscript{17}H\textsubscript{25}NO\textsubscript{4}: 307.1786 (calcd), 307.1786 (found).

#. Due to the presence of rotamers some carbon signals have more than one resonance.

5,7-Dimethoxy-3-hydroxy-(3H)-isobenzofuran-1-one (370)

To a stirred solution of N,N-diethyl-4,6-dimethoxy-2-formylbenzamide (294) (125 mg, 0.47 mmol) in glacial acetic acid (5 mL) was added aqueous solution of HCl (10%, 5 mL). The solution was heated at reflux under nitrogen for 6 h, then the solvent removed under reduced pressure. Chromatography on flash silica gel (50%, EtOAc : hexanes) afforded 5,7-dimethoxy-3-hydroxy-(3H)-isobenzofuran-1-one (370) (91 mg, 92%) as a colourless oil. The \textsuperscript{1}H NMR data compared favourably with the literature data.\textsuperscript{185}
Chapter 4.

Experimental

3-Acetoxy-5,7-dimethoxy-(3H)-isobenzofuran-1-one (369)

\[ \text{(370)} \quad \rightarrow \quad \text{(369)} \]

To a stirred solution of 3-hydroxy-5,7-dimethoxy-(3H)-isobenzofuran-1-one (370) (82 mg, 0.39 mmol) in CH₂Cl₂ (10 mL) was added Et₃N (120 mg, 117.0 mmol), Ac₂O (80 mg, 78.0 mmol) and 4-(dimethylamino)pyridine (5.0 mg). The mixture was stirred for 2 h at room temperature, then quenched with water (2 mL), extracted with CH₂Cl₂ (2 × 5 mL) and dried over MgSO₄. Removal of the solvent under reduced pressure gave a pale pink solid which was purified by chromatography on flash silica gel (50%, EtOAc : hexanes) to afford 3-acetoxy-5,7-dimethoxy-(3H)-isobenzofuran-1-one (369) (90 mg, 92%) as a white solid mp, 153-154 °C. IR (CH₂Cl₂) 1777, 1749, 1623, 1606, 1364, 1346, 1221, 1202, 1160, 959 cm⁻¹; MS (E.I.) m/z 252 (M⁺, 47), 209 (34), 193 (100), 164 (82), 135 (18), 43 (46); ¹H NMR (CDCl₃) δ 2.19 (s, 3H, COCH₃), 3.93 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 6.54 (d, 1H, J=1.8 Hz, H6), 6.60 (d, 1H, J=1.8 Hz, H4), 7.26 (s, 1H, H3); ¹³C NMR (CDCl₃) δ 20.8 (COCH₃), 56.1 (OCH₃), 56.2 (OCH₃), 91.5 (C3), 99.4 (C6), 100.7 (C4), 106.5 (C7a), 149.0 (C7), 159.5 (C5), 165.6 (C3a), 167.4 (C=O), 169.5 (COCH₃); HRMS for C₁₂H₁₂O₆: 252.0634 (calcd), 252.0636 (found).
5,7-Dimethoxy-3-(2'-propenyl)-(3H)-isobenzofuran-1-one (292)

To a stirred solution of \(N,N\)-diethyl-4,6-dimethoxy-2-(1-hydroxy-but-3-enyl)benzamide (293) (3.5 g, 11.3 mmol) in glacial acetic acid (25 mL) was added aqueous HCl (10%, 25 mL). The solution was heated at reflux under nitrogen for 6 h, then the solvent was removed under reduced pressure. Chromatography on flash silica gel (50% EtOAc : hexanes) afforded 5,7-dimethoxy-3-(2'-propenyl)-(3H)-isobenzofuran-1-one (292) (2.4 g, 92%) as a colourless oil. IR (CH\(_2\)Cl\(_2\)) 1749, 1614, 1463, 1433, 1333, 1219, 1159, 1035, 838 cm\(^{-1}\); MS (E.I.) \(m/z\) 234 (M\(^+\), 6), 193 (100), 165 (8); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.54-2.71 (m, 2H, H1'), 3.89 (s, 3H, OCH\(_3\)), 3.94 (s, 3H, OCH\(_3\)), 5.12-5.36 (m, 3H, H3'a, H3'b), 5.71-5.77 (m, 1H, H2'), 6.42 (d, 1H, \(J=1.7\) Hz, H6), 6.45 (d, 1H, \(J=1.7\) Hz, H4); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 38.7 (C1'), 55.8 (OCH\(_3\)), 55.9 (OCH\(_3\)), 78.8 (C3), 97.7 (C6), 98.7 (C4), 106.9 (C7a), 119.4 (C3'), 131.3 (C2'), 154.3 (C3a), 159.6 (C7), 166.6 (C5), 168.2 (C=O); HRMS for \(C_{13}H_{14}O_4\): 234.0892 (calcd), 234.0892 (found).
5,7-Dimethoxy-3-(3'-hydroxypropyl)-(3H)-isobenzofuran-1-one (291)

![Chemical Structure]

To a solution of 5,7-dimethoxy-3-(2'-propenyl)-(3H)-isobenzofuran-1-one (292) (1.3 g, 5.6 mmol) in dry THF (25 mL) under nitrogen at 0 °C was added BH₃·SMe₂ (13.9 mL, 2.0 mol L⁻¹, 27.8 mmol). The solution was allowed to stir at 0 °C for 5 h, then aqueous NaOH (3 mol L⁻¹, 5 mL) was added followed by H₂O₂ (35% w/w solution in water, 10 mL) and the mixture was stirred at 0 °C for a further 30 min. K₂CO₃ (150 mg) was added and the solvent was removed under reduced pressure. The residue was extracted with CH₂Cl₂ (3 x 15 mL), washed with brine (10 mL) and dried over MgSO₄. Chromatography on flash silica gel (75%, EtOAc : hexanes) afforded 5,7-dimethoxy-3-(3'-hydroxypropyl)-(3H)-isobenzofuran-1-one (291) (0.83 g, 60%) as a white solid mp, 118-120 °C. IR (CH₂Cl₂) 3456, 1781, 1606, 1465, 1434, 1369, 1278, 1216, 1054, 1089, 1059, 735 cm⁻¹; MS (E.I.) m/z 252 (M⁺, 37), 207 (30), 193 (100), 165 (18); ¹H NMR (CDCl₃) δ 1.69-1.82 (m, 3H, H₁'a, H₂'), 2.17-2.18 (m, 1H, H₁'b), 2.47 (s, 1H OH), 3.68-3.75 (m, 2H, H₃'), 3.89 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃), 5.35 (dd, 1H, J=3.7 and 7.3 Hz, H₃), 6.42 (d, 1H, J=1.6 Hz, H₆), 6.44 (d, 1H, J=1.6 Hz, H₄); ¹³C NMR (CDCl₃) δ 27.8 (C₂'), 31.2 (C₁'), 55.9 (OCH₃), 55.9 (OCH₃), 62.1 (C₃'), 79.7 (C₃), 97.4 (C₆), 98.8 (C₄), 106.8 (C₇a), 154.9 (C₃a), 159.6 (C₇), 166.8 (C₅), 168.4 (C=O); HRMS for C₁₃H₁₆O₅: 252.0998 (calcd), 252.0994 (found).
3-(3'-Bromopropyl)-5,7-dimethoxy-(3H)-isobenzofuran-1-one (530)

To a solution of 5,7-dimethoxy-3-(3'-hydroxypropyl)-(3H)-isobenzofuran-1-one (291) (167 mg, 0.662 mmol) in CH$_2$Cl$_2$ (20 mL) was added p-toluenesulfonyl chloride (250 mg, 1.32 mmol), Et$_3$N (0.28 mL, 1.99 mmol) and 4-(dimethylamino)pyridine (100 mg, 0.666 mmol). The solution was stirred for 12 h at room temperature, then washed with water (5 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure and the crude tosylate (0.27 g) was dissolved in acetone (30 mL). Lithium bromide (345 mg, 3.97 mmol) was added and the mixture was heated at reflux under nitrogen for 5 h. The solvent was removed under reduced pressure and the residue dissolved in CH$_2$Cl$_2$ (15 mL), washed with water (3 × 10 mL) and dried over MgSO$_4$. Chromatography on flash silica gel (75%, EtOAc : benzene) afforded 3-(3'-bromopropyl)-5,7-dimethoxy-(3H)-isobenzofuran-1-one (530) (0.14 g, 66%) as a colourless oil. IR (CH$_2$Cl$_2$) 2940, 1745, 1611, 1494, 1460, 1340, 1221, 1159, 1059, 1028, 834, 735, 691 cm$^{-1}$; MS (E.I.) m/z 316/314 (M$^+$, 5), 270/268 (5), 193 (100), 165 (15); $^1$H NMR (CDCl$_3$) δ 1.84-2.23 (m, 4H, H1', H2'), 3.42-3.48 (m, 2H, H3'), 3.91 (s, 3H, OCH$_3$), 3.94 (s, 3H, OCH$_3$), 5.31-5.36 (m, 1H, H3), 6.44 (s, br, 1H, H6), 6.47 (s, br, 1H, H4); $^{13}$C NMR (CDCl$_3$) δ 27.5 (C2'), 32.8 (C3'), 32.9 (C1'), 55.7 (OCH$_3$), 55.8 (OCH$_3$), 78.6 (C3), 97.3 (C6), 98.6 (C4), 106.8 (C7a), 154.2 (C3a), 159.4 (C7), 166.7 (C5), 168.1 (C=O); HRMS for C$_{13}$H$_{15}$BrO$_4$: 314.0154 (calcd), 314.0149 (found), C$_{13}$H$_{15}^{81}$BrO$_4$: 316.0133 (calcd), 316.0144 (found).
5,7-Dimethoxy-3-(3'-oxopropyl)-(3H)-isobenzofuran-1-one (288)

To a solution of 5,7-dimethoxy-3-(3'-hydroxypropyl)-(3H)-isobenzofuran-1-one (291) (830 mg, 3.29 mmol) in CH₂Cl₂ (30 mL) was added tetrapropylammonium perruthenate (57 mg, 0.16 mmol), NMO (580 mg, 4.94 mmol), and 4 O molecular sieves (1.6 g, 500 mg/mmol compound). The mixture was stirred at room temperature for 2 h then poured through a short pad of silica, washed with water (2 × 10 mL) and dried over MgSO₄. Chromatography on flash silica gel (75%, EtOAc : hexanes) afforded 5,7-dimethoxy-3-(3'-oxopropyl)-(3H)-isobenzofuran-1-one (288) (0.52 g, 64%) as a colourless oil which was immediately stored under nitrogen. IR (CH₂Cl₂) 2932, 1759, 1601, 1496, 1462, 1428, 1338, 1221, 1160, 1043, 985, 909, 830, 732, 691 cm⁻¹; MS (E.I.) m/z 250 (M⁺, 33), 206 (62), 193 (100), 176 (20), 165 (23), 135 (22); ¹H NMR (CDCl₃) δ 2.43-2.74 (m, 4H, H₁'–H₂'), 3.90 (s, 3H, OCH₃), 3.94 (s, 3H, OCH₃), 5.36 (dd, 1H, J=3.2 and 8.3 Hz, H₃), 6.44 (d, 1H, J=0.6 Hz, H₆), 6.47 (d, 1H, J=0.6 Hz, H₄), 9.81 (s, br, 1H, CHO); ¹³C NMR (CDCl₃) δ 26.8 (C₁'), 38.7 (C₂'), 55.8 (OCH₃), 55.8 (OCH₃), 78.3 (C₃), 97.4 (C₆), 98.9 (C₄), 106.5 (C₇a), 154.1 (C₃a), 159.5 (C₇), 166.8 (C₅), 167.9 (C=O), 200.6 (CHO); HRMS for C₁₃H₁₄O₅: 250.0841 (calcd), 250.0839 (found).
5,7-Dimethoxy-3-(3'-hydroxytetradec-13'-enyl)-(3H)-isobenzofuran-1-one (464)

A stock solution of undec-1-en-11-ylmagnesium bromide was prepared as follows. Magnesium powder (0.4 g, 16.7 mmol) and a magnetic stirrer were placed into a 3-necked round bottom flask with a reflux condenser attached. The glassware was flame-dried under vacuum and flushed with nitrogen. Dry Et₂O (8.0 mL) and a crystal of iodine were added. 11-Bromoundec-1-ene (1.8 mL, 8.33 mmol) in dry Et₂O ether (2.0 mL) was then added via cannula dropwise to the centre of the solution. Assuming 100% conversion, the concentration of the Grignard was estimated to be 0.83 mol L⁻¹.

In a flame-dried flask flushed with nitrogen, a vigorously stirred solution of 5,7-dimethoxy-3-(3'-oxopropyl)-(3H)-isobenzofuran-1-one (288) (0.13 g, 0.52 mmol) in dry Et₂O (10 mL) was cooled to -40 °C. Undec-1-en-11-ylmagnesium bromide (1.0 mL, 0.83 mol L⁻¹ in Et₂O, 0.78 mmol) was added dropwise over 1 min to the centre of the solution. The mixture was allowed to warm to room temperature over 12 h, then washed with brine (3 × 10 mL) and the organic layer was dried over MgSO₄. Chromatography on flash silica gel (75%, EtOAc : hexanes) afforded 5,7-dimethoxy-3-(3'-hydroxytetradec-13'-enyl)-(3H)-isobenzofuran-1-one (464) (0.06 g, 29%) as a colourless greasy oil. IR (CH₂Cl₂) 3454, 2926, 1745, 1613, 1463, 1433, 1338, 1219,
1159, 1056, 909, 837, cm⁻¹; MS (E.I.) m/z 404 (M⁺, 15), 386 (16), 206 (100), 193 (83); ¹H NMR (CDCl₃) δ 1.27-1.73 (m, br, 20H, H2', H4', H5', H6', H7', H8', H9', H10', H11', H12'), 2.00-2.05 (m, 2H, H1'), 3.61-3.66 (m, 1H, H3'), 3.88 (s, 3H, OCH₃), 3.95 (s, 3H, OCH₃), 4.91-5.02 (m, 2H, H14'a, H14'b), 5.29-5.39 (m, 1H, H3), 5.75-5.87 (m, 1H, H13'), 6.42 (s, br, 1H, H6), 6.43 (s, br, 1H, H4); ¹³C NMR (CDCl₃) δ 25.6 (C5'), 28.2 (C11'), 28.9 (C7'), 29.1 (C8'), 29.4 (C9'), 29.5 (C10'), 30.6 (C6'), 31.5, 31.7 (C1'), 32.8 (C2'), 33.8 (C12'), 37.7, 37.8 (C4'), 55.8 (OCH₃), 55.9 (OCH₃), 71.2, 71.7 (C3'), 79.5, 80.2 (C3), 97.4, (C6), 98.8 (C4), 106.9 (C7a), 114.1 (C14'), 139.2 (C13'), 155.1 (C3a), 159.6 (C7), 166.8 (C5), 168.4 (C=O); HRMS for C₂₄H₃₆O₅: 404.2563 (calcd), 404.2557 (found).

**Triphenyl(undec-10-en-1-yl)phosphonium bromide (468)**

\[ \text{Br} \quad \begin{array}{c} \text{Ph} \quad \text{P} \\ \text{Br} \end{array} \quad \begin{array}{c} \text{Br} \quad \text{Ph} \quad \text{P} \quad \text{Br} \\ \text{Br} \quad \text{Ph} \quad \text{P} \quad \text{Br} \end{array} \]

To a solution of 11-bromoundec-1-ene (290) (3 g, 2.8 mL, 12.9 mmol) in dry benzene (20.0 mL) was added triphenylphosphine (3.2 g, 12.3 mmol). The solution was heated at reflux for 24 h under an atmosphere of nitrogen. The solvent was removed under reduced pressure leaving a cloudy thick oil which was triturated with dry Et₂O (2 × 5 mL) then pumped on the high vacuum to afford triphenyl(undec-10-en-1-yl)phosphonium bromide (468) (6.15 g, 96%) as a thick colourless oil. The ³¹P NMR data compared favourably with the literature data: ³¹P δ 24.2 ppm (Lit ²²¹ ³¹P δ 24.3).²²¹
5,7-Dimethoxy-3-(tetradec-3',13'-dienyl)-(3H)-isobenzofuran-1-one (466)

In a flame-dried flask equipped with a reflux condenser and flushed with nitrogen, a vigorously stirred solution of triphenyl(undec-10-en-1-yl)phosphonium bromide (0.37 g, 0.74 mmol) in dry THF (10 mL) was cooled to -78 °C. n-BuLi (0.58 mL, 1.60 mol L⁻¹ in hexanes, 0.93 mmol) was added dropwise over 1 min to the centre of the solution. The resulting deep orange/red solution was left for 25 min then transferred via cannula to a solution of 5,7-dimethoxy-3-(3'-oxopropyl)-(3H)-isobenzofuran-1-one (288) (0.16 g, 0.64 mmol) in dry THF (7.0 mL) at -78 °C. The solution was left for 20 min, allowed to warm to room temperature, then heated to reflux under nitrogen for 1 h. The solvent was removed under reduced pressure, the residue dissolved into CH₂Cl₂ (10 mL), washed with brine (3 × 10 mL) and dried over MgSO₄. Chromatography on flash silica gel (33% EtOAc : hexanes) afforded 5,7-dimethoxy-3-(tetradec-3',13'-dienyl)-(3H)-isobenzofuran-1-one (466) (0.25 g, 68%) as a greasy colourless oil. IR (CH₂Cl₂) 2926, 2853, 1759, 1614, 1463, 1433, 1338, 1217, 1158, 1056, 1029, 910, 837, 732 cm⁻¹; MS (E.I.) m/z 386 (M⁺, 23), 261 (25), 247 (24), 208 (100), 193 (50); ¹H NMR (CDCl₃) δ (unresolved E/Z mixture) 1.25-1.42 (m, br, 12H, H6', H7', H8', H9', H10', H11'), 1.95-2.12 (m, 6H, H2', H5', H12'), 2.23-2.33 (m, 2H, H1'), 3.89 (s, 3H, OCH₃), 3.94 (s, 3H, OCH₃), 4.90-5.01 (m, 2H, H14'a, H14'b),
5.27-5.48 (m, 3H, H3, H3', H4'), 5.73-5.87 (m, 1H, H13'), 6.42 (s, br, 1H, H6), 6.42 (s, br, 1H, H4); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 22.5 (C2'), 27.0 (C5'), 28.7 (C11'), 28.9 (C6'), 29.1 (C10'), 29.3 (C9'), 29.3 (C8'), 29.4 (C7'), 33.6 (C12'), 34.8 (C1'), 55.7 (OCH\(_3\)), 55.8 (OCH\(_3\)), 79.1 (C3), 97.3 (C6), 98.5 (C4), 106.7 (C7a), 113.9 (C14'), 127.4 (C3'), 131.6 (C4'), 139.0 (C13'), 154.9 (C3a), 159.4 (C7), 166.6 (C5), 168.2 (C=O); HRMS for C\(_{24}\)H\(_{34}\)O\(_4\): 386.2457 (calcd), 386.2451 (found).

5,7-Dimethoxy-3-(13'-oxotetradec-3'-enyl)-(3H)-isobenzofuran-1-one (467)

![Diagram](466) \(\rightarrow\) ![Diagram](467)

To a solution of 5,7-dimethoxy-3-(tetradec-3',13'-diienyl)-(3H)-isobenzofuran-1-one (466) (68 mg, 0.18 mmol) in DMF : H\(_2\)O (4 : 0.5 mL) was added PdCl\(_2\) (12 mg, 0.07 mmol) and copper (I) chloride (20 mg, 0.19 mmol). The solution was stirred under an atmosphere of oxygen at room temperature until tlc analysis indicated that all of the starting material had been consumed. The solvent was removed under reduced pressure, and the residue was dissolved into CH\(_2\)Cl\(_2\) (10 mL), washed with brine (2 x 3 mL) and dried over MgSO\(_4\). Chromatography on flash silica gel (50%, EtOAc : hexanes) afforded 5,7-dimethoxy-3-(13'-oxotetradec-3'-enyl)-(3H)-isobenzofuran-1-one (467) (0.044 g, 63%) as a colourless greasy oil. IR (CH\(_2\)Cl\(_2\)) 2926, 2853, 1756, 1712, 1613, 1464, 1432, 1338, 1217, 1158, 1054, 1028, 837, 690
Chapter 4.

Experimental

cm\(^{-1}\); MS (E.I.) \(m/z\) 402 (M\(^+\), 25), 384 (18), 345 (14), 208 (100), 207 (88), 194 (75), 193 (72), 43 (46); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) (unresolved \(E/Z\) mixture) 1.27-1.79 (m, br, 12H, H6', H7', H8', H9', H10', H11'), 1.96-2.06 (m, 6H, H1', H2', H5'), 2.13 (s, 3H, H14'), 2.41 (t, 2H, \(J=7.4\) Hz, H12'), 3.89 (s, 3H, OCH\(_3\)), 3.94 (s, 3H, OCH\(_3\)), 5.29 (dd, 1H, \(J=3.1\) and 8.4 Hz, H3), 5.33-5.48 (m, 2H, H3', H4'), 6.41 (s, br, 1H, H6), 6.42 (s, br, 1H, H4'); \(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) 22.6 (C2'), 23.7 (C11'), 27.1 (C5'), 29.0 (C10'), 29.1 (C9'), 29.2 (C8'), 29.5 (C6'), 29.6 (C7'), 29.7 (C14'), 34.9 (C1'), 43.7 (C12'), 55.8 (OCH\(_3\)), 55.9 (OCH\(_3\)), 79.2 (C3), 97.3 (C6), 98.6 (C4), 106.8 (C7a), 127.5 (C3'), 131.6 (C4'), 154.9 (C3a), 159.5 (C7), 166.6 (C5), 168.3 (C=O, lactone), 209.2 (C=O, ketone); HRMS for C\(_{24}H_{34}O_5\): 402.2406 (calcd), 402.2403 (found).

5,7-Dimethoxy-3-(13'D-oxotetradecyl)-(3H)-isobenzofuran-1-one (62)

![Diagram](image)

To a solution of 5,7-dimethoxy-3-(13'-oxotetradec-3'-enyl)-(3H)-isobenzofuran-1-one (467) (20 mg, 0.05 mmol) in EtOAc (5 mL) was added 10% palladium on carbon (5.0 mg, 0.009 mmol). The solution was stirred under an atmosphere of hydrogen for 1 h at room temperature, then filtered through a short pad of Celite. The solvent was removed from the filtrate under reduced pressure, and the residue was dissolved into CH\(_2\)Cl\(_2\) (10 mL), washed with brine (2 × 3 mL) and dried over MgSO\(_4\). Chromatography on flash silica gel (50%, EtOAc : hexanes) afforded 5,7-dimethoxy-3-(13'-oxotetradecyl)-(3H)-isobenzofuran-1-one (62) (0.022 g, 99%) as a colourless
greasy oil. IR (CH$_2$Cl$_2$) 2915, 1758, 1701, 1660, 1469, 1336, 1221, 1162, 1053, 1026, 837 cm$^{-1}$; MS (E.I.) $m/z$ 404 (M$^+$, 32), 347 (65), 207 (57), 193 (100), 43 (19); $^1$H NMR (CDCl$_3$) $\delta$ 1.26-1.70 (m, br, 20H, H2', H3', H4', H5', H6', H7', H8', H9', H10', H11'), 1.92-1.96 (m, 2H, H1'), 2.13 (s, 3H, H14'), 2.41 (t, 2H, J = 7.4 Hz, H12'), 3.89 (s, 3H, OCH$_3$), 3.94 (s, 3H, OCH$_3$), 5.29 (dd, 1H, J = 3.7 and 7.8 Hz, H3), 6.40 (s, br, 1H, H6), 6.41 (s, br, 1H, H4); $^{13}$C NMR (CDCl$_3$) $\delta$ 23.8 (C11'), 24.6 (C2'), 29.1 (C10'), 29.3 (C9'), 29.4 (C8'), 29.4 (C7'), 29.4 (C6'), 29.5 (C5'), 29.7 (C4'), 29.8 (C14'), 29.9 (C3'), 34.8 (C1'), 43.8 (C12'), 55.9 (OCH$_3$), 55.9 (OCH$_3$), 79.9 (C3), 97.4 (C6), 98.6 (C4), 106.8 (C7a), 155.2 (C3a), 159.6 (C7), 166.6 (C5), 168.5 (C=O, lactone), 209.4 (C=O, ketone); HRMS for C$_{24}$H$_{36}$O$_5$: 404.2563 (calcd), 404.2559 (found).


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Chapter 5.

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Chapter 5.

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