INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

UMI®
The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author’s permission.

L’auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

L’auteur conserve la propriété du droit d’auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-48124-7
TABLE OF CONTENTS

Acknowledgements  
List of Figures  
List of Schemes  
List of Tables  
Abbreviations and symbols  
Abstract

Part A: The Syntheses of Dillapiol and its 4 - Thio Derivatives

Chapter 1
Introduction

1.1 Pesticide chemistry  
1.2 Pesticides synergists  
1.3 Sources of dillapiol

1.3.1 Natural sources

1.3.1.1 Anethum graveolens (Apiaceae)  
1.3.1.2 Piper aduncum (Piperaceae)

1.3.2 Synthetic sources

1.3.2.1 Baker's synthesis  
1.3.2.2 Dallacker's synthesis  
1.3.2.3 Cannon's synthesis
Results and Discussion

Chapter 2

A new synthesis of dillapiol and its 4-thio derivatives

2.1 Introduction

2.2 A new synthesis of dillapiol 7

2.3 Attempted synthesis of dillapiol 7 via alternate routes

2.3.1 Aromatic formylation

2.3.1.1 Ortho formylation of aromatic ring via Vilsmeier-Haack Reaction conditions

2.3.1.2 Ortho formylation via Casiraghi Reaction conditions

2.3.2 Aromatic hydroxylation

2.3.2.1 Enzymatic ortho hydroxylation via the use of tyrosinases

2.3.2.2 Copper catalyzed ortho hydroxylation via the activation of molecular oxygen

2.4 Synthesis of dillapiol derivatives

2.5 Biological activity

2.5.1 Synergists

2.5.2 Drug sparing agents

2.6 An improved route to dillapiol
Experimental Procedures

Chapter 3

Experimental

<table>
<thead>
<tr>
<th>Part B: The Synthesis of Trichiliasterone B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 4</td>
</tr>
</tbody>
</table>

| The total synthesis of 3b - hydroxypregnan - 2, 16 - dione 96 | 89 |
| 4.1 Introduction                                              | 89 |
| 4.2 The synthesis of 3\(\beta\) - hydroxypregnan - 2, 16 - dione 96 | 93 |
| 4.3 Cytotoxicity of the steroid 104 and its derivatives       | 105 |
| 4.4 Experimental                                             | 109 |

References 120

Claims to original research 123
Acknowledgements

My sincere thanks go to my supervisor, Dr. Tony Durst, for giving me the opportunity to study in his laboratory and for his gentle guidance throughout my academic career. Although very busy he was extremely patient and understanding and always willing to help.

I thank Dr. John Armasan from the Department of Biology (University of Ottawa) for his lasting interest in this project and Mireille Marcotte and Jason Budzinski for carrying out the biological assays on my compounds.

I thank Dr. Sasmita Tripathy for completing the final steps in the synthesis of Trichilisterone B which otherwise did not seem possible and Biochem Pharma for carrying out the cytotoxicity experiments.

I thank Dr. Prabhott Arya at the National Research Council for allowing me to use the facility to write my thesis.

I thank R. Capoor and G. Facey for NMR services and C. Kazakoff for mass spectroscopy services.

I thank Susan Hantos, Dr. Jeffrey Manwell, Neil Squires, Richard LeBlanc, Dr. Angela Barkley, Michael Barnes and Dr. Venu Rao for their friendship and for sharing their knowledge of chemistry with me.

I thank my parents and my two brothers, Naeem and Nasir, for their love and support throughout my life and academic career.

Lastly, I thank my fiancé Salim for his continuous love throughout my difficult times. He believed in me even when I had doubted myself, providing endless support to me.
# List of Figures

## Chapter 1

| Figure 1.1 | Structures of selected synergists for insecticides | 3 |

## Chapter 2

| Figure 2.1 | IUPAC numbering system of dillapiol skeleton | 12 |
| Figure 2.2 | $^1$H NMR spectrum of 4-formyl-5-methoxymethoxy-1,3-benzodioxole (41) | 16 |
| Figure 2.3 | $^{13}$C NMR spectrum of 4-formyl-5-methoxymethoxy-1,3-benzodioxole (41) | 17 |
| Figure 2.4 | $^1$H NMR spectrum of dillapiol (7) | 21 |
| Figure 2.5 | $^{13}$C NMR spectrum of dillapiol (7) | 22 |
| Figure 2.6 | Derivatives of dillapiol previously synthesized in our laboratory | 31 |
| Figure 2.7 | $^1$H NMR spectrum of 5-methoxymethoxy-4-thiomethyl-1,3-benzodioxole (86a) | 33 |
| Figure 2.8 | $^{13}$C NMR spectrum of 5-methoxymethoxy-4-thiomethyl-1,3-benzodioxole (86a) | 34 |
| Figure 2.9 | $^1$H NMR spectrum of 5-hydroxy-6-(2-propenyl)-4-thiomethyl-1,3-benzodioxole (89a) | 37 |
| Figure 2.10 | $^{13}$C NMR spectrum of 5-hydroxy-6-(2-propenyl)-4-thiomethyl-1,3-benzodioxole (89a) | 38 |
| Figure 2.11 | $^1$H NMR spectrum of 5-methoxy-6-(2-propenyl)-4-thiomethyl-1,3-benzodioxole (90a) | 39 |
Figure 2.12 $^{13}$C NMR spectrum of 5-methoxy-6-(2-propenyl)-4-thiomethyl-1,3-benzodioxole (90a) 40

Figure 2.13 $^1$H NMR spectrum of 5-methoxy-4-methylsulfinyl-6-(2-propenyl)-1,3-benzodioxole (91a) 41

Figure 2.14 Preliminary Results of the Inhibition of CYP3A4 by the Thio Derivatives of Dillapiol. The IC50 Values are Obtained by Interpolating the Graphs at 50% Inhibition. 47

Chapter 4

Figure 4.1 The basic skeleton of tetranortriterpenoids 89

Figure 4.2 IUPAC numbering system of the steroid skeleton 90

Figure 4.3 Plant steroids with 16-keto functionality 91

Figure 4.4 $^1$H NMR spectrum of 3β-acetoxy-16-ethylenedioxypregnan-2-one (113) and 2α-acetoxy-16-ethylenedioxypregnan-3-one (117) 98

Figure 4.5 $^1$H NMR spectrum of 2α-hydroxy-16-ethylenedioxypregnan-3-one (118) 100

Figure 4.6 $^1$H NMR spectrum of 2α-hydroxypregnan-3,16-dione (119) 103

Figure 4.7 $^1$H NMR spectrum of 3β-hydroxypregnan-2,16-dione (96) 104
List of Schemes

Chapter 1

Scheme 1.1 Baker's Synthesis of Dillapiol 7
Scheme 1.2 Dallacker's Synthesis of Dillapiol 7
Scheme 1.3 Cannon's Synthesis of Dillapiol 7
Scheme 1.4 Majerus' Synthesis of Dillapiol 7

Chapter 2

Scheme 2.1 A Retrosynthetic Scheme for the Formation of Dillapiol 13
Scheme 2.2 Electrophilic Substitution of Dihydropyran on 31 14
Scheme 2.3 Preparation of 4-Formyl-5-Methoxymethoxy-1,3-
Benzodioxole 46 15
Scheme 2.4 The Directed Ortho Metallation Reaction (DoM) 15
Scheme 2.5 Mechanism of the Baeyer Villiger Oxidation 18
Scheme 2.6 Preparation of 5-Hydroxy-4-Methoxy-1,3-Benzodioxole 51 19
Scheme 2.7 Preparation of 5-Hydroxy-4-Methoxy-6-(2-propenyl)-1,3-
Benzodioxole 53 20
Scheme 2.8 Methylolation of 53 to afford Dillapiol 7 20
Scheme 2.9 1,2 Wittig Rearrangement of Ally Ether 32 to afford 55 23
Scheme 2.10 General Overview of Various Schematic Routes Attempted to
Synthesize Dillapiol 7 25
Scheme 2.11 Mechanism of Vilsmeier-Haack Reaction 26
Scheme 2.12  Mechanistic pathway for the Casiraghi Reaction

Scheme 2.13  Ortho Hydroxylation of Phenols via the Use of Molecular Oxygen by Tyrosinase

Scheme 2.14  Copper Catalyzed Ortho Hydroxylation of Phenols via the Activation of Molecular Oxygen

Scheme 2.15  The Synthesis of the Thio Derivatives 89a, 90a, 91a and 92a of Dillapiol

Scheme 2.16  Preparations of the Thio Derivatives 89b-d, 90b-d, 91b-d and 92b-d of Dillapiol

Scheme 2.17  A New Improved Route to Dillapiol

Scheme 2.18  Formation of 88a via Treatment of 32 with nBuLi

Chapter 4

Scheme 4.1  Proposed Route for the Synthesis of Trichiliasterone B

Scheme 4.2  The Synthesis of Trichiliasterone B via Different Route

Scheme 4.3  Thermal Rearrangement of Epoxy Acetate 114

Scheme 4.4  Rearrangement of Acetoxy Ketones on Basic Alumina

Scheme 4.5  Thermal Rearrangement of the Epoxy Acetate 112

Scheme 4.6  De-acetylation of the Crude Mixture of Steroids 113 and 117 to afford the Steroid 118

Scheme 4.7  Hydrolysis of the Ketal Group at C-16 from the Steroid 118

Scheme 4.8  Hydrolysis of the Ketal Group at C-16 Position in Steroids
113 and 117

Scheme 4.9  Hydrolysis of the Acetyl Moiety in Steroid 120 and 121  105
Scheme 4.10 Preparation of the Steroid 122  106

List of Tables

Chapter 2
Table 2.1 Synergism Factors of Dillapiol and its Derivatives on Mosquito Larvae  31
Table 2.2 Synthetic Thio Derivatives of Dillapiol  32
Table 2.3 Percentage Yield of Each of the Synthetic Intermediate and the Target Sulfide, Corresponding Sulfoxide and Sulfone  43
Table 2.4 Synergism Factors of the Thio Derivatives of Dillapiol Relative to Dillapiol  45

Chapter 4
Table 4.1 The Synthetic Ester Derivatives of the Steroid 104  107
Table 4.2 The IC_{50} Values, Expressed in Micro Molar Concentrations, of Compounds 104, 122, 123, 124 and 125 Against Different Cancer Cell Lines Obtained by Biochem Pharma  108
## Abbreviations and Symbols

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>aluminum chloride</td>
</tr>
<tr>
<td>Al₂O₃</td>
<td>aluminum oxide</td>
</tr>
<tr>
<td>nBuLi</td>
<td>n butyllithium</td>
</tr>
<tr>
<td>BPO</td>
<td>piperonyl butoxide</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu₃N</td>
<td>tri-n-butylamine</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>Calc.</td>
<td>calculated</td>
</tr>
<tr>
<td>CH₂Br₂</td>
<td>dibromomethane</td>
</tr>
<tr>
<td>CH₂ClBr</td>
<td>bromochloromethane</td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>methylene chloride</td>
</tr>
<tr>
<td>CHCl₃</td>
<td>chloroform</td>
</tr>
<tr>
<td>CH₃I</td>
<td>methyl iodide</td>
</tr>
<tr>
<td>CH₂I₂</td>
<td>diiodomethane</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wave number</td>
</tr>
<tr>
<td>^13C NMR</td>
<td>carbon-13 nuclear magnetic resonance</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>human cytochrome P450 enzyme</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>ddt</td>
<td>doublets of doublets of triplets</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMG</td>
<td>direct metallating group</td>
</tr>
<tr>
<td>DoM</td>
<td>directed ortho metallation</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalents</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HCl</td>
<td>hydrochloric acid</td>
</tr>
<tr>
<td>&quot;H NMR</td>
<td>proton nuclear magnetic resonance</td>
</tr>
<tr>
<td>H₂O</td>
<td>water</td>
</tr>
<tr>
<td>H₂O₂</td>
<td>hydrogen peroxide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution liquid chromatography</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IC₅₀</td>
<td>concentration to inhibit growth by 50%</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>K₂CO₃</td>
<td>potassium carbonate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Substance</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>KF</td>
<td>potassium fluoride</td>
</tr>
<tr>
<td>KOH</td>
<td>potassium hydroxide</td>
</tr>
<tr>
<td>LiCuMe2</td>
<td>lithium dimethylcuprate</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiN(TMS)$_2$</td>
<td>lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
<tr>
<td>MDP</td>
<td>methylenedioxyphenyl</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Me$_2$SO$_4$</td>
<td>magnesium sulfate</td>
</tr>
<tr>
<td>MeI</td>
<td>methyl iodide</td>
</tr>
<tr>
<td>mfo</td>
<td>mixed-function oxidase</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>ml</td>
<td>milliliter</td>
</tr>
<tr>
<td>mM</td>
<td>millimolar</td>
</tr>
<tr>
<td>mmol</td>
<td>millimoles</td>
</tr>
<tr>
<td>mol</td>
<td>moles</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>MOMCl</td>
<td>methoxymethyl chloride</td>
</tr>
<tr>
<td>MnO$_2$</td>
<td>manganese dioxide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>MP</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>low resolution mass spectroscopy</td>
</tr>
<tr>
<td>N</td>
<td>normal</td>
</tr>
<tr>
<td>Na₂CO₃</td>
<td>sodium carbonate</td>
</tr>
<tr>
<td>NaI</td>
<td>sodium iodide</td>
</tr>
<tr>
<td>NaOH</td>
<td>sodium hydroxide</td>
</tr>
<tr>
<td>NH₄Cl</td>
<td>ammonium chloride</td>
</tr>
<tr>
<td>POCl₃</td>
<td>phosphorus oxychloride</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>SeO₂</td>
<td>selenium oxide</td>
</tr>
<tr>
<td>SnCl₄</td>
<td>tin tetrachloride</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>α-T</td>
<td>alpha terthienyl</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-butylhydroperoxide</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tlc</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-toluenesulfonic acid</td>
</tr>
<tr>
<td>μM</td>
<td>micromolar</td>
</tr>
</tbody>
</table>
ABSTRACT

Part A

This thesis describes a new route for the synthesis of dillapiol, a natural synergist, starting with the commercially available sessamol. It has potential for significant scale-up reactions. A key step in our synthesis is the introduction of an oxygen substituent at the C-4 position via an ortho metallation –DMF sequence on suitably protected sessamol followed by a Baeyer Villiger oxidation. The new route allowed us to prepare the first 4-thio, 4-sulfinyl and 4-sulfonyl derivatives of dillapiol.

The 4-thio derivatives have been screened for their ability to synergize the light-activated pesticide, α-T. Some of the 4-thio derivatives were more active than dillapiol; the 4-sulfinyl and the 4-sulfonyl compounds showed lower synergism with α-T than dillapiol.

The ability of these compounds to act as drug sparing agents by inhibiting CYP3A4 has also been briefly investigated. In this case the 4-sulfonyl derivatives were found to be potent in inhibiting CYP3A4 with IC_{50} values in micro molar range.

\[ \text{Dillapiol} \quad \text{4-Thio derivative} \]

Part B

The synthesis of trichiliasterone B was completed starting from an androsterone intermediate (16-ethylenedioxy pregnan-3-one) prepared earlier by Hantos. It involved converting the 3-keto functionality of the Hantos intermediate into a 2-keto-3β-hydroxy
arrangement. This was accomplished via preparation and thermolysis of 3\(\beta\)-acetoxy-2\(\alpha\),3\(\alpha\)-epoxy-16-ethylenedioxy pregnane followed by treatment with basic alumina.

![Trichiliasterone B](image)

Four ester derivatives of 3\(\beta\)-hydroxy androst-17(20)-en-16-one were prepared and sent for screening as potential anti-cancer agents based on the concept that the \(\alpha,\beta\)-unsaturated ketone should act as a potential Michael acceptor. Promising activity was found towards \textit{in vitro} tests against the human leukemia cell line.

![Ester derivative](image)
Part A: The Syntheses of Dillapiol and its 4 - Thio Derivatives
Chapter 1

Introduction

1.1 Pesticide chemistry

Insecticide resistance is a dynamic, multidimensional phenomenon dependent on genetic, physiological, biochemical and ecological factors.\textsuperscript{1} All these vary with species, population and geographic location. Resistant strains develop through the survival and reproduction of individuals carrying a genome altered by one or more of many possible mechanisms that allow survival after the exposure to an insecticide.\textsuperscript{1}

Insects have developed resistance to all major classes of insecticides such as DDT, cyanide, lindane, organophosphate, carbamates and pyrethroids. This is not surprising when viewed in ecological and evolutionary perspectives. Herbivorous insects have coexisted with higher plants for 250-million years.\textsuperscript{1} Plants produce many allelochemicals, such as alkaloids, terpenes and phenols, for defense against insects and pathogens. These chemicals are often appreciably toxic and have favored the evolution of counter adaptations, modified physiological processes and biochemical mechanisms. Insects often rely on complex defensive enzymes to overcome the potential toxicity of the plants they eat and thus adapt to the toxic allelochemicals.\textsuperscript{1}

Insecticide resistance is predominantly associated with an improved capacity to metabolically detoxify insecticides as well as decreased sensitivity due to modification in target sites.\textsuperscript{1} Lipophilic insecticides are primarily detoxified by microsomal oxidases, in particular cytochrome P-450, carboxyesterases (E.C 3.1.1.1 and E.C 3.1.1.2) and
glutathione transferases (E.C 2.5.1.18). They convert lipophilic foreign compounds to polar metabolites that can be excreted. In contrast to the slow evolution of resistance towards natural insecticides, resistance to synthetic insecticides has developed much more rapidly, perhaps because of the intense selection pressure created by highly toxic synthetics. One strategy for managing resistance or slowing it down is the use of pesticide synergists.

1.2 Pesticides synergists

Pesticides synergists are compounds that are either non-toxic or of negligible toxicity. They enhance the toxicity of a pesticide when combined with it. The development of synergists for the use in pest control stems from the premise that the individual chemicals or combinations can be found to be selective and preferentially control pests without harm to man and useful species.

The methylenedioxyphenyl (MDP) compounds, such as sesamolin 1, sesamin 2, piperonal butoxide 3, safrole 4, sulfoxide 6 and dillapiol 7, are the most important synergists from the stand point of historical development and current use. Synergistic activity with the insecticide chemicals is not restricted to MDP compounds because other materials are sometimes as, or even more active. Other groups of synergists include: N-alkyl compounds, such as SKF 525A and MGK 264, O- (2-propynyl) ethers and esters, such as RO 5-8019 and naphthyl propynl ether as shown in Figure 1.1.

Sesame oil was one of the first MDP compounds used as a synergist commercially. It is active because it contains sesamin and more potent sesamolin. The planar MDP group appears to bind preferentially to the heme of cytochrome P-450 in the mixed-function oxidase (mfo), forming relatively stable adducts. Thus, they act as inhibitors by serving as an
alternate substrate for the mfo system, sparing the insecticide chemical from detoxification.\textsuperscript{2,3,4}

\textbf{Methylenedioxyphenyl Compounds}

\textbf{a) Natural}

1. 

2. 

3. 

4. 

5. 

6. 

7. 

\textbf{b) Synthetic}

8. 

9. 

10. 

11. 

\textbf{N-Alkyl Compounds}

\textbf{O-(2-Propynyl) Ethers and Esters}

\textbf{Figure 1.1: Structures of selected synergists for insecticides}

Reference: Casida, J.E., 1970
Currently most widely used synthetic synergists such as piperonyl butoxide 3 and the sulfoxide 6 are prepared from the natural product safrole. N-Alkyl and O-(2-propynyl) ethers and esters compounds (Figure 1.1) are also inhibitors of microsomal oxidation in the similar manner as MDP compounds.\textsuperscript{5,6}

Piperonyl butoxide 3, a commonly used pyrethrum synergist, presently dominates the market but is under toxicological review and may be deregistered.\textsuperscript{3} Dillapiol 7, a major constituent (35%) of Indian dill \textit{(Anethum Sowa} Roxb.) seed oil was also found to have synergistic action \textsuperscript{1,7,8} and is potentially a safe alternative to piperonyl butoxide. Dillapiol offers several advantages over piperonyl butoxide, the most significant being its natural origin in food plants thereby suggesting non-toxicity to humans and other mammals. The synergistic activity of dillapiol towards insecticides has been shown in many instance to surpass that of piperonyl butoxide.\textsuperscript{3} Several new derivatives of dillapiol have shown good synergism of pyrethrum against flour beetles \textit{(Tribolium castaneum} Herbst.). \textsuperscript{7,8} Dillapiol, being a natural compound, is also limited in supply and it would be desirable to enhance its value by preparing more potent derivatives from it. With such an objective in mind, the synthesis of a number of derivatives of it has been investigated.

1.3 Sources of dillapiol

1.3.1 Natural sources

1.3.1.1 \textit{Anethum graveolens} (Apiaceae)

Dill, \textit{Anethum graveolens}, is a common yellow-flowered annual herb, from the same family as carrot or other aromatic herbs such as corriander, fennel or parsley.\textsuperscript{9} Its popularity is due to culinary and medicinal properties mainly of its seeds, from which oil is extracted. The
main constitute in dill seed oil in all *Anethum graveolens* sub species is carvone. Carvone, is the main odorant component of dill seeds\textsuperscript{10} and is well known for its anticarcinogenic\textsuperscript{9} and toxic properties.\textsuperscript{11} Other important constituents are phenolic compounds such as apiol and myristicin, an important odorant component of dill herb\textsuperscript{10} and insecticidal synergist.\textsuperscript{11} Dillapiol, an isomer of apiol, is known to co-occur in various dill subspecies out not in all. It is in highest amount in Indian dill, *Anethum Sowa* Roxb\textsuperscript{7,12,13} in about 27-35%. Majerus investigated the content of dillapiol in *Anethum Sowa* Roxb. and showed that the oil was mainly composed of carvone and dillapiol in a 7:1 ratio and the yield of dillapiol was 2%.\textsuperscript{3} Apiol and dillapiol being isomers were difficult to separate by distillation or chromatography. In contrast she also found that Canadian dill seed showed no trace of dillapiol.

![Chemical structures of Carvone, Apiol, and Dillapiol](image)

1.3.1.2 *Piper aduncum* (Piperaceae)

*Piper aduncum* is a tropical shrub coming from the family of Piperaceae.\textsuperscript{9} Humans have used *Piper aduncum* for various medicinal purposes such as a tonic, a diuretic, a digestive stimulant and homeostatic agents. *Piper aduncum* from different areas of the world was found to contain dillapiol as main constituent: the essential oil of piper plants from Fiji contained 58\% dillapiol \textsuperscript{14}; two varieties from Brazil were found to contain dillapiol in 74.5\%
and 88.4% and a variety from Panama contained 90% dillapiol. In 1994, fruits, leaves and wood chips/sawdust from *Piper aduncum* plant were collected from Costa Rica and later steam distilled by members of our research group. The seeds of the fruits contained 0.3% of dillapiol, a smaller amount (0.03%) in wood chips/sawdust and only a trace in leaves. The major advantage of *Piper aduncum* as a source of dillapiol is that the product of steam distillation is dillapiol of >95% purity and no apiol was found in the *Piper aduncum* extracts. The most recent study was a general evaluation of the chemistry of *Piper aduncum* found in Costa Rica. Essential oils in leaves of *Piper aduncum* were examined in two Costa Rican locations by the gas-chromatography / mass spectrometry method. The result showed the occurrence of fifty-three compounds among which dillapiol is in 32.9% in one population and 61.5% in other, hence *Piper aduncum* is a significant natural source of dillapiol.

1.3.2 Synthetic sources

Four syntheses of dillapiol have been reported. Despite the simplicity of this molecule which contains no chiral centers or unstable functional groups, all of these syntheses suffer from either low overall yield or reaction conditions which are not amenable to large scale synthesis. Thus a viable synthetic route to dillapiol would be valuable. Also, a new route may make the synthesis of potentially new, more potent analogs more efficient.

1.3.2.1 Baker’s synthesis

Baker et al were the first to synthesize dillapiol in 1934. Their synthesis consists of 5-steps, starting from gallacetophenone 14, which is now commercially available.
Gallacetophenone was treated with dimethyl sulfate and potassium carbonate to give the o-hydroxy acetophenone 15 in 50% yield. Oxidation of this acetyl function of 15 under Dakin Reaction conditions afforded 16 in 59% yield. The Dakin Reaction involves the initial attack of peroxide anion on the carbonyl carbon. Formation of an ester intermediate via phenyl migration is then followed by hydrolysis to give the desired catechol. Treatment of 16 with allyl bromide and potassium carbonate yielded monoallyl ether 17, which underwent Claisen rearrangement on heating to give 18 in 27% yield. The structure of 18 was based on the knowledge that the migration of allyl group yields either ortho or para hydroxyallyl benzenes.16,19 Methylenation of 18 yielded dillapiol 7 in 24% yield. The overall yield of dillapiol via this synthesis is 2%, which limits its usefulness in large-scale synthesis.

Reagents: (a) Me₂SO₄, K₂CO₃; (b) NaOH, 30% H₂O₂; (c) allyl bromide, K₂CO₃; (d) heat; (e) CH₂Cl₂, K₂CO₃

Scheme 1.1- Baker's Synthesis of Dillapiol 7
1.3.2.2 Dallacker's synthesis

Dallacker synthesis was developed in 1969. It started with the tri-substituted benzene, 2-hydroxy-3-methoxy-benzaldehyde (o-vanillin) 19, which was converted to 20 via Dakin oxidation. Compound 20 was treated with bromochloromethane under basic condition to give 21 in 56% yield. Formylation of 21 under Vilsmeir-Haack Reaction conditions afforded 22 in 44% yield. Oxidation of 22 under Dakin oxidation conditions gave phenol 23 in 64% yield. Compound 23 was treated with allyl bromide and potassium carbonate to give allyl ether 24, followed by Claisen rearrangement which afforded 25 in 72%. Treatment of 25 with dimethyl sulfate and potassium carbonate resulted in dillapiol 7. The overall yield of dillapiol via this sequence is 10%.

The Dallacker's synthesis is 2-steps longer than Baker's synthesis and despite this, it

Reagents: (a) NaOH, 30% H₂O₂; (b) CH₂ClBr, Na₂CO₃; (c) POCl₃, DMF; (d) allyl bromide, K₂CO₃; (e) 190°C; (f) Me₂SO₄, K₂CO₃

Scheme 1.2 - Dallacker's Synthesis of Dillapiol 7
gave higher yield than Baker's. Both the formations of methylenedioxy ring and Vilsmeir-Haack Reaction occur in relatively low yield.

1.3.2.3 Cannon's synthesis

Cannon's synthesis was reported in 1980.\textsuperscript{18} It commenced with 1,2,3-trimethoxy benzene 26. Treatment of 26 with acetyl chloride/AlCl\textsubscript{3} afforded 27 in 54\% yield. Treatment of 27 with allyl bromide and potassium carbonate yielded allyl ether 28 which underwent Claisen rearrangement to give phenolic ketone 29 in 53\% overall yield from 27. Compound 29 underwent Dakin oxidation affording a mixture of the desired compound 30 and unreacted starting material. Attempts to separate this mixture were not rewarding and as a result the reaction mixture was treated directly with dibromomethane and potassium fluoride giving dillapiol 7 in 38\% yield from 30 and 6\% overall yield. This low overall yield is once again mainly due to the difficulties encountered in the formation of methylenedioxy ring. A synthesis, which avoids this ring closure, could significantly improve the overall yield of dillapiol.

1.3.2.4 Majerus' synthesis

Majerus' synthesis was developed in 1997.\textsuperscript{3} It started with sesamol 31, which had the advantage of avoiding low yield associated with the formation of methylenedioxy ring. Sesamol was treated with allyl bromide and potassium carbonate to form allyl ether 32 in >99\% yield. The allyl ether was subjected to Claisen rearrangement condition to give 33 in 81\% yield. Formylation of 33 with tin tetrachloride, tri-n-butylamine and paraformaldehyde
gave 34 in 60% yield. Methylation of 34 with MeI in presence of potassium carbonate gave 35 in 97% yield. Baeyer-Villiger oxidation was carried out on 35 to give 36 in 71% yield, which was then hydrolyzed using 3N NaOH to give 37 in 82% yield. The final transformation involves methylation of phenol 37 with MeI and potassium carbonate to give dillapiol 7 in 78% yield. The overall yield of this synthesis is approximately 21%.

This synthesis has an advantage over the previously reported syntheses due to a substantially higher overall yield. It has one low yielding step, the introduction of formyl group with tin tetrachloride and paraformaldehyde and one tricky step, the Baeyer Villiger oxidation of 35. This reaction needed to be done carefully to avoid epoxidation of the allyl group. It is particularly difficult to carry out these steps on a multi gram scale.
Reagents: (a) allyl bromide, K$_2$CO$_3$; (b) 190°C; (c) SnCl$_4$, Bu$_3$N, paraformaldehyde; (d) CH$_3$I, K$_2$CO$_3$; (e) mCPBA; (f) 3N NaOH; (g) CH$_3$I, K$_2$CO$_3$

Scheme 1.4 - Majerus' Synthesis of Dillapiol 7
Results and Discussion
Chapter 2

A new synthesis of dillapiol and its 4-thio derivatives

2.1 Introduction

The synergistic activity of dillapiol and a large number of its derivatives towards pyrethrum have been reported earlier.\textsuperscript{7,8,20,21} These compounds owe their activity to the presence of a benzo-1,3-dioxole (MDP) group. Baker's, Dallacker's and Cannon's syntheses all had the disadvantage of low overall yield due to the problem during the formation of the methylenedioxy ring. Majerus' synthesis, although with a much improved overall yield, required careful manipulation to avoid the epoxidation of the allyl group during a Baeyer Villiger oxidation. Her synthesis was not suitable for the preparation of multi gram quantities of dillapiol. Thus a new synthesis of dillapiol that overcame these shortcomings was developed.

The nomenclature of the dillapiol and its derivatives in this thesis conforms to IUPAC regulation. Figure 2.1 illustrates the numbering system of the rings.

![1,3-benzodioxole](image)

Figure 2.1 - IUPAC numbering system of dillapiol skeleton
2.2 A new synthesis of dillapiol

This synthesis uses commercially available sessamol 31, as starting material. It also avoids the reported low yielding steps associated with the formation of the methylenedioxy ring. A retrosynthetic approach is shown in Scheme 2.1. The new synthesis is essentially a variation of that carried out by Majerus. It alters the sequence of the introduction of the 4-methoxy and 6-allyl groups and thereby avoids the care needed to carry out the peracid induced Baeyer Villiger rearrangement in the presence of the 6-allyl group as shown below.

Sessamol was treated with 2.2N nBuLi and MOM-chloride to give 38 in quantitative yield after purification by flash column chromatography (Scheme 2.3). Confirmation of this
transformation was obtained from both the $^1$H NMR and $^{13}$C NMR spectra. The appearance of three sharp singlets at 3.47 ppm, 5.08 ppm and 5.91 ppm in the $^1$H NMR corresponds to the methyl group, methylene group in the side chain and benzo-1,3-dioxole group respectively. The $^{13}$C NMR spectrum also accounted for the ether functionality by the appearance of peaks at 55.9 ppm, 95.5 ppm and 99.7 ppm. It was our initial goal to use the less expensive dihydropyran and protect the hydroxyl group as THP. This group, like the MOM group, is known to be effective in directing an ortho metallation. Unfortunately, reaction of 31 with dihydropyran in the presence of catalytic amount of TsOH afforded the product 40 rather than the desired product 39 (Scheme 2.2).

![Scheme 2.2 - Electrophilic Substitution of Dihydropyran on 31](image)

The product 38, when reacted with 2.2N nBuLi and DMF, underwent a directed ortho-metallation (DoM) reaction to give 41 in 85% yield (Scheme 2.3) as shown by both the $^1$H NMR and $^{13}$C NMR spectra (Figures 2.2 and 2.3 respectively). The appearance of a singlet at 10.35 ppm in the $^1$H NMR spectrum, the signal at 188.0 ppm in the $^{13}$C NMR spectrum and the 1683 cm$^{-1}$ stretching vibration in the infrared spectrum confirmed the aldehyde functionality.
Scheme 2.3 - Preparation of 4-Formyl-5-Methoxymethoxy-1,3-Benzodioxole 41

The experimental procedure used for this transformation was based on Snieckus’ review article. The DoM reaction (Scheme 2.4) involves the deprotonation of a site ortho to a heteroatom-containing metal chelating group, in our case the methoxy methyl ether, by a strong base, normally an alkyllithium reagent, leading to an ortho-lithiated species 44. This species upon treatment with electrophilic reagents yields 1,2 disubstituted products, for example 45.

For a successful deprotonation to occur, the DMG group must exhibit a good coordination site for the alkyllithium and a poor electrophilic site for attack by this strong base. A heteroatom is therefore an obligatory component of the DMG. Inductive effects also have been shown to play a major role in an ortho deprotonation of fluorobenzene and benzonitrile since neither can achieve normal coordination stabilized ortho-lithio intermediates. Snieckus has compiled a list of substituents and their relative ability to direct
Figure 2.2 – $^1$H NMR spectrum of 4-formyl-5-methoxymethoxy-1,3-benzodioxole (41)
Figure 2.3 – 13C NMR spectrum of 4-formyl-5-methoxymethoxy-1,3-benzodioxole (41)
ortho metallation via internal competition experiments. In this list the methoxy methyl (MOM) group is of average ability, better than OCH₃ but much weaker than groups such as N,N-diethylcarboamide(C(O)N(Et)₂) or the carbamate group (O-CONEt₂).

Baeyer Villiger oxidation was then performed on 41. This reaction, which was carried out at 0°C, afforded the product as a pale yellow liquid 48 in 91% yield. The presence of the formyl group is identified by the appearance of a singlet at 8.24 ppm in the ¹H NMR spectrum for the formyl hydrogen and a signal at 157.7 ppm in the ¹³C NMR spectrum for the carbonyl carbon. The carbonyl group also has a characteristic peak in the infrared spectrum at 1752 cm⁻¹.

The mechanism is essentially similar to the Dakin Reaction. It first involves the addition of the peracid to the carbonyl carbon ¹⁹,²³ (Scheme 2.5) to give 47 as the intermediate, which then collapses to give an ester 48.

Scheme 2.5 - Mechanism of the Baeyer-Villiger Oxidation
Hydrolysis of the ester 48 was carried out with 25% NaOH solution for 4 h at RT, affording the phenol 49 in 59% yield after acid work up. Methylation of phenol 49 with methyl iodide in the presence of potassium carbonate proceeded for 48 h at RT to give 50 in 96% yield as a pale yellow liquid. The $^1$H NMR spectrum showed an additional 3H singlet at 3.99 ppm corresponding to the methyl proton in the OMe functionality at the C-4 position.

Removal of the MOM group from 50 using NaI and 3N methanoic HCl after 4 h gave 51 as pale orange crystals in 73% yield. Lack of the methyl proton signals from OCH$_2$ and OCH$_3$ in the $^1$H NMR spectrum and the appearance of a 1H singlet at 5.43 ppm corresponding to the phenolic proton and an IR peak at 3541 cm$^{-1}$ confirmed the presence of 51.

Scheme 2.6 - Preparation of 5-Hydroxy-4-Methoxy-1,3-Benzodioxole 51

Allylation of 51 using allyl bromide and potassium carbonate formed allyl ether 52 in 86% yield as a yellow liquid after purification by flash column chromatography (Scheme 2.7). Confirmation of this transformation was obtained from both the $^1$H NMR and $^{13}$C NMR
spectra. The appearance of two doublets of triplets patterns at 5.22 ppm and 5.35 ppm and a multiplet in the region of 6.00-6.06 ppm in the $^1$H NMR spectrum corresponds to the vinylic hydrogens. The $^{13}$C NMR spectrum showed signals at 117.5 ppm, 133.6 ppm and 71.2 ppm corresponding to the two vinylic carbons and the carbon in the OCH$_2$ group respectively.

The allyl ether 52 underwent Claisen rearrangement to afford 53 in 87% yield as a pale yellow liquid. The lack of a proton signal for the OCH$_2$ group in the $^1$H NMR spectrum and the appearance of a 1H singlet at 4.03 ppm corresponding to the phenolic hydrogen confirmed the transformation. The appearance of a peak at 3538 cm$^{-1}$ in the infrared spectrum confirms the presence of the hydroxyl group.

Scheme 2.7 - Preparation of 5-Hydroxy-4-Methoxy-6-(2-propenyl)-1,3-benzodioxole 53

The final transformation involved the methylation of phenol 53 with methyl iodide and potassium carbonate in acetone at RT for 36 h to give the desired product, dillapiol 7, as a pale yellow liquid in 80% yield. The spectroscopic properties (Figures 2.4 and 2.5) of the synthetic material were identical to those cited in literature.$^{16,17,18}$ The overall yield of dillapiol starting with sessamol 31 is 19%. This is comparable to that of 21% obtained by Majerus. Our new synthesis has one relatively low yielding step, surprisingly the hydrolysis.

Scheme 2.8 - Methylation of 53 to afford Dillapiol 7
Figure 2.4 – $^1$H NMR spectrum of dillapiol (7)
Figure 2.5 – $^{13}$C NMR spectrum of dillapiol (7)
of the formate ester 48. It is suspected that the 59% yield is due to the isolation problem rather than the inefficiency of the hydrolysis. The fact that the removal of the MOM group from 50 to 51 also occurred in only 73% yield gives credance to the above suggestion. If the recovery of each of the phenols (49 and 51) could be improved to at least 80%, the overall yield of dillapiol 7 via this route would be around 27%. No attempts were made to optimize the isolation of the phenols 49 and 51.

Although the current overall yield in the new synthesis has not improved over that of the Majerus process, the synthesis offers the advantage of simpler reaction conditions which should be amenable to scale up. If a large scale synthesis of dillapiol was contemplated via this route, it would be worthwhile to consider carrying out the methylations of the phenols 49, 51 and 53 on the crude reaction products, probably using the less expensive dimethyl sulfate in place of methyl iodide. The use of basic hydrogen peroxide rather than mCPBA as the reagent for the Baeyer Villiger reaction should also be considered. Finally, the use of a less expensive alternative to the phenol protecting MOM group should be investigated. The ideal would be the allyl group itself since its use would save two steps in this synthesis. Unfortunately, metallation of 32 is likely to result in lateral metallation followed by 1,2-Wittig rearrangement to afford 55 rather than an ortho metallation (Scheme 2.9). However, see Section 2.6 at the end of this chapter.

Scheme 2.9 - Potential 1,2 Wittig Rearrangement of Allyl Ether 32 to 55
2.3 Attempted synthesis of dillapiol 7 via alternate routes

During the development of the above synthesis, a number of alternative routes to dillapiol were investigated with the hope of developing a simpler, cost-efficient approach. The allylation of aromatic Grignard reagents to give allyl benzene has been reported.\textsuperscript{24} Thus it appeared that 62 could be a penultimate intermediate to dillapiol. Possible approaches to 62 were investigated. These are outlined in Scheme 2.10. The ideal route from sessamol, 31, to 62 would involve bromination of sessamol to 56, followed by introduction of a second hydroxyl group and methylation of both the phenolic groups. If successful, this would constitute a four step conversion of sessamol, 31, to dillapiol, 7. Other somewhat longer routes from 56 to 62 were contemplated in case the most desirable one was unsuccessful.

The ortho bromination of sessamol 31 to give 56 was carried out using the procedure by Alexander et al.\textsuperscript{25} The $^1$H NMR and $^{13}$C NMR spectra were identical to those found in literature.\textsuperscript{25} 6-Bromo-5-hydroxy-1, 3-benzodioxole 56 was used as the intermediate material for several different approaches to introduce the fifth substituent at the C-4 carbon. The introduction of the fifth substituent was the greatest obstacle in this synthetic route. The different approaches investigated include: Vilsmeier-Haack Reaction conditions, Casiraghi Reaction conditions, enzymatic hydroxylation and copper catalyzed hydroxylation using molecular oxygen.
Approaches:
Ortho formylation of 56 via (A) Vilsmeier-Haack reaction conditions; (B) Casiraghi reaction conditions.
Ortho formylation of 59 via (D) Vilsmeier-Haack reaction conditions
Ortho hydroxylation of 56 via (E) Tyrosinase; (F) Copper catalyst using molecular oxygen.

Scheme 2.10 - General Overview of Various Schematic Routes Attempted to Synthesize Dillapiol 7

2.3.1 Aromatic formylation

2.3.1.1 Ortho formylation of aromatic ring via Vilsmeier-Haack Reaction conditions

The adducts of dimethylformamide (DMF) with acyl halides are the key reagents in the Vilsmeier-Haack Reaction. The most common halide used for the formylation of aromatic rings is phosphorous oxychloride.\(^{19,26}\) The mechanism of Vilsmeier-Haack Reaction is shown in Scheme 2.11, where the disubstituted formamide 63 reacts with
phosphorous oxychloride to give the reactive species 65. This species then reacts with a phenol or amine, 66, to give 68, which is unstable and hydrolyzes to the final product 70. When the phenol 56 was treated with these reagents under Vilsmeier-Haack Reaction conditions only starting material was recovered (Scheme 2.10, route A). Dallacker et al.\textsuperscript{17} have shown that the Vilsmeier-Haack Reaction worked on their system (Scheme 1.2) which is very similar to ours. The main difference is that they had a methoxy group ortho to the formylation site whereas in our case we have a hydroxyl group. In order to achieve similar structure to their system, phenol 56 was methylated to give 59 (Scheme 2.10, route C). The Vilsmeier-Haack reaction was attempted on 59 under the Dallacker conditions but was unsuccessful. A black solid, insoluble in any organic solvent, was obtained. No additional efforts were made in this direction.
2.3.1.2 Ortho formylation via Casiraghi Reaction conditions

Casiraghi et al.\textsuperscript{27} have developed an ortho formylation procedure for preparing salicylaldehyde from phenol, using tin tetrachloride, a base and paraformaldehyde. It was postulated that in the first stage of the reaction (Scheme 2.12), the phenol, \textbf{71}, reacts with tin tetrachloride to give the intermediate \textbf{72}. This intermediate is then believed to interact with paraformaldehyde giving a complex \textbf{73} in which the metal atom serves as a link between the two reacting species.

\textbf{71} \quad \text{SnCl}_4 \quad \text{-HCl} \quad \text{CH}_2\text{O} \quad \text{H}_2\text{C=O} \quad \text{SnCl}_4

\textbf{72} \quad \text{O} \quad \text{SnCl}_4

\textbf{73} \quad \text{H}_2\text{C=O} \quad \text{SnCl}_4

\textbf{74} \quad \text{H}

\textbf{75} \quad \text{CH}_2\text{O} \quad \text{SnCl}_4

\textbf{76} \quad \text{H}_2\text{C=O} \quad \text{SnCl}_4

\textbf{77} \quad \text{CHO} \quad \text{MeOSnCl}_3 \quad \text{MeOH}

\textbf{78}

Scheme 2.12 - Mechanistic Pathway for the Casiraghi Reaction.

A base, such as amine, is needed to trap the hydrogen chloride generated in the first stage of the reaction. The base must have poor affinity for coordination with metal atoms in
order to have a high concentration of metal complex 73 otherwise it will lower the yield of this metal complex product by competing with paraformaldehyde.

The donating ability of the solvent also plays an important role in the formation of the complex 73. Donor agents, such as DMF, can strongly solvate the phenolate metal counterion and hence retard the process, whereas solvents, which are poor donors, such as benzene or toluene, do not interfere in the formation of 73 are favored.

The subsequent intramolecular collapse of 73 leads to 75 via the dienone 74. Reaction with a second equivalent of paraformaldehyde led to the formation of salicylaldehyde 77 via a concerted hydride transfer. The last stage involved the alcoholysis of 71 with 78 leading to MeOH with re-formation of the active species 72. Attempts were made to formylate 56 using the described reaction conditions (Scheme 2.10, route B). None of the desired product was isolated and only starting material was recovered.

2.3.2 Aromatic hydroxylation

2.3.2.1 Enzymatic ortho hydroxylation via the use of tyrosinases

Klibanov et al\textsuperscript{28} have successfully developed a regioselective hydroxylation of phenols via tyrosinases. Tyrosinases are metallo-enzymes with an active site consisting of two neighboring copper atoms.\textsuperscript{29} These enzymes catalyze the hydroxylation of phenols, such as 79, with molecular oxygen to catechols 80 and subsequently dehydrogenation to \(\alpha\)-quinones 81 (Scheme 2.13). This reaction is not feasible in water due to polymerization of quinone but is feasible only in chloroform. Chloroform also allows a 10-fold higher solubility of \(O_2\) than water and a greater solubility to most phenols. The reactivity of this
reaction depends on the R substituent; it decreases upon a transition of R from electron donating to electron withdrawing substituent. Attempts to hydroxylate the phenol 56 using Klibanov conditions were unsuccessful as only starting material was recovered.

![Scheme 2.13 - Ortho Hydroxylation of Phenols via the Use of Molecular Oxygen by Tyrosinase](image)

2.3.2.2 Copper catalyzed ortho hydroxylation via the activation of molecular oxygen

Capdevielle and Maumy developed an ortho hydroxylation method that mimics the oxidation of phenols by tyrosinases. This method consists of the activation of molecular oxygen with cuprous salts which leads to exclusive formation of catechols. The oxidation of phenol is carried out in acetonitrile in the presence of a catalytic amount of cuprous chloride and consumes oxygen and elemental copper as indicated in Scheme 2.14. The most striking feature of this method is its total selectivity due to the stability of copper (II) catecholates.

![Scheme 2.14 - Copper Catalyzed Ortho Hydroxylation of Phenols via the Activation of Molecular Oxygen](image)
under the reaction conditions, conditions under which the free catechols are oxidized to quinones. Attempts to hydroxylate phenol 56 using these conditions were unsuccessful as only starting material was recovered.

2.4 Synthesis of dillapiol derivatives

Synergism plays an important role in the formulation of high-cost insecticides like pyrethrum\textsuperscript{21} since addition of a relatively low cost synergist, such as the commercial piperonyl butoxide (BPO), can increase the activity of the insecticide by a factor of 2 to 4. The synergistic activity of dillapiol towards several classes of insecticides is comparable to or somewhat higher than piperonyl butoxide. Both of these compounds and a number of other naturally occurring synergists such as saflrole 4 contain a benzo-1,3-dioxole group which binds to the heme of the mfos, the detoxification enzymes, to form adducts that are stable and not easily displayed by other ligands.\textsuperscript{2,3} Several dillapiol derivatives such as 83, 84 and 85 were synthesized previously in our laboratory and evaluated for their ability to synergize the insecticidal property of \(\alpha\)-terthienyl (\(\alpha\)-T), 82.

\[ \text{[image of chemical structures]} \]

\(\alpha\)-T, 82, is a light-activated insecticide which when exposed to light produces singlet oxygen which in turn causes the peroxidation of phospholipids and the oxidation of enzymes and other proteins. It is potent against mosquito larvae at a nano molar concentration.\textsuperscript{10} The
synergism factors of these derivatives were found to be comparable to that of dillapiol (Table 2.1).

![Chemical structures of compounds 83, 84, and 85](image)

**Figure 2.7 - Derivatives of dillapiol previously synthesized in our laboratory**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Synergism Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$-T + Dillapiol 7</td>
<td>1.89</td>
</tr>
<tr>
<td>$\alpha$-T + 83</td>
<td>2.40</td>
</tr>
<tr>
<td>$\alpha$-T + 84</td>
<td>1.78</td>
</tr>
<tr>
<td>$\alpha$-T + 85</td>
<td>1.73</td>
</tr>
</tbody>
</table>

There have been no reports on the preparation of thio analogs of dillapiol. The concept was to prepare analogs by replacing the alkoxy substituent at C-4 by a sulfur analog, either as the sulfide, sulfoxide or sulfone, and examine their activity as insecticide synergists. The availability of the three sulfur oxidation states would allow us also to probe the effect of electron donating vs electron withdrawing groups on the synergism factor. Four series of sulfides, sulfoxide and sulfone shown in Table 2.2 were prepared and evaluated as synergists.
Table 2.2- Synthetic Thio Derivatives of Dillapiol

<table>
<thead>
<tr>
<th>sulfides</th>
<th>sulfoxides</th>
<th>sulfones</th>
</tr>
</thead>
</table>
| \[
\begin{array}{c}
\text{S}^R \\
\text{O} \\
\text{O} \\
\text{Me} \\
\end{array}
\] | \[
\begin{array}{c}
\text{O} \cdot \text{S}^R \\
\text{O} \\
\text{O} \\
\text{Me} \\
\end{array}
\] | \[
\begin{array}{c}
\text{O} \cdot \text{S}=\text{O} \\
\text{O} \\
\text{O} \\
\text{Me} \\
\end{array}
\] |

where \( R = \text{methyl} \)
\( = \text{p-methoxy phenyl} \)
\( = \text{phenyl} \)
\( = \text{benzyl} \)

These series were synthesized in a similar manner to dillapiol (Scheme 2.1); the only difference was in the variation of the structure of the sulfur electrophile. The major goal was to prepare a small library of derivatives for evaluation of biological activity; hence little notice was paid to yield optimization. The overall yield of these compounds from sessamol when compared to dillapiol is much higher and thus a dozen derivatives were readily obtained.

The first set of thio derivatives of dillapiol, namely the sulfide 90a, the sulfoxide 91a and the sulfone 92a, were prepared starting from the protected sessamol 38 as outlined in Scheme 2.15. Thus reaction of 38 with nBuLi and dimethyl disulfide, afforded 86a as a yellow liquid in 91% yield. Confirmation of this transformation was obtained from both the \(^1\text{H} \) NMR and \(^{13}\text{C} \) NMR spectra (Figures 2.7 and 2.8 respectively). The appearance of a 3H singlet at 2.41 ppm in the \(^1\text{H} \) NMR spectrum corresponds to the methyl proton in S\text{CH}_3 and a peak at 16.9 ppm in the \(^{13}\text{C} \) NMR spectrum corresponds to the carbon atom in S\text{CH}_3. HRMS confirmed the molecular formula.
Figure 2.7 – $^1$H NMR spectrum of 5-methoxymethoxy-4-thiomethyl-1,3-benzodioxole (86a)
Figure 2.8 - $^{13}$C NMR spectrum of 5-methoxyethyl-4-thiomethyl-1,3-benzodioxole (86a)
Removal of the MOM group from 86a using NaI and 3N methanoic HCl afforded 87a as white powder in 80% yield. It is evidenced by the disappearance of the methyl signals from OCH₂ and OCH₃ from the H NMR spectrum and the appearance of a singlet at 6.22 ppm belonging to the hydroxyl hydrogen confirming the transformation had taken place. The infrared spectrum showed the characteristic peak at 3428 cm⁻¹ indicating the presence of the hydroxyl group.

Reagents: (a) BuLi, dimethyl disulfide; (b) NaI, methanoic HCl; (c) allyl bromide, K₂CO₃; (d) 190°C; (e) CH₃I, K₂CO₃; (f) 1.2eq mCPBA; (g) 4.0eq mCPBA

Scheme 2.15 - The Synthesis of the Thio Derivatives 89a, 90a, 91a and 92a of Dillapiol

Allylation of 87a using allyl bromide and potassium carbonate afforded the allyl ether 88a in 88% as a clear colorless liquid. As expected, the allyl ether 88a underwent Claisen rearrangement when subjected to its reaction conditions to afford a pale yellow liquid 89a in
87% yield upon purification by flash column chromatography. Confirmation of this transformation was obtained via both the $^1$H NMR and $^{13}$C NMR spectra (Figures 2.9 and 2.10 respectively).

Finally methylation of 89a with methyl iodide and potassium carbonate afforded 90a, the first sulfur derivative of dillapiol, in 87% yield after purification by flash column chromatography. The $^1$H NMR and $^{13}$C NMR spectra (Figures 2.11 and 2.12 respectively) closely resemble those of dillapiol, 7, except that one of the OCH$_3$ groups (3.99 ppm) in dillapiol had been replaced by SCH$_3$ (2.45 ppm) in 90a. The 4-thio analog 90a of dillapiol was thus obtained in six steps from sessamol in 48% yield. It represents the first sulfur analog of dillapiol. It is of considerable interest to compare the biological properties, in particular the synergist factors, of 90a with dillapiol. The availability of 90a gives rapid access to the corresponding sulfoxide and sulfone and potential information concerning the effect on biological activity of changing an electron donor substituent, SCH$_3$, into the strongly electron withdrawing SO$_2$CH$_3$ group.

The sulfide 90a was then transformed to the sulfoxide and sulfone using mCPBA. For the formation of sulfoxide 91a, a solution of 90a in ethyl acetate at -40°C was treated with 1.2e.q of mCPBA and then allowed to warm to RT. Workup after 24 h and purification by chromatography afforded the desired product as a pale yellow liquid in 63% yield. The $^1$H NMR spectrum of 91a closely resembles that of 90a except that the methyl peak of SCH$_3$ in 91a was shifted downfield to 3.01 ppm due to the electronegativity effects of the sulfoxide (Figure 2.13). The $^{13}$C NMR spectrum indicated a peak at 39.7 ppm belonging to the carbon atom of SOCH$_3$. Furthermore the presence of the S=O stretch of sulfoxide at 1050 cm$^{-1}$ was observed in the infrared spectrum. When 90a was treated with 4e.q of mCPBA at RT for
Figure 2.9 - $^1$H NMR spectrum of 5-hydroxy-6-(2-propenyl)-4-thiomethyl-1,3-benzodioxole (89a)
Figure 2.11 – $^1$H NMR spectrum of 5-methoxy-6(2-propenyl)-4-thiomethyl-1,3-benzodioxole (90a)
Figure 2.12 – $^{13}$C NMR spectrum of 5-methoxy-6(2-propenyl)-4-thiomethyl-1,3-benzodioxole (90a)
Figure 2.13 - $^1$H NMR spectrum of 5-methoxy-4-methylsulfinyl-6-(2propenyl)-1,3-benzodioxole (91a)
24 h, it afforded 92a as pale yellow crystals in 80% yield. The $^1$H NMR and $^{13}$C NMR spectra of 92a are similar to those of 91a except that the methyl peak in SO$_2$CH$_3$ is shifted further downfield to 3.26 ppm, as expected, once again due to the increased electron withdrawing effects of the sulfone relative to the sulfoxide. The infrared spectrum further confirmed the presence of the sulfone with its S=O symmetric stretch at 1136 cm$^{-1}$ and the asymmetric stretch at 1316 cm$^{-1}$.

Reagents: (a) BuLi, R-disulfide; (b) Nal, methanoic HCl; (c) allyl bromide, K$_2$CO$_3$; (d) 190°C; (e) MeI, K$_2$CO$_3$; (f) 1.2eq mCPBA; (g) 4.0eq mCPBA

Scheme 2.16 - Preparations of the Thio Derivatives 89b-d, 90b-d, 91b-d and 92b-d of Dillapiol

In a similar manner (Scheme 2.16) three more sets of sulfide, sulfoxide and sulfone were synthesized from the readily available disulfides. The yields for each step in the synthesis of the sulfide, sulfoxide and sulfone from sessamol are shown in Table 2.3. The structures of
the products were confirmed via the $^1$H NMR and $^{13}$C NMR spectra and the HRMS. The $^1$H NMR and $^{13}$C NMR spectra of each intermediate and the target sulfide, corresponding sulfoxide and sulfone are as expected. For each of the series of sulfide, sulfoxide and sulfone, the peaks for the hydrogens on carbons $\alpha$ to the sulfur function showed the expected downfield shift due to the increased electron withdrawing effect (i.e. from SR to SO$_2$R). Detailed spectroscopic data are found in the experimental section. Currently these derivatives are being investigated as synergists and drug sparing agents.

Table 2.3 - Percentage Yield of Each of the Synthetic Intermediate and the Target Sulfide, Corresponding Sulfoxide and Sulfone.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
</tr>
<tr>
<td>86</td>
<td>91</td>
</tr>
<tr>
<td>87</td>
<td>80</td>
</tr>
<tr>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td>91</td>
<td>63</td>
</tr>
<tr>
<td>92</td>
<td>80</td>
</tr>
</tbody>
</table>
2.5 Biological activity

2.5.1 Synergists

α-T is a naturally occurring phototoxin active against the mosquito larvae. It is activated by light, producing singlet oxygen which causes peroxidation of phospholipids. Previous work on this insecticide in collaboration with Dr. J. T. Arnason, University of Ottawa, have shown that dillapiol and several of its derivatives gave good synergism factors with α-T. As a result of this success, an investigation of the thio analogs of dillapiol was carried out in the hope of enhancing the synergism factor with α-T.

Mireille Marcotte, a fourth year undergraduate student in Biology at the University of Ottawa, carried out preliminary investigation of the synergistic effect of thio analogs of dillapiol. The results of the investigation are shown in Table 2.4 which represents the synergism factors of thio analogs relative to dillapiol.

When compared with dillapiol, compounds 90a and 90c were the only ones that showed slightly higher synergism factors of 1.15 and 1.21 respectively. All the other analogs showed synergistic effects lower than dillapiol. With the exception of the sulfoxide 91d, it appears that the better synergists are the sulfides. The various sulfoxides and sulfones have approximately half the synergist effect of dillapiol. However one must be careful in drawing firm conclusions since the investigation for the synergistic effect was carried out during the winter period when the growth and development of mosquito larvae is slow. Therefore these experiments need to be repeated. Due to the time constraints, this study was not repeated but will be investigated shortly by another researcher.
Table 2.4 - Synergism Factors of the Thio Derivatives of Dillapiol Relative to Dillapiol

<table>
<thead>
<tr>
<th>Compound</th>
<th>Synergism factor relative to Dillapiol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dillapiol 7</td>
<td>1.00</td>
</tr>
<tr>
<td>89b</td>
<td>0.68</td>
</tr>
<tr>
<td>89c</td>
<td>0.54</td>
</tr>
<tr>
<td>90a</td>
<td>1.15</td>
</tr>
<tr>
<td>90b</td>
<td>0.79</td>
</tr>
<tr>
<td>90c</td>
<td>1.21</td>
</tr>
<tr>
<td>90d</td>
<td>0.81</td>
</tr>
<tr>
<td>91b</td>
<td>0.57</td>
</tr>
<tr>
<td>91c</td>
<td>0.57</td>
</tr>
<tr>
<td>91d</td>
<td>0.86</td>
</tr>
<tr>
<td>92b</td>
<td>0.55</td>
</tr>
<tr>
<td>92c</td>
<td>0.74</td>
</tr>
<tr>
<td>92d</td>
<td>0.52</td>
</tr>
</tbody>
</table>

2.5.2 Drug sparing agents

CYP3A4 is a human cytochrome P450 enzyme found in high amounts in the small intestine and the liver. It is a major contributor to the metabolism of foreign compounds following oral drug administration and acts by detoxification of a drug before it reaches the bloodstream. CYP3A4 has an extremely wide range of substrate specificity and it has been suggested that it mediates the oxidation of approximately 40-50% of drugs administered to humans.32
Recently, many studies have shown that concomitant oral administration of grapefruit juice increases the bioavailability and/or prolongs the metabolic elimination of many drugs. Hence it significantly increases their plasma concentration by disrupting the detoxification pathway mediated by CYP3A4. Because of this it has been suggested that other natural products may inhibit CYP3A4. Therefore when taken concomitantly with prescription drugs, such drugs may decrease the required dosage and financial cost of an expensive drug regime, by acting as drug sparing agents. A potential negative effect is that such products could also increase the duration and severity of side effects due to the increase in drug concentration in plasma because of a decrease in metabolic breakdown.

Jason Budzinski, a graduate student in Biology at the University of Ottawa, screened pure plant compounds along with commercially available plant extracts for their ability to inhibit CYP3A4 in vitro using a fluorometric microtitre plate assay. Among the pure compounds studied was dillapiol. Dillapiol was found to be the most potent inhibitor of CYP3A4 with an IC₅₀ value of 17 μM. As a result of this discovery, the thio analogs are currently being tested for inhibitory activity towards CYP3A4. Preliminary results indicate that compounds 90c, 91c, 92b and 92d showed IC₅₀ values comparable to dillapiol for the inhibition of CYP3A4 (Figure 2.14) and thus can be considered to be potent inhibitors of CYP3A4. All the other compounds showed moderate inhibition of CYP3A4. With the exception of sulfide 90c and sulfoxide 91c, it appears sulfones are the better inhibitors of CYP3A4. Currently the investigation is ongoing and the determination of accurate IC₅₀ values is in progress.
Figure 2.14 – Preliminary Results of the Inhibition of CYP3A4 by the Thio Derivatives of Dillapiol. The IC\textsubscript{50} Values are Obtained by Interpolating the Graphs at 50% Inhibition Mark.
2.6 An improved route to dillapiol

As was mentioned in Section 2.2, we had considered the metallation of the allyl ether obtained from sessamol. After some thought it was decided that the 1,2-Wittig Rearrangement would be the most likely product upon treatment with nBuLi and this approach was not investigated.

![Chemical structure](image)

Cross reference: Scheme 2.9 - 1,2 Wittig Rearrangement of Allyl Ether 32 to afford 55

During the preparation of this thesis reactivity of the allyl ether toward base was reconsidered. If the Wittig rearrangement could be avoided, then the route from sessamol to dillapiol described in this thesis would be shortened by two steps: (1) the protection of phenols by MOM ether and (2) subsequent deprotection. The other advantage would be avoiding the expensive MOMCl reagent. The proposed route is shown in Scheme 2.17.

Indeed as demonstrated by Dr. Sasmita Tripathy treatment of 32 with nBuLi followed by addition of DMF gave the aldehyde 93 in 89% yield. This yield was comparable to that for the ortho metallation of MOM ether 38 and its trapping with DMF. There was no evidence of the feared 1,2-Wittig rearrangement. Interestingly the reaction of mCPBA with 93 was highly chemoselective and gave only the Baeyer Villiger product with no trace of
epoxidation of the allyl ether. The remaining steps of the synthesis were completed as planned and the overall unoptimized yield of dillapiole from sessamol was 40%.

Reagents: (a) K₂CO₃, allyl Bromide; (b) nBuLi/THF/-78°C, DMF; (c) mCPBA,CH₂Cl₂; (d) NaOH (e) 190°C; (f) CH₃J, acetone

Scheme 2.17 - A New Improved Route to Dillapiole 7

Once the ortho metallation of the allyl ether had been demonstrated, the synthesis of the thio derivatives should also be shortened since the allyl ether 88a might be prepared in two steps from sessamol rather than four. Surprisingly when this was attempted the formation of 88a was accompanied by a significant amount of an, as yet, unidentified byproducts. These results indicate that this route is not practicable for the synthesis of thio derivatives of dillapiole.

Scheme 2.18 - Formation of 88a via Treatment of 32 with nBuLi
Experimental Procedures
Chapter 3

Experimental

General procedure

Melting points were determined by use of a Thomas Hoover Capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Bomem-Michelson MB-100 FT-IR spectrometer by preparing thin methylene chloride films on potassium bromide plate. The $^1$H and $^{13}$C NMR spectra were obtained from either a Bruker AMX-500 spectrometer, Varian XL-300 or a Varian Gemini-200 spectrometer. The samples were run in spectroscopic grade deuterated chloroform. Chemical shifts are in parts per million relative to tetramethyl silane. The multiplicities of the NMR signals are reported as s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; t, triplet; q, quartet and m, multiplet. Mass spectrum analyses and high resolution mass spectra were performed by the analytical services available at University of Ottawa. Low resolution mass spectra were performed using electron impact ionization. High resolution mass spectroscopy was performed on a Kratos Concept-IIA mass spectrometer. Unstable compounds of high molecular weight were examined by FABH (Fast Atom Bombardment) accurate mass experiments.

Solvents used for reactions and chromatographic purifications were routinely distilled prior to use. Reactions were monitored by thin layer chromatography (tlc) using silica gel on alumina sheets, 60 F$_{254}$. Individual compounds were seen either by ultraviolet light or by staining. The stain that was used was a 5% solution of ammonium
molybdate in 10% aqueous H₂SO₄. The tlc plates were developed by dipping the plates into the stain and then heating the plates with heat gun. Silica gel 270-400 mesh was used for flash chromatography.

All reactions were performed under nitrogen unless otherwise stated. The glassware that was used for moisture sensitive reactions was either dried overnight in an oven or flame dried with a propane torch. Oven dried syringes were used to transfer chemical and solvents. "Drying" refers to removing the water from the organic mixture with anhydrous magnesium sulfate if it is not stated. "Concentrated" refers to the removal of solvent by roto-evaporation.
5-Methoxymethoxy-1,3-benzodioxole 38

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{38}
\end{array}
\]

To a cooled (0 °C) solution of sesamol 31 (5 g, 36.2 mmol) in dry THF (20 ml) was added 1 eq of nBuLi (16.5 ml, 2.2 M). The reaction mixture was stirred for 30 min and then 1.5 eq of methoxymethyl chloride (4.4 g, 4.1 ml) was added. The resulting mixture was stirred at room temperature and was monitored using thin layer chromatography (tlc), eluting with 3:1 hexane/ethyl acetate, and was found to be almost completed after 24 h. The reaction mixture was quenched using saturated NH₄Cl solution (10 ml) and the aqueous phase extracted with Et₂O (3 x 20 ml). The organic phase was then washed with NaOH solution (3 x 10 ml) and dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide compound 38 as colorless liquid (6.5 g, 98%).

\(^1\text{H NMR}\) (200 MHz, CDCl₃): δ ppm 3.47 (s, 3H), 5.08 (s, 2H), 5.91 (s, 2H), 6.49 (dd, 1H, J=8.4 Hz, 2.4 Hz), 6.62 (d, 1H, J=2.2 Hz), 6.70 (d, 1H, J=8.4 Hz).

\(^{13}\text{C NMR}\) (50 MHz, CDCl₃): δ ppm 55.9, 95.5, 99.7, 101.2, 108.0, 108.4, 142.5, 148.1, 152.5

EI-MS (m/z, %): 182 (M⁺, 100), 152 (75), 137 (30)

HRMS: Calc. for C₅H₁₀O₄: 182.0579; Found: 182.05830

IR (cm\(^{-1}\)): 1042, 1215
4-Formyl-5-methoxymethoxy-1,3-benzodioxole 46

![Diagram of compound 41]

To a cooled (0 °C) solution of 38 (5 g, 27.5 mmol) in dry THF (20 ml) was added 1eq of nBuLi (12.5 ml, 2.2 M). The reaction mixture was stirred for 30 min and then 1.5eq of DMF (3 g, 31.8 ml) was added. The resulting mixture was stirred at room temperature and was monitored using tlc, eluting with 3:1 hexane / ethyl acetate. It was completed after 4 h. The reaction mixture was quenched using NH₄Cl solution (sat., 10 ml) and then the aqueous phase extracted with EtOAc (3 x 20 ml). The organic phase was then washed with water (3 x 15 ml) and dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide orange powder, which upon purification by flash column chromatography (3:1 hexane / ethyl acetate) gave compound 41 as pale yellow crystals (4.9 g, 85%).

\[
\text{H NMR (500 MHz, CDCl₃): } \delta \text{ ppm } 3.48 \text{ (s, 3H), 5.17 (s, 2H), 6.09 (s, 2H), 6.58 (d, 1H, J=8.6 Hz), 6.86 (d, 1H, 8.6Hz), 10.35 (s, 1H).}
\]

\[
\text{C NMR (125 MHz, CDCl₃): } \delta \text{ ppm } 56.4, 95.7, 102.9, 106.4, 111.7, 113.1, 143.4, 148.1, 153.6, 188.0
\]

\[
\text{EI-MS (m/z, %): 210 (M⁺, 92), 178 (53), 164 (82)}
\]

\[
\text{HRMS: Calc. for C₁₀H₁₀O₅: 210.0528; Found: 210.05317}
\]

\[
\text{IR (cm}^{-1}): 1218, 1683
\]

\[
\text{MP: 85-87 ℃}
\]
4 - Formyloxy - 5 - methoxymethoxy -1, 3 - benzodioxole 48

To a cooled (0 °C) solution of aldehyde 41 (3 g, 14.3 mmol) in dry CHCl₃ (25 ml) was added 2eq of mCPBA (5.30 g, 30.7 mmol) in one portion. The reaction mixture was warmed up to room temperature and stirred for 24 h after which the reaction mixture was washed with sodium sulfite solution (sat., 2 x 15 ml), sodium bicarbonate (sat., 2 x 20 ml) and water (2 x 20 ml). The extract was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The resulting oily residue was purified by flash column chromatography (5:1 hexane / ethyl acetate) affording compound 48 as a pale yellow liquid (2.76 g, 91%).

¹H NMR (500 MHz, CDCl₃): δ ppm 3.45 (s, 3H), 5.06 (s, 2H), 5.96 (s, 2H), 6.64 (d, 1H, J=8.6 Hz), 6.62 (d, 1H, J=8.6 Hz), 8.24 (s, 1H)

¹³C NMR (50 MHz, CDCl₃): δ ppm 56.2, 96.2, 102.3, 105.5, 108.5, 124.1, 139.8, 143.9, 144.6, 157.7

EI-MS (m/z, %): 226 (M+, 6), 45 (100)

HRMS: Calc. for C₁₁H₁₀O₆: 226.077; Found: 226.04806

IR (cm⁻¹): 1216, 1752
4 - Hydroxy - 5 - methoxymethoxy - 1, 3 benzodioxole 49

\[
\begin{array}{c}
\text{OH} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

49

To a solution of 48 (20 mg, 0.094 mmol) in THF (5 ml) was added 25% NaOH solution (2 ml). The reaction mixture was stirred for 4 h at room temperature and extracted with water (4 x 5 ml). The aqueous phase was then acidified with conc. HCl and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 10 ml). The combined organic extracts were dried over anhydrous MgSO\textsubscript{4}, filtered and concentrated in vacuo to provide an oily residue. The resulting oily residue was purified using flash chromatography (9:1 hexane / ethyl acetate) affording phenol, 49, as a pale yellow liquid (1.1 mg, 59%).

\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}): \delta ppm 3.51 (s, 3H), 5.07 (s, 2H), 5.92 (s, 1H), 6.20 (s, 1H), 6.30 (d, 1H, J=8.4 Hz), 6.54 (d, 1H, J=8.4 Hz).

\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl\textsubscript{3}): \delta ppm 56.5, 97.6, 99.2, 101.7, 109.4, 132.23, 134.5, 141.5, 144.5

\textbf{EI-MS} (m/z, %): 198 (M\textsuperscript{+}, 100), 166 (29), 153 (33)

\textbf{HRMS}: Calc. for C\textsubscript{9}H\textsubscript{10}O\textsubscript{5}: 198.0528; Found: 198.05296

\textbf{IR (cm}\textsuperscript{-1}): 1049, 1217, 3540
4 - Methoxy - 5- methoxymethoxy - 1, 3 - benzodioxole 50

![Chemical Structure](image)

To a solution of phenol 49 (4.9 g, 24.7 mmol) in acetone (20 ml) was added K₂CO₃ (5.13 g, 37.1 mmol) and stirred for 30 min, after which CH₃I (15.5 ml, 247 mmol) was added and the resulting reaction mixture stirred at room temperature for 48 h. The solvent was then concentrated in vacuo and the crude residue was dissolved in water (10 ml) and 10% NaOH solution (25 ml). The aqueous phase was extracted with Et₂O (3 x 20 ml) and the combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated affording, after flash chromatography (9:1 hexane / ethyl acetate), compound 50 as a pale yellow liquid (5.05 g, 96%).

**¹H NMR (200 MHz, CDCl₃):** δ ppm 3.49 (s, 3H), 3.99 (s, 3H), 5.08 (s, 2H), 5.88 (s, 2H), 6.41 (d, 1H, J=8.4 Hz), 6.57 (d, 1H, J=8.6 Hz).

**¹³C NMR (50 MHz, CDCl₃):** δ ppm 56.1, 60.1, 96.6, 101.2, 101.4, 110.1, 135.4, 137.7, 144.1, 144.2

**EI-MS (m/z, %):** 212 (M⁺, 100), 182 (89), 167 (69)

**HRMS:** Calc. for C₁₀H₁₂O₅: 212.06846; Found: 212.07089

**IR (cm⁻¹):** 1056, 1155
5 - Hydroxy - 4 - methoxy - 1, 3 - benzodioxole 51

![Chemical Structure](image)

To a solution of 50 (4.86 g, 22.9 mmol) in acetone (15 ml) was added NaI (5.15 g, 34.3 mmol) and stirred for 30 min, after which 3N methanoic HCl (3:1 methanol / HCl, 40 ml) was added and the resulting reaction mixture stirred for 4 h. The solvent was concentrated and the crude residue dissolved in water (10 ml). The aqueous phase was extracted with Et₂O (3 x 15 ml) and the combined organic extracts were then washed with 10% NaOH solution (3 x 15 ml). The combined aqueous phase were acidified using conc. HCl and extracted with Et₂O (3 x 20 ml), dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide compound 51 as a pale orange crystals (2.81 g, 73%).

**¹H NMR** (200 MHz, CDCl₃): δ ppm 4.02 (s, 3H), 5.43 (s, 1H), 5.87 (s, 2H), 6.39 (s, 2H).

**¹³C NMR** (50 MHz, CDCl₃): δ ppm 59.9, 101.1, 101.8, 105.9, 131.4, 136.2, 142.1, 142.7

**EI-MS** (m/z, %): 168 (M⁺, 100), 153 (76)

**HRMS**: Calc. for C₈H₈O₄: 168.04224; Found: 168.04076

**IR (cm⁻¹)**: 1056, 1215, 3541

**MP**: 53-55 °C
To a solution of 51 (2.55 g, 15.2 mmol) in acetone (15 ml) was added anhydrous K$_2$CO$_3$ (3.15 g, 23.0 mmol) and allyl bromide (2 ml, 23.0 mmol). The resulting mixture was stirred and refluxes for 30 h. After cooling the reaction mixture to room temperature, the solvent was concentrated in vacuo and the crude residue was dissolved in water (20 ml) and 10% NaOH solution (10 ml). The aqueous phase extracted with Et$_2$O (3 x 20 ml) and the combined organic extracts were dried over anhydrous MgSO$_4$, filtered and concentrated to give the compound 52 as a yellow liquid (2.72 g, 86%).

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 3.97 (s, 3H), 4.47 (dt, 2H, J=5.4 Hz, 1.4 Hz), 5.22 (ddt, 1H, J=10.5 Hz, 1.6 Hz, 1.4 Hz), 5.35 (ddt, 1H, J=17.3 Hz, 1.6 Hz, 1.6 Hz), 5.86 (s, 1H), 6.00-6.06 (m, 1H), 6.32 (d, 1H, J=8.5 Hz), 6.38 (d, 1H, J=8.5 Hz).

$^{13}$C NMR (50 MHz, CDCl$_3$): δ ppm 60.2, 71.2, 101.1, 101.2, 107.2, 117.5, 133.6, 134.9, 138.1, 143.4, 146.2

EI-MS (m/z, %): 208 (M$^+$, 39), 167 (100)

HRMS: Calc. for C$_{11}$H$_{12}$O$_4$: 208.07356; Found: 208.07554

IR (cm$^{-1}$): 977, 929, 1247
5-Hydroxy - 4-methoxy - 6-(2-propenyl)-1,3-benzodioxole 53

A solution of allyl ether 52 (0.46 g, 20 mmol) in N,N-dimethylaniline (5 ml) was heated at 190 °C for 2.5 h by means of oil bath and then cooled to room temperature. The solution was diluted with Et₂O (7 ml) and washed several times with 10% NaOH solution. The alkaline extract was acidified with conc. HCl and extracted with Et₂O (3 x 15 ml). The combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) to give compound 53 as a pale yellowish liquid (0.40 g, 87%).

¹H NMR (200 MHz, CDCl₃): δ ppm 3.30 (d, 2H, J=6.6 Hz), 4.03 (s, 3H), 5.00-5.11 (m, 2H), 5.43 (s, 1H), 5.84 (s, 2H), 5.85-6.02 (m, 1H), 6.33 (s, 1H).

¹³C NMR (50 MHz, CDCl₃): δ ppm 33.7, 59.9, 100.9, 102.8, 115.4, 117.5, 131.1, 143.2, 136.7, 139.9, 141.6

EI-MS (m/z, %): 208 (M⁺, 100)

HRMS: Calc. for C₁₁H₁₂O₄: 208.07356; Found: 208.07308

IR (cm⁻¹): 926, 987, 1054, 1215
4, 5 - Dimethoxy - 6 - (2 - propenyl) -1, 3 - benzodioxole 7

To a stirred solution of phenol 53 (0.14 g, 0.70 mmol) in acetone (5 ml) was added K$_2$CO$_3$ (0.14 g, 1.0 mmol) and stirred for 30 min, after which CH$_3$I (0.5 ml, 8.0 mmol) was added and the resulting mixture was stirred at room temperature for 118 h. The solvent was concentrated and the crude residue dissolved in water (5 ml) and 10% NaOH solution (10 ml). The aqueous phase was extracted with Et$_2$O (3 x 10 ml) and the combined organic extracts were dried over anhydrous MgSO$_4$, filtered and concentrated to provide compound 7 as a pale yellowish liquid (0.13 g, 80%).

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 3.28 (dt, 2H, J=6.5 Hz, 1.4 Hz), 3.73 (s, 3H), 3.99 (s, 3H), 5.00-5.04 (m, 2H), 5.85 (s, 2H), 5.86-5.92 (m, 1H), 6.33 (s, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ ppm 33.9, 59.9, 61.2, 101.0, 102.7, 115.5, 126.0, 135.9, 137.3, 137.6, 144.3, 144.6

EI-MS (m/z, %): 222 (M$^+$, 100), 177 (22)

HRMS: Calc. for C$_{12}$H$_{14}$O$_4$: 222.08922; Found: 222.08817

IR (cm$^{-1}$): 923, 998, 1063, 1215
5 - Methoxymethoxy - 4 - thiomethyl - 1, 3 - benzodioxole 86a

\[ \text{86a} \]

To a cooled (0 °C) solution of 38 (5 g, 27.5 mmol) in dry THF was added 1 eq of nBuLi (12.5 ml, 2.2 M). The reaction mixture was stirred for 30 min and then 1.5 eq of dimethyl disulfide (4 ml, 41.2 mmol) was added. The resulting mixture was stirred at room temperature and was monitored using tlc, eluting with 3:1 hexane / ethyl acetate, and was found to be completed after 3 h. The reaction mixture was quenched using NH₄Cl solution (sat., 10 ml) and then the aqueous phase extracted with Et₂O (3 x 20 ml). The organic phase was then washed with water (3 x 15 ml) and dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide compound 86a as a pale yellow liquid (5.7 g, 91%).

\(^1\)H NMR (200 MHz, CDCl₃): \( \delta \) ppm 2.41 (s, 3H), 3.47 (s, 3H), 5.92 (s, 2H), 5.11 (s, 2H), 5.92 (s, 2H), 6.52 (d, 1H, J=8.6 Hz), 6.59 (d, 1H, J=8.6 Hz).

\(^13\)C NMR (50 MHz, CDCl₃): \( \delta \) ppm 16.9, 56.1, 95.9, 101.2, 106.7, 107.8, 108.8, 142.3, 148.5, 151.7

EI-MS (m/z): 228 (M⁺, 100), 198 (63), 182 (17)

HRMS: Calc. for C₁₀H₁₂O₄S: 228.04563; Found: 228.04679

IR (cm⁻¹): 1044, 1240
5-Hydroxy-4-thiomethyl-1,3-benzodioxole 87a

\[
\begin{align*}
\text{SCH}_3 & \\
\text{O} & \\
\text{O} & \\
\text{OH} & \\
87a
\end{align*}
\]

To a solution of 86a (4 g, 18 mmol) in acetone (15 ml) was added NaI (3.94 g, 26 mmol) and stirred for 30 min, after which 3N methanoic HCl (3:1 methanol / HCl, 40 ml) was added and the resulting reaction mixture stirred for 4 h. The solvent was concentrated and the crude residue was dissolved in water (10 ml). The aqueous phase was extracted with Et₂O (3 x 15 ml) and the combine organic extracts were then washed with 10% NaOH solution (3 x 15 ml). The combined alkaline phase was acidified using conc. HCl and extracted with Et₂O (3 x 20 ml), dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide phenol, 87a, as white powder (2.65g, 80%).

\(^1\)H NMR (500 MHz, CDCl₃): δ ppm 2.31 (s, 3H), 5.98 (s, 2H), 6.22 (s, 1H), 6.42 (d, 1H, J=8.4 Hz), 6.69 (d, 1H, J=8.4 Hz).

\(^13\)C NMR (50 MHz, CDCl₃): δ ppm 18.0, 101.6, 103.4, 105.4, 109.4, 140.7, 149.3, 151.2

EI-MS (m/z, %): 184 (M⁺, 100), 169 (30)

HRMS: Calc. for C₈H₆O₂S: 184.01941; Found: 184.01633

IR (cm\(^{-1}\)): 3428

MP: 51-53 °C
5 - (2 - Propenloxy) - 4 - thiomethyl - 1, 3 - benzodioxole 88a

![Chemical Structure](image)

To a solution of 87a (1.89 g, 10.3 mmol) and in acetone (15 ml) was added anhydrous K$_2$CO$_3$ (2.13 g, 15.0 mmol) and stirred for 30 min, after which allyl bromide (0.9 ml, 10.3 mmol) was added and the resulting mixture was stirred and refluxed for 23 h. After cooling the reaction mixture to room temperature, the solvent was concentrated in vacuo. The crude residue was dissolved in water (5 ml) and 10% NaOH solution (10 ml) and the aqueous phase extracted with Et$_2$O (3 x 10 ml). The combined organic extracts were dried over anhydrous MgSO$_4$, filtered and concentrated to give compound 88a as a clear liquid (2.03 g, 88%).

$^1$H NMR (200 MHz, CDCl$_3$): δ ppm 2.46 (s, 1H), 4.53 (dt, 2H, J=5.1 Hz, 1.4 Hz), 5.28 (dd, 1H, J=10.5 Hz, 1.5 Hz), 5.44 (dd, 1H, J=17.0 Hz, 1.6 Hz), 5.97 (s, 2H), 6.00-6.09 (m, 1H), 6.31 (d, 1H, J=8.5 Hz), 6.63 (d, 1H, J=8.5 Hz).

$^{13}$C NMR (50 MHz, CDCl$_3$): δ ppm 16.9, 70.3, 101.2, 104.5, 106.4, 117.4, 133.1, 133.8, 141.5, 148.7, 153.3

EI-MS (m/z, %): 224.1 (M$^+$, 100), 184 (13), 137 (98)

HRMS: Calc. for C$_{11}$H$_{12}$O$_3$S: 224.05073; Found: 224.05332

IR (cm$^{-1}$): 929, 953, 1448, 1606
5-Hydroxy - 6-(2-propenyl) - 4-thiomethyl - 1, 3-benzodioxole 89a

A solution of allyl ether 88a (1.0g, 4.0 mmol) in N, N-dimethylaniline (5 ml) was heated at 190 °C for 2.5 h by means of oil bath and then cooled to room temperature. The solution was diluted with Et₂O (7 ml) and washed several times with 10% NaOH solution. The alkaline extract was acidified with conc. HCl and extracted with Et₂O (3 x 15 ml). The combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) to give the compound 89a as a pale yellowish liquid (0.87 g, 87%).

¹H NMR (200 MHz, CDCl₃): δ ppm 2.31 (s, 3H), 3.32 (dt, 2H, J=6.8 Hz, 1.4 Hz), 5.01-5.11 (m, 2H), 5.95 (s, 2H), 5.88-6.02 (m, 1H), 6.40 (s, 1H), 6.62 (s, 1H).

¹³C NMR (50 MHz, CDCl₃): δ ppm 18.0, 34.4, 101.3, 102.9, 110.4, 115.5, 117.1, 136.6, 140.3, 147.5, 148.2

EI-MS (m/z, %): 224 (M⁺, 100), 197 (9), 176 (18)

HRMS: Calc. for C₁₁H₁₂O₃S: 224.05073; Found: 224.04925

IR (cm⁻¹): 927, 953, 3425
5-Methoxy-6-(2-propenyl)-4-thiomethyl-1,3-benzodioxole 90a

To a stirred solution of phenol 89a (0.4 g, 1.8 mmol) in acetone (5 ml) was added K₂CO₃ (0.37 g, 3.0 mmol) and stirred for 30 min, after which CH₃I (1.1 ml, 18.0 mmol) was added and the resulting mixture was stirred at room temperature for 77 h. The solvent was concentrated and the crude residue was dissolved in water (5 ml) and 10% NaOH solution (10 ml). The aqueous phase was extracted with Et₂O (3 × 10 ml) and the combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated to provide compound 90a as a pale yellowish liquid (0.37 g, 87%).

^1H NMR (500 MHz, CDCl₃): δ ppm 2.45 (s, 3H), 3.30 (dt, 2H, J=6.5 Hz, 1.4 Hz), 3.75 (s, 3H), 5.01-5.05 (m, 2H), 5.93 (s, 2H), 5.84-5.92 (m, 1H), 6.53 (s, 1H).

^13C NMR (125 MHz, CDCl₃): δ ppm 16.9, 34.0, 61.4, 101.3, 108.2, 112.3, 115.7, 125.8, 137.1, 143.4, 146.8, 151.8

EI-MS (m/z, %): 238 (M⁺, 100), 223 (13), 176 (41)

HRMS: Calc. for C₁₂H₁₄O₃S: 238.06639; Found: 238.06815

IR (cm⁻¹): 949, 996, 1054
5-Methoxy-4-methylsulfinyl-6-(2-propenyl)-1,3-benzodioxole 91a

To a cooled (-40°C) solution of 90a (100 mg, 42.0 mmol) in ethyl acetate (6 ml) was added 1.2eq of mCPBA (80 mg, 0.5 mmol). The reaction was allowed to warm up to room temperature and stirred for 24 h. After 24 h, the reaction mixture was washed with sodium sulfite (sat., 2 x10 ml), sodium bicarbonate (sat., 1 x 10 ml) and water (1 x 10 ml). The extract was dried over anhydrous MgSO4, filtered and evaporated to dryness. The resulting oily residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) affording compound 91a as a pale yellow liquid (6.7mg, 63%).

**1H NMR** (500 MHz, CDCl3): δ ppm 3.01 (s, 3H), 3.16 (dd, 2H, J=6.4 Hz, 1.5 Hz), 3.78 (s, 3H), 5.03-5.09 (m, 2H), 5.84-5.89 (m, 1H), 6.06 (s, 2H), 6.74 (s, 1H).

**13C NMR** (50MHz, CDCl3): δ ppm 33.1, 39.7, 63.4, 102.7, 112.3, 116.5, 120.8, 126.1, 136.3, 145.0, 145.5, 149.1

**EI-MS** (m/z, %): 254 (M+, 83), 237 (100)

**HRMS**: Calc. for C12H14O4S: 254.06129; Found: 254.06070

**IR** (cm⁻¹): 942, 994, 1050
5 - Methoxy - 4 - methylsulfonyl - 6 - (2 - propenyl) - 1,3 - benzodioxaole 92a

To a solution of 90a (50 mg, 0.21 mmol) in ethyl acetate (6 ml) was added 4eq of mCPBA (144 mg, 8.40 mmol). The reaction was stirred at room temperature for 24 h, after which it was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 2 x 10 ml) and water (4 x 10 ml). The extract was dried over anhydrous MgSO₄, filtered and evaporated to dryness, purified by flash column chromatography (9:1 hexane / ethyl acetate) to provide compound 92a as pale yellow crystals (45 mg, 80%).

1H NMR (500 MHz, CDCl₃): δ ppm 3.26 (s, 3H), 3.54 (d, 2H, J=6.5 Hz), 3.84 (s, 3H), 5.06-5.13 (m, 2H), 5.84-5.92 (m, 1H), 6.05 (s, 2H), 6.83 (s, 1H).

13C NMR (50 MHz, CDCl₃): δ ppm 32.1, 44.8, 63.8, 102.8, 113.9, 117.0, 118.1, 127.0, 135.9, 145.0, 145.2, 149.2

EI-MS (m/z, %): 270 (M⁺, 100)

HRMS: Calc. for C₁₂H₁₄O₂S: 270.05619; Found: 270.05406

IR (cm⁻¹): 950, 993, 1136, 1316
5-Methoxymethoxy-4-thiophenyl-1,3-benzodioxole 86b

To a cooled (0 °C) solution of 38 (1.5g, 8.0 mmol) in dry THF was added 1eq of nBuLi (3.3 ml, 2.5 M). The reaction mixture was stirred for 30 min and then 1eq of phenyl disulfide (1.8 g, 8.0 mmol) was added. The resulting mixture was stirred at room temperature and was monitored using tlc, eluting with 9:1 hexane / ethyl acetate. It was completed after 16 h. The reaction mixture was quenched using NH₄Cl solution (sat., 10 ml) and then the aqueous phase extracted with EtOAc (3 x 20 ml). The organic phase was then washed with water (3 x 15 ml) and dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide compound 86b, as white crystals (0.67 g, 30%)

^1H NMR (200 MHz, CDCl₃): δ ppm 3.33 (s, 3H), 5.05 (s, 2H), 5.93 (s, 2H), 6.63 (d, 1H, J=8.5 Hz), 6.77 (d, 1H, J=8.5 Hz), 7.08-7.20 (m, 5H).

^13C NMR (50 MHz, CDCl₃): δ ppm 56.1, 95.7, 101.6, 104.2, 107.8, 108.8, 125.5, 127.1, 128.7, 136.2, 142.5, 150.4, 152.7

EI-MS (m/z, %): 290 (M⁺, 51), 260 (25), 91 (50)

HRMS: Calc. for C₁₅H₁₄O₄S: 290.06129; Found: 290.06001

IR: 689, 1050, 1225, 1452, 1478

MP: 67-69 °C
5 - Hydroxy - 4-thiophenyl - 1, 3 - benzodioxole 87b

To a solution of 86b (0.67g, 2.30 mmol) in acetone (10 ml) was added NaI (0.52 g, 3.50 mmol) and stirred for 30 min, after which 3N methanoic HCl (3:1 methanol / HCl, 8 ml) was added and the resulting reaction mixture stirred for 1 h. The solvent was concentrated and the crude residue was dissolved in water (10 ml). The aqueous phase was extracted with EtOAc (3 x 15 ml), dried over anhydrous MgSO₄, filtered and concentrated in vacuo, purified by flash column chromatography (9: 1 hexane / ethyl acetate) to provide phenol, 87b, as white powder (0.60g, >99%).

^1H NMR (200 MHz, CDCl₃): δ ppm 5.96 (s, 2H), 6.18 (s, 1H), 6.52 (d, 1H, J=8.5 Hz), 6.81 (d, 1H, J=8.6 Hz), 7.12-7.26 (m, 5H).

^13C NMR (50 MHz, CDCl₃): δ ppm 99.5, 101.9, 105.9, 110.8, 126.5, 127.0, 129.3, 134.2, 141.0, 150.1, 151.9

EI-MS (m/z, %): 246 (M⁺, 100), 162 (23), 140 (49)

HRMS: Calc. for C₁₃H₁₀O₃S: 246.03507; Found: 246.03335

IR (cm⁻¹): 1050, 1453, 1478, 3441

MP: 119 - 122 °C
5 - (2 - Propenyl oxy) - 4 - thiophenyl - 1, 3 - benzodioxole 88b

To a solution of 87b (1.62 g, 6.60 mmol) and in acetone (15 ml) was added anhydrous K₂CO₃ (1.10 g, 8.0 mmol) and stirred for 30 min, after which allyl bromide (0.63 ml, 7.0 mmol) was added and the resulting mixture was stirred and refluxes for 23 h. After cooling the reaction mixture to room temperature, the solvent was concentrated in vacuo. The crude residue was dissolved in water (5 ml) and 10% NaOH solution (10 ml) and the aqueous phase extracted with Et₂O (3 x 10 ml). The combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated to give compound 88b as yellow oil (1.52 g, 81%).

¹H NMR (200 MHz, CDCl₃): δ ppm 4.44 (dt, 2H, J=5.0 Hz, 1.6 Hz), 5.15 (ddt, 1H, J=10.5 Hz, 1.6 Hz, 1.5 Hz), 5.25 (ddt, 1H, J=17.0 Hz, 1.7 Hz, 1.6 Hz), 5.76-5.95 (m, 1H), 5.93 (s, 2H), 6.35 (d, 1H, J=8.5 Hz), 6.75 (d, 1H, J=8.5 Hz), 7.07-7.22 (m, 5H).

¹³C NMR (50 MHz, CDCl₃): δ ppm 70.3, 101.6, 103.5, 104.9, 108.4, 117.2, 125.4, 127.3, 128.6, 132.8, 136.2, 141.7, 150.5, 145.1

EI-MS (m/z, %): 268 (M⁺, 52), 245 (52), 91 (100)

HRMS: Calc. for C₁₆H₁₄O₂S: 286.06639; Found: 286.06491

IR (cm⁻¹): 943, 996, 1059, 1234, 1684, 2893
5-Hydroxy-6-(2-propenyl)-4-thiophenyl-1,3-benzodioxole 89b

A solution of allyl ether 88b (1.50 g, 5.20 mmol) in N,N-dimethylaniline (5 ml) was heated at 190 °C for 3.5 h by means of oil bath and then cooled to room temperature. The solution was diluted with Et₂O (10 ml) and washed several times with 25% NaOH solution. The alkaline extract was acidified with conc. HCl and extracted with Et₂O (3x 15 ml). The combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 hexane/ethyl acetate) to give the compound 89b as a pale yellow oil (0.55 g, 37%).

¹H NMR (500 MHz, CDCl₃): δ ppm 3.35 (dt, 2H, J=6.4 Hz, 1.4 Hz), 5.05-5.09 (m, 2H), 5.92 (s, 2H), 5.93-5.99 (m, 1H), 6.31 (s, 1H), 6.73 (s, 1H), 7.13-7.23 (m, 5H).

¹³C NMR (125 MHz, CDCl₃): δ ppm 34.4, 99.0, 101.5, 111.9, 115.7, 117.6, 126.5, 127.0, 129.3, 134.3, 136.5, 140.6, 148.3, 148.9

EI-MS (m/z, %): 286 (M⁺, 100), 162 (8)

HRMS: Calc. for C₁₆H₁₄O₃S: 286.06639; Found: 286.06414

IR (cm⁻¹): 953, 997, 1050, 1638, 2897, 3443
4 - Methoxy - 6 - (2 - propenyl) - 4 - thiophenyl - 1, 3 - benzodioxole 90b

To a stirred solution of phenol 89b (0.55g, 1.9 mmol) in acetone (15 ml) was added K₂CO₃ (0.32 g, 2.0 mmol) and stirred for 30 min, after which CH₃I (1.21 ml, 13.0 mmol) was added and the resulting mixture was stirred at room temperature for 77 h. The solvent was concentrated and the crude residue dissolved in water (5 ml) and 10% NaOH solution (10 ml). The aqueous phase was extracted with Et₂O (3 x 10 ml) and the combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated to provide compound 90b as pale yellow oil (0.50 g, 87 %).

¹H NMR (200 MHz, CDCl₃): δ ppm 3.35 (dt, 2H, J=6.4 Hz, 1.4Hz), 3.73 (s, 3H), 5.02-5.11 (m, 2H), 5.91 (s, 2H), 5.86-6.05 (m, 1H), 6.71 (s, 1H), 7.10-7.22 (m, 5H).

¹³C NMR (50 MHz, CDCl₃): δ ppm 34.2, 62.2, 101.6, 107.6, 110.4, 116.0, 125.6, 126.2, 127.1, 128.9, 136.2, 137.1, 143.7, 148.6, 153.2

EI-MS (m/z, %): 300 (M⁺, 100), 176 (48), 162 (15)

HRMS: Calc. for C₁₇H₁₆O₃S: 300.08205; Found: 300.08021

IR (cm⁻¹): 948, 995, 1055, 1210, 1639
5-Methoxy-4-phenylsulfonyl-6-(2-propenyl)-1,3-benzodioxole 91b

To a cooled (−40°C) solution of 90b (0.10g, 0.03 mmol) in ethyl acetate (6 ml) was added 1.2 eq of mCPBA (0.07g, 0.40 mmol). The reaction was allowed to warm up to room temperature and stirred for 24 h. After 24 h, the reaction mixture was washed with sodium sulfite (sat., 2 x 10ml), sodium bicarbonate (sat., 1 x 10 ml) and water (1 x 10 ml). The extract was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The resulting oily residue was purified by flash column chromatography (3:1 hexane / ethyl acetate) affording compound 91b as white solid (0.08g, 76%).

$^1$H NMR (500 MHz, CDCl₃): δ ppm 3.29 (d, 2H, J=6.4 Hz), 3.85 (s, 3H), 5.00-5.07 (m, 2H), 5.82 (s, 1H), 5.82-5.88 (m, 1H), 5.97 (s, 1H), 6.68 (s, 1H), 7.24-7.71 (m, 5H).

$^{13}$C NMR (75 MHz, CDCl₃): δ ppm 33.0, 63.2, 102.6, 112.4, 116.5, 124.3, 125.8, 128.8, 130.3, 136.2, 143.8, 145.4

EI-MS (m/z, %): 316 (M⁺, 39), 299 (100), 190 (59)

HRMS: Calc. for C₁₇H₁₆O₅S: 316.07695; Found: 316.07656

IR (cm⁻¹): 948, 994, 1054, 1218, 1639

MP: 83-87 °C
5 - Methoxy - 4 - phenylsulfonyl - 6 - (2 - propenyl) - 1, 3 - benzodioxole 92b

![Chemical Structure](image)

To a solution of 90b (90mg, 0.21 mmol) in ethyl acetate (6 ml) was added 2eq of mCPBA (90 mg, 0.50 mmol). The reaction was stirred at room temperature for 24 h, after which it was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 2 x 10 ml) and water (4 x 10 ml). The extract was dried over anhydrous MgSO₄, filtered and evaporated to dryness, purified by flash column chromatography (3:1 hexane /ethyl acetate) to provide compound 92b as white solid (70 mg, 71%).

**¹H NMR (500 MHz, CDCl₃):** δ ppm 3.23 (dt, 2H, J=6.4 Hz, 1.5 Hz), 3.80 (s, 3H), 5.03-5.07 (m, 2H), 5.77-5.82 (m, 1H), 6.08 (s, 2H), 6.78 (s, 1H), 7.41-7.57 (m, 5H).

**¹³C NMR (75 MHz, CDCl₃):** δ ppm 33.0, 63.6, 102.8, 114.0, 116.9, 118.7, 126.9, 127.5, 128.7, 133.2, 136.0, 142.6, 145.0, 145.4, 149.3

**EI-MS (m/z, %):** 332 (M⁺, 100), 176 (34)

**HRMS:** Calc. for C₁₇H₁₆O₅S: 332.07185; Found: 332.06986

**IR (cm⁻¹):** 992, 953, 1148, 1319, 1701

**MP:** 86-88 °C
5 - Methoxymethoxy - 4 - thiomethylphenyl - 1, 3 - benzodioxole 86c

![Chemical Structure](image)

To a cooled (0 °C) solution of 38 (3.0 g, 16.0 mmol) in dry THF was added 1 eq of nBuLi (7.0 ml, 2.5 M). The reaction mixture was stirred for 30 min and then 1.2 eq of benzyl disulfide (5.35, 0.022mol) was added. The resulting mixture was stirred at room temperature and was monitored using tlc, eluting with 9:1 hexane / ethyl acetate. It was completed after 16 h. The reaction mixture was quenched using NH₄Cl solution (sat., 10 ml) and then the aqueous phase extracted with EtOAc (3 x 20 ml). The organic phase was then washed with water (3 x 15 ml) and dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide compound 86c as a yellow oil (2.37 g, 58%).

**¹H NMR (200 MHz, CDCl₃):** δ ppm 3.45 (s, 3H), 4.07 (s, 2H), 5.03 (s, 2H), 5.85 (s, 2H), 6.54 (d, 1H, J=8.5 Hz), 6.63 (d, 1H, J=8.5 Hz), 7.20 (s, 5H).

**¹³C NMR (50 MHz, CDCl₃):** δ ppm 38.0, 56.1, 96.0, 101.2, 106.5, 107.4, 107.9, 126.9, 128.1, 128.8, 138.0, 142.2, 149.5, 152.5

**EI-MS (m/z, %):** 304 (M⁺, 29), 259 (18), 182 (26), 91 (100)

**HRMS:** Calc. for C₁₆H₁₆O₄S: 304.07919; Found: 304.07584

**IR:** 1041, 1226, 1496, 1601
5 - Hydroxy - 4 - thiomethylphenyl - 1, 3 - benzodioxole 87c

To a solution of 86c (2.51 g, 8.20 mmol) in acetone (10 ml) was added NaI (1.86 g, 12.0 mmol) and stirred for 30 min, after which 3N methanoic HCl (3:1 methanol / HCl, 40 ml) was added and the resulting reaction mixture stirred for 1 h. The solvent was concentrated and the crude residue was dissolved in water (10 ml). The aqueous phase was extracted with EtOAc (3 x 15 ml), dried over anhydrous MgSO₄, filtered and concentrated in vacuo, purified by flash column chromatography (9: 1 hexane / ethyl acetate) to provide phenol, 87c, as yellow oil (1.68 g, 91%).

¹H NMR (500 MHz, CDCl₃): δ ppm 3.87 (s, 2H), 5.85 (s, 2H), 6.03 (s, 1H), 6.35 (d, 1H, J=8.4 Hz), 6.68 (d, 1H, J=8.4 Hz), 7.10-7.25 (m, 5H).

¹³C NMR (50 MHz, CDCl₃): δ ppm 39.3, 101.0, 101.5, 105.3, 109.8, 127.4, 128.4, 128.7, 137.2, 140.4, 149.8, 151.7

EI-MS (m/z, %): 260 (M⁺, 36), 169 (8.2), 91 (100)

HRMS: Calc. for C₁₄H₁₂O₃S: 260.0507; Found: 260.05124

IR (cm⁻¹): 1050, 1206, 1496, 1601, 3434
5 - (2-Propenyloxy) - 4 - thiomethylphenyl - 1,3 - benzodioxole 88c

![Chemical Structure](image)

To a solution of 87c (1.68g, 6.50 mmol) and in acetone (15 ml) was added anhydrous K₂CO₃ (1.10 g, 8.0 mmol) and stirred for 30 min, after which allyl bromide (0.63 ml, 7.0 mmol) was added and the resulting mixture was stirred and refluxed for 23 h. After cooling the reaction mixture to room temperature, the solvent was concentrated in vacuo. The crude residue was dissolved in water (5 ml) and 10% NaOH solution (10 ml) and the aqueous phase extracted with Et₂O (3 x 10 ml). The combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated to give compound 88c as white oil (1.39 g, 83%).

^1H NMR (CDCl₃): δ ppm 4.09 (s, 2H), 4.46 (d, 2H, J=5.1 Hz), 5.27 (dd, 1H, J=10.5 Hz, 1.5 Hz), 5.43 (dd, 1H, J=15.6 Hz, 1.6 Hz), 5.84 (s, 2H), 5.95-6.11 (m, 1H), 6.30 (d, 1H, J=8.4 Hz), 6.62 (d, 1H, J=9.2 Hz), 7.21 (s, 5H).

^13C NMR (CDCl₃): δ ppm 37.9, 70.3, 101.1, 104.6, 105.5, 107.1, 117.3, 126.8, 128.1, 128.8, 133.1, 138.0, 141.3, 149.7, 153.9

EI-MS (m/z, %): 300 (M⁺, 30), 259 (38), 91 (100)

HRMS: Calc. for C₁₇H₁₆O₃S: 300.08205; Found: 300.08198

IR (cm⁻¹): 953, 995, 1060, 1234, 1448, 1495, 1602
5-Hydroxy-6-(2-propenyl)-4-thiomethylphenyl-1,3-benzodioxole 89c

A solution of allyl ether 88c (0.43 g, 1.40 mmol) in N,N-dimethylaniline (4 ml) was heated at 190 °C for 2.5 h by means of oil bath and then cooled to room temperature. The solution was diluted with EtOAc (10 ml) and conc. HCl (3 ml) was added. The solution was extracted with EtOAc. The combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) to give the compound 34 as a pale yellow oil (0.42 g, 98%).

^1H NMR (200 MHz, CDCl₃): δ ppm 3.25 (d, 2H, J=6.4 Hz), 3.87 (s, 2H), 4.93-5.04 (m, 2H), 5.82-5.96 (m, 1H), 5.83 (s, 2H), 6.18 (s, 1H), 6.61 (s, 1H), 7.08-7.25 (m, 5H).

^13C NMR (75 MHz, CDCl₃): δ ppm 34.4, 39.4, 100.6, 101.2, 110.9, 115.3, 116.9, 127.4, 128.5, 128.7, 136.6, 137.2, 140.1, 148.0, 148.8

EI-MS (m/z, %): 300 (M⁺, 48), 224 (91), 209 (28), 176 (48)

HRMS: Calc. for C₁₇H₁₅O₃S: 300.08205; Found: 300.08239

IR: 954, 997, 1051, 1215, 1497, 1602, 1638, 3429
5-Methoxy-6-(2-propenyl)-4-thiomethylphenyl-1,3-benzodioxole 90c

To a stirred solution of phenol 89c (0.42 g, 1.40 mmol) in acetone (15 ml) was added K$_2$CO$_3$ (0.23 g, 1.70 mmol) and stirred for 30 min, after which CH$_3$I (0.88 ml, 14.0 mmol) was added and the resulting mixture was stirred at room temperature for 77 h. The solvent was concentrated and the crude residue dissolved in water (5 ml) and 10% NaOH solution (10 ml). The aqueous phase was extracted with Et$_2$O (3 x 10 ml) and the combined organic extracts were dried over anhydrous MgSO$_4$, filtered and concentrated to provide compound 90c as a pale yellow oil (0.42 g, 96%).

$^1$H NMR (200 MHz, CDCl$_3$): δ ppm 3.30 (dt, 2H, J=6.4 Hz, 1.5 Hz), 3.65 (s, 3H), 4.12 (s, 2H), 4.96-5.07 (m, 2H), 5.88 (s, 2H), 5.83-5.95 (m, 1H), 6.55 (s, 1H), 7.17-7.24 (m, 5H).

$^{13}$C NMR (CDCl$_3$): δ ppm 34.0, 37.9, 61.6, 101.3, 108.9, 109.9, 115.7, 125.7, 127.0, 128.3, 128.9, 137.2, 138.0, 143.2, 147.6, 152.5

EI-MS (m/z, %): 314 (M$^+$, 72), 223 (11), 91 (100)

HRMS: Calc. for C$_{18}$H$_{18}$O$_3$S: 314.09771; Found: 314.09530

IR (cm$^{-1}$): 950, 994, 1054, 1213, 1457, 1601, 1638
5 - Methoxy - 4 -(phenylmethane)sulfinyl - 6 -(2 - propenyl) - 1, 3 - benzodioxole 91c

To a cooled (-40°C) solution of 90c (0.11 g, 0.40 mmol) in ethyl acetate (10 ml) was added 1.2eq of mCPBA (0.07g, 0.40 mmol). The reaction was allowed to warm up to room temperature and stirred for 24 h. After 24 h, the reaction mixture was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 1 x 10 ml) and water (1 x 10ml). The extract was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The resulting oily was residue was purified by flash column chromatography (3:1 hexane / ethyl acetate) affording compound 91c as a pale yellow oil (0.07g, 61%).

^1H NMR (500 MHz, CDCl₃): δ ppm 3.24 (d, 2H, J=6.3 Hz), 3.56 (s, 3H), 4.34 (d, 1H, J=12.5 Hz), 4.45 (d, 1H, J=12.5 Hz), 5.00-5.06 (m, 2H), 5.82 (d, 1H, J=1.34), 5.90 (d, 1H, J=1.4 Hz), 5.81-5.87 (m, 1H), 6.67 (s, 1H), 7.10-7.24 (m, 5H).

^13C NMR (125 MHz, CDCl₃): δ ppm 33.0, 59.2, 63.0, 102.6, 112.3, 116.3, 118.6, 125.8, 128.1, 128.4, 130.2, 130.3, 136.4, 145.2, 145.8, 149.4

EI-MS (m/z, %): 330 (M⁺, 21), 283 (47), 91 (100)

HRMS: Calc. for C₁₈H₁₈O₄S: 330.09261; Found: 330.09099

IR (cm⁻¹): 951, 992, 1049, 1071, 1215, 1462
5 - Methoxy - 4 -(phenylmethane)sulfonyl - 6 -(2 - propenyl) - 1, 3 - benzodioxole 92c

To a solution of 90c (80 mg, 0.25 mmol) in ethyl acetate (6 ml) was added 2eq of mCPBA (90 mg, 0.50 mmol). The reaction was stirred at room temperature for 24 h, after which it was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 2 x 10 ml) and water (4 x 10 ml). The extract was dried over anhydrous MgSO₄, filtered and evaporated to dryness, purified by flash column chromatography (3:1 hexane / ethyl acetate) to provide compound 92c as a white solid (40 mg, 45%).

¹H NMR (500 MHz, CDCl₃): δ ppm 3.35 (d, 2H, J=6.4 Hz), 3.88 (s, 3H), 4.57 (s, 2H), 5.05-5.15 (m, 2H), 5.82 (s, 2H), 5.88-5.93 (m, 1H), 6.77 (s, 1H), 7.20-7.24 (m, 5H).

¹³C NMR (125 MHz, CDCl₃): δ ppm 33.2, 62.2, 63.9, 102.6, 114.1, 116.8, 126.7, 128.1, 128.3, 128.5, 130.9, 133.9, 144.9, 146.3, 149.4

EI-MS (m/z, %): 346 (M⁺, 34), 139 (16), 91 (100)

HRMS: Calc. for C₁₇H₁₈O₅S: 346.08751; Found: 346.08519

IR (cm⁻¹): 1052, 1149, 1215, 1320, 1462

MP: 133-136 °C
5 - Methoxymethoxy - 4 - thio (4-methoxyphenyl) - 1, 3 - benzodioxole 86d

![Chemical Structure](image)

To a cooled (0 °C) solution of 38 (420 mg, 2.0 mmol) in dry THF was added 1 eq of nBuLi (0.92 ml, 2.5 M). The reaction mixture was stirred for 30 min and then 1 eq of p-methoxy disulfide (0.53 g, 2.0 mmol) was added. The resulting mixture was stirred at room temperature and was monitored using tlc, eluting with 9:1 hexane / ethyl acetate. It was completed after 16 h. The reaction mixture was quenched using NH₄Cl solution (sat., 10 ml) and then the aqueous phase extracted with EtOAc (3 x 20 ml). The organic phase was then washed with water (3 x 15 ml) and dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide compound 86d as white crystals (250 mg, 40%).

**¹H NMR** (200 MHz, CDCl₃): δ ppm 3.34 (s, 3H), 3.69 (s, 3H), 5.03 (s, 2H), 5.88 (s, 2H), 6.56 (d, 1H, J=8.5 Hz), 6.68 (d, 1H, J=8.5 Hz), 6.74 (d, 2H, J=8.9 Hz), 7.22 (d, 2H, J=8.9 Hz).

**¹³C NMR** (50 MHz, CDCl₃): δ ppm 55.0, 55.9, 95.7, 101.4, 106.3, 107.7, 108.1, 114.2, 126.2, 130.7, 142.3, 149.8, 152.3, 158.3

**EI-MS (m/z, %):** 320 (M⁺, 8.6), 278 (46), 139 (100)

**HRMS:** Calc. for C₁₆H₁₆O₅S: 320.07182; Found: 320.07059

**IR:** 1050, 1286, 1493, 1593

**MP:** 82-84°C
5 - Hydroxy - 4 - thio (4-methoxyphenyl) -1, 3 - benzodioxole 87d

To a solution of 86d (0.25 g, 0.78 mmol) in acetone (10 ml) was added NaI (0.18 g, 1.20 mmol) and stirred for 30 min, after which 3N methanoic HCl (3:1 methanol / HCl, 8 ml) was added and the resulting reaction mixture stirred for 2 h. The solvent was concentrated and the crude residue was dissolved in water (10 ml). The aqueous phase was extracted with EtOAc (3 x 15 ml), dried over anhydrous MgSO₄, filtered and concentrated in vacuo. purified by flash column chromatography (9: 1 hexane / ethyl acetate) to provide phenol, 87d, as white powder (0.18 g, 83%).

^1H NMR (200 MHz, CDCl₃): δ ppm 3.74 (s, 3H), 5.94 (s, 2H), 6.31 (s, 1H), 6.47 (d, 1H, J=8.5 Hz), 6.75 (d, 1H, J=8.4 Hz), 6.79 (d, 1H, J=6.9 Hz), 7.20 (d, 1H, J=7.6Hz).

^13C NMR (50 MHz, CDCl₃): δ ppm 55.3, 101.5, 101.7, 105.8, 110.4, 114.9, 124.5,130.4, 140.9, 149.8, 151.6, 159.0

EI-MS (m/z, %): 276 (M⁺, 100), 162 (18), 140 (44)

HRMS: Calc. for C₁₄H₁₂O₄S: 276.04563; Found: 276.04656

IR (cm⁻¹): 1047, 1246, 1494, 1593, 3443

MP: 82-83 °C
To a solution of 87d (1.10 g, 4.0 mmol) and in acetone (15 ml) was added anhydrous K$_2$CO$_3$ (0.83 g, 6.0 mmol) and stirred for 30 min, after which allyl bromide (0.41 ml, 5.0 mmol) was added and the resulting mixture was stirred and refluxed for 23 h. After cooling the reaction mixture to room temperature, the solvent was concentrated in vacuo. The crude residue was dissolved in water (5 ml) and 10% NaOH solution (10 ml) and the aqueous phase extracted with Et$_2$O (3 x 10 ml). The combined organic extracts were dried over anhydrous MgSO$_4$, filtered and concentrated to give compound 88d as clear oil (0.96 g, 76%).

$^1$H NMR (200 MHz, CDCl$_3$): δ ppm 3.72 (s, 3H), 4.43 (dt, 2H, J=5.1 Hz, 1.5 Hz), 5.18 (ddt, 1H, J=12 Hz, 1.6 Hz, 1.5 Hz), 5.31 (ddt, 1H, J=18 Hz, 1.7 Hz, 1.6 Hz), 5.90 (s, 2H), 5.83-5.97 (m, 1H), 6.30 (d, 1H, J=8.5 Hz), 6.67 (d, 1H, J=8.5 Hz), 6.75 (d, 2H, J=9.0 Hz), 7.26 (d, 2H, J=9.0 Hz).

$^{13}$C NMR (50 MHz, CDCl$_3$): δ ppm 55.1, 70.3, 101.4, 104.8, 105.6, 107.8, 114.2, 117.2, 126.3, 131.0, 132.9, 141.6, 149.9, 153.7, 158.4.

EI-MS (m/z, %): 316 (M$^+$, 32), 275 (30), 149 (100)

HRMS: Calc. for C$_{17}$H$_{16}$O$_4$S: 316.07696; Found: 316.07664

IR (cm$^{-1}$): 931, 953, 1059, 1227, 1449, 1493, 1593
5 - Hydroxy - 6 - (2 - propenyl) - 4 - thio (4-methoxyphenyl) - 1, 3 - benzodioxole 89d

A solution of allyl ether 88d (0.30 g, 0.90 mmol) in N, N-dimethylaniline (3 ml) was heated at 190 °C for 2.5 h by means of oil bath and then cooled to room temperature. The solution was diluted with EtOAc (10 ml) and conc. HCl (3 ml) was added. The solution was extracted with EtOAc. The combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) to give the compound 89d as a pale yellow oil (0.29g, 97%).

$^1$H NMR (500 MHz, CDCl₃): $\delta$ ppm 3.32 (d, 2H, $J$=6.5 Hz), 3.74 (s, 3H), 5.02 (s, 1H), 5.05 (d, 2H, $J$=6 Hz), 5.91 (s, 2H), 5.89-5.97 (m, 1H), 6.42 (s, 3H), 6.67 (s, 1H), 6.78 (d, 2H, $J$=8.7 Hz), 7.19 (d, 2H, $J$=8.7 Hz).

$^{13}$C NMR (125 MHz, CDCl₃): $\delta$ ppm 34.5, 55.4, 101.1, 101.5, 111.5, 114.9, 115.6, 117.5, 124.7, 130.4, 136.6, 140.6, 148.0, 148.7, 159.0

EI-MS (m/z, %): 316 ($M^+$, 100), 208 (22), 180 (47)

HRMS: Calc. for C₁₇H₁₆O₄S: 316.07695; Found: 316.07487

IR (cm$^{-1}$): 949, 995, 1051, 1244, 1493, 1593, 1638, 3440
5 - Hydroxy - 6 - (2 - propenyl) - 4 - thio (4-methoxyphenyl) - 1, 3 - benzodioxole 90d

To a stirred solution of phenol 89d (0.17 g, 0.50 mmol) in acetone (5 ml) was added K₂CO₃ (0.09g, 0.60 mmol) and stirred for 30 min, after which CH₃I (0.34 ml, 10.0 mmol) was added and the resulting mixture was stirred at room temperature for 77 h. The solvent was concentrated and the crude residue dissolved in water (5 ml) and 10% NaOH solution (10 ml). The aqueous phase was extracted with Et₂O (3 x 10 ml) and the combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated to provide compound 90d as pale yellow oil (0.17 g, 96 %).

¹H NMR (500 MHz, CDCl₃): δ ppm 3.34 (dt, 2H, J=6.5 Hz, 1.5 Hz), 3.73 (s, 3H), 3.75 (s, 3H), 5.03-5.07 (m, 2H), 5.87 (s, 2H), 5.88-5.94 (m, 1H), 6.63 (s, 1H), 6.77 (d, 2H, J=8.9 Hz), 7.24 (d, 2H, J=8.9 Hz).

¹³C NMR (125 MHz, CDCl₃): δ ppm 34.1, 55.2, 62.0, 101.5, 109.7, 109.8, 114.5, 115.9, 126.0, 126.3, 130.7, 137.1, 143.6, 148.1, 152.7, 158.5

EI-MS (m/z, %): 330 (M⁺, 100), 176 (21), 121 (68)

HRMS: Calc. for C₁₅H₁₉O₃S: 330.09261; Found: 330.09421

IR (cm⁻¹): 949, 995, 1050, 1244, 1493, 1593, 1638
To a cooled (-40°C) solution of 90d (0.14g, 0.42 mmol) in ethyl acetate (6 ml) was added 1.2eq of mCPBA (0.08 g, 0.50 mmol). The reaction was allowed to warm up to room temperature and stirred for 24 h. After 24 h, the reaction mixture was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 1 x 10 ml) and water (1 x 10 ml). The extract was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The resulting oily residue was purified by flash column chromatography (3:1 hexane / ethyl acetate) affording compound 91d as a pale yellow oil (0.10 g, 68%).

^1H NMR (500 MHz, CDCl₃): δ ppm 3.27 (dt, 2H, J=6.4 Hz, 1.4 Hz), 3.77 (s, 3H), 3.82 (s, 3H), 4.99-5.06 (m, 2H), 5.81-5.84 (m, 1H), 5.87 (s, 1H), 5.98 (s, 1H), 6.66 (s, 1H), 6.92 (d, 2H, J=8.9 Hz), 7.64 (d, 2H, J=8.9 Hz).

^13C NMR (125 MHz, CDCl₃): δ ppm 33.1, 55.4, 63.2, 102.6, 112.1, 114.4, 116.5, 122.1, 125.9, 126.4, 135.4, 136.4, 144.7, 145.5, 149.2, 161.5

EI-MS (m/z, %): 330 (M⁺, 60), 190 (28), 121 (100)

HRMS: Calc. for C₁₈H₁₈O₅S: 346.08751; Found: 346.08748

IR (cm⁻¹): 949, 993, 1228, 1044, 1085, 1495, 1594, 1639
5-Methoxy-4-(4-methoxyphenyl)sulfonyl-6-(2-propenyl)-1,3-benzodioxole

92d

To a solution of 90d (90mg, 0.21 mmol) in ethyl acetate (6 ml) was added 2eq of mCPBA (0.09g, 0.50 mmol). The reaction was stirred at room temperature for 24 h, after which it was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 2 x 10 ml) and water (4 x 10 ml). The extract was dried over anhydrous MgSO₄, filtered and evaporated to dryness, purified by flash column chromatography (3:1 hexane / ethyl acetate) to provide compound 92d as a white solid (70 mg, 71%).

¹H NMR (500 MHz, CDCl₃): δ ppm 3.22 (dt, 2H, J=6.4 Hz, 1.4 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 4.99-5.07 (m, 2H), 5.75-5.83 (m, 1H), 6.05 (s, 2H), 6.92 (s, 1H), 6.84 (d, 2H, J=8.9Hz), 7.93 (d, 2H, J=8.9 Hz).

¹³C NMR (125 MHz, CDCl₃): δ ppm 33.1, 55.5, 63.6, 102.7, 113.7, 113.9, 116.9, 126.9, 129.8, 134.4, 136.0, 144.9, 145.1, 149.2, 163.4

EI-MS (m/z, %): 362 (M⁺, 38), 300 (100), 176 (52)

HRMS: Calc. for C₁₈H₁₈O₆S: 362.08241; Found: 362.08209

IR (cm⁻¹): 953, 992, 1145, 1315, 1499, 1596

MP: 82-85 °C
Part B: The Synthesis of Trichiliasterone B
Chapter 4

The total synthesis of 3\hspace{0.1cm} -\hspace{0.1cm} hydroxypregn\hspace{0.1cm} -\hspace{0.1cm} 2,16\hspace{0.1cm} -\hspace{0.1cm} dione 96

4.1 Introduction

Maliaceae is a family of woody tropical plants. Plants in this family are a rich source of limonoids and have attracted considerable attention due to a wide range of biological activity, including bacterial, anti-viral, anti-fungal and also as insect anti-feedant and growth inhibitory activity.\textsuperscript{33} Limonoids, also referred to as tetranortriterpenoids, consist of 26 carbons with the basic skeleton shown in Figure 4.1.

![Figure 4.1 - The basic skeleton of tetranortriterpenoids](image)

Several years ago, members of our research group screened various Maliaceae species in Central America for natural insecticidal activity.\textsuperscript{33} Ethanol extracts of Trichilia hirta, a Costa Rican tree, showed the most inhibitory growth pattern on larvae of Ostrinia nubilalis (European corn borer) and Peridroma saucia (the neonate variegated cutworm). The active extracts were further fractionalized in methylene chloride and other organic solvents in order
to identify the compounds responsible for observed activity. The methylene chloride fraction showed the highest growth inhibition of the insects. Two pure compounds, 2-hydroxyandrosta-1,4-diene-3,16-dione (95) and 3β-hydroxypregnan-2,16-dione (96), were isolated from the methylene chloride fraction via repeated column chromatography and preparatory reverse phase HPLC. Both of these compounds lacked the resonance for the furan ring in the $^1$H NMR spectrum, thus they did not belong to the limonoid family. These compounds were eventually assigned the structures 95 and 96 $^{13}$ and given the trivial name trichiliasterone A and trichiliasterone B respectively. $^{34}$

![2-hydroxyandrosta-1,4-diene-3,16-dione Trichiliasterone A](image)

![3β-hydroxypregnan-2,16-dione Trichiliasterone B](image)

The nomenclature of the steroids conforms to IUPAC regulation.

Figure 4.2 - IUPAC numbering system of the steroid skeleton

There are relatively few examples of plant steroids with 16-keto functionality. Plant steroids having this functionality are lanisterone E and Z (97a and 97b) from *Lansium*
**anamallayanum** Bedd, which like *Trichilia hirta* belongs to the Maliaceae family\(^{35}\); **Z** and **E** guggulsterone (99a and 99b) from *Commiphora mukul* in India\(^{36}\); **100** from the roots of *Solanum hainanense* Hance, a Vietnamese plant\(^{37}\); and more recently three more of these 16-keto steroids have been isolated from *Melia volkensii*, a plant also belonging to Maliaceae family\(^{38}\). These compounds include **E** and **Z** volkendousin (98a and 98b) and meliavosin 101.

![Chemical Structures]

**Figure 4.3 - Plant steroids with 16-keto functionality**
Trichiliasterone A and B were isolated in small quantity, 0.001% of each component based on dry sawdust. Thus to investigate biological activity, synthesis of trichiliasterone A and B were undertaken by our laboratory. The synthesis of trichiliasterone A, starting with testosterone acetate, was completed in our laboratory by Hantos.\textsuperscript{34} She also initiated work on the synthesis of trichiliasterone B but was unable to complete it. The completion of the synthesis of trichiliasterone B is described in the next section of this thesis.
4.2 The synthesis of 3β - hydroxypregnan -2,16 - dione 96

As mentioned previously the synthesis of trichiliasterone B had been started in our laboratory by Hantos.34 It started with wittig methylation of isoandrosterone 102 to afford 103 in 88% yield using 5 eq of methylene triphenyl phosphorane as shown in Scheme 4.1. Allylic oxidation at the C-16 position of 103 was then performed using SeO₂ and t-butyl hydroperoxide. This procedure gave a mixture of the desired enone 104 and also the C-16 allylic alcohol. The crude mixture was further oxidized using MnO₂ in dichloromethane to afford 104 in 48% yield. Reaction of 104 with lithium dimethyldicuprate in diethyl ether at 0°C resulted in 105 in 95% yield. The 16-oxo functionality of 105 was protected as the ethylene ketal 106 using ethylene glycol and catalytic amount of p-toluenesulfonic acid in benzene prior to modification of ring A. The 3-hydroxyl group of 106 was then oxidized to 107 in 96% yield using PDC in CH₂Cl₂. The final four steps planned for the completion of the synthesis of trichiliasterone B were aldol condensation of 107 with benzaldehyde to afford 108, reduction of 3-oxo group of 108 to afford 109, ozonolysis at the C-2 position of 109 to afford 110 and finally the hydrolysis of the C-16 ketal of 110 to afford the desired product 96. Initial attempts at aldol condensation via the procedure by Barton et al19 using 0.1M KOH in ethanol and benzaldehyde were unsuccessful. Due to time limitation Hantos did not continue with the synthesis.

To explore the aldol condensation reaction further, we reacted 107 with lithium hexamethyldisilazide or LDA as base at -78°C for 1 h followed by benzaldehyde. The reaction mixture was quenched after 30 min with aqueous NH₄Cl. These conditions led to
Scheme 4.1 - Proposed Route for the Synthesis of Trichiliasterone B

complex product mixtures with little, if any, of the desired product 108. Thus this route to trichiliasterone B was abandoned.
The route chosen to complete the synthesis of trichiliasterone B is shown in Scheme 4.2. Conceptually it involved introducing oxygen functionality at the C-2 position, initially in the form of an epoxide, specifically the epoxy acetate 112. It has been reported\(^{40}\) that thermal ring opening of \(\alpha\)-epoxy acetate such as 114 can lead to a 3-keto-2-acetoxy product that under basic conditions\(^{41}\) can be isomerized to afford mainly the 2-keto-3-acetoxy derivative. We therefore opted for this approach, recognizing that mixtures of 3\(\alpha\)- and 2\(\beta\)-hydroxy ketones will arise. We anticipated that we would be able to separate these mixtures and thus complete the synthesis of trichiliasterone B.

Scheme 4.2 - The Synthesis of Trichiliasterone B via Different Route
The 3-keto derivative 107 was treated with LiN(TMS)$_2$ and acetic anhydride to give the enol acetate 111 in 84% yield as white crystals, which melted at 100-104°C. The $^1$H NMR spectrum showed a singlet at 2.07 ppm corresponding to the methyl group in the acetyl moiety and a double doublets at 5.23 ppm, coupling constant J=5.8 Hz and J=1.4 Hz, corresponding to the proton at the C-2 position. The $^{13}$C NMR spectrum showed the signal at 147.0 ppm for the C-3 carbon in steroid 111 whereas in steroid 107 the signal for the C-3 carbon was at 211.8 ppm. The molecular ion was calculated to be 402.2771 and the HRMS of 111 showed a M$^+$ ion at m/z 402.2782.

Oxidation of 111 using mCPBA in dichloromethane for 24 h afforded epoxy acetate 112 in 72% yield as white crystals that melted at 95-100°C. A wide range of melting point is observed, suggesting a mixture of stereoisomers but the $^1$H NMR spectrum of 112 indicates the presence of only one product. Thus this wide range of melting point could be due to thermal decomposition of the product 112 since it has been reported that epoxy acetate can undergo thermal ring opening. The stereochemistry of 112 is based on the notion that the attack by mCPBA should occur from the less hindered α-face. The $^1$H NMR spectrum showed a doublet at 3.29 ppm, with coupling constant J=5.6 Hz, corresponding to the proton signal at the C-2 position. The $^{13}$C NMR spectrum showed the carbon signal of enol acetate 111 at the C-2 (112.5 ppm) and C-3 (147.0 ppm) positions to be replaced by the epoxy acetate signal at 58.3 ppm and 83.0 ppm respectively. The molecular ion was calculated to be 418.2720 and the HRMS of 112 showed a M$^+$ ion at m/z 418.2745.

It has been shown by Williamson et al$^{40}$ that the 2α,3α-oxido-3β-acetoxysterol 114 smoothly rearranges to the acetoxy ketone 115 by simply heating to 160°C for 5 minutes
(Scheme 4.3) and Bowers et al\textsuperscript{11} showed that acetoxy ketones like 115 may rearrange during chromatography on basic alumina to give more stable isomer 116 (Scheme 4.4). Thus the steroid 112 was heated at 160°C for 10 min and the product was mounted onto a basic alumina column and left there for 24 h, after which it was eluted with 3:1 hexane / ethyl acetate. A mixture of 113 and 117 in 68% yield was observed (Scheme 4.5).

\[ \text{Scheme 4.3 - Thermal Rearrangement of Epoxy Acetate 114} \]

\[ \text{Scheme 4.4 - Rearrangement of Acetoxy Ketones on Basic Alumina} \]

The \textsuperscript{1}H NMR spectrum (Figure 4.4) showed a multiplet at 5.17-5.31 ppm corresponding to the -CH attached to the acetate group and a singlet at 2.13 ppm corresponding to the methyl protons in the acetyl moiety for both the minor and major product. The methyl peaks at the C-18 and C-19 positions in the minor product 113 were at 0.69 ppm and 0.75 ppm whereas in
Figure 4.4 – $^1$H NMR spectrum of 3β-acetoxy-16-ethylenedioxy pregnan-2-one (113) and 2α-acetoxy-16-ethylenedioxy pregnan-3-one (117)
the major product 117, they were at 0.72 ppm and 1.10 ppm. The ratio of the minor 113 to
the major product 117 was calculated to be 1:4. The mixture was difficult to separate, hence
was subjected to hydrolysis of the acetate group.

Scheme 4.5 - Thermal Rearrangement of the Epoxy Acetate 112

De-acetylation of the crude mixture of 113 and 117 using LiOH in THF/water
mixture yielded 118 as a major product in 80% yield as white crystals, which melted at 126-
130°C. The $^1$H NMR spectrum (Figure 4.5) showed the disappearance of a singlet at 2.13
ppm corresponding to the methyl group in the acetyl moiety and the appearance of a doublet
at 3.48 ppm, coupling constant $J=3.3$ Hz, corresponding to the hydroxyl proton and a
multiplet at 4.23 ppm corresponding to the proton at the C-2 position. The IR spectrum
showed the broad band at 3615 cm$^{-1}$, characteristic of the hydroxyl group. The molecular ion
was calculated to be 376.2615 and the HRMS of 118 showed a M$^+$ ion at m/z 376.2592.
Alternatively, epoxy acetate 112 was reacted with LiOH in THF/water mixture to yield
steroid 118 in 30% yield.

Scheme 4.6 - De-acetylation of the Crude Mixture of Steroids 113 and 117 to afford the Steroid 118
Figure 4.5 - $^1$H NMR spectrum of 2α-hydroxy-16-ethylenedioxyprogesterone-3-one (118)
The final step was the hydrolysis of the ketal at the C-16 position. Steroid 118 was reacted with 10% HCl solution in ethyl acetate for 24 h. Work-up after 24 h led to a mixture of products, none of which was the desired product. Alternatively, we reacted the steroid 118 with p-toluenesulfonic acid in acetone for 24 h. Work up after 24 h led to a mixture of products, again none of which was the desired product (Scheme 4.7). Thus this route to the synthesis of trichiliasterone B was abandoned. A new route was suggested with the hope that

![Scheme 4.7 - Hydrolysis of the Ketal Group at C-16 from the Steroid 118](image)

it will lead us to the desired product 96. It involved the manipulation of the sequence of the removal of the ketal group at the C-16 position. Instead of the removal of the acetyl moiety first, we decided to remove the ketal group first, followed by the acetyl group.

With the help of Dr. Sasmita Tripathy in our group, the crude mixture of 113 and 117 was refluxed with pyridinium tosylate in acetone for 3 h after which the solvent was removed in vacuo. The residue was extracted into ethyl acetate and washed with sodium bicarbonate and brine. The organic layer was separated and dried with anhydrous MgSO₄. It afforded the crude products 120 and 121 in 90% yield (Scheme 4.8). The crude ¹H NMR spectrum
showed the absence of the signal due to the ethylenedioxy group in the region of 3.81-3.90 ppm.

![Chemical Structures](image)

Reagents: a) pyridinium tosylate / acetone; b) reflux, 3 h

Scheme 4.8 - Hydrolysis of the Ketal Group at C-16 Position in Steroids 113 and 117

The crude products 120 and 121 were not purified but de-acetylated using LiOH in THF/water mixture affording 96 as white crystals, which melted as 144-145°C, in 13% yield and 119 as white crystals, which melted at 136-137°C, in 43% yield. The ¹H NMR spectrum of the steroid 119 (Figure 4.6) showed a double doublets at 4.20 ppm, coupling constants J=12.0 Hz and 7.1 Hz, for the proton at the C-2 position, a singlet at 3.50 ppm corresponding to the hydroxyl group and the methyl groups at the C-18 and C-19 positions at 0.68 ppm and 1.08 ppm. The molecular ion was calculated to be 332.2351 and the HRMS of 119 showed a M+ ion at m/z 332.2359. The stereochemistry of the hydroxyl group was assigned as equatorial from the coupling constant of the proton at the C-2 position. The coupling constant J=12.0 Hz is due to the coupling of the axial proton at the C-2 position with the axial proton at the C-1 position and the coupling constant J=7.0 Hz is due to coupling of the axial proton at the C-2 with the equatorial proton at the C-1 position. If the position of the hydroxyl group was axial, then the proton at the C-2 position would show two small couplings in the range 0 - 7 ppm. The spectroscopic data of steroid 119 were compared with the available spectrum of trichiliasterone B and were found to be different. Steroid 119 was found to be the 2α-hydroxy-3-keto isomer of the natural product, trichiliasterone B, and
Figure 4.6 - $^1$H NMR spectrum of 2α-hydroxypregn-3,16-dione (119)
hence the intermediates were assigned the 2α-hydroxy-3-keto structures since the final product did not lead to the natural product.

The spectroscopic data of the minor product matched those of the natural product, trichiliasterone B, cited by Chauret et al.\textsuperscript{33} The molecular ion was calculated to be 332.2351 and the HRMS of 96 showed M\(^+\) ion at \(m/z\) 332.2336. The major differences between the

\[
\begin{align*}
\text{Scheme 4.9 - Hydrolysis of the Acetyl Moiety in Steroids 120 and 121}
\end{align*}
\]

two isomers is the position of the methyl peaks at the C-18 and C-19 positions in the \(^1\text{H}\) NMR spectrum (Figures 4.6 and 4.7). In steroid 119, the methyl peaks are at 0.70 ppm and 1.08 ppm whereas in the natural product, 96, the methyl peaks are at 0.67 ppm and 0.76 ppm.

4.3 Cytotoxicity of the steroid 104 and its derivatives

McLaughlin et al reported the isolation of 98a, 98b and 101 from the root bark of \textit{Melia volkensii} which occurs in Kenya, Africa.\textsuperscript{38} All three compounds showed biological activity and we speculate it could be due to the α, β unsaturated enone system in ring D being the excellent Michael receptor. The methylene ketone 104, prepared during the synthesis of trichiliasterone B, should be as potent as the isolated steroids 98a, 98b and 101.
or even more potent, since it is sterically unhindered and contains no electron donating group on the β-carbon of the α, β unsaturated enone. Thus with this in mind some ester derivatives of 104 were synthesized and tested for anti-cancer activity along with 104.

Steroid 104 was reacted with 1 eq of acetic anhydride in pyridine to afford 122 as white crystals in 53% yield. The \(^1\)H NMR spectrum showed the appearance of a singlet at 2.00 ppm corresponding to the methyl group in the acetyl moiety. The \(^{13}\)C NMR spectrum showed the carbonyl peak in the acetyl moiety at 170.6 ppm and the C-3 carbon peak at 73.4 ppm whereas in steroid 104 the C-3 carbon peak was at 71.2 ppm.

Other ester derivatives were prepared in a similar manner as steroid 122 and are tabulated in Table 4.1. The \(^1\)H NMR and \(^{13}\)C NMR spectra were as expected. They are summarized in the experimental section. Relatively little effort was made to optimize the yield. The major goal was to produce significant quantities of pure compounds for the biological screening.

All these five compounds show \textit{in vitro} sub micromolar toxicity to most cell lines when tested by Biochem Pharma. The results of the tests are shown in Table 4.2. Dr. Gourdeau, who carried out the assays at Biochem Pharma, pointed out that these compounds showed best activity against the leukemia cell line. Since there are currently a number of viable treatments specifically for childhood leukemia, there is relatively little interest in the
anti-leukemia compounds, unless it can be proven that the compounds mode of action is novel. She recommended that we submit our compounds' to the US National Cancer Institute. They carry out screening against several human cancer cell lines and produce a detailed profile for each compound. This profile is compared with those of known anti-cancer compounds and the unusual effects are highlighted. Based on such an extensive screening, a decision might be made whether to initiate \textit{in vitro} tests and possibly prepare additional analogs.

Table 4.1- The Synthetic Ester Derivatives of the Steroid 104

<table>
<thead>
<tr>
<th>Derivatives of Steroid 104</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Derivative 123" /></td>
<td>45%</td>
</tr>
<tr>
<td><img src="image2" alt="Derivative 124" /></td>
<td>58%</td>
</tr>
<tr>
<td><img src="image3" alt="Derivative 125" /></td>
<td>53%</td>
</tr>
</tbody>
</table>
Table 4.2 - The IC\textsubscript{50} Values, Expressed in Micro Molar Concentrations, of Compounds 104, 122, 123, 124 and 125 Against Different Cancer Cell Lines Obtained by Biochem Pharma.

<table>
<thead>
<tr>
<th>Cell Lines</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTT</td>
<td>3H-Thy, Inc.</td>
<td>MTT</td>
<td>3H-Thy, Inc.</td>
<td>MTT</td>
</tr>
<tr>
<td>Hep G 2</td>
<td>2.4</td>
<td>0.94</td>
<td>2.7</td>
<td>2.53</td>
<td>3</td>
</tr>
<tr>
<td>(Liver epitho. carc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL-60</td>
<td>0.17</td>
<td>0.177</td>
<td>0.14</td>
<td>0.093</td>
<td>0.027</td>
</tr>
<tr>
<td>(Leukemia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U87</td>
<td>1.5</td>
<td>0.652</td>
<td>0.33</td>
<td>0.13</td>
<td>0.37</td>
</tr>
<tr>
<td>(Normal Fibroblasts)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT-1080</td>
<td>0.36</td>
<td>0.28</td>
<td>0.39</td>
<td>0.3</td>
<td>0.96</td>
</tr>
<tr>
<td>((Fibrosarcoma)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT-29</td>
<td>0.77</td>
<td>0.24</td>
<td>1.81</td>
<td>0.48</td>
<td>1.68</td>
</tr>
<tr>
<td>(Colon Adenocarc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCF-7</td>
<td>0.42</td>
<td>0.25</td>
<td>0.16</td>
<td>0.35</td>
<td>0.24</td>
</tr>
<tr>
<td>(Breast Adenocarc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC-3</td>
<td>0.38</td>
<td>0.27</td>
<td>0.7</td>
<td>0.33</td>
<td>0.62</td>
</tr>
<tr>
<td>(Prostate Carc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend

1 = compound 104, 2 = compound 122, 3 = compound 123, 4 = compound 124 and 5 = compound 125
4.4 Experimental

*General procedure*: See experimental section, Chapter 3, for general procedure.

3 β - Hydroxy - 16 - ethylenedioxy pregnane 111

![Chemical Structure](image)

To a cooled solution (-78 °C) of steroid 107 (25 mg, 0.069 mmol) in dry THF was added 2 eq of LiN(TMS)₂ (1 M, 0.13 ml). The reaction mixture was stirred for 1 h after which 3 eq of acetic anhydride (0.02 ml) were added. The resulting mixture was stirred and monitored using thin layer chromatography (tlc), eluting with 12:1 toluene / acetone. It was completed after 30 min. The reaction mixture was quenched with water and extracted with EtOAc (3 x 10 ml). The organic phase was dried with anhydrous MgSO₄, filtered and concentrated in vacuo to provide compound 111 as white crystals (23 mg, 84%).

\[ ^1H \text{ NMR} \ (500 \text{ MHz, CDCl}_3): \delta \text{ ppm} \ 0.71-1.01 \ (m, \ 4H), \ 0.88 \ (t, \ 3H, J=7.0 \ Hz), \ 0.80 \ (s, \ 3H), \ 0.70 \ (s, \ 3H), \ 1.10-1.61 \ (m, \ 11H), \ 1.81 \ (ddd, \ 2H, J=12.8 \ Hz, \ 7.0 \ Hz), \ 1.74 \ (dt, \ 1H, J=6.7 \ Hz, \ 3.7 \ Hz), \ 1.91-1.95 \ (m, \ 2H), \ 2.00 \ (dd, \ 1H, J = 17.0 \ Hz, \ 3.3 \ Hz), \ 2.07 \ (s, \ 3H), \ 3.67-3.72 \ (m, \ 1H, \ ketal), \ 3.81-3.86 \ (m, \ 1H, \ ketal), \ 3.87-3.92 \ (m, \ 2H, \ ketal), \ 5.23 \ (d, \ 1H, J = 5.8 \ Hz, \ H-2). \]
$^{13}$C NMR (125 MHz, CDCl₃): δ ppm 11.7, 12.9, 13.5, 17.0, 20.7, 21.0, 28.3, 31.4, 31.6, 34.7, 38.1, 38.6, 40.0, 41.8, 42.1, 52.0, 53.7, 60.8, 62.9, 64.9, 112.5 (C-2), 117.5 (C-16), 147.0 (C-3), 169.5 (OAc)

EI-MS (m/z, %): 402 (M⁺, 9), 316 (30), 142 (50), 99 (100)

HRMS: Calc. for C$_{25}$H$_{38}$O₄: 402.2777; Found: 402.2782

MP: 100-104 °C

IR (cm$^{-1}$): 1030, 1046, 1333, 1424, 1602, 1745

3β - Acetoxy - 2α, 3α - epoxy - 16 - ethylenedioxy pregnane 112

![Chemical Structure](image)

To a cooled (0 °C) solution of 111 (174 mg, 0.432 mmol) in dry CH$_2$Cl$_2$ (25ml) was added 2eq of mCPBA (149 mg, 0.863mmol) in one portion. The reaction mixture was warmed to room temperature and stirred for 24 h after which the reaction mixture was washed with sodium sulfite solution (sat., 2 x 5 ml), sodium bicarbonate (sat., 2 x 5 ml) and water (2 x 10 ml). The organic extract was dried over anhydrous MgSO$_4$, filtered and evaporated to dryness. The resulting oily residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) affording compound 112 as white crystals (130 mg, 72%).
$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 0.78-0.84 (m, 1H), 0.66-0.69 (m, 1H), 0.68 (s, 3H),
0.87 (t, 3H, J = 7.0 Hz), 0.93 (s, 3H), 0.95-1.54 (m, 14H), 1.72 (dt, 1H, J = 9.0 Hz, 3.0 Hz),
1.79 (dd, 1H, J=12.9 Hz, 7.0 Hz), 1.88 (dd, 1H, J = 14.0 Hz, 11.0 Hz), 1.97-2.07 (m, 2H), 2.02 (s, 3H),
3.29 (d, 1H, J = 5.6 Hz, H-2), 3.67-3.70 (m, 1H, ketal), 3.81-3.86 (m, 1H, ketal), 3.87-3.90 (m, 2H, ketal).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ ppm 12.7, 12.8, 13.4, 16.9, 20.5, 21.1, 27.9, 30.7, 31.5, 34.4, 34.6, 38.4, 38.6, 38.7, 39.9, 41.9, 51.9, 53.5, 58.3 (C-2), 60.7, 62.9, 64.8, 83.0 (C-3), 117.4 (C-16), 169.3

EI-MS (m/z %): 418 (M+, 16), 319 (34), 142 (59), 99 (100)

HRMS: Calc. for C$_{25}$H$_{38}$O$_5$: 418.27204; Found: 418.27447

MP: 95-100 °C

IR (cm$^{-1}$): 1046, 1333, 1476, 1601, 1745

3β - Acetoxy - 16 - ethylenedioxy pregnan - 2 - one 113 and 2α - Acetoxy - 16 - ethylenedioxy pregnan - 3 - one 117

In a round bottom flask, compound 112 (25.5 mg, 0.061 mmol) was heated at 160 °C by means of oil bath for 15 min. The resulting yellow oily solution was mounted onto basic alumina column and left there for 24 h. After 24 h it was eluted using 3:1 hexane / ethyl
acetate. The resulting fractions were collected and concentrated in vacuo to give a mixture of 117 and 113 as white crystals (17.3 mg, 68%).

H NMR (500 MHz, CDCl₃): δ ppm major: 0.73 (s, 3H), 1.11 (s, 3H), 5.27 (dd, 1H, J=12.6 Hz, 7.0 Hz, H-2), minor: 0.69 (s, 3H), 0.75 (s, 3H), 5.18 (dd, 1H, J=11 Hz, 7.2 Hz, H-3), major + minor: 0.81-1.11 (m, 4H), 0.89 (t, 3H, J=7.5 Hz), 1.12-1.17 (m, 2H), 1.22-1.69 (m, 8H), 1.70-1.79 (m, 2H), 1.82 (dd, 1H, J=12.9 Hz, 7.0 Hz), 2.13 (s, 3H), 1.99-2.15 (m, 1H), 2.19 (dd, 1H, J=14.0 Hz, 3.6 Hz), 2.25 (dd, 1H, J=12.4 Hz, 9.4 Hz), 2.34-2.48 (m, 1H), 3.68-3.74 (m, 1H), 3.82-3.83 (m, 1H).

C NMR (125 MHz, CDCl₃): δ ppm major: 74.4 (C-2), 204.0 (C-3), minor: 76.1 (C-3), 204.3 (C-2), major + minor: 12.8, 13.0, 13.5, 17.0, 20.8, 21.2, 28.3, 31.6, 33.9, 37.3, 38.4, 40.0, 42.2, 43.5, 44.7, 47.8, 51.8, 54.0, 60.7, 63.0, 64.9, 117.4, 170.1.

EI-MS (m/z, %): 418 (M⁺, 9), 319 (20), 142 (44), 99 (100).

HRMS: Calc. for C₂₃H₃₈O₅: 418.27204; Found: 418.27247

MP: 178-184°C

IR (cm⁻¹): 1041, 1094, 1331, 1445, 1726, 1743, 2933, 2962

2α - Hydroxy - 16 - ethylenedioxy pregnan - 3 - one 118
To a crude solution of 117 and 113 (17.3 mg, 0.041 mmol) in 3:1 THF / water mixture at room temperature was added 2eq of LiOH. The resulting mixture was stirred overnight, after which it was diluted with EtOAc. The organic phase was washed with water (2 x 10 ml) and dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide whitish yellow powder, which upon purification by flash column chromatography (3:1 hexane / ethyl acetate) gave the major compound 118 as white crystals (12.4 mg, 80%).

**Different route for the synthesis of 118**

To a solution of 112 (26.9 mg, 0.064 mmol) in 3:1 THF / water at room temperature was added 2eq of LiOH. The resulting mixture was stirred overnight, after which it was diluted with EtOAc. The organic phase was washed with water (2 x 10 ml) and dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide whitish yellow powder, which upon purification by flash column chromatography (3:1 hexane / ethyl acetate) gave compound 118 as white crystals (8.1 mg, 30%).

**¹H NMR** (500 MHz, CDCl₃): δ ppm 0.72 (s, 3H), 0.80-0.93 (m, 4H), 0.88 (t, 3H, J=7.5 Hz), 1.07 (s, 3H), 1.08-1.62 (m, 12H), 1.75 (dt, 1H, J=6.7 Hz, 3.0Hz), 1.81 (dd, 1H, J=12.9 Hz, 7.1 Hz), 2.24 (dd, 1H, J=14.1 Hz, 3.8 Hz), 2.38 (dt, 1H, J=14.0 Hz, 1.2 Hz), 2.45 (dd, 1H, J=12.6 Hz, 7.1 Hz), 3.48 (d, 1H, J=3.3 Hz, OH), 3.69-3.71 (m, 1H, ketal), 3.82-3.83 (m, 1H, ketal), 3.84-3.92 (m, 2H, ketal), 4.20-4.25 (m, 1H, H-2).

**¹³C NMR** (125 MHz, CDCl₃): δ ppm 12.8, 12.9, 13.4, 16.9, 21.1, 28.4, 31.6, 33.8, 37.1, 38.4, 39.9, 42.1, 42.3, 48.3, 51.7, 53.9, 60.7, 62.9, 64.9, 72.7 (C-2), 117.4 (C-16), 210.9 (C-3).

**EI-MS** (m/z, %): 376 (M⁺, 9), 277 (17), 142 (57), 113 (100)
HRMS: Calc. for C_{23}H_{36}O_{4}: 376.26148; Found: 376.25920

MP: 126-130 °C

IR: 1034, 1046, 1424, 1476, 1713, 3620

3β - Hydroxypregnane-2,16-dione 96 and 2α - Hydroxypregnane-3,16-dione 119

To a solution of 113 and 117 (132 mg, 0.32 mmol) in aqueous acetone (5 mL), pyridinium tosylate (23.0 mg, 0.095 mmol) was added. The resultant reaction mixture was allowed to reflux for 3 h. The solvent was removed in vacuo to get the residue, which was extracted into ethyl acetate and washed with aqueous solution of sodium bicarbonate and brine. The organic layer was separated, dried and concentrated to get the crude products (120 and 121), which were used for the next reaction without any further purification. The crude mixture of 120 and 121 were confirmed from the ^1H NMR spectrum, which showed the absence of signal due to ethylenedioxy group in the region of 3.81-3.90 ppm.

Subsequently to a solution of 120 and 121 (106 mg, 0.28 mmol) in a 3:1 THF / water mixture (5 mL) was added 2eq of LiOH (1 M solution, 0.6 mL) at 0°C and stirred for 2 h. After 2 h, the reaction mixture was extracted into ethyl acetate (10 mL) and washed with water (2 mL). The organic layer was separated, dried and concentrated to get the crude residue. The resulting crude mixture was purified by flash column chromatography (3:7
ethyl acetate / hexane) affording the corresponding products 96 (12.0 mg, 13.2 %) and 119 (40.0 mg, 43.2 %) as white solid.

3β - Hydroxy pregnan - 2, 16 - dione 96

The spectroscopic properties were identical with the reported data.

**HRMS:** Calc. for C_{21}H_{32}O_3: 332.2351; found: 332.2356.

**MP:** 144-145°C.

[α]_D: -78° (c 0.47, MeOH).

2α - Hydroxy pregnan - 3, 16 - dione 119

**^1H NMR** (500 MHz, CDCl₃): δ ppm 4.20 (dd, J=7.1, 12.0 Hz, 1 H), 3.50 (bs, 1H, OH), 2.46 (dd, J=7.0, 12.5 Hz, 1 H), 2.39 (t, J=13.9 Hz, 1 H), 2.27 (dd, J=3.7, 14.1 Hz, 1 H), 2.19 (dd, J=7.6, 18.2 Hz, 1 H), 1.92 (dt, J=2.9, 12.5 Hz, 1H), 1.78-0.90 (m, 16 H), 1.08 (s, 3H), 0.97 (t, J=7.5 Hz, 3 H), 0.68 (s, 3 H).


**HRMS:** Calc. for C_{21}H_{32}O_3: 332.2351; Found: 332.2359.

**MP:** 136-137°C
3β - Acetoxyandrost - 17 (20) - ene 122

To a solution of 104 (50 mg, 0.165 mmol) in pyridine (1 ml) was added 1 eq of acetic anhydride (15 ml, 0.165 mmol). The resulting mixture was stirred at room temperature for 24 h. The mixture was diluted with EtOAc then washed with water (3 x 10 ml), the organic phase was dried over anhydrous MgSO₄, filtered and concentrated to give compound 122 as white crystals (30 mg, 53%).

¹H NMR (500 MHz, CDCl₃): δ ppm 0.81-0.83 (m, 1H), 0.85 (s, 3H), 0.92 (s, 3H), 0.96-1.03 (m, 1H), 1.18-1.75 (m, 14H), 1.79-1.83 (m, 1H), 1.85-1.95 (m, 1H), 1.97-2.00 (m, 1H), 2.00 (s, #H, OAc), 2.20 (dd, 1H, J=17.5 Hz, 6.9 Hz), 4.66 (m, 1H, H-3), 4.98 (s, 1H, =CH₂), 5.76 (s, 1H, =CH₂).

¹³C NMR (125 MHz, CDCl₃): δ ppm 12.2, 19.1, 20.6, 21.4, 27.3, 28.2, 31.8, 33.9, 34.4, 35.2, 35.7, 36.4, 37.9, 42.8, 44.6, 49.3, 54.2, 73.4 (C-3), 111.8 (=CH₂), 156.7 (C-17), 170.6 (C=O, OAc), 206.9 (C-16)

FAB (MH⁺): Calc. for C₂₂H₃₂O₃: 345.2323; Found: 345.2353

MP: 125-127 °C
3β - [(Phenylacetyl)oxy]androst - 17 (20) -ene 123

To a solution of 104 (50 mg, 0.165 mmol) in CH₂Cl₂ (2 ml) was added 1.5eq of phenylacetic acid (30 mg, 0.220 mmol), followed by DCC (34 mg, 0.202 mmol) and DMAP (1.3 mg.). The resulting mixture was stirred at room temperature for 24 h. The mixture was diluted with CH₂Cl₂ (5 ml) then washed with water (3x 10 ml), the organic phase was dried over anhydrous MgSO₄, filtered and concentrated to give compound 123 as white crystals (30 mg, 45%).

¹H NMR (500 MHz, CDCl₃): δ ppm 0.80-0.82 (m, 1H), 0.85 (s, 3H), 0.92 (s, 3H), 0.95-1.02 (m, 2H), 1.23-1.75 (m, 13H), 1.76-1.85 (m, 1H), 1.90-2.00 (m, 1H), 2.00 (dd, 1H, J=17 Hz, 14 Hz), 2.20 (dd, 1H, J=17 Hz, 6.9 Hz), 3.56 (s, 2H, benzylic CH₂), 4.67-4.71 (m, 1H), 4.98 (s, 1H), 5.77 (s, 1H), 7.23-7.31 (m, 5H).

¹³C NMR (125 MHz, CDCl₃): δ ppm 12.2, 19.1, 20.7, 27.3, 28.2, 31.8, 33.8, 34.4, 35.2, 35.7, 36.4, 37.9, 41.7, 42.8, 44.6 (benzylic C), 49.3, 54.2, 73.9 (C-3), 111.9, 126.9, 128.5, 129.1, 134.3, 156.7 (C-17), 171.1, 206.9 (C-16)

FAB (MH⁺): Calc. for C₂₈H₃₆O₃: 421.2666; Found: 421.3437

MP: 104-106 °C
3β - [(Benzoyl)oxy]androstan-17(20)-ene 124

To a solution of 104 (50 mg, 0.165 mmol) in pyridine (1 ml) was added 2eq of benzoyl chloride (38 ml, 0.330 mmol). The resulting mixture was stirred at room temperature for 24 h. The mixture was diluted with EtOAc then washed with water (3 x 10 ml), the organic phase was dried over anhydrous MgSO₄, filtered and concentrated to give compound 124 as white crystals (40 mg, 58%).

**¹H NMR** (500 MHz, CDCl₃): δ ppm 0.87 (s, 3H), 0.93 (s, 3H), 0.78-1.05 (m, 1H), 1.10 (dt, 1H, J=13.5 Hz, 3.8 Hz), 1.21-1.81 (m, 14H), 1.89-2.04 (m, 3H), 2.21 (dd, 1H, J=17.5 Hz, 6.9 Hz), 4.89-4.96 (m, 1H, H-3), 4.98 (s, 1H), 5.77 (s, 1H), 7.38-8.02 (m, 5H, Ph).

**¹³C NMR** (125 MHz, CDCl₃): δ ppm 12.3, 19.1, 20.7, 27.5, 28.3, 31.9, 34.0, 34.4, 35.3, 35.8, 36.5, 37.9, 42.8, 44.7, 49.3, 54.3, 74.0 (C-3), 111.8, 128.2, 129.5, 130.8, 132.7, 156.8 (C-17), 166.0, 206.9 (C-16)

**FAB (MH⁺)**: Calc. for C_{27}H_{34}O_{3}: 407.25096; Found: 407.3182

**MP**: 206-209 °C
3β-[(2-(3-indolyl)acetyl)oxy]androst-17(20)-ene 125

To a solution of 104 (50 mg, 0.165 mmol) in CH₂Cl₂ (2 ml) was added 1.5 eq of indole-3-acetic acid (29 mg, 0.248 mmol), followed by DCC (34 mg, 0.202 mmol) and DMAP (1.3 mg). The resulting mixture was stirred at room temperature for 24 h. The mixture was diluted with CH₂Cl₂ (5 ml) then washed with water (3 x 10 ml), the organic phase was dried over anhydrous MgSO₄, filtered and concentrated to give compound 125 as white crystals (30 mg, 53%).

¹H NMR (500 MHz, CDCl₃): δ ppm 0.78-0.86 (m, 1H), 0.85 (s, 3H), 0.92 (s, 3H), 0.94-1.05 (m, 2H), 1.16-1.74 (m, 15H), 1.81-1.84 (m, 1H), 1.89-1.92 (m, 1H), 2.01 (dd, 1H, J=17.5 Hz, 14 Hz), 2.21 (dd, 1H, J=17.5 Hz, 6.9 Hz), 3.72 (s, 2H), 4.70-4.74 (m, 1H, H-3), 4.98 (s, 1H), 5.77 (s, 1H), 7.09-7.19 (m, 2H), 7.33 (d, 1H, J=8.0 Hz), 7.60 (d, 1H, J=7.9 Hz).

¹³C NMR (125 MHz, CDCl₃): δ ppm 12.2, 19.1, 20.7, 27.3, 28.2, 29.6, 31.7, 31.8, 33.8, 35.2, 35.7, 36.4, 37.9, 42.8, 44.6, 49.3, 54.2, 73.9 (C-3), 108.7, 111.1, 111.9, 118.9, 119.5, 122.1, 122.9, 127.2, 136.1, 156.8 (C-17), 171.5, 207.0 (C-16)

EI-MS (m/z, %): 459 (M⁺, 41), 130 (100)

HRMS: Calc. for C₅₀H₃₇NO₃: 459.277748; Found: 459.27937

MP: 226-228 °C
References


Claims to original research

(1) A new synthesis of dillapiol, \( \mathcal{Z} \), starting from sessamol using an ortho directed metallation to introduce a substituent at the C-4 position.

(2) The first syntheses of 5-methoxy-6-(2-propenyl)-4-thiomethyl-1,3-benzodioxole 90a, and the sulfinyl and sulfonyl analogs, 91a and 92a.

(3) The syntheses of three additional 4-thio-, 4-sulfinyl- and 4-sulfonyl analogs of the compounds described in claim 2.

(4) The synthesis of trichiliasterone B by modifying Ring A of a previously synthesized intermediate.

(5) The preparation of esters of 3\(\beta\)-hydroxyandrost-17(20)-en-16-one for the purpose of evaluating their anti-cancer activity.