Synthesis of phenolic natural products of biological interest

A thesis submitted for the degree of Doctor of Philosophy
of the Australian National University

by

Satish Chand BSc, MSc(Hons)

Research School of Chemistry
Institute of Advanced Studies
Canberra, Australia

August 2004
Corrigendum

Page

xiii, line 31  trifluoromethansulfonate should read trifluoromethanesulfonate
5, Figure 1.3 legend  its source should read their source
37, line 5  overhauser should read Overhauser
44, reference (41)  pennings should read Pennings
48, third paragraph, line 5  NaBH₄ should read LiAlH₄
48, last paragraph, line 1  35% should read 39%
65, Table 3.2  (+)‐aiphanol XX should read (+)‐aiphanol
72, footnote  protection of phenol hydroxyl should read protection of the phenolic hydroxyl group
73, last sentence  One the basis should read On the basis
81, line 5  has acid should read has an acid
89, first paragraph, line 15  and/or Overhauser should read and/or nuclear Overhauser
104 and 105  The name of compounds (84) and (53) should begin with (E)‐methanesulphonamide should read methanesulfonamide
129, line 13  bisulphate should read bisulfate
131, first paragraph, line 5  methanesulphonamide should read methanesulfonamide
139, procedure, line 2  bisulphite should read bisulfite
141, line 3  venturella should read Venturella
176, reference (18)  methanesulphonamide should read methanesulfonamide

Throughout the thesis, all specific rotation values cited in the text, as well as experimental section, should not contain the degree sign. For example Page 50, last line
[α₀D -17.6° (c 1.75, CHCl₃)] should read [α₀D -17.6 (c 1.75, CHCl₃)]
Declaration

I declare that the material presented in this thesis represents the result of original work carried out by me during the period 2001-2004 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, where possible, by citation of the original publications from which they derive.

Satish Chand

August 2004
Acknowledgements

It is a great pleasure to thank the many people whose support, help and suggestions were so valuable in the course of this study.

Foremost, I would like to thank my supervisor, Prof. Martin G. Banwell, for his guidance, continuous support and helpful discussions throughout the course of this work. I am also grateful for his criticisms and meticulous attention to detail that have helped in the writing of this thesis.

I acknowledge the contributions of my advisors Prof. John A. Elix (Department of Chemistry, ANU), Dr. Max A. Keniry (Research School of Chemistry, ANU) and Dr. Paul G. Savage (CSIRO Molecular Science, Melbourne). I am also grateful to Prof. Christopher Parish and Ms Anna Bezos (John Curtin School of Medical Research, ANU), and Prof. Gerd Dannhardt and co-workers (University of Mainz, Germany) for conducting biological tests on some of the compounds described in this thesis.

I am indebted to Mr. Tony Herlt for his skillful assistance in HPLC separations and to Dr. Alison Edwards for X-ray analysis. I acknowledge the Research School of Chemistry’s NMR, mass-spectral and elemental analysis unit’s technical staff for their assistance and service. Herewith, I also thank all the Banwell group members for their support. Dr. David Loong is especially thanked for reading parts of this thesis.

I would like to thank the Australian National University and the Commonwealth Scientific and Industrial Research Organisation (CSIRO, Australia) for funding the work described in this thesis.

Finally, but by no means last in my thoughts, I thank my parents, brothers, sisters, and friends in Fiji for their support. My wife Varun has been, throughout, very understanding, and my daughter Ayesha, thank you for your love – even in my less fortunate days (including in the lab), I come home and always find happiness in you.
Abstract

Phenolic natural products can display a range of useful biological properties such as anti-viral, anti-malarial, anti-cancer, immunosuppressive, COX enzyme inhibitory and anti-angiogenic activities. Traditional and/or herbal medicines, for example, contain a multitude of such compounds that may be responsible for their beneficial properties. In the opening chapter of this thesis, various examples of phenolic natural products are discussed along with some of their biological properties.

Many of the naturally occurring phenolic compounds are only available in minute quantities from the source material. This situation often restricts the capacity for full structural elucidation and/or comprehensive biological evaluation. Synthetic studies have played an important role in securing more material and thus provided opportunities for further studies to be carried out. For such reasons, two novel compounds, aiphanol (26) and diversonol (49), became synthetic targets in the present study. Aiphanol possesses an unprecedented stilbenolignan skeleton and shows potent inhibition of the COX-1 and -2 enzymes with IC$_{50}$ values of 1.9 and 9.9 µM, respectively. Diversonol, a novel polyketide isolated from *Penicillium diversum*, has not been the subject of any biological studies despite the compound’s intriguing structure and origin. Clearly, the development of a total synthesis of this compound would help redress matters.

A biomimetic and convergent total synthesis of the racemic modification of aiphanol (26) as well as congeners (±)-50-52 is described (Chapter 2). The key steps include a Wittig reaction, to install the ethylenic bridge of the stilbene moiety, and a phenolic oxidative coupling reaction, to form the 1,4-benzodioxane ring system. Compounds (±)-26, (±)-50-52, together with “substructures” 53 and (±)-54, were tested for biological activities. Certain of these synthetically-derived materials display significant COX enzyme inhibitory as well as anti-angiogenic properties.
In Chapter 3, stereoselective total syntheses of both enantiomers, viz. the (−)- and (+)-forms, of compound 26 are described. The correct absolute stereochemistries at C-2 and C-3 on the 1,4-dioxane ring of the targets were installed by cyclisation of the key synthons 88d and ent-88d which were, in turn, prepared from epoxy-alcohols 90b and ent-90b, respectively. In addition to the nucleophilic and intramolecular ring-opening of chiral epoxides, other pivotal steps in the synthesis involved Sharpless asymmetric dihydroxylation (AD) and Mitsunobu reactions. The absolute stereochemistries at C-2 and C-3 in the natural (−)-isomer were established as being S in each case, thus completing the full structural characterisation of this compound. Both the enantiomers show strong inhibition of the COX-1 enzyme but only modest inhibition of the COX-2 enzyme.
In Chapter 4, studies directed towards the synthesis of diversonol (49) are described. In the proposed route, it was envisaged that reaction of epoxide 110b with phenol 111 would deliver product 113 which could be elaborated to the target compound. To such ends, the readily available and enantiomerically pure diol 109 was converted, via benzylidene acetal 114, into epoxide 110b. Compound 111 was prepared from commercially available starting materials using literature procedures. Results of preliminary studies on the ring-opening of epoxide 110b with phenol 111 as well as on the equivalent reaction between model epoxide 139 and phenol (140) are presented. Results of an intermolecular crossed aldehyde-ketone benzoin reaction involving model compounds 151 and 152 are also reported. These model studies have provided valuable information that can be exploited in the total synthesis of diversonol.
Publication and presentation arising from work carried out during the period of PhD candidature

*Publication:*


*Presentation:*

Glossary

The following abbreviations have been used throughout this thesis:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>AD</td>
<td>asymmetric dihydroxylation</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azobisisobutyronitrile</td>
</tr>
<tr>
<td>a.k.a.</td>
<td>also known as</td>
</tr>
<tr>
<td>anh.</td>
<td>anhydrous</td>
</tr>
<tr>
<td>APT</td>
<td>attached proton test</td>
</tr>
<tr>
<td>BAE</td>
<td>bovine aortic endothelial</td>
</tr>
<tr>
<td>BF₃·Et₂O</td>
<td>boron trifluoride diethyl etherate</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tertiary-butyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration (g/100 mL)</td>
</tr>
<tr>
<td>ca.</td>
<td>circa (approximately)</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionisation</td>
</tr>
<tr>
<td>CoA</td>
<td>coenzyme A</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>COX</td>
<td>cyclooxygenase</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>m-chloroperbenzoic acid</td>
</tr>
<tr>
<td>CsF</td>
<td>caesium fluoride</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift (parts per million)</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement of polarisation transfer</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethylamine (Hünig’s base)</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>2,2-DMP</td>
<td>2,2-dimethoxypropane</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>E</td>
<td>entgegen (opposite)</td>
</tr>
<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>e.g.</td>
<td>exempli gratia (for example)</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>ent</td>
<td>enantiomer</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>et al.</td>
<td>et alia (and others)</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>eV</td>
<td>electron volt</td>
</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
<tr>
<td>FGI</td>
<td>functional group interconversion(s)</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatograph</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>inter alia</td>
<td>among other things</td>
</tr>
<tr>
<td>HETCOR</td>
<td>heteronuclear correlation spectroscopy</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrum</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IC₅₀</td>
<td>inhibition concentration (normally expressed in molar units) of a ligand required to reduce specific binding of the natural or reference substrate for an enzyme or receptor by 50%</td>
</tr>
<tr>
<td>i.e.</td>
<td>id est (that is)</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (Hz)</td>
</tr>
<tr>
<td>lit.</td>
<td>literature</td>
</tr>
<tr>
<td>M⁺</td>
<td>molecular ion</td>
</tr>
<tr>
<td>MDR</td>
<td>multi-drug resistance</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
</tbody>
</table>
MHz  megahertz
min  minute(s)
mm  millimetre
mL  millilitre
mmol  millimole
mol  mole
MOM  methoxymethyl
MM2  molecular mechanics (Allinger modification)
m.p.  melting point
MS  mass spectrum
Ms  methanesulfonyl
m/z  mass-to-charge ratio
NEt₃  triethylamine
nm  nanometre
NMR  nuclear magnetic resonance
nOe  nuclear Overhauser enhancement
NSAID  non-steroidal anti-inflammatory drug(s)
νₘₐₓ  infrared absorption maxima (cm⁻¹)
PDC  pyridinium dichromate
Ph  phenyl
PPh₃  triphenylphosphine
Rᶠ  retardation factor
Rh  rhodium
Rᵗ  retention time
SAE  Sharpless asymmetric epoxidation
SAR  structure-activity-relationship
S⁡ₙ²  bimolecular nucleophilic substitution reaction
sp.  species
TBAF  tetra-n-butanammonium fluoride
TBS  tert-butyldimethylsilyl
TBSOTf  tert-butyldimethylsilyl trifluoromethansulfonate
Tf  trifluromethanesulfonfyl
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TLC  thin layer chromatography
TM  trade mark
p-Ts  p-toluenesulfonyl
p-TsOH  p-toluenesulfonic acid
µM  micromole
UV  ultraviolet
viz.  videlicet (namely)
vs  versus
HWE  Horner-Wadsworth-Emmons
>  greater than
Z  zusammen (together)
°C  degrees Celsius
Δ  heat
Table of contents

Chapter 1
Introduction

1.1 Background

1.2 An insight into biosynthetic pathways leading to the formation of phenolic compounds
   1.2.1 Shikimate pathway
   1.2.2 Polyketide pathway
   1.2.3 Mixed shikimate and polyketide pathways

1.3 Significance of phenolic compounds
   1.3.1 Phenolic compounds: diversity in applications and biological properties
   1.3.2 Phenolic lignans incorporating a 1,4-dioxane ring

1.4 Angiogenesis and the cyclooxygenase-2 enzyme
   1.4.1 Link between angiogenesis and the COX-2 enzyme
   1.4.2 Phenolic natural products as COX enzyme inhibitors or as anti-angiogenic agents

1.5 Phenolic compounds as synthetic targets
   1.5.1 Synthesis of (±)-aiphanol by Ohira and co-workers

1.6 Aim of the research detailed in this thesis

1.7 References
Chapter 2
The synthesis of (±)-aiphanol

2.1 Overview

2.2 The 1,4-benzodioxane ring system

2.2.1 Literature procedures for assembling the 1,4-benzodioxane ring system

2.2.2 Alternative approach to 1,4-benzodioxane ring system: preliminary study

2.3 Synthesis of (±)-aiphanol: a simple and convergent approach

2.3.1 Retrosynthetic analysis

2.3.2 Generation of (±)-aiphanol (26) and congeners (±)-50-52

2.4 Preliminary biological evaluation

2.5 Conclusion

2.6 References

Chapter 3
The synthesis of (−)- and (+)-aiphanol

3.1 Overview

3.2 Stereoselective synthesis of aiphanol

3.2.1 Retrosynthetic analysis

3.2.2 Synthesis of phosphonium salt 48 and 4-benzyloxy-3-hydroxybenzaldehyde (89)

3.2.3 Synthesis of (2S,3S)-aiphanol (26)

3.2.4 Synthesis of (2R,3R)-aiphanol (ent-26)
Chapter 4
Studies directed towards the synthesis of the phenolic natural product diversonol

4.1 Overview

4.2 Overall synthetic strategy and retrosynthetic analysis

4.3 Initial investigations towards the synthesis of diversonol
   4.3.1 Studies on the formation and reductive cleavage of benzylidene acetals
   4.3.2 Formation of epoxide 110
   4.3.3 Synthesis of atranol (111)
   4.3.4 Studies on the pivotal epoxide ring-opening reaction

4.4 Alternative strategy for the synthesis of diversonol

4.5 Conclusions and future work

4.6 References

Chapter 5
Experimental

5.1 General experimental procedures

5.2 Experimental procedures associated with work described in Chapter 2: The synthesis of (±)-aiphanol
5.3 Experimental procedures associated with work described in Chapter 3: The synthesis of (-)- and (+)-aiphanol

5.4 Experimental procedures associated with work described in Chapter 4: Studies directed towards the synthesis of diversonol

5.5 References

Appendices

A.1 Summary of key work described in Chapter 2
  Fold-out Schemes A-1 and A-2

A.2 Summary of key work described in Chapter 3
  Fold-out Scheme A-3
  Fold-out Scheme A-4

A.3 Summary of key work described in Chapter 4
  Fold-out Schemes A-5, A-6 and A-7
  Fold-out Schemes A-8, A-9 and A-10

A.4 X-ray reports for compounds 89, 106 and ent-106

A.5 Copy of publication arising from work described in Chapter 2 of this thesis
Chapter 1

Introduction

1.1 Background

Phenolic natural products are widely distributed in nature. Higher plants, in particular, produce a range of such compounds. Thus, for example, leaves of vascular plants contain esters, amides and glycosides of hydroxycinnamic acids as well as glycosylated flavonoids, proanthocyanadins and related compounds. Because of the ease of isolation of many phenolic natural compounds through extraction into aqueous alkali, a multitude of such compounds had already been isolated and their structures determined by the turn of the last century. These include, for example, the phenylpropanoids eugenol (1) and coniferyl alcohol (2), the coumarin umbelliferone (3), the anthraquinone hystazarin (4) and the flavonoid quercitin (5). Anthraquinones had, in the early days, found application as natural dyes. Many traditional and/or herbal medicines used for the treatment of a variety of ailments contain various phenolic compounds that may be responsible for their beneficial properties. Certain such compounds are discussed later in this Chapter (Section 1.3).
Phenolic natural products, including those of the flavonoid, lignoid and stilbene classes, are now recognised as being biosynthesised through the shikimate and/or the polyketide pathways. An overview of the biosynthetic pathways leading to the formation of various phenolic compounds is provided in the following section.

1.2 An insight into biosynthetic pathways leading to the formation of phenolic compounds

1.2.1 Shikimate pathway

Metabolites derived from the shikimate pathway give rise to a large number of aromatic compounds. Shikimate-derived phenols are formed from cinnamic acid moieties which are, in turn, biosynthesised from the carbohydrate erythrose-4-phosphate and phosphoenolpyruvate (Scheme 1.1). Oxidation of cinnamic acid derived from the shikimate pathway occurs at the para-position, and the product phenol is then further oxidised to give 3,4-dihydroxy or 3,4,5-trihydroxy compounds.

\[ \text{Erythrose-4-phosphate (P = phosphate)} + \text{Phosphoenolpyruvate (P = phosphate)} \rightarrow \text{Various steps} \rightarrow \text{Cinnamic acid (a C}_6\text{-C}_3 \text{unit)} \rightarrow \text{Oxidation} \rightarrow \text{Cyclisation or Dimerisation} \]

Cinnamic acid is the precursor to most phenylpropanoids which are often designated as having a C_6-C_3 composition. For instance, the coumarins (Scheme 1.1) arise from oxidation and cyclisation of such precursors. Dimerisation of the cinnamic acid moieties, i.e. to give (C_6-C_3)_2 systems, produces lignans and neolignans (Scheme 1.1). Lignans have two C_6-C_3 units linked via a \( \beta-\beta' \) carbon-carbon bond whereas neolignans have two C_6-C_3 units linked through an alternate carbon-carbon bond.
1.2.2 Polyketide pathway

Phenolic compounds arising through the polyketide pathway involve acetyl- and malonyl-coenzyme A “starter” units. Thus, for example, phloroglucinol is formed from one unit of acetyl- and two units of malonyl-coenzyme A (Scheme 1.2). By contrast with the outcomes associated with the operation of the shikimate pathway, the hydroxyl groups incorporated into aromatic precursor units arising via the polyketide pathway generally appear at the 1-, 3- and 5-positions, as seen in phloroglucinol. It is, however, possible for one or more of these hydroxyl groups to be eliminated during the biosynthetic process. In addition to phloroglucinol-based compounds, numerous other phenolic natural products arise through the polyketide pathway including resorcinols, anthraquinones and tetracyclines (Figure 1.1).

**Scheme 1.2: Biosynthesis of phloroglucinol**

![Scheme 1.2: Biosynthesis of phloroglucinol](image)

**Figure 1.1: Representative structures of a resorcinol, anthraquinone and tetracycline – products arising through the polyketide biosynthetic pathway**

1.2.3 Mixed shikimate and polyketide pathways

Many phenolic compounds incorporate sub-units arising from two or more metabolic pathways. Thus, for example, *p*-coumaryl coenzyme A (formed through the shikimate
pathway) and malonyl coenzyme A react to give a polyhydroxylated chalcone which is a precursor to flavanones and flavones, or isoflavonones and isoflavones (Scheme 1.3). Other metabolites of mixed biogenetic origin include, for example, stilbenes, xanthones, ubiquinones and cannabinoids (Figure 1.2).^{7}

**Scheme 1.3: Biosynthesis of chalcones, flavone/flavonone and isoflavone/isoflavanone compounds^{1,7}**

![Scheme 1.3: Biosynthesis of chalcones, flavone/flavonone and isoflavone/isoflavanone compounds](image)

**Figure 1.2: Representative structures of a stilbene, xanthone, ubiquinone and cannabinoid — products arising through mixed biosynthetic pathways**
1.3 Significance of phenolic compounds

Phenolic compounds are found in foods and in extracts used as traditional and/or herbal medicines. They have also been used as scaffolds in the discovery of new pharmaceuticals. Phytoestrogens, for example, are non-steroidal phenolic compounds that have the potential to affect human health through dietary intake. The three main classes of phytoestrogens (Figure 1.3) are the isoflavones, lignans and stilbenes. Soya bean-derived protein contains phenolic isoflavonones, mainly in the form of glycosides. Lignans, often found in the roots, stems, bark, fruit and seeds of many plant species, are considered an important source of phytoestrogens, particularly for consumers such as vegetarians whose diets are rich in plant-based foods. Stilbenes are synthesised by a wide range of plant species and are commonly found in the roots, bark, rhizomes and leaves. The major dietary sources of stilbenes are grapes, grape juice and wine as well as peanut and peanut products (e.g. butter and oil). Dietary phenolic compounds can also function as antioxidants.

![Figure 1.3: Selected phytoestrogens and its source: genistin – soya beans; matairesinol – grains, seeds, fruits and vegetables; and resveratrol – grapes, red wines.](image)

Contemporary studies on phenolic natural products are directed towards the identification, through bioassay-guided fractionation, of compounds with useful biological activity. As modern medicine demands new drugs, natural product-derived active principles and their semi-synthetic as well as fully synthetic analogs have served as a major route to new pharmaceuticals.

---

*a* A database of isoflavonoid and lignan concentrations in food has been released by United States Department of Agriculture (http://www.nal.usda.gov/fnic/foodcomp).
In the following Sections (1.3.1, 1.3.2 and 1.4.2), an overview of selected biologically active phenolic compounds, derived through various metabolic pathways (shikimate, polyketide, or mixed pathways), is presented to demonstrate the wide-ranging pharmacological potential of phenolic natural products.

### 1.3.1 Phenolic compounds: diversity in applications and biological properties

Extracts of plants used as traditional or herbal medicines are amongst the most common sources of phenolic compounds. For example, the Combretaceae family of shrubs and trees is widely employed in traditional medicine in Africa and India. A series of bibenzyls, particularly stilbenes, collectively called combretastatins was isolated from *Combretum cafferum* by Pettit and co-workers since 1987. Combretastatins A-1 (6) and A-4 (7) are potent cell growth and tubulin polymerisation inhibitors. As a consequence, compound 7 has already progressed through into clinical trials for the treatment of certain types of solid tumor. The leaves of *Piper gibbilimbum*, used in Papua New Guinea as an antiseptic to heal abscesses, ulceration of the skin and, also, to treat fevers, afforded alkenylphenol gibbilimbol (8) which showed anti-cancer properties against nasopharyngeal carcinoma cells (ED$_{50}$ 3.9 µg/mL).

Traditional healers in South Africa use *Helichrysum caespititium* as a wound treatment in male circumcision rites. Bioassay-guided studies on this species led to the isolation of compound 9 which inhibited the growth of several fungi species at low concentration (0.5 - 5 µg/mL). Plants of the *Saussurea* genus were used in both traditional Chinese and Tibetan medicines for curing rheumatic arthritis, dysmenorrhea and gynopathy. The phenolic flavonoid glycoside 10 and quercitin (5) have subsequently been isolated from the source plant *Saussurea medusa* and these may be responsible for the beneficial properties exploited in such tribal remedies.
Multi-drug resistance (MDR) is an increasing problem in the area of chemotherapy. This phenomenon involves drug depletion inside pathogenic bacterial cells due to the operation of membrane efflux proteins that serve to extrude foreign agents (including drugs) from the target cells. Some phenolic flavanoids, for example compound 11, target such a mechanism in methicillin$^\Phi$-resistant strains of *Staphylococcus aureus*.$^{19}$ Alopecurone B (12), a stilbene-flavanone phenol, when tested against several strains of methicillin-resistant *S. aureus* had potencies of between 3.13 and 6.25 µg/mL. These compare very favourably with methicillin (12.5 - > 100 µg/mL).$^{20}$

Other phenolic compounds of medicinal interest include those that exhibit anti-malarial properties, for example, nyasol (13), stilbenes 14 and 15 as well as 15-oxopuupehenol (16).$^{21-24}$ On the other hand, flavidulol B (17) and terprenin (18) display immunosuppressive activity while cinnamate 19 has been studied as part of a drug discovery program associated with developing treatments for Alzheimer’s disease.$^{25-27}$ Phenolic lignans which incorporate a 1,4-dioxane ring system, and compounds which inhibit cyclooxygenase enzymes and/or exhibit anti-angiogenic properties, are discussed separately in the following Sections (1.3.2 and 1.4.2).

$^\Phi$Methicillin, a synthetic penicillin, was developed in 1960 and resistance to it among staphylococci was reported within months of its release (Salgado, C. D.; Greenville, N. C.; Calfee, D. P. *Clin. Microbiol. Newsletter* 2003, 25, 137).
1.3.2 Phenolic lignans incorporating a 1,4-dioxane ring

MacRae and Towers reviewed the biological activity of various lignans, while Charlton has surveyed their anti-viral activity. Of particular relevance to the present study was a structurally unique group of compounds within the lignan class that incorporate a 1,4-benzodioxane ring system. For example, 5′-methoxyhydnocarpin-D (20) is a flavonolignan, that is to say a compound incorporating a flavone moiety coupled to a phenylpropane unit through a 1,4-dioxane ring system. Likewise, coumarinolignans [e.g. cleomiscosin-A (21)] have a coumarin moiety while xanthonolignans [e.g. kielcorin-D (22)] have a xanthone moiety coupled to a phenylpropane unit through such a 1,4-dioxane ring system.

Lignans incorporating a 1,4-benzodioxane ring have been shown to possess interesting biological properties. For example, flavonolignan 20 was active against multi-drug
resistant strains of *Staphylococcus aureus*, presumably because the compound disables the mechanism by which the bacterium protects itself from antibiotics. Coumarinolignan 21 shows anti-tumor activity *in vivo* in the P-388 lymphocytic leukemia test system.

Other compounds, for example americanin A (23) and isomericanol A (24), have a 1,4-dioxane ring which arises through dimerisation of two C₆-C₃ units. Neolignan isoamericanol A (24) exhibits neurotropic properties including a capacity to promote neurite outgrowth and to enhance choline acetyltransferase activity in the primary cultures of fetal rat cerebral hemisphere. Interestingly, the reduced form of caffeic acid (25) showed no neurotropic properties which implies that the dimeric structure having a 1,4-dioxane ring is probably essential for such activity.

Recently, Kinghorn and co-workers reported the bioassay-guided isolation of the stilbenolignan (−)-aiphanol (26). The compound not only possesses an unprecedented stilbenolignan skeleton in which a hydroxylated stilbene unit is connected to a C₆-C₃ or phenylpropane unit *via* a 1,4-dioxane bridge, but it also shows potent inhibition of the cyclooxygenase (COX-1 and COX-2) enzymes with IC₅₀ values of 1.9 and 9.9 µM, respectively.

---

Phenolic compounds, such as aiphanol (26), which exhibit COX enzyme inhibitory activity attracted attention in the present study because they are also likely to be anti-angiogenic agents due to a link between angiogenesis and the cyclooxygenase enzyme as delineated below.\textsuperscript{35}

### 1.4 Angiogenesis and the cyclooxygenase-2 enzyme

#### 1.4.1 Link between angiogenesis and the COX-2 enzyme

Angiogenesis, namely the formation of new blood vessels from existing ones, is an important process in tissue development and wound healing.\textsuperscript{36} In normal circumstances new blood vessels are formed during tissue growth and repair, and particularly during the development of the embryo.\textsuperscript{36} The angiogenic process, however, becomes pathologic when associated with tumor growth.\textsuperscript{36} For example, in a cancerous tissue tumors cannot grow without the development of new blood vessels that supply them with oxygen and pivotal nutrients. Tumor angiogenesis can lead to metastasis or spreading of cancer cells. Other examples of pathological conditions resulting from unregulated angiogenesis are cardiovascular diseases and rheumatoid arthritis together with certain other chronic inflammatory diseases.\textsuperscript{36,37}

The role of COX enzymes in angiogenesis modulation has attracted much attention. The cyclooxygenase enzymes catalyse the synthesis of prostaglandins from arachadonic acid.\textsuperscript{38-40} Two isoforms of the COX enzyme were known by the early 1990's, COX-1\textsuperscript{x} and COX-2. The COX-1 isoform is found in all tissues except red blood cells and is constitutively expressed in stomach, kidneys, platelets, and endothelial cells under normal conditions. It is responsible for keeping the stomach lining intact and maintaining functional kidneys.\textsuperscript{38-40} In contrast, proinflammatory substances such as lipopolysaccharides, platelet-derived growth factor, and other growth factors induce COX-2 production that leads to the synthesis of prostaglandins which trigger pain and inflammatory responses. Evidence has also linked the COX-2 enzyme with tumor angiogenesis.\textsuperscript{38-40} This link between COX-2 and various diseases led to the recognition that selective inhibitors of this enzyme would constitute a novel and non-toxic approach

\textsuperscript{x} Recently (late 1990's and early 2000), a variant form of COX-1 has been reported and dubbed as COX-3. This enzyme shows unusual drug sensitivity and is predicted to have a profound influence in the study of COX pharmacology (Chandrasekaran, N. V.; Dai, H.; Roos, K. L. T.; Evanson, N. K.; Tomsik, J.; Elton, T. S.; Simmons, D. L. Proc. Natl. Acad. Sci. U.S.A. 2002, 99, 13926).
to the treatment of inflammation and other diseases. For this reason, there are strong interests in the discovery of drugs that exhibit selectivity for the COX-2 over the COX-1 enzyme.

A general class of compounds known as non-steroidal anti-inflammatory drugs (NSAIDs) act on the cyclooxygenase portion of the enzyme prostaglandin synthase and disrupt the biosynthesis of prostaglandins via the cyclooxygenase pathway. NSAIDs are widely used for the treatment of inflammation, arthritis, cardiovascular diseases, to prevent colon cancer and Alzheimer’s disease as well as to relieve pain or fever. Many classical NSAIDs, such as aspirin, indomethicin, and ibuprofen, are non-selective and bind to both COX-1 and COX-2 enzymes. Since the normal functioning of the COX-1 enzyme is beneficial, the result is drugs that reduce pain and relieve swelling, but also damage the stomach lining (gastroduodenal ulcers) and kidneys. Celecoxib (Celebrex®) and rofecoxib (Vioxx®) are two examples of selective COX-2 enzyme inhibitors that have important therapeutic effects without displaying the just-mentioned side-effects. These two compounds are now “blockbuster” drugs.

The influence of natural products upon drug discovery, especially the general role of active substances derived from plants used as traditional medicine, has been very
significant. Many phenolic compounds with COX enzyme inhibitory properties have been reported, some of which may provide new scaffolds in the study of COX pharmacology or lead to anti-angiogenic agents.

1.4.2 Phenolic natural products as COX enzyme inhibitors or as anti-angiogenic agents

In addition to aiphanol (26), various other phenolic natural products have shown promising COX enzyme inhibitory activity. For example, belamcandaquinone A (32), isolated from a medicinal plant Belamcanda chinensis L. (Iridaceae) and used in Chinese medicine as an anti-tussive and anti-inflammatory agent as well as an expectorant, possess COX enzyme inhibitory properties. The polyphenolic stilbene, resveratrol (Figure 1.3, structure repeated below), is a natural product present in abundance in grape skins (and thus enriched in red wines), possesses anti-cancer activity and inhibits the COX-2 enzyme.

![](image)

Phenolic flavans, for example myristinin A (33), possess anti-fungal and COX-2 enzyme inhibitory properties. The roots of Piper methysticum (kava kava) yielded several compounds that were COX enzyme inhibitors, one of which is flavokawian (34). Likewise, Kinghorn and co-workers reported several prenylated stilbenoid derivatives (for example compound 35) and a benzofuran derivative 36 that act as COX enzyme inhibitors. These compounds were isolated from Artocarpus dadah, which, along with various congeners, are used as traditional medicines in Southeast Asia.
The fungal metabolite AGI-7 (37) exhibits anti-angiogenic activity while wondonin A (38) is a compound with similar properties obtained from a marine sponge.\textsuperscript{52,53} Bryoanthrathiophene (39) and lumanicin D (40) are anti-angiogenic compounds obtained from bryozoan *Watersipora subtirquata* and *Streptomyces* sp., respectively.\textsuperscript{54,55}
Many of the aforementioned compounds are only found at low levels in the natural source and, in many cases, the scarcity of the material limits any capacity to undertake comprehensive biological evaluation. Thus, total synthesis provides a means for securing more material, and presents an opportunity for further biological evaluation to be carried out. The interesting pharmacological properties of many polyphenols as well as their challenging molecular architectures have attracted the attention of synthetic chemists, and the total synthesis of many such compounds have been reported. Some pivotal examples are provided in the following section.

1.5 Phenolic compounds as synthetic targets

Useful synthetic routes to many of the biologically active phenolic natural products have emerged. For example, synthetic and/or SAR studies of the combretastain class of compounds have been reported by various research groups. Lewis and co-workers conducted equivalent studies on various phenolic flavans and flavonolignans. Avery and co-workers reported the first example of the synthesis of compound 15 with anti-malarial properties. Ward has reviewed the asymmetric synthesis of various phenolic lignans. In some cases, the synthesis of analogs with improved pharmacology have been reported. For example, flavopiridol (41), a synthetically derived analogue of the natural product rohitukine (42), is currently in Phase I/II clinical trials for the treatment of a broad range of tumors. Likewise, the anti-bacterial aureomycin® (43) is a synthetically-derived chlorinated derivative of a tetracycline obtained from Streptomyces sp.

The stilbenolignan aiphanol (26) became one of the synthetic targets in the present study for reasons that are discussed in Section 1.6 of this chapter. From a synthetic point-of-view, processes that lead to the formation of the ethylenic bridge in stilbenoids
as well as those that give rise to 1,4-benzodioxane systems were of particular interest in the present study. Methods commonly used to construct the 1,4-benzodioxane ring system involve processes such as phenolic oxidative coupling, intramolecular epoxide ring-opening and cycloaddition reactions. These methodologies are discussed in a more detail in Chapter 2. Various methods are reported in the literature for constructing the ethylenic bridge in stilbenes. Figure 1.4 provides an overview of selected but common methods for constructing the dioxane system as well as the C=C bond.

![Diagram of reactions](image)

**Figure 1.4**: Some common reactions used to construct the 1,4-dioxane ring, and the C=C bond in stilbenoids.

Owing to its biological properties and novel structural features, aiphanol (26) has attracted the attention of other groups and, in an independent study, Ohira and co-workers\(^{58}\) have recently reported a total synthesis of (±)-aiphanol. At the time this publication appeared, the author of this thesis was awaiting biological test results from Germany on his sample of synthetic (±)-aiphanol and its various congeners. The synthetic strategy utilised by Ohira and co-workers to access aiphanol is discussed briefly in the following Section (1.5.1).

**1.5.1 Synthesis of (±)-aiphanol by Ohira and co-workers\(^{58}\)**

*Scheme 1.4* outlines the strategy used by Ohira and co-workers\(^{58}\) to access (±)-aiphanol (26). The 1,4-dioxane system in target 26 was assembled *via* a [4+2]-cycloaddition reaction between ortho-benzoquinone 44 and TBS-protected sinapyl alcohol 45 which proceeded in 69% yield at ambient temperature using acetone-benzene as solvent. In this process, a single regio-isomeric dioxane system 46 was obtained and the one in which the aromatic substituent at C-2 and the TBS-protected hydroxymethyl at C-3 were trans-oriented with respect to one another as required for the natural product. The masked ketone within compound 46 was then revealed by treatment with aqueous acid,
and the hydroxyl groups were protected as MOM-ethers. An iodoform reaction performed on the methyl ketone followed by esterification furnished the ester 47 which was reduced to the corresponding aldehyde. This latter moiety was then engaged in a Wittig olefination reaction with phosphonium salt 48. MOM-group deprotection of the resulting product furnished the racemic modification of aiphanol (26). The synthesis involves 14 steps (longest linear sequence) and proceeds in an overall yield of 5.8%.

**Scheme 1.4: Ohira’s synthesis of (±)-aiphanol (26)**

1.6 **Aim of the research detailed in this thesis**

The aim of the present study was to develop concise synthetic routes to phenolic natural products of biological importance, especially those potentially capable of exhibiting useful activity such as COX-2 enzyme inhibition and/or anti-angiogenic effects. The novel natural product aiphanol (26) was considered an ideal target in this regard because:
(a) It has a low natural abundance (comprising just 0.00008% w/w of the dried seeds of \textit{A. aculeata}),\textsuperscript{34} so the scarcity of the compound from the natural source warrants total synthesis if the full range of the compound’s biological properties is to be examined;

(b) It shows potent inhibition of the COX-1 and -2 enzymes, and since the COX-2 enzyme has already been linked to tumor angiogenesis and because compounds exhibiting COX-2 inhibitory property can also act as anti-angiogenic agents,\textsuperscript{38-40} it was envisaged that the synthesis of aiphanol and various congeners would allow establishment of a preliminary structure-activity profile for this novel natural product;

(c) The unique structure of aiphanol makes it an interesting synthetic target - aiphanol represents the first natural product that has a dioxane ring system coupled to a stilbene moiety. Other notable structural features associated with target \textbf{26}, in addition to the \textit{E}-configured and hydroxylated stilbene, are the \textit{trans}-disposed aryl (at C-2) and hydroxymethyl (at C-3) substituents on the 1,4-dioxane ring;

(d) A stereoselective synthesis would allow for full characterisation of this novel compound. Aiphanol is an optically active and levorotatory compound ($\alpha_{D} = -21.8^\circ, c 0.13$ MeOH) but its absolute configuration has not been determined.\textsuperscript{34} Thus, it was envisioned that an enantioselective synthesis of both enantiomers would allow for the determination of the absolute configuration at C-2 and C-3. To the best of the author’s knowledge, no enantioselective synthesis of either enantiomeric form of aiphanol has been reported to date.

\textit{Thus, it was the aim of this study to achieve a total synthesis of (±)-, (+)- and (−)- forms of aiphanol (26) and various congeners.}
In the present study, another compound of interest from a synthetic point-of-view was the phenolic natural product diversonol (49). Turner isolated this compound from *Penicillium diversum* in 1978 but did not report on its biological properties. Indeed, there has been no further report on this compound since the late 1970's. However, given the wide-ranging biological activities displayed by phenolic compounds, as highlighted earlier in this Chapter, it was envisaged that diversonol could possess interesting but as yet unexploited biological properties. Clearly, a total synthesis of this novel compound would allow preliminary evaluation of such properties.

Thus, it was also the aim of the present study to investigate route(s) to the synthesis of diversonol (49), on the basis that success in this regard would allow the author to establish a preliminary biological profile for this intriguing molecule, particularly its potential as COX enzyme inhibitor and/or as an anti-angiogenic agent.

The remaining parts of this thesis are, therefore, organised in the following way:

- The total synthesis of (±)-aiphanol (26) and its various congeners, and results of their preliminary biological evaluations are described in Chapter 2;
- The total syntheses of (−)- and (+)-aiphanol (26) as well as the results of their preliminary biological evaluation are described in Chapter 3;
- Approaches to the synthesis of diversonol (49) are described in Chapter 4; and
- Experimental details associated with the work described in Chapters 2, 3 and 4 are presented in Chapter 5.
1.7 References


Chapter 1 Introduction


Chapter 2

The synthesis of (±)-aiphanol

2.1 Overview

In this chapter a simple and convergent but non-selective total synthesis of (±)-aiphanol (26) together with the isomeric (non-natural) congeners (±)-50-52 is described. Test results arising from assessments of the COX enzyme inhibitory and anti-angiogenic activities of these materials, as well as certain (±)-aiphanol substructures, specifically those represented by compounds 53 and (±)-54, are also reported.
Chapter 2 The synthesis of (±)-aiphanol

2.2 The 1,4-benzodioxane ring system

An important consideration in developing any synthesis of aiphanol (26) is the construction of a 1,4-benzodioxane ring (viz. the B-C-ring) incorporating appropriate functionality at the C-2 and C-3 positions and with trans- stereochemistry. In this connection, an overview of established literature procedures for construction of the 1,4-benzodioxane ring system is presented immediately below (Section 2.2.1). A novel route to the 1,4-benzodioxane ring system is then postulated and examined by way of a model study. The results of this preliminary investigation are presented in Section 2.2.2.

2.2.1 Literature procedures for assembling the 1,4-benzodioxane ring system

Various synthetic routes have emerged for the construction of the 1,4-benzodioxane ring moiety. A survey of the chemical literature revealed the most common method involved silver(I) ion-mediated oxidative phenolic coupling between an appropriately functionalised catechol and a cinnamyl alcohol. Such methodology has been used to construct the 1,4-benzodioxane ring moiety associated with various natural products.1-8 Thus, for example, 5′-methoxyhydnorcarpin-D (20), a potent inhibitor of a Staphlococcus aureus multidrug resistant efflux pump, was synthesised in a racemic form by an oxidative coupling between luteolin (55) and coniferyl alcohol (56) (Scheme 2.1).2 In the process, regio-isomer 57 was also formed although compound 20 was reported as the major product.2 In the synthesis of several natural products, related oxidative couplings initiated by Fe3+ species (e.g. potassium hexacyanoferrate(III)-sodium acetate) or an enzyme (horseradish peroxidase - HRP) have been used to construct the 1,4-benzodioxane moiety.3,9-12

The above-mentioned oxidative coupling reactions promoted by Ag+, Fe3+, or HRP are generally non-selective and lead to racemic and/or regio-isomeric products, or at best, in the cases involving HRP, products in very modest enantiomeric excesses.12 Merlini and co-workers,6,7,13 then Fukuyama,12 postulated a biomimetic type free radical mechanism for the oxidative couplings. Such a radical mechanism was also suggested for the biosynthesis of certain lignoids including, for example, silybin.7 Pathways involving ionic species have also been postulated.14
Other, and perhaps more useful (i.e. selective), procedures for preparing the 1,4-benzodioxane systems have been reported. For example, in the synthesis of the anti-hepatotoxic flavonolignan (±)-silybin and the neo-lignan americanin A, Tanaka and co-workers\textsuperscript{15,16} reported two procedures that rely, in the key step, on an intramolecular reaction to furnish the 1,4-benzodioxane ring moiety (Scheme 2.2). In the first case, an acid-mediated cyclisation of the diol 58 produced 1,4-benzodioxane system 59.\textsuperscript{16} In the second case, treatment of substrate 60 with base forms a phenoxyanion which attacks the tethered epoxide at the C-2 position in an S\textsubscript{N}2 reaction to form the 1,4-benzodioxane system 61.\textsuperscript{15} In both the cases, the intramolecular reactions proceeded in a completely regio-selective manner and delivered products incorporating \textit{trans}-disposed aryl (at C-2) and hydroxymethyl (at C-3) substituents on the dioxin ring (Scheme 2.2).

Xingfu and co-workers,\textsuperscript{17} using a similar epoxide ring-opening process to that reported by Tanaka and co-workers,\textsuperscript{15} established a method for installing the correct absolute stereochemistry at C-2 and C-3 on the 1,4-benzodioxane ring. These authors use an epoxide related to compound 60 (Scheme 2.2) but with defined absolute stereochemistry at the C-1 and C-2 positions then employed a base-promoted cyclisation reaction to deliver the chiral 1,4-benzodioxane system as a single regio-isomer in >92\% e.e. The chirality at C-1 of the epoxide ring in compound 60 was established \textit{via} Sharpless asymmetric dihydroxylation\textsuperscript{18} and subsequent stereoинversion.
Chapter 2 The synthesis of (±)-aiphanol

reactions. A monochiral epoxide precursor was used to construct the correct stereochemistry at C-2.

As noted in the preceding chapter, during the course of the studies reported in this thesis, Ohira and co-workers outlined the first total synthesis of (±)-aiphanol. In their approach, this Japanese group used a [4+2]-cycloaddition reaction involving ortho-benzoquinone 44 and TBS-protected sinapyl alcohol 45 to form the 1,4-benzodioxane system 46.

Scheme 2.2: Other common methods utilised in forming the 1,4-benzodioxane system

The synthetic route to (±)-aiphanol established in this study (Org. Biomol. Chem., 2003, 1, 2427) differs from that reported by Ohira and co-workers. To the best of the author’s knowledge, these two are the only reported syntheses of (±)-aiphanol.
2.2.2 Alternative approach to 1,4-benzodioxane ring system: preliminary study

In an effort to find an alternate and simpler method for accessing the 1,4-benzodioxane system associated with aiphanol, it was envisaged that reaction of catechol-derived anions with a non-tethered epoxide could lead to the formation of the desired 1,4-benzodioxane system via sequential inter- and intra-molecular epoxide ring-opening processes as shown in Scheme 2.3. This approach was tested by way of a model study using simple substrates. Thus, the base-promoted reaction of 3-methoxycatechol 62a with either mesylate 63 or the related chloride 64 was investigated. It was anticipated that the illustrated phenoxyanion 62b would react with the epoxide 63 or 64 at the C-1 position to give an intermediate epoxide 65 that would engage in a second, and now intramolecular, epoxide ring-opening process in the illustrated manner to give the target 1,4-benzodioxane system 66. If successful, this approach would allow for the installation of the desired absolute stereochemistry on the 1,4-benzodioxane ring through use of a chiral epoxide, likely to be accessible via a Sharpless asymmetric epoxidation (SAE) reaction.21

Scheme 2.3: Proposed route to the 1,4-benzodioxane ring system involving inter- and intra-molecular epoxide ring-opening processes

To test the merit of this proposal, the necessary precursors 62a, 63, and 64 were prepared (Scheme 2.4). Thus, monomethylation of the commercially available pyrogallol (67) with Me₂SO₄ and base afforded the methoxycatechol 62a in 74% yield. Mesylate 63 was obtained in reasonable overall yield (76%) by m-CPBA-mediated epoxidation of the commercially available cinnamyl alcohol (68) followed by treatment of the initial product, epoxycinnamyl alcohol 69, with MsCl.

Chloride 64 could be obtained via either of two distinct routes: by refluxing epoxycinnamyl alcohol 69 with CCl₄ and PPh₃, or by m-CPBA-mediated epoxidation of
Chapter 2 *The synthesis of (±)-aiphanol*

the commercially available cinnamyl chloride 70. The latter process was slightly more efficient (71% vs 78% yield).

**Scheme 2.4: Synthesis of catechol 62a, mesylate 63 and chloride 64**

Reagents and conditions: (i) H$_3$BO$_3$, Me$_2$SO$_4$, NaOH, 18 °C, 3.5 h, 74% (ii) m-CPBA, 0.5 m NaHCO$_3$, 18 °C, 3 h, 84%; (iii) MsCl, NEt$_3$, DCM, 0 °C, 0.5 h, 90%; (iv) PPh$_3$, CCl$_4$, reflux, 4 h, 71%; (v) m-CPBA, 0.5 m NaHCO$_3$, 0 - 18 °C, 3 h, 78%.

Next, the feasibility of the pivotal epoxide ring-opening reaction was investigated. As depicted in Scheme 2.5, base-promoted reaction of the mesylate 63 or chloride 64 with catechol 62a gave three products. The desired one, compound 66, was obtained in 8% yield from mesylate 63 and 11% yield from chloride 64. The major products, in each case, were the isomeric systems 71 and 72. These were obtained as a mixture of diastereoisomers in 30% and 39% yield, respectively, from mesylate 63, and 21% and 31% yield, respectively, from chloride 64. No seven-membered ring product (i.e. a 1,5-benzodioxepin) arising from reaction of the phenoxyanion at C-3 oxirane carbon of intermediate 65 was observed. This is consistent with earlier reports.$^{22}$

The 300 MHz $^1$H NMR spectrum of compound 66 displayed features fully consistent with the assigned structure. The diagnostic signal was that due to H-2 which appeared as a doublet at δ 5.00. A coupling constant of 8.9 Hz between H-2 and H-3 indicated a trans-disposition between the two protons and, therefore, a trans-relationship between the aryl substituent at C-2 and the hydroxymethyl moiety at C-3. An accurate mass measurement on the molecular ion established a molecular formula of C$_{16}$H$_{16}$O$_4$, in full agreement with the proposed structure.
**Scheme 2.5: Base-promoted reaction of mesylate 63 or chloride 64 with catechol 62a**

Reagents and conditions: (i) K₂CO₃, acetone, reflux, 20 h; overall yield of 77% from mesylate 63 and 63% from chloride 64; (ii) DMP, DCM, 18 °C, 2.5 h, 76%; (iii) DMP, DCM, 18 °C, 2.5 h, 78%.

The major products, i.e. compounds 71 and 72 (Scheme 2.5), most likely arise through reaction of the phenoxide ion derived from compound 62a at C-3 of mesylate 63 or chloride 64 followed by (intramolecular) ring-opening of the epoxide by the remaining phenoxy group. The structures of compounds 71 and 72 were confirmed by spectroscopic analysis of the derived ketones, 73 and 74 respectively, obtained through Dess-Martin periodinane oxidation.

Mass spectroscopic studies established that compounds 73 and 74 have the same molecular formula (viz. C₁₆H₁₄O₄). They also display similar 300 MHz ¹H NMR spectral properties. In the 75 MHz ¹³C NMR spectrum the ketone carbons appeared at δ 193.7 and 193.9 (for compounds 73 and 74, respectively) while the presence of such a motif was confirmed by IR spectroscopy (C=O stretching absorption at 1699 cm⁻¹ in each case). The DEPT ¹³C NMR spectra of compounds 73 and 74 revealed methylene carbon resonances at δ 65.3 and 65.7, respectively. This feature ruled out the presence of a hydroxymethyl group (as seen in compound 66) in the primary products (compounds 71 and 72) since such a group would have furnished an aldehyde and/or
The synthesis of (-)-aiphanol upon oxidation. The positions of attachment of the benzoyl group on the 1,4-benzodioxane ring associated with compounds 73 and 74 were secured by heteronuclear (H-C) multiple bond correlation (HMBC) experiments. Thus, after setting a long range $J$ value [$^{2,3}J(C,H)$] at 1.6 Hz, the HMBC cross peaks for H-3/C-4a (compound 73), and for H-2/C-8a (compound 74), were observed.

The aforementioned preliminary synthetic investigation led to a mixture of products. Thus, it was decided that this approach would not, in all likelihood, lend itself to an efficient construction of the 1,4-benzodioxane ring system as seen in aiphanol (26).

2.3 Synthesis of (±)-aiphanol: a simple and convergent approach

2.3.1 Retrosynthetic analysis

Having completed the model study detailed above and obtained a somewhat disappointing yield of the desired ring system, it was envisaged that a convergent and biomimetic approach, analogous to that employed in the synthesis of 5'-methoxyhydnorcarpin-D (20) (Scheme 2.1), could deliver the target 1,4-benzodioxane ring system. While it was recognised that the pivotal oxidative coupling step could lead to the formation of regio- and, possibly, stereo-isomeric products, this was not viewed as being entirely negative since analogues of the target system would be generated that, provided separation could be achieved, could also be evaluated biologically. As such, an early-stage SAR profile could be obtained for this class of compound.

Thus, (±)-aiphanol (26) could be assembled through biomimetic coupling of compounds 53 and 75 as illustrated in retrosynthetic form in Scheme 2.6. The necessary oxidative phenolic coupling reaction would be promoted by Ag(I) ion. The advanced intermediate identified through this analysis, namely tetrahydroxystilbene 53, is itself a natural product commonly known as piceatannol and has been isolated from Aiphanes aceulata (together with aiphanol), as well as other sources. In biosynthetic terms, hydroxystilbenes are believed to be metabolites of mixed biosynthetic origin (shikimate + malonate pathways). The phenylpropane unit sinapyl alcohol (75) is biosynthesised by a shikimate pathway, and so the proposed approach to aiphanol from precursors 53 and 75 of defined biosynthetic origins, and the use of a phenolic
oxidative coupling reaction to form the dioxane ring system, could be regarded as representing a biomimetic approach to aiphanol.

**Scheme 2.6: Retrosynthetic analysis of (±)-aiphanol (26) – a biomimetic and convergent approach**
Chapter 2 The synthesis of (±)-aiphanol

The ethylenic bridge of compound 53 would be constructed by a Wittig reaction from the phosphonium salt 76 and the aldehyde 77 which could, in turn, be prepared from the readily available starting materials 3,5-dihydroxybenzyl alcohol (78) and 3,4-dihydroxybenzaldehyde (79), respectively, via appropriate protection-deprotection steps and/or functional group interconversions. Sinapyl alcohol (75) should be accessible through esterification then reduction of the commercially available sinapinic acid (80).

2.3.2 Generation of (±)-aiphanol (26) and congeners (±)-50-52

The implementation of the ideas proposed above began with the synthesis of the advanced intermediate 53 (Scheme 2.7). Thus, the commercially available starting material 3,5-dihydroxybenzyl alcohol (78) was converted into the corresponding benzyl bromide 81 through treatment with PBr₃. To prevent polymerisation, the phenolic hydroxyls of product 81 were immediately protected as acetates using acetic anhydride/pyridine and thus affording compound 82. Next, reaction of compound 82 with excess PPh₃ in refluxing benzene yielded the phosphonium salt 83, and subsequent deacetylation with catalytic amounts of p-TsOH in methanol at reflux afforded the phosphonium salt 76 in 57% yield over the four steps.

Scheme 2.7: Synthesis of piceatannol 53

Reagents and conditions: (i) PBr₃, THF-PhH, 0 - 18 °C, 2.5 h, 80%; (ii) Ac₂O, pyridine, PhH, 18 °C, 16 h, 99%; (iii) PPh₃, PhH, reflux, 3 h, 85%; (iv) MeOH, p-TsOH, reflux, 5 h, 85%; (v) TBSOCl, imidazole, DMF, 18 °C, 16 h, 82%; (vi) compound 76 in THF, n-BuLi, then add compound 77 in THF, 0 - 18 °C, 18 h, 67%; (vii) TBAF, THF, 0 °C, 5 min, 91%.
Chapter 2 The synthesis of (±)-aiphanol

The 300 MHz $^1$H NMR and 75 MHz $^{13}$C NMR spectra of compound 76 were fully consistent with the assigned structure. In the $^1$H NMR spectrum, the protons of the phenolic hydroxyls appeared as a broad singlet at δ 9.36 (2 H) while the protons of the benzylic methylene moiety resonated as a doublet ($J$ 15.5 Hz) at δ 4.93. The aromatic protons appeared as a complex 18-proton envelope in the region δ 5.84-7.89.

Phosphonium salt 76 represents one of the coupling partners for the foreshadowed Wittig reaction. The other partner, compound 77, was prepared by bis-silylating the commercially available 3,4-dihydroxybenzaldehyde (79) with TBSCl under standard conditions. The ylide obtained by treatment of salt 76 with 3-equivalents of n-BuLi underwent $E$-selective Wittig coupling with aldehyde 77 leading to the bis-silylated stilbene 84 in 67% yield (Scheme 2.7). Stilbene 84 was desilylated through exposure to excess TBAF and thereby affording piceatannol 53 in 35% overall yield from compound 78.

The 300 MHz $^1$H NMR spectral data derived from compound 53 were consistent with the assigned structure and in excellent agreement with those reported previously for piceatannol. The 75 MHz $^{13}$C NMR spectrum of compound 53 (Figure 2.1) showed signals for 12 non-equivalent carbons, and an accurate mass measurement on the molecular ion established a molecular formula of C$_{14}$H$_{12}$O$_4$, in full agreement with the proposed structure.

![Figure 2.1: 75 MHz $^{13}$C NMR spectrum of compound 53 recorded in CD$_3$COCD$_3$.](image-url)
Although already noted in Chapter 1, it is worth reiterating, at this point, that in addition to the classical Wittig process,\textsuperscript{29} other methods, such as the Heck reaction\textsuperscript{32} and Suzuki cross-coupling protocols\textsuperscript{33} have been used to construct the ethylenic bridge of biologically active polyhydroxystilbenes.\textsuperscript{34,35}

The other advanced intermediate, sinapyl alcohol (75), was obtained in two steps (72\% yield) by converting the commercially available sinapinic acid (80) into the corresponding methyl ester 85, followed by 1,2-reduction of the latter with DIBAL-H (Scheme 2.8). The spectroscopic data obtained on compound 75 were in full agreement with the literature data reported for sinapyl alcohol.\textsuperscript{36}

\textbf{Scheme 2.8: Synthesis of sinapyl alcohol 75}

\begin{center}
\begin{tikzpicture}
\node at (0,0) [text=black, scale=0.8] {\textbf{Scheme 2.8: Synthesis of sinapyl alcohol 75}};\end{tikzpicture}
\end{center}

Reagents and conditions: (i) MeOH, H\textsubscript{2}SO\textsubscript{4}, reflux, 6 h, 90\%; (ii) DIBAL-H, PhCH\textsubscript{3}, 0 \textdegree C, 1 h, 80\%.

With serviceable quantities of the advanced intermediates 53 and 75 to hand the final, and pivotal, step of the proposed synthesis of (±)-aiphanol could be examined (Scheme 2.9). In the event, Ag\textsubscript{2}CO\textsubscript{3}-mediated oxidative coupling of compound 53 with sinapyl alcohol (75) gave a \textit{ca.} 2:1:2:1 mixture of compounds (±)-26 and (±)-50-52 (62\% overall yield) which could be separated into its component parts using semi-preparative HPLC techniques (Figure 2.2). Concentration of the most mobile and the second most abundant component, F1, yielded (17\%) a brown solid, m.p. 162-164 \textdegree C. This proved to be (±)-aiphanol (26) as judged by comparison of the derived spectroscopic data with those reported for the natural product.\textsuperscript{24}
Scheme 2.9: $\text{Ag}_2\text{CO}_3$-mediated oxidative coupling of compounds 53 and 75

Reagents and conditions: (i) $\text{Ag}_2\text{CO}_3$, PhH-acetone 2:1, 60 °C, 18 h, 62% [17% (+/-)-26, 12% (+/-)-50, 19% (+/-)-51, 14% (+/-)-52].

Figure 2.2: HPLC trace derived from analysis of the reaction mixture obtained from the oxidative coupling reaction depicted in Scheme 2.9. HPLC conditions: 300 x 10 mm 5 µm C$_{18}$ Alltech Alltima column, 50:49.9:0.1 v/v/v water-methanol-acetic acid elution, solvent flow rate of 5 mL/min, and UV peak detection at 325 nm.
Chapter 2 The synthesis of \((\pm)\)-aiphanol

The 300 MHz \(^1\)H NMR spectrum of the synthetic sample of compound 26 (Figure 2.3) was fully consistent with the data reported for the natural product.\(^{24}\) The significant features were the resonances associated with H-2, which appears at \(\delta 4.97\) (d, \(J 8.1\) Hz), and those due to the mutually coupled H-9 and H-10 at \(\delta 7.02\) and 6.94 (d, \(J 16.2\) Hz), respectively. The H-3 proton appears at \(\delta 4.14\) and diastereotopic protons of the hydroxymethyl group resonate upfield at \(\delta 3.78\) and 3.53. Other signals belonging to the methoxy protons (\(\delta 3.86\), singlet) and aromatic protons between \(\delta 6.28-7.14\) were in full agreement with the proposed structure. The \(^{13}\)C NMR data were also in good agreement with those reported for the natural product.\(^{24}\)

![Figure 2.3: 300 MHz \(^1\)H NMR spectrum of \((\pm)\)-aiphanol (26) recorded in CD$_3$COCD$_3$. Selected proton resonances have been assigned as indicated.](image)

Concentration of component F3 (Figure 2.2) yielded (19\%) a brown solid, m.p. 161-163 °C. The 300 MHz \(^1\)H NMR and 75 MHz \(^{13}\)C NMR spectra of this compound were very similar to the equivalent spectra of compound 26 and this is, therefore, most likely to be the regio-isomeric system 51. A vicinal coupling of 8.1 Hz observed between H-2
Chapter 2  *The synthesis of (±)-aiphanol*

and H-3 in the $^1$H NMR spectrum [the equivalent coupling in (±)-aiphanol (26) is identical] suggests a *trans*-relationship between the aryl and hydroxymethyl substituents on the newly formed dioxane ring.

To fully distinguish the regio-isomeric systems (±)-26 and (±)-51, heteronuclear multiple bond correlation (HMBC) and nuclear overhauser (nOe) experiments were carried out. The HMBC, $[^2^3^3^J(C,H)]$ set at 1.6 Hz, correlations and nOe’s observed for both compounds (±)-26 and (±)-51, as shown in Figure 2.4, were consistent with the proposed structures.

![Figure 2.4: Selected nOe and HMBC correlations of (±)-26 and (±)-51.](image)

Fraction F2 yielded compound (±)-50 (12%) which was obtained as a brown solid, m.p. 161-163 °C, while F4 afforded isomer (±)-52 (14%) as a brown solid, m.p. 161-163 °C. These compounds possess the same molecular formula, *viz*. C$_{25}$H$_{24}$O$_8$, as congeners (±)-26 and (±)-51 as determined by an accurate mass measurement on the molecular ion. The 300 MHz $^1$H NMR spectrum of compound (±)-52 was very similar to the equivalent spectrum of compound (±)-50 shown in Figure 2.5. In the proton spectra, a doublet for the H-2 proton at $\delta$ 5.29 ppm ($J_{2,3}$ 2.6 and 2.7 Hz, respectively) suggested a *cis*-relationship between the aryl and hydroxymethyl substituents associated with the dioxin core of these compounds.

Interestingly, upon treatment with K$_2$CO$_3$ compound (±)-52 underwent stereoinversion at the C-2 position via the sequence shown in Scheme 2.10. The product thus formed eluted, under appropriate HPLC conditions, in the same manner as compound (±)-51 and also displayed the same $^1$H NMR spectral properties. These results suggest
compounds (±)-52 and (±)-51 possess the same regiochemical relationship and only vary in stereochemistry at C-2 and C-3.

Figure 2.5: 300 MHz $^1$H NMR spectrum of compound (±)-50 recorded in CD$_3$COCD$_3$. Selected proton resonances have been assigned as indicated.

Scheme 2.10: Mechanistic pathway likely involved in the base-catalysed epimerisation of compound (±)-52 to (±)-51

Reagents and conditions: (i) K$_2$CO$_3$, DMF, 18 °C, 0.75 h, 81%.
Chapter 2 The synthesis of (±)-aiphanol

Finally, the similarities in the 75 MHz $^{13}$C NMR spectra of compounds (±)-26 and (±)-51, and compounds (±)-50 and (±)-52 (Figure 2.6) suggest they possess the same regiochemical relationships between the hydroxymethyl and aryl moieties in terms of their position of attachment to the 1,4-benzodioxin core.

![Figure 2.6: Stacked plot of the 75 MHz $^{13}$C NMR of compounds (±)-26 (F1), (±)-51 (F3), (±)-50 (F2) and (±)-52 (F4) (recorded in CD$_3$COCD$_3$).](image)

Having achieved the synthesis of (±)-aiphanol (26), as well as the isomers (±)-50-52, the next objective was to establish preliminary SAR for these compounds. It was also envisaged, based on the pharmaceutical potential of hydroxystilbenes and in order to establish the importance, or otherwise, of the 1,4-benzodioxane core for biological activity in certain systems, that tests on various substructures of aiphanol might provide useful insights. To such ends, compound (±)-54, embodying the 1,4-benzodioxane core plus the appended aryl and hydroxymethyl substituents of aiphanol, was prepared (as a 1:1 and chromatographically inseparable mixture of cis- and trans- isomers) by oxidative coupling of 3,4-dihydroxybenzaldehyde (79) with sinapyl alcohol (75) (Scheme 2.11). The absence of any of the regio-isomeric coupling products in this reaction is consistent with earlier work by Stermitz and Guz who have noted that the presence of an aldehyde moiety in the 4-position on the catechol residue results in a completely regio-selective “cycloaddition” reaction.
Scheme 2.11: Synthesis of compound (±)-54

Reagents and conditions: (i) Ag$_2$CO$_3$, PhH-acetone 2:1, 60 °C, 18 h, 57%.

2.4 Preliminary biological evaluation

With serviceable quantities of lignans (±)-26 and (±)-50-52, as well as congeners 53 and (±)-54, available via the pathways discussed above, biological evaluations could now be carried out. Assessment of compounds (±)-26 and (±)-50-52 as inhibitors of COX-1 and -2 was carried out in an in vitro assay. The results of such testing are presented in Table 2.1.

Table 2.1: COX-1/2 inhibitory properties of compounds (±)-26, (±)-50-52 and (−)-aiphanol

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ for COX-1 (µM)</th>
<th>IC$_{50}$ for COX-2 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-aiphanol (26)</td>
<td>7.3</td>
<td>0.17</td>
</tr>
<tr>
<td>(±)-50</td>
<td>6.3</td>
<td>9.5</td>
</tr>
<tr>
<td>(±)-51</td>
<td>9.0</td>
<td>41*</td>
</tr>
<tr>
<td>(±)-52</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>(−)-aiphanol$^{24}$</td>
<td>1.9</td>
<td>9.9</td>
</tr>
</tbody>
</table>

* % inhibition at 10 µM concentration.

Compounds (±)-26 and (±)-50-52 showed similar IC$_{50}$ values for COX-1 inhibition, and comparable IC$_{50}$ values for COX-2 inhibition, suggesting little or no structural (regio- or stereo-isomeric) effect on the inhibition of specific COX enzymes. Interestingly, (±)-

$^{2}$ The COX enzyme assay was carried out by Prof. Gerd Dannhardt, Werner Kiefer, Ulrike Nowe and Holger Ulbrich, University of Mainz, Germany.
Chapter 2 The synthesis of (±)-aiphanol

aiphanol (26) is a significant inhibitor of COX-2 but only a modest inhibitor of COX-1. This appears to be the reverse of the situation observed for the naturally occurring (−)-form24 and suggested that (+)-aiphanol could be a more potent COX-2 inhibitor. Whilst definitive comment on this matter could only be made by preparing and testing (+)-aiphanol, it is worth noting that the enantiomeric forms of other chiral ligands have been shown to vary in their COX-1 and -2 inhibitory properties.40,41

The anti-angiogenic properties of compounds (±)-26, (±)-50-52, 53 and (±)-54 were determined in an in vitro angiogenesis assay9 using rat aorta rather than human placental blood vessel fragments.42,43 Results are presented in Table 2.2. PI-88, a polysulfated oligosacchride which exhibits anti-angiogenic properties and is now in clinical development as an agent for the treatment of certain cancers,44 was used as a positive control. As can be seen from the table, compound 26 [(±)-aiphanol] completely inhibited blood vessel growth at 100 μg/mL while isomers (±)-50 and (±)-52 behaved similarly. Compound (±)-51 proved a lot less active as did “substructure” (±)-54. Interestingly, piceatannol 53 was almost as active as (±)-aiphanol thus further emphasising the pharmaceutical potential of hydroxystilbenes.37

Table 2.2: Anti-angiogenic properties of compounds (±)-26, (±)-50-52, 53 and (±)-54 as determined in a rat aorta assay

<table>
<thead>
<tr>
<th>Compound</th>
<th>% inhibition of vessel growth at 100 μg mL⁻¹</th>
<th>% inhibition of vessel growth at 10 μg mL⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-26</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td>(±)-50</td>
<td>99</td>
<td>25</td>
</tr>
<tr>
<td>(±)-51</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>(±)-52</td>
<td>96</td>
<td>32</td>
</tr>
<tr>
<td>53</td>
<td>80</td>
<td>34</td>
</tr>
<tr>
<td>(±)-54</td>
<td>57</td>
<td>35</td>
</tr>
<tr>
<td>PI-88</td>
<td>62</td>
<td>30</td>
</tr>
</tbody>
</table>

9 Anti-angiogenesis assay was carried out by Prof. Christopher R. Parish and Ms Anna Bezos; John Curtin School of Medical Research, Australian National University, Canberra, Australia.
2.5 Conclusion

A simple, biomimetic, and convergent synthesis of (±)-aiphanol (26), as well as the congeners (±)-50-52, has been achieved (combined yield of 22%) using a reaction sequence comprising only seven steps in the longest linear sequence. Preliminary SAR studies revealed that the aiphanol “class” of compounds inhibit the COX-1 and -2 enzymes. They also appear to possess significant anti-angiogenic properties.

The results of the study described in this chapter have been published in Organic & Biomolecular Chemistry, 2003, Vol. 1 (No. 14), pgs. 2427-2429. A copy of this publication is included as Appendix A.5 in this thesis.
Chapter 2 The synthesis of (±)-aiphanol

2.6 References


Chapter 2 The synthesis of (z)-aiphanol


(42) Brown, K. J.; Mayes, S. F.; Bezos, A.; Maguire, D. J.; Ford, M. D.; Parish, C. R. Lab. Invest. 1996, 75, 539.

(43) Parish, C. R.; Freeman, C.; Brown, K. J.; Francis, D. J.; Cowden, W. B. Cancer Res. 1999, 59, 3433.

Chapter 3

The synthesis of (−)- and (+)-aiphanol

3.1 Overview

Preliminary biological evaluation of (±)-aiphanol (26), as detailed in the preceding chapter, suggested that the non-natural enantiomer, viz. (+)-aiphanol, could be the more potent COX-2 inhibitor (Chapter 2). Thus, it was envisioned that tests on enantiopure samples of (−)- and (+)-aiphanol would allow definitive comment on their COX-1 and COX-2 enzyme inhibitory activities. A stereocontrolled synthesis of the natural isomer, (−)-aiphanol, would also allow the determination of the absolute configuration of the compound, a matter which had not been dealt with by Kinghorn and co-workers. Indeed, to date there have been no reports of a stereoselective synthesis of (−)-aiphanol.

Stereoselective total syntheses of (−)-(2S,3S)-aiphanol (26) and (+)-(2R,3R)-aiphanol (ent-26) are described in this chapter. The outcomes from testing these compounds for COX enzyme inhibitory and anti-angiogenic activity are also reported.
Chapter 3 The synthesis of (−)- and (+)-aiphanol

3.2 Stereoselective synthesis of aiphanol

3.2.1 Retrosynthetic analysis

As noted earlier, the absolute configuration of (−)-aiphanol has not been determined. However, as the relative stereochemistry at C-2 and C-3 is known, viz. the aryl and hydroxymethyl substituents are trans-disposed, then the absolute configurations at the C-2 and C-3 stereogenic centres must necessarily be either S,S or R,R. Thus, a total synthesis of both the 2S,3S and 2R,3R isomers in conjunction with optical rotation measurements should, in principle, reveal the absolute stereochemistry of the natural product.

Since both enantiomers of aiphanol viz. the (2S,3S)- and (2R,3R)-isomers were synthetic targets in the present study, a retrosynthetic analysis leading to the independent formation of both compounds is shown in Scheme 3.1. It was envisioned, based on the successful synthesis of (±)-aiphanol described in Chapter 2, that a similar convergent route would be adopted and in which the ethylenic bridge of each enantiomer would be constructed via a late-stage Wittig coupling reaction. This requires the enantioselective construction of the 1,4-benzodioxin system early in the synthesis. With this in mind, (2S,3S)-aiphanol (26) was seen as being accessible from the advanced precursors phosphonium salt 48 and the (2S,3S)-1,4-benzodioxane system 86 (Scheme 3.1). Likewise (2R,3R)-aiphanol or ent-26 was similarly reduced to the common precursor 48, and the (2R,3R)-1,4-benzodioxane system ent-86 (Scheme 3.1).

The phosphonium salt 48, common to the synthesis of both enantiomers of aiphanol, would be prepared from the commercially available 3,5-dihydroxymethyl benzoate (87) via standard functional group interconversions. The (2S,3S)-1,4-benzodioxane system 86 would be accessed via an enantioselective synthesis using methodology similar to that reported by Xingfu and co-workers. Thus, this chiron could be assembled through cyclisation of (1S,2R)-aryl ether 88. In the process, it was envisaged that debenzylation followed by base treatment would allow the resulting phenoxyanion of ether 88 to react, via an S_N_2 process, at the C-2 position of the epoxide ring thereby completely inverting the stereochemistry at this centre. Of necessity, then, the C-2 position of aryl ether 88 would have the opposite absolute configuration to that present at the equivalent position on the natural product. Similarly, the (2R,3R)-1,4-benzodioxane system ent-86,
necessary for the synthesis of (2R,3R)-aiphanol (ent-26), could be accessed from the (1R,2S)-aryl ether ent-88 (Scheme 3.1).

Scheme 3.1: Retrosynthetic analysis of (2S,3S)- and (2R,3R)-aiphanol (26)

Aryl ethers 88 and ent-88 could, in turn, be prepared by a Mitsunobu reaction of the epoxy-alcohols 90 and ent-90 with the phenoxide derived from aldehyde 89. In the
process, the absolute configuration at C-1 of epoxy-alcohols 90 and ent-90 would be inverted through another $S_N2$-type nucleophilic displacement reaction to give adducts 88 and ent-88, respectively.

Epoxy-alcohols 90 and ent-90 would be prepared from the commercially available aldehyde 91 via, *inter alia*, Sharpless asymmetric dihydroxylation\(^8\)\(^9\) using AD mix-β (or AD mix-α to access the enantiomer). Aldehyde 89, common to the synthesis of both the enantiomers of aiphanol, would be obtained by differentially protecting the 4-position of the commercially available 3,4-dihydroxybenzaldehyde (79).

### 3.2.2 Synthesis of phosphonium salt 48 and 4-benzyloxy-3-hydroxybenzaldehyde (89)

The implementation of the ideas discussed above began with the synthesis of the phosphonium salt 48 and 4-benzyloxy-3-hydroxybenzaldehyde (89) (Scheme 3.2), intermediates common to the proposed syntheses of each enantiomer of aiphanol. Thus, the hydroxyl groups of the commercially available 3,5-dihydroxymethyl benzoate (87) were protected as *bis*-MOM-ether 92 then NaBH\(_4\) reduction of the ester group afforded benzyl alcohol 93. This last compound was converted into chloride 94 upon reaction with NEt\(_3\) and MsCl\(^10\). Treatment of compound 94 with PPh\(_3\) at reflux then furnished the phosphonium salt 48 as a white powder which was obtained in an overall yield of 53% from compound 87.

The 300 MHz \(^1\)H NMR and 75 MHz \(^13\)C NMR data derived from salt 48 were consistent with the assigned structure. In particular, in the \(^1\)H NMR spectrum the methyl protons of the MOM-protecting group appeared as a six-proton singlet at \(\delta\) 3.21, while the methylene protons appeared as a four-proton singlet at \(\delta\) 4.91. The protons associated with the benzylic methylene unit resonated as a doublet (\(J\) 15.7 Hz) at \(\delta\) 5.20. The expected molecular formula of C\(_{29}\)H\(_{30}\)ClO\(_4\)P was established by accurate mass measurement and microanalytical methods.

4-Benzyloxy-3-hydroxybenzaldehyde (89) was obtained in 35% yield by monobenzylation of the commercially available 3,4-dihydroxybenzaldehyde (79) using the procedure of Kessar and co-workers\(^11\). The use of *ca.* 1 equivalent of base (NaH) in
the reaction meant that deprotonation of the C-4 hydroxyl of aldehyde 79 occurred preferentially due to the stabilising effects involving the carbonyl moiety. This anion engages in a reaction with benzyl chloride to form aldehyde 89 in a completely selective manner. The structure of this compound follows from a single crystal X-ray analysis, the derived plot being shown in Figure 3.1.

**Scheme 3.2: Synthesis of salt 48 and 4-benzyloxy-3-hydroxybenzaldehyde (89)**

![Scheme 3.2: Synthesis of salt 48 and 4-benzyloxy-3-hydroxybenzaldehyde (89) with reagents and conditions](image)

**Reagents and conditions:** (i) MOMCl, DIPEA, DCM, 0 - 18 °C, 18 h, 91%; (ii) LiAIH₄, THF, 0 - 18 °C, 4 h, 97%; (iii) MsCl, NEt₃, DCM, 0 - 18 °C, 18 h, 79%; (iv) PPh₃, toluene, reflux, 18 h, 76%; (v) NaH, BnCl, DMF, 18 °C, 18 h, 39%.

![Figure 3.1: Anisotropic ellipsoid plot (50% probability ellipsoid) of 4-benzyloxy-3-hydroxybenzaldehyde (89). The oxygen atoms are labelled (O).](image)

*X-ray analyses of compounds described in this thesis were performed by Dr. Alison Edwards, Research School of Chemistry, Australian National University, Canberra.*
3.2.3 Synthesis of (2S,3S)-aiphanol (26)

With intermediates 48 and 89 to hand, attention was next turned to the preparation of the substrate for the Mitsunobu reaction, namely (1R,2R)-epoxy-alcohol 90. To such ends, the phenolic unit of commercially available aldehyde 91 was protected as the corresponding benzyl ether, 95, which was subsequently engaged in a Horner-Wadsworth-Emmons\textsuperscript{12-14} (HWE) reaction using triethyl phosphonoacetate and NaH to afford the E-configured α,β-unsaturated ester 96 (Scheme 3.3) in 73% yield over the two steps. Consistent with expectations,\textsuperscript{13} no Z-configured compound was detected as judged by 300 MHz \textsuperscript{1}H NMR spectral analysis of the product.

Scheme 3.3: Synthesis of (1R,2R)-epoxy-alcohol 90a

\[
\text{Reagents and conditions: (i) BnBr, K}_2\text{CO}_3, \text{DMF, 120 °C, 18 h, 91%; (ii) NaH, triethyl phosphonoacetate, THF, 0 - 18 °C, 3.5 h, 80%; (iii) DIBAL-H, toluene, -10 °C, 0.75 h, 83%; (iv) AD mix-β, CH}_3\text{SO}_2\text{NH}_2, 1:1 v/v \text{BuOH-H}_2\text{O, 0 °C, 48 h, 94%; (v) TsCl, pyridine, 0 - 18 °C, 18 h, 88%; (vi) K}_2\text{CO}_3, \text{MeOH, 18 °C, 3 h, 85%}.}
\]

DIBAL-H reduction of the α,β-unsaturated ester 96 afforded the allylic alcohol 97 in 83% yield. Sharpless asymmetric dihydroxylation\textsuperscript{8,9} of the latter compound with AD mix-β then afforded triol 98 in 94% yield \([\alpha_D] -17.6° (c 1.75, \text{CHCl}_3)\). The absolute
The synthesis of (-)- and (+)-aiphanol

The stereochemistry of this material was assigned, in a preliminary fashion, as 1R,2R using the Sharpless mnemonic.\textsuperscript{15,16} The primary hydroxyl group of triol 98 was converted into a tosylate, \textit{viz.} compound 99, which participated in a base-promoted epoxide forming reaction to give (1R,2R)-epoxy-alcohol 90a [\(\alpha_D\) -8.6° (c 0.96, CHCl\(_3\))] in an overall yield of 70% from allylic alcohol 97.

With precursors 89 and 90a to hand, the pivotal Mitsunobu reaction\textsuperscript{6,7} could be investigated. In the event, treatment of a mixture of compounds 89 and 90a with DIAD and PPh\(_3\) afforded the Mitsunobu product 88a (Scheme 3.4) in 67% yield [\(\alpha_D\) +15.5° (c 0.31, CHCl\(_3\))]. Formation of the 1,4-benzodioxane moiety \textit{via} cyclisation required removal of the benzyl protecting groups within compound 88a. This was achieved through hydrogenolysis using 5% Pd-C as catalyst and ethyl acetate as solvent to afford compound 88b in 86% yield, and in which both the benzyl protecting groups were clearly absent as determined by \(^1\)H- and \(^{13}\)C-NMR spectral analysis.

\textbf{Scheme 3.4: Synthesis of compound 88b and attempted formation of (2S,3S)-86a}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme3.4.png}
\end{figure}
\end{center}

\textbf{Reagents and conditions:} (i) DIAD, PPh\(_3\), THF-toluene, 18 °C, 18 h, 67%; (ii) EtOAc, 5% Pd-C, H\(_2\), 18 °C, 16 h, 86%; (iii) K\(_2\)CO\(_3\), MeOH, 18 °C, 0.75 h.

Unfortunately, treatment of aryl ether 88b with anhydrous K\(_2\)CO\(_3\) (3 equivalents) in dry methanol, in an attempt to effect the desired cyclisation, failed to give the target product 86a (Scheme 3.4). Surprisingly, and contrary to observations made by Xingfu and co-workers\textsuperscript{5} on a somewhat similar system, only an inseparable mixture of compounds was obtained after the usual workup and flash chromatographic steps.\textsuperscript{5} The 300 MHz \(^1\)H NMR spectrum of this mixture did not show any signals due to H-2 of the dioxane
system, that is, a doublet at approximately δ 5 and with a coupling constant of approximately 8 Hz.

To understand the lack of 1,4-benzodioxane formation in the above-mentioned process the reaction mixture was treated with excess MOMCl, and upon chromatographic separation, bis-3,4-methoxymethoxybenzaldehyde (100) was isolated as the major component (88% yield over two steps) and its structure was confirmed by $^1$H- and $^{13}$C-NMR spectral analysis.

![Structure of bis-3,4-methoxymethoxybenzaldehyde (100)](image)

Thus, the failure to generate the target 1,4-benzodioxane ring via the foreshadowed cyclisation process can be explained, in part perhaps, by the resonance stabilisation of the phenoxyanion through the electron withdrawing effect of the carbonyl moiety, thus reducing the nucleophilic character of the anion. Furthermore, the phenoxyanion formed at C-4′ would then lead to the extrusion of the aldehyde component from the aryl ether 88b as illustrated in Figure 3.2.

![Proposed mechanistic pathway leading to the cleavage of C-1 – O bond in compound 88b.](image)

Based on the foregoing observations, it appeared that in order to obtain the 1,4-benzodioxane ring the hydroxyl group at C-4′ in compound 88b must remain protected whilst the base-promoted cyclisation reaction is carried out. Bearing such considerations in mind, a revised protecting group strategy was employed in an effort to set up the desired cyclisation process and thence generate the target 1,4-benzodioxane. To such ends, the hydroxyl group within the commercially available aldehyde 91 was
protected as a MOM-ether 101 (instead of a benzyl ether, as used in the initial strategy) and, following the reaction sequence depicted in Scheme 3.5 and involving the intermediates α,β-unsaturated ester 102 and allylic alcohol 103, triol 104 \( [\alpha_D -24^\circ \text{ (c 0.95, CHCl}_3)] \) was obtained in an overall yield of 51% from the starting aldehyde 91.

**Scheme 3.5: Synthesis of (1R,2R)-epoxy-alcohol 90b**

Reagents and conditions: (i) MOMCl, DIPEA, DMAP, 0 - 18 °C, 6 h, 95%; (ii) NaH, triethyl phosphonoacetate, THF, 0 - 18 °C, 4 h, 83%; (iii) DIBAL-H, toluene, -10 °C, 0.5 h, 81%; (iv) AD mix-β, CH\(_3\)SO\(_2\)NH\(_2\), 1:1 v/v BuOH-H\(_2\)O, 0 °C, 48 h, 80%, >95% e.e.; (v) TsCl, pyridine, 0 - 18 °C, 18 h, 72%; (vi) K\(_2\)CO\(_3\), MeOH, 18 °C, 3 h, 88%, >95% e.e.

In order to unequivocally confirm the absolute stereochemistry of the anticipated dioxane system, the absolute stereochemistry of the Sharpless product 104 was sought at this stage. To such ends, triol 104 was brominated with pyridinium hydrobromide perbromide\(^w\) to afford compound 105 then the MOM group was removed to give bromide 106 as a crystalline solid in 77% yield over the two steps (Scheme 3.6). Recrystallisation of this material from methanol-DCM afforded pure bromide 106 as colourless crystals suitable for single crystal X-ray analysis. Bromine was used as a

\(^w\) Pyridinium hydrobromide perbromide (C\(_5\)H\(_5\)N.HBr.Br\(_2\)) was prepared from pyridine and hydrobromic acid by the procedure reported by Djerassi and Scholz (*J. Am. Chem. Soc.*, 1948, 70, 417).
heavy atom in compound 106 to secure the appropriate anomalous scattering effects. Figure 3.3 shows the anisotropic plot of the product with the absolute stereochemistry at C-1 and C-2 unequivocally determined as R in each case. The absolute stereochemistry determined in this way is consistent with that predicted using the Sharpless mnemonic.\textsuperscript{15,16}

Scheme 3.6: Synthesis of bromide 106

![Scheme 3.6: Synthesis of bromide 106](image)

Reagents and conditions: (i) C\textsubscript{5}H\textsubscript{4}Br\textsubscript{3}N, DCM, 18 °C, 10 min., 85%; (ii) MeOH, trace HCl, 18 °C, 18 h, 91%.

Subsequently, (1R,2R)-triol 104 was converted, via tosylate 107, into epoxy-alcohol 90b [\(\alpha\textsubscript{D} -5.4^\circ (c 1.28, \text{CHCl}_3)\)] in 63% yield (Scheme 3.5) and with an enantiomeric purity of >95% e.e. as determined by chiral HPLC analysis (Figure 3.4).
Chapter 3 The synthesis of (−)- and (+)-aiphanol

Figure 3.4: (Top) HPLC trace derived from analysis of a ca. 1.6:1 mixture of compounds 90b and ent-90b (synthesis of ent-90b is described later in this Chapter). (Bottom) HPLC trace derived from analysis of compound 90b. Both analyses were performed using a CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution, solvent flow rate of 1 mL/min, and UV peak detection at 254 nm. Retention times and peak areas are indicated.

Next, Mitsunobu etherification⁶⁷ (Scheme 3.7) of compounds 89 and 90b using DIAD and PPh₃ afforded the adduct 88c (>95% e.e., αD +11.9° (c 0.56, CHCl₃)) in 60% yield. Removal of the benzyl group was effected by hydrogenolysis over 5% Pd-C as catalyst and using ethyl acetate as solvent to afford epoxide 88d in 71% yield.

---

² The HPLC trace derived from analysis of ent-90b is shown in Figure 3.10.
The conspicuous feature in the 300 MHz $^1$H NMR spectrum of compound 88d is, as expected, a lack of proton resonances associated with the benzyl-protecting group. The proton of the free phenolic hydroxyl group appeared as a broad singlet at δ 8.10. The H-1 proton resonated as a doublet at δ 4.99 (J 2.3 Hz) while H-2 proton appeared as a multiplet at δ 3.38. Singlets observed at δ 5.14 (2 H) and at δ 3.61 (3 H) are assigned to the methylene and methyl protons, respectively, of the MOM-ether. The 75 MHz $^{13}$C NMR spectrum of compound 88d showed 17 non-equivalent carbons, in full agreement with the assigned structure, while an accurate mass measurement revealed a molecular ion at m/z 390, as required for a compound of formula C$_{20}$H$_{22}$O$_8$. The optical rotation of compound 88d was, like congener 88c, dextrorotatory [α$_D$ +142.4° (c 0.41, CHCl$_3$)].

With confirmation of the structure, including absolute stereochemistry, of the required cyclisation precursor 88d to hand, the formation of the 1,4-benzodioxane system could now be pursued. In the event, upon treatment with K$_2$CO$_3$ epoxide 88d underwent the anticipated cyclisation (Scheme 3.7) to afford the desired 1,4-benzodioxane 86b [α$_D$ -48.4° (c 0.32, CHCl$_3$)] in 70% yield, and with an enantiomeric purity of >95% e.e. as determined by chiral HPLC analysis (Figure 3.5). In the 300 MHz $^1$H NMR spectrum of compound 86b, the H-2 proton appeared as a doublet at δ 4.95 (J 8.9 Hz). This, together with other resonances in the proton and also in the 75 MHz $^{13}$C NMR spectrum, were in full accord with the assigned structure. Interestingly, in an outcome consistent with present (Chapter 2) and earlier observations, the K$_2$CO$_3$-mediated cyclisation reaction did not give any seven-member ring product through reaction of the phenoxyanion at C-3 of the epoxide ring.
Figure 3.5: HPLC trace derived from analysis of compound 86b\(^w\) using a CHIRALPAK\(^r\) AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution, solvent flow rate of 1 mL/min, and UV peak detection at 254 nm. Retention times and peak areas are indicated.

Based on the absolute configuration of the Sharpless asymmetric dihydroxylation product 104, as determined by X-ray analysis of derivative 106 (Scheme 3.6 and Figure 3.3), and by virtue of the involvement of Mitsunobu\(^6,\(^7\) and epoxide ring-opening\(^5\) reactions that proceed with inversion of configuration to deliver 1,4-benzodioxane 86b, the absolute configuration at the stereogenic centres associated with the dioxane ring within this last compound is assumed to be S in each case.

With the desired dioxane system 86b and the phosphonium salt 48 now to hand, the final stages of the synthesis were performed as illustrated in Scheme 3.8.

Scheme 3.8: Synthesis of (2S,3S)-aiphanol (26)

Reagents and conditions: (i) MOMCl, DIPEA, DMAP, DCM, 0 - 18 °C, 3 h, 85%; (ii) compound 48, CsF, toluene, reflux, 6 h, 41%; (iii) MeOH, AcCl, 18 °C, 20 h, 65%, >95% e.e.

\(^w\) For comparison, the HPLC trace derived from analysis of ent-86b under the same chromatographic conditions is shown in Figure 3.11.
Prior to carrying out the foreshadowed Wittig olefination reaction, the hydroxyl group of compound 86b was first protected as MOM-ether to afford compound 86c in 85% yield (Scheme 3.8). Wittig coupling\textsuperscript{2,4} then followed using the procedure of Ohira and co-workers\textsuperscript{4} in which phosphonium salt 48 was treated with (2S,3S)-dioxane 86c in refluxing toluene and using CsF as base. In this manner, the fully protected (2S,3S)-aiphanol derivative 108 was obtained in 41% yield. Finally, global deprotection of MOM groups with MeOH and AcCl followed by subjection of the crude material to preparative HPLC afforded (2S,3S)-aiphanol (26) in >95% e.e. as determined by chiral HPLC analysis (Figure 3.6). An optical rotation measurement revealed this compound to be levorotatory (\(\alpha_D\) -20.1°, c 0.21 MeOH; lit.\textsuperscript{1} -21.8°, c 0.13, MeOH) implying that this 2S,3S configured material corresponds to the natural product.

![Figure 3.6](image)

**Figure 3.6**: HPLC trace derived from analysis of (2S,3S)-aiphanol (26)\textsuperscript{e} using a CHIRALPAK\textsuperscript{®} AS-H 250 x 4.6 mm column, 1:1 v/v isopropyl alcohol - hexane elution, solvent flow rate of 1.2 mL/min, and UV peak detection at 325 nm. Retention times and peak areas are indicated.

The 500 MHz \(^1\)H NMR and 125 MHz \(^{13}\)C NMR spectra of synthetic (–)-aiphanol (26) are shown in Figures 3.7 and 3.8, respectively. The diagnostic features associated with the \(^1\)H NMR spectrum include the doublet at \(\delta\) 4.99 which corresponds to the H-2 proton (\(J\) 7.8 Hz between H-2/H-3) implying a \textit{trans}-disposed aromatic substituent at C-2 and hydroxymethyl at C-3. The mutually coupled doublets at \(\delta\) 7.04 and 6.96 correspond to the protons of the C=C bond in the ethylenic bridge of the stilbene and the magnitude (\(J\) 16.3 Hz) of the observed coupling strongly suggests an E-configuration across the double bond. All other features within both the \(^1\)H- and \(^{13}\)C-NMR spectra were consistent with the data reported for the natural product,\textsuperscript{1} and essentially identical to the data obtained for the racemic compound as discussed in Chapter 2.

\textsuperscript{e} For comparison, the HPLC trace derived from analysis of ent-26 under the same chromatographic conditions is shown in Figure 3.12.
Chapter 3 The synthesis of (−)- and (+)-aiphanol

Figure 3.7: 500 MHz $^1H$ NMR spectrum of synthetic (−)-aiphanol (26) (recorded in CD$_3$COCD$_3$). An expansion in the region δ 7.16-6.91 is illustrated in the lower trace. Proton resonances have been assigned as indicated.

Figure 3.8: 125 MHz $^{13}C$ NMR spectrum of synthetic (−)-aiphanol (26) (recorded in CD$_3$COCD$_3$). Carbon resonances have been assigned as indicated.
The synthesis of (2R,3R)-aiphanol was carried out in a similar fashion as described for the synthesis of aforementioned (−)-(2S,3S)-aiphanol (26), but using AD mix-α in the Sharpless asymmetric dihydroxylation\(^8^9\) reaction to access the epoxy-alcohol \textit{ent-90b}. Thus, allylic alcohol \textit{103} (obtained as previously described, Scheme 3.5) was subjected to Sharpless asymmetric dihydroxylation conditions\(^8^9\) using AD mix-α to obtain triol \textit{ent-104} [78% yield, >95% e.e., \(\alpha_D +23.9^\circ \) (c 0.97, CHCl\(_3\))] as depicted in Scheme 3.9.

**Scheme 3.9: Synthesis of triol ent-104 and bromide ent-106**

\(\text{Reagents and conditions: (i) AD mix-α, CH}_3\text{SO}_2\text{NH}_2, 1:1 \text{ v/v} '\text{BuOH-H}_2\text{O}, 0^\circ \text{C}, 48 \text{ h}, 78\%, >95\% \text{ e.e.}; (ii) C}_6\text{H}_5\text{Br}_3\text{N, DCM, 18}^\circ \text{C, 10 min, 79\%; (iii) MeOH, trace HCl, 18}^\circ \text{C, 18 h, 93\%.}"

The optical rotation of \textit{ent-104} suggested the absolute stereochemistry at the C-1 and C-2 stereogenic centres of this compound to be S in each case. This was unequivocally confirmed by single crystal X-ray analysis of the bromine derivative \textit{ent-106} (Scheme 3.9). Figure 3.9 shows the derived anisotropic plot.
In the next step of the reaction sequence the triol ent-104 was converted, via tosylate ent-107, into the epoxy-alcohol ent-90b which was obtained in 60% yield (Scheme 3.10) and in >95% e.e. as determined by chiral HPLC analysis (Figure 3.10). Mitsunobu\textsuperscript{6,7} reaction between 4-benzyloxy-3-hydroxybenzaldehyde (89) and ent-90b using DIAD and PPh\textsubscript{3} then afforded aryl ether ent-88c in 61% yield [\textgreek{e} >95% e.e., \alpha\textsubscript{D} - 14.2° (c 1.87, CHCl\textsubscript{3})].

Figure 3.9: Anisotropic ellipsoid plot (50% probability ellipsoid) of ent-106. Selected carbons (C\textsubscript{1} and C\textsubscript{2}), oxygens (O), and bromine (Br) atom are labelled.

Figure 3.10: HPLC trace derived from analysis of ent-90b using a CHIRALPAK\textsuperscript{®} AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution, solvent flow rate of 1 mL/min, and UV peak detection at 254 nm. Retention times and peak areas are indicated.
Reagents and conditions: (i) TsCl, pyridine, 0 - 18 °C, 18 h, 73%; (ii) K₂CO₃, MeOH, 18 °C, 3 h, 82%, >95% e.e.; (iii) compound 89, DIAD, PPh₃, THF-toluene, 18 °C, 24 h, 61%, >95% e.e.; (iv) EtOAc, 5% Pd-C, H₂, 18 °C, 9 h, 70%, >95% e.e.; (v) K₂CO₃, MeOH, 18 °C, 0.75 h, 68%, >91% e.e.; (vi) MOMCl, DIPEA, DMAP, DCM, 0 - 18 °C, 3 h, 81%; (vii) compound 48, CsF, toluene, reflux, 6 h, 39%; (viii) MeOH, AcCl, 18 °C, 20 h, 56%, >91% e.e.

Removal of the benzyl group in compound ent-88c was effected by hydrogenolysis over 5% Pd-C and using ethyl acetate as solvent to afford ent-88d in 70% yield (Scheme 3.10). Upon treatment of aryl ether ent-88d with K₂CO₃, this compound underwent the anticipated cyclisation reaction to afford the desired 1,4-benzodioxane ent-86b [αD +43.6° (c 0.28, CHCl₃)] in 68% yield and in >91% e.e. as determined through chiral HPLC analysis (Figure 3.11).

Figure 3.11: HPLC trace derived from analysis of ent-86b using a CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution, solvent flow rate of 1 mL/min, and UV peak detection at 254 nm. Retention times and peak areas are indicated.
Based on the absolute configuration of the Sharpless asymmetric dihydroxylation product \textit{ent-104}, as determined by X-ray analysis of the derivative \textit{ent-106} (Figure 3.9), and by virtue of having used chemical transformations, viz. Mitsunobu\textsuperscript{6,7} and epoxide ring-opening\textsuperscript{5} reactions, that are known to proceed with inversion of configuration, the absolute configuration at C-2 and C-3 within 1,4-benzodioxane \textit{ent-86b} is assigned as $R$ in each case.

The hydroxyl group of the dioxane system \textit{ent-86b} was protected as the MOM-ether to furnish \textit{ent-86c} in 81\% yield. Wittig coupling\textsuperscript{2,4} between \textit{ent-86c} and the phosphonium salt 48 was carried out in toluene and using CsF as base. In this way, the fully protected (2R,3R)-aiphanol derivative \textit{ent-108} was obtained in 39\% yield. Finally, global deprotection followed by purification using preparative HPLC techniques afforded (2R,3R)-aiphanol (\textit{ent-26}) in >91\% e.e. as determined by chiral HPLC analysis (Figure 3.12).

![Figure 3.12](image)

\textbf{Figure 3.12:} \textit{HPLC} trace derived from analysis of (2R,3R)-aiphanol (\textit{ent-26}) using a CHIRALPAK\textsuperscript{8} AS-H 250 x 4.6 mm column, 1:1 v/v isopropyl alcohol - hexane elution, solvent flow rate of 1.2 mL/min, and UV peak detection at 325 nm. Retention times and peak areas are indicated.

The specific rotation of \textit{ent-26} was dextrorotatory ($\alpha_D$ +19.3\(^\circ\), c 0.17 MeOH; lit.\textsuperscript{1} -21.8\(^\circ\), c 0.13, MeOH) implying that it is the non-natural isomer.

The 500 MHz \textsuperscript{1}H NMR and 125 MHz \textsuperscript{13}C NMR spectra of compound \textit{ent-26} were identical to the equivalent spectra of (−)-(2S,3S)-aiphanol (26) shown in Figures 3.7 and 3.8.
3.3 Preliminary biological evaluation

With both the enantiomers of aiphanol in hand, biological evaluations could be carried out to establish if, indeed, the non-natural isomer, viz. (+)-aiphanol, is a more potent COX-2 inhibitor than the natural (−)-one as suggested in the preliminary biological assessments of the racemic material (Chapter 2). Assessment of synthetic (+)- and (−)-aiphanol as inhibitors of COX-1 and -2 was carried out\(^8\) in vitro\(^{18,19}\) and the results are presented in Table 3.1.

**Table 3.1: COX-1/2 inhibitory properties of (±)-aiphanol (26), (+)-aiphanol (ent-26), synthetic and natural (−)-aiphanol (26)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC(_{50}) for COX-1 (µM)</th>
<th>COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-aiphanol (26)(^a)</td>
<td>7.3</td>
<td>IC(_{50}) at 0.17 µM</td>
</tr>
<tr>
<td>(+)-aiphanol (ent-26)</td>
<td>0.67</td>
<td>19% inhibition at 1 µM</td>
</tr>
<tr>
<td>Synthetic (−)-aiphanol (26)</td>
<td>1.0</td>
<td>34% inhibition at 10 µM</td>
</tr>
<tr>
<td>Natural (−)-aiphanol(^b)</td>
<td>1.9</td>
<td>IC(_{50}) at 9.9 µM</td>
</tr>
</tbody>
</table>

\(^a\) Chapter 2 of this thesis.

Both synthetic and natural (−)-aiphanol showed strong inhibition of the COX-1 enzyme and only modest inhibition of the COX-2 enzyme. The non-natural (+)-isomer behaved similarly. Although the racemic modification was found to be a more potent COX-2 inhibitor, the notion that (+)-aiphanol could be a selective COX-2 inhibitor may not be true after all. A possible explanation for the observed high potency of (±)-aiphanol in the COX-2 inhibition assay is that there was contamination of the BAE cells used in this particular test.\(^9\) Further studies on the racemic compound are expected to commence shortly so as to verify the preliminary results reported for this material in Chapter 2.

---

\(^8\) COX enzyme assay was carried out by Prof. G. Dannhardt and co-workers; University of Mainz, Germany.

\(^9\) Prof. G. Dannhardt (University of Mainz, Germany), personal communication to Prof. Martin Banwell.
Chapter 3 The synthesis of (-)- and (+)-aiphanol

The anti-angiogenic properties of synthetic (+)- and (-)-aiphanol were determined in an in vitro\textsuperscript{20,21} rat aorta assay\textsuperscript{w} and the results presented in Table 3.2. PI-88, an anti-angiogenic compound now in clinical trials for the treatment of certain cancers,\textsuperscript{22} was used as a positive control.

Table 3.2: Anti-angiogenic properties of (±)-aiphanol (26), (+)-aiphanol (ent-26), synthetic (-)-aiphanol (26) and PI-88 as determined in a rat aorta assay

<table>
<thead>
<tr>
<th>Compound</th>
<th>% inhibition of vessel growth at 100 µg mL(^{-1})</th>
<th>% inhibition of vessel growth at 10 µg mL(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-aiphanol (26)\textsuperscript{x}</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td>Synthetic (-)-aiphanol (26)</td>
<td>100</td>
<td>43</td>
</tr>
<tr>
<td>(+)-aiphanol XX (ent-26)</td>
<td>100</td>
<td>51</td>
</tr>
<tr>
<td>PI-88\textsuperscript{22}</td>
<td>62</td>
<td>30</td>
</tr>
</tbody>
</table>

\textsuperscript{x} Chapter 2 of this thesis

As a result of such tests it is quite clear the both the (+)- and (-)- forms of aiphanol are potent angio-angiogenic agents. In each case, at 100 µg/mL, total inhibition of vessel growth was noted, while at 10 µg/mL, the potency observed was \textit{ca.} 45%. These results further emphasise that compounds that inhibit the COX enzymes could also be potential anti-angiogenic agents. In terms of anti-angiogenic activity, no difference was observed between the behaviours of (±), (-)- and (+)-forms of aiphanol. It is envisaged that further testing of the various analogues of aiphanol will commence shortly so as to establish the mode of action of such compounds as anti-angiogenic agents.

3.4 Summary

Enantioselective total syntheses of (-)-(2S,3S)- and (+)-(2R,3R)-aiphanol (26) have been achieved in 12 steps (longest linear sequence) and in \textit{ca.} 3% overall yield. The absolute configuration at the C-2 and C-3 stereogenic centres in the natural isomer was found to be \textit{S} in each case. Preliminary biological evaluations revealed the non-natural (+)-isomer to be as active as the natural (-)-isomer in COX enzyme inhibitory and anti-angiogenic activity studies.

\textsuperscript{w} Anti-angiogenic assay was carried out by Prof. C. R. Parish and Ms Anna Bezos; John Curtin School of Medical Research, Australian National University, Canberra.
3.5 References


(20) Brown, K. J.; Mayes, S. F.; Bezos, A.; Maguire, D. J.; Ford, M. D.; Parish, C. R. Lab. Invest. 1996, 75, 539.

(21) Parish, C. R.; Freeman, C.; Brown, K. J.; Francis, D. J.; Cowden, W. B. Cancer Res. 1999, 59, 3433.

Chapter 4

Studies directed towards the synthesis of the phenolic natural product diversonol

4.1 Overview

Diversonol (49) is a polyketide-derived natural product isolated from the fungus *Penicillium diversum* and features a polyhydroxyl- and methyl-substituted xanthenone skeleton incorporating four contiguous stereogenic centers. All of the substituents attached to these centres are trans-disposed and two are present at the junction between the A and B rings. To date, there have been no reports of a synthesis of diversonol or any evaluation of its biological properties. As noted in Chapter 1, phenolic compounds exhibit a range of such properties. Obviously, then, the development of a total synthesis of diversonol is worthwhile not least because this would allow preliminary biological evaluations to be carried out. In this chapter, early stage studies directed towards the synthesis of diversonol (49) are described.

4.2 Overall synthetic strategy and retrosynthetic analysis

(1S,2R)-3-Methylcyclohexa-3,5-diene-1,2-diol, commonly known as toluene diol or cis-3-methyl-1,2-dihydrocatechol (109), was envisaged as an ideal starting material for constructing the A-ring of diversonol (49). This compound is derived by cis-dihydroxylation of toluene using the recombinant microorganism *Escherichia coli* JM109 which contains the plasmid pDTG601A that over expresses the enzyme toluene...
dioxygenase responsible for this biotransformation. Compound 109 can be obtained in large quantity and high enantiomeric excess (>99.8%) by such means (Scheme 4.1). Within the Banwell group, a variety of similarly-derived cis-1,2-dihydrocatechols have been successfully employed in developing so-called chemoenzymatic total syntheses of a range of natural products.\textsuperscript{2-6}

Scheme 4.1: Formation of toluene diol (109)

An overview of the proposed synthetic approach to diversonol (49) is presented in Scheme 4.2. Two key synthons, viz. the A-ring precursor 110 (which would be derived from diol 109) and the C-ring precursor 111, were thought likely to be applicable in developing the synthesis. Thus, the stepwise annulation of these components should deliver the B-ring through an initial epoxide ring-opening process (to form the C-4a – O bond) and a subsequent intramolecular crossed aldehyde-ketone benzoin condensation reaction (to form the C-9 – C-9a bond) as illustrated.

Scheme 4.2: Key elements to be employed in the proposed synthesis of diversonol (49)
Thus, it was envisaged that the pyranone ring (B-ring) of diversonol (49) would be constructed at a late stage in the synthesis and via formation of the \( \alpha \)-hydroxyketone (C-9 – C-9a) bond (Process 2). Retrosynthetically speaking, then, dissection of the C-9 – C-9a bond in diversonol (49) leads to the advanced intermediate 112 as shown in **Scheme 4.3.** In the forward direction, this bond would be established via a crossed and intramolecular benzoin type reaction between the C-ring aldehyde and the A-ring ketone group. Recently, Suzuki and co-workers have successfully utilised a similar strategy in the synthesis of preanthraquinones.\(^7\)

**Scheme 4.3: Retrosynthetic analysis of diversonol (49)**

For the sake of discussion, carbon numbering in the intermediates refers to the equivalent positions in diversonol (49).

Compound 112 would itself be derived from *bis*-ether 113 which contains all the necessary functionality with the exception of the A-ring carbonyl moiety. Ideally, the bromobenzyl ether unit attached at C-9a of the cyclitol ring can act as a "self-oxidising"
hydroxyl protecting group. In the forward direction, removal of this group under "reductive" conditions with tributyltin hydride would be coupled with an oxidation of the substrate to form the A-ring ketone moiety via the pathway shown in Scheme 4.4.8,9

**Scheme 4.4: Proposed pathway in the formation of A-ring keto-group**

Disconnection of the C-4a – O bond of bis-ether 113 (Scheme 4.3) furnishes the key synthons viz. epoxide 110 (A-ring precursor) and aldehyde 111 (C-ring precursor) mentioned previously. In the forward direction, reaction of the hydroxyl group of phenol 111 at the C-4a position of epoxide 110 was expected to proceed in an $S_N$2 fashion so as to furnish the C-4a – O bond as well as the C-4 hydroxyl group, while subsequent stereoinversion of the newly formed C-4 hydroxyl group would deliver the desired subtarget 113.

Compound 111, commonly known as atranol,10 would be prepared from readily available starting materials via an established procedure,10 while epoxide 110 would be obtained through the reductive cleavage of benzylidene acetal 114 followed by hydroxyl-directed epoxidation. This latter compound would be obtained from the previously mentioned metabolite 109. In the forward direction, selective reduction of the less-hindered C=C bond of diol 109 followed by reaction with an appropriate benzaldehyde would deliver acetal 114.

---

8 For a discussion on the applications as well as the mechanism of the oxidative cleavage of self-oxidising protecting groups, see Curran *et al.*8 and Nicolaou *et al.*9
4.3 Initial investigations towards the synthesis of diversonol

4.3.1 Studies on the formation and reductive cleavage of benzylidene acetals

The above-mentioned reductive cleavage of the benzylidene acetal 114 was considered an important early step in the projected synthesis of diversonol. Ideally, the cleavage should proceed from the less-hindered side to selectively form the product in which the bromobenzyl ether unit is attached at C-9a. Thus, acetals 114a (R = H) and 114b (R = OCH₃) were synthesised so as to investigate the ease of formation of such systems as well as the selectivity of the ensuing reductive cleavage step. It was envisaged that the formation and cleavage of p-methoxybenzylidene acetal 114b would proceed more easily due to the electron donating effect of the p-methoxy group. The relevant study commenced with the synthesis of benzylidene acetals 114a and 114b, as illustrated in Scheme 4.5.

Scheme 4.5: Synthesis of benzylidene acetals 114a and 114b

Reagents and conditions: (i) 5% Rh on Al₂O₃, H₂, EtOH, 18 °C, 4 h, 90%; (ii) compound 116, p-TsOH (catalyst), toluene, reflux (Dean-Stark trap), 5 h, 90%; (iii) compound 117, p-TsOH (catalyst), toluene, reflux (Dean-Stark trap), 3 h, 95%.

Thus, the less-substituted C=C bond within diol 109 was reduced under a hydrogen atmosphere using 5% rhodium on alumina as catalyst and in this manner the previously reported diol 115 was obtained in 90% yield. Next, acid-catalysed reaction of diol 115 with the commercially available 2-bromobenzaldehyde (116) using a Dean-Stark trap

Footnote: Toluene diol (109) was obtained from TDC Research Inc. Florida as a solution in 0.1 M (pH 7) KH₂PO₄/K₂HPO₄ aqueous buffer. The extraction procedure used in isolating the neat compound from this solution is described in the experimental section (Chapter 5).
furnished acetal 114a as an inseparable ca. 1:1 mixture of epimers in 90% yield. Although acetal 114a and unreacted 2-bromobenzaldehyde (116) proved inseparable by column chromatography, the latter reacted selectively with saturated aqueous sodium metabisulphite and the so-formed bisulfite addition product was retained in the aqueous phase upon diethyl ether extraction of the product. By such means the former compound could be obtained in spectroscopically pure form.

In a similar fashion (Scheme 4.5), reaction of diol 115 with 2-bromo-4-methoxybenzaldehyde (117)* furnished the p-methoxybenzylidene acetal 114b (also as an inseparable ca. 1:1 mixture of epimers) in 95% yield.

Next, reductive cleavage of the acetals (114a and 114b) was investigated. In the event, upon treatment of acetal 114a with DIBAL-H, a ca. 2.3:1 mixture of regio-isomeric alcohols 118a and 119 was obtained (Scheme 4.6). Separation was achieved through selective oxidation of the latter compound. Thus, when this mixture was treated with activated MnO₂ for 24 h, and following purification by flash chromatography, homoallylic alcohol 118a (54% yield) together with the less polar enone 120 (23% yield), resulting from the oxidation of allylic alcohol 119, were isolated. These results clearly indicate that DIBAL-H cleavage of the acetal 114a occurred preferentially from the less-hindered side of the substrate acetal. This outcome is consistent with earlier observations made by other groups.¹¹

Scheme 4.6: Reductive cleavage of benzylidene acetal 114a

Reagents and conditions: (i) DIBAL-H, DCM, 0 - 18 °C, 20 h; (ii) MnO₂, Et₂O, 18 °C, 24 h.

* 2-Bromo-4-methoxybenzaldehyde (117) was obtained in an overall yield of 14% by subjection of 3-bromophenol to Riemer-Tiemann oxidation (see Kobayashi, S.; Azekawa, M.; Morita, H. Chem. Pharm. Bull. 1969, 17, 89) followed by protection of phenol hydroxyl within the product 2-bromo-4-hydroxybenzaldehyde as the methyl ether. Experimental details are presented in Chapter 5.
A similar investigation, as depicted in Scheme 4.7, using acetal 114b gave a mixture of homoallylic and allylic alcohols, compounds 121 and 122, respectively. Once again, this mixture was separated through selective oxidation of the latter followed by flash chromatography. The proportions of the isolated alcohol 121 (64%) and enone 123 (26%) indicate that DIBAL-H cleavage of the acetal 114b also occurred preferentially from the less-hindered side of the starting acetal.

Scheme 4.7: Reductive cleavage of benzylidene acetal 114b

Reagents and conditions: (i) DIBAL-H, DCM, -10 °C, 5 h; (ii) MnO₂, Et₂O, 18 °C, 24 h.

In an overall sense, then, both the acetals 114a and 114b were formed in ca. 90% yield, with the latter being generated more rapidly (Scheme 4.5). However, although the reaction of diol 115 with 2-bromo-4-methoxybenzaldehyde (117) to deliver acetal 114b proceeded more rapidly, a drawback to this process was that aldehyde 117 is not readily available and had to be synthesised (see footnote of page 72) and, then, by a rather inefficient process (14% overall yield). The reductive cleavage of p-methoxybenzylidene acetal 114b also proceeded more rapidly than the equivalent process involving the non-methoxylated system 114a (Schemes 4.6 and 4.7). Nevertheless, the isolated yields of compounds 118a (54%) and 121 (64%), obtained from reductive cleavage of benzylidene acetal 114a and p-methoxybenzylidene acetal 114b respectively, were not significantly different. One the basis of the foregoing observations, homoallylic alcohol 118a was identified as the preferred substrate for use in subsequent studies.
The next step in the projected synthesis of diversonol (Scheme 4.3) required formation of compound 110 through epoxidation of the homoallylic alcohol 118a. Studies along such lines are described in the following section.

4.3.2 Formation of epoxide 110

With alkene 118a to hand, epoxidation of this compound was carried out. It was envisaged that in its reaction with m-CPBA, and through possible coordination of the peroxycacid with the C-1 hydroxyl group, preferential formation of the required α-epoxide 110a would occur (Scheme 4.8). In the event, when compound 118a was treated with this peroxycacid then the chromatographically separable α- and β-epoxides, namely compounds 110a (42%) and 124a (36%) respectively, were obtained. The more polar component, obtained as an oil, proved to be the α-epoxide 110a as established through nOe studies.

**Scheme 4.8: m-CPBA-mediated epoxidation of compound 118a**

![Scheme 4.8](image)

**Reagents and conditions:** (i) m-CPBA, NaHCO₃, DCM, 0 °C, 20 h, 78%.

The disappointing ratio of the α:β epoxides so-formed presumably reflects the limited ability of the peroxycacid to coordinate to the C-1 hydroxyl group (of compound 118a), perhaps because of steric hindrance created by the α-oriented bromobenzyl ether unit.

A method that could lead to greater yields of the desired product 110a involved epoxide formation via base-promoted cyclisation reaction of a precursor bromohydrin (Scheme 4.9). To such ends, the hydroxyl group of homoallylic alcohol 118a was protected as
the corresponding TBS-ether, 118b, using TBSOTf\(^\circ\) (83% yield). The latter compound was then treated with NBS and water in DMSO. The resulting mixture of bromohydrins, 125 and 126 (and possibly accompanied by their regio-isomeric systems as minor components), was not separated but treated with K\(_2\)CO\(_3\) in MeOH to afford, after work-up of the reaction mixture and flash chromatography, the target \(\alpha\)-epoxide 110b (54% yield) although the less polar \(\beta\)-epoxide 124b (22% yield) was still observed. Nevertheless, this sequence was more selective than the preceding one. The isomers were, once again, distinguished through nOe studies.

**Scheme 4.9: Formation of epoxides 110b and 124b via base promoted cyclisation of the corresponding bromohydrins 125 and 126.**

Reagents and conditions: (i) TBSOTf, 2,6-lutidine, DCM, -40 °C, 2 h, 83%; (ii) NBS, DMSO, H\(_2\)O, 0 - 10 °C, 1 h, 81%; (iii) K\(_2\)CO\(_3\), MeOH, 18 °C, 0.5 h, 94%.

The 300 MHz \(^1\)H NMR spectrum of compound 110b was consistent with the assigned structure. In particular, the oxirane proton appeared as a multiplet at δ 2.98 (1 H), and the other two oxymethine protons resonated at δ 3.63 (m, 1 H) and 3.70 (d, \(J\) 4.1 Hz). The benzyl methylene protons appeared as an AB quartet at δ 4.85 (\(J\) 13.9 Hz). The 75

\(^\circ\) The use of TBSCI and imidazole gave 118b but in only modest yield (10%).
MHz $^{13}$C NMR spectrum of compound 110b, shown in Figure 4.1, was also in full agreement with the proposed structure.

![Figure 4.1: 75 MHz $^{13}$C NMR spectrum of compound 110b recorded in CDCl$_3$.](image)

The observed selectivity for the $\alpha$-epoxide 110b in the latter route, *i.e.* that involving cyclisation of intermediate bromohydrin(s), could be explained, in part perhaps, by the ease of formation of the intermediate bromonium ions 127 and 128 illustrated in Figure 4.2. The addition of bromine (a large moiety) to the C=C bond of compound 118b could be influenced by the bulkiness of the TBS- and bromobenzyl-ether groups. Thus, for steric reasons, bromine addition would occur preferentially from the opposite face ($\beta$-face) to these groups to form bromonium ion 127. Upon reaction with DMSO and water, bromohydrin 125 would then result. Subsequent base-promoted cyclisation of the latter compound would then furnish the $\alpha$-epoxide (110b) as the major product.

![Figure 4.2: Proposed bromonium ion intermediates 127 and 128](image)

As noted earlier, one of the key steps associated with the projected synthesis of diversonol (49) is the ring-opening of the epoxide (110b) with the hydroxyl group of the C-ring precursor atranol (111). With the epoxide system 110b to hand, attention was turned to this C-ring precursor. Since this compound is not commercially available, its synthesis was necessary. Details are provided in the following section.
4.3.3 Synthesis of atranol (111)

Vilsmeier-Haack formylation of the commercially available orcinol (129) afforded an isomer of atranol, namely 2,4-dihydroxy-6-methylbenzaldehyde (130) (Scheme 4.10). However, this isomer can be and was elaborated to compound 131, an established precursor to atranol. Thus, Pinnick oxidation of compound 130 followed by esterification afforded the corresponding ethyl benzoate 131 (Scheme 4.10) in 28% yield from compound 129. This procedure now represents an alternative and novel route to compound 131. Alternatively, and following the literature procedure, intermediate 131 could be obtained somewhat more efficiently through Robinson annulation of 1,3-dione 132 using α,β-unsaturated ester 133 in sodium ethoxide. By such means cyclohexadione 134 was obtained and then aromatized, via bromination, to furnish benzoate 135. Subsequent reductive debromination of compound 135 using hydrogenolytic conditions furnished ethyl benzoate 131 (Scheme 4.10) in 62% yield over the three steps. Gatterman formylation of compound 131 then gave the aldehyde 136 (Scheme 4.10) in 60% yield. Hydrolysis of ester 136 under basic conditions followed by thermally-induced decarboxylation then afforded the target compound atranol (111) in 58% yield from compound 136.

**Scheme 4.10:** Synthesis of 2,6-dihydroxy-4-methylbenzaldehyde (atranol, 111)

**Reagents and conditions:**
(i) POCl₃, DMF, 0 - 18 °C, 6 h, 65%;
(ii) NaClO₂, NaH₂PO₄, H₂O, DMSO, H₂O, 0 - 18 °C, 8 h, 60%;
(iii) H₂SO₄ (catalyst), EtOH, reflux, 5 h, 72%;
(iv) Na, EtOH (18 °C, 6 h) then add compounds 132 and 133, 18 °C - reflux, 3 h, 70%;
(v) Br₂, AcOH, 18 °C, 20 h, 94%;
(vi) H₂, 10% Pd-C, 2 M NaOH, 18 °C, 20 h, 95%;
(vii) Zn(CN)₂, AlCl₃, HCl(g), Et₂O, 0 - 18 °C, 18 h, 60%;
(viii) 15% w/v NaOHaq, reflux, 3 h, 79%;
(ix) Heat, 1 h, 74%.
The 300 MHz $^1$H- and 75 MHz $^{13}$C-NMR spectra derived from compound 111 were fully consistent with the assigned structure. In particular, the protons of the phenolic hydroxyl groups appeared at $\delta$ 10.80 as a broad singlet while a singlet observed at $\delta$ 10.20 was assigned to the aldehydic proton. The two chemically equivalent aromatic protons resonated, as a singlet, at $\delta$ 6.19. As expected, the $^{13}$C NMR spectrum revealed six chemically non-equivalent carbons, and accurate mass measurement established a molecular formula of C$_8$H$_8$O$_3$.

### 4.3.4 Studies on the pivotal epoxide ring-opening reaction

With both the key substrates, viz. epoxide 110b and atranol (111) to hand, the pivotal epoxide ring-opening reaction, hopefully leading to adduct 113a (Scheme 4.11), could now be investigated. In order to obtain diversonol (49) ring-opening of the epoxide must necessarily occur at the C-4a position as illustrated. However, the presence of the methyl substituent makes C-4a more sterically hindered than the alternate electrophilic site, C-4. In principle, then, regio-isomeric ring-opened products could form through nucleophilic addition to either the C-4 or C-4a centres.

Apart from the issues surrounding the regio-selectivity of the epoxide ring-opening process, another concern associated with this reaction sequence is the use of a relatively unreactive phenol as the nucleophile. Thus, for example, Shibasaki and co-workers$^{15}$ have noted that no ring-opening of cyclohexene oxide (137) by 4-methoxyphenol (138) occurs when using catalytic and/or stoichiometric amounts of BuLi, NaO'Bu, KO'Bu, or Cs$_2$CO$_3$ at 50 °C (Scheme 4.12). Lewis acids such as BF$_3$.Et$_2$O and ZnCl$_2$ were also ineffective promoters of this reaction.

**Scheme 4.11: Proposed formation of compound 113a**

![Scheme 4.11](image-url)
Indeed, Jacobsen and Ready have commented that available methods for the (intermolecular) addition of phenols to epoxides are extremely limited. Forcing conditions are normally required for uncatalysed reactions which are, as a result, often low yielding and unsuitable for sensitive substrates.

Scheme 4.12: Reaction of compounds 137 and 138

![Reaction Scheme](image)

Nevertheless, reaction of epoxide 110b with compound 111 using LiClO4 as a Lewis acid catalyst was investigated. Unfortunately, but perhaps not surprisingly, no ring-opened product was observed even after 68 h at 80 °C. A similar study with InCl3 as the catalyst gave a complex mixture of products. Other investigations carried out with base, e.g. K2CO3 in acetone at reflux or NaOH in methanol, did not give any epoxide ring-opened product. At this point it was decided, due to limited supply of starting materials, to conduct a model study using simple and readily available substrates to determine the optimal reaction conditions for this type of ring-opening sequence.

The model study comprised taking a diastereomeric mixture of (+)-limonene oxides (139) and excess phenol [(140), ca. 1.6 equiv.] and subjecting them to various reaction conditions (Scheme 4.13 and Table 4.1). Since the anticipated products were either 2°- or 3°-alcohols, namely isomers 141 and 142 respectively, any potential difficulties with the separation of the products could be solved by oxidation of the 2°-hydroxyl function. Then upon chromatographic separation, the ratio of the oxidised product 143 and unreactive 3°-alcohol 142 would, in principle, allow for the determination of the regio-selectivity of the original epoxide ring-opening reaction.

\[\text{LiClO}_4^{\oplus}\] has been used in a regio-selective synthesis of β-alkoxy alcohols by the direct ring-opening of epoxides, e.g. 1-methylecyclohexene oxide, with alcohols (Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. Synlett. 1992, 673).

\[\text{InCl}_3^{\oplus}\] has been used in the synthesis of β-amino alcohols by the direct ring-opening of epoxides, e.g. cyclohexene oxide, with aromatic amines (Reddy, L. R.; Reddy, M. A.; Bhanumathi, N.; Rao, K. R. New J. Chem. 2001, 25, 221).
Scheme 4.13: Reaction of (+)-limonene oxide (139) and phenol (140)

Reagents and conditions: (i) listed in Table 4.1; (ii) PDC, DCM, 18 °C, 5 h.

Table 4.1: Results of the epoxide ring opening reaction between epoxide 139 and phenol (140)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH, THF, 18 °C, 48 h.</td>
<td>No reaction with phenol.</td>
</tr>
<tr>
<td>2</td>
<td>AcOH (20 mol%), CH₃CN, 18 °C, 24 h.</td>
<td>15% ring-opened product but with acetate ion; regio-chemistry not determined.</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl₂, DCM, 18 °C, 48 h</td>
<td>No reaction with phenol.</td>
</tr>
<tr>
<td>4</td>
<td>High pressure reaction: DCM, 19 kBar, 20 h.</td>
<td>No reaction with phenol.</td>
</tr>
<tr>
<td>5</td>
<td>CF₃COOH (10 mol%), DCM, 18 °C, 20 h.</td>
<td>30% ring-opened product with phenol; regio-chemistry not determined.</td>
</tr>
<tr>
<td>6</td>
<td>Cu(BF₄)₂·nH₂O (10 mol%), DCM, 18 °C, 20 h. Longer reaction time (to 48 h), or increase in catalyst loading (to 50 mol%) had no appreciable effect in yield.</td>
<td>60% ring-opened product with phenol; regio-chemistry 2:1 in favour of reaction at the more sterically hindered carbon center.</td>
</tr>
</tbody>
</table>

*Application of the reaction conditions defined in entries 2, 5 and 6 led to ca. 5% of the trans-diols resulting from cleavage of compound 139 by water (or an equivalent there-of).
Reactions using trifluoroacetic acid and copper tetrafluoroborate hydrate\(^*\) as catalyst (Entries 5 and 6, Table 4.1) proved successful although the process involving first of these promoters gave the product in only 30% yield. Other conditions tested (Entries 1-4, Table 4.1) did not give the desired ring-opened product. In the real system epoxide 110b has acid sensitive protecting group (TBS-ether) and so the use of trifluoroacetic acid would be precluded. However, use of the Cu\(^{II}\)-catalyst gave a 60% combined yield of the ring-opened products 141 and 142 (Scheme 4.13 and Entry 6, Table 4.1). The desired regio-isomer 141 was obtained as the major product (in a ca. 2:1 ratio) as judged by the isolated yields of the oxidised product 143 (39%) and unreacted 3°-alcohol 142 (21%).

In light of the aforementioned positive results using Cu\(^{II}\) as catalyst, epoxide ring opening with atranol (111) was next investigated. Unfortunately, ring-opening of epoxide 139 with compound 111 using Cu\(^{II}\) (10 mol%) did not give the expected product (Scheme 4.14). Instead, upon extractive work-up of the reaction mixture, 1,2-diol 144 (30% yield) was obtained. Given that only a ca. 5% yield of 1,2-diol 144 was obtained in studies with phenol (140), it seems that the aldehydic oxygen within atranol (111) engages, as the nucleophilic moiety, in the ring-opening of the epoxide, as illustrated in Scheme 4.14. The proposed intermediate 145 then undergoes hydrolysis during work-up to form 1,2-diol 144.

\[ \text{Scheme 4.14: Reaction of atranol (111) with (+)-limonene oxide (139)} \]

\[^*\]Cu(BF\(_4\))\(_2\).nH\(_2\)O has been used to promote the ring-opening of cyclohexene oxides with methanol (Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. Org. Lett. 2002, 4, 2817).
The aforementioned observations indicate that the reactivity of the hydroxyl group present in atranol (111) was greatly diminished either by the electron withdrawing effect of the ortho-aldehyde group (inductive effect) and/or from the illustrated participation of the carbonyl group oxygen as the nucleophile.

It was envisaged that the undesirable effects of the atranol carbonyl group could be achieved by using the surrogate 1,3-dioxane 146. To such ends, NaBH₄-mediated reduction of the aldehyde group of compound 111 was undertaken which furnished the allylic alcohol 147 ready for 1,3-dioxane formation (Scheme 4.15). Unfortunately, attempts to form derivative 146 via treatment of compound 147 with 2,2-DMP in the presence of p-TsOH (as catalyst) only led to polymeric products, possibly arising through initial production of the highly reactive ortho-quinone methide 148 (Scheme 4.15).

Scheme 4.15: Attempted formation of compound 146

Reagents and conditions: (i) NaBH₄, EtOH/H₂O, 0 - 18 °C, 2 h, 90%; (ii) p-TsOH (catalyst), 2,2-DMP, dry acetone or DMF, 18 °C.

The above-mentioned difficulties encountered with the pivotal epoxide ring-opening protocol resulted in the development of an alternative strategy for the preparation of diversonol (49). A re-ordering of the sequence of events, such that the ring-opening of the epoxide would now be performed in an intramolecular fashion, is discussed in the following section.

4.4 Alternative strategy for the synthesis of diversonol

Intramolecular ring-opening of epoxides with phenols proceeds even under mild condition (e.g. with K₂CO₃ as base), as observed in this author's work on the synthesis of (-)- and (+)-aiphanol (Chapter 3) as well as in other studies.¹⁷,¹⁸ Thus, as an
alternative to the previously described route to diversonol (Scheme 4.3), it was envisaged that the pyranone ring (B-ring) could be formed via a late-stage intramolecular epoxide ring-opening process, with compound 149 now representing a key advanced intermediate as illustrated in Scheme 4.16. This approach, however, requires the formation of the α-hydroxyketone (C-9 – C-9a) bond early in the sequence via an intermolecular benzoin condensation reaction.

**Scheme 4.16: Alternative route to diversonol (49)**

Assuming the cyclisation step in the projected conversion 149 → 49 (Scheme 4.16) proceeded as anticipated, inversion of C-4 hydroxyl stereochemistry and removal of the C-1 protecting group would then furnish the natural product 49.

The pivotal intermediate, compound 149, required in such an approach should be accessible through reaction of epoxy-ketone 150 and atranol (111). Thus, an intermolecular crossed aldehyde-ketone benzoin reaction would furnish the α-hydroxyketone (C-9 – C-9a) bond. Epoxy-ketone 150 would be obtained from diol 115 through standard functional group interconversions.

In a preliminary study, the merit of the proposed intermolecular crossed aldehyde-ketone benzoin reaction was tested using simpler substrates (Scheme 4.17). Thus, when
epoxy-ketone 151 and 2-hydroxy-4-methoxybenzaldehyde (152) were subjected to standard benzoin condensation conditions [NaCN (30 mol%), DMF, 40 °C, 20 h], products with molecular ions at m/z 139, 264, and 291 were obtained, as determined by GC-MS analysis of the reaction mixture. 1H NMR spectral analysis of the chromatographically separable material indicated the presence of epoxide 153 (3% yield) as well as those derived from the ring-opening of the oxirane by cyanide ion, viz. compounds 154 (4% yield) and 155 (3% yield). This preliminary investigation suggests that benzoin condensation in the real system, viz. that involving reaction between compounds 150 and 111, could proceed as anticipated. However, the epoxide ring-opening by cyanide ion as well as the low yield of product 153 was of concern. There are, fortunately, other catalysts that can be used to promote the benzoin reaction. For example, thiazolium salt 156 has been used for this purpose and delivers products of such processes in a shorter time and in higher yield. Obviously, relevant benzoin reactions promoted by this catalyst will be pursued next.

Scheme 4.17: Benzoin reaction between compounds 151 and 152

Reagents and conditions: (i) NaCN (30 mol%), DMF, 45 °C, 20 h, 10% combined yield.

^{6} Compound 151 was prepared by treatment of 2-cyclohexenone with basic hydrogen peroxide, as detailed in Chapter 5.
4.5 Conclusions and future work

The strategies explored in work directed towards the synthesis of diversonol (49) have revealed certain areas of concern. For instance, in the first strategy the intermolecular ring-opening of the epoxide with phenol as a nucleophile has proved difficult to achieve. This problem was exacerbated when using a substrate such as atranol (111) in which the nucleophilicity of the hydroxyl group was further diminished by the carbonyl substituent. The catalysts used in these investigations were, however, by no means the only ones likely to be effective since there are various other Lewis acids reported in the literature that could be used in the ring-opening reaction of epoxides with phenols. These include, for example, gallium complexes, (salen)Co(III) complexes, Cr(III) complexes, or cyclodextrins. As part of a program of future work, it is envisaged that epoxide ring-opening reactions with at least some of these catalysts will be studied.

In the second strategy, the low yielding nature of the intermolecular benzoin condensation as well as the competing epoxide ring-opening by the cyanide ion was a problem. As alluded to earlier, thiazolium salt 156 could be used, instead of cyanide ion, to promote the benzoin reaction. The thiazolium catalyst 156 can easily be prepared by the reaction of the commercially available 4-methyl-5-thiazole ethanol (157) and bromoethane (158) (Scheme 4.18). Once in hand, benzoin condensations involving this catalyst and various model compounds will be investigated. The outcome of such studies would clearly determine if the second strategy (Scheme 4.15) was worth pursuing.

Scheme 4.18: Proposed formation of thiazolium salt 156

Assuming that the benzoin reaction associated with such model studies proceeds as anticipated, the establishment of a suitable synthetic route to epoxy-ketone 150 would then be warranted. Compound 150 could be prepared as proposed in Scheme 4.19. The C-1 hydroxyl of diol 115 would be differentially protected to give allylic alcohol 159. Oxidation of the hydroxyl group in compound 159 would form enone 160, which when
epoxidised, under nucleophilic conditions, would furnish epoxy-ketone 150. Alternatively, m-CPBA-mediated electrophilic epoxidation of the allylic alcohol 159 would deliver epoxide 161 then oxidation would produce the target epoxy-ketone 150.

\[ \text{Scheme 4.19: Proposed routes to epoxy-ketone 150} \]

Proposed reagents and/or conditions: (i) e.g. TBDPSCl, imidazole, DCM; (ii) Dess-Martin reagent\textsuperscript{22} or PCC, NaOAc; (iii) \( \text{H}_2\text{O}_2 \), \( \text{NaOH}_{\text{aq}} \), MeOH; (iv) \( \text{m-CPBA} \); (v) Dess-Martin reagent\textsuperscript{22} (with a base as buffer) or PCC, NaOAc.

Although studies on the intermolecular ring-opening of epoxide 110b (or model epoxide 139) with atranol 111, and the crossed aldehyde-ketone benzoin reaction in the model system (Scheme 4.17), have not worked well to date, it is believed that finding the right reaction conditions to achieve high yields of the desired products will ultimately be achieved.

Work directed towards such ends is expected to commence shortly.
**Chapter 4** Studies directed towards the synthesis of diversonol

### 4.6 References

Chapter 5

Experimental

5.1 General experimental procedures

Unless otherwise specified, proton ($^1\text{H}$) and carbon ($^{13}\text{C}$) NMR spectra were acquired at 20 °C on either a Gemini 300 NMR spectrometer, operating at 300 MHz (for proton) and 75 MHz (for carbon), or on a Varian Inova 500 spectrometer operating at 500 MHz (for proton) and 125 MHz (for carbon). NMR spectra were referenced to residual chloroform ($\delta$ 7.26, $^1\text{H}$; $\delta$ 77.0, $^{13}\text{C}$), methanol ($\delta$ 3.31, $^1\text{H}$; $\delta$ 49.0, $^{13}\text{C}$), acetone ($\delta$ 2.05, $^1\text{H}$; $\delta$ 29.8, 205.9, $^{13}\text{C}$) or DMSO ($\delta$ 2.50, $^1\text{H}$; $\delta$ 39.5, $^{13}\text{C}$). $^1\text{H}$ NMR data are recorded as follows: chemical shift ($\delta$) [multiplicity, coupling constant(s) $J$ (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combination of the above. Proton(s) associated with aromatic rings are designated as ArH. For $^{13}\text{C}$ NMR spectra, the data are given as chemical shift ($\delta$), (protonicity), where protonicity is defined as: C = quaternary; CH = methine; CH$_2$ = methylene; CH$_3$ = methyl. The assignment of signals in various NMR spectra was often assisted by conducting distortionless enhancement of polarization transfer (DEPT), attached proton test (APT), homonuclear ($^1\text{H}/^1\text{H}$) correlation spectroscopy (COSY), heteronuclear ($^1\text{H}/^{13}\text{C}$) correlation spectroscopy (HETCOR) and/or Overhauser effect (nOe) experiments.

Infrared spectra ($\nu_{\text{max}}$) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analysed as thin films on NaCl plates unless otherwise specified.

Mass spectra were recorded by the Australian National University’s Mass Spectral Services Unit based at the Research School of Chemistry, Canberra, Australia. A VG Fisons AutoSpec three sector (E/B/E) double focussing mass spectrometer was used to
obtain low and high resolution electron impact (EI) spectra. Low resolution fast atom bombardment (FAB) spectra were obtained on a Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer. Electrospray mass spectra (ESI) were obtained on a VG Quattro II triple quadrupole MS instrument operating in either positive and/or negative ionisation modes.

Optical rotations were measured with a Perkin–Elmer 241 polarimeter at the sodium-D line (589 nm) and at the concentrations (c) (g/100 mL) indicated using spectroscopic grade CHCl₃ or methanol unless otherwise specified. The measurements were carried out in a cell with a path length (l) of 1 dm. Specific rotations [α]₀ were calculated (at 20 °C) using the equation [α]₀ = 100. α/(c.l) and are given in 10⁻¹.deg.cm².g⁻¹.

Analytical and preparative HPLC separations were performed using Waters Associates model 510 pumps. Analytical HPLC separation methods were developed using a 250 x 4.6 mm Alltech Alltima 5 µm C₁₈ column, and preparative separations were performed with a 300 x 10 mm Alltech Alltima 5 µm C₁₈ column. Peak detection was through a Waters model 481 UV (or a Shimadzu SPD-10A UV-Vis) detector set at 325 nm unless otherwise specified.

Chiral HPLC analysis was carried out using a Shimadzu instrument comprising the following components: a LC-8A pump, SCL-10A system controller, SIL-10AD auto injector and LC-10AD liquid chromatograph. These were linked to SPD-10A UV-Vis and/or RID-10A detector. The instrument was fitted with a CHIRALPAK® AS-H 250 x 4.6 mm column. All solvents used were HPLC grade as obtained from Aldrich or Lab-Scan Analytical Sciences.

Enantiomeric excess (e.e.) was calculated according to the formula e.e. = [(%R enantiomer) – (%S enantiomer)] / (%R enantiomer), where the R enantiomer is assumed, in this example, to be the one in excess.

Melting points were measured on a Reichert hot-stage microscope apparatus and are uncorrected.
Elemental analyses were performed by the Australian National University’s Microanalytical Services Unit based at the Research School of Chemistry, Canberra, Australia.

Analytical thin layer chromatography (TLC) was performed on aluminium backed 0.2 mm thick silica gel 60 F254 plates as supplied by Merck. Eluted plates were visualised using 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included ones employing potassium permanganate [KMnO₄ (3 g), K₂CO₃ (20 g), NaOH (5 mL of a 5% aq. solution) water (300 ml)], anisaldehyde [ethanol (93 mL), anisaldehyde (2 mL) and conc. H₂SO₄ (5 mL)], or phosphomolybdic acid [phosphomolybdic acid (37.5 g), ceric sulfate (7.5 g), conc. sulfuric acid (37.5 g) and water (720 mL)]. Flash chromatography was performed using the analytical grade solvents indicated and silica gel 60 (0.040-0.0063 mm) as supplied by Merck.

Starting materials and reagents were obtained from Sigma-Aldrich, Fluka, Merck or Lancaster and were mostly used as supplied, or in the case of liquids, simply distilled. Drying agents and other inorganic salts were purchased from Sigma-Aldrich, AJAX, BDH or Unilab. DCM (CH₂Cl₂) was distilled, under nitrogen, from calcium hydride. Tetrahydrofuran (THF) and diethyl ether were distilled, under nitrogen, from sodium benzophenone ketyl. Methanol was distilled from magnesium methoxide. N,N-Dimethylformamide (DMF), pyridine, triethylamine and N,N-diisopropylethylamine (a.k.a. Hünig’s base) were all distilled from and stored over potassium hydroxide pellets. “Toluene diol” was obtained from TDC Research Inc. (Gainesville, Florida) as a ca. 10% w/v solution in KH₂PO₄/K₂HPO₄ aqueous buffer (pH 7).

Where necessary, reactions were performed under a nitrogen atmosphere. The organic phase from work-up of reaction mixtures were dried over anhydrous magnesium sulfate (MgSO₄) or sodium sulfate (Na₂SO₄) unless otherwise specified. The dried solution was then filtered and the filtrate concentrated under reduced pressure on a rotary evaporator using the water bath temperature not exceeding 40 °C unless otherwise specified.

Room temperature is assumed to be ~18 °C.
5.2 Experimental procedures associated with work described in Chapter 2: The synthesis of (+)-aiphanol

3-Methoxy-1,2-benzenediol (62a)

\[
\begin{align*}
\text{OH} & \quad \text{H}_2\text{BO}_3 \cdot \text{(C}_2\text{H}_5\text{)SO}_4 \quad \text{NaOH}, 18^\circ \text{C}, 3.5 \text{ h} \\
\text{67} & \quad \rightarrow \\
\text{OH} & \quad \text{OCH}_3 \quad \text{OH}
\end{align*}
\]

A magnetically stirred solution of pyrogallol (67) (1.50 g, 11.9 mmol) and boric acid (810 mg, 13.1 mmol) in NaOH (20 mL of a 1 M aqueous solution) maintained at 18 °C was treated, in one portion, with dimethyl sulfate (0.6 mL, 6.3 mmol). The pH of the reaction mixture was maintained at ca. 10 by adding NaOH (5 M aqueous solution) as required. Two more portions of dimethyl sulfate (2 x 0.5 mL, 10.5 mmol) were added after 0.25 and 1 h, and the ensuing mixture stirred for a further 2 h whilst continuing to maintain the pH of the solution at ca. 10 by the addition of further NaOH. The basic solution was then extracted with DCM (3 x 10 mL), to remove the trimethoxy-compound, then acidified with H$_2$SO$_4$ (98% conc. material) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 2:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions [R$_f$ 0.3(5)], the title compound 62a$^1$ (1.24 g, 74%) as a viscous, light-yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 6.76 (t, $J$ 8.3 Hz, 1H, ArH), 6.59 (dd, $J$ 8.3 and 1.4 Hz, 1H, ArH), 6.47 (dd, $J$ 8.3 and 1.4 Hz, 1H, ArH), 5.40 (broad s, OH), 3.86 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 147.7 (C), 144.5 (C), 133.0 (C), 120.1 (CH), 109.4 (CH), 103.8 (CH), 56.5 (OCH$_3$).

IR $\nu_{\text{max}}$ 3421 (broad), 2941, 2842, 1618, 1506, 1482, 1290, 1082, 934, 767, 717 cm$^{-1}$.

Mass spectrum (70 eV) m/z 140 (M$^+$, 100%), 125 (85), 108 (31), 97 (67), 80 (35).

HRMS Found M$^+$, 140.0474. C$_7$H$_8$O$_3$ requires 140.0473.
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

3-Phenyloxiranemethanol (69)

![Chemical Structure](image)

Powdered $m$-CPBA (1.10 g, 77% purity, 4.9 mmol) was added, in small portions over 5 minutes, to a magnetically stirred and cooled (ice-water bath) suspension of cinnamyl alcohol (68) (550 mg, 4.1 mmol) in NaHCO$_3$ (20 mL of a 0.5 M aqueous solution). After addition was complete, the mixture was allowed to warm to 18 °C and vigorously stirred for 3 h then saturated with NaCl (solid) and extracted with DCM (3 x 20 mL). The combined DCM extracts were then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 1:1 v/v diethyl ether - hexane elution) to afford, after concentration of the appropriate fractions ($R_f$ 0.2), the title compound 69 (520 mg, 84%) as a clear, colourless oil.

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$: 7.30 (m, 5H, ArH), 4.04 (dd, $J$ 12.7 and 2.3 Hz, 1H), 3.93 (d, $J$ 2.2 Hz, 1H), 3.80 (dd, $J$ 12.7 and 3.7 Hz, 1H), 3.22 (m, 1H), 2.51 (broad s, OH).

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$: 136.8 (C), 128.7 (CH), 128.6 (CH), 125.9 (CH), 62.9 (CH), 61.6 (CH$_2$), 55.9 (CH).

**IR** $\nu_{\text{max}}$ 3413 (broad), 2988, 2926, 2869, 1605, 1496, 1254, 1070, 1027, 767, 698 cm$^{-1}$.

**Mass spectrum** (70 eV) $m/z$ 150 (M$^+$, 18%), 132 (50), 107 (100), 90 (86), 79 (57), 63 (38).

**HRMS** Found M$^+$, 150.0680. C$_9$H$_{10}$O$_2$ requires 150.0681.
3-Phenoxyoxiranemethanol methanesulfonate (63)

![Chemical Structure](image)

A magnetically stirred solution of epoxy-alcohol 69 (240 mg, 1.6 mmol) and NEt₃ (350 µL, 2.5 mmol) in DCM (10 mL) maintained at 0 °C under an atmosphere of nitrogen was treated, dropwise, with MsCl (150 µL, 1.9 mmol). The resulting mixture was stirred for a further 0.5 h at 0 °C then transferred to a separatory funnel and washed with cold water (1 x 5 mL), cold HCl (1 x 5 mL of a 1 M aqueous solution) then NaHCO₃ (1 x 5 mL of a saturated aqueous solution). The separated organic layer was then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 2:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions (Rf 0.4), the title compound 63 (320 mg, 90%) as a white, crystalline solid, m.p. 47-48 °C.

**¹H NMR** (300 MHz, CDCl₃) δ: 7.36-7.24 (m, 5H, ArH), 4.60 (dd, J 12.0 and 2.9 Hz, 1H), 4.26 (dd, J 12.0 and 6.0 Hz, 1H), 3.87 (d, J 2.1 Hz, 1H), 3.34 (m, 1H), 3.10 (s, 3H).

**¹³C NMR** (75 MHz, CDCl₃) δ: 135.7 (C), 129.0 (CH), 128.9 (CH), 126.0 (CH), 69.4 (CH₂), 59.0 (CH), 56.6 (CH), 38.1 (CH₃).

**IR** ν_max 3030, 2940, 1497, 1464, 1356, 1175, 956, 853, 699, 528 cm⁻¹.

**Mass spectrum** (70 eV) m/z 228 (M⁺, 8%), 185 (85), 133 (79), 105 (100), 91 (70), 77 (54), 63 (24).

**HRMS** Found M⁺, 228.0457. C₁₀H₁₂O₄S requires 228.0456.
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

2-Chloromethyl-3-phenyloxirane (64)

*Method 1*

A solution of epoxy-alcohol 69 (150 mg, 1.0 mmol), carbon tetrachloride (5 mL) and PPh\(_3\) (300 mg, 1.1 mmol) was heated at reflux for 4 h then cooled and concentrated under reduced pressure. The resulting oil was purified by column chromatography (silica, 1:4 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions (R\(_f\) 0.6), the title compound 64\(^1\) (120 mg, 71%) as a clear, colourless oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.80-7.34 (m, 5H, ArH), 3.85 (d, J 1.9 Hz, 1H), 3.76 (dd, J 11.9 and 4.6 Hz, 1H), 3.65 (dd, J 11.9 and 6.0 Hz, 1H), 3.31 (m, 1H).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 136.3 (C), 128.9 (CH), 126.0 (CH), 61.3 (CH), 58.8 (CH), 44.8 (CH\(_2\)).

IR \(\nu_{\text{max}}\) 3066, 3021, 2990, 2959, 1603, 1497, 1462, 1421, 1265, 748, 697, 605 cm\(^{-1}\).

Mass spectrum (70 eV) \(m/\varepsilon\) 170 and 168 (M\(^+\), 3 and 8%, respectively), 133 (92), 105 (100), 89 (42), 79 (55), 63 (26).

HRMS Found M\(^+\), 170.0311 and 168.0340. C\(_9\)H\(_7\)ClO and C\(_9\)H\(_5\)ClO requires 170.0312 and 168.0342, respectively.

*Method 2*
Powdered \( m \)-CPBA (360 mg, 77\% purity, 1.6 mmol) was added, in small portions over 5 minutes, to a magnetically stirred and cooled (ice-water bath) suspension of cinnamyl chloride (70) (200 mg, 1.3 mmol) in NaHCO\(_3\) (10 mL of a 0.5 M aqueous solution). The reaction mixture was allowed to warm to 18 °C and stirred vigorously for 3 h then saturated with NaCl (solid) and extracted with DCM (3 x 20 mL). The combined organic extracts were then dried (MgSO\(_4\)), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 1:4 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions \( (R_f 0.6) \), compound 64 as a clear, colourless oil (170 mg, 78\%). The 300 MHz \(^1\)H NMR and 75 MHz \(^{13}\)C NMR spectral data derived from this compound were identical, in all respects, with those derived from the material obtained via Method 1.

2,3-Dihydro-8-methoxy-3-phenyl-1,4-benzodioxin-2-methanol (66),
2,3-Dihydro-8-methoxy-1,4-benzodioxin-2-phenylmethanol (71) and
2,3-Dihydro-5-methoxy-1,4-benzodioxin-2-phenylmethanol (72)

A solution of catechol 62a (180 mg, 1.3 mmol) and mesylate 63 (250 mg, 1.1 mmol) in acetone (20 mL) was treated with K\(_2\)CO\(_3\) (360 mg of anhydrous material, 2.6 mmol). The resulting mixture was heated at reflux for 20 h then cooled to room temperature, filtered, and the filtrate concentrated under reduced pressure. The ensuing residue was re-dissolved in ethyl acetate (30 mL) and washed with water (2 x 20 mL), NaOH (2 x 20 mL of a 5\% w/v aqueous solution) and brine (1 x 30 mL). The organic layer was then
dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 3:7 v/v ethyl acetate - hexane elution) to afford three fractions, F1-F3.

Concentration of the least polar fraction (F3) afforded the title compound 71 (89 mg, 30%) as a clear, colourless oil.

\[
\begin{align*}
^{1}H \text{ NMR} & (300 \text{ MHz, CDCl}_3) \delta: 7.40 \text{ (m, 5H, ArH)}, 6.78 \text{ (t, } J 8.4 \text{ Hz, 1H, ArH)}, 6.51 \text{ (m, 2H, ArH)}, 5.31 \text{ (d, } J 3.9 \text{ Hz, 1H)}, 4.30 \text{ (m, 2H)}, 4.10 \text{ (dd, } J 11.1 \text{ and } 2.2 \text{ Hz, 1H)}, 3.86 \text{ (s, 3H)}. \\
^{13}C \text{ NMR} & (75 \text{ MHz, CDCl}_3) \delta: 149.1 \text{ (C)}, 144.3 \text{ (C)}, 138.9 \text{ (C)}, 133.3 \text{ (C)}, 128.8 \text{ (CH)}, 128.2 \text{ (CH)}, 126.2 \text{ (CH)}, 120.6 \text{ (CH)}, 110.2 \text{ (CH)}, 104.6 \text{ (CH)}, 77.1 \text{ (CH)}, 72.8 \text{ (CH)}, 63.5 \text{ (CH}_2), 56.4 \text{ (OCH}_3). \\
\text{IR} & \nu_{\text{max}} 3496 \text{ (broad), 3030, 2938, 1598, 1497, 1478, 1453, 1281, 1253, 1097, 765 \text{ cm}^{-1}.} \\
\text{Mass spectrum} & (70 \text{ eV}) \ m/\text{z} \ 272 \text{ (M}^+\text{, 79%), 238 (9), 166 (100), 151 (76), 133.0 (29), 107 (67), 79 (50).}
\end{align*}
\]

Concentration of the fraction of intermediate polarity (F2) afforded the title compound 72 (119 mg, 39%) as a clear, colourless oil.

\[
\begin{align*}
^{1}H \text{ NMR} & (300 \text{ MHz, CDCl}_3) \delta: 7.40 \text{ (m, 5H, ArH)}, 6.78 \text{ (t, } J 8.4 \text{ Hz, 1H, ArH)}, 6.51 \text{ (m, 2H, ArH)}, 5.06 \text{ (d, } J 4.6 \text{ Hz, 1H)}, 4.30 \text{ (m, 3H)}, 3.84 \text{ (s, 3H)}. \\
^{13}C \text{ NMR} & (75 \text{ MHz, CDCl}_3) \delta: 149.1 \text{ (C)}, 143.9 \text{ (C)}, 139.4 \text{ (C)}, 133.2 \text{ (C)}, 128.8 \text{ (CH)}, 128.4 \text{ (CH)}, 126.4 \text{ (CH)}, 120.6 \text{ (CH)}, 110.3 \text{ (CH)}, 104.4 \text{ (CH)}, 76.5 \text{ (CH)}, 72.8 \text{ (CH)}, 64.5 \text{ (CH}_2), 56.4 \text{ (OCH}_3). \\
\text{IR} & \nu_{\text{max}} 3505 \text{ (broad), 3030, 2937, 1599, 1498, 1476, 1454, 1245, 1212, 1077, 765 \text{ cm}^{-1}.} \\
\text{Mass spectrum} & (70 \text{ eV}) \ m/\text{z} \ 272 \text{ (M}^+\text{, 81%), 238 (10), 166 (100), 151 (91), 107 (67), 79 (58).}
\end{align*}
\]

Concentration of the most polar fraction (F1) afforded the title compound 66 (24 mg, 8%) as an amorphous solid.
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.51-7.35 (m, 5H, ArH), 6.83 (t, $J$ 8.2 Hz, 1H, ArH), 6.60 (d, $J$ 8.2 Hz, 2H, ArH), 5.00 (d, $J$ 8.9 Hz, 1H), 4.71 (dd, $J$ 12.9 and 3.1 Hz, 1H), 4.40 (dd, $J$ 12.8 and 2.1 Hz, 1H), 4.20 (m, 1H), 3.90 (s, 3H), 2.00 (broad s, 1H, OH).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 151.3 (C), 146.3 (C), 139.0 (C), 132.9 (C), 128.9 (CH), 128.7 (CH), 127.1 (CH), 122.2 (CH), 114.0 (CH), 106.9 (CH), 85.8 (CH), 76.0 (CH), 75.5 (CH$_2$), 56.6 (OCH$_3$).

IR $\nu_{max}$ 3401 (broad), 2928, 1587, 1488, 1472, 1249, 1096, 772, 699 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 272 (M$^+$, 91%), 228 (32), 151 (47), 133 (100), 105 (68), 91 (57), 77 (31).

HRMS Found M$^+$, 272.1048. C$_{16}$H$_{16}$O$_4$ requires 272.1049.

The structures of alcohols 71 and 72 were confirmed through spectroscopic analysis of the derived ketones, namely compounds 73 and 74, respectively (see below).

2,3-Dihydro-8-methoxy-1,4-benzodioxin-2-phenylmethanone (73) and 2,3-Dihydro-5-methoxy-1,4-benzodioxin-2-phenylmethanone (74)

Dess-Martin periodinane (84 mg, 0.20 mmol) was added to a magnetically stirred solution of compound 71 (50 mg, 0.18 mmol) [or compound 72 (50 mg, 0.18 mmol)] in dry DCM (1 mL) at 18 °C and the ensuing reaction was monitored by TLC and shown to be complete in 2.5 h. At this point the reaction mixture was diluted with DCM (15 mL) and the resulting solution washed with Na$_2$S$_2$O$_3$/NaHCO$_3$ (1 x 15 mL of a 1:1 v/v
mixture of a 10% aqueous solution and a saturated aqueous solution, respectively) and brine (1 x 10 mL). The separated organic phase was then dried (MgSO₄), filtered, and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (silica, 3:7 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions, the *title compound 73* [RF 0.4(4), 37 mg, 76%] or *74* [RF 0.4(6), 38 mg, 78%]. Both products were obtained as amorphous solids.

**Data for compound 73**

$^1$H NMR (300 MHz, CDCl$_3$) δ: 7.95 (m, 2H, ArH), 7.60-7.40 (m, 3H, ArH), 6.75 (t, J 8.2 Hz, 1H, ArH), 6.60-6.40 (m, 2H, ArH), 5.43 (dd, J 6.8 and 2.6 Hz, 1H), 4.57 (dd, J 11.5 and 2.6 Hz, 1H), 4.31 (dd, J 11.5 and 6.7 Hz, 1H), 3.80 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 193.7 (C=O), 149.1 (C), 143.6 (C), 134.6 (C), 134.3 (CH), 132.9 (C), 129.2 (CH), 129.1 (CH), 121.0 (CH), 110.4 (CH), 104.8 (CH), 75.0 (CH), 65.7 (CH$_2$), 56.4 (OCH$_3$).

IR $\nu_{\text{max}}$ 2935, 1699, 1598, 1497, 1498, 1478, 1283, 1109, 950, 767, 714, 693 cm$^{-1}$.

Mass spectrum (70 eV) m/z 270 (M$^+$, 53%), 248 (6), 165 (24), 151 (12), 105 (100), 95 (22), 77 (67).

**Data for compound 74**

$^1$H NMR (300 MHz, CDCl$_3$) δ: 7.96 (m, 2H, ArH), 7.54-7.42 (m, 3H, ArH), 6.74 (t, J 8.2 Hz, 1H, ArH), 6.45 (m, 2H, ArH), 5.49 (dd, J 5.5 and 2.9 Hz, 1H), 4.44 (dd, J 11.7 and 2.9 Hz, 1H), 4.35 (dd, J 11.6 and 5.6 Hz, 1H), 3.79 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 193.9 (C=O), 149.2 (C), 143.8 (C), 134.2 (C), 129.1 (CH), 129.0 (CH), 128.7 (CH), 126.1 (C), 120.9 (CH), 110.1 (CH), 105.0 (CH), 75.2 (CH), 65.3 (CH$_2$), 56.5 (OCH$_3$).

IR $\nu_{\text{max}}$ 2934, 1699, 1599, 1500, 1474, 1283, 1134, 907, 766, 717, 693 cm$^{-1}$.

Mass spectrum (70 eV) m/z 270 (M$^+$, 67%), 248 (30), 231 (15), 165 (31), 151 (19), 105 (100), 77 (60).
Compounds 66, 71 and 72 formed by the reaction of catechol 62a with epoxy chloride 64.

![Chemical structure](image)

A solution of catechol 62a (180 mg, 1.3 mmol) and chloride 64 (200 mg, 1.2 mmol) in acetone (20 mL) was treated with K₂CO₃ (360 mg of anhydrous material, 2.6 mmol). The ensuing mixture was heated at reflux for 20 h then cooled to room temperature, filtered, and the filtrate concentrated under reduced pressure. The residue so-obtained was re-dissolved in ethyl acetate (30 mL) and washed with water (2 x 20 mL), NaOH (2 x 20 mL of a 5% w/v aqueous solution) and brine (1 x 30 mL). The separated organic layer was dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate - hexane elution) to afford three fractions [F1, Rf 0.3; F2, Rf 0.4(8); and F3, Rf 0.5(2)]. Concentration of these fractions followed by NMR spectroscopic analysis of the resulting oils established that these were compounds 66 (35 mg, 11%, F1), 72 (99 mg, 31%, F2), and 71 (68 mg, 21%, F3).

3,5-Dihydroxybenzyl bromide (81)

![Chemical structure](image)
A magnetically stirred solution of alcohol 78 (1.01 g, 7.1 mmol) in THF-benzene (25 mL of a 1:1 v/v mixture) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise over 10 minutes, with a solution of PBr₃ [240 µL (2.5 mmol) in 5 mL of a 1:1 v/v THF-benzene mixture]. After addition was complete, stirring was continued for a further 0.5 h at 0 °C then at 18 °C for 2 h. The reaction mixture was then poured into ice-cold water (20 mL) and extracted with diethyl ether (3 x 40 mL). The combined ethereal extracts were dried (MgSO₄), filtered, and concentrated under reduced pressure (water bath temperature 20 °C) to afford the title compound 81 (1.18 g, 80%) as a light-brown oil. This product was immediately used in the next step (see below).

3,5-Diacetoxybenzyl bromide (82)

A solution of bromide 81 (1.18 g, 5.8 mmol) in dry benzene (20 mL) containing pyridine (0.5 mL) and acetic anhydride (2.5 mL, 26.4 mmol) was stirred magnetically under an atmosphere of nitrogen for 16 h at 18 °C then warmed to 80 °C and stirred for 15 minutes at this temperature. The resulting solution was cooled to ca. 30 °C then concentrated under reduced pressure. The residue so-obtained was re-dissolved in diethyl ether (30 mL) and the ensuing solution stirred vigorously with NaHCO₃ (25 mL of a saturated aqueous solution) for 0.5 h at 18 °C. The diethyl ether layer was then separated, and the aqueous layer extracted with additional diethyl ether (2 x 30 mL). The combined ethereal extracts were washed with cold HCl (2 x 30 mL of a 0.5 M aqueous solution), water (1 x 30 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure to afford the title compound 82 (1.65 g, 99%) as a light-brown oil.

¹H NMR (300 MHz, CDCl₃) δ: 6.99 (d, J 2.1 Hz, 2H, ArH), 6.84 (t, J 2.1 Hz, 1H, ArH), 4.40 (s, 2H), 2.21 (s, 6H).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3 \] \( \delta \): 168.9 (C=O), 151.2 (C), 140.0 (C), 119.8 (CH), 115.6 (CH), 32.2 (CH\_2), 21.4 (CH\_3).

\[ \text{IR } v_{\text{max}} \] 2963, 1769, 1617, 1593, 1453, 1369, 1127, 1024, 906, 687 cm\(^{-1}\).

Mass spectrum (70 eV) \( m/z \) 286 and 288 (M\(^+\), \( C_{11}H_{11}^{79}\text{BrO}_4 \) and \( C_{11}H_{11}^{81}\text{BrO}_4 \) 12 and 11%, respectively), 244 and 246 (45 and 44), 207 (45), 204 and 202 (59 and 58), 165 (22), 123 (100), 94 (14), 77 (5).

HRMS Found M\(^+\), 285.9841 and 287.9820. \( C_{11}H_{11}^{79}\text{BrO}_4 \) and \( C_{11}H_{11}^{81}\text{BrO}_4 \) requires 285.9841 and 287.9820, respectively.

\( ^{3,5}\text{-Diacetoxybenzyl})\text{triphenylphosphonium bromide (83)} \)

![Reaction diagram]

A solution of bromide 82 (1.50 g, 5.2 mmol) in dry benzene (30 mL) was treated with PPh\(_3\) (1.65 g, 6.3 mmol) and the ensuing mixture stirred magnetically at 18 °C for 10 minutes then heated at reflux for 3 h during which time the product precipitated as a white solid. The reaction mixture was cooled to room temperature, the precipitate was filtered off and washed thoroughly with hexane then dried under high vacuum at 80 °C for 1 h to afford the title compound 83\(^5\) (2.44 g, 85%) as a white powder, m.p. 248-250 °C (lit.\(^5\) 249-251 °C).

\[ ^{1}H \text{ NMR (300 MHz, CDCl}_3 \] \( \delta \): 7.77-7.70 (m, 9H, ArH), 7.63-7.57 (m, 6H, ArH), 6.77 (d, J 2.5 Hz, 3H, ArH), 5.52 (d, J 14.9 Hz, 2H), 2.16 (s, 6H).

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3 \] \( \delta \): 168.7 (C=O), 150.9 (C), 135.2 (C), 135.1 (C), 134.6 (CH), 134.5 (CH), 130.5 (CH), 130.3 (CH), 122.6 (CH), 122.5 (CH), 118.0 (CH), 116.9 (CH), 116.2 (CH), 30.8 and 30.2 (CH\_2), 21.4 (CH\_3).

\[ \text{IR } v_{\text{max}} \] 2854, 2784, 1769, 1609, 1589, 1438, 1369, 1199, 1127, 922, 723, 690 cm\(^{-1}\).

Mass spectrum (Low resolution FAB) \( m/z \) 469 [(M-Br\(^-\)]\(^+\), 100%].

HRMS Found (M-Br\(^-\)]\(^+\), 469.1579. \( C_{20}H_{26}O_4P [(M-Br\(^-\)]\(^+\)] \) requires 469.1569.
(3,5-Dihydroxybenzyl)triphenylphosphonium bromide (76)

A solution of the phosphonium salt 83 (2.01 g, 3.7 mmol) in methanol (30 mL) was treated with p-TsOH (catalyst, 20 mg) then heated to reflux for 5 h. After cooling to room temperature, methanol was removed under reduced pressure and the resulting white solid flakes were recrystallised (from 1:4 v/v methanol - ethyl acetate) to afford the title compound 76 (1.45 g, 85%) as a white powder, m.p. 234-236 °C (lit. 228-238 °C).

$^1$H NMR (300 MHz, DMSO-$d_6$) δ: 9.36 (broad s, 2H, OH), 7.89-7.59 (complex m, 15H, ArH), 6.14 (d, J 2.0 Hz, 1H, ArH), 5.84 (t, J 2.0 Hz, 2H, ArH), 4.93 (d, J 15.5 Hz, 2H).

$^{13}$C NMR (75 MHz, DMSO-$d_6$) δ: 158.96, 158.92, 135.7, 134.5, 134.4, 130.8, 130.6, 130.0, 129.9, 119.2, 118.0, 109.9, 109.8, 103.0, 29.4, 28.8.

IR $\nu$ max 3546 (broad), 2924, 1602, 1453, 1377, 1147, 1105, 851, 686 cm$^{-1}$.

Mass spectrum (Low resolution FAB) $m/z$ 385 (M-Br$^-$)$^+$. 

HRMS Found (M-Br$^-$)$^+$, 385.1364. C$_{25}$H$_{22}$O$_2$P [(M-Br$^-$)$^+$] requires 385.1357.

3,4-bis-(tert-Butyldimethylsilyloxy)benzaldehyde (77)

A solution of imidazol (2.96 g, 43.5 mmol), aldehyde 79 (1.00 g, 7.2 mmol) and TBSCI (2.73 g, 18.1 mmol) in dry DMF (40 mL) was stirred magnetically at 18 °C under an atmosphere of nitrogen for 16 h. The reaction mixture was then diluted with water (40 mL) and the product extracted with diethyl ether (3 x 50 mL). The combined ethereal extracts were washed with NaHCO$_3$ (1 x 40 mL of a saturated aqueous
solution) and brine (1 x 40 mL) then dried (MgSO₄), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 1:9 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions (Rf 0.5), the title compound 77 (2.16 g, 82%) as a light-brown solid, m.p. 36-38 °C.

¹H NMR (300 MHz, CDCl₃) δ: 9.80 (s, 1H, CHO), 7.38-7.35 (m, 2H, ArH), 6.93 (dd, J 8.9 and 1.3 Hz, 1H, ArH), 1.00 (s, 9H), 0.99 (s, 9H), 0.25 (s, 6H), 0.23 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ: 190.9 (C=O), 153.5 (C), 147.8 (C), 130.9 (C), 125.5 (CH), 121.0 (CH), 120.7 (CH), 26.24 (CH₃), 26.20 (CH₃), 18.9 (C), 18.8 (C), -3.6 (CH₃), -3.7 (CH₃).

IR νmax 2956, 2931, 2859, 1697, 1592, 1573, 1507, 1430, 1295, 902, 841, 783 cm⁻¹.

Mass spectrum (70 eV) m/z 367 [(M+H)⁺, 7%], 309 (41), 195 (8), 73 (100).

HRMS Found (M+H)⁺, 367.2124. (C₁₉H₃₄O₄S₉H⁺)⁺ requires 367.2125.

3',4'-bis-(tert-Butyldimethylsilanyloxy)-3,5-dihydroxystilbene (84)

A magnetically stirred suspension of phosphonium salt 76 (401 mg, 0.9 mmol) in deoxygenated dry THF (10 mL) maintained at -78 °C (dry ice - acetone bath) under an oxygen-free nitrogen atmosphere was treated, dropwise over 10 minutes, with n-BuLi (2.7 mL of a 1 M solution in hexane, 2.7 mmol). The resulting red solution was warmed to 18 °C then stirred at this temperature for 20 minutes. Next, a solution of aldehyde 77 (320 mg, 0.9 mmol) in deoxygenated dry THF (5 mL) was added to the deep-red solution via cannula, and stirring was continued for a further 18 h at 18 °C. The reaction mixture was then quenched with HCl (5 mL of a 0.5 M cold aqueous solution), diluted with water (10 mL), and the product extracted with ethyl acetate (3 x 30 mL). The combined ethyl acetate extracts were washed with brine (1 x 30 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus
obtained was purified by column chromatography (silica, 3:7 v/v ethyl acetate - hexane elution) to afford, upon concentration of the appropriate fractions \([R_f 0.3(5)]\), the title compound 84\(^6\) (280 mg, 67\%) as a brown gum.

\[ ^1\text{H} \text{NMR} \ (300 \text{ MHz, CDCl}_3) \delta: 6.96 (d, J 1.7 \text{ Hz, } 1\text{H, ArH}), 6.95 (d, J 7.1 \text{ Hz, } 1\text{H, ArH}), 6.89 (d, J 16.1 \text{ Hz, } 1\text{H}), 6.80 (dd, J 6.9 and 1.9 \text{ Hz, } 1\text{H, ArH}), 6.73 (d, J 16.1 \text{ Hz, } 1\text{H}), 6.54 (d, J 2.2 \text{ Hz, } 2\text{H, ArH}), 6.26 (t, J 2.2 \text{ Hz, } 1\text{H, ArH}), 1.01 (s, 9\text{H}), 0.99 (s, 9\text{H}), 0.23 (s, 6\text{H}), 0.22 (s, 6\text{H}). \]

\[ ^{13}\text{C} \text{NMR} \ (75 \text{ MHz, CDCl}_3) \delta: 157.0 (\text{C}), 147.2 (\text{C}), 147.1 (\text{C}), 140.5 (\text{C}), 130.9 (\text{C}), 129.5 (\text{CH}), 126.3 (\text{CH}), 121.4 (\text{CH}), 120.4 (\text{CH}), 119.5 (\text{CH}), 106.2 (\text{CH}), 102.2 (\text{CH}), 26.4 (\text{CH}_3), 26.3 (\text{CH}_3), 18.9 (\text{C}), 18.8 (\text{C}), -3.6 (\text{CH}_3). \]

\[ \text{IR } \nu_{\text{max}} \text{ 3354 (broad), 2956, 2930, 2858, 1595, 1510, 1472, 1254, 1156, 909, 782 \text{ cm}^{-1}. \]

\[ \text{Mass spectrum } (70 \text{ eV}) \ m/z \ 472 (\text{M}^+, 47\%), 415 (49), 301 (12), 115 (35), 73 (100). \]

\[ \text{HRMS Found M}^+, 472.2470. \text{ C}_{26}\text{H}_{40}\text{O}_4\text{Si}_2 \text{ requires 472.2465}. \]

**3',4',3,5-Tetrahydroxystilbene (53)**

\[
\begin{align*}
\text{HO} & \quad \text{OTBS} \\
\text{84} & \quad \text{TBAF, THF} \\
0 \text{ °C, 5 min} & \quad \text{HO} \\
\text{53} & \quad \text{OH} \\
\end{align*}
\]

Tetra-n-butylammonium fluoride (TBAF, 2.0 mL of a 1 M solution in THF, 2.0 mmol) was added to a magnetically stirred solution of bis-silylated stilbene 84 (230 mg, 0.5 mmol) in dry THF (5 mL) maintained at 0 \text{ °C (ice-water bath)} under an atmosphere of nitrogen. After 5 minutes, at which point TLC analysis revealed no starting material remained, the reaction was quenched with ice-water (5 mL) and the product extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate extracts were washed with brine (1 x 20 mL) then dried (MgSO\(_4\)), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 3:2 v/v ethyl acetate - hexane elution) to afford, upon concentration of the appropriate
fractions ($R_f$ 0.3), the title compound 53 (120 mg, 91%) as a light-brown solid, m.p. 232-234 °C (lit. 229 °C).

$^1$H NMR (300 MHz, CD$_3$COCD$_3$) δ: 8.15 (broad s, OH), 7.07 (d, $J$ 2.1 Hz, 1H, ArH), 6.95 (d, $J$ 16.4 Hz, 1H), 6.90 (dd, $J$ 8.2 and 2.1 Hz, 1H, ArH), 6.82 (d, $J$ 16.4 Hz, 1H), 6.80 (d, $J$ 8.1 Hz, 1H, ArH), 6.52 (d, $J$ 2.2 Hz, 2H, ArH), 6.26 (t, $J$ 2.2 Hz, 1H, ArH).

$^{13}$C NMR (75 MHz, CD$_3$COCD$_3$) δ: 158.8 (C), 145.4 (C), 145.3 (C), 140.1 (C), 129.9 (C), 128.7 (CH), 126.2 (CH), 119.3 (CH), 115.5 (CH), 113.1 (CH), 104.9 (CH), 101.9 (CH).

IR ν$_{max}$ 3307 (broad), 2955, 2928, 2857, 1598, 1510, 1462, 1295, 1255, 1154, 782 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 244 (M$^+$, 100%), 227 (17), 197 (41), 178 (63), 165 (21), 115 (21), 76 (17).

HRMS Found M$^+$, 244.0735. C$_{14}$H$_{12}$O$_4$ requires 244.0736.

3-(4-Hydroxy-3,5-dimethoxyphenyl)methylacrylate (85)

A solution of sinapinic acid (80) (2.0 g, 9.3 mmol) in methanol (20 mL of anhydrous material) was treated with H$_2$SO$_4$ (2 drops of 98% material) and the ensuing mixture was heated at reflux for 6 hours. The resulting mixture was cooled, concentrated under reduced pressure and the residue dissolved in ethyl acetate (50 mL). The ensuing solution was washed with brine (1 x 20 mL) and water (1 x 20 mL) then the separated organic layer was dried (MgSO$_4$), filtered, and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 1:1 v/v ethyl acetate - hexane elution) to afford, upon concentration of the appropriate fractions ($R_f$ 0.5), the title compound 85 (1.91 g, 90%) as a white, crystalline solid, m.p. 89-91 °C (lit. 91-92 °C).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.61 (d, $J$ 15.9 Hz, 1H), 6.77 (s, 2H, ArH), 6.31 (d, $J$ 15.9 Hz, 1H), 5.76 (broad s, OH), 3.93 (s, 6H), 3.80 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 167.7 (C=O), 147.3 (C), 145.3 (CH), 137.3 (C), 126.0 (C), 115.7 (CH), 105.2 (CH), 56.6 (OCH$_3$), 52.0 (OCH$_3$).

IR $\nu_{\text{max}}$ 3407 (broad), 2948, 2842, 1702, 1632, 1514, 1456, 1285, 1216, 978, 828 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 238 (M$^+$, 100%), 223 (5), 207 (30), 163 (21), 135 (16), 121 (14), 77 (12), 65 (16).

HRMS Found M$^+$, 238.0837. C$_{12}$H$_{14}$O$_5$ requires 238.0841.

4-(3-Hydroxypropenyl)-2,6-dimethoxyphenol (75)

\[
\begin{align*}
\text{H}_3\text{C}-\text{C} & \quad \text{DIBAL-H, PhCH}_3 \\
\text{O} & \quad 0 \degree C, 1 \text{ h} \\
\text{OCH}_3 & \quad \text{75}
\end{align*}
\]

A magnetically stirred solution of ester 85 (1.61 g, 6.8 mmol) in freshly distilled toluene (50 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise over 10 minutes, with DIBAL-H (24 mL of a 1 M solution in hexane, 2.4 mmol). After addition was complete, stirring was continued for 1 h at 0 °C then the reaction mixture was slowly quenched (CAUTION) with ethanol (10 mL). The solvent was partially removed under reduced pressure, water (20 mL) was added to the residue, and the resulting gelatinous precipitate of aluminium salts was extracted with ethyl acetate (4 x 50 mL). The combined ethyl acetate extracts were washed with brine (1 x 50 mL) and water (1 x 50 mL) then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The resulting oil was crystallised (from DCM - light petroleum) to afford the title compound 75$^9$ (1.14 g, 80%) as a pale-yellow solid, m.p. 64-65 °C (lit.$^9$ 63-65 °C).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 6.61 (s, 2H, ArH), 6.47 (dt, \(J\) 15.8 and 1.2 Hz, 1H), 6.23 (dt, \(J\) 15.9 and 5.9 Hz, 1H), 5.41 (broad s, OH), 4.29 (dd, \(J\) 5.9 and 1.3 Hz, 2H), 3.88 (s, 6H).

\(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 147.3 (C), 134.9 (C), 131.6 (CH), 128.4 (C), 126.8 (CH), 103.5 (CH), 64.1 (CH\(_2\)), 56.6 (OCH\(_3\)).

IR \(v_{\text{max}}\) 3485 (broad), 2938, 2840, 1606, 1516, 1455, 1333, 1216, 1115, 966, 807 cm\(^{-1}\).

Mass spectrum (70 eV) \(m/z\) 210 (M\(^{+}\), 100%), 167 (78), 154 (45), 121 (26), 107 (18), 91 (21), 77 (33).

HRMS Found M\(^{+}\), 210.0891. C\(_{11}\)H\(_{14}\)O\(_4\) requires 210.0892.

cis- and trans-2,3-Dihydro-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(hydroxymethyl) benzo[1,4]dioxine-6-carbaldehyde (54)

\[
\begin{align*}
\text{H} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
79 & \quad + \\
\text{OH} & \quad \text{OCH}_3 \\
75 & \quad \text{Ag}_2\text{CO}_3 \text{ benzene-acetone} \\
& \quad 60^\circ\text{C}, 9\text{ h} \\
\text{H} & \quad \text{O} \\
\text{OH} & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OH} \\
(\pm)-54 & \quad \text{benzene-acetone}
\end{align*}
\]

A magnetically stirred solution of catechol 79 (50 mg, 0.36 mmol) and alcohol 75 (76 mg, 0.36 mmol) in benzene-acetone (25 mL of a 2:1 v/v mixture) was heated at 60 °C for 0.25 h then treated, in one portion, with silver carbonate (99 mg, 0.36 mmol). The resulting mixture was heated at 60 °C for 9 h then cooled and the precipitated silver salts removed by filtration. The filtrate was then concentrated under reduced pressure to give a brown gum. Subjection of this material to flash chromatography (silica, 1:1 v/v ethyl acetate - hexane elution) yielded, after concentration of the appropriate fractions \((R_f\ 0.1)\), the title compound 54 (71 mg, 57%) as a light-brown solid.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 9.82 (s, CHO), 7.51 (m, 2H, ArH), 7.10 (d, \(J\) 8.1 Hz, 1H, ArH), 6.60 (s, 2H, ArH), 5.40 (broad s, OH), 4.97 (d, \(J\) 8.3 Hz, 1H), 4.14 (m, 1H), 3.90 (s, 6H), 3.60 (m, 1H), 3.11 (m, 1H).
13C NMR (75 MHz, CDCl3) δ: 190.9 (CHO), 149.1 (C), 147.5 (C), 147.3 (C), 134.4 (C), 132.2 (C), 130.1 (C), 124.5 (CH), 118.8 (CH), 117.8 (CH), 102.3 (CH), 79.2 (CH), 72.1 (CH), 61.7 (CH2), 56.7 (OCH3).

IR νmax 3356 (broad), 1698, 1597, 1502, 1461, 1259, 1121, 1063, 861 cm⁻¹.

Mass spectrum (70 eV) m/z 346 (M⁺, 100%), 328 (6), 210 (40), 182 (24), 167 (43), 149 (22), 137 (8), 77 (10).

HRMS Found M⁺, 346.1049. C18H18O7 requires 346.1053.

2,3-trans-5-[(1E)-2-[2,3-Dihydro-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]ethenyl]-1,3-benzenediol (26),

2,3-cis-5-[(1E)-2-[2,3-Dihydro-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]ethenyl]-1,3-benzenediol (50),

2,3-trans-5-[(1E)-2-[2,3-Dihydro-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-7-yl]ethenyl]-1,3-benzenediol (51) and

2,3-cis-5-[(1E)-2-[2,3-Dihydro-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-7-yl]ethenyl]-1,3-benzenediol (52)
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

A magnetically stirred solution of stilbene 53 (94 mg, 0.38 mmol) and alcohol 75 (81 mg, 0.38 mmol) in benzene-acetone (30 mL of a 2:1 v/v mixture) was heated at 60 °C for 0.25 h then treated, in one portion, with silver carbonate (107 mg, 0.38 mmol). The resulting mixture was heated at 60 °C for 18 h then cooled and the precipitate removed by filtration. The filtrate was then concentrated under reduced pressure to give a brown gum. Subjected of this material to flash chromatography (silica, 4:1 v/v ethyl acetate-hexane elution) yielded, after concentration of the appropriate fractions [Rf 0.3(5)], a brown solid comprising a ca. 2:1:2:1 mixture of compounds 26, 50-52. Subjection of this material to HPLC (using a 300 x 10 mm 5µm C18 Alltech Alltima column, 50:49.9:0.1 v/v/v water-methanol-acetic acid elution, solvent flow rate of 5 mL/min, UV peak detection at 325 nm) afforded four fractions, F1-F4 – see Figure 2.2 (page 35) for the HPLC profile.

Concentration of F1 (Rf 15.06 min) under reduced pressure gave (±)-aiphanol (26)\textsuperscript{10,11} (30 mg, 17%) as a light-brown solid, m.p. 162-164 °C.
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^{1}$H NMR (300 MHz, CD$_3$COCD$_3$) δ: 7.14 (d, $J$ 2.1 Hz, 1H, ArH), 7.09 (dd, $J$ 8.5 and 2.1 Hz, 1H, ArH), 7.02 (d, $J$ 16.2 Hz, 1H), 6.94 (d, $J$ 16.2 Hz, 1H), 6.90 (d, $J$ 8.4 Hz, 1H, ArH), 6.84 (s, 2H, ArH), 6.55 (d, $J$ 2.1 Hz, 2H, ArH), 6.28 (t, $J$ 2.1 Hz, 1H, ArH), 4.97 (d, $J$ 8.1 Hz, 1H), 4.14 (m, 1H), 3.86 (s, 6H), 3.78 (m, 1H), 3.53 (m, 1H).

$^{13}$C NMR (75 MHz, CD$_3$COCD$_3$) δ: 159.2 (C), 148.4 (C), 144.7 (C), 144.1 (C), 140.2 (C), 136.9 (C), 131.5 (C), 128.3 (CH), 127.7(5) (C), 127.7(2) (CH), 120.5 (CH), 117.4 (CH), 115.0 (CH), 105.7 (CH), 105.4 (CH), 102.6 (CH), 79.4 (CH), 77.2 (CH), 61.6 (CH$_2$), 56.5 (OCH$_3$).

IR ν$_{max}$ 3370 (broad), 1595, 1504, 1463, 1270, 1115, 1048, 831 cm$^{-1}$.

Mass spectrum (70 eV) m/z 452 (M$^+$, 53%), 393 (10), 255 (13), 210 (40), 167 (100), 73 (35).

HRMS Found M$^+$, 452.1741. C$_{23}$H$_{24}$O$_8$ requires 452.1741.

Concentration of F2 (R: 16.65 min) under reduced pressure gave the title compound (±)-50 (20 mg, 12%) as a light-brown solid, m.p. 162-164 °C.

$^{1}$H NMR (300 MHz, CD$_3$COCD$_3$) δ: 7.17 (d, $J$ 2.1 Hz, 1H, ArH), 7.11 (dd, $J$ 8.5 and 2.2 Hz, 1H, ArH), 7.03 (d, $J$ 16.2 Hz, 1H), 6.95 (d, $J$ 16.2 Hz, 1H), 6.91 (d, $J$ 8.4 Hz, 1H, ArH), 6.79 (s, 2H, ArH), 6.56 (d, $J$ 2.1 Hz, 2H, ArH), 6.28 (t, $J$ 2.2 Hz, 1H, ArH), 5.29 (d, $J$ 2.7 Hz, 1H), 4.54 (m, 1H), 3.81 (s, 6H), 3.65 (m, 1H), 3.54 (m, 1H).

$^{13}$C NMR (75 MHz, CD$_3$COCD$_3$) δ: 159.2 (C), 148.4 (C), 144.1 (C), 142.6 (C), 140.2 (C), 136.4 (C), 131.8 (C), 128.3 (CH), 127.9 (C), 127.4 (CH), 120.8 (CH), 118.1 (CH), 115.2 (CH), 105.5 (CH), 104.6 (CH), 102.6 (CH), 78.7 (CH), 76.4 (CH), 59.3 (CH$_2$), 56.4 (OCH$_3$).

IR ν$_{max}$ 3339 (broad), 1596, 1505, 1463, 1272, 1117, 1060, 834 cm$^{-1}$.

Mass spectrum (70 eV) m/z 452 (M$^+$, 50%), 346 (19), 255 (15), 199 (45), 167 (100), 151 (84), 73 (71).

HRMS Found M$^+$, 452.1743. C$_{23}$H$_{24}$O$_8$ requires 452.1741.

Concentration of F3 (R: 21.36 min) under reduced pressure gave the title compound (±)-51 (32 mg, 19%) as a light-brown solid, m.p. 161-163 °C.
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^1$H NMR (300 MHz, CD$_3$COCD$_3$) δ: 7.13 (d, J 1.9 Hz, 1H, ArH), 7.08 (dd, J 8.4 and 1.9 Hz, 1H, ArH), 1.03 (d, J 16.2 Hz, 1H), 6.94 (d, J 16.2 Hz, 1H), 6.89 (d, J 8.4 Hz, 1H, ArH), 6.83 (s, 2H, ArH), 6.56 (d, J 2.1 Hz, 2H, ArH), 6.29 (t, J 2.1 Hz, 1H, ArH), 4.97 (d, J 8.1 Hz, 1H), 4.15 (m, 1H), 3.86 (s, 6H), 3.75 (dd, J 12.0 and 4.1 Hz, 1H), 3.53 (dd, J 12.0 and 4.1 Hz, 1H).

$^{13}$C NMR (75 MHz, CD$_3$COCD$_3$) δ: 159.2 (C), 148.4 (C), 143.8 (C), 142.9 (C), 140.1 (C), 136.4 (C), 131.9 (C), 128.3 (CH), 127.9 (C), 127.4 (CH), 120.6 (CH), 117.6 (CH), 115.5 (CH), 105.4 (CH), 104.6 (CH), 102.6 (CH), 78.5 (CH), 76.5 (CH), 59.2 (CH$_2$), 56.4 (OCH$_3$).

IR v$_{\text{max}}$ (KBr) 3386 (broad), 1594, 1505, 1463, 1270, 1114, 1047, 832 cm$^{-1}$.

Mass spectrum (70 eV) m/z 452 (M$^+$, 35%), 346 (15), 241 (32), 210 (42), 167 (100), 151 (47), 73 (44).

HRMS Found M$^+$, 452.1475. C$_{23}$H$_{24}$O$_8$ requires 452.1741.

Concentration of F4 (R$_t$ 23.89 min) under reduced pressure gave the title compound (±)-52 (22 mg, 14%) as a light-brown solid, m.p. 161-163 °C.

$^1$H NMR (300 MHz, CD$_3$COCD$_3$) δ: 7.15 (d, J 2.1 Hz, 1H, ArH), 7.10 (dd, J 8.4 and 2.1 Hz, 1H, ArH), 7.03 (d, J 16.4 Hz, 1H), 6.95 (d, J 16.4 Hz, 1H), 6.92 (d, J 8.2 Hz, 1H, ArH), 6.78 (s, 2H, ArH), 6.56 (d, J 2.1 Hz, 2H, ArH), 6.29 (t, J 2.1 Hz, 1H, ArH), 5.29 (d, J 2.6 Hz, 1H), 4.54 (m, 1H), 3.81 (s, 6H), 3.65 (dd, J 12.0 and 3.9 Hz, 1H), 3.54 (dd, J 12.0 and 3.9 Hz, 1H).

$^{13}$C NMR (75 MHz, CD$_3$COCD$_3$) δ: 159.2 (C), 148.4 (C), 143.8 (C), 142.9 (C), 140.1 (C), 136.4 (C), 131.9 (C), 128.3 (CH), 127.9 (C), 127.4 (CH), 120.6 (CH), 117.6 (CH), 115.5 (CH), 105.4 (CH), 104.6 (CH), 102.6 (CH), 78.5 (CH), 76.5 (CH), 59.2 (CH$_2$), 56.4 (OCH$_3$).

IR v$_{\text{max}}$ 3351 (broad), 1594, 1505, 1462, 1269, 1115, 1061, 860 cm$^{-1}$.

Mass spectrum (70 eV) m/z 452 (M$^+$, 30%), 434 (13), 346 (5), 210 (26), 167 (65), 100 (100), 73 (65).

HRMS Found M$^+$, 452.1469. C$_{23}$H$_{24}$O$_8$ requires 452.1741.
5.3 Experimental procedures associated with work described in Chapter 3: The synthesis of (−)- and (+)-aiphanol

Methyl 3,5-bis-Methoxymethoxybenzoate (92)

A magnetically stirred mixture of ester 87 (501 mg, 3 mmol), DMAP (5 mg, catalyst) and DIPEA (1.6 mL, 9 mmol) in DCM (20 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with MOMCl (600 µL, 8 mmol). The reaction mixture was then allowed to warm to 18 °C, stirred at this temperature for 18 h then poured into cold HCl (20 mL of a 0.1 M aqueous solution). The separated aqueous layer was extracted with DCM (2 x 20 mL) and the combined DCM extracts were washed with water (1 x 40 mL) and brine (1 x 40 mL) then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting gum was purified by column chromatography (silica, 2:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions (Rf 0.5), the title compound 92 (700 mg, 91%) as a clear, colourless oil.

¹H NMR (300 MHz, CDCl₃) δ: 7.35 (d, J 2.3 Hz, 2H, ArH), 6.91 (t, J 2.3 Hz, 1H, ArH), 5.17 (s, 4H), 3.88 (s, 3H), 3.46 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ: 166.5 (C=O), 158.0 (C), 132.1 (C), 110.5 (CH), 109.6 (CH₂), 94.3 (CH₂), 56.1 (OCH₃), 52.2 (OCH₃).

IR νmax 2955, 2905, 1724, 1597, 1438, 1302, 1146, 1032, 924, 770, 682 cm⁻¹.

Mass spectrum (70 eV) m/z 256 (M⁺, 100%), 225 (80), 196 (18), 139 (16), 63 (38).

HRMS Found M⁺, 256.0944. C₁₂H₁₆O₆ requires 256.0947.

Elemental analysis Found C, 56.40; H, 6.46. C₁₂H₁₆O₆ requires C, 56.25; H, 6.29%.
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

3,5-bis-Methoxymethoxybenzyl alcohol (93)

A magnetically stirred solution of ester 92 (502 mg, 2 mmol) in dry THF (25 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with LiAlH₄ (2.8 mL of a 1 M solution in THF, 2.8 mmol). After addition was complete, the reaction mixture was warmed to 18 °C and stirred for 2 h at this temperature then treated sequentially with water (200 µL), NaOH (200 µL of a 15% w/v aqueous solution), and again with water (200 µL) then stirred for a further 2 h. The mixture was then filtered through a pad of Celite™ and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 2:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions [R_f 0.2(5)], the title compound 93^[12] (430 mg, 97%) as an amorphous white solid.

^1H NMR (300 MHz, CDCl₃) δ: 6.69 (d, J 2.2 Hz, 2H, ArH), 6.63 (t, J 2.2 Hz, 1H, ArH), 5.14 (s, 4H), 4.59 (s, 2H), 3.45 (s, 6H), 2.28 (broad s, OH).

^13C NMR (75 MHz, CDCl₃) δ: 158.3 (C), 143.6 (C), 107.8 (CH), 103.9 (CH), 94.3 (CH₂), 64.9 (CH₂), 56.0 (OCH₃).

IR ν max 3418 (broad), 2955, 2903, 1599, 1459, 1291, 1145, 1083, 923, 846 cm⁻¹.

Mass spectrum (70 eV) m/z 228 (M⁺, 80%), 198 (23%), 168 (40), 107 (16%), 77 (17), 45 (100).

HRMS Found M⁺, 228.0997. C₁₁H₁₆O₅ requires 228.0998.

Elemental analysis Found C, 58.00; H, 7.30. C₁₁H₁₆O₅ requires C, 57.89; H, 7.07%.
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

3,5-bis-Methoxymethoxybenzyl chloride (94)

A magnetically stirred solution of alcohol 93 (350 mg, 1.5 mmol) and NEt₃ (240 µL, 1.7 mmol) in DCM (20 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with MsCl (130 µL, 1.7 mmol). After addition was complete, the mixture was allowed to warm to 18 °C, stirred at this temperature for 18 h, poured into cold water (20 mL), the DCM layer separated, and the aqueous layer extracted with additional DCM (2 x 15 mL). The combined organic phases were then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 2:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions (Rf 0.7), the title compound 94 (301 mg, 79%) as a clear, colourless oil.

¹H NMR (300 MHz, CDCl₃) δ: 6.73 (d, J 2.2 Hz, 2H, ArH), 6.69 (t, J 2.2 Hz, 1H, ArH), 5.16 (s, 4H), 4.50 (s, 2H), 3.47 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ: 158.3 (C), 139.6 (C), 109.7 (CH), 104.7 (CH), 94.3 (CH₂), 56.0 (OCH₃), 46.0 (CH₂).

IR ν max 2958, 2903, 1599, 1461, 1296, 1146, 1083, 1034, 933, 850, 717 cm⁻¹.

Mass spectrum (70 eV) m/z 246 (M⁺, 100%), 211 (61), 186 (16), 77 (46).

HRMS Found M⁺, 246.0659. C₁₁H₁₅O₄Cl requires 246.0659.

Elemental analysis Found C, 53.71; H, 6.22; Cl, 14.20. C₁₁H₁₅O₄Cl requires C, 53.56; H, 6.13; Cl, 14.37%.
3,5-bis-(Methoxymethoxy)benzyltriphenylphosphonium chloride (48)

A solution of chloride 94 (250 mg, 1 mmol) in toluene (30 mL) was treated with PPh₃ (301 mg, 1.2 mmol) then heated at reflux for 18 h. The mixture was cooled to ca. 18 °C and the resulting white precipitate filtered off, washed thoroughly with diethyl ether then dried at 80 °C for 3 h to afford the title compound 48¹¹ (401 mg, 76%) as a white, crystalline solid, m.p. 188-190 °C.

¹H NMR (300 MHz, DMSO-ᴅ₆) δ: 7.92-7.64 (m, 15H, ArH), 6.57 (d, ʃ 2.1 Hz, 1H, ArH), 6.33 (t, ʃ 2.2 Hz, 2H, ArH), 5.20 (d, ʃ 15.7 Hz, 2H), 4.91 (s, 4H), 3.21 (s, 6H).

¹³C NMR (75 MHz, DMSO-ᴅ₆) δ: 158.4 (C), 135.7 (C), 134.8 (CH), 134.7 (CH), 130.8 (CH), 130.7 (C), 130.6 (CH), 119.1 (CH), 117.9 (CH), 112.9 (C), 105.1 (C), 94.4 (CH₂), 56.2 (OCH₃), 29.4 (CH₂).

IR ν_max 3594, 3378, 2902, 2903, 1595, 1435, 1162, 1135, 1036, 879, 746, 693 cm⁻¹.

Mass spectrum (70 eV) m/z 472 [(M-HCl)⁺, 34%], 427 (8), 262 (100), 183 (66), 108 (26), 77 (9).

HRMS Found (M-HCl)⁺, 472.1801. C₂₉H₂₉O₄P (C₂₉H₃₀ClO₄P-HCl) requires 472.1803.

Elemental analysis Found C, 68.17; H, 6.07; Cl, 6.98; P, 5.86. C₂₉H₃₀ClO₄P requires C, 68.43; H, 5.94; Cl, 6.97; P, 6.09%.

4-Benzylxoy-3-hydroxybenzaldehyde (89)

A magnetically stirred suspension of NaH (160 mg, 60% suspension washed free of oil with hexane, 4 mmol) in DMSO (5 mL) maintained at 18 °C under an atmosphere of
nitrogen was treated, in portions over 10 minutes, with aldehyde 79 (499 mg, 3.6 mmol). The resulting mixture was stirred at 18 °C for 1 h then benzyl chloride (410 µL, 3.6 mmol) was added, dropwise, to the reaction mixture. Stirring was continued for 18 h then the ensuing mixture diluted with water (15 mL) and the basic solution washed with diethyl ether (3 x 10 mL). The aqueous phase was acidified with HCl (0.5 M aqueous solution) to pH ~ 4 then extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (7:3 v/v diethyl ether - hexane elution) to afford, after concentration of the appropriate fractions (R_f 0.5), a white solid. Recrystallisation (from absolute ethanol) of this material gave the title compound 89¹⁴,¹⁵ (320 mg, 39%) as colourless crystals, m.p. 120-121 °C (lit.¹⁵ 121-122 °C). The structure of this compound was confirmed by single crystal X-ray analysis (Appendix A.4).

¹H NMR (300 MHz, CD₃COCD₃) δ: 9.83 (s, CHO), 8.40 (broad s, OH), 7.55-7.20 (complex m, 8H, ArH), 5.26 (s, 2H).

¹³C NMR (75 MHz, CD₃COCD₃) δ: 190.9 (CHO), 152.3 (C), 147.6 (C), 136.6 (C), 131.1 (C), 128.7 (CH), 128.4 (CH), 128.3 (CH), 124.3 (CH), 114.4 (CH), 112.7 (CH), 70.8 (CH₂).

IR νmax 3210 (broad), 2870, 1674, 1605, 1580, 1513, 1344, 1288, 1117, 1016, 812 cm⁻¹.

Mass spectrum (70 eV) m/z 228 M⁺, 17%, 137 (3), 109 (3), 91 (100), 81 (6), 65 (21).

HRMS Found M⁺, 228.0789. C₁₄H₁₂O₃ requires 228.0786.

3,5-Dimethoxy-4-benzyloxybenzaldehyde (95)

A mixture of aldehyde 91 (500 mg, 2.75 mmol), K₂CO₃ (390 mg, 2.8 mmol) and benzyl bromide (340 µL, 2.8 mmol) in dry DMF (30 mL) maintained under an atmosphere of
nitrogen was stirred magnetically at 120 °C for 18 h then cooled to 18 °C and the solid filtered off. The filtrate was diluted with ethyl acetate (40 mL) then washed with NaOH (3 x 30 mL of a 10% w/v aqueous solution) and brine (1 x 30 mL) before being dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 2:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions ($R_f$ 0.5), the title compound 95\textsuperscript{16} (680 mg, 91%) as pale-yellow needles, m.p. 63-64 °C (lit.\textsuperscript{16} 62-63 °C).

\textsuperscript{1}H NMR (300 MHz, CDCl$_3$) δ: 9.81 (s, 1H, CHO), 7.50-7.40 (m, 2H, ArH), 7.35-7.25 (m, 3H, ArH), 7.08 (s, 2H, ArH), 5.10 (s, 2H), 3.84 (s, 6H).

\textsuperscript{13}C NMR (75 MHz, CDCl$_3$) δ: 190.9 (CHO), 153.6 (C), 142.0 (C), 136.9 (C), 131.6 (C), 128.1 (CH), 128.0 (CH), 127.8 (CH), 106.3 (CH), 74.7 (CH$_2$), 55.9 (OCH$_3$).

IR $\nu_{max}$ 2940, 2842, 1692, 1587, 1462, 1327, 1126, 981, 834, 741 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 272 (M$^+$, 100%), 181 (23), 125 (19), 91 (88), 65 (62), 39 (48).

HRMS Found M$^+$, 272.1051. C$_{16}$H$_{16}$O$_4$ requires 272.1049.

Ethyl 3,5-Dimethoxy-4-benzyloxycinnamate (96)

A magnetically stirred suspension of NaH (74 mg, 60% suspension washed free of oil with hexane, 1.85 mmol) in THF (30 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with triethyl phosphonoacetate (370 µL, 1.86 mmol). The resulting suspension was warmed to 18 °C and stirred until no further evolution of H$_2$ gas was observed (ca. 0.25 h). Next, a solution of aldehyde 95 (501 mg, 1.84 mmol) in THF (5 mL) was slowly introduced, via canula, to the reaction mixture which was then stirred at 18 °C for 3.5 h, diluted with water (30 mL) and extracted with
diethyl ether (3 x 40 mL). The combined organic phases were then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 3:7 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions (Rf 0.5), the title compound 96 (501 mg, 80%) as a white, crystalline solid, m.p. 69-71 °C (lit. 71-73 °C).

\[ \text{H NMR} \quad (300 \text{ MHz, CDCl}_3) \delta: 7.60 (d, J = 15.9 \text{ Hz}, 1H), 7.48 (m, 2H, ArH), 7.32 (complex m, 3H, ArH), 6.74 (s, 2H, ArH), 6.35 (d, J = 15.9 \text{ Hz}, 1H), 5.05 (s, 2H), 4.26 (q, J = 7.1 \text{ Hz}, 2H), 3.84 (s, 6H), 1.34 (t, J = 7.0 \text{ Hz}, 3H).
\]

\[ \text{C NMR} \quad (75 \text{ MHz, CDCl}_3) \delta: 166.9 (\text{C=O}), 153.6 (\text{C}), 144.5 (\text{CH}), 138.7 (\text{C}), 137.4 (\text{C}), 129.9 (\text{CH}), 128.4 (\text{CH}), 128.1 (\text{CH}), 127.9 (\text{CH}), 117.3 (\text{CH}), 105.0 (\text{CH}), 75.0 (\text{CH}_2), 60.4 (\text{CH}_2), 56.0 (\text{OCH}_3), 14.2 (\text{CH}_3).
\]

IR νmax 2939, 2841, 1709, 1636, 1583, 1455, 1274, 1128, 980, 828, 734 cm⁻¹.

Mass spectrum (70 eV) m/z 342 (M⁺, 27%), 297 (7), 251 (100), 91 (13).

HRMS Found M⁺, 342.1465. C₂₀H₂₂O₅ requires 342.1467.

4-Benzylx-3,5-dimethoxycinnamyl alcohol (97)

A magnetically stirred solution of ester 96 (400 mg, 1.17 mmol) in toluene (20 mL) maintained at -10 °C (ice-salt bath) under an atmosphere of nitrogen was treated, dropwise, with DIBAL-H (3 mL of a 1 M solution in hexane, 3 mmol). After addition was complete, the mixture was stirred for a further 0.75 h at -10 °C during which time TLC analysis indicated that no starting material remained. The reaction mixture was slowly quenched (CAUTION), at -10 °C, with ethanol (ca. 2 mL), and then most of the solvent was removed under reduced pressure. The residue was treated with water (15 mL), and the resulting gelatinous precipitate extracted with ethyl acetate (5 x 30 mL).
The combined organic phases were washed with water (1 x 50 mL) and brine (1 x 50 mL) then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 3:2 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions ($R_f$ 0.3), the title compound 97$^{17}$ (290 mg, 83%) as a white, crystalline solid, m.p. 60-62 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.49 (m, 2H, ArH), 7.32 (complex m, 3H, ArH), 6.60 (s, 2H, ArH), 6.52 (dt, $J$ 15.9 and 1.2 Hz, 1H), 6.27 (dt, $J$ 15.8 and 5.8 Hz, 1H), 5.01 (s, 2H), 4.30 (d, $J$ 5.4 Hz, 2H), 3.82 (s, 6H), 1.82 (brs, 1H, OH).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 153.5 (C), 137.6 (C), 136.6 (C), 132.4 (C), 131.0 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 103.5 (CH), 75.0 (CH$_2$), 63.5 (CH$_2$), 56.0 (OCH$_3$).

IR $\nu_{max}$ 3412 (broad), 2938, 2840, 1583, 1505, 1418, 1334, 1240, 1127, 966 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 300 (M$^+$, 16%), 251 (13), 209 (53), 149 (13), 91 (100), 59 (33).

HRMS Found M$^+$, 300.1360. $C_{18}H_{20}O_4$ requires 300.1362.

(1R,2R)-1-(4-Benzxyloxy-3,5-dimethoxyphenyl)-2,3-dihydroxypropanol (98)

A mixture of $t$-BuOH (10 mL) and water (10 mL) was treated with AD mix-β (961 mg) and methanesulphonamide (64 mg, 0.67 mmol) then stirred magnetically at 18 °C until both phases were clear. The ensuing mixture was cooled to 0 °C (ice-water bath), treated with allylic alcohol 97 (200 mg, 0.67 mmol) then stirred vigorously at 0 °C for 48 h. The reaction mixture was quenched, at 0 °C, by the addition of Na$_2$SO$_3$ (980 mg), warmed to 18 °C, stirred at this temperature for 0.5 h then extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with KOH (40 mL of a 2 M
aqueous solution) and water (1 x 40 mL) then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting solid was purified by column chromatography (silica, 9:1 v/v diethyl ether - methanol elution) to afford, after concentration of the appropriate fractions (Rf 0.5), the title compound 98 (210 mg, 94%) as a white, crystalline solid, m.p. 78-79 °C (lit. 77-79 °C).

¹H NMR (300 MHz, CDCl₃) δ: 7.48-7.44 (m, 2H, ArH), 7.36-7.26 (complex m, 3H, ArH), 6.55 (s, 2H, ArH), 4.96 (s, 2H), 4.57 (d, J 6.6 Hz, 1H), 3.78 (s, 6H), 3.72 (m, 1H), 3.57 (dd, J 11.5 and 3.3 Hz, 1H), 3.46 (dd, J 11.6 and 5.4 Hz, 1H), 3.06 (broad s, 3H, 3 x OH).

¹³C NMR (75 MHz, CDCl₃) δ: 153.5 (C), 137.6 (C), 136.3 (C), 128.5 (CH), 128.1 (CH), 127.9 (CH), 103.5 (CH), 75.8 (CH), 75.0 (CH₂), 74.9 (CH), 63.3 (CH₂), 56.1 (OCH₃).

IR νmax 3352 (broad), 2975, 2873, 1590, 1507, 1456, 1427, 1127, 995, 757 cm⁻¹.

Mass spectrum (70 eV) m/z 334 (M⁺, 10%), 273 (14), 183 (44), 123 (12), 91 (100).


Specific rotation [α]D -17.6° (c 1.75, CHCl₃) [lit. 17 -18° (c 1.60, CHCl₃)].

(1R,2R)-1-(4-Benzyl oxy-3,5-dimethoxyphenyl)-1,2-dihydroxypropyl tosylate (99)

A magnetically stirred solution of triol 98 (170 mg, 0.51 mmol) in dry pyridine (10 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, in one portion, with TsCl (101 mg, 0.53 mmol). The cooling bath was removed and the mixture was allowed to warm to 18 °C and stirred at this temperature for 18 h then diluted with ethyl acetate (25 mL) and washed with cold HCl (2 x 20 mL of a 0.1 M aqueous solution). The organic phase was then dried (Na₂SO₄), filtered, and the filtrate
concentrated under reduced pressure. The resulting gum was subjected to column chromatography (silica, 4:1 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions \([R_f \ 0.5(5)]\), the title compound \(99^{17}\) (220 mg, 88%) as a white, crystalline solid, m.p. 118-119 °C (lit.\(^{17}\) 121-122 °C).

\(\text{H NMR (300 MHz, CDCl}_3\): } \delta: 7.77 (d, \ J \ 8.4 \ Hz, 2H, ArH), 7.50-7.44 (m, 2H, ArH), 7.38-7.24 (complex m, 5H, ArH), 6.54 (s, 2H, ArH), 4.97 (s, 2H), 4.61 (d, \ J \ 6.0 \ Hz, 1H), 4.20-3.82 (m, 3H), 3.80 (s, 6H), 2.70 (broad s, 2H, 2 x OH), 2.41 (s, 3H).

\(\text{C NMR (75 MHz, CDCl}_3\): } \delta: 153.8 (C), 145.4 (C), 137.9 (C), 136.8 (C), 135.6 (C), 132.6 (C), 130.2 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 103.6 (CH), 75.2 (CH\(_2\)), 73.9(2) (CH), 73.9(0) (CH), 70.4 (CH\(_2\)), 56.3 (OCH\(_3\)), 21.9 (CH\(_3\)).

\((1R,2R)-2,3\text{-Epoxy-1-}(3,5\text{-dimethoxy-4-benzyl oxyphenyl)propanol (90a)}\)

A solution of tosylate \(99\) (200 mg, 0.41 mmol) in dry methanol (10 mL) was treated with \(K_2CO_3\) (60 mg of anhydrous material, 0.43 mol) and the resulting suspension stirred vigorously at 18 °C under an atmosphere of nitrogen for 3 h, then poured into water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL) then dried (\(Na_2SO_4\)), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 3:2 v:v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions \((R_f \ 0.3)\), the title compound \(90a^{17}\) (110 mg, 85%) as a white, crystalline solid, m.p. 97-99 °C (lit.\(^{17}\) 98-100 °C).

\(\text{H NMR (300 MHz, CDCl}_3\): } \delta: 7.51-7.46 (m, 2H, ArH), 7.38-7.25 (m, 3H, ArH), 6.62 (s, 2H, ArH), 5.00 (s, 2H), 4.39 (t, \ J \ 5.2 \ Hz, 1H), 3.83 (s, 6H), 3.22 (m, 1H), 2.84 (m, 2H), 2.70 (d, \ J \ 4.8 \ Hz, OH).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 153.6 (C), 137.6 (C), 136.6 (C), 135.9 (C), 128.4 (CH), 128.1 (CH), 127.8 (CH), 103.2 (CH), 74.9 (CH$_2$), 74.3 (CH), 56.1 (OCH$_3$), 55.8 (CH), 45.4 (CH$_2$).

IR $\nu_{\text{max}}$ 3443 (broad), 2939, 1592, 1459, 1420, 1330, 1231, 1126, 914 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 316 (M$^+$, 53%), 225 (57), 195 (35), 153 (25), 91 (100).

HRMS Found M$^+$, 316.1310. C$_{18}$H$_{20}$O$_5$ requires 316.1311.

Specific rotation $[\alpha]_D$ -8.6° (c 0.96, CHCl$_3$) [lit.$^{17}$ -8° (c 1.60, CHCl$_3$)].

$(1S,2R)$-4-Benzylxyloxy-3-[2,3-epoxy-1-(3,5-dimethoxy-4-benzyloxyphenyl)propoxy]benzaldehyde (88a)

\begin{align*}
\text{89} & \quad + \quad \text{90a} \\
& \quad \xrightarrow{\text{DIAD, PPh$_3$, THF-toluene}} \\
& \quad \xrightarrow{18 \degree C, 24 h} \\
\text{88a}
\end{align*}

A magnetically stirred solution of aldehyde 89 (73 mg, 0.32 mmol) and DIAD (63 µL, 0.32 mmol) in dry toluene (5 mL) maintained at 18 °C under an atmosphere of nitrogen was treated, dropwise, with a solution of PPh$_3$ (84 mg, 0.32 mmol) and epoxide 90a (90 mg, 0.29 mmol) in dry THF-toluene (1 mL of a 1:1 v/v mixture). The mixture was stirred at 18 °C for 24 h then the solvent was removed under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 3:2 v/v diethyl ether - hexane elution) to afford, after concentration of the appropriate fractions [$R_f$ 0.2(5)], the title compound 88a (99 mg, 67%) as an amorphous white solid.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 9.77 (s, 1H, CHO), 7.48-7.26 (complex m, 12H, ArH), 7.03 (d, $J$ 8.7 Hz, 1H, ArH), 6.67 (s, 2H, ArH), 5.20 (s, 2H), 5.17 (d, $J$ 4.7 Hz, 1H), 4.98 (s, 2H), 3.76 (s, 6H), 3.37 (m, 1H), 2.88 (dd, $J$ 5.2 and 2.6 Hz, 1H), 2.82 (dd, $J$ 5.2 and 3.8 Hz, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 190.5 (CHO), 154.8 (C), 153.6 (C), 147.7 (C), 137.7 (C), 136.8 (C), 136.0 (C), 132.8 (C), 130.1 (C), 128.6 (CH), 128.3 (CH), 128.2 (CH),
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

128.0 (CH), 127.7 (CH), 127.1 (CH), 115.8 (CH), 112.9 (CH), 103.8 (CH), 80.4 (CH), 74.9 (CH₂), 70.7 (CH₂), 56.0 (OCH₃), 54.1 (CH), 45.1 (CH₂).

IR ν<sub>max</sub> 2976, 2869, 1686, 1595, 1506, 1460, 1429, 1272, 1127, 995, 757 cm⁻¹.

Mass spectrum (70 eV) m/z 526 (M⁺, 9%), 435 (5), 405 (55), 299 (30), 91 (100).


Specific rotation [α]<sub>D</sub> +15.5° (c 0.31, CHCl₃).

(1S,2R)-4-Hydroxy-3-[2,3-epoxy-1-(3,5-dimethoxy-4-hydroxyphenyl)propoxy]benzaldehyde (88b)

A solution of compound 88a (85 mg, 0.16 mmol) in ethyl acetate (5 mL) containing 5% Pd-C (8 mg) was magnetically stirred at 18 °C for 16 h under a hydrogen atmosphere. The reaction mixture was then filtered and the filtrate concentrated under reduced pressure. The resulting material was subjected to column chromatography (silica, 5:4:1 v/v/v hexane - ethyl acetate - methanol elution) to afford, after concentration of the appropriate fractions (R<sub>f</sub> 0.2), the title compound 88b (48 mg, 86%) as an amorphous white solid.

<sup>1</sup>H NMR (300 MHz, CDCl₃) δ: 9.70 (s, 1H, CHO), 8.00 (brs, 1H, OH), 7.51 (dd, J 8.2 and 1.9 Hz, 1H, ArH), 7.29 (d, J 1.9 Hz, 1H, ArH), 7.06 (d, J 8.2 Hz, 1H, ArH), 6.63 (s, 2H, ArH), 5.66 (broad s, OH), 4.98 (d, J 2.5 Hz, 1H), 3.90 (s, 6H), 3.40 (m, 1H), 3.22 (m, 1H), 2.99 (m, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl₃) δ: 190.9 (CHO), 154.7 (C), 147.7 (C), 146.1 (C), 135.6 (C), 129.6 (C), 129.2 (C), 127.3 (CH), 119.5 (CH), 116.8 (CH), 103.9 (CH), 82.1 (CH), 56.7 (OCH₃), 54.8 (CH), 45.0 (CH₂).

IR ν<sub>max</sub> 3360 (broad), 2939, 1684, 1595, 1507, 1462, 1443, 1287, 1126, 964 cm⁻¹.
**Chapter 5** Details of the experimental work described in Chapters 2, 3 and 4

**Mass spectrum** (70 eV) m/z 347 [(M+H)$^+$, 82%], 174 (85), 116 (40), 88 (93), 50.5 (100).

**Attempted formation of compound 86a**

A solution of compound 88b (40 mg, 0.12 mmol) in dry methanol (5 mL) was treated with K$_2$CO$_3$ (49 mg of anhydrous material, 0.36 mmol) and the ensuing mixture stirred magnetically at 18 °C for 0.75 h. The methanol was then removed under reduced pressure and the residue treated with HCl (2.5 mL of a 0.5 M aqueous solution). The resulting mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions ($R_f$ 0.3), an inseparable mixture of compounds (36 mg). The 300 MHz $^1$H NMR spectrum of this mixture showed no signal attributable to the H-2 proton (i.e. a doublet at $\delta \sim 5$ ppm, $J \sim 8$ Hz) of the anticipated compound 86a.

The mixture obtained as described immediately above was dissolved in DCM (20 mL), and whilst maintaining a temperature of 0 °C and under a nitrogen atmosphere, DIPEA (200 µL, 1.2 mmol), DMAP (catalyst, 5 mg) and MOMCl (31 µL, 0.4 mmol) were added. The ensuing mixture was stirred for 5 minutes at 0 °C then allowed to warm to 18 °C, stirred for 4 h then quenched with NaHCO$_3$ (2 mL of a 0.5 M aqueous solution). The product was extracted into diethyl ether (3 x 5 mL) and the combined organic phases were washed with water (1 x 10 mL) then dried (MgSO$_4$), filtered, and
concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 3:2 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions \([R_f 0.5(5)]\), compound 100 (24 mg, 88% yield over two steps) as an amorphous white solid.

\[^{1}H \text{ NMR} \ (300 \text{ MHz, CDCl}_3) \delta: 9.83 \text{ (s, 1H, CHO)}, 7.68 \text{ (d, } J 1.9 \text{ Hz, 1H, ArH)}, 7.51 \text{ (dd, } J 8.3 \text{ and 1.9 Hz, 1H, ArH)}, 7.28 \text{ (d, } J 8.4 \text{ Hz, 1H, ArH)}, 5.33 \text{ (s, 2H)}, 5.30 \text{ (s, 2H)},
\]

3.5-Dimethoxy-4-methoxymethoxybenzaldehyde (101)

A magnetically stirred mixture of aldehyde 91 (2.50 g, 14 mmol), DIPEA (3.8 mL, 22 mmol) and DMAP (15 mg, catalyst) in DCM (40 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with MOMCl (1.3 mL, 17 mmol). After addition was complete, the reaction mixture was allowed to warm to 18 °C and then stirred at this temperature for 6 h before being treated with cold HCl (50 mL of a 0.1 M aqueous solution). The DCM layer was separated, and the aqueous layer extracted with more DCM (2 x 50 mL). The combined organic phases were washed with water (1 x 50 mL) then dried (Na\(_2\)SO\(_4\)), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 2:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions \([R_f 0.2(5)]\), the title compound 101\(^{18}\) (2.90 g, 95%) as a white, crystalline solid, m.p. 50-52 °C (lit.\(^{18}\) 52-53 °C).

\[^{1}H \text{ NMR} \ (300 \text{ MHz, CDCl}_3) \delta: 9.81 \text{ (s, 1H, CHO)}, 7.08 \text{ (s, 2H, ArH)}, 5.17 \text{ (s, 2H)}, 3.87 \text{ (s, 6H)}, 3.54 \text{ (s, 3H)}.\]
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

\(^{13}\text{C} \ \text{NMR} \ (75 \ \text{MHz, CDCl}_3) \ \delta: 190.9 \ (\text{CHO}), 153.56 (\text{C}), 139.8 (\text{C}), 132.0 (\text{C}), 106.3 (\text{CH}), 98.0 (\text{CH}_2), 57.1 (\text{OCH}_3), 56.0 (\text{OCH}_3).

\text{IR} \ \nu_{\text{max}} \ 2990, 2964, 2841, 1686, 1592, 1470, 1327, 1083, 951, 828, 723 \ \text{cm}^{-1}.

\text{Mass spectrum} \ (70 \ \text{eV}) \ m/z 226 (M^+ , 100\%), 196 (92), 181 (39), 125 (25), 95 (31).

\text{HRMS} \ \text{Found M}^+; 226.0842. \ C_{11}H_{14}O_5 \text{ requires 226.0841.}

\text{Elemental analysis} \ \text{Found C, 58.45; H, 6.34.} \ C_{11}H_{14}O_5 \text{ requires C, 58.40; H, 6.24%}.

\text{Ethyl 3,5-Dimethoxy-4-methoxymethoxycinnamate (102)}

\[
\begin{align*}
\begin{array}{c}
\text{H} \ \text{OCH}_3 \\
\text{OMOM} \\
\text{OCH}_3
\end{array}
\end{align*}
\]  

\[
\begin{align*}
\text{NaH, THF,} & \quad 0 - 18 \ ^\circ\text{C}, 4 \ \text{h} \\
\text{101} & \quad \text{NaH, THF,} \\
\text{102} & \quad \text{NaH, THF,}
\end{align*}
\]

A magnetically stirred suspension of NaH (480 mg, 60% suspension washed free of oil with hexane, 12 mmol) in THF (50 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with triethyl phosphonoacetate (2.2 mL, 11 mmol). The resulting suspension was warmed to 18 °C and stirred at this temperature until no further evolution of H\(_2\) gas was observed (ca. 0.5 h). At this point, a solution of aldehyde 101 (2.40 g, 10.6 mmol) in THF (15 mL) was slowly added, via canula, to the reaction mixture which was then stirred for a further 4 h, diluted with water (40 mL) and extracted with diethyl ether (3 x 60 mL). The combined organic phases were then dried (Na\(_2\)SO\(_4\)), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 2:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions [\(R_f\) 0.4(5)], the title compound 102\(^{19}\) (2.60 g, 83%) as a white, crystalline solid, m.p. 64-66 °C.

\(^1\text{H} \ \text{NMR} \ (300 \ \text{MHz, CDCl}_3) \ \delta: 7.55 (d, J 15.9 \ \text{Hz}, 1\text{H}), 6.71 (s, 2\text{H, ArH}), 6.31 (d, J 15.9 \ \text{Hz}, 1\text{H}), 5.12 (s, 2\text{H}), 4.21 (q, J 7.1 \ \text{Hz}, 2\text{H}), 3.83 (s, 6\text{H}), 3.56 (s, 3\text{H}), 1.30 (t, J 7.1 \ \text{Hz}, 3\text{H}).
\( \text{\textsuperscript{13}C NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \): 166.8 (C=O), 153.3 (C), 144.4 (CH), 136.1 (C), 130.2 (C), 117.4 (CH), 104.8 (CH), 98.0 (CH\(_2\)), 60.3 (CH\(_2\)), 57.0 (OCH\(_3\)), 55.9 (OCH\(_3\)), 14.2 (CH\(_3\)).

\( \text{IR} \) \( \nu_{\text{max}} \) 2953, 2840, 1691, 1586, 1463, 1424, 1250, 1124, 979, 817 cm\(^{-1}\).

Mass spectrum (70 eV) \( m/z \) 296 (M\(^{+}\), 98%), 266 (95), 251 (100), 206 (62), 191 (42), 177 (33), 135 (17), 77 (15).

HRMS Found M\(^{+}\), 296.1260. \( C_{13}H_{20}O_6 \) requires 296.1260.

Elemental analysis Found C, 61.09; H, 6.99. \( C_{15}H_{20}O_6 \) requires C, 60.80; H, 6.80%.

3,5-Dimethoxy-4-methoxymethoxycinnamyl alcohol (103)

A magnetically stirred solution of ester 102 (2.30 g, 7.8 mmol) in toluene (40 mL) maintained at -10 °C (ice-salt bath) under an atmosphere of nitrogen was treated, dropwise, with DIBAL-H (19.5 mL of a 1 M solution in hexane, 19.5 mmol). After addition was complete, stirring was continued at -10 °C for a further 0.5 h after which time TLC analysis indicated no starting material remained. The reaction mixture was slowly quenched (CAUTION), at -10 °C, with ethanol (ca. 5 mL) then most of the solvent was removed under reduced pressure. The residue was then treated with water (30 mL) and the resulting gelatinous precipitate of aluminium salts extracted with ethyl acetate (5 x 60 mL). The combined organic phases were washed with water (1 x 60 mL) and brine (1 x 60 mL) then dried (Na\(_2\)SO\(_4\)), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 3:2 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions (\( R_f \) 0.3), the title compound 103\(^{19}\) (1.60 g, 81%) as a white, crystalline solid, m.p. 54-56 °C.
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 6.60 (s, 2H, ArH), 6.52 (dt, $J$ 15.8 and 1.4 Hz, 1H), 6.26 (dt, $J$ 15.8 and 5.6 Hz, 1H), 5.11 (s, 2H), 4.29 (d, $J$ 5.2 Hz, 2H), 3.84 (s, 6H), 3.59 (s, 3H), 1.76 (broad s, OH).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 153.3 (C), 134.1 (C), 132.8 (C), 130.9 (CH), 128.1 (CH), 103.4 (CH), 98.1 (CH$_2$), 63.5 (CH$_2$), 57.1 (OCH$_3$), 55.9 (OCH$_3$).

IR $\nu_{\text{max}}$ 3425 (broad), 2939, 1585, 1505, 1419, 1335, 1155, 1127, 967 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 254 (M$^{+}$, 100%), 224 (52), 209 (58), 149 (83), 121 (30), 77 (26).

HRMS Found M$^{+}$, 254.1155. C$_{13}$H$_{18}$O$_5$ requires 254.1154.

Elemental analysis Found C, 61.22; H, 7.33. C$_{13}$H$_{18}$O$_5$ requires C, 61.41; H, 7.13%.

(1$R$,2$R$)-1-(3,5-Dimethoxy-4-methoxymethoxyphenyl)-2,3-dihydroxypropanol (104)

A mixture of $t$-BuOH (15 mL), water (15 mL), AD mix-$\beta$ (3.1 g) and methanesulphonamide (200 mg, 2.2 mmol) was stirred magnetically at 18 $^\circ$C until both phases were clear. The ensuing mixture was cooled to 0 $^\circ$C (ice-water bath), treated with allylic alcohol 103 (550 mg, 2.2 mmol) then stirred vigorously at 0 $^\circ$C for 48 h. After this time the reaction was quenched, at 0 $^\circ$C, by the addition of Na$_2$SO$_3$ (3.2 g) then warmed to 18 $^\circ$C and stirred at this temperature for 0.5 h before being extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were washed with KOH (1 x 50 mL of a 2 M aqueous solution) and water (1 x 50 mL) then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The resulting solid was purified by column chromatography (silica, 9:1 v/v diethyl ether - methanol elution) to afford, after concentration of the appropriate fractions [$R_f$ 0.2(5)], an off-white solid. Recrystallisation of this material (from methanol-DCM) afforded the title compound 104 (490 mg, 80%) as a white, crystalline solid, m.p. 73-75 $^\circ$C, in >95% e.e. (as
determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, $R_t$ 13.3 min).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 6.60 (s, 2H, ArH), 5.09 (s, 2H), 4.60 (d, $J$ 6.5 Hz, 1H), 3.82 (s, 6H), 3.73 (m, 1H), 3.61 (dd, $J$ 11.4 and 3.3 Hz, 1H), 3.58 (s, 3H), 3.55 (dd, $J$ 11.4 and 4.8 Hz, 1H), 2.99 (broad s, OH).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 153.4 (C), 136.7 (C), 133.9 (C), 103.4 (CH), 98.0 (CH$_2$), 75.7 (CH), 74.8 (CH), 63.3 (CH$_2$), 57.1 (OCH$_3$), 56.1 (OCH$_3$).

IR $\nu_{max}$ 3401 (broad), 2940, 1594, 1506, 1462, 1422, 1329, 1125, 968, 836 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 288 (M$^+$, 10%), 227 (45), 195 (20), 169 (17), 123 (11), 45 (100).

HRMS Found M$^+$, 288.1207. C$_{13}$H$_{20}$O$_7$ requires 288.1209.

Elemental analysis Found C, 54.57; H, 7.23. C$_{13}$H$_{20}$O$_7$ requires C, 54.16; H, 6.99%.

Specific rotation $[\alpha]_D$ -24° (c 0.95, CHCl$_3$).

**Pyridinium hydrobromide perbromide**

A magnetically stirred solution of HBr (5.0 g of a 45% w/v mixture in AcOH, 25 mmol) in AcOH (10 mL) maintained at 18 °C was treated with pyridine (2 mL, 25 mmol) and the resulting mixture was warmed to 65 °C then Br$_2$ (1.3 mL in 2 mL of AcOH, 25 mmol) was added. After addition was complete, the mixture was stirred vigorously at 65 °C for 0.25 h then cooled to 18 °C during which the product precipitated as orange-red crystalline needles. The product was filtered off and washed with cold ethanol (1 x 40 mL) then recrystallised (ethanol), washed thoroughly with diethyl ether, and dried under high vacuum to afford pyridinium hydrobromide perbromide$^{20}$ (2.40 g, 30%) as orange-red needles, m.p. 133-134 °C (lit.$^{20}$ 132-134 °C).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

(1R,2R)-1-(2-Bromo-4-hydroxy-3,5-dimethoxyphenyl)-2,3-dihydroxypropanol (106)

A magnetically stirred solution of compound 104 (25 mg, 0.09 mmol) in DCM (5 mL) maintained at 18 °C was treated, in one portion, with pyridinium hydrobromide perbromide (32 mg, 0.1 mmol) and the ensuing mixture stirred for a further 10 minutes at which time TLC analysis indicated no starting material remained. Consequently, the reaction was quenched with sodium bisulphate (0.5 mL of a 1 M aqueous solution) then NaHCO₃ (2 mL of a saturated solution) was added. The DCM layer was separated, and the aqueous layer extracted with DCM (2 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL) then dried (Na₂SO₄), filtered and the filtrate concentrated under reduced pressure. The resulting oil was subjected to high vacuum for 5 h to afford compound 105 (28 mg, 85%) as a clear, colourless oil. This material was used, as obtained, in the next step.

A solution of compound 105 (28 mg, 0.07 mmol) in MeOH (5 mL) was treated with conc. HCl (1 drop) and the ensuing mixture was stirred magnetically at 18 °C for 18 h. The methanol was then removed under reduced pressure, water (10 mL) was added to the residue and the resulting mixture extracted with ethyl acetate (3 x 10 mL). The combined organic phases were then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 19:1 v/v ethyl acetate - methanol elution) to afford, after concentration of the appropriate fractions (Rf 0.4), a white solid. Recrystallisation of this material (from methanol-DCM) afforded the title compound 106 (20 mg, 91%) as colourless crystals, m.p. 172-174 °C. The structure of this compound was determined by single crystal X-ray analysis (Appendix A.4).
1H NMR (300 MHz, CD$_3$OD) $\delta$: 7.05 (s, 1H, ArH), 5.04 (d, $J$ 3.8 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.75 (m, 1H), 3.60 (m, 2H).

13C NMR (75 MHz, CD$_3$OD) $\delta$: 148.2 (C), 144.6 (C), 139.8 (C), 132.1 (C), 108.1 (C), 107.5 (C), 74.9 (CH), 72.0 (CH), 63.6 (CH$_2$), 59.5 (OCH$_3$), 55.4 (OCH$_3$).

IR $\nu_{\text{max}}$ 3365 (broad), 2938, 1594, 1495, 1410, 1314, 1176, 1097, 856 cm$^{-1}$.

HRMS Found M$^+$, 324.0032 and 322.0053. C$_{11}$H$_{15}^{81}$BrO$_6$ and C$_{11}$H$_{15}^{79}$BrO$_6$ requires 324.0032 and 322.0052, respectively.

(1R,2R)-1-(3,5-Dimethoxy-4-methoxymethoxyphenyl)-1,2-dihydroxypropyl tosylate (107)

A magnetically stirred solution of compound 104 (350 mg, 1.2 mmol) in dry pyridine (15 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, in one portion, with TsCl (250 mg, 1.3 mmol). The cooling bath was removed and the mixture was allowed to warm to 18 °C and stirred at this temperature for 18 h then diluted with ethyl acetate (35 mL) and washed with cold HCl (2 x 30 mL of a 0.1 M aqueous solution). The separated organic phase was then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 7:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions [R$_f$ 0.2(5)], the title compound 107 (380 mg, 72%) as a white, crystalline solid, m.p. 68-70 °C.

1H NMR (300 MHz, CDCl$_3$) $\delta$: 7.75 (d, $J$ 8.2 Hz, 2H, ArH), 7.34 (d, $J$ 8.2 Hz, 2H, ArH), 6.57 (s, 2H, ArH), 5.09 (s, 2H), 4.63 (d, $J$ 6.2 Hz, 1H), 4.04-3.86 (m, 3H), 3.82 (s, 6H), 3.58 (s, 3H), 2.60 (broad s, OH), 2.44 (s, 3H).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 153.4 (C), 145.2 (C), 135.7 (C), 134.0 (C), 132.3 (C), 129.9 (CH), 127.9 (CH), 103.3 (CH), 98.0 (CH$_2$), 73.6 (CH), 73.5 (CH), 70.1 (CH$_2$), 57.1 (OCH$_3$), 56.0 (OCH$_3$), 21.6 (CH$_3$).

IR $\nu_{\text{max}}$ 3422 (broad), 2940, 1595, 1462, 1422, 1357, 1235, 1176, 1126, 967, 815 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 442 (M$^+$, 3%), 410 (7), 380 (4), 227 (20), 208 (22), 167 (65), 91 (92), 45 (100).

HRMS Found M$^+$, 442.1293. C$_{20}$H$_{26}$O$_9$S requires 442.1298.

Specific rotation $[\alpha]_D -13.9^\circ$ (c 0.98, CHCl$_3$).

(1R,2R)-2,3-Epoxy-1-(3,5-dimethoxy-4-methoxymethoxyphenyl)propanol (90b)

A solution of tosylate 107 (301 mg, 6.8 mmol) in dry methanol (20 mL) was treated with K$_2$CO$_3$ (98 mg of anhydrous material, 7.1 mol). The resulting suspension was stirred vigorously at 18 °C under an atmosphere of nitrogen for 3 h then poured into water (20 mL), and the product extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (1 x 30 mL) then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 7:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions [$R_f$ 0.3(5)], an off-white solid. Recrystallisation (from DCM-hexane) of this material afforded the title compound 90b (160 mg, 88%) as a white, crystalline solid, m.p. 71-73 °C, in >95% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, $R_t$ 16.1 min).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

^1^H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \): 6.63 (s, 2H), 5.11 (s, 2H), 4.40 (d, \( J \) 4.9 Hz, 1H), 3.85 (s, 6H), 3.59 (s, 3H), 3.20 (m, 1H), 2.84 (m, 2H), 2.56 (broad s, OH).

^1^C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \): 153.5 (C), 136.3 (C), 134.1 (C), 103.2 (CH), 98.1 (CH\textsubscript{2}), 74.4 (CH), 57.1 (CH), 56.0 (OCH\textsubscript{3}), 55.8 (OCH\textsubscript{3}), 45.4 (CH\textsubscript{2}).

IR \( \nu_{\text{max}} \) 3433 (broad), 2940, 1593, 1505, 1462, 1420, 1331, 1230, 1126, 969, 924 cm\textsuperscript{-1}.

Mass spectrum (70 eV) \( m/z \) 270 (M\textsuperscript{+}, 27%), 240 (10), 195 (16), 177 (23), 165 (32), 109 (12), 45 (100).

HRMS Found M\textsuperscript{+}, 270.1102. C\textsubscript{13}H\textsubscript{18}O\textsubscript{6} requires 270.1103.

Elemental analysis Found C, 57.90; H, 7.00. C\textsubscript{13}H\textsubscript{18}O\textsubscript{6} requires C, 57.77; H, 6.71%.

Specific rotation \([\alpha]_D\) -5.4° (c 1.28, CHCl\textsubscript{3}).

\((1S,2R)-4-Benzyloxy-3-[2,3-epoxy-1-(3,5-dimethoxy-4-methoxymethoxyphenyl)propoxy]benzaldehyde (88c)\)

\[
\begin{align*}
\text{89} & \quad + \quad \text{DIAD, PPh}_3 \\
& \quad \text{THF-toluene} \\
18 \, ^\circ \text{C, 24 h} & \quad \text{88c}
\end{align*}
\]

A magnetically stirred solution of aldehyde 89 (111 mg, 0.5 mmol) and DIAD (98 µL, 0.5 mmol) in dry toluene (10 mL) maintained at 18 °C under an atmosphere of nitrogen was treated, dropwise, with a solution of PPh\textsubscript{3} (130 mg, 0.5 mmol) and epoxide 90b (101 mg, 0.4 mmol) in dry THF-toluene (2 mL of a 1:1 v/v mixture). The ensuing mixture was stirred at 18 °C for 24 h then the solvent was removed under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 3:2 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions (\( R_t \) 0.3), the title compound 88c (99 mg, 60%) as a white, crystalline solid, m.p. 50-52 °C, in >95% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 0.8 mL/min and with UV peak detection at 254 nm, \( R_t \) 39.9 min).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^1$H NMR (300 MHz, CDCl$_3$) δ: 9.77 (s, 1H, CHO), 7.45-7.36 (m, 7H, ArH), 7.02 (d, J 8.7 Hz, 1H, ArH), 6.68 (s, 2H, ArH), 5.19 (m, 3H), 5.10 (s, 2H), 3.77 (s, 6H), 3.58 (s, 3H), 3.34 (m, 1H), 2.89 (dd, J 5.2 and 2.6 Hz, 1H), 2.80 (dd, J 5.2 and 3.8 Hz, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 190.5 (CHO), 154.8 (C), 153.5 (C), 147.8 (C), 136.0 (C), 134.4 (C), 133.2 (C), 130.1 (C), 128.6 (CH), 128.2 (CH), 127.1 (CH), 115.8 (CH), 113.0 (CH), 103.7 (CH), 98.1 (CH$_2$), 80.3 (CH), 70.7 (CH$_2$), 57.1 (CH), 56.0 (OCH$_3$), 54.2 (OCH$_3$), 45.1 (CH$_2$).

IR $\nu_{\max}$ 2939, 2840, 1687, 1596, 1507, 1462, 1436, 1272, 1128, 967, 739, 698 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 480 (M$^+$, 7%), 450 (6), 272 (11), 253 (96), 195 (47), 91 (95), 45 (100).

HRMS Found M$^+$, 480.1777. C$_{21}$H$_{28}$O$_8$ requires 480.1784.

Elemental analysis Found C, 67.07; H, 5.66. C$_{21}$H$_{28}$O$_8$ requires C, 67.49; H, 5.87%.

Specific rotation $[\alpha]_D +11.9^\circ$ (c 0.56, CHCl$_3$).

(1S,2R)-4-Hydroxy-3-[2,3-epoxy-1-(3,5-dimethoxy-4-methoxymethoxyphenyl) propoxy]benzaldehyde (88d)

A solution of compound 88c (60 mg, 0.13 mmol) in ethyl acetate (5 mL) was treated with 5% Pd-C (6 mg) and the resulting mixture stirred magnetically under a hydrogen atmosphere at 18 °C for 9 h. The reaction mixture was then filtered and the filtrate concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 3:2 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions [$R_t$ 0.3(5)], the title compound 88d (34 mg, 71%) as an amorphous solid in >95% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, $R_t$ 25.5 min).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 9.71 (s, 1H, CHO), 8.10 (broad s, OH), 7.52 (dd, $J$ 8.2 and 1.9 Hz, 1H, ArH), 7.32 (d, $J$ 1.9 Hz, 1H, ArH), 7.05 (d, $J$ 8.2 Hz, 1H, ArH), 6.63 (s, 2H, ArH), 5.14 (s, 2H), 4.99 (d, $J$ 2.3 Hz, 1H), 3.85 (s, 6H), 3.61 (s, 3H), 3.38 (m, 1H), 3.25 (m, 1H), 2.96 (t, $J$ 4.4 Hz, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 190.4 (CHO), 154.5 (C), 153.8 (C), 145.9 (C), 134.8 (C), 132.2 (C), 129.4 (C), 128.8 (CH), 119.8 (CH), 116.6 (CH), 103.5 (CH), 98.1 (CH$_2$), 81.9 (CH), 57.1 (CH), 56.1 (OCH$_3$), 54.7 (OCH$_3$), 44.7 (CH$_2$).

IR $\nu_{\text{max}}$ 3360 (broad), 2939, 1684, 1595, 1507, 1462, 1443, 1287, 1126, 964 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 390 (M$^+$, 100%), 345 (12), 253 (40), 195 (49), 149 (41), 137 (30), 99 (28).

HRMS Found M$^+$, 390.1312. C$_{20}$H$_{22}$O$_8$ requires 390.1315.

Specific rotation $[\alpha]_D +142.4^\circ$ (c 0.41, CHCl$_3$).

(2S,3S)-3-(3,5-Dimethoxy-4-methoxymethoxyphenyl)-2-hydroxymethyl-2,3-dihydro-1,4-benzodioxin-6-carbaldehyde (86b)

A solution of compound 88d (26 mg, 0.06 mmol) in dry methanol (5 mL) was treated with K$_2$CO$_3$ (10 mg of anhydrous material, 0.07 mmol) and the resulting suspension was stirred magnetically at 18 °C for 0.75 h. The methanol was then removed under reduced pressure and the residue treated with cold HCl (2 mL of a 0.1 M aqueous solution), extracted with ethyl acetate (4 x 5 mL), washed with brine (1 x 10 mL) then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 3:2 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions ($R_f$ 0.4), the title compound 86b (17 mg, 70%) as an amorphous solid in >95% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v
isopropyl alcohol - hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, $R_t$ 27.2 min).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 9.83 (s, 1H, CHO), 7.53-7.50 (m, 2H, ArH), 7.12 (d, $J$ 8.7 Hz, 1H, ArH), 6.74 (s, 2H, ArH), 5.15 (s, 2H), 4.95 (d, $J$ 8.9 Hz, 1H), 4.72 (dd, $J$ 13.0 and 3.0 Hz, 1H), 4.41 (dd, $J$ 12.9 and 1.5 Hz, 1H), 4.24 (m, 1H), 3.88 (s, 6H), 3.62 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 190.5 (CHO), 155.4 (C), 153.5 (C), 149.3 (C), 134.5 (C), 134.0 (C), 131.9 (C), 125.5 (CH), 122.9 (CH), 121.3 (CH), 103.6 (CH), 98.1 (CH$_2$), 85.7 (CH), 74.9 (CH), 74.8 (CH$_2$), 57.2 (OCH$_3$), 56.1 (OCH$_3$).

IR $\nu_{\text{max}}$ 3436 (broad), 2925, 1690, 1595, 1502, 1463, 1314, 1279, 1263, 1128, 959 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 390 (M$^+$, 95%), 346 (16), 316 (11), 253 (18), 195 (83), 149 (73), 57 (100).

HRMS Found M$^+$, 390.1310. C$_{20}$H$_{22}$O$_8$ requires 390.1315.

Specific rotation $[\alpha]_D$ -48.4° (c 0.32, CHCl$_3$).

5-[(1E)-2-[(2S,3S)-2,3-Dihydro-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]ethenyl]-1,3-benzenediol [(−)-Aphanol, 26]

A magnetically stirred solution of compound 86b (11 mg, 0.03 mmol), DIPEA (20 µL, 0.12 mmol) and DMAP (0.5 mg, catalyst) in DCM (2 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated with MOMCl (8 µL, 0.1 mmol). The resulting mixture was warmed to 18 °C, stirred at this temperature for 3 h then poured into water (5 mL), and the DCM layer separated. The aqueous layer was extracted with additional DCM (2 x 5 mL) and the combined organic phases were washed with brine.
(1 x 10 mL) then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was passed through a short pad of silica using ethyl acetate - hexane (3:2 v/v mixture), and the eluent concentrated under reduced pressure then dried under high vacuum to afford compound 86c (10.5 mg, 85%) as a light-brown gum. This material was used, as obtained, in the next step of the reaction sequence.

A solution of compound 86c (10.5 mg, 0.02 mmol) in dry toluene (5 mL) was treated with phosphonium salt 48 (20 mg, 0.04 mmol) and CsF (8 mg, 0.05 mmol). The ensuing suspension was heated at reflux for 6 h then cooled to 18 °C and treated with water (5 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL), and the combined organic phases were washed with brine (1 x 10 mL) then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was passed through a short pad of silica using ethyl acetate - hexane (3:2 v/v mixture), and concentration of the highly UV active eluent (Rf 0.5) afforded compound 108 (6 mg, 41%), which was used directly in the next step of the reaction sequence.

A magnetically stirred solution of compound 108 (6 mg, 0.01 mmol) in MeOH (2 mL) maintained under an atmosphere of nitrogen was treated with AcCl (10 µL) and the mixture stirred at 18 °C for 20 h then the MeOH removed under reduced pressure. HCl (5 mL of a 0.1 M aqueous solution) was added to the residue which was then extracted with ethyl acetate (3 x 5 mL). The combined organic phases were dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 4:1 v/v ethyl acetate - hexane elution) to afford, upon concentration of a highly UV active band [Rf 0.3(5)], a brown solid. Purification of this material by HPLC (using a 300 x 7.8 mm C$_{18}$ Alltech Alltima column, 50:49.95:0.05 v/v/v H$_2$O-MeOH-AcOH elution, solvent flow rate of 5 mL/min, UV peak detection at 325 nm, R$_t$ 15.05 min), afforded the title compound 26$^{10}$ as a light-brown solid (2.7 mg, 65%) in >95% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:1 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 1.2 mL/min and with UV peak detection at 325 nm, R$_t$ 12.1 min).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^1$H NMR (500 MHz, CD$_3$COCD$_3$) $\delta$: 8.25 (broad s, 2H, OH), 7.42 (broad s, 1H, OH), 7.15 (d, $J$ 1.9 Hz, 1H, ArH), 7.10 (dd, $J$ 8.3 and 2.0 Hz, 1H, ArH), 7.04 (d, $J$ 16.3 Hz, 1H), 6.96 (d, $J$ 16.3 Hz, 1H), 6.91 (d, $J$ 8.3 Hz, 1H, ArH), 6.84 (s, 2H, ArH), 6.57 (d, $J$ 1.9 Hz, 2H, ArH), 6.30 (t, $J$ 1.9 Hz, 1H, ArH), 4.99 (d, $J$ 7.8 Hz, 1H), 4.16 (m, 1H), 4.06 (t, 1H, OH), 3.87 (s, 6H), 3.76 (m, 1H), 3.55 (m, 1H).

$^{13}$C NMR (125 MHz, CD$_3$COCD$_3$) $\delta$: 159.3 (C), 148.5 (C), 144.5 (C), 144.4 (C), 140.3 (C), 137.0 (C), 131.7 (C), 128.4 (CH), 127.8 (CH and C), 120.3 (CH), 117.6 (CH), 115.0 (CH), 105.8 (CH), 105.5 (CH), 102.5 (CH), 79.2 (CH), 77.3 (CH), 61.6 (CH$_2$), 56.4 (OCH$_3$).

IR $\nu$_{max} 3370 (broad), 2925, 2920, 1595, 1505, 1463, 1270, 1115, 1048, 831 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 452 (M$^+$, 100%), 438 (40), 346 (18), 210 (82), 167 (60), 149 (32), 91 (67).

HRMS Found M$^+$, 452.1466. C$_{25}$H$_{24}$O$_8$ requires 452.1471.

Specific rotation $[\alpha]_D$ -20.1$^\circ$ (c 0.21, MeOH) [lit.$^{10}$ -21.8$^\circ$ (c 0.13, MeOH)].

(1S,2S)-1-(3,5-Dimethoxy-4-methoxymethoxyphenyl)-2,3-dihydroxypropanol (ent-104)

A mixture of $t$-BuOH (15 mL), water (15 mL), AD mix-$\alpha$ (3 g) and methanesulphonamide (180 mg, 2 mmol) was stirred magnetically at 18 $^\circ$C until both phases were clear. The ensuring mixture was cooled to 0 $^\circ$C (ice-water bath), treated with allylic alcohol 103 (520 mg, 2 mmol) then vigorously stirred at 0 $^\circ$C for 48 h. After this time, the reaction was quenched, at 0 $^\circ$C, by the addition of Na$_2$SO$_3$ (3.1 g) then warmed to 18 $^\circ$C and stirred at this temperature for 0.5 h before being extracted with ethyl acetate (4 x 50 mL). The combined organic extracts were washed with KOH (1 x 50 mL of a 2 M aqueous solution) and water (1 x 50 mL) then dried (Na$_2$SO$_4$),
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

filtered, and concentrated under reduced pressure. The resulting solid was purified by column chromatography (silica, 9:1 v/v diethyl ether - methanol elution) to afford, after concentration of the appropriate fractions \([R_f 0.2(5)]\), an off-white solid. Recrystallisation (from methanol-DCM) of this material afforded the title compound ent-104 (450 mg, 78%) as a white, crystalline solid, m.p. 73-75 °C, in >95% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, \(R_t 14.1\) min).

\(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta: 6.61 (s, 2H, ArH), 5.11 (s, 2H), 4.65 (d, J 6.5 Hz, 1H), 3.85 (s, 6H), 3.76 (m, 1H), 3.67 (dd, J 11.4 and 3.3 Hz, 1H), 3.60 (s, 3H), 3.55 (dd, J 11.4 and 4.8 Hz, 1H), 2.46 (broad s, OH).

\(^13C\) NMR (75 MHz, CDCl\(_3\)) \(\delta: 153.3 (C), 136.8 (C), 133.8 (C), 103.4 (CH), 97.9 (CH\(_2\)), 75.8 (CH), 74.7 (CH), 63.2 (CH\(_2\)), 57.1 (OCH\(_3\)), 56.0 (OCH\(_3\)).

IR \(\nu_{\text{max}}\) 3412 (broad), 2940, 2842, 1614, 1519, 1462, 1328, 1215, 1114, 1032, 914 cm\(^{-1}\).

Mass spectrum (70 eV) \(m/z\) 288 (M\(^+\), 11%), 239 (21), 227 (65), 183 (88), 167 (100), 123 (45), 77 (15).

HRMS Found M\(^+\), 288.1209. \(\text{C}_{13}\text{H}_{20}\text{O}_{7}\) requires 288.1209.

Elemental analysis Found C, 54.20; H, 7.10. \(\text{C}_{13}\text{H}_{20}\text{O}_{7}\) requires C, 54.16; H, 6.99%.

Specific rotation \([\alpha]_D^\circ +23.9^\circ\) (c 0.97, CHCl\(_3\)).

\((1R,2R)-1-(2-Bromo-4-hydroxy-3,5-dimethoxyphenyl)-2,3-dihydroxypropanol (ent-106)\)

A magnetically stirred solution of triol ent-104 (20 mg, 0.07 mmol) in DCM (5 mL) maintained at 18 °C was treated, in one portion, with pyridinium hydrobromide
perbromide (22 mg, 0.07 mmol) then stirred for 10 minutes after which TLC analysis indicated no starting material remained. Consequently, the reaction mixture was quenched with sodium bisulphite (0.5 mL of a 1 M aqueous solution) then treated with NaHCO₃ (2 mL of a saturated solution). The DCM layer was separated, and the aqueous layer extracted with additional DCM (2 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL) then dried (Na₂SO₄), filtered and concentrated under reduced pressure and the residue subjected to high vacuum for 4 h to afford compound \textit{ent-105} (21 mg, 79%) as a clear, colourless oil. This material was used as obtained in the next step.

A solution of ether \textit{ent-105} (21 mg, 0.06 mmol) in MeOH (5 mL) was treated with HCl (1 drop of conc. material) and the ensuing mixture stirred magnetically at 18 °C for 18 h. The methanol was then removed under reduced pressure, water (10 mL) was added to the residue and the product extracted with ethyl acetate (3 x 10 mL). The combined organic phases were then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 19:1 v/v ethyl acetate - methanol elution) to afford, after concentration of the appropriate fractions (\textit{R}₁ 0.4), a white solid. Recrystallisation (from methanol-DCM) of this material afforded the \textit{title compound} \textit{ent-106} (18 mg, 93%) as colourless crystals, m.p. 172-174 °C. The structure of this compound was determined by single crystal X-ray analysis (\textit{Appendix A.4}).

\textbf{\textit{1H NMR}} (300 MHz, CD₃OD) \(\delta\): 7.06 (s, 1H, ArH), 5.04 (d, \(J\) 3.8 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.76 (m, 1H), 3.60 (m, 2H).

\textbf{\textit{13C NMR}} (75 MHz, CD₃OD) \(\delta\): 148.4 (C), 144.6 (C), 139.9 (C), 132.2 (C), 108.3 (C), 107.6 (C), 75.0 (CH), 72.2 (CH), 63.8 (CH₂), 59.7 (OCH₃), 55.6 (OCH₃).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

(15,2S)-1-(3,5-Dimethoxy-4-methoxymethoxyphenyl)-1,2-dihydroxypropyl tosylate (ent-107)

A magnetically stirred solution of triol ent-104 (320 mg, 1.1 mmol) in dry pyridine (15 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, in one portion, with TsCl (230 mg, 1.2 mmol). The cooling bath was removed and the mixture was allowed to warm to 18 °C, stirred at this temperature for 18 h then diluted with ethyl acetate (35 mL) and washed with cold HCl (2 x 30 mL of a 0.1 M aqueous solution). The organic phase was then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resulting gum was purified by column chromatography (silica, 7:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions [Rf 0.2(5)], the title compound ent-107 (361 mg, 73%) as a white, crystalline solid, m.p. 67-69 °C.

¹H NMR (300 MHz, CDCl₃) δ: 7.76 (d, J 8.2 Hz, 2H, ArH), 7.34 (d, J 8.2 Hz, 2H, ArH), 6.58 (s, 2H, ArH), 5.10 (s, 2H), 4.65 (d, J 6.2 H, 1H), 4.00-3.80 (m, 3H), 3.83 (s, 6H), 3.59 (s, 3H), 2.55 (broad s, OH), 2.44 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ: 153.3 (C), 145.2 (C), 135.8 (C), 133.9 (C), 132.3 (C), 129.9 (CH), 127.9 (CH), 103.2 (CH), 98.0 (CH₂), 73.5(3) (CH), 73.4(6) (CH), 70.2 (CH₂), 57.1 (OCH₃), 56.0 (OCH₃), 21.6 (CH₃).

IR νmax 3423 (broad), 2940, 1595, 1460, 1426, 1237, 1175, 1127, 968, 815, 667 cm⁻¹.

Mass spectrum (70 eV) m/z 442 (M⁺, 5%), 410 (7), 380 (7), 227 (51), 183 (57), 91 (63), 45 (100).

HRMS Found M⁺, 442.1295. C₂₀H₂₆O₈S requires 442.1298.

Specific rotation [α]D +13.5° (c 0.82, CHCl₃).
A solution of tosylate `ent-107` (300 mg, 6.8 mmol) in dry methanol (20 mL) was treated with K$_2$CO$_3$ (98 mg of anhydrous material, 7.1 mol). The resulting suspension was stirred vigorously at 18 °C under an atmosphere of nitrogen for 3 h then poured into water (20 mL), and the product extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine (1 x 30 mL) then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 7:3 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions [R$_f$ 0.3(5)], an off-white solid. Recrystallisation (from DCM-hexane) yielded the title compound `ent-90b` (149 mg, 82%) as a white, crystalline solid, m.p. 71-73 °C, in >95% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, R$_t$ 20.4 min).

$^1$H NMR (300 MHz, CDCl$_3$) δ: 6.60 (s, 2H), 5.12 (s, 2H), 4.42 (t, J 5.0 Hz, 1H), 3.86 (s, 6H), 3.60 (s, 3H), 3.21 (m, 1H), 2.84 (m, 2H), 2.43 (d, J 4.9 Hz, OH).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 153.5 (C), 136.3 (C), 134.2 (C), 103.2 (CH), 98.1 (CH$_2$), 74.4 (CH), 57.2 (CH), 56.1 (OCH$_3$), 55.8 (OCH$_3$), 45.4 (CH$_2$).

IR ν$_{max}$ 3437 (broad), 2942, 1593, 1505, 1462, 1421, 1331, 1231, 1126, 1079, 969 cm$^{-1}$.

Mass spectrum (70 eV) m/z 270 (M$^+$, 45%), 240 (10), 197 (31), 165 (45), 45 (100).

HRMS Found M$^+$, 270.1101. C$_{13}$H$_{18}$O$_6$ requires 270.1103.

Elemental analysis Found C, 58.31; H, 6.96. C$_{13}$H$_{18}$O$_6$ requires C, 57.77; H, 6.71%.

Specific rotation [α]$_D$ +5.3° (c 0.68, CHCl$_3$).
Details of the experimental work described in Chapters 2, 3 and 4

(1R,2S)-4-Benzyl oxy-3-[2,3-epoxy-1-(3,5-dimethoxy-4-methoxymethoxyphenyl) propoxy]benzaldehyde (ent-88c)

A magnetically stirred solution of aldehyde 89 (110 mg, 0.5 mmol) and DIAD (98 µL, 0.5 mmol) in dry toluene (10 mL) maintained at 18 °C under an atmosphere of nitrogen was treated, dropwise, with a solution of PPh₃ (130 mg, 0.5 mmol) and epoxide ent-90b (0.10 g, 0.4 mmol) in dry THF-toluene (2 mL of a 1:1 v/v mixture). The ensuing mixture was stirred at 18 °C for 24 h then the solvent was removed under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 3:2 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions (R₆ 0.3), the title compound ent-88c (100 mg, 61%) as a white, crystalline solid, m.p. 50-52 °C, in >95% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 0.8 mL/min and with UV peak detection at 254 nm, Rₖ 41.2 min).

¹H NMR (300 MHz, CDCl₃) δ: 9.77 (s, 1H, CHO), 7.45-7.34 (m, 7H, ArH), 7.03 (d, J 8.8 Hz, 1H, ArH), 6.68 (s, 2H, ArH), 5.19 (m, 3H), 5.10 (s, 2H), 3.77 (s, 6H), 3.58 (s, 3H), 3.34 (m, 1H), 2.89 (dd, J 5.2 and 2.6 Hz, 1H), 2.81 (dd, J 5.2 and 3.8 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 190.5 (CHO), 154.8 (C), 153.4 (C), 147.8 (C), 136.0 (C), 134.4 (C), 133.2 (C), 130.1 (C), 128.6 (CH), 128.2 (CH), 127.1 (CH), 115.7 (CH), 112.9 (CH), 103.6 (CH), 98.0 (CH₂), 80.3 (CH), 70.7 (CH₂), 57.1 (CH), 56.0 (OCH₃), 54.2 (OCH₃), 45.1 (CH₂).

IR νₘₐₓ 2939, 1686, 1595, 1505, 1462, 1436, 1267, 1127, 966, 698 cm⁻¹.

Mass spectrum (70 eV) m/z 480 (M⁺, 13%), 450 (100), 405 (35), 272 (53).

HRMS Found M⁺, 480.1772. C₂₉H₂₅O₈ requires 480.1784.

Elemental analysis Found C, 66.96; H, 5.90. C₂₇H₂₈O₈ requires C, 67.49; H, 5.87%.
Specific rotation $[\alpha]_D -14.2^\circ$ (c 1.87, CHCl$_3$).

$(1R,2S)$-4-Hydroxy-3-[2,3-epoxy-1-(3,5-dimethoxy-4-methoxymethoxyphenyl) propoxy]benzaldehyde (ent-88d)

A solution of compound ent-88c (68 mg, 0.14 mmol) in ethyl acetate (5 mL) was treated with 5% Pd-C (7 mg) and the resulting mixture stirred magnetically under a hydrogen atmosphere at 18 °C for 9 h. The reaction mixture was then filtered and the filtrate concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 3:2 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions [$R_f 0.3(5)$], the title compound ent-88d (38 mg, 70%) as an amorphous solid in >95% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, $R_t 50.7$ min).

$^1$H NMR (300 MHz, CDCl$_3$) δ: 9.72 (s, 1H, CHO), 8.07 (broad s, OH), 7.54 (dd, $J$ 8.4 and 1.9 Hz, 1H, ArH), 7.33 (d, $J$ 1.9 Hz, 1H, ArH), 7.07 (d, $J$ 8.2 Hz, 1H, ArH), 6.63 (s, 2H, ArH), 5.15 (s, 2H), 4.99 (d, $J$ 2.3 Hz, 1H), 3.87 (s, 6H), 3.62 (s, 3H), 3.39 (m, 1H), 3.28 (m, 1H), 2.98 (t, $J$ 4.5 Hz, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 190.4 (CHO), 154.6 (C), 153.8 (C), 146.0 (C), 134.9 (C), 132.3 (C), 129.5 (C), 128.9 (CH), 120.1 (CH), 116.7 (CH), 103.5 (CH), 98.1 (CH$_2$), 82.0 (CH), 57.2 (CH), 56.2 (OCH$_3$), 54.7 (OCH$_3$), 44.7 (CH$_2$).

IR $\nu_{\text{max}}$ 3361 (broad), 2926, 1684, 1595, 1507, 1463, 1443, 1287, 1127, 965 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 390 (M$^{+}$, 38%), 253 (100), 195 (45), 149 (30), 137 (25), 77 (12).

HRMS Found M$^{+}$, 390.1315. C$_{20}$H$_{22}$O$_8$ requires 390.1315.
Specific rotation $[\alpha]_D - 139.2^\circ$ (c 0.64, CHCl$_3$).

**(2R,3R)-3-(3,5-Dimethoxy-4-methoxymethoxyphenyl)-2-hydroxymethyl-2,3-dihydro-1,4-benzodioxin-6-carbaldehyde (ent-86b)**

A solution of compound *ent-88d* (28 mg, 0.07 mmol) in dry methanol (5 mL) was treated with K$_2$CO$_3$ (11 mg of anhydrous material, 0.07 mmol) and the resulting suspension was stirred magnetically at 18 °C for 0.75 h. The methanol was then removed under reduced pressure and the residue treated with cold HCl (2 mL of a 0.1 M aqueous solution). The ensuing mixture was extracted with ethyl acetate (4 x 5 mL), and the combined organic phases were washed with brine (1 x 10 mL) then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (silica, 3:2 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions ($R_f$ 0.4), the *title compound* *ent-86b* (19 mg, 68%) as an amorphous white solid in >91% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:3 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 1 mL/min and with UV peak detection at 254 nm, $R_t$ 47.1 min).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 9.83 (s, 1H, CHO), 7.53-7.51 (m, 2H, ArH), 7.10 (d, $J$ 8.9 Hz, 1H, ArH), 6.74 (s, 2H, ArH), 5.15 (s, 2H), 4.95 (d, $J$ 8.8 Hz, 1H), 4.72 (dd, $J$ 12.9 and 2.9 Hz, 1H), 4.40 (dd, $J$ 13.0 and 1.6 Hz, 1H), 4.23 (m, 1H), 3.88 (s, 6H), 3.62 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 190.4 (CHO), 155.4 (C), 153.5 (C), 149.3 (C), 134.6 (C), 134.0 (C), 131.9 (C), 125.5 (CH), 122.9 (CH), 121.3 (CH), 103.6 (CH), 98.1 (CH$_2$), 85.7 (CH), 74.9 (CH), 74.8 (CH$_2$), 57.2 (OCH$_3$), 56.1 (OCH$_3$).

$\text{IR } v_{max}$ 3434 (broad), 2937, 1690, 1596, 1502, 1463, 1314, 1262, 1127, 959 cm$^{-1}$. 

![Diagram of chemical structure](image)
Mass spectrum (70 eV) $m/z$ 390 ($M^+$, 100%), 346 (15), 316 (10), 253 (20), 195 (66), 149 (35), 69 (26).

HRMS Found $M^+$, 390.1314. $C_{20}H_{22}O_8$ requires 390.1315.

Specific rotation $[\alpha]_D +43.6^\circ$ (c 0.28, CHCl$_3$).

5-[(1E)-2-[(2R,3R)-2,3-Dihydro-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]ethenyl]-1,3-benzenediol [(+)-Aiphanol, ent-26]

A magnetically stirred solution of compound ent-86b (13 mg, 0.03 mmol), DIPEA (20 µL, 0.12 mmol) and DMAP (0.5 mg, catalyst) in DCM (2 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated with MOMCl (8 µL, 0.1 mmol). The ensuing mixture was warmed to 18 °C and stirred at this temperature for 3 h then poured into water (5 mL), the DCM layer separated, and the aqueous layer extracted with additional DCM (2 x 5 mL). The combined organic phases were washed with brine (1 x 10 mL) then dried (Na$_2$SO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was passed through a short pad of TLC-grade silica using ethyl acetate - hexane (3:2 v/v mixture), and the eluent concentrated under reduced pressure and then dried under high vacuum to afford compound ent-86c (10 mg, 81%) as a light-brown gum. This material was used, as obtained, in the next step of the reaction sequence.

A solution of compound ent-86c (10 mg, 0.02 mmol) in dry toluene (5 mL) was treated with phosphonium salt 48 (20 mg, 0.04 mmol) and CsF (8 mg, 0.05 mmol). The ensuing suspension was heated at reflux for 6 h then cooled to 18 °C and treated with water (5 mL). The separated aqueous phase was extracted with ethyl acetate (3 x 5
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

mL), and the combined organic phases were washed with brine (1 × 10 mL) then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was passed through a short pad of TLC-grade silica using ethyl acetate - hexane (3:2 v/v mixture), and concentration of the highly UV active band (Rₚ 0.5) afforded compound ent-108 (5.8 mg, 39%), which was used directly in the next step of the reaction sequence.

A magnetically stirred solution of compound ent-108 (5.8 mg, 0.01 mmol) in MeOH (2 mL) maintained under an atmosphere of nitrogen was treated with AcCl (10 µL) and the ensuing mixture stirred at 18 °C for 20 h then the MeOH removed under reduced pressure. HCl (5 mL of a 0.1 M aqueous solution) was added to the residue, which was then extracted with ethyl acetate (3 × 5 mL). The combined organic phases were then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to column chromatography (silica, 4:1 v/v ethyl acetate - hexane elution) to afford, upon concentration of a highly UV active band [Rₚ 0.3(5)], a light-brown solid. Purification of this material by HPLC (using a 300 x 7.8 mm C₁₈ Alltech Alltima column, 50:49.95:0.05 v/v/v H₂O-MeOH-AcOH elution, solvent flow rate of 5 mL/min, UV peak detection at 325 nm, Rₜ 15.09 min) afforded the title compound ent-26 (2.3 mg, 56%) as a light-brown solid in >91% e.e. (as determined by chiral HPLC analysis using CHIRALPAK® AS-H 250 x 4.6 mm column, 1:1 v/v isopropyl alcohol - hexane elution at a solvent flow rate of 1.2 mL/min and with UV peak detection at 325 nm, Rₜ 19.8 min).

¹H NMR (500 MHz, CD₃COCD₃) δ: 8.25 (broad s, 2H, OH), 7.40 (broad s, 1H, OH), 7.15 (d, J 2.4 Hz, 1H, ArH), 7.10 (dd, J 8.3 and 2.0 Hz, 1H, ArH), 7.04 (d, J 16.4 Hz, 1H), 6.96 (d, J 16.4 Hz, 1H), 6.91 (d, J 8.3 Hz, 1H, ArH), 6.86 (s, 2H, ArH), 6.56 (d, J 1.9 Hz, 2H, ArH), 6.30 (t, J 1.9 Hz, 1H, ArH), 4.99 (d, J 7.8 Hz, 1H), 4.15 (m, 1H), 4.08 (t, 1H, OH), 3.88 (s, 6H), 3.75 (m, 1H), 3.54 (m, 1H).

¹³C NMR (125 MHz, CD₃COCD₃) δ: 159.3 (C), 148.5 (C), 144.5 (C), 144.4 (C), 140.3 (C), 137.0 (C), 131.7 (C), 128.4 (CH), 127.8 (CH and C), 120.3 (CH), 117.6 (CH), 115.0 (CH), 105.8 (CH), 105.5 (CH), 102.5 (CH), 79.2 (CH), 77.3 (CH), 61.6 (CH₂), 56.4 (OCH₃).

IR ν max 3370 (broad), 2925, 1596, 1504, 1464, 1273, 1115, 1007, 835 cm⁻¹.
Mass spectrum (70 eV) m/z 452 (M⁺⁺, 15%), 438 (5), 346 (10), 210 (31), 149 (37), 91 (85), 57 (100).

HRMS Found M⁺⁺, 452.1469. C_{25}H_{24}O_8 requires 452.1471.

Specific rotation [α]_D +19.3° (c 0.17, MeOH).
5.4 Experimental procedures associated with work described in Chapter 4: Studies directed towards the synthesis of diversanol

General procedure for the extraction of (1S,2R)-3-Methyl-3,5-cyclohexadiene-1,2-diol (109)

Diol 109, provided as a solution in KH₂PO₄/K₂HPO₄ 0.1 M aqueous buffer (pH 7), was stored in a 250 mL plastic container at -70 °C. Prior to extraction, the broth (ca. 60 mL) was thawed out of direct sunlight then poured into a separating funnel and diluted with ethyl acetate (150 mL) and brine (150 mL). The separated aqueous phase was extracted with ethyl acetate (4 x 100 mL) and the combined organic extracts were then dried (MgSO₄), filtered, and concentrated under reduced pressure (water bath temperature 30 °C) to afford diol 109 as an off-white solid (5.40 g). This unstable material was either used immediately or stored in a plastic container at -70 °C.

(1S,2R)-3-Methyl-3-cyclohexene-1,2-diol (115)

\[
\text{109} \xrightarrow{5\% \text{ Rh on Al₂O₃, H₂, EtOH, 18 °C, 4 h}} \text{115}
\]

A solution of diol 109 (3.50 g, 27.8 mmol) in absolute ethanol (80 mL) was treated with 5% Rh on alumina (35 mg) and the mixture was stirred magnetically under a hydrogen atmosphere at 18 °C. The reaction was monitored by TLC and found to be complete in 4 h. Filtration of the slurry through a pad of Celite™ and concentration of the filtrate under reduced pressure gave an off-white solid that was subjected to flash chromatography (silica, 8.5:1.5 v/v diethyl ether - hexane elution). Concentration of the appropriate fractions (Rf 0.3) then afforded the title compound 115 (3.20 g, 90%) as a white, crystalline solid, m.p. 74-75 °C (lit. 73-74 °C; lit. 82-83 °C).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

\( ^1H \text{ NMR} \) (300 MHz, CDCl\(_3\)) \( \delta: 5.58 \text{ (m, } 1H), 3.95 \text{ (d, } J=4.3 \text{ Hz, } 1H), 3.78 \text{ (m, } 1H), 2.20-1.62 \text{ (complex m, } 6H), 1.80 \text{ (s, } 3H).\)

\( ^{13}C \text{ NMR} \) (75 MHz, CDCl\(_3\)) \( \delta: 133.8 \text{ (C)}, 125.8 \text{ (CH)}, 70.5 \text{ (CH)}, 69.9 \text{ (CH)}, 25.8 \text{ (CH\(_2\))}, 24.3 \text{ (CH\(_2\))}, 21.2 \text{ (CH\(_3\))}.\)

\( \text{IR } \nu_{\text{max}} \) 3271 (broad), 2936, 2873, 1451, 1340, 1295, 1127, 1051, 982, 797 cm\(^{-1}\).

\( \text{Mass spectrum} \) (70 eV) \( m/z \) 128 (M\(^+\), 13%), 110 (24), 84 (100), 69 (19), 55 (41).

\( \text{HRMS} \) Found M\(^+\), 128.0834. \( \text{C}_7\text{H}_7\text{O}_2 \) requires 128.0837.

\( \text{Specific rotation} \) \([\alpha]_D^o -148.4^o \text{ (c } 0.58, \text{ CHCl}_3)\) [lit.\(^{22}\) -151.7\(^o \text{ (c } 0.6, \text{ CHCl}_3)].\)

2-Bromo-4-hydroxybenzaldehyde

A magnetically stirred mixture of \( m \)-bromophenol (8.0 g), Ca(OH)\(_2\) (14.4 g), Na\(_2\)CO\(_3\) (16.8 g) and water (120 mL) maintained at 75 °C in a three-neck flask equipped with a reflux condenser was treated, portion-wise over 1.5 h, with chloroform (8 mL). Stirring was continued for 0.5 h without heating and then for 2 h with heating (oil bath temperature 75 °C). The reaction mixture was acidified with HCl (5 M aqueous solution) and then steam distilled until ca. 1.5 L of distillate had been collected. The hot distillate was treated with charcoal then filtered. Upon chilling, the crude product crystallised from the filtrate. This material was filtered off then recrystallised (from DCM-ether) to afford 2-bromo-4-hydroxybenzaldehyde\(^{23}\) (1.24 g, 14%) as a white, crystalline solid, m.p. 157-158 °C (lit.\(^{23}\) 156.5-158 °C).

\( ^1H \text{ NMR} \) (300 MHz, CD\(_3\)COCD\(_3\)) \( \delta: 10.13 \text{ (s, } 1H, \text{ CHO}), 9.81 \text{ (broad s, } \text{OH}), 7.79 \text{ (d, } J=8.6 \text{ Hz, } 1H, \text{ ArH}), 7.17 \text{ (d, } J=2.3 \text{ Hz, } 1H, \text{ ArH}), 6.99 \text{ (m, } 1H, \text{ ArH}).\)

\( ^{13}C \text{ NMR} \) (75 MHz, CD\(_3\)COCD\(_3\)) \( \delta: 189.4 \text{ (CHO)}, 163.4 \text{ (C)}, 131.7 \text{ (CH)}, 128.1 \text{ (C)}, 126.4 \text{ (C)}, 120.3 \text{ (CH)}, 115.9 \text{ (CH)}.\)

\( \text{IR } \nu_{\text{max}} \) 3078 (broad), 2777, 1649, 1598, 1565, 1491, 1256, 1030, 856, 769 cm\(^{-1}\).
2-Bromo-4-methoxybenzaldehyde (117)

A mixture of 2-bromo-4-hydroxybenzaldehyde (1.05 g, 5.2 mmol), K$_2$CO$_3$ (850 mg of anhydrous material, 6.2 mmol) and methyl iodide (520 µL, 8.3 mmol) in acetone (50 mL) was heated at reflux for 6 h. The reaction mixture was then cooled, filtered, and the filtrate concentrated under reduced pressure. The residue thus obtained was dissolved in diethyl ether (40 mL) and the resulting solution washed with water (2 x 20 mL) then dried (MgSO$_4$), filtered, and concentrated under reduced pressure to give a light-brown solid. This material was recrystallised (from methanol) to afford the title compound 117$^{24}$ (1.04 g, 96%) as a white, crystalline solid, m.p. 70-71 °C (lit.$^{24}$ 70-71 °C).

$^1$H NMR (300 MHz, CDCl$_3$) δ: 10.18 (s, 1H, CHO), 7.84 (d, $J$ 8.8 Hz, 1H, ArH), 7.28 (d, $J$ 2.5 Hz, 1H, ArH), 7.07 (m, 1H, ArH), 3.98 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 189.9 (CHO), 165.3 (C), 131.8 (CH), 128.4 (C), 127.5 (C), 119.1 (CH), 115.1 (CH), 56.5 (OCH$_3$).

IR $\nu_{max}$ 3073, 2975, 1672, 1599, 1563, 1453, 1252, 1035, 877, 815, 607 cm$^{-1}$.

(3aS,7aR)-2-(2-Bromophenyl)-3a,4,5,7a-tetrahydro-7-methyl-1,3-benzodioxole (114a)

A magnetically stirred mixture of diol 115 (501 mg, 3.9 mmol), aldehyde 116 (860 mg, 4.6 mmol) and $p$-TsOH (15 mg, catalyst) in toluene (60 mL) was heated at reflux in an
apparatus connected to a Dean-Stark trap. The reaction was monitored by TLC and was found to be complete in 5 h. The reaction mixture was then cooled, and the solvent removed under reduced pressure. The residue so-obtained was dissolved in diethyl ether (50 mL) then the resulting solution stirred vigorously with sodium metabisulphite (20 mL of a saturated aqueous solution) for 0.5 h. The ether layer was separated, washed with water (1 x 20 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was passed through a short pad of TLC-grade silica using ether - hexane (1:1 v/v mixture), to afford, after concentration of the eluent, the title compound 114a (1.04 g, 90%) as a clear, colourless oil. Compound 114a was obtained as a ca. 1:1 mixture of epimers as determined by $^1$H- and $^{13}$C-NMR analysis.

$^1$H NMR (300 MHz, CDCl₃) δ: 7.68-7.50 (m, 4H, ArH), 7.38-7.16 (m, 4H, ArH), 6.25 (s, 1H), 6.19 (s, 1H). 5.80 (m, 1H), 5.67 (m, 1H), 4.80-4.70 (m, 2H), 4.40 (m, 2H), 2.20-1.70 (complex m, 8H), 1.82 (s, 6H).

$^{13}$C NMR (75 MHz, CDCl₃) δ: 137.6, 137.0, 133.2, 132.8, 131.7, 130.8, 130.7, 130.6, 128.9, 128.2, 127.8(2), 127.8(1), 127.6, 126.1, 123.5, 123.3, 102.3, 101.2, 76.5, 76.2, 75.1, 74.5, 26.3, 25.7, 21.6, 21.1, 20.9, 20.7.

IR νmax 2918, 1593, 1571, 1442, 1270, 1125, 1085, 1022, 757 cm⁻¹.

Mass spectrum (70 eV) m/z 295 (M⁺, 15%), 238 (17), 185 (56), 95 (100), 77 (50).

HRMS Found M⁺⁺, 296.0233 and 294.0259. C₁₄H₁₅⁸¹BrO₂ and C₁₄H₁₅⁷⁹BrO₂ requires 296.0235 and 294.0255, respectively.

(3aS,7aR)-2-(2-Bromo-4-methoxyphenyl)-3a,4,5,7a-tetrahydro-7-methyl-1,3-benzodioxole (114b)

$$\text{115} + \text{117} \xrightarrow{\text{p-TsOH toluene reflux, 3 h}} \text{114b}$$
A magnetically stirred mixture of diol 115 (500 mg, 3.9 mmol), aldehyde 117 (900 mg, 4.2 mmol) and p-TsOH (15 mg, catalyst) in toluene (60 mL) was heated at reflux in an apparatus connected to a Dean-Stark trap. No diol was left after 3 h of heating as determined by TLC analysis of the reaction mixture. Consequently, the reaction mixture was cooled, and the solvent was removed under reduced pressure. The residue so-obtained was dissolved in diethyl ether (50 mL) and the resulting solution stirred vigorously with sodium metabisulphite (20 mL of a saturated aqueous solution) for 0.5 h. The ether layer was separated, washed with water (1 x 20 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was passed through a short pad of TLC-grade silica using ether - hexane (1:1 v/v mixture), to afford, after concentration of the eluent, the title compound 114b (1.18 g, 95%) as a clear, colourless oil. Compound 114b was obtained as a ca. 1:1 mixture of epimers as determined ¹H- and ¹³C-NMR analysis.

¹H NMR (300 MHz, CDCl₃) δ: 7.54 (d, J 8.6 Hz, 1H, ArH), 7.47 (d, J 8.6 Hz, 1H, ArH), 7.08 (d, J 1.3 Hz, 1H, ArH), 7.06 (d, J 1.3 Hz, 1H, ArH), 6.89-6.84 (m, 2H, ArH), 6.16 (s, 1H), 6.08 (s, 1H), 5.80 (m, 1H), 5.67 (m, 1H), 4.60-4.42 (m, 2H), 4.40-4.38 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 2.30-1.40 (complex m, 8H), 1.80 (s, 3H), 1.78 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ: 160.7, 160.6, 131.8, 130.7, 129.7, 129.1, 128.9, 127.8, 126.0, 123.8, 123.5, 118.2, 117.6, 114.2, 113.7, 102.2, 101.1, 76.4, 76.1, 75.0, 74.5, 56.1, 56.0, 26.3, 25.7, 21.6, 21.0, 20.8, 20.6.

IR νmax 2930, 1604, 1570, 1497, 1290, 1241, 1083, 1026, 841 cm⁻¹.

Mass spectrum (70 eV) m/z 325 (M⁺, 10%), 217 (100), 215 (98).

HRMS Found M⁺, 326.0341 and 324.0346. C₁₅H₁₇⁸¹BrO₃ and C₁₅H₁₇⁷⁹BrO₃ requires 326.0341 and 324.0361, respectively.
A magnetically stirred solution of acetal 114a (900 mg, 3.1 mmol) in DCM (60 mL) maintained at 0 °C (ice-water bath) under an atmosphere of nitrogen was treated, dropwise, with DIBAL-H (7.8 mL of a 1 M solution in hexane, 7.8 mmol). After addition was complete, the mixture was stirred for a further 2 h at 0 °C at which point TLC analysis indicated most of the starting material remained. Consequently, the reaction mixture was allowed to warm to 18 °C, stirred at this temperature for 20 h then quenched (CAUTION) with methanol (ca. 2 mL), and treated with NaOH (10 mL of a 10% w/v aqueous solution). The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic phases were washed with brine (1 x 30 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue so-obtained was dissolved in diethyl ether (50 mL) and treated with activated MnO₂ (20 equivalents) then the mixture was magnetically stirred for 24 h at 18 °C, filtered through a short pad of Celite™ and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate - hexane elution) to afford two fractions, F1 and F2.

Concentration of F1 [Rf 0.3(5)] under reduced pressure afforded the title compound 118a (491 mg, 54%) as an amorphous solid.

^1H NMR (300 MHz, CDCl₃) δ: 7.60-7.48 (m, 2H, ArH), 7.38-7.10 (m, 2H, ArH), 5.58 (m, 1H), 4.80 (ABq, J 12.2 Hz, 2H), 4.01 (m, 1H), 3.86 (d, J 3.9 Hz, 1H), 2.22-1.60 (complex m, 4H), 1.80 (s, 3H).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 137.8 (C), 132.8 (C), 130.0 (CH), 129.5 (CH), 127.8 (CH), 126.3 (CH), 125.2 (CH), 123.2 (C), 79.2 (CH), 72.9 (CH$_2$), 67.7 (CH), 26.7 (CH$_2$), 23.0 (CH$_3$), 21.3 (CH$_2$).

IR $\nu_{\text{max}}$ 3436 (broad), 2916, 2877, 1440, 1089, 1044, 751 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 298 (M$^+$, 7%), 252 (42), 171 (100), 90 (59), 55 (36).

HRMS Found M$^+$, 298.0398 and 296.0421. $C_{14}H_{17}^{81}$BrO$_2$ and $C_{14}H_{17}^{79}$BrO$_2$ requires 298.0391 and 296.0412, respectively.

Specific rotation $[\alpha]_D^{-18.4^\circ}$ (c 0.83, CHCl$_3$).

Concentration of F$_2$ ($R_f$ 0.6) under reduced pressure afforded the title compound 120 (210 mg, 23%) as a light-yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.57-7.48 (m, 2H, ArH), 7.32-7.26 (m, 1H, ArH), 7.15-7.08 (m, 1H, ArH), 6.61 (m, 1H), 4.79 (ABq, $J$ 13.1 Hz, 2H), 3.95 (dd, $J$ 10.7 and 4.5 Hz, 1H), 2.25-2.05 (complex m, 4H), 1.80 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 198.8 (C=O), 145.1 (C), 137.9 (C), 134.8 (C), 132.6 (CH), 129.6 (CH), 129.2 (CH), 127.6 (CH), 122.9 (C), 79.8 (CH), 72.0 (CH$_2$), 30.1 (CH$_2$), 24.6 (CH$_3$), 16.0 (CH$_2$).

IR $\nu_{\text{max}}$ 2928, 1684, 1439, 1349, 1025, 751 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 295 (M$^+$, 25%), 238 (63), 110 (100), 69 (33).

Specific rotation $[\alpha]_D^{-81.8^\circ}$ (c 0.83, CHCl$_3$).

$^{1S,2R}$-2-(2-Bromo-4-methoxybenzyloxy)-3-methylcyclohex-3-enol (121) and $^{6S}$-(2-Bromo-4-methoxybenzyloxy)-2-methylcyclohex-2-enone (123)
A magnetically stirred solution of acetal 114b (901 mg, 2.7 mmol) in DCM (60 mL) maintained at -10 °C (ice-salt bath) under an atmosphere of nitrogen was treated, dropwise, with DIBAL-H (6.8 mL of a 1 M solution in hexane, 6.8 mmol). After addition was complete, stirring was continued at -10 °C. The reaction was monitored by TLC and was found to be complete in 5 h. Consequently, the resulting mixture was quenched, at -10 °C, with methanol (ca. 2 mL) then treated with NaOH (10 mL of a 10% w/v aqueous solution). The organic layer was separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organic phases were washed with brine (1 x 30 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue so-obtained was dissolved in diethyl ether (50 mL) and treated with activated MnO₂ (20 equivalents). The ensuing mixture was stirred magnetically for 24 h at 18 °C, filtered through a short pad of Celite™, and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, v/v 1:3 ethyl acetate - hexane elution) to afford two fractions, F1 and F2.

Concentration of F1 (Rf 0.4) under reduced pressure afforded the title compound 121 (560 mg, 64%) as white fluffy needles, m.p. 77-79 °C.

**1H NMR** (300 MHz, CDCl₃) δ: 7.37 (d, J 8.5 Hz, 1H, ArH), 7.11 (d, J 2.6 Hz, 1H, ArH), 6.85 (dd, J 8.2 and 2.6 Hz, 1H, ArH), 5.55 (m, 1H), 4.72 (ABq, J 11.4 Hz, 2H), 3.98 (m, 1H), 3.80 (s, 3H), 2.50 (d, J 4.1 Hz, OH), 2.22-1.60 (complex m, 4H), 1.80 (s, 3H).

**13C NMR** (75 MHz, CDCl₃) δ: 159.9 (C), 132.3 (C), 131.3 (CH), 129.8 (C), 126.1 (CH), 124.3 (C), 118.3 (CH), 113.7 (CH), 78.7 (CH), 72.8 (CH₂), 67.7 (CH), 55.9 (OCH₃), 26.9 (CH₂), 23.1 (CH₃), 21.4 (CH₂).

**IR** νmax 3279 (broad), 2934, 1605, 1569, 1491, 1234, 1037, 807 cm⁻¹.

**Mass spectrum** (70 eV) m/z 327 (M⁺, 7%), 282 (12), 201 (100).

**HRMS** Found M⁺, 328.0566 and 326.0521. C₁₅H₁₉⁸¹BrO₃ and C₁₅H₁₉⁷⁹BrO₃ requires 328.0497 and 326.0518, respectively.

**Specific rotation** [α]D -41.8° (c 0.64, CHCl₃).
Concentration of F2 \([R_f 0.6(5)]\) under reduced pressure afforded the *title compound* 123 (321 mg, 26%) as a light-yellow oil.

\[ ^1H\text{ NMR} (300 \text{ MHz}, \text{CDCl}_3) \delta: 7.44 (d, J 8.5 \text{ Hz}, 1\text{H}, \text{ArH}), 7.10 (d, J 2.5 \text{ Hz}, 1\text{H}, \text{ArH}), 6.84 (dd, J 8.5 \text{ and } 2.6 \text{ Hz}, 1\text{H}, \text{ArH}), 6.68 (m, 1\text{H}), 4.75 (\text{ABq}, J 12.2 \text{ Hz}, 2\text{H}), 3.94 (dd, J 10.7 \text{ and } 4.7 \text{ Hz}, 1\text{H}), 3.79 (s, 3\text{H}), 2.30-2.00 \text{ (complex m, } 4\text{H}), 1.80 (s, 3\text{H}). \]

\[ ^13\text{C NMR} (75 \text{ MHz}, \text{CDCl}_3) \delta: 196.9 (\text{C=O}), 159.7 (\text{C}), 132.3 (\text{C}), 131.2 (\text{CH}), 129.8 (\text{C}), 126.1 (\text{C}), 118.3 (\text{CH}), 113.7 (\text{CH}), 78.7 (\text{CH}), 72.8 (\text{CH}_2), 67.7 (\text{CH}_2), 55.9 (\text{OCH}_3), 26.9 (\text{CH}_2), 23.1 (\text{CH}_3), 21.4 (\text{CH}_2). \]

IR \( \nu_{\text{max}} \) 2926, 1684, 1604, 1494, 1239, 1034 cm\(^{-1}\).

\((1R,2S,3S,6R)-2-(2\text{-Bromobenzoyloxy})-1\text{-methyl-7-oxabicyclo[4.1.0]heptan-3-ol (110a) and} \]

\((1S,2S,3S,6S)-2-(2\text{-Bromobenzoyloxy})-1\text{-methyl-7-oxabicyclo[4.1.0]heptan-3-ol (124a)} \]

Powdered \( m\text{-CPBA} \) (230 mg, 77% purity, 1.0 mmol) was added, in portions over 10 minutes, to a magnetically stirred and cooled (ice-water bath) suspension of enol 118a (200 mg, 0.7 mmol) and \( \text{NaHCO}_3 \) (130 mg, 1.5 mmol) in DCM (25 mL). Stirring was continued for 18 h (at 5 °C) then the reaction mixture was filtered, the filtrate washed with \( \text{NaHCO}_3 \) (20 mL of a 1 M aqueous solution) then dried (\( \text{MgSO}_4 \)), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:1 v/v diethyl ether - hexane elution) to afford two fractions, F1 and F2.

Concentration of F1 \([R_f 0.2]\) under reduced pressure afforded the *title compound* 110a (88 mg, 42%) as a clear, colourless oil.
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.62-7.48 (m, 2H, ArH), 7.34-7.28 (m, 1H, ArH), 7.18-7.12 (m, 1H, ArH), 4.76 (ABq, $J$ 12.5 Hz, 2H), 4.12 (m, 1H), 3.66 (d, $J$ 4.0 Hz, 1H), 3.12 (m, 1H), 2.20-1.80 (complex m, 4H), 1.62 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 137.2 (C), 132.4 (CH), 129.7 (CH), 129.1 (CH), 127.4 (CH), 122.9 (C), 77.8 (CH), 70.1 (CH$_2$), 66.0 (CH), 61.6 (CH), 61.0 (C), 26.5 (CH$_2$), 20.3 (CH$_3$), 19.5 (CH$_2$).

IR $\nu_{\text{max}}$ 3480 (broad), 2930, 1721, 1571, 1429, 1126, 1099, 1025, 991, 754 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 314 and 312 (M$^+$, 5%), 169 and 171 (100 and 98), 110 (58), 90 (55), 69 (50), 43 (55).

HRMS Found M$^+$, 314.0341 and 312.0363. $C_{14}H_{17}^{81}\text{BrO}_3$ and $C_{14}H_{17}^{79}\text{BrO}_3$ requires 314.0341 and 312.0361, respectively.

Specific rotation $[\alpha]_D +37.4^\circ$ (c 0.54, CHCl$_3$).

Concentration of F2 ($R_f$ 0.4) under reduced pressure afforded the title compound 124a (76 mg, 36%) as a white, crystalline solid, m.p. 61-63 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.60-7.16 (complex m, 4H, ArH), 4.77 (ABq, $J$ 12.0 Hz, 2H), 3.99 (m, 1H), 3.67 (d, $J$ 3.6 Hz, 1H), 3.05 (m, 1H), 2.18-1.64 (complex m, 4H), 1.42 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 136.9 (C), 132.7 (CH), 129.8 (CH), 129.5 (CH), 127.6 (CH), 123.2 (C), 78.8 (CH), 73.1 (CH$_2$), 64.7 (CH), 60.4 (CH), 59.0 (C), 22.1 (CH$_2$), 20.2 (CH$_3$), 19.9 (CH$_2$).

IR $\nu_{\text{max}}$ 3511 (broad), 2881, 1699, 1428, 1107, 1027, 872, 751 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 314 and 312 (M$^+$, 4%), 169 and 171 (100 and 98), 127 (32), 90 (55), 82 (35), 43 (68).

HRMS Found M$^+$, 314.0332 and 312.0350. $C_{14}H_{17}^{81}\text{BrO}_3$ and $C_{14}H_{17}^{79}\text{BrO}_3$ requires 314.0341 and 312.0361, respectively.

Specific rotation $[\alpha]_D -3.6^\circ$ (c 0.25, CHCl$_3$).
**Chapter 5** Details of the experimental work described in Chapters 2, 3 and 4

**(1S,2R)-2-(2-Bromobenzyloxy)-3-methylcyclohex-3-enyloxy)tert-butyldimethylsilane (118b)**

TBSOTf (240 µL, 1.1 mmol) was added, dropwise, to a magnetically stirred solution of compound 118a (210 mg, 0.7 mmol) and 2,6-lutidine (240 µL, 2.1 mmol) in DCM (20 mL) maintained at -40 °C under an atmosphere of nitrogen. After 4 h the reaction mixture was poured into HCl (5 mL of a 2% v/v aqueous solution) then extracted with diethyl ether (3 x 20 mL). The combined organic phases were washed with water (1 x 30 mL) and brine (1 x 30 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate - hexane elution) to afford, after concentration of the appropriate fractions ($R_f$ 0.8), the title compound 118b (240 mg, 83%) as a clear, colourless oil.

**¹H NMR** (300 MHz, CDCl₃) δ: 7.60-7.48 (m, 2H, ArH), 7.38-7.08 (m, 2H, ArH), 5.40 (m, 1H), 4.92 (ABq, $J_{12.9}$ Hz, 2H), 3.88 (m, 1H), 3.72 (d, $J_{3.3}$ Hz, 1H), 2.22-1.60 (complex m, 4H), 1.80 (s, 3H).

**¹³C NMR** (75 MHz, CDCl₃) δ: 139.1 (C), 133.0 (C), 132.2 (CH), 129.6 (CH), 128.4 (CH), 127.2 (CH), 125.1 (CH), 122.4 (C), 80.1 (CH), 74.5 (CH₂), 73.1 (CH), 25.9 (CH₂), 25.6 (CH₂), 25.2 (CH₃), 21.3 (CH₃), 18.2 (C), -4.56 (CH₃), -4.60 (CH₃).

**Mass spectrum** (70 eV) m/z 411 (M⁺, 1%), 355 (35), 245 (62), 169 (100), 73 (52).

**HRMS** Found M⁺ 410.1274. C₂₀H₃₁BrO₂Si requires 410.1277.

**Specific rotation** $\left[\alpha\right]_D^{25} -71.3^\circ$ (c 0.15, CHCl₃).
(1R,2S,3S,6R)-2-(2-Bromobenzyloxy)-1-methyl-7-oxabicyclo[4.1.0]heptan-3-yloxy)tert-butyldimethylsilane (110b) and

(1S,2S,3S,6S)-2-(2-Bromobenzyloxy)-1-methyl-7-oxabicyclo[4.1.0]heptan-3-yloxy)tert-butyldimethylsilane (124b)

\[
\begin{align*}
\text{TBSO} & \quad \text{NBS, DMSO, H}_2\text{O} \\
\text{Br} & \quad 10^\circ\text{C, 1 h} \\
118b & \quad + \\
125 & \quad + \\
126 & \quad \text{K}_2\text{CO}_3,\text{MeOH} \\
& \quad 18^\circ\text{C, 0.5 h} \\
110b & \quad + \\
124b &
\end{align*}
\]

A magnetically stirred solution of compound 118b (180 mg, 0.4 mmol) in DMSO (5 mL) and water (20 µL, 1 mmol) maintained at ca. 10 °C (cold water temperature), was treated, in one portion, with freshly recrystallised NBS (150 mg, 0.8 mmol). After 1 h, the reaction mixture was treated with NaHCO₃ (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with water (1 x 15 mL) and brine (1 x 15 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure. The ensuing residue, containing a mixture of compounds 125 and 126 (180 mg, 81%), was dissolved in methanol (10 mL) then treated with K₂CO₃ (180 mg of anhydrous material, 1.3 mmol) and the resulting suspension stirred magnetically for 1 h at 18 °C. The methanol was removed under reduced pressure and the residue was dissolved in DCM (20 mL) then washed with water (1 x 10 mL) and brine (1 x 10 mL) before being dried (MgSO₄) then filtered. The filtrate was concentrated under reduced pressure and the residue so-obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate - hexane elution) to afford two fractions, F1 and F2.
Concentration of F1 \((R_f 0.6)\) under reduced pressure afforded the **title compound** \(110b\) (101 mg, 54% from compound \(118b\)) as a clear, colourless oil.

\[ ^1H \text{NMR} \quad (300 \text{ MHz, CDCl}_3) \delta: 7.73 \text{ (m, 1H, ArH)}, 7.49 \text{ (m, 1H, ArH)}, 7.30 \text{ (m, 1H, ArH)}, 7.11 \text{ (m, 1H, ArH)}, 4.85 \text{ (ABq, } J 13.9 \text{ Hz, 2H)}, 3.70 \text{ (d, } J 4.1 \text{ Hz, 1H)}, 3.63 \text{ (m, 1H)}, 2.92 \text{ (m, 1H)}, 2.18 \text{ (m, 1H)}, 1.90-1.80 \text{ (complex m, 1H)}, 1.35 \text{ (s, 3H)}, 1.24 \text{ (m, 1H)}, 0.90 \text{ (s, 9H)}, 0.10 \text{ (s, 3H)}, 0.08 \text{ (s, 3H)} \]

\[ ^{13}C \text{NMR} \quad (75 \text{ MHz, CDCl}_3) \delta: 138.7 \text{ (C), 132.0 \text{ (CH), 129.2 (CH), 128.4 (CH), 127.3 (CH), 121.8 (C), 79.7 (CH), 73.7 (CH}_2, 72.1 \text{ (CH), 58.6 \text{ (CH), 58.3 \text{ (C), 25.9 (CH}_3, 24.3 \text{ (CH}_2, 23.3 \text{ (CH}_3), 21.8 \text{ (CH}_2, 18.2 \text{ (C), -4.6 (CH}_3, -4.7 (CH}_3)} \]

**IR** \(\nu_{\text{max}} 2955, 2928, 2856, 1471, 1438, 1253, 1093, 904, 834, 775 \text{ cm}^{-1} \)

Mass spectrum (70 eV) \(m/z 369 \text{ and } 371 \quad [(\text{M-C}_4\text{H}_9\text{·})^+, 35\%], \quad 327 \text{ (96), 325 (93), 245 (13), 169 (100), 73 (42).} \)

**HRMS** Found \([\text{M-C}_4\text{H}_9\text{·}]^+ \quad 371.0505 \text{ and } 369.0518. \quad \text{C}_{20}\text{H}_{31}\text{BrO}_3\text{Si} - \text{C}_4\text{H}_9, \ i.e.} \quad \text{C}_{16}\text{H}_{22}^8\text{BrO}_3\text{Si and C}_{16}\text{H}_{22}^9\text{BrO}_3\text{Si requires 371.0501 and 369.0522, respectively.} \)

**Specific rotation** \([\alpha]_D^\circ +38.2^\circ (c 0.11, \text{CHCl}_3). \)

Concentration of F2 \((R_f 0.7)\) under reduced pressure afforded the **title compound** \(124b\) (41 mg, 22% from compound \(118b\)) as a clear, colourless oil.

\[ ^1H \text{NMR} \quad (300 \text{ MHz, CDCl}_3) \delta: 7.62-7.10 \text{ (complex m, 4H, ArH), 4.87 \text{ (ABq, } J 12.6 \text{ Hz, 2H), 4.05 \text{ (m, 1H), 3.76 (d, } J 3.6 \text{ Hz, 1H), 2.99 \text{ (m, 1H), 2.11-1.74 (complex m, 3H), 1.40 (s, 3H), 1.34 (m, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).} \]

\[ ^{13}C \text{NMR} \quad (75 \text{ MHz, CDCl}_3) \delta: 138.5 \text{ (C), 131.8 (CH), 129.0 (CH), 128.1 (CH), 127.2 (CH), 121.5 (C), 79.3 (CH), 73.3 (CH}_2, 72.0 \text{ (CH), 58.2 (CH), 58.1 (C), 25.2 (CH}_3, 24.1 \text{ (CH}_2, 23.0 \text{ (CH}_3), 21.4 \text{ (CH}_2, 18.1 \text{ (C), -4.3 (CH}_3, -4.4 (CH}_3)} \]

**IR** \(\nu_{\text{max}} 2967, 2931, 2859, 1471, 144I 1255, 904, 833, 775 \text{ cm}^{-1} \)

Mass spectrum (70 eV) \(m/z 369 \text{ and } 371 \quad [(\text{M-C}_4\text{H}_9\text{·})^+, 7\%], \quad 327 (8), 245 (15), 171 (100), 73 (52).} \)

**HRMS** Found \([\text{M-C}_4\text{H}_9\text{·}]^+ \quad 371.0507 \text{ and } 369.0534. \quad \text{C}_{20}\text{H}_{31}\text{BrO}_3\text{Si} - \text{C}_4\text{H}_9, \ i.e.} \quad \text{C}_{16}\text{H}_{22}^8\text{BrO}_3\text{Si and C}_{16}\text{H}_{22}^9\text{BrO}_3\text{Si requires 371.0501 and 369.0522, respectively.} \)

**Specific rotation** \([\alpha]_D^\circ -10.1^\circ (c 0.08, \text{CHCl}_3). \)
Preparation of Ethyl 2,4-Dihydroxy-6-methylbenzoate (131)

Method 1 (129 → 130 → 131)

2,4-Dihydroxy-6-methylbenzaldehyde (130)

Freshly distilled POCl₃ (450 µL, 4.8 mmol) was added, dropwise, to magnetically stirred DMF (0.5 mL) maintained under an atmosphere of nitrogen at 0 °C. After addition was complete, a solution of orcinol 129 (501 mg, 4 mmol) in DMF (2 mL) was added dropwise to the resulting mixture which was then warmed to 18 °C and stirred at this temperature for 6 h. After this time, the reaction mixture was poured into crushed ice-water (5 mL) and then allowed to stand for 14 h. The precipitate so-formed was filtered off, washed thoroughly with water then dried under high vacuum at 60 °C for 20 h to afford the title compound 130²⁵ (470 mg, 65%) as crystalline masses, m.p. 183-185 °C (lit.²⁵ 179-180 °C).

¹H NMR (300 MHz, CD$_3$COCD$_3$) δ: 12.49 (s, 1H, CHO), 10.09 (broad s, OH), 9.60 (broad s, OH), 6.30 (m, 1H, ArH), 6.18 (d, J 2.2 Hz, 1H, ArH), 2.54 (s, 3H).

¹³C NMR (75 MHz, CD$_3$COCD$_3$) δ: 193.9 (CHO), 166.8 (C), 165.8 (C), 145.7 (C), 113.5 (C), 111.2 (CH), 101.1 (CH), 18.1 (CH$_3$).

IR ν max 3135 (broad), 1626, 1482, 1275, 1232, 1168, 640 cm⁻¹.

Mass spectrum (70 eV) m/z 152 (M⁺, 80%), 151 (100), 134 (10), 106 (20), 94 (15), 77 (16), 69 (28).
Ethyl 2,4-Dihydroxy-6-methylbenzoate (131)

A solution of NaH$_2$PO$_4$.H$_2$O (1.02 g, 6.5 mmol) in water (15 mL) was added to a solution of aldehyde 130 (401 mg, 2.6 mmol) in DMSO (45 mL) maintained at 0 °C. A solution of NaClO$_2$ (560 mg, 6.2 mmol) in water (15 mL) was added to the resulting mixture which was then allowed to warm to 18 °C and stirred at this temperature for 8 h. The ensuing mixture was diluted with Na$_2$CO$_3$ (35 mL of a saturated aqueous solution) then washed with ethyl acetate (1 x 40 mL). The aqueous layer was acidified with HCl (2 M aqueous solution) then extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried (MgSO$_4$), filtered, and concentrated under reduced pressure to afford the corresponding carboxylic acid (260 mg, 60% yield) as an off-white solid.

The crude acid obtained as described immediately above was dissolved in EtOH (20 mL) and the resulting solution treated with H$_2$SO$_4$ (2 drops of 98% material) then heated at reflux for 5 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue dissolved in ethyl acetate (20 mL) then washed with NaHCO$_3$ (10 mL of a 0.5 M aqueous solution). The organic layer was separated then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was passed through a short pad of TLC-grade silica using ethyl acetate to afford, after concentration of the eluent, the title compound 131 (220 mg, 43% from compound 130) as a white, crystalline solid, m.p. 130-131 °C (lit.$^{26}$ 131-132 °C).

$^1$H NMR (300 MHz, CD$_3$COCD$_3$) δ: 11.73 (s, OH), 9.60 (broad s, OH), 6.28 (m, 1H, ArH), 6.24 (m, 1H, ArH), 4.37 (q, J 7.1 Hz, 2H), 2.47 (s, 3H), 1.39 (t, J 7.1 Hz, 3H).

$^{13}$C NMR (75 MHz, CD$_3$COCD$_3$) δ: 172.1 (C=O), 165.9 (C), 162.7 (C), 144.0 (C), 111.9 (CH), 105.0 (C), 101.3 (CH), 61.6 (CH$_2$), 24.2 (CH$_3$), 18.1 (CH$_3$).

IR ν$_{max}$ 3357 (broad), 1640, 1560, 1482, 1585, 1321, 1272, 1177, 836 cm$^{-1}$.
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

**Mass spectrum (70 eV) m/z 196 (M⁺, 62%), 168 (21), 150 (100), 122 (69), 94 (34), 69 (35).**

**HRMS** Found M⁺, 196.0737. C₁₀H₁₂O₄ requires 196.0736.

**Method 2 (132 + 133 → 134 → 135 → 131)**

**Ethyl 2-Methyl-4,6-dioxocyclohexanecarboxylate (134)**

Dry ethanol (1.5 mL, 2.6 mmol) was added dropwise to sodium metal (499 mg, 2.2 mmol; cut in small pieces and washed free of oil with hexane) maintained under an atmosphere of nitrogen at 18 °C (CAUTION: exothermic reaction accompanied by evolution of dihydrogen). After addition of ethanol was complete, the mixture was stirred until all the sodium had reacted (ca. 3 h). The resulting solution of sodium ethoxide was treated with a solution of ethyl acetoacetate (132) (280 µL, 2.2 mmol) and ethyl trans-crotonate (133) (270 µL, 2.2 mmol) in ethanol (2 mL). The ensuing mixture was stirred for 0.5 h then heated at reflux for 2 h, cooled, and acidified with H₂SO₄ (5% v/v aqueous solution). The resulting precipitate was filtered off and the filtrate was diluted with water (10 mL) then extracted with chloroform (3 x 20 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated under reduced pressure. The resulting oil was dissolved in a minimum volume of hexane then cooled (ice-salt bath) during which the product precipitated from the mixture. The precipitate was filtered off, washed once with cold hexane then dried under high vacuum to afford the title compound 134₂₇ (300 mg, 70%) as a white solid, m.p. 88-89 °C (lit.²⁷ 89-89 °C).

**¹H NMR** (300 MHz, CDCl₃) δ: 9.30 (broad s, OH), 4.15 (q, J 7.1 Hz, 2H), 4.00 (q, J 7.1 Hz, 2H), 3.40-2.10 (complex m), 1.20 (t, J 7.1 Hz, 3H), 1.10 (t, J 7.1 Hz, 3H).
These data indicate that compound 134 exists predominantly in the bis-enolic tautomeric form.

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 175.3, 171.0, 118.6, 117.8, 61.3, 61.0, 39.1, 30.9, 26.1, 19.8, 19.7, 18.8, 14.5, 14.4.

IR ν$_{max}$ 3010 (broad), 2966, 1737, 1597, 1180, 1033, 851 cm$^{-1}$.

Mass spectrum (70 eV) $m/z$ 198 (M$^+$, 42%), 183 (32), 170 (27), 153 (43), 115 (51), 84 (46), 69 (100).

HRMS Found M$^+$, 198.0890. C$_{10}$H$_{14}$O$_4$ requires 198.0892.

**Ethyl 3,5-Dibromo-2,4-dihydroxy-6-methylbenzoate (135)**

A solution of bromine (220 µL, 4.4 mmol) in glacial acetic acid (1 mL) was added, dropwise over 0.25 h, to a magnetically stirred solution of compound 134 (280 mg, 1.4 mmol) in glacial acetic acid (2 mL) maintained at 18 °C. The ensuing mixture was stirred for 1 h then allowed to stand for 19 h. The product precipitated from the reaction mixture over this period and was filtered off, washed thoroughly with water then dried at 80 °C for 5 h to afford the title compound 135$^{27}$ (460 mg, 94%) as a white, crystalline solid, m.p. 143-144 °C (lit.$^{27}$ 143-145 °C).

$^1$H NMR (300 MHz, CD$_2$COCD$_3$) δ: 11.80 (broad s, OH), 4.43 (q, $J$ 7.0 Hz, 2H), 2.61 (s, 3H), 1.41 (t, $J$ 7.0 Hz, 3H).

$^{13}$C NMR (75 MHz, CD$_2$COCD$_3$) δ: 170.3 (C=O), 158.6 (C), 155.1 (C), 139.8 (C), 108.2 (C), 105.8 (C), 96.8 (C), 62.4 (C), (CH$_2$), 22.7 (CH$_3$), 13.7 (CH$_3$).
Reductive debromination of compound 135

![Chemical structure of compounds 135 and 131]

Compound 135 (450 mg, 1.3 mmol) was dissolved in NaOH (5 mL of a 2 M aqueous solution) then 5 mg of 10% Pd-C was added. The mixture was allowed to warm to 18 °C then stirred magnetically under an atmosphere of H₂ for 20 h. The resulting mixture was filtered through a pad of Celite™ and the filtrate was acidified with HCl (2 M aqueous solution) then extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (1 x 20 mL) then dried (MgSO₄), filtered, and concentrated under reduced pressure to afford compound 131 (240 mg, 95%) as a white, crystalline solid, m.p. 130-131 °C (lit. 131-132 °C). The spectral data derived from this material were identical, in all respects, to those of the compound obtained by Method 1.

Ethyl 3-Formyl-2,4-dihydroxy-6-methylbenzoate (136)

![Chemical structure of compounds 131 and 136]

Compound 131 (390 mg, 2.0 mmol) and Zn(CN)₂ (710 mg, 6.0 mmol) were mixed in diethyl ether (25 mL) then gaseous HCl was added until all the Zn(CN)₂ had dissolved (CAUTION). The mixture was cooled to 0 °C, and whilst being magnetically stirred, was treated, in portions over 0.25 h, with a solution of AlCl₃ (801 mg of anhydrous material, 6.0 mmol) in diethyl ether (10 mL). After addition was complete, the mixture was allowed to warm to 18 °C and saturated with gaseous HCl then left standing for 16 h at 18 °C. The oily layer formed was separated and hydrolysed in water (20 mL). The
product precipitated from the mixture was filtered off then washed thoroughly with water before being dried at 80 °C for 5 h to afford the title compound 136 (270 mg, 60%) as pale-yellow needles, m.p. 114-116 °C (lit. 112-113 °C).

\[ ^1H \text{NMR (300 MHz, CD}_3\text{COCD}_3\] δ: 13.01 (broad s, 1H, OH), 12.30 (broad s, 1H, OH), 10.30 (s, 1H, CHO), 6.38 (m, 1H, ArH), 4.42 (q, J 7.1 Hz, 2H), 2.58 (s, 3H), 1.44 (t, J 7.1 Hz, 3H).

\[ ^13C \text{NMR (75 MHz, CD}_3\text{COCD}_3\] δ: 194.2 (CHO), 172.0 (C=O), 168.5 (C), 166.8 (C), 153.3 (C), 112.3 (CH), 109.0 (C), 105.1 (C), 68.2 (CH\textsubscript{2}), 25.1 (CH\textsubscript{3}), 14.4 (CH\textsubscript{3}).

IR \[ \nu_{\text{max}} \] 2997, 1648, 1567, 1415, 1317, 1262, 1185, 815 cm\textsuperscript{-1}.

Mass spectrum (70 eV) \[ m/z \] 224 (M\textsuperscript{+}, 48%), 196 (30), 178 (32), 150 (100), 122 (25), 94 (20), 65 (17).

2,6-Dihydroxy-4-methylbenzaldehyde (atranol, 111)

\[ \text{H}_2\text{O} \]

\[ \text{Cu}_2\text{O} \]

\[ \text{H} \]

\[ \text{C}_8\text{H}_6\text{O}_2\text{H} \]

\[ \text{CH}_3 \]

\[ \text{H} \]

\[ \text{O} \]

\[ \text{OH} \]

\[ \text{OH} \]

\[ \text{CH}_3 \]

\[ \text{CH}_3 \]

1. 15% w/v NaOH (aq), reflux, 3 h
2. Heat, 0.5 h

Compound 136 (240 mg, 1.1 mmol) was dissolved in NaOH (20 mL of a 15% w/v aqueous solution) then heated at reflux for 3 h. The resulting mixture was cooled and acidified with HCl (4 M aqueous solution) then extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed with brine (1 x 40 mL) then dried (MgSO\textsubscript{4}), filtered, and concentrated under reduced pressure to afford an off-white solid (170 mg, 79%).

\[ ^1H \text{NMR (300 MHz, CD}_3\text{COCD}_3\] δ: 10.70 (broad s, OH), 10.25 (s, CHO), 6.28 (S, 1H, ArH), 2.22 (s, 3H)

IR \[ \nu_{\text{max}} \] 3197 (broad), 1650, 1605, 1454, 1356, 1280, 1206, 823 cm\textsuperscript{-1}. 

Mass spectrum (70 eV) m/z 196 (M⁺, 2%), 180 (29), 151 (100), 134 (18), 106 (29), 95 (17), 77 (21).

The mouth of the flask containing the aforementioned crude product was covered with cotton wool then uniformly heated with a portable heat gun. A conspicuous puff of gas was evolved after ca. 3 minutes of heating. This was followed by the gradual formation, through sublimation, of yellowish crystals on the inside of the flask. These crystals proved to be the title compound 111 (97 mg, 58% from compound 136), m.p. 121-122 °C (lit.²⁶ 120-121 °C).

¹H NMR (300 MHz, CD₃COCD₃) δ: 10.80 (broad s, OH), 10.20 (s, CHO), 6.19 (s, 2H, ArH), 2.19 (s, 3H).

¹³C NMR (75 MHz, CD₃COCD₃) δ: 191.9 (CHO), 160.8 (C), 149.3 (C), 107.1 (C), 106.3 (CH), 20.5 (CH₃).

IR νₘₐₓ 3202 (broad), 1653, 1606, 1454, 1206, 823 cm⁻¹.

Mass spectrum (70 eV) m/z 152 (M⁺, 92%), 151 (100), 134 (20), 106 (32), 95 (17), 77 (23).

HRMS Found M⁺, 152.0476. C₈H₈O₃ requires 152.0473.

Attempted formation of compound 113a

Compounds 110b (ca. 10 mg, 0.02 mmol) and 111 (ca. 5 mg, 0.03 mmol) were subjected to each of the various reaction conditions described below.

(i) LiClO₄ (2 mg, catalyst), DCM (5 mL), stirred at 18 °C, 18 h.
(ii) InCl$_3$ (2 mg, catalyst), DCM (5 mL), stirred at 18 °C, 18 h.

(iii) K$_2$CO$_3$ (10 mg, 0.07 mmol) acetone (10 mL), reflux, 16 h.

(iv) NaOH (5 mg, 0.1 mmol), MeOH (2 mL), stirred at 18 °C, 18 h.

The reaction was monitored by TLC technique. Using InCl$_3$ as catalyst [condition (ii)], gave a complex mixture of products (not characterised), whereas under conditions (i), (iii), and (iv) no products could be detected by TLC techniques.

**General procedure for the ring-opening of epoxide 139 with phenol (140)**

2-Methyl-2-phenoxy-5-(propen-2-yl)cyclohexanone (143) and 1-Methyl-2-phenoxy-4-(propen-2-yl)cyclohexanol (142)

![Diagram](image)

Compounds 139 (ca. 50 mg, 0.3 mmol) and 140 (ca. 50 mg, 0.5 mmol) were subjected to each of the various sets of reaction conditions depicted in **Table 5.1**. With the exception of the process summarised in entry 4, the reactions were stirred at the specified temperatures and were monitored by TLC techniques. Where products were formed (entries 2, 5 and 6), the mixture was subjected to the general work-up procedure given below.

**Work-up procedure:** The reaction mixture was quenched with water (ca. 5 mL) then extracted with DCM (3 x 5 mL). The combined organic phases were washed with brine
(1 x 10 mL) then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate - hexane elution) and in the process the unreacted starting materials were recovered together with an inseparable mixture of compounds 141 and 142 ($R_f$ 0.3(5)).

Table 5.1: Reaction of compounds 139 and 140 - conditions and outcome.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH (1 equiv.), THF (5 mL), 18 °C, 48 h.</td>
<td>No reaction with phenol.</td>
</tr>
<tr>
<td>2</td>
<td>AcOH (20 mol%)$^6$, CH$_3$CN (5 mL), 18 °C, 24 h.</td>
<td>15% ring-opened product but with acetate ion. Regio-chemistry of the product(s) were not determined.</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl$_2$ (5 mg), DCM (5 mL), 18 °C, 48 h</td>
<td>No reaction with phenol.</td>
</tr>
<tr>
<td>4</td>
<td>High pressure reaction: DCM, 19 kBar, 20 h.</td>
<td>No reaction with phenol.</td>
</tr>
<tr>
<td>5</td>
<td>CF$_3$COOH (20 mol%)$^6$, DCM (5 mL), 18 °C, 20 h.</td>
<td>30% ring-opened product with phenol. Regio-chemistry of the product(s) were not determined</td>
</tr>
<tr>
<td>6</td>
<td>Cu(BF$_4$)$_2$.nH$_2$O (10 mol%)$^6$, DCM (5 mL), 18 °C, 20 h.</td>
<td>60% ring-opened product with phenol; regio-chemistry 2:1 in favour of reaction at the more sterically hindered carbon center.</td>
</tr>
</tbody>
</table>

$^*$In entries 2, 5 and 6, ca. 5% product (1,2-diol) was obtained through ring-opening of the epoxide by water (possibly during aqueous work-up of the reaction mixture).

$^6$With respect to compound 139.

The crude product derived using the conditions defined in entry 6 was oxidised [PDC (2 equiv.), DCM, 18 °C, 6 h] to afford, after work-up and flash chromatography (silica, 1:4 v/v ethyl acetate - hexane elution), two fractions, F1 and F2.

Concentration of F1 ($R_f$ 0.7) under reduced pressure afforded the title compound 143 (31 mg, 39%).

$^1$H NMR (300 MHz, CDCl$_3$) δ: 7.26-6.78 (m, 5H, ArH), 4.88 (broad s, 2H), 2.60-2.20 (complex m, 4H), 1.76 (s, 3H), 1.68-1.60 (complex m, 2H), 1.40 (s, 3H).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

\[\text{\textsuperscript{13}C NMR (75 MHz, CDCl}_3\text{)} \delta: 213.8 (C=O), 155.9 (C), 147.4 (C), 129.8 (CH), 122.1 (CH), 118.1 (CH), 110.3 (CH\textsubscript{2}), 82.8 (C), 48.7 (CH), 44.2 (CH\textsubscript{2}), 42.1 (CH\textsubscript{2}), 26.1 (CH\textsubscript{2}), 20.6 (CH\textsubscript{3}), 19.3 (CH\textsubscript{3}).\]

Mass spectrum (70 eV) \textit{m/z} 244 (M\textsuperscript{+}, 35\%), 151 (75), 94 (100), 81 (50), 67 (31).

HRMS Found M\textsuperscript{+}, 244.1465. \(C_{16}H_{20}O_2\) requires 244.1463.

Concentration of F2 [\(R_f 0.3(5)\)] under reduced pressure afforded the \textit{title compound 142 (17 mg, 21\%)}.\n
\[\text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3\text{)} \delta: 7.30 (m, 2H, ArH), 6.72 (m, 3H, ArH), 4.68 (broad s, 2H), 4.18 (broad s, OH), 2.35-1.80 (complex m, 4H), 1.70 (s, 3H), 1.68-1.60 (complex m, 2H), 1.31 (s, 3H).\]

\[\text{\textsuperscript{13}C NMR (75 MHz, CDCl}_3\text{)} \delta: 158.2 (C), 149.7 (C), 129.8 (CH), 121.1 (CH), 116.3 (CH), 109.0 (CH\textsubscript{2}), 79.6 (C), 71.2 (C), 37.8 (CH), 34.5 (CH\textsubscript{2}), 29.9 (CH\textsubscript{2}), 27.8 (CH\textsubscript{2}), 26.5 (CH\textsubscript{3}), 21.2 (CH\textsubscript{3}).\]

Mass spectrum (70 eV) \textit{m/z} 246 (M\textsuperscript{+}, 17\%), 153 (14), 94 (100), 77 (15).

HRMS Found M\textsuperscript{+}, 246.1622. \(C_{16}H_{22}O_2\) requires 246.1620.

2-(Hydroxymethyl)-5-methylbenzene-1,3-diol (147)

A magnetically stirred suspension of atranol (111) (20 mg, 0.1 mmol) in ethanol-water (5 mL of a 1:1 v/v mixture) maintained at 0 °C was treated with NaBH\textsubscript{4} (4 mg). The ensuing mixture was allowed to warm to 18 °C and stirred at this temperature for 2 h then extracted with ethyl acetate (3 x 5 mL). The combined organic phases were then dried (MgSO\textsubscript{4}), filtered, and concentrated under reduced pressure to afford the \textit{title compound 147 (18 mg, 90\%)} as a white, crystalline solid.
\(^1\)H NMR (300 MHz, CD\(_3\)COCD\(_3\)) \(\delta\): 8.90 (broad s, OH), 6.40 (s, 2H, ArH), 3.80 (m, 2H), 2.01 (s, 3H).

**Attempted formation of compound 146**

Compound 147 (ca. 7 mg) was dissolved in dry acetone (or dry DMF, second attempt with ca. 8 mg of compound 147) and the resulting solution treated with excess 2,2-DMP (5 equiv.) then a small crystal of p-TsOH (catalyst). The ensuing mixture was stirred magnetically and monitored, every 0.5 h, by TLC techniques. No starting material was left after 1.5 h of stirring. Removal of the solvent, or in case of the second attempt, work-up of the reaction mixture after treatment with NaHCO\(_3\) (1 mL of a 0.1 M aqueous solution), gave a red-brown solid which was insoluble in all common organic solvents including diethyl ether, ethyl acetate, acetone and methanol.

7-Oxabicyclo[4.1.0]heptan-2-one (151)

![Chemical Structure](image)

A solution of 2-cyclohexenone (501 mg, 5.2 mmol) dissolved in methanol (20 mL) maintained at 0 °C was treated with H\(_2\)O\(_2\) (1.2 mL of a 30% w/w aqueous solution, 10.5 mmol) and NaOH (400 µL of a 6 M aqueous solution, 2.4 mmol) then stirred magnetically for 1 h. After treating the reaction mixture with Na\(_2\)SO\(_3\) (2 mL of a 10% w/v aqueous solution) and NH\(_4\)Cl (5 mL of a saturated aqueous solution), the methanol was removed under reduced pressure. The resulting mixture was extracted with diethyl ether (3 x 5 mL) and the combined ether extracts were then dried (MgSO\(_4\)), filtered, and concentrated under reduced pressure. The residue so-obtained was subjected to column chromatography (silica, 1:1 v/v diethyl ether - hexane elution) to afford, upon concentration of the appropriate fractions \([R_f 0.3(5)]\), the title compound 151\(^{28}\) (480 mg, 81%) as a clear, colourless oil.
Chapter 5 *Details of the experimental work described in Chapters 2, 3 and 4*

\[ ^1\text{H} \text{NMR (300 MHz, CDCl}_3 \] \( \delta \): 3.50 (m, 1H), 3.30 (d, \( J \) 3.8 Hz, 1H), 2.48-1.50 (complex m, 6H).

\[ ^{13}\text{C NMR (75 MHz, CDCl}_3 \] \( \delta \): 205.7 (C=O), 55.6 (CH), 54.8 (CH), 36.1 (CH\(_2\)), 22.5 (CH\(_2\)), 16.7 (CH\(_2\)).

**Mass spectrum (70 eV) \( m/z \) 112 (M\(^+\), 25%), 83 (22), 55 (100), 41 (32).**

**HRMS** Found M\(^+\), 112.0522. C\(_6\)H\(_8\)O\(_2\) requires 112.0524.

**Formation of compounds 153, 154 and 155 via intermolecular crossed aldehyde-ketone benzoin reaction**

A magnetically stirred solution of epoxy-ketone 151 (100 mg, 0.9 mmol) and aldehyde 152 (136 mg, 0.9 mmol) in DMF (10 mL) maintained under an atmosphere of nitrogen at 45 °C was treated with NaCN (13 mg, 0.27 mmol, 30 mol%) and the ensuing mixture was stirred at this temperature for 20 h then cooled, quenched with water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (1 x 10 mL) then dried (MgSO\(_4\)), filtered, and concentrated under reduced pressure. The residue so-obtained was subjected to flash chromatography (silica, 2:3 v/v ethyl acetate - hexane elution) to afford three fractions, F1-F3.

Concentration of F1 \([R_f \ 0.2(5)]\) under reduced pressure afforded *compound 153* (4 mg, 3%).

\[ ^1\text{H NMR (300 MHz, CDCl}_3 \] \( \delta \): 7.23 (m, 1H, ArH), 6.50 (complex m, 2H, ArH), 2.80-1.80 (complex m, 8H), 3.79 (s, 3H).
Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4

Mass spectrum (70 eV) $m/z$ 264 (M<sup>+</sup>, 40%), 245 (52), 218 (63), 190 (100), 151 (92), 135 (20), 73 (39).

Concentration of F2 ($R_f$ 0.2) under reduced pressure afforded compound 155 (7 mg, 3%).

$^1$H NMR (300 MHz, CDCl<sub>3</sub>) δ: 4.80 (m, 1H), 3.60-3.20 (complex m, 3H), 2.20-1.70 (complex m, 4H).

Mass spectrum (70 eV) $m/z$ 139 (M<sup>++</sup>, 11%), 112 (19), 95 (22), 83 (44), 55 (100).

Concentration of F3 ($R_f$ 0.1) under reduced pressure afforded compound 154 (10 mg, 4%).

$^1$H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.40 (1H, ArH), 6.50 (complex m, 2H, ArH), 3.90-1.60 (complex m, 8H), 3.78 (s, 3H).

Mass spectrum (70 eV) $m/z$ 291 (M<sup>++</sup>, 26%), 264 (17), 218 (37), 190 (54), 153 (100), 83 (30).
5.5 References

Chapter 5 Details of the experimental work described in Chapters 2, 3 and 4


Appendices
Appendix A.1: Summary of key work described in Chapter 2

Fold-out Scheme A.1: Synthesis of piceatannol (53)

Reagents and conditions: (i) PBr₃, THF-PhH, 0 - 18 °C, 2.5 h, 80%; (ii) Ac₂O, pyridine, PhH, 18 °C, 16 h, 99%; (iii) PPh₃, PhH, reflux, 3 h, 85%; (iv) MeOH, p-TsOH, reflux, 5 h, 85%; (v) TBSCI, imidazole, DMF, 18 °C, 16 h, 82%; (vi) compound 76 in THF, n-BuLi, then add compound 77 in THF, 0 - 18 °C, 18 h, 67%; (vii) TBAF, THF, 0 °C, 5 min., 91%.

Fold-out Scheme A.2: Ag₂CO₃-mediated oxidative coupling of piceatannol (53) and sinapyl alcohol (75)

Reagents and conditions: (i) Ag₂CO₃, PhH-acetone 2:1, 60 °C, 18 h, 62% [17% (±)-26, 12% (±)-50, 19% (±)-51, 14% (±)-52].
Appendix A.2: Summary of key work described in Chapter 3

Fold-out Scheme A.3: Synthesis of (2S,3S)-αphanol (26)

Reagents and conditions: (i) MOMCl, DIPEA, DMAP, 0 - 18 °C, 6 h, 95%; (ii) NaH, triethyl phosphonoacetate, THF, 0 - 18 °C, 4 h, 83%; (iii) DIBAL-H, toluene, -10 °C, 0.5 h, 81%; (iv) AD mix-β, CH₃SO₂NH₂, 1:1 v/v 'BuOH-H₂O, 0 °C, 48 h, 80%, >95% e.e.; (v) TsCl, pyridine, 0 - 18 °C, 18 h, 72%; (vi) K₂CO₃, MeOH, 18 °C, 3 h, 88%, >95% e.e.; (vii) compound 89, DIAD, PPh₃, THF-toluene, 18 °C, 24 h, 60%, >95% e.e.; (viii) EtOAc, 5% Pd-C, H₂, 18 °C, 9 h, 71%, >95% e.e.; (ix) K₂CO₃, MeOH, 18 °C, 0.75 h, 70%, >95% e.e.; (x) MOMCl, DIPEA, DMAP, DCM, 0 - 18 °C, 3 h, 85%; (xi) compound 48, CsF, toluene, reflux, 6 h, 41%; (xii) MeOH, AcCl, 18 °C, 20 h, 65%, >95% e.e.
Summary of key work described in Chapter 3 (continued).

Fold-out Scheme A.4: Synthesis of (2R,3R)-aiphanol (ent-26)

Reagents and conditions: (i) AD mix-α, CH₂SO₂NH₂, 1:1 v/v BuOH-H₂O, 0 °C, 48 h, 78%, >95% e.e.; (ii) TsCl, pyridine, 0 - 18 °C, 18 h, 73%; (iii) K₂CO₃, MeOH, 18 °C, 3 h, 82%, >95% e.e.; (iv) compound 89, DIAD, PPh₃, THF-toluene, 18 °C, 24 h, 61%, >95% e.e.; (v) EtOAc, 5% Pd-C, H₂, 18 °C, 9 h, 70%, >95% e.e.; (vi) K₂CO₃, MeOH, 18 °C, 0.75 h, 68%, >91% e.e.; (vii) MOMCl, DIPEA, DMAP, DCM, 0 - 18 °C, 3 h, 81%; (viii) compound 48, CsF, toluene, reflux, 6 h, 39%; (ix) MeOH, AcCl, 18 °C, 20 h, 56%, >91% e.e.
Appendix A.3: Summary of key work described in Chapter 4

Fold-out Scheme A.5: *Formation of benzylidene acetal 114a and p-methoxybenzylidene acetal 114b*

Reagents and conditions: (i) 5% Rh on Al₂O₃, H₂, EtOH, 18 °C, 4 h, 90%; (ii) compound 116, p-TsOH (catalyst), toluene, reflux (Dean-Stark trap), 5 h, 90%; (iii) compound 117, p-TsOH (catalyst), toluene, reflux (Dean-Stark trap), 3 h, 95%.

Fold-out Scheme A.6: *DIBAL-H cleavage of benzylidene acetal 114a*

Reagents and conditions: (i) DIBAL-H, DCM, 0 - 18 °C, 20 h; (ii) MnO₂, Et₂O, 18 °C, 24 h.

Fold-out Scheme A.7: *DIBAL-H cleavage of p-methoxybenzylidene acetal 114b*

Reagents and conditions: (i) DIBAL-H, DCM, -10 °C, 5 h; (ii) MnO₂, Et₂O, 18 °C, 24 h.
Summary of key work described in Chapter 4 (continued)

Fold-out Scheme A.8: m-CPBA epoxidation of compound 118a

\[
\begin{align*}
\text{Reagents and conditions:} \quad & (i) \text{m-CPBA, NaHCO}_3, \text{DCM, } 0^\circ\text{C, } 20 \text{ h, } 78\%. \\
\end{align*}
\]

Fold-out Scheme A.9: Formation of compounds 110a and 124b

\[
\begin{align*}
\text{Reagents and conditions:} \quad & (i) \text{DIBAL-H, DCM, } 0 - 18^\circ\text{C, } 20 \text{ h; (ii) MnO}_2, \text{Et}_2\text{O, } 18^\circ\text{C, } 24 \text{ h.} \\
\end{align*}
\]

Fold-out Scheme A.10: Formation of atranol (111)

\[
\begin{align*}
\text{Reagents and conditions:} \quad & (i) \text{POCl}_3, \text{DMF, } 0 - 18^\circ\text{C, } 6 \text{ h, } 65\%; \quad (ii) \text{NaClO}_3, \text{NaH}_2\text{PO}_4, \text{H}_2\text{O, DMSO, } \\
& \text{H}_2\text{O, } 0 - 18^\circ\text{C, } 8 \text{ h, } 60\%; \quad (iii) \text{H}_2\text{SO}_4 (\text{catalyst}), \text{EtOH, reflux, } 5 \text{ h, } 72\%; \quad (iv) \text{Na, EtOH (18 }^\circ\text{C, } 6 \text{ h) then add compounds } 132 \text{ and } 133, \text{18 }^\circ\text{C - reflux, } 3 \text{ h, } 70\%; \quad (v) \text{Br}_2, \text{AcOH, } 18^\circ\text{C, } 20 \text{ h, } 94\%; \quad (vi) \text{H}_2, 10\% \text{ Pd-C, } 2 \text{ N NaOH, } 18^\circ\text{C, } 20 \text{ h, } 95\%; \quad (vii) \text{Zn(CN)}_2, \text{AlCl}_3, \text{HCl}_{2\text{aq}b}, \text{Et}_2\text{O, } 0 - 18^\circ\text{C, } 18 \text{ h, } 60\%; \quad (viii) 15\% \text{ w/v aqueous NaOH, reflux, } 3 \text{ h, } 79\%; \quad (ix) \text{Heat, } 1 \text{ h, } 74\%. \\
\end{align*}
\]
Appendix A.4: X-ray reports for compounds 89, 106 and ent-106
Appendices

192

X-ray report for compound 89

Abstract

Comment
The compound has crystallized in the chiral spacegroup P212121. The chirality present in the structure is in the propeller sense - i.e the molecular conformation. There is insufficient anomalous dispersion present to determine the extent of any spontaneous resolution which may have occurred.

Experimental

Crystal data
C_{14}H_{12}O_3
M_r = 228.247
Orthorhombic
P_{2_1}2_12_1;
a = 6.47820 (10) Å
b = 11.1466 (2) Å
c = 15.7989 (3) Å
V = 1140.84 (3) Å^3
Z = 4
D_x = 1.329 Mg m^{-3}
D_m not measured

Mo Kα radiation
λ = 0.71073 Å
Cell parameters from 4562 reflections
θ = 2.910–27.485°
μ = 0.093 mm^{-1}
T = 200 K
Prism
Colourless
0.45 × 0.37 × 0.35 mm
Crystal source: local laboratory
Appendices

Data collection
KappaCCD diffractometer

CCD scans

Absorption correction:
- by integration Gaussian by integration
  (Coppens, 1970)

- \( T_{\text{min}} = 0.963, T_{\text{max}} = 0.974 \)

Refinement
Refinement on \( F \)

- \( R = 0.0279 \)
- \( wR = 0.0319 \)
- \( S = 1.0624 \)

- 1193 reflections
- 158 parameters

H atoms treated by a mixture of independent and constrained refinement

Chebychev polynomial with 3 parameters,
  Carruthers & Watkin, 1979, 0.458 0.189
  0.139

- \( (\Delta/\sigma)_{\text{max}} = 0.000317 \)
- \( \Delta \rho_{\text{max}} = 0.14 \text{ e Å}^{-3} \)
- \( \Delta \rho_{\text{min}} = -0.10 \text{ e Å}^{-3} \)

Extinction correction: none

Scattering factors from International Tables for X-ray Crystallography (Vol. IV)

Table 1. Selected geometric parameters (Å, °)

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
<th>Bond</th>
<th>Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O8—C3</td>
<td>1.3632 (18)</td>
<td>C5—C6</td>
<td>1.384 (2)</td>
</tr>
<tr>
<td>O8—C9</td>
<td>1.4353 (19)</td>
<td>C6—C7</td>
<td>1.388 (2)</td>
</tr>
<tr>
<td>O16—C1</td>
<td>1.215 (2)</td>
<td>C9—C10</td>
<td>1.505 (2)</td>
</tr>
<tr>
<td>O17—C4</td>
<td>1.3534 (19)</td>
<td>C10—C11</td>
<td>1.385 (3)</td>
</tr>
<tr>
<td>C1—C2</td>
<td>1.467 (2)</td>
<td>C10—C15</td>
<td>1.388 (2)</td>
</tr>
<tr>
<td>C2—C3</td>
<td>1.395 (2)</td>
<td>C11—C12</td>
<td>1.399 (3)</td>
</tr>
<tr>
<td>C2—C7</td>
<td>1.394 (2)</td>
<td>C12—C13</td>
<td>1.369 (3)</td>
</tr>
<tr>
<td>C3—C4</td>
<td>1.383 (2)</td>
<td>C13—C14</td>
<td>1.374 (3)</td>
</tr>
<tr>
<td>C4—C5</td>
<td>1.407 (2)</td>
<td>C14—C15</td>
<td>1.391 (3)</td>
</tr>
</tbody>
</table>
Appendices

C5—O8—C9 117.52 (12) C5—C6—C7 119.87 (15)
O16—C1—C2 124.25 (15) C2—C7—C6 119.97 (16)
C1—C2—C3 119.38 (14) C8—C9—C10 106.07 (13)
C1—C2—C7 120.66 (14) C9—C10—C11 122.63 (15)
C3—C2—C7 119.96 (13) C9—C10—C15 118.32 (15)
C2—C3—C4 120.47 (15) C11—C10—C15 119.01 (15)
O17—C4—C3 119.32 (14) C10—C11—C12 120.15 (18)
O17—C4—C5 121.65 (13) C11—C12—C13 120.20 (19)
C3—C4—C5 119.03 (14) C12—C13—C14 120.13 (17)
O8—C5—C4 114.07 (13) C13—C14—C15 120.18 (19)
O8—C5—C6 125.31 (14) C10—C15—C14 120.32 (19)
C4—C5—C6 120.62 (13)


References


Appendices

Supplementary data

Table S1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

\[ U_{eq} = (1/3)\sum_{i<j} a_i^T a_j U_{ij} \]

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Ueq</th>
</tr>
</thead>
<tbody>
<tr>
<td>O8</td>
<td>0.39426 (18)</td>
<td>0.12973 (12)</td>
<td>0.62392 (7)</td>
<td>0.0418</td>
</tr>
<tr>
<td>O16</td>
<td>0.4537 (2)</td>
<td>-0.00074 (12)</td>
<td>0.23080 (7)</td>
<td>0.0481</td>
</tr>
<tr>
<td>O17</td>
<td>0.03976 (19)</td>
<td>0.04945 (15)</td>
<td>0.56556 (7)</td>
<td>0.0520</td>
</tr>
<tr>
<td>C1</td>
<td>0.3137 (3)</td>
<td>0.01022 (14)</td>
<td>0.2814 (1)</td>
<td>0.0383</td>
</tr>
<tr>
<td>C2</td>
<td>0.3426 (2)</td>
<td>0.03954 (14)</td>
<td>0.3711 (1)</td>
<td>0.0354</td>
</tr>
<tr>
<td>C3</td>
<td>0.1752 (3)</td>
<td>0.03151 (16)</td>
<td>0.4263 (1)</td>
<td>0.0377</td>
</tr>
<tr>
<td>C4</td>
<td>0.1979 (2)</td>
<td>0.06020 (16)</td>
<td>0.51097 (9)</td>
<td>0.0526</td>
</tr>
<tr>
<td>C5</td>
<td>0.3913 (2)</td>
<td>0.10005 (1)</td>
<td>0.54022 (9)</td>
<td>0.0351</td>
</tr>
<tr>
<td>C6</td>
<td>0.5589 (3)</td>
<td>0.10556 (16)</td>
<td>0.4604 (9)</td>
<td>0.0392</td>
</tr>
<tr>
<td>C7</td>
<td>0.5335 (3)</td>
<td>0.07427 (16)</td>
<td>0.4016 (1)</td>
<td>0.0395</td>
</tr>
<tr>
<td>C9</td>
<td>0.5878 (3)</td>
<td>0.16710 (17)</td>
<td>0.6594 (1)</td>
<td>0.0406</td>
</tr>
<tr>
<td>C10</td>
<td>0.5512 (3)</td>
<td>0.21599 (16)</td>
<td>0.7470 (1)</td>
<td>0.0369</td>
</tr>
<tr>
<td>C11</td>
<td>0.3653 (3)</td>
<td>0.26679 (16)</td>
<td>0.77121 (12)</td>
<td>0.0471</td>
</tr>
<tr>
<td>C12</td>
<td>0.3425 (4)</td>
<td>0.31472 (18)</td>
<td>0.85248 (14)</td>
<td>0.0586</td>
</tr>
<tr>
<td>C13</td>
<td>0.5041 (4)</td>
<td>0.31288 (19)</td>
<td>0.90829 (12)</td>
<td>0.0595</td>
</tr>
<tr>
<td>C14</td>
<td>0.6897 (4)</td>
<td>0.26304 (19)</td>
<td>0.88467 (12)</td>
<td>0.0581</td>
</tr>
<tr>
<td>C15</td>
<td>0.7134 (3)</td>
<td>0.21734 (18)</td>
<td>0.80435 (11)</td>
<td>0.0482</td>
</tr>
</tbody>
</table>

Table S2. Anisotropic displacement parameters (Å²)

\[
\begin{align*}
U_{11} & \quad U_{12} & \quad U_{13} & \quad U_{22} & \quad U_{23} & \quad U_{33} \\
0.0362 (6) & \quad 0.0632 (7) & \quad 0.0259 (5) & \quad -0.0075 (5) & \quad -0.0015 (5) & \quad -0.0025 (5) \\
0.0482 (7) & \quad 0.0663 (8) & \quad 0.0300 (5) & \quad -0.0011 (6) & \quad 0.0006 (5) & \quad -0.0037 (5) \\
0.0313 (6) & \quad 0.0945 (11) & \quad 0.0300 (6) & \quad -0.0056 (7) & \quad -0.0005 (5) & \quad 0.0014 (6) \\
0.0420 (8) & \quad 0.0412 (8) & \quad 0.0315 (7) & \quad -0.0001 (7) & \quad -0.0043 (7) & \quad -0.0014 (6) \\
0.0411 (8) & \quad 0.0373 (8) & \quad 0.0279 (6) & \quad -0.0012 (7) & \quad -0.0004 (7) & \quad 0.0013 (6) \\
0.0341 (8) & \quad 0.0477 (9) & \quad 0.0314 (7) & \quad -0.0013 (7) & \quad -0.0064 (6) & \quad 0.0014 (7) \\
0.0320 (7) & \quad 0.0489 (9) & \quad 0.0284 (7) & \quad 0.0006 (7) & \quad 0.0002 (6) & \quad 0.0036 (7) \\
0.0378 (8) & \quad 0.0419 (8) & \quad 0.0254 (6) & \quad -0.0023 (7) & \quad -0.0032 (6) & \quad 0.0024 (6) \\
0.0364 (8) & \quad 0.0490 (9) & \quad 0.0291 (7) & \quad -0.0084 (7) & \quad -0.0021 (7) & \quad 0.0015 (7) \\
0.0390 (8) & \quad 0.0484 (9) & \quad 0.0313 (7) & \quad -0.0044 (8) & \quad 0.0020 (7) & \quad 0.0007 (7) \\
0.0377 (9) & \quad 0.0505 (9) & \quad 0.0338 (8) & \quad -0.0075 (7) & \quad -0.0043 (7) & \quad -0.0046 (7) \\
0.0425 (9) & \quad 0.0357 (8) & \quad 0.0224 (7) & \quad -0.0029 (7) & \quad -0.0015 (7) & \quad 0.0006 (6) \\
0.050 (1) & \quad 0.0440 (9) & \quad 0.0475 (9) & \quad 0.0049 (8) & \quad -0.0004 (9) & \quad 0.0001 (8) \\
0.0700 (13) & \quad 0.046 (1) & \quad 0.0602 (12) & \quad 0.005 (1) & \quad 0.0167 (12) & \quad -0.0082 (9) \\
0.0916 (17) & \quad 0.0494 (11) & \quad 0.0375 (9) & \quad -0.0110 (11) & \quad 0.0095 (11) & \quad -0.0094 (8) \\
0.0743 (14) & \quad 0.0622 (12) & \quad 0.0376 (9) & \quad -0.0075 (11) & \quad -0.014 (1) & \quad -0.0044 (5) \\
0.049 (1) & \quad 0.0553 (11) & \quad 0.0399 (9) & \quad 0.0017 (9) & \quad -0.0078 (8) & \quad -0.0038 (8) \\
\end{align*}
\]
<table>
<thead>
<tr>
<th>Bond</th>
<th>Geometric parameters (Å, °)</th>
<th>Bond</th>
<th>Geometric parameters (Å, °)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O8—C5</td>
<td>1.3632 (18)</td>
<td>C7—H71</td>
<td>1.000</td>
</tr>
<tr>
<td>O8—C9</td>
<td>1.4533 (19)</td>
<td>C9—C10</td>
<td>1.505 (2)</td>
</tr>
<tr>
<td>O16—C1</td>
<td>1.215 (2)</td>
<td>C9—H91</td>
<td>1.000</td>
</tr>
<tr>
<td>O17—C4</td>
<td>1.3534 (19)</td>
<td>C9—H92</td>
<td>1.000</td>
</tr>
<tr>
<td>O17—H1</td>
<td>0.95 (3)</td>
<td>C10—C11</td>
<td>1.385 (3)</td>
</tr>
<tr>
<td>C1—C2</td>
<td>1.467 (2)</td>
<td>C10—C15</td>
<td>1.388 (2)</td>
</tr>
<tr>
<td>C1—H11</td>
<td>1.000</td>
<td>C11—C12</td>
<td>1.390 (3)</td>
</tr>
<tr>
<td>C2—C3</td>
<td>1.395 (2)</td>
<td>C11—H11</td>
<td>1.000</td>
</tr>
<tr>
<td>C2—C7</td>
<td>1.394 (2)</td>
<td>C12—C13</td>
<td>1.359 (3)</td>
</tr>
<tr>
<td>C3—C4</td>
<td>1.383 (2)</td>
<td>C12—H121</td>
<td>1.000</td>
</tr>
<tr>
<td>C3—H31</td>
<td>1.000</td>
<td>C13—C14</td>
<td>1.374 (3)</td>
</tr>
<tr>
<td>C4—C5</td>
<td>1.407 (2)</td>
<td>C13—H131</td>
<td>1.000</td>
</tr>
<tr>
<td>C5—C6</td>
<td>1.384 (2)</td>
<td>C14—C15</td>
<td>1.391 (3)</td>
</tr>
<tr>
<td>C6—C7</td>
<td>1.388 (2)</td>
<td>C14—H141</td>
<td>1.000</td>
</tr>
<tr>
<td>C6—H61</td>
<td>1.000</td>
<td>C15—H151</td>
<td>1.000</td>
</tr>
<tr>
<td>C5—O8—C9</td>
<td>117.92 (12)</td>
<td>O8—C9—H91</td>
<td>109.70 (9)</td>
</tr>
<tr>
<td>C4—O17—H1</td>
<td>112.3 (19)</td>
<td>C10—C9—H91</td>
<td>109.58 (9)</td>
</tr>
<tr>
<td>O16—C1—C2</td>
<td>124.25 (15)</td>
<td>O8—C9—H92</td>
<td>109.38 (8)</td>
</tr>
<tr>
<td>O16—C1—H11</td>
<td>117.98 (9)</td>
<td>C10—C9—H92</td>
<td>109.62 (9)</td>
</tr>
<tr>
<td>C2—C1—H11</td>
<td>117.77 (9)</td>
<td>H91—C9—H92</td>
<td>109.467</td>
</tr>
<tr>
<td>C1—C2—C5</td>
<td>119.38 (14)</td>
<td>C9—C10—C11</td>
<td>122.63 (15)</td>
</tr>
<tr>
<td>C1—C2—C7</td>
<td>120.66 (14)</td>
<td>C9—C10—C15</td>
<td>118.32 (15)</td>
</tr>
<tr>
<td>C3—C2—C7</td>
<td>119.96 (13)</td>
<td>C11—C10—C15</td>
<td>119.01 (15)</td>
</tr>
<tr>
<td>C2—C3—C4</td>
<td>120.47 (15)</td>
<td>C10—C11—C12</td>
<td>120.15 (18)</td>
</tr>
<tr>
<td>C2—C3—H31</td>
<td>119.89 (9)</td>
<td>C10—C11—H111</td>
<td>119.6 (1)</td>
</tr>
<tr>
<td>C4—C3—H31</td>
<td>119.6 (1)</td>
<td>C12—C11—H111</td>
<td>120.20 (13)</td>
</tr>
<tr>
<td>O17—C4—C3</td>
<td>119.32 (14)</td>
<td>C11—C12—C13</td>
<td>120.20 (19)</td>
</tr>
<tr>
<td>O17—C4—C5</td>
<td>121.65 (13)</td>
<td>C11—C12—H121</td>
<td>119.60 (13)</td>
</tr>
<tr>
<td>C3—C4—C5</td>
<td>119.03 (14)</td>
<td>C13—C12—H121</td>
<td>120.20 (12)</td>
</tr>
<tr>
<td>O8—C5—C4</td>
<td>114.07 (13)</td>
<td>C12—C13—C14</td>
<td>120.13 (17)</td>
</tr>
<tr>
<td>O8—C5—C6</td>
<td>125.31 (14)</td>
<td>C12—C13—H131</td>
<td>119.62 (12)</td>
</tr>
<tr>
<td>C4—C5—C6</td>
<td>120.62 (13)</td>
<td>C14—C13—H131</td>
<td>120.25 (11)</td>
</tr>
<tr>
<td>C5—C6—C7</td>
<td>119.87 (15)</td>
<td>C13—C14—C15</td>
<td>120.18 (19)</td>
</tr>
<tr>
<td>C5—C6—H61</td>
<td>119.55 (9)</td>
<td>C13—C14—H141</td>
<td>118.74 (11)</td>
</tr>
<tr>
<td>C7—C6—H61</td>
<td>120.57 (11)</td>
<td>C15—C14—H141</td>
<td>120.09 (13)</td>
</tr>
<tr>
<td>C2—C7—C6</td>
<td>119.97 (16)</td>
<td>C16—C15—C14</td>
<td>120.32 (19)</td>
</tr>
<tr>
<td>C2—C7—H71</td>
<td>119.92 (9)</td>
<td>C10—C15—H151</td>
<td>119.4 (1)</td>
</tr>
<tr>
<td>C6—C7—H71</td>
<td>120.10 (11)</td>
<td>C14—C15—H151</td>
<td>120.25 (13)</td>
</tr>
<tr>
<td>O8—C9—C10</td>
<td>109.07 (13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
X-ray report for compound 106

Abstract

Comment

The molecule is clearly demonstrated to possess the absolute stereochemistry depicted in the attached diagram.

An extensive three dimensional hydrogen bonding network is noted.

Experimental

Crystal data

\[ C_{11}H_{15}BrO_5 \]

\[ M_r = 323.144 \]

Orthorhombic

\[ P2_12_12_1 \]

\[ a = 6.64640 (10) \text{ Å} \]

\[ b = 11.2215 (2) \text{ Å} \]

\[ c = 17.0114 (4) \text{ Å} \]

\[ V = 1268.75 (4) \text{ Å}^3 \]

\[ Z = 4 \]

\[ D_x = 1.692 \text{ Mg m}^{-3} \]

\[ D_m \text{ not measured} \]

Mo Kα radiation

\[ \lambda = 0.71073 \text{ Å} \]

Cell parameters from 15204 reflections

\[ \theta = 2.910-27.485^\circ \]

\[ \mu = 3.26 \text{ mm}^{-1} \]

\[ T = 200 \text{ K} \]

Prism

Colourless

\[ 0.36 \times 0.28 \times 0.27 \text{ mm} \]

Crystal source: local laboratory
Appendices

Data collection
KappaCCD diffractometer
CCD scans
Absorption correction:
by integration Gaussian by integration
(Coppens, 1970)
\[ T_{\text{min}} = 0.404, \quad T_{\text{max}} = 0.501 \]

Refinement
Refinement on \( F \)
\[ R = 0.0231 \]
\[ wR = 0.0229 \]
\[ S = 1.0641 \]
2055 reflections
180 parameters
H atoms treated by a mixture of independent and constrained refinement
Chebyshev polynomial with 5 parameters, Carruthers & Watkin, 1979
\[ 1.64 \quad 0.216 \]
\[ 2.00 \quad 0.690E-01 \]
\[ 0.590 \]

Extinction correction: none
Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)
Absolute structure: Flack, 1215 Friedel-pairs
Flack parameter = -0.002 (8)

<table>
<thead>
<tr>
<th>Table 1. Selected geometric parameters (Å, °)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br13—C5</td>
</tr>
<tr>
<td>O10—C1</td>
</tr>
<tr>
<td>O11—C2</td>
</tr>
<tr>
<td>O12—C3</td>
</tr>
<tr>
<td>O14—C6</td>
</tr>
<tr>
<td>O14—C15</td>
</tr>
<tr>
<td>O16—C7</td>
</tr>
<tr>
<td>O17—C8</td>
</tr>
<tr>
<td>O17—C18</td>
</tr>
</tbody>
</table>

2055 reflections with
\( >3.00\sigma(I) \)
\[ R_{\text{int}} = 0.049 \]
\[ \theta_{\text{max}} = 27.48° \]
\[ h = -8 \rightarrow 8 \]
\[ k = -13 \rightarrow 14 \]
\[ l = -22 \rightarrow 22 \]

\[ (\Delta/\sigma)_{\text{max}} = 0.000991 \]
\[ \Delta \rho_{\text{max}} = 0.42 \text{ e Å}^{-3} \]
\[ \Delta \rho_{\text{min}} = -0.86 \text{ e Å}^{-3} \]
C8--O17--Cl8 117.4 (2) C4--C5--C6 122.2 (2)
C10--C1--C2 108.5 (2) O14--C6--C5 122.2 (2)
O10--C1--C4 111.1 (2) O14--C6--C7 118.1 (2)
C2--C1--C4 111.18 (19) C5--C6--C7 119.5 (2)
O11--C2--C1 108.5 (2) O16--C7--C6 121.6 (2)
O11--C2--C3 107.9 (2) O16--C7--C8 119.2 (2)
C1--C2--C3 113.5 (2) C6--C7--C8 119.2 (2)
O12--C3--C2 114.0 (2) C17--C8--C7 114.4 (2)
C1--C4--C5 122.7 (2) O17--C8--C9 125.0 (2)
C1--C4--C9 120.2 (2) C7--C8--C9 120.6 (2)
C5--C4--C9 117.0 (2) C4--C9--C8 121.4 (2)
Br13--C5--C6 117.28 (18)
Br13--C5--C6 122.2 (2)
C2--Cl--C4 111.88 (19)
C5--C4--C9 120.55 (19)


References
### Supplementary data

#### Table S1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)

\[
U_{eq} = \frac{1}{3} \Sigma_{i,j} a_i^* a_j^* a_i \cdot a_j
\]

<table>
<thead>
<tr>
<th>Br13</th>
<th>1.21342 (4)</th>
<th>0.18572 (2)</th>
<th>0.268929 (18)</th>
<th>0.0350</th>
</tr>
</thead>
<tbody>
<tr>
<td>O10</td>
<td>0.8268 (4)</td>
<td>0.3058 (2)</td>
<td>0.40974 (12)</td>
<td>0.0388</td>
</tr>
<tr>
<td>O11</td>
<td>0.5801 (3)</td>
<td>0.12459 (19)</td>
<td>0.41221 (12)</td>
<td>0.0264</td>
</tr>
<tr>
<td>O12</td>
<td>1.0553 (3)</td>
<td>0.0169 (2)</td>
<td>0.49088 (13)</td>
<td>0.0331</td>
</tr>
<tr>
<td>O14</td>
<td>1.0445 (2)</td>
<td>0.31128 (18)</td>
<td>0.1542 (1)</td>
<td>0.0320</td>
</tr>
<tr>
<td>O16</td>
<td>0.6870 (3)</td>
<td>0.42823 (16)</td>
<td>0.1098 (1)</td>
<td>0.0290</td>
</tr>
<tr>
<td>O17</td>
<td>0.4541 (2)</td>
<td>0.47325 (15)</td>
<td>0.23169 (12)</td>
<td>0.0304</td>
</tr>
<tr>
<td>C1</td>
<td>0.8631 (4)</td>
<td>0.23314 (2)</td>
<td>0.40572 (14)</td>
<td>0.0231</td>
</tr>
<tr>
<td>C2</td>
<td>0.7931 (4)</td>
<td>0.10894 (19)</td>
<td>0.41306 (13)</td>
<td>0.0219</td>
</tr>
<tr>
<td>Cl</td>
<td>0.8468 (4)</td>
<td>0.0451 (2)</td>
<td>0.49009 (15)</td>
<td>0.0276</td>
</tr>
<tr>
<td>C4</td>
<td>0.8472 (3)</td>
<td>0.28824 (19)</td>
<td>0.32754 (14)</td>
<td>0.0226</td>
</tr>
<tr>
<td>C5</td>
<td>0.9693 (3)</td>
<td>0.27345 (19)</td>
<td>0.26186 (16)</td>
<td>0.0243</td>
</tr>
<tr>
<td>C6</td>
<td>0.9195 (3)</td>
<td>0.3264 (2)</td>
<td>0.18844 (14)</td>
<td>0.0249</td>
</tr>
<tr>
<td>C7</td>
<td>0.7428 (4)</td>
<td>0.38511 (19)</td>
<td>0.19029 (14)</td>
<td>0.0334</td>
</tr>
<tr>
<td>C8</td>
<td>0.6202 (4)</td>
<td>0.4032 (2)</td>
<td>0.24594 (14)</td>
<td>0.0333</td>
</tr>
<tr>
<td>C9</td>
<td>0.6708 (3)</td>
<td>0.3550 (2)</td>
<td>0.31754 (14)</td>
<td>0.0242</td>
</tr>
<tr>
<td>C15</td>
<td>1.0985 (6)</td>
<td>0.2073 (3)</td>
<td>0.29845 (16)</td>
<td>0.0346</td>
</tr>
<tr>
<td>C18</td>
<td>0.3427 (4)</td>
<td>0.5134 (3)</td>
<td>0.29887 (16)</td>
<td>0.0346</td>
</tr>
<tr>
<td>H1</td>
<td>0.905 (5)</td>
<td>0.316 (4)</td>
<td>0.488 (2)</td>
<td>0.036 (11)</td>
</tr>
<tr>
<td>H2</td>
<td>0.522 (7)</td>
<td>0.076 (4)</td>
<td>0.396 (3)</td>
<td>0.081 (17)</td>
</tr>
<tr>
<td>H3</td>
<td>1.098 (5)</td>
<td>0.070 (3)</td>
<td>0.505 (2)</td>
<td>0.032 (11)</td>
</tr>
<tr>
<td>H4</td>
<td>0.739 (7)</td>
<td>0.449 (4)</td>
<td>0.089 (3)</td>
<td>0.085 (15)</td>
</tr>
<tr>
<td>H11</td>
<td>1.0423 (4)</td>
<td>0.2205 (2)</td>
<td>0.40789 (14)</td>
<td>0.0272</td>
</tr>
<tr>
<td>H21</td>
<td>0.8453 (4)</td>
<td>0.05971 (19)</td>
<td>0.36940 (13)</td>
<td>0.0250</td>
</tr>
<tr>
<td>H31</td>
<td>0.8229 (4)</td>
<td>0.0960 (2)</td>
<td>0.35318 (15)</td>
<td>0.0331</td>
</tr>
<tr>
<td>H32</td>
<td>0.7725 (4)</td>
<td>0.03241 (2)</td>
<td>0.49146 (15)</td>
<td>0.0331</td>
</tr>
<tr>
<td>H91</td>
<td>0.5781 (3)</td>
<td>0.3675 (2)</td>
<td>0.36317 (14)</td>
<td>0.0276</td>
</tr>
<tr>
<td>H151</td>
<td>1.1050 (6)</td>
<td>0.2905 (3)</td>
<td>0.3091 (2)</td>
<td>0.0627</td>
</tr>
<tr>
<td>H152</td>
<td>1.0275 (6)</td>
<td>0.1337 (3)</td>
<td>0.1093 (2)</td>
<td>0.0627</td>
</tr>
<tr>
<td>H153</td>
<td>0.8673 (6)</td>
<td>0.2097 (3)</td>
<td>0.0565 (2)</td>
<td>0.0627</td>
</tr>
<tr>
<td>H181</td>
<td>0.2262 (4)</td>
<td>0.5626 (3)</td>
<td>0.50609 (16)</td>
<td>0.0433</td>
</tr>
<tr>
<td>H182</td>
<td>0.4531 (4)</td>
<td>0.5626 (3)</td>
<td>0.33282 (16)</td>
<td>0.0433</td>
</tr>
<tr>
<td>H183</td>
<td>0.2922 (4)</td>
<td>0.4434 (3)</td>
<td>0.32900 (16)</td>
<td>0.0433</td>
</tr>
</tbody>
</table>

#### Table S2. Anisotropic displacement parameters (Å²)

<table>
<thead>
<tr>
<th></th>
<th>(U_{11})</th>
<th>(U_{22})</th>
<th>(U_{33})</th>
<th>(U_{12})</th>
<th>(U_{13})</th>
<th>(U_{23})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br13</td>
<td>0.02648 (11)</td>
<td>0.03497 (12)</td>
<td>0.04636 (15)</td>
<td>0.00972 (11)</td>
<td>0.00424 (13)</td>
<td>0.00848 (13)</td>
</tr>
</tbody>
</table>
Table S3. Geometric parameters (Å, °)

<table>
<thead>
<tr>
<th>Bond/Angle</th>
<th>Length/Value</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br13--C5</td>
<td>1.902 (2)</td>
<td></td>
</tr>
<tr>
<td>O10--C1</td>
<td>1.441 (3)</td>
<td></td>
</tr>
<tr>
<td>O11--C2</td>
<td>1.427 (3)</td>
<td></td>
</tr>
<tr>
<td>O11--H2</td>
<td>0.72 (3)</td>
<td></td>
</tr>
<tr>
<td>O12--C3</td>
<td>1.423 (3)</td>
<td></td>
</tr>
<tr>
<td>O12--H3</td>
<td>0.65 (3)</td>
<td></td>
</tr>
<tr>
<td>O14--C6</td>
<td>1.381 (3)</td>
<td></td>
</tr>
<tr>
<td>O14--C15</td>
<td>1.436 (4)</td>
<td></td>
</tr>
<tr>
<td>O16--C7</td>
<td>1.364 (3)</td>
<td></td>
</tr>
<tr>
<td>O16--H4</td>
<td>0.84 (3)</td>
<td></td>
</tr>
<tr>
<td>O17--C8</td>
<td>1.376 (3)</td>
<td></td>
</tr>
<tr>
<td>O17--C18</td>
<td>1.425 (3)</td>
<td></td>
</tr>
<tr>
<td>C1--C2</td>
<td>1.533 (3)</td>
<td></td>
</tr>
<tr>
<td>C1--C4</td>
<td>1.506 (3)</td>
<td></td>
</tr>
<tr>
<td>C1--H11</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>C2--C3</td>
<td>1.522 (3)</td>
<td></td>
</tr>
<tr>
<td>C1--O10--H1</td>
<td>102.5 (35)</td>
<td></td>
</tr>
<tr>
<td>C2--O11--H2</td>
<td>116.4 (39)</td>
<td></td>
</tr>
<tr>
<td>C3--O12--H3</td>
<td>105.3 (32)</td>
<td></td>
</tr>
<tr>
<td>C6--O14--C15</td>
<td>113.7 (2)</td>
<td></td>
</tr>
<tr>
<td>C7--O15--H4</td>
<td>102.2 (32)</td>
<td></td>
</tr>
<tr>
<td>C8--O16--C18</td>
<td>117.4 (2)</td>
<td></td>
</tr>
<tr>
<td>C10--O11--C2</td>
<td>108.5 (2)</td>
<td></td>
</tr>
<tr>
<td>C10--C1--C4</td>
<td>111.1 (2)</td>
<td></td>
</tr>
<tr>
<td>C2--C11--C4</td>
<td>111.88 (19)</td>
<td></td>
</tr>
<tr>
<td>C10--C11--H11</td>
<td>110.33 (15)</td>
<td></td>
</tr>
<tr>
<td>C2--C11--H11</td>
<td>108.45 (13)</td>
<td></td>
</tr>
<tr>
<td>C4--C11--H11</td>
<td>106.50 (13)</td>
<td></td>
</tr>
<tr>
<td>O11--C2--C3</td>
<td>108.5 (2)</td>
<td></td>
</tr>
<tr>
<td>O11--C2--H2</td>
<td>107.9 (2)</td>
<td></td>
</tr>
<tr>
<td>O11--C2--C3</td>
<td>113.5 (2)</td>
<td></td>
</tr>
<tr>
<td>O11--C2--H21</td>
<td>113.36 (12)</td>
<td></td>
</tr>
<tr>
<td>C1--C2--H21</td>
<td>106.00 (12)</td>
<td></td>
</tr>
<tr>
<td>C3--C2--H21</td>
<td>107.68 (13)</td>
<td></td>
</tr>
<tr>
<td>O12--C3--C2</td>
<td>114.0 (2)</td>
<td></td>
</tr>
<tr>
<td>O12--C3--H31</td>
<td>109.29 (15)</td>
<td></td>
</tr>
<tr>
<td>C2--C3--H31</td>
<td>108.38 (13)</td>
<td></td>
</tr>
<tr>
<td>O12--C3--H32</td>
<td>107.43 (15)</td>
<td></td>
</tr>
<tr>
<td>C2--C3--H32</td>
<td>108.25 (13)</td>
<td></td>
</tr>
<tr>
<td>H31--C3--H32</td>
<td>109.466</td>
<td></td>
</tr>
<tr>
<td>C1--C4--C5</td>
<td>122.7 (2)</td>
<td></td>
</tr>
<tr>
<td>C1--C4--C9</td>
<td>120.2 (2)</td>
<td></td>
</tr>
<tr>
<td>C5--C4--C9</td>
<td>117.0 (2)</td>
<td></td>
</tr>
<tr>
<td>C8</td>
<td>0.0231 (11)</td>
<td>0.023 (1)</td>
</tr>
<tr>
<td>C9</td>
<td>0.0248 (14)</td>
<td>0.0294 (11)</td>
</tr>
<tr>
<td>C15</td>
<td>0.075 (2)</td>
<td>0.048 (2)</td>
</tr>
<tr>
<td>C18</td>
<td>0.0350 (16)</td>
<td>0.0381 (14)</td>
</tr>
</tbody>
</table>
X-ray report for compound *ent-106*

*ent-106*

**Abstract**

The absolute structure is determined unambiguously in this study. A complex 3-D hydrogen bonded network is noted but not analysed.

**Comment**

**Experimental**

*Crystal data*

C_{11}H_{15}BrO_{6}

\( M_r = 323.144 \)

Orthorhombic

\( P2_12_12_1 \)

\( a = 6.64850 \) (10) \( \) Å

\( b = 11.2214 \) (2) \( \) Å

\( c = 17.0146 \) (3) \( \) Å

\( V = 1269.38 \) (4) \( \) Å\(^3\)

\( Z = 4 \)

\( D_x = 1.691 \) Mg \( \) m\(^{-3}\)

\( D_m \) not measured

Mo K\( \alpha \) radiation

\( \lambda = 0.71073 \) Å

Cell parameters from 18264 reflections

\( \theta = 2.910-27.485^\circ \)

\( \mu = 3.25 \) mm\(^{-1}\)

\( T = 200 \) K

Prism

Colourless

0.40 × 0.40 × 0.36 mm

Crystal source: local laboratory
Appendices

Data collection
KappaCCD diffractometer
CCD scans
Absorption correction:
by integration Gaussian by integration
(Coppens, 1970)
$T_{\text{min}} = 0.268, T_{\text{max}} = 0.457$

Refinement
Refinement on $F$
$R = 0.0222$
$wR = 0.0235$
$S = 1.0719$
2360 reflections
164 parameters
H-atom parameters not refined
Chebyshev polynomial with 3 parameters,
Carruthers & Watkin, 1979, $0.741 - 0.109$
$0.424$

Table 1. Selected geometric parameters ($\AA, {}^\circ$)

<table>
<thead>
<tr>
<th>Bond</th>
<th>$d$ ($\AA$)</th>
<th>Bond</th>
<th>$d$ ($\AA$)</th>
<th>Bond</th>
<th>$d$ ($\AA$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br12—C4</td>
<td>1.898 (2)</td>
<td>C1—C2</td>
<td>1.392 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O7—C1</td>
<td>1.373 (3)</td>
<td>C1—C6</td>
<td>1.383 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O7—C8</td>
<td>1.424 (3)</td>
<td>C2—C3</td>
<td>1.387 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O9—C2</td>
<td>1.392 (3)</td>
<td>C3—C4</td>
<td>1.401 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O10—C3</td>
<td>1.382 (3)</td>
<td>C4—C5</td>
<td>1.389 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O10—C11</td>
<td>1.434 (4)</td>
<td>C5—C6</td>
<td>1.401 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O16—C13</td>
<td>1.436 (3)</td>
<td>C5—C13</td>
<td>1.509 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O17—C14</td>
<td>1.429 (3)</td>
<td>C13—C14</td>
<td>1.532 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O18—C15</td>
<td>1.423 (3)</td>
<td>C14—C15</td>
<td>1.525 (3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$(\Delta / \sigma)_{\text{max}} = 0.000420$
$\Delta \rho_{\text{max}} = 0.36 \text{ e } \AA^{-3}$
$\Delta \rho_{\text{min}} = -0.65 \text{ e } \AA^{-3}$
Extinction correction: none
Scattering factors from International Tables for X-ray Crystallography (Vol. IV)
Absolute structure: Flack, 1200 Friedel-pairs
Flack parameter = 0.002 (8)
Appendices


References


### Supplementary data

**Table S1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)**

\[
U_{eq} = \frac{1}{3} \Sigma_i \Sigma_j U_{ij} a_i^* a_j^* \text{a}_{ij}
\]

<table>
<thead>
<tr>
<th>Symbol</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>(U_{eq})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br12</td>
<td>1.21322 (4)</td>
<td>0.31421 (2)</td>
<td>0.269135 (16)</td>
<td>0.0358</td>
</tr>
<tr>
<td>O7</td>
<td>0.4545 (2)</td>
<td>0.02667 (15)</td>
<td>0.23175 (11)</td>
<td>0.0307</td>
</tr>
<tr>
<td>O9</td>
<td>0.6875 (3)</td>
<td>0.06729 (15)</td>
<td>0.10981 (9)</td>
<td>0.0291</td>
</tr>
<tr>
<td>O10</td>
<td>1.0451 (2)</td>
<td>0.19865 (17)</td>
<td>0.12430 (9)</td>
<td>0.0318</td>
</tr>
<tr>
<td>O16</td>
<td>0.8268 (3)</td>
<td>0.19425 (16)</td>
<td>0.45983 (9)</td>
<td>0.0371</td>
</tr>
<tr>
<td>O17</td>
<td>0.5800 (2)</td>
<td>0.37539 (16)</td>
<td>0.4122 (1)</td>
<td>0.0276</td>
</tr>
<tr>
<td>O18</td>
<td>1.0549 (2)</td>
<td>0.48033 (16)</td>
<td>0.4982 (1)</td>
<td>0.0330</td>
</tr>
<tr>
<td>Cl1</td>
<td>0.2020 (3)</td>
<td>0.09653 (19)</td>
<td>0.24563 (13)</td>
<td>0.0238</td>
</tr>
<tr>
<td>Cl2</td>
<td>0.7425 (3)</td>
<td>0.11470 (18)</td>
<td>0.18030 (12)</td>
<td>0.0339</td>
</tr>
<tr>
<td>Cl3</td>
<td>0.9189 (3)</td>
<td>0.1705 (2)</td>
<td>0.18854 (12)</td>
<td>0.0240</td>
</tr>
<tr>
<td>Cl4</td>
<td>0.9606 (3)</td>
<td>0.22669 (18)</td>
<td>0.26215 (15)</td>
<td>0.0337</td>
</tr>
<tr>
<td>Cl5</td>
<td>0.8471 (3)</td>
<td>0.21185 (18)</td>
<td>0.32755 (13)</td>
<td>0.0227</td>
</tr>
<tr>
<td>Cl6</td>
<td>0.6708 (3)</td>
<td>0.1451 (2)</td>
<td>0.31768 (13)</td>
<td>0.0242</td>
</tr>
<tr>
<td>Cl7</td>
<td>0.3429 (4)</td>
<td>-0.0132 (2)</td>
<td>0.29615 (15)</td>
<td>0.0346</td>
</tr>
<tr>
<td>Cl11</td>
<td>1.0102 (6)</td>
<td>0.2025 (3)</td>
<td>0.07708 (18)</td>
<td>0.0353</td>
</tr>
<tr>
<td>Cl13</td>
<td>0.8926 (3)</td>
<td>0.2684 (2)</td>
<td>0.40603 (13)</td>
<td>0.0235</td>
</tr>
<tr>
<td>Cl14</td>
<td>0.7932 (4)</td>
<td>0.39100 (18)</td>
<td>0.41396 (11)</td>
<td>0.0219</td>
</tr>
<tr>
<td>Cl15</td>
<td>0.8462 (3)</td>
<td>0.4548 (2)</td>
<td>0.49036 (14)</td>
<td>0.0271</td>
</tr>
<tr>
<td>H61</td>
<td>0.5789 (3)</td>
<td>0.1321 (2)</td>
<td>0.36340 (13)</td>
<td>0.0284</td>
</tr>
<tr>
<td>H81</td>
<td>0.2269 (4)</td>
<td>-0.0029 (2)</td>
<td>0.28025 (15)</td>
<td>0.0433</td>
</tr>
<tr>
<td>H82</td>
<td>0.2918 (4)</td>
<td>0.0570 (2)</td>
<td>0.32835 (15)</td>
<td>0.0433</td>
</tr>
<tr>
<td>H83</td>
<td>0.4327 (4)</td>
<td>-0.0620 (2)</td>
<td>0.32359 (15)</td>
<td>0.0433</td>
</tr>
<tr>
<td>H111</td>
<td>1.1069 (6)</td>
<td>0.2931 (3)</td>
<td>0.03205 (16)</td>
<td>0.0636</td>
</tr>
<tr>
<td>H112</td>
<td>0.8694 (6)</td>
<td>0.2903 (3)</td>
<td>0.06648 (16)</td>
<td>0.0636</td>
</tr>
<tr>
<td>H113</td>
<td>1.0296 (6)</td>
<td>0.3660 (2)</td>
<td>0.10045 (18)</td>
<td>0.0636</td>
</tr>
<tr>
<td>H131</td>
<td>1.0419 (3)</td>
<td>0.2786 (2)</td>
<td>0.40651 (13)</td>
<td>0.0381</td>
</tr>
<tr>
<td>H141</td>
<td>0.8452 (4)</td>
<td>0.44027 (18)</td>
<td>0.36940 (11)</td>
<td>0.0360</td>
</tr>
<tr>
<td>H151</td>
<td>0.7716 (3)</td>
<td>0.5321 (2)</td>
<td>0.49197 (14)</td>
<td>0.0340</td>
</tr>
<tr>
<td>H152</td>
<td>0.8026 (3)</td>
<td>0.4037 (2)</td>
<td>0.53539 (14)</td>
<td>0.0340</td>
</tr>
<tr>
<td>H2</td>
<td>0.9091 (3)</td>
<td>0.17334 (16)</td>
<td>0.50045 (9)</td>
<td>0.0500</td>
</tr>
<tr>
<td>H4</td>
<td>0.5212 (2)</td>
<td>0.43497 (16)</td>
<td>0.3979 (1)</td>
<td>0.0500</td>
</tr>
<tr>
<td>H3</td>
<td>1.1384 (2)</td>
<td>0.41881 (16)</td>
<td>0.4981 (1)</td>
<td>0.0500</td>
</tr>
<tr>
<td>H1</td>
<td>0.8028 (3)</td>
<td>0.06044 (15)</td>
<td>0.08719 (9)</td>
<td>0.0500</td>
</tr>
</tbody>
</table>

**Table S2. Anisotropic displacement parameters (Å²)**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>(U_{11})</th>
<th>(U_{22})</th>
<th>(U_{33})</th>
<th>(-U_{12})</th>
<th>(-U_{13})</th>
<th>(-U_{23})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br12</td>
<td>0.0251 (1)</td>
<td>0.03591 (11)</td>
<td>0.04647 (13)</td>
<td>-0.0100 (1)</td>
<td>0.00438 (11)</td>
<td>-0.00885 (12)</td>
</tr>
<tr>
<td>O7</td>
<td>0.0282 (8)</td>
<td>0.03777 (8)</td>
<td>0.0262 (7)</td>
<td>-0.0131 (6)</td>
<td>-0.0006 (8)</td>
<td>-0.0070 (8)</td>
</tr>
<tr>
<td>O9</td>
<td>0.0278 (9)</td>
<td>0.0367 (8)</td>
<td>0.0229 (7)</td>
<td>-0.0001 (6)</td>
<td>0.0021 (7)</td>
<td>-0.0066 (6)</td>
</tr>
<tr>
<td>O10</td>
<td>0.0314 (8)</td>
<td>0.0330 (8)</td>
<td>0.0311 (8)</td>
<td>-0.0007 (8)</td>
<td>0.0012 (6)</td>
<td>-0.0024 (8)</td>
</tr>
<tr>
<td>O16</td>
<td>0.0561 (12)</td>
<td>0.0305 (8)</td>
<td>0.0247 (7)</td>
<td>-0.0018 (9)</td>
<td>-0.0116 (7)</td>
<td>0.0085 (7)</td>
</tr>
<tr>
<td>O17</td>
<td>0.0186 (8)</td>
<td>0.0352 (9)</td>
<td>0.0289 (8)</td>
<td>-0.0039 (6)</td>
<td>-0.0019 (8)</td>
<td>0.0013 (7)</td>
</tr>
<tr>
<td>O18</td>
<td>0.0276 (9)</td>
<td>0.042 (1)</td>
<td>0.0294 (8)</td>
<td>-0.0040 (7)</td>
<td>-0.0032 (7)</td>
<td>-0.0064 (8)</td>
</tr>
<tr>
<td>C1</td>
<td>0.022 (1)</td>
<td>0.0231 (9)</td>
<td>0.0262 (12)</td>
<td>-0.0034 (8)</td>
<td>-0.0014 (8)</td>
<td>-0.0007 (8)</td>
</tr>
<tr>
<td>C2</td>
<td>0.0280 (14)</td>
<td>0.0227 (9)</td>
<td>0.021 (1)</td>
<td>0.0005 (8)</td>
<td>-0.0007 (8)</td>
<td>0.0022 (8)</td>
</tr>
<tr>
<td>C3</td>
<td>0.025 (1)</td>
<td>0.0220 (9)</td>
<td>0.025 (1)</td>
<td>0.0002 (1)</td>
<td>0.0045 (8)</td>
<td>-0.0001 (1)</td>
</tr>
<tr>
<td>C4</td>
<td>0.0184 (9)</td>
<td>0.0197 (8)</td>
<td>0.0331 (11)</td>
<td>-0.0004 (7)</td>
<td>-0.0003 (9)</td>
<td>0.0008 (9)</td>
</tr>
<tr>
<td>C5</td>
<td>0.0221 (9)</td>
<td>0.0220 (11)</td>
<td>0.024 (1)</td>
<td>0.0019 (7)</td>
<td>-0.0037 (8)</td>
<td>-0.0004 (8)</td>
</tr>
<tr>
<td>C6</td>
<td>0.0244 (12)</td>
<td>0.027 (1)</td>
<td>0.021 (1)</td>
<td>-0.0018 (8)</td>
<td>-0.0007 (8)</td>
<td>-0.0018 (8)</td>
</tr>
<tr>
<td>C8</td>
<td>0.0351 (14)</td>
<td>0.0391 (14)</td>
<td>0.0296 (11)</td>
<td>-0.016 (1)</td>
<td>0.0031 (9)</td>
<td>-0.002 (1)</td>
</tr>
</tbody>
</table>
### Table S3. Geometric parameters (Å, °)

<table>
<thead>
<tr>
<th>Bond</th>
<th>Distance (Å)</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br12—C4</td>
<td>1.898 (2)</td>
<td>C4—C5 1.389 (3)</td>
</tr>
<tr>
<td>O7—C1</td>
<td>1.373 (3)</td>
<td>C5—C6 1.401 (3)</td>
</tr>
<tr>
<td>O7—C2</td>
<td>1.424 (3)</td>
<td>C6—C13 1.509 (3)</td>
</tr>
<tr>
<td>O9—C2</td>
<td>1.392 (3)</td>
<td>C6—H61 1.000</td>
</tr>
<tr>
<td>O9—H1</td>
<td>0.862</td>
<td>C8—H81 1.000</td>
</tr>
<tr>
<td>O10—C3</td>
<td>1.382 (3)</td>
<td>C8—H82 1.000</td>
</tr>
<tr>
<td>O10—C11</td>
<td>1.434 (4)</td>
<td>C8—H83 1.000</td>
</tr>
<tr>
<td>O16—C13</td>
<td>1.436 (3)</td>
<td>C11—H111 1.000</td>
</tr>
<tr>
<td>O16—H2</td>
<td>0.791</td>
<td>C11—H112 1.000</td>
</tr>
<tr>
<td>O17—C14</td>
<td>1.429 (3)</td>
<td>C11—H113 1.000</td>
</tr>
<tr>
<td>O17—H4</td>
<td>0.811</td>
<td>C13—C14 1.523 (3)</td>
</tr>
<tr>
<td>O18—C15</td>
<td>1.423 (3)</td>
<td>C13—H31 1.000</td>
</tr>
<tr>
<td>C1—C2</td>
<td>1.392 (3)</td>
<td>C14—C15 1.525 (3)</td>
</tr>
<tr>
<td>C1—C6</td>
<td>1.383 (3)</td>
<td>C14—H41 1.000</td>
</tr>
<tr>
<td>C2—C3</td>
<td>1.387 (3)</td>
<td>C15—H151 1.000</td>
</tr>
<tr>
<td>C3—C4</td>
<td>1.401 (3)</td>
<td>C15—H152 1.000</td>
</tr>
<tr>
<td>C1—O7—C8</td>
<td>117.47 (19)</td>
<td>O7—C8—H83 109.03 (13)</td>
</tr>
<tr>
<td>C2—O9—H1</td>
<td>100.89 (12)</td>
<td>H81—C8—H83 109.475</td>
</tr>
<tr>
<td>C3—O10—C11</td>
<td>113.9 (2)</td>
<td>H82—C8—H83 109.476</td>
</tr>
<tr>
<td>C13—O16—H2</td>
<td>117.32 (11)</td>
<td>O16—C11—H111 109.33 (14)</td>
</tr>
<tr>
<td>C14—O17—H4</td>
<td>112.52 (11)</td>
<td>O10—C11—H112 109.15 (17)</td>
</tr>
<tr>
<td>C15—O18—H5</td>
<td>116.98 (12)</td>
<td>H111—C11—H112 109.476</td>
</tr>
<tr>
<td>O7—C1—C2</td>
<td>114.52 (19)</td>
<td>O16—C11—H113 109.92 (16)</td>
</tr>
<tr>
<td>O7—C1—C6</td>
<td>124.9 (2)</td>
<td>H111—C11—H113 109.476</td>
</tr>
<tr>
<td>C2—C1—C6</td>
<td>120.54 (19)</td>
<td>H112—C11—H113 109.476</td>
</tr>
<tr>
<td>O9—C2—C1</td>
<td>119.26 (19)</td>
<td>O16—C13—C15 111.34 (18)</td>
</tr>
<tr>
<td>O9—C2—C3</td>
<td>121.40 (19)</td>
<td>O16—C13—C14 108.80 (18)</td>
</tr>
<tr>
<td>C1—C2—C3</td>
<td>119.33 (19)</td>
<td>C5—C13—C14 111.65 (18)</td>
</tr>
<tr>
<td>O10—C3—C2</td>
<td>118.18 (19)</td>
<td>O16—C13—H131 109.67 (11)</td>
</tr>
<tr>
<td>O10—C3—C4</td>
<td>122.22 (19)</td>
<td>C5—C13—H131 106.52 (12)</td>
</tr>
<tr>
<td>C2—C3—C4</td>
<td>118.48 (19)</td>
<td>C14—C13—H131 108.81 (12)</td>
</tr>
<tr>
<td>Br12—C4—C3</td>
<td>117.29 (16)</td>
<td>C14—C14—C15 108.44 (18)</td>
</tr>
<tr>
<td>Br12—C4—C5</td>
<td>120.82 (17)</td>
<td>C14—C14—C15 107.73 (18)</td>
</tr>
<tr>
<td>C3—C4—C5</td>
<td>121.96 (19)</td>
<td>C13—C14—C15 113.38 (18)</td>
</tr>
<tr>
<td>C4—C5—C6</td>
<td>117.29 (19)</td>
<td>C17—C14—H141 113.25 (11)</td>
</tr>
<tr>
<td>C4—C5—C13</td>
<td>122.73 (19)</td>
<td>C13—C14—H141 106.29 (11)</td>
</tr>
<tr>
<td>C6—C5—C13</td>
<td>119.93 (19)</td>
<td>C15—C14—H141 107.87 (12)</td>
</tr>
<tr>
<td>C1—C6—C5</td>
<td>121.3 (2)</td>
<td>O18—C15—C14 113.56 (19)</td>
</tr>
<tr>
<td>C1—C6—H61</td>
<td>118.92 (12)</td>
<td>O18—C15—H151 107.84 (12)</td>
</tr>
<tr>
<td>C3—C6—H61</td>
<td>119.73 (12)</td>
<td>C14—C15—H151 108.44 (12)</td>
</tr>
<tr>
<td>O7—C8—H81</td>
<td>109.63 (12)</td>
<td>C18—C15—H152 109.01 (13)</td>
</tr>
<tr>
<td>O7—C8—H82</td>
<td>109.73 (14)</td>
<td>C14—C15—H152 108.47 (12)</td>
</tr>
<tr>
<td>H81—C8—H82</td>
<td>109.476</td>
<td>H151—C15—H152 109.467</td>
</tr>
</tbody>
</table>
Appendix A.5

Publication
Convergent synthesis and preliminary biological evaluations of the stilbenolignan (±)-aiphanol and various congeners

Martin G. Banwell,* Anna Bezos, Satish Chand, Gerd Dannhardt, Werner Kiefer, Ulrike Nowe, Christopher R. Parish, G. Paul Savage and Holger Ulbrich

* Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia. E-mail: mgb@rsc.anu.edu.au

b John Curtin School of Medical Research, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia

c Institut für Pharmazie, Johannes Gutenberg-Universität, Staudinger Weg 5, D-55099 Mainz, Germany

d CSIRO Molecular Science, Private Bag 10, Clayton South MDC, Victoria 3169, Australia

Received 9th May 2003, Accepted 13th June 2003

First published as an Advance Article on the web 23rd June 2003

Treatment of an equimolar mixture of stilbene 7 and certain dihydrobenzofuran lignans have recently been shown to function in the latter mode we became interested in developing simple syntheses of compound (±)-aiphanol (1) and congeners 2-4 each of which show significant anti-angiogenic and COX-2 inhibitory properties.

Kinghorn and co-workers have recently reported the bioassay-guided isolation of the stilbenolignan (±)-aiphanol (1) from the seeds of Alpinia officinarum. The compound not only possesses the unprecedented stilbene unit in which a stilbene unit is connected to a phenylpropane unit via a dioxane bridge but it also shows potent inhibition of cyclooxygenase-1 and -2 (COX-1 and -2) with IC50 values of 1.9 and 9.9 µM, respectively. Since compounds exhibiting COX-2 activity can also act as anti-angiogenic agents (i.e. they inhibit the growth of blood vessels) and because certain dihydrobenzofuran lignans have recently been shown to function in the latter mode we became interested in developing simple syntheses of compound 1 and various congeners with a view to establishing preliminary structure-activity profiles for this novel type of natural product. In this connection we now describe a simple and convergent (but non-selective) route to (±)-aiphanol (1) and the regio- and/or stereo-isomeric systems 2-4. Preliminary biological evaluations of compounds 1-4, and certain substructures as COX-2 and angiogenesis inhibitors are also reported herein.

The synthetic route employed in obtaining the racemic modifications of compounds 1-4 is shown in Scheme 1. Thus, the previously reported and readily available ylide 5 was reacted with the known benzaldehyde 6 to give, after an extractive work up and a fluoride ion treatment which resulted in two-fold desilylation of the primary product, the stilbene piceatannol (itself a natural product) in 67% yield (mp 232–234 °C; lit. mp 229 °C). Following Stermitz’s modification of the classic procedures developed by Merlini et al., silver carbonate-promoted oxidative coupling of compound 7 with commercially available sinapyl alcohol (8) gave a ca. 2 : 1 : 2 : 1 mixture of the stilbenolignans (±)-aiphanol (1) and congeners 2-4 each of which show significant anti-angiogenic and COX-2 inhibitory properties.

The mobile and second most abundant component, F1, proved to be rac-aiphanol (±-1) as judged by comparison of the derived 1H and 13C NMR spectral data with those reported for the natural product. The major product, F3, is most likely the stereo-isomeric system 3 which is assigned as such by virtue of the observation of a vicinal coupling of 8.1 Hz between H2 and H3 (the equivalent coupling in rac-aiphanol is the same) suggesting a trans-relationship between the aryl and hydroxymethyl substituents on the newly formed dioxane ring. In compounds 2 and 4, arising from fractions F2 and F4, respectively, J2,3 = 2.6–2.7 Hz suggesting a cis-relationship between these same groupings. The similarities in the 13C NMR spectral data (Fig. 2) derived from compounds 1 and 2 suggest they possess the same regiochemical relationships between the styrene, hydroxymethyl and aryl moieties in terms of their positions of attachment to the 1,4-benzodioxin core. In principle the use of horseradish peroxidase to promote oxidative coupling of compounds 7 and 8 could deliver (±)-aiphanol selectively but related experiments by Fukuyama et al. suggest that the enantiomeric excesses likely to be observed in such processes would be very modest indeed.

For the sake of establishing more comprehensive structure-activity relationships within the aiphanol “class”, compound...
Table 1 COX-1/2 inhibitory properties of compounds (±)-1-4

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC_{50} for COX-1/µM</th>
<th>IC_{50} for COX-2/µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.3</td>
<td>0.17</td>
</tr>
<tr>
<td>2</td>
<td>6.3</td>
<td>9.5</td>
</tr>
<tr>
<td>3</td>
<td>9.0</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>7.7</td>
<td>7.7</td>
</tr>
</tbody>
</table>

*Assays conducted according to the method of Dannhardt et al.*

% Inhibition at 10 µM concentration.

---

**Scheme 1**  Reagents and conditions: (i) THF, 18 °C, 18 h then HCl (aq.); (ii) TBAF (4 mol equiv.), THF, 0 °C, 5 min; (iii) Ag_2CO_3 (1 mol equiv.), 1:2 v/v acetone–benzene, 60 °C, 18 h.

**Fig. 1** HPLC trace derived from analysis of the reaction mixture obtained on oxidative coupling of compounds 7 and 8 with silver carbonate (see Experimental section for details).

9 (71%), embodying the 1,4-benzodioxin core plus the appended aryl and hydroxymethyl substituents of aiphanol, was prepared (as a ca. 1 : 1 and chromatographically inseparable mixture of cis- and trans-isomers) by oxidative coupling of 3,4-dihydroxybenzaldehyde with sinapyl alcohol. The absence of any of the regio-isomeric coupling products in this reaction is consistent with earlier work where it has been noted that the presence of an aldehyde moiety in the 4-position on the catechol residue results in a completely regioselective conversion.

With serviceable quantities of lignans 1-4 as well as congeners 7 and 9 available via the pathways described above, biological evaluations could be carried out. Assessment of compounds 1-4 as inhibitors of COX-1 and -2 was conducted in vitro under conditions defined previously and the results presented in Table 1. Interestingly, (±)-aiphanol is a significant inhibitor of COX-2 but only a modest inhibitor of COX-1. This appears to be the reverse of the situation observed for the naturally occurring (-)-form and suggests that (+)-aiphanol could be a more potent COX-2 inhibitor. Whilst definitive comment on this matter must await the preparation and testing of (+)-1, it is worth noting that the enantiomeric forms of other chiral ligands have been shown to vary in their COX-1 and -2 inhibitory properties. The anti-angiogenic forms of compounds 1-4, 7 and 9 were determined in an in vitro angiogenesis assay using rat aorta rather than human placental blood vessel fragments and the results shown in Table 2 indicate that rac-aiphanol [(±)-1] completely inhibited blood vessel growth at 100 µg mL⁻¹ while isomers 2 and 4 behaved similarly. Compound 3 proved a lot less active as did "substructure" 9. Interestingly, piceatannol (7) was almost as active as rac-aiphanol thus further emphasizing the pharmaceutical potential of hydroxystilbenes. It is also worth noting that compounds 1-3 and 7 are all more active, at the 100 µg mL⁻¹ level, than PI-88, a polysulfated oligosaccharide which exhibits anti-angiogenic properties and is now in clinical development as an agent for the treatment of certain cancers.

---

**Experimental**

**Compounds 1-4**

A magnetically stirred solution of stilbene 7 (94 mg, 0.38 mmol) and alcohol 8 (81 mg, 0.38 mmol) in benzene-acetone (30 mL of a 2 : 1 v/v mixture) was heated at 60 °C for 0.25 h then treated, in one portion, with silver carbonate (107 mg, 0.38 mmol). The resulting mixture was heated at 60 °C for 18 h then cooled and the precipitate removed by filtration. The filtrate was then concentrated under reduced pressure to give a brown solid comprising a mixture of F1-F4 thus further emphasizing the pharmaceutical potential of hydroxystilbenes. It is also worth noting that compounds 1-3 and 7 prove a lot less active as did "substructure" 9. Interestingly, piceatannol (7) is almost as active as rac-aiphanol thus further emphasizing the pharmaceutical potential of hydroxystilbenes. It is also worth noting that compounds 1-3 and 7 are all more active, at the 100 µg mL⁻¹ level, than PI-88, a polysulfated oligosaccharide which exhibits anti-angiogenic properties and is now in clinical development as an agent for the treatment of certain cancers.
Table 2  Anti-angiogenic properties of compounds (±)-1-4, 7 and 9 as determined in a rat aorta assay.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibition of vessel growth at 100 μg mL⁻¹ (%)</th>
<th>Inhibition of vessel growth at 10 μg mL⁻¹ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>99</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>96</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>34</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>35</td>
</tr>
<tr>
<td>PL-88</td>
<td>62</td>
<td>30</td>
</tr>
</tbody>
</table>

*Assays conducted according to the method of Parish et al.¹²⁰

Fig. 2  Stacked-plot presentation of the 75 MHz ¹³C NMR spectra of compounds (±)-1-4 (CD₃COCD₃, as solvent).

Acknowledgements

We thank the Institute of Advanced Studies (IAS) and CSIRO Molecular Science for financial support. Mr Tony Herit is warmly acknowledged for his skilful assistance with HPLC studies. MGB is the grateful recipient of an Alexander von Humboldt Research Award which enabled visits to Germany in 2001–2002 and during this time the collaboration with Professor Dannhardt was established. AB and CP are supported by an NHMRC Program grant.

References