TOTAL SYNTHESIS OF THE XYLOKETAL NATURAL PRODUCTS AND ALBOATRIN

by

Jeremy David Pettigrew
Bachelor of Science (Co-Op.), Simon Fraser University, 2001

THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

In the
Department of Chemistry

© Jeremy David Pettigrew 2006

SIMON FRASER UNIVERSITY

Summer 2006

All rights reserved. This work may not be reproduced in whole or in part, by photocopy or other means, without permission of the author.
APPROVAL

Name: Jeremy David Pettigrew

Degree: Doctor of Philosophy

Title of Thesis: Total Synthesis Of The Xyloketal Natural Products and Alboatrin

Examing Committee:
Chair: Dr. R.H. Hill (Professor)

Dr. P.D. Wilson (Associate Professor)
Senior Supervisor

Dr. N.R. Branda (Professor)
Committee Member

Dr. D.B. Leznoff (Associate Professor)
Committee Member

Dr. R.A. Britton (Assistant Professor)
Internal Examiner

Dr. V.A. Snieckus (Professor)
External Examiner
Department of Chemistry
Queen’s University

Date Approved: June 16, 2006
DECLARATION OF PARTIAL COPYRIGHT LICENCE

The author, whose copyright is declared on the title page of this work, has granted to Simon Fraser University the right to lend this thesis, project or extended essay to users of the Simon Fraser University Library, and to make partial or single copies only for such users or in response to a request from the library of any other university, or other educational institution, on its own behalf or for one of its users.

The author has further granted permission to Simon Fraser University to keep or make a digital copy for use in its circulating collection, and, without changing the content, to translate the thesis/project or extended essays, if technically possible, to any medium or format for the purpose of preservation of the digital work.

The author has further agreed that permission for multiple copying of this work for scholarly purposes may be granted by either the author or the Dean of Graduate Studies.

It is understood that copying or publication of this work for financial gain shall not be allowed without the author's written permission.

Permission for public performance, or limited permission for private scholarly use, of any multimedia materials forming part of this work, may have been granted by the author. This information may be found on the separately catalogued multimedia material and in the signed Partial Copyright Licence.

The original Partial Copyright Licence attesting to these terms, and signed by this author, may be found in the original bound copy of this work, retained in the Simon Fraser University Archive.

Simon Fraser University Library
Burnaby, BC, Canada
ABSTRACT

The isolation and structural characterization of seven closely related natural products, the xyloketalts, from a mangrove fungus of the Xylaria species have been reported recently by Lin and co-workers. Of these natural products, all of which incorporate identical chiral nonracemic 5,6-bicyclic acetal moieties, xyloketal A has a unique and aesthetically pleasing $C_3$-symmetric molecular structure that was elucidated by detailed spectroscopic studies and by X-ray crystallography. Xyloketal A, B, C and D have also been shown to be potent inhibitors of acetylcholine esterase and so represent important lead compounds for the treatment of neurological diseases. In addition, xyloketal A, B and F have been shown to have L-calcium channel blocking activity. Thus, the total synthesis of these natural products, and structural analogues thereof, is of notable significance.

Towards these ends, a series of novel synthetic routes to prepare these compounds were developed. The initial route, in which the key synthetic transformation involved an inverse electron demand hetero Diels-Alder reaction between appropriately substituted ortho-quinone methides and dihydrofurans, afforded (±), (+) and (−)-xyloketal D. In addition, demethyl analogues of xyloketal A and D were prepared. However, the application of this synthetic route to prepare the more structurally complex xyloketalts was unsuccessful.

A second route, utilizing a phenylboronic acid-mediated condensation reaction as the key synthetic transformation, afforded a series of novel tris-2H-chromenes that represent structural analogues of the natural product xyloketal A. However, due to the
instability of a key synthetic intermediate, the total synthesis of xyloketal A was not completed by this route.

A third route was also investigated that featured a boron trifluoride diethyl etherate-promoted electrophilic aromatic substitution reaction as a key step. This synthetic route was used to complete total syntheses of xyloketal A, B, D, E, F and G. Moreover, demethyl analogues of xyloketal A, B, C, D, E and G were also prepared.

The application of the electrophilic aromatic substitution reaction towards the total synthesis of the structurally related and biologically active natural product alboatrin was also investigated. This led to the first asymmetric total synthesis of this natural product as well as a demethyl analogue.
To Nicolette and my parents, Carol and Alan.
“Chance favours the prepared mind”

Louis Pasteur, 1854
ACKNOWLEDGEMENTS

My senior supervisor, Dr. Peter Wilson, is thanked for his advice, guidance and mentorship over the course of my doctoral studies. I am extremely grateful to Dr. Wilson for the training I received during my time as a member of his research group.

The other members of my supervisor committee, Dr. Neil Branda and Dr. Daniel Leznoff, are thanked for their suggestions and encouragement throughout my studies.

Mr. Michael Katz and Dr. Kimberly Jantunen (Simon Fraser University) are thanked for obtaining the data and solving the X-ray crystal structures found in this thesis. Mr. Jason Bexrud is thanked for his preliminary investigations of the Diels-Alder reactions that are discussed in Chapter 2. Dr. Rebecca Freeman is thanked for her assistance in making the racemic and optically active dihydrofurans that are described in Chapter 2. Mr. Simon So is thanked for his preliminary investigations of the phenylboronic acid-mediated reactions that are discussed in Chapter 3. Dr. Jean-Jacques Cadieux is thanked for the preparation of some of the aldehydes that are discussed in Chapter 3. Professor Yongcheng Lin (Zongshan University) is thanked for providing $^1$H and $^{13}$C NMR spectra of the xyloketals for comparison purposes. Professor Krohn (University of Paderborn) is thanked for checking the melting point of xyloketal D.

My past and present lab colleagues (Dr. Jean-Jacques Cadieux, Mr. Patrick Chen, Dr. Rebecca Freeman, Dr. Hongjuan Hu, Dr. Summon Koul, Mr. Jason Lamontagne, Dr. Michael Lyle, Mr. Darren McMurtrie, Dr. Arun Narine, Dr. Peggy Paduraru and Mr. Brendan Whelan) are thanked for their friendship and helpful discussions over the years.
The technical assistance of Dr. David McGillivray (University of Victoria, HRMS), Mrs. Marcy Tracey (NMR), Dr. Andrew Lewis (NMR), Mr. Greg Owen (MS), Mr. Philip Ferreira (MS), Mr. Simon Wong (MS) and Mr. Mickey Yang (CHN microanalysis) is gratefully acknowledged.

Finally, Simon Fraser University (Special Entrance Scholarship and President’s Ph. D. Research Stipend) and the Natural Sciences and Engineering Research Council of Canada (PGS-A and PGS-D) are thanked for their financial support.
# TABLE OF CONTENTS

Approval ............................................................................................................................ ii
Abstract ............................................................................................................................ iii
Dedication ........................................................................................................................ v
Quotation ........................................................................................................................ vi
Acknowledgements ......................................................................................................... vii
Table of Contents ........................................................................................................... ix
List of Figures ................................................................................................................ xvi
List of Schemes ............................................................................................................... xviii
List of Tables .................................................................................................................. xxiii
List of Abbreviations ....................................................................................................... xxiv

1  
Introduction to the Xyloketal Natural Products and Alboatrin .................................. 1
  1.1 Thesis Introduction .................................................................................................. 1
  1.2 The Xyloketal Natural Products ......................................................................... 1
    1.2.1 Isolation and Structural Characterization of the Xyloketal Natural Products .......... 1
    1.2.2 X-Ray Crystal Structures of the Xyloketals ...................................................... 4
  1.3 Biological Properties of the Xyloketal Natural Products ....................................... 5
    1.3.1 Acetylcholine Esterase Inhibition ................................................................. 5
    1.3.2 L-Calcium Channel Inhibition ........................................................................ 5
  1.4 Literature Syntheses of the Xyloketal Natural Products and Analogues ............... 6
    1.4.1 Krohn’s Synthesis of the Xyloketal D and G Analogues [(±)-12] and [(±)-13] .............. 6
    1.4.2 Krohn’s Synthesis of the Xyloketal A and B Analogues [(±)-18], [(±)-19], [(±)-16] and [(±)-17] ......................................................................................... 7
    1.4.3 Krohn’s Synthesis of Racemic Xyloketal D [(±)-4] and G [(±)-7] ......................... 9
    1.4.4 Krohn’s Attempted Synthesis of Racemic Xyloketal A [(±)-1] and B [(±)-2] .................................................. 11
    1.4.5 Krohn’s Asymmetric Synthesis of (-)-Xyloketal D [(-)-4] ............................... 12
  1.5 Alboatrin .............................................................................................................. 14
    1.5.1 Isolation and Structural Characterization of Alboatrin (48) ................................ 14
    1.5.2 X-Ray Crystal Structure of Alboatrin (48) ..................................................... 15
  1.6 Biological Properties of Alboatrin ......................................................................... 15
    1.6.1 Root Growth Inhibition of Alfalfa ................................................................. 15
  1.7 Literature Syntheses of Alboatrin .......................................................................... 16
    1.7.1 Ichihara’s Synthesis of Racemic Alboatrin [(±)-48] ........................................... 16
    1.7.2 Murphy’s Synthesis of Racemic Alboatrin [(±)-48] ........................................... 17
    1.7.3 Baldwin’s Synthesis of Racemic Alboatrin [(±)-48] .......................................... 19
2 Towards the Synthesis of the Xyloketais: Diels-Alder Approach

2.1 Introduction

2.2 Retrosynthetic Analysis: Diels-Alder Approach

2.2.1 Retrosynthetic Analysis of Xyloketal D (4)

2.2.2 Retrosynthetic Analysis of Xyloketal A (1)

2.2.3 Retrosynthetic Analysis of Xyloketal B (2) and C (3)

2.3 Brief Overview of ortho-Quinone Methide Chemistry

2.3.1 Generation of ortho-Quinone Methides

2.3.2 Reactions of ortho-Quinone Methides

2.4 Synthesis of Mannich Bases as Precursors to ortho-Quinone Methides

2.4.1 Preparation of Mannich Bases for the Synthesis of Xyloketal D (4)

2.4.2 Preparation of Mannich Bases for the Synthesis of Xyloketal A (1)

2.4.3 Preparation of Mannich Bases for the Synthesis of Xyloketal B (2) and C (3)

2.5 Model Studies: Diels-Alder Approach

2.5.1 Synthesis of (+)-11-Norxyloketal D [(+)-12]

2.5.2 Synthesis of (+)-11-Trinorxyloketal A [(+)-18] and (+)-2,6-epi-11,11',11''-Trinorxyloketal A [(+)-19]

2.5.3 Attempted Synthesis of the Xyloketal B and C Analougues [(+)-115] and [(+)-116]

2.6 Synthesis of Racemic 2,4-Dimethyl-4,5-dihydrofuran

2.6.1 Preparation of Racemic 2,4-Dimethyl-4,5-dihydrofuran [(±)-61] Based on Literature Procedures

2.7 Total Synthesis of Racemic Xyloketais: Diels-Alder Approach

2.7.1 Total Synthesis of (±)-Xyloketal D [(±)-4]

2.7.2 Attempted Synthesis of (±)-Xyloketal A [(±)-1]

2.8 Synthesis of Chiral Nonracemic 2,4-Dimethyl-4,5-dihydrofuran

2.8.1 Synthesis of (2R)-2-Methylpent-4-ynoic Acid [(2R)-70] and (2S)-2-Methyl-pent-4-ynoic Acid [(2S)-70] Employing a Resolution Procedure

2.8.2 Synthesis of (2R)-2-Methylpent-4-yn-1-ol [(2R)-69] and (2S)-2-Methyl-pent-4-yn-1-ol [(2S)-69]

2.8.3 Synthesis of (4R)-2,4-Dimethyl-4,5-dihydrofuran [(4R)-61] and (4S)-2,4-Dimethyl-4,5-dihydrofuran [(4S)-61]

2.9 Synthesis of Chiral Nonracemic Xyloketals: Diels-Alder Approach

2.9.1 Synthesis of (−)-Xyloketal D [(−)-4]

2.9.2 Synthesis of (−)-Xyloketal D [(−)-4]

2.9.3 Attempted Synthesis of (−)-Xyloketal A [(−)-1]

2.10 Conclusions

3 Towards the Synthesis of Xyloketal A: Phenylboronic Acid-Mediated Reactions

3.1 Introduction

3.2 Retrosynthetic Analysis: Phenylboronic Acid-Mediated Reactions

3.2.1 Retrosynthetic Analysis of Xyloketal A (1)
3.3 Brief Overview of the Phenylboronic Acid-Mediated Reaction of Phenols and Aldehydes

3.3.1 Development and Application of the Phenylboronic Acid-Mediated Reaction

3.4 Formation of tris-2H-Chromenes

3.4.1 Formation of tris-2H-Chromenes: Optimization of Reaction Conditions

3.5 Hydrogenation of tris-2H-Chromenes

3.5.1 Synthesis of the tris-Chromane (148)

3.6 Phenylboronic Acid-Mediated Reactions of a Series of α,β-Unsaturated Carbonyl Compounds

3.6.1 Synthesis of α,β-Unsaturated Aldehydes

3.6.2 Synthesis of tris-2H- and 4H-Chromenes

3.6.3 X-Ray Crystal Structure Analysis of the tris-2H-Chromene (174)

3.7 Synthesis of (4R)-2,4-Dimethyl-3-formyl-4,5-dihydrofuran

3.7.1 Attempted Synthesis of the Aldehyde (127) from an Acyclic Precursor

3.7.2 Elaboration of 2-Methyl-4,5-dihydrofuran (114)

3.7.3 Synthesis of Chiral Nonracemic (4R)-2,4-Dimethyl-3-formyl-4,5-dihydrofuran [(4R)-127]

3.8 Attempted Synthesis of Xyloketal A: Phenylboronic Acid-Mediated Reaction

3.8.1 Attempted Synthesis of the tris-2H-Chromene (126)

3.9 Conclusions

4 Synthesis of the Xyloketalts: Electrophilic Aromatic Substitution Reactions

4.1 Introduction

4.2 Retrosynthetic Analysis: Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethylfuran

4.2.1 Retrosynthetic Analysis of Xyloketal A (1)

4.3 Attempted Synthesis of Xyloketal A: Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethylfuran

4.3.1 Synthesis of 2,4-Dimethyl-3-hydroxymethylfuran (50)

4.3.2 Attempted Electrophilic Aromatic Substitution Reactions of Phloroglucinol (14) with 2,4-Dimethyl-3-hydroxymethylfuran (50)

4.3.3 Attempted Derivatization of 2,4-Dimethyl-3-hydroxymethylfuran (50)

4.4 Retrosynthetic Analysis of the Xyloketalts: Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran

4.4.1 Retrosynthetic Analysis of Xyloketal A (1)

4.4.2 Retrosynthetic Analysis of Xyloketal B (2) and C (3)

4.4.3 Retrosynthetic Analysis of Xyloketal D (4) and G (7)

4.4.4 Retrosynthetic Analysis of Xyloketal E (5) from Xyloketal B (2) and 2,4-Dimethyl-4,5-dihydrofuran (61)

4.4.5 Retrosynthetic Analysis of Xyloketal F (6) from Xyloketal B (2)
4.4.6 Retrosynthetic Analysis of Xyloketal F (6) from 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)

4.5 Model Studies: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran

4.5.1 Synthesis of (+)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-epi-11,11',11''-Trinorxyloketal A [(±)-19]

4.5.2 Synthesis of (+)-11,11'-Dinorxyloketal B [(±)-16] and (±)-2,6-epi-11,11'-Dinorxyloketal B [(±)-17]

4.5.3 Attempted Synthesis of the Xyloketal C Analogues [(±)-247] and (248)

4.5.4 Synthesis of (+)-11-Norxyloketal D [(±)-12] and (±)-10-Norxyloketal G [(±)-13]

4.5.5 Synthesis of (+)-11,11',20-Trinorxyloketal E [(±)-257], (±)-14-epi-11,11',20-Trinorxyloketal E [(±)-258], (±)-2,6-epi-11,11',20-Trinorxyloketal E [(±)-259] and (±)-2,6,14-epi-11,11',20-Trinorxyloketal E [(±)-260] from the Xyloketal B Analogues [(±)-16] and [(±)-17]

4.6 Asymmetric Synthesis of the Xyloketals: Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran

4.6.1 Total Synthesis of (-)-Xyloketal A [(-)-1]

4.6.2 Total Synthesis of (-)-Xyloketal B [(-)-2]

4.6.3 Total Synthesis of (-)-Xyloketal D [(-)-4] and G [(-)-7]

4.6.4 Total Synthesis of Xyloketal E (5) from (-)-Xyloketal B [(-)-2]

4.6.5 Two Alternative Syntheses of (-)-Xyloketal F [(-)-6]

4.7 Conclusions

5 Total Synthesis of (+)-Alboatrin

5.1 Introduction

5.2 Attempted Synthesis of Alboatrin: Diels-Alder Approach

5.2.1 Retrosynthetic Analysis of Alboatrin (48)

5.2.2 Attempted Synthesis of the Mannich Base (270) for the Synthesis of Alboatrin (48)

5.3 Total Synthesis of Alboatrin: Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran

5.3.1 Retrosynthetic Analysis of Alboatrin: Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)

5.3.2 Model Studies: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)

5.3.3 Total Synthesis of (+)-Alboatrin [(+)-48]

5.4 Conclusions

6 Experimental

6.1 General Experimental Details

6.2 Experimental Concerning Chapter Two
6.2.1 3-Morpholin-4-yl-methyl-2,4-dihydroxyacetophenone (104) ..................... 169
6.2.2 3-Dibenzyaminomethyl-2,4-dihydroxyacetophenone (106) ......................... 170
6.2.3 2,4,6-tris[Dibenzyaminomethyl]phloroglucinol (108) .............................. 171
6.2.4 2,4,6-tris[3-Morpholin-4-yl-methyl]phloroglucinol (107) ......................... 172
6.2.5 Iodophloroglucinol Trihydrate (109) .................................................. 172
6.2.6 Methyl 2,4,6-trihydroxybenzoate (112) ............................................ 173
6.2.7 Methyl 2,4,6-trihydroxy-3,5-dibenzyaminomethylbenzoate (113) ............. 174
6.2.8 (+)-11-Norxyloketal D [(+)−12] ....................................................... 175
6.2.9 (+)−11-Trinorxyloketal A [(+)−18] and (+)−2,6-epi-11,11′,11″-
Trinorxyloketal A [(+)−19] ........................................................................ 176
6.2.10 (+)−2-Methylpent-4-ynoic Acid [(+)−70] ............................................ 178
6.2.11 (+)−2-Methylpent-4-yn-1-ol [(+)−69] ................................................ 179
6.2.12 (+)−2,4-Dimethyl-4,5-dihydrofuran [(+)−61] ...................................... 180
6.2.13 (+)−Xyloketal D [(+)−4], (+)−2,6-epi-Xyloketal D [(+)−26] and the
Diastereoisomeric (+)-Spiroacetals [(+)−117] and [(+)−118] ......................... 180
6.2.14 (R)-Phenylglycinol [(+)−119] ............................................................. 183
6.2.15 (2R)−N−[(1R)−1-Phenyl-2-hydroxyethyl]-2-methyl-4-pentynamide
[(−)−120] and (2S)−N−[(1R)−1-Phenyl-2-hydroxyethyl]-2-methyl-4-
pentynamide [(−)−121] ............................................................................. 184
6.2.16 X-Ray Crystallographic Analysis of (2S)−N−[(1R)−1-Phenyl-2-
hydroxyethyl]-2-methyl-4-pentynamide [(−)−121] ..................................... 185
6.2.17 (2R)−2-Methylpent-4-ynoic Acid [(2R)−70] ......................................... 193
6.2.18 (2S)−2-Methylpent-4-ynoic Acid [(2S)−70] ......................................... 193
6.2.19 (2R)−2-Methylpent-4-yn-1-ol [(2R)−69] ............................................. 194
6.2.20 (2S)−2-Methylpent-4-yn-1-ol [(2S)−69] ............................................. 195
6.2.21 (2R)−Benzyl-(2-methylpent-4-ynyl)ether [(2R)−122] ......................... 196
6.2.22 (2S)−Benzyl-(2-methylpent-4-ynyl)ether [(2S)−122] ......................... 197
6.2.23 (4R)−2,4-Dimethyl-4,5-dihydrofuran [(4R)−61] .................................. 198
6.2.24 (4S)−2,4-Dimethyl-4,5-dihydrofuran [(4S)−61] .................................. 198
6.2.25 (−)−Xyloketal D [(−)−4], 2,6-epi-Xyloketal D (26) and the
Diastereoisomeric Spiroacetals (117) and (118) ............................................. 199
6.2.26 Xyloketal D-(R)−α-methoxy-α-trifluoromethyl-phenylacetate [(−)−
124] and ent-Xyloketal D-(R)−α-methoxy-α-trifluoromethyl-
phenylacetate (125) .................................................................................. 202
6.2.27 Xyloketal D (R)−α-methoxy-α-trifluoromethyl-phenylacetate [(−)−
124] ........................................................................................................... 202
6.2.28 (+)−Xyloketal D [(+)−4], 2,6-epi-ent-Xyloketal D [(ent)−26] and the
Diastereoisomeric Spiroacetals [(ent)−117] and [(ent)−118] ......................... 204
6.3 Experimental Concerning Chapter Three .......................................................... 207
6.3.1 3-Methyl-but-2-enal [Senecialdehyde (134)] ............................................ 207
6.3.2 2,2,6,6,10,10-Hexamethyl-2H,6H,10H-dipyranol[6,5−f,6′,5′−h]
chromene (142) and 2,2,8,8-Tetramethyl-2H,8H-pyranol[5,6-
g]chromen-5-ol (143) ............................................................................... 208
6.3.3 2,2,6,6,10,10-Hexamethyl-3,4,7,8,11,12-hexahydro-2H,6H,10H-
dipyranol[6,5−f,6′,5′−h]chromene (148) ...................................................... 212
6.3.4 Cyclopentylideneacetaldehyde (152) ........................................................ 212
<table>
<thead>
<tr>
<th>Section</th>
<th>Formula/Structure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.3.5</td>
<td>Cyclohexylideneacetaldehyde (156)</td>
<td>214</td>
</tr>
<tr>
<td>6.3.6</td>
<td>Adamantylideneacetaldehyde (160)</td>
<td>215</td>
</tr>
<tr>
<td>6.3.7</td>
<td>2-Methylcyclopentene-1-carboxaldehyde (165)</td>
<td>217</td>
</tr>
<tr>
<td>6.3.8</td>
<td>Methyl-2-methyl-4,5-dihydrofuran-3-carboxylate (167)</td>
<td>219</td>
</tr>
<tr>
<td>6.3.9</td>
<td>2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)</td>
<td>220</td>
</tr>
<tr>
<td>6.3.10</td>
<td>2-Methyl-3-formyl-4,5-dihydrofuran (169)</td>
<td>221</td>
</tr>
<tr>
<td>6.3.11</td>
<td>2,6,10-Tricyclopentylidene-2H,6H,10H-dipyrano[6,5-f',6',5'-h]chromene (172)</td>
<td>221</td>
</tr>
<tr>
<td>6.3.12</td>
<td>2,6,10-Tricyclohexylidene-2H,6H,10H-dipyrano[6,5-f',6',5'-h]chromene (173)</td>
<td>222</td>
</tr>
<tr>
<td>6.3.13</td>
<td>2,6,10-Triadamantylidene-2H,6H,10H-dipyrano[6,5-f',6',5'-h]chromene (174)</td>
<td>223</td>
</tr>
<tr>
<td>6.3.14</td>
<td>X-Ray Crystallographic Analysis of 2,6,10-Triadamantylidene-2H,6H,10H-dipyrano[6,5-f',6',5'-h]chromene (174)</td>
<td>224</td>
</tr>
<tr>
<td>6.3.15</td>
<td>2,2,6,6,10-Hexahenyl-3,4,7,8,11,12-hexahydro-2H,6H,10H-dipyrano[6,5-f',6',5'-h]chromene (176-6H)</td>
<td>236</td>
</tr>
<tr>
<td>6.3.16</td>
<td>(2RS,6RS,10RS)-2,6,10-Trimethyl-2,6,10-tri-(4-methylpent-3'-enyl)-2H,6H,10H-dipyrano[6,5-f',6',5'-h]chromene ([±]-178)</td>
<td>237</td>
</tr>
<tr>
<td>6.3.17</td>
<td>(1a-RS,6a-SR,11a-SR)-3,4,4a,1a,8,9,8a,6a,12,13,14a,11a-Dodecahydro-1a,6a,11a-trimethyl-tricyclooctadec-11,13-diyl-(b',b'']-1aH,6aH,11aH-dipyrano[6,5,i,6',5'-k]chromene (193-a) and (1a-RS,6a-RS,11a-RS)-3,4,4a,1a,8,9,8a,6a,12,13,14a,11a-Dodecahydro-1a,6a,11a-trimethyl-tricyclooctadec-11,13-diyl-(b',b'']-1aH,6aH,11aH-dipyrano[6,5,i,6',5'-k]chromene (193-b)</td>
<td>238</td>
</tr>
<tr>
<td>6.3.18</td>
<td>2,6,10-Trimethyl-4H,8H,12H-dipyrano[6,5-f',6',5'-h]chromene (196)</td>
<td>239</td>
</tr>
<tr>
<td>6.3.19</td>
<td>(±)-1-(4-Methoxybenzyloxy)propan-2-ol ([±]-210)</td>
<td>240</td>
</tr>
<tr>
<td>6.3.20</td>
<td>(±)-1-(4-Methoxybenzyloxy)-2-bromopropane ([±]-131)</td>
<td>240</td>
</tr>
<tr>
<td>6.3.21</td>
<td>2-Methyl-3-trichloroacetyl-4,5-dihydrofuran (213) and 1,1,1-Trichloro-3-[4-dihydrofuran-2'E-ylidene]propane-2-one (214)</td>
<td>241</td>
</tr>
<tr>
<td>6.3.22</td>
<td>2-Methyl-4,5-dihydrofuran-3-carboxylic Acid (215)</td>
<td>243</td>
</tr>
<tr>
<td>6.3.23</td>
<td>Methyl-2-methyl-4,5-dihydrofuran-3-carboxylate (167)</td>
<td>244</td>
</tr>
<tr>
<td>6.3.24</td>
<td>(S)-Phenylalaninol [(S)-217]</td>
<td>244</td>
</tr>
<tr>
<td>6.3.25</td>
<td>(S)-4-(Phenylmethyl)-2-oxazolidinone [(4S)-218]</td>
<td>245</td>
</tr>
<tr>
<td>6.3.26</td>
<td>(4S)-4-Benzyl-3-propionyloxazolidin-2-one [(4S)-219]</td>
<td>246</td>
</tr>
<tr>
<td>6.3.27</td>
<td>(2'R,4S)-4-Benzyl-3-[2'-methylpent-4'-ynoyl]oxazolidin-2-one [(+)220]</td>
<td>247</td>
</tr>
<tr>
<td>6.3.28</td>
<td>(2R)-2-Methylpent-4-yn-1-ol [(2R)-69]</td>
<td>251</td>
</tr>
<tr>
<td>6.3.29</td>
<td>(4R)-2,4-Dimethyl-3-trichloroacetyl-4,5-dihydrofuran [(4R)-223] and (4'R)-1,1,1-Trichloro-3-[4'-methylhydrofuran-2'E-ylidene]propane-2-one [(4R)-224]</td>
<td>252</td>
</tr>
<tr>
<td>6.3.30</td>
<td>(4R)-Methyl-2,4-dimethyl-4,5-dihydrofuran-3-carboxylate [(4R)-206]</td>
<td>254</td>
</tr>
<tr>
<td>6.3.31</td>
<td>(4R)-2,4-Dimethyl-4,5-dihydrofuran-3-carboxylic Acid [(4R)-225]</td>
<td>255</td>
</tr>
<tr>
<td>6.3.32</td>
<td>(4R)-2,4-Dimethyl-4,5-dihydrofuran-3-carboxaldehyde [(4R)-127]</td>
<td>256</td>
</tr>
<tr>
<td>6.4</td>
<td>Experimental Concerning Chapter Four</td>
<td>257</td>
</tr>
<tr>
<td>6.4.1</td>
<td>Ethyl-2,4-dimethyl-3-furan-2-one (49)</td>
<td>257</td>
</tr>
</tbody>
</table>
6.4.2 2,4-Dimethyl-3-hydroxymethylfuran (50) .......................................................... 258
6.4.3 2,4-Dimethyl-3-t-butyldimethylsilyloxyethylfuran (230) ................................. 258
6.4.4 2,4-Dimethyl-3-furanoic Acid (237) ................................................................. 261
6.4.5 2,4-Dimethyl-5-bromo-3-furanoic Acid (238) ................................................... 262
6.4.6 (+)-11-Trinorxyloketal A [(+)-18] and (+)-2,6-epi-11,11',11''-Trinorxyloketal A [(+)-19] ................................................................. 262
6.4.7 (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-6,8-dihydroxy-1a-methyl-furo[b]chromane-7-methylcarboxylate [(±)-241], (±)-11,11'-Dinorxyloketal B-13-methylcarboxylate [(±)-115], (±)-2,6-epi-11,11'-Dinorxyloketal B-13-methylcarboxylate [(±)-242], (±)-11,11'-Dinorxyloketal C-13-methylcarboxylate [(±)-116] and (±)-2,6-epi-11,11'-Dinorxyloketal C-13-methylcarboxylate (243) ................................................................. 267
6.4.8 (+)-11,11'-Dinorxyloketal B [(±)-16] and (+)-2,6-epi-11,11'-Dinorxyloketal B [(±)-17] ........................................................................................................... 271
6.4.9 Methyl 2,6-Dihydroxy-4-methoxybenzoate (244) and Methyl 2,4-Dimethoxy-6-hydroxybenzoate (45) ................................................................. 272
6.4.10 (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-6-methoxy-8-hydroxy-1a-methyl-furo[b]chromane-9-methylcarboxylate [(±)-246] ......................................................... 273
6.4.11 (+)-11-Norxyloketal D [(±)-12] and (±)-10-Norxyloketal G [(±)-13] .............. 274
6.4.12 (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-7-ethyl-8-hydroxy-1a-methyl-furo[b]chromane [(±)-250] ................................................................. 277
6.4.13 (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-8-hydroxy-1a-methyl-furo[b]chromane [(±)-254] ........................................................................................................... 278
6.4.15 (−)-Xyloketal A [(−)-1] and 2,6-epi-Xyloketal A (40) ........................................ 280
6.4.16 (−)-(1aR,4R,4aR)-3,4,4a,1a-Tetrahydro-6,8-dihydroxy-1a,4-dimethylfuro[b]-7-chromene Methylcarboxylate [(−)-261] and (−)-13-Xyloketal B Methylcarboxylate [(−)-262] ................................................................. 283
6.4.17 (−)-Xyloketal B [(−)-2] ......................................................................................... 286
6.4.18 (−)-Xyloketal D [(−)-4] and (−)-Xyloketal G [(−)-7] .......................................... 287
6.4.19 20-Norxyloketal E (263) and 14-epi-20-Norxyloketal E (264) ....................... 289
6.4.20 Xyloketal E (5) and 14-epi-Xyloketal E (265) ....................................................... 291
6.4.21 (−)-Xyloketal F [(−)-6] .......................................................................................... 292
6.4.22 bis-(2,4,6-Trihydroxyphenyl)methane Monohydrate (240) ......................... 293
6.4.23 (−)-Xyloketal F [(−)-6] and the Regioisomers (266) and (267) ......................... 294
6.5 Experimental Concerning Chapter Five ................................................................ 296
6.5.1 (+)-10-Noralboatin [(±)-271] and the (+)-bis-Adducts (272), [(±)-273], [(±)-274] and [(±)-275] ................................................................. 296
6.5.2 (+)-Alboatin [(±)-48] and the (−)-bis-Adduct [(−)-276] ...................................... 300

References ...................................................................................................................... 302
### LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1.1</td>
<td>Molecular structures of xyloketal A (1), B (2), C (3), D (4), E (5), F (6) and G (7).</td>
</tr>
<tr>
<td>1.2.2.1</td>
<td>X-Ray crystal structure of xyloketal A (1) (the thermal ellipsoids are drawn at a 50% probability level and the hydrogen atoms have been omitted for clarity).</td>
</tr>
<tr>
<td>1.5.1.1</td>
<td>Ichihara’s assigned molecular structure (47) and Murphy’s revised molecular structure (48) of alboatrin.</td>
</tr>
<tr>
<td>1.5.2.1</td>
<td>X-Ray crystal structure of alboatrin [(±)-48] (the thermal ellipsoids are drawn at a 50% probability level).</td>
</tr>
<tr>
<td>2.3.1.1</td>
<td>Common precursors for the generation of ortho-quinone methides.</td>
</tr>
<tr>
<td>2.3.1.2</td>
<td>ortho-Quinone methide generation from Mannich bases (79).</td>
</tr>
<tr>
<td>2.3.1.3</td>
<td>ortho-Quinone methide generation from ortho-hydroxyalkyl phenols (80) and derivatives (86) and (89).</td>
</tr>
<tr>
<td>2.3.1.4</td>
<td>ortho-Quinone methide generation from salicylaldehydes (80) and derivatives (90).</td>
</tr>
<tr>
<td>2.3.2.1</td>
<td>Nucleophilic addition reactions of ortho-quinone methides.</td>
</tr>
<tr>
<td>2.3.2.2</td>
<td>Net [4+4] cycloaddition reactions of ortho-quinone methides.</td>
</tr>
<tr>
<td>2.3.2.3</td>
<td>[4+2] Cycloaddition reactions of ortho-quinone methides.</td>
</tr>
<tr>
<td>2.3.2.4</td>
<td>6π Electroyclic rearrangements of ortho-quinone methides.</td>
</tr>
<tr>
<td>2.5.1.1</td>
<td>( ^1 )H NMR spectrum (400 MHz, CDCl₃) of (±)-11-norxyloketal D [(±)-12].</td>
</tr>
<tr>
<td>2.5.1.2</td>
<td>COSY NMR spectrum (400 MHz, CDCl₃) of (±)-11-norxyloketal D [(±)-12].</td>
</tr>
<tr>
<td>2.5.1.3</td>
<td>( ^{13} )C NMR spectrum (101 MHz, CDCl₃) of (±)-11-norxyloketal D [(±)-12].</td>
</tr>
<tr>
<td>2.5.1.4</td>
<td>Observed nOe contacts for (±)-11-norxyloketal D [(±)-12].</td>
</tr>
<tr>
<td>2.7.1.1</td>
<td>( ^1 )H NMR spectrum (400 MHz, CDCl₃) of (±)-xyloketal D [(±)-4].</td>
</tr>
<tr>
<td>2.8.1.1</td>
<td>X-Ray crystal structure of the amide [(−)-121] (the thermal ellipsoids are drawn at a 50% probability level).</td>
</tr>
<tr>
<td>3.3.1.1</td>
<td>Synthesis of precocene I (137) and II (138).</td>
</tr>
<tr>
<td>3.3.1.2</td>
<td>Application of the phenylboronic acid-mediated reaction for the synthesis of daurichromenic acid analogues (140) by Wilson and co-workers.</td>
</tr>
<tr>
<td>3.4.1.1</td>
<td>Molecular structures of the borate ester intermediates (144) and (145).</td>
</tr>
<tr>
<td>3.4.1.2</td>
<td>Rapid interconversion of the two possible conformers (146) and (147) of the tris-2H-chromene (142).</td>
</tr>
</tbody>
</table>
Proposed reaction mechanism for the formation of the tris-4H-
chromene derivative (196). .................................................................84
Unit cell of the X-ray crystal structure of the tris-2H-chromene
(174) (the thermal ellipsoids are drawn at a 50% probability
level and the hydrogen atoms have been omitted for clarity). ..........85
Intermediates involved in the formation of the dihydrofuran
ester (169). ...........................................................................................86
Evans’ stereochemical rationale for the alkylation reactions of
the oxazolidinone [(4S)-219]. ................................................................95
Observed nOe contacts for the methyl ester [(±)-241]. ...............123
Observed nOe contacts for the bis-demethyl xyloketal B
analogues [(±)-16] and [(±)-17]. .........................................................125
Observed nOe contacts for the demethyl xyloketal G analogue
[(±)-13] ..................................................................................................129
1H NMR spectrum (500 MHz, CDC13) of (−)-xyloketal A [(−)-1] ....138
Observed nOe contacts for the monoo-adduct [(−)-261]. .............140
Observed nOe contacts for the bis-adduct [(−)-262]....................140
1H NMR spectrum (500 MHz, CDC13) of (−)-xyloketal B [(−)-2] ....142
1H NMR spectrum (500 MHz, CDC13) of (−)-xyloketal G [(−)-7] ....145
1H NMR spectrum (500 MHz, CDC13) of xyloketal E (5) and 14-
epi-xyloketal E (265) .......................................................................148
1H NMR spectrum (500 MHz, CDC13) of (−)-xyloketal F [(−)-6] ....149
Selected regions of the 1H NMR spectrum (500 MHz, CDC13)
obtained during the isomerization of the regioisomeric adducts
(266) and (267) to (−)-xyloketal F [(−)-6] .............................................152
Observed nOe contacts for the alboatrin analogue [(±)-271]. .......162
Symmetry elements present in the linear bis-adducts (272) and
[(±)-273] ..................................................................................................163
1H NMR spectrum (500 MHz, CDC13) of (+)-alboatrin [(+)-48] ....165
Observed nOe contacts for (+)-alboatrin [(+)-48] .........................165
ORTEP representation of the amide [(−)-121] (the thermal
ellipsoids are drawn at a 50% probability level). ..............................187
ORTEP representation of the chromene (174) (the thermal
ellipsoids are drawn at a 50% probability level and the hydrogen
atoms have been omitted for clarity). ............................................226
LIST OF SCHEMES

Scheme 1.4.1.1 Krohn’s Synthesis of the Xyloketal D and G Analogues [(±)-12] and [(±)-13]........................................................................................................6

Scheme 1.4.2.1 Krohn’s Synthesis of the Xyloketal A and B Analogues [(±)-18], [(±)-19], [(±)-16] and [(±)-17].................................................................................8

Scheme 1.4.3.1 Krohn’s Synthesis of Racemic Xyloketal D [(±)-4] and G [(±)-7].....10

Scheme 1.4.4.1 Krohn’s Attempted Synthesis of Racemic Xyloketal A [(±)-1] and B [(±)-2]................................................................................................................11

Scheme 1.4.5.1 Krohn’s Asymmetric Synthesis of (-)-Xyloketal D [(–)-4].............13

Scheme 1.7.1.1 Ichihara’s Synthesis of Racemic Alboatrin [(±)-48]......................16

Scheme 1.7.2.1 Murphy’s Synthesis of Racemic Alboatrin [(±)-48].......................18

Scheme 1.7.3.1 Baldwin’s Synthesis of Racemic Alboatrin [(±)-48].....................19

Scheme 2.2.1.1 Retrosynthetic Analysis of Xyloketal D (4): Diels-Alder Approach.................................................................................................................22

Scheme 2.2.1.2 Retrosynthetic Analysis of 2,4-Dimethyl-4,5-dihydrofuran (61)........23

Scheme 2.2.2.1 Retrosynthetic Analysis of Xyloketal A (1): Diels-Alder Approach.........................................................................................................................24

Scheme 2.2.3.1 Retrosynthetic Analysis of Xyloketal B (2) and C (3): Diels-Alder Approach...........................................................................................................25

Scheme 2.4.1.1 Synthesis of Mannich Bases from 2,4-Dihydroxyacetophenone (11)..................................................................................................................32

Scheme 2.4.2.1 Synthesis of Mannich Bases from Phloroglucinol (14).................33

Scheme 2.4.3.1 Attempted Synthesis of Mannich Base (110).........................35

Scheme 2.4.3.2 Synthesis of the bis-Mannich Base (113)....................................36

Scheme 2.5.1.1 Synthesis of (±)-11-Norxyloketal D [(±)-12]: Diels-Alder Approach.....................................................................................................................37

Scheme 2.5.2.1 Synthesis of (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-epi-11,11',11''-Trinorxyloketal A [(±)-19]: Diels-Alder Approach ..............42

Scheme 2.5.3.1 Attempted Synthesis of the Methyl Esters [(±)-115] and [(±)-116]: Diels-Alder Approach..........................................................43

Scheme 2.6.1.1 Synthesis of the Alcohol [(±)-69] from Propionic Acid (72) and Propargyl Bromide (71).................................................................44

Scheme 2.6.1.2 Synthesis of (±)-2,4-Dimethyl-4,5-dihydrofuran [(±)-61] from the Alcohol [(±)-69].........................................................................................45

Scheme 2.7.1.1 Synthesis of (±)-Xyloketal D [(±)-4]: Diels-Alder Approach ......46

Scheme 2.7.2.1 Attempted Synthesis of (±)-Xyloketal A [(±)-1]: Diels-Alder Approach..............................................................................................................48
<table>
<thead>
<tr>
<th>Scheme 2.8.1.1</th>
<th>Resolution of $(\pm)$-2-Methylpent-4-ynoic Acid $[(\pm)-70]$ with $(R)$-Phenylglycinol $[(R)-119]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme 2.8.2.1</td>
<td>Synthesis of the Alcohols $[(2R)-69]$ and $[(2S)-69]$ from the Corresponding Carboxylic Acids $[(2R)-70]$ and $[(2S)-70]$.</td>
</tr>
<tr>
<td>Scheme 2.8.2.2</td>
<td>Confirmation of Absolute Stereochemistry of the Alcohols $[(2R)-69]$ and $[(2S)-69]$ by the Synthesis of the Known Benzyl Ethers $[(2R)-122]$ and $[(2S)-122]$.</td>
</tr>
<tr>
<td>Scheme 2.8.3.1</td>
<td>Synthesis of the Dihydrofurans $[(4R)-61]$ and $[(4S)-61]$ from the Corresponding Alcohols $[(2R)-69]$ and $[(2S)-69]$.</td>
</tr>
<tr>
<td>Scheme 2.9.1.1</td>
<td>Synthesis of $(-)$-Xyloketal D [(-)-4]: Diels-Alder Approach</td>
</tr>
<tr>
<td>Scheme 2.9.1.2</td>
<td>Mosher’s Ester Derivatization of $(\pm)$-Xyloketal D [$(\pm)$-4] and Synthetic $(-)$-Xyloketal D [$(\pm)$-4].</td>
</tr>
<tr>
<td>Scheme 2.9.2.1</td>
<td>Synthesis of $(\pm)$-Xyloketal D [$(\pm)$-4]: Diels-Alder Approach</td>
</tr>
<tr>
<td>Scheme 2.9.3.1</td>
<td>Attempted Synthesis of $(-)$-Xyloketal A [$(\pm)$-1]: Diels-Alder Approach</td>
</tr>
<tr>
<td>Scheme 3.2.1.1</td>
<td>Retrosynthetic Analysis of Xyloketal A (1): Phenylboronic Acid-Mediated Reactions</td>
</tr>
<tr>
<td>Scheme 3.2.1.2</td>
<td>Retrosynthetic Analyses of the Aldehyde (127)</td>
</tr>
<tr>
<td>Scheme 3.4.1.1</td>
<td>Phenylboronic Acid-Mediated Reaction of Phloroglucinol (14) and Senecialdehyde (134).</td>
</tr>
<tr>
<td>Scheme 3.5.1.1</td>
<td>Hydrogenation of the $tris-2H$-Chromene (148).</td>
</tr>
<tr>
<td>Scheme 3.6.1.1</td>
<td>Synthesis of Cyclopentylideneacetaldehyde (152) from Cyclopentanone (149).</td>
</tr>
<tr>
<td>Scheme 3.6.1.2</td>
<td>Synthesis of Cyclohexylideneacetaldehyde (156) from Cyclohexanone (153).</td>
</tr>
<tr>
<td>Scheme 3.6.1.3</td>
<td>Synthesis of Adamantylideneacetaldehyde (160) from 2-Adamantanone (157).</td>
</tr>
<tr>
<td>Scheme 3.6.1.4</td>
<td>Synthesis of 2-Methylocyclopentene-1-carboxaldehyde (165) from 1-Methylcyclohexene (161).</td>
</tr>
<tr>
<td>Scheme 3.6.1.5</td>
<td>Synthesis of 4-Formyl-5-methyl-2,3-dihydrofuran (169) from $\alpha$-Acetyl-$\gamma$-butyrolactone (166).</td>
</tr>
<tr>
<td>Scheme 3.6.2.1</td>
<td>Phenylboronic Acid-Mediated Reactions of Phloroglucinol (14) and $\alpha,\beta$-Unsaturated Carbonyl Compounds (170).</td>
</tr>
<tr>
<td>Scheme 3.7.1.1</td>
<td>Attempted Synthesis of the Ester (211) from Propylene Oxide (209).</td>
</tr>
<tr>
<td>Scheme 3.7.2.1</td>
<td>Attempted Direct Synthesis of the Dihydrofuran Ester (212).</td>
</tr>
<tr>
<td>Scheme 3.7.2.2</td>
<td>Synthesis of the Trichloroketones (213) and (214) from 2-Methyl-4,5-dihydrofuran (114).</td>
</tr>
<tr>
<td>Scheme 3.7.2.3</td>
<td>Attempted Synthesis of the Alcohol (168) from the Carboxylic Acid (215).</td>
</tr>
<tr>
<td>Scheme 3.7.2.4</td>
<td>Synthesis of the Ester (167) from the Trichloroketone (213).</td>
</tr>
</tbody>
</table>
Scheme 3.7.3.1  Synthesis of the Chiral Oxazolidinone [(4S)-219] According to Literature Procedures.................................................................92
Scheme 3.7.3.2  Optimization of the Diastereoselective Alkylation Reaction of the Oxazolidinone [(4S)-219] with a Propargyl Halide........................................92
Scheme 3.7.3.3  Synthesis of the Dihydrofuran [(4R)-61] from the Oxazolidinone [(+)-220]........................................................................................................96
Scheme 3.7.3.4  Synthesis of the Methyl Ester [(4R)-206] from the Dihydrofuran [(4R)-61].........................................................................................................97
Scheme 3.7.3.5  Synthesis of the Chiral Nonracemic Carboxylic Acid [(4R)-225] from the Trichloroketone [(4R)-223]...............................................................97
Scheme 3.7.3.6  Conversion of the Ester [(4R)-206] into the Aldehyde [(4R)-127]......98
Scheme 3.7.3.11  Attempted Synthesis of the tris-2H-Chromene (126)................99
Scheme 4.2.1.1  Retrosynthetic Analysis of Xyloketal A (1): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethylfuran (50).................................................................103
Scheme 4.3.1.1  Synthesis of the 2,4-Dimethyl-3-hydroxymethylfuran (50) from Propargyl Bromide (71) ..........................................................104
Scheme 4.3.2.1  Attempted Synthesis of the Hexasubstituted Benzene Derivative (50) from Phloroglucinol (228).................................................................105
Scheme 4.3.3.1  Attempted Direct C-Silylation of the Furan (50)........................108
Scheme 4.3.3.2  Attempted Two Step Synthesis of the C-Silylated Furan (234) ....110
Scheme 4.3.3.3  Attempted Synthesis of the Brominated Furans (235) and (236) ......110
Scheme 4.4.1.1  Retrosynthetic Analysis of Xyloketal A (1): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226).................................................................112
Scheme 4.4.2.1  Retrosynthetic Analysis of Xyloketal B (2) and C (3): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226).................................................................113
Scheme 4.4.3.1  Retrosynthetic Analysis of Xyloketal D (4) and G (7): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226).................................................................114
Scheme 4.4.4.1  Retrosynthetic Analysis of Xyloketal E (5) from Xyloketal B (2) and 2,4-Dimethyl-4,5-dihydrofuran (61).................................................................114
Scheme 4.4.5.1  Retrosynthetic Analysis of Xyloketal F (6) from Xyloketal B (2) ......115
Scheme 4.4.6.1  Retrosynthetic Analysis of Xyloketal F (6) from 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226).................................................................116
Scheme 4.5.1.1  Synthesis of (+)-11-Trinorxyloketal A [(±)-18] and (+)-2,6-epi-11,11',11"-Trinorxyloketal A [(±)-19]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168).................................................................................................................................117
Scheme 4.5.2.1 Synthesis of the Methyl Ester Xyloketal B and C Analogues [(±)-115], [(±)-242], [(±)-116] and (243): Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)........................................................................................................121

Scheme 4.5.2.2 Synthesis of the bis-Demethyl Xyloketal B Analogues [(±)-16] and [(±)-17] ........................................................................................................124

Scheme 4.5.3.1 Synthesis of the Methyl Esters (244) and (245) .........................................................................................................................126

Scheme 4.5.3.2 Attempted Synthesis of the Methoxy Xyloketal C Analogues [(±)-247] and (248): Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168) ........................................................................................................127

Scheme 4.5.4.1 Synthesis of (±)-11-Norxyloketal D [(±)-12] and (±)-10Norxyloketal G [(±)-13]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168) ........................................................................................................127

Scheme 4.5.4.2 Synthesis of (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-7-ethyl-8-hydroxy-1a-methyl-furo[5]chromane [(±)-250]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168) ........................................................................................................130

Scheme 4.5.4.3 Attempted Synthesis of the Xyloketal G Analogue [(±)-13] from the Bicyclic Acetal [(±)-250] .........................................................................................................................131

Scheme 4.5.4.4 Synthesis of (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-8-hydroxy-1a-methyl-furo[5]chromane [(±)-254]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168) ........................................................................................................132

Scheme 4.5.4.5 Attempted Synthesis of the Xyloketal G Analogue [(±)-13] from the Bicyclic Acetal [(±)-245] .........................................................................................................................133

Scheme 4.5.5.1 Synthesis of the Xyloketal E Analogues [(±)-257], [(±)-258], [(±)-259] and [(±)-260] from the Xyloketal B Analogues [(±)-16] and [(±)-17] ........................................................................................................134

Scheme 4.6.1.1 Total Synthesis of (−)-Xyloketal A [(−)-1]: Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-226] ........................................................................................................136

Scheme 4.6.1.2 Synthesis of the Xyloketal B Methyl Esters [(−)-261] and [(−)-262]: Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-226] ........................................................................................................139

Scheme 4.6.2.2 Total Synthesis of (−)-Xyloketal B [(−)-2] from the Xyloketal B Methyl Ester [(−)-262] .........................................................................................................................141

Scheme 4.6.3.1 Total Synthesis of (−)-Xyloketal D [(−)-4] and G [(−)-7]: Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-226] ........................................................................................................144

xxi
LIST OF TABLES

Table 3.4.1.1 Reaction Conditions Corresponding to Scheme 3.4.1.1 .......................69
Table 3.6.2.1 Results Corresponding to Scheme 3.6.2.1 ........................................78
Table 3.7.1.1 Reaction Conditions Corresponding to Scheme 3.7.1.1 ......................87
Table 3.7.3.1 Reaction Conditions Corresponding to Scheme 3.7.3.2 .....................92
Table 4.3.2.1 Catalysts Corresponding to Scheme 4.3.2.1 .......................................105
Table 4.3.3.1 Reagents and Conditions Corresponding to Scheme 4.3.3.1 .................108
Table 4.5.1.1 Reagents and Conditions Corresponding to Scheme 4.5.1.1 .................117
Table 4.5.2.1 Reagents and Conditions Corresponding to Scheme 4.5.2.1 .................121
Table 4.5.4.1 Reagents and Conditions Corresponding to Scheme 4.5.4.3 .................131
Table 4.6.1.1 Reagents and Conditions Corresponding to Scheme 4.6.1.1 .................136
Table 5.2.2.1 Reagents and Conditions Corresponding to Scheme 5.2.2.1 .................157
Table 5.3.2.1 Reagents and Conditions Corresponding to Scheme 5.3.2.1 .................160
Table 6.2.16.1 Summary of Crystallographic Data for the Amide [(−)-121] ............187
Table 6.2.16.2 Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [U(iso), (Å²)] for the Amide [(−)-121] ........................................................................................................188
Table 6.2.16.3 Bond Lengths (Å) for the Amide [(−)-121] ......................................189
Table 6.2.16.4 Bond Angles (°) for the Amide [(−)-121] ......................................190
Table 6.3.14.1 Summary of Crystallographic Data for the Chromene (174) ..........226
Table 6.3.14.2 Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [U(iso), (Å²)] for the Chromene (174) .................................................................227
Table 6.3.14.3 Bond Lengths (Å) for the Chromene (174) ..................................230
Table 6.3.14.4 Bond Angles (°) for the Chromene (174) ..................................232
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\alpha]_D$</td>
<td>specific rotation</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>bottom face (steroid nomenclature)</td>
</tr>
<tr>
<td>$\beta$</td>
<td>top face (steroid nomenclature)</td>
</tr>
<tr>
<td>$\delta$</td>
<td>chemical shift (NMR spectroscopy)</td>
</tr>
<tr>
<td>(+)-</td>
<td>dextrorotatory</td>
</tr>
<tr>
<td>(-)-</td>
<td>laevorotatory</td>
</tr>
<tr>
<td>(±)-</td>
<td>racemic</td>
</tr>
<tr>
<td>2D</td>
<td>two dimensional</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azo-<em>bis</em>-isobutyronitrile</td>
</tr>
<tr>
<td>amu</td>
<td>atomic mass units (mass spectroscopy)</td>
</tr>
<tr>
<td>Anal.</td>
<td>elemental analysis</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic group</td>
</tr>
<tr>
<td>atm</td>
<td>atmospheres</td>
</tr>
<tr>
<td>Å</td>
<td>Ångstrom (0.1 nm)</td>
</tr>
</tbody>
</table>
BINAP [1,1'-binaphthalene]-2,2'-diylbis(diphenylphosphine)

Bn benzyl (phenylmethyl)

B.p. boiling point

br broad (spectroscopy)

brsm based on recovered starting material

Calcd. calculated (elemental analysis)

CAN ceric ammonium nitrate

cat. catalytic (amount)

CD circular dichroism

CI chemical ionization (mass spectroscopy)

\( \text{cm}^{-1} \) wavenumbers (IR spectroscopy)

\( ^{13}\text{C} \text{NMR} \) carbon nuclear magnetic resonance spectroscopy

conc. concentrated

COSY \( ^{1}\text{H}-{^{1}\text{H}} \) correlation spectroscopy

D sodium D-line (589 nm)

d doublet (NMR spectroscopy)

dd doublet of doublets (NMR spectroscopy)

ddd doublet of doublet of doublets (NMR spectroscopy)

dr diastereoisomeric ratio
dt        doublet of triplets (NMR spectroscopy)
DIBAL-H    diisobutylaluminum hydride
DMAP       2,4-dimethylpyridine-6-carboxaldehyde N,N-dimethyl-4-aminopyridine
DMF        N,N-dimethylformamide
DMS        dimethyl sulfide
ef         evaporated film (IR spectroscopy)
El         electron impact ionization (mass spectroscopy)
equiv      equivalent(s)
Et         ethyl
EtOAc      ethyl acetate
EtOH       ethanol
Et2O       diethyl ether (ether)
FAB-HRMS   fast atom bombardment high resolution mass spectrosocpy
GC         gas chromatography
h          hour(s)
hfc        3-(heptafluoropropylhydroxymethylene)-(+)camphorate
HMPA       hexamethylphosphoramide
HMQC       heteronuclear multiple quantum coherence spectroscopy
1H NMR     proton nuclear magnetic resonance spectroscopy
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz (cycles per second)</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>median inhibition concentration</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectrometry</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (NMR spectrometry)</td>
</tr>
<tr>
<td>KBr</td>
<td>Potassium bromide disc (IR spectrometry)</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium N,N-diisopropylamide</td>
</tr>
<tr>
<td>lit.</td>
<td>literature value for a physical or spectroscopic property</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (NMR spectrometry)</td>
</tr>
<tr>
<td>M</td>
<td>molarity of a solution</td>
</tr>
<tr>
<td>M</td>
<td>molecular ion (mass spectrometry)</td>
</tr>
<tr>
<td>M + H</td>
<td>molecular ion plus a proton (mass spectrometry)</td>
</tr>
<tr>
<td>M + K</td>
<td>molecular ion plus potassium (mass spectrometry)</td>
</tr>
<tr>
<td>M + Na</td>
<td>molecular ion plus sodium (mass spectrometry)</td>
</tr>
<tr>
<td>M - H₂O</td>
<td>molecular ion minus water (mass spectrometry)</td>
</tr>
<tr>
<td>M - OMe</td>
<td>molecular ion minus methoxide (mass spectrometry)</td>
</tr>
<tr>
<td>MALDI-TOF</td>
<td>matrix assisted laser desorption ionization-time of flight (mass spectrometry)</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Symbol</td>
<td>Full Form</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>Me$_2$CO</td>
<td>acetone</td>
</tr>
<tr>
<td>MeI</td>
<td>methyl iodide (iodomethane)</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol (methyl alcohol)</td>
</tr>
<tr>
<td>Me$_2$SO$_4$</td>
<td>dimethyl sulfate</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz (NMR spectroscopy)</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mL</td>
<td>millilitres</td>
</tr>
<tr>
<td>mm Hg</td>
<td>millimetres of mercury</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole(s)</td>
</tr>
<tr>
<td>M.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>$m/z$</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>$\mu$L</td>
<td>microlitre(s)</td>
</tr>
<tr>
<td>N/A</td>
<td>not applicable</td>
</tr>
<tr>
<td>$n$-BuLi</td>
<td>$n$-butyl lithium</td>
</tr>
<tr>
<td>NBS</td>
<td>$N$-bromosuccinimide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>OAc</td>
<td>acetate</td>
</tr>
<tr>
<td>ORTEP</td>
<td>Oakridge thermal ellipsoid plot</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PhH</td>
<td>benzene</td>
</tr>
<tr>
<td>PhMe</td>
<td>toluene</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million (NMR spectroscopy)</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium $p$-toluenesulfonate</td>
</tr>
<tr>
<td>$p$-TsOH$\cdot$H$_2$O</td>
<td>$p$-toluenesulfonic acid monohydrate</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR spectroscopy)</td>
</tr>
<tr>
<td>rel.</td>
<td>relative</td>
</tr>
<tr>
<td>$R_f$</td>
<td>retention factor (thin-layer chromatography)</td>
</tr>
<tr>
<td>s</td>
<td>singlet (NMR spectroscopy)</td>
</tr>
<tr>
<td>t</td>
<td>triplet (NMR spectroscopy)</td>
</tr>
<tr>
<td>TBS</td>
<td>$t$-butyldimethylsilyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>TBSCI</td>
<td>t-butyldimethylsilyl chloride</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>t-butyl lithium</td>
</tr>
<tr>
<td>td</td>
<td>triplet of doublets (NMR spectroscopy)</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>Tebbe reagent</td>
<td>(CH$_3$)$_2$(C$_5$H$_5$)$_2$CH$_2$AICITi</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin-layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMSCI</td>
<td>trimethylsilyl chloride</td>
</tr>
<tr>
<td>tq</td>
<td>triplet of quartets (NMR spectroscopy)</td>
</tr>
<tr>
<td>UV</td>
<td>ultra violet</td>
</tr>
<tr>
<td>v/v</td>
<td>volume by volume</td>
</tr>
<tr>
<td>w/v</td>
<td>weight by volume</td>
</tr>
<tr>
<td>w/w</td>
<td>weight by weight</td>
</tr>
</tbody>
</table>
CHAPTER ONE

Introduction to the Xyloketal Natural Products and Alboatrin

1. Thesis Introduction

This thesis concerns a series of novel syntheses of the seven membered xyloketal family of natural products that was isolated from a mangrove fungus of the *Xylaria* species. The chiral nonracemic and polycyclic molecular architecture of these compounds, in addition to the high symmetry of several members of the family, make these natural products attractive targets for total synthesis. In addition, several of these compounds were shown to have potent and notable biological activity. Therefore, these compounds could serve as potential lead compounds for drug discovery. Moreover, the syntheses described in this thesis should be easily adaptable for the synthesis of structural analogues for further biological evaluation. Also presented in this thesis is a novel total synthesis of the structurally related natural product alboatrin. Several racemic syntheses of this biologically active natural product have been reported in the literature to date. However, the synthesis reported herein is the first asymmetric total synthesis of the natural product.

1.2 The Xyloketal Natural Products

1.2.1 Isolation and Structural Characterization of the Xyloketal Natural Products

In 2001, Lin and co-workers reported the isolation and structural characterization of five structurally related natural products, xyloketal A (1), B (2), C (3), D (4) and E (5), from a South China Sea mangrove fungus of the *Xylaria* species (Figure 1.2.1.1).
Subsequent to this initial report, an improved isolation procedure has been reported.\textsuperscript{2} Moreover, Lin and co-workers have recently reported the isolation and structural characterization of two additional members of this family of natural products, xyloketals F (6) and G (7).\textsuperscript{3,4}

![Molecular Structures of Xyloketals](image-url)

Figure 1.2.1.1 Molecular structures of xyloketals A (1), B (2), C (3), D (4), E (5), F (6) and G (7).
The molecular structures and relative stereochemistries of these natural products were determined by extensive spectroscopic studies and by X-ray crystallography. The absolute stereochemistries of xyloketal A (1), D (4), F (6) and G (7) were determined by interpretation of their CD spectra. The absolute stereochemistries of the remaining members of this family of natural products were assigned by analogy.

The xyloketals incorporate identical 5,6-bicyclic acetal moieties that are fused to an aromatic core. In all cases, the cis-ring junctions of the bicyclic acetals are syn to the methyl substituents at C-5 of the five-membered rings. Xyloketal A (1) has a unique and remarkable C$_3$-symmetric molecular structure that incorporates three bicyclic acetal moieties. Xyloketal B (2) and the minor C$_2$-symmetric component, xyloketal C (3), incorporate two bicyclic acetal moieties. Xyloketal D (4) and the corresponding regioisomer, xyloketal G (7), are the simplest members of this family of natural products in that they only contain one bicyclic acetal moiety.

Xyloketal C (3) is relatively unstable as compared to the regioisomeric natural product, xyloketal B (2), and undergoes isomerization to afford the latter substance in solution. It is reasonable to assume that this is a result of unfavourable dipole interactions which are minimized in the case of xyloketal B (2).

The isolation and structural characterization of xyloketal E (5), a derivative of xyloketal B (2), suggests that (4R)-2,4-dimethyl-4,5-dihydrofuran is a common biogenic precursor to all of these natural products. It is reasonable to conclude that this natural product is formed by a direct substitution reaction of the electron rich aromatic ring of

(*) The numbering scheme employed for the xyloketals, and analogues thereof, in this thesis is based upon that reported by Lin and co-workers (See: Ref. 1, 3 and 4).
xyloketal B (2) on protonation of the aforementioned dihydrofuran precursor. In addition, the semi-synthesis of the $C_2$-symmetric natural product, xyloketal F (6), from xyloketal B (2), on condensation with formaldehyde under acidic reaction conditions, further supports a common biogenic origin of all of these novel secondary metabolites.\(^3\)

1.2.2 X-Ray Crystal Structures of the Xyloketals

The X-ray crystal structures of xyloketal A (1), C (3), D (4), E (5) and F (6) have been solved.\(^1,3\) In the solid state, xyloketal A (1) adopts a bowl-shaped conformation (Figure 1.2.2.1). The other xyloketals also exhibit this puckered conformation which is presumably enforced by anomeric effects.

![Figure 1.2.2.1](image)

Figure 1.2.2.1 X-Ray crystal structure of xyloketal A (1) (the thermal ellipsoids are drawn at a 50% probability level and the hydrogen atoms have been omitted for clarity).
1.3 Biological Properties of the Xyloketal Natural Products

1.3.1 Acetylcholine Esterase Inhibition

During preliminary biological evaluation of the xyloketsals, xyloketal A (1), B (2), C (3) and D (4) were shown to inhibit acetylcholine esterase with IC$_{50}$ values of 29.9, 137.4, 109.3 and 425.6 $\mu$mol/L, respectively.$^{15}$ This enzyme is responsible for the metabolic saponification of the active neurotransmitter acetylcholine to inactive choline within the human nervous system. Patients suffering from the neurological disorder Alzheimer's disease show a depressed level of acetylcholine in their brain tissue. The only therapeutic strategy that has been shown to be widely useful in treating this disorder is to inhibit acetylcholine esterase.$^{6}$ This strategy increases the levels of acetylcholine in the brain by decreasing the metabolism of this compound at the neurotransmitter synapse and is referred to as the "cholinergic hypothesis".$^{7}$ Therefore, xyloketal A (1), B (2), C (3) and D (4) are potential lead compounds for drug discovery for the treatment of this disease.

1.3.2 L-Calcium Channel Inhibition

In subsequent biological evaluations, it was shown that xyloketal A (1), B (2) and F (6) block L-calcium channels by 21, 12 and 50%, respectively, at 0.03 $\mu$mol/L.$^{3}$ These channels are responsible for regulating the movement of calcium ions into and out of muscle cells. There is a high concentration of these channels in heart muscle and the movement of calcium ions is directly related to heart muscle contraction. As a result, calcium channel blockers have been widely targeted for the treatment of cardiovascular diseases such as angina and hypertension.$^{8}$ Therefore, xyloketal A (1), B (2) and F (6) are potential lead compounds for the treatment of various cardiovascular diseases.
1.4 Literature Syntheses of the Xyloketal Natural Products and Analogues

Concurrent with the execution of the work described in this thesis, there have been several reports regarding the synthesis of members of the xyloketal family of natural products. A brief summary of these investigations is presented below.

1.4.1 Krohn’s Synthesis of the Xyloketal D and G Analogues [(±)-12] and [(±)-13]

Krohn and co-workers have reported the synthesis of the xyloketal D analogue (±)-12 and the xyloketal G analogue (±)-13 (Scheme 1.4.1.1).³

Scheme 1.4.1.1 Krohn’s Synthesis of the Xyloketal D and G Analogues [(±)-12] and [(±)-13]

Reagents and conditions: (a) MeLi, Et₂O, −30 to 0 °C, 90 min, 21% (9), 55% (10); (b) enone 10, PhMe, reflux, 4 h, 83% [(±)-12], 8% [(±)-13].

The key step in this synthesis involved a conjugate addition reaction of the 2,4-dihydroxyacetophenone (11) to the enone 10 followed by a spontaneous acetal formation process. The reaction was regioselective and favoured the formation of the xyloketal D analogue (±)-12 rather than the xyloketal G analogue (±)-13 (~10:1). In both analogues,
the cis-ring junction of the 5,6-bicyclic acetals was installed stereoselectively. The lactone starting material 8 was prepared in single step from commercially available butyrolactone.

1.4.2 Krohn’s Synthesis of the Xyloketal A and B Analogues [(±)-18], [(±)-19], [(±)-16] and [(±)-17]

Krohn and co-workers have also extended the above reaction sequence to prepare the xyloketal A analogues (±)-18 and (±)-19 as well as the xyloketal B analogues (±)-16 and (±)-17, from the enone 10 and 1,3,5-trihydroxybenzene [phloroglucinol (14)] (Scheme 1.4.2.1).
Scheme 1.4.2.1 Krohn’s Synthesis of the Xyloketal A and B Analogues [(±)-18], [(±)-19], [(±)-16] and [(±)-17]

Reagents and conditions: (a) Enone 10 (0.5 equiv), PhMe, reflux, 4 h, 50% [(±)-15], 27% [(±)-16 and (±)-17], 6% [(±)-18 and (±)-19] or enone 10 (3.0 equiv), PhMe, reflux, 4 h, 19% [(±)-15], 63% [(±)-16 and (±)-17], 7% [(±)-18 and (±)-19] or enone 10 (6.0 equiv), PhMe, reflux, 20 h, 7% [(±)-15], 22% [(±)-16 and (±)-17], 58% [(±)-18 and (±)-19].

On variation of the number of equivalents of the enone 10 relative to phloroglucinol (14), it was found that the ratio of the resultant mono-, bis- and tris-adducts could be controlled. In all cases, the xyloketal B analogues [(±)-16 and (±)-17 were isolated as an inseparable mixture (dr = 2:3) with the syn,anti-isomer (±)-17 being the predominate reaction product. This product ratio varied slightly from the expected 1:1 statistical mixture. Of note, none of the regioisomeric bis-adducts, corresponding to the xyloketal C (3), were obtained. In the case of the xyloketal A analogues [(±)-18 and
(±)-19, an inseparable mixture (dr = 1:4) was formed. The unsymmetric syn,syn,anti-isomer (±)-19 was the predominate reaction product isolated. Again, this varied to a small extent from the expected 1:3 statistical mixture.

1.4.3 Krohn's Synthesis of Racemic Xyloketal D [(±)-4] and G [(±)-7]

On completion of model studies, Krohn and co-workers synthesized the racemic enone (±)-25 and used this material to prepare racemic xyloketal D [(±)-4] and G [(±)-7] (Scheme 1.4.3.1).⁹
Scheme 1.4.3.1  Krohn’s Synthesis of Racemic Xyloketal D [(±)-4] and G [(±)-7]

Reagents and conditions: (a) LiAlH₄, 73% [21:22], 17:3; (b) H₂, 10% Pd/C, 72%; (c) NaH, HCO₂Et, EtOH, Et₂O, room temperature, 30 min then paraformaldehyde, Et₂O, reflux, 1 h, 63%;
(d) MeLi, Et₂O, -50 to 0 °C, 90 min, 75%; (e) enone (±)-25, PhMe, reflux, 4h, 80%, dr = 17:3 [(±)-4:(±)-26], 9% [(±)-7:(±)-27].

Although the four step synthesis of the enone (±)-25 was concise the initial reduction step in this sequence led to the undesired formation of the regioisomer 21 as the major reaction product. The final step of the reaction sequence afforded xyloketal D [(±)-4] regioselectivity (~8:1) as had been observed with the model system. Furthermore, the bicyclic acetal moiety was cis-fused and good diastereoselectivity was observed relative to the stereogenic centre at C-5 (dr = 17:3). No comment was made on the selectivity between the formation of xyloketal G [(±)-7] and its epimer (±)-27. However,
it is reasonable to assume that a similar ratio was obtained as for that observed for xyloketal D [(±)-4] and its epimer (±)-26.

1.4.4 Krohn's Attempted Synthesis of Racemic Xyloketal A [(±)-1] and B [(±)-2]

Krohn and co-workers have also applied the above synthetic method towards the preparation of racemic xyloketal A [(±)-1] and B [(±)-2] from phloroglucinol (14) (Scheme 1.4.4.1).9

Scheme 1.4.4.1 Krohn's Attempted Synthesis of Racemic Xyloketal A [(±)-1] and B [(±)-2]

Reagents and conditions: (a) Enone (±)-25 (1 equiv), PhMe, reflux, 4 h, 50% [(±)-28 and (±)-29], 31% [(±)-2 and (±)-30-36], 6% [(±)-1 and (±)-37-43].
Reaction of the racemic enone (±)-25 with phloroglucinol (14) afforded the mono-adducts (±)-28 and (±)-29, the bis-adducts (±)-2 and (±)-30-36 as well as the tris-adducts (±)-1 and (±)-37-43. The mono-adducts (±)-28 and (±)-29 were obtained as an inseparable mixture of epimers (dr = 17:3), which was similar to that observed for xyloketal D [(±)-4]. The bis-adducts (±)-2 and (±)-30-36 were also obtained as an inseparable mixture of eight compounds. In addition, the tris-adducts (±)-1 and (±)-37-43 were obtained in low yield (6%) and as an inseparable mixture of eight compounds.

1.4.5 Krohn’s Asymmetric Synthesis of (−)-Xyloketal D [(−)-4]

Krohn and co-workers subsequently completed an asymmetric total synthesis of (−)-xyloketal D [(−)-4] (Scheme 1.4.5.1).9,10
Scheme 1.4.5.1 Krohn’s Asymmetric Synthesis of (-)-Xyloketal D [(-)-4]

Reagents and conditions: (a) SeO₂, AcOH, reflux, 4 h, 37%; (b) H₂, (R)-BINAP-Ru(OAc)₂, MeOH, room temperature, 12 h, 100%, 93% ee; (c) HCl (aq), CHCl₃, reflux, 75%; (d) NaH, HCO₂Et, EtOH, Et₂O, room temperature, 30 min then paraformaldehyde, Et₂O, reflux, 1 h; (e) MeLi, Et₂O, -50 to 0 °C, 90 min, 54% (over two steps); (f) enone (R)-25, PhMe, reflux, 4 h, 81%, dr = 17:3 [(-)-4:26].

The absolute stereochemistry in this synthesis was introduced by an asymmetric hydrogenation reaction of the carboxylic acid 45 using a ruthenium/BINAP catalytic system. The resultant alcohol (R)-46 was converted to the optically active lactone (R)-23 which corresponded to an intermediate in the racemic synthesis discussed above. This material was then elaborated to afford (-)-xyloketal D [(-)-4] and the 2,6-epimer 26, again in a 17:3 ratio. Of note, no comment was made regarding the possible formation of the optically active natural product xyloketal G (7).
1.5 Alboatrin

1.5.1 Isolation and Structural Characterization of Alboatrin (48)

In 1988, Ichihara and co-workers reported the isolation, structural characterization and total synthesis of the natural product alboatrin (48) from the fungus *Verticillium albo-atrum* (Figure 1.5.1.1).\(^{11}\) The assigned structure 47 featured a 5,6-bicyclic acetal moiety that was fused to an aromatic core. At this time, the C-3 methyl substituent was assigned as being anti to the cis-ring junction of the bicyclic acetal.\(^*\) No comment regarding the absolute stereochemistry of the natural product was made in this initial report.

![Ichihara's assigned molecular structure (47) and Murphy's revised molecular structure (48)](image)

**Figure 1.5.1.1** Ichihara’s assigned molecular structure (47) and Murphy’s revised molecular structure (48) of alboatrin.

In 1999, Murphy and co-workers completed a total synthesis of the assigned structure of alboatrin (47).\(^{12}\) The spectral data for their synthetic material did not match the data reported for the natural product. X-Ray crystal structure analysis of their synthetic material confirmed that the major reaction product corresponded to the structure reported by Ichihara and co-workers. However, their minor reaction product 48, the C-3 epimer of the assigned structure for alboatrin (47), matched the spectral data of the natural product. Therefore, the molecular structure for alboatrin (48) was revised. Of

\(^*\) The numbering scheme employed for alboatrin (48), and analogues thereof, is based upon that reported by Ichihara and co-workers (See: Ref. 11).
note, the correct molecular structure of alboatrin (48) incorporates an identical 5,6-bicyclic acetal moiety as to that found in the xyloketal family of natural products.

1.5.2 X-Ray Crystal Structure of Alboatrin (48)

Baldwin and co-workers have recently reported a total synthesis and X-ray crystal structure analysis of racemic alboatrin [(±)-48] (Figure 1.5.2.1). Similar to the xyloketalts, alboatrin (48) adopts a puckered conformation in the solid state.

Figure 1.5.2.1 X-Ray crystal structure of alboatrin [(±)-48] (the thermal ellipsoids are drawn at a 50% probability level).

1.6 Biological Properties of Alboatrin

1.6.1 Root Growth Inhibition of Alfalfa

Alboatrin (48) is a phytotoxic metabolite associated with vascular-wilt disease of alfalfa. It has been reported that alboatrin (48) inhibits the root growth of the host plant,
Maris Kabul, by 49% at a concentration of 50 ppm. This disease causes stunted growth, reduced quality, wilted and dead foliage as well as a reduction in life span of the plant. This causes crop production to become uneconomical after two to three years in infected alfalfa fields. In addition, infected plants are more susceptible to death from environmental stresses such as the lack of precipitation and temperature.

1.7 Literature Syntheses of Alboatrin

1.7.1 Ichihara’s Synthesis of Racemic Alboatrin [(±)-48]

Ichihara and co-workers described the first total synthesis of racemic alboatrin [(±)-48] concurrently with their report on the isolation of the natural product (Scheme 1.7.1.1).\(^\text{11}\)

Scheme 1.7.1.1 Ichihara’s Synthesis of Racemic Alboatrin [(±)-48]

Reagents and conditions: (a) LiAlH\(_4\), Et\(_2\)O, 85%; (b) 1-methyl-3,5-dihydroxybenzene, BF\(_3\)·Et\(_2\)O, CH\(_2\)Cl\(_2\), 10%; (c) H\(_2\), Pd/C, AcOH, 64%.

The key steps in this synthesis featured an electrophilic aromatic substitution process and a subsequent hydrogenation reaction. Presumably, the less substituted
double bond of the furan 51 was reduced selectively, based on steric factors, which led to the spontaneous formation of the bicyclic acetal moiety. The relative stereochemistry of the C-3 methyl substituent was \textit{syn} to the bridgehead hydrogen atom of the acetal moiety. Of note, this racemic product was resolved by chiral HPLC to afford both enantiomers of alboatrin (48). The enantiomers were shown to exhibit similar biological activity.

1.7.2 Murphy’s Synthesis of Racemic Alboatrin [\((\pm)-48\)]

Murphy and co-workers have also reported a total synthesis of racemic alboatrin [\((\pm)-48\)] (Scheme 1.7.2.1).\textsuperscript{12}
Scheme 1.7.2.1  Murphy’s Synthesis of Racemic Alboatrin [(±)-48]

Reagents and conditions: (a) Acrylic acid, Amberlyst 15® resin, PhMe, 4 h, 87%; (b) TBSCI, TEA, CH₂Cl₂, room temperature, 6 h, 97%; (c) Tebbe reagent, PhMe, −40 °C to room temperature, 4 h, 70%; (d) Amberlyst 15® resin, CHCl₃, 60 °C, 12 h, 100%; (e) allyl alcohol, NBS, CH₂Cl₂, 0 °C to room temperature, 6 h, 72%; (f) 1-ethylpiperidine hypophosphite, AIBN, PhH, 4 h, 77%, dr = 7:1 [(±)-47:(±)-48].

The key step in this synthesis was the use of a 1-ethylpiperidine hypophosphite-mediated radical cyclization process to install the 5,6-bicyclic acetal moiety. From the outset of this synthesis, it was expected that this reaction would afford predominately compound 47, that was the original structure assigned to alboatrin (48), based on the steric arguments that are associated with 5-exo-trig radical cyclizations. As mentioned earlier, only on comparison of the spectral data of the major product of this reaction with...
that reported for alboatrin (48) was it discovered that the minor reaction product corresponded to the correct molecular structure of alboatrin (48).

1.7.3 Baldwin’s Synthesis of Racemic Alboatrin [(±)-48]

Recently, Baldwin and co-workers have reported an additional total synthesis of racemic alboatrin [(±)-48] (Scheme 1.7.3.1).

Scheme 1.7.3.1 Baldwin’s Synthesis of Racemic Alboatrin [(±)-48]

Reagents and conditions: (a) BH₃-DMS, THF, 0 °C to room temperature, 1 h, 84%; (b) PhH, reflux, 36 h, 68%, dr = 13:1 [(±)-62:(±)-63], 25%, dr = 3:2 [(±)-64:(±)-65]; (c) K₂CO₃, CH₂Cl₂:MeOH:H₂O (12:7:10), room temperature, 6 h, 90%.

The key step in this synthesis was an inverse electron demand hetero Diels-Alder reaction between an ortho-quinone methide and a dihydrofuran. This reaction proceeded in high yield and in good diastereoselectivity (dr = 13:1) for the desired reaction product (±)-62. However, during this key synthetic step, a substantial quantity (25%) of the
undesired spiroacetals (±)-64 and (±)-65 were also formed (vide infra). Of note, the known acetate 59 was prepared in two steps from 5-methyl-1,3-dihydroxybenzene [orcinol (53)]. This material was then converted to the ortho-quinone methide precursor 60 in a one pot reaction sequence that involved reduction of the formyl group and migration of the adjacent acetate. (±)-2,4-Dimethyl-4,5-dihydrofuran [(±)-61] was prepared by a four step procedure from simple precursors.
CHAPTER TWO

Towards the Synthesis of the Xyloketal: Diels-Alder Approach

2.1 Introduction

In this chapter, the application of a Diels-Alder reaction towards the synthesis of the xyloketal natural products is discussed. The key feature of this synthetic route is based on the generation of ortho-quinone methides and subsequent reactions with appropriately functionalized dihydrofurans. Demethyl analogues of xyloketal A (1) and D (4) were prepared during the course of the optimization of appropriate reaction conditions. In addition, this synthetic route led to the completion of total syntheses of (+)-, (+)- and (−)-xyloketal D (4).

2.2 Retrosynthetic Analysis: Diels-Alder Approach

2.2.1 Retrosynthetic Analysis of Xyloketal D (4)

Retrosynthetic analysis of xyloketal D (4) suggested that it could be prepared by a [4+2] cycloaddition reaction of the ortho-quinone methide 66 and the dihydrofuran 61 (Scheme 2.2.1.1). It was anticipated that this inverse electron demand hetero Diels-Alder reaction would afford the target compound in a regio- and stereoselective manner.\textsuperscript{16,17,18,19} There are a variety of precursors for the generation of ortho-quinone methides including Mannich bases.\textsuperscript{20} The Mannich base 67 could be prepared from commercially available 2,4-dihydroxyacetophenone (11), a formaldehyde source and secondary amines.\textsuperscript{21}

\textsuperscript{†} The results discussed in this chapter have been reported in part, see: (a) Total Synthesis of (±)-Xyloketal D and Model Studies Towards the Synthesis of (−)-Xyloketal A. Pettigrew, J. D.; Bexrud, J. A.; Freeman, R. P.; Wilson, P. D. Heterocycles 2004, 62, 445; (b) Total Synthesis of (−)-Xyloketal D and its Enantiomer – Confirmation of Absolute Stereochemistry. Pettigrew, J. D.; Freeman, R. P.; Wilson, P. D. Can. J. Chem. 2004, 82, 1640.
Scheme 2.2.1.1  Retrosynthetic Analysis of Xyloketal D (4): Diels-Alder Approach

The required dihydrofuran 61 can be prepared via the thermal isomerization of the corresponding exo-cyclic double bond isomer 68 which in turn can be formed from the intramolecular 5-exo-dig cyclization of the alcohol 69 upon exposure to a base (Scheme 2.2.1.2).\textsuperscript{22,23} The alcohol 69 can be prepared by reduction of the corresponding carboxylic acid 70,\textsuperscript{24} which in turn, is available on alkylation of the dianion of propionic acid (72) with propargyl bromide (71).\textsuperscript{25}
Scheme 2.2.1.2  Retrosynthetic Analysis of 2,4-Dimethyl-4,5-dihydrofuran (61)

\[
\begin{align*}
&\text{Me} \
&\text{Me} \
&\text{Me} 
\end{align*}
\]

2.2.2 Retrosynthetic Analysis of Xyloketal A (1)

In a similar fashion, it was envisioned that xyloketal A (1) could be prepared from the Mannich base 74 and three equivalents of the dihydrofuran 61 (Scheme 2.2.2.1). This direct synthetic process would involve the stepwise generation and subsequent cycloaddition reaction of a series of ortho-quinone methide reaction intermediates (cf. structure 73). The Mannich base 74 could be prepared from commercially available phloroglucinol (14), a formaldehyde source and a secondary amine.26,27
2.2.3 Retrosynthetic Analysis of Xyloketal B (2) and C (3)

The application of this retrosynthetic scheme towards the synthesis of xyloketal B (2) and C (3) would require the preparation of a bis-Mannich base 77 (R = H) of phloroglucinol (14) (Scheme 2.2.3.1). It was expected that the synthesis of this compound would be difficult as the reactivity of the aromatic ring would presumably increase with an increasing number of electron donating substituents. As a result, the bis-adduct formed by the reaction of phloroglucinol (14) with two equivalents of formaldehyde and the secondary amine would be expected to react at a faster rate than phloroglucinol (14) or the corresponding mono-substituted intermediate. Therefore, it was anticipated that one of the aromatic positions of phloroglucinol (14) would need to be blocked (R = protecting group) with a readily removable functional group prior to the Mannich reaction. After the execution of the proposed Diels-Alder reactions, this group (R = protecting group) would then be removed to afford the desired natural products, xyloketal B (2) and C (3).
Scheme 2.2.3.1 Retrosynthetic Analysis of Xyloketal B (2) and C (3): Diels-Alder Approach

2.3 Brief Overview of ortho-Quinone Methide Chemistry

As the use of ortho-quinone methides in synthetic chemistry is not widespread, a brief overview of several of the key aspects associated with these species is presented below. More comprehensive reviews on the chemistry of ortho-quinone methides can be found in the chemical literature.20,28
2.3.1 Generation of *ortho*-Quinone Methides

The precursors used to generate *ortho*-quinone methides have a common structural motif, a phenol with a substituent in the *ortho* position that can be readily converted to an alkylidene usually by either the elimination of a leaving group or by coordination to an additive in the reaction mixture. Consequently, there are numerous ways to generate *ortho*-quinone methides. Three commonly employed precursors are *ortho*-hydroxyl Mannich bases 79, *ortho*-hydroxyalkyl phenols 80 as well as salicylaldehydes and derivatives 81 (Figure 2.3.1.1).

![Figure 2.3.1.1 Common precursors for the generation of *ortho*-quinone methides.](image)

When the Mannich bases 79 are used as the precursors of *ortho*-quinone methides, the amino group is generally converted into a good leaving group to facilitate the reaction. One common method for this process is an alkylation reaction of the nitrogen atom to form the corresponding ammonium salt 82 which readily undergoes an elimination reaction upon heating or on exposure to light (Figure 2.3.1.2). Oxidation with hydrogen peroxide to generate the corresponding N-oxides 84, which can undergo a thermal elimination process, has also been demonstrated. In addition, it has been shown that *ortho*-quinone methides can be produced directly on photolysis of Mannich bases 79.
Figure 2.3.1.2  *ortho*-Quinone methide generation from Mannich bases (79).

Direct photolysis has also been used to generate *ortho*-quinone methides from *ortho*-hydroxyalkyl phenols 80 (Figure 2.3.1.3). The hydroxyl group can also be chemically modified to facilitate its departure as a leaving group. For example, it has been demonstrated that the *ortho*-acetoxymethyl phenol 86 can be readily converted to an *ortho*-quinone methide upon heating. In addition, cyclic borate esters 87 have been used to generate *ortho*-quinone methides under thermal or acidic conditions. These types of readily available precursors allow for the introduction of substituents at the benzylic site of the *ortho*-quinone methide.
Figure 2.3.1.3 *ortho-Quinone methide generation from ortho-hydroxyalkyl phenols (80) and derivatives (86) and (89).

It has also been reported that salicylaldehydes 88, and derivatives thereof, can be used to generate *ortho-quinone methides* by co-ordination to additives in the reaction mixture (Figure 2.3.1.4). These additives have included both Lewis and Brønsted acids. These types of precursors provide an additional benefit in that heteroatom substituents at the benzylic site provide a handle for further manipulations during target-oriented synthesis.
Figure 2.3.1.4 ortho-Quinone methide generation from salicylaldehydes (80) and derivatives (90).

In many cases, it has been possible to isolate the resultant ortho-quinone methides. However, this is generally only so when the ortho-quinone methides are part of an extended π-system. It is more common to generate ortho-quinone methides *in situ* for direct use in the next step of an intended reaction sequence.

### 2.3.2 Reactions of ortho-Quinone Methides

Once generated, ortho-quinone methides can be utilized in a variety of reaction types. These extended π-systems are excellent acceptors of nucleophiles in 1,4/1,8-conjugate addition reactions that result in the restoration of aromaticity. A variety of nucleophiles, including carbanions, nitriles, amines, alcohols, thiols, halogens and phosphites, have been shown to react with ortho-quinone methides (Figure 2.3.2.1).
Figure 2.3.2.1 Nucleophilic addition reactions of ortho-quinone methides.

Of particular interest to the research described in this thesis is the extensive array of pericyclic reactions that are associated with ortho-quinone methides. For example, Soucek and co-workers have reported a series of net [4+4] dimerization reactions of ortho-quinone methides (Figure 2.3.2.2).

Figure 2.3.2.2 Net [4+4] cycloaddition reactions of ortho-quinone methides.

However, the most common types of pericyclic reactions are [4+2] cycloaddition reactions and 6π electrocyclic rearrangements. ortho-Quinone methides are excellent dienes in inverse electron demand hetero Diels-Alder reactions. A variety of dienophiles have been employed in these reactions, including alkenes (95, X = alkyl, H), enol ethers (95, X = OR), enamines (95, X = NR₂), dihydrofurans (97, n = 1) and dihydropyrans (97, n = 2) (Figure 2.3.2.3). In addition, these reactions are often highly regio- and stereoselective.
Figure 2.3.2.3 [4+2] Cycloaddition reactions of ortho-quinone methides.

In the absence of a suitable nucleophile or diene, certain ortho-quinone methides can undergo $6\pi$ electrocyclic rearrangements to form biaryl ethers 100$^{41}$ and 2H-chromenes 102$^{19,42,43}$ (Figure 2.3.2.4).

Figure 2.3.2.4 $6\pi$ Electroyclic rearrangements of ortho-quinone methides.
2.4 Synthesis of Mannich Bases as Precursors to ortho-Quinone Methides

2.4.1 Preparation of Mannich Bases for the Synthesis of Xyloketal D (4)

The synthesis of Mannich bases from 2,4-dihydroxyacetophenone (11), paraformaldehyde and secondary amines has been reported by Shigesmasa and co-workers. Thus, the Mannich bases 104 and 106 were prepared in good yield and as single regioisomeric products by heating a solution of 2,4-dihydroxyacetophenone (11) and formaldehyde with morpholine (103) or dibenzylamine (105) in aqueous methanol (Scheme 2.4.1.1).

Scheme 2.4.1.1 Synthesis of Mannich Bases from 2,4-Dihydroxyacetophenone (11)

Reagents and conditions: (a) CH₂O, H₂O, MeOH, reflux, 3 h, 82%; (b) CH₂O, H₂O, MeOH, reflux, 48 h, 73%.

The structures of the reaction products and the regioselectivity of these aromatic substitution reactions were determined by analysis of the ^1H NMR spectra. The aromatic protons were strongly coupled (J ~ 9 Hz) which indicated that they were located on adjacent carbon atoms. The origin of the high regioselectivity of this process is not
fully understood. However, these results are in agreement with the reported syntheses of other Mannich bases from 2,4-dihydroxyacetophenone (11).  

### 2.4.2 Preparation of Mannich Bases for the Synthesis of Xyloketal A (1)

Several triple Mannich bases of phloroglucinol (14) have been reported in the chemical literature. The synthesis of the Mannich bases 107 and 108 proved to be exceedingly facile (Scheme 2.4.2.1). This involved the addition of an aqueous solution of formaldehyde to a solution of phloroglucinol (14) and the amine 103 or 105 in ethanol. Within several minutes, the reaction products 107 or 108 precipitated from the reaction mixture. The amorphous powders that were isolated were found to be analytically pure.

#### Scheme 2.4.2.1 Synthesis of Mannich Bases from Phloroglucinol (14)

Reagents and conditions: (a) CH₂O, H₂O, EtOH, room temperature, 18 h, 79%; (b) CH₂O, H₂O, EtOH, room temperature, 18 h, 93%.

The ^1^H NMR spectra of these compounds were very simple. This is a consequence of the inherent C₃-symmetry of the reaction products. The ^13^C NMR spectra
contained two signals at approximately δ 99 and 156 ppm which corresponded to the hexasubstituted electron rich aromatic core.

2.4.3 Preparation of Mannich Bases for the Synthesis of Xyloketal B (2) and C (3)

As mentioned earlier, the direct formation of the bis-Mannich bases of phloroglucinol (14) would not be possible (See: Section 2.2.3). Thus, the synthesis of an appropriate mono-substituted derivative of phloroglucinol (14) was required. Initially, it was decided to employ an iodide substituent as a blocking group. It was anticipated that this functional group could be readily removed at a later stage of the proposed synthetic route by a variety of methods. For example, this could involve reduction with lithium aluminum hydride\textsuperscript{44} or sodium borohydride\textsuperscript{45} as well as by transmetallation followed by the introduction of a proton source such as water. Therefore, phloroglucinol (14) (1 equiv) was allowed to react with iodine (1 equiv) and sodium bicarbonate in a mixture of tetrahydrofuran and water to afford a mixture of the known mono- and di-iodides as well as the unreacted starting material 14 (Scheme 2.4.3.1).\textsuperscript{46} The desired reaction product 109 was obtained by repetitive precipitation of the minor undesired compounds from a mixture of acetone and chloroform. Of note, this procedure afforded the trihydrate of iodophloroglucinol (109), as indicated by the large singlet at δ 2.94 ppm in the $^1$H NMR spectrum.
Attempted Synthesis of the bis-Mannich Base (110)

Reagents and conditions: (a) I₂, NaHCO₃, THF, H₂O, room temperature, 15 min, 87%; (b) morpholine (103), CH₂O, H₂O, EtOH, room temperature, 17 h.

Iodophloroglucinol trihydrate (109) was then treated with formaldehyde and morpholine (103) in aqueous ethanol and the resultant precipitate was isolated. Unexpectedly, this material was found to be the tris-Mannich base 107 of phloroglucinol (14) and not the desired bis-adduct 110. Subsequent concentration of the filtrate afforded a complex mixture of products from which the desired Mannich base 110 could not be isolated. It was rationalized that the iodide moiety had been transferred in this reaction to afford a mixture of products of the generic formula C₆H₃O₃Iₙ(CH₂NR₂)₃₋ₙ, where n = 0, 1, 2 and 3. This transfer process of iodide between iodophloroglucinol (109), and derivatives thereof, has also been observed by other research groups.⁴⁶

Given the above findings, an alternative blocking group was selected. It was decided to prepare a carboxylate methyl ester derivative of phloroglucinol (14). Of note, aromatic esters, which are located in the ortho or para positions to phenols, are known to undergo facile decarboxylation reactions on saponification.⁴⁷,⁴⁸,⁴⁹ Towards these ends, 2,4,6-trihydroxybenzoic acid (111) was allowed to react with dimethylsulfate in the presence of sodium bicarbonate to afford the methyl ester 112 according to a literature procedure (Scheme 2.4.3.2).⁵⁰
Scheme 2.4.3.2  Synthesis of Mannich Base (113)

Reagents and conditions: (a) Me₂SO₄, NaHCO₃, DMF, room temperature, 6 days, 66%; (b) dibenzylamine (105), CH₂O, H₂O, EtOH, room temperature, 20 h, 44%.

This material was subsequently used to prepare the Mannich base 113 on reaction with formaldehyde and dibenzylamine (105) in aqueous ethanol. The precipitate from this reaction was impure and the filtrate contained substantial quantities of the desired reaction product 113. Therefore, the crude reaction mixture was concentrated and the product 113 was isolated by flash chromatography.

2.5  Model Studies: Diels-Alder Approach

2.5.1  Synthesis of (±)-11-Norxyloketal D [(±)-12]

In order to determine the feasibility of the proposed cycloaddition reaction for the synthesis of xyloketal D (4), commercially available 2-methyl-4,5-dihydrofuran (114) was employed as a model dieneophile. It was found on heating the Mannich base 104 (1 equiv) and the dihydrofuran 114 (3 equiv) with methyl iodide (1.05 equiv) in benzene at reflux for five days, that the xyloketal D analogue [(±)-12] could be isolated in 43% yield (Scheme 2.5.1.1). When the Mannich base 106 was subjected to the above reaction conditions the desired reaction product (±)-12 was also obtained, but in slightly lower yield (38%). In addition, increasing the number of equivalents of methyl iodide employed lowered the yield of these reactions. This was caused by competing
methylation reactions of one or more of the phenol groups of the Mannich bases 104 and 106.

Scheme 2.5.1.1 Synthesis of (±)-11-Norxyloketal D [(±)-12]: Diels-Alder Approach

Reagents and conditions: (a) MeI, PhH, reflux, 5 days, 43%; (b) MeI, PhH, reflux, 5 days, 38%.

The regioselectivity of the cycloaddition process, with respect to the two phenols, was determined on the basis of a peak at δ 13.09 ppm in the $^1$H NMR spectrum that corresponded to the unreacted phenolic proton (Figure 2.5.1.1). This sharp downfield signal suggested that the phenol group was adjacent to the carbonyl group.\textsuperscript{1,21}
Figure 2.5.1.1 $^1$H NMR spectrum (400 MHz, CDCl$_3$) of (±)-11-norxyloketal D [(±)-12].

The structure of the desired reaction product (±)-12 was assigned from the COSY NMR spectrum (Figure 2.5.1.2). The multiplet at $\delta$ 3.98 ppm was assigned to the protons adjacent to the acetal oxygen (H-4). This signal showed correlations to the two peaks that corresponded to the H-5 protons at $\delta$ 1.74 and 2.08 ppm. These signals were also coupled with H-6 at $\delta$ 2.47 ppm. In addition, H-6 was coupled to H-7$_\beta$ at $\delta$ 2.75 ppm and H-7$_\beta$ was coupled to H-7$_\alpha$ at $\delta$ 3.02 ppm. The aromatic proton, H-15, was assigned to the upfield signal at $\delta$ 6.37 ppm in the aromatic region based on its para-relationship to the electron releasing hydroxyl group. The remaining aromatic proton at $\delta$ 7.52 ppm was
therefore assigned as $H$-14. The two methyl substituents, $Me$-10 and $Me$-17, corresponded to the signals at $\delta$ 1.54 and 2.54 ppm, respectively.

![COSY NMR spectrum (400 MHz, CDCl₃) of (±)-11-norxyloketal D (±)-12.](image)

The $^{13}$C NMR spectrum contained fourteen distinct signals that accounted for all of the carbons in the molecule (Figure 2.5.1.3). Furthermore, the $^{13}$C NMR spectrum showed a characteristic signal that could be assigned to the acetal carbon, C-2, at $\delta$ 107 ppm.
The stereochemistry of the ring junction was confirmed as being *cis* based on the observation of a nOe contact between Me-10 and H-6 (Figure 2.5.1.4). Also of note, a nOe contact was observed between the proton that had been assigned as H-7\(\beta\) (\(\delta\) 2.75 ppm) and Me-10. In addition, nOe contacts were observed between Me-17, the OH and H-14 that confirmed the regioselectivity of the cycloaddition process and the assignment of the signals corresponding to the aromatic protons.

Figure 2.5.1.3  \(^{13}\)C NMR spectrum (101 MHz, CDCl\(_3\)) of (±)-11-norxyloketal D [(±)-12].
Figure 2.5.1.4 Observed nOe contacts for (±)-11-norxyloketal D [(±)-12].

2.5.2 Synthesis of (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-epi-11,11',11''-Trinorxyloketal A [(±)-19].

The feasibility of using this cycloaddition strategy to prepare xyloketal A (1) was then demonstrated successfully in a model study (Scheme 2.5.2.1). A mixture of the Mannich base 108 (1 equiv), 2-methyl-4,5-dihydrofuran (114) (9 equiv) and methyl iodide (3 equiv) was heated at reflux for 24 h to afford an inseparable mixture (dr = 1:4) of the desired $C_3$-symmetric xyloketal A analogue (±)-18 and the unsymmetric diastereoisomer (±)-19 in 19% yield. The use of Mannich base 107 as the ortho-quinone methide precursor also afforded the desired reaction products (±)-18 and (±)-19 although in a slightly lower yield (14%).
Scheme 2.5.2.1 Synthesis of (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-epi-11,11',11''-Trinorxyloketal A [(±)-19]: Diels-Alder Approach

Reagents and conditions: (a) 2-Methyl-4,5-dihydrofuran (114) (9 equiv), MeI (3 equiv), PhH, reflux, 24 h, 19%, dr = 1:4 [(±)-18:(±)-19]; (b) 2-methyl-4,5-dihydrofuran (114) (9 equiv), MeI (3 equiv), PhH, reflux, 24 h, 14%, dr = 1:4 [(±)-18:(±)-19].

This mixture of compounds was fully characterized by spectroscopic methods. The $^1$H NMR spectrum of the mixture showed four signals corresponding to Me-10 [one from the $C_3$-symmetric analogue (±)-18 and three from the diastereoisomer (±)-19]. The relative intensities of these signals were used to determine the product ratio. The $^{13}$C NMR spectrum also showed groups of either three or four signals corresponding to the $C_3$-symmetric isomer (±)-18 and the unsymmetric isomer (±)-19. Of note, the mass spectrum (CI) contained the parent molecular ion (M + H) at 415 amu as well as daughter ions that could be attributed to fragmentation by retro Diels-Alder reactions. In addition, a large signal for an ion that corresponded to the dihydrofuran 114 was also observed.
The yield of this reaction (19%), although low, is indeed respectable when one considers that this direct process involves nine individual reactions (three alkylation reactions, three elimination reactions and three subsequent cycloaddition reactions). Furthermore, it was anticipated that the C-4 methyl substituent of the dihydrofuran 61 required to prepare xyloketal A (1) would control the diastereoselectivity of the proposed reaction in an absolute sense.

2.5.3 Attempted Synthesis of the Xyloketal B and C Analogues [(±)-115] and [(±)-116]

In a similar manner to that described previously for the synthesis of the xyloketal D analogue (±)-12 and the xyloketal A analogues (±)-18 and (±)-19, the Mannich base 113 (1 equiv) was allowed to react with the dihydrofuran 114 (6 equiv) and methyl iodide (2 equiv) in benzene at reflux for 24 h (Scheme 2.5.3.1). However, in this instance, a complex mixture of reaction products was obtained from which the desired reaction products (±)-115 and (±)-116 could not be isolated despite extensive chromatographic efforts.

Scheme 2.5.3.1 Attempted Synthesis of the Methyl Esters [(±)-115] and [(±)-116]: Diels-Alder Approach

Reagents and conditions: (a) 2-Methyl-4,5-dihydrofuran (114) (6 equiv), Mel (2 equiv), PhH, reflux, 24 h.
On the basis of this result, the application of the Mannich base 113 in the synthesis of xyloketal B (2) and C (3) was not investigated.

2.6 Synthesis of Racemic 2,4-Dimethyl-4,5-dihydrofuran

In order to undertake the total synthesis of the xyloketal natural products, the synthesis of the known racemic dihydrofuran (±)-61 was accomplished by adaptation of literature procedures.

2.6.1 Preparation of Racemic 2,4-Dimethyl-4,5-dihydrofuran [(±)-61] Based on Literature Procedures

The synthesis of the dihydrofuran (±)-61 began from propionic acid (72) and propargyl bromide (71). This involved generation of the corresponding dianion of propionic acid (72) with excess lithium N,N-diisopropylamide (2.3 equiv) in a mixture of hexamethylphosphoramide and tetrahydrofuran (Scheme 2.6.1.1). This dianion was then treated with propargyl bromide (71) (1.2 equiv) to afford the desired product (±)-70 in good yield (68%). This acid was subsequently reduced to the corresponding acetylenic alcohol (±)-69 with lithium aluminum hydride.

Scheme 2.6.1.1 Synthesis of the Alcohol [(±)-69] from Propionic Acid (72) and Propargyl Bromide (71)

Reagents and conditions: (a) LDA, HMPA, THF, 0 °C to room temperature, 1 h then propargyl bromide (71), 0 °C to room temperature, 3 h, 68%; (b) LiAlH₄, THF, 0 °C to room temperature, 16 h, 82%.
The alcohol (±)-69 was then heated at reflux with a substoichiometric amount of sodium amide (Scheme 2.6.1.2). This induced a 5-exo-dig cyclization to afford the exocyclic dihyrofuran (±)-68 which was isomerized to the desired 2,4-dimethyl-4,5-dihydrofuran [(±)-61] upon heating at reflux (~100 °C) in the absence of solvent.

Scheme 2.6.1.2 Synthesis of (±)-2,4-Dimethyl-4,5-dihydrofuran [(±)-61] from the Alcohol [(±)-69]

Reagents and conditions: (a) NaNH2 (cat.), reflux, 2 h, 66%; (b) reflux, 16 h, 87%.

2.7 Total Synthesis of Racemic Xyloketals: Diels-Alder Approach

2.7.1 Total Synthesis of (±)-Xyloketal D [(±)-4]

The cycloaddition reaction of the Mannich base 104 (1 equiv) with the dihydrofuran (±)-61 (3 equiv) as described in the model studies afforded (±)-xyloketal D [(±)-4] and (±)-2,6-epi-xyloketal D [(±)-26] as well as the diastereoisomeric spiroacetals (±)-117 and (±)-118 as a mixture of products (11:1:3:3) in a combined yield of 54% (Scheme 2.7.1.1). Similar to the results observed in the model studies, the use of Mannich base 106 afforded these reaction products in a slightly lower combined yield (47%).
Scheme 2.7.1.1 Synthesis of (±)-Xyloketal D [(±)-4]: Diels-Alder Approach

Reagents and conditions: (a) (±)-2,4-Dimethyl-4,5-dihydrofuran [(±)-61] (3 equiv), MeI (1.05 equiv), PhH, reflux, 5 days, 54%, 11:1:3:3 [±-4:(±)-26:(±)-117:(±)-118]; (b) (±)-2,4-dimethyl-4,5-dihydrofuran [(±)-61] (3 equiv), MeI (1.05 equiv), PhH, reflux, 5 days, 47%, 11:1:3:3 [(±)-4:(±)-26:(±)-117:(±)-118].

It was possible to separate these reaction products by repetitive chromatography and the spectral data (1H and 13C NMR) for synthetic (±)-xyloketal D [(±)-4] were in agreement with those reported for the natural product (Figure 2.7.1.1).1 Of note, the 1H NMR signal of natural (−)-xyloketal D [(−)-4] centred at δ 2.15 ppm should have been
reported at $\delta$ 2.08 ppm. Thus, the relative stereochemistry of the expected major reaction product was firmly established.

![Chemical Structure](image)

**Figure 2.7.1.1** $^1$H NMR spectrum (400 MHz, CDCl$_3$) of (±)-xyloketal D [(±)-4].

The formation of the spiroacetal by-products (±)-117 and (±)-118 in this reaction was attributed to the isomerization of the double bond of the dihydrofuran (±)-61 to afford the corresponding exocyclic double bond isomer (±)-68 which then underwent a subsequent Diels-Alder reaction.** It is of interest that a spiroacetal by-product was not identified in the cycloaddition reaction of 2-methyl-4,5-dihydrofuran (114). Thus, it

(*) Professor Lin kindly provided the $^1$H and $^{13}$C NMR spectra of the xyloketal D (4) for comparison purposes.

(**) Baldwin and co-workers have subsequently applied a similar synthetic approach towards the total synthesis of alboatrin (48) and have also observed the formation of undesired spiroacetal reaction products by a similar process (See: Ref. 13 and 14).
appears that the additional methyl substituent decreases the reactivity of the endocyclic double bond of the dihydrofuran \((\pm)-61\) in this cycloaddition reaction, possibly as a result of steric hindrance.

2.7.2 Attempted Synthesis of \((\pm)-Xyloketal\) A \([\pm)-1\]

The cycloaddition reactions of the Mannich bases 107 and 108 (1 equiv) with the dihydrofuran \((\pm)-61\) (9 equiv) to prepare \((\pm)-xyloketal\) A \([\pm)-1\] were attempted (Scheme 2.7.2.1). However, these reactions afforded highly complex mixtures of products from which the desired product \((\pm)-1\) could not be isolated.

**Scheme 2.7.2.1 Attempted Synthesis of \((\pm)-Xyloketal\) A \([\pm)-1\]: Diels-Alder Approach**

Reagents and conditions: (a) \((\pm)-2,4\)-Dimethyl-4,5-dihydrofuran \([\pm)-61\] (9 equiv), Mel (3 equiv), PhH, reflux, 24 h; (b) \((\pm)-2,4\)-dimethyl-4,5-dihydrofuran \([\pm)-61\] (9 equiv), Mel (3 equiv), PhH, reflux, 24 h.
2.8 Synthesis of Chiral Nonracemic 2,4-Dimethyl-4,5-dihydrofuran

In order to complete an asymmetric synthesis of xyloketal D (4) and attempt the asymmetric synthesis of xyloketal A (1), it was decided to prepare optically active 2,4-dimethyl-4,5-dihydrofuran (61) and use this material in the Diels-Alder reactions. The use of chiral nonracemic dihydrofuran 61 in the synthesis of xyloketal D (4) would firmly establish the absolute stereochemistry of this natural product. Furthermore, this modification was expected to reduce the number of possible stereoisomeric reaction products produced in the triple Diels-Alder reactions and facilitate the isolation of the natural product, xyloketal A (1). Towards these ends, it was decided to investigate the resolution of one of the intermediates from the previously described racemic synthetic route.

2.8.1 Synthesis of (2R)-2-Methylpent-4-ynoic Acid [(2R)-70] and (2S)-2-Methyl-pent-4-ynoic Acid [(2S)-70] Employing a Resolution Procedure

A variety of methods were investigated in order to identify an efficient resolution procedure for the racemic carboxylic acid (±)-70. It was not possible to separate the diastereoisomeric salts that were formed between the carboxylic acid (±)-70 and (R)-α-methylbenzylamine or (R)-(1-naphthy1)-ethylamine by fractional recrystallization. In addition, the racemic carboxylic acid (±)-70 was condensed with (R)-phenylglycinol [(R)-119] to afford the corresponding diastereoisomeric oxazolines.\textsuperscript{51} Unfortunately, these derivatives were found to be chromatographically inseparable. The racemic carboxylic acid (±)-70 was also converted to the corresponding acid chloride and condensed with menthol, isomenthol and (2R)-butan-2-ol. All of the diastereoisomeric esters could not
be separated by fractional recrystallization or by chromatographic methods. The corresponding acid chloride of the carboxylic acid (±)-70 was also condensed with an extensive series of chiral nonracemic amines including (R)-α-methylbenzylamine and (R)-(1-naphthyl)-ethylamine, the methyl esters of (S)-alanine, (S)-isoleucine, (S)-leucine, (S)-phenylalanine, (S)-proline, (S)-tryptophan and (R)-phenylglycine, as well as (S)-valinol and (1S,2R)-norephedrine. It was found that the diastereoisomeric amides (−)-120 and (−)-121 prepared from (R)-phenylglycinol [(R)-119] could be readily separated by flash chromatography on a multigram scale (Scheme 2.8.1.1).\textsuperscript{52,53} Of note, the diastereoisomeric amides that were prepared from (S)-valinol were also chromatographically separable. However, the (R)-phenylglycinol-derived amides (−)-120 and (−)-121 were employed due to the ease of handling these compounds (UV chromophore for TLC analysis, high crystallinity and greater difference in R\textsubscript{f} value). The chiral nonracemic carboxylic acids (2R)-70 and (2S)-70 were then prepared by hydrolysis of the diastereoisomeric amides (−)-120 and (−)-121, respectively, under acidic reaction conditions.\textsuperscript{54}
Scheme 2.8.1.1 Resolution of (±)-2-Methylpent-4-ynoic Acid [(±)-70] with (R)-Phenylglycinol [(R)-119]

Reagents and conditions: (a) (COC1)2, CH2Cl2, DMF (cat.), 0 °C to room temperature, 2 h then (R)-phenylglycinol [(R)-119], TEA, CH2Cl2, 0 °C to room temperature, 16 h, 36% [(-)-120], 34% [(-)-121]; (b) 3 M H2SO4, p-dioxane, reflux, 7 h, 76% [(2R)-70]; (c) 3 M H2SO4, p-dioxane, reflux, 7 h, 86% [(2S)-70].

The amide [(-)-121] was a crystalline solid which on recrystallization from ethyl acetate afforded colourless needles that were suitable for X-ray crystal structure analysis (Figure 2.8.1.1). Inspection of the X-ray crystal structure revealed that this amide had the S configuration at the carboxylic acid stereogenic centre. Therefore, the amide [(-)-121] had an appropriate absolute stereochemistry to prepare the enantiomer of the natural product, (+)-xyloketal D [(+)-4], and the amide [(-)-120] had the appropriate absolute stereochemistry to prepare the natural product [(-)-xyloketal D [(-)-4]].
2.8.1.1 X-Ray crystal structure of the amide [(-)-121] (the thermal ellipsoids are drawn at a 50% probability level).

2.8.2 Synthesis of (2R)-2-Methylpent-4-yn-1-ol [(2R)-69] and (2S)-2-Methylpent-4-yn-1-ol [(2S)-69]

The chiral nonracemic carboxylic acids (2R)-70 and (2S)-70 were then reduced with lithium aluminum hydride to afford the corresponding alcohols (2R)-69 and (2S)-69 (Scheme 2.8.2.1).
Scheme 2.8.2.1 Synthesis of the Alcohols [(2R)-69] and [(2S)-69] from the Corresponding Carboxylic Acids [(2R)-70] and [(2S)-70]

Reagents and conditions: (a) LiAlH₄, THF, 0 °C to room temperature, 16 h, 89%; (b) LiAlH₄, THF, 0 °C to room temperature, 16 h, 85%.

Of note, the chiral nonracemic alcohol (2R)-69 is a known compound and has been prepared in six steps from commercially available (2R)-methyl-3-hydroxy-2-methylpropanoate. However, the optical rotation of this compound has not been reported. The corresponding benzyl ether (2R)-122 has also been prepared from this expensive starting material. In this case, the optical rotation of this material has been reported. Therefore, a sample of the alcohol (2R)-69 was converted to the benzyl ether (2R)-122 (Scheme 2.8.2.2). The optical rotation of the product was identical in both sign and magnitude to the reported literature values. Thus, the absolute stereochemistry and high optical purity of the resolved alcohol (2R)-69 was firmly established. A sample of the alcohol (2S)-69 was also converted to the corresponding benzyl ether (2S)-122 which proved to be the enantiomer of the known compound.
2.8.2.2 Confirmation of Absolute Stereochemistry of the Alcohols [(2R)-69] and [(2S)-69] by the Synthesis of the Known Benzyl Ethers [(2R)-122] and [(2S)-122]

Reagents and conditions: (a) NaH, BnBr, DMF, THF, room temperature, 6 h, 90%; (b) NaH, BnBr, DMF, THF, room temperature, 6 h, 90%.

2.8.3 Synthesis of (4R)-2,4-Dimethyl-4,5-dihydrofuran [(4R)-61] and (4S)-2,4-Dimethyl-4,5-dihydrofuran [(4R)-61]

The chiral nonracemic alcohol (2R)-69 was then used to prepare the dihydrofuran (4R)-61 as described earlier for the racemic compound (Scheme 2.8.3.1). This compound would serve as the precursor of (−)-xyloketal D [(-)-4] and would allow for the confirmation of the absolute stereochemistry of the natural product. In an identical fashion, the alcohol (2S)-69 was used to prepare the dihydrofuran (4S)-61. This compound would serve as the precursor of the enantiomer of the natural product, (+)-xyloketal D [(+)-4].
Scheme 2.8.3.1 Synthesis of the Dihydrofurans [(4R)-61] and [(4S)-61] from the Corresponding Alcohols [(2R)-69] and [(2S)-69]

Reagents and conditions: (a) NaNH₂ (cat.), reflux, 2 h; (b) reflux, 2 h, 44% (over two steps); (c) NaNH₂ (cat.), reflux, 2 h; (d) reflux, 2 h, 36% (over two steps).

2.9 Synthesis of Chiral Nonracemic Xyloketals: Diels-Alder Approach

2.9.1 Synthesis of (−)-Xyloketal D [(−)-4]

The chiral nonracemic dihydrofuran (4R)-61 (3 equiv) and the Mannich base 104 (1 equiv) were heated in benzene at reflux with methyl iodide (1 equiv) for eight days (Scheme 2.9.1.1). This reaction afforded a mixture (8:1:2:2) of (−)-xyloketal D [(−)-4], 2,6-epi-xyloketal D (26) and the diastereoismeric spiroacetals 117 and 118 in a combined yield of 40%. The reaction was also repeated using dimethylsulfate (1 equiv) instead of methyl iodide. This reaction proceeded at a faster rate and afforded a mixture of reaction products (16:1:4:4) in a similar combined yield. A diastereoisomerically and analytically pure sample of the synthetic natural product, (−)-xyloketal D [(−)-4], was obtained by repetitive chromatography and recrystallization. An analytically pure sample of the diastereoisomorphic spiroacetals 117 and 118 was also obtained as a mixture (dr = 4:5) by repetitive chromatography and recrystallization. Of note, the Mannich base 106
was not employed as an ortho-quinone methide precursor as the use of this material had led to slightly poorer yields in both the model studies and when the racemic dihydrofuran (±)-61 was employed as a reaction partner.

Scheme 2.9.1.1 Synthesis of (−)-Xyloketal D [(−)-4]: Diels-Alder Approach

Reagents and conditions: (a) Dihydrofuran (4R)-61 (3 equiv), MeI (1 equiv), PhH, reflux, 8 days, 40%, 8:1:2:2 [(−)-4:26:117:118] or dihydrofuran (4R)-61 (3 equiv), Me₂SO₄ (1 equiv), PhH, reflux, 3 days, 37%, 16:1:4:4 [(−)-4:26:117:118].

The ¹H NMR and ¹³C NMR spectra of synthetic (−)-xyloketal D [(−)-4] were identical to those of the natural product and to the racemic material prepared previously. The sign of the optical rotation of synthetic (−)-xyloketal D [(−)-4] was in agreement with that reported for the natural product.¹ This confirmed the absolute stereochemistry of the natural product that had been assigned previously by the interpretation of CD data.¹ However, the magnitude of the rotation was slightly lower than that reported for the natural product (92% ee based on the reported optical rotation of the natural product). In
order to determine the enantiomeric purity of synthetic $(-)$-xyloketal D \([(-)-4]\), efforts were also made to separate the enantiomers of a sample of racemic xyloketal D \([(\pm)-4]\). This was not possible by analytical chiral HPLC (Daicel Chiralcel OD column) or by GC (Cyclosil-B column). Similarly, $^1$H NMR spectroscopy using a chiral shift reagent \([\text{Eu(hfc)}_3]\) was unsuccessful. Derivatization of the phenol moiety of racemic xyloketal D \([(\pm)-4]\) with \((S)-(\pm)-\alpha\text{-methoxy-}\alpha\text{-trifluoromethyl-phenylacetyl chloride} [\text{(S)-123}]\) afforded the corresponding Mosher's ester derivatives (Scheme 2.9.1.2).\(^{59,60}\) In this case, the $^1$H NMR (600 MHz) signals of the methoxy substituents were clearly resolved at $\delta$ 3.72 and 3.73 ppm. However, the $^{19}$F NMR (470 MHz) signals of the Mosher's ester derivatives, although separate, were poorly resolved. Subsequent derivatization of synthetic $(-)$-xyloketal D \([-(-)-4]\) afforded the corresponding Mosher's ester as a single diastereoisomer with the signal for the methoxy substituent at $\delta$ 3.72 ppm. This indicated that the synthetic material was of high optical purity.
Scheme 2.9.1.2 Mosher’s Ester Derivatization of (±)-Xyloketal D [(±)-4] and Synthetic (−)-Xyloketal D [(−)-4]

Reagents and conditions: (a) DMAP, THF, reflux, 3 h, 82%, dr = 1:1 [(−)-124:125]; (b) DMAP, THF, reflux, 2.5 h, 84%.

Interestingly, the melting point of synthetic (−)-xyloketal D [(−)-4] (71-73 °C) was significantly lower than that reported for the natural product (111-113 °C). Repeated recrystallization of the synthetic material from petroleum ether did not increase the melting point. Krohn and co-workers have reported that synthetic (−)-xyloketal D [(−)-4] (93% ee calculated from the reported optical rotation of the natural product and 93% ee based on the enantiomeric purity of a synthetic precursor) also had a lower melting point.
They also reported that subsequent recrystallization from a mixture of ether and pentane afforded material which had a melting point of 110-111 °C. Therefore, our sample of synthetic (−)-xyloketal D [(−)-4] was recrystallized from this solvent system. However, this procedure did not increase the melting point. Thus, it was concluded that this difference in melting point resulted from contamination with a trace amount of the enantiomer which had significantly depressed the melting point of our sample of synthetic (−)-xyloketal D [(−)-4].

2.9.2 Synthesis of (+)-Xyloketal D [(+)-4]

The Mannich base 104 (1 equiv) was also allowed to react with the enantiomeric chiral nonracemic dihydrofuran (4S)-61 (3 equiv) in the presence of methyl iodide (1 equiv) or dimethylsulfate (1 equiv) using the two procedures described above (Scheme 2.9.2.1). These reactions afforded mixtures of (+)-xyloketal D [(+)-4], ent-2,6-epi-xyloketal D [(ent)-26] and the diastereoisomeric spiroacetals (ent)-117 and (ent)-118.

(*) Professor Krohn graciously recorded the melting point of a sample of natural (−)-xyloketal D [(−)-4] which was provided to him by Professor Lin. This material was found to have a melting point of 107-108 °C (Büchi SMP-2 melting point apparatus).
Scheme 2.9.2.1  Synthesis of (+)-Xyloketal D [(+)-4]: Diels-Alder Approach

![Scheme 2.9.2.1](image)

Reagents and conditions: (a) Dihydrofuran (4S)-61 (3 equiv), MeI (1 equiv), PhH, reflux, 6 days, 46%, 13:1:3:3 [(+)-4:(ent)-26:(ent)-117:(ent)-118] or dihydrofuran (4S)-61 (3 equiv), Me₂SO₄ (1 equiv), PhH, reflux, 3 days, 36%, 20:1:3:3 [(+)-4:(ent)-26:(ent)-117:(ent)-118].

A diastereoisomerically and analytically pure sample of the enantiomeric natural product, (+)-xyloketal D [(+)-4], was also prepared and fully characterized following repetitive chromatography and recrystallization. The melting point and the magnitude of the optical rotation were in agreement with our synthetic (−)-xyloketal D [(−)-4].

2.9.3  Attempted Synthesis of (−)-Xyloketal A [(−)-1]

The total synthesis of (−)-xyloketal A [(−)-1] was also attempted (Scheme 2.9.3.1). The Mannich base 108 (1 equiv) and a large excess of the chiral nonracemic dihydrofuran (4R)-61 (9 equiv) were heated in benzene at reflux with methyl iodide (3 equiv) as well as with dimethyl sulfate (3 equiv). Unfortunately, the natural product
could not be isolated from the complex mixtures of products that were produced in these reactions.

**Scheme 2.9.3.1 Attempted Synthesis of (−)-Xyloketal A [(-)-1]: Diels-Alder Approach**

Reagents and conditions: (a) Dihydrofuran (4R)-61 (9 equiv), MeI (1 equiv), PhH, reflux, 24 h or dihydrofuran (4R)-61 (9 equiv), Me₂SO₄ (1 equiv), PhH, reflux, 24 h.

It was anticipated that the stereochemistry of this attempted cycloaddition reaction would have been directed efficiently by the C-4 methyl substituent of the chiral nonracemic dihydrofuran (4R)-61 [as was observed in the case of the syntheses of xyloketal D (4)]. Thus, it appears that the competing isomerization reaction of the dihydrofuran (4R)-61 and the subsequent non-stereoselective cycloaddition reaction of the exocyclic dihydrofuran (4R)-68 was a dominant complicating factor which prevented the isolation of (−)-xyloketal A [(-)-1].

**2.10 Conclusions**

The Mannich bases 104 and 106, which were prepared in a single step from commercially available starting materials, were shown to be appropriate precursors for the generation of ortho-quinone methides which served as dienes for inverse electron demand hetero Diels-Alder reactions. When commercially available 2-methyl-4,5-
dihydrofuran (114) was employed in the reaction, a highly regio- and stereoselective reaction occurred to afford the xyloketal D analogue (±)-12 as the sole reaction product. The synthesis of racemic 2,4-dimethyl-4,5-dihydrofuran [(±)-61] was accomplished according to adaptation of literature procedures. The use of this dihydrofuran led to the first total synthesis of (±)-xyloketal D [(±)-4] (9% overall yield in six steps from commercially available starting materials). This reaction exhibited excellent regioselectivity and good stereoselectivity (dr = 11:1). However, this process was complicated by the unexpected formation of the spiroacetals (+)-17 and (−)-18. Both enantiomers of the dihydrofuran (4R)-61 and (4S)-61 were subsequently prepared, on resolution of the racemic carboxylic acid (±)-69 precursor with (R)-phenylglycinol [(R)-119]. These compounds were used to prepare (−)- and (+)-xyloketal D [(−)-4] (3% overall yield in eight steps from commercially available starting materials) and [(+)-4] (3% overall yield in eight steps from commercially available starting materials), respectively and confirmed the absolute stereochemistry of the natural product.

The synthesis of the tris-Mannich bases 107 and 108 was found to be exceedingly facile. These compounds proved to be effective for the stepwise formation of ortho-quinone methides which were used to prepare the xyloketal A analogues (±)-18 and (±)-19. Although the overall yield of these reaction was low (19%), the process involved nine individual reaction steps and the coupling of four reaction components. The application of this synthetic process for the synthesis of racemic or optically active xyloketal A (1) was unsuccessful. This result was attributed to thermal isomerization reactions of the dihydrofuran 61 and the subsequent formation of spiroacetal by-products.
The Mannich base 113, required for the synthesis of xyloketals B (2) and C (3), was prepared in two steps from commercially available starting materials. However, this compound was found to be unsuitable as a precursor for the stepwise generation of the ortho-quinone methides in a model study. Therefore, no further efforts to synthesize these natural products were made by this approach.
CHAPTER THREE

Towards the Synthesis of Xyloketal A: Phenylboronic Acid-Mediated Reactions

3.1 Introduction

In this chapter the application of a phenylboronic acid-mediated reaction to the synthesis of xyloketal A (1), and analogues thereof, is described.† The key feature of this synthetic route is a triple condensation reaction of phloroglucinol (14) with α,β-unsaturated carbonyl compounds. This synthetic route did not afford xyloketal A (1) but a series of derivatives which represent structural analogues of the natural product were prepared.

3.2 Retrosynthetic Analysis: Phenylboronic Acid-Mediated Reactions

3.2.1 Retrosynthetic Analysis of Xyloketal A (1)

In addition to containing three ketal moieties, xyloketal A can be considered to be a tris-chromane. Therefore, retrosynthetic analysis of xyloketal A (1) suggested that it could be prepared from the C$_3$-symmetric 2H-chromene derivative 126 by a stereoselective hydrogenation reaction (Scheme 3.2.1.1). Here it would be expected that hydrogen would be added to the convex face of the molecule. There are a variety of methods for the synthesis of 2H-chromene derivatives.$^{61,62,63,64,65}$ Of particular relevance is the phenylboronic acid-mediated condensation reaction of phenols and α,β-unsaturated

† The results discussed in this chapter have been reported in part, see: (a) Phenylboronic Acid Mediated Triple Condensation Reactions of Phloroglucinol and Unsaturated Carbonyl Compounds. Pettigrew, J. D.; Cadieux, J. A.; So, S. S. S.; Wilson, P. D. Org. Lett. 2005, 7, 467; (b) Total Synthesis of (-)-Xyloketal A. Pettigrew, J. D.; Wilson, P. D. Org. Lett. 2006, 8, 1427.
aldehydes. Accordingly, the tris-chromene derivative 126 could be prepared from phloroglucinol (14) and three equivalents of the \(\alpha,\beta\)-unsaturated aldehyde 127. This process would involve three ortho-specific electrophilic aromatic substitution reactions followed by three subsequent dehydrative-cyclization reactions.\(^{66,67,68}\)

**Scheme 3.2.1.1 Retrosynthetic Analysis of Xyloketal A (1): Phenylboronic Acid-Mediated Reactions**

The aldehyde 127, which is a natural product isolated from the marine sponge fungi *A. cruciatus*,\(^{69}\) could be prepared by reduction of the ester 128 (Scheme 3.2.1.2). This ester could be prepared by isomerization of the corresponding hydroxy ester 129 under acidic reaction conditions.\(^{70,71}\) This latter compound, in principle, should be readily available from an ester of acetoacetate 130 and the bromide 131. Alternatively, the aldehyde 127 could be prepared by elaboration of the dihydrofuran 61.\(^{72}\)
3.3 Brief Overview of the Phenylboronic Acid-Mediated Reaction of Phenols and Aldehydes

A brief overview of the development and application of the phenylboronic acid-mediated reaction of phenols and aldehydes to afford 2H-chromenes is presented below.

3.3.1 Development and Application of the Phenylboronic Acid-Mediated Reaction

In 1992, Lau and co-workers reported the facile synthesis of cyclic borate esters from phenols, aldehydes and phenylboronic acid. This regiospecific reaction afforded products which proved to be isolable ortho-quinone methide precursors as discussed previously (See: Section 2.3.1). This initial work was subsequently followed by a report on the extension of this reaction towards the total synthesis of several biologically active natural products, such as precocene I (137) and II (138) (Figure 3.3.1.1). In this report, the authors used $\alpha,\beta$-unsaturated aldehydes to generate the borate esters, which in the
presence of a small amount of propionic acid (72), spontaneously underwent further reactions to afford the corresponding ortho-quinone methides. These reactive species then underwent 6π electrocyclic rearrangements to afford 2H-chromenes in a one-pot reaction sequence.

Figure 3.3.1.1 Synthesis of precocene I (137) and II (138).

Further studies by Snieckus and co-workers have shown that this synthetic method can be applied to napthols and phenanthrols. In addition, it was demonstrated that this reaction is sensitive to the electronic nature of the aromatic system employed. For example, the use of electron rich para-methoxyphenol as a reaction substrate afforded the desired 2H-chromene when allowed to react with 3-methyl-2-butenal [senecialdehyde (134)]. In contrast, the use of para-bromophenol afforded the corresponding reaction product in poor yield and para-nitrophenol did not afford the desired product under the same reaction conditions.
Wilson and co-workers have also applied this synthetic method to the synthesis of analogues of the potent anti-HIV natural product daurichromenic acid (139) (Figure 3.3.1.2).\(^{73}\)

![Daurichromenic acid (139) and Daurichromenic acid analogues (140)](image)

**Figure 3.3.1.2 Application of the phenylboronic acid-mediated reaction for the synthesis of daurichromenic acid analogues (140) by Wilson and co-workers.**

### 3.4 Formation of tris-2H-Chromenes

In order to optimize the reaction conditions for the preparation of tris-2H-chromenes from phloroglucinol (14), model studies were performed with senecialdehyde (134) as the \(\alpha,\beta\)-unsaturated aldehyde reaction component.

#### 3.4.1 Formation of tris-2H-Chromenes: Optimization of Reaction Conditions

Senecialdehyde (134) is commercially available but it is relatively expensive as compared to the corresponding alcohol 141. Therefore, this model compound was prepared in a single step from the alcohol 141 by oxidation with pyridinium dichromate according to a literature procedure (Scheme 3.4.1.1).\(^{74}\) Phloroglucinol (14) (1 equiv) was treated with this aldehyde (4 equiv), propionic acid (72) and phenylboronic acid in benzene at reflux with azeotropic removal of water to afford the chromene derivatives 142 and 143. The results of these model studies are presented below (Table 3.4.1.1).
Scheme 3.4.1.1 Phenylboronic Acid-Mediated Reaction of Phloroglucinol (14) and Senecialdehyde (134)

Reagents and conditions: (a) PDC, CH₂Cl₂, room temperature, 16 h, 56%; (b) see below: Table 3.4.1.1.

Table 3.4.1.1 Reaction Conditions Corresponding to Scheme 3.4.1.1*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Yield of (142) (%)</th>
<th>Yield of (143) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhB(OH)₂ (0.25 equiv), propionic acid (72) (cat.), PhH, reflux, 22 h</td>
<td>55</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>PhB(OH)₂ (1 equiv), propionic acid (72) (cat.), PhH, reflux, 22 h</td>
<td>74</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>PhB(OH)₂ (2 equiv), propionic acid (72) (cat.), PhH, reflux, 22 h</td>
<td>81</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>PhB(OH)₂ (3 equiv), propionic acid (72) (cat.), PhH, reflux, 22 h</td>
<td>92</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>PhB(OH)₂ (3 equiv), PhH, reflux, 22 h</td>
<td>Trace</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>Propionic acid (72) (cat.), PhH, reflux, 22 h</td>
<td>Trace</td>
<td>Trace</td>
</tr>
<tr>
<td>7</td>
<td>B(OH)₃ (0.25 equiv), propionic acid (72) (cat.), PhH, reflux, 22 h</td>
<td>45</td>
<td>30</td>
</tr>
</tbody>
</table>

(*) All reactions were performed with four equivalents of the aldehyde 134 and one equivalent of phloroglucinol (14).
The initial reaction of phloroglucinol (14) and senecialdehyde (134) with phenylboronic acid (0.25 equiv), in the presence of propionic acid (72) (cat.) afforded a mixture of the condensation products 142 and 143 in good yield (entry 1). These reaction products had the core ring systems of xyloketal A (1) and C (3), respectively. It was then found that increasing the amount of phenylboronic acid used in this reaction led to an increase in the amount of the triple condensation product 142 that was formed, up to 92% (entries 2-4). It was also found that only trace amounts of these reaction products were formed when propionic acid (72) was omitted from the reaction (entry 5). This suggested that the cyclic borate esters formed during the course of the reaction were stable, although no attempts were made to isolate these intermediates. When phenylboronic acid was omitted from the reaction mixture only trace amounts of the products were formed that indicated a requirement for a suitable promoter in the reaction (entry 6). Given the high reactivity of phloroglucinol (14) towards electrophilic substitution processes, attempts were made to promote this reaction with the inexpensive but less reactive reagent, boric acid (entries 7-9). The reactions with boric acid afforded the reaction products 142 and 143 albeit in lower yields. Of note, boric acid was only sparingly soluble in benzene. Therefore, the similar yields observed in all of these latter reactions could reflect that the concentration of boric acid in solution was the same.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Yield of (142) (%)</th>
<th>Yield of (143) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>B(OH)₃ (1 equiv), propionic acid (72) (cat.), PhH, reflux, 22 h</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>B(OH)₃ (3 equiv), propionic acid (72) (cat.), PhH, reflux, 22 h</td>
<td>44</td>
<td>27</td>
</tr>
</tbody>
</table>
In the example where three equivalents of phenylboronic acid were employed, presumably three electrophilic aromatic substitution reactions occurred prior to the cyclization reactions (entry 4). The formation of significant quantities of the disubstituted product 143, when less than three equivalents of phenylboronic acid were used, was attributed to the formation and subsequent cyclization reactions of intermediate 144 (Figure 3.4.1.1). The disubstituted product 143 cannot undergo a subsequent phenylboronic acid-directed electrophilic aromatic substitution reaction as the ortho-positions, with respect to the remaining phenol moiety, are blocked.\textsuperscript{66,67,68} Of note, the unsymmetric disubstituted intermediate 145 or the product formed from subsequent cyclization reactions could react further with senecialdehyde (134) to afford the tris-adduct 142.

![Molecular structures of the borate ester intermediates (144) and (145).](image)

Figure 3.4.1.1 Molecular structures of the borate ester intermediates (144) and (145).

The two reaction products 142 and 143 were readily separated by flash chromatography. The \textsuperscript{1}H NMR spectrum of the tris-2H-chromene 142 was very simple and showed two doublets corresponding to the chromene double bond protons at \(\delta 5.43\) and \(6.59\) ppm and a single sharp singlet corresponding to the methyl groups at \(\delta 1.40\) ppm. The appearance of one set of signals for the three chromene moieties indicated that the two possible conformers of the reaction product 142, neither of which would be expected to show a single signal for the methyl groups, were rapidly interconverting on
the NMR timescale (Figure 3.4.1.2). Consequently, a time averaged spectra was observed. The $^{13}$C NMR spectrum contained peaks at δ 103.4 and 149.1 ppm that corresponded to the two chemically inequivalent carbon atoms of the aromatic core. In addition, four signals for the chromene moieties were also observed. The mass spectrum (CI) showed large peaks at 325 and 324 amu that corresponded to the protonated molecular ion and the molecular ion, respectively.

![Figure 3.4.1.2 Rapid interconversion of the two possible conformers (146) and (147) of the tris-$2H$-chromene (142).](image)

The bis-$2H$-chromene product 143 showed an additional peak in the $^1$H NMR spectrum at δ 6.46 ppm that corresponded to the remaining aromatic proton and two additional peaks at δ 99.0 and 147.6 ppm in the $^{13}$C NMR spectrum for this less symmetrical aromatic core. This material also showed a molecular ion peak at 258 amu in the mass spectrum (CI).

### 3.5 Hydrogenation of tris-$2H$-Chromenes

On having determined reaction conditions to prepare a model tris-$2H$-chromene in good yield, the conversion of this compound to the corresponding tris-$2H$-chromane was investigated.
3.5.1 Synthesis of the tris-Chromane (148)

The model compound 142 was subjected to standard hydrogenation reaction conditions (H₂, Pd/C) (Scheme 3.5.1.1). This reaction afforded the analytically pure known tris-chromane 148 in excellent yield (96%).

Scheme 3.5.1.1 Hydrogenation of the tris-2H-Chromene (148)

Reagents and conditions: (a) H₂, Pd/C, MeOH, room temperature, 20 h, 96%.

3.6 Phenylboronic Acid-Mediated Reactions of a Series of α,β-Unsaturated Carbonyl Compounds

In order to examine the scope of the above reaction, it was decided to use a series of either commercially or readily available α,β-unsaturated carbonyl compounds as substrates for the phenylboronic acid-mediated reaction of phloroglucinol (14).

3.6.1 Synthesis of α,β-Unsaturated Aldehydes

An efficient three step procedure for the conversion of ketones to the corresponding dialkylideneacetaldehydes has been reported in the literature by Snowden and co-workers. Following this procedure, a Horner-Wadsworth-Emmons reaction between cyclopentanone (149) and trimethyl phosphonoacetate afforded the α,β-unsaturated ester 150 (Scheme 3.6.1.1). This material was then reduced to the corresponding allylic alcohol 151 with lithium aluminum hydride and this product was...
subsequently oxidized with manganese dioxide to afford the known aldehyde 152. This procedure afforded the aldehyde 152 in 72% overall yield.

Scheme 3.6.1.1 Synthesis of Cyclopentylideneacetaldehyde (152) from Cyclopentanone (149)

Reagents and conditions: (a) Trimethyl phosphonoacetate, NaH, THF, room temperature, 1 h then cyclopentanone (149), reflux, 24 h; (b) LiAlH₄, Et₂O, 0 °C to room temperature, 1 h; (c) MnO₂, CH₂Cl₂, room temperature, 6 h, 72% (over three steps).

This three step procedure was then used to prepare the known aldehyde 156 in 81% overall yield from cyclohexanone (153) (Scheme 3.6.1.2).

Scheme 3.6.1.2 Synthesis of Cyclohexylideneacetaldehyde (156) from Cyclohexanone (153)

Reagents and conditions: (a) Trimethyl phosphonoacetate, NaH, THF, room temperature, 1 h then cyclohexanone (153), reflux, 24 h; (b) LiAlH₄, Et₂O, 0 °C to room temperature, 1 h; (c) MnO₂, CH₂Cl₂, room temperature, 3 h, 81% (over three steps).

In a similar manner, the adamantane derivative 160 was prepared in 83% overall yield from the commercially available ketone 157 (Scheme 3.6.1.3).
Scheme 3.6.1.3 Synthesis of Adamantylideneacetaldehyde (160) from 2-Adamantanone (157)

Reagents and conditions: (a) Trimethyl phosphonoacetate, NaH, THF, room temperature, 1 h then 2-adamantanone (157), reflux, 24 h, 95%; (b) LiAlH₄, Et₂O, 0 °C to room temperature, 1 h, 97%; (c) MnO₂, CH₂Cl₂, room temperature, 3 h, 90%.

The aldehyde 165, which would lead to the synthesis of a carbocyclic analogue of xyloketal A (1), was prepared in 54% overall yield from methylcyclohexene (161) on a modification of the four step procedure (ozonolysis followed be reductive work-up, acetal hydrolysis, enamine formation and aldol cyclization) of Hudlicky’s variant of the method of White and co-workers (Scheme 3.6.1.4).⁸¹,⁸² An aqueous solution of sulfuric acid (3% v/v) was substituted for the aqueous solution of perchloric acid (3% v/v) that was used by Hudlicky and co-workers in the acetal hydrolysis step. This had no detrimental effect on the yield.
Scheme 3.6.1.4 Synthesis of 2-Methylcyclopentene-1-carboxaldehyde (165) from 1-Methylcyclohexene (161)

Reagents and conditions: (a) O₃, MeOH, CH₂Cl₂, −78 °C then Me₂S, p-TsOH·H₂O, −78 °C to room temperature, 3 h, 75%; (b) H₂SO₄, THF, 0 °C, 2 h, room temperature 1.5 h; (c) piperidine, Et₂O, 0 °C, 3 h; (d) AcOH, Et₂O, reflux, 6 h, 67% (over three steps).

The dihydrofuran aldehyde 169, which would afford a demethyl analogue of xyloketal A (1), was prepared in three steps (Scheme 3.6.1.5). Commercially available α-acetyl-γ-butyrolactone (166) was converted to the ester 167 on saponification and subsequent dehydration under acidic conditions. Direct conversion of this material to the corresponding aldehyde 169 with diisobutyl aluminum hydride in dichloromethane at −78 °C afforded a mixture of the unstable alcohol 168 and the unreacted ester 167. Therefore, a two step reaction sequence (reduction to the alcohol 168 with lithium aluminum hydride followed by oxidation to the aldehyde 169 with managanese dioxide) as described above was employed. Of note, although the reduction of the ester 167 proceeded in very high yield (>95%), the resultant alcohol 168 was found to be unstable. Therefore, the overall low yield of this process was attributed to the decomposition of this alcohol during oxidation to the corresponding aldehyde 169. In an attempt to increase the overall yield of this process, the use of alternative oxidants was investigated. However, the use of pyridinium dichromate, pyridinium dichromate and potassium
carbonate, Swern conditions\textsuperscript{84} or sulfur trioxide pyridine complex\textsuperscript{85} did not afford the desired reaction product 169.

**Scheme 3.6.1.5 Synthesis of 4-Formyl-5-methyl-2,3-dihydropyran (169) from α-Acetyl-γ-butyrolactone (166)**

![Chemical Structure]

Reagents and conditions: (a) HCl (g), MeOH, reflux, 4 days then distill; (b) H\textsubscript{2}SO\textsubscript{4} (cat.), distill, 19\% (over two steps); (c) LiAlH\textsubscript{4}, Et\textsubscript{2}O, 0 °C to room temperature, 20 min; (d) MnO\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, room temperature, 54 h, 41\% (over two steps).

### 3.6.2 Synthesis of tris-2H- and 4H-Chromenes

The optimized reaction conditions described above were employed systematically as part of an investigation into the scope of tris-2H-chromenes that can be prepared by this process. Accordingly, phloroglucinol (14) (1 equiv) was treated with a series of α,β-unsaturated carbonyl compounds 170 (4 equiv), phenylboronic acid (3 equiv) and propionic acid (72) (cat.) in benzene at reflux with azeotropic removal of water to afford the chromene derivatives 171 (Scheme 3.6.2.1). The results of these studies are presented below (Table 3.6.2.1).
Scheme 3.6.2.1  Phenylboronic Acid-Mediated Reactions of Phloroglucinol (14) and $\alpha,\beta$-Unsaturated Carbonyl Compounds (170)

Reagents and conditions: (a) Carbonyl compound 170 (4 equiv), PhB(OH)$_2$ (3 equiv), propionic acid (72) (cat.), PhH, reflux.

Table 3.6.2.1  Results Corresponding to Scheme 3.6.2.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>$\alpha,\beta$-Unsaturated Carbonyl Compound</th>
<th>Chromene Derivative</th>
<th>Reaction Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>152</td>
<td>172</td>
<td>4 h</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>156</td>
<td>173</td>
<td>135 min</td>
<td>52</td>
</tr>
<tr>
<td>Entry</td>
<td>$\alpha,\beta$-Unsaturated Carbonyl Compound</td>
<td>Chromone Derivative</td>
<td>Reaction Time</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------</td>
<td>---------------------</td>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td>3</td>
<td><img src="image160" alt="Image of compound 160" /></td>
<td><img src="image174" alt="Image of compound 174" /></td>
<td>22 h</td>
<td>79</td>
</tr>
</tbody>
</table>

(150 min) Isolated as the corresponding chromane following hydrogenation ($H_2$, Pd/C, MeOH, 18 h).

<table>
<thead>
<tr>
<th>Entry</th>
<th>$\alpha,\beta$-Unsaturated Carbonyl Compound</th>
<th>Chromone Derivative</th>
<th>Reaction Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image175" alt="Image of compound 175" /></td>
<td><img src="image176" alt="Image of compound 176" /></td>
<td>150 min</td>
<td>28*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>$\alpha,\beta$-Unsaturated Carbonyl Compound</th>
<th>Chromone Derivative</th>
<th>Reaction Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td><img src="image177" alt="Image of compound 177" /></td>
<td><img src="image178" alt="Image of compound 178" /></td>
<td>4 h</td>
<td>61</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>$\alpha,\beta$-Unsaturated Carbonyl Compound</th>
<th>Chromone Derivative</th>
<th>Reaction Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><img src="image179" alt="Image of compound 179" /></td>
<td><img src="image180" alt="Image of compound 180" /></td>
<td>150 min</td>
<td>0</td>
</tr>
</tbody>
</table>

(*) Isolated as the corresponding chromane following hydrogenation ($H_2$, Pd/C, MeOH, 18 h).
<table>
<thead>
<tr>
<th>Entry</th>
<th>$\alpha,\beta$-Unsaturated Carbonyl Compound</th>
<th>Chromene Derivative</th>
<th>Reaction Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td><img src="181.png" alt="181" /></td>
<td><img src="182.png" alt="182" /></td>
<td>24 h</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td><img src="183.png" alt="183" /></td>
<td><img src="184.png" alt="184" /></td>
<td>22 h</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td><img src="185.png" alt="185" /></td>
<td><img src="186.png" alt="186" /></td>
<td>105 min</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td><img src="187.png" alt="187" /></td>
<td><img src="188.png" alt="188" /></td>
<td>19 h</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td><img src="189.png" alt="189" /></td>
<td><img src="190.png" alt="190" /></td>
<td>4 h</td>
<td>0</td>
</tr>
<tr>
<td>Entry</td>
<td>$\alpha,\beta$-Unsaturated Carbonyl Compound</td>
<td>Chromene Derivative</td>
<td>Reaction Time</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>12</td>
<td><img src="image1" alt="191" /></td>
<td><img src="image2" alt="192" /></td>
<td>4 h</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td><img src="image3" alt="165" /></td>
<td><img src="image4" alt="193" /></td>
<td>6 h</td>
<td>31*</td>
</tr>
<tr>
<td>14</td>
<td><img src="image5" alt="169" /></td>
<td><img src="image6" alt="194" /></td>
<td>105 min</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td><img src="image7" alt="195" /></td>
<td><img src="image8" alt="196" /></td>
<td>6 h</td>
<td>14</td>
</tr>
</tbody>
</table>

Further examples of achiral 2,2-disubstituted chromenes were prepared when the reaction was performed with the three symmetric alkylidene aldehydes 152, 156 and 160

(*) Isolated as an inseparable mixture of two diastereoisomers (dr = 20:1, $\alpha,\beta$).
(entries 1-3). In addition, when β-phenylcinnamaldehyde (175) was subjected to the reaction conditions, an unstable 2,2-disubstituted chromene derivative 176 was formed (entry 4). This instability was attributed to a 6π electrocyclic ring-opening reaction that afforded the corresponding ortho-quinone methides which could undergo further reactions. Therefore, the chromene 176 was immediately reduced (H₂, Pd/C, MeOH, 18 h) to afford the corresponding tris-chromane which proved to be a stable compound. It was appreciated that if an unsymmetric 2,2-disubstituted α,β-unsaturated aldehyde was employed in this reaction two possible diastereoisomers could be produced. To investigate the stereoselectivity of this process, the commercially available unsymmetric α,β-unsaturated aldehyde 177 (citral, E:Z = ~2:1) was employed as a reaction substrate (entry 5). The triple condensation product (±)-178 was isolated in good yield. Interestingly, this chromene derivative was formed (based on inspection of the ¹H NMR spectrum of the crude reaction mixture) and isolated as a single C₃-symmetric diastereoisomer. Furthermore, unpublished research by the Wilson research group has shown that very high stereoselectivities can be obtained in this process with a variety of unsymmetric aldehydes.

A series of corresponding mono-substituted aldehydes were also used as reaction substrates. However, this led to the formation of a complex mixture of reaction products and the desired chromene products could not be isolated (entries 6-9). Similarly, the use of the aldehyde 187 did not lead to the formation of the 3-substituted chromene 188 nor were the 2,3-disubstituted chromene derivatives 190 and 192 prepared from the reactions of the aldehydes 189 and 191, respectively (entries 10-12). Thus, it appears that the α,β-unsaturated aldehyde substrate needs to be 2,2-disubstituted.
Two attempts to prepare 2,2,3-trisubstituted tris-2H-chromenes were also performed. When the aldehyde 165 was employed as a reaction substrate, the desired carbocyclic xyloketal A analogue 193 was obtained in moderate yield (entry 13). In this case, the product was obtained as a mixture of diastereoisomers and the unsymmetric diastereoisomer was the major product (dr = 20:1, αβ). Unfortunately, the use of the dihydrofuran aldehyde 169 did not afford the desired demethyl xyloketal A analogue 194 possibly due to the instability of the aldehyde (entry 14).

Finally, the reaction of methyl vinyl ketone (195) with phloroglucinol (14) was performed in an attempt to prepare a 4-substituted tris-2H-chromene (entry 15). Unexpectedly, this resulted in the isolation of the isomeric 4H-chromene derivative 196, in relatively low yield, from a complex mixture of reaction products. In this instance, the reaction substrate employed was an α,β-unsaturated ketone and presumably the isolated product was formed by a different reaction mechanism (Figure 3.6.2.1). Initial 1,4-addition of phloroglucinol (14) to methyl vinyl ketone (195) would afford the ketone 198. The formation of a hemiacetal of the ketone and one of the phenol moieties followed by a subsequent dehydration reaction would afford the 4H-chromene 200. Repetition of this process would afford the observed reaction product 196.
Figure 3.6.2.1 Proposed reaction mechanism for the formation of the \textit{tris-4H}-
chromene derivative (196).

Of final note, the corresponding double condensation reaction products were not
isolated from any of the above condensation reactions.

3.6.3 \textbf{X-Ray Crystal Structure Analysis of the \textit{tris-2H}-Chromene (174)}

The chromene derivative 174 proved to be a highly crystalline solid. Crystals that
were suitable for X-ray crystallography were obtained on recrystallization from
chloroform upon slow evaporation of the solvent (Figure 3.6.3.1). The unit cell was
found to contain two molecules with the adamantyl group of one molecule positioned
over the aromatic core of an adjacent molecule. It was noted that the chromene 174
adopts an unsymmetric conformation in the solid state in which one of the adamantyl moieties is positioned below the plane of the aromatic core.

Figure 3.6.3.1 Unit cell of the X-ray crystal structure of the tris-2H-chromene (174) (the thermal ellipsoids are drawn at a 50\% probability level and the hydrogen atoms have been omitted for clarity).

3.7 Synthesis of (4R)-2,4-Dimethyl-3-formyl-4,5-dihydrofuran

The synthesis of 2,4-dimethyl-3-formyl-4,5-dihydrofuran (127) for the preparation of xyloketal A (1) was subsequently investigated.
3.7.1 Attempted Synthesis of the Aldehyde (127) from an Acyclic Precursor

In principle, the synthetic process used for the preparation of 2-methyl-3-formyl-4,5-dihydrofuran (169) (See: Section 3.6.1) could be adapted to prepare the aldehyde 127 (Figure 3.7.1.1). In the original synthesis, the lactone 166 was converted to the methyl ester 167 on reaction with hydrochloric acid in methanol. This process would have afforded the intermediate 202 which in turn cyclized to afford the hemi-acetal 204. Subsequent elimination of water (or methanol) then would have afforded the reaction product 167. It was anticipated that the synthesis of the lactone 201 or the ester 203 would provide the corresponding substrate for the synthesis of the fully substituted dihydrofuran 206. The ester group of this compound could then be reduced to afford the desired aldehyde 127.

![Reaction scheme](image)

**Figure 3.7.1.1** Intermediates involved in the formation of the dihydrofuran ester (169).

Towards this objective, propylene oxide (209) was allowed to react with p-methoxybenzyl alcohol (208) in the presence of sodium hydroxide to afford the
secondary alcohol \((\pm)-210\) (Scheme 3.7.1.1).\textsuperscript{86,87} This alcohol was then converted to the corresponding bromide \((\pm)-131\) in good yield on reaction with triphenylphosphine, carbon tetrabromide and 2,6-lutidine.\textsuperscript{88} A variety of methods were subsequently investigated to achieve reaction of this bromide with the anion of methyl acetoacetate (Table 3.7.1.1). The desired product of this reaction would be a protected version of the required alcohol 203.

**Scheme 3.7.1.1 Attempted Synthesis of the Ester (211) from Propylene Oxide (209)**

\[
\begin{align*}
\text{MeO} & \quad \begin{array}{c}
\text{O} \\
\text{OH}
\end{array} \\
\text{208} & \quad \begin{array}{c}
\text{O} \\
\text{209}
\end{array} \\
\text{MeO} & \quad \begin{array}{c}
\text{O} \\
\text{OH}
\end{array} \\
(\pm)-210 & \quad \begin{array}{c}
\text{Me}
\end{array}
\end{align*}
\]

Reagents and conditions: (a) NaOH, 65 °C, 24 h, 53%; (b) Ph\textsubscript{3}P, CBr\textsubscript{4}, 2,6-lutidine, THF, 56 h, 68%; (c) see below: Table 3.7.1.1.

**Table 3.7.1.1 Reaction Conditions Corresponding to Scheme 3.7.1.1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methyl acetoacetate (1.25 equiv), Na (1.25 equiv), MeOH, reflux, 5.5 h</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Methyl acetoacetate (5 equiv), Na (5 equiv), MeOH, reflux, 45 h</td>
<td>0</td>
</tr>
</tbody>
</table>
3.7.2 Elaboration of 2-Methyl-4,5-dihydrofuran (114)

Stetter and Lorenz have reported the direct conversion of 2,3-dihydrofuran to ethyl 2,3-dihydrofuran-4-carboxylate on reaction with ethyl chloroformate. A similar reaction with 2,4-dimethyl-4,5-dihydrofuran (61) would directly afford the corresponding ester which could be converted to the aldehyde 127 (See: Section 3.6.1). To test if this process would be feasible, commercially available 2-methyl-4,5-dihydrofuran (114) was
allowed to react with ethyl chloroformate (Scheme 3.7.2.1). However, this reaction afforded a complex mixture of reaction products from which the desired reaction product 212 could not be isolated.

Scheme 3.7.2.1 Attempted Direct Synthesis of the Dihydrofuran Ester (212)

Reagents and conditions: (a) ClCO$_2$Et (1.5 equiv), Et$_2$O, room temperature, 4 h.

An alternative reaction sequence to elaborate the model dihydrofuran 114 was then investigated. According to the work of Hojo and co-workers, this dihydrofuran was allowed to react with trichloroacetyl chloride and pyridine in dichloromethane at room temperature (Scheme 3.7.2.2). This afforded the trichloroketone 213 and the regioisomeric ketone 214 in very high overall yield (98%). Presumably, the latter compound was formed via isomerization of the endo-cyclic dihydrofuran 114 to the corresponding exo-cyclic isomer under the reaction conditions. Of note, the trichloroketone 214 was isolated as a single geometrical isomer. The geometry of the double bond was not determined but it is reasonable to assume, based on electronic and steric considerations, that it is trans. To suppress the formation of the regioisomeric trichloroketone 214, the reaction was repeated at $-20^\circ$C. This reaction afforded the above products in a similar overall yield (95%) but with better regioselectivity (6:1) in favour of the desired reaction product 213.
Scheme 3.7.2.2  Synthesis of the Trichloroketones (213) and (214) from 2-Methyl-4,5-dihydrofuran (114)

![Scheme 3.7.2.2](image)

Reagents and conditions: (a) Cl₃CCOCl, py, CH₂Cl₂, room temperature, 15 min, 62% (213), 36% (214) or Cl₃CCOCl, py, CH₂Cl₂, −20 °C to room temperature, 21 h, 79% (213), 16% (214).

The trichloroketone 213 was then converted to the corresponding carboxylic acid 215 on reaction with aqueous sodium hydroxide (Scheme 3.7.2.3). However, the reduction of this material to the alcohol 168 with lithium aluminum hydride proved to be difficult and only trace amounts of this alcohol were obtained. This unexpected result was attributed to the formation of a relatively stable aluminum carboxylate salt which subsequently precipitated from solution and did not undergo reduction.

Scheme 3.7.2.3  Attempted Synthesis of the Alcohol (168) from the Carboxylic Acid (215)

![Scheme 3.7.2.3](image)

Reagents and conditions: (a) NaOH, H₂O, room temperature, 2 h, 48%; (b) LiAlH₄, Et₂O, 0 °C to room temperature, 20 min.

Therefore, according to the work of de Buyck and co-workers, the ketone 213 was allowed to react with sodium bicarbonate in methanol to afford the previously prepared methyl ester 167 in high yield (Scheme 3.7.2.4). Thus, a method for the elaboration of a dihydrofuran had been successfully identified and developed.
Scheme 3.7.2.4  Synthesis of the Ester (167) from the Trichloroketone (213)

\[
\begin{align*}
\text{Cl}_3C^\text{\text{\footnotesize\textbf{Me}}} & \quad \text{MeO} \\
213 & \quad \rightarrow \quad 167
\end{align*}
\]

Reagents and conditions: (a) MeOH, NaHCO₃, reflux, 45 min, 96%.

3.7.3 Synthesis of Chiral Nonracemic \((4R)-2,4\text{-dimethyl-3-formyl-4,5-dihydrofuran} [(4R)-127]\)

A suitable procedure for the proposed synthesis of \((4R)-2,4\text{-dimethyl-3-formyl-4,5-dihydrofuran} [(4R)-127]\) from \((4R)-2,4\text{-dimethyl-4,5-dihydrofuran} [(4R)-61]\) was outlined in the previous section. However, at this stage, it was decided to prepare the dihydrofuran \((4R)-61\) in an asymmetric fashion rather than using the relatively inefficient resolution procedure that was discussed previously (See: Section 2.8).

Towards these ends, the chiral oxazolidinone \((4S)-219\) was prepared in three steps based on literature procedures (Scheme 3.7.3.1). Accordingly, commercially available \((S)-\text{phenylalanine} [(S)-216]\) was reduced with lithium aluminum hydride to afford the alcohol \((S)-217\). This material was then allowed to react with diethyl carbonate to afford the Evans auxiliary \((4S)-218\). Attachment of the appropriate substrate was accomplished by reaction of the corresponding lithium amide of the auxiliary \((4S)-218\), prepared by deprotonation with \(n\)-butyl lithium, with propionyl chloride. Of note, the oxazolidinone \((4S)-219\), and all of the intermediates en route to its preparation, had spectral data identical to those reported in the literature. In addition, the optical rotations of these compounds were in agreement, in both sense and magnitude, to the reported literature values. This confirmed the optical purity of these materials.
Scheme 3.7.3.1 Synthesis of the Chiral Oxazolidinone [(4S)-219] According to Literature Procedures

Reagents and conditions: (a) LiAlH₄, THF, reflux, 5 h, room temperature, 15 h, 63%; (b) (EtO)₂CO, K₂CO₃, 135 °C, 1.5 h, 79%; (c) n-BuLi, THF, −78 °C, 25 min then EtCOCl, −78 °C, 35 min, room temperature, 45 min, 94%.

The conversion of the oxazolidinone (4S)-219 to the acetylenic compound (+)-220 was subsequently investigated (Scheme 3.7.3.2). Accordingly, the corresponding enolate of the oxazolidinone (4S)-219 was generated and allowed to react with a propargyl halide under a variety of conditions. The results of these investigations are presented below (Table 3.7.3.1).

Scheme 3.7.3.2 Optimization of the Diastereoselective Alkylation Reaction of the Oxazolidinone [(4S)-219] with a Propargyl Halide

Reagents and conditions: (a) See below: Table 3.7.3.1.

Table 3.7.3.1 Reaction Conditions Corresponding to Scheme 3.7.3.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA (1.1 equiv), THF, −78 °C, 30 min then propargyl bromide (71) (1.5 equiv), −78 °C, 30 min, 0 °C, 2 h</td>
<td>49</td>
<td>7:1</td>
</tr>
<tr>
<td>Entry</td>
<td>Reagents and Conditions</td>
<td>Yield (%)</td>
<td>dr</td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>2</td>
<td>LDA (1.1 equiv), THF, −78 ºC, 30 min then propargyl bromide (71) (1.5 equiv), −78 to −20ºC, 20 h</td>
<td>55</td>
<td>6:1</td>
</tr>
<tr>
<td>3</td>
<td>LDA (1.1 equiv), THF, −78 ºC, 30 min then propargyl bromide (71) (4 equiv), −78 to 0ºC, 23 h</td>
<td>53</td>
<td>6:1</td>
</tr>
<tr>
<td>4</td>
<td>LDA (1.5 equiv), THF, −78 ºC, 30 min then propargyl bromide (71) (4 equiv), −78 to 0ºC, 23 h</td>
<td>55</td>
<td>6:1</td>
</tr>
<tr>
<td>5</td>
<td>TiCl₄, CH₂Cl₂, 0 ºC, 5 min then N,N,N-diisopropylethylamine (1.05 equiv), 0 ºC, 5 min then propargyl chloride (2 equiv), 0 ºC to room temperature, 18 h</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>TiCl₄, CH₂Cl₂, 0 ºC, 5 min then N,N,N-diisopropylethylamine (1.05 equiv), 0 ºC, 5 min then propargyl bromide (71) (2 equiv), 0 ºC to room temperature, 18 h</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>LDA (1.5 equiv), THF, −78 ºC, 30 min then HMPA −78 ºC, 30 min then propargyl bromide (71) (4 equiv), −78 ºC, 20 h</td>
<td>77</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

In the first instance, the oxazolidinone (4S)-219 was deprotonated with lithium N,N-diisopropylamide (1.1 equiv) in tetrahydrofuran at −78 ºC and the resultant enolate was subsequently allowed to react with propargyl bromide (71) (1.5 equiv) at 0 ºC for 2 h (entry 1). This afforded the desired alkylated product (+)-220 in moderate yield (49%) as a mixture of two diastereoisomers (dr = 7:1). It was attempted to improve the yield and diastereoselectivity of this process by repeating the above reaction and allowing it to warm slowly from −78 to −20 ºC over 20 h (entry 2). In this case, the alkylated oxazolidinone (+)-220 was isolated in 55% yield as a mixture of diastereoisomers (dr = 6:1). The use of an increased amount of lithium N,N-diisopropylamide (1.5 equiv) and
propargyl bromide (71) (4 equiv) did not significantly increase the yield and diastereoselectivity of the reaction (entries 3 and 4). The use of titanium tetrachloride and N,N,N-diisopropylethylamine to deprotonate the oxazolidinone (4S)-219, employing propargyl chloride or propargyl bromide (71) as alkylating agents, did not afford the desired compound (+)-220 (entries 5 and 6). However, it was subsequently found that use of hexamethylphosphoramide as an additive in this reaction led to an increase in both the yield and diastereoselectivity of the process (entry 7). Accordingly, deprotonation of the oxazolidinone (4S)-219 in a mixture of tetrahydrofuran and hexamethylphosphoramide (~10%) with lithium N,N-diisopropylamide (1.5 equiv), and on subsequent reaction with propargyl bromide (71) (4 equiv) at -78°C for 20 h, led to the formation of the desired reaction product (+)-220 in good yield (77%) and as a single diastereoisomer.

The diastereoselectivity of the above reactions were determined by inspection of the crude ¹H NMR spectrum (400 MHz, CDCl₃). A doublet that corresponded to the methyl group of the major diastereoisomer (+)-220 was observed at δ 1.29 ppm in addition to a signal corresponding to the minor diastereoisomer at δ 1.43 ppm. The absolute stereochemistry of the newly formed stereogenic centre was tentatively assigned as R based on consideration of the model proposed by Evans (Figure 3.7.3.1). In this model, the electrophile approaches the less sterically hindered α-face of the predominate (Z)-lithium enolate (4S)-221 to afford the major reaction product (2'R,4S)-222.
Figure 3.7.3.1 Evans’ stereochemical rationale for the alkylation reactions of the oxazolidinone [(4S)-219].

The increased diastereoselectivity observed when hexamethylphosphoramide was added to the reaction mixture can be attributed to the increased reactivity of the enolate at low temperature. The alkylation reaction of the enolate of the oxazolidinone (4S)-219 occurred between −40 and −50 °C in tetrahydrofuran. In contrast, this reaction proceeded smoothly at −78 °C in tetrahydrofuran in the presence of hexamethylphosphoramide.

The alkylated oxazolidinone was then reduced with lithium aluminum hydride to afford the chiral nonracemic alcohol (2R)-69 (Scheme 3.7.3.3). Comparison of the sign of the optical rotation of this material with the material prepared by the resolution procedure, confirmed the absolute stereochemistry of the product. Furthermore, the high optical purity of this material was confirmed by comparison of the magnitude of the optical rotation to the material made by the resolution procedure. This acetylenic alcohol was subsequently converted to the endo-cyclic dihydrofuran (4R)-68 on heating with a sub-stoichiometric amount of sodium amide followed by thermal-isomerization of the corresponding exo-cyclic dihydrofuran (4R)-61 as previously discussed (See: Section 2.8.3).
Scheme 3.7.3.3 Synthesis of the Dihydrofuran [(4R)-61] from the Oxazolidinone [(+)-220]

Reagents and conditions: (a) LiAlH₄, THF, 0 °C, 45 min, 73%; (b) NaNH₂, reflux, 4 h; (c) reflux, 18 h, 74% (over two steps).

In order to prepare the methyl ester (4R)-206, the dihydrofuran (4R)-61 was allowed to react with trichloroacetyl chloride and pyridine at room temperature (Scheme 3.7.3.4). As observed in the model studies, this afforded a readily separable mixture of the desired trichloroketone (4R)-223 (45%) and a substantial quantity of the regioisomeric trichloroketone (4R)-224 (46%). The ketone (4R)-224 was isolated as a single geometric isomer which was again assumed to be the trans isomer. To suppress the formation of the undesired trichloroketone (4R)-224, the reaction was repeated at −78 °C. This resulted in the isolation of the desired trichloroketone (4R)-223 in very good yield (93%). Of note, the dihydrofuran (4R)-61 used in this reaction was contaminated with approximately 7% of the exo-cyclic double bond isomer (4R)-68. Therefore, it is reasonable to conclude that at −78 °C the migration of the double bond from the endo-cyclic to the exo-cyclic position does not occur. Subsequent methanolysis of the trichloroketone (4R)-223, as previously described, afforded the methyl ester (4R)-206 in excellent yield.
Scheme 3.7.3.4  Synthesis of the Methyl Ester [(4R)-206] from the Dihydrofuran [(4R)-61]

\[
\begin{align*}
(4R)-61 & \xrightarrow{(a)} (4R)-223 + (4R)-224 & \xrightarrow{(b)} (4R)-206 \\
& & \\
\text{Reagents and conditions: (a) } \text{Cl}_3\text{COCl, py, CH}_2\text{Cl}_2, \text{room temperature, 30 min, 45\% [(4R)-223],} \\
& & \text{46\% [(4R)-224] or Cl}_3\text{COCl, py, CH}_2\text{Cl}_2, -78 \degree \text{C to room temperature, 21 h, 93\% [(4R)-223];} \\
& & \text{(b) trichloroketone (4R)-223, NaHCO}_3, \text{MeOH, reflux, 1 h, 98\%.}
\end{align*}
\]

It should also be noted that it was not possible to obtain satisfactory elemental analysis or a high-resolution mass spectrum of the ketone (4R)-223 or the methyl ester (4R)-206. The ketone (4R)-223 readily underwent hydrolysis upon storage. Attempted purification of the methyl ester (4R)-206 by flash column chromatography resulted in partial loss of material and did not significantly increase the purity of the reaction product. Therefore, a sample of the trichloroketone (4R)-223 was hydrolyzed to afford the carboxylic acid (4R)-225 which proved to be stable and satisfactory elemental analysis was obtained (Scheme 3.7.3.5).

Scheme 3.7.3.5  Synthesis of the Chiral Nonracemic Carboxylic Acid [(4R)-225] from the Trichloroketone [(4R)-223]

\[
\begin{align*}
(4R)-223 & \xrightarrow{(a)} (4R)-225 \\
& & \\
\text{Reagents and conditions: (a) LiOH-H}_2\text{O, THF, H}_2\text{O, room temperature, 15 min, 88\%.}
\end{align*}
\]

The ester (4R)-206 was converted to the aldehyde (4R)-127 according to the procedure developed in the model studies (See: Section 3.6.1). Accordingly, the ester
(4R)-206 was reduced to the alcohol (4R)-226 with lithium aluminum hydride (Scheme 3.7.3.6). This material was then immediately converted to the desired aldehyde (4R)-127 upon reaction with manganese dioxide in dichloromethane.

**Scheme 3.7.3.6  Conversion of the Ester [(4R)-206] into the Aldehyde [(4R)-127]**

Reagents and conditions: (a) LiAlH₄, Et₂O, 0 °C to room temperature, 20 min; (b) MnO₂, CH₂Cl₂, room temperature, 46 h, 34% (over two steps).

Of note, the aldehyde (4R)-127 obtained by this method was not particularly pure (~70%). Further purification by distillation or flash chromatography did not significantly increase the purity of the product. Derivatization of a portion of this material to the corresponding N,N-diphenyl hydrazone (which was expected to be a crystalline solid and aid in purification) was unsuccessful.¹⁰⁷ The sense of the optical rotation of the aldehyde (4R)-127 was in agreement with that reported for the natural product.⁶⁹ Thus, the absolute stereochemistry of this natural product can be tentatively assigned as being R. Of note, this is the first total synthesis of this relatively simple natural product.

### 3.8 Attempted Synthesis of Xyloketal A: Phenylboronic Acid-Mediated Reaction

The application of the phenylboronic acid-mediated reaction to prepare (−)-xyloketal A [(−)-1] from chiral nonracemic (4R)-2,4-dimethyl-3-formyl-4,5-dihydrofuran [(4R)-127] was subsequently investigated.
3.8.1 Attempted Synthesis of the tris-2H-Chromene (126)

The chiral nonracemic aldehyde (4R)-127 (4 equiv) was allowed to react with phloroglucinol (14) (1 equiv), phenylboronic acid (3 equiv) and propionic acid (72) (cat.) in benzene as previously described (Scheme 3.8.1.1). After 7 h, analysis by thin-layer chromatography indicated that the limiting reagent, phloroglucinol (14), had been consumed and a complex mixture of reaction products had formed. Inspection of the $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the crude reaction mixture showed only trace amounts (<5%) of signals corresponding to 2H-chromene double bonds at $\delta \sim 6.6$ ppm. Unfortunately, none of the desired reaction product 126 could be isolated from the reaction mixture.

Scheme 3.8.1.1 Attempted Synthesis of the tris-2H-Chromene (126)

Reagents and conditions: (a) PhB(OH)$_2$ (3 equiv), propionic acid (72) (cat.), PhH, reflux, 7 h.

3.9 Conclusions

An unprecedented phenylboronic acid-mediated triple condensation reaction of phloroglucinol (14) with a series of $\alpha,\beta$-unsaturated aldehydes was developed. This experimentally simple reaction afforded novel $C_3$-symmetric chromene derivatives that represent structural analogues of the natural product xyloketal A (1). tris-2H-Chromenes with a 2,2-disubstitution or a 2,2,3-trisubstitution pattern were found to be stable. The
synthesis of derivatives that had alternative substitution patterns, proved to be less successful. In addition, the reduction of tris-2H-chromenes to the corresponding tris-chromanes proved to be an exceedingly facile process.

An asymmetric total synthesis of the chiral nonracemic dihydrofuran \((4R)-61\) employing a chiral auxiliary to control the asymmetry of an alkylation reaction as a key step was developed in order to avoid the resolution procedure that was described previously. The elaboration of this material to the corresponding aldehyde \((4R)-127\), which constitutes the synthesis of this natural product, was also demonstrated. However, the subsequent reaction of this compound with phloroglucinol \((14)\) did not provide the tris-2H-chromene derivative \(126\) required for the preparation of xyloketal A \((1)\).
CHAPTER FOUR

Synthesis of the Xyloketal: Electrophilic Aromatic Substitution Reactions

4.1 Introduction

In this chapter the development and application of electrophilic aromatic substitution reactions for the synthesis of the xyloketal natural products is described. An initial approach employing an appropriately substituted hydroxymethyl furan as the electrophile did not afford the natural products. However, the use of an appropriately substituted hydroxymethyl dihydrofuran in an exceedingly facile and diastereoselective boron trifluoride diethyl etherate-promoted electrophilic aromatic substitution reaction that was coupled to a bicyclic acetal formation reaction proved to be very successful. The optimization of this synthetic route led to syntheses of demethyl analogues of xyloketal A (1), B (2), C (3), D (4), E (5) and G (7). In addition, the asymmetric total syntheses of xyloketal A (1), B (2), D (4), E (5), F (6) and G (7) were completed.

4.2 Retrosynthetic Analysis: Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethylfuran

An initial approach, featuring a proposed electrophilic aromatic substitution reaction of phloroglucinol (14), for the total synthesis of xyloketal A (1) was based on the total synthesis of alboatrin (48) that was reported by Ichihara and co-workers.¹¹

¹¹ The results discussed in this chapter have been reported in part, see: (a) Synthesis of Xyloketal A, B, C, D, and G Analogues. Pettigrew, J. D.; Wilson, P. D. J. Org. Chem. 2006, 71, 1620; (b) Total Synthesis of (−)-Xyloketal A. Pettigrew, J. D.; Wilson, P. D. Org. Lett. 2006, 8, 1427.
4.2.1 Retrosynthetic Analysis of Xyloketal A (1)

Xyloketal A (1) could be formed by three bicyclic acetal formation reactions of the intermediate 227 upon hydrogenation of the less substituted double bonds of compound 228 (Scheme 4.2.1.1). This compound could, in principle, be prepared by a triple electrophilic aromatic substitution of phloroglucinol (14) with an electrophile generated on ionization of the alcohol 50. Of note, the yield of an analogous electrophilic aromatic substitution reaction used in the synthesis of alboatrin (48) was poor (~10%).

It is reasonable to assume that the low yield of this reaction was a result of multiple alkylation reactions of the electron rich phenolic precursor. In this system, however, exhaustive C-alkylation was required. The synthesis of the alcohol 50 has been reported from the ester 49 which in turn was prepared from ethyl acetoacetate (229) and propargyl bromide (71).
4.3 Attempted Synthesis of Xyloketal A: Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethylfuran (50)

4.3.1 Synthesis of 2,4-Dimethyl-3-hydroxymethylfuran (50)

The ester 49 was prepared in two steps from propargyl bromide (71) based on literature procedures (Scheme 4.3.1.1). Accordingly, the bromide 71 was treated with dimethylsulfide to afford dimethylprop-2-ynylsulfonyl bromide. This material
was then allowed to react with ethyl acetoacetate (229) in the presence of sodium ethoxide. This two step reaction sequence afforded the ester 49 in good overall yield (87%).

**Scheme 4.3.1.1 Synthesis of the 2,4-Dimethyl-3-hydroxymethylfuran (50) from Propargyl Bromide (71)**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reagents and conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me₂S, MeCN, room temperature, 24 h, 89%</td>
</tr>
<tr>
<td>b</td>
<td>ethyl acetoacetate (229), Na, EtOH, reflux, 10 h, 98%</td>
</tr>
<tr>
<td>c</td>
<td>LiAlH₄, Et₂O, 0 °C to room temperature, 20 min, 92%</td>
</tr>
</tbody>
</table>

The initial attempt to reduce the ester 49 to the corresponding alcohol 50 according to a literature procedure with lithium aluminum hydride (1 equiv) proceeded in poor yield (13%). In addition, a considerable amount of polymeric material was produced which suggested that the alcohol 50 was not a stable compound in the presence of the Lewis acidic aluminum salts. In subsequent reactions, it was found that increasing the number of equivalents of lithium aluminum hydride (4 equiv) and performing the reaction for a short period of time cleanly afforded the desired reaction product 50 in high yield (up to 92%).

### 4.3.2 Attempted Electrophilic Aromatic Substitution Reactions of Phloroglucinol (14) with 2,4-Dimethyl-3-hydroxymethylfuran (50)

A variety of reagents were screened in order to effect the triple electrophilic aromatic substitution reaction between phloroglucinol (14) and the hydroxymethyl furan 50 (Scheme 4.1.1.1). Accordingly, phloroglucinol (14) was allowed to react with the alcohol 50 (6 equiv, 2 equiv per phenolic site) in the presence of anhydrous magnesium
sulfate and a catalyst (20 mol%) in ether. The results of this extensive study are presented below (Table 4.3.2.1).

Scheme 4.3.2.1 Attempted Synthesis of the Hexasubstituted Benzene Derivative (50) from Phloroglucinol (228)

Reagents and conditions: (a) 20 mol% Catalyst (see below: Table 4.3.2.1), MgSO₄, Et₂O, room temperature, 15 min to 24 h.

Table 4.3.2.1 Catalysts Corresponding to Scheme 4.3.2.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃·Et₂O</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>AlCl₃</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>TiCl₄</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>BBr₃</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>MgCl₂</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>Alumina</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>ZnCl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>Ti(i-PrO)₄</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>9</td>
<td>HBF₄</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>10</td>
<td>SiCl₄</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>11</td>
<td>InCl₃</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>12</td>
<td>Et₂AlCl</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>13</td>
<td>CuCl₂</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>Entry</td>
<td>Catalyst</td>
<td>Result</td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>14</td>
<td>SnCl₂</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>15</td>
<td>FeCl₃</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>16</td>
<td>CdCl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>17</td>
<td>MgBr₂·Et₂O</td>
<td>No reaction</td>
</tr>
<tr>
<td>18</td>
<td>NiCl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>19</td>
<td>MnCl₂·4H₂O</td>
<td>No reaction</td>
</tr>
<tr>
<td>20</td>
<td>CoCl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>21</td>
<td>NbF₅</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>22</td>
<td>NbCl₅</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>23</td>
<td>NbBr₅</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>24</td>
<td>4Å Molecular sieves</td>
<td>No reaction</td>
</tr>
<tr>
<td>25</td>
<td>Silica gel</td>
<td>No reaction</td>
</tr>
<tr>
<td>26</td>
<td>CrCl₃·3THF</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>27</td>
<td>GdCl₃·6H₂O</td>
<td>No reaction</td>
</tr>
<tr>
<td>28</td>
<td>Sc(OTf)₃</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>29</td>
<td>HBF₄</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>30</td>
<td>HCl</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>31</td>
<td>TsOH·H₂O</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>32</td>
<td>PPTS</td>
<td>No reaction</td>
</tr>
<tr>
<td>34</td>
<td>AcOH</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

The initial reaction conditions attempted were based on literature reports of the use of boron trifluoride diethyl etherate to promote electrophilic aromatic substitution reactions between allylic alcohols and phenols (entry 1). However, these conditions afforded a complex mixture of reaction products from which the desired product 228 could not be isolated. In an attempt to identify suitable reaction conditions,
alternative solvents (THF, dioxane, DMF, DMSO), reaction temperatures (0 °C, –78 °C) and catalyst loadings (0.5%, 2%, 10%, 50%) were investigated. However, similar complex mixtures of reaction products were obtained.

Further attempts to effect the desired reaction were focused on the identification of a suitable catalyst. An extensive series of Lewis acids (entries 2-28)\textsuperscript{112,113,114,115} and Brønsted acids (entries 29-33)\textsuperscript{116,117} were employed as potential promoters of the reaction. However, these reagents either caused the formation of complex mixtures of products or no reaction was observed.

Regardless of the reaction conditions employed, inspection of the crude \textsuperscript{1}H NMR spectra of the complex mixtures that were formed in some of these reactions indicated that the C-5 position of the furan had taken part in the reaction. This suggested that the electron rich furan 50 acting as a competing site for electrophilic aromatic substitution under these reaction conditions. Thus, it was decided to temporarily block this site.

### 4.3.3 Attempted Derivatization of 2,4-Dimethyl-3-hydroxymethylfuran (50)

It was initially decided to employ a silicon protecting group, either a \textit{t}-butyldimethylsilyl (TBS) or a trimethylsilyl (TMS), as the blocking group on the furan. It was anticipated that the dianion generated from the furan 50, upon reaction with two or more equivalents of a strong base, could be allowed to react with a trialkylsilyl chloride to afford the desired C-silylated product 232 or 233 (Scheme 4.3.3.1).\textsuperscript{118} Towards these objectives, the furan 50 (1 equiv) was metalated with either \textit{n}-butyl lithium or \textit{t}-butyl lithium (≥ 2.2 equiv) and then a trialkylsilyl chloride. The results of these studies are presented below (Table 4.3.3.1).
Scheme 4.3.3.1 Attempted Direct C-Silylation of the Furan (50)

Reagents and conditions: (a) See below: Table 4.3.3.1.

Table 4.3.3.1 Reagents and Conditions Corresponding to Scheme 4.3.3.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Yield of O-Silylated Product (230) or (231) (%)</th>
<th>Yield of C-Silylated Product (232) or (233) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi (2.2 equiv), THF, 0 °C, 2 h then TBSCl (1 equiv), 0 °C to room temperature, 18 h</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>n-BuLi (2.5 equiv), THF, room temperature, 2 h then TBSCl (1 equiv), room temperature, 18 h</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi (2.5 equiv), THF, reflux, 2 h then TBSCI (1 equiv), room temperature, 20 h</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>n-BuLi (5 equiv), THF, 0 °C, 2 h then TMSCl (8 equiv), 0 °C to room temperature, 22 h then acidic work-up</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>t-BuLi (2.2 equiv), THF, -78 °C to room temperature, 4 h then TBSCI (1 equiv), room temperature, 18 h</td>
<td>68</td>
<td>0</td>
</tr>
</tbody>
</table>

In the initial instance, a related procedure described by Keay and co-workers was employed. Thus, the furan 50 was deprotonated with n-butyl lithium (2.2 equiv) at 0 °C
for 2 h and then allowed to warm to room temperature in the presence of \( t \)-butyldimethylsilyl chloride (1 equiv) over 18 h (entry 1).\(^{118} \) The product of this reaction was not the desired C-silylated 232 product but was the corresponding O-silylated compound 230 which was isolated in 52% yield. This suggested that the dianion had not formed. In an effort to generate the dianion of this furan, the reaction was repeated at room temperature and at reflux (entries 2 and 3). However, in these instances, the O-silylated product 230 was again isolated (57 and 35% yield, respectively). An attempt to form the trimethylsilyl derivative 233 according to the work reported by Schultz and co-workers (involving exhaustive silylation and selective cleavage of the resultant trimethylsiloxy moiety) did not afford the desired reaction product (entry 4).\(^{119} \) This again suggested that the dianion had not formed. The final attempt to form the dianion of the furan 50 involved the use of \( t \)-butyl lithium. However, this also resulted in isolation of the O-silylated product 230 in modest yield (68%) (entry 5).

Since the dianion of the furan 50 could not be generated, the furan 50 was converted to the O-silylated product 230 under standard conditions\(^{120} \) (Scheme 4.3.3.2). This material was then treated with \( n \)-butyl lithium followed by \( t \)-butyldimethylsilyl chloride. However, the desired product 234 was not formed and the starting material 230 was recovered.
Scheme 4.3.3.2  Attempted Two Step Synthesis of the C-Silylated Furan (234)

\[
\begin{array}{c}
\text{OH} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\hline
50
\end{array} \xrightarrow{a} \begin{array}{c}
\text{OTBS} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\hline
230
\end{array} \xrightarrow{b} \begin{array}{c}
\text{OTBS} \\
\text{TBS} \\
\text{Me} \\
\text{Me} \\
\hline
234
\end{array}
\]

Reagents and conditions: (a) TBSCI, imidazole, DMF, room temperature, 46 h, 99%; (b) n-BuLi, THF, 0 °C, 1 h or 5 h then TBSCI (1.2 equiv), 0 °C to room temperature, 20 h.

Given the unsuccessful installation of a silicon protecting group, it was decided to use a halogen as a blocking group as aromatic halides can be reduced under hydrogenation reaction conditions.\textsuperscript{121} Thus, the alcohol 50 and the corresponding ester 49 were allowed to react with bromine and \(N\)-bromosuccinimide (Scheme 4.3.3.3).\textsuperscript{122,123}

Unfortunately, complex mixtures of products were formed in the reactions.

Scheme 4.3.3.3  Attempted Synthesis of the Brominated Furans (235) and (236)

\[
\begin{array}{c}
\text{R} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\hline
50 \ (R = \text{CH}_2\text{OH})
\end{array} \xrightarrow{a} \begin{array}{c}
\text{R} \\
\text{Me} \\
\text{Me} \\
\text{Br} \\
\hline
235 \ (R = \text{CH}_2\text{OH})
\end{array}
\]

\[
\begin{array}{c}
\text{R} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\hline
49 \ (R = \text{CO}_2\text{Et})
\end{array} \xrightarrow{a} \begin{array}{c}
\text{R} \\
\text{Me} \\
\text{Me} \\
\text{Br} \\
\hline
236 \ (R = \text{CO}_2\text{Et})
\end{array}
\]

Reagents and conditions: (a) \(\text{Br}_2\), CHCl\(_3\), room temperature, 20 h \textit{or} NBS, AcOH, room temperature, 2 h.

The ester 49 was subsequently converted to the corresponding carboxylic acid 237 (Scheme 4.3.3.4).\textsuperscript{124} This material was then successfully converted to the bromofuran 238 upon treatment with bromine in acetic acid.\textsuperscript{125}
Scheme 4.3.3.4  Attempted Synthesis of the Furan (235) from the Carboxylic Acid (237)

Reagents and conditions: (a) NaOH, H₂O, reflux, 3.5 h, 97%; (b) Br₂, AcOH, 0 °C to room temperature, 20 min, 54%; (c) LiAlH₄, Et₂O, 0 °C to room temperature, 15 min or BH₃·THF, THF, room temperature, 20 h or BH₃·DMS, THF, room temperature, 24 h.

Unfortunately, subsequent reduction of this carboxylic acid 238 with lithium aluminum hydride, borane tetrahydrofuran complex or borane dimethyl sulfide complex resulted in the formation of complex mixtures of products from which the desired alcohol 235 could not be isolated.

4.4 Retrosynthetic Analysis of the Xyloketal: Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran

As a result of the above findings, an alternative approach to xyloketal A (1) and the other members of the xyloketal family of natural products was envisioned.

4.4.1  Retrosynthetic Analysis of Xyloketal A (1)

It was realized that a similar triple electrophilic aromatic substitution between phloroglucinol (14) and the reactive intermediate 239 would afford adducts that would then rearrange, under the reaction conditions, to afford the thermodynamically stable cis-fused bicyclic acetal moieties of xyloketal A (1) (Scheme 4.4.1.1). The reactive intermediate 239 in this reaction could, in principle, be generated by ionization of the alcohol 226 that had been prepared from the dihydrofuran 61 (See: Section 3.7.3). It was
expected that the stereochemistry of the acetal formation reactions would be controlled, based on steric arguments, by the C-4 methyl substituent of the parent alcohol 226.

Scheme 4.4.1.1 Retrosynthetic Analysis of Xyloketal A (1): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)

4.4.2 Retrosynthetic Analysis of Xyloketal B (2) and C (3)

In a similar manner, xyloketal B (2) and C (3) could be prepared on execution of a selective double electrophilic aromatic substitution reaction of phloroglucinol (14) (R = H) or with the previously prepared substituted triphenol 112 (R = CO₂Me) (Scheme 4.4.2.1). A subsequent decarboxylative saponification reaction of the latter products, would then afford the target compounds 2 and 3.
Scheme 4.4.2.1 Retrosynthetic Analysis of Xyloketal B (2) and C (3): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)

4.4.3 Retrosynthetic Analysis of Xyloketal D (4) and G (7)

Xyloketal D (4) and, in principle, the regioisomer, xyloketal G (7), could also be prepared from the corresponding aromatic phenol, 2,4-dihydroxyacetophenone (11), and the alcohol 226 (Scheme 4.4.3.1). In previous examples of electrophilic substitution reactions of the acetophenone 11, only the regioisomeric products that corresponded to xyloketal D (4) were isolated (See: Section 2.4.1). However, Krohn and co-workers have reported that both xyloketal D (4) and G (7) can be prepared by a conjugate addition reaction of 2,4-dihydroxyacetophenone (11) and an enone.\(^\text{9,10}\)
4.4.3.1 Retrosynthetic Analysis of Xyloketal D (4) and G (7): Electrophilic Aromatic Substitution Reactions with 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)

![Reaction Scheme 4.4.3.1](image)

4.4.4 Retrosynthetic Analysis of Xyloketal E (5) from Xyloketal B (2) and 2,4-Dimethyl-4,5-dihydrofuran (61)

It was anticipated that xyloketal B (2) could be subsequently converted to xyloketal E (5) on reaction with 2,4-dimethyl-4,5-dihydrofuran (61) under acidic conditions (Scheme 4.4.4.1).\textsuperscript{128,129,130,131}

![Reaction Scheme 4.4.4.1](image)
4.4.5 Retrosynthetic Analysis of Xyloketal F (6) from Xyloketal B (2)

Xyloketal F (6)* could be made by reacting two equivalents of xyloketal B (2) with one equivalent of formaldehyde (Scheme 4.4.6.1).\textsuperscript{132,133,134}

Scheme 4.4.5.1 Retrosynthetic Analysis of Xyloketal F (6) from Xyloketal B (2)

4.4.6 Retrosynthetic Analysis of Xyloketal F (6) from 2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)

An alternative direct synthesis of xyloketal F (6) was also conceived. This would involve the execution of a quadruple electrophilic aromatic substitution reaction of the known hexaphenol 240 and the alcohol 226 (Scheme 4.4.6.1).\textsuperscript{135,136}

\(*\) Professor Lin informed us of the molecular structure of xyloketal F (6) before it was reported in the chemical literature. As such, our initial investigation towards the synthesis of xyloketal F (6) from xyloketal B (2) was independently proposed and executed prior to his semi-synthesis of this natural product by a similar set of conditions (See: Ref. 3).
It was possible that this direct method would produce a mixture of three regioisomers including xyloketal F (6). However, it was expected that the other regioisomers, which have structures that are related to the unstable natural product xyloketal C (3), could be isomerized to give exclusively xyloketal F (6).

4.5 Model Studies: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran

4.5.1 Synthesis of (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-epi-11,11',11"-Trinorxyloketal A [(±)-19]

In order to optimize the reaction conditions required for the total synthesis of the xyloketals, model studies were performed (Scheme 4.5.1.1). Accordingly, phloroglucinol (14) (1 equiv) was allowed to react with the alcohol 168 (6 equiv, 2 equiv per phenolic site) and a catalyst in the presence of anhydrous magnesium sulfate in ether. The results of these studies are presented below (Table 4.5.1.1).
Scheme 4.5.1.1 Synthesis of (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-epi-11,11',11''-Trinorxyloketal A [(±)-19]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)

Reagents and condition: (a) See below: Table 4.5.1.1.

Table 4.5.1.1 Reagents and Conditions Corresponding to Scheme 4.5.1.1*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Yield of [(±)-18] and [(±)-19] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃·Et₂O (2.7 equiv), MgSO₄, Et₂O, 0 °C, 15 min</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>BF₃·Et₂O (2.7 equiv), MgSO₄, Et₂O, −78 °C, 15 min</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>BF₃·Et₂O (1.3 equiv), MgSO₄, Et₂O, 0 °C, 15 min</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>BF₃·Et₂O (1.0 equiv), MgSO₄, Et₂O, 0 °C, 15 min</td>
<td>93</td>
</tr>
</tbody>
</table>

(*) All reactions afforded an inseparable mixture of the xyloketal A analogues (±)-18 and (±)-19 (dr = 2:7).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Yield of [(±)-18] and [(±)-19] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>BF$_3$·Et$_2$O (0.5 equiv), MgSO$_4$, Et$_2$O, 0 °C, 15 min</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>BF$_3$·Et$_2$O (0.25 equiv), MgSO$_4$, Et$_2$O, 0 °C, 15 min</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>HF (cat), MgSO$_4$, Et$_2$O, 0 °C, 15 min</td>
<td>77</td>
</tr>
<tr>
<td>8</td>
<td>p-TsOH·H$_2$O (1.0 equiv), MgSO$_4$, Et$_2$O, 0 °C, 15 min</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>Acetic acid (2.7 equiv), MgSO$_4$, Et$_2$O, 0 °C to room temperature, 72 h</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>MgSO$_4$, Et$_2$O, 0 °C to room temperature, 4 h</td>
<td>0</td>
</tr>
</tbody>
</table>

The initial reaction conditions selected for the triple electrophilic aromatic substitution reaction of phloroglucinol (14) with the alcohol 168 were based on a report by Razdan and co-workers on the synthesis of $\Delta^1$-tetrahydrocannabinol (THC) from p-mentha-2,8-dienol and olivetol.$^{110}$ A two-fold excess of the unstable alcohol 168 was employed per phenolic reaction site and the initial reaction involved stirring a mixture of the phloroglucinol (14) (1 equiv) and the alcohol 168 (6 equiv) in ether at 0 °C in the presence of anhydrous magnesium sulfate and boron trifluoride diethyl etherate (2.7 equiv) (entry 1). The xyloketal A analogues (±)-18 and (±)-19 were formed rapidly and the limiting starting material, phloroglucinol (14), was consumed in less than 15 min. These compounds were isolated, in pure form and in reasonable yield (36%), as an inseparable mixture of two diastereoisomers (dr = 2:7). The corresponding mono- and bis-adducts were not isolated from this reaction. In addition, no evidence for the
formation of these intermediates was observed by thin layer chromatography during the course of the reaction. It would be expected that these more substituted and electron-rich intermediates would react at a faster rate than the limiting starting material, phloroglucinol (14).

In order to improve the efficiency of this new reaction, the reaction was repeated at a lower temperature (−78 °C) (entry 2). However, the desired products were isolated in essentially the same yield and diastereoselectivity after 15 min. In this instance, as in the initial experiment, phloroglucinol (14) was completely consumed and highly polar or polymeric reaction by-products were also formed. Thus, it was decided to systematically decrease the number of equivalents of boron trifluoride diethyl etherate and explore the use of different acid promoters. On employing boron trifluoride diethyl etherate (1.3 equiv), at 0 °C, a dramatic improvement in the isolated yield of the xyloketal A analogues (±)-18 and (±)-19 (69%) was recorded (entry 3). Moreover, the use of one equivalent of boron trifluoride diethyl etherate (−0.3 equiv per phenolic reaction site) led to an exceptionally clean synthetic transformation and the isolation of the xyloketal A analogues (±)-18 and (±)-19 in excellent yield (93%) (entry 4). The isolated yield of these reaction products is truly remarkable in view of the fact that this transformation involves, minimally, six individual reactions. Decreasing the number of equivalents of boron trifluoride diethyl etherate further resulted in the isolation of the desired reaction products (±)-18 and (±)-19 in lower yields (entries 5 and 6). It was found that concentrated hydrofluoric acid (which could have been involved in the reactions described above) and p-toluenesulfonic acid also promoted this reaction in good yield (entries 7 and 8). None of the desired products were formed on performing the reactions.
at room temperature in the absence of an acid promoter or in the presence of acetic acid (entries 9 and 10, respectively).

Of note, the desired $C_3$-symmetric diastereoisomer ($\pm$)-18, which has the same relative stereochemistry as xyloketal A (1), was the minor component in all of these reactions. This was indicated by the $^1$H and $^{13}$C NMR spectra which were dominated by the complex series of signals of the major unsymmetric diastereoisomer ($\pm$)-19 (See: Section 2.5.2). However, it was anticipated that the stereochemistry of the C-4 methyl substituent of the chiral nonracemic alcohol (4R)-226 would correctly direct the diastereoselectivity of the triple condensation reactions, in an absolute sense, on attempting the asymmetric total synthesis of (−)-xyloketal A [(−)-1].

4.5.2 Synthesis of (±)-11,11'-Dinorxyloketal B [(±)-16] and (±)-2,6-epi-11,11'-Dinorxyloketal B [(±)-17]

It was considered that analogues of xyloketal B (2) and C (3) could be prepared by decreasing the number of the equivalents of the alcohol 168 employed in the above optimized reaction with phloroglucinol (14). However, given the relative instability of this alcohol and the observed propensity for the preferential formation of the tris-adducts ($\pm$)-18 and ($\pm$)-19 [as well as to prepare analogues of xyloketal B (2) and C (3) in acceptable yield], it was decided to employ the ester 112 as a reaction substrate (Scheme 4.5.2.1). Accordingly, the ester 112 (1 equiv) was allowed to react with the alcohol 168 (4 equiv, 2 equiv per phenolic site) and boron trifluoride diethyl etherate in the presence of anhydrous magnesium sulfate in ether. The results of these studies are presented below (Table 4.5.2.1).
Scheme 4.5.2.1  Synthesis of the Methyl Ester Xyloketal B and C Analogues ([±)-115], ([±)-242], ([±)-116] and (243): Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)

Reagents and conditions: (a) See below: Table 4.5.2.1.

Table 4.5.2.1  Reagents and Conditions Corresponding to Scheme 4.5.2.1

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃·Et₂O (1.0 equiv), MgSO₄, Et₂O, 0 °C to room temperature, 4 h</td>
<td>6</td>
<td>50</td>
<td>6:6:1:1</td>
</tr>
<tr>
<td>2</td>
<td>BF₃·Et₂O (1.0 equiv), MgSO₄, Et₂O, 0 °C to room temperature, 36 h</td>
<td>0</td>
<td>51</td>
<td>10:10:1:1</td>
</tr>
</tbody>
</table>
In the first instance, the methyl ester 112 (1 equiv) was allowed to react with the alcohol 168 (4 equiv), boron trifluoride diethyl etherate (1 equiv) and magnesium sulfate in ether and the resultant mixture was allowed to warm from 0 °C to room temperature over 4 h (entry 1). On subsequent purification of the crude reaction mixture by flash chromatography, the mono-adduct (+)-241 (6%) and a mixture (6:6:1:1) of the substituted xyloketal B analogues (+)-115 and (+)-242 as well as the substituted xyloketal C analogues (+)-116 and 243 (50% combined yield) were isolated. On performing the above reaction for an extended period of time (36 h), a mixture (10:10:1:1) of the substituted xyloketal B analogues (+)-115 and (+)-242 as well as the substituted xyloketal C analogues (+)-116 and 243 was isolated (51% combined yield) (entry 2). In this instance, none of the mono-adduct (+)-241 was present in the crude reaction mixture and less of the unstable xyloketal C analogues (+)-116 and 243 were formed. The xyloketal C analogues (+)-116 and 243 presumably were converted to the xyloketal B analogues (+)-115 and (+)-242 during the extended reaction time. The substituted xyloketal B analogues (+)-115 and (+)-242 could also be separated from the substituted xyloketal C analogues (+)-116 and 243, in this instance, following further purification by flash chromatography. It was subsequently found that the above products could be prepared in

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>BF₃·Et₂O (0.7 equiv), MgSO₄, Et₂O, 0 °C to room temperature, 46 h</td>
<td>0</td>
<td>58</td>
<td>10:10:1:1</td>
</tr>
</tbody>
</table>

In the table above, the yield and product ratio of the reaction products are shown.
improved yield (58%) on decreasing the amount of boron trifluoride diethyl etherate employed in the process (0.7 equiv, ~0.3 equiv per phenolic reaction site) and on performing the reaction for 46 h (entry 3). Of note, the slower rate and lower isolated yields of these latter reactions as compared to that used to prepare the xyloketal A analogues (±)-18 and (±)-19 reflects the decreased reactivity of the less electron-rich phenol 112 as compared to phloroglucinol (14).

The $^1$H and $^{13}$C NMR spectra of the mono-adduct (±)-241 were very similar to the xyloketal D analogue (±)-12 (See: Section 2.5.1). Similar methods were used to determine the structure of the product. In particular, nOe contacts were observed between Me-1a and H-4a and between Me-1a and H-9 (Figure 4.5.2.1). Therefore, the relative stereochemistry and the regiochemistry of the product (±)-241 were firmly established.

![Figure 4.5.2.1 Observed nOe contacts for the methyl ester [(±)-241].](image)

The regiochemistry of major reaction products (±)-115 and (±)-242 (dr = 1:1) was assigned based upon inspection of the $^1$H and $^{13}$C NMR spectra. The $^1$H NMR spectrum contained two sharp down field signals ($\delta$ 11.99 and 12.00 ppm) indicating that the phenol moieties were hydrogen-bonded to an adjacent carbonyl group. In addition, both the $^1$H and $^{13}$C NMR spectra contained groups of complex multiplets which could only result from the xyloketal B analogues (±)-115 and (±)-242 (the corresponding
xyloketal C analogues (±)-116 and 243 contain a C₂-axis and a mirror plane, respectively, and would be expected to be less complex. Observed nOe contacts confirmed the expected relative stereochemistry of the major reaction products (±)-115 and (±)-242 as being cis.

The synthesis of the demethyl xyloketal B analogues (±)-16 and (±)-17 was subsequently accomplished on execution of a facile and high yielding decarboxylative saponification reaction (96%) of a mixture (dr = 1:1) of the substituted xyloketal B analogues (±)-115 and (±)-242 (Scheme 4.5.2.2). 47,48,49

Scheme 4.5.2.2  Synthesis of the bis-Demethyl Xyloketal B Analogues [(±)-16] and [(±)-17]

Reagents and conditions: (a) NaOH, MeOH, H₂O, reflux, 6 h, 96%, dr = 1:1 [(±)-115:(±)-242].

Extensive analysis of 2D NMR spectral data confirmed the structure of the demethyl analogues of xyloketal B (2). The ¹H NMR spectrum contained signals at δ 6.16 and 6.17 ppm corresponding to the aromatic protons. In addition, signals at δ 5.88 and 5.92 ppm corresponding to nonhydrogen-bonded phenols were also observed.
Observed nOe contacts between the aromatic protons and the phenols as well as between the bridgehead methyl groups and the angular protons confirmed that the regio- and stereochemistry of the reaction products \((\pm)-16\) and \((\pm)-17\) had not been altered during the course of the final synthetic transformation (Figure 4.5.2.2).

![Observed nOe contacts for the bis-demethyl xyloketal B analogues [(±)-16 and (±)-17].](image)

**Figure 4.5.2.2** Observed nOe contacts for the bis-demethyl xyloketal B analogues [(±)-16 and (±)-17].

### 4.5.3 Attempted Synthesis of the Xyloketal C Analogues [(±)-247] and (248)

Given that the reaction of neither phloroglucinol (14) nor the methyl ester 112 had provided practical syntheses of the demethyl analogues of xyloketal C (3), the use of an alternative phenol which could only undergo the desired bis-alkylation process with the appropriate regiochemistry was investigated. Thus, the phenol 244 was prepared according to literature procedures from the methyl ester 112 in moderate yield (39%) (Scheme 4.5.3.1).\(^{137,138,139,140}\) Extending the reaction time from 23 h to 84 h did not result in an improvement in the yield of this reaction. In addition, a substantial amount of methyl 2,4-dimethoxy-6-hydroxy-benzoate (245) (28%) was also isolated in this instance.\(^{141}\)
Scheme 4.5.3.1  Synthesis of the Methyl Esters (244) and (245)

Reagents and conditions: (a) MeI (1 equiv), K₂CO₃, acetone, room temperature, 23 h, 39% (244) or MeI (1 equiv), K₂CO₃, acetone, room temperature, 84 h, 39% (244), 28% (245).

The methoxy methyl ester 244 (1 equiv) was then allowed to react with the alcohol 168 (4 equiv), boron trifluoride diethyl etherate (1 equiv) and magnesium sulfate in ether and the resultant mixture was allowed to warm from 0 °C to room temperature over 50 h (Scheme 4.5.3.2). On subsequent purification of the crude reaction mixture by flash chromatography, only the mono-adduct (±)-246 was obtained. When this material was re-subjected to the reaction conditions [alcohol 168 (5 equiv), BF₃·Et₂O (1 equiv), MgSO₄, Et₂O] no further reaction occurred to afford the desired xyloketal C analogues (±)-247 and 248 and the unreacted starting material (±)-246 was recovered. This result could be attributed to the increased steric crowding, as compared to the ester 112, of the aromatic position by the methoxy substituent.
Scheme 4.5.3.2 Attempted Synthesis of the Methoxy Xyloketal C Analogues [(±)-247] and (248): Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)

Reagents and conditions: (a) Alcohol 168 (4 equiv), BF$_3$·Et$_2$O (1 equiv), MgSO$_4$, Et$_2$O, 0 °C to room temperature, 50 h, 47%; (b) alcohol 168 (5 equiv), BF$_3$·Et$_2$O (1 equiv), MgSO$_4$, Et$_2$O, 0 °C to room temperature, 23 h.

As a result of this finding, no further investigations directed towards the total synthesis of the unstable natural product, xyloketal C (3), were made.

4.5.4 Synthesis of (±)-11-Norxyloketal D [(±)-12] and (±)-10-Norxyloketal G [(±)-13]

In a similar way to that described above, the synthesis of the xyloketal D and G analogues (±)-12 and (±)-13 was undertaken from the commercially available phenol, 2,4-dihydroxyacetophenone (11) (Scheme 4.5.4.1).

Scheme 4.5.4.1 Synthesis of (±)-11-Norxyloketal D [(±)-12] and (±)-10-Norxyloketal G [(±)-13]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)

Reagents and conditions: (a) Alcohol 168 (2 equiv), BF$_3$·Et$_2$O (0.3 equiv), MgSO$_4$, Et$_2$O, 0 °C to room temperature, 46 h, 13% (41% brsm) [(±)-12], 11% (34% brsm) [(±)-13] or alcohol 169 (4 equiv), BF$_3$·Et$_2$O (0.3 equiv), MgSO$_4$, Et$_2$O, 0 °C to room temperature, 46 h, 17% (54% brsm) [(±)-12], 10% (32% brsm) [(±)-13].
Accordingly, the acetophenone 11 (1 equiv) was allowed to react with the alcohol 168 (2 equiv), boron trifluoride diethyl etherate (0.3 equiv) and magnesium sulfate in ether. On allowing the reaction mixture to warm from 0 °C to room temperature over 46 h and following purification of the crude reaction mixture by flash chromatography, the xyloketal D analogue (±)-12 [13% (41% brsm)] and the xyloketal G analogue (±)-13 [11% (34% brsm)] were isolated. A substantial quantity of the unreacted acetophenone 11 (62%) was also recovered. In view of the relative low reactivity of this less electron-rich phenol, the above reaction was repeated with an increased amount of the alcohol 168 (4 equiv). In this instance, the xyloketal D analogue (±)-12 [17% (54% brsm)] and the xyloketal G analogue (±)-13 [10% (32% brsm)] were isolated in slightly improved overall yield. In addition, the unreacted acetophenone 11 (68%) was also recovered from the crude reaction mixture.

The spectral data for the xyloketal D analogue (±)-12 was identical to the material prepared by the Diels-Alder approach (See: Section 2.5.1). The structure of the xyloketal G analogue (±)-13 was assigned on the basis of extensive analysis of 2D NMR data. The regiochemistry of this process was determined on inspection of the ¹H NMR spectrum. A sharp downfield signal at δ 12.37 ppm corresponding to the phenolic proton was observed. This suggested that the phenol group was adjacent to the carbonyl substituent. In addition, the signals for the aromatic protons (δ 6.36 and 7.44 ppm) were singlets. As shown below, nOe contacts were observed that confirmed both the relative stereochemistry and the regiochemistry of this product (Figure 4.5.4.1).
In view of the results of the above non-regioselective and low yielding reaction, it was decided to investigate the use of alternative phenols for the preparation of these natural product analogues. In the first instance, 4-ethyl resorcinol (249) (1 equiv) was allowed to react with the alcohol 168 (1.25 equiv), boron trifluoride diethyl etherate (1 equiv) and magnesium sulfate in ether (Scheme 4.5.4.2). This afforded the bicyclic acetal (±)-250 in good yield (61%) as a single regioisomer corresponding to the structure of xyloketal G (7). The potential regioisomeric products (±)-251 and (±)-252 were not isolated.
Scheme 4.5.4.2 Synthesis of (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-7-ethyl-8-hydroxy-1a-methyl-furo[6]chromane [(±)-250]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)

Reagents and conditions: (a) Alcohol 168 (1.25 equiv), BF$_3$•Et$_2$O (1 equiv), MgSO$_4$, Et$_2$O, 0 °C to room temperature, 23 h, 61% [(±)-250].

The assignment of the regiochemistry of the above product was determined on inspection of the $^1$H NMR spectrum. Of the three possible regioisomers, (±)-250, (±)-251 and (±)-252, only the isomer (±)-250 would be expected to have the observed pair of singlets for the aromatic protons.

Three attempts were made to oxidize this compound in a regioselective fashion (Scheme 4.5.4.3). In the first instance, the bicyclic acetal (±)-250 was allowed to react with potassium permanganate in acetonitrile at room temperature for 21 h according to a procedure reported by Lee (entry 1). However, this resulted in rapid decomposition of the starting material. Subsequently, the bicyclic acetal (±)-250 was reacted with potassium permanganate and copper (II) sulfate pentahydrate in dichloromethane at reflux for 5 h according to the procedure of Noureldin and co-workers (entry 2). These reaction conditions have been reported to be milder than initial reaction conditions that were employed. In addition, this reagent system has been shown to oxidize a benzylic ethyl moiety and not to oxidize a chromane. However, these reaction conditions resulted
in a complex mixture of compounds from which the desired product (±)-13 could not be isolated. The final attempt to oxidize this compound with selenium dioxide in ethanol at reflux for 7 days according to the method reported by Fisher was made (entry 3). However, these relatively mild reaction conditions resulted in slow decomposition of the starting material (±)-250.

Scheme 4.5.4.3 Attempted Synthesis of the Xyloketal G Analogue [(±)-13] from the Bicyclic Acetal [(±)-250]

Reagents and conditions: (a) See below: Table 4.5.4.1.

Table 4.5.4.1 Reagents and Conditions Corresponding to Scheme 4.5.4.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KMnO₄, MeCN, room temperature, 21 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>KMnO₄, CuSO₄·5H₂O, CH₂Cl₂, reflux, 5 h</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>SeO₂, EtOH, reflux, 7 days</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

The use of commercially available resorcinol (253) as a phenolic precursor was subsequently investigated. Accordingly, resorcinol (253) (1 equiv) was allowed to react with the alcohol 168 (1.25 equiv), boron trifluoride diethyl etherate (1 equiv) and magnesium sulfate in ether (Scheme 4.5.4.4). This afforded the bicyclic acetal (±)-254,
in moderate yield (35%) and as the single regioisomer that corresponded to the molecular structure of xyloketals G (7). The potential regioisomeric products (±)-255 and (±)-256 were not isolated.

**Scheme 4.5.4.4** Synthesis of (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-8-hydroxy-1a-methyl-furo[b]chromane [(±)-254]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)

Reagents and conditions: (a) Alcohol 168 (1.25 equiv), BF₃·Et₂O (1 equiv), MgSO₄, Et₂O, 0 °C to room temperature, 22 h, 35% [((±)-254].

Similar to the previous bicyclic acetal (±)-250, the regiochemistry of the reaction product (±)-254 was determined by analysis of the coupling constants in the aromatic region of the ¯H NMR spectrum.

Two attempts were made to install a methyl ketone into this adduct (Scheme 4.5.4.5). In the first instance, this material was allowed to react with acetyl chloride and aluminum trichloride at 180 °C for 30 min according to a procedure described by Kim and co-workers.¹⁴⁵ This resulted in rapid and complete decomposition of the starting material (±)-254. In the second instance, the bicyclic acetal (±)-254 was reacted with acetic anhydride and boron trifluoride diethyl etherate at room temperature for 22 h.
according to the procedure of Mateeva and co-workers. This resulted in the isolation of a thick red oil from which the desired reaction product (±)-13 could not be isolated.

Scheme 4.5.4.5  Attempted Synthesis of the Xyloketal G Analogue [(±)-13] from the Bicyclic Acetal [(±)-245]

Reagents and conditions: (a) AcCl, AlCl₃, 180 °C, 30 min or Ac₂O, BF₃·Et₂O, room temperature, 22 h.

No further attempts were made to improve the syntheses of these analogues in view of the fact that xyloketal D (4) and G (7) are minor metabolites and that insignificant biological activity has been reported for these natural products.

4.5.5 Synthesis of (±)-11,11',20-Trinorxyloketal E [(±)-257], (±)-14-epi-11,11',20-Trinorxyloketal E [(±)-258], (±)-2,6-epi-11,11',20-Trinorxyloketal E [(±)-259] and (±)-2,6,14-epi-11,11',20-Trinorxyloketal E [(±)-260] from the Xyloketal B Analogues [(±)-16] and [(±)-17]

Various methods for electrophilic aromatic substitution reactions of phenols with dihydrofurans or dihydropyrans have been reported. To investigate the possibility of the conversion of xyloketal B (2) into xyloketal E (5), model studies using a mixture (dr = 1:1) of the xyloketal B analogues (±)-16 and (±)-17 with commercially available 2-methyl-4,5-dihydrofuran (114) were performed. Thus, the two starting materials were allowed to react in the presence of pyridinium p-toluenesulfonate according to the procedure described by Cottet and co-workers (Scheme 4.5.5.1). This
cleanly afforded an inseparable mixture (dr = 2:1:2:1) of the xyloketal E analogues (±)-257, (±)-258, (±)-259 and (±)-260.

Scheme 4.5.5.1 Synthesis of the Xyloketal E Analogues [(±)-257], [(±)-258], [(±)-259] and [(±)-260] from the Xyloketal B Analogues [(±)-16] and [(±)-17]

Reagents and conditions: (a) 2-Methyl-4,5-dihydrofuran (114), PPTS, CH₂Cl₂, room temperature, 20 h, 73%, dr = 2:1:2:1 [(±)-257:(±)-258:(±)-259:(±)-260].

The ¹H NMR spectrum of this mixture did not show any signals corresponding to aromatic protons but did show four well resolved peaks corresponding to hydrogen-bonded phenols at δ 10.72, 10.75, 10.78 and 10.80 ppm. This confirmed that the reaction had occurred by the desired electrophilic aromatic substitution process and that acetals were not formed by reaction of the phenol moiety with the dihydrofuran 114. The stereoselectivity of this process was difficult to rationalize. The starting material was a mixture (dr = 1:1) of the xyloketal B analogues (±)-16 and (±)-17. Therefore, it is reasonable to assume that each isomer afforded a pair of diastereoisomers in a 2:1 ratio. However, the relative stereochemistry within each set was not determined. It was
anticipated that the stereochemistry of chiral nonracemic xyloketal B (2) and/or the
stereochemistry of chiral nonracemic 2,4-dimethyl-4,5-dihydrofuran (61) would direct
the stereochemistry of this process on attempting the synthesis of the natural product
xyloketal E (5).

4.6 Asymmetric Synthesis of the Xyloketals: Electrophilic
Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-
hydroxymethyl-4,5-dihydrofuran

4.6.1 Total Synthesis of (−)-Xyloketal A [(−)-1]

As shown previously (See: Section 3.7.3), the chiral nonracemic ester (4R)-206
could be cleanly reduced to the desired alcohol (4R)-226 with lithium aluminum hydride.
However, the latter compound was found to be somewhat unstable to isolation and
purification and so it was used directly in the subsequent electrophilic aromatic
substitution reactions. Therefore, phloroglucinol (14) (1 equiv) was allowed to react with
the alcohol (4R)-226 and boron trifluoride diethyl etherate (1 equiv) in the presence of
anhydrous magnesium sulfate in ether (Scheme 4.6.1.1). The results of these studies are
presented below (see Table 4.6.1.1).
Scheme 4.6.1.1  Total Synthesis of (−)-Xyloketal A [(−)-1]: Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-226]

Reagents and conditions: (a) See below: Table 4.6.1.1.

Table 4.6.1.1  Reagents and Conditions Corresponding to Scheme 4.6.1.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of [(4R)-226]</th>
<th>Additional Reagents and Conditions</th>
<th>Yield (%)</th>
<th>dr [(−)-1:40]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>BF₃·Et₂O (1 equiv), MgSO₄, Et₂O, 0 °C, 20 min</td>
<td>85</td>
<td>5:2</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>BF₃·Et₂O (1 equiv), MgSO₄, Et₂O, −78 °C, 20 min</td>
<td>79</td>
<td>4:1</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>BF₃·Et₂O (1 equiv), MgSO₄, Et₂O, 0 °C, 2 h</td>
<td>14</td>
<td>5:2</td>
</tr>
</tbody>
</table>
In the first instance, a mixture of a two-fold excess [per phenolic reaction site of phloroglucinol (14)] of the alcohol (4R)-226 and phloroglucinol (14) (1 equiv) in ether at 0 °C was stirred with boron trifluoride diethyl etherate (1 equiv) and anhydrous magnesium sulfate (entry 1). Within 20 minutes, an exceptionally clean synthetic transformation occurred that led to the isolation of a chromatographically inseparable mixture (dr = 5:2) of xyloketal A [(-)-1] and a single additional diastereoisomer, tentatively assigned as 2,6-epi-xyloketal A (40), in 85% yield. Although the diastereoselectivity of the overall process was not exceptional, the diastereoselectivity of each of the three individual ring formation reactions was certainly respectable (dr = ~9:1). Moreover, the ¹H NMR spectrum of the crude reaction mixture was dominated by signals that corresponded to the C₃-symmetric natural product. In order to improve the overall diastereoselectivity of this remarkable process, the above reaction was repeated at −78 °C (entry 2). This led to the isolation of a mixture of xyloketal A [(-)-1] and 2,6-epi-xyloketal A (40) in similar yield (79% yield). However, the diastereoselectivity of the overall process was increased (dr = 4:1). In this case, the diastereoselectivity of each of the three individual ring formation reactions had reached an impressive level (dr = ~19:1). The reaction was also repeated at 0 °C with four equivalents of the alcohol (4R)-226 (entry 3). In this instance, a mixture (dr = 5:2) of xyloketal A [(-)-1] and 2,6-epi-xyloketal A (40) was isolated in 14% yield. In addition, no evidence for the formation of mono- or bis-addition products was recorded. This reflected the relative instability of the alcohol (4R)-226 and the increased reactivity of the more electron-rich mono- and bis-addition products towards electrophilic aromatic substitution processes.
An analytically pure sample of synthetic (−)-xyloketal A [(−)-I] was subsequently obtained on crystallization from petroleum ether. The $^1$H and $^{13}$C NMR spectra of this material were identical to those recorded for the natural product (Figure 4.6.1.1).¹

![NMR spectrum](image)

**Figure 4.6.1.1** $^1$H NMR spectrum (500 MHz, CDCl₃) of (−)-xyloketal A [(−)-I].

The optical rotation (in both sense and magnitude) as well as the melting point of the synthetic material were in close agreement with those reported in the original isolation paper.¹ Thus, the absolute stereochemistry of the natural product was firmly established.
4.6.2 Total Synthesis of (−)-Xyloketal B [(−)-2]

According to the optimized reaction conditions from the model studies, the ester 112 (1 equiv) was allowed to react with the alcohol (4R)-226 (4 equiv) and boron trifluoride diethyl etherate (0.7 equiv) in the presence of anhydrous magnesium sulfate (Scheme 4.6.2.1). After 38 h, a clean synthetic transformation occurred that led to the isolation of a chromatographically separable mixture of the mono-adduct (−)-261 (17%) and the bis-adduct (−)-262 (73%). It was subsequently found that extending the reaction time to 46 h afforded exclusively the bis-adduct (−)-262 in very good yield (91%). Of note, a single diastereoisomer was obtained. Furthermore, none of the regioisomer corresponding to the thermodynamically unstable natural product xyloketal C (3) was isolated in these reactions.

Scheme 4.6.2.1 Synthesis of the Xyloketal B Methyl Esters [(−)-261] and [(−)-262]: Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-226]

Reagents and conditions: (a) Alcohol (4R)-226 (4 equiv), BF$_3$·Et$_2$O (0.7 equiv), MgSO$_4$, Et$_2$O, 0 °C to room temperature, 38 h, 17% [(−)-261], 73% [(−)-262] or alcohol (4R)-226 (4 equiv), BF$_3$·Et$_2$O (0.7 equiv), MgSO$_4$, Et$_2$O, 0 °C to room temperature, 46 h, 91% [(−)-262].

The spectral data for mono-adduct (−)-261 was very similar to the spectral data of xyloketal D (4). Extensive analysis of the 2D NMR data led to the unambiguous assignment of the molecular structure of this compound. The regiochemistry of this product was confirmed by a nOe contact that was observed between Me-10$_β$ and H-9.
In addition, nOe contacts were observed between $Me-10\beta$, $H-4a\beta$, and $Me-11\beta$ which confirmed the cis relationship between these moieties.

Figure 4.6.2.1  Observed nOe contacts for the mono-adduct [(-)-261].

The $^1$H NMR spectrum for the bis-adduct [(-)-262] contained signals that were well resolved. Therefore, based on analysis of the COSY NMR spectrum and the observed nOe contacts, unambiguous assignment of both the regio- and stereochemistry were made. This confirmed that the product had the desired substitution pattern for the synthesis of xyloketal B (2) (Figure 4.6.2.2).

Figure 4.6.2.2  Observed nOe contacts for the bis-adduct [(-)-262].

The bis-adduct [(-)-262] was subsequently saponified and decarboxylated in a single step upon reaction with sodium hydroxide in aqueous methanol at reflux to afford [(-)-xyloketal B [(--)-2] in excellent yield (95%) (Scheme 4.6.2.2).
Scheme 4.6.2.2 Total Synthesis of (−)-Xyloketal B [(−)-2] from the Xyloketal B Methyl Ester [(−)-262]

Reagents and conditions: (a) NaOH, H₂O, MeOH, reflux, 3.5 h, 95%.

The ¹H and ¹³C NMR spectra of this material were slightly different to that reported for the natural product (Figure 4.6.2.3).¹ In particular, the signals corresponding to the phenol and aromatic protons had slightly different chemical shifts. It was subsequently found that the chemical shift of these signals varied depending on the concentration of the NMR sample. Thus, it is reasonable to assume that these differences arose from the degree of intermolecular hydrogen bonding at the different sample concentrations. Therefore, 2D NMR experiments were performed to confirm the molecular structure of the product. Of note, the ¹H NMR signal of natural xyloketal B (2) centred at δ 4.10 ppm should have been reported at δ 4.18 ppm by Lin and co-workers.²

(*) Professor Lin kindly provided the ¹H and ¹³C NMR spectra of xyloketal B (2) for comparison purposes.
The melting point of the synthetic material and the magnitude of the optical rotation were in close agreement with those reported in the original isolation paper. However, the sign of the optical rotation of the synthetic (-)-xyloketal B [(-)-2] was opposite to that reported. There are two possible explanations for this discrepancy. First, natural xyloketal B (2) could have the opposite absolute stereochemistry to that reported in the isolation paper. However, the work described in this thesis and the results described by Krohn and co-workers have shown that the absolute stereochemistries of the other members of the xyloketal family of natural products were assigned correctly. Since it is reasonable to assume that the xyloketal natural products result from a common biosynthetic pathway, this possibility is unlikely.

Figure 4.6.2.3 1H NMR spectrum (500 MHz, CDCl₃) of (-)-xyloketal B [(-)-2].
Alternatively, the sign of the reported optical rotation could have been reported incorrectly. Furthermore, Lin and co-workers have reported a semi-synthesis of (−)-xyloketal F [(−)-6] from natural xyloketal B (2).³ However, when our synthetic (−)-xyloketal B [(−)-2] was allowed to react under similar reaction conditions (See: Section 4.6.5), (−)-xyloketal F [(−)-6] was also obtained. Thus, it appears that the optical rotation reported for the natural product is incorrect*

4.6.3 Total Synthesis of (−)-Xyloketal D [(−)-4] and G [(−)-7]

The application of the electrophilic aromatic substitution reactions towards the total synthesis of xyloketal D (4) and G (7) proceeded in a similar fashion to that described in the corresponding model studies. 2,4-Dihydroxyacetophenone 11 (1 equiv) was allowed to with the alcohol (4R)-226 (4 equiv) in the presence of boron trifluoride diethyl etherate (0.3 equiv) to afford (−)-xyloketal D [(−)-4] [14% (51% brsm)] and (−)-xyloketal G [(−)-7] [8% (29% brsm)] that were separated by flash chromatography (Scheme 4.6.3.1).

(* In an effort to clarify this inconsistency, Professor Lin agreed to record the optical rotation of natural xyloketal B (2). However, this information has not been reported to us.
Scheme 4.6.3.1 Total Synthesis of (−)-Xyloketals D [(−)-4] and G [(−)-7]:
Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-226]

Reagents and conditions: (a) Alcohol (4R)-226 (4 equiv), BF₃·Et₂O (0.3 equiv), MgSO₄, Et₂O, 0 °C to room temperature, 46 h, 14% (51% brsm) [(−)-4], 8% (29% brsm) [(−)-7].

All of the spectral data of (−)-xyloketals D [(−)-4] were identical to that of the natural product and to the material prepared by the Diels-Alder route as discussed previously (See: Section 2.9.1). The melting point and optical rotation (both sign and magnitude) were identical to the material produced by the Diels-Alder approach but varied from the values reported for the natural product (See: Section 2.9.1).

The ¹H and ¹³C NMR data for (−)-xyloketals G [(−)-7] were identical to the natural product (Figure 4.6.3.1). Furthermore, extensive 2D NMR analysis independently confirmed the molecular structure of this material.

(*) The synthesis of (−)-xyloketals G [(−)-7] was completed prior to the publication of the isolation of the natural product (See: Ref. 4). Therefore, complete structure characterization of this reaction product was performed.
Figure 4.6.3.1 $^1$H NMR spectrum (500 MHz, CDCl$_3$) of (-)-xyloketal G [(−)-7].

The melting point and sign of the optical rotation of synthetic (-)-xyloketal G [(−)-7] were in agreement with the natural product. However, the magnitude of the optical rotation was lower than that reported for the natural product. No further attempts were made to investigate the cause of the depressed optical rotation in view of the fact that xyloketal G [(−)-7] is a minor metabolite and that no biological activity has been reported for this natural product.

4.6.4 Total Synthesis of Xyloketal E (5) from (-)-Xyloketal B [(−)-2]

In the model studies towards the synthesis of xyloketal E (5), modest diastereoselectivity (dr = 2:1) was observed during the electrophilic aromatic substitution

(*) Professor Lin agreed to record the optical rotation for the natural xyloketal G [(−)-7]. However, this information has not been reported to us.
reaction of the xyloketal B analogues \((\pm)-16\) and \((\pm)-17\) with the achiral dihydrofuran \(114\). However, it was not possible to separate the resultant mixture of products to determine if the relative stereochemistry of the major reaction products corresponded to xyloketal E (5). Therefore, further investigations into the stereoselectivity of this process were performed. Accordingly, synthetic \((-\)-xyloketal B \[(-)-2\]) was allowed to react with commercially available 2-methyl-4,5-dihydrofuran \((114)\) as previously described to afford the xyloketal E analogues 263 and 264 in good yield (78\%) (Scheme 4.6.4.1). Interestingly, no diastereoselectivity \((dr = 1:1)\) was observed in this reaction with chiral nonracemic \((-\)-xyloketal B \[(-)-2\]).

**Scheme 4.6.4.1  Synthesis of Analogues of Xyloketal E (5) from \((-\)-Xyloketal B \[(-)-2\])**

![Reaction Scheme]

Reagents and conditions: (a) PPTS, \(CH_2Cl_2\), room temperature, 22 h, 78\%, \(dr = 1:1\) \((263:264)\).

The completion of the total synthesis of xyloketal E (5) involved the reaction of \((-\)-xyloketal B \[(-)-2\]) with chiral nonracemic \((4R)-2,4\)-dimethyl-4,5-dihydrofuran \((4R)-61\) and pyridinium \(p\)-toluenesulfonate (Scheme 4.6.4.2). This afforded an inseparable mixture \((dr = 2:9)\) of xyloketal E (5) and 14-\(epi\)-xyloketal E (265).
Scheme 4.6.4.2  Total Synthesis of the Xyloketal E (5) and 14-epi-Xyloketal E (265) from (-)-Xyloketal B [(-)-2]

Reagents and conditions: (a) PPTS, CH₂Cl₂, room temperature, 21 h, 82%, dr = 2:9 (5:265).

The diastereoselectivity of this process (dr = 2:9) was readily determined by inspection of the $^1$H NMR spectra as the signals corresponding to the two hydrogen bonded phenol moieties of the reaction products 5 and 265 were well resolved at $\delta$ 10.81 and 10.86 ppm, respectively (Figure 4.6.4.1). Previous model studies had shown that the stereochemistry of (-)-xyloketal B [(-)-2] did not effect the diastereoselectivity of this process. Therefore, the product ratio was controlled by the C-4 methyl substituent of the dihydrofuran (4R)-61 which led to the preferential formation of the undesired diastereoisomer of the natural product (which had been expected based on steric arguments). Therefore, it is reasonable to assume that the formation of the natural xyloketal E (5) is controlled by an enzyme or that 14-epi-xyloketal E (265) has not yet been isolated from the natural source.
4.6.5 Two Alternative Syntheses of (-)-Xyloketal F [(-)-6]

The potentially biomimetic synthesis of xyloketal F [(-)-6] via the coupling of two equivalents of xyloketal B (2) was initially investigated. (-)-Xyloketal B [(-)-2] (2 equiv) was allowed to react with paraformaldehyde under mild acidic conditions at room temperature (Scheme 4.6.5.1).

This facile reaction cleanly afforded (-)-xyloketal F [(-)-6] in good yield (84%).
Scheme 4.6.5.1  Synthesis of (−)-Xyloketal F [(−)-6] from (−)-Xyloketal B [(−)-2]

Reagents and conditions: (a) Paraformaldehyde, PPTS, CH$_2$Cl$_2$, room temperature, 23 h, 84%.

The $^1$H and $^{13}$C NMR spectra of this material were identical to those recorded for the natural product (Figure 4.6.5.1).³

Figure 4.6.5.1  $^1$H NMR spectrum (500 MHz, CDCl$_3$) of (−)-xyloketal F [(−)-6].
The melting point as well as the sign of the optical rotation of synthetic (-)-xyloketal F [(-)-6] were in close agreement with those reported in the original isolation paper. However, the magnitude of the optical rotation was slightly lower than the value reported for the natural product.

An alternative and more direct synthesis of xyloketal F [(-)-6] was subsequently investigated. The known biaryl compound 240 was prepared in one step according to literature procedures from phloroglucinol (14) (Scheme 4.6.5.2). Although the overall yield of this process was low (34%), the starting materials are readily available and inexpensive. In addition, the isolation of this product was straightforward. This material was then subjected to the electrophilic aromatic substitution reaction with the alcohol (4R)-226 (8 equiv) and boron trifluoride diethyl etherate (1.3 equiv). Within 75 min, a clean synthetic transformation of this electron rich phenol had occurred to afford an inseparable mixture (10:7:3) of xyloketal F [(-)-6] and the regioisomers 266 and 267 in good combined yield (71%).
Scheme 4.6.5.2 Total Synthesis of (−)-Xyloketal F [(−)-6] from the Regioisomeric Adducts (266) and (267)

Reagents and conditions: (a) Paraformaldehyde (0.5 equiv), HCl, H2O, 4 °C, 16 h, 34%; (b) alcohol (4R)-226 (8 equiv), BF3·Et2O (1.3 equiv), MgSO4, Et2O, 0 °C to room temperature, 75 min, 71% [(−)-6:266:267], 10:7:3; (c) p-TsOH·H2O, CDCl3, 23 °C, 18 h, >99%.

Of note, the regioisomers 266 and 267 contain moieties that correspond to the molecular structure of xyloketal C (3). In addition, it should be noted that, a methyl ester precursor to xyloketal C (3) was not formed in the reaction of the relatively electron poor phenol 112 and the dihydrofuran (4R)-226 (See: Section 4.6.2). In the latter case, the
reaction proceeded slowly and so the regioisomeric product, corresponding to xyloketal C (3), had sufficient time to undergo isomerization processes and afforded the more stable xyloketal B derivative (±)-262. However, when the electron rich phenol 240 was used as a substrate in the former case, the reaction proceeded relatively quickly and so there was presumably insufficient time for the isomerization process to occur.

From the beginning of these investigations, it was anticipated that a mixture of the three regioisomers (−)-6, 266 and 267 would be formed. However, it was also anticipated that the undesired regioisomers 266 and 267 would be unstable as compared to xyloketal F [(-)-6] and under appropriate conditions could be isomerized to the natural product. Therefore, a portion of this mixture of products (~7 mg) was dissolved in deuterated chloroform (~0.75 mL) and a crystal of p-toluenesulfonic acid monohydrate was added. Over the course of 18 h at 23 °C, the resultant mixture was shown to cleanly convert into (−)-xyloketal F [(-)-6] by 1H NMR spectroscopy (Figure 4.6.5.2).

![Figure 4.6.5.2 Selected regions of the 1H NMR spectrum (500 MHz, CDCl3) obtained during the isomerization of the regioisomeric adducts (266) and (267) to (−)-xyloketal F [(-)-6].]
4.7 Conclusions

A series of demethyl analogues of xyloketal A (1), B (2), C (3), D (4), E (5) and G (7) were prepared in a notably direct manner from 2-methyl-3-hydroxymethyl-4,5-dihydrofuran (168) and a series of corresponding phenols via an electrophilic aromatic substitution reaction that was promoted by boron trifluoride diethyl etherate. In the case of the synthesis of the xyloketal A analogues (±)-18 and (±)-19, the process was found to be highly efficient (up to 93% yield). This remarkable transformation involved six individual reactions (three electrophilic aromatic substitution reactions and three subsequent acetal formation reactions). Analogues of xyloketal B (2) and C (3) were prepared from methyl 2,4,6-trihydroxybenzoate (112) and analogues of xyloketal D (4) and G (7) were also prepared from 2,4-dihydroxyacetophenone (11). The lower isolated yields of the desired analogues, in these instances, reflected the decreased reactivity of these phenolic substrates towards electrophilic aromatic substitution reactions. The xyloketal B analogues (±)-115 and (±)-242 were subsequently converted to a mixture of the xyloketal E analogues (±)-257, (±)-258, (±)-259 and (±)-260. Since all of these syntheses were non-diastereoselective, the synthesis of analogues of xyloketal F (6) was not attempted (a mixture of eight diastereoisomers would be expected).

The application of this potentially biomimetic synthetic method employing (4R)-2,4-dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-226] and a variety of phenols led to the total synthesis of (−)-xyloketal A [(−)-1] (21% overall yield in nine steps from commercially available starting materials), (−)-xyloketal B [(−)-2] (19% overall yield twelve steps from commercially available starting materials), (−)-xyloketal D [(−)-4] [5% (17% brsm) overall yield in nine steps from commercially available starting materials],
xyloketal E (5) (3% overall yield in thirteen steps from commercially available starting materials), (-)-xyloketal F [(-)-6] (16% overall yield in thirteen steps or 8% overall yield in eleven steps from commercially available starting materials) and (-)-xyloketal G [(-)-7] [3% (10% brsm) in nine steps from commercially available starting materials]. The decreased reactivity of (4R)-2,4-dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-226] as compared to 2-methyl-3-hydroxymethyl-4,5-dihydrofuran (168) used in the model studies, meant that this synthetic route was not applicable to the synthesis of xyloketal C (3). These syntheses are the first reported practical asymmetric syntheses of xyloketal A (1), B (2), E (5) and F (6). The spectral data of these natural products was in agreement with the data recorded for the isolated natural products. There were some differences between the optical rotations and meting points of some of the synthetic compounds and the values reported for the isolated natural products. Professor Lin agreed to record the optical rotation for the natural xyloketals. However, this information has not been reported to us. The depressed melting points were attributed to trace amounts of the enantiomer which had significantly depressed the melting point of our sample of synthetic xyloketals.

In view of the general applicability and success of this route to the total synthesis of the xyloketal natural products, the synthesis of structural analogues can now be pursued. In particular, this synthetic route could be adapted to prepare; a) the enantiomeric series of compounds, b) derivatives with different aromatic cores, c) compounds with alternative heteroatom substitution (i.e. nitrogen, sulphur and selenium), d) 5,6-bicyclic acetal derivatives with alternative substitution patterns and e) 6,6-bicyclic

acetal derivatives with various substitution patterns from the corresponding dihydropyran precursors. These analogues may show improved biological activity and enable the structure-activity relationships of the xyloketal natural products to be determined.
CHAPTER FIVE

Total Synthesis of (+)-Alboatrin

5.1 Introduction

In this chapter the further application of the Diels-Alder approach and the electrophilic aromatic substitution reaction for the synthesis of alboatrin (48) is discussed. The latter process led to the successful synthesis of a demethyl analogue of alboatrin (48) during optimization of reaction conditions. In addition, the first asymmetric total synthesis of (+)-alboatrin [(+)-48] was also accomplished with this process that established the absolute stereochemistry of the natural product.

5.2 Attempted Synthesis of Alboatrin: Diels-Alder Approach

5.2.1 Retrosynthetic Analysis of Alboatrin (48)

In a similar manner to that conceived for the synthesis of the xyloketals, retrosynthetic analysis of alboatrin (48) suggested that it could be prepared by a [4+2] cycloaddition reaction of the ortho-quinone methide 268 and the dihydrofuran 61 (Scheme 5.2.1.1). The Mannich base 269, which would serve as a precursor for the generation of the ortho-quinone methide 268 could, in principle, be prepared from commercially available orcinol (53), a formaldehyde source and a secondary amine.
5.2.1 Retrosynthetic Analysis of Alboatrin (48): Diels-Alder Approach

Scheme 5.2.1.1

\[
\begin{align*}
\text{HO-} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{HO-} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{HO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{HO-} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{HO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{HO-} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{HO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

5.2.2 Attempted Synthesis of the Mannich Base (270) for the Synthesis of Alboatrin (48)

The synthesis of the desired Mannich base 270 from orcinol (53), aqueous formaldehyde and morpholine (103) was attempted (Scheme 5.2.2.1). The results of these studies are presented below (Table 5.2.2.1).

Scheme 5.2.2.1 Attempted Synthesis of the Mannich Base (270) from Orcinol (53)

\[
\begin{align*}
\text{HO-} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{HO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{HO-} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{HO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{HO-} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{HO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{HO-} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{HO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

Reagents and conditions: (a) See below: Table 5.2.2.1.

Table 5.2.2.1 Reagents and Conditions Corresponding to Scheme 5.2.2.1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Equivalents of Morpholine (103)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃O (1.1 equiv), H₂O, MeOH, reflux, 3.5 h</td>
<td>1.1</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>
The initial reaction attempted involved identical conditions to that which had been used to make the precursors to xyloketal D (4) (See: Section 2.4.1). This involved the reaction of orcinol (53) (1 equiv) with aqueous formaldehyde (1.1 equiv) and morpholine (103) (1.1 equiv) in methanol at reflux (entry 1). However, this afforded a complex mixture of reaction products. Analysis of the $^1$H NMR spectrum of the crude reaction mixture indicated that mono-, bis- and tris-adducts had formed. In an effort to suppress the formation of these undesired products, the reaction was performed at room temperature (entry 2). However, this afforded a similar mixture of products. Of note, Ichihara and co-workers have shown that related reactions of orcinol (53) afford complex mixtures of products from which the desired mono-adducts can be isolated in low yield. Therefore, the number of equivalents of formaldehyde and morpholine (103) were decreased in attempt to limit the undesired multiple reactions (entry 3). Unfortunately, a complex mixture of reaction products was again obtained and so no further attempts to prepare the Mannich base 270 were made.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and Conditions</th>
<th>Equivalents of Morpholine (103)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>CH$_2$O (1.1 equiv), H$_2$O, MeOH, room temperature, 18 h</td>
<td>1.1</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>CH$_2$O (0.2 equiv), H$_2$O, MeOH, reflux, 7 h</td>
<td>0.2</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>
5.3 Total Synthesis of Alboatrin: Electrophilic Aromatic Substitution Reactions with \((4R)-2,4\text{-dimehtyl-3-hydroxymethyl-4,5-dihydrofuran}\)

5.3.1 Retrosynthetic Analysis of Alboatrin: Electrophilic Aromatic Substitution Reactions with \(2,4\text{-dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)}\)

An alternative retrosynthetic analysis employing the successful electrophilic aromatic substitution reaction described earlier was also applied to the synthesis of alboatrin \((48)\) (Scheme 5.3.1.1). In this instance, the reactive intermediate \(239\) could be allowed to react with orcinol \((53)\) to afford alboatrin \((48)\).

Scheme 5.3.1.1 Retrosynthetic Analysis of Alboatrin \((48)\): Electrophilic Aromatic Substitution Reactions with \(2,4\text{-dimethyl-3-hydroxymethyl-4,5-dihydrofuran (226)}\)

![Scheme of retrosynthetic analysis](image)

5.3.2 Model Studies: Electrophilic Aromatic Substitution Reactions with \(2\text{-methyl-3-hydroxymethyl-4,5-dihydrofuran (168)}\)

In order to optimize the reaction conditions for the preparation of alboatrin \((48)\), model studies were performed (Scheme 5.3.2.1). Accordingly, orcinol \((53)\) (1 equiv) was allowed to react with the alcohol \(168\) and boron trifluoride diethyl etherate in the presence of anhydrous magnesium sulfate in ether. The results of these studies are presented below (Table 5.3.2.1).
Scheme 5.3.2.1 Synthesis of 10-Noralboatin [(±)-271]: Electrophilic Aromatic Substitution Reactions with 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)

![Chemical Diagram]

Reagents and conditions: (a) See below: Table 5.3.2.1.

Table 5.3.2.1 Reagents and Conditions Corresponding to Scheme 5.3.2.1.∗

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of the Alcohol (168)</th>
<th>Reagents and Conditions</th>
<th>Yield of [(±)-271] (%)</th>
<th>Yield of [272:(±)-273:(±)-274:(±)-275] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.25</td>
<td>BF3·Et2O (1 equiv), MgSO4, Et2O, 0 °C to room temperature, 28 h</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>1.05</td>
<td>BF3·Et2O (1 equiv), MgSO4, Et2O, 0 °C to room temperature, 24 h</td>
<td>34 (75 brsm)</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>BF3·Et2O (1 equiv), MgSO4, Et2O, 0 °C to room temperature, 24 h</td>
<td>36</td>
<td>trace</td>
</tr>
</tbody>
</table>

(*) The bis-adducts 272, (±)-273, (±)-274 and (±)-275 were obtained as an inseparable mixture (3:3:1:1).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of the Alcohol (168)</th>
<th>Reagents and Conditions</th>
<th>Yield of [(±)-271] (%)</th>
<th>Yield of [272:(±)-273:(±)-274:(±)-275] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1.05</td>
<td>BF₃·Et₂O (0.3 equiv), MgSO₄, Et₂O, 0 °C to room temperature, 45 h</td>
<td>48 (72 brsm)</td>
<td>34</td>
</tr>
</tbody>
</table>

During the attempted synthesis of the Mannich base 270 derived from orcinol (53), multiple electrophilic aromatic substitution reactions were observed. Thus, in the initial attempt, orcinol (53) (1 equiv) was allowed to react with the alcohol 168 (1.25 equiv) in the presence of boron trifluoride diethyl etherate (1 equiv) (entry 1). This afforded the desired mono-adduct (±)-271 in modest yield (31%). In addition, a substantial amount of an inseparable mixture (3:3:1:1) of the bis-adducts 272, (±)-273, (±)-274 and (±)-275 was also obtained (25% combined yield). Unexpectedly, none of the corresponding regioisomeric mono-adduct was obtained. In an effort to reduce the amount of the bis-adducts 272, (±)-273, (±)-274 and (±)-275 formed, the quantity of the alcohol 168 was reduced (1.05 equiv) (entry 2). Although the amount of the bis-adducts 272, (±)-273, (±)-274 and (±)-275 produced in this reaction was less (8%), a large amount of unreacted orcinol (53) was also recovered. The overall yield of the desired reaction was not significantly increased (34%). However, based on the amount of starting material 53 that was recovered, the yield of the desired reaction product (±)-271 was 75%. Further reduction of the number of equivalents of the alcohol 168 (0.3 equiv) did not significantly increase the yield of the desired reaction product (±)-271 (36%) (entry 3). It was subsequently found that reducing the number of equivalents of boron
trifluoride diethyl etherate (0.3 equiv), resulted in a significant increase in the yield of the desired reaction product (±)-271 (48%) (entry 4). This increased yield was attributed to a reduction in the level of decomposition of the unstable alcohol 168.

The structure of the single mono-adduct (±)-271 was determined to have the desired relative stereo- and regiochemistry based upon extensive spectral studies. In particular, nOe contacts were observed between Me-12 and H-3a that supported the desired relative stereochemistry of the product (Figure 5.3.2.1). Furthermore, nOe contacts between Me-12 and H-8 and between Me-11, H-4 and H-6 indicated that the reaction product had the desired regiochemistry.

Figure 5.3.2.1 Observed nOe contacts for the alboatrin analogue [(±)-271].

The regiochemistry of the bis-adducts 272, (±)-273, (±)-274 and (±)-275 was determined on the basis of the $^1$H and $^{13}$C NMR spectra. The aromatic region of the $^1$H NMR spectrum contained four aromatic signals from which the product ratio could be determined (3:3:1:1). Inspection of the $^{13}$C NMR spectrum revealed that the major reaction products, based on the intensities of the signals, had a high degree of symmetry and therefore they were the linear regioisomers 272 and (±)-273 (Figure 5.3.2.2). Of note, this was the opposite regiochemistry to that which had been observed previously during the corresponding work towards xyloketal B (2) and C (3).
5.3.3 Total Synthesis of (+)-Alboatrin [(+)-48]

Having completed model studies and demonstrated the feasibility of the electrophilic aromatic substitution reactions for the total synthesis of alboatrin (48), the reaction between orcinol (53) (1 equiv) and the chiral nonracemic alcohol (4R)-226 (1.05 equiv) in the presence boron trifluoride diethyl etherate (0.3 equiv) was performed (Scheme 5.3.3.1). This reaction afforded the desired natural product (+)-alboatrin [(+)-48] in moderate yield [36%, (78% brsm)]. In addition, a single regioisomeric bis-adduct (-)-276 was also isolated in low yield (14%).

Figure 5.3.2.2 Symmetry elements present in the linear bis-adducts (272) and [(±)-273].
Scheme 5.3.3.1 Total Synthesis of (+)-Alboatrin [(+)-48]: Electrophilic Aromatic Substitution Reactions with (4R)-2,4-Dimethyl-3-hydroxymethyl-4,5-dihydrofuran [(4R)-226]

Reagents and conditions: (a) Alcohol (4R)-226 (1.05 equiv), BF₃·Et₂O (0.3 equiv), MgSO₄, Et₂O, 0 °C to room temperature, 48 h, 36% (78% brsm) [(+)-48], 14% [(-)-276].

The ¹H and ¹³C NMR spectra of synthetic (+)-alboatrin [(+)-48] were identical to those recorded for the natural product (Figure 5.3.3.1). The structural characterization of this material was also performed using 2D NMR methods for comparison purposes to our studies on the total synthesis of the xyloketalts.
Thus, nOe contacts were observed between Me-10, H-3a and Me-12 that confirmed the relative stereochemistry of these substituents (Figure 5.3.3.2). The regiochemistry of this product was further confirmed on the basis of nOe contacts observed between Me-12 and H-8 and between Me-11, H-4 and H-6.

Figure 5.3.3.2 Observed nOe contacts for (+)-alboatrin [(+)-48].
The optical rotation (in both sense and magnitude) as well as the melting point of the synthetic material [(+)-48] were also in close agreement with those reported in the original isolation paper.\textsuperscript{11} Thus, the absolute stereochemistry of the natural product is now firmly established.

The structure of the single regioisomeric bis-adduct (-)-276 was also determined by 2D NMR analysis. The relative simplicity of the $^1$H and $^{13}$C NMR spectra confirmed the $C_2$-symmetry of the reaction product.

### 5.4 Conclusions

The application of the Diels-Alder approach towards the synthesis of alboatrin (48) was not successful. The preparation of the Mannich base 270 required for the generation of an appropriately substituted ortho-quinone methide proved to be exceedingly difficult as the result of competitive multiple electrophilic substitution reactions of the electron rich aromatic phenol, orcinol (53).

The use of the alcohol 168 as the source of a reactive intermediate in model studies for the electrophilic aromatic substitution reaction of orcinol (53) afforded the demethyl analogue (±)-271 of alboatrin (48). It was noted that this phenolic substrate displayed a propensity to undergo multiple reactions to afford the bis-adducts 272, (±)-273, (±)-274 and (±)-275. However, careful control of the number of equivalents of the alcohol 168 and the boron trifluoride diethyl etherate employed in the reaction resulted in the isolation of the desired reaction product (±)-271 in moderate yield [48\% (72\% brsm)]. The use of the chiral nonracemic alcohol (4R)-226 in this electrophilic aromatic substitution process led to the first asymmetric total synthesis of (+)-alboatrin [(−)-48]
[12% (27% brsm) overall yield, 9 steps] and allowed for the absolute stereochemistry of this natural product to be assigned.
CHAPTER SIX

Experimental

6.1 General Experimental Details

All non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven- or flame-dried glassware. The reaction temperatures stated were those of the external bath. Diethyl ether (ether) and tetrahydrofuran were dried over sodium/benzophenone ketyl and distilled under an atmosphere of dry nitrogen immediately prior to use. Dichloromethane and benzene were dried over calcium hydride and distilled under an atmosphere of dry nitrogen immediately prior to use. All other solvents and reagents were purified by standard techniques or used as supplied. Silica gel column chromatography ("flash chromatography") was carried out using Merck silica gel 60 (230 to 400 mesh) unless stated otherwise. Brine refers to a saturated aqueous solution of sodium chloride. Melting points (M.p.) were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. Optical rotations ([α]D) were measured using a Perkin-Elmer 341 digital polarimeter. All proton, carbon and fluorine nuclear magnetic resonance spectra (1H NMR, 13C NMR and 19F NMR, respectively) were recorded on 400 MHz (operating frequencies: 1H, 400.13 MHz; 13C, 100.61 MHz), 500 MHz (operating frequencies: 1H, 499.77 MHz; 13C, 125.68 MHz; 19F, 470.22 MHz) and 600 MHz (operating frequencies: 1H, 600.14 MHz) FT spectrometers at ambient temperature. The chemical shifts (δ) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an internal reference. The reference values used for deuterated chloroform (CDCl3) were δ 7.26 and 77.00 ppm for
$^1$H and $^{13}$C NMR spectra, respectively. The reference values used for deuterated benzene (C$_6$D$_6$) were $\delta$ 7.15 and 128.02 ppm, respectively. The reference values used for deuterated acetone [(CD$_3$)$_2$CO] were $\delta$ 2.05 and 30.83 ppm, respectively. $^{19}$F NMR spectra were recorded in deuterated chloroform (CDCl$_3$) and the chemical shifts ($\delta$) for all compounds are listed in parts per million downfield from trifluoroacetic acid which was used as an external reference. Infrared spectra (IR) were recorded as evaporated films (ef) or as KBr discs (KBr) using a Perkin Elmer 599B IR spectrophotometer. Low-resolution mass spectra (MS) were recorded on a Varian 4000 GC/MS/MS. The mode of ionization used was electron impact (EI, 70 eV) or chemical ionization (CI) with methanol as the ionization gas. Matrix-assisted laser desorption/ionization time-of-flight mass spectra (MALDI-TOF) were recorded using 2,4-dihydroxybenzoic acid as the matrix. High-resolution mass spectra using fast atom bombardment (FAB-HRMS) were recorded on a Kratos Concept IH mass spectrometer. Microanalyses (Anal.) were performed on a Carlo Erba Model 1106 CHN analyzer.

6.2 Experimental Concerning Chapter Two

6.2.1 3-Morpholin-4-yl-methyl-2,4-dihydroxyacetophenone (104)$^{21}$

To a solution of 2,4-dihydroxyacetophenone (11) (504 mg, 3.31 mmol) in methanol (9 mL) at room temperature was added morpholine (103) (315 $\mu$L, 3.61 mmol) and an aqueous formaldehyde solution (290 $\mu$L, 37% w/v, 3.58 mmol). The reaction mixture was heated at reflux for 3 h and then concentrated in vacuo to afford a cream
coloured solid. Purification by flash chromatography using ether:hexanes (1:1) as the eluant afforded the title compound 104 (687 mg, 83%) as a white solid. \( R_f = 0.22 \), ether:hexanes (4:1); M.p. 100-102 °C; hexanes:ether; \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \( \delta \) 2.53 (s, 3H, Me), 2.65 (m, 4H, NCH\(_2\)), 3.78 (m, 4H, OCH\(_2\)), 3.87 (s, 2H, ArCH\(_2\)), 6.36 (d, \( J = 8.9 \text{ Hz}, 1\text{H}, H-5 \)), 7.57 (d, \( J = 8.9 \text{ Hz}, 1\text{H}, H-6 \)), 8.64 (broad s, 1H, 4-OH), 13.15 (s, 1H, 2-OH); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \( \delta \) 26.1, 53.0, 54.0, 66.78, 106.9, 108.5, 112.8, 131.9, 162.7, 166.0, 202.7; \( \text{IR (ef)} \) 3432, 2948, 2854, 1615, 1493, 1274, 1260, 1116, 1060, 817 cm\(^{-1}\); \( \text{MS (Cl)} \) \( m/z \) (rel. intensity) 252 (M + H, 100), 88 (24); \( \text{Anal. Calcd. for C}_{13}\text{H}_{17}\text{N}O_4: } \) C, 62.14; H, 6.82; N, 5.57. Found: C, 61.84; H, 6.95; N, 5.25.

**6.2.2 3-Dibenzylaminomethyl-2,4-dihydroxyacetophenone (106)**

![Image](image_url)

To a solution of 2,4-dihydroxyacetophenone (11) (502 mg, 3.30 mmol) in methanol (9 mL) at room temperature was added dibenzylamine (105) (690 \( \mu \)L, 3.60 mmol) and an aqueous formaldehyde solution (290 \( \mu \)L, 37% w/v, 3.58 mmol). The reaction mixture was heated at reflux for 48 h and then concentrated in vacuo to afford a yellow gum. Purification by flash chromatography using ether:hexanes (1:1) as the eluant afforded the title compound 106 (868 mg, 73%) as a thick yellow syrup. \( R_f = 0.61 \), ether:hexanes (4:1); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \( \delta \) 2.53 (s, 3H, Me), 3.65 (m, 4H, NCH\(_2\)Ph), 3.90 (m, 2H, NCH\(_2\)Ar), 6.37 (d, \( J = 8.8 \text{ Hz}, 1\text{H}, H-5 \)), 7.31 (m, 3H, ArH), 7.55 (d, \( J = 8.8 \text{ Hz}, 1\text{H}, H-6 \)), 13.17 (s, 1H, 2-OH); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \( \delta \) 26.2, 48.8, 58.1, 108.1, 108.5, 112.8, 128.0, 128.8, 129.8, 131.8, 136.4, 162.7, 166.1, 202.7;
IR (ef) 3072, 3029, 2924, 2830, 1622, 1494, 1368, 1270, 1059 cm⁻¹; MS (Cl) m/z (rel. intensity) 362 (M + H, 2), 254 (2), 236 (3), 198 (100); Anal. Calcd. for C_{23}H_{23}NO₃: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.61; H, 6.56; N, 3.93.

6.2.3 2,4,6-tris[Dibenzylaminomethyl]phloroglucinol (108)²⁶,²⁷

![Chemical Structure of 108]

To a solution of phloroglucinol (14) (3.00 g, 23.8 mmol) in ethanol (100 mL) at room temperature were added dibenzylamine (105) (14.2 mL, 78.5 mmol) and an aqueous formaldehyde solution (6.0 mL, 37% w/v, 74 mmol). The reaction mixture was stirred for 18 h and then the resultant precipitate was collected by filtration, washed with ethanol (3 × 15 mL) and dried in vacuo to afford the title compound 108 (16.7 g, 93%) as a white powder. R_f = 0.70, hexanes:ether (1:4); M.p. 156-160 °C, ethanol; ^1H NMR (400 MHz, CDCl₃) δ 3.60 (s, 12H, 6 × PhCH₂), 3.78 (s, 6H, 3 × ArCH₂), 7.22-7.33 (m, 30H, ArH); ^13C NMR (101 MHz, CDCl₃) δ 49.2, 57.8, 99.5, 110.3, 127.4, 128.5, 129.6, 137.2, 155.9; IR (KBr) 3454, 3093, 3067, 3031, 2897, 2830, 2794, 1743, 1630, 1491, 1450, 1383, 1352, 1254, 1115 cm⁻¹; MS (Cl) m/z (rel. intensity) 212 (96), 198 (100), 89 (18). Anal. Calcd for C_{51}H_{51}N_{3}O₃: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.21; H, 7.04; N, 5.62.
6.2.4 2,4,6-tris[3-Morpholin-4-yl-methyl]phloroglucinol (107)$^{26,27}$

![Image]

To a solution of phloroglucinol (14) (2.00 g, 15.9 mmol) in ethanol (100 mL) at room temperature were added morpholine (103) (4.30 mL, 49.2 mmol) and an aqueous formaldehyde solution (4.0 mL, 37% w/v, 49 mmol). The reaction mixture was stirred for 18 h and the resultant precipitate was collected by filtration, washed with ethanol (3 x 15 mL) and dried in vacuo to afford the title compound 107 (5.32 g, 79%) as a beige powder. $^{R_F} = 0.65$, hexanes:ether (1:4); M.p. 150-151 °C, ethanol; $^{1}H$ NMR (400 MHz, CDCl$_3$, 2.58 (m, 12H, NCH$_2$), 3.72 (m, 18H, OCH$_2$ and ArCH$_2$); $^{13}C$ NMR (101 MHz, CDCl$_3$, δ 52.8, 54.2, 66.3, 98.2, 156.2; IR (KBr) 3511, 2840, 1630, 1460, 1115 cm$^{-1}$; MS (EI) m/z (rel. intensity) 100 (100). Anal. Calcd for C$_{21}$H$_{33}$N$_3$O$_6$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.47; H, 8.01; N, 9.79.

6.2.5 Iodophloroglucinol Trihydrate (109)$^{26}$

![Image]

To a solution of phloroglucinol (14) (3.78 g, 30.0 mmol) in tetrahydrofuran (30 mL) and water (30 mL) at room temperature were added iodine (7.70 g, 30.3 mmol) and sodium bicarbonate (2.72 g, 32.4 mmol) and the resultant mixture was stirred for 15 min.
The reaction mixture was then diluted with water (40 mL), extracted with ether (3 × 80 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The resultant yellow oil was dissolved in acetone (5 mL) and chloroform (40 mL) and refrigerated at −20 °C overnight. The resultant precipitate was removed by filtration and the filtrate was concentrated in vacuo to afford the impure title compound 109. This process was repeated to afford the pure title compound 109 (6.83 g, 90%) as a yellow powder. \( R_f = 0.40 \), chloroform:methanol (17:3); **M.p.** 147-149 °C, acetone:chloroform; **\(^1\)H NMR** [400 MHz, (CD\(_3\))\(_2\)CO] \( \delta \) 2.94 (s, 6H, \( 3 \times H_2O \)), 6.10 (s, 2H, ArH), 8.33 (s, 1H, OH), 8.67 (s, 2H, \( 2 \times OH \)); **\(^{13}\)C NMR** [101 MHz, (CD\(_3\))\(_2\)CO] \( \delta \) 64.3, 96.3, 160.0, 161.1; **IR** (ef) 3373, 1598, 1460, 1365, 1275, 1158 cm\(^{-1}\); **MS** (Cl) \( m/z \) (rel. intensity) 253 (M + H, 100).

### 6.2.6 Methyl 2,4,6-trihydroxybenzoate (112)

![Structure](image)

To a mixture of 2,4,6-trihydroxybenzoic acid (111) [90% (Aldrich), 10.0 g, 47.9 mmol] and sodium bicarbonate (5.41 g, 64.4 mmol) in N\(_2\)-dimethylformamide (30 mL) was added a solution of dimethyl sulfate (5.0 mL, 53 mmol) in N\(_2\)-dimethylformamide (5 mL). The resultant mixture was stirred at room temperature for six days and then ice (~100 g) was added. The reaction mixture was then extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with water (200 mL), a saturated aqueous solution of sodium bicarbonate (200 mL), brine (200 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using chloroform:methanol (9:1) as the eluant afforded the title compound 112 (5.84 g, 66%) as a white solid. \( R_f = 0.54 \), chloroform:methanol (9:1); **M.p.** 166-168 °C,
chloroform:methanol (lit. 180-180.5 °C, ethyl acetate:cyclohexane); \textsuperscript{1}H NMR [500 MHz, (CD$_3$)$_2$CO] δ 4.04 (s, 3H, Me), 5.93 (s, 2H, ArH), 9.31 (broad s, 1H, OH), 9.98 (broad s, 2H, OH); \textsuperscript{13}C NMR [101 MHz, (CD$_3$)$_2$CO] δ 53.9, 95.1, 97.3, 164.7, 166.6, 172.1; IR (ef) 3528, 3455, 3387, 3088, 3008, 2701, 2652, 1650, 1606, 1480, 1461, 1326, 1294, 1256, 1190 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 185 (M + H, 100).

\textbf{6.2.7 Methyl 2,4,6-trihydroxy-3,5-dibenzylaminomethylbenzoate (113)}

To a solution of the methyl ester 112 (200 mg, 1.09 mmol) in methanol (7 mL) at room temperature were added dibenzylamine (105) (440 µL, 2.4 mmol) and an aqueous formaldehyde solution (200 µL, 37% w/v, 2.4 mmol). The reaction mixture was stirred for 20 h and then concentrated \textit{in vacuo}. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the title compound 137 (289 mg, 44%) as a white solid. 

\begin{itemize}
  \item R$_f$ = 0.40, hexanes:ether (1:1);  
  \item M.p. 46-48 °C, hexanes:ether;  
  \item \textsuperscript{1}H NMR (400 MHz, CDCl$_3$) δ 3.65 (s, 8H, 4 × PhCH$_2$), 3.81 (s, 4H, 3 × ArCH$_2$), 3.98 (s, 3H, CO$_2$Me), 7.32 (m, 20H, ArH);  
  \item \textsuperscript{13}C NMR (101 MHz, CDCl$_3$) δ 48.7, 52.1, 57.5, 94.3, 99.7, 127.6, 128.5, 129.6, 136.5, 161.0, 162.7, 172.1;  
  \item IR (ef) 3424, 3029, 2953, 2848, 1647, 1496, 1463, 1439, 1314, 1213, 1130 cm$^{-1}$;  
  \item MS (Cl) m/z (rel. intensity) 198 (100).
\end{itemize}

\textbf{Anal.} Calcd for C$_{38}$H$_{38}$N$_2$O$_5$: C, 75.72; H, 6.35; N, 4.65. Found: C, 75.88; H, 6.26; N, 4.53.
6.2.8 (±)-11-Norxyloketal D [(±)-12]9

Method A: To a solution of the Mannich base 104 (199 mg, 0.793 mmol) in benzene (8 mL) at room temperature were added 2-methyl-4,5-dihydrofuran (114) (220 μL, 2.41 mmol) and methyl iodide (52 μL, 0.84 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base 104 had undergone complete reaction (5 days). The reaction mixture was then cooled to room temperature, filtered with ether (8 mL) and concentrated in vacuo. Purification by flash chromatography using hexanes:ether (16:1) as the eluant afforded the title compound (±)-12 (86 mg, 43%) as a white solid.

Method B: To a solution of the Mannich base 106 (290 mg, 0.803 mmol) in benzene (8 mL) at room temperature were added 2-methyl-4,5-dihydrofuran (114) (220 μL, 2.41 mmol) and methyl iodide (52 μL, 0.84 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base 106 had undergone complete reaction (5 days). The reaction mixture was then cooled to room temperature, filtered with ether (8 mL) and concentrated in vacuo. Purification by flash chromatography using hexanes:ether (16:1) as the eluant afforded the title compound (±)-12 (75 mg, 38%) as a white solid.

Title compound (±)-12:  \( R_f = 0.25 \), hexanes:ether (4:1);  M.p. 104-105 °C, hexanes:ether (lit.9 114-116 °C, pentane:ether);  \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \): 1.54 (s, 3H, Me-10), 1.74 (m, 1H, H-5), 2.08 (m, 1H, H-5), 2.47 (m, 1H, H-6p), 2.54 (s, 3H, Me-10), 1.74 (m, 1H, H-5), 2.08 (m, 1H, H-5), 2.47 (m, 1H, H-6p), 2.54 (s, 3H, Me-
2.75 (dd, $J = 17.9$, 6.4 Hz, 1H, $H-7\beta$), 3.02 (dd, $J = 17.9$, 1.1 Hz, 1H, $H-7\alpha$), 3.98 (apparent q, $J = 8.5$ Hz, 1H, $H-4$), 4.06 (apparent td, $J = 9.5$, 2.9 Hz, 1H, $H-4$), 6.37 (d, $J = 8.9$ Hz, 1H, $H-15$), 7.52 (d, $J = 8.9$ Hz, 1H, $H-14$), 13.10 (s, 1H, $OH$); 

**Observed NMR contacts**

$Me-11$ to $H-6\beta$, $Me-11$ to $H-7\beta$

**$^{13}$C NMR** (101 MHz, CDCl$_3$) $\delta$ 19.4 ($C-7$), 22.2 ($C-10$), 26.1 ($C-17$), 28.5 ($C-5$), 39.6 ($C-6$), 66.9 ($C-4$), 106.1, 107.4 ($C-2$), 108.8 ($C-15$), 113.1, 130.0 ($C-14$), 159.6, 162.9, 202.6; 

**IR (ef)** 3232 (br), 2987, 2930, 2897, 1622, 1491, 1420, 1370, 1330, 1271, 1177, 1107, 1085, 1004, 852 cm$^{-1}$; 

**MS (CI)** $m/z$ (rel. intensity) 249 (M + H, 100), 231 (30); 

**Anal.** Calcd. for C$_{14}$H$_{16}$O$_4$: C, 67.73; H, 6.50. 

Found: C, 67.85; H, 6.61.

### 6.2.9 (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-epi-11,11',11''-Trinorxyloketal A [(±)-19]

**Method A:** To a solution of the Mannich base 108 (754 mg, 1.00 mmol) in benzene (10 mL) at room temperature were added 2-methyl-4,5-dihydrofuran (114) (820 $\mu$L, 8.99 mmol) and methyl iodide (190 $\mu$L, 3.05 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base 108 had undergone complete reaction (24 h). The reaction mixture was then cooled to room temperature, filtered with ether (10 mL) and concentrated *in vacuo*. Purification by repetitive flash chromatography using hexanes:ether (1:1) then dichloromethane:ether (18:1) as eluants
afforded an inseparable mixture (dr = 1:4) of the title compounds (±)-18 and (±)-19 (78 mg, 19%) as a solid white foam.

**Method B:** To a solution of the Mannich base 107 (170 mg, 0.40 mmol) in benzene (10 mL) at room temperature were added 2-methyl-4,5-dihydrofuran (114) (330 μL, 3.62 mmol) and methyl iodide (75 μL, 1.21 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base 114 had undergone complete reaction (24 h). The reaction mixture was then cooled to room temperature, filtered with ether (10 mL) and concentrated *in vacuo.* Purification by repetitive flash chromatography using hexanes:ether (1:1) then dichloromethane:ether (18:1) as eluants afforded an inseparable mixture (dr = 1:4) of the title compounds (±)-18 and (±)-19 (23 mg, 14%) as a solid white foam.

Recrystallization of the title compounds (±)-18 and (±)-19 from petroleum ether, on slow evaporation of the solvent, afforded an analytically pure mixture (dr = 1:4) of the title compounds (±)-18 and (±)-19 as a white solid. *Rf* = 0.43, ether:hexanes (4:1), 0.27, dichloromethane:ether (9:1); **M.p.** 145-147 °C, petroleum ether (lit. 9 155-157 °C, petroleum ether for a mixture (dr = 1:4) of the title compounds (±)-18 and (±)-19); **¹H NMR** (600 MHz, C₆D₆) δ 1.44 (s, 3H, Me of (±)-19), 1.45 (s, 3H, Me of (±)-19), 1.47 (s, 3H, Me of (±)-19), 1.48 (s, 9H, Me of (±)-18), 1.51 (m, 3H, H-5), 1.65 (m, 3H, H-5), 1.95 (m, 3H, H-6), 2.73 (m, 3H, H-7), 3.05 (m, 3H, H-7), 3.62 (m, 3H, H-4), 3.90 (m, 3H, H-4); **¹³C NMR** (126 MHz, C₆D₆) δ 20.81, 20.84, 20.9, 22.8, 22.9, 23.1, 23.2, 29.3, 29.36, 40.6, 40.66, 40.69, 66.56, 66.57, 66.59, 99.4, 99.57, 99.63, 99.65, 106.8, 106.91, 106.95, 107.1, 150.8, 150.88, 150.89, 151.1; **IR** (ef) 2981, 2936, 2885, 2852, 1617, 1455, 1371,
1179, 1105, 1003 cm\(^{-1}\); \textbf{MS (Cl)} \(m/z\) (rel. intensity) 415 (M + H, 31), 414 (M, 15), 373 (10), 331 (100), 97 (9), 43 (32); \textbf{Anal}. Calcd. for C\(_{24}\)H\(_{30}\)O\(_6\): C, 69.54; H, 7.30. Found: C, 69.34; H, 7.30.

6.2.10 (\(\pm\))-2-Methylpent-4-ynoic Acid [(\(\pm\))-70]\(^{24,25}\)

\[
\begin{align*}
\text{\(\pm\)-70} & \\
\text{Me} & \\
\begin{array}{c}
\text{CH} \\
\text{OH}
\end{array}
\end{align*}
\]

To a solution of \(N,N\)-diisopropylamine (44.0 mL, 312 mmol) in tetrahydrofuran (300 mL) at 0 °C was added \(n\)-butyl lithium (124 mL, 2.5 M in hexanes, 310 mmol). The resultant solution was stirred at 0 °C for 30 min and then propionic acid (72) (10.1 mL, 135 mmol) and hexamethylphosphoramide (23.5 mL, 134 mmol) were added. The reaction mixture was stirred at room temperature for 1 h and then cooled to 0 °C. A solution of propargyl bromide (71) (18.1 mL, 80 % w/w in toluene, 162 mmol) was then added dropwise. The resultant mixture was allowed to warm to room temperature and was stirred for 16 h. The reaction mixture was then acidified to pH ~2 with hydrochloric acid (3 M) and extracted with ether (3 \(\times\) 150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous magnesium sulfate and concentrated \textit{in vacuo}. Purification of the resultant residue by distillation at reduced pressure afforded the \textit{title compound} (\(\pm\)-70) (10.3 g, 68%) as a colourless oil. \(R_f = 0.48\), hexanes:ethyl acetate (1:2); \textbf{B.p.} 103-106 °C, 5 mm Hg (lit.\(^{24}\) 106.5-109.5 °C, 14-15 mm Hg); \(\textbf{\textit{\textit{\textit{H}}}}\) \textbf{NMR} (500 MHz, CDCl\(_3\)) \(\delta\) 1.31 (d, \(J = 7.1\) Hz, 3H, CH\(_3\)), 2.02 (t, \(J = 2.7\) Hz, 1H, HCC), 2.40 (m, 1H, CHH), 2.57 (m, 1H, CHH), 2.71 (m, 1H, CHCO\(_2\)H), 10.73 (m, 1H, OH); \(\textbf{\textit{\textit{\textit{C}}}}\) \textbf{NMR} (126 MHz, CDCl\(_3\)) \(\delta\) 16.1, 22.3, 38.6, 70.1, 81.1, 181.3; \textbf{IR (ef)} 3293, 2978, 2923, 1742, 1454, 1382, 1300, 1254, 1160, 1051, 928, 838, 776 cm\(^{-1}\).
2668, 1701, 1420, 1295, 1240, 1200, 940, 659 cm\(^{-1}\);  MS (Cl) \(m/z\) (rel. intensity) 113 (M + H, 100).

**6.2.11 (±)-2-Methylpent-4-yn-1-ol [(±)-69]\(^{24}\)**

\[\text{Me} \quad \text{OH} \quad (±)-69\]

To a suspension of lithium aluminum hydride (3.73 g, 98.2 mmol) in tetrahydrofuran (150 mL) at 0 °C was added a solution of the carboxylic acid (±)-70 (5.51 g, 49.1 mmol) in tetrahydrofuran (150 mL) and the resultant suspension was stirred at room temperature for 16 h. Water (3.7 mL), an aqueous solution of sodium hydroxide (2 M, 3.7 mL) and water (11.2 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (200 mL) and the combined organic filtrates were concentrated in vacuo. Purification by distillation at reduced pressure afforded the *title compound* (±)-69 (3.98 g, 82%) as a colourless oil. R\(_f\) = 0.55, hexanes:ethyl acetate (1:2);  **B.p.** 61-66 °C, ~20 mm Hg (lit.\(^{24}\) 64-64.5 °C, 10 mm Hg); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.01 (d, \(J = 6.9 \text{ Hz}\), 3H, \(CH_3\)), 1.56 (broad s, 1H, \(OH\)), 1.90 (m, 1H, \(CHCH_3\)), 1.98 (t, \(J = 2.7 \text{ Hz}\), 1H, \(HCC\)), 2.21 (ddd, \(J = 16.8, 6.4, 2.7 \text{ Hz}\), 1H, \(CCHH\)), 2.29 (ddd, \(J = 16.8, 6.2, 2.7 \text{ Hz}\), 1H, \(CCHH\)), 3.59 (d, \(J = 6.1 \text{ Hz}\), 2H, \(CH_2O\));  \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 16.0, 22.2, 34.8, 66.8, 69.6, 82.6;  **IR** (ef) 3409, 2961, 2922, 2117, 1461, 1430, 1037, 651 cm\(^{-1}\);  MS (Cl) \(m/z\) (rel. intensity) 99 (M + H, 100).
6.2.12 (±)-2,4-Dimethyl-4,5-dihydrofuran [(±)-61]²²,²³

![Chemical structure of (±)-61](image)

The alcohol (±)-69 (3.95 g, 40.3 mmol) and sodium amide (150 mg, 3.84 mmol) were heated at reflux for 2 h. Direct distillation of the reaction mixture afforded the exocyclic double bond isomer (±)-68 as a colourless liquid (2.60 g, 66%). A sample of this material (1.20 g, 12.2 mmol) was heated at reflux for 16 h and then distilled to afford the title compound (±)-61 (1.04 g, 87%) as a colourless liquid. B.p. -100 °C, -760 mm Hg; ¹H NMR (400 MHz, C₆D₆) δ 0.84 (d, J = 6.6 Hz, 3H, Me-4), 1.68 (apparent t, J = 1.5 Hz, 3H, Me-2), 2.76 (m, 1H, H-4), 3.71 (dd, J = 8.7, 6.5 Hz, 1H, H-5), 4.21 (dd, J = 9.5, 8.6 Hz, 1H, H-5), 4.43 (m, 1H, H-3); ¹³C NMR (101 MHz, C₆D₆) δ 13.6, 20.9, 37.9, 77.2, 101.4, 155.0; IR (ef) 2961, 2875, 1674, 1453, 1383, 1243, 1043, 1008, 886 cm⁻¹. MS (CI) m/z (rel. intensity) 99 (M + H, 100).

6.2.13 (±)-Xyloketal D [(±)-4], (±)-2,6-epi-Xyloketal D [(±)-26] and the Diastereoisomeric (±)-Spiroacetals [(±)-117] and [(±)-118]⁹

![Chemical structures of (±)-4, (±)-26, (±)-117/118](image)

**Method A:** To a solution of the Mannich base 104 (177 mg, 0.704 mmol) in benzene (7 mL) at room temperature were added the dihydrofuran (±)-61 (207 mg, 2.11 mmol) and methyl iodide (46 µL, 0.74 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base 104 had undergone complete
reaction (5 days). The reaction mixture was then cooled to room temperature, filtered with ether (7 mL) and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (40:1) as the eluant afforded a mixture (11:1:3:3) of the *title compounds* (±)-4, (±)-26, (±)-117 and (±)-118 (99 mg, 54%) as a yellow oil. Further purification by flash chromatography using hexanes:ether (4:1) as the eluant on TLC grade silica gel afforded an inseparable mixture (dr = 11:1) of the *title compounds* (±)-4 and (±)-26 as a pale cream solid and an inseparable mixture (dr = 1:1) of the *title compounds* (±)-117 and (±)-118 as a pale cream solid.

**Method B:** To a solution of the Mannich base 106 (255 mg, 0.706 mmol) in benzene (7 mL) at room temperature were added the dihydrofuran (±)-61 (207 mg, 2.11 mmol) and methyl iodide (46 μL, 0.74 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base 106 had undergone complete reaction (5 days). The reaction mixture was then cooled to room temperature, filtered with ether (7 mL) and concentrated in vacuo. Purification by flash chromatography using dichloromethane as the eluant afforded a mixture (11:1:3:3) of the *title compounds* (±)-4, (±)-26, (±)-117 and (±)-118 (86 mg, 47%) as a yellow oil. Further purification by flash chromatography using hexanes:ether (4:1) as the eluant on TLC grade silica gel afforded an inseparable mixture (dr = 11:1) of the *title compounds* (±)-4 and (±)-26 as a pale cream solid and an inseparable mixture (dr = 1:1) of the *title compounds* (±)-117 and (±)-118 as a pale cream solid.

*Title compound* (±)-4: Recrystallization of the *title compounds* (±)-4 and (±)-26 from petroleum ether, on slow evaporation of the solvent, afforded an analytically pure
sample of (±)-xyloketal D [(±)-4]. \( R_f = 0.24 \), hexanes:ether (14:1); **M.p.** 66-67 °C, petroleum ether (lit. 82 °C, ether); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.08 (d, \( J = 6.5 \) Hz, 3H, Me-11), 1.52 (s, 3H, Me-10), 1.98 (dd, \( J = 11.3, 6.3, 1.2 \) Hz, 1H, H-6), 2.06 (m, 1H, H-5), 2.53 (s, 3H, Me-17), 2.71 (dd, \( J = 17.9, 6.2 \) Hz, 1H, H-7), 2.96 (d, \( J = 18.0 \) Hz, 1H, H-7), 3.56 (apparent t, \( J = 8.4 \) Hz, 1H, H-4), 4.20 (apparent t, \( J = 8.3 \) Hz, 1H, H-4), 6.36 (d, \( J = 8.9 \) Hz, 1H, H-15), 7.52 (d, \( J = 8.9 \) Hz, 1H, H-14), 13.10 (s, 1H, OH); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 15.8, 18.0, 22.7, 26.1, 35.1, 47.0, 74.3, 106.1, 108.3, 108.8, 113.1, 130.0, 159.5, 162.9, 202.7; IR (ef) 3399, 2968, 2898, 1621, 1491, 1421, 1382, 1370, 1332, 1272, 1117, 1070, 1006 cm\(^{-1}\); MS (CI) \( m/z \) (rel. intensity) 263 (M + H, 100) **Anal.** Calcd. for C\(_{15}\)H\(_{18}\)O\(_4\): C, 68.68; H, 6.92. Found: C, 68.88; H, 6.85.

**Title compound (±)-26:** \(^1\)H NMR [400 MHz, CDCl\(_3\) (additional signals observed for the title compound (±)-26)] \( \delta \) 0.80 (d, \( J = 7.1 \) Hz, 3H, Me-11), 3.68 (q, \( J = 5.0 \) Hz, 1H, H-4).

**Title compounds (±)-117 and (±)-118 (dr = 1:1):** Recrystallization of the title compounds (±)-117 and (±)-118 from petroleum ether, on slow evaporation of the solvent, afforded analytically pure colourless needles. \( R_f = 0.32 \), hexanes:ether (4:1); **M.p.** 57-59 °C, petroleum ether; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.10 (d, \( J = 6.6 \) Hz, 3H, Me-11), 1.18 (d, \( J = 6.6 \) Hz, 3H, Me-11), 1.55 (dd, \( J = 12.8, 9.5 \) Hz, 1H, H-6), 2.00 (m, 5H, \( 2 \times H-5, H-6 and 2 \times H-7 \)), 2.28 (dd, \( J = 13.4, 9.5 \) Hz, 1H, H-6), 2.36 (dd, \( J = 12.9, 7.3 \) Hz, 1H, H-6), 2.46 (m, 1H, H-7), 2.54 (s, 3H, Me-17), 2.55 (s, 3H, Me-17), 2.78 (m, 5H, H-7 and 4 × H-8), 3.54 (t, \( J = 7.7 \) Hz, 1H, H-4), 3.64 (t, \( J = 8.4 \) Hz, 1H, H-4), 4.09 (t, \( J = 7.9 \) Hz, 1H, H-4), 4.21 (t, \( J = 7.9 \) Hz, 1H, H-4), 6.34 (d, \( J = 8.9 \) Hz, 1H, H-15), 6.37
(d, J = 9.0 Hz, 1H, H-15), 7.50 (d, J = 8.9 Hz, 1H, H-14), 7.51 (d, J = 8.9 Hz, 1H, H-14), 13.01 (s, 1H, OH), 13.02 (s, 1H, OH); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 16.3, 16.5, 17.6, 18.0, 26.2, 29.3, 29.6, 31.9, 33.0, 45.2, 45.3, 75.0, 75.4, 108.1, 108.9, 109.0, 110.0, 110.1, 113.16, 113.24, 129.58, 129.62, 159.6, 162.2, 202.7, 202.8; IR (ef) 3423, 2958, 2878, 1626, 1488, 1419, 1369, 1331, 1270, 1247, 1136, 1060, 1018, 853 cm\(^{-1}\); MS (Cl) \(m/z\) (rel. intensity) 263 (M + H, 100), 111 (12); Analytical. Calcd for C\(_{15}\)H\(_{18}\)O\(_4\): C, 68.68; H, 6.92. Found: C, 68.47; H, 7.16.

**6.2.14 (R)-Phenylglycinol\([\pm]-119\)\(^{149, 150}\)**

To a suspension of lithium aluminum hydride (11.0 g, 289 mmol) in tetrahydrofuran (500 mL) at 0 °C was added (R)-phenylglycine (20.0 g, 132 mmol) in portions over 1 h. The resultant mixture was heated at reflux for 8 h and then stirred for an additional 15 h at room temperature. A saturated aqueous solution of potassium carbonate (70 mL) was then added slowly over 3 h. The resultant mixture was filtered, the filter-cake was washed ethyl acetate (3 \(\times\) 150 mL) and the combined filtrates were concentrated in vacuo. Purification by recrystallization from ethyl acetate:hexanes (3:1) afforded the title compound \((\pm)-119\) (14.6 g, 80%) as yellow needles. M.p. 74-75 °C, ethyl acetate:hexanes (lit\(^{150}\) 75-78 °C); \([\alpha]\)_D\(^{20}\) = –29.8 (c 6.37, methanol) [lit\(^{150}\) \([\alpha]\)_D\(^{20}\) = –27.1 (c 5.36, methanol)]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.13 (s, 3H, OH and NH\(_2\)), 3.56 (dd, J = 10.8, 8.3 Hz, 1H, CHHOH), 3.74 (dd, J = 10.8, 4.4 Hz, 1H, CHHOH), 4.04 (dd, J = 8.3, 4.4 Hz, 1H, NCH), 7.30 (m, 5H, ArH); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\)
57.6, 68.3, 126.7, 127.8, 128.9, 143.0; IR (KBr) 3330, 3058, 2910, 1605, 1496, 1453, 1198, 1079, 1050 cm⁻¹; MS (Cl) m/z (rel. intensity) 138 (M + H, 100).

6.2.15 (2R)-N-[(1R)-1-Phenyl-2-hydroxyethyl]-2-methyl-4-pentynamide [(−)-120] and (2S)-N-[(1R)-1-Phenyl-2-hydroxyethyl]-2-methyl-4-pentynamide [(−)-121]⁵²,⁵³

To a solution of the racemic carboxylic acid (±)-70 (5.40 g, 48.2 mmol) in dichloromethane (100 mL) at 0 °C were added oxalyl chloride (5.5 mL, 58 mmol) and N,N-dimethylformamide (2 drops). The resultant solution was allowed to warm to room temperature over 2 h and then was concentrated in vacuo to afford the corresponding acid chloride. A solution of this acid chloride in dichloromethane (50 mL) was then added to a stirred solution of (R)-phenylglycinol [(R)-119] (6.60 g, 48.2 mmol) and triethylamine (8.0 mL, 58 mmol) in dichloromethane (150 mL) at 0 °C. The resultant solution was allowed to warm to room temperature over 16 h and then water (50 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using petroleum ether:ethyl acetate (1:2) as the eluant afforded the title compounds (−)-120 (4.01 g, 36%) and (−)-121 (3.82 g, 34%) as white solids.

*Title compound* (−)-120: *R*ₚ = 0.37, petroleum ether:ethyl acetate (1:2); M.p. 78-82 °C, petroleum ether:ethyl acetate; [α]D²⁴ = −63 (c 1.31, chloroform); ¹H NMR (400 MHz, CDCl₃) δ 1.25 (d, J = 6.5 Hz, 3H, Me), 2.07 (t, J = 2.6 Hz, 1H, HCC), 2.30 (broad
s, 1H, OH), 2.38 (m, 1H, CHCO), 2.51 (m, 2H, CH₂), 3.91 (d, J = 4.6 Hz, 2H, CH₂O), 5.10 (dt, J = 7.0, 4.8 Hz, 1H, PhCH), 6.32 (broad d, J = 4.9 Hz, 1H, NH), 7.34 (m, 5H, ArH); ¹³C NMR (101 MHz, CDCl₃) δ 17.1, 23.1, 40.4, 55.6, 66.2, 70.2, 82.1, 126.6, 127.7, 128.7, 138.9, 175.0; IR (ef) 3314, 3286, 1650, 1544, 1052, 758, 702 cm⁻¹; MS (Cl) m/z (rel. intensity) 232 (M + H, 100); Anal. Calcd. for C₁₄H₁₇NO₂: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.86; H, 7.35; N, 5.87.

Title compound (−)-121: Rᵢ = 0.27, petroleum ether:ethyl acetate (1:2); M.p. 90-93 °C, petroleum ether:ethyl acetate; [α]₂₃° = −33 (c 0.80, chloroform); ¹H NMR (400 MHz, CDCl₃) δ 1.29 (d, J = 6.7 Hz, 3H, Me), 2.01 (t, J = 2.7 Hz, 1H, HCC), 2.32 (broad s, 1H, OH), 2.39 (ddd, J = 15.8, 6.2, 2.8 Hz, 1H, CCHH), 2.51 (m, 2H, CCHH and CHCO), 3.90 (m, 2H, CH₂O), 5.08 (dt, J = 6.8, 4.8 Hz, 1H, PhCH), 6.37 (d, J = 4.3 Hz, 1H, NH), 7.32 (m, 5H, ArH); ¹³C NMR (126 MHz, CDCl₃) δ 17.2, 23.2, 40.4, 55.8, 66.4, 70.4, 82.0, 126.7, 127.8, 128.8, 138.8, 175.1; IR (ef) 3282, 1645, 1545, 1038, 699 cm⁻¹; MS (Cl) m/z (rel. intensity) 232 (M + H, 100); Anal. Calcd. for C₁₄H₁₇NO₂: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.45; H, 7.54; N, 5.77.

6.2.16 X-Ray Crystallographic Analysis of (2RS)-N-[{(1R)-1-Phenyl-2-hydroxyethyl}-2-methyl-4-pentynamide [(−)-121]*

A single crystal of the amide (−)-121, a colourless needle, was mounted on a glass fibre using epoxy adhesive. The data for this crystal was acquired at 293 K on a Rigaku RAXIS-RAPID curve image plate area detector with graphite monochromatic Cu Kα radiation. Indexing for the crystal was performed using three, 5° oscillations that were

(*) The data for this X-ray crystal structure was obtained by Dr. K. Jantunen (Simon Fraser University). The X-ray crystal structure was solved by Mr. M. Katz (Simon Fraser University).
exposed for 425 seconds. The following data range was collected: $7.95^\circ \leq 2\theta \leq 144.56^\circ$ and a total of twenty seven images were collected. A sweep of data was then collected using $\omega$ scans from $50.0^\circ$ to $230.0^\circ$ in $20^\circ$ steps at $\chi = 50.0^\circ$ and $\phi = 0.0^\circ$. A second sweep of data was collected using $\omega$ scans from $50.0^\circ$ to $230.0^\circ$ in $20^\circ$ steps at $\chi = 50.0^\circ$ and $\phi = 90.0^\circ$. A final sweep of data was collected using $\omega$ scans from $50.0^\circ$ to $230.0^\circ$ in $20^\circ$ steps at $\chi = 50.0^\circ$ and $\phi = 180.0^\circ$. The exposure rate was 90 sec$^\circ$ and in each case, the crystal to detector distance was 127.40 mm. For the amide (−)-121, coordinates and anisotropic displacement parameters for the non-carbon and hydrogen atoms were refined; carbon atoms, not including the phenyl ring, were refined using isotropic thermal parameters. Hydrogen atoms were placed in calculated positions (C-H 0.95 Å) or detected and their coordinate shifts were linked with those of the respective carbon, nitrogen or oxygen atoms during refinement. Isotropic thermal parameters for the hydrogen atoms were initially assigned proportionately to the equivalent isotropic thermal parameters of their respective carbon, nitrogen or oxygen atoms. Subsequently, the isotropic thermal parameters for the C-H hydrogen atoms were constrained to have identical shifts during refinement. The programs used for all absorption corrections, data reduction, and processing of the amide (−)-121 were from Rigaku CrystalClear package. The structure was refined using CRYSTALS. An ORTEP representation of the amide (−)-121 is provided below (Figure 6.2.16.1). Crystallographic data, fractional atomic coordinates and equivalent isotropic thermal displacement parameters, selected bond lengths as well as selected bond angles for the amide (−)-121 are also listed below (Table 6.2.16.1, Table 6.2.16.2, Table 6.2.16.3 and Table 6.2.16.4, respectively).
Figure 6.2.16.1 ORTEP representation of the amide [(-)-121] (the thermal ellipsoids are drawn at a 50% probability level).

Table 6.2.16.1 Summary of Crystallographic Data for the Amide [(-)-121]

<table>
<thead>
<tr>
<th>Empirical Formula</th>
<th>C_{14}H_{17}NO_{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>$FW$ (g mol$^{-1}$)</td>
<td>231.29</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>293</td>
</tr>
<tr>
<td>Wavelength (Cu $K\alpha$, Å)</td>
<td>1.5419</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P212121</td>
</tr>
<tr>
<td>$a$ (Å)</td>
<td>5.084</td>
</tr>
<tr>
<td>$b$ (Å)</td>
<td>13.729</td>
</tr>
<tr>
<td>$c$ (Å)</td>
<td>18.937</td>
</tr>
<tr>
<td>$\alpha$ (°)</td>
<td>90</td>
</tr>
<tr>
<td>$\beta$ (°)</td>
<td>90</td>
</tr>
<tr>
<td>$\gamma$ (°)</td>
<td>90</td>
</tr>
</tbody>
</table>
Reflections collected 2334
Independent reflections 2334
Reflections observed \([I > 2.0\sigma(I)]\) 805
Goodness-of-fit on \(F\) 1.0142

\(R_1, R_w [I > 2.0\sigma(I)]\) 0.0866, 0.1370

Table 6.2.16.2 Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters \([U(\text{iso}), \AA^2]\) for the Amide \((-)\) 121

<table>
<thead>
<tr>
<th>Atom</th>
<th>(X)</th>
<th>(Y)</th>
<th>(Z)</th>
<th>(U(\text{iso}))</th>
<th>Occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>1.1607(16)</td>
<td>0.5001(7)</td>
<td>-0.1155(4)</td>
<td>0.0828</td>
<td>1</td>
</tr>
<tr>
<td>O2</td>
<td>0.5838(14)</td>
<td>0.7086(5)</td>
<td>-0.0130(4)</td>
<td>0.0668</td>
<td>1</td>
</tr>
<tr>
<td>N1</td>
<td>0.7319(17)</td>
<td>0.5297(6)</td>
<td>-0.0890(5)</td>
<td>0.0567</td>
<td>1</td>
</tr>
<tr>
<td>C1</td>
<td>0.586(4)</td>
<td>0.2885(11)</td>
<td>-0.3186(7)</td>
<td>0.117</td>
<td>1</td>
</tr>
<tr>
<td>C2</td>
<td>0.688(4)</td>
<td>0.3245(10)</td>
<td>-0.2721(8)</td>
<td>0.0975</td>
<td>1</td>
</tr>
<tr>
<td>C3</td>
<td>0.836(3)</td>
<td>0.3656(9)</td>
<td>-0.2109(7)</td>
<td>0.1114</td>
<td>1</td>
</tr>
<tr>
<td>C4</td>
<td>0.829(3)</td>
<td>0.4761(9)</td>
<td>-0.2076(5)</td>
<td>0.0734</td>
<td>1</td>
</tr>
<tr>
<td>C5</td>
<td>0.998(3)</td>
<td>0.5227(9)</td>
<td>-0.2627(6)</td>
<td>0.105</td>
<td>1</td>
</tr>
<tr>
<td>C6</td>
<td>0.931(3)</td>
<td>0.5037(10)</td>
<td>-0.1337(6)</td>
<td>0.0731</td>
<td>1</td>
</tr>
<tr>
<td>C7</td>
<td>0.791(2)</td>
<td>0.5486(7)</td>
<td>-0.0131(5)</td>
<td>0.0572</td>
<td>1</td>
</tr>
<tr>
<td>C8</td>
<td>0.576(2)</td>
<td>0.6143(7)</td>
<td>0.0186(6)</td>
<td>0.0589</td>
<td>1</td>
</tr>
<tr>
<td>C9</td>
<td>0.803(2)</td>
<td>0.4554(8)</td>
<td>0.0298(5)</td>
<td>0.059(3)</td>
<td>1</td>
</tr>
<tr>
<td>C10</td>
<td>0.618(2)</td>
<td>0.3799(8)</td>
<td>0.0181(5)</td>
<td>0.062(4)</td>
<td>1</td>
</tr>
<tr>
<td>C11</td>
<td>0.624(2)</td>
<td>0.2955(8)</td>
<td>0.0602(6)</td>
<td>0.076(4)</td>
<td>1</td>
</tr>
<tr>
<td>C12</td>
<td>0.813(2)</td>
<td>0.2861(8)</td>
<td>0.1114(6)</td>
<td>0.070(4)</td>
<td>1</td>
</tr>
<tr>
<td>C13</td>
<td>0.987(3)</td>
<td>0.3593(8)</td>
<td>0.1248(6)</td>
<td>0.074(4)</td>
<td>1</td>
</tr>
<tr>
<td>C14</td>
<td>0.985(2)</td>
<td>0.4429(8)</td>
<td>0.0842(5)</td>
<td>0.063(3)</td>
<td>1</td>
</tr>
<tr>
<td>Atom</td>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td>U (iso)</td>
<td>Occupancy</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>H11</td>
<td>0.4808</td>
<td>0.258</td>
<td>-0.3629</td>
<td>0.174(11)</td>
<td>1</td>
</tr>
<tr>
<td>H21</td>
<td>0.448</td>
<td>0.7431</td>
<td>-0.0125</td>
<td>0.129(11)</td>
<td>1</td>
</tr>
<tr>
<td>H31</td>
<td>1.013</td>
<td>0.3439</td>
<td>-0.2123</td>
<td>0.224(11)</td>
<td>1</td>
</tr>
<tr>
<td>H32</td>
<td>0.7531</td>
<td>0.3416</td>
<td>-0.1694</td>
<td>0.224(11)</td>
<td>1</td>
</tr>
<tr>
<td>H41</td>
<td>0.6451</td>
<td>0.4913</td>
<td>-0.2159</td>
<td>0.118(11)</td>
<td>1</td>
</tr>
<tr>
<td>H51</td>
<td>1.0148</td>
<td>0.5942</td>
<td>-0.248</td>
<td>0.199(11)</td>
<td>1</td>
</tr>
<tr>
<td>H52</td>
<td>1.1597</td>
<td>0.4935</td>
<td>-0.2595</td>
<td>0.200(11)</td>
<td>1</td>
</tr>
<tr>
<td>H53</td>
<td>0.9127</td>
<td>0.52</td>
<td>-0.3058</td>
<td>0.199(11)</td>
<td>1</td>
</tr>
<tr>
<td>H71</td>
<td>0.9562</td>
<td>0.5807</td>
<td>-0.0147</td>
<td>0.073(11)</td>
<td>1</td>
</tr>
<tr>
<td>H81</td>
<td>0.6062</td>
<td>0.6192</td>
<td>0.0681</td>
<td>0.089(11)</td>
<td>1</td>
</tr>
<tr>
<td>H82</td>
<td>0.4141</td>
<td>0.5823</td>
<td>0.0064</td>
<td>0.089(11)</td>
<td>1</td>
</tr>
<tr>
<td>H101</td>
<td>0.4935</td>
<td>0.3868</td>
<td>-0.0151</td>
<td>0.065(11)</td>
<td>1</td>
</tr>
<tr>
<td>H111</td>
<td>0.5068</td>
<td>0.2462</td>
<td>0.0501</td>
<td>0.081(11)</td>
<td>1</td>
</tr>
<tr>
<td>H121</td>
<td>0.8231</td>
<td>0.2312</td>
<td>0.1415</td>
<td>0.071(11)</td>
<td>1</td>
</tr>
<tr>
<td>H131</td>
<td>1.1171</td>
<td>0.3559</td>
<td>0.1614</td>
<td>0.078(11)</td>
<td>1</td>
</tr>
<tr>
<td>H141</td>
<td>1.1105</td>
<td>0.4899</td>
<td>0.0896</td>
<td>0.065(11)</td>
<td>1</td>
</tr>
<tr>
<td>H12</td>
<td>0.6597</td>
<td>0.5866</td>
<td>-0.1073</td>
<td>0.069</td>
<td>0.5</td>
</tr>
<tr>
<td>H13</td>
<td>0.6066</td>
<td>0.4804</td>
<td>-0.09</td>
<td>0.069</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 6.2.16.3 Bond Lengths (Å) for the Amide [(-)-121]

<table>
<thead>
<tr>
<th>Atoms</th>
<th>Bond Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1-C6</td>
<td>1.217(13)</td>
</tr>
<tr>
<td>O2-C8</td>
<td>1.427(10)</td>
</tr>
<tr>
<td>O2-H21</td>
<td>0.838</td>
</tr>
<tr>
<td>N1-C6</td>
<td>1.369(12)</td>
</tr>
<tr>
<td>N1-C7</td>
<td>1.490(11)</td>
</tr>
<tr>
<td>N1-H12</td>
<td>0.93</td>
</tr>
<tr>
<td>N1-H13</td>
<td>0.93</td>
</tr>
<tr>
<td>C1-C2</td>
<td>1.135(16)</td>
</tr>
<tr>
<td>C1-H11</td>
<td>1.078</td>
</tr>
<tr>
<td>Atoms</td>
<td>Bond Length (Å)</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
</tr>
<tr>
<td>C2-C3</td>
<td>1.493(18)</td>
</tr>
<tr>
<td>C3-C4</td>
<td>1.519(14)</td>
</tr>
<tr>
<td>C3-H31</td>
<td>0.95</td>
</tr>
<tr>
<td>C3-H32</td>
<td>0.95</td>
</tr>
<tr>
<td>C4-C5</td>
<td>1.494(14)</td>
</tr>
<tr>
<td>C4-C6</td>
<td>1.541(15)</td>
</tr>
<tr>
<td>C4-H41</td>
<td>0.972</td>
</tr>
<tr>
<td>C5-H51</td>
<td>1.024</td>
</tr>
<tr>
<td>C5-H52</td>
<td>0.915</td>
</tr>
<tr>
<td>C5-H53</td>
<td>0.926</td>
</tr>
<tr>
<td>C7-C8</td>
<td>1.539(13)</td>
</tr>
<tr>
<td>C7-C9</td>
<td>1.517(13)</td>
</tr>
<tr>
<td>C7-H71</td>
<td>0.949</td>
</tr>
<tr>
<td>C8-H81</td>
<td>0.953</td>
</tr>
<tr>
<td>C8-H82</td>
<td>0.96</td>
</tr>
<tr>
<td>C9-C10</td>
<td>1.417(13)</td>
</tr>
<tr>
<td>C9-C14</td>
<td>1.395(13)</td>
</tr>
<tr>
<td>C10-C11</td>
<td>1.408(13)</td>
</tr>
<tr>
<td>C10-H101</td>
<td>0.896</td>
</tr>
<tr>
<td>C11-C12</td>
<td>1.370(13)</td>
</tr>
<tr>
<td>C11-H111</td>
<td>0.923</td>
</tr>
<tr>
<td>C12-C13</td>
<td>1.364(14)</td>
</tr>
<tr>
<td>C12-H121</td>
<td>0.947</td>
</tr>
<tr>
<td>C13-C14</td>
<td>1.382(13)</td>
</tr>
<tr>
<td>C13-H131</td>
<td>0.958</td>
</tr>
<tr>
<td>C14-H141</td>
<td>0.914</td>
</tr>
</tbody>
</table>

Table 6.2.16.4  Bond Angles (°) for the Amide [(−)-121]

<table>
<thead>
<tr>
<th>Atoms</th>
<th>Bond Angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C8-O2-H21</td>
<td>119</td>
</tr>
<tr>
<td>Atoms</td>
<td>Bond Angles (°)</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>C6-N1-C7</td>
<td>119.5(9)</td>
</tr>
<tr>
<td>C6-N1-H12</td>
<td>106.3</td>
</tr>
<tr>
<td>C7-N1-H12</td>
<td>107</td>
</tr>
<tr>
<td>C6-N1-H13</td>
<td>107.7</td>
</tr>
<tr>
<td>C7-N1-H13</td>
<td>106.6</td>
</tr>
<tr>
<td>H12-N1-H13</td>
<td>109.5</td>
</tr>
<tr>
<td>C2-C1-H11</td>
<td>176.5</td>
</tr>
<tr>
<td>C1-C2-C3</td>
<td>175.7(20)</td>
</tr>
<tr>
<td>C2-C3-C4</td>
<td>113.5(11)</td>
</tr>
<tr>
<td>C2-C3-H31</td>
<td>109.8</td>
</tr>
<tr>
<td>C4-C3-H31</td>
<td>109.6</td>
</tr>
<tr>
<td>C2-C3-H32</td>
<td>106.7</td>
</tr>
<tr>
<td>C4-C3-H32</td>
<td>107.7</td>
</tr>
<tr>
<td>H31-C3-H32</td>
<td>109.5</td>
</tr>
<tr>
<td>C3-C4-C5</td>
<td>112.7(11)</td>
</tr>
<tr>
<td>C3-C4-C6</td>
<td>106.0(10)</td>
</tr>
<tr>
<td>C5-C4-C6</td>
<td>109.6(11)</td>
</tr>
<tr>
<td>C3-C4-H41</td>
<td>103.2</td>
</tr>
<tr>
<td>C5-C4-H41</td>
<td>110.5</td>
</tr>
<tr>
<td>C6-C4-H41</td>
<td>114.7</td>
</tr>
<tr>
<td>C4-C5-H51</td>
<td>105.6</td>
</tr>
<tr>
<td>C4-C5-H52</td>
<td>106.4</td>
</tr>
<tr>
<td>H51-C5-H52</td>
<td>109.2</td>
</tr>
<tr>
<td>C4-C5-H53</td>
<td>109.1</td>
</tr>
<tr>
<td>H51-C5-H53</td>
<td>108.4</td>
</tr>
<tr>
<td>H52-C5-H53</td>
<td>117.6</td>
</tr>
<tr>
<td>C4-C6-N1</td>
<td>112.2(11)</td>
</tr>
<tr>
<td>C4-C6-O1</td>
<td>124.8(12)</td>
</tr>
<tr>
<td>N1-C6-O1</td>
<td>123.0(12)</td>
</tr>
<tr>
<td>N1-C7-C8</td>
<td>109.5(9)</td>
</tr>
<tr>
<td>Atoms</td>
<td>Bond Angles (°)</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>N1-C7-C9</td>
<td>112.2(9)</td>
</tr>
<tr>
<td>C8-C7-C9</td>
<td>108.3(9)</td>
</tr>
<tr>
<td>N1-C7-H71</td>
<td>103.2</td>
</tr>
<tr>
<td>C8-C7-H71</td>
<td>111.7</td>
</tr>
<tr>
<td>C9-C7-H71</td>
<td>112</td>
</tr>
<tr>
<td>C7-C8-O2</td>
<td>110.4(8)</td>
</tr>
<tr>
<td>C7-C8-H81</td>
<td>108</td>
</tr>
<tr>
<td>O2-C8-H81</td>
<td>110.1</td>
</tr>
<tr>
<td>C7-C8-H82</td>
<td>104.3</td>
</tr>
<tr>
<td>O2-C8-H82</td>
<td>109.8</td>
</tr>
<tr>
<td>H81-C8-H82</td>
<td>114</td>
</tr>
<tr>
<td>C7-C9-C10</td>
<td>120.4(10)</td>
</tr>
<tr>
<td>C7-C9-C14</td>
<td>121.7(11)</td>
</tr>
<tr>
<td>C10-C9-C14</td>
<td>117.8(11)</td>
</tr>
<tr>
<td>C9-C10-C11</td>
<td>119.8(11)</td>
</tr>
<tr>
<td>C9-C10-H101</td>
<td>120</td>
</tr>
<tr>
<td>C11-C10-H101</td>
<td>120.1</td>
</tr>
<tr>
<td>C10-C11-C12</td>
<td>119.7(11)</td>
</tr>
<tr>
<td>C10-C11-H111</td>
<td>118.1</td>
</tr>
<tr>
<td>C12-C11-H111</td>
<td>122.1</td>
</tr>
<tr>
<td>C11-C12-C13</td>
<td>121.2(12)</td>
</tr>
<tr>
<td>C11-C12-H121</td>
<td>122.7</td>
</tr>
<tr>
<td>C13-C12-H121</td>
<td>116</td>
</tr>
<tr>
<td>C12-C13-C14</td>
<td>120.2(12)</td>
</tr>
<tr>
<td>C12-C13-H131</td>
<td>123.2</td>
</tr>
<tr>
<td>C14-C13-H131</td>
<td>116.6</td>
</tr>
<tr>
<td>C9-C14-C13</td>
<td>121.3(11)</td>
</tr>
<tr>
<td>C9-C14-H141</td>
<td>117.4</td>
</tr>
<tr>
<td>C13-C14-H141</td>
<td>121.2</td>
</tr>
</tbody>
</table>
6.2.17 (2R)-2-Methylpent-4-ynoic Acid [(2R)-70]52,54

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{O} & \quad \text{Me}
\end{align*}
\]

(2R)-70

To a solution of the amide (−)-120 (5.44 g, 23.5 mmol) in \( p \)-dioxane (60 mL) at room temperature was added sulfuric acid (3 M, 60 mL). The resultant solution was heated at reflux for 7 h and then was cooled to 0 °C. The reaction mixture was basified to pH ~10 with an aqueous solution of sodium hydroxide (50% w/w), diluted with water (50 mL) and extracted with dichloromethane (3 × 50 mL). The aqueous layer was acidified to pH ~2 with sulfuric acid (3 M) and then extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. Purification by distillation at reduced pressure afforded the title compound (2R)-70 (2.01 g, 76%) as a colourless oil. Rf = 0.48, hexanes:ethyl acetate (1:2); B.p. 103-106 °C, 5 mm Hg; \([\alpha]_D^{20} = + 6.5 (c 1.50, \text{chloroform})\); \(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 1.31 (d, \text{J} = 7.1 \text{ Hz, 3H, CH}_3), 2.02 (t, \text{J} = 2.7 \text{ Hz, 1H, HCC}), 2.40 (m, 1H, CHH), 2.57 (m, 1H, CHH), 2.71 (m, 1H, CHCO₂H), 10.73 (m, 1H, OH); \(^{13}\text{C} \text{NMR} (126 \text{ MHz, CDCl}_3) \delta 16.1, 22.3, 38.6, 70.1, 81.1, 181.3; \text{IR (ef)} 3293, 2978, 2668, 1701, 1295, 1240, 1200, 940, 659 \text{ cm}^{-1}; \text{MS (Cl)} m/z (\text{rel. intensity}) 113 (M + H, 100).

6.2.18 (2S)-2-Methylpent-4-ynoic Acid [(2S)-70]52,54

\[
\begin{align*}
\text{Me} & \quad \text{OH} \\
\text{O} & \quad \text{Me}
\end{align*}
\]

(2S)-70

To a solution of the amide (−)-121 (4.56 g, 19.7 mmol) in \( p \)-dioxane (50 mL) at room temperature was added sulfuric acid (3 M, 50 mL). The resultant solution was heated at reflux for 7 h and then was cooled to 0 °C. The reaction mixture was basified to
pH ~10 with an aqueous solution of sodium hydroxide (50% w/w), diluted with water (50 mL) and extracted with dichloromethane (3 × 50 mL). The aqueous layer was acidified to pH ~2 with sulfuric acid (3 M) and then extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by distillation at reduced pressure afforded the title compound (2S)-70 (1.91 g, 86%) as a colourless oil. R<sub>f</sub> = 0.48, hexanes:ethyl acetate (1:2); B.p. 103-106 °C, 5 mm Hg; [α]<sub>D</sub> = −6.5 (c 1.50, chloroform); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.31 (d, <i>J</i> = 7.1 Hz, 3H, <i>CH<sub>3</sub></i>), 2.02 (t, <i>J</i> = 2.7 Hz, 1H, <i>HCC</i>), 2.40 (m, 1H, <i>CHH</i>), 2.57 (m, 1H, <i>CHH</i>), 2.71 (m, 1H, <i>CHCO<sub>2</sub>H</i>), 10.73 (m, 1H, <i>OH</i>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 16.1, 22.3, 38.6, 70.1, 81.1, 181.3; IR (ef) 3293, 2978, 2668, 1701, 1295, 1240, 940, 659 cm<sup>−1</sup>; MS (Cl) m/z (rel. intensity) 113 (M + H, 100).

6.2.19 (2R)-2-Methylpent-4-yn-1-ol [(2R)-69]<sup>55,56</sup>

![Structure of (2R)-69](image)

To a suspension of lithium aluminum hydride (0.79 g, 20.8 mmol) in tetrahydrofuran (35 mL) at 0 °C was added a solution of the carboxylic acid (2R)-70 (1.17 g, 10.4 mmol) in tetrahydrofuran (10 mL) and the resultant suspension was stirred at room temperature for 16 h. Water (0.8 mL), an aqueous solution of sodium hydroxide (2 M, 0.8 mL) and water (2.4 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (100 mL) and the combined organic filtrates were concentrated in vacuo. Purification by distillation at reduced pressure afforded the title compound (2R)-69 (0.91 g, 89%) as a colourless oil. R<sub>f</sub> = 0.55, hexanes:ethyl acetate (1:2); B.p. 61-66 °C, ~20 mm Hg; [α]<sub>D</sub> = +10.9 (c 1.10,
chloroform); $^1$H NMR (400 MHz, CDCl₃) $\delta$ 1.01 (d, $J = 6.9$ Hz, 3H, CH₃), 1.56 (broad s, 1H, OH), 1.90 (m, 1H, CHCH₃), 1.98 (t, $J = 2.7$ Hz, 1H, HCC), 2.21 (ddd, $J = 16.8$, 6.4, 2.7 Hz, 1H, CCHH), 2.29 (ddd, $J = 16.8$, 6.2, 2.7 Hz, 1H, CCHH), 3.59 (d, $J = 6.1$ Hz, 2H, CH₂O); $^{13}$C NMR (101 MHz, CDCl₃) $\delta$ 16.0, 22.2, 34.8, 66.8, 69.6, 82.6; IR (ef) 3409, 2961, 2922, 2117, 1461, 1430, 1037, 651 cm⁻¹; MS (Cl) m/z (rel. intensity) 99 (M + H, 100).

6.2.20 (2S)-2-Methylpent-4-yn-1-ol [(2S)-69]$^{55,56}$

![Structure](structure.png)

To a suspension of lithium aluminum hydride (1.07 g, 28.0 mmol) in tetrahydrofuran (35 mL) at 0 °C was added a solution of the carboxylic acid (2S)-70 (1.57 g, 14.0 mmol) in tetrahydrofuran (10 mL) and the resultant suspension was stirred at room temperature for 16 h. Water (1.1 mL), an aqueous solution of sodium hydroxide (2 M, 1.1 mL) and water (3.3 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (100 mL) and the combined organic filtrates were concentrated in vacuo. Purification by distillation at reduced pressure afforded the title compound (2S)-69 (1.17 g, 85%) as a colourless oil. $R_f = 0.55$, hexanes:ethyl acetate (1:2); B.p. 61-66 °C, ~20 mm Hg; $\left[\alpha\right]_{D}^{20} = -11.1$ (c 1.10, chloroform); $^1$H NMR (400 MHz, CDCl₃) $\delta$ 1.01 (d, $J = 6.9$ Hz, 3H, CH₃), 1.56 (broad s, 1H, OH), 1.90 (m, 1H, CHCH₃), 1.98 (t, $J = 2.7$ Hz, 1H, HCC), 2.21 (ddd, $J = 16.8$, 6.4, 2.7 Hz, 1H, CCHH), 2.29 (ddd, $J = 16.8$, 6.2, 2.7 Hz, 1H, CCHH), 3.59 (d, $J = 6.1$ Hz, 2H, CH₂O); $^{13}$C NMR (101 MHz, CDCl₃) $\delta$ 16.0, 22.2, 34.8, 66.8, 69.6, 82.6; IR
To a suspension of sodium hydride (81 mg, 60% w/w in mineral oil, 2.0 mmol, pre-washed with hexanes) in N,N-dimethylformamide (4.0 mL) at 0 °C were added a solution of the alcohol (2R)-69 (181 mg, 1.84 mmol) in tetrahydrofuran (1 mL) and benzyl bromide (230 µL, 1.93 mmol). The resultant mixture was stirred at room temperature for 6 h. The reaction mixture was diluted then with ether (10 mL) and washed with water (3 x 10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes:ether (50:1) as the eluant afforded the title compound (2R)-122 (313 mg, 90%) as a colourless oil. \( R_f = 0.77 \), hexanes:ether (4:1); \( \alpha \)^D + 16.1 (c 1.40, chloroform) [lit.\(^57\) \( \alpha \)^D + 16 (c 1.20, chloroform); lit.\(^58\) \( \alpha \)^D + 16.3 (c 0.95, chloroform)]; \(^1\)H NMR (400 MHz, CDCl\(_3\) ) \( \delta \) 1.03 (d, \( J = 6.8 \) Hz, 3H, Me), 1.95 (t, \( J = 2.6 \) Hz, 1H, HCC), 2.02 (m, 1H, CH\(_2\)CH\(_3\) ), 2.21 (ddd, \( J = 16.7, 6.9, 2.6 \) Hz, 1H, CCHH), 2.35 (ddd, \( J = 16.7, 5.5, 2.7 \) Hz, 1H, CCHH), 3.39 (d, \( J = 6.5 \) Hz, 2H, CH\(_2\)O), 4.52 (s, 2H, OCH\(_2\)Ph), 7.33 (m, 5H, ArH); \(^13\)C NMR (126 MHz, CDCl\(_3\) ) \( \delta \) 16.4, 22.5, 32.9, 69.3, 73.0, 74.1, 82.7, 127.5, 127.5, 128.3, 138.5; IR (ef) 3289, 3031, 2857, 2117, 1496, 1454, 1112, 749 cm\(^{-1}\); MS (Cl) \( m/z \) (rel. intensity) 189 (M + H, 78), 171 (17), 111 (M – Ph, 100).

\(^{57}\)S. \(^{58}\)M. \(^{59}\)S.
6.2.22 (2S)-Benzyl-(2-methylpent-4-ynyl)ether [(2S)-122]

To a suspension of sodium hydride (144 mg, 60% w/w in mineral oil, 1.47 mmol, pre-washed with hexanes) in N,N-dimethylformamide (4.0 mL) at 0 °C were added a solution of the alcohol (2S)-69 (144 mg, 1.47 mmol) in tetrahydrofuran (1 mL) and benzyl bromide (184 μL, 1.54 mmol). The resultant mixture was stirred at room temperature for 6 h. The reaction mixture was diluted then with ether (10 mL) and washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes:ether (50:1) as the eluant afforded the title compound (2S)-122 (248 mg, 90%) as a colourless oil. \( R_f = 0.77 \), hexanes:ether (4:1); \([\alpha]_D^{20} = -15.9 \) (c 1.05, chloroform); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta 1.03 \) (d, \( J = 6.8 \) Hz, 3H, Me), 1.95 (t, \( J = 2.6 \) Hz, 1H, HCC), 2.02 (m, 1H, CHCH\(_3\)), 2.21 (ddd, \( J = 16.7, 6.9, 2.6 \) Hz, 1H, CCHH), 2.35 (ddd, \( J = 16.7, 5.5, 2.7 \) Hz, 1H, CCH\(_2\)), 3.39 (d, \( J = 6.5 \) Hz, 2H, CH\(_2\)O), 4.52 (s, 2H, OCH\(_2\)Ph), 7.33 (m, 5H, ArH); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta 16.4, 22.5, 32.9, 69.3, 73.0, 74.1, 82.7, 127.5, 127.5, 128.3, 138.5; \) IR (ef) 3289, 3031, 2857, 2117, 1496, 1454, 1112, 749 cm\(^{-1}\); MS (Cl) \( m/z \) (rel. intensity) 189 (M + H, 78), 171 (17), 111 (M – Ph, 100).
6.2.23 (4R)-2,4-Dimethyl-4,5-dihydrofuran [(4R)-61][22,23]

The alcohol (2R)-69 (0.91 g, 9.3 mmol) and sodium amide (50 mg, 1.3 mmol) were heated at reflux for 2 h. Direct distillation of the reaction mixture at atmospheric pressure afforded the exocyclic dihydrofuran (4R)-68 as a colourless oil. This material was heated at reflux for 2 h and then distilled at atmospheric pressure to afford the title compound (4R)-69 (0.40 g, 44%) as a colourless oil. B.p. 97-103 °C, ~760 mm Hg; [α]_D^24 = -118 (c 0.82, chloroform); ^1H NMR (400 MHz, C₆D₆) δ 0.84 (d, J = 6.6 Hz, 3H, Me-4), 1.68 (apparent t, J = 1.5 Hz, 3H, Me-2), 2.76 (m, 1H, H-4), 3.71 (dd, J = 8.7, 6.5 Hz, 1H, H-5), 4.21 (dd, J = 9.5, 8.6 Hz, 1H, H-5), 4.43 (m, 1H, H-3); ^13C NMR (101 MHz, C₆D₆) δ 13.6, 20.9, 37.9, 77.2, 101.4, 155.0; IR (ef) 2961, 2875, 1674, 1453, 1383, 1243, 1043, 1008, 886 cm⁻¹. MS (Cl) m/z (rel. intensity) 99 (M + H, 100).

6.2.24 (4S)-2,4-Dimethyl-4,5-dihydrofuran [(4S)-61][22,23]

The alcohol (2S)-69 (1.17 g, 11.9 mmol) and sodium amide (60 mg, 1.5 mmol) were heated at reflux for 2 h. Direct distillation of the reaction mixture at atmospheric pressure afforded the exocyclic dihydrofuran (4S)-68 as a colourless oil. This material was heated at reflux for 2 h and then distilled at atmospheric pressure to afford the title compound (4S)-61 (0.42 g, 36%) as a colourless oil. B.p. 97-103 °C, ~760 mm Hg; [α]_D^24 = +120 (c 0.44, chloroform); ^1H NMR (400 MHz, C₆D₆) δ 0.84 (d, J = 6.6 Hz,
3H, Me-4), 1.68 (apparent t, J = 1.5 Hz, 3H, Me-2), 2.76 (m, 1H, H-4), 3.71 (dd, J = 8.7, 6.5 Hz, 1H, H-5), 4.21 (dd, J = 9.5, 8.6 Hz, 1H, H-5), 4.43 (m, 1H, H-3); $^{13}$C NMR (101 MHz, C$_6$D$_6$) δ 13.6, 20.9, 37.9, 77.2, 101.4, 155.0; IR (ef) 2961, 2875, 1674, 1453, 1383, 1243, 1008, 886 cm$^{-1}$. MS (Cl) m/z (rel. intensity) 99 (M + H, 100).

6.2.25 (−)-Xyloketal D [(−)-4], 2,6-epi-Xyloketal D (26) and the Diastereoisomeric Spiroacetals (117) and (118)$^{1,9,10}$

Method A: To a solution of the dihydrofuran (4R)-61 (295 mg, 3.01 mmol) in benzene (10 mL) at room temperature were added the Mannich base 104 (251 mg, 1.00 mmol) and methyl iodide (65.0 µL, 1.05 mmol). The resultant solution was then heated at reflux until TLC analysis indicated that the Mannich base 104 had undergone complete reaction (8 days). The reaction mixture was then cooled to room temperature, filtered with ether (10 mL) and concentrated in vacuo. Purification by flash chromatography using dichloromethane as the eluant afforded a mixture (8:1:2:2) of the title compounds (−)-4, 26, 117 and 118 (105 mg, 40%) as a yellow solid. Repetitive flash chromatography using hexanes:ether (4:1) as the eluant on TLC grade silica gel afforded a mixture (dr = 20:1) of the title compounds (−)-4 and 26 as a pale cream solid and a separate mixture (dr = 4:5) of the title compounds 117 and 118 as a pale cream solid.

Method B: To a solution of the dihydrofuran (4R)-61 (121 mg, 1.23 mmol) in benzene (5 mL) at room temperature were added the Mannich base 104 (103 mg, 0.41 mmol) and dimethyl sulfate (41 µL, 0.43 mmol). The resultant solution was heated at
reflux until TLC analysis indicated that the Mannich base 104 had undergone complete reaction (3 days). The reaction mixture was then cooled to room temperature and decanted. The remaining solid residue was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts were concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (16:1:4:4) of the *title compounds* (−)-4, 26, 117 and 118 (40 mg, 37%) as a yellow solid.

*Title compound* (−)-4: An analytically pure sample of the *title compound* (−)-4, as pale pink prisms, was prepared by recrystallization from petroleum ether. \( R_f = 0.24 \), hexanes:ether (4:1); \textbf{M.p.} 71-73 °C, petroleum ether and 68-71 °C, ether:pentane (lit.\(^1\) 111-113 °C; lit.\(^9\) 110-111 °C, ether:pentane; lit.\(^10\) 110-111 °C); \([\alpha]_D^{20} = -110 \) (c 0.102, chloroform) [lit.\(^1\) \([\alpha]_D^{25} = -119.5 \) (c 0.113, chloroform); lit.\(^9\) \([\alpha]_D^{25} = -118 \) (c 0.10, chloroform)]; \([\alpha]_D^{25} = -118 \) (c 0.10, chloroform)]; \textbf{H NMR} (500 MHz, CDCl\(_3\)) \( \delta \) 1.07 (d, \( J = 6.5 \) Hz, 3H, Me-11), 1.53 (s, 3H, Me-10), 1.98 (ddd, \( J = 11.3, 6.5, 1.1 \) Hz, 1H, H-6), 2.08 (m, 1H, H-5), 2.55 (s, 3H, Me-17), 2.72 (dd, \( J = 17.9, 6.5 \) Hz, 1H, H-7), 2.97 (d, \( J = 18.0, 1H, H-7 \), 3.57 (apparent t, \( J = 8.4 \) Hz, 1H, H-4), 4.20 (apparent t, \( J = 8.3 \) Hz, 1H, H-4), 6.36 (d, \( J = 8.9 \) Hz, 1H, H-15), 7.52 (d, \( J = 8.9 \) Hz, 1H, H-14), 13.12 (s, 1H, \( \text{OH} \)); \textbf{C NMR} (101 MHz, CDCl\(_3\)) \( \delta \) 15.8, 18.0, 22.7, 26.1, 35.1, 47.0, 74.3, 106.2, 108.3, 108.8, 113.2, 130.0, 159.5, 162.9, 202.6; \textbf{IR} (ef) 3399, 2967, 2927, 2884, 1620, 1491, 1421, 1382, 1370, 1332, 1272, 1117, 1070, 1006 cm\(^{-1}\); \textbf{MS} (Cl) \textit{m/z} (rel. intensity) 263 (M + H, 100); \textbf{Anal. Calcd for C\(_{15}\)H\(_{18}\)O\(_4\):} C, 68.68; H, 6.92. Found: C, 68.52; H, 6.98.
Title compound 26: $^1$H NMR [400 MHz, CDCl$_3$] (additional signals observed for the title compound 26) $\delta$ 0.80 (d, $J = 7.1$ Hz, 3H, Me-11), 3.68 (q, $J = 5.0$ Hz, 1H, H-4).

Title compounds 117 and 118 (dr = 4:5): An analytically pure sample of a mixture (dr = 4:5) of the title compounds 117 and 118, as colourless needles, was also prepared by recrystallization from petroleum ether. $R_f$ = 0.32, hexanes:ether (4:1); M.p. 60-61 °C, petroleum ether; $[\alpha]^{20}_D = +26.9$ (c 0.71, chloroform); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.10 (d, $J = 6.6$ Hz, 3H, Me-11), 1.18 (d, $J = 6.6$ Hz, 3H, Me-11), 1.55 (dd, $J = 12.8$, 9.5 Hz, 1H, H-6), 2.00 (m, 5H, 2 $\times$ H-5, H-6 and 2 $\times$ H-7), 2.28 (dd, $J = 13.4$, 9.5 Hz, 1H, H-6), 2.36 (dd, $J = 12.9$, 7.3 Hz, 1H, H-6), 2.46 (m, 1H, H-7), 2.54 (s, 3H, Me-17), 2.55 (s, 3H, Me-17), 2.78 (m, 5H, H-7 and 4 $\times$ H-8), 3.54 (t, $J = 7.7$ Hz, 1H, H-4), 3.64 (t, $J = 8.4$ Hz, 1H, H-4), 4.09 (t, $J = 7.9$ Hz, 1H, H-4), 4.21 (t, $J = 7.9$ Hz, 1H, H-4), 6.34 (d, $J = 8.9$ Hz, 1H, H-15), 6.37 (d, $J = 9.0$ Hz, 1H, H-15), 7.50 (d, $J = 8.9$ Hz, 1H, H-14), 7.51 (d, $J = 8.9$ Hz, 1H, H-14), 13.01 (s, 1H, OH), 13.02 (s, 1H, OH); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 16.3, 16.5, 17.6, 18.0, 26.2, 29.3, 29.6, 31.9, 33.0, 45.2, 45.3, 75.0, 75.4, 108.1, 108.9, 109.0, 110.0, 110.1, 113.16, 113.24, 129.58, 129.62, 159.6, 162.2, 202.7, 202.8; IR (ef) 3423, 2958, 2878, 1626, 1488, 1419, 1369, 1331, 1270, 1247, 1136, 1060, 1018, 853 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 263 (M + H, 100), 111 (12); Anal. Calcd for C$_{15}$H$_{18}$O$_4$: C, 68.68; H, 6.92. Found: C, 68.58; H, 6.99.
6.2.26 Xyloketal D-(R)-α-methoxy-α-trifluoromethyl-phenylacetate [(−)-124] and ent-Xyloketal D-(R)-α-methoxy-α-trifluoromethyl-phenylacetate (125)

To a solution of (±)-xyloketal D [(±)-4], that contained a trace amount of the 2,6-epimer (±)-26, (24 mg, 0.093 mmol) in tetrahydrofuran (2 mL) were added N,N-dimethyl-4-aminopyridine (13 mg, 0.11 mmol) and a freshly prepared sample of (S)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride (34 µL, 0.18 mmol). The resultant mixture was heated at reflux for 3 h and then allowed to cool to room temperature. The reaction mixture was then diluted with ether (25 mL) and was washed with hydrochloric acid (1 M, 7 mL), a saturated aqueous solution of sodium bicarbonate (7 mL) and water (7 mL). The organic layer was then dried over anhydrous sodium sulfate and concentrated in vacuo. Filtration of the resultant residue through a pad of silica gel using hexanes:ether (2:1) as the eluant afforded a mixture (dr = 1:1) of the title compounds (−)-124 and 125 (36 mg, 82%) as a solid pale yellow foam. Rf = 0.16, hexanes:ether (2:1); M.p. 37-41 °C, hexanes:ether; [α]$_D^{20}$ = +13.8 (c 1.76, chloroform); $^1$H NMR (600 MHz, CDCl$_3$) δ 0.95 (d, J = 6.4 Hz, 3H, Me-11), 0.97 (d, J = 6.6 Hz, 3H, Me-11), 1.51 (s, 3H, Me-10), 1.53 (s, 3H, Me-10), 1.85 (m, 2H, 2 × H-6), 1.99 (m, 2H, 2 × H-5), 2.46 (s, 3H, Me-17), 2.48 (s, 3H, Me-17), 2.54 (m, 4H, 4 × H-7), 3.50 (m, 2H, 2 × H-4), 3.72 (s, 3H, OMe), 3.73 (s, 3H, OMe), 4.14 (apparent t, J = 8.4 Hz, 2H, H-4), 4.16 (apparent t, J = 8.5 Hz, 1H, H-4), 6.81 (d, J = 8.5 Hz, 2H, 2 × H-15), 7.46 (m, 6H, ArH), 7.64 (d, J = 8.6...
Hz, 2H, 2 × H-14), 7.79 (m, 4H, ArH); $^{13}$C NMR (126 MHz, CDCl$_3$, observed signals) δ 15.5, 15.7, 18.6, 18.7, 22.8, 23.1, 28.50, 28.52, 35.0, 35.1, 46.8, 47.0, 55.70, 55.73, 74.2, 108.3, 108.4, 113.3, 113.6, 114.88, 114.90, 122.0, 122.1, 123.2, 123.3, 124.3, 124.4, 128.2, 128.3, 128.4, 128.5, 129.79, 129.81, 129.83, 129.85, 131.0, 131.1, 147.6, 147.7, 157.68, 157.72, 164.4, 164.5, 196.09, 196.13; $^{19}$F NMR (470 MHz, CDCl$_3$) δ 3.85 (s), 3.91 (s); IR (ef) 2948, 1764, 1686, 1485, 1264, 1171, 1116, 1052, 1004 cm$^{-1}$; MS (MALDI-TOF) m/z (rel. intensity) 517 (M + K, 22), 501 (M + Na, 82), 479 (M + H, 100) and (CI) m/z (rel. intensity) 479 (M + H, 13), 263 (68), 189 (20), 163 (100); Anal. Calcd. for C$_{25}$H$_{25}$F$_3$O$_6$: C, 62.76; H, 5.27; Found: C, 62.82; H, 5.37.

6.2.27 Xyloketal D (R)-α-methoxy-α-trifluoromethyl-phenylacetate [(-)-124]$^{59}$

To a solution of synthetic (-)-xyloketal D [(-)-4] (15 mg, 0.058 mmol) in tetrahydrofuran (1.8 mL) were added N,N-dimethyl-4-aminopyridine (10 mg, 0.082 mmol) and a freshly prepared sample of (S)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride (22 µL, 0.12 mmol). The resultant mixture was heated at reflux for 2.5 h and then allowed to cool to room temperature. The reaction mixture was then diluted with ether (25 mL) and was washed with hydrochloric acid (1 M, 7 mL), a saturated aqueous solution of sodium bicarbonate (7 mL) and water (7 mL). The organic layer was then dried over anhydrous sodium sulfate and concentrated in vacuo. Filtration of the resultant residue through a pad of silica gel using hexanes:ether (2:1) as the eluant
afforded the title compound (-)-I24 (23 mg, 84%) as a solid white foam. \( R_f = 0.16, \) hexanes:ether \( (2:1) \); M.p. 92-93 °C, on evaporation from chloroform; \([\alpha]_D^{20} = -36.6 \) (c 1.10, chloroform); \(^1\)H NMR \((600 \text{ MHz}, \text{CDCl}_3\) \( \delta 0.95 \) (d, \( J = 6.5 \text{ Hz}, 3\text{H, Me-11} \)), \( 1.53 \) (s, \( 3\text{H, Me-10} \)), \( 1.85 \) (m, \( 1\text{H, H-6} \)), \( 1.99 \) (m, \( 1\text{H, H-5} \)), \( 2.46 \) (s, \( 3\text{H, H-17} \)), \( 2.54 \) (m, \( 2\text{H, H-7} \)), \( 3.50 \) (apparent t, \( J = 8.5 \text{ Hz}, 1\text{H, H-4} \)), \( 3.72 \) (s, \( 3\text{H, OMe} \)), \( 4.14 \) (apparent t, \( J = 8.5 \text{ Hz}, 1\text{H, H-4} \)), \( 6.81 \) (d, \( J = 8.5 \text{ Hz}, 1\text{H, H-15} \)), \( 7.47 \) (m, \( 3\text{H, ArH} \)), \( 7.64 \) (d, \( J = 8.5 \text{ Hz}, 1\text{H, H-14} \)), \( 7.80 \) (m, \( 2\text{H, ArH} \)); \(^{13}\)C NMR \((126 \text{ MHz}, \text{CDCl}_3\) \( \delta 15.5, 18.6, 23.1, 28.6, 35.0, 47.0, 55.7 \) (apparent d, \( J = 1.1 \text{ Hz} \)), \( 74.2, 84.8 \) (q, \( J = 28 \text{ Hz} \)), \( 108.4, 113.5, 114.91, 122.2, 123.2 \) (q, \( J = 289 \text{ Hz} \)), \( 128.2 \) (apparent d, \( J = 1.1 \text{ Hz} \)), \( 128.4, 129.8, 129.9, 130.9, 147.7, 157.7, 164.5, 196.1\); \(^{19}\)F NMR \((470 \text{ MHz}, \text{CDCl}_3\) \( \delta 3.85 \) (s); IR (ef) \( 2948, 1764, 1686, 1485, 1264, 1171, 1116, 1052, 1004 \text{ cm}^{-1}; \) MS (MALDI-TOF) m/z (rel. intensity) \( 517 \) (M + K, 65), \( 501 \) (M + Na, 100), \( 479 \) (M + H, 85); Anal. Calcd. for C25H25F3O6: C, 62.76; H, 5.27; Found: C, 62.84; H, 5.37.

6.2.28 (+)-Xyloketal D [(+)-4], 2,6-epi-ent-Xyloketal D [(ent)-26] and the Diastereoisomeric Spiroacetals [(ent)-117] and [(ent)-118]

Method A: To a solution of the dihydrofuran \((4S)-61 \) (237 mg, 2.42 mmol) in benzene (8 mL) at room temperature were added the Mannich base 104 (202 mg, 0.804 mmol) and methyl iodide (52 µL, 0.84 mmol). The resultant solution was then heated at reflux until TLC analysis indicated that the Mannich base 104 had undergone complete reaction (6 days). The reaction mixture was then cooled to room temperature, filtered
with ether (8 mL) and concentrated in vacuo. Purification by flash chromatography using dichloromethane as the eluant afforded a mixture (13:1:3:3) of the *title compounds* (+)-4, (ent)-26, (ent)-117 and (ent)-118 (96 mg, 46%) as a yellow solid. Repetitive flash chromatography using hexanes:ether (4:1) as the eluant on TLC grade silica gel afforded a mixture (dr = 14:1) of the *title compounds* (+)-4 and (ent)-26 as a pale cream solid and a separate mixture (dr = 4:5) of the *title compounds* (ent)-117 and (ent)-118 as a pale cream solid.

**Method B:** To a solution of the dihydrofuran (4S)-61 (198 mg, 2.02 mmol) in benzene (8 mL) at room temperature were added the Mannich base 104 (170 mg, 0.67 mmol) and dimethyl sulfate (67 μL, 0.70 mmol). The resultant solution was heated at reflux until TLC analysis indicated that the Mannich base 104 had undergone complete reaction (3 days). The reaction mixture was then cooled to room temperature and decanted. The remaining solid residue was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts were concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (20:1:3:3) of the *title compounds* (+)-4, (ent)-26, (ent)-117 and (ent)-118 (64 mg, 36%) as a yellow solid.

**Title compound (+)-4:** An analytically pure sample of the *title compound* (+)-4, as pale pink prisms, was prepared by recrystallization from petroleum ether. *Rf* = 0.24, hexanes:ether (4:1); *M.p.* 70-71 °C, petroleum ether; [α]D20 = +113 (c 0.122, chloroform); 1H NMR (500 MHz, CDCl3) δ 1.07 (d, J = 6.5 Hz, 3H, Me-11), 1.53 (s, 3H, Me-10), 1.98 (ddd, J = 11.3, 6.5, 1.1 Hz, 1H, H-6), 2.08 (m, 1H, H-5), 2.55 (s, 3H, Me-17), 2.72 (dd, J = 17.9, 6.5 Hz, 1H, H-7), 2.97 (d, J = 18.0, 1H, H-7), 3.57 (apparent
t, $J = 8.4$ Hz, 1H, H-4), 4.20 (apparent t, $J = 8.3$ Hz, 1H, H-4), 6.36 (d, $J = 8.9$ Hz, 1H, H-15), 7.52 (d, $J = 8.9$ Hz, 1H, H-14), 13.12 (s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 15.87, 18.0, 22.7, 26.1, 35.1, 74.3, 106.2, 108.3, 108.8, 113.2, 130.0, 159.5, 162.9, 202.6; IR (ef) 3399, 2967, 2927, 2884, 1620, 1491, 1421, 1382, 1370, 1332, 1272, 1171, 1070, 1006 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 263 (M + H, 100)); Anal. Calcd for C$_{15}$H$_{18}$O$_4$: C, 68.68; H, 6.92. Found: C, 68.72; H, 6.79.

**Title compound (ent)-26**: $^1$H NMR [400 MHz, CDCl$_3$ (additional signals observed for the title compound (ent)-26)] δ 0.80 (d, $J = 7.1$ Hz, 3H, Me-11), 3.68 (q, $J = 5.0$ Hz, 1H, H-4).

**Title compounds (ent)-117 and (ent)-118 (dr = 4:5)**: An analytically pure sample of a mixture (dr = 4:5) of the title compounds (ent)-117 and (ent)-118, as colourless needles, was also prepared by recrystallization from petroleum ether. $R_f = 0.32$, hexanes:ether (4:1); M.p. 59-61 °C, petroleum ether; $[\alpha]_{D}^{20} = -26.7$ (c 1.05, chloroform); $^1$H NMR (400 MHz, CDCl$_3$) δ 1.10 (d, $J = 6.6$ Hz, 3H, Me-11), 1.18 (d, $J = 6.6$ Hz, 3H, Me-11), 1.55 (dd, $J = 12.8$, 9.5 Hz, 1H, H-6), 2.00 (m, 5H, 2 × H-5, H-6, and 2 × H-7), 2.28 (dd, $J = 13.4$, 9.5 Hz, 1H, H-6), 2.36 (dd, $J = 12.9$, 7.3 Hz, 1H, H-6), 2.46 (m, 1H, H-7), 2.54 (s, 3H, Me-17), 2.55 (s, 3H, Me-17), 2.78 (m, 5H, H-7 and 4 × H-8), 3.54 (t, $J = 7.7$ Hz, 1H, H-4), 3.64 (t, $J = 8.4$ Hz, 1H, H-4), 4.09 (t, $J = 7.9$ Hz, 1H, H-4), 4.21 (t, $J = 7.9$ Hz, 1H, H-4), 6.34 (d, $J = 8.9$ Hz, 1H, H-15), 6.37 (d, $J = 9.0$ Hz, 1H, H-15), 7.50 (d, $J = 8.9$ Hz, 1H, H-14), 7.51 (d, $J = 8.9$ Hz, 1H, H-14), 13.01 (s, 1H, OH), 13.02 (s, 1H, OH); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 16.3, 16.5, 17.6, 18.0, 26.2, 29.3, 29.6, 31.9, 33.0, 45.2, 45.3, 75.0, 75.4, 108.1, 108.9, 109.0, 110.0, 110.1, 113.16, 113.24,
129.58, 129.62, 159.6, 162.2, 202.7, 202.8; \textbf{IR} (ef) 3423, 2958, 2878, 1626, 1488, 1419, 1369, 1331, 1270, 1247, 1136, 1060, 1018, 853 cm\textsuperscript{-1}; \textbf{MS} (CI) \textit{m/z} (rel. intensity) 263 (M + H, 100), 111 (12); \textbf{Anal.} Calcd for C\textsubscript{15}H\textsubscript{18}O\textsubscript{4}: C, 68.68; H, 6.92. Found: C, 68.53; H, 7.02.

### 6.3 Experimental Concerning Chapter Three

#### 6.3.1 3-Methyl-but-2-enal [Senecialdehyde (134)]\textsuperscript{74,152}

![Chemical Structure](image)

To a solution of 3-methyl-but-2-enol (141) (7.00 g, 81.3 mmol) in dichloromethane (100 mL) was added pyridinium dichromate (39.9 g, 106 mmol) at 0 °C. The reaction was stirred at room temperature for 16 h and then filtered through celite. The filter-cake was washed with ether (50 mL) and the combined filtrates were concentrated \textit{in vacuo}. Purification of the crude product by distillation at reduced pressure afforded the \textit{title compound} 134 (3.81 g, 56%) as a colourless oil. \textbf{R}_{f} = 0.41, hexanes:ether (1:1); \textbf{B.p.} \sim 50 °C, \sim 35 mm Hg (lit.\textsuperscript{152} 133-135 °C, 760 mm Hg); \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \delta 1.97 (s, 3H, \textit{Me}), 2.16 (s, 3H, \textit{Me}), 5.87 (d, \textit{J} = 8 Hz, 1H, \textit{H}-2), 9.94 (d, \textit{J} = 8 Hz, 1H, \textit{CHO}); \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \delta 18.9, 27.2, 128.1, 160.6, 191.0; \textbf{IR} (ef) 2980, 2845, 1681, 1634, 1616, 1378, 1198, 1131, 1047, 835 cm\textsuperscript{-1}; \textbf{MS} (CI) \textit{m/z} (rel. intensity) 85 (M + H, 100).
6.3.2 2,2,6,6,10,10-Hexamethyl-2H,6H,10H-dipyran[6,5-f,6',5'-h]chromene (142) and 2,2,8,8-Tetramethyl-2H,8H-pyrano[5,6-g]chromen-5-ol (143)

Method A: A mixture of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (134) (109 mg, 1.30 mmol, 4 equiv), phenylboronic acid (9 mg, 0.07 mmol, 0.25 equiv), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated in vacuo. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the title compound 142 (53 mg, 55%) as a white solid and the title compound 143 (30 mg, 39%) as a waxy yellow solid.

Method B: A mixture of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (134) (104 mg, 1.24 mmol, 4 equiv), phenylboronic acid (38 mg, 0.31 mmol, 1 equiv), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated in vacuo. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the title compound 142 (72 mg, 74%) as a white solid and the title compound 143 (18 mg, 23%) as a waxy yellow solid.

Method C: A mixture of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (134) (103 mg, 1.23 mmol, 4 equiv), phenylboronic acid (74 mg, 0.61
mmol, 2 equiv), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated in vacuo. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the title compound 142 (79 mg, 81%) as a white solid and the title compound 143 (9 mg, 11%) as a waxy yellow solid.

**Method D:** A mixture of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (134) (103 mg, 1.23 mmol, 4 equiv), phenylboronic acid (110 mg, 0.90 mmol, 3 equiv), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated in vacuo. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the title compound 142 (89 mg, 92%) as a white solid and the title compound 143 (5 mg, 6%) as a waxy yellow solid.

**Method E:** A mixture of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (134) (103 mg, 1.23 mmol, 4 equiv), phenylboronic acid (110 mg, 0.90 mmol, 3 equiv) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h after which time TLC analysis indicated only trace amounts of the title compound 142 and the title compound 143 had formed.

**Method F:** A mixture of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (134) (104 mg, 1.24 mmol, 4 equiv), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h after which time TLC
analysis indicated only trace amounts of the *title compound* 142 and the *title compound* 143 had formed.

**Method G:** A mixture of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (134) (107 mg, 1.27 mmol, 4 equiv), boric acid (5 mg, 0.08 mmol, 0.25 equiv), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant mixture was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* 142 (44 mg, 45%) as a white solid and the *title compound* 143 (23 mg, 30%) as a waxy yellow solid.

**Method H:** A mixture of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (134) (109 mg, 1.29 mmol, 4 equiv), boric acid (19 mg, 0.31 mmol, 1 equiv), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant mixture was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*. Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the *title compound* 142 (49 mg, 50%) as a white solid and the *title compound* 143 (19 mg, 25%) as a waxy yellow solid.

**Method I:** A mixture of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), senecialdehyde (134) (104 mg, 1.24 mmol, 4 equiv), boric acid (56 mg, 0.91 mmol, 3 equiv), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant mixture was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated *in vacuo*.
Purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the title compound 142 (43 mg, 44%) as a white solid and the title compound 143 (21 mg, 27%) as a waxy yellow solid.

*Title compound 142:* \( R_f = 0.59, \) hexanes:ether (4:1); \( \text{M.p.} \) 110-113 °C, hexanes:ether; \( ^1H \text{NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 1.40 (s, 18H, CH\(_3\)), 5.43 (d, \( J = 9.9 \) Hz, 3H, ArCHCH), 6.59 (d, \( J = 9.9 \) Hz, 3H, ArCHCH); \( ^{13}C \text{NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \) 27.9, 76.5, 103.4, 116.8, 125.8, 149.1; \( \text{IR} \) (ef) 2972, 2928, 2853, 1626, 1590, 1463, 1425, 1366, 1242, 1177, 1136 cm\(^{-1}\); \( \text{MS (CI)} \) \( m/z \) (rel. intensity) 325 (M + H, 100), 324 (M, 76), 309 (19); \( \text{Anal.} \) Calcd. for C\(_{21}\)H\(_{24}\)O\(_3\): C, 77.75; H, 7.46. Found: C, 77.49; H, 7.82.

*Title compound 143:* \( R_f = 0.27, \) hexanes:ether (4:1); \( \text{M.p.} \) 107-109 °C, hexanes:ether; \( ^1H \text{NMR} \) (400 MHz, C\(_6\)D\(_6\)) \( \delta \) 1.24 (s, 12H, CH\(_3\)), 5.14 (d, \( J = 9.9 \) Hz, 2H, ArCHCH), 6.23 (d, \( J = 9.9 \) Hz, 2H, ArCHCH), 6.46 (s, 1H, ArH); \( ^{13}C \text{NMR} \) (101 MHz, C\(_6\)D\(_6\)) \( \delta \) 27.8, 76.1, 99.0, 103.5, 116.2, 126.6, 147.6, 155.4; \( \text{IR} \) (ef) 3353, 2978, 2928, 1638, 1613, 1563, 1481, 1360, 1139, 1106, 1071 cm\(^{-1}\); \( \text{MS (CI)} \) \( m/z \) (rel. intensity) 258 (M, 21), 243 (100), 114 (13); \( \text{Anal.} \) Calcd. for C\(_{16}\)H\(_{18}\)O\(_3\): C, 74.39; H, 7.02. Found: C, 74.24; H, 7.02.
6.3.3 2,2,6,6,10,10-Hexamethyl-3,4,7,8,11,12-hexahydro-2H,6H,10H-dipyran[6,5-f,6',5'-h]chromene (148)

A mixture of the chromene 142 (200 mg, 0.62 mmol) and palladium on charcoal (199 mg, 10% w/w) in methanol (20 mL) under an atmosphere of hydrogen (balloon pressure) was stirred at room temperature for 20 h. The resultant mixture was filtered through a pad of celite with dichloromethane (3 × 20 mL) and then concentrated in vacuo to afford the title compound 148 (197 mg, 96%) as a white solid. \( R_f = 0.64 \), hexanes:ether (4:1); \( \text{M.p.} \) 96-97 °C, 95% ethanol (lit. 75 103.5-104.5 °C, 95% ethanol); \( ^1H \text{ NMR} \) (400 MHz, CDCl₃) \( \delta \) 1.29 (s, 18H, CH₃), 1.71 (t, \( J = 6.8 \) Hz, 6H, ArCH₂CH₂), 2.55 (t, \( J = 6.8 \) Hz, 6H, ArCH₂CH₂); \( ^{13}C \text{ NMR} \) (101 MHz, CDCl₃) \( \delta \) 16.7, 26.9, 32.5, 73.4, 100.3, 149.9; \( \text{IR} \) (ef) 2973, 2934, 2853, 1614, 1447, 1382, 1367, 1322, 1260, 1157, 1119, 1041 cm\(^{-1}\); \( \text{MS (EI)} \) \( m/z \) (rel. intensity) 330 (M, 70), 275 (86), 219 (100); Anal. Calcd. for C₂₁H₃₀O₃: C, 76.33; H, 9.15. Found: C, 76.30; H, 9.13.

6.3.4 Cyclopentylideneacetaldehyde (152)

To a suspension of sodium hydride (2.20 g, 60% w/w in mineral oil, 55.0 mmol) in tetrahydrofuran (80 mL) at room temperature was added a solution of trimethyl phosphonoacetate (8.50 mL, 52.5 mmol). The resultant mixture was stirred for 1 h and
then cyclopentanone (149) (4.40 mL, 49.7 mmol) was added. The reaction mixture was heated at reflux for 24 h and then cooled to 0 °C after which a saturated aqueous solution of ammonium chloride (50 mL) was added. The resultant mixture was extracted with ether (2 × 50 mL) and the combined organic extracts were washed with brine (2 × 50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by distillation at reduced pressure (B.p. 115-120 °C, ~2 mm Hg) afforded the corresponding α,β-unsaturated ester. A solution of this material (5.90 g, 42.1 mmol) in ether (20 mL) was added to a suspension of lithium aluminum hydride (2.60 g, 68.6 mmol) in ether (100 mL) at 0 °C and the resultant mixture was allowed to warm to room temperature over 1 h. Water (2.6 mL), an aqueous solution of sodium hydroxide (2 M, 2.6 mL) and water (7.8 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (3 × 50 mL) and the combined filtrates were concentrated in vacuo to afford the corresponding alcohol. To a solution of this material (4.70 g, 42.0 mmol) in dichloromethane (200 mL) at room temperature was added manganese dioxide (32.9 g, 378 mmol) and the resultant mixture stirred for 6 h. The reaction mixture was filtered through a pad of celite, the filter-cake was washed with dichloromethane (3 × 50 mL) and the combined filtrates were concentrated in vacuo. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the title compound 152 (3.97 g, 72% over three steps) as a clear oil. Rf = 0.42, hexanes:ether (1:1); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 1.72 (m, 2H, \(CH_2\)), 1.83 (m, 2H, \(CH_2\)), 2.54 (t, \(J = 7.2\) Hz, 2H, \(CH_2C\)), 2.80 (t, \(J = 7.2\) Hz, 2H, \(CH_2C\)), 5.97 (m, 1H, \(CHCHO\)), 9.85 (d, \(J = 8.0\) Hz, 1H, \(CHO\)); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 25.0, 26.4, 30.3, 35.9, 123.2, 173.8, 191.7; IR
(ef) 2962, 2874, 1671, 1625, 1446, 1090 \text{ cm}^{-1}; \textbf{MS (EI)} m/z \text{ (rel. intensity)} 110 \text{ (M, 13)}, 109 \text{ (9)}, 85 \text{ (11)}, 67 \text{ (14)}, 46 \text{ (83)}, 45 \text{ (75)}, 29 \text{ (100)}.

6.3.5 Cyclohexylideneacetaldehyde (156)\textsuperscript{77,79}

![Structure of 156]

To a suspension of sodium hydride (2.20 g, 60\% w/w in mineral oil, 55.0 mmol) in tetrahydrofuran (100 mL) at room temperature was added a solution of trimethyl phosphonoacetate (8.50 mL, 52.5 mmol). The resultant mixture stirred for 1 h and then cyclohexanone (153) (5.20 mL, 50.2 mmol) was added. The reaction mixture was heated at reflux for 24 h and then cooled to 0 °C after which a saturated aqueous solution of ammonium chloride (50 mL) was added. The resultant mixture was extracted with ether (2 × 50 mL) and the combined organic extracts were washed with brine (2 × 50 mL), dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. Purification by distillation at reduced pressure (B.p. 120-130 °C, ~2 mm Hg) afforded the corresponding \(\alpha,\beta\)-unsaturated ester. A solution of this material (4.00 g, 25.9 mmol) in ether (25 mL) was added to a suspension of lithium aluminum hydride (1.00 g, 26.4 mmol) in ether (80 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature over 1 h and then was cooled to 0 °C. Water (1.0 mL), an aqueous solution of sodium hydroxide (2 M, 1.0 mL) and water (3.0 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (3 × 50 mL) and the combined filtrates were concentrated \textit{in vacuo} to afford the corresponding alcohol. To a solution of this material (3.27 g, 25.9 mmol) in dichloromethane (150 mL) at room
temperature was added manganese dioxide (33.0 g, 380 mmol) and the resultant mixture was stirred for 3 h. The reaction mixture was filtered through a pad of celite, the filter-cake was washed with dichloromethane (3 × 50 mL) and the combined filtrates were concentrated in vacuo. Purification by flash chromatography using hexanes:ether (2:1) as the eluant afforded the title compound 156 (2.62 g, 81% over three steps) as a clear oil. 

R_f = 0.45, hexanes:ether (1:1); ^1H NMR (400 MHz, CDCl_3) δ 1.69 (m, 6H, CH_2), 2.29 (t, J = 6.4 Hz, 2H, CH_2C), 2.71 (t, J = 6.4 Hz, 2H, CH_2C), 5.82 (d, J = 8.2 Hz, 1H, CHCHO), 10.01 (d, J = 8.2 Hz, 1H, CHO); ^13C NMR (101 MHz, CDCl_3) δ 26.3, 28.2, 28.5, 29.7, 38.1, 125.4, 168.1, 190.6; IR (ef) 2934, 1856, 2773, 1674, 1625, 1449, 1194, 1141, 1120 cm⁻¹; MS (Cl) m/z (rel. intensity) 125 (M + H, 100), 123 (45), 95 (22), 81 (27), 65 (15), 53 (21).

### 6.3.6 Adamantylideneacetaldehyde (160)

![160](image)

To a suspension of sodium hydride (731 mg, 60% w/w in mineral oil, 18.3 mmol) in tetrahydrofuran (70 mL) at room temperature was added a solution of trimethyl phosphonoacetate (2.80 mL, 17.3 mmol). The resultant mixture was stirred for 1 h and then 2-adamantanone (157) (2.50 g, 16.6 mmol) was added. The reaction mixture was heated at reflux for 24 h and then cooled to 0 °C after which a saturated aqueous solution of ammonium chloride (50 mL) was added. The resultant mixture was extracted with ether (2 × 50 mL) and the combined organic extracts were washed with brine (2 × 50 mL) and...
mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the corresponding \( \alpha,\beta \)-unsaturated ester (3.26 g, 95%) as a colourless solid. \( R_f = 0.50, \) hexanes:ether (9:1); M.p. 46–47 °C, hexanes:ether; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.82 (m, 6H, \( CH \)), 1.95 (m, 6H, \( CH \)), 2.41 (s, 1H, \( CHC \)), 3.66 (s, 3H, \( CO_2CH_3 \)), 4.05 (s, 1H, \( CHC \)), 5.57 (s, 1H, \( CHCO_2CH_3 \)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 28.0, 33.0, 36.9, 39.3, 40.2, 41.5, 50.8, 108.3, 167.5, 172.6; IR (ef) 2995, 2912, 2845, 1710, 1640, 1444, 1382, 1326, 1236, 1205, 1160 cm\(^{-1}\); MS (Cl) \( m/z \) (rel. intensity) 207 (M + H, 100), 175 (11).

A solution of the above material (3.26 g, 15.8 mmol) in ether (10 mL) was added to a suspension of lithium aluminum hydride (600 mg, 15.8 mmol) in ether (50 mL) at 0 °C and the resultant mixture was allowed to warm to room temperature over 1 h. Water (0.6 mL), an aqueous solution of sodium hydroxide (2 M, 0.6 mL) and water (1.8 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (3 \( \times \) 25 mL) and the combined filtrates were concentrated in vacuo. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the corresponding \( \alpha,\beta \)-unsaturated alcohol (2.72 g, 97%) as a clear oil. \( R_f = 0.25, \) hexanes:ether (1:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.69 (m, 2H, \( CH \)), 1.79 (m, 4H, \( CH \)), 1.88 (m, 4H, \( CH \)), 1.94 (m, 2H, \( CH \)), 2.36 (m, 1H, \( CHC \)), 2.85 (m, 1H, \( CHC \)), 4.11 (d, \( J = 7.0 \) Hz, 2H, \( CH_2OH \)), 5.35 (t, \( J = 7.0 \) Hz, 1H, \( CHCH_2OH \)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 28.4, 32.4, 37.1, 39.1, 39.7, 40.4, 58.1, 115.5, 152.6; IR (ef) 3427 (br), 3064, 2920, 2850, 1596, 1513, 1358 cm\(^{-1}\); MS (Cl) \( m/z \) (rel. intensity) 177 (M, 5), 161 (M – OH, 100), 41 (9), 39 (11).
To a solution of the above material (2.00 g, 11.3 mmol) in dichloromethane (70 mL) at room temperature was added manganese dioxide (20.0 g, 230 mmol) and the resultant mixture was stirred for 3 h. The reaction mixture was then filtered through a pad of celite, the filter-cake was washed with dichloromethane (3 × 20 mL) and the combined filtrates were concentrated in vacuo. Purification by flash chromatography using hexanes:ether (3:1) as the eluant afforded the title compound 160 (1.77 g, 90%) as a colourless solid. \( R_f = 0.55 \), hexanes:ether (1:1); \textbf{M.p.} 48-49 °C, hexanes:ether; \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \( \delta 1.90 \) (m, 6H, CH), 2.01 (m, 6H, CH), 2.51 (s, 1H, CHC), 3.61 (s, 1H, CHC), 5.78 (d, \( J = 8.4 \) Hz, 1H, CHCHO), 10.00 (d, \( J = 8.4 \) Hz, 1H, CHCHO); \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \( \delta 28.1, 33.4, 36.7, 39.7, 40.0, 41.6, 121.4, 176.9, 190.0 \); \textbf{IR} (ef) 2913, 2850, 1669, 1622, 1450, 1196, 1132 cm\textsuperscript{-1}; \textbf{MS} (CI) \( m/z \) (rel. intensity) 175 (M + H, 100), 39 (15).

\textbf{6.3.7 2-Methylcyclopentene-1-carboxaldehyde (165)} \textsuperscript{81,82}

\begin{center}
\includegraphics[width=0.2\textwidth]{165.png}
\end{center}

Ozone was bubbled into a solution of methylcyclohexene (161) (18.0 mL, 152 mmol) in dichloromethane (40 mL) and methanol (75 mL) at -78 °C until a blue colour developed. The resultant solution was degassed by bubbling nitrogen through it and then was poured into a mixture of dimethyl sulfide (40 mL) and \( p \)-toluenesulfonic acid monohydrate (400 mg, 2.11 mmol). After 16 h at room temperature, the resultant mixture was diluted with dichloromethane (200 mL) and then washed with hydrochloric acid (3 M, 75 mL), water (75 mL) and brine (75 mL). The organic layer was dried over
anhydrous sodium sulfate and concentrated in vacuo. Purification by distillation at reduced pressure (B.p. ~140 °C, 4 mm Hg) afforded 1,1-dimethoxyheptan-6-one (19.7 g, 75%) as a colourless oil. To a solution of this material (5.00 g, 28.7 mmol) in tetrahydrofuran (50 mL) at 0 °C was added an aqueous solution of sulfuric acid (50 mL, 3% v/v). The reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 1.5 h. The resultant mixture was diluted with dichloromethane (150 mL) and then washed with a saturated aqueous solution of sodium bicarbonate (2 × 25 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo to afford 6-ketoheptanal (3.68 g). To a solution of this material in ether (75 mL) at 0 °C was added piperidine (3.1 mL, 32 mmol). After 3 h, the reaction mixture was washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to afford the corresponding ketoenamine (5.20 g). A solution of this material (5.20 g, 26.6 mmol) and acetic acid (3.7 mL) in ether (70 mL) was heated at reflux for 6 h. The resultant mixture was allowed to cool to room temperature and a saturated aqueous solution of sodium bicarbonate (35 mL) was added. The organic layer was washed with brine (35 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by distillation at reduced pressure afforded the title compound 165 (2.11 g, 67% over three steps) as a colourless oil. \( R_f = 0.60 \), hexanes:ether (1:1); \textbf{B.p.} 80-85 °C, 1 mm Hg (lit.\textsuperscript{81} 30-75 °C, 0.05 mm Hg). \textbf{\( ^1\)H NMR} (400 MHz, CDCl\(_3\)) \( \delta \) 1.85 (m, 2H, CH\(_2\)), 2.14 (m, 3H, CH\(_3\)), 2.56 (m, 4H, CH\(_2\)), 9.99 (s, 1H, CHO); \textbf{\( ^{13}\)C NMR} (101 MHz, CDCl\(_3\)) \( \delta \) 14.4, 20.8, 30.1, 41.0, 138.2, 163.6, 188.7; \textbf{IR} (ef) 2959, 2861, 1664, 1449, 1381, 1259 cm\(^{-1}\); \textbf{MS} (Cl) \( m/z \) (rel. intensity) 111 (M + H, 100), 99 (8), 61 (64), 43 (90).
6.3.8 Methyl-2-methyl-4,5-dihydrofuran-3-carboxylate (167)

A solution of α-acetyl-γ-butyrolactone (166) (70.0 mL, 0.650 mmol) and hydrogen chloride (11.2 g, 0.307 mmol) in methanol (600 mL) was heated at reflux for 4 days. The resultant mixture was allowed to cool to room temperature and a saturated aqueous solution of sodium bicarbonate (1.6 L) was added. The resultant mixture was extracted with ether (9 × 150 mL) and the combined organic layers were washed with water (2 × 200 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Distillation (B.p. 50-123 °C, ~15 mm Hg) of the resultant oil afforded the impure title compound 167 (35.6 g) as a clear oil. Redistillation of this material, in the presence of concentrated sulfuric acid (4 drops), afforded the title compound 167 (17.8 g, 19%) as colourless crystals. \( R_f = 0.63, \text{ether} \); \( \text{B.p.} \ 78-84 \degree \text{C}, \sim 15 \text{mm Hg} \) (lit.\(^{70}\) 72-73 \degree \text{C}, \sim 12 \text{mm Hg})\); \( \text{M.p.} \ 28-29 \degree \text{C} \) (lit.\(^{71}\) 31.5-32.5 \degree \text{C}, petroleum ether); \( ^{1} \text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \ 2.17 \) (s, 3H, \( \text{Me} \)), 2.87 (apparent t, \( J = 9.6 \) Hz, 2H, OCH\(_2\)CH\(_2\)), 3.70 (s, 3H, CO\(_2\)Me), 4.39 (apparent t, \( J = 9.6 \) Hz, 2H, OCH\(_3\)); \( ^{13} \text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \ 13.8, 29.5, 50.6, 70.2, 101.7, 166.5, 168.7 \); \( \text{IR} \) (ef) 2952, 1705, 1651, 1438, 1388, 1334, 1229, 1084, 998 cm\(^{-1}\); \( \text{MS} \) (El) \( m/z \) (rel. intensity) 143 (M + H, 38), 142 (M, 18), 43 (100).
6.3.9 2-Methyl-3-hydroxymethyl-4,5-dihydrofuran (168)

A solution of the ester 167 (1.88 g, 13.2 mmol) in ether (15 mL) was added to a suspension of lithium aluminum hydride (753 mg, 19.8 mmol) in ether (40 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature over 20 min and then was cooled to 0 °C. Water (0.75 mL), an aqueous solution of sodium hydroxide (2 M, 0.75 mL) and water (2.25 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (3 × 50 mL) and the combined filtrates were concentrated in vacuo to afford the title compound 168 (1.45 g, 96%) as pale yellow oil. This material proved to be unstable to purification (Kugelrohr distillation or flash chromatography on silica gel) and to storage. Thus, the crude title compound 168 (>95% pure) was used immediately in subsequent experiments. 

\[ \text{Rf} = 0.31, \text{ether; } \] 

\[ ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 1.64 (s, 1H, OH), 1.78 (t, J = 1.8 Hz, 3H, Me), 2.72 (\text{apparent t, } J = 9.4 \text{ Hz, 2H, OCH}_2\text{CH}_2\text{)}, 4.18 (d, J = 5.3 \text{ Hz, 2H, CH}_2\text{OH}), 4.29 (\text{apparent t, } J = 9.4 \text{ Hz, 2H, OCH}_2\text{)}; \] 

\[ ^13\text{C NMR (101 MHz, CDCl}_3\text{)} \delta 11.1, 31.4, 57.9, 68.3, 106.8, 151.1; \] 

\[ \text{IR (ef) 3335 (broad), 2917, 2817, 1693, 1378, 1215, 998, 972 cm}^{-1}; \] 

\[ \text{MS (EI) } m/z \text{ (rel. intensity) 115 (M + H, 27), 97 (M – H}_2\text{O, 23), 43 (100).} \]
6.3.10 2-Methyl-3-formyl-4,5-dihydrofuran (169)\(^{153}\)

![Image of compound 169]

A suspension of the alcohol 168 [prepared from the corresponding ester 167 (2.50 g, 17.6 mmol)] and manganese dioxide (24.3 g, 27.9 mmol) in dichloromethane (100 mL) was stirred at room temperature for 54 h. The reaction mixture was then filtered through a pad of celite, the filter-cake was washed with dichloromethane (3 × 100 mL) and the combined filtrates were concentrated \textit{in vacuo}. Purification by distillation at reduced pressure afforded the \textit{title compound} 169 (0.80 g, 41%) as a pale yellow oil. \textbf{B.p.} 95-100 °C, ~2 mm Hg; \textbf{\(^1H\) NMR} (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 1.45 (s, 3H, Me), 2.47 (apparent t, \(J = 9.5\) Hz, OCH\(_2\)CH\(_2\)), 3.67 (apparent t, \(J = 9.5\) Hz, OCH\(_2\)), 9.61 (s, 1H, CHO); \textbf{\(^{13}C\) NMR} (101 MHz, C\(_6\)D\(_6\)) \(\delta\) 11.9, 27.2, 71.6, 115.7, 173.7, 184.1; \textbf{IR} (ef) 2975, 2930, 1651, 1393, 1237, 972; \textbf{MS} (El) \(m/z\) (rel. intensity) 112 (M, 67), 84 (100).

6.3.11 2,6,10-Tricyclopentylidene-2\(\text{H}\),6\(\text{H}\),10\(\text{H}\)-dipyran\[6,5-f,6',5'-h\]chromene (172)

![Image of compound 172]

A mixture of phloroglucinol (14) (38 mg, 0.30 mmol), cyclopentylideneacetaldehyde (152) (139 mg, 1.26 mmol), phenylboronic acid (113 mg, 0.93 mmol), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 4 h. The resultant solution was cooled to room temperature and on
filtration through a pad of silica gel with ether (125 mL) was concentrated in vacuo. Purification by flash chromatography using hexanes:ether (99:1) as the eluant afforded the title compound 172 (69 mg, 57%) as a solid white foam. \( R_f = 0.28 \), hexanes:ether (99:1); \textit{M.p.} 41-44 °C, hexanes:ether; \( ^1H \text{NMR} \) (400 MHz, \( C_6D_6 \)) \( \delta \) 1.32 (m, 6H, \( CH_2 \)), 1.45 (m, 6H, \( CH_2 \)), 1.83 (m, 6H, \( CH_2 \)), 2.15 (m, 6H, \( CH_2 \)), 5.32 (d, \( J = 10.0 \) Hz, 3H, \( ArCHCH \)), 6.87 (d, \( J = 9.9 \) Hz, 3H, \( ArCHCH \)); \( ^13C \text{NMR} \) (101 MHz, \( C_6D_6 \)) \( \delta \) 23.8, 39.4, 87.8, 104.9, 118.4, 124.8, 149.7; IR (ef) 2959, 1638, 1592, 1445, 1373, 1154, 1009 cm\(^{-1} \); MS (EI) \( m/z \) (rel. intensity) 402 (M, 54), 57 (54), 44 (100), 18 (49), 14 (66); FAB- HRMS Calcd. for \( C_{27}H_{30}O_3 \): 402.2195. Found: 402.2198.

6.3.12 2,6,10-Tricyclohexylidene-2H,6H,10H-dipyran-6,5-f,6',5'-h]chromene (173)

\[ \text{A mixture of phloroglucinol (14) (38 mg, 0.30 mmol), cyclohexylideneacetaldehyde (156) (152 mg, 1.23 mmol), phenylboronic acid (114 mg, 0.94 mmol), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 135 min. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated in vacuo. Purification by flash chromatography using hexanes:ether (99:1) as the eluant afforded the title compound 173 (69 mg, 52%) as a solid white foam. \( R_f = 0.38 \), hexanes:ether (99:1); \textit{M.p.} 50-52 °C, hexanes:ether; \( ^1H \text{NMR} \) (400 MHz, \( C_6D_6 \)) \( \delta \) 1.10 (m, 3H, \( CH_2 \)),}
1.31 (m, 12H, CH₂), 1.49 (m, 3H, CH₂), 1.76 (m, 6H, CH₂), 2.01 (m, 6H, CH₂), 5.32 (d, J = 9.9 Hz, 3H, ArCHCH), 6.96 (d, J = 9.9 Hz, 3H, ArCHCH); \(^{13}\)C NMR (101 MHz, C₆D₆) δ 21.9, 25.7, 36.2, 77.4, 104.8, 117.9, 126.0, 149.8; IR (ef) 3052, 2931, 2857, 1637, 1591, 1447, 1372, 1272, 1187, 1139 cm\(^{-1}\); MS (El) m/z (rel. intensity) 444 (M, 5), 91 (5), 56 (5), 55 (10), 18 (100); Anal. Calcd. for C₃₀H₃₆O₃: C, 81.04; H, 8.16. Found: C, 80.92; H, 8.34.

6.3.13 2,6,10-Triadamantylidene-2H,6H,10H-dipyran[6,5-f,6',5'-h]chromene (174)

A mixture of phloroglucinol (14) (38 mg, 0.30 mmol), adamantylideneacetaldehyde (160) (214 mg, 1.22 mmol), phenylboronic acid (112 mg, 0.92 mmol), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 22 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with chloroform (200 mL) was concentrated in vacuo. Purification by flash chromatography using chloroform as the eluant afforded the title compound 174 (141 mg, 79%) as a white solid. \(R_f = 0.79\) (chloroform); M.p. 234-235 °C, chloroform; \(^1\)H NMR (400 MHz, CDCl₃) δ 1.52 (m, 3H, CH), 1.55 (m, 3H, CH), 1.69 (m, 3H, CH), 1.73 (m, 9H, CH), 1.87 (m, 6H, CH), 1.94 (m, 3H, CH), 1.97 (m, 3H, CH), 2.11 (m, 6H, CH), 2.30 (m, 3H, CHC), 2.34 (m, 3H, CHC), 6.00 (d, J = 10.0 Hz,
3H, ArCHCH), 6.75 (d, J = 10.0 Hz, 3H, ArCHCH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$
26.9, 27.3, 32.7, 33.8, 35.8, 38.0, 80.7, 105.3, 117.9, 124.1, 148.9; IR (ef) 2902, 2855,
1633, 1588, 1445, 1189, 1133, 1097 cm$^{-1}$; MS (MALDI-TOF) m/z (rel. intensity) 640 (M
+ K, 16), 623 (M + Na, 19), 601 (M + H, 100); FAB-HRMS Calcd. for C$_{42}$H$_{48}$O$_3$:
600.3603. Found: 600.3606.

6.3.14 X-Ray Crystallographic Analysis of 2,6,10-Triadamantylidene-
2H,6H,10H-dipyran0[6,5-f,6',5'-h]chromene (174)*

A single crystal of the chromene 174, a yellow block that had the dimensions 0.43
$\times$ 0.42 $\times$ 0.04 mm, was mounted on a glass fibre using epoxy adhesive. The data for this
crystal was acquired at 293 K on an Enraf Nonius CAD4F diffractometer with graphite
monochromatic Mo K$\alpha$ radiation. The following data range was recorded: 4° $\leq$ 20 $\leq$ 45°.
The data was corrected by integration for the effects of absorption using a Gaussian
method with the following transmission range: 0.974433 – 0.993929. Data reduction for
the crystal of the chromene 174 included corrections for Lorentz and polarization effects.
Final unit-cell dimensions were determined based on the following well-centred
reflections: 40 reflections with range 22° $\leq$ 20 $\leq$ 24°.

For the chromene 174, coordinates and anisotropic displacement parameters for
the non-carbon and hydrogen atoms were refined; carbon atoms were refined using
isotropic thermal parameters. Hydrogen atoms were placed in calculated positions (C-H
0.95 Å) and their coordinate shifts were linked with those of the respective carbon atoms
during refinement. Isotropic thermal parameters for the hydrogen atoms were initially
assigned proportionately to the equivalent isotropic thermal parameters of their respective

(*) The data for this X-ray crystal structure was obtained and solved by Mr. M. Katz (Simon Fraser
University).
carbon atoms. Subsequently the isotropic thermal parameters for the C-H hydrogen atoms were constrained to have identical shifts during refinement. The programs used for all absorption corrections, data reduction and processing of the chromene 174 were from the NRCVAX Crystal Structure System. The structure was refined using CRYSTALS. An ORTEP representation of the chromene 174 is provided below (Figure 6.3.14.1). Crystallographic data, fractional atomic coordinates and equivalent isotropic thermal displacement parameters, selected bond lengths as well as selected bond angles for the chromene 174 are also listed below (Table 6.3.14.1, Table 6.3.14.2, Table 6.3.14.3 and Table 6.3.14.4, respectively).
Figure 6.3.14.1 ORTEP representation of the chromene (174) (the thermal ellipsoids are drawn at a 50% probability level and the hydrogen atoms have been omitted for clarity).

Table 6.3.14.1 Summary of Crystallographic Data for the Chromene (174)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>C\textsubscript{42}H\textsubscript{48}O\textsubscript{3}</td>
</tr>
<tr>
<td>FW (g mol\textsuperscript{-1})</td>
<td>600.84</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>293</td>
</tr>
<tr>
<td>Wavelength (Mo K(\alpha), Å)</td>
<td>0.71073</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space Group</td>
<td>P(\bar{1})</td>
</tr>
<tr>
<td>(a) (Å)</td>
<td>9.533(2)</td>
</tr>
<tr>
<td>(b) (Å)</td>
<td>11.808(3)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>$c$ (Å)</td>
<td>15.530(3)</td>
</tr>
<tr>
<td>$\alpha$ (°)</td>
<td>109.000(18)</td>
</tr>
<tr>
<td>$\beta$ (°)</td>
<td>91.953(18)</td>
</tr>
<tr>
<td>$\gamma$ (°)</td>
<td>106.166(19)</td>
</tr>
<tr>
<td>$Z$</td>
<td>2</td>
</tr>
<tr>
<td>$U$ (Å$^3$)</td>
<td>1572.6(7)</td>
</tr>
<tr>
<td>$D_{\text{calc}}$ (g cm$^{-3}$)</td>
<td>1.269</td>
</tr>
<tr>
<td>$2\theta$ limits (°)</td>
<td>4-45</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>4632</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4632</td>
</tr>
<tr>
<td>Reflections observed [$I &gt; 2.5\sigma(I)$]</td>
<td>2523</td>
</tr>
<tr>
<td>Goodness-of-fit on $F$</td>
<td>1.9364</td>
</tr>
<tr>
<td>$R_1$, $R_w$ [$I &gt; 2.5\sigma(I)$]</td>
<td>0.0667, 0.0909</td>
</tr>
</tbody>
</table>

Table 6.3.14.2 Fractional Atomic Coordinates (Å) and Equivalent Isotropic Thermal Displacement Parameters [$U$(iso), (Å$^2$)] for the Chromene (174)*

<table>
<thead>
<tr>
<th>Atom</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>U (iso)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.5924(4)</td>
<td>0.3281(3)</td>
<td>0.2032(2)</td>
<td>0.0469</td>
</tr>
<tr>
<td>O2</td>
<td>0.5841(4)</td>
<td>0.2156(3)</td>
<td>0.4700(2)</td>
<td>0.0447</td>
</tr>
<tr>
<td>O3</td>
<td>0.1788(4)</td>
<td>0.0117(3)</td>
<td>0.2307(2)</td>
<td>0.0437</td>
</tr>
<tr>
<td>C1</td>
<td>0.5199(6)</td>
<td>0.2522(5)</td>
<td>0.2484(3)</td>
<td>0.0353</td>
</tr>
<tr>
<td>C2</td>
<td>0.5934(5)</td>
<td>0.2728(5)</td>
<td>0.3348(3)</td>
<td>0.0359</td>
</tr>
<tr>
<td>C3</td>
<td>0.7438(6)</td>
<td>0.3483(5)</td>
<td>0.3701(3)</td>
<td>0.0459</td>
</tr>
<tr>
<td>C4</td>
<td>0.7974(6)</td>
<td>0.3718(5)</td>
<td>0.4568(4)</td>
<td>0.0495</td>
</tr>
<tr>
<td>C5</td>
<td>0.6944(6)</td>
<td>0.3344(5)</td>
<td>0.5229(3)</td>
<td>0.0425</td>
</tr>
<tr>
<td>C6</td>
<td>0.5184(6)</td>
<td>0.2065(5)</td>
<td>0.3858(3)</td>
<td>0.0366</td>
</tr>
<tr>
<td>C7</td>
<td>0.3796(6)</td>
<td>0.1189(5)</td>
<td>0.3548(3)</td>
<td>0.0347</td>
</tr>
<tr>
<td>C8</td>
<td>0.2998(6)</td>
<td>0.0383(5)</td>
<td>0.4034(3)</td>
<td>0.041</td>
</tr>
<tr>
<td>C9</td>
<td>0.1599(6)</td>
<td>-0.0297(5)</td>
<td>0.3730(3)</td>
<td>0.0436</td>
</tr>
</tbody>
</table>

(*) The occupancies for all atoms listed in this table are 1.0.
<table>
<thead>
<tr>
<th>Atom</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>U (iso)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10</td>
<td>0.0761(6)</td>
<td>-0.0176(5)</td>
<td>0.2935(3)</td>
<td>0.0392</td>
</tr>
<tr>
<td>C11</td>
<td>0.3138(5)</td>
<td>0.1008(4)</td>
<td>0.2688(3)</td>
<td>0.0329</td>
</tr>
<tr>
<td>C12</td>
<td>0.3806(6)</td>
<td>0.1669(5)</td>
<td>0.2133(3)</td>
<td>0.0362</td>
</tr>
<tr>
<td>C13</td>
<td>0.3137(6)</td>
<td>0.1624(5)</td>
<td>0.1271(3)</td>
<td>0.0458</td>
</tr>
<tr>
<td>C14</td>
<td>0.3943(6)</td>
<td>0.2220(5)</td>
<td>0.0763(4)</td>
<td>0.0467</td>
</tr>
<tr>
<td>C15</td>
<td>0.5591(6)</td>
<td>0.2838(5)</td>
<td>0.1028(3)</td>
<td>0.0429</td>
</tr>
<tr>
<td>C16</td>
<td>0.6197(6)</td>
<td>0.4346(5)</td>
<td>0.5646(4)</td>
<td>0.0465</td>
</tr>
<tr>
<td>C17</td>
<td>0.5069(6)</td>
<td>0.3905(6)</td>
<td>0.6249(4)</td>
<td>0.0559</td>
</tr>
<tr>
<td>C18</td>
<td>0.5835(7)</td>
<td>0.3676(6)</td>
<td>0.6998(4)</td>
<td>0.0556</td>
</tr>
<tr>
<td>C19</td>
<td>0.6980(7)</td>
<td>0.4861(6)</td>
<td>0.7590(4)</td>
<td>0.0675</td>
</tr>
<tr>
<td>C20</td>
<td>0.8140(7)</td>
<td>0.5319(6)</td>
<td>0.7034(4)</td>
<td>0.0627</td>
</tr>
<tr>
<td>C21</td>
<td>0.7388(8)</td>
<td>0.5562(5)</td>
<td>0.6243(4)</td>
<td>0.0672</td>
</tr>
<tr>
<td>C22</td>
<td>0.8869(6)</td>
<td>0.4313(6)</td>
<td>0.6603(4)</td>
<td>0.0579</td>
</tr>
<tr>
<td>C23</td>
<td>0.7702(5)</td>
<td>0.3103(5)</td>
<td>0.5987(3)</td>
<td>0.0367</td>
</tr>
<tr>
<td>C24</td>
<td>0.6588(6)</td>
<td>0.2672(5)</td>
<td>0.6595(4)</td>
<td>0.0485</td>
</tr>
<tr>
<td>C25</td>
<td>-0.0002(6)</td>
<td>0.0834(5)</td>
<td>0.3242(3)</td>
<td>0.0409</td>
</tr>
<tr>
<td>C26</td>
<td>-0.1186(7)</td>
<td>0.0446(6)</td>
<td>0.3829(4)</td>
<td>0.059</td>
</tr>
<tr>
<td>C27</td>
<td>-0.2356(6)</td>
<td>-0.0789(6)</td>
<td>0.3260(4)</td>
<td>0.0554</td>
</tr>
<tr>
<td>C28</td>
<td>-0.3044(7)</td>
<td>-0.0629(7)</td>
<td>0.2429(4)</td>
<td>0.0651</td>
</tr>
<tr>
<td>C29</td>
<td>-0.1882(7)</td>
<td>-0.0267(6)</td>
<td>0.1848(4)</td>
<td>0.057</td>
</tr>
<tr>
<td>C30</td>
<td>-0.0756(7)</td>
<td>0.0982(5)</td>
<td>0.2424(4)</td>
<td>0.0528</td>
</tr>
<tr>
<td>C31</td>
<td>-0.1136(6)</td>
<td>-0.1271(5)</td>
<td>0.1528(3)</td>
<td>0.0476</td>
</tr>
<tr>
<td>C32</td>
<td>-0.0397(6)</td>
<td>-0.1442(5)</td>
<td>0.2340(3)</td>
<td>0.0372</td>
</tr>
<tr>
<td>C33</td>
<td>-0.1590(6)</td>
<td>-0.1795(5)</td>
<td>0.2934(4)</td>
<td>0.0547</td>
</tr>
<tr>
<td>C34</td>
<td>0.6179(6)</td>
<td>0.4032(5)</td>
<td>0.0781(3)</td>
<td>0.0418</td>
</tr>
<tr>
<td>C35</td>
<td>0.7817(6)</td>
<td>0.4632(5)</td>
<td>0.1124(4)</td>
<td>0.0519</td>
</tr>
<tr>
<td>C36</td>
<td>0.8660(6)</td>
<td>0.3722(6)</td>
<td>0.0695(4)</td>
<td>0.0509</td>
</tr>
<tr>
<td>C37</td>
<td>0.8422(6)</td>
<td>0.3358(6)</td>
<td>-0.0337(4)</td>
<td>0.0574</td>
</tr>
<tr>
<td>C38</td>
<td>0.6787(7)</td>
<td>0.2742(6)</td>
<td>-0.0706(3)</td>
<td>0.0537</td>
</tr>
<tr>
<td>C39</td>
<td>0.5952(7)</td>
<td>0.3669(5)</td>
<td>-0.0269(3)</td>
<td>0.0486</td>
</tr>
<tr>
<td>Atom</td>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td>U (iso)</td>
</tr>
<tr>
<td>------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>C40</td>
<td>0.6198(7)</td>
<td>0.1586(5)</td>
<td>-0.0458(3)</td>
<td>0.0542</td>
</tr>
<tr>
<td>C41</td>
<td>0.6453(6)</td>
<td>0.1928(5)</td>
<td>0.0598(3)</td>
<td>0.043</td>
</tr>
<tr>
<td>C42</td>
<td>0.8110(6)</td>
<td>0.2547(5)</td>
<td>0.0936(4)</td>
<td>0.0539</td>
</tr>
<tr>
<td>H31</td>
<td>0.8045</td>
<td>0.3845</td>
<td>0.3326</td>
<td>0.068(8)</td>
</tr>
<tr>
<td>H41</td>
<td>0.9001</td>
<td>0.409</td>
<td>0.4776</td>
<td>0.072(8)</td>
</tr>
<tr>
<td>H81</td>
<td>0.349</td>
<td>0.0333</td>
<td>0.4556</td>
<td>0.070(8)</td>
</tr>
<tr>
<td>H91</td>
<td>0.1098</td>
<td>-0.086</td>
<td>0.4019</td>
<td>0.074(8)</td>
</tr>
<tr>
<td>H131</td>
<td>0.2127</td>
<td>0.1164</td>
<td>0.1057</td>
<td>0.069(8)</td>
</tr>
<tr>
<td>H141</td>
<td>0.3475</td>
<td>0.2269</td>
<td>0.0232</td>
<td>0.077(8)</td>
</tr>
<tr>
<td>H161</td>
<td>0.571</td>
<td>0.449</td>
<td>0.5166</td>
<td>0.049(3)</td>
</tr>
<tr>
<td>H171</td>
<td>0.4612</td>
<td>0.4533</td>
<td>0.6513</td>
<td>0.062(3)</td>
</tr>
<tr>
<td>H172</td>
<td>0.4341</td>
<td>0.3151</td>
<td>0.5875</td>
<td>0.062(3)</td>
</tr>
<tr>
<td>H181</td>
<td>0.513</td>
<td>0.3394</td>
<td>0.736</td>
<td>0.056(3)</td>
</tr>
<tr>
<td>H191</td>
<td>0.7438</td>
<td>0.4719</td>
<td>0.8082</td>
<td>0.066(3)</td>
</tr>
<tr>
<td>H192</td>
<td>0.652</td>
<td>0.5494</td>
<td>0.7832</td>
<td>0.066(3)</td>
</tr>
<tr>
<td>H201</td>
<td>0.8867</td>
<td>0.6072</td>
<td>0.741</td>
<td>0.063(3)</td>
</tr>
<tr>
<td>H211</td>
<td>0.6945</td>
<td>0.6199</td>
<td>0.6511</td>
<td>0.070(3)</td>
</tr>
<tr>
<td>H212</td>
<td>0.8077</td>
<td>0.583</td>
<td>0.5867</td>
<td>0.070(3)</td>
</tr>
<tr>
<td>H221</td>
<td>0.9332</td>
<td>0.4162</td>
<td>0.7088</td>
<td>0.060(3)</td>
</tr>
<tr>
<td>H222</td>
<td>0.9588</td>
<td>0.4594</td>
<td>0.6248</td>
<td>0.060(3)</td>
</tr>
<tr>
<td>H231</td>
<td>0.8165</td>
<td>0.2477</td>
<td>0.5731</td>
<td>0.036(3)</td>
</tr>
<tr>
<td>H241</td>
<td>0.708</td>
<td>0.2546</td>
<td>0.7081</td>
<td>0.049(3)</td>
</tr>
<tr>
<td>H242</td>
<td>0.5867</td>
<td>0.1907</td>
<td>0.6233</td>
<td>0.049(3)</td>
</tr>
<tr>
<td>H251</td>
<td>0.0708</td>
<td>0.161</td>
<td>0.3598</td>
<td>0.045(3)</td>
</tr>
<tr>
<td>H261</td>
<td>-0.0727</td>
<td>0.0349</td>
<td>0.4342</td>
<td>0.057(3)</td>
</tr>
<tr>
<td>H262</td>
<td>-0.1651</td>
<td>0.1081</td>
<td>0.4039</td>
<td>0.057(3)</td>
</tr>
<tr>
<td>H271</td>
<td>-0.3088</td>
<td>-0.102</td>
<td>0.3624</td>
<td>0.060(3)</td>
</tr>
<tr>
<td>H281</td>
<td>-0.3472</td>
<td>0.0031</td>
<td>0.2642</td>
<td>0.070(3)</td>
</tr>
<tr>
<td>H282</td>
<td>-0.3785</td>
<td>-0.1383</td>
<td>0.2069</td>
<td>0.070(3)</td>
</tr>
<tr>
<td>H291</td>
<td>-0.2325</td>
<td>-0.0173</td>
<td>0.1328</td>
<td>0.066(3)</td>
</tr>
<tr>
<td>Atom</td>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td>U (iso)</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>H301</td>
<td>-0.1254</td>
<td>0.1591</td>
<td>0.2646</td>
<td>0.053(3)</td>
</tr>
<tr>
<td>H302</td>
<td>-0.0046</td>
<td>0.1252</td>
<td>0.206</td>
<td>0.053(3)</td>
</tr>
<tr>
<td>H311</td>
<td>-0.1864</td>
<td>-0.2041</td>
<td>0.118</td>
<td>0.049(3)</td>
</tr>
<tr>
<td>H312</td>
<td>-0.0425</td>
<td>-0.1045</td>
<td>0.1151</td>
<td>0.049(3)</td>
</tr>
<tr>
<td>H321</td>
<td>0.0068</td>
<td>-0.2079</td>
<td>0.2133</td>
<td>0.033(3)</td>
</tr>
<tr>
<td>H331</td>
<td>-0.1146</td>
<td>-0.1882</td>
<td>0.3456</td>
<td>0.057(3)</td>
</tr>
<tr>
<td>H332</td>
<td>-0.2305</td>
<td>-0.257</td>
<td>0.2581</td>
<td>0.057(3)</td>
</tr>
<tr>
<td>H341</td>
<td>0.5663</td>
<td>0.4612</td>
<td>0.1052</td>
<td>0.037(3)</td>
</tr>
<tr>
<td>H351</td>
<td>0.817</td>
<td>0.5359</td>
<td>0.0959</td>
<td>0.050(3)</td>
</tr>
<tr>
<td>H352</td>
<td>0.7975</td>
<td>0.4868</td>
<td>0.1774</td>
<td>0.050(3)</td>
</tr>
<tr>
<td>H361</td>
<td>0.9679</td>
<td>0.4115</td>
<td>0.092</td>
<td>0.056(3)</td>
</tr>
<tr>
<td>H371</td>
<td>0.878</td>
<td>0.4084</td>
<td>-0.0502</td>
<td>0.060(3)</td>
</tr>
<tr>
<td>H372</td>
<td>0.8946</td>
<td>0.278</td>
<td>-0.0596</td>
<td>0.060(3)</td>
</tr>
<tr>
<td>H381</td>
<td>0.6649</td>
<td>0.2519</td>
<td>-0.1355</td>
<td>0.052(3)</td>
</tr>
<tr>
<td>H391</td>
<td>0.6287</td>
<td>0.4396</td>
<td>-0.0435</td>
<td>0.058(3)</td>
</tr>
<tr>
<td>H392</td>
<td>0.4933</td>
<td>0.3269</td>
<td>-0.0491</td>
<td>0.058(3)</td>
</tr>
<tr>
<td>H401</td>
<td>0.6687</td>
<td>0.099</td>
<td>-0.0743</td>
<td>0.053(3)</td>
</tr>
<tr>
<td>H402</td>
<td>0.5171</td>
<td>0.1234</td>
<td>-0.0669</td>
<td>0.053(3)</td>
</tr>
<tr>
<td>H411</td>
<td>0.6103</td>
<td>0.1194</td>
<td>0.0754</td>
<td>0.041(3)</td>
</tr>
<tr>
<td>H421</td>
<td>0.8633</td>
<td>0.198</td>
<td>0.0648</td>
<td>0.056(3)</td>
</tr>
<tr>
<td>H422</td>
<td>0.8275</td>
<td>0.2754</td>
<td>0.1584</td>
<td>0.056(3)</td>
</tr>
</tbody>
</table>

Table 6.3.14.3 Bond Lengths (Å) for the Chromene (174)

<table>
<thead>
<tr>
<th>Atoms</th>
<th>Bond Lengths (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1-C1</td>
<td>1.368(5)</td>
</tr>
<tr>
<td>O1-C15</td>
<td>1.465(6)</td>
</tr>
<tr>
<td>O2-C5</td>
<td>1.456(6)</td>
</tr>
<tr>
<td>O2-C6</td>
<td>1.389(6)</td>
</tr>
<tr>
<td>O3-C10</td>
<td>1.457(6)</td>
</tr>
<tr>
<td>O3-C11</td>
<td>1.379(5)</td>
</tr>
</tbody>
</table>

230
<table>
<thead>
<tr>
<th>Atoms</th>
<th>Bond Lengths (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-C2</td>
<td>1.406(7)</td>
</tr>
<tr>
<td>C1-C12</td>
<td>1.387(7)</td>
</tr>
<tr>
<td>C2-C3</td>
<td>1.438(7)</td>
</tr>
<tr>
<td>C2-C6</td>
<td>1.372(7)</td>
</tr>
<tr>
<td>C3-C4</td>
<td>1.335(7)</td>
</tr>
<tr>
<td>C4-C5</td>
<td>1.528(7)</td>
</tr>
<tr>
<td>C5-C16</td>
<td>1.526(8)</td>
</tr>
<tr>
<td>C5-C23</td>
<td>1.505(7)</td>
</tr>
<tr>
<td>C6-C7</td>
<td>1.387(7)</td>
</tr>
<tr>
<td>C7-C8</td>
<td>1.469(7)</td>
</tr>
<tr>
<td>C7-C11</td>
<td>1.380(7)</td>
</tr>
<tr>
<td>C8-C9</td>
<td>1.327(7)</td>
</tr>
<tr>
<td>C9-C10</td>
<td>1.516(7)</td>
</tr>
<tr>
<td>C10-C25</td>
<td>1.521(8)</td>
</tr>
<tr>
<td>C10-C32</td>
<td>1.556(7)</td>
</tr>
<tr>
<td>C11-C12</td>
<td>1.399(6)</td>
</tr>
<tr>
<td>C12-C13</td>
<td>1.442(7)</td>
</tr>
<tr>
<td>C13-C14</td>
<td>1.346(7)</td>
</tr>
<tr>
<td>C14-C15</td>
<td>1.514(7)</td>
</tr>
<tr>
<td>C15-C34</td>
<td>1.542(7)</td>
</tr>
<tr>
<td>C15-C41</td>
<td>1.529(8)</td>
</tr>
<tr>
<td>C16-C17</td>
<td>1.544(7)</td>
</tr>
<tr>
<td>C16-C21</td>
<td>1.537(8)</td>
</tr>
<tr>
<td>C17-C18</td>
<td>1.489(8)</td>
</tr>
<tr>
<td>C18-C19</td>
<td>1.496(8)</td>
</tr>
<tr>
<td>C18-C24</td>
<td>1.527(8)</td>
</tr>
<tr>
<td>C19-C20</td>
<td>1.515(8)</td>
</tr>
<tr>
<td>C20-C21</td>
<td>1.547(9)</td>
</tr>
<tr>
<td>C20-C22</td>
<td>1.521(9)</td>
</tr>
<tr>
<td>C22-C23</td>
<td>1.532(7)</td>
</tr>
<tr>
<td>Atoms</td>
<td>Bond Lengths (Å)</td>
</tr>
<tr>
<td>------------</td>
<td>------------------</td>
</tr>
<tr>
<td>C23-C24</td>
<td>1.535(7)</td>
</tr>
<tr>
<td>C25-C26</td>
<td>1.539(7)</td>
</tr>
<tr>
<td>C25-C30</td>
<td>1.521(7)</td>
</tr>
<tr>
<td>C26-C27</td>
<td>1.529(8)</td>
</tr>
<tr>
<td>C27-C28</td>
<td>1.517(8)</td>
</tr>
<tr>
<td>C27-C33</td>
<td>1.523(8)</td>
</tr>
<tr>
<td>C28-C29</td>
<td>1.510(8)</td>
</tr>
<tr>
<td>C29-C30</td>
<td>1.524(8)</td>
</tr>
<tr>
<td>C29-C31</td>
<td>1.507(9)</td>
</tr>
<tr>
<td>C31-C32</td>
<td>1.519(7)</td>
</tr>
<tr>
<td>C32-C33</td>
<td>1.541(7)</td>
</tr>
<tr>
<td>C34-C35</td>
<td>1.519(7)</td>
</tr>
<tr>
<td>C34-C39</td>
<td>1.536(7)</td>
</tr>
<tr>
<td>C35-C36</td>
<td>1.515(8)</td>
</tr>
<tr>
<td>C36-C37</td>
<td>1.508(8)</td>
</tr>
<tr>
<td>C36-C42</td>
<td>1.513(8)</td>
</tr>
<tr>
<td>C37-C38</td>
<td>1.524(8)</td>
</tr>
<tr>
<td>C38-C39</td>
<td>1.526(8)</td>
</tr>
<tr>
<td>C38-C40</td>
<td>1.502(8)</td>
</tr>
<tr>
<td>C40-C41</td>
<td>1.548(7)</td>
</tr>
<tr>
<td>C41-C42</td>
<td>1.535(8)</td>
</tr>
</tbody>
</table>

Table 6.3.14.4 Bond Angles (°) for the Chromene (174)

<table>
<thead>
<tr>
<th>Atoms</th>
<th>Bond Angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-O1-C15</td>
<td>118.3(4)</td>
</tr>
<tr>
<td>C5-O2-C6</td>
<td>117.0(4)</td>
</tr>
<tr>
<td>C10-O3-C11</td>
<td>117.5(4)</td>
</tr>
<tr>
<td>O1-C1-C2</td>
<td>115.0(4)</td>
</tr>
<tr>
<td>O1-C1-C12</td>
<td>121.9(4)</td>
</tr>
<tr>
<td>C2-C1-C12</td>
<td>123.0(4)</td>
</tr>
<tr>
<td>Atoms</td>
<td>Bond Angles (°)</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>C1-C2-C3</td>
<td>125.5(4)</td>
</tr>
<tr>
<td>C1-C2-C6</td>
<td>116.7(4)</td>
</tr>
<tr>
<td>C3-C2-C6</td>
<td>117.6(5)</td>
</tr>
<tr>
<td>C2-C3-C4</td>
<td>120.2(5)</td>
</tr>
<tr>
<td>C3-C4-C5</td>
<td>120.2(5)</td>
</tr>
<tr>
<td>C4-C5-O2</td>
<td>107.2(4)</td>
</tr>
<tr>
<td>C4-C5-C16</td>
<td>110.6(5)</td>
</tr>
<tr>
<td>O2-C5-C16</td>
<td>110.0(4)</td>
</tr>
<tr>
<td>C4-C5-C23</td>
<td>113.4(5)</td>
</tr>
<tr>
<td>O2-C5-C23</td>
<td>106.0(4)</td>
</tr>
<tr>
<td>C16-C5-C23</td>
<td>109.4(4)</td>
</tr>
<tr>
<td>O2-C6-C2</td>
<td>121.0(4)</td>
</tr>
<tr>
<td>O2-C6-C7</td>
<td>115.3(4)</td>
</tr>
<tr>
<td>C2-C6-C7</td>
<td>123.4(4)</td>
</tr>
<tr>
<td>C6-C7-C8</td>
<td>125.5(4)</td>
</tr>
<tr>
<td>C6-C7-C11</td>
<td>117.4(4)</td>
</tr>
<tr>
<td>C8-C7-C11</td>
<td>117.0(4)</td>
</tr>
<tr>
<td>C7-C8-C9</td>
<td>119.9(5)</td>
</tr>
<tr>
<td>C8-C9-C10</td>
<td>121.1(5)</td>
</tr>
<tr>
<td>C9-C10-O3</td>
<td>108.7(4)</td>
</tr>
<tr>
<td>C9-C10-C25</td>
<td>112.8(4)</td>
</tr>
<tr>
<td>O3-C10-C25</td>
<td>109.4(4)</td>
</tr>
<tr>
<td>C9-C10-C32</td>
<td>112.2(4)</td>
</tr>
<tr>
<td>O3-C10-C32</td>
<td>104.3(4)</td>
</tr>
<tr>
<td>C25-C10-C32</td>
<td>109.1(4)</td>
</tr>
<tr>
<td>C7-C11-O3</td>
<td>121.4(4)</td>
</tr>
<tr>
<td>C7-C11-C12</td>
<td>122.9(4)</td>
</tr>
<tr>
<td>O3-C11-C12</td>
<td>115.6(4)</td>
</tr>
<tr>
<td>C11-C12-C1</td>
<td>116.5(4)</td>
</tr>
<tr>
<td>C11-C12-C13</td>
<td>126.2(5)</td>
</tr>
<tr>
<td>Atoms</td>
<td>Bond Angles (°)</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>C1-C12-C13</td>
<td>117.1(5)</td>
</tr>
<tr>
<td>C12-C13-C14</td>
<td>120.3(5)</td>
</tr>
<tr>
<td>C13-C14-C15</td>
<td>121.2(5)</td>
</tr>
<tr>
<td>C14-C15-O1</td>
<td>108.4(4)</td>
</tr>
<tr>
<td>C14-C15-C34</td>
<td>113.6(5)</td>
</tr>
<tr>
<td>O1-C15-C34</td>
<td>104.5(4)</td>
</tr>
<tr>
<td>C14-C15-C41</td>
<td>111.9(4)</td>
</tr>
<tr>
<td>O1-C15-C41</td>
<td>109.4(4)</td>
</tr>
<tr>
<td>C34-C15-C41</td>
<td>108.7(4)</td>
</tr>
<tr>
<td>C5-C16-C17</td>
<td>109.9(5)</td>
</tr>
<tr>
<td>C5-C16-C21</td>
<td>108.4(5)</td>
</tr>
<tr>
<td>C17-C16-C21</td>
<td>109.4(5)</td>
</tr>
<tr>
<td>C16-C17-C18</td>
<td>109.6(5)</td>
</tr>
<tr>
<td>C17-C18-C19</td>
<td>110.2(5)</td>
</tr>
<tr>
<td>C17-C18-C24</td>
<td>110.4(5)</td>
</tr>
<tr>
<td>C19-C18-C24</td>
<td>108.6(5)</td>
</tr>
<tr>
<td>C18-C19-C20</td>
<td>110.8(5)</td>
</tr>
<tr>
<td>C19-C20-C21</td>
<td>109.1(6)</td>
</tr>
<tr>
<td>C19-C20-C22</td>
<td>110.2(5)</td>
</tr>
<tr>
<td>C21-C20-C22</td>
<td>107.5(5)</td>
</tr>
<tr>
<td>C16-C21-C20</td>
<td>109.3(5)</td>
</tr>
<tr>
<td>C20-C22-C23</td>
<td>109.8(5)</td>
</tr>
<tr>
<td>C22-C23-C5</td>
<td>110.2(4)</td>
</tr>
<tr>
<td>C22-C23-C24</td>
<td>107.5(4)</td>
</tr>
<tr>
<td>C5-C23-C24</td>
<td>110.5(4)</td>
</tr>
<tr>
<td>C23-C24-C18</td>
<td>109.6(5)</td>
</tr>
<tr>
<td>C10-C25-C26</td>
<td>108.7(5)</td>
</tr>
<tr>
<td>C10-C25-C30</td>
<td>111.4(4)</td>
</tr>
<tr>
<td>C26-C25-C30</td>
<td>108.2(5)</td>
</tr>
<tr>
<td>C25-C26-C27</td>
<td>110.5(4)</td>
</tr>
<tr>
<td>Atoms</td>
<td>Bond Angles (°)</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
</tr>
<tr>
<td>C26-C27-C28</td>
<td>109.2(5)</td>
</tr>
<tr>
<td>C26-C27-C33</td>
<td>107.8(5)</td>
</tr>
<tr>
<td>C28-C27-C33</td>
<td>109.0(5)</td>
</tr>
<tr>
<td>C27-C28-C29</td>
<td>110.5(5)</td>
</tr>
<tr>
<td>C28-C29-C30</td>
<td>108.7(5)</td>
</tr>
<tr>
<td>C28-C29-C31</td>
<td>109.8(5)</td>
</tr>
<tr>
<td>C30-C29-C31</td>
<td>110.0(5)</td>
</tr>
<tr>
<td>C29-C30-C25</td>
<td>109.7(5)</td>
</tr>
<tr>
<td>C29-C31-C32</td>
<td>111.1(4)</td>
</tr>
<tr>
<td>C10-C32-C31</td>
<td>109.4(4)</td>
</tr>
<tr>
<td>C10-C32-C33</td>
<td>108.1(4)</td>
</tr>
<tr>
<td>C31-C32-C33</td>
<td>108.0(5)</td>
</tr>
<tr>
<td>C32-C33-C27</td>
<td>111.2(5)</td>
</tr>
<tr>
<td>C15-C34-C35</td>
<td>110.0(5)</td>
</tr>
<tr>
<td>C15-C34-C39</td>
<td>109.1(4)</td>
</tr>
<tr>
<td>C35-C34-C39</td>
<td>108.5(5)</td>
</tr>
<tr>
<td>C34-C35-C36</td>
<td>110.5(5)</td>
</tr>
<tr>
<td>C35-C36-C37</td>
<td>109.5(5)</td>
</tr>
<tr>
<td>C35-C36-C42</td>
<td>109.9(5)</td>
</tr>
<tr>
<td>C37-C36-C42</td>
<td>108.7(5)</td>
</tr>
<tr>
<td>C36-C37-C38</td>
<td>110.4(4)</td>
</tr>
<tr>
<td>C37-C38-C39</td>
<td>108.9(5)</td>
</tr>
<tr>
<td>C37-C38-C40</td>
<td>110.1(5)</td>
</tr>
<tr>
<td>C39-C38-C40</td>
<td>108.6(5)</td>
</tr>
<tr>
<td>C34-C39-C38</td>
<td>109.8(5)</td>
</tr>
<tr>
<td>C38-C40-C41</td>
<td>110.2(4)</td>
</tr>
<tr>
<td>C40-C41-C15</td>
<td>107.9(5)</td>
</tr>
<tr>
<td>C40-C41-C42</td>
<td>108.7(5)</td>
</tr>
<tr>
<td>C15-C41-C42</td>
<td>110.8(4)</td>
</tr>
<tr>
<td>C41-C42-C36</td>
<td>109.9(5)</td>
</tr>
</tbody>
</table>
A mixture of phloroglucinol (14) (38 mg, 0.30 mmol), \( \beta \)-phenylcinnamaldehyde (175) (250 mg, 1.20 mmol), phenylboronic acid (111 mg, 0.91 mmol), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 150 min. The resultant mixture was cooled to room temperature and concentrated in vacuo to afford the chromene 176 as a brown gum. Palladium on charcoal (210 mg, 10% w/w) was then added to a solution of the crude chromene 176 in methanol (20 mL). The reaction mixture was stirred under an atmosphere of hydrogen (balloon pressure) for 18 h. The resultant mixture was filtered through a pad of celite with dichloromethane (3 \times 20 mL) and then the combined filtrates were concentrated in vacuo. The resultant residue was dissolved in ether (10 mL) and on filtration through a pad of silica gel with ether (125 mL) was concentrated in vacuo. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the title compound 176-6H (59 mg, 28%) as a pale pink solid. \( R_f = 0.24 \), hexanes:ether (9:1); \text{M.p.} >245 ^\circ \text{C}, \text{hexanes:ether} ; ^1\text{H NMR} (400 MHz, CDCl\textsubscript{3}) \delta 2.66 (t, J = 5.7 Hz, 6H, ArCH\textsubscript{2}CH\textsubscript{2}), 2.72 (t, J = 5.7 Hz, 6H, ArCH\textsubscript{2}CH\textsubscript{2}), 7.20 (m, 18H, ArH), 7.34 (m, 12H, ArH); \text{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \delta 17.6, 31.5, 81.3, 102.3, 125.8, 126.8, 128.2, 144.9, 149.8; \text{IR} \text{(ef)} 2975, 1629, 1617, 1560, 1482, 1360, 1139, 1106, 1071 \text{ cm}^{-1} ; \text{MS (El)} \text{m/z} \text{(rel. intensity)} 702 \text{ (M, 3)}, 675
6.3.16 (2RS,6RS,10RS)-2,6,1O-Trimethyl-2,6,1O-tri-(4'-methylpent-3'-enyl)-2H,6H,10H-dipyranophenylboronic acid (113 mg, 0.93 mmol), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 4 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated in vacuo. Purification by flash chromatography using hexanes:ether (99:1) as the eluant afforded the title compound (+)-178 (97 mg, 61%) as a colourless oil. Rf = 0.26, hexanes:ether (99:1); 1H NMR (400 MHz, C6D6) δ 1.28 (apparent dd, J = 4.1, 2.4 Hz, 9H, CH3), 1.51 (s, 9H, CH3), 1.63 (s, 9H, CH3), 1.69 (m, 6H, CH2), 2.21 (m, 6H, CH2), 5.11 (m, 3H, CHCMe2), 5.20 (d, J = 10.0 Hz, 3H, Ho), 6.93 (d, J = 10.0 Hz, 3H, ArCHCH); 13C NMR (101 MHz, C6D6) δ 17.6, 23.2, 25.8, 26.5, 41.6, 79.1, 103.5, 117.8, 124.87, 124.93, 131.3, 150.1; IR (ef) 2969, 2924, 2851, 1639, 1593, 1451, 1375, 1152, 1129 cm⁻¹; MS (El) m/z (rel. intensity) 528 (M, 100), 446 (46), 69 (67), 45 (30); Anal. Calcd. for C36H48O3: C, 81.77; H, 9.15. Found: C, 82.01; H, 9.31.
6.3.17 (1a-RS,6a-SR,11a-SR)-3,4,4a,1a,8,9,8a,6a,12,13,14a,11a-Dodecahydro-1a,6a,11a-trimethyl-tricyclopenta[b,b',b'"]-1aH,6aH,11aH-dipyranolo[6,5-i,6',5'-k]chromene (193-α) and (1a-RS,6a-RS,11a-RS)-3,4,4a,1a,8,9,8a,6a,12,13,14a,11a-Dodecahydro-1a,6a,11a-trimethyl-tricyclopenta[b,b',b'"]-1aH,6aH,11aH-dipyranolo[6,5-i,6',5'-k]chromene (193-β)

A mixture of phloroglucinol (14) (38 mg, 0.30 mmol), 2-methylcyclopent-1-ene carboxaldehyde (165) (134 mg, 1.22 mmol), phenylboronic acid (112 mg, 0.92 mmol), propionic acid (72) (4 drops) and benzene (10 mL) in a Dean-Stark trap was heated at reflux for 6 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated in vacuo. Purification by flash chromatography using hexanes:ether (49:1) as the eluant afforded an inseparable mixture (dr = 20:1) of the title compounds 193-α and 193-β (37 mg, 31%) as a yellow solid. \( R_f = 0.26 \), hexanes:ether (49:1); M.p. 196 °C (dec.), hexanes:ether; \(^1H\) NMR (600 MHz, CDCl\(_3\)) \( \delta \) 1.26 (s, 6H, \( 2 \times CH_3 \) of 193-α), 1.28 (s, 3H, \( 1 \times CH_3 \) of 193-α), 1.29 (s, 9H, \( 3 \times CH_3 \) of 193-β), 1.72 (m, 3H, \( CH_2 \)), 1.84 (m, 3H, \( CH_2 \)), 2.01 (m, 3H, \( CH_2 \)), 2.10 (m, 3H, \( CH_2 \)), 2.51 (m, 6H, \( CH_2 \)), 6.39 (apparent t, \( J = 2.1 Hz \), 3H, \( 3 \times ArCH \) of 195-β), 6.40 (apparent t, \( J = 2.1 Hz \), 1H, \( 1 \times ArCH \) of 193-α), 6.42 (apparent t, \( J = 2.1 Hz \), 1H, \( 1 \times ArCH \) of 193-α); \(^13C\) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 21.3, 21.4, 21.5, 22.2, 22.4, 22.6, 22.8, 27.7, 27.8, 27.89, 27.94, 39.30, 39.34, 39.39, 39.42, 83.1, 83.3, 83.4, 106.0, 106.1, 106.4, 110.17, 110.20,
110.25, 139.3, 139.6, 147.0, 147.1, 147.4; \textbf{IR} (ef) 2963, 1667, 1595, 1431, 1366, 1151, 1125 cm$^{-1}$; \textbf{MS} (EI) $m/z$ (rel. intensity) 402 (M, 7), 307 (8), 132 (6), 96 (6), 85 (6), 79 (15), 67 (18), 55 (27), 43 (40), 28 (100); \textbf{FAB-HRMS} Calcd. for C$_{27}$H$_{30}$O$_3$: 402.2195. Found: 402.2196.

6.3.18 2,6,10-Trimethyl-4\textit{H},8\textit{H},12\textit{H}-dipyranol[6,5-\textit{f};6',5'-\textit{h}]chromene (196)

![Chemical Structure]

A mixture of phloroglucinol (14) (63 mg, 0.50 mmol), methyl vinyl ketone (195) (160 $\mu$L, 1.98 mmol), phenylboronic acid (184 mg, 1.51 mmol), propionic acid (72) (7 drops) and benzene (16 mL) in a Dean-Stark trap was heated at reflux for 6 h. The resultant solution was cooled to room temperature and on filtration through a pad of silica gel with ether (125 mL) was concentrated in vacuo. Purification by flash chromatography using hexanes:ether (99:1) as the eluant afforded the title compound 196 (20 mg, 14%) as a white solid. \textbf{Rf} = 0.57, hexanes:ether, 99:1; \textbf{M.p.} 111 °C (dec.); hexanes:ether; $^1\text{H NMR}$ (400 MHz, CDCl$_3$) $\delta$ 1.82 (d, $J = 1.1$ Hz, 9H, CH$_3$), 3.15 (m, 6H, ArCH$_2$), 4.65 (m, 3H, ArCH$_2$CH$_2$); $^{13}\text{C NMR}$ (101 MHz, CDCl$_3$) $\delta$ 19.1, 19.2, 95.3, 101.5, 147.2, 147.9; \textbf{IR} (ef) 2928, 1707, 1621, 1467, 1379, 1326, 1303, 1184, 1101 cm$^{-1}$; \textbf{MS} (CI) $m/z$ (rel. intensity) 283 (M + H, 100); \textbf{FAB-HRMS} Calcd. for C$_{18}$H$_{18}$O$_3$: 282.1256. Found: 282.1259.
6.3.19 (±)-1-(4-Methoxybenzyloxy)propan-2-ol [(±)-210]^{86,87}

![Chemical Structure](image)

Propylene oxide (209) (7.3 mL, 10 mmol) was slowly added to a suspension of p-methoxybenzyl alcohol (208) (65 mL, 520 mmol) and sodium hydroxide (145 mg, 3.63 mmol) at 65 °C and the resultant mixture was stirred for 24 h. Purification by direct distillation of the reaction mixture at reduced pressure afforded the title compound (±)-210 (10.3 g, 53%) as a colourless oil. **B.p.** 169-171 °C, 15 mm Hg; **^1H NMR** (400 MHz, CDCl₃) δ 1.14 (d, J = 6.4 Hz, 3H, Me), 2.08 (s, 1H, OH), 3.25 (dd, J = 9.4, 8.3 Hz, 1H, OCH₃), 3.44 (dd, J = 9.4, 3.5 Hz, 1H, OCH₂), 3.25 (s, 3H, OMe), 3.99 (m, 1H, HOCH), 4.49 (s, 2H, ArCH₂O), 6.88 (d, J = 8.6 Hz, 2H, ArH), 7.27 (d, J = 8.6 Hz, 2H, ArH); **^13C NMR** (101 MHz, CDCl₃) δ 18.6, 55.1, 66.3, 72.8, 75.4, 113.7, 129.2, 130.0, 159.1; **IR** (ef) 3451, 2969, 2933, 2904, 2860, 2837, 1613, 1514, 1087, 1035 cm⁻¹; **MS** (CI) m/z (rel. intensity) 195 (M + H, 8), 121 (100), 45 (7).

6.3.20 (±)-1-(4-Methoxybenzyloxy)-2-bromopropane [(±)-131]^{88}

![Chemical Structure](image)

To a mixture of the alcohol (±)-210 (9.16 g, 46.7 mmol), 2,6-lutidine (1.30 mL, 11.7 mmol) and triphenylphosphine (15.31 g, 58.4 mmol) in tetrahydrofuran (115 mL) at room temperature was added carbon tetrabromide (18.6 g, 56.0 mmol). After 56 h, the
reaction mixture was diluted with hexanes (150 mL) and filtered. The filter-cake was washed with ether:hexanes (1:1, 200 mL) and the combined filtrates were concentrated *in vacuo*. Distillation at reduced pressure afforded the *title compound* (±)-131 (8.22 g, 68%) as a yellow oil. **B.p.** 157-165 °C, 2 mm Hg; **1H NMR** (400 MHz, CDCl₃) δ 1.70 (d, *J* = 6.7 Hz, 3H, *Me*), 3.55 (dd, *J* = 10.3, 6.6 Hz, 1H, OCHH), 3.66 (dd, *J* = 10.3, 6.2 Hz, 1H, OCHH), 3.81 (s, 3H, OMe), 4.18 (m, 1H, BrCH), 4.52 (s, 2H, ArCH₂O), 6.88 (d, *J* = 8.6 Hz, 2H, ArH), 7.27 (d, *J* = 8.6 Hz, 2H, ArH); **13C NMR** (101 MHz, CDCl₃) δ 22.7, 46.9, 55.3, 72.8, 75.3, 113.8, 129.3, 129.9, 159.3; **IR** (ef) 2956, 2931, 2859, 2836, 1613, 1513, 1248, 1080, 1035 cm⁻¹; **MS** (Cl) *m/z* (rel. intensity) 260 [M⁺, 3], 259 [M⁺⁻Br, 5], 258 [M⁺⁻Br, 4], 257 [M⁺⁻Br, 5], 179 (M – Br, 6), 149 (19), 121 (100), 39 (20); **Anal.** Calcd. for C₁₁H₁₅BrO₂: C, 50.98; H, 5.83. Found: C, 50.72; H, 5.91.

### 6.3.21 2-Methyl-3-trichloroacetyl-4,5-dihydrofuran (213) and 1,1,1-Trichloro-3-[4-dihydrofuran-2′E-ylidene]propane-2-one (214)\(^{93,94}\)

![Structures 213 and 214](image)

**Method A:** To a solution of 2-methyl-4,5-dihydrofuran (114) (0.60 mL, 6.5 mmol) and pyridine (0.79 mL, 10 mmol) in dichloromethane (8 mL) at room temperature was added trichloroacetyl chloride (1.1 mL, 10 mmol) dropwise (**CAUTION:** exothermic process). The reaction mixture was stirred for 15 min and then a saturated aqueous solution of sodium bicarbonate (10 mL) was added. The resultant mixture was diluted with chloroform (10 mL), washed with water (3 x 5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the resultant oil by flash
chromatography using hexanes:ether (2:1) as the eluant afforded the title compound 213 (931 mg, 62%) as a pale yellow oil and the title compound 214 (542 mg, 36%) as a pale yellow solid.

**Method B:** To a solution of 2-methyl-4,5-dihydrofuran (114) (0.20 mL, 2.2 mmol) and pyridine (0.26 mL, 3.3 mmol) in dichloromethane (5 mL) at −20 °C was added a solution of trichloroacetyl chloride (0.36 mL, 3.3 mmol) dropwise (CAUTION: exothermic process). The reaction mixture was allowed to warm to room temperature over 21 h and then a saturated aqueous solution of sodium bicarbonate (10 mL) was added. The resultant mixture was diluted with chloroform (10 mL), washed with water (2 × 10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the resultant oil by flash chromatography using hexanes:ether (2:1) as the eluant afforded the title compound 213 (393 mg, 79%) as a pale yellow oil and title compound 214 (80 mg, 16%) as a pale yellow solid.

**Title compound 213:** $^{84}$ $R_f = 0.57$, hexanes:ether (2:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.35 (t, $J = 1.0$ Hz, 3H, $Me$), 3.30 (apparent tq, $J = 9.2$, 1.1 Hz, 2H, OCH$_2$CH$_2$), 4.56 (apparent t, $J = 9.3$ Hz, 2H, OCH$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 16.2, 30.6, 72.3, 97.4, 104.0, 177.3, 180.2; IR (ef) 2979, 2907, 1766, 1682, 1674, 1567, 1386, 1242, 1115 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 235 [M (3 × $^{37}$Cl) + H, 3], 233 [M (35Cl + 2 × $^{37}$Cl) + H, 31], 231 [M (2 × $^{35}$Cl + $^{37}$Cl) + H, 100], 229 [M (3 × $^{35}$Cl) + H, 88], 196 (8), 165 (22), 111 (22), 43 (30).

**Title compound 214:** $R_f = 0.32$, hexanes:ether (2:1); M.p. 47-49 °C, hexanes:ether; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.14 (m, 2H, OCH$_2$CH$_2$), 3.17 (apparent td, $J = 7.8$, 1.5 Hz, 2H, OCCH$_2$), 4.35 (apparent t, $J = 7.3$ Hz, 2H, OCH$_2$), 6.23 (t, $J = 1.5$
Hz, 1H, C\textsubscript{6}H\textsubscript{4}C\textsubscript{6}H\textsubscript{4}Cl\textsubscript{3}); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \delta 23.1, 31.9, 73.3, 89.7, 97.4, 181.0, 184.3; IR (ef) 3073, 3006, 2972, 3911, 1680, 1591, 1391, 1246, 1110, 1028 cm\textsuperscript{-1}; MS (Cl) \textit{m/z} (rel. intensity) 235 [M (3 \times \text{Cl}) + H, 1], 233 [M (\text{\textsuperscript{35}Cl} + 2 \times \text{Cl}) + H, 8], 231 [M (2 \times \text{Cl} + \text{Cl}) + H, 26], 229 [M (3 \times \text{Cl}) + H, 27], 165 (45), 111 (100), 69 (23), 39 (44); Anal. Calcd. for C\textsubscript{7}H\textsubscript{7}Cl\textsubscript{3}O\textsubscript{2}: C, 36.64; H, 3.07. Found: C, 36.82; H, 3.25.

6.3.22 2-Methyl-4,5-dihydrofuran-3-carboxylic Acid (215)\textsuperscript{70,95}

\begin{center}
\includegraphics[width=1in]{215.png}
\end{center}

A mixture of the trichloroketone 213 (524 mg, 2.29 mmol) and an aqueous solution of sodium hydroxide (1 M, 3.4 mL, 3.4 mmol) was stirred at room temperature for 2 h and then cooled to 0 °C. The pH was adjusted to ~3 with hydrochloric acid (1 M) and the resultant precipitate was collected and washed with water (2 x 5 mL) and then dried \textit{in vacuo} to afford the \textit{title compound} 215 (140 mg, 48%) as a beige powder. \textit{Rf} = 0.53, ether; M.p. 136-139 °C, water (lit.\textsuperscript{70} 153-154 °C, benzene); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 2.21 (s, 3H, Me), 2.90 (apparent t, J = 9.4 Hz, 2H, OCH\textsubscript{2}CH\textsubscript{2}), 4.44 (apparent t, J = 9.5 Hz, 2H, OCH\textsubscript{2}); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \delta 14.2, 29.3, 70.8, 101.8, 171.3, 171.9; IR (ef) 3484, 3000, 2904, 2859, 1654, 1229 cm\textsuperscript{-1}; MS (Cl) \textit{m/z} (rel. intensity) 129 (M + H, 100), 111 (15), 85 (75), 43 (50).
6.3.23 Methyl-2-methyl-4,5-dihydrofuran-3-carboxylate (167)\textsuperscript{70,71,96}

![Structure of 167]

To a solution of the trichloroketone 213 (216 mg, 0.939 mmol) in methanol (5 mL) was added sodium bicarbonate (75 mg, 0.89 mmol) and the resultant mixture was heated at reflux for 45 min. The reaction mixture was then allowed to cool to room temperature and water (20 mL) was added. The resultant mixture was extracted with ether (9 \times 10 mL) and the combined organic extracts were washed with water (2 \times 15 mL), dried over anhydrous magnesium sulfate and concentrated \textit{in vacuo} to afford the title compound 167 (128 mg, 96%) as a white solid. \(R_f = 0.43\), hexanes:ether (2:1); M.p. 28-29 °C, ether (lit.\textsuperscript{70} 31.5-32.5 °C, petroleum ether); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 2.17 (s, 3H, Me), 2.87 (apparent t, \(J = 9.6\) Hz, 2H, OCH\(_2\)CH\(_2\)), 3.70 (s, 3H, CO\(_2\)Me), 4.39 (apparent t, \(J = 9.6\) Hz, 2H, OCH\(_2\)); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 13.8, 29.5, 50.6, 70.2, 101.7, 166.5, 168.7; \(\text{IR}\) (ef) 2952, 1705, 1651, 1438, 1388, 1334, 1229, 1084, 998 cm\(^{-1}\); \(\text{MS}\) (EI) \(m/z\) (rel. intensity) 143 (M + H, 38), 142 (M, 18), 43 (100).

6.3.24 (S)-Phenylalaninol [(S)-217]\textsuperscript{97,99}

![Structure of (S)-217]

To a suspension of lithium aluminum hydride (26.6 g, 675 mmol) in tetrahydrofuran (700 mL) at 0 °C was added (S)-phenylalanine [(S)-216] (74.3 g, 450 mmol) in portions over 80 min. The resultant mixture was heated at reflux for 5 h and then stirred for an additional 15 h at room temperature before being diluted with ether (600 mL) and cooled to 0 °C. Water (26 mL), an aqueous solution of sodium hydroxide
(2 M, 26 mL) and water (78 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed with ether (3 × 100 mL) and the combined filtrates were concentrated in vacuo. Purification by recrystallization from ethyl acetate afforded the title compound (S)-217 (43.1 g, 93%) as colourless needles. M.p. 87-88 °C, ethyl acetate (lit. 88.5-91 °C, ethyl acetate); $[\alpha]_D^{20} = -23.7$ (c 0.88, ethanol) [lit. $[\alpha]_D^{100} = -24.7$ (c 1.03, ethanol)]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.88 (s, 3H, OH and NH$_2$), 2.52 (dd, $J = 13.5$, 8.6 Hz, 1H, CHHPh), 2.79 (dd, $J = 13.5$, 5.2 Hz, 1H, CHHPh), 3.12 (m, 1H, NCH), 3.39 (dd, $J = 10.6$, 7.2 Hz, 1H, CHHOH), 3.64 (dd, $J = 10.6$, 3.9 Hz, 1H, CHHOH), 7.25 (m, 5H, ArH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 40.6, 54.1, 66.0, 126.3, 128.5, 129.1, 138.6; IR (ef) 3355, 3289, 2918, 2847, 1584, 1495, 1454, 1059 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 152 (M + H, 100), 117 (13), 42 (7).

6.3.25 (S)-4-(Phenylmethyl)-2-oxazolidinone [(4S)-218]$^{99,155}$

A round bottom flask, that was fitted with a Vigreux column, a distillation head and a receiving flask, was charged with the amino alcohol (S)-217 (43.0 g, 285 mmol), potassium carbonate (3.95 g, 28.5 mmol) and diethyl carbonate (71 mL, 586 mmol). The resultant mixture was heated at 135 °C. After the generation of ethanol had ceased (~90 min), the reaction mixture was allowed to cool to room temperature, was diluted with dichloromethane (250 mL) and washed with water (250 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by recrystallization from ethyl acetate:hexanes (2:1) afforded the title compound (4S)-218
(39.9 g, 79%) as colourless plates. M.p. 86-87 °C, ethyl acetate:hexanes (lit.99 84.5-86.5 °C, ethyl acetate:hexanes); [α]_D^{20} = -62 (c 1.18, chloroform) [lit.155 [α]_D^{20} = -62 (c 1.00, chloroform)]; ¹H NMR (400 MHz, CDCl₃) δ 2.87 (d, J = 6.9 Hz, 2H, CH₂Ph), 4.12 (m, 2H, NCH and OCHH), 4.45 (apparent t, J = 8.3 Hz, 1H, OCHH), 5.53 (s, 1H, NH), 7.17 (m, 2H, ArH), 7.30 (m, 3H, ArH); ¹³C NMR (101 MHz, CDCl₃) δ 41.0, 53.5, 69.2, 126.9, 128.6, 128.9, 135.7, 159.7; IR (ef) 3287, 2922, 1754, 1711, 1406, 1064, 1096, 1021 cm⁻¹; MS (Cl) m/z (rel. intensity) 178 (M + H, 100).

6.3.26 (4S)-4-Benzyl-3-propionyloxazolidin-2-one [(4S)-219]₁₀¹

To a solution of the oxazolidinone (4S)-218 (39.7 g, 224 mmol) in tetrahydrofuran (650 mL) at -78 °C was added n-butyl lithium (90 mL, 2.5 M in hexanes, 225 mmol). The resultant mixture was allowed to stir for 15 min and then propionyl chloride (22 mL, 250 mmol) was added. The reaction mixture was stirred at -78 °C for 30 min and then was allowed to warm to room temperature over 45 min after which a saturated solution of ammonium chloride (135 mL) was added. The resultant mixture was concentrated in vacuo and the residue was then extracted with dichloromethane (3 × 150 mL). The combined organic extracts were washed with sodium hydroxide (1 M, 150 mL), brine (150 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The resultant crystalline solid was pulverized and triturated with cold hexanes (200 mL). Filtration and drying of the solid in vacuo afforded the title compound (4S)-219 (48.9 g, 94%) as a white powder. M.p. 42-46 °C, hexanes (lit.₁₀¹ 44-46 °C, hexanes); [α]_D^{20} = +92 (c 1.38,
ethanol) [lit.101 $[\alpha]_D^{20} = + 92.9$ (c 1.01, ethanol)]; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.20 (t, $J = 7.3$ Hz, 3H, Me), 2.77 (dd, $J = 13.3, 9.7$ Hz, 1H, CH/HPh), 2.95 (m, 2H, CH$_2$Me), 3.29 (dd, $J = 13.3, 3.2$ Hz, 1H, CH/HPh), 4.18 (m, 2H, OCH$_2$), 4.67 (m, 1H, NCH), 7.30 (m, 5H, ArH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 8.2, 29.0, 37.7, 55.0, 66.1, 127.2, 128.8, 129.3, 135.2, 153.4, 173.9; IR (ef) 3029, 2982, 2941, 1790, 1706, 1455, 1352, 1249, 1210 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 234 (M + H, 100), 178 (8).

6.3.27 (2'R,4S)-4-Benzyl-3-[2'-methylpent-4'-ynoyl]oxazolidin-2-one [(+) -220]

Method A.102 To a solution of N,N-diisopropylamine (2.7 mL, 19 mmol) in tetrahydrofuran (15 mL) at 0 °C was added n-butyl lithium (7.6 mL, 2.5 M in hexanes, 19 mmol, 1.1 equiv). The reaction mixture was stirred for 30 min and then cooled to −78 °C. A solution of (4S)-4-benzyl-3-propionyloxazolidin-2-one [(4S)-219] (3.98 g, 17.1 mmol, 1 equiv) in tetrahydrofuran (5 mL) was added and the resultant mixture was stirred for 30 min. Propargyl bromide (71) (2.9 mL, 80% w/w in toluene, 26 mmol, 1.5 equiv) was then added dropwise. The reaction mixture was then stirred at −78 °C for 30 min and subsequently at 0 °C for 2 h. A saturated aqueous solution of ammonium chloride (10 mL) and water (10 mL) were then added. The resultant mixture was extracted with ether (3 $\times$ 30 mL) and the combined organic extracts were washed with water (3 $\times$ 30 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the resultant oil by flash chromatography using hexanes:ether (2:1) as the eluant afforded
the title compound (+)-220 (2.27 g, 49%) as a brown solid and as a mixture of two diastereoisomers (dr = 7:1).

**Method B:** To a solution of N,N-diisopropylamine (1.4 mL, 10 mmol) in tetrahydrofuran (10 mL) at 0 °C was added n-butyl lithium (3.8 mL, 2.5 M in hexanes, 9.5 mmol, 1.1 equiv). The reaction mixture was stirred for 30 min and then cooled to −78 °C. A solution of (4S)-4-benzyl-3-propionyloxazolidin-2-one [(4S)-219] (2.00 g, 8.58 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added and the resultant mixture was stirred for 30 min. Propargyl bromide (71) (1.5 mL, 80% w/w in toluene, 13 mmol, 1.5 equiv) was then added dropwise and the reaction mixture was allowed to warm from −78 to −20 °C over 20 h. A saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL) were then added. The resultant mixture was extracted with ether (3 × 20 mL) and the combined organic extracts were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the resultant oil by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant afforded the title compound (+)-220 (1.27 g, 55%) as a yellow solid and as a mixture of two diastereoisomers (dr = 6:1).

**Method C:** To a solution of N,N-diisopropylamine (1.4 mL, 10 mmol) in tetrahydrofuran (10 mL) at 0 °C was added n-butyl lithium (3.8 mL, 2.5 M in hexanes, 9.5 mmol, 1.1 equiv). The reaction mixture was stirred for 30 min and then cooled to −78 °C. A solution of (4S)-4-benzyl-3-propionyloxazolidin-2-one [(4S)-219] (2.00 g, 8.58 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added and the resultant mixture was stirred for 30 min. Propargyl bromide (71) (3.8 mL, 80% w/w in toluene, 34 mmol, 4 equiv) was then added dropwise and the reaction mixture was allowed to warm from −78
to 0 °C over 23 h. A saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL) were then added. The resultant mixture was extracted with ether (3 × 20 mL) and the combined organic extracts were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the resultant oil by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant afforded the title compound (+)-220 (1.24 g, 53%) as a yellow solid and as a mixture of two diastereoisomers (dr = 6:1).

**Method D:**\(^{102}\) To a solution of \(N,N\)-diisopropylamine (1.9 mL, 14 mmol) in tetrahydrofuran (10 mL) at 0 °C was added \(n\)-butyl lithium (5.0 mL, 2.5 M in hexanes, 13 mmol, 1.5 equiv). The reaction mixture was stirred for 30 min and then cooled to −78 °C. A solution of \((4S)-4\text{-benzyl-3-propionyloxazolidin-2-one} [(4S)-219] (2.00 g, 8.58 mmol, 1 equiv) in tetrahydrofuran (3 mL) was added and the resultant mixture was stirred for 30 min. Propargyl bromide (71) (3.8 mL, 80% w/w in toluene, 34 mmol, 4 equiv) was then added dropwise and the reaction mixture was allowed to warm from −78 to 0 °C over 23 h. A saturated aqueous solution of ammonium chloride (5 mL) and water (5 mL) were then added. The resultant mixture was extracted with ether (3 × 20 mL) and the combined organic extracts were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the resultant oil by flash chromatography using hexanes:ethyl acetate (3:1) as the eluant afforded the title compound (+)-220 (1.27 g, 55%) as a yellow solid and as a mixture of two diastereoisomers (dr = 6:1).

**Method E:**\(^{103}\) To a solution of \((S)-4\text{-benzyl-3-propionyloxazolidin-2-one} [(4S)-219] (1.17 g, 5.02 mmol) in dichloromethane (20 mL) at 0 °C was added titanium
tetrachloride (0.57 mL, 5.2 mmol) and the resultant mixture was allowed to stir for 5 min after which time \( N,N,N \)-diisopropylethylamine (0.91 mL, 5.2 mmol) was added. After 1 h, propargyl chloride (0.72 mL, 10 mmol) was then added. The resultant mixture was stirred at 0 °C for 6 h and then allowed to warm to room temperature over 18 h. TLC analysis indicated that none of the desired product had formed.

**Method F:** To a solution of (S)-4-benzyl-3-propionyl-oxazolidin-2-one (4S)-219] (1.16 g, 4.98 mmol) in dichloromethane (20 mL) at 0 °C was added titanium tetrachloride (0.57 mL, 5.2 mmol) and the resultant mixture was allowed to stir for 5 min after which time \( N,N,N \)-diisopropylethylamine (0.91 mL, 5.2 mmol) was added. After 1 h, propargyl bromide (71) (1.1 mL, 80% w/w in toluene, 10 mmol) was then added. The resultant mixture was stirred at 0 °C for 6 h and then allowed to warm to room temperature over 18 h. TLC analysis indicated that none of the desired product had formed.

**Method G:** To a solution of \( N,N \)-diisopropylamine (31 mL, 220 mmol) in tetrahydrofuran (170 mL) at 0 °C was added \( n \)-butyl lithium (81 mL, 2.5 M in hexanes, 200 mmol). The reaction mixture was stirred for 30 min and then cooled to −78 °C. Hexamethylphosphoramide (25 mL) and a solution of (4S)-4-benzyl-3-propionyl-oxazolidin-2-one [(4S)-219] (32.5 g, 139 mmol) in tetrahydrofuran (50 mL) were then added. The resultant mixture was stirred for 30 min and then propargyl bromide (71) (62 mL, 80% w/w in toluene, 560 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 20 h and then a saturated aqueous solution of ammonium chloride (80 mL) and water (80 mL) were added. The resultant mixture was extracted with ether (3 × 200 mL) and the combined organic extracts were washed with water (6 × 15 mL),
dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the resultant oil by flash chromatography using hexanes:ethyl acetate (2:1) as the eluant afforded the title compound (+)-220 (29.1 g, 77%) as a brown solid and as a single diastereoisomer. This material was recrystallized from ether:hexanes (2:1) to afford the title compound (+)-220 as a cream coloured solid.

**Title compound (+)-220:** \( R_f = 0.34 \), hexanes:ethyl acetate (2:1); *M.p.* 52-54 °C, ether:hexanes; \([\alpha]^{20}_D = +56.2 \) (c 1.18, chloroform); \(^1H NMR\) (400 MHz, CDCl\(_3\)) \( \delta \) 1.29 (d, \( J = 6.8 \) Hz, 3H, Me), 2.03 (apparent t, \( J = 2.7 \) Hz, 1H, CCH), 2.49 (ddd, \( J = 16.8, 6.6, 2.7 \) Hz, 1H, CHHCC), 2.61 (ddd, \( J = 16.8, 6.7, 2.7 \) Hz, 1H, CHHCC), 2.78 (dd, \( J = 13.4, 9.5 \) Hz, 1H, CHHPh), 3.31 (dd, \( J = 13.4, 3.2 \) Hz, 1H, CHHPh), 3.95 (m, 1H, CHMe), 4.00 (m, 2H, CH\(_2\)O), 4.70 (m, 1H, CHN), 7.30 (m, 5H, Ph); \(^{13}C NMR\) (101 MHz, CDCl\(_3\)) \( \delta \) 16.4, 22.4, 37.1, 37.7, 55.1, 66.0, 70.0, 81.2, 127.2, 128.8, 129.3, 135.1, 152.9, 174.9; \( IR\) (ef) 3288, 3029, 2987, 2977, 2917, 1779, 1698, 1389, 1350, 1244, 1209 cm\(^{-1}\); \( MS\) (CI) \( m/z \) (rel. intensity) 272 (M + H, 100), 217 (22), 135 (14), 39 (27); **Anal.** Calcd. for C\(_{16}\)H\(_{17}\)NO\(_3\): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.80; H, 6.46; N, 5.33.

**6.3.28 (2R)-2-Methylpent-4-yn-1-ol [(2R)-69]**

\[ \begin{array}{c}
\text{Me} \\
\text{OH} \\
(2R)-69
\end{array} \]

To a suspension of lithium aluminum hydride (11.3 g, 298 mmol) in tetrahydrofuran (300 mL) at 0 °C was added a solution of the oxazolidinone (+)-220 (26.8 g, 99.0 mmol) in tetrahydrofuran (65 mL) and the resultant suspension was stirred for 45 min. Water (11 mL), an aqueous solution of sodium hydroxide (2 M, 11 mL) and an additional quantity of water (34 mL) were then added. The resultant mixture was
filtered and the filter-cake was washed with ether (3 × 150 mL). The combined filtrates were concentrated in vacuo and the resultant oil was purified by distillation at reduced pressure to afford the *title compound* (2R)-69 (7.1 g, 73%) as a colourless oil. \( R_f = 0.47 \), ethyl acetate:hexanes (2:1); \textbf{B.p.} 67-72 °C, ~12 mm Hg; \( [\alpha]_D^{20} = +11.4 \) (c 1.10, chloroform); \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta 1.01 \) (d, \( J = 6.9 \) Hz, 3H, CH\(_3\)), 1.56 (broad s, 1H, OH), 1.90 (m, 1H, CHCH\(_3\)), 1.98 (t, \( J = 2.7 \) Hz, 1H, HCC), 2.21 (dd, \( J = 16.8, 6.4, 2.7 \) Hz, 1H, CCHH), 2.29 (dd, \( J = 16.8, 6.2, 2.7 \) Hz, 1H, CCHH), 3.59 (d, \( J = 6.1 \) Hz, 2H, CH\(_2\)O); \(^{13}\text{C} \) NMR (101 MHz, CDCl\(_3\)) \( \delta 16.0, 22.2, 34.8, 66.8, 69.6, 82.6; \) IR (ef) 3409, 2961, 2922, 2117, 1461, 1430, 1037, 651 cm\(^{-1}\); MS (Cl) \( m/z \) (rel. intensity) 99 (M + H, 100).

6.3.29 (4R)-2,4-Dimethyl-3-trichloroacetyl-4,5-dihydrofuran [(4R)-223] and (4'R)-1,1,1-Trichloro-3-[4'-methyldihydrofuran-2'E-ylidene]propane-2-one [(4R)-224]\(^{93,94}\)

![Chemical Structure](image)

**Method A:** To a solution of the dihydrofuran (2R)-61 (699 mg, 7.13 mmol) and pyridine (0.87 mL, 11 mmol) in dichloromethane (5 mL) at room temperature was added trichloroacetyl chloride (1.2 mL, 11 mmol) dropwise (CAUTION: exothermic process). The reaction mixture was stirred for 30 min and then a saturated aqueous solution of sodium bicarbonate (10 mL) was added. The resultant mixture was diluted with dichloromethane (20 mL), was washed with water (2 × 10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the resultant oil by flash chromatography using hexanes:ether (19:1) as the eluant afforded the *title compound*
(4R)-223 (788 mg, 45%) as a pale yellow oil and the title compound (4R)-224 (790 mg, 46%) as a pale yellow solid.

**Method B:** To a solution of the dihydrofuran (2R)-61 (4.58 g, 46.7 mmol) and pyridine (5.6 mL, 70 mmol) in dichloromethane (90 mL) at −78 °C was added a solution of trichloroacetyl chloride (7.8 mL, 70 mmol) in dichloromethane (10 mL). The reaction mixture was allowed to warm to room temperature over 21 h and then a saturated aqueous solution of sodium bicarbonate (50 mL) was added. The resultant mixture was washed with water (2 × 50 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification of the resultant oil by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the title compound (4R)-223 (10.5 g, 93%) as a pale yellow oil.

**Title compound (4R)-223:** \( R_f = 0.41 \), hexanes:ether (9:1); \([\alpha]_D^{20} = +44.1 \) (c 1.20, chloroform); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \( \delta \) 1.28 (d, \( J = 6.4 \) Hz, 3H, Me-4), 2.29 (s, 3H, Me-2), 3.57 (m, 1H, CHMe), 4.21 (dd, \( J = 8.9, 2.3 \) Hz, 1H, OCH\(_2\)), 4.48 (apparent t, \( J = 8.5 \) Hz, 1H, OCH\(_2\)); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \( \delta \) 16.2, 21.2, 37.6, 79.4, 108.6, 111.6, 176.7, 178.3; \(^{1}\text{IR (ef)}\) 2972, 2929, 2896, 1801, 1687, 1558, 1387, 1374, 1322, 1248, 1182 cm\(^{-1}\); \(^{13}\text{MS (Cl)}\) m/z (rel. intensity) 249 [M (3 \times ^{37}\text{Cl}) + H, 3], 247 [M (\(^{35}\text{Cl} + 2 \times ^{37}\text{Cl}) + H, 31], 245 [M (2 \times ^{35}\text{Cl} + ^{37}\text{Cl}) + H, 100], 243 [M (3 \times ^{35}\text{Cl}) + H, 86], 180 (17), 125 (33), 83 (7) 39 (34).

**Title compound (4R)-224:** \( R_f = 0.15 \), hexanes:ether (19:1); \( \text{M.p.} \) 39-40 °C, hexanes:ether; \([\alpha]_D^{20} = +51.5 \) (c 1.41, chloroform); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \( \delta \) 1.15 (d, \( J = 6.8 \) Hz, 3H, Me), 2.62 (m, 1H, CHMe), 2.86 (ddd, \( J = 19.0, 6.8, 1.5 \) Hz, 1H,
$CHCHMe), 3.43 (ddd, J = 19.0, 8.1, 1.4 Hz, 1H, CHHCHMe), 3.95 (dd, J = 8.8, 6.7
Hz, 1H, CHHO), 4.45 (dd, J = 8.8, 6.7 Hz, 1H, CHHO), 6.30 (apparent t, J = 1.5 Hz, 1H,
CHCOCCl$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 17.5, 31.4, 40.0, 79.2, 90.3, 97.6, 181.0,
184.3; IR (ef) 2967, 2906, 1694, 1600, 1391, 1365, 1237, 1102 cm$^{-1}$; MS (CI) m/z (rel.
intensity) 249 [M (3 \times 37Cl) + H, 3], 247 [M (1 \times 35Cl + 2 \times 37Cl) + H, 31], 245 [M (2 \times
35Cl + 1 \times 37Cl) + H, 100], 243 [M (3 \times 35Cl) + H, 84], 210 (414), 180 (6), 125 (6), 39

6.3.30 (4R)-Methyl-2,4-dimethyl-4,5-dihydrofuran-3-carboxylate [(4R)-206]$^{96}$

To a solution of the trichloroketone (4R)-223 (10.1 g, 41.6 mmol) in methanol
(250 mL) was added sodium bicarbonate (1.33 g, 15.8 mmol) and the resultant mixture
was heated at reflux for 1 h. The reaction mixture was then allowed to cool to room
temperature and water (650 mL) was added. The resultant mixture was extracted with
ether (9 \times 80 mL) and the combined organic extracts were washed with water (2 \times 75
mL), dried over anhydrous magnesium sulfate and concentrated in vacuo to afford the
title compound (4R)-206 (6.34 g, 98%) as a yellow oil. Attempted purification of this
material by flash column chromatography using hexanes:ether (9:1) as the eluant resulted
in partial loss of material and did not significantly increase the purity of the reaction
product. $R_f = 0.32$, hexanes:ether (9:1); $[\alpha]_D^{20} = + 27.2$ (c 1.10, chloroform); $^1$H NMR
(400 MHz, CDCl$_3$) $\delta$ 1.14 (d, J = 6.7 Hz, 3H, Me-4), 2.14 (s, 3H, Me-2), 3.18 (m, 1H,
CHMe), 3.67 (s, 3H, CO$_2$Me), 3.95 (dd, J = 8.9, 5.1 Hz, 1H, OCHH), 4.41 (apparent t, J
= 9.0 Hz, 1H, OCHH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.2, 19.9, 36.8, 50.5, 77.7, 107.6, 166.5, 168.6; IR (ef) 2955, 1800, 1700, 1648, 1436, 1387, 1340, 1185 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 157 (M + H, 100), 125 (7), 39 (12).

6.3.31 (4R)-2,4-Dimethyl-4,5-dihydrofuran-3-carboxylic Acid [(4R)-225]$^{95}$

To a solution of the trichloroketone (4R)-223 (711 mg, 293 mmol) in tetrahydrofuran (5 mL) and water (5 mL) was added lithium hydroxide dihydrate (248 mg, 5.90 mmol) at room temperature. After 15 min, the pH was adjusted to ~ 3 with concentrated hydrochloric acid and the resultant mixture was extracted with chloroform (3 × 15 mL), dried over anhydrous sodium sulfate and concentrated in vacuo to afford the title compound (4R)-225 (363 mg, 88%) as a waxy yellow solid. $R_f = 0.50$, ethyl acetate:hexanes (2:1); M.p. 35-36 °C, ethyl acetate:hexanes; $[\alpha]^{20}_D = + 46.0$ (c 1.12, chloroform); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.21 (d, $J = 6.7$ Hz, 3H, Me-4), 2.21 (d, $J = 1.1$ Hz, 3H, Me-2), 3.25 (m, 1H, CHMe), 4.02 (dd, $J = 9.1, 5.2$ Hz, 1H, OCHH), 4.49 (apparent t, $J = 9.3$ Hz, 1H, OCHH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.6, 19.9, 36.6, 78.2, 107.4, 171.2, 171.9; IR (ef) 3434 (br), 2963, 2903, 2643, 2588, 1671, 1619, 1441, 1387, 1331, 1229 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 143 (M + H, 100); Anal. Calcd. for C$_7$H$_{10}$O$_3$: C, 59.14; H, 7.09. Found: C, 59.41; H, 7.23.
A solution of the ester (4R)-206 (656 mg, 4.21 mmol) in ether (10 mL) was added to a suspension of lithium aluminum hydride (243 mg, 6.39 mmol) in ether (20 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature over 20 min and then was cooled to 0 °C. Water (0.24 mL), an aqueous solution of sodium hydroxide (2 M, 0.24 mL) and water (0.72 mL) were then added in succession and the resultant mixture was filtered. The filter-cake was washed ether (3 × 25 mL) and the combined filtrates were concentrated in vacuo to afford the alcohol 226 as pale yellow oil. A suspension of this material and manganese dioxide (13.1 g, 151 mmol) in dichloromethane (70 mL) was stirred at room temperature for 46 h. The reaction mixture was then filtered through a pad of celite, the filter-cake was washed with dichloromethane (3 × 50 mL) and the combined filtrates were concentrated in vacuo. Purification by distillation at reduced pressure afforded the impure title compound (4R)-127 (180 mg, ~70 % pure, 34% over two steps) as a pale yellow oil. Attempted further purification did not significantly increase the purity of the product. \([\alpha]^D_20 = + 26.5 \text{ (c 1.04, chloroform)}\) [lit.\(^69\) \([\alpha]^D_20 = + 38.9 \text{ (c 0.61, chloroform)}\)]; \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta 1.19\) (d, \(J = 6.7\) Hz, 3H, Me-4), 2.15 (s, 3H, Me-2), 3.32 (m, 1H, H-4), 4.04 (dd, \(J = 9.2, 5.2\) Hz, 1H, H-5), 4.53 (apparent t, \(J = 9.2\) Hz, 1H, H-5), 9.69 (s, 1H, CHO); \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta 12.4, 19.2, 34.8, 79.2, 174.6, 185.0\); \(^\text{IR}\) (ef) 2966, 2930, 2902, 1754, 1683, 1652, 1632, 1453, 1393, 1243 cm\(^{-1}\). \(^\text{MS}\) (Cl) \(m/z\) (rel. intensity) 127 (M + H, 100), 39 (12).
6.4 Experimental Concerning Chapter Four

6.4.1 Ethyl-2,4-dimethyl-3-furanoate (49)\textsuperscript{108,156}

\begin{center}
\includegraphics[width=0.2\textwidth]{49}
\end{center}

To a solution of propargyl bromide (71) (24.0 mL, 80\% w/w in toluene, 216 mmol) in acetonitrile at room temperature was added dimethyl sulfide (16.0 mL, 216 mmol) and the reaction mixture was stirred for 24 h. The resultant precipitate was collected and washed with ether (3 \times 75 mL) and then dried \textit{in vacuo} to afford dimethyl-2-propynyl sulfonium bromide (34.7 g, 89\%) as a colourless crystalline solid. A portion of this material (24.0 g, 133 mmol) was added to a solution of sodium ethoxide (133 mmol) and ethyl acetoacetate (16.9 mL, 133 mmol) in ethanol (250 mL) at 0 °C. The resultant mixture was heated at reflux for 10 h and then allowed to cool to room temperature. The solvent was removed by distillation at atmospheric pressure and the residue was suspended in ether (300 mL). The resultant mixture was filtered and the filtrate was concentrated \textit{in vacuo}. Purification by distillation at reduced pressure afforded the \textit{title compound} 49 (21.9 g, 98\%) as a colourless oil. $R_f = 0.64$, hexanes:ether (1:1); B.p. 73-79 °C, \~2 mm Hg (lit.\textsuperscript{156} 100 °C, 16 mm Hg); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 1.35 (t, $J = 7.0$ Hz, 3H, CH\textsubscript{2}Me), 2.13 (d, $J = 1.2$ Hz, 3H, Me-4), 2.53 (s, 3H, Me-2), 4.27 (q, $J = 7.2$ Hz, 3H, CH\textsubscript{2}Me), 7.02 (d, $J = 1.2$ Hz, 1H, H-5); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) $\delta$ 9.9, 14.2, 59.7, 113.4, 121.1, 137.5, 159.9, 164.8; IR (ef) 2981, 2876, 1707, 1638, 1611, 1406, 1069 cm$^{-1}$; MS (Cl) \textit{m/z} (rel. intensity) 169 (M + H, 100).
6.4.2 2,4-Dimethyl-3-hydroxymethylfuran (50)\(^{109}\)

A solution of the ester 49 (7.51 g, 44.7 mmol) in ether (15 mL) was added to a suspension of lithium aluminum hydride (6.79 g, 179 mmol) in ether (75 mL) at 0 °C. The resultant mixture was allowed to warm to room temperature over 20 min and then was cooled to 0 °C. Water (7 mL), an aqueous solution of sodium hydroxide (2 M, 7 mL) and water (20.5 mL) were then added in succession. The resultant mixture was filtered and the filter-cake was washed with ether (3 × 60 mL) and then the combined filtrates were concentrated in vacuo. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the title compound 50 (5.16 g, 92%) as a cream coloured solid. \(R_f = 0.26, \text{hexanes:ether (1:1)}; \text{M.p.} 34-35 °C, \text{hexanes:ether}; ^1\text{H NMR} (400 MHz, C\textsubscript{6}D\textsubscript{6}) \delta 1.85 (d, J = 1.1 Hz, 3H, Me-4), 1.96 (s, 3H, Me-2), 4.12 (s, 2H, \text{CH}_2\text{OH}), 6.88 \text{(apparent d, J = 0.9 Hz, 1H, H-5)}; ^13\text{C NMR} (101 MHz, C\textsubscript{6}D\textsubscript{6}) \delta 8.2, 11.5, 55.0, 119.9, 120.8, 137.3, 149.8; \text{IR (ef)} 3357, 2938, 2884, 1635, 1571, 1443, 1408, 1279, 1118 cm\(^{-1}\); \text{MS (El) m/z (rel. intensity) 127 (M + H, 36), 109 (M - OH, 100).}

6.4.3 2,4-Dimethyl-3-\(t\)-butyldimethylsilyloxyethylfuran (230)

**Method A:**\(^{118}\) To a solution of the alcohol 50 (63 mg, 0.50 mmol) in tetrahydrofuran (4 mL) at 0 °C was added \(t\)-butyl lithium (0.44 mL, 2.5 M in hexanes,
1.1 mmol). After 2 h, a solution of $t$-butyldimethylsilyl chloride (77 mg, 0.51 mmol) in tetrahydrofuran (3 mL) was added and the resultant mixture was allowed to warm to room temperature over 18 h. The reaction mixture was then diluted with ether (10 mL), was washed with a saturated aqueous solution of ammonium chloride (3 × 10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the title compound 230 (62 mg, 52%) as a colourless oil.

**Method B:** To a solution of the alcohol 50 (31 mg, 0.25 mmol) in tetrahydrofuran (2 mL) at room temperature was added $n$-butyl lithium (0.25 mL, 2.5 M in hexanes, 0.63 mmol). After 2 h, a solution of $t$-butyldimethylsilyl chloride (37 mg, 0.25 mmol) in tetrahydrofuran (2 mL) was added and the resultant mixture was stirred for 18 h. The reaction mixture was then diluted with ether (10 mL), was washed with a saturated aqueous solution of ammonium chloride (3 × 10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes:ether (1:1) as the eluant afforded the title compound 230 (34 mg, 57%) as a colourless oil.

**Method C:** To a solution of the alcohol 50 (38 mg, 0.30 mmol) in tetrahydrofuran (3 mL) at room temperature was added $n$-butyl lithium (0.30 mL, 2.5 M in hexanes, 0.75 mmol). The resultant mixture was heated at reflux for 2 h. After cooling to room temperature, a solution of $t$-butyldimethylsilyl chloride (46 mg, 0.31 mmol) in tetrahydrofuran (3 mL) was added and the resultant mixture was allowed to stir 20 h. The reaction mixture then was diluted with ether (10 mL), was washed with a saturated aqueous solution of ammonium chloride (3 × 10 mL), dried over anhydrous
sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the title compound 230 (25 mg, 35%) as a colourless oil.

**Method D:** To a solution of the alcohol 50 (64 mg, 0.51 mmol) in tetrahydrofuran (5 mL) at −78 °C was added t-butyl lithium (0.65 mL, 1.7 M in pentane, 1.11 mmol) and the resultant mixture was allowed to warm to room temperature over 4 h. A solution of t-butyldimethylsilyl chloride (75 mg, 0.51 mmol) in tetrahydrofuran (3 mL) was then added and the reaction mixture was stirred at room temperature for 18 h. The resultant mixture was then diluted with ether (10 mL), was washed with a saturated aqueous solution of ammonium chloride (3 × 10 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the title compound 230 (81 mg, 68%) as a colourless oil.

**Method E:** To a solution of the alcohol 50 (101 mg, 0.80 mmol) and t-butyldimethylsilyl chloride (130 mg, 0.87 mmol) in N,N-dimethylformamide (3 mL) at room temperature was added imidazole (190 mg, 2.75 mmol). After 46 h, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with brine (4 × 15 mL). The combined aqueous layers were extracted with ethyl acetate (4 × 25 mL) and the combined organic layers were then dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using hexanes:ether (9:1) as the eluant afforded the title compound 230 (192 mg, 99%) as a colourless oil.

**Title compound 230:** \( R_f = 0.63, \) hexanes:ether (9:1); \( \textsuperscript{1}H \text{ NMR} \) (500 MHz, \( C_6D_6 \)) \( \delta \) 0.03 (s, 6H, 2 × SiMe), 0.95 (s, 9H, 3 × Si-t-Bu), 1.94 (s, 3H, Me-4), 2.05 (s, 3H, Me-2),
4.37 (s, 2H, CH₂O), 6.91 (s, 1H, ArH); $^{13}$C NMR (126 MHz, C₆D₆) δ -5.2, 8.6, 11.8, 18.4, 26.1, 56.3, 119.7, 120.9, 137.3, 148.9; IR (ef) 2953, 2928, 2853, 1569, 1476, 1413, 1255, 1063 cm⁻¹; MS (Cl) m/z (rel. intensity) 241 (M + H, 100), 183 (38), 109 (92);

**Anal.** Calcd. for C₁₃H₂₄O₂Si: C, 64.95; H, 10.06. Found: C, 64.73; H, 9.86.

### 6.4.4 2,4-Dimethyl-3-furanoic Acid (237)$^{124}$

![Structure of 2,4-Dimethyl-3-furanoic Acid (237)]

The ester 49 (6.04 g, 36.0 mmol) and an aqueous solution of sodium hydroxide (125 mL, 5% w/v) were heated at reflux for 3.5 h and then cooled to room temperature. The pH was adjusted to ~ 2 with hydrochloric acid (1 M) and the resultant mixture was extracted with chloroform (3 × 120 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using ether as the eluant afforded the title compound 237 (4.90 g, 97%) as a white solid. Purification by crystallization from petroleum ether afforded fine colourless needles. $R_f = 0.57$, ether; **M.p.** 118-119 °C, petroleum ether (lit.$^{124}$ 122 °C); $^1$H NMR (400 MHz, CDCl₃) δ 2.16 (s, 3H, Me-4), 2.58 (s, 3H, Me-2), 7.06 (s, 1H, H-5), 10.27 (s, 1H, CO₂H); $^{13}$C NMR (101 MHz, CDCl₃) δ 9.9, 14.6, 112.8, 121.5, 137.9, 162.0, 170.8; IR (ef) 3590, 2978, 2929, 1673, 1611, 1562, 1441, 1312, 1281, 1118, 916 cm⁻¹; MS (Cl) m/z (rel. intensity) 141 (M + H, 100).
6.4.5 2,4-Dimethyl-5-bromo-3-furanoic Acid (238)<sup>125</sup>

![Chemical Structure](image)

To a solution of the carboxylic acid 237 (200 mg, 1.43 mmol) in acetic acid (2 mL) at 0 °C was added bromine (108 μL, 2.13 mmol) and the resultant mixture was allowed to warm to room temperature over 20 min. The reaction mixture was then concentrated in vacuo and the residue was poured onto crushed ice (~3 g). The resultant solid was collected by filtration, rinsed with cold water (3 x 2 mL) and dried in vacuo. Purification by recrystallization from water afforded the title compound 238 (169 mg, 54%) as a yellow solid. R<sub>f</sub> = 0.33, hexanes:ether (1:1); M.p. 147 °C (dec.), water [lit.<sup>125</sup> 154 °C (dec.), water]; <sup>1</sup>H NMR [400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO] δ 2.09 (s, 3H, Me-4), 2.53 (s, 3H, Me-2), 11.14 (s, 1H, CO<sub>2</sub>H); <sup>13</sup>C NMR [101 MHz, (CD<sub>3</sub>)<sub>2</sub>CO] δ 11.8, 15.2, 117.0, 120.4, 122.2, 162.5, 165.4; IR (ef) 3348, 2919, 2852, 1680, 1606, 1562, 1442, 1297, 1115 cm<sup>-1</sup>; MS (Cl) m/z (rel. intensity) 221 [M (<sup>81</sup>Br + H, 100], 219 [M (<sup>79</sup>Br + H, 100], 141 (92).

6.4.6 (±)-11-Trinorxyloketal A [(±)-18] and (±)-2,6-epi-11,11',11''-Trinorxyloketal A [(±)-19]<sup>9,11,10,111</sup>

![Chemical Structure](image)

**Method A:** To a suspension of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), the alcohol 168 [prepared from the corresponding ester 167 (260 mg, 1.83 mmol, 6
equiv]) and anhydrous magnesium sulfate (0.25 g) in ether (5 mL) at 0 °C was added boron trifluoride diethyl etherate (0.10 mL, 0.80 mmol, 2.7 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the title compounds (+)-18 and (+)-19 (45 mg, 36%) as a solid white foam.

**Method B:** To a suspension of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), the alcohol 168 [prepared from the corresponding ester 167 (254 mg, 1.79 mmol, 6 equiv)] and anhydrous magnesium sulfate (0.25 g) in ether (5 mL) at -78 °C was added boron trifluoride diethyl etherate (0.10 mL, 0.80 mmol, 2.7 equiv). The resultant mixture was stirred at -78 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the title compounds (+)-18 and (+)-19 (43 mg, 35%) as a solid white foam.

**Method C:** To a suspension of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), the alcohol 168 [prepared from the corresponding ester 167 (254 mg, 1.79 mmol, 6 equiv)] and anhydrous magnesium sulfate (0.25 g) in ether (5 mL) at 0 °C was added boron trifluoride diethyl etherate (50 µL, 0.40 mmol, 1.3 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 ×
10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the title compounds (+)-18 and (−)-19 (85 mg, 69%) as a solid white foam.

**Method D:** To a suspension of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol 168 in ether [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester 167 (854 mg, 6.01 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added boron trifluoride diethyl etherate (38 μL, 0.30 mmol, 1 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the title compounds (±)-18 and (±)-19 (115 mg, 93%) as a solid white foam.

**Method E:** To a suspension of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol 168 [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester 167 (854 mg, 6.01 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added boron trifluoride diethyl etherate (19 μL, 0.15 mmol, 0.5 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the title compounds (±)-18 and (±)-19 (95 mg, 77%) as a solid white foam.
**Method F:** To a suspension of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol 168 [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester 167 (854 mg, 6.01 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added boron trifluoride diethyl etherate (9 µL, 0.08 mmol, 0.25 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 x 10 mL). The combined filtrates were washed with water (3 x 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the title compounds (+)-18 and (+)-19 (95 mg, 77%) as a solid white foam.

**Method G:** To a suspension of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol 168 [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester 167 (860 mg, 6.06 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added an aqueous solution of hydrogen fluoride (1 drop, 48% w/v). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 x 10 mL). The combined filtrates were washed with water (3 x 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the title compounds (±)-18 and (±)-19 (88 mg, 71%) as a solid white foam.

**Method H:** To a suspension of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol 168 [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester 167 (860 mg, 6.06 mmol) in ether (10.0 mL)] and anhydrous...
magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added p-toluenesulfonic acid monohydrate (57 mg, 0.30 mmol, 1 equiv). The resultant mixture was stirred at 0 °C for 15 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using ether:hexanes (3:1) as the eluant afforded a mixture (dr = 2:7) of the title compounds (±)-18 and (±)-19 (96 mg, 77%) as a solid white foam.

**Method I:** To a suspension of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), a solution of the alcohol 168 [(3.0 mL, 1.8 mmol, 6 equiv) prepared from the corresponding ester 167 (860 mg, 6.06 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added acetic acid (17 μL, 0.30 mmol). The resultant mixture was stirred at allowed to warm up to room temperature and was stirred for 72 h. TLC analysis indicated that none of the desired reaction products (±)-18 and (±)-19 had formed.

**Method J:** A suspension of phloroglucinol (14) (38 mg, 0.30 mmol, 1 equiv), the alcohol 168 [prepared from the corresponding ester 167 (254 mg, 1.79 mmol, 6 equiv)] and anhydrous magnesium sulfate (0.25 g) in ether (5 mL) at 0 °C was allowed to warm to room temperature over 4.5 h. TLC analysis indicated that none of the desired reaction products (±)-18 and (±)-19 had formed.

Recrystallization from petroleum ether, on slow evaporation of the solvent, afforded an analytically pure mixture (dr = 2:7) of the title compounds (±)-18 and (±)-19 as a white solid. \( R_f = 0.32, \) ether:hexanes (3:1); \textbf{M.p.} 139-143 °C, petroleum ether [lit.\(^9\) 155-157 °C, petroleum ether for a mixture (dr = 1:4) of the title compounds (±)-18 and
(±)-19]; \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) δ 1.44 (s, 3H, Me-10 of (±)-19), 1.45 (s, 3H, Me-10 of (±)-19), 1.47 (s, 3H, Me-10 of (±)-19), 1.48 (s, 9H, Me-10 of (±)-18), 1.51 (m, 3H, H-5), 1.65 (m, 3H, H-5), 1.94 (m, 3H, H-6), 2.74 (m, 3H, H-7), 3.05 (m, 3H, H-7), 3.62 (m, 3H, H-4), 3.90 (m, 3H, H-4); \(^{13}\)C NMR (101 MHz, C\(_6\)D\(_6\)) δ 20.8, 20.9, 22.9, 23.0, 23.2, 23.3, 29.4, 29.5, 66.57, 66.59, 99.7, 99.8, 106.9, 107.0, 107.1, 107.2, 150.86, 150.93, 151.0, 151.1; IR (ef) 2981, 2936, 2885, 2852, 1617, 1455, 1371, 1179, 1105, 1003 cm\(^{-1}\);
MS (Cl) m/z (rel. intensity) 415 (M + H, 31), 414 (M, 15), 373 (10), 331 (100), 97 (9), 43 (32); Anal. Caled. for C\(_{24}\)H\(_{30}\)O\(_6\): C, 69.54; H, 7.30. Found: C, 69.34; H, 7.48.

6.4.7 (1\(a\)RS,4\(a\)RS)-3,4,4\(a\),1\(a\)-Tetrahydro-6,8-dihyroxy-1\(a\)-methyl-furo[\(b\)]chromane-7-methylcarboxylate [(±)-241], (±)-11,11'-Dinorylxyloketal B-13-methylcarboxylate [(±)-115], (±)-2,6-\(epi\)-11,11'-Dinorylxyloketal B-13-methylcarboxylate [(±)-242], (±)-11,11'-Dinorylxyloketal C-13-methylcarboxylate [(±)-116] and (±)-2,6-\(epi\)-11,11'-Dinorylxyloketal C-13-methylcarboxylate (243)

Method A: To a suspension of the methyl ester 112 (165 mg, 0.896 mmol, 1 equiv), a solution of the alcohol 168 [(3.6 mL, 3.6 mmol, 4 equiv) prepared from the corresponding ester 167 (1.42 g, 10.0 mmol) in ether (10.0 mL)] and anhydrous
magnesium sulfate (0.75 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (115 μL, 0.916 mmol, 1 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 4 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the title compound (±)-241 (15 mg, 6%) as a white solid and a mixture (6:6:1:1) of the title compounds (±)-115, (±)-242, (±)-116 and 243 (169 mg, 50%) as a solid white foam.

**Method B:** To a suspension of the methyl ester 112 (166 mg, 0.90 mmol, 1 equiv), a solution of the alcohol 168 [(3.6 mL, 3.6 mmol, 4 equiv) prepared from the corresponding ester 167 (1.42 g, 10.0 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.75 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (115 μL, 0.916 mmol, 1 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 36 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (12:1) as the eluant afforded a mixture (10:10:1:1) of the title compounds (±)-115, (±)-242, (±)-116 and 243 (174 mg, 51%) as a solid white foam. Further purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (dr = 1:1) of the analytically pure title compounds (±)-115 and (±)-242 as a solid white foam.
Method C: To a suspension of the methyl ester 112 (139 mg, 0.76 mmol, 1 equiv), a solution of the alcohol 168 [(4 mL, 3.0 mmol, 4 equiv) prepared from the corresponding ester 167 (1.07 g, 7.5 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.75 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (63 µL, 0.50 mmol, 0.7 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (12:1) as the eluant afforded a mixture (10:10:1:1) of the title compounds (±)-115, (±)-242, (±)-116 and 243 (165 mg, 58%) as a solid white foam. Further purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (dr = 1:1) of the analytically pure title compounds (±)-115 and (±)-242 as a solid white foam.

Title compound (±)-241: \(R_f = 0.46\), ether:hexanes (19:1); **M.p.** 94-95 °C, dichloromethane:ether; \(^1H\) NMR (500 MHz, CDCl₃) \(\delta\) 1.52 (s, 3H, \(Me\)), 1.74 (m, 1H, \(H-4_{a}\)), 2.05 (m, 1H, \(H-4_{b}\)), 2.43 (m, 1H, \(H-4a_{b}\)), 2.67 (dd, \(J = 17.2, 6.4\) Hz, 1H, \(H-5_{b}\)), 2.88 (dd, \(J = 17.2, 1.3\) Hz, 1H, \(H-5_{a}\)), 3.95 (apparent q, \(J = 8.5\) Hz, 1H, \(H-3\)), 4.02 (s, 3H, CO₂\(Me\)), 4.03 (m, 1H, \(H-3\)), 5.96 (s, 1H, \(H-9\)), 8.96 (broad s, 2H, \(OH\)); **Observed nOe contacts** \(Me\) to \(H-4a_{b}\), \(Me\) to \(H-5_{b}\), \(Me\) to \(H-9\), \(H-4a_{b}\) to \(H-4_{b}\), \(H-4a_{b}\) to \(H-5_{b}\); \(^{13}C\) NMR (126 MHz, CDCl₃) \(\delta\) 19.4 (C-5), 22.2 (\(Me\)), 28.4 (C-4), 39.7 (C-4a), 52.4 (CO₂\(Me\)), 66.8 (C-3), 93.5, 96.3 (C-9), 98.0, 107.5, 160.2, 169.8; **IR** (ef) 3423 (br), 2981, 2955, 2897, 1667, 1642, 1591, 1435, 1308, 1269, 1157, 1106 cm⁻¹; **MS** (Cl) \(m/z\) (rel. intensity) 281
(M + H, 100), 249 (M – OMe, 10), 197 (28), 97 (8), 43 (10); Anal. Calcd. for C₁₄H₁₆O₆:
C, 59.99; H, 5.75. Found: C, 60.10; H, 5.82.

*Title compounds* (±)-115 and (±)-242 (dr = 1:1): \( R_f = 0.21 \), ether:hexanes (19:1); M.p. 137-138 °C, dichloromethane:ether; \(^1\)H NMR (500 MHz, CDCl₃) \( \delta 1.51 \) (s, 3H, Me-10), 1.52 (s, 3H, Me-10), 1.53 (s, 6H, 2 × Me-10), 1.73 (m, 4H, \( H-5_\alpha \)), 2.05 (m, 4H, \( H-5_\beta \)), 2.41 (m, 4H, \( H-6_\beta \)), 2.63 (apparent dt, \( J = 17.0, 7.0 \) Hz, 2H, \( H-7_\beta \)), 2.70 (apparent dt, \( J = 17.3, 7.0 \) Hz, 2H, \( H-7_\beta \)), 2.83 (apparent ddd, \( J = 17.0, 8.1, 2.2 \) Hz, 2H, \( H-7_\alpha \)), 2.93 (apparent ddd, \( J = 17.3, 3.6, 1.5 \) Hz, 2H, \( H-7_\alpha \)), 3.90 (s, 2 × 3H, CO₂Me), 3.98 (m, 8H, H-4), 11.99 (s, 1H, OH), 12.00 (s, 1H, OH); Observed nOe contacts Me-10 to \( H-6_\beta \), Me-10 to 2 × \( H-7_\beta \), \( H-6_\beta \) to \( H-5_\beta \), \( H-6_\beta \) to 2 × \( H-7_\beta \); \(^1\)C NMR (126 MHz, CDCl₃) \( \delta \) 19.7 (C-7), 19.8 (C-7), 20.26 (C-7), 20.30 (C-7), 22.5 (Me-10), 22.6 (Me-10), 22.8 (Me-10), 22.9 (Me-10), 28.58 (C-5), 28.62 (C-5), 29.4 (C-5), 29.5 (C-5), 39.8 (C-6), 40.07 (C-6), 40.14 (C-6), 52.1 (CO₂Me), 66.81 (C-4), 66.84 (C-4), 96.18, 96.22, 98.3, 98.4, 99.5, 107.5, 107.6, 107.76, 107.83, 153.7, 153.8, 156.3, 156.4, 160.79, 160.81, 172.1; IR (ef) 3425 (broad), 2981, 2898, 2852, 1648, 1615, 1338, 1227, 1177, 1105, 1002 cm⁻¹; MS (CI) m/z (rel. intensity) 377 (M + H, 8), 376 (M, 4), 345 (15), 293 (100), 85 (11), 43 (17); Anal. Calcd. for C₂₀H₂₄O₇: C, 63.82; H, 6.43. Found: C, 63.93; H, 6.54.

*Title compounds* (±)-115, (±)-242, (±)-116 and 243 (10:10:1:1): M.p. 48-51 °C, dichloromethane:ether; \(^1\)H NMR [500 MHz, CDCl₃ (additional signals observed for the *title compounds* (±)-116 and 243)] \( \delta 1.20 \) (s, 3H, Me-10), 1.22 (s, 3H, Me-10), 1.59 (m), 1.87 (m), 3.56 (m); Anal. Calcd. for C₂₀H₂₄O₇: C, 63.82; H, 6.43. Found: C, 63.58; H, 6.60.
6.4.8 (±)-11,11'-Dinorxyloketal B [(±)-16] and (±)-2,6-epi-11,11'-Dinorxyloketal B [(±)-17]9,47,48,49

To a suspension of the esters (±)-115 and (±)-242 (dr = 1:1, 57 mg, 0.15 mmol) in methanol (2 mL) and water (2 mL) was added an aqueous solution of sodium hydroxide (2 M, 0.75 mL). The resultant mixture was heated at reflux for 6 h and then allowed to cool to room temperature. The reaction mixture was then diluted with ethyl acetate (30 mL). The resultant solution was washed with a saturated aqueous solution of ammonium chloride (2 × 8 mL), brine (8 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (17:3) as the eluant afforded a mixture (dr = 1:1) of the title compounds (±)-16 and (±)-17 (46 mg, 96%) as a white solid. \( R_f = 0.29 \), ether:hexanes (17:3); M.p. 236 °C (dec.), dichloromethane:ether [lit.9 244-245 °C (dec.), for a mixture (dr = 1:1) of the title compounds (±)-16 and (±)-17]; \(^1\text{H NMR} \) (500 MHz, CDCl₃) \( \delta \) 1.52 (s, 3H, Me-10), 1.53 [2 × (s, 3H, Me-10)], 1.54 (s, 3H, Me-10), 1.79 (m, 4H, H-5α), 2.04 (m, 4H, H-5β), 2.42 (m, 4H, H-6β), 2.64 (dd, \( J = 17.1, 6.3 \) Hz, 2H, H-7β), 2.73 (m, 2H, H-7β), 2.88 (m, 4H, H-7α), 3.94 (m, 4H, H-4β), 4.03 (m, 4H, H-4α), 5.88 (s, 1H, OH), 5.92 (s, 1H, OH), 6.16 (s, 1H, H-13), 6.17 (s, 1H, H-13); Observed nOe contacts Me-10 to H-6β, Me-10 to 2 \times H-7β, H-6β to H-5β, H-6β to 2 \times H-7β, H-5β to H-7β, H-5β to H-4β, H-5α to H-7α, H-5α to H-4α, H-13 to OH; \(^{13}\text{C NMR} \) (126 MHz, CDCl₃) \( \delta \) 20.0 (C-7), 20.08 (C-7), 20.12 (C-7), 22.5 (Me), 22.6 (Me), 22.8 (Me), 28.9 (C-5), 29.00 (C-5), 29.04 (C-5), 40.0 (C-6), 40.1
(C-6), 40.3 (C-6), 66.69 (C-4), 66.71 (C-4), 66.8 (C-4), 95.91 (C-13), 95.94 (C-13), 98.5, 98.7, 99.4, 99.5, 106.67 106.72, 106.8, 106.9, 151.9, 152.13, 152.16, 152.2, 153.2, 153.3; IR (ef) 3364 (br), 2981, 2933, 2896, 2848, 1618, 1509, 1453, 1381, 1175, 1131, 1106, 1082, 1002 cm⁻¹; MS (Cl) m/z (rel. intensity) 319 (M + H, 15), 318 (M, 30), 277 (32), 235 (5), 180 (8), 85 (18), 43 (100); Anal. Calcd. for C₁₈H₂₂O₅: C, 67.91; H, 6.97. Found: C, 67.55; H, 7.09.

6.4.9 Methyl 2,6-Dihydroxy-4-methoxybenzoate (244) and Methyl 2,4-Dimethoxy-6-hydroxybenzoate (245)

Method A: To a suspension of the ester 112 (207 mg, 1.13 mmol) and potassium carbonate (308 mg, 2.23 mmol) in acetone (10 mL) at room temperature was added methyl iodide (70 μL, 1.1 mmol). The resultant mixture was stirred at room temperature for 23 h and then was filtered. The filter-cake was washed with acetone (2 × 5 mL) and the combined filtrates were concentrated in vacuo. Purification by flash chromatography using chloroform as the eluant afforded the title compound 244 (84 mg, 39%) as a white solid.

Method B: To a suspension of the ester 112 (207 mg, 1.13 mmol) and potassium carbonate (318 mg, 2.30 mmol) in acetone (10 mL) at room temperature was added methyl iodide (70 μL, 1.1 mmol). The resultant mixture was stirred at room temperature for 84 h and then was filtered. The filter-cake was washed with acetone (2 × 5 mL) and the combined filtrates were concentrated in vacuo. Purification by flash chromatography
using chloroform as the eluant afforded the title compound 244 (85 mg, 39%) as a white solid and the title compound 245 (67 mg, 28%) as a white solid.

**Title compound 244:** $R_f = 0.27$, chloroform; **M.p.** 114-116 °C, chloroform (lit.$^{137}$ 115-116 °C); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.79 (s, 3H, OMe), 4.03 (s, 3H, CO$_2$Me), 6.03 (s, 2H, ArH), 9.94 (broad s, 2H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 52.5, 55.4, 93.9, 94.4, 162.4, 166.4, 169.6; IR (ef) 3416, 3098, 3018, 2958, 2848, 1679, 1650, 1583, 1345, 1256, 1154, 1105, 1073, 1033 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 199 (M + H, 100).

**Title compound 245:** $R_f = 0.21$, chloroform; **M.p.** 108-110 °C, chloroform (lit.$^{141}$ 107-109 °C); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.79 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.91 (s, 3H, CO$_2$Me), 5.96 (s, 1H, ArH), 6.10 (s, 1H, ArH), 12.04 (s, 1H, OH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 52.1, 55.4, 56.0, 91.5, 93.4, 96.5, 162.1, 165.3, 165.9, 171.6; IR (ef) 2918, 2853, 1640, 1613, 1434, 1333, 1312, 1275 cm$^{-1}$; MS (Cl) $m/z$ (rel. intensity) 213 (M + H, 100), 181 (M – OMe, 6).

6.4.10 (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-6-methoxy-8-hydroxy-1a-methylfuro[b]chromane-9-methylcarboxylate [(±)-246]

![Chemical Structure](image)

To a suspension of the ester 245 (137 mg, 0.69 mmol, 1 equiv), the alcohol 168 [(399 mg, 2.8 mmol, 4 equiv) prepared from the corresponding ester 167] and anhydrous magnesium sulfate (0.51 g) in ether (9 mL) at 0 °C was added boron trifluoride diethyl etherate (90 µL, 0.69 mmol, 1.0 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 50 h. The reaction mixture was then filtered and
the filter-cake was washed with ethyl acetate (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the title compound (±)-246 (96 mg, 47%) as a white solid. R_f = 0.49, dichloromethane:ether (19:1); M.p. 184-186 °C, dichloromethane:ether; 1H NMR (500 MHz, CDCl_3) δ 1.51 (s, 3H, Me-1aβ), 1.79 (m, 1H, H-4a), 2.04 (m, 1H, H-4β), 2.39 (m, 1H, H-4αβ), 2.60 (dd, J = 17.0, 6.5 Hz, 1H, H-5β), 2.80 (dd, J = 17.0, 1.8 Hz, 1H, H-5α), 3.81 (s, 3H, OMe), 3.90 (s, 3H, CO_2Me), 3.92 (m, 1H, H-3β), 4.01 (m, 1H, H-3α), 6.08 (s, 1H, H-7), 11.80 (s, 1H, OH); Observed nOe contacts Me-1αβ to H-4α, Me-1αβ to H-5β, H-4αβ to H-5β, H-4αβ to H-4β, H-4αβ to H-4α, H-4α to H-4αβ, H-5β to H-5α, H-7 to OH, H-7 to OMe; 13C NMR (126 MHz, CDCl_3) δ 20.1 (C-5), 22.6 (Me-1α), 29.2 (C-4), 39.9 (C-4α), 52.1 (CO_2Me), 55.5 (OMe), 66.8 (C-3), 91.9 (C-7), 96.6, 99.8, 107.7, 155.1, 162.7, 163.7, 171.8; IR (ef) 3247 (broad), 2934, 2847, 1632, 1594, 1435, 1328, 1305, 1257, 1162, 997 cm⁻¹; MS (Cl) m/z (rel. intensity) 295 (M + H, 22), 263 (M – OMe, 7), 211 (100), 43 (8); Anal. Calcd. for C_{15}H_{18}O_6: C, 61.22; H, 6.16. Found: C, 61.06; H, 6.12.

6.11.11 (±)-11-Norxyloketal D [(±)-12] and (±)-10-Norxyloketal G [(±)-13]

Method A: To a suspension of 2,4-dihydroxyacetophenone (11) (227 mg, 1.49 mmol, 1 equiv), a solution of the alcohol 168 [(4.0 mL, 3.0 mmol, 2 equiv) prepared from
the corresponding ester 167 (1.07 g, 7.53 mmol) in ether (10.0 mL) and anhydrous magnesium sulfate (1.0 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using a gradient of dichloromethane:ether (100:0 then 98:2) as the eluant afforded the title compound (±)-12 [57 mg, 13% (41% brsm)] as a white solid (on evaporation from petroleum ether), the title compound (±)-13 [48 mg, 11% (34% brsm)] as a white solid (also on evaporation from petroleum ether) and the unreacted acetophenone 11 (142 mg, 62%).

**Method B:** To a suspension of the 2,4-dihydroxyacetophenone (11) (230 mg, 1.51 mmol, 1 equiv), a solution of the alcohol 168 [(7.5 mL, 6.0 mmol, 4 equiv) prepared from the corresponding ester 167 (1.14 g, 8.03 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.0 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using a gradient of dichloromethane:ether (99:1 then 98:2) as the eluant afforded the title compound (±)-12 [63 mg, 17% (54% brsm)] as a white solid (on evaporation from petroleum ether), the title compound (±)-13
[37 mg, 10% (32% brsm)] as a white solid (also on evaporation from petroleum ether) and the unreacted acetophenone 11 (158 mg, 68%).

*Title compound* (±)-12:  \( R_f = 0.48 \), dichloromethane:ether (99:1);  **M.p.** 103-105 °C, petroleum ether [lit.\(^9\) 114-116 °C];  \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.54 (s, 3H, Me-10), 1.74 (m, 1H, H-5), 2.08 (m, 1H, H-5), 2.47 (m, 1H, H-6\( \beta \)), 2.54 (s, 3H, Me-17), 2.75 (dd, \( J = 17.9, 6.4 \) Hz, 1H, H-7\( \beta \)), 3.02 (dd, \( J = 17.9, 1.1 \) Hz, 1H, H-7\( \alpha \)), 3.98 (apparent q, \( J = 8.5 \) Hz, 1H, H-15), 7.52 (d, \( J = 8.9 \) Hz, 1H, H-14), 13.10 (s, 1H, OH); Observed nOe contacts Me-11 to H-6\( \beta \), Me-11 to H-7\( \beta \);  \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 19.4, 22.2, 26.1, 28.5, 39.6, 66.9, 106.1, 107.4, 108.7, 113.1, 130.0, 159.6, 162.9, 202.6;  **IR** (ef) 3232 (br), 2987, 2930, 2897, 1622, 1491, 1420, 1370, 1330, 1271, 1177, 1107, 1085, 1004, 852 cm\(^{-1}\); **MS** (CI) \( m/z \) (rel. intensity) 249 (M + H, 100), 231 (30);  **Anal. Calcd.** for C\(_{14}\)H\(_{16}\)O\(_4\):  C, 67.73; H, 6.50. Found: C, 67.38; H, 6.81.

*Title compound* (±)-13:  \( R_f = 0.35 \), dichloromethane:hexanes (99:1);  **M.p.** 131-133 °C, petroleum ether [lit.\(^9\) 134-135 °C];  \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 1.58 (s, 3H, Me-11), 1.73 (m, 1H, H-3\( \alpha \)), 2.05 (m, 1H, H-3\( \beta \)), 2.48 (m, 1H, H-3a\( \beta \)), 2.54 (s, 3H, Me-13), 2.77 (dd, \( J = 16.3, 1.2 \) Hz, 1H, H-4\( \alpha \)), 3.00 (dd, \( J = 16.3, 5.4 \) Hz, 1H, H-4\( \beta \)), 3.97 (m, 2H, 2 \( \times \) H-2), 6.36 (s, 1H, H-8), 7.44 (s, 1H, H-5), 12.37 (s, 1H, OH); Observed nOe contacts Me-11 to H-3a\( \beta \), Me-11 to H-4\( \beta \), Me-11 to H-8, H-3a\( \beta \) to H-3\( \beta \), H-3a\( \beta \) to H-4\( \beta \), H-4\( \beta \) to H-4\( \alpha \), H-4\( \beta \) to H-5, H-4\( \alpha \) to H-5, H-5 to Me-13, Me-13 to OH, OH to H-8, H-3\( \beta \) to H-2, H-3\( \beta \) to H-3\( \alpha \), H-3\( \alpha \) to H-2;  \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 23.0 (C-11), 25.3 (C-4), 26.2 (C-13), 28.0 (C-3), 40.7 (C-3a), 66.9 (C-2), 104.5 (C-8), 108.1, 110.4, 114.4, 132.2 (C-5), 160.4, 163.3, 202.3;  **IR** (ef) 3399 (br), 2988, 2927, 2899, 1650, 1615, 1494, 1390,
1364, 1284, 1160, 1099, 1074, 1000 cm⁻¹; MS (Cl) m/z (rel. intensity) 249 (M + H, 100), 248 (M, 26), 231 (30), 165 (7), 43 (59); Anal. Calcd. for C₁₄H₁₆O₄: C, 67.73; H, 6.50. Found: C, 67.60; H, 6.65.

6.4.12 (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-7-ethyl-8-hydroxy-1a-methyl-furo[b]chromane [(±)-250]

To a suspension of 4-ethyl-resorcinol (249) (332 mg, 2.41 mmol, 1 equiv), a solution of the alcohol 168 [(6.0 mL, 3.0 mmol, 1.25 equiv) prepared from the corresponding ester 167 (713 mg, 5.0 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.0 g) in ether (12 mL) at 0°C was added boron trifluoride diethyl etherate (0.30 mL, 2.4 mmol, 1.0 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 23 h. The reaction mixture was then filtered and the filter-cake was washed with ether (2 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the title compound (±)-250 (341 mg, 61%) as a white solid. Rᵣ = 0.25, dichloromethane:ether (9:1); M.p. 124-125 °C, dichloromethane:ether; ¹H NMR (500 MHz, CDCl₃) δ 1.20 (apparent t, J = 7.6 Hz, 3H, CH₂Me), 1.59 (s, 3H, Me-1α), 1.80 (m, 1H, H-4γ), 2.03 (m, 1H, H-4β), 2.48 (m, 1H, H-4aβ), 2.56 (m, 2H, CH₂Me), 2.69 (apparent d, J = 16.1 Hz, 1H, H-5α), 2.96 (dd, J = 16.2, 5.7 Hz, 1H, H-5β), 3.91 (apparent
q, J = 8.3 Hz, 1H, H-3β), 4.01 (apparent td, J = 8.8, 3.4 Hz, 1H, H-3α), 5.93 (s, 1H, OH), 6.56 (s, 1H, H-9), 6.80 (m, 1H, H-6); **Observed nOe contacts** Me-1aβ to H-4aβ, Me-1aβ to H-5β, Me-1aβ to H-9, Me-1aβ to OH, H-4aβ to H-4β, H-4aβ to H-3β, H-4β to H-4α, H-4β to H-3β, H-4β to Me-1aβ, H-4α to H-3α, H-9 to OH, H-6 to H-5α, H-6 to CH₂Me, H-6 to CH₂Me; ¹³C NMR (101 MHz, CDCl₃) δ 14.3 (CH₂Me), 22.4 (CH₂Me), 23.6 (Me-1a), 25.6 (C-5), 28.8 (C-4), 41.4 (C-4α), 66.8 (C-3), 103.7 (C-9), 107.5, 111.1, 123.0 (C-6), 129.1, 151.7, 153.3; IR (ef) 3359 (br), 2973, 2931, 2893, 2867, 2847, 1625, 1606, 1513, 1447, 1382, 1102, 1008 cm⁻¹; MS (CI) m/z (rel. intensity) 235 (M + H, 100), 151 (8), 97 (40), 43 (20); **Anal.** Calcd. for C₁₄H₁₈O₃: C, 71.77; H, 7.74. Found: C, 71.56; H, 7.63.

6.4.13 (1aRS,4aRS)-3,4,4a,1a-Tetrahydro-8-hydroxy-1a-methyl-furo[b]chromane [(±)-254]

![Structure](image)

To a suspension of resorcinol (253) (140 mg, 1.25 mmol, 1 equiv), the alcohol 168 [(235 mg, 1.65 mmol, 1.3 equiv) prepared from the corresponding ester 167] and anhydrous magnesium sulfate (1.00 g) in ether (15 mL) at 0 °C was added boron trifluoride diethyl etherate (160 μL, 1.25 mmol, 1.0 equiv). The resultant mixture was allowed to warm to room temperature and was stirred for 22 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using
dichloromethane:ether (19:1) as the eluant afforded the title compound (+)-254 (89 mg, 35%) as a white solid. \( R_f = 0.25 \), dichloromethane:ether (19:1); M.p. 106-108 °C, hexanes; \(^1H\ NMR\) (500 MHz, CDCl₃) \( \delta \) 1.58 (s, 3H, Me-1α), 1.78 (m, 1H, H-4), 2.04 (m, 1H, H-4), 2.46 (m, 1H, H-4β), 2.73 (apparent d, \( J = 16.2 \) Hz, 1H, H-5α), 2.97 (dd, \( J = 16.2, 5.7 \) Hz, 1H, H-5β), 3.94 (m, 1H, H-3), 4.01 (m, 1H, H-3), 5.59 (s, 1H, OH), 6.41 (m, 1H, H-7), 6.49 (m, 1H, H-9), 6.93 (d, \( J = 8.1 \) Hz, 1H, H-6); Observed nOe contacts Me-1α to H-4αβ, Me-1α to H-5β, Me-1α to OH, Me-1α to H-9; \(^{13}C\ NMR\) (126 MHz, CDCl₃) \( \delta \) 23.4, 25.6, 28.7, 41.3, 66.8, 103.9, 107.5, 108.4, 111.4, 129.8, 154.0, 155.7; IR (ef) 3380 (br), 2980, 2938, 2898, 2843, 1623, 1597, 1509, 1458, 1381, 1301, 1153, 1110 cm\(^{-1}\); MS (Cl) \( m/z \) (rel. intensity) 207 (M + H, 100), 189 (13), 97 (31), 43 (30); Anal. Calcd. for C₁₂H₁₃O₃: C, 69.68; H, 6.84. Found: C, 69.48; H, 6.96.


To a solution of the xyloketal B analogues (±)-16 and (±)-17 (dr = 1:1, 40 mg, 0.16 mmol) and 2-methyl-4,5-dihydrofuran (114) (42 µL, 0.46 mmol, 2.9 equiv) in dichloromethane (4 mL) was added pyridinium p-toluenesulfonate (7 mg, 0.03 mmol) and the resultant solution was stirred at room temperature for 20 h. The reaction mixture was then diluted with dichloromethane (25 mL), was washed with brine (3 × 5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash
chromatography using dichloromethane:ether (9:1) as the eluant afforded an inseparable mixture (dr = 2:1:2:1) of the title compounds (+)-257, (+)-258, (+)-259 and (+)-260 (37 mg, 72%) as a white solid. Rf = 0.55, dichloromethane:ether (9:1); M.p. 119-124 °C, dichloromethane:ether; \( ^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 1.486, 1.491, 1.498, 1.504, 1.515, 1.520, 1.53, 1.540, 1.544, 1.55 (10 x s, 9H total), 1.61-1.99 (m, 4H), 2.03 (m, 2H), 2.25-2.63 (m, 5H), 2.70 (m, 1H), 2.87 (m, 2H, 2 x H-7), 3.90 (m, 4H), 4.03 (m, 2H), 10.72, 10.75, 10.78, 10.80 (4 x s, 1H total, 4 x OH); \( ^13\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 20.0, 20.16, 20.22, 20.3, 20.4, 22.3, 22.5, 22.6, 22.7, 22.8, 22.9, 25.3, 27.6, 27.7, 28.9, 29.1, 39.57, 39.64, 40.0, 40.1, 40.2, 66.6, 67.76, 67.83, 88.34, 88.42, 88.44, 98.4, 98.6, 98.9, 99.0, 106.28, 106.32, 106.50, 106.52, 106.8, 107.0, 107.1, 110.0, 110.1, 110.2, 148.52, 148.55, 148.6, 150.1, 150.3, 152.2, 152.36, 152.43, 152.5; IR (ef) 3170 (br), 2977, 2940, 2894, 1621, 1439, 1379, 1328, 1003 cm\(^{-1}\); MS (Cl) m/z (rel. intensity) 319 (55), 235 (28), 97 (47), 85 (100), 43 (43); Anal. Calcd. for C\(_{23}\)H\(_{30}\)O\(_6\): C, 68.64; H, 7.51. Found: C, 68.73; H, 7.54.

6.4.15 (-)-Xyloketal A [(-)-1] and 2,6-epi-Xyloketal A (40)

**Method A:** To a suspension of phloroglucinol (14) (42 mg, 0.33 mmol, 1 equiv), a solution of the alcohol (4R)-226 in ether [(4.0 mL, 2.0 mmol, 6 equiv) prepared from the corresponding ester (4R)-206 (783 mg, 5.02 mmol) in ether (10.0 mL)] and anhydrous
magnesium sulfate (0.30 g) in ether (3 mL) at 0 °C was added boron trifluoride diethyl etherate (42 μL, 0.33 mmol, 1 equiv). The resultant mixture was stirred at 0 °C for 20 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (2 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (dr = 5:2) of the title compounds (−)-I and 40 (128 mg, 85%) as a colourless oil.

Method B: To a suspension of phloroglucinol (14) (42 mg, 0.33 mmol, 1 equiv), a solution of the alcohol (4R)-226 in ether [(4.0 mL, 2.0 mmol, 6 equiv) prepared from the corresponding ester (4R)-206 (783 mg, 5.02 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.30 g) in ether (3 mL) at −78 °C was added boron trifluoride diethyl etherate (42 μL, 0.33 mmol, 1 equiv). The resultant mixture was stirred at 0 °C for 20 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (2 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (dr = 4:1) of the title compounds (−)-I and 40 (119 mg, 79%) as a colourless oil.

Method C: To a suspension of phloroglucinol (14) (32 mg, 0.25 mmol, 1 equiv), a solution of the alcohol (4R)-226 in ether [(2.0 mL, 1.0 mmol, 4 equiv) prepared from the corresponding ester (4R)-206 (783 mg, 5.02 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.25 g) in ether (2 mL) at 0 °C was added boron trifluoride diethyl etherate (32 μL, 0.25 mmol, 1 equiv). The resultant mixture was allowed to warm to room temperature over 2 h. The reaction mixture was then filtered and the filter-cake
was washed with ether (3 x 10 mL). The combined filtrates were washed with water (2 x 10 mL), dried over anhydrous magnesium sulfate and concentrated \textit{in vacuo}. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (dr = 5:2) of the \textit{title compounds} \textsc{(-)-1} and \textsc{40} (16 mg, 14\%) as a colourless oil.

\textit{Title compound \textsc{(-)-1}}: Crystallization of the \textit{title compounds} \textsc{(-)-1} and \textsc{40} from petroleum ether, on slow evaporation of the solvent, afforded the analytically pure \textsc{(-)-xyloketal A} \textsc{(-)-1} as colourless shards and as a single diastereoisomer. \textbf{Rf} = 0.45, dichloromethane:ether (19:1); \textbf{M.p.} 158-160 °C, petroleum ether (lit.\textsuperscript{1} 164-166 °C); $[\alpha]_D^{20} = -6.3 \ (c \ 0.43, \ \text{chloroform}) \ [\text{lit.}\textsuperscript{1} \ [\alpha]_D^{20} = -4.88 \ (c \ 0.205, \ \text{chloroform})]$; \textbf{1H NMR} (500 MHz, CDCl\textsubscript{3}) $\delta$ 1.05 (d, $J = 6.6$ Hz, 9H, Me-11), 1.49 (s, 9H, Me-10), 1.88 (dd, $J = 10.9, 6.4$ Hz, 3H, H-6), 2.13 (m, 3H, H-5), 2.64 (dd, $J = 17.6, 6.8$ Hz, 3H, H-7), 2.85 (apparent d, $J = 17.6$ Hz, 3H, H-7), 3.53 (apparent t, $J = 8.4$ Hz, 3H, H-4), 4.16 (apparent t, $J = 8.4$ Hz, 3H, H-4); \textbf{13C NMR} (126 MHz, CDCl\textsubscript{3}) $\delta$ 16.0, 18.9, 22.9, 35.5, 47.5, 74.0, 98.9, 107.3, 149.7; \textbf{IR} (ef) 2955, 2934, 2876, 1615, 1455, 1378, 1205, 1115, 1008 cm$^{-1}$; \textbf{MS} (Cl) m/z (rel. intensity) 457 (M + H, 34), 401 (M, 15), 359 (100), 111 (33), 43 (33); \textbf{Anal.} Calcd. for C\textsubscript{27}H\textsubscript{36}O\textsubscript{6}: C, 71.03; H, 7.95. Found: C, 71.10; H, 8.11.

\textit{Title compound \textsc{40}}: \textbf{1H NMR} [500 MHz, CDCl\textsubscript{3} (additional signals observed for the \textit{title compound \textsc{40}})] $\delta$ 0.83 (d, $J = 7.1$ Hz, 3H, Me-11), 1.45 (s, 3H, Me-10), 1.50 (s, 3H, Me-10), 1.51 (s, 3H, Me-10), 2.35 (m, 1H, H-5 or H-6), 2.50 (m, 1H, H-5 or H-6), 2.68 (m, 1H, H-7), 2.84 (m, 1H, H-7), 3.55 (m, 1H, H-4), 4.09 (t, $J = 8.1$ Hz, 1H, H-4).
6.4.16 (−)-(1aR,4R,4aR)-3,4,4a,1a-Tetrahydro-6,8-dihydroxy-1a,4-dimethylfuro[b]-7-chromane Methylcarboxylate [(−)-261] and (−)-13-Xyloketal B Methylcarboxylate [(−)-262]

Method A: To a suspension of the methyl ester 112 (139 mg, 0.755 mmol, 1 equiv), a solution of the alcohol (4R)-226 in ether [(3.0 mL, 3.0 mmol, 4 equiv) prepared from the corresponding ester (4R)-206 (1.57 g, 10.1 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.75 g) in ether (12 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.7 equiv). The resultant mixture was allowed to warm to room temperature over 38 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 15 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane followed by dichloromethane:ether (19:1) as the eluant afforded the title compound (−)-261 (37 mg, 17%) as a white solid and the title compound (−)-262 (222 mg, 73%) as a solid white foam.

Method B: To a suspension of the methyl ester 112 (138 mg, 0.750 mmol, 1 equiv), a solution of the alcohol (4R)-226 in ether [(3.0 mL, 3.0 mmol, 4 equiv) prepared from the corresponding ester (4R)-206 (1.57 g, 10.1 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.75 g) in ether (12 mL) at 0 °C was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.7 equiv). The resultant mixture was
allowed to warm to room temperature over 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the title compound (−)-262 (277 mg, 91%) as a solid white foam.

**Title compound (−)-261:** This compound was recrystallized from petroleum ether to afford colourless needles. Rf = 0.32, dichloromethane; M.p. 85-87 °C, petroleum ether; [α]D20 = −59.8 (c 0.48, chloroform); 1H NMR (500 MHz, CDCl3) δ 1.06 (d, J = 6.5 Hz, 3H, Me-4β), 1.51 (s, 3H, Me-1αβ), 1.93 (ddd, J = 11.2, 6.4, 1.0 Hz, 1H, H-4αβ), 2.08 (m, 1H, H-4α), 2.62 (dd, J = 17.4, 6.4 Hz, 1H, H-5α), 2.84 (dd, J = 17.5, 1.1 Hz, 1H, H-5α), 3.54 (apparent t, J = 8.6 Hz, 1H, H-3β), 4.03 (s, 3H, CO2Me), 4.18 (apparent t, J = 8.5 Hz, 1H, H-9), 8.71 (broad s, 1H, OH), 10.78 (broad s, 1H, OH); Observed nOe contacts Me-4β to H-4αβ, Me-4β to H-4α, Me-4β to H-5α, Me-4β to H-3β, Me-1αβ to H-9, Me-1αβ to H-4αβ, Me-1αβ to H-5β, H-9 to CO2Me, H-9 to Me-1αβ; 13C NMR (126 MHz, CDCl3) δ 15.9, 18.0, 22.7, 35.0, 47.1, 52.4, 74.2, 93.5, 96.4, 98.1, 108.4, 160.2, 169.8; IR (ef) 3435 (br), 2962, 2929, 2897, 1673, 1648, 1591, 1441, 1308, 1268, 1162, 1139, 1116, 1073, 1005 cm⁻¹; MS (CI) m/z (rel. intensity) 295 (M + H, 100), 263 (M – OMe, 12), 197 (17), 111 (21), 43 (9); Anal. Calcd. for C15H18O6: C, 61.22; H, 6.16. Found: C, 61.41; H, 6.06.

**Title compound (−)-262:** This compound was evaporated from petroleum ether to afford a solid white foam. Rf = 0.56, dichloromethane:ether (19:1); M.p. 127-129 °C,
petroleum ether; $[\alpha]_D^{20} = -6.7$ (c 0.48, chloroform); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.05 (d, $J = 6.6$ Hz, 3H, $Me-11\beta$), 1.08 (d, $J = 6.5$ Hz, 3H, $Me-11'\beta$), 1.49 (s, 3H, $Me-10\beta$), 1.52 (s, 3H, $Me-10'\beta$), 1.88 (ddd, $J = 10.5$, 6.8, 1.3 Hz, 1H, $H-6\beta$), 1.94 (ddd, $J = 11.0$, 6.3, 0.7 Hz, 1H, $H-6'\beta$), 2.08 (m, 2H, $H-5a$ and $H-5'a$), 2.60 (dd, $J = 17.4$, 6.9 Hz, 1H, $H-7\beta$), 2.66 (dd, $J = 17.5$, 6.5 Hz, 1H, $H-7'\beta$), 2.77 (dd, $J = 17.3$, 1.3 Hz, 1H, $H-7a$), 2.89 (apparent d, $J = 17.5$ Hz, 1H, $H-7'a$), 3.49 (apparent t, $J = 8.4$ Hz, 1H, $H-4p$), 3.56 (apparent t, $J = 8.4$ Hz, 1H, $H-4'p$), 3.90 (s, 3H, CO$_2$Me), 4.18 (apparent q, $J = 8.1$ Hz, 2H, $H-4a$ and $H-4'a$), 12.03 (s, 1H, $OH$); Observed NOe contacts CO$_2$Me to OH, CO$_2$Me to $Me-10\beta$, OH to $H-7'a$, $H-7a$ to $H-7\beta$, $H-7'a$ to $H-7'\beta$, $Me-10\beta$ to $H-6\beta$, $Me-10\beta$ to $H-7\beta$, $Me-10'\beta$ to $H-6'\beta$, $Me-10'\beta$ to $H-7'\beta$, $Me-11\beta$ to $H-4\beta$, $Me-11\beta$ to $H-5\beta$, $Me-11\beta$ to $H-6\beta$, $Me-11\beta$ to $H-7\alpha$, $Me-11'\beta$ to $H-4'\beta$, $Me-11'\beta$ to $H-5\beta$, $Me-11'\beta$ to $H-6'\beta$, $Me-11'\beta$ to $H-7'a$; $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 16.0 (C-11 or C-11'), 16.1 (C-11 or C-11'), 18.3 (C-7), 19.0 (C-7), 22.9 (C-10 or C-10'), 23.0 (C-10 or C-10'), 35.1 (C-5 or C-5'), 36.0 (C-5 or C-5'), 47.2 (C-6), 47.5 (C-6), 52.1 (CO$_2$Me), 74.0 (C-4 or C-4'), 74.2 (C-4 or C-4'), 96.2, 98.3, 99.2, 108.2, 108.5, 153.4, 156.4, 160.8, 172.2; IR (ef) 3367 (br), 2964, 2925, 2852, 1644, 1620, 1433, 1334, 1229, 1115, 1008 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 405 (M + H, 11), 404 (M, 3), 373 (M – OMe, 15), 333 (5), 307 (100), 111 (20), 99 (50), 43 (24); Anal. Calcd. for C$_{22}$H$_{28}$O$_7$: C, 65.33; H, 6.98. Found: C, 65.27; H, 6.99.
To a suspension of the ester (-)-262 (299 mg, 0.740 mmol) in methanol (9 mL) and water (9 mL) was added an aqueous solution of sodium hydroxide (2 M, 3.7 mL). The resultant mixture was heated at reflux for 3.5 h then was allowed to cool to room temperature. The resultant mixture was diluted with ethyl acetate (50 mL) and was washed with a saturated aqueous solution of ammonium chloride (2 × 20 mL), brine (20 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded the title compound (-)-2 (243 mg, 95%) as a solid white foam. 

**M.p.** 85-86 °C, chloroform (lit.1 84-86 °C);  

\[ \alpha \] = -8.5 (c 0.34, chloroform)  

\[ \alpha \] = + 8.2 (c 0.061, chloroform);  

**1H NMR** (500 MHz, CDCl₃) δ 1.02 (d, J = 6.5 Hz, 3H, Me-11₀), 1.04 (d, J = 6.6 Hz, 3H, Me-11₁), 1.48 (s, 3H, Me-10₀), 1.50 (s, 3H, Me-10₁), 1.88 (m, 2H, H-6₀ and H-6₁), 2.12 (m, 2H, H-5₀ and H-5₁), 2.61 (dd, J = 17.4, 6.6 Hz, 1H, H-7), 2.68 (dd, J = 17.2, 6.5 Hz, 1H, H-7'), 2.83 (apparent d, J = 17.4 Hz, 1H, H-7), 2.84 (apparent d, J = 17.0 Hz, 1H, H-7'), 3.48 (apparent t, J = 8.5 Hz, 1H, H-4₀), 3.52 (apparent t, J = 8.4 Hz, 1H, H-4₁), 4.14 (apparent q, J = 8.5 Hz, 2H, H-4₀ and H-4₁), 6.19 (s, 1H, H-13), 7.05 (s, 1H, OH);  

**Observed nOe contacts**  


**13C NMR** (126 MHz, CDCl₃) δ 15.7 (C-11),
6.4.18 (-)-Xyloketal D [(-)-4] and (-)-Xyloketal G [(-)-7] \(^{1,4,9,10}\)

![Chemical structures of (-)-4 and (-)-7]

To a suspension of 2,4-dihydroxyacetophenone (11) (227 mg, 0.1.49 mmol, 1 equiv), a solution of the alcohol (4R)-226 in ether [(6.0 mL, 6.0 mmol, 4 equiv) prepared from the corresponding ester (4R)-206 (1.57 g, 10.1 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.0 g) in ether (9 mL) at 0 °C was added boron trifluoride diethyl etherate (63 µL, 0.50 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature over 46 h. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 15 mL). The combined filtrates were washed with water (3 × 20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded a mixture (3:2) of the title compounds (-)-4 and (-)-7 [95 mg, 24%, (86% brsm)] as a yellow oil and the unreacted acetophenone 11 (163 mg, 71%). Further purification by flash chromatography using hexanes:ether (4:1) as the eluant afforded the
title compound (-)-4 [56 mg, 14%, (51% brsm)] as a solid white foam and the title compound (-)-7 [32 mg, 8%, (29% brsm)] as a white solid.

*Title compound* (-)-4: This compound was recrystallized from pentane:ether to afford colourless prisms. \( R_f = 0.27 \), hexanes:ether (4:1); **M.p.** 79-81 °C, pentane:ether (lit.\(^1\) 111-113 °C, lit.\(^9\) 110-111 °C, pentane:ether, lit.\(^10\) 110-111 °C); \([\alpha]^{20}_D = -110.2\) (c 0.61, chloroform) [lit.\(^1\) \([\alpha]^{25}_D = -119.5\) (c 0.113, chloroform), lit.\(^9\) \([\alpha]^{25}_D = -118\) (c 0.10, chloroform)]; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 1.07 (d, \( J = 6.5\) Hz, 3H, Me-11\(\beta\)), 1.52 (s, 3H, Me-5\(\beta\)), 1.97 (ddd, \( J = 11.2\), 6.4, 0.7 Hz, 1H, H-6\(\beta\)), 2.05 (m, 1H, H-5), 2.54 (s, 3H, Me-17), 2.71 (dd, \( J = 17.0\), 6.5 Hz, 1H, H-7), 2.96 (apparent d, \( J = 18.0\) Hz, 1H, H-7), 3.56 (apparent t, \( J = 8.5\) Hz, 1H, H-4), 4.19 (apparent t, \( J = 8.4\) Hz, 1H, H-4), 6.35 (d, \( J = 8.9\) Hz, 1H, H-15), 7.50 (d, \( J = 8.9\) Hz, 1H, H-14), 13.10 (s, 1H, OH); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 15.7 (C-11), 18.0 (C-7), 22.7 (C-10), 26.1 (C-17), 35.1 (C-5), 46.9 (C-6), 74.3 (C-4), 106.1 (C-8), 108.2 (C-2), 108.7 (C-15), 113.1 (C-13), 130.0 (C-14), 159.5 (C-9), 162.9 (C-12), 202.6 (C-16); IR (ef) 3232 (br), 2955, 2930, 2898, 1616, 1490, 1419, 1332, 1272, 1117, 1070, 1066 cm\(^{-1}\); MS (Cl) \( m/z \) (rel. intensity) 263 (M + H, 100), 245 (7), 111 (6), 43 (18); Anal. Calcd. for C\(_{15}\)H\(_{18}\)O\(_4\): C, 68.68; H, 6.92. Found: C, 68.72; H, 6.95.

*Title compound* (-)-7: This compound was recrystallized from petroleum ether:ether to afford colourless flakes. \( R_f = 0.16 \), hexanes:ether (4:1); **M.p.** 137-139 °C, petroleum ether:ether [lit.\(^4\) 144 °C]; \([\alpha]^{20}_D = -19.1\) (c 0.11, chloroform) [lit.\(^4\) \([\alpha]^{20}_D = -111\) (c 0.1, chloroform)]; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 1.07 (d, \( J = 6.5\) Hz, 3H, Me-11\(\beta\)), 1.56 (s, 3H, Me-11\(\beta\)), 1.97 (ddd, \( J = 11.0\), 5.7, 1.7 Hz, 1H, H-3a\(\beta\)), 2.08 (m, 1H, H-
3\(_a\)) 2.54 (s, 3H, \(Me-13\)), 2.76 (dd, \(J = 16.6, 1.2\) Hz, 1H, \(H-4\)), 2.97 (ddd, \(J = 16.5, 5.7, 0.8\) Hz, 1H, \(H-4\)), 3.53 (apparent t, \(J = 8.4\) Hz, 1H, \(H-2\alpha\)), 4.16 (apparent t, \(J = 8.4\) Hz, 1H, \(H-2\alpha\)), 6.35 (s, 1H, \(H-8\)), 7.45 (s, 1H, \(H-5\)), 12.35 (s, 1H, \(OH\)); **Observed nOe contacts** \(H-3\alpha\) to \(Me-10\alpha\), \(H-3\alpha\) to \(Me-11\beta\), \(H-3\alpha\) to \(H-2\gamma\); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 16.0 (C-10), 23.4 (C-11), 23.8 (C-4), 26.2 (C-13), 34.6 (C-3), 48.1 (C-3a), 74.1 (C-2), 104.6 (C-8), 108.9 (C-9a), 110.3 (C-4a), 114.4 (C-6), 132.1 (C-5), 160.2 (C-8a), 163.3 (C-7), 202.2 (C-12); **IR** (ef) 3440 (br), 2961, 2891, 2871, 1644, 1614, 1494, 1387, 1364, 1286, 1205, 1166, 1114, 1103 cm\(^{-1}\)** MS (Cl) \(m/z\) (rel. intensity) 263 (M + H, 100), 245 (5), 111 (14), 43 (10); **Anal.** Calcd. for C\(_{15}\)H\(_{18}\)O\(_4\): C, 68.68; H, 6.92. Found: C, 68.60; H, 7.07.

**6.4.19 20-Norxyloketal E (263) and 14-epi-20-Norxyloketal E (264)**

To a solution of synthetic \((-\))-xyloketal B \([(-)]-2\) (21 mg, 0.061 mmol) and 2-methyl-4,5-dihydrofuran (114) (20 \(\mu\)L, 0.22 mmol, 3.6 equiv) in dichloromethane (2 mL) was added pyridinium \(p\)-toluenesulfonate (3 mg, 0.01 mmol) and the resultant solution was stirred at room temperature for 22 h. The reaction mixture was then diluted with dichloromethane (20 mL), was washed with brine (3 \(\times\) 5 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded an inseparable mixture (dr = 1:1) of

289
the title compounds 263 and 264 (20 mg, 78%) as a colourless oil. $R_f = 0.66,$
dichloromethane:ether (9:1); \([\alpha]^{20}_D = -2.6 (c 0.34, \text{chloroform})$; $^1\text{H NMR}$ (500 MHz, 
CDCl$_3$) \(\delta\) 1.04 (d, $J = 6.6$ Hz, 6H, 2 × Me-11), 1.06 (d, $J = 6.2$ Hz, 3H, Me-11), 1.07 (d, $J = 6.5$ Hz, 3H, Me-11), 1.47 (s, 3H, Me-10), 1.48 (s, 3H, Me-10), 1.49 (s, 3H, Me-10), 1.50 (s, 3H, Me-10), 1.54 (s, 6H, 2 × Me-19), 1.89 (m, 8H), 2.06 (m, 2H), 2.17 (m, 2H), 2.25 (m, 1H), 2.33 (m, 1H), 2.45 (m, 1H), 2.55 (m, 3H), 2.65 (m, 2H), 2.81 (m, 2H, H-7), 2.85 (m, 2H, H-7), 3.48 (apparent t, $J = 8.2$ Hz, 2H, H-4), 3.52 (apparent t, $J = 8.4$ Hz, 2H, H-4), 3.86 (dd, $J = 15.3$, 8.4 Hz, 2H, H-16), 4.04 (m, 2H, H-16), 4.08 (apparent t, $J = 8.4$ Hz, 2H, H-4), 4.16 (apparent t, $J = 8.4$ Hz, 2H, H-4), 10.73 (s, 1H, OH), 10.80 (s, 1H, OH); $^{13}\text{C NMR}$ (126 MHz, CDCl$_3$) \(\delta\) 16.1, 16.2, 16.28, 16.31, 18.83, 18.85, 18.9, 22.5, 22.8, 23.0, 25.3, 25.4, 27.76, 27.79, 35.4, 35.7, 39.7, 40.1, 47.58, 47.64, 47.7, 47.77, 47.79, 67.79, 67.83, 73.8, 73.9, 74.0, 88.3, 88.4, 98.2, 98.8, 107.32, 107.34, 107.5, 107.6, 110.1, 148.28, 148.34, 150.2, 152.3, 152.4; $\text{IR}$ (ef) 3178 (br), 2957, 2923, 2884, 1622, 1456, 1381, 1112, 1008 cm$^{-1}$; $\text{MS}$ (CI) $m/z$ (rel. intensity) 431 (M + H, 6), 430 (M, 16), 375 (8), 346 (14), 291 (12), 111 (8), 85 (7), 43 (100); $\text{FAB-HRMS}$ Calcd. for C$_{25}$H$_{34}$O$_6$: 430.2355. Found: 430.2356.
6.4.20 Xyloketal E (5) and 14-epi-Xyloketal E (265)\(^{1,128}\)

To a solution of synthetic (−)-xyloketal B [(−)-2] (35 mg, 0.10 mmol) and (4R)-2,4-dimethyl-4,5-dihydrofuran [(4R)-61] (25 mg, 0.25 mmol, 2.5 equiv) in dichloromethane (3 mL) was added pyridinium p-toluenesulfonate (3 mg, 0.01 mmol) and the resultant solution was stirred at room temperature for 21 h. The reaction mixture was then diluted with dichloromethane (20 mL), was washed with brine (3 × 5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded an inseparable mixture (dr = 2:9) of the title compounds 5 and 265 (37 mg, 82%) as a colourless oil. \(R_f\) = 0.47, dichloromethane:ether (99:1); \(\left[\alpha\right]^{20}_D = -2.4\) (c 0.33, chloroform) [lit.\(^1\) \(\left[\alpha\right]^{25}_D = +5.35\) (c 0.113, chloroform) for title compound 5]; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.00 (d, \(J = 6.5\) Hz, 3H, Me-20 of 5), 1.06 (m, 9H, 2 × Me-11 and Me-20), 1.47 (s, 3H, Me-10), 1.49 (s, 3H, Me-10), 1.53 (s, 3H, Me-19 of 5), 1.66 (s, 3H, Me-19 of 265), 1.77 (dd, \(J = 13.2, 7.8\) Hz, 1H), 1.87 (m, 2H), 2.06 (m, 1H), 2.16 (m, 1H), 2.28 (m, 1H of 265), 2.38 (m, 1H of 5), 2.56 (dd, \(J = 17.4, 6.6\) Hz, 1H, H-7), 2.66 (dd, \(J = 17.4, 6.7\) Hz, 1H, H-7), 2.82 (m, 3H), 3.38 (dd, \(J = 10.1, 8.3\) Hz, 1H of 5), 3.50 (m, 3H, 2 × H-4 and H-16), 4.03 (apparent t, \(J = 7.6\) Hz, 1H), 4.08 (apparent t, \(J = 7.6\) Hz, 1H of 5), 4.09 (apparent t, \(J = 8.3\) Hz, 1H), 4.16 (apparent t, \(J = 8.4\) Hz, 1H), 10.81 (s, 1H, OH of 5), 10.86 (s, 1H, OH of 265); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 15.5, 16.1, 16.2, 16.3, 17.4, 18.8, 18.9, 18.9, 18.9,
22.4, 22.7, 22.9, 23.0, 28.4, 28.9, 32.7, 33.9, 35.4, 35.7, 47.57, 47.63, 47.7, 47.9, 49.3, 73.8, 73.9, 74.0, 74.2, 89.1, 89.5, 98.2, 98.3, 98.8, 107.28, 107.32, 107.4, 107.6, 109.5, 110.7, 148.1, 148.2, 150.1, 150.14, 152.0, 153.0; IR (ef) 3180 (br), 2962, 2923, 2878, 1616, 1455, 1371, 1204, 1107, 1004 cm$^{-1}$; MS (Cl) m/z (rel. intensity) 445 (M + H, 34), 444 (M, 72), 389 (36), 348 (34), 347 (16), 292 (10), 111 (21), 99 (49), 43 (100); FAB-HRMS Calcd. for C$_{26}$H$_{36}$O$_6$: 444.2512. Found: 444.2513.

6.4.21 (−)-Xyloketal F [(−)-6]$^3$

To a mixture of synthetic (−)-xyloketal B [−(−)-2] (70 mg, 0.20 mmol) and paraformaldehyde (10 mg, 0.33 mmol) in dichloromethane (3 mL) was added pyridinium p-toluenesulfonate (52 mg, 0.21 mmol) and the resultant mixture was allowed to stir at room temperature for 23 h. The reaction mixture was then diluted with dichloromethane (20 mL), was washed with brine (3 × 5 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded the title compound (−)-6 (60 mg, 84%) as a white solid. $R_f = 0.45$, dichloromethane:ether (19:1); M.p. 158-159 °C, chloroform (lit.$^3$ 160-162 °C, ethyl acetate:petroleum ether); $[\alpha]_D^{20} = -42.3$ (c 0.57,
methanol) [lit.³ [α]20D = −50.6 (c 0.2, methanol)]; ¹H NMR (500 MHz, CDCl₃) δ 1.02 (d, J = 6.5 Hz, 6H, Me-11), 1.04 (d, J = 6.6 Hz, 6H, Me-11′), 1.48 (s, 6H, Me-10), 1.58 (s, 6H, Me-10′), 1.87 (dd, J = 11.0, 6.6 Hz, 2H, H-6), 1.91 (dd, J = 11.0, 6.5 Hz, 2H, H-6′), 2.06 (m, 2H, H-5a or H-5′a), 2.12 (m, 2H, H-5a or H-5′a), 2.66 (dd, J = 17.7, 6.6 Hz, 2H, H-7), 2.71 (dd, J = 17.7, 6.5 Hz, 2H, H-7′), 3.03 (apparent d, J = 17.6 Hz, 2H, H-7′), 3.87 (apparent d, J = 17.5 Hz, 2H, H-7′), 3.51 (apparent t, J = 8.5 Hz, 2H, H-4), 3.61 (apparent t, J = 8.6 Hz, 2H, H-4′), 3.73 (s, 2H, H-14), 4.15 (apparent t, J = 8.4 Hz, 2H, H-4), 4.30 (apparent t, J = 8.4 Hz, 2H, H-4′), 8.44 (s, 2H, OH); ¹³C NMR (126 MHz, CDCl₃) δ 15.78 (C-1′), 15.80 (C-1), 17.1 (C-14), 18.8 (C-7 or C-7′), 19.1 (C-7′ or C-7), 22.2 (C-10′), 22.8 (C-10), 35.1 (C-5), 35.2 (C-5′), 47.3 (C-6′ or C-6), 47.4 (C-6′ or C-6), 73.9 (C-4), 74.4 (C-4′), 97.9 (C-8′), 100.0 (C-8), 106.0 (C-13), 107.4 (C-2), 109.2 (C-2′), 114.0 (C-9′), 150.1 (C-9), 152.5 (C-12); IR (ef) 3353, 2957, 2933, 2888, 2851, 1615, 1460, 1382, 1340, 1205, 1115, 1078, 1004 cm⁻¹; MS (MALDI-TOF) m/z (rel. intensity) 744 (M + K, 8), 727 (M + Na, 26), 704 (M, 11), 608 (62), 509 (100), 412 (83), 360 (45), 317 (49); FAB-HRMS Calcd. for C₄₁H₅₂O₁₀: 704.3560. Found: 704.3544.

6.4.22 bis-(2,4,6-Trihydroxyphenyl)methane Monohydrate (240)¹³⁵,¹³⁶

To a solution of phloroglucinol (14) (1.26 g, 10.0 mmol) and concentrated hydrochloric acid (5 mL) in water (200 mL) at 0 °C was added an aqueous solution of formaldehyde (0.40 mL, 37% w/w, 4.9 mmol) and the resultant mixture was stirred at 4 °C for 16 h. The reaction product was collected via vacuum filtration, washed with ice
cold water (3 × 15 mL) and dried in vacuo. Purification by flash chromatography using ether as the eluant afforded the title compound 240 (474 mg, 34%) as a beige solid. Rf = 0.25, ether; M.p. 218 °C (dec.), ether [lit.135 230 °C (dec.) for the dihydrate]; 1H NMR [500 MHz, (CD3)2CO] δ 3.25 (s, 2H, H2O), 3.69 (s, 2H, CH2), 6.00 (s, 4H, ArH), 8.08 (s, 2H, 4-OH), 9.02 (s, 4H, 2-OH and 6-OH); 13C NMR [101 MHz, (CD3)2CO] δ 18.0, 97.4, 107.6, 157.5, 159.0; IR (ef) 3209 (br), 1627, 1521, 1479, 1146, 1076, 1005 cm⁻¹; MS (Cl) m/z (rel. intensity) 223 (5), 167 (6), 140 (7), 139 (6), 127 (34), 126 (25), 59 (18), 43 (100).

6.4.23 (-)-Xyloketal F [(-)-6] and the Regioisomers (266) and (267)

To a suspension of the hexaphenol 240 (31 mg, 0.15 mmol, 1 equiv), the alcohol (4R)-226 [prepared from the corresponding ester (4R)-206 (191 mg, 1.22 mmol, 8 equiv)]
and anhydrous magnesium sulfate (0.50 g) in ether (5 mL) at 0 °C was added boron trifluoride diethyl etherate (25 μL, 0.20 mmol, 1.3 equiv). The resultant mixture was allowed to warm to room temperature over 75 min. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 5 mL). The combined filtrates were washed with water (3 × 5 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded an inseparable mixture (10:7:3) of the title compounds (−)-6, 266 and 267 (74 mg, 71%) as a solid white foam.

To a solution of this mixture of products (6.9 mg, 0.098 mmol) in deuterated chloroform (0.75 mL) at 23 °C was added p-toluenesulfonic acid monohydrate (one crystal). The resultant mixture was then monitored by $^1$H NMR spectroscopy (500 MHz) at two-hour intervals. After 18 h, the $^1$H NMR spectrum indicated quantitative conversion to the title compound (−)-6.

Title compounds (−)-6, 266 and 267 (10:7:3): $R_f = 0.45$, dichloromethane:ether (19:1); M.p. 135-141 °C, dichloromethane:ether; $[\alpha]^20_D = -17$ (c 0.57, methanol); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.80 (d, $J = 5.8$ Hz, 3H, Me-11), 0.83 (d, $J = 7.4$ Hz, 3H, Me-11), 0.86 (d, $J = 7.2$ Hz, 3H, Me-11), 1.01 (d, $J = 6.2$ Hz, 6H, Me-11), 1.04 (d, $J = 6.6$ Hz, 6H, Me-11), 1.44 (s, 3H, Me-10), 1.48 (s, 6H, Me-10 of (−)-6), 1.56 (s, 3H, Me-10), 1.58 (s, 6H, Me-10 of (−)-6), 1.63 (s, 3H, Me-10), 1.67 (s, 3H, Me-10), 1.89 (m, 4H, H-6), 2.08 (m, 4H, H-5), 2.50 (m, 4H, H-7 of 266 or 267), 2.68 (m, 4H, H-7), 2.85 (m, 4H, H-7), 3.51 (m, 2H, H-4), 3.60 (m, 2H, H-4), 3.73 (s, 2H, H-14 of (−)-6), 3.74 (s, 2H, H-14 of 266), 3.76 (s, 2H, H-14 of 267), 4.14 (m, 2H, H-4), 4.30 (m, 2H, H-4), 8.34 (s, 1H, OH of 266), 8.36 (s, 1H, OH of 266), 8.42 (s, 2H, OH of 267), 8.44 (s, 2H, OH of (−)-6); $^{13}$C
**NMR** (126 MHz, CDCl₃) δ 15.5, 15.7, 15.77, 15.79, 15.89, 15.91, 16.0, 17.06, 17.13, 17.7, 18.1, 18.5, 18.76, 18.79, 19.1, 19.3, 22.1, 22.24, 22.5, 22.6, 22.8, 22.86, 22.94, 24.2, 34.9, 35.07, 35.14, 35.23, 35.26, 35.32, 35.33, 35.4, 35.5, 47.3, 47.4, 47.45, 47.48, 73.92, 73.93, 73.94, 73.98, 74.41, 74.43, 74.46, 74.5, 97.8, 98.8, 100.0, 100.1, 106.00, 106.03, 107.2, 107.3, 107.38, 107.42, 107.6, 109.1, 109.17, 109.24, 147.96, 147.99, 148.0, 148.1, 149.7, 150.0, 151.0, 152.1, 152.2, 152.3, 152.4; **IR** (ef) 3353, 2957, 2933, 2888, 2851, 1615, 1460, 1382, 1340, 1205, 1115, 1078, 1004 cm⁻¹; **MS** (MALDI-TOF) m/z (rel. intensity) 744 (M + K, 29), 727 (M + Na, 35), 703 (M, 15), 608 (87), 509 (100), 412 (65), 360 (99), 317 (16); **FAB-HRMS** Calcd. for C₄₁H₅₂O₁₀: 704.3560. Found: 704.3550.

### 6.5 Experimental Concerning Chapter Five

#### 6.5.1 (±)-10-Noralboatin [((±)-271] and the (±)-bis-Adducts (272), [((±)-273], [((±)-274] and [(±)-275]

![Chemical Structures](image)

**Method A:** To a suspension of orcinol (53) (185 mg, 1.49 mmol, 1 equiv), the alcohol 168 [prepared from the corresponding ester 167 (267 mg, 1.88 mmol, 1.3 equiv)] and anhydrous magnesium sulfate (1.01 g) in ether (15 mL) at 0 °C was added boron trifluoride diethyl etherate (190 µL, 1.51 mmol, 1 equiv). The resultant mixture was
allowed to warm to room temperature over 28 h in the dark. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (19:1) as the eluant afforded a mixture (3:3:1:1) of the title compounds 272, (±)-273, (±)-274 and (±)-275 (75 mg, 25%) as a colourless oil and the title compound (±)-271 (102 mg, 31%) as a solid white foam.

**Method B:** To a suspension of orcinol (53) (237 mg, 1.91 mmol, 1 equiv), a solution of the alcohol 168 in ether [(4.0 mL, 2.0 mmol, 1.05 equiv) prepared from the corresponding ester 167 (711 mg, 5.00 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.02 g) in ether (10 mL) at 0 °C was added boron trifluoride diethyl etherate (240 μL, 1.91 mmol, 1 equiv). The resultant mixture was allowed to warm to room temperature over 24 h in the dark. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded a mixture (3:3:1:1) of the title compounds 272, (±)-273, (±)-274 and (±)-275 (25 mg, 8%) as a colourless oil, the title compound (±)-271 [141 mg, 34% (75% brsm)] as a solid white foam and unreacted orcinol (53) (131 mg).

**Method C:** To a suspension of orcinol (53) (554 mg, 4.47 mmol, 1 equiv), a solution of the alcohol 168 in ether [(3.0 mL, 1.5 mmol, 0.3 equiv) prepared from the corresponding ester 167 (711 mg, 5.00 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.04 g) in ether (11 mL) at 0 °C was added boron trifluoride diethyl
etherate (190 μL, 1.51 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature over 24 h in the dark. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant, afforded the title compound (±)-271 (120 mg, 36%) as a solid white foam.

**Method D:** To a suspension of orcinol (53) (186 mg, 1.50 mmol, 1 equiv), a solution of the alcohol 168 in ether [(2.0 mL, 1.6 mmol, 1.07 equiv) prepared from the corresponding ester 167 (1.14 g, 8.03 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (1.02 g) in ether (10 mL) at 0 ºC was added boron trifluoride diethyl etherate (63 μL, 0.50 mmol, 0.3 equiv). The resultant mixture was allowed to warm to room temperature over 45 h in the dark. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded a mixture (3:3:1:1) of the title compounds 272, (±)-273, (±)-274 and (±)-275 (85 mg, 34%) as a colourless oil, the title compound (±)-271 [159 mg, 48% (72% brsm)] as a solid white foam and unreacted orcinol (53) (62 mg).

**Title compound (±)-271:** R<sub>f</sub> = 0.29, dichloromethane:ether (9:1); **M.p.** 148-149 ºC, dichloromethane:ether; **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1.54 (s, 3H, Me-12), 1.80 (m, 1H, H-3<sub>a</sub>D), 2.05 (m, 1H, H-3<sub>b</sub>D), 2.17 (s, 3H, Me-11), 2.46 (m, 1H, H-3<sub>a</sub>D), 2.74 (m, 2H, H-4), 3.94 (apparent q, J = 8.2 Hz, 1H, H-2<sub>b</sub>D), 4.04 (td, J = 8.3, 3.2 Hz, 1H, H-2<sub>a</sub>D), 5.71 (broad s, 1H, OH), 6.32 (d, J = 2.5 Hz, 1H, H-6), 6.38 (d, J = 2.5 Hz, 1H, H-8);
**Observed nOe contacts** *Me*-12 to *H*-3αβ, *Me*-12 to *H*-8, *Me*-11 to *H*-4, *Me*-11 to *H*-6, *H*-3αβ to *H*-3β, *H*-3β to *H*-2β; 13C NMR (126 MHz, CDCl₃) δ 19.3 (*Me*-11), 22.7 (*Me*-12), 23.0 (*C*-4), 29.0 (*C*-3), 40.8 (*C*-3α), 66.7 (*C*-2), 101.7 (*C*-8), 106.5, 109.6, 109.9 (*C*-6), 138.2, 153.8, 155.0; IR (ef) 3369 (br), 2981, 2943, 2897, 2848, 1620, 1600, 1494, 1467, 1382, 1334, 1145, 1109, 1012 cm⁻¹; MS (Cl) *m/z* (rel. intensity) 221 (*M* + H, 27), 220 (*M*, 53), 203 (100), 179 (79), 97 (12), 43 (64); Anal. Calcd. for C₁₃H₁₆O₃: C, 70.89; H, 7.32. Found: C, 70.78; H, 7.52.

**Title compounds** 272, (+)-273, (−)-274 and (±)-275 (3:3:1:1): *R*<sub>f</sub> = 0.45, dichloromethane:ether (9:1); 1H NMR (400 MHz, CDCl₃) δ 1.486, (s, 6H, *Me*-12), 1.490 (s, 6H, *Me*-12), 1.51 (s, 6H, *Me*-12), 1.80 (m, 2H, *H*-3), 2.02 (m, 2H, *H*-3), 2.08, (s, 3H, *Me*-11), 2.14 (s, 3H, *Me*-11), 2.19 (s, 3H, *Me*-11), 2.41 (m, 2H, *H*-3a), 2.71 (apparent d, *J* = 5.9 Hz, 4H, *H*-4), 2.74 (apparent d, *J* = 9.0 Hz, 4H, *H*-4), 2.78 (apparent d, *J* = 4.3 Hz, 4H, *H*-4), 2.91 (apparent d, *J* = 17.3 Hz, 4H, *H*-4), 3.92 (m, 2H, *H*-2), 4.02 (m, 2H, *H*-2), 6.02 (s, 1H, *ArH*), 6.24 (d, *J* = 2.9 Hz, 1H, *ArH*), 6.25 (d, *J* = 2.1 Hz, 1H, *ArH*), 6.31 (s, 1H, *ArH*); 13C NMR (101 MHz, CDCl₃) δ 14.6, 20.0, 20.3, 21.1, 22.2, 22.3, 22.6, 22.9, 23.3, 23.6, 23.8, 28.8, 29.0, 29.1, 40.0, 40.7, 66.5, 66.6, 102.9, 105.7, 105.8, 106.1, 107.9, 109.6, 110.4, 110.07, 110.14, 110.3, 135.17, 135.23, 137.5, 152.2, 152.3, 153.8, 154.4; IR (ef) 2980, 2929, 2895, 2845, 1608, 1591, 1471, 1381, 1326, 1109, 1006 cm⁻¹; MS (Cl) *m/z* (rel. intensity) 330 (M + MeOH - H₂O, 11), 317 (M + H, 45), 329 (49), 316 (M, 49), 299 (15), 275 (100), 97 (7), 43 (83); Anal. Calcd. for C₁₉H₂₄O₄: C, 72.13; H, 7.65. Found: C, 72.22; H, 7.73.
To a suspension of orcinol (53) (118 mg, 0.95 mmol, 1 equiv), a solution of the alcohol (4R)-226 in ether [(1.0 mL, 1.0 mmol, 1.05 equiv) prepared from the corresponding ester (4R)-206 (1.57 g, 10.0 mmol) in ether (10.0 mL)] and anhydrous magnesium sulfate (0.75 g) in ether (9 mL) at 0 °C was added boron trifluoride diethyl etherate (40 μL, 0.32 mmol, 0.34 equiv). The resultant mixture was allowed to warm to room temperature over 48 h in the dark. The reaction mixture was then filtered and the filter-cake was washed with ether (3 × 10 mL). The combined filtrates were washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification by flash chromatography using dichloromethane:ether (9:1) as the eluant afforded the title compound (−)-276 (24 mg, 14%) (that was contaminated with a trace amount of isomeric by-products) as a solid white foam, the title compound (+)-48 [79 mg, 36% (78% brsm)] as a solid yellow foam and unreacted orcinol (53) (64 mg).

**Title compound (+)-48:** This compound was recrystallized from ether:petroleum ether (1:1) on slow evaporation of the solvent to afford colourless prisms. \(R_f = 0.29\), dichloromethane:ether (9:1); \textbf{M.p.} 145-147 °C, ether:petroleum ether (lit.\textsuperscript{11} 146-149 °C); \([\alpha]_D^{20} = + 5.5 \ (c \ 0.58, \text{chloroform}) \ [\text{lit.}\textsuperscript{11} [\alpha]_D^{22.5} = + 8.8 \ (c \ 0.5, \text{chloroform})]; \textbf{1H NMR} (500 MHz, CDCl\textsubscript{3}) \delta 1.05 (d, \ J = 6.6 \text{ Hz}, 3H, Me-10\textsubscript{b}), 1.52 (s, 3H, Me-12\textsubscript{b}), 1.94 (ddd, \ J = 11.0, 5.7, 2.3 \text{ Hz}, 1H, H-3a\textsubscript{b}), 2.12 (m, 1H, H-3a\textsubscript{a}), 2.19 (s, 3H, Me-11), 2.68 (dd, \ J = 17.0, 2.1 \text{ Hz}, 1H, H-4), 2.70 (dd, \ J = 17.0, 5.6 \text{ Hz}, 1H, H-4), 3.51 (apparent t, \ J = 8.6 \text{ Hz}, 1H, H-4).
1H, H-2β), 4.17 (apparent t, J = 8.6 Hz, 1H, H-2α), 4.91 (s, 1H, OH), 6.27 (d, J = 2.2 Hz, 1H, H-8), 6.29 (d, J = 2.3 Hz, 1H, H-6); **Observed nOe contacts** Me-12 to H-3αβ, Me-12 to H-8, Me-12 to H-2β, Me-11 to H-4, Me-11 to H-6, Me-10 to H-2β, Me-10 to H-3αβ; 13C NMR (126 MHz, CDCl3) δ 15.9, 19.4, 21.5, 22.9, 35.4, 48.2, 73.9, 101.7, 107.2, 109.5, 109.7, 138.2, 153.7, 154.8; IR (ef) 3379 (broad), 2955, 1622, 1599, 1495, 1461, 1383, 1336, 1149, 1118, 1003 cm⁻¹; MS (CI) m/z (rel. intensity) 235 (M + H, 100), 217 (13), 179 (82), 137 (11), 111 (63), 99 (9), 43 (15); Anal. Calcd. for C14H18O3: C, 71.77; H, 7.74. Found: C, 71.78; H, 7.96.

**Title compound** (-)-276: This compound was recrystallized from ether:petroleum ether (1:1) on slow evaporation of the solvent to afford colourless blocks. Rf = 0.50, dichloromethane:ether (9:1); M.p. 189-190 °C, ether:petroleum ether; [α]D⁻²⁰ = -11.3 (c 0.84, chloroform); ¹H NMR (500 MHz, CDCl₃) δ 1.05 (d, J = 6.6 Hz, 6H, Me-10β), 1.49 (s, 6H, Me-12α), 1.91 (apparent dt, J = 11.0, 4.3 Hz, 2H, H-3αβ), 2.13 (s, 3H, Me-11), 2.14 (m, 2H, H-3α), 2.73 (apparent d, J = 3.4 Hz, 4H, H-4), 3.50 (apparent t, J = 8.5 Hz, 2H, H-2β), 4.17 (apparent t, J = 8.4 Hz, 2H, H-2α), 6.25 (s, 1H, ArH); **Observed nOe contacts** H-3αβ to Me-10, H-3αβ to Me-12β, H-3αβ to H-4, H-3αβ to H-2β; 13C NMR (126 MHz, CDCl₃) δ 14.8, 16.0, 22.4, 22.7, 35.5, 48.3, 73.9, 103.2, 106.7, 110.0, 135.1, 152.3; IR (ef) 2955, 2936, 2891, 1610, 1590, 1474, 1381, 1327, 1115, 1005 cm⁻¹; MS (CI) m/z (rel. intensity) 345 (M + H, 86), 247 (100), 235 (26), 111 (61), 43 (21); Anal. Calcd. for C₂₁H₂₈O₄: C, 73.23; H, 8.19. Found: C, 73.55; H, 8.25.
REFERENCES


