This thesis and the work described within it are entirely my own, except where I have either acknowledged help from a named person or where a reference is given to a published source or thesis. Text taken from another source will be enclosed in quotation marks or written in italics and a reference given.

# University Of Southampton

SYNTHESIS AND DIELS-ALDER REACTION OF NOVEL $C_2$-SYMMETRIC CHIRAL DIENES

Philip John Clarke

A thesis submitted for the degree of Doctor of Philosophy

**FACULTY OF ENGINEERING, SCIENCE AND MATHS**

Department of Chemistry

**September 2004**

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHS

CHEMISTRY

Doctor of Philosophy

# SYNTHESIS AND DIELS-ALDER REACTION OF NOVEL $C_2$-SYMMETRIC CHIRAL DIENES

The development and synthesis of a novel class of $C_2$-symmetric outer ring dienes is described. Six novel chiral dienes, based upon the butane diacetal group, were synthesised from tartaric acid derivatives and the Diels-Alder reaction of three of these dienes was carried out. The diastereoselectivity of the Diels-Alder reaction with a range of dienophiles was investigated. The removal of the chiral auxiliary after the Diels-Alder reaction was also investigated.

In an additional study *tris*-1,1,1-(hydroxymethyl)ethane was converted to a series of mono- and disubstituted derivatives. An indirect protocol, utilising chemoselective reactions, for the differentiation of the alcohol groups was employed for the synthesis of partially and fully differentiated *tris*-1,1,1-(hydroxymethyl)ethane containing a protected aldehyde unit.

# Table Of Contents


Chapter 1: Introduction ..... 1

1.1. General remarks ..... 1

1.2. Frontier molecular orbital theory ..... 4

1.2.1. Reactivity ..... 4

1.2.2. Regiochemistry ..... 5

1.2.3. Diastereoselectivity ..... 9

1.3. The Asymmetric Diels-Alder reaction ..... 11

1.3.1. Chiral Catalysts ..... 12

1.3.2. Chiral dienophiles ..... 15

1.3.3. Chiral dienes ..... 17

1.4. The aim of the project ..... 22

1.5. 1,2-Diacetals in synthesis ..... 24

1.5.1. Formation of the 1,2-diacetals ..... 24

1.5.2. 1,2-Diacetals as protecting groups: Carbohydrate chemistry ..... 26

1.5.3. 1,2-Diacetals as protecting groups: For glyceraldehyde ..... 26

1.5.4. 1,2-Diacetals as protecting groups: For tartaric diester ..... 28

1.5.5. The 1,2-diacetal group as an auxiliary: Glycolic acid auxiliary ..... 29

1.5.6. The 1,2-diacetal group as an auxiliary: [2+2] Cycloaddition ..... 32

1.5.7. The 1,2-diacetal group as an auxiliary: Michael reaction ..... 33

1.6. Classification of dienes ..... 33

Chapter 2: Synthesis and structural conformation of the chiral dienes ..... 36

2.1. Introduction ..... 36

2.2. Synthesis of diene 183 ..... 37

2.2.1. Synthesis ..... 37

2.1.2. Optimisation of the reduction step to 139 on a large scale ..... 40

2.3. Synthesis of diene 184 ..... 42

2.4. Synthesis of diene 185 ..... 43

2.5. Attempted synthesis of other chiral dienes ..... 43

2.5.1. Synthesis of diene 186 ..... 44

2.5.2. Synthesis of diene 187 ..... 44

2.5.3. Synthesis of diene 188 ..... 46

2.6. Structural analysis ..... 47
2.7. Conclusions ..... 48

Chapter 3: Diels-Alder reactions of the chiral dienes ..... 49
3.1 Introduction ..... 49
3.1.1. Thermal Diels-Alder reaction of diene 183: Results ..... 50
3.1.2. Selectivity of the Diels-Alder reaction ..... 53
3.1.3. Thermal Diels-Alder reaction of diene 184 ..... 55
3.1.4. Thermal Diels-Alder reaction of diene 185 ..... 56
3.1.5. Conclusions about the thermal Diels-Alder reaction ..... 58
3.2. Lewis acid Catalysed Diels-Alder reaction ..... 58
3.2.1. Lewis acid catalysed Diels-Alder reaction of diene 183 ..... 58
3.2.2. The Lewis acid catalysed reaction of diene 184 ..... 59
3.2.3. Lewis acid catalysed Diels-Alder reaction of diene 185 ..... 60
3.2.4. Conclusions about the Lewis-acid catalysed Diels-Alder reaction ..... 61
3.3. Deprotection of 209 ..... 61
3.4. Conclusions ..... 62

Chapter 4: Full and partial differentiation of tris-1,1,1-(hydroxymethyl)ethane via indirect methodology ..... 63
4.1. Introduction ..... 63
4.2. Results and discussion ..... 66
4.2.1 Indirect differentiation of tris-1,1,1-(hydroxymethyl)ethane ..... 66
4.3. Conclusions ..... 70

Chapter 5: Experimental ..... 71
5.1. General experimental ..... 71
5.2. Synthesis of diene 183 ..... 72
5.2.1. (2*R*,3*R*,5*R*,6*R*)-Dimethyl-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2,3-dicarboxylate (138) ..... 72
5.2.2. ((*2S,3S,5R,6R*)-2,3-(dihydroxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane) (139) ..... 72
5.2.3. (*2S,3S,5R,6R*)-5,6-Di(iodomethyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (191) ..... 73

5.2.4. (*2R,3R*)-2,3-Dimethoxy-2,3-dimethyl-1,4-dimethylene-1,4-dioxane (183) ..... 74
5.3. Synthesis of diene 184 ..... 75
5.3.1. (*2R,3R,5R,6R*)-Diethyl-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2,3-dicarboxylate (193) ..... 75
5.3.2. (*2S,3S,5R,6R*)-2,3-(dihydroxymethyl)-5,6-diethoxy-5,6-dimetyl-1,4-dioxane (194) ..... 76
5.3.3. (*2S,3S,5R,6R*)-5,6-di(iodomethyl)-2,3-diethoxy-2,3-dimethyl-1,4-dioxane (195) ..... 76
5.3.4. (*2R,3R*)-2,3-Diethoxy-2,3-dimethylene-1,4-dioxane (184) ..... 77
5.4. Synthesis of diene 185 ..... 78
5.4.1. (2*R*,3*R*,5*R*,6*R*)-2,3-di(iodomethyl-5,6-dimethyl-1,4-dioxane (196) ..... 78
5.4.2. (2*R*,3*R*)-2,3-dimethyl-1,4-dimethylene-1,4-dioxane (185) ..... 79
5.5. Synthesis of diene 186 ..... 79
5.5.1. (6*R*,7*R*,14*R*,15R)-dimethyl 1,8,13,16-tertraoxasipiro-[5.0.5.4] hexadecane-14,15-dicarboxylate (197) ..... 79
5.5.2. (6*R*,7*R*,14*S*,15*S*)-14,15-dihydroxymethyl-1,8,13,16-tertraoxasipiro-[5.0.5.4]-hexadecane (198) ..... 80
5.5.3. 4-Toluenesulfonic acid 15-[4'-toluenesulfonyloxymethyl]-1,8,13,16-tetraoxa-dispiro[5.0.5.4]hexadec-14-ylmethyl ester (199) ..... 81
5.5.4. 14,15-Dimethylene-1,8,13,16-tetraoxa-dispiro[5.0.5.4]hexadecane (186) ..... 81
5.6. Synthesis of diene 187 ..... 82
5.6.1. *(2R,3R)* Dimethyl-6, 6- dimethoxy-1, 4-dioxaspiro[4.5]decane dicarboxylate (200) and *(2R,3R,4R,8R)* Dimethyl-4, 8-dimethoxy perhydro-1,4-benzodioxin dicarboxylate (201) ..... 82
5.6.2. *(2R,3R,4R,8R)-2,*3-(dihydroxymethyl)-4, 8-dimethoxyperhydro-1,4-benzodioxin-2yl (204) ..... 84
5.6.3. *(2R,3R,4R,8R)*-2, 3-(diiodomethyl)-4, 8 dimethoxyperhydro-1, 4-benzodioxin (205) ..... 84
5.6.4. *(4R, 8R)*-4,8-Dimethoxy-2,3-dimethylene perhydro1,4-benzodioxin (187) ..... 85
5.7. Synthesis of diene 188 ..... 86

5.7.1. (*2R,3R,5R,6R*)-Diphenyl-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2,3-dicarboxylate (206) ..... 86
5.7.2. ((*2R,3R,5R,6R*)-3-(Hydroxymethyl)-5,6-dimethoxy-5,6-diphenyl-1,4-dioxane) methanol (207) ..... 87
5.7.4. (*2R,3R*)-2,3-Dimethoxy-2,3-diphenyl-1,4-dimethylene-1,4-dioxane (188) ..... 89
5.8. Thermal Diels-Alder reactions of diene 183 ..... 89
5.8.1. (*2R,3R,6R,7R*) 2,3-dimethoxy-2,3-dimethyl-2,3,5,6,7,8-hexahydro-1,4-benzodioxin-6,7-dicarboxlate (215) ..... 89
5.8.2. (*2R,3R,6R,7R*) Diethyl-2,3-dimethoxy-2,3-dimethyl-2,3,5,6,7,8-hexahydro-1,4-benzodioxin-6,7-dicarboxlate (209) ..... 90
5.8.3. (*2R,3R,6R,7R*)-Ethyl-2,3-dimethoxy-2,3-dimethyl-7-(trifluoromethyl)-2,3,5,6,7,8-hexahydro1,4-benzodioxan-6-carboxylate (210) ..... 91
5.8.4. (*2R,3R,6R,7R*) 2,3-dimethoxy-2,3-dimethyl-2,3,5,6,7,8-hexahydro-1,4-benzodioxin-6,7-dicyanide (216) ..... 92
5.8.5. 1((*2R*,3*R*,6*R*)-2,3-dimethoxy- 2,3-dimethyl perhydro-1,4-benzodioxin-6-yl)-1 ethanone (211) ..... 92
5.8.6. (*2R,3R,6R*)-Methyl -2,3-dimethoxy-2,3-dimethyl perhydro–1,4-benzodioxin-6-carboxylate (212) ..... 93
5.8.7. (*2R,3R,6R*)-2,3-dimethoxy-2,3-dimethyl perhydro –1,4-benzodioxin-6-al (217) ..... 94
5.8.8. (*2R,3R,6R,7R*)-Ethyl - 2,3 dimethoxy-2,3,7 trimethyl perhydro-1,4 benzodioxin-6-carboxylate (213) ..... 95
5.8.9. 1-((*2R,3R,6R,7R*)-2,3-dimethoxy-2,3,7-trimethyl perhydro-1,4-benzodioxin-6-yl)-1-ethanone (214) ..... 96
5.9. Thermal Diels-Alder reactions of diene 184 ..... 96
5.9.1. (2*R*,3*R*,6*R*,7*R*)Dimethyl-2,3-diethoxy-2,3-dimethyl-2,3,5,6,7,8-hexahydro-1,4benzodioxin-6,7-dicarboxlate (218) ..... 96
5.9.2. (2*R*,3*R*,6*R*,7*R*) Diethyl-2,3-diethoxy-2,3-dimethyl-2,3,5,6,7,8-hexahydro-1,4benzodioxin-6,7-dicarboxlate (219) ..... 97
5.9.3. (2R,3*R*,6*R*,7*R*) Ethyl-2,3diethoxy-2,3dimethly-7-(trifluoromethyl)-2,3,5,6,7,8-hexahydro-1,4-benzodioxan-6-carboxylate (220) ..... 98
5.9.4. ((2*R*,3*R*,6*R*)-2,3 diethoxy- 2,3-dimethyl perhydro-1,4-benzodioxin-6-yl)-1 ethanone (221) ..... 99

5.9.5. (2*R*,3*R*,6*R*)-Methyl-2,3-diethoxy-2,3-dimethylperhydro–1,4-benzodioxin-6-carboxylate (222) ..... 100
5.9.6. 1-((2*R*,3*R*,6*R*,7*R*)-2,3 diethoxy-2,3,7-trimethyl perhydro-1,4-benzodioxin-6-yl)-1-ethanone (223) ..... 100
5.10. Thermal Diels-Alder reaction of diene 185 ..... 101
5.10.1. *2R,3R*-Dimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R, 7R*-dicarboxylic acid dimethyl ester (224) ..... 101
5.10.2. 2*R*,3*R*-Dimethyl-7*R*-trifluoromethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-carboxylic acid ethyl ester (225) ..... 102
5.10.3. 1-(*2R, 3R*-Dimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-yl)-ethanone (226) ..... 103
5.10.4. *2R,3R*-Dimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-carboxylic acid methyl ester (227) ..... 103
5.10.5. 1-(*2R, 3R, 7R*-Trimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-yl)-ethanone (228) ..... 104
5.11. Lewis acid catalysed Diels-Alder reaction of diene 183 ..... 105
5.11.1. 1((2*R*,3*R*,6*R*)-2,3-dimethoxy-2,3-dimethyl perhydro-1,4-benzodioxin-6-yl)-1 ethanone (211) ..... 105
5.11.2. (*2R,3R,6R*)-Methyl-2,3-dimethoxy-2,3-dimethyl perhydro –1,4-benzodioxin-6-carboxylate (212) ..... 105
5.11.3. 1-((*2R,3R,6R,7R*)-2,3-Dimethoxy-2,3,7-trimethyl perhydro-1,4-benzodioxin-6-yl)-1-ethanone (214) ..... 106
5.12. Lewis acid catalysed Diels-Alder reaction of diene 184 ..... 106
5.12.1 ((2*R*,3*R*,6*R*)-2,3 Diethoxy- 2,3-dimethyl perhydro-1,4-benzodioxin-6-yl)-1 ethanone (221) ..... 106
5.12.2. (2*R*,3*R*,6*R*) Methyl -2,3 -diethoxy-2,3-dimethyl perhydro –1,4-benzodioxin-6-carboxylate (222) ..... 107
5.12.3. 1-((2*R*,3*R*,6*R*,7*R*)-2,3-Diethoxy-2,3,7-trimethylperhydro-1,4-benzodioxin-6-yl)-1-ethanone (223) ..... 108
5.13. Lewis acid catalysed Diels-Alder reaction of diene 185 ..... 108
5.13.1. 1-(*2R, 3R*-Dimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-yl)-ethanone (226) ..... 108
5.13.2. *2R, 3R* -Dimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-carboxylic acid methyl ester (227) ..... 109

5.13.3. 1-(*2R, 3R, 7R*-Trimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-yl)-ethanone (228) ..... 109
5.14. Deprotection of the Diels-Alder adduct 209 ..... 110
5.14.1. (*1R,2R*)-Diethyl-4-hydroxy-5-oxocyclohaxane-1,2-dicarboxylate (230) ..... 110
5.15. Full and partial differentiation of Tris-1,1,1-(hydroxymethyl)ethane ..... 111
5.15.1. "Dimers" of (1-Methyl-4-phenyl-3,5-dioxanyl) methanol (246) ..... 111
5.15.2. (1-Methyl-4-phenyl-3,5-dioxanyl) methanol (232) ..... 113
5.15.3. [2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-5yl]methanol (247) ..... 114
5.15.4. 2-Phenyl-5-methyl-1,3-dioxane-5-carbaldehyde (248) ..... 115
5.15.5. 2-(4-Methoxyphenyl)-5-methyl-1,3-dioxane-5-carbaldehyde (249) ..... 116
5.15.6. 5-(1,3-Dioxalan-2-yl)-2-phenyl-5-methyl-1,3-dioxane (250) ..... 117
5.15.7. 5-(1,3-dioxalan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (251) ..... 119
5.15.8. 2-(1,3-Dioxolan-2yl)-2methyl-1,3-propanediol (252) ..... 120
5.15.9. 3-Benzyloxy-2-[1,3]dioxolan-2-yl-2-methyl-propan-1-ol (253) ..... 121
5.15.10. 2-[1,3]Dioxolan-2-yl-3-(4-methoxy-benzyloxy)-2-methyl-propan-1-ol (254) ..... 122
5.15.11. 5-Dimethoxymethyl-5-methyl-2-phenyl-[1,3]dioxane (256) ..... 122
5.15.12. 5-Dimethoxymethyl-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxane (257) ..... 123
5.15.13. Benzoic acid 2-hydroxymethyl-3,3-dimethoxy-2-methyl-propyl ester (258) ..... 124
5.15.14. 4-Methoxy-benzoic acid 2-hydroxymethyl-3,3-dimethoxy-2-methyl-propyl ester (259) ..... 125

Appendices: X-Ray Crystallographic Analysis ..... 126
Compound 143 ..... 126
Compound 191 ..... 128
Compound 183 ..... 130
Compound 256 ..... 134
Compound 257 ..... 136

References ..... 138

# Acknowledgments

Firstly I would like to thank Dr Bruno Linclau for taking me on in the first place and also all of his help during and after my studies. Professor Richard Whitby has also been of help by way of the comments in my quarterly reports.

I would also like to thank all those who have helped in the acquisition of data; Dr John Langley and Julie Herniman were absolutely fantastic by getting data on compounds that just refused to fly when I ran the mass spectrum; Dr Neil Wells and Joan Street for running NMR when necessary, and keeping the whole system going! I would also like to thank Dr Mark Light and Dr Simon Coles as I have very little idea how to run the X-ray crystallography apparatus and they are incredibly helpful.

Next I think I have to thank my group for putting up with me and also avoiding eye contact when anything has gone really wrong; Henry for introducing me to so much music (and also "99 red balloons" in many different forms); Rob for just being a good laugh (don't get me wrong Rob, I'm not saying that your jokes are funny); Helen for all of the lifts home (also for listening to the word "monkey" more times than can be good for you); Benedetta for all the cigarettes that I have "borrowed" from you (and the word "stciopa"); Nadia for being easy to tease (hmm anything else I write would get me in trouble); James for taking on the position of lab monkey (you have done well my young apprentice); Leo simply for the amusement of your middle name and Solen for knowing a lot and listening when I had a thesis related quandary.

Also a big thank you for those who have supported me whilst I wrote the thesis; Mum and Tony have been a major support and this wouldn't have been possible without you; Marlies, Helen and James (again) thank you so much for allowing me to stay at your house when in Southampton; Sarah, Rob and Freya have bailed me out when things were a bit tight and have also allowed me to escape to see them every once in a while; Gran and Gramps thank you for the handshakes that have allowed me to have a bit of cash.

I would also like to thank Jim, Mike, James, Marlies, Helen, Neil and Claire who have all had the dubious pleasure of living in the same house as me. All of you were fantastic but special thanks to Jim, James and Neil who are the sort of people that make me glad that I came to Southampton in the first place.

I also must thank Mell and Pom for being clubbing buddies supreme.

# Abbreviations

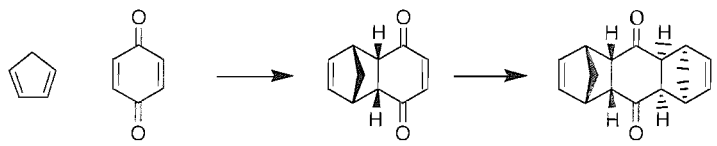
| | |
|---|---|
| BDA | Butane diacetal |
| CDA | Cyclohexyl diacetal |
| CIMS | Chemical ionisation mass spectrometry |
| CSA | Camphor sulphonic acid |
| d | Days |
| de | diastereomeric excess |
| DHP | Dihydropyran |
| Dispoke | Dispiroketal |
| DMAP | Dimethylaminopyridine |
| DMF | Dimethyl formamide |
| DMSO | Dimethyl sulphoxide |
| ds | Diastereoselectivity |
| ee | Enantiomeric excess |
| EIMS | Electron ionisation mass spectrometry |
| ESMS | Electrospray mass spectrometry |
| equiv. | Equivalents |
| FMO | Frontier molecular orbital |
| GC | Gas chromatography |
| h | Hours |
| HOMO | Highest occupied molecular orbital |
| HPLC | High performance liquid chromatography |
| HRMS | High resolution mass spectrometry |
| IR | Infrared |
| LHMDS | Lithium hexamethyl disilazane |
| LUMO | Lowest unoccupied molecular orbital |
| M.p. | Melting point |
| NMR | Nuclear magnetic resonance |
| PTAD | N-Phenyl-1,2,4-triazolinedione |
| Py | Pyridine |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMOF | Trimethyl orthoformate |

| | |
|---|---|
| UV | Ultraviolet |

# Chapter 1: Introduction

## 1.1. General remarks

The Diels-Alder reaction is a cycloaddition between a conjugated diene and a dienophile (an alkene or alkyne) to form an unsaturated six-membered ring. The [4+2] cycloaddition reaction was discovered in 1928 by Professor Otto Diels and his student Kurt Alder when they correctly identified the product of the reaction between cyclopentadiene **1** and quinone **2** (Scheme 1).[1]



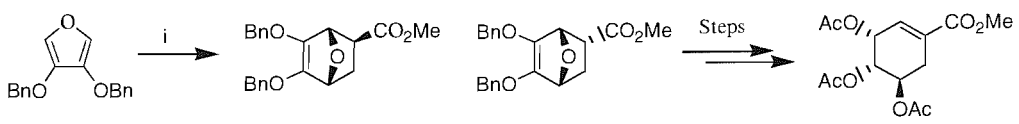

**1** **2** **3** Monoadduct **4** Diadduct

**Scheme 1:** The [4+2] cycloaddition of cyclopentadiene and quinone.

The Diels-Alder reaction is one of the best-known ways in which to construct six membered rings in a stereo- and regio- controlled manner. As the six-membered rings that are produced may have up to four consecutive stereocentres, the Diels-Alder reaction is a powerful and versatile synthetic tool for the construction of both simple and complex molecules.

Scheme 2 shows the synthesis of a relatively simple synthetic target by use of the Diels-Alder reaction. Reaction of 3,4-dibenzyloxy-furan (**5**) with methyl acrylate produces a 15.3:1 *endo*:*exo* mixture of isomers. The *endo* isomer (**7**) was then elaborated to give (±)-methyl triacetylshikimate (**8**).[2]

**Scheme 2:** Example of the construction of small molecules by the Diels-Alder.

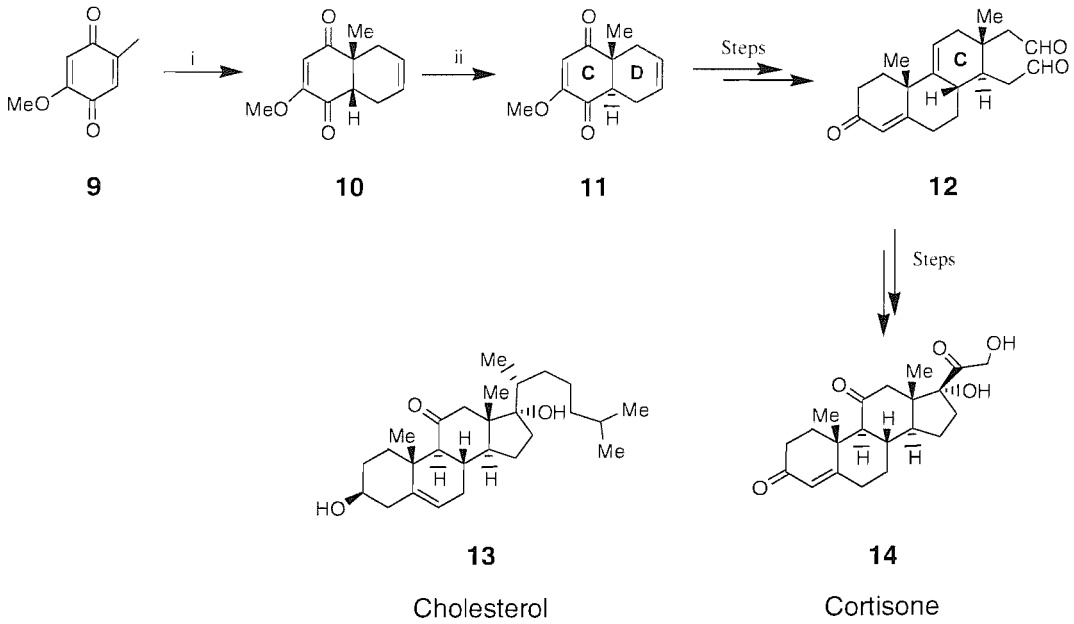



**5** **6** **7** **8**

1 : 15.3

**Reagents and conditions:** (a) Methyl acrylate, $ZnI_2$ (0.1eq), neat, r.t., 1h, 98%.

**Scheme 3:** Example of the Diels-Alder in the synthesis of complex molecules.




**9** **10** **11** **12**

**13** **14**

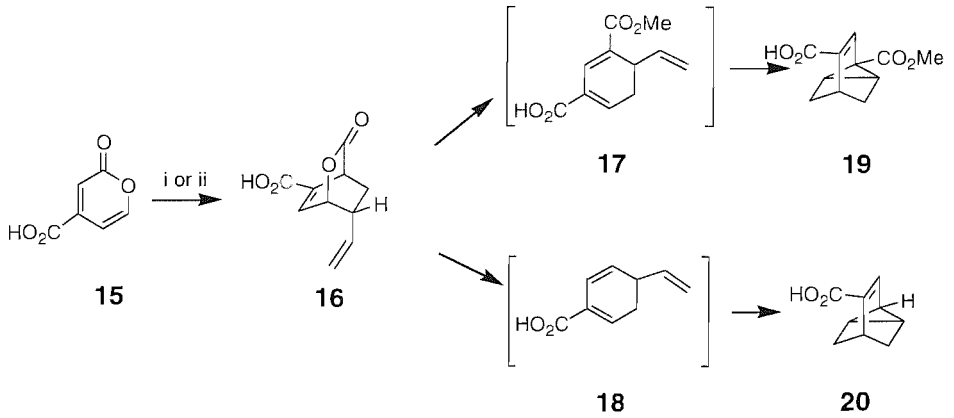
Cholesterol Cortisone

**Reagents and conditions:** (i) Butadiene, benzene, 100°C, 96h, 87%; (ii) 1M NaOH, dioxane, then 1M HCl, 90%.

An example of a Diels-Alder reaction in the synthesis of complex targets is shown in scheme 3. The reaction of 2-methyl-5-methoxyquinone **9** with butadiene gives rise to adduct **10**.[3] The olefins present in **9** are differentiated due to substitution. The more electron rich double bond is typically less reactive in a Diels-Alder reaction (see below) hence butadiene exclusively reacts with the methyl substituted enedione. This leads to *cis*-fused bicycle **10**. Base catalysed epimerisation of the ring junction subsequently gives rise to the thermodynamically more stable *trans* ring junction. Contraction of the D ring and annelation of the A and B rings led to the steroid skeleton, which was then elaborated to provide both racemic cholesterol **13** and cortisone **14**.

The Diels-Alder can also be used to construct complex structures rapidly. Multi-step reactions may be carried out in a one-pot procedure, for example, two consecutive Diels-Alder reactions (Scheme 4).

**Scheme 4:** Domino Diels-Alder reaction

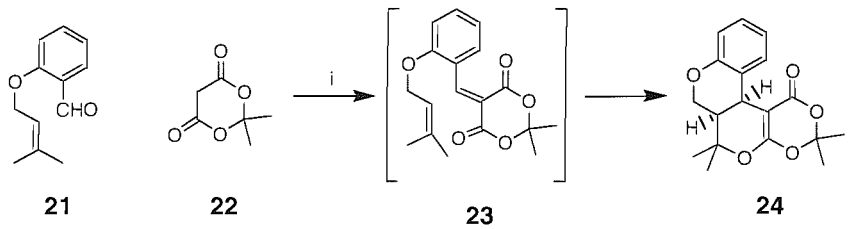



**Reagents and conditions:** i) Butadiene, MeOH, pressure jar, 100°C, 70%; ii) benzene reflux.

The simple synthesis of the tricyclo[3.2.1.$0^{2,7}$]oct-3-ene ring system has been reported[4] via a domino Diels-Alder reaction. If coumalic acid 15 is heated to 100°C in methanol with an excess of butadiene then a Diels-Alder reaction takes place to form intermediate **16**. The strained lactone **16** then undergoes methanolysis and subsequent dehydration to form triene **17.** A second Diels-Alder reaction then takes place to yield adduct **19** in 70% yield. Lactone **16** may be isolated if the reaction is conducted in an aprotic solvent at lower temperatures (benzene, reflux). If lactone **16** is submitted to the methanolic Diels-Alder conditions then a decarboxylation may occur to form triene **18**. The second Diels-Alder reaction would then form adduct **20**. The submission of **16** to the methanolic reaction conditions leads the formation of **19** and **20** in a 1:3 ratio.[5]

Other reactions may be utilised in a one-pot strategy in conjunction with the Diels-Alder reaction (Scheme 5).

**Scheme 5:** Domino Knoevenagel Hetero Diels-Alder reaction.




**Reagents and conditions:** i) Ethylenediammonium diacetate, $CH_2Cl_2$, r.t., 5h, 73%.

The aldehyde **21** and Meldrum's acid **22** undergo the Knoevenagel condensation and form intermediate **23**.[6] This sets the stage for a Diels-Alder reaction to take place,

however, as one of the atoms of the diene moiety is an oxygen, the reaction is termed a Hetero Diels-Alder reaction. The dihydropyran derivative **24** that is obtained from the reaction is formed exclusively as the *cis* isomer.

Obviously the Diels-Alder reaction is a versatile synthetic tool and thus predicting the outcome of the reaction is an area of major interest.

## 1.2. Frontier molecular orbital theory

Frontier molecular orbital theory states that the outcome of chemical reactions may be predicted by the consideration of the reacting orbitals;[7,8] that is the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). The theory has been applied to the Diels-Alder reaction in predicting the reactivity, regiochemical and stereochemical outcome of the reaction.

### 1.2.1. Reactivity

The rate of a Diels-Alder reaction depends upon the difference in energy levels between the HOMO and the LUMO of the diene and dienophile; the lower the energy difference the lower the energy of the transition state and hence the greater the rate of reaction.

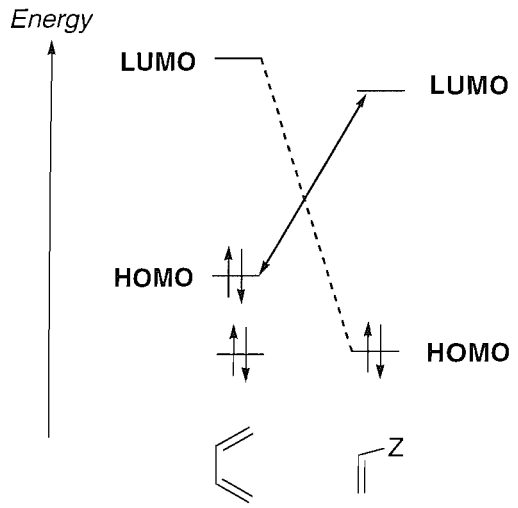



**Figure 1:** The orbital diagram for the "normal" Diels-Alder reaction.

Figure 1 shows the frontier orbital interactions for a "normal" Diels-Alder reaction. It can be seen that the energy of the HOMO of the diene is higher than the HOMO of the dienophile. In the course of the reaction the HOMO of the diene interacts with the LUMO of the dienophile. Hence electron-donating groups on the diene, which will

lead to an increased energy level of the HOMO, will accelerate the rate of reaction. Similarly an electron-withdrawing group on the dienophile would lead to a decreased energy level of the LUMO, which will also accelerate the rate of reaction.

Lewis acids can greatly affect the reaction rate of the "normal" Diels-Alder reaction. Lewis acids co-ordinate to the carbonyl of the dienophile, increasing the electron withdrawing capability of the carbonyl and further lowering the energy of the dienophile's LUMO.[9]

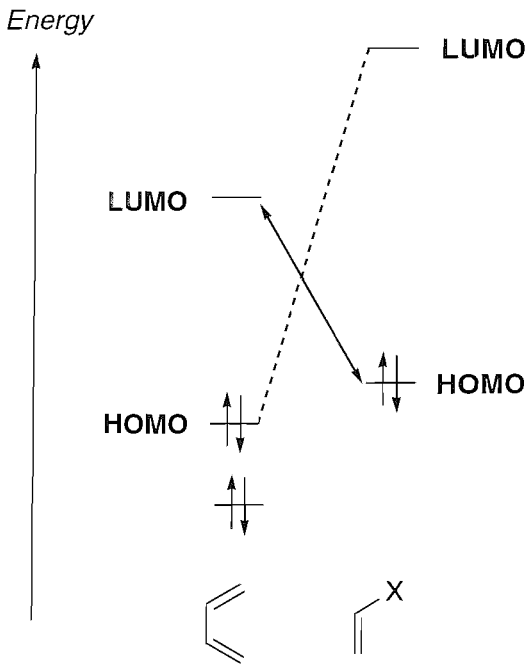



**Figure 2:** The orbital diagram for the "inverse" Diels-Alder reaction.

Figure 2 shows the frontier molecular orbital interactions for an "inverse demand" Diels-Alder reaction. In this case the HOMO of the dienophile is the highest in energy and will attack the LUMO of the diene. Hence electron-donating groups on the dienophile and electron-withdrawing groups on the diene will accelerate the rate of reaction.

### 1.2.2. Regiochemistry

The Diels-Alder reaction between an unsymmetrical diene and an unsymmetrical dienophile can produce two regioisomeric adducts.

The regioselectivity of a Diels-Alder reaction can be derived when the sign and coefficients of the interacting molecular orbitals are taken into consideration.[7,10] Obviously only when the orbitals of the diene and dienophile are in phase may they

interact, so this premise shall be taken as read and only allowed interactions shall be discussed.

The coefficients of the 1 and 4 positions of the diene and the coefficients of the dienophile olefin are considered when determining the regiochemistry. The coefficients of the diene and dienophile are affected by any substituents that are present. There are three types of substituent, electron donating (X), electron withdrawing (Z) and conjugated (C).

The molecular orbital coefficients are estimated by adding together the coefficients of two species that bear structural and electronic similarity to the desired target. For example, the estimation of the coefficients of a diene with an electron-donating group in the C1 position is based upon the HOMO of butadiene and the HOMO of the pentadienyl anion. These two species represent the extreme electronic polarisations of the target diene and the combination of them leads to a result that models the molecular orbital in question (Figure 3). If the electron-donating group were in the C2 position the molecular orbital of the allyl anion would be used in combination with the molecular orbital of butadiene to estimate the coefficients of the 2-substitued diene (Figure 3).

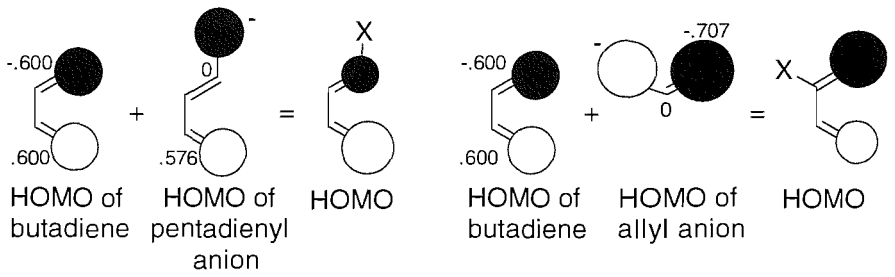



**Figure 3:** The HOMO of dienes substituted at the 1 or 2 positions with electron donating substituents.

The estimation of the coefficients of the LUMO of the dienophile is undertaken in a similar manner. In the case of a normal dienophile an electron-withdrawing group would be present. The estimation of the molecular coefficients would be the combination of the LUMO of butadiene and the LUMO of the allyl cation (Figure 4). The LUMO of the allyl cation is utilised, as this is representative of a highly electron-withdrawing group, and combination with the LUMO of butadiene produces a molecular orbital that is a close approximation of the LUMO in question.

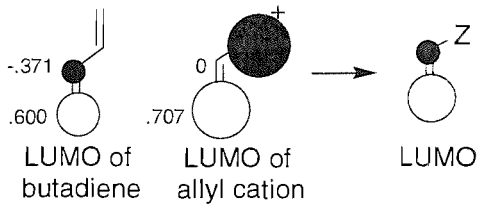



**Figure 4:** The LUMO of a dienophile containing an electron withdrawing substituent.

In determining the regiochemistry of the reaction the most favourable interaction between the orbitals is that where the largest coefficients interact and the smallest coefficients are likewise paired (Figure 5).

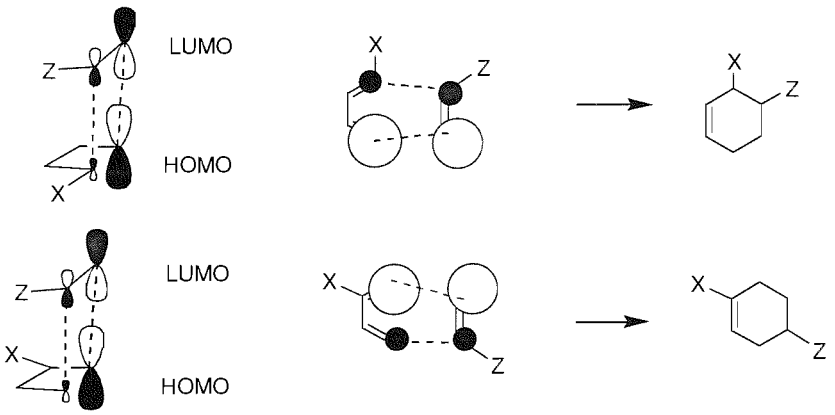
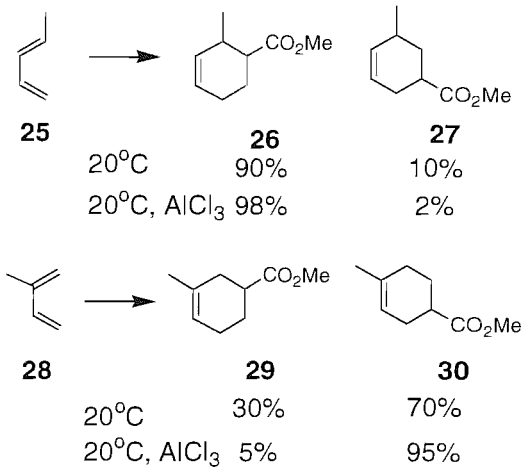



**Figure 5:** FMO theory prediction of regiochemistry.

When the diene has an electron-donating group in the C1 position it would be predicted that the substituents would bear an *ortho* relationship in the final adduct. When the electron-donating substitution is in the C2 position the substituents in the Diels-Alder product should bear a *para* relationship.

The reactions between 1-methylbutadiene and methyl acrylate and 2-methylbutadiene and methyl acrylate are shown below (Scheme 6).[11-13]

**Scheme 6:** The reaction of unsymmetrical dienes and dienophiles.




**Reagents and conditions:** (a) neat, 20°C.

The major product of the reaction between 1-methylbutadiene and methyl acrylate is **26**, the *ortho* product, which is the product that FMO theory predicted. The prediction that the *para* product should be the major product of the reaction between 2-methylbutadiene and methyl acrylate has also been proven.

It can also be seen that the addition of a Lewis acid can increase the regioselectivity that is observed. As has been stated earlier, the mode of action of a Lewis acid is in coordinating to the carbonyl of the dienophile and that this will increase the electron-withdrawing capability of the carbonyl. This effect will increase the allyl cation character of the coefficients of the molecular orbital and hence increase the regioselectivity.[9,14]

When there are two substituents present on the diene the molecular orbital coefficients of two types of mono substituted diene are combined.

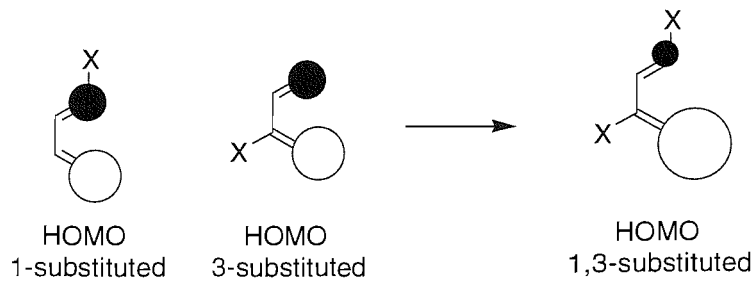
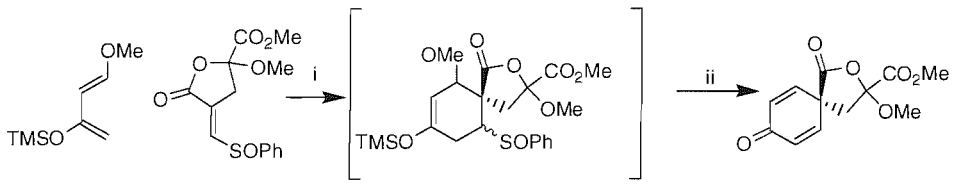



**Figure 6:** The estimation of the coefficients of a 1,3 disubstituted butadiene.

The example illustrated above shows the combination of two electron-donating groups. The coefficients reinforce each other and dienes of this type would be

predicted to show exceptional regioselectivity. The classic example of a diene of the type is Danishefsky's diene (Scheme 7).[15]

**Scheme 7:** Regioselective reaction of Danishefsky's diene.




**31** **32** **33** **34**

**Reagents and conditions:** i) Neat, sealed tube, 100°C, 80%; ii) 2.4% acetic acid , EtOAc, 21h, 31%.

The intermediate **33** is formed with complete regioselectivity and then upon deprotection, undergoes an elimination to form the unsaturated product **34**.[16]

## 1.2.3. Diastereoselectivity

The Diels-Alder reaction is generally a pericyclic process.[17] The relative stereochemistry of the diene at positions 1 and 4 is preserved, as is the relative stereochemistry of the dienophile. This can be rationalised via a closed "boat" transition state (Figure 7).[18]

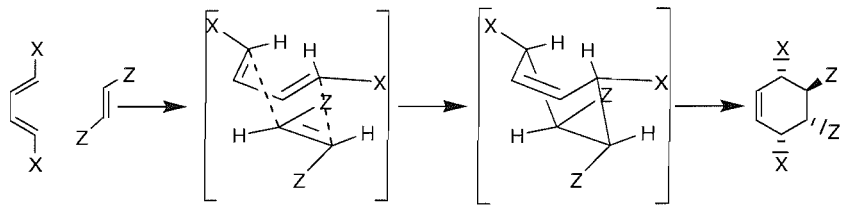
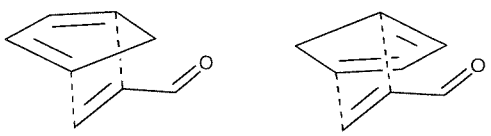



**Figure 7:** The preservation of relative stereochemistry in the Diels-Alder reaction.

The relative stereochemistry of these two sets of substituents in the final adduct is set by two possible suprafacial approaches named *exo* and *endo* (Figure 8).




*exo* *endo*

**Figure 8:** The two approaches of the dienophile.

If the two approaches are considered solely on steric grounds it would be expected that the *exo* approach would be preferred, as in this attack the smallest part of both

molecules are interacting. However early work by Kurt Alder showed this not to be the case.[19-21] Therefore, there is an electronic factor that is operating to enforce the *endo* selectivity that is observed in Alder's rule.

FMO theory explains the selectivity that is observed in terms of an additional non-bonding interaction, the secondary orbital interaction (Figure 9).

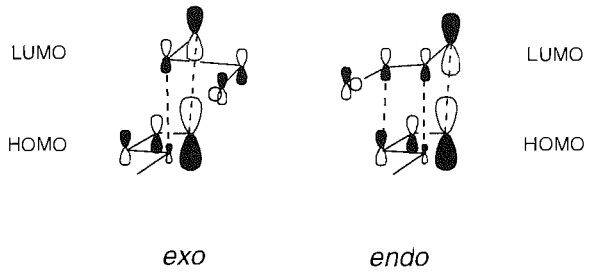
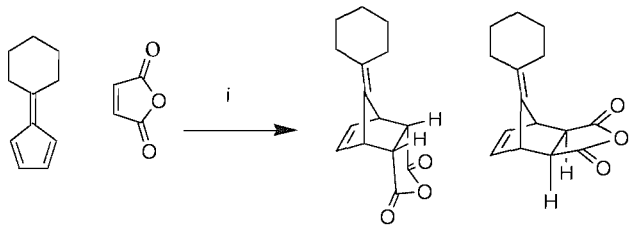



**Figure 9:** The non-bonding secondary orbital interaction.

The secondary orbital interaction can only be present in the *endo* transition state. The orbital interactions make the *endo* transition state lower in energy versus the *exo* transition state; therefore the reaction via the *endo* transition state is quicker than the *exo* reaction pathway and the kinetically formed *endo* product is formed preferentially.

Further evidence that the *endo* transition state is kinetically favoured can be observed in the reaction of maleic anhydride **36** with 6,6-pentamethylfulvene **35** (Scheme 8).

**Scheme 8:** Reaction of maleic anhydride with 6,6-pentamethylfulvene.




**Reagents and conditions:** (i) benzene, 20°C or reflux.

The isomer **37** is formed very rapidly at 20°C.[22] However, isomer **38** is formed if the reaction time is very long or if the reaction temperature is raised to reflux. This shows that the *endo* isomer is kinetically formed whilst the *exo* isomer is thermodynamically more stable.

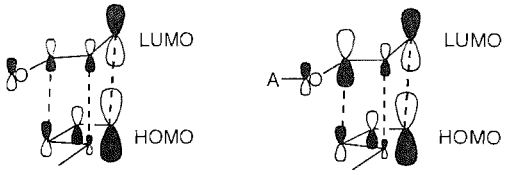
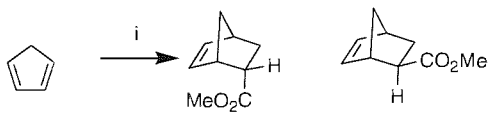



**Figure 10:** The effect of Lewis acids on *endo:exo* selectivity.

Once again, the use of Lewis Acids can have an impact upon this aspect of the Diels-Alder reaction (Figure 10).[9] The Lewis acid that is coordinated to the carbonyl oxygen changes the coefficient of the carbonyl carbon. This carbon is involved in the secondary orbital interaction and the change of coefficient, generally an increase of size, is favourable in this non-bonding interaction. Hence an increase in *endo* selectivity should be observed. The reaction of cyclopentadiene (**1**) with methyl acrylate is shown below (Scheme 9).[23]

**Scheme 9:** The reaction of cyclopentadiene and methyl acrylate under a variety of Lewis acidic conditions.




| 1 | 39 | | 40 | Yield |
|---|---|---|---|---|
| No catalyst | 3.1 | : | 1 | 32% |
| $BF_3.Et_2O$ (1eq) | 6.4 | : | 1 | 36% |
| $PhBF_2$ (1eq) | 4.0 | : | 1 | 44% |
| $PhBF_2$ (cat) | 9.1 | : | 1 | 31% |

**Reagents and conditions:** (i) neat, 0°C, 1h then r.t., 3h.

It can be seen that the reaction does indeed improve the selectivity for the *endo* adduct **39** with the addition of Lewis acids. The biggest improvement can be observed when a catalytic amount of $PhBF_2$ is used.

## 1.3. The Asymmetric Diels-Alder reaction

As has been explained, the Diels-Alder reaction shows remarkable relative stereochemical integrity. However, a racemic mixture is still formed when using an achiral diene and an achiral dienophile. For controlling the absolute stereochemistry of the Diels-Alder reaction there have been three major approaches: the use of chiral catalysts, and the use of chiral auxiliaries for both diene and dienophile.

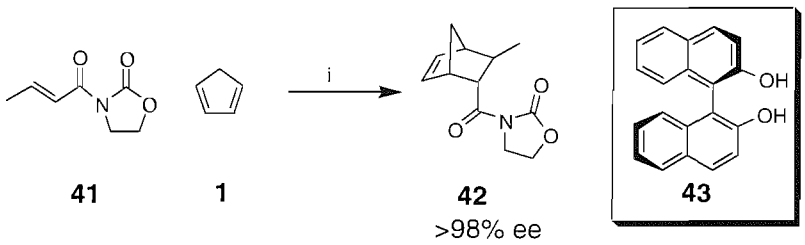
## 1.3.1. Chiral Catalysts

The most popular way to control the Diels-Alder reaction is by use of chiral Lewis acid catalysts. They offer an economic way to induce enantioselectivity, as often the catalyst is only present in small amounts.

The method in which Lewis acids control the stereochemistry of the Diels-Alder reaction is in controlling the approach of the diene to the dienophile. Although there have been numerous types of chiral Lewis acids based around many different metal centres, such as silicon,[24] scandium[25] and palladium[26] the major metal centres that have been utilised are aluminium, titanium and boron.

When aluminium is used as the catalytic centre enantioselectivity has been induced in high levels with the use of bidentate ligands.

**Scheme 10:** Enhancement of enantioselectivity by use of chiral diol.



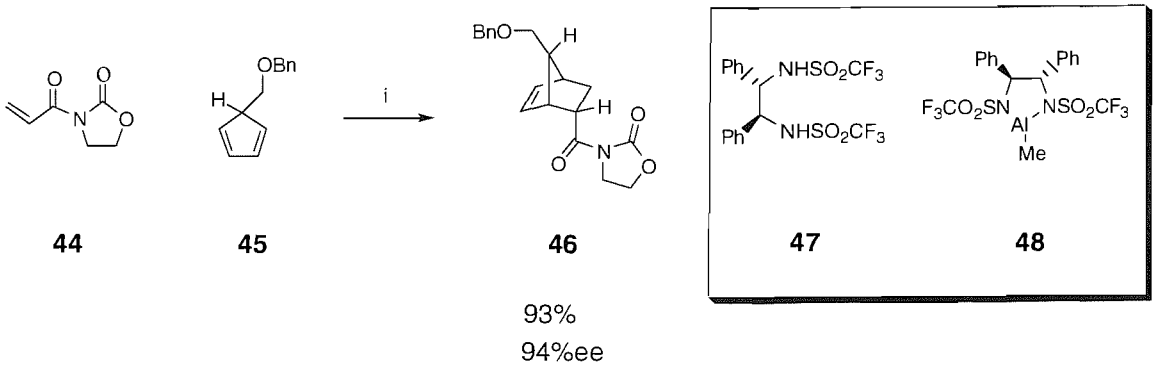

41 1 42 >98% ee 43

**Reagents and conditions:** i) **43,** 2 equiv. $EtAlCl_2$, toluene, –78°C.

Although the enantioselectivity was high, it was found to be necessary to use one equivalent of the Lewis acid and the reaction is also specific for dienophile **41**.[27]

Chiral *bis* sulfonamides have also been used to achieve high levels of enantioselectivity in the Diels-Alder reaction (Scheme 11). [28]

**Scheme 11:** Chiral induction by *bis* sulfonamide chiral catalyst.



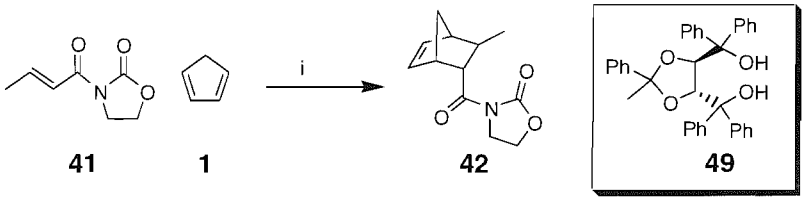

44 45 46 93% 94%ee 47 48

**Reagents and conditions:** i) 10 mol% **47**, $AlMe_3$, –78°C.

The chiral *bis* sulfonamide **47** reacts *in situ* with trimethylaluminium to form active species **48**, which is the active catalyst.[29] In this reaction the adduct **46** has been produced in 94% ee.

One of the most famous chiral titanium reagents is the tartrate-derived titanium TADDOLate complex (Scheme 12).[30-32]

**Scheme 12:** The use of TADDOLate complex to induce enantioselectivity.

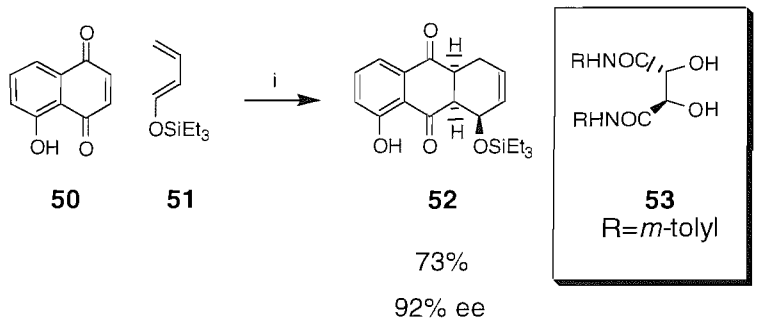



**Reagents and conditions:** i) 10 mol% **49**, $TiCl_2(OiPr)_2$, toluene, molecular sieves, 0°C.

Adduct **42** is formed in high enantioselectivity when the oxazolidenone **41** is used as the dienophile. The enantioselectivity may be further enhanced to 95% ee by changing the solvent to a mixture of toluene and petroleum ether.

Boron has also been utilised in the asymmetric Diels-Alder reaction. Chiral auxiliary **53** has been used in conjunction with boron in the preparation of optically active anthraquinones (Scheme 13).

**Scheme 13:** Synthesis of optically active anthraquinone adduct.

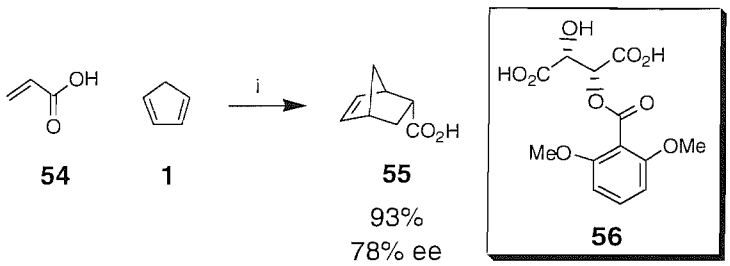



**Reagents and conditions:** i) **55**, $B(OMe)_3$, $CH_2Cl_2$, r.t.

The product **52** is formed in good yield with excellent enantioselectivity. The trimethoxyborane reacts with tartrate derived **53** followed by the formation of the boronic ester of **50**. The implication of this mode of action is that an equivalent of the chiral boron is required.[33]

Obviously the use of boron in a catalytic manner would be advantageous. Acyloxyborane prepared from monoacylated (L)-tartaric acids and borane has been used catalytically in the reaction of acrylic acid (**54**) with cyclopentadiene.

**Scheme 14:** Catalytic chiral boron Diels-Alder reaction.

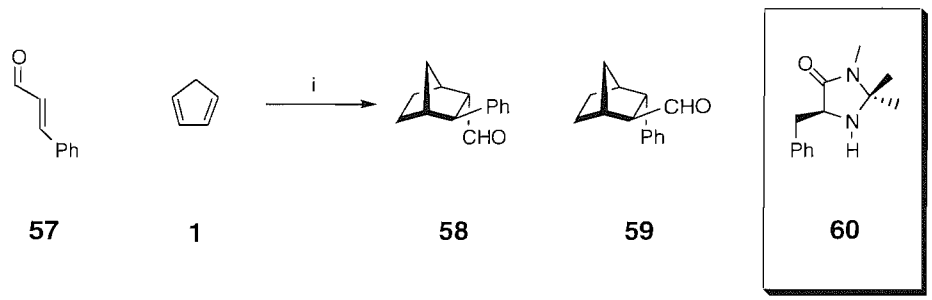



**Reagents and conditions:** i) 10 mol% **56**, $BH_3$.THF, $CH_2Cl_2$, –78°C.

The reaction forms the *endo* adduct **55** with 78% ee when the auxiliary **56** is used.[34]

Recently there has been huge interest in the field of organocatalysis, in which the catalyst is an organic molecule without a metal centre. The organocatalyst reacts with the substrate to form an intermediate which has an increased reactivity. After the reaction, the organocatalyst is released back into solution via a reversible reaction. In the case of the Diels-Alder reaction a dienophile that bears a carbonyl may be converted to an imminium ion by the addition of a secondary amine. When the amine used is chiral an enantioselective reaction may take place (Scheme 15).[35]

**Scheme 15:** Organocatalysis of a Diels-Alder reaction.




**Reagents and conditions:** i) 5 mol% **60**, MeOH-$H_2O$, 23°C, 21 h, 99%, *exo*:*endo* 1.3:1, *exo* ee 93% (2*S*), *endo* ee 93% (2*S*).

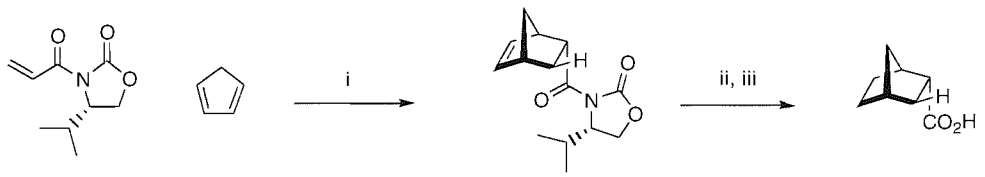
The imminium ion that is formed from **57** and **60** reacts with cyclopentadiene **1** under extremely mild conditions. Although in this instance there is low *exo*:*endo* selectivity the separate adducts are formed in high enantioselectivity (93% ee).[35]

## 1.3.2. Chiral dienophiles

The addition of a chiral auxiliary to a dienophile is another method in which the stereoselectivity of the Diels-Alder reaction may be enhanced.

The most famous chiral auxiliary that has been used with dienophiles is the Evans auxiliary (Scheme 16).[36]

**Scheme 16:** Use of the Evans auxiliary in the Diels-Alder reaction.



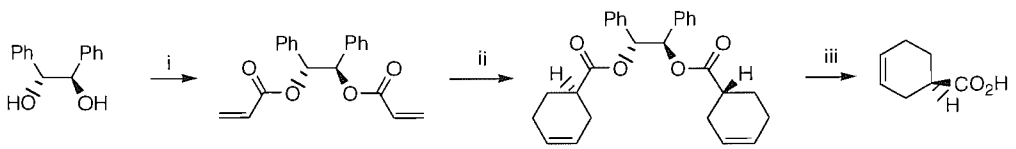

**61** **1** **62** **63**

**Reagents and conditions:** i) 1.4 eq $Et_2AlCl$, $C_6H_6$, –100°C, 2-5 min, 81%, *endo*:*exo* 100:1, *endo* ds 93:7; ii) LiOBn, *n*BuLi, THF, –78°C, 3h , 95%; iii) 5% Pd on charcoal, EtOH, $H_2$, 24h, 100%.

Under these conditions adduct **62** is formed with a high *endo*:*exo* ratio and the diastereomeric ratio of the *endo* adduct is also very high (97:3). Removal of the chiral auxiliary and subsequent hydrogenation yields carboxylic acid **63.** The optical rotation of compound **63** is consistent with known values.[36]

Other chiral auxiliaries have also been utilised with acrylate dienophiles. Reaction of *R*,*R*-hydrobenzoin with acryloyl chloride leads to the diene **65**, which may then be reacted with 1,3-butadiene to yield the Diels-Alder adduct **66** (Scheme 17).

**Scheme 17:** The synthesis and Diels-Alder reaction of a hydrobenzoin derived chiral dienophile.




**64** **65** **66** **67**

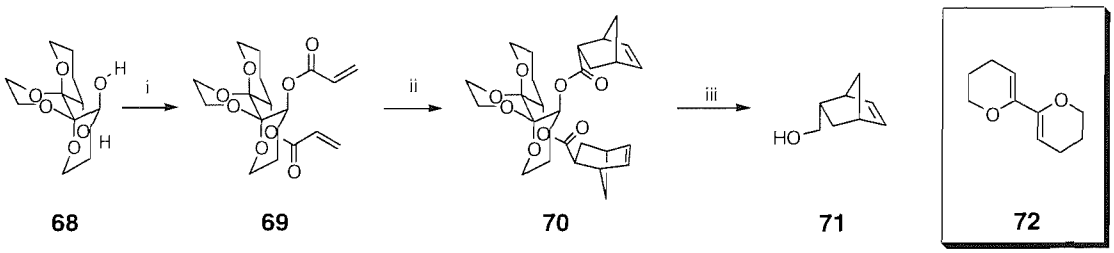
**Reagents and conditions:** i) acryloyl chloride, $NEt_3$, $CH_2Cl_2$, 0°C, 20 min, 98%; ii) 1,3-butadiene, $TiCl_4$, $CH_2Cl_2$, –50°C, 3d, 84%; iii) LiOH, MeOH, $H_2O$, r.t., 24h, 92%.

Saponification of the Diels-Alder adduct **66** provided the carboxylic acid **67** in 92% yield and 95% ee, as well as the recovery of the hydrobenzoin in 93% yield.

The dispiroketal (dispoke) protecting group is a 1,2-vicinal diol protecting group that is important to this project that will be discussed later. A dispoke protecting group has been used as a chiral auxiliary for acrylates in the Diels-Alder reaction.

Enantiomerically pure **68** can be synthesised from *bis*-DHP **72** in three steps in 9% overall yield.[37,38] Diol **68** was then reacted with acryloyl chloride in the presence of base to furnish chiral diene **69** in 82% (Scheme 18).

**Scheme 18:** Diels-Alder reaction of enantiomerically pure dispiroketal diene **69.**



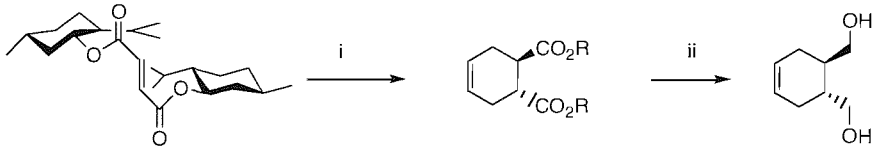

**68** **69** **70** **71** **72**

**Reagents and conditions:** i) KO$^t$Bu, THF, 0°C then acryloyl chloride, –78°C, 82%;ii) Cyclopentadiene, $EtAlCl_2$, $CH_2Cl_2$, -78°C, 1 h, 99%; iii) $LiAlH_4$, $Et_2O$, -30°C, 93%.

The diene **69** was then used in the Diels-Alder reaction with cyclopentadiene. The products achieved in this reaction were a mixture of *bis-endo* adduct **70** and a small amount of *exo-endo* adduct in a ratio of 23.5:1. The removal of the chiral auxiliary was accomplished by reduction with lithium aluminium hydride. The norbornenol **71** was isolated in 93% yield and the dispoke chiral auxiliary was also recovered with a 93% yield.

Chiral auxiliaries have also been applied to fumarate dienophiles. (–)-Dimenthyl fumarate (**73**) has been used in the Diels-Alder reaction (Scheme 19).[39]

**Scheme 19:** Chiral induction via use of (–)-dimenthyl fumarate.




**73** **74** **75**

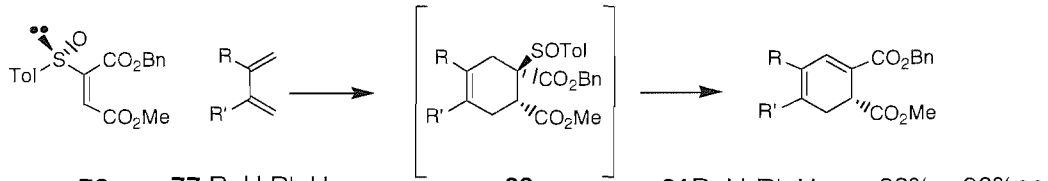
R=Menthyl

**Reagents and conditions:** i) $AlCl_3$, 1,3-butadiene, benzene, 23°C; ii) $LiAlH_4$, $Et_2O$, 71% two steps.

Upon reduction to the glycol **75** it was discovered that the observed selectivity for the (1*R*,2*R*)-enantiomer has moderate enantiomeric excess (57% ee).

Chiral auxiliaries may also be positioned upon the carbon backbone of the dienophile. An excellent example of this approach can be seen in the use of chiral sulfoxides (Scheme 20).[40]

**Scheme 20:** Chiral induction by use of a chiral dienophile.




**76** **77** R=H R'=H; **78**R=Me R'=Me; **79** R=H R'=OMe — **80** — **81**R=H R'=H 83%, >96%ee; **82**R=Me R'=Me 66%,>96%ee; **83** R=H R'=OMe 87%, 83% ee

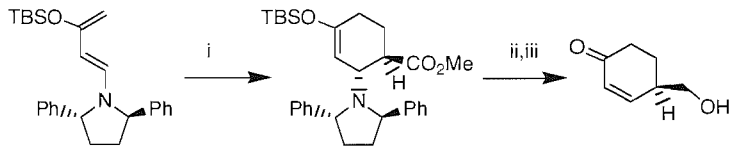
**Reagents and conditions:** (a) $CH_2Cl_2$, $TiCl_4$, –78°C, 28-90h, (b) $CH_2Cl_2$, r.t., 24-48h.

The intermediate **80** eliminates spontaneously at r.t. to give the products **81-83**. The products show that the reaction is completely regioselective with high *endo* and facial selectivity as they exhibit a high enantiomeric excess with no side products.

## 1.3.3. Chiral dienes

The chiral auxiliary can also be attached to the diene moiety, which is probably the least well-developed area of stereoselective Diels-Alder chemistry. Auxiliaries are normally placed on open chain dienes, commonly singly substituted in the 1 or the 2 position.

**Scheme 21:** Open chain diene with position 1 chiral substitution in the Diels-Alder reaction.




**84** **85** **86**

**Reagents and conditions:** i) Methyl acrylate, toluene, 0°C to r.t. 24h; ii) $LiAlH_4$, $Et_2O$ r.t; iii) HF, MeCN, r.t., 1h, 68% two steps.

The diene **84** has a chiral auxiliary in the 1 position with a subsidiary substitution in the 3 position. The Diels-Alder reaction gives rise to a mixture of three diastereomers in a 20:2:1 ratio, however upon reduction of the ester and hydrolysis of the resulting product the cyclohexanone species **86** was obtained in a 96.5:3.5 ratio (93% ee). This can be explained by the following transition states (Figure 11).[41]

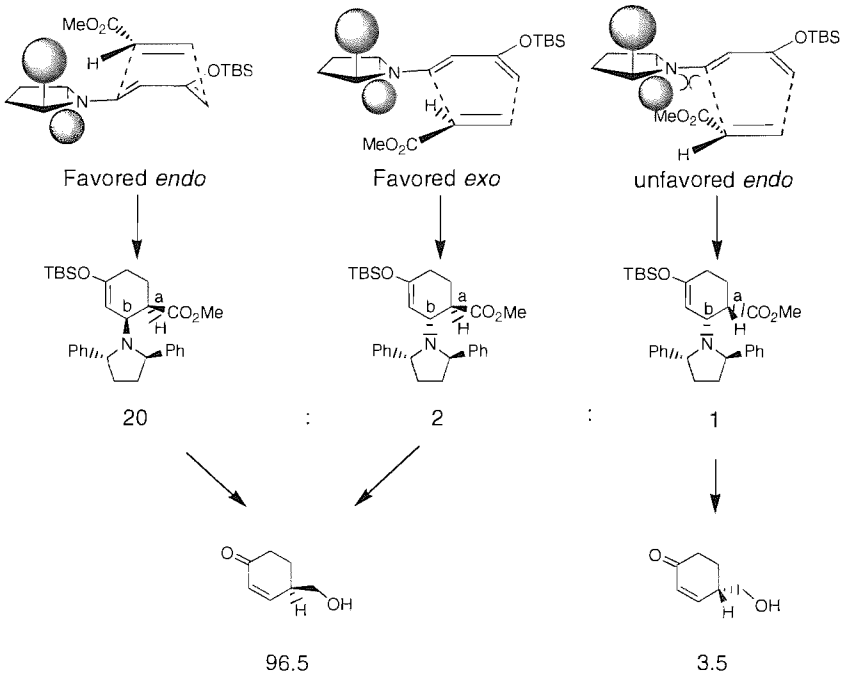
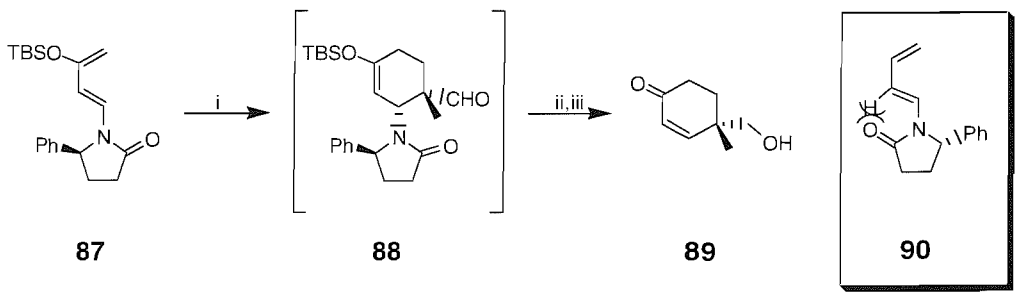



**Figure 11:** Transition states for the Diels-Alder reaction of **84**.

It can be seen that the favoured *endo* approach and the favoured *exo* approach are at opposite faces of the diene, due to the $C_2$-symmetry of the auxiliary. This means that the same face of the dienophile is being approached. Hence the developing chiral centre **a** will have the same absolute configuration in both cases. However, as the opposite face of the diene is approached, the developing chiral centre **b** will have the opposite configuration. When the chiral auxiliary is removed the chiral centre **b** is destroyed and this results in an enhancement of the enantiopurity of the product with regard to the original diastereoselectivity.

A non-$C_2$-symmetric version of this auxiliary has also been used to promote an asymmetric Diels-Alder reaction (Scheme 22).[42]

**Scheme 22:** Open chain diene at C1 non $C_2$-symmetric chiral substitution in the Diels-Alder reaction.

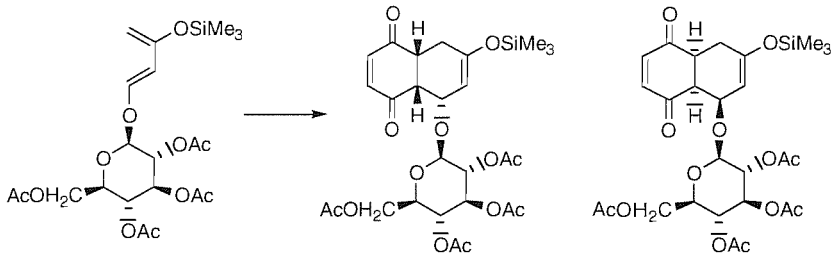



**Reagents and conditions:** i) methacrolein, toluene, 35°C, 24h, quant; ii) $LiAlH_4$, $Et_2O$ r.t, iii) HF, MeCN, r.t., 1h. 67% overall.

The diene **87** stays in the conformation drawn as this minimises steric interactions between the oxazolidenone carbonyl and the hydrogen at C2 of the diene (**90**). The consequence of this is that the phenyl group is locked into position and thus is able to direct the approach of the dienophile towards the rear face of the diene. This leads to a selective reaction that yields the enone **89** in a 92% ee and in 67% yield from the diene.

Carbohydrates have also been used as chiral auxiliaries in the C1 position with excellent results (Scheme 23).[43]

**Scheme 23:** Use of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside as a chiral auxiliary in the C1 position.




**91** **92** **93**

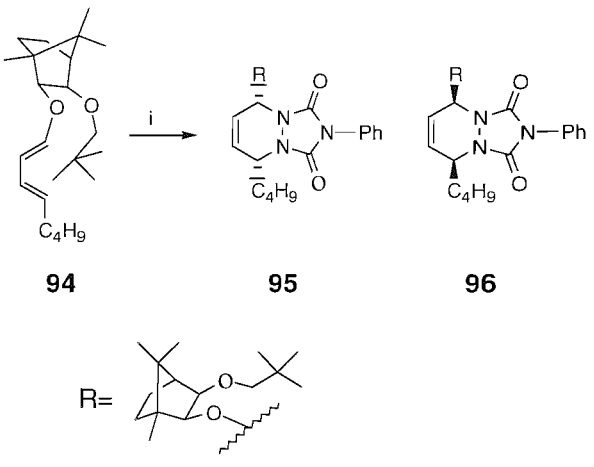
8 : 1

**Reagents and conditions:** i) *p*-Benzoquinone, $C_6H_6$, r.t., 45%.

The reaction of the diene **91** provided the adducts **92** and **93** in 45 % yield and an 8:1 ratio. The stereochemistry achieved in the reaction is consistent with attack from the face *anti* to the chiral auxiliary of the diene as would be expected.

Extremely bulky substituents have been used to good effect in influencing the stereochemical outcome of the Diels-Alder reaction.[44]

**Scheme 24:** Reaction of the diene **94** in the Diels-Alder reaction.



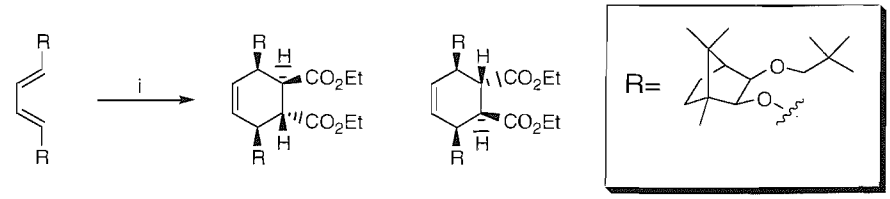

**94** **95** **96**

**Reagents and conditions:** i) PTAD, THF, –25°C, seconds, 100%.

The reaction proceeds in quantitative yield and the product is obtained with high diastereoselectivity (94.5:5.5, **95**:**96**).

The use of the same auxiliary but substituted into the 1 and 4 positions of the diene also gives rise to a highly selective reaction.[45]

**Scheme 25:** Diels-Alder reaction of **97**.




**97** **98** **99**

**Reagents and conditions:** i) Ethyl fumarate, *m*-Xylene, 85°C, 48h, 63%.

The Diels-Alder reaction of diene **97** proceeds in 63% yield and a diastereoselectivity of >20:1. The reason for this selectivity is readily apparent if the transition state is considered.

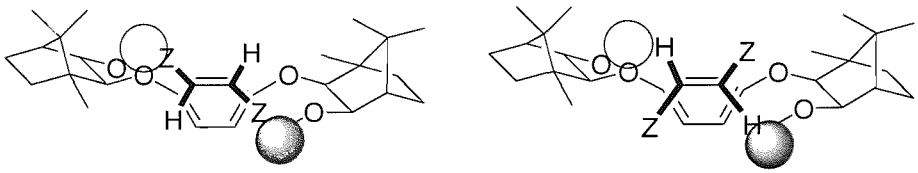
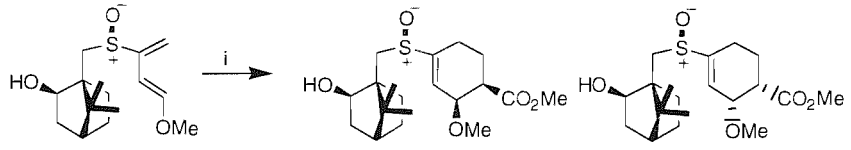



**Figure 12:** Transition states for the Diels-Alder reaction of **97**.

It can be seen that the approach of the dienophile in approach A places the ester functionality into close proximity with the bulky groups of the chiral auxiliary, whereas the approach B minimises these interactions. In this case diene facial selectivity is meaningless as the faces of the diene are homotopic because the diene is $C_2$-symmetric.

A chiral group in the 2 position may also achieve control of the absolute stereochemistry.[46]

**Scheme 26:** Open chain diene with position 2 chiral substitution in the Diels-Alder reaction.

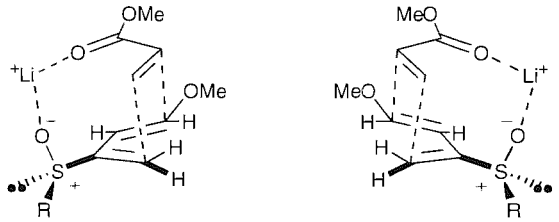


**100** **101** **102**

96 : 4

**Reagents and conditions:** i) Methyl acrylate, $LiClO_4$, $CH_2Cl_2$, r.t. 7h.

When the Diels-Alder reaction of diene **100** is catalysed by lithium perchlorate a highly selective reaction takes place. The regiochemistry is completely selective and the diastereoselectivity that is observed is very high. It is believed that the selectivity that arises in this reaction is not due to the bulky isoboronyl group but to the electrostatic interactions of the chiral sulfur.

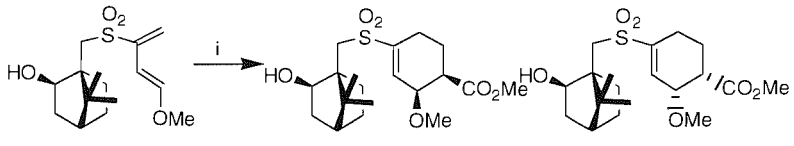


A B

**Figure 13:** Electrostatic interactions controlling the Diels-Alder transition state.

In order to prove that the electrostatic interactions were governing the selectivity in this reaction diene **103** was synthesised and subjected to similar reaction conditions.

**Scheme 27:** Reaction of sulfonyldiene **103** with methyl acrylate.



**103** **104** **105**

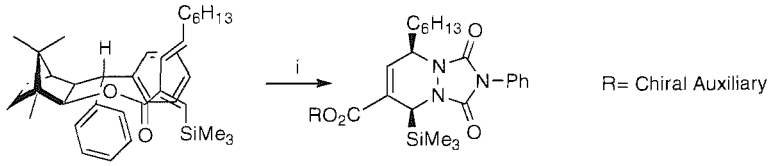
1 : 1

**Reagents and conditions:** i) Methyl acrylate, $ZnCl_2$, $CH_2Cl_2$, r.t. 7h.

The reaction did not proceed with complete *endo* selectivity and an *endo*:*exo* ratio of 10:1 was obtained. The stereoselectivity of the endo products was shown to be 1:1 showing that these reactions were governed by the chirality at sulfur and electrostatic interactions.

Steric interactions are still an important factor when the chiral auxiliary is incorporated at C2.

**Scheme 28:** Diels-Alder reaction with an ester based chiral auxiliary.



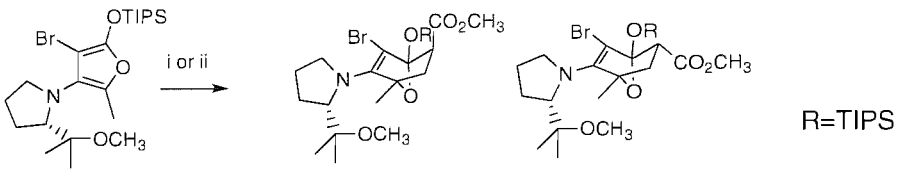

**106** **107**

**Reagents and conditions:** i) PTAD, $CH_2Cl_2$, –30°C, 80%.

The diene **106** has a bulky chiral auxiliary that entirely shields one face of the diene and is stabilised by possible π-stacking. Obviously attack from this side is highly unfavoured and the product **107** is obtained as a single diastereomer.

Other types of diene have been utilised in the Diels-Alder reaction apart from the open chain 1,3-butadienes previously mentioned. The furan **108** is a chiral inner ring diene.[47]

**Scheme 29:** Diels-Alder reaction of a conformationally constrained chiral diene.




**108** **109** **110**

| | | | |
|---|---|---|---|
| Conditions i | 10 | : | 1 |
| Conditions ii | 15 | : | 1 |

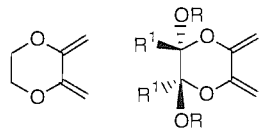
**Reagents and conditions:** i) methyl acrylate, $CH_2Cl_2$, r.t. 12h, 93%; ii) Ti $(O^iPr)_3Cl$, $CH_2Cl_2$, r.t.

The adducts formed in the Diels-Alder reaction of the diene **108** are formed in a ratio of 10:1. This ratio could be improved by the addition of chlorotitanium triisopropoxide to 15:1.

## 1.4. The aim of the project

The field of stereoselective Diels-Alder reaction via chiral dienes is less well developed than that of chiral catalysts or chiral dienophiles. Most chiral dienes that are currently in the literature are open chain dienes and have one attachment point to the diene; this leads to a degree of conformational flexibility. It was anticipated that

the use of a cyclic auxiliary connected to the diene via the C2 and C3 positions would produce a rigid diene, possibly resulting in a high diastereoselection in a Diels-Alder reaction. The auxiliary would need to be cleaved when the reaction was complete and so the 1,4-dioxane system was selected to be the parent system of the diene.

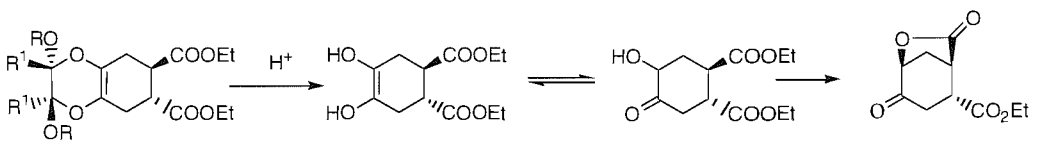


**111** **112**

**Figure 14:** Design of the new class of diene.

The auxiliary obviously has to be chiral and as regiochemistry is not an issue with symmetrical dienes the use of a symmetrical auxiliary would be beneficial. This has led us to investigate diacetals such as **112** as suitable chiral auxiliaries. As the 1,2-diacetal group has been used in protection group chemistry it was expected that the cleavage of the auxiliary would prove to be a simple matter. The diacetal motif exhibits a strong anomeric effect that should produce $C_2$-symmetric dienes of the type **112**.

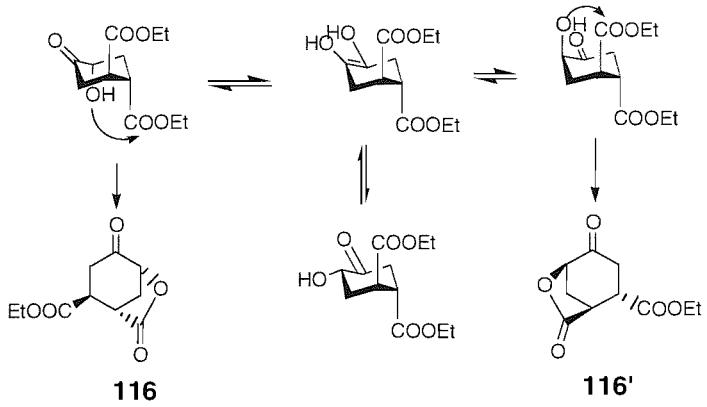
The Diels-Alder adducts obtained via reaction of the diene **112** with a dienophile will then be subjected to acidic cleavage conditions. The removal of the BDA group should reveal an α-hydroxyketone (Scheme 30).



**113** **114** **115** **116**

**Scheme 30:** Proposed cleavage of the auxiliary from the Diels-Alder adducts

It is hoped that the acidic cleavage conditions will cause **115** to undergo a spontaneous ring closure between the free alcohol functionality and the ester functionality (Figure 15).




**116** **116'**

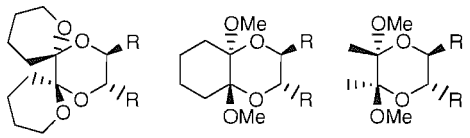
**Figure 15:** Cyclisation of the α-hydroxyketone.

It can be seen that **116** and **116'** are identical and hence it does not matter which hydroxyl group attacks. The other important note is that the hydroxyl groups can only attack when they are in the axial position, however, as the steps are reversible, this is not a problem.

It is hoped that this methodology could give rise to enantiopure chiral building blocks in a short number of steps.

## 1.5. 1,2-Diacetals in synthesis

1,2-diacetals are typically used for the protection of *trans* 1,2-diols. The three major 1,2-diacetal groups that have been utilised are the dispiroketal (dispoke)[48] **117**, the cyclohexane-1,2-diacetal (CDA)[49] **118** and the butane-1,2-diacetal (BDA)[50] **119** (Figure 16). The dispoke protecting group was the first group to be developed by Ley *et al* followed by the CDA protecting group. Berens *et al* later discovered the BDA group by accident but the utility of the new group became readily apparent.




**117** **118** **119**

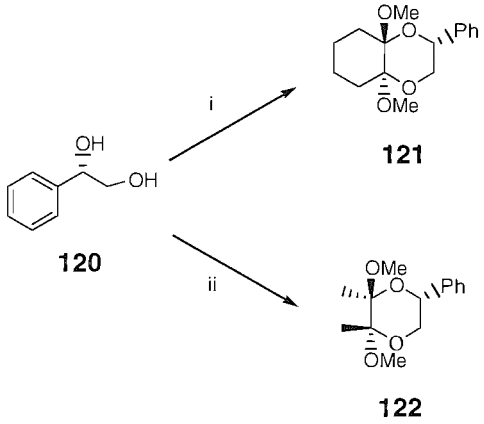
**Figure 16:** The dispoke, CDA and BDA protecting groups.

### 1.5.1. Formation of the 1,2-diacetals

The protection of diols as CDA and BDA protecting groups takes place in acidic methanol. Originally the tetramethoxy-acetal of 1,2-cyclohexanedione and 2,3-butanedione was used for the formation of these compounds, however, it was

discovered that the protecting group could be formed directly using the diketones in methanol (Scheme 31).[51,52]

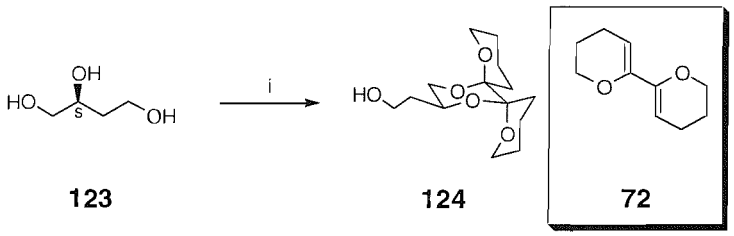
**Scheme 31:** Formation of the CDA and BDA diacetals.




**Reagents and conditions:** i) 1,2-cyclohexanedione, MeOH, $CH(OCH_3)_3$, cat CSA, 64%; ii) 2,3-butanedione, MeOH, $CH(OCH_3)_3$, cat CSA, 94%.

When diols are protected as a dispoke group, *bis*-DHP **72** is heated in an aprotic solvent such as toluene or chloroform in the presence of a acid (Scheme 32). [48]

**Scheme 32:** Formation of dispoke diacetal.




**Reagents and conditions:** i) **72**, CSA, toluene, 110°C, 2h, 96%.

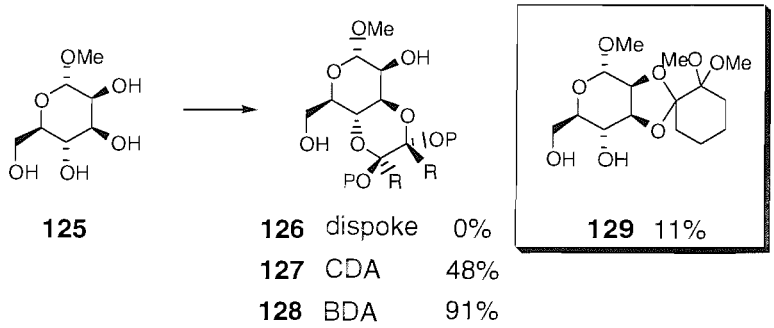
The products that are formed show a predilection for the O-alkyl part of the protecting group to be axial with respect to the newly formed ring. This is unsurprising when the anomeric effect is considered. The anomeric effect is a strong stabilising force which imparts rigidity to the newly formed ring system. The anomeric effect also means that when the starting material is chiral the product that is formed is obtained as a single diastereomer.

Like acetals, 1,2-diacetals are cleaved under acidic conditions.[49,51,53,54] The usual deprotection conditions are trifluoroacetic acid and water.

## 1.5.2. 1,2-Diacetals as protecting groups: Carbohydrate chemistry

In the field of carbohydrate chemistry the protection of 1,2-diequatorial vicinal diols is a desired process. The 1,2-diacetal protection groups are able to make selective protections for diequatorial hydroxyl groups in the presence of axial alcohol functionality (Scheme 33). [49,55]

**Scheme 33:** Protection of D-mannose with the 1,2-diacetal protection protocols.




**125**

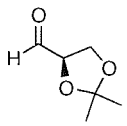
**126** dispoke 0%
**127** CDA 48%
**128** BDA 91%

**129** 11%

The protection of D-mannose **125** does not proceed at all as the dispoke diacetal but the CDA and BDA protection both lead selectively to the 3,4 protected product selectively. However, in the case of protection as the CDA diacetal a small amount of the 2,3-protected product **129** is obtained.

## 1.5.3. 1,2-Diacetals as protecting groups: For glyceraldehyde

The production of small chiral building blocks is of importance in organic synthesis.[56] D-glyceraldehyde acetonide **130** has been used as a three-carbon building block in organic synthesis. The acetonide itself, however, is unstable and will undergo polymerisation, racemisation and will form hydrates.[57]




**130**

**Figure 17:** D-glyceraldehyde acetonide.

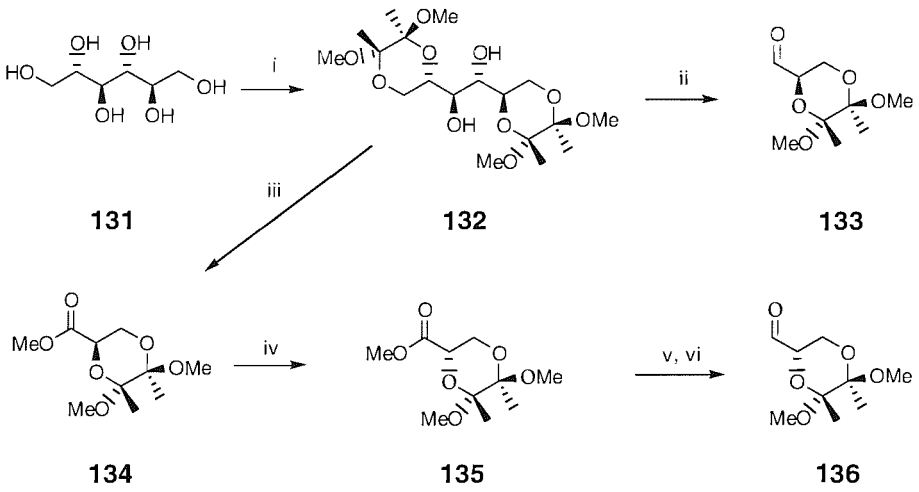
Dispoke protected glyceraldehyde was investigated as a potential replacement for glyceraldehyde acetonide.[48] The dispoke protected glyceraldehyde was a much more stable adduct than D-glyceraldehyde acetonide **130**. When the dispoke protected

glyceraldehyde was subjected to alkylation conditions the products showed were obtained in an 80:20 *anti:syn* ratio.

However, the dramatic increase in molecular mass and the difficulties involved in large scale production, meant that the dispoke protected glyceraldehyde was not suitable as a replacement for the glyceraldehyde acetonide **130**.[58]

The BDA protected glyceraldehyde **133** has a much lower molecular mass than dispoke protected glyceraldehyde and is easily prepared from D-mannitol (**131**) on large scale (Scheme 34). It is also a more stable glyceraldehyde equivalent than the glyceraldehyde acetonide **130**.[59]

**Scheme 34:** Synthesis of *R* and *S* BDA protected glyceraldehyde from D-mannitol.

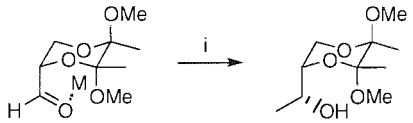



**Reagents and conditions:** i) 2,3-butanedione, $HC(OMe)_3$, MeOH, $BF_3.Et_2O$, r.t., 5h; ii) $NaIO_4$, $CH_2Cl_2$, r.t., 40% over two steps; iii) $NaIO_4$, $MeOH/H_2O$, r.t., overnight then $NaHCO_3$, $Br_2$, r.t., 45% over two steps; iv) LDA, THF, –78°C, 0.5h, *t*BuOH, further 0.5h, 48%; v) $LiAlH_4$, THF, 0°C-r.t. overnight; vi) $(COCl)_2$, DMSO, $CH_2Cl_2$, $NEt_3$, –60°C, 15 min, 95% over two steps.

Alkylation upon the D-glyceraldehyde equivalent **133** gave products with approximately an 80:20 ratio in favour of the *anti* product. The ester **134** could be produced from the protected mannitol **132** and the chiral centre could then be inverted with LDA. Reduction followed by oxidation gave the L-glyceraldehyde equivalent **136** in good yield.

The glyceraldehyde equivalent **136** has the aldehyde in the axial position. Previously when an alkylation had taken place upon these substrates the aldehyde was in an equatorial position and the selectivity that arose was induced solely by the steric interaction of the chiral auxiliary.

**Scheme 35:** Alkylation of glyceraldehyde butane diacetal **136** under chelation control.



**136** **137**

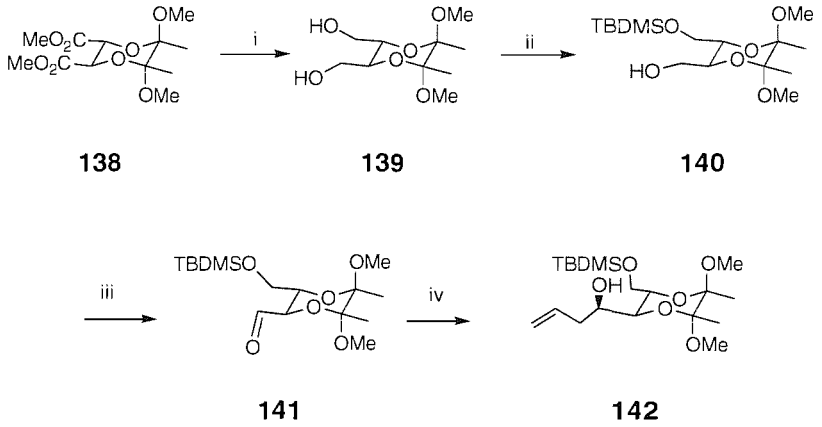
**Reagents and conditions:** i) MeMgBr in $CH_2Cl_2$, toluene, –95°C, 81%.

However, when the alkylation is carried out upon the aldehyde, coordination is now possible between a metal ion, the aldehyde and the dioxane ring, increasing the observed selectivity to 25:1 in favour of the *syn* product.[58,59]

## 1.5.4. 1,2-Diacetals as protecting groups: For tartaric diester

Protection of the dimethyl tartaric acid derivative with a BDA group leads to product **138**.[50]

**Scheme 36:** Synthesis of tartrate derived aldehyde **141** and its alkylation reaction.



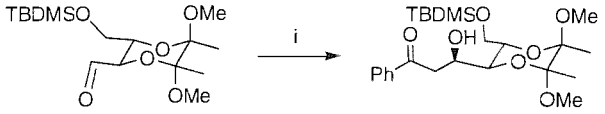
**138** **139** **140**

**141** **142**

**Reagents and conditions:** i) $LiAlH_4$, THF, 0°C-r.t., 0.5h, 100%; ii) NaH, THF, r.t. then TBDMSCl, 2 h, 86%; iii) $(COCl)_2$, DMSO, –78°C,then $NEt_3$, –78°C - r.t. 0.5 h, 88%; iv) $Bu_3SnCH_2CHCH_2$, $LiClO_4$, $Et_2O$, 0°C-r.t., overnight, 97%.

The reduction of the BDA protected tartrate derivative **138** proceeded with excellent yield and the mono-protection with *tert*-butyldimethylsilyl chloride also proceeded smoothly.[60] The oxidation of the remaining hydroxyl group gave rise to the aldehyde **141**. The reaction of **141** with allyltributylstannane and lithium perchlorate gave product **142** in excellent yield and diastereoselectivity (96% de). The stereoisomers were readily separable by chromatography and the new stereocentre of the major isomer was found to have the *R* configuration by production of a Mosher ester, which is consistent with the addition occurring under chelation control.

**Scheme 37:** Mukaiyama aldol reaction of aldehyde **141.**




**141** **143**

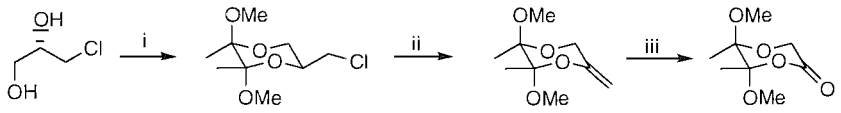
**Reagents and conditions:** $MgBr_2$, $Et_2O$, r.t. - 0°C then 2-trimethylsilyloxypropene, 0°C, 0.5 h, 89%.

The aldehyde **141** has also shown selectivity in the Mukaiyama aldol reaction. Aldehyde **141** was precomplexed with magnesium bromide at r.t. followed by addition of 2-trimethylsilyloxypropene at 0°C. The Mukaiyama aldol product **143** was formed in 89% yield and in excellent selectivity (>98% de).[60]

## 1.5.5. The 1,2-diacetal group as an auxiliary: Glycolic acid auxiliary

The BDA group has also been used for the production of a protected chiral glycolic acid equivalent.[61]

**Scheme 38:** Synthesis of BDA protected glycolic acid equivalent **147**.

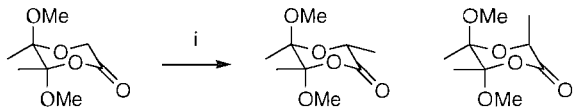



**144** **145** **146** **147**

**Reagents and conditions:** i) MeCOCOMe, CSA, $CH(OMe)_3$, MeOH, 2 h; ii) *t*-BuOK, THF, reflux, 2 h; iii) $O_3$, $CH_2Cl_2$ (1:1) –78°C then DMS, –78°C-r.t. 56% over three steps.

The treatment of the glycolic acid equivalent **147** with base to produce an enolate and then quenching that enolate with an electrophile, proved to be a highly stereoselective reaction. Adducts **148** and **149** were obtained in a 70:1 ratio and 84% overall yield (Scheme 39).[61]

**Scheme 39:** Alkylation of BDA protected glycolic acid equivalent **147**.

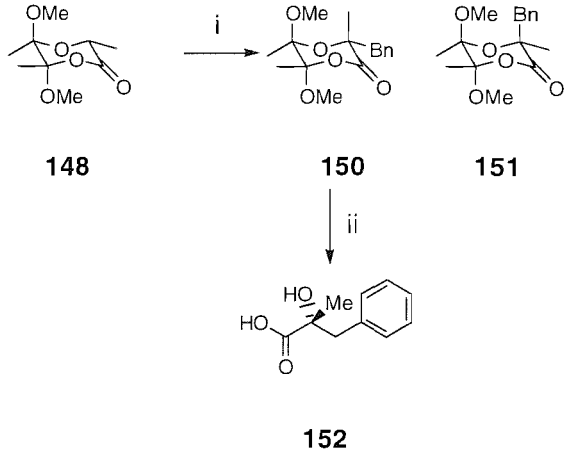



**147** **148** **149**

**Reagents and conditions:** i) LHMDS, THF, –78°C then MeI –78°C to –30°C 2 h, then AcOH, 84%.

The product **148** may then undergo a second alkylation, which also proceeds in a selective manner.

**Scheme 40:** Alkylation of BDA protected glycolic acid equivalent **148**.

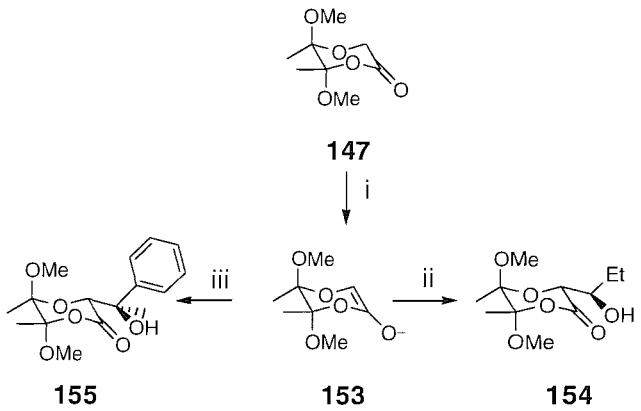



**Reagents and conditions:** i) LHMDS, THF, –78°C then BnBr –78°C to 0°C 2 h, then AcOH, 84%. ii) TFA/$H_2O$ (9:1), 10 min, r.t., 85%.

The adducts **150** and **151** were obtained in a 99:1 ratio. Both alkylations have shown the preference for the electrophile to approach in a manner that minimises steric interactions and, therefore, the reaction must be proceeding under steric control. The removal of the BDA group from adduct **150** gave the adduct **152** in an 85% yield and in enantiopure form.[61]

BDA protected glycolic acid equivalent **147** may also participate in the aldol condensation (Scheme 41).[62,63]

**Scheme 41:** Aldol reaction of BDA protected glycolic acid equivalent **147**.




**Reagents and conditions:** i) LHMDS, THF, –78°C, 10 min; ii) propanal, THF, –78°C, 5 min, 86%; iii) acetophenone, THF, –78°C, 1 h , 79%.

The adduct **147** was exposed to lithium hexamethyldisilazane at –78°C to form the lithium enolate. Enolate **153** was then exposed to propanal and the reaction was allowed to stir for five minutes before addition of acetic acid. The product **154** was recovered in good yield and in over 95% diastereomeric excess. The relative

stereochemistry was shown to be consistent to attack of the *re* face of the lithium glycolate enolate (Figure 18).

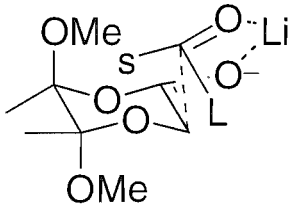
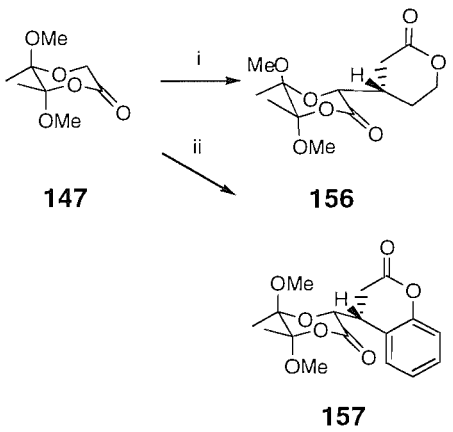



**Figure 18:** Transition state of the aldol reaction.

The transition state shown in Figure 18 places the oxygen of the aldehyde and the enolate in a position where both may coordinate to the lithium and the smallest group (hydrogen) in the closest proximity to the butane diacetal backbone. This minimises steric interaction and it can be seen when enolate **153** is exposed to a ketone the product that is obtained also is that which would be expected from the transition state.

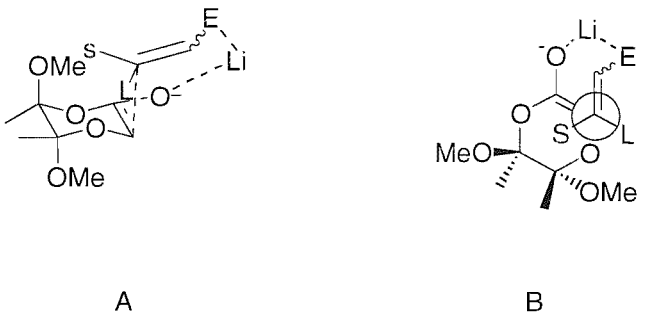
The lithium enolate of BDA-protected glycolic acid may also take part in Michael additions (Scheme 42).[64]

**Scheme 42:** The Michael reaction of BDA protected glycolic acid equivalent **147**.




**Reagents and conditions:** i) LHMDS, THF, –78°C, 10 min then 5,6-dihydro-2H-pyran-1-one, 20 min, 63%; ii) LHMDS, THF, –78°C, 10 min then coumarin, 20 min, 90%.

The Michael addition between the enolate of **147** and 5,6-dihydro-2H-pyran-1-one showed a good selectivity of 22:1, however, when the Michael acceptor was changed to coumarin the selectivity that arose was 65:1. This dramatic increase in selectivity must be the product of increased steric interactions (Figure 19).




A B

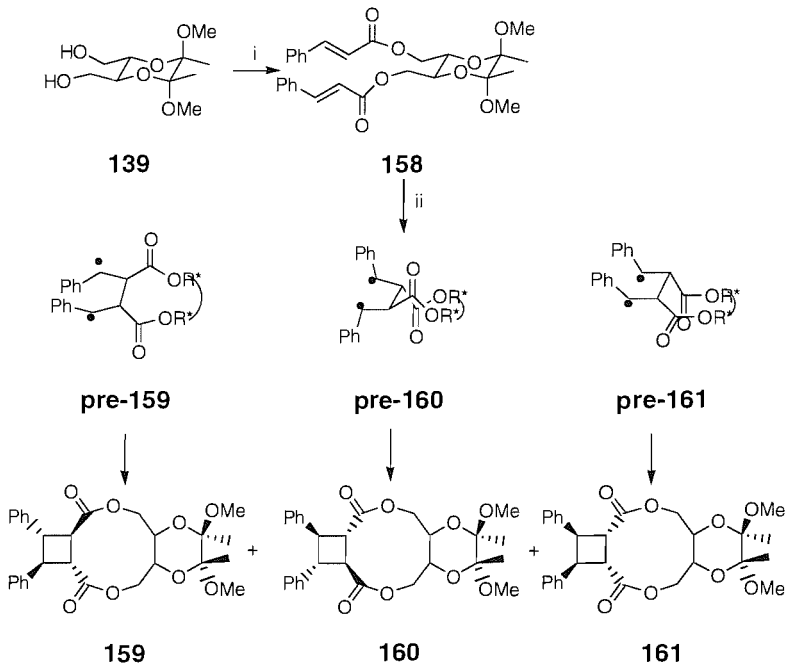
**Figure 19:** Transition state of the Michael addition.

The observed stereochemistry is consistent with the Michael acceptor approaching from the face opposite the axial-1,3-related methoxy group (view A). So it can be seen that the steric factor has a large influence upon this reaction.

## 1.5.6. The 1,2-diacetal group as an auxiliary: [2+2] Cycloaddition

The diol **139** has been elaborated to yield the diene **158**, which was then used in an intramolecular [2+2] photocycloaddition.[65]

**Scheme 43:** Synthesis of diene **158** and subsequent photocyclisation.




**Reagents and conditions:** i) PhCHCHCOCl, DMAP, Py, $CH_2Cl_2$, r.t., 20h, 96%; ii) *hv*, toluene, –60°C, 60h, 89%.

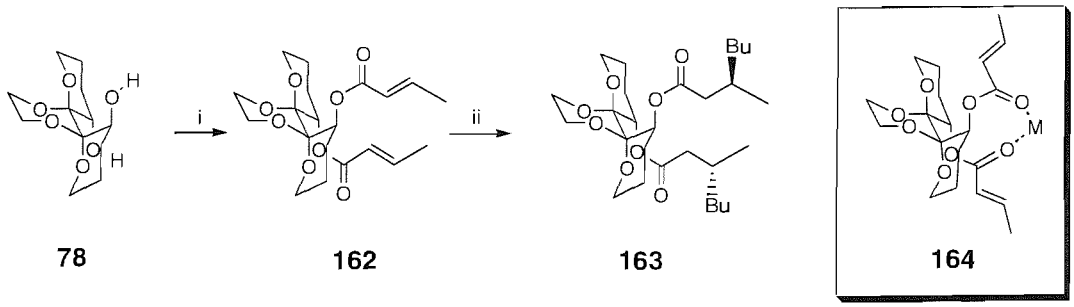
The products of the irradiation of diene **158** were obtained in a 27:1:4.5 ratio (**159:160:161**) and this is consistent with the transition states as **pre-159** shows the least amount of ring strain or steric interaction. The high level of selectivity is attributed to the stabilisation of the 1,4-dioxane ring chair conformation due to the

double anomeric effect of the BDA group and the minimal number of degrees of freedom that this system imposes.

### 1.5.7. The 1,2-diacetal group as an auxiliary: Michael reaction

The diol **78** was also reacted with crotyl chloride to form diene **162**, which was then used in Michael additions (Scheme 44). [66]

**Scheme 44:** Michael reaction of diene **162**




**Reagents and conditions:** i) KO$^t$Bu, THF, 0°C then crotyl chloride, –78°C, 78%; ii) BuCu.$BF_3$.$PBu_3$, –60°C, 16 h, 88%.

When the diene **162** was used as a bifunctional Michael acceptor a remarkably selective reaction occurred. The yield was 88% and the enantiomeric excess of the reaction was 96% with an *R* configuration. This is consistent with the proposed coordination model **164**.

## 1.6. Classification of dienes

The component of the Diels-Alder reaction that this project is concerned with is the diene. There are five main types of diene that have been used in the Diels-Alder reaction, inner ring, outer ring, inner outer ring, across ring and open chain.[67]

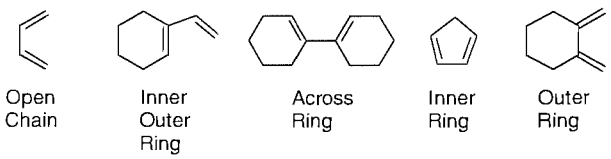



**Figure 20:** Types of dienes that are reactive in the Diels-Alder reaction.

The target diene type in this project belongs to the outer ring subclass. Outer ring dienes are locked into the *cisoid* conformation that is necessary for the Diels-Alder reaction to take place. The relative reactivity of a diene can be gauged by the 1-4 dienic distance (Table 1).[67]

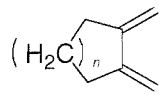
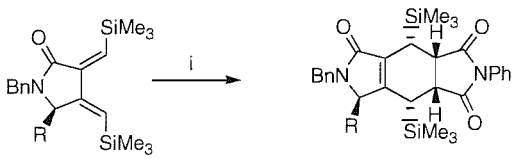
| Diene | | $k_2 \times 10^5$ ($L \cdot mol^{-1} \cdot s^{-1}$) | $r_{1,4}$ (Å) |
|---|---|---|---|
|  | $n = 0$ | 20.8 | 3.34 |
| | $n = 1$ | 3590 | 3.14 |
| | $n = 2$ | 960 | 3.17 |

**Table 1:** Relative rate constants of various dienes with maleic anhydride and the 1,4-dienic distance.

It can be seen the outer ring dienes of cyclobutanes ($n$=0) react relatively poorly with respect to the five ($n$=1) and six-membered ($n$=2) ring systems due to the ring strain holding the diene termini further apart. The five membered ring systems and the six membered ring system show a similar dienic distance and reactivity to maleic anhydride.[67]

Outer ring dienes have shown high *endo* preference and when the diene is chiral, a high diastereoselectivity.[68]

**Scheme 45:** Chiral outer ring diene in the Diels-Alder reaction.



**165** R= H **167** 83%

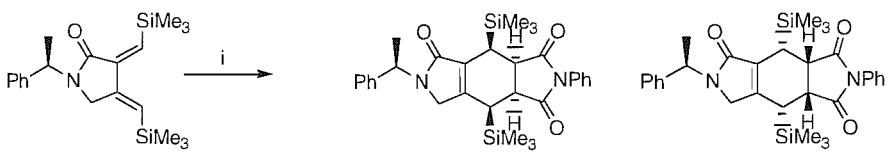
**166** R= *i*-Pr **168** 95% ds=>95:5

**Reagents and conditions**: i) N-Phenylmaleimide, toluene, reflux.

The diene **165** has been produced as a single adduct and this shows the very high preference for *endo* attack in this system. The chiral diene **166** reacts with N-phenylmaleimide to give the adduct **168** in ca 90% de.

Outer ring dienes may even instil selectivity when the stereogenic centre is remote.

**Scheme 46:** Remote chiral centre influencing the Diels-Alder reaction.



**169** **170** : **171**

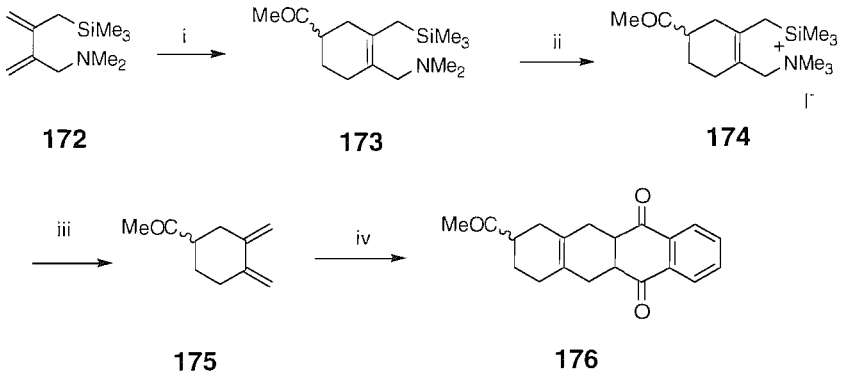
2 : 1

**Reagents and conditions:** i) N-Phenylmaleimide, toluene, reflux, 72%.

Diene **169** contains a stereogenic centre that is five carbons distant from the reacting centre. Incredibly, this remote stereocentre has an effect upon the stereoselectivity. This is thought to be because of the rigid, planar shape of the diene.

Outer ring dienes have been synthesised and used in a one-pot process (Scheme 47).

**Scheme 47:** One-pot synthesis and Diels-Alder reaction of outer ring diene.



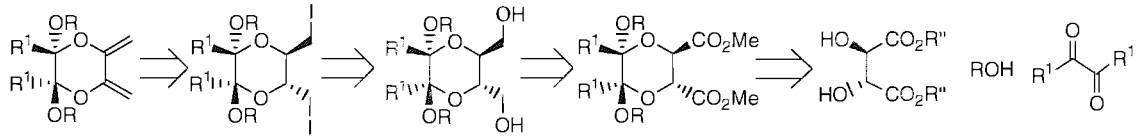

**Reagents and conditions:** i) methyl vinyl ketone, $CH_3CN$, r.t.; ii) MeI, $CH_3CN$, r.t.; iii) TBAF, $CH_3CN$, r.t., iv)1,4-naphthoquinone, $CH_3CN$, r.t., 85%.

The Diels-Alder reaction of diene **172** with methyl vinyl ketone yields adduct **173** as a mixture of regiomeric adducts. Reaction of the amine group with methyl iodide yields an ammonium ion **174** which on subsequent treatment with TBAF reveals outer ring diene **175**. The second Diels-Alder reaction with 1,4-naphthoquinone furnishes the adduct **176**, which is a key intermediate for the synthesis of anthracycline antibiotics, in 85% overall yield.[69]

# Chapter 2: Synthesis and structural conformation of the chiral dienes

## 2.1. Introduction

A prerequisite for the potential usefulness of an auxiliary controlled system is its ease of formation from cheap materials on large scale. The synthesis of the diacetal dienes was envisioned to be possible from dimethyl tartrate in four steps as shown in the retrosynthetic analysis (Scheme 48).



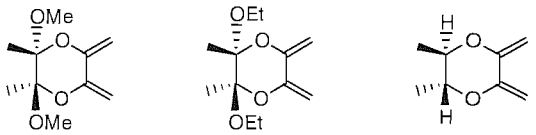
**112** **177** **178** **179** **180** **181** **182**

**Scheme 48:** Retrosynthetic analysis of the generalised diene.

The diene unit could be generated from a 1,4-diiodide by a double elimination reaction. The diiodide would be obtained from tartrate derivate **178** which in turn would be obtained from diester **179**. Diacetals such as **178** and **179** are known compounds and are reported to be readily accessible from dimethyl tartrate.

Hence, there is an inherent versatility present in that different R or $R^1$ groups could be introduced in order to investigate a range of different auxiliary substitutions, though the different substitutions would have to be introduced at the first step.

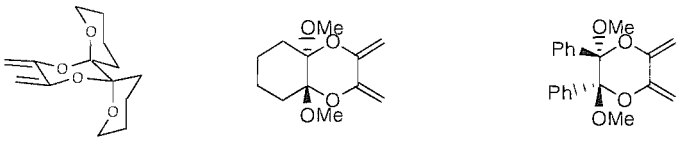
The initial plan was to focus on a change in R group. The following chiral dienes were synthesised in enantiopure form (Figure 21).



**183** **184** **185**

**Figure 21:** Original target dienes.

Next variation of the $R^1$ group was also desired and dienes **186/187/188** were synthesised (Figure 22). However, the synthesis of these dienes met with practical difficulties.



186 187 188

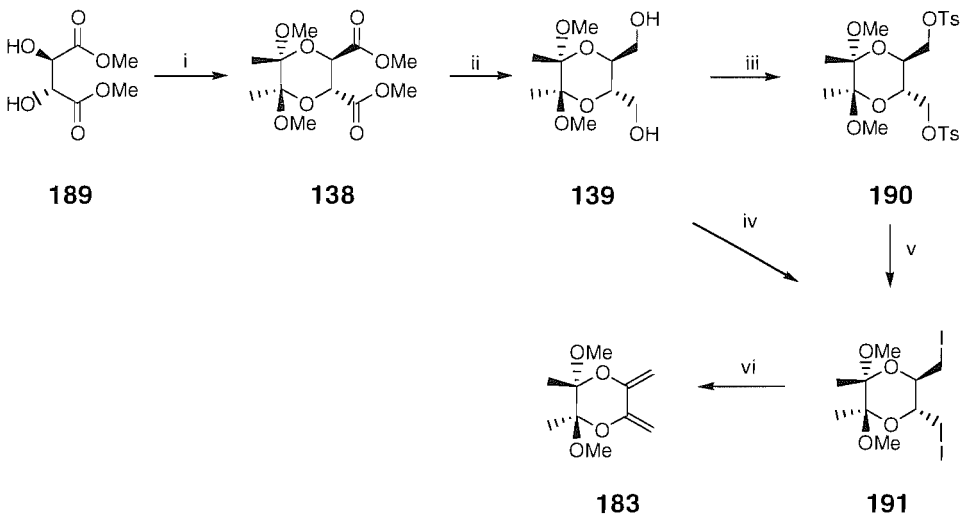
**Figure 22:** Second generation chiral dienes.

## 2.2. Synthesis of diene 183

### 2.2.1. Synthesis

The synthesis of diene **183** started with the cheap commercially available L-dimethyl tartrate (Scheme 49).

**Scheme 49:** Synthesis of diene **183**




189 138 139 190 183 191

**Reagents and conditions:** i) 2,3 butanedione, CSA, MeOH, TMOF, 65°C, 1 d, 82%; ii) $LiAlH_4$, THF, 0°C, 15 min, 96%; iii) *p*-TsCl, Py, 0°C, 24 h, 66%; iv) NaI, acetone, reflux, 24 h, 64%; v) $PPh_3$, imidazole, $I_2$, benzene, reflux, 1 h, 95%; vi) *t*BuOK, DMF, 0°C, 20 min, 92%

The protection of L-dimethyl tartrate with 2,3-butandione and methanol has been executed according to literature precedence.[50,52] The reaction was very straightforward and it was possible to perform the reaction on a very large scale (40-50g) with minimal work-up, a short column followed by recrystallisation, to give a yield of 82% in a reproducible manner.

The BDA derivative **138** was obtained as a single diastereomer. The tartrate chiral centres efficiently induce the formation of the two BDA chiral centres and this process is also controlled by the anomeric effect. This is a stabilising effect caused by the overlap of axial lone pair with the σ* orbital of C–O bond of the methoxy group.

This orbital overlap is only efficient if the orbitals involved are parallel, hence the methoxy group must be axially oriented (Figure 23). As the acetal formation is thermodynamically controlled, the most stable system is formed.

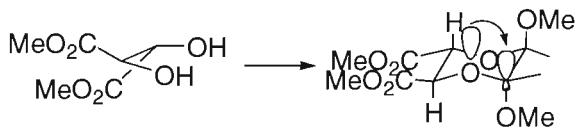



**Figure 23:** Formation of the BDA group.

The result of the stereoinduction was clearly observable from the X-ray crystal structure of the diester **138** (Figure 24).

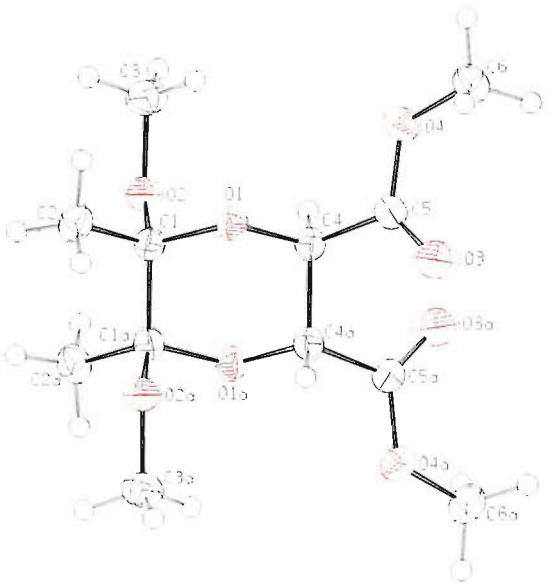


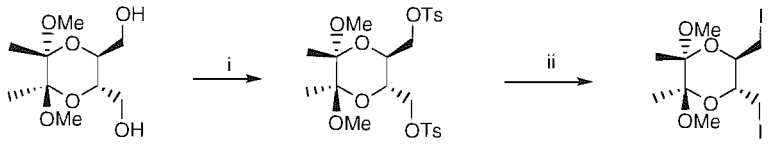
**Figure 24:** X-ray structure of diester **138**.

The next step, the reduction of the diester **138**, is also reported in the literature.[50] However, the described experimental procedure was judged unsatisfactory for large-scale work. For example, a two-week continuous extraction was described to yield 85%. Although there are other examples in the literature[70,71] of this and similar reductions, experimental detail was not provided. Hence this step was optimised, and it was found that workup by addition of saturated aqueous solution of $Na_2SO_4$ provided a fast and efficient (89%) method of working up excess $LiAlH_4$ on small scale. Excess hydride was quenched with the water and the $Na_2SO_4$ is a suitable carrier for the aluminium salts to precipitate. However, this workup proved not to be

convenient on a large scale, and considerable optimisation efforts were necessary. These are described in the next section.

For the subsequent conversion of the diol **139** to the diiodide **191**, two methods were investigated. A two-step process involving tosylation of the diol and then Finkelstein reaction with NaI in acetone (Scheme 50) was only moderately successful.

**Scheme 50:** Synthesis of **191** via a two-step procedure.




**139** **190** **191**

**Reagents and conditions:** i) *p*-TsCl, Py, 0°C, 24 h. 66%; ii) NaI, acetone, reflux, 24 h, 64%.

However, the direct conversion of the diol **139** to the diiodide **191** by the use of triphenyl phosphine, imidazole and iodine proved to be very successful.[72] The workup of this reaction involved the trituration of the triphenylphosphine oxide from the reaction mixture followed by column chromatography. The trituration was later determined to be obsolete as better yields were obtained when this step was omitted.

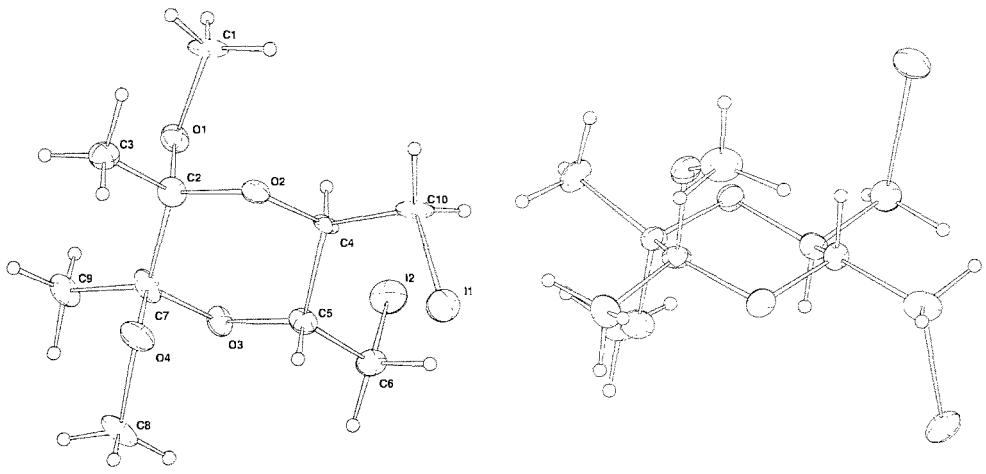



**Figure 25:** X-ray structure of the diiodide **191.**

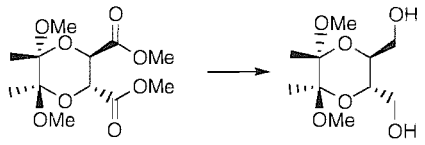
The $C_2$-symmetric nature of the highly crystalline diiodide **191** can be clearly observed from the X-ray crystallographic analysis. The other features that can be observed from the X-ray analysis are the chair conformation of the six-membered ring and the axial nature of the alkoxy groups. Interestingly, it can be seen that the

hydrogen at C5 and the iodine at C6 are positioned in an antiperiplanar arrangement. This has the implication that the elimination should proceed smoothly.

Elimination reactions to form vinyl ethers are precedented in the literature, and a variety of bases have been used for that purpose. The double elimination of the diiodide **191** leading to the diene **183** was first attempted with DBU in toluene.[73] However, no reaction was observed in this case and hence the use of sodium hydride in DMF was attempted.[74] The reaction seemed to proceed to completion as judged by TLC but only a 45% yield was obtained. Fortunately, the use of $^{t}$BuOK in DMF led to the formation of the chiral diene **183** in excellent yield. The diene proved to be a stable compound and no decomposition was observed upon purification. However, it was found to be necessary to store the diene **183** at low temperatures and protected from light or decomposition would take place.

### 2.1.2. Optimisation of the reduction step to 139 on a large scale

As the synthesis of the chiral dienes involves four steps, convenient large-scale synthesis was considered essential, not least to facilitate subsequent investigations into the diastereoselectivity of the Diels-Alder reaction. The only problematic step was the reduction of the diester **138** to the diol **139** on a large scale. When the saturated aqueous $Na_2SO_4$ workup was used on large scale, as described above for small-scale work, it was found that the yield was drastically reduced (66%). Therefore, a different workup procedure was required. A range of different methods of workup were attempted and the results are summarised below (Table 2).



**138** **139**

| Entry | Quantity of ester **138** | Workup conditions | Yield of diol **139** |
|---|---|---|---|
| 1 | 2.0 g 6.8 mmol | 20 mL of Rochelle salt solution (sat) added, separated with ether | 66% |
| 2 | 5g 17mmol | 5 mL of water, 25 mL NaOH solution (sat), 50 mL of water, separate with ether | 94% |
| 3 | 5g 17mmol | 50 mL of NaOH solution (sat) added, 50 mL, water added, separate with ether | 95% |
| 4 | 2.2g 6.8 mmol | 2.2 mL of water, 11 mL 15 % NaOH, 22 mL of water, $MgSO_4$ added and stirred over night, filter, evaporate | 64% |
| 5 | 2.2g 6.8 mmol | 2.2 mL of water, 11 mL 15 % NaOH, $MgSO_4$ added and stirred over night, filter, evaporate | 90% |
| 6 | 20g 68.5 mmol | 10 mL of water, 50 mL 15 % NaOH, $MgSO_4$ added and stirred over night, filter, evaporate | 98% |

**Table 2:** Various sets of work up conditions for the $LiAlH_4$ reduction of diester **139.**

The difficulties in the workup of $LiAlH_4$ mediated reactions relates to the efficient removal of the aluminium waste. There are three well known ways to achieve this: the use of strong acid or strong base, both leading to the dissolution of the aluminium species, and precipitation of aluminium salts, in neutral medium. In strongly acidic media, $Al^{3+}$ is formed, and in strongly basic media, aluminate ($AlO_2^-$) is formed. Under neutral conditions $Al(OH)_3$ is generated, which is insoluble but often does not lead to a granular precipitate. Typically, the desired product is trapped inside the precipitate, leading to reduced yield.

The acidic workup is obviously incompatible with the acid sensitive BDA protecting group.

It was thought that the best manner in which to handle the aluminium salts would be via basic dissolution. When Rochelle salts (sodium potassium tartrate) were used in

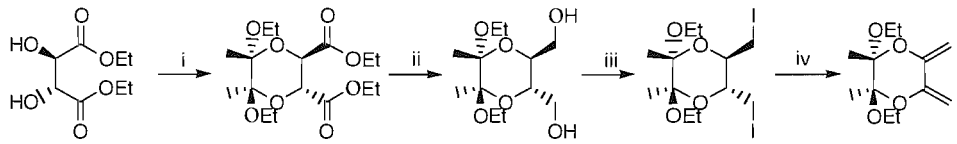
an attempt to dissolve the aluminium salts (entry 1), a low yield (66%) was obtained. Better results (94%) were obtained with the use of saturated sodium hydroxide solution (entries 2 and 3), however, the use of such a strong base on large scale is not necessarily desirable.

When precipitation of the salts was attempted the results obtained were mixed. In entry 4 a small amount of water was added followed by a greater amount of 15% NaOH solution and then an even larger amount of water, this was then dried with $MgSO_4$, stirred overnight and filtered. A low yield (64%) was obtained as this method produced a sticky mass of salts, which was difficult to rinse thoroughly. However, when the second aliquot of water was omitted and the amount of $MgSO_4$ increased, the salts obtained were free flowing and the yield of product was increased dramatically (90%, entry 5). It was thought that the magnesium sulphate not only dried the reaction mixture but also provided a matrix for the sticky aluminium hydroxide to adhere to, which enabled them to be washed more thoroughly, liberating more of the product. This procedure was used as the workup of choice due to its simplicity and high yields, and eventually was optimised to yield 98% on a 20g reaction (entry 6).

## 2.3. Synthesis of diene 184

The synthesis of diene **184** (Scheme 51), which possesses two axial ethoxy groups instead of two methoxy groups, is very similar to the synthesis of diene **183**. The initial protection step was carried out with ethanol instead of methanol,[50] as described in the literature, and proceeded in good yield (92%).

**Scheme 51:** Synthesis of diene **184.**




**192** **193** **194** **195** **184**

**Reagents and conditions:** i) 2,3 Butanedione, CSA, EtOH, TMOF, 65°C, 3 d, 92%; ii) $LiAlH_4$, THF, 0°C, 1 h, 84%; iii) $PPh_3$, imidazole, $I_2$, benzene, reflux, 1 h, 88%; iv) $^tBuOK$, DMF, 0°C, 15 min, 78%.

Reduction of diester **193** to the diol **194** proceeded smoothly in 84% yield using the sodium sulphate solution workup as the synthesis was on a small scale. The diiodide **195** was formed in 88% yield by the direct conversion from the diol **194**. Diiodide **195** was then reacted with $^tBuOK$ to give diene **184** in 78% yield as a light yellow oil.

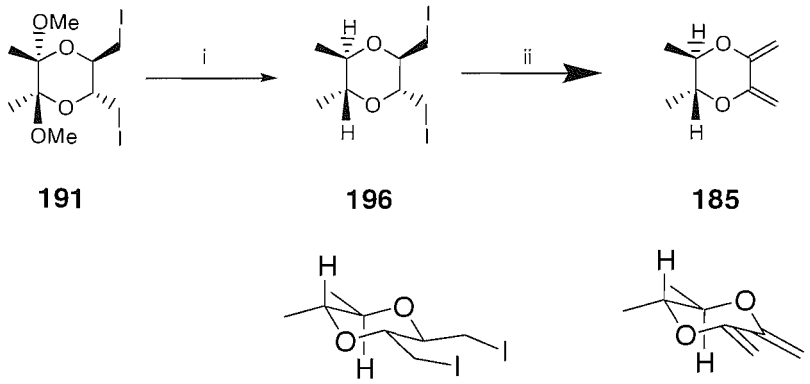
## 2.4. Synthesis of diene 185

For reasons that will be explained in detail in chapter 3, the synthesis of the chiral diene **185** lacking the axial alkoxy groups was desired. The synthesis of diene **185** was based upon the known reduction of the BDA group with triethylsilane and tin tetra chloride.

The diiodide **191** was synthesised as previously described (Scheme 49) and was then subjected to tin tetrachloride and triethylsilane.[75] The diiodide **196** is produced and the NMR spectra show that this product is $C_2$-symmetrical. The conformation of the product **196** should place all of the substituents in an equatorial position (Scheme 52).

The reaction of **196** with potassium *tert*-butoxide in DMF leads to diene **185**. However the diene **185** is volatile and unstable and as such proved difficult to isolate. Following a typical procedure, the yield of the diene **185** was much lower than expected (10%) and the procedure was modified to try and remove more of the contaminating DMF by adding more aqueous washes followed by Kügelrohr distillation. Pleasingly, this procedure gave the diene **185** in better yield (81%) and higher purity (Scheme 52).

**Scheme 52:** Synthesis of a diene lacking alkoxy groups.




**Reagents and conditions:** i) $SnCl_4$, $Et_3SiH$, $CH_2Cl_2$, 0°C, 93%; ii) $^tBuOK$, DMF, 0°C, 81%

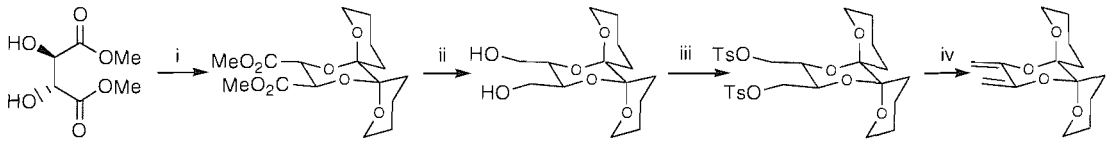
## 2.5. Attempted synthesis of other chiral dienes

In the course of the project other dienes have been synthesised. However, the synthesis of these dienes proved to be cumbersome and unfortunately, not enough substrate could be synthesised in order to investigate the Diels-Alder reaction.

## 2.5.1. Synthesis of diene 186

The synthesis of diene **186** was attempted following the usual diene synthesis (Scheme 53).

**Scheme 53:** Synthesis of a dispoke-protected diene.



**189** **197** **198** **199** **186**

**Reagents and conditions:** i) *bis*-DHP, Toluene, HCl in $OEt_2$, 48h, r.t., 15%; ii) $LiAlH_4$, THF, 1h, 43%; iii) TsCl, Py, 0°C, 18h, 72%; *t*BuOK, DMF, r.t., 20 min, 75%.

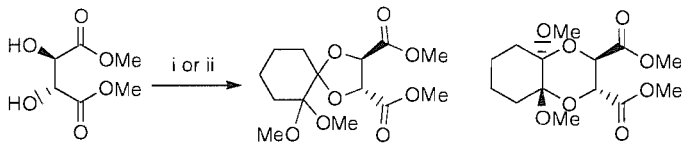
The protection of L-dimethyl tartrate with *bis*-DHP is known[76,77] to occur in dichloromethane saturated with HCl. However, when this method of protection was attempted it was unsuccessful. When L-dimethyl tartrate and *bis*-DHP were dissolved in toluene and treated with a small amount of 1 M HCl in diethyl ether[78] product **197** was obtained in low yield and poor purity. The reduction of the ester was carried out on impure material which was purified after the reaction had been carried out and, thus a lower yield than might be expected was obtained. Tosylation of diol **198** was attempted in order to see if the iodination, which is conducted in benzene, could be replaced with a reaction with less hazardous solvent. However, this reaction and the subsequent elimination proceeded with only moderate yield.

The scale of the reactions was small as the initial protection proceeded with such a poor yield.

## 2.5.2. Synthesis of diene 187

It was thought that the protection of L-dimethyl tartrate with 1,2-cyclohexanedione would prove to be a simple matter, although no literature examples were available.

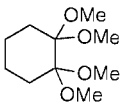
**Scheme 54:** Protection of L-dimethyl tartrate as a CDA.



**189** **200** **201**

62% 4%

**202**



92 7%

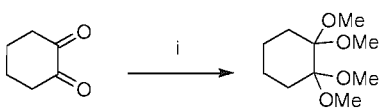
**203**

**Reagents and conditions:** i) Cyclohexanedione **202**, CSA, $CH(OMe)_3$, $CH_3OH$, reflux, 3d, **200** 62%, **201** 4%; ii) 1,1;2,2-tetramethoxycyclohexane **203**, CSA, $CH(OMe)_3$, $CH_3OH$, reflux, 3d, **200** 92%, **201** 7%.

Our original attempt was the protection of L-dimethyl tartrate with cyclohexanedione **202** and CSA in methanol.[52] This produced a yield of 4% of desired product **201** and 62% of the spirocyclic compound **200**. In the case of carbohydrates it has been shown that the six-membered ring is thermodynamically more stable than the five membered ring.[79,80] However, when the compound **200** was resubjected to the reaction conditions, the expected isomerisation did not occur.

1,1:2,2-Tetramethoxycyclohexane **203** has been described as a preferable reagent to cyclohexanedione and can be prepared in methanol using concentrated $H_2SO_4$ (Scheme 55).[79]

**Scheme 55:** Synthesis of 1,1:2,2-tetramethoxycyclohexane **203.**



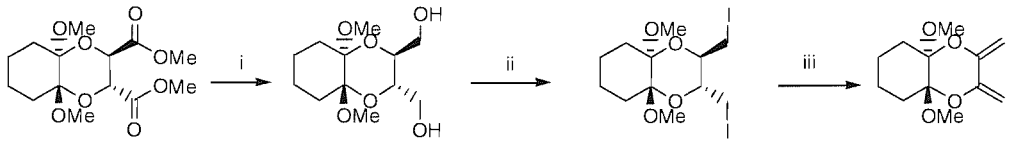
**202** **203**

**Reagents and conditions:** i) Cyclohexanedione **202**, concentrated $H_2SO_4$, $CH(OMe)_3$, $CH_3OH$.

When 1,1:2,2-tetramethoxycyclohexane **203** was used for the protection of L-dimethyl tartrate the yields of **200** and **201** were improved to 92 and 7% respectively.

Protection was also attempted using the tetramethoxycyclohexane and $BF_3.OEt_2$, however, in this instance, only 53% of the undesired product **200** was recovered and none of the desired product.

**Scheme 56:** Synthesis of diene **187.**



**201** **204** **205** **187**

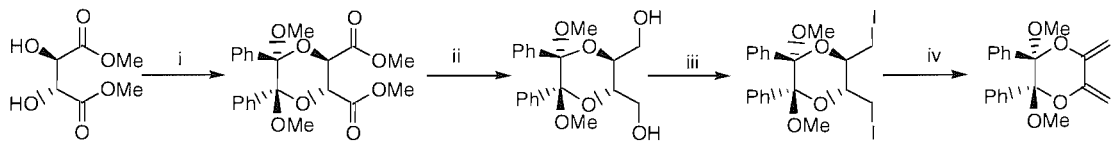
**Reagents and conditions:** i) $LiAlH_4$, THF, 1h, 89%; ii) $PPh_3$, Imidazole, $I_2$, Benzene, reflux, 92%; iii) *t*BuOK, DMF, r.t., 89%.

The reduction of the protected diester **201** proceeded smoothly with an 89 % yield. The iodination of the diol **204** also proceeded with high yield (92%). The double elimination of diiodide **205** provided diene **187** in 89% and high purity.

## 2.5.3. Synthesis of diene 188

Benzil is a highly unreactive ketone and will not form a diacetal system under protic conditions (Scheme 57).

**Scheme 57:** Synthesis of a diene **188**.



**189** **206** **207** **208** **188**

**Reagents and conditions:** i) Benzil, MeOTMS, TMSOTf, $CH_2Cl_2$, 0°c to r.t., 3d, 7.2%; ii) $LiAlH_4$, THF, 1h, r.t., 98%; iii) $PPh_3$, Imidazole, $I_2$, Benzene, Reflux, 1h, 95%; iv) *t*BuOK, DMF, 20 min, 32%.

However, a diacetal of benzil may be formed if a diol is dissolved in dichloromethane and is reacted with methoxytrimethyl silane and trifluoromethane sulfonate.[81] When this methodology is applied to L-dimethyl tartrate a low yielding reaction takes place.

After the initial protection step had taken place, the reduction of the ester **206** was achieved in good yield. Conversion of the diol **207** to diiodide **208** also proceeded smoothly. The elimination of the diiodide to the diene proceeded in poor yield.

## 2.6. Structural analysis

It is expected that the diastereoselectivity in the thermal Diels-Alder reaction involving the dienes with the diacetal auxiliary would arise purely from steric hindrance, without any chelation-directing effects. Hence, in order to predict and explain any selectivity, knowledge about the actual conformation of the diene is necessary. The $C_2$-symmetry of the dienes that were synthesised is obvious from the $^1$H NMR and $^{13}$C NMR spectra. Fortunately diene **183** proved to be crystalline, allowing for crystallographic analysis (Figure 26).

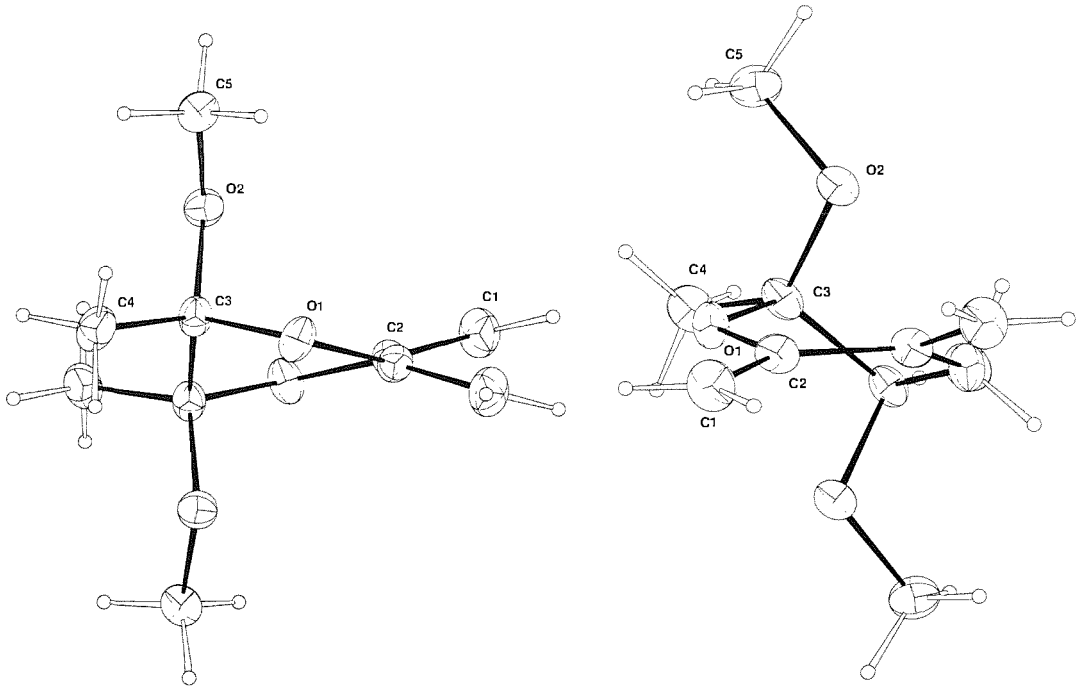



**Figure 26:** Crystallographic analysis of diene **183.**

The obtained structure clearly shows the six-membered ring adopting a half-chair conformation, with *pseudo*-axial methoxy groups. The diene moiety has a 1-4 dienic distance of 3.04Å and appears to have a helical nature, with a twist angle of 30.02°.

The helicity of the diene results in a loss of conjugation between the individual alkenes. This can be conformed by analysis of the UV-spectrum. It is, therefore, expected that both the $\lambda_{max}$ value and the molecular extinction coefficient are decreased compared to typical values of 2,3-butadiene systems (Table 3). The obtained values for $\lambda_{max}$ matched well with the reported data[82] for known outer ring

systems. The extinction coefficient is seen to decrease from the acylic diene to the cyclic dienes as would be expected.

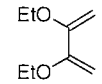
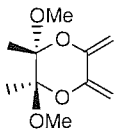
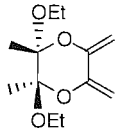
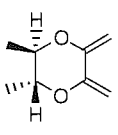
| |  |  |  **183** |  **184** |  **185** |
|---|---|---|---|---|---|
| $\lambda_{max}$ | 225 nm[82] | 254 nm[82] | 254 nm | 254.5 nm | 254 nm |
| ε | 16218 | 6456 | 6543 | 6069 | 23392 |

**Table 3:** UV spectral detail for the chiral dienes and for literature examples.

Unfortunately, neither of the dienes **184** or **185** were crystalline, but the obtained values for $\lambda_{max}$ and ε indicate that the diene moiety also was present as a helix. For **185**, ε was much larger and as this result is anomalous. Therefore, this result is viewed as uncertain as the unstable compound **185** could have degraded, changing the concentration of the solution that was measured and giving rise to other UV reactive degradation products.

It was attempted to obtain information about the absolute configuration of the diene helix from the Cotton effect, but the spectra obtained were complex and no conclusions could be drawn from this data.

## 2.7. Conclusions

Six chiral dienes have been synthesised in enantiopure form, each in four steps from dialkyl tartrate. The synthesis of the dienes **183-185** was successfully optimised on large scale. Notably, a convenient workup procedure for large scale $LiAlH_4$ mediated reduction step was developed. All steps proceeded in excellent yield.

However, the synthesis of dienes **186-188** was only achieved on small scale, with the main reason being difficulties in the protection of dimethyl tartrate.

The structure of diene **183** was determined by X-ray crystallography and the most striking feature of the diene **183** was the apparent helicity of the diene moiety. Further evidence of this structural feature can be found in the UV data and diene **184** can also be seen to have a helical nature from this spectroscopic method.

# Chapter 3: Diels-Alder reactions of the chiral dienes

## 3.1 Introduction

The dienes that have been synthesised are $C_2$-symmetric and this leads to the faces of the dienes being homotopic. Therefore, whether the top or bottom face of the dienophile is approached is irrelevant.

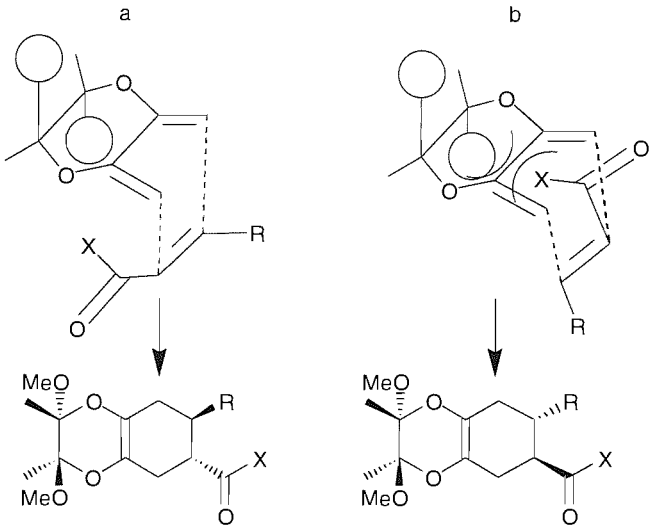



**Figure 27:** *Endo* approaches of the dienophile.

Figure 27 shows what is expected to be the favoured *endo* transition state (a) and the disfavoured *endo* transition state (b). It can be seen that the two transition states give rise to two diastereomeric products.

However, there is a possibility that an *exo* transition state may play a role in the reaction if the energy difference between *exo* and *endo* is not large enough.

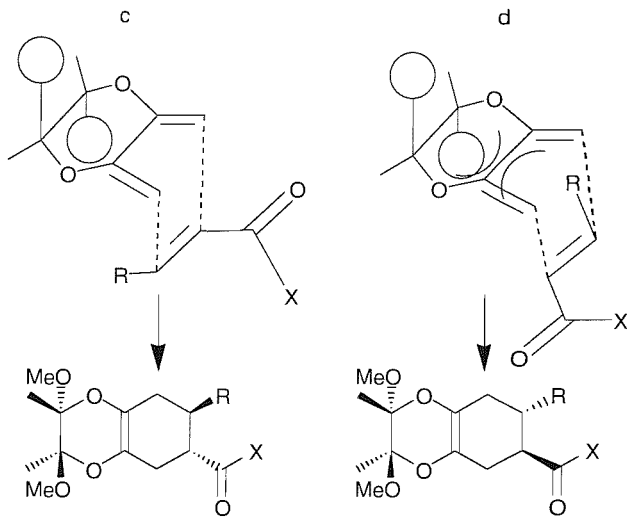



**Figure 28:** *Exo* approaches of the dienophile.

The favoured *exo* transition state (c) gives rise to the same diastereomer as the favoured *endo* transition state (a). It is unlikely that the disfavoured *exo* transition state (d) will contribute to the products obtained as it is both energetically and sterically unfavourable.

### 3.1.1. Thermal Diels-Alder reaction of diene 183: Results

When the diene **183** had been synthesised the thermal Diels-Alder reaction could be investigated. The first experiments in this area were carried out in refluxing hexane (0.02 M) and the results are shown below (Table 4).

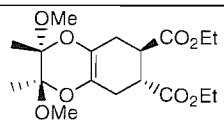
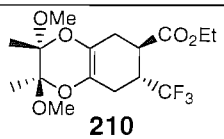
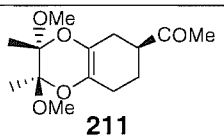
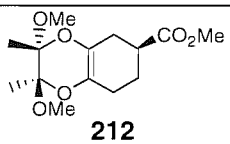
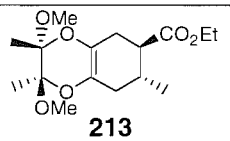
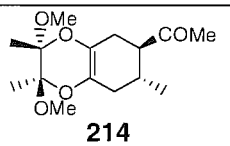
| | | **0.02 M Hexane/reflux** | **0.02 M Toluene/reflux** |
|---|---|---|---|
| **Dienophile** | **Diels-Alder products*** | **Yield/ Selectivity ($^{13}$C NMR)** | **Yield/ Selectivity ($^{1}$H NMR)** |
| Diethyl fumarate |  **209** | 73%/10:1[a] | 67%/4.1:1[a] |
| Ethyl-4,4,4-trifluorocrotonate |  **210** | 61%/5.3:1[a] | 71%/3.7:1[a] |
| Methyl vinyl ketone |  **211** | No reaction | 98%/2:1[b] |
| Methyl acrylate |  **212** | No reaction | 63%/1.8:1[b] |
| Ethyl crotonate |  **213** | No reaction | 28%/3:1[b] |
| 3-Pentene-2-one |  **214** | No reaction | 38%/3.2:1[b] |

**Table 4:** Early results of the Diels-Alder reaction: [a] 24h, [b]72h. * Isolated as mixture of diastereomers, major diastereomer shown. 2 equiv. dienophile used in all reactions.

Only the most reactive dienophiles reacted with diene **183** under these conditions. This shows that the reaction of diene **183** is a normal electron demand reaction, as would be expected. It was thought that an increase in temperature would cause the other dienophiles to react and hence the reaction solvent was changed to toluene. The reaction of the more electron rich dienophiles occurred in refluxing toluene, although the yield obtained was less than satisfactory.

The reaction obviously required optimisation; in addition the accuracy of the method of determining the selectivity of the reaction (estimation from NMR data) needed improvement. The reaction was carried out at a higher concentration (0.05 M) with a higher amount of dienophile (8 equiv.). The ratio of diastereomers was determined by GC-analysis of the crude reaction mixture. In all cases, the observed retention times of the diastereomers were verified by comparison with a sample of the diastereomeric mixture, obtained after column chromatography and/or preparative HPLC. (Table 5).

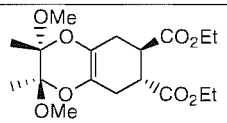
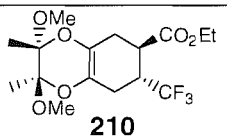
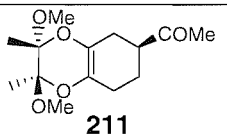
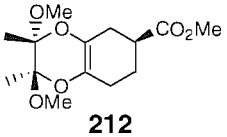
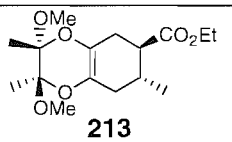
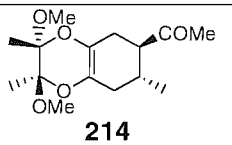
| **Dienophile** | **Diels-Alder products*** | **Time h** | **0.05 M Toluene/reflux** |
|---|---|---|---|
| Diethyl fumarate |  **209** | 24 | 67%/86:14 |
| Ethyl-4,4,4-trifluorocrotonate |  **210** | 24 | 71%/79:21 |
| Methyl vinyl ketone |  **211** | 24 | 82%/56:43 |
| Methyl acrylate |  **212** | 24 | 74%/71:30 |
| Ethyl crotonate |  **213** | 24 | 75%/91:9 |
| 3-Pentene-2-one |  **214** | 24 | 80%/89:11 |

**Table 5:** Optimised thermal Diels-Alder reaction. * Isolated as mixture of diastereomers, major diastereomer shown. 8 equiv. dienophile used for all reactions.

The yields have all been improved and the method of determining the selectivity of the reaction was seen to be repeatable. However, the use of such an excessive amount of dienophile was deemed to be overly costly and thus another set of conditions was attempted. The concentration was further increased (0.25 M), while the number of equivalents of dienophile was reduced (2 equiv.). At this high concentration it was discovered that it was necessary to base-wash the glassware and protect the reaction from light as otherwise decomposition of the diene and subsequent loss of yield occurred (Table 6, Table 7).

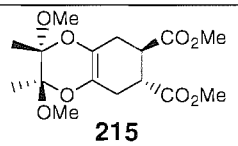
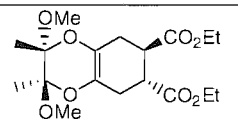
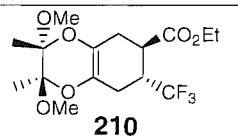
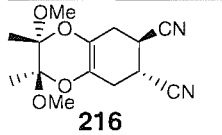
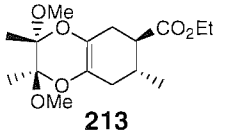
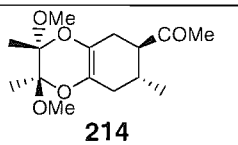
| Entry | Dienophile | Diels-Alder products* | Temperature °C | 0.25 M Toluene |
|---|---|---|---|---|
| 1 | Dimethyl fumarate |  **215** | 111 | 88% 88:12 |
| 2 | Diethyl fumarate |  **209** | 70 | 92% 89:11 |
| 3 | Ethyl-4,4,4-trifluorocrotonate |  **210** | 70 | 86% 82: 18 |
| 4 | Fumaronitrile |  **216** | 111 | 82% 72:28 |
| 5 | Ethyl crotonate |  **213** | 111 | 58% 91:9 |
| 6 | 3-Pentene-2-one |  **214** | 111 | 62% 89:11 |

**Table 6:** Thermal Diels-Alder reaction of diene **183** with disubstituted dienophiles.* Isolated as mixture of diastereomers, major diastereomer shown. 2 equiv. dienophile used for all reactions.

The isolated yields of the products were good to excellent (Table 6). Unfortunately, the obtained diastereomeric products could not be separated via column chromatography or preparative HPLC. In all but one of the cases the identity of the diastereomeric mixture was confirmed by combustion analysis.

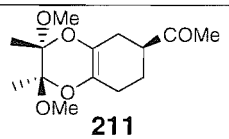
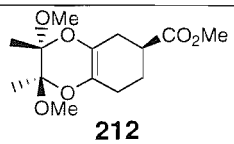
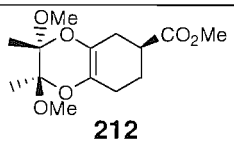
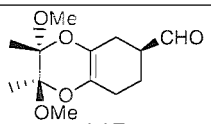
| Entry | Dienophile | Diels-Alder products* | Temperature °C | 0.25 M Toluene |
|---|---|---|---|---|
| 1 | Methyl vinyl ketone |  **211** | 111 | 95% 60:40 |
| 2 | Methyl acrylate |  **212** | 70 | 75% 70:30 |
| 3 | Methyl acrylate |  **212** | 111 | 99% 69:31 |
| 4 | Acrolein |  **217** | 111 | 88% 55:45 |

**Table 7:** Thermal Diels-Alder reaction of diene **183** with mono-substituted dienophiles.* Isolated as mixture of diastereomers, major diastereomer shown. 2 equiv. dienophile used for all reactions.

The obtained diastereomeric product ratios vary from low (60:40, Table 7, entry 1) to moderate (91:9, Table 6, entry 5)

The nature of the substituents present has an effect upon the yield of the reaction. When both substituents are electron withdrawing (Table 6, entries 1-4) the reaction proceeds in good yield but when an electron withdrawing group and an electron-donating group are present (Table 6 ,entries 5 and 6) the reaction gives a much lower yield. When only one substituent is present (Table 7, entries 1-4) the yield is high.

### 3.1.2. Selectivity of the Diels-Alder reaction

The diastereoselectivity that has been observed seems to depend upon the dienophile. When the dienophile has *trans* substituents (Table 6, entries 1–6) the diastereoselectivity is acceptable. However, when only one substituent is present the diastereoselectivity is poor.

The identification of the relative stereochemistry of the major isomer was a very important part of the project. The expected mode of attack is shown below:

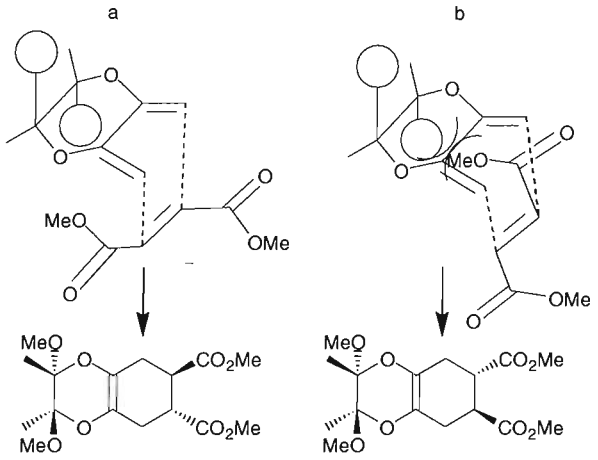



**Figure 29:** Transition state for formation of adduct **215.**

The favoured transition state **a** is shown in figure 29, this transition state leads to the product shown as **215**.

Fortunately, product **215** is a crystalline material allowing for X-ray crystallographic analysis (Figure 30).

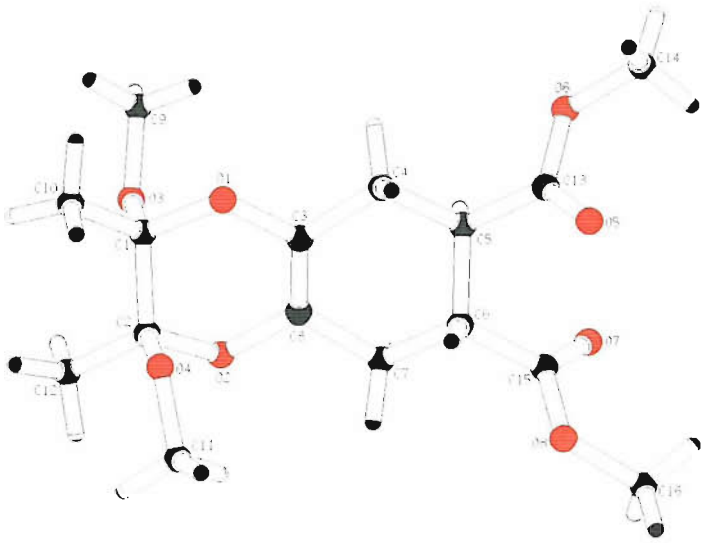


**Figure 30:** X-ray crystallographic analysis of adduct **215**.

It can be seen that the relative stereochemistry of the major isomer is consistent with the product predicted by the favoured transition state.

### 3.1.3. Thermal Diels-Alder reaction of diene 184

The thermal Diels-Alder reaction of diene **184** was carried out under the same optimised conditions that were found for the diene **183** (Table 8).

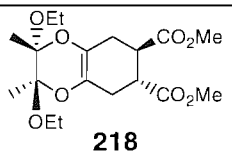
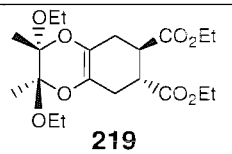
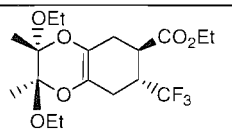
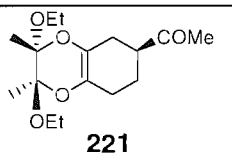
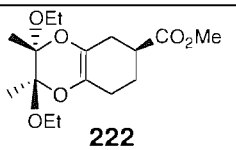
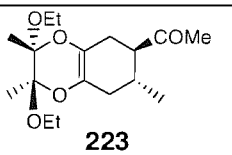
| Entry | Dienophile | Product* | 0.25 M Toluene |
|---|---|---|---|
| 1 | Dimethyl fumarate |  **218** | 75%/85:15 |
| 2 | Diethyl fumarate |  **219** | 83%/83:17 |
| 3 | Ethyl-4,4,4-trifluorocrotonate |  **220** | 56%/82:18 |
| 4 | Methyl vinyl ketone |  **221** | 93%/63:37 |
| 5 | Methyl acrylate |  **222** | 99%/69:31 |
| 6 | 3-Pentene-2-one |  **223** | 48%/>98:2 |

**Table 8:** Thermal Diels-Alder reaction of diene **184.** *Isolated as mixture of diastereomers, major diastereomer shown. 2 eq of dienophile used in all reactions.

It can be seen that the reactions with the fumarate type dienophiles (Table 8, entries 1 and 2) proceed in good yield and good selectivity. However, when compared to the equivalent reaction of diene **183** the yield was low (Table 6, entries 1 and 2). Table 8, entry 3, shows the reaction of ethyl-4,4,4-trifluorocrotonate. This reaction did not go as well as would be expected from the result from the methoxy series (Table 6, entry 3) in terms of yield.

Entries 4 and 5 show the results from the thermal Diels-Alder reaction of methyl vinyl ketone and methyl acrylate. As would be expected from the results in the methoxy series (Table 7, entries 1-3) these reactions went in excellent yield but poor selectivity.

The reaction of 3-pentene-2-one and **184** (Table 8, entry 6) gave a fair yield and much higher selectivity than was expected from the methoxy series (Table 6, entry 6).

The selectivity of the ethoxy series, when compared with their methoxy analogues, however, does not seem to have been improved as much as expected. Only one reaction (Table 8, entry 8 vs Table 6, entry 6) has shown a dramatic improvement in selectivity, and some have shown less selectivity than in the methoxy series (Table 8, entry 1 vs Table 6, entry 1).

### 3.1.4. Thermal Diels-Alder reaction of diene 185

We desired to gauge the effect of the axial R group on the diastereoselectivity more closely. It was decided to synthesise diene **185** which did not have the axial alkoxy groups.

With the diene **185** available the Diels-Alder reaction could be investigated. The thermal Diels-Alder reaction of the diene follows the basic trends that have been observed before in the methyl and ethyl series, in that dienophiles with two electron withdrawing groups (table 9, entries 1 and 2) have good yield and selectivity, dienophiles with only one electron donating group (Table 9, entries 3 and 4) show poorer selectivity and the dienophiles with one withdrawing and one donating group (Table 9, entry 5) show good selectivity but poorer yields.

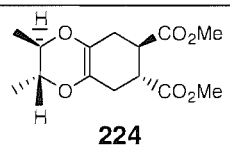
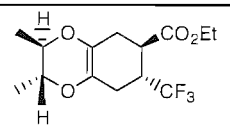
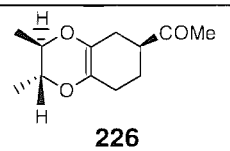
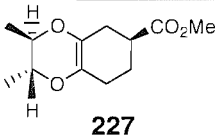
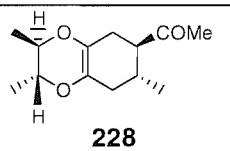
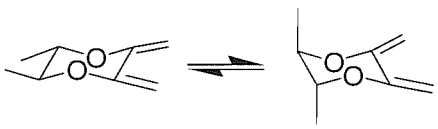
| Entry | Dienophile | Product* | 0.25 M Toluene |
|---|---|---|---|
| 1 | Dimethyl fumarate |  **224** | 64.8% 73:27 |
| 2 | Ethyl-4,4,4-trifluorocrotonate |  **225** | 97% 69:31 |
| 3 | Methyl vinyl ketone |  **226** | 64% 62:38 |
| 4 | Methyl acrylate |  **227** | 91%64:36 |
| 5 | 3-Pentene-2-one |  **228** | 52% 72:28 |

**Table 9:** Thermal Diels-Alder reaction of diene **185.** *Isolated as a mixture of diastereomers. 2 eq. of dienophile used in all reactions.

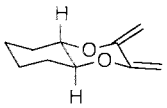
The selectivity of the Diels-Alder reaction of the diene **185** are lower than those seen in the previous two series. The removal of the axial alkoxy groups, and hence the anomeric stabilisation, has the consequence that the diene may exist in two conformations (Figure 31). Conformation **a** has the vicinal methyl groups in the equatorial positions, however, ring inversion could take place giving rise to conformation **b**.



a b

**Figure 31:** The two possible conformations of diene **185.**

This is likely to occur at reflux temperature and could be the cause of the observed selectivity in the Diels-Alder reaction. This could have been confirmed by the synthesis of diene **229**.



229

**Figure 32:** Structure of diene **229.**

Unfortunately, the difficulties encountered in the synthesis of the precursors of this compound meant that there was not enough material to complete this synthesis.

### 3.1.5. Conclusions about the thermal Diels-Alder reaction

The thermal Diels-Alder reactions of the dienes proceed in good to moderate yield and show diastereoselectivity, ranging from 91:9 to 1.7:1. This selectivity seems to be mainly influenced by the steric bulk of the remote chiral centre and the steric demand of the dienophile.

The dienes **183** and **184** show a similar level of stereoinduction, whereas diene **185** shows a reduced level of stereoselectivity in the Diels-Alder reaction. It is believed that this shows the role that the steric interactions play in the transition state and that the selectivity does not arise from the helical nature of the diene.

In all of the diene series disubstituted dienophiles show the highest diastereoselectivity, whilst singly substituted dienophiles show much poorer selectivity. The electronic nature of the substituents present has an effect upon the yield of the reaction.

## 3.2. Lewis acid Catalysed Diels-Alder reaction

It has been shown that Lewis acids may have a dramatic effect upon the outcome of the Diels-Alder reaction. As the selectivity in the thermal Diels-Alder reaction for the dienes **183**, **184** and **185** has proved to be variable, the use of Lewis acids would be advantageous.

### 3.2.1. Lewis acid catalysed Diels-Alder reaction of diene 183

It is desirable for the Diels-Alder reaction to be catalysed by Lewis acids so that the reaction can take place at lower temperatures. This should then lead to an increase in the observed selectivity.

The reaction of diene **183** in the presence of a Lewis acid proved to be problematic. The diene **183** showed a propensity to decompose in the presence of Lewis acids such

as boron trifluoride diethyl etherate complex and scandium triflate. However, the reaction of the diene **183** at –78°C with a dienophile in the presence of diethyl aluminium chloride (20 mol%) produced Diels-Alder adducts with enhanced selectivity (Table 10).[83]

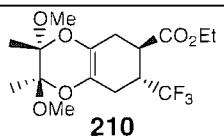
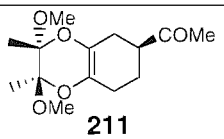
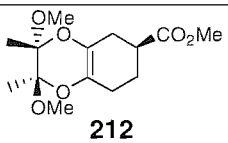
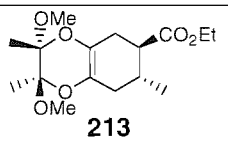
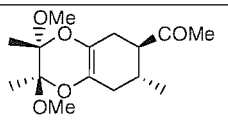
| Entry | Dienophile | Diels-Alder products* | Thermal reaction | Lewis acid reaction |
|---|---|---|---|---|
| 1 | Ethyl-4,4,4-trifluorocrotonate |  **210** | 86% 82:18 | Reaction fail |
| 2 | Methyl vinyl ketone |  **211** | 95% 60:40 | 62% 66:34 |
| 3 | Methyl acrylate |  **212** | 75% 70:30 | 59% >98:2 |
| 4 | Ethyl crotonate |  **213** | 55% 91:9 | Reaction fail |
| 5 | 3-Pentene-2-one |  **214** | 62% 89:11 | 45% 94:6 |

**Table 10:** $Et_2AlCl$ catalysed Diels-Alder reaction of **183.** *Isolated as mixture of diastereomers, major diastereomer shown. 2 eq. of dienophile used in all reactions.

Unfortunately, reaction with ethyl-4,4,4-trifluorocrotonate and ethyl crotonate did not yield results. The reaction with methyl vinyl ketone and 3-pentene-2-one has only shown a modest improvement in selectivity. Reaction with methyl acrylate, however, shows a very large increase in selectivity; improving by virtually 30%. However, the yields of these reactions are relatively low in comparison to the thermal reactions.

### 3.2.2. The Lewis acid catalysed reaction of diene 184

The Lewis acid catalysed Diels-Alder reaction of diene **184** was carried out under the same conditions as the reaction of diene **183**.

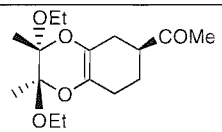
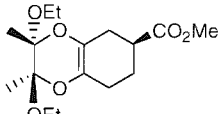
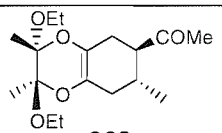
| Entry | Dienophile | Diels-Alder products* | Thermal reaction | Lewis acid reaction |
|---|---|---|---|---|
| 1 | Methyl vinyl ketone |  **221** | 93%/63:37 | 38%/67:33 |
| 2 | Methyl acrylate |  **222** | 99%/69:31 | 49%/>98:2 |
| 3 | 3-Pentene-2-one |  **223** | 48%/>98:2 | 45%/>98:2 |

**Table 11:** $Et_2AlCl$ catalysed Diels-Alder reaction of **184.** *Isolated as mixture of diastereomers, major diastereomer shown. 2 eq. of dienophile used in all reactions.

The Lewis acid catalysed reactions are similar to the reactions that were observed in the thermal reaction of diene **184**. The reaction of methyl vinyl ketone showed a small increase in selectivity, while methyl acrylate exhibited a much larger increase in selectivity. It is difficult to gauge the effect of the Lewis acid upon the reaction of 3-pentene-2-one as the observed selectivity in the thermal reaction is already large.

### 3.2.3. Lewis acid catalysed Diels-Alder reaction of diene 185

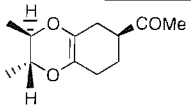
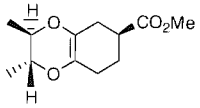
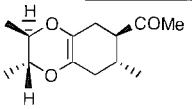
| Entry | Dienophile | Diels-Alder products* | Thermal reaction | Lewis acid reaction |
|---|---|---|---|---|
| 1 | Methyl vinyl ketone |  **226** | 64% 62:38 | 65% 77:23 |
| 2 | Methyl acrylate |  **227** | 91%64:36 | 49% 61:39 |
| 3 | 3-Pentene-2-one |  **228** | 52% 72:28 | 39% 80:20 |

**Table 12:** $Et_2AlCl$ catalysed Diels-Alder reaction of **185**. *Isolated as mixture of diastereomers, major diastereomer shown. 2 eq. of dienophile used in all reactions.

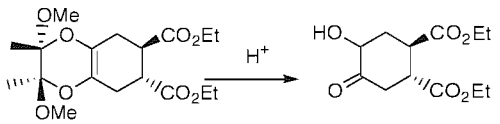
The selectivities of the products obtained from the Lewis acid catalysed Diels Alder reaction of diene **182** shows little difference to the selectivities obtained from the thermal reaction.

This means that the ring inversion thought to be responsible for the stereoselectivity, must be operating at a low temperature.

### 3.2.4. Conclusions about the Lewis-acid catalysed Diels-Alder reaction

The diastereoselectivity of the Lewis acid catalysed reaction shows improvement over the selectivity achieved in the thermal Diels-Alder reaction. Methyl acrylate shows a very high improvement in selectivity, whilst the other dienophiles investigated show a much more modest improvement. The yields obtained in the Lewis acid catalysed reaction are lower than the yields obtained in the thermal reaction.

## 3.3. Deprotection of 209




**209** **230**

**Scheme 58:** Deprotection of the BDA protection group.

It was hoped that the deprotection of the Diels-Alder adducts would lead to easily accessed chiral building blocks. The standard conditions for deprotection of the butane diacetal group is to dissolve the adduct in aqueous trifluoroacetic acid. Unfortunately, in this instance this led to a complex mixture of compounds, thus these conditions were not suitable.

It was thought that trifluoroacetic acid was too strong an acid, and this was degrading the molecules, so milder deprotection conditions were sought. The use of camphor sulfonic acid in a variety of solvents (EtOH, MeOH, and toluene) did not give any success in the deprotection of adduct **209**. Ethanedithiol in the presence of boron trifluoride diethyl etherate does seem to have deprotected the butane diacetal group. However, it is believed that the ethanedithiol then proceeds to react with the revealed ketone as a complex mixture of compounds is recovered. The reaction of iron trichloride[84] with the Diels-Alder product did yield a small amount of deprotected

product (19%), however, attempts to improve the yield of the deprotection with the inclusion of two equivalents of methanol failed. Thus the deprotection of the Diels-Alder adducts is not an easy process and further work would be required to produce the desired chiral building blocks.

## 3.4. Conclusions

The thermal and Lewis acid catalysed Diels-Alder reactions of the dienes **183**, **184** and **185** have been carried out. From the results it seems that the steric interactions between the diene and dienophile determine the diastereoselectivity that is observed in the products. The thermal reaction tends to show higher yields than the Lewis acid catalysed Diels-Alder reaction, but the Lewis acid catalysed reaction can show enhanced selectivity. Deprotection of the Diels-Alder adducts has been achieved in low yield as this transformation seems to be non-trivial.

# Chapter 4: Full and partial differentiation of tris-1,1,1-(hydroxymethyl)ethane via indirect methodology

## 4.1. Introduction

Tris-1,1,1-(hydroxymethyl)ethane $CH_3C(CH_2OH)_3$ **231** and pentaerythritol $C(CH_2OH)_4$ are poly-functional, symmetrical, low molecular weight compounds and are available as very cheap bulk materials. They have been employed as starting materials for processes such as low-molecular weight scaffolds in combinatorial chemistry,[85-87] as initiators for polymerisation reactions,[88,89] as building blocks for dendrimer synthesis[90,91] and for a range of other purposes.[92-96] In most instances, a chemical differentiation of the alcohol functionalities is required before use in the aforementioned applications.

There are three different levels of differentiation for **231** that are commonly seen in the literature, and these are illustrated in Figure 33.

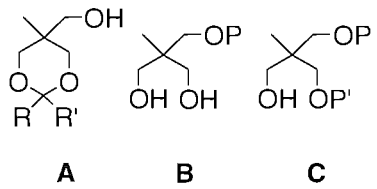
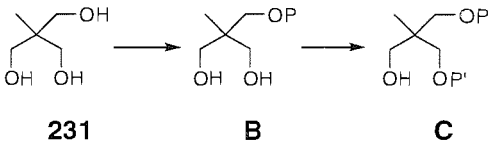



**Figure 33:** Differentiation levels of tris-1,1,1-(hydroxymethyl)ethane.

In Type A differentiation, two of the alcohol functionalities are protected in a cyclic structure, leaving one alcohol functionality free for reaction. When only one alcohol functionality is protected, then Type B differentiation has been achieved. Type C differentiation is similar to Type A in that two of the alcohol functionalities are protected, however, in this case the protecting groups are different, resulting in a chiral quaternary carbon.

Two types of differentiation can be considered: direct and indirect differentiation. Direct differentiation protocols (Scheme 59) involves a monofunctionalisation of a substrate, either the triol **231** or diol **B**. Direct differentiation of **231** leads to type B structures. There are surprisingly few examples of this in the literature. Monotritylation using 5.5 equiv of **231**, in 68% yield.[97] Monoalkylation of **231** via a Williamson alkylation was reported in good yield as well (80%).[98] With a weak base

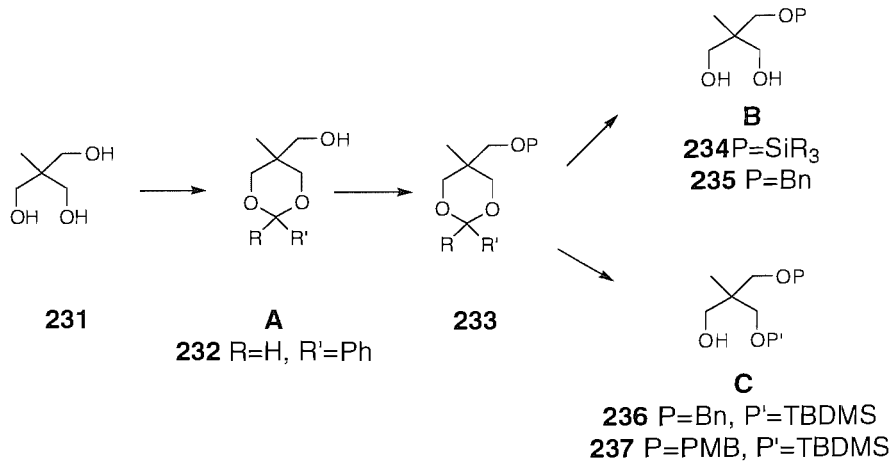
($K_2CO_3$) and a reactive alkylating agent (allyl bromide), a 6:1 ratio of mono- to diallylation product was achieved in 85% combined yield.[99]




**Scheme 59:**Direct differentiation of tris-1,1,1-(hydroxymethyl)ethane.

Type C products were obtained from Type B structures. Monoalkylation (All, Bn) proceeds in moderate to good yields (56%, 76% respectively).[88,99] Monoesterification (Ac, $C(O)CMe_2Br$) was achieved in good yields (77-78%).[89,99] This methodology would give rise to Type C differentiated products in two steps from **231** with both protection groups still present in the final molecule.

An indirect differentiation strategy involves temporary protection (Scheme 60). The most common protection is that of an acetal. This leads to a Type A differentiation giving **232**. Protection of the remaining alcohol functionality is now possible, leading to **233**. Complete removal of the acetal group gives rise to Type B differentiation. Following this methodology monosilylated product **234** has been synthesised.[88,89] This differentiation method has also been applied to dendrimer synthesis with **231** as a building block (where, in this case, P represents attachment to the dendrimer core.[90,91] Alternatively, Type B differentiated product **235** can be obtained directly from **232** by reductive acetal-opening with $LiAlH_4$-$BF_3$.

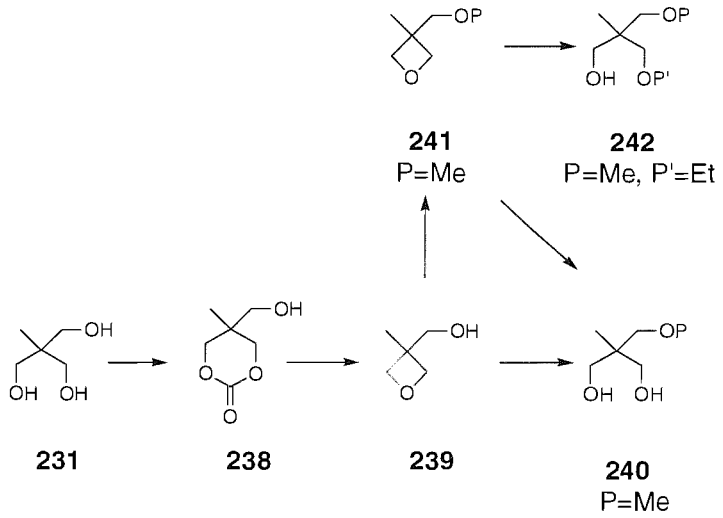



**Scheme 60:** Indirect differentiation methods for tris-1,1,1-(hydroxymethyl)ethane.

When **233** is subjected to reductive acetal cleavage, the Type C product is obtained in a three-step sequence. Following this methodology, the synthesis of Type C

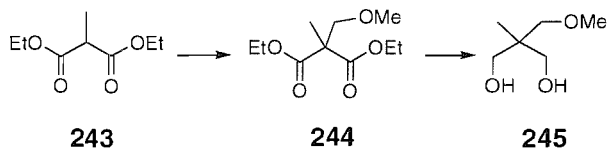
products **236** and **237** via DIBAl-H cleavage of the corresponding benzylidene or paramethoxy benzylidene acetals has been reported. [100]

Triol **231** can also be protected as cyclic carbonate **238.** When carbonate **238** is subjected to pyrolysis conditions oxetane-containing ring **239** is formed (Scheme 61).[95,101]




**Scheme 61:** Alternate indirect differentiation.

Acid catalysed opening of the oxetane ring with an alcohol such as methanol would lead to the methyl ether **240** in three steps. Alternatively the free hydroxyl may be protected with an alkyl halide to form ether **241** which may then either be ring opened with an alcohol go give rise to Type C differentiated **242** in four steps or subjected to hydrolysis to give rise to **240**. As the alcohol must be used as solvent in both of the ring opening steps there are obvious problems with the scope of this reaction pathway. Another method for the synthesis of (alkylated) Type B differentiation products was achieved starting from diethyl methyl malonate **243** (Scheme 62). Alkylation with chloromethyl methyl ether gives rise to **244**, which subsequently is reduced to give **245**.[92]




**Scheme 62:** Formation of type B molecule from diethyl methyl malonate.

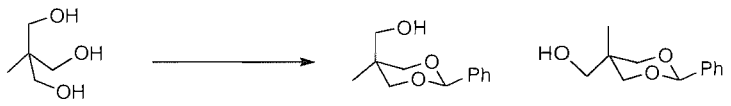
The direct differentiation protocol obviously involves fewer steps than the indirect methodology, however, the indirect differentiation of **231** can be of use if substitution is desired that cannot be introduced via monofunctionalisation.

As part of a different project being carried out within the group, in the last period of this PhD an indirect differentiation protocol was investigated utilising chemoselective reactions.

## 4.2. Results and discussion

### 4.2.1 Indirect differentiation of tris-1,1,1-(hydroxymethyl)ethane

The indirect differentiation of tris-1,1,1-(hydroxymethyl)ethane started with the protection of **231** as a benzylidene acetal. There are several conditions that have been described in the literature and these are shown below (Table 13).




**231** **232a** **232b**

| Entry | PhCHO (equiv) | Conditions | Yield (%) | c/t ratio | ref |
|---|---|---|---|---|---|
| 1 | 1.0 | HCl (cat), $H_2O$, 70-80°C, 3h | 60 | [a] | 102 |
| 2 | 2.2 | Toluene, pTSA (cat), Dean&Stark, 6h | 66 | [a] | 103 |
| 3 | 1.05[b] | THF, pTSA (cat), r.t., 3h | 74 | [a] | 88,89 |
| 4 | 5.9 | $ZnCl_2$ (0.9 equiv), r.t., 12h | 81 | 7:1 | 96 |

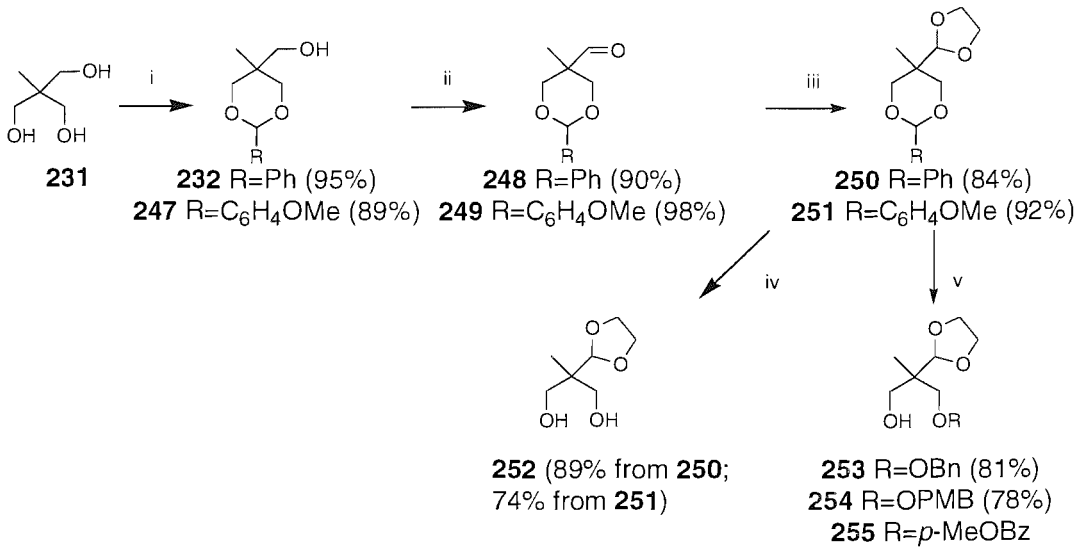
**Table 13:** Reaction of tris-1,1,1-(hydroxymethyl)ethane with benzaldehyde.

[a] not determined
[b] benzaldehyde dimethyl acetal was used

When the reaction was performed in aqueous medium (entry 1), the acetal product was reported to precipitate from the reaction mixture, albeit with a yield of only 60%. Benzaldehyde dimethyl acetal (entry 3), though still cheap, is five times as expensive as benzaldehyde itself. It was also thought that, for large scale work, the use of zinc (II) chloride (entry 4) was impractical due to a workup that was described as difficult.[96]

Hence it was decided to optimise the acetal formation reaction (Scheme 63).

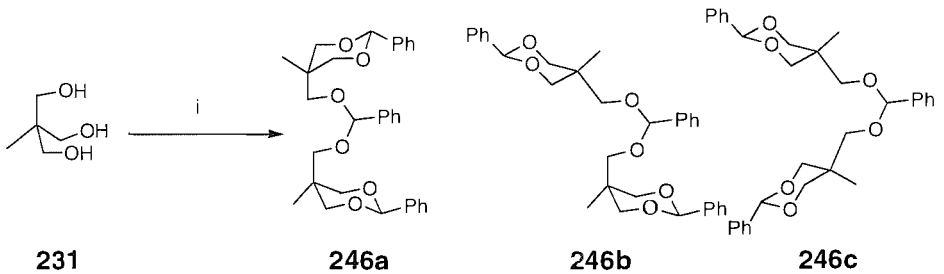
**Scheme 63:** Indirect differentiation of tris-1,1,1-(hydroxymethyl)ethane.




**Reagents and conditions:** (i) ArCHO, PPTS, toluene, reflux (Dean & Stark), 1 h. (ii) $SO_3$.py, DMSO, $Et_3N$, $CH_2Cl_2$, 0°C, 3–6 h. (iii) $TMSOCH_2CH_2OTMS$, TMSOTf, $CH_2Cl_2$, 0°C, 1 h. (iv) $Pd(OH)_2/C$, MeOH, r.t., 18 h. (v) $BH_3.SMe_2$, TMSOTf, $CH_2Cl_2$ –78°C, 3h.

Refluxing **231** and benzaldehyde (1.5 equiv) in toluene with PPTS as catalyst and $MgSO_4$ to bind the liberated water[104] returned only 43% of the desired material. When these conditions were used in conjunction with a Dean & Stark trap, a mixture of *cis* and *trans* **232** was formed. However, the remaining primary alcohol subsequently reacted with excess benzaldehyde to form the corresponding acyclic acetal "dimer" as a mixture of isomers, which could be separated by extensive preparative HPLC (Scheme 64).

**Scheme 64:** Synthesis of "dimeric" species.




**Reagents and conditions:** (i) 2.2 eq ArCHO, PPTS, toluene, reflux (Dean & Stark), 18 h.

Hence, when a limiting amount of benzaldehyde was used, subsequent acetal formation involving the free alcohol in **232** did not take place, and a 95% yield was obtained, with a 3.8:1 ratio of *cis/trans* isomers.

Structural assignment of the isomers was easily achieved based on the characteristic downfield shift of the equatorial methyl group of the *cis* isomer compared to the upfield shift of the axial methyl group of the *trans* isomer.[105]

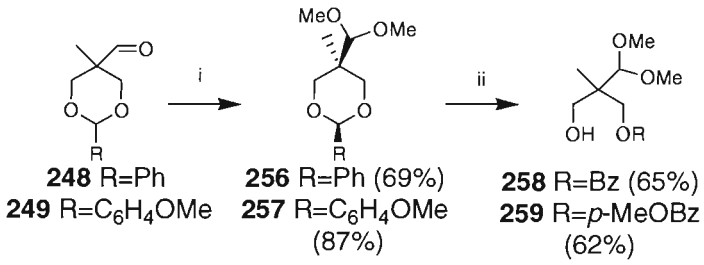
Reaction of **231** with *p*-anisaldehyde under identical conditions provided the acetal **247** as a *cis/trans* mixture of isomers in good yield. The Parikh-Doering oxidation[106] of these acetals was carried out in excellent yield, however, the subsequent protection of the aldehyde as 1,3-dioxolane acetals proved troublesome. Reaction of **248** with 1,2-ethanediol in toluene or cyclohexane with a range of acid-catalysts under Dean & Stark conditions did not provide the desired product **250**. However, reaction of **248** with 1,2-ethanediol in toluene with *p*TSA at r.t. gave **250** in 69% yield. In the event, the mild Noyori-conditions[107] using 1,2-bis-(trimethylsilyloxy)ethane and trimethylsilyltriflate as a catalyst were found to give the highest yield for the protection reaction (84%). The protection of **249**, which contains a more acid-sensitive *para*-methoxybenzylidene acetal group, was also successfully achieved under Noyori conditions, leading to **251** in 92% yield. Type B diol **252**, was obtained in good yields from the acetals **250** and **251** via hydrogenolysis. It is clear that **252** would be difficult to synthesise in a direct differentiation protocol from **231**.

The transformation of the diacetals **250** and **251** in to Type C differentiated molecules would rely upon chemoselective acetal cleavage reactions. Treatment of **250** with trimethylsilyl trifluoromethane sulfonate and borane dimethyl sulfide complex[108] resulted in selective reduction of the benzylidene acetal to give the corresponding benzyl ether **253** in 81% yield. Similarly, selective reductive cleavage of the *para*-methoxybenzylidene acetal **251** under the same conditions gave **254** in 78% yield. This transformation relies upon competition reactions. It has been shown[108] that 1,3-dioxane acetals are more reactive towards reduction than 1,3-dioxalane acetals. However, there are relatively few examples of the selective reductive cleavage being exploited in the case of the *para*-methoxybenzylidene acetal and, to the best of our knowledge, no examples in the case of the less reactive benzylidene acetal.

It was hoped that the use of DDQ could provide an oxidative cleavage of diacetal **251**, however, when this reaction was attempted, it did not yield a significant amount of Type C differentiated product. It is known[109] that the oxidation of cyclic acetals with ozone proceeds much faster than the oxidation of acyclic ones, and on this basis

it was decided to change the 1,3-dioxolane protecting group to an acyclic dimethyl acetal (Scheme 65).

**Scheme 65:** Chemoselective oxidation of **256** and **257.**




**Reagents and conditions:** (i) $TMSOCH_3$, $CF_3SO_3H$ (cat), $CH_2Cl_2$ , –78°C, 3 h. (ii) $O_3$, EtOAc, –78°C, 1 h.

The protection of aldehyde **248** as an acyclic dimethyl acetal was accomplished under Noyori conditions at –78°C with triflic acid as catalyst. It had been found that the reaction did not proceed with trimethylsilyl trifluoromethane sulfonate at –78°C and that at 0°C **258** would degrade in this reaction with either catalyst. Remarkably, with triflic acid as catalyst at –78°C, the diacetal **256** was formed as a single isomer even though the starting material was a mixture of *cis/trans* isomers. A similar result was achieved when **249** was the starting material. The structures of **256** and **257** have been determined by X-ray crystallography and have both been shown to be the *cis* isomer (Figure 34).

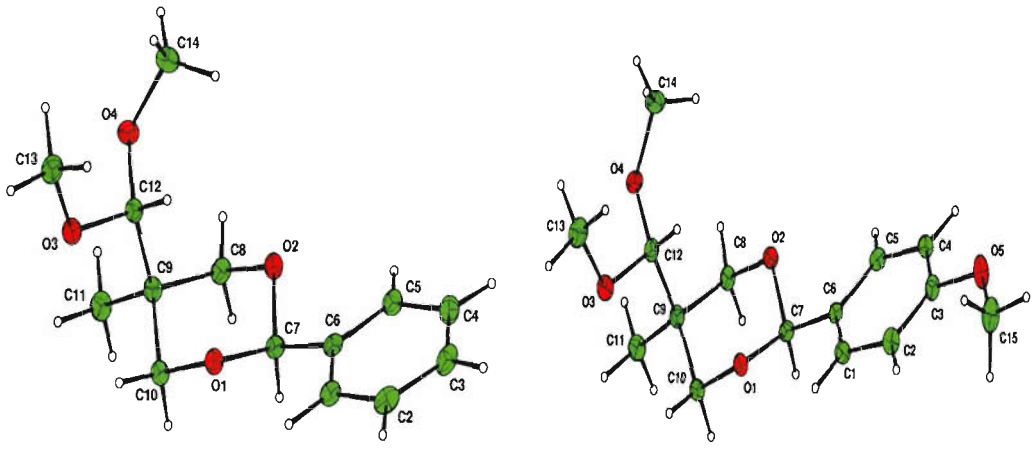



**Figure 34:** X-ray crystallography on the acyclic dimethyl acetals **256** and **257**.

The oxidation of the diacetals[110] **256** and **257** was carried out in ethyl acetate at –78°C. The reaction turned out to be chemoselective with the acyclic acetals left

untouched. The corresponding benzoate and *para*-methoxybenzoate esters **258** and **259** were obtained in 65 and 62% yield respectively. It is believed that this is the first example of such a selective oxidative cleavage between these two types of acetals.
It can be noted that the selective acetal cleavage of the benzylidene acetal occurs in similar yield compared to the *para*-methoxybenzylidene acetal, which adds to the versatility of the described indirect differentiation process, as a range of protecting groups are made accessible.

## 4.3. Conclusions

An indirect differentiation strategy, based on the initial protection of **231** as a benzylidene acetal, has been used to prepare fully differentiated derivatives of **231** where one hydroxyl group was converted to an acetal-protected aldehyde. A key aspect in this synthesis was the selective oxidative or reductive ring-opening of the benzylidene and *para*-methoxybenzylidene acetal groups in the presence of respectively a cyclic 1,3-dioxolane type acetal and an acyclic dimethyl acetal. These investigations resulted in an extension of the scope of selective transformations between different acetal groups. In addition, an improved preparation of the benzylidene acetal of **231** is reported.[111]

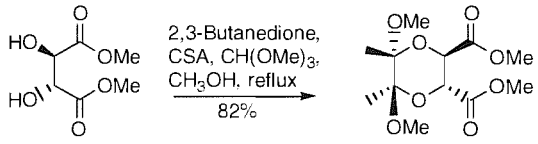
# Chapter 5: Experimental

## 5.1. General experimental

L-dimethyl tartrate, L-diethyl tartrate, 2,3-butanedione and 1,1,1-tris(hydroxymethyl)ethane were obtained from commercial sources and used without further purification. Trimethyl orthoformate and triethyl orthoformate were distilled prior to use. Reaction solvents were dried immediately prior to use as follows: $Et_3N$ and $CH_2Cl_2$ were distilled from $CaH_2$. EtOAc was distilled from $CaCl_2$. MeOH was dried with $Mg/I_2$, followed by distillation. THF was distilled from Na/benzophenone. Toluene was distilled from Na. DMSO was distilled from $CaH_2$ under reduced pressure and stored over molecular sieves. Anhydrous DMF was purchased from commercial sources and stored in a Schlenk flask. All non-aqueous reactions were carried out under an atmosphere of nitrogen. Chromatography refers to column chromatography and was performed on 230-400 mesh silica gel. Reactions were monitored by TLC (Merck) with detection by UV illumination or through alkaline $KMnO_4$ oxidation. The melting points are reported uncorrected. $^1H$ NMR (400MHz) and $^{13}C$ NMR (100MHz) were recorded on a Bruker DPX400 at 300K spectrometer in either $d_6$-actetone or $CDCl_3$ referenced to residual solvent peaks; chemical shifts are quoted in ppm and $J$ values given in Hz. $^{13}C$ experiments are supported by DEPT experiments. IR spectra were recorded on a Nicolet Impact 400 spectrometer. The MS were run on a Thermoquest 2000 spectrometer. The UV spectra were recorded on a Shimadzu UV-1601 spectrometer.

## 5.2. Synthesis of diene 183

### 5.2.1. (2*R*,3*R*,5*R*,6*R*)-Dimethyl-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2,3-dicarboxylate (138)




**189** **138**

Following the method of Ley *et al.*[52] To a solution of L-dimethyl tartrate (1.62 g, 9.11 mmol) in methanol (100 mL) was added CSA (0.3 g, 1.29 mmol), trimethyl orthoformate (4.5 mL, 41.2 mmol) and 2,3-butanedione (2.3 mL, 27.3 mmol). The reaction mixture was then heated to reflux for 24 h. The reaction was allowed to cool and was then quenched by addition of solid $NaHCO_3$ (2 g, 0.2 mmol). The methanol was then removed from the reaction mixture under reduced pressure. The crude product was purified by column chromatography (5:1 hexane:ethyl acetate) to give **138** (2.18 g, 7.46 mmol, 82 %) as a white crystalline material. The data observed compared well to the literature values.[50]

**M.p.** 106–108 °C **lit** - 107 °C[50]

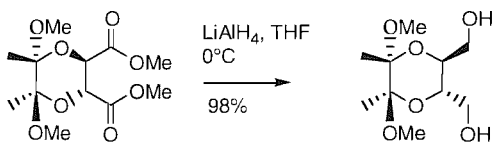
**IR** (solid): 2931 (w), 1743 (s), 1441 (m), 1363 (m), 1203 (m), 1140 (s), 1111 (s), 1042 (s), 904 (w) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 4.46 (2H, s, 2×C<u>H</u>); 3.69 (6H, s, 2×$CO_2C\underline{H_3}$); 3.32 (6H, s, 2×$OC\underline{H_3}$); 1.28 (6H, s, 2×$C\underline{H_3}$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 168.8 (2×C), 99.6 (2×C), 69.1 (2×$CH_3$), 52.8 (2×$CH_3$), 48.8 (2×CH), 17.7 (2×$CH_3$).

**CIMS**: m/z (%): 278 ($(M+H-Me)^+$, 6), 261 ($(M+H-MeOH)^+$, 100), 144 (34), 113 (94).

### 5.2.2. ((2*S*,3*S*,5*R*,6*R*)-2,3-(dihydroxymethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane) (139)




**143** **139**

To a stirred suspension of lithium aluminium hydride (10.2 g, 268 mmol) in THF (400 mL) at 0 °C was added a solution of protected ester **138** (20 g, 65.8 mmol) in THF (150 mL). The reaction was stirred for 15 min at 0 °C and then for a further 30 min at r.t. After this time water (10 mL) was added dropwise and then saturated sodium hydroxide (50 mL) was added slowly. Ether (200 mL) was added to ensure even stirring and then $MgSO_4$ (80 g) was added and the mixture stirred over night. The solid was filtered and rinsed with ether (3×100 mL) then the solvent was removed *in vacuo*. Purification by column chromatography (6:4 hexane:acetone) yielded **139** (15.2 g, 64.4 mmol, 98 %) of white solid. The data observed compared well to the literature values.[50]

**M.p.** 116–118 °C **lit.** 120 °C.[50]

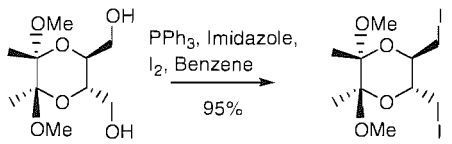
**IR** (solid): 3652 (w); 2923 (w), 1436 (w), 1377 (m), 1218 (m), 1121 (s), 1044 (s), 961 (m), 856 (s) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 3.73 (2H, m, 2×C<u>H</u>); 3.64 (4H, m, 2×HOC<u>H</u>$_2$); 3.19 (6H, s, 2×OC<u>H</u>$_3$); 2.59 (2H, bs, 2×O<u>H</u>); 1.23 (6H, s, 2×C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 99.2 (2×C), 69.8 (2×CH), 62.6 (2×$CH_2$), 48.3 (2×$CH_3$), 18.1 (2×$CH_3$).

**CIMS**: m/z (%): 193 ((M+-Me-MeOH)$^+$, 6), 173 ((M+H-2MeOH)$^+$,100).

### 5.2.3. *(2S,3S,5R,6R)*-5,6-Di(iodomethyl)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane (191)




**144** **191**

To diol **144** (0.26 g, 0.1 mmol) in benzene (10 mL) was added triphenylphosphine (0.65 g, 2.5 mmol), imidazole (0.37 g, 2.5 mmol) and iodine (0.64 g, 2.5 mmol). The reaction mixture was refluxed for 1 h and then allowed to cool to r.t. The mixture was washed with sat. aq. sodium thiosulfate solution (50 mL) and the aqueous phase extracted with ether (3×100 mL). The combined organic phases were then dried ($Na_2SO_4$) and filtered. The solvent was removed *in vacuo* and the crude material triturated with hexane. The trituration was filtered and the filtrate concentrated *in vacuo*. The crude product was then purified by column chromatography (8:2

hexane:acetone) to yield the product **191** (0.043 g, 0.095 mmol, 95 %) as white crystals.

**M.p.** 104–106 °C.

$[\alpha]_D$ = -48.5 (c=1.0, $CHCl_3$, 25°C).

**IR** (solid) 2950 (w), 1375 (w), 1266 (m), 1137 (s), 1115 (s), 1031 (s), 914 (m), 854 (m) $cm^{-1}$.

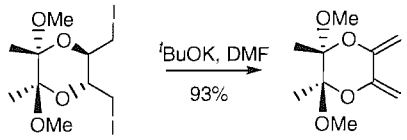
**$^1$H NMR** (300 MHz, $CDCl_3$): δ 3.59 (2H, m, 2×C<u>H</u>$CH_2$I); 3.32 (6H, s, 2×OC<u>H</u>$_3$); 3.26 (2H, m, 2×CHC<u>H</u>HI); 3.12 (2H, m, 2×CHCH<u>H</u>I); 1.34 (6H, s, 2×C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 99.7 (2×C), 71.2 (2×CH), 48.3 (2×$CH_3$), 17.2 (2×$CH_3$), 3.6 (2×$CH_2$).

**CIMS**: m/z (%) 425 ($(M+H-MeOH)^+$, 14), 181 ($(CH_2CHCHCH_2I)^+$, 100).

**Anal.** Calcd for $C_{10}H_{18}O_4I_2$: C, 26.34; H, 3.98. Found: C, 26.39; H, 3.93.

### 5.2.4. (*2R,3R*)-2,3-Dimethoxy-2,3-dimethyl-1,4-dimethylene-1,4-dioxane (183)




**191** **183**

$^t$BuOK (6.92 g, 5.6 mmol) was dissolved in DMF (100 mL) and stirred under $N_2$ at r.t. Diiodide **191** (6.81 g, 1.4 mmol) was dissolved in DMF (125 mL) and the mixture was added slowly over 5 min to the $^t$BuOK solution. The reaction mixture was stirred for 20 min. Water (200 mL) was added and was hence extracted with ether (3×200 mL). The organic phases were combined and dried ($Na_2SO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane:acetone) to provide the title product as a white crystalline material (2.59 g, 1.3 mmol, 93 %)

**M.p.** 74–76 °C.

$[\alpha]_D$ = -46.3 (c=1.0, $CHCl_3$, 25°C).

**IR** (solid) 2941 (w), 1744 (w), 1621 (w), 1379 (m), 1299 (m), 1487 (s), 1110 (s), 1006 (s), 859 (m) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 4.61 (2H, d, *J* = 1.3Hz, 2×C=C<u>H</u>H); 4.37 (2H, d, *J* = 1.5Hz, 2×C=CH<u>H</u>); 3.27 (6H, s, 2×OC<u>H</u>$_3$); 1.36 (6H, s, 2×C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 148.8 (2×C), 99.7 (2×C), 90.2 (2×$CH_2$), 49.0 (2×$CH_3$), 17.6 (2×$CH_3$).

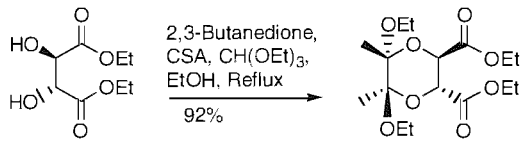
**CIMS**: m/z (%) 200 ($(M)^+$, 36), 185 (12), 169 ($(M+H-MeOH)^+$, 92), 115 (60), 89 (100).

**HRMS** (CI): for $C_{10}H_{16}O_4$ $(M)^+$: calcd 200.1049, found 200.1050.

**Anal.** Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C 60.10; H, 8.15.

## 5.3. Synthesis of diene 184

### 5.3.1. (*2R,3R,5R,6R*)-Diethyl-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2,3-dicarboxylate (193)




**192** **193**

Following the method of Ley *et al.*[52] To a solution of L-diethyl tartrate (1.7 mL, 10.01 mmol) in ethanol (25 mL) was added CSA (0.3 g, 1.29 mmol), triethyl orthoformate (7.3 mL, 41.1 mmol) and 2,3-butanedione (2.3 mL, 27.3 mmol). The reaction mixture was then heated at reflux for 36 h. The reaction was allowed to cool and was then quenched by addition of solid $NaHCO_3$ (2 g, 0.2 mmol). The ethanol was then removed from the reaction mixture *in vacuo*. Purification by column chromatography (5:1 hexane:ethyl acetate) gave the product **193** as a yellow oil (0.32 g, 9.2 mmol, 92 %). The data observed compared well to the literature values.[50]

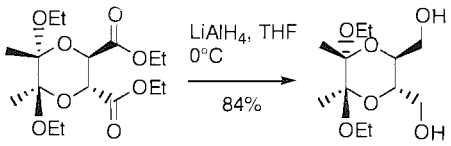
**IR** (film) 2968 (w), 1753 (s), 1379 (m), 1120 (s), 1094 (s), 906 (m) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 4.47 (2H, s, 2×OC<u>H</u>$CO_2CH_2CH_3$); 4.20 (4H, m, 2×$OCHCO_2C$<u>H</u>$_2CH_3$); 3.58 (4H, dq, *J* = 7.2, 2.0 Hz, 2×$CH_3COC$<u>H</u>$_2CH_3$); 1.35 (6H, s, 2×C<u>H</u>$_3COCH_2CH_3$); 1.26 (6H, t, *J* = 7.0 Hz, 2×$OCHCO_2CH_2C$<u>H</u>$_3$); 1.24 (6H, t, *J* = 7.2 Hz, 2×$CH_3COCH_2C$<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 168.1 (2×C), 98.9 (2×C), 68.4 (2×CH), 61.3 (2×$CH_2$), 56.3 (2×$CH_2$), 18.0 (2×$CH_3$), 15.3 (2×$CH_3$), 13.9 (2×$CH_3$).

**CIMS**: m/z (%) 303 ($(M+H–EtOH)^+$, 100), 257 ($(M+H–2EtOH)^+$, 22), 126 (28).

### 5.3.2. (*2S,3S,5R,6R*)-2,3-(dihydroxymethyl)-5,6-diethoxy-5,6-dimetyl-1,4-dioxane (194)




**193** **194**

To a stirred suspension of lithium aluminium hydride (3.31 g, 90 mmol) in THF (150 mL) at 0 °C was added a solution of protected ester **193** (3.22 g, 9.2 mmol) in THF (50 mL). The reaction was stirred for 15 min at 0 °C and then for 16 h at r.t. After this time sat. aq. sodium sulphate solution (5 mL) was added slowly and stirred for 1 h. The reaction mixture was filtered through Celite and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (6:4 hexane:acetone) to yield **194** (1.99 g, 7.5 mmol, 84 %) as a colourless oil. The data observed compared well to the literature values.[50]

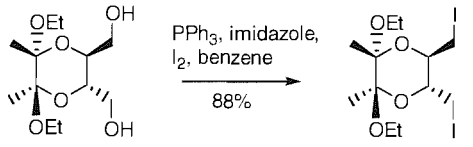
**IR** (film) 3385 (w), 2968 (w), 1437 (w), 1360 (w), 1129 (s), 1048 (s), 944 (m) $cm^{-1}$.

**$^1$H NMR** (400MHz, $CDCl_3$): δ 3.73 (2H, m, 2×$HOCH_2CH$); 3.56 (4H, m, 2×$HOCH_2$); 3.45 (4H, m, 2×$OCH_2CH_3$); 2.43 (2H, bs, 2×OH); 1.25 (6H, s, 2×$CH_3$); 1.14 (6H, t, *J* = 7.0 Hz, 2×$OCH_2CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, $CDCl_3$): δ 99.2 (2×C), 69.8 (2×CH), 62.6 (2×$CH_2$), 56.26 (2×$CH_2$), 18.1 (2×$CH_3$), 15.8 (2×$CH_3$).

**CIMS**: m/z (%)173 ($(M+H-2EtOH)^+$, 100).

### 5.3.3. (*2S,3S,5R,6R*)-5,6-di(iodomethyl)-2,3-diethoxy-2,3-dimethyl-1,4-dioxane (195)




**194** **195**

To **194** (1.99 g, 7.5 mmol) in benzene (89 mL) was added triphenylphosphine (4.36 g, 16.6 mmol), imidazole (2.31 g, 16.6 mmol) and iodine (4.27 g, 16.6 mmol). The reaction mixture was then refluxed for 1 h and allowed to cool to r.t. The mixture was washed with sat. aq. sodium thiosulfate solution (100 mL), and the aqueous layer extracted with diethyl ether (3×100 mL). The combined organic phases were dried

($Na_2SO_4$) and filtered. The solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane:acetone) to yield the product **195** as a yellow oil (3.25 g, 6.7 mmol, 88 %).

$[\alpha]_D$ = -30.5° (c = 1.0, $CHCl_3$, 25°C).

**IR** (film) 2978 (w), 1366 (w), 1153 (m) 1136 (s), 859 (m) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): δ 3.68–3.53 (6H, m, 2×OC<u>H</u>$_2$CH$_3$, 2×C<u>H</u>); 3.28 (2H, m, 2×CHC<u>H</u>HI); 3.11 (2H, m, 2×CHCH<u>H</u>I); 1.41 (6H, s, 2×C<u>H</u>$_3$); 1.22 (6H, t, *J* = 7.0 Hz, 2×OCH$_2$C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 99.7 (2×C), 71.2 (2×CH), 56.2 (2×$CH_2$), 18.0 (2×$CH_3$), 15.4 (2×$CH_3$), 4.1 (2×$CH_2$).

**CIMS**: m/z (%) 439 ($(M+H-EtOH)^+$, 28), 181 ($(CH_2CHCHCH_2I)^+$, 100), 132 (18), 115 (33).

**HRMS** (EI) for $C_{10}H_{17}O_3I_2$ $(M+H-EtOH)^+$: calcd 438.9267, found 438.9271.

### 5.3.4. (*2R,3R*)-2,3-Diethoxy-2,3-dimethylene-1,4-dioxane (184)


**187** **184**

$^t$BuOK (3.00 g, 26.8 mmol) was dissolved in DMF (50 mL) and stirred under $N_2$ at r.t. Diiodide **187** (3.23 g, 6.7 mmol) was dissolved in DMF (50 mL) and was added slowly over 5 min to the $^t$BuOK solution. The reaction mixture was stirred for 20 min. Water (100 mL) was added and was hence extracted with ether (3×100 mL). The organic phases were combined and dried ($Na_2SO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (95:5 hexane:acetone) to provide the title product as a light yellow oil (1.19 g, 5.2 mmol, 78 %).

$[\alpha]_D$ = -19.8° (c = 1.0, $CHCl_3$, 25°C).

**IR** (film) 2973 (w), 1606, (w), 1379(w), 1318 (w), 1218(m) 1158 (s), 1123 (s), 1090 (s), 1001 (s), 968 (m) $cm^{-1}$.

**$^1$H NMR** (300MHz, $CDCl_3$): δ 4.56 (2H, d, *J* = 1.3 Hz, 2×C=C<u>H</u>H); 4.32 (2H, d, *J* = 1.3 Hz, 2×C=CH<u>H</u>); 3.55 (4H, m, 2×OC<u>H</u>$_2$CH$_3$); 1.37 (6H, s, 2×C<u>H</u>$_3$); 1.11 (6H, t, *J* = 7.0 Hz, 2×OCH$_2$C<u>H</u>$_3$).

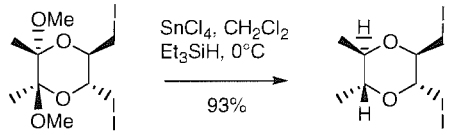
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 149.7 (2×C), 99.9 (2×C), 89.9 (2×$CH_2$), 57.7 (2×$CH_2$), 18.5 (2×$CH_3$), 15.7 (2×$CH_3$).

**CIMS**: m/z (%) 229 ($(M+H)^+$, 9%), 213 ($(M-Me)^+$, 2), 199 ($(M-Et)^+$, 14), 183 (M+H-$OEt^+$, 100), 143 (30).

**HRMS** (EI) for $C_{12}H_{20}O_4$ $(M)^+$: calcd 228.1362, found 228.1364.

## 5.4. Synthesis of diene 185

### 5.4.1. (2*R*,3*R*,5*R*,6*R*)-2,3-di(iodomethyl-5,6-dimethyl-1,4-dioxane (196)




**191** **196**

Following the procedure of Berens *et al.*[75] To a stirred solution of triethyl silane (3.3 mL, 23.6 mmol) and **191** (3.6 g, 7.9 mmol) in $CH_2Cl_2$ (25 mL) at 0°C was added tin tetrachloride (2.7 mL, 23.5 mmol) in $CH_2Cl_2$ (20 mL) over 30 min. During this time a yellow precipitate formed. When the addition of the tin tetrachloride was complete the precipitate was filtered off and washed thoroughly with $CH_2Cl_2$ (3×100mL). The dichloromethane phase was then washed with 20% NaOH solution (300 mL) and dried ($Na_2SO_4$). After filtration the solvent was removed *in vacuo* and the residue was subjected to column chromatography (95:5 hexane:ethyl acetate) to give the product **196** as a colourless oil (2.93 g, 7.4 mmol, 93 %).

$[\alpha]_D$ = -66.4° (c = 1.0, $CDCl_3$, 25°C).

**IR** (film): 2968 (m), 2931 (w), 2864 (m), 1445 (w), 1417 (w), 1379 (m), 1195 (s), 1110 (s), 1072 (s), 1020 (m), 958 (w), 906 (m).

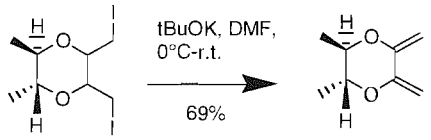
**$^1$H NMR** (300MHz, $CDCl_3$): δ 3.39 (2H, m, $CH_3$C<u>H</u>O); 3.29 (2H, dd, *J* = 10.8, 1.5 Hz, CHC<u>H</u>$_2$I); 3.18–3.11 (4H, m, 2×C<u>H</u>CH$_2$I, CHC<u>H</u>$_2$I); 1.15 (6H, m, C<u>H</u>$_3$CHO).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 78.1 (2×CH), 77.9 (2×CH), 17.4 (2×$CH_2$), 5.2 (2×$CH_3$).

**EIMS**: m/z (%): 396 ($M^+$, 6), 197 (4), 101 (100).

**HRMS** (EI): for $C_8H_{14}O_2I_2$ $(M)^+$: calcd 395.9083, found 395.9096.

### 5.4.2. (2*R*,3*R*)-2,3-dimethyl-1,4-dimethylene-1,4-dioxane (185)




**196** **185**

$^t$BuOK (12.64 g, 28.2 mmol) was dissolved in DMF (150 mL) and stirred under $N_2$ at 0 °C. Diiodide **196** (11.18 g, 28.2 mmol) was dissolved in DMF (55 mL) and was added to the $^t$BuOK solution. The reaction mixture was warmed to r.t. and stirred for 20 min. Water (250 mL) was added and was hence extracted with pentane (3×200 mL). The organic phases were combined, washed with brine (200 mL) and dried ($Na_2SO_4$). The drying agent was removed by filtration and the solvent removed by distillation. The crude product was purified by Kügelrohr distillation to provide the title product as a colourless oil (2.72 g, 19.4 mmol, 69 %).

$[\alpha]_D$: not pure enough

**IR** (film); 2997 (s), 2935 (m), 2889 (m), 1682 (m), 1620 (s), 1460 (m), 1441 (m), 1379 (s), 1299 (s), 1086 (s), 821 (s).

**$^1$H NMR** (300MHz, $CDCl_3$): δ 4.58 (2H, d, *J* = 1.3 Hz, 2×CC<u>H</u>H); 4.35 (2H, d, *J* = 1.4 Hz, 2×CCH<u>H</u>); 3.89–3.83 (2H, m, 2×$CH_3C\underline{H}$); 1.23–1.21 (6H, m, 2×$C\underline{H}_3CH$).

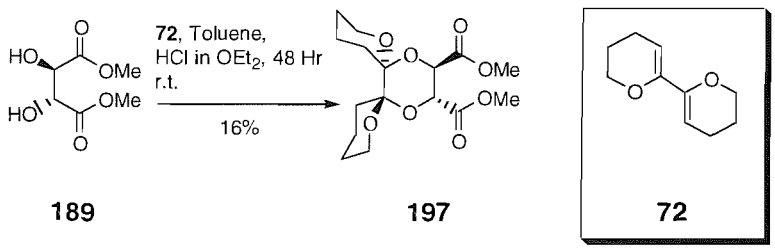
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 151.8 (2×C), 88.9 (2×CH), 75.6 (2×CH), 17.0 (2×$CH_3$).

**EIMS**: m/z (%): 140 ($M^+$, 34), 84, (20), 56 (82), 41 (100).

**HRMS** (EI): for $C_8H_{12}O_2$ $(M)^+$: calcd 140.0837, found 140.0835.

## 5.5. Synthesis of diene 186

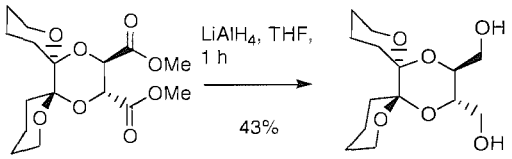
### 5.5.1. (6*R*,7*R*,14*R*,15R)-dimethyl 1,8,13,16-tertraoxasipiro-[5.0.5.4] hexadecane-14,15-dicarboxylate (197)




**189** **197** **72**

Dimethyl tartrate (3.65 g, 20.5 mmol) and **72** (3.41 g, 20.5 mmol) were dried *in vacuo* for 1 h. The reaction was placed under argon and toluene (25 mL) was added. 1.0 M HCl (4 mL) in ether was added and the reaction mixture was stirred for 48 h. The solvent was then evaporated and the reaction mixture loaded on to a column for chromatography (8:2 hexane/ethyl acetate). The crude product was recovered as an oily yellow solid (1.11 g, 3.22 mmol, 16 %). This product was carried forward as a crude product as it was thought that purification would be easier at a later stage. Only crude NMR were taken but these showed peaks that were consistent with the literature.[112]

### 5.5.2. (6*R*,7*R*,14*S*,15*S*)-14,15-dihydroxymethyl-1,8,13,16-tertraoxasipiro-[5.0.5.4]-hexadecane (198)




**197** **198**

To a stirred suspension of lithium aluminium hydride (0.45 g, 11.9 mmol) in THF (4 mL) at 0 °C was added a solution of protected ester **197** (0.93 g, 2.71 mmol) in THF (6 mL). The reaction was stirred for 15 min at 0 °C and then for a further 30 min at r.t.. After this time water (0.4 mL) was added dropwise and then 20% sodium hydroxide solution (2 mL) was added slowly. Magnesium sulfate (3 g) was added and the reaction mixture stirred overnight. The aluminium salts were filtered through Celite and washed with ether (3×100 mL). Purification by column chromatography (6:4 hexane:acetone) yielded **198** (0.38 g, 0.12 mmol, 43 %) of white solid.

**M.p.** 118–120°C

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$) 3408 (s), 2940 (s), 2879 (s), 1431 (m), 1351 (m), 1214 (m), 1185 (m), 1072 (s), 991 (s), 731 (m) $cm^{-1}$.

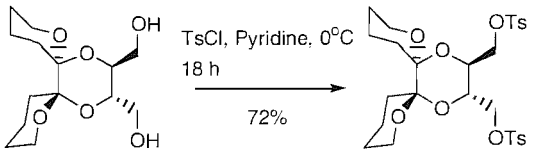
**$^1$H NMR** (300MHz, $CDCl_3$): δ 3.87 (2H, m, 2×C<u>H</u>); 3.73–3.65 (8H, m, 2×C<u>H</u>$_2$OH, 2×C<u>H</u>$_2$ (ring)); 2.36 (2H, br s, 2×O<u>H</u>); 1.78–1.73 (4H, m, 2×C<u>H</u>$_2$ (ring)); 1.63–1.49 (8H, m, 4×C<u>H</u>$_2$ (ring)).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 96.1 (2×C), 68.5 (2×CH), 62.3 (2×$CH_2$), 60.8 (2×$CH_2$), 28.2 (2×$CH_2$), 24.8 (2×$CH_2$), 18.0 (2×$CH_2$).

**CIMS**: m/z (%) 311 $(M+Na)^+$,100).

**HRMS** (ES): for $C_{14}H_{24}O_6Na$ $(M+Na)^+$: calcd 311.1465, found 311.1467.

### 5.5.3. 4-Toluenesulfonic acid 15-[4'-toluenesulfonyloxymethyl]-1,8,13,16-tetraoxa-dispiro[5.0.5.4]hexadec-14-ylmethyl ester (199)




**198** **199**

Diol **198** (0.29 g, 1.03 mmol) was dissolved in pyridine (2 mL) and was cooled to -5°C. *p*-Tosyl chloride (0.41 g, 2.15 mmol) was added and the reaction stirred at 0°C for 15 h. Water (8 mL) was added and this was extracted with $CH_2Cl_2$ (3×5 mL). The combined organic phases were washed with 1M HCl solution (3×4 mL) and brine (4 mL). The organic phase was then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was subjected to column chromatography (6:4 hexane/acetone) to yield the product as a white solid (0.46 g, 0.77 mmol, 72 %).

**M.p.** 94–96°C

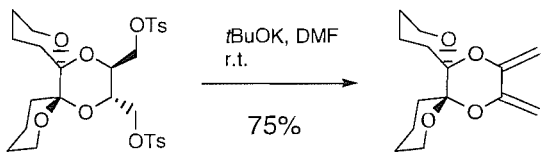
**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$) 2941 (s), 2874 (m), 1597 (m), 1450 w), 1351 (s), 1176 (s), 1081 (s), 972 (m) $cm^{-1}$.

**$^1$H NMR** (300MHz, $CDCl_3$): δ 7.80 (4H, d, $J$ = 8.4 Hz, ArH); 7.35 (4H, d, $J$ = 8.1 Hz, ArH); 4.07–4.06 (4H, m, 2×TsOC$H_2$); 3.88–3.87 (2H, m, 2×CH); 3.56–3.48 (4H, m, 2×C$H_2$ (ring)); 2.46 (6H, s, 2×C$H_3$); 1.62–1.39 (12H, m, 6×C$H_2$ (ring)).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 145.0 (2×C), 132.5 (2×C), 129.9 (2×CH), 128 (2×CH), 96.2 (2×C), 68.8 (2×$CH_2$), 66.2 (2×CH), 60.8 (2×$CH_2$), 28.0 (2×$CH_2$), 27.7 (2×$CH_2$), 21.7 (2×$CH_3$), 17.8 (2×$CH_2$).

**ESMS**: m/z (%) 619 ($(M+Na)^+$, 22), 275.3 (100).

### 5.5.4. 14,15-Dimethylene-1,8,13,16-tetraoxa-dispiro[5.0.5.4]hexadecane (186)




**199** **186**

$^t$BuOK (0.32 g, 2.9 mmol) was dissolved in DMF (3 mL) and stirred under $N_2$. Di-tosylate **199** (0.43 g, 0.72 mmol) was dissolved in DMF (2 mL) and was added slowly over 5 min to the $^t$BuOK solution. The reaction mixture was stirred for 20 min. Water (15 mL) was added and was hence extracted with ether (3×20 mL). The organic phases were combined and dried ($Na_2SO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane:acetone) to provide the title product as a white crystalline material (0.14 g, 0.54 mmol, 75 %).

**M.p.** 56–58 °C

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$) 2950 (m), 2879 (w), 1611 (w), 1313 (m), 1218 (m), 1200 (s), 1077 (s), 1015 (s) $cm^{-1}$.

**$^1$H NMR** (300MHz, $CDCl_3$): δ 4.72 (2H, d, *J* = 1.3 Hz, C<u>H</u>H); 4.48 (2H, d, *J* = 1.3 Hz, C<u>H</u>H); 3.85–3.69 (4H, m, 2×C<u>H</u>$_2$ (ring)); 2.01–1.82 (4H, 2×C<u>H</u>$_2$ (ring)); 1.63–1.52 (8H, m, 4×C<u>H</u>$_2$ (ring)).

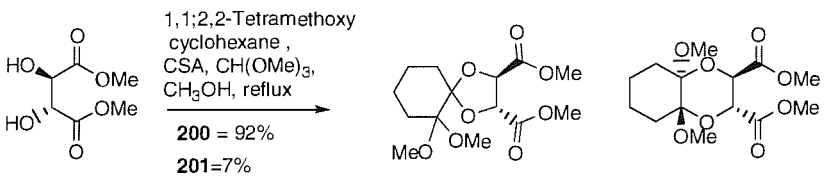
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 148.5 (2×C), 97.3 (2×C), 90.5 (2×$CH_2$), 62.4 (2×$CH_2$), 28.5 (2×$CH_2$), 24.9 (2×$CH_2$), 18.0 (2×$CH_2$).

**CIMS**: m/z (%) 252 ($M^+$, 10), 167 (86), 55 (100).

**HRMS** (ES): for $C_{14}H_{20}O_4Na$ $(M+Na)^+$: calcd 275.1254, found 275.1250.

## 5.6. Synthesis of diene 187

### 5.6.1. *(2R,3R)* Dimethyl-6, 6- dimethoxy-1, 4-dioxaspiro[4.5]decane dicarboxylate (200) and *(2R,3R,4R,8R)* Dimethyl-4, 8-dimethoxy perhydro-1,4-benzodioxin dicarboxylate (201)




**189** **200** **201**

To a solution of L-dimethyl tartrate (2.72 g, 15.3 mmol) in methanol (22 mL) was added CSA (0.3g, 1.3 mmol), trimethyl orthoformate (1.53 mL, 14.0 mmol) and 1, 1; 2, 2 Tetramethoxycyclohexane (5.0 g, 24.5 mmol). The reaction mixture was then heated to reflux for 72 h. The reaction was allowed to cool and was then quenched by addition of solid $NaHCO_3$ (2g, 0.2 mmol). The methanol was then removed from the

reaction mixture *in vacuo*. The crude product was purified by column chromatography (9:1 hexane:acetone) to give **200** (4.54 g, 14.2 mmol, 92 %) yellow oil and **201** (0.33 g, 1.04 mmol, 7%) as a colourless oil.

Data for **200**

$[\alpha]_D$ = -26.1 (c=0.22, $CHCl_3$, 25°C).

**IR** (film) 2941 (s), 2865 (m), 2836 (m), 1743 (s), 1431 (s) 1346 (m), 1195 (s), 1105 (s), 1020 (s), 977 (s), 873 (m).

**$^1$H NMR** (300MHz, $CDCl_3$): δ 5.00 (1H, d, *J* = 4.8 Hz, C<u>H</u>$CO_2CH_3$); 4.56 (1H, d, *J* = 4.9 Hz, C<u>H</u>$CO_2CH_3$); 3.66 (3H, s, $CHCO_2C\underline{H}_3$); 3.65 (3H, s, $CHCO_2C\underline{H}_3$); 3.11 (3H, s, $OC\underline{H}_3$); 3.04 (3H, s, $OC\underline{H}_3$); 1.70–1.62 (4H, m, 2×$C\underline{H}_2$ (ring)); 1.52–1.47 (2H, m, $C\underline{H}_2$ (ring)); 1.39–1.35 (2H, m, $C\underline{H}_2$ (ring)).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 170.2 (C), 169.5 (C), 114.3 (C), 100.6 (C), 78.1 ($CH_3$), 77.3 ($CH_3$), 52.2 ($CH_3$), 51.8 ($CH_3$), 48.9 (CH), 48.1 (CH), 33.3 ($CH_2$), 30.6 ($CH_2$), 22.3 ($CH_2$), 21.1 ($CH_2$).

**CIMS**: m/z (%) 318 ($(M)^+$, 8), 303 ($(M\text{-}CH_3)^+$, 10), 287 ($(M\text{-}OCH_3)^+$,100) 255 ($(M\text{-}2 \times OCH_3)^+$,72), 215 (32).

**Anal.** Calcd for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97. Found: C, 52.97; H, 6.75.

Data for **201**

$[\alpha]_D$ = -66.8 (c=0.69, $CHCl_3$, 25°C).

**IR** (film) 2945 (s), 2860 (s), 2827 (s), 1748 (s), 1460 (s), 1299 (s), 1185 (s), 1062 (s), 954 (s), 883 (s).

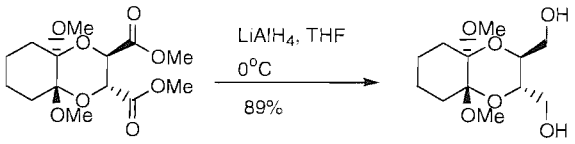
**$^1$H NMR** (300MHz, $CDCl_3$): δ 4.61 (2H, s, 2×C<u>H</u>$CO_2CH_3$); 3.72 (6H, s, 2×$CHCO_2C\underline{H}_3$); 3.23 (6H, s, 2×$OC\underline{H}_3$); 1.83–1.67 (4H, m, 2×$C\underline{H}_2$ (ring)); 1.52–1.49 (2H, m, $C\underline{H}_2$ (ring)); 1.35–1.27 (2H, m, $C\underline{H}_2$ (ring)).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 168.4 (2×C), 97.7 (2×C), 68.6 (2×$CH_3$), 52.4 (2×$CH_3$), 47.1 (2×CH), 25.6 (2×$CH_2$), 21.2 (2×$CH_2$).

**CIMS**: m/z (%) 304 ($(M+H\text{-}CH_3)^+$,8), 287 ($(M\text{-}OCH_3)^+$,100), 255 ($(M\text{-}2$ x $OCH_3)^+$,58).

**HRMS** (ES): for $C_{14}H_{22}O_8Na$ $(M+Na)^+$: calcd 341.1207, found 341.1205.

### 5.6.2. *(2R,3R,4R,8R)*-2,3-(dihydroxymethyl)-4, 8-dimethoxyperhydro-1,4-benzodioxin-2yl (204)




**201** **204**

To a stirred suspension of lithium aluminium hydride (0.209 g, 5.52 mmol) in THF (4 mL) at 0 °C was added a solution of protected ester **201** (0.44 g, 1.38 mmol) in THF (6 mL). The reaction was stirred for 15 min at 0 °C and then for a further 30 min at r.t. After this time water (0.2 mL) was added dropwise and then 20% sodium hydroxide solution (1 mL) was added slowly. Magnesium sulfate (1.5 g) was added and the reaction mixture stirred overnight. The aluminium salts were filtered through Celite and washed with ether (3×100 mL). Purification by column chromatography (6:4 hexane:acetone) yielded **204** (0.32 g, 1.22 mmol, 89%) as a white solid.

**M.p.** 148–150°C

$[\alpha]_D$ = -104.4 (c=0.5, $CHCl_3$, 25°C).

**IR** (solution $CH_2Cl_2$ *ca* 1 mg $mL^{-1}$) 3588 (m), 2940 (w), 1181 (m), 1058 (s), 1048 (m).

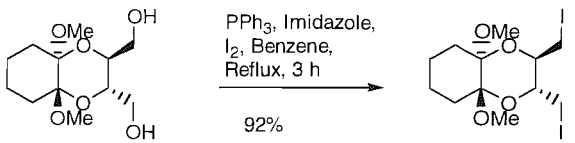
**$^1$H NMR** (300MHz, $CDCl_3$): δ 3.93 (2H, m, 2×C<u>H</u>); 3.74–3.60 (4H, m, 2×C<u>H</u>$_2$OH); 3.15 (6H, s, 2×OC<u>H</u>$_3$); 2.53 (2H, dd, $J$ = 6.4, 6.2 Hz, 2×CH$_2$O<u>H</u>); 1.82–1.63 (4H, m, 2×$CH_2$ (ring)); 1.56–1.52 (2H, m, $CH_2$ (ring)); 1.14–1.32 (2H m, $CH_2$ (ring)).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 97.4 (2×C), 69.4 (2×$CH_3$), 62.4 (2×$CH_2$), 40.9 (2×CH), 26.8 (2×$CH_2$), 21.3 (2×$CH_2$).

**EIMS**: m/z (%) 247 ($(M-CH_3)^+$, 3), 199 (9), 167 (12), 143 (52), 111 (54), 55 (100).

**Anal.** Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.74; H, 8.56.

### 5.6.3. *(2R,3R,4R,8R)*-2, 3-(diiodomethyl)-4, 8 dimethoxyperhydro-1, 4-benzodioxin (205)




**204** **205**

To diol **204** (0.30 g, 1.12 mmol) in benzene (40 mL) was added triphenylphosphine (0.65 g, 2.5 mmol), imidazole (0.37 g, 2.5 mmol) and iodine (0.64 g, 2.5 mmol). The reaction mixture was refluxed for 3 h and then allowed to cool to r.t. The mixture was washed with sat. aq. sodium thiosulfate solution (50 mL), and the aqueous phase extracted with ether (3×100 mL). The combined organic phases were then dried ($Na_2SO_4$) and filtered. The solvent was removed *in vacuo*. The crude reaction mixture was subjected to column chromatography (9:1 hexane:acetone) to give the product as a white solid (0.49 g, 1.03 mmol, 92 %).

**M.p.** 102–104 °C.

$[\alpha]_D$ = -163.9 (c=0.5, $CHCl_3$, 25°C).

**IR** (solution $CH_2Cl_2$ *ca* 2 mg $mL^{-1}$) 3044 (w), 2950 (m), 2860 (w), 2831 (w), 1464 (m), 1417(m), 1356 (w), 1332 (m), 1261 (s), 1171 (m), 1101 (s), 1058 (s), 963 (m), 897, (m), 840 (w).

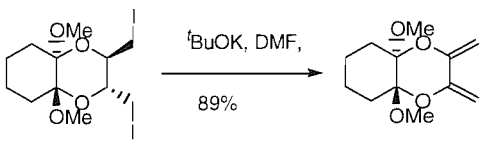
**$^1$H NMR** (300MHz, $CDCl_3$): δ 3.69 (2H, m, 2×C<u>H</u>); 3.30 (2H, m, 2×C<u>H</u>HI); 3.27 (6H, s, 2×OC<u>H</u>$_3$); 3.17 (2H, m, 2×CH<u>H</u>I); 1.87–1.83 (2H, m, ring C<u>H</u>$_2$); 1.72 (2H, dt, *J* = 7.3, 3.5 Hz, ring C<u>H</u>$_2$); 1.57–1.55 (2H, m, ring $CH_2$); 1.43–1.34 (2H, m, ring $CH_2$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 98.4 (2×C), 71.7 (2×$CH_3$), 47.1 (2×CH), 26.6 (2×$CH_2$), 21.3 (2×$CH_2$), 3.8 (2×$CH_2$).

**EIMS**: m/z (%) 467 ($(M-CH_3)^+$, 5), 451 ($(M+H-MeOH)^+$, 4), 181 ($(CH_2CHCHCH_2I)^+$, 51), 54 (94), 39 (100).

**Anal.** Calcd for $C_{12}H_{20}O_4I_2$: C, 29.90; H, 4.18. Found: C, 30.14; H, 4.25.

### 5.6.4. *(4R, 8R)*-4,8-Dimethoxy-2,3-dimethylene perhydro1,4-benzodioxin (187)




**205** **187**

$^t$BuOK (0.33 g, 2.2 mmol) was dissolved in DMF (10 mL) and stirred under $N_2$ at 0°C. Diiodide **205** (0.36 g, 0.74 mmol) was dissolved in DMF (5 mL) and the mixture was added to the $^t$BuOK solution. The reaction mixture was warmed to r.t. and stirred for 20 min. Water (45 mL) was added and was hence extracted with ether

(3×45 mL). The organic phases were combined and dried ($Na_2SO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane:acetone) to provide the title product as a white solid (0.15 g, 0.66 mmol, 89 %).

**IR** (film) 2970 (s), 2850 (s), 1445 (m), 1346 (w), 1166 (w), 1105 (m), 1039 (m), 972 (w).

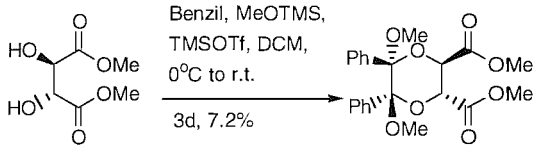
**$^1$H NMR** (300MHz, $CDCl_3$): δ 4.68 (2H, d, *J* = 1.5 Hz, 2×CC<u>H</u>H); 4.45 (2H, d, *J* = 1.5 Hz, 2×CCH<u>H</u>); 3.29 (6H, s, 2×OC<u>H</u>$_3$); 2.04–1.99 (2H, m, C<u>H</u>$_2$ (ring)); 1.74 (2H, td, *J* = 13.6, 3.6 Hz, C<u>H</u>$_2$ (ring)); 1.61–1.56 (2H, m, C<u>H</u>$_2$ (ring)); 1.38–1.29 (2H, m, $CH_2$ (ring)).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 149.2 (2×C), 98.2 (2×C), 90.2 (2×$CH_2$), 48.1 (2×$CH_3$), 26.9 (2×$CH_2$), 21.2 (2×$CH_2$).

**CIMS**: m/z (%) 227 ($(M+H)^+$, 100), 211 $(M+H-CH_3)^+$, 8), 195 $(M+H-OCH_3)^+$, 64), 141 (58).

## 5.7. Synthesis of diene 188

### 5.7.1. (*2R,3R,5R,6R*)-Diphenyl-5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2,3-dicarboxylate (206)




**189** **206**

Reaction carried out according to the procedure of Lence *et al.*[81] Benzil (6.09 g, 29 mmol) and L-dimethyl tartrate (6.92 g, 39 mmol) were dissolved in $CH_2Cl_2$ (29 mL) and cooled to 0°C. MeOTMS (25 g, 230 mmol) was added followed by dropwise addition of TMSOTf (0.52 mL, 2.9 mmol). The reaction was stirred for 3 h at 0°C. No reaction had taken place and the reaction was left at r.t. for three days. After this time TMSOTf (3 mL, 17 mmol) was added and the reaction left for an additional 18 h. The reaction was poured on to sat. $NaHCO_3$ sol. (100 mL) and extracted with $CH_2Cl_2$ (3×50 mL). The combined organic phases were dried ($Na_2SO_4$), filtered and the solvent removed *in vacuo*. The residue was subjected to chromatography (9:1 hexane/acetone) to yield the product as a white foam (0.955 g, 2.29 mmol, 7.2 %).

**M.p.** 124–126°C

$[\alpha]_D$ = -112 ° (c=0.31, $CHCl_3$, 28°C)

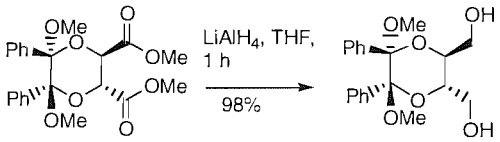
**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$) 2955 (m), 2822 (w), 1743 (s), 1445 (m), 1256 (w), 1200 (m), 1095 (s), 1039 (s), 731 (s) $cm^{-1}$.

**$^1$H NMR** (300MHz, $CDCl_3$): δ 7.34–7.21 (6H, m, ArH); 7.11–7.07 (4H, m, ArH); 4.89 (2H, s, 2×CH); 3.87 (6H, s, 2×$CO_2CH_3$); 3.05 (6H, s, 2×$OCH_3$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 168.5 (2×C), 134.5 (2×C), 129.5 (4×CH), 128.3 (4×CH), 126.7 (2×CH), 100.7 (2×C), 68.7 (2×CH), 52.6 (2×$CH_3$), 49.5 (2×$CH_3$).

**CIMS**: m/z (%) 385 ($(M-OCH_3)^+$, 100), 105 (92).

### 5.7.2. ((*2R,3R,5R,6R*)-3-(Hydroxymethyl)-5,6-dimethoxy-5,6-diphenyl-1,4-dioxane) methanol (207)




**206** **207**

To a stirred suspension of lithium aluminium hydride (0.33 g, 8.5 mmol) in THF (4 mL) at 0 °C was added a solution of protected ester **206** (0.96 g, 2.13 mmol) in THF (6 mL). The reaction was stirred for 15 min at 0 °C and then for a further 30 min at r.t.. After this time water (0.2 mL) was added dropwise and then 20% sodium hydroxide solution (1 mL) was added slowly. Magnesium sulfate (1.5 g) was added and the reaction mixture stirred overnight. The aluminium salts were filtered through Celite and washed with ether (3×100 mL). Purification by column chromatography (6:4 hexane:acetone) yielded **207** (0.75 g, 2.08 mmol, 98 %) as a white solid.

**M.p.** 70–72°C

$[\alpha]_D$ = -275 ° (c=1.31, $CHCl_3$, 28°C)

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$) 3408 (w), 3016 (w), 2931 (w), 1450 (m), 1218 (m), 1095 (w), 1039 (w), 755 (s) $cm^{-1}$.

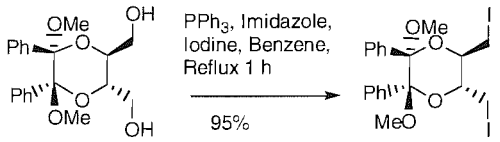
**$^1$H NMR** (300MHz, $CDCl_3$): δ 7.33–7.21 (6H, m, ArH); 7.07–7.03 (4H, m, ArH); 4.19 (2H, m, 2×CH); 3.92 (4H, br s, 2×$CH_2OH$); 3.00 (6H, s, 2×$OCH_3$); 2.52 (2H, br s, 2×$CH_2OH$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 135.5 (2×C), 129.4 (4×CH), 128.1 (4×CH), 126.6 (2×CH), 100.4 (2×C), 69.3 (2×CH), 62.4 (2×$CH_2$), 49.2 (2×$CH_3$).

**ESMS**: m/z (%) 383 ($(M+Na)^+$, 100).

**HRMS** (ES): for $C_{20}H_{24}O_6Na$ $(M+Na)^+$: calcd 383.1465, found 383.1469.

### 5.7.3. (*2R,3R,5R,6R*)-5,6-Di(iodomethyl)-2,3-dimethoxy-2,3-diphenyl-1,4-dioxane (208)




**207** **208**

To diol **207** (0.72 g, 2.0 mmol) in benzene (80 mL) was added triphenylphosphine (2.24 g, 8.5 mmol), imidazole (0.58 g, 8.5 mmol), and iodine (2.16 g, 8.5 mmol). The reaction mixture was refluxed for 3 h and then allowed to cool to r.t. The mixture was washed with sat. aq. sodium thiosulfate solution (50 mL). The organic phase was then dried ($Na_2SO_4$) and filtered. The solvent was removed *in vacuo*. The crude reaction mixture was subjected to column chromatography (9:1 hexane:acetone) to give the product as a white solid (1.11g, 1.9 mmol, 95 %).

**M.p.** 52–54°C

$[\alpha]_D$ = -141 ° (c=2.3, $CHCl_3$, 28°C)

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$) 2950 (w), 2836 (w), 1734 (w), 1450 (w), 1185 (m), 1101 (s), 1039 (s), 760 (s) $cm^{-1}$.

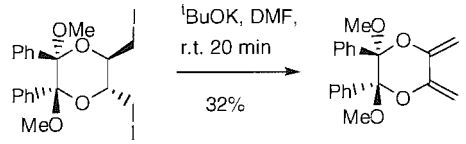
**$^1$H NMR** (300MHz, $CDCl_3$): δ 7.34–7.21 (8H, m, Ar<u>H</u>); 7.15–7.05 (2H, m, Ar<u>H</u>); 3.83 (2H, m, 2×C<u>H</u>); 3.40 (4H, m, 2×C<u>H</u>$_2$I); 3.03 (6H, s, 2×OC<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ 135.3 (2×C), 129.5 (4×CH), 128.1 (4×CH), 126.6 (2×CH), 101.2 (2×C), 70.2 (2×CH), 49.4 (2×$CH_3$), 4.3 (2×$CH_2$).

**ESMS**: m/z (%) 603 ($(M+Na)^+$, 100), 139 (45).

**HRMS** (ES): for $C_{20}H_{22}O_4I_2Na$ $(M+Na)^+$: calcd 602.9499, found 602.9483.

### 5.7.4. (*2R,3R*)-2,3-Dimethoxy-2,3-diphenyl-1,4-dimethylene-1,4-dioxane (188)




**208** **188**

$^t$BuOK (0.77 g, 6.89 mmol) was dissolved in DMF (6 mL) and stirred under $N_2$. Diiodide **208** (1.0 g, 1.7 mmol) was dissolved in DMF (5 mL) and was added slowly over 5 min to the $^t$BuOK solution. The reaction mixture was stirred for 20 min. Water (20 mL) was added and was hence extracted with ether (3×20 mL). The organic phases were combined and dried ($Na_2SO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane:acetone) to provide the title product as a white crystalline material (0.18 g, 0.6 mmol, 32 %).

**M.p.** 112–114°C

$[\alpha]_D$ = -104 ° (c=1.06, $CHCl_3$, 28°C)

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$) 3030 (w), 2964 (w), 2945 (w), 1606 (w), 1441 (w), 1304 (s), 1204 (s), 1110 (s), 1048 s), 760 (s) $cm^{-1}$.

**$^1$H NMR** (300MHz, $CDCl_3$): δ 7.20 (2H, m, ArH); 7.19 (4H, m, ArH); 6.93 (4H, br s, ArH); 4.83 (2H, d, *J* = 1.2, 2×CHH); 4.63 (2H, d, *J* = 1.2, 2×CHH); 3.04 (6H, s, 2×$OCH_3$).

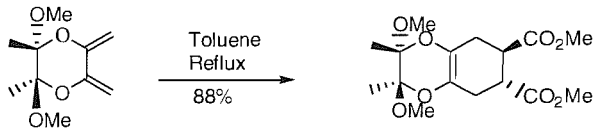
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): δ148.9 (2×C), 134.3 (4×C), 129.4 (4×CH), 128.4 (2×CH), 126.8 (2×CH), 101.7 (2×C), 90.9 (2×$CH_2$), 50.1 (2×$CH_3$).

**CIMS**: m/z (%) 325 ($M+H^+$, 64), 309 ($(M-CH_3)^+$,8), 293 (20), 105 (100).

**HRMS** (ES): for $C_{19}H_{18}O_4Na$ $(M+Na-CH_2)^+$: calcd 333.1097, found 333.1096.

## 5.8. Thermal Diels-Alder reactions of diene 183

### 5.8.1. (*2R,3R,6R,7R*) 2,3-dimethoxy-2,3-dimethyl-2,3,5,6,7,8-hexahydro-1,4-benzodioxin-6,7-dicarboxlate (215)




**183** **215**

To a solution of diene **183** (0.1g, 0.5 mmol) in toluene (2 mL) was added dimethyl fumarate (0.21 g, 1 mmol). The reaction mixture was then refluxed for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by chromatography (9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone) The pure product (0.15g, 0.43 mmol, 88%) was recovered as a white solid which was a mixture of diastereomers (88:12).

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $ml^{-1}$): 3054 (w), 2992 (w), 2945 (m), 2907 (w), 2855 (w), 2839 (w), 1729, (s), 1431 (m), 1365 (m).

**$^1$H NMR** (300MHz, $CDCl_3$): (mixture) δ 3.71 (6H, s, 2×$CO_2C\underline{H}_3$); 3.27 (6H, s, 2×$COC\underline{H}_3$); 3.02 (2H, m, 2×C<u>H</u>); 2.46 (4H, m, 2×$C\underline{H}_2$); 1.44 (6H, s, 2×$C\underline{H}_3COCH_3$).

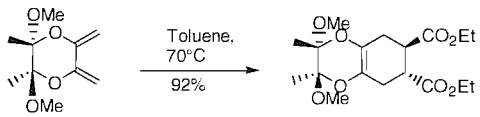
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): (major isomer) δ 174.1 (2×C), 124.7 (2×C), 98.17 (2×C) 52.1 (2×$CH_3$), 48.8 (2×$CH_3$), 41.2 (2×CH), 27.7 (2×$CH_2$), 17.3 (2×$CH_3$).

**CIMS**: m/z (%) 330 ($(M + H - Me)^+$, 6), 313 ($(M+H–MeOH)^+$, 14), 298 (8), 271 (55), 116 (100).

**HRMS** (EI) for $C_{16}H_{24}O_8$ $(M)^+$: calcd 344.1471, found 344.1483.

**Anal.** Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.02. Found: C 55.50; H, 6.95.

## 5.8.2. (*2R,3R,6R,7R*) Diethyl-2,3-dimethoxy-2,3-dimethyl-2,3,5,6,7,8-hexahydro-1,4-benzodioxin-6,7-dicarboxlate (209)




**183** **209**

To a solution of diene **183** (0.1g, 0.5 mmol) in toluene (2 mL) was added diethylfumarate (0.12 mL, 1 mmol). The reaction mixture was then heated at 70°C for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone). The pure product (0.17 g, 0.46 mmol, 92%) was recovered as a mixture of diastereomers (89:11) which was a light yellow oil.

**IR** (film) 2945 (w), 1738 (s), 1455 (w), 1375 (w), 1294 (m), 1182 (s), 1166 (s), 1138 (s), 1123 (s), 1039 (s) 939 (w) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): (mixture) δ 4.13 (4H, m, 2×$CO_2C\underline{H}_2CH_3$); 3.26 (6H, s, 2×$OC\underline{H}_3$); 2.93 (2H, m, 2×C<u>H</u>); 2.44 (4H, m, 2×$C\underline{H}_2CH$); 1.34 (6H, s, 2×$C\underline{H}_3$); 1.23 (6H, t, *J* = 7.0Hz, 2×$CO_2CH_2C\underline{H}_3$).

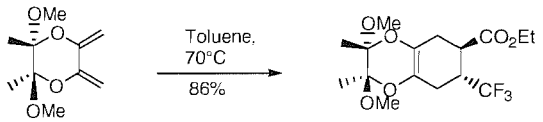
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): (major diastereomer) δ 173.8 (2×C), 124.8 (2×C), 98.3 (2×C), 60.9 (2×$CH_2$), 48.9 (2×$CH_3$), 41.6 (2×CH), 27.7 (2×$CH_2$), 17.4 (2×$CH_3$), 14.2 (2×$CH_3$).

**CIMS**: m/z (%): 372 ($(M)^+$, 4), 358 ($(MH\text{-}Me)^+$, 52), 299, (90), 116 (100).

**HRMS** (CI) for $C_{18}H_{28}O_8$ $(M)^+$: Calcd 372.1784, found 372.1774.

**Anal.** Calcd for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C 58.13; H, 7.82.

### 5.8.3. (*2R,3R,6R,7R*)-Ethyl-2,3-dimethoxy-2,3-dimethyl-7-(trifluoromethyl)-2,3,5,6,7,8-hexahydro1,4-benzodioxan-6-carboxylate (210)




**183** **210**

To a solution of diene **183** (0.1g, 0.5 mmol) in toluene (2 mL) was added ethyl 4,4,4 trifluorocrotonate (0.2 mL, 1 mmol). The reaction mixture was then heated at 70°C for 48 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone). The pure product (0.16 g, 0.43 mmol, 86 %) was recovered as a light yellow oil which was a mixture of diastereomers (82:18).

**IR** (film) 2935 (w), 1732 (m), 1455 (w), 1375 (w), 1266 (w), 1218 (m), 1153 (s), 1114 (s), 1043, (m), 939 (w) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): (mixture) δ 4.11 (2H, m, $CO_2C\underline{H}_2CH_3$); 3.18 (3H, s, $OC\underline{H}_3$); 3.17 (3H, s, $OC\underline{H}_3$); 2.81 (2H, m, $C\underline{H}_2CH$); 2.63 (1H, m, $C\underline{H}CF_3$); 2.36 (3H, m, $CH_2C\underline{H}$, $C\underline{H}_2CHCF_3$); 1.37 (6H, s, 2×$C\underline{H}_3$); 1.19 (3H, t, *J* = 7.3 Hz, $CO_2CH_2C\underline{H}_3$).

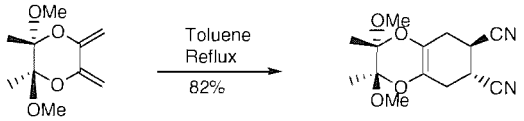
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): (major diastereomer) δ 171.6 (C), 127.2 (q, *J*=279.9 Hz; C), 123.2 (C), 122.3 (C), 97.3 (C), 97.2 (C), 60.2 ($CH_2$), 47.7 ($CH_3$), 39.2 (q, *J*= 27 Hz; CH), 38.6 (CH), 26.4 ($CH_3$), 22.2 (2×$CH_2$), 16.2 (2×$CH_3$), 12.9 ($CH_3$).

**CIMS**: m/z (%) 368 ($(M)^+$, 6), 354 ($(M+H-Me)^+$, 44), 337 ($(M+H–MeOH)^+$, 30), 322 ($(M-Me-OMe)^+$, 50), 295 (50), 116 (100).

**HRMS** (EI) for $C_{16}H_{23}O_6F_3$ $(M)^+$: calcd 368.1446, found 368.1459.

**Anal.** Calcd for $C_{16}H_{23}O_6F_3$: C, 52.17; H, 6.29. Found: C, 52.03; H, 6.27.

### 5.8.4. (*2R,3R,6R,7R*) 2,3-dimethoxy-2,3-dimethyl-2,3,5,6,7,8-hexahydro-1,4-benzodioxin-6,7-dicyanide (216)




**183** **216**

To a solution of diene **183** (0.1g, 0.5 mmol) in toluene (2 mL) was added fumaronitrile (0.078 g, 1 mmol). The reaction mixture was then refluxed for 48 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone). The pure product (0.16 g, 0.43 mmol, 82 %) was recovered as a light yellow oil which was a mixture of diastereomers (72:28).

**IR** (film) 2997 (w), 2936 (w), 2855 (w), 2831 (w), 2255 (m), 1725 (m), 1455 (w), 1365 (m), 1218 (s), 1143 (s), 1114 (s), 1039 (s), 930 (s) $cm^{-1}$.

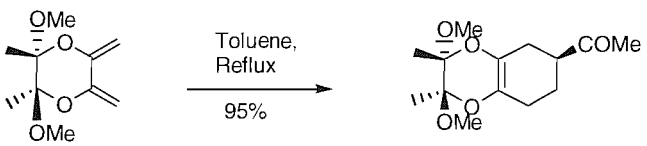
**$^1$H NMR** (300 MHz, $CDCl_3$): (mixture) δ 3.28 (6H, s, 2×OC<u>H</u>$_3$); 2.82–2.69 (4H, m, 2×C<u>H</u>$_2$); 2.64–2.58 (2H, m, 2×C<u>H</u>); 1.46 (6H, s, 2×C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): (major diastereomer) δ 123.4 (2×C), 117.7 (2×C), 98.6 (2×C), 48.9 (2×$CH_3$), 28.3 (CH), 27.5 (CH), 27.4 (2×$CH_2$), 17.1 (2×$CH_3$).

**EIMS**: m/z (%): 278 ($M^+$, 9), 247 ($(M-OMe)^+$, 26), 116 (100).

**Anal.** Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.06. Found: C, 60.36; H, 6.57; N, 10.01.

### 5.8.5. 1((*2R,3R,6R*)-2,3-dimethoxy- 2,3-dimethyl perhydro-1,4-benzodioxin-6-yl)-1 ethanone (211)




**183** **211**

To a solution of diene **183** (0.1g, 0.5 mmol) in toluene (2 mL) was added methyl vinyl ketone (0.1 mL, 1 mmol). The reaction mixture was then refluxed for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by column chromatography ( 9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone). The product **211** (0.13 g, 0.47 mmol, 95 %) was recovered as a yellow oil which was a mixture of diastereomers (60:40).

**IR** (film) 2935 (w), 1720 (s), 1460 (w), 1351 (m), 1209 (m), 1143 (s), 1135 (s), 1034 (m), 930 (m) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): (mixture) δ 3.26 (3H, s, $OC\underline{H}_3$); 3.22 (3H, s, $OC\underline{H}_3$); 2.65–2.21 (3H, s, $C\underline{H}_2C\underline{H}$); 2.16 (3H, s, $COC\underline{H}_3$); 2.15 (2H, m, $C\underline{H}_2CH_2$); 1.73 (2H, m, $CH_2C\underline{H}_2$); 1.42 (3H, s, $C\underline{H}_3$); 1.41 (3H, s, $C\underline{H}_3$).

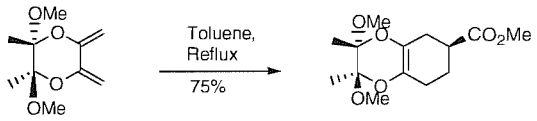
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$) (mixture): δ 210.1 and 209.9 (C) 126.5 and 126.4 (C), 125.5 and 125.3 (C), 98.1 and 97.9 (C), 97.8 and 97.8 (C), 50.1 and 49.9 ($CH_3$), 48.7 and 48.6 ($CH_3$), 47.3 and 47.1 ($CH_3$), 32.0 and 32.1 ($CH_2$), 28.3 and 28.1 (CH), 26.4 ($CH_2$) 24.7 and 24.6 ($CH_2$), 17.4 and 17.3 ($CH_3$), 17.2 and 17.1 ($CH_3$).

**CIMS**: m/z (%): 239 ($(M+H-MeOH)^+$, 22), 116 (100).

**HRMS** (EI) for $C_{14}H_{22}O_5$ $(M)^+$: calcd 270.1467, found 270.1468.

**Anal.** Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 61.80; H, 8.31.

## 5.8.6. (*2R,3R,6R*)-Methyl -2,3-dimethoxy-2,3-dimethyl perhydro–1,4-benzodioxin-6-carboxylate (212)




**183** **212**

To a solution of diene **183** (0.1g, 0.5 mmol) in toluene (2 mL) was added methyl acrylate (0.1 mL, 1 mmol). The reaction mixture was then refluxed for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by chromatography (9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone). The pure product (0.107g, 0.37 mmol, 75 %) was recovered as a colourless oil and as a mixture of diastereomers (70:30).

**IR** (film) 2940 (w), 1729 (s), 1445 (w), 1379 (w), 1215 (s), 1134 (s), 1135 (s), 1034 (s), 935 (s) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): (mixture) δ 3.65 (3H, s, $CO_2C\underline{H}_3$); 3.25 (3H, s, $OC\underline{H}_3$); 3.24 (3H, s, $OC\underline{H}_3$); 2.66 (1H, m, C<u>H</u>); 2.48–2.08 (2H, m, $CH_2C\underline{H}_2$); 2.06–1.82 (2H, m, $C\underline{H}_2CH$) 1.76–1.64 (2H, m, $C\underline{H}_2CH_2$); 1.40 (3H, s, $C\underline{H}_3$); 1.39 (3H, s, $C\underline{H}_3$).

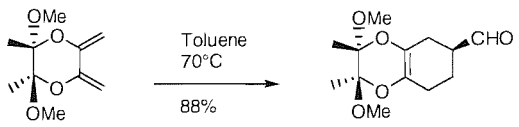
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): (major isomer) δ 174.9 (C), 126.5 (C), 125.3 (C), 98.1 (C), 98.0 (C), 51.9 ($CH_3$), 48.8 ($CH_3$), 48.3 ($CH_3$), 39.7 (CH), 27.7 ($CH_2$), 25.0 ($CH_2$), 24.2 ($CH_2$), 17.4 (2×$CH_3$).

**CIMS**: m/z (%): 271 ($(M+H-Me)^+$, 4), 255 ($(M+H-OMe)^+$, 20), 240 ($(M+H-Me-OMe)^+$, 8), 116 (100).

**HRMS** (EI) for $C_{13}H_{19}O_6$ $(M+H-Me)^+$: calcd 271.1186, found 271.1185

**Anal.** Calcd for $C_{13}H_{19}O_6$: C, 58.73; H, 7.74. Found: C, 58.81; H, 7.58.

## 5.8.7. (*2R,3R,6R*)-2,3-dimethoxy-2,3-dimethyl perhydro –1,4-benzodioxin-6-al (217)




**183** **217**

To a solution of diene **183** (0.1g, 0.5 mmol) in toluene (2 mL) was added acrolein (0.08 mL, 1 mmol). The reaction mixture was then hetated to 70°C for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone). The pure product (0.113 g, 0.44 mmol, 88 %) was recovered as a light yellow oil which was a mixture of diastereomers (55:45).

**IR** (film) 2992 (w), 2954 (m), 2841 (w), 1725 (s), 1455 (w), 1375 (m), 1365 (m), 1214 (s), 1143 (s), 1034 (s), 935 (m) $cm^{-1}$.

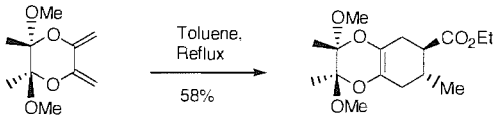
**$^1$H NMR** (300 MHz, $CDCl_3$): (mixture) δ 9.66 (1H, s, C<u>H</u>O); 3.28 (3H, s, $OC\underline{H}_3$); 3.27 (3H, s, $OC\underline{H}_3$); 2.55 (1H, m, CHOC<u>H</u>); 2.36–2.19 (2H, m, $CHC\underline{H}_2CH_2$); 2.18–2.00 (2H, m, $CHOCHC\underline{H}_2$); 1.96–1.88 (2H, m, $CHCH_2C\underline{H}_2$); 1.44 (6H, s, 2×$C\underline{H}_3$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): (major isomer) δ 203.5 (CH), 126.8 (C), 125.0 (C), 98.0 (C), 97.9 (C), 48.8 ($CH_3$), 48.7 ($CH_3$), 45.4 (CH), 24.9 ($CH_2$), 24.1 ($CH_2$), 21.9 ($CH_2$), 17.26 (2×$CH_3$).

**EIMS**: m/z (%) 256 ($M^+$, 44), 225 ($(M-OMe)^+$, 13), 183 (69), 167 (30), 116 (100).

**HRMS** (EI) for $C_{13}H_{20}O_5$ ($M^+$): calcd 256.1310, found 256.1311.

### 5.8.8. (*2R,3R,6R,7R*)-Ethyl - 2,3 dimethoxy-2,3,7 trimethyl perhydro-1,4 benzodioxin-6-carboxylate (213)




**183** **213**

To a solution of diene **183** (0.1g, 0.5 mmol) in toluene (2 mL) was added ethyl crotonate (0.1 mL, 1 mmol). The reaction mixture was then refluxed for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by chromatography (9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone). The pure product (0.086 g, 0.27 mmol, 58 %) was recovered as a yellow oil (mixture of diastereomers 91:9).

**IR** (film) 2935 (m), 1739 (m), 1464 (w), 1375 (m), 1204 (m), 1139 (s), 1125 (s), 931 (s) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): (mixture) δ 4.12 (2H, m, $CO_2C\underline{H}_2CH_3$); 3.24 (3H, s, $OC\underline{H}_3$); 3.22 (3H, s, $OC\underline{H}_3$); 2.58 (1H, m, $C\underline{H}CO_2CH_2CH_3$); 2.34–2.22 (1H, m, $C\underline{H}CH_3$); 2.19–2.04 (4H, m, $C\underline{H}_2CHCO_2CH_2CH_3$, $C\underline{H}_2CHCH_3$); 1.37 (6H, s, 2×$C\underline{H}_3$); 1.25 (3H, t, $J$ = 4.0 Hz, $CO_2CH_2C\underline{H}_3$); 0.98 (3H, d, $J$ = 6.1 Hz, $CHC\underline{H}_3$).

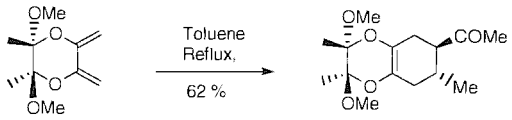
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): (major diastereomer) δ 174.7 (C), 126.0 (C), 125.1 (C), 99.1 (C), 98.3 (C), 60.4 ($CH_2$), 48.8 (2×$CH_3$), 47.1 (CH), 32.7 (CH), 31.5 ($CH_2$), 28.5 ($CH_2$), 19.3 ($CH_3$), 17.4 (2×$CH_3$), 14.4 ($CH_3$).

**CIMS**: m/z (%): 315 ($(MH)^+$, 8), 300($(M-Me)^+$, 10), 283 ($(M+H-OMe)^+$, 16), 268 (8), 116 (100).

**HRMS** (EI) for $C_{16}H_{26}O_6$: calcd 314.1729, found 314.1734.

**Anal.** Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.31; H, 8.41.

### 5.8.9. 1-((*2R,3R,6R,7R*)-2,3-dimethoxy-2,3,7-trimethyl perhydro-1,4-benzodioxin-6-yl)-1-ethanone (214)




**183** **214**

To a solution of diene **183** (0.1g, 0.5 mmol) in toluene (2 mL) was added 3-pentene-2-one (0.1 mL, 1 mmol). The reaction mixture was then refluxed for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by chromatography (9:1 hexane:acetone), and then further purified by HPLC (9:1 hexane:acetone). The product (0.088 g, 0.31 mmol, 62 %) was recovered as a white solid which was a mixture of diastereomers (89:11).

**M.p.** 46-48 °C

**IR** (solid) 2935 (w), 1739 (m), 1375 (m), 1214 (m), 1143 (s), 1114 (s), 1043 (s), 934 (m) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): (mixture) δ 3.24 (3H, s, $OC\underline{H}_3$); 3.22 (3H, s, $OC\underline{H}_3$); 2.47 (1H, m, $C\underline{H}COCH_3$); 2.27–2.12 (2H, m, $C\underline{H}_2CHCOCH_3$); 2.10 (3H, s, $COC\underline{H}_3$); 2.01–1.93 (2H, m, $C\underline{H}_2CHCH_3$); 1.76 (1H, m, $CH_2C\underline{H}CH_3$); 1.40 (6H, s, $2\times C\underline{H}_3$); 0.95 (3H, d, $J$ = 6.0 Hz, $CH_2CHC\underline{H}_3$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): (major diastereomer) δ 210.9 (C), 125.4 (C), 124.5 (C), 98.1 (C), 97.9 (C), 53.9 ($CH_3$), 48.7 ($CH_3$), 48.6 ($CH_3$), 32.3 (CH), 30.3 ($CH_2$), 28.7 ($CH_2$), 27.3 (CH), 19.2 ($CH_3$), 17.3 ($CH_3$), 17.2 ($CH_3$).

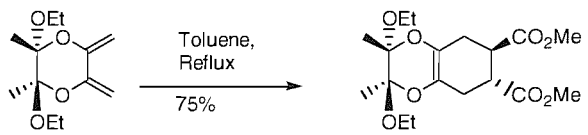
**CIMS**: m/z (%): 284 ($(M)^+$, 4), 253 ($(M+H-MeOH)^+$, 12), 116 (100).

**HRMS** (EI) for $C_{15}H_{24}O_5$ $(M)^+$: calcd 284.1623, found 284.1621.

**Anal.** Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.25; H, 8.55.

## 5.9. Thermal Diels-Alder reactions of diene 184

### 5.9.1. (*2R,3R,6R,7R*)Dimethyl-2,3-diethoxy-2,3-dimethyl-2,3,5,6,7,8-hexahydro-1,4benzodioxin-6,7-dicarboxlate (218)




**184** **218**

To a solution of diene **184** (0.12 g, 0.50 mmol) in toluene (2 mL) was added dimethyl fumarate (0.21 g, 1 mmol). The reaction mixture was then refluxed for 18 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. Chromatography was carried out (9:1 hexane:acetone) and the product **218** was isolated as a white solid (0.192 g, 0.37 mmol, 75 %) which was a mixture of diastereomers (85:15).

**M.p.** 80–82 °C

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$): 3054 (w), 2978 (w), 2945 (w), 2893 (w), 2851 (w), 1739 (s), 1436 (w), 1370 (w), 1266.22 (s), 1209 (m), 1166 (m), 1138 (m), 1053 (w), 949 (w).

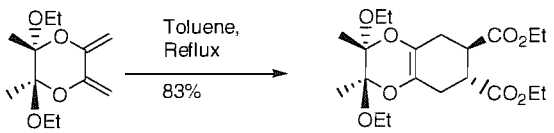
**$^1$H NMR** (300 MHz, $CDCl_3$) (mixture): δ 3.69 (6H, s, 2×$CO_2C\underline{H}_3$); 3.58 (4H, m, 2×$CH_3C\underline{H}_2O$); 3.02 (2H, m, 2×C<u>H</u>); 2.52–2.31 (4H, m, 2×$C\underline{H}_2CH$); 1.44 (6H, s, 2×$C(O)C\underline{H}_3$); 1.13 (6H, t, $J$ = 6.9 Hz, 2×$C\underline{H}_3CH_2O$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$) (major component): δ 174.1 (2×C), 124.4 (2×C), 97.9 (2×C), 56.7 (2×$CH_3$), 52.0 (2×$CH_2$), 41.0 (2×$CH_2$), 27.0 (2×CH), 18.1 (2×$CH_3$), 15.8 (2×$CH_3$).

**CIMS**: m/z (%) 372 ($(M)^+$, 6), 285 (14), 144 (100).

**Anal.** Calcd for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 57.87; H, 7.60.

### 5.9.2. (2*R*,3*R*,6*R*,7*R*) Diethyl-2,3-diethoxy-2,3-dimethyl-2,3,5,6,7,8-hexahydro-1,4benzodioxin-6,7-dicarboxlate (219)




**184** **219**

To a solution of diene **184** (0.12 g, 0.50 mmol) in toluene (2 mL) was added diethyl fumarate (0.12 mL, 1 mmol). The reaction mixture was then refluxed for 18 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. Chromatography was carried out (9:1 hexane:acetone) and the product **219** was isolated as a colourless oil (0.16 g, 0.41 mmol, 83%) which was a mixture of diastereomers (83:17).

**IR** (film) 2935 (w), 1739 (s), 1445 (w), 1366 (w), 1289 (m), 1145 (s), 1110 (s), 1058 (s),930 (w) $cm^{-1}$.

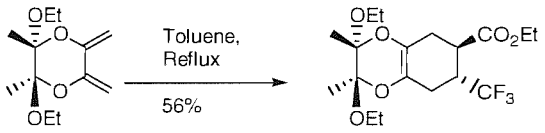
**$^1$H NMR** (300 MHz, $CDCl_3$) (mixture): δ 4.15 (4H, m, 2×$CO_2C\underline{H}_2CH_3$); 3.53 (4H, m, 2×$CH_3C\underline{H}_2O$); 2.97 (2H, m, 2×C<u>H</u>): 2.47 (4H, m, 2×$C\underline{H}_2CH$); 1.42 (6H, s, 2×$C(O)C\underline{H}_3$); 1.24 (6H, t, *J* = 7.2 Hz, 2×$CO_2CH_2C\underline{H}_3$); 1.12 (6H, t, *J* = 7.2 Hz. 2×$C\underline{H}_3CH_2O$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$) (major component): δ 173.5 (2×C), 124.4 (2×C), 97.9 (2×C), 60.7 (2×$CH_2$), 56.6 (2×$CH_2$), 41.2 (2×CH), 27.3 (2×$CH_2$), 17.9 (2×$CH_3$), 15.7 (2×$CH_3$), 14.0 (2×$CH_3$).

**CIMS**: m/z (%) 400 ($(M)^+$, 4), 372 (10), 355 (12), 313 (65), 144 (100).

**Anal.** Calcd for $C_{20}H_{32}O_8$: C, 59.98; H, 8.05. Found: C, 60.38; H, 8.26.

### 5.9.3. (2R,3*R*,6*R*,7*R*) Ethyl-2,3diethoxy-2,3dimethly-7-(trifluoromethyl)-2,3,5,6,7,8-hexahydro-1,4-benzodioxan-6-carboxylate (220)




**184** **220**

To a solution of diene **184** (0.12 g, 0.50 mmol) in toluene (2 mL) was added ethyl 4,4,4 trifluorocrotonate (0.21 mL, 1 mmol). The reaction mixture was then refluxed for 18 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. Chromatography was carried out (9:1 hexane:acetone) and the product **220** was isolated as a colourless oil (0.118 g, 0.28 mmol, 56%) which was a mixture of diastereomers (82:18).

**IR** (film): 2973 (m), 2921 (m), 2884 (w), 1739 (s), 1446 (w), 1370 (m), 1313 (m), 1218 (s), 1119 (s), 1053 (s), 939 (m).

**$^1$H NMR** (300 MHz, $CDCl_3$) (mixture): δ 4.16 (2H, m, $CO_2C\underline{H}_2CH_3$); 3.52–2.98 (4H, m, 2×$CH_3C\underline{H}_2O$); 2.98–2.86 (2H, m, $C\underline{H}CO_2CH_2CH_3$, $C\underline{H}CF_3$); 2.70 (1H, dd, *J* = 20.4, 6.2 Hz, $C\underline{H}HCHCO_2CH_2CH_3$); 2.41 (2H, m, $CH\underline{H}CHCO_2CH_2CH_3$, $CH\underline{H}CHCF_3$); 2.39 (1H, dd, *J* = 15.6, 5.9 Hz, $C\underline{H}HCHCF_3$); 2.29 (3H, s, $C(O)C\underline{H}_3$); 2.28 (3H, s, $C(O)C\underline{H}_3$); 1.44 (3H, t, *J* = 7.1 Hz, $CO_2CH_2C\underline{H}_3$); 1.13 (6H, m, 2×$C\underline{H}_3CH_2O$).

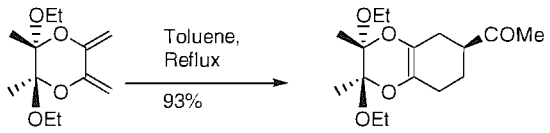
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$) (major component): δ 172.4 (C), 126.4 (q, *J* = 279 Hz, C), 124.1 (C), 123.1 (C), 98.1 (C), 98.0 (C), 61.2 ($CH_2$), 56.8 ($CH_2$), 56.7

($CH_2$), 39.4 (q, *J*= 27 Hz, CH), 38.5 (CH), 27.7 ($CH_2$), 22.8 ($CH_2$), 18.0 ($CH_3$), 17.9 ($CH_3$), 15.9 ($CH_3$), 15.6 ($CH_3$), 14.7 ($CH_3$).

**CIMS**: m/z (%) 396 ($(M)^+$, 14), 351 (18), 309 (40), 144 (100)

**Anal.** Calcd for $C_{18}H_{27}O_6F_3$: C, 54.54; H, 6.87. Found: C, 54.45; H, 6.83.

### 5.9.4. ((2*R*,3*R*,6*R*)-2,3 diethoxy- 2,3-dimethyl perhydro-1,4-benzodioxin-6-yl)-1 ethanone (221)




**184** **221**

To a solution of diene **184** (0.12 g, 0.50 mmol) in toluene (2 mL) was added methyl vinyl ketone (0.1 mL, 1 mmol). The reaction mixture was then refluxed for 18 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. Chromatography was carried out (9:1 hexane:acetone) and the product **221** was isolated as a colourless oil (0.14 g, 0.46 mmol, 93%) which was a mixture of diastereomers (63:37).

**IR** (film) 2968 (m), 2926 (m), 2884 (m), 2845 (m), 1715 (s), 1436 (w), 1356 (m), 1209 (s), 1138 (s), 1048 (s), 930 (m).

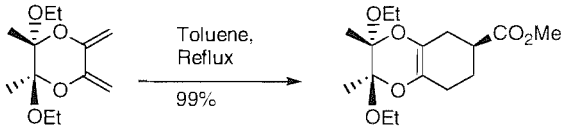
**$^1$H NMR** (300 MHz, $CDCl_3$) (mixture): δ 3.75 (4H, m, 2×$CH_3C\underline{H}_2O$); 2.61 (1H, m, $C\underline{H}COCH_3$); 2.45 (1H, m, $CH_2C\underline{H}_2CH$); 2.33–2.09 (4H, m, $CH_2C\underline{H}_2CH$, $COC\underline{H}_3$); 2.08–1.84 (2H, m, $C\underline{H}_2CHCOCH_3$); 1.80–1.74 (2H, m, $C\underline{H}_2CH_2CH$); 1.44 (3H, s, $C(O)C\underline{H}_3$); 1.43 (3H, s, $C(O)C\underline{H}_3$); 1.14 (6H, m, 2×$C\underline{H}_3CH_2O$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$) (major component): δ 210.0 (C), 126.2 (C), 125.1 (C), 97.9 (C), 97.7 (C), 56.7 ($CH_2$), 56.6 ($CH_2$), 47.6 ($CH_3$), 47.1 (CH), 27.7 ($CH_2$), 27.1 ($CH_2$), 24.1 ($CH_2$), 18.3 ($CH_3$), 18.2 ($CH_3$), 15.8 ($CH_3$), 15.7 ($CH_3$).

**CIMS**: m/z (%) 298 ($(M)^+$, 8), 211 (12), 144 (100).

**Anal.** Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.71; H, 8.87.

### 5.9.5. (2*R*,3*R*,6*R*)-Methyl-2,3-diethoxy-2,3-dimethylperhydro–1,4-benzodioxin-6-carboxylate (222)




**184** **222**

To a solution of diene **184** (0.12 g, 0.50 mmol) in toluene (2 mL) was added the methyl acrylate (0.12 mL, 1 mmol). The reaction mixture was then refluxed for 18 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. Chromatography was carried out (9:1 hexane:acetone) and the product **222** was isolated as a colourless oil (0.15 g, 0.49 mmol, 99%) which was a mixture of diastereomers (69:31).

**IR** (film) 2978 (m), 2945 (m), 2883 (m), 2850 (m), 1739 (s), 1436 (m), 1375 (m), 1204 (s), 1129, (s), 1043 (s), 939 (m), 878 (w).

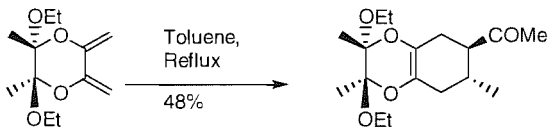
**$^1$H NMR** (300 MHz, $CDCl_3$) (mixture): δ 3.69 (3H, s, $CO_2C\underline{H}_3$); 3.60 (4H, m, 2×$CH_3C\underline{H}_2O$); 2.65–2.41 (2H, m, $C\underline{H}_2CHCO_2CH_2CH_3$); 2.39–2.18 (3H, m, $C\underline{H}CO_2CH_2CH_3$, $CH_2C\underline{H}_2CH$); 2.09–1.80 (2H, m, $C\underline{H}_2CH_2$); 1.44 (3H, s, $C(O)C\underline{H}_3$); 1.43 (3H, s, $C(O)C\underline{H}_3$); 1.12 (6H, m, 2×$C\underline{H}_3CH_2O$).

**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$) (major component): δ 174.8 (C), 126.1 (C), 124.9 (C), 97.8 (C), 97.7 (C), 56.7 ($CH_2$), 56.6 ($CH_2$), 51.6 ($CH_3$), 39.3 (CH), 27.6 ($CH_2$), 24.8 ($CH_2$), 24.6 ($CH_2$), 18.1 ($CH_3$), 18.0 ($CH_3$), 15.8 (2×$CH_3$).

**CIMS**: m/z (%) 314, ($(M)^+$, 12), 269 (6), 227 (24), 114 (100).

**Anal.** Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.02; H, 8.48.

### 5.9.6. 1-((2*R*,3*R*,6*R*,7*R*)-2,3 diethoxy-2,3,7-trimethyl perhydro-1,4-benzodioxin-6-yl)-1-ethanone (223)




**184** **223**

To a solution of diene **184** (0.12 g, 0.50 mmol) in toluene (2 mL) was added the 3-penten-2-one (0.12 mL, 1 mmol). The reaction mixture was then refluxed for 18 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. Chromatography was carried out (9:1 hexane:acetone). The product **223** was

isolated as a colourless oil (0.074 g, 0.24 mmol, 48%) which was a mixture of diastereomers ( >98:2).

$[\alpha]_D$ = -97.6° (c = 1.0, $CDCl_3$, 25°C)

**IR** (film) 2964 (m), 2931 (m), 2845 (m), 1710 (s), 1445 (m), 1365 (m), 1209 (s), 1129 (s), 1043 (s), 930 (m), 887 (w).

**$^1$H NMR** (300MHz, $CDCl_3$) (mixture): δ 3.55 (4H, m, 2×$CH_3C\underline{H}_2O$); 2.44 (2H, m, $C\underline{H}_2CHCOCH_3$); 2.17–2.07 (5H, m, $COC\underline{H}_3$, $C\underline{H}_2CHCH_3$); 1.96 (1H, m, $C\underline{H}COCH_3$); 1.72 (1H, m, $C\underline{H}CH_3$); 1.45 (3H, s, $C(O)C\underline{H}_3$); 1.44 (3H, s, $C(O)C\underline{H}_3$); 1.14 (6H, m, 2×$C\underline{H}_3CH_2OC(O)CH_3$); 0.97 (3H, d, $J$ = 6.4, $CH_2CHC\underline{H}_3$).

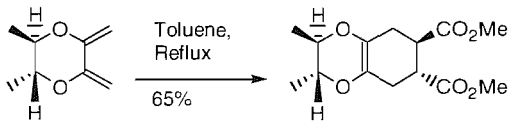
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$) (major component): δ 211.0 (C), 125.1 (C), 124.2 (C), 97.9 (C), 97.8 (C), 56.7 ($CH_2$), 56.6 ($CH_2$), 53.6 ($CH_3$), 31.8 ($CH_2$), 30.0 (CH), 28.6 (CH), 26.6 ($CH_2$), 19.3 ($CH_3$), 18.1 ($CH_3$), 18.0 ($CH_3$), 15.8 ($CH_3$), 15.7 ($CH_3$).

**CIMS**: m/z (%) 312 ($(M)^+$, 8), 225 (14), 144 (100).

**Anal.** Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.19; H, 8.89.

## 5.10. Thermal Diels-Alder reaction of diene 185

### 5.10.1. *2R,3R*-Dimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*, *7R*-dicarboxylic acid dimethyl ester (224)




**185** **224**

To a solution of diene **185** (0.07g, 0.5 mmol) in toluene (2 mL) was added methyl fumarate (0.1 g, 1 mmol). The reaction mixture was then refluxed for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane/ether). The product **224** was recovered as a colourless oil (0.092 g, 0.32 mmol, 65%) which was a mixture of diastereoisomers (73:27).

**IR** (film) 2983 (s), 2950 (s), 2883 (s), 2883 (w), 2732 (w), 2628 (w), 1734 (s), 1625 (m), 1209 (br s).

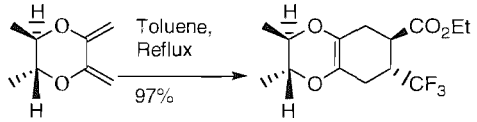
**$^1$H NMR** (400MHz, $CDCl_3$): (mixture) δ 3.68 (6H, s, 2×$CO_2C\underline{H}_3$); 3.63–3.57 (2H, m, 2×$CH_3C\underline{H}$); 3.03–2.99 (2H, m, 2×$C\underline{H}CO_2CH_3$); 2.45–2.31 (4H, m, 2×$C\underline{H}_2CH$); 1.20–1.18 (6H, m, 2×$C\underline{H}_3CH$).

**$^{13}$C NMR + DEPT** (100 MHz, $CDCl_3$): (major isomer) δ 174.0 (2×C), 127.1 (2×C), 74.4 (2×CH), 51.9 (2×$CH_3$), 40.9 (2×CH), 27.3 (2×$CH_2$), 16.8 (2×$CH_3$).

**EIMS**: m/z (%): 285 ($(M+H)^+$, 43), 284 ($(M)^+$, 100), 253 ($(M\text{-}OMe)^+$, 38), 225 ($(M\text{-}CO_2Me)^+$, 55), 140 (99).

**Anal**. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H,7.09. Found C, 59.16; H, 7.23.

## 5.10.2. 2*R*,3*R*-Dimethyl-7*R*-trifluoromethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-6*R*-carboxylic acid ethyl ester (225)




To a solution of diene **185** (0.07g, 0.5 mmol) in toluene (2 mL) was added ethyl-4,4,4-trifluorocrotonate (0.2 mL, 1 mmol). The reaction mixture was then refluxed for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane/ether). The product was a colourless oil (0.149 g, 0.48 mmol, 97%) which was recovered as a mixture of diastereoisomers (69:31).

**IR** (film) 2983 (s), 2945 (m), 2869 (m), 1734 (s), 1445 (m), 1379 (s0) 1318 (s), 1200 (s), 935 (w).

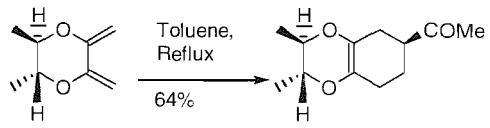
**$^1$H NMR** (400MHz, $CDCl_3$): (mixture) δ 4.21–4.13 (2H, m, 2×$C\underline{H}CH_3$); 3.66–3.60 (2H, m, $CO_2C\underline{H}_2CH_3$); 2.98–2.77 (2H, m, $C\underline{H}CO_2CH_2CH_3$, $C\underline{H}CF_3$); 2.42–2.36 (4H, m, 2×$CH_2$); 1.26 (3H, t, $J$ = 7.0 Hz, $CO_2C\underline{H}_3$); 1.22–1.20 (6H, m, 2×$CHC\underline{H}_3$).

**$^{13}$C NMR + DEPT** (100 MHz, $CDCl_3$): (major isomer) δ 172.5 (C), 126.8 (C, q, $J$ = 430 Hz), 126.7 (C), 125.6 (C), 74.3 (2×CH), 61.2 ($CH_2$), 40.4 (CH, q, $J$ = 27 Hz), 39.5 (CH), 28.2 ($CH_2$), 26.9 ($CH_2$), 16.8 ($CH_3$), 13.9 ($CH_3$), 13.8 ($CH_3$).

**EIMS**: m/z (%): 308 ($(M)^+$, 25), 235 ($(M\text{-}CO_2Me)^+$, 12), 56 (100).

**Anal**. For $C_{14}H_{19}O_4F_4$ calcd C, 54.54; H, 6.21. Found C, 54.80; H, 6.47.

### 5.10.3. 1-(*2R*, *3R*-Dimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-yl)-ethanone (226)




185 226

To a solution of diene **185** (0.07 g, 0.5 mmol) in toluene (2 mL) was added methyl vinyl ketone (0.1 mL, 1 mmol). The reaction mixture was then refluxed for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane/ether). The product was isolated as a colourless oil (0.068 g, 0.32 mmol, 64 %) which was a mixture of diastereoisomers (62:38).

**IR** (film) 2973 (s), 2935 (s), 2879 (s), 2737 (w), 2642 (w), 1715 (s), 1507 (m), 1162 (br s), 845 (s).

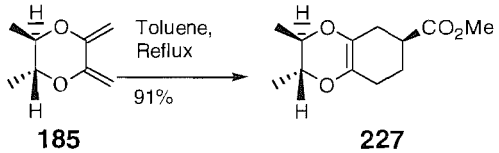
**$^1$H NMR** (400MHz, $CDCl_3$): (mixture) δ 3.63–3.60 (2H, m, 2×C<u>H</u>CH$_3$); 2.65 (1H, m, C<u>H</u>H); 2.42 (1H, m, C<u>H</u>H); 2.37–2.14 (4H, m, C<u>H</u>COC<u>H</u>$_3$); 1.99 (1H, m, C<u>H</u>H); 1.92 (1H, m, C<u>H</u>H); 1.79–1.71 (2H, m, 2×C<u>H</u>H); 1.27–1.25 (6H, m, 2×CHC<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (100 MHz, $CDCl_3$): (major isomer) δ 209.8 (C), 128.7 (C), 127.6 (C), 74.4 (CH), 73.3 (CH), 47.9 ($CH_3$), 28.3 (CH), 28.1 ($CH_2$), 28.0 ($CH_2$), 27.9 ($CH_2$), 16.9 (2×$CH_3$).

**EIMS**: m/z (%): 211 ($(M+H)^+$, 14), 210 ($(M)^+$, 80), 167 ($(M-COMe)^+$, 26), 98 (100).

**Anal.** Calcd for $C_{12}H_{18}O_3$: C, 69.61; H, 8.99. Found: C, 69.27; H, 9.27.

### 5.10.4. *2R,3R*-Dimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-carboxylic acid methyl ester (227)




185 227

To a solution of diene **185** (0.07 g, 0.5 mmol) in toluene (2 mL) was added methyl acrylate (0.1 mL, 1 mmol). The reaction mixture was then refluxed for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane/ether). The

product was isolated as a colourless oil (0.102 g, 0.45 mmol, 91 %) which was a mixture of diastereoisomers (64:36).

**IR** (film) 2964 (s), 2959 (s), 2879 (s), 2642 (w), 1743 (s), 1611 (s), 1502 (s), 1280 (br s), 769 (s).

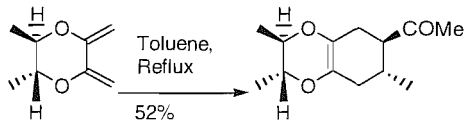
**$^1$H NMR** (400MHz, $CDCl_3$): (mixture) δ 3.69 (3H, s, $CO_2C\underline{H}_3$); 3.65–3.60 (2H, m, 2×C$\underline{H}$CH$_3$); 2.68 (1H, m, C$\underline{H}$CO$_2$CH$_3$); 2.27–2.46 (4H, m, 2×C$\underline{H}_2$); 1.97–1.82 (2H, m, C$\underline{H}_2$CH$_2$CH); 1.22–1.20 (6H, m, 2×CHC$\underline{H}_3$).

**$^{13}$C NMR + DEPT** (100 MHz, $CDCl_3$): (major isomer) δ 174.9 (C), 128.7 (C), 127.5 (C), 74.1 (CH), 51.7 ($CH_3$), 39.2 (CH), 27.9 ($CH_2$), 24.9 ($CH_2$), 24.5 ($CH_2$), 16.9 (2×$CH_3$).

**EIMS**: m/z (%): 226 ($(M)^+$, 46), 170 ($(M-[CH_3CH]_2)^+$, 12), 114 (100).

**Anal.** For $C_{12}H_{18}O_4$ calcd C, 63.70; H, 8.02. Found C, 63.93; H, 8.07.

### 5.10.5. 1-(*2R, 3R, 7R*-Trimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-yl)-ethanone (228)




**185** **228**

To a solution of diene **185** (0.07 g, 0.5 mmol) in toluene (2 mL) was added methyl crotonate (0.1 mL, 1 mmol). The reaction mixture was then refluxed for 24 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (9:1 hexane/ether). The product was isolated as a white solid (0.059 g, 0.26 mmol, 52%) which was a mixture of diastereoisomers (72:28).

**M.p.** 104–105°C

**IR** (film) 3058 (m), 2987 (s), 2931 (m), 2874 (m), 1720 (s), 1573 (m), 1256 (s).

**$^1$H NMR** (400MHz, $CDCl_3$): (mixture) δ 3.59 (2H, m, 2×C$\underline{H}$CH$_3$); 2.45–2.39 (2H, m, 2×C$\underline{H}$H); 2.33 (1H, m, C$\underline{H}$COCH$_3$); 2.12–2.05 (4H, m, CHCOC$\underline{H}_3$, C$\underline{H}$CH$_3$); 1.89–1.82 (2H, m, 2×C$\underline{H}$H); 1.17–1.15 (6H, m, 2×(O)CHC$\underline{H}_3$); 0.92 (3H, d, $J$ = 6.2 Hz, CHC$\underline{H}_3$).

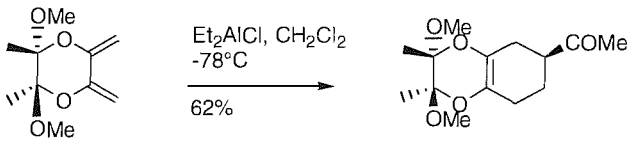
**$^{13}$C NMR + DEPT** (100 MHz, $CDCl_3$): (major isomer) δ 210.8 (C), 127.7 (C), 126.8 (C), 74.1 (2×CH), 53.8 ($CH_3$), 32.8 ($CH_2$), 30.2 (CH), 29.9 (CH), 27.5 ($CH_2$), 18.9 ($CH_3$), 17.0 ($CH_3$), 16.9 ($CH_3$).

**EIMS**: m/z (%): 225 ($(M+H)^+$, 9), 224 ($(M)^+$, 53), 181 ($(M\text{-Come})^+$, 27), 98 (100).

**Anal.** For $C_{13}H_{20}O_3$ calcd C, 69.61; H, 8.99. Found C, 69.50; H, 9.22.

## 5.11. Lewis acid catalysed Diels-Alder reaction of diene 183

### 5.11.1. 1((2*R*,3*R*,6*R*)-2,3-dimethoxy-2,3-dimethyl perhydro-1,4-benzodioxin-6-yl)-1 ethanone (211)

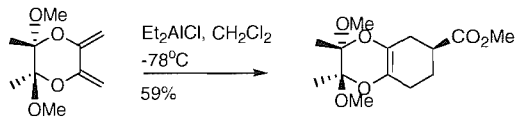



**183** **211**

To a solution of diene **183** (0.1 g, 0.5 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) in $CH_2Cl_2$ (2 mL) at –78°C was added diethyl aluminium chloride (0.2 mL, 0.2 mmol, 1.0 M in heptane). The resulting mixture was stirred for 6 h at -78°C. Sat. aq. sodium bicarbonate solution (5 mL) was added and the mixture allowed to warm to r.t. The reaction mixture was diluted with ether and the layers separated. The organic layer was washed with brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone). The product was recovered as a light yellow oil (0.084 g, 0.31 mmol, 62 %) which was a mixture of diastereomers (66:44).

The data obtained was consistent with that achieved earlier.

### 5.11.2. (*2R,3R,6R*)-Methyl-2,3-dimethoxy-2,3-dimethyl perhydro –1,4-benzodioxin-6-carboxylate (212)



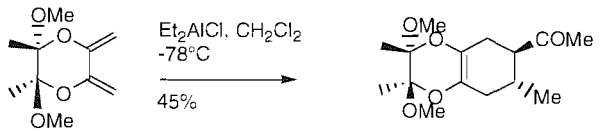

**183** **212**

To a solution of diene **183** (0.1 g, 0.5 mmol) and methyl acrylate (0.1 mL 1 mmol) in $CH_2Cl_2$ (2 mL) at –78°C was added diethyl aluminium chloride (0.2 mL, 0.2 mmol, 1.0 M in heptane). The resulting mixture was stirred for 6 h at -78°C. Sat. aq. sodium

bicarbonate solution (5 mL) was added and the mixture allowed to warm to r.t. The reaction mixture was diluted with ether and the layers separated. The organic layer was washed with brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone). The product (0.074 g, 0.26 mmol, 59 %) was recovered as a light yellow oil which was a mixture of diastereomers (>98:2).

The data obtained was consistent with that achieved earlier.

### 5.11.3. 1-((*2R,3R,6R,7R*)-2,3-Dimethoxy-2,3,7-trimethyl perhydro-1,4-benzodioxin-6-yl)-1-ethanone (214)



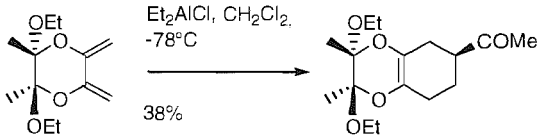

**183** **214**

To a solution of diene **183** (0.1 g, 0.5 mmol) and methyl acrylate (0.1 mL, 1 mmol) in $CH_2Cl_2$ (2 mL) at –78°C was added diethyl aluminium chloride (0.2 mL, 0.2 mmol, 1.0 M in heptane). The resulting mixture was stirred for 6 h at -78°C. Sat. aq. sodium bicarbonate solution (5 mL) was added and the mixture allowed to warm to r.t. The reaction mixture was diluted with ether and the layers separated. The organic layer was washed with brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (9:1 hexane:acetone) and then further purified by HPLC (9:1 hexane:acetone). The product (0.074 g, 0.26 mmol, 45%) was recovered as a light yellow oil which was a mixture of diastereomers (94:6).

The data obtained was consistent with that achieved earlier.

## 5.12. Lewis acid catalysed Diels-Alder reaction of diene 184

### 5.12.1 ((*2R,3R,6R*)-2,3 Diethoxy- 2,3-dimethyl perhydro-1,4-benzodioxin-6-yl)-1 ethanone (221)

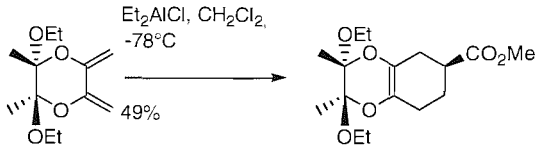



**184** **221**

To a solution of diene **184** (0.12 g, 0.5 mmol) and methyl vinyl ketone (0.12 mL, 1 mmol) in $CH_2Cl_2$ (2 mL) at –78°C was added diethylaluminium chloride (0.2 mL, 0.2 mmol, 1.0 M in heptane). The resulting mixture was stirred for 6 h at -78°C. Sat. aq. sodium bicarbonate solution (5 mL) was added and the mixture allowed to warm to r.t. The reaction mixture was diluted with ether and the layers separated. The organic layer was washed with brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography was carried out (eluent 9:1 hexane:acetone) and the product **221** was isolated as a colourless oil (0.056 g, 0.19 mmol, 38%) which was a mixture of diastereomers (67:33).

The data obtained was consistent with that achieved earlier.

## 5.12.2. (2*R*,3*R*,6*R*) Methyl -2,3 -diethoxy-2,3-dimethyl perhydro –1,4-benzodioxin-6-carboxylate (222)



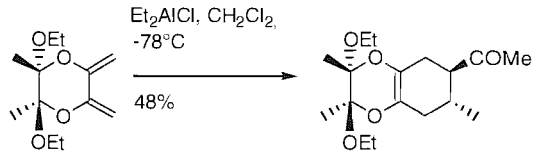

**184** **222**

To a solution of diene **184** (0.12 g, 0.5 mmol) and methyl acrylate (0.12 mL, 1 mmol) in $CH_2Cl_2$ (2 mL) at –78°C was added diethylaluminium chloride (0.2 mL, 0.2 mmol, 1.0 M in heptane). The resulting mixture was stirred for 6 h at –78°C. Sat. aq. sodium bicarbonate solution (5 mL) was added and the mixture allowed to warm to r.t. The reaction mixture was diluted with ether and the layers separated. The organic layer was washed with brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography was carried out (eluent 9:1 hexane:acetone) and the product **222** was isolated as a colourless oil (0.077 g, 0.24 mmol, 49%) which was a mixture of diastereomers (>98:2).

$[\alpha]_D$ = -127.7° (c = 1.0, $CDCl_3$, 25°C)

The other data obtained was consistent with that achieved earlier.

### 5.12.3. 1-((2*R*,3*R*,6*R*,7*R*)-2,3-Diethoxy-2,3,7-trimethylperhydro-1,4-benzodioxin-6-yl)-1-ethanone (223)



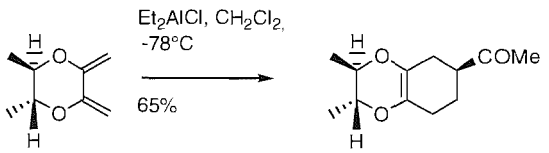

184 223

To a solution of diene **184** (0.12 g, 0.5 mmol) and 3-pentene-2-one (0.12 mL, 1 mmol) in $CH_2Cl_2$ (2 mL) at –78°C was added diethylaluminium chloride (0.2 mL, 0.2 mmol, 1.0 M in heptane). The resulting mixture was stirred for 6 h at –78°C. Sat. aq. sodium bicarbonate solution (5 mL) was added and the mixture allowed to warm to r.t. The reaction mixture was diluted with ether and the layers separated. The organic layer was washed with brine and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography was carried out (eluent 9:1 hexane:acetone) and the product 227 was isolated as a colourless oil (0.075 g, 0.24 mmol, 48%) which was a mixture of diastereomers (>98:2).

The data obtained was consistent with that achieved earlier.

## 5.13. Lewis acid catalysed Diels-Alder reaction of diene 185

### 5.13.1. 1-(*2R*, *3R*-Dimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-yl)-ethanone (226)

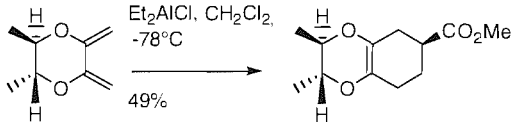



185 226

To a solution of diene **185** (0.07 g, 0.5 mmol) and methyl vinyl ketone (0.1 mL, 1 mmol) in $CH_2Cl_2$ (2 mL) at –78°C was added diethylaluminium chloride (0.2 mL, 0.2 mmol, 1.0 M in heptane). The resulting mixture was stirred for 6 h at –78°C. Sat. aq. sodium bicarbonate solution (5 mL) was added and the mixture allowed to warm to r.t. The reaction mixture was diluted with ether (10 mL) and the layers separated. The organic layer was washed with brine (5 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (9:1 hexane/ether). The product was isolated as a colourless oil (0.068 g, 0.32 mmol,

65%) which was a mixture of diastereoisomers (77:23). The data obtained was consistent with that achieved earlier.

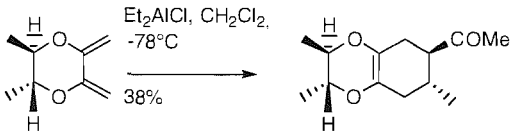
### 5.13.2. *2R*, *3R* -Dimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-carboxylic acid methyl ester (227)




**185** **227**

To a solution of diene **185** (0.07g, 0.5 mmol) and methyl acrylate (0.1 mL, 1 mmol) in $CH_2Cl_2$ (2 mL) at –78°C was added diethylaluminium chloride (0.2 mL, 0.2 mmol, 1.0 M in heptane). The resulting mixture was stirred for 6 h at –78°C. Sat. aq. sodium bicarbonate solution (5 mL) was added and the mixture allowed to warm to r.t. The reaction mixture was diluted with ether (10 mL) and the layers separated. The organic layer was washed with brine (5 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (9:1 hexane/ether). The product was isolated as a colourless oil (0.055 g, 0.24 mmol, 49%) which was a mixture of diastereoisomers (61:39). The data obtained was consistent with that achieved earlier.

### 5.13.3. 1-(*2R*, *3R*, *7R*-Trimethyl-2,3,5,6,7,8-hexahydro-benzo[1,4]dioxine-*6R*-yl)-ethanone (228)



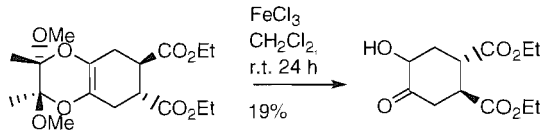

**185** **228**

To a solution of diene **185** (0.07 g, 0.5 mmol) and 3-pentene-2-one (0.1 mL, 1 mmol) in $CH_2Cl_2$ (2 mL) at –78°C was added diethylaluminium chloride (0.2 mL, 0.2 mmol, 1.0 M in heptane). The resulting mixture was stirred for 6 h at –78°C. Sat. aq. sodium bicarbonate solution (5 mL) was added and the mixture allowed to warm to r.t. The reaction mixture was diluted with ether (10 mL) and the layers separated. The organic layer was washed with brine (5 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (9:1 hexane/ether). The product was isolated a colouless oil (0.043 g, 0.19 mmol,

38%) which was a mixture of diastereoisomers (80:20). The data matched that previously obtained.

## 5.14. Deprotection of the Diels-Alder adduct 209

### 5.14.1. (*1R,2R*)-Diethyl-4-hydroxy-5-oxocyclohaxane-1,2-dicarboxylate (230)




**209** **230**

Following the procedure of Ley *et* al.[84] To a solution of **209** (0.11 g, 0.26 mmol) in $CH_2Cl_2$ (3 mL) was added $FeCl_3$ (0.21 g, 1.3 mmol). The slurry was stirred for 24 h at r.t.. Water (10 mL) was added to the reaction mixture and was extracted with $CH_2Cl_2$ (3×20 mL). The combined organic phases were dried ($Na_2SO_4$), filtered and solvent removed *in vacuo*. The crude material was subjected to chromatography (9:1 hexane:acetone) and **230** recovered as a light yellow oil (0.012 g, 0.05 mmol, 19%).

**IR** (film) 3465 (w), 2983 (w), 1729 (br s), 1375, (w), 1270, m), 1185 (m), 1100 (m), 1025 (m) $cm^{-1}$.

**$^1$H NMR** (300 MHz, $CDCl_3$): (mixture) δ 4.26–4.13 (5H, m, 2×$CO_2C\underline{H}_2CH_3$, HOC<u>H</u>CO); 3.56 (1H, bs, O<u>H</u>); 3.13 (1H, dt, *J* = 3.3, 12.8 Hz C<u>H</u>$CO_2CH_2CH_3$); 3.04 (1H, m, C<u>H</u>$CO_2CH_2CH_3$); 2.86 (1H, dd, *J* = 4.6, 14.6 Hz, C(O)C<u>H</u>HCH$CO_2CH_2CH_3$); 2.69 (1H, ddd, *J* = 3.3, 6.7, 12.9 Hz, HOCHC<u>H</u>H); 2.61 (1H, m, C(O)CH<u>H</u>CH$CO_2CH_2CH_3$); 1.67 (1H, q, *J* = 12.5 Hz, HOCHCH<u>H</u>); 1.29 (6H, t, *J* = 7.1 Hz, 2×$CO_2CH_2C\underline{H}_3$)

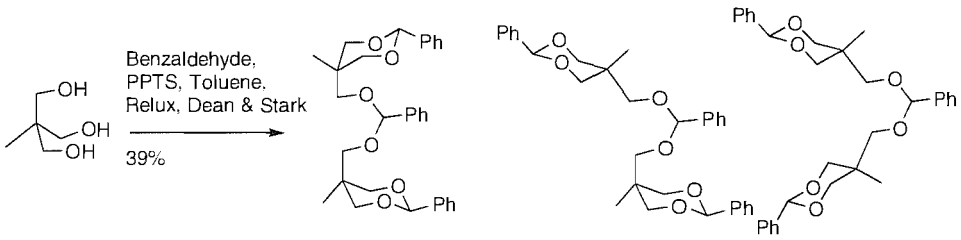
**$^{13}$C NMR + DEPT** (75 MHz, $CDCl_3$): (major diastereomer) δ 207.4 (C), 172.3 (C), 172.1 (C), 73.6 (CH), 61.7 ($CH_2$), 61.4 ($CH_2$), 45.6 (CH), 42.6 (CH), 40.0 ($CH_2$), 36.9 ($CH_2$), 14.2 (2×$CH_3$).

**CIMS**: m/z (%): 258 ($(M+H)^+$, 3), 212 ($(M–OEt)^+$, 20), 168 ($(M –2×OEt)^+$, 40), 140 (100).

**HRMS** (EI) for $C_{12}H_{18}O_6$ $(M)^+$: calcd 258.1103, found 284.1106.

## 5.15. Full and partial differentiation of Tris-1,1,1-(hydroxymethyl)ethane

### 5.15.1. "Dimers" of (1-Methyl-4-phenyl-3,5-dioxanyl) methanol (246)




**231** **246a** **246b** **246c**

To a stirred solution of 1,1,1-*tris*(hydroxymethyl)ethane **231** (8.93 g, 74.48 mmol) in toluene (250 mL) was added PPTS (86 mg) and $MgSO_4$ (13.4 g). Benzaldehyde (11.3 mL, 111.7 mmol) was added dropwise and the mixture was refluxed under Dean and Stark conditions overnight. 5% $NaHCO_3$ (100 mL) solution was added and the reaction allowed to cool to r.t. The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (2×100 mL). The organic phases were combined and dried ($Na_2SO_4$). When the drying agent had been filtered the solvents were removed *in vacuo*. The crude product was purified by column chromatography (95:5 haxane/ethyl acetate) to yield **246** as three isomers (7.30 g, 14.5 mmol, 39%, a:b:c 4.6:2.3:1). The isomers were separated by HPLC (95:5 haxane/ethyl acetate) for identification purposes.

Data for **246a**

**M.p.** 110–111 °C

**IR** (solid) 2950 (w), 2868 (w), 1454 (w), 1393 (m), 1205 (m), 1095 (s), 1045 (s), 1025 (s), 967 (m) 756 (s) $cm^{-1}$

**$^1$H NMR** (400MHz, *$d_6$-Acetone*): δ 7.57–7.55 (2H, m, ArH); 7.45–7.39 (4H, m, ArH); 7.38–7.37 (2H, m, ArH); 7.35–7.32 (7H, m, ArH); 5.72 (1H, s, CHPh); 5.46 (2H, s, 2×CHPh (ring)); 4.07–4.02 (4H, m, 4×CHHOCHPh (ring)); 3.89 (2H, d, *J* = 9.0 Hz, 2× CHHOCHPh); 3.80 (2H, d, *J*= 8.9 Hz, 2×CHHOCHPh); 3.65 (4H, d, *J* = 12.5 Hz, 4×CHHOCHPh (ring)); 0.95 (6H, s, 2×$CH_3$).

**$^{13}$C NMR + DEPT** (100MHz, *$d_6$-acetone*): δ 140.8 (2×C), 140.5 (C), 130.1 (2×CH), 129.7 (2×CH), 129.67 (2×CH), 129.4 (2×CH), 128.3 (2×CH), 127.9 (5×CH), 103.3

(CH), 103.0 (2×CH), 74.8 (2×$CH_2$), 74.4 (2×$CH_2$), 69.0 (2×$CH_2$), 35.6 (2×C), 18.6 (2×$CH_3$).

**ESMS**: m/z (%) 543 ($(M+K)^+$, 30), 527 ($(M+Na)^+$, 35), 225 (100).

**HRMS** (ES) Calcd for $C_{31}H_{36}O_6Na$ $(M+Na)^+$ 527.2404, found 527.2399.

Data for **246b**

**M.p.** 96–98 °C

**IR** (solid) 2950 (w), 2868 (w), 1454 (w), 1393 (m), 1205 (m), 1095 (s), 1045 (s), 1025 (s), 968 (m), 756 (s) $cm^{-1}$

**$^1$H NMR** (400MHz, *$d_6$-Acetone*): δ 7.47–7.31 (15H, m, ArH); 5.66 (1H, s, CHPh); 5.49 (1H, s, CHPh); 5.30 (1H, s, CHPh); 4.09 (1H, dd, *J* = 6.0, 2.5 Hz, CHHOCHPh (ring)); 4.07 (1H, dd, *J* = 6.0, 2.5 Hz, CHHOCHPh (ring)); 3.92 (1H, d, *J* = 10.8 Hz, CHHOCHPh (ring)); 3.89 (1H, d, *J* = 10.5 Hz, CHHOCHPh (ring)); 3.86 (1H, d, *J* = 9.0 Hz, CHHOCHPh (ring)); 3.80 (1H, dd, *J* = 7.3, 2.5 Hz, CHHOCHPh (ring)); 3.78 (1H, dd, *J* = 7.0, 2.3 Hz, CHHOCHPh (ring)); 3.76 (1H, d, *J* = 9.0 H z, CHHOCHPh); 3.69 (2H, d, *J* = 11.3 Hz, 2×CHHOCHPh (ring)); 3.34 (1H, d, *J* = 9.5 Hz, CHHOCHPh); 3.28 (1H, d, *J* = 9.5 Hz, CHHOCHPh); 1.29 (3H, s, $CH_3$); 0.89 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100MHz, *$d_6$-Acetone*): δ 140.9 (C), 140.7 (C), 140.3 (C), 130.1 (CH), 130.0 (CH), 129.9 (CH), 129.8 (2×CH), 129.5 (3×CH), 128.5 (2×CH), 127.9 (2×CH), 127.8 (3×CH), 103.02 (CH), 130.00 (CH), 102.9 (CH), 75.48 ($CH_2$), 75. 45 ($CH_2$), 74.56 ($CH_2$), 74.54 ($CH_2$), 70.1 ($CH_2$), 68.8 ($CH_2$), 35.8 (C), 35.7 (C), 20.3 ($CH_3$), 18.6 ($CH_3$).

**ESMS**: m/z (%) 543 ($(M+K)^+$, 8), 527 ($(M+Na)^+$, 5), 225 (100).

**HRMS** (ES) calcd for $C_{31}H_{36}O_6Na$ $(M+Na)^+$ 527.2404, found 527.2409.

Data for **246c**

**M.p.** 104–106 °C

**IR** (solid) 2992 (w), 2972 (w), 2907 (w), 2869 (w), 1453 (m), 1382 (m), 1100 (s), 1038 (s), 1025 (s), 994 (s), 980 (s), 745 (s) $cm^{-1}$

**$^1$H NMR** (400MHz, *$d_6$-Acetone*): δ 7.52–7.48 (6H, m, ArH); 7.46–7.42 (2H, m, ArH); 7.39–7.34 (7H, m, ArH); 5.58 (1H, s, CHPh); 5.46 (2H, s, 2×CHPh (ring)); 4.00 (2H, d, *J* = 10.8 Hz, 2×CHHOCHPh (ring)); 3.97 (2H, d, *J* = 9.5 Hz, 2×CHHOCHPh (ring)); 3.86 (2H, dd, *J* = 7.0, 2.5 Hz, 2×CHHOCHPh (ring)); 3.84 (2H, dd, *J* = 7.0,

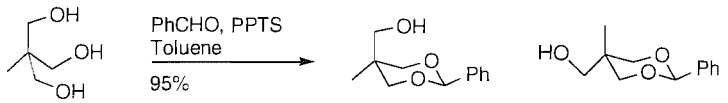
2.3 Hz, 2×CH<u>H</u>OCHPh (ring)); 3.36 (2H, d, $J$ = 9.5 Hz, 2×C<u>H</u>HOCHPh); 3.29 (2H, d, $J$= 9.5 Hz, 2×CH<u>H</u>OCHPh); 1.34 (6H, s, 2×C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (100MHz, *$d_6$-Acetone*): δ 140.95 (2×C), 140.0 (C), 130.1 (2×CH), 129.9 (2×CH), 129.5 (5×CH), 128.3 (2×CH), 127.9 (4×CH), 103.3 (2×CH), 103.2 (CH), 75.5 (2×$CH_2$), 75.4(2×$CH_2$), 70.6 (2×$CH_2$), 35.9 (2×C), 20.4 (2×$CH_3$).

**ESMS**: m/z (%)527 ($(M+Na)^+$, 100), 522 ($(M+NH_4)^+$, 40).

**HRMS** (ES) calcd for $C_{31}H_{36}O_6Na$ $(M+Na)^+$ 527.2404, found 527.2399.

## 5.15.2. (1-Methyl-4-phenyl-3,5-dioxanyl) methanol (232)




**231** **232a** **232b**

To a stirred solution of 1,1,1-tris(hydroxymethyl)ethane **231** (4.32 g, 36.0 mmol) in toluene (125 mL) was added PPTS (86 mg). Benzaldehyde (3.05 mL, 30.0 mmol) was added dropwise and the mixture was refluxed for 1 h using a Dean and Stark trap. A 5% $NaHCO_3$ (100 mL) solution was added and the reaction allowed to cool to r.t. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2×100 mL). The organic phases were combined, dried ($Na_2SO_4$), and after filtration the solvents were removed *in vacuo*. The crude product was purified by chromatography (haxane/acetone 8:2) to yield **232** as a white solid (5.95 g, 95 %, 3.8:1 *cis:trans*). The isomers were separated for identification purposes by preparative HPLC (hexane/acetone 8:2).

Major Isomer: **232a**

**M.p.** 100–102° C.

**IR** ($CH_2Cl_2$-solution *ca* 10 mg $mL^{-1}$): 3054 (m), 2978 (w), 2959 (w), 2850 (w), 1460 (m), 1420 (m), 1379 (m), 1195 (s), 1043 (s), 888 (m) $cm^{-1}$.

**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.51–7.49 (2H, m, Ar<u>H</u>); 7.38–7.36 (3H, m, Ar<u>H</u>); 5.46 (1H, s, ArC<u>H</u>); 4.02 (2H, br d, $J$ = 11.5 Hz, 2×C<u>H</u>HOCHAr); 3.93 (1H, t, $J$ = 5.3 Hz, OH); 3.84 (2H, d, $J$ = 4.8 Hz C<u>H</u>$_2$OH); 3.62 (2H, dd, $J$ = 10.3, 1.3 Hz, 2×C<u>H</u>HOCHAr); 0.79 (3H, s, C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 140.8 (C), 129.4 (CH), 129.3 (2×CH), 127.8 (2×CH), 102.8 (CH), 74.2 (2×$CH_2$), 65.6 ($CH_2$), 36.2 (C), 18.0 ($CH_3$).

**CIMS**: m/z (%): 209 ($(M+H)^+$, 100).

Minor Isomer: **232b**

**M.p.** 60–62° C.

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$): 339 (m), 2950 (w), 2860 (w), 1451 (m), 1100 (s), 1039 (s), 741 (m) $cm^{-1}$.

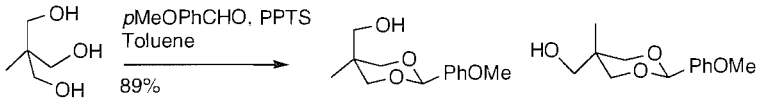
**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.52–7.49 (2H, m, ArH); 7.37–7.34 (3H, m, ArH); 5.42 (1H, s, ArCH); 3.94 (2H, m, 2×CHHOCHAr); 3.87 (1H, m, OH); 3.78 (2H, m, 2×CHHOCHAr); 3.35 (2H, m, $CH_2OH$); 1.25 (3H, m, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 141.0 (C), 130.0 (CH), 129.5 (2×CH), 127.9 (2×CH), 103.0 (CH), 75.4 (2×$CH_2$), 67.5 ($CH_2$), 36.7 (C), 19.9 ($CH_3$).

**CIMS**: m/z (%): 209 ($(M+H)^+$, 100), 105 (10).

**Anal.** (mixture of isomers) Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found C, 69.26; H, 7.80.

### 5.15.3. [2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-5yl]methanol (247)




**231** **247a** **247b**

An identical procedure was followed as for the preparation of **232** (same scale). The crude product was recrystallised (hexane/ethyl acetate 9:2) and the residue purified by chromatography (haxane/acetone 8:2) to yield **247** as two ring isomers (6.36 g, 89%, 2.9:1 *cis:trans*). The isomers were separated for identification purposes by preparative HPLC (hexane/acetone 8:2).

Major Isomer: **247a**

**M.p.** 82–84 ° C.

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$): 3290 (m), 2968 (m), 2935 (m), 2864 (m), 1620 (w), 1502 (w), 1379 (m), 1247 (s), 1006 (s), 816 (m) $cm^{-1}$.

**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.39 (2H, d, $J$ = 8.5 Hz, ArH); 6.90 (2H, d, $J$ = 8.7 Hz, ArH); 5.39 (1H, s, ArCH); 3.89 (2H, m, 2×CHHOCHAr); 3.87 (1H, br. s, OH); 3.81 (2H, s, $CH_2OH$); 3.77 (3H, s, $OCH_3$); 3.59 (2H, m, 2×CHHOCHAr); 0.77 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 161.4 (C), 133.2 (C), 129.0 (2×CH), 114.7 (2×CH) 102.8 (CH), 74.2 (2×$CH_2$), 65.6 ($CH_2$), 56.2 ($CH_3$), 36.1 (C), 18.0 ($CH_3$).

**CIMS**: m/z (%): 239 ($(M+H)^+$, 100), 137 (27), 121, (82).

Minor Isomer: **247b**

**M.p.** 122–123° C.

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$): 3465 (m), 2968 (w), 2907 (w), 2850 (w), 1611 (m), 1516 (m), 1266 (s), 1062 (s), 987 (m), 835 (s) $cm^{-1}$.

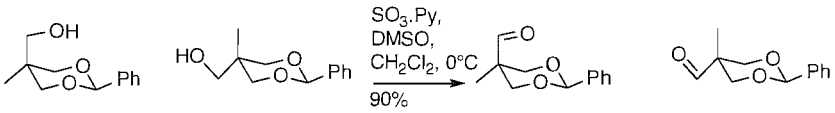
**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.41 (2H, d, *J* = 8.8 Hz, ArH); 6.91 (2H, d, *J* = 8.8 Hz, ArH); 5.35 (1H, s, ArCH); 3.91 (2H, br d, *J* = 10.8 Hz, 2×CHHOCHAr); 3.83 (1H, t, *J* = 5.3 Hz, OH); 3.78 (3H, s, $ArOCH_3$); 3.75 (2H, dd, *J* = 10.0, 1.0 Hz, 2×CHHOCHAr); 3.34 (2H, d, *J* = 5.3 Hz, $CH_2OH$); 1.24 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 161.5 (C), 133.5 (C), 129.2 (2 × CH), 114.8 (2×CH) 103.0 (CH), 75.4 (2×$CH_2$), 67.5 ($CH_2$), 56.3 ($CH_3$), 36.6 (C), 19.9 ($CH_3$).

**CIMS**: m/z (%): 239 ($(M+H)^+$, 20), 137 (52), 121, (100).

Anal. (mixture of isomers) Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61 Found C, 65.69; H, 7.79.

### 5.15.4. 2-Phenyl-5-methyl-1,3-dioxane-5-carbaldehyde (248)




**232a** **232b** **248a** **248b**

A suspension of $SO_3$.pyridine (10.06 g, 63.3 mmol) in $CH_2Cl_2$ (50 mL) was dissolved in DMSO (50 mL) and $Et_3N$ (10.6 mL, 76.5 mmol). This solution was immediately added dropwise to a stirred solution of **232** (6.01 g, 28.8 mmol) in $CH_2Cl_2$ (62 mL) at 0°C, and the reaction mixture was stirred at 0°C for 3 h. The reaction mixture was poured into a mixture of sat. aq. aqueous $NH_4Cl$ : water : $Et_2O$ : pentane (1:1:1:1 300 mL), and the aqueous phase extracted with an $Et_2O$ : pentane mixture (1:1 3×100 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$. After removing the solvent *in vacuo* the pale yellow oil was purified by chromatography (hexane/ethyl acetate 9:1) to yield a white solid (5.34 g, 90%). The isomers were separated for identification purposes by preparative HPLC (hexane/ethyl acetate 9:1).

Major Isomer: **248a**

**M.p.** 58–60° C.

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$): 2968 (w), 2860 (w), 1725 (s), 1460 (m), 1375 (m), 1095 (s), 1015 (w) $cm^{-1}$.

**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 9.89 (1H, s, C<u>H</u>O); 7.44–7.41 (2H, m, Ar<u>H</u>); 7.37–7.32 (3H, m, Ar<u>H</u>); 5.55 (1H, s, ArC<u>H</u>); 4.50 (2H, d, *J* = 12.0 Hz, 2×C<u>H</u>HOCHAr); 3.86 (2H, d, *J* = 11.3 Hz, 2×CH<u>H</u>OCHAr); 0.84 (3H, s, C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 205.8 (CH), 140.2 (C), 130.2 (CH), 129.5 (2×CH), 127.8 (2×CH), 102.7 (CH), 73.3 (2×$CH_2$), 46.7 (C), 15.1 ($CH_3$).

**CIMS**: m/z (%): 205 ($M-H^+$, 15), 123 (25), 105 (100), 77 (53).

Minor Isomer: **248b**

**M.p.** 56–58° C.

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$): 2954 (w), 2850 (w), 2727 (w), 1715 (s), 1455 (m), 1379 (m), 1105 (w), 987 (m) $cm^{-1}$.

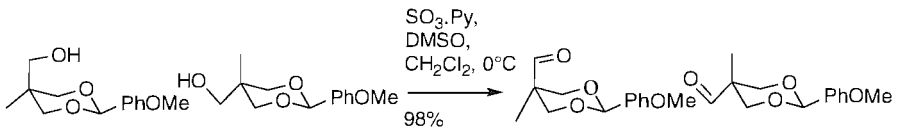
**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 9.56 (1H, s, C<u>H</u>O); 7.51–7.48 (2H, m, Ar<u>H</u>); 7.39–7.36 (3H, m, Ar<u>H</u>); 5.52 (1H, s, ArC<u>H</u>); 4.19 (2H, m, 2×C<u>H</u>HOCHAr); 3.97 (2H, m, 2×CH<u>H</u>OCHAr); 1.48 (3H, s, C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 204.5 (CH), 140.0 (C), 130.4 (CH), 129.6 (2×CH), 127.9 (2×CH), 103.0 (CH), 72.2 (2×$CH_2$), 47.6 (C), 17.4 ($CH_3$).

**EIMS**: m/z (%): 206 ($M^+$, 34), 205 (70), 123 (51), 105 (100), 77 (78).

**Anal.** (mixture of isomers) Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84 Found C, 69.77; H, 6.89.

## 5.15.5. 2-(4-Methoxyphenyl)-5-methyl-1,3-dioxane-5-carbaldehyde (249)




**247a** **247b** **249a** **249b**

An identical procedure was followed as for the preparation of **248** (2.50 mmol scale). The crude product (pale yellow oil) was purified by chromatography (8:2 hexane/acetone) to yield a white solid (0.58 g, 98%). The isomers were separated for identification purposes by preparative HPLC (hexane/ethyl acetate 9:1).

Major Isomer: **249a**

**M.p.** 102–104 ° C.

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$): 2973 (m), 2940 (m), 2874 (m), 2836 (m), 1715 (s), 1611 (s), 1524 (s), 1393 (s), 1242 (s), 1001 (s), 821 (s) $cm^{-1}$.

**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 9.89 (1H, s, CHO); 7.33 (2H, d, *J* = 8.3 Hz, ArH); 6.89 (2H, d, *J* = 9.0 Hz, ArH); 5.48 (1H, s, ArCH); 4.47 (2H, d, *J*=11.8 Hz, 2×CHHOCHAr); 3.83 (2H, dd, *J* = 11.8, 1.0 Hz, 2×CHHOCHAr); 3.77 (3H, s, $OCH_3$); 0.83 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 205.9 (CH), 161.6 (C), 132.6 (C), 129.1 (2×CH), 114.8 (2×CH), 102.6 (CH), 73.3 (2×$CH_2$), 56.2 ($CH_3$), 46.6 (C), 15.1 ($CH_3$).

**EIMS**: m/z (%): 236 ($M^+$, 7), 235 (M-$H^+$, 12), 135 (100).

Minor Isomer: **249b**

**M.p.** 108–110° C.

**IR** (solution $CH_2Cl_2$ *ca* 10 mg $mL^{-1}$): 3049 (w), 2959 (w), 2831 (w), 1720 (m), 1621(m), 1516 (m), 1270 (w), 1171 (m), 736 (s) $cm^{-1}$.

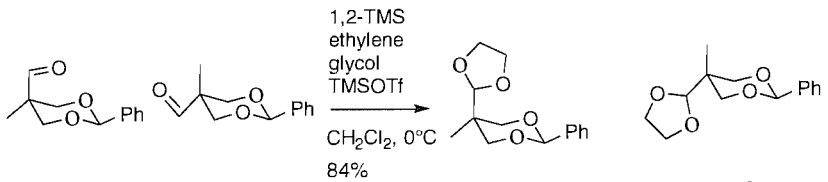
**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 9.59 (1H, s, CHO); 7.41 (2H, d, *J* = 8.8 Hz, ArH); 6.92 (2H, d, *J* = 8.8 Hz, ArH); 5.46 (1H, s, ArCH); 4.15 (2H, m, 2×CHHOCHAr); 3.94 (2H, m, 2×CHHOCHAr); 3.80 (3H, s, $OCH_3$); 1.47 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 204.5 (CH), 161.8 (C), 132.7 (C), 129.2 (2×CH), 114.9 (2×CH), 102.9 (CH), 72.1 (2×$CH_2$), 56.3 ($CH_3$), 47.5 (C), 17.4 ($CH_3$).

**EIMS**: m/z (%): 235 (M-$H^+$, 13), 152 (20), 135 (100).

**Anal.** (mixture of isomers) Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found C, 66.17; H, 6.89.

### 5.15.6. 5-(1,3-Dioxalan-2-yl)-2-phenyl-5-methyl-1,3-dioxane (250)




**248a** **248b** **250a** **250b**

Aldehyde **248** (0.78 g, 3.78 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and was then cooled to 0°C. 1,2-*bis*-(Trimethylsilyloxy)ethane (1.4 mL, 5.7 mmol) was added and the trimethylsilyl trifluoromethane sulpfonate (0.3 mL, 1.9 mmol) was added dropwise. The solution was stirred at 0°C for 1 h. Pyridine (3 mL) was added and the mixture poured on to sat. $NaHCO_3$ solution (75 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2×90 mL) and the combined organic phases dried ($Na_2SO_4$).

After filtration the $CH_2Cl_2$ was removed *in vacuo*. The crude product was subjected to chromatography (hexane/acetone 85:15) to yield the product as a mixture of ring isomers (0.79 g, 3.2 mmol, 84 %). The isomers were separated for identification purposes by preparative HPLC (haxane/acetone 95:5).

Major Isomer: **250a**

**M.p.** 104–106° C.

**IR** ($CH_2Cl_2$ solution *ca* 10 mg $mL^{-1}$) 3054 (w), 2988 (w), 2889 (w) 2865 (w), 1451 (w), 1385 (w), 1266 (s), 1214 (m), 1105 (m), 1015 (w), 722 (s) $cm^{-1}$.

**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.47–7.44 (2H, m, ArH); 7.35–7.34 (3H, m, ArH); 5.50 (1H, s, ArCH); 5.47 (1H, s, CH$(OCH_2)_2$); 4.20 (2H, m, 2×CHHOCHAr); 3.93 (4H, m, CH$(OCH_2)_2$); 3.72 (2H, m, 2×CHHOCHAr); 0.67 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 138.9 (C), 130.7 (CH), 129.5 (2×CH) 127.9 (2×CH), 104.8 (CH), 103.0 (CH), 74.9 (2×$CH_2$), 66.9 (2×$CH_2$), 38.1 (C), 13.1 ($CH_3$).

**CIMS**: m/z (%): 251 ($(M+H)^+$, 38), 105 (30), 73 (100).

Minor Isomer: **250b**

**M.p.** 68–70° C.

**IR** ($CH_2Cl_2$ solution *ca* 10 mg $mL^{-1}$) 2964 (w), 2893 (w), 2845 (w), 1445 (m), 1384 (s), 1328 (m), 1162 (w), 1082 (s), 1034 (m), 935 (m), 750 (m) $cm^{-1}$.

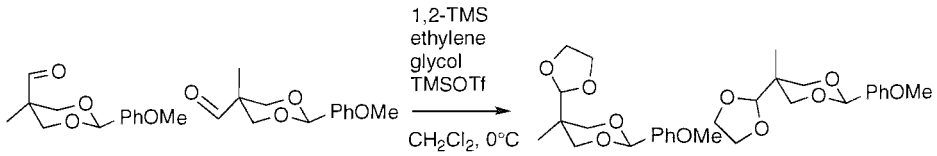
**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.53–7.51 (2H, m, ArH); 7.40–7.37 (3H, m, ArH); 5.54 (1H, s, ArCH); 4.58 (1H, s, CH$(OCH_2)_2$); 4.03–3.96 (4H, m, 2×CHHOCHAr, CH$(OCHH)_2$); 3.89–3.83 (4H, m, 2×CHHOCHAr, CH$(OCHH)_2$); 1.31 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 140.9 (C), 130.1 (CH), 129.5 (2×CH), 127.9 (2×CH), 107.1 (CH), 103.2 (CH), 73.7 (2×$CH_2$), 66.6 (2×$CH_2$), 38.6 (C), 17.3 ($CH_3$).

**CIMS**: m/z (%): 251 ($(M+H)^+$, 100), 105 (20), 73 (80).

**Anal.** (mixture of isomers) Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found C, 67.38; H, 7.36.

### 5.15.7. 5-(1,3-dioxalan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane (251)




**249a** **249b** **251a** **251b**

An identical procedure was followed as for the preparation of **250** (8.47 mmol scale). The crude product was subjected to chromatography (hexane/acetone 85:15) to yield the product as a mixture of ring isomers (2.18 g, 92 %). The isomers were separated for identification purposes by preparative HPLC (hexane/acetone 95:5).

Major Isomer: **251a**

**M.p.** 126–128° C.

**IR** ($CH_2Cl_2$ solution *ca* 10 mg $mL^{-1}$) 3054 (w), 2974 (m), 2889 (m), 2846 (m), 1621 (m), 1512 (s), 1470 (m), 1389 (s), 1262 (s), 1186 (s), 1087 (s), 826 (m), 727 (s) $cm^{-1}$.

**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.37 (2H, d, *J* = 7.8 Hz, ArH); 6.89 (2H, d, *J* = 8.7 Hz, ArH); 5.47 (1H, s, ArCH); 5.44 (1H, s, CH$(OCH_2)_2$); 4.17 (2H, m, 2×CHHOCHAr); 3.87 (4H, m, CH$(OCH_2)_2$); 3.71 (3H, s, $OCH_3$); 3.69 (2H, m, 2×CHHOCHAr); 0.66 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 161.6 (C), 133.1 (C), 129.1 (2xCH), 114.8 (2×CH), 104.9 (CH), 102.9 (CH), 74.9 (2×$CH_2$), 66.9 (2×$CH_2$), 56.3 ($CH_3$), 38.0 (C), 13.1 ($CH_3$).

**CIMS**: m/z (%): 281 $(M+H)^+$, 29), 151 (10), 133 (100).

Minor Isomer: **251b**

**M.p.** 116–118° C.

**IR** ($CH_2Cl_2$ solution *ca* 10 mg $mL^{-1}$) 3045 (m), 2978 (m), 2931 (m), 2832 (m), 1620 (m), 1522 (s), 1465 (m), 1389 (s), 1270 (s), 1176 (s), 1086 (s), 1034 (m), 822 (m), 736 (s) $cm^{-1}$.

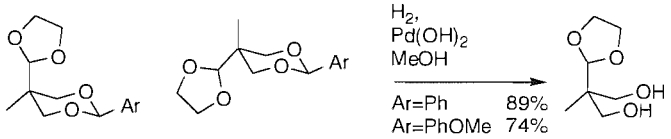
**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.39 (2H, m, ArH); 6.91 (2H, m, ArH); 5.36 (1H, s, ArCH); 4.53 (1H, s, CH$(OCH_2)_2$); 3.96–3.91 (4H, m, CH$(OCH_2)_2$); 3.83–3.77 (7H, m, $OCH_3$ + 2×$CH_2$OCHAr); 1.27 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 161.8 (C), 133.5 (C), 129.4 (2×CH), 115.0 (2×CH), 107.3 (CH), 103.3 (CH), 73.8 (2×$CH_2$), 66.7 (2×$CH_2$), 56.5 ($CH_3$), 38.7 (C), 17.5 ($CH_3$).

**CIMS**: m/z (%): 281 $(M+H)^+$, 64), 136 (78), 73 (100).

**Anal.** (mixture of isomers) Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found C, 64.43; H, 7.31.

### 5.15.8. 2-(1,3-Dioxolan-2yl)-2methyl-1,3-propanediol (252)




**250a** Ar=Ph **250b** Ar=Ph **252**
**251a** Ar=PhOMe **251b** Ar=PhOMe

To a stirred solution of **250** (0.76 g, 3.04 mmol) in methanol (20 mL) was added 20% palladium hydroxide on carbon (201 mg). The flask was evacuated and filled with hydrogen three times and was then left under an atmosphere of hydrogen, at r.t. for 18 h. The reaction mixture was then filtered through a plug of Celite and was washed with methanol (2×25 mL). The solvent was removed *in vacuo* and the residue chromatographed on silica (hexane/acetone 6:4) to give the product **252** as a white solid (0.437 g, 89 %). Starting from **251** (1.02 g, 3.6 mmol, MeOH (25 mL), 20 $Pd(OH)_2$/C (238 mg), **252** was obtained (0.43 g, 74%) using an identical procedure (but with a reaction time of 48 h).

**M.p.** 48–52°C.

**IR** ($CH_2Cl_2$ solution *ca* 10 mg $mL^{-1}$) 3380 (br s), 2959 (m), 2889 (s), 1696 (m), 1649 (m), 1394 (m), 1091 (s), 1044 (s), 727 (s) $cm^{-1}$.

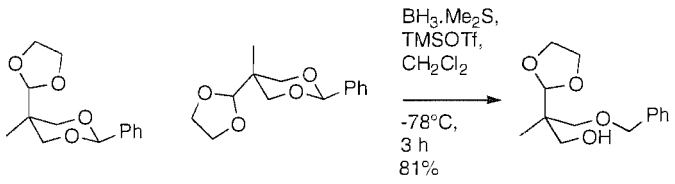
**$^1$H NMR** (400 MHz, *$d^6$-Acetone*): δ 4.83 (1H, s, $(CH_2O)_2C\underline{H}$); 3.96–3.82 (4H, m, $(C\underline{H_2}O)_2CH$); 3.66 (2H, d, $J$ = 10.0 Hz, 2×C<u>H</u>HOH); 3.57 (2H, d, $J$ = 11.0 Hz, 2×CH<u>H</u>OH); 3.54 (2H, br s, $CH_2O\underline{H}$); 0.89 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 107.7 (CH), 66.4 (2×$CH_2$), 66.3 (2×$CH_2$), 44.8 (C), 14.9 ($CH_3$).

**CIMS**: m/z (%) 163 ($(M+H)^+$, 12), 115 (18), 73 (100).

**Anal.** Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found C, 51.40; H, 8.63.

## 5.15.9. 3-Benzyloxy-2-[1,3]dioxolan-2-yl-2-methyl-propan-1-ol (253)




**250a** **250b** **253**

Diacetal **250** (0.25g, 1 mmol) was dissolved in $CH_2Cl_2$ (5 mL) and cooled to –78°C. Borane dimethyl sulfide complex (0.19 mL, 2 mmol) was then added followed by dropwise addition of trimethyl trifluoromethane sulfonate (0.36 mL, 2 mmol). The reaction mixture was then stirred at –78°C for 3h. After this time NaOMe/ MeOH (0.5 M, 16 mL) was added followed by sat. $NaHCO_3$ sol. (5 mL). When the reaction mixture had warmed to r.t. it was poured on to sat. $NaHCO_3$ sol. (15 mL) and water (15 mL) and was extracted with $CH_2Cl_2$ (3×30 mL) and the organic phases were combined and dried ($MgSO_4$). After filtration the $CH_2Cl_2$ was removed *in vacuo*. The crude product was subjected to chromatography (hexane/ethyl acetate 6:4) to yield the product as a colourless oil (0.20 g, 81 %).

**IR** (film) 3494 (m), 2983 (m), 2936 (m), 2874 (s), 1503 (w), 1451 (s), 1366 (m), 1101 (s), 1034 (s), 945 (s), 741 (s), 703 (s) $cm^{-1}$.

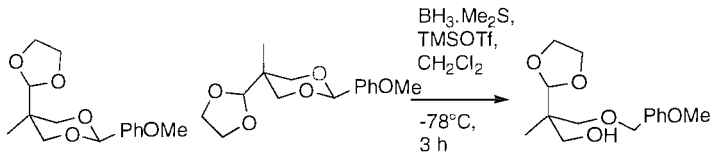
**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.39–7.35 (4H, m, ArH); 7.32 (1H, m, ArH); 4.88 (1H, s, CH(OCH$_2$)$_2$); 4.55 (2H, s, CH$_2$OCH$_2$Ar); 3.95–3.81 (4H, m, CH(OCH$_2$)$_2$); 3.68 (1H, dd, $J$ = 10.8, 4.5 Hz, CHHOH); 3.64 (1H, m, CHHOH); 3.60 (1H, d, $J$ = 8.7 Hz, CHHOCH$_2$Ar); 3.52 (1H, d, $J$ = 8.8 Hz, CHHOCH$_2$Ar); 3.35 (1H, br s, CH$_2$OH); 0.95 (3H, s, CH$_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 140.7 (C), 129.8 (CH), 128.8 (4×CH), 107.1 (CH), 74.7 ($CH_2$), 74.0 ($CH_2$), 66.42 ($CH_2$), 66.36 ($CH_2$), 65.8 ($CH_2$), 44.9 (C), 15.1 ($CH_3$).

**CIMS**: m/z (%): 253 ((M+H)$^+$, 28), 205 (12), 115 (40), 73 (100).

**HRMS** (EI$^+$) calcd for $C_{14}H_{19}O_4$ (M-H)$^+$ 251.1283, found 251.1279.

### 5.15.10. 2-[1,3]Dioxolan-2-yl-3-(4-methoxy-benzyloxy)-2-methyl-propan-1-ol (254)




**251a** **251b** **254**

Starting from **251**, an identical procedure was followed as for the preparation of **253** (same scale). The crude product was subjected to chromatography (hexane/ethyl acetate 6:4) to give the product as a colourless oil (0.221 g, 78 %).

**IR** (film) 3489 (m), 2936 (s), 2988 (s), 2841 (s), 1621 (s), 1516 (s), 1465 (s), 1304 (s), 1034 (m), 1252 (s), 1105 (s), 1025 (s) $cm^{-1}$.

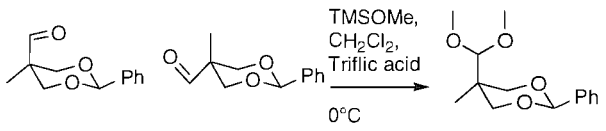
**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.31 (2H, m, ArH); 6.93 (2H, m, ArH); 4.86 (1H, s, CH(OCH$_2$)$_2$); 4.47 (2H, s, CH$_2$OCH$_2$Ar); 3.94–3.81 (4H, m, CH(OCH$_2$)$_2$); 3.82 (3H, s, ArOCH$_3$); 3.64 (1H, dd, *J* = 10.8, 5.5 Hz, CHHOH); 3.58 (1H, m, CHHOH); 3.55 (1H, d, *J* = 8.8 Hz, CHHOCH$_2$Ar); 3.47 (1H, d, *J* = 9.0 Hz, CHHOCH$_2$Ar); 3.29 (1H, t, *J* = 5.5 Hz, CH$_2$OH); 0.93 (3H, s, CH$_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 160.8 (C), 132.6 (C), 130.5 (2×CH), 115.2 (2×CH), 107.2 (CH), 74.4 ($CH_2$), 73.8 ($CH_2$), 66.43 ($CH_2$), 66.37 ($CH_2$), 65.9 ($CH_2$), 56.2 ($CH_3$), 44.8 (C), 15.1 ($CH_3$).

**EIMS**: m/z (%): 281 ($(M–H)^+$, 4), 220 (12), 189 (27), 121 (100).

**HRMS** (EI$^+$) calcd for $C_{15}H_{22}O_5$ $(M)^+$ 282.1467, found 282.1460.

### 5.15.11. 5-Dimethoxymethyl-5-methyl-2-phenyl-[1,3]dioxane (256)




**248a** **248b** **256**

Aldehyde **248** (2.99 g, 14.5 mmol) was dissolved in $CH_2Cl_2$ (58 mL) and was then cooled to –78°C. Methoxytrimethylsilane (6.0 mL, 43.5 mmol) was added and then triflic acid (0.76 mL, 4.2 mmol) was added dropwise. The solution was stirred at –78°C for 3 h. Pyridine (7 mL) was added and the mixture poured on to sat. $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3×100 mL) and the combined organic phases dried ($Na_2SO_4$). After filtration the $CH_2Cl_2$ was removed *in*

*vacuo*. The crude product was subjected to chromatography (hexane/acetone 9:1) to yield the product as a single isomer (2.53 g, 69 %).

**M.p.** 108–112° C.

**IR** ($CH_2Cl_2$ solution *ca* 10 mg $mL^{-1}$) 3054 (m), 2978 (m), 1393 (w), 1209 (w), 1167 (w), 1101 (m), 1072 (m) $cm^{-1}$.

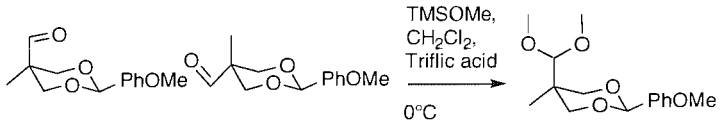
**$^1$H NMR** (400MHz, $CDCl_3$): δ 7.51–7.49 (2H, m, ArH); 7.42–7.37 (3H, m, ArH); 5.47 (1H, s, ArCH); 4.89 (1H, s, $CH(OCH_3)_2$); 4.24 (2H, m, 2×CHHOCHAr); 3.62 (6H, s, $CH(OCH_3)_2$); 3.59 (2H, m, 2×CHHOCHAr); 0.74 (3H, s, $CH_3$).

**$^{13}$C NMR + DEPT** (100 MHz, $CDCl_3$): δ 138.4 (C), 128.9 (CH), 128.3 (2×CH), 126.1 (2×CH), 107.1 (CH), 102.0 (CH), 74.1 (2×$CH_2$), 58.8 (2×$CH_3$), 39.0 (C), 12.2 ($CH_3$).

**CIMS**: m/z (%): 221 ($(M+H-MeOH)^+$, 30), 105 (35), 75 (100).

**Anal**. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found C, 66.64; H, 8.03.

## 5.15.12. 5-Dimethoxymethyl-2-(4-methoxy-phenyl)-5-methyl-[1,3]dioxane (257)




**249a** **249b** **257**

Aldehyde **249** (0.58 g, 2.45 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and was then cooled to –78°C. Methoxytrimethylsilane (1.0 mL, 7.34 mmol) was added and then triflic acid (0.09 mL, 4.2 mmol) was added dropwise. The solution was stirred at –78°C for 3 h. Pyridine (5 mL) was added and the mixture poured on to sat. $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2×15 mL) and the combined organic phases dried ($Na_2SO_4$). After filtration the $CH_2Cl_2$ was removed *in vacuo*. The crude product was subjected to chromatography (hexane/acetone 9:1) to yield the product as a single isomer (0.60 g, 87 %).

**M.p.** 118–119° C.

**IR** ($CH_2Cl_2$ solution *ca* 10 mg $mL^{-1}$) 2964 (m), 2860 (m), 2827 (m), 1616, (m), 1497 (s), 1384 (s), 1261 (s), 1152 (s), 1053 (s), 816 (m) $cm^{-1}$.

**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 7.43 (2H, d, *J*=8.6 Hz, ArH); 6.94 (2H, d, *J*=8.8 Hz, ArH); 5.48 (1H, s, ArCH); 4.90 (1H, s, $CH(OCH_3)_2$); 4.13 (2H, m,

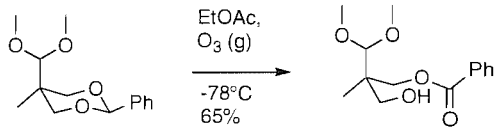
2×C<u>H</u>HOCHAr); 3.82 (3H, s, ArOC$H_3$); 3.61 (2H, m, 2×CH<u>H</u>OCHAr); 3.59 (6H, s, CH(OC<u>H</u>$_3$)$_2$); 0.68 (3H, s, C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 161.7 (C), 133.3 (C), 129.1 (2×CH), 114.9 (2×CH), 108.5 (CH), 103.2 (CH), 75.1 (2×$CH_2$), 59.4 (2×$CH_3$), 56.3 ($CH_3$), 40.3 (C), 13.3 ($CH_3$).

**CIMS**: m/z (%): 283 ((M+H)$^+$, 4), 251 (6), 133 (100).

**Anal**. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found C, 64.06; H, 8.11.

### 5.15.13. Benzoic acid 2-hydroxymethyl-3,3-dimethoxy-2-methyl-propyl ester (258)




**256** **258**

Diacetal **256** (0.12 g, 0.5 mmol) was dissolved in ethyl acetate (40 mL). The solution was cooled to –78 °C. Ozone was passed through the solution for 1 h. After this time nitrogen was passed through the solution until the blue colouration disappeared. The ethyl acetate was removed *in vacuo* and the residue subjected to chromatography (hexane/acetone 8:2). The product **258** was recovered as a colourless oil (0.087g, 65% ).

**IR** (film) 3503 (br s), 2936 (s), 2837 (s), 1725 (s), 1592 (s), 1469 (w), 1445 (s), 1271 (s), 1176 (s), 1105 (s), 1067 (s), 703 (s) cm$^{-1}$.

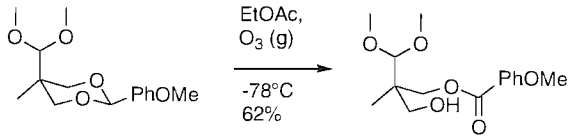
**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 8.09 (2H, m, Ar<u>H</u>); 7.66 (1H, m, Ar<u>H</u>); 7.55 (2H, m, Ar<u>H</u>); 4.47 (1H, s, C<u>H</u>(OC$H_3$)$_2$); 4.33 (2H, s, C<u>H</u>$_2$OCOAr); 3.66 (3H, m, C<u>H</u>$_2$O<u>H</u>); 3.57 (3H, s, 1×CHOC<u>H</u>$_3$); 3.55 (3H, s, 1×CHOC<u>H</u>$_3$); 1.03 (3H, s, C<u>H</u>$_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): 167.5 (C), 134.6 (CH), 132.3 (C), 130.9 (2×CH), 130.2 (2×CH), 110.7 (CH), 67.8 ($CH_2$), 65.2 ($CH_2$), 59.5 ($CH_3$), 59.2 ($CH_3$), 46.6 (C), 15.4 ($CH_3$).

**CIMS**: m/z (%): 237 ((M+H–MeOH)$^+$, 54), 105 (62), 85 (72), 75 (100).

**HRMS** (ES$^+$) calcd for $C_{14}H_{20}O_5Na$ (M+Na)$^+$ 291.1203, found 291.1204.

### 5.15.14. 4-Methoxy-benzoic acid 2-hydroxymethyl-3,3-dimethoxy-2-methyl-propyl ester (259)




**257** **259**

Diacetal **257** (0.134 g, 0.47 mmol) was dissolved in ethyl acetate (40 mL). The solution was cooled to –78 C. Ozone was passed through the solution for 1 h. After this time nitrogen was passed through the solution until the blue colouration disappeared. The ethyl acetate was removed *in vacuo* and the residue subjected to chromatography (hexane/acetone 8:2). The product **259** was obtained as a colourless oil (0.092g, 62%).

**IR** (film) 3522 (br m), 2936 (m), 2841 (m), 1706 (s), 1606 (s), 1507 (s), 1469 (s), 1261 (s), 1167 (s), 1072 (s), 845 (m), 765 (m), 689 (m) $cm^{-1}$.

**$^1$H NMR** (400MHz, *$d^6$-Acetone*): δ 8.03 (2H, d, *J* = 9.0 Hz, ArH); 7.06 (2H, d, *J* = 8.8 Hz, ArH); 4.45 (1H, s, CH(OCH$_3$)$_2$); 4.29 (2H, s, CH$_2$OCOAr); 3.92 (3H, s, ArOCH$_3$); 3.67–3.63 (3H, m, CH$_2$OH); 3.56 (3H, s, CHOCH$_3$); 3.54 (3H, s, CHOCH$_3$); 1.01 (3H, s, CH$_3$).

**$^{13}$C NMR + DEPT** (100 MHz, *$d^6$-Acetone*): δ 167.3 (C), 165.2 (C), 133.0 (2×CH), 124.5 (C), 115.4 (2×CH), 110.7 (CH), 67.5 ($CH_2$), 65.2 ($CH_2$), 59.6 ($CH_3$), 59.3 ($CH_3$), 56.7 ($CH_3$), 46.7 (C), 15.4 ($CH_3$).

**CIMS**: m/z (%): 268 ($M^+$, 6), 267 (28), 135 (40), 85 (100).

**HRMS** ($ES^+$) calcd for $C_{15}H_{22}O_6Na$ $(M+Na)^+$ 321.1308, found 321.1311.

# Appendices: X-Ray Crystallographic Analysis

## Compound 143

**Table 14:** Crystal data and structure refinement.

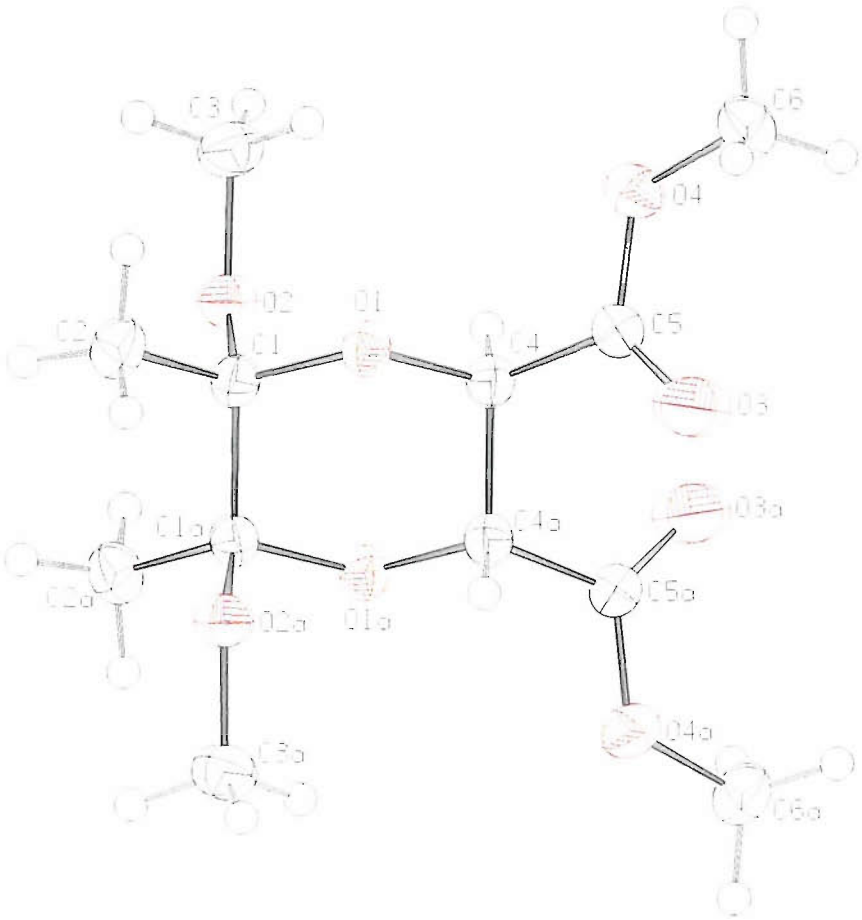
| | | |
|---|---|---|
| Identification code | **01sot036** | |
| Empirical formula | $C_{12}H_{20}O_8$ | |
| Formula weight | 292.28 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12$ | |
| Unit cell dimensions | $a$ = 10.321(2) Å | $\alpha = 90°$ |
| | $b$ = 7.6384(15) Å | $\beta = 90°$ |
| | $c$ = 9.1744(18) Å | $\gamma = 90°$ |
| Volume | 723.3(2) Å$^3$ | |
| $Z$ | 2 | |
| Density (calculated) | 1.342 Mg / m$^3$ | |
| Absorption coefficient | 0.114 mm$^{-1}$ | |
| *F(000)* | 312 | |
| Crystal | Block; colourless | |
| Crystal size | 0.35 × 0.30 × 0.30 mm$^3$ | |
| $\theta$ range for data collection | 2.97 – 27.47° | |
| Index ranges | $-13 \le h \le 13$, $-9 \le k \le 9$, $-10 \le l \le 11$ | |
| Reflections collected | 3787 | |
| Independent reflections | 1628 [$R_{int}$ = 0.0547] | |
| Completeness to $\theta$ = 27.47° | 99.2 % | |
| Absorption correction | Semi–empirical from equivalents | |
| Max. and min. transmission | 0.9667 and 0.9614 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1628 / 0 / 96 | |
| Goodness-of-fit on $F^2$ | 1.053 | |
| Final $R$ indices [$F^2 > 2\sigma(F^2)$] | $R1$ = 0.0449, $wR2$ = 0.1139 | |
| $R$ indices (all data) | $R1$ = 0.0541, $wR2$ = 0.1204 | |
| Absolute structure parameter | 0.0(12) | |
| Extinction coefficient | 0.074(16) | |
| Largest diff. peak and hole | 0.249 and –0.199 e Å$^{-3}$ | |

**Diffractometer**: *Nonius KappaCCD* area detector ($\phi$ scans and $\omega$ scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

**Special details**: All hydrogen atoms were placed in idealised positions and refined using a riding model.

**Table 15** Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| Atom | *x* | *y* | *z* | $U_{eq}$ | *S.o.f.* |
|---|---|---|---|---|---|
| C1 | 545(2) | 705(2) | 4230(2) | 25(1) | 1 |
| C2 | 386(2) | 2054(2) | 3034(2) | 34(1) | 1 |
| C3 | 2875(2) | 748(2) | 4156(2) | 35(1) | 1 |
| C4 | 587(2) | 579(2) | 6829(2) | 26(1) | 1 |
| C5 | 650(2) | 1816(2) | 8127(2) | 29(1) | 1 |
| C6 | 2006(2) | 3752(3) | 9427(2) | 40(1) | 1 |
| O1 | 515(1) | 1682(1) | 5566(1) | 26(1) | 1 |
| O2 | 1705(1) | −253(1) | 4135(1) | 29(1) | 1 |
| O3 | −253(1) | 2167(3) | 8880(2) | 62(1) | 1 |
| O4 | 1829(1) | 2460(2) | 8286(1) | 35(1) | 1 |



## Compound 191

**Table 16:** Crystal data and structure refinement.

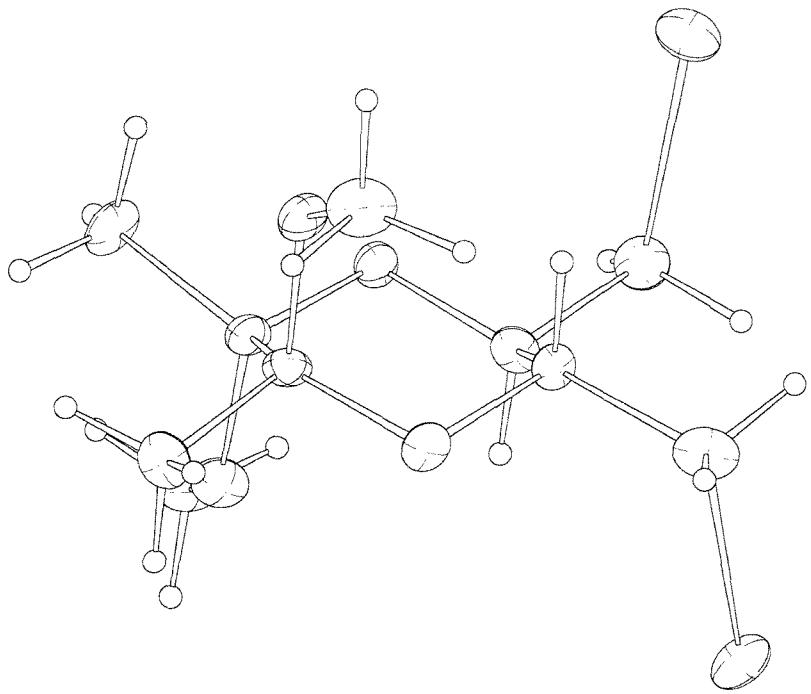
| | | |
|---|---|---|
| Identification code | 01SOT034 | |
| Empirical formula | $C_{10}H_{18}I_2O_4$ | |
| Formula weight | 456.04 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | $a$ = 6.6048(2) Å | $\alpha$ = 90° |
| | $b$ = 6.8241(2) Å | $\beta$ = 90° |
| | $c$ = 31.8242(12) Å | $\gamma$ = 90° |
| Volume | 1434.37(8) Å$^3$ | |
| $Z$ | 4 | |
| Density (calculated) | 2.112 Mg / m$^3$ | |
| Absorption coefficient | 4.383 mm$^{-1}$ | |
| $F(000)$ | 864 | |
| Crystal | Colourless Block | |
| Crystal size | 0.10 × 0.10 × 0.10 mm$^3$ | |
| $\theta$ range for data collection | 3.05 – 23.25° | |
| Index ranges | $-6 \le h \le 7, -7 \le k \le 7, -33 \le l \le 35$ | |
| Reflections collected | 3795 | |
| Independent reflections | 1975 [$R_{int}$ = 0.0838] | |
| Completeness to $\theta$ = 23.25° | 98.6 % | |
| Max. and min. transmission | 0.6683 and 0.6683 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1975 / 0 / 146 | |
| Goodness-of-fit on $F^2$ | 0.962 | |
| Final $R$ indices [$F^2 > 2\sigma(F^2)$] | $R1$ = 0.0635, $wR2$ = 0.1704 | |
| $R$ indices (all data) | $R1$ = 0.0688, $wR2$ = 0.1744 | |
| Absolute structure parameter | 0.00(9) | |
| Extinction coefficient | 0.011(2) | |
| Largest diff. peak and hole | 1.192 and −1.895 e Å$^{-3}$ | |

**Diffractometer**: *Nonius KappaCCD* area detector ($\phi$ scans and $\omega$ scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

**Special details**: All hydrogen atoms were placed in idealised positions and refined using a riding model.

**Table 17:** Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| Atom | *x* | *y* | *z* | $U_{eq}$ | *S.o.f.* |
|---|---|---|---|---|---|
| C1 | −6690(20) | 4230(20) | 655(5) | 37(3) | 1 |
| C2 | −3301(19) | 5710(18) | 697(4) | 25(3) | 1 |
| C3 | −2570(20) | 5000(20) | 273(4) | 32(3) | 1 |
| C4 | −3390(18) | 4820(16) | 1419(3) | 20(2) | 1 |
| C5 | −2392(19) | 6776(17) | 1538(4) | 25(3) | 1 |
| C6 | −2999(18) | 7510(20) | 1972(4) | 31(3) | 1 |
| C7 | −2482(19) | 7748(19) | 816(4) | 28(3) | 1 |
| C8 | 830(20) | 9192(18) | 897(5) | 34(3) | 1 |
| C9 | −3290(20) | 9429(18) | 548(4) | 34(3) | 1 |
| C10 | −2933(19) | 3070(20) | 1704(4) | 31(3) | 1 |
| O1 | −5461(13) | 5974(12) | 698(3) | 27(2) | 1 |
| O2 | −2739(14) | 4310(11) | 996(2) | 24(2) | 1 |
| O3 | −3008(13) | 8219(12) | 1239(2) | 25(2) | 1 |
| O4 | −373(14) | 7515(11) | 777(3) | 32(2) | 1 |
| I1 | 207(1) | 2775(1) | 1886(1) | 36(1) | 1 |
| I2 | −6134(1) | 8056(2) | 2061(1) | 39(1) | 1 |



## Compound 183

**Table 18:** Crystal data and structure refinement.

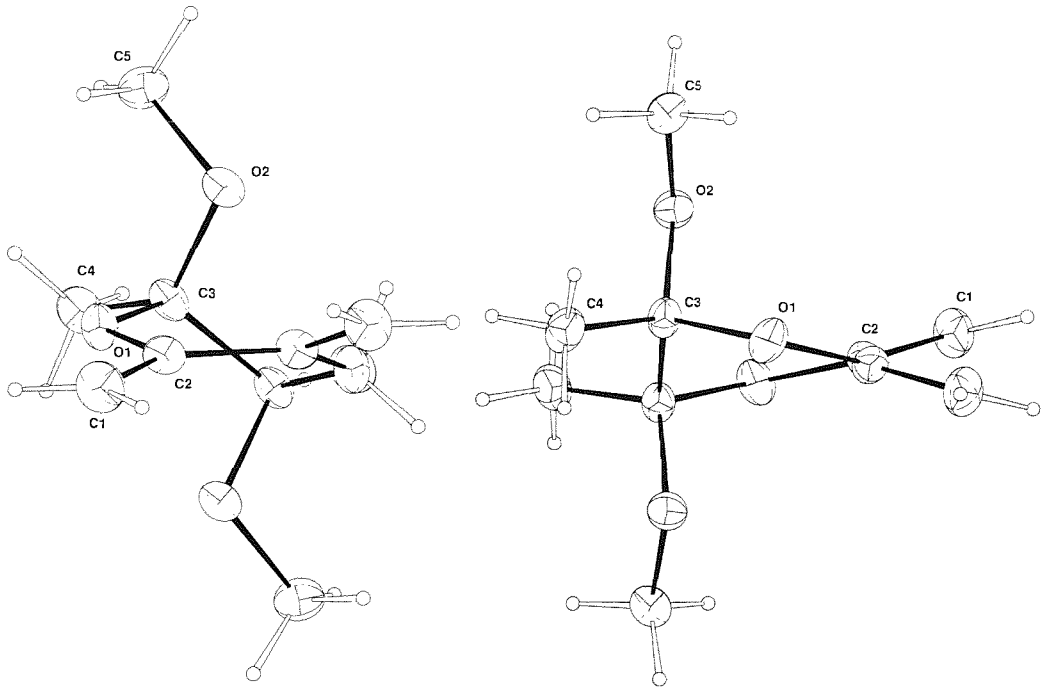
| | |
|---|---|
| Identification code | **01SOT035** |
| Empirical formula | $C_{10}H_{16}O_4$ |
| Formula weight | 200.23 |
| Temperature | 150(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Tetragonal |
| Space group | $P4_32_12$ |
| Unit cell dimensions | $a$ = 9.0608(8) Å<br>$b$ = 9.0608(8) Å<br>$c$ = 12.9150(9) Å |
| Volume | 1060.30(15) Å$^3$ |
| $Z$ | 4 |
| Density (calculated) | 1.254 Mg / m$^3$ |
| Absorption coefficient | 0.096 mm$^{-1}$ |
| *F(000)* | 432 |
| Crystal | Colourless Block |
| Crystal size | 0.20 × 0.20 × 0.20 mm$^3$ |
| $\theta$ range for data collection | 3.55 – 23.25° |
| Index ranges | $-10 \le h \le 6$, $-9 \le k \le 10$, $-14 \le l \le 14$ |
| Reflections collected | 2919 |
| Independent reflections | 756 [$R_{int}$ = 0.0679] |
| Completeness to $\theta$ = 23.25° | 98.8 % |
| Max. and min. transmission | 0.9810 and 0.9810 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 756 / 0 / 65 |
| Goodness-of-fit on $F^2$ | 1.127 |
| Final $R$ indices [$F^2 > 2\sigma(F^2)$] | $R1$ = 0.0435, $wR2$ = 0.1274 |
| $R$ indices (all data) | $R1$ = 0.0488, $wR2$ = 0.1315 |
| Absolute structure parameter | 2(3) |
| Extinction coefficient | 0.030(16) |
| Largest diff. peak and hole | 0.198 and –0.187 e Å$^{-3}$ |

**Diffractometer**: *Nonius KappaCCD* area detector ($\phi$ scans and $\omega$ scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

**Special details**: All hydrogen atoms were placed in idealised positions and refined using a riding model.

**Table 19**: Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| Atom | *x* | *y* | *z* | $U_{eq}$ | *S.o.f.* |
|---|---|---|---|---|---|
| O2 | 6002(2) | 3568(2) | 1151(1) | 32(1) | 1 |
| O1 | 6440(2) | 5653(2) | 2146(1) | 32(1) | 1 |
| C3 | 6685(3) | 4093(3) | 2052(2) | 29(1) | 1 |
| C4 | 8348(3) | 3898(3) | 2065(2) | 39(1) | 1 |
| C5 | 6651(3) | 4014(3) | 193(2) | 40(1) | 1 |
| C2 | 5046(3) | 6091(3) | 2435(2) | 30(1) | 1 |
| C1 | 4830(3) | 7524(3) | 2587(2) | 43(1) | 1 |



## Compound 212

**Table 20:** Crystal data and structure refinement.

| | | |
|---|---|---|
| Identification code | **01sot156** | |
| Empirical formula | $C_{16}H_{24}O_8$ | |
| Formula weight | 344.35 | |
| Temperature | 566(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1$ | |
| Unit cell dimensions | $a$ = 11.4457(8) Å | $\alpha$ = 90° |
| | $b$ = 7.1306(6) Å | $\beta$ = 116.005(3)° |
| | $c$ = 12.2987(12) Å | $\gamma$ = 90° |
| Volume | 902.13(13) Å$^3$ | |
| Z | 2 | |
| Density (calculated) | 1.268 Mg / m$^3$ | |
| Absorption coefficient | 0.102 mm$^{-1}$ | |
| *F(000)* | 368 | |
| Crystal | Block; colourless | |
| Crystal size | 0.36 × 0.18 × 0.15 mm$^3$ | |
| $\theta$ range for data collection | 3.24 – 27.49° | |
| Index ranges | $-14 \le h \le 14$, $-9 \le k \le 8$, $-15 \le l \le 13$ | |
| Reflections collected | 4431 | |
| Independent reflections | 3096 [$R_{int}$ = 0.0292] | |
| Completeness to $\theta$ = 27.49° | 90.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9849 and 0.9643 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3096 / 1 / 225 | |
| Goodness-of-fit on $F^2$ | 0.933 | |
| Final $R$ indices [$F^2 > 2\sigma(F^2)$] | $R1$ = 0.0444, $wR2$ = 0.1080 | |
| $R$ indices (all data) | $R1$ = 0.0874, $wR2$ = 0.1338 | |
| Absolute structure parameter | 1.0(15) | |
| Extinction coefficient | 0.052(9) | |
| Largest diff. peak and hole | 0.112 and –0.132 e Å$^{-3}$ | |

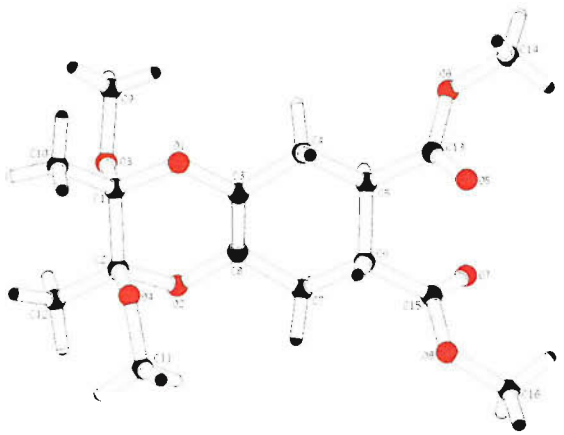
**Diffractometer**: *Enraf Nonius KappaCCD* area detector ($\phi$ scans and $\omega$ scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick
(1997), University of Göttingen, Germany).

**Further information**: http://www.soton.ac.uk/~xservice/strat.htm

**Special details**:

**Table 21:** Atomic coordinates [× $10^4$], equivalent isotropic displacement parameters [$Å^2$ × $10^3$] and site occupancy factors. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| Atom | *x* | *y* | *z* | $U_{eq}$ | *S.o.f.* |
|---|---|---|---|---|---|
| C1 | 75(3) | 1589(4) | 2722(3) | 50(1) | 1 |
| C2 | –407(3) | 3322(4) | 1897(3) | 50(1) | 1 |
| C3 | 2131(3) | 2272(4) | 2785(3) | 49(1) | 1 |
| C4 | 3453(3) | 1512(5) | 3118(3) | 58(1) | 1 |
| C5 | 4423(3) | 3120(5) | 3318(3) | 54(1) | 1 |
| C6 | 3824(3) | 4564(5) | 2311(3) | 55(1) | 1 |
| C7 | 2684(3) | 5503(4) | 2432(3) | 62(1) | 1 |
| C8 | 1801(3) | 4048(4) | 2536(2) | 50(1) | 1 |
| C9 | 920(4) | 986(6) | 4855(3) | 79(1) | 1 |
| C10 | –857(3) | –60(5) | 2308(3) | 69(1) | 1 |
| C11 | –888(5) | 4094(6) | –150(3) | 103(2) | 1 |
| C12 | –1596(3) | 4217(5) | 1893(3) | 67(1) | 1 |
| C13 | 5665(3) | 2330(5) | 3369(3) | 59(1) | 1 |
| C14 | 7613(4) | 777(8) | 4564(4) | 96(2) | 1 |
| C15 | 4778(3) | 6018(5) | 2308(3) | 67(1) | 1 |
| C16 | 5374(4) | 7924(7) | 1057(5) | 103(2) | 1 |
| O1 | 1256(2) | 897(3) | 2751(2) | 54(1) | 1 |
| O2 | 581(2) | 4721(3) | 2299(2) | 52(1) | 1 |
| O3 | 297(2) | 2252(3) | 3880(2) | 62(1) | 1 |
| O4 | –595(2) | 2672(3) | 747(2) | 60(1) | 1 |
| O5 | 5919(2) | 2216(5) | 2515(2) | 84(1) | 1 |
| O6 | 6427(2) | 1674(5) | 4444(2) | 83(1) | 1 |
| O7 | 5624(3) | 6675(5) | 3192(3) | 106(1) | 1 |
| O8 | 4525(2) | 6523(4) | 1191(2) | 81(1) | 1 |



## Compound 256

**Table 22:** Crystal data and structure refinement.

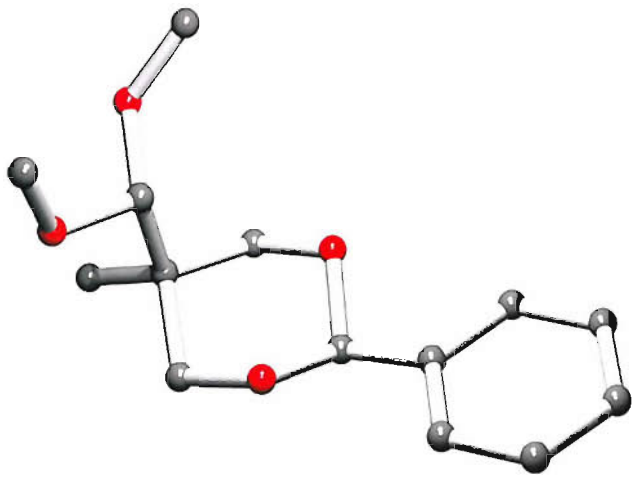
| | | |
|---|---|---|
| Identification code | **03SOT0109 (PC135681_21)** | |
| Empirical formula | $C_{14}H_{20}O_4$ | |
| Formula weight | 252.30 | |
| Temperature | 120(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | *P*-1 | |
| Unit cell dimensions | $a$ = 6.4621(2) Å | $\alpha$ = 100.056(2)° |
| | $b$ = 9.4254(4) Å | $\beta$ = 99.033(2)° |
| | $c$ = 11.0785(5) Å | $\gamma$ = 90.100(2)° |
| Volume | 655.87(5) Å$^3$ | |
| $Z$ | 2 | |
| Density (calculated) | 1.278 Mg / m$^3$ | |
| Absorption coefficient | 0.093 mm$^{-1}$ | |
| *F(000)* | 272 | |
| Crystal | Colourless Block | |
| Crystal size | 0.20 × 0.20 × 0.10 mm$^3$ | |
| $\theta$ range for data collection | 3.14 – 25.03° | |
| Index ranges | $-7 \le h \le 7, -10 \le k \le 11, -13 \le l \le 13$ | |
| Reflections collected | 11941 | |
| Independent reflections | 2321 [$R_{int}$ = 0.0527] | |
| Completeness to $\theta$ = 25.03° | 99.7 % | |
| Absorption correction | Semi–empirical from equivalents | |
| Max. and min. transmission | 0.9908 and 0.9817 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2321 / 0 / 243 | |
| Goodness-of-fit on $F^2$ | 0.841 | |
| Final $R$ indices [$F^2 > 2\sigma(F^2)$] | $R1$ = 0.0472, $wR2$ = 0.1675 | |
| $R$ indices (all data) | $R1$ = 0.0551, $wR2$ = 0.1871 | |
| Largest diff. peak and hole | 0.342 and –0.371 e Å$^{-3}$ | |

**Diffractometer**: *Nonius KappaCCD* area detector ($\phi$ scans and $\omega$ scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

**Special details**: All hydrogen atoms were located from the difference map and fully refined.

**Table 23:** Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| Atom | *x* | *y* | *z* | $U_{eq}$ | *S.o.f.* |
|---|---|---|---|---|---|
| C1 | 4442(3) | −1819(2) | 3798(2) | 25(1) | 1 |
| C2 | 6131(3) | −2723(2) | 3824(2) | 29(1) | 1 |
| C3 | 6589(3) | −3538(2) | 2738(2) | 31(1) | 1 |
| C4 | 5377(3) | −3414(2) | 1612(2) | 28(1) | 1 |
| C5 | 3679(3) | −2512(2) | 1577(2) | 25(1) | 1 |
| C6 | 3184(2) | −1719(2) | 2670(2) | 21(1) | 1 |
| C7 | 1196(2) | −885(2) | 2652(1) | 21(1) | 1 |
| C8 | −1235(2) | 350(2) | 1460(2) | 23(1) | 1 |
| C9 | −1275(2) | 1566(2) | 2565(2) | 22(1) | 1 |
| C10 | −606(2) | 918(2) | 3737(2) | 23(1) | 1 |
| C11 | −3502(2) | 2125(2) | 2546(2) | 28(1) | 1 |
| C12 | 287(2) | 2774(2) | 2517(1) | 20(1) | 1 |
| C13 | 1860(3) | 4935(2) | 3751(2) | 29(1) | 1 |
| C14 | 1314(3) | 3365(2) | 679(2) | 29(1) | 1 |
| O1 | 1370(2) | 229(1) | 3694(1) | 23(1) | 1 |
| O2 | 767(2) | −331(1) | 1534(1) | 23(1) | 1 |
| O3 | 252(2) | 3842(1) | 3575(1) | 24(1) | 1 |
| O4 | −306(2) | 3365(1) | 1420(1) | 25(1) | 1 |



## Compound 257

**Table 24:** Crystal data and structure refinement.

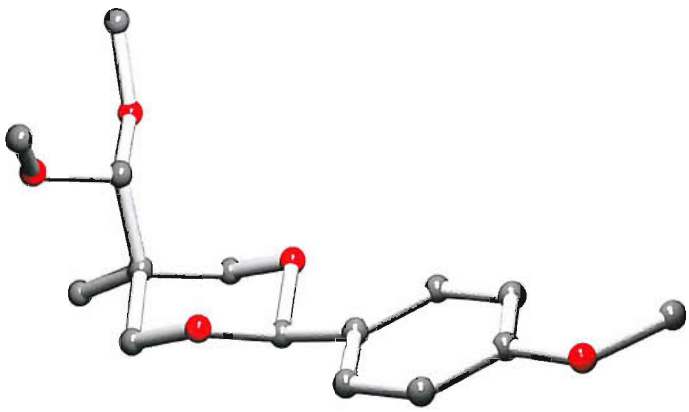
| | | |
|---|---|---|
| Identification code | **03SOT0108 (PC/3568/22)** | |
| Empirical formula | $C_{15}H_{22}O_5$ | |
| Formula weight | 282.33 | |
| Temperature | 120(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | *P*-1 | |
| Unit cell dimensions | $a$ = 8.0637(3) Å | $\alpha$ = 89.605(2)° |
| | $b$ = 8.6180(2) Å | $\beta$ = 86.878(2)° |
| | $c$ = 10.4645(4) Å | $\gamma$ = 87.450(2)° |
| Volume | 725.40(4) Å$^3$ | |
| $Z$ | 2 | |
| Density (calculated) | 1.293 Mg / m$^3$ | |
| Absorption coefficient | 0.096 mm$^{-1}$ | |
| *F(000)* | 304 | |
| Crystal | Colourless Slab | |
| Crystal size | 0.20 × 0.20 × 0.10 mm$^3$ | |
| $\theta$ range for data collection | 3.07 – 25.03° | |
| Index ranges | $-9 \le h \le 9$, $-10 \le k \le 10$, $-12 \le l \le 12$ | |
| Reflections collected | 12143 | |
| Independent reflections | 2557 [$R_{int}$ = 0.0419] | |
| Completeness to $\theta$ = 25.03° | 99.6 % | |
| Absorption correction | Semi–empirical from equivalents | |
| Max. and min. transmission | 0.9904 and 0.9810 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2557 / 0 / 270 | |
| Goodness-of-fit on $F^2$ | 1.031 | |
| Final $R$ indices [$F^2 > 2\sigma(F^2)$] | $R1$ = 0.0366, $wR2$ = 0.0936 | |
| $R$ indices (all data) | $R1$ = 0.0475, $wR2$ = 0.1005 | |
| Extinction coefficient | 0.034(7) | |
| Largest diff. peak and hole | 0.226 and –0.198 e Å$^{-3}$ | |

**Diffractometer**: *Nonius KappaCCD* area detector ($\phi$ scans and $\omega$ scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997). University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

**Special details**: All hydrogen atoms were located from the difference map and fully refined.

**Table 25:** Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. $U_{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| Atom | *x* | *y* | *z* | $U_{eq}$ | *S.o.f.* |
|---|---|---|---|---|---|
| C1 | 1983(2) | 5031(2) | 11432(1) | 21(1) | 1 |
| C2 | 1766(2) | 4389(2) | 12653(1) | 24(1) | 1 |
| C3 | 2699(2) | 4895(2) | 13630(1) | 23(1) | 1 |
| C4 | 3852(2) | 6028(2) | 13387(1) | 23(1) | 1 |
| C5 | 4074(2) | 6639(2) | 12168(1) | 21(1) | 1 |
| C6 | 3137(2) | 6149(1) | 11171(1) | 19(1) | 1 |
| C7 | 3521(2) | 6721(1) | 9833(1) | 19(1) | 1 |
| C8 | 4459(2) | 8806(2) | 8604(1) | 21(1) | 1 |
| C9 | 3132(2) | 8589(2) | 7642(1) | 20(1) | 1 |
| C10 | 2643(2) | 6903(2) | 7750(1) | 22(1) | 1 |
| C11 | 3851(2) | 8925(2) | 6292(1) | 27(1) | 1 |
| C12 | 1629(2) | 9692(1) | 7986(1) | 21(1) | 1 |
| C13 | −1084(2) | 10359(2) | 7360(2) | 35(1) | 1 |
| C14 | 1727(2) | 12152(2) | 9035(2) | 30(1) | 1 |
| C15 | 1445(2) | 3148(2) | 15146(2) | 37(1) | 1 |
| O1 | 2174(1) | 6492(1) | 9054(1) | 21(1) | 1 |
| O2 | 3900(1) | 8305(1) | 9864(1) | 20(1) | 1 |
| O3 | 413(1) | 9442(1) | 7102(1) | 28(1) | 1 |
| O4 | 2118(1) | 11248(1) | 7911(1) | 23(1) | 1 |
| O5 | 2579(1) | 4347(1) | 14864(1) | 32(1) | 1 |



## References


(1) Diels, O.; Alder, K. *Liebigs Ann.* **1928**, *460*, 98-122.

(2) Koreeda, M.; Jung, K.; Ichita, J. *J. Chem. Soc.; Perkin Trans. 1* **1989**, 2129–2130.

(3) Woodward, R. B.; Sondheimer, F.; Taab, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223–4251.

(4) Tietze, L. F.; Stegelmeiter, H.; Harms, K.; Brumby, T. *Angew. Chem. Int. Ed.* **1982**, *21*, 863–864.

(5) Imagawa, T.; Nakagawa, T.; Kawanisi, M.; Sisido, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1506–1510.

(6) Tietze, L. F. *Chem. Rev* **1996**, *96*, 115–136.

(7) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley, 1976.

(8) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57–64.

(9) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094–4096.

(10) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092–4094.

(11) Inukai, T.; Kojima, T. *J. Org. Chem.* **1966**, *31*, 1121–1123.

(12) Inukai, T.; Kojima, T. *J. Org. Chem.* **1967**, *32*, 869–871.

(13) Inukai, T.; Kojima, T. *J. Org. Chem.* **1971**, *36*, 924–928.

(14) Nunes, R. L.; Bieber, L. W. *Tetrahedron Lett.* **2001**, *42*, 219–221.

(15) Danishefsky, S.; Kitahara, M. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808.

(16) Danishefsky, S.; Hirama, M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7013–7018.

(17) Houk, K. N.; Lin, Y.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554–556.

(18) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129–1134.

(19) Alder, K.; Stein, G.; von Rodenbrock, F.; Eckardt, W.; Frercks, W.; Schneider *Liebigs Ann.* **1934**, *514*, 1–33.

(20) Alder, K.; Stein, G.; Liebmann, M.; Rolland, E. *Liebigs Ann.* **1934**, *514*, 157–211.

(21) Alder, K.; Stein, G.; Rolland, E.; Schulze, G. *Liebigs Ann.* **1934**, *514*, 211–227.

(22) Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1944**, *66*, 645–649.

(23) de la Torre, M.; Cruz Caballero, M.; Whiting, A. *Tetrahedron* **1999**, *55*, 8547–8554.

(24) Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 9561–9564.

(25) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758–3759.

(26) Pignat, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160–5167.

(27) Chapuis, C.; Jurczalac, J. *Helev. Chim. Acta.* **1987**, *70*, 436–440.

(28) Corey, E. J.; Imwinkelred, R.; Pikul, S.; Xiang, X. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495.

(29) Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938–7939.

(30) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109.

(31) Narasaka, K.; Inoue, M.; Yamada, T. *Chem. Lett.* **1986**, 1967.

(32) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J. *Chem. Lett.* **1987**, 2409–2412.

(33) Maruoka, K.; Sakurai, M.; Fujiwara, J.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4895–4898.

(34) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254–6255.

(35) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

(36) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.

(37) Bezuidenhoudt, B. C. B.; Castle, G. H.; Geden, J. V.; Ley, S. V. *Tetrahedron Lett.* **1994**, *35*, 7451–7454.

(38) Bezuidenhoudt, B. C. B.; Castle, G. H.; Ley, S. V. *Tetrahedron Lett.* **1994**, *35*, 7447–7450.

(39) Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.* **1961**, *26*, 4778–4779.

(40) Alonso, I.; Carretero, J. C.; Garcia Ruano, J. L. *J. Org. Chem.* **1993**, *58*, 3231–3232.

(41) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165–7166.

(42) Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **2000**, *65*, 9059–9068.

(43) Gupta, R. C.; Slawin, A. M. Z.; Stoodley, R. J.; Williams, D. J. *J. Chem. Soc.; Chem. Commn.* **1986**, 668–670.

(44) Virgili, M.; Pericàs, M. A.; Moyano, A.; Riera, A. *Tetrahedron* **1997**, *53*, 13427–13447.

(45) Virgili, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1999**, *55*, 3959–3986.

(46) Adams, H.; Jones, D. N.; Aversa, M. C.; Bonaccorsi, P.; Giannetto, P. *Tetrahedron Lett.* **1993**, *34*, 6481–6484.

(47) Schlessinger; H., R.; Pettus, T. R. R.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1994**, *59*, 3246–3247.

(48) Ley, S. V.; Woods, M.; Zanotti-Gerosa, A. *Synthesis* **1992**, 52–54.

(49) Ley, S. V.; Priepke, H. W. M.; Warriner, S. L. *Angew. Chem. Int. Ed.* **1994**, *33*, 2290–2292.

(50) Berens, U.; Leckel, D.; Oepen, S. C. *J. Org. Chem.* **1995**, *60*, 8204–8208.

(51) Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J. F.; Warriner, S. L.; Wesson, K. E. *J. Chem. Soc.; Perkin Trans. 1* **1997**, 2023–2031.

(52) Douglas, N. L.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Priepke, H. W. M.; Warriner, S. L. *Synlett* **1996**, 793–795.

(53) Díez, E.; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodriguez, F. *Synlett* **2003**, *8*, 1186-1188.

(54) Dixon, D. J.; Foster, A. C.; Ley, S. V. *Org. Lett.* **2000**, *2*, 123–125.

(55) Montchamp, J.-L.; Tian, F.; Hart, M. F.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897–3899.

(56) Jurczak, J.; Pikul, S.; Bauer, S. *Tetrahedron* **1986**, *42*, 477–488.

(57) Jäger, V.; Wehner, V. *Angew. Chem. Int. Ed.* **1989**, *28*, 469–470.

(58) Michel, P.; Ley, S. V. *Angew. Chem. Int. Ed.* **2002**, *41*, 3898–3901.

(59) Ley, S. V.; Michel, P. *Synthesis* **2004**, 147–150.

(60) Barlow, J. S.; Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc.; Perkin Trans. 1* **1999**, 1627–1629.

(61) Díez, E.; Dixon, D. J.; Ley, S. V. *Angew. Chem. Int. Ed.* **2001**, *40*, 2906–2909.

(62) Dixon, D. J.; Guarna, A.; Ley, S. V. *Synthesis* **2002**, 1973–1978.

(63) Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Org. Lett.* **2001**, *3*, 3753–3755.

(64) Dixon, D. J.; Ley, S. V.; Rodriguez, F. *Org. Lett.* **2001**, *3*, 3753–3755.

(65) Haag, D.; Scharf, H. D. *J. Org. Chem.* **1996**, *61*, 6127–6135.

(66) Castle, G. H.; Ley, S. V. *Tetrahedron Lett.* **1994**, *35*, 7455–7458.

(67) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder reaction*; Wiley-Interscience, 1990.

(68) Urabe, H.; Nakajima, R.; Sato, F. *Org. Lett.* **2000**, *2*, 3481–3438.

(69) Hosomi, A.; Otaka, K.; Sakurai, H. *Tetrahedron* **1986**, *27*, 2881–2884.

(70) Dixon, D. J.; Krause, L.; Ley, S. V. *J. Chem. Soc.; Perkin Trans. 1* **2001**, 2516–2518.

(71) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc.; Perkin Trans. 1* **1999**, 1631–1633.

(72) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc.; Perkin Trans. 1* **1980**, 2866–2869.

(73) Lee, J. W.; Oh, D. Y. *Heterocycles* **1990**, *31*, 1417–1421.

(74) Chretien, F. *Synth. Commn.* **1989**, *19*, 1015–1024.

(75) Berens, U.; Selke, R. *Tetrahedron: Asymmetry* **1996**, *7*, 2055–2064.

(76) Cook, A. S.; Williams, D. B. G.; White, A. J. P.; Williams, D. J.; Lange, S. J.; Barrett, A. G. M.; Hoffman, B. M. *Angew. Chem. Int. Ed.* **1997**, *36*, 760–761.

(77) Li, W.; Waldkirch, J. P.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 7618–7623.

(78) Downham, R.; Kim, K. S.; Ley, S. V.; Woods, M. *Tetrahedron Lett.* **1994**, *35*, 769–772.

(79) Grice, P.; Ley, S. V.; Pietruszka, J.; Priepke, H. W. M.; Warriner, S. L. *J. Chem. Soc.; Perkin Trans. 1* **1997**, 351–363.

(80) Gebauer, O.; Bruckner, R. *Liebigs Ann.* **1996**, 1559–1563.

(81) Lence, E.; Castedo, L.; González, C. *Tetrahedron Lett.* **2002**, *43*, 7917–7918.

(82) Scharf, H. D.; Plum, H.; Fleischhauer, J.; Scleker, W. *Chem. Ber.* **1979**, *112*, 862–886.

(83) Chen, D.; Wang, J.; Totah, N. *J. Org. Chem.* **1999**, *64*, 1776–1777.

(84) Entwistle, D. A.; Hughes, A. B.; Ley, S. V.; Visentin, G. *Tetrahedron Lett.* **1994**, *35*, 777–780.

(85) Farcy. N.; De Muynck, H.; Madder, A.; Hosten, N.; De Clercq, P. J. *Org. Lett.* **2001**, *3*, 4299–4301.

(86) Heinonen, P.; Virta, P.; Lönnberg, H. *Tetrahedron* **1999**, *55*, 7613–7624.

(87) Hanessian, S. Q., D.; Prabhanjan, H.; Reddy, G. V.; Lou, B. *Can. J. Chem.* **1996**, *74*, 1738–1747.

(88) Glauser, T.; Stancik, C. M.; Möller, M.; Voytek, S.; Gast, A. P.; Hedrick, J. L. *Macromolecules* **2002**, *35*, 5774–5781.

(89) Würsch, A.; Möller, M.; Glauser, T.; Lim, L. S.; Voytek, S.; Hedrick, J. L. *Macromolecules* **2001**, *34*, 6601–6615.

(90) Grayson, S. M.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2000**, *122*, 10335–10344.

(91) Grayson, S. M.; Jayaraman, M.; Fréchet, J. M. J. *J. Chem. Soc.; Chem. Commn.* **1999**, 1329–1330.

(92) Doherty, S.; Robins, E. G.; Nieuwenhuyzen, M.; Champkin, P. A.; Clegg, W. *Organometallics* **2002**, *21*, 4147–4158.

(93) Liu, B.; Roy, R. *J. Chem. Soc.; Chem. Commn.* **2002**, 594–595.

(94) Pegenau, A.; Hegmann, T.; Tschierske, C.; Diele, S. *Eur. J. Chem.* **1999**, *5*, 1643–1660.

(95) Dale, J.; Fredriksen, S. B. *Acta Chimica Scandanavia* **1992**, *46*, 271–277.

(96) Coxon, A. C.; Stoddart, J. F. J. *J. Chem. Soc.; Perkin Trans. 1* **1977**, 767–785.

(97) Leznoff, C. C.; Marcuccio, S. M.; Greenberg, S.; Lever, A. B. P.; Tomer, K. B. *Can. J. Chem.* **1985**, *63*, 623–631.

(98) Hisamoto, H.; Tani, M.; Mori, S.; Yamada, T.; Ishigaki, T.; Tohma, H.; Suzuki, K. *Analytical Chemistry* **1999**, *71*, 259–264.

(99) Omotowa, B. A.; Judd, M. R.; Twamley, B.; Shreeve, J. *J. Org. Chem.* **2002**, *67*, 1588–1594.

(100) Gardiner, J. M.; Mather, P.; Morjan, R.; Pritchard, R. G.; Warren, J. E.; Cooper, M. L.; Ferwanah, A. E.-R. S.; Abu-Thiem, O. S. *Tetrahedron Lett.* **2002**, *43*, 2091–2094.

(101) Pattison, D. B. J. *J. Am. Chem. Soc.* **1957**, *79*, 3455–3456.

(102) Nassar, R. F.; Issidorides, C. H. *J. Org. Chem.* **1959**, *24*, 1832–1833.

(103) Conrad, W. E.; Gesner, B. D.; Levasseur, L. A.; Murphy, R. F.; Conrad, H. M. *J. Org. Chem.* **1961**, *26*, 3571–3574.

(104) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483–7498.

(105) Eliel, E. L.; Enanoza, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 8072–8081.

(106) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

(107) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.

(108) Bartels, B.; Hunter, R. *J. Org. Chem.* **1993**, *58*, 6756–6765.

(109) Delongchamps, P.; Moreau, C. *Can. J. Chem.* **1971**, *49*, 2465–2467.

(110) Delongchamps, P.; Moreau, C.; Frehel, D.; Chenevert, R. *Can. J. Chem.* **1975**, *53*, 1204–1211.

(111) Clarke, P. J.; Jeffery, M. J. J.; Boydell, A. J.; Whiting, S.; Linclau, B. *Tetrahedron* **2004**, *60*, 3625–3636.

(112) Bellec, N.; Montalban, A. G.; Williams, D. B. G.; Cook, A. S.; Anderson, M. E.; Feng, X.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **2000**, *65*, 1774–1779.