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The First Enantioselective Synthesis of the Natural Pesticide, Rotenone

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A dissertation submitted to the Faculty of Science,
University of the Witwatersrand,
Johannesburg

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October 2011

Declaration

I declare that the work presented in this dissertation was carried out exclusively by myself under the supervision of Professor C. B. de Koning and Dr S. C. Pelly. It is being submitted for the degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

_____

26th day of October, 2011

Abstract

The 2-isopropenyl-2,3-dihydrobenzofuran moiety is found in many naturally occurring compounds including rotenone, a complex pentacyclic molecule isolated from several leguminous plants of the *Derris* and *Lonchocarpus* species. Interest in rotenone stems from the fact that it possesses significant pesticidal and piscicidal properties which have been employed for centuries. Furthermore, as it has three stereogenic centres, rotenone poses an interesting and challenging synthetic target for organic chemists. Although various syntheses of this natural compound have been reported, none of these were stereoselective. The first stereoselective total synthesis of rotenone is described in this dissertation.

Initially, a model study was conducted in which the simplest of the natural rotenoids, munduserone, was synthesised. The key step in this transformation involves the use of a platinum catalysed 6-*endo*-hydroarylation reaction of an alkynone intermediate, thus affording munduserone in 6 steps and an overall yield of 23%. We then attended to the synthesis of the more complex rotenoid, rotenone. Rotenone was synthesised by the initial assembly of a chiral (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol moiety, asymmetrically accessible using a stereoselective Pd π-allyl mediated cyclisation of *(E)*-4-(2,6-dihydroxyphenyl)-2-methylbut-2-enyl methyl carbonate. Having constructed the dihydrobenzofuran in an enantiomeric excess of 94.8%, the chromene part of rotenone could then be synthesised. To this end, the LDA mediated coupling reaction of the formylated dihydrobenzofuran and 1,2-dimethoxy-4-(prop-2-ynyloxy)benzene, gave a secondary alcohol which was subsequently oxidised to the corresponding alkynone, (-)-*(R)*-(6,7-dimethoxy-2*H*-chromen-4-yl)(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)methanone. A 6-*endo*-hydroarylation reaction was employed as a mild strategy to construct the chromene moiety, (-)-*(R)*-(6,7-dimethoxy-2*H*-chromen-4-yl)(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)methanone. Finally, a deprotection and a base-catalysed intramolecular oxo-Michael addition concluded the first stereoselective synthesis of rotenone in 17 steps and an overall yield of 0.02%.

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Table of contents

Declaration i
Abstract ii
Acknlowledgements iii

CHAPTER 1 – INTRODUCTION 1
1.1 A possible link between rotenone and Parkinson's disease 2
1.2 Industry's response 3
1.3 An improved model 4
1.4 Rotenone makes headlines 5
1.5 The biosynthesis of rotenoids 7
1.6 Isolation, structure elucidation and syntheses of rotenone and munduserone 8
1.6.1 Synthesis of the dehydrorotenoid core 11
1.6.2 A direct route to the rotenoid core 13
1.6.3 Rotenone from dalpanol 17
1.6.4 Claissen rearrangement of acetylenic intermediates 17
1.6.5 Palladium-catalysed intramolecular arylation 18
1.6.6 Aroylation of substituted chromans 19
1.6.7 Synthesis from protected cyanohydrins 20
1.7 The Wits approach – aims of this project 21
1.8 Selected syntheses of the 2,3-dihydrobenzofuran moiety 23
1.8.1 Background on racemic syntheses of the 2,3-dihydrobenzofuran moiety 24
1.8.2 Stereoselective syntheses of the 2,3-dihydrobenzofuran moiety 27
1.8.2.1 The Asymmetric Wacker oxidation 28
1.8.2.2 Asymmetric synthesis via enantioselective epoxidation 30
1.8.2.3 Sharpless asymmetric dihydroxylation 31
1.8.2.4 Asymmetric allylic alkylation (AAA) 33
1.9 Construction of the chromene moiety 37
CHAPTER 2 - PLANNED APPROACH 44
2.1 Towards rotenone 44
2.2 Towards munduserone - A model study 46
CHAPTER 3 – RESULTS AND DISCUSSION 48
3.1 Synthesis of munduserone – 8 48
3.1.1 Synthesis of 3,4-Dimethoxyphenol – 176 48
3.1.2 Synthesis of 1,2-dimethoxy-4-(prop-2-ynyloxy)benzene – 52 49
3.1.3 Synthesis of 2-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde – 178 50
3.1.4 Synthesis of 1-(2-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl)-4-(3,4-dimethoxyphenoxy)but-2-yn-1-ol – 179 51
3.1.5 Synthesis of 1-(2-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl)-4-(3,4-dimethoxyphenoxy)but-2-yn-1-one – 180 52

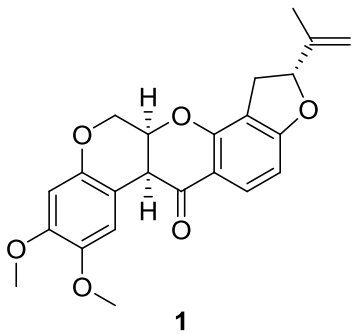
3.1.6 Synthesis of (2-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl)(6,7-dimethoxy-*2H*-chromen-4-yl)methanone – 181 53
3.1.7 Synthesis of (6,7-dimethoxy-*2H*-chromen-4-yl)(2-hydroxy-4-methoxyphenyl)methanone – 182 56
3.1.8 Synthesis of (±)-munduserone – (±)-8 57
3.2 Synthesis of rotenone 60
3.2.1 Synthesis of 1,3-bis(methoxymethoxy)benzene – 183 60
3.2.2 Synthesis of allyl-1,3-*bis*(methoxymethoxy)benzene – 184 61
3.2.3 Synthesis of 2-allylbenzene-1,3-diol – 185 62
3.2.4 Synthesis of 2-allyl-1,3-*bis*(*tert*-butyldimethylsilyloxy)benzene – 186 63
3.2.5 Synthesis of 2-(2,6-*bis*(*tert*-butyldimethylsilyloxy)-phenyl)acetaldehyde – 188 64
3.2.6 Synthesis of *(E)*-ethyl-4-(2,6-*bis*(*tert*-butyl-dimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 193 66
3.2.7 Synthesis of *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 195 69
3.2.8 Synthesis of *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 196 70
3.2.9 Synthesis of *(E)*-4-(2,6-dihydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 127 73
3.2.10 Synthesis of racemic 2-isopropenyl-2,3-dihydrobenzofuran-4-ol – *rac*-78 74
3.2.11 Synthesis of (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – *(R)*-78 75
3.2.12 Synthesis of 2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate – *(R)*-198 and *rac*-198 77
3.2.13 Synthesis of (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate – *(R)*-199 79
3.2.14 Synthesis of *(R)*-4-(methoxymethoxy)-2-isopropenyl-2,3-dihydrobenzofuran – *(R)*-200 81
3.2.15 Synthesis of *(R)*-4-(methoxymethoxy)-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde and *(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-201 and *(R)*-202 83
3.2.16 Synthesis of (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde and *(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-7-carbaldehyde – *(R)*-202 and *(R)*-203 84
3.2.17 Synthesis of (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-202 86
3.2.18 Synthesis of (-)-*(R)*-4-(*tert*-butyldimethylsilyloxy)-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-204 87
3.2.19 Attempted synthesis of 1-((*R)*-4-(*tert*-butyldimethylsilyloxy)-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)-4-(3,4-dimethoxyphenoxy)but-2-yn-1-ol – *(R)*-205 88
3.2.20 Synthesis of (-)-*(R)*-4-isopropoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-206 89
3.2.21 Attempted synthesis of 4-(3,4-dimethoxyphenoxy)-1-((*R)*-4-isopropoxy-2- isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-ol – *(R)*-207 90
3.2.22 Synthesis of (-)-*(R)*-4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-208 91
3.2.23 Synthesis of (-)-*(R)*-4-(3,4-Dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-ol –209 92
3.2.24 Back to a model system: Synthesis of 4-(3,4-dimethoxyphenoxy)-1-(2,4-dimethoxyphenyl)but-2-yn-1-ol – 211 95
A model system –*n*-Butyllithium and manganese dioxide 95
A model system – Sodium amide 96
A model system – Lithium 2,2,6,6-tetramethylpiperidine 96
A model system – Lithium diisopropylamide 97

3.2.25 Synthesis of (-)-*(R)*-4-(3,4-Dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-ol – 209 ... 98
3.2.26 Synthesis of (-)-*(R)*-4-(3,4-dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-one – *(R)*-212 ... 98
3.2.27 Synthesis of (-)-*(R)*-(6,7-dimethoxy-2*H*-chromen-4-yl)(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)methanone – *(R)*-213 ... 99
3.2.28 Synthesis of (-)-*(R)*-(6,7-dimethoxy-2*H*-chromen-4-yl)(4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)methanone – *(R)*-214 ... 101
3.2.29 Synthesis of rotenone and its diastereomer – 1a and 1b ... 102
3.3 Concluding remarks ... 108
3.3.1 Project summary ... 108
3.3.2 Interesting observations noted ... 111
3.3.3 Future work to utilise an asymmetric Michael addition ... 112
CHAPTER 4 – EXPERIMENTAL PROCEDURES ... 114
4.1 General Procedures ... 114
4.1.1 Purification of solvents and reagents ... 114
4.1.2 Chromatography ... 114
4.1.3 Spectroscopic and physical data ... 114
4.1.4 High pressure liquid chromatography ... 115
4.1.5 Other general procedures ... 115
4.2 Experimental work pertaining to the synthesis of munduserone ... 116
4.2.1 3,4-Dimethoxyphenol – 176 ... 116
4.2.2 1,2-Dimethoxy-4-(prop-2-ynyloxy)benzene – 52 ... 116
4.2.3 2-(*Tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde – 178 ... 117
4.2.4 1-(2-(*Tert*-butyldimethylsilyloxy)-4-methoxyphenyl)-4-(3,4-dimethoxyphenoxy)but-2-yn-1-ol – 179 ... 118
4.2.5 1-(2-(*Tert*-butyldimethylsilyloxy)-4-methoxyphenyl)-4-(3,4-dimethoxyphenoxy)but-2-yn-1-one – 180 ... 119
4.2.6 (2-(*Tert*-butyldimethylsilyloxy)-4-methoxyphenyl)(6,7-dimethoxy-*2H*-chromen-4-yl)methanone – 181 ... 119
4.2.7 (6,7-Dimethoxy-*2H*-chromen-4-yl)(2-hydroxy-4-methoxyphenyl)methanone – 182 ... 120
4.2.8 (±)-Munduserone – 8 ... 121
4.3 Experimental work pertaining to the synthesis of rotenone ... 122
4.3.1 1,3-*Bis*(methoxymethoxy)benzene – 183 ... 122
4.3.2 2-Allyl-1,3-*bis*(methoxymethoxy)benzene – 184 ... 122
4.3.3 2-Allylbenzene-1,3-diol – 185 ... 123
4.3.4 2-Allyl-1,3-*bis*(*tert*-butyldimethylsilyloxy)benzene – 186 ... 124
4.3.5 2-(2,6-*Bis*(*tert*-butyldimethylsilyloxy)-phenyl)acetaldehyde – 188 ... 125
4.3.6 *(E)*-Ethyl-4-(2,6-*bis*(*tert*-butyl-dimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 193 ... 125
4.3.7 *(E)*-4-(2,6-*Bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 195 ... 126
4.3.8 *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 196 ... 127
4.3.9 *(E)*-4-(2,6-Dihydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 127 ... 128
4.3.10 (±)-2-Isopropenyl-2,3-dihydrobenzofuran-4-ol – *rac*-78 ... 128
4.3.11 (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – *(R)*-78 ... 129
4.3.12 2-Isopropenyl-2,3-dihydrobenzofuran-4-yl acetate – *rac*-198 ... 130

4.3.13 (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate – *(R)*-199 131
4.3.14 *(R)*-4-(methoxymethoxy)-2-isopropenyl-2,3-dihydrobenzofuran – *(R)*-200 131
4.3.15 *(R)*-4-(methoxymethoxy)-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde and (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-201 and *(R)*-202 132
4.3.16 (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde and (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-7-carbaldehyde – *(R)*-202 and *(R)*-203 133
4.3.17 (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-202 134
4.3.18 (-)-*(R)*-4-(*tert*-butyldimethylsilyloxy)-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-204 135
4.3.19 (-)-*(R)*-4-isopropoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde –*(R)*-206 136
4.3.20 (-)-*(R)*-4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-208 137
4.3.21 (-)-*(R)*-4-(3,4-Dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-ol – 209 138
4.3.22 (-)-*(R)*-4-(3,4-dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-ol – 209 139
4.3.23 (-)-*(R)*-4-(3,4-dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-one – *(R)*-212 140
4.3.24 (-)-*(R)*-(6,7-dimethoxy-2*H*-chromen-4-yl)(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)methanone – *(R)*-213 140
4.3.25 (-)-*(R)*-(6,7-dimethoxy-2*H*-chromen-4-yl)(4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)methanone – *(R)*-214 141
4.3.26 Rotenone – 1a and 1b 142
CHAPTER 5 – APPENDIX I 144
A1 X-ray crystallographic data 144
A1.1 X-ray crystallographic data for (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2- nitrobenzenesulfonate – *(R)*-199 144
A1.2 X-ray crystallographic data for munduserone – 8 145
A1.3 X-ray crystallographic data for rotenone – 1a 146
CHAPTER 5 – REFERENCES 148

CHAPTER 1 – INTRODUCTION

The eradication of pests in agriculture is an unremitting problem that has plagued mankind since the dawn of agriculture. Early farmers relied on natural resources as pesticides such as for example, root extracts of the *Derris elliptica* which were employed as a pesticide in nutmeg cultivation in the East Indies.[1] In fact, the use of similar plant extracts by native tribes as an aid in catching fish was reported by travellers to the East Indies, South America and Africa. They observed that when the crushed root of the *Derris* plant was added to lakes and ponds, the fish would swim up to the surface of the water body where they could then be easily harpooned.[2] Not much was known about these extracts until the beginning of the 20th century when they were studied by a researcher in Japan by the name of Roten.[3] Little did he know that the primary toxic ingredient was a complex pentacyclic natural product which would later be named 'rotenone' **1** (Figure 1). This compound is responsible for both the pesticidal and piscicidal activities observed in the extracts and has therefore become one of the most popular and well-known natural products amongst scientists and the general community alike. Indeed, the entire class of related compounds were subsequently discovered and were suitably named 'rotenoids'.



1

Figure 1

Although rotenone had been used for over a century, it wasn't until 1912 that it was patented for commercial use.[4] Due to its complex structure, the synthesis of this pesticide on an industrial scale has remained impractical. Rather, the product is extracted from several leguminous plants of the *Derris* and *Lonchocarpus* species. Rotenone was particularly appealing as a pesticide in that, owing to its natural origins, it could be exploited in "organic agriculture" where the use of chemically synthesised pesticides is prohibited.[3] In fact in 2007, approximately 14,500 pounds of rotenone was utilised in the United States of America alone for agricultural purposes.[5, 6] The chemical also has a relatively short half-life as it photodegrades to non-toxic compounds within several days, thus

limiting human contact and consumption.[3] Moreover, since rotenone is relatively non-polar, it was believed to be less toxic to mammals as absorption through their relatively hydrophilic gastrointestinal tract was thought to be inefficient. In contrast to this, the chemical is readily absorbed through the hydrophobic trachea of insects, hence its efficacy as a pesticide. Likewise, effective absorption through the liphophylic gills of fish allows for irreversible binding of rotenone to NADH-Q oxidoreductase (complex I), the first of four complexes in the electron transport chain of cellular respiration. The chain ordinarily terminates with the reduction of oxygen and the synthesis of ATP. Upon binding of rotenone to complex I, the respiratory chain is inhibited and since fish are unable to utilise oxygen in the blood, they swim to the surface in a desperate attempt to seek more highly oxygenated water. These piscicidal effects are reversible and fish that are transferred in time to a rotenone free water body are able to recover.

1.1 A possible link between rotenone and Parkinson's disease

Parkinson's disease is one of the most common neurodegenerative disorders in elderly people. Although the primary cause is still unknown, it is believed to originate from a combination of both genetic and environmental factors. The disease is characterised by the degeneration of dopaminergic neurons in the brain as a result of mitochondrial dysfunction, brought about by the inhibition of complex I in the electron transport chain.[7] Since rotenone is a known complex I inhibitor, it was associated with this disease and has thus received a considerable amount of negative publicity, especially following a study conducted at Emory University.[8] In this research, rats were infused with rotenone over a period of weeks and an onset of symptoms similar to those in Parkinson's disease was observed. Rotenone has since been the subject of much controversy and consequently, there has been an increase in research regarding this matter. The general consensus amongst researchers is that a link does indeed exist between rotenone and Parkinson's disease.[7, 9] There has however, been pressing need for better models as many scientific organisations believe that these studies were unrealistic in that they do not mimic the way in which rotenone would normally be ingested. Consequently, the response to these studies varied and whilst rotenone was banned in several countries, others chose to continue using the compound, simply adopting more stringent regulations.

1.2 Industry's response

In an attempt to alter the negative image of rotenone, various efforts were made to reduce the concentration of rotenone in commercially available products. For instance, a new product called 'True Stop' was developed in which rotenone was mixed with cow manure, thus combining a fertiliser and a pesticide in a single product. This was a significant improvement on many other available formulations as low concentrations of the active ingredient rotenone were adequate, and organic solvents were no longer required as the carrier. It also provided a practical solution to the environmental issue faced by dairy farmers who had to dispose of large amounts of cow manure.[10] True Stop was made available on the market in 1994, however, this formulation was short-lived as, along with many other rotenone-containing agricultural products, it was banned in 2007 when the European Union and the United States of America prohibited the use of rotenone as a pesticide.

In the years prior to the banning of rotenone, many countries continued to use the pesticide, however, lower concentration limits were set. Several studies were carried out in order to ascertain the time period required between the last spray and harvesting, so that concentrations of rotenone would decrease to the legal limits. For example, in Italy, a pre-harvest period of 10 days was set at which point the concentration of rotenone was believed to have decreased to the maximum residue level of 0.04 mg/kg. In an interesting study, the concentration of rotenone on olives and in olive oil (one of Italy's major commodities) was evaluated.[3] Olives were monitored under normal environmental conditions and following a preharvest period of 10 days, the concentrations of rotenone on the harvested crop and in the olive oil produced therefrom, were measured. The results were disturbing in that the concentration of rotenone on the fruit was found to be three times higher than the legal limit, and this was subsequently transferred to the olive oil. Clearly, rotenone had a longer half-life when used on olives. Interestingly, this was attributed to the waxy coating on the fruit into which rotenone could penetrate, thus protecting it against photodegradation. The pre-harvest period was therefore extended to 20 days which was deemed adequate for sufficient decomposition of the chemical when applied to olives. The results of this study are rather unsettling if one considers the countless number of times that olive oil or any other organic produce has been consumed, potentially still containing rotenone. Whilst many may argue that rotenone is not harmful to humans when consumed orally, a recent study released in the earlier part of this year would suggest otherwise.[6] It has finally been concluded, using a reasonable model, that Parkinson's disease is most certainly connected to rotenone exposure.

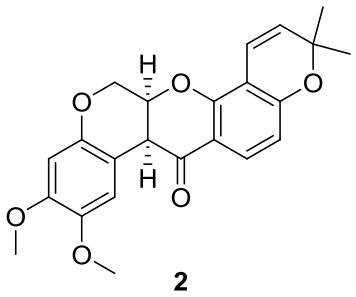
1.3 An improved model

The earlier models used to study the effects of rotenone were based upon the administration of rotenone by injection into the jugular vein of rats. There was a need for newer and better models which would more closely mimic the actual entry of rotenone into the human body. At the beginning of 2011, yet another journal article regarding the safety of rotenone was released.[11] A better model was developed in which rotenone was administered orally to rats over a period of weeks. The results showed that although rotenone was believed to be poorly absorbed through the gastrointestinal tract of mammals, oral administration of the chemical resulted in symptoms related to Parkinson's disease. A flaw in this study however, pertains to the doses of rotenone administered. The rats were dosed at 30-100 mg/kg daily. This is equivalent to 1.8-3.0 kg per person of an average weight of 60 kg. It is very unlikely that such quantities of rotenone would ever be consumed even accidently!

In June 2011 a report was released in which a unique and sensible approach to the study of rotenone and Parkinson's disease was adopted.[6] Unlike preceding studies in the laboratory, the effects of rotenone and its association with Parkinson's disease specifically in humans, was presented. The field study was based upon the effect of rotenone on 84,740 applicators of the pesticide and their partners, primarily in farming areas. All individuals were examined and diagnoses were made by two professionals. The results were astonishing. The symptoms of Parkinson's disease were 2.5 times more prevalent in individuals who had used the pesticide compared to non-users. It was concluded that individuals who had used rotenone-containing products in the past, including household insecticides, may have been exposed to its harmful effects. Nevertheless, there is one positive outcome that emanated from this controversy. Extensive research has provided scientists with a better understanding of the causes and biochemical changes accompanying Parkinson's disease, and in better understanding the cause of the disease, researchers have come one step closer to finding a cure.

Ironically, the biological studies of rotenone have also revealed that it exhibits anticancer properties against a variety of cells such as human B-cell lymphomas, promyelocytic leukemias, neuroblastomas and more recently, MCF-7 breast cancer cells.[12] Similarly, the related rotenoid deguelin **2** possesses chemotherapeutic properties (Figure 2).[13] Although the exact mode of action is

yet to be established, several accompanying biochemical processes within the cell have been identified and apoptosis-inducing mechanisms proposed.[12] The fate of a cell is essentially controlled by the three MAPK subfamilies which can either promote cell division, cell differentiation or cell apoptosis. When treated with rotenone, an increase in the concentration of reactive oxygen species within the cell was observed as a result of complex I inhibition, followed by phosphorylation and hence activation of the MAPK protein kinases responsible for cell apoptosis. An increase in the concentration of Bax (an apoptotic protein), and a decrease in the antiapoptotic protein Bcl-2 was also observed, resulting in an overall increase in the permeability of the mitochondrial membrane, thus effecting cell apoptosis. These results do not necessarily suggest that rotenone be used as an anticancer agent. Rather, invaluable information may be gathered from these studies, providing scientists with a better understanding of the disease. New targets and unique ways to combat cancer may be revealed in establishing the mode of action of rotenone. Furthermore, structure-activity studies may disclose key features within the rotenoid core that facilitate the anticancer action of both rotenone **1** and deguelin **2**.



2

Figure 2

1.4 Rotenone makes headlines

Although rotenone was banned as a pesticide in 2007, it is still exploited as a chemical means to eradicate potentially harmful organisms from various rivers and lakes. Its use as a piscicide has been well-documented and numerous examples are described below.

A serious issue was faced by Norway in 2008 in that approximately 10% of Norway's 400 rivers had been infected with a parasite called Gyrodactylus Salaris, the consequence of which was a dramatic decrease in the population of the wild Atlantic salmon over the last 30 years. Extreme situations called for extreme measures and as a last resort, the parasite was exterminated by chemical means. Rotenone was deposited onto the banks of the River Ogna and the salmon were

simultaneously collected using nets and transferred to a salt water tank where they were decontaminated and allowed to recover.[14]

In 2009 another problem was resolved using rotenone. In the Great Lakes in the United States of America, scientists were concerned about the survival of various indigenous species that were threatened by the Asian Carp. This fish can grow up to 1.2 m in length and weigh up to 45 kg. Given that they are able to consume up to 40% of their body mass per day, the risk of this species eradicating the smaller indigenous fish presented a very real threat. Fearing permanent damage to the ecosystem, it was decided that the Asian Carp would have to be eradicated by chemical means using rotenone. This decision was supported by the fact that the Asian Carp were a danger to local fisherman as they are able to jump up to 2.5 m out of the water and this had resulted in many fishermen being injured.[15]

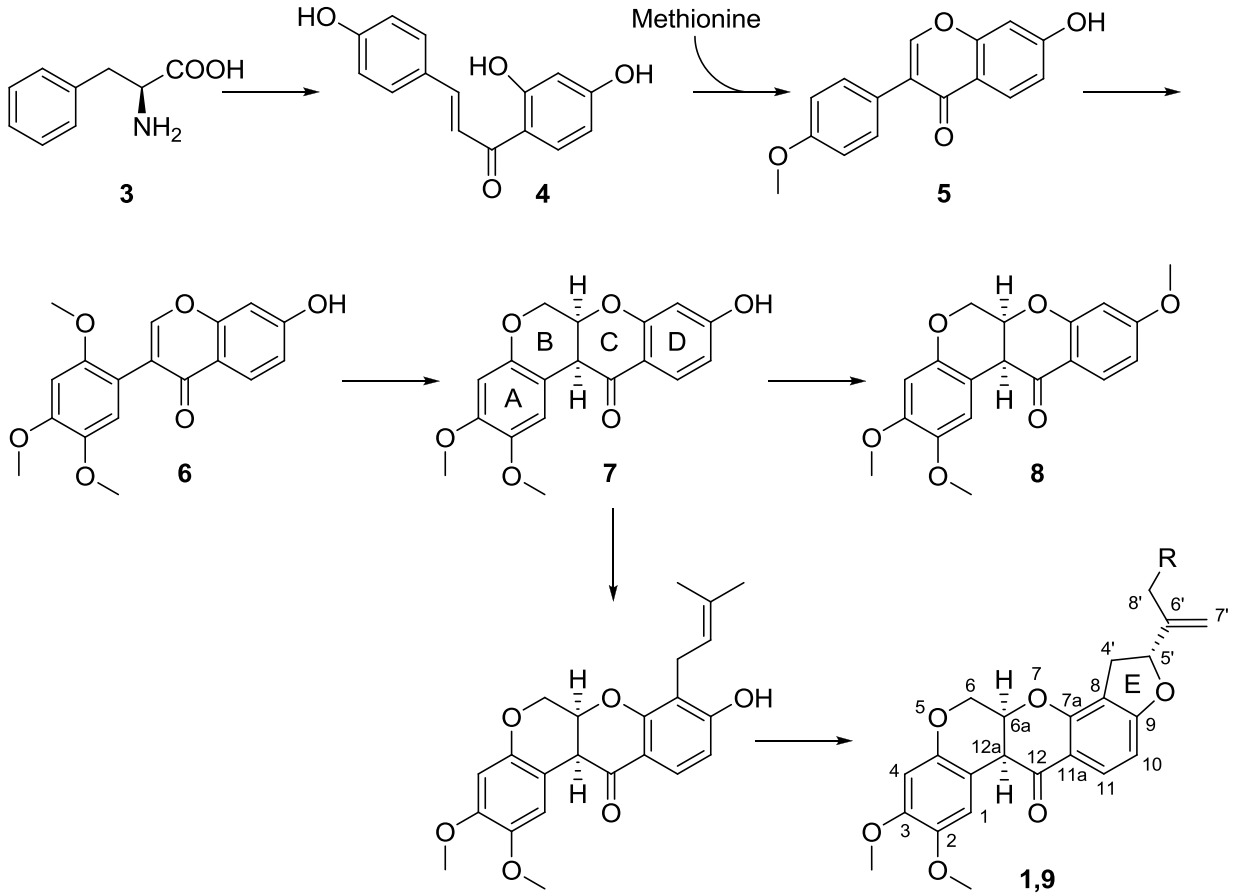
Worldwide, rotenone has been utilised to eradicate alien invasive fish species from rivers and lakes. Locally, rotenone will be used in the Western Cape to eliminate bass from the Cape Floristic Region. The bass species was originally introduced into South African waters in the late 19th century purely for recreational purposes. Over a decade later, their population has escalated to the point that they now threaten the survival of native species, many of which have since been classified as endangered. In response to this matter, an environmental impact assessment was conducted and various alternatives were considered in order to eradicate the bass.[16] It was reported that the extent of the problem is such that physical methods are no longer an option and chemical means would have to be employed to remove this alien species. Failure to do so may result in extinction of some species and vulnerability of others. The environmental impact assessment concluded that rotenone would have to be used in the Cape Floristic Region to eradicate the bass species specifically in four streams in which the removal of alien fish is feasible. The bass would not be removed from regions in which angling is common, as this activity is a means of income for many locals. Special care would have to be taken to preserve the indigenous aquatic faunas of the region, e.g. prior to the addition of the poison, indigenous species such as the Eastern Cape Krom would have to be physically removed and kept in porta-pools for the duration of the treatment. The success of this procedure is not only dependent upon the complete eradication of bass, but also on the ability of native organisms to repopulate their home following this treatment. With the support of the environmental impact assessment, the South African Water Research Commission recently

announced that the rehabilitation process would commence as of February 2011, although this process has been somewhat delayed due to undisclosed reasons.

1.5 The biosynthesis of rotenoids

In light of the fact that rotenone is a naturally occurring compound let us take a moment to consider the possible biosynthesis of this interesting molecule and other related rotenoids, all of which contain the *cis*-fused tetrahydrochromeno[3,4-*b*]chromene nucleus.

As is often the case in discussing these natural pathways, a definitive biosynthetic pathway toward the rotenoid ring system is yet to be established. Despite this, the majority of proposed pathways suggest that a link exists between the isoflavone and rotenoid class of compounds.[17-19] Crombie and co-workers have made a significant contribution to this area of rotenoid chemistry.[17, 18] Experimental work pertaining to the synthesis of rotenoids has shown that this class of compounds may emanate from the amino acid phenylalanine **3**, which is converted into a chalcone **4** and then in the presence of methionine, an isoflavone **5** is formed (Scheme 1). The phenyl ring migrates from the 6a to the 12a-position as designated in the desired rotenoid (a conventional labelling system for rotenoids is adopted throughout this dissertation, as illustrated in **1**). These processes are commonly observed in flavanoid chemistry and are generally accepted amongst the several proposed biosynthetic pathways toward rotenoids. The carbon atom eventually ending up at the 6-position is believed to be introduced by methionine. Next, cyclisation of the 2-methoxyisoflavone **6**, possibly by isomerisation, allows for the formation of the B-ring system and thus the tetracyclic compound **7**. The pathway may terminate at this point upon methylation of the hydroxyl, producing the natural product munduserone **8**. Alternatively, prenylation at the 8-position will give rise to the more complex rotenoids such as rotenone **1** (R=H) and amorphigenin **9** (R=OH), possessing the E-ring system.



Scheme 1

1.6 Isolation, structure elucidation and syntheses of rotenone and munduserone

Although the structure of rotenone was established in 1932 based on work by LaForge, Butenandt and Takei,[2, 20, 21] it took scientists approximately another 30 years to synthesise this complex molecule and even then the synthesis was not enantioselective.[22] One of the earliest syntheses was reported in 1958 when rotenone was partially synthesised from derrisic acid **10**, a product of the degradation of rotenone (Figure 3).[23, 24]

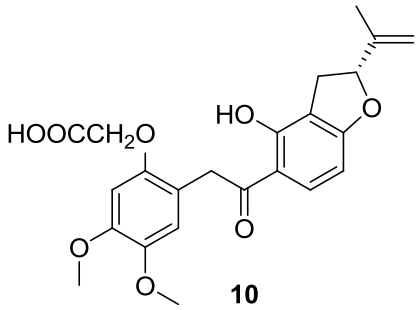
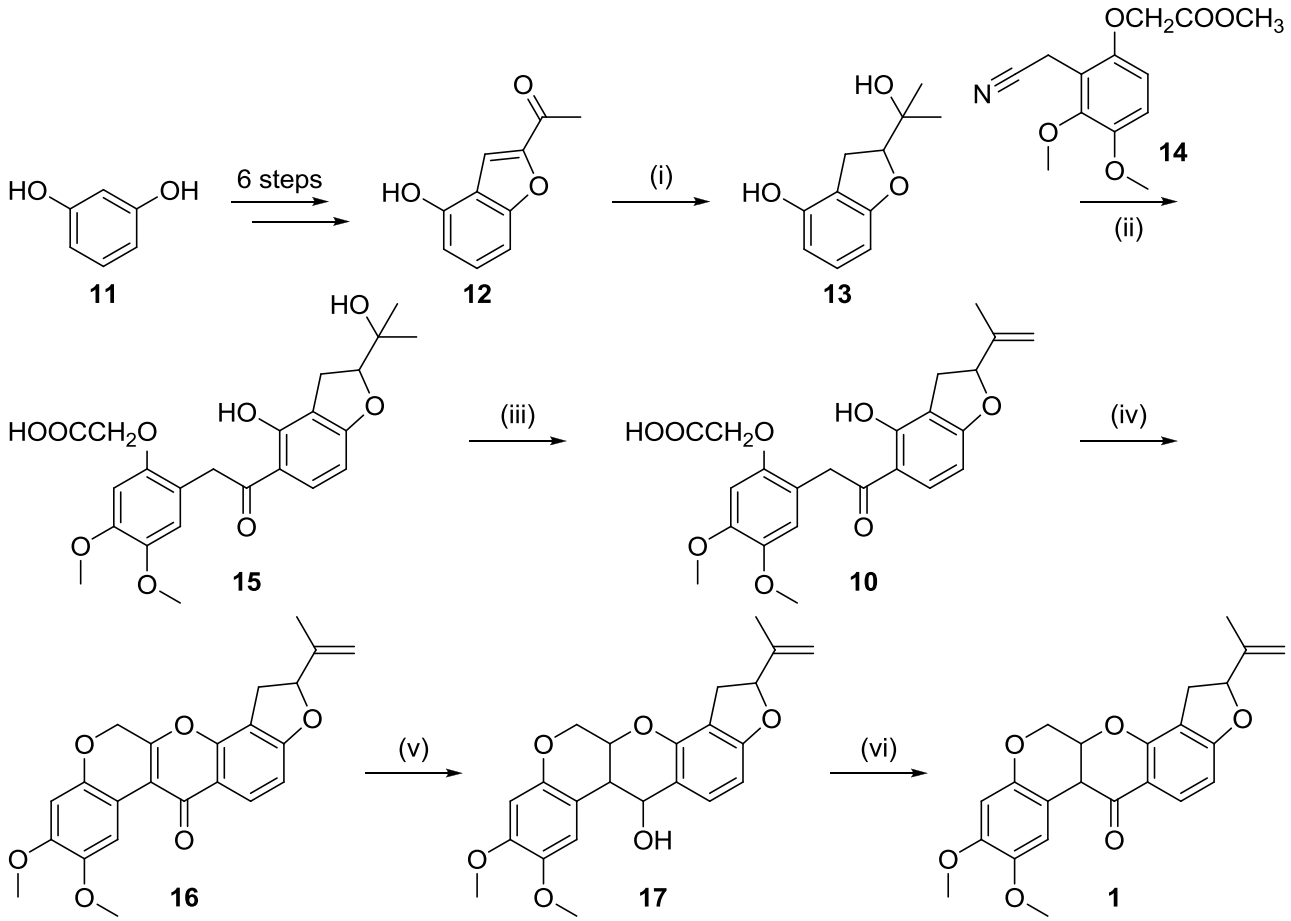


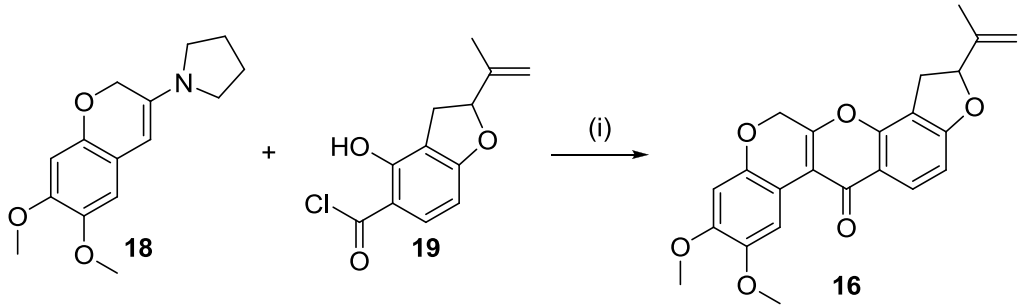
Figure 3

The first non-stereoselective total synthesis of rotenone **1** was subsequently reported in 1960.[22] In this synthesis, rotenone was obtained in 17 steps from commercially available resorcinol **11** (Scheme 2). The synthesis commenced with the construction of the benzofuran **12** using available methodology.[25] Following this, the isopropyl functionality was introduced by means of a Grignard reaction (later to be converted to the required isopropenyl group) and then hydrogenation over Raney nickel afforded the required dihydrobenzofuran **13**. By means of a Hoesch condensation with **14**,[26] Miyano and co-workers began to construct the rest of the molecule. At this stage the isopropyl functionality of **15** was dehydrated to afford the isopropenyl group as required for rotenone, thereby forming the advanced racemic intermediate, derrisic acid **10**. Ring closure was achieved by boiling **10** in a solution of acetic anhydride and sodium acetate according to the procedure by Takei, giving dehydrorotenone **16**.[21] Conversion to rotenone was attained firstly by reduction with sodium borohydride, followed by oxidation of rotenol **17** to mutarotenone, a mixture of diastereomers of natural rotenone.[22]

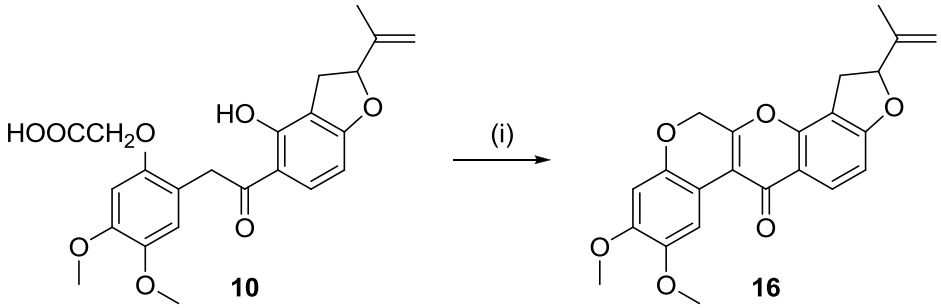


Scheme 2: *Reagents and conditions:* (i) a: MeMgBr, b: Raney Ni; (ii) a: $ZnCl_2$, HCl, b: KOH; (iii) a: Diazomethane, b: PBr_3, pyridine, overall 0.01%; (iv) Acetic anhydride, NaOAc, 23%; (v) $NaBH_4$; (vi) $Al(OiPr)_3$.

In the original procedure by Miyano and co-workers,[22] derrisic acid **10** had been synthesised in a disappointingly poor yield of 0.01%. They had attributed this to the instability of the isopropenyl moiety under acidic conditions. Moreover, dehydrorotenone **16** was afforded according to the procedure by Takei through the cyclisation of derrisic acid, also in a poor yield (23%). In an attempt to improve on this, Miyano presented yet another procedure in which dehydrorotenone was synthesised from pyrrolidine enamine **18** and tubaacyl chloride **19** in a yield of 15% (Scheme 3).[27] Alternatively, derrisic acid could be treated with dicyclohexylcarbodimide (DCC) and a tertiary base to give dehydrorotenone in a slightly improved 40% yield (Scheme 4).[28]



Scheme 3: *Reagents and conditions*: HCl, Δ, 15%.

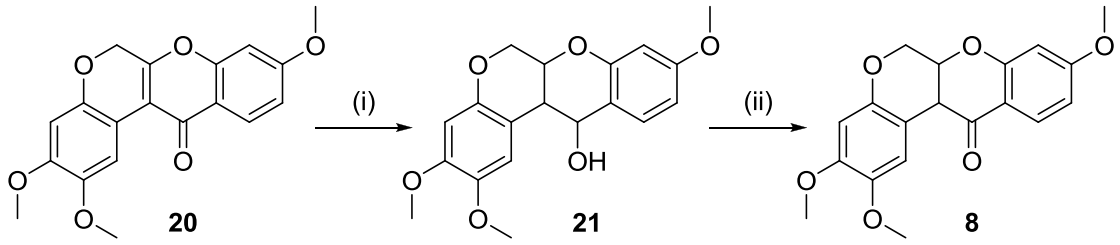


Scheme 4: *Reagents and conditions*: (i) a: DCC, pyridine, b: Potassium propanoate, EtOH, reflux, 1 h, 40%.

Shortly after the first total racemic synthesis of rotenone, the absolute configuration was elucidated by Büchi and co-workers.[29] The absolute stereochemistry was determined upon comparison of the degradation products of rotenone to compounds of known stereochemistry, thus establishing the (6a*S*, 12a*S*, 5'*R*) configuration. This presented an interesting and challenging synthetic target for organic chemists, hence the surge in rotenoid chemistry in the 1960's. Research in this area was subsequently fuelled by a need to better understand the activity of rotenoids within biological systems, as rotenone had been linked to Parkinson's disease. Thus, several of the following reported

syntheses commenced from advanced intermediates obtained from natural sources, as the focus was to include radioactive labels for biological studies. A discussion pertaining to several syntheses, many in this category, are highlighted in the following sections.

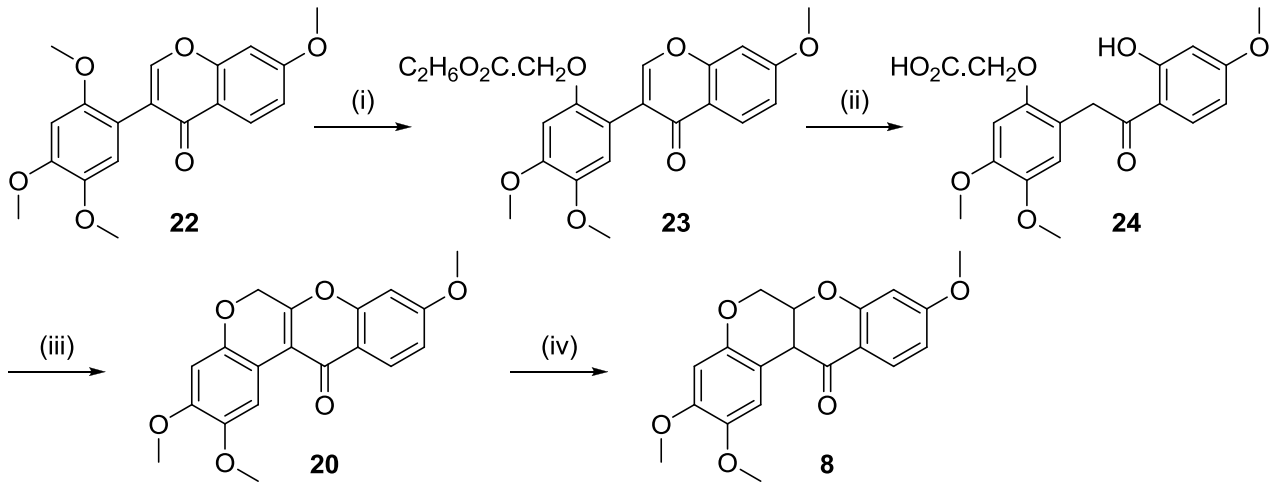
In 1960, Ollis and Finch isolated and identified the simplest of the rotenoids, namely munduserone **8**, from the bark of *Mundulea sericea*.[30] They also proceeded with a partial synthesis of the compound starting from dehydromunduserone **20** (Scheme 5).[31] This involved the transformation of **20** to munduserol **21** using sodium borohydride, followed by an Oppenauer oxidation using aluminium isopropoxide, to furnish munduserone **8**. This was a significant discovery as a simple target was presented upon which methodology could be tested, prior to attempting the synthesis of the more complex rotenoids, such as rotenone and deguelin. We shall now give a brief review of the progress to date with regard to the synthesis of munduserone and rotenone, specifically.



Scheme 5: *Reagents and conditions:* (i) $NaBH_4$, dioxane; (ii) $Al(OiPr)_3$, acetone/benzene.

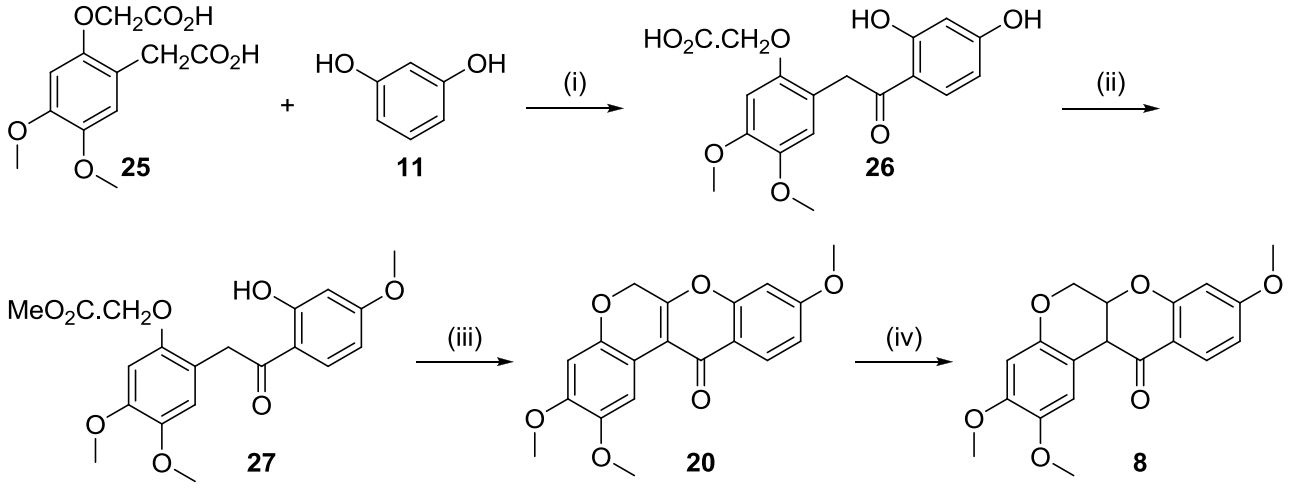
1.6.1 Synthesis of the dehydrorotenoid core

In 1967, Fukui and co-workers presented a new synthesis of the rotenoid class of compounds.[32] Their approach was consistent with the notion that rotenoids could be derived from isoflavones as the core structure, to which the rings B and E could later be added (Scheme 6). They attempted this in a somewhat reverse manner, however, in that the tricyclic structure was degraded *en route* to munduserone **8**. Having synthesised the isoflavone **22**, selective demethylation was achieved using aluminium trichloride. Conversion to the phenoxyacetic ester **23** allowed for the addition of a carbon atom, eventually at the 6-position in munduserone. Alkaline hydrolysis to give methyltephrosic acid **24** was followed by an intramolecular cyclisation using acetic anhydride and sodium acetate, affording dehydromunduserone **20** which could be converted to munduserone **8** on application of the methodology described by Ollis *et al.*[31] Unfortunately, this methodology has not been extended to the syntheses of more complex rotenoids such as rotenone.



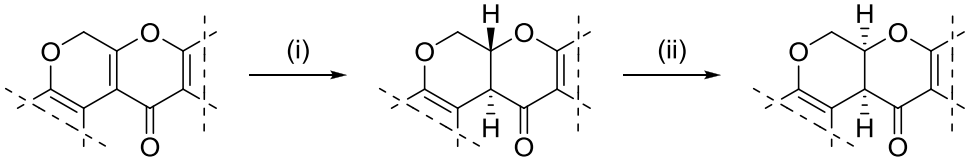
Scheme 6: *Reagents and conditions:* (i) a: $AlCl_3$, 85%, b: Ethyl bromoacetate, 94%; (ii) Dilute alkali, 71%; (iii) Acetic anhydride, NaOAc; (iv) a: $NaBH_4$, dioxane, b: $Al(OiPr)_3$, acetone/benzene.

The total synthesis of munduserone **8** reported by Nakatani and Matsui a year later resembled the above process.[33] A similar bicyclic system was synthesised upon which cyclisation afforded dehydromunduserone (Scheme 7). In contrast to the above methodology, Nakatani constructed the bicyclic tephrosic acid **26** from derric acid **25** and resorcinol **11**, rather than from an isoflavone intermediate. The coupled product **26** was treated with diazomethane thus affording the partially methylated compound **27**. Finally, refluxing in the presence of sodium ethoxide afforded dehydromunduserone **20** which was converted to **8** according to the procedure by Ollis *et al.*[31]



Scheme 7: *Reagents and conditions:* (i) P_2O_5, H_3PO_4, 69%; (ii) Diazomethane, 80%; (iii) NaOEt, EtOH, reflux, 3 h, 83%; (iv) a: $NaBH_4$, dioxane, 60 °C for 45 min, 100 °C for 15 min, 57%, b: $Al(OiPr)_3$, acetone/benzene, reflux, 14 h, 88%.

In an attempt to circumvent the reduction-oxidation procedures required for the dehydrorotenoid to the rotenoid routes, Crombie and co-workers presented an alternative method.[34] Treatment of the dehydrorotenoid **28** with DIBAL (Scheme 8) provided the unnatural *trans* B/C ring system **29** as confirmed by an X-ray crystallographic structure. Epimerisation under acidic conditions then gave the natural *cis* product **30**.



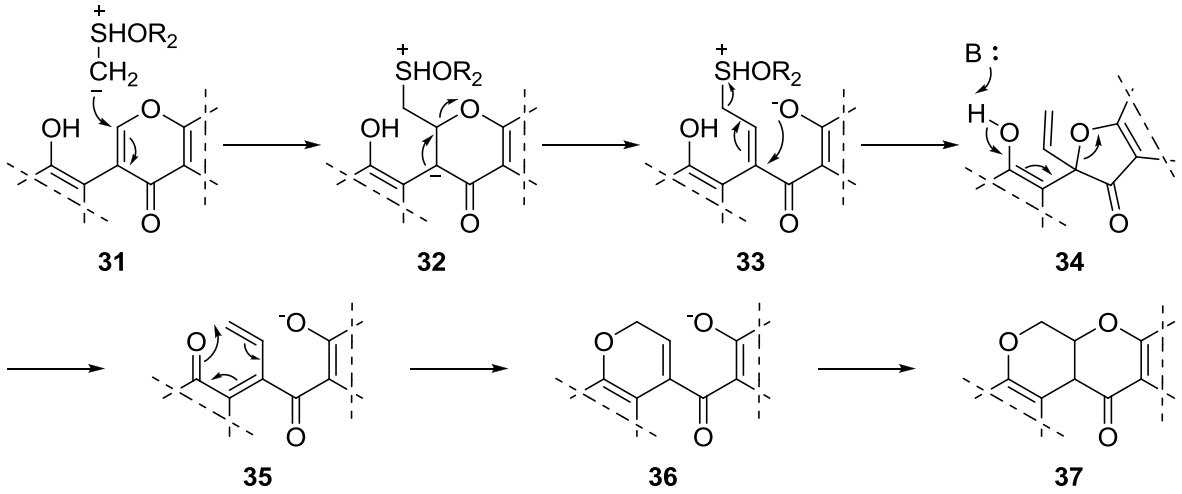
Scheme 8: *Reagents and conditions:* (i) DIBAL, toluene/THF, -78 °C to 0 °C; (ii) HCl.

1.6.2 A direct route to the rotenoid core

Inspired by their interests in the biosynthetic pathway of rotenoids as well as their biological effects, Crombie and co-workers made several attempts to construct various natural rotenoids and unnatural derivatives.[35] In the process of isotopic labelling which formed the key feature of their research in elucidation of the biosynthetic routes, new synthetic approaches to the rotenoid core were developed. Not only did this shed light on the biosynthesis of these interesting compounds, but a significant contribution to the laboratory synthesis of various rotenoids was attained.

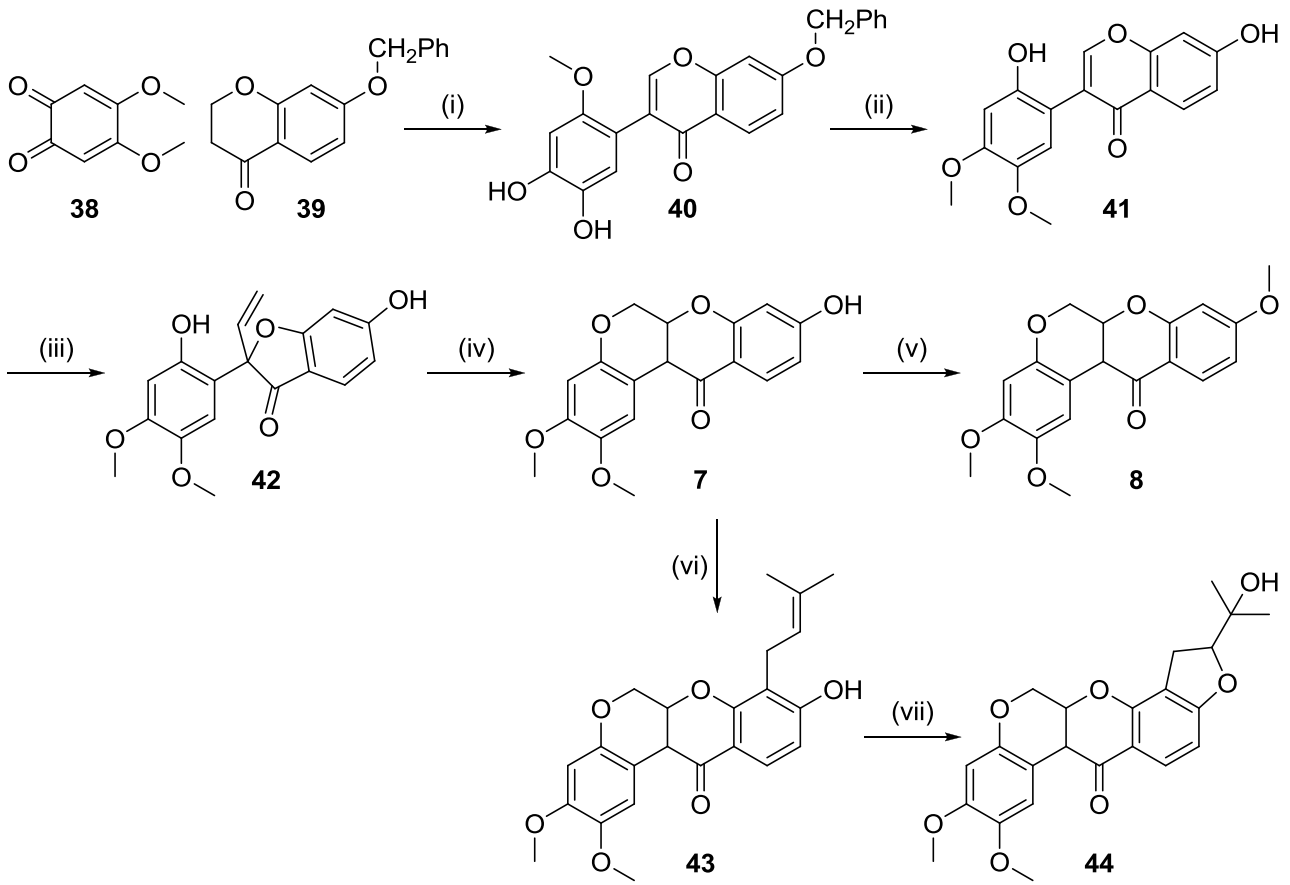
Whilst many of the available methods at the time afforded the dehydrorotenoid, Crombie and co-workers had developed several methods providing direct access to the tetracyclic core at the correct oxidation level, thus eliminating the need for further reduction-oxidation procedures. This was particularly of value when synthesising compounds such as rotenone, in which the isopropenyl functionality was sensitive to these conditions. Indeed, the procedure developed by Crombie was effective for the synthesis of both munduserone **8** and rotenone **1**.[36] In designing their approach, they envisaged that munduserone and rotenone could be synthesised from hydroxyisoflavones **31**, thereby closely aligning themselves with the biosynthetic route (Scheme 9). This approach would require a methylene insertion and it was envisaged that dimethylsulfoxonium methylide could be employed as an analogous reagent to methionine in nature. It was predicted that treatment of **31** with dimethylsulfoxonium methylide would afford **32** by way of a Michael addition, which would be followed by a rearrangement and concomitant ring opening of the chromanone to give **33**. Recyclisation would then lead to the vinylcoumaranone **34** as a key intermediate in this approach.

Finally, in the presence of base and dimethylsulfoxonium methylide, further reaction would yield the dienone **35** which, upon electrocyclic rearrangement, would give the dehydrorotenol **36**. An intramolecular cyclisation would finally afford the rotenoid **37** at the correct oxidation level.



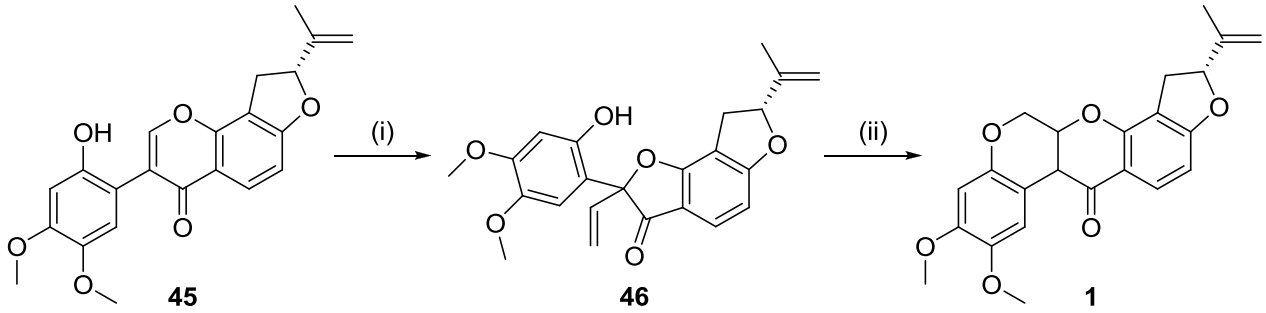
Scheme 9

It was envisaged that this interesting proposal could be used to synthesise both munduserone and rotenone by way of a common intermediate, 9-demethylmunduserone **7**. In putting the proposal into practice (Scheme 10), a reaction of 4,5-dimethoxy-*o*-benzoquinone **38** with 7-benzyloxychroman-4-one **39** afforded the isoflavone **40** which was subsequently methylated on all three phenolic hydroxyl groups and then selectively demethylated. Removal of the benzyl protecting group furnished the dihydroxydimethoxyisoflavone **41**. Subsequent reaction with dimethylsulfoxonium methylide produced the vinylcoumaranone **42** which, upon treatment with pyridine, afforded **7** (although in a poor yield). Finally, methylation employing diazomethane afforded munduserone **8**. In an attempt to apply this methodology to the synthesis of rotenone, prenylation at the 8-position of **7** by means of a Lewis acid catalysed condensation produced rot-2-enonic acid **43**. Reaction with MCPBA afforded dalpanol **44** which is believed to be the immediate precursor to rotenone in the biosynthetic pathway. The conversion of dalpanol to rotenone had not been achieved at the time. This was however, accomplished several years later by Nakatani and Matsui (see later).[37]



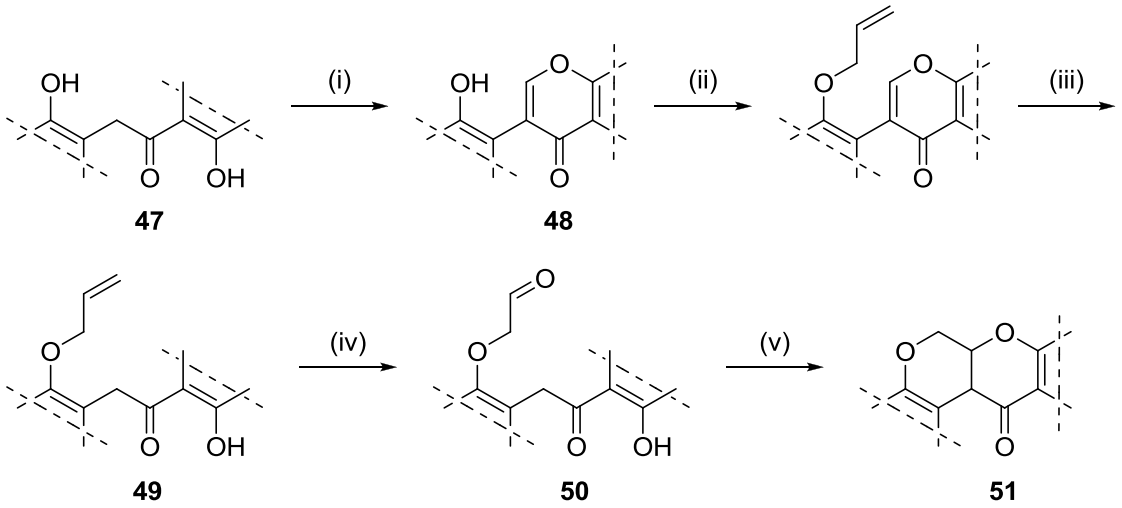
Scheme 10: *Reagents and conditions:* (i) NaH, DMSO, 2 h, 71% (ii) a: MeI, K_2CO_3, reflux, b: $AlCl_3$, MeCN, reflux, 16 h, 60%; (iii) NaH, DMSO, 2 h; (iv) Pyridine, 100 °C, 14% over 2 steps; (v) Diazomethane, 18% over 3 steps; (vi) 3-Methylbut-2-en-1-ol, $BF_3.(OEt)_2/CH_2Cl_2$, 5 °C, 4 h, 23%; (vii) MCPBA, Na_2CO_3, $CHCl_3$, 0 °C, 40 min, 13%.

As a compromise, rotenone could be synthesised starting from a slightly different precursor in the form of derritol isoflavone **45**, a product of the degradation of rotenone (Scheme 11). A reaction with dimethylsulfoxonium methylide afforded the vinylcoumaranone **46** as predicted. Pyridine was then added to the mixture of diastereomers which, upon heating, afforded rotenone **1** and its epimer. Interestingly, the *trans*-fused ring system was acquired in this process unlike natural rotenone which adopts a *cis* arrangement for the B/C ring junction. Nevertheless, the *cis* form of rotenone could be isolated from this epimeric mixture by fractional crystallisation.[36]



Scheme 11: *Reagents and conditions:* (i) DMSO, 3 h; (ii) Pyridine, 100 °C, 48 h, 26%.

In light of this work, Crombie and co-workers attempted yet another synthesis of the tetracyclic rotenoid core (Scheme 12).[35] The phenolic ketone **47**, which was accessible by various methods such as the classical Hoesch reaction, was treated with sodium ethyl formate to give the isoflavone **48**. An allyl side chain was then introduced using sodium hydride and allyl bromide and upon alkaline hydrolysis, the bicyclic, allylated compound **49** was afforded. Following an oxidation to the aldehyde **50** using osmium tetroxide and sodium periodate, the product was heated to reflux in pyridine thus giving the rotenoid skeleton **51**. This methodology was used to synthesise isorotenone, a derivative of rotenone in which the double bond is situated within the furan ring rather than on the isopropyl moiety. The procedure had not been extended to the synthesis of rotenone, possibly due to susceptibility of the isopropenyl double bond to oxidation by osmium tetroxide.

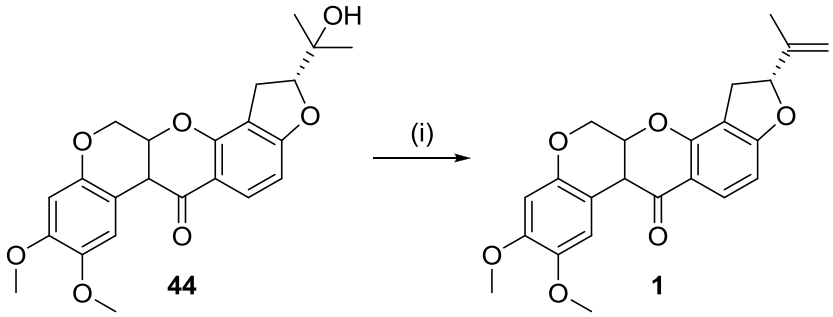


Scheme 12: *Reagents and conditions:* (i) Sodium ethyl formate; (ii) NaH, allyl bromide, DMF, 3 h, 64%; (iii) NaOH, EtOH, reflux, 58%; (iv) OsO_4, sodium periodate, dioxane/water, rt, 2 h, 31%; (v) Pyridine, 30 min, 30%.

Miyano and Crombie, together with their respective research groups, were pioneers in the synthesis of rotenone and other related structures. Several additional interesting approaches to the rotenoid core have been reported over a number of decades. These include partial syntheses from other naturally occurring rotenoids, the use of Claisen rearrangements as a key step, palladium-catalysed arylations and the use of protected cyanohydrins. A brief description of these routes follows.

1.6.3 Rotenone from dalpanol

Many examples are available in the literature in which rotenone was synthesised from an advanced intermediate, itself attained from rotenone degradation products or from other natural rotenoid compounds. An example of the latter is illustrated in the synthesis of rotenone **1** from the natural product dalpanol **44** (Scheme 13), a compound nearly identical to rotenone in that the only difference lies in the fact that it possesses an isopropyl alcohol side chain.[37] A simple dehydration reaction of **44** using PBr_3-pyridine furnished **1** in a single step![22]



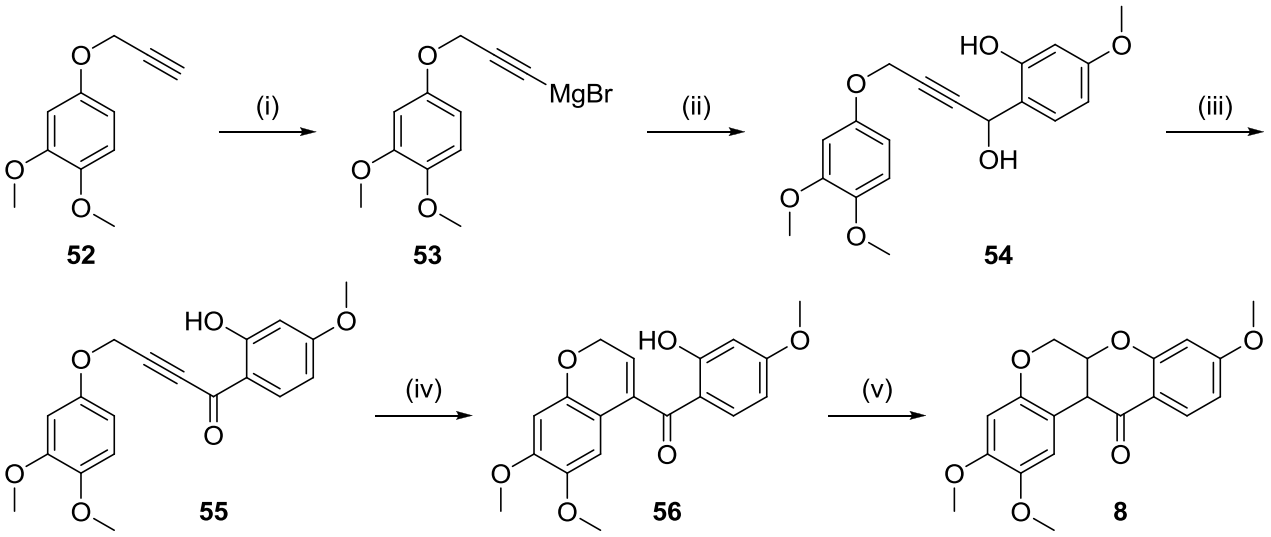
44 **1**

Scheme 13 *Reagents and conditions:* PBr_3, pyridine, 0-5 °C, 10 h, 31%.

1.6.4 Claisen rearrangement of acetylenic intermediates

A novel synthesis toward the rotenoid skeleton was presented in 1973 by Omakawa and Yamashita.[38] Their synthetic strategy also circumvented the need for reduction and oxidation steps of a dehydrorotenoid, as the compound was afforded at the correct oxidation level (Scheme 14). A key step in their synthesis involved a cleverly employed Claisen rearrangement of an acetylenic intermediate. The synthesis commenced with the propargyl ether **52** which was converted to the Grignard reagent **53** and then reacted with 4-methoxysalicaldehyde to afford the coupled alcohol **54**. An oxidation to the ketone **55**, followed by a Claisen rearrangement (although under rather harsh conditions), gave the key chromene moiety **56**. Ring closure in the form of an internal Michael addition produced munduserone **8**. Although the yield over the last two steps was only 17%, this was still an improvement on preceding methods. Hence, the methodology was adopted

several years later by Crombie and co-workers in the synthesis of several rotenoid derivatives for the purpose of structure-activity studies.[39, 40]



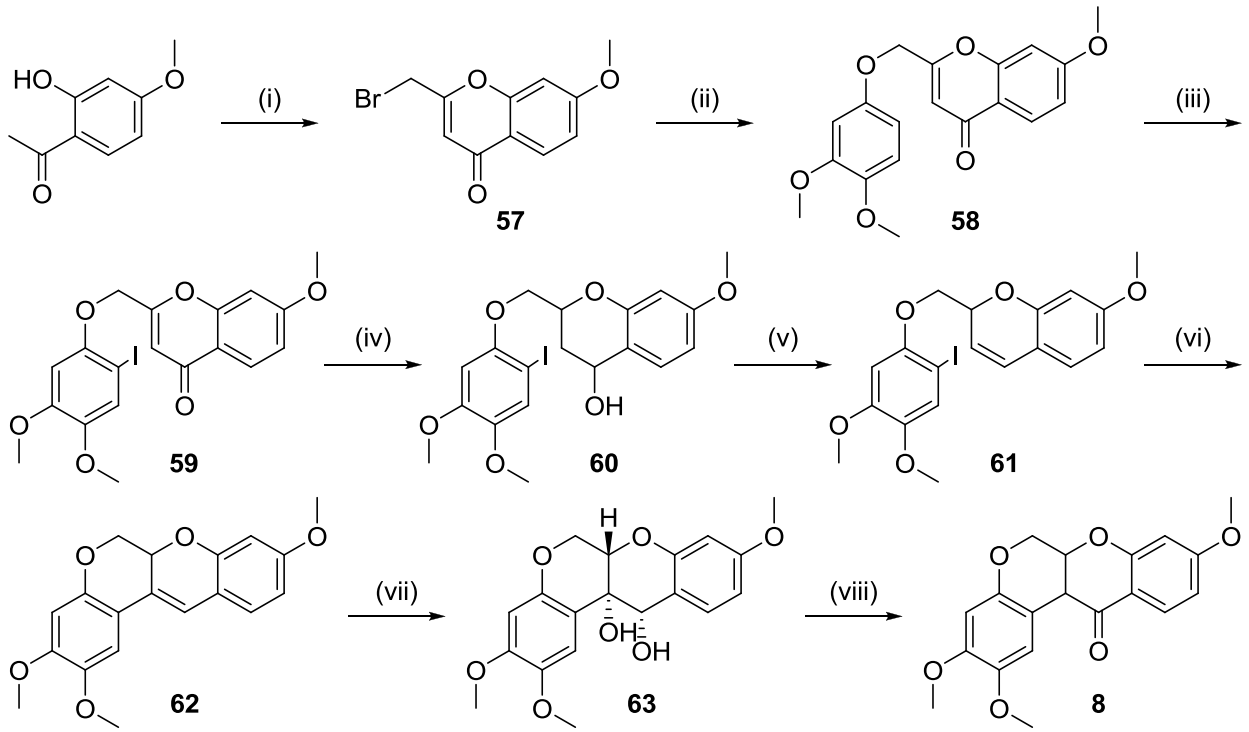
Scheme 14: *Reagents and conditions:* (i) EtMgBr, THF, rt, 2 h; (ii) 2-hydroxy-4-methoxybenzaldehyde, THF, 5-10 °C for 30 min, rt for 2 h; (iii) MnO_2, CH_2Cl_2, rt, 45 min, 65% over 3 steps; (iv) N,N-diethylaniline, 185 °C, 2.5 h; (v) NaOAc, EtOH, reflux, 2.5 h, 17% over 2 steps.

In 1978, the methodology was extended to the synthesis of rotenone, this time coupling a suitably substituted dihydrobenzofuran with the propargyl ether **52** by means of a Grignard reaction.[41] The remainder of the synthesis was identical to that applied in the construction of munduserone. However, one of the major downsides to this procedure was that the dihydrobenzofuran was synthesised as a racemic mixture. Although enantiomerically pure material could be obtained by subsequent resolution methods, this did not constitute a stereoselective synthesis. The yields were also particularly concerning as the only reported value was that of the key Claisen rearrangement, obtained in a modest 40% yield.

1.6.5 Palladium-catalysed intramolecular arylation

A transition metal mediated synthesis of munduserone was described by Whiting and co-workers.[42, 43] The chromone **58** was afforded upon treatment of **57** with 3,4-dimethoxyphenol (Scheme 15). Iodination to give **59**, followed by reduction with sodium borohydride yielded the chromanol **60** which was dehydrated to **61.** Treatment with palladium acetate furnished the B-ring, and hence the tetracyclic rotenoid skeleton **62**, by means of an apparent radical reaction. Conversion to the diol **63** was achieved using osmium tetroxide-*N*-methylmorpholine-*N*-oxide following which, oxidation to

the ketone and deoxygenation at the 12a-position afforded munduserone **8**. One of the main disadvantages of this synthesis pertains to the final transformations which were achieved in a relatively poor yield. The procedure was also unsuitable for the synthesis of rotenone as the isopropenyl moiety would not be stable under the reaction conditions of the final few steps.

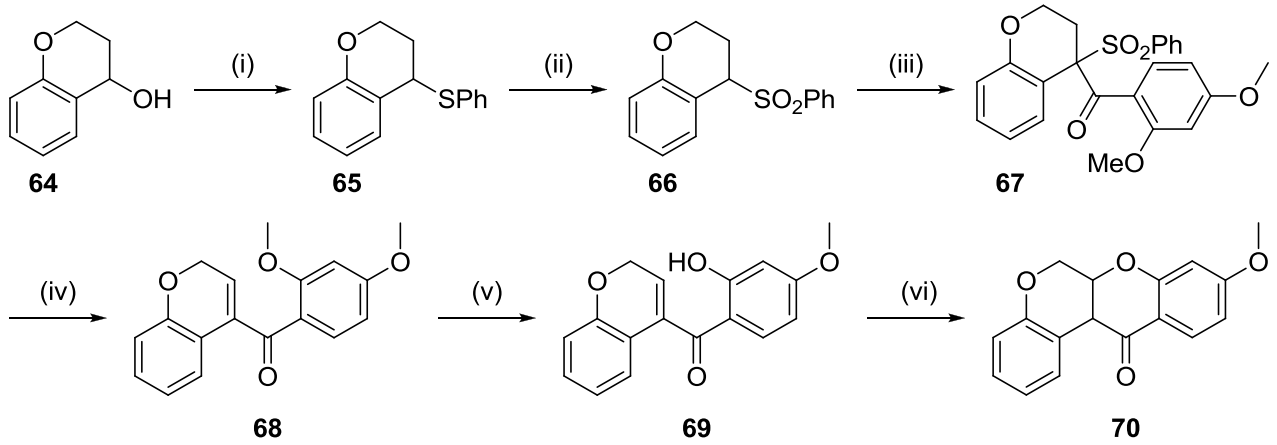


Scheme 15: *Reagents and conditions:* (i) a: $EtOCH_2CO_2Et$, Na, Et_2O, 24 h, 53%, b: H_2SO_4, EtOH, reflux, 30 min, c: HBr, AcOH, 50 °C, 24 h, 53%; (ii) 3,4-dimethoxyphenol, K_2CO_3, acetone, reflux, 48 h, 79%; (iii) HgO, I_2, EtOH, 50 °C, 30 min, 61%; (iv) $NaBH_4$, THF, 1.5 h, 83%; (v) Acetyl chloride, 30 min, then benzene, reflux, 1 h, 88%; (vi) $Pd(OAc)_2$, PPh_3, NEt_3, MeCN, 80 °C, 12 h, 56%; (vii) OsO_4, *tert*-butanol, acetone/water, rt, 14 days, 92%; (viii) a: MnO_2,CH_2Cl_2, 12 h, rt, b: Zn, AcOH, 20% over 2 steps.

1.6.6 Aroylation of substituted chromans

Concerned with the fact that many of the available methods were lengthy, low yielding and restrictive in terms of the versatility of starting materials and subsequent products, Lai and co-workers wished to develop a more efficient procedure that could provide access to a variety of rotenoids, both natural and unnatural which, given their many applications, could then be subjected to structure-activity studies. In 1989, Lai and co-workers presented their novel synthesis of the rotenoid nucleus, derived from a chroman substituted with an anion stabilising group such as a sulfone (Scheme 16).[44] To this end, 4-(phenylthio)chroman **65** was synthesised from chroman-4-ol **64** and thiophenol upon treatment with zinc iodide. Subsequent reaction with MCPBA afforded the

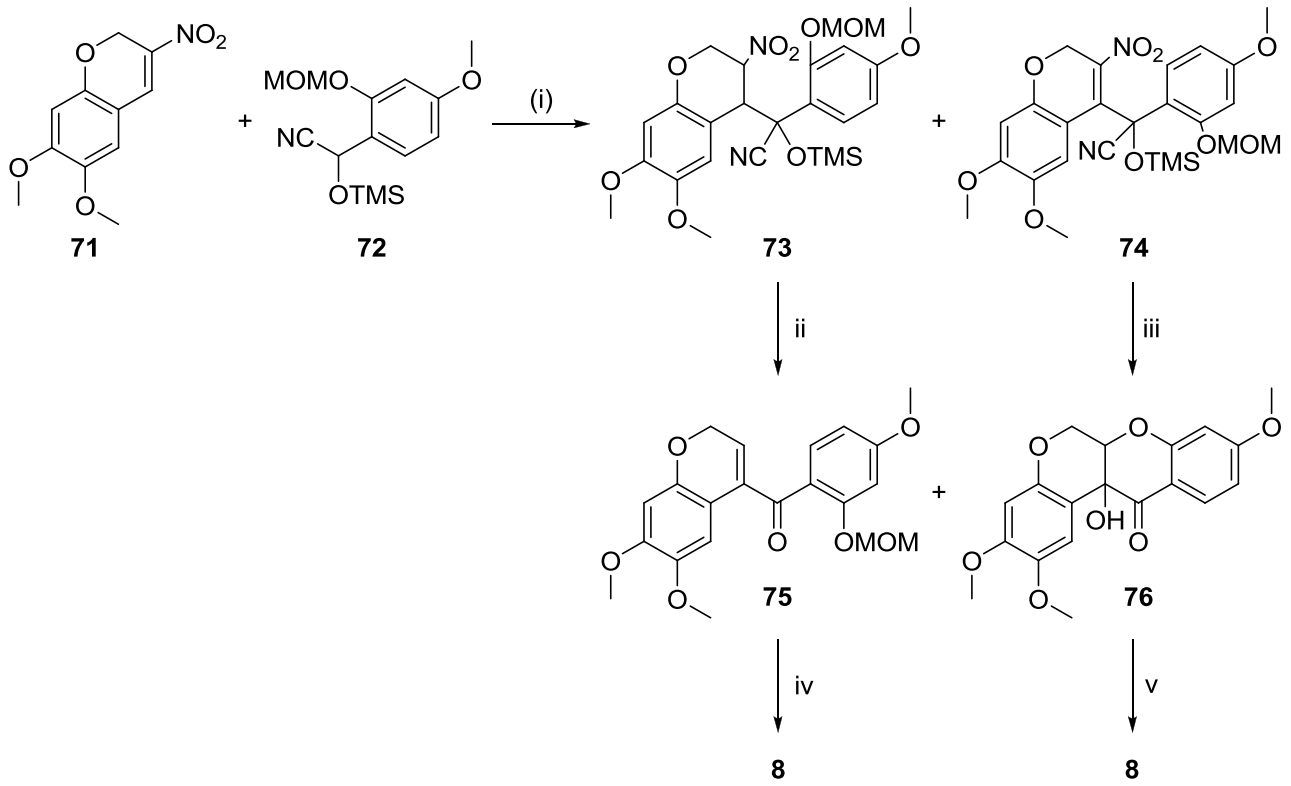
sulfonyl-chroman **66** which was then coupled to 2,4-dimethoxybenzoyl chloride in an aroylation reaction. The chromene moiety **67** was then released from the sulfone by using Raney Nickel, following which, a dehydrogenation reaction using iodine in ethanol formed the Michael acceptor **68**. Selective removal of the methyl group was achieved using boron trichloride, thus setting the stage for an internal Michael addition of **69** to afford the rotenoid skeleton **70** in a modest yield. Loss of product was potentially due to oxidation of the final rotenoid, as the dehydrorotenoid and hydroxyrotenoids were isolated along with the desired product.



Scheme 16: *Reagents and conditions:* (i) PhSH, ZnI_2, EDC, rt, 1 h, 87%; (ii) MCPBA, CH_2Cl_2, 0 °C, 18 h, 81%; (iii) 2,4-dimethoxybenzoyl chloride, *n*BuLi, THF, HMPA, -75 °C to rt, 63%; (iv) a: Raney Ni, EtOAc, 4 h, 99%, b: I_2, KOAc, EtOH, 2 h; (v) BCl_3, CH_2Cl_2, 0 °C to rt; (vi) KOAc, EtOH, reflux, 2.5 h.

1.6.7 Synthesis from protected cyanohydrins

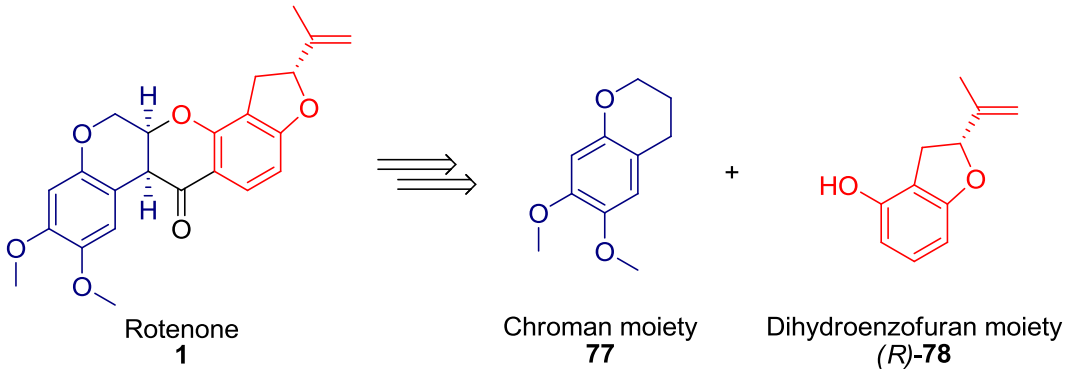
In 2009, a novel synthesis of munduserone was reported, involving the coupling of the nitrochromene **71** and a protected cyanohydrin **72**.[45] Each of these intermediates was accessible starting from commercially available materials, 4,5-dimethoxysalicaldehyde and 4-methoxysalicaldehyde, respectively (Scheme 17). Following LDA coupling, the crude products **73** and **74** were subjected to mildly acidic and then basic conditions to facilitate the removal of the TMS protecting group and then HCN and HNO_2, respectively. The two products afforded in the process, the desired enone **75** and hydroxymunduserone **76**, were produced in poor yields. Both of these compounds, however, could be converted to munduserone **8** in a good yield. Ring closure of the enone was automatically achieved upon removal of the MOM protecting group under acidic conditions. Hydroxymunduserone was treated with zinc in acetic acid, also affording the desired rotenoid, munduserone. This approach was unsuitable for the synthesis of rotenone as extended exposure to acidic conditions may have resulted in epimerisation at the stereogenic 5'-centre.



Scheme 17: *Reagents and conditions:* (i) LDA, THF, -70 °C to rt; (ii) a: 5% H_2SO_4, THF, 50 °C, b: Et_3N, Me_2CO, rt, 21% overall; (iii) a: 5% H_2SO_4, THF, 50 °C, b: Et_3N, Me_2CO, rt; 28% overall (iv) 10% HCl, MeOH, 65 °C, 2 h, 86%; (v) Zn, AcOH, 115 °C, 45 min, 71%.

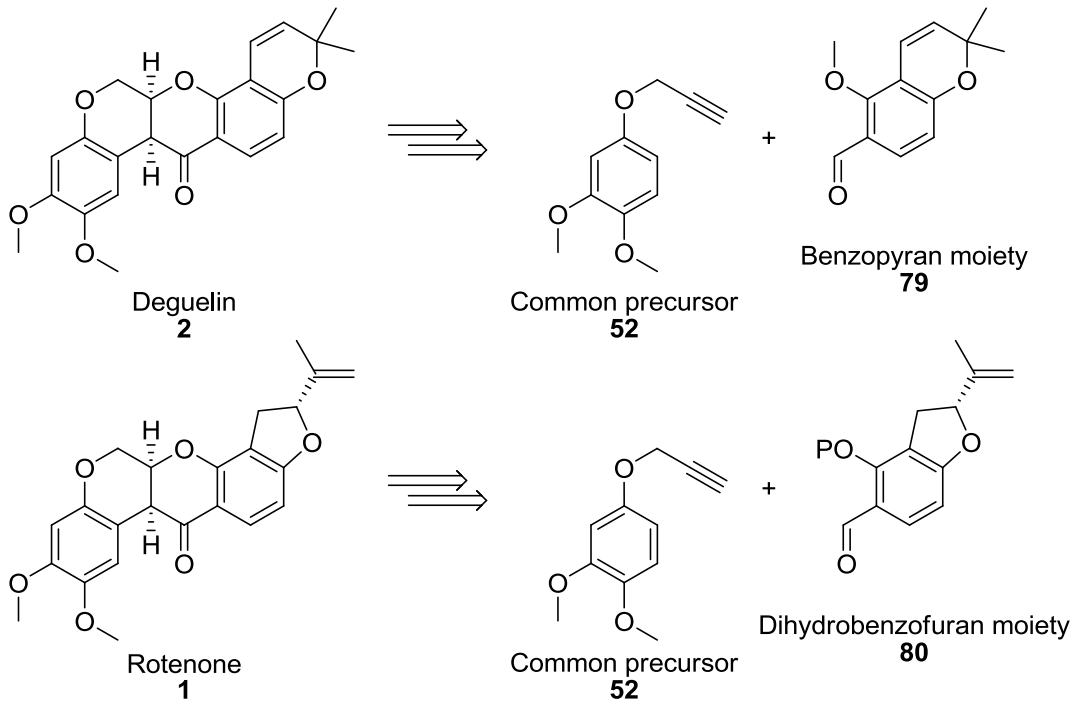
1.7 The Wits approach – aims of this project

In 2007 the Wits organic research group, in collaboration with the Schmalz research group at the University of Köln, became interested in developing the first stereoselective synthesis of rotenone.[46] A convergent procedure was envisaged whereby a suitably substituted chroman **77** and a chiral dihydrobenzofuran **78** would be synthesised separately and then coupled leading to rotenone **1** (Scheme 18). Since at this time the Schmalz group were already working towards the chroman moiety, de Koning and Pelly at Wits University decided to tackle the synthesis of the chiral 2-isopropenyl-2,3-dihydrobenzofuran *(R)*-**78**. To this end, the Wits group successfully completed the synthesis of the dihydrobenzofuran moiety by way of a key Pd π-allyl mediated cyclisation, in an excellent yield and enantiomeric excess.[46, 47] Despite a significant effort on behalf of the Schmalz group, all attempts to obtain the desired chroman were thwarted in light of the fact that the molecule turned out to be very unstable. In particular, it appeared that the chroman nucleus was very susceptible to oxidation at the 2-position.



Scheme 18

With the knowledge that the originally planned synthesis could not proceed due to the instability of the chroman, we turned our attention to an alternative method that would allow us to capitalise on work already completed toward the chiral dihydrobenzofuran. To this end, a recent publication by Sames and Pastine in their synthesis of deguelin, revitalised our rotenone project as we envisaged being able to use similar methodology to complete the synthesis of rotenone.[48, 49] In their synthesis, a novel platinum-catalysed 6-*endo*-hydroarylation method was developed, providing direct access to the chromene scaffold under mild conditions and in a good yield.[49, 50] The simplified disconnection below illustrates the alkyne **52** and benzopyran **79** precursors from which deguelin was synthesised in this procedure (Scheme 19). If we were to reconstruct our chiral dihydrobenzofuran *(R)*-**78** with the appropriate functionality *(R)*-**80**, we were confident that we could similarly employ the alkyne precursor **52** in order to synthesise the chroman moiety in rotenone.



Scheme 19

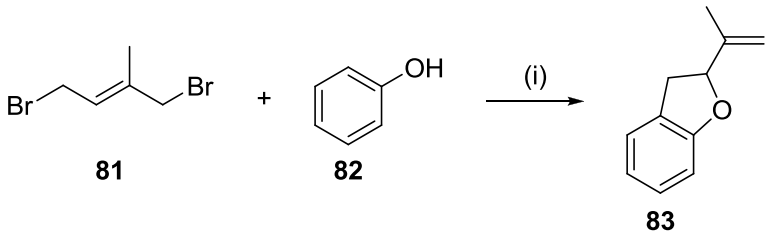
In the discussion to follow, we will outline several approaches to the synthesis of the crucial dihydrobenzofuran and provide a detailed description of the methodology employed in our laboratories by de Koning and Pelly for the synthesis of *(R)*-**78**.[47] We shall also give a brief overview of the key 6-*endo*-hydroarylation reaction and events leading up to its use in the construction of deguelin and its envisaged importance in our planned synthesis of rotenone.

1.8 Selected syntheses of the 2,3-dihydrobenzofuran moiety

Over the years, the synthesis of the dihydrobenzofuran has been extensively investigated, owing to its prevalence in a variety of natural products. A multitude of approaches have been established, providing access to a range of substituted 2,3-dihydrobenzofurans. Here, we present several interesting synthetic processes, briefly considering racemic syntheses and eventually placing emphasis on transition metal catalysed reactions, with particular interest in those that delivered an enantioselective approach towards the assembly of 2-substituted dihydrobenzofurans.

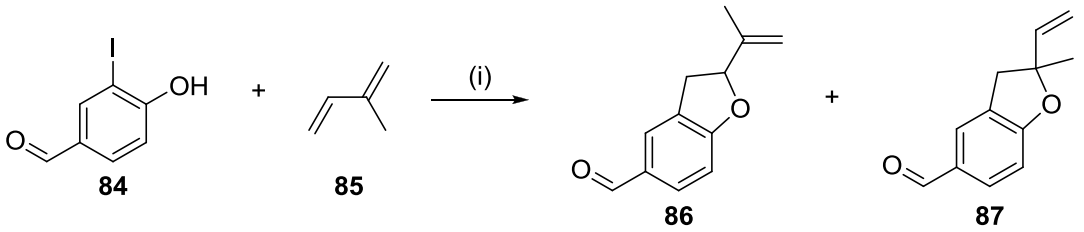
1.8.1 Background on racemic syntheses of the 2,3-dihydrobenzofuran moiety

One of the earliest recorded syntheses of the 2,3-dihydrobenzofuran dates back to 1958 when 2-isopropenyl-2,3-dihydrobenzofuran **83** was synthesised from isoprene dibromide **81** and sodium with fluoroacetophenone.[51] Twenty years later, a variation on this reaction was conducted by Kawasa and co-workers, using phenol **82**, rather than fluoroacetophenone, under harsh conditions (Scheme 20). [52] Although this reaction yielded **83** as is found in rotenone, the synthesis below is of course non-stereoselective.



Scheme 20: *Reagents and conditions:* (i) Na, 43%

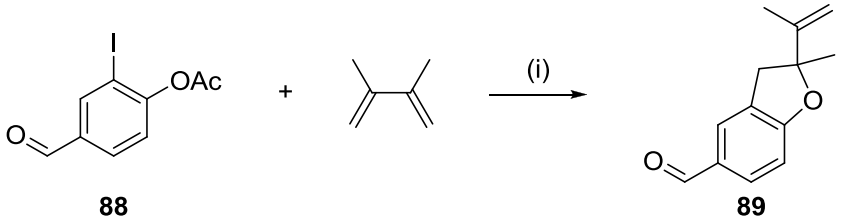
In 1990, Larock and co-workers described the synthesis of a variety of oxygen heterocyclic compounds, including the dihydrobenzofurans **86** and **87** obtained using a palladium-catalysed annulation of a 1,3-diene **85** by the *o*-iodophenol **84** (Scheme 21).[53] Unfortunately, the reaction was specifically restricted to electron-deficient *o*-iodophenols and sterically unhindered dienes. Moreover, this procedure was poor yielding, non-stereoselective and in fact led to a mixture of products as shown below.



Scheme 21: *Reagents and conditions:* (i): 5 mol% $Pd(OAc)_2$, NaOAc, *n*-Bu_4NCl, DMF, 100 °C, 3 days, 43%.

A more recent development emanating from the same research group showed that use of the *o*-acetate **88**, rather than the phenol **84**, resulted in a significant improvement in the reaction, which could now be applied to a broader range of substrates (Scheme 22).[54] Terminal, cyclic and internal dienes as well as electron-rich and electron-deficient *o*-iodoaryl acetates were utilised, giving rise to

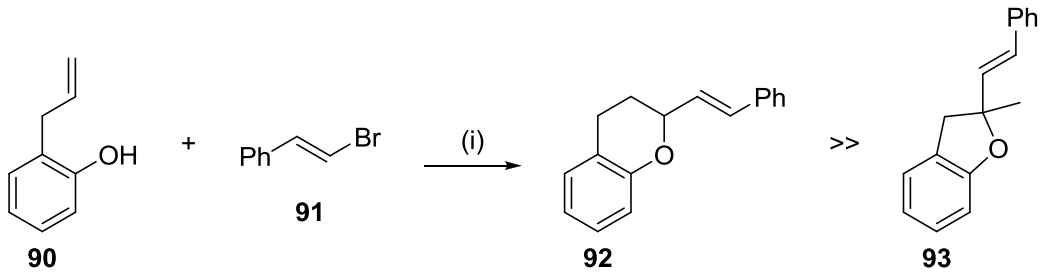
many compounds in good yields which were previously inaccessible by this methodology. Amongst these, were several derivatives of the 2-isopropenyl-2,3-dihydrobenzofuran unit such as **89**. Interestingly, regarding chirality at the 2-position, the report states that the reaction is stereoselective, although no mention was made beyond this and enantiomeric excesses had been omitted. Since we wished to approach the synthesis of rotenone stereoselectively, this was an issue of particular concern.



88 **89**

Scheme 22: *Reagents and conditions:* (i) 5 mol% $Pd(dba)_2$, 5 mol% dppe, Ag_2CO_3, dioxane/H_2O, 100 °C, 24 h, 98%.

In a concurrent study by Larock and co-workers, a slightly different approach to heterocyclic compounds was provided.[55] A palladium-catalysed cross-coupling reaction of *o*-allylic phenols **90** with vinylic halides (or triflates) **91** was described (Scheme 23). Various benzopyran **92** and dihydrobenzofuran moieties **93** were constructed in the process. Unfortunately, the methodology was not widely applicable and the dihydrobenzofuran moiety was only obtained in selected examples. It was usually formed as a by-product as the reactions strongly favoured the formation of the corresponding pyrans.

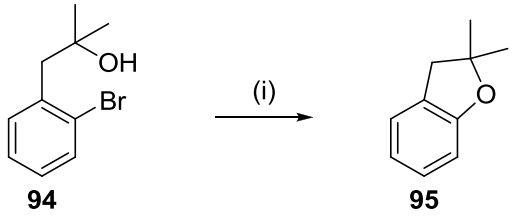


90 **91** **92** **93**

Scheme 23: *Reagents and conditions:* (i) 5 mol% $Pd(OAc)_2$, Na_2CO_3, *n*-Bu_4NCl, DMF, 80 °C, 24 h, **92:** 82%, **93:** 8%.

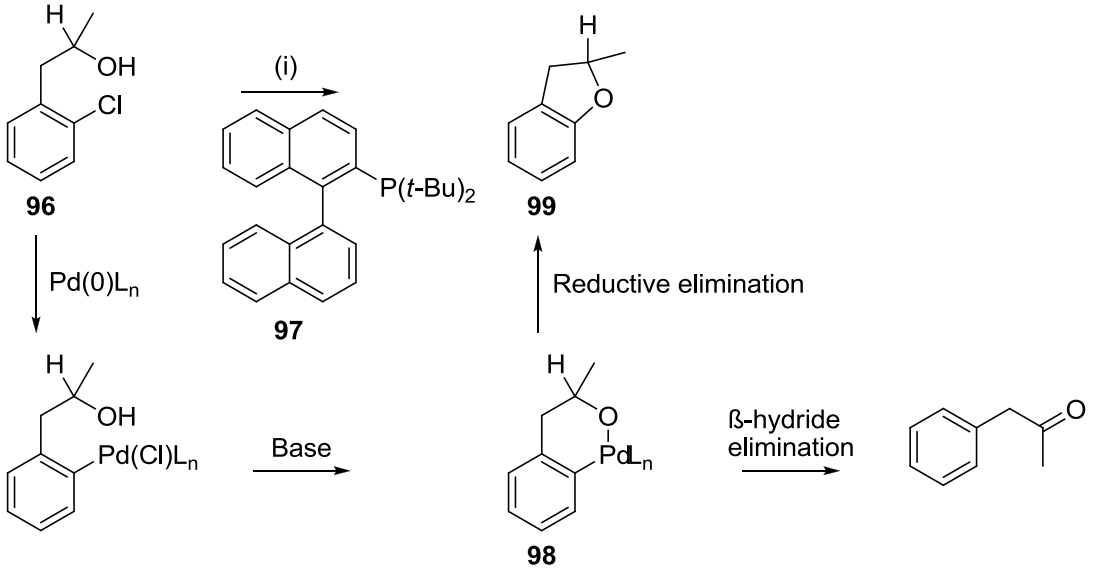
Intramolecular Pd-catalysed coupling reactions of aryl halides with alcohols have provided a route to cyclic aryl ethers. Reactions of this sort were reported for the first time in 1996 by Buchwald and co-workers upon synthesising several five-, six- and seven-membered heterocycles in moderate to

good yields.[56] An example is illustrated in Scheme 24 below in which the arylbromo alcohol **94** was subjected to catalytic $Pd(OAc)_2$ in the presence of a bidentate phosphorous-based ligand, thus affording the dihydrobenzofuran **95** substituted at the 2-position in a good yield. The reaction was unfortunately limited to tertiary alcohols as application of these conditions to primary and secondary alcohols afforded the corresponding dehalogenated aldehydes or ketones with the desired compound only in low yields. This was attributed to a β-hydride elimination which competed with a reductive elimination at the palladacycle stage **98** (Scheme 25).



Scheme 24: *Reagents and conditions:* (i) 5 mol% $Pd(OAc)_2$, 6 mol% Tol-BINAP ligand, K_2CO_3, toluene, 100 °C, 89%.

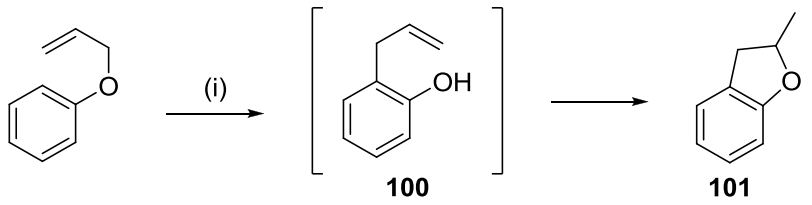
More recently, focus was placed on the development of a new ligand that would accelerate the reductive elimination step, increasing the yields of the desired product (Scheme 25).[57] To this end, seven electron-rich *o*-biphenyl- and binaphthylphosphine ligands were tested. The binaphthyl ligand **97** was the most generally effective in the cyclisation of primary, secondary **96** and tertiary alcohols, affording the corresponding dihydrobenzofurans **99** in good yield.



Scheme 25: *Reagents and conditions:* (i) 3 mol% $Pd(OAc)_2$, $Cs_2(CO)_3$, 2.5-3.5 mol% ligand, toluene, 60 °C, 26 h, 71-75%.

Interestingly, upon applying these conditions to optically active alcohols, conservation of enantiomeric purity was observed. However, this had only been applied to the synthesis of 6-membered molecules and had not been extended to the construction of the chiral dihydrobenzofuran unit. An additional disadvantage to this study was that substituents at the 2-position were restricted to simple methyl groups and the methodology seemed unlikely to furnish the necessary isopropenyl functionality required for rotenone.

Although palladium has been more frequently employed in transition metal catalysed cyclisations towards the dihydrobenzofuran, a few examples in the literature describe procedures in which other metals are utilised. In the presence of an iridium catalyst, Liu and co-workers showed that the well-known Claisen rearrangement could be conducted under much milder conditions than those normally employed (Scheme 26).[58] In turn, the catalyst would promote a cyclisation reaction of **100**, thus yielding the dihydrobenzofuran **101**. A wide range of catalysts were screened and a combination of $IrCl_3$ and AgOTf were found to be the most efficient system in catalysing the tandem Claisen hydroaryloxylation. Although a variety of simple dihydrobenzofurans were synthesised, the method was restricted to just a methyl group at the 2-position.



Scheme 26: *Reagents and conditions:* (i) 5 mol% $IrCl_3$, 10 mol% AgOTF, $ClCH_2CH_2Cl$, 60 °C, 24 h, 65%.

1.8.2 Stereoselective syntheses of the 2,3-dihydrobenzofuran moiety

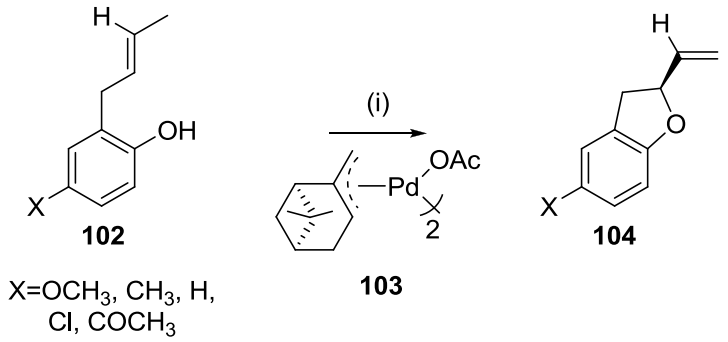
Having considered several racemic syntheses, we will now describe various routes in which the dihydrobenzofuran was acquired as a single enantiomer. In several approaches, a single isomer was obtained, although by resolution methods of the racemic mixture. One such method was described by Bowen and co-workers in which the dihydrobenzofuran, a product of the reduction of the corresponding benzofuran unit, was separated into its enantiomers by resolution methods.[59] Yamaguchi and co-workers synthesised various naturally occurring 2-isopropenyl dihydrobenzofuran derivatives,[60] and upon subjecting the racemic mixture to diastereoselective

kinetic resolution methods such as the Sharp asymmetric dihydroxylation, excellent enantiomeric excesses were obtained, although yields were poor.

Since we were particularly interested in stereoselective syntheses, a few of the more pertinent approaches shall now be presented in which the assembly of the stereogenic centre at the 2-position was optimised towards a single isomer.

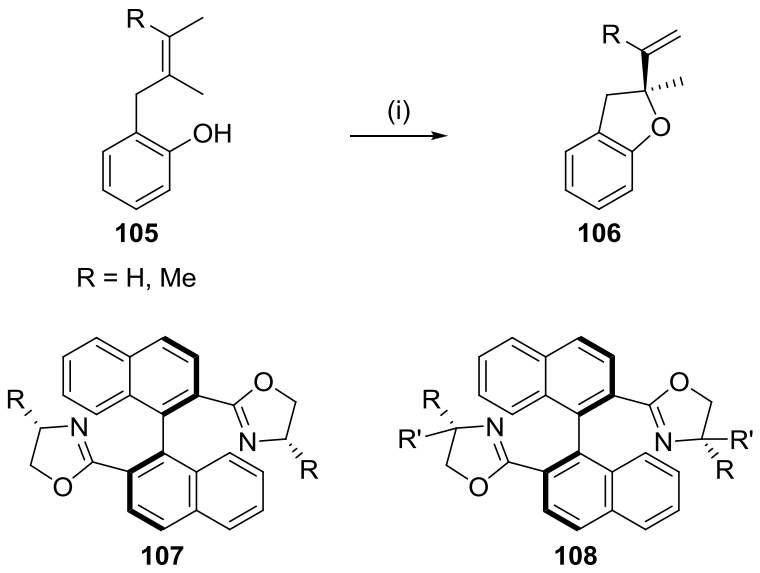
1.8.2.1 The Asymmetric Wacker oxidation

The Wacker oxidation has been employed in several stereoselective syntheses of 2-substituted dihydrobenzofurans with varying degrees of success. Uozumi attempted a Wacker-type cyclisation on prochiral *o*-allylphenols **102** using a chiral (η^3-pinene)palladium(II) complex **103**, affording various dihydrobenzofurans **104**.[63, 64] The reaction was poorly stereoselective, affording a maximum enantiomeric excess of just 26% (Scheme 27).



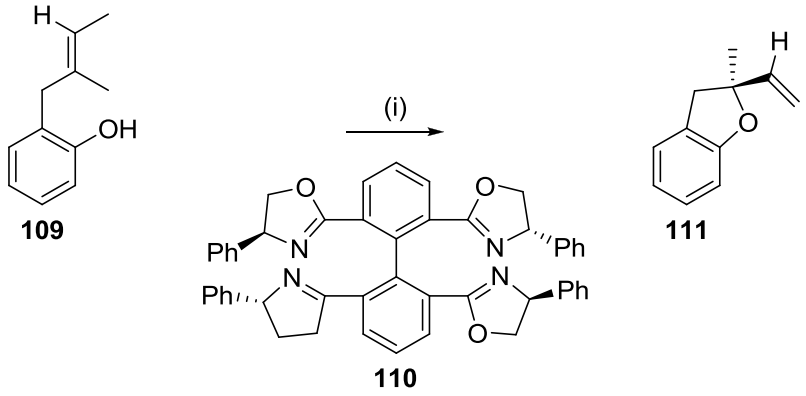
Scheme 27: *Reagents and conditions:* (i) 5 mol% (η^3-pinene)palladium(II) dimer, 10 mol% $Cu(OAc)_2$-O_2 or ^{t}BuOOH, MeOH, 35 °C, 19-74%, 0.1-26% ee.

Over a decade later, a modified procedure was described by Uozumi and co-workers (Scheme 28).[61-63] This was a noteworthy achievement as, upon cyclisation of the *o*-tetra- (R=Me) and *o*-trisubstituted (R=H) allylphenols **105** using the chiral bis(oxazoline) ligands (boxax) **107** and **108**, respectively, the dihydrobenzofurans **106** were obtained in enantiomeric excesses as high as 96% and 97%. The optimised conditions involved the use of an excess of benzoquinone and a methanolic solvent system.



Scheme 28: Reagents and conditions: (i) 10 mol% $Pd(OCOCF_3)_2$, boxax ligand, benzoquinone, MeOH, 60 °C, 24 h, 96-97% ee.

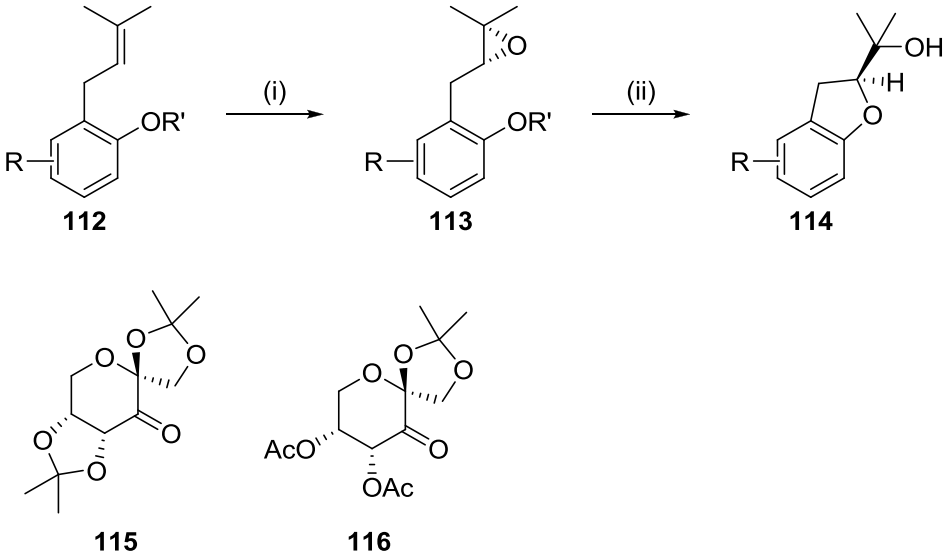
The Wacker oxidation was further modified by Zhang and co-workers.[64] Several chiral ligands were developed and upon applying these to the Wacker cyclisation of *o*-tetrasubstituted allylphenols, enantiomeric excesses as high as 99% were obtained. Shortly thereafter, the most promising of these ligands **110** was applied to the cyclisation of *o*-trisubstituted allylphenols **109** (Scheme 29). High catalytic activities and enantiomeric excesses were maintained, yielding a variety of cyclised dihydrobenzofuran products such as **111** in high enantiomeric excesses. Once again, the methodology was not extended to the synthesis of chiral 2-isopropenyl dihydrobenzofurans as required in our synthesis of rotenone (i.e. without the methyl substituent at the 2-position).



Scheme 29: *Reagents and conditions:* (i) 10 mol% $Pd(CF_3COO)_2$, 10 mol% ligand, benzoquinone, acetone, 20 °C, 72 h, 87%, 94% ee.

1.8.2.2 Asymmetric synthesis via enantioselective epoxidation

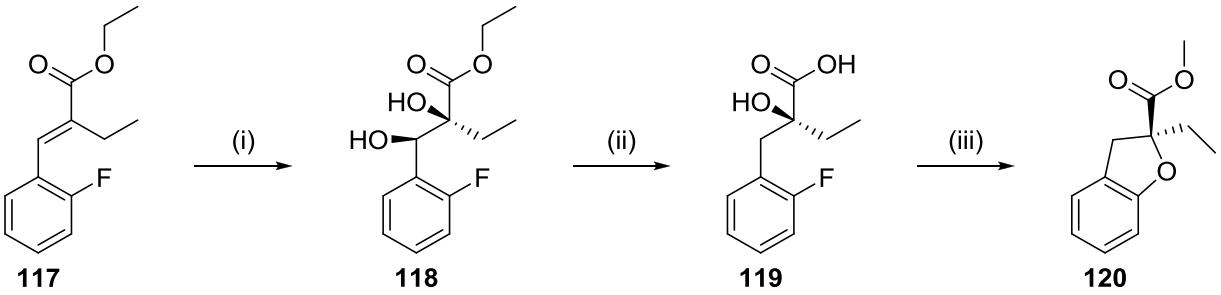
As an alternative to the Wacker oxidation, asymmetric epoxidations have also been utilised in the synthesis of various dihydrobenzofuran-containing natural products.[65, 66] Hamada and co-workers recently described a procedure in which a variety of *ortho* allylphenols were subjected to the Shi-type asymmetric epoxidation and subsequent cyclisation to afford the dihydrobenzofuran nucleus (Scheme 30).[67] In this study, reaction conditions were optimised, affording high yields and enantiomeric excesses. Initially, the Shi ketone **115** was utilised as a chiral catalyst in the asymmetric epoxidation reaction. When applied to the unprotected phenols **112** (i.e. R'=H), the resulting epoxides would spontaneously cyclise to the corresponding dihydrobenzofurans **114**, resulting in poor yields and poor enantiomeric excesses. Interestingly, on application of the same reaction conditions to the silyl-protected phenols **112** (R'=TBS), the stable epoxides **113** were afforded in good enantiomeric excesses and these were then subjected to a cyclisation reaction in a more controlled manner upon deprotection using TBAF, to give the dihydrobenzofurans **114** in good enantiomeric excesses. Whilst the protecting group allowed for better enantiomeric excesses, the yields of the reaction were still low. This problem was overcome by switching to the alternative Shi ketone **116**, thereby affording the desired dihydrobenzofurans **114** in excellent yields and enantiomeric excesses. These reaction conditions were applied to a range of substrates, varying the degree of substitution on the alkene and the bulkiness of the protecting group. Excellent enantiomeric excesses were obtained for di- and trisubstituted alkenes whereas enantiomeric excesses were very low for the mono- and tetra-substituted variants. It was also shown that bulky protecting groups facilitated better enantiomeric excesses as deduced upon comparison of the *tert*-butyl dimethylsilyl and *tert*-butyl diphenylsilyl derivatives.



Scheme 30: *Reagents and conditions:* (i) 30 mol% catalyst, $(n\text{-Bu})_4NHSO_4$, oxone, K_2CO_3, CH_3CN-DMM buffer, 0 °C, 23 h; (ii) TBAF, THF, overall 88%, 97% ee (for R=dihydropyranone).

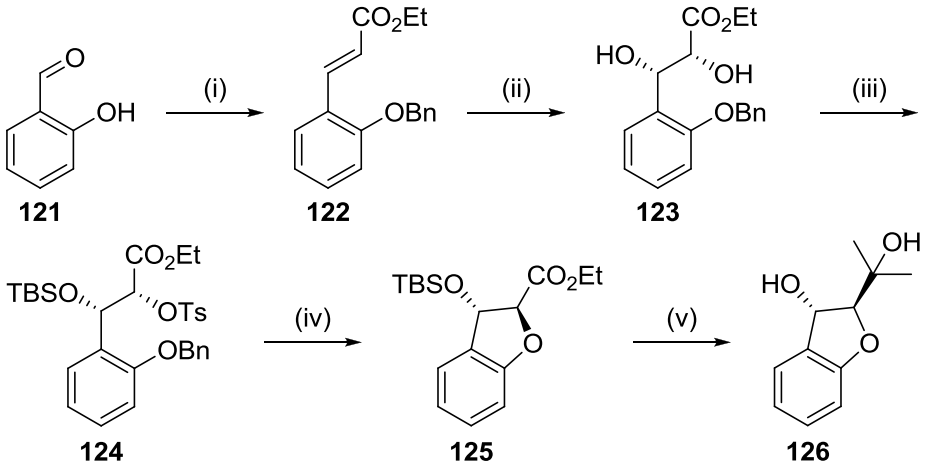
1.8.2.3 Sharpless asymmetric dihydroxylation

The majority of the stereoselective syntheses of 2-substituted dihydrobenzofurans undergo construction of a stereogenic centre during the cyclisation step, employing specific catalysts and ligands. In a somewhat different approach, Shi and co-workers envisaged creating the stereogenic centre prior to the construction of the furan ring system (Scheme 31).[68] To this end, the unsaturated ester **117** was subjected to a Sharpless asymmetric dihydroxylation using AD-mix-*β*, thus affording the diol **118** in an excellent yield and enantiomeric excess. The benzylic carbon was selectively defunctionalised and the ester was hydrolysed to the carboxylic acid **119**. A cyclisation reaction using sodium hydride was then performed during which the stereogenic centre was retained. Conversion of the carboxylic acid to the ester was then achieved using trimethylsilyldiazomethane and methanol, affording the chiral dihydrobenzofuran **120** as a useful precursor amenable to further derivatisation.



Scheme 31: Reagents and conditions: (i) AD-mix-*β*, methylsulfonamide, *t*-BuOH/H_2O, 4 °C, 2 days, 96%, 98% ee; (ii) a: 10% Pd/C, cat. H_2SO_4, H_2, EtOH, 48 h, b: NaOH, MeOH, 2 h; (iii) a: NaH, DMF/toluene, 110 °C, 4 h, b: $TMSCHN_2$, benzene/MeOH.

Panda and Das employed similar methodology *en route* to (2*S*,3*S*)-2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-3-ol **126** (Scheme 32).[69] In this synthetic sequence, readily available salicaldehyde **121** was benzylated and then converted to the *trans* cinnamate ester **122** by means of a Wittig reaction. Sharpless asymmetric dihydroxylation subsequently afforded the dihydroxyl derivative **123** in an excellent yield and enantiomeric excess. Selective protection of the diol to **124** was achieved firstly by regioselective α-tosylation with tosyl chloride and triethylamine, followed by conversion of the benzylic alcohol to the *tert*-butyl dimethylsilyl ether using *tert*-butyl dimethylsilyl triflate. Finally, debenzylation of the phenol set the stage for a cyclisation reaction thus affording the dihydrobenzofuran **125**, which could readily be converted to the corresponding 2-isopropyl substituted dihydrobenzofuran **126** by methyl double addition carried out by means of a Grignard reaction. This methodology was applied to a range of substrates, producing a variety of substituted dihydrobenzofuran compounds.

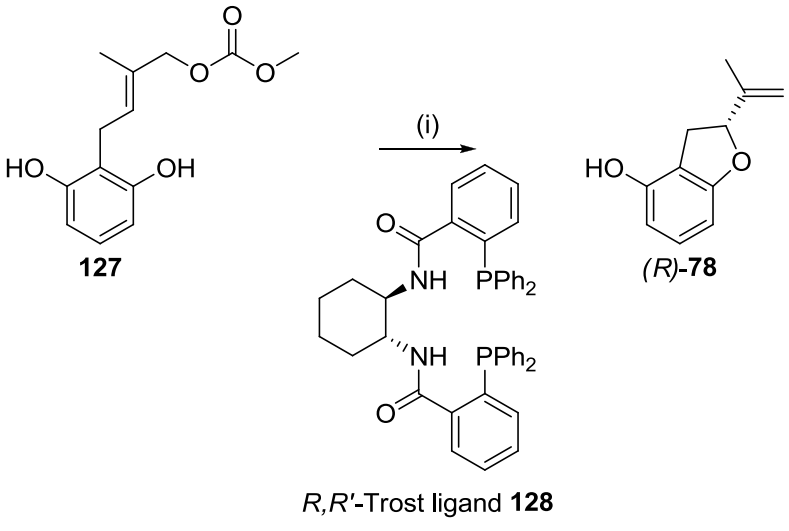


Scheme 32: Reagents and conditions: (i) a: BnBr, K_2CO_3, acetone, reflux, 4 h, 85%, b: $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 2 h, 78%; (ii) AD-mix-α, *t*-BuOH/H_2O, methanesulfonamide, rt to 0 °C, 28 h, 92%, 99% ee; (iii)

a: TsCl, Et_3N, CH_2Cl_2, 3 days, 87%, b: TBDMS-OTf, 2,6-lutidine, CH_2Cl_2, rt, 6 h, 85%; (iv) a: 10% Pd/C, H_2, 4 h, b: K_2CO_3, acetone, rt, 6 h, 69%; (v) a: MeMgI, THF, reflux, 4 h, 77%, b: TBAF, 0 °C, 5 h, 91%.

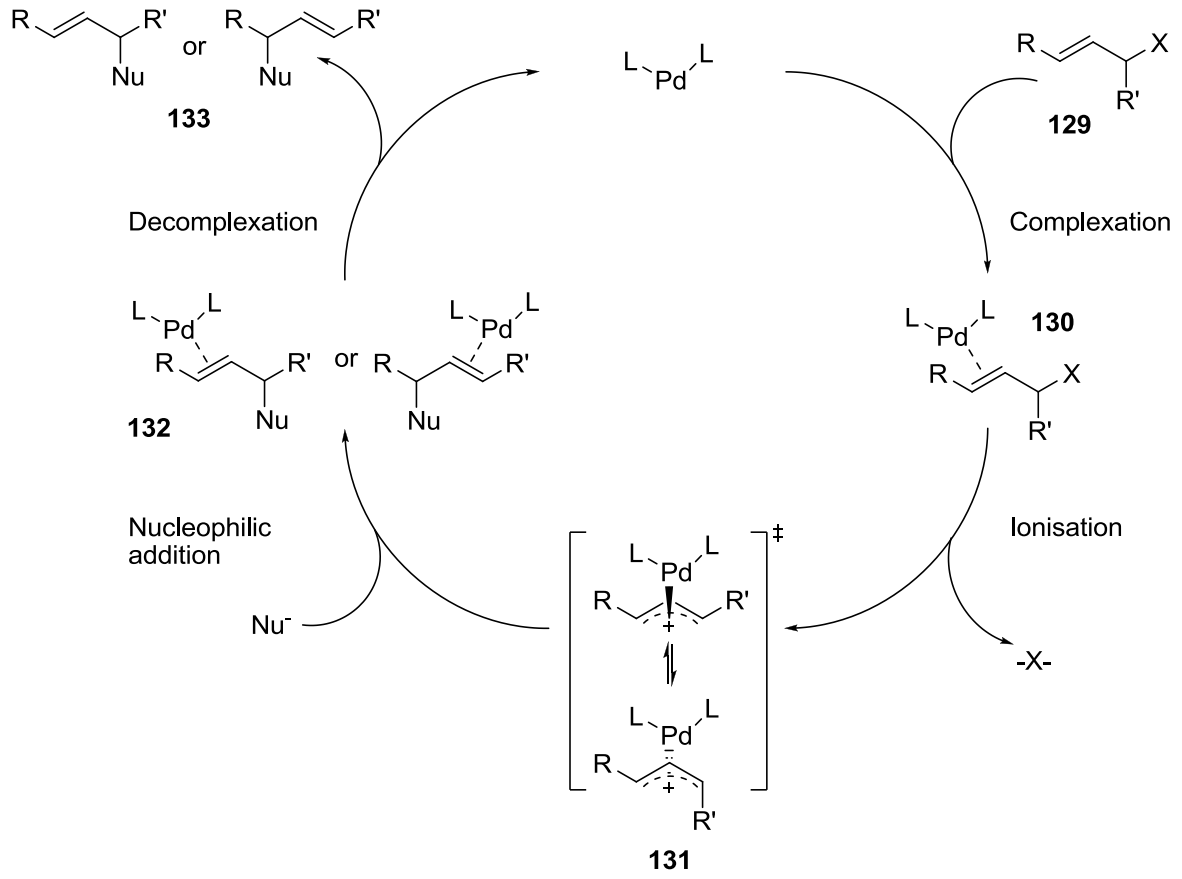
1.8.2.4 Asymmetric allylic alkylation (AAA)

In 2007 de Koning and Pelly described the first stereoselective synthesis of *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol.[46, 47] Until this time, a stereoselective synthesis of this molecule had never been achieved other than by employing resolution methods. As mentioned previously, we intended to utilise the asymmetric synthesis by Pelly since it afforded the dihydrobenzofuran with the isopropenyl and phenolic substituents at the 2- and 4-positions, respectively, making it a promising precursor to rotenone. In the key chiral cyclisation step, *(E)*-4-(2,6-dihydroxyphenyl)-2-methyl-2-butenyl methyl carbonate **127** was treated with catalytic palladium in the presence of the commercially available *R,R'*-Trost ligand **128**, thereby affording *(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol *(R)*-**78** in an excellent enantiomeric excess (Scheme 33).[46] This was a noteworthy achievement as these moieties are found in a number of natural products such as trematone, hydroxytrematone, fommanoxin and rotenone. Of significant importance leading up to this reaction was the construction of the *(E)*- geometrical isomer **127** as the *(Z)*- geometrical isomer would produce the opposite enantiomer (although in a poor ee) when cyclised with the same chiral ligand using Trost's conditions. Therefore, a mixture of geometrical isomers would have resulted in a diminished enantiomeric excess.



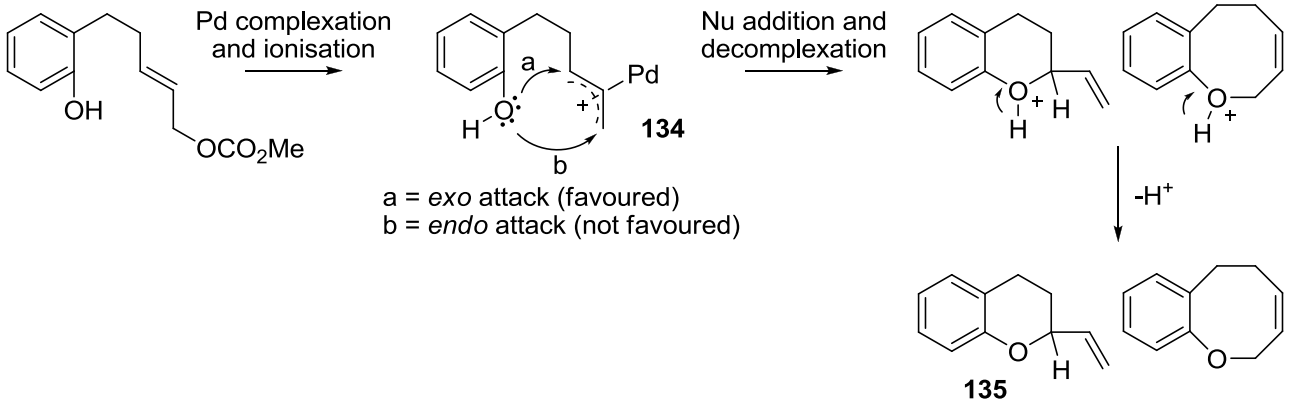
Scheme 33: *Reagents and conditions:* (i) 3 mol% $Pd(dba)_2$, 8 mol% *R,R'*-Trost ligand, AcOH, CH_2Cl_2, rt, 18 h, 80%, 92% ee.[46]

This interesting cyclisation reaction employed by Pelly *et al.* was initially developed by Trost and co-workers.[47] One of the most useful synthetic applications is activation of the α-position of carbonyl groups in the synthesis of new C-C bonds. Trost and co-workers hoped to similarly capitalise on activated olefins, hence the development of the AAA reaction.[70] Reactions of this sort are achieved using catalytic palladium metal which allows for the addition of a nucleophile onto an olefin which contains a suitable leaving group such as an acetate or a carbonate. The reaction proceeds via a working catalytic cycle which is illustrated below (Scheme 34). At the start, the palladium coordinates to the alkene **129,** thus forming an alkenylpalladium complex **130**. Ionisation occurs as the leaving group is released to form the charged π-allyl palladium complex **131** which is now susceptible to attack by the nucleophile. The resulting product is subject to both stereochemical as well as regiochemical factors. Regarding the stereochemistry, since the palladium is able to coordinate to either face in the π-allyl palladium complex **131**, the nucleophile may attack on either face provided it is opposite to the palladium, in the course of which opposite enantiomers will be generated. The regiochemical issue arises as the nucleophile may attack at either of the two β carbons to the palladium, resulting in one of two products illustrated in **132**. Finally, decomplexation releases **133** and the palladium catalyst is regenerated.[71]

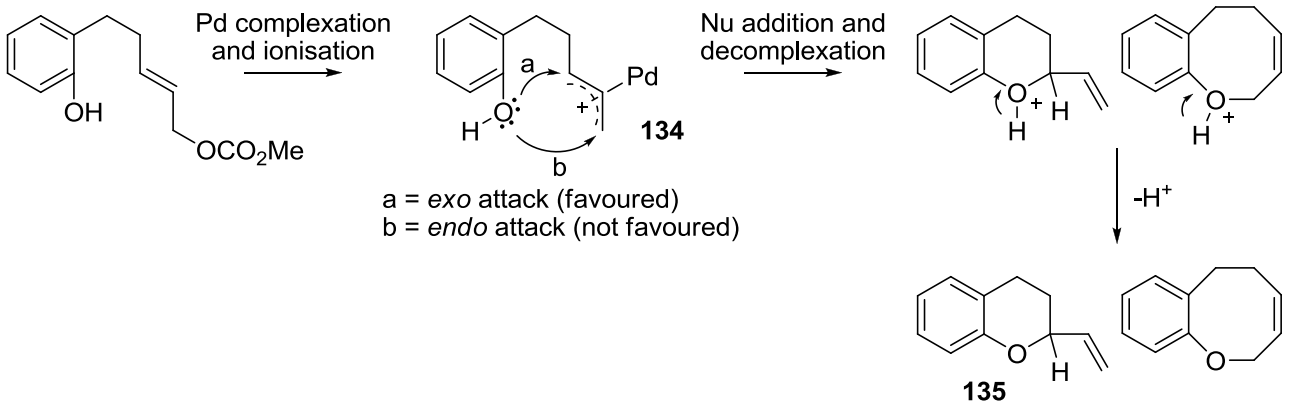


Scheme 34

The regioselectivity issue is demonstrated more clearly by way of an example illustrated in

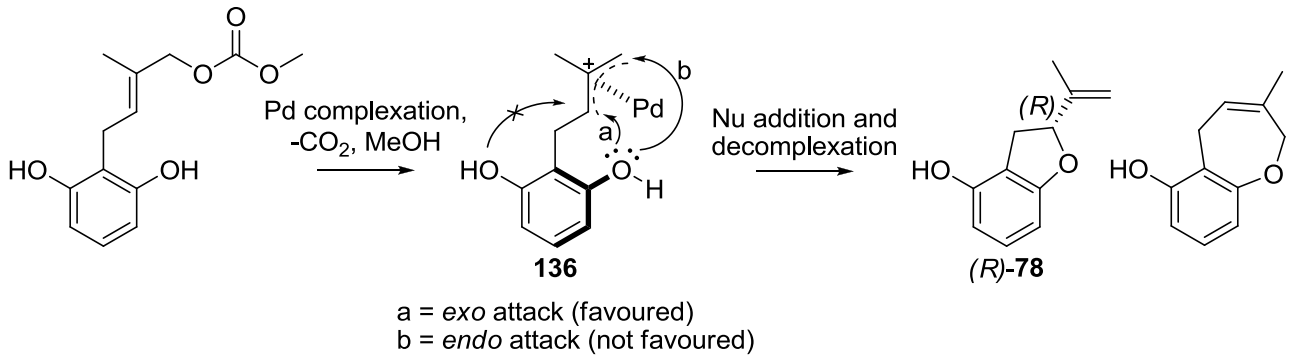


Scheme **35** below, in which the nucleophile may attack at either of the two β positions to the palladium in complex **134**. In this particular example, the site of attack is subject to the favourability of the product that is formed in that upon an *exo* attack, a 6-membered ring is generated which is significantly more stable than the alternative 8-membered ring, hence the formation of product **135**.[72]



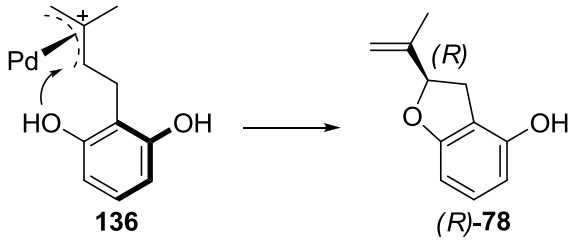
Scheme 35

The synthesis by Pelly was ideal in that both the regiochemical and stereochemical outcome of the reaction could be controlled.[47] Regarding the regiochemistry, an intramolecular nucleophilic attack in **136** could generate a 5- or 7-membered product (Scheme 36). Since 5-membered rings are more favourable, *(R)*-**78** was afforded. Also illustrated below is the fact that for a specific configuration only one of the two phenolic OH's will attack in the π-allyl palladium complex. Since the Pd is coordinated on the bottom face in **136**, front facial attack will selectively occur by the nearby OH as the other phenolic group is too far away, thus resulting in a single product.



Scheme 36

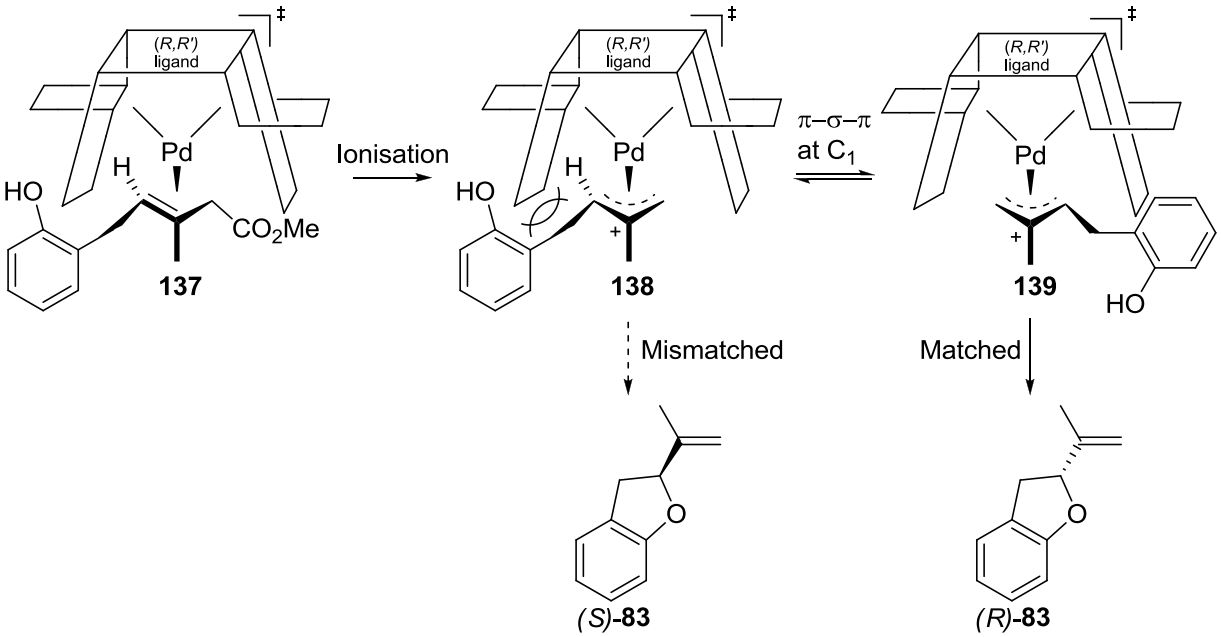
Should rotation take place about the benzylic single bond, the palladium will be on the top face and so the nearby phenolic group which is also able to attack on the bottom face, is now the other OH. This will result in the same *(R)*- enantiomer **78** (Scheme 37).



Scheme 37

In using a chiral Trost ligand, Pelly was able to control the face of the alkene to which palladium coordinated and hence, the attack of the nucleophile so that the stereochemical outcome of the reaction was directed towards a single enantiomer.[47] This is rationalised by way of the mechanistic model proposed by Trost (Scheme 38).[72] Schematically, the *R,R'*-Trost ligand is represented by the chiral scaffold where the walls and flaps spatially represent the phenyl groups of the triarylphosphine moieties of the ligand. In the initial stages of approach and complexation, the carbonate leaving group is accommodated under the right flap of the ligand, illustrated in **137**. The subsequent loss of the leaving group (and hence the steric bulk associated with it) results in an intermediate **138** which is no longer in the most favourable spatial arrangement, and may be regarded as a mismatched system. This is overcome by a π-σ-π rearrangement of the π-allyl palladium complex, giving rise to the thermodynamically preferred matched intermediate **139**. Attack of the nucleophile now positioned on the bottom face gives the favourable *(R)*-**83**. Of course, should the nucleophile attack in the mismatched scenario, the mismatched *(S)*-**83** will form,

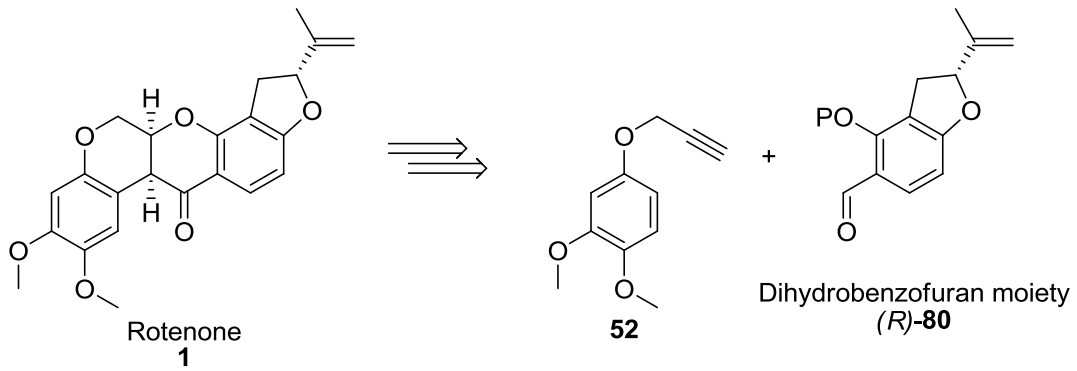
although in a poor enantiomeric excess. This is due to the fact that **139** is more thermodynamically favourable than **138** and therefore the matched *(R)*-**83** will always form. The key to inducing a matched cyclisation reaction is to provide enough time for the π-σ-π rearrangement to occur. This is accomplished by the addition of a weak acid such as acetic acid, thereby reducing the nucleophilicity of the phenolic group and hence reducing the rate of the reaction.



Scheme 38

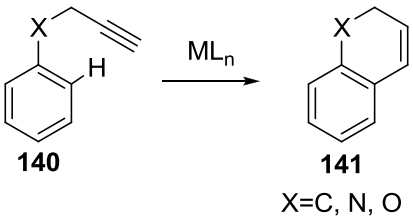
1.9 Construction of the chromene moiety

Having considered a viable approach to the chiral synthesis of the dihydrobenzofuran moiety *(R)*-**80** of rotenone, we would then need to turn our attention to the other (chromene) half of the natural product that needed to be synthesised (Scheme 39). We believed that the chromene portion could be synthesised from the propargyl ether **52** by means of a hydroarylation reaction.



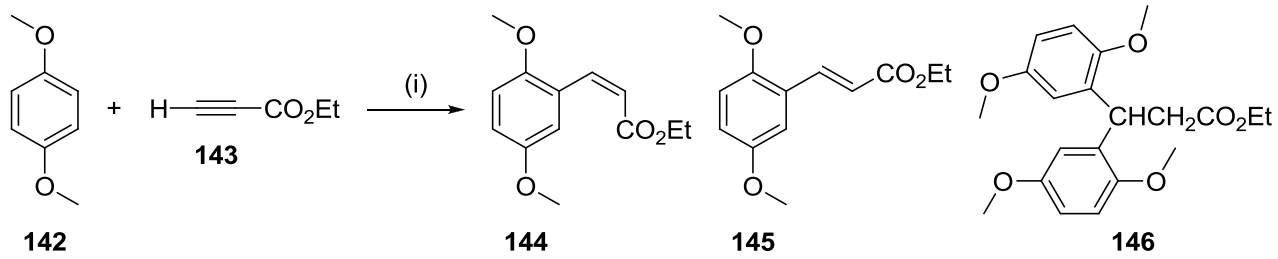
Scheme 39

An intramolecular hydroarylation is the addition of an aromatic C-H bond across multiple bonds of an attached alkene or alkyne thus converting, for example, **140** to **141** (Scheme 40).[73, 50] The reaction has developed progressively over a number of years. Presently, hydroarylations can be applied intramolecularly to arene-yne type systems of both terminal as well as internal alkynes bearing a variety of substituents. The reaction has also been extended to propargyl ethers (X=O) and amines (X=NH).[50] As a consequence of this extensive research, convenient methods now exist providing direct access to a variety of annulated arene carbocyclic and heterocyclic structures such as dihydronaphthalenes,[74-76] napthalenes,[77] carbenes,[49, 50, 76] and coumarins.[78] Early forms of this reaction suffered from selectivity issues and a number of products were often formed. Over the years, the selectivity of this reaction has been improved to the point that in many cases, under the right conditions, a single product can be synthesised.



Scheme 40

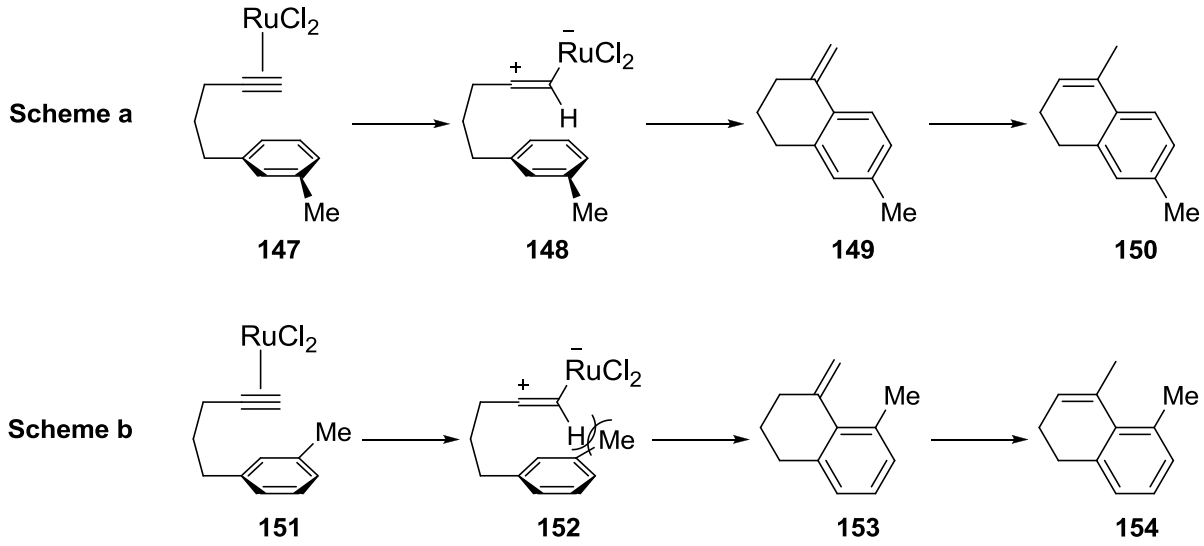
Leading up to the development of this reaction, several breakthroughs were made in 2000 in the area of C-H bond activation and functionalisation. Fujiwara and co-workers conducted a study on the intermolecular hydroarylation of a variety of alkynes **143** with simple aromatic systems **142** in the presence of Pd(II) or Pt(II) catalysts (Scheme 41).[79] It was envisaged that this would provide a simple and clean method for synthesising substituted aromatic compounds without prior functionalisation of the aromatic ring. In applying this methodology, desired coupled product was usually obtained, although the formation of by-products was problematic. These problems were the result of the reaction not being completely stereoselective and in addition to the predominant *cis* isomer **144**, a small amount of the *trans* geometrical isomer **145** was also produced. Additional side products **146** were obtained as a result of multiple reactions of a single arene with more than one alkyne, or *vice versa*. Trifluoroacetic acid (TFA) was utilised in this reaction and attempts to exclude or even reduce the amount of TFA used, only resulted in lower yields. The necessary addition of TFA in this reaction limited its use to functional groups that were resistant to the acid.



Scheme 41: *Reagents and conditions:* (i) 1 mol% $Pd(OAc)_2$, TFA, CH_2Cl_2, 0 °C to rt, 45 h, **144:** 72%, **145:** 6%, **146:** 5%.

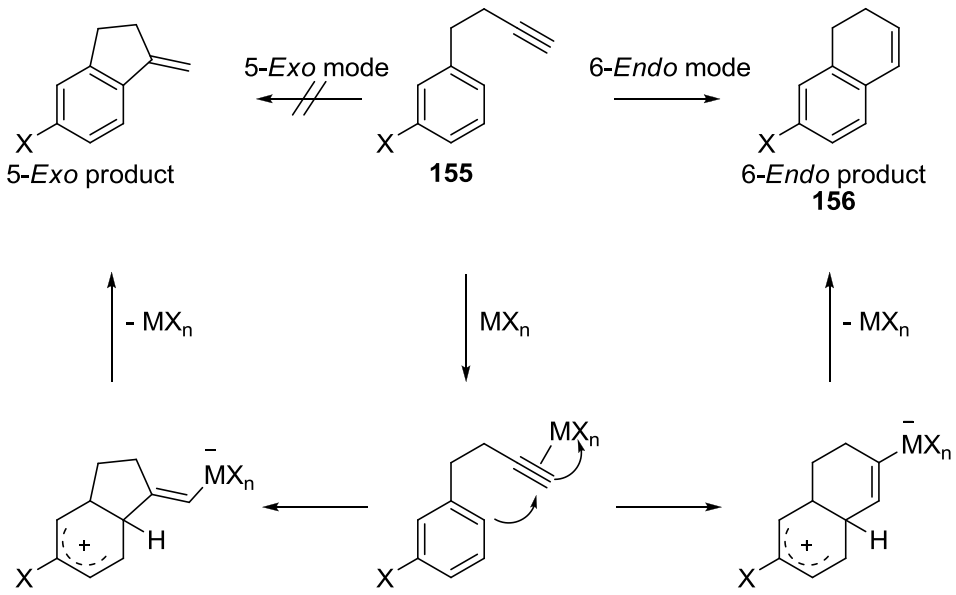
In a parallel study, Chatani *et al*. presented an intramolecular hydroarylation of aryl-1-alkynes.[74] Terminal alkynes bonded directly to the aromatic system were subjected to hydroarylation reactions in the presence of $PtCl_2$ and $RuCl_2(CO)_3$ catalysts, thus providing access to various carbocyclic systems such as dihydronaphthalene derivatives. Unfortunately, this study was limited to terminal alkynes and when Chatani applied the reaction conditions to substituted alkynes, a number of products formed. In extending the reaction to propargyl ethers, the alkyne C-O bond would be cleaved, yielding the benzylic alcohol.

A mechanistic model was also proposed from which the issue of site selectivity could be rationalised by steric considerations (Scheme 42). The reaction begins with the addition of the metal chloride to the alkyne (**147**, **151**) and subsequent formation of a vinyl cationic intermediate (**148**, **152**). Less steric congestion observed in intermediate **148** compared to **152** justifies the predominance of the final product **150** compared to **154**. The vinyl cationic intermediate undergoes electrophilic aromatic substitution to give the carbocyclic intermediates **149** and **153**. The double bond may isomerise to the more stable internal position to afford the dihydronaphthalene derivatives **150** and **154** which, upon application of this methodology, were obtained in a 96:4 mixture, respectively. The study of terminal aryl-alkynes was later extended to the use of $GaCl_3$ as the catalyst.[75]

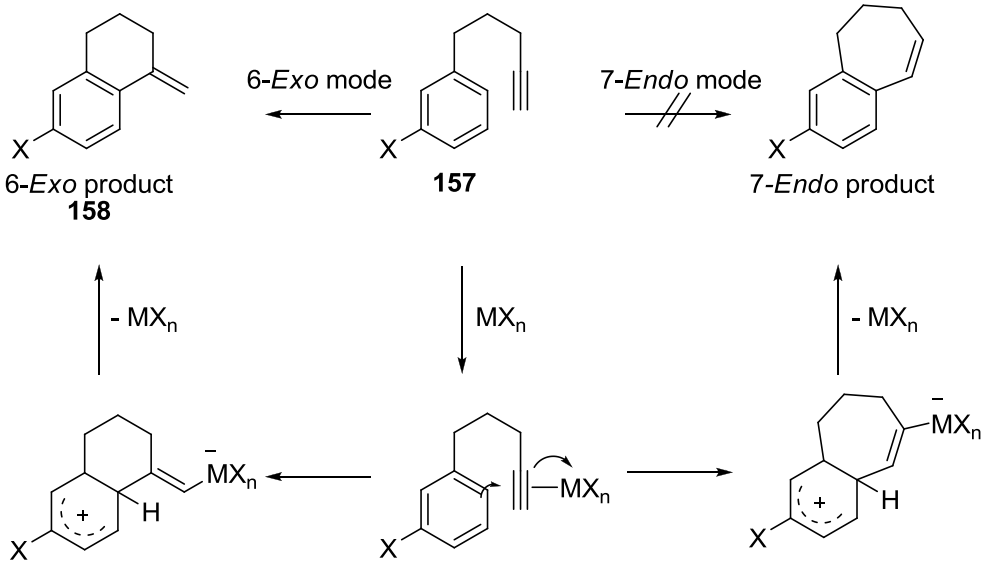


Scheme 42

Several mechanisms have been proposed for the hydroarylation reaction and most of these are along the lines of the mechanisms illustrated in Scheme 43 and Scheme 44 which differ in the number of atoms in the tether.[74, 80] The reaction begins with η^2-coordination of the transition metal to the alkyne (**155** or **157**). This complexation renders the alkyne susceptible to intra- or intermolecular nucleophilic attack. The formation of a vinyl cationic intermediate has also been proposed (Scheme 42), although this intermediate has never been isolated. Electrophilic aromatic substitution followed by a 1,2 or 1,3-hydrogen shift then gives rise to the *exo* and *endo* products, respectively. The selectivity observed between the *exo* and *endo* products is in fact subject to the number of atoms in the tether, separating the alkene and arene. Arene-yne systems **155** containing two atoms in the tether (Scheme 43), show a pronounced preference for the 6-*endo* pathway over the 5-*exo* mode, exclusively forming the 6-*endo* product **156**.[80] With three or four atoms in the tether **157** (Scheme 44), the *exo* product **158** is usually formed, however, the double bond may isomerise to the more stable, internal position.[74, 80]

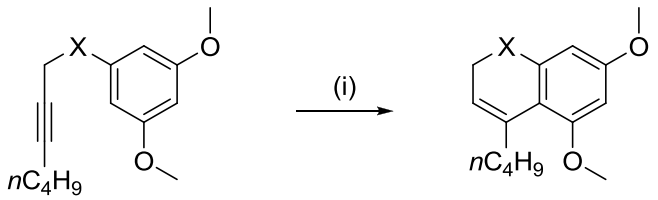


Scheme 43



Scheme 44

Having acquired some level of understanding regarding the mechanism of this reaction, many other hydroarylation reactions were performed, thus improving the available methodology. Nishizawa and co-workers were able to expand on the synthesis of dihydronaphthalenes by intramolecular hydroarylations (Scheme 45, X=C).[76] The importance of this modified approach is that cyclisation of internal alkynes such as **159** to form substituted dihydronaphthalenes **160** had become feasible. In utilising mercuric triflate, the cyclisation of propargyl ethers to various chromene derivatives (X=O) was also achieved.



159 **160**

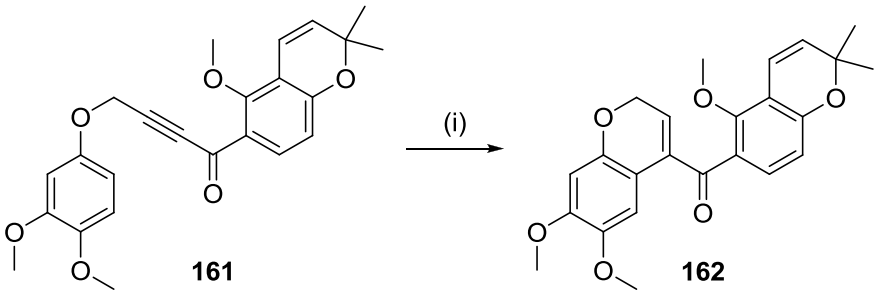
Scheme 45: *Reagents and conditions:* (i) For X=C: 0.1 mol% $Hg(OTf)_2$-$(TMU)_3$, MeCN, rt, 4 h, 95%; for X=O: 0.2 mol% $Hg(OTf)_2$-$(TMU)_3$, MeCN, -20 °C, 7 h, 96%.

Sames and co-workers demonstrated that one single catalyst could play the role and have the beneficial properties of all the above mentioned catalysts.[49, 50] They discovered that $PtCl_4$ proved to be a far superior catalyst to Pt(II), Ga(III) and Pd(II) under mild and neutral conditions. The latter two catalysts had until then been considered the most efficient catalysts for intramolecular hydroarylations (however, their complexes were sensitive to substitution on the alkyne and hence limited with respect to their substrate scope). By comparison, Pt(IV) was a much more efficient and consistent hydroarylation catalyst, compatible with a wider range of substrates. The reaction was selective for the 6-*endo* product and good to excellent yields were obtained when applied to propargyl ethers, amines and alkynoate esters. The reaction was further appealing in that both terminal and internal alkynes as well as highly substituted aromatic systems were amenable to the hydroarylation reaction in the presence of $PtCl_4$. In addition to its higher reactivity, Pt(IV) was also more selective in that the activated alkyne was more susceptible to the nucleophilic arene as opposed to other nucleophiles which may be present such as water, hence competing processes were significantly slower.

A comparison of Pt(II) and Pt(IV) showed that the two catalysts produced comparable results on aromatic systems containing two or more electron donating substituents, e.g. methoxy groups. When applied to electron deficient alkynones, however, Pt(IV) was superior to Pt(II). Alkynoate esters were also converted to their respective chromenes in good yields when using Pt(IV) which is not the case for Pt(II). In addition to its higher electrophilicity, the superior reactivity of Pt(IV) was also attributed to its higher solubility in organic solvents.[49, 50]

In optimising the conditions for the hydroarylation reaction, Sames and co-workers set the stage for the reaction with the advanced alkynone **161**, obtained in three steps from 3,4-dimethoxyphenol

(Scheme 46).[48] Surprisingly, Pt(II) appeared to be the superior of the two catalysts despite the fact that previous studies indicated that it was not well suited to electron-deficient alkynes. Nevertheless, the 6-*endo*-hydroarylation had provided access to the tetracyclic compound **162** which could easily be converted to deguelin. This was an important achievement as *in vitro* and *in vivo* studies had demonstrated deguelin's chemotherapeutic activity.[13]

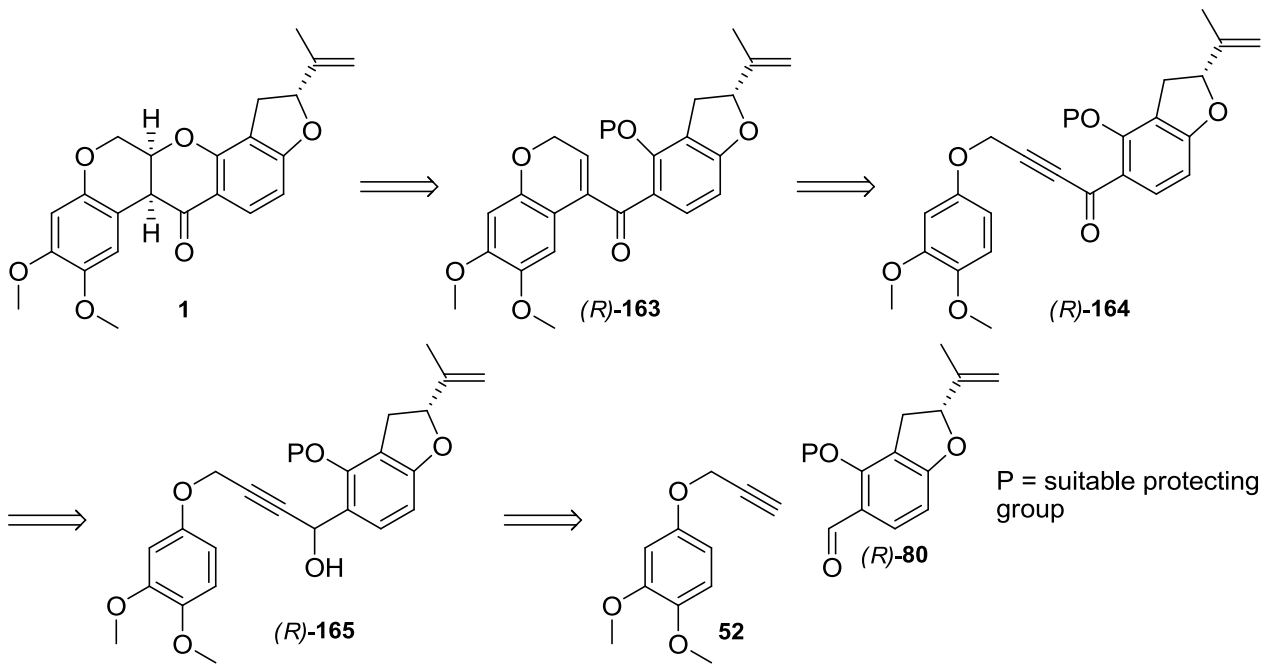


Scheme 46: *Reagents and conditions:* (i) 5 mol% $PtCl_2$, toluene, 55 °C, 10 h, 91%.

CHAPTER 2 - PLANNED APPROACH

2.1 Towards rotenone

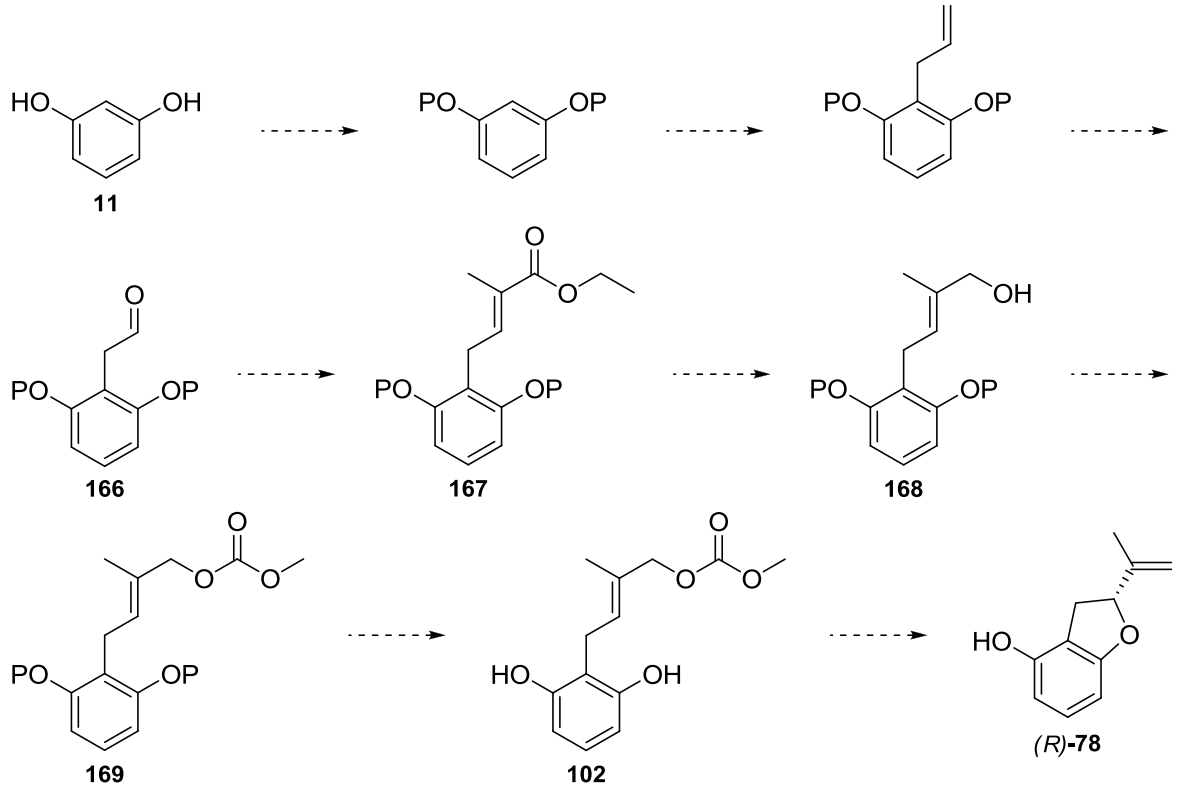
In our retro-synthetic strategy for rotenone we wished to capitalise on the fact that the chiral dihydrobenzofuran moiety of the molecule had previously been synthesised stereoselectively in our laboratories.[47] To this end, we envisaged that rotenone **1** would be the product of several transformations, beginning with the appropriately substituted dihydrobenzofuran building block *(R)*-**80** illustrated in the disconnection below, obtained by means of the procedure developed by de Koning and Pelly (Scheme 47). The final pentacyclic molecule **1** would be the product of an intramolecular Michael addition of the chromene moiety *(R)*-**163**, acquired by means of the key transition metal catalysed hydroarylation reaction of the alkynone *(R)*-**164**. We envisaged that the alkynone could be accessed from an oxidation reaction of the corresponding alcohol *(R)*-**165**, the product of a coupling reaction of the alkyne **52** and dihydrobenzofuran *(R)*-**80** intermediates.



Scheme 47

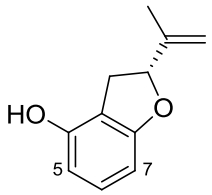
Since we envisaged that rotenone would be synthesised from the dihydrobenzofuran, a brief description of the synthesis of this key intermediate follows (Scheme 48). At the start of the synthesis, commercially available resorcinol **11** would be protected and then allylated. Conversion to the aldehyde **166** by way of an ozonolysis reaction would set the stage for a Horner-Wadsworth-Emmons reaction, yielding the *(E)*- alkene **167**, exclusively. Reduction of the ester **167** to the alcohol **168** would be followed by conversion to the carbonate **169**. A deprotection would liberate

the phenols thus allowing us to carry out the crucial, stereoselective, Pd π-allyl cyclisation. We were confident that the dihydrobenzofuran *(R)*-**78** would be synthesised in a high enantiomeric excess.



Scheme 48

The procedure according to de Koning and Pelly would afford the dihydrobenzofuran *(R)*-**78**.[47] Therefore, before commencing with the coupling reaction to the alkyne *en route* to rotenone, a key formyl group would need to be introduced at the 5-position to form the required intermediate *(R)*-**80**. However, there were potential problems that had to be considered before doing so. Firstly, whilst there are numerous formylation procedures available, many of these are not completely selective for the position *ortho* to the hydroxyl, i.e. the 5-position, and the formyl group could just as easily be introduced in the *para* 7-position (Figure 4). The issue of regioselectivity was further complicated by the benzylic ether which could *ortho*-direct the formyl group into the 7-position.



(R)-**78**

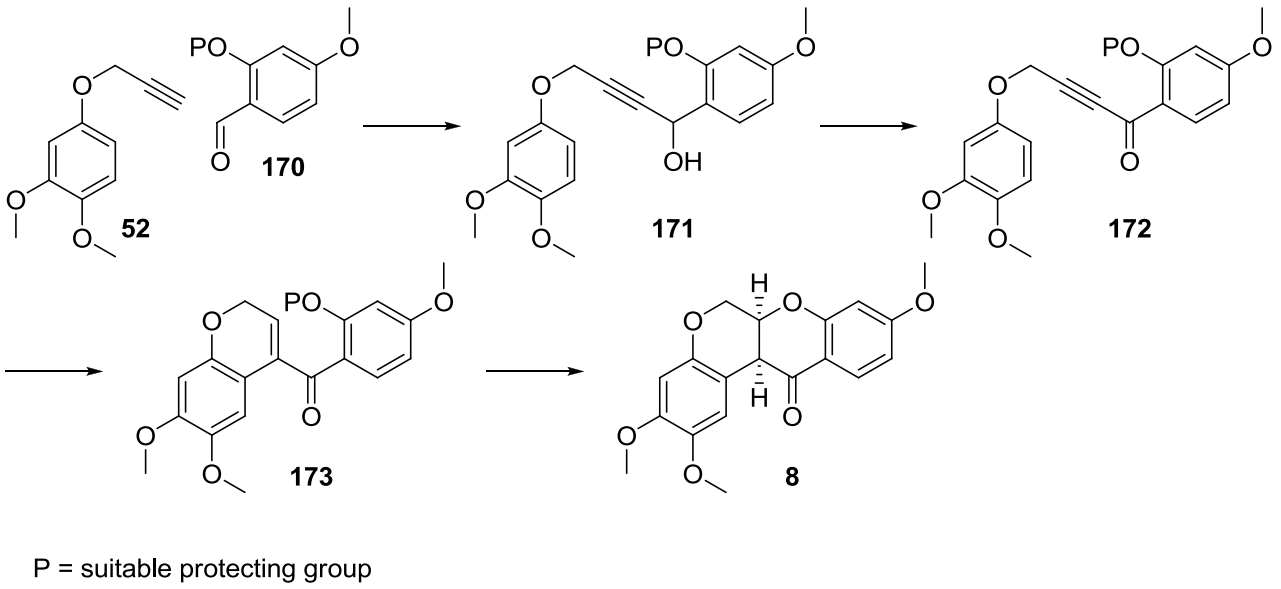
The hydroxyl and benzylic ether could direct the formyl group to the *ortho* 5- and 7- positions or to the *para* 7- and 5-positions, respectively

Figure 4

The second issue lay in the fact that many formylation procedures employ harsh conditions which could potentially affect the crucial stereogenic centre. We were also reluctant to use strong bases such as *n*BuLi as deprotonation at the acidic benzylic position may have affected the carefully constructed furan ring. Yet, we were somewhat reassured by the fact that according to Cahn and co-workers, the furan ring and even more importantly, the stereogenic 5' centre in rotenone, is stable under basic conditions.[81, 82] Hopefully, this would hold in its precursors as we proceeded through our planned synthesis. The issue of chirality would also add a level of complexity to the synthesis compared to that of deguelin, for example, and once we had the dihydrobenzofuran unit in hand, we would have to take special care to retain the meticulously constructed chiral centre, not only during the planned formylation step, but indeed throughout the rest of the synthesis.

2.2 Towards munduserone - A model study

Prior to the challenging synthesis of rotenone, we decided to embark on a model study in which the methodology developed by Sames in his synthesis of deguelin would be applied to the simplest of the natural rotenoids, munduserone **8**.[48] This would allow us to gain a better understanding of the reactions and to optimise yields in preparation for the synthesis of the more complex rotenoid. The proposed synthesis would commence with the coupling of the alkyne **52** and benzaldehyde **170** intermediates to form the secondary alcohol **171** (Scheme 49). An oxidation reaction would then allow for the synthesis of the alkynone **172**, a key intermediate in the envisaged crucial hydroarylation reaction. With the chromene moiety **173** in hand, all that would remain in the synthesis of munduserone would be the base-catalysed intramolecular oxo-Michael addition of the deprotected chromene **173** to hopefully afford munduserone **8**.



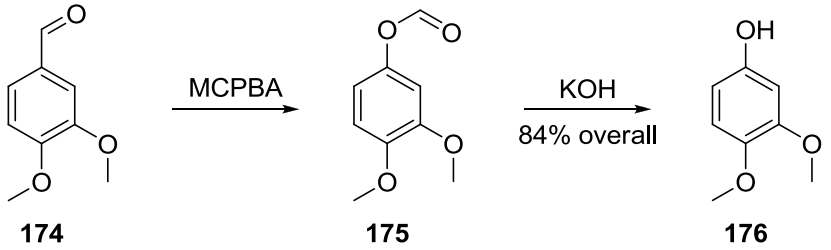
Scheme 49

In the section to follow, we describe the synthesis of munduserone, the dihydrobenzofuran and finally, rotenone.

CHAPTER 3 – RESULTS AND DISCUSSION

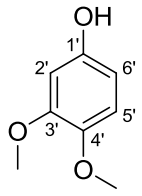
3.1 Synthesis of munduserone – 8

3.1.1 Synthesis of 3,4-Dimethoxyphenol – 176



Scheme 50

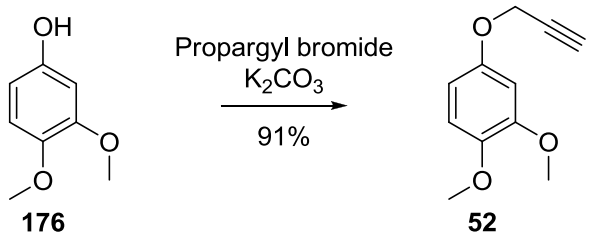
We began our envisaged total synthesis of munduserone from the commercially available vanillin methyl ether **174**, which could be transformed to the required dimethoxyphenol **176** by way of a Baeyer-Villiger oxidation followed by hydrolysis of the corresponding ester **175** (Scheme 50). To this end, a slight excess of MCPBA was added to a solution of the aldehyde **174** dissolved in dichloromethane and the reaction was stirred at rt for 15 h before being quenched with dimethyl sulfide. The procedure was based upon the synthesis described by Roengsumran wherein base hydrolysis of the ester **175** was achieved by dissolving the crude material in methanol, treating with potassium carbonate and stirring for 30 minutes.[83] After several hours of stirring under these reaction conditions, most of the substrate remained as the ester. Harsher conditions were then applied in which **175** was hydrolysed by dissolving the crude material in a methanolic solution of KOH and heating to reflux for 18 h. Following a workup and purification by column chromatography, the product **176** was obtained as a white solid in a good yield.



The simple phenol **176** gave rise to a relatively uncomplicated ^{1}H NMR spectrum. The first indication of a successful reaction was given by the broad singlet at 5.70 ppm due to the O*H* proton. Protons $H_{5'}$ and $H_{2'}$ appeared as *ortho* and *meta* coupled doublets at 6.73 ppm and 6.48 ppm, respectively. Proton $H_{6'}$ which coupled to both $H_{5'}$ and $H_{2'}$, appeared as a doublet of doublets with coupling constants of 8.6 Hz and 2.8 Hz, consistent with the *J* values of protons $H_{5'}$ and $H_{2'}$, respectively. The protons on the two methoxy groups appeared as intense singlets in the upfield region at 3.81 ppm and 3.79 ppm. In the ^{13}C NMR spectrum, the presence of eight signals due to the six aromatic and two methoxy groups as well as the absence of a carbonyl signal, attested to the success of the reaction. In the IR spectrum, an OH stretch was

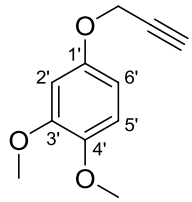
observed at 3419 cm^{-1}. The measured melting point of 79-81 °C compared well with reported value.[83]

3.1.2 Synthesis of 1,2-dimethoxy-4-(prop-2-ynyloxy)benzene – 52



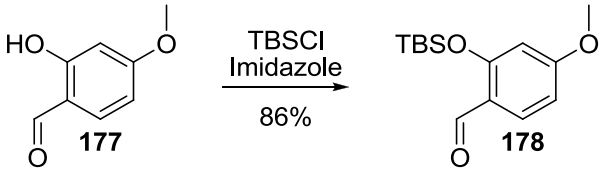
Scheme 51

Having attained the phenol **176**, we were now able to introduce the propargyl moiety essential for the coupling reaction (Scheme 51). The alkylation proceeded smoothly upon the addition of a slight excess of propargyl bromide and potassium carbonate to a solution of the phenol **79** dissolved in dimethylformamide. The reaction was monitored by TLC and after several hours of stirring under Ar, a less polar product of higher R_f had begun to form. The reaction was left to stir for 18 h so as to allow for complete conversion of **176**. Following a workup and purification by column chromatography, the propargyl ether **52** was obtained as a pale yellow solid in a good yield. Although our recorded melting point was higher than the literature value by 3 °C,[38] a close to perfect match in the spectroscopic data reported by Sames and co-workers reassured us that the desired product had indeed been synthesised.[48]



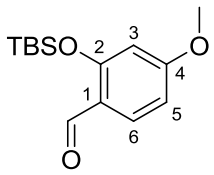
In the ^{1}H NMR spectrum, the doublet and triplet at 4.65 ppm and 2.52 ppm accounted for the methylene and acetylene protons of the propargyl moiety, coupled to one another with a *J* value of 2.8 Hz. In conjunction with this, the previously observed broad O*H* singlet in the ^{1}H NMR spectrum of the precursor was no longer present. The remainder of the spectrum was similar to the precursor, although all the signals had shifted slightly downfield. The accompanying changes in the ^{13}C NMR spectrum included three additional signals at 78.80 ppm, 75.38 ppm and 56.46 ppm due to the propargyl functionality. The phenol signal in the IR spectrum was no longer present.

3.1.3 Synthesis of 2-(*tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde – 178



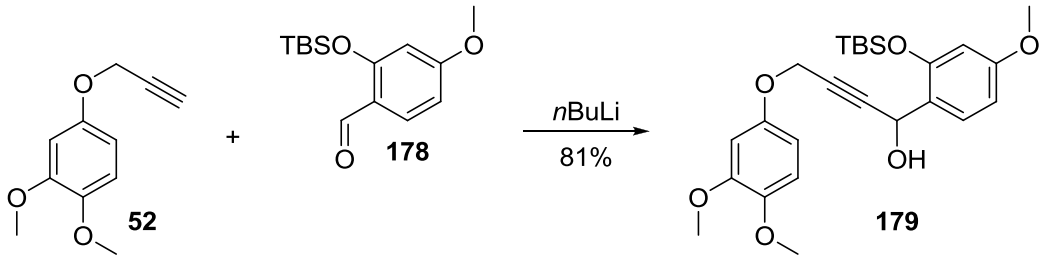
Scheme 52

Having synthesised the first of our required two precursors for munduserone, we now moved onto the preparation of the silyl protected benzaldehyde **178**. In the synthesis of deguelin by Sames and co-workers, a methyl protecting group was employed at position 2, however, since there would be an additional three methoxy groups in the coupled product, we felt that an alternative protecting group would be more easily monitored. Indeed, silyl protecting groups in the form of a *tert*-butyldimethylsilyl moiety would produce distinct signals in the far upfield region, thus allowing us to closely monitor them. Furthermore, TBS groups are stable under most conditions and would be selectively removed at an advanced stage of the synthesis using fluoride-containing reagents such as TBAF. Therefore, a TBS group was introduced by adding TBSCl to a solution of 2-hydroxy-4-methoxy benzaldehyde **177** in acetonitrile followed by the base, imidazole (Scheme 52). After 18 h, TLC analysis indicated complete conversion of **177** to a less polar compound. Following a workup and purification by column chromatography, the desired product **178** was obtained in a good yield.



Two distinct upfield singlets at 1.02 ppm and 0.29 ppm integrating for nine and six protons, respectively, attested to the formation of the desired silyl ether. The remainder of the spectrum was comprised of a singlet in the far downfield region due to the aldehyde proton, three aromatic signals and a methoxy singlet. As for the aromatic protons, H_5 produced an interesting doublet of doublets as it *ortho* coupled to H_6 and also *meta* coupled to H_3. In the ^{13}C NMR spectrum, the three most upfield signals were accounted for by the three TBS carbons. The far downfield signal at 188.61 ppm was as a result of the aldehyde which also appeared in the IR spectrum as an intense carbonyl signal at 1680 cm^{-1}.

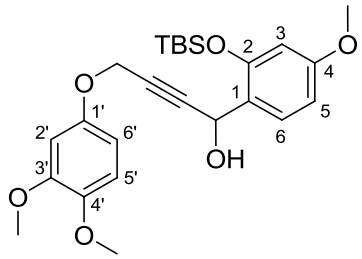
3.1.4 Synthesis of 1-(2-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl)-4-(3,4-dimethoxyphenoxy)but-2-yn-1-ol – 179



Scheme 53

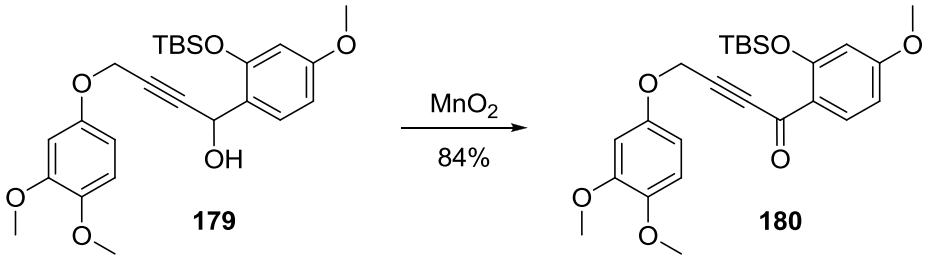
With the two components in hand, we were now in a position to couple them together by way of a nucleophilic attack of the alkyne anion onto the aldehyde **178**. In the similar process, Sames carried out their related coupling reaction and then with the crude product in hand, proceeded directly to the oxidation. We adopted this approach in our initial attempts to synthesise the secondary alcohol **179**. To this end, the propargyl ether **52** was dissolved in tetrahydrofuran and cooled to -85 °C. Treatment with *n*BuLi for 30 minutes was followed by the addition of the aldehyde **178**. The reaction was allowed to warm to rt and stirred for an hour. Following a workup, the crude material was dissolved in dichloromethane and manganese dioxide was added. After stirring under Ar for 18 h, TLC analysis indicated that five compounds were present relatively close to one another on the TLC plate. A challenging purification allowed us to identify these as the deprotected aldehyde **177**, the two intermediates **52** and **178**, the alcohol **179** and the alkynone **180**. The reaction was attempted several times, varying the reaction times and conditions in order to allow for full conversion of the starting materials. We had hoped that this would not only improve yields, but also allow for an easier separation. However, this proved unsuccessful as full conversion of the starting materials to **179** was never observed, making for a difficult separation, sometimes requiring repeated column chromatography. The yields were also very poor, usually in the range of 30%.

Having encountered these difficulties, it was decided that the crude material would be properly purified prior to performing the oxidation reaction. Thus, the coupling reaction was carried out as per the procedure described above (Scheme 53) and following purification, the alcohol **179** was afforded in a good yield of 81%.



Interestingly, the ^{1}H NMR spectrum of this coupled product was quite similar to the combined spectra of the individual starting materials. Clearly observable were the six aromatic signals, the bridging methylene signal and the three methoxy signals. In the far upfield region of the spectrum, the two distinct singlets from the TBS group were present. New signals as a result of the coupling reaction were the two doublets at 5.70 ppm and 2.58 ppm, due to the C*H*OH and O*H* protons, respectively, thereby confirming the success of the reaction. In the IR spectrum a broad absorption at 3490 cm^{-1} also confirmed the presence of the OH group. The *C*HOH appeared in the ^{13}C NMR spectrum at 60.29 ppm and as expected, the aldehyde signal was no longer present.

3.1.5 Synthesis of 1-(2-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl)-4-(3,4-dimethoxyphenoxy)but-2-yn-1-one – 180

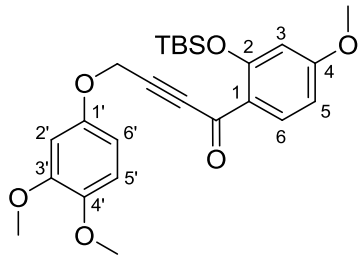


Scheme 54

In order to optimise the required oxidation of the alcohol **179** to the alkynone **180**, we investigated several solvent systems, specifically toluene, acetonitrile and dichloromethane. The best yields were obtained when using dichloromethane. Thus in the methodology employed, the alcohol **179** was dissolved in dichloromethane and an excess of 20 equivalents of activated manganese dioxide were added (Scheme 54), in accordance with the procedure by Sames. The reaction was left to stir for 18 h at rt at which point TLC analysis indicated that a trace amount of starting material was present. After several days of stirring, the reaction was stopped despite persistent traces of **179**. After filtration and purification, the desired product **180** was obtained as a yellow oil in a good yield of 84%.

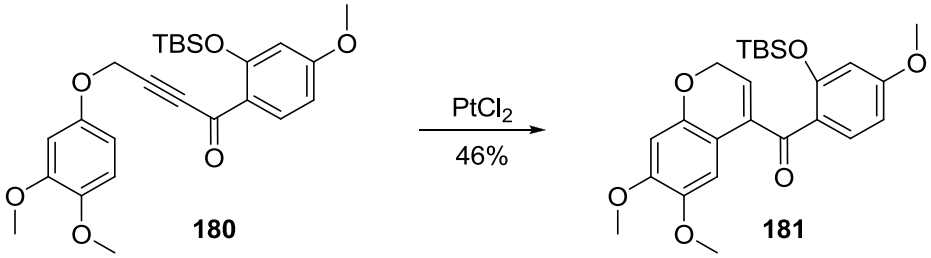
In an attempt to reduce the reaction time and promote the reaction to proceed to completion, the mixture was heated to reflux. The results were somewhat confusing as TLC analysis indicated

complete consumption of the starting material and conversion to the alkynone **180**, yet yields were lower than before. In a second attempt to reduce the reaction times, another addition of manganese dioxide was made during the course of the reaction, however, yields were once again lower and we reverted to the original procedure.



In the ^{1}H NMR spectrum, confirmation of the oxidation to the alkynone was attested to by the fact that both the C*H*OH and O*H* signals were no longer present. Moreover, the H_6 aromatic signal had shifted downfield as we would expect being *ortho* to the new carbonyl functionality. In the ^{13}C NMR spectrum, the downfield signal at 174.54 ppm attested to the presence of the carbonyl. The effect of added delocalisation was observed in the C_6 and C≡*C* signals, which were shifted noticeably downfield. The transformation to the alkynone was also observed in the IR spectrum, where the broad OH peak was replaced by a carbonyl signal at 1737 cm^{-1}.

3.1.6 Synthesis of (2-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl)(6,7-dimethoxy-*2H*-chromen-4-yl)methanone – 181



Scheme 55

There is a significant amount of literature precedence for the hydroarylation reaction, using a variety of catalysts and solvent systems. We investigated the reaction using three different catalytic systems and then applied the highest yielding conditions to the synthesis of the more complex target, rotenone.

In our first attempt at this reaction, we decided to employ a gold catalyst, similar to the procedure by Echavarren.[80] To this end, the alkynone **180** was dissolved in dichloromethane and the reaction

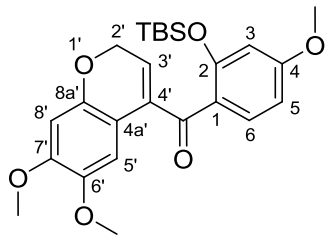
was degassed by bubbling Ar directly into the solution by means of a Pasteur pipette. $Au(PPh_3)Cl$ and $AgSbF_6$ were added and the reaction was left to stir at 23 °C for 2 h. TLC analysis at the end of this period indicated that no reaction had taken place. The reaction was therefore heated to 30 °C and left to proceed for another 18 h. Analysis by TLC now indicated that in addition to the alkynone, a second compound was present. The reaction was worked up and the crude material was purified by column chromatography. Interestingly, this new product was identified as the deprotected chromene **182.** The formation of **182** would have been a desirable outcome were it not for the fact that it was only obtained in an 8% yield.

As our second option for this reaction, we turned to the conditions employed by Sames and co-workers. In previous studies, the 6-*endo*-hydroarylation had been attempted using a range of catalysts such as $PtCl_2$ and $PtCl_4$.[48] Between the two, $PtCl_4$ was the superior of the two catalysts in that it had been more generally applicable to a wider range of substrates. Unexpectedly, in synthesising deguelin, higher yields were obtained when using $PtCl_2$. We therefore decided to test both of these Pt catalytic systems in our approach towards munduserone.

In our first attempt at these new conditions, we opted to use the Pt(IV) catalyst. To this end, the starting material **180** was dissolved in dioxane and the system was degassed by bubbling Ar directly into the solution. $PtCl_4$ was added against a flow of Ar and the reaction was heated to 65 °C. Following 2 h of stirring, TLC analysis indicated that the alkynone had not reacted and the temperature was then raised to 90 °C in an attempt to promote the reaction. After 18 h under these conditions, TLC analysis indicated that a new product had formed, although the starting material was still the predominant species. Purification by column chromatography afforded a small amount of the desired chromene **181** in a 10% yield.

Disappointed by the results, we decided to utilise the $PtCl_2$ catalytic system. Thus, into a two neck round bottom flask was placed the starting material **180** and dry toluene. The solution was degassed, and $PtCl_2$ was added (Scheme 55). The reaction was heated to 70 °C and allowed to stir under Ar for 18 h following which, TLC analysis indicated that a product of slightly higher R_f than the starting material had formed. Purification and NMR spectroscopic analysis confirmed that this was the desired chromene **181**. The highest yield obtained under these conditions was a poor 46%, although this was significantly better than the above two procedures.

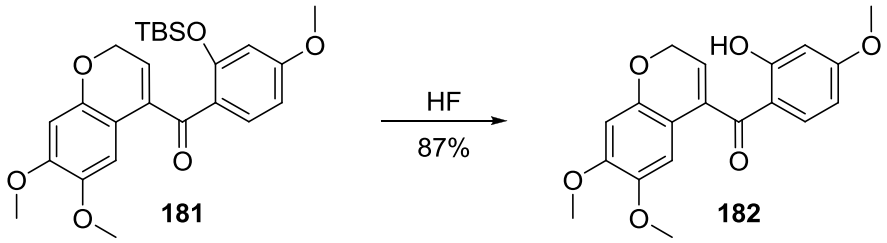
In light of the fact that we consistently recovered starting material from this reaction, we envisaged that a second addition of $PtCl_2$ would be made 18 h after the first. However, this saw a serious drop in yields to a dismal 10%! In a second attempt, a catalytic bed was set up in which a mixture of the catalyst and celite were packed tightly and the alkynone passed through it. We envisaged that the continuous removal of the product as it progressed through the catalytic bed would potentially drive the reaction, allowing for better yields. This proved to be unsuccessful and only starting material was recovered. In the end, we concluded that the disappointing yield could be attributed to steric effects caused by the bulky TBS group. This is a likely assumption as Sames and co-workers had employed small methyl protecting groups in the synthesis of their desired chromene which had been afforded in an excellent yield. Nevertheless, we were pleased to obtain the 6-*endo* chromene **181** as the exclusively produced product.



The somewhat different ^{1}H NMR spectrum in comparison with that of the starting material was the first pleasant sign that the reaction had proceeded. In the first instance, confirmation of the product was obtained by the number of aromatic protons which had been reduced to five, as we would have expected. The former proton situated on $C_{4a'}$ was lost upon conversion to the chromene, inevitably simplifying the signal of protons $H_{5'}$ and $H_{8'}$ to singlets. Protons H_6, H_5 and H_3 remained unchanged as an *ortho* coupled doublet, a doublet of doublets and a *meta* coupled doublet, respectively. Whilst the methylene protons were still present in the ^{1}H NMR spectrum, they no longer appeared as a singlet, but rather a doublet as they coupled to the alkene proton $H_{3'}$. Proton $H_{3'}$ appeared as a triplet in the alkene region at 6.11 ppm with a matching *J* value. The three closely spaced singlets, each integrating for three protons, and the far upfield singlets, integrating for nine and six protons, were consistent with the three methoxy and silyl protecting groups in the molecule. In the ^{13}C NMR spectrum, the number of carbon signals remained unchanged, however, there were several distinct features in the spectrum worth mentioning. The alkyne carbons at approximately 86 ppm in the precursor were both no longer present. These were replaced by two alkene signals of which the signal at 128.26 ppm could be assigned to $C_{3'}$, this being testament to the success of the reaction.

Regardless of the poor results obtained in the hydroarylation reaction, we decided to move forward with the synthesis of munduserone. Of course, this was only a model study and we were hopeful that with a bit of luck, the yields would be higher *en route* to rotenone.

3.1.7 Synthesis of (6,7-dimethoxy-*2H*-chromen-4-yl)(2-hydroxy-4-methoxyphenyl)methanone – 182



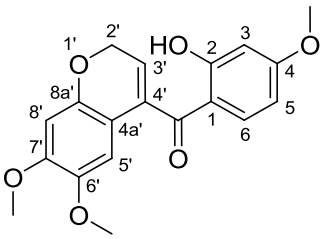
Scheme 56

With the desired chromene moiety **181** in hand, all that remained in the synthesis of munduserone was a desilylation to reveal the phenol, followed by the final ring closure. The deprotection was originally attempted using TBAF as the source of fluoride ions, and then the crude material was subjected to a ring closure using sodium acetate. A mixture of products was obtained which proved difficult to separate by chromatography. Indeed, analysis of the mixture by NMR spectroscopy revealed the presence of the silylated chromene **181**, the deprotected chromene **182**, as well as munduserone **8**.

Having encountered these difficulties, we decided to carry out the deprotection and ring closure steps sequentially. The silyl groups were cleaved by adding TBAF to a solution of the starting material **181** in tetrahydrofuran at 0 °C. Following 5 minutes of stirring, saturated ammonium chloride was added in order to protonate the phenoxide anion, thus preventing ring closure. Efforts to do so appeared to be in vain as a mixture of products was once again obtained, certainly due to spontaneous ring closure of the phenoxide anion upon deprotection. We hoped to take advantage of this and upon repeating the reaction, longer reaction times and higher temperatures were allowed in an attempt to synthesise munduserone in one step. Once again, a mixture of products was obtained.

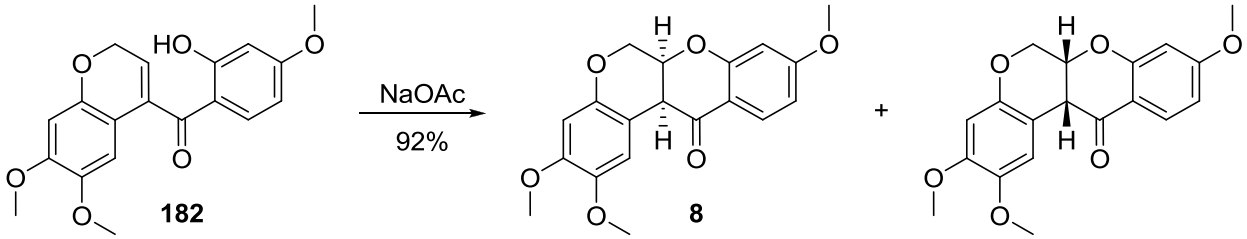
In a final attempt at the reaction, the deprotection was conducted using an acidic source of fluoride ions in the form of HF as this would facilitate immediate protonation of the formed phenoxide anion, thereby purposefully preventing the ring closure (Scheme 56). To this end, HF was added to a solution of starting material **181** in acetonitrile and the reaction was closely monitored by TLC. Following 30 minutes of stirring, TLC analysis showed that only starting material was present and a second addition of HF was made. TLC analysis after 1.5 h indicated that all the starting material

had reacted to what we hoped was the phenol. Following a workup and purification, the desired phenol **182** was obtained as a yellow solid in a good yield.



In the ^{1}H NMR spectrum, the absence of the two distinctive far upfield signals due to the TBS group attested to the success of the deprotection. The phenolic O*H* was observed as a singlet in the far downfield region at 12.60 ppm. The remainder of the spectrum was unchanged, although the chemical shift values of all signals varied slightly. In the ^{13}C NMR spectrum, the three signals due to the TBS group in the precursor were no longer present. The carbonyl functionality was seen in the IR spectrum as a stretching band at 1615 cm^{-1}.

3.1.8 Synthesis of (±)-munduserone – (±)-8



Scheme 57

With the phenol **182** in hand we were able to carry out the final step of the synthesis - the base-catalysed intramolecular oxo-Michael addition (Scheme 57). Although a number of mild bases can be utilised for this type of reaction, we opted for sodium acetate as this had been successfully used on our specific substrate **182** in an alternative synthesis of munduserone.[84] Thus, sodium acetate was added to a solution of the phenol **182**, dissolved in ethanol and the reaction was heated to reflux at 90 °C. Analysis of the reaction mixture by TLC after 10 minutes indicated that the reaction was progressing smoothly and after 2 h all the starting material had been consumed and a single product had formed. Following a workup and purification by column chromatography, munduserone was obtained in an excellent yield. Recrystallisation of the material in diethyl ether produced crystals suitable for X-ray analysis and confirmed that we had racemically synthesised **8** as the structure belonged to the racemic space group P-1. The enantiomers consisted of the *cis*-fused products with respect to protons H_{6a} and H_{12a}. The following unit cell dimensions were reported: a = 4.61 Å, b = 12.40 Å and c = 13.80 Å. The crystal structure was refined to an R-factor of 4.45% (Figure 5).

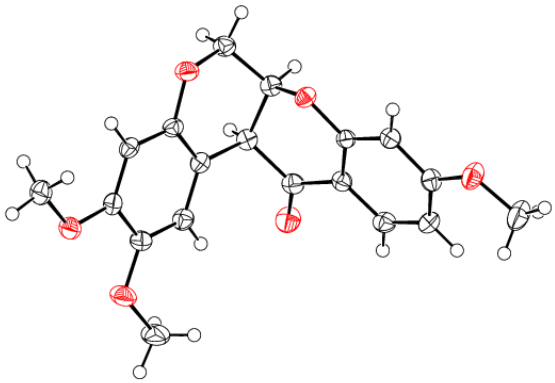
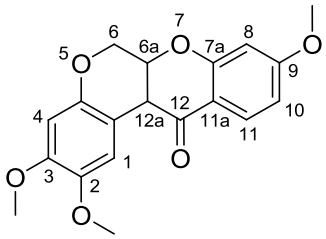


Figure 5



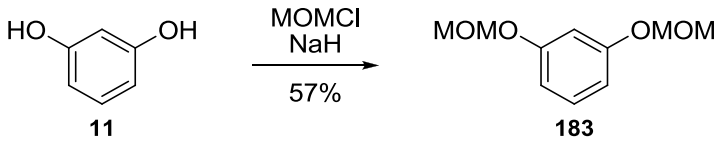
Several syntheses of munduserone have been achieved and these are well documented in the literature.[36, 42, 45] We were delighted by the fact that the accompanying analytical data in the form of NMR spectra and melting points compared well with those obtained for our product.[45] In the ^{1}H NMR spectrum, the loss of the O*H* singlet in the downfield region was one of several changes that attested to the success of the reaction. In the aromatic region, signals remained unchanged apart from their chemical shift values. Protons H_6, being adjacent to a stereogenic centre, were non-equivalent and gave rise to separate signals at 4.61 ppm and 4.18 ppm. These signals were identified using the HSQC spectrum, on the basis that they were the only methylene protons in the molecule. For clarity purposes, these shall be denoted H_6 and $H_{6'}$. Proton H_6 at 4.18 ppm was coupled only to $H_{6'}$, hence the doublet. Over and above this, proton $H_{6'}$ was also coupled to H_{6a}. Therefore, $H_{6'}$ and H_{6a} gave rise to the doublet of doublets and an apparent triplet at 4.61 ppm and 4.94 ppm, respectively. By process of elimination, the signal at 3.84 ppm was assigned to proton H_{12a}, appearing as a doublet as a result of coupling to proton H_{6a}. Finally, the methoxy groups gave rise to the three singlets in the downfield region of the spectrum. In the ^{13}C NMR spectrum, the far downfield signal at 189.19 ppm was consistent with the carbonyl group. This was visible in the IR spectrum as a sharp absorption at 1673 cm^{-1}. The measured melting point compared well with the literature value.[84]

Thus, we had successfully synthesised munduserone from commercially available 3,4-dimethoxyphenol in six steps and an overall yield of 23%. Having completed the model study, we then proceeded to the synthesis of rotenone. In the section to follow we will describe the synthesis

of the dihydrobenzofuran and subsequent application of the methodology used in the model study to complete the synthesis of rotenone.

3.2 Synthesis of rotenone

3.2.1 Synthesis of 1,3-bis(methoxymethoxy)benzene – 183

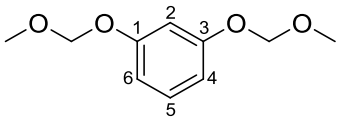


Scheme 58

Having completed the model study, we had established that our proposed synthesis of rotenone was viable. We began our synthesis of rotenone with commercially available resorcinol. At the start of the synthesis, protecting groups were needed that would satisfy the following requirements: Firstly, we required them to be good *ortho* directors, thus facilitating lithiation between the two oxygen substituents to install the required allyl group. We also had to consider that these protecting groups would have to be selectively removed at a later stage in the synthesis and that the conditions required for this would need to be compatible with the remaining functional groups on the molecule. Although MOM groups are well-reputed *ortho* directors, these would be incompatible later in the synthesis and so a protecting group switch was needed. Therefore we envisaged that, following allylation, the diol would be protected as a silyl ether for the remainder of the synthesis.

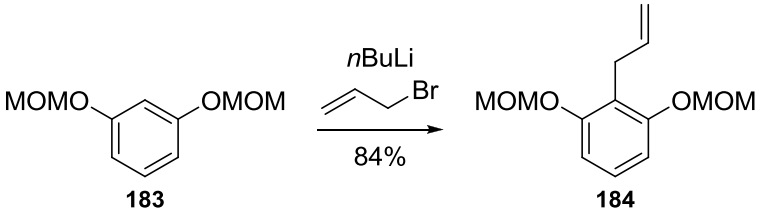
The protection of commercial resorcinol **11** to form 1,3-*bis*(methoxymethoxy)benzene **183** is a well-known reaction and many procedures are available, using a variety of solvent systems and bases.[85, 86] Accordingly, resorcinol **11** in dimethylformamide was treated with sodium hydride and methoxymethyl chloride (Scheme 58). The reaction was left to stir at rt for 18 h and was then treated with ammonia solution to quench the unreacted toxic methoxymethyl chloride. Following a workup, purification was achieved by Kugelrohr distillation to afford the MOM protected product **183** as a clear oil.

The ^{1}H NMR spectrum was pleasantly uncomplicated owing to symmetry within the molecule and compared well with that in the literature.[86, 87] Three signals appeared in the aromatic region, as expected. The two triplets owing to protons H_5 and H_2 were a result of coupling to protons H_4 and H_6. *Ortho* and *meta* coupling constants of 8.1 Hz and 2.1 Hz allowed us to distinguish between protons H_5 and H_2, respectively. Protons H_4 and H_6 gave rise to a doublet of doublets, and their



coupling constants matched those of protons H_5 and H_2. Two singlets integrating for four and six protons were consistent with the methylene and methyl groups, respectively, of the MOM protecting groups, and verified that we had synthesised the desired product. In the IR spectrum, an intense peak at 1073 cm^{-1} was characteristic of a C-O stretch in an aromatic ether.

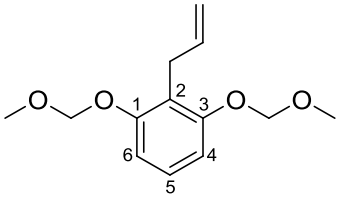
3.2.2 Synthesis of allyl-1,3-*bis*(methoxymethoxy)benzene – 184



183 **184**

Scheme 59

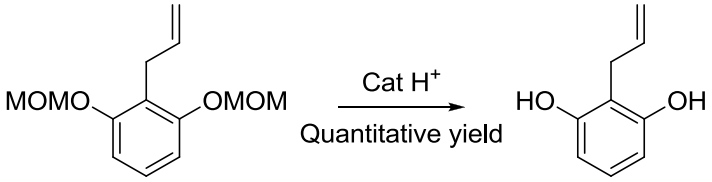
With the MOM protecting groups in place, we were now able to introduce the allyl moiety by means of directed *ortho* metalation (DoM). By inductive effects, methoxymethyl ethers increase the acidity at the *ortho* position on an aromatic ring and upon lithiation, stabilise the aryllithium in a six-membered chelate.[87, 88] With two MOM groups in place we were confident that lithiation, followed by allylation, would take place in a position *ortho* to both groups (Scheme 59). To this end, *n*BuLi was added to a solution of the *bis*-MOM protected resorcinol **183** in tetrahydrofuran at 0 °C and the reaction was stirred for 1.5 h during which the colour intensified from yellow to orange. The solution became clear as an excess of allyl bromide was added. The reaction was stirred for 1 h at 0 °C and then allowed to warm to rt. TLC analysis after 18 h indicated that a new product, with a slightly higher R_f than the starting material, had formed and after workup and purification, the desired allylated product **184** was produced in a good yield.



As a result of installing the allyl chain, the aromatic signals were reduced to a simple triplet at 7.10 ppm and a doublet further upfield at 6.77 ppm, due to protons H_5 and H_4 and H_6, respectively, which were also *ortho* coupled to one another. The single triplet for proton H_5 indicated that symmetry within the molecule had been maintained. This was supported by the fact that the triplet due to proton H_2 no longer existed. New signals in the alkene region integrating for

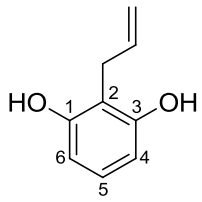
three protons in total, acted as confirmation of a successful reaction. The internal alkene proton produced a multiplet as a result of coupling to the adjacent methylene protons and non-equivalent geminal alkene protons. Finally, the MOM groups still appeared to be intact as the singlet integrating for the four equivalent methylene protons was still present. The methoxy protons existed as an overlapping signal with the benzylic methylene protons, integrating for eight hydrogens in total. The additional three signals in the ^{13}C NMR spectrum could be accounted for by the allyl side chain.

3.2.3 Synthesis of 2-allylbenzene-1,3-diol – 185



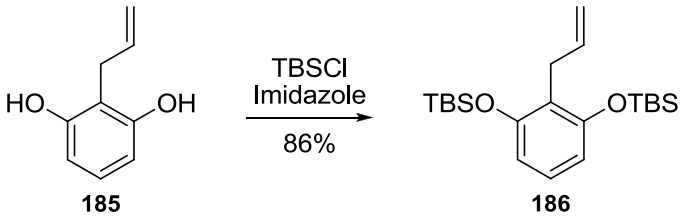
Scheme 60

Having successfully utilised the MOM groups as *ortho* directors to install the allyl chain, we then carried out the protecting group switch at this point in the synthesis, as no other acid sensitive groups were present. The deprotection was conducted by dissolving the allylated compound **184** in tetrahydrofuran and methanol and adding a catalytic amount of aqueous HCl (Scheme 60). The reaction was heated to reflux for 18 h at which point TLC analysis indicated that in addition to the starting material, two more polar species were present which could be accounted for as the mono- and completely deprotected compounds. A second addition of acid was made and the reaction was left to proceed for 18 h, upon which TLC indicated complete conversion to what we had assumed to be the fully deprotected compound. Following a workup, the product was purified by column chromatography and identified as the diphenol **185**, obtained as a pale yellow oil in quantitative yield. Reaction times varied based on the scale of the reaction, requiring up to three days in some cases. Acid was added in small portions according to previous work by Pelly which showed that increasing the amount of acid initially added, would not allow for faster reaction times and in fact, had an adverse effect on the yield.[46, 47]



The deprotection proved to be successful as confirmed by the absence of the intense OCH_2 and OCH_3 singlets associated with the MOM group in the ^{1}H NMR spectrum. In connection with this, the diol appeared as a singlet integrating for both protons at 5.09 ppm, due to symmetry within the molecule. The aromatic and alkene signals were unchanged apart from their chemical shifts and in fact, the methylene protons could now be clearly seen as a doublet, where they previously overlapped with the methoxy groups. One of our main concerns with this particular reaction was that of potential isomerisation of the double bond into the internal, more substituted position, also in conjugation with the aromatic system. If the double bond had isomerised, two alkene protons and a methyl group would have appeared in the ^{1}H NMR spectrum. Since there were still three protons in the alkene region and a methylene rather than a methyl group, we were confident that isomerisation had not taken place upon heating. In the ^{13}C NMR spectrum, signals associated with the MOM protecting groups had also disappeared. Carbons C_1 and C_3 had shifted slightly upfield due to less of a deshielding effect upon loss of the MOM groups. A broad stretch in the IR spectrum at 3381 cm^{-1} attested to the presence of the alcohols.

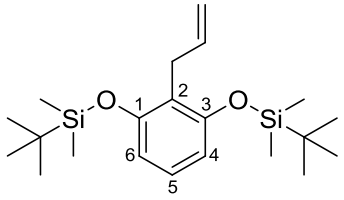
3.2.4 Synthesis of 2-allyl-1,3-*bis*(*tert*-butyldimethylsilyloxy)benzene – 186



Scheme 61

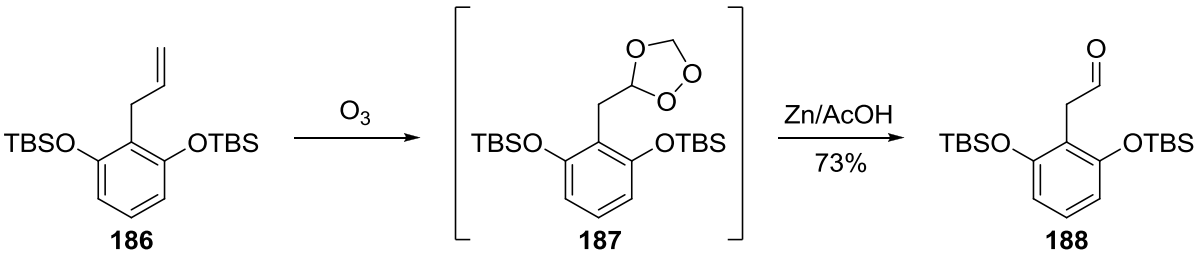
Tert-butyldimethylsilyl protecting groups were then introduced which we intended to use for the remainder of the synthesis *en route* to the required dihydrobenzofuran (Scheme 61). TBS groups would be stable under the envisaged steps to follow and could be cleaved under mild conditions later in the synthesis. Therefore, the allylated diol **185** was dissolved in acetonitrile and treated with an excess of imidazole and TBSCl. The reaction was stirred at rt under Ar and was analysed by TLC at 1 h intervals. After the first 2 h, TLC analysis indicated that, in addition to the starting material, two new compounds with a significantly higher R_f had formed. We had assumed that these were the mono-protected species and the desired product. After 18 h, the presumed mono-protected

species was only present in trace amounts by TLC. Following a workup and purification by column chromatography, the *bis*-silyl ether **186** was furnished as a yellow oil in a good yield.



The appearance of two new intense signals in the far upfield region of the ^{1}H NMR spectrum was a pleasing sign that the silyl protection reaction had been successful. The two singlets at 1.00 ppm and 0.22 ppm integrated for 18 and 12 protons, respectively, due to the two TBS protecting groups. These manifested as just two signals due to symmetry within the molecule. The signal at 1.00 ppm accounted for the two C(CH_3)$_3$ groups and the signal at 0.22 ppm, for the two Si(CH_3)$_2$ protons. This was accompanied by changes in the ^{13}C NMR spectrum as three new signals appeared in the far upfield region at 25.89 ppm, 18.32 ppm and -4.05 ppm. As for the remaining aromatic and alkene signals, these were almost identical to that of their precursor apart from slight changes in their chemical shifts. The distinctive OH stretch in the IR spectrum of the precursor was no longer present.

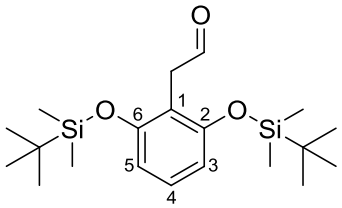
3.2.5 Synthesis of 2-(2,6-*bis*(*tert*-butyldimethylsilyloxy)-phenyl)acetaldehyde – 188



Scheme 62

With the silyl protecting groups in place, we could now proceed with the remaining steps in the synthesis. The first of these required that the alkene **186** be converted to the aldehyde **188** by employing one of several methodologies at our disposal, e.g. use of osmium tetroxide allows for the formation of the corresponding diol which, upon treatment with sodium periodate, is oxidatively cleaved, affording the desired aldehyde.[89] As an alternative method, ozonolysis provides for a convenient conversion of the alkene to the aldehyde. In this process, a pericyclic reaction between the alkene and ozone followed by a rearrangement gives way to an ozonalide intermediate **187** which, when treated with a reducing agent, can be converted to the aldehyde. This may be achieved using reagents such as dimethylsulfide, triphenylphosphine or a zinc/acetic acid combination.[90] We

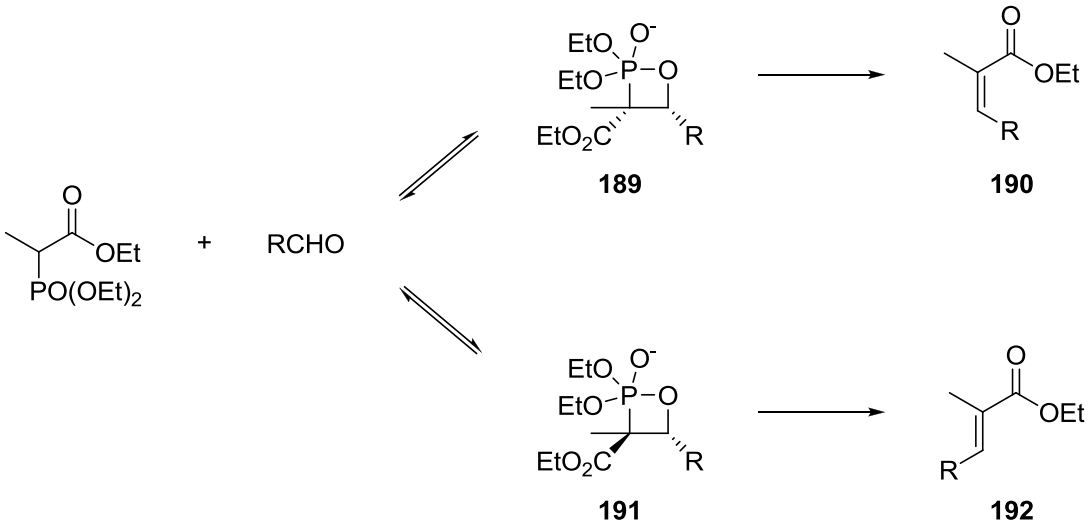
opted for the ozonolysis reaction as we had access to an ozone generator (Scheme 62). Thus, a round bottom flask containing the starting material **186** in dichloromethane was immersed in a frozen acetone slurry bath which was approximately at -80 °C. These low temperature conditions were a precaution in order to avoid over oxidation of the electron rich aromatic ring system. Ozone gas was bubbled into the reaction mixture for three minutes, then the ozone generator was switched off and oxygen gas was bubbled into the reaction in order to purge excess ozone from the solution. TLC analysis was used to monitor the reaction after every addition of ozone gas. After 15 minutes of repeating this process, we were satisfied that the reaction had gone to completion and an excess of zinc and acetic acid were added in order to reduce the ozonalide intermediate **187**. The reaction was slowly warmed up to 5 °C at which point TLC analysis, using DNPH as a dye, indicated complete conversion of the intermediate to the corresponding aldehyde. At this elevated temperature a second product also began to form. We believed that this was the diol as TBS groups may be cleaved under acidic conditions. At this point, the zinc was immediately filtered off and the reaction was quenched using sodium bicarbonate in order to neutralise excess acetic acid. Following a workup, the crude material was purified by column chromatography to afford to the aldehyde **188** in an unexceptional, 73% yield.



The fact that ozonolysis had successfully occurred was immediately confirmed upon scrutinising the ^{1}H and ^{13}C NMR spectra. Amongst the ^{1}H NMR spectral signals, the most pertinent signal was the new downfield singlet at 9.60 ppm owing to the newly formed aldehyde. The alkene protons had also disappeared and all that remained was a simple doublet integrating for two protons, due to the methylene functionality. The methylene protons had shifted slightly downfield as a result of the deshielding effect of the carbonyl. They were also coupled weakly to the aldehyde proton as was seen by the small coupling constant of 1.5 Hz. Shoulders on the aldehyde signal confirmed the coupling to its adjacent protons. The obvious addition to the ^{13}C NMR spectrum at 200.86 ppm attested to the presence of a carbonyl. The two alkene carbons had also disappeared whilst the methylene carbon was present. The existence of the carbonyl was further verified by a strong absorption band in the IR spectrum at 1728 cm^{-1} due to the C=O stretch.

3.2.6 Synthesis of *(E)*-ethyl-4-(2,6-*bis*(*tert*-butyl-dimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 193

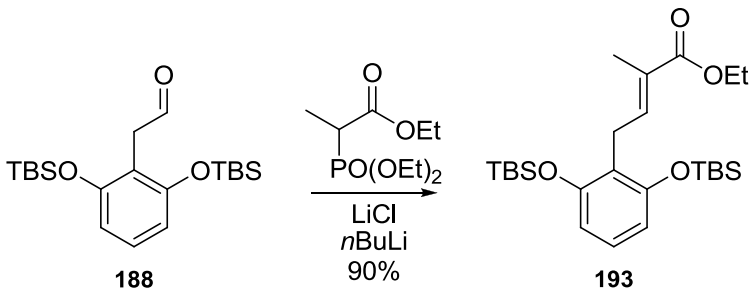
With the aldehyde in place, we were now in a position to carry out a Wittig reaction to begin the process of constructing the required functionality for the Trost cyclisation to follow later. In generating the alkene it is important to consider that Wittig reactions can give rise to both the *(E)*- and *(Z)*- geometrical isomers, and the predominating isomer depends on the nature of the ylide. The *(Z)*- geometrical isomer **190** is generally the product of a reaction between an unstabilised ylide and an aldehyde, proceeding via the kinetically preferred *syn* arrangement of the oxaphosphetane ring intermediate. In contrast to this, a modification on the Wittig reaction known as the Horner-Wadsworth-Emmons reaction, in known for its high selectivity of the *(E)*- alkene **192** (Scheme 63). The key feature in this method is that it employs a stabilised ylide (in which the anion is stabilised by conjugation into the carbonyl system) and, in light of the fact that formation of the *syn* intermediate **189** is reversible, thermodynamic control dominates, eventually leading to the more stable *anti* arranged intermediate **191** and hence the *(E)*- isomer **192**.[91, 92] In our synthesis, selective formation of the *(E)*- isomer was a crucial factor that would become important in the planned stereoselective Pd π-allyl cyclisation which was to follow as contamination by the opposite geometrical isomer would lead to diminished ee's.



Scheme 63

Therefore, we set our sights on converting the aldehyde **188** to the ester 1**93** using this methodology. The required Horner-Wadsworth-Emmons reagent ethyl 2-

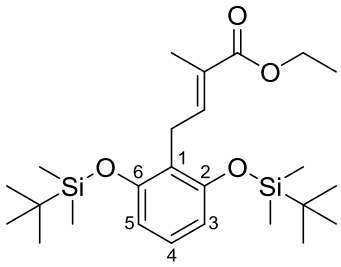
(diethoxyphosphoryl)propanoate was synthesised from ethyl 2-bromopropanoate and triethylphosphite. With this reagent in hand, we then proceeded to the Horner-Wadsworth-Emmons reaction. LiCl and 2-(diethoxyphosphoryl)propanoate were dissolved in acetonitrile and the solution was cooled to 0 °C. DBU was added slowly and the reaction was left to proceed at 0 °C for 15 minutes, thus allowing for the formation of the ylide. The aldehyde **188**, dissolved in acetonitrile, was then added dropwise and the reaction was allowed to warm to rt. After several hours, TLC analysis indicated that starting material was still present and the reaction was left to proceed for 18 h during which the colour changed from yellow to brown. TLC analysis indicated that in addition to the newly formed product and the phosphine oxide, starting material was still present. Despite this, the reaction was quenched and following a workup, the crude material was purified by column chromatography to indeed afford the product **193**, although in a disappointing yield of 28%. In an attempt to overcome this problem, a longer time period was permitted for the formation of the ylide upon the addition of DBU. Once the aldehyde **188** was added, the temperature was maintained at 0 °C for several hours before allowing to warm to room temperature. These changes only improved the yield marginally to 39%. We therefore decided on a different strategy - rather than adding the aldehyde to the ylide, we opted to generate the ylide separately and then add this by canula to a flask containing the aldehyde dissolved in acetonitrile. Disappointingly, the yield remained consistent at 38%.



Scheme 64

Having considered various strategies for the combination of the ylide and aldehyde **188** without success, we now turned our attention to using a different base such as *n*BuLi (Scheme 64).[72] To this end, the ylide was generated in tetrahydrofuran by adding LiCl and the phosphonate ester and then after cooling to at 0 °C, the *n*BuLi was added dropwise. After 30 minutes of stirring, the ylide was carefully transferred by canula to a round bottom flask containing the aldehyde **188** dissolved in acetonitrile, also at 0 °C. The reaction was left to stir under Ar for 18 h. The best yields of the desired product **193** were obtained when maintaining the reaction temperature at 0 °C for the full

18 h period and we were eventually able to significantly improve the yield to a very acceptable 90%.



The ^{1}H NMR spectrum was pleasingly different from its precursor. One of many new features in the spectrum included a quartet and a triplet, which were coupled to one another as part of the ethyl propanoate moiety. In addition, the downfield aldehyde signal was no longer present. The aromatic region was once again marked by the familiar triplet and doublet at 6.94 ppm and 6.46 ppm, respectively. There was also an additional signal in the downfield region at 6.80 ppm due to the alkene proton. This proton was significantly more deshielded than the alkene protons in its precursors, certainly due to conjugation of the alkene into the carbonyl system. This interesting signal appeared as a triplet of quartets due to coupling to the adjacent methylene protons (J=6.3 Hz), followed by weak, long range coupling to the methyl group (J=1.1 Hz). The methylene and methyl protons appeared as doublets at 3.48 ppm and 1.92 ppm, respectively. The ^{13}C NMR spectrum exhibited five additional signals, as expected. The signal at 168.20 ppm due to the carbonyl of the ester was predictably further upfield than that of its aldehyde precursor. Also worth mentioning are the additional alkene signals at 142.40 ppm and 121.16 ppm, the latter being the quaternary carbon of the alkene. The ethyl signals that appeared at 60.14 ppm and 14.25 ppm attested to the success of the reaction. In the IR spectrum, a strong signal at 1709 cm^{-1} provided for additional verification that the carbonyl of the ester was present.

A very important feature of this reaction was our desire to obtain exclusively the *(E)*- geometrical isomer and indeed, by means of 2D NOE experiments, we were able to confirm that the *(E)*- alkene had been synthesised (Figure 6). Several intense enhancements were observed, yet the weakest of these provided the most convincing evidence. Upon irradiation of the benzylic protons, an enhancement in the methyl group was observed. This confirmed that the *(E)*- geometrical isomer **193** had been synthesised as these protons would be too far apart in the *(Z)*- isomer **194** to see an enhancement (Figure 7). Naturally, we were aware of the fact that a single interaction does not necessarily provide for conclusive evidence and we were cautious of our deductions. These would be verified in subsequent steps of the synthesis where further NOESY experiments would provide for more definitive results.

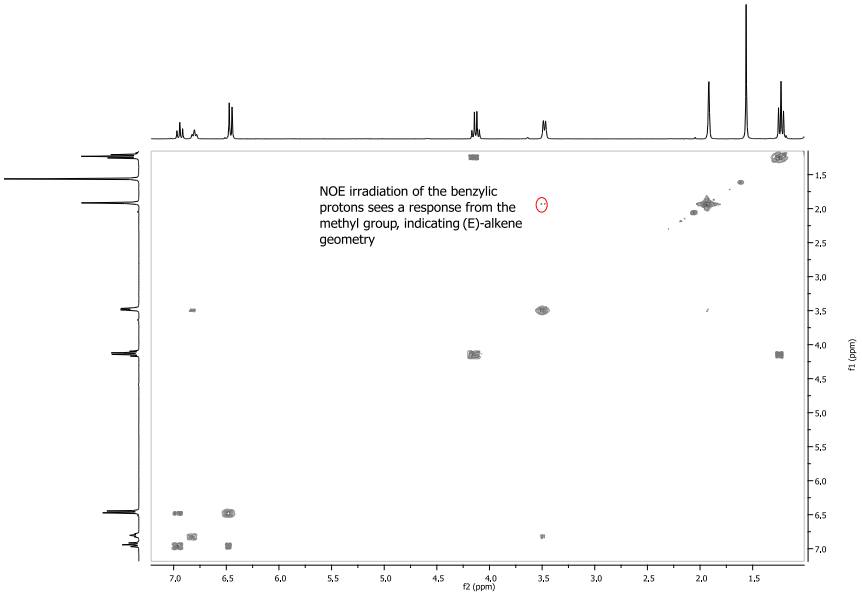
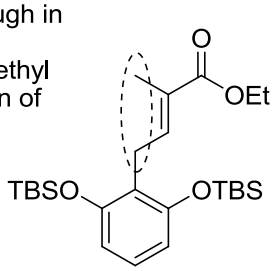
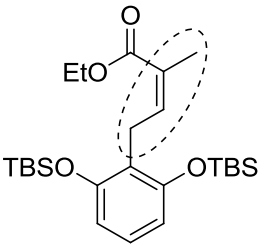


Figure 6

Protons are close enough in the *(E)*- isomer and an enhancement in the methyl protons upon irradiation of the benzylic protons is observed.



(E)- geometrical isomer
193

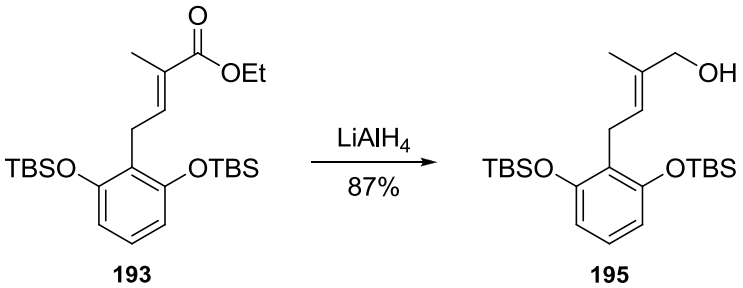


(Z)- geometrical isomer
194

Benzylic and methyl protons are too far apart in the *(Z)*- isomer, hence an enhancement would not be observed.

Figure 7

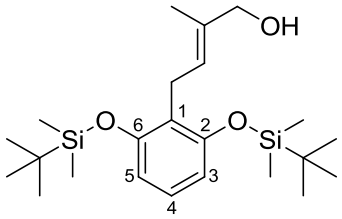
3.2.7 Synthesis of *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 195



193 **195**

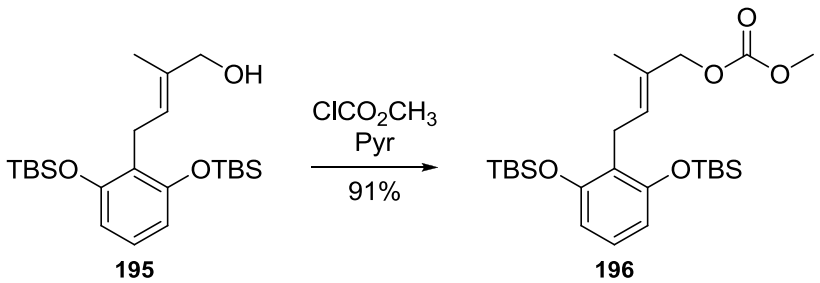
Scheme 65

In order to introduce the carbonate functionality needed in the succeeding Pd mediated reaction, the ester **193** would first have to be reduced to the alcohol **195**, following which, the carbonate would be installed (Scheme 65). To this end, the ester **193** was dissolved in dry tetrahydrofuran and once cooled to 0 °C, $LiAlH_4$ was added in small portions. The reaction was closely monitored by TLC at 20 minute intervals as we found that upon prolonged exposure to these reaction conditions, a base spot would form due to cleavage of the silyl protecting groups. After approximately 1 h, TLC analysis indicated that most of the starting material had been converted to a more polar product of lower R_f. The reaction was left to proceed until complete consumption of the starting material was observed. This varied based on the scale of the reaction, sometimes requiring up to 3 h. Following a workup, the crude material was purified by column chromatography, giving the desired alcohol **195** in a good yield.



In the ^{1}H NMR spectrum, absence of the triplet and quartet signals due to the ethyl side chain provided the first evidence that the reduction had successfully taken place. Whilst the alkene signal was still present, it was noticeably less deshielded at 5.43 ppm as it was no longer in conjugation with a carbonyl. Since it was still coupled to the benzylic and methyl protons, its signal continued to be a triplet of quartets. The new signal appearing at 3.92 ppm integrating for two protons, was due to the new methylene C*H*$_2$OH protons. The O*H* produced a broad singlet at 1.33 ppm. In the ^{13}C NMR spectrum, the downfield carbonyl signal that was observed in the precursor had disappeared. Signals due to the ethyl moiety were also absent, however, there was a new signal at 69.18 ppm due to the *C*H$_2$OH carbon. We could also deduce, from the broad stretch at 3330 cm^{-1} in the IR spectrum, that an alcohol had been synthesised.

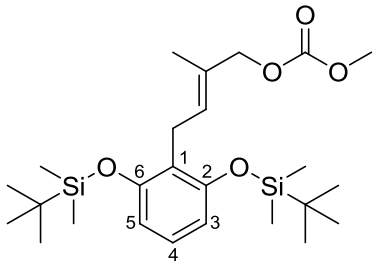
3.2.8 Synthesis of *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 196



Scheme 66

In one of the last few transformations of this sequence, the alcohol **195** was converted to a carbonate **196** as this would act as a good leaving group in the cyclisation step. With an acetate in place, Pelly *et al.* showed that yields obtained in the Pd mediated synthesis were poor, attributing this to the potential re-attack of the acetate anion onto the Pd complex.[46, 47] Subsequent use of the carbonate saw a drastic improvement in the yield. This is due to the fact that upon decarboxylation, carbon dioxide and methanol are released thus circumventing the potential re-attack, not to mention the favourable entropic effects in driving the reaction forward.

To this end, pyridine and methyl chloroformate were added to a solution of the alcohol **195** in dichloromethane, at 0 °C (Scheme 66). The reaction was allowed to warm to rt and once full conversion to a new product was observed by TLC, the reaction was stopped. Generally, the reaction required 1 h to go to completion, or slightly longer for larger scale reactions. Following a workup, the crude material was purified by column chromatography, furnishing the carbonate **196** as a clear oil in an excellent yield.



The most convincing evidence for the formation of the carbonate was the presence of the new singlet in the upfield region at 3.76 ppm, due to the OCH_3 protons. The OCH_2 signal had also shifted significantly downfield as would be expected on introducing a nearby carbonyl. Other than this, the ^{1}H NMR spectrum of the product and precursor were very similiar, apart from slight shifts further downfield in all signals. The ^{13}C NMR spectrum exhibited, *inter alia*, a signal at 155.83 ppm due to the carbonyl of the carbonate functionality. A new signal at 54.58 ppm as a result of the methoxy group also attested to the success of the reaction. Over and above the information derived from the NMR spectra, the C=O stretching absorption observed in the carbonyl region of the IR spectrum at 1749 cm^{-1}, acted as final confirmation that the carbonate had indeed been synthesised.

We were now in a position to obtain more convincing evidence that we had indeed synthesised the desired *(E)*- geometric isomer. As observed before in the NOESY experiments of **193**, an interaction between the benzylic and methyl protons of **196** was once again consistent with the desired isomer. More concrete evidence came in the form of a second enhancement as upon

irradiation of the alkene proton, a clear response was observed from the newly installed OCH_2 protons (Figure 8). Clearly, the *(E)*- alkene **196** had been synthesised as this interaction would not be possible in the *(Z)*- alkene **197** where these protons would spatially be very far from one another (Figure 9). In the *(E)*- geometry **196** the alkene proton is in close proximity to the OCH_2, hence the observed enhancement. We could now be confident that the *(E)*- alkene had indeed been synthesised in the earlier Horner-Wadsworth-Emmons reaction!

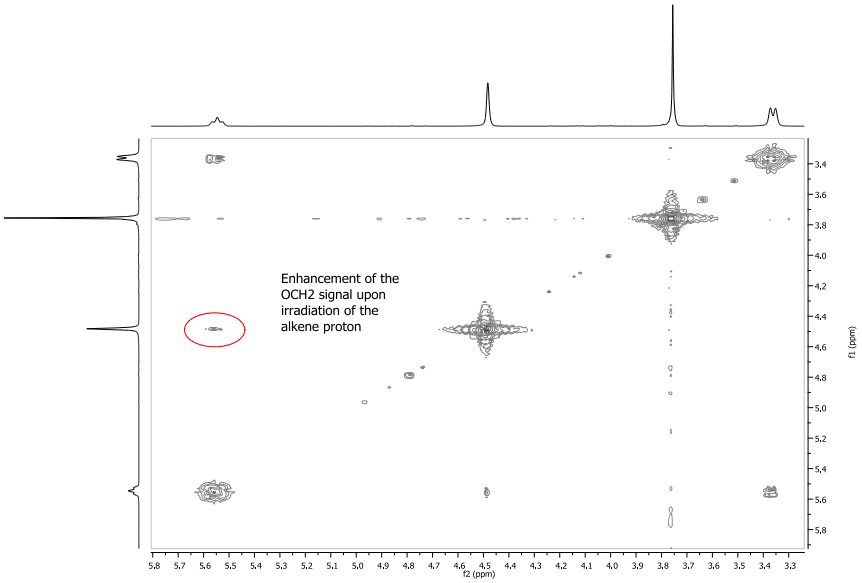
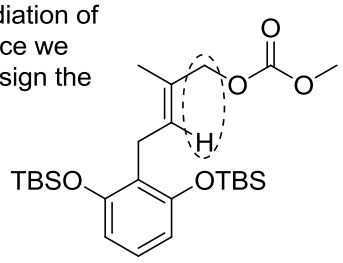
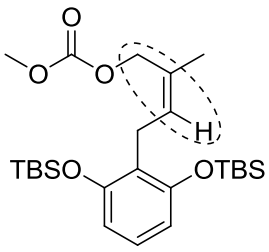


Figure 8

An enhancement is observed in the OCH_2 upon irradiation of the alkene proton, hence we can unambiguously assign the *(E)*- geometry.



(E)- geometrical isomer
196

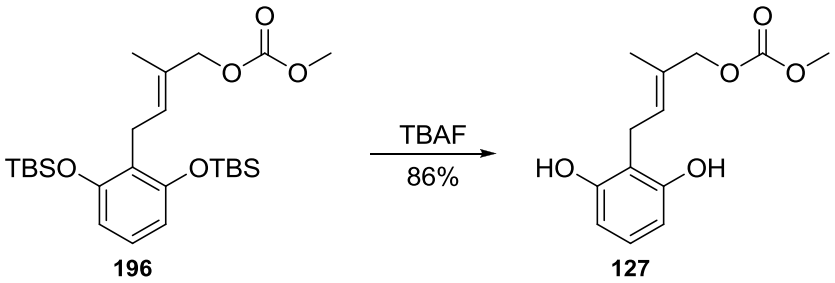


(Z)- geometrical isomer
197

The protons are too far apart in the *(Z)*- isomer to observe an enhancement.

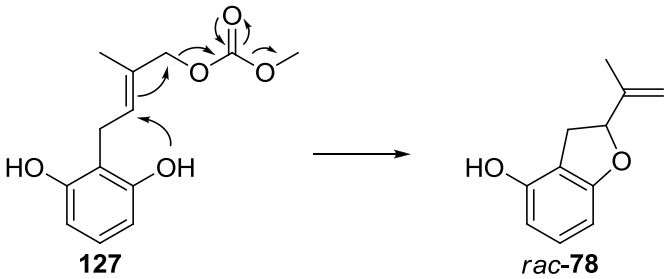
Figure 9

3.2.9 Synthesis of *(E)*-4-(2,6-dihydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 127

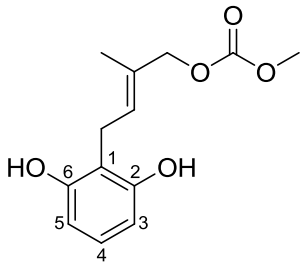


Scheme 67

All that remained in preparation for the key step of the synthesis was to liberate our phenolic nucleophile by the removal of the silyl protecting groups (Scheme 67). Therefore, **196** in tetrahydrofuran was treated with TBAF at 0 °C. TLC analysis after 5 minutes indicated complete conversion to a single product. Following a workup using ammonium chloride, purification by column chromatography afforded the diol **127** in a good yield. Interestingly, the diol **127** would spontaneously cyclise with time to afford the dihydrobenzofuran *rac*-**78** (Scheme 68). Although the diol would be cyclised in the subsequent step, we hoped to carry out the cyclisation stereoselectively and contamination by *rac*-**78** would have eroded our enantiomeric excess. Hence, the diol was kept in the freezer so as to prevent spontaneous cyclisation prior to our stereocontrolled reaction.



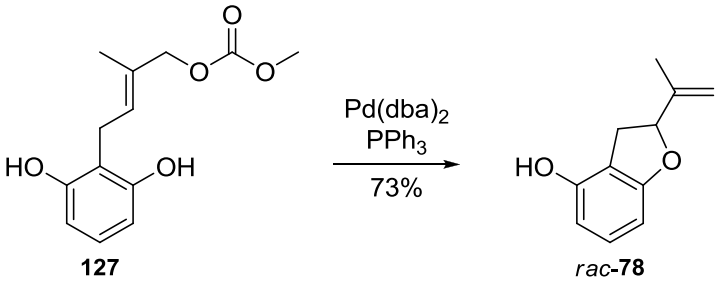
Scheme 68



The deprotection was clearly evident from two main changes observed in the ^{1}H NMR spectrum of the diol **127**. The noticeable loss of the intense, far upfield signals due to the former protecting TBS groups meant that the deprotection had proceeded successfully. In conjunction with this, a prominent, broad singlet integrating for two protons at 5.00 ppm indicated

that the two equivalent phenolic hydroxyl protons were present. The remaining signals continued to follow the familiar pattern and had only changed slightly in their chemical shifts. In the ^{13}C NMR spectrum, the three far upfield signals due to the TBS group had disappeared. The OH was present in the IR spectrum as a broad stretching band at 3397 cm^{-1}. Unfortunately, not all the ethyl acetate could be removed from the product despite many hours on high vac. This was possibly an effect of hydrogen bonding to the alcohol groups.

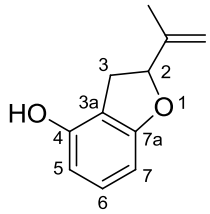
3.2.10 Synthesis of racemic 2-isopropenyl-2,3-dihydrobenzofuran-4-ol – *rac*-78



127 *rac*-**78**

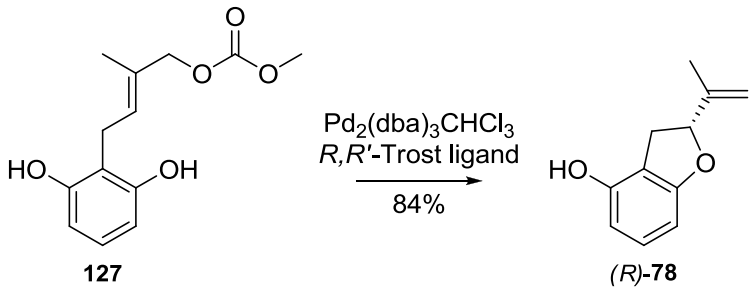
Scheme 69

Having successfully synthesised substrate **127**, we were now in a position to carry out the key Pd π-allyl mediated cyclisation. We decided that the dihydrobenzofuran would initially be synthesised without stereochemical control in order to optimise the yields before utilising the costly Trost ligand (Scheme 69). In conducting the reaction racemically, triphenylphosphine was utilised as the ligand. To this end, a solution of dichloromethane and $Pd(dba)_2$ was degassed by bubbling Ar directly into the solution. Four equivalents of triphenylphosphine were added and the violet solution eventually turned light orange as ligand exchange occurred, thus generating $Pd(PPh_3)_4$ *in situ*. Acetic acid was added followed by the carbonate **127** and the reaction was heated to reflux for 18 h. Although acetic acid was not necessarily required in the racemic synthesis, it was added to the reaction so that the system closely resembled the chiral cyclisation reaction in which acetic acid was used to slow down the reaction, allowing for a high enantiomeric excess. TLC analysis after 18 h indicated complete conversion of the starting material to a single product. Following purification by column chromatography, the dihydrobenzofuran *rac*-**78** was afforded as a clear oil in a moderate yield and as expected, racemically (confirmed by chiral HPLC of the acetate derivative as we found that the enantiomers of *rac*-**78** did not separate well on the chiralcel OJ column).



The ^{1}H NMR spectrum was completely different from its starting material. The OC*H*$_2$ and OC*H*$_3$ singlets associated with the carbonate had disappeared and in their place, a number of more complex signals were present. Where there were previously two aromatic signals, loss of symmetry within the molecule had led to three signals as protons H_5 and H_7 were no longer in equivalent environments. Despite the lack of symmetry, H_6 appeared to produce a triplet at 6.99 ppm as it coupled to its adjacent protons. Protons H_7 and H_5 coupled to H_6, thereby generating two doublets at 6.43 ppm and 6.31 ppm, respectively. The coupling constants of these protons matched one another at 8.0 Hz. Proton H_2 coupled to the benzylic protons H_3 to produce a triplet at 5.21 ppm with a coupling constant of 8.8 Hz. The alkene protons were non-equivalent thereby giving rise to two signals with coupling constants so small, they appeared as singlets at 5.09 ppm and 4.91 ppm. The phenolic O*H* existed as a singlet at 4.88 ppm. Being adjacent to a stereogenic centre, the diastereotopic protons H_3 found themselves in different chemical environments thus each produced a doublet of doublets upon coupling to one another as well as to proton H_2. Finally, the single CH_3 in the molecule was observed as a singlet in the upfield region at 1.78 ppm.

3.2.11 Synthesis of (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – *(R)*-78



127 *(R)*-**78**

Scheme 70

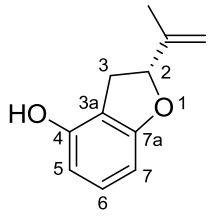
Having synthesised the dihydrobenzofuran racemically, we then moved on to the stereoselective synthesis (Scheme 70). In the chiral synthesis, the bidentate *R,R'*-Trost ligand was employed in place of triphenylphosphine. In theory, two ligands will complex to a single Pd and in using 2.9 equivalents of the Trost ligand to the palladium in our initial attempt, the ligand was in slight excess of the metal. This was important as previous work showed that Pd(dba)$_2$ itself was capable of catalysing the reaction, although racemically. In using a slight excess of the ligand, an enantiomeric excess of 86% of *(R)*-**78** was obtained, however, this was lower than the 92% ee attained by Pelly *et al.*[47] We were concerned that sufficient exchange of the chiral ligands onto the Pd had not occurred

and with that in mind we decided to increase the equivalents of Trost ligand (exactly 4.7 equivalents). Having added the chiral ligand, the mixture also was stirred for 5 minutes longer than in our prior attempt in order to ensure complete exchange of the chiral ligand onto the Pd. We were once again disappointed by the results, this time even more so than before. An excess of Trost ligand appeared to counter the desired effect of the chiral ligand as the enantiomeric excess dropped to a disappointing 59%. We therefore embarked upon a strategy whereby the reaction was attempted several times, each time varying a single element until conditions were optimised to the point that an enantiomeric excess of 94.8% was obtained. The improved ee was a function of the following factors. Firstly, there appeared to be a very fine balance between using enough but not too much ligand, and 2.6 equivalents of ligand for every Pd provided the best results. A new bottle of the Trost ligand was also purchased and a new batch of $Pd_2(dba)_3CHCl_3$ was synthesised. The acetic acid was also distilled and degassed prior to use. Finally, on a scale of approximately 200 mg, the starting material was dissolved in dichloromethane and added slowly by means of a dropping funnel, rather than adding this in a single portion. Unfortunately, upon doubling the scale of the reaction to 400 mg of starting material, the enantiomeric excess decreased to 90%. This batch was employed in the synthesis of rotenone.

The dihydrobenzofuran was eventually synthesised as follows: dichloromethane and $Pd_2(dba)_3CHCl_3$ were placed in a round bottom flask fitted with a dropping funnel and the violet solution was degassed. The chiral *R,R'*-Trost ligand was then added and the solution was stirred for 25 minutes during which a colour change occurred to a light orange. Acetic acid was added and after 5 minutes of stirring, the dropping funnel was charged with dichloromethane and the carbonate **127** which was then added dropwise to the reaction. After allowing the reaction to proceed for 18 h at rt, the mixture was concentrated and purified by column chromatography to afford the dihydrobenzofuran *(R)*-**78** in a good yield and excellent enantiomeric excess. The absolute stereochemistry was at this point assumed to be the *(R)*- isomer based on the model proposed by Trost.

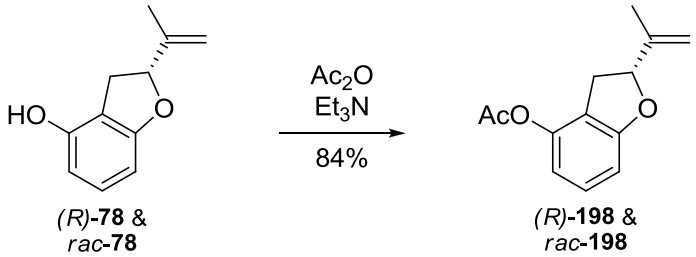
For the above mentioned reaction, new $Pd_2(dba)_3(CHCl_3)$ was synthesised by adding $PdCl_2$ to a solution of hot methanol, dba (dibenzylideneacetone) and sodium acetate. The reaction was stirred for 4 h at 40 °C during which a maroon precipitate formed. The reaction was allowed to cool and the precipitate filtered off and washed successively with water and acetone. The precipitate was dissolved in hot chloroform and any impurities were filtered off. Diethyl ether was slowly added

allowing for precipitation of deep purple crystals which were filtered off and dried *in vacuo*. The composition of the catalyst was identified as $Pd_2(dba)_3(CHCl_3)$ by X-ray crystallographic analysis.[93]



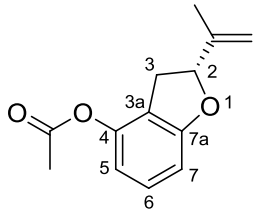
The NMR and IR spectra were as expected, identical to those of the racemic mixture. A chiral synthesis was confirmed by optical measurements, although the actual enantiomeric excess could not be determined at this stage as the enantiomers of the phenol did not separate effectively on our Chiralcel OJ column. The enantiomeric excess was determined from chiral HPLC work of the corresponding acetate derivative.

3.2.12 Synthesis of 2-isopropenyl-2,3-dihydrobenzofuran-4-yl acetate – *(R)*-198 and *rac*-198

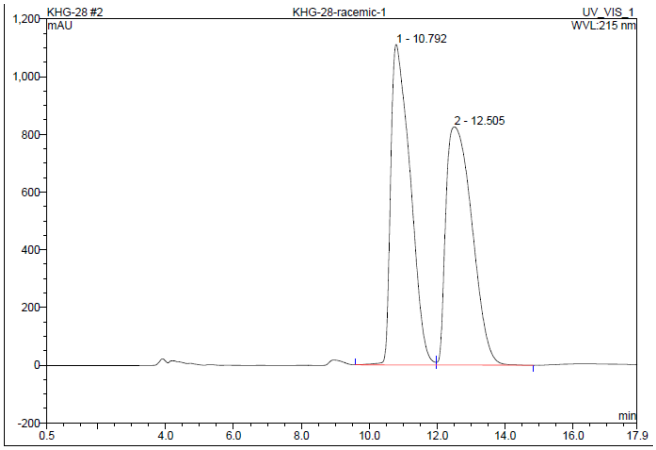


Scheme 71

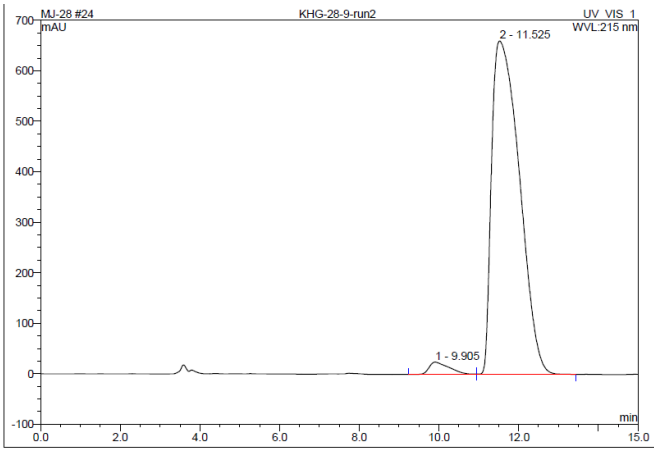
Since we were unable to accurately determine the enantiomeric excess (ee) of our reaction using the phenol **78**, the dihydrobenzofuran was modified to the corresponding acetate **198** for which good separation of the enantiomers was obtained. In this reaction, transformation to the acetate was achieved by adding triethylamine, DMAP and acetic anhydride to a solution of the phenol **78** in dichloromethane (Scheme 71). The reaction was stirred under Ar for 18 h at which point TLC analysis indicated that all the starting material had reacted, forming a new product at a higher R_f value. Purification by column chromatography afforded the acetate **198** as a clear oil in good yield which was then analysed by chiral HPLC. Effective separation of the enantiomers was first optimised on the racemic material and we found the best mobile phase to be 10% isopropyl alcohol in hexane (Figure 10). Having separated the racemic mixture, we then employed the same conditions to analyse our stereoselective cyclisation reaction. An enantiomeric excess as high as 94.8% was obtained, although on larger scales it was just in excess of 90%.



Conversion to the acetate was confirmed by the fact that the O*H* signal previously seen in the ^{1}H NMR spectrum of its precursor, was absent. It was replaced by a single new methyl signal at 2.29 ppm due to the acetate. The methyl protons of the acetate appeared to be rather isolated, hence the clear singlet. This methyl signal was downfield to the CH_3C=CH$_2$ signal due to the nearby carbonyl. The assignment of this methyl was confirmed as upon scrutinising the signal at 1.76 ppm, shoulders were revealed, a feature due to long range coupling and only possible in the CH_3C=CH$_2$ methyl protons. The remainder of the signals were almost identical to that of its precursor apart from proton H$_6$ which had shifted downfield to 6.65 ppm, no doubt due to the acetate. In the ^{13}C NMR spectrum, the far downfield carbonyl signal at 168.43 ppm and the new methyl signal at 20.86 ppm further confirmed that the acetate had been synthesised. With the strong carbonyl absorption at 1759 cm^{-1} in the IR spectrum, we could assuredly say that the acetate had been synthesised.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.79	n.a.	1110.377	738.589	50.00	n.a.	BM
2	12.51	n.a.	825.672	738.451	50.00	n.a.	MB
Total:			1936.049	1477.040	100.00	0.000	

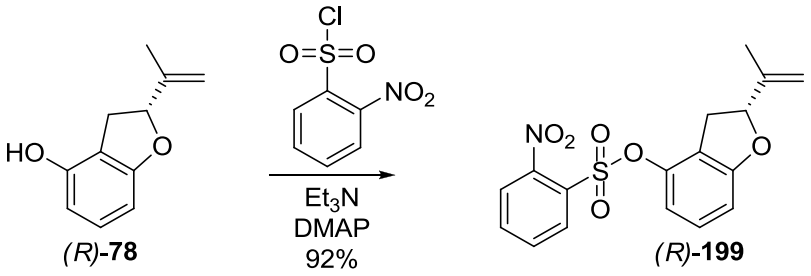


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.91	n.a.	24.429	14.295	2.61	n.a.	BM
2	11.53	n.a.	660.045	532.461	97.39	n.a.	MB
Total:			684.474	546.756	100.00	0.000	

Figure 10

Note: the peaks are located at different positions as the initial method used for the racemic mixture would take 0.5 s as the starting point.

3.2.13 Synthesis of (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate – *(R)*-199



Scheme 72

We had optimised the reaction conditions for obtaining a good yield and enantiomeric excess and we now needed to confirm that the *R,R'*-Trost ligand had indeed provided us with what we had assumed until now to be the *(R)*- enantiomer, as depicted by the Trost model. Information of this sort could be derived from a crystal structure and since the dihydrobenzofuran *(R)*-**78** existed as an oil, it had to be derivatised so as to obtain a solid (Scheme 72). A sulphur-containing moiety was added as a heavy atom was required to unambiguously assign the absolute stereochemistry. Therefore, 2-isopropenyl-2,3-dihydrobenzofuran-4-ol *(R)*-**78** was dissolved in dichloromethane and triethylamine and 2-nitrobenzenesulfonyl chloride were added. The reaction was stirred at rt for 18 h after which TLC analysis indicated full conversion to the nitrobenzenesulfonate derivative *(R)*-**199**. Purification by column chromatography followed by recrystallisation from diethyl ether afforded crystals suitable for X-ray analysis. The absolute stereochemistry of the major enantiomer was confirmed as the *(R)*- isomer (Figure 11). X-ray crystallographic analysis revealed that the dihydrobenzofuran derivative belonged to the chiral space group $P2_12_12_1$ with the following unit cell dimensions: a = 5.73 Å, b = 13.07 Å, c = 22.16 Å. A suitable R-factor of 3.66% was obtained for this crystal structure.

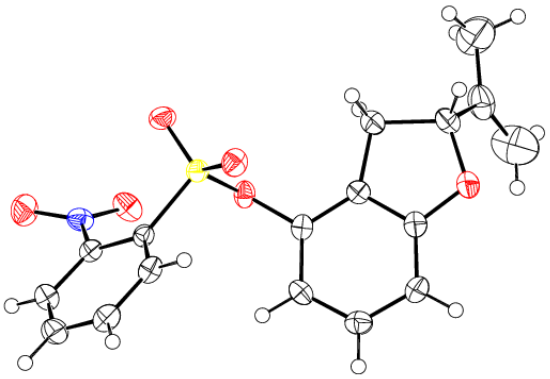
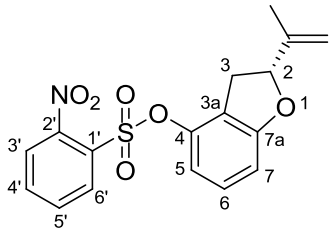


Figure 11

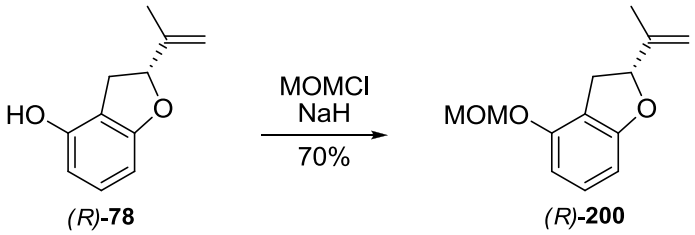


The ^{1}H NMR spectrum exhibited several new aromatic signals in the downfield region. The deshielding effect of the nitro group shifted the aromatic protons in the nitrobenzenesulfonate moiety further downfield so that there was no overlap with the aromatic protons of the dihydrobenzofuran. Proton $H_{3'}$ produced a doublet and since it was adjacent to the nitro group, it was found furthest downfield at 7.99 ppm. Following this, protons $H_{5'}$ and $H_{6'}$ gave an overlapping signal at 7.85 ppm. Proton $H_{4'}$ was the least deshielded and since it coupled to all of the above mentioned hydrogens, it gave rise to a complex multiplet at 7.78-7.65 ppm. The remainder of the spectrum was unaffected, apart from slight changes in the chemical shifts. Characteristically, the aromatic protons H_6, H_7 and H_5 appeared as a triplet and two doublets at 7.05 ppm, 6.74 ppm and 6.55 ppm. Proton H_2 coupled to the adjacent methylene protons to give a triplet at 5.19 ppm and further upfield, each of the geminal alkene protons gave rise to individual singlets at 5.05 ppm and 4.90 ppm. This was followed by the characteristic doublet of doublets at 3.41 ppm and 3.03 ppm, due to protons H_3. Furthest upfield was the methyl singlet at 1.71 ppm. Loss of the O*H* signal in both the ^{1}H NMR and the IR spectra further attested to the fact that the alcohol had been derivatised. In the ^{13}C NMR spectrum, six additional signals provided for the most obvious affirmation of the addition of the benzene ring. The measured melting point deviated by a single degree from the reported melting point of 82-83 °C.[47]

Since we had completed the enantioselective synthesis of the required dihydrobenzofuran *(R)*-**78**, we could now forge ahead with the synthesis of rotenone. A key feature, however, was that in order

to couple this unit to the alkyne, a formyl group would first have to be introduced into the position *ortho* to the phenol of *(R)*-**78**. For this purpose, several methods were at our disposal, e.g. a formyl group could be introduced by electrophilic substitution. This would require an activated phenol which meant that at the outset of the synthesis, we would have to introduce an *ortho* directing moiety such as a MOM group. Alternatively, a Vilsmeier-Haack reaction could be used which would not necessarily require an activating group. A description of the formylation reactions that we had attempted follows, eventually leading to the development of a successful procedure.

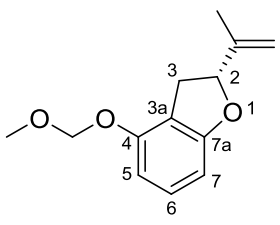
3.2.14 Synthesis of *(R)*-4-(methoxymethoxy)-2-isopropenyl-2,3-dihydrobenzofuran – *(R)*-200



(R)-**78** *(R)*-**200**

Scheme 73

Several attempts were made to introduce the formyl group into the 5-position. We initially decided to employ an electrophilic substitution reaction and this required the introduction of a MOM protecting group as it is a good *ortho* director (Scheme 73). Therefore, to a solution of the alcohol *(R)*-**78** dissolved in dimethylformamide and immersed in an ice bath, was added sodium hydride followed by methoxymethyl chloride. The reaction was allowed to warm to rt and stirred under Ar for 18 h. TLC analysis indicated that a new product of higher R_f had formed and only trace amounts of starting material were present. Despite the long reaction times, a small amount of starting material was consistently recovered from this reaction. Following a work-up and purification by column chromatography, the MOM protected dihydrobenzofuran *(R)*-**200** was afforded as a yellow oil in a moderate yield.



The MOM protection was confirmed by the fact that, in addition to the normal dihydrobenzofuran signals, singlets at 5.18 ppm and 3.48 ppm appeared due to the OCH_2 and OCH_3 groups. The effect of this on the remaining signals was minimal with only slight deshielding of the aromatic

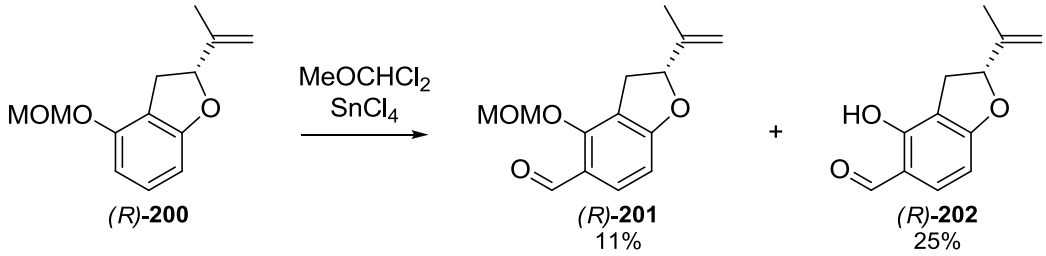
protons and hence shifting of these signals downfield. Disappearance of the OH signal in the ^{1}H NMR and the IR spectra verified the conversion of the phenol to the MOM ether. This was further confirmed in the ^{13}C NMR spectrum by the addition of two new signals in the more upfield region.

With the well reputed *ortho* director in place, we could now carry out the electrophilic substitution using *n*BuLi and *p*-formaldehyde. The reaction would hopefully afford the benzylic alcohol which, upon oxidation, could be converted to the benzaldehyde at the 5-position. To this end, the MOM protected dihydrobenzofuran *(R)*-**200** was dissolved in tetrahydrofuran and cooled to -78 °C by means of an acetone slurry bath. TMEDA (2 equiv.) was added followed by the dropwise addition of *n*BuLi (2 equiv.). After 1.5 h, *p*-formaldehyde (2 equiv.) was added and the reaction was maintained at -78 °C for an hour before warming up to rt. Following 18 h of stirring under Ar, TLC analysis indicated that the starting material was still present with only trace amounts of two other products. These were recovered in such low quantities that we were not able to elucidate their structure and the only information that could be gathered from their NMR spectra was that the furan had most likely decomposed under these conditions as characteristic signals of this moiety were no longer visible.

Our main concern at this point was that the temperature employed was too low for lithiation and hence formylation to occur. The reaction was repeated, this time increasing the temperature of lithiation to 0 °C. However, this did not have the effect we were hoping for as the results were identical to those in the previous experiment.

At this stage it was unclear whether the problem was associated with ineffective lithiation or perhaps poor nucleophilic attack of the lithiated benzene ring on *p*-formaldehyde. To solve this we decided to carry out a test reaction employing MeI as the electrophile. Once again, the starting material was recovered as the major compound in addition to trace amounts of two other products, uncharacterisable beyond the fact that they appeared to indicate decomposition of the furan ring. Clearly, the problem did not lie in the electrophile but rather in the fact that lithiation was not successful. We also concluded that the decomposition of the furan ring occurred as a result of prolonged exposure to the strongly basic conditions, which could have potentially deprotonated the acidic benzylic position.

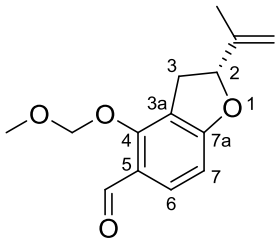
3.2.15 Synthesis of *(R)*-4-(methoxymethoxy)-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde and *(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-201 and *(R)*-202



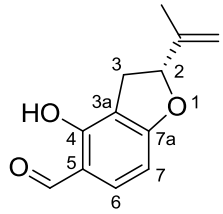
(R)-**200** *(R)*-**201** 11% *(R)*-**202** 25%

Scheme 74

Since our electrophilic substitution had proven to be unsuccessful, we decided to attempt the formylation using a variation of the Vilsmeier-Haack reaction (Scheme 74).[94] Unlike conventional Vilsmeier Haack reactions, this procedure combined the starting material *(R)*-**200** and the dichloromethyl methyl ether prior to adding the stannic chloride, resulting in what appeared to be a reaction between the dihydrobenzofuran and the dichloromethyl methyl ether. The ^{1}H NMR spectrum once again indicated that the furan ring was absent. In repeating the reaction, the tin tetrachloride and the dichloromethyl methyl ether were first combined at -78 °C and after 20 minutes, the starting material *(R)*-**200** was added. The reaction was maintained at -78 °C for 1 h at which point TLC analysis indicated that two new products had formed. The reaction was quenched and following a workup and purification, NMR revealed that both products contained the formyl substituent. The minor product produced in an 11% yield was the desired MOM protected formylated compound *(R)*-**201**. The major formylated product in a higher yield of 25% was that of the deprotected phenol *(R)*-**202**.

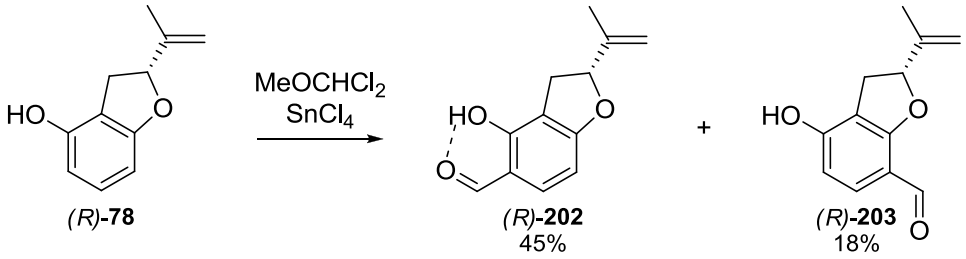


The fact that formylation had successfully occurred was immediately confirmed upon examining the ^{1}H NMR spectrum. The new, far downfield singlet confirmed the presence of the aldehyde. As a result, the aromatic region was simplified to two doublets at 7.61 ppm and 6.69 ppm. Proton H_6 was further downfield than H_7 due to the deshielding effect of the adjacent formyl group. The remainder of the signals were unchanged. In the ^{13}C NMR spectrum, the carbonyl signal in the far downfield region at 187.43 ppm was immediately obvious. NOE experiments were inconclusive with regards to the *ortho* or *para* position of formylation.



In the process of formylation, the second product showed that the MOM protecting groups had also been cleaved. This was confirmed firstly by the fact that the OC*H*$_2$ and OC*H*$_3$ signals were absent, and secondly by the new singlet at 11.47 ppm due to the O*H* proton, identified by proton exchange upon the addition of D_2O to the NMR sample. Once again, the aromatic region had been simplified to two doublets at 7.36 ppm and 6.50 ppm due to protons H_6 and H_7, respectively. Proton H_6 was further downfield as it was closer to the formyl group and hence more susceptible to deshielding. All attempts to unambiguously assign the position of the formyl group by NOE experiments were once again inconclusive. However, we were optimistic that favourable hydrogen bonding between the alcohol and the formyl group would have directed formylation into the *ortho* rather than the *para* position. This was somewhat confirmed by the intense carbonyl absorption peak at 1630 cm^{-1} in the IR spectrum which was at a slightly lower wavenumber than what is normally observed, potentially due to hydrogen bonding to the adjacent O*H*. The *ortho* position of the formyl group was verified in the subsequent reactions.

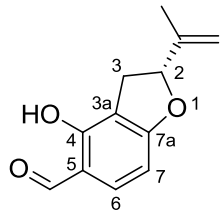
3.2.16 Synthesis of (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde and *(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-7-carbaldehyde – *(R)*-202 and *(R)*-203



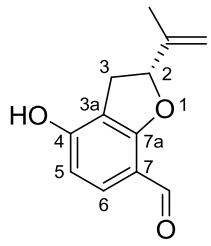
Scheme 75

In light of the fact that the MOM deprotected compound *(R)*-**202** was obtained in the preceding Vilsmeier reaction, we decided to attempt the reaction on the unprotected phenol *(R)*-**78** (Scheme 75). To this end, tin tetrachloride and dichloromethyl methyl ether were combined at -78 °C and stirred for 20 minutes. The Vilsmeier salt was then transferred by canula to a round bottom flask containing the dihydrobenzofuran *(R)*-**78**. In this strategy the starting material was therefore in excess of the harsh Vilsmeier reagents so as to avoid any potential side reactions. After 5 minutes of

stirring, two new products were present with significantly different R_f values. TLC analysis after 1 h indicated that starting material was still present and the reaction was warmed to 0 °C for an additional hour. Following a workup and purification, both products were identified by NMR spectroscopy as the formylated phenol. Both the *ortho (R)*-**202** and *para (R)*-**203** products had been synthesised, however, NOE experiments would not allow us to distinguish between the two compounds. Nevertheless, we could tentatively assign the regioisomers by rationalising the R_f values and yields of the respective products. The isomer of higher R_f had also been produced in excess of the other product. This was assumed to be the *ortho* substituted product *(R)*-**202**, driven by the favourable hydrogen bonding interaction illustrated in Scheme 75. The higher R_f value was perhaps due to the intramolecular interaction between the phenolic O*H* and the adjacent carbonyl, effectively reducing the interaction of the molecule with the silica, thus allowing the product to travel more quickly on the TLC plate.

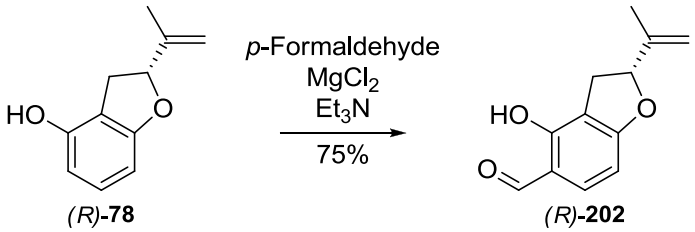


The spectroscopic data was identical to that obtained in the previous synthesis (Scheme 74). In the ^{1}H NMR spectrum, two far downfield signals at 11.47 ppm and 9.68 ppm attested to the presence of the phenolic O*H* and the aldehyde, respectively. In the ^{13}C NMR spectrum, the single additional signal in the downfield region at 194.32 ppm was assigned to the carbonyl, thus acting as affirmation of the successful reaction.



We had assumed that the minor product was one in which formylation had taken place in the 7-position. This was in response to the fact that all signals as a result of the dihydrobenzofuran nucleus were equivalent to those in the major product, with exception of two slight differences. The O*H* and carbonyl signals in *(R)*-**203** were situated further upfield compared to its regioisomer, at 7.43 ppm and 10.04 ppm, respectively. This key difference between the two products was used to distinguish between the *ortho* and *para* compounds. Hydrogen bonding between the hydroxyl and formyl group in *(R)*-**202** would shift the O*H* signal further downfield, hence it was situated at 11.47 ppm. In stark contrast to this, the O*H* signal in the *para* substituted product *(R)*-**203** was found further upfield at 7.43 ppm.

3.2.17 Synthesis of (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-202

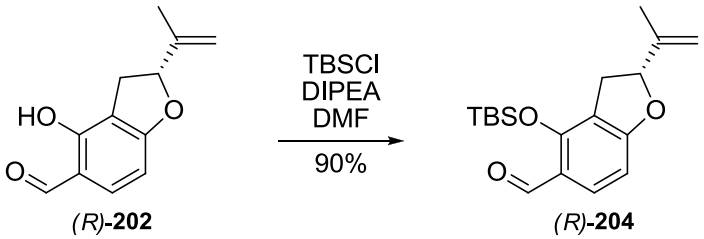


(R)-**78** *(R)*-**202**

Scheme 76

Owing to the fact that we had encountered these difficulties with the formylation reaction, we once again returned to the literature to search for alternative procedures. In this process we discovered an interesting magnesium mediated formylation which appeared to selectively install the desired functionality in the position *ortho* to a phenolic O*H* (Scheme 76).[95] We were further drawn to this method as mild reagents were used, unlike the harsher conditions employed in the electrophilic substitution and Vilsmeier-Haack reactions. In applying this procedure to our compound, *p*-formaldehyde was added to a round bottom flask under Ar containing the starting material *(R)*-**78**, anhydrous magnesium chloride and triethylamine in dry tetrahydrofuran. The mixture was heated to reflux and after 2 h, TLC analysis indicated that a single new product had formed. A workup, followed by purification by column chromatography gave the formylated product *(R)*-**202** as a yellow oil. The R_f and spectroscopic data were identical to the previously assumed *ortho* product, although the new method saw a significant improvement in the yield of 75%. The enantiomeric excess could not be elucidated using chiral HPLC as the product could not be resolved into its isomers. However, the product remained optically active which meant that we had not racemised the material. In the remainder of the synthesis, reactions were first conducted on a small scale and specific rotations were measured and taken as an indication of the fact that one enantiomer was still in excess of the other, prior to conducting the experiment on a larger scale.

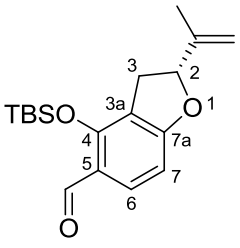
3.2.18 Synthesis of (-)-*(R)*-4-(*tert*-butyldimethylsilyloxy)-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-204



(R)-**202** *(R)*-**204**

Scheme 77

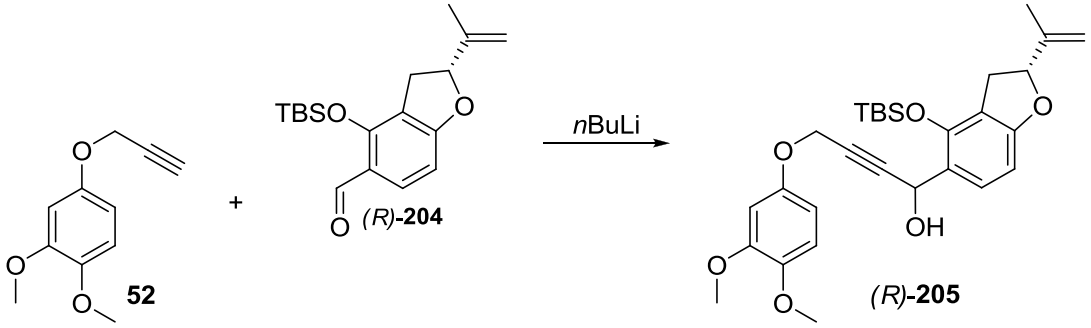
Prior to the coupling reaction, the phenol was protected using a TBS silyl group as these had been successfully utilised in the parallel synthesis of munduserone. The previously employed methodology using imidazole and TBSCl did not work and after 18 h of stirring, only starting material was present. This was attributed to the stabilising hydrogen bond interaction which may have hindered deprotonation of the phenol and hence silylation. A different solvent had to be used which could potentially disrupt the hydrogen bond between the alcohol and the formyl group, thus facilitating deprotonation and hence silylation. The method used was based upon silylation of the similarly substituted compound, salicaldehyde.[96] A slight excess of diisopropylethylamine was added to a solution of the starting material *(R)*-**202** dissolved in dimethylformamide (Scheme 77). Following 5 minutes of stirring, TBSCl was added. The reaction progressed at a very fast rate and TLC analysis after 10 minutes indicated full conversion to a product of slightly higher R_f. Following a workup and purification by column chromatography, the silylated product *(R)*-**204** was obtained as a yellow oil in a good yield of 90%.



In the ^{1}H NMR spectrum, the silyl ether manifested itself as two intense, upfield singlets, thus confirming the success of the reaction. These signals at 1.04 ppm and 0.20 ppm integrated for nine and six protons, respectively. In fact, the two methyl groups attached to the silicon atom appeared to be non-equivalent as these produced very closely spaced singlets at 0.22 ppm and 0.20 ppm. This was an interesting feature which indicated that rotation of the bulky TBS group was restricted and hence the methyl groups were in different environments, thus producing the two singlets. The far downfield O*H* singlet had accordingly disappeared and although the carbonyl signal was still present, it had shifted slightly downfield to 10.15 ppm. The remaining signals indicated that the dihydrobenzofuran was unchanged. Three additional signals in the ^{13}C NMR

spectrum at 18.46 ppm, 16.93 ppm and -3.79 ppm verified the presence of a TBS group. The intense absorption in the IR spectrum at 1674 cm^{-1} was consistent with the presence of the formyl group.

3.2.19 Attempted synthesis of 1-((*R*)-4-(*tert*-butyldimethylsilyloxy)-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)-4-(3,4-dimethoxyphenoxy)but-2-yn-1-ol – *(R)*-205



Scheme 78

The coupling reaction was then carried out with the second of the two intermediates also used in the model study, the propargyl ether **52** (Scheme 78). The alkyne **52** (1.05 equiv.) was dissolved in tetrahydrofuran and once cooled to -78 °C, 1.1 equivalents of *n*BuLi were added. After stirring for 30 minutes, the dihydrobenzofuran *(R)*-**204** (1 equiv.), also dissolved in tetrahydrofuran, was added by canula. The reaction was left to warm to rt and stirred for 1 h and then quenched by adding saturated ammonium chloride solution. Following purification, mainly the starting materials were recovered as well as a trace amount of an unknown product which we could say with certainty was not the desired product *(R)*-**205** as characteristic signals of the product such as those of the methoxy groups were absent in the ^{1}H NMR spectrum. In an effort to drive the reaction forward it was repeated, this time using *n*BuLi in excess of two equivalents. Unfortunately, this only resulted in a number of compounds forming, none of which were the desired product.

We were initially confused by the failure of this reaction as it had been successful in the model study. In considering the differences between the two compounds, we surmised that perhaps this was due to increased steric hindrance of the dihydrobenzofuran compared to compound **178** of the model study. This is illustrated in Figure 12 where dashed lines represent atoms only present in the dihydrobenzofuran *(R)*-**204** (and not in the model compound **178**). It is entirely possible that the presence of the methylene in *(R)*-**204** may significantly alter the position of the bulky silyl group,

pushing it towards the carbonyl in what is known as the buttressing effect.[97] This would result in a more sterically hindered aldehyde which would be less susceptible to attack by the alkyne **52**. We therefore attempted the coupling reaction again, this time with a smaller protecting group in place.

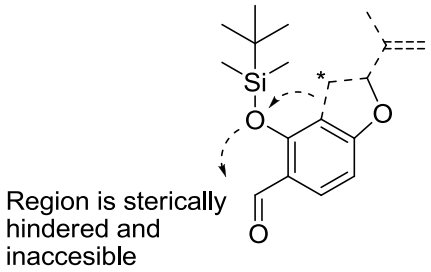
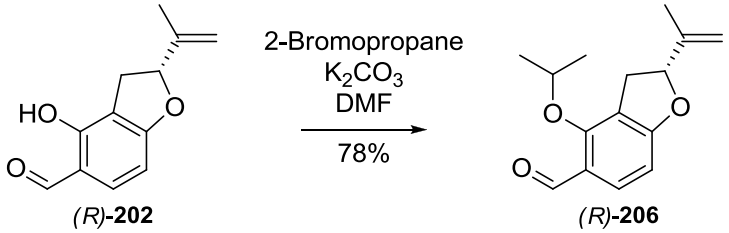


Figure 12

3.2.20 Synthesis of (-)-*(R)*-4-isopropoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-206

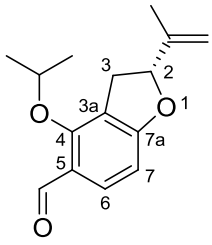


Scheme 79

Concerned with the steric bulk associated with the TBS group, we next opted for the smaller isopropyl group. The procedure employed in introducing this protecting group was once again based on the protection of a salicaldehyde derivative, this time with an isopropyl moiety.[98] The formylated dihydrobenzofuran *(R)*-**202** was thus dissolved in dimethylformamide and potassium carbonate and 2-bromoporopane were added (Scheme 79). The reaction was then immersed in an oil bath preheated to 45 °C. TLC analysis after 30 minutes indicated that a new product had formed, although a large amount of starting material was still present. The reaction was left to stir at this temperature for 18 h following which, a workup and purification yielded the desired compound *(R)*-**206** as a yellow oil in an acceptable yield of 78%.

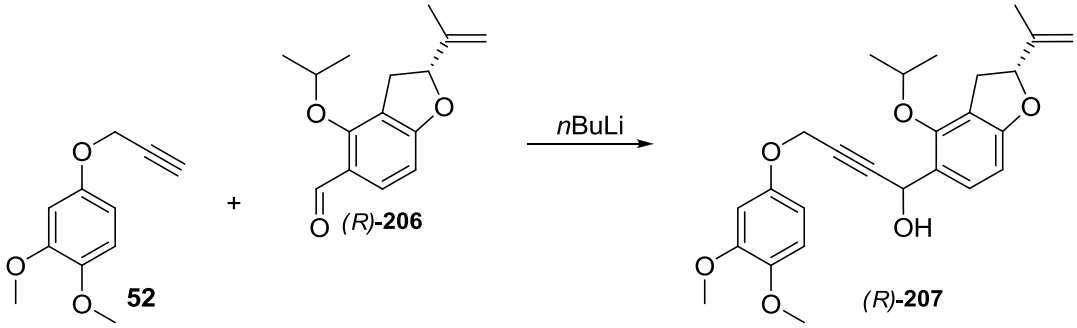
Interestingly, one would have expected the less polar alkylated dihydrobenzofuran *(R)*-**206** to travel further up the TLC plate compared to the phenol precursor *(R)*-**202**. A rather unusual observation was made in that the R_f of the phenol was higher than that of the alkylated compound. This

observation supported the notion that, since the formyl group was in a position *ortho* to the phenolic OH, hydrogen bonding between the two significantly decreased the interaction of the phenol with the silica. This was a fortuitous observation of our previous summations that the formyl group had been introduced in the desired *ortho* position.



The isopropyl groups could be easily detected in the ^{1}H NMR spectrum of the product. The characteristic septet and doublet integrating for one and six protons, respectively, were indeed present in the ^{1}H NMR spectrum of the product, thus confirming a successful reaction. As a result, the O*H* signal had disappeared in the downfield region of the ^{1}H NMR spectrum. As for the dihydrobenzofuran nucleus, protons maintained their respective splitting patterns, although several of their chemical shifts had changed slightly. In the ^{13}C NMR spectrum, introduction of the isopropyl group was accompanied by two additional signals at 75.34 ppm and 22.45 ppm. The IR spectrum contained a C=O absorption peak at 1671 cm^{-1}.

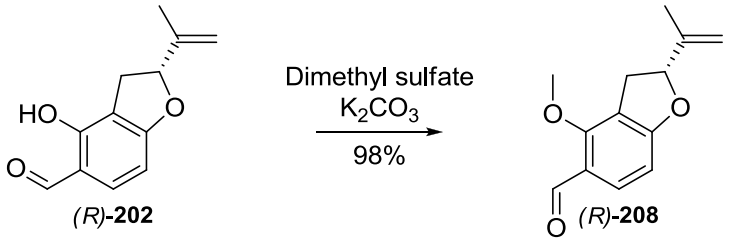
3.2.21 Attempted synthesis of 4-(3,4-dimethoxyphenoxy)-1-((*R*)-4-isopropoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-ol – *(R)*-207



Scheme 80

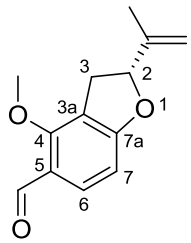
With the somewhat less sterically encumbering isopropyl protecting group in place, the coupling reaction was once again attempted using the dihydrobenzofuran *(R)*-**206** (Scheme 80). Once again, the coupling reaction did not proceed and the desired product *(R)*-**207** was not synthesised. Seemingly, the only option available to us was to switch to the smallest feasible protecting group, namely a methoxy. This was a concerning strategy as we knew that this may pose deprotection problems later on in the synthesis as other methoxy groups were present in the molecule.

3.2.22 Synthesis of (-)-*(R)*-4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-208



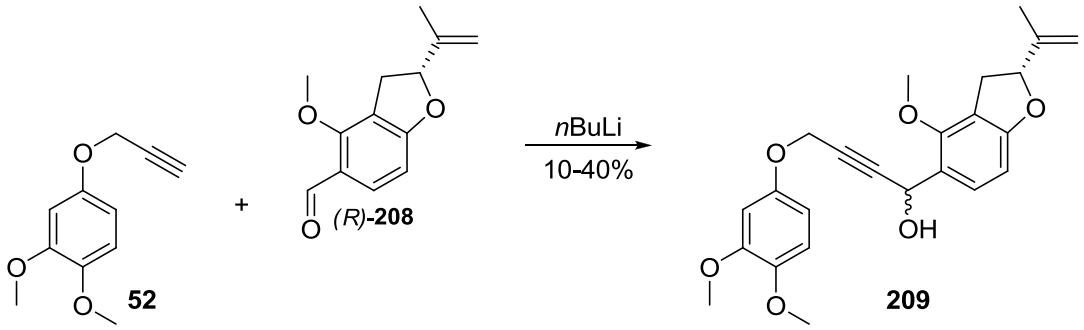
Scheme 81

As expected, the introduction of the methyl group proceeded smoothly using dimethyl sulfate. In this process, potassium carbonate was added to a solution of the starting material *(R)*-**202** in acetone (Scheme 81). The reaction was heated to reflux and whilst stirring under Ar, a colour change was observed from clear to a milky white. TLC analysis at 1 h indicated complete conversion to a compound of lower R_f and a workup was then performed, followed by purification by column chromatography to afford the methylated product *(R)*-**208** as a waxy solid in an excellent yield of 98%.



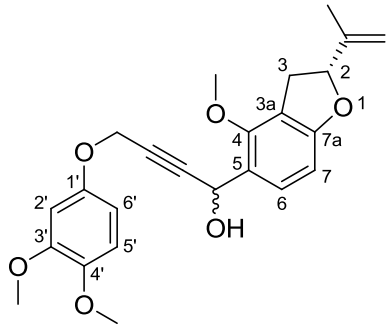
The large singlet at 4.00 ppm in the ^{1}H NMR spectrum clearly indicated the transformation from the phenol to an aromatic methoxy. There was also no sign of the phenolic O*H* proton. The carbonyl signal was still clearly present as a downfield singlet at 10.22 ppm. As for the remaining signals, these were similar in appearance to their precursor, only shifted slightly downfield. The ^{13}C NMR spectrum contained a new signal at 60.12 ppm, indicative of the methoxy group.

3.2.23 Synthesis of (-)-*(R)*-4-(3,4-Dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-ol –209



Scheme 82

With the smallest of our feasible protecting groups in place, it was now time to once again attempt the coupling reaction and hope that the problems associated with steric crowding could be overcome (Scheme 82). To this end, *n*BuLi was added to a solution of the alkyne **52** dissolved in tetrahydrofuran at -78 °C. The reaction was stirred for 30 minutes and the methylated dihydrobenzofuran *(R)*-**208**, also dissolved in tetrahydrofuran, was added by canula. The solution was allowed to warm to rt and following 1 h of stirring, TLC analysis indicated that a trace amount of a new product was present. The reaction was heated to 40 °C and monitored hourly by TLC over the next 5 h. After this time, the reaction mixture was cooled and following a workup and purification, the first signs of a success were evident as the desired product **209** was obtained, albeit in a very modest 17% yield. This improved slightly to 40% upon increasing the reaction time to 18 h, however, TLC analysis at the end of this period indicated that a significant amount of starting material was still present. This was especially problematic as the two starting materials (**52** and *(R)*-**208**) had the same R_f values and so the precious, unreacted dihydrobenzofuran could not be recovered in these reactions.



Spectroscopic evidence for the formation of the secondary alcohol **209** was obtained from the ^{1}H, ^{13}C and COSY NMR spectra. The most obvious indication that the coupling reaction had worked was given by the three singlets at 3.88 ppm, 3.84 ppm and 3.82 ppm, each integrating for three protons due to the three methoxy groups. The two singlets at 5.58 ppm and 2.78 ppm integrating for one proton each, were assigned to the newly formed C*H*OH and the O*H* protons, respectively. An

interesting feature in the ^{1}H NMR spectrum was the doubling up of several peaks as a result of the formation of diastereomers. This was particularly evident in the C*H*OH and the O*H* signals which were each comprised of closely spaced singlets. In the aromatic region, four signals integrated for five protons in total. These signals were assigned to their respective protons upon inspection of their coupling patterns and coupling constants. The first and most obvious assignment was that of proton $H_{2'}$ which was the only *meta* coupled aromatic proton. Therefore, $H_{2'}$ could be assigned to the doublet at 6.58 ppm adopting a coupling constant of magnitude 2.7 Hz. The COSY spectrum (Figure 13) showed that $H_{2'}$ was coupled to one of the overlapping signals at 6.50-6.48 ppm, due to proton $H_{6'}$. Proton $H_{6'}$ in turn coupled to the doublet at 6.77 ppm, due to proton $H_{5'}$. This was supported by the *ortho* coupling constant of 8.7 Hz adopted by proton $H_{5'}$. In the dihydrobenzofuran nucleus, protons H_6 and H_7 only coupled to one another and were expected to give two doublets with *ortho* coupling constants in the range of 6-10 Hz. This relationship was observed in the doublet furthest downfield at 7.22 ppm which coupled to one of the overlapping signals at 6.50-6.48 ppm, with an *ortho* coupling constant of 8.2 Hz. The doublet further downfield was due to proton H_6, and proton H_7 existed as one of the overlapping signals. The protons associated with the dihydrobenzofuran moiety could be easily assigned. As for the remainder of the signals, the singlet integrating for two protons could only be assigned to the remaining methylene protons CH_2-C≡C. As expected, 24 signals were produced in the ^{13}C NMR spectrum, although the presence of diastereomers was once again evident in the doubling up of several peaks. The first five, far downfield signals were assigned to the five Ar*C*O's in the molecule. This was followed by the quaternary alkene signal at 143.50 ppm which remained unwavering in its position in the ^{13}C NMR spectrum. The quaternary carbons of the alkyne moiety gave the signals at 87.53 ppm and 80.70 ppm. As for the remaining signals, these were assigned using the HSQC spectrum. In the IR spectrum, the broad stretch at 3489 cm^{-1} verified the formation of the alcohol by way of the coupling reaction.

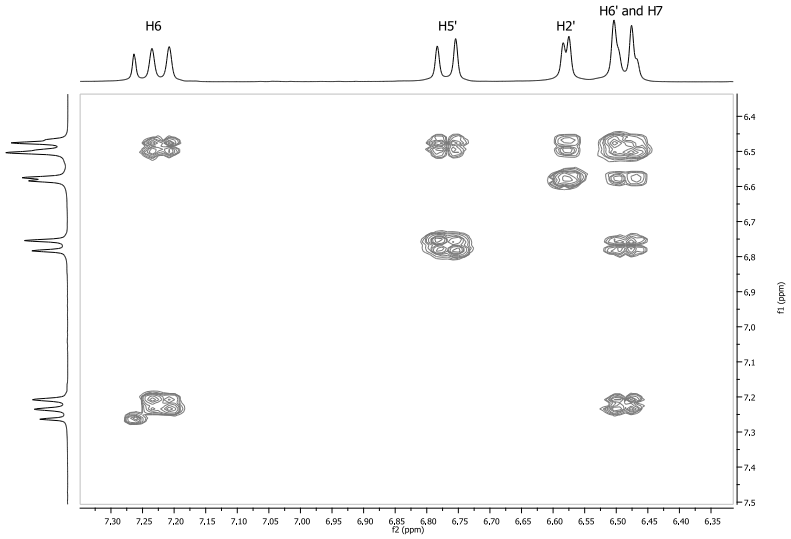


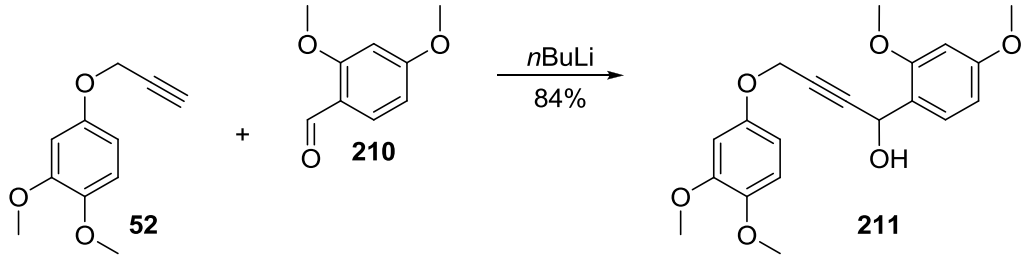
Figure 13

Concerned with the yield of the reaction, we surmised that once deprotonated, the alkyne could behave as a strong base, thus deprotonating the acidic benzylic protons rather than acting as a nucleophile and attacking the carbonyl. The obvious solution to this was to increase the amount of *n*BuLi to two equivalents. In this attempt, we observed by TLC that after an hour at 40 °C the product had started to form, yet shortly after this, complete conversion to a new product was observed. Following a workup and purification, the product was analysed spectroscopically and although it could not be completely characterised, distinct multiplets in the far upfield region of the ^{1}H NMR spectrum indicated that the nucleophilic butyl group had added to the molecule, however, we could not elucidate exactly where and how this had happened.

Due to the dismal and inconsistent yields in the coupling reaction, we decided to employ various other bases in an attempt to couple the two compounds. We tested several methods using a variety of bases on a new model system closely resembling the methylated dihydrobenzofuran. This is described in the next section.

3.2.24 Back to a model system: Synthesis of 4-(3,4-dimethoxyphenoxy)-1-(2,4-dimethoxyphenyl)but-2-yn-1-ol – 211

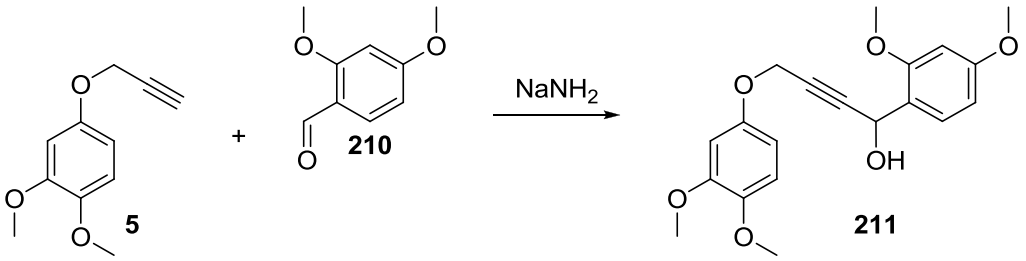
A model system – *n*-Butyllithium and manganese dioxide



Scheme 83

The recovery of starting material in the coupling reactions was not only observed in the synthesis of rotenone, but also in our synthesis of munduserone. Thus, we decided to conduct a model study to see if we could drive the coupling reaction to completion by oxidising the newly formed alkoxide *in situ* with the addition of manganese dioxide to the reaction mixture. We would first have to investigate the feasibility of the coupling reaction on the new model system (Scheme 83). To this end, the alkyne **52** (1.05 equiv.) was dissolved in tetrahydrofuran and *n*BuLi (1.075 equiv.) was added at -78 °C. Following 30 minutes of stirring, the aldehyde **210** (1 equiv.), also dissolved in tetrahydrofuran, was added. The reaction afforded the coupled product **211** as a yellow oil in an 84% yield, despite the fact that the starting materials were recovered. Having verified that the coupling reaction worked in the model system, our next step was to add manganese dioxide to oxidise the alkoxide in order to drive the reaction in the forward direction. Therefore, once the aldehyde (1 equiv.) had been added to the deprotonated alkyne (1.05 equiv.) and stirred for 30 minutes at 40 °C, manganese dioxide (20 equiv.) was added and the reaction was monitored by TLC. We were delighted to see that the alkynone had indeed formed, however, starting material was still present even after several hours. In this modified process the alkynone was obtained in a disappointing 27% yield. Since we could not improve the yield in this manner, we decided to test a number of bases on the model system.

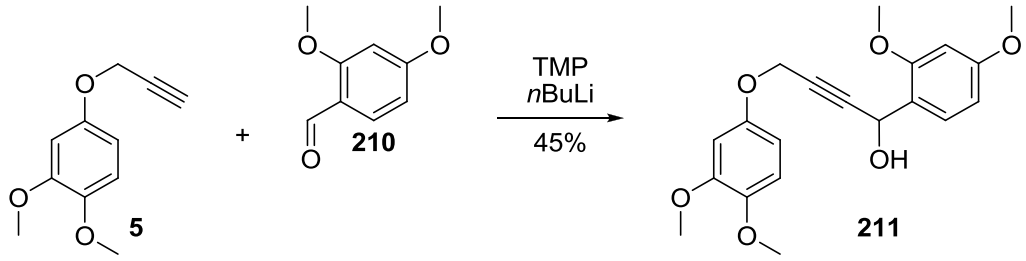
A model system – Sodium amide



Scheme 84

Since sodium amide has been used extensively to deprotonate the acidic proton of alkynes, we decided to employ this base in our coupling reaction.[92, 99] Therefore, the alkyne **52** was added to a stirred solution of sodium amide in anhydrous diethyl ether under Ar. The mixture was heated to reflux gently for 2.5 h following which, the reaction was cooled to 0 °C and diluted with diethyl ether. At this point, the aldehyde **210** was dissolved in ether and added by means of a dropping funnel (Scheme 84). The reaction was allowed to warm to rt and monitored by TLC. After stirring for several days, only trace amounts of two other products were recovered relative to the vast amount of starting material. Neither of these was the desired product **211**.

A model system – Lithium 2,2,6,6-tetramethylpiperidine

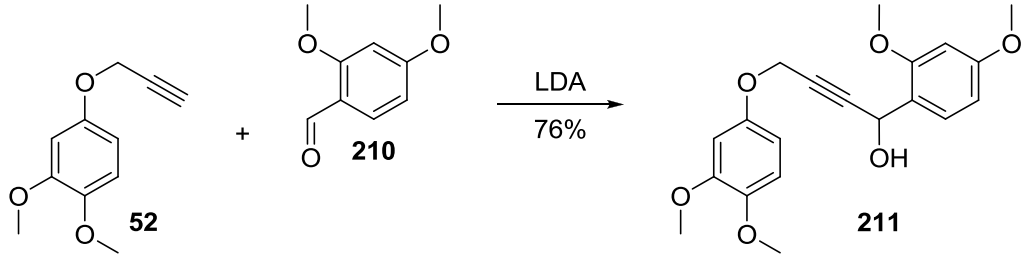


Scheme 85

Since bases such as *n*BuLi could act as a nucleophile, we decided to attempt the coupling reaction using a more hindered lithium base such as LiTMP which was less likely to add to the molecule. This was generated *in situ* by adding *n*BuLi (1.1 equiv.) to a slight excess of 2,2,6,6-tetramethylpiperidine (1.3 equiv.) at -78 °C. The reaction was stirred at this temperature and then warmed to 0 °C by means of an ice bath (to ensure complete reaction of *n*BuLi with TMP) and then

cooled back to -78 °C. The alkyne **52** (1.05 equiv.) was dissolved in tetrahydrofuran and added dropwise to the yellow solution which subsequently became clear (Scheme 85). After stirring at this temperature for 1 h, the aldehyde **210** (1.0 equiv.) was dissolved in tetrahydrofuran and added dropwise by means of a dropping funnel. The pale yellow solution was stirred at -78 °C for 30 minutes before warming to rt. The reaction was monitored by TLC and after several hours, heated up to 40 °C. When the reaction did not appear to progress any further, a workup and purification were performed to afford the product **211** in a mediocre 45% yield.

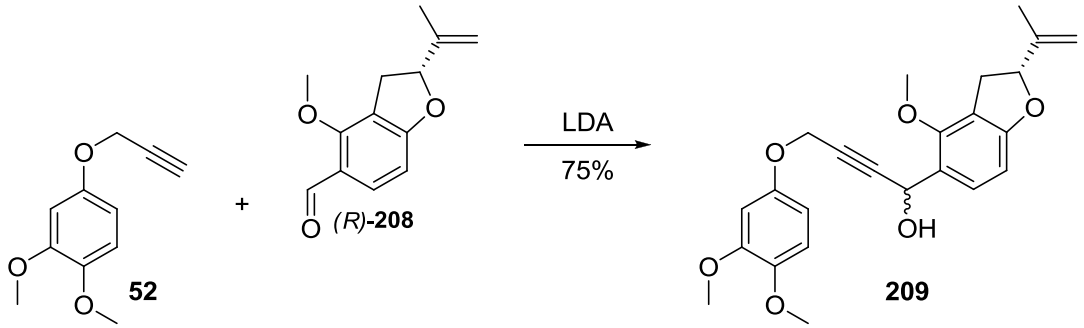
A model system – Lithium diisopropylamide



Scheme 86

As an alternative to LiTMP, we decided to use the bulky base LDA which would hopefully afford the coupled product in a better yield. Although LDA could be generated *in situ* using diisopropyl amine and *n*BuLi, we had direct access to the commercially available material. To this end, LDA (1.6 equiv.) was added to a round bottom flask containing tetrahydrofuran and cooled to -78 °C (Scheme 86). The alkyne **52** (1.05 equiv.) was dissolved in tetrahydrofuran and added dropwise by means of a dropping funnel. The resulting yellow solution was stirred at this temperature for 2 h. The aldehyde **210** (1.0 equiv.) was dissolved in tetrahydrofuran and added dropwise to the solution, resulting in a colour change to clear. After stirring at -78 °C for another 30 minutes, the reaction was warmed to rt. TLC analysis after stirring for 30 minutes indicated that the product **211** was present. The reaction was left to proceed for 3 h during which the colour intensified. By TLC analysis, the concentrations of starting material and product appeared constant and a workup was performed. Following purification by column chromatography, the product **211** was afforded as a yellow oil in a pleasing 76% yield. Having finally had success in optimising the coupling reaction on the model system using LDA, we now returned to the synthesis of rotenone to apply this same methodology.

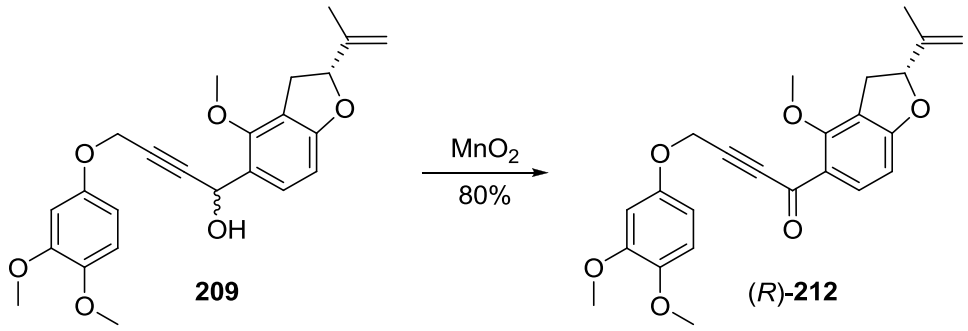
3.2.25 Synthesis of (-)-*(R)*-4-(3,4-Dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-ol – 209



Scheme 87

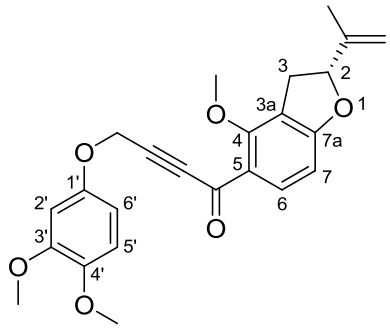
The experimental procedure was analogous to that in the model study. LDA (1.6 equiv.) was added to a round bottom flask containing tetrahydrofuran and cooled to -78 °C (Scheme 87). The alkyne **52** (1.05 equiv.) was added and the reaction was stirred at this temperature for 2 h. As the aldehyde *(R)*-**208** (1.0 equiv.) was added dropwise, the solution changed colour from clear to yellow. The reaction was left to warm to rt during which the solution became yellow again. Following 1.5 h of stirring, TLC analysis indicated that most of the starting material had converted to the product and saturated ammonium chloride was added. A workup, followed by purification finally afforded the desired secondary alcohol **209** in a very satisfying 75% yield! As expected, the spectroscopic data was identical to that obtained when using *n*BuLi.

3.2.26 Synthesis of (-)-*(R)*-4-(3,4-dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-one – *(R)*-212



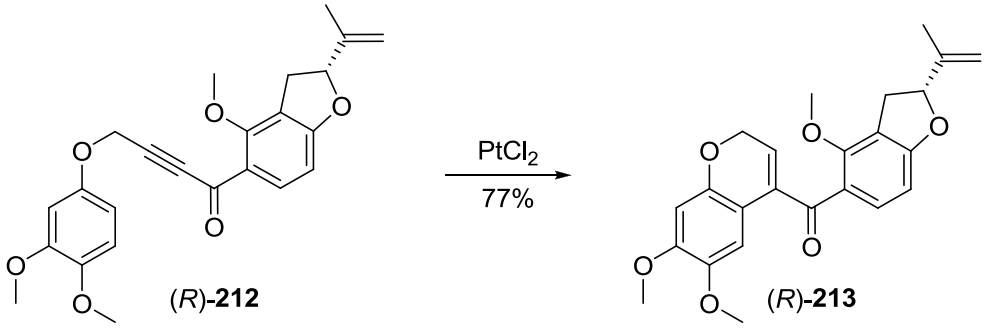
Scheme 88

In preparation for the key 6-*endo*-hydroarylation to follow, we now set about oxidising the secondary alcohol **209** using manganese dioxide as the oxidising agent (Scheme 88). In this reaction, manganese dioxide was added to a solution of the phenol **209** dissolved in dichloromethane. The reaction was left to stir at rt and monitored by TLC. Following 1 h of stirring, TLC analysis indicated complete conversion to a product of slightly higher R_f. The oxidising agent was removed by filtration and the solvent evaporated *in vacuo* before purifying by column chromatography to furnish the alkynone *(R)*-**212** as an orange oil in a good yield (80%).



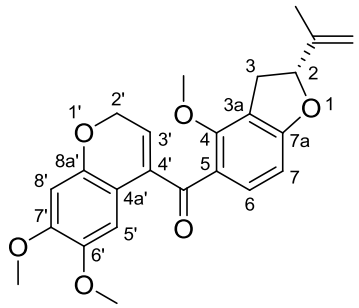
Although the alkynone's spectroscopic data was very similar to that of its precursor, several key differences provided for convincing evidence of the successful oxidation. In the ^{1}H NMR spectrum, loss of the signals due to the C*H*OH and O*H* protons attested to the conversion of **209** into *(R)*-**212.** The remaining signals appeared to be unaffected apart from changes in the chemical shift values of the aromatic and CH_2C≡C protons. Proton H_6 was shifted considerably downfield, certainly due to increased conjugation with the new carbonyl system. In the ^{13}C NMR spectrum, the new downfield carbonyl signal at 174.17 ppm and loss of the *C*HOH signal verified the conversion of the alcohol to the alkynone functionality. Presence of the carbonyl was further supported by an absorption peak at 1635 cm^{-1} in the IR spectrum.

3.2.27 Synthesis of (-)-*(R)*-(6,7-dimethoxy-2*H*-chromen-4-yl)(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)methanone – *(R)*-213



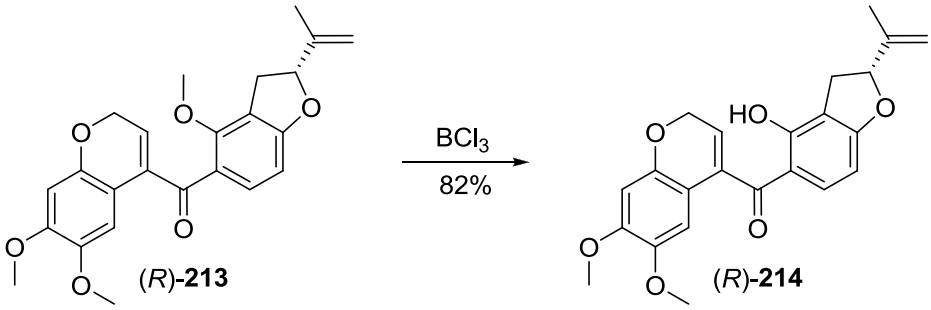
Scheme 89

In our model study, the 6-*endo*-hydroarylation reaction facilitated the synthesis of the chromene portion of munduserone, although we consistently obtained the product in poor yields and large amounts of starting material was recovered. In light of the fact that we were unable to effectively optimise this reaction in the model study and decided to accept a poor yielding step, we now needed to apply this methodology to rotenone. The procedure involved the addition of $PtCl_2$ to a solution of the alkynone *(R)*-**212** in toluene and the reaction was heated to 70 °C (Scheme 89). TLC analysis at regular intervals indicated that after 2 h, all the starting material had reacted which was the first positive sign that perhaps this reaction had proceeded better than in the model study. Indeed, much to our surprise the desired product *(R)*-**213** was obtained in a good yield of 77%! We rationalised this pleasant outcome by virtue of the fact that the less bulky methyl protecting group (compared to the TBS group employed in the model study) may have allowed for a more efficient reaction.



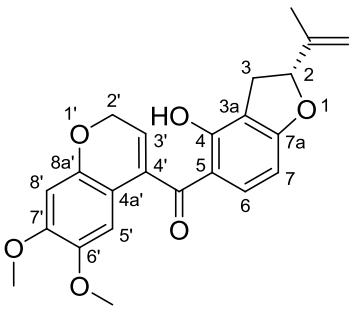
Several distinct changes in the ^{1}H and ^{13}C NMR spectra confirmed that the chromene moiety had been synthesised, thus bringing us one step closer to the target molecule. The ^{1}H NMR spectrum indicated that the number of aromatic protons had been reduced from five in the precursor to four in the product. Several of the aromatic signals were also simplified since, in the formation of the chromene moiety of the molecule, an aromatic proton was substituted and *ortho* coupling in this system no longer existed. Hence, the two singlets at 7.14 ppm and 6.50 ppm accounted for the protons $H_{8'}$ and $H_{5'}$. Protons H_6 and H_7 remained unchanged as doublets. A new triplet at 6.10 ppm integrating for a single proton attested to the presence of the single alkene proton, $H_{3'}$. This proton was coupled to the methylene protons $H_{2'}$, hence the doublet at 4.79 ppm integrating for two protons. In the ^{13}C NMR spectrum, the far downfield signal at 193.97 ppm indicated that a resonance stabilised carbonyl was present. The carbon signals of the alkyne had also disappeared whilst new alkene signals acted as testament to the reaction. The HMBC NMR spectrum was used to assign the quaternary carbons. In the IR spectrum, a peak at 1650 cm^{-1} certified the presence of a carbonyl within the product *(R)*-**213**.

3.2.28 Synthesis of (-)-*(R)*-(6,7-dimethoxy-2*H*-chromen-4-yl)(4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)methanone – *(R)*-214



Scheme 90

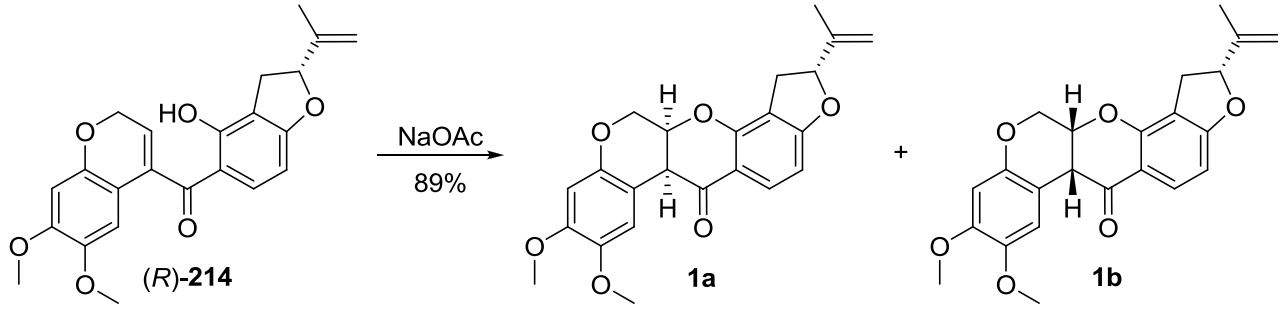
Having constructed the chromene *(R)*-**213**, we now needed to carry out a concerning step - the selective deprotection of the methyl ether group at the 4-position (Scheme 90). In our original synthetic plan, this step would ideally have involved the removal of a silyl protecting group which would be accomplished selectively under mild conditions. However, due to the steric problems we discussed earlier, we were forced to employ the trickier methyl protecting group. We envisaged that selective deprotection of the desired methoxy could be achieved using the Lewis acid, boron trichloride, which upon coordinating to the oxygen carbonyl, would exclusively deprotect the adjacent methoxy group. Of course we also envisaged that the reaction would have to be monitored carefully by TLC so as to avoid prolonged exposure to the reagent which could potentially cleave the methoxy groups at positions 6' and 7'. To this end, a solution of the methylated compound *(R)*-**213** in dichloromethane was immersed in an acetone slurry bath at -78 °C. Boron trichloride was added and the reaction was stirred at this temperature for 1 h before being transferred to an ice bath to allow the reaction to warm to 0 °C. After 1 h at this temperature, TLC indicated that all the starting material had been converted to a single new product. The reaction was quenched and a workup, followed by column chromatography, revealed that we had indeed successfully carried out the selective deprotection, thus affording the phenol *(R)*-**214** as a yellow oil in a yield of 82%.



Transformation to the phenol was clearly observed in the ^{1}H NMR spectrum of the product. The three methoxy singlets had been reduced to two methoxy signals, this being a clear indication of the successful deprotection. The alcohol was revealed as a new, far downfield singlet

at 12.59 ppm, indicating possible hydrogen bonding to the adjacent carbonyl. Accompanying changes included a shift in the aromatic signals slightly downfield. The ^{13}C NMR spectrum contained one less signal as a result of the selective cleavage of a methyl group. The carbonyl signal had shifted slightly downfield to 198.54 ppm perhaps due to the hydrogen bonding interaction to the phenolic O*H*. The peaks in the IR spectrum at 3081 cm^{-1} and 1635 cm^{-1} attested to the presence of both the alcohol and the carbonyl, respectively. The chemical shift of the carbonyl signal was indicative of a hydrogen bonded ketone.

3.2.29 Synthesis of rotenone and its diastereomer – 1a and 1b



Scheme 91

Having finally obtained our penultimate compound *(R)*-**214**, we were now in a position to carry out the final transformation in the synthesis of rotenone in the form of a base-catalysed intramolecular oxo-Michael addition (Scheme 91). This was achieved by adding sodium acetate to a solution of the chromene in absolute ethanol and heating the reaction to reflux at 90 °C. Following 30 minutes of stirring, TLC analysis indicated that two new products of similar R_f were present in addition to a small amount of starting material. The reaction was stirred for a further 2 hours and then worked up despite the trace amounts of starting material which persisted. Separation of the two products by flash chromatography proved to be problematic as a significant amount of co-eluted material was obtained. To resolve this problem, these mixed fractions were separated by preparative layer chromatography. NMR spectroscopic analysis indicated that the two products were almost identical and only slight differences in the chemical shift values of several signals was observed. As expected, we had synthesised the diastereomers **1a** and **1b**. Upon comparison of their NMR spectra to the spectrum of commercially available rotenone, we were able to identify compound **1a** as being the correct diastereomer as its NMR spectra were analogous to those of the commercially available material, obtained from natural sources. Figure 14 and Figure 15 below illustrate the means by

which we were able to identify the correct diastereomer **1a** from our two products, as being analogous to natural rotenone. An overlay of the spectra illustrates that the ^{1}H NMR spectrum of diastereomer **1a** in green matches the NMR spectrum of commercial rotenone (blue). Quite clearly, the diastereomer **1b** is different from the commercial form of rotenone and these differences have been highlighted below (black line).

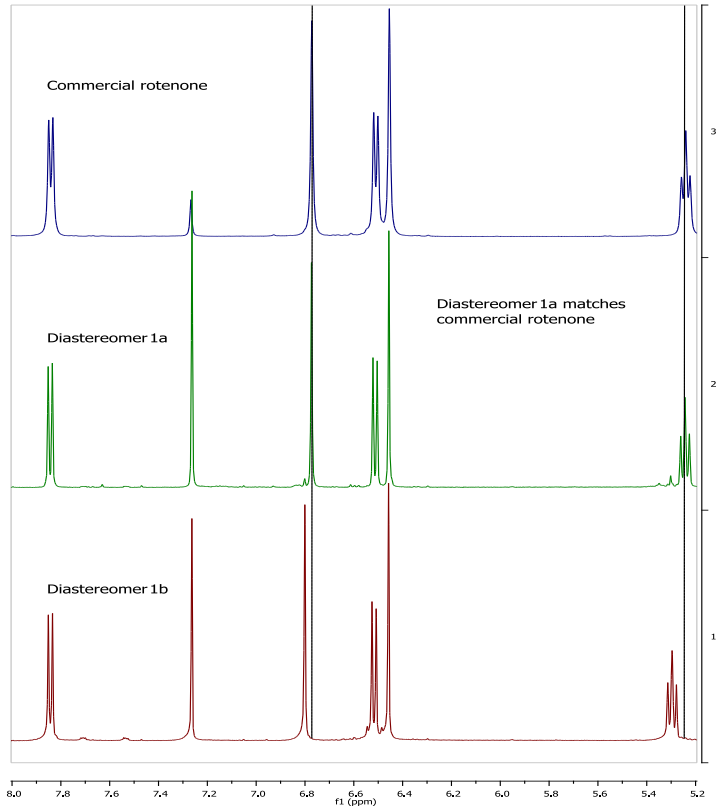


Figure 14

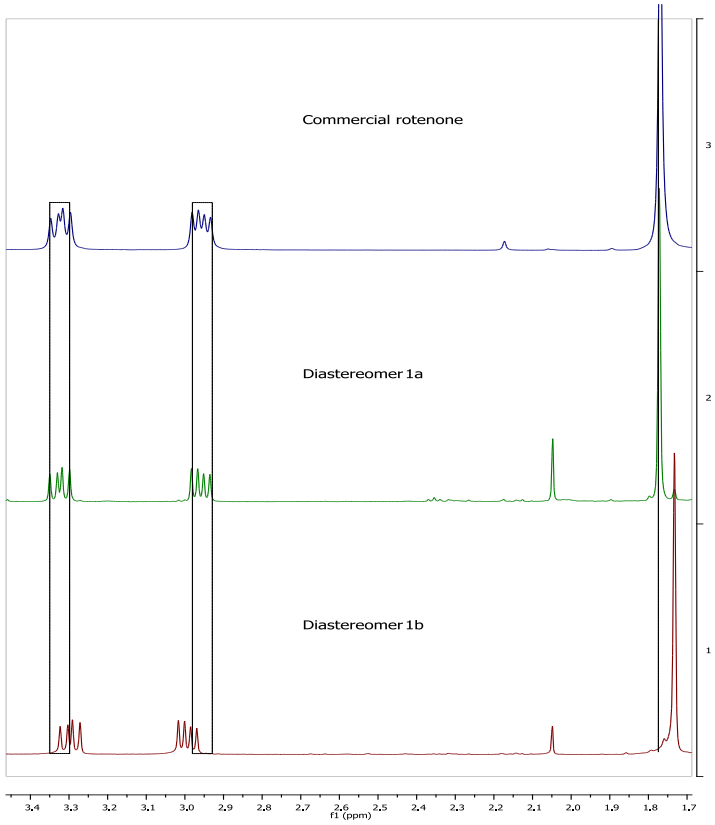
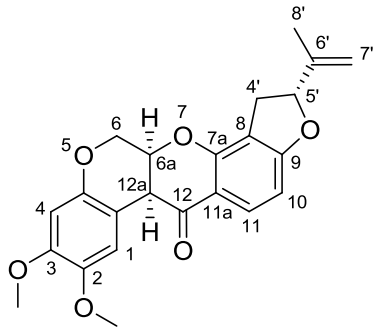


Figure 15



The most obvious change in the ^{1}H NMR spectrum in going from the precursor *(R)*-**214** to rotenone **1a** was the disappearance of the phenolic proton in the far downfield region. The aromatic signals as well as those of the dihydrobenzofuran moiety remain unchanged except for slight alterations in their chemical shift values. Once these signals had been assigned to their respective protons, we could begin with the assignment of the remaining protons H_6, H_{6a} and H_{12a}. Being adjacent to a stereogenic centre, protons H_6 were non-equivalent and produced individual signals as a doublet of doublets and a doublet at 4.62 ppm and 4.19 ppm, respectively. The COSY spectrum proved useful in identification of the remaining signals. The proton at 4.19 ppm was simply coupled to the other proton H_6 hence the doublet. In addition to this, the proton at 4.62 ppm was coupled to a second proton at 4.94 ppm which must therefore be proton H_{6a}. The actual coupling pattern was not clear as this signal overlapped with that of the alkene proton $H_{7'}$. Proton H_{6a} was in turn coupled to H_{12a} at 3.85 ppm, hence the doublet. Analysis of the coupling constant between protons H_{6a} and H_{12a} showed that we had indeed synthesised *cis* rotenone. This was confirmed upon comparison to the physical data of both *cis* and *trans* rotenone available in the

literature in which c*is* coupling gave a *J* value of 3.9 Hz, unlike *trans* coupling which is 12.8 Hz.[100] Regarding signals in the ^{13}C NMR spectrum, these were assigned using an HSQC and an HMBC spectrum. In the IR spectrum, loss of the broad OH stretch present in the precursor further attested to the success of the reaction.

The specific rotation, which was similar in magnitude and identical in sign to natural rotenone, verified that one enantiomer was in excess of the other. However, the specific rotation is unreliable in determining the enantiomeric excess as the literature values vary significantly. Moreover, the presence of a trace amount of the opposite diastereomer may have also altered this value.

Nevertheless, subsequent recrystallisation of the matching diastereomer **1a** from carbon tetrachloride afforded crystals from which an X-ray structure was obtained (Figure 16). The structure showed that rotenone had been synthesised and that all three stereogenic centres were identical to the naturally occurring form of rotenone. Indeed, the compound belonged to the chiral space group $P2_12_12_1$ which meant that the carefully constructed stereogenic centre at the 5'-position had been maintained throughout the chemical transformations leading to rotenone. The unit cell contained two molecules of rotenone in which slightly different conformations had been adopted. However, both molecules had the correct stereochemistry at the 5', 6a and 12a-centres. A suitable R-factor of 4.79% was obtained for this crystal structure.

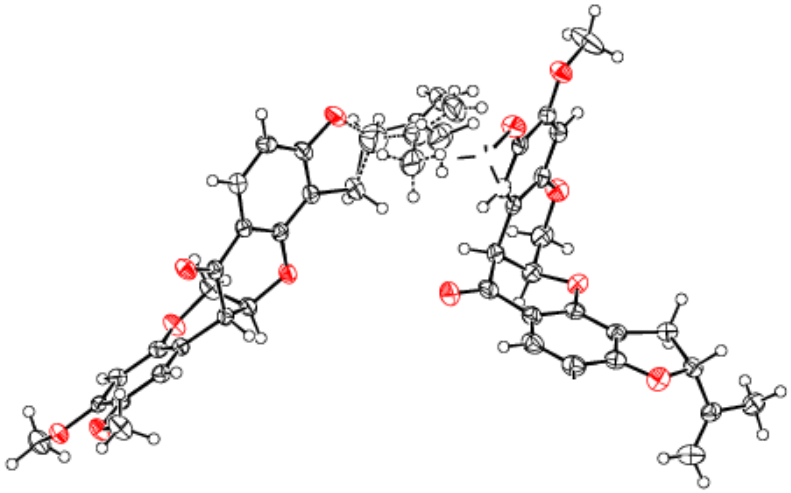
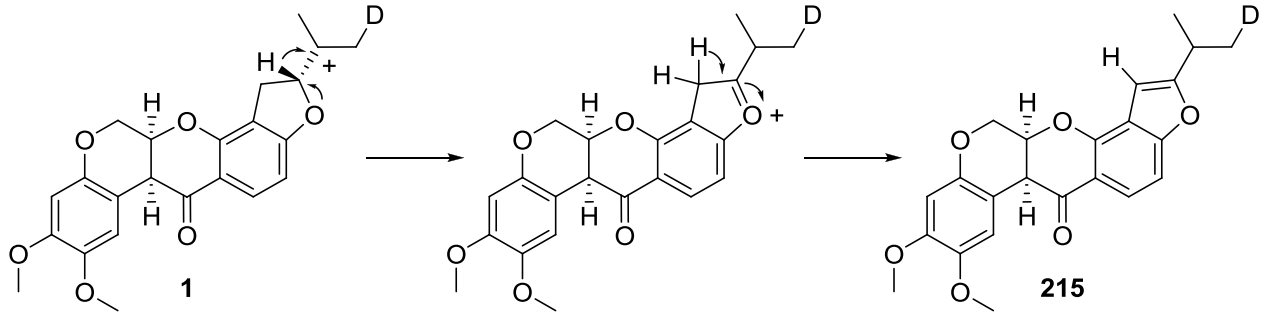


Figure 16

The results obtained from the X-ray structure were verified by chiral HPLC which was exhaustively employed as a means to separate the enantiomers. The results in using the chiralcel OJ column, chiralcel OD-H column and the chiral Supelco Chirobiotic T column were in agreement with the fact that we had not eroded the enantiomeric excess in the synthesis towards rotenone.

Although the recorded melting point of **1a** was slightly lower than the melting points available in the literature, it should be mentioned that these values are also somewhat inconsistent across several publications. The melting point depression of **1a** could be due to one or both of the following reasons. Firstly, the presence of a small amount of the diastereomer **1b** (indicated by means of HPLC work) may have lowered the melting point. The type of capillary used has also been shown to affect the melting point, specifically of rotenone. Therefore, the melting point of rotenone should not be taken as a measure of the purity of the sample.[101]

Interestingly, after several hours of being in $CDCl_3$, a rerun of the spectrum showed several small additional signals. This was clearly visible as the deuterated solution changed colour from clear to yellow within one day. Whilst this may be due to the decomposition of rotenone, isomerisation of rotenone **1a** to isorotenone **215** is also a common feature observed in acidic deuterated solvents. The is believed to take place by means of a 1,2-hydrogen shift from $C_{5'}$ to $C_{6'}$, as illustrated below (Scheme 92).[81, 82, 102]



Scheme 92

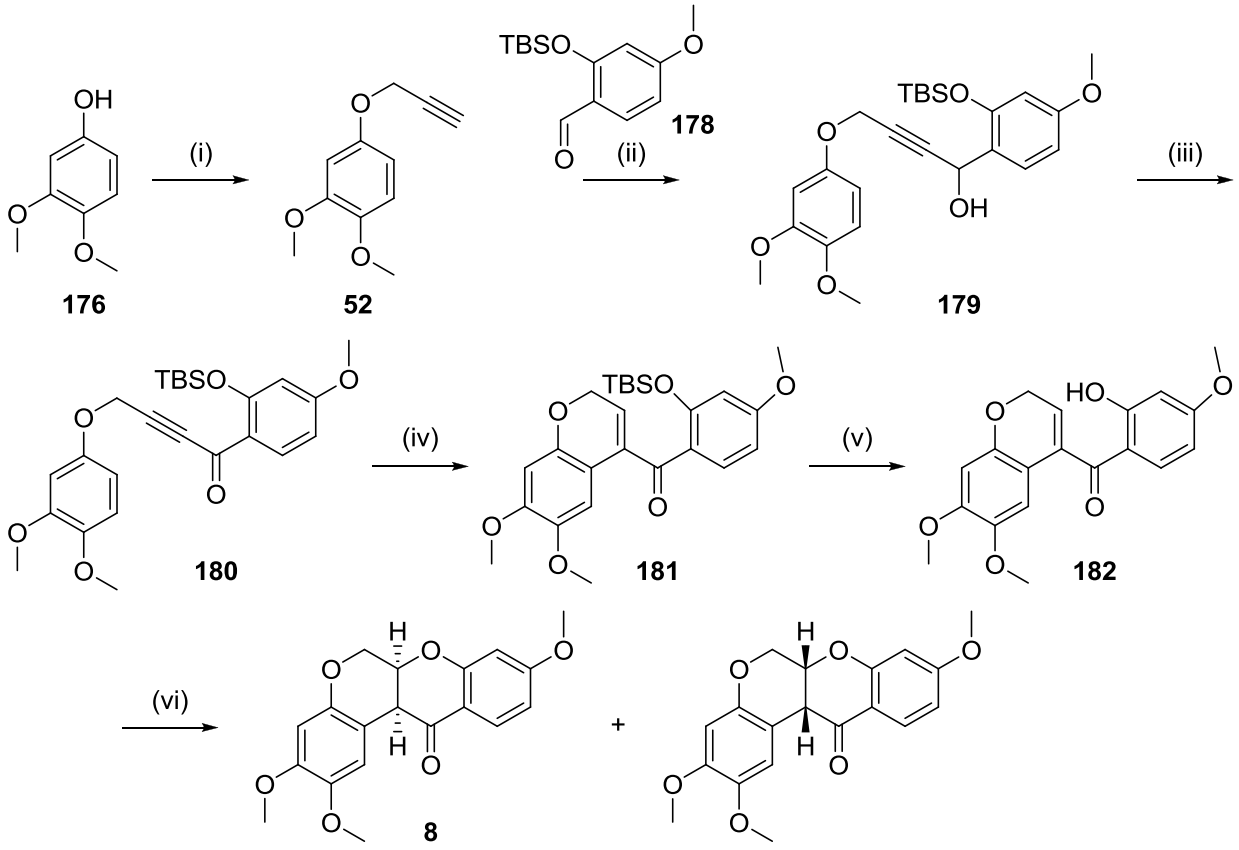
In summary of the final transformation, we had synthesised two diastereomers of rotenone. These were in fact both *cis* products, as confirmed by the coupling constants between protons H_{6a} and $H_{12a.}$ We were able to identify the desired diastereomer by comparison of their NMR spectra to that of commercially available rotenone extracted from Nature. The matching diastereomer was recrystallised and an X-ray structure confirmed that we had assuredly synthesised the natural form

of rotenone and that this had been achieved stereoselectively as the compound belonged to a chiral space group. The X-ray structure together with information gathered from chiral HPLC confirmed the natural pesticide, rotenone had been synthesised enantioselectively.

3.3 Concluding remarks

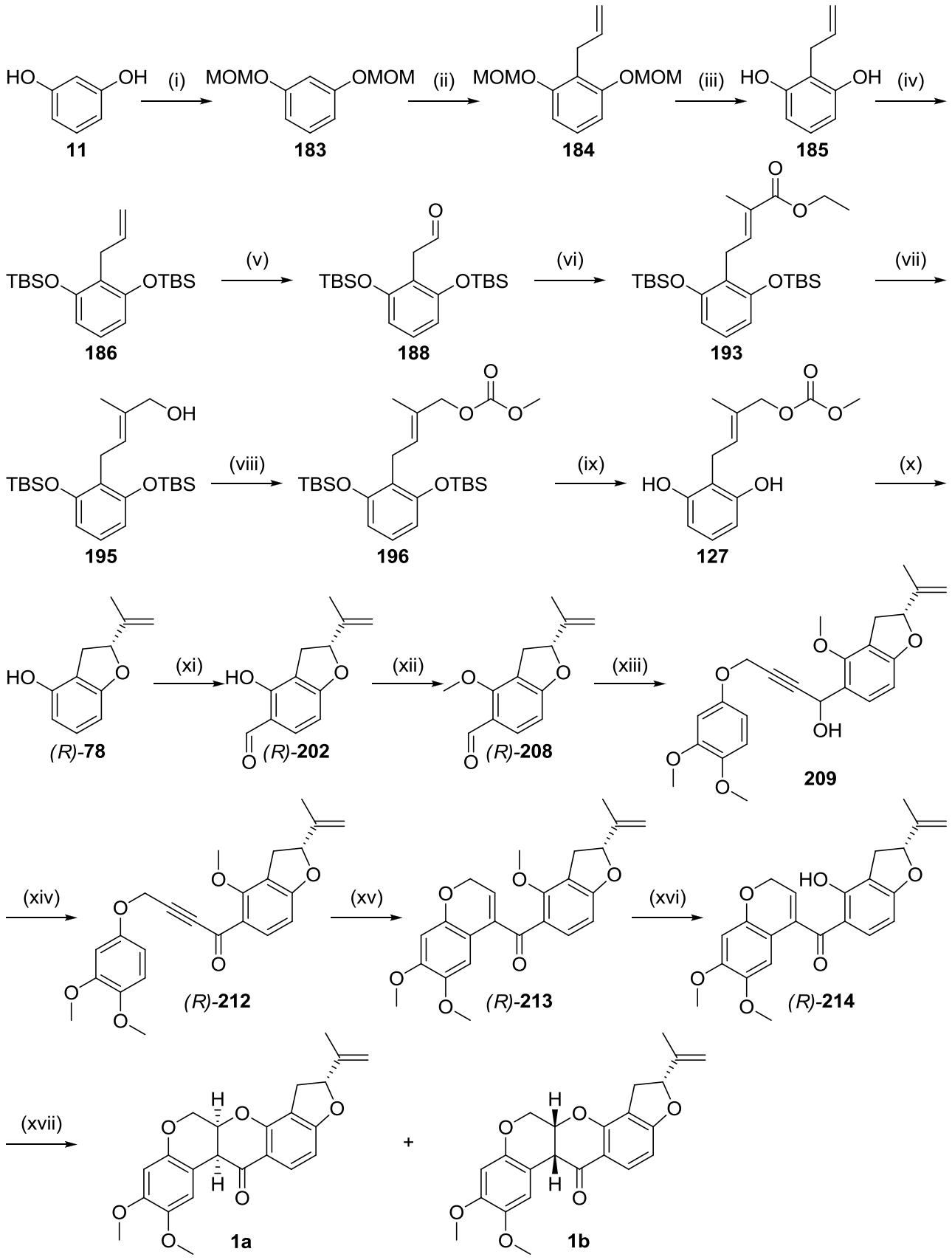
3.3.1 Project summary

In conclusion, we have successfully synthesised the two natural rotenoids, munduserone and rotenone. Munduserone **8** was synthesised racemically in six steps starting from commercially available 3,4-dimethoxyphenol **176** (Scheme 93). An alkylation reaction, followed by convergence with an appropriately substituted benzaldehyde **178**, afforded the coupled alcohol **179**. Oxidation to the alkynone **180**, followed by the crucial 6-*endo*-hydroarylation reaction, yielded the required chromene moiety **181**. The silyl protecting group was cleaved and a final intramolecular Michael addition furnished (±)-munduserone in six synthetic steps and a satisfactory overall yield of 23%. No diastereomers (containing the *trans*-fused ring system) were obtained in this synthesis and in fact, an X-ray crystal structure confirmed that munduserone had been synthesised as the *cis*-fused ring system.



Scheme 93: *Reagents and conditions:* (i) Propargyl bromide, K_2CO_3, DMF, rt, 18 h, 91%; (ii) a: **52**, *n*BuLi, THF, -78 °C, 30 min, b: **178**, 1 h, rt, 81%; (iii) MnO_2, CH_2Cl_2, rt, 18 h, 84%; (iv) $PtCl_2$, toluene, 70 °C, 18 h, 46%; (v) HF, MeCN, rt, 1.5 h, 87%; (vi) NaOAc, EtOH, 90 °C , 2 h, 92% of racemate.

Having successfully synthesised munduserone, we then proceeded to the synthesis of rotenone from commercially available resorcinol **11** (Scheme 94). The synthesis was based upon two key reactions of which the first was a Pd π-allyl mediated cyclisation as a means to the assembly of the dihydrobenzofuran moiety. In the latter part of the synthesis, the chromene half of rotenone was synthesised by means of a 6-*endo*-hydroarylation. Hence, in commencing with the dihydrobenzofuran synthesis, resorcinol was converted to the MOM ether **183** and following an allylation in the *ortho* position, a protecting group switch was conducted and TBS groups were introduced. The silylated compound **186** was oxidised by means of an ozonolysis reaction to the aldehyde **188**, which was then subjected to a Horner-Wadsworth-Emmons reaction, affording the *(E)*- alkene **193** exclusively. The resulting ester **193** was reduced to an alcohol **195** and then converted to the carbonate **196**. Finally, a deprotection afforded the diol **127** which was subjected to a Pd π-allyl mediated cyclisation in the presence of a chiral Trost ligand, thus affording the dihydrobenzofuran **78** in an excellent enantiomeric excess. The dihydrobenzofuran was subsequently formylated, protected as a methoxy and then coupled to the propargyl ether to afford the secondary alcohol **209**. Following an oxidation reaction, the key 6-*endo*-hydroarylation was conducted to furnish the chromene **213**. Finally, a deprotection followed by an internal Michael addition afforded rotenone **1a** and its diastereomer **1b**, separable by PLC. Our desired diastereomer was identified upon comparison of the NMR spectra of each diastereomer to that of commercially available rotenone. An accompanying X-ray crystal structure verified that the desired diastereomer had been synthesised, which also belonged to a chiral space group, thereby confirming that we had indeed synthesised rotenone stereoselectively. This result was verified by chiral HPLC work. This project therefore constitutes the first total, stereoselective synthesis of the natural pesticide, rotenone in 17 steps and an overall yield of 0.02%!



Scheme 94: *Reagents and conditions:* (i) NaH, MOMCl, DMF, 0 °C to rt, 18 h, 57%; (ii) *n*BuLi, allyl bromide, THF, 0 °C to rt, 18 h, 84%; (iii) HCl, THF/MeOH, reflux, 2 days, quant.; (iv) TBSCl, imidazole,

MeCN, RT, 18 h, 86%; (v) O_3, Zn/AcOH, CH_2Cl_2, -78 °C, 73%; (vi) LiCl, ethyl-2-(diethoxyphosphoryl)propanoate, *n*BuLi, THF, 0 °C, 18 h, 90%; (vii) $LiAlH_4$, THF, 0 °C, 3 h, 87%; (viii) Methyl chloroformate, pyridine, CH_2Cl_2, 0 °C to rt, 35 min, 91%;, (ix) TBAF, THF, O °C, 5 min, 86%; (x) 1.5 mol% $Pd_2(dba)_3CHCl_3$, 8 mol% *R,R'*-Trost ligand, AcOH, CH_2Cl_2, 18 h, 23°C, 85%, 94% ee; (xi) *p*-Formaldehyde, $MgCl_2$, NEt_3, THF, reflux, 2 h, 75%; (xii) K_2CO_3, dimethyl sulfate, acetone, reflux, 1 h, 98%; (xiii) a: LDA, **52**, THF, -78 °C, 2 h, b: **208**, rt, 1.5 h, 75%; (xiv) MnO_2, $CHCl_2$, rt, 1 h, 80%; (xv) $PtCl_2$ toluene, 70 °C, 2 h, 77%; (xvi) BCl_3, $CHCl_2$, -78 °C to 0 °C, 2 h, 82%; (xvii) NaOAc, EtOH, 90 °C, 2.5 h, overall 89% of diastereomers.

3.3.2 Interesting observations noted

In the synthesis of both rotenoids, several interesting observations were made which warrant further discussion. The first of these pertains to the coupling reaction of the alkyne to the appropriate benzaldehyde. In the synthesis of munduserone, this reaction proceeded smoothly using *n*BuLi as the coupling reagent and the silylated benzaldehyde **178**, thus affording the secondary alcohol in a good yield (Scheme 93). In contrast to this, the analogous reaction *en route* to rotenone was unsuccessful when using the TBS-protected dihydrobenzofuran *(R)*-**204** (Figure 17). This was attributed to the fact that the dihydrobenzofuran was more bulky than the analogous aldehyde **178** synthesis of munduserone, thereby pushing the TBS group toward the aldehyde so that the reactive site was crowded and the coupling reaction was inhibited. In fact, in switching to the less bulky methyl protecting groups, the dihydrobenzofuran *(R)*-**208** could be coupled to the alkyne, although in a poor yield when using *n*BuLi. The yield of this reaction was further improved by using LDA as a base.

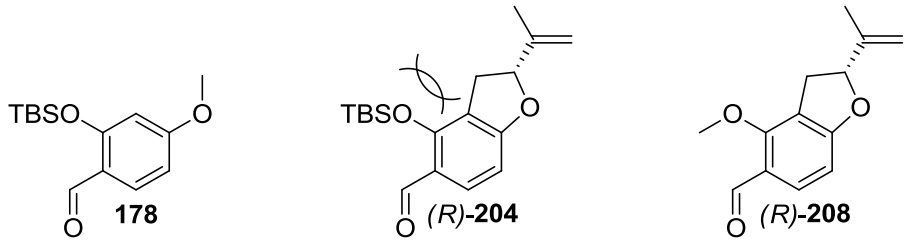


Figure 17

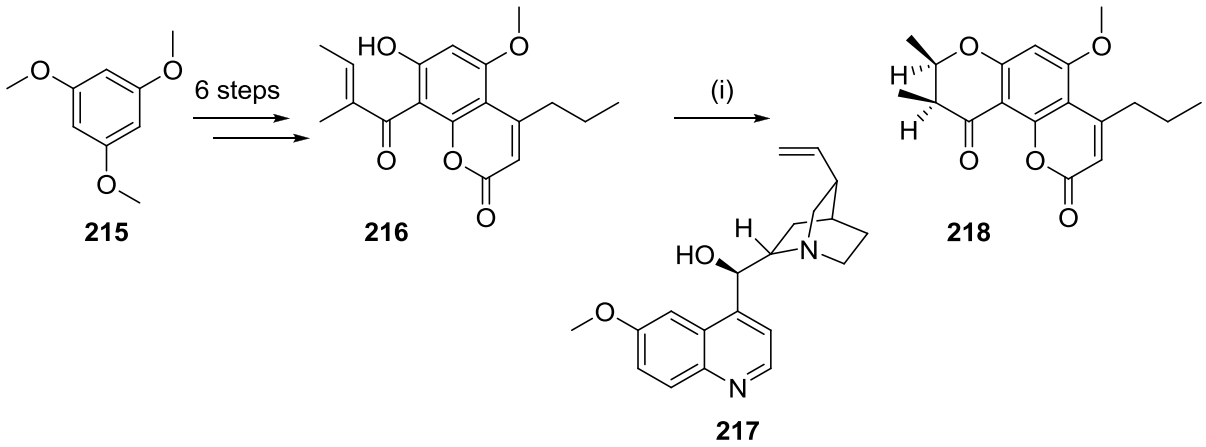
Another reaction that appeared to be limited by steric bulk was the key 6-*endo*-hydroarylation. In the synthesis of munduserone, the 6-*endo*-hydroarylation was low yielding. Fortunately, the reaction proceeded smoothly in the route towards rotenone in which the significantly less bulky methyl protecting group was employed. Since this reaction had been attempted using a variety of

catalyst and solvent systems, we were confident that the difference in results was a matter of sterics. In utilising TBS groups in the synthesis of munduserone, the alkyne was perhaps sterically congested, thus obstructing initial coordination of the platinum catalyst to the alkyne. However, in using a less bulky protecting group, the alkyne was accessible for coordination to the metal catalyst, thereby rendering it susceptible to attack by the nucleophile which, in this case, was the tethered aromatic system.

3.3.3 Future work to utilise an asymmetric Michael addition

In the final intramolecular Michael addition, two stereogenic centres at the 6a and 12a-positions were created. In the synthesis of munduserone, a racemic mixture of enantiomers was afforded, although both were the *cis* isomers, i.e. the (S_{6a}, S_{12a}) and (R_{6a}, R_{12a}) enantiomers were present. Since in the synthesis of rotenone a stereogenic centre was already present at the 5'-carbon centre, diastereomers **1a** - (S_{6a}, S_{12a}, $R_{5'}$) and **1b** - (R_{6a}, R_{12a}, $R_{5'}$) were synthesised which fortunately could be separated by chromatographic methods. However, several examples exist in the literature in which Michael additions have been conducted stereoselectively. Therefore, had these been applied to the synthesis of rotenone, a single diastereomer may have been assembled. Although stereoselective intramolecular Michael additions that afford only one *cis* isomer at a ring junction are numbered, a brief description of a selected literature example is discussed below.

Intramolecular Michael additions have been utilised extensively in the synthesis of polycyclic compounds, many of which are chiral natural products. Therefore, there is pressing need for asymmetric reactions that will favour a specific enantiomer at the newly formed ring junction. In a selected example, Ishikawa and co-workers developed a quinine-catalysed asymmetric Michael addition which satisfied these requirements (Scheme 95).[103] The synthesis commenced with 1,3,5-trimethoxybenzene **215** which was converted over a number of steps to the 5-hydroxycoumarin derivative **216**. In using quinine **217** and chlorobenzene as the solvent, the Michael addition afforded the chromanone **218** enriched with a single *cis* enantiomer, attained in an enantiomeric excess of 98%. In fact, the stereochemistry of the major enantiomer at the newly formed ring junction mimics that at the 6a and 12a-positions in rotenone (both hydrogens pointing downwards), thus making this a feasible approach. Therefore, in an effort to circumvent the separation of diastereomers, future work in our laboratories could entail the application of the above methodology to the synthesis of rotenone as this may afford a single diastereomer.



Scheme 95: *Reagents and conditions:* (i) 10 mol% quinine, PhCl, 14 °C, 21 h, 100%, 98% ee of the *cis* isomer.

CHAPTER 4 – EXPERIMENTAL PROCEDURES

4.1 General Procedures

4.1.1 Purification of solvents and reagents

Solvents used for reactions were dried over an appropriate drying agent and then distilled under nitrogen gas. Tetrahydrofuran was distilled over sodium wire using benzophenone as an indicator. Toluene was distilled from sodium metal lumps. Dichloromethane and acetonitrile were distilled from calcium hydride. Reagents were obtained from commercial sources and used without purification or purified by standard procedures outlined by Perrin *et al.*[104] The solvents used for chromatographic purposes were distilled prior to use by means of conventional distillation procedures.

4.1.2 Chromatography

Purification of compounds by column chromatography was achieved using Macherey-Nagel silica gel 60 (particle size 0.063 mm to 0.200 mm) as the adsorbent. Silica gel of particle size 0.040 mm to 0.070 mm was occasionally utilised for flash chromatography. Mixtures of ethyl acetate and hexane were used as the mobile phase. The reported R_f values are for analytical thin layer chromatography (TLC) performed using aluminium-backed Macherey-Nagel Alugram Sil G/UV_{254} plates pre-coated 0.25 mm silica gel 60. Adsorbed compounds were either viewed under UV light or by dipping into $KMnO_4$ or 2,4-Dinitrophenyl hydrazine staining solutions.

4.1.3 Spectroscopic and physical data

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ADVANCE 300 spectrophotometer at 300.13 MHz and 75.47 MHz, respectively. Occasionally, a Bruker DRX 400 spectrometer was employed for ^{1}H (400.13 MHz) and ^{13}C (100.63 MHz) spectra. The final compound was recorded on a Bruker Ultrashield 500 Plus spectrophotometer at 500.13 MHz for the ^{1}H NMR spectrum and 125.76 MHz for the ^{13}C NMR spectrum. Spectra were recorded in deuterated chloroform ($CDCl_3$) and are reported in parts per million relative to tetramethylsilane in ^{1}H NMR spectra and the central deuterated chloroform signal in ^{13}C NMR spectra. *J*-values are given in Hz. HSQC spectra were used to assign protonated carbon signals. In most instances quaternary carbons were simply listed, especially for more complicated molecules. On occasion, these were assigned using HMBC spectra.

Infra-red spectra were recorded on a Bruker Tensor-27 Fourier Transform spectrometer. Measurements were made by loading the sample directly onto a diamond cell. The signals are reported on the wavenumber scale (ν/cm^{-1}).

Specific rotations were measured using a Jasco DIP-370 Digital Polarimeter at the D-line of sodium (589 nm).

Melting points were measured using the X-4 Melting-Point Apparatus with microscope and are uncorrected.

High resolution mass spectra were recorded in either the EI^+ or EI^- mode on a Waters Synapt G2 mass spectrometer.

Intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 Kv, 30 mA). APEX 2 data collection software was used and the collection method involved ω-scans of width 0.5° and 512 x 512 bit data frames. Data reduction was carried out using the program *SAINT+* version 6.02 and face indexed absorption corrections were made using *XPREP*. Crystal structures were solved by direct methods using *SHELXS-97*. Non-hydrogen atoms were first refined isotropically and then anisotropically by full-matrix least-squares calculations based on F^2 using *SHELXL-97*. Hydrogen atoms were located in the difference map and then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL, PLATON[105] and ORTEP-3.[106]

4.1.4 High pressure liquid chromatography

High pressure liquid chromatography (HPLC) was performed on an UltiMate 3000 HPLC using a Chiralcel OJ 10μ 250 x 4.6 mm chiral column at flow rates of 1.0 $ml.min^{-1}$. A mixture of isopropyl alcohol and hexane was used as the mobile phase. The eluted compounds were detected using an UltiMate 3000 photodiode array detector at 215 nm. All calculations were based on peak area. Occasionally, the Chiralcel OD-H 5μ 250 x 4.6 mm chiral column was used at a flow rate of 1.0 $ml.min^{-1}$.

4.1.5 Other general procedures

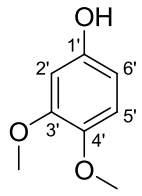
All reactions were carried out under Ar (g) and reaction vessels were dried prior to use, either in the oven or flame-dried whilst under vacuum. "*In vacuo*" refers to the removal of solvent using a rotary

evaporator. Following purification of products, residual solvent was removed using a high vacuum pump (*ca*. 0.1 mm Hg) at ambient temperature.

4.2 Experimental work pertaining to the synthesis of munduserone

4.2.1 3,4-Dimethoxyphenol – 176

Into a two neck round bottom flask under Ar was placed 3,4-dimethoxybenzaldehyde **174** (4.00 g, 24.1 mmol) followed by dry dichloromethane (80 ml). *m*-Chloroperbenzoic acid (5.71 g with 20% water, 26.5 mmol) was added and the reaction was left to proceed at rt for 15 h. The reaction mixture was quenched with dimethyl sulfide (ca. 5 ml) and the solvent evaporated *in vacuo*. The crude material was transferred to a separating funnel and diluted with ethyl acetate (50 ml) and water was added (50 ml). After mixing, the phases were separated and the organic fraction was sequentially extracted with water (2 × 50 ml) and then brine (50 ml). The solvent was removed *in vacuo* and the residue dissolved in a methanolic solution of KOH (5% w/v, 121 ml, 108 mmol) and then heated to reflux for 18 h. The reaction was allowed to cool to rt, neutralised with ice-cooled aqueous HCl (20 ml), transferred to a separating funnel and ethyl acetate (100 ml) and water (50 ml) were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with brine (150 ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. After purification by column chromatography (30% EtOAc/Hexane), the phenol **176** was obtained as a white solid (3.12 g, 84%).

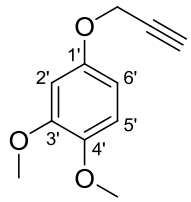


R_f = 0.48 (50% EtOAc/Hexane). **Mp.** = 79-81 °C, (Sigma-Aldrich Lit. 79-82 °C). **δ_H /ppm:** 6.73 (1H, d, *J*=8.6 Hz, $H_{5'}$), 6.48 (1H, d, *J*=2.8 Hz, $H_{2'}$), 6.36 (1H, dd, *J*=8.6 Hz and 2.8 Hz, $H_{6'}$), 5.70 (1H, br s, O*H*), 3.81 (3H, s, OCH_3), 3.79 (3H, s, OCH_3). **δ_C /ppm:** 150.22 (Ar*C*O), 149.78 (Ar*C*O), 142.94 (Ar*C*O), 112.48 ($C_{5'}$), 105.87 ($C_{6'}$), 100.60 ($C_{2'}$), 56.53 (OCH_3), 55.70 (OCH_3). **ν_{max} /cm^{-1}:** 3419 (OH str), 2936 (CH str), 1608, 1506, 1289, 1126, 1022.

4.2.2 1,2-Dimethoxy-4-(prop-2-ynyloxy)benzene – 52

Propargyl bromide (80 wt % in toluene, 0.17 ml, 1.6 mmol) and potassium carbonate (0.22 g, 1.6 mmol) were added to a solution of 3,4-dimethoxyphenol **176** (0.20 g, 1.3 mmol) in freshly

distilled dimethylformamide (6.5 ml). The reaction was left to stir at rt under Ar for 18 h and saturated aqueous ammonium chloride (50 ml) and ethyl acetate (50 ml) were then added. The reaction mixture was transferred to a separating funnel and after mixing and separating the phases, the organic phase was extracted with water (2 × 50 ml), brine (50 ml) and dried over anhydrous magnesium sulfate. Following filtration and evaporation of the volatiles *in vacuo*, the crude oil was purified by column chromatography (20% EtOAc/Hexane) to afford the desired alkylated compound **52** as a pale yellow solid (0.23 g, 91%).

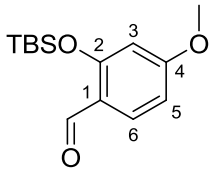


R_f = 0.71 (50% EtOAc/Hexane). **Mp.** = 51-52 °C, (Lit.[38] 48-48.5 °C). **δ_H /ppm:** 6.79 (1H, d, *J*=8.7 Hz, $H_{5'}$), 6.59 (1H, d, *J*=2.8 Hz, $H_{2'}$), 6.49 (1H, dd, *J*=8.7 Hz and 2.8 Hz, $H_{6'}$), 4.65 (2H, d, *J*=2.4 Hz, $CH_2C{\equiv}CH$), 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 2.52 (1H, t, *J*=2.4 Hz, $CH_2C{\equiv}CH$). **δ_C /ppm:** 152.12 (Ar*C*O), 149.85 (Ar*C*O), 144.16 (Ar*C*O), 111.56 ($C_{5'}$), 104.40 ($C_{6'}$), 101.40 ($C_{2'}$), 78.80 ($CH_2C{\equiv}CH$), 75.38 ($CH_2C{\equiv}CH$), 56.46 (OCH_3), 56.36 (OCH_3), 55.85 ($CH_2C{\equiv}CH$).[48] **ν_{max} /cm^{-1}:** 3283 (≡CH str), 2937 (CH str), 1598, 1508, 1451, 1225, 1193, 1023. **HRMS** (ESI, +ve) $C_{11}H_{13}O_3^+$ [MH^+] requires *m/z* 193.0866, found 193.0864.

Note: the numbering scheme in **176** was adopted so as to allow for easy reading.

4.2.3 2-(*Tert*-butyldimethylsilyloxy)-4-methoxybenzaldehyde – 178

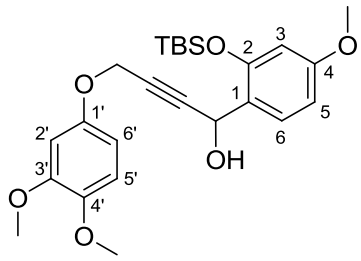
Into a dry two neck round bottom flask under Ar was placed 2-hydroxy-4-methoxybenzaldehyde **177** (0.50 g, 3.3 mmol) followed by dry acetonitrile (50 ml). Imidazole (0.29 g, 4.3 mmol) and then TBSCl (0.64 g, 4.2 mmol) were added in a single portion and after 15 min the imidazole hydrochloride salt appeared. Following 18 h of stirring, analysis by TLC indicated that all of the starting material had reacted. The acetonitrile was evaporated and the crude mixture was taken up in ethyl acetate (50 ml) and water (50 ml), thus facilitating the dissolution of the imidazole hydrochloride salt into the aqueous phase upon mixing. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were washed with brine (150 ml), separated and dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo*, the crude product was purified by column chromatography (10% EtOAc/Hexane), yielding the silyl-protected product **178** as an oil (5.34 g, 86%).



R_f = 0.66 (20% EtOAc/Hexane). **δ_H /ppm:** 10.30 (1H, s, C*H*O), 7.79 (1H, d, *J*=8.8 Hz, H_6), 6.59 (1H, dd, *J*=8.8 Hz and 1.7 Hz, H_5), 6.34 (1H, d, *J*=2.3 Hz, H_3), 3.84 (3H, s, OCH_3), 1.02 (9H, s, C(CH_3)$_3$), 0.29 (6H, s, Si(CH_3)$_2$). **δ_C /ppm:** 188.61 (*C*HO), 165.70 (Ar*C*O), 160.68 (Ar*C*O), 130.05 (C_6), 121.36 (C_1), 107.78 (C_5), 105.18 (C_3), 55.48 (O*C*H_3), 25.62 (C(*C*H_3)$_3$), 18.31 (*C*(CH$_3$)$_3$), -4.35 (Si(*C*H_3)$_2$). **ν_{max} /cm^{-1}:** 2934 (CH str), 1680 (C=O str), 1600, 1292, 1167. **HRMS** (ESI, +ve) $C_{14}H_{23}O_3Si^+$ [MH^+] requires *m/z* 267.1418, found 267.1417.

4.2.4 1-(2-(*Tert*-butyldimethylsilyloxy)-4-methoxyphenyl)-4-(3,4-dimethoxyphenoxy)but-2-yn-1-ol – 179

Into a two neck round bottom flask filled with Ar was placed the alkyne **52** (1.53 g, 7.96 mmol) followed by dry tetrahydrofuran (75 ml). The solution was cooled to -78 °C using a frozen acetone slurry bath and *n*BuLi (1.4 M, 5.8 ml, 8.1 mmol) was added dropwise. The reaction was stirred for 30 min and then the aldehyde **178** (2.00 g, 7.51 mmol), also dissolved in tetrahydrofuran (50 ml) and under Ar, was added via canula. An accompanying colour change was observed as the reaction went from a milky white to clear upon the addition of the aldehyde. The reaction was allowed to warm to rt and stirred for 1 h during which the solution turned yellow. Once quenched with NH_4Cl (50 ml), the reaction mixture was transferred to a separating funnel and diluted further with ethyl acetate (100 ml). After mixing, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were washed with brine (150 ml), dried over anhydrous magnesium sulfate and the solvent evaporated *in vacuo*. Purification was achieved by column chromatography (20% EtOAc/Hexane), furnishing the coupled product **179** as a yellow oil (2.79 g, 81%).

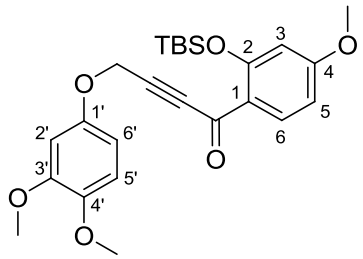


R_f = 0.33 (30% EtOAc/Hexane). **δ_H /ppm:** 7.39 (1H, d, *J*=8.5 Hz, H_6), 6.77 (1H, d, *J*=8.7 Hz, $H_{5'}$), 6.59 (1H, d, *J*=2.8 Hz, $H_{2'}$), 6.53 – 6.44 (2H, overlapping signals, H_5 and $H_{6'}$), 6.38 (1H, d, *J*=2.4 Hz, H_3), 5.70 (1H, d, *J*=5.5 Hz, C*H*OH), 4.72 (2H, s, CH_2C≡C), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 2.58 (1H, d, *J*=5.6 Hz, O*H*), 1.01 (9H, s, C(CH_3)$_3$)), 0.27 (6H, s, Si(CH_3)$_2$). **δ_C /ppm:** 160.60 (Ar*C*O), 153.92 (Ar*C*O), 152.25 (Ar*C*O), 149.75 (Ar*C*O), 144.01 (Ar*C*O), 128.81 (C_6), 123.38 (C_1), 111.57 ($C_{5'}$), 105.82 (ArC*H*), 105.31 (ArC*H*), 104.73 (C_5), 101.43 ($C_{2'}$), 87.02 (*C*≡C), 80.95 (C≡*C*), 60.29

(*C*HOH), 56.94 (*C*H_2C≡C), 56.34 (O*C*H_3), 55.78 (O*C*H_3), 55.29 (O*C*H_3), 25.71 (C(*C*H_3)$_3$), 18.16 (*C*(CH$_3$)$_3$), -4.18 (Si(*C*H_3)$_2$). **ν_{max} /cm^{-1}:** 3490 (OH str), 2932 (CH str), 1608, 1506, 1195, 1160, 1025. **HRMS** (ESI, +ve) $C_{25}H_{34}O_6SiNa^+$ [MNa$^+$] requires *m/z* 481.2022, found 481.2023.

4.2.5 1-(2-(*Tert*-butyldimethylsilyloxy)-4-methoxyphenyl)-4-(3,4-dimethoxyphenoxy)but-2-yn-1-one – 180

To a solution of the alcohol **179** (0.26 g, 0.57 mmol) in dry dichloromethane (30 ml) stirring at rt and under Ar was added manganese dioxide (0.98 g, 11 mmol). After 18 h TLC analysis indicated that although the product had formed, a significant amount of starting material remained. The reaction was left to stir for an additional three days until only a trace amount of starting material remained. The suspension was filtered through a bed of celite and the solvent removed *in vacuo*. The crude material was purified by column chromatography (20% EtOAc/Hexane), yielding the alkynone **180** as a yellow oil (0.22 g, 84%).

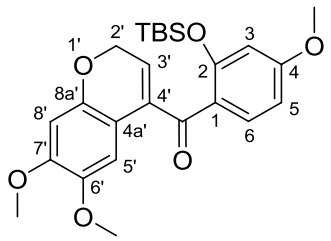


R_f = 0.40 (30% EtOAc/Hexane). **δ_H /ppm:** 7.85 (1H, d, *J*=8.8 Hz, H_6), 6.80 (1H, d, *J*=8.7 Hz, $H_{5'}$), 6.62 (1H, d, *J*=2.8 Hz, $H_{2'}$), 6.57 – 6.45 (2H, overlapping signals, H_5 and $H_{6'}$), 6.35 (1H, d, *J*=2.3 Hz, H_3), 4.86 (2H, s, C*H*$_2$C≡C), 3.86 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 1.02 (9H, s, C(C*H*$_3$)$_3$)), 0.24 (6H, s, Si(C*H*$_3$)$_2$). **δ_C /ppm:** 174.54 (*C*=O), 164.84 (Ar*C*O), 158.27 (Ar*C*O), 151.94 (Ar*C*O), 149.80 (Ar*C*O), 144.32 (Ar*C*O), 135.60 (C_6), 121.80 (C_1), 111.51 ($C_{5'}$), 106.88 (ArC*H*), 106.83 (C_3), 104.90 (ArC*H*), 101.62 ($C_{2'}$), 86.20 (*C*≡C), 86.12 (C≡*C*), 56.86 (*C*H$_2$C≡C), 56.29 (O*C*H$_3$), 55.82 (O*C*H$_3$), 55.43 (O*C*H$_3$), 25.75 (C(*C*H$_3$)$_3$), 18.45 (*C*(CH$_3$)$_3$), -4.29 (Si(*C*H$_3$)$_2$). **ν_{max} /cm^{-1}:** 2931 (CH str), 1737 (C=O str), 1598, 1509, 1228. **HRMS** (ESI, +ve) $C_{25}H_{33}O_6Si^+$ [MH$^+$] requires *m/z* 457.2048, found 457.2046.

4.2.6 (2-(*Tert*-butyldimethylsilyloxy)-4-methoxyphenyl)(6,7-dimethoxy-*2H*-chromen-4-yl)methanone – 181

Into a 2 neck round bottom flask fitted with a condenser and under Ar was placed the alkynone **180** (0.50 g, 1.1 mmol) followed by dry toluene (11 ml). The reaction was degassed by bubbling Ar directly into the solution for 5 min and $PtCl_2$ (0.034 g, 0.13 mmol, 12 mol%) was then added. The

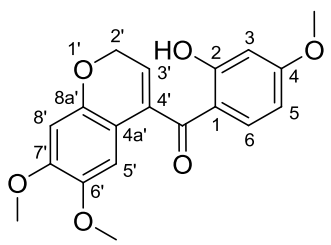
reaction was heated to 70 °C and stirred for 18 h. The solvent was removed *in vacuo* and the crude material adsorbed onto silica gel for purification by flash chromatography (10% EtOAc/Hexane). This afforded the desired chromene **181** as a yellow oil (0.23 g, 46%). A notable amount of starting material was also recovered.



R_f = 0.53 (30% EtOAc/Hexane). **δ_H /ppm:** 7.44 (1H, d, *J*=8.6 Hz, H_6), 7.35 (1H, s, $H_{8'}$), 6.57 (1H, dd, *J*=8.6 Hz and 2.3 Hz, H_5), 6.47 (1H, s, $H_{5'}$), 6.37 (1 H, d, *J*=2.2 Hz, H_3), 6.11 (1H, t, *J*=4.1 Hz, $H_{3'}$), 4.78 (2H, d, *J*=4.1 Hz, $H_{2'}$), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 0.87 (9H, s, C(CH_3)$_3$), 0.15 (6H, s, Si(CH_3)$_2$). **δ_C /ppm:** 194.56 (*C*=O), 163.14, 155.84, 149.89, 148.72, 143.35, 135.66, 132.40, 128.26, 124.29, 111.96, 109.21 ($C_{8'}$), 106.56 (C_5), 106.11 (C_3), 100.39 ($C_{5'}$), 64.85 ($C_{2'}$), 56.21 (O*C*H$_3$), 55.87 (O*C*H$_3$), 55.41 (O*C*H$_3$), 25.59 (C(*C*H$_3$)$_3$), 18.20 (*C*(CH$_3$)$_3$), -4.30 (Si(*C*H$_3$)$_2$). **ν_{max} /cm^{-1}:** 2931 (CH str), 1655 (C=O str), 1600, 1505, 1253, 1195, 1156. **HRMS** (ESI, +ve) $C_{25}H_{33}O_6Si^+$ [MH$^+$] requires *m/z* 457.2048, found 457.2025.

4.2.7 (6,7-Dimethoxy-*2H*-chromen-4-yl)(2-hydroxy-4-methoxyphenyl)methanone – 182

The silylated compound **181** (0.43 g, 0.94 mmol) was placed in a two neck round bottom flask containing dry acetonitrile (100 ml). HF (48%, 0.068 µl, 0.038 g, 1.9 mmol) was added and the solution was left to stir under Ar at rt. After 30 min, TLC analysis indicated that the deprotected alcohol had not formed and a second addition of HF (48%, 0.068 µl, 0.038 g, 1.9 mmol) was made. After 1.5 h of stirring, TLC showed that the reaction had gone to completion. Water (30 ml) was added and the reaction mixture was transferred to a separating funnel. The aqueous layer was extracted with ethyl acetate (3 × 50 ml) and the combined organic fractions were dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography (30% EtOAc/Hexane), revealing the deprotected phenol **182** as a yellow solid (0.28 g, 87%).



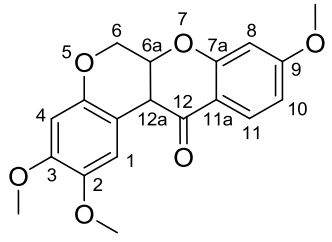
R_f = 0.44 (30% EtOAc/Hexane). **Mp.** = 119-121 °C. **δ_H /ppm:** 12.60 (1H, s, O*H*), 7.61 (1H, d, *J*=9.0 Hz, H_6), 6.70 (1H, s, $H_{8'}$), 6.51 (1H, s,

$H_{5'}$), 6.48 (1H, d, *J*=2.5 Hz, H_3), 6.38 (1H, dd, *J*=9.0 Hz and 2.5 Hz, H_5), 5.88 (1H, t, *J*=4.0 Hz, $H_{3'}$), 4.85 (2H, d, *J*=4.0 Hz, $H_{2'}$), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.73 (3H, s, OCH_3). **δ_C /ppm:** 198.39 (*C*=O), 166.83, 166.41, 150.57, 148.58, 143.74, 134.73 (C_6), 134.34, 122.02 ($C_{3'}$), 113.23, 111.92, 108.45 ($C_{8'}$), 107.61 (C_5), 100.98, 100.81 ($C_{5'}$), 64.60 ($C_{2'}$), 56.49 (OCH$_3$), 55.95 (OCH$_3$), 55.65 (OCH$_3$). **ν_{max} /cm^{-1}:** 2959 (CH str), 1615 (C=O str), 1582, 1502, 1243, 1200, 1182, 1159. **HRMS** (ESI, +ve) $C_{19}H_{19}O_6^+$ [MH^+] requires *m/z* 343.1183, found 343.1182.

4.2.8 (±)-Munduserone – 8

Into a two neck round bottom flask fitted with a condenser and under Ar was placed the alcohol **182** (0.19 g, 0.56 mmol) followed by absolute ethanol (100 ml). Sodium acetate (0.20 g, 2.5 mmol) was added and the reaction was set to reflux at 90 °C. The reaction was monitored regularly by TLC and after 2 h the reaction had gone to completion. Water (50 ml) and ethyl acetate (100 ml) were added to the cooled reaction mixture which was then transferred to a separating funnel. After mixing, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were washed with brine (150 ml) and dried over magnesium sulfate. Filtration and evaporation of the solvent *in vacuo* was followed by purification by column chromatography to furnish the final compound munduserone **8** as a racemic mixture (0.17 g, 92%). Recrystallisation from diethyl ether afforded off-white needle-like crystals (0.099g, 52%) suitable for X-ray analysis.

Note: A conventional rotenoid numbering scheme was adopted.[29, 107]



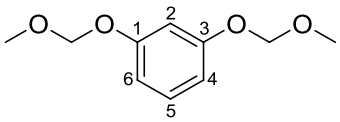
R_f = 0.60 (50% EtOAc/Hexane). **Mp.** = 168-170 °C. **δ_H /ppm**: 7.87 (1H, d, *J*=8.8 Hz, H_{11}), 6.76 (1H, s, H_4), 6.57 (1H, dd, *J*=8.8 Hz and 2.4 Hz, H_{10}), 6.46 (1H, s, H_1), 6.42 (1H, d, *J*=2.3 Hz, H_8), 4.94 (1H, t, *J*=3.1 Hz, H_{6a}), 4.62 (1H, dd, *J*=12.0 Hz, 3.1 Hz, H_6), 4.18 (1H, d, *J*=12.0 Hz, H_6), 3.84 (1H, d, *J*=4.0 Hz, H_{12a}), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.76 (3H, s, OCH_3). **δ_C /ppm:** 189.19 (*C*=O**),** 166.48, 162.75, 149.50, 147.37, 143.90, 129.31 (C_{11}), 112.74, 110.65 (C_{10}), 110.34 (C_4), 104.70, 100.98 (C_1), 100.67 (C_8), 72.36 (C_{6a}), 66.27 (C_6), 56.28 (OCH$_3$), 55.82 (OCH$_3$), 55.60 (OCH$_3$), 44.54 (C_{12a}). **ν_{max} /cm^{-1}:** 2938 (CH str), 1673 (C=O str), 1613, 1514, 1445, 1347, 1150, 1125. **HRMS** (ESI, +ve) $C_{19}H_{19}O_6^+$ [MH^+] requires *m/z* 343.1183, found 343.1182. **X-ray data:** $C_{19}H_{18}O_6$; *M*=342.33; triclinic; 0.71073 Å; *a*=4.6143(2) Å, *b*=12.4005(6) Å, *c*=13.8039(7) Å, *U*=779.42(6) Å^3; 296(2) K, space group, P-1,

Z=2;. μ(Mo-Kα)=0.109 mm^{-1} 12559 reflections measured, 3875 unique [R(int)=0.0608] which were used in all calculations. Final R indices [$I>2\sigma(I)$] R_1=0.0445, Wr(F^2)=0.0899.

4.3 Experimental work pertaining to the synthesis of rotenone

4.3.1 1,3-*Bis*(methoxymethoxy)benzene – 183

Into a two neck round bottom flask containing Ar was placed distilled dimethylformamide (100 ml) followed by commercially available resorcinol **11** (20.0 g, 0.182 mol). The reaction flask was immersed in an ice bath and sodium hydride (60% dispersion in oil, 16.8 g, 0.420 mol) was slowly added resulting in effervescence of the solution. This was followed by the addition of methoxymethyl chloride (35.6 g, 33.0 ml, 0.443 mol). The ice bath was allowed to melt and the reaction stirred at rt for 18 h. Ammonia solution was added and the reaction mixture was decanted into a separating funnel. Ethyl acetate (200 ml) and 0.1M NaOH (200 ml) were added and after mixing, the phases were separated. The organic layer was extracted with NaOH (200 ml) and brine (200 ml) and then dried over anhydrous magnesium sulfate. Following filtration and evaporation of the solvent *in vacuo*, the crude material was purified by Kugelrohr distillation. The *bis*-methoxymethyl ether **183** was afforded as a clear oil (20.6 g, 57%).

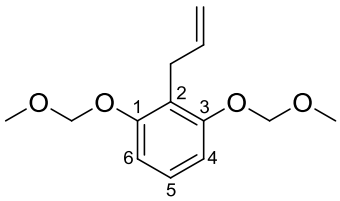


R_f = 0.34 (10% EtOAc/Hexane). **δ_H /ppm:** 7.18 (1H, t, *J*=8.1 Hz, H_5), 6.74 (1H, t, *J*=2.1 Hz, H_2), 6.70 (2H, dd, *J*=8.2 Hz and 2.2 Hz, H_4 and H_6), 5.16 (4H, s, 2 × OC*H*$_2$), 3.47 (6H, s, 2 × OC*H*$_3$). **δ_C /ppm:** 158.32 (C_1 and C_3), 129.89 (C_5), 109.58 (C_4 and C_6), 104.96 (C_2), 94.42 (2 × O*C*H$_2$), 55.96 (2 × OCH$_3$). **ν_{max} /cm^{-1}:** 2901 (CH str), 1591, 1488, 1137, 1073. **HRMS** (ESI, +ve) $C_{10}H_{15}O_4^+$ [MH^+] requires *m/z* 199.0972, found 199.0972.

4.3.2 2-Allyl-1,3-*bis*(methoxymethoxy)benzene – 184

A solution of 1,3-*bis*(methoxymethoxy)benzene **183** (3.20 g, 16.1 mmol) in dry tetrahydrofuran (180 ml) was placed in a two neck round bottom flask fitted with a dropping funnel and under Ar. The solution was cooled to 0 °C and the dropping funnel was charged with *n*BuLi (1.40 M in hexane, 13.6 ml, 19.0 mmol) which was added dropwise over a 5 minute period, thus forming a yellow solution. The reaction was stirred for a further 1.5 h at 0 °C during which the colour intensified and eventually turned orange. Allyl bromide (3.91 g, 2.80 ml 32.4 mmol) in

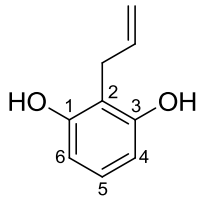
tetrahydrofuran (10 ml) was added dropwise to the reaction mixture resulting in a colour change from orange to clear. The temperature was maintained at 0 °C for an additional hour and the reaction was then allowed to warm to room temperature and stirred for 18 h. The orange reaction mixture was transferred to a separating funnel and water (100 ml) was added and the reaction was diluted with ethyl acetate (100 ml). After mixing, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with brine (200 ml) and dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo*, the crude oil was purified by flash chromatography (2% EtOAc/Hexane) to afford the desired allylated compound **184** as a clear oil (3.22 g, 84%).



R_f = 0.40 (10% EtOAc/Hexane). **δ_H /ppm:** 7.10 (1H, t, *J*=8.3 Hz, H_5), 6.77 (2H, d, *J*=8.3 Hz, H_4 and H_6), 6.03-5.90 (1H, m, $CH_2CH{=}CH_2$), 5.18 (4H, s, 2 × OCH_2), 5.01-4.92 (2H, overlapping signals, $CH_2CH{=}CH_2$), 3.46 (8H, overlapping s and d, 2 × OCH_3 and $CH_2CH{=}CH_2$). **δ_C /ppm:** 155.84 (C_1 and C_3), 136.75 ($CH_2CH{=}CH_2$), 127.17 (C_5), 118.39 (C_2), 114.12 ($CH_2CH{=}CH_2$), 107.96 (C_4 and C_6), 94.48 (2 × OCH_2), 55.98 (2 × OCH_3), 27.63 ($CH_2CH{=}CH_2$). **ν_{max} /cm^{-1}:** 2900 (CH str), 1594, 1468, 1152, 1031. **HRMS** (ESI, +ve) $C_{13}H_{19}O_4^+$ [MH^+] requires *m/z* 239.1285, found 239.1285.

4.3.3 2-Allylbenzene-1,3-diol – 185

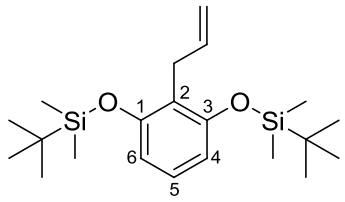
Into a 250 ml round bottom flask fitted with a condenser was placed 2-allyl-1,3-*bis*(methoxymethoxy)benzene **184** (3.07 g, 12.9 mmol) followed by dry tetrahydrofuran (100 ml) and methanol (50 ml). Once acidified with 3 drops of 32% HCl, the solution was heated to reflux for 18 h. Analysis by TLC indicated that three compounds were present which we had assumed to be the starting material and the completely deprotected product in small amounts as well as the mono-deprotected compound as the major species. Another 3 drops of acid were added and the solution was refluxed again for 18 h, allowing for full conversion to the fully deprotected diol. The solvent was evaporated *in vacuo* and the crude product was dissolved in ethyl acetate (150 ml) and dried over magnesium sulfate. Filtration and removal of the solvent *in vacuo* followed by purification by column chromatography (10% EtOAc/Hexane) gave the allylated diol **185** as a pale yellow oil in quantitative yield.



R_f = 0.42 (30% EtOAc/Hexane). **δ_H /ppm:** 6.97 (1H, t, *J*=8.1 Hz, H_5), 6.42 (2H, d, *J*=8.1 Hz, H_4 and H_6), 6.10-5.91 (1H, m, CH_2CH=CH_2), 5.22-5.11 (2H, overlapping signals, CH_2CH=CH_2), 5.09 (2H, s, 2 × O*H*), 3.47 (2H, d, *J*=6.0 Hz, CH_2CH=CH_2). **δ_C /ppm:** 154.95 (C_1 and C_3), 135.87 (CH_2CH=CH_2), 127.67 (C_5), 116.05 (CH_2CH=CH_2), 111.94 (C_2), 108.32 (C_4 and C_6), 27.47 (CH_2CH=CH_2). **ν_{max} /cm^{-1}:** 3381 (OH str), 1703, 1609, 1463, 1260. **HRMS** (ESI, +ve) $C_9H_{11}O_2^+$ [MH^+] requires *m/z* 151.0761, found 151.0760.

4.3.4 2-Allyl-1,3-*bis*(*tert*-butyldimethylsilyloxy)benzene – 186

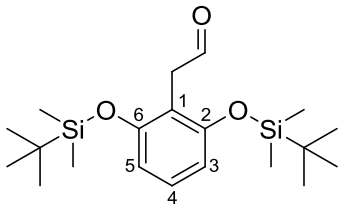
The diol **185** (2.47 g, 16.4 mmol) was dissolved in dry acetonitrile (180 ml) in a two neck round bottom flask under Ar. Imidazole (3.35 g, 49.2 mmol) and then TBSCl (6.18 g, 41.0 mmol) was added in a single portion and after 15 min the imidazole hydrochloride salt appeared. Following 18 h of stirring, analysis by TLC indicated that all of the starting material had reacted. The acetonitrile was evaporated and the crude mixture was taken up in ethyl acetate (150 ml) and water (150 ml), thus facilitating the dissolution of the imidazole hydrochloride salt into the aqueous phase upon mixing. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with brine (200 ml), separated and dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo*, the crude product was purified by column chromatography (2% EtOAc/Hexane) to yield the silyl-protected compound **186** as a yellow oil (5.34 g, 86%).



R_f = 0.86 (10% EtOAc/Hexane). **δ_H /ppm:** 6.92 (1H, t, *J*=8.2 Hz, H_5), 6.44 (2H, d, *J*=8.2 Hz, H_4 and H_6), 5.96-5.85 (1H, m, CH_2CH=CH_2), 5.05-4.78 (2H, overlapping signals, CH_2CH=CH_2), 3.37 (2H, d, *J*=5.8 Hz, CH_2CH=CH_2), 1.00 (18H, s, 2 × C(CH_3)$_3$), 0.22 (12H, s, 2 × Si(CH_3)$_2$). **δ_C /ppm:** 154.92 (C_1 and C_3), 136.83 (CH_2CH=CH_2), 126.32 (C_5), 121.65 (C_2), 114.11 (CH_2CH=CH_2), 111.53 (C_4 and C_6), 28.41 (CH_2CH=CH_2), 25.89 (2 × C(*C*H_3)), 18.32 (2 × *C*(CH_3)), -4.05 (2 × Si(*C*H_3)$_2$). **ν_{max} /cm^{-1}:** 2930 (CH str), 1587, 1462, 1244, 1070. **HRMS** (ESI, +ve) $C_{21}H_{39}O_2Si_2^+$ [MH^+] requires *m/z* 379.2490, found 379.2483.

4.3.5 2-(2,6-*Bis*(*tert*-butyldimethylsilyloxy)-phenyl)acetaldehyde – 188

A round bottom flask containing **186** (4.00 g, 10.6 mmol) dissolved in dry dichloromethane (180 ml) was immersed into an acetone bath cooled to -78 °C. Ozone gas was bubbled into the reaction mixture for several minutes followed by oxygen gas in order to purge excess ozone from the solution. TLC analysis of the reaction mixture indicated that a significant amount of the starting material had been consumed and the ozonide intermediate was forming. The process was repeated in 3 minute intervals, bubbling ozone gas followed by molecular oxygen until TLC analysis indicated that no starting material was present. Excess acetic acid and zinc dust were added and the reaction mixture was warmed to 5 °C at which point TLC indicated complete conversion of the ozonide to the aldehyde. The reaction mixture was filtered, washed twice with sodium bicarbonate solution (150 ml), once with brine (150 ml) and finally dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent *in vacuo*, the crude product was purified by column chromatography (2% EtOAc/Hexane) to afford **188** as a clear oil at rt or a waxy solid at 0 °C (2.93 g, 73%).

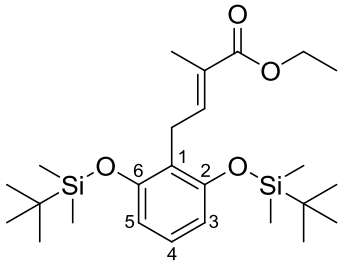


R_f = 0.37 (5% EtOAc/Hexane). **δ_H /ppm:** 9.60 (1H, s, C*H*O), 7.03 (1H, t, *J*=8.2 Hz, H_4), 6.50 (2H, d, *J*=8.2 Hz, H_3 and H_5), 3.64 (2H, d, *J*=1.5 Hz, CH_2CHO), 0.97 (18H, s, 2 × C(CH_3)$_3$), 0.22 (12H, s, 2 × Si(CH_3)$_2$). **δ_C /ppm:** 200.86 (*C*HO), 155.33 (C_2 and C_6), 127.86 (C_4), 115.04 (C_1), 111.43 (C_3 and C_5), 39.42 (*C*H_2CHO), 25.74 (2 × C(*C*H_3)), 18.21 (2 × *C*(CH_3)), -4.17 (2 × Si(*C*H_3)$_2$). **ν_{max} /cm^{-1}:** 2931 (CH str), 1728 (C=O str), 1588, 1463, 1247, 1084. **HRMS** (ESI, +ve) $C_{20}H_{37}O_3Si_2^+$ [MH^+] requires *m/z* 381.2283, found 381.2284.

4.3.6 *(E)*-Ethyl-4-(2,6-*bis*(*tert*-butyl-dimethylsilyloxy)phenyl)-2-methylbut-2-enoate – 193

Into a 2 neck round bottom flask fitted with a dropping funnel and under Ar was placed LiCl (0.10 g, 2.4 mmol) followed by dry tetrahydrofuran (5 ml). Ethyl 2-(diethoxyphosphoryl)propanoate (0.31 g, 0.28 ml, 1.3 mmol) was added in a single portion and the reaction mixture was cooled by means of an ice bath to 0 °C. The dropwise addition of *n*BuLi (1.40 M in hexane, 0.826 ml, 1.16 mmol) over a 5 min period facilitated the dissolution of the LiCl salt, thus forming a homogeneous solution. The reaction was allowed to stir for 30 min before being transferred to a second round bottom flask containing the aldehyde **188** (0.40 g, 1.1 mmol) in dry

acetonitrile (10 ml), also under Ar and cooled to 0 °C. The reaction mixture was maintained at approximately 5 °C for 18 h during which the colour changed from clear to a pale yellow. The solution was transferred to a separating funnel and water (50 ml) and ethyl acetate (50 ml) were added. After mixing, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were washed with brine (150 ml) and dried over magnesium sulfate before filtering and removing the solvent *in vacuo*. The crude material was purified by column chromatography (2% EtOAc/Hexane) to furnish the ester **193** as a clear oil (0.44 g, 90%).

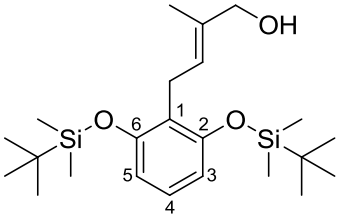


R_f = 0.38 (5% EtOAc/Hexane). **δ_H /ppm:** 6.94 (1H, t, *J*=8.2 Hz, H_4), 6.80 (1H, tq, *J*=6.3 Hz and 1.1 Hz, CH_2CH=C), 6.46 (2H, d, *J*=8.2 Hz, H_3 and H_5), 4.13 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 3.48 (2H, d, *J*=6.3 Hz, CH_2CH=C), 1.92 (3H, d, *J*=1.1 Hz CH_3C=C), 1.23 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 0.98 (18H, s, 2 × $C(CH_3)_3$), 0.23 (12H, s, 2 × $Si(CH_3)_2$). **δ_C /ppm:** 168.20 (*C*=O), 154.85 (C_2 and C_6), 142.40 (CH_2CH=C), 126.99 (C_1), 126.60 (C_4), 121.16 (CH_2CH=*C*), 111.54 (C_3 and C_5), 60.14 (OCH_2CH_3), 25.76 (2 × $C(CH_3)_3$), 24.10 (CH_2CH=C), 18.26 (2 × *C*$(CH_3)_3$), 14.25 (OCH_2CH_3), 12.64 (CH_3C=C), -4.09 (2 × $Si(CH_3)_2$). **ν_{max} /cm^{-1}:** 2931 (CH str), 1709 (C=O str), 1586, 1463, 1242. **HRMS** (ESI, +ve) $C_{25}H_{45}O_4Si_2^+$ [MH^+] requires *m/z* 465.2858, found 465.2851.

4.3.7 *(E)*-4-(2,6-*Bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-en-1-ol – 195

The ester **193** (1.51 g, 3.25 mmol) was placed in a two neck round bottom flask containing dry tetrahydrofuran (30 ml) and under Ar. Once cooled to 0 °C by means of an ice bath, $LiAlH_4$ (0.16 g, 4.2 mmol) was added resulting in effervescence of the solution. The reaction was maintained at 0 °C and was monitored every 20 min by TLC. After approximately 3 h, all the starting material had been consumed. Ice cold water was added (100 ml) and the reaction mixture was diluted with ethyl acetate (100 ml). The reaction was transferred to a separating funnel and the emulsion that formed upon mixing was broken by the addition of a small amount of 1 M HCl solution. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were filtered through celite and washed with brine (200 ml). Once dried over anhydrous magnesium sulfate, filtered and the solvent evaporated, the crude product was purified

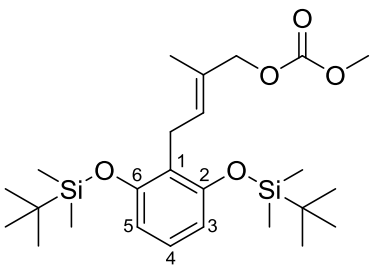
by column chromatography (2% EtOAc/Hexane), giving the alcohol **195** as a clear oil (1.19 g, 87%).



R_f = 0.27 (10% EtOAc/Hexane). **δ_H /ppm:** 6.88 (1H, t, *J*=8.2 Hz, H_4), 6.42 (2H, d, *J*=8.2 Hz, H_3 and H_5), 5.43 (1H, tq, *J*=6.2 Hz and 0.9 Hz, CH_2CH=C), 3.92 (2H, s, CH_2OH), 3.34 (2H, d, *J*=6.0 Hz, CH_2CH=C), 1.74 (3H, d, *J*=0.9 Hz CH_3C=C), 1.33 (1H, s, O*H*), 0.96 (18H, s, 2 × $C(CH_3)_3$), 0.20 (12H, s, 2 × $Si(CH_3)_2$). **δ_C /ppm:** 154.70 (C_2 and C_6), 134.06 (CH_2CH=*C*), 126.20 (CH_2CH=C), 126.08 (C_4), 122.81 (C_1), 111.70 (C_3 and C_5), 69.18 (CH_2OH), 25.78 (2 × $C(CH_3)_3$), 22.94 (CH_2CH=C), 18.29 (2 × $C(CH_3)_3$), 14.03 (CH_3C=C), -4.06 (2 × $Si(CH_3)_2$). **ν_{max} /cm^{-1}:** 3330 (OH str), 2930 (CH str), 1586, 1461, 1242, 1062. **HRMS** (ESI, +ve) $C_{23}H_{42}O_3Si_2^+$ [MH^+] requires *m/z* 423.2752, found 423.2746.

4.3.8 *(E)*-4-(2,6-*bis*(*tert*-butyldimethylsilyloxy)phenyl)-2-methylbut-2-enyl methyl carbonate – 196

Into a two neck round bottom flask containing Ar was placed the alcohol **195** (3.55 g, 8.40 mmol) followed by dry dichloromethane (70 ml). The reaction was cooled to 0 °C by means of an ice bath and pyridine (2.74 g, 2.80 ml, 34.6 mmol) was added in one portion followed by the dropwise addition of methyl chloroformate (1.59 g, 1.30 ml, 16.8 mmol). After stirring for 5 min at 0 °C, the ice bath was removed and the reaction was allowed to proceed at rt for 30 min. Water was carefully added (80 ml) and the reaction was decanted into a separating funnel, diluting further with water (150 ml) and dichloromethane (150 ml). After mixing the phases, the organic phase was separated and the aqueous phase was extracted with dichloromethane (150 ml). The organic phases were combined, washed with HCl (0.2 M, 2 × 100 ml), water (150 ml) and finally brine (200 ml). After drying over anhydrous magnesium sulfate and filtering, the solvent was removed *in vacuo* and the crude oil was purified by column chromatography (5% EtOAc/Hexane), furnishing the carbonate **196** as a clear oil (3.67 g, 91%).

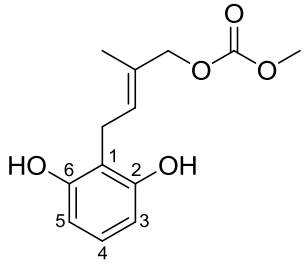


R_f = 0.35 (10% EtOAc/Hexane). **δ_H /ppm:** 6.91 (1H, t, *J*=8.2 Hz, H_4), 6.44 (2H, d, *J*=8.2 Hz, H_3 and H_5), 5.55 (1H, tq, *J*=5.6 Hz and 0.6 Hz, CH_2CH=C), 4.48 (2H, s, OCH_2), 3.76 (3H, s, OCH_3), 3.36

(2H, d, *J*=6.0 Hz, CH_2CH=C), 1.76 (3H, d, *J*=0.6 Hz, CH_3C=C), 0.98 (18H, s, 2 × C(CH_3)$_3$), 0.22 (12H, s, 2 × Si(CH_3)$_2$). **δ_C /ppm:** 155.80 (*C*=O), 154.76 (C_2), 130.35 (CH$_2$*C*H=C), 128.75 (CH$_2$CH=*C*), 126.22 (C_4), 122.33 (C_1), 111.65 (C_3 and C_5), 73.88 (O*C*H$_2$), 54.58 (O*C*H$_3$), 25.78 (2 × C(*C*H$_3$)$_3$), 23.07 (*C*H$_2$CH=C), 18.28 (2 × *C*(CH$_3$)$_3$), 14.21 (*C*H$_3$C=C), -4.08 (2 × Si(*C*H$_3$)$_2$). **ν_{max} /cm^{-1}:** 2930 (CH str), 1749 (C=O str), 1586, 1462, 1243, 1064. **HRMS** (ESI, +ve) $C_{25}H_{45}O_5Si_2^+$ [MH$^+$] requires *m/z* 481.2807, found 481.2808.

4.3.9 *(E)*-4-(2,6-Dihydroxyphenyl)-2-methylbut-2-enyl methyl carbonate – 127

Into a two neck round bottom flask containing Ar was placed the silylated carbonate **196** (3.09 g, 6.43 mmol) followed by dry tetrahydrofuran (180 ml). The solution was cooled to 0 °C by means of an ice bath and TBAF (1.00 M in THF, 12.9 ml, 12.9 mmol) was added in a single portion. After 5 min of stirring, TLC analysis indicated that the reaction was complete. Saturated ammonium chloride was added (100 ml) and the solution was diluted with ethyl acetate (150 ml). After mixing, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic fractions were washed with brine (200 ml), dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* and column chromatography (20% EtOAc/Hexane) of the crude material afforded the purified diol **127** as a clear oil which turned brown overnight at 0 °C (1.39 g, 86%).

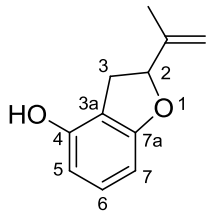


R_f = 0.47 (40% EtOAc/Hexane). **δ_H /ppm:** 6.93 (1H, t, *J*=8.1 Hz, H_4), 6.38 (2H, d, *J*=8.1 Hz, H_3 and H_5), 5.64 (1H, t, *J*=7.1 Hz, CH$_2$C*H*=C), 5.00 (2H, br s, 2 × O*H*), 4.53 (2H, s, OCH_2), 3.78 (3H, s, OCH_3), 3.45 (2H, d, *J*=7.1 Hz, CH_2CH=C), 1.86 (3H, s, CH_3C=C). **δ_C /ppm:** 155.83 (*C*=O), 154.91 (C_2 and C_6), 130.84 (CH$_2$CH=*C*), 127.82 (CH$_2$*C*H=C), 127.23 (C_4), 113.31 (C_1), 108.04 (C_3 and C_5), 73.59 (O*C*H$_2$), 54.77 (O*C*H$_3$), 21.99 (*C*H$_2$CH=C), 13.89 (*C*H$_3$C=C). **ν_{max} /cm^{-1}:** 3397 (OH str), 2959(CH str), 1719(C=O str), 1610, 1464, 1273. **HRMS** (ESI, -ve) $C_{13}H_{15}O_5^-$ [MH$^-$] requires *m/z* 251.0918, found 251.0923.

4.3.10 (±)-2-Isopropenyl-2,3-dihydrobenzofuran-4-ol – *rac*-78

Dichloromethane (4 ml) and Pd(dba)$_2$ (0.011 g, 0.020 mmol) were introduced into a dry two neck round bottom flask under Ar and equipped with a condenser. The violet solution was degassed for

5 min by bubbling Ar directly into the solvent by means of a Pasteur pipette. Triphenylphosphine (0.021 g, 0.079 mmol) was added against a flow of Ar and the reaction was left to stir until the solution changed to a light orange colour indicating the formation of $Pd(PPh_3)_4$ *in situ.* Degassed acetic acid (0.032 g, 0.030 ml, 0.53 mmol) was added and the reaction was stirred for another 5 min. The carbonate **127** (0.10 g, 0.40 mmol) was then introduced against a flow of Ar and the reaction was set to reflux for 18 h. Once complete, the crude mixture was transferred to a round bottom flask, adsorbed directly onto silica and purified by column chromatography (5% EtOAc/Hexane), furnishing the cyclised product *rac*-**78** as a clear oil (0.051 g, 73%).

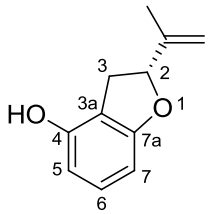


R_f = 0.38 (20% EtOAc/Hexane). **δ_H /ppm:** 6.99 (1H, t, *J*=8.0 Hz, H_6), 6.43 (1H, d, *J*=8.0 Hz, H_7), 6.31 (1H, d, *J*=8.1 Hz, H_5), 5.21 (1H, t, *J*=8.8 Hz, H_2), 5.09 (1H, s, $CH_3C=CH(H)$), 4.91 (1H, s, $CH_3C=CH(H)$), 4.88 (1H, s, O*H*), 3.30 (1H, dd, *J*=15.3 Hz and 9.6 Hz, H_3), 2.97 (1H, dd, *J*=15.3 Hz and 8.0 Hz, H_3), 1.78 (3H, s, $CH_3C=CH_2$). **δ_C /ppm:** 161.53 (C_{7a}), 152.41 (C_4), 143.85 ($CH_3C=CH_2$), 129.18 (C_6), 112.20 (C_{3a}), 112.14 ($CH_3C=CH_2$), 107.64 (C_5), 102.26 (C_7), 86.16 (C_2), 31.70 (C_3), 17.14 ($CH_3C=CH_2$). **ν_{max} /cm^{-1}:** 3347 (OH str), 2947 (CH str), 1605, 1459, 1316, 1277, 1228. **HRMS** (ESI, +ve) $C_{11}H_{13}O_2^+$ [MH^+] requires *m/z* 177.0917, found 177.0915.

4.3.11 (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-ol – *(R)*-78

Into a two neck round bottom flask fitted with a dropping funnel and under Ar was placed dry dichloromethane (5 ml) followed by $Pd_2(dba)_3CHCl_3$ (0.012 g, 0.012 mmol, 1.5 mol%). Ar was bubbled directly into the solution for 5 min and the chiral *R,R'*-Trost ligand (0.044 g, 0.063 mmol, 8 mol%) was introduced against a flow of Ar. A colour change occurred over a 25 min period from violet to light orange as ligand exchange occurred. The reaction was left to stir at room temperature for another 10 min and degassed glacial acetic acid (0.052 g, 0.050 ml, 0.87 mmol) was then added in one portion. Following 5 min of stirring, the dropping funnel was charged with the carbonate **127** (0.20 g, 0.79 mmol) and dichloromethane (5 ml) and the solution was added dropwise to the reaction mixture. The reaction was left to proceed at 23 °C for 18 h during which the colour changed to a pale yellow. The reaction mixture was transferred to a round bottom flask, concentrated *in vacuo* and the crude material adsorbed onto silica gel. Purification by column chromatography (5% EtOAc/Hexane) afforded the dihydrobenzofuran *(R)*-**78** (0.12 g, 84%, 90-94.8% ee). The ee was determined by HPLC analysis of the acetate derivative **198** as the

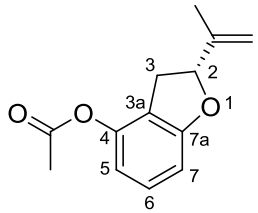
enantiomers of **78** did not resolve well using the Chiralcel OJ Column. Enantiomeric excesses as high as 94.8% were obtained, however, these values decreased slightly to 90% upon doubling the scale of the reaction.



R_f = 0.37 (20% EtOAc/Hexane). **δ_H /ppm:** 6.99 (1H, t, *J*=8.0 Hz, H_6), 6.43 (1H, d, *J*=8.0 Hz, H_7), 6.31 (1H, d, *J*=8.1 Hz, H_5), 5.21 (1H, t, *J*=8.8 Hz, H_2), 5.09 (1H, s, CH_3C=CH(*H*)), 4.91 (1H, s, CH_3C=CH(*H*)), 4.88 (1H, s, O*H*), 3.30 (1H, dd, *J*=15.3 Hz and 9.6 Hz, H_3), 2.97 (1H, dd, *J*=15.3 Hz and 8.0 Hz, H_3), 1.78 (3H, s, C*H*$_3$C=CH_2). **δ_C /ppm:** 161.53 (C_{7a}), 152.41 (C_4), 143.85 (CH_3*C*=CH_2), 129.18 (C_6), 112.20 (C_{3a}), 112.14 (CH_3C=*C*H_2), 107.64 (C_5), 102.26 (C_7), 86.16 (C_2), 31.70 (C_3), 17.14 (*C*H_3C=CH_2). **ν_{max} /cm^{-1}:** 3347 (OH str), 2947 (CH str), 1605, 1459, 1316, 1277, 1228. **HRMS** (ESI, +ve) $C_{11}H_{13}O_2^+$ [MH^+] requires *m/z* 177.0917, found 177.0915. **$[\alpha]_D^{19}$** = -22.5 ($CHCl_3$).

4.3.12 2-Isopropenyl-2,3-dihydrobenzofuran-4-yl acetate – *rac*-198

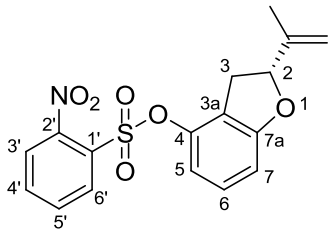
To a solution of *rac*-**78** (0.030 g, 0.17 mmol) in dry dichloromethane (2 ml) and under Ar was added triethylamine (0.034 g, 0.46 ml, 0.34 mmol) followed by a catalytic amount of DMAP and acetic anhydride (0.022 g, 0.021 ml, 0.22 mmol). The reaction was left to proceed at rt for 18 h after which TLC analysis indicated that all the starting material had reacted. The solvent was removed *in vacuo* and the crude material was adsorbed onto silica gel and purified by column chromatography (5% EtOAc/Hexane) to furnish the acetate *rac*-**198** (0.031 g, 84%) as a clear oil which was analysed by HPLC. The procedure was repeated in the acetylation of *(R)*-**78**.



R_f = 0.38 (20% EtOAc/Hexane). **δ_H /ppm:** 7.12 (1H, t, *J*=8.1 Hz, H_6), 6.69 (1H, d, *J*=8.0 Hz, H_5), 6.57 (1H, d, *J*=8.1 Hz, H_7), 5.20 (1H, t, *J*=8.8 Hz, H_2), 5.08 (1H, s, CH_3C=CH(*H*)), 4.91 (1H, s, CH_3C=CH(*H*)), 3.23 (1H, dd, *J*=15.7 Hz and 9.6 Hz, one of H_3), 2.93 (1H, dd, *J*=15.7 Hz and 8.1 Hz, one of H_3), 2.29 (3H, s, C*H*$_3CO_2$), 1.76 (3H, s, C*H*$_3$C=CH_2). **δ_C /ppm:** 168.43 (*C*=O), 161.30 (C_{7a}), 147.30 (C_4), 143.58 (CH_3*C*=CH_2), 129.01 (C_6), 119.28 (C_{3a}), 113.41 (C_7), 112.36 (CH_3C=*C*H_2), 106.99 (C_5), 86.21 (C_2), 32.63 (C_3), 20.86 (*C*H_3CO_2), 17.07 (*C*H_3C=CH_2). **ν_{max} /cm^{-1}:** 2920 (CH str), 1763 (C=O str), 1620, 1461, 1369, 1197. **HRMS** (ESI, +ve) $C_{13}H_{15}O_3^+$ [MH^+] requires *m/z* 219.1023, found 219.1022. **$[\alpha]_D^{19}$** = -40.3 ($CHCl_3$).

4.3.13 (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2-nitrobenzenesulfonate – *(R)*-199

Into a two neck round bottom flask under Ar was placed *(R)*-**78** (0.025 g, 0.14 mmol) followed by dry dichloromethane (5 ml). Triethylamine (0.027 g, 0.038 ml, 0.27 mmol) was added followed by 2-nitrobenzenesulfonyl chloride (0.039 g, 0.18 mmol) and the reaction was stirred at rt for 18 h following which, TLC analysis indicated that all the starting material had been consumed and a new product had formed. The reaction mixture was concentrated *in vacuo* and the crude product adsorbed onto silica gel. Purification by column chromatography (20% EtOAc/Hexane) afforded the product *(R)*-**199** as a white solid (0.047 g, 92%). Recrystallisation from diethyl ether afforded white needle-like crystals suitable for crystal structure analysis.

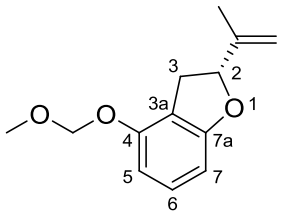


R_f = 0.41 (50% EtOAc/Hexane). **Mp.** = 83-84 °C. **δ_H /ppm:** 7.99 (1H, d, *J*=7.8 Hz, $H_{3'}$), 7.86-7.85 (2H, m, $H_{6'}$ and $H_{5'}$), 7.78-7.65 (1H, m, $H_{4'}$), 7.05 (1H, t, *J*=8.2 Hz, H_6), 6.74 (1H, d, *J*=8.0 Hz, H_7), 6.55 (1H, d, *J*=8.3 Hz, H_5), 5.19 (1H, t, *J*=8.7 Hz, H_2), 5.05 (1H, s, $CH_3C=CH(H)$), 4.90 (1H, s, $CH_3C=CH(H)$), 3.41 (1H, dd, *J*=16.3 Hz and 9.6 Hz, one of H_3), 3.03 (1H, dd, *J*=16.3 Hz and 7.9 Hz, one of H_3), 1.71 (3H, s, $CH_3C=CH_2$). **δ_C /ppm:** 161.80 (C_{7a}), 145.58 (C_4), 143.14 ($CH_3C=CH_2$), 135.39 (Ar*C*H), 132.03 (Ar*C*H), 132.01 (Ar*C*H), 129.29 (C_6), 128.84 ($C_{2'}$), 124.85 (Ar*C*H), 120.75 (C_{3a}), 113.89 (C_5), 112.62 ($CH_3C=CH_2$), 108.68 (C_7), 86.47 (C_2), 32.65 (C_3), 17.00 ($CH_3C=CH_2$). **ν_{max} /cm^{-1}:** 2924 (CH str), 1620, 1542, 1460, 1380, 1165, 1010. **HRMS** (ESI, +ve) $C_{17}H_{16}NO_6S^+$ [MH^+] requires *m/z* 362.0700, found 362.0706. **X-ray data:** $C_{17}H_{15}NO_6S$; *M*=361.36; orthorhombic; 0.71073 Å; *a*=5.72710(10) Å, *b*=13.0745(3) Å, *c*=22.1624(4) Å, *U*=1659.50(6) Å^3; 296(3) K, space group, $P2_12_12_1$, Z=4;. μ(Mo-Kα)=0.229 mm^{-1} 17953 reflections measured, 3998 unique [R(int)=0.0366] which were used in all calculations. Final R indices [$I>2\sigma(I)$] R_1=0.0365, Wr(F^2)=0.0951. **$[\alpha]_D^{19}$** = -12.903 ($CHCl_3$).

4.3.14 *(R)*-4-(methoxymethoxy)-2-isopropenyl-2,3-dihydrobenzofuran – *(R)*-200

Into a two neck round bottom flask containing Ar was placed distilled dimethylformamide (8 ml) followed by *(R)*-**78** (0.39 g, 2.2 mmol). The reaction flask was immersed in an ice bath and sodium hydride (60% dispersion in oil, 0.11 g, 2.6 mmol) was slowly added resulting in effervescence of the solution. Methoxymethyl chloride (0.22 g, 0.21 ml, 0.28 mmol) was then added and the ice bath

was allowed to melt and the reaction was stirred at rt for 18 h. Ammonia solution was added and the reaction mixture was decanted into a separating funnel and ethyl acetate (50 ml) and 0.1M NaOH (50 ml) were added. After mixing, the phases were separated and the organic layer was extracted with NaOH (100 ml) and then brine (150 ml). The organic fraction was dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo.* Purification by column chromatography (10% EtOAc/Hexane) afforded the desired product *(R)*-**200** as a light yellow oil (0.34 g, 70%).

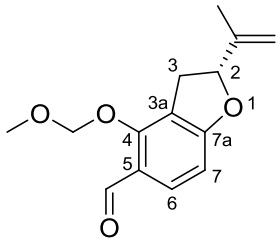


R_f = 0.68 (20% EtOAc/Hexane). **δ_H /ppm:** 7.06 (1H, t, *J*=8.1 Hz, H_6), 6.59 (1H, d, *J*=8.3 Hz, H_7), 6.51 (1H, d, *J*=8.0 Hz, H_5), 5.18 (3H, overlapping signals, H_2 and O*C*H_2), 5.09 (1H, s, CH_3C=CH(*H*)), 4.91 (1H, s, CH_3C=CH(*H*)), 3.48 (3H, s, O*C*H_3), 3.33 (1H, dd, *J*=15.7 Hz and 9.7 Hz, one of H_3), 2.99 (1H, dd, *J*=15.7 Hz and 8.1 Hz, one of H_3), 1.78 (3H, s, *C*H_3C=CH_2). **δ_C /ppm:** 161.17 (C_{7a}), 154.04 (C_4), 143.99 (CH_3*C*=CH_2), 129.09 (C_6), 114.73 (C_{3a}), 111.93 (CH_3C=*C*H_2), 106.43 (C_7), 103.42 (C_5), 94.39 (O*C*H_2), 86.13 (C_2), 56.11 (O*C*H_3), 32.33 (C_3), 17.23 (*C*H_3C=CH_2). **ν_{max} /cm^{-1}:** 2951 (CH str), 1607, 1461, 1230, 1152, 1040. **HRMS** (ESI, +ve) $C_{13}H_{17}O_3^+$ [MH^+] requires *m/z* 221.1179, found 221.1176.

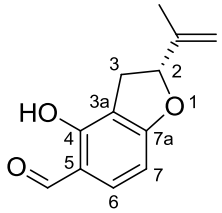
4.3.15 *(R)*-4-(methoxymethoxy)-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde and (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-201 and *(R)*-202

Into a two neck round bottom flask fitted with a dropping funnel and under Ar was placed dry dichloromethane (10 ml) followed by tin tetrachloride (0.13 g, 0.058 ml, 0.50 mmol). The solution was cooled to -78 °C using a frozen acetone slurry bath and dichloromethyl methyl ether (0.062 g, 0.049 ml, 0.55 mmol) was added. Following 20 min of stirring, *(R)*-**200** (0.10 g, 0.45 mmol) dissolved in dichloromethane (5 ml) was added dropwise. The reaction was maintained at -78 °C for 1 h at which point TLC analysis indicated that two products were present. Saturated sodium bicarbonate solution (20 ml) and ethyl acetate (50 ml) were added and the reaction mixture was transferred to a separating funnel. After mixing, the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were washed with brine (100 ml), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/Hexane) to yield both the

protected *(R)*-**201** (0.012 g, 11%) and deprotected *(R)*-**202** (0.023 g, 25%) formylated products as orange and yellow oils, respectively.



R_f = 0.42 (20% EtOAc/Hexane). **δ_H /ppm:** 10.12 (1H, s, C*H*O), 7.61 (1H, d, *J*=8.8 Hz, H_6), 6.69 (1H, d, *J*=8.8 Hz, H_7), 5.37 (1H, t, *J*=8.8 Hz, H_2), 5.25 (2H, s, OCH_2), 5.12 (1H, s, CH_3C=CH(*H*)), 4.96 (1H, s, CH_3C=CH(*H*)), 3.49 (3H, s, OCH_3), 3.33 (1H, dd, *J*=15.9 Hz and 9.8 Hz, one of H_3), 2.98 (1H, dd, *J*=15.8 Hz and 7.8 Hz, one of H_3), 1.79 (3H, s, CH_3C=CH_2). **δ_C /ppm:** 187.43 (C*H*O), 163.88 (C_{7a}), 158.85 (C_4), 143.10 (CH_3C=CH_2), 129.39 (C_6), 115.38 (Ar*C*), 114.90 (Ar*C*), 112.65 (CH_3C=CH_2), 107.13 (C_7), 94.09 (OCH_2), 87.95 (C_2), 56.43 (OCH_3), 31.38 (C_3), 17.10 (CH_3C=CH_2).

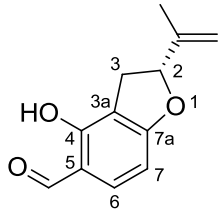


R_f = 0.62 (20% EtOAc/Hexane). **δ_H /ppm:** 11.47 (1H, s, O*H*), 9.68 (1H, s, C*H*O), 7.36 (1H, d, *J*=8.3 Hz, H_6), 6.50 (1H, d, *J*=8.3 Hz, H_7), 5.34 (1H, t, *J*=8.8 Hz, H_2), 5.09 (1H, s, CH_3C=CH(*H*)), 4.95 (1H, s, CH_3C=CH(*H*)), 3.35 (1H, dd, *J*=15.7 Hz and 9.9 Hz, one of H_3), 3.00 (1H, dd, *J*=15.8 Hz and 7.7 Hz, one of H_3), 1.77 (3H, s, CH_3C=CH_2). **δ_C /ppm:** 194.32 (*C*HO), 167.76 (C_{7a}), 159.38 (C_4), 143.01 (CH_3C=CH_2), 136.44 (C_6), 116.07 (Ar*C*), 112.85 (CH_3C=CH_2), 112.76 (Ar*C*), 102.93 (C_7), 88.14 (C_2), 30.57 (C_3), 16.99 (CH_3C=CH_2). **ν_{max} /cm^{-1}:** 2841 (CH str), 1630 (C=O str), 1484, 1437, 1252, 1070. **HRMS** (ESI, +ve) $C_{12}H_{13}O_3^+$ [MH^+] requires *m/z* 205.0866, found 205.0864. **$[\alpha]_D^{19}$** = -125.6 ($CHCl_3$).

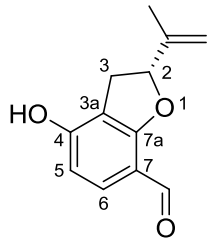
4.3.16 (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde and (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-7-carbaldehyde – *(R)*-202 and *(R)*-203

To a solution of tin tetrachloride in dry dichloromethane (5 ml) at -78 °C and under Ar, was added dichloromethyl methyl ether (0.031 g, 0.024 ml, 0.27 mmol). After 20 min, the reaction mixture was transferred by canula to another round bottom flask also under Ar and at -78 °C, containing *(R)*-**78** (0.039 g, 0.22 mmol) dissolved in dichloromethane (5 ml). After 5 min, TLC analysis indicated that two new products had formed, however, a significant amount of starting material remained. This persisted after 1 h at -78 °C and the temperature was raised to 0 °C. Following an hour of stirring at this temperature, sodium bicarbonate (10 ml) and dichloromethane (50 ml) were added and the reaction was transferred to a separating funnel. After mixing, the phases were

separated and the aqueous layer was extracted with dichloromethane (3 × 50 ml). The combined organic fractions were washed with brine (100 ml), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. Purification by column chromatography (5% EtOAc/Hexane) yielded the two formylated products as light and dark yellow oils. By NMR analysis these appeared to be very similar apart from a few differences. This led us to believe that both the *ortho (R)*-**202** (0.020 g, 45%) and *para (R)*-**203** (0.0081 g, 18%) substituted products had formed.



R_f = 0.62 (20% EtOAc/Hexane). **δ_H /ppm:** 11.47 (1H, s, O*H*), 9.68 (1H, s, C*H*O), 7.36 (1H, d, *J*=8.3 Hz, H_6), 6.50 (1H, d, *J*=8.3 Hz, H_7), 5.34 (1H, t, *J*=8.8 Hz, H_2), 5.09 (1H, s, CH_3C=CH(*H*)), 4.95 (1H, s, CH_3C=CH(*H*)), 3.35 (1H, dd, *J*=15.7 Hz and 9.9 Hz, one of H_3), 3.00 (1H, dd, *J*=15.8 Hz and 7.7 Hz, one of H_3), 1.77 (3H, s, C*H*$_3$C=CH$_2$). **δ_C /ppm:** 194.32 (*C*HO), 167.76 (C_{7a}), 159.38 (C_4), 143.01 (CH_3*C*=CH_2), 136.44 (C_6), 116.07 (Ar*C*), 112.85 (CH_3C=*C*H_2), 112.76 (Ar*C*), 102.93 (C_7), 88.14 (C_2), 30.57 (C_3), 16.99 (*C*H_3C=CH_2). **ν_{max} /cm^{-1}:** 2841 (CH str), 1630 (C=O str), 1484, 1437, 1252, 1070. **HRMS** (ESI, +ve) $C_{12}H_{13}O_3^+$ [MH^+] requires *m/z* 205.0866, found 205.0864. **$[\alpha]_D^{19}$** = -125.6 ($CHCl_3$).

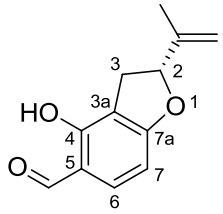


R_f = 0.12 (20% EtOAc/Hexane). **δ_H /ppm:** 10.04 (1H, s, C*H*O), 7.54 (1H, d, *J*=8.6 Hz, H_6), 7.43 (1H, br s, O*H*), 6.46 (1H, d, *J*=8.6 Hz, H_5), 5.37 (1H, m, H_2), 5.11 (1H, s, CH_3C=CH(*H*)), 4.95 (1H, s, CH_3C=CH(*H*)), 3.33 (2H, dd, *J*=15.6 Hz and 9.8 Hz, one of H_3), 2.99 (2H, dd, *J*=15.6 Hz and 7.7 Hz, one of H_3), 1.78 (3H, s, C*H*$_3$C=CH$_2$). **δ_C /ppm:** 188.09 (*C*HO), 165.06 (C_{7a}), 159.08 (C_4), 142.97 (CH_3*C*=CH_2), 129.47 (C_6), 113.56 (Ar*C*), 112.99 (CH_3C=*C*H_2), 112.86 (Ar*C*), 109.72 (C_5), 88.17 (C_2), 30.82 (C_3), 16.99 (*C*H_3C=CH_2).

4.3.17 (-)-*(R)*-4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-202

Paraformaldehyde (0.46 g, .012 mmol) was added to a round bottom flask under Ar containing *(R)*-**78** (0.30 g, 1.5 mmol), anhydrous magnesium chloride (0.24 g, 2.6 mmol) and triethylamine (0.65 g, 0.90 ml, 6.4 mmol) dissolved in dry tetrahydrofuran (30 ml). The mixture was heated to reflux and after 2 h, TLC analysis indicated that the reaction had gone to completion and a single product had formed. The reaction was allowed to cool to rt and transferred to a separating funnel,

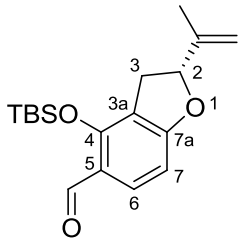
diluting with water (50 ml) and ethyl acetate (50 ml). Upon mixing, an emulsion formed which was broken by the addition of a small amount of 1 M HCl. After separating the layers, the aqueous phase was extracted with ethyl acetate (3 × 50 ml). The combined organic fractions were washed with brine (100 ml), dried over anhydrous sodium sulfate and filtered. Evaporation of the solvent *in vacuo* followed by purification by column chromatography (5% EtOAc/Hexane) afforded a single formylated product *(R)*-**202** as a yellow oil (0.23 g, 75%).



R_f = 0.62 (20% EtOAc/Hexane). **δ_H /ppm:** 11.47 (1H, s, O*H*), 9.68 (1H, s, C*H*O), 7.36 (1H, d, *J*=8.3 Hz, H_6), 6.50 (1H, d, *J*=8.3 Hz, H_7), 5.34 (1H, t, *J*=8.8 Hz, H_2), 5.09 (1H, s, CH_3C=CH(*H*)), 4.95 (1H, s, CH_3C=CH(*H*)), 3.35 (1H, dd, *J*=15.7 Hz and 9.9 Hz, one of H_3), 3.00 (1H, dd, *J*=15.8 Hz and 7.7 Hz, one of H_3), 1.77 (3H, s, C*H*$_3$C=CH_2). **δ_C /ppm:** 194.32 (*C*HO), 167.76 (C_{7a}), 159.38 (C_4), 143.01 (CH_3*C*=CH_2), 136.44 (C_6), 116.07 (Ar*C*), 112.85 (CH_3C=*C*H_2), 112.76 (Ar*C*), 102.93 (C_7), 88.14 (C_2), 30.57 (C_3), 16.99 (*C*H_3C=CH_2). **ν_{max} /cm^{-1}:** 2841 (CH str), 1630 (C=O str), 1484, 1437, 1252, 1070. **HRMS** (ESI, +ve) $C_{12}H_{13}O_3^+$ [MH^+] requires *m/z* 205.0866, found 205.0864. **$[\alpha]_D^{19}$** = -125.6 ($CHCl_3$).

4.3.18 (-)-*(R)*-4-(*tert*-butyldimethylsilyloxy)-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-204

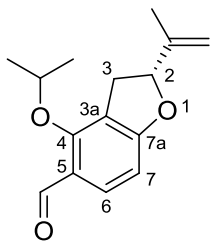
To a solution of *(R)*-**202** (0.050 g, 0.24 mmol) in dimethylformamide (2 ml) was added diisopropylethylamine (0.048 g, 0.065 ml, 0.37 mmol). The reaction was stirred for 5 min under Ar and TBSCl (0.044 g, 0.29 mmol) was added. After 10 min of stirring at rt, TLC analysis indicated that all the starting material had been consumed and a single product formed. Ice was added and the mixture was transferred to a separating funnel and diluted with diethyl ether (20 ml). After mixing, the phases were separated and the ethereal layer was extracted with cold water (2 × 20 ml) and saturated sodium bicarbonate (2 × 20 ml). The organic fraction was dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo.* The crude material was purified by column chromatography (5% EtOAc/Hexane) to yield the silylated compound *(R)*-**204** as a yellow oil (0.069 g, 90%).



R_f = 0.68 (20% EtOAc/Hexane). **δ_H /ppm:** 10.15 (1H, s, C*H*O), 7.72 (1H, d, *J*=8.5 Hz, H_6), 6.57 (1H, d, *J*=8.4 Hz, H_7), 5.27 (1H, t, *J*=8.7 Hz, H_2), 5.09 (1H, s, CH_3C=CH(*H*)), 4.95 (1H, s, CH_3C=CH(*H*)), 3.31 (1H, dd, *J*=15.5 Hz and 9.8 Hz, one of H_3), 2.96 (1H, dd, *J*=15.5 Hz and 7.7 Hz, one of H_3), 1.77 (3H, s, C*H*$_3$C=CH_2), 1.04 (9H, s, C(C*H*$_3$)$_3$), 0.20 (6H, s, Si(C*H*$_3$)$_2$). **δ_C /ppm:** 188.18 (*C*HO), 166.91 (C_{7a}), 156.02 (C_4), 143.09 (CH_3*C*=CH_2), 130.79 (C_6), 122.45 (Ar*C*), 117.34 (Ar*C*), 112.96 (CH_3C=*C*H_2), 104.77 (C_7), 87.22 (C_2), 32.50 (C_3), 25.70 (C(*C*H$_3$)$_3$), 18.46 (*C*(CH$_3$)$_3$), 16.93 (*C*H$_3$C=CH_2), -3.79 (Si(*C*H$_3$)$_2$). **ν_{max} /cm^{-1}:** 2930 (CH str), 1674 (C=O str), 1588, 1453, 1391, 1330, 1250, 1067. **HRMS** (ESI, +ve) $C_{18}H_{27}O_3Si^+$ [MH^+] requires *m/z* 319.1731, found 319.1729. **$[\alpha]_D^{19}$** = -4.03 ($CHCl_3$).

4.3.19 (-)-*(R)*-4-isopropoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-206

Into a two neck round bottom flask fitted with a condenser was placed the dihydrobenzofuran *(R)*-**202** (0.089 g, 0.44 mmol) followed by dimethylformamide (2 ml). Potassium carbonate (0.076 g, 0.55 mmol) and 2-bromopropane (0.068 g, 0.052 ml, 0.55 mmol) were added and the reaction was immersed in an oil bath preheated to 45 °C. The yellow reaction mixture intensified in colour and eventually turned brown after 3 h of stirring. TLC analysis indicated that starting material was still present and the reaction was left to stir for 18 h. The mixture was allowed to cool to rt, transferred to a separating funnel and water (20 ml) and diethyl ether (20 ml) were added. After mixing and allowing the phases to separate, the organic phase was extracted with water (2 × 20 ml) and washed with brine (50 ml). The organic fraction was dried over anhydrous sodium sulfate, filtered, the solvent removed *in vacuo* and the crude material purified by column chromatography (5% EtOAc/Hexane), giving the desired compound *(R)*-**206** as a yellow oil (0.084 g, 78%).

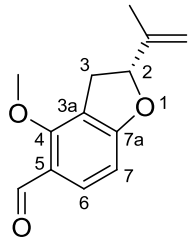


R_f = 0.50 (20% EtOAc/Hexane). **δ_H /ppm:** 10.23 (1H, s, C*H*O), 7.74 (1H, d, *J*=8.4 Hz, H_6), 6.62 (1H, d, *J*=8.4 Hz, H_7), 5.28 (1H, t, *J*=8.8 Hz, H_2), 5.10 (1H, s, CH_3C=CH(*H*)), 4.96 (1H, s, CH_3C=CH(*H*)), 4.49 (1H, spt, *J*=5.8 Hz, CH_3CHCH_3), 3.42 (1H, dd, *J*=15.5 Hz and 9.7 Hz, one of H_3), 3.06 (1H, dd, *J*=15.5 Hz and 7.8 Hz, one of H_3), 1.78 (3H, s, C*H*$_3$C=CH_2), 1.35 (6H, d, *J*=5.8 Hz, C*H*$_3$CHC*H*$_3$). **δ_C /ppm:** 188.75 (*C*HO), 167.00 (C_{7a}), 158.34 (C_4), 143.07 (CH_3*C*=CH_2), 130.77 (C_6), 123.45 (Ar*C*), 117.31 (Ar*C*), 112.86 (CH_3C=*C*H_2), 105.48 (C_7), 87.08 (C_2), 75.34

(CH_3CHCH_3), 33.04 (C_3), 22.45 (CH_3CHCH_3), 17.01 ($CH_3C=CH_2$). **ν_{max} /cm^{-1}:** 2976 (CH str), 1672 (C=O str), 1583, 1446, 1320, 1246, 1104, 1058. **HRMS** (ESI, +ve) $C_{15}H_{19}O_3^+$ [MH^+] requires *m/z* 247.1336, found 247.1336. **$[\alpha]_D^{19}$** = -52.3 ($CHCl_3$).

4.3.20 (-)-*(R)*-4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-carbaldehyde – *(R)*-208

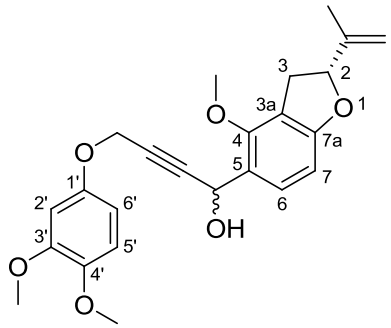
Into a two neck round bottom flask fitted with a condenser and under Ar was placed *(R)*-**202** (0.40 g, 2.0 mmol) and acetone (20 ml) followed by potassium carbonate (0.68 g, 4.9 mmol). After stirring at rt for 30 min, dimethyl sulfate (0.62 g, 0.46 ml, 4.9 mmol) was added and the reaction was heated to reflux. From a clear solution, the reaction turned yellow and eventually a milky white over a 1 h period. TLC analysis indicated that the reaction was complete and the mixture was filtered through a bed of celite and the acetone removed *in vacuo*. Once cooled, diethyl ether (50 ml) was added and the ethereal layer was washed with 10% ammonia (50 ml) solution until frothing stopped. The aqueous layer was extracted with diethyl ether (3 × 50 ml) and dichloromethane (1 × 50 ml). The organic fractions were combined, washed with anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* and the material purified by column chromatography to afford the desired methylated product *(R)*-**208** as a waxy off-white solid (0.42 g, 98%).



R_f = 0.37 (20% EtOAc/Hexane). **Mp.** = 56-58 °C. **δ_H /ppm:** 10.22 (1H, s, C*H*O), 7.72 (1H, d, *J*=8.4 Hz, H_6), 6.60 (1H, d, *J*=8.4 Hz, H_7), 5.28 (1H, t, *J*=8.8 Hz, H_2), 5.11 (1H, s, $CH_3C=CH(H)$), 4.97 (1H, s, $CH_3C=CH(H)$), 4.00 (3H, s, OCH_3), 3.55 (1H, dd, *J*=15.4 Hz and 9.7 Hz, one of H_3), 3.19 (1H, dd, *J*=15.4 Hz and 7.9 Hz, one of H_3), 1.79 (3H, s, $CH_3C=CH_2$). **δ_C /ppm:** 188.32 (*C*HO), 167.31 (C_{7a}), 160.09 (C_4), 142.96 ($CH_3C=CH_2$), 131.00 (C_6), 121.89 (Ar*C*), 115.30 (Ar*C*), 112.89 ($CH_3C=CH_2$), 105.23 (C_7), 87.05 (C_2), 60.12 (OCH_3), 33.02 (C_3), 17.03 ($CH_3C=CH_2$). **ν_{max} /cm^{-1}:** 2869 (CH str), 1652 (C=O str), 1574, 1318, 1248, 1067. **HRMS** (ESI, +ve) $C_{13}H_{15}O_3^+$ [MH^+] requires *m/z* 219.1023, found 219.1031. **$[\alpha]_D^{19}$** = -50.3 ($CHCl_3$).

4.3.21 (-)-*(R)*-4-(3,4-Dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-ol – 209

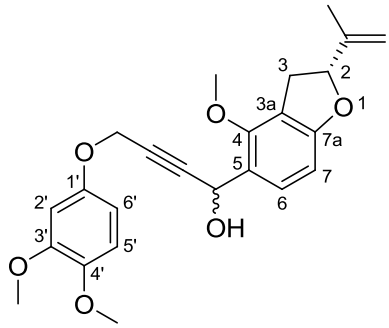
Into a 2 neck round bottom flask under Ar was placed the alkyne **52** (0.075 g, 0.39 mmol) followed by dry tetrahydrofuran (4 ml). The solution was cooled to -78 °C using a frozen acetone slurry bath and *n*BuLi (1.4 M, 0.17 ml, 0.24 mmol) was added dropwise. The reaction was stirred for 30 min at which point the dihydrobenzofuran *(R)*-**208** (0.049 g, 0.220 mmol), dissolved in THF (2 ml) and under Ar, was added via canula. The solution was allowed to warm to rt and stirred for 1 h. TLC analysis showed that a trace amount of product had formed, however, most of the starting material remained. The reaction was heated to 40 °C and monitored hourly by TLC for the next 5 h. Since a significant amount of starting material was present, the reaction was left to stir for 18 h. Saturated ammonium chloride (10 ml) was added and the reaction was transferred to a separating funnel and diluted further with ethyl acetate (20 ml). After mixing, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 30 ml). The combined organic fractions were washed with brine (100 ml), dried over anhydrous magnesium sulfate and the solvent evaporated *in vacuo*. Purification was achieved by column chromatography (30% EtOAc/Hexane), giving the coupled product *(R)*-**209** as a yellow oil (0.038 g, 10-42%).



R_f = 0.31 (40% EtOAc/Hexane). **δ_H /ppm:** 7.22 (1H, d, *J*=8.2 Hz, H_6), 6.77 (1H, d, *J*=8.7 Hz, $H_{5'}$), 6.58 (1H, d, *J*=2.7 Hz, $H_{2'}$), 6.50-6.48 (2H, overlapping signals, $H_{6'}$ and H_7), 5.59 (1H, s, C*H*OH), 5.18 (1H, t, *J*=8.8 Hz, H_2), 5.09 (1H, s, CH_3C=CH(*H*)), 4.93 (1H, s, CH_3C=CH(*H*)), 4.73 (2H, s, CH_2C≡C), 3.88 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.47 (1H, dd, *J*=15.1 Hz and 9.4 Hz, one of H_3), 3.13 (1H, dd, *J*=15.3 Hz and 8.4 Hz, one of H_3), 2.79 (1H, s, CHO*H*), 1.78 (3H, s, CH_3C=CH_2). **δ_C /ppm:** 162.24 (Ar*C*O), 154.32 (Ar*C*O), 152.23 (Ar*C*O), 149.77 (Ar*C*O), 144.03 (Ar*C*O), 143.50 (CH_3C=CH_2), 128.31 (C_6), 124.11 (Ar*C*)), 115.77 (Ar*C*)), 112.49 (CH_3C=CH_2), 111.55 ($C_{5'}$), 104.71 (Ar*C*H), 104.02 (Ar*C*H), 101.40 ($C_{2'}$), 87.53 (*C*≡C), 86.22 (C_2), 80.70 (C≡*C*), 61.16 (*C*HOH), 59.36 (O*C*H_3), 56.93 (*C*H_2C≡C), 56.38 (O*C*H_3), 55.84 (O*C*H_3), 33.56 (C_3), 17.16 (*C*H_3C=CH_2). **ν_{max} /cm^{-1}:** 3489 (OH str), 2936 (CH str), 1600, 1512, 1465, 1226. **HRMS** (ESI, +ve) $C_{24}H_{26}O_6Na^+$ [MNa^+] requires *m/z* 433.1627, found433.1621. **$[\alpha]_D^{19}$** = -10.3 ($CHCl_3$).

4.3.22 (-)-*(R)*-4-(3,4-dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-ol – 209

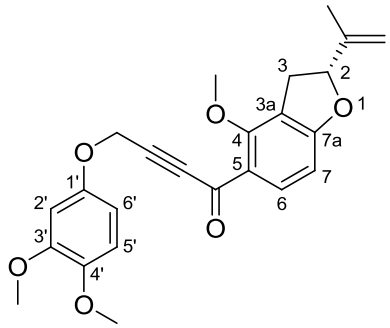
Into a three neck round bottom flask fitted with a dropping funnel and under Ar was placed dry tetrahydrofuran (4 ml). Once immersed in a frozen acetone slurry bath at -78 °C, lithium diisopropylamide (2.0 M, 0.19 ml, 0.37 mmol) and the alkyne **52** (0.048 g, 0.25 mmol) were added. After 2 h, the aldehyde *(R)*-**208** (0.050 g, 0.23 mmol) was dissolved in tetrahydrofuran (2 ml) and added dropwise, resulting in a colour change from yellow to clear. The reaction was left to warm to rt and stirred for 1.5 h during which the reaction turned yellow. TLC analysis indicated that most of the starting material had converted to product and ammonium chloride (10 ml) was added. The mixture was transferred to a separating funnel and diluted with ethyl acetate (20 ml). After mixing, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 30 ml). The combined organic fractions were washed with brine (100 ml), dried over anhydrous magnesium sulfate and the solvent evaporated *in vacuo*. Purification was achieved by column chromatography (30% EtOAc/Hexane) to furnish the coupled product *(R)*-**209** as a yellow oil (0.070 g, 75%).



R_f = 0.31 (40% EtOAc/Hexane). **δ_H /ppm:** 7.22 (1H, d, *J*=8.2 Hz, H_6), 6.77 (1H, d, *J*=8.7 Hz, $H_{5'}$), 6.58 (1H, d, *J*=2.7 Hz, $H_{2'}$), 6.50-6.48 (2H, overlapping signals, $H_{6'}$ and H_7), 5.58 (1H, d, *J*=6.5 Hz, C*H*OH), 5.18 (1H, t, *J*=8.8 Hz, H_2), 5.09 (1H, s, CH_3C=CH(*H*)), 4.93 (1H, s, CH_3C=CH(*H*)), 4.73 (2H, s, CH_2C≡C), 3.88 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.47 (1H, dd, *J*=15.1 Hz and 9.4 Hz, one of H_3), 3.13 (1H, dd, *J*=15.3 Hz and 8.4 Hz, one of H_3), 2.78 (1H, d, *J*=6.9 Hz, CHO*H*), 1.78 (3H, s, CH_3C=CH_2). **δ_C /ppm:** 162.24 (Ar*C*O), 154.32 (Ar*C*O), 152.23 (Ar*C*O), 149.77 (Ar*C*O), 144.03 (Ar*C*O), 143.50 (CH_3*C*=CH_2), 128.31 (C_6), 124.11 (Ar*C*), 115.77 (Ar*C*), 112.49 (CH_3C=*C*H_2), 111.55 ($C_{5'}$), 104.71 (Ar*C*H), 104.02 (Ar*C*H), 101.40 ($C_{2'}$), 87.53 (*C*≡C), 86.22 (C_2), 80.70 (C≡*C*), 61.16 (*C*HOH), 59.36 (O*C*H_3), 56.93 (*C*H_2C≡C), 56.38 (O*C*H_3), 55.84 (O*C*H_3), 33.56 (C_3), 17.16 (*C*H_3C=CH_2). **ν_{max} /cm^{-1}:** 3489 (OH str), 2936 (CH str), 1600, 1512, 1465, 1226. **HRMS** (ESI, +ve) $C_{24}H_{26}O_6Na^+$ [MNa^+] requires *m/z* 433.1627, found 433.1621. **$[\alpha]_D^{19}$** = -10.3 ($CHCl_3$).

4.3.23 (-)-*(R)*-4-(3,4-dimethoxyphenoxy)-1-(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)but-2-yn-1-one – *(R)*-212

The alcohol *(R)*-**209** (0.060 g, 0.15 mmol) was dissolved in dry dichloromethane (10 ml) in a two neck round bottom flask under Ar. Manganese dioxide (0.25 g, 2.9 mmol) was added and the reaction was left to stir at rt for 1 h. TLC analysis indicated that the starting material had been consumed and the reaction was left to stir for another 15 min before filtering the suspension though a bed of celite. The solvent was removed *in vacuo* and the crude material purified by column chromatography (20% EtOAc/Hexane) to furnish the alkynone *(R)*-**212** as an orange oil (0.048 g, 80%).

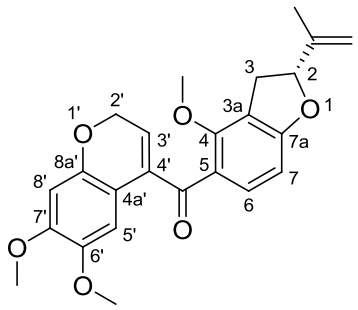


R_f = 0.43 (40% EtOAc/Hexane). **δ_H /ppm:** 7.85 (1H, d, *J*=8.5 Hz, H_6), 6.80 (1H, d, *J*=8.7 Hz, $H_{5'}$), 6.62 (1H, d, *J*=2.8 Hz, $H_{2'}$), 6.59-6.50 (2H, overlapping signals, $H_{6'}$ and H_7), 5.28 (1H, t, *J*=8.8 Hz, H_2), 5.08 (1H, s, CH_3C=CH(*H*)), 4.95 (1H, s, CH_3C=CH(*H*)), 4.90 (2H, s, CH_2C≡C), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.45 (1H, dd, *J*=15.7 Hz and 9.7 Hz, one of H_3), 3.09 (1H, dd, *J*=15.7 Hz and 7.8 Hz, one of H_3), 1.76 (3H, s, CH_3C=CH_2). **δ_C /ppm:** 174.17 (*C*=O), 166.68 (Ar*C*O), 158.44 (Ar*C*O), 152.01 (Ar*C*O), 149.89 (Ar*C*O), 144.37 (Ar*C*O), 142.91 (CH_3*C*=CH_2), 135.31 (C_6), 122.84 (Ar*C*), 118.13 (Ar*C*), 112.83 (CH_3C=*C*H_2), 111.62 ($C_{5'}$), 104.97 (Ar*C*H), 104.85 (Ar*C*H), 101.52 ($C_{2'}$), 87.39 (C_2), 86.78 (*C*≡C), 86.44 (C≡*C*), 60.05 (O*C*H_3), 56.81 (*C*H_2C≡C), 56.36 (O*C*H_3), 55.89 (O*C*H_3), 32.38 (C_3), 16.99 (*C*H_3C=CH_2). **ν_{max} /cm^{-1}:** 2938 (CH str), 1635 (C=O str), 1594, 1509, 1464, 1226. **HRMS** (ESI, +ve) $C_{24}H_{25}O_6^+$ [MH^+] requires *m/z* 409.1653, found 409.1647. **$[\alpha]_D^{19}$** = -38.3 ($CHCl_3$).

4.3.24 (-)-*(R)*-(6,7-dimethoxy-2*H*-chromen-4-yl)(4-methoxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)methanone – *(R)*-213

Into a 2 neck round bottom flask fitted with a condenser and under Ar was placed the alkynone *(R)*-**212** (0.20 g, 0.49 mmol) followed by dry toluene (40 ml). The solution was degassed by bubbling Ar directly into the solution for 5 min and $PtCl_2$ (0.021 g, 0.079 mmol, 16 mol%) was then added. The reaction was heated to 70 °C and stirred for 2 h. TLC analysis indicated that the starting material had been consumed and the solvent was removed *in vacuo*. The crude material was

adsorbed onto silica gel for purification by flash chromatography (20% EtOAc/Hexane), yielding the desired chromene *(R)*-**213** as an orange oil (0.15 g, 77%).

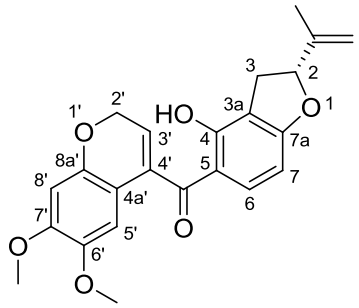


R_f = 0.52 (40% EtOAc/Hexane). **δ_H /ppm:** 7.43 (1H, d, *J*=8.3 Hz, H_6), 7.14 (1H, s, ArC*H*), 6.58 (1H, d, *J*=8.3 Hz, H_7), 6.50 (1H, s, ArC*H*), 6.10 (1H, t, *J*=4.1 Hz, $H_{3'}$), 5.25 (1H, t, *J*=8.7 Hz, H_2), 5.10 (1H, s, CH_3C=CH(*H*)), 4.95 (1H, s, CH_3C=CH(*H*)), 4.79 (2H, d, *J*=4.1 Hz, $H_{2'}$), 3.86 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.44 (1H, dd, *J*=15.6 Hz and 9.7 Hz, one of H_3), 3.09 (1H, dd, *J*=15.6 Hz and 7.9 Hz, one of H_3), 1.77 (3H, s, CH_3C=CH_2). **δ_C /ppm:** 193.97 (*C*=O), 164.93 (C_{7a}), 156.84 (C_4), 149.94 (Ar*C*O), 148.68 ($C_{8a'}$), 143.42 (Ar*C*O), 143.16 (CH_3C=CH_2), 136.70 ($C_{4a'}$), 132.52 (C_6), 126.18 ($C_{3'}$), 124.29 (C_5), 116.85 (C_{3a}), 112.68 (CH_3C=CH_2), 112.31 ($C_{4'}$), 108.70 ($C_{5'}$), 104.27 (C_7), 100.48 ($C_{8'}$), 86.81 (C_2), 64.77 ($C_{2'}$), 59.96 (OCH_3), 56.20 (OCH_3), 55.90 (OCH_3), 32.89 (C_3), 17.07 (CH_3C=CH_2). **ν_{max} /cm^{-1}:** 2937 (CH str), 1650 (C=O str), 1589, 1506, 1453, 1218. **HRMS** (ESI, +ve) $C_{24}H_{25}O_6^+$ [MH^+] requires *m/z* 409.1653, found 409.1644. **$[\alpha]_D^{19}$** = -34.4 ($CHCl_3$).

Note: quaternary carbons were assigned using an HMBC spectrum.

4.3.25 (-)-*(R)*-(6,7-dimethoxy-2*H*-chromen-4-yl)(4-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran-5-yl)methanone – *(R)*-214

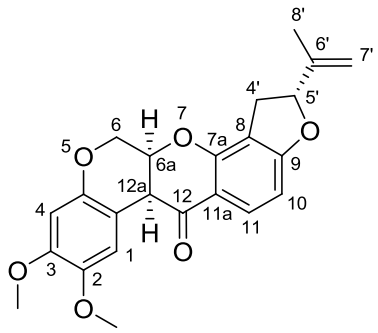
Into a two neck round bottom flask under Ar was placed *(R)*-**213** (0.11 g, 0.27 mmol) followed by dry dichloromethane (7 ml). The solution was immersed in a frozen acetone slurry bath and boron trichloride (1 M, 0.32 ml, 0.32 mmol) was added resulting in a colour change from yellow to a dark red. The reaction was stirred at -78 °C for 1 h before being transferred to an ice bath. Following 1 h at 0 °C, TLC indicated that all the starting material had been converted to a single product and saturated ammonium chloride (10 ml) was added. The reaction was transferred to a separating funnel and diluted with ethyl acetate (30 ml). After mixing, the phases were separated and the aqueous phase was extracted with ethyl acetate (2 × 30 ml) and dichloromethane (30 ml). The combined organic fractions were dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification by column chromatography (10% EtOAc/Hexane) afforded the deprotected product *(R)*-**214** as a yellow oil (0.087 g, 82%).



R_f = 0.66 (40% EtOAc/Hexane). **δ_H /ppm:** 12.59 (1H, s, O*H*), 7.61 (1H, d, *J*=8.7 Hz, H_6), 6.71 (1H, s, ArC*H*), 6.51 (1H, s, ArC*H*), 6.36 (1H, d, *J*=8.7 Hz, H_7), 5.86 (1H, t, *J*=4.0 Hz, $H_{3'}$), 5.35 (1H, dd, *J*=9.5 Hz and 8.0 Hz, H_2), 5.09 (1H, s, CH_3C=CH(*H*)), 4.95 (1H, s, CH_3C=CH(*H*)), 4.85 (2H, d, *J*=4.0 Hz, $H_{2'}$), 3.87 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.39 (1H, dd, *J*=15.8 Hz and 9.9 Hz, one of H_3), 3.04 (1H, dd, *J*=15.8 Hz and 7.7 Hz, one of H_3), 1.78 (3H, s, CH_3C=CH_2). **δ_C /ppm:** 198.54 (*C*=O), 167.73 (C_{7a}), 161.26 (Ar*C*O), 150.57 (Ar*C*O), 148.61 (Ar*C*O), 143.75 (Ar*C*O), 143.07 (CH_3*C*=CH_2), 135.87 (C_6), 134.51, 121.77 ($C_{3'}$), 114.10, 113.15, 112.69 (CH_3C=*C*H_2), 112.01, 108.47 (Ar*C*H), 102.03 (C_7), 100.83 (Ar*C*H), 88.20 (C_2), 64.62 ($C_{2'}$), 56.52 (O*C*H_3), 55.97 (O*C*H_3), 30.90 (C_3), 17.00 (*C*H_3C=CH_2). **ν_{max} /cm^{-1}:** 3081 (OH str), 2935 (CH str), 1635 (C=O str), 1600, 1507, 1431, 1260, 1097. **HRMS** (ESI, +ve) $C_{24}H_{23}O_6^+$ [MH^+] requires *m/z* 395.1496, found 395.1485. **$[\alpha]_D^{19}$** = -44.2 ($CHCl_3$).

4.3.26 Rotenone – 1a and 1b

Into a two neck round bottom flask fitted with a condenser and under Ar was placed the phenol *(R)*-**214** (0.023 g, 0.058 mmol) followed by absolute ethanol (10 ml). Sodium acetate (0.022 g, 0.27 mmol) was added and the reaction was set to reflux at 90 °C. The reaction was monitored by TLC and after 30 min, two new closely spaced products had formed. A small amount of starting material was still present and the reaction was left to proceed for another 2 h. Despite the persistent traces of starting material, water (20 ml) and ethyl acetate (20 ml) were added to the cooled reaction mixture and transferred to a separating funnel. After mixing, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 30 ml). The combined organic fractions were washed with brine (100 ml) and dried over magnesium sulfate. Filtration and evaporation of the solvent *in vacuo* was followed by purification by flash chromatography (20% EtOAc/Hex). The two closely spaced products could only be partially separated by and the mixed fractions were separated by preparative layer chromatography (15% EtOAc/Hex) to furnish the two products **1a** and **1b** in an approximate 1:1 ratio (0.0205 g, 89%). NMR analysis of the two compounds confirmed that the two closely spaced products were in fact diastereomers of one another, as expected. Comparison of the NMR spectra of the two products with that of commercially available resorcinol allowed us to identify the naturally occurring form of rotenone **1a**, which was recrystallised from diethyl ether to afford the product as off-white crystals suitable for X-ray analysis.



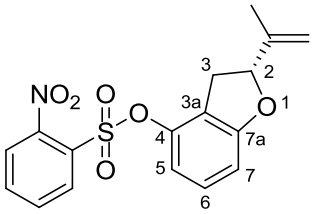
R_f = 0.54 (40% EtOAc/Hexane). **Mp.** = 155-157 °C. **δ_H /ppm:** 7.84 (1H, d, *J*=8.5 Hz, H_{11}), 6.77 (1H, s, ArC*H*), 6.51 (1H, d, *J*=8.6 Hz, H_{10}), 6.46 (1H, s, ArC*H*), 5.24 (1H, t, *J*=8.9 Hz, $H_{5'}$), 5.08 (1 H, s, one of $H_{7'}$), 4.94 (2H, overlapping signals, one of $H_{7'}$ and H_{6a}), 4.62 (1H, dd, *J*=12.0 Hz and 2.9 Hz, one of H_6), 4.19 (1 H, d, *J*=12.0 Hz, one of H_6), 3.85 (1 H, d, *J*=3.8 Hz, H_{12a}), 3.81 (3 H, s, OCH_3), 3.77 (3 H, s, OCH_3), 3.32 (1 H, dd, *J*=15.7 Hz and 9.8 Hz, one of $H_{4'}$), 2.96 (1 H, dd, *J*=15.8 Hz and 8.2 Hz, one of $H_{4'}$), 1.77 (3 H, s, $H_{8'}$). **δ_C /ppm:** 188.96 (*C*=O), 167.38 (C_9), 157.95 (C_{7a}), 149.47 (Ar*C*O), 147.35 (Ar*C*O), 143.87 (Ar*C*O), 143.03 ($C_{6'}$), 130.00 (C_{11}), 113.34 (C_{11a}), 112.97 (C_8), 112.60 ($C_{7'}$), 110.29 (Ar*C*H), 104.91 (C_{10}), 104.79 (C_{12b}), 100.88 (Ar*C*H), 87.85 ($C_{5'}$), 72.21 (C_{6a}), 66.28 (C_6), 56.31 (O*C*H$_3$), 55.86 (O*C*H$_3$), 44.60 (C_{12a}), 31.28 ($C_{4'}$), 17.14 ($C_{8'}$). **ν_{max} /cm^{-1}:** 2920 (CH str), 1734(C=O str), 1672, 1606, 1511, 1455, 1213. **HRMS** (ESI, +ve) $C_{23}H_{23}O_6^+$ [MH^+] requires *m/z* 395.1496, found 395.1486. **X-ray data:** $C_{23}H_{22}O_6$; *M*=394.41; orthorhombic; 0.71073 Å; *a*=8.3722(7) Å, *b*=19.7994(17) Å, *c*=23.3482(19) Å, *U*=3870.3(6) Å^3; 173(2) K, space group, $P2_12_12_1$, Z=8, μ(Mo-Kα)=0.098 mm^{-1} 28006 reflections measured, 5209 unique [R(int)=0.0650] which were used in all calculations. Final R indices [$I>2\sigma(I)$] R_1=0.0479, Wr(F^2)=0.0845. **$[\alpha]_D^{18}$** = -97.959 ($CHCl_3$).

Note: A conventional numbering scheme normally employed for rotenoids was adopted.[29, 107] Quaternary carbons were assigned using an HMBC spectrum. R_f of diastereomer = 0.51

CHAPTER 5 – APPENDIX I

A1 X-ray crystallographic data

A1.1 X-ray crystallographic data for (-)-*(R)*-2-isopropenyl-2,3-dihydrobenzofuran-4-yl-2- nitrobenzenesulfonate – *(R)*-199



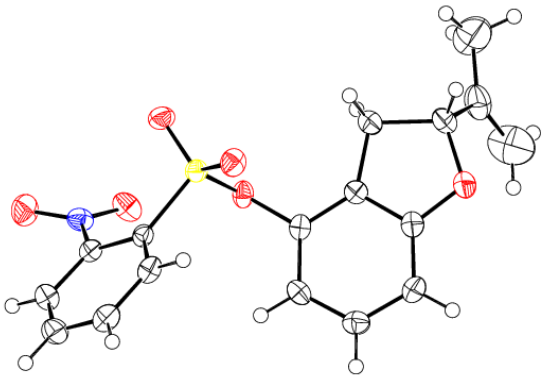
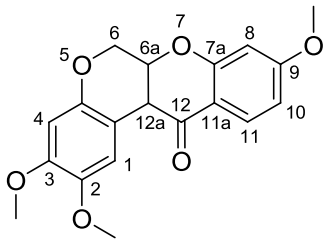


Table A1.1.1. Crystal data and structure refinement for compound *(R)*-199

Identification code	Compound *(R)*-**199**	
Empirical formula	C17 H15 N O6 S	
Formula weight	361.36	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 5.72710(10) Å	α = 90°.
	b = 13.0745(3) Å	β = 90°.
	c = 22.1624(4) Å	γ = 90°.
Volume	1659.50(6) $Å^3$	
Z	4	
Density (calculated)	1.446 Mg/m^3	
Absorption coefficient	0.229 mm^{-1}	
F(000)	752	
Crystal size	0.42 x 0.16 x 0.14 mm^3	
Theta range for data collection	1.81 to 27.99°.	
Index ranges	-7<=h<=6, -15<=k<=17, -29<=l<=29	
Reflections collected	17953	
Independent reflections	3998 [R(int) = 0.0366]	
Completeness to theta = 27.99°	100.0 %	

Absorption correction	None
Max. and min. transmission	0.9686 and 0.9098
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3998 / 0 / 226
Goodness-of-fit on F^2	1.083
Final R indices [I>2sigma(I)]	R1 = 0.0365, wR2 = 0.0951
R indices (all data)	R1 = 0.0417, wR2 = 0.0976
Absolute structure parameter	-0.02(7)
Largest diff. peak and hole	0.525 and -0.344 e.Å^{-3}

A1.2 X-ray crystallographic data for munduserone – 8



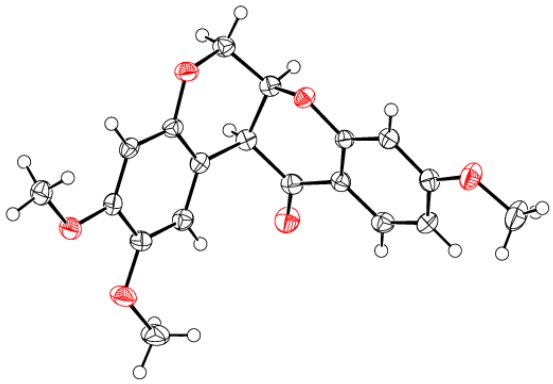
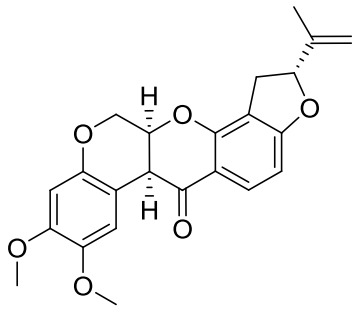


Table A1.2.1. Crystal data and structure refinement for munduserone - 8

Identification code	Munduserone **8**	
Empirical formula	C19 H18 O6	
Formula weight	342.33	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 4.6143(2) Å	α = 90.116(2)°.
	b = 12.4005(6) Å	β = 97.386(2)°.
	c = 13.8039(7) Å	γ = 95.639(2)°.
Volume	779.42(6) Å^3	
Z	2	
Density (calculated)	1.459 Mg/m^3	
Absorption coefficient	0.109 mm^{-1}	

F(000)	360
Crystal size	0.32 x 0.11 x 0.07 mm^3
Theta range for data collection	1.49 to 28.31°.
Index ranges	-6<=h<=6, -16<=k<=16, -18<=l<=18
Reflections collected	12559
Independent reflections	3875 [R(int) = 0.0608]
Completeness to theta = 28.31°	99.8 %
Absorption correction	None
Max. and min. transmission	0.9924 and 0.9660
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3875 / 0 / 226
Goodness-of-fit on F^2	0.909
Final R indices [I>2sigma(I)]	R1 = 0.0445, wR2 = 0.0889
R indices (all data)	R1 = 0.0839, wR2 = 0.1010
Largest diff. peak and hole	0.244 and -0.241 $e.Å^{-3}$

A1.3 X-ray crystallographic data for rotenone – 1a



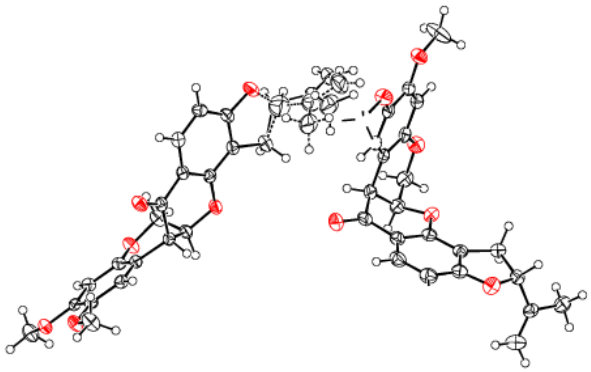


Table A1.3.1. Crystal data and structure refinement for rotenone 1a

Identification code	Rotenone 1a	
Empirical formula	C23 H22 O6	
Formula weight	394.41	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.3722(7) Å	α = 90°.
	b = 19.7994(17) Å	β = 90°.

	c = 23.3482(19) Å γ = 90°.
Volume	3870.3(6) $Å^3$
Z	8
Density (calculated)	1.354 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	1664
Crystal size	0.41 x 0.26 x 0.06 mm^3
Theta range for data collection	1.35 to 28.00°.
Index ranges	-11<=h<=6, -26<=k<=26, -18<=l<=30
Reflections collected	28006
Independent reflections	5209 [R(int) = 0.0650]
Completeness to theta = 28.00°	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5209 / 20 / 558
Goodness-of-fit on F^2	1.151
Final R indices [I>2sigma(I)]	R1 = 0.0479, wR2 = 0.0845
R indices (all data)	R1 = 0.0716, wR2 = 0.0913
Absolute structure parameter	-10(10)
Largest diff. peak and hole	0.229 and -0.264 $e.Å^{-3}$

CHAPTER 5 – REFERENCES

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