Ceric Ammonium Nitrate Mediated Oxidations for the Synthesis of Xanthones and Related Products

Myron Mario Johnson

A dissertation submitted to the Faculty of Science,
University of the Witwatersrand,
Johannesburg
In fulfilment of the requirements for the Degree of Master of Science
February 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. It is being submitted for the degree of Master of Science at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University

_____________
Myron Johnson

24 February 2011
Abstract

Xanthones are a class of secondary metabolites widely found in many natural organisms. Their diverse pharmacological activities have elicited much interest, particularly in their synthesis. This class of compound contains the basic dibenzo-γ-pyrone ring system. The dissertation involves the use of a ceric ammonium nitrate (CAN) mediated oxidation reaction as a key step to form a range of xanthone and dione compounds, which include 2,3-dimethoxy-9H-xanthen-9-one, 12a-methoxy-5H-benzo[c]xanthenes-5,7(12aH)-dione and the unexpected spiro compound 5-chloro-2',5'-dimethoxy-3H-spiro(benzofuran-2,1'-cyclohexa[2,5]diene)-3,4'-dione.

The synthesis of 2,3-dimethoxy-9H-xanthen-9-one started with the preparation of (2-(benzyloxy)-5-chlorophenyl)(2,4,5-trimethoxyphenyl)methanone from benzyl-2-(benzyloxy)benzoate and 1-bromo-2,4,5-trimethoxybenzene. This was followed by deprotection to afford hydroxyphenyl(2,4,5-trimethoxyphenyl)methanone. CAN was then utilized to execute the ring closure thus forming the xanthone nucleus in 91% yield. Using similar methodology 12a-methoxy-5H-benzo[c]xanthenes-5,7(12aH)-dione was afforded from CAN mediated oxidation reaction of (1,4-dimethoxynaphthalene-2-yl)2-hydroxyphenyl methanone in 72% yield. Having successfully produced xanthones and diones using simple systems, we then decided to determine how generalized the synthetic route is. The addition of halogens is believed to be important as they add to the biological activity by increasing the binding capacity, especially against malaria. For example in one transformation we prepared (5-chloro-2-hydroxyphenyl)(2,4,5-trimethoxyphenyl)methanone by similar methodology used for the preparation of hydroxyphenyl(2,4,5-trimethoxyphenyl)methanone. CAN oxidation of this precursor lead to the isolation of three products. The first two were the expected 7-chloro-2,3-dimethoxy-9H-xanthene-9-one and 7-chloro-3,4a-dimethoxy-2H-xanthene-2,9(4aH)-dione products while the third unexpected product was the spiro compound 5-chloro-2',5'-dimethoxy-3H-spiro(benzofuran-2,1'-cyclohexa[2,5]diene)-3,4'-dione, the structure of which was confirmed using x-ray crystallography.
Acknowledgements

I would like to extend my sincere gratitude to my supervisor, Prof Charles de Koning for his wisdom and guidance throughout my project. Without his support and continual encouragement, none of this would have been possible. You are truly an inspiration to me.

Thank you to Prof Joseph Michael, Dr Stephen Pelly, Dr Willem van Otterlo and Dr Andy Dinsmore for their valuable input and support.

I would like to give my sincere thanks to Mr Richard Mampa and Prof Laurence Carlton for running numerous NMR spectra; Dr Manuel Fernandes for his assistance in data collection and analysis of my crystal structures.

Thank you to Dr Andy Dinsmore and Mrs Marelize Ferreira of the MS department as well as Dr Willem van Otterlo for countless mass spectral analyses. I am indebted for all the work you have put in on my behalf.

To the rest of the organic group both past and present; specifically Stefania, Saleem, Siyanda, Tlabo, Winston, Susan, Susen, Sameshnee, Jenny, Kathy and Gail. You guys have really made it a pleasurable environment to work in.

The financial assistance of the National Research Foundation and the University of the Witwatersrand is highly appreciated.

I would like to thank my parents and brother for all their support and encouragement. Without you, this MSc would not have been possible. Finally, I would like to thank Stefania Scalzullo. Your continual support, understanding and encouragement cannot be expressed enough.
1 Chapter 1: Introduction and Aims ........................................................................ 1

1.1 Naturally occurring xanthones ........................................................................ 1

1.1.1 Simple oxygenated xanthones ................................................................ 1

1.1.2 Glycoside xanthones ............................................................................. 2

1.1.3 Prenylated xanthones .......................................................................... 3

1.1.4 Xanthonolignoids ............................................................................... 3

1.1.5 Chlorinated xanthones ....................................................................... 4

1.2 Biological Activity ...................................................................................... 4

1.2.1 Anti-viral activity .................................................................................. 4

1.2.2 Anti-malarial activity .......................................................................... 7

1.2.3 Anti-tumour activity ........................................................................... 9

1.3 Biosynthesis ............................................................................................... 13

1.3.1 Acetate polyketide route ..................................................................... 13

1.3.2 Shikimate-polyketide route ................................................................. 14

1.4 Synthetic strategies towards xanthones .................................................... 15

1.4.1 Classical methods ............................................................................... 16

1.4.1.1 The Grover, Shah and Shah (GSS) reaction ...................................... 16

1.4.1.2 Benzophenone route .................................................................... 17

1.4.1.3 Diaryl ether route ........................................................................ 21

1.4.2 Unconventional methods .................................................................... 24

1.4.2.1 Claisen cyclisation of poly-β-ketide ................................................. 24

1.4.2.2 The Robinson-Nishikawa method ................................................. 25

1.4.2.3 Synthesis of xanthones from thioxanthone .................................... 26

1.4.2.4 The Tanase Method for synthesis of xanthones ......................... 27

1.4.3 New methodology ............................................................................... 28

1.4.3.1 The Hauser method for the synthesis of xanthones ...................... 28

1.4.3.2 The Liebeskind method for the synthesis of xanthones .............. 30

1.4.3.3 The Casillas method for the synthesis of xanthones ................... 32

1.4.3.4 The Ghosh method for the synthesis of xanthones .................... 33

1.5 Background to, and aims of, this project .................................................. 35
Chapter 2: Results and Discussion ................................................................. 43

2.1 Synthesis of phenol 159............................................................................... 43
2.2 Oxygen heterocycle formation by CAN mediated oxidations ...................... 48
  2.2.1 Synthesis of dione 163.......................................................................... 49
2.3 Synthesis of dione 167 and xanthone 168.................................................... 51
2.4 Synthesis of xanthone 187.......................................................................... 58
2.5 Synthesis of Ester 189.................................................................................. 61
2.6 Synthesis of benzophenones 191, 192 and 193............................................ 62
2.7 Synthesis of phenols 194, 195 and 196 .......................................................... 65
2.8 Synthesis of dione 197.................................................................................. 68
2.9 Synthesis of xanthone 198 and dione 199 .................................................... 69
2.10 Synthesis of xanthone 200, dione 201 and spiro compound 202 ............... 71

Chapter 3: Conclusions and Future work ........................................................... 75

3.1 Summary of results achieved........................................................................ 75
3.2 Future prospects for xanthone synthesis....................................................... 78

Chapter 4: Experimental Procedures ............................................................... 81

4.1 General Experimental Procedures ............................................................... 81
  4.1.1 Purification of solvents and reagents....................................................... 81
  4.1.2 Chromatography...................................................................................... 81
  4.1.3 Spectroscopic and physical data............................................................... 82
  4.1.4 Other general procedures........................................................................ 83
4.2 Synthesis of 2-bromo-1,4-dimethoxynaphthalene 156 .................................. 84
4.3 Synthesis of benzy-2-(benzyloxy)benzoate 157 ............................................ 85
4.4 Synthesis of [2-(benzyloxy)phenyl](1,4-dimethoxynaphthalen2-yl) methanone 158 ................................................................. 86
4.5 Synthesis of (1,4-dimethoxynaphthalen-2yl)(2-hydroxyphenyl)methanone 159 ................................................................. 87
4.6 Synthesis of 12a-methoxy-5H-benzo[c]xanthenes-5,7 (12aH)-dione 163 ........ 88
4.7 Synthesis of 2-bromo-1,4-dimethoxybenzene 164 ....................................... 89
4.8 Synthesis of [2-(benzyloxy)phenyl](2,5-dimethoxyphenyl)methanone 165 ...... 90
4.9 Synthesis of (2,5-dimethoxyphenyl)(2-hydroxyphenyl)methanone 166 ......... 91
4.11 Synthesis of 1-bromo-2,4,5-trimethoxynaphthalene 184 ............................. 93
4.12 Synthesis of [2-(benzyloxy)phenyl](2,4,5-trimethoxyphenyl) methanone 185 .. 94
4.13 Synthesis of (2'-hydroxyphenyl)(2,4,5-trimethoxyphenyl)methanone 186 .... 95
4.14 Synthesis of 2,3-dimethoxy-9H-xanthen-9-one 187 ......................................................... 95
4.15 Synthesis of benzyl-2-(benzyloxy)-5-chlorobenzoate 189 .............................................. 96
4.16 Synthesis of [2'-(benzyloxy)-5'-chlorophenyl](1,4-dimethoxy-9H-naphthalen-2-yl) methanone 191 .................................................................................................................. 97
4.17 Synthesis of (5-chloro-2-hydroxyphenyl)(1,4-dimethoxy-9H-naphthalen-2-yl) methanone 194 .................................................................................................................. 98
4.19 Synthesis of [2'-(benzyloxy)-5' chlorophenyl](2,5-dimethoxyphenyl) methanone 192 .................................................................................................................. 100
4.20 Synthesis of (5'-chloro-2'-hydroxyphenyl)(2,5-dimethoxyphenyl) methanone 195 .................................................................................................................. 100
4.21 Synthesis of 2-chloro-7-methoxy-9H-xanthen-9-one 198 and 7-chloro-4a-methoxy-9H-xanthen-2,9(4aH)-dione 199 ................................................................. 101
4.22 Synthesis of [2'-(benzyloxy)-5'-chlorophenyl](2,4,5-trimethoxyphenyl) methanone 193 .................................................................................................................. 102
4.23 Synthesis of (5-chloro-2-hydroxyphenyl)(2,4,5-trimethoxyphenyl) methanone 196 .................................................................................................................. 103
4.24 Synthesis of 7-chloro-2,3-dimethoxy-9H-xanthene-9-one 200, 7-chloro-3,4a-dimethoxy-2H-xanthene-2,9(4aH)-dione 201 and 5-chloro-2',5'-dimethoxy-3H-spiro(benzofuran-2,1'-cyclohexa[2,5]diene)-3,4'-dione 202 .................................................................................................................. 104

5 References .................................................................................................................. 106

6 Appendix .................................................................................................................. 109

A1: Selected $^1$H and $^{13}$C NMR Spectra ...................................................................... 110
A2: Single Crystal Data and Structure for 5-chloro-2'5'-dimethoxy-3H-spiro[benzofuran-7,2',5'-cyclohexa[2,5]diene]-3,4'-dione 202 .......................................................................................................... 120
A3: Literature Published during this Masters ............................................................... 129
1 Chapter 1: Introduction and Aims

In nature there are many oxygenated heterocycles which play an important role as pharmacologically active compounds. One such class of these oxygenated heterocycles is the xanthones. Xanthones are known to be secondary metabolites that are found to occur in higher plant families, fungi and lichen. Xanthones are typified by the presence of a 9\(^\)-xanthenone or dibenzo-\(\gamma\)-pyrone ring system. To date approximately 200 different naturally occurring xanthones have been described. The tricyclic scaffold present in these xanthones as well as the variety and position of different substituents contribute to their pharmacological activities.

1.1 Naturally occurring xanthones

The xanthone family displays an extensive range of biological activity which includes anti-fungal and anti-bacterial activities, anti-tumour activity as well as antiviral activity. Xanthones can be classed into five major groups, those being simple oxygenated xanthones, xanthone glycosides, prenylated xanthones, xanthonolignoids and miscellaneous xanthones. Each of these classes will be discussed in more detail below.

1.1.1 Simple oxygenated xanthones

Simple oxygenated xanthones represent a diverse class of xanthones which range from mono-oxygenated to hexa-oxygenated compounds. This class of xanthones arises as a result of their degree of oxygenation. Simple examples of this class are euxanthone and norathyriol. Euxanthone, which has been isolated from the roots of the medicinal herb Polygala caudata, has been shown to be a potent...
neuropharmacologically active compound\textsuperscript{6}. Norathyriol \textbf{3}, a xanthone aglycone has been isolated from the aerial parts of \textit{Tripterospermum lanceolactum} and exhibits inhibition of phorbol ester-induced respiratory burst which arises from the direct suppression of the PKC activity\textsuperscript{7}.

\begin{center}
\includegraphics[width=0.8\textwidth]{images/chapter1.png}
\end{center}

\textbf{1.1.2 Glycoside xanthones}

Glycoside xanthones are further divided into two sub-groups depending on the position and nature of the glycosidic linkage. The two sub-groups are \textit{O}-glycoside xanthones and \textit{C}-glycoside xanthones. \textit{C}-glycosides are known to be resistant to acid and enzymatic hydrolysis. Examples of this are swertifranceside \textbf{4}, which shows anti-HIV activity, and mangiferin \textbf{5}, which exhibits an immunoprotective role by mediating the inhibition of reactive intermediate-induced oxidative stress in lymphocytes\textsuperscript{8}. They have been isolated from \textit{Swertia franchetiana} and \textit{Mangifera indica} respectively.\textsuperscript{9}
1.1.3 Prenylated xanthones

This class of xanthones constitutes the major group of naturally occurring xanthones. There are a number of prenylated xanthones known both synthetic and natural. Examples of this class of xanthones are α-mangostin 6, which induces apoptosis of human leukemia cells \(^\text{10}\), and jacareubin 7 which inhibited the mycelial growth of the brown rot fungus *Postia placenta*\(^\text{11}\). These xanthones were isolated from the pericarps of mangosteen (*Garcinia mangostana* Linn.) and the heartwood of *Calophyllum neo-ebudicum* respectively.

\[
\text{6} \quad \text{7}
\]

1.1.4 Xanthonolignoids

The xanthonolignoid class of xanthones are compounds which consist of a phenylpropane skeleton which is linked to an ortho-dihydroxyxanthone via a dioxane ring. This is formed by radical oxidative coupling. These compounds are considered to be very promising due to their biological activities associated with both the xanthone and the benzodioxane moiety\(^\text{12}\). Examples of these xanthonolignoids include kielcorin 8 and hipericorin 9, which have been isolated from *Kielmeyera rubriflora* and *Hypericum mysorense* respectively\(^\text{13}\).

\[
\text{8} \quad \text{9}
\]
Chapter 1: Introduction and Aims

1.1.5 Chlorinated xanthones

The final class of xanthone compounds acquired its name due to the unusual substitutions that the xanthones possess. These compounds were isolated from a variety of plant sources. Examples of these compounds include 1,3,6-tri-O-methylarthotheline \(10\) and 4,5-dichloro-6-O-methylnorlichexanthone \(11\) and are generally called the "chlorine compounds"\(^{14, 15}\).

\[
\text{\begin{center} \includegraphics[width=0.5\textwidth]{chlorinated_xanthones.png} \end{center}}
\]

1.2 Biological Activity

To date there have been numerous reports appearing in the literature concerning the pharmacological properties of both naturally occurring and synthetic xanthones. These properties range from anti-bacterial, anti-oxidant, anti-viral, anti-malarial as well as anti-tumour activity\(^{16, 17}\).

1.2.1 Anti-viral activity

In recent years, naturally occurring xanthones have shown activity against a number of human viruses. One such virus of great interest and importance is the human immunodeficiency virus (HIV). The life cycle of the virus is dependent on three essential HIV enzymes. The first of these enzymes is reverse transcriptase which is responsible for viral replication. The second is HIV protease whose function is the processing of viral polyproteins into functional enzymes and structural proteins, which enable the maturation and increase the infectivity of the virion particles. The third enzyme is HIV integrase whose function is to mediate HIV integration into the host chromosome. Therefore, much research is currently being focused into the development of inhibitors of these enzymes\(^{18}\). These xanthones are of importance as
they not only act against HIV but they are also known to act against fungal infections which occur in immune-compromised patients such as HIV patients\textsuperscript{19}.

Swertifancheside, was the first isolated flavonexanthone from \textit{Swertia franchetiana} in 1994 by Wang \textit{et al.}\textsuperscript{9}. This compound was found to be a moderately potent inhibitor of DNA polymerase activity of HIV-1 reverse transcriptase. Wang \textit{et al.} determined that this compound \textbf{4} displayed inhibitory activity of 99.8\% at 200 µg/mL (ED\textsubscript{50} = 30.9 µg/mL) against HIV-1 reverse transcriptase while the dimer xanthone swertpunicoside \textbf{12} displayed inhibitory activity at ED\textsubscript{50} = 3.0 µg/mL. Furthermore, this study also showed that compound \textbf{4} displayed no cytotoxicity and anti-malarial activity.

It is known that reverse transcriptase is essential for early proviral DNA synthesis. Therefore, inhibition of the reverse transcriptase catalysed polymerisation ultimately leads to inhibition of virus replication. In a study conducted by Pengsuparp and co-workers, data were collected which suggested that compound \textbf{4} binds to DNA thus mediating inhibition. Furthermore, the data suggest that the aromaticity present within the xanthone scaffold leads to the binding of \textbf{4} to DNA. However, it was also noted that although compound \textbf{4} showed activity against reverse transcriptase, the activity was negligible when compared to that of azidothymidine (AZT), a known compound for HIV treatment.\textsuperscript{20}
A study conducted by Groweiss and co-workers in 2000 resulted in the isolation of macluraxanthone B 13 and macluraxanthone C 14 from *Maclura tinctoria*.

![Chemical structures of macluraxanthone B (13) and macluraxanthone C (14).](image)

Of all the compounds subjected to anti-HIV screening in this study, compounds 13 and 14 were found to display the best potential at an EC$_{50}$ value of 1.1-2 µg/mL. It appears that the catechol functionality of compounds 13 and 14 offers an enhancement in their HIV-inhibitory activity. Furthermore, these compounds also exhibited high toxicity toward CEM-SS host cells with IC$_{50}$ levels of 2.2-17 µg/mL.

A recent study by Magadula showed the isolation and structural elucidation of a new novel isoprenylated xanthone, commonly referred to as garceduxanthone 15. This new xanthone was isolated from the root bark of *Garcinia edulis*, a plant species found in tropical Africa. Solvent-solvent extraction of the ethanol extract followed by a rigorous purification yielded three pentacyclic triterpenoids as well as the novel xanthone 15 and a known xanthone, forbexanthone 16.

![Chemical structures of garceduxanthone (15) and forbexanthone (16).](image)

The results from this study found that the crude extract exhibited mild anti-HIV-1PR activity with IC$_{50}$ value of 51.7 µg/mL. Once purified, the new xanthone 15 exhibits strong anti-HIV-1PR activity with IC$_{50}$ value 11.3 µg/ml while the known xanthone 16 was inactive.
1.2.2 Anti-malarial activity

Malaria is believed to have plagued the human race through antiquity. It has therefore become of utmost importance to develop a long lasting vaccine to try and eradicate this disease. Xanthones have been shown to display potent biological activity against Plasmodium parasites, the protozoan parasite responsible for the disease. Due to the emergence of chloroquine drug resistant strains of Plasmodium falciparum it has become important for the discovery and development of mechanistically novel of anti-malarial compounds.

The digestive food vacuole is an acidic proteolytic compartment and is the site of haemoglobin digestion. It therefore could be regarded as the parasite’s Achilles heel. Digestion of the haemoglobin leads to the release of unbounded haem which is highly reactive as well as toxic to the malaria parasite. The breakdown of haemoglobin serves to provide amino acids which aid the growth of the parasite the liberated haem is detoxified by the parasite to form hemozoin which is a non-toxic substance to the parasite, due to its insolubility. Therefore, it seems a feasible approach to target the digestive vacuole of the parasite by forming a soluble drug-haem complex. This will therefore halt hemozoin formation and aggregation and lead to an increase in the toxic haem which will eventually result in the rupture of the parasites digestive vacuole.

Ignatushchenko and co-workers studied the effect that a highly substituted xanthone X5 has on the digestive vacuole of the parasite. In vitro studies confirmed that X5 did in fact form soluble complexes with the haem monomers and oligomers tested and interfered with the formation of hemozoin.
Chapter 1: Introduction and Aims

Riscoe and co-workers conducted a study in which they synthesized and tested the cytotoxicity of the xanthone 3,6-bis(ω-N,N-diethylaminoamlyloxy)-4,5-difluoroxanthone (F2C5)\(^{18,25}\).

![Diagram of F2C5](image1)

F2C5 was tested against multidrug resistant malaria strains W2 and D6 of *P. falciparum* and IC\(_{50}\) values of 150 nM and 93 nM were observed for the respective strains. Chloroquine shows activity against W2 and D6 with IC\(_{50}\) values of 290 nm and 7.8 nm respectively. The value of F2C5 against W2 is comparable to chloroquine, however, the IC\(_{50}\) value for D6 is considerably lower\(^{25}\). It is believed that the carbonyl bridge in the xanthone tricyclic scaffold co-ordinates to the haem iron atom. The aromatic rings on either side of the carbonyl bridge undergo π-π stacking with co-planar aromatic rings of the haem\(^{23}\). The presence of protonatable amine chains of five carbon length increases the reactivity of 18 due to the ionic interaction with haem propionate groups. These basic protonatable amine groups also assist in the drug being directed to the parasite’s acidic vacuole\(^{23}\). Incorporation of halogens, such as highly electronegative fluorine, in positions 4 and 5 of the xanthone scaffold is believed to enhance binding to the haem. This is due to the increased partial positive charge on these positions which will lead to enhanced electrostatic
Chapter 1: Introduction and Aims

interaction with the negative haem ring\textsuperscript{27}. This stronger interaction will also result in the stabilisation of the drug-haem complex which will prevent further hemozoin formation\textsuperscript{28}.

The position of the hydroxyl groups is believed to be of importance as observed in a study conducted by Hay and co-workers\textsuperscript{29}. Their study tested demethylcalabaxanthone \textbf{20} and calowaitesixanthone \textbf{21} against chloroquine-resistant strains of the malaria parasite. Xanthones \textbf{20} and \textbf{21} showed activity with an IC\textsubscript{50} value of 0.9 µg/ml and IC\textsubscript{50} value 1.0 µg/ml respectively. They concluded that the increased activity was also due to either the presence of a 1,1-dimethylallyl chain or an additional pyran ring.

![Chemical structures](image)

Therefore, all the research being conducted confirms that the xanthone scaffold is pivotal in the activity of a haem poison such as F2C5. This is due to the xanthone scaffold being positioned in an orientation where all its structural features maximises its inhibitory potential.

1.2.3 Anti-tumour activity

Xanthones are known to possess a range of biological activity as mentioned earlier. However, among these, the \textit{in vitro} inhibitory activity on the growth of a wide range of different tumour cell lines proves to be quite remarkable\textsuperscript{4}.

Psorospermin \textbf{22} is a naturally occurring xanthone isolated from the dried roots of \textit{Psorospermum febrifugum}, which is indigenous to tropical Africa. Kupchan and co-workers conducted the isolation studies as well as cytotoxic assays on the isolated extract\textsuperscript{30}. In their study they managed to elucidate the structure of \textbf{22}, however, the
Chapter 1: Introduction and Aims

absolute stereochemistry of the dihydrofuran ring and epoxide moiety was not assigned.

The initial study also included the first biological activity studies of 22. The extract of P. febrifugum was found to exhibit significant activity both in vivo and in vitro. Biological activity was shown in vivo against P-338 lymphocytic leukemia at doses ranging from 8 to 0.1mg/kg and in vitro against a human epidermoid carcinoma at ED₅₀ = 0.1 µg/ml.

Years later, Cassady and co-workers assigned the absolute configuration of both the dihydrofuran ring and epoxide moiety. They further attempted to synthesized three psorospermin derivatives which showed activity considerably lower than their parent compound, psorospermin. This therefore proved the importance that the dihydrofuran ring and epoxide moiety is essential for biological activity. In the same year, they reported another study toward the total synthesis of 22. However, their study resulted in the epimer 23 of 22 being prepared, which was further confirmation of the absolute stereochemistry earlier assigned.

In recent years, psorospermin remains of interest and its first total synthesis was reported in 2005 by Schwaeb and co-workers. Their synthetic route started with the classical Grover, Shah and Shah reaction (see section 1.4.1.1) to achieve the
Chapter 1: Introduction and Aims

hydroxyxathone, and utilised a zipper-type reaction similar to that used in the synthesis attempted by Cassady and co-workers.

In 2003, Hurley et al. conducted a study on 22 and its possible mode of biological action\textsuperscript{34}. It was shown that the xanthone backbone is pivotal for 22 to be biologically active. Psorospermin is believed to intercalate DNA in a parallel fashion resulting in the tricyclic xanthone chromophore being adjacent to DNA base pairs. This places the epoxide moiety in a position in which electrophilic attack of the epoxide by N7 of guanine, located at the 3’ side of DNA intercalation, to take place. This results in a lesion which is cationic and may depurinate inside cells.  

Topoisomerase II is an enzyme which acts as a catalyst and induces changes in the topology of DNA. It plays several important roles in DNA metabolism and chromosome structure and acts via a mechanism that involves transient double-strand breakages and rejoining of phosphodiester bonds. This enzyme is therefore the primary target for a number of potent anti-cancer drugs\textsuperscript{35}. Anti-cancer drugs such as psorospermin are known as topoisomerase poisons and interact with the topoisomerase II-DNA complex. These interactions interferes with the breaking and rejoining reaction of the enzyme and traps the reaction intermediate, the covalently bonded topoisomerase II-DNA complex\textsuperscript{36}. The efficacy of the drug is dependent on how well it binds to the reaction intermediate and the duration of this interaction as loss of this binding will result in the continuation of enzymatic activity. Therefore, compounds which are able to irreversibly bind to the reaction intermediate are likely to show potent cytotoxicity toward cancer cells\textsuperscript{37}.

The first known vascular-disrupting agent to enter phase III trials is 5,5-dimethylxanthenone-4-acetic acid 24, also known as ASA404 or DMXAA. This drug is known to disrupt the functioning of tumour blood vessels by inducing apoptosis in the tumour cells, which in turn leads to vascular collapse as well as haemorrhagic necrosis. This entire process results in the tumour being deprived of oxygen in a process called tumour hypoxia\textsuperscript{38}. Yang and Denny illustrated a new short synthesis of 24 and use of DMXAA in combination with docetaxel has been suggested to show increased activity in advanced prostate cancer\textsuperscript{38, 39}. 
Research has also been conducted into the possible use of xanthones as inhibitors of Epstein-Barr virus (EBV) by Ito and co-workers. These xanthones will ultimately function as anti-tumour promoters. In their study, 20 xanthones were tested and it was found that activity was observed for most of the xanthones tested. The study showed that the presence of the 1,3-dihydroxy-2,4-diprenylxanthone unit was important for more potent inhibitory activity while the essential component for the activity of these xanthones was the presence of the prenyl group at C-2 and C-4 position of the 1,3-dihydroxyxanthone nucleus. Examples of such compounds are dulxanthone-B \(25\) and latisxanthone-C \(26\)\(^{40}\).

Recently, Cho et al. conducted a study which involved the synthesis of a number of xanthone derivatives. These compounds were then tested against various cancer cell lines\(^{35}\). Their study prepared 12 benzoxanthone derivatives, with most compounds showing effective cancer cell growth inhibition against cancer cell lines HT29 and DU145 which are human intestinal epithelial cells and human prostate carcinoma cell lines respectively. Compounds showed activity on topoisomerase I and II, with some showing comparable activity to camptothecin. Examples of the compounds tested in this study are \(27\) and \(28\).
1.3 **Biosynthesis**

Compounds with the benzophenone skeleton are suggested to be biosynthesized by two types of routes, namely the acetate-polyketide route and the mixed shikimate-polyketide pathway. The acetate-polyketide route is believed to occur in fungi while the shikimate-polyketide route in higher plants. The mechanisms for both pathways have yet to be elucidated, however mechanisms for these have been speculated over the years.

1.3.1 **Acetate polyketide route**

Birch *et al.* used radioactive carbon labelling to determine the biosynthetic pathway of ravenelin 29, a naturally occurring xanthone isolated from two species in the fungal family *Helminthosporium*. Their study confirmed that ravenelin is produced completely from polyketides. The polyketide pathway is similar to the pathway in which fatty acids are synthesized. The cyclisation of the polyketide produces an anthraquinone intermediate 30 which rearranges to produce the xanthone as shown in Scheme 1.
Chapter 1: Introduction and Aims

Their study also confirmed that oxygenated benzophenone intermediate 31 is derived from polyketides and is the intermediate in the biosynthesis of ravenelin. The benzophenone intermediate 31 is acetate-derived and is formed from two distinct units, these units being derived from acetate and malonate. An alternative route to the benzophenone intermediate 31 is via anthrone and anthraquinone intermediates which are themselves derived from a single polyketide chain.

An example using the anthrone or anthraquinone intermediate is the biosynthesis of the benzophenone sulochrin 32.

1.3.2 Shikimate-polyketide route

The generally accepted idea in this biosynthetic pathway is that one of the aromatic rings with the carbonyl group is derived from the shikimate acid pathway while the other aromatic ring arises from the acetate-polyketide pathway. These two moieties then condense to form the benzophenone intermediate which in turn reacts intramolecularly to produce the xanthone product^2.
Carpenter and co-workers proposed that the benzophenone intermediate 33 is formed by condensation of phenol 34, which is acetate-derived with benzoic acid 35, which is shikimate-derived\(^42\). The benzophenone intermediate 33 can then undergo intramolecular reactions to afford the xanthones 36 and 37 (Scheme 2).

\[\text{Scheme 2}\]

1.4 Synthetic strategies towards xanthones

In recent years there has been an increase in the interest in xanthone synthesis. This is partly due to the diverse pharmacological activities which xanthones exhibit. Another reason for the increase in xanthone research is in the medicinal chemistry industry where these compounds have been shown to bind to different classes of receptors\(^43\). Not only are xanthones of interest due to their biological activity, the fact that they possess photochemical properties allows for their use in other areas of medicinal chemistry, for example the preparation of fluorescence probes. For these reasons there are numerous synthetic strategies that have been developed. Some of these will be discussed below\(^44\).
Chapter 1: Introduction and Aims

1.4.1 Classical methods

These reaction pathways include the Grover, Shah and Shah (GSS) reaction; the synthesis using benzophenone intermediates and the synthesis via diphenyl ester intermediates. However, the first xanthone synthesis was performed by Michael and Kostanecki\textsuperscript{45} and thus serves as the foundation from which the three traditional methods were developed.

1.4.1.1 The Grover, Shah and Shah (GSS) reaction

The GSS reaction still enjoys great popularity today because it provides a convenient route to xanthone preparation, specifically hydroxyxanthones, as well as the accessibilities of the starting materials. Another reason for its popularity is the fact that the reaction is a one-pot synthesis which therefore allows for the ease of the reaction. As shown in Scheme 3 the reaction requires a salicylic acid derivative 38 as well as a suitable phenol 34. These two substrates are then heated together with zinc chloride in phosphoryl chloride to yield the hydroxyxanthone 39. This method can, however, only afford the desired xanthone if a benzophenone intermediate 40 carries an additional hydroxyl group (*) which provides an alternative cyclisation site.

![Scheme 3](image)

Although the GSS proves to be very efficient and versatile, it does have a number of limitations such as the presence of a phenolic group to direct cyclisation to the xanthone using the method developed by Tanase\textsuperscript{46}. These limitations proved sufficient such that other methods have superseded this xanthone synthesis.
Chapter 1: Introduction and Aims

The GSS reaction remains a common and popular method for xanthone synthesis. Modifications to the GSS reaction are the use of Eaton’s reagents in place of the classical phosphoryl chloride-zinc chloride catalyst. This approach was used by Wu et al. in the synthesis of mangiferin 41, homomangiferin 42 and isomangiferin 43.\(^7\)

![Chemical structures of 41, 42, and 43](image)

2,4-Dihydroxybenzoic acid 44 was monomethylated to afford 4-methoxy-2-hydroxybenzoic acid 45 which was subsequently converted into 4-methoxy-2,5-dihydroxybenzoic acid 46 under aqueous conditions. Once 46 was assembled, the GSS reaction with phloroglucinol 34 in the presence of Eaton’s reagent was conducted to afford the xanthone 47 (Scheme 4).

![Chemical structures of 44, 45, 46, 34, and 47](image)

**Scheme 4 Reagents and conditions:** (i) \(\text{Me}_2\text{SO}_4, 20\%\ \text{aq. NaOH, rt, 59\%}\); (ii) \(\text{K}_2\text{S}_2\text{O}_8, 10\%\ \text{aq. NaOH, 0 °C to rt, 60\%}\); (ii) \(\text{P}_2\text{O}_5, \text{MeSO}_3\text{H, 80 °C, 40\%}\).

### 1.4.1.2 Benzophenone route

The synthesis of xanthones via the benzophenone route results in a benzophenone derivative which is easily obtained by the Friedel-Crafts acylation of an appropriately substituted benzoyl chloride 48 with a phenolic derivative 49. Cyclisation of the benzophenone intermediate 50 could involve either a nucleophilic substitution, a nucleophilic addition-elimination reaction or an oxidation process (Scheme 5).
Chapter 1: Introduction and Aims

Scheme 5

Quillinnan and Scheinmann\textsuperscript{48} illustrated a more useful and efficient alternative to the Grover, Shah and Shah method in their synthesis of polyoxygenated xanthones. Their study illustrated the preparation of numerous analogues, which proved a limitation to the GSS method which was accompanied by unwanted demethylations.

The benzophenone intermediates suitable for cyclisation to the xanthone can conveniently be achieved by Friedel-Crafts acylation in the presence of aluminium chloride in diethyl ether at room temperature. Para-acylation has been shown to be preferential, however, an extended reaction time of 30 hours has led to ortho-acylation. This result thus allows for the convenient synthesis 2-hydroxy-2'-methoxybenzophenone 51 which cyclises to the desired xanthone 52 by the elimination of methanol, as shown in **Scheme 6**.

\[
\begin{align*}
\text{Scheme 6 Reagents and conditions: } & (i) \text{ AlCl}_3, \text{ dry ether, rt, } 20 \text{ h}; (ii) \text{ piperidine/H}_2\text{O}, \text{ reflux, } 46 \text{ h.}
\end{align*}
\]

To date, there are various methods which are used to access the benzophenone intermediate. One such modification was achieved by Elix and co-workers\textsuperscript{49} in which trifluoroacetic anhydride was used in the Friedel-Crafts acylation instead of aluminium chloride (**Scheme 7**). The cyclisation step to the xanthone 53 was achieved by heating an aqueous solution of the benzophenone 55 under pressure.
Recently, the synthesis of α-mangostin 55 by Iikubo and co-workers followed the benzophenone route\textsuperscript{50}. The benzophenone intermediate 56 was prepared from the parent alcohol 57 which was furnished by the coupling of 58 and a protected aryl anion generated from 59. The coupling of these two starting materials proved to be a slightly different approach involving ortho-lithiation as the key step for the preparation of the benzophenone intermediate. Cyclisation of the benzophenone to afford α-mangostin was accomplished using triphenylphosphine and carbon tetrachloride protocols, which constitutes a new method for xanthone synthesis (\textbf{Scheme 8}).
Finnegan and co-workers accessed the benzophenone intermediate 60 through a photo-Fries rearrangement in their synthesis of 2,5 and 4,5-dihydroxyxanthones\textsuperscript{51}. Their initial study aimed to prepare benzophenone 61 via the condensation of 2,3-dimethoxybenzoic acid 62 with para-dimethoxybenzene 63. However, upon analysis of their reaction product, it was determined that 61 was in fact not achieved but rather the ester 64 was prepared. This ester was then subjected to a photo-Fries rearrangement reaction to afford 60, the benzophenone intermediate, and the solvolysis product 65, with the former being the major product. Demethylation using hydrogen bromide afforded benzophenone 66 which was then subjected to heating in water in a sealed vessel furnished the xanthone 67 (Scheme 9).
Chapter 1: Introduction and Aims

Scheme 9 Reagents and conditions: (i) Pyridine, reflux, 4.5 h; (ii) Irradiation, EtOH, 30-40 °C, 9 h; (iii) Glacial acetic acid, 48% HBr, reflux, 4 h; (iv) H2O, bomb, 225 °C, 17 h.

1.4.1.3 Diaryl ether route

Xanthones synthesized from diaryl ethers incorporate an Ullmann condensation or a related ether synthesis. The general reaction involves phenols 68 reacting with ortho-halogenated benzoic acids 69 to yield the diaryl ether intermediate 70. This intermediate can then be cyclised to the xanthone 71 by the electrophilic cycloaddition of the diaryl ether, as shown in Scheme 10.
Chapter 1: Introduction and Aims

Scheme 10

This synthetic route was used by Sousa and co-workers in the synthesis of kielcorin derivatives\textsuperscript{52}. Ether formation 72 was achieved by the condensation of methyl-2-bromobenzoate 73 and 3,4-dimethoxyphenol 74 in the presence of copper. The ester containing diaryl ether 72 was hydrolysed to form the acid 75. Cyclisation of 75 was achieved by reacting it with either LDA in THF or with AcCl in the presence of sulfuric acid to yield xanthones 76 and 77. Demethylation afforded xanthones 78 and 79 (Scheme 11).

Scheme 11 Reagents and conditions: (i) Cu, K\textsubscript{2}CO\textsubscript{3}, Pyridine, reflux, 26 h; (ii) MeOH/THF, H\textsubscript{2}O, NaOH, rt, 96 h; (iii) AcCl, H\textsubscript{2}SO\textsubscript{4}, rt, 10 min; (iv) LDA, THF, 0°C to rt, 2 h (v) Toluene, AlCl\textsubscript{3}, reflux, 8 h
Chapter 1: Introduction and Aims

Reisch and co-workers have prepared xanthone derivatives in their synthesis toward acronycin isosters\textsuperscript{53}. The diaryl ether intermediate 80 was prepared by the Ullmann condensation of 2-chloronicotinic acid 81 with 3,5-dimethoxyphenol 82. Cyclisation of the diaryl ether 80 to furnish azaxanthone 83 was achieved by using polyphosphoric acid (Scheme 12).

![Scheme 12 Reagents and conditions: (i) Cu, K$_2$CO$_3$, DMF; reflux, 10 h; (ii) Polyphosphoric acid, 110 °C, 3 h.]

Elix and co-workers accessed the diaryl ether 84 via a Smiles rearrangement of the diaryl ester 85\textsuperscript{49}. Ester 85 formation was effected by the condensation of benzoic acid 86 and phenol 87 in the presence of $N,N'$-dicyclohexylcarbodiimide (DCC). The diaryl ester was treated with potassium carbonate in dry DMSO to effect the Smiles rearrangement to afford the carboxylic acid 85. Cyclisation was then achieved by treating the carboxylic acid with trifluoroacetic anhydride to furnish the xanthone 88 (Scheme 13).
Chapter 1: Introduction and Aims

Scheme 13 Reagents and conditions: (i) DCC, toluene, dry ether, rt, 24 h; (ii) K₂CO₃, dry DMSO, 80 °C, N₂, 16 h; (iii) dry toluene, TFAA, rt, 17 h.

1.4.2 Unconventional methods

Over the years, some non-conventional methods for the synthesis of xanthones have been reported. Although limited in their application, these methods laid the foundation for more efficient and high-yielding methods⁴⁴. Some of these non-conventional methods will be highlighted in the following section.

1.4.2.1 Claisen cyclisation of poly-β-ketide

Harris and co-workers demonstrated a biomimetic pathway for the synthesis of lichexanthone ⁸⁹, a naturally occurring secondary metabolite⁵⁴. The first step in their synthesis was the reaction of dilithioacetylacetone ⁹¹ with methyl orsellinate ⁹⁰ to furnish the triketone ⁹². Carboxylation of ⁹² afforded triketo acid ⁹³ which was then esterified to afford the ester ⁹⁴. Under basic conditions the ester ⁹⁴ was converted into the benzophenone intermediate ⁹⁵ which involved Claisen cyclisation and chain cleavage reactions. The benzophenone intermediate ⁹⁵ was then heated in methanolic KOH followed by methylation to afford the xanthone ⁸⁹ (Scheme 14).
Chapter 1: Introduction and Aims

Scheme 14 Reagents and conditions: (i) THF, 16 h, rt; (ii) THF, 0 °C, CO₂ bubbling, 5 min; (iii) Diethyl ether, CH₂N₂, 30 sec; (iv) KOH(aq), rt, 70 h; (v) 10% KOH/MeOH, reflux, 7.5 h; (vi) Diethyl ether, CH₂N₂, rt, 1 min.

1.4.2.2 The Robinson-Nishikawa method

This method is a variant of the Hoesch synthesis and is known to proceed via benzophenones involving ketimine intermediates. In 1922, Robinson demonstrated the ketimine intermediate pathway for the preparation of 1,3-dihydroxyxanthone 96\(^{55}\). The reaction involved the condensation of phloroglucinol 34 and salicylonitrile 97 in the presence of zinc chloride to afford the ketimine intermediate 98. Under basic hydrolysis conditions, the ketimine intermediate was converted into the xanthone 96 (Scheme 15).
1.4.2.3 Synthesis of xanthones from thioxanthone

Bennet et al. synthesized 99 via thioxanthone intermediates. Thioxanthone 100 was converted into hydroxybenzophenone sulfinic acid 101 by conducting the reaction under basic conditions followed by acidification. The hydroxybenzophenone sulfinic acid 101 was then heated under basic condition to afford the xanthone 99 as shown in Scheme 16.

Scheme 15 Reagents and conditions: (i) ZnCl₂, HCl, 2 h; (ii) NaOHₐq, reflux
Chapter 1: Introduction and Aims

Scheme 16 Reagents and conditions: (i) NaOH, dioxane/H₂O, reflux, 5 h; (ii) NaOHₐq, reflux, 4 h

1.4.2.4 The Tanase Method for synthesis of xanthones

This method has proved to be useful in the preparation of partially methylated polyhydroxyxanthones and involves xanthene intermediates. Davies et al. applied the Tanase method in their preparation of 3,8-dihydroxy-1-methoxyxanthone 102. 2,6-Dihydroxybenzaldehyde 103 was reacted with 1,3-dihydroxy-5-methoxybenzene 104 under acidic conditions to afford the tricyclic ketone 105. Compound 105 was then reduced using H₂ and a catalyst to afford the xanthene intermediate 106. The phenol on the xanthene intermediate 106 was protected to give 107 and then oxidised to yield xanthone 108 which was then converted into the desired xanthone 102 with the loss of acetic acid (Scheme 17).
1.4.3 New methodology

In more recent years, the emergence of other methods to construct the xanthone core has risen. The main advantages of these new methods include the regioselective construction of highly substituted xanthones. In this section, some of these methods will be highlighted.

1.4.3.1 The Hauser method for the synthesis of xanthones

Hauser and co-workers accomplished one of the first total syntheses of bikaverin 109, by condensing (phenylsulfonyl)isobenzofuranones with chromones to afford xanthones regiospecifically.

**Scheme 17 Reagents and conditions:** (i) AcOH, HCl; (ii) cat. H₂; (iii) Ac₂O; (iv) CrO₃.
Chapter 1: Introduction and Aims

In the classical methods, either the carbonyl bridge or ether linkage is synthesized first before the pyranone ring is formed. The approach followed by Hauser et al. followed a different approach in which the oxygen containing ring is incorporated into the starting materials. Condensation of the anion of 110 and chromone 111 afforded the xanthone 112. Xanthone 112 was then subjected to an oxidation followed by demethylation to afford bikaverin 109 (Scheme 18).

![Scheme 18](image)

**Scheme 18** Reagents and conditions: (i) LiO-t-Bu, THF, –78°C and reflux; (ii) Ag$_2$CO$_3$-Celite; (iii) LiI, DMF

The methodology was then extended to the preparation of xanthones which contain angular polycyclic aromatic systems 113. This was achieved by condensing benzopyranophthalide 114 with various Michael acceptors 115. One example is shown in Scheme 19.

![Scheme 19](image)

**Scheme 19** Reagents and conditions: (i) LiO-t-Bu, THF, –78°C and reflux
This method provided a high yielding, general approach to xanthone preparation, both linear and polycyclic. Michael acceptors such as chromones therefore expand the use of sulfone annelation for regiospecific xanthone preparation.

1.4.3.2 The Liebeskind method for the synthesis of xanthones

Liebeskind and co-workers have developed a flexible approach for the synthesis of highly-substituted xanthones. Their methods relied on cyclobutenediones as scaffolds for the construction of these xanthones. The synthetic strategy involved benzannulation of the intermediate 116 which undergoes benzannulation and deprotection to afford the xanthone nucleus 117. To prepare intermediate 116, the dianion of dithiane-protected salicylaldehyde 118 was fused to a squaric acid derivative 119, which yielded the dithiane-protected benzopyrone-fused cyclobutenedione 120. Nucleophilic addition of various lithiates such as 121 to cyclobutenedione 120 followed by O-acetylation afforded intermediate 116. Attack by the lithiate occurred exclusively at the carbonyl group opposite to the bulky dithiane moiety. The intermediate is exceptionally prone to benzannulation and results in the benzannulated product 122 which is deprotected to afford the xanthone 117 (Scheme 20).
Scheme 20 Reagents and conditions: (i) t-BuLi, THF, –78 °C to 0 °C; (ii) 10 mol % pTSA, CH₂Cl₂, rt, 72 h; (iii) THF, –78 °C, Ac₂O, reflux; (iv) HgCl₂/CaCO₃, mesitylene/H₂O, reflux

Liebeskind and co-workers also attempted the preparation of angular-fused xanthone using the cyclobutenedione-based methodology⁶¹. Cyclobutenedione 123 was reacted with the substituted N-methylpyrrole 124 to afford adduct 125. Xanthone 126 was then produced through the benzannulation of 127. This transformation is believed to be produced by a cascade of electrocyclization reactions and elimination of methanol which is initiated by the ring-opening of cyclobutenedione 125 (Scheme 21).
Chapter 1: Introduction and Aims

Scheme 21 Reagents and conditions: (i) THF, –78 °C; (ii) MeOTf, -78 °C to rt, 64 h; (iii) mesitylene, reflux

These methods developed by Liebeskind and co-workers allow for control of the regiochemistry of the desired products. Another aspect is the short reaction times as well as being high yielding which will allow for application in the total synthesis of natural xanthones.

1.4.3.3 The Casillas method for the synthesis of xanthones

Casillas and co-workers described a new synthetic method for the preparation of xanthones which takes advantage of the high electrophilicity of N-alkynitrilium salts. Their study was based on an earlier study by Meerwein which demonstrated that nitriles are able to be activated by N-alkylation in the presence of Lewis acids. This allows these nitriles to become highly electrophilic nitrilium salts. The acylation reaction of these alkynitrilium salts proves to surpass the Houben-Hoesch acylation method. This is due to the enhanced electrophilicity of the intermediate.
Chapter 1: Introduction and Aims

2-Fluoro-6-methoxybenzonitrile 128 was reacted with Lewis base, SbCl$_5$ and 2-chloropropane to afford the N-isopropynitrilium salt 129. Intermolecular iminoacylation of ester 130 by the nitrilium salt 129 furnished the benzophenone ketimine 131. The benzophenone ketimine 131 was then treated with excess base to hydrolyse the intermediate 131 to the desired xanthone 132 as shown in Scheme 22.

![Chemical structure](image)

**Scheme 22** Reagents and conditions: (i) SbCl$_5$, 2-chloropropane, CH$_2$Cl$_2$, rt, 2 h; (ii) reflux, 60 h, CH$_2$Cl$_2$; (iii) K$_2$CO$_3$, MeCN, reflux, 23 h, MeOH/H$_2$O.

Casillas et al. therefore provided a general route to prepare highly substituted xanthones. They achieved this by taking advantage of the reactivity of N-alkynitriilium salts by employing Friedel-Crafts methodology$^{64}$.

1.4.3.4 The Ghosh method for the synthesis of xanthones

In 1993 Ghosh and Sahana reported on a method for the preparation of xanthones by an intermolecular Michael initiated ring closure (MIRC)$^{65}$. Chromones 133 and 134 undergo an MIRC in the presence of a base to afford benzoaxanthene 135. These benzoaxanthenes then undergo a base catalysed deacyxidative hydroxyl elimination followed by pyran ring opening to furnish xanthones, such as 136 (Scheme 23).
Chapter 1: Introduction and Aims

Scheme 23 Reagents and conditions: (i) Pyridine, piperidine, reflux, 8h

Ghosh et al. then discovered a method for the preparation of xanthones using a Diels-Alder [4+2] cycloaddition reaction. The method involved the cycloaddition of chromone 137, which acts as a dienophile, and enamine 138 to afford intermediate 139. Intermediate 139 then undergoes base catalysed deacylative hydroxyl elimination followed by pyran ring opening to yield xanthone 140 (scheme 24).

Scheme 24 Reagents and conditions: (i) DMF, reflux, 8 h
Chapter 1: Introduction and Aims

This Diels-Alder cycloaddition has also been used on alkyne substrates to prepare xanthones. This method also showed that the diene undergoes a Diels-Alder cycloaddition with relatively weak dienophiles as well as reactive dienophiles. 

1.5 Background to, and aims of, this project

Interest of our research laboratories in these xanthones started in 1988 by de Koning and Giles with the synthesis of bikaverin, 109. Bikaverin 109 was isolated by both Kjaer and Cornforth simultaneously. Kjaer also isolated norbikaverin 141, a derivative of bikaverin. Bikaverin is known to be a wine-red pigment and has been isolated from several species of the fungal genera Fusarium, Gibberella as well as Mycogone. Among the biological activities bikaverin is known to possess, an important one is its antitumour activity.

de Koning and co-workers started the xanthone synthesis by constructing the carbonyl bridge which was prepared using a mild Friedel Crafts reaction. This was achieved using trifluoroacetic anhydride (TFAA) with the prepared naphthalene derivative 142 and the aryl acid 143, to afford the intermediate as a single regioisomer 144. Compound 144 was then deprotected using palladium on carbon in the presence of hydrogen under pressure to afford the phenol 145 which was followed by oxidation using DDQ, which afforded the unexpected spiro-compound 146. The spiro compound 146 was then hydrolyzed to the desired trione 147 using aqueous trifluoroacetic acid (TFA) followed by pyrolytic isomerisation to yield xanthone 109 as shown in Scheme 25.
Chapter 1: Introduction and Aims

Scheme 25 Reagents and conditions: (i) TFAA, CH₂Cl₂, rt, 90 h, 51%; (ii) 10% Pd/C, H₂, 5 bar, 1 h, 80%; (iii) DDQ, benzene, rt, 68 h, 61%; (iv) TFA (aq), CH₂Cl₂, rt, 5 min, 94%; (v) 200 °C, 1.1 bar, 1 h, 93%.

Initial studies conducted at Wits aimed to test the flexibility of the de Koning and Giles methodology towards the synthesis of simple and complex xanthones. Previously in our laboratories, the synthesis of the xanthones using the de Koning and Giles method proved to be unsuccessful. Following de Koning et al., the carbonyl bridged intermediate 148 was constructed using a Friedel Crafts reaction with trifluoroacetic anhydride (TFAA) with the naphthalene derivative 149 and the aryl acid 150, in a yield of 30% (Scheme 26). Owing to the low yield achieved from the Friedel Crafts reaction, another method was sought to form the carbonyl bridge.
Chapter 1: Introduction and Aims

Scheme 26 Reagents and conditions: (i) TFAA, CH₂Cl₂, rt, 48 h, 30%.

A procedure followed by Argade and co-workers in their pursuit to synthesize nigroline xanthone 151 and osajaxanthone 152 was applied. In their approach they constructed the carbonyl bridge of 153 by reacting n-butyllithium with 2-bromo-1,3,5-trimethoxybenzene 154 followed by methyl 2-5-(dibenzylxyloxy)benzoate 155 as shown in Scheme 27.

Scheme 27 Reagents and conditions: (i) n-BuLi, THF, –78 °C, 90 min.

The construction of the carbonyl bridge was then performed using the method of Argade and co-workers. In our work commercially available 1,4-dimethoxynaphthalene was brominated to yield 156. Compound 156 was then reacted with n-butyllithium followed by benzyl 2-(benzyloxy)benzoate 157 to afford the ketone 158 in a yield of 89%. Removal of the benzyl group using palladium on carbon in a hydrogen atmosphere produced phenol 159, shown in Scheme 28.
Chapter 1: Introduction and Aims

Scheme 28 Reagents and conditions: (i) n-BuLi, THF, –78 °C, 90 min, 89%; (ii) 5% Pd/C, H₂, methanol, 5 atm, 18 h, 97%.

The phenol 159 was then subjected to oxidation using DDQ as employed by de Koning and Giles, which was the key step in the formation of the spiro-complex 160 (Scheme 29). After many attempts and the changing of various reaction parameters, only starting material was recovered.

Scheme 29 Reagents and conditions: (i) DDQ, benzene, rt, 72 h; (ii) DDQ, benzene, reflux, 72 h; (iii) DDQ, chloroform, rt, 72 h; (iv) DDQ, chloroform, reflux, 72 h.

After the oxidation reaction using DDQ met with failure, another oxidising agent was used, namely ceric ammonium nitrate (CAN). This was attempted due to literature precedence by Whalley and co-workers who found that 1,4-benzoquinones can undergo 1,4-Michael addition to afford xanthone compounds. Using CAN, Naidoo attempted the oxidation of 159 in the hopes of producing quinone 161 which could...
undergo 1,4-Michael addition to afford the xanthone 162. However, the reaction surprisingly produced the dione 163 (Scheme 30).

Scheme 30 Reagents and conditions: CAN, CH$_3$CN/H$_2$O, rt, 1.5 h, 72%

Having produced the unexpected dione 163, the synthetic route was tested on a simpler, less substituted system. The route produced the expected intermediates. Therefore a simpler carbonyl bridge compound was prepared from 2-bromo-1,4-dimethoxybenzene 164 and benzyl 2-(benzyloxy)benzoate 157 which affording intermediate 165 was then deprotected to afford the phenol 166 in excellent yield. The phenol 166 was then oxidised using CAN to afford the expected dione 167 and an additional product, in higher yield the xanthone 168, shown in Scheme 31.
Chapter 1: Introduction and Aims

Scheme 31 Reagents and conditions: (i) n-BuLi, THF, –78 °C, 90 min, 72%; (ii) 5% Pd/C, H₂, 5 atm, rt, 24 h, 90%; (iii) CAN, CH₃CN, rt, 1.5 h, 168 74% and 167 15%

The aims of this project have therefore been divided into two parts. Firstly, it was aimed to reproduce and confirm the findings of Naidoo and elucidate the mechanism for both the xanthone and dione formation. Secondly with these methods in place, we hope to utilise the synthetic strategy developed for the synthesis of a range of xanthones and diones, differing in their substitution patterns.

The starting point of this project was the synthesis of dione 163. Dione 163 can be disconnected to the benzophenone intermediate 159 (following the work of Naidoo) which we planned to synthesize using a DOM reaction with n-BuLi. The precursors for this step was the protected salicylic acid 157 and 1,4-dimethoxynaphthalene 148.

Scheme 32
Chapter 1: Introduction and Aims

In a similar manner and following the work of Naidoo, xanthone 168 could be disconnected to the benzophenone intermediate 166, which we planned to synthesize from the protected salicylic acid 157 and 1,4-dimethoxybenzene 169.

Scheme 33

Scheme 34 details the proposed steps for the formation of the ester 157 and 2-bromo-1,4-dimethoxynaphthalene 156, which were the initial starting materials for the proposed synthesis. The commercially available salicylic acid 149 is protected using benzyl bromide while 1,4-naphthoquinone 170 is converted into the hydroquinone 171 followed by the protection of the hydroxyl groups as methyl ethers 148.

Scheme 34
Chapter 1: Introduction and Aims

Using DOM reaction methodology, 2-bromo-1,4-dihydroxynaphthalene 156 is expected to undergo halogen-metal exchange with butyllithium before reaction with ester 157 to afford the benzophenone 158. This benzophenone intermediate should then undergo deprotection to furnish the free alcohol 159. Compound 159 will then be subjected to oxidation conditions using CAN to afford the xanthone related product 163.

Scheme 35

Using similar methodology to that for the preparation of 163, xanthone 168 and dione 167 are expected to be prepared. Once this methodology has been applied to these systems to afford relatively simple xanthones, it will be applied to more complex systems, e.g. substituted salicylic acids to afford more complex xanthones as shown in Scheme 36.

Scheme 36
Chapter 2: Results and Discussion

2 Chapter 2: Results and Discussion

2.1 Synthesis of phenol 159

The present synthesis began with the preparation of the starting materials benzyl 2-(benzyloxy)benzoate 157 and 2-bromo-1,4-dimethoxynaphthalene 156 (Figure 1).

![Figure 1](image-url)

Salicylic acid 149 was treated with 3 equivalents of both potassium carbonate and benzyl bromide in acetone. Concentrated solutions were found to be optimal for the synthesis of the dibenzylated product 157. Both the carboxylic acid proton (pKa- 5) and the phenolic proton (pKa- 10) are acidic enough to be deprotonated by the weak potassium carbonate base. Addition of benzyl bromide results in the dibenzylated compound. The desired compound 157 was synthesized in a yield of 94%.
The presence of two singlets at δ 5.13 and 5.33 in the $^1$H NMR spectrum of 157, each integrating for two protons, was a clear indication that both hydroxyl groups had been protected as the benzyl ether and ester respectively. These signals corresponded to the methylene groups. The singlet further downfield was assigned 7-H, as the ester methylene protons are the more deshielded due to the electron withdrawing effects of the carbonyl group. The doublet of doublet furthest downfield was assigned to 3-H, as similar to 7-H it is the most deshielded aromatic proton due to the electron withdrawing effects of the carbonyl group. This doublet of doublet clearly shows ortho and meta coupling to 5-H and 4-H respectively, with coupling constants of $J = 7.7$ and $1.7$ Hz respectively. The $^{13}$C NMR spectrum showed two signals at δ 70.5 and 66.6 which correspond to the two methylene carbons. As observed in the $^1$H MNR spectrum, the signal at δ 70.5 which appears further downfield is assigned to the benzyl ester moiety. Another characteristic signal in the $^{13}$C NMR spectrum is the signal at δ 166.2 which is an indication of the carbonyl functional group. Further confirmation of the identity of the dibenzylated compound is observed in the IR spectrum. The IR spectrum showed a strong signal at 1716 cm$^{-1}$ which is characteristic of carbonyl stretching. The absence of a broad signal at around 3300 cm$^{-1}$ is a clear indication that compound 157 did not contain hydroxyl groups which further confirmed the absence of both the carboxylic acid proton and the phenolic proton. A final comparison was made using the melting point of compound 157. The melting point of compound 157 was determined as 48-50 °C which is close to that reported in the literature being 50-51 °C$^{74}$. 

Scheme 37 Reagents and conditions: (i) K$_2$CO$_3$, benzyl bromide, acetone, Δ, 18h, 94%
Commercially available 1,4-dimethoxynaphthalene 148 was treated with 1 mole equivalent of N-bromosuccinimide (NBS) in dichloromethane (DCM). NBS has been used as a mild brominating agent for polyalkoxyaromatic systems such as 1,4-dimethoxybenzene 169. 1,4-Dimethoxynaphthalene 148 is electron rich and is therefore known to undergo electrophilic aromatic substitution under mild conditions. Hence, the reaction between 1,4-dimethoxynaphthalene 148 and NBS was expected to be high yielding. The methoxy groups present donate electron density into the ring and are known to be ortho directors. Having only added one equivalent of NBS, bromination at one position was expected and achieved. The desired compound 156 was obtained in a yield of 92% (Scheme 38).

Scheme 38 Reagents and conditions: (i) NBS, DCM, ∆, 18h, 92%

The formation of 156 was confirmed spectroscopically by examining the $^1$H and $^{13}$C NMR spectra. The $^1$H NMR spectrum of 156 showed the presence of two singlets at δ 3.97 and 3.98, each integrating for three protons. This observation was an indication that the symmetry of 1,4-dimethoxynaphthalene 148 was now absent and that the environments of the two methoxy groups were thus different suggesting bromination ortho to one of these methoxy groups. Another singlet, further downfield at δ 6.91 which integrated for one proton was assigned as 3-H. The $^{13}$C NMR spectrum showed two upfield signals at δ 55.7 and 61.3 which are characteristic of methoxy group carbons. Two downfield signals at δ 146.7 and 152.1 indicated the presence of carbons attached directly to methoxy groups. Further confirmation was provided by the signal at δ 111.8 which is in the expected region for an aromatic carbon directly attached to a halogen. The NMR spectra analysed for compound 156.

45
Chapter 2: Results and Discussion

compared well with the literature. The melting point obtained (56-58 °C) was in reasonable agreement with that reported in the literature of 54-55 °C.

Having O-benzylated the salicylic acid 149 to afford 157 and brominated the 1,4-dimethoxynaphthalene 148 to yield 156, the formation of the ketone could be performed. This was achieved over two steps using halogen-metal exchange followed by coupling of the metalated species to the ester (Scheme 39). Lithium-halogen exchange using n-BuLi (1.0 equiv.) was conducted on 2-bromo-1,4-dimethoxynaphthalene 156, which was followed by treatment of the lithiated species with benzyl 2-(benzyloxy)benzoate 157 to produce the benzophenone intermediate, [2-(benzyloxy)phenyl](1,4-dimethoxynaphthalen-2-yl)methanone 158 in 84% yield (Scheme 39). Great care needed to be taken in the addition of the lithiated species to benzyl 2-(benzyloxy)benzoate 157 in order to prevent the reactive lithiated species from adding twice to the ester. However, the presence of the bulky benzyloxy groups are believed to assist in single addition, possibly due to steric hindrance.

Scheme 39: Reagents and conditions: (i) THF, –78 °C, n-BuLi (1.0 equiv.), 45 min, benzyl 2-(benzyloxy)benzoate 157, 30 min, 84%

Confirmation of the successful synthesis of 158 was obtained from both the 1H and 13C NMR spectra. The 1H NMR spectrum of 158 showed two singlets at δ 3.59 and 3.91 which integrated for three protons each and were assigned to the methoxy groups at positions 1 and 4. The presence of a singlet at δ 4.98 integrating for two...
protons was due to the methylene substituent. Another characteristic feature of 158 was the singlet at δ 6.88 which was due to the isolated proton at 3-H. Further confirmation that the carbonyl bridge was formed was evident from the downfield signal at δ 196.3 in the $^{13}$C NMR spectrum which is characteristic of the presence of a ketone. The peaks at δ 55.8 and 63.6 correspond to the methoxy group carbons while the signal at δ 70.3 was due to the methylene carbon. The $^{13}$C NMR spectrum also showed three peaks at δ 157.5, 151.7 and 150.3 which all correspond to carbons attached to alkoxy groups. The peaks at δ 151.7 and 150.3 are due to the carbons attached to the methoxy groups. A slight shift in the δ values compared to that of the precursor 156, suggests that the carbon-halogen bond is no longer present. The peak at δ 157.5 is thus due to the carbon bonded to the benzyloxy group. The IR spectrum contained a strong signal at 1734 cm$^{-1}$ which is indicative of the presence of a carbonyl group. Conclusive proof for the formation of 158 was obtained from the high resolution mass spectrum of the product, which showed a molecular ion at $m/z$ 398.1523 in good agreement with the expected mass of the molecule ($m/z$ 398.1518).

The benzophenone intermediate 158 then underwent a hydrogenolysis reaction to facilitate the removal of the O-benzyl group. This was easily achieved by stirring 158 and palladium on carbon in methanol and subjecting this mixture to hydrogen gas at a pressure of 1 atmosphere (Scheme 40).

![Scheme 40 Reagents and conditions: (i) 5% Pd/C, methanol, H$_2$(g), 1 atm, 24h, 97%](image-url)
There was a very small shift in the $R_f$ of the product as compared to the starting material 158 which may be due to intermolecular hydrogen bonding to the ketone. The removal of the benzyl group to furnish the phenol was unequivocally confirmed by NMR spectroscopic data. The most prominent change was the appearance of a singlet at $\delta$ 12.25, integrating for one proton suggesting the presence of a hydrogen-bonded hydroxyl group, and the absence of the singlet at $\delta$ 4.89 due to the methylene group of the benzyl substituent. This confirmed that the benzyl group was no longer present. The $^{13}$C NMR spectrum was simplified by the disappearance of a range of signals, corresponding to aromatic carbons and more importantly to the methylene carbon which was previously present at $\delta$ 70.3. The IR spectrum also indicated the absence of the benzyl group by the presence of a broad stretching band at 2970 cm$^{-1}$, which is characteristic of a hydrogen-bonded hydroxyl group. The high resolution mass spectrum of the molecule 159 found at $m/z$ 308.1048 was also in good agreement with the expected mass of $m/z$ 308.1049.

With 159 in hand, we were now at the stage to form the ether bridge to hopefully afford the xanthone or our xanthone-related product, upon treatment with ceric ammonium nitrate.

### 2.2 Oxygen heterocycle formation by CAN mediated oxidations

Ceric ammonium nitrate (CAN) has recently emerged as a versatile reagent for oxidative electron transfer. Castagnoli Jnr and co-workers$^{76}$ demonstrated the use of CAN as an oxidizing agent for the preparation of quinones from hydroquinones and even formulated a mechanism for this transformation. In their study, they oxidised 1,4-dimethoxy-2,3,5,6-tetramethylbenzene 172 in the presence of 95% isotopically enriched H$_2$O ($^{18}$O). This provided a doubly labelled duroquinone 173. The reaction is believed to proceed by aryl-oxygen bond cleavage with a net formation of the quinone and 2 moles of methanol (Scheme 41).
Chapter 2: Results and Discussion

Scheme 41

Due to the advantages associated with CAN, which range from low toxicity to its solubility in a range of organic solvents, a large number of research papers and review articles have been published on its applications in recent years\textsuperscript{77}.

2.2.1 Synthesis of dione 163

Unfortunately, when 159 was treated with ceric ammonium nitrate in aqueous acetonitrile, neither the expected quinone 161 nor the corresponding xanthone 162 was isolated from the reaction (Scheme 30). Surprisingly the reaction went to completion rather quickly and upon analysis the expected xanthone-related product 163 was isolated (Scheme 30). This result was in agreement with that obtained by Naidoo\textsuperscript{73}.

Scheme 30 Reagents and conditions: (i) CAN, H\textsubscript{2}O/CH\textsubscript{3}CN/CHCl\textsubscript{3}, rt, DCM, Δ, 10 min, 72%
Chapter 2: Results and Discussion

Upon analysis of the $^1$H NMR spectrum, showed the presence of a singlet at δ 3.03 which integrated for three protons, and which could be assigned to a methoxy group. This suggested that the expected products 161 or 162 had in fact not formed. The methoxy signal appeared further upfield and on closer inspection it was found that this was a consequence of it being a constituent of an acetal. The absence of the hydroxyl signal at δ 12.25 suggests that the ether linkage of the xanthone was formed. The $^1$H NMR spectrum also showed a singlet at δ 7.26 which is characteristic of a quinone proton, 6-H. Furthermore, the doublet furthest downfield at δ 8.16 is characteristic of an aromatic proton adjacent to a carbonyl group. This signal appears furthest downfield as it is the most deshielded proton due to the electron withdrawing effects of the carbonyl bridge. The $^{13}$C NMR spectrum showed two signals at δ 184.0 and 181.0 which suggested that the product contained two carbonyl carbons while the presence of the signals at δ 157.8 and 51.5 which are due to a carbon bonded to a methoxy group and a methoxy carbon respectively, confirms that the a methoxy group was present in our product. Further confirmation that the ether linkage was possibly achieved was absence of a hydroxyl peak at 2970 cm$^{-1}$ in the IR spectrum. The high resolution mass spectrum showed a molecular ion at m/z 292.0778 which coincided with the expected mass of m/z 292.0778. A crystal structure was obtained in the initial xanthone study conducted by Naidoo\textsuperscript{73}. This result confirmed Naidoo’s unexpected finding.

The mechanism postulated for the formation of 163 is shown in Scheme 41. It is believed that the CAN oxidises the dimethoxynapthalene system which results in a radical cation 174 or which may proceed via the phenoxy oxygen radical 175. The aromatic radical cation can then undergo nucleophilic addition with the phenol to afford radical 176 which can undergo further oxidation with another equivalent of CAN to afford a cation 177 which is stabilised as the oxonium ion 178 to which water can add to yield 179. Following elimination of methanol from 179 the obtained product 163 would be formed. This reaction represents new unexpected methodology for making a xanthone-like product.
2.3 Synthesis of dione 167 and xanthone 168

After this unexpected result (initially obtained by Naidoo) we then decided to try the reaction on related substrates to gauge the versatility of this novel reaction. Instead of using 1,4-dimethoxynaphthalene 148 as the starting material 1,4-dimethoxybenzene 169 was used in this investigation. We envisaged a similar
synthetic route as followed for the synthesis of synthesis of 12a-methoxy-5H-benzo[c]xanthenes-5,7(12aH)-dione 163 (Scheme 42).

Scheme 42

Commercially available 1,4-dimethoxybenzene 169 was treated with 1 mole equivalent of NBS in DCM and underwent electrophilic substitution to afford the halogenated product, 2-bromo-1,4-dimethoxybenzene 164. The desired compound 164 was obtained in a yield of 89% as a colourless oil using the procedure by Bloomer and co-workers.

Scheme 43 Reagents and conditions: (i) NBS, DCM, Δ, 48 h, 89%
The $^1$H NMR spectrum showed the presence of two singlets at $\delta$ 3.74 and 3.82, each integrating for three protons. These two signals correspond to the methoxy groups and appeared as two separate signals due to the loss in symmetry of the starting material 169 upon halogenation. The $^1$H NMR spectrum also clearly indicated a downfield singlet which integrates for one proton and was assigned as 3-H. In the $^{13}$C NMR spectrum, the presence of three quaternary carbons attested to the fact that halogenation of 169 occurred successfully. These three signals are at $\delta$ 154.0 and 150.3, which are characteristic of a carbon bonded to a methoxy group, and $\delta$113.6 which is due to the carbon bonded to the bromine atom. The NMR spectroscopic results unambiguously confirmed that the compound was 2-bromo-1,4-dimethoxybenzene 164.

With the starting materials prepared, the linking carbonyl bridge could then be constructed in a similar manner as before. Lithiation using $n$-BuLi (1.0 equiv.) on substrate 2-bromo-1,4-dimethoxybenzene 164 was conducted. Treatment of benzyl (2-benzyloxy)benzoate 157 with the lithiated species produced the benzophenone intermediate, [2-(benzyloxy)phenyl](2,5-dimethoxyphenyl)methanone 165 in 88% yield. Once again great care needed to be taken in the addition of the lithiated species to benzyl 2-(benzyloxy)benzoate 157 in order to prevent the reactive lithiated species from adding twice to the ester (Scheme 44).

![Scheme 44](image_url)

**Scheme 44** Reagents and conditions: (i) THF, $-78 \, ^{\circ}\text{C}$, $n$-BuLi (1.0 equiv.), 45 min, benzyl 2-(benzyloxy)benzoate, 30 min, 88%
Chapter 2: Results and Discussion

Confirmation that the reaction was successful for the synthesis of 165 was obtained from both the $^1$H and $^{13}$C NMR spectra. The $^1$H NMR spectrum of 165 showed a singlet at $\delta$ 4.94 integrating for two protons which was due to the methylene group. Another characteristic feature of 165 was the doublet of doublets at $\delta$ 7.59 which was due to the proton at 4-H and showed ortho and meta coupling of $J$= 7.6 and 1.7 Hz to 3-H and 6-H respectively. The observation of the meta coupling was likely due to a loss of the highly electron-withdrawing bromine. The $^{13}$C NMR spectrum showed a downfield signal at $\delta$ 195.4 which further confirmed the presence of the carbonyl bridge. The peaks at $\delta$ 55.9 and 56.5 correspond to the methoxy group carbons while the signal at $\delta$ 70.1 was due to the methylene carbon. The $^{13}$C NMR spectrum also showed three peaks at $\delta$ 157.2, 153.5 and 152.8, which all correspond to aryl carbons attached to alkoxy groups. The IR spectrum contained a strong signal at 1734 cm$^{-1}$ in the IR spectrum, which is characteristic of a carbonyl group. The high resolution mass spectrum showed a molecular ion at $m/z$ 348.1346 consistent with the formula C$_{22}$H$_{20}$O$_4$ (calculated 348.1362) thus further confirming the formation of product 165.

![Scheme 45](image)

**Scheme 45** Reagents and conditions: (i) 5% Pd/C, methanol, H$_2$(g), 1 atm, 24 h, 89%

The ether 165, was then subjected to hydrogenolysis in methanol to afford the phenol 166 in 89% yield. In the $^1$H NMR spectrum of 166, the signal for the methylene proton was no longer present while a new signal at $\delta$ 12.04 was observed which is characteristic of the proton of the phenol group. Conclusive evidence for the formation of 166 was obtained from the mass spectrum of the product, which showed a molecular ion at $m/z$ 258.0883 in good agreement with the expected mass
Chapter 2: Results and Discussion

of m/z 258.0892. The analytical data for the prepared compound compared well with those presented in the literature\(^79\).

Oxidation of the phenol 166 was achieved by stirring an aqueous acetonitrile solution of 166 in the presence of CAN at room temperature for 24 hours. TLC analysis of the reaction mixture showed the formation of two new product spots. The first and major product was the expected product 2-methoxyxanthone 168 while the second and minor product 167 was the expected dione.

\[
\text{HO} \quad \text{O} \quad \text{O}
\]
\[
\text{11} \quad \text{12} \quad \text{166}
\]

\[
\text{O} \quad \text{O} \quad \text{O}
\]
\[
\text{13} \quad \text{14} \quad \text{168}
\]

\[
\text{O} \quad \text{O} \quad \text{O}
\]
\[
\text{167}
\]

Scheme 46 Reagents and conditions: (i) CAN, H\(_2\)O/CH\(_3\)CN/CHCl\(_3\), rt, 10 min, 168 74\% and 167 15\%.

Confirmation of the structure of the major product was evident in the \(^1\)H NMR spectrum. The signal at \(\delta 3.83\) integrated for three protons, which is characteristic for an aromatic methoxy group, and not that of an acetal. Similarly to the starting material 166, xanthone 168 showed a doublet of doublets at \(\delta 8.25\) which was assigned to 8-H and showed ortho and meta coupling to 7-H and 6-H, with coupling constants \(J = 8.0\) and 1.6 Hz, respectively. A singlet which integrated for one proton at \(\delta 7.29\) was assigned as 1-H. The \(^{13}\)C NMR spectrum showed a signal at \(\delta 176.0\) which corresponds to the carbonyl group. The signals at \(\delta 155.0\) and 154.9 are characteristic of carbons single-bonded to oxygen which suggest ether bond formation. Strongest confirmation was received from the high resolution mass spectrum. The molecular ion was found at m/z 226.0620, and the molecule C\(_{14}\)H\(_{10}\)O\(_3\) required \(M^+\) 226.0630. A crystal structure obtained by Naidoo confirmed the xanthone formation. Once again, these results correlated those reported by Naidoo.
Chapter 2: Results and Discussion

It would appear that the xanthone 168 is formed in a similar manner to the dione 163. CAN oxidation results in the formation of a radical cation 180 or which may proceed via the phenoxy oxygen radical 181. This radical cation then cyclises by nucleophilic addition of the phenol to radical 182. The radical formed 182 then undergoes the elimination of a methoxy radical which results in the re-formation of the aromatic ring to give the observed product, xanthone 168. Presumably in this case the lack of an extra aromatic ring, as compared to the naphthalene example, results in the major product being the fully aromatic xanthone 168 (Scheme 47).

The structure of the minor product 167 was confirmed by spectroscopic analysis. The \(^1\)H NMR spectrum showed a singlet which integrated for three protons at \(\delta 3.25\) which is due to the methoxy involved in acetal formation. The \(^1\)H NMR spectrum also showed a singlet at \(\delta 6.81\) which is characteristic of a quinone proton and was assigned 1-H. Furthermore, the doublet furthest downfield at \(\delta 7.94\) is characteristic
of an aromatic proton adjacent to a carbonyl group and was assigned as 8-H. This signal appears furthest downfield as it is the most deshielded proton due to the electron withdrawing effects of the carbonyl bridge. The $^{13}$C NMR spectrum showed two signals at $\delta$ 185.1 and 180.9 which confirmed that the product contained two carbonyl carbons. The presence of the signal at $\delta$ 51.5 which is due to a carbon bonded to a methoxy carbon confirms that a methoxy group was present in our product. Also observed in the $^{13}$C NMR spectrum was the presence of a signal at $\delta$ 95.1 which is characteristic of an acetal carbon.

Using the same rationale for the formation of dione 163, it could be concluded that dione 167 was formed. Confirmation of the formation of the dione came from the high resolution mass spectrum, which showed a molecular ion of $m/z$ 242.0568 ($C_{14}H_{10}O_{4}$ requires $M^+$ 242.0579).

Having tested these CAN oxidation reactions on both substrates we wanted to try it on other substituted benzene precursors not tried by Naidoo. We therefore used 1,2,4-trimethoxybenzene 183 in this investigation. We envisaged a similar synthetic route as followed for the synthesis of 12a-methoxy-5H-benzo[c]xanthene-5,7(12aH)-dione (Scheme 48).
2.4 Synthesis of xanthone 187

Commercially available 1,2,4-trimethoxybenzene 183 was treated with 1 mole equivalent of NBS in DCM which underwent electrophilic substitution to afford the known halogenated product, 1-bromo-2,4,5-trimethoxybenzene 184. The desired compound 184 was furnished in 89% yield as a peach coloured oil. Halogenation occurred exclusively at position 2 of 183, due to the ortho and para electron directing properties of the methoxy groups at positions 1 and 5. Halogenation was not observed at position 6 due to the size of the bromine group (Scheme 49).

![Scheme 49 Reagents and conditions: (i) NBS, DCM, Δ, 48 h, 89%](image)

The $^1$H NMR spectrum of 184 was fairly simple, showing only five singlets. The two singlets observed at δ 7.03 and 6.56 each integrating for one proton was assigned to 6-H and 3-H respectively. The remaining three singlets at δ 3.88, 3.86 and 3.83 all integrated for three protons and correspond to the methoxy group protons. The $^{13}$C NMR spectrum showed the presence of four quaternary carbons. The NMR spectroscopic results analysed for product 184 compared well with the literature and unambiguously confirmed that the product was 1-bromo-2,4,5-trimethoxybenzene 184. 80

Having prepared the starting materials successfully, we were now able to construct the required precursor ketone. Lithiation of 1-bromo-2,4,5-trmethoxybenzene 184 using n-BuLi (1.0 equiv.) followed by the benzylation of the lithiated species with
benzyl 2-(benzyloxy)benzoate 157 afforded the benzophenone intermediate, [2-(benzyloxy)phenyl][2,4,5-trimethoxyphenyl]methane 185 in 52% yield. However, despite having followed all precautions to allow single addition, the product was obtained in a moderate yield. No other characteristic product could be identified by NMR spectroscopy (Scheme 50).

Scheme 50 Reagents and conditions: (i) THF, −78 °C, n-BuLi (1.0 equiv.), 45 min, benzyl 2-(benzyloxy)benzoate, 30 min, 52%

Confirmation that the reaction was successful for the synthesis of 185 was obtained from both the $^1$H and $^{13}$C NMR spectra. Characteristic signals in the $^1$H NMR spectrum included a singlet at $\delta$ 7.26 which was assigned as 6-H. The high resolution mass spectrum of the molecular ion C$_{23}$H$_{23}$O$_5$ was found at [M + H]$^+$ 379.1543. The required mass was calculated to be m/z 379.1545.

The benzophenone intermediate 185 then underwent a hydrogenolysis reaction to facilitate the removal of the O-benzyl substituent. This was easily achieved by stirring 185 in methanol with 5% Pd/C under a hydrogen atmosphere at a pressure of 1 atm to give the phenol 186 (Scheme 51).
The formation of the phenol 186 was confirmed spectroscopically, using $^1$H and $^{13}$C NMR spectra. The most significant change in the spectrum of the starting material 185 was the formation of a singlet at $\delta$ 12.18 which is due to the proton of the phenol and is a clear indication of the successful deprotection. Another prominent indication is the simplification of the aromatic region as well as the loss of the methylene proton signals which occurred at $\delta$ 4.96 in the starting material and was absent in the product. This change was also observed in the $^{13}$C NMR spectrum with the absence of the methylene carbon of the benzyl substituent in the product which occurred at $\delta$ 70.0 in the starting material.

With the phenol 186 in hand, a ring-closure using CAN was performed in the hopes of forming the dione and/or xanthone as previously observed (Scheme 52). The oxidation of the phenol 186 proceeded in the presence of CAN, and afforded xanthone 187 in 91% yield as white grains. The identity of the structure was immediately confirmed upon analysis of the $^1$H NMR spectrum. As the first indication, the singlet previously obtained for the phenol was now absent. The doublet of doublets furthest downfield at $\delta$ 8.32 was assigned 8-$\text{H}$ due to electron withdrawing effects of the carbonyl group. This aromatic proton showed both ortho and meta coupling to 7-$\text{H}$ and 6-$\text{H}$ with coupling constants $J = 8.0$ and 1.0 Hz respectively. A singlet at $\delta$ 7.64 was assigned to 1-$\text{H}$ and showed no coupling due to its position adjacent to the carbonyl group. The doublet at $\delta$ 6.88 was assigned as 4-$\text{H}$ and showed very small para coupling to 1-$\text{H}$ with a coupling constant $J = 1.0$ Hz. The $^{13}$C NMR spectrum provided further evidence that xanthone 187 was formed, with the
disappearance of one of the aromatic methoxy groups and the presence of two carbons involved in ether formation at δ 156.0 and 155.4. The data obtained compared well with that reported in the literature for the compound 80.

\[
\begin{array}{c}
\text{186} \\
\end{array}
\xrightarrow{\text{O}}
\begin{array}{c}
\text{187}
\end{array}
\]

\textbf{Scheme 52 Reagents and conditions:} (i) CAN, H$_2$O/CH$_3$CN/CHCl$_3$, rt, 10 min, 91%

As a result of the success of the preceding transformations, we attempted three other related transformations. The same synthetic route was followed to afford a phenol on which CAN-mediated oxidations could be performed to achieve the xanthone or the xanthone-related product. This is described in the following sections.

\section*{2.5 Synthesis of Ester 189}

Commercially available 5-chlorosalicylic acid 190 was treated with 3 equivalents each of potassium carbonate and benzyl bromide in DMF at 60 °C, which was found to be optimal for the synthesis of the dibenzylated product 189. The desired compound 189 was obtained in a yield of 85% (\textbf{Scheme 53}).
Confirmation that the desired product 189 had been formed was evident in the $^1$H NMR spectrum with the appearance of two singlets at $\delta$ 5.13 and 5.33 for the methylene units of the benzylic groups. The doublet furthest downfield was assigned as 6-H, as it is the most deshielded aromatic proton due to the electron withdrawing effects of the carbonyl group and the chlorine substituent. This doublet clearly shows meta coupling to 4-H, with coupling constant $J = 2.7$ Hz. The doublet at $\delta$ 6.94 was assigned 3-H and showed ortho coupling to 4-H, with a coupling constant of $J = 8.9$ Hz. The $^{13}$C NMR spectrum showed two signals at $\delta$ 71.0 and 67.1 which correspond to the two methylene carbons. As observed in the $^1$H NMR spectrum, the signal at $\delta$ 70.5 which appears further downfield was assigned to the ester moiety. Further confirmation of the dibenzylated compound is observed in the IR spectrum. The IR spectrum showed a strong signal at 1716 cm$^{-1}$ which is characteristic of carbonyl stretching while the absence of a broad signal at around 3300 cm$^{-1}$ is a clear indication that the product 189 is free of hydroxyl groups.

2.6 Synthesis of benzophenones 191, 192 and 193

Having all the starting materials prepared we could now continue with our synthesis of related xanthones. The first step in these routes was the formation of the ketones 191, 192 and 193. The carbonyl bridge was constructed using the same procedure used for the preparation of [2-(benzyloxy)phenyl][1,4-dimethoxynaphthalen-2-yl]methanone 148. This was achieved by lithiation of the brominated aromatic compound using $n$-BuLi (1.0 equiv.) followed by the benzylation of the lithiated
Chapter 2: Results and Discussion

species with benzyl 2-(benzyloxy)-5-chlorobenzoate 189 to produce the benzophenone intermediates 191, 192 and 193. These transformations are shown in Scheme 54.

Scheme 54 Reagents and conditions: (i) THF, –78 °C, n-BuLi (1.0 equiv.), 45 min, benzyl 2-(benzyloxy)benzoate, 30 min, 191 19% (un-optimized), 192 78%, 193 87%

1. Equation A

Purification of benzophenone 191 proved to be difficult. The TLC of the reaction mixture showed a number of products. Both normal silica chromatography and flash silica chromatography afforded impure products. Recrystallisation, however, yielded
pure product, albeit in a low yield. Compound 191, was obtained in an unoptimised recrystallised yield of 19% and its structure was confirmed by NMR spectroscopic studies.

The $^1$H NMR spectrum of 191, showed that the formation of the ketone was quite evident. The most notable indication is the presence of only one methylene singlet at $\delta$ 4.86. Furthermore, the $^1$H NMR spectrum showed a doublet at $\delta$ 7.63 and was assigned 6'-H, showing meta coupling to 9-H, with a coupling constant of $J = 2.6$ Hz. The $^{13}$C NMR spectrum of 191 also confirmed the formation of the ketone, showing a signal at $\delta$ 194.7 which is characteristic for a carbonyl carbon. Further confirmation was the presence of the signal at $\delta$ 70.7 which was due to the methylene carbon and assigned 7-C. This compound, unlike its precursors, 156 and 189, was a yellow solid with a melting point of 160-162 °C.

2. Equation B

The most significant observation in the $^1$H NMR spectrum of compound 192 is the presence of a singlet due to the benzyl methylene protons which occurred at $\delta$ 4.91. In the $^{13}$C NMR spectrum there was a carbonyl peak at $\delta$ 193.8 indicative of a ketone, as well as a peak at $\delta$ 70.5 indicating the methylene carbon of the benzyl group. The high resolution mass spectrum of 192 matched the expected value for the product ($m/z$ 383.1047).

3. Equation C

The spectroscopic analysis of the product 193 was in line with our expectations and thus confirmed the success of the reaction. In the $^1$H NMR spectrum, the first clear indication was the presence of only one methylene signal at $\delta$ 4.95, integrating for two protons. The aromatic region for the product 193 was similar to that of its
Chapter 2: Results and Discussion

precursors 184 and 189. In the $^{13}$C NMR spectrum, the presence of a peak at $\delta$ 192.3 was indicative of a ketone carbon. A signal at $\delta$ 70.5 indicated the methylene carbon of the benzyl group which further confirmed the success of the reaction. The high resolution mass spectrum showed a molecular ion at ($M^+ + H$) 413.1142, consistent with the formula $C_{20}H_{22}O_5Cl$ (calculated 413.1150) thus confirming the formation of the benzophenone intermediate 193.

2.7 Synthesis of phenols 194, 195 and 196

Having successfully constructed the carbonyl bridge in all three required compounds as shown in Scheme 54, it was now necessary to remove the benzyl group from these compounds. The removal was achieved by subjecting the benzophenone intermediates in Scheme 55 to a hydrogenolysis reaction.
Chapter 2: Results and Discussion

Scheme 55 Reagents and conditions: (i) 5% Pd/C, EtOAc, H₂(g), 1 atm, 24 h, 194 96%, 195 56%, 196 99%

Having easily removed the benzyl group to furnish the phenol in methanol, we attempted the debenzylation of 194 in methanol. Unfortunately, when we attempted this methodology, two products were formed for each of the three substrates. The reaction was monitored using TLC and it appeared that the O-debenzylation occurred but then loss of aromatic chlorine also occurred. This was confirmed by spectroscopic analysis of the two products. The solvent in which the reaction was performed was then changed to ethyl acetate. A procedure by de Koning and co-workers was then employed in which they demonstrated debenzylation reactions in ethyl acetate. Ethyl acetate proved to be an excellent solvent to perform the hydrogenations in as the aromatic chlorine was still in place once the reaction was complete.
Chapter 2: Results and Discussion

1. Equation A

Compound 191 was subjected to hydrogenation in the presence of palladium on carbon as the catalyst in pure ethyl acetate. The removal of the benzyl group progressed smoothly and complete conversion to the phenol was obtained after 4 hours. The product was then purified using standard silica chromatography to afford the phenol 194 in 96% yield. The identity of the product was confirmed using $^1$H and $^{13}$C NMR spectroscopy. The most prominent change in $^1$H NMR spectrum was the disappearance of the signal at δ 4.86 due to the methylene protons as well as a simplification of the aromatic region. Another noteworthy change was the appearance of a downfield singlet at δ 12.14 which is due to the phenol. The $^{13}$C NMR spectrum was significantly different in that number of carbons in the aromatic region decreased. The upfield region only contains two methoxy signals. The absence of the methylene carbon which occurred at δ 4.86 in the $^1$H NMR spectrum was an unmistakable indication that the benzyl group was removed. Analysis of the high resolution mass spectrum revealed an observed mass of $m/z$ 341.0581, in good agreement with the expected mass of $m/z$ 341.0581 for C$_{19}$H$_{14}$O$_4$Cl.

2. Equation B

The removal of the benzyl group from compound 192 was performed in the same way as that for compound 191. Once again, the reaction proceeded smoothly and complete conversion to the phenol 195 was observed after 4 hours. The product was obtained in 56 % yield after purification by column chromatography. Confirmation of the structure of the desired product was indicated firstly by the presence of a new singlet at δ 11.93 indicative of the phenol, and secondly by the absence of the distinctive singlet at δ 4.91, previously indicative of the methylene protons. The most noteworthy change in the $^{13}$C NMR spectrum was the absence of the methylene carbon which occurred at δ 70.5 and was distinctive indication that the benzyl group has been removed. The decrease in the number of aromatic carbon signals was also
evident. The presence of a broad spectral band at 2931 cm\(^{-1}\) for the hydroxyl group in the IR spectrum further confirmed the formation of benzophenone 195.

### 3. Equation C

Benzophenone 193 was also subjected to reduction using catalytic palladium on carbon under a hydrogen atmosphere of 1 atm to produce the phenol 196 in a near quantitative yield of 99 % after column chromatography. Again, the most distinctive change of the product spectrum was a new singlet at \(\delta\) 12.04 in the \(^1\)H NMR spectrum, indicative of the new free phenol substituent. Moreover, the characteristic singlet previously occurring at \(\delta\) 4.95 in the \(^1\)H NMR spectrum of the starting material was absent. The decrease in the number of aromatic signals in the \(^{13}\)C NMR spectrum, as well as the absence of the methylene carbon peak at \(\delta\) 70.5, further attested to the fact that we had removed the benzyl group.

We were now in a position to attempt the ring closure on our phenol compounds 194, 195 and 196 using CAN.

#### 2.8 Synthesis of dione 197

Phenol 194 was oxidised by stirring an aqueous acetonitrile/chloroform solution of 194 in the presence of CAN at room temperature for 24 hours. TLC analysis of the reaction mixture showed the formation of only one new product. This result was consistent with the unhalogenated dione formation, as observed before (Scheme 56).
Chapter 2: Results and Discussion

Scheme 56 Reagents and conditions: (i) CAN, H₂O/CH₃CN/CHCl₃, rt, 10 min, 93%

Spectroscopic analysis of the compound 197 confirmed that we had once again prepared the dione compound. The \(^1\)H NMR spectrum showed a singlet at \(\delta\) 3.02 which integrated for three protons and which was assigned to the methoxy group. Moreover, the absence of the phenol signal at \(\delta\) 12.14 confirms that the phenol has reacted possibly forming the acetal linkage of the dione. The \(^1\)H NMR spectrum also showed a singlet at \(\delta\) 7.21 which is characteristic of a quinone proton and is assigned 6-H. Further evidence was obtained from the \(^{13}\)C NMR spectrum which showed two signals at \(\delta\) 183.7 and 180.1 which validated that the product contained two carbonyl carbons.

2.9 Synthesis of xanthone 198 and dione 199

In the same manner, oxidation of the alcohol 195 was achieved by stirring an aqueous acetonitrile solution of 195 in the presence of CAN at room temperature for 24 hours. TLC analysis of the reaction mixture showed the formation of two new product spots, which was expected as this observation was made earlier with the formation of 2-methoxyxanthone. The first and major product 198 was 2-chloro-7-methoxyxanthone, obtained in 63% yield, while the second and minor product 199 was the expected dione, isolated in a yield of 17% (Scheme 57).
Confirmation of the major product was evident in the $^1$H NMR spectrum. The first indication that the xanthone had formed was the presence of a signal at $\delta$ 3.92 integrating for three protons, which is characteristic for an aromatic methoxy group. The position of the methoxy signal was a clear indication that the methoxy was not involved in acetal formation. Another feature of the $^1$H NMR spectrum was the presence of a doublet at $\delta$ 8.29 which was assigned 1-H and showed meta coupling to 3-H with a coupling constant $J = 2.6$ Hz. A singlet which integrated for one proton at $\delta$ 7.29 was assigned 1-H. The $^{13}$C NMR spectrum showed a signal at $\delta$ 176.0 which corresponds to the carbonyl group. The signals at $\delta$ 155.0 and 154.9 are characteristic of carbons single bonded to oxygen on an aromatic ring. The mass spectrum showed a molecular ion which coincided with the expected mass of $m/z$ 261.0318.

The $^1$H and $^{13}$C NMR spectra were used to confirm the structure of the minor product. As observed in the previous dione products, the $^1$H NMR spectrum showed a singlet, integrating for three protons at $\delta$ 3.35 which is due to the methoxy group involved in acetal formation due to the upfield nature of this signal. The $^1$H NMR spectrum also showed a doublet at $\delta$ 6.89, which is characteristic of a quinone proton, and is assigned 1-H, showing meta coupling to 2-H with a coupling constant $J = 2.0$ Hz. Furthermore, the doublet furthest downfield at $\delta$ 7.96, which is characteristic of an aromatic proton adjacent to a carbonyl group, was assigned as 6-H and showed meta coupling to 5-H with a coupling constant $J = 2.6$. This signal appears furthest downfield as it is the most deshielded proton due to the electron withdrawing effects of the carbonyl bridge and the chlorine substituent. The $^{13}$C spectrum showed two signals at $\delta$ 184.7 and 180.0 which indicated that the
compound contained two carbonyl carbons. The upfield methoxy carbon signal at δ 51.4 further confirmed that the presence of a methoxy group. The absence of the hydroxyl peak at 2941 cm$^{-1}$ in the IR spectrum further confirmed the formation of the dione. Additional proof for the formation of the dione was found from the mass spectrum which gave a molecular ion \( m/z \) 277.0266. The dione \( 199 \) required a mass \( m/z \) 277.0262.

2.10 Synthesis of xanthone 200, dione 201 and spiro compound 202

Our final oxidation reaction of alcohol \( 196 \) was once again achieved by stirring an aqueous acetonitrile solution of \( 196 \) in the presence of CAN at room temperature for 24 hours (Scheme 58). TLC analysis of the reaction mixture showed the formation of three new products after 10 minutes. This result was unexpected as the oxidation of \( 186 \) resulted in only one product which was determined as being the xanthone \( 187 \). To our surprise the reaction yielded two possible products \( 200 \) and \( 201 \) as well as an unexpected spiro-compound \( 202 \). The yields obtained for the expected xanthone \( 200 \) and dione \( 201 \) are relatively similar with the dione being the major product. The spiro compound \( 202 \) was the minor product. Purification of the dione and spiro compound proved to be quite time consuming as these compounds had the same \( R_f \) values. These were separated through several silica gel columns.
Confirmation of the structure of xanthone 200 and dione 201 was easily achieved with the major difference between the two being the position of the methoxy group. The dione 201 was unambiguously confirmed using the $^1$H NMR spectrum. The first indication that the dione had formed was the presence of two signals at $\delta$ 3.92 and 3.33, each integrating for three protons. The large separation between these two signals is a consequence of one of the methoxy groups being tied up in acetal formation (the upfield signal) while the other methoxy was not (downfield signal). The $^1$H NMR spectrum also showed a singlet at $\delta$ 6.87 which integrates for one proton; its position is characteristic of that observed for quinone protons and was assigned as 1-H. Another singlet at $\delta$ 5.94 integrating for one proton was also observed and was assigned as 4-H. A doublet furthest upfield at $\delta$ 7.96 showed meta coupling with a coupling constant of $J = 2.6$ Hz and was assigned to 8-H. The position of the signal was due to the electron withdrawing properties of the adjacent carbonyl group as well as the adjacent chlorine substituent. The $^{13}$C NMR spectrum showed two downfield signals at $\delta$ 180.2 and 179.9 which corresponds to the two carbonyl groups, the quinone carbonyl and the xanthone carbonyl respectively. Furthermore, the signal at $\delta$ 98.2 has become the familiar signal for the quaternary carbon central to acetal formation.
Chapter 2: Results and Discussion

Confirmation of the successful formation of the xanthone 200 was obtained from the $^1$H and $^{13}$C NMR spectra. The relatively simple spectrum clearly shows a doublet furthest downfield at $\delta$ 8.27 which shows meta coupling. This signal was assigned 8-H and showed coupling to 6-H with a coupling constant of $J = 2.6$ Hz. The next signal upfield was a signal at $\delta$ 7.62 which integrated for one proton and was assigned 1-H. The methoxy groups were located at $\delta$ 4.02 and 4.00. The closeness of these signal indicated similar environments as well indicating that these methoxy groups are bonded to an aromatic ring and not part of an acetal. In the $^{13}$C NMR spectrum the furthest signal downfield was at $\delta$ 174.9 which indicates the presence of a carbonyl group. Final confirmation of the xanthone molecule was obtained from the mass spectrum which was in line with our expectations showing a molecular ion $m/z$ 291.0438, which corresponds well with the expected value $m/z$ 291.0424.

The structure of the minor compound from the reaction proved to be difficult to confirm. The relatively simply $^1$H NMR spectrum showed two quinone-type protons integrating for one proton each at $\delta$ 5.76 and 5.17 and were assigned 3'-H and 6'-H respectively. Another feature is the two singlets at $\delta$ 3.69 and 3.68 which integrate for three protons each and correspond to the methoxy groups. The $^{13}$C NMR spectrum showed two downfield peaks at $\delta$ 194.4 and 181.1 which indicated that the compound contained two carbonyl groups. Having scrutinised the spectroscopic data, many questions still remained as these proved inconclusive.

However, we were fortunate at this stage to obtain a crystal structure of our product (Figure 2), enabling us to unambiguously confirm our structure. Structural features worth mentioning are the spirocyclic compound. It is presumed that the oxygen substituent in the para position to the newly formed five membered ring facilitates the reaction resulting in the spiro compound 202.
Figure 2: ORTEP diagram for the crystal structure (5-chloro-2',5'-dimethoxy-3H-spiro[benzofuran-2,1'-cyclohexa[2,5]dien]-3,4'-dione 202.
3 Chapter 3: Conclusions and Future work

3.1 Summary of results achieved

The primary aim of this project was the synthesis of the diones 163 and 188 as well as xanthone 187. The dione 163 was successfully synthesised over 4 steps from the commercially available salicyclic acid 149 and 1,4-dimethoxynaphthalene 148 (Scheme 59). The synthesis commenced with the preparation of the starting materials 156 and 157. Salicyclic acid 149 was protected using benzyl protecting groups to afford benzyl 2-(benzyloxy)benzoate 157 in 94%. In a parallel synthesis, 1,4-dimethoxynaphthalene 148 was brominated to furnish 2-bromo-1,4-dimethoxynaphthalene 156 in a yield of 92%. Lithiation of 2-bromo-1,4-dimethoxynaphthalene 156 followed by the benzoylation of the lithiated species with benzyl 2-(benzyloxy)benzoate 157 afforded the benzophenone intermediate 158, in 84% This product was then subjected hydrogenation to produce the phenol 159 in 97%. Oxidative cyclisation of the phenol 159 resulted in the formation of the dione 163 in 72% yield.

Scheme 59 Reagents and conditions: (i) THF, –78 °C, n-BuLi (1.0 equiv.), 45 min, benzyl 2-(benzyloxy)benzoate, 30 min, 84%, (ii) 5% Pd/C, methanol, H₂(g), 1 atm, 24 h, 97%, (iii) CAN, H₂O/CH₃CN/CHCl₃, rt, DCM, Δ, 10 min, 72%
Using the same procedure detailed above, xanthone 187 and dione 188 were prepared in overall yields of 74% and 15% respectively, from commercially available salicylic acid 149, 1,4-dimethoxybenzene 169b (Scheme 60).

![Scheme 60](image)

The syntheses of diones 163 and 188, and xanthone 187 were successfully reproduced and in agreement with the results obtained by Naidoo.

The study was then expanded to test the flexibility and the efficiency of the methodology. Substitution patterns of both the aryl and the acid were varied to determine the effect CAN mediated oxidations have in the formation of xanthone and dione analogues.

We then used 1,2,4-trimethoxybenzene 183 as one of our precursors, thereby varying the aryl group. Following the same methodology, xanthone 187 was exclusively achieved in 91% (Scheme 61).

![Scheme 61](image)
Chapter 3: Conclusions and Future work

Following the success of these reactions, we then varied the benzoic acid functionality with the incorporation of a chlorine substituent onto the 5 position of the aromatic ring. We then followed the same synthetic scheme; to yield dione 197 in 93% from 1,4-dimethoxynaphthalene 148 and 5-chlorosalicyclic acid 190. The second transformation furnished xanthone 198 and dione 199 from 1,4-dimethoxybenzene 169 and 5-chlorosalicyclic acid 190 in yields of 63% and 17% respectively (Scheme 62).

![Scheme 62]

The final transformation commenced from 5-chlorosalicyclic acid 190 and 1,2,4-trimethoxybenzene 183 to afford the xanthone 200, dione 201 and the unexpected spiro-compound 202, in yields of 21%, 29% and 9% respectively (Scheme 63).
3.2 Future prospects for xanthone synthesis

The results from this research project demonstrate the use of CAN as a key reagent in the synthesis of the xanthones, diones and possibly spiro-compounds. Although the final product did not always afford the xanthone exclusively, chemical transformations could be carried out on the diones as well as the spiro-compound, in so doing converting these into xanthone compounds. Scheme 64 shows the conversion of diones 188 and 163 to xanthones 203 and 204, respectively when subjected to a hydrogen atmosphere in the presence of palladium on carbon as a catalyst. Similar transformations were achieved by Franck and Zeidler in their transformation of dione 205 to xanthone 206 (Scheme 64).
Chapter 3: Conclusions and Future work

Scheme 64

The spiro-compound 202 could also be converted into the xanthone 207 by heating under reduced pressure followed by sublimation. This type of transformation was demonstrated by de Koning and Giles 68.

Scheme 65

With this synthetic procedure in hand, naturally occurring xanthenes such as 208 and 209, which are believed to be biologically active against cancer, malaria as well as HIV could be prepared (Scheme 66).
In conclusion, the aims of the project were achieved with a proposal towards the mechanism. The synthetic route developed using CAN as a key reagent in the oxidative cyclisation step provides an alternative route to the synthesis of complex xanthones. This methodology could therefore be extended to the synthesis of naturally occurring xanthones, many of which are of biological importance.
4 Chapter 4: Experimental Procedures

4.1 General Experimental Procedures

4.1.1 Purification of Solvents and Reagents

All reagents used for reactions and preparative chromatography were distilled. Solvents used in reactions were pre-dried over the appropriate drying agents in their reagent bottles and then distilled over the appropriate drying mediums under a nitrogen atmosphere. Tetrahydrofuran (THF) was pre-dried over sodium wire and distilled from sodium metal wire and benzophenone. Dichloromethane, acetonitrile and methanol were distilled from calcium hydride. When necessary, solvents were stored over activated molecular sieves (4Å) under a nitrogen atmosphere. Reagents were obtained from commercial sources and used without further purification or purified by standard methods as recommended by Perrin et al.\textsuperscript{83}

4.1.2 Chromatography

Thin layer chromatography (TLC) was performed on aluminium-backed Machery-Nagel ALUGRAMSil G/UV\textsubscript{254} plates pre-coated with 0.25mm silica gel 60 or Aldrich TLC plates, silica gel on aluminium. Machery-Nagel Silica gel 60 (particle size 0.063-0.200mm) was used as the adsorbent for conventional preparative column chromatography. When performing flash chromatography, silica gel of particle size 0.035 mm to 0.070 mm was used. Mixtures of ethyl acetate and hexane were used as the mobile phase.
4.1.3 Spectroscopic and physical data

All melting points were obtained on a Reichert hot-stage microscope, and are uncorrected.

Infrared spectra were obtained on a Bruker Vector 22 spectrometer. Measurements were made by loading the sample directly onto a diamond cell. The signals are reported on the wavenumber scale (v/cm$^{-1}$).

Hydrogen ($^1$H NMR) and carbon ($^{13}$C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance-300 at 300.13 MHz and 75.47 MHz respectively. All spectra were recorded in deuterated chloroform (CDCl$_3$) unless otherwise stated and chemical shifts are reported in parts per million downfield from tetramethylsilane for $^1$H NMR spectra and relative to the central signal of deuterated chloroform, taken at δ 77.00 for $^{13}$C NMR spectra. Coupling constants are given in Hertz.

Some high resolution electrospray ionization mass spectra (ESI-FTMS) were recorded at the Technical University Dortmund, Germany, using a Thermo LTQ Orbitrap (high resolution mass spectrometer from Thermo Electron) coupled to an “Accela” HPLC System supplied with a “Hypersil GOLD” column (Thermo Electron). Others were recorded at the University of Stellenbosch, South Africa on a Waters API Q-TOF Ultima. At the University of the Witwatersrand mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer.

For X-ray crystallography, intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo $K_{\alpha}$ radiation (50kV, 30mA) using the APEX 2$^{64}$ data collection software. The collection method involved ω-scans of width 0.5° and 512x512 bit data frames. Data reduction was carried out using the program SAINT+ and face indexed absorption corrections were made.
Chapter 4: Experimental Procedures

using the program \textit{XPREP}\(^{85}\). The crystal structure was solved by direct methods using \textit{SHELXTL}\(^{86}\). Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on \(F^2\) using \textit{SHELXTL}. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using \textit{SHELXTL, PLATON}\(^{87}\) and \textit{ORTEP-3}.\(^{88}\)

4.1.4 Other general procedures

All reactions, unless otherwise stated, were carried out under an inert atmosphere and the reaction vessels were dried in an oven. \textit{In vacuo} refers to the removal of solvent under reduced pressure (\(\sim 20\) mm Hg, \(45^\circ\)C) on a rotary evaporator and final drying on an oil pump (\(\sim 1-2\) mm Hg) at ambient temperature until constant mass was achieved.
4.2 Synthesis of 2-bromo-1,4-dimethoxynaphthalene 156

NBS (3.80 g, 0.0214 moles) was added to the 1,4-dimethoxynaphthalene 148 (4.00 g, 0.0213 moles) in dry CH$_2$Cl$_2$ (30 ml). The mixture was stirred for 18 h at rt. The mixture was washed with an aqueous saturated sodium sulfite solution (25 ml) and extracted into CH$_2$Cl$_2$ (3 × 50 ml). The organic layer was dried over MgSO$_4$. The solvent was removed in vacuo and then purified using column chromatography (5% EtOAc/hexane) to afford the product 156 as white grains (5.30 g, 92%). M.p. 56–58°C, lit. M.p. 75 54-55°C; IR (solid): $\nu_{\text{max}}$ (cm$^{-1}$): 1662, 1615, 1576, 1505, 1458, 1440, 1410; $^1$H NMR (CDCl$_3$, 300MHz) $\delta$= 8.28–8.19 (m, 1H), 8.08–8.05 (m, 1H), 7.63–7.48 (m, 2H), 6.91 (s, 1H), 3.97 (s, 3H), 3.98 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75MHz) $\delta$= 152.1, 146.7, 128.9, 127.3, 125.5, 122.2, 121.7, 111.8, 107.8, 61.3, 55.7; MS (m/z) 267.03 (M$^+$, 100%), 269.03 (94).
4.3 Synthesis of benzyl (2-benzyloxy)benzoate 157

2-Hydroxybenzoic acid 149 (5.05 g, 0.0366 moles) was dissolved in dry acetone (120 ml). Dry potassium carbonate (15.0 g, 0.109 moles) was added and the mixture left stirring at rt for 10 mins. Benzyl bromide (12.9 ml, 0.109 moles) was added to the stirring mixture and the solution was heated under reflux for 18 h under a N₂ atmosphere. The cooled reaction mixture was filtered through celite, which was washed with dry acetone (3 x 50 ml). The solvent was removed in vacuo and the residue dissolved in CH₂Cl₂ (25 ml). The organic layer was washed consecutively with 5% aqueous NaOH (25 ml), brine (20 ml) and distilled water (20 ml). The organic layer was dried over MgSO₄ and the solvent removed in vacuo. The residue was subjected to column chromatography (5%-20% EtOAc/hexane) to afford the product 157 as a white crystalline solid (11.01 g, 94%). M.p. 48-50 °C, lit. M.p.⁷⁴ 50-51 °C; IR (solid): ʋ_max(cm⁻¹): 1716, 1598, 1580, 1495, 1466; ¹H NMR (CDCl₃, 300MHz) δ= 7.85 (dd, J = 7.7, 1.7, 1H), 7.52–7.23 (m, 11H), 6.93–6.99 (m, 2H), 5.33 (s, 2H), 5.13 (s, 2H); ¹³C NMR (CDCl₃, 75MHz) δ= 166.2, 158.1, 136.5, 136.0, 133.4, 131.8, 128.4, 128.4, 128.1, 128.0, 127.7, 127.0, 120.6, 120.4, 113.6, 70.5, 66.6; MS (m/z) 319.20 (M⁺, 100%), 320.21 (23).
4.4 Synthesis of [2-(benzyloxy)phenyl] (1,4-dimethoxynaphthalen2-yl) methanone 158

2-Bromo-1,4-dimethoxynaphthalene 156 (4.05 g, 0.0152 moles) was dissolved in dry THF (20 ml) and stirred at -78°C for 5 mins under an N₂ atmosphere. n-Butyl lithium (1.2 M, 0.015 moles, 18 ml) was added dropwise at -78°C and the mixture stirred at -78°C for 45 mins under N₂. The lithiated mixture was added dropwise to the benzyl-2-(benzyloxy) benzoate 157 (4.78 g, 0.0143 moles) in dry THF (20 ml) at -78°C. The mixture was stirred then for an additional 30 mins at -78°C under an N₂ atmosphere. The mixture was quenched with a saturated aqueous solution of NH₄Cl (25 ml) at -78°C and allowed to reach rt. The THF was removed in vacuo and EtOAc (50 ml) was added. The organic layer was washed consecutively with water (25 ml) and brine (25 ml) and dried over MgSO₄. The solvent was removed in vacuo and subjected to column chromatography (5%-20% EtOAc/hexane) to afford the product 158 as pale green plate crystals (5.01 g, 84%). M.p. 105-107°C (methanol); IR (solid): ν_max (cm⁻¹): 1734, 1633, 1619, 1594, 1508, 1486, 1449, 1408; ¹H NMR (CDCl₃, 300MHz) δ= 8.31–8.20 (m, 1H), 8.13–8.04 (m, 1H), 7.69 (d, J = 7.5, 1H), 7.61–7.42 (m, 3H), 7.15–6.96 (m, 3H), 6.96–6.84 (m, 2H), 6.88 (s, 1H), 6.78–6.70 (m, 2H), 4.89 (s, 2H), 3.91 (s, 3H), 3.59 (s, 3H); ¹³C NMR (CDCl₃, 75MHz) δ= 196.3, 157.5, 151.7, 150.3, 135.92, 132.91, 130.7, 130.2, 129.1, 128.8, 128.4, 127.9, 127.5, 127.2, 126.8, 126.8, 123.1, 122.4, 120.7, 112.3, 103.0, 70.3, 63.6, 55.8; MS (m/z) 399.11 (M⁺, 100%), 400.13 (26), 279.17 (24), 229.22 (15); HRMS (m/z) calculated for C₂₆H₂₂O₄, 398.1518, found 398.1523.
5% Pd/C (0.25 g) was added to (2-(benzylxoy)phenyl)(1,4 dimethoxynaphthalen-2-yl) methanone 158 (2.50 g, 6.27 mmoles) in dry MeOH (30 ml). The mixture was stirred under a H₂ atmosphere at a pressure of 4.5 atms for 24 h. The mixture was filtered through celite and washed with CH₂Cl₂ (3 × 50 ml). The organic layer was dried over MgSO₄. The solvent was removed in vacuo and column chromatography with a 10% EtOAc/hexane afforded the product 159 as pale green needles (1.88 g, 97%). M.p. 116-118 °C (methanol); IR (solid): ν_{max}(cm⁻¹): 2970, 1620, 1604, 1592, 1508, 1486, 1456, 1410; ¹H NMR (CDCl₃, 300MHz) δ= 12.25 (s, 1H), 8.36–8.27 (m, 1H), 8.18 – 8.14 (m, 1H), 7.69–7.39 (m, 4H), 7.05 (d, J = 8.7, 1H), 6.82–6.72 (m, 1H), 6.68 (s, 1H), 3.94 (s, 3H), 3.81 (s, 3H); ¹³C NMR (CDCl₃, 75MHz) δ= 202.4, 163.1, 151.9, 147.5, 136.9, 134.2, 128.5, 127.7, 127.4, 127.2, 126.4, 122.7, 122.6, 121.0, 119.1, 118.1, 102.3, 63.7, 55.8; MS (m/z) 309.18 (M⁺, 100%), 310.18 (19), 331.17 (4); HRMS (m/z) calculated for C₁₉H₁₆O₄, 308.1049, found 308.1048.
4.6 Synthesis of 12a-methoxy-5\(H\)-benzo[c]xanthene-5,7 (12a\(H\))-dione 163

CAN (13.3 g, 0.0243 moles) in water (25 ml) was added dropwise to a stirring mixture of (1,4-dimethoxynaphthalene-2-yl)(2-hydroxyphenylmethanone 159 (1.50 g, 4.86 mmoles) in MeCN (25 ml) and CHCl\(_3\) (5 ml). The mixture was stirred at rt for 10 mins. The reaction mixture was filtered through celite and washed with EtOAc (3 \(\times\) 25 ml). The organic layer was washed consecutively with a saturated aqueous NaHCO\(_3\) solution (25 ml), brine (25 ml) and water (25 ml). The organic layer was dried over MgSO\(_4\). The solvent was removed in vacuo and column chromatography with a 5% EtOAc/hexane to afford the product 163 as orange rod crystals (1.02 g, 72%). M.p. 125–127°C (EtOAc); IR (solid): \(\nu_{\text{max}}\) (cm\(^{-1}\)): 1713, 1689, 1667, 1636, 1607, 1596, 1459; \(^1\)H NMR (CDCl\(_3\), 300MHz) \(\delta=\) 8.16 (d, \(J = 7.8\), 1H), 8.07–8.02 (m, 2H), 7.83–7.57 (m, 3H), 7.24–7.08 (m, 3H), 3.03 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75MHz) \(\delta=\) 184.0, 181.0, 157.8, 143.8, 137.0, 136.6, 133.9, 130.8, 130.6, 130.2, 127.6, 126.9, 126.5, 123.2, 121.5, 118.6, 96.5, 51.5; MS (m/z) 293.07 (M\(^+\), 100%), 294.09 (22); HRMS (m/z) calculated for C\(_{18}\)H\(_{12}\)O\(_4\), 292.0736, found 292.0778.
4.7 Synthesis of 2-bromo-1,4-dimethoxybenzene 164

NBS (6.65 g, 37.3 moles) was added to the 1,4-dimethoxybenzene 169 (5.02 g, 36.3 mmoles) in dry CH₂Cl₂ (30 ml). The mixture was stirred for 48 h at reflux. The mixture was allowed to cool to rt and washed with a saturated aqueous sodium sulfite solution (25 ml). The mixture was extracted with CH₂Cl₂ (3 × 50 ml) and the organic layer was dried over MgSO₄. The solvent was removed in vacuo and column chromatography with a 5% EtOAc/hexane mixture afforded the product 164 as a colourless oil (7.01 g, 89%). IR (solid): ν_max (cm⁻¹): 1607, 1575, 1530, 1460, 1436;¹H NMR (CDCl₃, 300MHz) δ= 7.11 (s, 1H), 6.91–6.74 (m, 2H), 3.82 (s, 3H), 3.74 (s, 3H);¹³C NMR (CDCl₃, 75MHz) δ= 154.0, 150.3, 119.0, 113.6, 112.9, 111.9, 56.8, 55.9; MS (m/z) 217.05 (M⁺, 100%), 219.13 (94), 220.05 (12).
4.8 Synthesis of [2-(benzylxy)phenyl](2,5-dimethoxyphenyl)methanone 165

2-Bromo-1,4-dimethoxybenzene 164 (2.51 g, 0.0115 moles) was dissolved in dry THF (15 ml) and stirred at -78°C for 5 mins under an N₂ atmosphere. n-Butyl lithium (1.2 M, 0.0115 moles, 14 ml) was added dropwise at -78°C and the mixture stirred at -78°C for 45 mins under N₂. The lithiated mixture was added dropwise to the benzyl 2-(benzylxy) benzoate 157 (3.72 g, 0.0117 moles) in dry THF (20 ml) at -78°C over 30 mins. The mixture was stirred for an additional 30 mins at -78°C under N₂. The mixture was quenched with a saturated solution of NH₄Cl (25 ml) at -78°C and allowed to reach rt. The THF was removed in vacuo and EtOAc (50 ml) was added. The organic layer was washed consecutively with water (25 ml) and brine (25 ml) and dried over MgSO₄. The solvent was removed in vacuo and column chromatography with a 5%-20% EtOAc/hexane mixture afforded the product 165 as a light yellow oil (3.22 g, 88%). IR (solid): ν_max (cm⁻¹): 1644, 1587, 1491, 1448, 1419; ¹H NMR (CDCl₃, 300MHz) δ= 7.59 (dd, J = 7.6, 1.7, 1H), 7.48–7.32 (m, 2H), 7.22–7.15 (m, 2H), 7.12–7.08 (m, 6H), 6.76 (d, J = 7.4, 1H), 4.94 (s, 2H), 3.75 (s, 3H), 3.52 (s, 3H); ¹³C NMR (CDCl₃, 75MHz) δ= 195.4, 157.2, 153.5, 152.8, 136.4, 132.6, 130.8, 130.4, 130.2, 128.8, 128.4, 127.5, 120.8, 118.5, 114.5, 113.5, 112.3, 70.1, 56.5, 55.9; MS (m/z) 349.15 (M⁺, 100%), 350.15 (19), 165.10 (14), 197.13 (12); HRMS (m/z) calculated for C₂₂H₂₀O₄, 348.1362, found 348.1346.
Chapter 4: Experimental Procedures

4.9 Synthesis of (2,5-dimethoxyphenyl)(2-hydroxyphenyl)methanone 166

![Chemical structure](image)

5% Pd/C (0.05g) was added to (2-(benzyloxy)phenyl)(2,5 dimethoxyphenyl)methanone 165 (1.00 g, 0.00287 moles) in MeOH (30 ml). The mixture was stirred under a H₂ atmosphere at a pressure of 4.5 atms for 24 h. The mixture was filtered through celite and washed with CH₂Cl₂ (3 × 50 ml). The organic layer was dried over MgSO₄. The solvent was removed in vacuo and column chromatography with a 10% EtOAc/hexane solution afforded the product 166 as white needles (0.66 g, 89%). M.p. 96–98°C (methanol), lit. M.p. 79 98–100°C; IR (solid): ν_max (cm⁻¹): 2941, 1617, 1575, 1481, 1464, 1446, 1420; ¹H NMR (CDCl₃, 300MHz) δ= 12.04 (s, 1H) 7.41–7.31 (m, 1H), 7.26 (dd, J = 8.0, 1.5, 1H), 6.96–6.87 (m, 2H), 6.85 (s, 1H), 6.78–6.55 (m, 2H), 3.67 (s, 3H), 3.60 (s, 3H); ¹³C NMR (CDCl₃, 75MHz) δ= 200.7, 161.8, 152.4, 149.5, 135.5, 132.8, 127.2, 119.0, 117.7, 117.0, 116.0, 112.9, 111.9, 55.2, 54.7; MS (m/z) 259.14 (M⁺, 100%), 260.18 (15), 281.11 (5); HRMS (m/z) calculated for C₁₅H₁₄O₄, 258.0892, found 258.0883.

CAN (1.06 g, 1.94 mmoles) in water (5 ml) was added dropwise to a stirring mixture of (2,5 dimethoxyphenyl)(2-hydroxyphenyl)methanone (166) (0.100 g, 0.388 mmoles) in MeCN (10 ml) and CHCl₃ (2.5 ml). The mixture was then stirred at rt for 24 h. The reaction mixture was filtered through celite and washed with EtOAc (3 × 25 ml). The organic layer was washed consecutively with a saturated aqueous NaHCO₃ solution (25 ml), brine (25 ml) and water (25 ml). The organic layer was then dried over MgSO₄. The solvent was removed in vacuo and column chromatography (5% ethyl acetate/hexane) afforded the products 168 and 167 as white needles (0.065 g, 74%) and orange grains respectively (0.015 g, 15%).

2-Methoxy-9H-xanthen-9-one (168). M.p. 131-133°C (EtOAc), lit. M.p. 134-135°C; IR (solid): νₓ max(cm⁻¹): 1647, 1614, 1488, 1462, 1430; ¹H NMR (CDCl₃, 300MHz) δ= 8.25 (dd, J = 8.0, 1.6, 1H), 7.65–7.55 (m, 2H), 7.42–7.31 (dd, J = 7.8, 1.4, 1H), 7.29 (s, 1H), 7.28–7.14 (m, 2H), 3.83 (s, 3H); ¹³C NMR (CDCl₃, 75MHz) δ= 176.0, 155.0, 154.9, 149.9, 133.5, 125.6, 123.8, 122.7, 121.0, 120.2, 118.4, 116.9, 104.8, 54.9; MS (m/z) 227.10 (M⁺, 100%), 228.10 (12), 249.08 (5); HRMS (m/z) calculated for C₁₄H₁₀O₃, 226.0630, found 226.0620. 4a-Methoxy-9H-xanthen-2,9(4aH)-dione (167). M.p. 110-112°C (EtOAc); IR (solid): νₓ max(cm⁻¹): 1693, 1669, 1644, 1604, 1577, 1464; ¹H NMR (CDCl₃, 300MHz) δ= 7.94 (d, J = 7.8, 1H), 7.53 (t, J = 7.8, 1H), 7.11 (t, J = 7.5, 1H), 7.03 (d, J = 10.0, 1H), 6.81 (s, 1H), 6.37 (dd, J = 10.4, 1.9, 1H), 3.25 (s, 3H); ¹³C NMR (CDCl₃, 75MHz) δ= 185.1, 180.9, 157.0, 144.5, 140.1, 137.0, 130.7, 128.5, 127.5, 123.3, 121.6, 118.5, 95.1, 51.3; MS (m/z) 243.12 (M⁺, 100%), 244.12 (15); HRMS (m/z) calculated for C₁₄H₁₀O₄, 242.0579, found 242.0568.
4.11 Synthesis of 1-bromo-2,4,5-trimethoxybenzene 184

In a 100 cm³ RB flask equipped with a reflux condenser, N-bromosuccinimide (5.61 g, 30.8 mmol) was added to a clear solution of 1,2,4-trimethoxybenzene 183 (3.65 ml, 5.18 g, 30.8 mmol) in dry CH₂Cl₂ (30 ml). The reaction mixture was then heated under N₂ at reflux for 48 h, during which time a dark brown solution was formed. The reaction mixture was then allowed to cool to rt and washed with saturated sodium sulfite solution (25 ml). The reaction mixture was extracted into CH₂Cl₂ (3 × 50 ml). The organic extracts were combined and dried with anhydrous MgSO₄ before filtering through celite. The solvent was then removed in vacuo. The residue was purified by silica gel column chromatography (10% EtOAc /Hexane) to afford product 184 as a peach coloured oil (8.1 g, 70%). ¹H NMR (CDCl₃, 300 MHz): δ= 7.03 (s, 1H), 6.56 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H).
4.12 Synthesis of [2-(benzyloxy)phenyl][2,4,5-trimethoxyphenyl] methanone

Following a similar procedure as for the preparation of 158, 1-bromo-2,4,5-trimethoxybenzene 184 (2.03 g, 8.23 mmol) and 157 (3.440 g, 10.81 mmol) resulted in the formation of a yellow solid 185 (2.10 g, 52%) after flash silica gel chromatography (10% EtOAc /Hexane). M.p. 97–102 °C; IR (solid): ν max (cm⁻¹): 1633, 1597, 1508, 1449, 1434, 1401; ¹H NMR (CDCl₃, 300 MHz): δ = 7.49 (dd, J=7.5, 1.7, 1H), 7.42–7.36 (m, 1H), 7.26 (s, 1H), 7.21–7.19 (m, 3H), 7.05–6.93 (m, 4H), 6.33 (m, 1H), 4.96 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.48 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ = 194.0, 156.5, 155.1, 153.5, 143.2, 136.6, 132.3, 131.7, 129.5, 128.1, 127.5, 126.6, 121.5, 120.8, 113.3, 112.1, 97.3, 70.0, 56.6, 56.5, 56.0; HRMS (m/z) calculated for C₂₃H₂₃O₅ (M + H), 379.1545, found 379.1543.
Chapter 4: Experimental Procedures

4.13 Synthesis of (2'-hydroxyphenyl)(2,4,5-trimethoxyphenyl)methanone 186

Following a similar procedure as for the preparation of 159, (2-(benzyloxy)phenyl)(2,4,5-trimethoxyphenyl)methanone 185 (1.013 g, 2.677 mmol) was stirred under a H₂ atmosphere in MeOH (50 ml) with 10% Pd/C (0.0518 g) to yield after work-up and silica gel chromatography (20% EtOAc /Hexane) a yellow solid 186 (0.7501 g, 93%). mp. 107–110°C; IR (solid): νₘₐₓ (cm⁻¹): 1613, 1590, 1521, 1483, 1467, 1439, 1403; ¹H NMR (CDCl₃, 300 MHz): δ= 12.18 (s, 1H), δ 7.48–7.37 (m, 2H), 7.01 (d, J = 8.1, 1H), 6.89 (s, 1H,), 6.87–6.75 (m, 1H), 6.60 (s, 1H), 3.97 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ= 201.0, 162.7, 152.2, 152.0, 143.1, 136.2, 133.8, 120.3, 118.9, 118.6, 118.0, 112.6, 97.4, 56.5 (× 2), 56.2; HRMS (m/z) calculated for C₁₆H₁₇O₅ (M + H), 289.1076, found 289.1081.

4.14 Synthesis of 2,3-dimethoxy-9H-xanthen-9-one 187

Following a similar procedure as for the preparation of 163 hydroxyphenyl(2,4,5-trimethoxyphenyl)methanone 186 (269 mg, 0.931 mmol) was treated with CAN (2.200 g, 4.013 mmol) to give compound 187 (210 mg, 91%) as white grains after flash silica gel chromatography (20% EtOAc /Hexane). M.p. 170-172°C; ¹H NMR (CDCl₃, 300 MHz): δ= 8.32 (dd, J = 8.0, 1.6, 1H), 7.78–7.67 (m, 1H), 7.64 (s, 1H),
Chapter 4: Experimental Procedures

7.50–7.33 (m, 2H), 6.88 (d, J = 1.0, 1H), 4.00 (s, 3H), 3.99 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ= 176.0, 156.0, 155.4, 152.4, 146.7, 133.9, 126.5, 123.7, 121.5, 117.6, 114.9 105.3, 99.6, 56.4, 56.3.

4.15 Synthesis of benzyl-2-(benzyloxy)-5-chlorobenzoate 189$^{89}$

In a flask equipped with a reflux condenser, potassium carbonate (8.82 g, 63.8 mmol) was added to a clear solution of 5-chloro-salicylic acid 190 (5.007 g, 29.01 mmol) in dry DMF (120 ml). The resulting mixture was stirred at rt under N$_2$. Benzyl bromide (7.59 ml, 10.65 g, 63.82 mmol) was added to the solution using a dropping funnel. The reaction mixture was then heated at 60°C for 18 h, during which time it became a white paste. The reaction was then cooled, filtered through celite and the acetone then removed in vacuo. The residue was dissolved in CH$_2$Cl$_2$ and was washed consecutively with 5% aqueous NaOH (25 ml), brine (20 ml) and distilled water (20 ml). The organic extracts were combined and dried with anhydrous MgSO$_4$ before filtering through celite. The solvent was then removed in vacuo. The residue was purified by silica gel column chromatography (5-10% EtOAc /Hexane) to afford the product, benzyl-2-(benzyloxy)-5-chlorobenzoate 189 as a colorless oil which solidified overnight (8.70 g, 85%). M.p. 64-66°C; IR (solid): $v_{\text{max}}$(cm$^{-1}$): 1688, 1600, 1492, 1455, 1411; $^1$H NMR (CDCl$_3$, 300 MHz): δ= 7.81 (d, $J = 2.7$, 1H), 7.42–7.31 (m, 11H), 6.94 (d, $J = 8.9$, 1H), 5.33 (s, 2H), 5.13 (s, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ= 165.0, 156.8, 136.2, 135.8, 133.1, 131.6, 128.6, 128.3, 128.0, 127.1, 125.6, 122.0, 115.2, 71.0, 67.1.
4.16 Synthesis of [2′-(benzyloxy)-5′-chlorophenyl](1,4-dimethoxynaphthalen-2-yl) methanone 191

Following a similar procedure for the preparation of 159, 2-bromo-1,4-dimethoxynaphthalene 156 (1.092 g, 1.202 mmol) and 189 (0.854 g, 2.420 mmol) a yellow solid precipitated out of solution (241 mg, 19%). The solid was filtered off to provide an un-optimized yield of the desired product, (2′-(benzyloxy)-5′-chlorophenyl)(1,4-dimethoxynaphthalen-2-yl)methanone 191. M.p. 160-162°C; IR (solid): ν<sub>max</sub>(cm<sup>-1</sup>): 1637, 1621, 1592, 1489, 1452, 1406; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ= 8.25 (dd, J = 7.8, 1.4, 1H), 8.06 (dd, J = 7.7, 1.5, 1H), 7.63 (d, J = 2.6, 1H), 7.60–7.50 (m, 2H), 7.42 (dd, J = 8.8, 2.7, 1H), 7.08–7.03 (m, 1H), 6.96–6.84 (m, 4H), 6.72 (brd, J = 7.5, 2H), 4.86 (s, 2H), 3.93 (s, 3H), 3.60 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ= 194.7, 156.0, 151.9, 150.8, 135.5, 132.2, 129.5, 128.7, 128.3, 128.0, 127.6, 127.5, 127.0, 126.8, 125.9, 123.1, 122.5, 113.8, 102.7, 70.7, 63.76, 55.80; HRMS (m/z) calculated for C<sub>26</sub>H<sub>22</sub>O<sub>4</sub>Cl (M + H), 433.1207, found 433.1217.
4.17 Synthesis of (5-chloro-2-hydroxyphenyl)(1,4-dimethoxynaphthalen-2-yl) methanone 194

Following a similar procedure for the preparation of 159, (2-(benzyloxy)-5-chlorophenyl)(1,4-dimethoxynaphthalen-2-yl)methanone 191 (258mg, 0.597mmol) was stirred under a H₂ atmosphere in EtOAc (20 ml) with 10% Pd/C (12.9 mg) to furnish a pale yellow solid 194 (125 mg, 96%) after flash silica gel chromatography (20% EtOAc /Hexane). M.p. 109–111°C (solid): ν_max (cm⁻¹) 1629, 1614, 1596, 1510, 1460, 1414; ¹H NMR (CDCl₃, 300 MHz): δ = δ 12.14 (s, 1H), 8.59–7.99 (m, 2H), 7.84–7.51 (m, 2H), 7.46–7.41 (m, 2H), 7.02 (d, J = 9.6, 1H), 6.65 (s, 1H), 3.98 (s, 3H), 3.82 (s, 3H); ¹³C NMR (CDCl₃, 75MHz) δ = 201.6, 161.5, 152.0, 147.8, 136.7, 132.9, 128.4, 127.9, 127.5, 127.4, 125.7, 123.8, 122.8, 122.7, 120.6, 119.8, 101.9, 63.9, 55.9; HRMS (m/z) calculated for C₁₉H₁₄O₄Cl (M + H), 341.0581, found 341.0581.
4.18 Synthesis of 9-chloro-12a-methoxy-5H-benzo[c]xanthene-5,7(12aH)-dione 197

Following a similar procedure as for the preparation of 163 precursor 194 (103.3 mg, 0.300 mmol) and CAN (0.665 g, 1.212 mmol) in a mixture of CHCl₃, H₂O and MeCN as solvent resulted in the formation of 197 (92 mg, 93%) as a yellow solid after flash silica gel chromatography (20% EtOAc/Hexane). M.p. 162-165°C; IR (solid): \( \nu_{\text{max}}(\text{cm}^{-1}) \): 1726, 1687, 1667, 1633, 1594, 1461, 1419; \(^1\)H NMR (CDCl₃, 300 MHz): \( \delta = 8.16 (dd, J = 7.8, 1.0, 1H), 8.05-7.94 (m, 2H), 7.81 (td, J = 7.7, 1.3, 1H), 7.64 (td, J = 7.7, 1.1, 1H), 7.56 (dd, J = 8.8, 2.6, 1H), 7.21 (s, 1H), 7.16 (d, J = 8.8, 1H), 3.02 (s, 3H); \(^13\)C NMR (CDCl₃, 75MHz) \( \delta = 183.7, 180.1, 156.2, 143.0, 136.7, 136.2, 134.0, 131.1, 130.8, 130.4, 128.9, 127.0, 126.9, 126.5, 122.4, 120.3, 96.6, 51.4; \) HRMS (m/z) calculated for C₁₅H₁₂O₄Cl (M + H), 327.0424, found 327.0413.

4.19 Synthesis of [2’-(benzylxylo)-5’-chlorophenyl][2,5-dimethoxyphenyl)methanone 192

Compound 164 (2.068 g, 9.528 mmol) and benzyl-2-(benzylxylo)-5-chlorobenzoate 189 (3.368 g, 9.546 mmol) were treated following a similar procedure as for the
preparation of 158. This resulted in the formation of a yellow solid of the product, (2(benzyloxy)-5-chlorophenyl)(2,5-dimethoxyphenyl)methanone 192 (2.90 g, 78%) after flash silica gel chromatography (20% EtOAc /Hexane). M.p. 170-172°C; IR (solid): \( \nu_{\text{max}}(\text{cm}^{-1}) \): 1645, 1586, 1494, 1457, 1420; \( ^1\text{H} \) NMR (CDCl\(_3\), 300 MHz): \( \delta= \) 7.52 (d, \( J = 2.7, 1\)H), 7.35 (dd, \( J = 8.8, 2.7, 1\)H), 7.21 (m, 3H), 7.11 (d, \( J = 3.2, 1\)H), 6.95 (m, 3H), 6.88 (d, \( J = 8.8, 1\)H), 6.76 (d, \( J = 9.0, 1\)H), 4.91 (s, 2H), 3.76 (s, 3H), 3.52 (s, 3H); \( ^{13}\text{C} \) NMR (CDCl\(_3\), 75 MHz): \( \delta= \) 193.8, 155.6, 153.6, 152.9, 136.0, 131.9, 129.7, 127.7, 125.9, 119.3, 114.4, 113.7, 113.3, 70.5, 56.3, 55.9; MS (ESI-FTMS) (m/z) 383.10 (M\(^+\), 100%), 365.09 (10), 282.28 (25), 165.05 (37); HRMS (m/z) calculated for C\(_{22}\)H\(_{20}\)O\(_4\)Cl (M + H), 383.1050, found 383.1047.

4.20 Synthesis of (5'-chloro-2'-hydroxyphenyl)(2,5-dimethoxyphenyl)methanone 195

(2(Benzyloxy)-5-chlorophenyl)(2,5-dimethoxyphenyl)methanone 192 (1.006 g, 2.627 mmol) dissolved in EtOAc (40 ml) was treated in a similar manner as for the preparation of 159 with 10% Pd/C (100.3 mg) to give compound 195 as a yellow solid (0.43 g, 56%) after silica gel chromatography (30% EtOAc /Hexane). M.p. 74-76°C; IR (solid): \( \nu_{\text{max}}(\text{cm}^{-1}) \): 2931, 1632, 1589, 1568, 1491, 1462, 1422; \( ^1\text{H} \) NMR (CDCl\(_3\), 300 MHz): \( \delta= \) 11.93 (s, 1H), 7.32 (dd, \( J = 8.9, 2.6, 1\)H), 7.22 (d, \( J = 2.6, 1\)H), 6.95 (dd, \( J = 9.0, 3.0, 1\)H), 6.88 (m, 2H), 6.76 (d, \( J = 3.0, 1\)H) 3.70 (s, 3H), 3.64 (s, 3H); \( ^{13}\text{C} \) NMR (CDCl\(_3\), 75 MHz): \( \delta= \) 199.8, 160.3, 152.6, 149.5, 135.3, 131.6 126.5, 122.4, 119.6, 118.7, 116.6, 112.9, 112.0, 55.2, 54.8; MS (ESI-FTMS) (m/z) 393.05 (M\(^+\) +H, 10%), 282.28 (100), 227.11 (67); HRMS (m/z) calculated for C\(_{15}\)H\(_{14}\)O\(_4\)Cl (M + H), 293.0581, found 293.0576.
4.21 Synthesis of 2-chloro-7-methoxy-9H-xanthen-9-one 198 and 7-chloro-4a-methoxy-9H-xanthen-2,9(4aH)-dione 199

(5-Chloro-2-hydroxyphenyl)(2,5-dimethoxyphenyl)methanone 195 (104.4 mg, 0.3567 mmol) together with CAN (0.9801 g, 1.788 mmol) was treated following a similar procedure as for the preparation of 166 to give two products, 198 and 199 after flash silica gel chromatography (10% EtOAc /Hexane). The first was the xanthone 198 which was produced as white needles (53 mg, 63%). M.p. 130-133°C; IR (solid): ν\textsubscript{max}(cm\textsuperscript{-1}): 1655, 1614, 1486, 1461, 1446; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): δ= 8.29 (d, J = 2.6, 1H), 7.70–7.59 (m, 2H), 7.46 (d, J = 3.0, 1H), 7.43 (d, J = 3.2, 1H), 7.34 (dd, J = 9.2, 3.1, 1H), 3.92 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): δ= 176.0, 156.2, 154.4, 150.9, 134.7, 129.5, 125.9, 125.3, 122.1, 121.8, 119.7, 119.5, 105.8, 56.0; HRMS (m/z) calculated for C\textsubscript{14}H\textsubscript{10}O\textsubscript{3}Cl (M + H), 261.0318, found 261.0318. The second was the dione 199 which was formed as orange grains (17 mg, 17%). M.p. 122-124°C; IR (solid): ν\textsubscript{max}(cm\textsuperscript{-1}): 1743, 1656, 1616, 1488, 1463, 1447; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): δ= 7.97 (d, J = 2.6, 1H), 7.54 (dd, J = 8.8, 2.7, 1H), 7.09 (d, J = 10.4, 1H), 7.07 (d, J = 8.8, 1H), 6.89 (d, J = 2.0, 1H), 6.46 (dd, J = 10.4, 2.0, 1H), 3.35 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): δ= 184.7, 180.0, 155.4, 143.8, 139.7, 136.7, 130.9, 129.0, 126.9, 122.5, 120.2, 95.3, 51.4; HRMS (ESI-FTMS) (m/z) calculated for C\textsubscript{14}H\textsubscript{10}O\textsubscript{4}Cl (M + H), 277.0268, found 277.0266.
4.22 Synthesis of [2’-(benzyloxy)-5’-chlorophenyl](2,4,5-trimethoxyphenyl)methanone 193

1-Bromo-2,4,5-trimethoxybenzene 184 (2.01 g, 8.14 mmol) and benzyl-2-(benzyloxy)-5-chlorobenzoate 189 (3.76 g, 10.66 mmol) were treated following a similar procedure as for the preparation of 158 to furnish (2-(benzyloxy)-5-chlorophenyl)(2,4,5-trimethoxyphenyl)methanone 193 as a yellow solid (3.80 g, 87%) after flash silica gel chromatography (10% EtOAc /Hexane). M.p. 109-111°C; IR (solid): νmax (cm⁻¹): 1633, 1599, 1508, 1488, 1451, 1434, 1410; ¹H NMR (CDCl₃, 300 MHz): δ= 7.42 (d, J = 2.6, 1H), 7.32 (dd, J = 8.7, 2.7, 1H), 7.28 (s, 1H), 7.25–7.17 (m, 3H), 7.03–6.93 (m, 2H), 6.87 (d, J = 8.8, 1H), 6.32 (s, 1H), 4.95 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.50 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ= 192.3, 155.4, 154.9, 154.0, 143.3, 136.2, 134.0, 130.9, 129.0, 128.2, 127.7, 126.5, 125.9, 120.6, 113.5, 113.0, 96.9, 70.5, 56.5, 56.4, 56.1; MS (ESI-FTMS) (m/z) 413.1142 (M⁺ +H, 100%); HRMS (m/z) calculated for C₂₃H₂₂O₅Cl (M + H), 413.1156, found 413.1142.
4.23 Synthesis of (5-chloro-2-hydroxyphenyl)(2,4,5-trimethoxyphenyl) methanone 196

(2-(Benzyloxy)-5-chlorophenyl)(2,4,5-trimethoxyphenyl)methanone 193 (1.008 g, 2.442 mmol) and 10%Pd/C (50.6 mg) in EtOAc (50 ml) were stirred for 3.5 h under an H₂ atmosphere following a similar procedure as for the preparation of 159 resulting in the formation of (5-chloro-2-hydroxyphenyl)(2,4,5-trimethoxyphenyl)methanone 196 as a yellow solid (0.780 g, 99%) after silica gel chromatography (30% EtOAc /Hexane). M.p. 161-163°C; IR (solid): νₘₐₓ(cm⁻¹): 1625, 1586, 1511, 1470, 1435, 1402; ¹H NMR (CDCl₃, 300 MHz): δ= 12.04 (s, 1H), 7.41–7.00 (m, 2H), 6.98 (d, J = 9.6, 1H), (s, 1H), 6.60 (s, 1H), 3.99 (s, 3H), 3.86 (s, 3H), 3.77 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ= 199.9, 161.1, 152.8, 152.2, 143.3, 135.9, 132.7, 123.2, 121.0, 119.6, 118.2, 112.6, 97.3, 56.5, 56.5, 56.2; MS (ESI-FTMS) (m/z) 323.07 (M⁺ +H, 100%), 195.07 (20), 227.11 (6); HRMS (m/z) calculated for C₁₆H₁₆O₅Cl (M + H), 323.0686, found 323.0680.

5-Chloro-2-hydroxyphenyl)(2,4,5-trimethoxyphenyl)methanone 196 (1.000 g, 3.117 mmol) together with CAN (8.486 g, 15.48 mmol) was treated following a similar procedure as for the preparation of 159 to afford three products, 200, 201 and 202 after flash silica gel chromatography (5-10% EtOAc / Hexane).

7-chloro-2,3-dimethoxy-9H-xanthen-9-one 200 was formed as orange needles (185 mg, 21%). M.p.: 202-204°C; IR (solid): ν\text{max}(\text{cm}^{-1}): 1643, 1616, 1562, 1507, 1481, 1460, 1435; \text{^1H NMR (CDCl}_3, 300 MHz): \text{δ= 8.27 (d, J = 2.6, 1H), 7.62–7.58 (m, 2H), 7.39 (d, J = 8.9, 1H), 6.88 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H)}; \text{^13C NMR (CDCl}_3, 75 MHz): \text{δ= 174.9, 155.7, 154.3, 152.4, 147.0, 134.0, 129.5, 125.8, 122.4, 119.4, 114.5, 105.3, 99.6, 56.5, 56.4}; HRMS (m/z) calculated for C_{15}H_{12}O_4Cl (M + H), 291.0424, found 291.0438.

7-chloro-3,4a-dimethoxy-2H-xanthen-2,9(4aH)-dione 201 was formed as yellow needles (262 mg, 28%). M.p. 118-120°C; IR (solid): ν\text{max}(\text{cm}^{-1}): 1736, 1696, 1674, 1651, 1600, 1466, 1441, 1421; \text{^1H NMR (CDCl}_3, 300 MHz): \text{δ= 7.96 (d, J = 2.6, 1H), 7.53 (dd, J = 8.8, 2.6, 1H), 7.04 (d, J = 8.8, 1H), 6.87 (s, 1H), 5.94 (s, 1H), 3.82 (s, 3H), 3.33 (s, 3H); ^13C NMR (CDCl}_3, 75 MHz): δ= 180.2, 179.9, 156.0, 152.5, 144.3, 136.6, 128.1(3), 128.1(1), 126.9, 122.6, 120.1, 106.8, 98.2, 55.7, 51.2; HRMS (m/z) calculated for C_{15}H_{12}O_5Cl (M + H), 307.0373, found 307.0381.
Chapter 4: Experimental Procedures

5-chloro-2',5'-dimethoxy-3H-spiro[benzofuran-2,1'-cyclohexa[2,5]dien]-3,4'-dione 202 was formed as a light brown solid (89 mg, 9%); M.p. 223-225°C IR (solid): \( \nu_{\text{max}}(\text{cm}^{-1}) \): 1727, 1666, 1614, 1509, 1462; \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta = 7.67–7.64 \) (m, 2H), 7.19 (d, \( J = 8.5, 0.6, 1 \)H), 5.76 (s, 1H), 5.17 (s, 1H), 3.69 (s, 3H), 3.68 (s, 3H); \(^13\)C NMR (CDCl\(_3\), 75 MHz): \( \delta = 194.4, 181.1, 170.8, 167.5, 153.4, 138.8, 128.3, 124.9, 121.1, 115.1, 104.1, 102.3, 87.0, 56.7, 55.6 \); HRMS (m/z) calculated for C\(_{15}\)H\(_{12}\)O\(_5\)Cl (M + H), 307.0373, found 307.0365.
References

5 References

References

References

6 Appendix
Appendix

A1: Selected $^1$H and $^{13}$C NMR Spectra

A1.1.1 The $^1$H NMR Spectrum of compound 163

A1.1.2 The $^{13}$C NMR Spectrum of compound 163
A1.1.3 The $^1$H NMR Spectrum of compound 168

A1.1.4 The $^{13}$C NMR Spectrum of compound 168
Appendix

A1.1.5 The $^1$H NMR Spectrum of compound 167

![The $^1$H NMR Spectrum of compound 167](image)

A1.1.6 The $^{13}$C NMR Spectrum of compound 167

![The $^{13}$C NMR Spectrum of compound 167](image)
Appendix

A1.1.7 The $^1$H NMR Spectrum of compound 187

A1.1.8 The $^{13}$C NMR Spectrum of compound 187
Appendix

A1.1.9 The $^1$H NMR Spectrum of compound 197

A1.1.10. The $^{13}$C NMR Spectrum of compound 197
Appendix

A1.1.11 The $^1$H NMR Spectrum of compound 198

A1.1.12 The $^{13}$C NMR Spectrum of compound 198
**Appendix**

A1.1.13 The $^1$H NMR Spectrum of compound 199

A1.1.14 The $^{13}$C NMR Spectrum of compound 199
Appendix

A1.1.15 The $^1$H NMR Spectrum of compound 200

A1.1.16 The $^{13}$C NMR Spectrum of compound 200
Appendix

A1.1.17 The $^{13}$C NMR Spectrum of compound 201

A1.1.18 The $^{13}$C NMR Spectrum of compound 201
Appendix

A1.1.19 The $^1$H NMR Spectrum of compound 202

A1.1.20 The $^{13}$C NMR Spectrum of compound 202
Appendix

A2: Single Crystal Data and Structure for 5-chloro-2',5'-dimethoxy-3H-spiro[benzofuran-2,1'cyclohexa[2,5]diene-3,4'dione 202

Table 1. Crystal data and structure refinement for 202.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{15}H_{11}ClO_{5}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>306.69</td>
</tr>
<tr>
<td>Temperature</td>
<td>173(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 5.2102(3) Å</td>
</tr>
<tr>
<td></td>
<td>b = 30.1686(16) Å</td>
</tr>
<tr>
<td></td>
<td>c = 8.4028(5) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>1316.59(13) Å^{3}</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.547 Mg/m^{3}</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.310 mm^{-1}</td>
</tr>
</tbody>
</table>
### Appendix

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>F(000)</td>
<td>632</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.49 x 0.05 x 0.03 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.35 to 25.00°.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-6&lt;=h&lt;=6, -35&lt;=k&lt;=35, -9&lt;=l&lt;=9</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>12081</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2315 [R(int) = 0.0950]</td>
</tr>
<tr>
<td>Completeness to theta = 25.00°</td>
<td>100.0 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2315 / 0 / 192</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.039</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0479, wR2 = 0.0886</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0927, wR2 = 0.1029</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.220 and -0.243 e.Å⁻³</td>
</tr>
</tbody>
</table>

#### Table 2. Atomic coordinates ( x 10⁴) and equivalent isotropic displacement parameters (Å² x 10³) for 202 U(eq) is defined as one third of the trace of the orthogonalized Uᵢⱼ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>9574(5)</td>
<td>1160(1)</td>
<td>5349(3)</td>
<td>23(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>11091(6)</td>
<td>1580(1)</td>
<td>6002(3)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>9603(6)</td>
<td>1957(1)</td>
<td>5348(3)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>9962(6)</td>
<td>2411(1)</td>
<td>5541(4)</td>
<td>29(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>8193(6)</td>
<td>2682(1)</td>
<td>4760(4)</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>6073(6)</td>
<td>2517(1)</td>
<td>3807(4)</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>5708(6)</td>
<td>2067(1)</td>
<td>3623(4)</td>
<td>27(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>7514(6)</td>
<td>1790(1)</td>
<td>4420(3)</td>
<td>23(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>11253(5)</td>
<td>896(1)</td>
<td>4334(3)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>12389(5)</td>
<td>519(1)</td>
<td>4846(3)</td>
<td>26(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>11812(6)</td>
<td>323(1)</td>
<td>6347(3)</td>
<td>24(1)</td>
</tr>
</tbody>
</table>
Appendix

|        |  
|--------|------------------|
| C(12)  | 9757(6) 535(1) 7227(3) 25(1)  
| C(13)  | 8644(5) 912(1) 6717(3) 24(1)  
| C(14)  | 13130(6) 884(1) 1847(4) 35(1)  
| C(15)  | 7398(6) 487(1) 9506(4) 32(1)  
| O(1)   | 7376(4) 1338(1) 4361(2) 25(1)  
| O(2)   | 13066(4) 1571(1) 6857(2) 34(1)  
| O(3)   | 11568(4) 1108(1) 2949(2) 30(1)  
| O(4)   | 12937(4)  7(1) 6889(2) 37(1)  
| O(5)   | 9251(4)  300(1) 8539(2) 31(1)  

Table 3. Bond lengths [Å] and angles [°] for 202

|        |  
|--------|------------------|
| C(1)-O(1) | 1.462(3)  
| C(1)-C(13) | 1.485(4)  
| C(1)-C(9)  | 1.498(4)  
| C(1)-C(2)  | 1.571(4)  
| C(2)-O(2)  | 1.207(3)  
| C(2)-C(3)  | 1.458(4)  
| C(3)-C(8)  | 1.383(4)  
| C(3)-C(4)  | 1.390(4)  
| C(4)-C(5)  | 1.361(4)  
| C(4)-H(4)  | 0.9500  
| C(5)-C(6)  | 1.404(4)  
| C(5)-Cl(1) | 1.740(3)  
| C(6)-C(7)  | 1.379(4)  
| C(6)-H(6)  | 0.9500  
| C(7)-C(8)  | 1.390(4)  
| C(7)-H(7)  | 0.9500  
| C(8)-O(1)  | 1.365(3)  
| C(9)-C(10) | 1.338(4)  
| C(9)-O(3)  | 1.349(3)  
| C(10)-C(11)| 1.446(4)  

122
## Appendix

<table>
<thead>
<tr>
<th>Bond</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(10)-H(10)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(11)-O(4)</td>
<td>1.225(3)</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.492(4)</td>
</tr>
<tr>
<td>C(12)-C(13)</td>
<td>1.331(4)</td>
</tr>
<tr>
<td>C(12)-O(5)</td>
<td>1.355(3)</td>
</tr>
<tr>
<td>C(13)-H(13)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(14)-O(3)</td>
<td>1.448(3)</td>
</tr>
<tr>
<td>C(14)-H(14A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(14)-H(14B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(14)-H(14C)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(15)-O(5)</td>
<td>1.427(3)</td>
</tr>
<tr>
<td>C(15)-H(15A)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(15)-H(15B)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(15)-H(15C)</td>
<td>0.9800</td>
</tr>
<tr>
<td>O(1)-C(1)-C(13)</td>
<td>109.6(2)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(9)</td>
<td>109.8(2)</td>
</tr>
<tr>
<td>C(13)-C(1)-C(9)</td>
<td>114.5(2)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(2)</td>
<td>104.5(2)</td>
</tr>
<tr>
<td>C(13)-C(1)-C(2)</td>
<td>108.8(2)</td>
</tr>
<tr>
<td>C(9)-C(1)-C(2)</td>
<td>109.1(2)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(3)</td>
<td>130.2(3)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(1)</td>
<td>124.7(3)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(1)</td>
<td>105.1(2)</td>
</tr>
<tr>
<td>C(8)-C(3)-C(4)</td>
<td>121.2(3)</td>
</tr>
<tr>
<td>C(8)-C(3)-C(2)</td>
<td>107.4(2)</td>
</tr>
<tr>
<td>C(4)-C(3)-C(2)</td>
<td>131.4(3)</td>
</tr>
<tr>
<td>C(5)-C(4)-C(3)</td>
<td>117.2(3)</td>
</tr>
<tr>
<td>C(5)-C(4)-H(4)</td>
<td>121.4</td>
</tr>
<tr>
<td>C(3)-C(4)-H(4)</td>
<td>121.4</td>
</tr>
<tr>
<td>C(4)-C(5)-C(6)</td>
<td>122.2(3)</td>
</tr>
<tr>
<td>C(4)-C(5)-Cl(1)</td>
<td>119.5(2)</td>
</tr>
<tr>
<td>C(6)-C(5)-Cl(1)</td>
<td>118.2(2)</td>
</tr>
<tr>
<td>C(7)-C(6)-C(5)</td>
<td>120.6(3)</td>
</tr>
<tr>
<td>C(7)-C(6)-H(6)</td>
<td>119.7</td>
</tr>
</tbody>
</table>
### Appendix

<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(5)-C(6)-H(6)</td>
<td>119.7</td>
</tr>
<tr>
<td>C(6)-C(7)-C(8)</td>
<td>117.2(3)</td>
</tr>
<tr>
<td>C(6)-C(7)-H(7)</td>
<td>121.4</td>
</tr>
<tr>
<td>C(8)-C(7)-H(7)</td>
<td>121.4</td>
</tr>
<tr>
<td>O(1)-C(8)-C(3)</td>
<td>114.9(2)</td>
</tr>
<tr>
<td>O(1)-C(8)-C(7)</td>
<td>123.4(3)</td>
</tr>
<tr>
<td>C(3)-C(8)-C(7)</td>
<td>121.6(3)</td>
</tr>
<tr>
<td>C(10)-C(9)-O(3)</td>
<td>126.8(3)</td>
</tr>
<tr>
<td>C(10)-C(9)-C(1)</td>
<td>122.2(3)</td>
</tr>
<tr>
<td>O(3)-C(9)-C(1)</td>
<td>110.9(2)</td>
</tr>
<tr>
<td>C(9)-C(10)-C(11)</td>
<td>120.7(3)</td>
</tr>
<tr>
<td>C(9)-C(10)-H(10)</td>
<td>119.7</td>
</tr>
<tr>
<td>C(11)-C(10)-H(10)</td>
<td>119.7</td>
</tr>
<tr>
<td>O(4)-C(11)-C(10)</td>
<td>122.0(3)</td>
</tr>
<tr>
<td>O(4)-C(11)-C(12)</td>
<td>120.4(3)</td>
</tr>
<tr>
<td>C(10)-C(11)-C(12)</td>
<td>117.6(3)</td>
</tr>
<tr>
<td>C(13)-C(12)-O(5)</td>
<td>126.9(3)</td>
</tr>
<tr>
<td>C(13)-C(12)-C(11)</td>
<td>121.2(3)</td>
</tr>
<tr>
<td>O(5)-C(12)-C(11)</td>
<td>111.9(2)</td>
</tr>
<tr>
<td>C(12)-C(13)-C(1)</td>
<td>121.3(3)</td>
</tr>
<tr>
<td>C(12)-C(13)-H(13)</td>
<td>119.4</td>
</tr>
<tr>
<td>C(1)-C(13)-H(13)</td>
<td>119.4</td>
</tr>
<tr>
<td>O(3)-C(14)-H(14A)</td>
<td>109.5</td>
</tr>
<tr>
<td>O(3)-C(14)-H(14B)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(14A)-C(14)-H(14B)</td>
<td>109.5</td>
</tr>
<tr>
<td>O(3)-C(14)-H(14C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(14A)-C(14)-H(14C)</td>
<td>109.5</td>
</tr>
<tr>
<td>O(5)-C(15)-H(15A)</td>
<td>109.5</td>
</tr>
<tr>
<td>O(5)-C(15)-H(15B)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(15A)-C(15)-H(15B)</td>
<td>109.5</td>
</tr>
<tr>
<td>O(5)-C(15)-H(15C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(15A)-C(15)-H(15C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(15B)-C(15)-H(15C)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(8)-O(1)-C(1)</td>
<td>108.1(2)</td>
</tr>
</tbody>
</table>
Table 4. Anisotropic displacement parameters (Å^2 x 10^3) for 202. The anisotropic displacement factor exponent takes the form: -2\pi^2 [ h^2 a^* U_{11} + ... + 2 h k a^* b^* U_{12} ]
Appendix

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 202.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(4)</td>
<td>11381</td>
<td>2527</td>
<td>6189</td>
<td>34</td>
</tr>
<tr>
<td>H(6)</td>
<td>4878</td>
<td>2717</td>
<td>3283</td>
<td>36</td>
</tr>
<tr>
<td>H(7)</td>
<td>4283</td>
<td>1951</td>
<td>2980</td>
<td>32</td>
</tr>
<tr>
<td>H(10)</td>
<td>13588</td>
<td>378</td>
<td>4217</td>
<td>31</td>
</tr>
<tr>
<td>H(13)</td>
<td>7228</td>
<td>1024</td>
<td>7238</td>
<td>29</td>
</tr>
<tr>
<td>H(14A)</td>
<td>14875</td>
<td>842</td>
<td>2351</td>
<td>52</td>
</tr>
<tr>
<td>H(14B)</td>
<td>13203</td>
<td>1063</td>
<td>880</td>
<td>52</td>
</tr>
<tr>
<td>H(14C)</td>
<td>12369</td>
<td>594</td>
<td>1564</td>
<td>52</td>
</tr>
<tr>
<td>H(15A)</td>
<td>7929</td>
<td>788</td>
<td>9824</td>
<td>48</td>
</tr>
<tr>
<td>H(15B)</td>
<td>7278</td>
<td>304</td>
<td>10461</td>
<td>48</td>
</tr>
<tr>
<td>H(15C)</td>
<td>5715</td>
<td>498</td>
<td>8896</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 6. Torsion angles [°] for 202

<table>
<thead>
<tr>
<th>Bond</th>
<th>Torsion Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(1)-C(2)-O(2)</td>
<td>-179.0(3)</td>
</tr>
<tr>
<td>C(13)-C(1)-C(2)-O(2)</td>
<td>64.0(4)</td>
</tr>
<tr>
<td>C(9)-C(1)-C(2)-O(2)</td>
<td>-61.6(4)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(2)-C(3)</td>
<td>0.8(3)</td>
</tr>
<tr>
<td>C(13)-C(1)-C(2)-C(3)</td>
<td>-116.3(2)</td>
</tr>
<tr>
<td>C(9)-C(1)-C(2)-C(3)</td>
<td>118.2(2)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(3)-C(8)</td>
<td>179.1(3)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)-C(8)</td>
<td>-0.7(3)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(3)-C(4)</td>
<td>-1.9(5)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)-C(4)</td>
<td>178.3(3)</td>
</tr>
<tr>
<td>C(8)-C(3)-C(4)-C(5)</td>
<td>-0.9(4)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)-C(5)</td>
<td>-179.7(3)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)-C(6)</td>
<td>0.5(4)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)-Cl(1)</td>
<td>179.4(2)</td>
</tr>
<tr>
<td>Bond</td>
<td>Angle (deg)</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>C(4)-C(5)-C(6)-C(7)</td>
<td>-0.1(5)</td>
</tr>
<tr>
<td>Cl(1)-C(5)-C(6)-C(7)</td>
<td>-179.0(2)</td>
</tr>
<tr>
<td>C(5)-C(6)-C(7)-C(8)</td>
<td>0.1(4)</td>
</tr>
<tr>
<td>C(4)-C(3)-C(8)-O(1)</td>
<td>-178.8(3)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(8)-O(1)</td>
<td>0.3(3)</td>
</tr>
<tr>
<td>C(4)-C(3)-C(8)-C(7)</td>
<td>0.9(4)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(8)-C(7)</td>
<td>180.0(3)</td>
</tr>
<tr>
<td>C(6)-C(7)-C(8)-O(1)</td>
<td>179.2(3)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(9)-C(10)</td>
<td>-141.3(3)</td>
</tr>
<tr>
<td>C(13)-C(1)-C(9)-C(10)</td>
<td>-17.5(4)</td>
</tr>
<tr>
<td>C(2)-C(1)-C(9)-C(10)</td>
<td>104.7(3)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(9)-C(10)</td>
<td>43.2(3)</td>
</tr>
<tr>
<td>C(13)-C(1)-C(9)-O(3)</td>
<td>166.9(2)</td>
</tr>
<tr>
<td>C(2)-C(1)-C(9)-O(3)</td>
<td>-70.8(3)</td>
</tr>
<tr>
<td>O(3)-C(9)-C(10)-C(11)</td>
<td>-178.3(3)</td>
</tr>
<tr>
<td>C(1)-C(9)-C(10)-C(11)</td>
<td>6.9(4)</td>
</tr>
<tr>
<td>C(9)-C(10)-C(11)-O(4)</td>
<td>-175.5(3)</td>
</tr>
<tr>
<td>C(9)-C(10)-C(11)-C(12)</td>
<td>5.0(4)</td>
</tr>
<tr>
<td>O(4)-C(11)-C(12)-C(13)</td>
<td>175.1(3)</td>
</tr>
<tr>
<td>C(10)-C(11)-C(12)-C(13)</td>
<td>-5.5(4)</td>
</tr>
<tr>
<td>O(4)-C(11)-C(12)-O(5)</td>
<td>-4.7(4)</td>
</tr>
<tr>
<td>C(10)-C(11)-C(12)-O(5)</td>
<td>174.8(2)</td>
</tr>
<tr>
<td>O(5)-C(12)-C(13)-C(1)</td>
<td>173.6(3)</td>
</tr>
<tr>
<td>C(11)-C(12)-C(13)-C(1)</td>
<td>-6.1(4)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(13)-C(12)</td>
<td>140.8(3)</td>
</tr>
<tr>
<td>C(9)-C(1)-C(13)-C(12)</td>
<td>16.9(4)</td>
</tr>
<tr>
<td>C(2)-C(1)-C(13)-C(12)</td>
<td>-105.5(3)</td>
</tr>
<tr>
<td>C(3)-C(8)-O(1)-C(1)</td>
<td>0.3(3)</td>
</tr>
<tr>
<td>C(7)-C(8)-O(1)-C(1)</td>
<td>-179.4(3)</td>
</tr>
<tr>
<td>C(13)-C(1)-O(1)-C(8)</td>
<td>115.9(2)</td>
</tr>
<tr>
<td>C(9)-C(1)-O(1)-C(8)</td>
<td>-117.6(2)</td>
</tr>
<tr>
<td>C(2)-C(1)-O(1)-C(8)</td>
<td>-0.7(3)</td>
</tr>
<tr>
<td>C(10)-C(9)-O(3)-C(14)</td>
<td>5.5(4)</td>
</tr>
<tr>
<td>C(1)-C(9)-O(3)-C(14)</td>
<td>-179.2(2)</td>
</tr>
</tbody>
</table>
### Appendix

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C(13)-C(12)-O(5)-C(15)</td>
<td>-2.7(4)</td>
</tr>
<tr>
<td>C(11)-C(12)-O(5)-C(15)</td>
<td>177.0(2)</td>
</tr>
</tbody>
</table>
Appendix

A3: Literature Published during this Masters

The following paper was published online in the American chemical Society Journal, *Journal of Organic Chemistry* in 2010.

**CAN-Mediated Oxidations for the Synthesis of Xanthones and Related Products**

Myron M. Johnson, Jeremy M. Naidoo, Manuel A. Fernandes, Edwin M. Mmutlane, Willem A. L. Van Otterlo and Charles B. De koning*

Received 23rd September 2010, Accepted 18th November 2010

*Molecular Science Institute, School of Chemistry, University of the Witwatersrand, PO Wits 2050, South Africa. E-mail: Charles.deKoning@wits.ac.za; Fax: +27 11 717 6749; Tel: +27 11 717 6724*