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

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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

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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-9*H*-xanthen-9-one, 12a-methoxy-5*H*-benzo[*c*]xanthenes-5,7(12*aH*)-dione and the unexpected spiro compound 5-chloro-2',5'-dimethoxy-3*H*-spiro(benzofuran-2,1'-cyclohexa[2,5]diene)-3,4'-dione.

The synthesis of 2,3-dimethoxy-9*H*-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-5*H*-benzo[*c*]xanthenes-5,7(12a*H*)-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-9*H*-xanthene-9-one and 7-chloro-3,4a-dimethoxy-2*H*-xanthene-2,9(4a*H*)-dione products while the third unexpected product was the spiro compound 5-chloro-2’,5’-dimethoxy-3*H*-spiro(benzofuran-2,1'-cyclohexa[2,5]diene])-3,4-dione, the structure of which was confirmed using x-ray crystallography.

Acknowledgements

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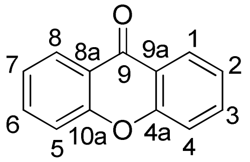
1 Chapter 1: Introduction and Aims

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[1]. Xanthones are typified by the presence of a 9-xanthenone or dibenzo-γ-pyrone ring system, **1**[2, 3]. 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.[3, 4]



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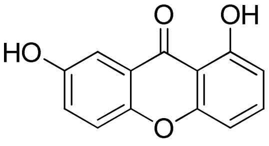
1.1 Naturally occurring xanthones

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[2]. Xanthones can be classed into five major groups, those being simple oxygenated xanthones, xanthone glycosides, prenylated xanthones, xanthonolignoids and miscellaneous xanthones [3, 5]. 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[2]. Simple examples of this class are euxanthone **2** and norathyriol **3**[4]. Euxanthone **2**, which has been isolated from the roots of the medicinal herb *Polygala caudata* has been shown to be a potent neuropharmacologically active compound[6]. Norathyriol **3**, a xanthone aglycone has been isolated from the aerial parts of *Tripterospermum lanceolactum* and exhibits inhibition of phorbol ester-induced respiratory burst which arises from the direct suppression of the PKC activity[7].



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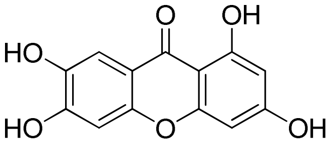

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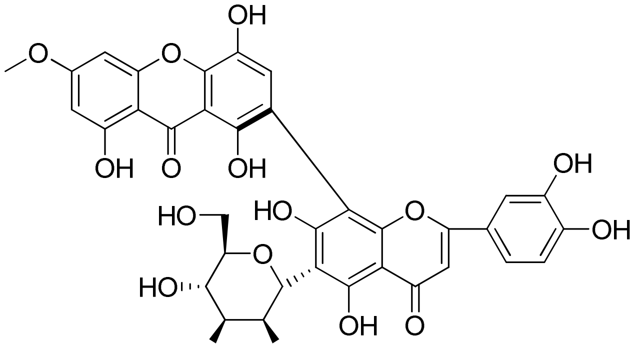
1.1.2 Glycoside xanthones

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



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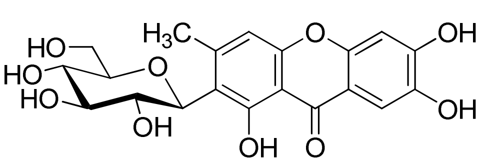

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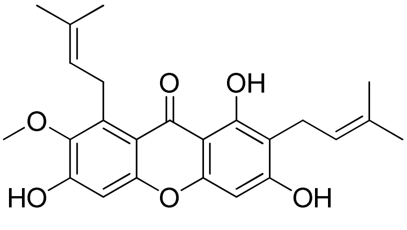
1.1.3 Prenylated xanthones

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 [10], and jacareubin **7** which inhibited the mycelial growth of the brown rot fungus *Postia placenta*[11]. These xanthones were isolated from the pericarps of mangosteen (*Garcinia mangostana* Linn.) and the heartwood of *Calophyllum neo-ebudicum* respectively*.*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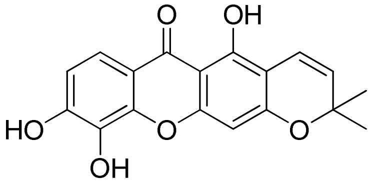
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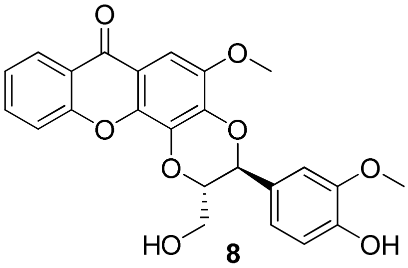
1.1.4 Xanthonolignoids

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[12]. Examples of these xanthonolignoids include kielcorin **8** and hipericorin **9**, which have been isolated from *Kielmeyera rubriflora* and *Hypericum mysorense* respectively[13].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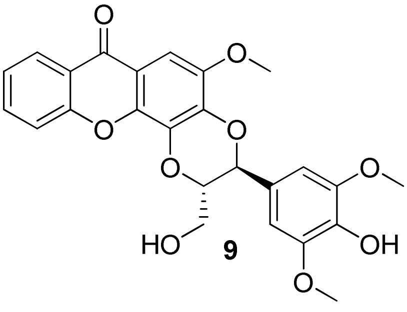
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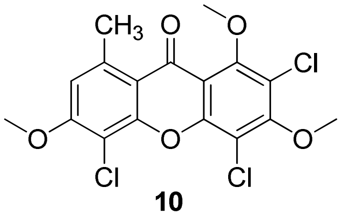
1.1.5 Chlorinated xanthones

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].



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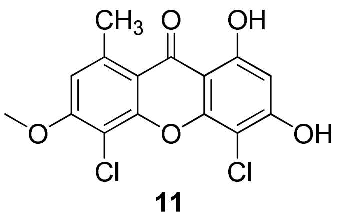

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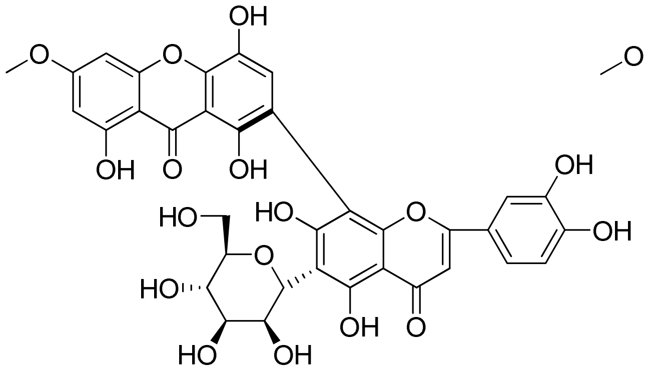
1.2 Biological Activity

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[19].

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



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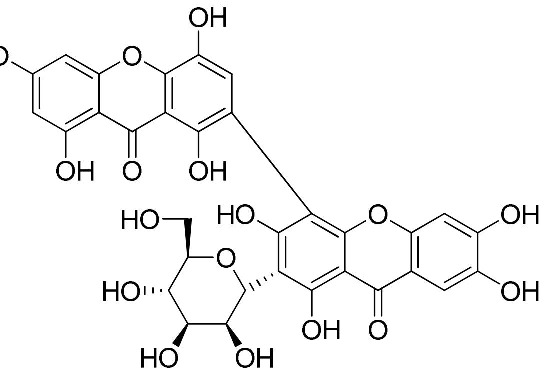

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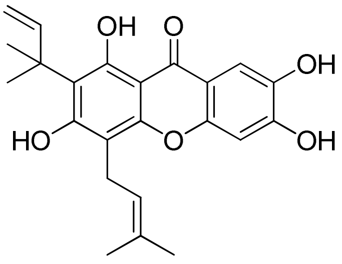
It is known that reverse transcriptase is essential for early proviral DNA synthesis. Therefore, inhibition of the reverse transcriptase catalysed polymerisation ultimately leads to inhibition of virus replication. In a study conducted by Pengsuparp and co-workers, data were collected which suggested that compound **4** binds to DNA thus mediating inhibition. Furthermore, the data suggest that the aromaticity present within the xanthone scaffold leads to the binding of **4** to DNA. However, it was also noted that although compound **4** showed activity against reverse transcriptase, the activity was negligible when compared to that of azidothymidine (AZT), a known compound for HIV treatment.[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*[21].



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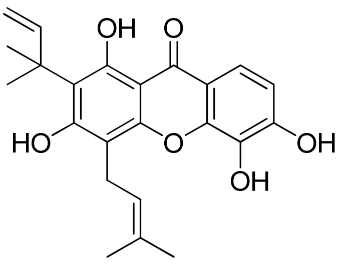

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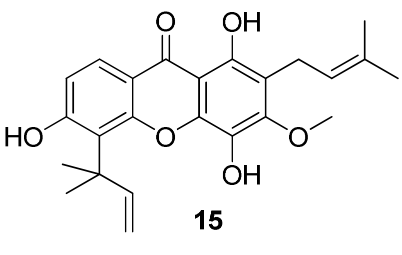
Of all the compounds subjected to anti-HIV screening in this study, compounds **13** and **14** were found to display the best potential at an EC_{50} value of 1.1-2 μg/mL. It appears that the catechol functionality of compounds **13** and **14** offers an enhancement in their HIV-inhibitory activity. 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 xathone, commonly referred to as garceduxanthone **15**[22]. 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 xathone, forbexanthone **16**.



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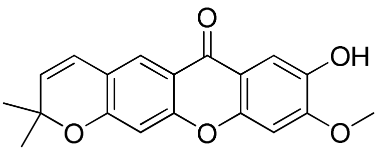

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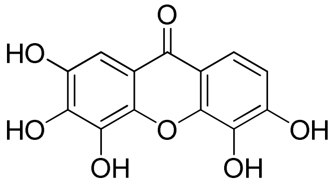
The results from this study found that the crude extract exhibited mild anti-HIV-1PR activity with IC_{50} value of 51.7 μg/mL. Once purified, the new xanthone **15** exhibits strong anti-HIV-1PR activity with IC_{50} value 11.3 μg/ml while the known xanthone **16** was inactive.

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 [23]. 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[24].

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[24]. 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[25].

Ignatushchenko and co-workers studied the effect that a highly substituted xanthone X5 **17** has on the digestive vacuole of the parasite[24]. *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[26].



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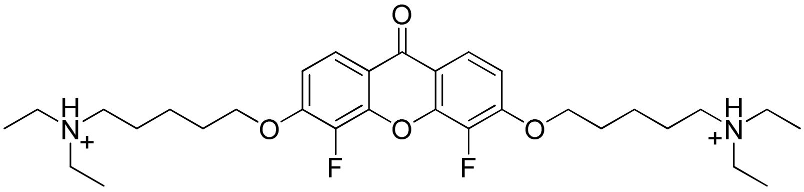
Riscoe and co-workers conducted a study in which they synthesized and tested the cytotoxicity of the xanthone 3,6-bis(ω-*N*,*N*-diethylaminoamyloxy)-4,5-difluoroxanthone (F2C5)**18**[25].



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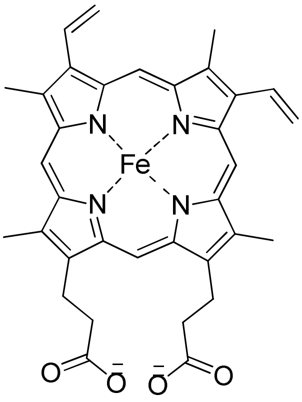

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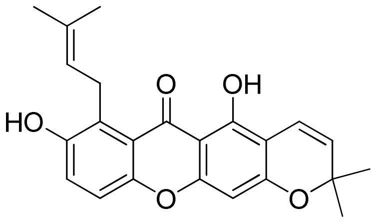
F2C5 was tested against multidrug resistant malaria strains W2 and D6 of *P. falciparum* and IC_{50} values of 150 nM and 93 nM were observed for the respective strains. Chloroquine shows activity against W2 and D6 with IC_{50} values of 290 nm and 7.8 nm respectively. The value of F2C5 against W2 is 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 **19** 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 interaction with the negative haem ring[27]. This stronger interaction will also result in the stabilisation of the drug-haem complex which will prevent further hemozoin formation[28].

The position of the hydroxyl groups is believed to be of importance as observed in a study conducted by Hay and co-workers[29]. Their study tested demethylcalabaxanthone **20** and calowaitesixanthone **21** against chloroquine-resistant strains of the malaria parasite. Xanthones **20** and **21** showed activity with an IC_{50} value of 0.9 µg/ml and IC_{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.



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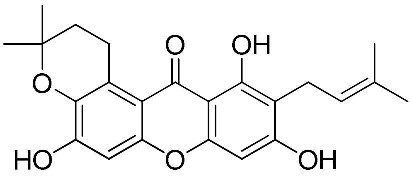

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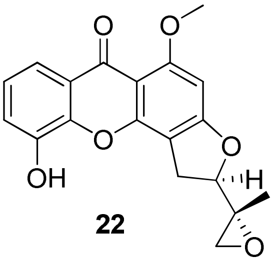
Therefore, all the research being conducted confirms that the xanthone scaffold is pivotal in the activity of a haem poison such as F2C5. This is due to the xanthone scaffold being positioned in an orientation where all its structural features maximises its inhibitory potential.

1.2.3 Anti-tumour activity

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

Psorospermin **22** is a naturally occurring xanthone isolated from the dried roots of *Psorospermun febrifugum*, which is indigenous to tropical Africa. Kupchan and co-workers conducted the isolation studies as well as cytotoxic assays on the isolated extract[30]. In their study they managed to elucidate the structure of **22**, however, the absolute stereochemistry of the dihydrofuran ring and epoxide moiety was not assigned.



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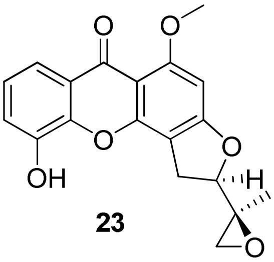
The initial study also included the first biological activity studies of **22**. The extract of *P. febrifugum* was found to exhibit significant activity both *in vivo* and *in vitro*. Biological activity was shown *in vivo* against P-338 lymphocytic leukemia at doses ranging from 8 to 0.1mg/kg and *in vitro* against a human epidermoid carcinoma at ED_{50} = 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[31]. 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[32].



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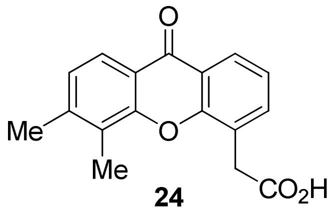
In recent years, psorospermin remains of interest and its first total synthesis was reported in 2005 by Schwaebe and co-workers[33]. Their synthetic route started with the classical Grover, Shah and Shah reaction (see section 1.4.1.1) to achieve the hydroxyxathone, and utilised a zipper-type reaction 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[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[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[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[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[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[38, 39].



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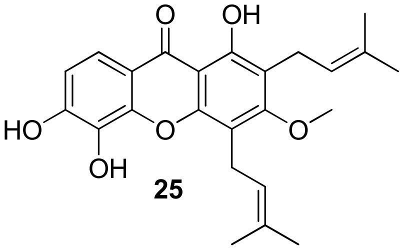
Research has also been conducted into the possible use of xanthones as inhibitors of Epstein-Barr virus (EBV) by Ito and co-workers. These xanthones will ultimately function as anti-tumour promoters. In their study, 20 xanthones were tested and it was found that activity was observed for most of the 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].



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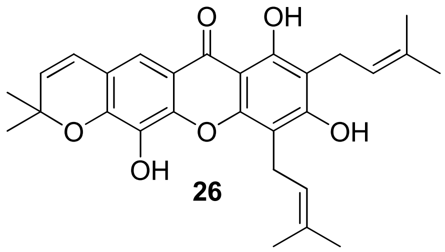

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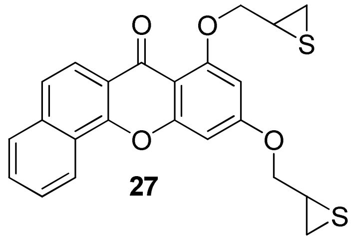
Recently, Cho *et al.* conducted a study which involved the synthesis of a number of xanthone derivatives. These compounds were then tested against various cancer cell lines[35]. Their study prepared 12 benzoxanthone derivatives, with most compounds showing effective cancer cell growth inhibition against 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**.



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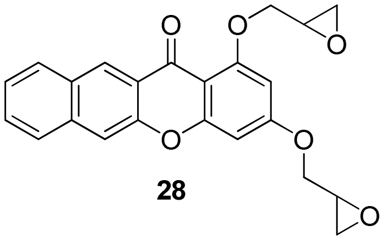

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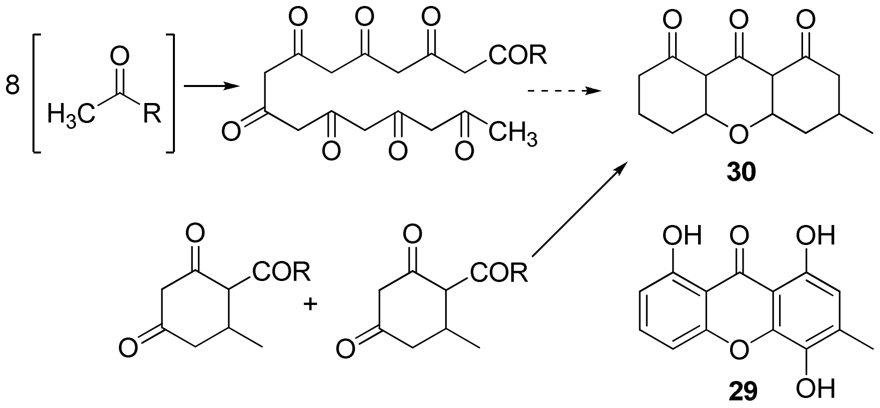
1.3 Biosynthesis

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[2]. 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

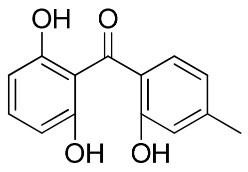
Birch *et al.* used radioactive carbon labelling to determine the biosynthetic pathway of ravenelin **29**, a naturally occurring xanthone isolated from two species in the fungal family *Helminthosporium*[41]. Their study confirmed that ravenelin is produced completely from polyketides. The polyketide 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**.



Scheme 1

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**.



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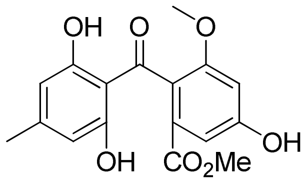

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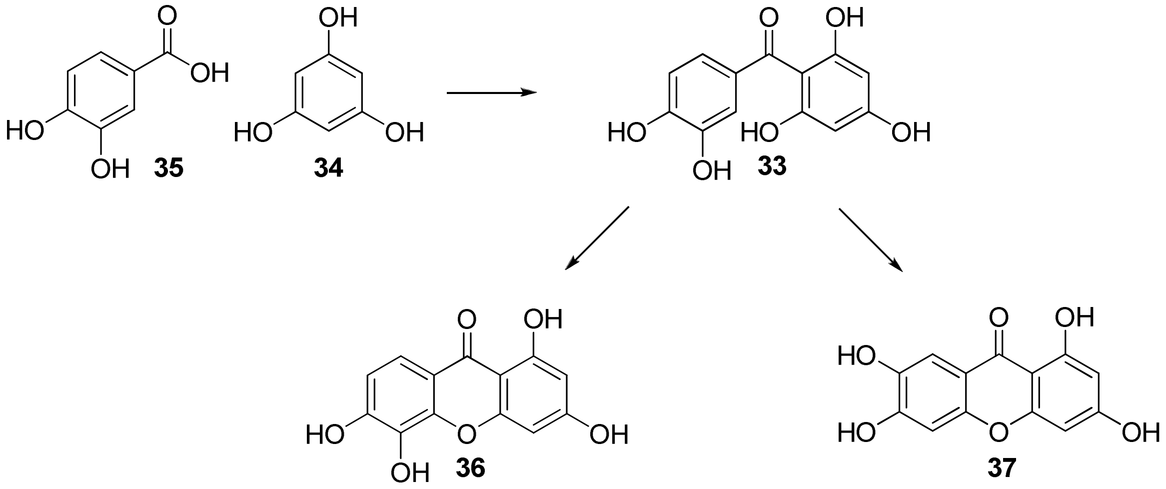
1.3.2 Shikimate-polyketide route

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**).



Scheme 2

1.4 Synthetic strategies towards xanthones

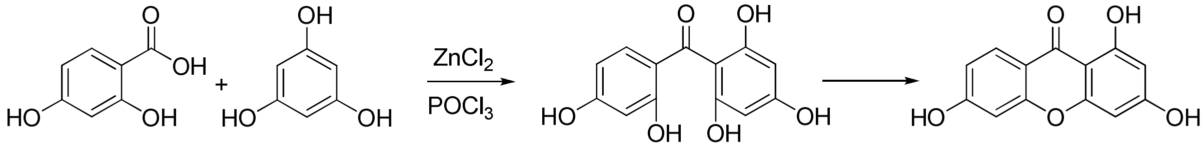
In recent years there has been an increase in the interest in xanthone synthesis. This is partly due to the diverse pharmacological activities which xanthones exhibit. Another reason for the increase in xanthone research is in the medicinal chemistry industry where these compounds have been shown to 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].

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[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 salicyclic 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.

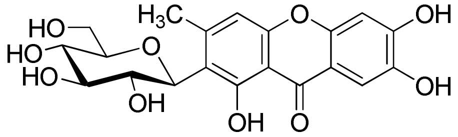


38 **34** **40** (*) **39**

Scheme 3

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[46]. These limitations proved sufficient such that other methods have superseded this xanthone synthesis.

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**[47].



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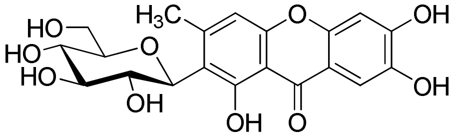

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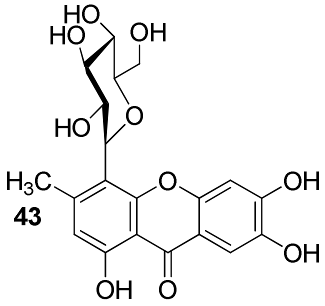

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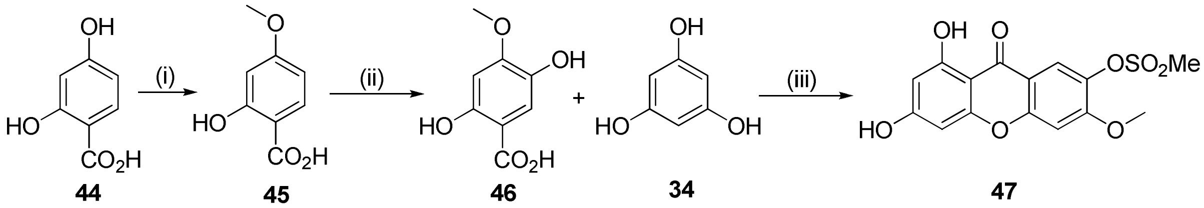
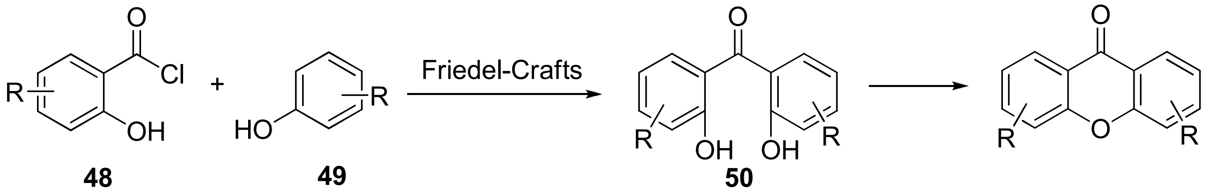
2,4-Dihydroxybenzoic acid **44** was monomethylated to afford 4-methoxy-2-hydroxybenzoic acid **45** which was subsequently converted into 4-methoxy-2,5-dihydroxybenzoic acid **46** under aqueous conditions. Once **46** was assembled, the GSS reaction with phloroglucinol **34** in the presence of Eaton's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



Scheme 4 *Reagents and conditions:* (i) Me_2SO_4, 20% aq. NaOH, rt, 59%; (ii) $K_2S_2O_8$, 10% aq. NaOH, 0 °C to rt, 60%; (ii) P_2O_5, $MeSO_3H$, 80 °C, 40%.

1.4.1.2 Benzophenone route

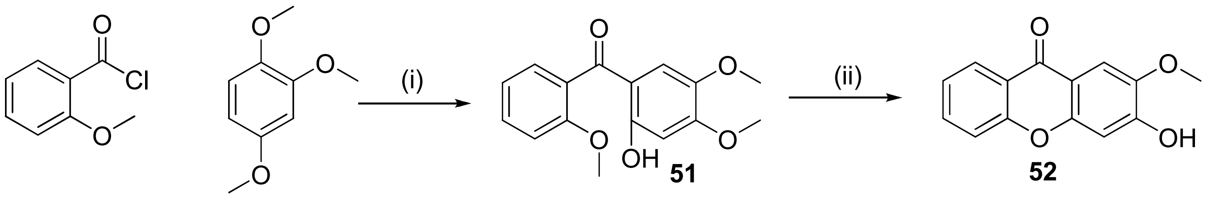
The synthesis of xanthones via the benzophenone route results in a benzophenone derivative which is easily obtained by the Friedel-Crafts acylation of an appropriately substituted benzoyl chloride **48** with a phenolic derivative **49**. Cyclisation of the benzophenone intermediate **50** could involve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



Scheme 5

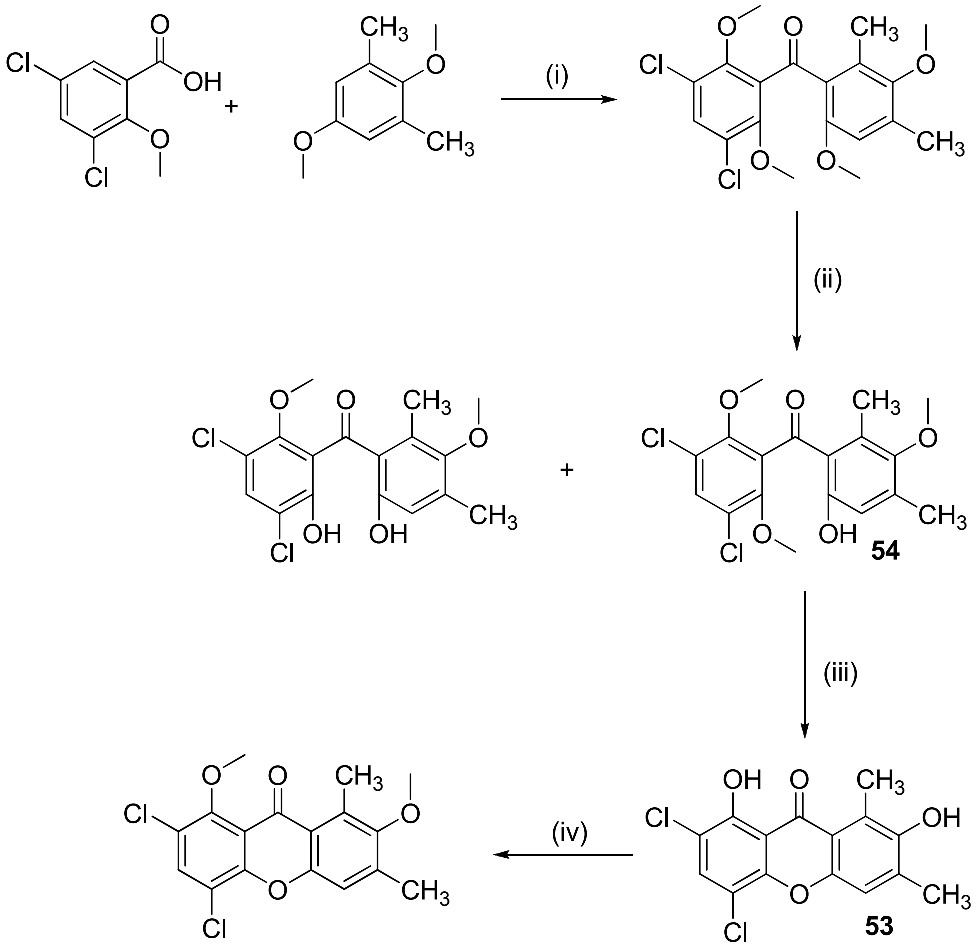
Quillinan and Scheinmann[48] illustrated a more useful and efficient alternative to the Grover, Shah and Shah method in their synthesis of polyoxygenated xanthones. Their study illustrated the preparation of numerous analogues, which proved a limitation to the GSS method which was accompanied by unwanted 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**.



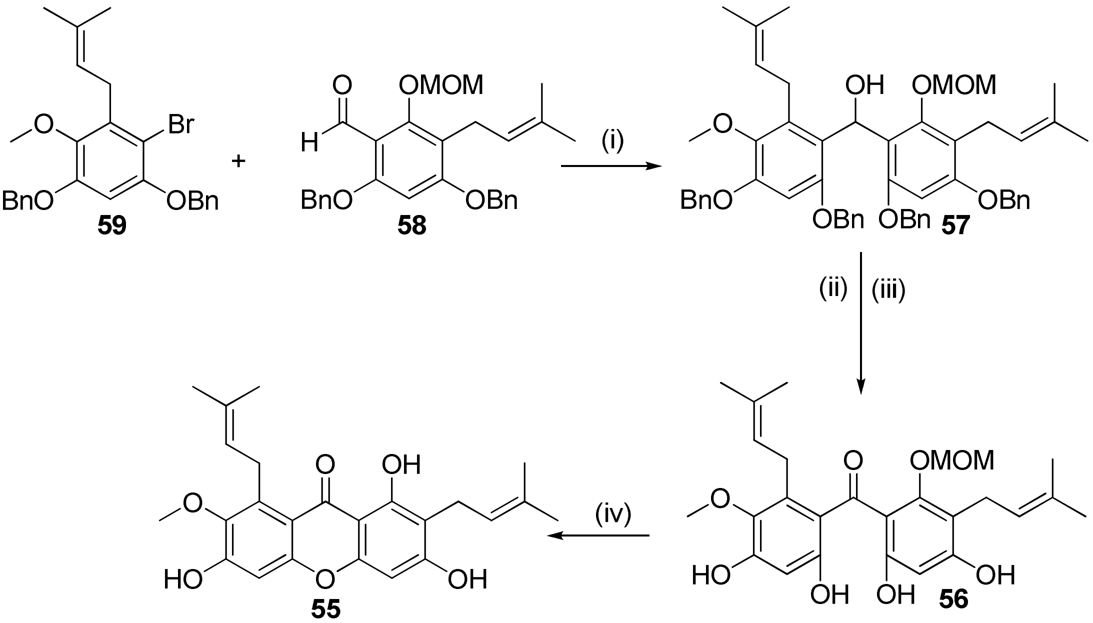
Scheme 6 *Reagents and conditions*: (i) $AlCl_3$, dry ether, rt, 20 h; (ii) piperidine/H_2O, reflux, 46 h.

To date, there are various methods which are used to access the benzophenone intermediate. One such modification was achieved by Elix and co-workers[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.



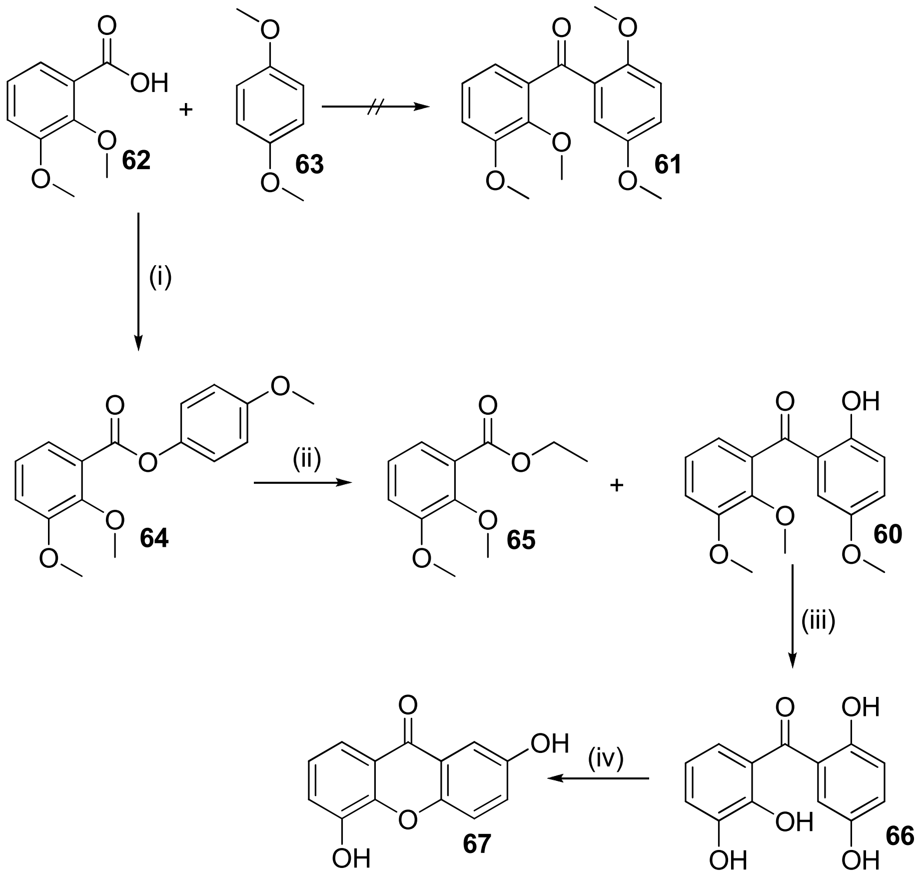
Scheme 7 *Reagents and conditions:* (i)TFAA, 1,2-dichloroethane, 0°C-reflux, 18 h; (ii) BBr_3, CH_2Cl_2, –10 °C, 2 h, rt, 20 min; (iii) H_2O, 120 °C, 16 h; (iv) Me_2SO_4, K_2CO_3, Acetone, 18 h

Recently, the synthesis of α-mangostin **55** by Iikubo and co-workers followed the benzophenone route[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 (**Scheme 8**).



Scheme 8 *Reagents and conditions:* (i) *s*-BuLi, THF, –78 °C; (ii) 2-Iodobenzoic acid, toluene/DMSO (1:1), rt; (iii) 10% Pd/C, HCO_2NH_4, acetone, rt; (iv) PPh_3, CCl_4, THF, silica gel, rt.

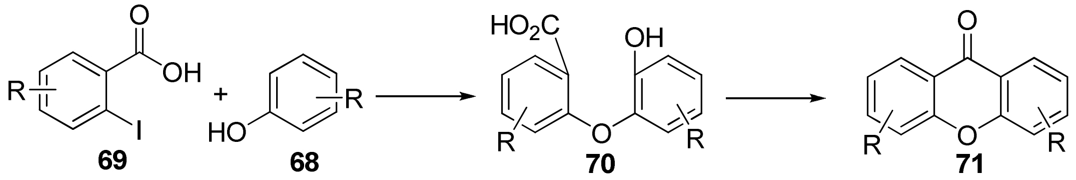
Finnegan and co-workers accessed the benzophenone intermediate **60** through a photo-Fries rearrangement in their synthesis of 2,5 and 4,5-dihydroxyxanthones[51]. Their initial study aimed to prepare benzophenone **61** via the condensation of 2,3-dimethoxybenzoic acid **62** with *para*-dimethoxybenzene **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**).



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) H_2O, bomb, 225 °C, 17 h.

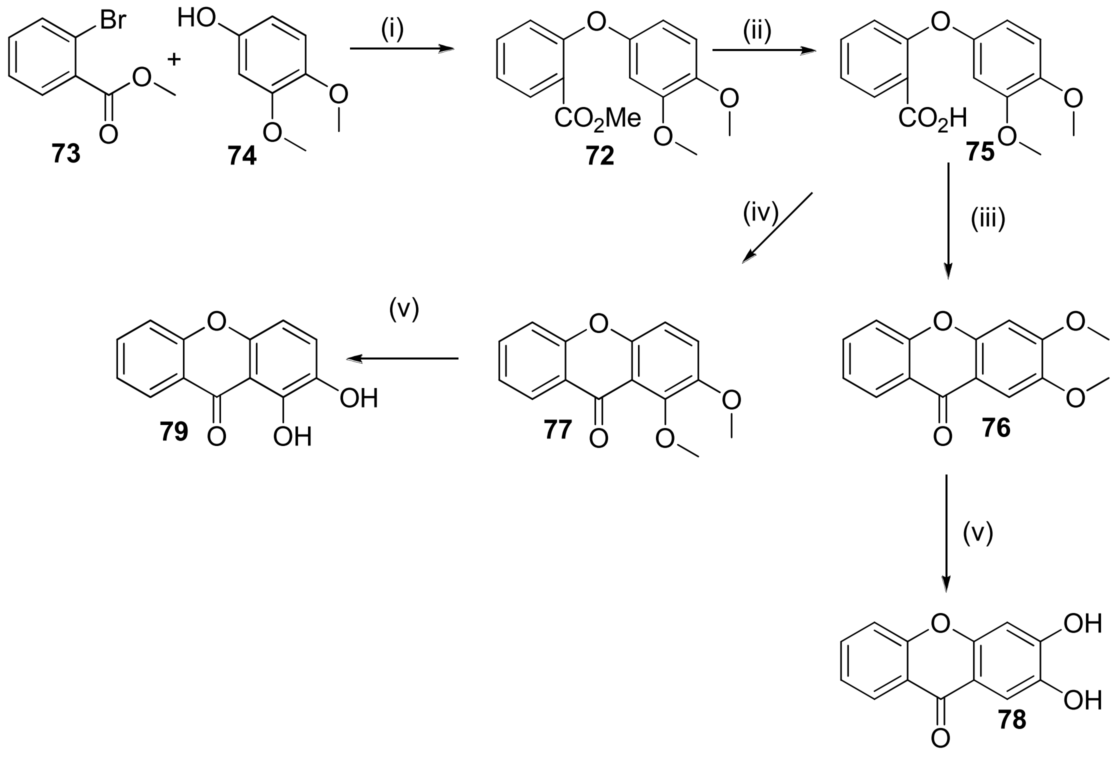
1.4.1.3 Diaryl ether route

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**.



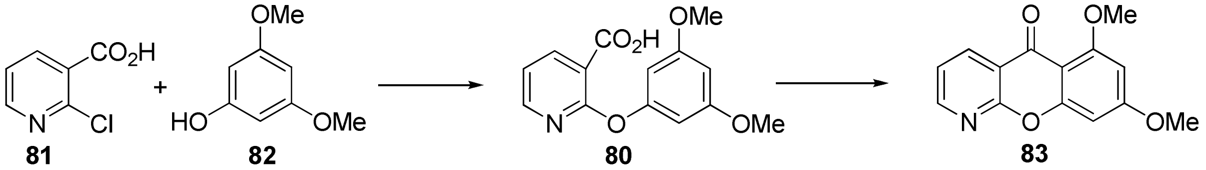
Scheme 10

This synthetic route was used by Sousa and co-workers in the synthesis of kielcorin derivatives[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**).



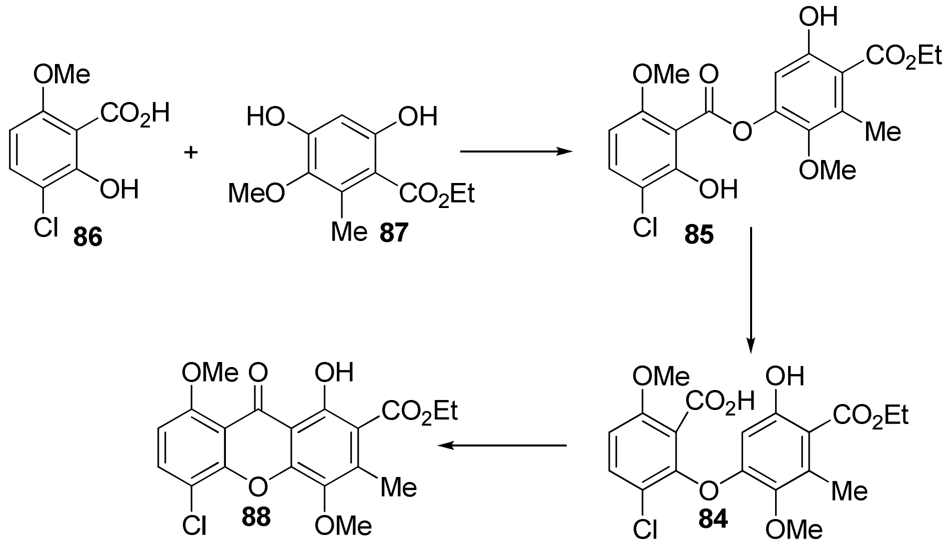
Scheme 11 *Reagents and conditions:* (i) Cu, K_2CO_3, Pyridine, reflux, 26 h; (ii) MeOH/THF, H_2O, NaOH, rt, 96 h; (iii) AcCl, H_2SO_4, rt, 10 min; (iv) LDA, THF, 0°C to rt, 2 h (v) Toluene, $AlCl_3$, reflux, 8 h

Reisch and co-workers have prepared xanthone derivatives in their synthesis toward acronycine isosters[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_2CO_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**[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**).



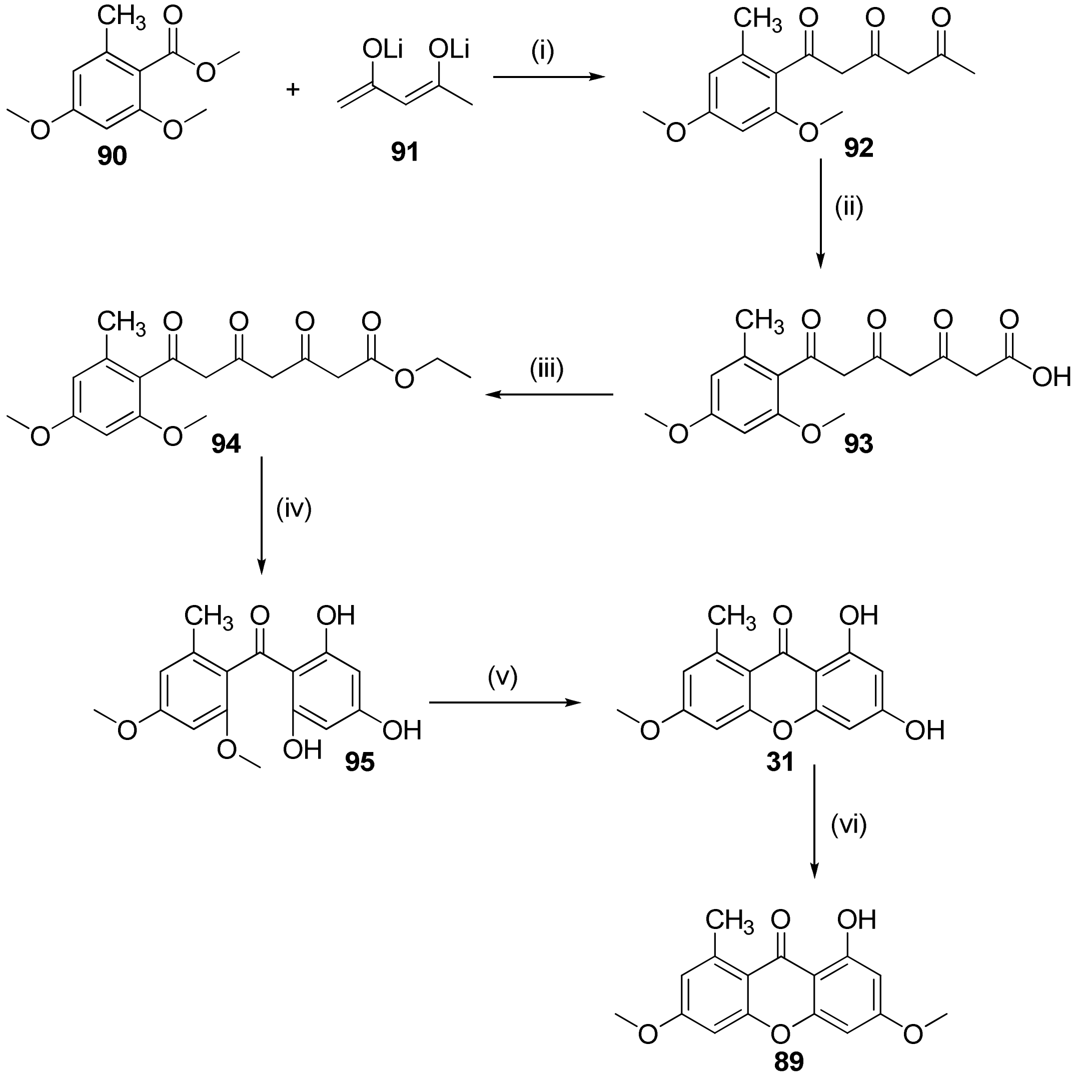
Scheme 13 *Reagents and conditions:* (i) DCC, toluene, dry ether, rt, 24 h; (ii) K_2CO_3, dry DMSO, 80 °C, N_2, 16 h; (iii) dry toluene, TFAA, rt, 17 h.

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 methods[44]. Some of these non-conventional methods will be highlighted in the following section.

1.4.2.1 Claisen cyclisation of poly-β-ketide

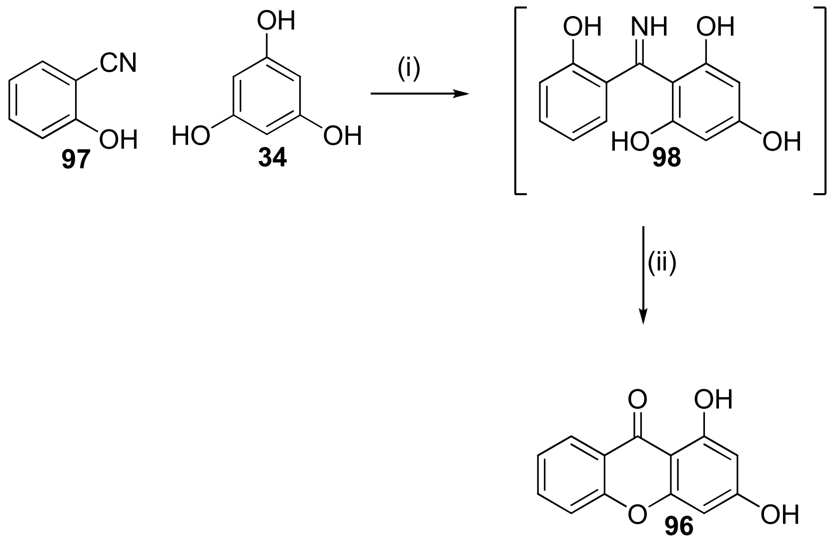
Harris and co-workers demonstrated a biomimetic pathway for the synthesis of lichexanthone **89**, a naturally occurring secondary metabolite[54]. The first step in their synthesis was the reaction of dilithioacetylacetone **91** with methyl orsellinate **90** to furnish the triketone **92**. Carboxylation 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**).



Scheme 14 *Reagents and conditions:* (i) THF, 16 h, rt; (ii) THF, 0 °C, CO_2 bubbling, 5 min; (iii) Diethyl ether, CH_2N_2, 30 sec; (iv) $KOH_{(aq)}$, rt, 70 h; (v) 10% KOH/MeOH, reflux, 7.5 h; (vi) Diethyl ether, CH_2N_2, rt, 1 min.

1.4.2.2 The Robinson-Nishikawa method

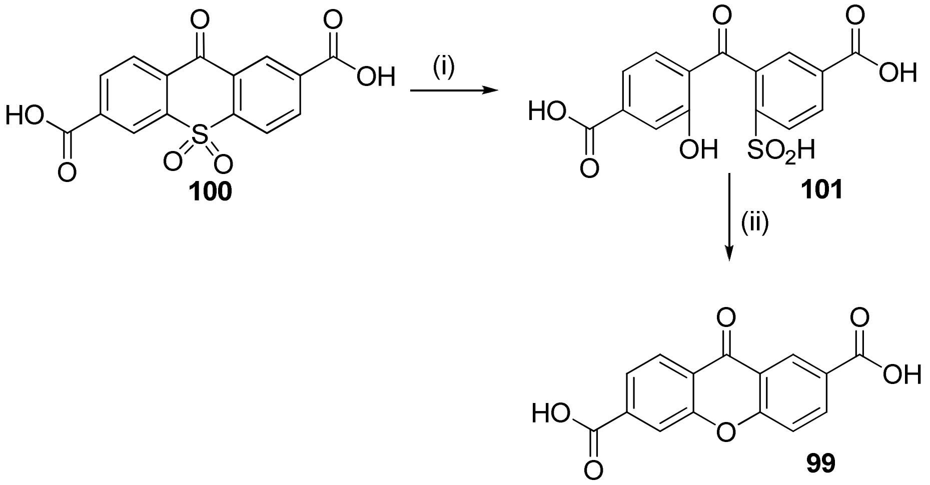
This method is a variant of the Hoesch synthesis and is known to proceed via benzophenones involving ketimine intermediates. In 1922, Robinson demonstrated the ketimine intermediate pathway for the preparation of 1,3-dihydroxyxanthone **96**[55]. The reaction involved the condensation of phloroglucinol **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**).



Scheme 15 *Reagents and conditions:* (i) $ZnCl_2$, HCl, 2 h; (ii) $NaOH_{aq}$, reflux

1.4.2.3 Synthesis of xanthones from thioxanthone

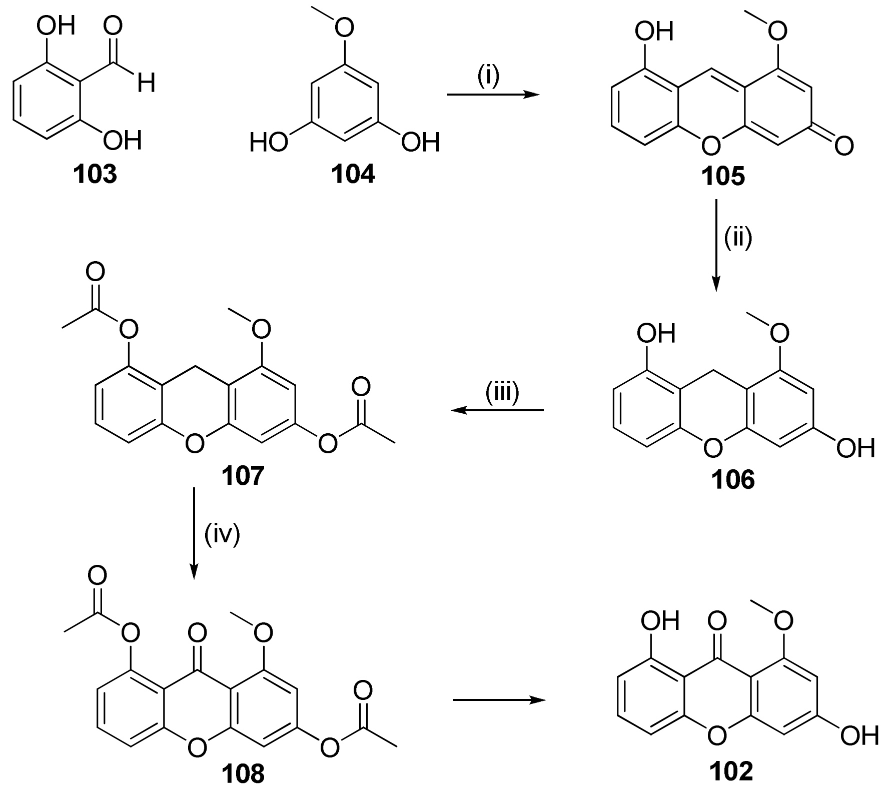
Bennet *et al.* synthesized **99** via thioxanthone intermediates[56]. Thioxanthone **100** was converted into hydroxybenzophenone sulfinic acid **101** by conducting the reaction under basic conditions followed by acidification. The hydroxybenzophenone sulfinic acid **101** was then heated under basic condition to afford the xanthone **99** as shown in **Scheme 16**.



Scheme 16 *Reagents and conditions:* (i) NaOH, dioxane/H_2O, reflux, 5 h; (ii) $NaOH_{aq}$, 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**[57]. 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 H_2 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**).



Scheme 17 *Reagents and conditions:* (i) AcOH, HCl; (ii) cat. H_2; (iii) Ac_2O; (iv) CrO_3;

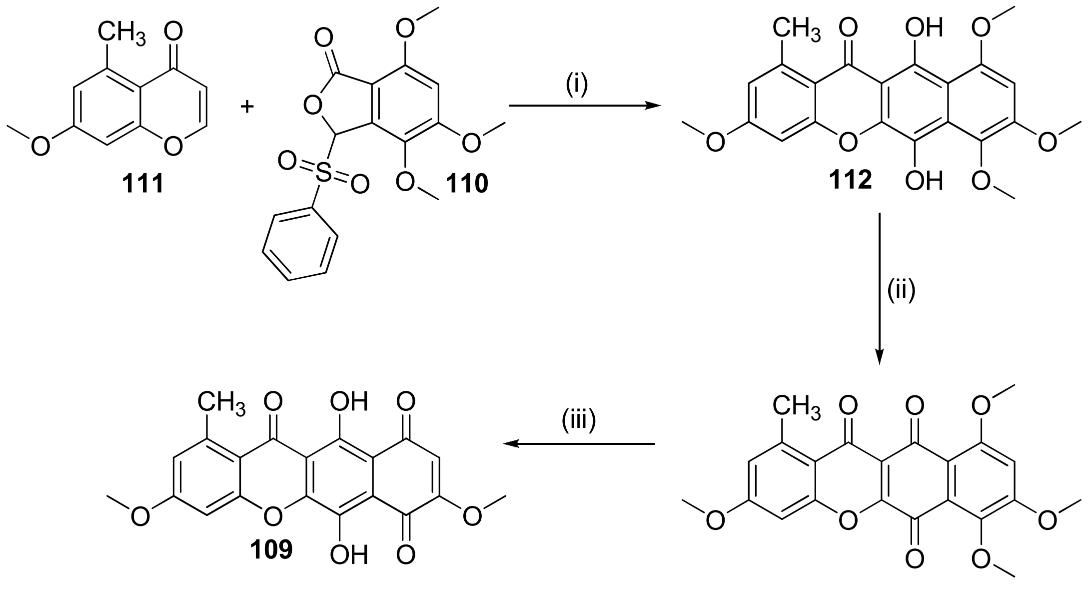
1.4.3 New methodology

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 [58]

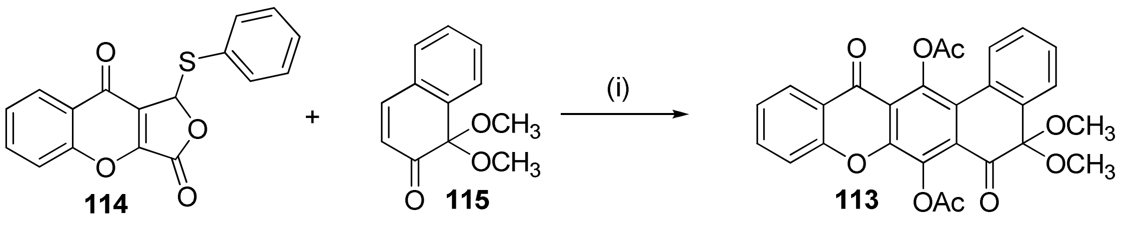
Hauser and co-workers accomplished one of the first total syntheses of bikaverin **109**, by condensing (phenylsulfonyl)isobenzofuranones with chromones to afford xanthones regiospecifically.

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 *Reagents and conditions:* (i) LiO-*t*-Bu, THF, –78°C and reflux; (ii) Ag_2CO_3-Celite; (iii) LiI, DMF

The methodology was then extended to the preparation of xanthones which contain angular polycyclic aromatic systems **113** [59]. This was achieved by condensing benzopyranophthalide **114** with various Michael acceptors **115**. One example is shown in **Scheme 19**.

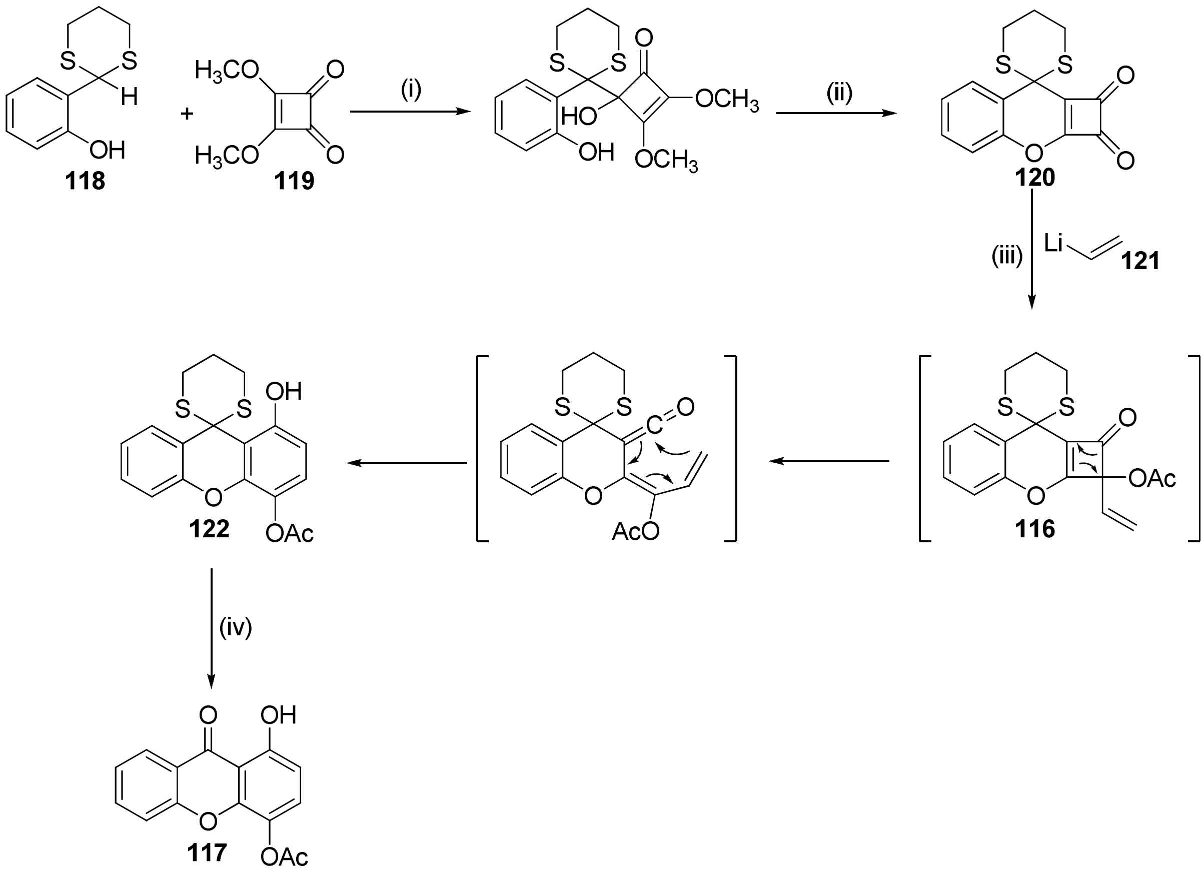


Scheme 19 *Reagents and conditions*: (i) LiO-t-Bu, THF, –78°C and reflux

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[58].

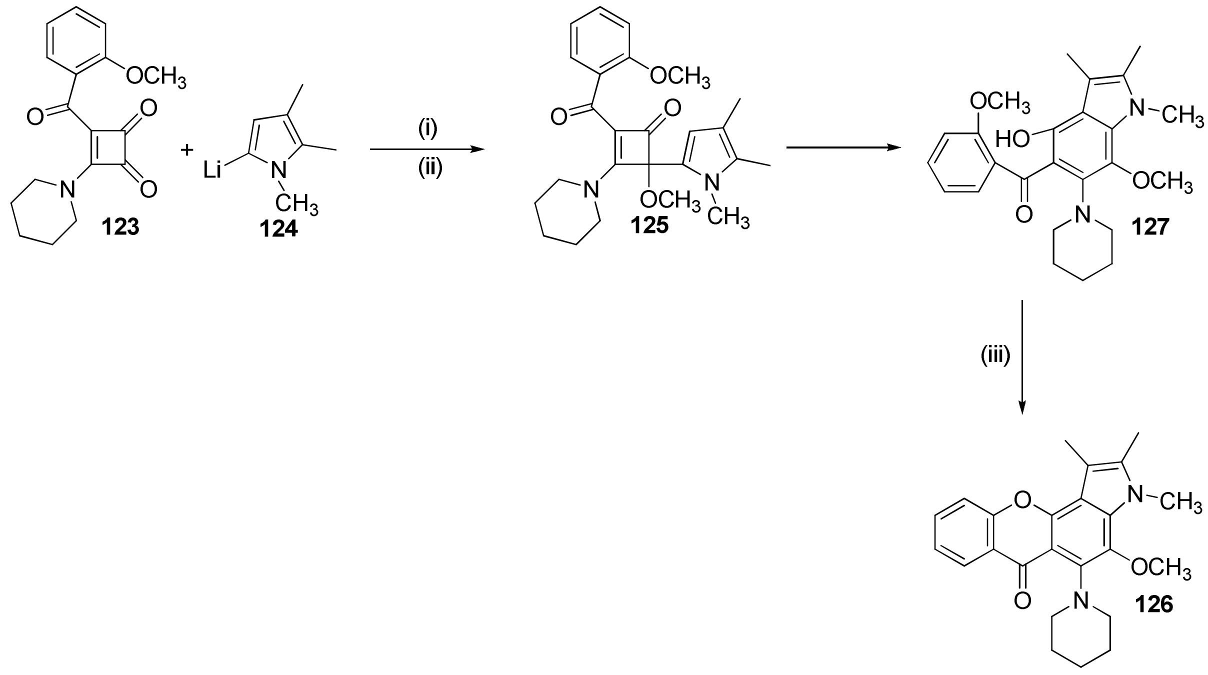
1.4.3.2 The Liebeskind method for the synthesis of xanthones [60]

Liebeskind and co-workers have developed a flexible approach for the synthesis highly-substituted xanthones. Their methods relied on cyclobutenediones as scaffolds for the construction of these xanthones. The synthetic strategy involved the 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 % *p*TSA, CH_2Cl_2, rt, 72 h; (iii) THF, –78 °C, Ac_2O, reflux; (iv) $HgCl_2/CaCO_3$, mesitylene/H_2O, reflux

Liebeskind and co-workers also attempted the preparation of angular-fused xanthone using the cyclobutenedione-based methodology[61]. 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**).



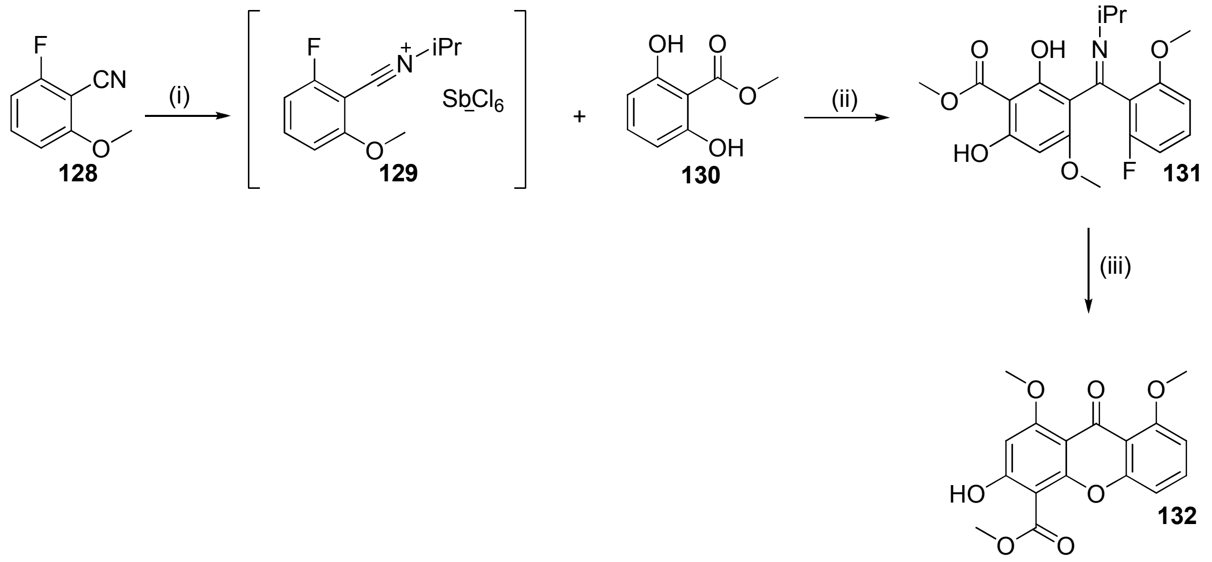
Scheme 21 *Reagents and conditions:* (i) THF, –78 °C; (ii) MeOTf, -78 °C to rt, 64 h; (iii) mesitylene, reflux

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[62]

Casillas and co-workers described a new synthetic method for the preparation of xanthones which takes advantage of the high electrophilicity of N-alkylnitrilium 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[63]. The acylation reaction of these alkylnitrilium salts proves to surpass the Houben-Hoesch acylation method. This is due to the enhanced electrophilicity of the intermediate.

2-Fluoro-6-methoxybenzonitrile **128** was reacted with Lewis base, $SbCl_5$ and 2-chloropropane to afford the N-isopropylnitrilium salt **129**. Intermolecular imino-acylation 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**.

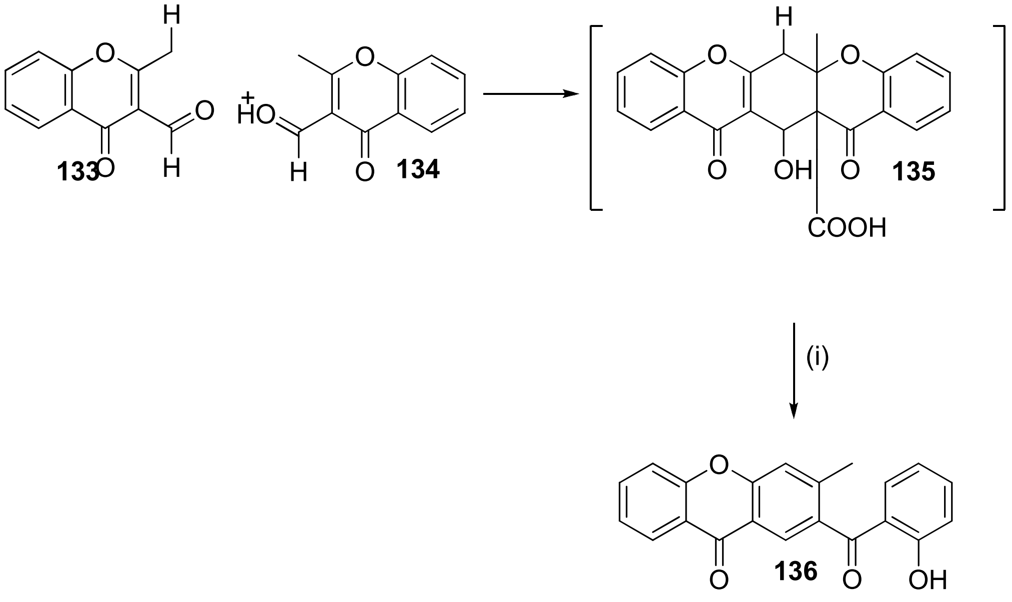


Scheme 22 *Reagents and conditions*: (i) $SbCl_5$, 2-chloropropane, CH_2Cl_2, rt, 2 h; (ii) reflux, 60 h, CH_2Cl_2; (iii) K_2CO_3, MeCN, reflux, 23 h, $MeOH/H_2O$.

Casillas *et al.* therefore provided a general route to prepare highly substituted xanthones. They achieved this by taking advantage of the reactivity of N-alkylnitrilium salts by employing Friedel-Crafts methodology[64].

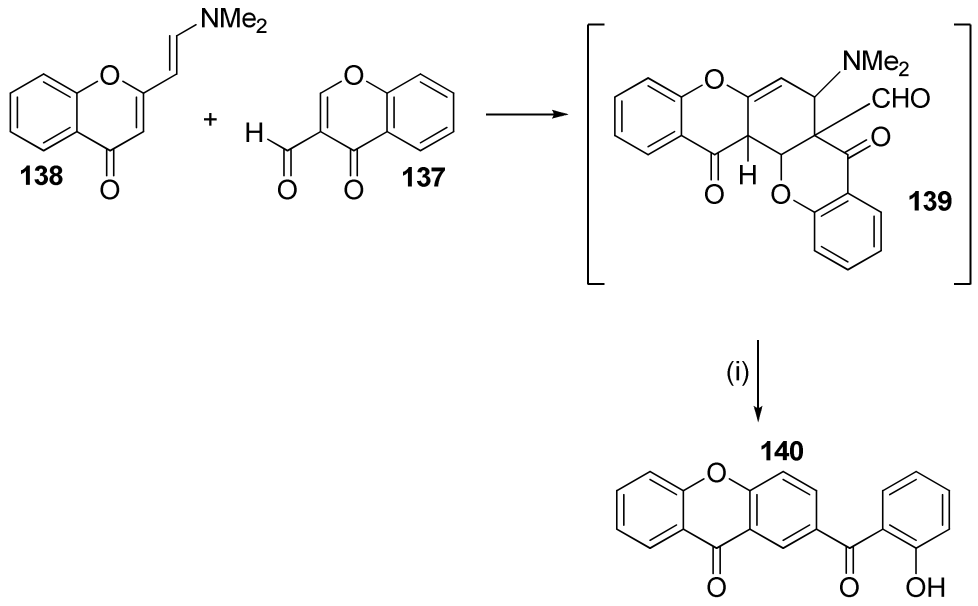
1.4.3.4 The Ghosh method for the synthesis of xanthones

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 benzoxanthene **135**. These benzoxanthenes then undergo a base catalysed deacylative hydroxyl elimination followed by pyran ring opening to furnish xanthones, such as **136** (**Scheme 23**).



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[66]. 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**).

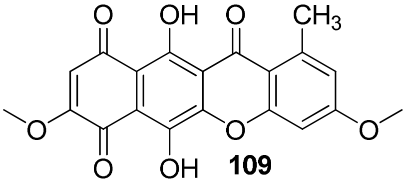


Scheme 24 *Reagents and conditions*: (i) DMF, reflux, 8 h

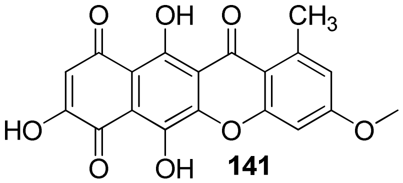
This Diels-Alder cycloaddition has also been used on alkyne substrates to prepare xanthones. This method also showed that the diene undergoes a Diels-Alder cycloaddtion with relatively weak dienophiles as well as reactive dienophiles[67].

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**[68]. Bikaverin **109** was isolated by both Kjaer[69] and Cornforth[70] 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.



109



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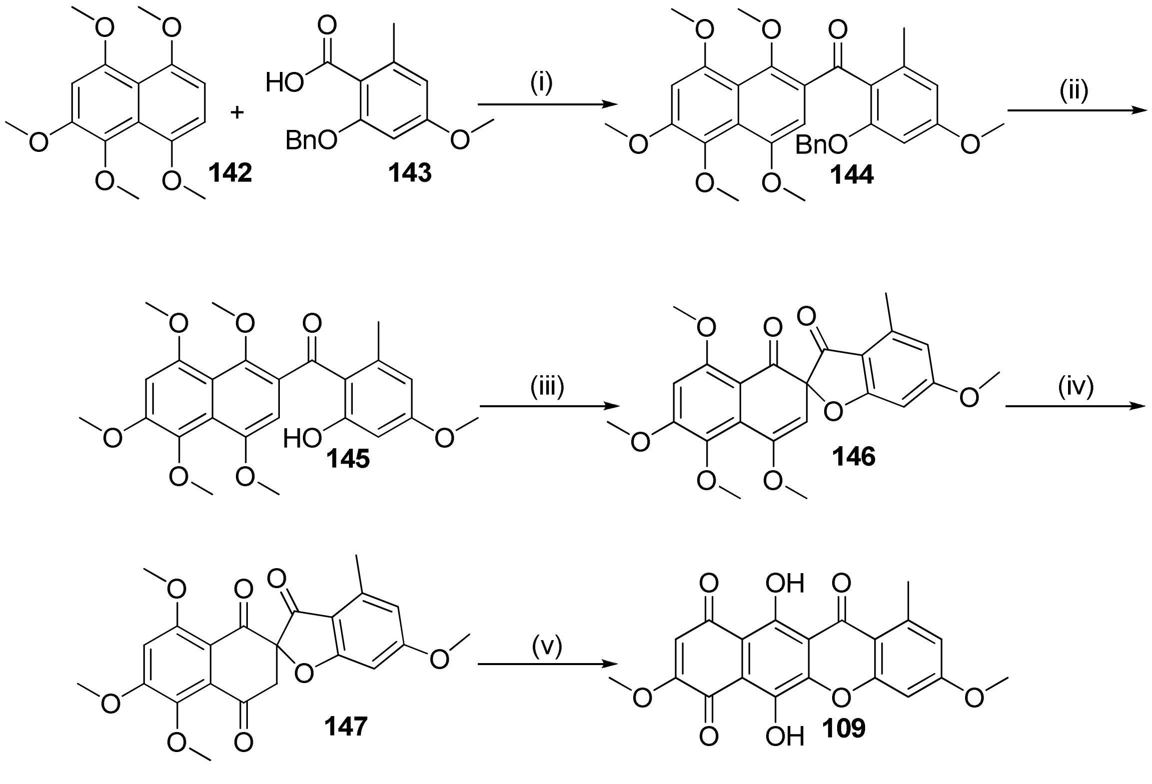
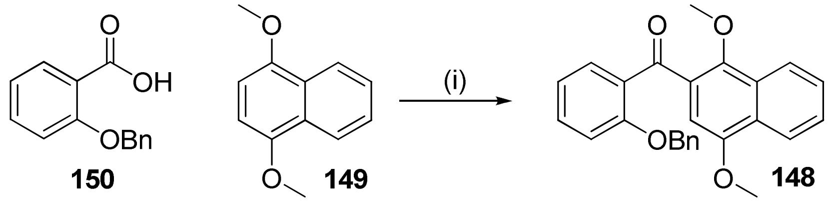
de Koning and co-workers started the xanthone synthesis by constructing the carbonyl bridge which was prepared using a mild Friedel Crafts reaction. This was achieved using trifluoroacetic anhydride (TFAA) with the prepared naphthalene derivative **142** and the aryl acid **143**, to afford the intermediate 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**.



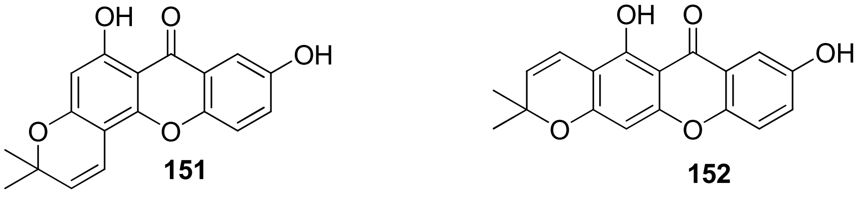
Scheme 25 *Reagents and conditions*: (i) TFAA, CH_2Cl_2, rt, 90 h, 51%; (ii) 10% Pd/C, H_2, 5 bar, 1 h, 80%; (iii) DDQ, benzene, rt, 68 h, 61%; (iv) TFA (aq), CH_2Cl_2, rt, 5 min, 94%; (v) 200 °C, 1.1 bar, 1 h, 93%.

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.

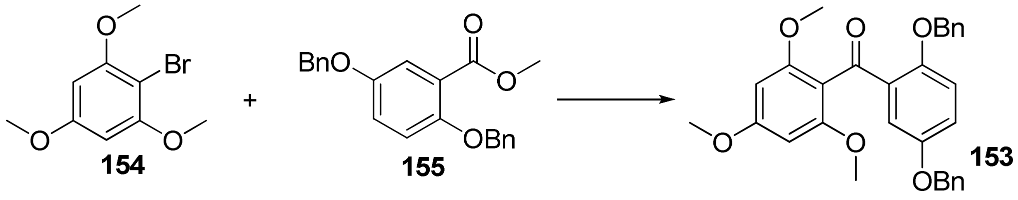


Scheme 26 *Reagents and conditions*: (i) TFAA, CH_2Cl_2, rt, 48 h, 30%.

A procedure followed by Argade and co-workers in their pursuit to synthesize nigrolineaxanthone **151** and osajaxanthone **152** was applied[71].

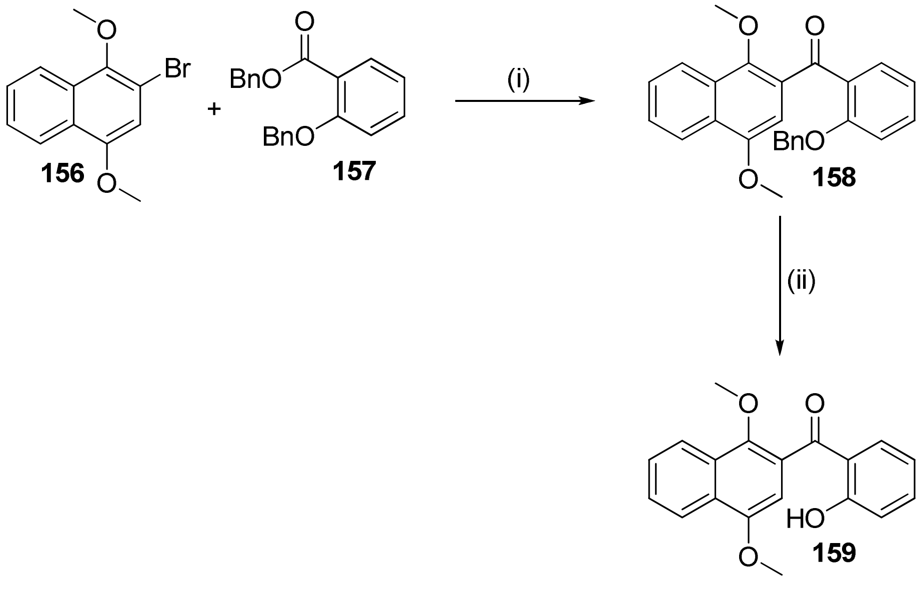


In their approach they constructed the carbonyl bridge of **153** by reacting *n*-butyllithium with 2-bromo-1,3,5-trimethoxybenzene **154** followed by methyl 2-5-(dibenzyloxy)benzoate **155** as shown in **Scheme 27**.



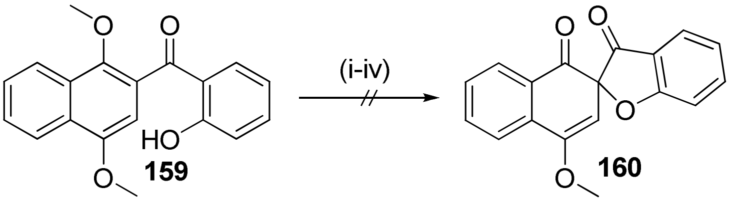
Scheme 27 *Reagents and conditions*: (i) *n*-BuLi, THF, –78 °C, 90 min.

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**.



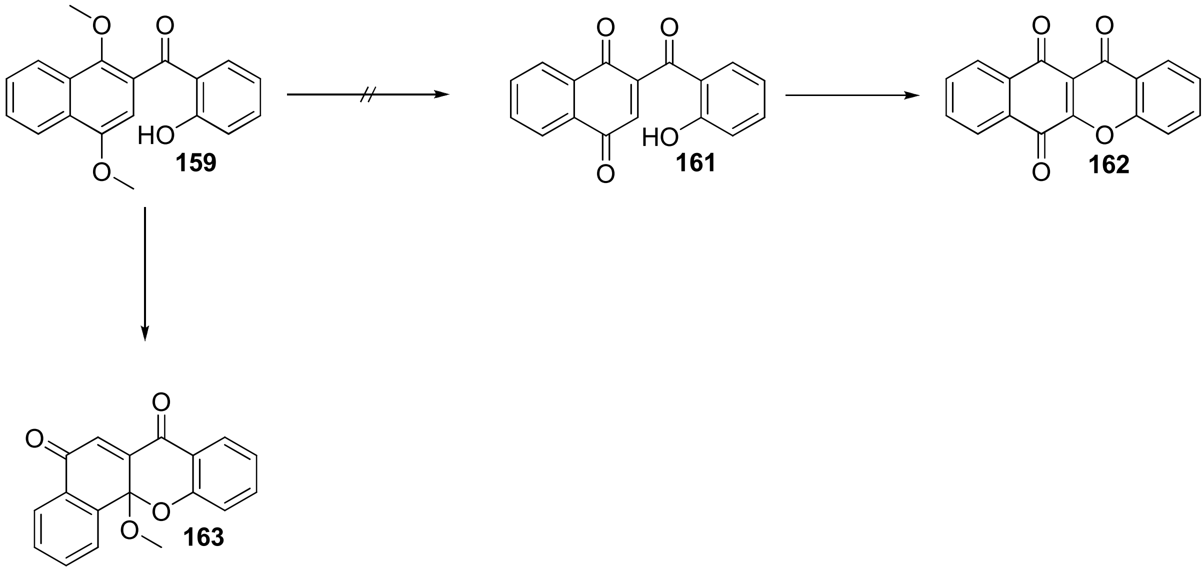
Scheme 28 *Reagents and conditions*: (i) *n*-BuLi, THF, –78 °C, 90 min, 89%; (ii) 5% Pd/C, H_2, methanol, 5 atm, 18 h, 97%.

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.



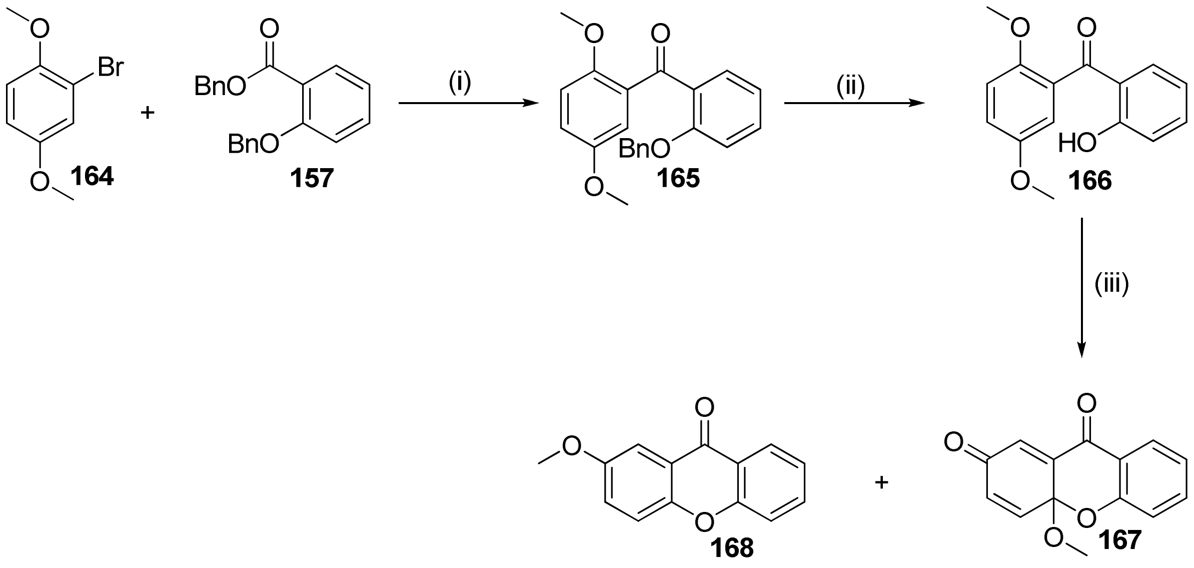
Scheme 29 *Reagents and conditions*: (i) DDQ, benzene, rt, 72 h; (ii) DDQ, benzene, reflux, 72 h; (iii) DDQ, chloroform, rt, 72 h; (iv) DDQ, chloroform, reflux, 72 h.

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[72]. 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**[73]. However, the reaction surprisingly produced the dione **163** (**Scheme 30**).



Scheme 30 *Reagents and conditions*: CAN, CH_3CN/H_2O, rt, 1.5 h, 72%

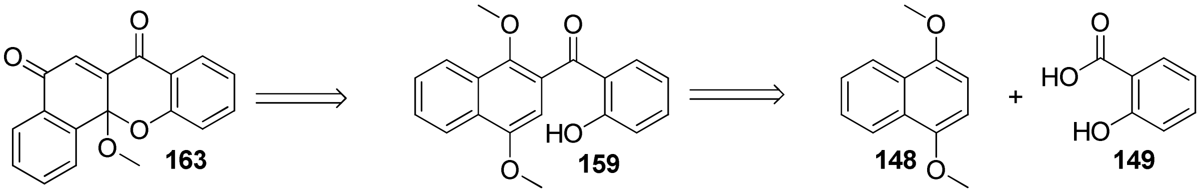
Having produced the unexpected dione **163**, the synthetic route was tested on a simpler, less substituted system. The route produced the expected intermediates. Therefore a simpler carbonyl bridge compound was prepared from 2-bromo-1,4-dimethoxybenzene **164** and benzyl 2-(benzyloxy)benzoate **157** 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**.



Scheme 31 *Reagents and conditions*: (i) *n*-BuLi, THF, –78 °C, 90 min, 72%; (ii) 5% Pd/C, H_2, 5 atm, rt, 24 h, 90%; (iii) CAN, CH_3CN, rt, 1.5 h, **168** 74% and **167** 15%

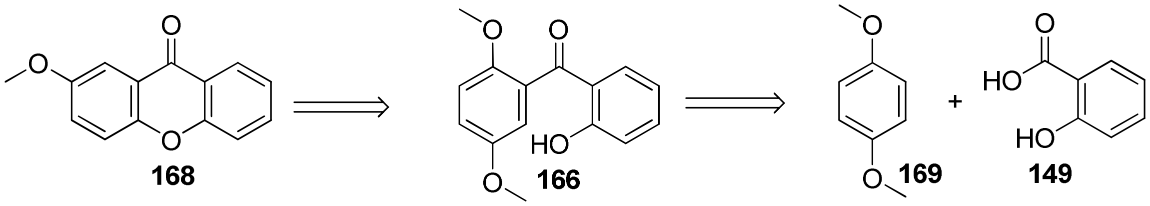
The aims of this project have therefore been divided into two parts. Firstly, it was aimed to reproduce and confirm the findings of Naidoo and elucidate the mechanism for both the xanthone and dione formation. Secondly with these methods in place, we hope to utilise the synthetic strategy developed for 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 salicyclic acid **157** and 1,4-dimethoxynaphthalene **148**.



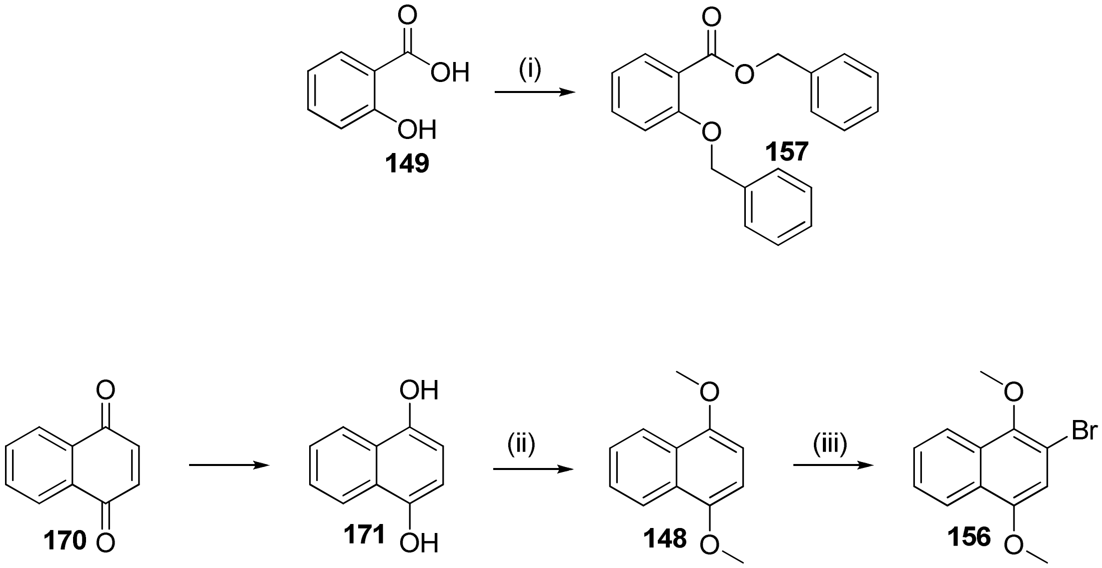
Scheme 32

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 salicyclic acid **157**and 1,4-dimethoxybenzene **169**.



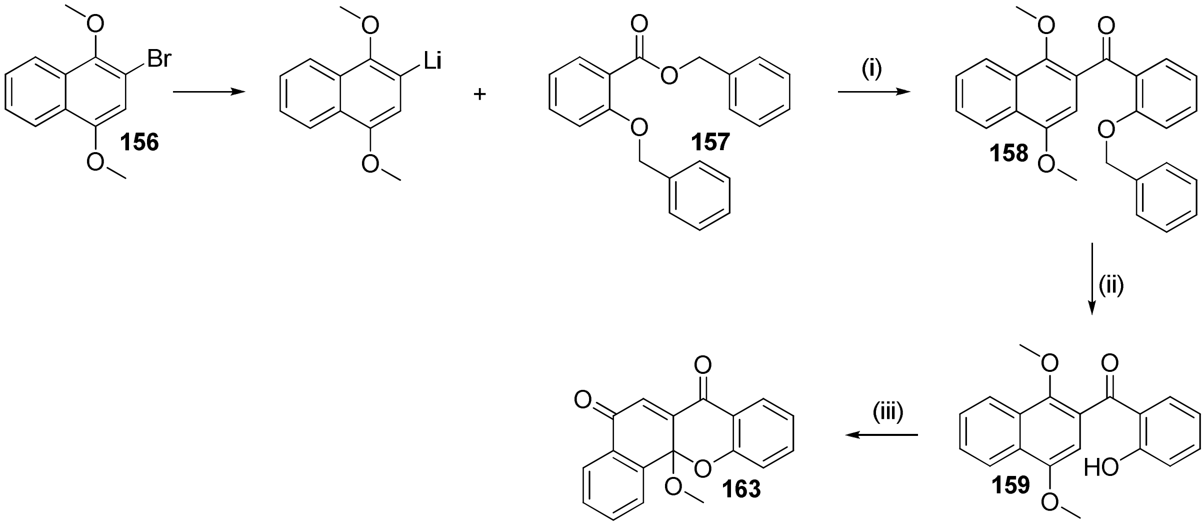
Scheme 33

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 salicyclic 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**.



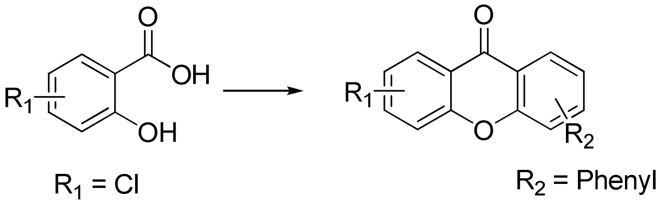
Scheme 34

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 salicyclic acids to afford more complex xanthones as shown in **Scheme 36**.

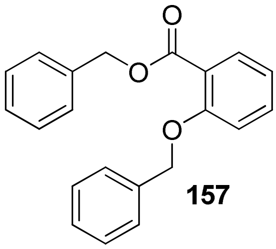


Scheme 36

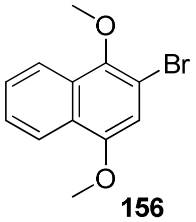
2 Chapter 2: Results and Discussion

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**).



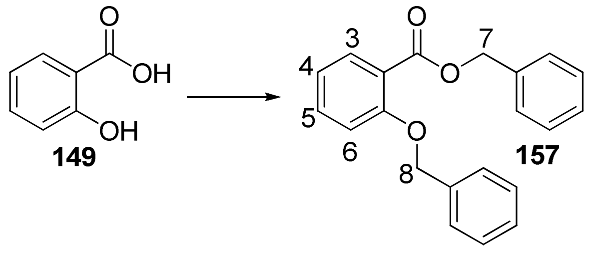
157



156

Figure 1

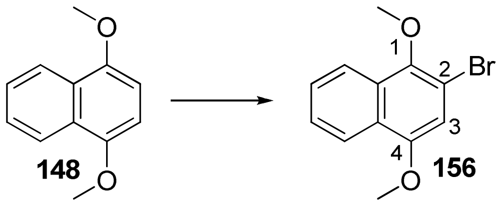
Salicyclic acid **149** was treated with 3 equivalents of both potassium carbonate and benzyl bromide in acetone. Concentrated solutions were found to be optimal for the synthesis of the dibenzylated product **157**. Both the carboxylic acid proton (pKa~ 5) and the phenolic proton (pKa~ 10) are acidic 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%.



Scheme 37 *Reagents and conditions*: (i) K_2CO_3, benzyl bromide, acetone, Δ, 18h, 94%

The presence of two singlets at δ 5.13 and 5.33 in the ^1H 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 ^1H 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].

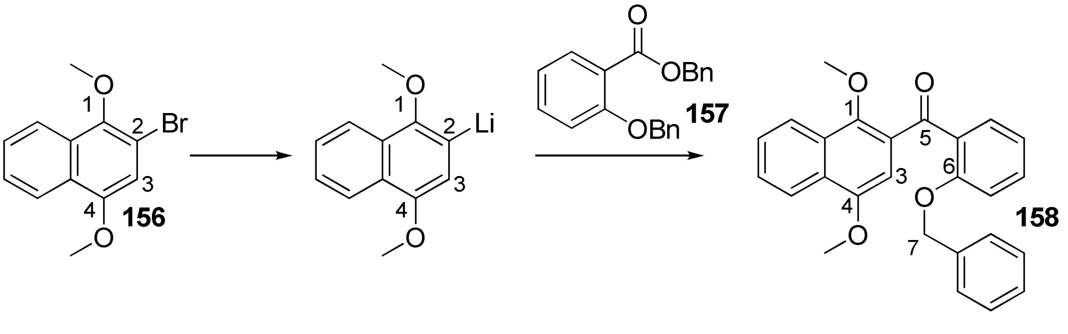
Commercially available 1,4-dimethoxynaphthalene **148** was treated with 1 mole equivalent of N-bromosuccinimide (NBS) in dichloromethane (DCM). NBS has been used as a mild brominating agent for polyalkoxyaromatic systems such as 1,4-dimethoxybenzene **169**. 1,4-Dimethoxynaphthalene **148** is electron 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, Δ, 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** 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[75].

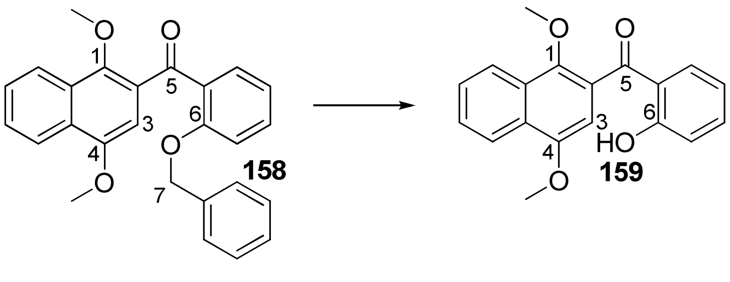
Having *O*-benzylated the salicyclic acid **149** to afford **157** and brominated the 1,4-dimethoxynaphthalene **148** to yield **156**, the formation of the ketone could be performed. This was achieved over two steps using halogen-metal exchange followed by coupling of the metalated species to the 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 ^{1}H and ^{13}C NMR spectra. The ^{1}H 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 benzophenenone 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**).



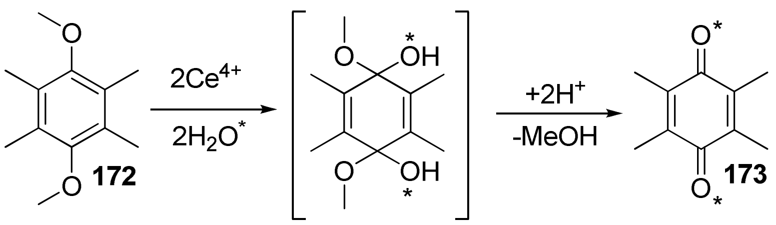
Scheme 40 *Reagents and conditions*: (i) 5% Pd/C, methanol, $H_{2(g)}$, 1 atm, 24h, 97%

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 δ 12.25, integrating for one proton suggesting the presence of a hydrogen-bonded hydroxyl group, and the absence of the singlet at δ 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 δ 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_2O (^{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**).

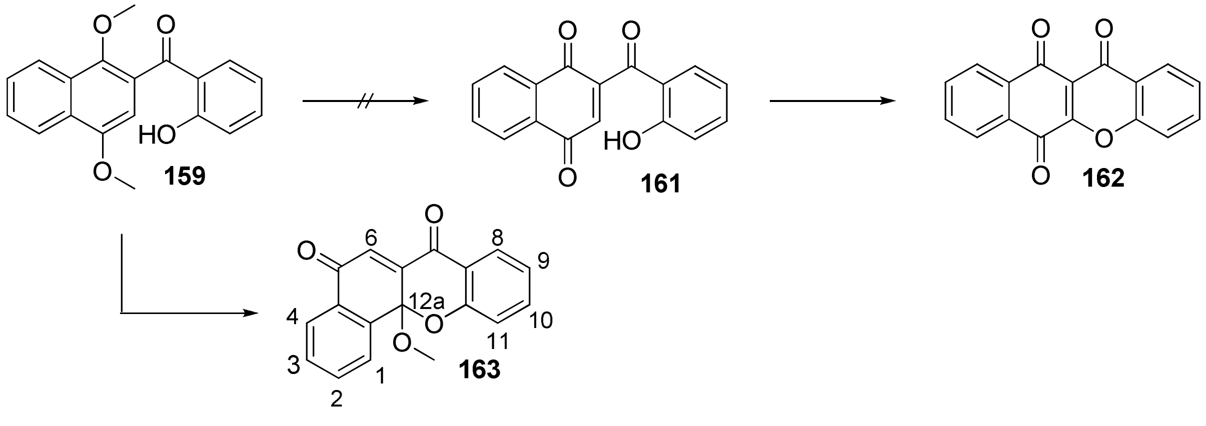


Scheme 41

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[77].

2.2.1 Synthesis of dione 163

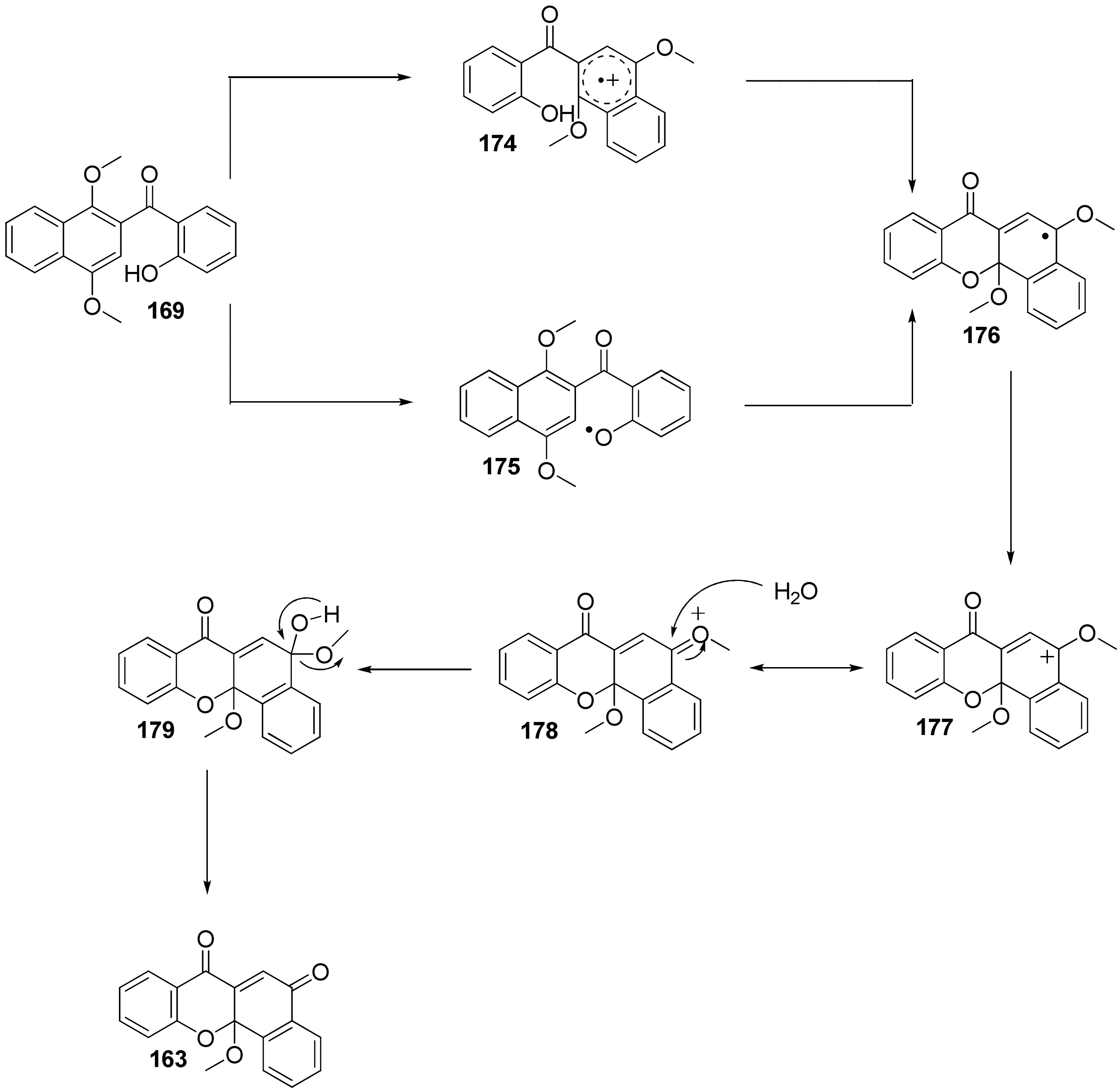
Unfortunately, when **159** was treated with ceric ammonium nitrate in aqueous acetonitrile, neither the expected quinone **161** nor the corresponding xanthone **162** was isolated from the reaction (**Scheme 30**). Surprisingly the reaction went to completion rather quickly and upon analysis the expected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



Scheme 30 *Reagents and conditions*: (i) CAN, $H_2O/CH_3CN/CHCl_3$, rt, DCM, Δ, 10 min, 72%

Upon analysis of the ^1H 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 ^1H 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[73]. This result confirmed Naidoo's unexpected finding.

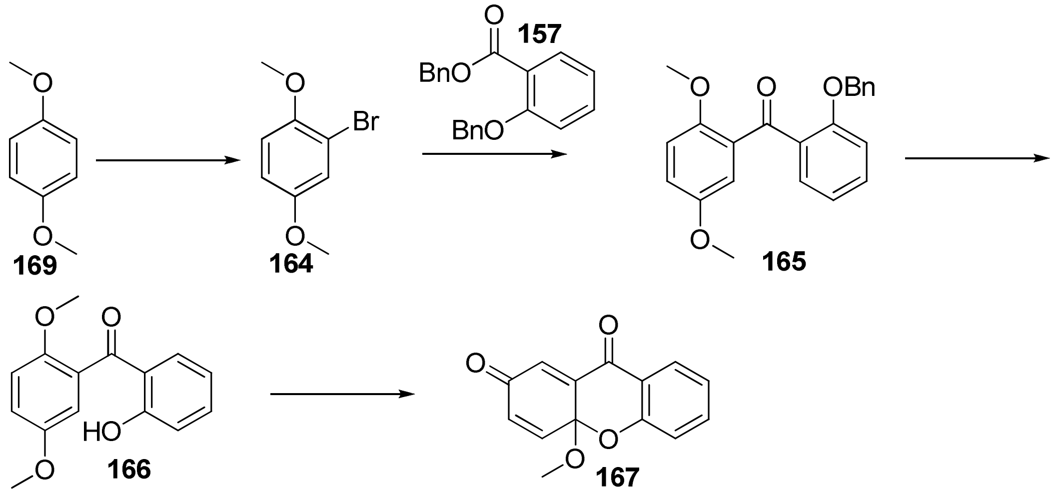
The mechanism postulated for the formation of **163** is shown in **Scheme 41**. It is believed that the CAN oxidises the dimethoxynapthalene system which results in a radical cation **174** or which may proceed via the phenoxy oxygen radical **175**. The aromatic radical cation can then undergo nucleophilic 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.



Scheme 41

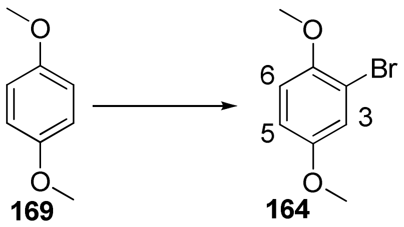
2.3 Synthesis of dione 167 and xanthone 168

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-5*H*-benzo[*c*]xanthenes-5,7(12a*H*)-dione **163** (**Scheme 42**).



Scheme 42

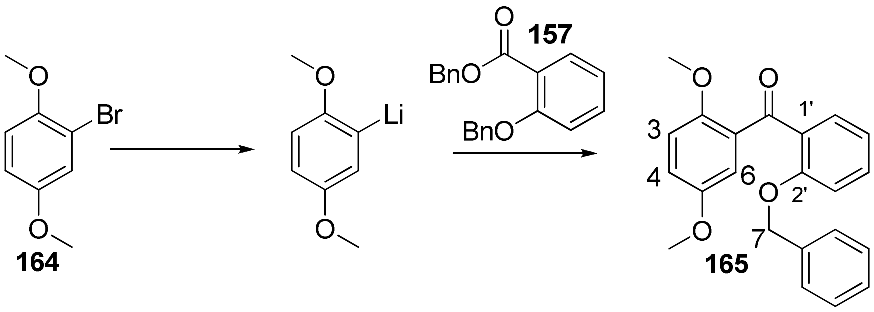
Commercially available 1,4-dimethoxybenzene **169** was treated with 1 mole equivalent of NBS in DCM and underwent electrophilic substitution to afford the halogenated product, 2-bromo-1,4-dimethoxybenzene **164**. The desired compound **164** was obtained in a yield of 89% as a colourless oil using the procedure by Bloomer and co-workers[78].



Scheme 43 *Reagents and conditions*: (i) NBS, DCM, Δ, 48 h, 89%

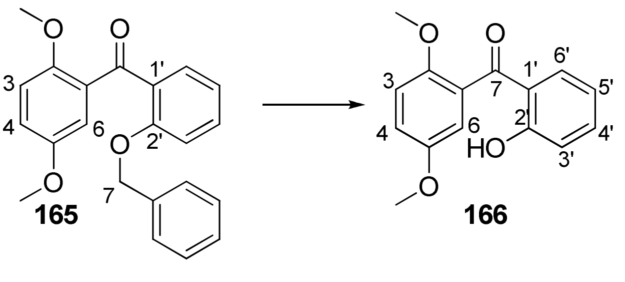
The ^{1}H NMR spectrum showed the presence of two singlets at δ 3.74 and 3.82, each integrating for three protons. These two signals correspond to the methoxy groups and appeared as two separate signals due to the loss in symmetry of the starting material **169** upon halogenation. The ^{1}H NMR spectrum 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 δ 154.0 and 150.3, which are characteristic of a carbon bonded to a methoxy group, and δ113.6 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 *Reagents and conditions*: (i) THF, –78 °C, *n*-BuLi (1.0 equiv.), 45 min, benzyl 2-(benzyloxy)benzoate, 30 min, 88%

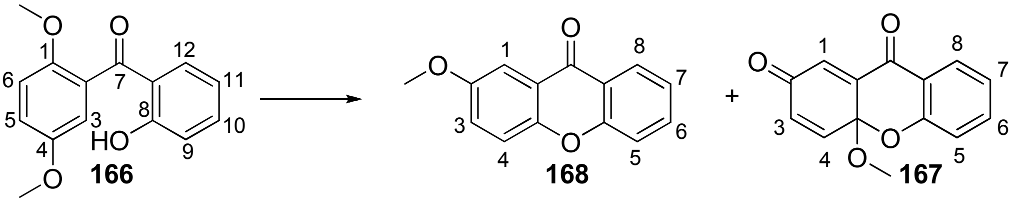
Confirmation that the reaction was successful for the synthesis of **165** was obtained from both the ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **165** showed a singlet at δ 4.94 integrating for two protons which was due to the methylene group. Another characteristic feature of **165** was the doublet of doublets at δ 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 δ 195.4 which further confirmed the presence of the carbonyl bridge. The peaks at δ 55.9 and 56.5 correspond to the methoxy group carbons while the signal at δ 70.1 was due to the methylene carbon. The ^{13}C NMR spectrum also showed three peaks at δ 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 *Reagents and conditions*: (i) 5% Pd/C, methanol, $H_{2(g)}$, 1 atm, 24 h, 89%

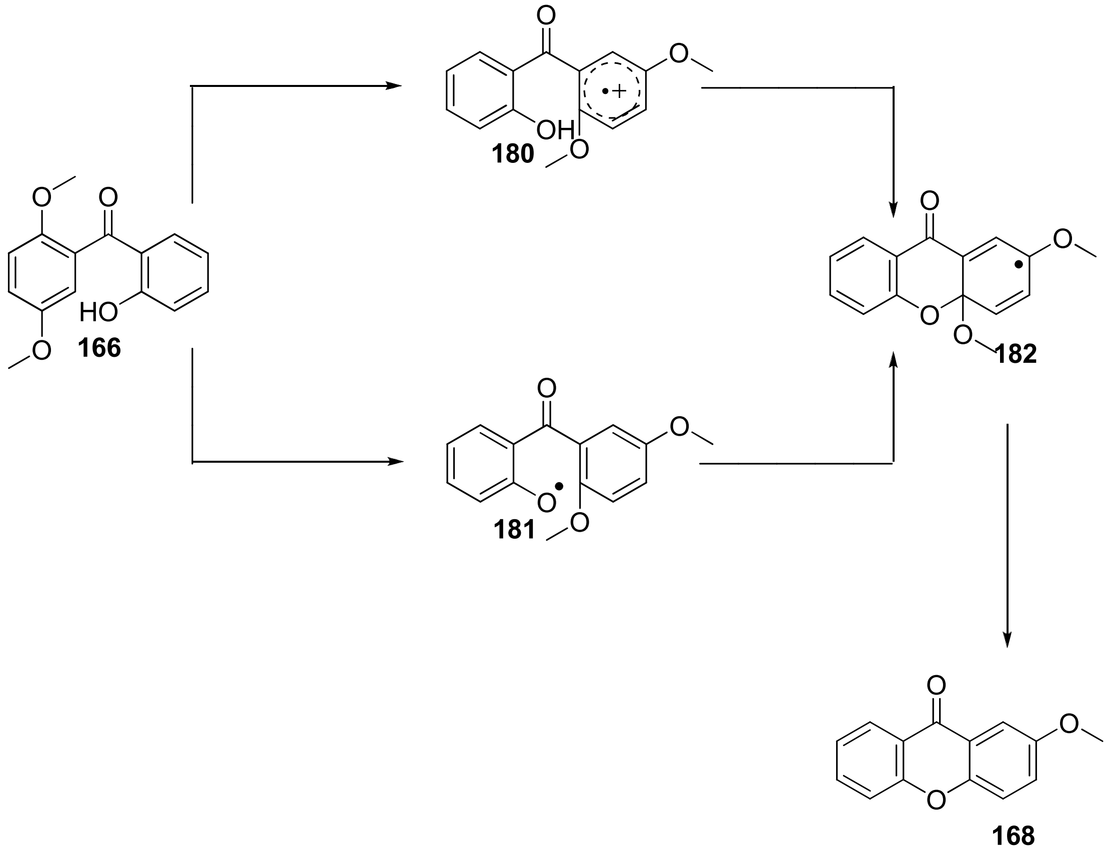
The ether **165**, was then subjected to hydrogenolysis in methanol to afford the phenol **166** in 89% yield. In the ^{1}H NMR spectrum of **166**, the signal for the methylene proton was no longer present while a new signal at δ 12.04 was observed which is characteristic of the proton of the phenol 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 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.



Scheme 46 *Reagents and conditions*: (i) CAN, $H_2O/CH_3CN/CHCl_3$, 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 δ 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 δ 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 δ 7.29 was assigned as 1-H. The ^{13}C NMR spectrum showed a signal at δ 176.0 which corresponds to the carbonyl group. The signals at δ 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.



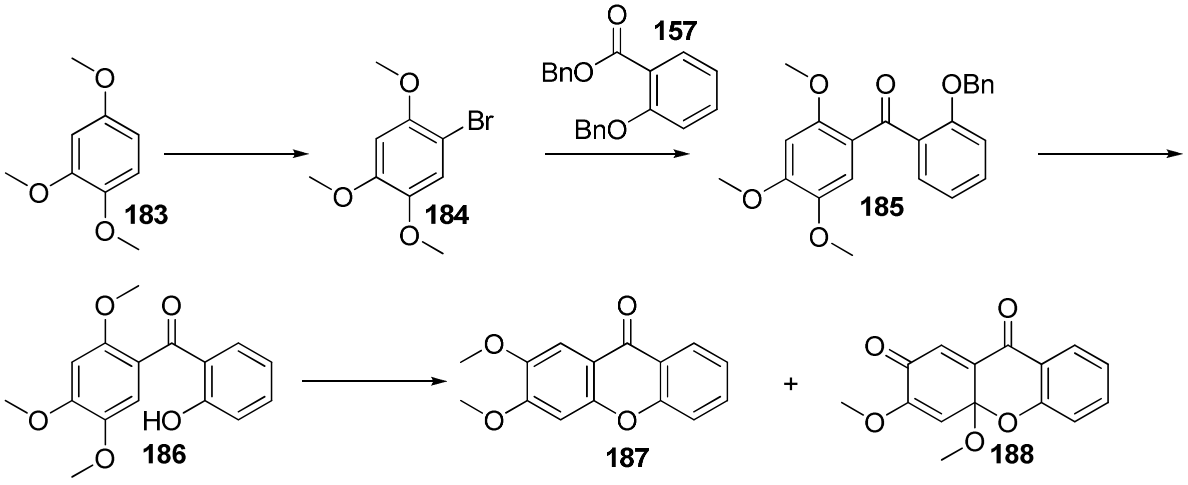
Scheme 47

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 δ 3.25 which is due to the methoxy involved in acetal formation. The ^{1}H NMR spectrum also showed a singlet at δ 6.81 which is characteristic of a quinone proton and was assigned 1-H. Furthermore, the doublet furthest downfield at δ 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 δ 185.1 and 180.9 which confirmed that the product contained two carbonyl carbons. The presence of the signal at δ 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 δ 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).

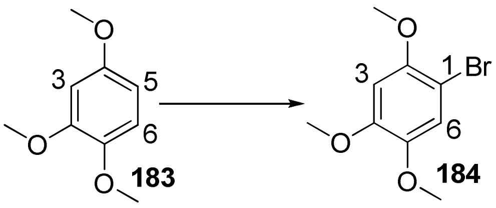
Having tested these CAN oxidation reactions on both substrates we wanted to try it on other substituted benzene precursors not tried by Naidoo. We therefore used 1,2,4-trimethoxybenzene **183** in this investigation. We envisaged a similar synthetic route as followed for the synthesis of 12a-methoxy-5*H*-benzo[*c*]xanthene-5,7(12a*H*)-dione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



Scheme 48

2.4 Synthesis of xanthone 187

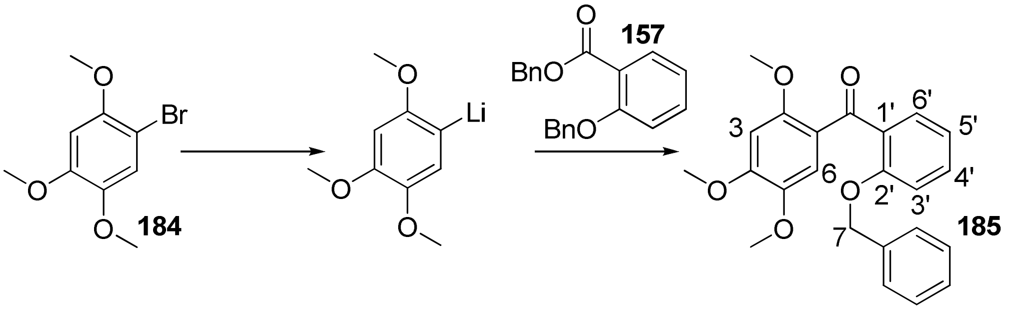
Commercially available 1,2,4-trimethoxybenzene **183** was treated with 1 mole equivalent of NBS in DCM which underwent electrophilic substitution to afford the known halogenated product, 1-bromo-2,4,5-trimethoxybenzene **184**. The desired compound **184** was furnished in 89% yield as a peach coloured 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%

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].

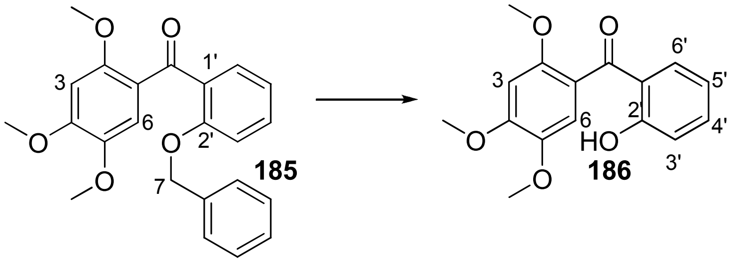
Having prepared the starting materials successfully, we were now able to construct the required precursor ketone. Lithiation of 1-bromo-2,4,5-trmethoxybenzene **184** using *n*-BuLi (1.0 equiv.) followed by the benzoylation of the lithiated species with benzyl 2-(benzyloxy)benzoate **157** afforded the benzophenone intermediate, [2-(benzyloxy)phenyl](2,4,5-trimethoxyphenyl)methanone **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 δ 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.

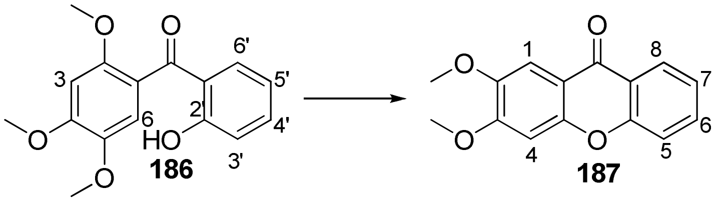
The benzophenenone intermediate **185** then underwent a hydrogenolysis reaction to facilitate the removal of the *O*-benzyl substituent. This was easily achieved by stirring **185** in methanol with 5% Pd/C under a hydrogen atmosphere at a pressure of 1 atm to give the phenol **186** (**Scheme 51**).



Scheme 51 *Reagents and conditions*: (i) 5% Pd/C, methanol, $H_{2(g)}$, 1 atm, 24 h, 93%

The formation of the phenol **186** was confirmed spectroscopically, using ^1H and ^{13}C NMR spectra. The most significant change in the spectrum of the starting material **185** was the formation of a singlet at δ 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 δ 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 δ 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 ^1H NMR spectrum. As the first indication, the singlet previously obtained for the phenol was now absent. The doublet of doublets furthest downfield at δ 8.32 was assigned 8-H due to electron withdrawing effects of the carbonyl group. This aromatic proton showed both *ortho* and *meta* coupling to 7-H and 6-H with coupling constants J = 8.0 and 1.0 Hz respectively. A singlet at δ 7.64 was assigned to 1-H and showed no coupling due to its position adjacent to the carbonyl group. The doublet at δ 6.88 was assigned as 4-H and showed very small *para* coupling to 1-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].

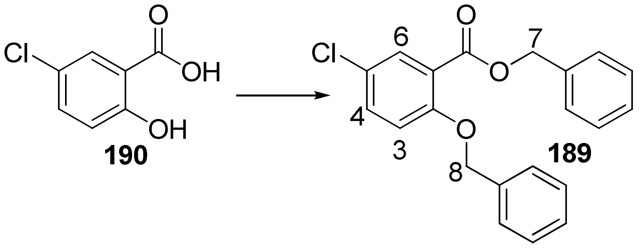


Scheme 52 *Reagents and conditions*: (i) CAN, $H_2O/CH_3CN/CHCl_3$, rt, 10 min, 91%

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.

2.5 Synthesis of Ester 189

Commercially available 5-chlorosalicyclic 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% (**Scheme 53**).

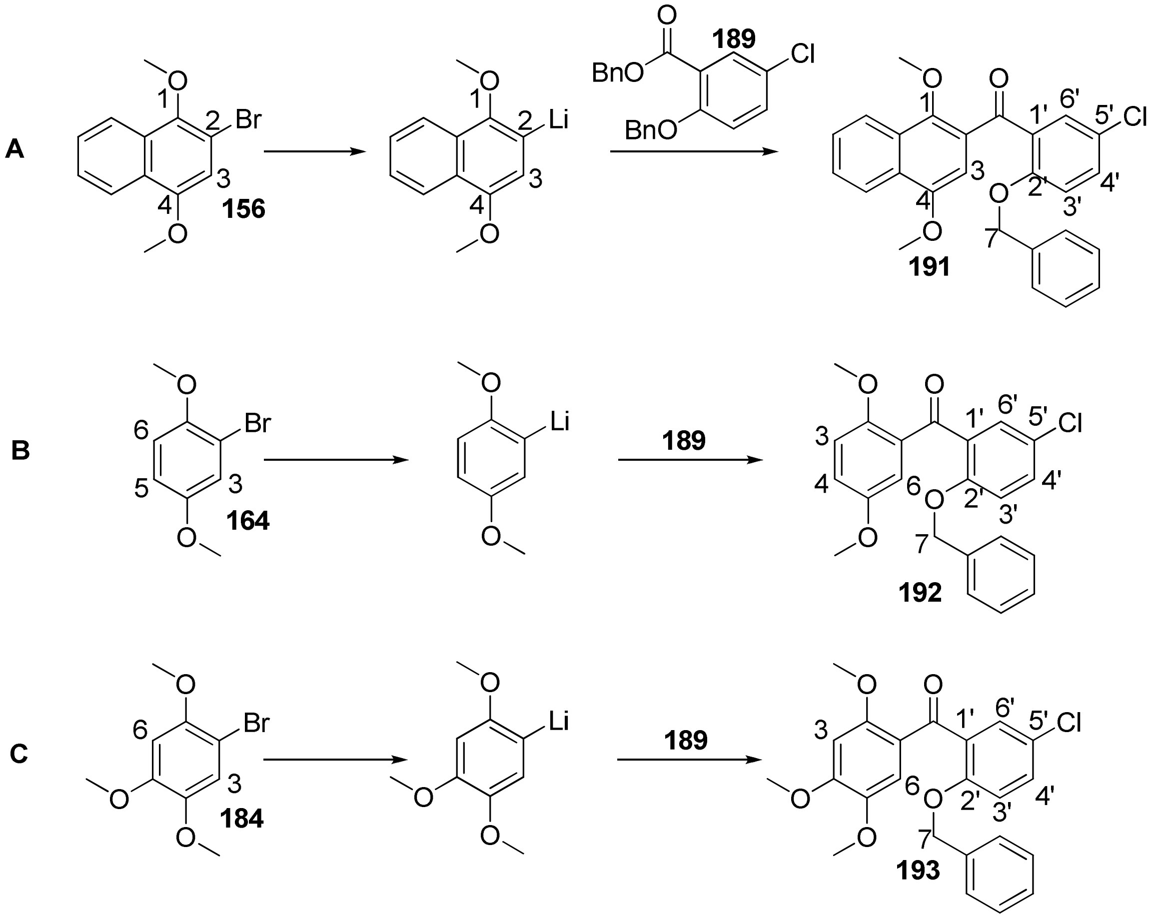


Scheme 53 *Reagents and conditions*: (i) K_2CO_3, benzyl bromide, acetone, 60 °C, 18 h, 85%

Confirmation that the desired product **189** had been formed was evident in the ^{1}H NMR spectrum with the appearance of two singlets at δ 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 δ 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 δ 71.0 and 67.1 which correspond to the two methylene carbons. As observed in the ^{1}H NMR spectrum, the signal at δ 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 benzoylation of the lithiated 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 δ 4.86. Furthermore, the ^{1}H NMR spectrum showed a doublet at δ 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 δ 194.7 which is characteristic for a carbonyl carbon. Further confirmation was the presence of the signal at δ 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

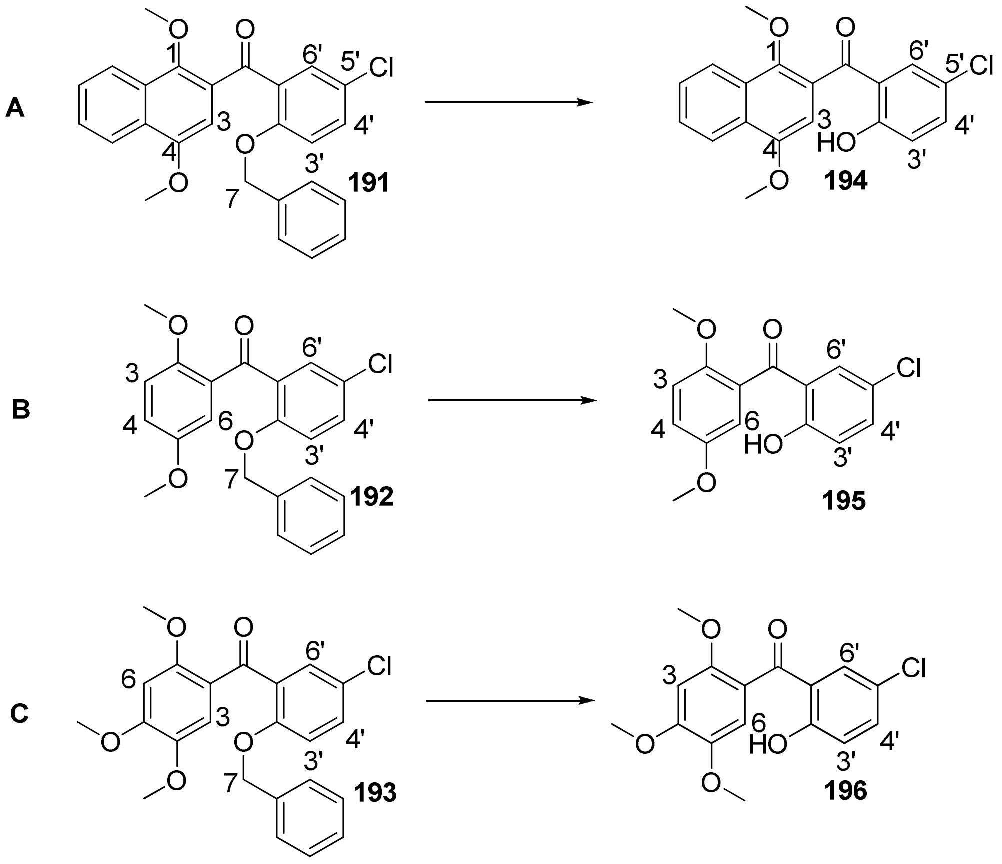
The most significant observation in the ^{1}H NMR spectrum of compound **192** is the presence of a singlet due to the benzyl methylene protons which occurred at δ 4.91. In the ^{13}C NMR spectrum there was a carbonyl peak at δ 193.8 indicative of a ketone, as well as a peak at δ 70.5 indicating the 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 δ 4.95, integrating for two protons. The aromatic region for the product **193** was similar to that of its precursors **184** and **189**. In the ^{13}C NMR spectrum, the presence of a peak at δ 192.3 was indicative of a ketone carbon. A signal at δ 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.



Scheme 55 *Reagents and conditions*: (i) 5% Pd/C, EtOAc, $H_{2(g)}$, 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[81]. 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.

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 $C_{19}H_{14}O_4Cl$.

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**.

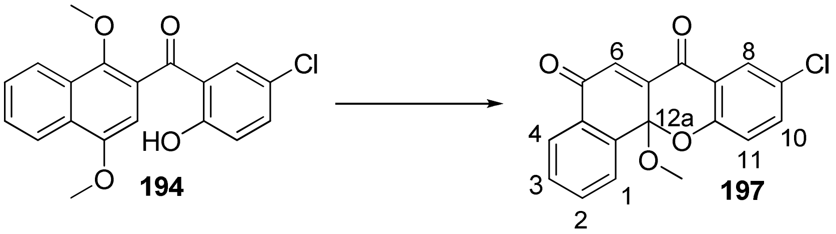
3. Equation C

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 δ 12.04 in the ^{1}H NMR spectrum, indicative of the new free phenol substituent. Moreover, the characteristic singlet previously occurring at δ 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 δ 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**).

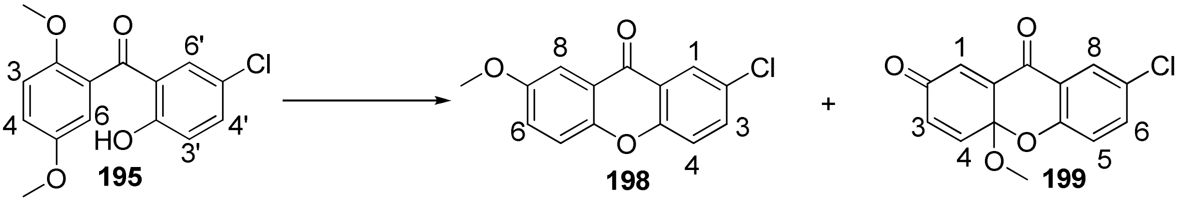


Scheme 56 *Reagents and conditions*: (i) CAN, $H_2O/CH_3CN/CHCl_3$, rt, 10 min, 93%

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 δ 3.02 which integrated for three protons and which was assigned to the methoxy group. Moreover, the absence of the phenol signal at δ 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 δ 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 δ 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**).



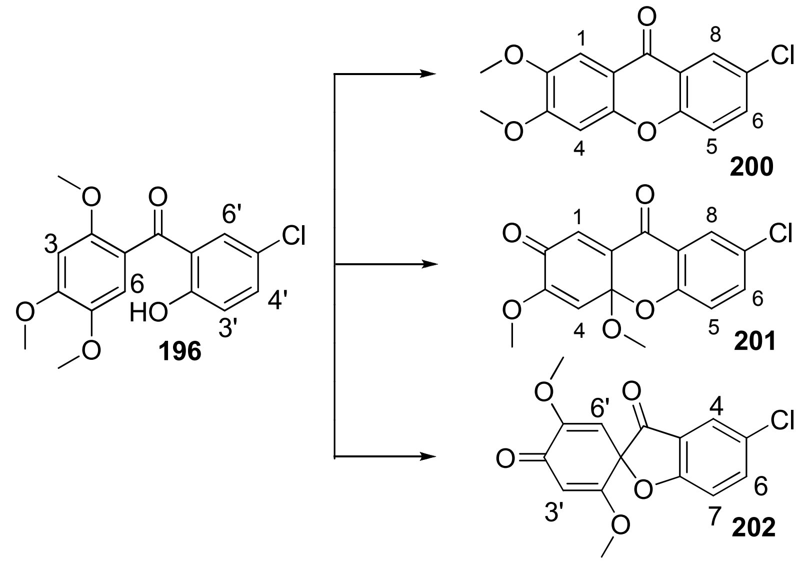
Scheme 57 *Reagents and conditions*: (i) CAN, $H_2O/CH_3CN/CHCl_3$, rt, 10 min, **198** 63%, **199** 17%

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 δ 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 δ 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 δ 7.29 was assigned 1-H. The ^{13}C NMR spectrum showed a signal at δ 176.0 which corresponds to the carbonyl group. The signals at δ 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 δ 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 δ 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 δ 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 δ 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.



Scheme 58 *Reagents and conditions*: (i) CAN, $H_2O/CH_3CN/CHCl_3$, rt, 10 min, **200** 21%, **201** 29%, **202** 9%.

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 δ 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 δ 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 δ 5.94 integrating for one proton was also observed and was assigned as 4-H. A doublet furthest upfield at δ 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 δ 180.2 and 179.9 which corresponds to the two carbonyl groups, the quinone carbonyl and the xanthone carbonyl respectively. Furthermore, the signal at δ 98.2 has become the familiar signal for the quaternary carbon central to acetal formation.

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 δ 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 δ 7.62 which integrated for one proton and was assigned 1-H. The methoxy groups were located at δ 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 δ 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 δ 5.76 and 5.17 and were assigned 3'-H and 6'-H respectively. Another feature is the two singlets at δ 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 δ 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**.

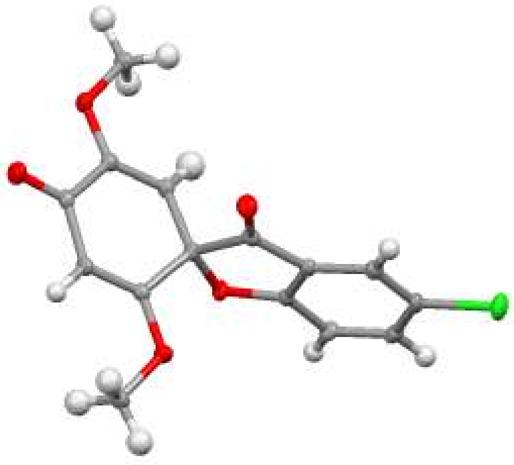
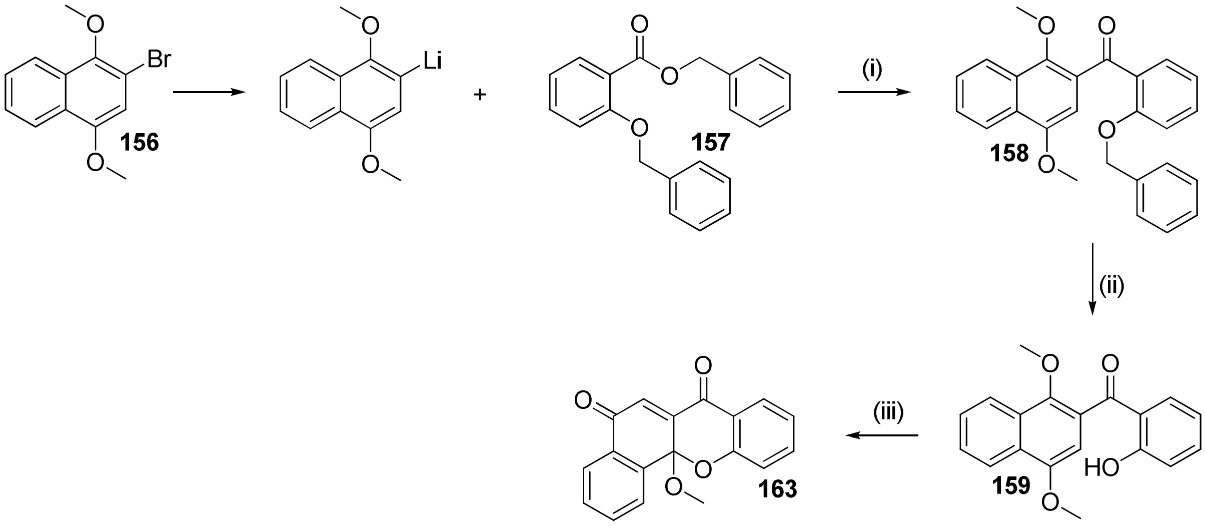


Figure 2: ORTEP diagram for the crystal structure (5-chloro-2',5'-dimethoxy-3*H*-spiro[benzofuran-2,1'-cyclohexa[2,5]diene]-3,4'-dione **202**.

3 Chapter 3: Conclusions and Future work

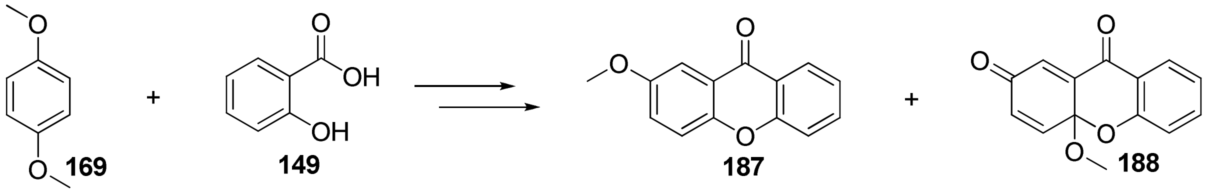
3.1 Summary of results achieved

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, $H_{2(g)}$, 1 atm, 24 h, 97%, (iii) CAN, $H_2O/CH_3CN/CHCl_3$, 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 **169bScheme 60**).

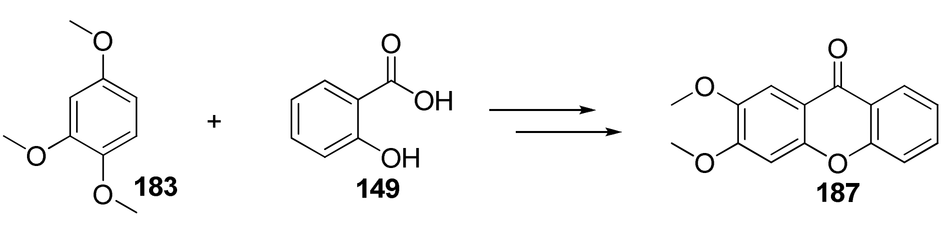


Scheme 60

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

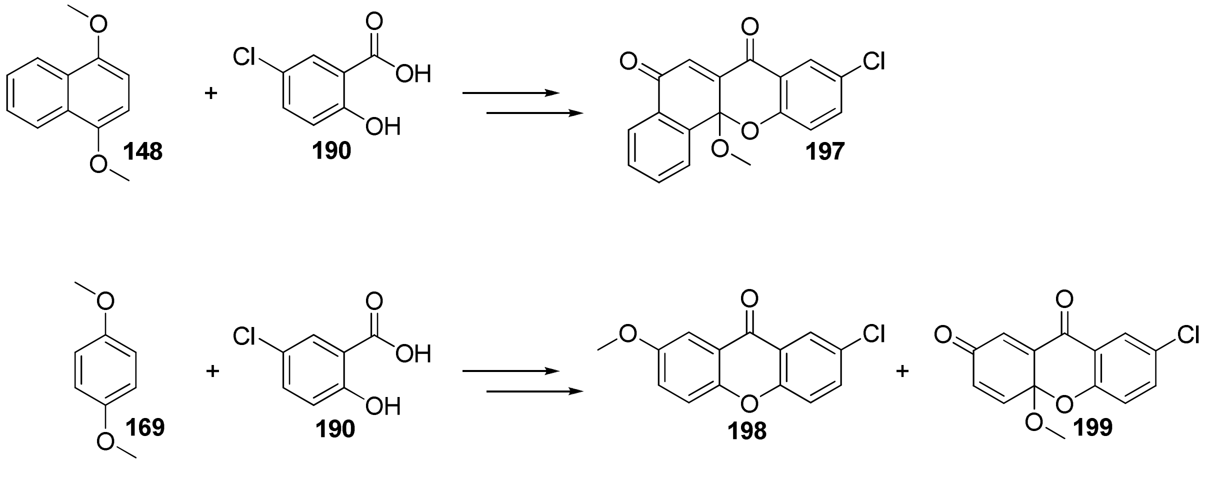
The study was then expanded to test the flexibility and the efficiency of the methodology. Substitution patterns of both the aryl and the acid were varied to determine the effect CAN mediated oxidations have in the formation of xanthone and dione analogues.

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**).



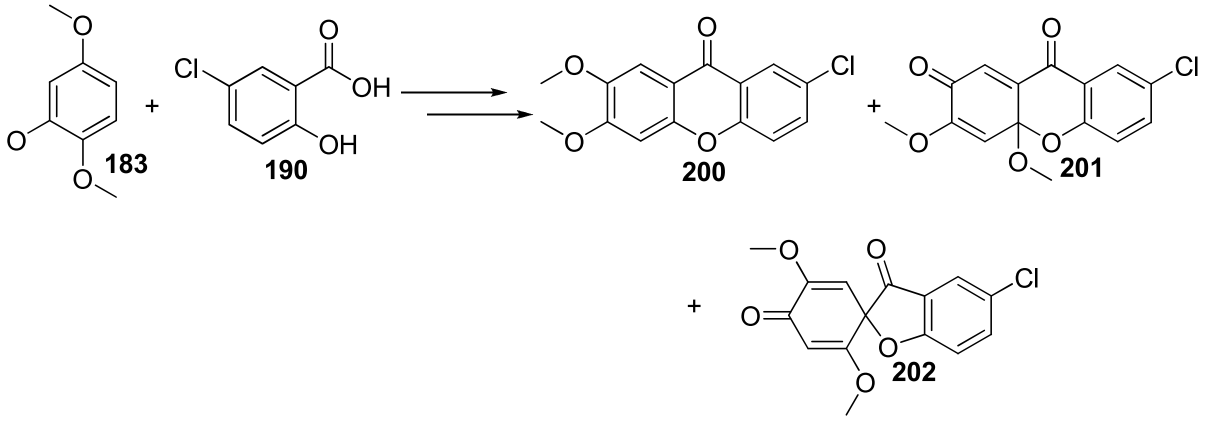
Scheme 61

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

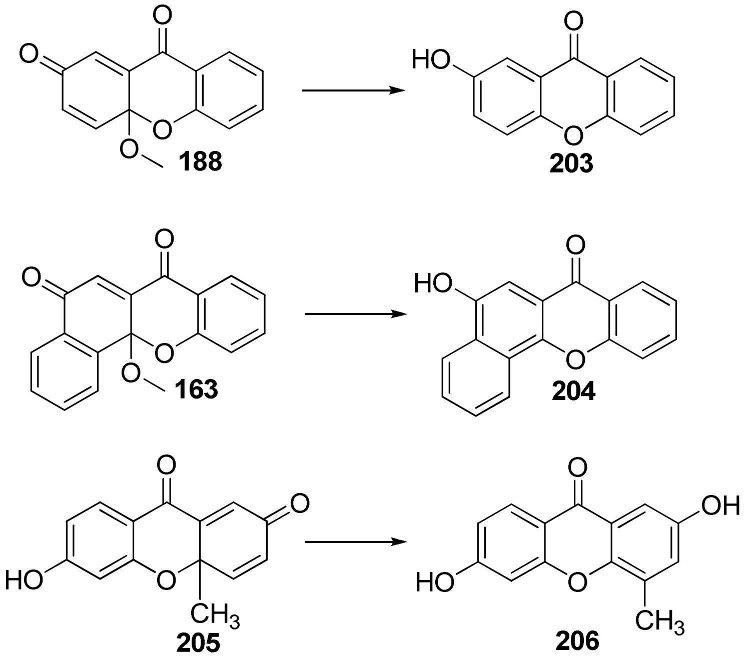
The final transformation commenced from 5-chlorosalicyclic acid **190** and 1,2,4-trimethoxybenzene **183** to afford the xanthone **200**, dione **201** and the unexpected spiro-compound **202**, in yields of 21%, 29% and 9% respectively (**Scheme 63**).



Scheme 63

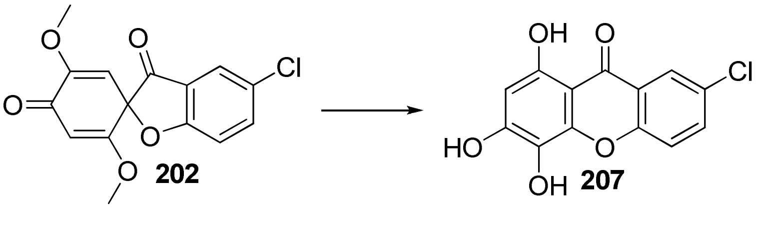
3.2 Future prospects for xanthone synthesis

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**)[82].



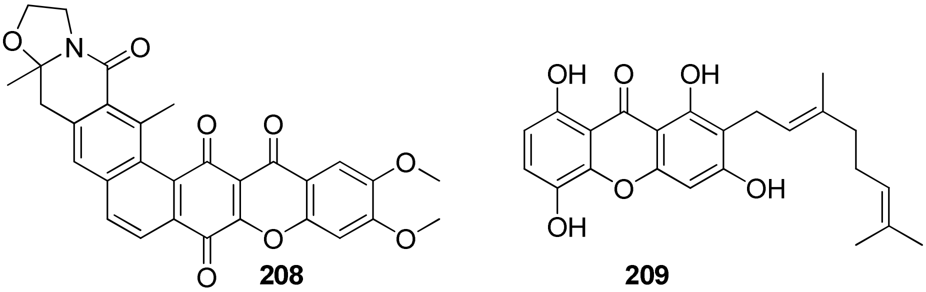
Scheme 64

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 xanthones such as **208** and **209**, which are believed to be biologically active against cancer, malaria as well as HIV could be prepared (**Scheme 66**).



208 **209**

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 (4Ǻ) 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*.[83]

4.1.2 Chromatography

Thin layer chromatography (TLC) was performed on aluminium-backed Machery-Nagel ALUGRAMSil G/UV$_{254}$ 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 (ν/cm^{-1}).

Hydrogen (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance-300 at 300.13MHz 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 ^1H 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.

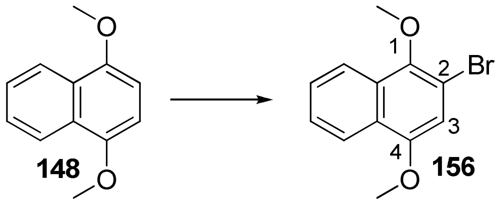
Some high resolution electrospray ionization mass spectra (ESI-FTMS) were recorded at the Technical University Dortmund, Germany, using a Thermo LTQ Orbitrap (high resolution mass spectrometer from Thermo Electron) coupled to an "Accela" HPLC System supplied with a "Hypersil GOLD" column (Thermo Electron). 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_{α} radiation (50kV, 30mA) using the APEX 2[84] 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 using the program *XPREP*[85]. The crystal structure was solved by direct methods using *SHELXTL*[86]. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *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 SHELXTL, PLATON[87] and ORTEP-3.[88]

4.1.4 Other general procedures

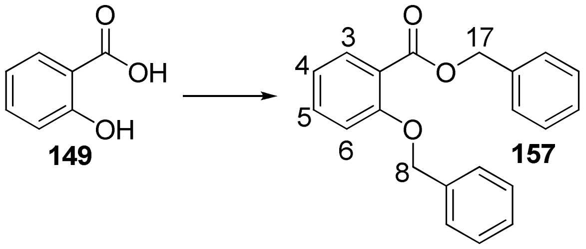
All reactions, unless otherwise stated, were carried out under an inert atmosphere and the reaction vessels were dried in an oven. *In vacuo* refers to the removal of solvent under reduced pressure (~20 mm Hg, 45°C) on a rotary evaporator and final drying on an oil pump (~1-2 mm Hg) at ambient temperature until constant mass was achieved.

4.2 Synthesis of 2-bromo-1,4-dimethoxynaphthalene 156



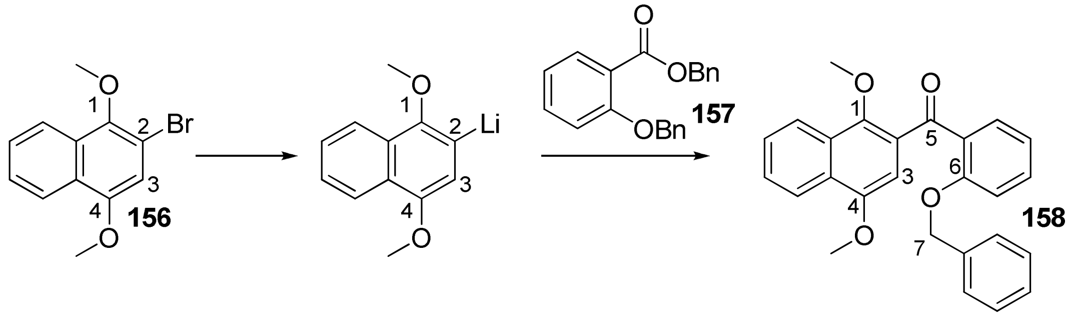
NBS (3.80 g, 0.0214 moles) was added to the 1,4-dimethoxynaphthalene **148** (4.00 g, 0.0213 moles) in dry CH_2Cl_2 (30 ml). The mixture was stirred for 18 h at rt. The mixture was washed with an aqueous saturated sodium sulfite solution (25 ml) and extracted into CH_2Cl_2 (3 × 50 ml). The organic layer 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): v_{max} (cm^{-1}): 1662, 1615, 1576, 1505, 1458, 1440, 1410; ^1H NMR ($CDCl_3$, 300MHz) δ= 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) δ= 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



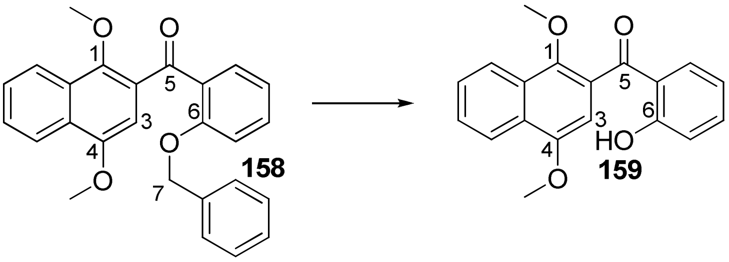
2-Hydroxybenzoic acid **149** (5.05 g, 0.0366 moles) was dissolved in dry acetone (120 ml). Dry potassium carbonate (15.0 g, 0.109 moles) was added and the mixture left stirring at rt for 10 mins. Benzyl bromide (12.9 ml, 0.109 moles) was added to the stirring mixture and the solution was heated under reflux for 18 h under a N$_2$ atmosphere. The cooled reaction mixture was filtered through celite, which was washed with dry acetone (3 × 50 ml). The solvent was removed *in vacuo* and the residue dissolved in CH$_2$Cl$_2$ (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 MgSO$_4$ 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): v_{max}(cm^{-1}): 1716, 1598, 1580, 1495, 1466; ^{1}H NMR (CDCl$_3$, 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); ^{13}C NMR (CDCl$_3$, 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



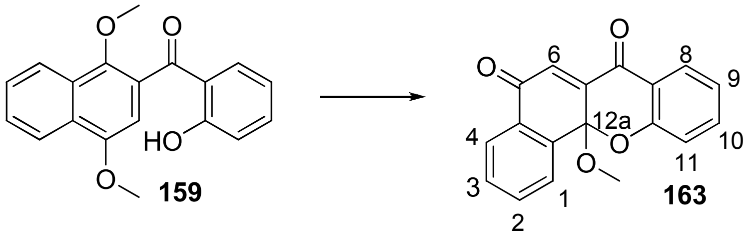
2-Bromo-1,4-dimethoxynaphthalene **156** (4.05 g, 0.0152 moles) was dissolved in dry THF (20 ml) and stirred at -78°C for 5 mins under an N_2 atmosphere. *n*-Butyl lithium (1.2 M, 0.015 moles, 18 ml) was added dropwise at -78°C and the mixture stirred at -78°C for 45 mins under N_2. The lithiated mixture 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 N_2 atmosphere. The mixture was quenched with a saturated aqueous solution of NH_4Cl (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 $MgSO_4$. 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): $v_{max}(cm^{-1})$: 1734, 1633, 1619, 1594, 1508, 1486, 1449, 1408; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{26}H_{22}O_4$, 398.1518, found 398.1523.

4.5 Synthesis of (1,4-dimethoxynaphthalen-2yl)(2-hydroxyphenyl)methanone 159



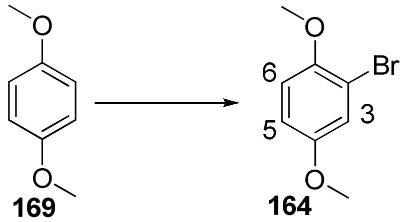
5% Pd/C (0.25 g) was added to (2-(benzyloxy)phenyl)(1,4 dimethoxynaphthalen-2-yl) methanone **158** (2.50 g, 6.27 mmoles) in dry MeOH (30 ml). The mixture was stirred under a H_2 atmosphere at a pressure of 4.5 atms for 24 h. The mixture was filtered through celite and washed with CH_2Cl_2 (3 × 50 ml). The organic layer was dried over $MgSO_4$. 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): $v_{max}(cm^{-1})$: 2970, 1620, 1604, 1592, 1508, 1486, 1456, 1410; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{19}H_{16}O_4$, 308.1049, found 308.1048.

4.6 Synthesis of 12a-methoxy-5*H*-benzo[c]xanthene-5,7 (12aH)-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 × 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): $\nu_{max}(cm^{-1})$: 1713, 1689, 1667, 1636, 1607, 1596, 1459; ^{1}H NMR ($CDCl_3$, 300MHz) δ= 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) δ= 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.

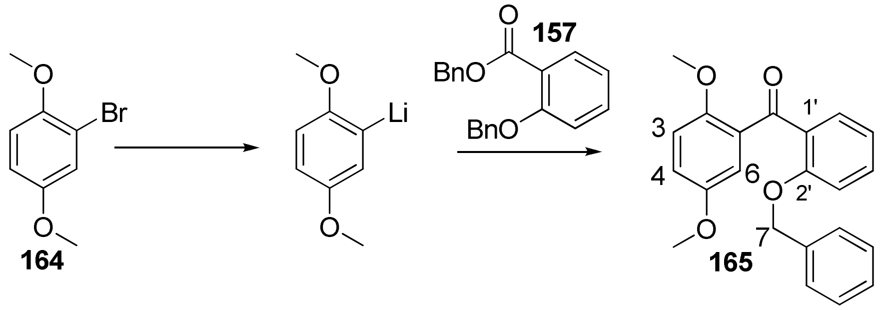
4.7 Synthesis of 2-bromo-1,4-dimethoxybenzene 164[78]



NBS (6.65 g, 37.3 moles) was added to the 1,4-dimethoxybenzene **169** (5.02 g, 36.3 mmoles) in dry CH_2Cl_2 (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 CH_2Cl_2 (3 × 50 ml) and the organic layer was dried over $MgSO_4$. 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): $\nu_{max}(cm^{-1})$: 1607, 1575, 1530, 1460, 1436; ^1H NMR ($CDCl_3$, 300MHz) δ= 7.11 (s, 1H), 6.91–6.74 (m, 2H), 3.82 (s, 3H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 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).

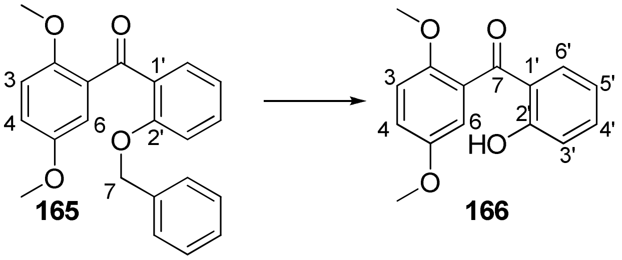
.

4.8 Synthesis of [2-(benzyloxy)phenyl](2,5-dimethoxyphenyl)methanone 165



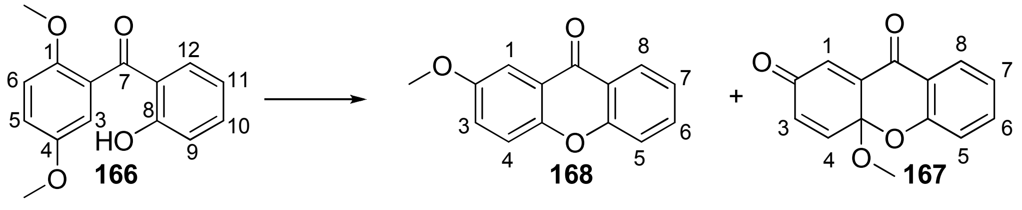
2-Bromo-1,4-dimethoxybenzene **164** (2.51 g, 0.0115 moles) was dissolved in dry THF (15 ml) and stirred at -78°C for 5 mins under an N_2 atmosphere. *n*-Butyl lithium (1.2 M, 0.0115 moles, 14 ml) was added dropwise at -78°C and the mixture stirred at -78°C for 45 mins under N_2. The lithiated mixture was added dropwise to the benzyl 2-(benzyloxy) 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 N_2. The mixture was quenched with a saturated solution of NH_4Cl (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 $MgSO_4$. 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): $v_{max}(cm^{-1})$: 1644, 1587, 1491, 1448, 1419; ^1H NMR ($CDCl_3$, 300MHz) δ= 7.59 (dd, *J* = 7.6, 1.7, 1H), 7.48–7.32 (m, 2H), 7.22–7.15 (m, 2H), 7.12–7.6.88 (m, 6H), 6.76 (d, *J* = 7.4, 1H), 4.94 (s, 2H), 3.75 (s, 3H), 3.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 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 $C_{22}H_{20}O_4$, 348.1362, found 348.1346.

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



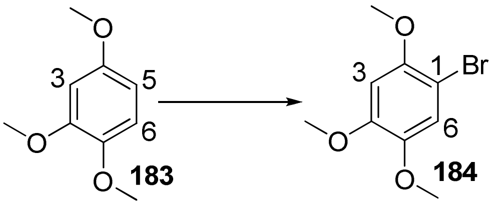
5% Pd/C (0.05g) was added to (2-(benzyloxy)phenyl)(2,5 dimethoxyphenyl)methanone **165** (1.00 g, 0.00287 moles) in MeOH (30 ml). The mixture was stirred under a H_2 atmosphere at a pressure of 4.5 atms for 24 h. The mixture was filtered through celite and washed with CH_2Cl_2 (3 × 50 ml). The organic layer was dried over $MgSO_4$. 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; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{15}H_{14}O_4$, 258.0892, found 258.0883.

4.10 Synthesis of 4a-methoxy-9*H*-xanthen-2,9(4a*H*)-dione 167 and 2-methoxy-9*H*-xanthen-9-one 168



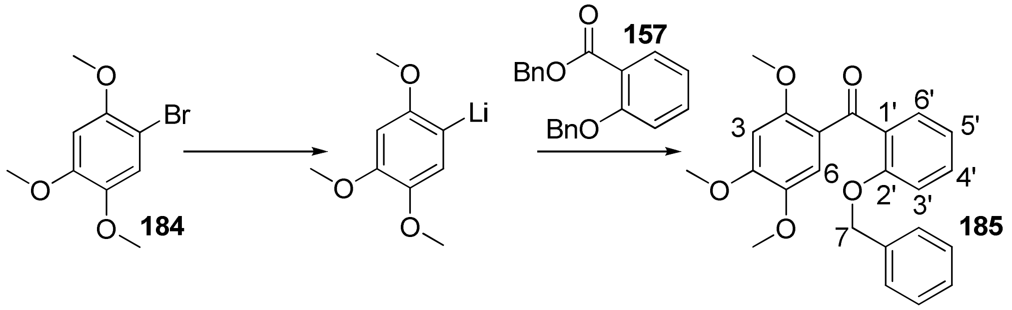
CAN (1.06 g, 1.94 mmoles) in water (5 ml) was added dropwise to a stirring mixture of (2,5 dimethoxyphenyl)(2-hydroxyphenyl)methanone (**166**) (0.100 g, 0.388 mmoles) in MeCN (10 ml) and $CHCl_3$ (2.5 ml). The mixture was then stirred at rt for 24 h. The reaction mixture was filtered through celite and washed with EtOAc (3 × 25 ml). The organic layer was washed consecutively with a saturated aqueous $NaHCO_3$ solution (25 ml), brine (25 ml) and water (25 ml). The organic layer was then dried over $MgSO_4$. 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-9*H*-xanthen-9-one (**168**). M.p. 131-133°C (EtOAc), lit. M.p.[56] 134-135°C; IR (solid): v_{max}(cm^{-1}): 1647, 1614, 1488, 1462, 1430; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{14}H_{10}O_3$, 226.0630, found 226.0620. 4a-Methoxy-9*H*-xanthen-2,9(4a*H*)-dione (**167**). M.p. 110-112°C (EtOAc); IR (solid): v_{max}(cm^{-1}): 1693, 1669, 1644, 1604, 1577, 1464; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{14}H_{10}O_4$, 242.0579, found 242.0568.

4.11 Synthesis of 1-bromo-2,4,5-trimethoxybenzene 184[80]



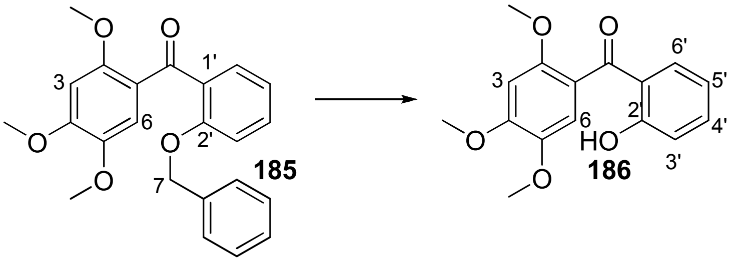
In a 100 cm^3 RB flask equipped with a reflux condenser, *N*-bromosuccinimide (5.61 g, 30.8 mmol) was added to a clear solution of 1,2,4-trimethoxybenzene **183** (3.65 ml, 5.18 g, 30.8 mmol) in dry CH_2Cl_2 (30 ml). The reaction mixture was then heated under N_2 at reflux for 48 h, during which time 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 CH_2Cl_2 (3 × 50 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 (10% EtOAc /Hexane) to afford product **184** as a peach coloured oil (8.1 g, 70%). ^{1}H NMR ($CDCl_3$, 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 185



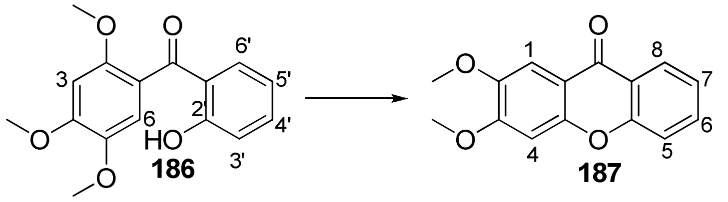
Following a similar procedure as for the preparation of **158**, 1-bromo-2,4,5-trimethoxybenzene **184** (2.03 g, 8.23 mmol) and **157** (3.440 g, 10.81 mmol) resulted in the formation of a yellow solid **185** (2.10 g, 52%) after flash silica gel chromatography (10% EtOAc /Hexane). M.p. 97-102°C; IR (solid): v_{max}(cm^{-1}):1633, 1597, 1508, 1449, 1434, 1401; ^{1}H NMR (CDCl$_3$, 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); ^{13}C NMR (CDCl$_3$, 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 $C_{23}H_{23}O_5$ (M + H), 379.1545, found 379.1543.

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



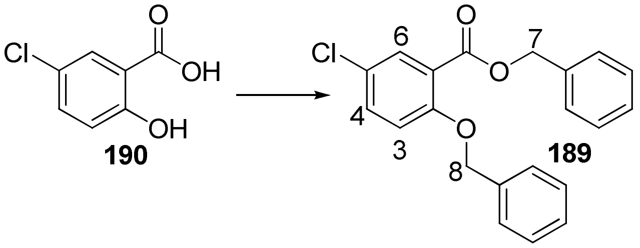
Following a similar procedure as for the preparation of **159**, (2-(benzyloxy)phenyl)(2,4,5-trimethoxyphenyl)methanone **185** (1.013 g, 2.677 mmol) was stirred under a H_2 atmosphere in MeOH (50 ml) with 10% Pd/C (0.0518 g) to yield after work-up and silica gel chromatography (20% EtOAc /Hexane) a yellow solid **186** (0.7501 g, 93%). mp. 107-110°C; IR (solid): ν_{max}(cm^{-1}): 1613, 1590, 1521, 1483, 1467, 1439, 1403; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{16}H_{17}O_5$ (M + H), 289.1076, found 289.1081.

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



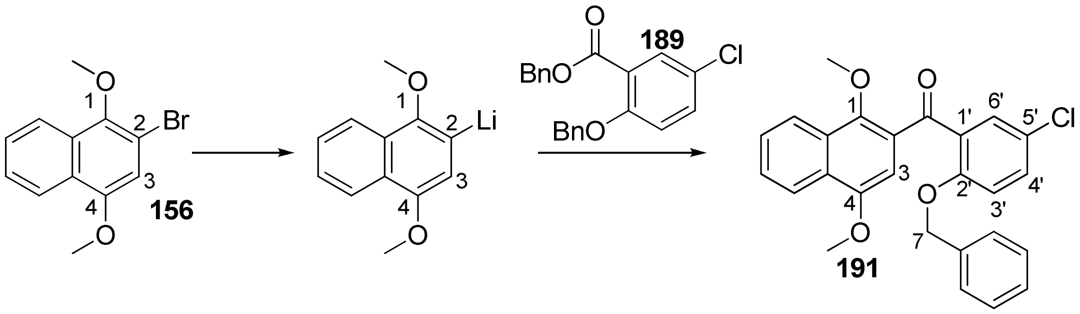
Following a similar procedure as for the preparation of **163** hydroxyphenyl(2,4,5-trimethoxyphenyl)methanone **186** (269 mg, 0.931 mmol) was treated with CAN (2.200 g, 4.013 mmol) to give compound **187** (210 mg, 91%) as white grains after flash silica gel chromatography (20% EtOAc /Hexane). M.p. 170-172°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 8.32 (dd, *J* = 8.0, 1.6, 1H), 7.78–7.67 (m, 1H), 7.64 (s, 1H), 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]



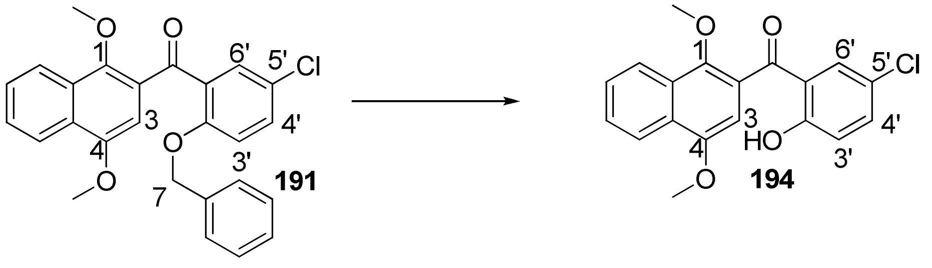
In a flask equipped with a reflux condenser, potassium carbonate (8.82 g, 63.8 mmol) was added to a clear solution of 5-chloro-salicyclic acid **190** (5.007 g, 29.01 mmol) in dry DMF (120 ml). The resulting mixture was stirred at rt under N_2. Benzyl bromide (7.59 ml, 10.65 g, 63.82 mmol) was added 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_2Cl_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_{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): v_{max}(cm^{-1}): 1637, 1621, 1592, 1489, 1452, 1406; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{26}H_{22}O_4Cl$ (M + H), 433.1207, found 433.1217.

4.17 Synthesis of (5-chloro-2-hydroxyphenyl)(1,4-dimethoxynaphthalen-2-yl) methanone 194

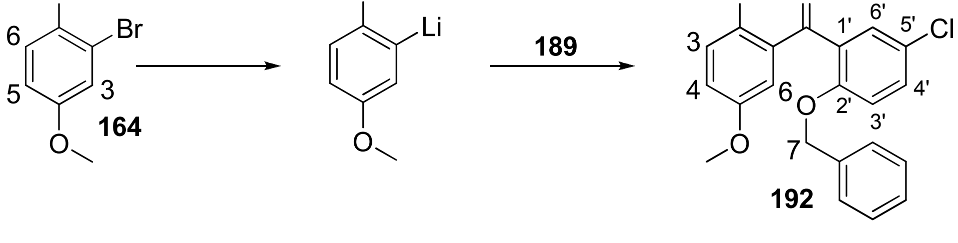


Following a similar procedure for the preparation of **159**, (2-(benzyloxy)-5-chlorophenyl)(1,4-dimethoxynaphthalen-2-yl)methanone **191** (258mg, 0.597mmol) was stirred under a H_2 atmosphere in EtOAc (20 ml) with 10% Pd/C (12.9 mg) to furnish a pale yellow solid **194** (125 mg, 96%) after flash silica gel chromatography (20% EtOAc /Hexane). M.p. 109-111°C IR (solid): $\nu_{max}(cm^{-1})$ 1629, 1614, 1596, 1510, 1460, 1414; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{19}H_{14}O_4Cl$ (M + H), 341.0581, found 341.0581.

4.18 Synthesis of 9-chloro-12a-methoxy-5H-benzo[*c*]xanthene-5,7(12*a*H)- dione 197

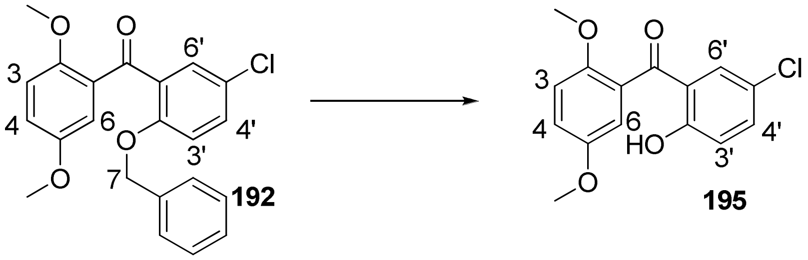
Following a similar procedure as for the preparation of **163** precursor **194** (103.3 mg, 0.300 mmol) and CAN (0.665 g, 1.212 mmol) in a mixture of $CHCl_3$, H_2O and MeCN as solvent resulted in the formation of **197** (92 mg, 93%) as a yellow solid after flash silica gel chromatography (20% EtOAc /Hexane). M.p. 162-165°C**;** IR (solid): $\nu_{max}(cm^{-1})$: 1726, 1687, 1667, 1633, 1594, 1461, 1419; ^1H NMR ($CDCl_3$, 300 MHz): δ= 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 ($CDCl_3$, 75MHz) δ= 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 $C_{18}H_{12}O_4Cl$ (M + H), 327.0424, found 327.0413.

4.19 Synthesis of [2'-(benzyloxy)-5'-chlorophenyl](2,5-dimethoxyphenyl) methanone 192



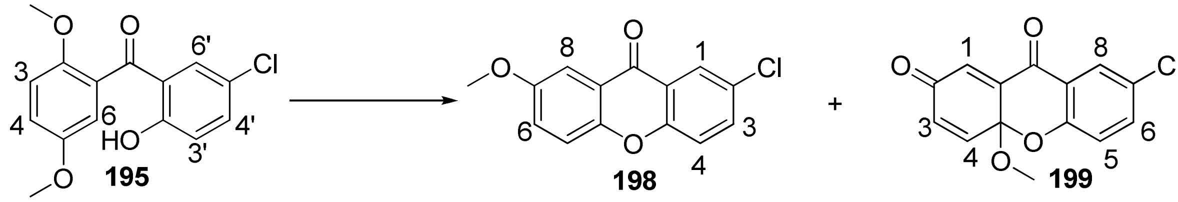
Compound **164** (2.068 g, 9.528 mmol) and benzyl-2-(benzyloxy)-5-chlorobenzoate **189** (3.368 g, 9.546 mmol) were treated following a similar procedure as for the preparation of **158**. This resulted in the formation of a yellow solid of the product, (2(benzyloxy)-5-chlorophenyl)(2,5-dimethoxyphenyl)methanone **192** (2.90 g, 78%) after flash silica gel chromatography (20% EtOAc /Hexane). M.p. 170-172°C; IR (solid): ν_{max}(cm^{-1}): 1645, 1586, 1494, 1457, 1420; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.52 (d, *J* = 2.7, 1H), 7.35 (dd, *J* = 8.8, 2.7, 1H), 7.21 (m, 3H), 7.11 (d, *J* = 3.2, 1H), 6.95 (m, 3H), 6.88 (d, *J* = 8.8, 1H), 6.76 (d, *J* = 9.0, 1H), 4.91 (s, 2H), 3.76 (s, 3H), 3.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 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 $C_{22}H_{20}O_4Cl$ (M + H), 383.1050, found 383.1047.

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



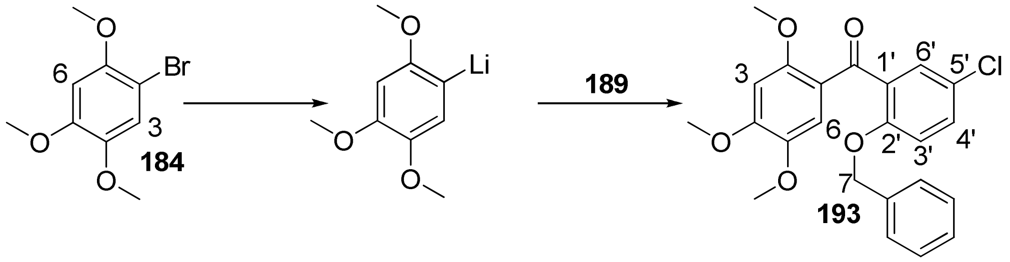
(2(Benzyloxy)-5-chlorophenyl)(2,5-dimethoxyphenyl)methanone **192** (1.006 g, 2.627 mmol) dissolved in EtOAc (40 ml) was treated in a similar manner as for the preparation of **159** with 10% Pd/C (100.3 mg) to give compound **195** as a yellow solid (0.43 g, 56%) after silica gel chromatography (30% EtOAc /Hexane). M.p. 74-76°C; IR (solid): ν_{max}(cm^{-1}): 2931, 1632, 1589, 1568, 1491, 1462, 1422; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 11.93 (s, 1H), 7.32 (dd, *J* = 8.9, 2.6, 1H), 7.22 (d, *J* = 2.6, 1H), 6.95 (dd, *J* = 9.0, 3.0, 1H), 6.88 (m, 2H), 6.76 (d, *J* = 3.0, 1H) 3.70 (s, 3H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 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 $C_{15}H_{14}O_4Cl$ (M + H), 293.0581, found 293.0576.

4.21 Synthesis of 2-chloro-7-methoxy-9*H*-xanthen-9-one 198 and 7-chloro-4a-methoxy-9*H*-xanthen-2,9(4a*H*)-dione 199



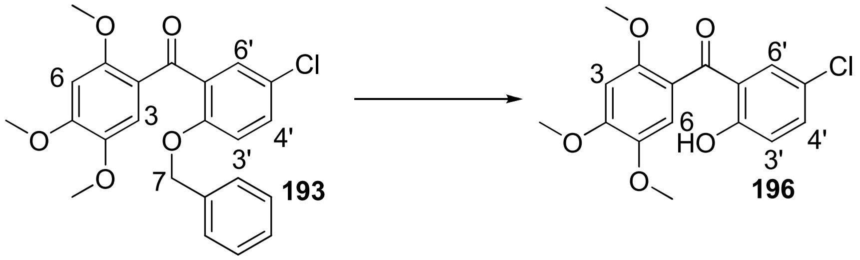
(5-Chloro-2-hydroxyphenyl)(2,5-dimethoxyphenyl)methanone **195** (104.4 mg, 0.3567 mmol) together with CAN (0.9801 g, 1.788 mmol) was treated following a similar procedure as for the preparation of **166** to give two products, **198** and **199** after flash silica gel chromatography (10% EtOAc /Hexane). The first was the xanthone **198** which was produced as white needles (53 mg, 63%). M.p. 130-133°C; IR (solid): ν_{max}(cm^{-1}): 1655, 1614, 1486, 1461, 1446; ^{1}H NMR (CDCl$_3$, 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).; ^{13}C NMR (CDCl$_3$, 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 $C_{14}H_{10}O_3Cl$ (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_{max}(cm^{-1}): 1743, 1656, 1616, 1488, 1463, 1447; ^{1}H NMR (CDCl$_3$, 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); ^{13}C NMR (CDCl$_3$, 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 $C_{14}H_{10}O_4Cl$ (M + H), 277.0268, found 277.0266.

4.22 Synthesis of [2'-(benzyloxy)-5'-chlorophenyl](2,4,5-trimethoxyphenyl)methanone 193



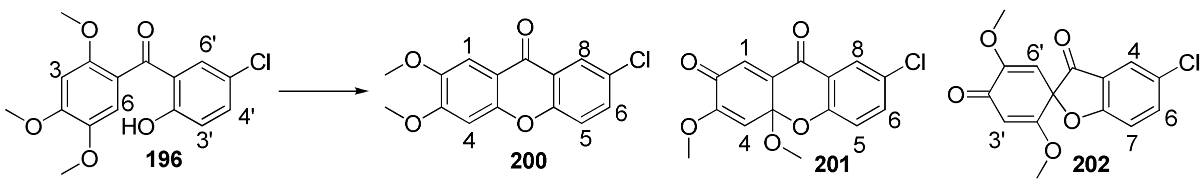
1-Bromo-2,4,5-trimethoxybenzene **184** (2.01 g, 8.14 mmol) and benzyl-2-(benzyloxy)-5-chlorobenzoate **189** (3.76 g, 10.66 mmol) were treated following a similar procedure as for the preparation of **158** to furnish (2-(benzyloxy)-5-chlorophenyl)(2,4,5-trimethoxyphenyl)methanone **193** as a yellow solid (3.80 g, 87%) after flash silica gel chromatography (10% EtOAc /Hexane). M.p. 109-111°C; IR (solid): v_{max}(cm^{-1}): 1633, 1599, 1508, 1488, 1451, 1434, 1410; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{23}H_{22}O_5Cl$ (M + H), 413.1156, found 413.1142.

4.23 Synthesis of (5-chloro-2-hydroxyphenyl)(2,4,5-trimethoxyphenyl) methanone 196

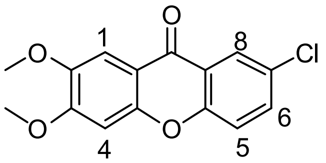


(2-(Benzyloxy)-5-chlorophenyl)(2,4,5-trimethoxyphenyl)methanone **193** (1.008 g, 2.442 mmol) and 10%Pd/C (50.6 mg) in EtOAc (50 ml) were stirred for 3.5 h under an H_2 atmosphere following a similar procedure as for the preparation of **159** resulting in the formation of (5-chloro-2-hydroxyphenyl)(2,4,5-trimethoxyphenyl)methanone **196** as a yellow solid (0.780 g, 99%) after silica gel chromatography (30% EtOAc /Hexane). M.p. 161-163°C; IR (solid): $\nu_{max}(cm^{-1})$: 1625, 1586, 1511, 1470, 1449, 1435, 1402; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{16}H_{16}O_5Cl$ (M + H), 323.0686, found 323.0680.

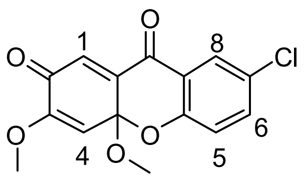
4.24 Synthesis of 7-chloro-2,3-dimethoxy-9*H*-xanthene-9-one 200 7-chloro-3,4a-dimethoxy-2*H*-xanthene-2,9(4a*H*)-dione 201 and 5-chloro-2',5'-dimethoxy-3*H*-spiro(benzofuran-2,1'-cyclohexa[2,5]diene)-3,4'-dione 202.



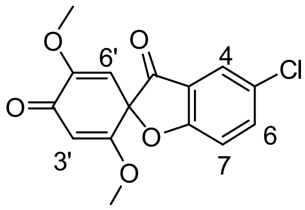
5-Chloro-2-hydroxyphenyl)(2,4,5-trimethoxyphenyl)methanone **196** (1.000 g, 3.117 mmol) together with CAN (8.486 g, 15.48 mmol) was treated following a similar procedure as for the preparation of **159** to afford three products, **200**, **201** and **202** after flash silica gel chromatography (5-10%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



7-chloro-2,3-dimethoxy-9*H*-xanthen-9-one **200** was formed as orange needles (185 mg, 21%). M.p.. 202-204°C; IR (solid): v_{max}(cm^{-1}): 1643, 1616, 1562, 1507, 1481, 1460, 1435; ^{1}H NMR (CDCl$_3$, 300 MHz): 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); ^{13}C NMR (CDCl$_3$, 75 MHz): 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-2*H*-xanthene-2,9(4a*H*)-dione **201** was formed as yellow needles (262 mg, 28%). M.p. 118-120°C; IR (solid): v_{max}(cm^{-1}): 1736, 1696, 1674, 1651, 1600, 1466, 1441, 1421; ^{1}H NMR (CDCl$_3$, 300 MHz): 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); ^{13}C 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.



5-chloro-2',5'-dimethoxy-3*H*-spiro[benzofuran-2,1'-cyclohexa[2,5]diene]-3,4'-dione **202** was formed as a light brown solid (89 mg, 9%); M.p. 223-225°C IR (solid): v_{max}(cm^{-1}): 1727, 1666, 1614, 1509, 1462; ^{1}H NMR (CDCl$_3$, 300 MHz): δ= 7.67–7.64 (m, 2H), 7.19 (d, *J* = 8.5, 0.6, 1H), 5.76 (s, 1H), 5.17 (s, 1H), 3.69 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ= 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 $C_{15}H_{12}O_5Cl$ (M + H), 307.0373, found 307.0365.

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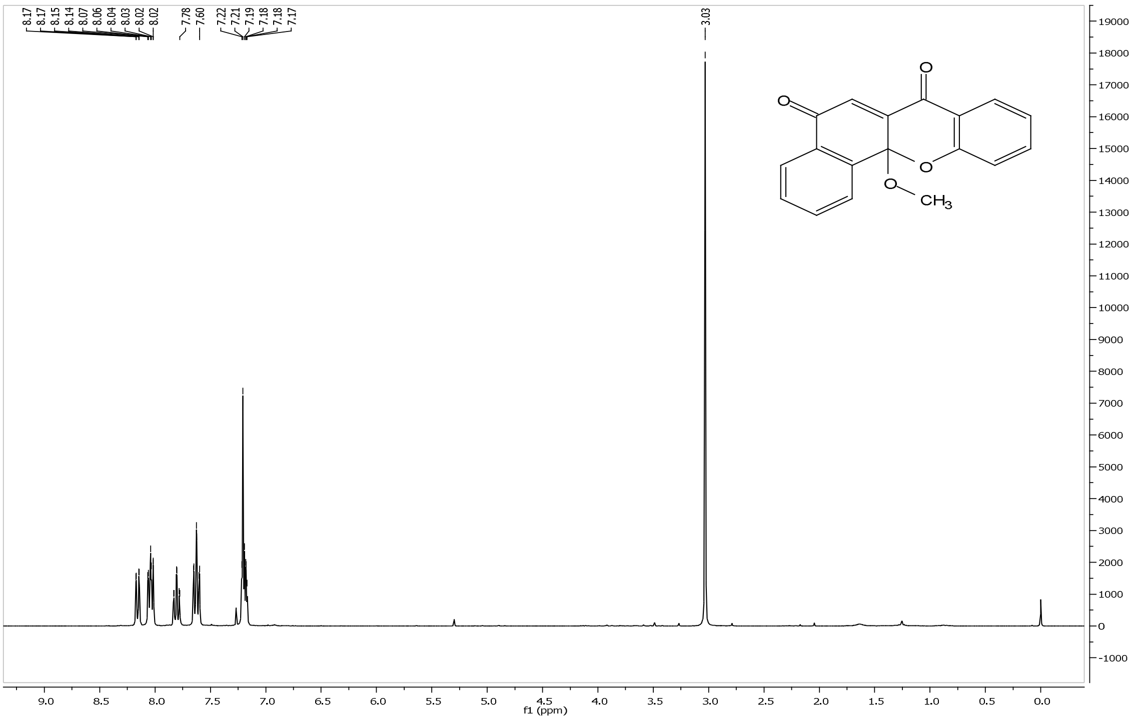
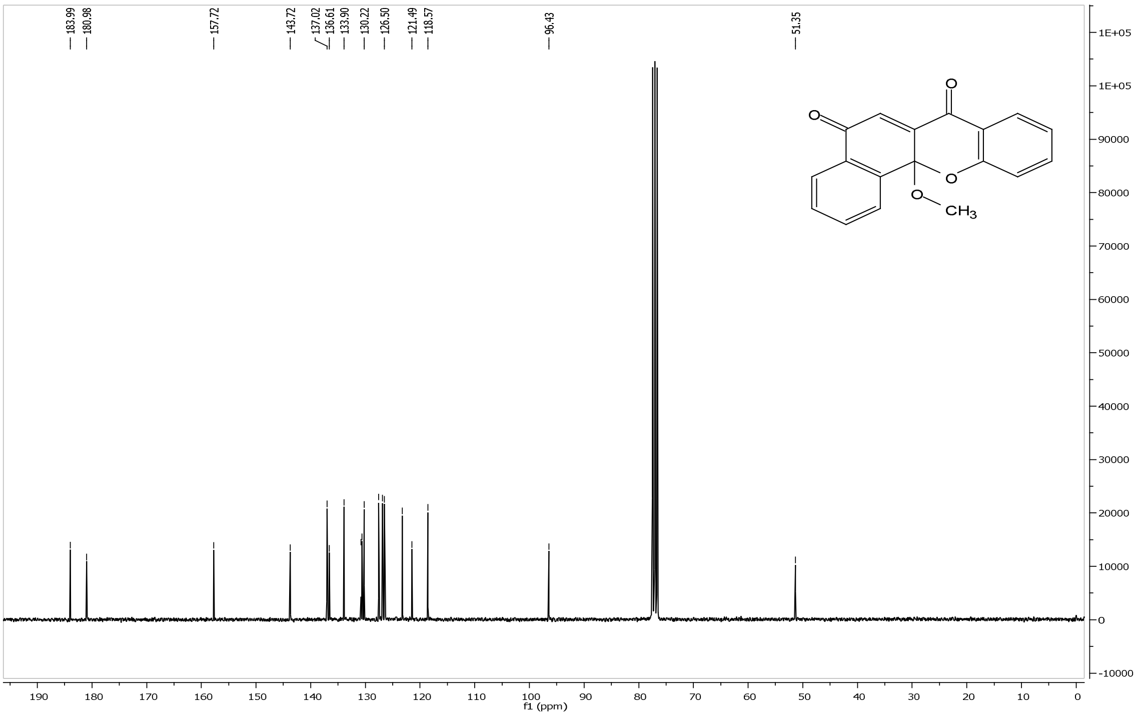
6 Appendix

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

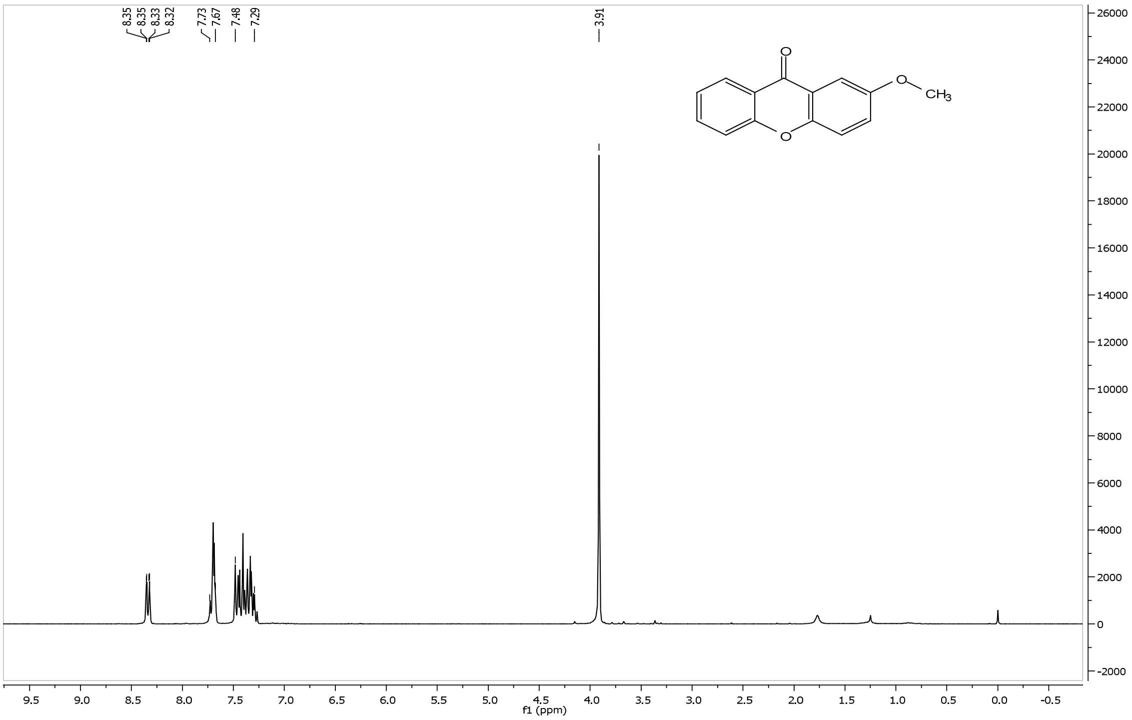
A1.1.1 The ^{1}H NMR Spectrum of compound 163



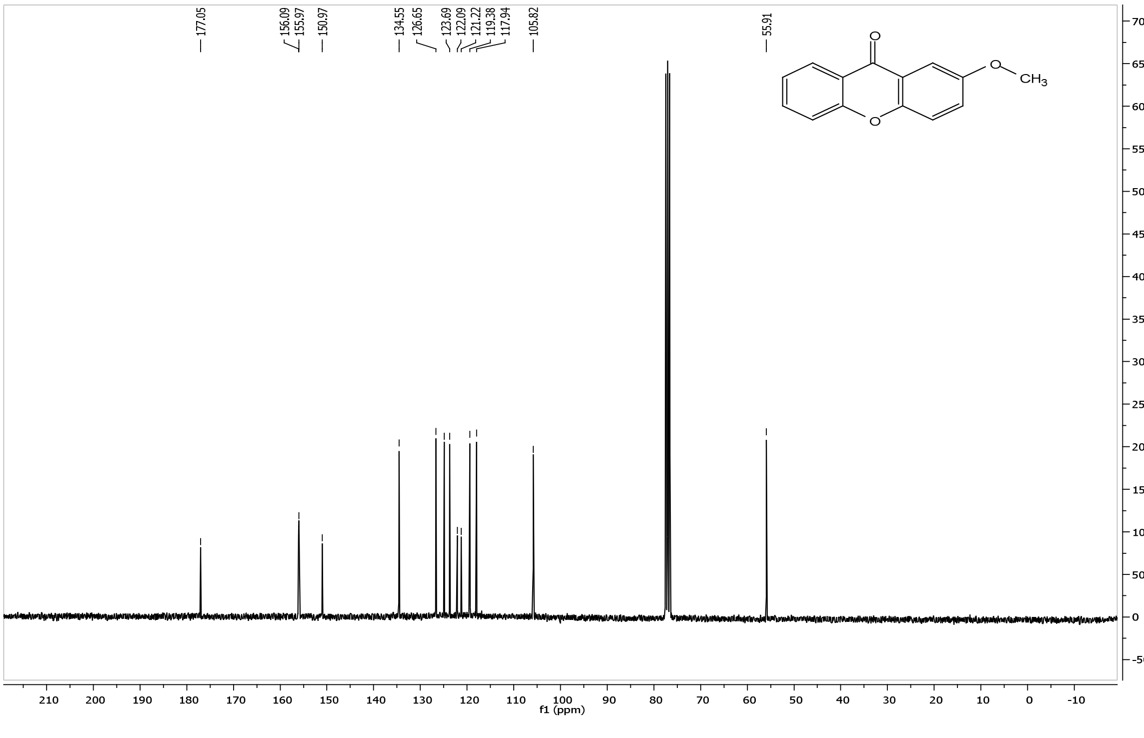
A1.1.2 The ^{13}C NMR Spectrum of compound 163



A1.1.3 The ^{1}H NMR Spectrum of compound 168

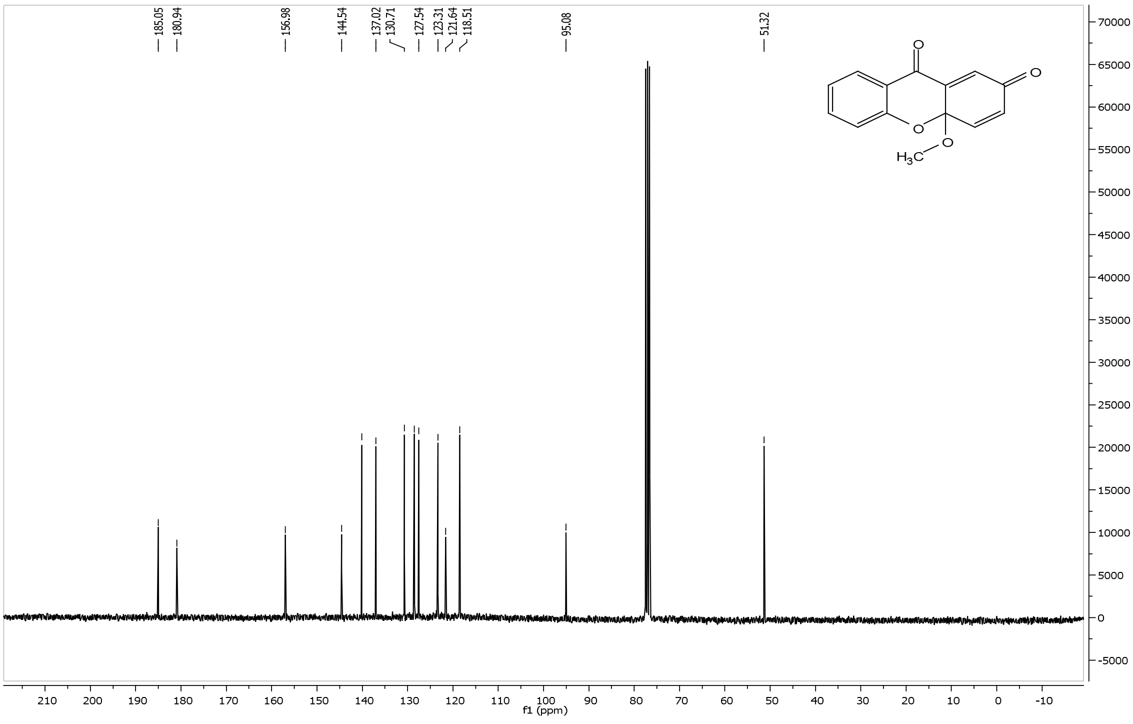


A1.1.4 The ^{13}C NMR Spectrum of compound 168

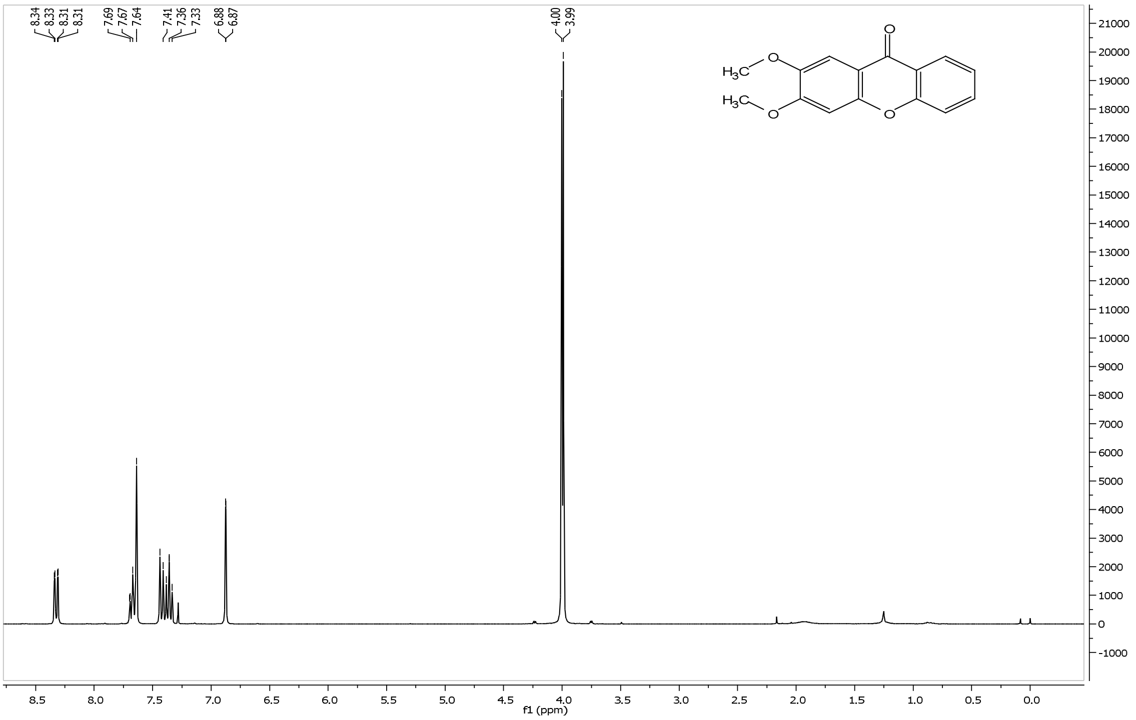


A1.1.5 The ^{1}H NMR Spectrum of compound 167

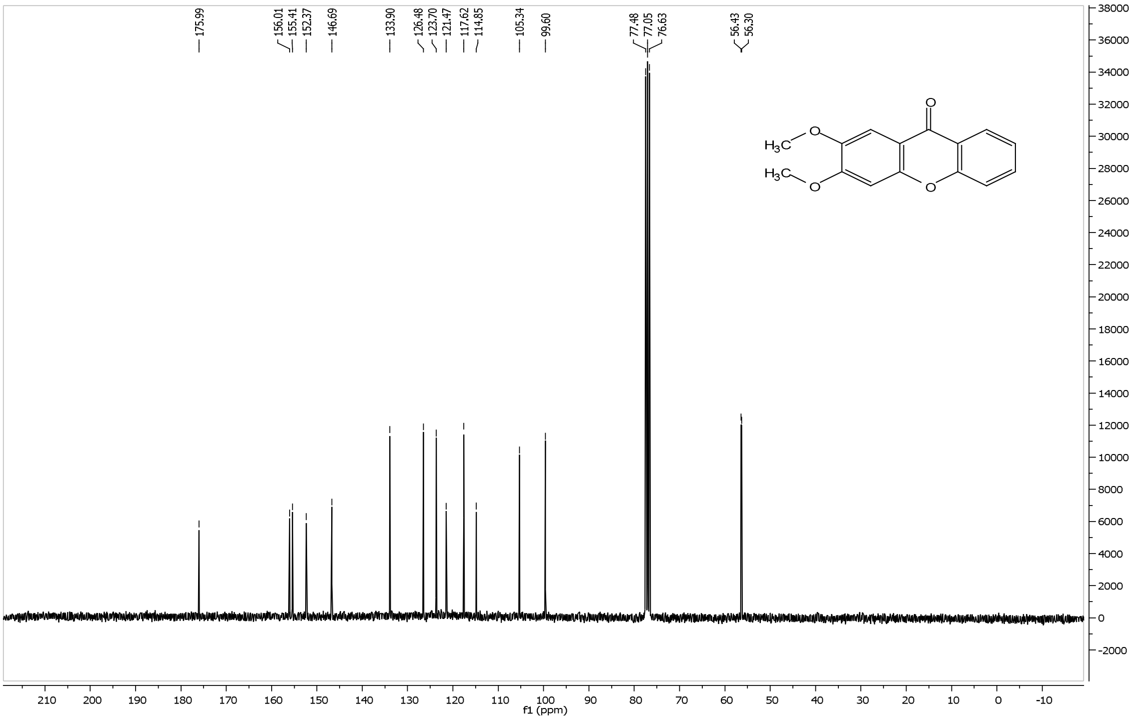
A1.1.6 The ^{13}C NMR Spectrum of compound 167



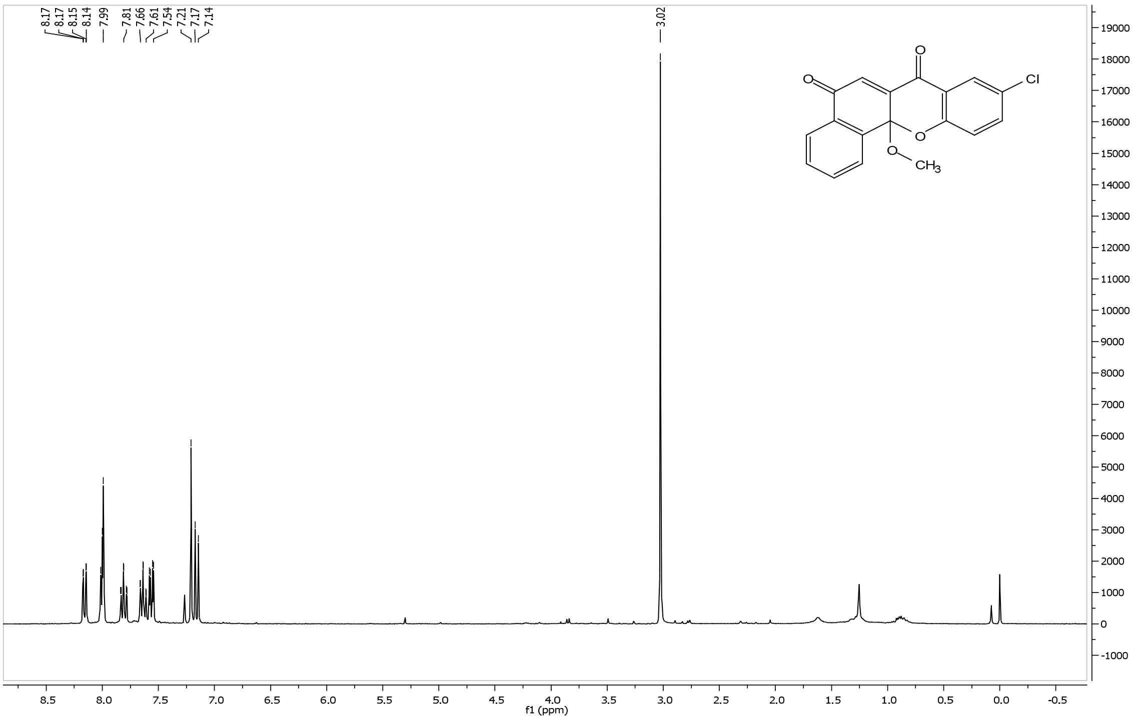
A1.1.7 The ^{1}H NMR Spectrum of compound 187



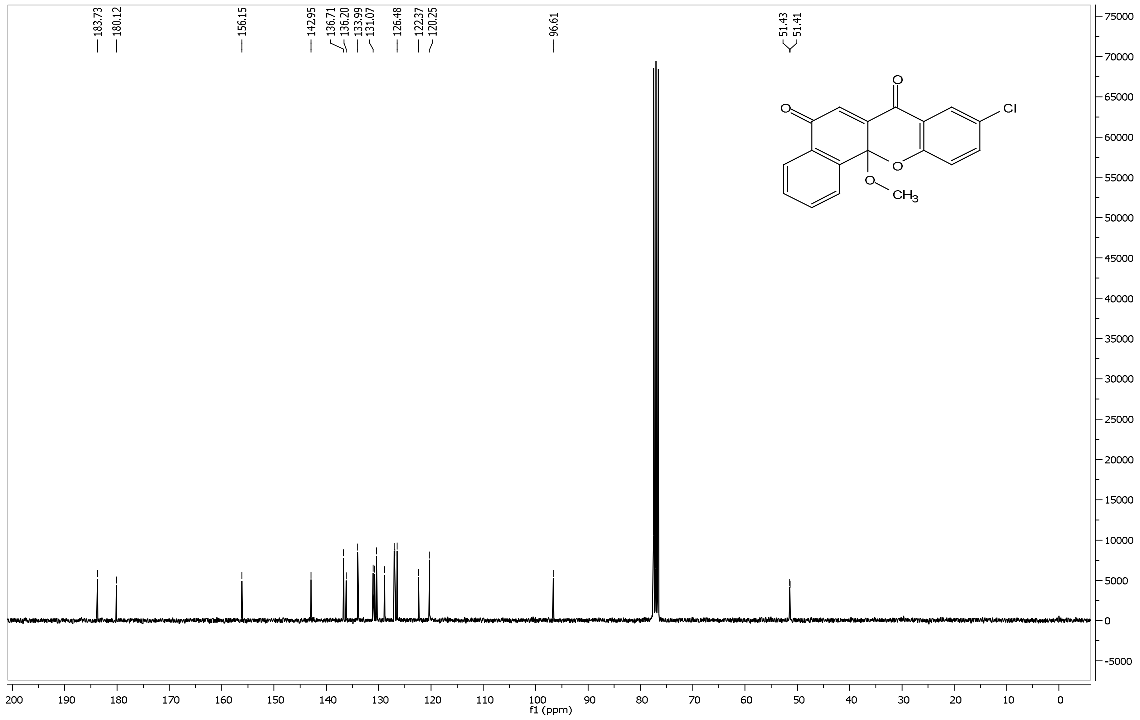
A1.1.8 The ^{13}C NMR Spectrum of compound 187



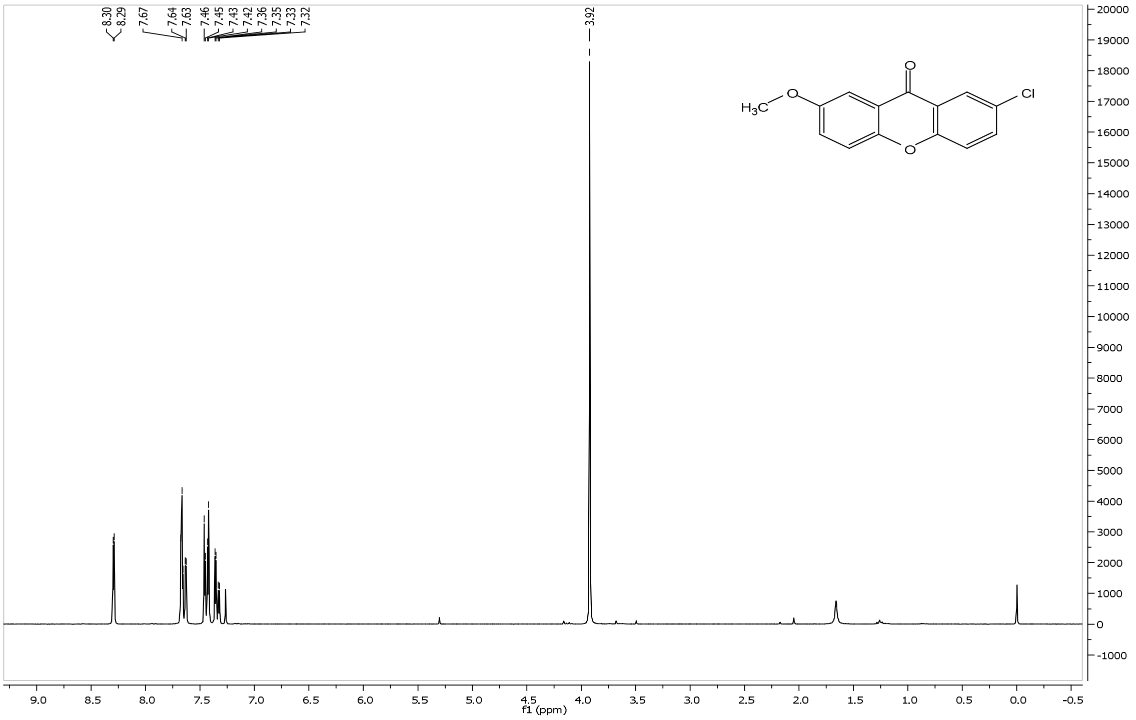
A1.1.9 The ^{1}H NMR Spectrum of compound 197



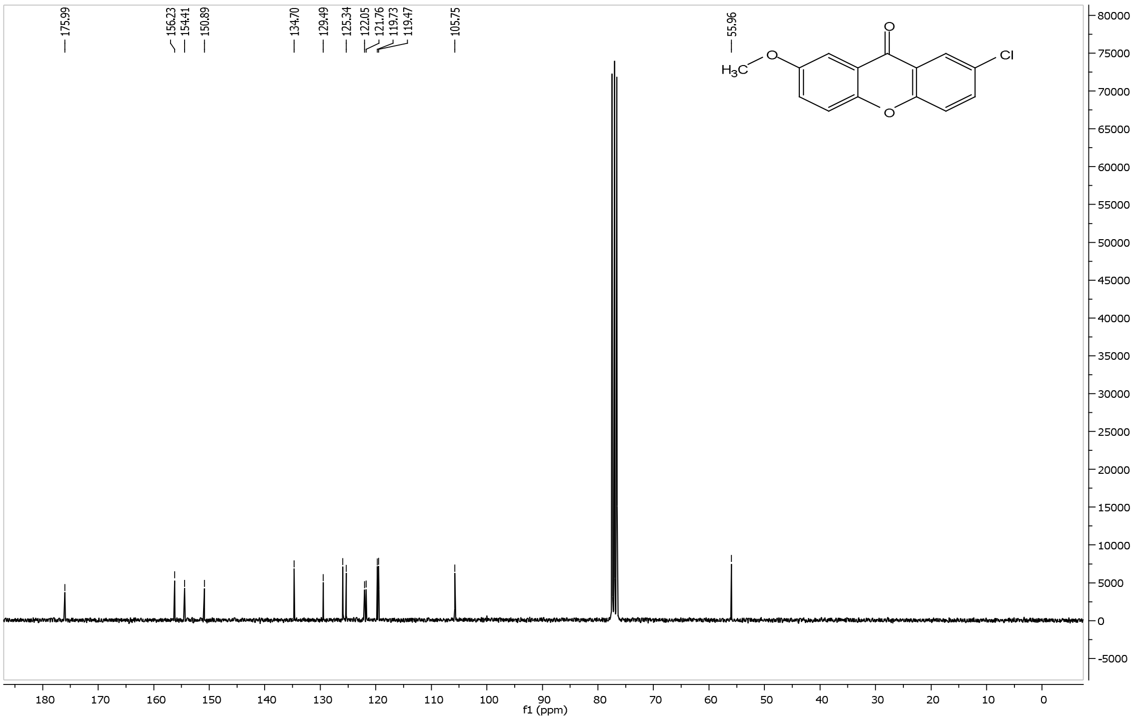
A1.1.10. The ^{13}C NMR Spectrum of compound 197



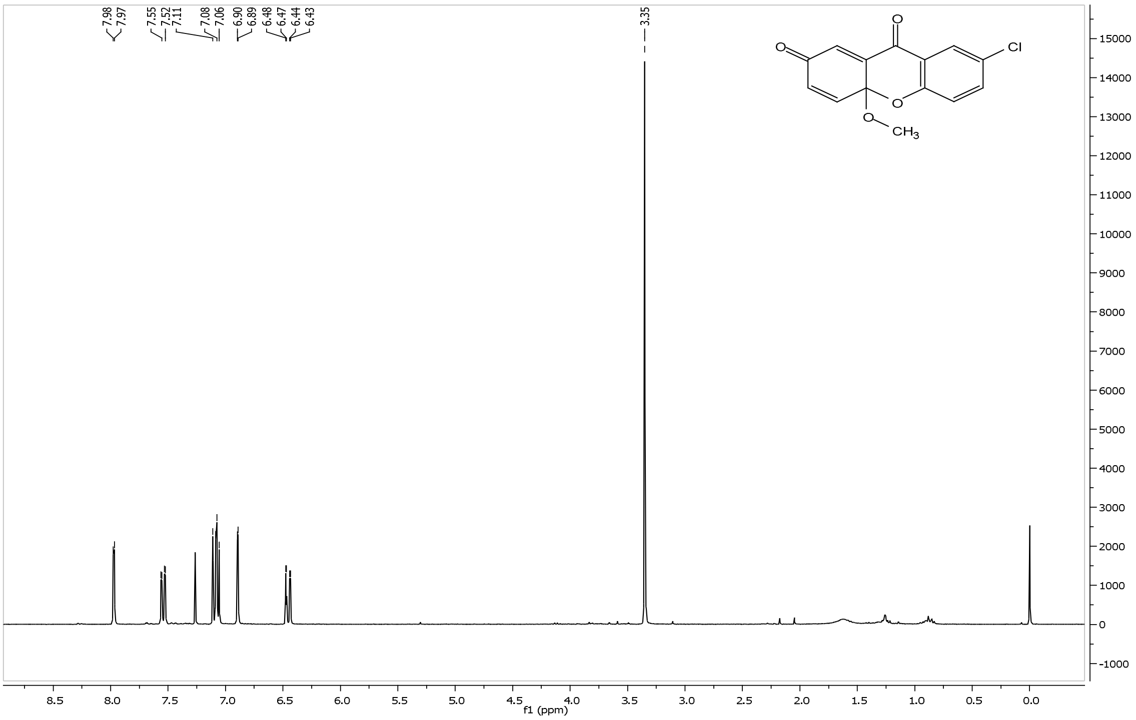
A1.1.11 The ^{1}H NMR Spectrum of compound 198



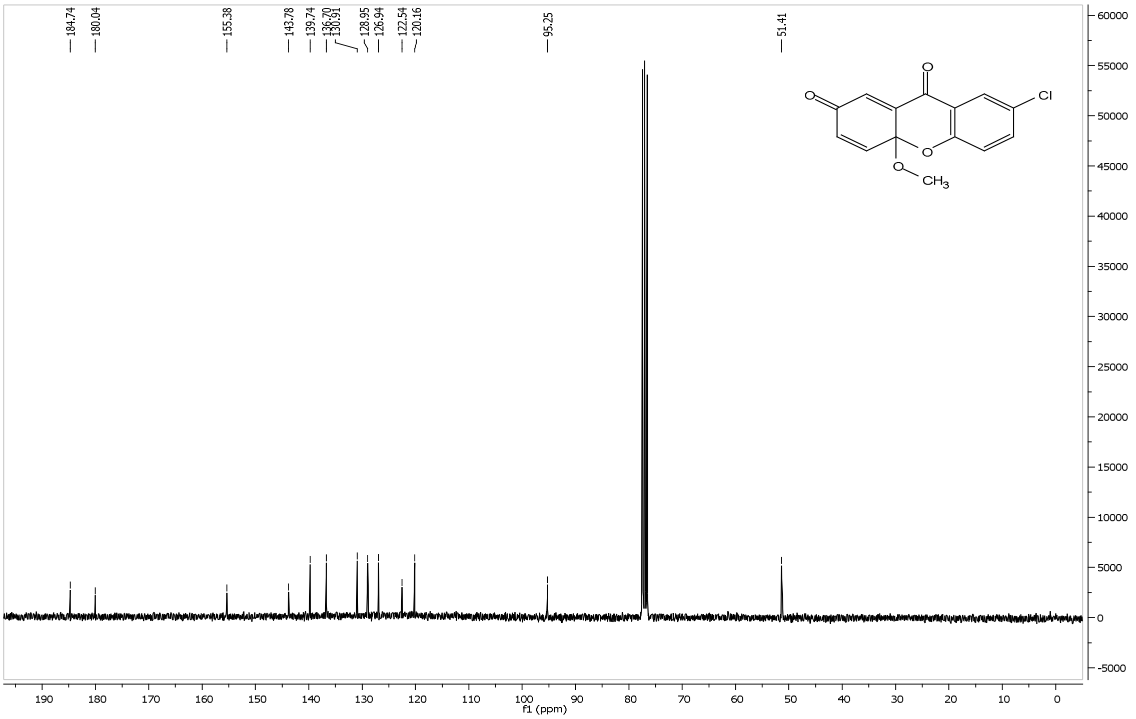
A1.1.12 The ^{13}C NMR Spectrum of compound 198



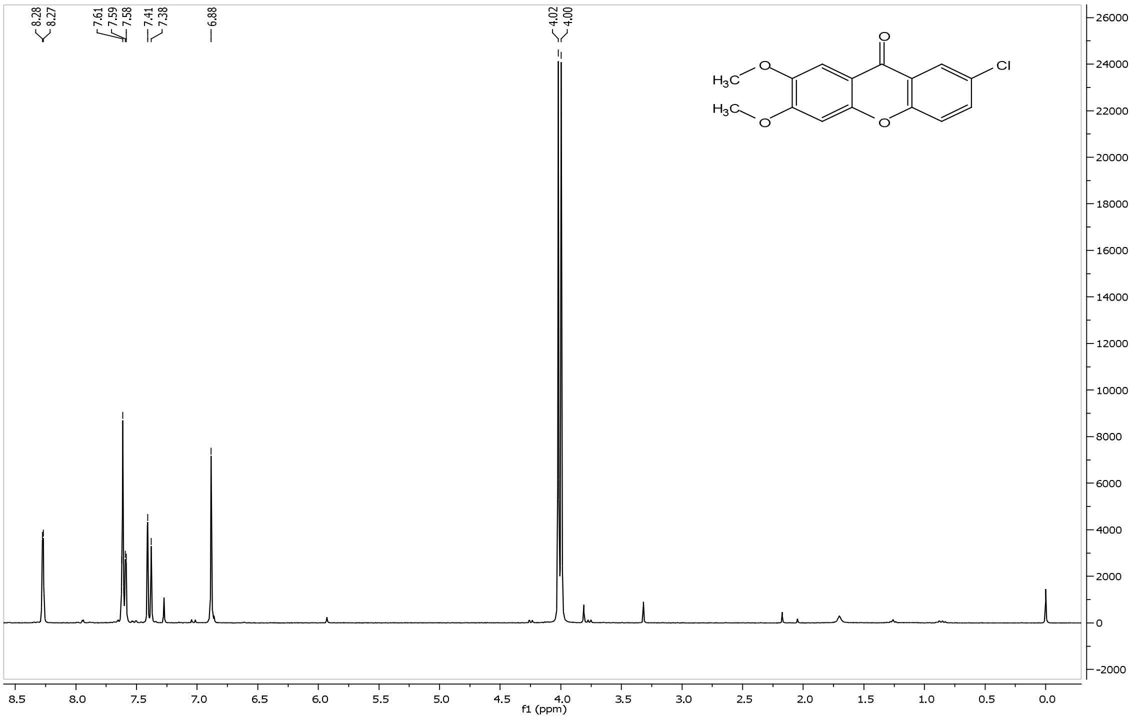
A1.1.13 The ^{1}H NMR Spectrum of compound 199



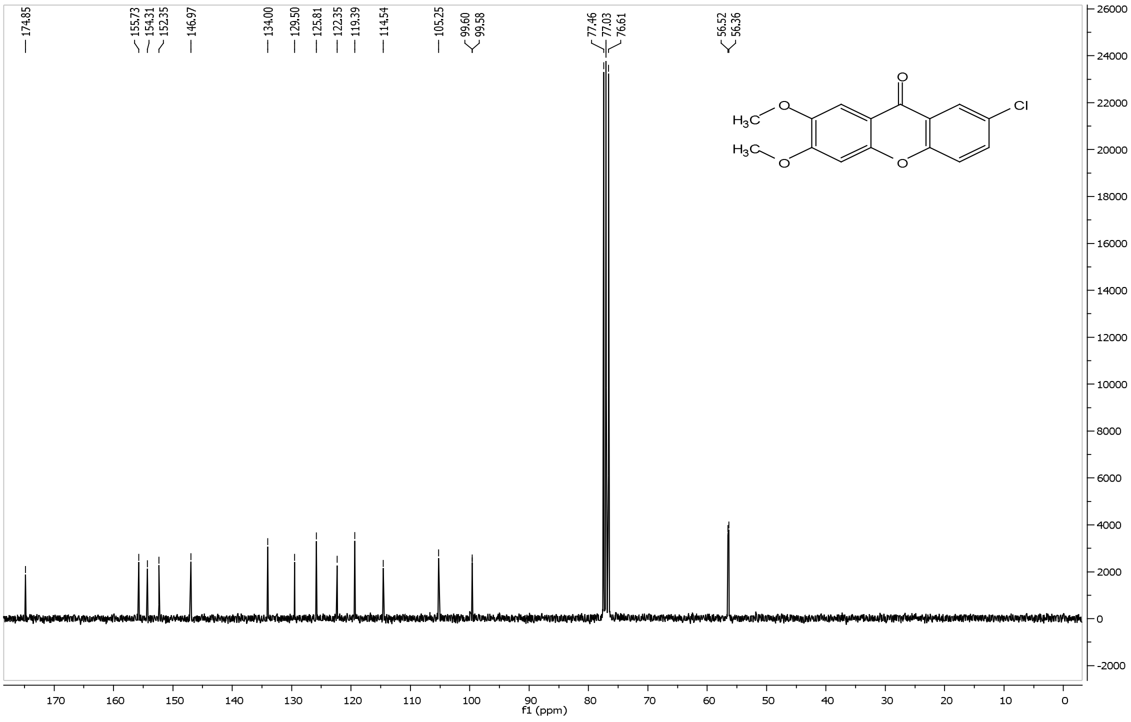
A1.1.14 The ^{13}C NMR Spectrum of compound 199



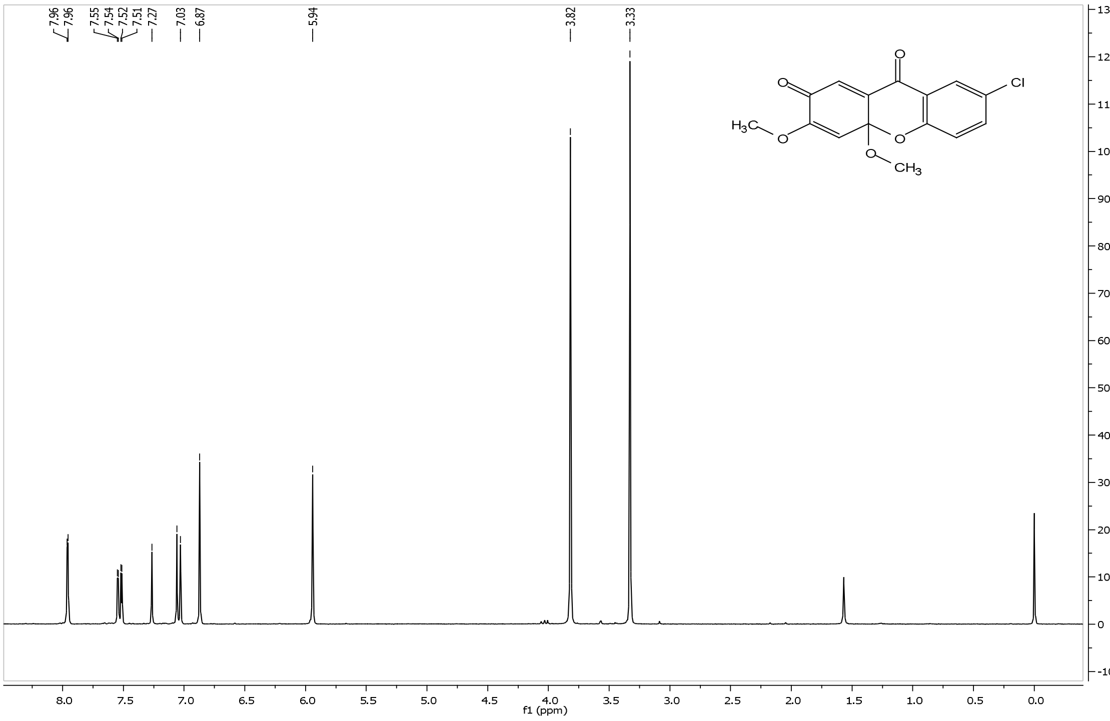
A1.1.15 The ^{1}H NMR Spectrum of compound 200



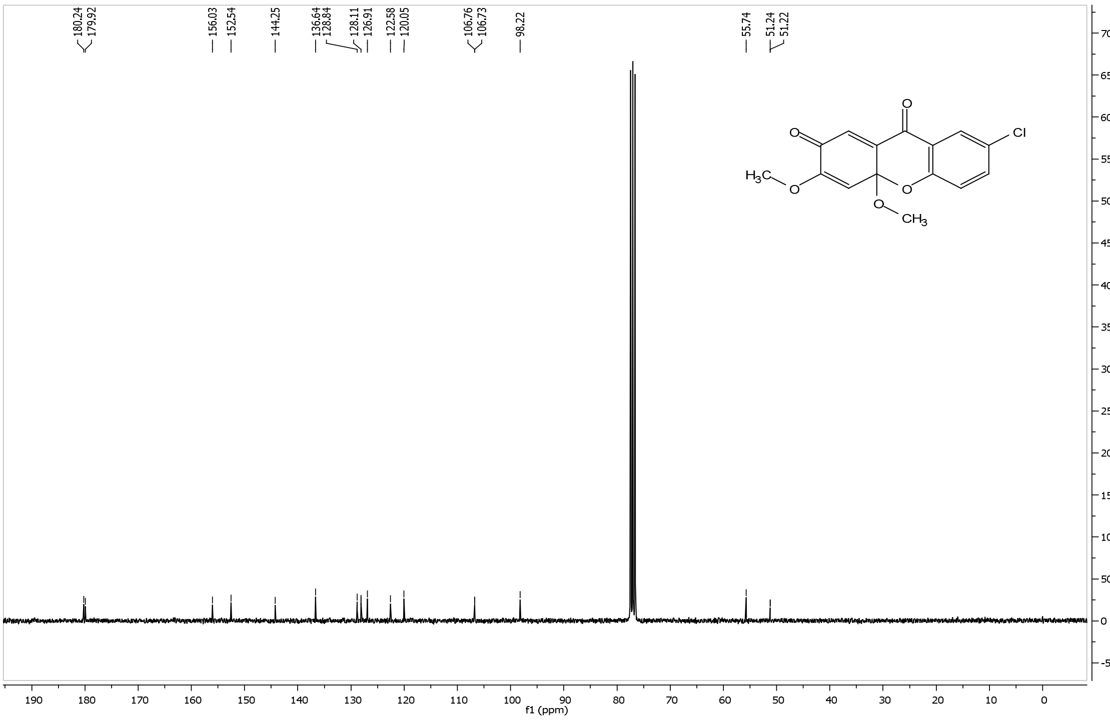
A1.1.16 The ^{13}C NMR Spectrum of compound 200



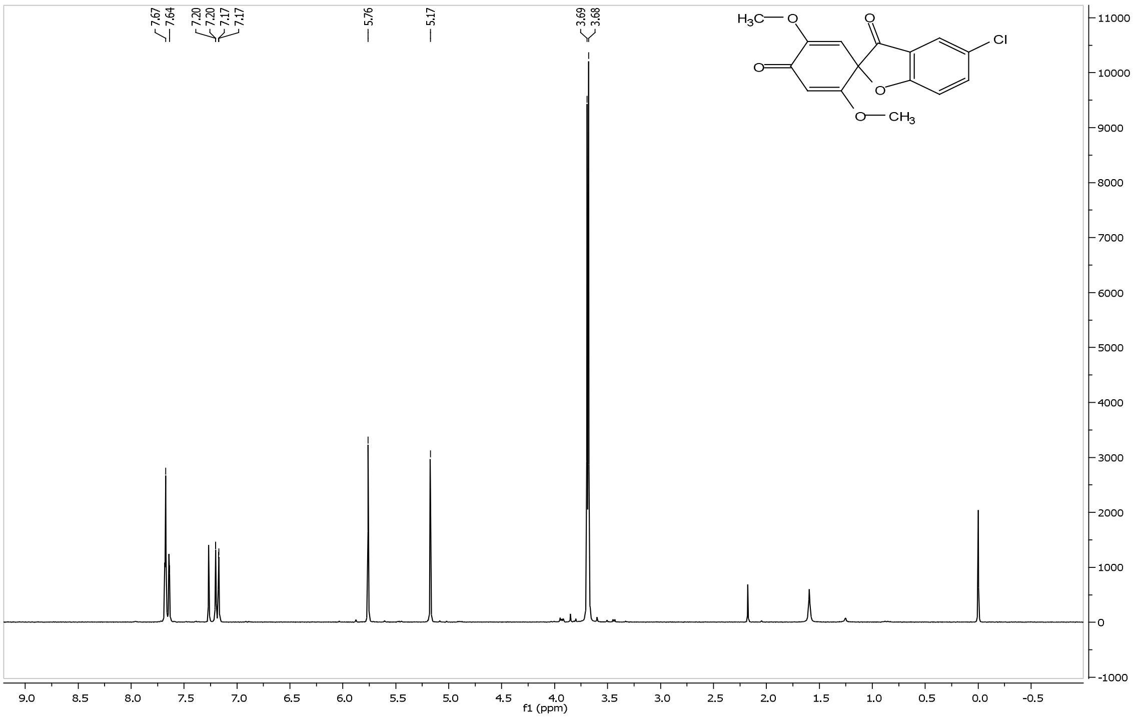
A1.1.17 The ^{13}C NMR Spectrum of compound 201



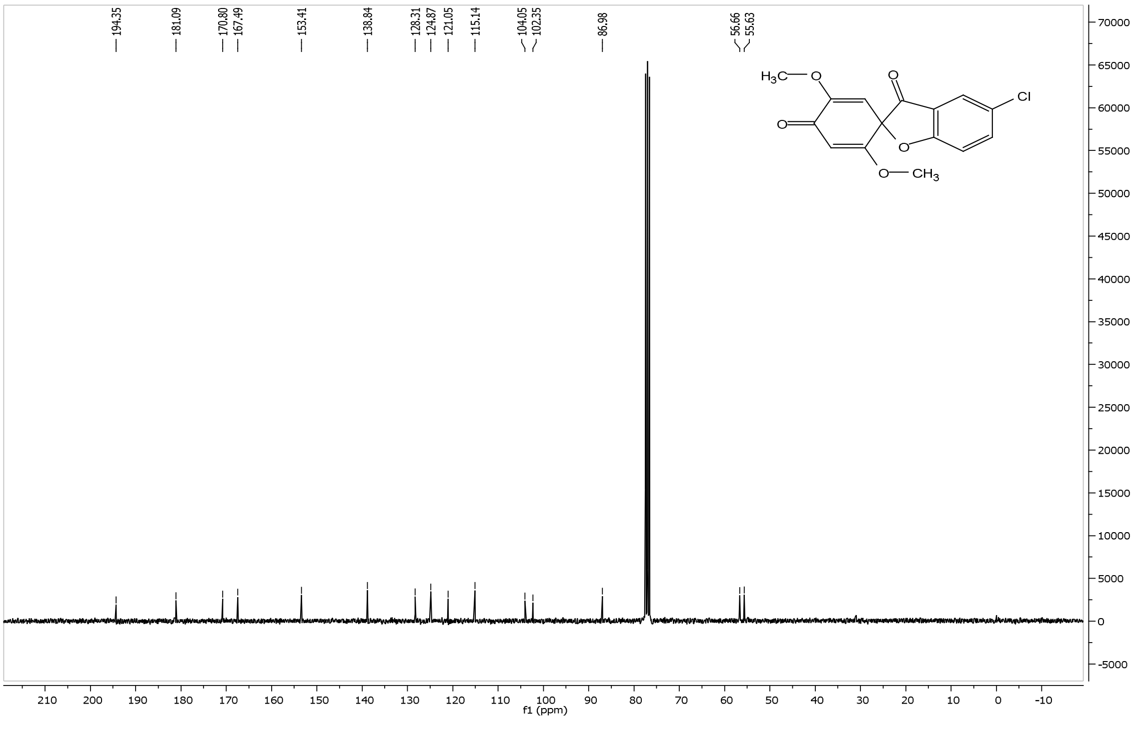
A1.1.18 The ^{13}C NMR Spectrum of compound 201



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

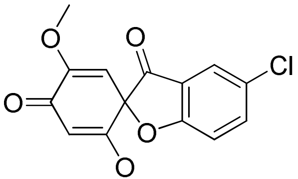


A1.1.20 The ^{13}C NMR Spectrum of compound 202



Appendix

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



202

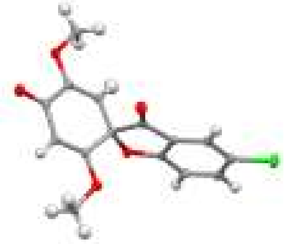


Table 1. Crystal data and structure refinement for 202.

Empirical formula	$C_{15}H_{11}ClO_5$
Formula weight	306.69
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 5.2102(3) Å
□= 90°.	
	b = 30.1686(16) Å
□= 94.569(4)°.	
	c = 8.4028(5) Å
□ = 90°.	
Volume	1316.59(13) Å^3
Z	4
Density (calculated)	1.547 Mg/m^3
Absorption coefficient	0.310 mm^{-1}

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

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for 202 U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

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

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)
Cl(1)	8512(2)	3254(1)	4965(1)	49(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)

C(10)-H(10)	0.9500
C(11)-O(4)	1.225(3)
C(11)-C(12)	1.492(4)
C(12)-C(13)	1.331(4)
C(12)-O(5)	1.355(3)
C(13)-H(13)	0.9500
C(14)-O(3)	1.448(3)
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-O(5)	1.427(3)
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
O(1)-C(1)-C(13)	109.6(2)
O(1)-C(1)-C(9)	109.8(2)
C(13)-C(1)-C(9)	114.5(2)
O(1)-C(1)-C(2)	104.5(2)
C(13)-C(1)-C(2)	108.8(2)
C(9)-C(1)-C(2)	109.1(2)
O(2)-C(2)-C(3)	130.2(3)
O(2)-C(2)-C(1)	124.7(3)
C(3)-C(2)-C(1)	105.1(2)
C(8)-C(3)-C(4)	121.2(3)
C(8)-C(3)-C(2)	107.4(2)
C(4)-C(3)-C(2)	131.4(3)
C(5)-C(4)-C(3)	117.2(3)
C(5)-C(4)-H(4)	121.4
C(3)-C(4)-H(4)	121.4
C(4)-C(5)-C(6)	122.2(3)
C(4)-C(5)-Cl(1)	119.5(2)
C(6)-C(5)-Cl(1)	118.2(2)
C(7)-C(6)-C(5)	120.6(3)
C(7)-C(6)-H(6)	119.7

C(5)-C(6)-H(6)	119.7
C(6)-C(7)-C(8)	117.2(3)
C(6)-C(7)-H(7)	121.4
C(8)-C(7)-H(7)	121.4
O(1)-C(8)-C(3)	114.9(2)
O(1)-C(8)-C(7)	123.4(3)
C(3)-C(8)-C(7)	121.6(3)
C(10)-C(9)-O(3)	126.8(3)
C(10)-C(9)-C(1)	122.2(3)
O(3)-C(9)-C(1)	110.9(2)
C(9)-C(10)-C(11)	120.7(3)
C(9)-C(10)-H(10)	119.7
C(11)-C(10)-H(10)	119.7
O(4)-C(11)-C(10)	122.0(3)
O(4)-C(11)-C(12)	120.4(3)
C(10)-C(11)-C(12)	117.6(3)
C(13)-C(12)-O(5)	126.9(3)
C(13)-C(12)-C(11)	121.2(3)
O(5)-C(12)-C(11)	111.9(2)
C(12)-C(13)-C(1)	121.3(3)
C(12)-C(13)-H(13)	119.4
C(1)-C(13)-H(13)	119.4
O(3)-C(14)-H(14A)	109.5
O(3)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
O(3)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
O(5)-C(15)-H(15A)	109.5
O(5)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
O(5)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(8)-O(1)-C(1)	108.1(2)

C(9)-O(3)-C(14)	116.4(2)
C(12)-O(5)-C(15)	116.1(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for 202. The anisotropic displacement factor exponent takes the form: $-2\pi^2$[$h^2a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(2)	22(2)	26(2)	2(1)	0(1)	4(1)
C(2)	20(2)	28(2)	25(2)	-3(1)	4(2)	-1(2)
C(3)	23(2)	24(2)	25(2)	2(1)	5(1)	1(1)
C(4)	31(2)	26(2)	29(2)	0(1)	6(2)	-2(2)
C(5)	45(2)	16(2)	32(2)	0(1)	8(2)	1(2)
C(6)	32(2)	29(2)	30(2)	10(1)	6(2)	7(2)
C(7)	22(2)	27(2)	30(2)	6(1)	-3(1)	2(2)
C(8)	25(2)	21(2)	23(2)	0(1)	7(1)	2(1)
C(9)	21(2)	26(2)	25(2)	-4(1)	1(1)	0(1)
C(10)	25(2)	25(2)	28(2)	-2(1)	4(1)	7(2)
C(11)	24(2)	19(2)	30(2)	-3(1)	-2(1)	2(1)
C(12)	26(2)	23(2)	26(2)	0(1)	2(1)	-2(1)
C(13)	20(2)	23(2)	30(2)	-1(1)	4(1)	2(1)
C(14)	35(2)	36(2)	34(2)	-6(2)	7(2)	6(2)
C(15)	33(2)	30(2)	34(2)	1(2)	8(2)	5(2)
O(1)	22(1)	19(1)	32(1)	0(1)	-4(1)	4(1)
O(2)	26(1)	33(1)	41(1)	-3(1)	-4(1)	0(1)
O(3)	32(1)	30(1)	27(1)	3(1)	9(1)	9(1)
O(4)	43(1)	29(1)	40(1)	4(1)	9(1)	13(1)
O(5)	37(1)	24(1)	33(1)	2(1)	9(1)	7(1)
Cl(1)	69(1)	22(1)	57(1)	2(1)	0(1)	0(1)

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

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

Table 6. Torsion angles [°] for 202

_

O(1)-C(1)-C(2)-O(2)	-179.0(3)
C(13)-C(1)-C(2)-O(2)	64.0(4)
C(9)-C(1)-C(2)-O(2)	-61.6(4)
O(1)-C(1)-C(2)-C(3)	0.8(3)
C(13)-C(1)-C(2)-C(3)	-116.3(2)
C(9)-C(1)-C(2)-C(3)	118.2(2)
O(2)-C(2)-C(3)-C(8)	179.1(3)
C(1)-C(2)-C(3)-C(8)	-0.7(3)
O(2)-C(2)-C(3)-C(4)	-1.9(5)
C(1)-C(2)-C(3)-C(4)	178.3(3)
C(8)-C(3)-C(4)-C(5)	-0.9(4)
C(2)-C(3)-C(4)-C(5)	-179.7(3)
C(3)-C(4)-C(5)-C(6)	0.5(4)
C(3)-C(4)-C(5)-Cl(1)	179.4(2)

C(4)-C(5)-C(6)-C(7)	-0.1(5)
Cl(1)-C(5)-C(6)-C(7)	-179.0(2)
C(5)-C(6)-C(7)-C(8)	0.1(4)
C(4)-C(3)-C(8)-O(1)	-178.8(3)
C(2)-C(3)-C(8)-O(1)	0.3(3)
C(4)-C(3)-C(8)-C(7)	0.9(4)
C(2)-C(3)-C(8)-C(7)	180.0(3)
C(6)-C(7)-C(8)-O(1)	179.2(3)
C(6)-C(7)-C(8)-C(3)	-0.5(4)
O(1)-C(1)-C(9)-C(10)	-141.3(3)
C(13)-C(1)-C(9)-C(10)	-17.5(4)
C(2)-C(1)-C(9)-C(10)	104.7(3)
O(1)-C(1)-C(9)-O(3)	43.2(3)
C(13)-C(1)-C(9)-O(3)	166.9(2)
C(2)-C(1)-C(9)-O(3)	-70.8(3)
O(3)-C(9)-C(10)-C(11)	-178.3(3)
C(1)-C(9)-C(10)-C(11)	6.9(4)
C(9)-C(10)-C(11)-O(4)	-175.5(3)
C(9)-C(10)-C(11)-C(12)	5.0(4)
O(4)-C(11)-C(12)-C(13)	175.1(3)
C(10)-C(11)-C(12)-C(13)	-5.5(4)
O(4)-C(11)-C(12)-O(5)	-4.7(4)
C(10)-C(11)-C(12)-O(5)	174.8(2)
O(5)-C(12)-C(13)-C(1)	173.6(3)
C(11)-C(12)-C(13)-C(1)	-6.1(4)
O(1)-C(1)-C(13)-C(12)	140.8(3)
C(9)-C(1)-C(13)-C(12)	16.9(4)
C(2)-C(1)-C(13)-C(12)	-105.5(3)
C(3)-C(8)-O(1)-C(1)	0.3(3)
C(7)-C(8)-O(1)-C(1)	-179.4(3)
C(13)-C(1)-O(1)-C(8)	115.9(2)
C(9)-C(1)-O(1)-C(8)	-117.6(2)
C(2)-C(1)-O(1)-C(8)	-0.7(3)
C(10)-C(9)-O(3)-C(14)	5.5(4)
C(1)-C(9)-O(3)-C(14)	-179.2(2)

C(13)-C(12)-O(5)-C(15)	-2.7(4)
C(11)-C(12)-O(5)-C(15)	177.0(2)

A3: Literature Published during this Masters

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

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