# SYNTHESIS OF OXYGEN CONTAINING HETEROCYCLES AS POTENTIAL IDO INHIBITORS

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# ABSTRACT

One potentially attractive approach to cancer therapy is to recruit the body's own immune system to reject solid tumours. The enzyme indoleamine 2,3-dioxygenase (IDO) has been shown to play a major role in supressing immune response, and there is now growing evidence to support the hypothesis that inhibition of IDO produces significant anticancer effects. The development of chemotherapeutic agents for cancer based on the inhibition of indoleamine 2,3-dioxygenase is the purpose of this present work.

Chapter I contains an overview of indoleamine 2,3-dioxygenase, describing its structure, activation cycle, catalytic mechanism and inhibitors.

Chapter II is divided in two parts. Initially the efforts towards the synthesis of a simple analogue, containing the isobenzofuranquinone moiety of annulins A and C are described. The aim was to verify which part of the molecule was important for IDO inhibiton. Four main approaches to the analogue are described. Next, investigations into the total synthesis of annulins A and C are discussed. These led to the synthesis of the naphthoquinone core of both natural products by performing a Diels Alder reaction. Attempts to introduce the furan ring proved challenging, and different approaches to this problem are described in this Chapter.

In Chapter III, the synthetic approaches towards annulin B are discussed. The possibility to access this natural product *via* Diels Alder reaction, prompted us to investigate the synthesis of the required dienophile – a chroman-3-one substrate. We succeeded in constructing this highly advanced intermediate using two different strategies, namely a Dieckmann condensation and an intramolecular O-H insertion reaction.

Finally, the synthesis and biological evaluation of a narrow range of benzofuranquinones with varying substituents are presented in Chapter IV. Their synthesis was based on the structure of the benzofuran **ACH488**, previously identified as a good IDO inhibitor.

The experimental details of the above work are described in Chapter V.

# ACKNOWLEDGEMENTS

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# ABBREVIATIONS

| | |
|---|---|
| aq | aqueous |
| CAN | cerium(IV) ammonium nitrate |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | *N*,*N*′-dicyclohexylcarbodiimide |
| DMAP | 4-dimethylaminopyridine |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| EOM | ethoxymethyl ether |
| eq | equivalent(s) |
| ESI | electrospray ionisation |
| $IC_{50}$ | half maximum inhibitory concentration |
| IDO | indoleamine 2,3-dioxygenase |
| IDO-2 | indoleamine 2,3-dioxygenase-2 |
| IFN | interferon |
| KHMDS | potassium bis(trimethylsilyl)amide |
| $K_i$ | inhibition constant |
| LiHMDS | lithium bis(trimethylsilyl)amide |

| | |
|---|---|
| LPS | lipopolysaccharide |
| MOM | methoxymethyl ether |
| MW | microwave |
| NaHMDS | sodium bis(trimethylsilyl)amide |
| NBS | *N*-bromosuccinimide |
| NOESY | nuclear Overhauser effect spectroscopy |
| QM/MM | quantum mechanics/molecular mechanisms |
| PG | protecting group |
| S.M. | starting material |
| TBAF | tetrabutylammonium fluoride |
| TBSCl | *tert*-butyldimethylsilyl chloride |
| TDO | tryptophan-2,3-dioxygenase |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TMSCl | trimethylsilyl chloride |
| TNF | tumour necrosis factor |
| wt% | weight percent |

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# CHAPTER I

## INDOLEAMINE 2,3-DIOXYGENASE

## 1.1. Introduction

Cancer remains a major cause of death worldwide. In 2008, in Europe there were an estimated 3.2 million cancer cases diagnosed and 1.7 million deaths from cancer.[1] According to the World Health Organization, from a total of 58 million deaths worldwide in 2008, cancer accounts for 7.6 million (13%) and are projected to continue rising, with an estimated 12 million deaths in 2030.

Nowadays, the leading treatment options for cancer are chemotherapy, surgery and radiotherapy. However, given the intrinsic nature of cancer cells, the full efficacy of these therapies is limited.[1] Typical therapies, such as, chemo- and radio-therapy are not tumour targeted and, as a result, these treatments have undesirable effects on normal tissues. Furthermore, even when the majority of cancer cells are destroyed by treatment with a chemotherapeutic drug, a small number of residual cells, resistant to the drug, can be enough to begin the regrowth of the tumour. These situations have led to the development of alternative strategies that are expected to change the landscape of the anticancer drug market.[2,3]

The study of how cancer interacts with the immune system is now bringing new treatment approaches. One of these approaches readdresses the focus of attack from the tumour cell itself to the environment that keeps its growth and survival and the alternative approach works by boosting the cancer patient immune system.[2]

Until now all the strategies involving immunotherapy have focused mainly on presenting tumour antigens. Strategies such as cytokine-based therapies, antibody-based therapies, adoptive cell transfer and therapeutic vaccines, currently dominate the immunotherapeutic

field, and are based on the premises that stimulation of the immune system will enable the recognition of antigens expressed by the tumour. Although undoubtedly important, these strategies have produced only a small proportion of positive clinical response.

Recent progress in the understanding of tumour-host interactions at the molecular level have revealed new targets for small-molecule inhibitor designs. These include key effectors of tumoural immune tolerance, such as, enzymes, receptors and cytokine signalling pathways that are present in stromal and in tumour cells, and which can through several mechanisms, lead to a reduction on the activation or efficacy of the immune system, observed in cancer patients.[4]

## 1.2. Indoleamine 2,3-dioxygenase – general remarks

Indoleamine 2,3-dioxygenase (IDO), an enzyme originally isolated from rabbit intestine,[5] has emerged as a promising molecular target for the development of a new class of anticancer agents. The interest in IDO arises from its supposed role to promote tumoural immune tolerance, by inhibiting the activation of immune cells known as T-cells, through its capacity to catabolise the amino acid tryptophan and generate kynurenine.[6,7]

L-Tryptophan **1** is the least abundant essential amino acid in mammals and is a biochemical precursor of several biologically active compounds. These include the neurotransmitter serotonin **2**, the neurohormone melatonin **3**, products of the kynurenine pathway and the amine tryptamine **4**.[8,9]

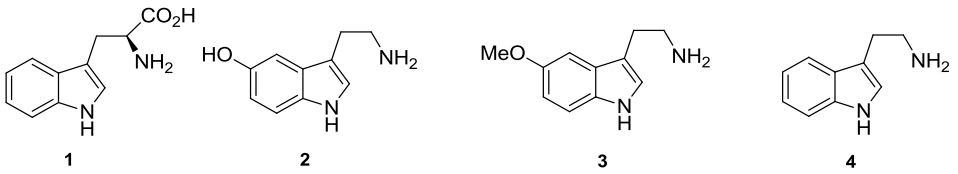
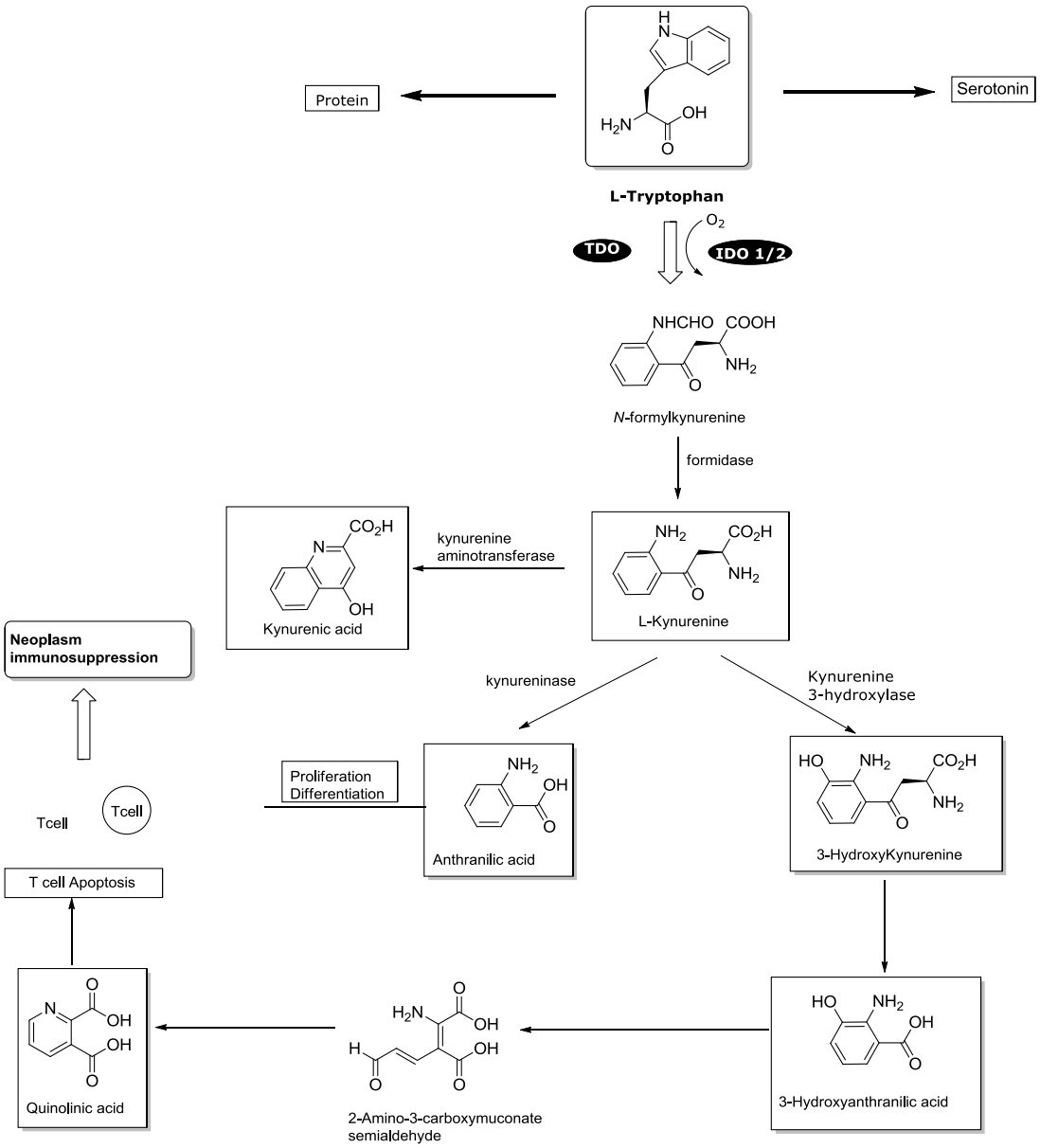



**Figure 1** Some biologically active end-products of L-Trp metabolism.

Although tryptophan metabolism comprises several pathways that lead to its incorporation into proteins and to the synthesis of biologically active compounds, 99% of the food intake of L-Trp is routed to the kynurenine pathway, which leads, for example, to the formation of the central nervous system active metabolites quinolinic acid and kynurenic acid.[8,9]

The initial and rate limiting step of the kynurenine pathway involves the oxidative cleavage of the 2,3-double bond in the indole moiety, resulting in the production of *N*-formylkynurenine (**Scheme 1**). Since the 1970s it has been believed that this reaction was catalysed by IDO or tryptophan 2,3-dioxygenase (TDO), depending on the tissue and cell type. However, more recently a novel enzymatic form of IDO was discovered and named IDO-2 and subsequently demonstrated also to have the ability to catabolise tryptophan.[10] IDO and IDO-2 share 43% identity and are not structurally related to TDO. IDO expression is found in many tissues, with especially high activities in the lung, small intestine and placenta, and is regulated by complex immunological signals, such as, interferons (IFN-γ), lipopolysaccharide (LPS), inflammatory citokynes and tumour necrosis factor (TNF-α). Like IDO, IDO-2 catalyses the oxidative cleavage of a broad range of indole bearing derivatives, such as, tryptamine, serotonin, as well as, L-Trp, and is predominantly expressed in the kidney, liver, male and female reproductive system.[9-14]




**Scheme 1** IDO-mediated tryptophan catabolism.

Although it was initially supposed that TDO expression was mainly confined to the liver and that it was not induced by signals from the immune system,[8] recently Platten's[15] and van den Eynde's groups[16] reported that TDO is strongly expressed in several human tumours and *in vitro* experiments confirmed that kynurenine, generated from TDO, had the same capacity as IDO to suppress antitumour immune responses.[17]

After the revolutionary discovery of the involvement of IDO in maintaining maternal tolerance towards the foetus,[18] IDO has been implicated in mediating several

immunosuppressive mechanisms, such as, T-cell tolerance to tumours. The mechanism by which IDO disables T-cells is still not completely clear and two main theories have been proposed. The tryptophan starvation theory proposes that over expression of IDO results in depletion of L-tryptophan in the tumour microenvironment inducing a stress response, such that T-lymphocytes arrest in G1 and fail to proliferate. The second theory, the tryptophan metabolite theory, postulates that some metabolites from the kynurenine pathway, mainly kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid are toxic to lymphocytes. These metabolites suppress T-cell proliferation and differentiation, and accelerate apoptosis, preventing immunological rejection of the tumour.[6,17]

Several studies have indicated that IDO is chronically activated in many cancer patients and its expression or enzyme activity correlates with a poor prognosis in patients with melanomas, colon and ovarian cancers, among others.[4,6,19] In addition to cancer cells, dendritic cells and regulatory B-cells of the immune system may be essential sites of IDO action. Dendritic cells and regulatory B-cells can move to lymph nodes stimulating the production of regulatory T-cells and facilitating metastasis.[6,7,19,20]

### 1.2.1. Structure of IDO

The crystal structure of human IDO was released in 2006 by Sugimoto *et al.*[21] The overall structure show that IDO is a monomeric enzyme (MW ≈ 45 KDa) folded into two distinct domains (small and large) with the haem prosthetic group situated between them (**Figure 2**).

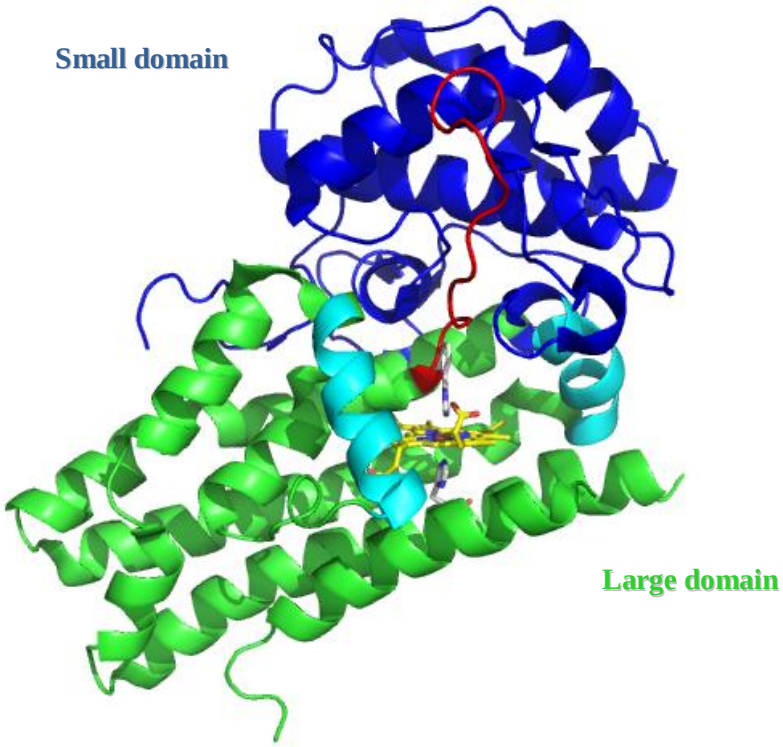



**Figure 2** Representation of the overall structure of human IDO complexed with the ligand inhibitor 4-phenylimidazole (pdb file "2D0T").

The small domain consists of nine α-helices and two β-sheets and the large domain is composed of thirteen α-helices and two β-sheets, and contains the catalytic pocket. The haem-binding pocket is comprised by four long helices (G, I, Q, S) and three short helices (K, L, N). The iron is penta-coordinated to the active site through a histidine imidazole (His346) provided by the third long helix (helix Q). The interface between the two domains is formed by several interactions, such as, hydrogen bonding, salt bridges and hydrophobic interactions. The entrance for the substrate or ligand to the catalytic site is delimited by a flexible loop. The distal haem pocket, which is a coordination site of the haem iron for the sixth external ligand (where the substrate binds), is formed by residues belonging to both small and large domains and to the loop (**Figure 3**).[9]

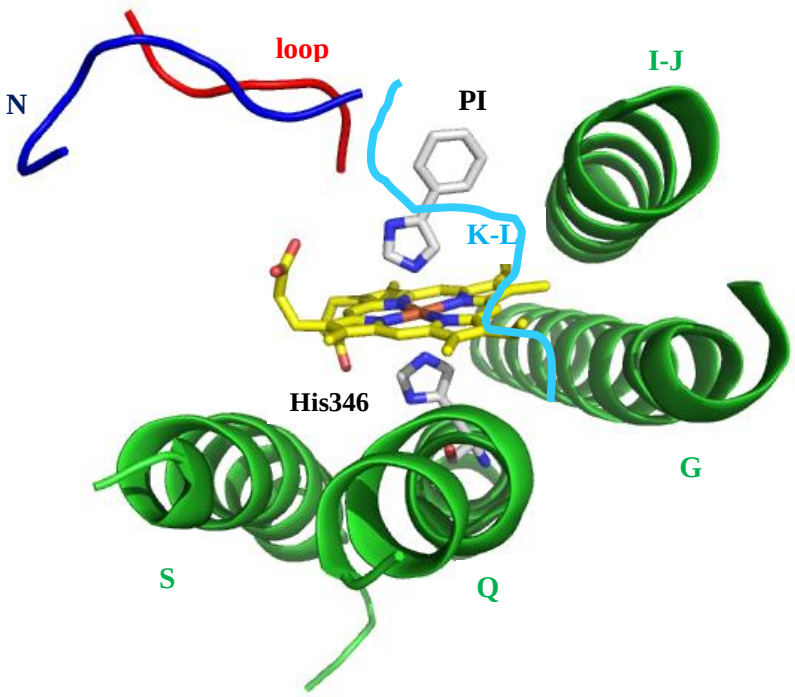
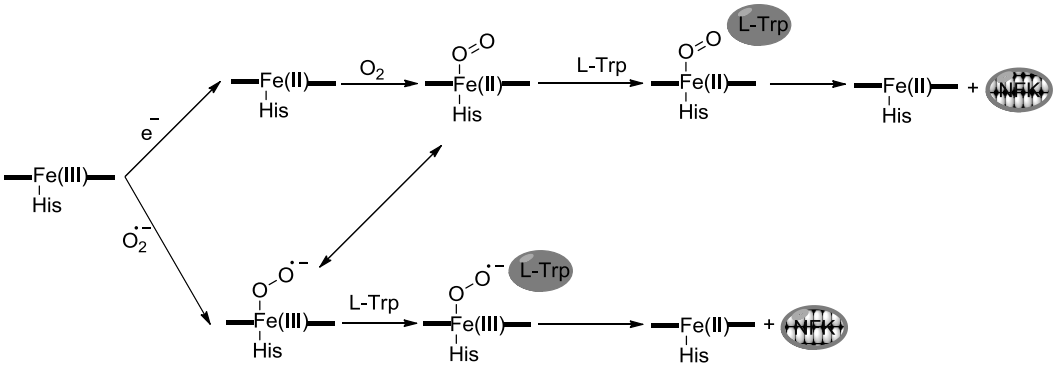



**Figure 3** Structure of IDO complexed with the ligand inhibitor 4-phenylimidazole (PI) (pdb file "2D0T").

### 1.2.2. Activation cycle of IDO

In 1996, Sono and co-workers[22] proposed a model for the catalytic activation cycle of IDO (**Scheme 2**). According to this model, the tryptophan-free ferric enzyme (IDO-Fe(III)) is either reduced to the ferrous state (IDO-Fe(II)), which then binds oxygen and L-tryptophan to form the ternary complex (IDO-Fe(II)/oxygen/L-Trp) or, if superoxide is available, the ferric state first combines with this reactive oxygen species, to generate the oxygenated binary complex of the enzyme (IDO-Fe(III)/superoxide) followed by L-tryptophan binding. In this alternative route, the oxygenated enzyme can be presented as a resonance hybrid of IDO-Fe(III)/superoxide and IDO-Fe(II)/oxygen. Sono and co-workers postulate that under physiological conditions, utilisation of superoxide is probably insignificant because of the ubiquity of superoxide dismutase, which is an inhibitor of IDO activity. Noteworthy, recent

Raman and computational studies[23,24] have suggested that oxygen gains superoxide character after binding to the haem iron. The final step of the catalytic cycle is the decomposition of the ternary complex to the ferrous enzyme and product (*N*-formylkynurenine). In order for IDO to be catalytically active it is essential to mantain the haem iron in the ferrous state. Since the enzyme is susceptible to autooxidation, a reductant is needed for preserving the enzyme activity. Studies by Vottero *et al.*[25] and Maghzal *et al.*[26] suggest that cytochrome $b_5$ and cytochrome $b_5$ reductase play this role *in vivo*.

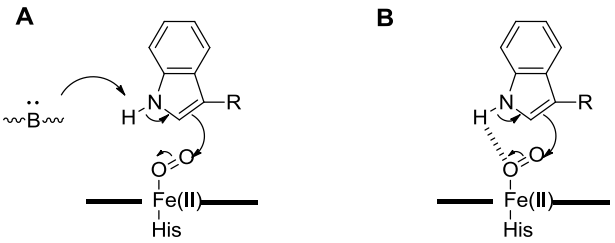



**Scheme 2** Proposed activation cycles of IDO.

### 1.2.3. Catalytic mechanism of IDO

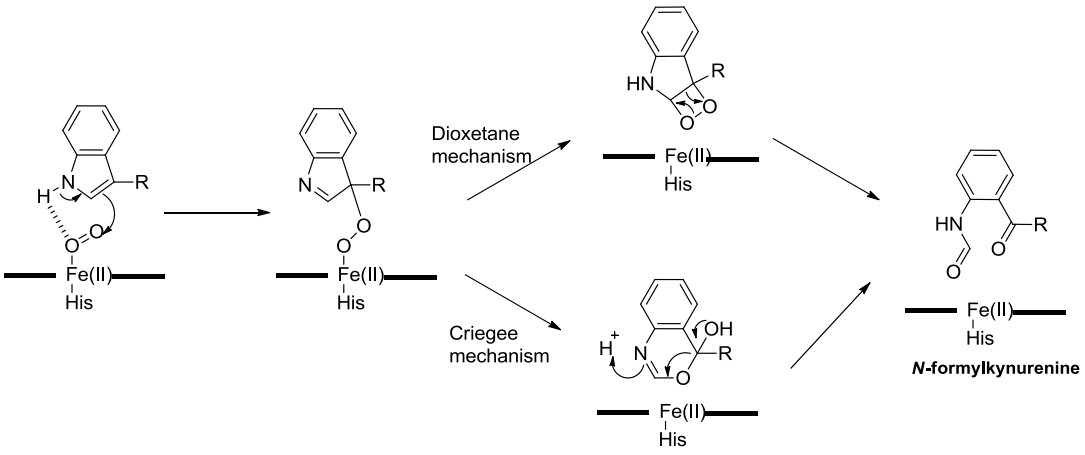
Despite decades of research the reaction mechanism by which oxygen is inserted into tryptophan by IDO has still not been clarified. Early studies[22] suggested that the reaction starts with deprotonation of the indole proton by an active site base that stimulates the electrophilic addition of the haem-bound dioxygen intermediate to the carbon-3 of the deprotonated tryptophan, producing a 3-indolenylperoxy-Fe(II) complex (**Scheme 3**). However, and given the fact that human IDO does not contain an active site base, the proposed mechanism seemed problematic. This led to an alternative proposal[27] which did not require a base (**Scheme 3**). Nonetheless, several sources of evidence, such as, inconsistency with the chemistry of indoles (that do not react by loss of the indole proton), significant IDO activity when tryptophan was replaced by 1-methyltryptophan[28,29] and also the fact that

several studies[30,31] revealed that proton transfer from the indole to the haem—bound dioxygen exhibit a very high activation barrier, suggested that both proposals are not feasible.[32,33]




**Scheme 3** Abstraction of the indole proton by an active site base (A); Abstraction of the indole proton by the haem-bound dioxygen (B).

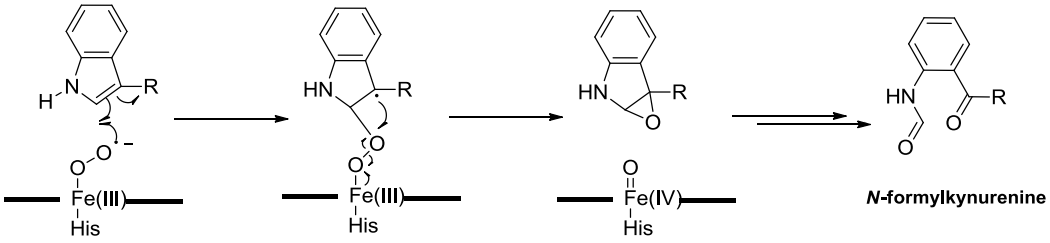
The last steps of the reaction leading to *N*-formylkynurenine are proposed to occur by either a Criegee or dioxetane rearrangements, even though there is no experimental evidence (**Scheme 4**).[22]




**Scheme 4** Proposed dioxetane and Criegee reaction mechanisms for formation of *N*-formylkynurenine.

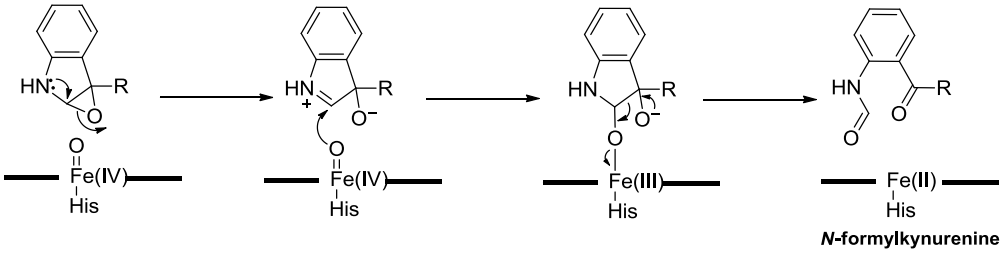
Recent Raman spectroscopy[23] and mass spectrometry[32] have suggested that the mechanism of formation of *N*-formylkynurenine by IDO may proceed *via* a two-step reaction, in which the two atoms of dioxygen are inserted into the substrate one at a time. This finding is not consistent with haem-based dioxygenase chemistry, which was believed to proceed *via* simultaneous incorporation of both atoms of dioxygen.[22] According to several authors[23,32,33]

the ternary complex of IDO is activated by partial electron transfer from the haem to the dioxygen, which is consistent with the superoxide character observed by $\nu_{O-O}$ at 1137 $cm^{-1}$, and then inserted into the C(2)=C(3) bond of tryptophan to produce a 2-indolenylperoxy radical, which spontaneously convert to a ferryl haem and a 2,3-epoxide, through a homolytic O-O bond cleavage (**Scheme 5**).




**Scheme 5** Proposed ferryl-based mechanism.

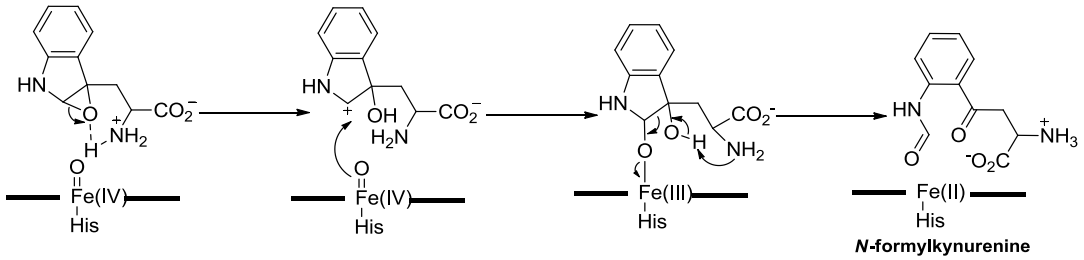
The last steps of the mechanism leading to *N*-formylkynurenine are not yet clarified. In view of mass spectrometry data, Basran and co-workers[32] proposes that ring opening of the 2,3-epoxide followed by attack of the ferryl haem on the substrate, should give an intermediate that after cleavage of the C(2)-C(3) bond will produce *N*-formylkynurenine (**Scheme 6**).




**Scheme 6** Final steps of *N*-formylkynurenine formation as proposed by Basran *et al.*[32]

More recently Capece and co-workers[33] using QM/MM methods postulate that the mechanism starts with proton transfer from tryptophan-$NH_3^+$ to the epoxide oxygen, resulting in epoxide opening, followed by nucleophilic attack of the ferryl oxygen to the C(2) of tryptophan. The resulting intermediate is then converted into the desired product, after

cleavage of the C(2)-C(3) bond and proton transfer from the oxygen to the indoleamine (**Scheme 7**).




**Scheme 7** Final steps of *N*-formylkynurenine formation as proposed by Capece *et al.*[33]

### 1.2.4. IDO inhibitors

Until recently, the best known IDO inhibitors were mainly analogues of tryptophan, that are active only at concentrations of >10 µM. Examples shown in **Figure 4** include 1-methyltryptophan **5** ($K_i$ = 32 µM),[4,34,35] the natural product brassinin **6** ($K_i$≈98 µM)[36] and methylthiohydantoin-tryptophan **7** ($K_i$=11.4 µM).[37]

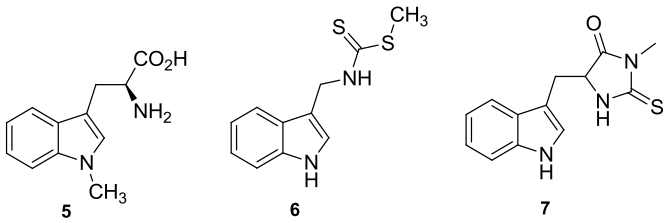



**Figure 4** Inhibitors of IDO.

In 2006, a screen of natural compounds disclosed the marine natural products annulins A **8** ($K_i$ =690 nM), B **9** ($K_i$ =120 nM) and C **10** ($K_i$=140 nM), isolated from the orange hydroid *Garveia annulata*, as potent inhibitors of IDO.[38,39] Exiguamine A **11**, an alkaloid of the marine sponge *Neopetrosia exigua*, was also reported as potent IDO inhibitor ($K_i$=40 nM) (**Figure 5**).[40]

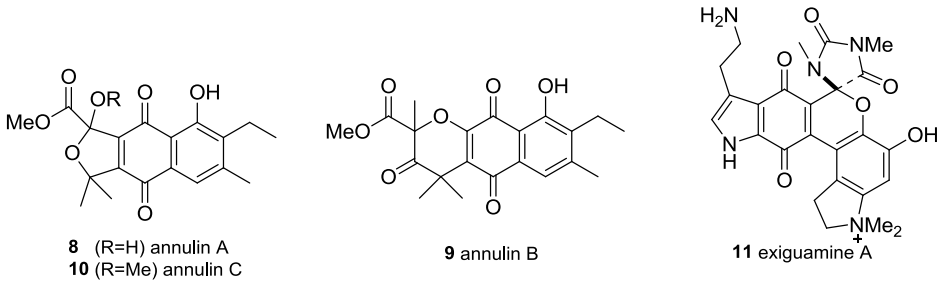



**Figure 5** Some naturally occurring IDO inhibitors.

Based on the earlier discovery of the marine invertebrate inhibitors, Carr and coworkers[41] identified the tryptamine quinone moiety as a fundamental pharmacophore of exiguamine A and reported several derivatives, the best showing a $K_i$ of 200 nM (**Figure 6**).

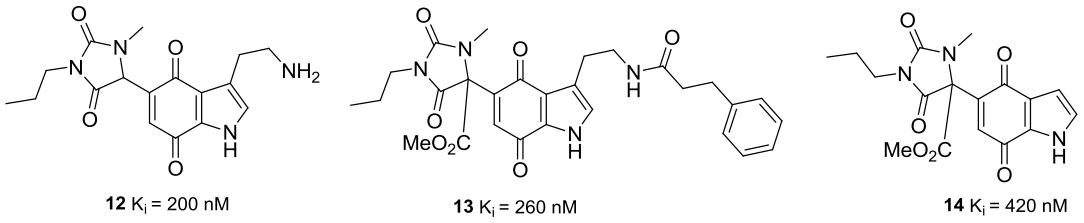



**Figure 6** IDO inhibitors reported by Carr *et al.*

Kumar *et al.*[42] focused on the naphthoquinone core of annulin B and designed various derivatives with $IC_{50}$ values down to 55 nM (**Figure 7**).

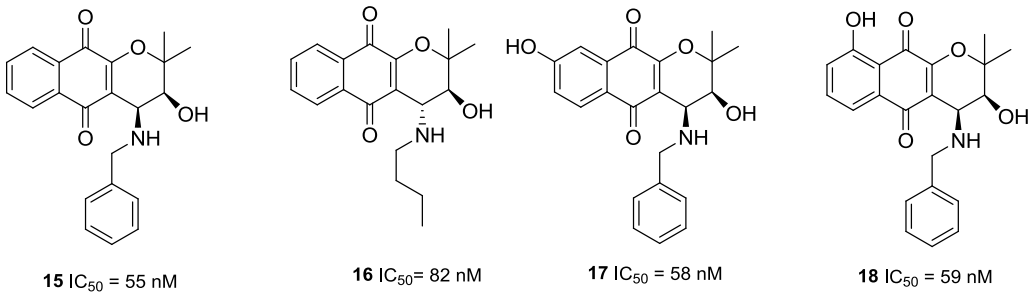



**Figure 7** IDO inhibitors reported by Kumar *et al.*

Further screening of IDO inhibitors have revealed new natural product inhibitors, including plectosphaeroic acids A **19**, B **20** and C **21** ($IC_{50}\approx 2$ μM),[43] trans-avicennol **22** ($K_i$ = 635

μM)[44] and potent synthetic competitive inhibitors, such as, hydroxyamidine derivatives **23**[45] ($IC_{50}$ values down to 60 nM) and S-benzyl*iso*thiourea analogues **24**[46] ($IC_{50}$ values down to 100 nM) (**Figure 8**).

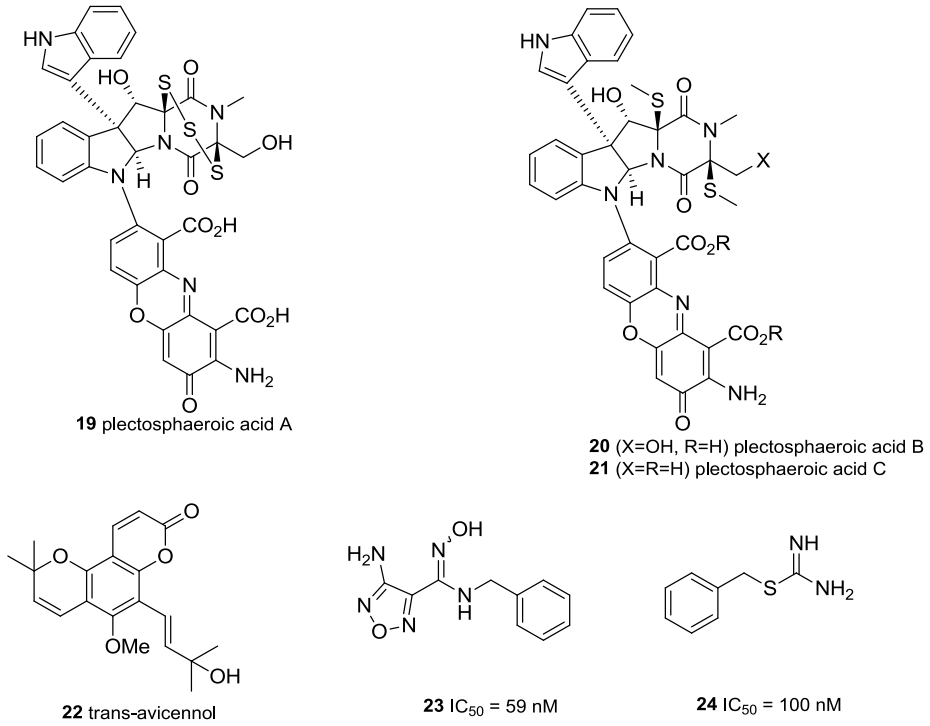



**Figure 8** IDO inhibitors.

Despite extensive work, until now only 1-methyl-D-tryptophan and a derivative of hydroxyamidine series have achieved phase 1 clinical testing.[47] As a result there is a continuing need for novel and potent IDO inhibitors.

## 1.3. Conclusion

Interest in IDO is increasing continuously since the discovery of its involvement in the mechanisms of immune tolerance and tumour immune escape. Despite great advances on the structure, activity and expression, intense research is still necessary in order to clarify several aspects and to use that information to synthesise IDO inhibitors that might be used in clinical oncology.

# CHAPTER II

## STUDIES TOWARDS THE SYNTHESIS OF ANNULINS A AND C

## 2.1. Introduction

In many forms of human efforts, Nature often provides the inspiration, and searching for new anticancer compounds is no exception. Natural products have emerged *via* biosynthesis by proteins, and these evolutionary selected ligands generally fulfill the prerequisites for binding to proteins and penetrating cell membranes.[48] Natural products have contributed significantly to the development of anticancer drugs. According to a review by Newman *et al*,[49] in the period between 1981 to 2006, of the 81 new small molecules approved as anticancer drugs, only 18 of them can be classified as truly synthetic. The majority are natural product derived or inspired.

In an attempt to find better IDO inhibitors that could be used as drug leads, some groups have screened libraries of marine invertebrate extracts for their ability to inhibit recombinant human IDO *in vitro*. Among the compounds discovered using the *in vitro* screen are the polyketides annulins A **8**, B **10** and C **9**, 2-hydroxygarveatin E **25** and garveatin E **26**, as well as, exiguamine A **11** (**Figure 9**).[38,40]

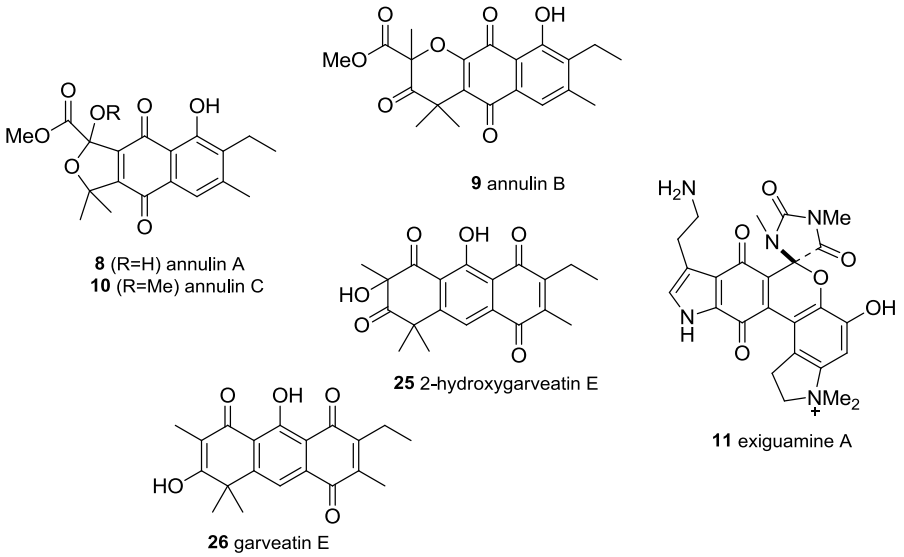



**Figure 9** IDO inhibitors discovered by *in vitro* screening of marine natural products libraries.

## 2.2. Annulins A and C – discovery and description

Annulins A and C are two naphthalene-based polyketides isolated by Fahy and coworkers and Pereira and coworkers, respectively, from a Northeastern Pacific hydroid *Garveia annulata*. Their structures were elucidated by high resolution ionization impact mass spectroscopy (HREIMS), NMR and X-ray crystallography (for annulin A).[38,39]

Annulin A is a naturally occurring racemate with only one chiral centre, C-1, that eventually epimerizes in solution (**Figure 10**).[39] NMR data for annulins A and C revealed a strong similarity, indicating that the molecules were directly related. The main difference in the $^{1}$H-NMR spectra was the lack of the hemiketal OH signal, in the spectrum of **10** and a new methyl singlet signal. Further HMBC studies suggested that the hemiketal in annulin A was replaced by a methyl ketal in annulin C. Pereira and coworkers suggested that annulin C is probably an "isolation artifact" with the methyl ketal being formed by reaction of the natural occurring metabolite annulin A with the methanol extraction solvent.[38]

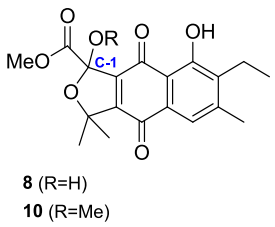



**Figure 10** Annulins A and C.

## 2.3. Aim of the project

In view of our interest in developing novel cancer therapeutic agents based on the inhibition of IDO, we decided to investigate routes to prepare the natural compounds annulins **A** and **C**. In parallel and for comparison purposes the synthesis of a simple analogue, containing the isobenzofuranquinone moiety was also attempted.

## 2.4. Results and discussion

### 2.4.1. Advances towards the synthesis of analogue 27

In order to evaluate which part of the molecule of annulins A and C was important for IDO inhibition we first decided to attempt the synthesis of the analogue **27** (**Figure 11**).

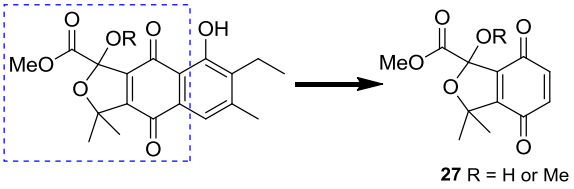
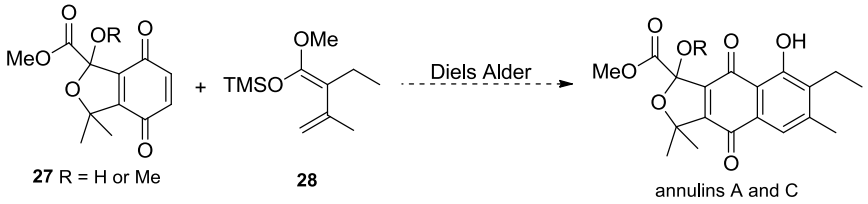



**Figure 11** Analogue **27**.

The preparation of this analogue was of great interest because it could be used in the synthesis of the natural compounds annulins A and C, by applying a Diels Alder reaction between the analogue and a suitable diene **28** (**Scheme 8**).

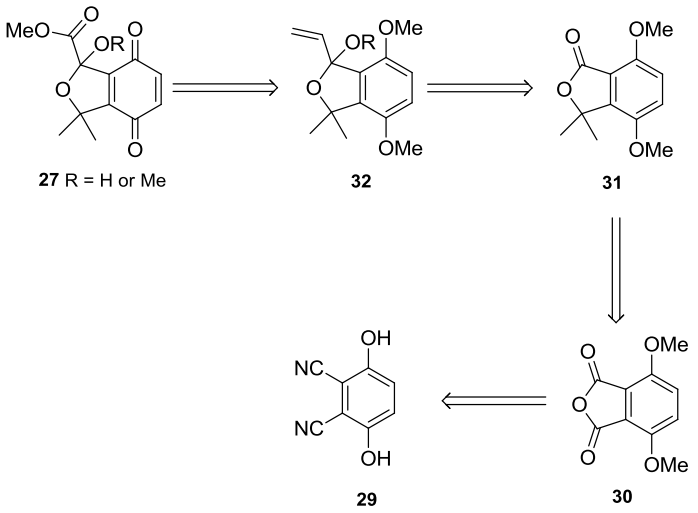



**Scheme 8** Diels-Alder reaction between analogue **27** and diene **28**.

#### 2.4.1.1. Initial synthetic route

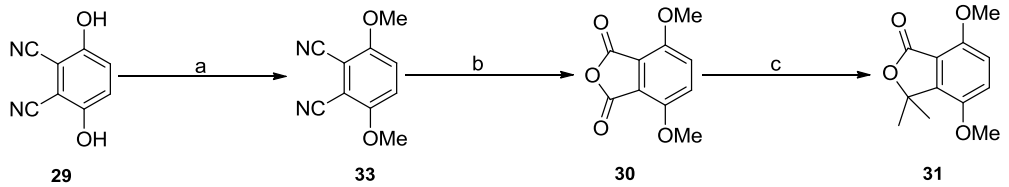
A first retrosynthesis was proposed for analogue **27** (**Scheme 9**). The plan was to perform the oxidation to the quinone at the end of the synthesis and to introduce a vinyl group as a carboxyl precursor at C-1. Therefore, dimethylation of the commercially available 2,3-dicyanohydroquinone **29** followed by hydrolysis and cyclodehydration would provide the phthalic anhydride **30**. Then, addition of methylmagnesium bromide should result in the formation of the tertiary alcohol that is expected to cyclise to the desired phthalide **31**.

Thereafter, addition of vinylmagnesium bromide was expected to provide the lactol **32** (R=H), that after treatment with acidic methanol should lead to the ketal (R=Me). Finally, oxidative cleavage of the vinyl group should install the carboxylate, readily esterified, and oxidative demethylation of the 1,4-dimethoxybenzene moiety should provide the desired quinone **27**.



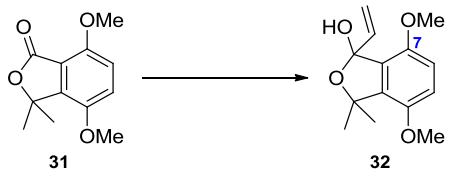

**Scheme 9** Retrosynthesis of analogue **27**.

The synthesis started with protection of the hydroquinone **29** with dimethyl sulfate in 81% yield. Then, hydrolysis with concentrated sulfuric acid followed by treatment with an excess of acetic anhydride gave the desired phthalic anhydride **30** (51% yield).[50] Next, the anhydride was reacted with an excess of methylmagnesium bromide to give phthalide **31** in 68% yield (**Scheme 10**).[51]




**Scheme 10** *Reagents and conditions:* (a) $Me_2SO_4$, $K_2CO_3$, 2-butanone, reflux, 18 h, 81%. (b) *1.* $H_2SO_4$ conc., 100 ºC, 1 h; *2.* rt, 16 h; *3.* Acetic anhydride, reflux, 1 h; 51%. (c) *1.* MeMgBr, THF, 0 ºC; *2.* rt, 16 h; *3.* HCl 10%, 0º C, 1 h, 68%.

It was then planned to react the phthalide **31** with vinylmagnesium bromide to provide the lactol **32**. This conversion proved more difficult than anticipated and several reaction conditions were investigated (**Table 1**).




| Entry | Reagents | Solvent | Temperature/ ºC | Isolated Products |
|---|---|---|---|---|
| **1** | vinylMgBr (1.3 eq.) | THF | -78-0 | starting material + degradation |
| **2** | vinylMgBr (1.3 eq.) | THF | 0-rt | starting material + degradation |
| **3** | vinylMgBr (1.3 eq.) | $Et_2O$ | 0-reflux | starting material |
| **4** | vinylMgBr (1.3 eq.), LiCl (1 eq.) | THF | -78-0 | degradation |
| **5** | vinylMgBr (1.3 eq.), LiCl (3 eq.) | THF | -78-0 | starting material + degradation |
| **6** | vinylMgBr (2.2 eq.) | THF | -20-0 | degradation |
| **7** | vinylMgBr (1.3 eq.) | THF | -20-0 | degradation |
| **8** | vinyl lithium (1.3 eq.) | THF | -20-0 | complex mixture |

**Table 1** Conditions screened to obtain compound **32**.

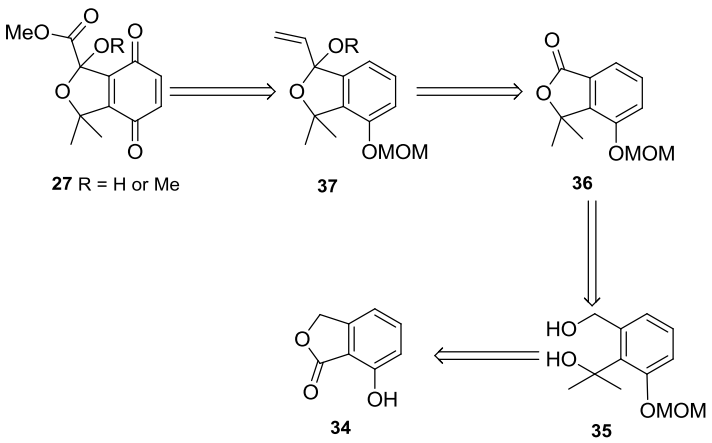
To our surprise, none of the experimental conditions tested produced the desired product, returning either starting material or degradation products. The lack of reactivity is probably due to the electron-donating character of the methoxy group in position 7 that deactivates the carbonyl group and prevents the Grignard addition. As a result, this strategy was no longer

investigated and it was decided to redesign the synthesis plan considering the influence of the electron-density of the aromatic moiety.

### 2.4.1.2 Revised retrosynthetic approach 1

As mentioned earlier, conversion of phthalide **31** into lactol **32** was impossible to perform, and this was probably due to the electron-donating group in position 7. Therefore, it was decided to design a new synthetic route that included a more electron deficient aromatic ring, such as compound **37**.

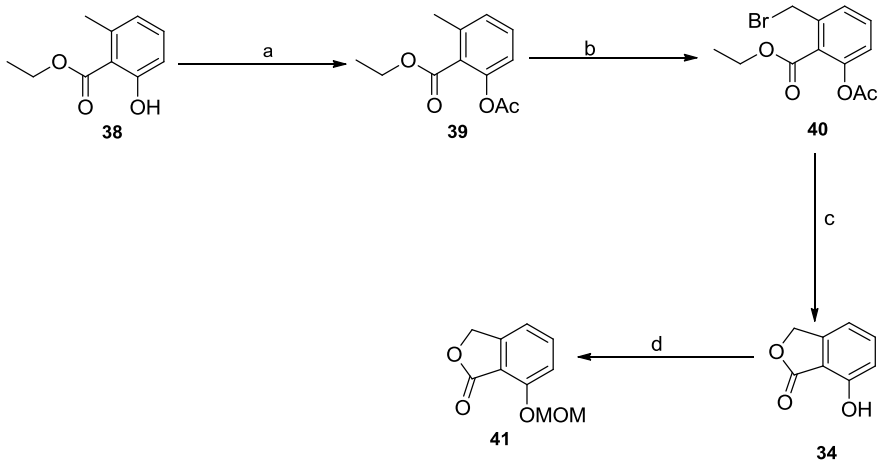
Similarly to the previous synthetic route, the ester group in **27** was expected to be obtained by oxidative cleavage of the vinyl group in **37**. The latter would be the result of the addition reaction of vinylmagnesium bromide to compound **36** and this lactone would stem from the diol **35** *via* oxidation. This intermediate would be available by addition of methylmagnesium bromide to the suitably protected phenol **34** (**Scheme 11**).




**Scheme 11** Improved retrosynthesis of the analogue **27**.

The starting material **34** was prepared according to Hamada *et al.*[52] and Tabacchi *et al.*[53] in three steps. The synthesis started with acetylation of the commercially available compound

**38** with acetic anhydride and pyridine. Thereafter, benzylic bromination with *N*-bromosuccinimide (NBS) in carbon tetrachloride gave compound **40** that underwent cyclisation in water/dioxane at reflux to yield the desired compound in 81% yield, over three steps. Finally, protection of the free alcohol **34** with methoxymethyl chloride in the presence of Hünig's base, at room temperature, gave the MOM-protected phthalide **41** in very good yield. It must be noted that the success of this protection depends extremely on the degree of purity of the starting material (**Scheme 12**).

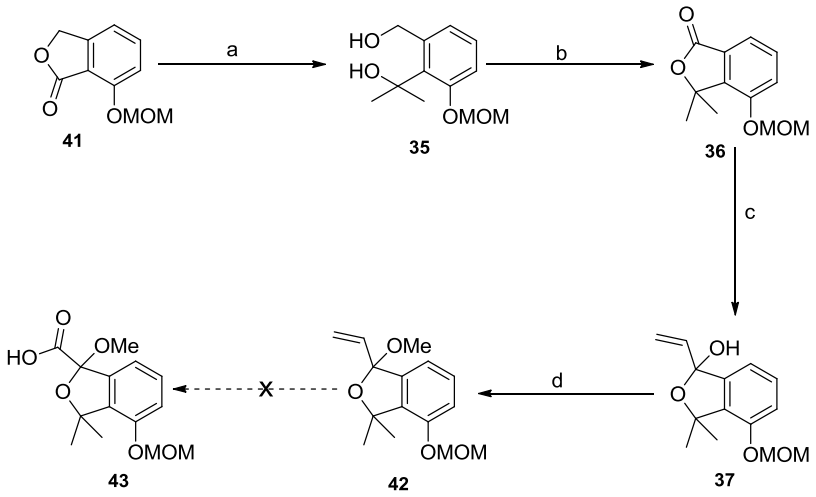



**Scheme 12** *Reagents and conditions:* (a) Acetic anhydride, pyridine, rt, 3 h, quantitative; (b) NBS, benzoyl peroxide, $CCl_4$, reflux, 4 h; (c) $H_2O$/dioxane, reflux, 18 h, 81%; (d) MOMCl, $i$Pr$_2$NEt, $CH_2Cl_2$, rt, 6.5 h, 81%.

Methylmagnesium bromide was then added to the MOM-protected phthalide to give the desired diol **35** that is prone to degradation during purification by column chromatography on silica-gel. For the oxidation step of diol **35** it was feared that the MOM protecting group might not be stable to oxidation methods in acidic conditions. Therefore, initial attempts were made under mild conditions, using *N*-iodosuccinimide and silver acetate as described by Beebe *et al.*[54] Unfortunately, this method failed to provide the desired lactone. Unexpectedly, the highly acidic Jones' reagent in acetone cleanly oxidized compound **35** to the corresponding lactone **36** in good yield.[55] Next, addition of vinylmagnesium bromide to lactone **36** in THF at room temperature yielded the desired lactol **37**. A reaction time of five hours and 1.5 equivalents of the Grignard reagent were required to obtain complete

conversion into the lactol. The hydroxyl group had now to be protected. Initial attempts using hydrochloric acid or sulfuric acid in methanol only led to degradation. Best conditions were found by reacting the lactol with methyl iodide and silver(I) oxide at room temperature for 24 hours, or with methyl iodide and sodium hydride in DMF at room temperature for 1.5 hours (**Scheme 13**).

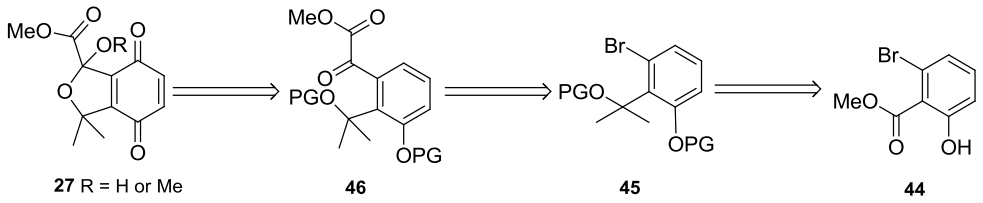
Next, the plan was to install the carboxylate *via* oxidative cleavage of the vinyl group. Usual procedures imply the use of ozone followed by a oxidative work-up[56] in different solvents, osmium tetroxide followed by sodium periodate (Lemieux-Johnson reagent)[57] or osmium tetroxide and then oxone[58] to give directly the carboxylic acid. Several attempts, using these conditions, failed, and only complex mixtures were obtained. Possible side reactions and instability of the starting material are to be accounted for. A new approach was therefore designed.




**Scheme 13** *Reagents and conditions:* (a) MeMgBr, THF, rt, 1 h, 60-74%; (b) Jones' reagent 1.98 M, acetone, 0 ºC, 1.5 h, 78%; (c) vinylMgBr, THF, rt, 5 h, 93%; (d) $Ag_2O$, MeI, rt, 24 h, 84%.

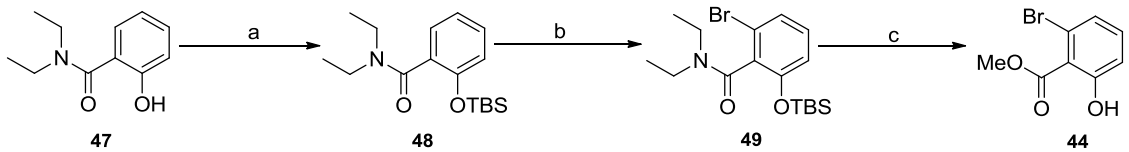
### 2.4.1.3 Revised retrosynthetic approach 2

As the original plan to install the carboxyl group *via* oxidative cleavage of the vinyl group proved unsuccessful it was next planned to introduce directly the α-ketoester moiety by addition of methyl oxalyl chloride or dimethyl oxalate to the corresponding lithiated derivative **45**. The latter would derive from phenol **44**, after reaction with methylmagnesium bromide (**Scheme 14**).




**Scheme 14** Revised retrosynthetic approach 2.

The most straightforward strategy to access phenol **44** was to protect the commercially available phenol **47** with *tert*-butyldimethylsilyl chloride (TBSCl), selectively *ortho* lithiate and quench the resulting anion with bromine to give bromo-amide **49**. Conversion of the amide functionality into methyl ester and removal of TBS protecting group was effected using trimethyloxonium tetrafluoroborate (**Scheme 15**).[59]

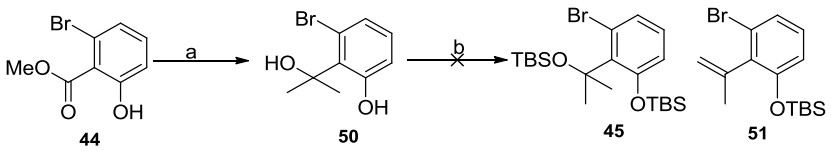



**Scheme 15** *Reagents and conditions:*(a) TBSCl, *i*-$Pr_2NEt$, DMF, rt, 17 h, quantitative; (b) *1*. *t*-BuLi, THF, -78 ºC, 1 h; *2*. $Br_2$, -78 ºC, 30 min.; *3*. -78 ºC–rt, 21 h, 68%; (c) *1*.$Na_2HPO_4$, $Me_3OBF_4$, $CH_3CN$, 16 h, rt; *2*. $NaHCO_3$ sat. (aq.), rt, 23 h, 69%.

With compound **44** in hand, the access to the tertiary alcohol intermediate **50** was conveniently accomplished by addition of methylmagnesium bromide in excess. This

reaction gave the desired tertiary alcohol **50** in moderate yield, along with the corresponding olefinic product, that results from the dehydration of the tertiary alcohol.

Next, the plan was to protect both hydroxyl groups as TBS ethers that are known to resist basic conditions (*n*-BuLi, *s*-BuLi, *t*-BuLi) and can be easily removed with tetrabutylammonium fluoride (TBAF) in THF at 0 ºC.[60,61] Initial attempts, using TBS protection standard conditions for hindered alcohols (silyl triflate with a hindered amine base at low temperature)[62,63] only gave the olefinic product **51** (53%) (**Scheme 16**). Repeating the reaction using TBSCl as reagent with either imidazole or 4-dimethylaminopyridine as catalyst gave similar results. In fact, tertiary alcohols are known to easily undergo elimination, producing the corresponding olefinic by-product in high yields.[64,65]




**Scheme 16** *Reagents and conditions:* (a) *1.*MeMgBr, THF, 0 ºC, 1.5 h; *2.* 0 ºC-rt, 2 h 45 min., 63%; (b) TBSOTf, 2,6-lutidine, dichloromethane, rt, 3 h.

Although we were unable to protect both hydroxyl groups it was decided to continue into the next step and react compound **50** with an excess of *t*-BuLi and dimethyl oxalate. Unfortunately this reaction failed to provide the desired compound, but instead compound **52** (25%) was isolated along with degradation products. The structure of compound **52** was ascertained by NMR spectroscopy (**Figure 12**).

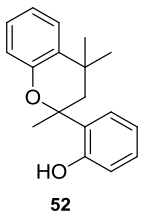
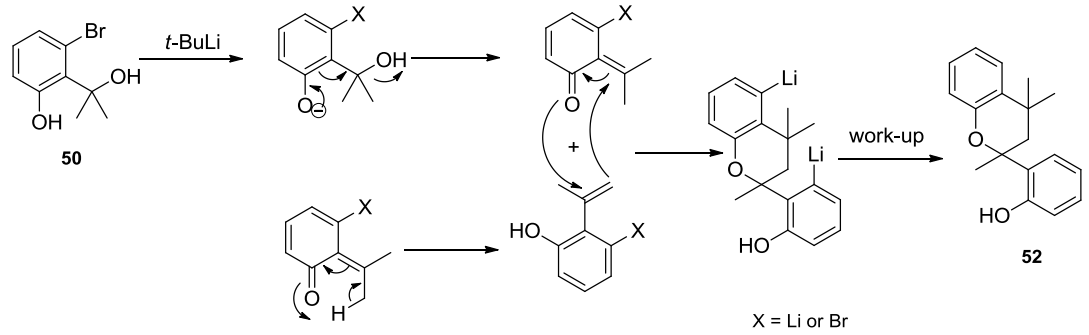



**Figure 12** Structure of compound **52**.

Compound **52** is probably generated by hetero Diels-Alder reaction between a quinone methide and an alkene, the latter being formed by 1,5-H shift of the quinone methide (**Scheme 17**).

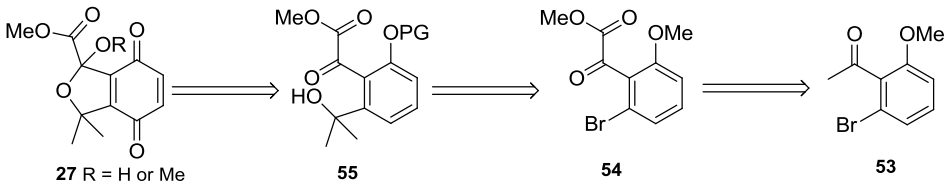



**Scheme 17** Proposed mechanism for the formation of compound **52**.

Given the instability of the tertiary alcohol it was clear that it was essential to introduce the α-keto ester moiety before generating the tertiary alcohol. It was from this context that a new strategy emerged.

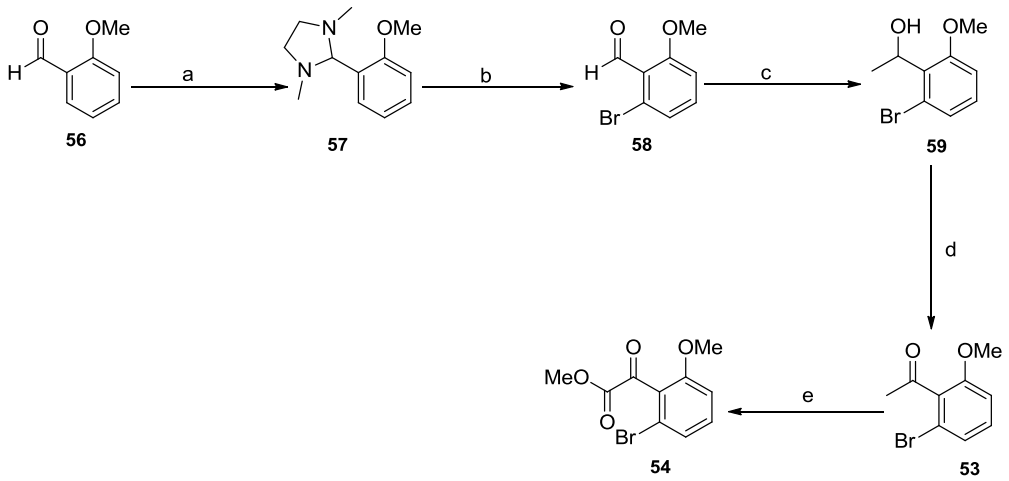
### 2.4.1.4 Revised retrosynthetic approach 3

In this modified synthetic strategy, it was proposed to generate the α-ketoester moiety through oxidation of methylketone **53** using selenium dioxide, followed by reaction with thionyl chloride in methanol, according to the conditions described by Zhuang *et al.*[66] The required tertiary alcohol was expected to be accessed from intermediate **54** by halogen-metal exchange and reaction with acetone. Similarly to the previous synthetic plans described, it was proposed to perform the oxidation of the free phenol to the *para*-quinone at the end of the synthesis, using for example, Fremy's salt (**Scheme 18**).




**Scheme 18** Revised retrosynthetic approach 3.

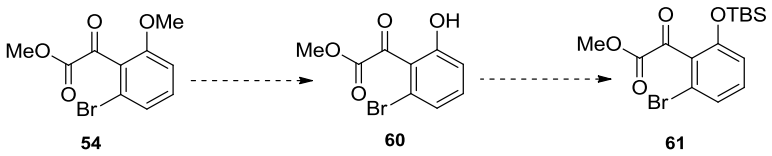
Our first, and relatively simple, task was to synthesise the requisite methylketone **53**. This assignment was successfully accomplished using the synthetic sequence shown in **Scheme 19**. Thus, commercially available 2-methoxybenzaldehyde **56** was protected as the corresponding imidazolidine **57**. Directed metalation of the latter and then bromination with dibromotetrachloroethane followed by acidic work up provided 2-bromoanisaldehyde **58** in good yield.[67] Final conversion to ketone **53** was accomplished by addition of methyl magnesiumbromide to aldehyde **58**, revealing the secondary alcohol **59** that was oxidized with Dess-Martin periodinane[68,69] in excellent yield. With compound **53** synthesised, we proceeded to perform the oxidation of the methylketone, using selenium dioxide, followed by esterification *via* the chloride intermediate. Using a protocol taken directly from the literature,[66] the desired aryl α-keto ester **54** was obtained in very good yield.




**56** **57** **58** **59** **54** **53**

**Scheme 19** *Reagents and conditions:* (a) *N*,*N*'-dimethylethylenediamine, EtOH, rt, 24 h, 75%; (b) *1*. *t*-BuLi, $Et_2O$, -40 ºC, 1 h; *2*. -20 ºC, 7 h; *3*. $(CBrCl_2)_2$, 0 ºC-rt, 14 h, 53-59%; (c) MeMgBr, THF, 0 ºC-rt, 1 h, quantitative; (d) Dess-Martin periodinane, 0 ºC-rt, 1.5 h, 90%; (e) *1*. $SeO_2$, pyridine, 100 ºC, 23 h; *2*. $SOCl_2$, MeOH, rt, 15 h; *3*. $HClO_4$, MeCN, $H_2O$, 0.5 h, rt, 81%.

In order to avoid using harsh conditions generally needed to cleave methyl ethers, in the last steps of the synthesis, it was decided to examine at this stage demethylation of **54** to phenol **60** that would then be protected with the more easily removable TBS group (**Scheme 20**).

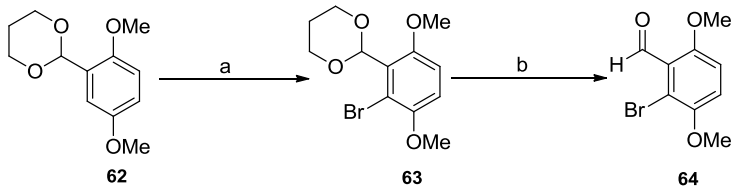



**Scheme 20** Prospective demethylation and TBS protection steps.

Initial attempts using $BCl_3$, $BBr_3$, $CeCl_3.7H_2O$ or TMSI only led to recovery of starting material.[60,61] Additional experimentation using other demethylating agents such as, $AlCl_3$, $AlBr_3$, or a combination of both, once again failed to furnish the desired phenol, leading to recovery of starting material, degradation products or a mixture of compounds, in which both the methyl ester and methoxy groups, or only the methyl ester group, were removed.

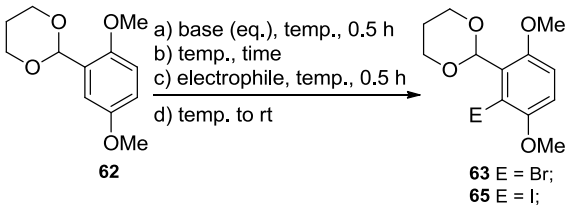
These results led us to examine an alternative starting material, namely 2,5-dimethoxybenzaldehyde, that allowed us to avoid the demethylation step. In this case, the dimethoxybenzene intermediate could be directly subjected to oxidative demethylation leading to the desired quinone.

The aldehyde **64** has previously been prepared by Li and co-workers.[70] Their synthesis involved the directed lithiation of 1,3-dioxane derivative **62**, using *n*-BuLi in a mixture of hexane and benzene, followed by bromination with dibromotetrafluoroethane and acidic hydrolysis to provide benzaldehyde **64** in very good yield (**Scheme 21**).




**Scheme 21** *Reagents and conditions:* (a) *1. n*-BuLi, hexane/benzene (3:1), –25 ºC, 10 h; *2.*$BrCF_2CF_2Br$, THF, rt, 0.5 h, 70%; (b) 13 M HCl, THF, rt, 10 min., 100%.[70]

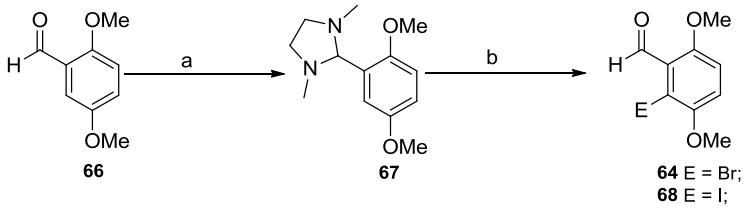
When this reaction was repeated under the reported conditions, the desired compound **63** was obtained in considerable lower yield (27 %), along with starting material (**Table 2**, entry 1). In order to optimize this reaction and to avoid using benzene as solvent, several reaction conditions, including, base, electrophile, temperature and time, were screened. The best results were obtained by reacting **62** with *t*-BuLi at –40 ºC, followed by addition of iodine at the same temperature. The desired iodinated compound **65** was obtained in moderate yield (entry 8).




| Entry | Base | Electrophile | Solvent | Temp./ ºC | Time/ h | Isolated Products |
|---|---|---|---|---|---|---|
| **1** | *n*-BuLi (1.5 eq.) | $(CBrF_2)_2$ | Hexane/ benzene | –25 | 10 | **63** (27%) |
| **2** | *n*-BuLi (1.5 eq.) | $(CBrCl_2)_2$ | Hexane/ benzene | –25 | 6 | starting material |
| **3** | *t*-BuLi (2.0 eq.) | $Br_2$ | $Et_2O$ | –78 | 0.5 | starting material |
| **4** | *t*-BuLi (2.0 eq.) | $I_2$ | $Et_2O$ | –78 | 0.5 | **65** (8%) + starting material (74%) |
| **5** | *t*-BuLi (2.0 eq.) | $I_2$ | $Et_2O$ | –40 | 0.5 | **65** (24%) + starting material (55%) |
| **6** | *t*-BuLi (2.0 eq.) | $I_2$ | $Et_2O$ | –20 | 0.5 | **65** (24%) + starting material (61%) |
| **7** | *t*-BuLi (2.0 eq.) | $I_2$ | THF | –40 | 0.5 | starting material |
| **8** | *t*-BuLi (3.0 eq.) | $I_2$ | $Et_2O$ | –40 | 0.5 | **65** (35%) + starting material (52%) |

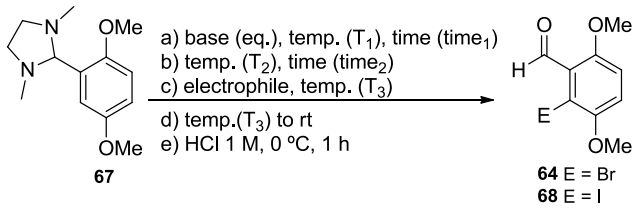
**Table 2** Directed metalation/halogenation of 1,3-dioxane derivative **62**.

As an alternative, we next examined directed metalation/halogenation of aldehyde **66** by first protecting it as its corresponding imidazolidine **67** and subsequently to react it with different electrophiles, under varied experimental conditions (**Scheme 22**).




**Scheme 22** *Reagents and conditions:* (a) *N*,*N*'-dimethylethylenediamine, EtOH, rt, 24 h, 95% (b) see Table 3;

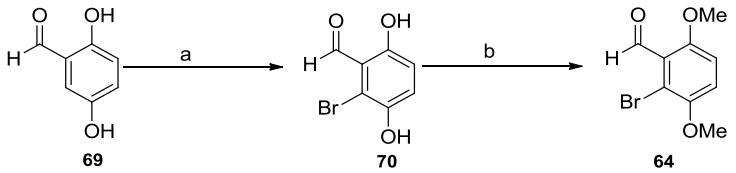
Unfortunately, all attempts failed to provide the desired halogenated benzaldehyde in better yields, than those described before (**Table 3**).




| Entry | Base | Electrophile | Solvent | $T_1$/ ºC | $T_2$/ ºC | $T_3$/ ºC | $Time_1$ / h | $Time_2$ / h | Isolated Products |
|---|---|---|---|---|---|---|---|---|---|
| **1** | *n*-BuLi (1.5 eq.) | $(CBrCl_2)_2$ | Hexane/ toluene | –25 | –25 | –25 | 0.5 | 7.5 | deprotected starting material |
| **2** | *t*-BuLi (2.3 eq.) | $(CBrCl_2)_2$ | $Et_2O$ | –40 | –20 | 0 | 1 | 7 | **64** (26%) |
| **3** | *t*-BuLi (2.3 eq.) | $(CBrCl_2)_2$ | THF | –40 | –20 | 0 | 0.75 | 0.5 | deprotected starting material |
| **4** | *t*-BuLi (2.3 eq.) | $Br_2$ | $Et_2O$ | –78 | –78 | –78 | 0.5 | 0.5 | deprotected starting material |
| **5** | *t*-BuLi (2.3 eq.) | $I_2$ | $Et_2O$ | –78 | –78 | –78 | 0.5 | 0.5 | deprotected starting material |

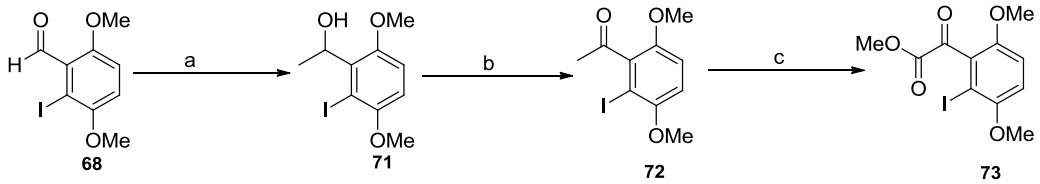
**Table 3** Directed metalation/halogenation of imidazolidine derivative **67**.

Alternatively, the desired halogenated benzaldehyde, in this case, the bromoderivative **64** was synthesised through a two step sequence involving bromination[71] of the commercially available 2,5-dihydroxybenzaldehyde **69** in position 6, followed by methylation of both hydroxyl groups, using dimethyl sulfate in the presence of potassium carbonate (**Scheme 23**).



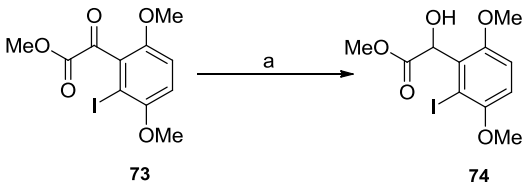

**Scheme 23** *Reagents and conditions:* (a) $Br_2$, $CHCl_3$, rt, 2.5 h, 95%; (b) $Me_2SO_4$, $K_2CO_3$, DMF, rt, 24 h, 28%.

As mentioned in the retrosynthetic analysis, the formation of the tertiary alcohol in position 6 was envisaged to be accessed through metal-halogen exchange followed by reaction with acetone. Given the fact that metal-halogen exchange reactions with lithium or magnesium, are known to be faster with iodinated compounds than with the corresponding brominated compounds it was decided to pursue the next steps using the iodinated derivative **68**. Therefore, following the same synthetic sequence, previously described for the synthesis of compound **54**, iodobenzaldehyde **68** was converted into the desired aryl α-ketoester **73** in very good yield (**Scheme 24**).




**Scheme 24** *Reagents and conditions:* (a) MeMgBr, THF, 0 ºC-rt, 2.5 h, 98%; (b) Dess-Martin periodinane, 0 ºC–rt, 3.5 h, 75%; (c) *1*. $SeO_2$, pyridine, 100 ºC, 23 h; *2*. $SOCl_2$, MeOH, rt, 16 h; *3*. $HClO_4$, MeCN, $H_2O$, 1 h, rt, 79%.

Before performing the metal-halogen exchange it was decided to first reduce the ketone function and then protect the exposed alcohol, in order to avoid possible side reactions. Reduction was carried out in the presence of sodium borohydride at room temperature for 1 h, giving the desired product **74** in excellent yield (**Scheme 25**).

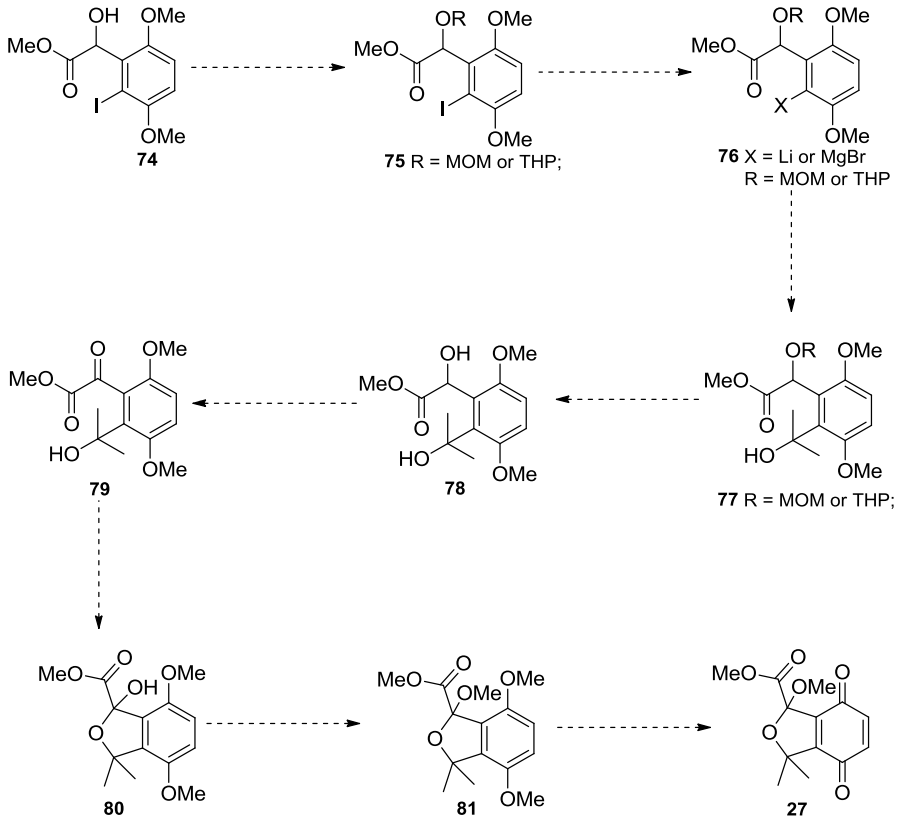



**73** **74**

**Scheme 25** *Reagents and conditions:* (a) $NaBH_4$, MeOH, rt, 1 h, 89%.

Due to a lack of material and time restriction, no more experiments could be carried out to complete the synthesis of the analogue **27**.

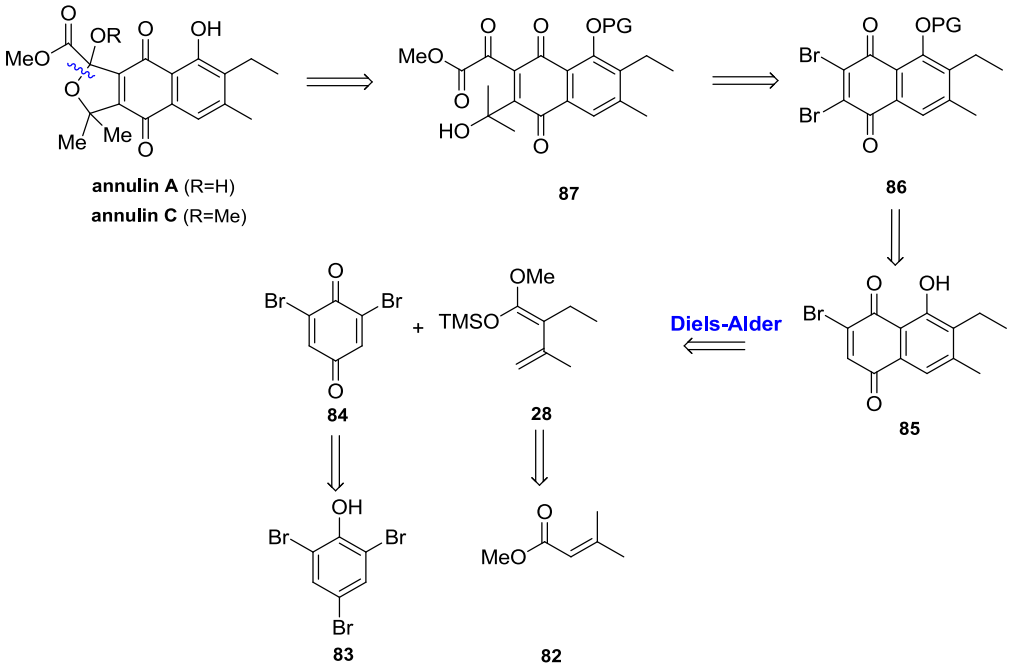
Future work will include the protection of the free alcohol with a protecting group resistant to basic conditions and acid labile, such as, MOM or THP, followed by conversion of the latter into the corresponding lithiated- or Grignard derivative[72] **76** and reaction with acetone (**Scheme 26**). After installing the tertiary alcohol, the hydroxyl protecting group could be removed with the use of a mild acid, such as, hydrochloric acid in ether[73] or with pyridinium *p*-toluenesulfonate in *t*-butanol.[74] Oxidation of the secondary alcohol with Dess-Martin periodinane should install the ketone **79** that after intramolecular reaction with the tertiary alcohol should provide the desired lactol **80**. Finally, treatment of the lactol with methyl iodide and silver(I) oxide should lead to the ketal **81**, and oxidative demethylation of the 1,4-dimethoxybenzene moiety should provide the desired product **27**.




**Scheme 26** Prospective completion of the synthesis.

### 2.4.2 Advances towards the synthesis of annulins A and C

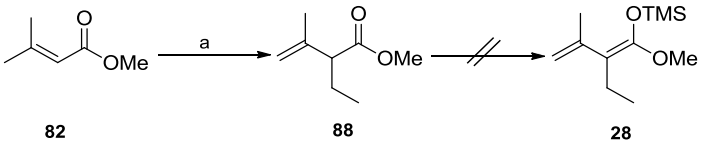
Our first hypothesis, when considering how to approach the synthesis of these compounds, was that the naphthoquinone core of annulins A and C could be assembled using a Diels-Alder reaction between diene **28** and dienophile **84**. The [4+2] cycloaddition of an electron rich diene to a halogenated quinone is known to proceed with very high regioselectivity, with the nucleophilic end of the diene forming a bond to the unhalogenated dienophile carbon.[75,76] We therefore proposed that diene **28** and dienophile **84** could be synthesised from methyl ester **82** and tribromophenol **83**, respectively .The furan ring was envisioned to be introduced by chemical manipulations of a dibrominated compound, such as **86** (**Scheme 27**).




**Scheme 27** Retrosynthesis of annulins A and C.

### 2.4.2.1 Construction of the naphthoquinone core

Our first task was to synthesise the requisite diene **28** and dienophile **84** that had been envisioned as key fragments for the synthesis of the naphthoquinone core. To access the dienophile **84**, commercially available phenol **83** was reacted with periodic acid, as described by Bhatt *et al.*[77] The synthesis of diene **28** began with alkylation of methyl senecionate **82** with ethyl iodide in the presence of lithium di*iso*propylamide (LDA), according to the procedure described by Wenkert *et al.*[78] It was then planned to convert butenoate **88** into the corresponding trimethylsilyloxy derivative **28**, using the classical conditions - trimethylsilyl chloride (TMSCl) and LDA as base. Unfortunately, these conditions proved to be ineffective, as no silylated product was observed (**Scheme 28**).




82 88 28

**Scheme 28** *Reagents and conditions:* (a) *1.* LDA, -70 ºC, 1 h; *2.*-70 ºC to 0 ºC; *3.* 0 ºC 1 h; *4.* $CH_3CH_2I$, 0 ºC; *5.* 0 ºC to rt; *6.* rt, 2 h; 73%.

A MeOD quenching experiment revealed that LDA was not deprotonating C-2 and, as a result, a range of different bases and temperatures were screened (**Table 4**).

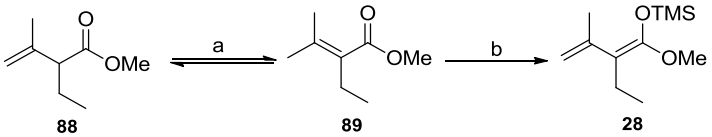
| Entry | Base | Temperature/ ºC | Isolated Products |
|---|---|---|---|
| **1** | LDA | –20 ─ 0 | no reaction |
| **2** | *n*-BuLi | 0 ─ rt | * |
| **3** | NaH | –78 ─ 0 | no reaction |
| **4** | *t*-BuLi | –78 ─ 0 | * |
| **5** | DBU | rt | degradation |
| **6** | KHMDS | –78 ─ –20 | degradation |

*-Base adds to the carbonyl group;

**Table 4** Conditions screened to obtain compound **28**

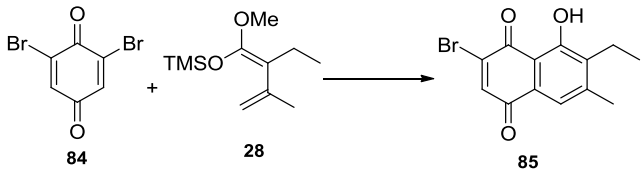
Several attempts using LDA, NaH, *n*-BuLi, *t*-BuLi, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or potassium hexamethyldisilazide (KHMDS) produced either no reaction, eventual decomposition of starting material or attack onto the carbonyl group. As an alternative, the terminal olefin of **88** was isomerised to the internal one by potassium *t*-butoxide[79] and the intermediate thus obtained was treated with LDA-TMSCl to give the desired silyl enol ether

**28** (**Scheme 29**). The configuration of the C-1 double bond was found to be most likely *Z*, on the basis of the observation of NOESY correlations from the methyl-TMS to the methoxy group at C-1 and the methyl group at C-3.




**Scheme 29** *Reagents and conditions:* (a) *t*-BuOK, 0 ºC-rt, 2 h; (b) *1*. LDA, -78 ºC, 1.5 h; *2*.TMSCl, -78 ºC, 1.5 h; *3*. -78 ºC - rt, 1.5 h, 74%;

With the key intermediates now synthesised, it was time to attempt the naphthoquinone core formation. The Diels-Alder cycloaddition of diene **28** to dienophile **84** was carried out at room temperature in toluene, for 16 h, followed by addition of silica in dichloromethane. Upon flash chromatography the desired adduct **85** was obtained in very good yield and as a single regioisomer (**Scheme 30**). The structure of compound **85** was confirmed by X-ray crystallography (**Figure 13**).




**Scheme 30** *Reagents and conditions: 1*. toluene, 0 ºC – rt, 16 h; *2*. $SiO_2$, dichloromethane, rt, 48 h, 70-82%.

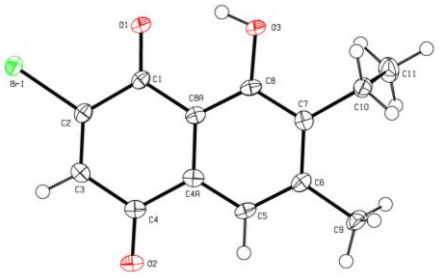
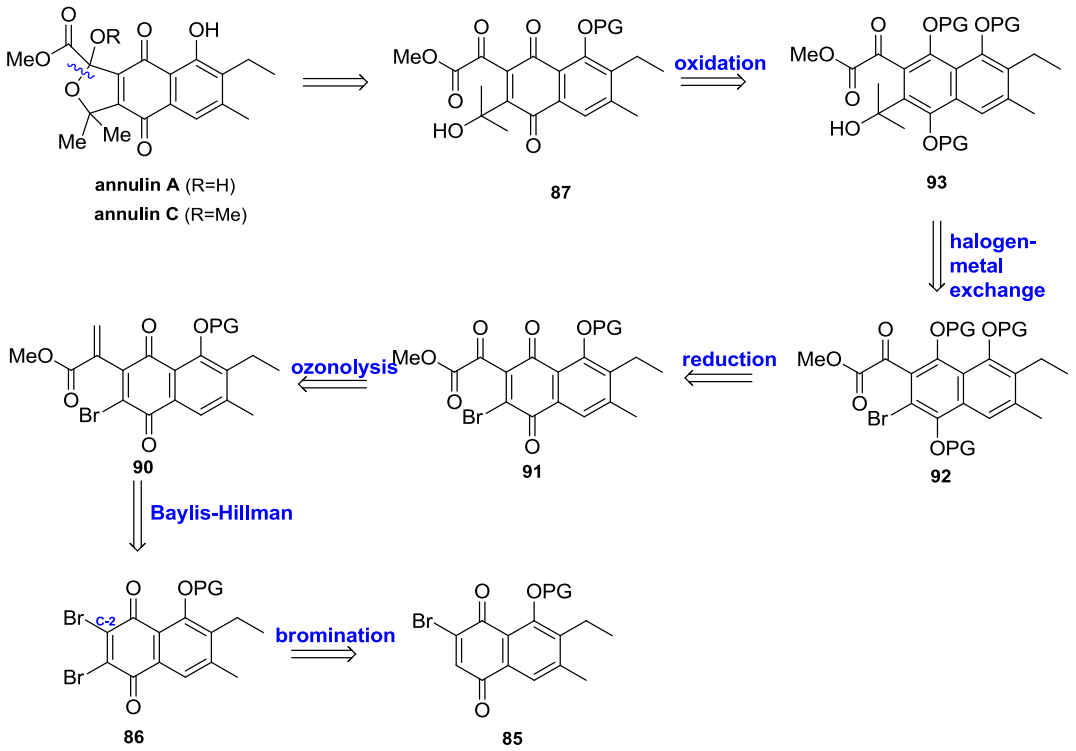


**Figure 13** X-ray crystal structure of compound **85**.

As already suggested by some authors[75,76] the result of this reaction shows that bromine probably acts as a key element in the regiospecific formation of a new carbon-carbon bond. In this case, the nucleophilic attack occurs from the electron-rich end of the diene to the unsubstituted carbon of the quinone.

### 2.4.2.2 Attempts towards the introduction of the furan ring

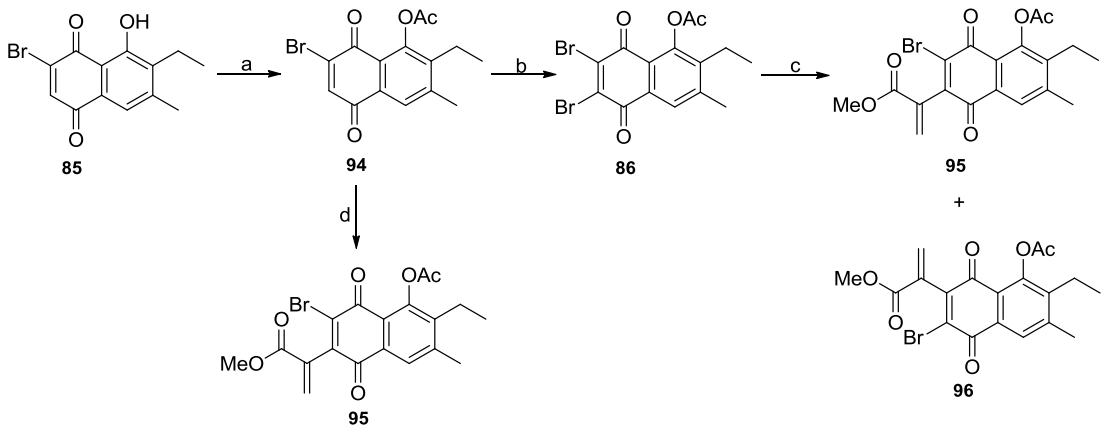
Our initial plan to assemble the furan ring was to introduce a α-vinyl ester in C-2 *via* a Baylis-Hillman reaction between dibromoquinone **86** and methylacrylate, by using a similar procedure described by Lee *et al.*[80] The product resulting from this reaction (**90**) would then be subjected to ozonolysis, hopefully affording the α-ketoester **91**. Finally, we envisaged to prepare the tertiary alcohol in **93** by halogen-metal exchange of compound **92** with lithium and then reaction with acetone (**Scheme 31**).




**Scheme 31** Initial plan to construct the furan ring.

The construction of the furan ring began with **85** that was protected as its acetate **94** and then reacted with molecular bromine in acetic acid to give dibromoquinone **86** in excellent yield.

The possibility of performing a Baylis-Hillman reaction was then examined. The Baylis-Hillman reaction allows the preparation of acrylic compounds from the coupling between the α-position of an activated vinylic system and carbon electrophiles, under the catalytic influence of a tertiary amine.[81] In 2004, Lee and co-workers[80] reported the preparation of α-vinylquinones under Baylis-Hillman conditions. In our case, reaction of compound **86** and methyl acrylate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) resulted in the formation of an inseparable 2:1 mixture of the regioisomers **95** and **96.** The same reaction was attempted, using the mono-bromoquinone **94**, unfortunately, it was also unsuccessful yielding the undesired regioisomer **95** (**Scheme 32**).

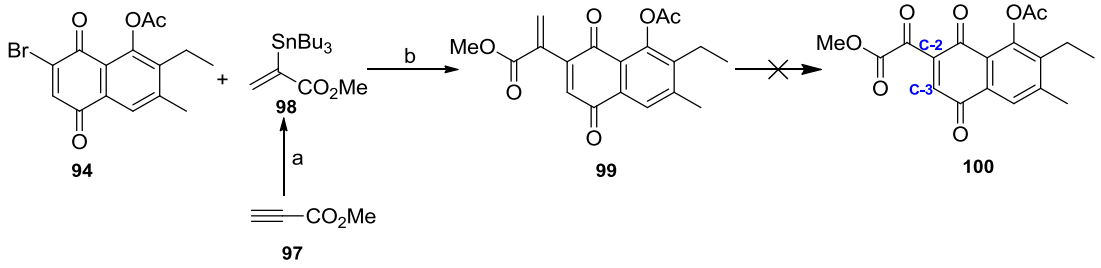



**Scheme 32** *Reagents and conditions:* (a) *1.* Acetyl chloride, pyridine, dichloromethane, 0 ºC, 30 min.; *2.* rt, 30 min., 56%. (b) $Br_2$, AcOH, rt, 4 h, 91%: (c) methyl acrylate, DABCO, THF, rt, 30 h, 55% (2:1 **95**/**96**); (d) methyl acrylate, DABCO, neat, rt, 1 h 15 min., 19%.

Given the poor results obtained so far, we decided to explore other methods to introduce the α-vinylester unit. The Stille coupling was one of the elected methods. This process involved initial palladium mediated *syn*-hydrostannation of methyl propiolate **97** to give vinylstannane **98**[82] that then underwent a palladium-catalysed cross coupling reaction (Stille) with

bromoquinone **94**, to give the desired α,β-unsaturated carbonyl compound **99** in very good yield (**Scheme 33**).

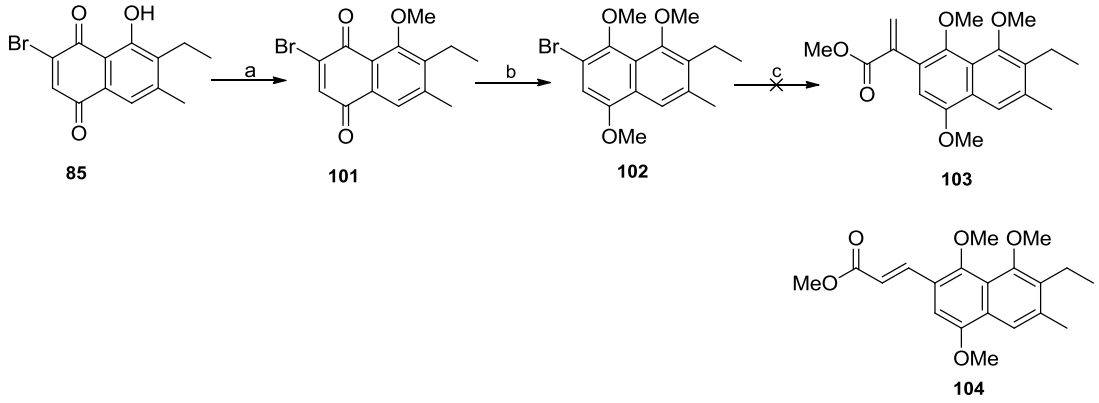
Having successfully introduced the α-vinylester unit, we next proceeded to attempt the ozonolysis step. Unfortunately, no conditions could be found to produce the desired compound **100**, despite a wide ranging experimentation through the possible reaction conditions (ozone followed by a reductive work-up, osmium tetroxide and sodium periodate) and extensive experimentation with other reaction variables (e.g., temperature, solvent, reaction times). Degradation was seen under all the reaction conditions tested. This failure could be due to the presence of an additional vinylic bond around C(2)-C(3). In fact, there are no examples in the literature of oxidative cleavage of vinylic groups directly linked to a quinone.




**Scheme 33** *Reagents and conditions:* (a) $Bu_3SnH$, $(Ph_3P)_2PdCl_2$, toluene, rt, 2 h, 52%; (b) $Pd(PPh_3)_4$, toluene, 75 ºC, 23 h, 84%.

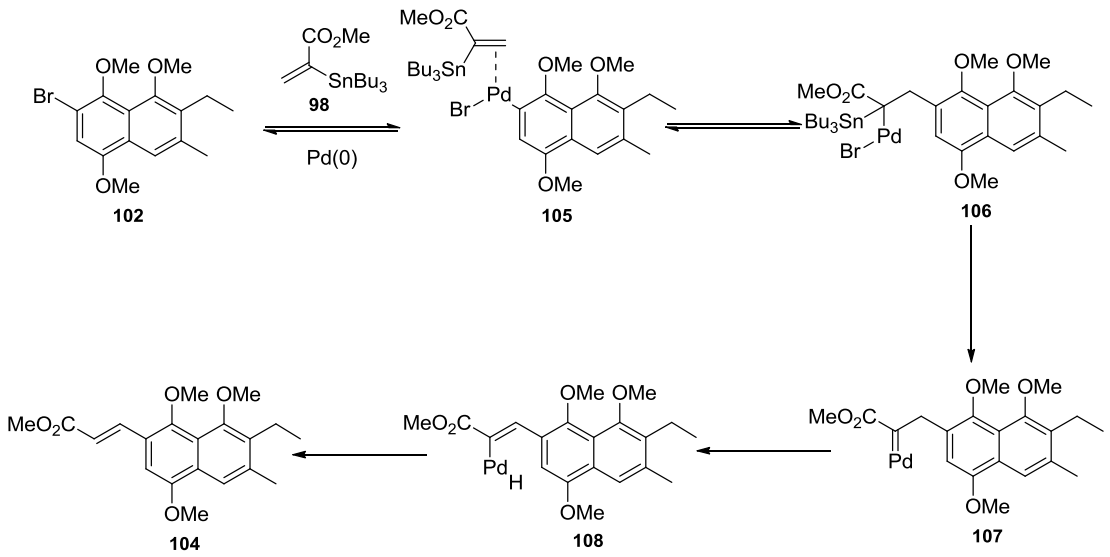
On the basis of this result, it was decided to reduce the quinone core, by first protecting the phenol in **85** as its methyl ether **101**, and then subjecting it to reductive methylation. An extensive screen of conditions revealed that sodium dithionite in dichloromethane followed by potassium carbonate and dimethyl sulfate in degassed acetone[83] provided the best results, with the desired naphthalene **102** produced in 76% yield. Regrettably, when compound **102** was subjected to Stille coupling, under the reaction conditions described for the synthesis of **99**, only starting material was recovered. Other reaction conditions were also attempted on substrate **102**, including use of DMF or THF at various temperatures. Recovery of starting

material, degradation and/or formation of the cinnamate derivative **104** was seen under these reaction conditions (**Scheme 34**).



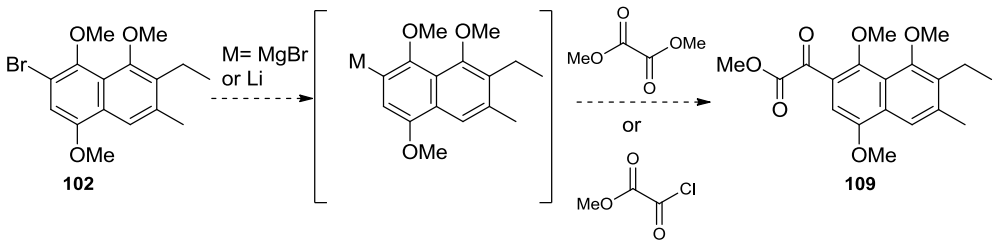

**Scheme 34** *Reagents and conditions:* (a) MeI, $Ag_2O$, reflux, 5.5 h, 68%; (b) *1.* $Na_2S_2O_4$, dichloromethane, rt, 1.5 h; *2.* $K_2CO_3$, $Me_2SO_4$, acetone, reflux, 2 h, 76%; (c) stannane **98**, $Pd(PPh_3)_4$, DMF, 150 ºC, 16 h, **103** (0%), **104** (30%).

An examination of the literature[84,85] revealed that cinnamates had previously been observed in Stille-type couplings of vinylstannanes. In 1994, Busacca *et al.*[84] proposed a reaction mechanism for the formation of these unexpected products. According to the authors, the mechanism starts by oxidative addition of Pd(0) to arylbromide **102** followed by formation of a complex with stannane **98** to give the intermediate **105**. The latter is considered to be a precursor for the supposed Heck intermediate **106**. Transmetallation of this intermediate leads to palladium (II) carbene derivative **107** that is then expected to undergo β-hydride elimination to palladium hydride **108,** which could reductively eliminate to give the observed product, **104** (**Scheme 35**).




**Scheme 35** Proposed reaction mechanism for the formation of compound **104**.[84]

At this point, we decided to investigate whether compound **102** could be converted directly to the α-ketoester **109** by preparation of the corresponding Grignard reagent or by lithium-bromine exchange, followed by reaction with the commercially available compounds, monomethyl oxalyl chloride or dimethyl oxalate (**Scheme 36**).

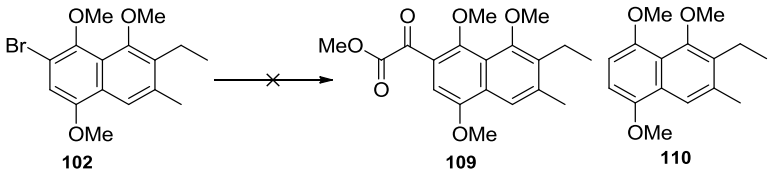



**Scheme 36** Prospective synthesis of compound **109**.

Attempts to prepare the Grignard reagent using the conventional method – Mg, $I_2$, THF - only led to recovered starting material. Different conditions involving a lithium chloride mediated Br/Mg exchange reaction with *i*PrMgCl[86] at different temperatures were also screened. However, under any of the conditions tested, the reaction failed and only starting material was recovered. The inability to perform the magnesium/bromide exchange is

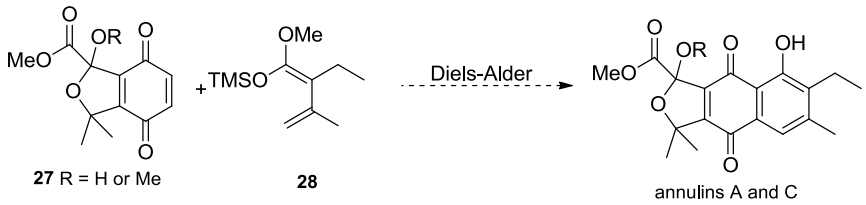
probably due to the high electron density in the aromatic ring. In fact, Shi *et al.*[87] stated that the rate of Br-Mg exchange is slow for electron rich bromides.

Our attention turned next to the lithium-bromine exchange. To access the desired compound **109**, intermediate **102** was first reacted with 1 equivalent of *n*-butyllithium in THF at -78 ºC and then treated with monomethyl oxalyl chloride or dimethyl oxalate. Unfortunately, in both cases, the reaction gave only the debrominated compound **110**. Several attempts, using other bases (*s*-BuLi, *t*-BuLi) at various temperatures gave similar results, indicating, however, under these circumstances, the conversion of **102** into its lithium salt by bromine-lithium exchange (**Scheme 37**).




**Scheme 37** *Reagents and conditions:* lithium base, monomethyl oxalyl chloride or dimethyl oxalate, THF.

Once again, due to time restriction, the studies towards annnulins A and C couldn't be completed. Given the difficulties encountered while trying to install the α-keto ester moiety, future work will focus on completing the synthesis of the analogue **27** and then to perform a Diels Alder reaction between the latter and the diene **28** (**Scheme 38)**.




**Scheme 38** Prospective completion of the synthesis of annulins A and C.

## 2.5. Conclusion

This Chapter has described our efforts towards the synthesis of the isobenzofuranquinone analogue **27** and the natural products annulins A and C.

Four main approaches to analogue **27** have been described. In a first route we accessed the phthalide **31**, but then we were unable to convert it into the desired lactol. The electron-donating character of the methoxy group in position 7 probably accounts for the lack of reactivity. As a result, this strategy was abandoned.

In view of these results, the second approach included a more electron deficient aromatic ring. In this case, although we were able to add vinylmagnesium bromide to the phthalide, the oxidative cleavage of the vinyl group was not feasible.

As the original plan to install the carboxyl group *via* oxidative cleavage of the vinyl group proved unsuccessful, in a third approach to the analogue **27**, our aim was to initially form the required tertiary alcohol, and then to introduce directly the α-ketoester moiety by addition of methyl oxalyl chloride or dimethyl oxalate to a suitable lithiated derivative. Although we accessed an advanced intermediate, this route was abandoned due to the instability of the tertiary alcohol. It was clear that it was essential to introduce the α-ketoester moiety before generating the tertiary alcohol.

Due to the lack of time, a fourth approach involving the formation of the α-ketoester moiety *via* oxidation of a suitable methylketone with selenium dioxide followed by reaction with thionyl chloride in methanol, could not be completed. Until now we succeeded in introducing the α-ketoester moiety (**73**).

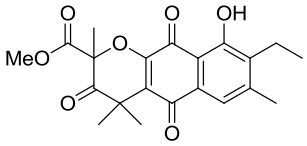
In our efforts towards the synthesis of annulins A and C we succeeded in constructing the naphthoquinone core in good yields by performing a Diels-Alder reaction between diene **28** and dienophile **84**. Introduction of the furan ring proved difficult, although several synthetic strategies were investigated.

# CHAPTER III

## STUDIES TOWARDS THE SYNTHESIS OF ANNULIN B

## 3.1. Annulin B – discovery and description

Annulin B was isolated by Fahy and coworkers[39] in 1986, from a Northeastern Pacific hydroid *Garveia annulata*, together with annulin A (Chapter II). It was obtained as an optically active orange oil, but its absolute configuration was not assigned. The proposed structure for annulin B was inferred from its spectroscopic data, namely, IR, UV/VIS, HREIMS, $^{1}H$ and $^{13}C$ NMR.

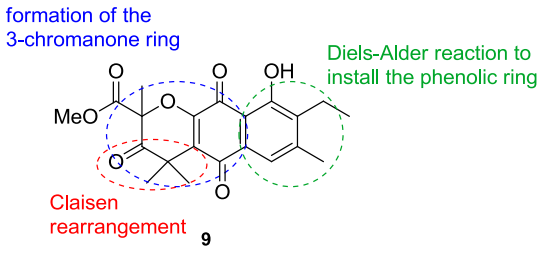



**9**

**Figure 14** Annulin B.

## 3.2. Aim of the project

In view of our continuing interest in IDO inhibitors and in the annulin family, we also decided to investigate routes to racemic annulin B. For the synthesis of this compound, a few key steps would have to be taken into consideration: a Claisen rearrangement to install an allyl chain that will give access to the ketone function at C-3, the formation of the chroman-3-one ring and the Diels-Alder reaction to introduce the phenolic moiety (**Figure 15**). The most relevant examples from the literature will be discussed below.




**9**

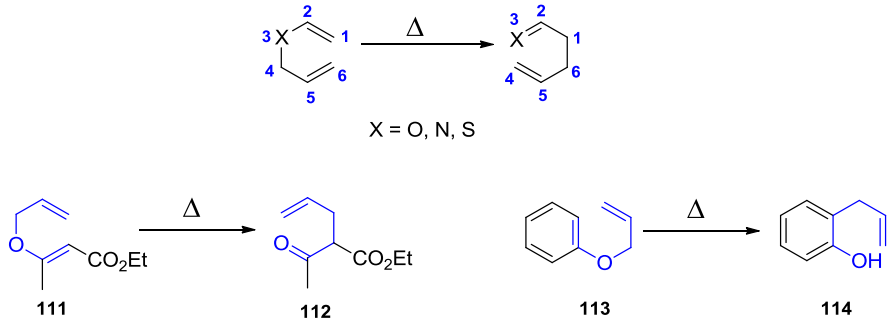
**Figure 15** Key transformations in the synthesis of annulin B.

## 3.3. Background

### 3.3.1. The aromatic Claisen rearrangement

#### 3.3.1.1. Overview

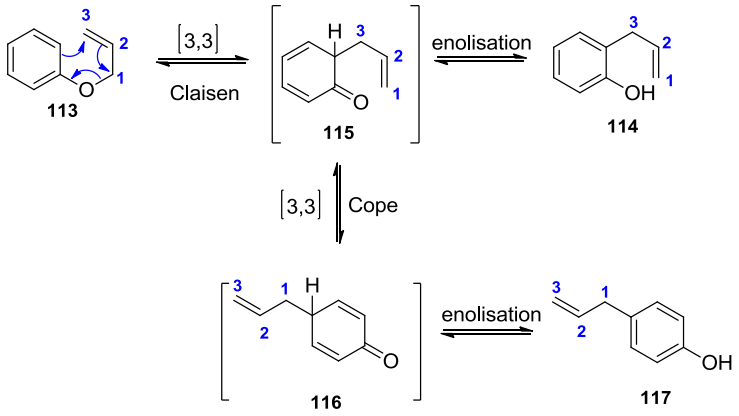
The aromatic Claisen rearrangement is a very effective tool for the preparation of *ortho*- or *para*-substituted phenol derivatives. Since its discovery by Ludwig Claisen,[88] several research groups have contributed for the understanding of the mechanism and the factors that influence the regio- and steroselectivity of this reaction.[89] It was first reported in 1912 and it was described as the rearrangement of an allyl vinyl ether **111** into a α,δ-unsaturated carbonyl compound **112**, as well as the transformation of allyl phenyl ether **113** into *C*-allyl phenol **114** (**Scheme 39)**.




**Scheme 39** First reported examples of Claisen rearrangements on aromatic and aliphatic substrates.

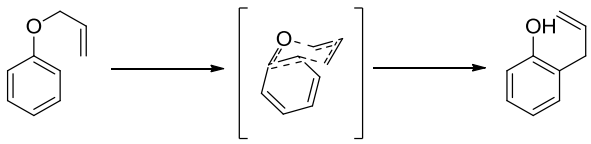
The thermal rearrangement of an allyl aryl ether **113** generally yields an *ortho*-allylated phenol. This reaction starts with a [3,3]-sigmatropic migration, generating an *ortho*-dienone **115** as intermediate. If the *ortho*-carbon bearing the allyl group is not substituted, rearomatisation *via* enolisation occurs, resulting in the formation of the *ortho*-allyl phenol **114**. On the other hand, when both *ortho*-positions are substituted, rearomatisation is not viable and a second [3,3]-sigmatropic rearrangement (Cope rearrangement) occurs. This rearrangement places the allyl chain at the *para* position, leading to an intermediate **116** that enolises to the *para*-allyl phenol **117** (**Scheme 40**). In some cases, *para*-Claisen

rearrangement competes with the *ortho* rearrangement, even without a substituent on the *ortho*-position.[90]




**Scheme 40** Mechanism of the *ortho*- and *para*-Claisen rearrangement of an allyl aryl ether.

The Claisen rearrangement is generally regarded as a concerted pericyclic process and it is commonly accepted that it proceeds through a chair-like transition state.[89] This transition state corresponds to a suprafacial reaction pathway and, therefore allowed by Woodward-Hoffmann rules.[91]



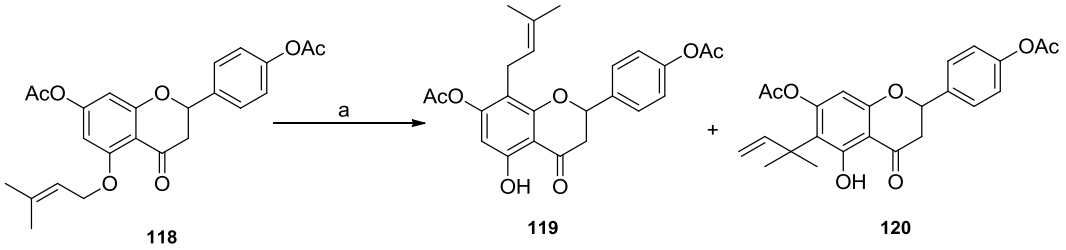

**Scheme 41** Chair-like transition state in the Claisen rearrangement.

The aromatic Claisen rearrangement usually requires high temperatures, in the range of 180-225 ºC, and long reaction times. Under such conditions, undesired side reactions can occur competitively. The rearrangement can be performed under milder conditions by use of catalysts, such as, Lewis acids.[89]

### 3.3.1.2. Competition between *ortho*- and *para*-Claisen rearrangement of allyl aryl ethers

It is well known that under Claisen rearrangement conditions, the allyl group migrates almost exclusively to an *ortho* position, if at least one is free. Hence, *para*-Claisen rearrangements can occur when the *ortho*-position is substituted or when the *ortho*-dienone intermediate cannot enolise due to steric hindrance.[92] When only one *ortho*-position is free, competition between *ortho* and *para* rearrangement can be observed.[93]

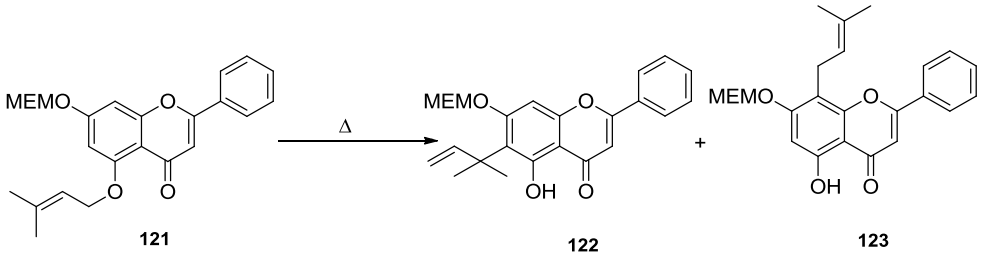
Gester and coworkers observed major *para* compound formation with prenyl ether 118. After 2 h at reflux in decalin substrate **118** gave a 3:1 mixture of *para* and *ortho* Claisen products. Upon extending the reaction to 2 days only the *para* compound **119** was observed.[94]




118 119 120

**Scheme 42** *Reagents and conditions:* (a) decalin, reflux, 188 ºC.

Daskiewicz and coworkers reported the regioselective control of the Claisen rearrangement of 5-prenylchrysin **121** using microwave irradiation. According to the authors, the products obtained were highly dependent on the type of solvent and by the microwave irradiation power. When the rearrangement was performed at 750 W in *N*, *N*-diethylaniline, almost only *para* product **123** was obtained. Conversely, when the power was decreased the amount of *ortho* product **122** increased. Heating the ether **121** in *N*, *N*-diethylbutylamine under reflux, gave almost exclusive rearrangement to the *ortho* position (**Table 5**).[95]



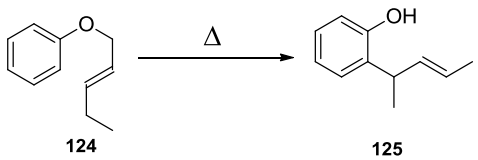

121 122 123

| Entry | Solvent | Heating | Irradiation power / (W) | 122/123 ratio | Total yield / (%) |
|---|---|---|---|---|---|
| **1** | *N*,*N*-diethylaniline | MW | 750 | 0.02 | 83 |
| **2** | *N*,*N*-diethylaniline | MW | 620 | 0.18 | 90 |
| **3** | *N*,*N*-diethylaniline | MW | 570 | 0.5 | 90 |
| **4** | *N*,*N*-dimethylaniline | MW | 570 | 0.81 | 87 |
| **5** | *N*,*N*-diethylbutylamine | Δ | – | 16.2 | 86 |

**Table 5** Claisen rearrangement of 5-prenylchrysin **121** using microwave irradiation and conventional heating.[95]

### 3.3.1.3. Abnormal Claisen rearrangement

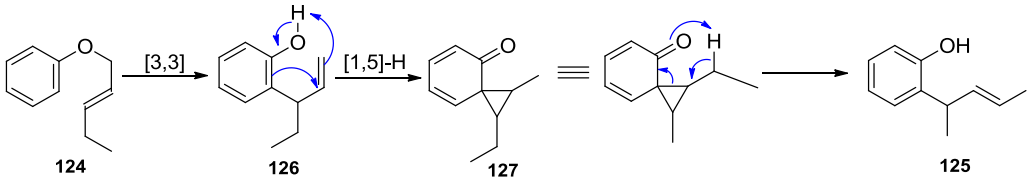
The abnormal Claisen rearrangement is the most common side reaction for the thermally induced rearrangements of ethers bearing γ-alkyl substituents on the allyl group. This rearrangement was first reported by Lauer and Filbert[96] where they describe the formation of *ortho*-(α,γ-dimethylallyl)-phenol **125** from γ-ethylallyl phenyl ether **124 (Scheme 43)**.




124 125

**Scheme 43** Abnormal Claisen rearrangement described by Lauer and Filbert.[96]

The mechanism of this reaction has been identified as the result of three consecutive processes, i.e. the normal Claisen rearrangement of γ-alkyl allyl aryl ether followed by [1,5]-hydrogen shifts (**Scheme 44**).[97]




**Scheme 44** Mechanism for the abnormal Claisen rearrangement.

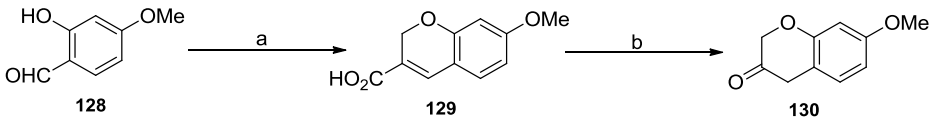
Several groups have reported methods for preventing this side reaction, by using a trapping agent to prevent participation of the phenolic hydrogen in a [1,5]-hydrogen shift. Jefferson *et al.*[98] reported the use of butyric anhydride in *N*-*N*-dimethylaniline and Karanewsky *et al.*[99] used the trapping of acetic anhydride in sodium or potassium acetate. More recently, Fukuyama and coworkers showed the suppression of abnormal Claisen rearrangement products by trapping the normal Claisen products as their silyl ethers, using both 1,1,1,3,3,3-hexamethyldisilazane and *N*,*O*-bis-(trimethylsilyl)acetamide.[100]

### 3.3.2. Synthetic methods for the preparation of chroman-3-ones

#### 3.3.2.1. From chromene-3-carboxylic acid

Several chroman-3-ones have been prepared from the appropriate chromene-3-carboxylic acid.[101-104] A typical route starts from basic condensation of salicylaldehyde **128** with acrylonitrile to form 2*H*-chromen-3-carbonitrile under refluxing conditions, with subsequent basic hydrolysis and acidification. The carboxylic acid **129** thus formed is then converted into the acid chloride, which on reaction with sodium azide or diphenyl phosphoryl azide forms the acyl azide. Successive Curtius rearrangement and acidic hydrolysis of the resulting

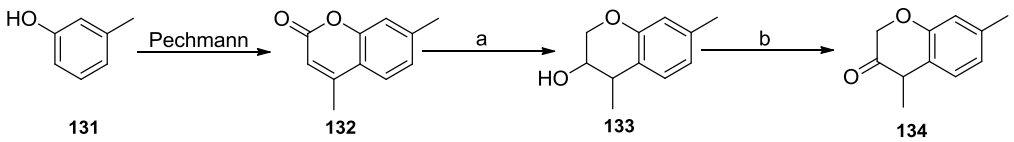
vinyl isocyanate leads to chroman-3-ones **130**, *via* hydrolysis of the enamine-like 3-aminochromene (**Scheme 45**).




**Scheme 45** *Reagents and conditions:* (a) *1.*acrylonitrile, DABCO, reflux, 24 h, 85%; *2.* 10% aq. NaOH, reflux, 24 h, 90%; (b) *1.* diphenyl phosphoryl azide, $Et_3N$, 45 ºC; *2.* Toluene, 80 ºC; *3.*HCl (6 N), reflux, 78%.[101]

### 3.3.2.2. From coumarins

Goldsmith and coworkers reported the preparation of chroman-3-ones **134** by oxidation of the corresponding chromanols **133**. The latter were obtained by hydroboration-oxidation of coumarins **132**, prepared by Pechmann reaction of *m*-cresol and acetoacetic ester (**Scheme 46**).[105,106]

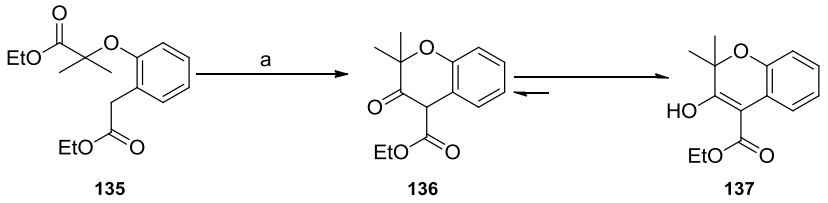



**Scheme 46** *Reagents and conditions:* (a) $BH_3$, THF, $H_2O_2/HO^-$, 49%; (b) DCC, DMSO, benzene, 84%.[105]

### 3.3.2.3. Using Dieckmann condensation

One of the most commonly used routes for the synthesis of chroman-3-ones involves a Dieckmann condensation of an appropriate dimethyl- or diethylester.[107,108] This cyclisation has been successfully used and exploited by a number of research groups.[109-114] Anastasis *et al.* reported the preparation of 4-ethoxycarbonyl-7-methoxy-2,2-dimethylchroman-3-one, exclusively in the enolic form **137**, by cyclisation of ethyl 2-(2-(2-ethoxy-2-

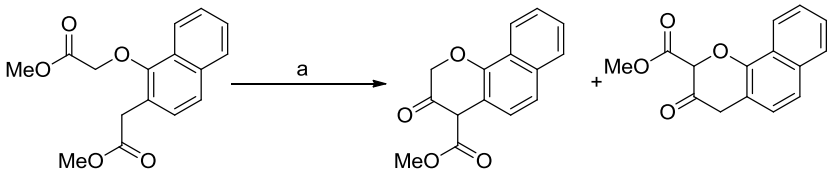
oxoethyl)phenoxy)-2-methylpropanoate **135** with sodium ethoxide in refluxing ethanol (**Scheme 47**).[114]




**135** **136** **137**

**Scheme 47** *Reagents and conditions:* (a) sodium ethoxide, ethanol, reflux, 3 h, 85%.[114]

In 1980, Verhé and coworkers reported the isolation of the two possible isomeric chroman-3-ones, **139** and **140**, by cyclisation of methyl 2-(2-(2-methoxy-2-oxoethoxy)naphthalen-1-yl)acetate **138** (**Scheme 48**).[110]

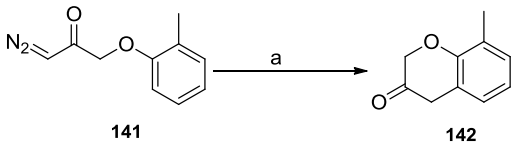



**138** **139** (32%) **140** (43%)

**Scheme 48** *Reagents and conditions:* (a) ethanol, sodium, toluene, reflux, 4 h.[110]

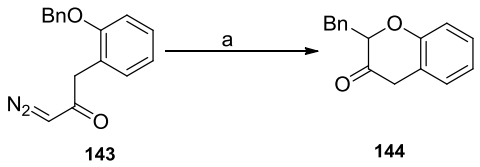
### 3.3.2.4. From α-diazoketones

An alternative approach to the synthesis of chroman-3-ones involves the use of α-diazoketones.[115-119] Saba and coworkers reported the preparation in high yields of a series of benzo- and naphthopyran-3-ones by intramolecular C-H insertion of 1-diazo-3-aryloxy-2-propanones, in the presence of bis[hexafluoroacetoacetonato]copper II (**Scheme 49**). The requisite diazoketones were prepared in good yield from the corresponding carboxylic acids by *in situ* formation of acid chloride and subsequent condensation with diazomethane.[116]




**Scheme 49** *Reagents and conditions:* (a) [Cu(hfacac)$_2$], $CH_2Cl_2$, rt, 78%.[116]

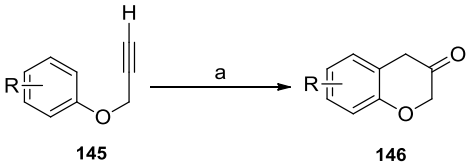
In 1992, Eberlein *et al.* prepared 2-benzyl-3-chromanone **144** from an appropriate α-diazoketone **143**, by formation of a cyclic oxonium ylide, followed by concerted [1,2]-shift (**Scheme 50**).[119]




**Scheme 50** *Reagents and conditions:* (a) dirhodium tetraacetate, $CH_2Cl_2$, rt, 0.5 h, 67%.

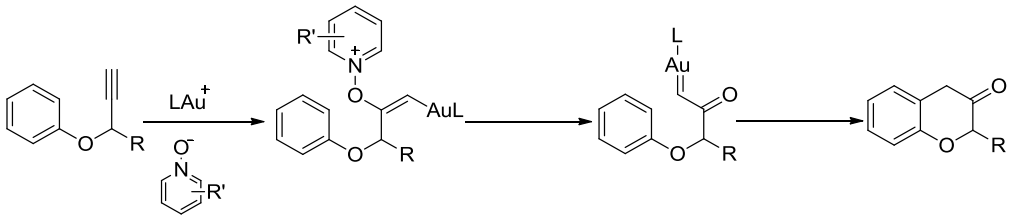
### 3.3.2.5. From propargyl aryl ethers

Recently Zhang and coworkers reported the synthesis of chroman-3-ones **146** through gold-catalysed oxidation of propargyl aryl ethers **145** (**Scheme 51**).[120]




**Scheme 51** *Reagents and conditions:* (a) pyridine *N*-oxide, $Me_4{}^tBuXPhosAuNTf_2$, dichloroethane, rt, 1-3 h.[120]

According to the authors, these alkynes can be used as equivalents of α-diazoketones, generally toxic and difficult to access, in generating α-oxo metal carbenes that are most likely the intermediates of these reactions (**Scheme 52**).




**Scheme 52** Mechanism for the gold-catalysed oxidation of propargyl aryl ethers.

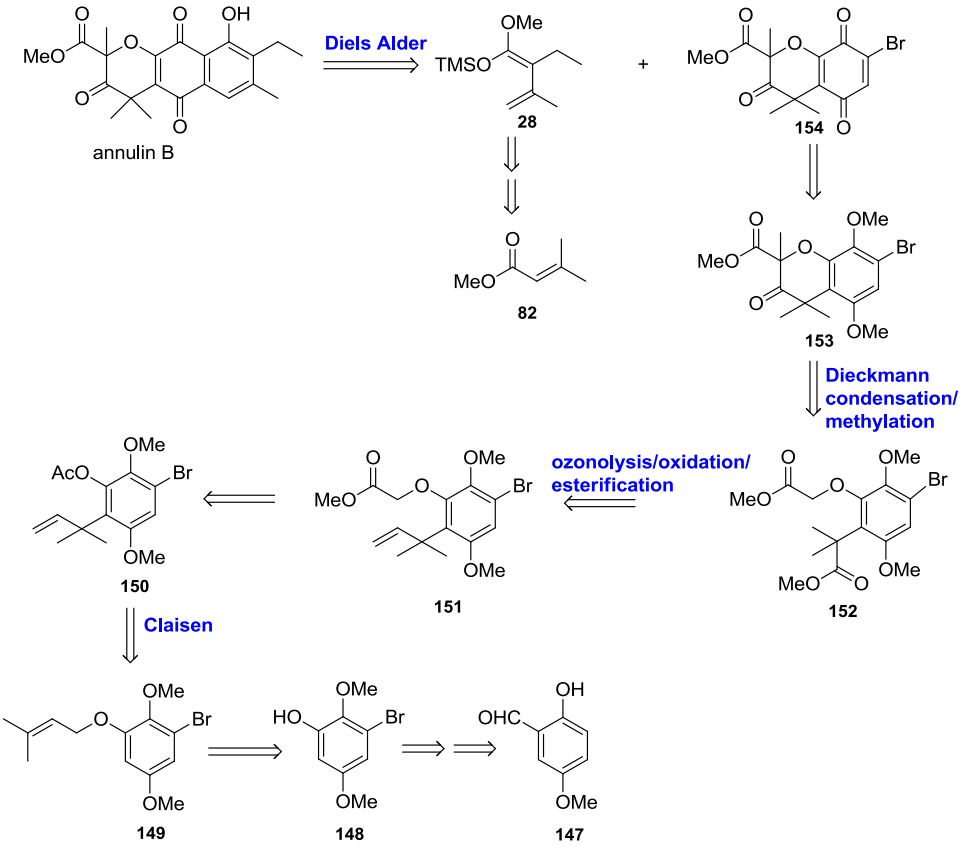
### 3.3.3. Diels Alder reaction

As described in Chapter II, the Diels Alder reaction between an electron rich diene and an halogenated quinone, used to prepare the naphthoquinone core of annulins A and C, could be applied to the synthesis of annulin B.

## 3.4. Results and discussion

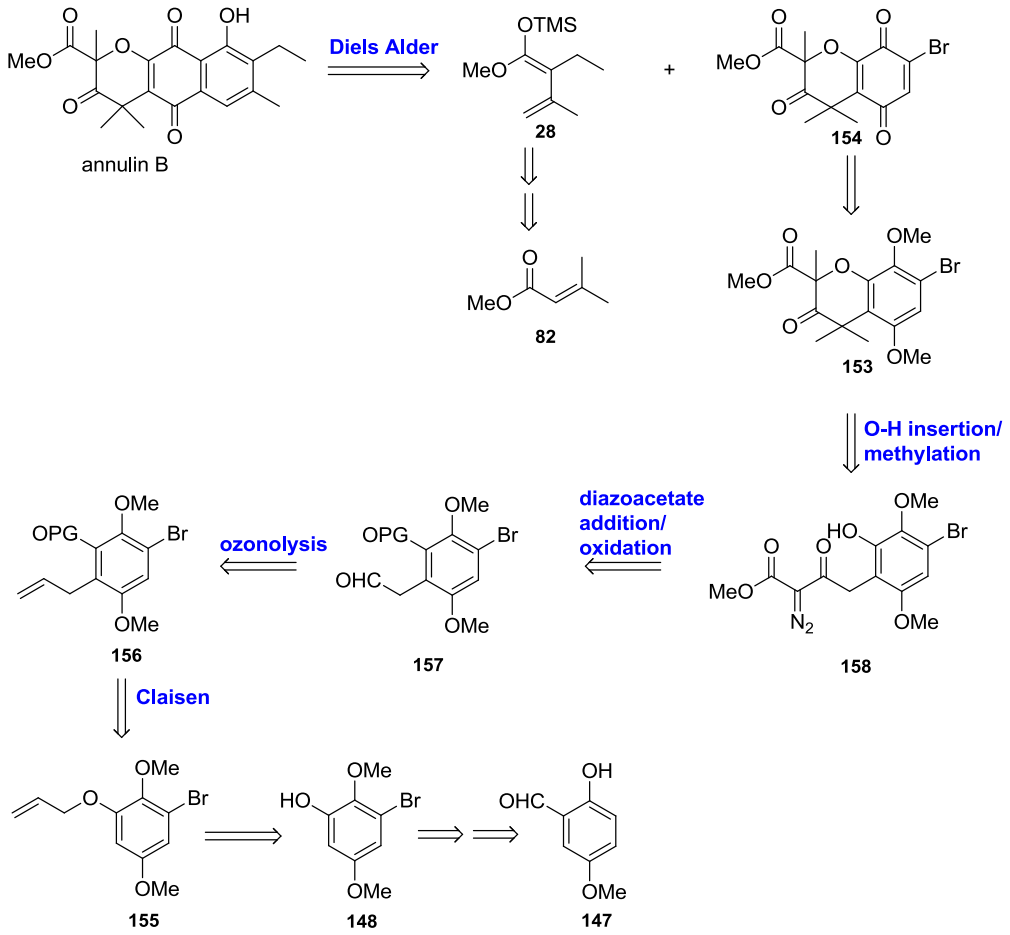
### 3.4.1. Retrosynthetic analysis

In our analysis of annulin B, we envisioned the natural product arising from a Diels Alder reaction between chroman-3-one **154** and the diene **28** (**Scheme 53**). As already described in Chapter II, the required diene **28** can be easily prepared, in a few steps, from commercially available methyl senecionate **82**. To prepare the chroman 3-one intermediate **154**, we decided to perform a Dieckmann condensation using the dimethyl ester **152** as precursor, followed by adjustment of the oxidation states of the arene. Dimethyl ester **152** could be synthesised by ozonolysis of dimethylallyl aryl ether **151** and subsequent oxidation and esterification. The required allylic substitution would stem from prenyl ether **149** *via* Claisen rearrangement. This compound would in turn be derived from phenol **148** and this intermediate could be readily obtained from commercially available 2-hydroxy-5-methoxybenzaldehyde **147**.




**Scheme 53** Retrosynthetic analysis of annulin B based on a Dieckmann condensation.

A second possible strategy for the synthesis of annulin B is based on an intramolecular rhodium carbene O-H insertion reaction to form the chroman-3-one ring (**Scheme 54**). Therefore a diazocarbonyl compound **158** would be required as a key intermediate, and this would be accessed from the corresponding aldehyde **157** *via* reaction with methyl diazoacetate, followed by oxidation. Aldehyde **157** was expected to be obtained by ozonolysis of 2-allyl-bromobenzene **156**, which could in turn arise *via* a Claisen rearrangement of the allyloxybenzene **155**. This compound could be derived from phenol **148** and this intermediate could be readily obtained from commercially available 2-hydroxy-5-methoxybenzaldehyde **147**.

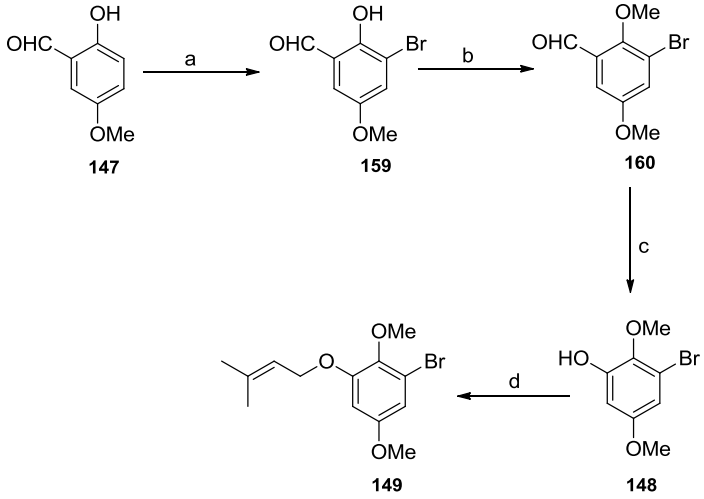



**Scheme 54** Retrosynthetic analysis of annulin B based on an intramolecular rhodium carbene O-H insertion reaction.

### 3.4.2. Synthetic strategy based on a Dieckmann condensation reaction

#### 3.4.2.1. Initial synthetic route

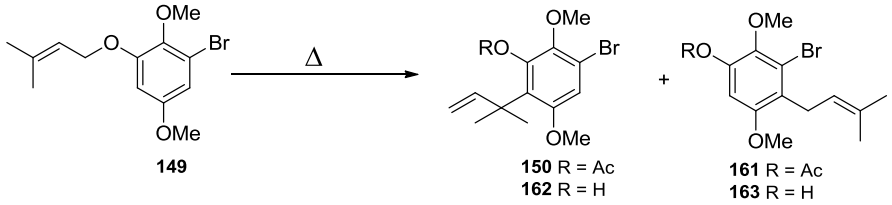
The synthesis of annulin B started with a regioselective bromination of commercially available 2-hydroxy-5-methoxybenzaldehyde **147**, using standard conditions. Protection of the phenol as a methyl ether **160**, followed by Baeyer-Villiger oxidation under hydrolytic conditions gave the desired phenol in good yield.[121,122] At this stage, phenol **148** was reacted with 3,3-dimethylallyl bromide in the presence of sodium hydride to yield the desired allyloxy intermediate **149** in excellent yield (**Scheme 55**).




**Scheme 55** *Reagents and conditions:* (a) AcOH, NaOAc, $Br_2$, rt, 1 h, 79%; (b) $K_2CO_3$, DMF, dimethyl sulfate, rt, 24 h, 93%; (c) *1.* *m*-CPBA, $CH_2Cl_2$, rt, 18 h; *2.* MeOH, KOH (aq.), rt, 1 h, 79%; (c) 3,3-dimethylallyl bromide, NaH, DMF, rt, 2.5 h, 99%.

Once the prenyl ether **149** was available, we focused our attention on the Claisen rearrangement. As already mentioned above, it is known that heating γ-alkyl substituted allyl groups often results in the formation of the so-called abnormal Claisen product.[96,97,123] It is also well-known that the formation of these products can be prevented by trapping the initial phenol with an acylating agent under basic conditions.[98,99] Hence, reaction of prenyl ether 149 at 200 ºC in acetic anhydride and potassium acetate gave both *ortho* and *para* rearranged products **150** and **161** in 15 and 28% yield, respectively (**Table 6**, entry 1). Similar results were obtained by replacing potassium acetate with sodium acetate (entry 2). Using *N*,*N*-

diethylaniline in the presence of acetic anhydride again gave disappointing results. The undesired *para* rearranged product **161** was isolated in 63% yield, along with starting material (entry 3). On the basis of the work reported by Daskiewicz and coworkers,[95] where they describe the regioselective control of the Claisen rearrangement of 7-allyloxyflavones, by changing the type of solvent and the microwave irradiation power we expected that by using a similar strategy the prenyl ether would behave similarly. In the event, heating compound **149** in *N*, *N*-diethylbutylamine did not show any product formation, even after stirring for 41 h at 140 ºC (entry 4). Using microwave irradiation gave similar results (entry 5). Last attempts to obtain the desired *ortho* rearranged product by heating in DMF, either using conventional heating or with microwave irradiation, only gave the undesired *para* product (entries 6 and 7).



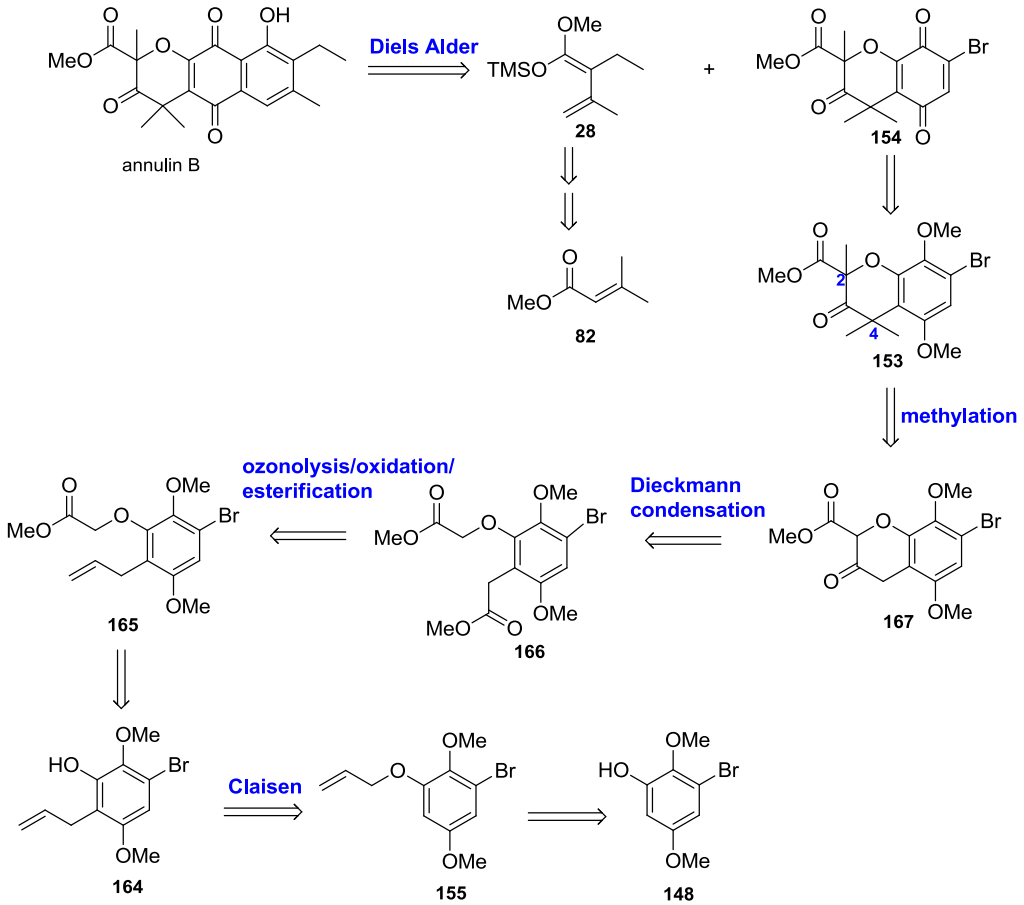

| Entry | Conditions | Isolated products |
|---|---|---|
| **1** | Acetic anhydride, potassium acetate, 200 ºC, 16 h | **150** (15%) + **161** (28%) |
| **2** | Acetic anhydride, sodium acetate, 200 ºC, 21 h | **150** (12%) + **161** (31%) + **S.M.** (27%) |
| **3** | *N*,*N*-diethylaniline, acetic anhydride, 200 ºC, 21 h | **161** (63%) + **S.M**. (25%) |
| **4** | *N*,*N*-diethylbutylamine, 140 ºC, 41 h | **S.M**. |
| **5** | *N*,*N*-diethylbutylamine, 140 ºC, 1.5 h, MW | **S.M.** |
| **6** | DMF, 160 ºC, 21 h | **163** (80% ) |
| **7** | DMF, 200 ºC, 60 min., MW | **163** (87% ) |

**Table 6** Claisen rearrangement of prenyl ether **149**.

In view of these results, we quickly realized that a revised synthetic plan was needed.

### 3.4.2.2. Revised retrosynthetic approach 1

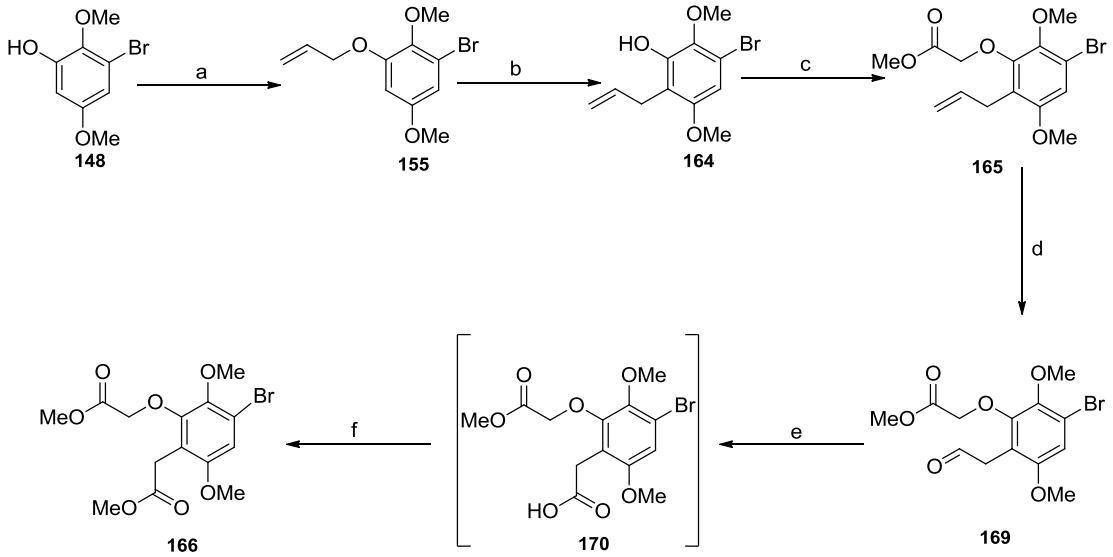
As the Claisen rearrangement of prenyl ether **149** was disappointingly selective for the *para* position it was decided to revise the original synthetic plan (**Scheme 56**). We hoped that Claisen rearrangement of allyl ether **155**, without any methyl groups at γ-position, would give mainly the desired *ortho* rearranged product **164**. It was still expected that the chroman-3-one ring could be accessed by a Dieckmann condensation. In this revised strategy, the methyl groups at positions 2 and 4 would be introduced after cyclisation.




**Scheme 56** Revised retrosynthetic approach 1.

### 3.4.2.2.1. Synthesis of the Dieckmann condensation precursor 166

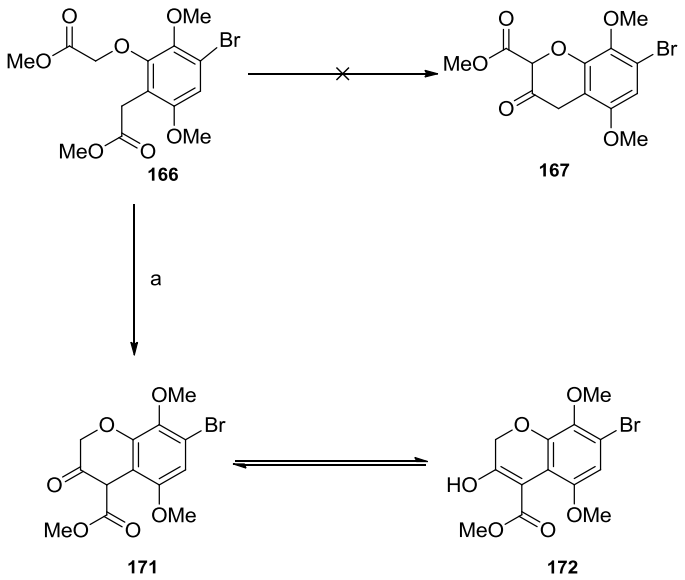
With a new synthetic plan in mind, we investigated the synthesis of substrate **166** (**Scheme 57**). To this end, phenol **148** was reacted with allyl bromide to provide **155**, which was then subjected to Claisen rearrangement. Microwave heating of compound **155** in DMF at 200 ºC for 40 minutes gave a separable mixture of the desired *ortho* rearranged product **164** along with the *para*-isomer **168**, in 57% and 29% yield, respectively. Treatment of compound **164** with potassium carbonate and methyl 2-chloroacetate gave the desired methyl ester **165** in excellent yield. Oxidative cleavage of the allylic double bond using ozone followed by a reductive work-up gave aldehyde **169**. The aldehyde was then converted to the corresponding carboxylic acid **170** using Pinnick oxidation,[124,125,126] with subsequent esterification to yield the Dieckmann condensation precursor **166** in very good yield.




**Scheme 57** *Reagents and conditions*: (a) allyl bromide, NaH, DMF, rt, 1.5 h, quantitative. (b) DMF, 200 ºC, 40 min. (MW), 57%; (c) $ClCH_2CO_2Me$, $K_2CO_3$, DMF, 16 h, 100 ºC, 85%; (d) *1.* $O_3$, $CH_2Cl_2$, -78 ºC, 10 min.; *2.* $PPh_3$, -78 ºC–rt, 2 h, 85%; (e) $NaClO_2$, $NaH_2PO_4$, $H_2O$, 2-methyl-2-butene, *t*-BuOH, rt, 1 h; (f) MeOH, $SOCl_2$, 0 ºC–rt, 16 h, 88% (over 2 steps).

### 3.4.2.2.2. Dieckmann condensation reaction on substrate 166

With dimethyl ester **166** in hand, we next investigated the Dieckmann cyclisation. Initial attempts using potassium *t*-butoxide or sodium hydride only returned unreacted starting material. After substantial experimentation it was discovered that the use of potassium *bis*(trimethylsilyl)amide in tetrahydrofuran, generated the undesired cyclised product **171** along with its enol tautomer **172** (ratio 5:1), in high yield. Use of other bases such as, sodium methoxide, sodium *bis*(trimethylsilyl)amide (NaHMDS) or lithium *bis*(trimethylsilyl)amide (LiHMDS) gave identical results. The $^{1}$H-NMR spectrum of **171** showed two signals at δ 4.74 and 4.68 ppm thus confirming the presence of the $-OCH_2$ function. A benzylic function would exhibit the corresponding $-CH_2$ signal at δ 3.50-4.00 ppm.



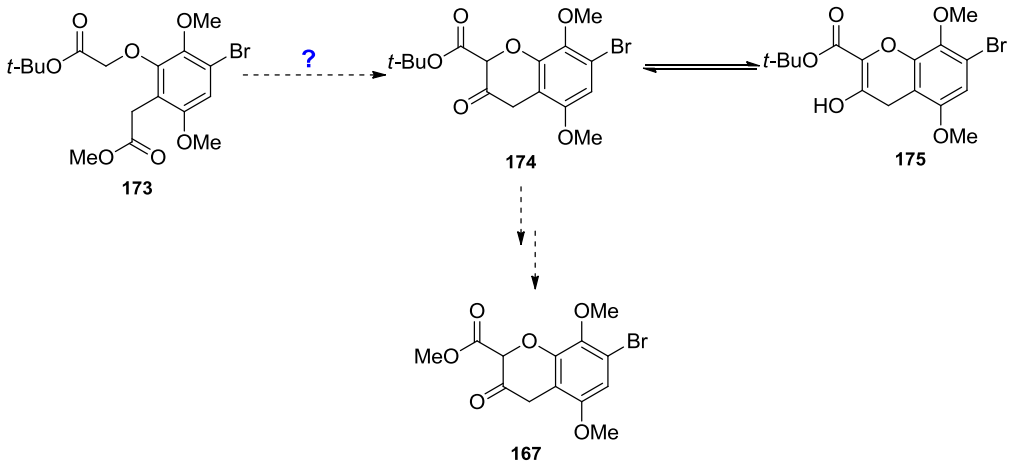

**Scheme 58** *Reagents and conditions*: (a) LiHMDS, THF, 0 ºC–rt, 2 h, 74% (ratio 5:1).

In principle, Dieckmann condensation of diester **166** could give two cyclised products. Nevertheless, we found no trace of the desired isomeric chroman-3-one **167** even in the crude reaction mixture, on the basis of NMR spectroscopy.

As mentioned above, Dieckmann condensation of dimethyl ester **166** was not successful leading to the undesired cyclised product **171**. Therefore an alternative route was investigated.

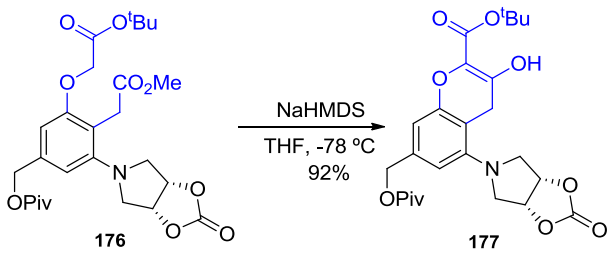
### 3.4.2.2.3. Dieckmann condensation reaction on substrate 173

In the course of our studies towards the desired 3-chromanone **167**, it was thought that the latter could be accessed by Dieckmann condensation of the mixed *tert*-butylmethyl diester **173**, followed by treatment with TFA and methanol, to generate the methyl ester (Scheme 59).



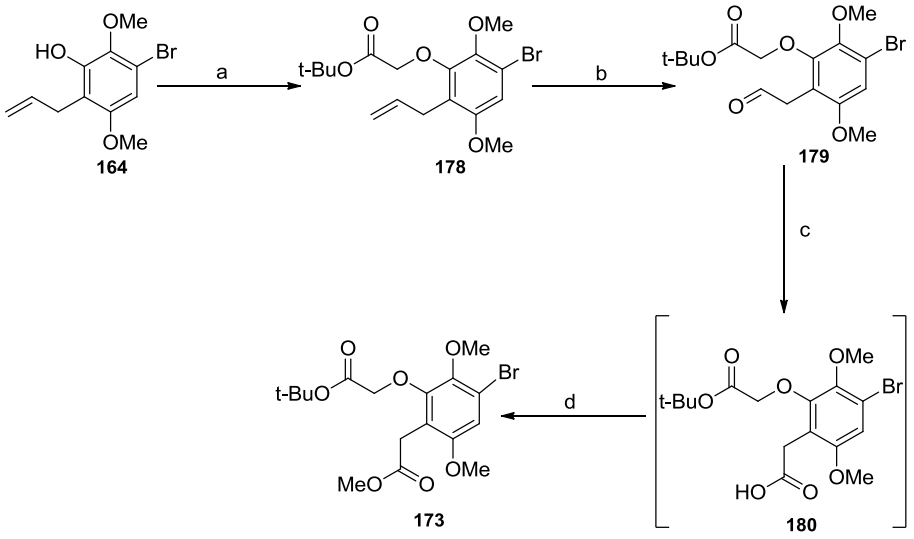

**Scheme 59** Prospective synthesis of chroman-3-one **167**.

This assumption was based on the work reported by Lim and Sulikowski[112] where they describe the preparation of a 3-chromanone ring **177**, with the ester group at the required 2-position, using diester **176** as substrate (**Scheme 60**).



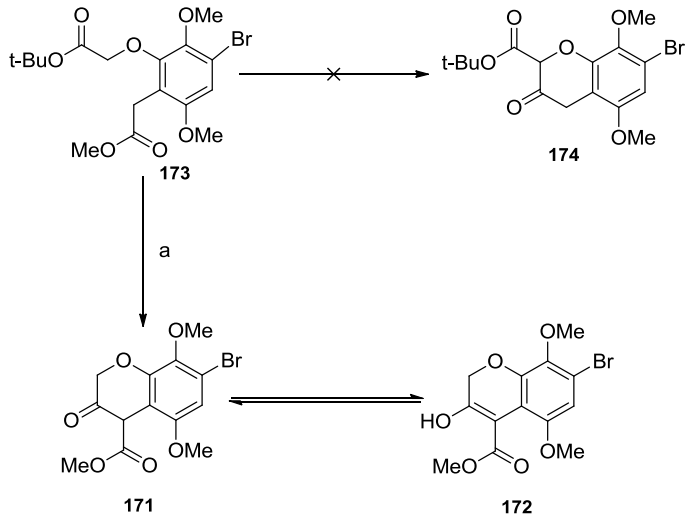

**Scheme 60** Dieckmann condensation reaction reported by Lim and Sulikowski.[112]

Hence, after following the synthetic route previously described for intermediate **164**, the latter was alkylated with *tert*-butyl bromoacetate to yield compound **178** in excellent yield. Ozonolysis of **178**, followed by oxidation and esterification produced diester **173** in very good yield (**Scheme 61**).




**Scheme 61** *Reagents and conditions*: (a) $BrCH_2CO_2t$-Bu, $K_2CO_3$, MeCN, NaI, 15 h, reflux, 88%; (d) *1*. $O_3$, $CH_2Cl_2$, -78 ºC, 40 min.; *2*. $PPh_3$, -78 ºC–rt, 2 h, 59%; (e) $NaClO_2$, $NaH_2PO_4$, $H_2O$, 2-methyl-2-butene, *t*-BuOH, rt, 1 h; (f) $TMSCHN_2$, MeOH/toluene, rt, 1.5 h, 93% (over 2 steps).

With diester **173** in hand, we next attempted the Dieckmann cyclisation applying the same reaction conditions used by Lim and Sulikowski.[112] Unfortunately, treatment of **173** with NaHMDS gave the undesired cyclised product **171** in 72% yield (**Scheme 62**).



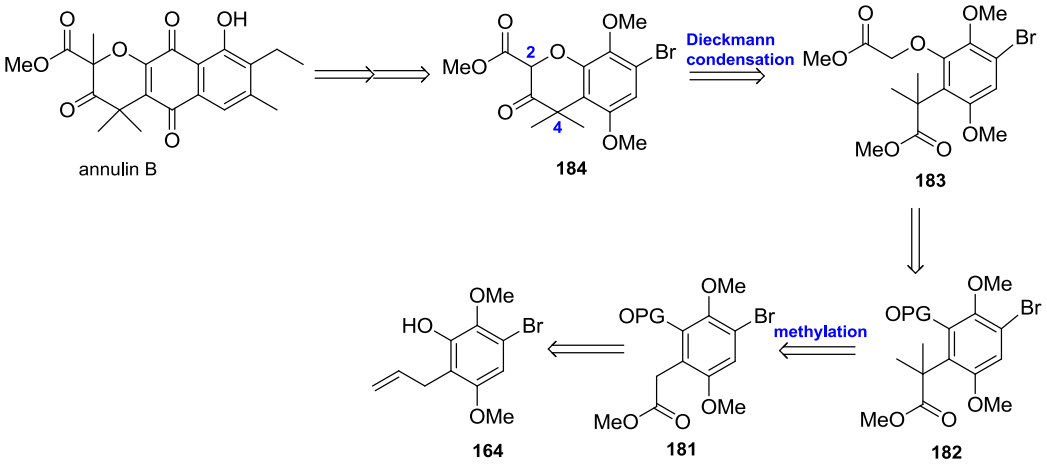

**Scheme 62** *Reagents and conditions*: (a) NaHMDS, THF, -78 ºC, 45 min., 72% (ratio 5:1).

With the evident inability of mixed ester **173** to undergo selective cyclisation to the desired 3-chromanone we decided to revise our strategy.

### 3.4.2.3. Intitial synthetic strategy revisited

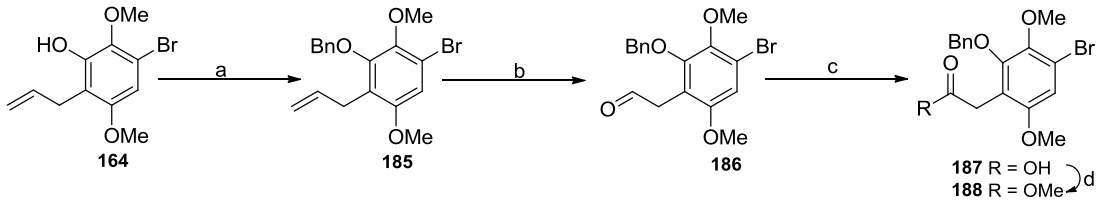
After the disappointing results described above, it became clear that in order to obtain the desired chroman-3-one, with the required ester group at C-2, it was essential to introduce the requisite methyl groups at C-4 before Dieckmann cyclisation. In view of this, we revisited the original retrosynthetic plan and examined an alternative strategy to introduce the required methyl groups.

Our aim was to prepare the allyl substituted benzene **164**, described before and then to perform ozonolysis followed by oxidation and esterification to access methyl ester **181**. Then dimethylation of the latter would hopefully yield the desired intermediate **182** that after reaction with methyl bromoacetate should give the Dieckmann condensation precursor **183** (**Scheme 63**).




**Scheme 63** Intitial synthetic strategy revisited.

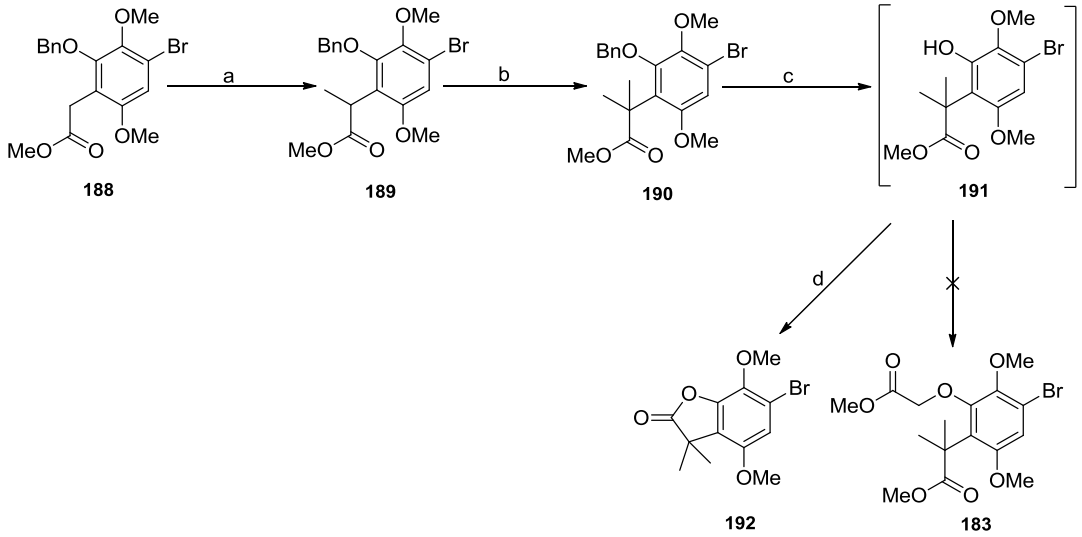
The synthesis started with preparation of intermediate **164**, using the same synthetic sequence described before. Protection of the phenol as a benzyl ether and subsequent ozonolysis of the allylic double bond gave the desired aldehyde **186** in excellent yield. The latter was then converted into the methyl ester **188**, after oxidation and esterification (**Scheme 64**).




**Scheme 64** *Reagents and conditions*: (a) BnBr, NaH, TBAI, THF, rt, 16 h, 91%; (b) *1*. $O_3$, $CH_2Cl_2$, -78 ºC, 10 min.; *2*. $PPh_3$, -78 ºC–rt, 2 h, 86%; (c) $NaClO_2$, $NaH_2PO_4$, $H_2O$, 2-methyl-2-butene, *t*-BuOH, rt, 1 h; (d) MeOH, $SOCl_2$, 0 ºC–rt, 16 h, 91% (over 2 steps).

With compound **188** synthesised we turned our attention to the preparation of the *gem*-dimethyl intermediate **190** (**Scheme 65**). Initial attempts using NaH (2.2 equivalents) or *t*-BuOK (2.2 equivalents) and iodomethane only returned unreacted starting material. After extensive experimentation this reaction was effected by reacting ester **188** with LiHMDS and iodomethane in THF, to give the monoalkylated ester **189**. Further treatment of the latter with an excess of LiHMDS and iodomethane gave the desired *gem*-dimethyl ester in very

good yield. Next the plan was to remove the benzyl protecting group. Reacting compound **190** with a vast excess of boron trichloride in dichloromethane gave lactone **192** in 74% yield. Alternatively **190** was reacted with only 3 equivalents of boron trichloride to give the desired phenol **191**. Sadly, this compound proved to be extremely unstable, and upon exposure to methyl chloroacetate and potassium carbonate or on standing at room temperature, cyclisation occurred and the lactone product **192** was isolated.

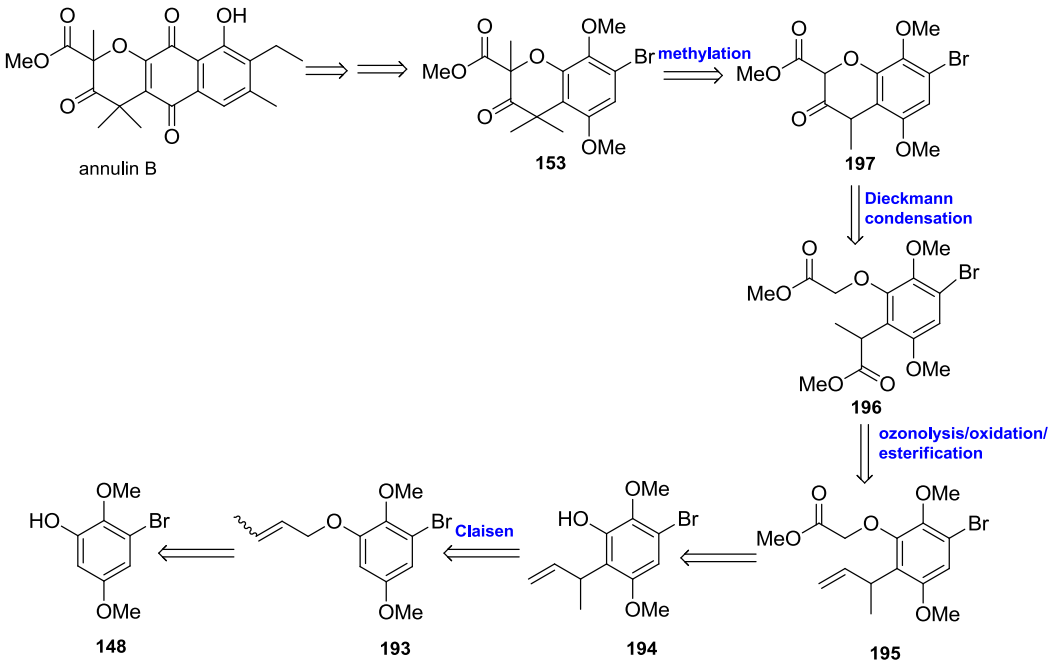



**Scheme 65** *Reagents and conditions*: (a) LiHMDS, MeI, THF, -78 ºC–rt, 18 h, 94%; (b) LiHMDS, MeI, THF, 0 ºC –rt, 21 h, 76%; (c) $BCl_3$, $CH_2Cl_2$, -78 ºC, 2.5 h, quantitative; (d) $ClCH_2CO_2Me$, $K_2CO_3$, DMF, 1 h, 100 ºC, 60%.

Formation of the cyclised product can be due to the *gem*-dialkyl effect that is known to cause an increase in the rate of cyclisation reactions. This effect was originally observed by Beesley, Ingold and Thorpe and named the Thorpe-Ingold effect.[127] According to them the observed rate increase of cyclisation when adding a *gem*-dialkyl functionality is caused by the reduction of the angle between the relevant ring atoms, resulting from compression by the substituents. An alternative explanation for this effect is called the reactive rotamer effect and subscribes that substitution lowers the rotational barrier so that the probability of the reactive *gauche* conformation being reached is increased.[128]

### 3.4.2.4. Revised retrosynthetic approach 2

In light of the evident inability to prepare the desired dimethyl ester with the *geminal* methyl groups we decided to alter our retrosynthetic analysis once more (**Scheme 66**). Upon consideration it was thought that instead of incorporating the two methyl groups before Dieckmann cyclisation, we could alternatively add only one, hoping that this would lead to the exclusive formation of the desired cyclysed product **197**. For the installation of the methyl group at the required position we planned to perform a Claisen rearrangement of crotyl ether **193** assuming that this would give mainly the desired *ortho*-(α-methylallyl)-phenol **194**.

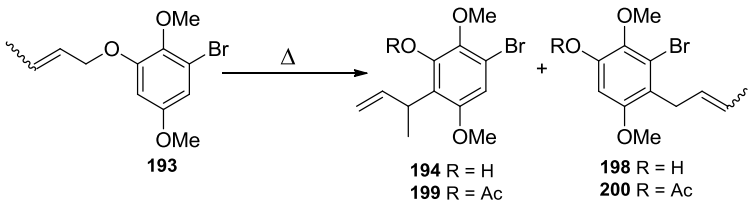



**Scheme 66** Revised retrosynthetic approach 2.

#### 3.4.2.4.1. Synthesis of the Dieckmann condensation precursor 196

After following the synthetic sequence previously described for the preparation of intermediate **148**, the latter was reacted with crotyl bromide to deliver the Claisen

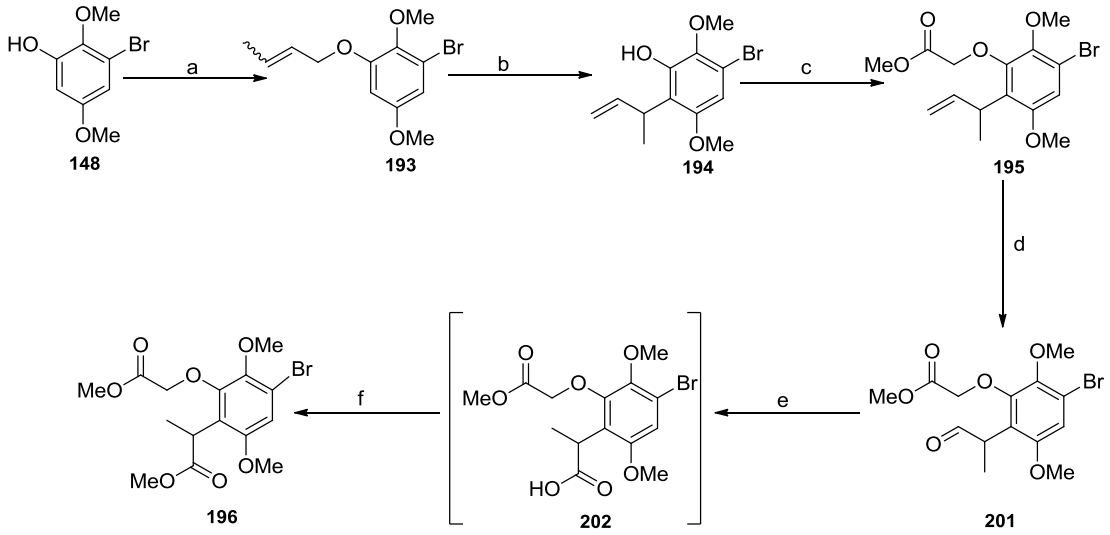
rearrangement substrate **193** in 87% yield as a 5:1 (*E*/*Z*) mixture of isomers (**Scheme 67**). With this intermediate in hand, we next investigated the Claisen rearrangement reaction (**Table 7**). Heating the allyl ether to 160 ºC in neat conditions or using DMF provided a low yield of both *ortho*- and *para*-rearranged products (entries 1 and 2). The use of acetic anhydride and *N*,*N*-diethylaniline gave similar results (entry 3). To our delight, improved yields of the desired *ortho* Claisen product were obtained when the allyl ether in DMF was heated to 200 ºC under microwave irradiation (entry 4).




| Entry | Conditions | Isolated products |
|---|---|---|
| **1** | neat, 160 ºC, 48 h | **194** (23%) + **198** (26%, E/Z 2:1) |
| **2** | DMF, 160 ºC, 48 h | **194** (31%) + **198** (26%, E/Z 2:1) |
| **3** | *N*,*N*-diethylaniline, acetic anhydride, 200 ºC, 19 h | **199** (35%) + **200** (36%, E/Z 1.8:1) |
| **4** | DMF, 200 ºC, 60 min., MW | **194** (53%) + **198** (29%, E/Z 2:1) |

**Table 7** Claisen rearrangement of crotyl ether **193**.

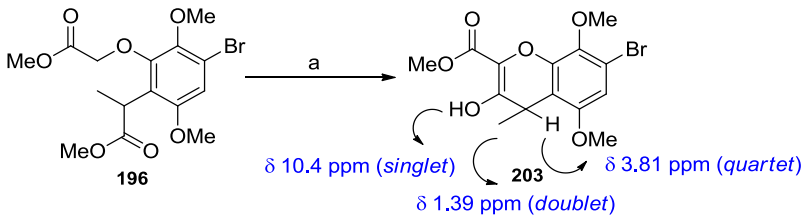
After the successful synthesis of the desired *ortho*-(α-methylallyl)-phenol **194**, this intermediate was elaborated into the Dieckmann cyclisation substrate **196** through the usual sequence (**Scheme 67**).




**Scheme 67** *Reagents and conditions:* (a) crotyl bromide, NaH, DMF, rt, 2.5 h, 87% (b) DMF, 200 ºC, 60 min. (MW), 53%; (c) $BrCH_2CO_2Me$, $K_2CO_3$, DMF, 50 ºC, 3 h, 88%; (d) *1.* $O_3$, $CH_2Cl_2$, -78 ºC, 15 min.; *2.* $PPh_3$, -78 ºC–rt, 2 h, 75%; (e) $NaClO_2$, $NaH_2PO_4$, $H_2O$, 2-methyl-2-butene, *t*-BuOH, rt, 1 h; (f) MeOH, $SOCl_2$, 0 ºC–rt, 16 h, 68% (over 2 steps).

### 3.4.2.4.2. Dieckmann condensation

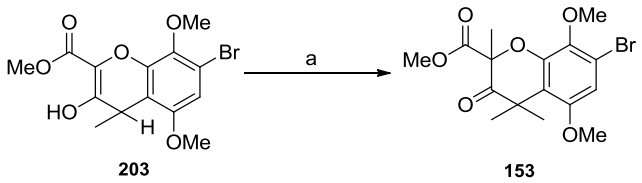
The proposed Dieckmann condensation was accomplished by reacting dimethyl ester **196** with LiHMDS at -78 ºC for 3 h. This reaction provided a compound with NMR spectroscopic data consistent with the enol tautomer of the desired chroman-3-one. The $^1$H-NMR spectrum showed a singlet at δ 10.4 ppm consistent with the hydroxyl group at position 3, as well as a quartet and a singlet at δ 3.81 and 1.39 ppm, corresponding to the methyl group and hydrogen at position 4 (**Scheme 68**).




**Scheme 68** *Reagents and conditions*: (a) LiHMDS, THF, -78 ºC, 3 h, 96%.

### 3.4.2.4.3. Completion of the synthesis

With the desired chroman 3-one successfully prepared, we began the final campaign towards annulin B. Initial attempts to methylate positions 2 and 4 involved the addition of potassium *t*-butoxide and iodomethane to a solution of **203** in THF. These conditions resulted in the formation of the desired compound, although in low yield.

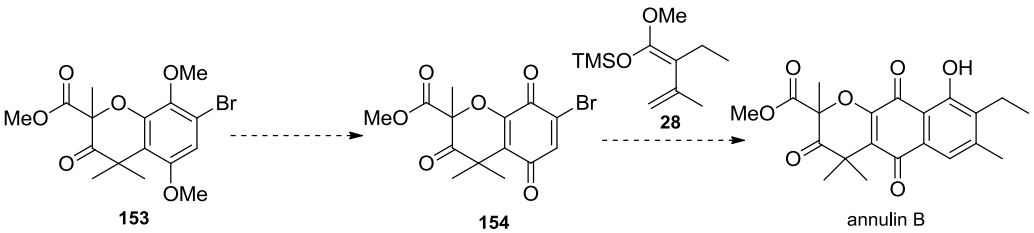



**203** **153**

**Scheme 69** *Reagents and conditions*: (a) *1. t*-BuOK, THF, 0 ºC, 1 h; *2.*$CH_3I$, 0 ºC, 1 h; *3.* 0 ºC–10 ºC, 1 h, 21%.

Due to a lack of material and time restriction, the studies towards annulin B had to be interrupted.

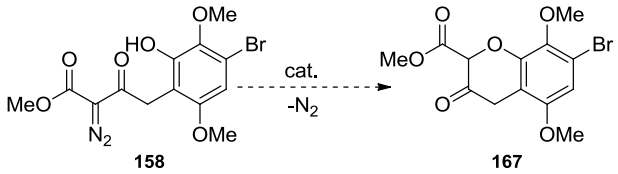
The remaining steps for converting **153** into annulin B are the oxidative demethylation of the dimethoxybenzene moiety to provide the desired quinone **154** and the Diels Alder reaction, between the latter and diene **28**, whose preparation has already been described.




**Scheme 70** Prospective completion of the synthesis.

### 3.4.3. Intramolecular O-H insertion approach

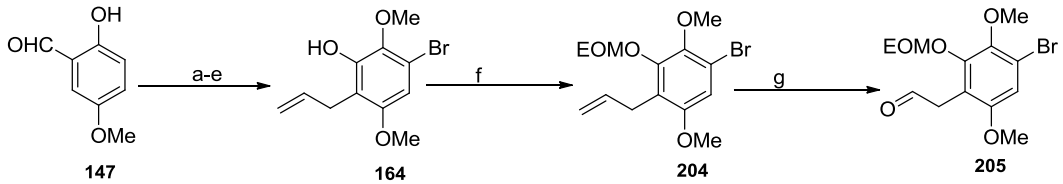
Although there are some examples in the literature on the preparation of oxygenated heterocycles, *via* an O-H insertion reaction,[129-132] there is no literature precedent for the preparation of chroman-3-ones using this strategy. As a result, we considered that it would be interesting to investigate in parallel a route for the synthesis of the chroman-3-one ring of annulin B based on O-H insertion chemistry.




**Scheme 71** Prospective O-H insertion reaction.

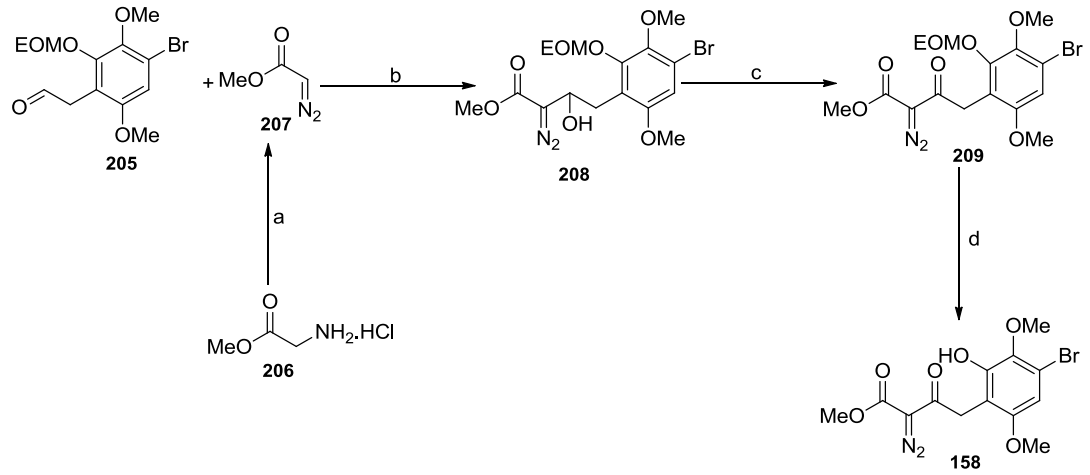
#### 3.4.3.1. Synthesis of α-diazo-β-ketoester 158

The synthesis started with the commercially available 2-hydroxy-5-methoxybenzaldehyde **147**, which was converted into allyl benzene **164**, using the same synthetic sequence described in Sections 3.4.2.1 and 3.4.2.2.1. The phenol **164** thus formed was protected as its ethoxymethyl ether (EOM) and then subjected to ozonolysis conditions to convert the terminal alkene into the desired aldehyde **205**, in very good yield (**Scheme 72**).




**Scheme 72** *Reagents and conditions:* (a) AcOH, NaOAc, $Br_2$, rt, 79%; (b) $K_2CO_3$, DMF, dimethylsulfate, rt, 24 h, 93%; (c) *1*. *m*-CPBA, $CH_2Cl_2$, rt, 18 h; *2*. MeOH, KOH (aq.), rt, 1 h, 79%; (d) allyl bromide, NaH, DMF, rt, 2.5 h, quantitative. (e) DMF, 200 ºC, 40 min. (MW), 57% (f) EOMCl, *i*$Pr_2NEt$, $CH_2Cl_2$, rt, 17 h, 81%; (g) *1*. $O_3$, $CH_2Cl_2$, -78 ºC, 10 min.; *2*. $PPh_3$, -78 ºC–rt, 2 h, 86%;

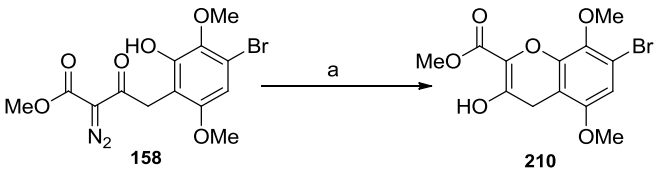
The installation of the required diazo functionality was effected in two steps. Following the precedents established by Jiang *et al.*,[133] aldehyde **205** was reacted with methyl diazoacetate[134] in the presence of DBU to give α-diazo-β-hydroxy compound **208** in 80% yield.[135] Oxidation of the resulting alcohol using IBX in DMSO[136] gave the desired α-diazo-β-ketoester **209** that was subsquently treated with a solution of hydrochloric acid in methanol to reveal the substrate for the key intramolecular O-H insertion reaction, in excellent yield (**Scheme 73**).




**Scheme 73** *Reagents and conditions:* (a) *1.* $NaNO_2$ (aq.), $H_2O$, $CH_2Cl_2$, rt; *2.* $H_2SO_4$ (aq.), –10 ºC, 20 min., 80%; (b) DBU, MeCN, rt, 3 h, 74%; (c) IBX, DMSO, 60 ºC, 20 min., 80%; HCl, MeOH, rt, 2 h, 96%.

### 3.4.3.2. Intramolecular O-H insertion

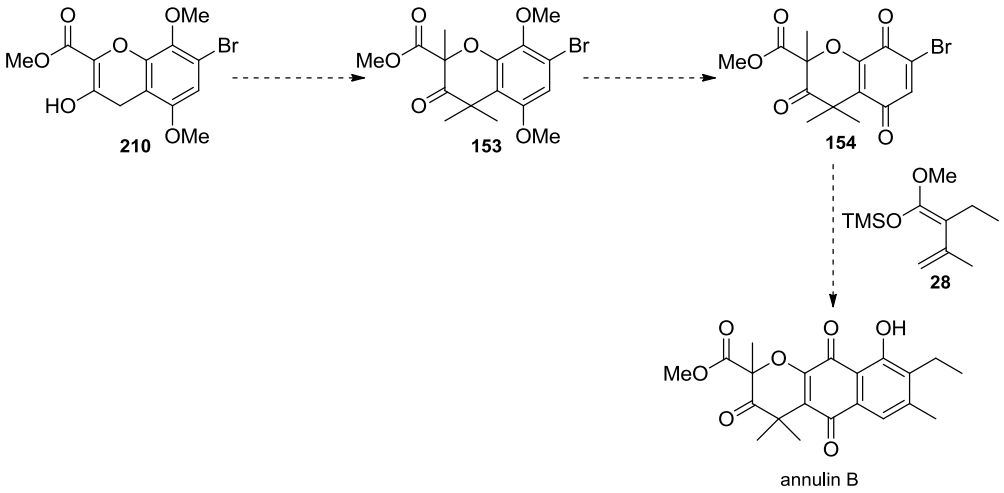
The stage was now set for the intramolecular rhodium carbene O-H insertion. This reaction was effected by adding rhodium(II) acetate catalyst to a solution of the diazo compound **158** in dichloromethane. This resulted in the formation of the desired chroman-3-one as its enol tautomer **210**, in excellent yield (**Scheme 74**).




**Scheme 74** *Reagents and conditions:* (a) $Rh_2(OAc)_4$, $CH_2Cl_2$, rt, 1 h, 98%.

The appearance of two singlets at δ 10.5 and 3.50 ppm, corresponding to the hydroxyl and the $–CH_2$ groups, confirmed the successful transformation. Due to the lack of time, no more experiments could be carried out to complete the synthesis of annulin B.

Similarly to the synthetic route described above, future work will include the methylation at positions 2 and 4, followed by oxidative demethylation of the benzene core to the desired quinone **154** and Diels Alder reaction, between the latter and diene **28**.




**Scheme 75** Prospective completion of the synthesis.

## 3.5. Conclusion

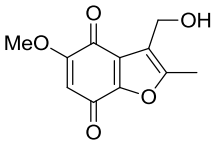
This Chapter has described our synthetic efforts towards the synthesis of annulin B. In order to access the chroman-3-one ring two different strategies were investigated. In a first approach, our aim was to synthesise the chroman-3-one ring through a Dieckmann condensation reaction. For the preparation of the substrate for this key reaction we performed a Claisen rearrangement of three intermediates, namely, prenyl ether **149**, crotyl ether **195** and allyl ether **155**. Claisen rearrangement of prenyl ether **149** was disappointing and gave mainly the undesired *para* rearranged product **163**. To our delight, crotyl and allyl ethers gave the desired *ortho* rearranged products in good yields. After transformation of *ortho*-allylphenol **164** and *ortho*-(α-methylallyl)-phenol **194** into the corresponding dimethylesters, **166** and **196**, both compounds were subjected to Dieckmann condensation. Initial attempts, using dimethylester **166** were not successful leading to the undesired cyclised product **171**. Fortunately, reaction of dimethyl ester **196**, which contains one of the required methyl groups, resulted in the formation of the desired 3-chromanone as its enol tautomer **203**, in excellent yield (96%). Using this synthetic route the desired chroman-3-one **203** was obtained in 12% yield, over 10 steps. In a second approach, we successfully prepared the 3-chromanone ring of annulin B using an intramolecular carbene O-H insertion reaction, by dirhodium(II) catalysed reaction of α-diazo-β-ketoester **158**. This alternative approach allowed the preparation of the desired 3-chromanone ring **210** in 13% yield, over 11 steps.

# CHAPTER IV

## SYNTHESIS OF BENZOFURANQUINONES

## 4.1 Introduction

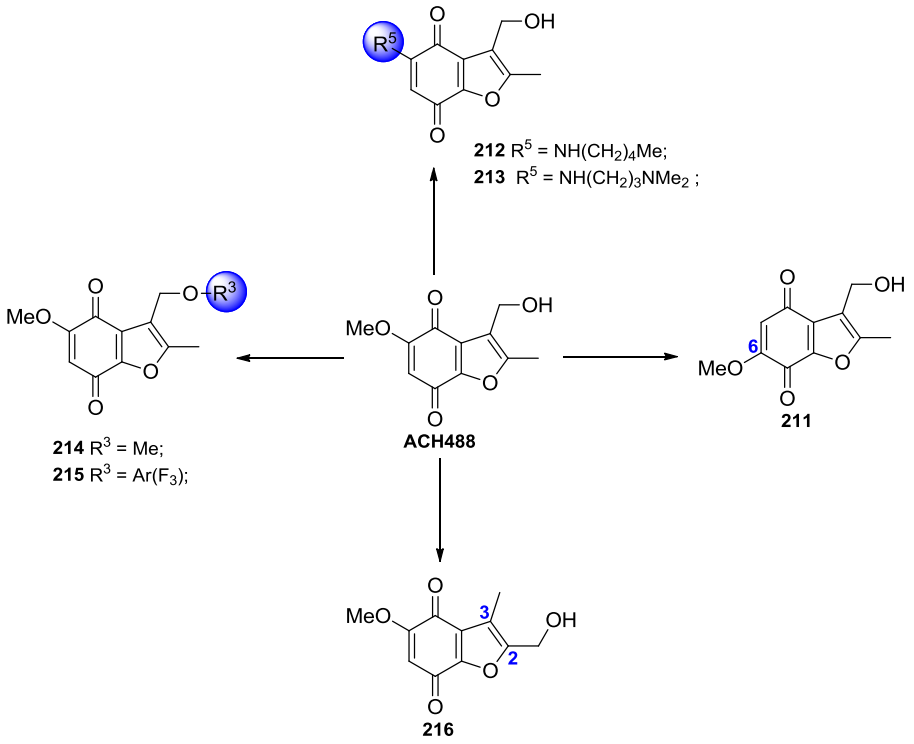
Earlier biological assays identified the benzofuran **ACH488**, previously synthesised in the Moody group, as a good IDO inhibitor. The $IC_{50}$ value for this compound, 237 nM, is comparable to the most potent IDO inhibitors discovered so far, including naphthoquinones and the marine sponge alkaloid exiguamine A.[40,42]




ACH488

**Figure 16** Structure of ACH488.

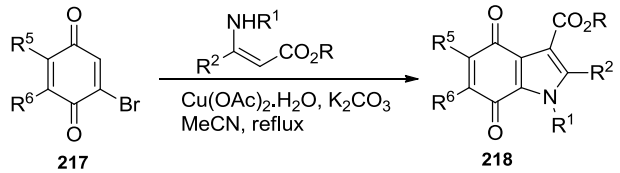
Aiming to extend our studies on the inhibition of IDO a selection of benzofurans, based on the **ACH488** core, was prepared (**Scheme 76**). Our initial aim was to investigate the effects of IDO inhibition by modifying the substituents at positions 5 and 6. The synthesis of the 6-methoxy regioisomer of **ACH488** was initially investigated and following this, the 5-position was substituted with aminoalkyl groups. Further investigations looked at protecting the hydroxyl group at the 3-position, with a methyl and with an electron-withdrawing group. In addition, we decided to modify the order of substituents at positions 2- and 3- and to prepare analogue **216**.




**Scheme 76** Structure of benzofuranquinones analogues.

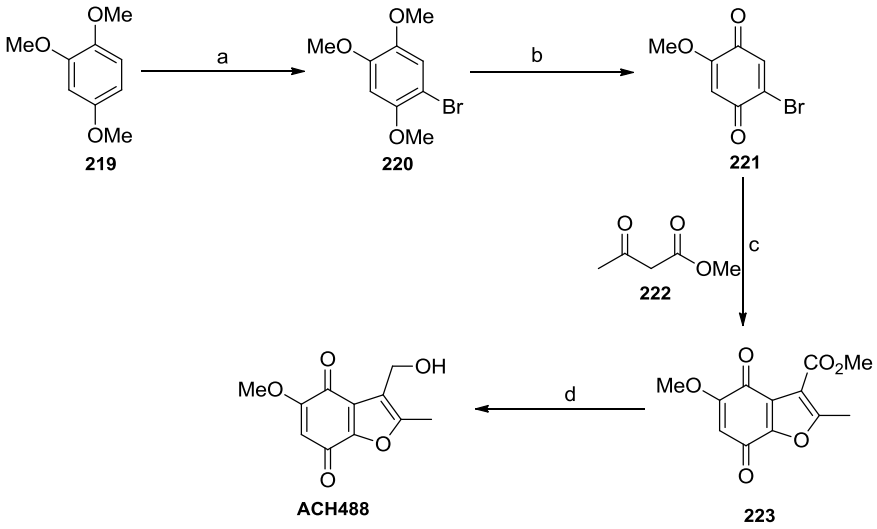
## 4.2 Synthesis of ACH488

Benzofuran **ACH488** was prepared using a modified version of the methodology developed by Murphy *et al.*[137,138] in 1992. The authors reported the regioespecific synthesis of the pyrrolo[1,2-*a*]indoloquinone framework, employing a bromoquinone-enamine annulation, in the presence of potassium carbonate and copper(II) bromide. Improved conditions for this reaction were developed within the Moody group, using stoichiometric copper(II) acetate (**Scheme 77**).[139]



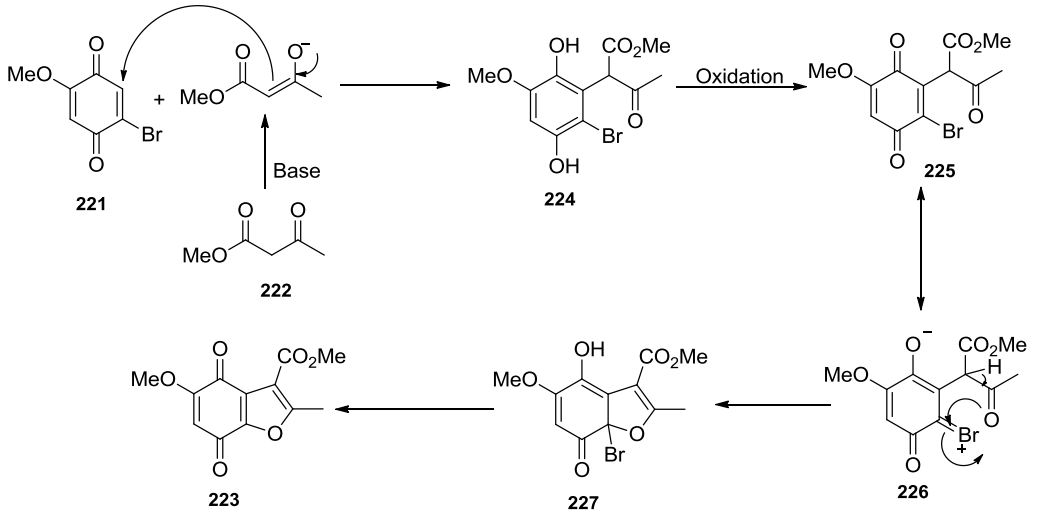

**Scheme 77** Cu(II)-mediated synthesis of indolequinones from the corresponding bromoquinones and enamines.

The synthesis started with bromination of the commercial available compound **219** followed by oxidation with cerium ammonium nitrate, to give bromoquinone **221** in 2 steps, in 85% yield. Then, reaction of the latter with methyl acetoacetate, in the presence of potassium carbonate or potassium *t*-butoxide and copper(II) acetate monohydrate yielded the desired benzofuran **223**. The yield varied from 9% to 34%, depending whether the reaction was performed in gram or milligram scale. Treatment with lithium aluminium hydride in THF reduced the ester group to the corresponding alcohol, and oxidation with iron trichloride gave the expected benzofuran **ACH488** as an orange solid in 30% yield (**Scheme 78**).




**Scheme 78** *Reagents and conditions:* (a) $Br_2$, $CH_2Cl_2$, 0 ºC, 1 h 96%; (b) CAN, $H_2O$, MeCN, rt, 16 h, 89%; (c) methyl acetoacetate, $Cu(OAc)_2.H_2O$, $K_2CO_3$, MeCN, 80 ºC, 1.5 h, 34%; (d) *1.* $LiAlH_4$, THF, rt 1 h; *2.* Acetone, $FeCl_3.H_2O$ (1 M), 5 min, 30%.

The mechanism proposed by Murphy *et al.*[140] for the annulation reaction between 2-bromo-5-methoxyquinone **221** and methyl acetoacetate is shown in **Scheme 79**. The key steps are (a) the Michael type addition of **222** to C6 of the bromoquinone **221** to give hydroquinone **224**, after enolisation, (b) oxidation of the hydroquinone to quinone **225**, and (c) cyclisation to **223**. The main role of Cu(II) is to oxidise the hydroquinone to the corresponding quinone under aerobic conditions.




**Scheme 79** Proposed mechanism for the annulation reaction.

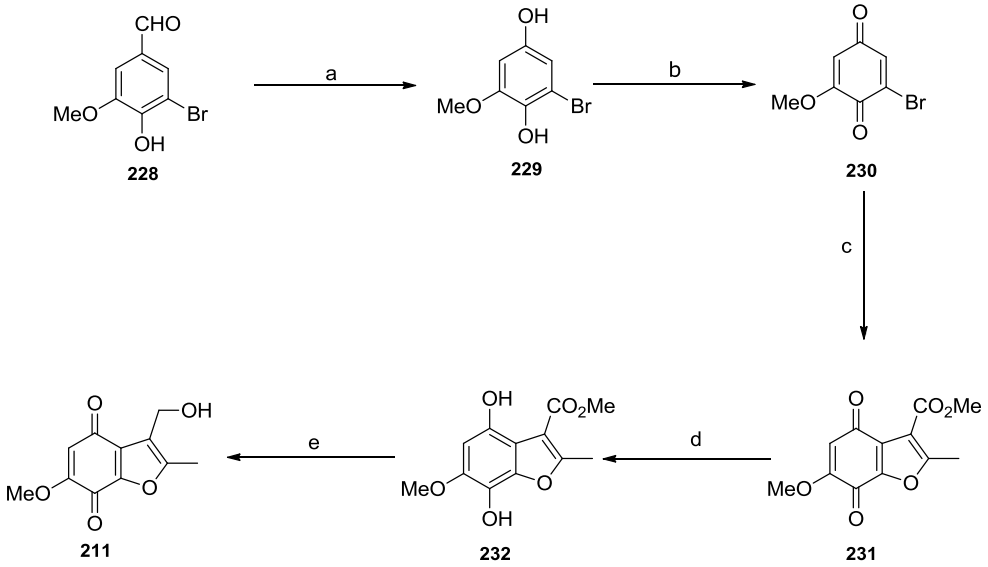
## 4.3 Synthesis of ACH488 analogues

### 4.3.1 Synthesis of 6-methoxy-2-methylbenzofuran-4,7-dione 211

The first analogue to be synthesised was the 6-methoxy regioisomer of **ACH488**. The initial aim was to investigate if switching the methoxy group, from the 5- to the 6-position, would effect IDO inhibition. Although this may appear a trivial change, the switch of the electron releasing methoxy group from the 5- to the 6-position affects the electronic properties of the quinone ring system.

The same strategy, previously applied to the synthesis of **ACH488**, was used to prepare the 6-methoxy regioisomer (**Scheme 80**). The synthesis started with Dakin oxidation of 5-bromovanillin **228** with sodium percarbonate to give hydroquinone **229** in 81% yield. Subsequent oxidation of **229** with iron(III) chloride yielded quinone **230**, which was reacted with methyl acetoacetate in the presence of potassium carbonate and copper(II) acetate monohydrate to give benzofuran **233** in 49% yield. To perform the reduction of the methyl ester to the alcohol, the quinone moiety was first reduced with sodium dithionite to the corresponding hydroquinone **232** and then treated with lithium aluminium hydride. The

work-up was conducted by treating the reaction mixture with ethyl acetate, water, sodium hydroxide and silica in the presence of air to induce the spontaneous reoxidation of the hydroquinone, giving the desired benzofuran **211** in 52% yield.




**Scheme 80** *Reagents and conditions:* (a) sodium percarbonate, THF/$H_2O$, rt, 4 h, 81%; (b) $FeCl_3.H_2O$, MeOH, rt, 1 h, 91%; (c) methyl acetoacetate, $Cu(OAc)_2.H_2O$, $K_2CO_3$, MeCN, 80ºC, 1.5 h, 49%; (d) $Na_2S_2O_4$, $CHCl_3$, $H_2O$, rt, 3 h, 79%; (e) 1. $LiAlH_4$, THF, 0 ºC, 2. rt, 1.5 h, 52%.

### 4.3.2 Synthesis of 5-aminoalkyl substituted benzofuranquinones 212 and 213

Synthesis of benzofuranquinones **212** and **213** (**Figure 17**) was of interest as the introduction of another heteroatom containing substituent could eventually help in the solubility of the compound. It would also enable us to verify if IDO can accept longer chain substituents at the 5-position.

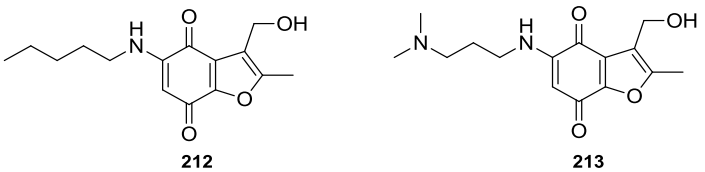
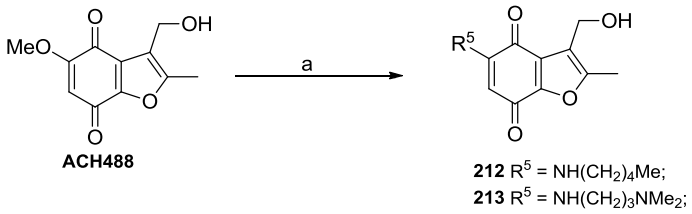



**Figure 17** Structure of compounds **212** and **213**.

Analogues **212** and **213** were prepared by nucleophilic substitution of the 5-methoxy group, by an excess of pentylamine or *N*,*N*-dimethylpropane-1,3-diamine in acetonitrile at room temperature (**Scheme 81**).




**Scheme 81** *Reagents and conditions:* (a) $NH_2R$, acetonitrile, rt.

Compounds **212** and **213** were obtained in 64% and 55% yields, respectively. Complete characterisation of each compound confirmed that the substitution reactions were successful.

### 4.3.3 Synthesis of analogues 214 and 215

In order to investigate whether the free hydroxyl group at the 3-position was essential for IDO inhibition we decided to synthesise two analogues, in which the hydroxyl group was protected with a methyl group **214** or with a electron-withdrawing group **215**, in this case, a trifluorophenyl (**Figure 18**).

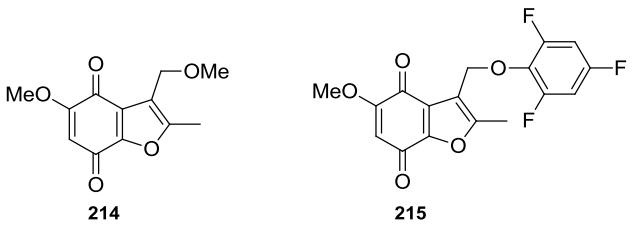
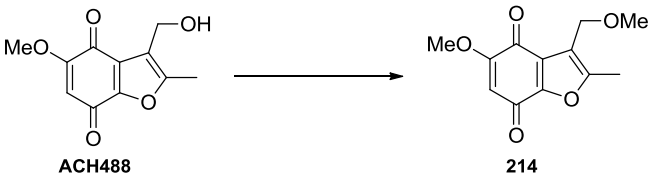



**Figure 18** Structure of compounds **214** and **215**.

Initial efforts to prepare methyl ether **214** included attempts to react **ACH488** with mild bases, such as, sodium methoxide, caesium carbonate or pyridine in the presence of 4-dimethylaminopyridine, or strong bases, such as, sodium hydride (**Table 8**). Nevertheless, all of these approaches proved to be unsatisfactory, leading to degradation products or recovery

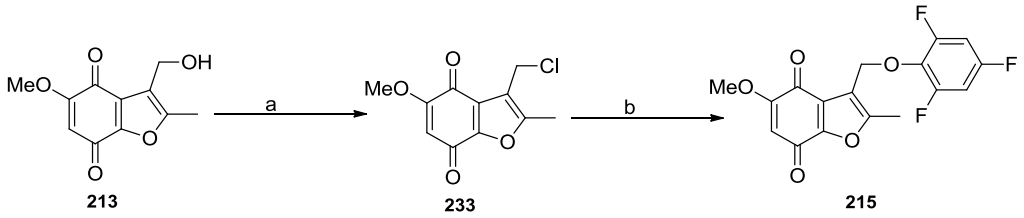
of starting material. Alternatively, **ACH488** was treated with thionyl chloride and then reacted with methanol, in the presence of potassium carbonate. These conditions, however, only gave the chlorinated compound or degradation products. A final attempt using silver(I) oxide and methyl iodide at reflux was carried out. Using this method, **ACH488** was converted into the desired methyl ether **214** in 51%.




| Entry | Reagents | Temperature/ ºC | Time/ h | Isolated Products |
|---|---|---|---|---|
| **1** | DMAP, pyridine, MeI,$CH_2Cl_2$ | rt | 8 | starting material + degradation |
| **2** | DMAP, pyridine, MeI, DMF | 40 | 48 | starting material + degradation |
| **3** | NaH, MeI, THF | rt | 20 | degradation |
| **4** | a) $SOCl_2$, $CH_2Cl_2$<br>b) MeOH, $K_2CO_3$, DMF | rt | a) 1<br>b) 16 | chlorinated compound |
| **5** | a) $SOCl_2$, $CH_2Cl_2$<br>b) MeOH, $K_2CO_3$ | rt | a) 1<br>b) 2 | degradation |
| **6** | NaOMe, MeI, MeOH, THF | rt | 2 | degradation |
| **7** | $Cs_2CO_3$, MeI, DMF | rt | 32 | degradation |
| **8** | $Ag_2O$, MeI | reflux | 22 | **214** (51%) |

**Table 8** Conditions screened to obtain compound **214**.

The synthesis of analogue **215** was carried out in two steps. First, the free hydroxyl group was chlorinated with thionyl chloride and then treated with 2,4,6-trifluorophenol in the presence of sodium hydride. The desired compound **215** was obtained in 34% yield over two steps (**Scheme 82**). Attempts to obtain directly compound **215** without isolation of the chlorinated intermediate **233** failed. It was necessary to isolate the chlorinated compound in order to perform the coupling reaction.




**Scheme 82** *Reagents and conditions:* (a) $SOCl_2$, $CH_2Cl_2$, rt, 2 h, 58%; (b) 2,4,6-trifluorophenol, NaH, DMF, rt, 5 h, 58%.

### 4.3.4 Synthesis of analogue 216

In order to explore the influence of changing the order of substituents at positions 2 and 3, compound **216** was synthesised (**Figure 19**).

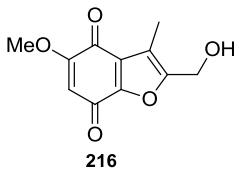
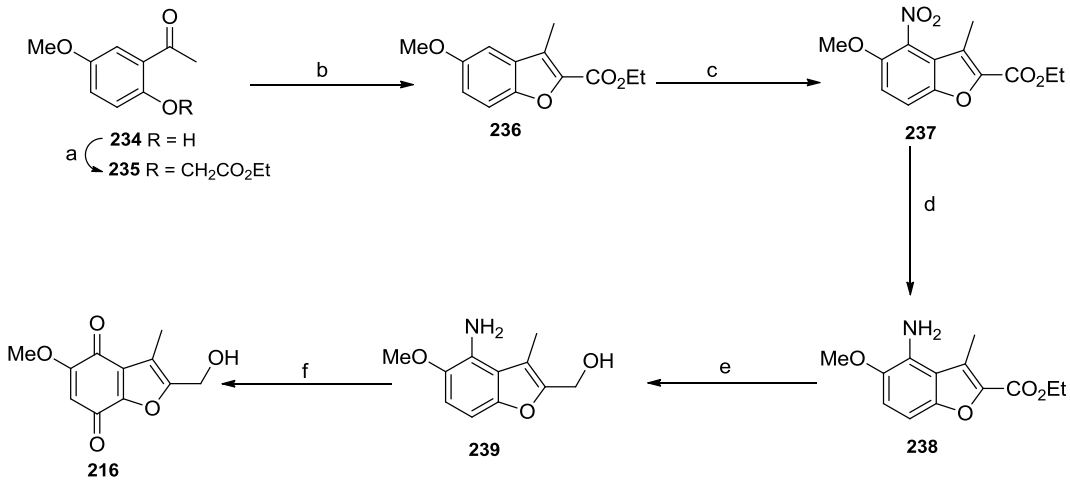



**Figure 19** Structure of compound **216**.

The synthesis started with alkylation of 2-hydroxyacetophenone **234** with ethyl bromoacetate under basic conditions (**Scheme 83**). The resulting ethyl phenoxyacetate **235** was then treated with sodium ethoxide to give the corresponding benzofuran **236** in 36% yield. Nitration using fuming nitric acid in acetic acid provided an entry to the desired 4-nitrobenzofuran **237** in 58% yield, along with the isomeric 6-nitrobenzofuran. $^1$H-NMR spectroscopy confirmed the position of the nitro group on **237,** by the appearance of two doublet signals with a 9.2 Hz coupling constant.

Reduction of the nitro group using tin powder in hydrochloric acid and ethanol at reflux yielded the aminobenzofuran **238** in 93% yield. Treatment with lithium aluminium hydride in THF reduced the ester group to the corresponding alcohol, and oxidation with potassium nitrosodisulfonate (Fremy's salt) gave the expected quinone **216** in 89% yield.




**Scheme 83** *Reagents and conditions:* (a) ethyl bromoacetate, $K_2CO_3$, acetone, 60 ºC, 18 h, 97%; (b) NaOEt (21 wt% in ethanol), EtOH, 75 ºC, 2 h, 36%; (c) $HNO_3$ (fuming), AcOH (glacial), rt, 18 h, 58%; (d) Sn, HCl, ethanol, reflux, 1.5 h, 93%; (e) $LiAlH_4$, THF, rt, 2.5 h, 87%; (f) Fremy's salt, acetone, $NaH_2PO_4$ buffer, rt, 1 h, 89%.

## 4.4 Biological evaluation of benzofuranquinones

Some of the benzofuranquinones described in this chapter were evaluated for their ability to inhibit purified recombinant human IDO. All these experiments were carried out in the laboratories of Professor David Ross by Dr David Siegel and colleagues, within the University of Colorado, Department of Pharmaceutical Sciences and Cancer Center in Denver.

### 4.4.1 Biochemical Assay

Recombinant human IDO was expressed and purified as described by Littlejohn *et al.*[141] The method used to evaluate inhibition efficiency is shown in **Figure 20**. IDO expression was

activated by stimulation of the tumour cells in culture with interferon-γ (IFN-γ) and lipopolysaccharide (LPS). 48 h after stimulation, the cell culture medium was collected and the levels of L-tryptophan, L-kynurenine and L-kynurenic acid were measured by capillary liquid chromatography-electrospray ionisation tandem mass spectrometry. In the presence of IDO inhibition, the levels of tryptophan in the cell culture medium remained unchanged and the levels of kynurenine and kynurenic acid decreased, relative to non-inhibited controls.

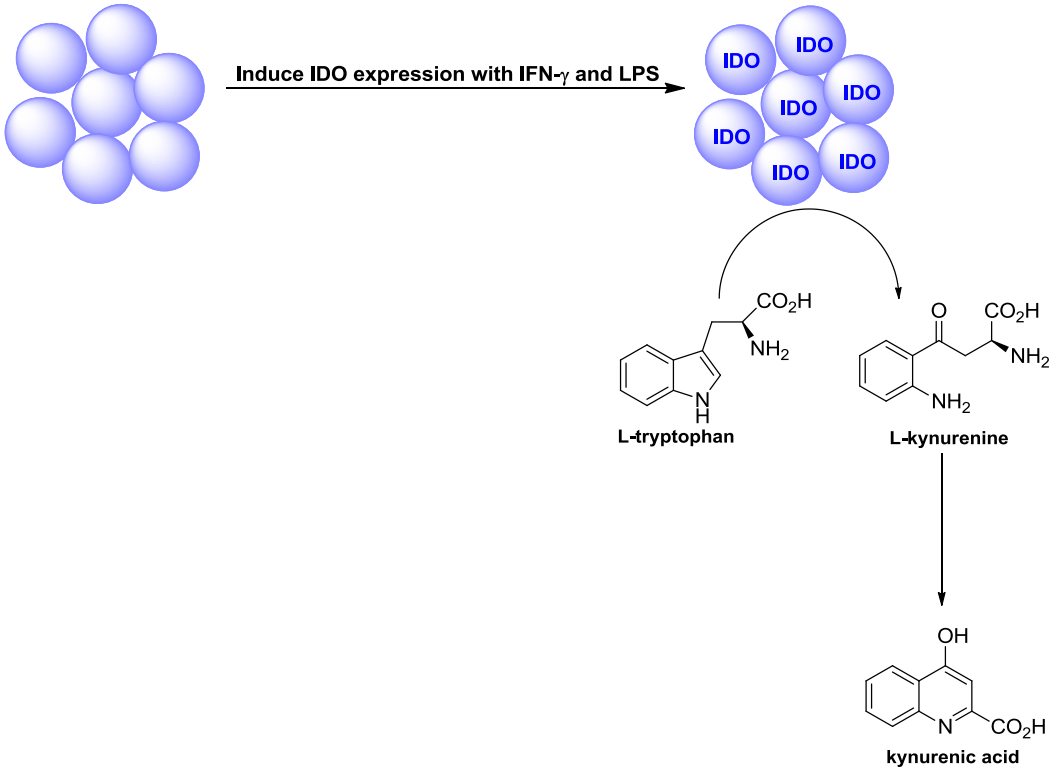
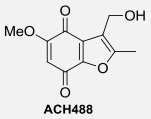
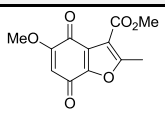
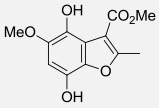
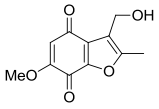
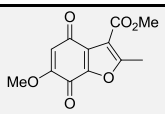
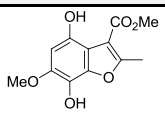
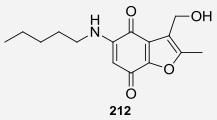
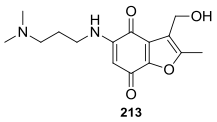
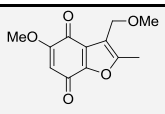
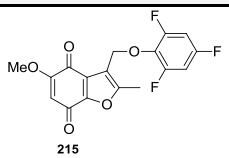



**Figure 20** IDO inhibition assay.

### 4.4.2 Biological results

The results of the biological assays are provided in **Table 9** and include the $IC_{50}$ determined for inhibition by **ACH488**, the related 6-methoxy regioiosomer **211** and the corresponding synthetic precursors **223**, **240** and **231**, **232**. The percent activity remaining of IDO at 1 µM for benzofurans **212**, **213**, **214** and **215** is also displayed. Biological data of compound **216**, described in this Chapter, is awaited from our collaborators.

| Compounds | $IC_{50}$ (μM) | Percent activity remaining of IDO at 1 μM |
|---|---|---|
|  ACH488 | 0.237 | 17.0 |
|  223 | 7.20 | – |
| *  240 | 94.2 | – |
|  211 | 0.499 | – |
|  231 | 33.8 | – |
|  232 | >100 | – |
|  212 | – | 71.9 |
|  213 | – | 57.1 |
|  214 | – | 26.2 |
|  215 | – | 41.0 |

*Synthesised using the same procedure as described for **232**;

**Table 9** In vitro inhibition of IDO.

The data clearly shows that **ACH488**, the 6-methoxy regioisomer **211** and the 3-methoxymethyl derivative **214** were the most potent IDO inhibitors. In contrast, hydroquinones **240** and **232** were very poor inhibitors, demonstrating that the quinone functionality is critical for activity. The poor results with the methyl ester derivatives confirm the importance of the hydroxymethyl group.

Protecting the hydroxyl group at position 3 with a trifluorophenyl group (**215**) resulted in a considerable loss of activity. In contrast, the protection of the hydroxyl group with a methyl group resulted in a compound (**214**) which activity is roughly equal to that of **ACH488**. This result suggests that it is likely that the oxygen atom at position 3 is exploiting hydrogen bonding interactions with some residues of the enzyme.

Incorporation of aminoalkyl chains at the 5-position clearly have a detrimental effect. This probably suggests that only small groups are tolerated at this position.

## 4.5 Conclusion

Several compounds were synthesised around the **ACH488** scaffold. From the biological results obtained, it can be concluded that the presence of a quinone moiety is essential for potent IDO inhibition. In addition, these preliminary studies also indicate that the oxygen atom at position 3 might be important for IDO inhibitory effect. The dramatic loss in activity observed with the 5-aminoalkyl substituted benzofurans probably suggests that only small groups are tolerated at this position. These results will enable us to further exploit modifications of the **ACH488** structure, with the goal of generating even more potent IDO inhibitors.

# CHAPTER V

## EXPERIMENTAL SECTION

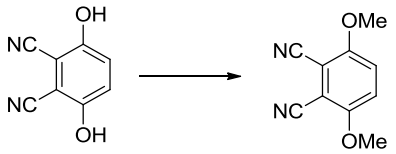
## General experimental details

Commercially available reagents were used throughout without further purification unless otherwise stated. All anhydrous solvents were purchase from Aldrich except tetrahydrofuran and dichloromethane that were distilled from sodium benzophenone ketyl and calcium hydride, respectively. All other solvents were obtained as spectroscopic grade and used as received. Light petroleum refers to the fraction with bp 40-60 ºC and ether refers to diethyl ether. All reactions were routinely carried out under a nitrogen or argon atmosphere and all glassware was flame-dried before use. Microwave reactions were carried out in a CEM Discover S-class (300W) microwave reactor with IR temperature sensor. Analytical thin layer chromatography was carried out on aluminium backed plates coated with silica gel (Merck Kieselgel 60 $GF_{254}$), and visualised under UV light at 254 and/or 360 nm and/or potassium permanganate or ethanolic vanillin dip. Chromatography was carried out using Merck Kieselgel 60 H silica with the eluent specified. Infrared spectra were recorded on a Perkin ELMER 1600 FTIR spectrometer, in the range 4000-600 $cm^{-1}$ using chloroform as solvent. Ultraviolet spectra were recorded in the range 200-600 nm as solutions in spectrometric grade acetonitrile using either Perkin Elmer Lambda 5 spectrophotometer or ATI Unicam UV4. $^{1}$H-NMR and $^{13}$C-NMR spectra were recorded using Bruker Avance III-500, Avance III-400, Avance 400, DPX 400 and DPX 300 instruments ($^{1}$H frequencies are 300, 400 and 500 MHz, corresponding $^{13}$C frequencies 75, 100 and 125 MHz). Chemical shifts are quoted in ppm and are referenced against residual proton in the deuterated solvents. *J* values are recorded in Hz. In the $^{13}$C spectra, signals corresponding to CH, $CH_2$ or Me groups are assigned from DEPT-90 and -135 spectra; all others are quaternary C. Mass spectra were recorded on a Bruker MicroTOF mass spectrometer using electrospray ionization (ESI) or electron ionization (EI). Elemental analysis was carried out on a CE-440 elemental analyzer. Melting points were measured on a Reichard-Köfler hot stage apparatus

or on a Eletrothermal IA9200 apparatus and are uncorrected. Ozone was generated by electric discharge, passing pure oxygen through a Fisher ozone generator 500.

## *Experimental details for Chapter II*

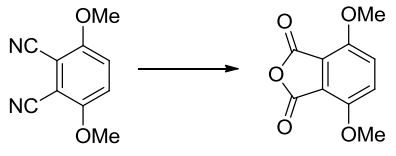
### 2,3-Dicyano-1,4-dimethoxybenzene 33[50]




**29** **33**

Dimethyl sulfate (13.1 mL, 137 mmol) and anhydrous potassium carbonate (19.8 g, 143 mmol) were added to a solution of 2,3-dicyanohydroquinone **29** (2.62 g, 16.0 mmol) in 2-butanone (105 mL). The reaction mixture was heated under reflux for 18 h, cooled to room temperature and the solid collected by filtration. The residue was added to water (90 mL) and the insoluble material was collected by filtration. Recrystallisation from acetic acid yielded the *title compound* **33** as colourless needles (2.45 g, 81%); mp 288-289 ºC (lit.,[50] mp 273-274 ºC); (Found: M+$Na^+$, 211.0474. $C_{10}H_8N_2O_2$+$Na^+$ requires 211.0483); $\nu_{max}$ (KBr)/$cm^{-1}$ 3019, 2227, 1215, 769, 699; $\delta_H$ (400 MHz; DMSO-$d_6$) 7.63 (2 H, s, ArH), 3.93 (6 H, s, OMe); $\delta_C$ (100 MHz; DMSO-$d_6$) 155.4 (C), 119.5 (CH), 113.5 (C), 102.4 (C), 57.1 (Me); *m/z* (ESI) 211 (M+$Na^+$, 100%). Data in agreement with literature values.[50]

### 4,7-Dimethoxyisobenzofuran-1,3-dione 30[50]

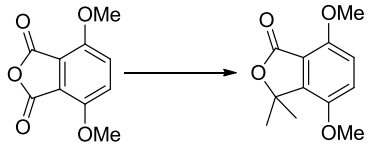



**33** **30**

A mixture of 2,3-dicyano-1,4-dimethoxybenzene **33** (300 mg, 1.59 mmol) in concentrated sulfuric acid (1.41 mL) was heated to 100 ºC for 1 h. After standing at room temperature overnight, the reaction mixture was added to ice and the solid was collected by filtration. The solid was dissolved in acetic anhydride (5 mL) and stirred at room temperature for 1 h. After evaporation of the solvent, the residue was recrystallised from chloroform, yielding the *title*

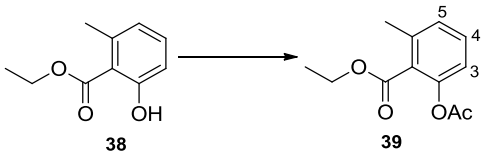
*compound* **30** as a yellow powder (191 mg, 51%); mp 258-259 ºC (lit.,[50] mp 259-260 ºC); (Found: M+$Na^+$, 231.0261. $C_{10}H_8O_5$+$Na^+$ requires 231.0372); $\delta_H$ (400 MHz; DMSO-$d_6$) 7.61 (2 H, s, ArH), 3.95 (6 H, s, OMe); $\delta_C$ (100 MHz; DMSO-$d_6$) 160.4 (C), 151.1 (C), 122.3 (CH), 116.7 (C), 56.5 (Me); *m/z* (ESI) 231 (M+$Na^+$, 100%). Data in agreement with literature values.[50]

**4,7-Dimethoxy-3,3-dimethyl*iso*benzofuran-1(3*H*)-one 31**



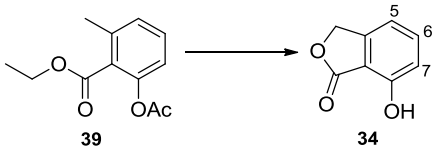

Methylmagnesium bromide (3 M in ether; 0.53 mL, 1.58 mmol) was added to a solution of 4,7-dimethoxyisobenzofuran-1,3-dione **30** (150 mg, 0.72 mmol) in THF (2 mL) at 0 ºC. The reaction mixture was allowed to warm to room temperature over 17 h and then a solution of hydrochloric acid (10%; 0.93 mL) was added and the reaction mixture was stirred at 0 ºC for 1 h. The mixture was poured into water (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure and the residue was purified *via* silica-gel column chromatography using dichloromethane/ether (9:1) to give the *title compound* **31** as a beige solid (109 mg, 68%), after precipitation with light petroleum; mp 123-124 ºC; (Found: M+$Na^+$, 245.0782. $C_{12}H_{14}O_4$+$Na^+$ requires 245.0784); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2985, 2840, 2360, 1749, 1505, 1296, 961; $\delta_H$ (300 MHz; $CDCl_3$) 7.04 (1 H, d, *J* 8.8, ArH), 6.84 (1 H, d, *J* 8.8, ArH), 3.92 (3 H, s, OMe), 3.85 (3 H, s, OMe), 1.66 (6 H, s, Me); $\delta_C$ (75 MHz; $CDCl_3$) 167.7 (C), 152.0 (C), 147.2 (C), 144.1 (C), 117.2 (CH), 114.5 (C), 111.5 (CH), 84.0 (C), 56.2 (Me), 55.8 (Me), 25.2 (Me); *m/z* (ESI) 267 (2M+$Na^+$, 100%), 245 (M+$Na^+$, 32%).

**Ethyl 2-acetoxy-6-methylbenzoate 39**[52]




Ethyl 6-methylsalicylate **38** (500 mg, 2.77 mmol) was dissolved in dry pyridine (1.39 mL) and acetic anhydride (0.55 mL, 5.54 mmol) was added at room temperature. After being stirred for 3 h, the reaction mixture was diluted with ethyl acetate (15 mL), washed with hydrochloric acid (1 M), until lower layer became pH 1-2, water (2 × 15 mL), saturated aqueous sodium hydrogen carbonate (15 mL), brine (15 mL) and dried ($MgSO_4$). Filtration followed by evaporation gave the *title compound* **39** as colourless crystals (615 mg, quantitative yield); mp 34-35 ºC (lit.,[52] mp 36-37 ºC); (Found: $M+Na^+$, 245.0781. $C_{12}H_{14}O_4+Na^+$ requires 245.0784); $\delta_H$ (400 MHz; $CDCl_3$) 7.32 (1 H, t, *J* 7.9, H-4), 7.10 (1 H, d, *J* 7.9, H-3), 6.96 (1 H, d, *J* 7.9, H-5), 4.37 (2 H, q, *J* 7.2, C<u>H</u>$_2$Me), 2.41 (3 H, s, Me), 2.27 (3 H, s, Me), 1.37 (3 H, t, *J* 7.2, CH$_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 169.1 (C), 166.5 (C), 148.3 (C), 138.0 (C), 130.5 (CH), 128.1 (CH), 126.6 (C), 120.3 (CH), 61.2 ($CH_2$), 20.8 (Me), 20.0 (Me), 14.2 (Me); *m/z* (ESI) 467 ($2M+Na^+$), 245 ($M+Na^+$). Data in agreement with literature values.[52]

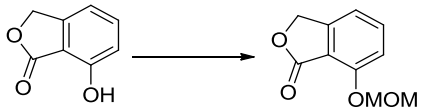
**7-Hydroxy*iso*benzofuran-1(3*H*)-one 34**[53]




A mixture of ethyl 2-acetoxy-6-methylbenzoate **39** (4.16 g, 18.7 mmol), NBS (3.67 g, 20.6 mmol) and benzoyl peroxide (449 mg, 1.87 mmol) in carbon tetrachloride (16 mL) was heated to reflux for 4 h, then cooled to room temperature and evaporated to give ethyl 2-acetoxy-6-(bromomethyl)benzoate **40** as a pale yellow oil. The residue was suspended

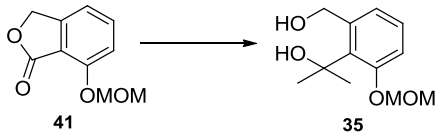
without further purification in water/dioxane (1:1; 34 mL) and then heated under reflux for 18 h. The solvent was evaporated and the resulting solid recrystallised from light petroleum to give the *title compound* **34** as an off-white solid (2.28 g, 81%); mp 138-141 ºC (lit.,[53] mp 135-136 ºC); (Found: M+$Na^+$, 173.0210, $C_8H_6O_3$+$Na^+$ requires 173.0209); $\delta_H$ (400 MHz; $CDCl_3$) 7.74 (1 H, s, OH), 7.56 (1 H, t, *J* 8.0, H-5), 6.98-6.93 (2 H, m, H-4,6), 5.32 (2 H, s, $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 172.6 (C), 156.6 (C), 146.7 (C), 137.0 (CH), 115.3 (CH), 113.4 (CH), 110.9 (C), 70.6 ($CH_2$); *m/z* (ESI) 173 (M+$Na^+$, 100%). Data in agreement with literature values.[53]

**7-(Methoxymethoxy)*iso*benzofuran-1(3*H*)-one 41**




To a solution of 7-hydroxy*iso*benzofuran-1(3*H*)-one **34** (417 mg, 2.77 mmol) in dichloromethane (3.47 mL) were added di*iso*propylamine (0.96 mL, 5.56 mmol) and methoxymethyl chloride (0.42 mL, 5.56 mmol) dropwise at 0 ºC under argon. After stirring for 6.5 h at room temperature, saturated aqueous ammonium chloride solution (2 mL) was added and the mixture extracted into ether (3 × 3 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate/light petroleum (9:1 to 7:3) to give the *title compound* **41** as a colourless solid (437 mg, 81%); mp 76-78 ºC; (Found: C, 61.64; H, 5.18. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.19); (Found: M+$Na^+$, 217.0477. $C_{10}H_{10}O_4$+$Na^+$ requires 217.0471); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1765, 1615, 1604, 1485, 1316, 1027, 935; $\delta_H$ (400 MHz; $CDCl_3$) 7.58 (1 H, t, *J* 8.0, H-5), 7.19 (1 H, d, *J* 8.0, ArH), 7.06 (1 H, d, *J* 8.0, ArH), 5.38 (2 H, s, $CH_2$-MOM), 5.24 (2 H, s, $OCH_2$), 3.53 (3 H, s, Me-MOM); $\delta_C$ (100 MHz; $CDCl_3$) 168.8 (C), 156.3 (C), 149.1 (C), 136.0 (CH), 114.9 (CH), 114.6 (CH), 114.2 (C), 94.7 ($CH_2$), 68.7 ($CH_2$), 56.7 (Me); *m/z* (ESI) 411 (2M+$Na^+$, 100%), 217 (M+$Na^+$,69%).

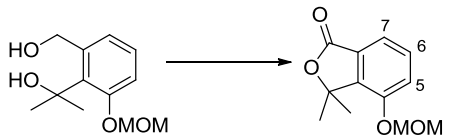
**2-(2-(Hydroxymethyl)-6-(methoxymethoxy)phenyl)propan-2-ol 35**




41 35

To a solution of 7-(methoxymethoxy)*iso*benzofuran-1(3*H*)-one **41** (250 mg, 1.28 mmol) in dry THF (4 mL) at 0 ºC was added dropwise methylmagnesium bromide (3 M in ether; 0.93 mL, 2.82 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride solution (2 mL) and extracted with dichloromethane (3 x 3 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography eluting with light petroleum/ethyl acetate (7:3) to give the *title compound* **35** as a colourless oil (213 mg, 74%) (prone to decomposition); (Found: $M+Na^+$, 249.1099. $C_{12}H_{18}O_4+Na^+$ requires 249.1097); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3690, 3606, 3011, 2927, 1602, 1239; $\delta_H$ (400 MHz; $CDCl_3$) 7.14-7.13 (2 H, m, ArH), 6.90-6.88 (1 H, m, ArH), 5.19 (2 H, s, $CH_2$-MOM), 4.86 (2 H, s, $C\underline{H}_2OH$), 3.49 (3 H, s, Me-MOM), 1.75 (6 H, s, Me); $\delta_C$ (75 MHz; $CDCl_3$) 154.8 (C), 138.8 (C), 135.6 (C), 127.5 (CH), 126.0 (CH), 115.2 (CH), 94.6 ($CH_2$), 75.7 (C), 67.6 ($CH_2$), 56.2 (Me), 31.1 (Me); *m/z* (ESI) 249 ($M+Na^+$, 51%).

**4-(Methoxymethoxy)-3,3-dimethyl*iso*benzofuran-1(3*H*)-one 36**

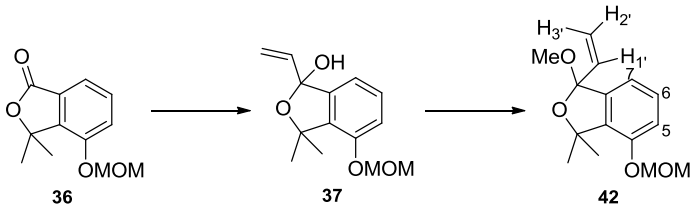



35 36

*Preparation of Jones' reagent (1.98 M):* Chromium trioxide (992 mg) in water (2.5 mL) was placed in a 5 mL volumetric flask. Sulfuric acid (95-98%; 1.3 mL) was added with cooling. The mixture was then diluted with water to a total volume of 5 mL.

To a solution of 2-(2-(hydroxymethyl)-6-(methoxymethoxy)phenyl)propan-2-ol **35** (202 mg, 0.89 mmol) in acetone (6.0 mL) at 0 ºC was added dropwise a freshly prepared solution of Jones' reagent (1.98 M; 1.12 mL, 2.22 mmol). The reaction mixture was stirred at 0 ºC for 1.5 h and then quenched by the addition of 2-propanol (2 mL), followed by solid sodium hydrogen carbonate. The mixture was extracted with ethyl acetate (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue purified by column chromatography, eluting with light petroleum/ethyl acetate (7:3) to give the *title compound* **36** as a colourless solid (156 mg, 78%); mp 75-76 ºC; (Found: C, 64.78; H, 6.36. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35); (Found: M+$Na^+$, 245.0784. $C_{12}H_{14}O_4$+$Na^+$ requires 245.0784); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1754, 1606, 1488, 1260, 1156; $\delta_H$ (400 MHz; $CDCl_3$) 7.49 (1 H, d, *J* 7.8, H-7), 7.42 (1 H, t, *J* 7.8, H-6), 7.32 (1 H, d, *J* 7.8, H-5), 5.30 (2 H, s, $CH_2$-MOM), 3.49 (3 H, s, Me-MOM), 1.72 (6 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 169.6 (C), 151.2 (C), 142.5 (C), 130.7 (CH), 127.7 (C), 118.4 (CH), 118.4 (CH), 93.9 ($CH_2$), 85.4 (C), 56.3 (Me), 25.5 (Me); *m/z* (ESI) 245 (M+$Na^+$,100%).

**1,3-Dihydro-1-methoxy-4-(methoxymethoxy)-3,3-dimethyl-1-vinyl*iso*benzofuran 42**

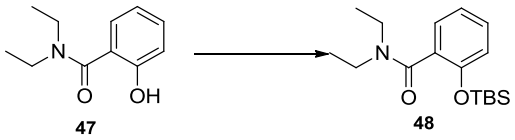


36 37 42

To a solution of 4-(methoxymethoxy)-3,3-dimethyl*iso*benzofuran-1(3*H*)-one **36** (85.7 mg, 0.386 mmol) in THF (1.2 mL) at 0 ºC under argon was added vinylmagnesium bromide (1 M in THF; 0.58 mL, 0.579 mmol) dropwise. After stirring at room temperature for 5 h, saturated aqueous ammonium chloride solution (2 mL) was added and the mixture was extracted with ethyl acetate (3 × 3 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo* to give 1,3-dihydro-4-(methoxymethoxy)-3,3-dimethyl-1-

vinyl*iso*benzofuran-1-ol **37** as a colourless oil (89.5 mg, 93%), that was used in the next step without further purification. To a solution of lactol **37** (89.5 mg, 0.357 mmol) in iodomethane (1.8 mL, 28.6 mmol) was added silver(I) oxide (124 mg, 0.534 mmol). The reaction mixture was stirred at room temperature for 24 h, filtered through Celite® and washed with dichloromethane (15 mL). The filtrate and the washings were combined and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel, previously inactivated with triethylamine, eluting with light petroleum/ethyl acetate (9:1) to give the *title compound* **42** as a colourless oil (87 mg, 84%) that solidified in the freezer; mp 50-52 $^{o}$C; (Found: M+Na$^{+}$, 287.1247. $C_{15}H_{20}O_4$+Na$^{+}$ requires 287.1254); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 2434, 2414, 1521, 1476, 1239, 660; $\delta_H$ (400 MHz; acetone-$d_6$) 7.29 (1 H, t, *J* 7.8, H-6), 7.08 (1 H, d, *J* 7.8, H-5 or H-7), 6.86 (1 H, d, *J* 7.8, H-5 or H-7), 6.12 (1 H, dd, *J* 17.2, 10.4, H-1'), 5.41 (1 H, dd, *J* 17.2, 2.0, H-3'), 5.30 (2 H, s, $CH_2$-MOM), 5.17 (1 H, dd, *J* 10.4, 2.0, H-2'), 3.44 (3 H, s, Me-MOM), 3.08 (3 H, s, OMe), 1.65 (3 H, s, Me), 1.57 (3 H, s, Me); $\delta_C$ (100 MHz; acetone-$d_6$) 153.2 (C), 142.8 (C), 141.2 (CH), 136.6 (C), 131.3 (CH), 117.7 (CH), 116.6 ($CH_2$), 115.6 (CH), 110.9 (C), 95.6 ($CH_2$), 86.7 (C), 57.3 (Me), 51.0 (Me), 28.8 (Me), 28.6 (Me); *m/z* (ESI) 287 (M+Na$^{+}$, 100%).

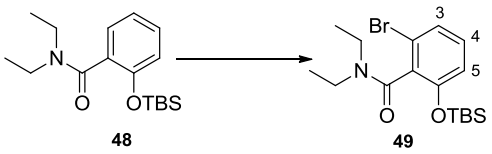
**2-(*tert*-Butyldimethylsiloxy)-*N*,*N*-diethylbenzamide 48**[59]




To a solution of *N*,*N*-diethyl-2-hydroxybenzamide (2.00 g, 10.3 mmol) in anhydrous DMF (50 mL) was added *N*,*N*-di*iso*propylethylamine (6.49 mL, 37.26 mmol) and *tert*-butyldimethylsilyl chloride (3.90 g, 25.9 mmol) under a nitrogen atmosphere at room temperature. After 16 h, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by

column chromatography eluting with light petroleum to light petroleum/ethyl acetate (9:1) to give the *title compound* **48** as a yellow oil (3.16 g, quantitative); (Found: M+H$^+$, 308.2026. $C_{17}H_{30}NO_2Si+H^+$ requires 308.2040); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$1620, 1482, 1292, 1040, 1007; $\delta_H$ (400 MHz; $CDCl_3$) 7.24-7.18 (2 H, m, ArH), 6.96 (1 H, td, *J* 7.5, 1.1, ArH), 6.81 (1 H, d, *J* 7.5, ArH), 3.66-3.41 (2 H, m, NC<u>H</u>$_2$Me), 3.28-3.09 (2 H, m, NC<u>H</u>$_2$Me), 1.24 (3 H, t, *J* 7.0, NCH$_2$<u>Me</u>), 1.01 (3 H, t, *J* 7.0, NCH$_2$<u>Me</u>), 0.96 (9 H, s, *t*-Bu-TBS), 0.22 (6 H, s, Me-TBS); $\delta_C$ (100 MHz; $CDCl_3$) 169.0 (C), 151.1 (C), 129.8 (C), 129.5 (CH), 127.8 (CH), 121.3 (CH), 119.2 (CH), 42.8 ($CH_2$), 39.1 ($CH_2$), 25.6 (Me), 18.1 (C), 14.9 (Me), 13.2 (Me), -4.13 (Me), -4.51 (Me); *m/z* (ESI) 308 (M+H$^+$, 100%). Data in agreement with literature values.[59]

**2-Bromo-6-(6-*tert*-butyldimethylsiloxy)-*N*,*N*-diethylbenzamide 49[59]**

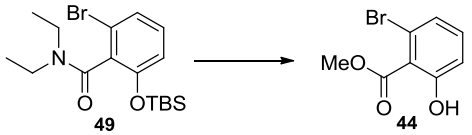



**48** **49**

A solution of 2-(*tert*-butyldimethylsiloxy)-*N*,*N*-diethylbenzamide **48** (500 mg, 1.63 mmol) in anhydrous THF (18 mL), under a nitrogen atmosphere, was cooled to −78 ºC and *tert*-butyllithium (1.6 M in pentane; 1.5 mL, 2.44 mmol) was added dropwise over 30 min. The solution was stirred at −78 ºC for an additional 30 min and bromine (0.13 mL, 2.44 mmol) was slowly added over 30 min. The bath was removed and the solution allowed to warm to room temperature. After 20 h, saturated aqueous sodium thiosulfate solution (20 mL) and ethyl acetate (20 mL) were added. The organic layer was separated, washed with brine, dried ($MgSO_4$), concentrated and purified by flash chromatography, eluting with light petroleum to light petroleum/ethyl acetate (15%), to give the *title compound* **49** as a colourless solid (430 mg, 68%); mp 72-73 ºC; (Found: M+Na$^+$, 408.0977. $C_{17}H_{28}{}^{79}BrNO_2Si+Na^+$ requires 408.0965); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 1627, 1602, 1445, 1239, 937; $\delta_H$ (300 MHz; $CDCl_3$) 7.14 (1 H, dd, *J* 10.8, 1.2, H-3), 7.05 (1 H, t, *J* 10.8, H-4), 6.76 (1 H, dd, *J* 10.8, 1.2, H-5), 3.80-3.74 (1

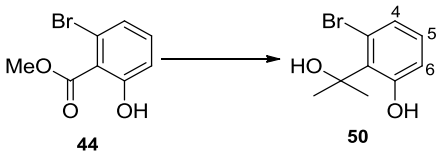
H, m, C<u>H</u>$_2$Me), 3.38-3.26 (1 H, m, C<u>H</u>$_2$Me), 3.20-3.07 (2 H, m, CH$_2$), 1.26 (3 H, t, *J* 9.6, NCH$_2$<u>Me</u>), 1.09 (3 H, t, *J* 9.6, NCH$_2$<u>Me</u>), 0.95 (9 H, s, *t*-Bu-TBS), 0.24 (3 H, s, Me-TBS), 0.21 (3 H, s, Me-TBS); $\delta_C$ (75 MHz; $CDCl_3$) 166.2 (C), 152.7 (C), 131.2 (C), 129.8 (CH), 125.2 (CH), 120.4 (C), 117.9 (CH), 42.9 (CH$_2$), 39.1 (CH$_2$), 25.5 (Me), 18.1 (C), 13.8 (Me), 12.7 (Me), -4.06 (Me), -4.70 (Me); *m/z* (ESI) 410/408 (M+Na$^+$, 100/95%). Data in agreement with literature values.[59]

**Methyl 2-bromo-6-hydroxybenzoate 44**[59]



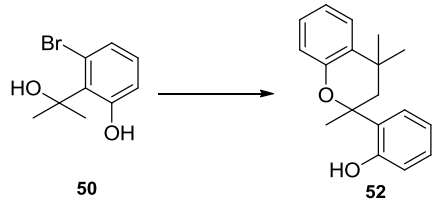

2-Bromo-6-(6-*tert*-butyldimethylsiloxy]-*N*,*N*-diethylbenzamide **49** (300 mg, 0.776 mmol) was dissolved in anhydrous acetonitrile (5.2 mL) and dibasic sodium phosphate (165 mg, 1.16 mmol) and trimethyloxonium tetrafluoroborate (344 mg, 2.32 mmol) were sequentially added. The resulting mixture was stirred for 17 h at room temperature, upon which a saturated aqueous sodium hydrogen carbonate solution (5.16 mL) was added followed by solid sodium hydrogen carbonate. After stirring for 23 h at room temperature the resulting mixture was extracted with ethyl acetate (3 × 20 mL), dried ($MgSO_4$), concentrated and purified by flash chromatography, eluting with light petroleum/ethyl acetate (0-10%) to give the *title compound* **44** as a colourless solid (123 mg, 69%); mp 55-57 ºC; (Found: M+Na$^+$, 252.9469. $C_8H_7{}^{79}BrO_3$+Na$^+$ requires 252.9471); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3044, 2956, 1669, 1601, 1571, 1441, 1345, 1345, 1182, 880; $\delta_H$ (400 MHz; $CDCl_3$) 10.9 (1 H, s, OH), 7.22-7.18 (2 H, m, ArH), 6.98-6.93 (1 H, m, ArH), 3.99 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 169.8 (C), 162.9 (C), 134.5 (CH), 126.4 (CH), 122.4 (C), 117.2 (CH), 113.8 (C), 52.4 (Me); *m/z* (ESI) 255/253 (M+Na$^+$, 99/100%). Data in agreement with literature values.[59]

**3-Bromo-2-(2-hydroxyprop-2-yl)phenol 50**




To a solution of methyl 2-bromo-6-hydroxybenzoate **44** (109 mg, 0.470 mmol) in dry THF (2 mL) was added methylmagnesium bromide (3.0 M in ether; 0.78 mL, 2.35 mmol), at 0 ºC, under nitrogen atmosphere. The reaction mixture was stirred at 0 ºC for 1.5 h and then warmed to room temperature over 3 h. After re-cooling to 0 ºC a solution of hydrochloric acid (10%; 1.37 mL) was added and the reaction mixture was stirred for 30 min. Water (5 mL) was then added and the mixture extracted into ethyl acetate (3 × 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified *via* silica-gel column chromatography, eluting with light petroleum/ethyl acetate (5 to 20%) to give the *title compound* **50** as a colourless solid (67.9 mg, 63%); mp 72-73 ºC; (Found: M+Na$^+$, 252.9827. $C_9H_{11}{}^{79}BrO_2$ requires 252.9835); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3227, 1603, 1438, 1283, 869; $\delta_H$ (400 MHz; $CDCl_3$) 10.7 (1 H, s, OH), 7.10 (1 H, dd, *J* 7.7, 1.2, H-4), 6.93 (1 H, t, *J* 7.7, H-5), 6.81 (1 H, dd, *J* 7.7, 1.2, H-6), 1.95 (6 H, s, Me); $\delta_C$ (75 MHz; $CDCl_3$) 157.9 (C), 128.9 (CH), 128.2 (C), 126.6 (CH), 120.1 (C), 118.0 (CH), 80.2 (C), 30.6 (Me); *m/z* (ESI) 255/253 (M+Na$^+$, 99/100%).

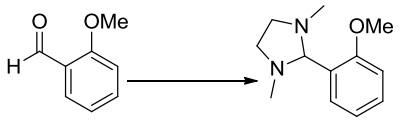
**2-(2,4,4-Trimethylchroman-2-yl)phenol 52**




A solution of 3-bromo-2-(2-hydroxyprop-2-yl)phenol **50** (20.0 mg, 0.086 mmol) in anhydrous THF (0.57 mL), under a nitrogen atmosphere, was cooled to −78 ºC and *tert*-

butyllithium (1.6 M in pentane; 0.19 mL, 0.31 mmol) was added dropwise over 30 min. The solution was stirred at −78 ºC for an additional 30 min and a solution of dimethyloxalate (36.6 mg, 0.31 mmol) in THF (0.57 mL) was slowly added. The reaction mixture was stirred at -78 ºC for 30 min and then warmed to room temperature over 4 h. After re-cooling to 0 ºC a solution of hydrochloric acid (10%; 0.5 mL) was added and the reaction mixture was stirred for 30 min. Water (2 mL) was then added and the mixture extracted into diethyl ether (3 × 3 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give the *title compound* **52** as a colourless oil (5.7 mg, 25%); (Found: M+$Na^+$, 291.1343. $C_{18}H_{20}O_2$ requires 291.1361); $\delta_H$ (400 MHz; $CDCl_3$) 8.13 (1 H, s, OH), 7.29 (1 H, dd, *J* 7.7, 1.3, ArH), 7.18-7.12 (3 H, m, ArH), 6.99 (1 H, td, *J* 7.7, 1.3, ArH), 6.94 (1 H, dd, *J* 8.1, 0.9, ArH), 6.84 (2 H, d, *J* 7.7, ArH), 2.61 (1 H, d, *J* 14.4, H-3), 2.10 (1 H, d, *J* 14.4, H-3), 1.72 (3 H, s, Me), 1.45 (3 H, s, Me), 1.18 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 154.4 (C), 150.2 (C), 131.9 (C), 129.6 (C), 128.9 (CH), 127.3 (CH), 126.9 (CH), 126.5 (CH), 122.2 (CH), 119.7 (CH), 117.8 (CH), 81.6 (C), 47.5 ($CH_2$), 32.9 (Me), 32.2 (Me), 31.0 (C), 27.9 (Me); *m/z* (ESI) 291 (M+$Na^+$, 100%).

**2-(2-Methoxyphenyl)-1,3-dimethylimidazolidine 57**[67]

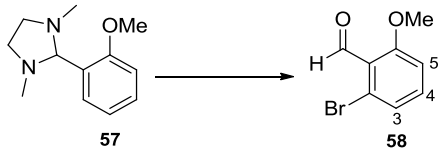



**56** **57**

To a solution of 2-methoxybenzaldehyde **56** (15.0 g, 0.110 mol) in ethanol (225 mL) was added *N,N'*-dimethylethylenediamine (85%; 15.17 mL, 0.121 mol) and the reaction mixture was stirred at room temperature for 24 h. Magnesium sulfate (ca. 20 g) was added, and the resulting mixture was stirred for a further 15 min. The reaction mixture was filtered and the filter cake was washed with ether (100 mL). The ether/ethanol solution was concentrated *in*

*vacuo* to yield the crude compound, which was recrystallised from *n*-hexane to give the *title compound* **57** as a colourless solid (17.1 g, 75%); mp 44-46 ºC (lit.,[67] mp 41-42 ºC); (Found: $M+H^+$, 207.1488. $C_{12}H_{19}N_2O+H^+$ requires 207.1492); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3076, 3010, 1601, 1491, 1281, 973, 660; $\delta_H$ (400 MHz; $CDCl_3$) 7.67 (1 H, dd, *J* 7.6, 2.0, ArH), 7.28-7.23 (1 H, m, ArH), 6.99 (1 H, t, *J* 7.6, ArH), 6.88 (1 H, d, *J* 7.6, ArH), 4.06 (1 H, s, CH), 3.81 (3 H, s, OMe), 3.35-3.31 (2 H, m, $CH_2$), 2.63-2.59 (2 H, m, $CH_2$), 2.19 (6 H, s, Me); $\delta_C$ (125 MHz; $CDCl_3$) 158.9 (C), 129.2 (CH), 128.9 (CH), 127.6 (C), 121.1 (CH), 110.37 (CH), 82.8 (CH), 55.5 (Me), 53.5 ($CH_2$), 39.7 (Me); *m/z* (ESI) 207 ($M+H^+$, 100%). Data in agreement with literature values.[67]

**2-Bromo-6-methoxybenzaldehyde 58[67]**

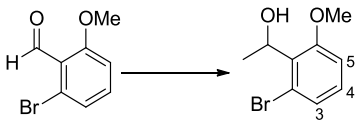



**57** **58**

To a solution of 2-(2-methoxyphenyl)-1,3-dimethylimidazolidine **57** (500 mg, 2.42 mmol) in dry ether (10 mL) at –40 ºC, was added *tert*-butyllithium (1.6 M in pentane; 3.53 mL, 5.66 mmol), dropwise over 1 h. Upon completion of the addition, the resulting orange reaction contents were warmed slowly to –20 ºC, stirred for an additional 7 h and then transferred by cannula into a flask containing 1,2-dibromotetrachloroethane (1.84 g, 5.66 mmol) in dry ether (10 mL) at 0 ºC. The reaction contents were stirred for 14 h, during which time they were warmed to room temperature. Upon completion, the solution was recooled to 0 ºC and aqueous hydrochloric acid (1 M; 17 mL) was added slowly. The resulting solution was stirred for 1 h at 0 ºC, quickly warmed to room temperature, and then water (17 mL) was added. The reaction contents were then extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting yellow solid was purified by column

chromatography, eluting with light petroleum/ethyl acetate (9:1) to yield the *title compound* **58** as a colourless solid (278 mg, 53%); mp 50-51 ºC (lit.,[67] mp 57-58 ºC); (Found: M+$Na^+$, 236.9516. $C_8H_7{}^{79}BrO_2$+$Na^+$ requires 236.9522); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2943, 1698, 1586, 1462, 1352, 1034; $\delta_H$ (400 MHz; $CDCl_3$) 10.4 (1 H, s, CHO), 7.32 (1 H, d, *J* 8.0, H-4), 7.24 (1 H, dd, *J* 8.0, 0.8, H-3), 6.95 (1 H, d, *J* 8.0, H-5), 3.92 (3 H, s, OMe); $\delta_C$ (75 MHz; $CDCl_3$) 190.4 (CH), 161.9 (C), 134.8 (CH), 126.5 (CH), 124.9 (C), 123.5 (C), 111.0 (CH), 56.2 (Me); *m/z* (ESI) 239/237 (M+$Na^+$, 97/100%). Data in agreement with literature values.[67]

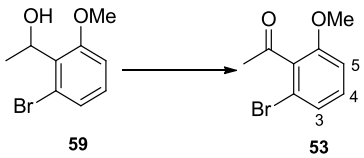
**(*R*/*S*)-1-(2-Bromo-6-methoxyphenyl)ethanol 59**




**58** **59**

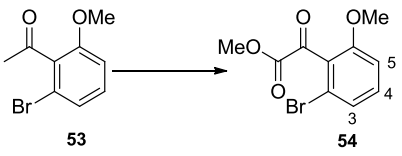
To a solution of 2-bromo-6-methoxybenzaldehyde **58** (1.00 g, 4.65 mmol) in dry THF (20 mL) was added methylmagnesium bromide (4.6 M in ether; 1.2 mL, 5.58 mmol) dropwise, at 0 ºC under an argon atmosphere. The resulting mixture was stirred for 1 h, during which time it was warmed to room temperature, and then quenched by addition of saturated aqueous ammonium chloride solution (10 mL) and extracted into ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* **59** as a yellow oil (1.07 g, quantitative yield); (Found: M+$Na^+$, 252.9840. $C_9H_{11}{}^{79}BrO_2$+$Na^+$ requires 252.9835); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3561, 1590, 1571, 1462, 1274, 1079; $\delta_H$ (400 MHz; $CDCl_3$) 7.17 (1 H, d, *J* 8.3, H-3), 7.06 (1 H, t, *J* 8.3, H-4), 6.87 (1 H, d, *J* 8.3, H-5), 5.31 (1 H, s br, C<u>H</u>OH(Me), 3.91 (3 H, s, OMe), 1.53 (3 H, d, *J* 6.8, Me); $\delta_C$ (75 MHz; $CDCl_3$) 158.2 (C), 132.0 (C), 128.7 (CH), 125.8 (CH), 122.8 (C), 110.6 (CH), 70.9 (CH), 55.8 (Me), 22.7 (Me); *m/z* (ESI) 255/253 (M+$Na^+$, 37/37%).

**1-(2-Bromo-6-methoxyphenyl)ethanone 53**




To a solution of 1-(2-bromo-6-methoxyphenyl)ethanol **59** (0.869 g, 3.76 mmol) in dry dichloromethane (18 mL) was added Dess-Martin periodinane (2.39 g, 5.64 mmol), at 0 ºC under argon. The reaction mixture was allowed to warm to room temperature over 1.5 h and then a mixture of saturated aqueous sodium thiosulfate solution and saturated aqueous sodium hydrogen carbonate solution (1:1; 50 mL) was added and the reaction contents were stirred for 1 h. The organic phase was separated and washed again with a mixture of saturated aqueous sodium thiosulfate solution and saturated aqueous sodium hydrogen carbonate solution (1:1; 30 mL), dried with magnesium sulfate and evaporated *in vacuo*. Purification by flash chromatography using light petroleum/ethyl acetate (9:1) gave the *title compound* **53** as a colourless solid (0.775 g, 90%); mp 32-33 ºC (lit.,[142] mp 35 ºC); (Found: M+$Na^+$, 250.9681. $C_9H_9{}^{79}BrO_2$+$Na^+$ requires 250.9678); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1710, 1589, 1462, 1260, 1052, 831; $\delta_H$ (400 MHz; $CDCl_3$) 7.19 (1 H, t, *J* 7.9, H-4), 7.15 (1 H, dd, *J* 7.9, 1.4, H-3), 6.86 (1 H, dd, *J* 7.9, 1.4, H-5), 3.82 (3 H, s, OMe), 2.51 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 202.2 (C), 156.5 (C), 132.8 (CH), 130.7 (CH), 124.8 (CH), 117.8 (C), 109.9 (CH), 55.9 (Me), 31.4 (Me); *m/z* (ESI) 253/251 (M+$Na^+$, 99/100%).

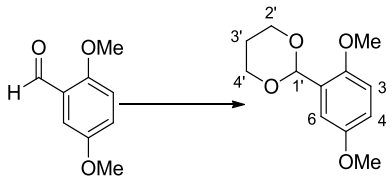
**Methyl 2-(2-bromo-6-methoxyphenyl)-2-oxoacetate 54**




A mixture of 1-(2-bromo-6-methoxyphenyl)ethanone **53** (2.44 g, 10.7 mmol), selenium dioxide (1.78 g, 16.0 mmol) in dry pyridine (3.97 mL) was heated to 100 ºC for 23 h under

an argon atmosphere. After this time, the reaction mixture was cooled in an ice-bath and molecular sieves 4 Å (0.628 g) and dry methanol (7.79 mL, 0.19 mol) were added, and the mixture was stirred for an additional 10 min. Thionyl chloride (3.87 mL, 53.5 mmol) was then added dropwise, over 10 min, and the ice-bath was removed. The resulting brown solution was stirred for 16 h at room temperature before a mixture of perchloric acid, acetonitrile and distilled water (6.8 mL: 135.9 mL: 13.59 mL) was poured into the flask and stirred for 30 min. Excess acid was neutralised with saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and purified by column chromatography, eluting with light petroleum/ethyl acetate (8:2) to give the *title compound* **54** as an off-white solid (2.36 g, 81%); mp 64-65 ºC; (Found: C, 43.96; H, 3.27. $C_{10}H_9BrO_4$ requires C, 43.98; H, 3.32), (Found: M+$Na^+$, 294.9572. $C_{10}H_9{}^{79}BrO_4$+$Na^+$ requires 294.9576); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1740, 1589, 1572, 1462, 1432, 1311; $\delta_H$ (400 MHz; $CDCl_3$) 7.30 (1 H, t, *J* 8.2, H-4), 7.23 (1 H, dd, *J* 8.2, 0.9, H-3), 6.92 (1 H, dd, *J* 8.2, 0.9, H-5), 3.91 (3 H, s, Me), 3.82 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 185.6 (C), 161.3 (C), 159.3 (C), 133.0 (CH), 126.7 (C), 125.6 (CH), 120.8 (C), 110.3 (CH), 56.3 (Me), 53.2 (Me); *m/z* (ESI) 297/295 (M+$Na^+$, 64/67%).

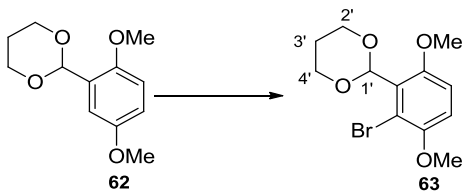
**2-(2,5-Dimethoxyphenyl)-1,3-dioxane 62[143]**




To a solution of 2,5-dimethoxybenzaldehyde **66** (5.00 g, 30.1 mmol) and trimethyl orthoformate (7.24 mL, 66.2 mmol) in 1,3-propanediol (13.1 mL) was added tetrabutylammonium tribromide (290 mg, 0.601 mmol). The resulting mixture was stirred at room temperature for 26 h and then poured into saturated aqueous sodium hydrogen

carbonate solution (30 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Column chromatography, eluting with light petroleum/dichloromethane/ether (8:1:1) gave the *title compound* **62** as a colourless oil (5.32 g, 79%); (Found: M+$Na^+$, 247.0945. $C_{12}H_{16}O_4$+$Na^+$ requires 247.0941); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 2959, 2936, 1503, 1466, 1379, 1095, 995; $\delta_H$ (400 MHz; $CDCl_3$) 7.20 (1 H, d, *J* 3.2, H-6), 6.86-6.80 (2 H, m, H-3,4), 5.85 (1 H, s, H-1'), 4.28-4.23 (2 H, m, H-2' and H-4'), 4.04-3.98 (2 H, m, H-2' and H-4'), 3.80 (3 H, s, OMe), 3.79 (3 H, s, OMe), 2.31-2.17 (1 H, m, H-3'), 1.46-1.41 (1 H, m, H-3'); $\delta_C$ (100 MHz; $CDCl_3$) 153.8 (C), 150.6 (C), 127.7 (C), 116.0 (CH), 112.3 (CH), 111.8 (CH), 96.8 (CH), 67.6 ($CH_2$), 56.4 (Me), 55.8 (Me), 25.9 ($CH_2$); *m/z* (ESI) 472 (2M+$Na^+$, 100%), 247 (M+$Na^+$, 50%). Data in agreement with literature values.[143]

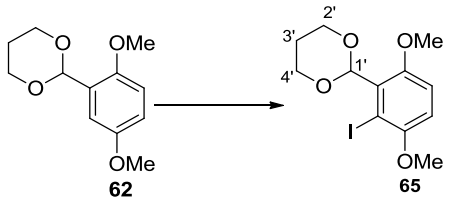
**2-(2-Bromo -3,6-dimethoxyphenyl)-1,3-dioxane 63[70]**




2-(2,5-Dimethoxy phenyl)-1,3-dioxane **62** (100 mg, 0.445 mmol) was dissolved in 3 mL hexane and the reaction was cooled to -25°C. To the cooled solution was added 1 mL freshly distilled benzene followed by dropwise addition of *n*-BuLi (1.6 M in hexane; 0.42 mL, 0.667 mmol). After 10 h, dibrotetrafluoroethane (0.10 mL, 0.830 mmol) in 1 mL THF was added and the reaction was warmed up to rt and stirred for 0.5 h. After removal of most of the solvent by evaporation, the residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (8:2) to give the *title compound* **63** as a yellow solid (36.4 mg, 27%); mp 102-103 °C (lit.,[144] mp 105-106 ºC); (Found: M+$Na^+$, 325.0055. $C_{12}H_{15}{}^{79}BrO_4$+$Na^+$ requires 325.0051); $\delta_H$ (400 MHz; $CDCl_3$) 6.82 (2 H, s, ArH), 6.18 (1 H, s, H-1'), 4.27-4.23 (2 H, m, H-2' and H-4'), 3.97-3.91 (2 H, m, H-2' and H-4'), 3.79 (3 H, s,

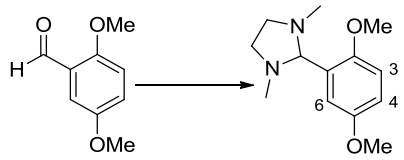
OMe), 3.78 (3 H, s, OMe), 2.40-2.20 (1 H, m, H-3'), 1.38-1.35 (1 H, m, H-3'); $\delta_C$ (100 MHz; $CDCl_3$) 152.9 (C), 151.1 (C), 127.3 (C), 114.2 (CH), 113.5 (CH), 112.4 (CH), 99.8 (C), 67.9 ($CH_2$), 57.3 (Me), 57.3 (Me), 25.9 ($CH_2$); *m/z* (ESI) 327/325 ($M+Na^+$, 97/100%). Data in agreement with literature values.[70]

**2-(2-Iodo-3,6-dimethoxyphenyl)-1,3-dioxane 65**




To a solution of 2-(2,5-dimethoxyphenyl)-1,3-dioxane **62** (154 mg, 0.687 mmol) in dry ether (6.1 mL) at –40 ºC, was added *tert*-butyllithium (1.6 M in pentane; 1.29 mL, 2.06 mmol) dropwise, over 30 min. Upon completion, the resulting mixture was stirred at –40 ºC for an additional 30 min and then a solution of iodine (261 mg, 1.03 mmol) in dry ether (3.6 mL) was added dropwise, over 30 min. The mixture was allowed to warm slowly to room temperature over 18 h, upon which time a saturated aqueous thiosulfate solution (10 mL) was added and the mixture extracted into ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (8:2) to give the *title compound* **65** as a colourless solid (84.6 mg, 35%); mp 138-140 ºC; (Found: $M+Na^+$, 372.9900. $C_{12}H_{15}IO_4+Na^+$ requires 372.9907); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 1574, 1474, 1431, 1280, 1103, 999; $\delta_H$ (400 MHz; $CDCl_3$) 6.89 (1 H, d, *J* 9.2, ArH), 6.79 (1 H, d, *J* 9.2, ArH), 6.18 (1 H, s, H-1'), 4.33-4.29 (2 H, m, H-2' and H-4'), 4.04-3.97 (2 H, m, H-2' and H-4'), 3.82 (6 H, s, OMe), 2.49-2.37 (1 H, m, H-3'), 1.42-1.36 (1 H, m, H-3'); $\delta_C$ (100 MHz; $CDCl_3$) 153.1 (C), 152.4 (C), 129.7 (C), 113.5 (CH), 112.1 (CH), 101.6 (CH), 90.6 (C), 67.7 ($CH_2$), 57.4 (Me), 57.3 (Me), 25.6 ($CH_2$); *m/z* (ESI) 373 ($M+Na^+$, 98%).

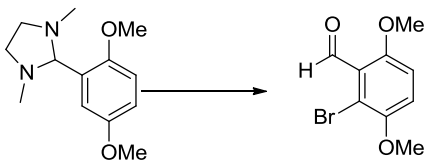
**2-(2,5-Dimethoxyphenyl)-1,3-dimethylimidazolidine 67**




**66** **67**

To a stirred solution of 2,5-dimethoxybenzaldehyde **66** (1.00 g, 6.02 mmol) in ethanol (25 mL) was added *N*,*N'*-dimethylethylenediamine (85%; 0.90 mL, 7.22 mmol). After being stirred for 24 h at room temperature magnesium sulfate (ca. 2 g) was added, and the resulting mixture was stirred for a further 15 min. The reaction mixture was then filtered and the filter cake was washed with ether (20 mL). The ether/ethanol solution was concentrated *in vacuo*, and the residue was recrystallised from *n*-hexane to give the *title compound* **67** as a colourless solid (1.37 g, 95%); mp 79-80 ºC; (Found: $M+H^+$, 237.1619. $C_{13}H_{20}N_2O_2+H^+$ requires 237.1598); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2947, 2787, 1498, 1466, 1274, 1239, 1046; $\delta_H$ (400 MHz; $CDCl_3$) 7.22 (1 H, d, *J* 3.2, H-6), 6.91 (1 H, d, *J* 9.1, H-3), 6.81 (1 H, dd, *J* 9.1 and 3.2, H-4), 3.95 (1 H, s, CH), 3.76 (3 H, s, OMe), 3.72 (3 H, s, OMe), 3.25-3.21 (2 H, m, $CH_2$), 2.54-2.50 (2 H, m, $CH_2$), 2.10 (6 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 154.2 (C), 153.3 (C), 128.8 (C), 114.8 (CH), 113.6 (CH), 112.0 (CH), 82.9 (CH), 56.3 (Me), 55.8 (Me), 53.5 ($CH_2$), 39.7 (Me); *m/z* (ESI) 237 ($M+H^+$, 100%).

**2-Bromo-3,6-dimethoxybenzaldehyde 64**

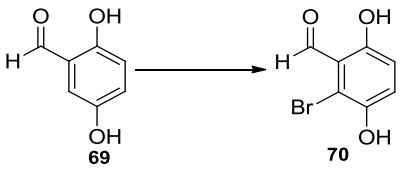



**67** **64**

To a solution of 2-(2,5-dimethoxyphenyl)-1,3-dimethylimidazolidine **67** (300 mg, 1.27 mmol) in dry ether (7 mL) at –40 ºC, was added *tert*-butyllithium (1.6 M in pentane; 1.86 mL, 2.97 mmol), dropwise over 1 h. Upon completion, the reaction contents were warmed

slowly to –20 ºC, stirred for an additional 7 h and then transferred by cannula into a flask containing 1,2-dibromotetrachloroethane (967 mg, 2.97 mmol) in dry ether (7 mL) at 0 ºC. The reaction contents were stirred for 12 h, during which time they were warmed to room temperature. Upon completion, the solution was recooled to 0 ºC, and an aqueous solution of hydrochloric acid (1 M; 9 mL) was added slowly. The resulting mixture was stirred for 1 h at 0 ºC, quickly warmed to room temperature and water (9 mL) was added. The reaction contents were then extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated. The resulting yellow solid was purified by column chromatography, eluting with light petroleum/ethyl acetate (8:2) to yield the *title compound* **64** as a light yellow solid (81 mg, 26%); mp 97-99 ºC (lit.,[144] mp 102-103 ºC); (Found: $M+Na^+$, 266.9624. $C_9H_9{}^{79}BrO_3+Na^+$ requires 266.9627); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2434, 2414, 1522, 1424, 1239, 929; $\delta_H$ (400 MHz; $CDCl_3$) 10.4 (1 H, s, CHO), 7.07 (1 H, d, *J* 9.0, ArH), 6.93 (1 H, d, *J* 9.0, ArH), 3.88 (3 H, s, OMe), 3.87 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 190.9 (CH), 155.4 (C), 150.4 (C), 124.8 (C), 117.1 (CH), 114.8 (C), 111.5 (CH), 57.1 (Me), 56.6 (Me); *m/z* (ESI) 269/267 ($M+Na^+$, 97/100%).

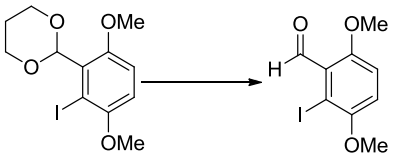
**2-Bromo-3,6-dihydroxybenzaldehyde 70[71]**




To a solution of 2,5-dihydroxybenzaldehyde **69** (500 mg, 3.62 mmol,) in chloroform (15 mL) was added a solution of bromine (0.19 mL, 3.77 mmol) in chloroform (3 mL) dropwise, over 30 min. After the addition was complete, the reaction mixture was stirred for 2.5 h, whereupon saturated aqueous sodium thiosulfate solution (10 mL) was added and stirring was continued for an additional 5 min. After extraction with dichloromethane (3 × 10 mL),

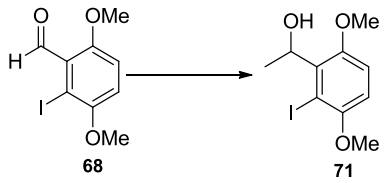
the combined organic layers were washed with brine (2 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give 2-bromo-3,6-dihydroxybenzaldehyde **70** as a yellow solid (748 mg, 95%); mp 131-133 ºC (lit.,[121] mp 130-131 ºC); (Found: M-$H^+$, 214.9351. $C_7H_5{}^{79}BrO_5$+$Na^+$ requires 214.9349); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3531, 3011, 1655, 1612, 1586, 1470, 1382, 1317, 1283, 1173, 861, 831; $\delta_H$ (400 MHz; $CDCl_3$) 11.6 (1 H, s, CHO), 10.3 (1 H, s, OH), 7.24 (1 H, d, *J* 9.0, ArH), 6.92 (1 H, d, *J* 9.0, ArH), 5.35 (1 H, s, OH); $\delta_C$ (100 MHz; $CDCl_3$) 196.9 (CH), 158.3 (C), 145.6 (C), 125.4 (CH), 118.7 (CH), 116.5 (C), 111.9 (C); *m/z* (ESI) 217/215 (M-$H^+$, 95/100%). Data in agreement with literature values.[121]

**2-Iodo-3,6-dimethoxybenzaldehyde 68**



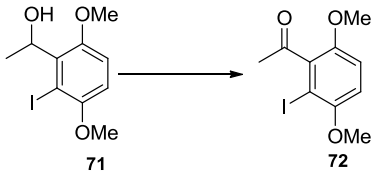

To a solution of 2-(2-iodo-3,6-dimethoxyphenyl)-1,3-dioxane **65** (1.18 g, 3.38 mmol) in THF (100 mL) was added aqueous hydrochloric acid (2 M; 95 mL, 0.19 mol). After stirring for 1 h at room temperature, the mixture was extracted with ether (2 × 100 mL) and the combined organic layers washed with brine (150 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* **68** as a yellow solid (987 mg, quantitative); mp 113-115 ºC (lit.,[145] mp 114-115 ºC); (Found: M+$Na^+$, 314.9482. $C_9H_9IO_3$+$Na^+$ requires 314.9489); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1695, 1566, 1467, 1432, 1394, 1286, 1030; $\delta_H$ (400 MHz; $CDCl_3$) 10.2 (1 H, s, CHO), 6.99 (1 H, d, *J* 9.0, ArH), 6.97 (1 H, d, *J* 9.0, ArH), 3.88 (3 H, s, OMe), 3.87 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 193.1 (CH), 155.6 (C), 152.7 (C), 126.7 (C), 115.9 (CH), 112.6 (CH), 90.3 (C), 57.4 (Me), 56.7 (Me); *m/z* (ESI) 315 (M+$Na^+$, 100%).

**(*R*/*S*)-1-(2-Iodo-3,6-dimethoxyphenyl)ethanol 71**




To a solution of 2-iodo-3,6-dimethoxybenzaldehyde **68** (1.00 g, 3.42 mmol) in THF (25 mL) at 0 ºC under argon was added methylmagnesium bromide (1 M in ether; 4.45 mL, 4.45 mmol) dropwise. The reaction mixture was allowed to warm to room temperature over 1 h, stirred for 1.5 h and then quenched with saturated aqueous ammonium chloride (14 mL). The mixture was extracted into ethyl acetate (3 × 20 mL) and the combined organic fractions were washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the *title compound* **71** as a yellow solid (1.04 g, 98%); mp 72-73 ºC; (Found: M+$Na^+$, 330.9802. $C_{10}H_{13}IO_3$+$Na^+$ requires 330.9802); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3548, 3010, 2971, 2838, 1618, 1466, 1452, 1260, 1053, 1031, 866; $\delta_H$ (400 MHz; $CDCl_3$) 6.87 (1 H, d, *J* 9.0, ArH), 6.68 (1 H, d, *J* 9.0, ArH), 5.26 (1 H, q, *J* 6.6, C<u>H</u>OH(Me)), 3.87 (3 H, s, OMe), 3.26 (3 H, s, OMe), 1.49 (3 H, d, *J* 6.6, Me); $\delta_C$ (100 MHz; $CDCl_3$) 152.6 (C), 151.3 (C), 136.4 (C), 111.7 (CH), 109.1 (CH), 92.3 (C), 77.0 (CH), 57.0 (Me), 56.0 (Me), 22.4 (Me); *m/z* (ESI) 639 (2M+$Na^+$, 100%), 331 (M+$Na^+$, 79%).

**1-(2-Iodo-3,6-dimethoxyphenyl)ethanone 72**




To a solution of 1-(2-iodo-3,6-dimethoxyphenyl)ethanol **71** (800 mg, 2.59 mmol) in dry dichloromethane (12 mL) was added Dess-Martin periodinane (2.19 g, 5.18 mmol) at 0 ºC under argon. The reaction mixture was allowed to warm to room temperature over 1.5 h,

stirred at this temperature for 2 h, and then a mixture of saturated aqueous sodium thiosulfate solution and saturated aqueous sodium hydrogen carbonate solution (1:1; 50 mL) was added and the reaction contents were stirred for1 h. The organic phase was separated and washed again with a mixture of saturated aqueous sodium thiosulfate solution and saturated aqueous sodium hydrogen carbonate solution (1:1; 30 mL), dried with magnesium sulfate and evaporated *in vacuo*. Purification by flash chromatography using light petroleum/ethyl acetate (8:2) gave the *title compound* **72** as a colourless solid (600 mg, 75%); mp 82-83 ºC; (Found: M+$Na^+$, 328.9645. $C_{10}H_{11}IO_3$+$Na^+$ requires 328.9645); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3009, 2963, 2941, 1838, 1706, 1570, 1471, 1431, 1407, 1267, 1252, 1033; $\delta_H$ (400 MHz; $CDCl_3$) 6.90 (1 H, d, *J* 8.8, ArH), 6.81 (1 H, d, *J* 8.8, ArH), 3.87 (3 H, s, OMe), 3.80 (3 H, s, OMe), 2.54 (3 H, s, Me); $\delta_C$ (75 MHz; $CDCl_3$) 203.7 (C), 152.5 (C), 150.0 (C), 138.4 (C), 111.8 (CH), 111.1 (CH), 83.2 (C), 57.1 (Me), 56.5 (Me), 30.7 (Me); *m/z* (ESI) 329 (M+$Na^+$, 100%).

**Methyl 2-(2-iodo-3,6-dimethoxyphenyl)-2-oxoacetate 73**

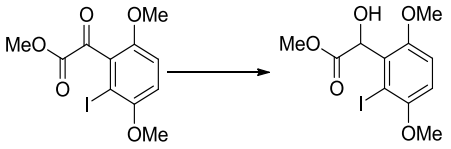



72 73

A mixture of 1-(2-iodo-3,6-dimethoxyphenyl)ethanone **72** (420 mg, 1.37 mmol) and selenium dioxide (228 mg, 2.06 mmol) in dry pyridine (0.7 mL) was heated at 100 ºC for 23h, under an argon atmosphere. The reaction mixture was allowed to reach room temperature, cooled in an ice-bath and then molecular sieves 4 Å (96.0 mg) and dry methanol (1.00 mL, 24.7 mmol) were added and stirred for an additional 10 min. Thionyl chloride (0.50 mL, 6.86 mmol) was added dropwise over 15 min and the ice-bath was removed. After stirring for 16 h at room temperature a mixture of perchloric acid, acetonitrile and distilled water (1.2 mL:24 mL:2.4 mL) was poured into the flask and stirred

for 1 h. Excess acid was neutralised with saturated aqueous sodium hydrogen carbonate and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the residue purified by column chromatography, eluting with light petroleum/ethyl acetate (6:4 to 1:1) to give the *title compound* **73** as a yellow solid (379 mg, 79%); mp 97-98 ºC; (Found: M+$Na^+$, 372.9544. $C_{11}H_{11}IO_5$+$Na^+$ requires 372.9543); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1735, 1591, 1573, 1470, 1431, 1412, 1261, 1030, 1018; $\delta_H$ (400 MHz; $CDCl_3$) 6.96 (1 H, d, *J* 9.2, ArH), 6.93 (1 H, d, *J* 9.2, ArH), 3.94 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.79 (3 H, s, $CO_2$Me); $\delta_C$ (100 MHz; $CDCl_3$) 186.8 (C), 160.4 (C), 152.8 (C), 152.7 (C), 132.1 (C), 113.6 (CH), 112.2 (CH), 85.4 (C), 57.2 (Me), 56.8 (Me), 53.3 (Me); *m/z* (ESI) 373 (M+$Na^+$, 100%).

**(*R*/*S*)-Methyl 2-hydroxy-2-(2-iodo-3,6-dimethoxyphenyl)acetate 74**

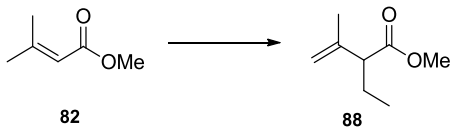



**73** **74**

To a suspension of methyl 2-(2-iodo-3,6-dimethoxyphenyl)-2-oxoacetate **73** (50.0 mg, 0.14 mmol) in dry methanol (1.5 mL) at –30 ºC under argon was added sodium borohydride (27.0 mg, 0.07 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with hydrochloric acid (1 M), until evolution of gas stopped, diluted with water (5 mL) and extracted into ethyl acetate (3 × 5 mL). The combined organic fractions were washed with brine (2 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* **74** as a colourless solid (45 mg, 89%); mp 110-112 ºC; (Found: M+$Na^+$, 374.9700. $C_{11}H_{13}IO_5$+$Na^+$ requires 374.9700); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3542, 3011, 2955, 2839, 1743, 1574, 1473, 1433, 1259, 1083, 1064, 987; $\delta_H$ (400 MHz; $CDCl_3$) 6.85 (1 H, d, *J* 8.8, ArH), 6.78 (1 H, d, *J* 8.8, ArH), 5.73 (1 H, d, *J* 8.0, CHOH), 3.84 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.73 (3 H, s, $CO_2$Me), 3.70 (1 H, d, *J* 8.0, OH); $\delta_C$ (100 MHz; $CDCl_3$) 173.7 (C),

152.9 (C), 151.7 (C), 131.9 (C), 111.9 (CH), 111.2 (CH), 95.2 (C), 76.4 (CH), 57.1 (Me), 56.4 (Me), 52.7 (Me); *m/z* (ESI) 375 ($M+Na^+$, 100%).

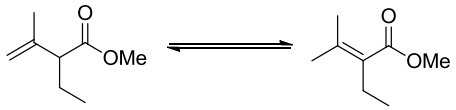
**Methyl 2-ethyl-3-methylbut-3-enoate 88**[78]




82 88

A mixture of methyl 3-methyl-2-butenoate **82** (1.28 mL, 10.5 mmol) in THF (4.4 mL) was added to a stirring solution of LDA (12.0 mmol), prepared from *n*-butyllithium and di*iso*propylamine in THF (13 mL) at −78 ºC, and the stirring was continued for 1 h. The solution was allowed to warm to 0 ºC over 1 h, and iodoethane (1.56 mL, 19.4 mmol) was added dropwise. The mixture was warmed to room temperature, over 1 h, and stirred for 2 h, before being poured into water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were then washed with water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* without heating. The residue was subjected to flash chromatography on silica gel, using light petroleum/ethyl acetate (25:1) to give the *title compound* **88** as a colourless oil (1.09 g, 73%); (Found: $M+Na^+$, 165.0884. $C_8H_{14}O_2+Na^+$ requires 165.0891); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3081, 2954, 1731, 1646, 1601, 1457, 1376, 1249, 1170, 902; $\delta_H$ (300 MHz; $CDCl_3$) 4.89-4.86 (2 H, m, H-4), 3.67 (3 H, s, OMe), 2.95-2.90 (1 H, m, H-2), 1.73 (3 H, s, Me); 1.60-1.87 (2 H, m, C<u>H</u>$_2$Me); 0.87 (3 H, t, *J* 7.5, CH$_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 174.2 (C), 142.4 (C), 113.7 ($CH_2$), 54.8 (CH), 51.7 (Me), 23.2 ($CH_2$), 20.0 (Me), 11.9 (Me); *m/z* (ESI) 165 ($M+Na^+$, 21%). Data in agreement with literature values.[78]

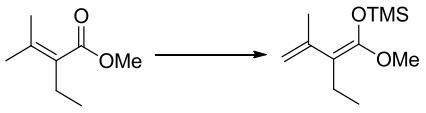
**Methyl 2-ethyl-3-methylbut-2-enoate 89**




88 89

To a solution of methyl 2-ethyl-3-methylbut-3-enoate **88** (5.00 g, 35.2 mmol) in THF (40 mL) at -78 ºC was added potassium *tert*-butoxide (4.34 g, 38.6 mmol) and the reaction mixture was allowed to reach 0 ºC over the course of 2 h. The mixture was washed with water (30 mL) and extracted with dichloromethane (30 mL). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* without heating. Evaporation of the solvent gave the *title compound* **89** as a yellow oil (4.92 g) contaminated with *t*-BuOH. The material was used in the next step without further purification; $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 1707, 1435, 876; $\delta_H$ (300 MHz; $CDCl_3$) 3.72 (3 H, s, OMe), 2.29 (2 H, q, *J* 7.5, C<u>H</u>$_2$Me), 1.94 (3 H, s, Me), 1.79 (3 H, s, Me), 0.97 (3 H, t, *J* 7.5, CH$_2$<u>Me</u>); $\delta_C$ (75 MHz; $CDCl_3$); 170.2 (C),141.6 (C), 129.1 (C), 51.1 (Me), 23.1 ($CH_2$) 22.9 (Me), 21.4 (Me), 13.4 (Me); *m/z* (EI) 142 ($M^+$).

**(*Z*)-((2-Ethyl-1-methoxy-3-methylbuta-1,3-dien-1-yl)oxy)trimethylsilane 28**

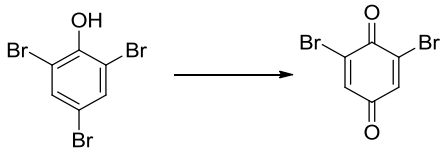



89 28

*n*-Butyllithium (1.6 M in hexane; 14.0 mL, 22.3 mmol) was added dropwise to a stirring solution of di*iso*propylamine (3.75 mL, 26.8 mmol) in THF (14 mL) at 0 ºC. The resulting solution was stirred at 0 ºC for 1 h and then cooled to −78 ºC. Methyl 2-ethyl-3-methylbut-2-enoate **89** (2.79 g, 19.6 mmol) dissolved in THF (28 mL) was added dropwise and the mixture was stirred at −78 ºC for 1.5 h. Freshly distilled chlorotrimethylsilane (4.01 mL, 31.4 mmol) was added and the reaction mixture was stirred for another 1.5 h and then warmed to room temperature over 1.5 h. The solvent was removed under reduced pressure

and the resulting slurry was suspended in pentane (10 mL), filtered and the filtrate was concentrated *in vacuo*. The residue was distilled under reduced pressure (water aspirator) to give the desired compound **28** as a colourless oil (3.11 g, 74%); bp 70-80 ºC (15 mm Hg); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3081, 3011, 1726, 1661, 1636, 1438, 1253, 1175, 1115, 1060, 860, 850; $\delta_H$ (400 MHz; $CDCl_3$) 4.90-4.89 (1 H, m, H-4), 4.83-4.82 (1 H, m, H-4), 3.54 (3 H, s, OMe), 2.14 (2 H, q, *J* 7.6, C<u>H</u>$_2$Me), 1.86 (3 H, s, Me), 0.94 (3 H, t, *J* 7.6, $CH_2$<u>Me</u>), 0.20 (9 H, s, Si<u>Me</u>$_3$); $\delta_C$ (100 MHz; $CDCl_3$) 150.2 (C), 142.3 (C), 112.9 ($CH_2$), 104.5 (C), 56.7 (Me), 23.4 (Me), 22.0 ($CH_2$), 14.0 (Me), 0.03 (Me); *m/z* (FT-MS) 214 ($M^+$, 22%).

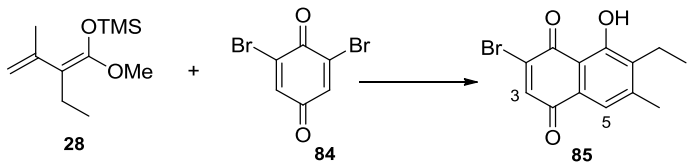
**2,6-Dibromo-1,4-benzoquinone 84**[77]




**83** **84**

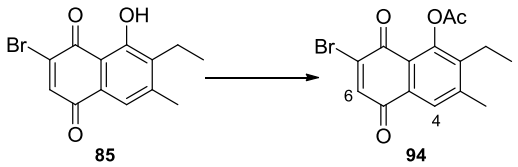
A solution of 2,4,6-tribromophenol **83** (1.00 g, 3.02 mmol) in acetonitrile (40 mL) was added to a solution of periodic acid (1.75 g, 7.68 mmol) in water (5.7 mL) and stirred at 80 ºC for 6 h. After setting aside for 2 h, the mixture was extracted with ether (3 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from ethanol gave the *title compound* **84** as a yellow solid (421 mg, 52%); mp 128-130 ºC (lit.,[77] mp 130 ºC); $\delta_H$ (400 MHz; $CDCl_3$) 7.32 (2 H, s, H-3,5); $\delta_C$ (100 MHz; $CDCl_3$) 182.3 (C), 172.4 (C), 130.2 (CH), 135.7 (C); *m/z* (EI) 268/266/264 ($M^+$, 24/46/23%). Data in agreement with literature values.[77]

**2-Bromo-7-ethyl-8-hydroxy-6-methylnaphthalene-1,4-dione 85**



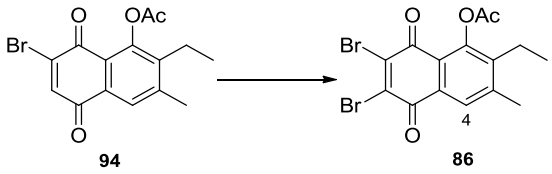

To a solution of 2,6-dibromo-1,4-benzoquinone **84** (1.71 g, 6.43 mmol) in dry toluene (20 mL) at 0 ºC, under a nitrogen atmosphere was added a solution of (*Z*)-((2-ethyl-1-methoxy-3-methylbuta-1,3-dien-1-yl)oxy)trimethylsilane **28** (2.08 g, 9.61 mmol) in dry toluene (6 mL), dropwise, over 10 min. The reaction mixture was allowed to reach room temperature over the course of 16 h, before being poured into a flask containing silica gel (≈75 g) and dichloromethane (100 mL). After stirring for 48 h at room temperature, the mixture was filtered and the filter cake was washed with dichloromethane (2 × 100 mL) under reduced pressure and the solvent evaporated. Purification by flash chromatography using first light petroleum and then light petroleum/ethyl acetate (2%), gave the *title compound* **85** as an orange solid (1.56 g, 82%); mp 131-132 ºC (dichloromethane/*n*-hexane); (Found: C, 52.65; H, 3.66. $C_{13}H_{11}BrO_3$ requires C, 52.91; H, 3.76); (Found: M+$Na^+$, 316.9790. $C_{13}H_{11}{}^{79}BrO_3$+$Na^+$ requires 316.9784); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3691, 1601, 1350, 854; $\lambda_{max}$ (acetonitrile)/nm 222 (log ε 4.70), 256 (log ε 3.99), 289 (log ε 4.17), 441 (log ε 3.77); $\delta_H$ (400 MHz; $CDCl_3$) 12.1 (1 H, s, OH), 7.44 (1 H, s, H-5), 7.41 (1 H, s, H-3), 2.77 (2 H, q, *J* 7.6, $\underline{CH_2}Me$), 2.42 (3 H, s, Me), 1.15 (3 H, t, *J* 7.6, $CH_2\underline{Me}$); $\delta_C$ (100 MHz; $CDCl_3$); 182.6 (C), 181.9 (C), 160.6 (C), 146.3 (C), 140.9 (CH), 139.4 (C), 139.2 (C), 128.6 (C), 122.1 (CH), 111.7 (C), 20.1 (Me), 19.6 ($CH_2$), 12.6 (Me); *m/z* (ESI) 316 (M+$Na^+$, 100%).

**7-Bromo-2-ethyl-3-methyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate 94**



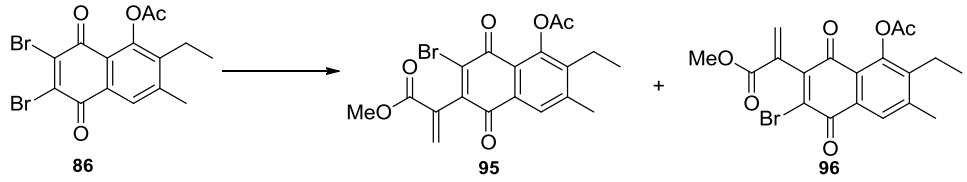

To a solution of acetyl chloride (0.06 mL, 0.93 mmol) in dichloromethane (2.5 mL) was added a solution of 2-bromo-7-ethyl-8-hydroxy-6-methylnaphthalene-1,4-dione **85** (245 mg, 0.83 mmol) in pyridine (4 mL) and dichloromethane (30 mL), dropwise at 0 ºC under argon. The reaction mixture was stirred at 0 ºC for 30 min and then the ice-bath was removed and the stirring was continued for 30 min at room temperature. The mixture was concentrated and the residue was taken up in dichloromethane (20 mL) and washed with water (2 × 10 mL). The organic phase was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with light petroleum/ethyl acetate (9:1) to give the *title compound* **94** as a yellow solid (154 mg, 56%); mp 139-141 ºC (dichloromethane/*n*-hexane); (Found: C, 53.27; H, 3.81. $C_{15}H_{13}BrO_4$ requires C, 53.43; H, 3.89); (Found: M+$Na^+$, 358.9891. $C_{15}H_{13}{}^{79}BrO_4$+$Na^+$ requires 358.9889); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3690, 3045,1772, 1676, 1369, 850; $\lambda_{max}$ (acetonitrile)/nm 206 (log ε 4.65), 260 (log ε 4.30), 285 (log ε 4.19), 358 (log ε 3.63); $\delta_H$ (400 MHz; $CDCl_3$) 7.83 (1 H, s, H-4), 7.43 (1 H, s, H-6), 2.73-2.54 (2 H, m, C<u>H</u>$_2$Me), 2.50 (3 H, s, Me), 2.49 (3 H, s, Me), 1.13 (3 H, t, *J* 7.6, $CH_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 181.9 (C), 176.2 (C), 169.5 (C), 148.5 (C), 145.6 (C), 143.7 (C), 141.3 (C), 139.1 (CH), 130.5 (C), 126.7 (CH), 120.1 (C), 21.1 (Me), 20.7 ($CH_2$), 20.1 (Me), 12.9 (Me); *m/z* (ESI) 361/359 (M+$Na^+$, 99/100%).

**6,7-Dibromo-2-ethyl-3-methyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate 86**



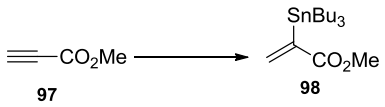

To a solution of 7-bromo-2-ethyl-3-methyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate **94** (80.0 mg, 0.24 mmol) in acetic acid (0.32 mL) at room temperature was added a solution of bromine (12 µL, 0.24 mmol) in acetic acid (32 µL), dropwise over 5 min. After stirring for 4 h at room temperature, the reaction mixture was diluted with dichloromethane (3 mL), washed successively with water (3 × 5 mL), saturated aqueous sodium carbonate (3 × 5 mL), brine (5 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel with light petroleum/ethyl acetate (9:1) gave the *title compound* **86** as a yellow solid (89.6 mg; 91%); mp 207-210 ºC (dichloromethane/*n*-hexane); (Found: $M+Na^+$, 436.8992. $C_{15}H_{12}{}^{79}Br_2O_4+Na^+$ requires 436.8995); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3691, 2337, 1771, 1677, 1600, 1177, 885; $\lambda_{max}$ (acetonitrile)/nm 208 (log ε 4.50), 254 (log ε 4.20), 262 (log ε 4.19), 298 (log ε 4.10) 362 (log ε 3.55); $\delta_H$ (400 MHz; $CDCl_3$) 7.92 (1 H, s, H-4), 2.73-2.60 (2 H, m, C<u>H</u>$_2$Me), 2.50 (6 H, s, 2 × Me), 1.13 (3 H, t, *J* 7.6, CH$_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 175.6 (C), 174.1 (C), 169.3 (C), 148.7 (C), 145.6 (C), 144.3 (C), 143.7 (C), 140.9 (C), 129.5 (C), 128.0 (CH), 120.0 (C), 21.1 (Me), 20.8 ($CH_2$), 20.1 (Me), 12.9 (Me); *m/z* (ESI) 441/439/437 ($M+Na^+$, 37/71/36%).

**Methyl 2-(5-acetoxy-3-bromo-6-ethyl-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acrylate 95 and methyl 2-(8-acetoxy-3-bromo-7-ethyl-6-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acrylate 96**



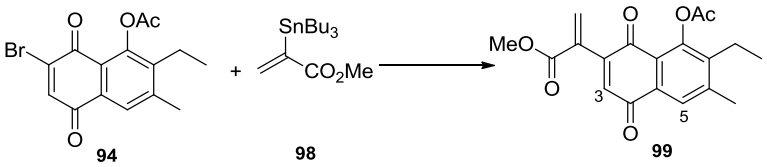

A mixture of 6,7-dibromo-2-ethyl-3-methyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate **86** (50.0 mg, 0.12 mmol), methyl acrylate (30 µL, 0.36 mmol) and DABCO (18.8 mg, 0.14 mmol) in THF (2 mL) was stirred at rt for 30 h. The reaction mixture was diluted with water (1 mL) and extracted with dichloromethane (3 × 2 mL). The combined organic layers were dried ($MgSO_4$), evaporated *in vacuo* and the resulting residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give a 2:1 mixture of the regioisomers **95** and **96** as a yellow oil (27.8 mg, 55%); (Found: $M+Na^+$, 443.0072. $C_{19}H_{17}{}^{79}BrO_6+Na^+$ requires 443.0106); Regioisomer **95**: $\delta_H$ (400 MHz; $CDCl_3$) 7.87 (1 H, s, ArH), 6.78 (1 H, s, C=C$\underline{H}_2$), 5.87 (1 H, s, C=C$\underline{H}_2$), 3.76 (3 H, s, Me), 2.74-2.62 (2 H, m, C$\underline{H}_2$Me), 2.51 (3 H, s, Me), 2.49 (3 H, s, Me), 1.14 (3 H, t, *J* 7.6, $CH_2\underline{Me}$); $\delta_C$ (100 MHz; $CDCl_3$) 180.3 (C), 179.3 (C), 169.5 (C), 164.3 (C), 148.3 (C), 145.6 (C), 143.7 (C), 140.7 (C), 135.0 (C), 132.1 ($CH_2$), 130.2 (C), 127.1 (CH), 126.4 (C), 120.2 (C), 52.5 (Me), 21.1 (Me), 20.7 ($CH_2$), 20.1 (Me), 13.0 (Me); Regioisomer **96**: 7.93 (1 H, s, ArH), 6.78 (1 H, s, C=C$\underline{H}_2$), 5.87 (1 H, s, C=C$\underline{H}_2$), 3.75 (3 H, s, Me), 2.74-2.62 (2 H, m, C$\underline{H}_2$Me), 2.49 (3 H, s, Me), 2.43 (3 H, s, Me), 1.12 (3 H, t, *J* 7.6, $CH_2\underline{Me}$); $\delta_C$ (100 MHz; $CDCl_3$) 177.4 (C), 175.9 (C), 169.3 (C), 163.9 (C), 145.5 (C), 145.0 (C), 144.1 (C), 137.6 (C), 134.9 (C), 132.1 ($CH_2$), 129.8 (C), 127.5 (CH), 127.1 (C), 120.6 (C), 52.5 (Me), 21.0 (Me), 20.7 ($CH_2$), 20.0 (Me), 13.0 (Me); *m/z* (ESI) 445/443 ($M+Na^+$, 99/100%);

**Methyl 2-(tributylstannyl)acrylate 98**[82]




To a solution of bis(triphenylphosphine)palladium(II) dichloride (83.5 mg, 0.12 mmol) in toluene (120 mL), stirred at room temperature for 10 min was added methyl propiolate **97** (1.06 mL, 11.9 mmol) and then tributyltin hydride (3.84 mL, 14.3 mmol) in toluene (35 mL), dropwise over 5 min. After stirring for 2 h at room temperature the reaction mixture was concentrated and purified by column chromatography on silica gel, using 2% ether in light petroleum. The *title compound* **98** was collected as a colourless oil (2.31 g, 52%); (Found: $M+Na^+$, 399.1330. $C_{16}H_{32}O_2Sn+Na^+$ requires 399.1316); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2957, 2927, 2872, 2854, 1695, 1463, 1266; $\delta_H$ (400 MHz; $CDCl_3$) 6.89 (1 H, dd, *J* 108.9, 2.8, SnC=C$\underline{H}_2$), 5.92 (1 H, dd, *J* 53.4, 2.8, SnC=C$\underline{H}_2$), 3.73 (3 H, s, OMe), 1.55-0.87 (27 H, m, Sn-$\underline{n}$Bu); $\delta_C$ (100 MHz; $C_6D_6$) 170.2 (C), 146.6 (C), 139.8 ($CH_2$), 51.4 (Me), 29.4 ($CH_2$), 27.6 ($CH_2$), 13.9 (Me), 10.3 ($CH_2$); *m/z* (ESI) 399 ($M+Na^+$, 100%). Data in agreement with literature values.[82]

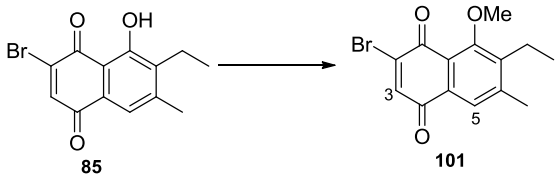
**Methyl 2-[8-(acetyloxy)-7-ethyl-6-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl]prop-2-enoate 99**




7-Bromo-2-ethyl-3-methyl-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate **94** (64.7 mg, 0.191 mmol) was dissolved in dry toluene (3 mL) and a solution of methyl 2-(tributylstannyl)acrylate **98** (286 mg, 0.762 mmol) in dry toluene (1 mL) and *tetrakis*(triphenylphosphine)palladium (15.8 mg, 0.014 mmol) were sequentially added. The reaction mixture was stirred at 75 ºC for 23 h, under a nitrogen atmosphere and then diluted with water (5 mL), extracted with dichloromethane (3 × 5 mL), washed with brine (15 mL),

dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/light petroleum (2-20%) to give the *title compound* **99** as a yellow solid (55 mg, 84%); mp 160-162 ºC (dichloromethane/*n*-hexane); (Found: M+$Na^+$, 365.1009. $C_{19}H_{18}O_6$+$Na^+$ requires 365.0996); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3046, 2977, 1770, 1729, 1665, 1192, 1063; $\delta_H$ (400 MHz; $CDCl_3$) 7.83 (1 H, s, H-5), 6.84 (1 H, s, H-3), 6.49 (1 H, d, *J* 0.8, C=C<u>H</u>$_2$), 5.91 (1 H, d, *J* 0.8, C=C<u>H</u>$_2$), 3.76 (3 H, s, Me), 2.69-2.64 (2 H, m, C<u>H</u>$_2$Me), 2.48 (3 H, s, Me), 2.43 (3 H, s, Me), 1.13 (3 H, t, *J* 7.6, $CH_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 184.5 (C), 182.5 (C), 169.5 (C), 165.5 (C), 147. 8 (C), 147.7 (C), 144.9 (C), 143.5 (C), 136.8 (C), 134.2 (CH), 130.9 (C), 130.0 ($CH_2$), 126.0 (CH), 121.0 (C), 52.4 (Me), 21.1 (Me), 20.6 ($CH_2$), 20.1 (Me), 13.0 (Me); *m/z* (ESI) 365 (M+$Na^+$, 100%).

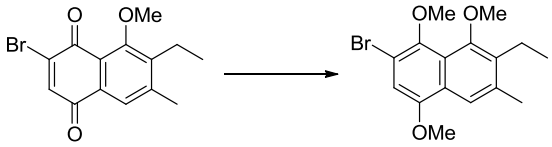
**2-Bromo-7-ethyl-8-methoxy-6-methylnaphthalene-1,4-dione 101**




A mixture of 2-bromo-7-ethyl-8-hydroxy-6-methylnaphthalene-1,4-dione **85** (400 mg, 1.35 mmol), silver(I) oxide (469 mg, 2.00 mmol) and iodomethane (6.75 mL, 0.108 mol) was heated to reflux for 5.5 h. The mixture was filtered through Celite® and the filter cake was washed with dichloromethane (15 mL). The filtrate and the washings were combined and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel, using light petroleum to light petroleum/ethyl acetate (95:5) to give the *title compound* **101** as a yellow solid (287 mg, 68%); mp 83-86 ºC (dichloromethane/*n*-hexane); (Found: C, 53.98; H, 4.31. $C_{14}H_{13}BrO_3$ requires C, 54.39; H, 4.31); (Found: M+$Na^+$, 330.9931. $C_{14}H_{13}{}^{79}BrO_3$+$Na^+$ requires 330.9940); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1724, 1674, 1585, 1465, 1451, 1381, 1336, 1303, 1255, 1175, 1101, 1034; $\lambda_{max}$ (acetonitrile)/nm 211 (log ε 4.54), 262 (log ε 4.14), 283 (log ε 4.07), 374 (log ε 3.57); $\delta_H$ (400 MHz; $CDCl_3$) 7.70 (1 H, s, H-5), 7.42 (1 H,

s, H-3), 3.89 (3 H, s, OMe), 2.78 (2 H, q, *J* 7.6, C<u>H</u>$_2$Me), 2.45 (3 H, s, Me), 1.16 (3 H, t, *J* 7.6, CH$_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 182.6 (C), 176.4 (C), 159.3 (C), 145.53 (C), 145.49 (C), 142.0 (C), 138.7 (CH), 130.9 (C), 125.1 (CH), 120.8 (C), 62.3 (Me), 20.3 ($CH_2$), 20.1 (Me), 13.7 (Me); *m/z* (ESI) 331/333 (M+$Na^+$, 53/51%).

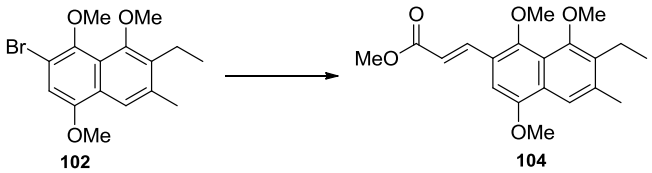
**7-Bromo-2-ethyl-1,5,8-trimethoxy-3-methylnaphthalene 102**




To a solution of 2-bromo-7-ethyl-8-methoxy-6-methylnaphthalene-1,4-dione **101** (122 mg, 0.39 mmol) in dichloromethane (29 mL) was added a saturated aqueous solution of sodium dithionite (15 mL). After stirring vigorously for 1.5 h at room temperature, the organic phase was separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic phases were washed with brine (2 × 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure yielding pure hydroquinone, which was used in the next step without further purification. The hydroquinone was purged with nitrogen over 30 min, dissolved in degassed acetone (8.7 mL) and potassium carbonate anhydrous (502 mg, 3.62 mmol) followed by dimethyl sulfate (0.34 mL, 3.62 mmol) were added. The solution was heated to reflux for 2 h, cooled and filtered through a plug of Celite®. The residue was purified by column chromatography on silica gel, eluting with light petroleum/ethyl acetate (9.5:5 to 8:2) to give the *title compound* **102** as an off-white solid (102 mg, 76%); mp 97-99 $^oC$; (Found: M+$Na^+$, 361.0410. $C_{16}H_{19}{}^{79}BrO_3$+$Na^+$ requires 361.0410); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2971, 2935, 1584, 1455, 1330, 1061, 976; $\delta_H$ (400 MHz; $CDCl_3$) 7.81 (1 H, s, ArH), 6.86 (1 H, s, ArH), 3.95 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.83 (3 H, s, OMe), 2.85 (2 H, q, *J* 7.6, C<u>H</u>$_2$Me), 2.47 (3 H, s, Me), 1.22 (3 H, t, *J* 7.6, CH$_2$<u>Me</u>); $\delta_C$ (75 MHz; $CDCl_3$) 152.2 (C), 151.7 (C), 145. 3 (C), 136.0 (C), 136.0 (C), 126.3 (C), 121.9 (C), 118.9 (CH), 113.4 (C),

107.8 (CH), 63.0 (Me), 61.7 (Me), 55.9 (Me), 20.0 (Me), 19.9 ($CH_2$), 14.7 (Me); *m/z* (ESI) 363/361 ($M+Na^+$, 86/87%).

**(*E*)-Methyl-3-(7-ethyl-1,4,8-trimethoxy-6-methylnaphthalen-2-yl)acrylate 104**

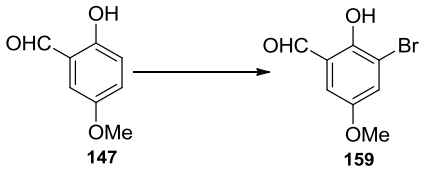



**102** **104**

7-Bromo-2-ethyl-1,5,8-trimethoxy-3-methylnaphthalene **102** (50.0 mg, 0.147 mmol) was dissolved in dry DMF (1 mL) and a solution of methyl 2-(tributylstannyl)acrylate **98** (286 mg, 0.762 mmol) in dry DMF (0.2 mL) and *tetrakis*(triphenylphosphine)palladium (8.5 mg, 0.0073 mmol) were sequentially added. The reaction mixture was stirred at 150 ºC for 16 h, under a nitrogen atmosphere and then diluted with water (3 mL), extracted with dichloromethane (3 × 3 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with light petroleum/ethyl acetate (9:1) to give the *compound* **104** as a yellow solid (15.3 mg, 30%); mp 145-149 ºC; (Found: $M+Na^+$, 367.1527. $C_{20}H_{24}O_5+Na^+$ requires 367.1521); $\delta_H$ (400 MHz; $CDCl_3$) 8.34 (1 H, d, *J* 16, C<u>H</u>=CHCO$_2$Me), 7.87 (1 H, s, ArH), 6.86 (1 H, s, ArH), 6.49 (1 H, d, *J* 16, CH=C<u>H</u>CO$_2$Me), 4.02 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.85 (3 H, s, OMe), 2.88 (2 H, q, *J* 7.6, C<u>H</u>$_2$Me), 2.52 (3 H, s, Me), 1.25 (3 H, t, *J* 7.6, CH$_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 167.8 (C), 153.5 (C), 151.5 (C), 149.7 (C), 140.1 (CH), 137.5 (C), 136.0 (C), 128.5 (C), 123.0 (C), 121.2 (C), 118.9 (CH), 117.3 (CH), 99.5 (CH), 63.0 (Me), 62.9 (Me), 55.6 (Me), 51.6 (Me), 20.1 (Me), 19.9 ($CH_2$), 14.7 (Me); *m/z* (ESI) 367 ($M+Na^+$, 100%).

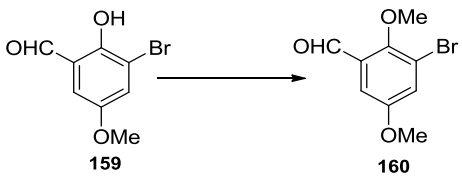
## *Experimental details for Chapter III*

### 3-Bromo-2-hydroxy-5-methoxybenzaldehyde 159[122]




To a solution of 2-hydroxy-5-methoxybenzaldehyde **147** (20.0 g, 131 mmol) in glacial acetic acid (600 mL) was added sodium acetate anhydrous (17.1 g, 209 mmol) and bromine (8.69 ml, 169 mmol). The resulting mixture was stirred at room temperature for 1 h and concentrated. The residue was then dissolved in dichloromethane (1 L), washed with saturated aqueous sodium thiosulfate solution (500 mL), water (500 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting solid was recrystallised from ethanol to yield the *title compound* **159** as a yellow solid (24.0 g, 79%); mp 107-108 ºC (lit.,[121] mp 108 ºC); (Found: M+Na$^+$, 252.9470. $C_8H_7{}^{79}BrO_3$+Na$^+$ requires 252.9471); $\delta_H$ (400 MHz; $CDCl_3$) 11.13 (1 H, s, CHO), 9.83 (1 H, s, OH), 7.42 (1 H, d, *J* 3.0, ArH), 7.04 (1 H, d, *J* 3.0, ArH), 3.82 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 195.6 (CH), 152.8 (C), 152.5 (C), 127.4 (CH), 120.4 (C), 115.8 (CH), 111.5 (C), 56.2 (Me); *m/z* (ESI) 255/253 (M+Na$^+$, 100/99%). Data in agreement with literature values.[122]

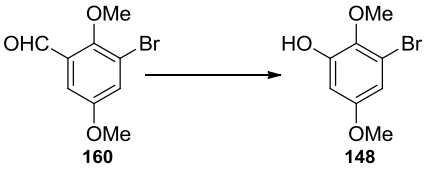
### 3-Bromo-2,5-dimethoxybenzaldehyde 160[122]




To a solution of 3-bromo-2-hydroxy-5-methoxybenzaldehyde **159** (2.50 g, 10.8 mmol) in dry DMF (50 mL) was added potassium carbonate (2.10 g, 15.1 mmol) and dimethylsulfate (1.43 mL, 15.1 mmol). The resulting mixture was stirred at room temperature for 24 h, upon which water (50 mL) was added. The organic layer was separated and the aqueous layer was

extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (8:2) to give the *title compound* **160** as a colourless solid (2.47 g, 93%); mp 65-66 ºC (lit.,[121] mp 68 ºC); (Found: M+$Na^+$, 266.9627. $C_9H_9{}^{79}BrO_3$+$Na^+$ requires 266.9627); $\delta_H$ (400 MHz; $CDCl_3$) 10.31 (1 H, s, CHO), 7.38 (1 H, d, *J* 2.8, ArH), 7.27 (1 H, d, *J* 2.8, ArH), 3.93 (3 H, s, OMe), 3.82 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 189.0 (CH), 156.4 (C), 154.4 (C), 130.5 (C), 126.5 (CH), 118.5 (C), 110.2 (CH), 63.8 (Me), 56.0 (Me); *m/z* (ESI) 269/267 (M+$Na^+$, 96/100%). Data in agreement with literature values.[122]

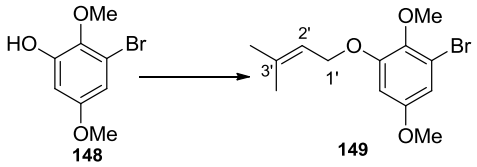
**3-Bromo-2,5-dimethoxyphenol 148**




To a solution of 3-bromo-2,5-dimethoxybenzaldehyde **160** (2.16 g, 8.80 mmol) in dry dichloromethane (44 mL) at 0 ºC under argon, was added *meta*-chloroperoxybenzoic acid (5.92, 26.4 mmol) portionwise. After stirring for 18 h at room temperature, the reaction mixture was diluted with dichloromethane (20 mL) and washed successively with sodium thiosulfate solution (1 M; 50 mL), saturated aqueous sodium hydrogen carbonate solution (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, concentrated *in vacuo* and taken up in methanol (44 mL). Aqueous potassium hydroxide solution (1 M; 1 mL) was then added and the resulting mixture was stirred at room temperature for 1 h, upon which an aqueous hydrochloric acid solution (1 M; 2 mL) and water (44 mL) were added. The mixture was extracted into ethyl acetate (2 × 40 mL) and the combined organic layers were washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by column chromatography,

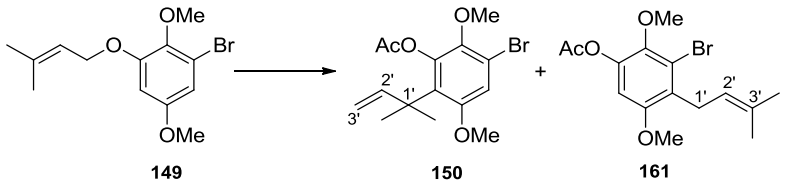
eluting with light petroleum/ethyl acetate (1:1) to give the *title compound* **148** as an off-white solid (1.62 g, 79%); mp 70-71 ºC (lit.,[122] mp 73-74 ºC); (Found: M+$Na^+$, 254.9631. $C_8H_9{}^{79}BrO_3$+$Na^+$ requires 254.9627); $\delta_H$ (300 MHz; $CDCl_3$) 6.62 (1 H, d, *J* 3.0, ArH), 6.50 (1 H, d, *J* 3.0, ArH), 5.67 (1 H, s, OH), 3.86 (3 H, s, OMe), 3.74 (3 H, s, OMe); $\delta_C$ (75 MHz; $CDCl_3$) 157.0 (C), 150.2 (C), 138.6 (C), 115.7 (C), 109.7 (CH), 101.3 (CH), 61.3 (Me), 55.7 (Me); *m/z* (ESI) 257/255 (M+$Na^+$, 95/100%).

**1-Bromo-2,5-dimethoxy-3-((3-methylbut-2-en-1-yl)oxy)benzene 149**




To a stirred solution of 3-bromo-2,5-dimethoxyphenol **148** (300 mg, 1.29 mmol) in dry DMF (7 mL) under argon at 0 ºC was added sodium hydride (60% dispersion in mineral oil, 57.0 mg, 1.42 mmol). After stirring for 5 min, 3,3-dimethylallyl bromide (1.29 mL, 1.54 mmol) was added dropwise and the resulting mixture stirred at room temperature for 2.5 h. Saturated aqueous ammonium chloride solution (10 mL) was then added and the mixture was extracted into ether (3 × 10 mL). The combined organic extracts were washed with water (2 × 30 mL), dried over magnesium sulfate and concentrated *in vacuo* to give the *title compound* **149** as a light yellow oil (385 mg, 99%); (Found: M+$Na^+$, 323.0267. $C_{13}H_{17}{}^{79}BrO_3$+$Na^+$ requires 323.0259); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2938, 1766, 1599, 1572, 1488, 1239, 1175, 831; $\delta_H$ (400 MHz; $CDCl_3$) 6.63 (1 H, d, *J* 2.8, ArH), 6.45 (1 H, d, *J* 2.8, ArH), 5.50-5.46 (1 H, m, H-2'), 4.53 (2 H, d, *J* 6.8, H-1'), 3.79 (3 H, s, OMe), 3.75 (3 H, s, OMe), 1.79 (3 H, s, Me), 1.74 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 156.3 (C), 153.2 (C), 141.2 (C), 138.2 (C), 119.4 (CH), 117.5 (C), 108.1 (CH), 101.5 (CH), 65.9 ($CH_2$), 60.6 (Me), 55.7 (Me), 25.8 (Me), 18.3 (Me); *m/z* (ESI) 325/323 (M+$Na^+$, 62/63%).

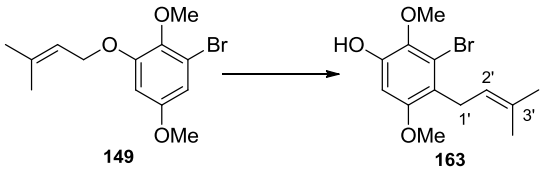
**3-Bromo-2,5-dimethoxy-6-(2-methylbut-3-en-2-yl)phenyl acetate 150**




1-Bromo-2,5-dimethoxy-3-((3-methylbut-2-en-1-yl)oxy)benzene **149** (182 mg, 0.60 mmol), acetic anhydride (4.4 mL) and anhydrous sodium acetate (99.0 mg, 1.21 mmol) were placed in a sealed tube and heated at 200 ºC for 21 h. After cooling to room temperature the reaction mixture was poured into water (10 mL) and stirred vigorously for 0.5 h. The resulting aqueous mixture was extracted into ether (2 × 10 mL) and the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate solution, until the washings were neutral, brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (5% to 20%) to give compounds **150** and **161** along with starting material (49.9 mg, 27%). The *title compound* **150** was obtained as a colourless oil (24.6 mg, 12%); (Found: $M+H^+$, 343.0550. $C_{15}H_{19}{}^{79}BrO_4+H^+$ requires 343.0539); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 2954, 1756, 1737, 1596, 1576, 1479, 1438, 1239, 1169, 1122, 1047; $\delta_H$ (400 MHz; $CDCl_3$) 6.91 (1 H, s, H-4), 6.21 (1 H, dd, *J* 17.4, 10.6, H-2'), 4.87 (1 H, dd, *J* 17.4, 1.0, H-3'$_{trans}$), 4.82 (1 H, dd, *J* 10.6, 1.0, H-3'$_{cis}$), 3.76 (3 H, s, OMe), 3.75 (3 H, s, OMe), 2.22 (3 H, s, Me-Ac), 1.46 (6 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 169.0 (C), 155.5 (C), 149.3 (CH), 144.1 (C), 143.9 (C), 129.7 (C), 114.4 (C), 114.0 (CH), 106.6 ($CH_2$), 60.9 (Me), 55.9 (Me), 41.7 (C), 21.0 (Me); *m/z* (ESI) 345/343 ($M+H^+$, 98/100%), 365 ($M+Na^+$, 59%); Compound **161** (64.1 mg, 31%) was obtained as an orange oil; (Found: $M+Na^+$, 365.0361. $C_{15}H_{19}{}^{79}BrO_4+Na^+$ requires 365.0364); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3097, 3055, 3006, 1769, 1596, 1577, 1477, 1395, 1148, 1040; $\delta_H$ (400 MHz; $CDCl_3$) 6.56 (1 H, s, H-6), 5.11 (1 H, t, *J* 6.8, H-2'), 3.78 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.51 (2 H, d, *J* 6.8, H-1'), 2.33 (3 H, s, Me-Ac), 1.79 (3 H, s, Me), 1.68 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 169.0 (C), 153.9 (C), 142.8 (C), 142.4 (C), 132.3 (C), 129.1 (C), 121.1 (C),

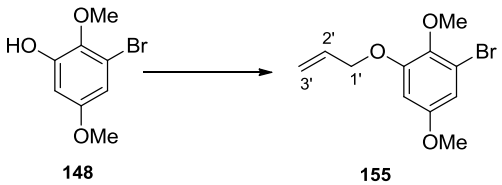
120.9 (CH), 105.1 (C), 61.0 (Me), 56.1 (Me), 29.3 ($CH_2$), 25.8 (Me), 20.7 (Me), 18.1 (Me); *m/z* (ESI) 367/365 ($M+Na^+$, 99/100%);

**3-Bromo-2,5-dimethoxy-4-(3-methylbut-2-en-1-yl)phenol 163**



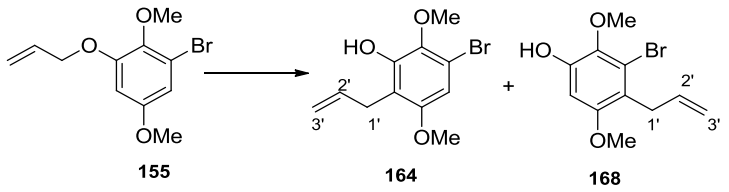

A solution of 1-bromo-2,5-dimethoxy-3-((3-methylbut-2-en-1-yl)oxy)benzene **149** (113 mg, 0.376 mmol) in dry DMF (1.3 mL) was placed in a sealed tube and heated at 160 ºC for 21 h. The solvent was evaporated and the resulting oil purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give the *title compound* **163** as a beige solid (91.0 mg, 80%); mp 73-75 ºC; (Found: $M+Na^+$, 323.0242. $C_{13}H_{17}{}^{79}BrO_3+Na^+$ requires 323.0253); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3533, 3010, 2967, 2915, 1608, 1584, 1478, 1465, 1453, 1417, 1315, 1192, 1168, 1034, 984; $\delta_H$ (400 MHz; $CDCl_3$) 6.51 (1 H, s, H-6), 5.54 (1 H, s, OH), 5.12-5.08 (1 H, t, *J* 6.9, H-2'), 3.84 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.44 (2 H, d, *J* 6.9, H-1'), 1.78 (3 H, s, Me), 1.68 (3 H, s, Me); $\delta_C$ (125 MHz; $CDCl_3$) 154.8 (C), 147.7 (C), 137.8 (C), 131.9 (C), 122.4 (C), 121.6 (CH), 119.0 (C), 98.4 (CH), 61.1 (Me), 56.0 (Me), 28.6 ($CH_2$), 25.8 (Me), 18.0 (Me); *m/z* (ESI) 325/323 ($M+Na^+$, 100/99%);

**1-(Allyloxy)-3-bromo-2,5-dimethoxybenzene 155**



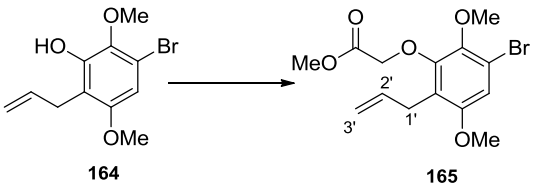

To a stirred solution of 3-bromo-2,5-dimethoxyphenol **148** (300 mg, 1.29 mmol) in dry DMF (7 mL) was added sodium hydride (60% dispersion in mineral oils; 57.0 mg, 1.42 mmol), under argon at 0 ºC. After stirring for 5 min, allyl bromide (0.13 mL, 1.54 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 1.5 h. Saturated aqueous ammonium chloride solution (10 mL) was then added and the mixture was extracted into ether (3 × 10 mL). The combined organic extracts were washed with water (2 × 30 mL), dried over magnesium sulfate and concentrated *in vacuo* to give the *title compound* **155** as a light yellow oil (350 mg, quantitative yield); (Found: C, 48.67; H, 4.79. $C_{11}H_{13}BrO_3$ requires C, 48.37; H, 4.80); (Found: M+$Na^+$, 294.9960. $C_{11}H_{13}{}^{79}BrO_3$+$Na^+$ requires 294.9940); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2964, 2838, 1601, 1572, 1489, 1424, 1319, 1148, 834; $\delta_H$ (400 MHz; $CDCl_3$) 6.65 (1 H, d, *J* 2.8, ArH), 6.44 (1 H, d, *J* 2.8, ArH), 6.05 (1 H, ddt, *J* 17.2, 10.6, 5.2, H-2'), 5.43 (1 H, dd, *J* 17.2, 1.6, H-3'$_{trans}$), 5.30 (1 H, dd, *J* 10.6, 1.6, H-3'$_{cis}$), 4.56 (2 H, d, *J* 5.2, H-1'), 3.81 (3 H, s, OMe), 3.75 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 156.3 (C), 152.9 (C), 141.1 (C), 132.7 (CH), 117.9 ($CH_2$), 117.6 (C), 108.4 (CH), 101.5 (CH), 69.7 ($CH_2$), 60.7 (Me), 55.7 (Me); *m/z* (ESI) 297/295 (M+$Na^+$, 99/100%).

**2-Allyl-5-bromo-3,6-dimethoxyphenol 164**



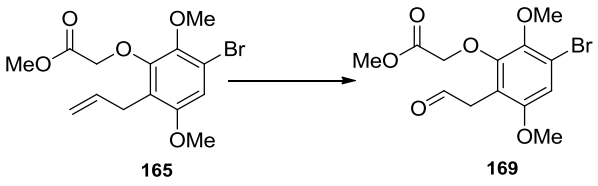

A solution of 1-(allyloxy)-3-bromo-2,5-dimethoxybenzene **155** (418 mg, 1.53 mmol) in dry DMF (13 mL) was heated at 200 ºC for 40 min in a microwave reactor (300 W). The solvent was evaporated and the resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1 to 8:2) to give the *title compound* **164** as a colourless solid (237 mg, 57%); mp 72-73 ºC; (Found: C, 48.16; H, 4.78. $C_{11}H_{13}BrO_3$ requires C, 48.37; H, 4.80); (Found: M+$Na^+$, 294.9940. $C_{11}H_{13}{}^{79}BrO_3$+$Na^+$ requires 294.9940); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3527, 2927, 2854, 1681, 1580, 1186, 1034, 913; $\delta_H$ (400 MHz; $CDCl_3$) 6.57 (1 H, s, H-4), 5.87 (1 H, ddt, *J* 16.9, 10.2, 6.1, H-2'), 5.75 (1 H, s, OH), 5.01 (1 H, dd, *J* 16.9, 1.7, H-3'$_{trans}$), 4.97 (1 H, dd, *J* 10.2, 1.7, H-3'$_{cis}$), 3.86 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.37 (2 H, dt, *J* 6.1 and 1.6, H-1'); $\delta_C$ (100 MHz; $CDCl_3$) 154.8 (C), 148.3 (C), 138.8 (C), 135.7 (CH), 114.8 (C), 114.7 ($CH_2$), 112.4 (C), 106.3 (CH), 61.3 (Me), 56.0 (Me), 27.6 ($CH_2$); *m/z* (ESI) 297/295 (M+$Na^+$, 97/100%); as well as the regioisomer **168** (121 mg, 29%); (Found: M+$Na^+$, 294.9926. $C_{11}H_{13}{}^{79}BrO_3$+$Na^+$ requires 294.9946); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3532, 3010, 2838, 1637, 1608, 1479, 1454, 1314, 1092, 1032, 863; $\delta_H$ (400 MHz; $CDCl_3$) 6.52 (1 H, s, H-6), 5.88 (1 H, ddt, *J* 16.4, 10.8, 6.1, H-2'), 5.58 (1 H, s, OH), 5.00 (1 H, dd, *J* 10.8, 1.7, H-3$_{cis}$'), 4.99 (1 H, dd, *J* 16.4, 1.7, H-3'$_{trans}$), 3.84 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.50 (2 H, d, *J* 6.1, H-1'); $\delta_C$ (75 MHz; $CDCl_3$) 154.9 (C), 148.1 (C), 137.9 (C), 135.4 (CH), 120.5 (C), 119.3 (C), 114.9 ($CH_2$), 98.4 (CH), 61.1 (Me), 56.1 (Me), 33.4 ($CH_2$); *m/z* (ESI) 297/295 (M+$Na^+$, 92/100%);

**Methyl 2-(2-allyl-5-bromo-3,6-dimethoxyphenoxy)acetate 165**




To a solution of 2-allyl-5-bromo-3,6-dimethoxyphenol **164** (400 mg, 1.46 mmol) in DMF (18 mL) was added potassium carbonate (304 mg, 2.19 mmol) and methyl 2-chloroacetate (191 mg, 1.76 mmol). The reaction mixture was stirred for 16 h at 100 ºC, before water was added (50 mL) and the mixture extracted with ether (3 × 50 mL). The combined organic extracts were washed with water (3 × 150 mL), dried over magnesium sulfate and concentrated *in vacuo* to give the *title compound* **165** as a colourless oil (431 mg, 85%); (Found: C, 48.90; H, 4.95. $C_{14}H_{17}BrO_5$ requires C, 48.71; H, 4.96); (Found: M+$Na^+$, 367.0143. $C_{14}H_{17}{}^{79}BrO_5$+$Na^+$ requires 367.0152); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3008, 2956, 1759, 1594, 1572, 1475, 1412, 1134, 1038; $\delta_H$ (400 MHz; $CDCl_3$) 6.82 (1 H, s, H-4), 5.92 (1 H, ddt, *J* 16.9, 10.9, 6.0, H-2'), 4.95 (1 H, dd, *J* 10.9, 1.3, H-3'$_{cis}$), 4.94 (1 H, dd, *J* 16.9, 1.3, H-3'$_{trans}$), 4.63 (2 H, s, $OCH_2$), 3.80 (6 H, s, OMe), 3.78 (3 H, s, OMe), 3.46 (2 H, d, *J* 6.0, H-1'); $\delta_C$ (100 MHz; $CDCl_3$) 169.5 (C), 154.5 (C), 151.0 (C), 144.0 (C), 136.4 (CH), 122.7 (C), 114.7 (C), 114.6 ($CH_2$), 110.7 (CH), 69.9 ($CH_2$), 61.0 (Me), 56.1 (Me), 51.9 (Me), 28.0 ($CH_2$); *m/z* (ESI) 369/367 (M+$Na^+$, 100/98%).

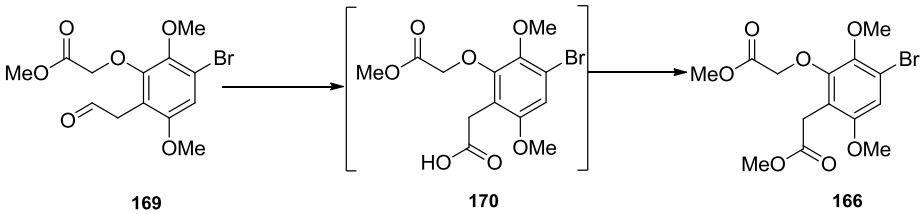
**Methyl 2-(3-bromo-2,5-dimethoxy-6-(2-oxoethyl)phenoxy)acetate 169**




Ozone was bubbled through a solution of methyl 2-(2-allyl-5-bromo-3,6-dimethoxyphenoxy)acetate **165** (371 mg, 1.07 mmol) in anhydrous dichloromethane (20 mL)

at −78 ºC, until the solution turned blue (≈ 10 min). Triphenylphosphine (874 mg, 3.33 mmol) was then added and the reaction mixture was warmed to room temperature over 2 h. The reaction mixture was then diluted with ether (8 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and the resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1 to 7:3) to give the *title compound* **169** as a colourless solid (318 mg, 85%); mp 49-50 ºC; (Found: C, 44.93; H, 4.35. $C_{13}H_{15}BrO_6$ requires C, 44.98; H, 4.36); (Found: M+$Na^+$, 368.9938. $C_{13}H_{15}{}^{79}BrO_6$+$Na^+$ requires 368.9944); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3008, 2893, 1757, 1724, 1477, 1439, 1127, 1050; $\delta_H$ (400 MHz; $CDCl_3$) 9.68 (1 H, t, *J* 1.2, CHO), 6.85 (1 H, s, H-4), 4.72 (2 H, s, $OCH_2$), 3.86 (2 H, d, *J* 1.2, $C\underline{H_2}CHO$), 3.80 (3 H, s, OMe), 3.76 (3 H, s, OMe), 3.75 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 199.5 (CH), 169.6 (C), 154.5 (C), 151.2 (C), 143.7 (C), 116.5 (C), 116.0 (C), 110.6 (CH), 69.5 ($CH_2$), 60.9 (Me), 56.1 (Me), 52.0 (Me), 39.2 ($CH_2$); *m/z* (ESI) 371/369 (M+$Na^+$, 96/100%).

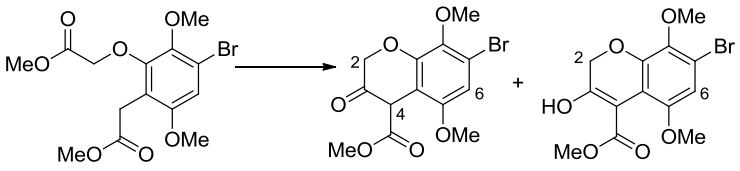
**Methyl 2-(3-bromo-2,5-dimethoxy-6-(2-methoxy-2-oxoethyl)phenoxy)acetate 166**




To a stirred solution of methyl 2-(3-bromo-2,5-dimethoxy-6-(2-oxoethyl)phenoxy)acetate **169** (316 mg, 0.91 mmol) in 2-methyl-2-butene (2 mL) and *tert*-butanol (11 mL) at 0 ºC was added a solution of sodium chlorite (140 mg, 1.54 mmol) in aqueous sodium dihydrogen phosphate (1 M; 1.33 mL, 1.33 mmol). After the addition, the ice-bath was removed and the reaction mixture was stirred at room temperature for 1 h, quenched with citric acid (0.5 M; 5.5 mL), and extracted with dichloromethane (3 × 6 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude acid was dissolved in dry methanol (3 mL), cooled to 0 ºC and stirred for 10 min. To this was added thionyl

chloride (0.33 mL, 4.52 mmol) dropwise, over 5 min and the resulting mixture was allowed to warm to room temperature over 16 h. The solvent was then evaporated under reduced pressure and the resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1 to 7:3) to give the *title compound* **166** as a colourless solid (303 mg, 88%); mp 80-81 ºC; (Found: C, 44.45; H, 4.50. $C_{14}H_{17}BrO_7$ requires C, 44.58; H, 4.54); (Found: M+$Na^+$, 399.0072. $C_{14}H_{17}{}^{79}BrO_7$+$Na^+$ requires 399.0050); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 2954, 1756, 1737, 1596, 1576, 1479, 1438, 1239, 1169, 1122, 1047; $\delta_H$ (400 MHz; $CDCl_3$) 6.83 (1 H, s, H-4), 4.70 (2 H, s, $OCH_2$), 3.80 (3 H, s, OMe), 3.79 (2 H, s, C<u>H</u>$_2$$CO_2$Me), 3.77 (3 H, s, OMe), 3.76 (3 H, s, OMe), 3.67 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 171.9 (C), 169.6 (C), 154.5 (C), 151.3 (C), 143.8 (C), 117.5 (C), 116.2 (C), 110.6 (CH), 69.7 ($CH_2$), 60.9 (Me), 56.1 (Me), 52.0 (Me), 51.9 (Me), 29.4 ($CH_2$); *m/z* (ESI) 401/399 (M+$Na^+$, 98/100%).

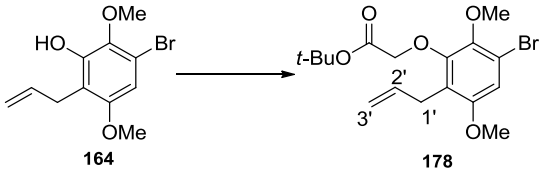
**(*R*/*S*)-Methyl 7-bromo-5,8-dimethoxy-3-oxochroman-4-carboxylate 171**




To a stirring solution of methyl 2-(3-bromo-2,5-dimethoxy-6-(2-methoxy-2-oxoethyl)phenoxy)acetate **166** (30.0 mg, 0.08 mmol) in THF (2 mL) at 0 ºC under argon, was added potassium *bis*(trimethylsilyl)amide (0.5 M in toluene; 0.41 mL, 0.21 mmol) dropwise. The reaction mixture was allowed to warm to room temperature over 2 h, quenched with aqueous sodium dihydrogen phosphate (0.3 M; 2 mL) and extracted into ethyl acetate (3 × 2 mL). The combined organic extracts were washed with brine (6 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a 5:1 mixture of methyl 7-bromo-5,8-dimethoxy-3-oxochroman-4-carboxylate **171** and the corresponding enol tautomer **172** as a yellowish oil (20.2 mg, 74%); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1733, 1601, 1582, 1484, 1463, 1422, 1240, 909; Major

tautomer **171**: $\delta_H$ (400 MHz; $CDCl_3$) 6.77 (1 H, s, H-6), 4.74 (1 H, d, *J* 17.0, H-2), 4.68 (1 H, s br, H-4), 4.34 (1 H, dd, *J* 17.0 and 1.2, H-2), 3.85 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.73 (3 H, s, $CO_2\underline{Me}$); $\delta_C$ (100 MHz; $CDCl_3$) 199.7 (C), 166.6 (C), 153.3 (C), 148.7 (C), 141.2 (C), 117.4 (C), 110.1 (C), 109.0 (CH), 71.8 ($CH_2$), 61.4 (Me), 56.2 (Me), 53.2 (CH), 51.3 (Me); Minor tautomer **172**: $\delta_H$ (400 MHz; $CDCl_3$) 11.3 (1 H, s, OH), 6.75 (1 H, s, H-6), 4.55 (2 H, s, H-2), 3.84 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.78 (3 H, s, $CO_2\underline{Me}$); $\delta_C$ (100 MHz; $CDCl_3$) 169.7 (C), 166.0 (C), 151.5 (C), 146.6 (C), 140.5 (C), 114.8 (C), 111.6 (C), 109.7 (CH), 96.0 (C), 66.6 ($CH_2$), 61.2 (Me), 56.1 (Me), 51.9 (Me).

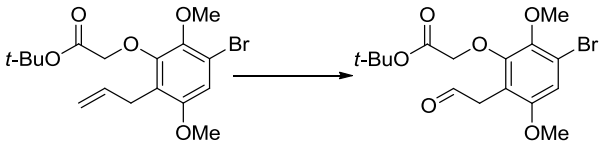
**_tert_-Butyl 2-(2-allyl-5-bromo-3,6-dimethoxyphenoxy)acetate 178**




To a solution of 2-allyl-5-bromo-3,6-dimethoxyphenol **164** (0.744 g, 2.72 mmol) in dry acetonitrile (45 mL) was added anhydrous potassium carbonate (0.564 g, 4.08 mmol) and sodium iodide (40.6 mg, 0.27 mmol). The resulting mixture was heated to reflux, under argon, for 30 min, upon which *tert*-butyl bromoacetate (0.48 mL, 3.26 mmol) was added dropwise. After heating for 15 h, the reaction mixture was allowed to cool to room temperature and then water (40 mL) and ethyl acetate (40 mL) were added. The organic phase was separated and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with water (100 mL), dried over magnesium sulfate and evaporated *in vacuo*. The resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give the *title compound* **178** as colourless oil (0.928 g, 88%); (Found: M+$Na^+$, 409.0612. $C_{17}H_{23}{}^{79}BrO_5$+$Na^+$ requires 409.0621); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 2982, 2939, 1749, 1637, 1590, 1572, 1475, 1412, 1240, 1159, 1133, 1038, 909, 843; $\delta_H$ (400 MHz; $CDCl_3$) 6.80 (1 H, s, ArH), 5.93 (1 H, ddt, *J* 17.5, 9.8, 6.0, H-

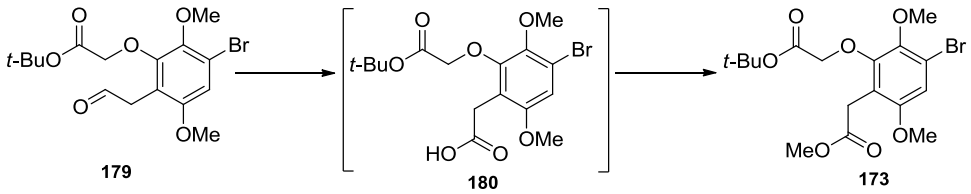
2'), 4.95 (1 H, dd, *J* 17.5, 1.7, H-3'$_{trans}$), 4.93 (1 H, dd, *J* 9.8, 1.7, H-3'$_{cis}$), 4.49 (2 H, s, $OCH_2$), 3.80 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.47 (2 H, d, *J* 6.0, H-1'), 1.50 (9 H, s, *t*-butyl); $\delta_C$ (100 MHz; $CDCl_3$) 168.2 (C), 154.4 (C), 151.3 (C), 144.0 (C), 136.5 (CH), 122.7 (C), 114.7 (C), 114.6 ($CH_2$), 110.5 (CH), 81.8 (C), 70.6 ($CH_2$), 61.0 (Me), 56.1 (Me), 28.1 ($CH_2$), 27.8 (Me); *m/z* (ESI) 411/409 ($M+Na^+$, 99/100%).

**_tert_-Butyl 2-(3-bromo-2,5-dimethoxy-6-(2-oxoethyl)phenoxy)acetate 179**



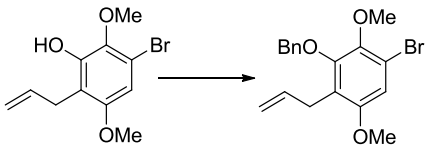

Ozone was bubbled through a solution of *tert*-butyl 2-(2-allyl-5-bromo-3,6-dimethoxyphenoxy)acetate **178** (887 mg, 2.29 mmol) in dichloromethane (15 mL) at –78 ºC, over 40 min. Triphenylphosphine (1.862 g, 7.10 mmol) was added and the reaction mixture was warmed to room temperature over 2 h and washed with water (15 mL) and brine (15 mL). The organic layer was dried over magnesium sulfate, concentrated *in vacuo* and the resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (5% to 20%), to give the *title compound* **179** as colourless oil (523 mg, 59%) and starting material (221 mg, 25%); (Found: $M+Na^+$, 411.0402. $C_{16}H_{21}{}^{79}BrO_6+Na^+$ requires 411.0414); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2982, 2940, 2838, 2733, 1724, 1593, 1477, 1413, 1370, 1241, 1125, 909, 842; $\delta_H$ (400 MHz; $CDCl_3$) 9.67 (1 H, t, *J* 1.4, CHO), 6.83 (1 H, s, ArH), 4.57 (2 H, s, $OCH_2$), 3.87 (2 H, d, *J* 1.4, $CH_2$), 3.79 (3 H, s, OMe), 3.75 (3 H, s, OMe), 1.46 (9 H, s, *t*-butyl); $\delta_C$ (100 MHz; $CDCl_3$) 199.6 (CH), 168.2 (C), 154.5 (C), 151.5 (C), 143.7 (C), 116.4 (C), 116.0 (C), 110.3 (CH), 82.1 (C), 70.2 ($CH_2$), 60.9 (Me), 56.1 (Me), 39.2 ($CH_2$), 28.1 (Me); *m/z* (ESI) 413/411 ($M+Na^+$,60/62%).

***tert*-Butyl 2-(3-bromo-2,5-dimethoxy-6-(2-methoxy-2-oxoethyl)phenoxy)acetate 173**



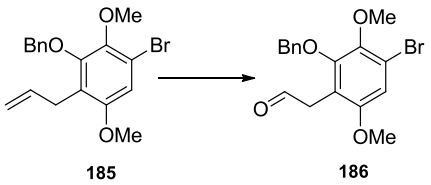

To a stirred solution of *tert*-butyl 2-(3-bromo-2,5-dimethoxy-6-(2-oxoethyl)phenoxy)acetate **179** (462 mg, 1.18 mmol) in 2-methyl-2-butene (2.6 mL) and *tert*-butanol (14 mL) at 0 ºC was added a solution of sodium chlorite (182 mg, 2.02 mmol) in aqueous sodium dihydrogen phosphate (1 M; 1.73 mL, 1.73 mmol). After 1 h, the reaction was quenched with water (7 mL) and extracted with dichloromethane (3 × 8 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude acid was dissolved in toluene:methanol (20 mL: 5 mL) and trimethylsilyldiazomethane (2.0 M in ether; 0.59 mL, 1.18 mmol) was added dropwise. The resulting mixture was stirred at room temperature until bubbling ceased (1.5 h). The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give the *title compound* **173** as a yellow oil (462 mg, 93%); (Found: M+$Na^+$, 441.0528. $C_{17}H_{23}{}^{79}BrO_7$+$Na^+$ requires 441.0519); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2982, 2940, 1746, 1596, 1576, 1479, 1414, 1243, 1121, 1047, 1004; $\delta_H$ (400 MHz; $CDCl_3$) 6.81 (1 H, s, ArH), 4.56 (2 H, s, $OCH_2$), 3.81 (2 H, s, $CH_2$), 3.80 (3 H, s, OMe), 3.76 (3 H, s, OMe), 3.70 (3 H, s, $CO_2$Me), 1.48 (9 H, s, *t*-butyl); $\delta_C$ (100 MHz; $CDCl_3$) 171.9 (C), 168.3 (C), 154.5 (C), 151.6 (C), 143.8 (C), 117.5 (C), 116.1 (C), 110.4 (CH), 81.8 (C), 70.4 ($CH_2$), 61.0 (Me), 56.1 (Me), 51.9 (Me), 29.4 ($CH_2$), 28.1 (Me); *m/z* (ESI) 443/441 (M+$Na^+$, 100/98%).

**2-Allyl-3-(benzyloxy)-5-bromo-1,4-dimethoxybenzene 185**



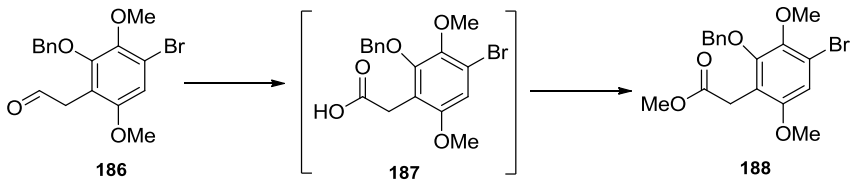

To a solution of 2-allyl-5-bromo-3,6-dimethoxyphenol **164** (1.32 g, 4.84 mmol) in THF (40 mL) at 0 ºC under argon, was added sodium hydride (60% dispersion in mineral oil; 213 mg, 5.32 mmol). After 15 min, benzyl bromide (0.63 mL, 5.32 mmol) was added dropwise, followed by tetrabutylammonium iodide (357 mg, 0.968 mmol). After stirring for 16 h at room temperature, water (40 mL) was added and the mixture was extracted into ether (2 × 40 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by column chromatography, eluting with light petroleum to light petroleum/ethyl acetate (9:1) to give the *title compound* **185** as a colourless solid (1.60 g, 91%); mp 60-62 ºC; (Found: $M+Na^+$, 385.0414. $C_{18}H_{19}Br^{79}BrO_3+Na^+$ requires 385.0410);$\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2939, 2838, 1637, 1588, 1572, 1474, 1413, 1129, 996, 913; $\delta_H$ (400 MHz; $CDCl_3$) 7.46 (2 H, d, *J* 6.8, H-Bn), 7.42-7.33 (3 H, m, H-Bn), 6.83 (1 H, s, H-6), 5.91 (1 H, ddt, *J* 17.7, 9.4, 6.1, H-2'), 5.02 (2 H, s, $CH_2$-Bn), 4.94 (1 H, dd, *J* 17.7, 1.6, H-3'$_{trans}$), 4.93 (1 H, dd, *J* 9.4, 1.6, H-3'$_{cis}$), 3.84 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.36 (2 H, d, *J* 6.1, H-1'); $\delta_C$ (100 MHz; $CDCl_3$) 154.6 (C), 151.4 (C), 144.9 (C), 137.4 (C), 136.4 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 123.0 (C), 114.8 (C), 114.7 ($CH_2$), 110.3 (CH), 75.3 ($CH_2$), 60.9 (Me), 56.1 (Me), 28.3 ($CH_2$); *m/z* (ESI) 387/385 ($M+Na^+$, 94/100%).

**2-(2-(Benzyloxy)-4-bromo-3,6-dimethoxyphenyl)acetaldehyde 186**




Ozone was bubbled through a solution of 2-allyl-3-(benzyloxy)-5-bromo-1,4-dimethoxybenzene **185** (150 mg, 0.413 mmol) in anhydrous dichloromethane (15 mL) at –78 ºC, until the solution turned blue (≈ 10 min). Triphenylphosphine (325 mg, 1.24 mmol) was then added and the reaction mixture was warmed to room temperature over 2 h, before being washed with water (15 mL) and brine (15 mL). The organic layer was dried over magnesium sulfate, concentrated in *vacuo* and the resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1), to give the *title compound* **186** as a colourless solid (130 mg, 86%); mp 56-57 ºC; (Found: M+$Na^+$, 387.0185. $C_{17}H_{17}{}^{79}BrO_4$+$Na^+$ requires 387.0202); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2965, 2940, 2732, 1724, 1574, 1476, 1415, 1117, 1049; $\delta_H$ (400 MHz; $CDCl_3$) 9.43 (1 H, t, *J* 2.0, CHO), 7.38-7.33 (5 H, m, H-Bn), 6.85 (1 H, s, ArH), 5.04 (2 H, s, $CH_2$-Bn), 3.87 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.55 (2 H, d, *J* 2.0, $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 199.5 (CH), 154.5 (C), 151.6 (C), 144.8 (C), 136.7 (C), 128.6 (CH), 128.4 (CH), 116.5 (C), 116.3 (C), 110.3 (CH), 75.5 ($CH_2$), 61.0 (Me), 56.0 (Me), 39.2 ($CH_2$); *m/z* (ESI) 389/387 (M+$Na^+$, 95/100%).

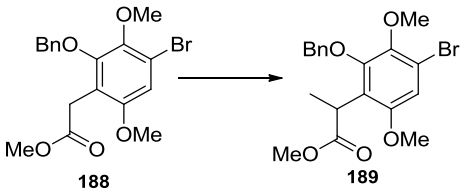
**Methyl 2-(2-(benzyloxy)-4-bromo-3,6-dimethoxyphenyl)acetate 188**




To a stirred solution of 2-(2-(benzyloxy)-4-bromo-3,6-dimethoxyphenyl)acetaldehyde **186** (1.10 g, 3.01 mmol) in 2-methyl-2-butene (6.6 mL) and *tert*-butanol (33 mL) at 0 ºC was

added a solution of sodium chlorite (463 mg, 5.12 mmol) in aqueous sodium dihydrogen phosphate (1 M; 4.40 mL, 4.40 mmol). After addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 1 h, before being quenched with citric acid (0.5 M; 17 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude acid was dissolved in dry methanol (19 mL), cooled to 0 ºC and stirred for 10 min. To this was added thionyl chloride (1.05 mL, 14.4 mmol) dropwise, over 5 min and the resulting mixture was allowed to warm to room temperature over 16 h. The solvent was then evaporated under reduced pressure and the resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate 9:1 to give the *title compound* **188** as a colourless solid (1.09 g, 91 %); mp 62-63 ºC; (Found: C, 54.58; H, 4.85. $C_{18}H_{19}BrO_5$ requires C, 54.70; H, 4.85); (Found: M+$Na^+$, 417.0293. $C_{18}H_{19}{}^{79}BrO_5$+$Na^+$ requires 417.0308); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3009, 2940, 2840, 1735, 1592, 1575, 1478, 1465, 1341, 1113, 1002; $\delta_H$ (400 MHz; $CDCl_3$) 7.43-7.32 (5 H, m, H-Bn), 6.83 (1 H, s, H-5), 5.05 (2 H, s, $CH_2$-Bn), 3.85 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.62 (3 H, s, $CO_2$Me), 3.59 (2 H, s, $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 171.8 (C), 154.5 (C), 151.6 (C), 144.6 (C), 137.1 (C), 128.5 (CH), 128.3 (CH), 128.2 (CH), 117.8 (C), 116.2 (C), 110.3 (CH), 75.3 ($CH_2$), 60.9 (Me), 56.1 (Me), 51.9 (Me), 29.5 ($CH_2$); *m/z* (ESI) 419/417 (M+$Na^+$, 95/100%);

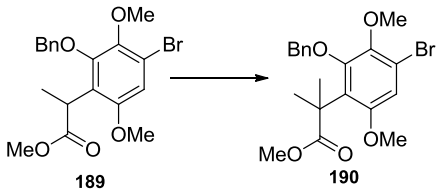
**(*R*/*S*)-Methyl 2-(2-(benzyloxy)-4-bromo-3,6-dimethoxyphenyl)propanoate 189**




To a solution of methyl 2-(2-(benzyloxy)-4-bromo-3,6-dimethoxyphenyl)acetate **188** (400 mg, 1.01 mmol) in dry THF (16 mL) at −78 ºC under argon, was added lithium *bis*(trimethylsilyl)amide (1.0 M in THF; 2.63 mL, 2.63 mmol), dropwise over 10 min. After

stirring for 1.5 h at −78 ºC, iodomethane (0.19 mL, 3.03 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature over 18 h. Saturated aqueous ammonium chloride solution (15 mL) was then added and the mixture was extracted into ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water (30 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (8:2) to give the *title compound* **189** as a colourless solid (391 mg, 94%); mp 60-63 ºC; (Found: $M+Na^+$, 431.0477. $C_{19}H_{21}{}^{79}BrO_5+Na^+$ requires 431.0465); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2940, 1734, 1589, 1572, 1497, 1476, 1463, 1373, 1239, 1124, 1031; $\delta_H$ (400 MHz; $CDCl_3$) 7.45-7.34 (5 H, m, H-Bn), 6.82 (1 H, s, H-5), 5.07 (1 H, d, *J* 14.2, $CH_2$-Bn), 5.05 (1 H, d, *J* 14.2, $CH_2$-Bn), 4.10 (1 H, q, *J* 7.0, C<u>H</u>(Me)$CO_2$Me), 3.84 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.57 (3 H, s, $CO_2$<u>Me</u>), 1.31 (3 H, d, *J* 7.0, Me); $\delta_C$ (100 MHz; $CDCl_3$) 174.7 (C), 153.9 (C), 150.7 (C), 144.7 (C), 137.1 (C), 128.5 (CH), 128.3 (CH), 128.2 (CH), 124.9 (C), 115.7 (C), 110.6 (CH), 75.4 ($CH_2$), 60.8 (Me), 56.0 (Me), 51.7 (Me), 35.5 (CH), 15.9 (Me); *m/z* (ESI) 433/431 ($M+Na^+$, 98/100%).

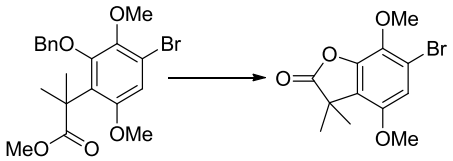
**Methyl 2-(2-(benzyloxy)-4-bromo-3,6-dimethoxyphenyl)-2-methylpropanoate 190**




To a solution of methyl 2-(2-(benzyloxy)-4-bromo-3,6-dimethoxyphenyl)propanoate **189** (301 mg, 0.74 mmol) in THF (7 mL) at 0 ºC under argon, was added lithium *bis*(trimethylsilyl)amide (1.0 M in THF; 1.25 mL, 1.25 mmol), dropwise over 10 min. The resulting mixture was stirred at 0 ºC for 45 min and then iodomethane (0.27 mL, 4.42 mmol) was added dropwise. After stirring for 20 h at room temperature, saturated aqueous ammonium chloride solution (10 mL) was added and the mixture was extracted into ethyl

acetate (3 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (8:2) to give the *title compound* **190** as a colourless solid (238 mg, 76%); mp 101-102 ºC; (Found: M+$Na^+$, 445.0615. $C_{20}H_{23}{}^{79}BrO_5$+$Na^+$ requires 445.0621); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3091, 3067, 2982, 1809, 1731, 1580, 1567, 1462, 1408, 1241, 1136, 1021, 847; $\delta_H$ (400 MHz; $CDCl_3$) 7.49-7.32 (5 H, m, H-Bn), 6.82 (1 H, s, H-5), 5.02 (2 H, s, $CH_2$-Bn), 3.77 (3 H, s, OMe), 3.74 (3 H, s, OMe), 3.57 (3 H, s, $CO_2$Me), 1.59 (6 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 178.2 (C), 154.4 (C), 152.1 (C), 145.5 (C), 137.1 (C), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.7 (C), 115.6 (C), 111.1 (CH), 75.8 ($CH_2$), 60.9 (Me), 56.0 (Me), 51.8 (Me), 45.4 (C), 26.6 (Me); *m/z* (ESI) 447/445 (M+$Na^+$, 99/100%).

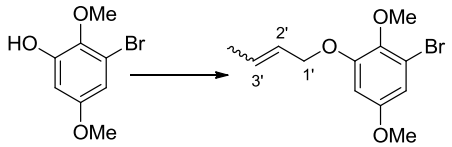
**6-bromo-4,7-dimethoxy-3,3-dimethylbenzofuran-2(3*H*)-one 192**




To a solution of methyl 2-(2-(benzyloxy)-4-bromo-3,6-dimethoxyphenyl)-2-methylpropanoate **191** (50.0 mg, 0.118 mmol) in anhydrous dichloromethane (5 mL) at –78 ºC under an argon atmosphere was added boron trichloride (1 M in hexane; 2.39 mL, 2.39 mmol) dropwise. After 3.5 h, methanol (5 mL) and saturated aqueous sodium hydrogen carbonate solution (5 mL) were added. The reaction mixture was allowed to reach room temperature over 30 min, stirred at room temperature for an additional 30 min and extracted into ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (8:2) to give the *title compound* **192** as a colourless solid (26.3 mg, 74%); mp 146-147 ºC; (Found: M+$H^+$,

301.0062. $C_{12}H_{13}{}^{79}BrO_4+H^+$ requires 301.0070); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2434, 2412, 1809, 1600, 1521, 1493, 1459, 1239, 952, 662; $\delta_H$ (400 MHz; $CDCl_3$) 6.82 (1 H, s, H-5), 3.94 (3 H, s, OMe), 3.82 (3 H, s, OMe), 1.54 (6 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 179.9 (C), 151.5 (C), 144.2 (C), 136.0 (C), 120.8 (C), 115.6 (C), 110.9 (CH), 61.1 (Me), 56.0 (Me), 43.5 (C), 23.0 (Me); *m/z* (ESI) 303/301 ($M+H^+$, 100/100%).

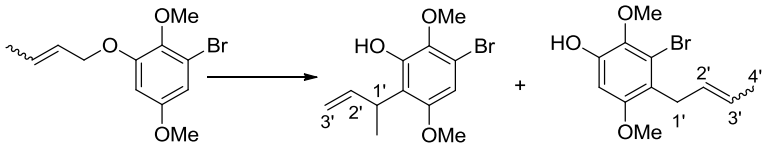
**(*E*/*Z*)-1-Bromo-3-(but-2-en-1-yloxy)-2,5-dimethoxybenzene 193**




To a stirred solution of 3-bromo-2,5-dimethoxyphenol **148** (2.58 g, 11.1 mmol) in anhydrous DMF (50 mL) under argon at 0 ºC was added sodium hydride (60% dispersion in mineral oils; 94 mg, 2.36 mmol). After stirring for 5 min, *trans*-1-bromo-2-butene (85%; 1.61 mL, 13.3 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 2.5 h. Saturated aqueous ammonium chloride solution (50 mL) was then added and the mixture was extracted into ether (3 × 50 mL). The combined organic extracts were washed with water (2 × 100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give the *title compound* **193** as a colourless oil (2.58 g, 87%, inseparable mixture *E*/*Z* 5:1); (Found: $M+Na^+$, 309.0091. $C_{12}H_{15}{}^{79}BrO_3+Na^+$ requires 309.0097); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2940, 160, 1572, 1489, 1428, 1377, 1266, 1175, 1055, 1003, 909; $\delta_H$ (400 MHz; $CDCl_3$) 6.64 (1 H, d, *J* 2.6, ArH-*Z*), 6.63 (1 H, d, *J* 2.8, ArH-*E*), 6.45 (1 H, d, *J* 2.6, ArH-*Z*), 6.44 (1H, d, *J* 2.8, ArH-*E*), 5.89-5.81 (1 H, m, H-2'-*E*), 5.79-5.68 (3 H, m, H-3'-*E* + H-2',3'-*Z*), 4.62 (2 H, d, *J* 6.0, H-1'-*Z*), 4.47 (2 H, d, *J* 5.6, H-1'-*E*), 3.80 (6 H, s, OMe-*E* + OMe-*Z*), 3.75 (6 H, s, OMe-*E* + OMe-*Z*), 1.75 (3 H, d, *J* 6.4, Me-*E*), 1.74 (3 H, d, *J* 5.2, Me-*Z*); $\delta_C$ (100 MHz; $CDCl_3$) 156.2 (C-*E*+*Z*), 153.1 (C-*E*+*Z*), 141.2 (C-*E*+*Z*), 130.6

(CH-*E*), 128.9 (CH-*Z*), 125.6 (CH-*E*), 125.2 (CH-*Z*), 117.5 (C-*E*+*Z*), 108.2 (CH-*Z*), 108.1 (CH-*E*), 101.5 (CH-*E*), 101.4 (CH-*Z*), 69.7 ($CH_2$-*E*), 64.9 ($CH_2$-*Z*), 60.6 (Me-*E*+*Z*), 55.7 (Me-*E*+*Z*), 17.8 (Me-*E*), 13.4 (Me-*Z*); *m/z* (ESI) 311/309 ($M+Na^+$, 99/100%).

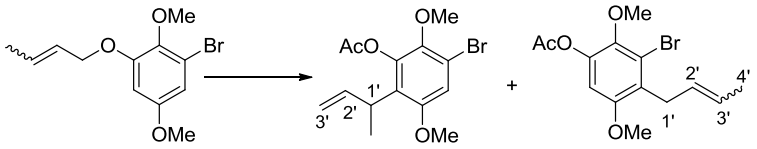
**(*R*/*S*)-3-Bromo-6-(but-3-en-2-yl)-2,5-dimethoxyphenol 194**




A solution of 1-bromo-3-(but-2-en-1-yloxy)-2,5-dimethoxybenzene **193** (123.9 mg, 0.43 mmol) in anhydrous DMF (2 mL) was heated to 200 ºC for 60 min in a microwave reactor (300 W). The solvent was evaporated and the resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give compounds **194** and **198**; the *title compound* **194** (65.6 mg, 53%) was collected as a colourless oil; (Found: $M+Na^+$, 309.0092. $C_{12}H_{15}{}^{79}BrO_3+Na^+$ requires 309.0097); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3520, 3078, 3010, 2967, 2908, 2839, 1603, 1577, 1483, 1417, 1369, 1239, 1104, 1045, 915; $\delta_H$ (400 MHz; $CDCl_3$) 6.56 (1 H, s, H-4), 6.24 (1 H, ddd, *J* 17.1, 10.1, 6.6, H-2'), 5.87 (1 H, s, OH), 5.07 (1 H, ddd, *J* 17.1, 1.7, 1.6, H-3'$_{trans}$), 4.99 (1 H, ddd, *J* 10.1, 1.7, 1.6, H-3'$_{cis}$), 4.09-4.02 (1 H, m, H-1'), 3.85 (3 H, s, OMe), 3.76 (3 H, s, OMe), 1.37 (3 H, d, *J* 7.2, Me); $\delta_C$ (100 MHz; $CDCl_3$) 154.6 (C), 148.4 (C), 141.9 (CH), 139.1 (C), 119.8 (C), 113.1 ($CH_2$), 112.4 (C), 106.7 (CH), 61.2 (Me), 56.0 (Me), 33.9 (CH), 18.0 (Me); *m/z* (ESI) 311/309 ($M+Na^+$, 98/100%); Compound **198** was collected as a colourless oil (35.9 mg, 29%, inseparable mixture *E*+*Z* 2:1); (Found: $M+Na^+$, 309.0090. $C_{12}H_{15}{}^{79}BrO_3+Na^+$ requires 309.0097); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3532, 3010, 2940, 1608, 1584, 1479, 1465, 1417, 1314, 1192, 1123, 1033, 985, 831; $\delta_H$ (400 MHz; $CDCl_3$) 6.51 (2 H, s, H-6-*E* + H-6-*Z*), 5.58 (2 H, s, OH-*E* + OH-*Z*), 5.54-5.33 (4 H, m, H-2',3'-*E* + H-2',3'-*Z*), 3.84 (6 H, s, OMe-*E* + OMe-*Z*), 3.77 (6 H, s, OMe-*E* + OMe-*Z*), 3.50 (2 H, d, *J* 6.8, H-1'-*Z*), 3.42-3.40 (2 H, m, H-1'-*E*), 1.78 (3 H, d, *J* 6.8, Me-*Z*),

1.62 (3 H, d, *J* 4.4, Me-*E*); $\delta_C$ (100 MHz; $CDCl_3$) 154.8 (C-*Z*). 154.7 (C-*E*), 147.9 (C-*E*+*Z*), 137.9 (C-*E*+*Z*), 127.8 (CH-E), 127.7 (CH-*Z*), 125.7 (CH-*E*), 124.2 (CH-*Z*), 121.8 (C-*Z*), 121.4 (C-*E*), 119.2 (C-*E*), 119.0 (C-*Z*), 98.5 (CH, *E*+*Z*), 61.1 (Me, *E*+*Z*), 56.1 (Me, *E*), 56.0 (Me, *Z*), 32.2 ($CH_2$, *E*), 27.5 ($CH_2$, *Z*), 17.9 (Me, *E*), 13.1 (Me, *Z*); *m/z* (ESI) 311/309 ($M+Na^+$, 98/100%).

**(*R*/*S*)-3-Bromo-6-(but-3-en-2-yl)-2,5-dimethoxyphenyl acetate 199**

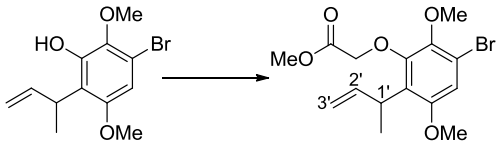



193 199 200

1-Bromo-3-(but-2-en-1-yloxy)-2,5-dimethoxybenzene **193** (71.8 mg, 0.25 mmol), acetic anhydride (1.83 mL) and *N*,*N*-diethylaniline (1.83 mL) were stirred together at 200 ºC for 19 h and then cooled to room temperature. Ice was added to the reaction and the resulting mixture was stirred vigorously for 15 min, and then extracted into ether (3 × 2 mL). The combined organic extracts were washed with water (4 × 2 mL), hydrochloric acid (2 M; 4 × 2 mL), saturated sodium hydrogen carbonate (4 × 2 mL) and brine (10 mL), before being dried over magnesium sulfate and concentrated *in vacuo*. The resulting residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give compounds **199** and **200**; The *title compound* **199** (29.0 mg, 35%) was collected as a yellow oil; (Found: $M+Na^+$, 351.0202. $C_{14}H_{17}{}^{79}BrO_3+Na^+$ requires 351.0202); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2970, 2939, 1770, 1636, 1596, 1477, 1464, 1369, 1192, 1096, 1016, 929, 877, 834; $\delta_H$ (400 MHz; $CDCl_3$) 6.91 (1 H, s, H-4), 6.07 (1 H, ddd, *J* 17.0, 10.3, 5.8, H-2'), 5.02 (1 H, ddd, *J* 17.0, 1.7, 1.6, H-3'$_{trans}$), 4.98 (1 H, ddd, *J* 10.3, 1.7, 1.6, H-3'$_{cis}$), 3.85-3.79 (1 H, m, H-1'), 3.79 (3 H, s, OMe), 3.77 (3 H, s, OMe), 2.29 (3 H, s, Me-Ac), 1.32 (3 H, d, *J* 7.2, Me); $\delta_C$ (100 MHz; $CDCl_3$) 168.6 (C), 154.1 (C), 143.7 (C), 143.7 (C), 141.1 (CH), 127.3 (C), 114.4 (C), 112.9 (CH), 112.8 ($CH_2$), 61.0 (Me), 56.1 (Me), 34.1 (CH), 20.7 (Me), 17.5 (Me);

*m/z* (ESI) 353/351 ($M+Na^+$, 98/100%); Compound **200** was collected as a colourless oil (29.7 mg, 36%, inseparable mixture *E*+*Z* 1.8:1); (Found: $M+Na^+$, 351.0204. $C_{14}H_{17}{}^{79}BrO_3+Na^+$ requires 351.0202); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2939, 2853, 1767, 1597, 1578, 1477, 1396, 1370, 1328, 1192, 1112, 1038, 911; $\delta_H$ (400 MHz; $CDCl_3$) 6.57 (2 H, s, H-6-*E* + H-6-*Z*), 5.56-5.34 (4 H, m, H-2',3'-*E* + H-2',3'-*Z*), 3.78 (6 H, s, OMe-E + OMe-*Z*), 3.77 (6 H, s, OMe-*E* + OMe-*Z*), 3.57 (2 H, d, *J* 6.9, H-1'-*Z*), 3.49-3.48 (2 H, m, H-1'-*E*), 2.34 (6 H, s, Me-Ac-*E* + Me-Ac-*Z*), 1.78 (3 H, d, *J* 6.0, Me-*Z*), 1.63 (3 H, d, *J* 4.5, Me-*E*); $\delta_C$ (100 MHz; $CDCl_3$) 168.9 (C-*E*+*Z*), 154.0 (C-*Z*), 153.9 (C-*E*), 142.8 (C-*E*+*Z*), 142.5 (C-*Z*), 142.4 (C-*E*), 128.5 (C-*Z*), 128.1 (C-*E*), 127.0 (CH-*E*), 126.9 (CH-*Z*), 126.3 (CH-*E*), 124.7 (CH-*Z*), 121.2 (C-*E*), 121.1 (C-*Z*), 105.2 (CH, *E*+*Z*), 61.0 (Me-*E*+*Z*), 56.1 (Me, *E*), 56.0 (Me, *Z*), 32.9 ($CH_2$-*E*), 28.1 ($CH_2$-*Z*), 20.7 (2 Me-*E*+*Z*), 17.9 (Me-*E*), 13.1 (Me-*Z*); *m/z* (ESI) 353/351 ($M+Na^+$, 96/100%)

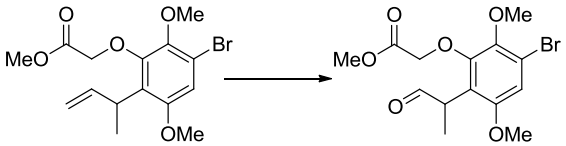
**(*R*/*S*)-Methyl 2-(3-bromo-6-(but-3-en-2-yl)-2,5-dimethoxyphenoxy)acetate 195**




To a solution of 3-bromo-6-(but-3-en-2-yl)-2,5-dimethoxyphenol **194** (1.19 g, 4.15 mmol) in anhydrous DMF (10 mL) under argon, was added anhydrous potassium carbonate (2.29 g, 16.6 mmol) followed by methyl bromoacetate (0.47 mL, 4.98 mmol). After stirring at 50 ºC for 3 h, the reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted into ethyl acetate (3 × 10 mL). The combined organic extracts were washed with water (3 × 20 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give the *title compound* **195** as a colourless oil (1.31 g, 88%); (Found: $M+Na^+$, 381.0307. $C_{15}H_{19}{}^{79}BrO_5+Na^+$ requires 381.0308); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3080, 3002,

2838, 1759, 1635, 1587, 1473, 1410, 1239, 1128, 1016, 917 ; $\delta_H$ (400 MHz; $CDCl_3$) 6.80 (1 H, s, H-4), 6.17 (1 H, ddd, *J* 17.2, 10.2, 6.9, H-2'), 4.97 (1 H, dd, *J* 17.2, 1.4, H-3'$_{trans}$), 4.92 (1 H, dd, *J* 10.2, 1.4, H-3'$_{cis}$), 4.58 (2 H, d, *J* 3.8, OC$\underline{H_2}$), 4.11 (1 H, quin, *J* 6.9, H-1'), 3.81 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.76 (3 H, s, $CO_2\underline{Me}$), 1.37 (3 H, d, *J* 6.9, Me); $\delta_C$ (100 MHz; $CDCl_3$) 169.4 (C), 154.7 (C),150.6 (C), 144.3 (C), 142.2 (CH), 128.0 (C), 114.7 (C), 112.9 ($CH_2$), 111.3 (CH), 69.9 ($CH_2$), 61.1 (Me), 55.9 (Me), 51.9 (Me), 34.5 (CH), 18.7 (Me); *m/z* (ESI) 383/381 ($M+Na^+$, 95/100%);

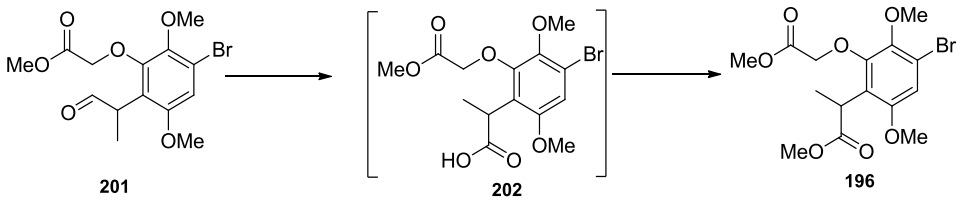
**(*R*/*S*)-Methyl 2-(3-bromo-2,5-dimethoxy-6-(1-oxopropan-2-yl)phenoxy)acetate 201**




Ozone was bubbled through a solution of methyl 2-(3-bromo-6-(but-3-en-2-yl)-2,5-dimethoxyphenoxy)acetate **195** (1.25 g, 3.48 mmol) in dichloromethane (30 mL) at −78 ºC, until the solution turned blue (≈ 15 min). Triphenylphosphine (2.84 g, 10.8 mmol) was added and the reaction mixture was warmed to room temperature over 2 h, before being washed with water (30 mL) and brine (30 mL). The organic layer was dried over magnesium sulfate, concentrated in *vacuo* and the resulting crude product was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1 to 8:2), to give the *title compound* **201** as a colourless solid (939 mg, 75%); mp 79-81 ºC; (Found: C, 46.53; H, 4.69. $C_{14}H_{17}BrO_6$ requires C, 46.56; H, 4.74); (Found: $M+Na^+$, 383.0100. $C_{14}H_{17}{}^{79}BrO_6+Na^+$ requires 383.0101); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3008, 2940, 2839, 1758, 1725, 1590, 1572, 1476, 1411, 1306, 1239, 1131, 1011, 908; $\delta_H$ (400 MHz; $CDCl_3$) 9.65 (1 H, s, CHO), 6.85 (1 H, s, H-4), 4.79 (1 H, d, *J* 16.1, OC$\underline{H_2}CO_2$Me), 4.64 (1 H, d, *J* 16.1, OC$\underline{H_2}CO_2$Me), 4.18 (1 H, q, *J* 7.0, C$\underline{H}$MeCHO), 3.80 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.73 (3 H, s, $CO_2\underline{Me}$), 1.36 (3 H, d, *J* 7.0, Me); $\delta_C$ (100 MHz; $CDCl_3$) 202.1 (CH), 169.3 (C), 154.2 (C), 150.7 (C), 143.9 (C),

122.6 (C), 116.5 (C), 111.0 (CH), 69.6 ($CH_2$), 61.0 (Me), 56.0 (Me), 52.0 (Me), 43.4 (CH), 13.1 (Me); *m/z* (ESI) 385/383 ($M+Na^+$, 100/99%).

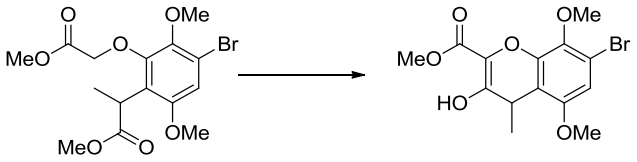
**(*R*/*S*)-Methyl 2-(4-bromo-3,6-dimethoxy-2-(2-methoxy-2-oxoethoxy)phenyl)propanoate 196**




To a stirred solution of methyl 2-(3-bromo-2,5-dimethoxy-6-(1-oxopropan-2-yl)phenoxy)acetate **201** (205 mg, 0.57 mmol) in 2-methyl-2-butene (1.3 mL) and *tert*-butanol (6.8 mL) at 0 ºC was added a solution of sodium chlorite (87 mg, 0.97 mmol) in aqueous sodium dihydrogen phosphate (1 M; 0.83 mL, 0.83 mmol). After addition, the ice-bath was removed and the reaction mixture was stirred at room temperature for 1 h, before being quenched with citric acid (0.5 M; 3.5 mL), extracted with dichloromethane (3 × 7 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude acid was dissolved in dry methanol (3.6 mL), cooled to 0 ºC and stirred for 10 min. To this, was added thionyl chloride (0.2 mL, 2.75 mmol) dropwise, over 5 min, and the resulting mixture was allowed to warm to room temperature, over 16 h. The solvent was then evaporated under reduced pressure and the resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give the *title compound* **196** as a colourless oil (151 mg, 68%); (Found: $M+Na^+$, 413.0209. $C_{15}H_{19}{}^{79}BrO_7+Na^+$ requires 413.0206); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3007, 2953, 2840, 1759, 1736, 1591, 1573, 1477, 1462, 1413, 1375, 1239, 1131, 1087, 1031, 974; $\delta_H$ (400 MHz; $CDCl_3$) 6.82 (1 H, s, H-5), 4.68 (1 H, d, *J* 15.8, OC<u>H</u>$_2$$CO_2$Me), 4.61 (1 H, d, *J* 15.8, OC<u>H</u>$_2$$CO_2$Me), 4.27 (1 H, q, *J* 7.1, C<u>H</u>Me$CO_2$Me), 3.80 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.75 (3 H, s, $CO_2$Me), 3.63 (3 H, s, $CO_2$Me), 1.40 (3 H, d, *J* 7.1, CH<u>Me</u>$CO_2$Me); $\delta_C$ (100 MHz; $CDCl_3$) 174.6 (C), 169.3 (C), 153.9 (C), 150.3 (C), 143.9 (C), 124.5 (C), 115.7

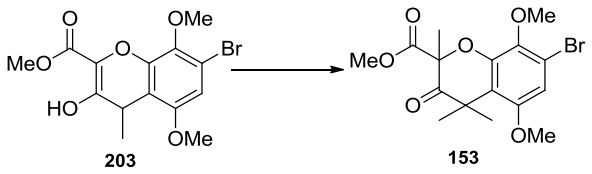
(C), 111.1 (CH), 69.9 ($CH_2$), 61.1 (Me), 56.1 (Me), 52.0 (Me), 51.8 (Me), 35.4 (CH), 15.9 (Me); *m/z* (ESI) 415/413 ($M+Na^+$, 98/100%).

**(*R*/*S*)-Methyl 7-bromo-3-hydroxy-5,8-dimethoxy-4-methyl-4*H*-chromene-2-carboxylate 203**



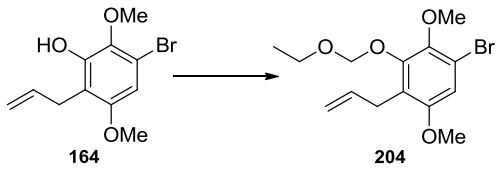

To a stirred solution of methyl 2-(4-bromo-3,6-dimethoxy-2-(2-methoxy-2-oxoethoxy)phenyl)propanoate **196** (461 mg, 1.18 mmol) in THF (11 mL) at −78 ºC under argon, was added lithium *bis*(trimethylsilyl)amide (1 M in THF/ethylbenzene; 2.57 mL, 2.57 mmol) dropwise. After stirring for 3 h at −78 ºC, the reaction mixture was poured into an ice-cooled mixture of ethyl acetate (20 mL) and aqueous phosphate buffer pH 7.0 solution (20 mL). The organic phase was separated and the aqueous phase was further extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* **203** (406 mg, ≈96%) as a yellow oil, which was used in the next step without further purification; (Found: $M+Na^+$, 380.9953. $C_{14}H_{15}{}^{79}BrO_6+Na^+$ requires 380.9944); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2940, 2840, 1733, 1677, 1645, 1582, 1484, 1461, 1243, 1157, 1115, 1086, 986; $\delta_H$ (400 MHz; $CDCl_3$) 10.4 (1 H, s, OH), 6.68 (1 H, s, H-6), 3.92 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.80 (3 H, s, $CO_2Me$), 3.81 (1 H, q, *J* 6.8, H-4), 1.39 (1 H, d, *J* 6.8, Me); $\delta_C$ (100 MHz; $CDCl_3$) 167.1 (C), 158.3 (C), 152.8 (C), 144.9 (C), 139.6 (C), 121.0 (C), 114.9 (C), 114.0 (C), 108.1 (CH), 60.9 (Me), 55.9 (Me), 52.3 (Me), 30.2 (CH), 20.0 (Me); *m/z* (ESI) 383/381 ($M+Na^+$, 100/96%).

**(*R*/*S*)-Methyl 7-bromo-5,8-dimethoxy-2,4,4-trimethyl-3-oxochroman-2-carboxylate 153**



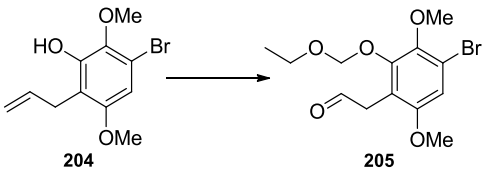

To a solution of methyl 7-bromo-3-hydroxy-5,8-dimethoxy-4-methyl-4*H*-chromene-2-carboxylate **203** (40.0 mg, 0.11 mmol) in THF (1.0 mL) at 0 ºC was added a solution of potassium *tert*-butoxide (27.6 mg, 0.25 mmol) in THF (1.0 mL), under an argon atmosphere. After stirring for 1 h at 0 ºC, iodomethane (41 µL, 0.67 mmol) was added and the reaction mixture was stirred for another hour at 0 ºC. After being warmed to 10 ºC over 1 h, water (3.0 mL) was added and the resulting mixture was extracted into ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine (9 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9.5:0.5 to 9:1) to give the *title compound* **153** as a colourless oil (8.9 mg, 21%); (Found: M+$Na^+$, 409.0259. $C_{16}H_{19}{}^{79}BrO_6$+$Na^+$ requires 409.0257); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 2941, 1754, 1731, 1594, 1572, 1482, 1457, 1435, 1254, 1136, 1094, 1042, 1024, 986; $\delta_H$ (400 MHz; $CDCl_3$) 6.71 (1 H, s, H-6), 3.95 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.69 (3 H, s, $CO_2$Me), 1.77 (3 H, s, Me-2), 1.53 (3 H, s, Me-4), 1.48 (3 H, s, Me-4); $\delta_C$ (125 MHz; $CDCl_3$) 205.2 (C), 168.9 (C), 154.4 (C), 146.7 (C), 140.9 (C), 118.9 (C), 115.9 (C), 109.3 (CH), 82.7 (C), 60.8 (Me), 55.6 (Me), 52.8 (Me), 44.8 (C), 26.9 (Me), 24.0 (Me), 20.8 (Me); *m/z* (ESI) 411/409 (M+$Na^+$, 100/100%).

**2-Allyl-5-bromo-3-(ethoxymethoxy)-1,4-dimethoxybenzene 204**



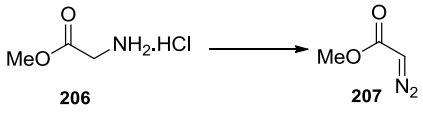

To a solution of 2-allyl-5-bromo-3,6-dimethoxyphenol **164** (430 mg, 1.57 mmol) in dichloromethane (20 mL) were added *N*,*N*-di*iso*propylethylamine (0.55 mL, 3.15 mmol) and chloromethylethyl ether (0.29 mL, 3.15 mmol) dropwise at 0 ºC under argon. After stirring for 17 h at room temperature, saturated aqueous ammonium chloride solution (15 mL) was added and the mixture was extracted into ether (2 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. The resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1) to give the *title compound* **204** as colourless oil (422 mg, 81%); (Found: $M+Na^+$, 353.0360. $C_{14}H_{19}{}^{79}BrO_4+Na^+$ requires 353.0359); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 2980, 2939, 1637, 1589, 1572, 1474, 1421, 1307, 960; $\delta_H$ (400 MHz; $CDCl_3$) 6.80 (1 H, s, H-6), 5.94 (1 H, ddt, *J* 17.5, 9.8, 6.0, H-2'), 5.16 (2 H, s, $OC\underline{H_2}OCH_2Me$), 4.97 (1 H, dd, *J* 17.5, 1.7, H-3'$_{trans}$), 4.95 (1 H, dd, *J* 9.8, 1.7, H-3'$_{cis}$), 3.82 (2 H, q, *J* 7.2, $OCH_{\underline{2}}Me$), 3.79 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.41 (2 H, d, *J* 6.0, H-1'), 1.25 (3 H, t, *J* 7.2, $OCH_2\underline{Me}$); $\delta_C$ (100 MHz; $CDCl_3$) 154.6 (C), 149.7 (C), 144.3 (C), 136.3 (CH), 122.9 (C), 114.7 ($CH_2$), 114.7 (C), 110.5 (CH), 98.0 ($CH_2$), 65.7 ($CH_2$), 60.7 (Me), 56.1 (Me), 28.3 ($CH_2$), 15.2 (Me); *m/z* (ESI) 355/353 ($M+Na^+$, 93/100%).

**2-(4-Bromo-2-(ethoxymethoxy)-3,6-dimethoxyphenyl)acetaldehyde 205**




Ozone was bubbled through a solution of 2-allyl-5-bromo-3-(ethoxymethoxy)-1,4-dimethoxybenzene **204** (84.8 mg, 0.26 mmol) in dichloromethane (10 mL) at –78 ºC, until the solution turned blue (≈ 10 min). Triphenylphosphine (201 mg, 0.77 mmol) was then added and the reaction mixture was warmed to room temperature over 2 h. The reaction mixture was washed with water (10 mL), brine (10 mL) and the organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The resulting oil was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1), to give the *title compound* **205** as a colourless solid (73.0 mg, 86%); mp 63-64 ºC; (Found: M+$Na^+$, 355.0142. $C_{13}H_{17}{}^{79}BrO_5$+$Na^+$ requires 355.0152); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 2980, 2940, 1724, 1591, 1575, 1476, 1107, 954; $\delta_H$ (400 MHz; $CDCl_3$) 9.68 (1 H, t, *J* 1.6, CHO), 6.85 (1 H, s, H-5), 5.17 (2 H, s, OC<u>H</u>$_2$OCH$_2$Me), 3.80 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.74 (2 H, q, *J* 7.2, OC<u>H</u>$_2$Me), 3.71 (2 H, d, *J* 1.6, C<u>H</u>$_2$CHO), 1.22 (3 H, t, *J* 7.2, OCH$_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 199.6 (CH), 154.5 (C), 150.4 (C), 144.2 (C), 116.5 (C), 116.3 (C), 110.4 (CH), 98.1 ($CH_2$), 65.9 ($CH_2$), 60.7 (Me), 56.1 (Me), 39.2 ($CH_2$), 15.1 (Me); *m/z* (ESI) 357/355 (M+$Na^+$, 99/100%).

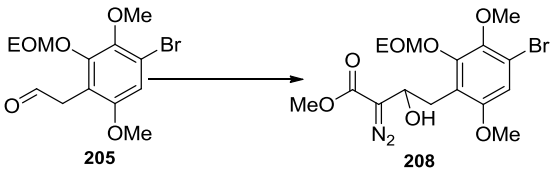
**Methyl diazoacetate 207[134]**




To a solution of glycine methyl ester hydrochloride **206** (1.64 g, 13.1 mmol) in water (3 mL) at room temperature, and protected from incident light was added dichloromethane (6.8 mL)

followed by aqueous sodium nitrite (5.0 M; 2.8 mL). The resulting mixture was cooled to −10 ºC and an aqueous solution of sulfuric acid (5 wt %; 1.1 mL) was added dropwise at a rate that maintained the temperature below −8 ºC. The mixture was allowed to stir for 20 min and the layers were separated in a cold separatory funnel. The aqueous layer was extracted into dichloromethane (3 × 6 mL) and the combined organic layers were washed with saturated aqueous hydrogen carbonate until neutral, dried over magnesium sulfate, filtered and concentrated *in vacuo* at room temperature. The *title compound* **207** was collected as a yellow oil (1.05 g, 80%); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2116, 1690, 1485, 1439, 1373, 1343, 1257, 1156, 1048; $\delta_H$ (400 MHz; $CDCl_3$) 4.74 (1 H, s, CH), 3.75 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 167.2 (C), 51.9 (Me), 46.1 (CH). Data in agreement with literature values.[134]

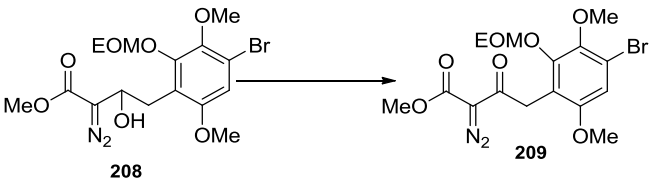
**(*R*/*S*)-Methyl 4-(4-bromo-2-(ethoxymethoxy)-3,6-dimethoxyphenyl)-2-diazo-3-hydroxybutanoate 208**




To a solution of freshly prepared methyl diazoacetate **207** (410 mg, 4.10 mmol) in anhydrous acetonitrile (16 mL) at room temperature, under argon atmosphere, were added a solution of 2-(4-bromo-2-(ethoxymethoxy)-3,6-dimethoxyphenyl)acetaldehyde **205** (810 mg, 2.43 mmol) in anhydrous acetonitrile (24 mL) and a solution of DBU (0.99 mL, 6.66 mmol) in anhydrous acetonitrile (24 mL), dropwise, over 1 h. The mixture was stirred for 3 h at room temperature, upon which phosphate buffer pH 7 solution (48 mL) was added. The mixture was extracted into ethyl acetate (3 × 50 mL) and the combined organic layers were washed with water (60 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (9:1 to 7:3) to give the *title compound* **208** as a yellow oil (784 mg, 74%); (Found: M+$Na^+$,

455.0430. $C_{16}H_{21}{}^{79}BrN_2O_7$+$Na^+$ requires 455.0424); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2099, 1686, 1599, 1574, 1475, 1439, 909; $\delta_H$ (400 MHz; $CDCl_3$) 6.82 (1 H, s, H-5), 5.23 (1 H, d, *J* 6.0, OC<u>H</u>$_2$OCH$_2$CH$_3$), 5.19 (1 H, d, *J* 6.0, OC<u>H</u>$_2$OCH$_2$Me), 4.89 (1 H, dd, *J* 13.5 and 5.6, CH$_2$C<u>H</u>OH) 3.80 (2 H, q, *J* 7.1, OC<u>H</u>$_2$Me), 3.79 (3 H, s, OMe), 3.77 (3 H, s, OMe), 3.76 (3 H, s, CO$_2$<u>Me</u>), 3.22-3.17 (2 H, m, C<u>H</u>$_2$CH<u>OH</u>), 3.09 (1 H, dd, *J* 13.5 and 5.6, C<u>H</u>$_2$CHOH), 1.25 (3 H, t, *J* 7.1, OCH$_2$<u>Me</u>); $\delta_C$ (125 MHz; $CDCl_3$) 166.6 (C), 154.6 (C), 150.7 (C), 144.1 (C), 119.6 (C), 115.8 (C), 110.4 (CH), 98.3 ($CH_2$), 66.1 (CH), 65.9 ($CH_2$), 60.6 (Me), 56.0 (Me), 51.8 (Me), 29.9 ($CH_2$), 15.1 (Me), diazo C unobserved; *m/z* (ESI) 457/455 (M+$Na^+$, 100/99%).

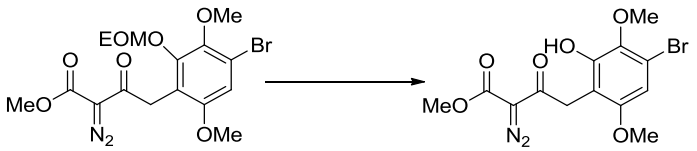
**Methyl 4-(4-bromo-2-(ethoxymethoxy)-3,6-dimethoxyphenyl)-2-diazo-3-oxobutanoate 209**




To a solution of methyl 4-(4-bromo-2-(ethoxymethoxy)-3,6-dimethoxyphenyl)-2-diazo-3-hydroxybutanoate **208** (763 mg, 1.76 mmol) in DMSO (30 mL) at room temperature under argon, was added 2-iodoxybenzoic acid (45 wt.%; 2.45 g, 8.80 mmol). The reaction mixture was warmed to 60 ºC and stirred for 20 min. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (50 mL) and washed successively with saturated aqueous sodium thiosulfate solution (50 mL), saturated aqueous sodium hydrogen carbonate (5 × 30 mL), water (3 × 30 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography, eluting with light petroleum/ethyl acetate (8:2) to give the *title compound* **209** as a colourless oil (608 mg, 80%); (Found: M+$Na^+$, 453.0267. $C_{16}H_{19}{}^{79}BrN_2O_7$+$Na^+$ requires 453.0268); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2137, 1719, 1658, 1594, 1576, 1475, 1438, 1305, 1239, 1104, 1047, 1021,

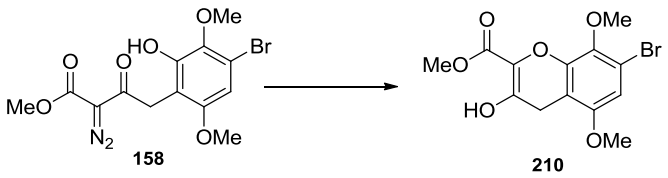
957; $\delta_H$ (400 MHz; $CDCl_3$) 6.81 (1 H, s, H-5), 5.14 (2 H, s, OC<u>H</u>$_2$OCH$_2$Me), 4.22 (2 H, s, C<u>H</u>$_2$CO), 3.88 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.72 (2 H, q, *J* 7.1, OC<u>H</u>$_2$Me), 3.73 (3 H, s, OMe), 1.21 (3 H, t, *J* 7.1, OCH$_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 189.1 (C), 161.9 (C), 154.6 (C), 150.3 (C), 144.1 (C), 117.9 (C), 116.1 (C), 110.4 (CH), 98.0 ($CH_2$), 65.8 ($CH_2$), 60.7 (Me), 56.1 (Me), 52.2 (Me), 36.2 ($CH_2$), 15.1 (Me), diazo C unobserved; *m/z* (ESI) 455/453 ($M+Na^+$, 99/100%).

**Methyl 4-(4-bromo-2-hydroxy-3,6-dimethoxyphenyl)-2-diazo-3-oxobutanoate 158**




Methyl 4-(4-bromo-2-(ethoxymethoxy)-3,6-dimethoxyphenyl)-2-diazo-3-oxobutanoate **209** (585 mg, 1.36 mmol) was dissolved in a solution of hydrochloric acid (37%) in methanol (v/v 3%; 16.5 mL) and stirred at room temperature for 2 h. After addition of water (16 mL), the resulting mixture was extracted into ethyl acetate (2 × 20 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (7:3), to give the *title compound* **158** as a colourless solid (488 mg, 96%); mp 146-147 ºC; (Found: $M+Na^+$, 394.9851. $C_{13}H_{13}{}^{79}BrN_2O_6+Na^+$ requires 394.9849); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3527, 2138, 1720, 1657, 1617, 1584, 1491, 1460, 1307, 1241, 1132, 1041, 939; $\delta_H$ (400 MHz; $CDCl_3$) 6.58 (1 H, s, H-5), 5.99 (1 H, s, OH), 4.19 (2 H, s, C<u>H</u>$_2$CO), 3.88 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.73 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 189.4 (C), 162.0 (C), 155.0 (C), 148.9 (C), 138.9 (C), 113.9 (C), 109.8 (C), 106.4 (CH), 61.3 (Me), 56.0 (Me), 52.3 (Me), 35.2 ($CH_2$), diazo C unobserved; *m/z* (ESI) 397/395 ($M+Na^+$, 100/97%).

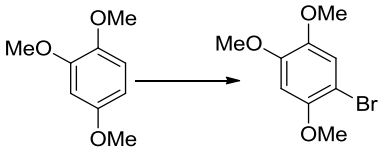
**Methyl 7-bromo-3-hydroxy-5,8-dimethoxy-4*H*-chromene-2-carboxylate 210**




To a solution of methyl 4-(4-bromo-2-hydroxy-3,6-dimethoxyphenyl)-2-diazo-3-oxobutanoate **158** (479 mg, 1.28 mmol) in anhydrous dichloromethane (18 mL) at room temperature, under argon, was added rhodium(II) acetate dimer (113 mg, 0.26 mmol). After stirring for 1 h, the mixture was filtered through Celite® and the solvent was removed *in vacuo* to give the *title compound* **210** as a beige solid (434 mg, 98%); mp 160-161 ºC; (Found: M+$Na^+$, 366.9784. $C_{13}H_{13}{}^{79}BrO_6$+$Na^+$ requires 366.9788); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1745, 1680, 1600, 1584, 1488, 1452, 1439, 1400, 1315, 1248, 1154, 1046; $\delta_H$ (400 MHz; $CDCl_3$) 10.5 (1 H, s, OH), 6.64 (1 H, s, ArH), 3.92 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.78 (3 H, s, $CO_2$Me), 3.50 (2 H, s, H-4); $\delta_C$ (100 MHz; $CDCl_3$) 166.9 (C), 153.4 (C), 153.0 (C), 144.7 (C), 139.5 (C), 121.6 (C), 115.0 (C), 107.9 (C), 107.4 (CH), 60.9 (Me), 55.9 (Me), 52.3 (Me), 24.5 ($CH_2$); *m/z* (ESI) 369/367 (M+$Na^+$, 98/100%).

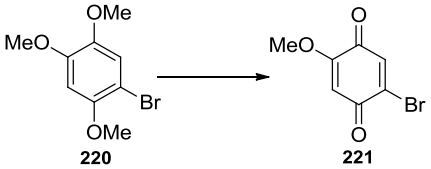
## *Experimental details for Chapter IV*

### 1-Bromo-2,4,5-trimethoxybenzene 220[147]




A solution of bromine (1.59 mL, 30.9 mmol) in dichloromethane (50 mL) was added dropwise at 0 ºC to a solution of 1,2,4-trimethoxybenzene **219** (4.39 mL, 29.4 mmol) in dichloromethane (200 mL) over 1 h. The resulting solution was stirred at 0 ºC for 2 min, washed with saturated aqueous sodium thiosulfate solution (100 mL), saturated sodium hydrogen carbonate solution (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the *title compound* **220** as a colourless oil which solidified on standing at room temperature (6.94 g, 96%); mp 52-54 ºC (lit.,[147] mp 53-54 ºC); (Found: $M+Na^+$, 268.9780. $C_9H_{11}{}^{79}BrO_3+Na^+$ requires 268.9784); $\delta_H$ (300 MHz; $CDCl_3$) 7.05 (1 H, s, ArH), 6.58 (1 H, s, ArH), 3.90 (3 H, s, OMe), 3.88 (3 H, s, OMe), 3.85 (3 H, s, OMe); $\delta_C$ (75 MHz; $CDCl_3$) 150.3 (C), 149.1 (C), 143.8 (C), 116.5 (CH), 101.9 (C), 98.9 (CH), 57.2 (Me), 56.7 (Me), 56.3 (Me); *m/z* (ESI) 271/269 ($M+Na^+$, 100/98%). Data in agreement with literature values.[139]

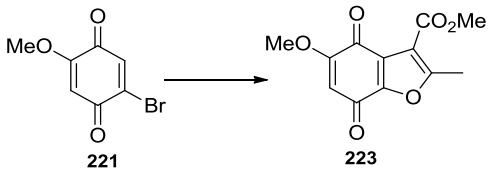
### 2-Bromo-5-methoxy-1,4-benzoquinone 221




A solution of ammonium cerium(IV) nitrate (20.5 g, 37.5 mmol) in water (100 mL) was added in one portion to a stirred solution of 1-bromo-2,4,5-trimethoxybenzene **220** (3.71 g, 15.2 mmol) in acetonitrile (100 mL) at room temperature. The resulting mixture was stirred

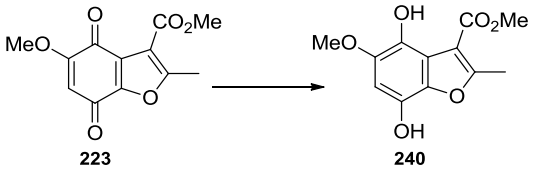
at room temperature for 16 h, concentrated to approximately half its volume *in vacuo* and extracted with dichloromethane (2 × 150 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to give the *title compound* **221** as an orange solid (2.91 g, 89%); mp 185-187 ºC (lit.,[148] mp 192-194 ºC); (Found: M+$Na^+$, 238.9309. $C_7H_5BrO_3$+$Na^+$ requires 238.9314); $\delta_H$ (300 MHz; $CDCl_3$) 7.26 (1 H, s, ArH), 6.14 (1 H, s, ArH), 3.88 (3 H, s, OMe); $\delta_C$ (75 MHz; $CDCl_3$) 179.2 (C), 158. 9 (C), 139.2 (C), 135.8 (CH), 106.9 (CH), 56.6 (Me); 1 C unobserved; *m/z* (ESI) 241/239 (M+$Na^+$, 59/59%). Data in agreement with literature values.[139]

**Methyl 4,7-dihydro-5-methoxy-2-methyl-4,7-dioxobenzofuran-3-carboxylate 223**



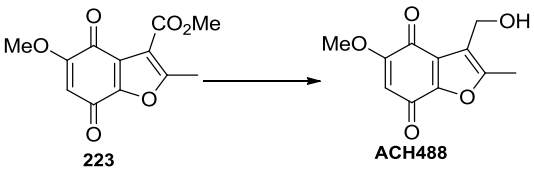

Acetonitrile (10 mL) was added to copper(II) acetate (299 mg, 1.38 mol), potassium carbonate (381 mg, 2.76 mmol), methyl acetoacetate (99 µL, 0.92 mmol) and 2-bromo-5-methoxy-1,4-benzoquinone **221** (200 mg, 0.92 mmol). The resulting mixture was stirred at reflux for 1.5 h, diluted with dichloromethane (40 mL), filtered through Celite® and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (2:1) to give the *title compound* **223** as a yellow solid (78.5 mg, 34%); mp 203-205 ºC; (Found: M+$Na^+$, 273.0365. $C_{12}H_{10}O_6$+$Na^+$ requires 273.0375); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1718, 1701, 1661, 1610, 1551, 1456, 1248, 1187, 1026, 992; $\lambda_{max}$ (acetonitrile)/nm 232 (log ε 4.17), 267 (log ε 3.87), 302 (log ε 3.92), 404 (log ε 3.08); $\delta_H$ (400 MHz; $CDCl_3$) 5.80 (1 H, s, H-6), 3.92 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.68 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 175.4 (C), 174.7 (C), 164.0 (C), 162.4 (C), 160.6 (C), 150.2 (C), 123.6 (C), 112.5 (C), 104.6 (CH), 57.0 (Me), 52.2 (Me), 14.0 (Me); *m/z* (ESI) 523 (2M+$Na^+$, 100%), 273 (M+$Na^+$, 65%).

**Methyl 4,7-dihydroxy-5-methoxy-2-methylbenzofuran-3-carboxylate 240**




To a solution of methyl 4,7-dihydro-5-methoxy-2-methyl-4,7-dioxobenzofuran-3-carboxylate **223** (200 mg, 0.80 mmol) in chloroform (4 mL) was added a solution of sodium dithionite (835 mg, 4.80 mmol) in water (8 mL) and the reaction mixture was stirred at room temperature for 3 h. The precipitate formed was filtered and dried *in vacuo* to yield the *title compound* **240** as a colourless solid (161 mg, 80%); mp 238-239 ºC; (Found: $M+Na^+$, 275.0527. $C_{12}H_{12}O_6+Na^+$ requires 275.0526); $\delta_H$ (400 MHz; DMSO-$d_6$) 9.64 (1 H, s, OH), 9.52 (1 H, s, OH), 6.52 (s, 1 H, H-6), 3.94 (3 H, s, $CO_2$Me), 3.72 (3 H, s, OMe), 2.67 (3 H, s, Me); $\delta_C$ (100 MHz; DMSO-$d_6$) 167.5 (C), 163.3 (C), 142.6 (C), 136.9 (C), 133.8 (C), 131.3 (C), 114.8 (C), 108.5 (C), 100.8 (CH), 57.0 (Me), 53.0 (Me), 14.9 (Me); *m/z* (ESI) 527 ($2M+Na^+$, 100%), 275 ($M+Na^+$, 40%).

**3-Hydroxymethyl-5-methoxy-2-methylbenzofuran-4,7-dione ACH488**




A solution of compound **223** (75.0 mg, 0.30 mmol) in THF (3 mL) was added at 0 ºC to a suspension of lithium aluminium hydride (57.0 mg, 1.50 mmol) in THF (6 mL), under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1.5 h, and then acetone (0.72 mL) and a solution of $FeCl_3.H_2O$ (1 M; 0.36 mL) in HCl (1 M; 0.36 mL) were added. The mixture was stirred at room temperature for 5 min and then extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with $H_2O$ (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting

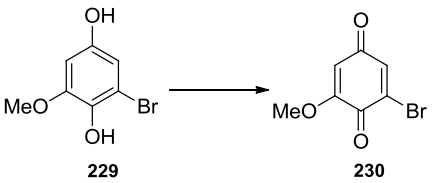
product was purified by column chromatography using light petroleum/EtOAc (2:1) to give the *title compound* **ACH488** (19.8 mg, 30%) as an orange solid; mp 183 ºC; (Found: M+$Na^+$, 245.0424. $C_{11}H_{10}O_5$+$Na^+$ requires 245.0420); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2360, 1666, 1602, 1554, 1187; $\delta_H$ (400 MHz; $CDCl_3$) 5.79 (s, 1 H, H-6), 4.62 (2 H, s, $CH_2$), 3.87 (3 H, s, OMe), 2.42 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 179.2 (C), 175.3 (C), 159.7 (C), 154.9 (C), 150.3 (C), 125.8 (C), 119.7 (C), 105.9 (CH), 56.9 (Me), 54.8 ($CH_2$), 12.0 (Me); *m/z* (ESI) 245 (M+$Na^+$, 42%).

**2-Bromo-6-methoxybenzene-1,4-diol 229**[149]




Sodium percarbonate (4.28 g, 27.3 mmol) was added as a single portion to a solution of 5-bromovanillin **228** (6.02 g, 26.0 mmol) in THF/water (75/30 mL). The resulting mixture was stirred at room temperature for 4 h, concentrated *in vacuo* to a solid, dissolved in acetone (250 mL), filtered and concentrated *in vacuo*. Chromatography of the residue eluting with light petroleum/ethyl acetate (2:1) gave the *title compound* **229** as a pale pink solid (4.61 g, 81%); mp 138-139 ºC; (Found: M+$Na^+$, 240.9462. $C_7H_7Br_1O_3$+$Na^+$ requires 240.9471); $\delta_H$ (400 MHz; acetone-$d_6$) 8.03 (1 H, s, OH); 7.45 (1 H, s, OH), 6.57 (1 H, s, ArH), 6.49 (1H, s, ArH), 3.81 (3 H, s, OMe); $\delta_C$ (100 MHz; acetone-$d_6$) 152.6 (C), 150.5 (C), 139.2 (C), 111.9 (CH), 110.0 (C), 101.5 (CH), 57.5 (Me); *m/z* (ESI) 243/241 (M+$Na^+$, 68/68%). Data in agreement with literature values.[149]

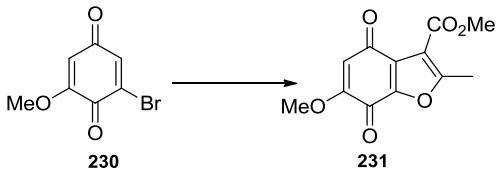
**2-Bromo-6-methoxycyclohexa-2,5-diene-1,4-dione 230**[148]




**229** **230**

A solution of iron(III) chloride hexahydrate (24.6 g, 91.2 mmol) in water (183 mL) was added as a single portion to a stirred solution of 2-bromo-6-methoxybenzene-1,4-diol **229** (4.00 g, 18.3 mmol) in methanol (37 mL). The resulting mixture was stirred at room temperature for 1 h and then water (122 mL) was added. The precipitate was collected by filtration and dried *in vacuo* to give the *title compound* **230** (3.62 g; 91%) as a brown solid; mp 161-163 ºC (lit.,[148] mp 162-163 ºC); (Found: M+$Na^+$, 238.9303. $C_7H_5Br_1O_3$+$Na^+$ requires 238.9314); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1695, 1643, 1590, 1355, 1130, 1006, 909; $\delta_H$ (400 MHz; $CDCl_3$) 7.20 (1 H, s, H-3), 5.96 (1 H, s, H-5), 3.85 (3 H, s, OMe); $\delta_C$ (100 MHz; $CDCl_3$) 184.6 (C), 174.5 (C), 158.3 (C), 138.5 (CH), 134.3 (C), 107.6 (CH), 56.8 (Me); *m/z* (ESI) 241/239 (M+$Na^+$, 50/48%). Data in agreement with literature values.[139]

**Methyl 4,7-dihydro-6-methoxy-2-methyl-4,7-dioxobenzofuran-3-carboxylate 231**

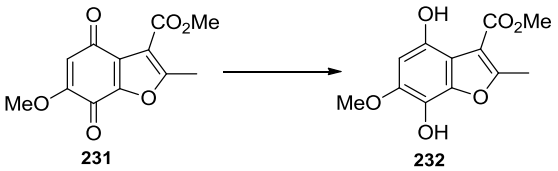



**230** **231**

Acetonitrile (10 mL) was added to copper(II) acetate (299 mg, 1.38 mol), potassium carbonate (381 mg, 2.76 mmol), methyl acetoacetate (99 µL, 0.92 mmol) and 2-bromo-6-methoxycyclohexa-2,5-diene-1,4-dione **230** (200 mg, 0.92 mmol). The mixture was stirred at reflux for 1.5 h, before being diluted with dichloromethane (250 mL), filtered through Celite® and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (2:1) to give the *title compound* **231** as a yellow solid (114 mg, 49%); mp 191-193 ºC; (Found: M+$Na^+$, 273.0369. $C_{12}H_{10}O_6$+$Na^+$ requires

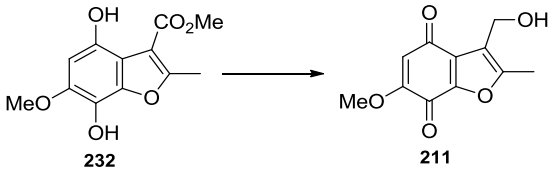
273.0375); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3011, 1690, 1662, 1611, 1458, 1313, 1248, 1094, 848; $\lambda_{max}$ (acetonitrile)/nm 232 (log ε 4.11), 259 (log ε 3.84), 303 (log ε 4.12), 402 (log ε 2.90); $\delta_H$ (400 MHz; $CDCl_3$) 5.85 (1 H, s, H-5), 3.94 (3 H, s, OMe), 3.86 (3 H, s, OMe), 2.68 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 179.9 (C), 169.4 (C), 165.2 (C), 162.3 (C), 158.1 (C), 148.6 (C), 127.0 (C), 113.1 (C), 108.2 (CH), 56.9 (Me), 52.3 (Me), 14.3 (Me); *m/z* (ESI) 273 ($M+Na^+$, 100%).

**Methyl 4,7-dihydroxy-6-methoxy-2-methylbenzofuran-3-carboxylate 232**



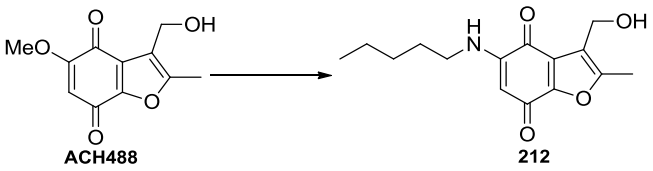

To a solution of methyl 4,7-dihydro-6-methoxy-2-methyl-4,7-dioxobenzofuran-3-carboxylate **231** (439 mg, 1.75 mmol) in chloroform (3.7 mL) was added a solution of sodium dithionite (1.84 g, 10.5 mmol) in water (7.3 mL). After being stirred at room temperature for 3 h, the precipitate formed was filtered and dried *in vacuo* to yield the *title compound* **232** as a colourless solid (351 mg, 79%); mp 183-184 ºC; (Found: $M+Na^+$, 275.0525. $C_{12}H_{12}O_6+Na^+$ requires 275.0526); $\delta_H$ (400 MHz; DMSO-$d_6$) 9.78 (1 H, s, OH), 8.70 (1 H, s, OH), 6.41 (1 H, s, H-5), 3.94 (3 H, s, $CO_2$Me), 3.78 (3 H, s, OMe), 2.66 (3 H, s, Me); $\delta_C$ (100 MHz; DMSO-$d_6$) 167.5 (C), 162.0 (C), 146.5 (C), 143.7 (C), 141.4 (C), 124.3 (C), 108.1 (C), 107.1 (C), 96.7 (CH), 56.5 (Me), 53.0 (Me), 14.6 (Me); *m/z* (ESI) 275 ($M+Na^+$, 47%), 253 ($M+H^+$, 46%).

**3-Hydroxymethyl-6-methoxy-2-methylbenzofuran-4,7-dione 211**




A solution of methyl 4,7-dihydroxy-6-methoxy-2-methylbenzofuran-3-carboxylate **232** (96.8 mg, 0.38 mmol) in THF (3 mL) was added at 0 ºC to a suspension of lithium aluminium hydride (75.0 mg, 1.98 mmol) in THF (6 mL). The reaction mixture was stirred at room temperature for 1.5 h, cooled to 0 ºC and quenched by addition of water (0.15 mL), sodium hydroxide (1 M; 0.15 mL) and silica gel (150 mg). The granular precipitate was filtered off through a pad of Celite®. The filtrate was dried ($Na_2SO_4$) and concentrated *in vacuo* to give the *title compound* **211** as an orange solid (44.7 mg, 52%); mp 142-144 ºC; (Found: M+$Na^+$, 245.0424. $C_{11}H_{10}O_5$+$Na^+$ requires 245.0420); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3479, 3011, 1686, 1647, 1588, 1321, 1095; $\lambda_{max}$ (acetonitrile)/nm 222 (log ε 4.30), 267 (log ε 4.06), 318 (log ε 3.99), 433 (log ε 3.05); $\delta_H$ (400 MHz; $CDCl_3$) 5.83 (s, 1 H, H-5), 4.60 (2 H, s, $CH_2$), 3.88 (3 H, s, OMe), 2.43 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 184.6 (C), 168.5 (C), 160.1 (C), 156.7 (C), 148.2 (C), 129.4 (C), 121.0 (C), 106.3 (CH), 57.1 (Me), 55.0 ($CH_2$), 12.3 (Me); *m/z* (ESI) 245 (M+$Na^+$, 42%).

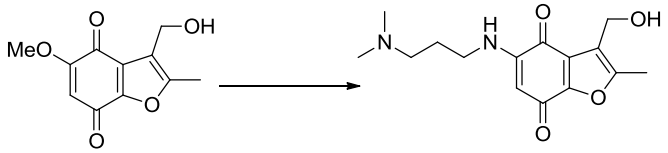
**3-Hydroxymethyl-2-methyl-5-(pentylamino)benzofuran-4,7-dione 212**




Pentylamine (0.15 mL, 1.31 mmol) was added to a solution of 3-(hydroxymethyl)-5-methoxy-2-methylbenzofuran-4,7-dione **ACH488** (29.1 mg, 0.13 mmol) in anhydrous acetonitrile (1.5 mL) and the resulting mixture was stirred at room temperature for 45 min. The solvent was removed *in vacuo* and the crude product was purified by column

chromatography on silica gel, previously inactivated with triethylamine, eluting with light petroleum/ethyl acetate (1:1) to give the *title compound* **212** as a purple solid (23.4 mg, 64%); mp 102 $^{o}$C (dichloromethane/light petroleum); (Found: M+Na$^{+}$, 300.1199. $C_{15}H_{19}NO_4$+Na$^{+}$ requires 300.1212); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3491, 338, 3007, 2961, 2863, 1671, 1633, 1591, 1467, 1390, 1190; $\lambda_{max}$ (acetonitrile)/nm 214 (log ε 4.76), 245 (log ε 4.56), 341 (log ε 4.17), 518 (log ε 3.82); $\delta_H$ (400 MHz; $CDCl_3$) 5.84 (1 H, s br, NH), 5.28 (1 H, s, H-6), 4.59 (2 H, s, $CH_2$), 3.14 (2 H, q, *J* 6.9, $CH_2$), 2.38 (3 H, s, Me), 1.72-1.65 (2 H, quin, *J* 6.9, $CH_2$), 1.39-1.35 (4 H, m, 2 × $CH_2$), 0.93 (3 H, t, *J* 6.9, Me); $\delta_C$ (100 MHz; $CDCl_3$) 180.7 (C), 175.1 (C), 153.2 (C), 152.9 (C), 147.9 (C), 123.5 (C), 118.9 (C), 95.8 (CH), 55.0 ($CH_2$), 43.0 ($CH_2$), 29.1 ($CH_2$), 27.8 ($CH_2$), 22.3 ($CH_2$), 13.9 (Me), 11.8 (Me); *m/z* (ESI) 300 (M+Na$^{+}$, 100%).

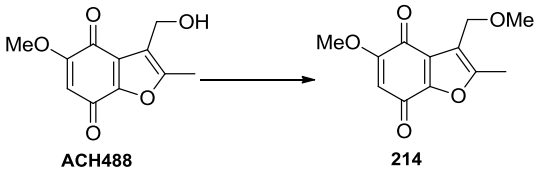
**5-(3-(Dimethylamino)propylamino)-3-(hydroxymethyl)-2-methylbenzofuran-4,7-dione 213**




*N*,*N*-Dimethylpropane-1,3-diamine (0.16 mL, 1.28 mmol) was added to a solution of 3-hydroxymethyl-5-methoxy-2-methylbenzofuran-4,7-dione **ACH488** (28.5 mg, 0.13 mmol) in anhydrous acetonitrile (1.5 mL) and the resulting mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue purified by column chromatography, eluting with methanol/dichloromethane (0-20%) to give the *title compound* **213** as a purple solid (20.5 mg, 55%); mp 127-128 $^{o}$C (dichloromethane/light petroleum); (Found: M+H$^{+}$, 293.1495. $C_{15}H_{20}N_2O_4$+H$^{+}$ requires 293.1496); $\nu_{max}$ ($CHCl_3$)/cm$^{-1}$ 3053, 2360, 2341, 1733, 1716, 1698, 1192, 1007 ; $\lambda_{max}$ (acetonitrile)/nm 215 (log ε 4.29), 246 (log ε 4.02), 343 (log ε 3.64), 315 (log ε 3.31); $\delta_H$ (400 MHz; $CDCl_3$) 7.83 (1 H, s br, NH), 5.23

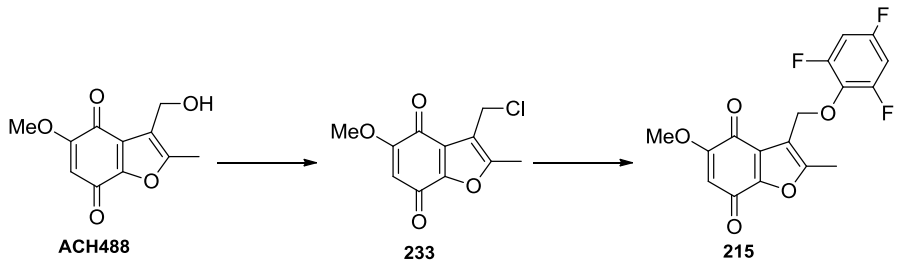
(1 H, s, H-6), 4.59 (2 H, s, $CH_2$), 3.26 (2 H, q, *J* 6.0, $CH_2$), 2.53 (2 H, t, *J* 6.0, $CH_2$), 2.37 (3 H, s, Me), 2.34 (6 H, s, Me), 1.86 (2 H, quin, *J* 6.0, $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 180.8 (C), 175.1 (C), 153.4 (C), 152.6 (C), 148.8 (C), 123.5 (C), 118.9 (C), 95.2 (CH), 57.9 ($CH_2$), 55.0 ($CH_2$), 45.0 (Me), 42.9 ($CH_2$), 24.2 ($CH_2$), 11.8 (Me); *m/z* (ESI) 293 ($M+H^+$, 100%).

**5-Methoxy-3-(methoxymethyl)-2-methylbenzofuran-4,7-dione 214**



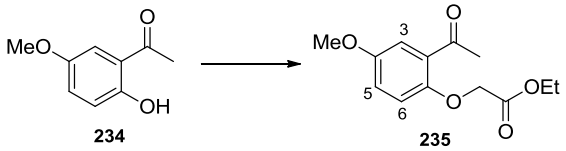

A mixture of 3-hydroxymethyl-5-methoxy-2-methylbenzofuran-4,7-dione **ACH488** (15.0 mg, 0.067 mmol), silver(I) oxide (23.4mg, 0.10 mmol) and iodomethane (1 mL) was heated to reflux for 22 h and then filtered through Celite®. The filter cake was washed with dichloromethane (5 mL) and the filtrate and washings were combined and concentrated *in vacuo*. The crude product was purified by column chromatography, eluting with light petroleum/ethyl acetate (1:1) to give the *title compound* **214** (8.2 mg, 51%) as an orange solid; mp 164-165 $^oC$; (Found: $M+Na^+$, 259.0549. $C_{12}H_{12}O_5+Na^+$ requires 259.0582); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 1691, 1658, 1533, 1390, 1121, 1020, 842; $\lambda_{max}$ (acetonitrile)/nm 225 (log ε 4.07), 259 (log ε 3.92), 310 (log ε 3.65), 426 (log ε 3.02); $\delta_H$ (400 MHz; $CDCl_3$) 5.75 (1 H, s, H-6), 4.54 (2 H, s, $CH_2$), 3.84 (3 H, s, Me), 3.41 (3 H, s, Me), 2.46 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 177.7 (C), 175.5 (C), 159.9 (C), 157.6 (C), 149.9 (C), 125.2 (C), 116.5 (C), 105.4 (CH), 63.3 ($CH_2$), 58.5 (Me), 56.8 (Me), 12.3 (Me); *m/z* (ESI) 259 ($M+Na^+$, 100%).

**3-((2,4,6-Trifluorophenoxy)methyl)-5-methoxy-2-methylbenzofuran-4,7-dione 215**




Thionyl chloride (0.64 mL, 8.87 mmol) was added at 0 ºC to a solution of 3-hydroxymethyl-5-methoxy-2-methylbenzofuran-4,7-dione **ACH488** (37.5 mg, 0.17 mmol) in dichloromethane (2 mL). After being stirred at room temperature for 2 h, the solvent was removed *in vacuo* and the resulting residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (2:1) to give the chlorinated compound **233** as a yellow solid (23.5 mg, 58%). To 3-chloromethyl-5-methoxy-2-methylbenzofuran-4,7-dione **233** (23.5 mg, 0.097 mmol) in anhydrous DMF (2 mL) was added sodium hydride (60% dispersion in mineral oils; 4.68 mg, 0.195 mmol) followed by 2,4,6-trifluorophenol (31.0 mg, 0.211 mmol) and the reaction mixture was stirred at room temperature for 5 h. Water (3 mL) was then added and the reaction mixture was extracted with ether (3 × 5 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by column chromatography, eluting with light petroleum/ethyl acetate (2:1) to give the *title compound* **215** as a yellow solid (20.1 mg, 58%); mp 124-125 ºC; (Found: M+$Na^+$, 375.0459 $C_{17}H_{11}F_3O_5$+$Na^+$ requires 375.0451); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2927, 2855, 1692, 1660, 1509, 1454, 1390, 1120, 1042, 842; $\delta_H$ (400 MHz; $CDCl_3$) 6.66 (2 H, t, *J* 8.0, ArH), 5.76 (1 H, s, ArH), 5.20 (2 H, s, $CH_2$), 3.84 (3 H, s, OMe), 2.46 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 177.3 (C), 175.4 (C), 159.9 (C), 159.0 (C), 157.6-157.4 (m, CF), 155.2-154.9 (m, CF), 149.9 (C), 147.3 (C), 124.7 (C), 114.8 (C), 105.5 (CH), 100.8 (ddd, $J_{CF}$ 27, 19, 8, CH), 64.7 ($CH_2$), 56.8 (Me), 12.0 (Me); *m/z* (ESI) 375 (M+$Na^+$, 100%).

**Ethyl 2-(2-acetyl-4-methoxyphenoxy)acetate 235**[150]




A solution of 5-methoxy-2-hydroxyacetophenone **234** (5.0 g, 30.1 mmol) and potassium carbonate (8.42 g, 60.24 mmol) in acetone (19.8 mL) was stirred at room temperature for 30 min, before ethyl bromoacetate (6.68 mL, 60.2 mmol) was added dropwise. The reaction mixture was heated to 60 ºC for 18 h, cooled to room temperature, diluted with brine (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resulting residue was purified by column chromatography, eluting with dichloromethane to dichloromethane/methanol (5%) to yield the *title compound* **235** as a colourless solid (7.35 g, 97%); mp 70-72 ºC (lit.,[150] mp 72-74 ºC); (Found: $M+Na^+$, 275.0897. $C_{13}H_{16}O_5+Na^+$ requires 275.0890); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 1755, 1674, 1603, 1493, 1142, 877; $\delta_H$ (400 MHz; $CDCl_3$) 7.30 (1 H, d, *J* 3.2, H-3), 7.00 (1 H, dd, *J* 9.0, 3.2, H-5), 6.80 (1 H, d, *J* 9.0, H-6), 4.67 (2 H, s, $OCH_2$), 4.27 (2 H, q, *J* 7.2, $OC\underline{H_2}Me$), 3.79 (3 H, s, OMe), 2.72 (3 H, s, Me), 1.30 (3 H, t, *J* 7.2, $OCH_2\underline{Me}$); $\delta_C$ (75 MHz; $CDCl_3$) 199.3 (C), 168.4 (C), 154.2 (C), 151.4 (C), 129.2 (C), 120.1 (CH), 114.1 (CH), 114.1 (CH), 66.3 ($CH_2$), 61.5 ($CH_2$), 55.8 (Me), 32.0 (Me), 14.1 (Me); *m/z* (ESI) 527 ($2M+Na^+$, 100%), 275 ($M+Na^+$, 69%). Data in agreement with literature values.[150]

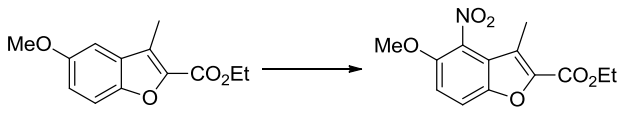
**Ethyl 5-methoxy-3-methylbenzofuran-2-carboxylate 236**




Sodium ethoxide (21 wt.% in ethanol; 8.89 mL, 23.8 mmol,) was added dropwise to ethyl (2-acetyl-4-methoxyphenoxy)acetate **235** (6.00 g, 23.8 mmol) in anhydrous ethanol (200 mL).

The reaction mixture was stirred at 75 ºC for 2 h, cooled to 0 ºC, quenched with hydrochloric acid (1 M) until neutral and diluted with water (100 mL). The product was extracted with ethyl acetate (3 × 100 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography, eluting with light petroleum/dichloromethane (1:1) to yield the *title compound* **236** as a colourless solid (2.01 g, 36%); mp 102-103 ºC (lit.,[151] mp 105 ºC); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3010, 1709, 1590, 1479, 1320, 1153, 909; (Found: M+$Na^+$, 257.0774. $C_{13}H_{14}O_4$+$Na^+$ requires 257.0784); $\delta_H$ (300 MHz; $CDCl_3$) 7.44 (1 H, d, *J* 8.9, H-7), 7.05 (1 H, dd, *J* 8.9 and 2.4, H-6), 7.00 (1 H, d, *J* 2.4, H-4), 4.45 (2 H, q, *J* 7.2, OC<u>$H_2$</u>Me), 3.87 (3 H, s, OMe), 2.57 (3 H, s, Me), 1.44 (3 H, t, *J* 7.2, $OCH_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 160.5 (C), 156.2 (C), 149.4 (C), 141.6 (C), 129.5 (C), 125.6 (C), 117.6 (CH), 112.9 (CH), 102.2 (CH), 61.1 ($CH_2$), 55.9 (Me), 14.4 (Me), 9.5 (Me); *m/z* (ESI) 491 (2M+$Na^+$, 100%), 257 (M+$Na^+$, 77%). Data in agreement with literature values.[152]

**Ethyl 5-methoxy-3-methyl-4-nitrobenzofuran-2-carboxylate 237**

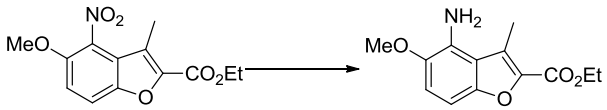



**236** **237**

A solution of fuming nitric acid (1.46 mL, 35.8 mmol) in glacial acetic acid (23.1 mL) was added dropwise to ethyl 5-methoxy-3-methyl-benzofuran-2-carboxylate **236** (839 mg, 3.58 mmol) at room temperature. The mixture was stirred at room temperature for 18 h , before being poured into ice/water and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), evaporated *in vacuo* and the residue was purified by column chromatography, eluting with light petroleum/ethyl acetate (8:2) to yield the *title compound* **237** as a yellow solid (575 mg, 58%); mp 107-108 ºC (lit.,[152] mp 115 ºC); (Found: M+$Na^+$, 302.0641. $C_{13}H_{13}NO_6$+$Na^+$ requires 302.0635); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2983, 1716, 1601, 1462, 1240, 1092, 909; $\delta_H$ (400 MHz, $CDCl_3$) 7.64 (1 H, d, *J* 9.2, ArH), 7.19 (1 H, d, *J*

9.2, ArH), 4.46 (2 H, q, *J* 7.2, OC<u>H</u>$_2$Me), 3.96 (3 H, s, OMe), 2.47 (3H, s, Me), 1.44 (3 H, t, *J* 7.2, OCH$_2$<u>Me</u>); $\delta_C$ (100 MHz, $CDCl_3$) 159.7 (C), 148.7 (C), 147.5 (C), 143.5 (C), 133.5 (C), 122.7 (C), 121.5 (C), 115.1 (CH), 113.4 (CH), 61.7 ($CH_2$), 57.6 (Me), 14.3 (Me), 8.9 (Me); *m/z* (ESI) 581 (2M+$Na^+$, 100%), 302 (M+$Na^+$, 45%). Data in agreement with literature values.[152]

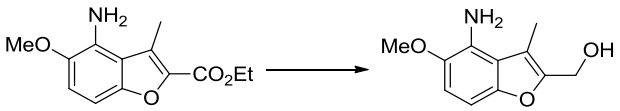
**Ethyl 4-amino-5-methoxy-3-methylbenzofuran-2-carboxylate 238**




**237** **238**

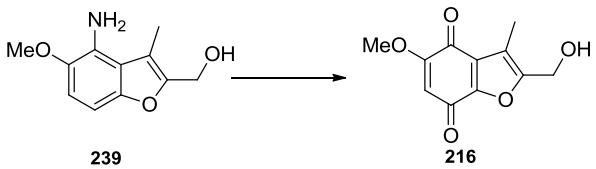
To a suspension of ethyl 5-methoxy-3-methyl-4-nitrobenzofuran-2-carboxylate **237** (439 mg, 1.57 mmol) in ethanol (27 mL) was added tin powder (851 mg, 7.11 mmol) and aqueous hydrochloric acid (3 M; 11 mL). The reaction mixture was stirred under reflux for 1.5 h, cooled to room temperature and then neutralised with saturated aqueous sodium hydrogen carbonate. The suspension obtained was filtered through Celite® and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield the *title compound* **238** as a colourless solid (365 mg, 93%), that is prone to degradation on exposure to air and light; mp 70-71 ºC; (Found: M+$Na^+$, 272.0900 $C_{13}H_{15}NO_4$+$Na^+$ requires 272.0893); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3400, 2253, 1704, 1592, 1376, 907, 651; $\delta_H$ (400 MHz; $CDCl_3$) 6.98 (1 H, d, *J* 9.0, ArH), 6.85 (1 H, d, *J* 9.0, ArH), 4.43 (2 H, q, *J* 7.2, OC<u>H</u>$_2$Me), 4.32 (2 H, s br, $NH_2$), 3.87 (3 H, s, OMe), 2.81 (3 H, s, Me), 1.43 (3 H, t, *J* 7.2, OCH$_2$<u>Me</u>); $\delta_C$ (100 MHz; $CDCl_3$) 160.6 (C), 150.6 (C), 141.6 (C), 139.9 (C), 131.7 (C), 125.7 (C), 117.2 (C), 113.5 (CH), 100.4 (CH), 60.9 ($CH_2$), 57.2 (Me), 14.4 (Me), 11.4 (Me); *m/z* (ESI) 521 (2M+$Na^+$, 100%), 272 (M+$Na^+$, 23%).

**(4-Amino-5-methoxy-3-methylbenzofuran-2-yl)methanol 239**




To a suspension of lithium aluminium hydride (249 mg, 6.50 mmol) in THF (9 mL) at 0 ºC was added a solution of ethyl 4-amino-5-methoxy-3-methylbenzofuran-2-carboxylate **238** (405 mg, 1.62 mmol) in THF (5 mL). The reaction was allowed to warm to room temperature over 30 min and then stirred for 2 h. The mixture was recooled to 0 ºC and quenched by addition of water (1 mL), aqueous sodium hydroxide (1 M; 1 mL) and silica gel (≈ 10g). The granular precipitate was filtered through a pad of Celite® and the resulting filtrate was dried ($MgSO_4$) and concentrated *in vacuo* to yield the *title compound* **239** as an off-white solid (294 mg, 87%); mp 137-138 ºC; (Found: M+$Na^+$, 230.0792. $C_{11}H_{13}NO_3$+$Na^+$ requires 230.0788); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2934, 2253, 1612, 1496, 1384, 911; $\delta_H$ (400 MHz; $CDCl_3$) 6.83 (1 H, d, *J* 8.8, ArH), 6.77 (1 H, d, *J* 8.8, ArH), 4.68 (2 H, s, C$\underline{H_2}$OH), 4.14 (2 H, s br, $NH_2$), 3.86 (3 H, s, OMe), 2.44 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 150.5 (C), 150.3 (C), 141.8 (C), 130.4 (C), 117.5 (C), 112.3 (C), 110.3 (CH), 100.1 (CH), 57.2 (Me), 55.6 ($CH_2$), 10.2 (Me); *m/z* (ESI) 230 (M+$Na^+$, 100%).

**2-Hydroxymethyl-5-methoxy-3-methylbenzofuran-4,7-dione 216**

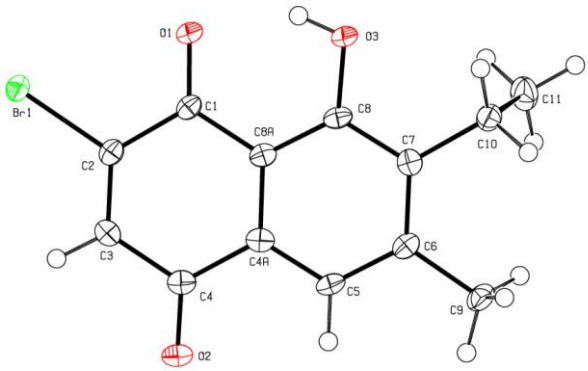



To a solution of (4-amino-5-methoxy-3-methylbenzofuran-2-yl)methanol **239** (286 mg, 1.38 mmol) in acetone (83 mL) was added a solution of potassium nitrosodisulfonate in sodium dihydrogen phosphate buffer (0.3 M; 66.5 mL). After being stirred at room temperature for 1 h, the excess acetone was removed *in vacuo* and the resulting residue was extracted with

dichloromethane (3 × 50 mL). The combined organic layers were concentrated *in vacuo* and the resulting residue was stirred at room temperature for 1 h, in a mixture of aqueous hydrochloric acid (2 M)/acetone (1:1; 170 mL). The acetone was removed *in vacuo* and the resulting product extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to yield the *title compound* **216** as a dark orange solid (274 mg, 89%); mp 203-204 ºC (dichloromethane/*n*-hexane); (Found: M+$Na^+$, 245.0425. $C_{11}H_{10}O_5$+$Na^+$ requires 245.0420); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3045, 2936, 2363, 1690, 1661, 1547, 1334, 1172, 909, 660; $\lambda_{max}$ (acetonitrile)/nm 226 (log ε 4.20), 261 (log ε 4.12), 317 (log ε 3.63), 422 (log ε 3.18); $\delta_H$ (400 MHz; $CDCl_3$) 5.79 (1 H, s, H-6), 4.69 (2 H, s, C$\underline{H_2}$OH), 3.86 (3 H, s, OMe), 2.31 (3 H, s, Me); $\delta_C$ (100 MHz; $CDCl_3$) 177.9 (C), 175.8 (C), 160.2 (C), 155.3 (C), 150.6 (C), 125.6 (C), 118.2 (C), 105.8 (CH), 56.9 (Me), 55.0 ($CH_2$), 8.5 (Me); *m/z* (ESI) 467 (2M+$Na^+$, 100%), 245 (M+$Na^+$, 82%).

# APPENDIX

**Crystal data and structure refinement for compound 85 at 90(2)K**




| | |
|---|---|
| Empirical formula | C13 H11 Br O3 |
| Formula weight | 295.13 |
| Crystal description | colourless block |
| Crystal size | 0.6699 x 0.1320 x 0.0715 mm |
| Crystal system | monoclinic |
| Space group | P 21/c |
| Unit cell dimensions | a = 15.3653(3) Å alpha = 90º |
| | b = 4.77008(10) Å beta = 96.9069(18)º |
| | c = 15.7486(3) Å gamma = 90º |
| Volume | 1145.90(4) $Å^3$ |
| Reflections for cell refinement | 4502 |
| Range in theta | 3.79 to 73.85º |
| Z | 4 |
| Density (calculated) | 1.711 $mg/m^3$ |
| Absorption coefficient | 4.848 $mm^{-1}$ |
| F(000) | 592 |
| Diffractometer type | SuperNova, Single source at offset, Atlas |
| Wavelength | 1.5418 Å |
| Reflections collected | 5195 |
| Theta range for data collection | 5.66 to 67.49º |
| Index ranges | -16<=h<=18, -4<=k<=5, -18<=l<=18 |

| | |
|---|---|
| Independent reflections | 2067 [R(int) = 0.0176] |
| Observed reflections | 1857 [II>2\s(I)] |
| Absorption correction | Analytical (Tmin = 0.268, Tmax = 0.748) |
| Decay correction | 0% |
| Structure solution by | direct and difmap methods |
| Hydrogen atom location | geom |
| Hydrogen atom treatment | constr |
| Data / restraints / parameters | 2067/0/157 (least-squares on $F^2$) |
| Final R indices [I>2sigma(I)] | R1 = 0.0265, wR2 = 0.0722 |
| Final R indices (all data) | R1 = 0.0307, wR2 = 0.0861 |
| Goodness-of-fit on $F^2$ | 1.126 |
| Final maximum delta/sigma | 0.001 |
| Largest diff. peak and hole | 0.545 and -0.729 e. $Å^{-3}$ |

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