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The development of novel synthetic methodology for the synthesis of oxygenated heterocycles

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The Development of Novel Synthetic Methodology for the Synthesis of Oxygenated Heterocycles

Myron Mario Johnson

A thesis submitted to the Faculty of Science

University of the Witwatersrand

Johannesburg

In fulfilment of the requirements for the Degree of Doctor of Philosophy

15 May 2014

Declaration

I declare that the work presented in this thesis was carried out extensively by myself under the supervision of Professor Charles B. de Koning and Dr Amanda L. Rousseau. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

_____

Myron Mario Johnson

15 May 2014

Abstract

A number of oxygenated heterocycles have been described in nature as having a myriad of biological activities. Owing to these biological activities and their complex structure, these compounds are of interest to us and the preparation of selected oxygenated heterocycles is described in this thesis. Three main sections form this thesis, with each representing a class of oxygenated heterocycle.

The first part of the thesis deals with pyranonaphthoquinone analogues where a model study was performed to construct the skeleton of the isochromane kalafungin. The synthesis of isochromane 6,9-dimethoxy-3,3*a*,5,9*b*-tetrahydro-2*H*-furo[3,2-*c*]isochromen-2-one was successfully achieved from commercially available 2,5-dihydroxybenzoic acid in an overall yield of 9.5%. The key steps employed in the synthesis of the isochromane were a cross metathesis reaction between (2-allyl-3,6-dimethoxyphenyl)methanol and ethyl acrylate to afford the α,β-unsaturated ester (*E*)-ethyl-4-(2-(hydroxymethyl)-3,6-dimethoxyphenyl)but-2-enoate which, after several synthetic steps, was converted to the isochromane via a radical induced lactonization using a hypervalent iodine reagent. The success of this route led us to the preparation of iscochromane (3*aR*, 5*R*, 9*bR*)-6,9-dimethoxy-5-methyl-3,3*a*,5,9*b*-tetrahydro-2*H*-furo[3,2-*c*]isochromen-2-one. Our initial aim was to enzymatically resolve intermediate racemic alcohol 1-(2-allyl-3,6-dimethoxyphenyl)ethanol, however, the use of *Candida antarctica* lipase B (CALB) to facilitate the kinetic resolution was not as successful as we hoped. Therefore, using racemic alcohol 1-(2-allyl-3,6-dimethoxyphenyl)ethanol and the key reaction conditions developed in the model study of 6,9-dimethoxy-3,3*a*,5,9*b*-tetrahydro-2*H*-furo[3,2-*c*]isochromen-2-one, we successfully prepared isochromane (3*aR*, 5*R*, 9*bR*)-6,9-dimethoxy-5-methyl-3,3*a*,5,9*b*-tetrahydro-2*H*-furo[3,2-*c*]isochromen-2-one in an overall yield of 0.4%, albeit racemically.

The second part of this thesis involved the use of nitroalkanes as precursors to spiroketals. In this section, we managed to successfully elucidate the mechanism of a novel Nef reaction previously described in our laboratories using three different substrates. The key steps involved during the elucidation of the mechanism were a Henry condensation reaction and a key modified Nef reaction. The preparation of the spiroketal skeleton of the griseusins was also attempted.

The last part of this PhD thesis focused on the formation of angucycline analogues, specifically analogues related to the landomycins. We have successfully managed to prepare landomycin analogues tetraphene-7,12-dione, 3-methoxytetraphene-7,12-dione and 3,8-dimethoxytetraphene-7,12-dione. A Suzuki reaction followed by a Wittig reaction, isomerisation and final ring closing metathesis allowed for the smooth preparation of these analogues. The preparation of related analogues bearing seven-membered rings has also been achieved and is described.

Dedication

I would like to dedicate this thesis to my grandfather, Jan (Joe) Johnson. I feel so privileged to have had you as my grandfather. Thank you for all the conversations we had, for all the memories we created and for all your unconditional love you so willingly gave. My only wish is that I become half the man that you were. You will forever be in my heart.

In memory of my grandfather

Jan Johnson

February 1932 – October 2013

Acknowledgements

I would like to extend my sincere gratitude to my supervisors, Prof Charles de Koning and Dr M. Rousseau for all their wisdom and guidance throughout my project, especially during the write-up phase. Without your continual support and encouragement, none of this would have been possible. I would also like to thank Prof Joseph Michael and Dr Moira Bode for all the discussions and valuable input during this project.

A huge thank you to Dr Richard Mampa and Prof Laurence Carlton for running countless NMR spectra; Dr Andreas Lemmerer for his assistance in data collection and analysis of my X-ray crystal structures. To Prof Willem van Otterlo and the MS department at Stellenbosch for countless mass spectral analyses. I am indebted for all the work you have put in on my behalf.

To the organic group both past and present; specifically Stefania, Saleem, Adushan, Hanna, Priya, Susen, Sameshnee, and Jenny, thank you for making the laboratory a pleasurable environment to work in. To Sameshnee and Jenny, thank you for taking the time and having the patience to teach me when I first joined the organic group, your guidance and nurturing provided me with the first stepping stone in my career.

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To my family, especially my parents and brother, thank you for all your support and encouragement and for always letting me know how proud you are of me and for granting me this opportunity. Without you, this PhD would not have been possible.

Finally to the love of my life Dr Stefania Scalzullo. The day I met you was one of the greatest days in my life. I feel completely blessed and honoured to have shared these past few years with you. Thank you for all your patience and understanding throughout this project and for always supporting and encouraging me. I am looking forward to the rest of our lives together and know that as long as I have you by mind side, my life would be complete.

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Chapter 1: Pyranonaphthoquinones - An Introduction

1.1. Biological importance of pyranonaphthoquinones

A large number of isochromane containing compounds exist in nature. The main class of isochromanes relating to this thesis are the pyranonaphthoquinones, which have been isolated from various strains of bacteria and fungi. The basic structure of these compounds (**Figure 1.1**) is the naphtho[2,3-*c*]pyran-5,10-dione ring system shown in structure **1**. Another feature found in some members of this class of compounds is the γ-lactone ring as shown in structure **2**, which is fused to the pyran moiety. Some members possess a carboxylic acid side chain at C3 **3**.[1,2]

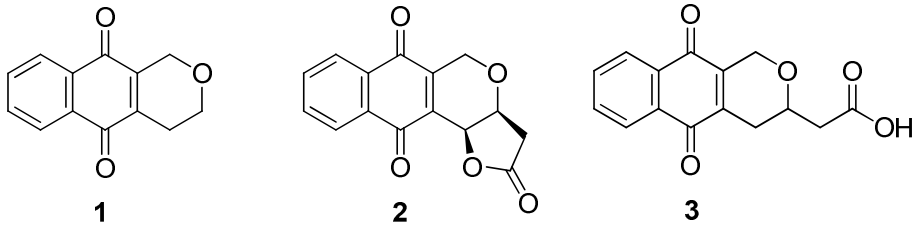

Figure 1.1

These compounds are of interest as they exhibit a wide variety of pharmacological properties. Derivatives of such compounds are also found to exhibit plant-growth and herbicidal activities, while others have been found in fragrances, e.g. galaxolide **4**, shown in **Figure 1.2**.[3] As a result, there is a growing interest in developing improved methods for the synthesis of these isochromane containing compounds. It is for this reason that scientific research directed towards the synthesis of compounds of this class is necessary.

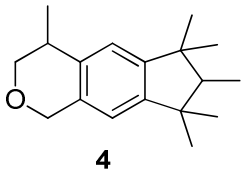

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Figure 1.2

1.2. Naturally occurring pyran fused quinones

The literature contains many examples of naturally occurring quinones isolated from various fungal and bacterial strains. These can be classified into three types of pyranonaphthoquinones, namely monomeric, dimeric and carbohydrate derived pyranonaphthoquinones. Each of these classes of quinones will be briefly discussed in the following sections.

1.2.1. Monomeric pyranonaphthoquinones

1.2.1.1. Simple and *Fusarium* based quinones

One of the simplest compounds which contains the naphthopyrandione system is psychorubin, **5** (**Figure 1.3**), which was isolated from *Psychotria rubra*. This compound bears a hydroxyl substituent at the C3 position of the pyran ring making it a hemiacetal. It has been found to exhibit significant cytotoxicity against KB cancer cells.[4] Anhydrofusarubin **6**, shown in **Figure 1.3**, has recently been isolated from the sea-fan-derived fungus *Fusarium spp.* and is of interest due to its excellent biological activity. It has been shown to exhibit better cytotoxicity against both oral and breast cancer cell lines than the current drugs of choice: ellipticine and doxorubicin respectively.[5] As will be discussed later, this quinone has been synthesised in our laboratories.[4]

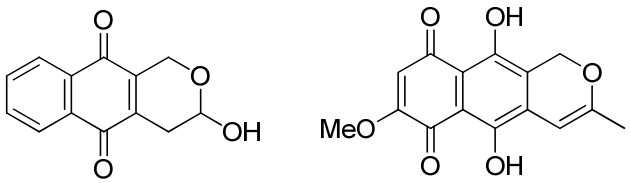

Figure 1.3

1.2.1.2. Monomeric pyranonaphthoquinones

An example of a monomeric pyran fused quinone is thysanone, **7** shown in **Figure 1.4**, which was isolated from cultures of *Thysanophora penicilloides*. Thysanone has been shown to exhibit potent activity against HRV 3C-protease, which is a human rhinovirus (HRV) from the family of picornaviruses which are responsible for human diseases such as hepatitis A and polio. Thysanone is therefore one of the lead compounds in the development of a cure for the common cold.[6,7] Another type of monomeric quinone containing a pyran ring is 5-hydroxy-6-methoxy-α-lapachome, **8**, which has been isolated from the stem bark of *Melloa quadivalvis*. This compound has been found to exhibit cytotoxic activity against the lung carcinoma cell line, NC1H292.[2] An important monomeric quinone which contains an additional γ-lactone ring fused to the basic naphtho[2,3-*c*]pyran-5,10-dione ring system that is important to this thesis is kalafungin, **9** (**Figure 1.4)**.[1] This antifungal pigment was isolated from *Streptomyces tanashiensis* as well as *Nocardia dassonvillie*.

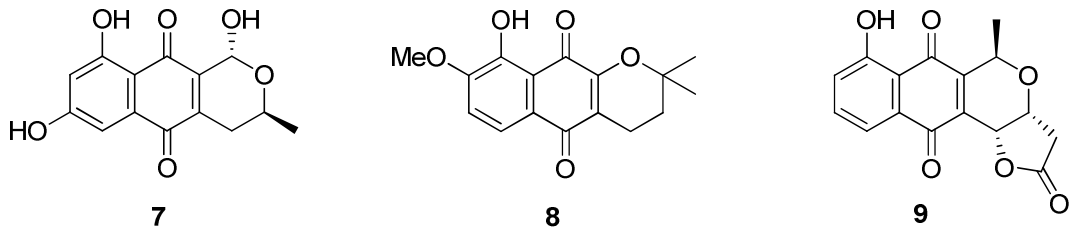

Figure 1.4

Kalafungin, **9** (**Figure 1.4**), has been found to be inhibitory *in vitro* against a variety of pathogenic fungi, protozoa, yeasts as well as gram-positive bacteria. Recent studies have shown that kalafungin displays inhibitory activity against L5178Y mouse leukemic cells *in vitro*. [8] The stereochemistry present in kalafungin has also made it an attractive substrate to pursue synthetically.

1.2.2. Dimeric pyranonaphthoquinones

Research conducted at the University of the Witwatersrand on dimeric quinones includes the synthesis of pyranonaphthoquinone-type pigments, known as the cardinalins. This group of compounds is the first class of pyranonaphthoquinones to be discovered in higher order fungi. Cardinalins 1 to 6 have been isolated from the New Zealand toadstool *Dermocybe cardinalis* which is known to produce distinctive purple and orange fruit bodies. All six cardinalins display good anticancer activities. Studies conducted at the University of the Witwatersrand focused on the synthesis of cardinalin 3, **10**, a dimer of ventiloquinone L, **11** (**Figure 1.5**), which has been isolated from *Ventolago goughii*. This study used a bidirectional synthetic approach to assemble cardinalin 3, **10**.[9]

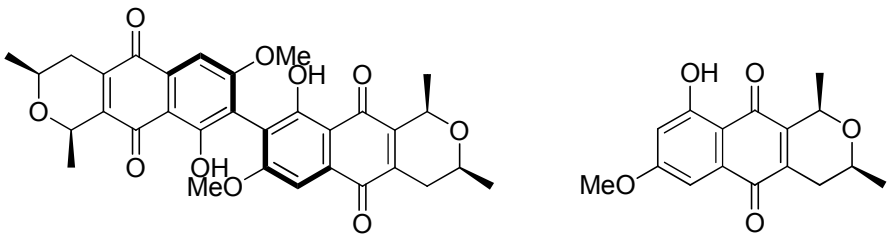

Figure 1.5

Other research which has occurred in the Wits laboratories includes the synthesis of chiral isochromanquinones using Corey-Bakshi-Shibata reductions.[10] In addition, the synthesis of isochroman-4-ols and isochroman-3-ols has been accomplished in our laboratories using the key steps of an oxidative mercury-mediated ring closure and ozonolysis reaction respectively.[10] The synthesis of the oxygen analogue of the michellamines, which has been isolated for *Ancistrocladus korupensis* has also been accomplished in the Wits laboratories. Interest in michellamines has risen as a result of their reported anti-HIV activity. [11]

1.2.3. Carbohydrate derived pyranonaphthoquinones

Medermycin, **12** (**Figure 1.6**) is a compound that has been isolated from *Streptomyces tanashiensis* as a monohydrochloride salt. It was found to have a similar structure to kalafungin due to the fused lactone ring. This compound is known to exhibit biological activity against gram-positive bacteria. It has also shown toxicity against cell lines of K562 human myeloid leukemia as well as P-388 murine leukemia.[1,12] A related quinone named after the red garnet-like crystals isolated from *Streptomyces olivaceus*, granaticin A, **13**, has been shown to exhibit antibiotic activity against gram-positive bacteria. It has also been shown to possess antitumour activity against lymphatic leukemia in mice, as well as being cytotoxic against KB cells which are cells associated with mouth epidermal carcinoma.

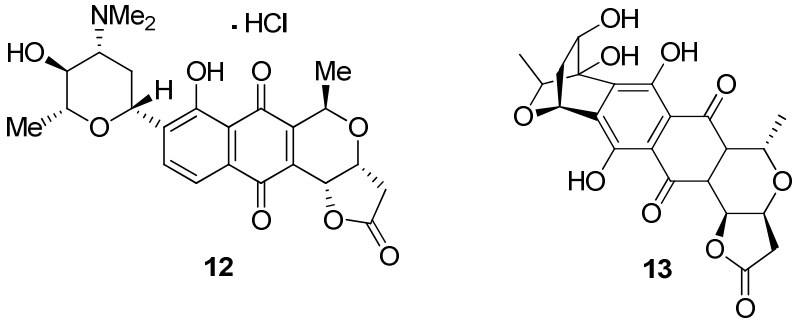

Figure 1.6

1.2.4. Other interesting isochromane compounds

The isolation of an isochromane fungal metabolite, pseudodeflectitusin, **14** (**Figure 1.7**), from a culture broth of *Aspergillus pseudodeflectus* has been reported. This compound was identified as an isochromane derivative using spectrometric and physicochemical techniques. Ogawa *et al.* reported that one enantiomer of these compounds showed an inhibitory effect on the cell growth of the NUGC-3 human stomach cancer cell line. Similar results were observed for the HeLa human cervix cancer line and the HL-60 human peripheral blood cancer line. [13]

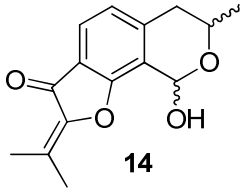

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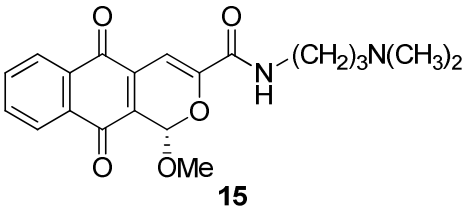
Figure 1.7

The synthesis of BCH-2051 **15**, an interesting isochromane containing compound, by Wang *et al.*, and its subsequent biological screening showed that BCH-2051 is a very potent analogue of anthracycline compounds.[14] Furthermore, it has been shown to exhibit even better activity than adriamycin **16**, shown in **Figure 1.8**, which stabilises the topoisomerase-DNA cleavage complex which leads to DNA damage.



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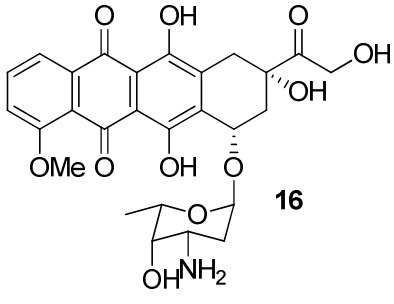

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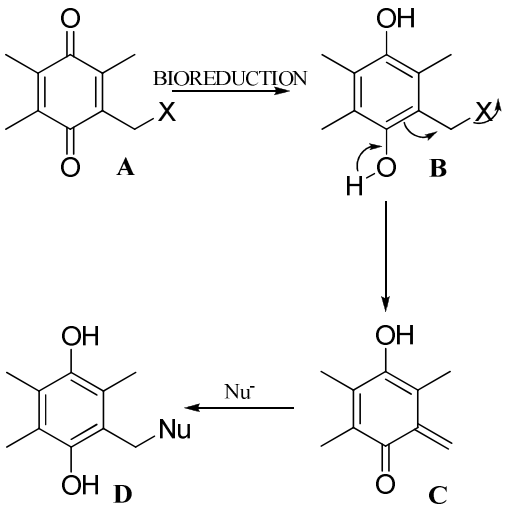
Figure 1.8

1.3. Proposed mechanisms of biological activity of pyranonaphthoquinone antibiotics

In **Section 1.2** we highlighted a few examples of the different classes of the pyranonaphthoquinones and briefly discussed the biological activities of the classes mentioned. In this section we will outline the proposed mechanisms of action of these quinones. The pyranonapthoquinone antibiotics have been postulated to act as bioreductive alkylating agents by Moore and coworkers.[15] Compounds which are considered to be bioreductive alkylating agents become potent alkylating agents after they undergo a reduction *in vivo*. These types of compounds have also been shown to possess a high level of antineoplastic activity.[15] Furthermore, there have been various studies conducted which have described topoisomerase II inhibition by pyranonaphthoquinones, thus revealing new possibilities in the design of anti-cancer drugs.[16,17]

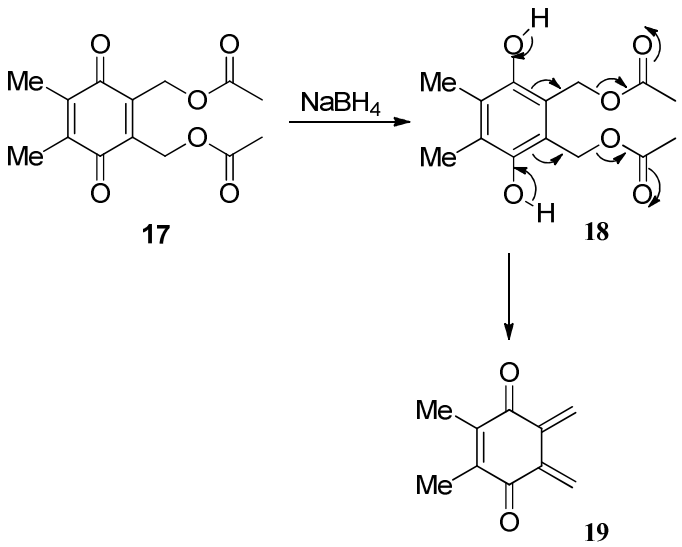
1.3.1. Simple quinone methides

A generalised model for their activity is shown in **Scheme 1.1**. The first step in this process is the *in vivo* bioreduction of quinone, **A**, resulting in the formation of hydroquinone **B**. Cleavage of a benzylic substituent from **B** results in the formation of a quinone methide **C**. Structure **C** now has the potential to act as an alkylating agent, by reacting with a nucleophile in a Michael addition step. An example is the formation of a covalent adduct with DNA, which will lead to cell death. In particular, the nucleophile is expected to be the nitrogenous base of a DNA molecule, in a cancer cell.



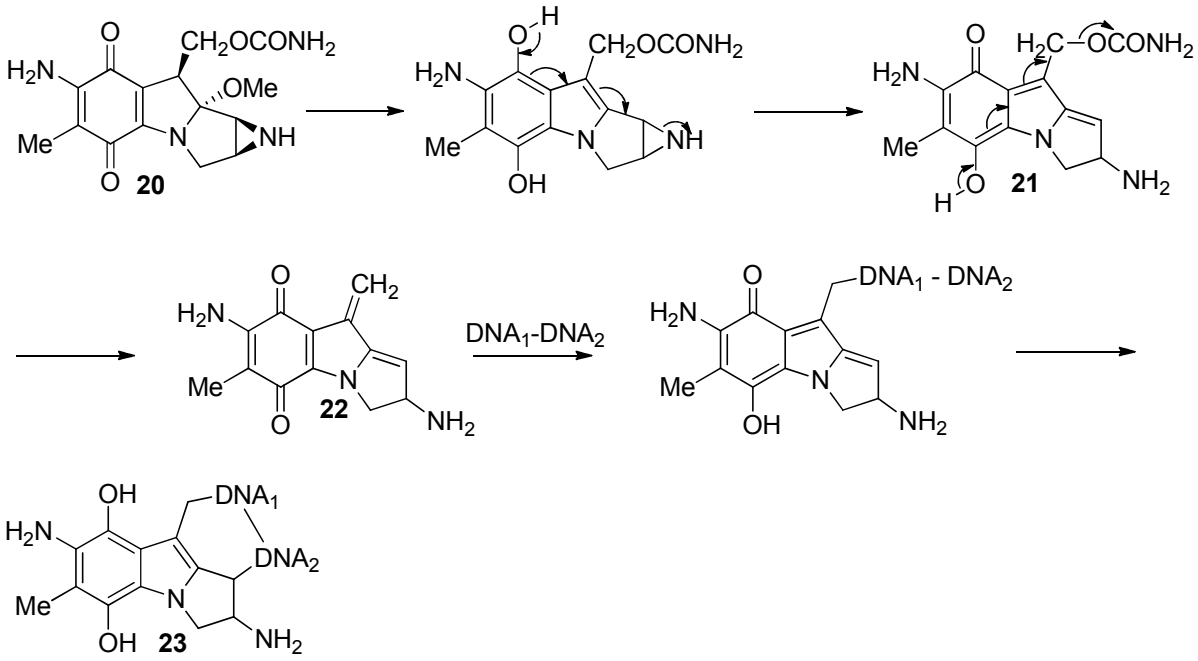
Scheme 1.1

The ability of these quinones to act as bioreductive alkylating agents has been demonstrated by Lin *et al*. who synthesised benzoquinone derivatives with one or two side chains. These derivatives form highly reactive Michael acceptors as shown in **Scheme 1.2**.[18] Lin and co-workers performed a reduction on 2,3-dimethyl-5,6-bis(acetoxymethyl)-1,4-benzoquinone, **17**, to afford hydroquinone **18**. This hydroquinone then decomposed to form the quinone methide **19** which acts as the alkylating agent (**Scheme 1.2**).[19] Quinone methide **19** was reacted with aniline and morpholine to demostrate its potential to alkylate biological materials *in vivo*.[19]



Scheme 1.2

A known example of a bioreductive alkylating agent is mitomycin C, **20**, which has been isolated from strains of *Streptomyces* species. Mitomycin C is an antineoplastic antibiotic and has been used to inhibit the synthesis of nucleic acids, such as DNA and RNA. It is believed that mitomycin C performs its function by joining together the two polynucleotide strands of DNA, forming a covalent cross-link. This cross-link results in the interference of DNA functions and ultimately the inhibition of DNA synthesis.[19] It is believed that the function of the drug arises from the enzymatic reduction of mitomycin C **20**, as shown in **Scheme 1.3**, followed by the loss of methanol and subsequent aziridine ring opening affording intermediate **21**. Displacement of the carbamate group in **21** allows for the attack of intermediate **22** by nucleophilic sites on DNA resulting in the formation of the cross-linked DNA product **23**.[20]



Scheme 1.3

1.3.2. Inhibition of the DNA topoisomerase II enzyme

The topoisomerase enzyme II (TopoII) has become a desirable target for potential anti-cancer drugs due to its important catalytic function. This enzyme has various functions which can be simplified to the maintenance of the topological state of DNA during processes such as replication, transcription and recombination.[21,22] The function of the topoisomerase enzyme can be interrupted in two ways. These include the stabilization of the covalent intermediate of the enzyme with DNA by compounds known as topoisomerase II poisons, or by compounds, known as catalytic inhibitors, which target any step in the catalytic cycle.[23] Topoisomerase II was identified as a possible target for anticancer drugs such as doxorubicin, **24**, and mitoxantrone, **25**, which are potent TopoII poisons (**Figure 1.9**).[16] The quinone moiety is known to possess anti-proliferative activity against a wide range of organisms and cancer cells. It has also been stated that the quinone moieties combine features of poisons and catalytic inhibitors which allow them to possess enhanced activity. Eleutherin, **26**, isolated from the bulb of *Eleutherine Americana*, has been shown to exhibit catalytic inhibition of TopoII.[17]

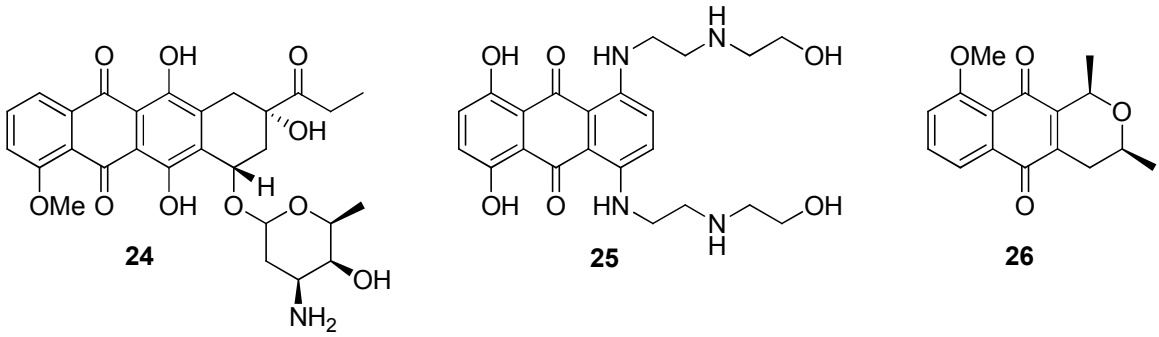


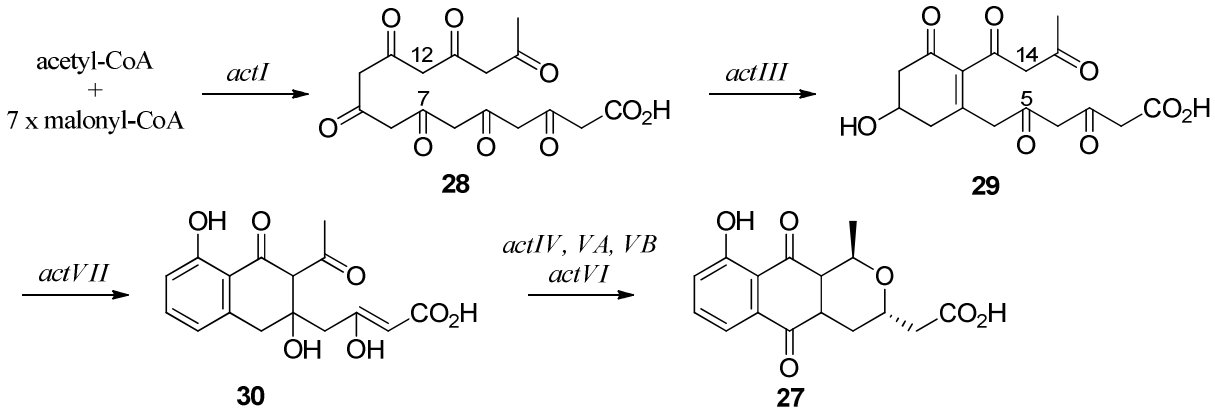
Figure 1.9

The biological activities discussed in the previous sections have therefore made the pyranonaphthoquinones synthetically attractive compounds. This has led to numerous synthetic strategies being developed towards the assembly of these compounds. A few selected synthetic strategies will be discussed in the sections that follow. However, before we discuss the synthetic literature, it is important to highlight how the construction of the isochromane core is accomplished through biosynthesis.

1.4. Biosynthesis of pyranonaphthoquinone antibiotics

It has been proposed that the biosynthesis of pyranonaphthoquinone antibiotics involves a polyketide synthase (PKS) pathway. A comprehensive report into the biosynthesis of polyketide metabolites has been published by O'Hagan where polyketides have been shown to originate from various sources, ranging from mammals to bacteria and fungi.[24] Actinomycetes, in particular have been shown to produce polyketides which are important antibiotics or chemotherapeutic agents, as compared to the polyketides originating from other bacteria, fungi and higher plants which have been shown to act as toxins, flavours and pigments.[25] The same biosynthetic mechanism is followed regardless of the vastness of the polyketide structural classes, in which single, simple carboxylic acid subunits are used. An oligoketide intermediate results in the formation of six-membered rings, characteristic of pyranonaphthoquinones, due to several intramolecular Aldol or Dieckmann cyclisation reactions.[25]

This biosynthetic process is exemplified by the biosynthesis of actinorhodin **27**, as shown in **Scheme 1.4**. The monomeric unit of actinorhodin, **27**, can essentially be derived from a reaction of an acetylCoA unit and seven malonylCoA units to afford linear polyketide **28**. A regiospecific intramolecular Aldol condensation of C7 with C12 results in the formation of intermediate **29**. A second condensation reaction between C5 and C14 will result in the formation of **30**. The condensation reactions involved during the biosynthesis of actinorhodin are controlled by an aldolase enzyme, and gene clusters allow for the correct bond formation to occur.[25]



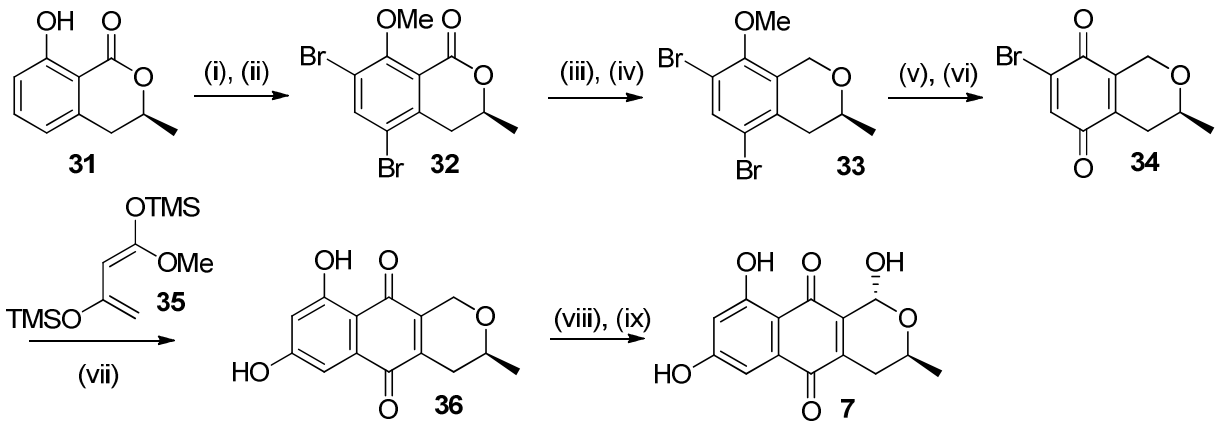
Scheme 1.4

1.5. Synthetic strategies for the assembly of Isochromanes

There are a number of synthetic strategies which have been employed to access the isochromane core. The following sections will highlight only a few selected routes with some emphasis placed on the research conducted in our laboratories over the past few years.

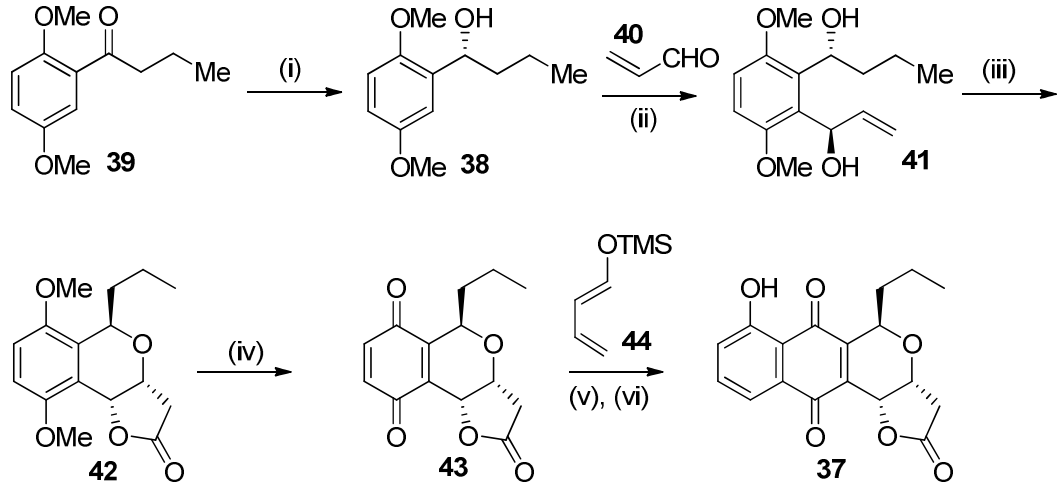
1.5.1. Diels-Alder cycloadditions

One of the most common strategies for pyranonaphthoquinone preparation employs Diels-Alder methodology. An example is the total synthesis of thysanone **7** in which a Diels-Alder cycloaddition was used as the key step.[7] The synthesis commenced with the bromination of (*S*)-mellein **31** followed by *O*-methylation to yield the methyl ether **32**. The lactone ring was then reduced to the benzopyran ring, **33**, followed by oxidation to the (*S*)-pyranobenzoquinone **34**, which was the dienophile component for the Diels-Alder cycloadditon step. A Diels-Alder reaction between (*S*)-pyranobenzoquinone **34** and diene **35** afforded pyranonaphthoquinone **36** which underwent a final stereospecific hydroxylation to afford thysanone **7** (**Scheme 1.5**).



Scheme 1.5 *Reagents and conditions*: (i) NBS, DMF, RT, dark, 16 h, 91%; (ii) Me_2SO_4, K_2CO_3, acetone, Δ, 1 h, 98%; (iii) DIBAL-H, toluene, -70°C; (iv) $NaBH_4$, THF, 30°C, 1 h 90% over 2 steps; (v) $(PhCH_2Se)_2$, $NaBH_4$, DMF, Δ, 1 h, 86%; (vi) CAN, MeCN-H_2O, RT, 30 min, 82%, (vii) diene **35**, toluene, Δ, 3 h, 73%; (viii) Br_2, CCl_4, *hv*, 30 min; (ix) THF-H_2O, RT, 1 h, 85% over 2 steps.

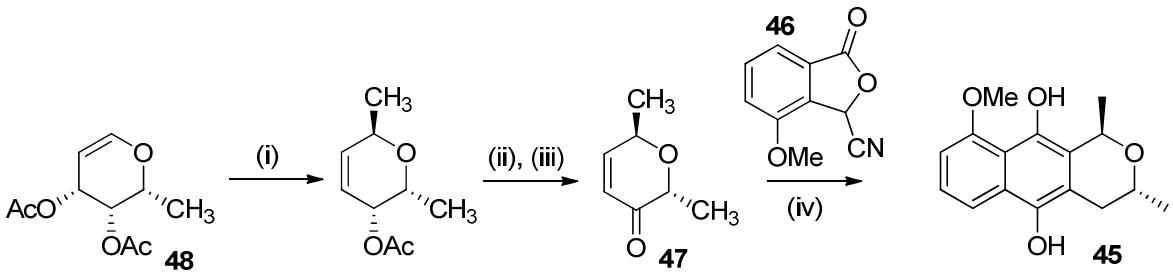
The synthesis of frenolicin B, **37**, has been achieved by Kraus and co-workers, also using Diels-Alder methodology as a key step.[26] The synthesis commenced with the synthesis of alcohol **38** via an enantioselective reduction of ketone **39**. The dianion formed through metalation of alcohol **38**, was reacted with acrolein **40** to afford **41** as a mixture of diastereomers in a 1:1.5 ratio. Lactone **42** was then formed by a palladium catalysed carbonylation and cyclisation of diol **41**, followed by oxidation to the corresponding quinone **43**. Reaction of **43** with diene **44** to furnish the Diels-Alder adduct followed by treatment with Jones reagent afforded frenolicin B, **37** (**Scheme 1.6**).



Scheme 1.6 *Reagents and conditions*: (i) THF, –25°C, (+)-Ipc_2BCl, 100%; (ii) Et_2O, Bu^nLi, 0°C to RT, then –78°C, **36**, 44%; (iii) $Pd(OAc)_2$, CO (g), THF, 65%; (iv) AgO, THF, 6N HNO_3, RT, 95%; (v) CH_2Cl_2, – 78°C; (vi) Me_2CO, Jones reagent 0°C, 81% over 2 steps.

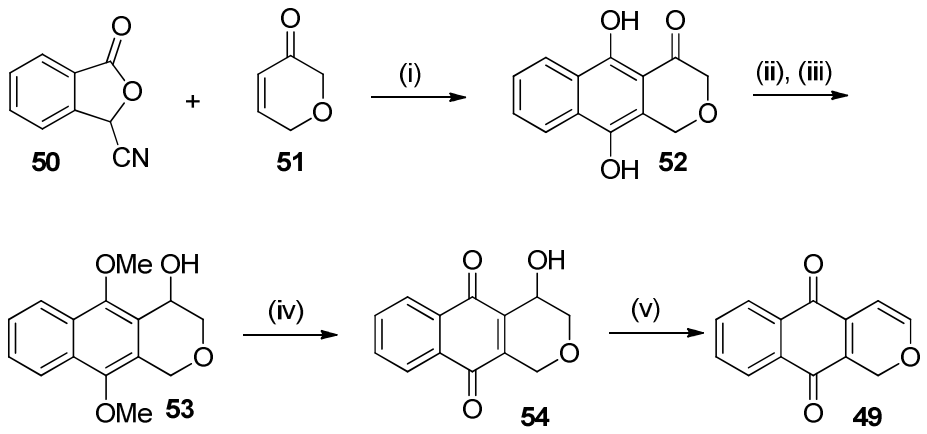
1.5.2. Phthalide annulation strategy

The use of the phthalide annulation to access pyranonaphthoquinones was first described by Kraus and Sugimoto and has subsequently been used in the preparation of many pyranonaphthoquinones.[27] In the total synthesis of (–)-hongconin **45** described by Baker and co-workers,[28] a phthalide annulation reaction between methoxy cyanophthalide **46** and heterocyclic compound **47** furnished hongconin **45**, as shown in **Scheme 1.7**. The synthesis commenced with the Lewis acid-catalysed C-1 alkylation of glycal **48** followed by the formation of enone **47**. The reaction between enone **47** phthalide **46** resulted in the formation of hongconin **45**.



Scheme 1.7 *Reagents and conditions*: (i) $AlCl_3$, $TiCl_4$, 85%; (ii) NH_3, MeOH; (iii) pyridinium dichromate, Ac_2O, 60% over 2 steps; (iv) THF, –78°C, LiCl (cat.), ~65%.

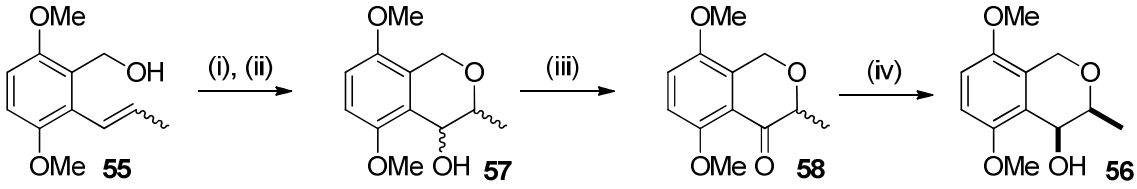
In the preparation of pentalongin **49**, De Kimpe *et al.* employed a phthalide annulation reaction between cyanophthalide **50** and the heterocyclic compound **51**.{Claessens, 2006 #230} This annulation reaction resulted in the formation of a hongconin analogue **52**. Protection of the hydroquinone followed by reduction of the ketone afforded alcohol **53**. Oxidation of alcohol **53** to quinone **54** and subsequent dehydration gave pentalongin **49** (**Scheme 1.8**).



Scheme 1.8 *Reagents and conditions*: (i) Bu^{n}Li, Bu^{t}OH, LiCl, THF, –78°C to RT, 88%; (ii) K_2CO_3, Me_2SO_4, acetone, Δ, 50%; (iii) $NaBH_4$, MeOH–CH_2Cl_2, RT, 52%; (iv) CAN, CH_3CN–H_2O, 0°C then RT, 95%; (v) *p*-TsOH, benzene, Δ, 37%.

1.5.3. Reductive mercury(II) acetate-mediated cyclisations

In our laboratories, de Koning and co-workers have shown that the oxidative ring closure of benzylic alcohol **55** with mercury(II) acetate, followed by two functional group interconversions affords the *cis*-isochromanol **56** (**Scheme 1.9**). Their synthesis involved the treatment of benzyl alcohol **55** with mercury(II) acetate followed by exposure to oxygen, and then sodium borohydride, to yield a 1:1 mixture of the *cis:trans* alcohols **57**. These alcohols were then oxidised to the ketone **58** using PCC followed by a reduction using lithium aluminium hydride to afford exclusively the *cis*-isochroman-4-ol **56** as a mixture of enantiomers. The only requirement for the oxidative ring closure was the presence of a vinyl group *ortho* to the benzyl alcohol. [10]



Scheme 1.9 *Reagents and conditions*: (i) $Hg(OAc)_2$, THF, 15 min; (ii) $NABH_4$, DMF, O_2, 86%; (iii) PCC, CH_2Cl_2, 74%; (iv) $LiAlH_4$, Et_2O, 80%.

1.5.4. Ring-closing metathesis (RCM)

Another strategy used to prepare pyranonaphthoquinones is ring-closing metathesis, which has been demonstrated by de Kimpe and co-workers in the total synthesis of pentalongin **49** and its precursor psychorubin **5**. [30]

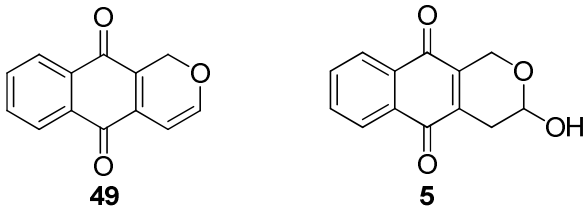
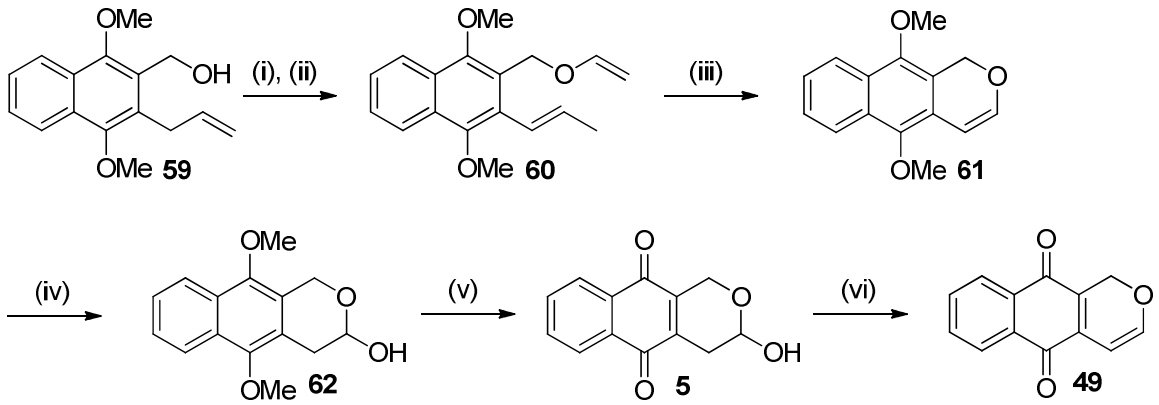


Figure 1.10

In their synthesis, compound **59** was subjected to based-induced isomerisation of the allyl group. The intermediate was then treated with vinyl acetate in the presence of chloro(1,5-cyclooctadiene)iridium(I) to afford *E*-vinyl ether **60**. Ring-closing metathesis was then accomplished upon treatment of *E*-vinyl ether **60** with Grubbs' first-generation catalyst furnishing cyclic ether **61**, which was converted to hemiacetal **62** when subjected to reflux in aqueous acetonitrile in the presence of tosic acid. Psychorubin **5** was then formed by the oxidative demethylation of **62** using ceric ammonium nitrate, followed by heating with tosic acid in benzene to furnish pentalongin **49** (**Scheme 1.10**).



Scheme 1.10 *Reagents and conditions*: (i) Bu^{t}OK, THF, RT, 3 h, 95%; (ii) vinyl acetate, Na_2CO_3, $[IrCl(cod)]_2$, 100°C, 12 h, 96%; (iii) Grubbs' I catalyst, PhMe, RT, 12 h, then 100°C, 12 h, 86%; (iv) *p*-TsOH, MeCN-H_2O, 100°C, 3 h, 75%; (v) CAN, MeCN-H_2O, RT, 30 min, 91%; (vi) *p*-TsOH, benzene, 80°C, 20 min, 72%.

1.6. Project objectives

Over the past few years, research conducted in our laboratories has focused on the synthesis of pyranonaphthoquinones. To date, we have managed to successfully prepare ventiloquinone L **11** (**Figure 1.11**) which is the monomer of cardinalin 3 **10**.[9,31] The bidirectional racemic synthesis of cardinalin 3 **10** has also been achieved in our laboratories. More recently, the synthesis of dehydroherbarin **63** and anhydrofusarubin **6** has also been achieved, using Wacker oxidation methodology as the key step.[4] This section of the PhD thesis will describe the approach to be used in this work leading to the synthesis of the isochromane core of the pyranonaphthoquinones containing a γ-fused lactone ring as found in frenolicin B **37** and medermycin **12**, as shown in **Figure 1.12**.

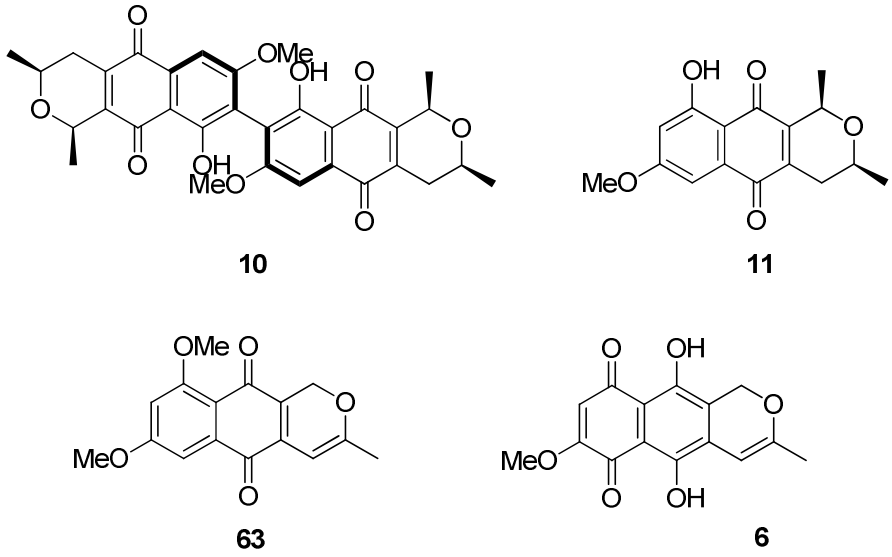


Figure 1.11

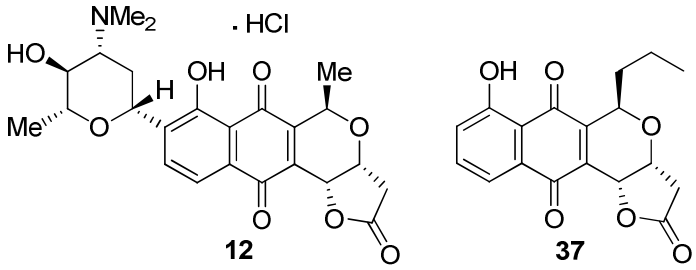
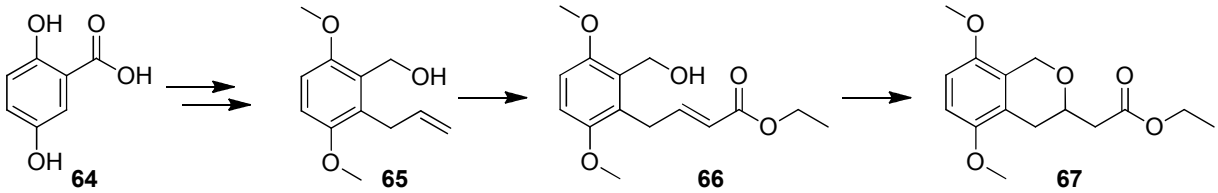


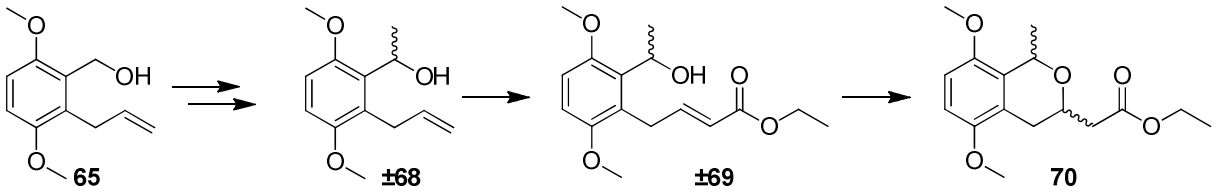
Figure 1.12

As has been demonstrated by de Koning and Pelly,[32] and shown in **Scheme 1.11**, 2,5-dihydroxybenzoic acid **64** has been converted into the aromatic alcohol **65**. We envisaged that this alcohol **65** could be converted into the Michael acceptor **66** utilising cross metathesis as the key step. Subsequent Michael addition would then result in the formation of the 3 substituted isochromane **67**.



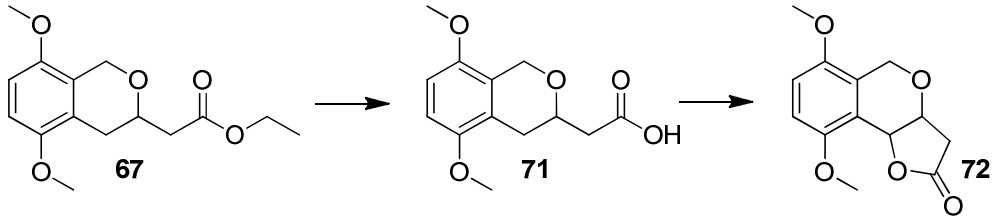
Scheme 1.11

Once the methodology for construction of the C3 substituted pyran ring is in place, we will then turn our focus to the formation of 1,3-disubstituted pyran rings. We envisaged that we could access this substitution pattern using a Grignard reaction on the oxidised aldehyde formed from **65** which would yield the secondary alcohol **±68**. A cross metathesis reaction would then furnish the 1,3-disubstituted pyran ring, **±69** which subsequent to an intramolecular oxa-Michael addition would afford **±70** (**Scheme 1.12**).



Scheme 1.12

Once the pyran ring has been constructed, we will turn our efforts to the preparation of the lactone ring shown in **Scheme 1.13**, which would provide us with the desired tricyclic system. This would initially be conducted on the model system **67** lacking the C1 methyl substituent. The ester chain positioned at C3 would be used to construct the lactone ring. To achieve this, ester **67** could be hydrolysed to the carboxylic acid **71**. The acid **71** would then pave the way, using a radical mediated lactone formation discussed in **Section 2.4.1**, to give the desired tricyclic ring system **72**, as found in various pyranonaphthoquinone natural products.



Scheme 1.13

We would like to prepare the 1,3-disubstitued pyranonaphthoquinone core stereoselectively, as this would more closely resemble the core found in natural products like kalafungin **9** (**Figure 1.13**). An ever increasingly popular route is the use of enzymatic kinetic resolution or dynamic kinetic resolution, which we hope will afford a single enriched enantiomer of an advanced precursor, as will be discussed below, from which we hoped to prepare the desired 1,3-disubstituted isochromane core **73**.

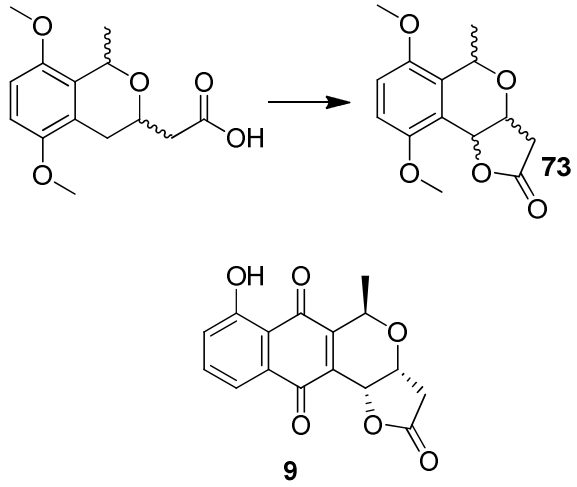
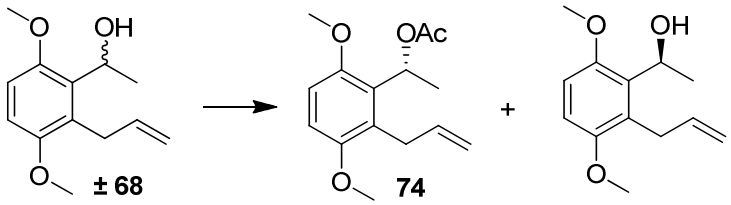


Figure 1.13

Hence, in practice we envisage that if our racemic benzylic alcohol ±**68** could be selectively acetylated to afford ±**74**, we would be able to separate the enantiomers using enzymatic resolution, as shown in **Scheme 1.14**. This would provide us with an enantiomerically enriched benzylic alcohol which we could employ in the construction of the 1,3-disubstituted pyran ring.



Scheme 1.14

Thus, the central theme of this part of the project is the preparation of the isochromane core found in a number of natural products. We aim to achieve this by using cross metathesis methodology to provide us with the C3 substituted pyran. A novel radical type transformation will be then employed to furnish the desired tricyclic isochromane core. Finally, we will attempt the resolution of racemic alcohol **±68**, providing us with an enriched alcohol from which we can construct the isochromane core.

Chapter 2: Approaches toward the isochromane core

2.1. Introduction

Kalafungin **9** (**Figure 2.1**) was initially isolated from *Streptomyces tanashiensis* in 1968. [33] Its interesting biological activity as well as its stereochemical features, has made it the subject of a number of total syntheses. The key steps, some of which were outlined in the previous chapter, include asymmetric dihydroxylation, Oxa-Pictet-Spengler cyclization and acid mediated isomerisations;[34] tandem Michael-Dieckmann approaches;[35] and approaches using Diels-Alder reactions.[36]

The results discussed in this section of the PhD thesis will focus on our attempts to construct the isochromane core, starting with a model study to construct the γ-lactone isochromane nucleus **72**, shown in **Figure 2.1**. The success of the model study will allow us to expand the methodology to the preparation of 1,3-disubstituted isochromanes, e.g. **75**, however, lacking the naphthalene nucleus which occurs in natural products like kalafungin **9**.

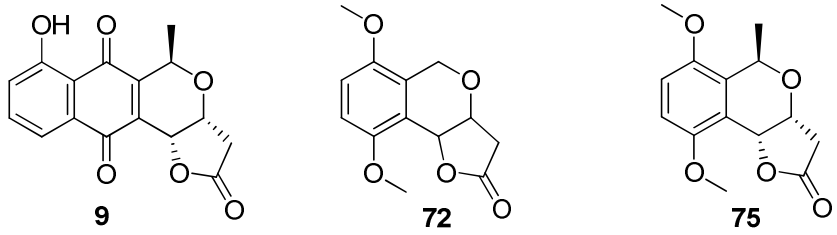
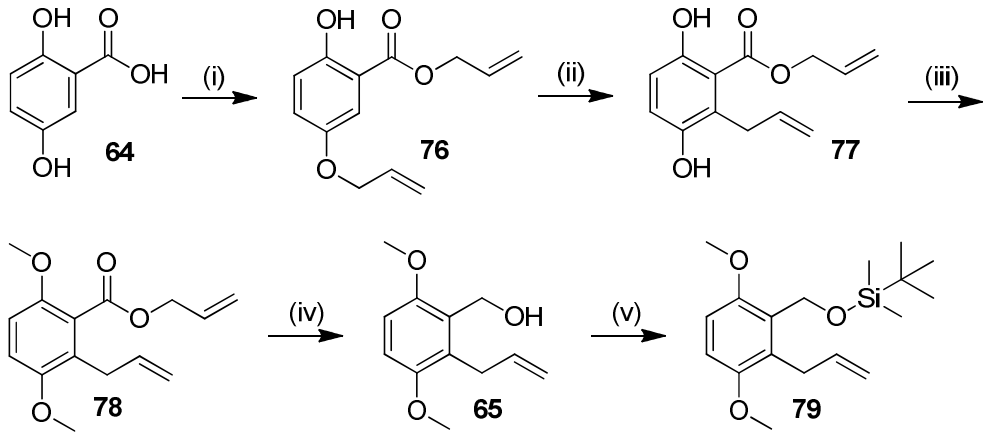


Figure 2.1

In her PhD thesis, a fellow student, Pelly described her approach to the construction of the pyran ring systems.[32] Related work has been published by Hume and coworkers describing the construction of pyranonaphthoquinones using cross metathesis as one of their key steps.[37] Using methodology developed at the University of the Witwatersrand, we will firstly prepare isochromane **72** (discussed in **Section 2.2 and 2.4**), which will serve as the model study. We will

then conduct the racemic/diastereomeric synthesis of **75** (discussed in **Section 2.5**). Finally our attempts to synthesise **75** enantioselectively will be discussed. Our results will therefore contribute to the research on the construction of this tricyclic quinone scaffold of isochromanes. Improvements to existing methodology will also be highlighted.

2.2. Preparation of ((2-allyl-3,6-dimethosybenzyl)oxy)(*tert*-butyl)dimethylsilane 79



Scheme 2.1 *Reagents and conditions*: (i) K_2CO_3, allyl bromide, acetone, Δ, 18 h, 82%; (ii) 170°C, 18 h, 78%; (iii) K_2CO_3, dimethylsulfate, acetone, Δ, 18 h, 95%; (iv) $LiAlH_4$, THF, 40°C, 2 h, 77%; (v) NaH, TBDMSCl, THF, RT, 18 h, 90%.

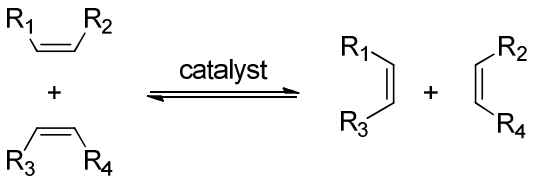
The preparation of [(2-allyl-3,6-dimethoxybenzyl)oxy](*tert*-butyl)dimethylsilane **79** was achieved starting from the commercially available 2,5-dihydroxbenzoic acid **64** over 5 steps using methods previously developed in our laboratories. The synthesis commenced with the selective diallylation of both the carboxylic acid and the 5-OH positions of **64** to give the diallylated product **76** in an 82% yield. The dilute reaction conditions and hydrogen bonding of the 2-OH to the carbonyl group of the benzoic acid ensured selectivity. This was confirmed by the presence of a broad singlet at δ 10.36 in the ^{1}H NMR spectrum, which is characteristic of a hydrogen bonded phenol. Thermal Claisen rearrangement of the diallylated compound **76** afforded the desired product **77** in 78% yield. The ^{1}H NMR spectrum confirmed that the product was obtained owing to the simplification of the aromatic region, which shows two doublets at

δ 6.99 ppm and δ 6.81 ppm with *ortho* coupling contants of 8.9 Hz each. The hydroquinone **77** was then methylated using dimethyl sulfate in the presence of potassium carbonate to afford the product **78** as an oil in 95% yield. This proved to be an improved yield, (95% vs 82%) compared to that obtained by Pelly.[32] The most distinctive features of the ^{13}C NMR spectrum are the presence of two upfield signals at δ 56.38 ppm and δ 56.26 ppm which are due to the newly introduced methoxy substituents. Reduction of ester **78** was achieved using lithium aluminium hydride to afford the primary alcohol **65** in 77% yield. The absence of a signal above δ 160 ppm in the ^{13}C NMR spectrum confirmed the loss of the carbonyl group which was present in the starting material. Primary alcohol **65** was then protected using *tert*-butyldimethyl silyl chloride, in the presence of sodium hydride. The product **79** was obtained in 90% yield. Spectroscopic data compared well with that of Pelly with the dimethyl and *t*-butyl groups of the silyl protecting group appearing as signals at δ 0.93 ppm and δ 0.10 ppm respectively in the ^{1}H NMR spectrum.

With both our free alcohol **65** and silicon-protected alcohol **79** in hand, we could turn our focus towards the cross metathesis reaction which would ultimately provide us with a C3 carboxylic acid substituted isochromane.

2.3. Background and mechanism of the olefin metathesis reaction

In the early 1950's, Karl Ziegler first noted that certain heterogeneous catalysts not only promoted the polymerization of olefins under mild conditions but that they also facilitated the cleavage and formation of double bonds. This is generally referred to as alkene metathesis.[38] The term metathesis is derived from the Greek words *meta* meaning change and *thesis* meaning position and therefore it is the exchange of parts of two substances as shown in **Scheme 2.2**.



Scheme 2.2

First generation heterogeneous metathesis catalysts were unattractive to synthetic chemists due to their limited scope in advanced organic synthesis. This was mainly due to their poor compatibility, especially with polar functional groups, even though they exhibited high activity. This then importantly led to the development of second and third generation homogeneous catalysts that were considered to perform better, more importantly, with higher tolerance towards functional groups. These catalysts also showed an increased thermal stability and were more stable to air and moisture.[39] The two most popular and versatile homogeneous catalysts (shown in **Figure 2.2**) are the tungsten or molybdenum catalyst, **80**, developed by Schrock and co-workers and the ruthenium carbene, **81** developed by Grubbs and co-workers.

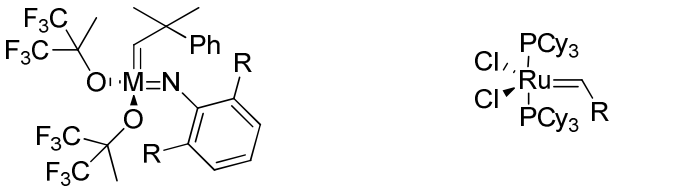
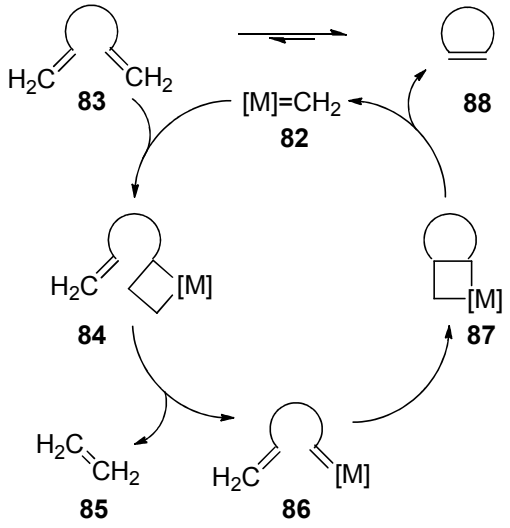


Figure 2.2

The generally accepted mechanism, also known as the Chauvin mechanism, consists of formal [2+2] cycloadditions involving alkenes and metal carbenes. The catalytic cycle shown in **Scheme 2.3** shows the metal carbene acting as a catalyst. The metal alkylidene **82** reacts with one olefin of the diene **83** forming the metallocyclobutane intermediate **84**. Cleavage of this intermediate results in the loss of ethylene **85** and the formation of a new metal alkylidene **86**. This newly formed metal alkylidene reacts intramolecularly with the second olefin to form a

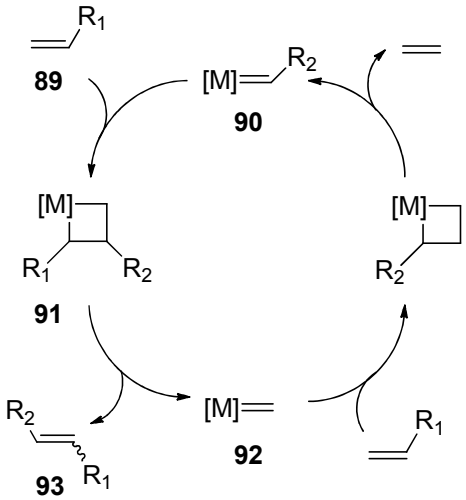
metallocyclobutane intermediate **87**. This undergoes a second [2+2] cycloreversion to yield alkene **88** while the metal carbene catalyst reenters the catalytic cycle. These developments led to Grubbs, Schrock and Chauvin being awarded the Nobel prize for chemistry in 2005.



Scheme 2.3

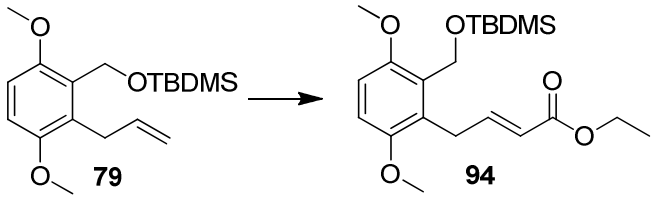
All the individual steps of the catalytic cycle are reversible and therefore results in an equilibrium mixture of olefins. It is therefore necessary to shift this equilibrium forward. In the ring closing metathesis catalytic scheme shown above, the process is both entropically driven, as the process cleaves one substrate molecule into two products liberating ethene **85**, and equilibrium driven since the ethene liberated is volatile and therefore leaves the cycle.[38]

The metathesis of interest to us is cross metathesis as we hope to use this reaction to introduce the C3 substituent to the pyran ring system. The catalytic mechanism for the cross-metathesis of two alkenes is shown in **Scheme 2.4** and is similar to the Chauvin mechanism shown in **Scheme 2.3**. The catalytic cycle commences with a [2+2] cycloaddition reaction between alkene **89** and metal carbene **90** forming the metallacyclobutane intermediate **91**. This is followed by cleavage to afford a new metal alkylidene **92** and the newly formed alkene product **93**. The new metal alkylidene **92** then reenters the catalytic cycle to react with another alkene.

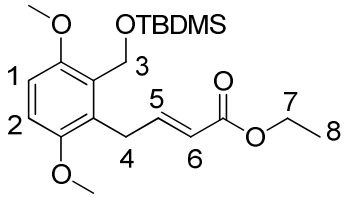


Scheme 2.3

2.4. Preparation of isochromane 72

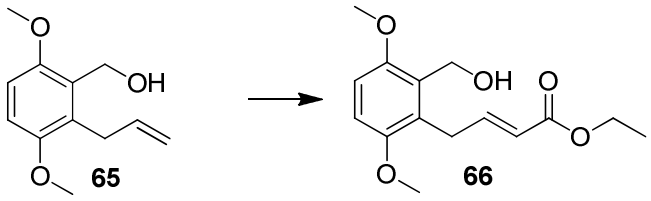


Scheme 2.4 *Reagents and conditions*: (i) Ethyl acrylate, Grubbs II catalyst, toluene, 90°C, 18 h, 78%.



With the protected alkene **79** in hand, we were now in a position to build the pyran ring of compound **72**. We anticipated that cross metathesis of alkene **79** with ethyl acrylate would afford ester **94** as a result of one alkene being electron rich and the other electron poor as this favours cross-metathesis. Indeed this was found to be the case, with the desired product **77** isolated in a yield of 78% in the presence of Grubbs II (**Scheme 2.5**). The formation of the *trans* product was evident by ^{1}H NMR analysis showing a doublet of triplets at δ 5.68 ppm assigned as H_6 with a coupling constant of 15.6 Hz to a signal at δ 7.13 ppm due to H_5. The

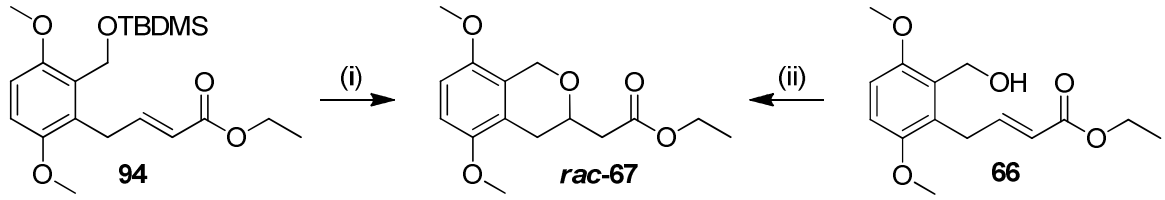
presence of a quartet at δ 4.15 ppm and a triplet at δ 1.26 ppm in the ^{1}H NMR spectrum owing to the ethyl group and a signal at δ 166.9 ppm due to the carbonyl carbon further confirmed the formation of the desired product.



Scheme 2.6 *Reagents and conditions*: (i) Ethyl acrylate, Grubbs II catalyst, CH_2Cl_2, 40°C, 4 h, 86%.

We also attempted cross metathesis on the free benzylic alcohol **65**, even though we suspected that the free alcohol may interfere with the catalyst's activity. To this end, in the presence of Grubbs second generation catalyst, the free alcohol and ethyl acrylate were dissolved in dichloromethane and refluxed for 4 hours. Much to our delight, the *α,β*-unsaturated ester **66** was obtained as a clear oil in 86% yield (**Scheme 2.6**). The use of dichloromethane instead of toluene as solvent allowed for a cleaner reaction and for shorter reaction times than that of the silylated alcohol **79**. This allowed us to avoid both the protection and deprotection steps thus shortening the synthesis. In the analysis of the ^{1}H NMR spectrum we found a quartet and triplet at δ 4.14 and δ 1.26 ppm due to the newly added ester functional group. The ^{13}C NMR spectrum showed the presence of a carbonyl group at δ 171.2 ppm and a strong absorption at 1714 cm^{-1} was noted in the IR spectrum due to the carbonyl group, further confirming that the reaction had been successful.

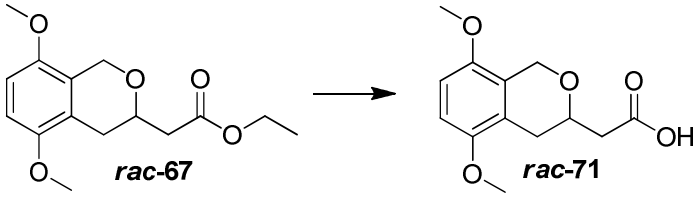
Having successfully formed both metathesis products **94** and **66**, we attempted the internal oxa-Michael addition ring closure to form the pyran ring. Ester **94** was deprotected using tetrabutylammonium fluoride, which in turn led to the formation of the pyran ring system **67** in 88% yield with the ester substituent present on the C3 position of the isochromane nucleus. Alternatively, stirring ester **66** in the presence of sodium hydride afforded the same pyran ring system **67** in 86% yield (**Scheme 2.7**).



Scheme 2.7 *Reagents and conditions*: (i) TBAF, AcOH, THF, 0°C–RT, 18 h, 88%; (ii) NaH, THF, RT, 30 min, 86%.

Analysis of the ^{1}H NMR spectrum of ester **67** showed a clear absence of the *t*-butyl and dimethyl groups of the silyl protecting group of the starting material which were present at δ 0.90 and δ 0.07 ppm respectively. The C1 position of the pyran ring contained hydrogens that were now non-equivalent and gave rise to signals at δ 4.91 and δ 4.62 ppm as compared to the starting materials which showed equivalent hydrogens at the benzylic position producing a singlet at δ 4.74 and δ 4.66 ppm for **94** and **66** respectively. The alkene protons in the starting materials observed as signals at δ 5.68 and δ 5.63 ppm were also noticeably absent which further provided evidence for the formation of the pyran ring. Interestingly, the downfield region of the ^{1}H NMR spectrum was only occupied by two *ortho* coupled aromatic protons. Lastly the most notable feature in the ^{13}C NMR spectrum was the clear absence of the signals previously associated with the alkene carbons at δ 70.7 and δ 41.1 ppm.

With the pyran ring in place, we could now focus on the formation of the γ-lactone ring. This would give us the tricyclic product we required. In order to achieve this we envisaged that the ester group of **67** needed to be converted into the free carboxylic acid to afford **71**, followed by the formation of the lactone ring. Pyran ester **67** was therefore subjected to a KOH–methanol saponification which afforded the desired acid product **71** as a white powder in 95% yield, as shown in **Scheme 2.8**.[40]

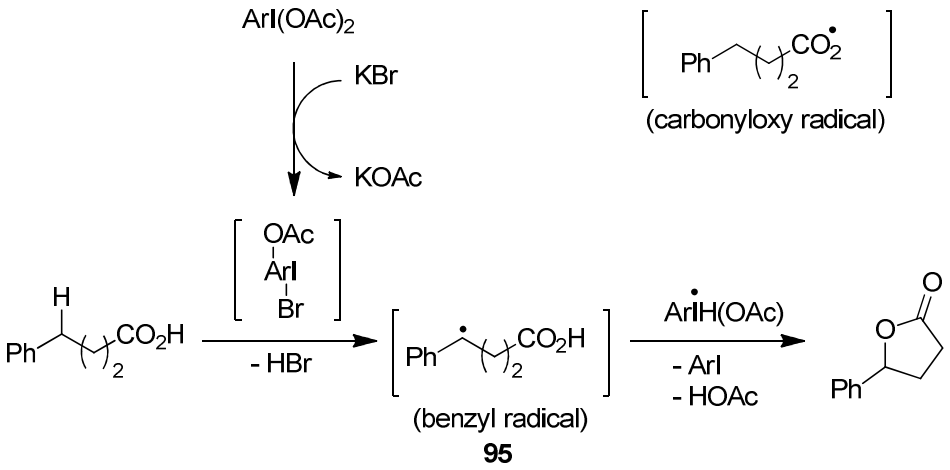


Scheme 2.8 *Reagents and conditions*: (i) KOH, MeOH, RT, 3 h, 88%.

Interpretation of the ^{1}H NMR spectrum unequivocally confirmed the presence of the product through the appearance of a broad singlet at δ 11.00 ppm, which is characteristic of a carboxylic acid. The quartet and triplet at δ 4.19 and δ 1.28 ppm observed in ethyl 2-(5,8-dimethoxyisochroman-3-yl)acetate **67** were also noticeably absent. Similarly, a broad stretch at 3015 cm^{-1} in the IR spectrum further attested to the formation of the carboxylic acid **71**.

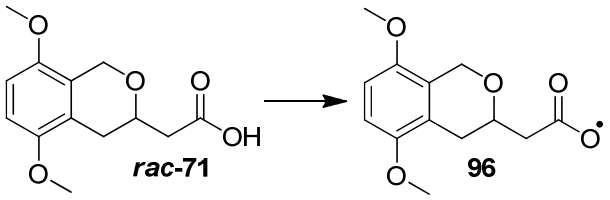
2.4.1. Lactone formation using hypervalent iodine reagents

Having formed acid **71**, the final step remaining in the synthesis of our model compound was formation of the lactone ring of **72**. Kita and coworkers recently reported on methodology to achieve lactone ring closure from similar precursors to our substrate.[41] In their study they developed a method using hypervalent iodine(III) reagents with potassium bromide to form aryl lactones from carboxylic and benzoic acids. In particular, they were able to prepare a range of lactones using *p*-anisiodine diacetate. The proposed reaction mechanism is shown in **Scheme 2.9**. Initially, selective benzylic hydrogen abstraction occurs due to action of the iodine(III) oxidants with KBr. The resulting benzylic radical **95** then paves the way for the successive oxidative lactone formation step.



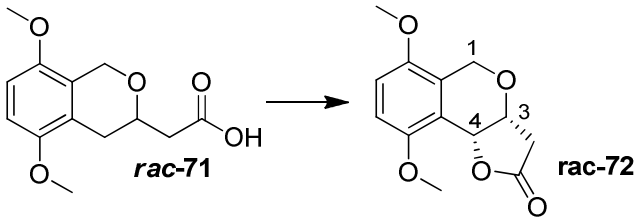
Scheme 2.9: Possible reaction mechanism for the formation of lactones from carboxylic acids

Using the reaction conditions proposed by Kita and co-workers, we attempted the novel lactone forming reaction from our substrate, acid **71**. To this end, potassium bromide and *p*-anisiodine diacetate were added to the acid **71** dissolved in dry dichloromethane and the reaction stirred at room temperature. Disappointingly, TLC analysis of the reaction was inconclusive and only showed that starting material was being consumed, with no new product of different R_f visible by UV. We then turned to TLC stains in an attempt to visualize the forming lactone. After testing a range of TLC stains, ceric ammonium sulfate proved to be the best stain to visualize the forming lactone. Purification of the reaction mixture proved quite difficult and a low yield of 29% of the desired lactone was obtained. We suspect that there are two possible reasons for this outcome. The first reason is that the reaction is low yielding and possible side products may be forming under the radical reaction conditions, such as the possible formation of the carbonyloxy radical **96**, mentioned by Kita, shown in **Scheme 2.10**.



Scheme 2.10

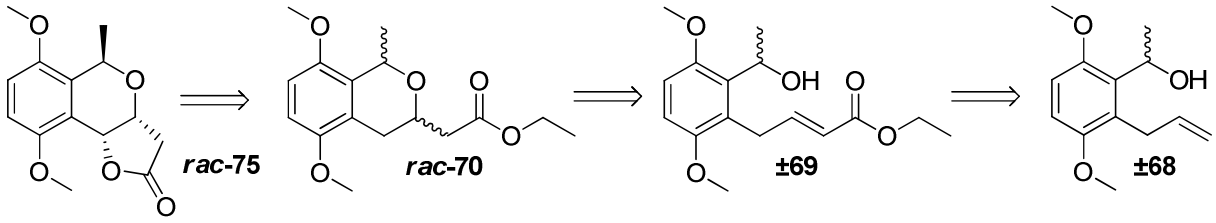
However, TLC analysis did not show the formation of any other products and no other products were isolated by column chromatography. The second reason may be due to the fact that the lactone could not be visualized readily by TLC. Although this result was disappointing, we were pleased that we had synthesised lactone **72**, albeit in a low yield.



Scheme 2.11 *Reagents and conditions*: (i) *p*-Anisiodine diacetate, KBr, CH_2Cl_2, RT, 18 h, 29%.

The most notable feature of the ^{1}H NMR spectrum of lactone **72** was the absence of the OH signal previously observed at δ 11.00 ppm. Simplification of the upfield region of δ 2.50–3.00 ppm was also observed, with the protons in the position α to the carbonyl giving rise to a doublet at δ 2.71 ppm and a doublet of doublets at δ 2.91 ppm. H_4 was now observed slightly downfield as a doublet at δ 5.33 ppm indicating that these protons were now more deshielded owing to the adjacent oxygen atom. The signal at δ 2.71 ppm only showed geminal coupling of 17.5 Hz, while the signal at δ 2.91 showed ^{3}J coupling to the proton at the C3 position of 4.9 Hz in addition to the geminal coupling of 17.5 Hz. The ^{13}C NMR spectrum also clearly showed the downfield shifting of the carbon at C4 from δ 28.15 to δ 71.84 ppm which indicates that this carbon is now bonded to a more electronegative atom. The spectroscopic data compares well with literature,[42] however, the melting point obtained (173–175°C) was higher than the literature value of 162–165°C.

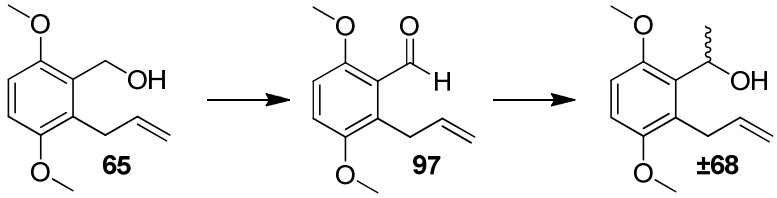
Having had success with the preparation of **72**, we decided to continue with our synthesis of the C1 methyl containing analogue **75**. Using the methodology developed for both the pyran and lactone ring closures, we envisaged that we could begin with racemic alcohol **±68** (**Scheme 2.12**). The racemic synthesis of **75** will be discussed in the next section.



Scheme 2.12: Proposed retrosynthesis of isochromane **75**.

2.5. Preparation of isochromane 75

In order to prepare racemic secondary alcohol **±68**, we would begin the synthesis using our previously prepared alcohol **65**. This would then be oxidised to aldehyde **97**. We would then use a Grignard reaction to introduce the methyl group at C1, thus preparing the desired racemic alcohol ±**68**, shown in **Scheme 2.13**.

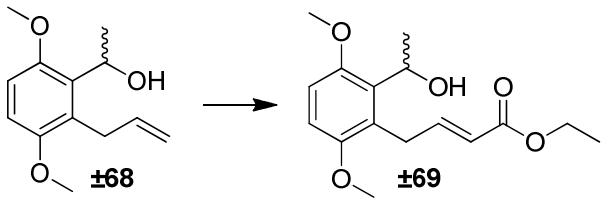


Scheme 2.13: Proposed synthesis of racemic alcohol **±65**.

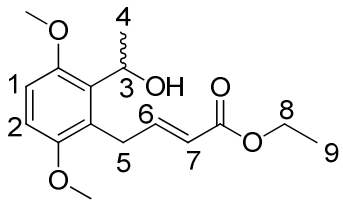
To achieve this, alcohol **65** was oxidised using pyridinium chlorochromate adsorbed onto neutral alumina in dry dichloromethane to afford the aldehyde **97** as a clear yellow oil in 90% yield. The downfield singlet at δ 10.57 ppm in the ^{1}H NMR spectrum, which is characteristic of an aldehyde, proved unequivocally that the product had formed. Additional evidence was the presence of a carbonyl signal at δ 192.5 ppm in the ^{13}C NMR spectrum. With the aldehyde **97** in hand, we turned to the preparation of our Grignard reagent. This was achieved by stirring magnesium turnings with methyl iodide in dry diethyl ether. Once the Grignard reagent had formed, the aldehyde was dissolved in dry THF and added dropwise to the newly formed Grignard reagent. After work-up and purification, the racemic alcohol was isolated as a clear oil

in 84% yield. The IR spectrum showed a broad stretch at 3549 cm^{-1} due to an OH group suggesting the formation of the racemic alcohol ±**68**. In the ^{13}C NMR spectrum, the loss of the aldehyde peak previously observed at δ 192.5 ppm further confirmed that the Grignard reaction was successful. Finally, a signal integrating for three protons at δ 1.53 ppm confirmed the addition of the methyl substituent.

With the racemic alcohol in hand, we could now continue our synthesis of isochromane **75**, the retrosynthesis of which is outlined in **Scheme 2.12**. In order to achieve this, we subjected alcohol ±**68** to a cross metathesis reaction with ethyl acrylate in dry dichloromethane while stirring under reflux. After 18 hours, the crude material was purified to yield the *α,β*-unsaturated ester **69** as a brown oil in an excellent yield of 94% (**Scheme 2.14**). This reaction proved even better yielding than the previous model study.



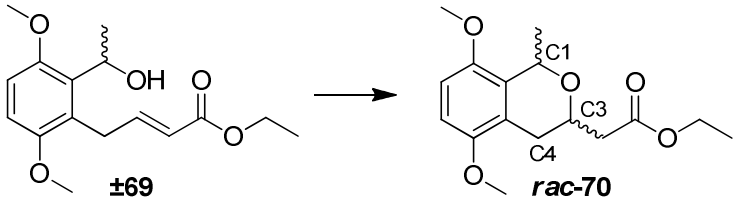
Scheme 2.14 *Reagents and conditions*: (i) ethyl acrylate, Grubbs II catalyst, CH_2Cl_2, 40°C, 4 h, 94%.



The presence of additional signals due to the ethyl acrylate moiety in the ^1H NMR spectrum was an immediate indication of the success of the reaction. Interestingly, a doublet of triplets due to the *β* alkene proton H_6, was significantly deshielded and was found slightly downfield of the aromatic protons at δ 7.05 ppm. This signal showed coupling to the benzylic CH_2, H_5 and the *α*-alkene proton, H_7 found at δ 3.60 and δ 5.66 ppm respectively. The coupling constant between the *α* and *β* alkene protons of J = 15.6 Hz clearly indicates that the *trans* product was obtained. The two upfield signals, a doublet at δ 1.51 and a triplet at δ 1.24 ppm could easily be assigned as H_4 and H_9 respectively based on their multiplicity. Analysis of the ^{13}C NMR and IR spectra showed a downfield signal at δ 166.66 ppm and a stretch at 1712 cm^{-1} respectively which are clear indications of a carbonyl group. High resolution mass

spectroscopic analysis of this compound was in good agreement with the expected value (303.1198 amu, the calculated value for $C_{15}H_{20}O_5$ is 303.1211 amu).

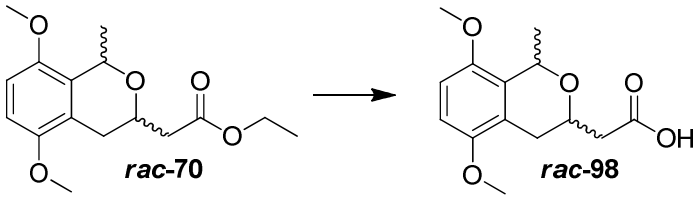
Once again we were ready to attempt the formation of the pyran ring. To effect this, the *α,β*-unsaturated alkene ±**69** in THF was treated with sodium hydride as shown in **Scheme 2.15**. The reaction proceeded smoothly with a colour change from light brown to clear indicating that the Michael addition pyran ring closure was occurring. The product **70** was isolated after purification by column chromatography in 85% yield as a clear oil.



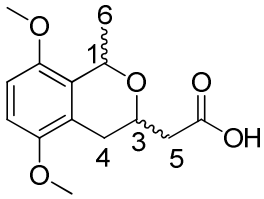
Scheme 2.15 *Reagents and conditions*: (i) NaH, THF, RT, 16 h, 85%.

Subsequent analysis of the ^{1}H NMR spectrum of the product showed the presence of a 50:50 mixture of diastereomers, owing to the additional methyl group at the C1 position of the pyran ring. The most apparent feature of the spectrum was the doubling up of signals, in particular those associated with the two stereogenic centres. This was evident for the quartets at δ 5.08 and δ 4.99 ppm which each integrate for one proton and are due to the benzylic proton at the C1 position of each diastereomer. Similarly, the multiplets at δ 4.44–4.34 and δ 4.00–3.88 ppm were each due to the proton at the second stereogenic centre at the C3 position. Although complex, the multiplet at δ 2.90–2.31 ppm was characteristic of the benzylic CH_2 at C4 as well as the CH_2 *alpha* to the carbonyl group. The presence of this multiplet confirms that the Michael addition reaction was successful as it was not observed in the starting *α,β*-unsaturated ester, but was previously observed for the ring closed product **67**. The additional signals in the ^{13}C NMR spectrum also confirmed that diastereomers were present. This was evident by the two carbonyl signals at δ 171.27 and δ 171.23 ppm. Noticeably, we no longer observed signals due to alkene carbons, with signals only visible in the aliphatic and aromatic regions of the spectrum.

As before, with the pyran ring in place we moved our attention to the formation of the lactone ring. Therefore, using the saponification conditions used in the model system we stirred the ester **70** in a KOH–methanol mixture for 2 hours. After this time, the product was extracted from the acidified aqueous phase to afford carboxylic acid **98** as a mixture of diastereomers in 73% yield (**Scheme 2.16**).



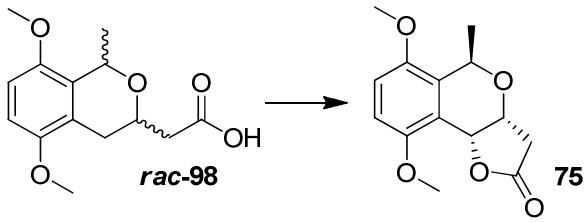
Scheme 2.16 *Reagents and conditions*: (i) KOH, MeOH, rt, 2 h, 73%.



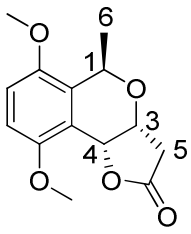
An analysis of the ^{1}H NMR spectrum showed that the 50:50 mixture of diastereomers was still evident. The most distinctive feature in the ^{1}H NMR and IR spectra respectively, was the broad singlet at δ 10.42 ppm and the broad stretch at 2974 cm^{-1} due to the OH group. The ^{1}H NMR spectrum also showed the absence of the quartet and triplet at δ 4.25 and δ 1.29 ppm which were due to the CH_2 and CH_3 groups of the ethyl group. Accordingly, the carbon signals associated with these two groups were also not present in the ^{13}C NMR spectrum. Mass determination of *m/z* 267.1279 amu by high resolution mass spectrometry was in good agreement with the expected value, *m/z* 267.1223 amu. We can therefore confidently say that the desired carboxylic acid was formed.

All that remained now was to induce lactone formation to furnish the tricyclic system **75**. To this end, we dissolved the acid **98** in dry dichloromethane. Potassium bromide and *p*-anisiodine diacetate were then added and the reaction was allowed to stir for 18 hours. Having determined the optimal conditions to visualize the lactone, we once again used CAS as the TLC stain. After work up and purification, we obtained the lactone as a white solid in 26% yield. As before, the yield was disappointingly low and numerous attempts at optimizing this were unsuccessful.

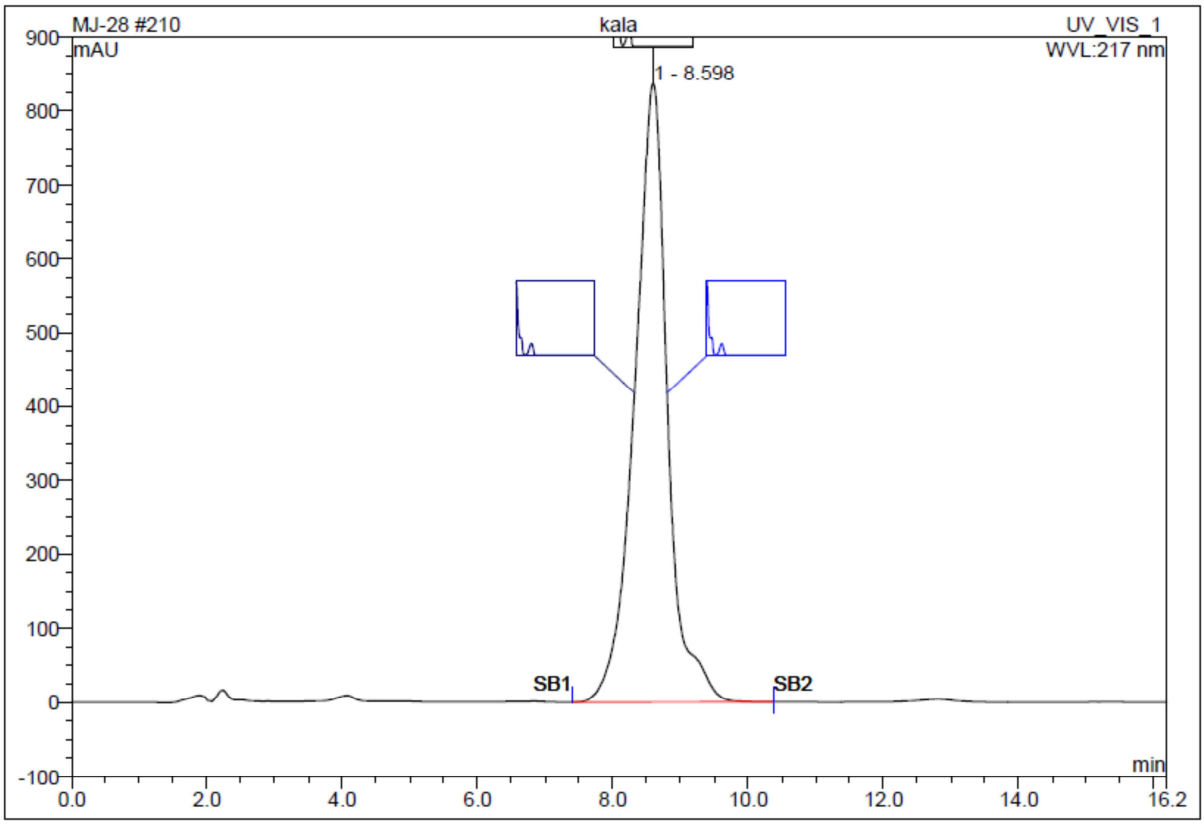
However, we now appeared to have only formed a single diastereomer, presumably the thermodynamic *trans* product, shown in **Scheme 2.17**.



Scheme 2.17 *Reagents and conditions*: (i) *p*-Anisiodine diacetate, KBr, CH_2Cl_2, RT, 18 h, 26%.



In the ^{1}H NMR spectrum, the most distinctive change was that there was no longer doubling up of the signals, as depicted in structure **98**, in the δ 2.50–3.00 ppm region, where previously we observed the mutiplet due to the benzylic CH_2 and the CH_2 *alpha* to the carbonyl. The benzylic proton at C4 shifted downfield due to bonding to the more electronegative oxygen atom, and was observed as a doublet at δ 5.34 ppm with a coupling constant of 2.8 Hz showing coupling to the proton at C3. The non-equivalent CH_2 *alpha* to the carbonyl occurs as a doublet and a doublet of doublets at δ 2.65 and δ 2.92 ppm respectively, where the latter shows coupling of 5.2 Hz to the proton at C3. The COSY spectrum unambiguously confirmed the assignment of H_3 as the doublet of doublets at δ 4.69 ppm with coupling constants of 4.9 and 2.9 Hz. The ^{13}C NMR spectrum clearly showed the downfield shifting of the carbon at C4 from two signals at δ 29.10 and δ 28.19 ppm to a single peak at δ 71.52 ppm, indicating that the lactone had formed as a single diastereomer. HPLC analysis of **75** further proved the formation of one diastereomer, with the presence of a single peak at a retention time of 8.60 min as shown is **Figure 2.3**. The spectroscopic data compared well with literature and confirmed that we had isolated the *trans* product as depicted in structure **75**.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.60	n.a.	836.443	472.596	100.00	n.a.	BMB
Total:			836.443	472.596	100.00	0.000	

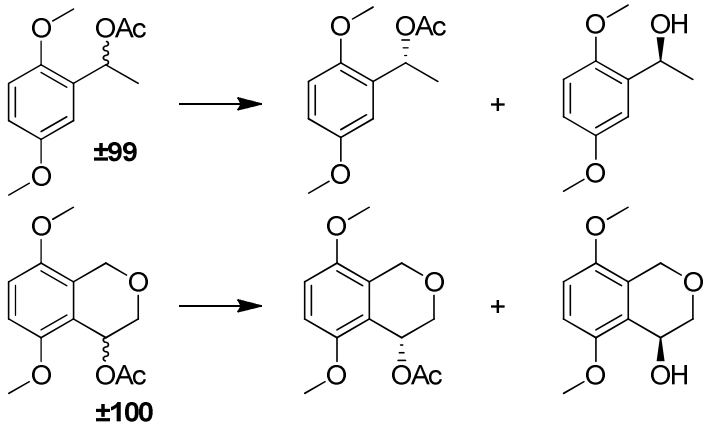
Figure 2.3: HPLC chromatogram of lactone **75**

2.6. Enantiomeric discrimination

The next section will focus on our attempts to prepare isochromane **75** enantioselectively. There are various ways in which to introduce chirality into molecules, including chiral reduction of ketones, the use of chromium complexes to selectively make one enantiomer and more recently, enzymatic routes for the preparation of chiral molecules. During the synthesis of **75**, a racemate of compound ±**68** was obtained which led to the formation of diastereomers along the synthetic route we successfully followed. We were therefore interested in producing the individual enantiomers of **68** which would then potentially allow for the enantioselective synthesis of the desired isochromane **75**.

2.6.1. Background

In recent years, we have investigated the use of enzymes to kinetically resolve racemic mixtures of alcohols. This was first attempted in our laboratories by Govender in her MSc research,[43] where she attempted to kinetically resolve a range of secondary alcohols including ±**99** and ±**100**, and found that the most suitable enzyme for this transformation was Novozyme 525 (also known as CALB). The two transformations that Govender successfully accomplished are highlighted in **Scheme 2.18**[43], which gave rise to both the enantiomerically pure ester and alcohol through kinetic resolution.



Scheme 2.18 *Reagents and conditions*: Toluene, buffer sol (pH 7.5), lipase enzyme, RT, 2h.

In our studies we aim to build on this foundation and develop this synthetic tool within our research group. In the section below, we will briefly introduce the family of lipase enzymes as well as outline the mechanism by which these enzymes operate.

2.6.2. Introduction to Biocatalysis

In recent years, biocatalysis has become a valuable tool used by organic chemists, especially in homochiral molecule production. This is because enzymes are remarkable catalysts that display high chemo-, regio- and enantio-selectivity, but are also capable of accepting a wide range of substrates. The availability and price of most classes of enzymes have significantly decreased and thus enzymes have become economically attractive as catalysts in recent years.[44]

Enzymes are macromolecules which belong to the protein biochemical family. Their unique three-dimensional structure arises from the folding of a linear polypeptide chain. This polypeptide chain in turn consists of a linear sequence of α–amino acids joined by amide bonds. Enzymes possess catalytic activity, where a part of their tertiary structure is responsible for this catalytic activity. This is called the active site of the enzyme and is where enzyme chemistry occurs. The active site is a cavity in which the amino acid side chains are responsible for binding the substrate. Due to the chiral nature of the active site, it is often able to naturally bind one enantiomer of the substrate over the other. This high substrate selectivity is one of the hallmarks of enzyme catalysis. Our aim was to employ a lipase enzyme to kinetically resolve a racemic mixture of alcohols in order to isolate the individual optically active enantiomers.[44]

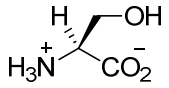
2.6.3. Transesterification reactions using lipase enzymes

Hydrolysis reactions remain vital to cellular metabolism. Lipase enzymes are known to hydrolyse the ester functional groups of fats, lipids and oils, which is an important aspect of food digestion. Not only is the lipase enzyme able to hydrolyse ester groups, but it can also facilitate the reverse acylation reaction when employed with an acyl donor and an alcohol acceptor. This is possible due to the formation of a covalent acyl enzyme intermediate. In synthetic organic chemistry, the use of vinyl acetate as a solvent in acylation reactions has resulted in these

reactions being high-yielding.[44] As mentioned earlier, the chiral nature of the active site will allow one enantiomer of a stereogenic alcohol to be acetylated while the other remains unreacted resulting in regio- and more importantly, enantio-specificity. This ultimately allows for the separation of the enantiomers using standard chromatographic methods.

2.6.4. Lipase reaction mechanism

The CALB lipase enzyme belongs to the *α/β*-hydrolase-fold superfamily, an esterase class of hydrolases.[45] The reaction mechanism by which CALB operates is believed to be that of the serine hydrolases. The active site contains a catalytic triad consisting of serine, histidine and glutamate or aspartate, often referred to as Ser105-His224-Asp187, common to all serine hydrolases. The amino acid serine **101**, shown in **Figure 2.4**, contains a hydroxyl side chain which assists with hydrogen bonding during the substrate and enzyme interaction.[46]

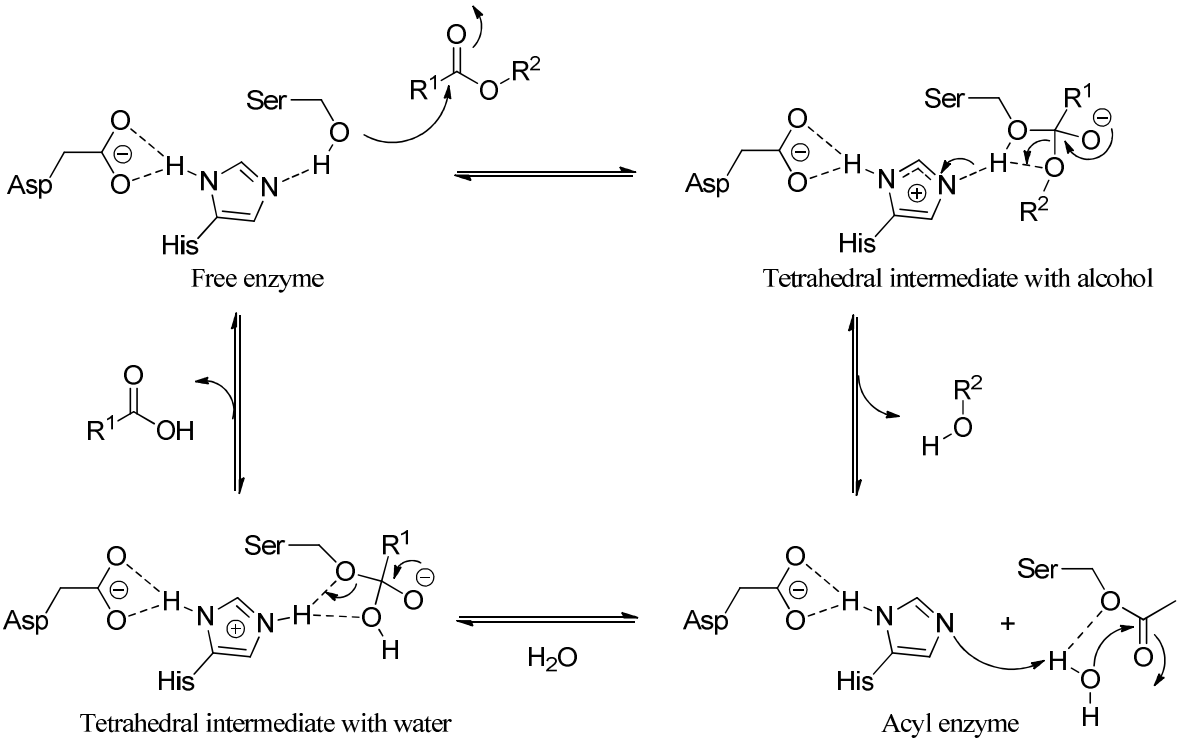


101

Figure 2.4

There have been numerous molecular modelling studies which have been performed to rationalize and predict the enantioselectivity of CALB towards different substrates.[47] The active site of CALB contains an oxyanion hole which is believed to stabilize the transition state as well as the oxyanion reaction intermediate. Also present within the active site is a small cavity called the stereospecificity pocket. This pocket is the site in which secondary alcohols orient one of the substituent during catalysis. The steric requirements of this pocket is what gives CALB its enantioselectivity towards secondary alcohols. As we can see in **Scheme 2.19**, the serine amino acid forms a tetrahedral intermediate with the substrate. Transesterification follows by the formation of a covalent bond with the substrate to form a covalent acyl enzyme and with the release of the secondary alcohol. In the presence of water as the solvent the alcohol will not be re-acetylated and the reaction will not be reversed. The acylated enzyme then forms a tetrahedral

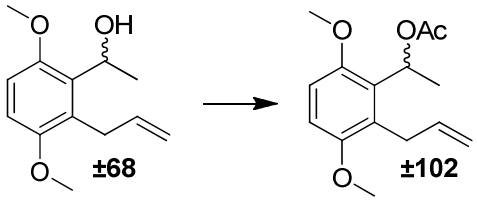
intermediate with water bound in the active site. Subsequent release of the acid results in regeneration of the active site and the enzyme is ready to undergo another catalytic cycle.[47]



Scheme 2.19

In this project, we aimed to employ the natural hydrolysis reaction in an attempt to resolve a racemic mixture of benzylic secondary alcohols. It was therefore necessary to prepare the acetylated alcohol **±102**, which we could subject to the lipase enzyme hydrolysis reaction.

2.6.5. Preparation of 1-(2-allyl-3,6-dimethoxyphenyl)ethyl acetate 102

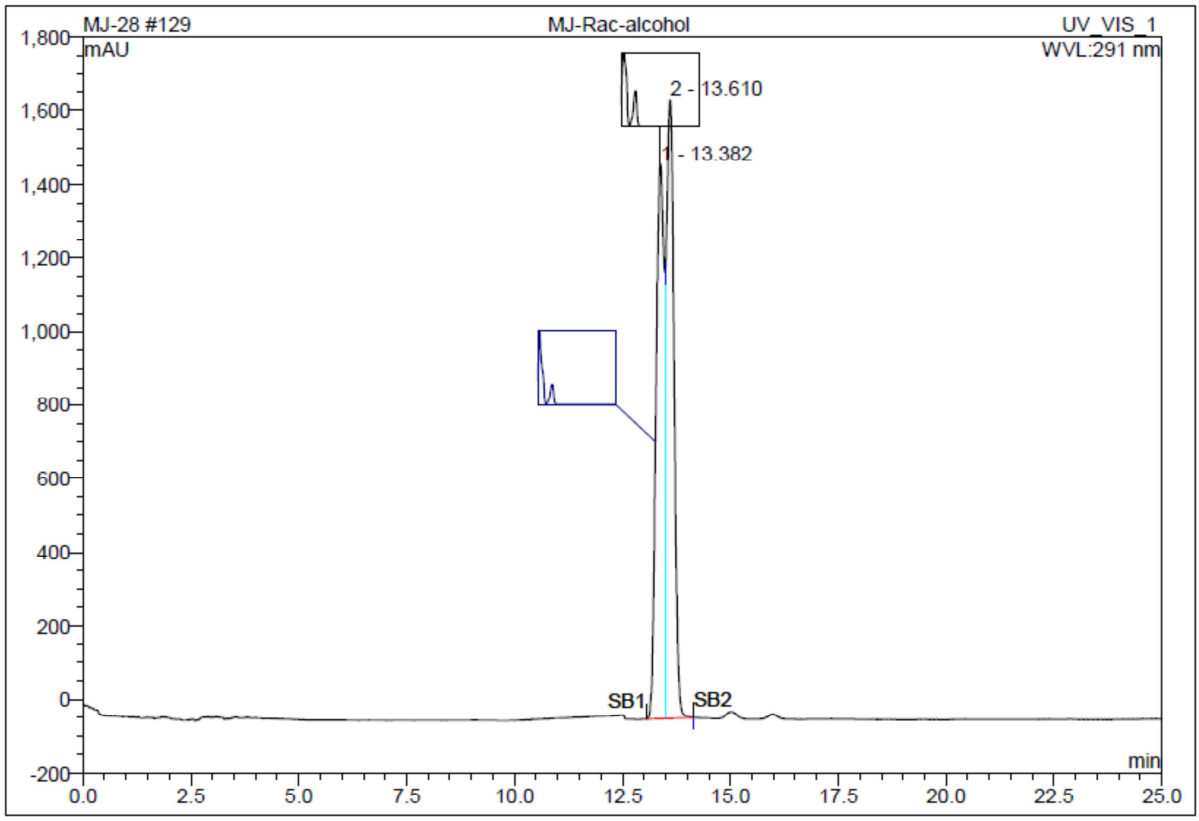


Scheme 2.20 *Reagents and conditions*: Acetic anhydride, DMAP, TEA, THF, RT, 18 h, 75%.

Racemic benzylic alcohol **±68** was converted into the racemic acetate ±**102** in a yield of 75%. This transformation was achieved by dissolving the racemic alcohol **±68** in dry THF and reacting it with acetic anhydride and triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine. The success of the reaction was evident due to the large change in the R_f value of the product as compared to the staring material. The ^{1}H NMR spectrum showed the clear absence of the doublet at δ 4.07 ppm previously due to the secondary hydroxyl group. An additional upfield singlet integrating for three protons was observed at δ 2.02 ppm which is due to the methyl of the newly introduced acetate group. The clear downfield shift of H_4 from δ 5.12–4.88 to δ 6.39 ppm shows that this proton is experiencing additional deshielding due to the acetate group attached. The ^{13}C NMR spectrum further confirmed the formation of the product by the downfield signal at δ 170.57 ppm due to the carbonyl group of the newly formed ester

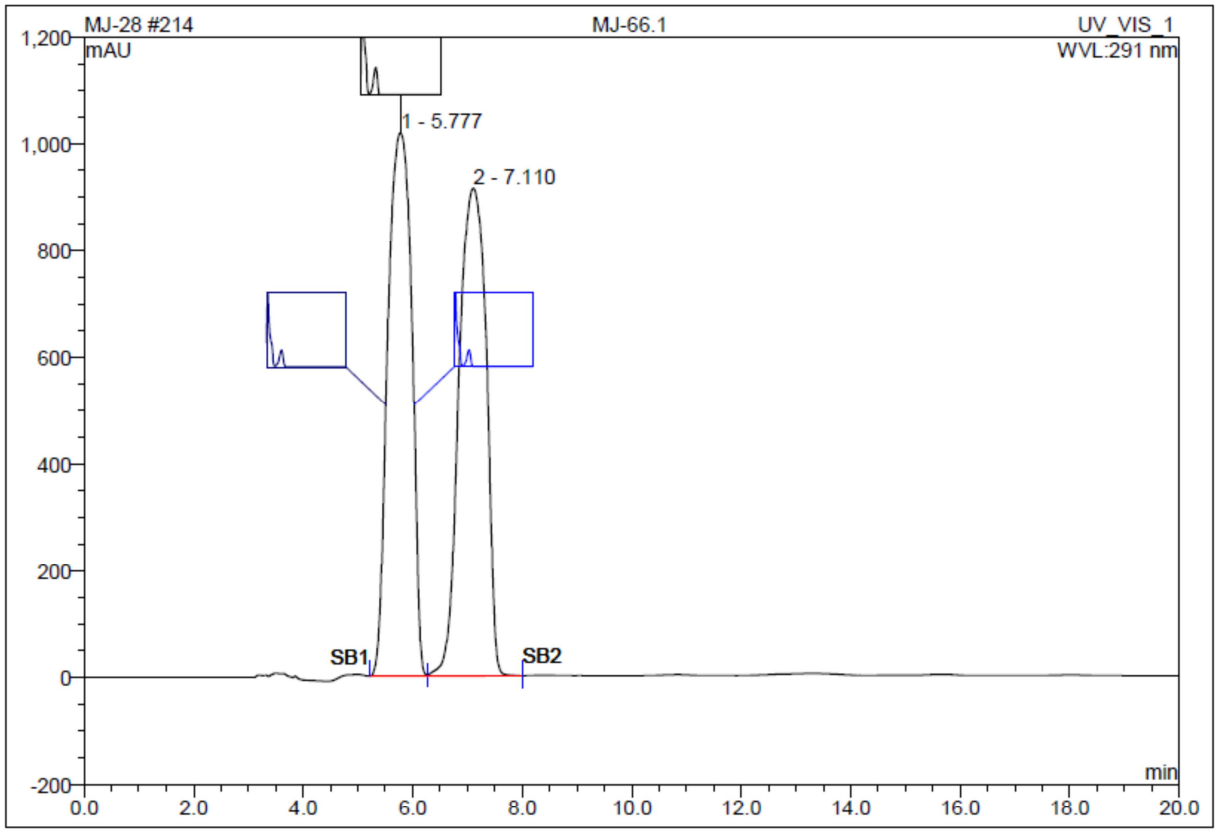
As mentioned before, in her screening process, Govender determined that CALB lipase was suitable for the transformations shown in **Scheme2.18**.[43] With our racemic acetate **±102** in hand we were now in a position to attempt the kinetic resolution of racemic acetate **±102**. Before we could commence with our enzyme-catalysed reaction, we needed to determine the enantiomeric ratio of our racemate which should be 1:1. We tested the separation of the two enantiomers using two chiral high pressure liquid chromatography chiral columns, namely the Chiralcel OJ and the Chiralcel OD columns, and found that the latter showed better separation with a mixture of hexane and isopropyl alcohol as the mobile phase. The separation of the enantiomers of the substrate **±102** and hydrolysis product **±68** proved quite difficult and we decided that a 7.5:92.5 isopropyl alcohol to hexane mixture was the best to use as the mobile phase, as this again

provided us with the best separation. The HPLC chromatograms for **±68** and **±102**, in **Figure 2.5** and **Figure 2.6** respectively show that we have a 1:1 racemic mixture of the two enantiomers of each compound, although for compound **65** the HPLC chromatogram was not ideal.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.38	n.a.	1509.335	318.158	46.94	n.a.	BM
2	13.61	n.a.	1680.530	359.602	53.06	n.a.	MB
Total:			3189.865	677.760	100.00	0.000	

Figure 2.5: HPLC chromatogram of the hydrolysis product **±68**.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.78	n.a.	1018.805	514.622	49.40	n.a.	BM
2	7.11	n.a.	913.741	527.182	50.60	n.a.	MB
Total:			1932.546	1041.804	100.00	0.000	

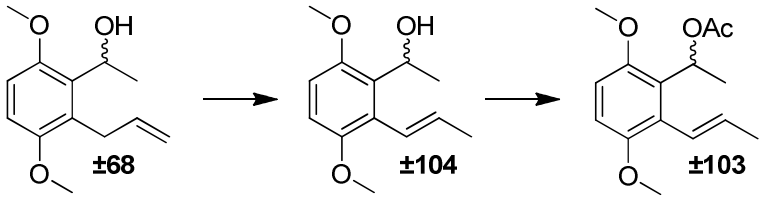
Figure 2.6: HPLC chromatogram of the acetylated product **±102**.

2.6.6. Resolution of ±102 and ±68

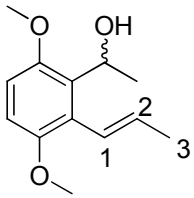
Having determined the optimal conditions for the separation of our enantiomers in the racemic mixture, we were in a position to attempt our enzymatic kinetic resolution of acetate **102**. We decided initially to use CALB as the enzyme cacalyst as it previously showed promising results in our laboratories in a similar transformation. At this point, we decided to test the enzymatic hydrolysis reaction on a simple substrate to determine whether the enzyme we were using was in fact active. To this end, we subjected the test substrate benzyl acetate to our enzyme mediated reaction and, as expected, we observed the formation of the hydrolysed product. This was clearly shown by the change in R_f value by TLC, therefore confirming that the enzyme was active.

We subjected our racemic acetate **±102** to an enzymatic hydrolysis reaction in the hope of yielding a single enriched enantiomer of the corresponding alcohol. The hydrolysis reaction is regarded as the simpler reaction as no acyl donor is required and more importantly, the ester hydrolysis is the natural reaction of the CALB lipase. The reaction conditions required a buffered reaction mixture for the optimal functioning of the enzyme. We therefore employed a tris(hydroxymethyl)amino methane (Tris HCl) buffer set to pH 7.5, which maintained our reaction suspension at pH 7.5. The racemic acetate **±102** was dissolved in a minimum of organic solvent, toluene, and added to the buffer solution. The reaction was vigorously stirred while being maintained at 30°C. Aliquots were taken at intervals and analysed by TLC and HPLC to determine reaction progress. To our disappointment, after several days of stirring, the reaction was not successful as no hydrolysis was observed. We then injected the recovered material on the HPLC Chiralcel OD column which showed our unreacted starting racemic acetate **±102** was untouched in a 1:1 mixture of enantiomers.

We suspected that the steric crowding around the racemic stereocentre of our molecule, especially the *ortho* methoxy and allyl groups, could be hindering the kinetic resolution. We then decided to isomerise the terminal alkene in the hope of changing the sterics around the racemic stereocentre. To achieve this we subjected racemic alcohol **±68** to an isomerization reaction using potassium *t*-butoxide in dry THF at room temperature followed by acetylation to yield racemic acetate **±103**, as shown in **Scheme 2.21**.



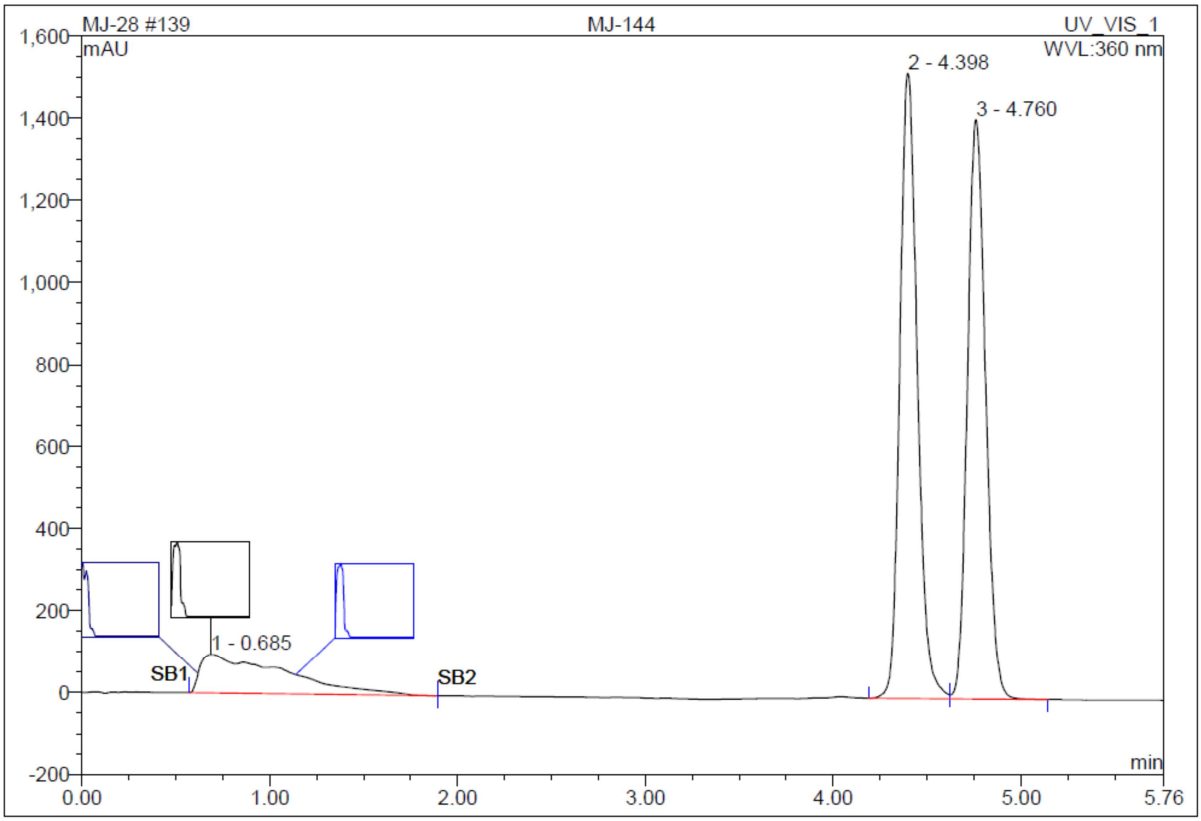
Scheme 2.21 *Reagents and conditions*: (i) KO^{t}Bu, THF, RT, 2 h, 75%; (ii) acetic anhydride, pyridine, RT, 18 h, 68%.



The isomerized alkene **±104** was isolated in 75% yield as a clear oil after purifying the crude material using flash silica gel column chromatography. The presence of an additional upfield signal integrating for three protons at δ 1.91 ppm in the ^{1}H NMR spectrum, indicates that the isomerization was successful. This doublet of doublets at δ 1.91 ppm due to H_3, showed coupling to H_1 and H_2 with coupling constants of 6.5 and 1.7 Hz. The ^{1}H NMR spectrum also showed the change in the nature of the benzylic protons which were previously observed as a multiplet at δ 3.46 ppm integrating for two protons. The benzylic proton, H_1, now integrated for only one proton and was found downfield at δ 6.35 ppm and showed *trans* coupling to H_2 with a coupling constant of 16.1 Hz. This therefore confirmed the exclusive formation of only the *trans* alkene, **±104**. Finally, a doublet of quartets was observed at δ 5.74 ppm and was due to H_2. This alkene proton showed *trans* coupling to H_1 with a coupling constant of 16.0 Hz and coupling to H_3 with a coupling constant of 6.5 Hz. We could therefore confidently confirm that the isomerized racemic alcohol **±104** had formed.

With the isomerized alcohol successfully prepared, all that remained was to acetylate **±104** to form the racemic acetate **±103** which we planned to resolve using our enzymatic hydrolysis reaction. To achieve this, we reacted racemic alcohol **±104** with acetic anhydride in pyridine. The reaction was stirred overnight and after standard work up and purification the racemic acetate **±104** was afforded in a 68% yield. In the ^{13}C NMR spectrum, a downfield signal at δ 170.40 ppm, due to the newly introduced carbonyl group was observed. The carbonyl group was also evident in the IR spectrum which showed a peak at 1727 cm^{-1}. The ^{1}H NMR spectrum further confirmed that the acetate had formed due to the absence of the alcohol which was

previously observed as a doublet at δ 3.96 ppm. Before we could attempt our enzyme resolution reaction, we subjected **±103** to HPLC chromatography. The results, shown in **Figure 2.7**, indicated a 1:1 racemic mixture of enantiomers of **±103**.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	0.69	n.a.	94.801	49.920	13.37	n.a.	BMB
2	4.40	n.a.	1524.636	164.981	44.18	n.a.	BM
3	4.76	n.a.	1412.389	158.498	42.45	n.a.	MB
Total:			3031.827	373.399	100.00	0.000	

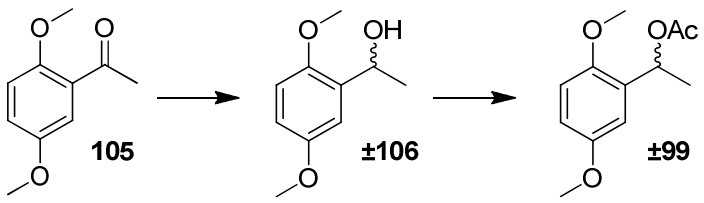
Figure 2.7: HPLC chromatogram of the acetylated product **±103**.

With the isomerized racemic acetate **±103** in hand, we again attempted our enzymatic kinetic resolution reaction. Employing the same reaction conditions as that for the resolution of **±102**, we dissolved acetate **±103** in a minimum of solvent. The dissolved acetate was then added to the buffer solution and the reaction stirred at 30°C. TLC analysis of the reaction did not show any apparent evidence that the product had formed. Nevertheless we continued with HPLC analysis of the reaction mixture. This, however, proved that the unreacted racemic acetate **±103** was still present and thus that the desired hydrolysis reaction was not taking place.

Unfortunately, our suspicions regarding the steric crowding of our substrate appeared to be confirmed. This result clearly proves that the CALB lipase is not as versatile as previously thought and that our compounds which contain an allyl group *ortho* to the benzylic alcohol, cannot be hydrolysed using CALB lipase. To test this theory, we aimed to try the hydrolysis of a similar substrate without the allyl group *ortho* to the benzylic stereogenic centre.

2.6.7. Preparation of 1-(2,5-dimethoxyphenyl)ethyl acetate

We decided to test the kinetic resolution using a simpler adduct, namely 1–(2,5-dimethoxyphenyl)ethyl acetate **±99**, shown in **Scheme 2.22**.

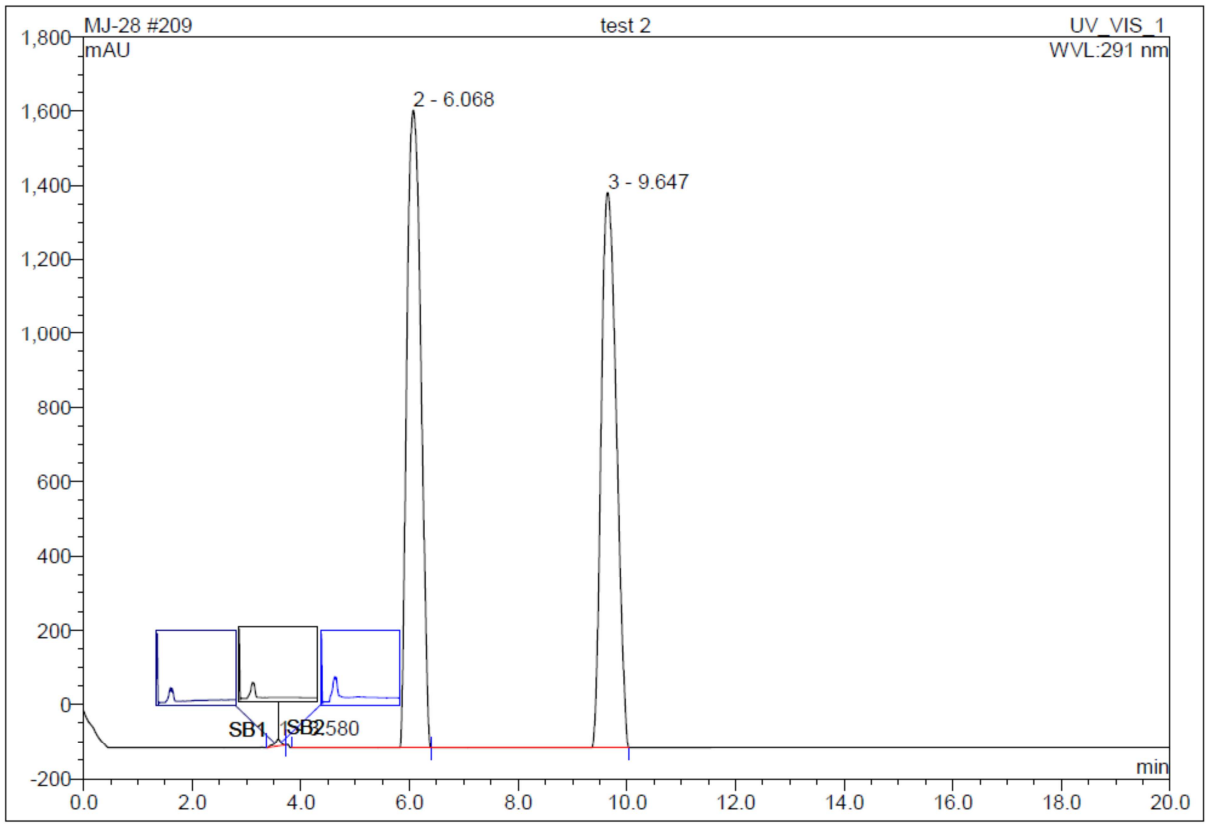


Scheme 2.22 *Reagents and conditions*: (i) $LiAlH_4$, THF, RT, 18 h, 99%; (ii) acetic anhydride, pyridine, RT, 2 h, 98%.

Therefore, commercially available 2,5-dimethoxyacetophenone **105** was reduced to the secondary alcohol **±106** using lithium aluminium hydride in dry THF and the reaction stirred for 2 hours at 40°C. Upon completion of the reaction as monitored by TLC, the mixture was cooled to 0°C and quenched with water. Purification of the crude material furnished the racemic alcohol

in quantitative yield. The ^{1}H NMR spectrum unequivocally proved that we had formed the racemic alcohol **±106** with the presence of a broad singlet at δ 3.01 ppm due to the hydroxyl group. The IR spectrum also confirmed the presence of the hydroxyl group with a broad peak visible at 3410 cm^{-1}. The racemic alcohol **±106** was readily acetylated by reacting it with acetic anhydride and triethylamine in the presence of a catalytic amount of DMAP affording the racemic acetate **±99** in 98% yield. The ^{1}H NMR spectrum attested to the success of the reaction showing an additional upfield signal at δ 2.09 ppm integrating for three protons due to the methyl of the acetate group. The ^{13}C NMR spectrum also clearly showed a downfield signal at δ 170.07 ppm due to the carbonyl group which further confirmed the successful acetylation of our alcohol.

All that remained was to determine whether the racemic acetate could be selectively hydrolysed enzymatically. We once again dissolved racemic acetate **±99** in a minimum of solvent and added this to the prepared buffer. The reaction was stirred at 30°C with vigorous stirring. After stirring for 18 hours, completion of the reaction was determined by HPLC analysis of an aliquot of the reaction mixture. We were pleased to see that as expected, we had a 50% conversion of the starting acetate to what we hoped was a single enantiomer of the corresponding alcohol. This can be seen in **Figure 2.8**, where the ratio of peaks are equal, but with a shift in retention time of one of the peaks to 6.07 min, while the acetate starting material had a retention time of 9.65 min. Pleased with this result, we then extracted the organic material into EtOAc, and separated the products using column chromatography to yield the expected alcohol **±106** in 43% yield and the acetate **±99** in 56% yield.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	3.58	n.a.	20.248	2.747	0.27	n.a.	BMB
2	6.07	n.a.	1720.493	513.690	51.36	n.a.	BMB
3	9.65	n.a.	1498.840	483.805	48.37	n.a.	BMB
Total:			3239.581	1000.242	100.00	0.000	

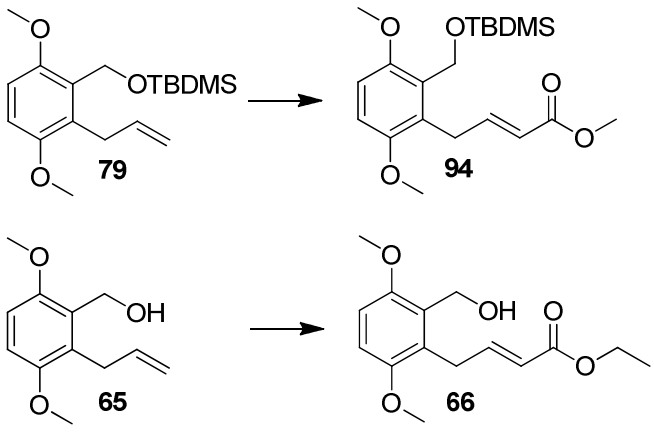
Figure 2.8: HPLC chromatogram confirming an equal ratio of acetylated product **±99** and hydrolysis product **±106**.

Satisfied with this result we could confidently say that the allyl or styrene substituent in racemic acetate **±102** was hindering the enantioselective hydrolysis of the acetate group of **±102**.

2.7. Concluding remarks pertaining to the synthesis of isochromane

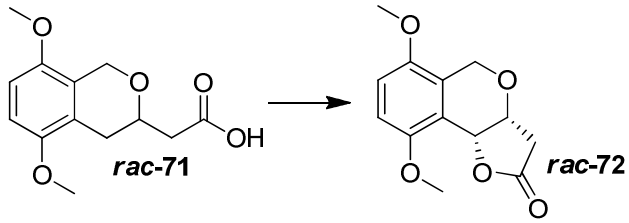
In this section of the PhD thesis we aimed to develop a feasible method to access the isochromane core of the pyranonaphthoquinones and in particular, 1,3-disubstituted isochromanes containg a fused *γ*-lactone ring. Our keys steps in this study were the use of cross metathesis as well as a novel radical lactone cyclisation reaction to afford both 1,3-disubstituted isochromanes and the tricyclic isochromanes which are prevalent in many pyranonaphthoquinone compounds. We also hoped to use CALB lipase to kinetically resolve a racemic mixture of the isochromane precursors, as part of a stereoselective approach to the isochromanes.

Our initial synthetic scheme successfully resulted in the formation of isochromane **72** in an overall yield of 9.5% over 8 steps. As mentioned, the first of our two key steps was a cross metathesis reaction. Our initial strategy was to protect alcohol **65** thus forming the silylated product **79**. This was thought to be crucial as the Grubbs catalyst would be incompatible with the free alcohol. However, we attempted our metathesis reaction on the free alcohol **65** and were pleasantly surprised to find that the metathesis reaction worked better than on the silylated alkene **79**, thereby, shortening our synthetic route (**Scheme 2.23**).



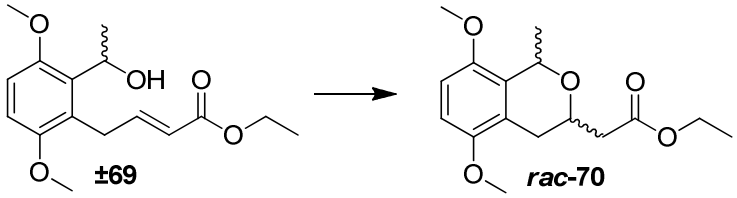
Scheme 2.23

We were then able to construct the required pyran ring readily by using an oxa-Michael addition reaction. All that then remained was the formation of our γ-fused lactone ring to furnish **72**. The formation of the lactone ring was more challenging than originally thought and we encountered a few problems with this step, including with visualization of the lactone product **72** by TLC. We eventually managed to isolate our lactone **72**, shown in **Scheme 2.24**, albeit in a disappointing yield.



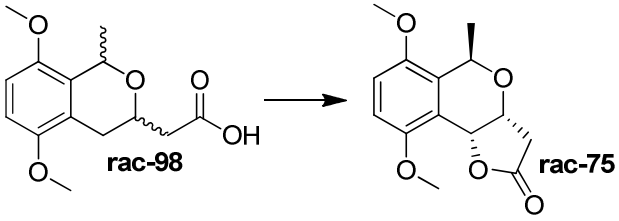
Scheme 2.24

Employing the same reaction methodology used for the synthesis of isochromane **72** we formed the pyran ring **70** in 2.3% over 8 steps, as highlighted in **Scheme 2.25**.



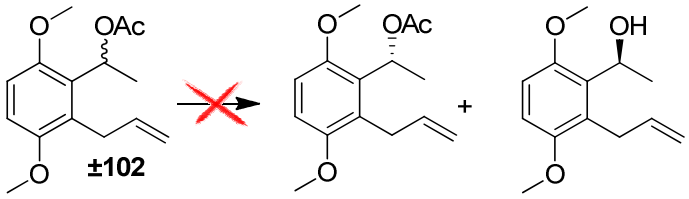
Scheme 2.25

With the pyran ring constructed, we moved on to forming our lactone ring containing compound **75** (**Scheme 2.26**). Once again, we obtained a poor yield for our lactone ring closure using the hypervalent iodine reagents. Upon closer inspection we were pleased to determine that we had formed only one diastereomer of the expected lactone **75**. This was corroborated with literature spectroscopic data, and by HPLC analysis of our product.



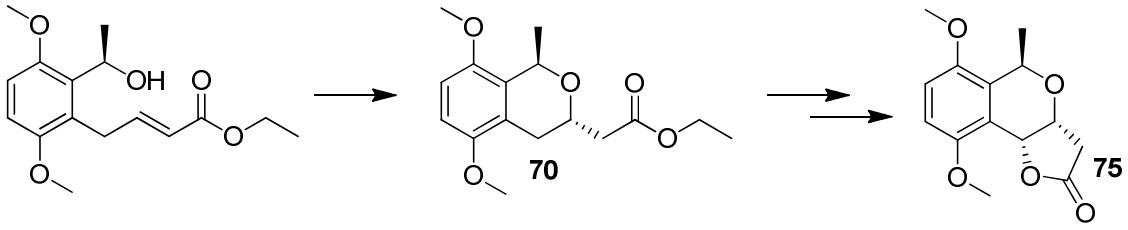
Scheme 2.26

We then turned our focus to the enantioselective preparation of isochromane **75**. We initially envisaged that we could kinetically resolve our racemic alcohol using CALB lipase. Unfortunately, we were unable to resolve racemic acetate ±**102** with this enzyme (**Scheme 2.27**). A major factor in the enzymatic hydrolysis reaction is the ability of the substrate to enter the active site and undergo hydrolysis. This was clearly evident as we suspected that the secondary alcohol of our substrate was too sterically crowded. A simple omission of the allyl group was all that was needed to effect kinetic resolution. There have been numerous research articles regarding kinetic resolution,[48-50] and it is reported that CALA allows substrates containing larger groups attached to the stereogenic centre to be kinetically resolved. In recent months, the knowledge base regarding enzyme reactions has significantly increased and various enzymes, CALA among others, are being tested to resolve racemic acetate ±**102**.



Scheme 2.27

Although our enzymatic hydrolysis didn't give us the desired outcome, the results obtained during this study bodes well for future research. Looking into the future, CALA lipase enzyme could be assessed in the kinetic resolution of alcohol ±**68**. If this transformation is successful, a single enantiomer of alcohol **68** could be used in the enantioselective synthesis of isochromane **75**, first by forming a single diastereomer of pyran ring **70** and finally the lactone ring of the desired product **75**, as shown in **Scheme 2.28**.



Scheme 2.28

This completes our section on pyranonaphthoquinones. The work reported here serves as a foundation for the development of a stereoselective route to isochromanes.

Chapter 3: Spiroketals - An Introduction

3.1. Introduction

The spiroketal functionality is prevalent in a number of naturally occurring substances that have been isolated from various sources such as insects, microbes, plants, fungi and marine organisms. These sources have been reviewed in the literature and can be divided into two categories, namely the Pre-1970 metabolites and the Post-1970 metabolites. Compounds which contain the spiroketal functionality have been shown to possess a range of biological activities and as such have attracted synthetic attention.[51]

3.1.1. Pre-1970 metabolites

The first spiroketal containing structures observed in nature were the saponins and the sapogenins.[52] These metabolites were isolated from plant sources and are generally named after their natural sources. They were found to possess a steroidal nucleus which contains a spiroketal assembly. There is very little variation in the structure of these spiroketal-containing compounds, with only a few variants known. **Figure 3.1** shows two of the most common spiroketals of this class **107** and **108**, where the difference between them occurs at C25. Tomatidine **109** is an interesting structural variant that is an aza analogue of **107**.[53]

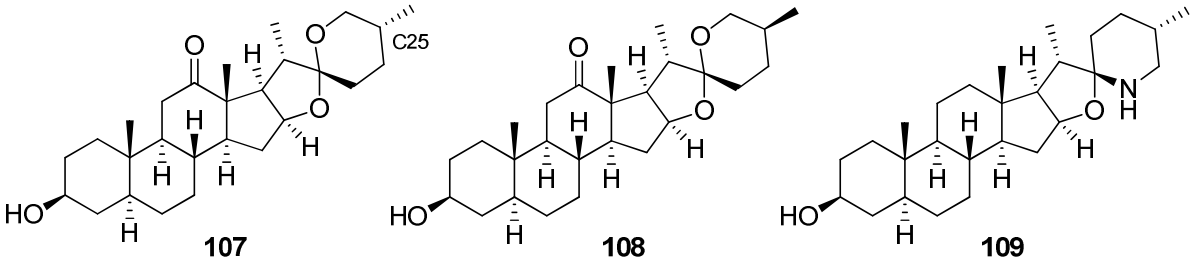


Figure 3.1

Examples of other spiroketals found in nature are the spiroketal enol ethers that have been isolated from the *Asteraceae* plant family. These types of spiroketals contain one or more characteristic acetylene units in the side chain. They are also found as either the *Z*- or *E*-isomer of the enol ether alkene. Variation of the side chain has been shown with the presence of the common enediyne types **110** and **111** or the thioether **112** or thiophene **113** containing derivatives (**Figure 3.2**).[54]

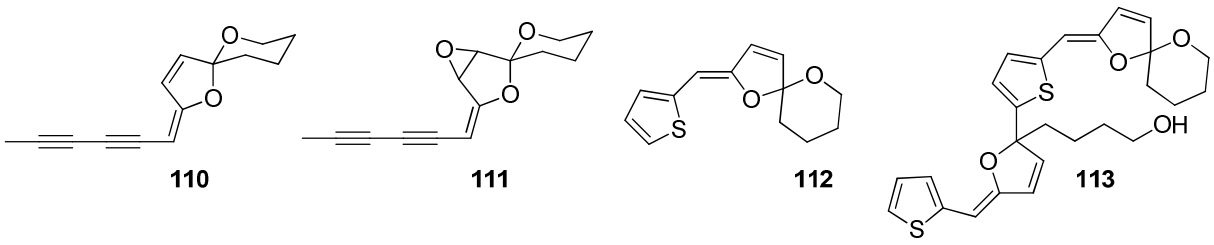


Figure 3.2

Spiroketal containing compounds range from the simplest, such as oxetone **114**, shown in **Figure 3.3**, and its derivative **115**, isolated from Japanese hop oil;[55] to the more complex spiroketal oligomycin **116** which has been demonstrated to act as a potent oxidative phosphorylation inhibitor.[56] The identity of spiroketal **116** has been determined by X-ray crystallography.[57]

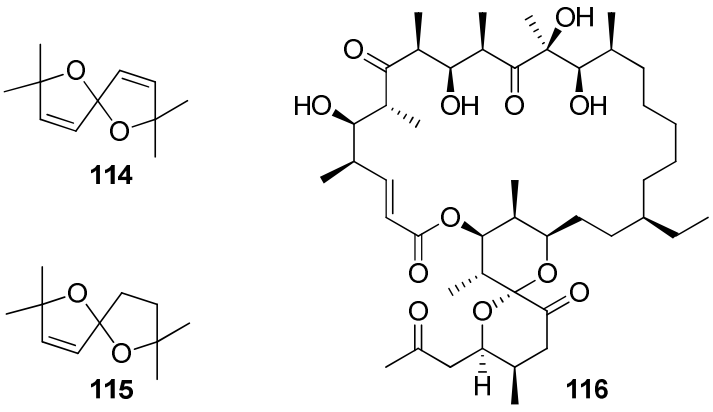
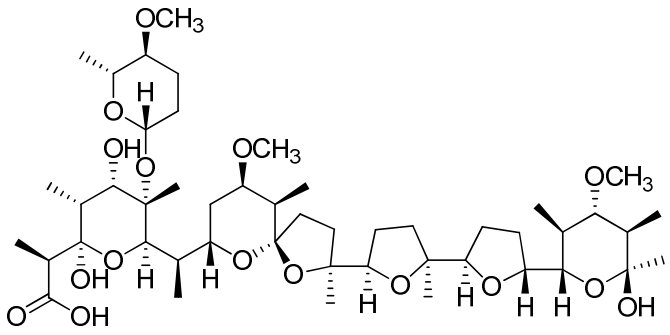


Figure 3.3

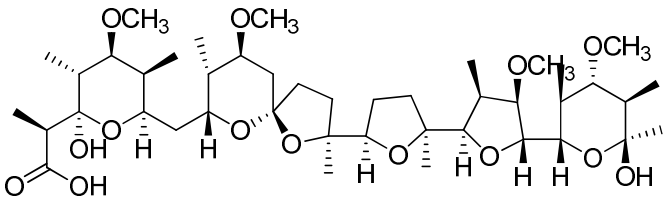
3.1.2. Post-1970 metabolites

3.1.2.1. Polyether ionophores

Another class of these naturally occurring spiroketals have been derived from polyketides and as such have been named polyketide-derived polyether antibiotics. These antibiotics have been isolated from filamentous branching bacteria *Actinomycetes* and characterisation of these metabolites has shown that the spiroketal functionality forms only a very small part of more elaborate structures. Examples of some of these spiroketal ring systems, **117** and **118** are shown in **Figure 3.4** where the 1,6–dioxaspiro[4.5]decanes predominate.[51]



117



118

Figure 3.4

Also members of this class are the trioxadispiroketal-containing compounds. These metabolites contain two spiroketal substructures, as shown in lenoremycin **119**[58] and dianemycin **120**[59] in **Figure 3.5**.

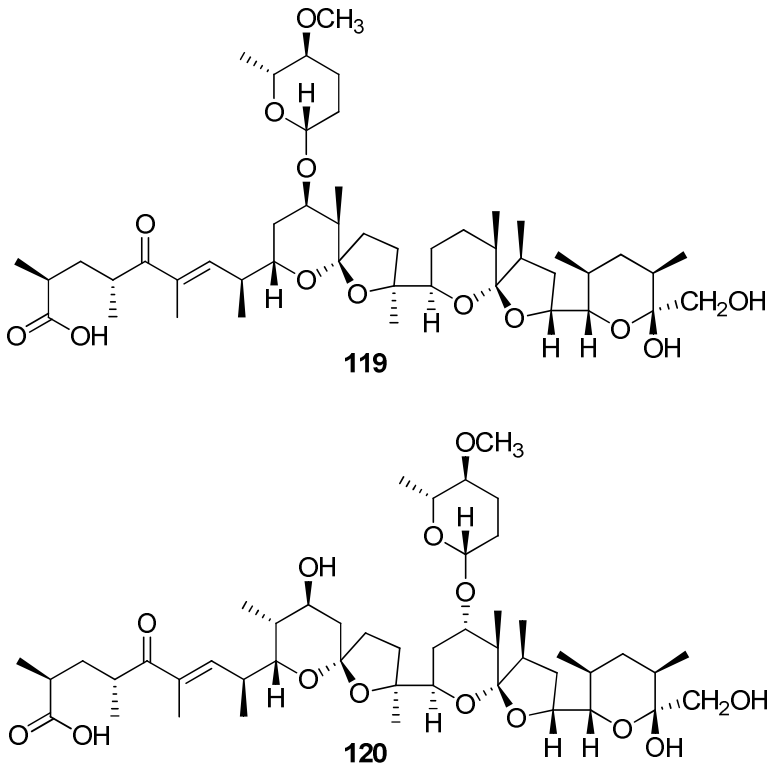


Figure 3.5

3.1.2.2. Spiroketals from insect pheromones

Simple spiroketals have been isolated from many species of flying insects. These species include bees, wasps, beetles and flies, and have been found to exhibit pheromonal activity.[60-62] The majority of spiroketal compounds isolated contain an unbranched carbon skeleton and functionalisation does not readily occur. Spiroketals **121** and **122**, (**Figure 3.6**) have been identified as odours of wasps of *Paravespula vulgaris* and possess an unbranched dihydroxynonanone skeleton.[60] A second example of this class is the major sex pheromone of the olive fly, *Dacus oleae*, which has been identified as 1,7-dioxaspiro[5.5]undecane **123**.[62] The olive fly is generally found throughout the Mediterranean basin as well as parts of North Africa. It is one of the major pests of olives, hence its name. Compound **123** was the first spiroketal to be identified as a sex pheromone.

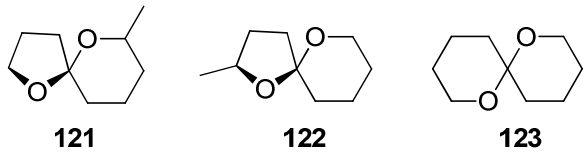


Figure 3.6

3.1.2.3. Milbemycin and avermeticin antibiotics

This class of antibiotics has generated the most interest in spiroketal synthesis due to the medicinal properties which they exhibit. These properties include insecticidal and acaricidal activity, however, the fact that they possess low mammalian toxicity has piqued interest in them as potential treatments for parasitic infections. One particular spiroketal, ivermectin **124**, has been shown to inhibit the transmission of *Onchocerca volvulus* microfilariae by the black fly *Simulium yahense* (**Figure 3.7**).[63] The transmission of *Onchocerca volvulus* microfilariae is responsible for the parasitic disease onchocerciasis (also known as river blindness) which sometimes results in permanent blindness. The current course of treatment for this disease involves the use of ivermectin and has been generously donated by Merck & Co for the control of this disease.[64]

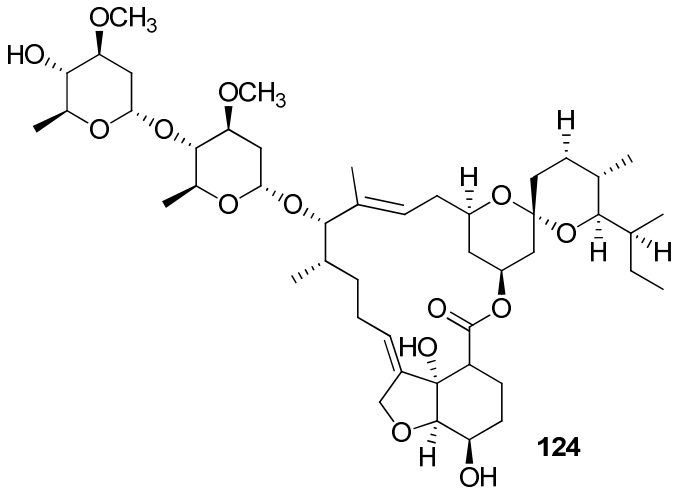
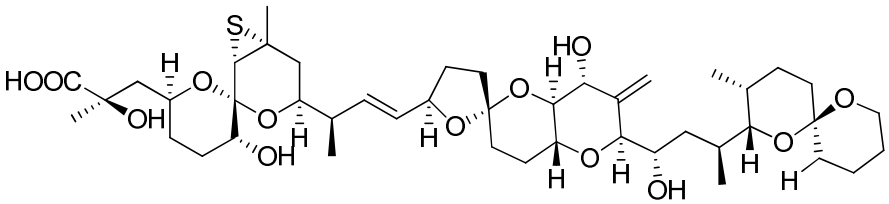


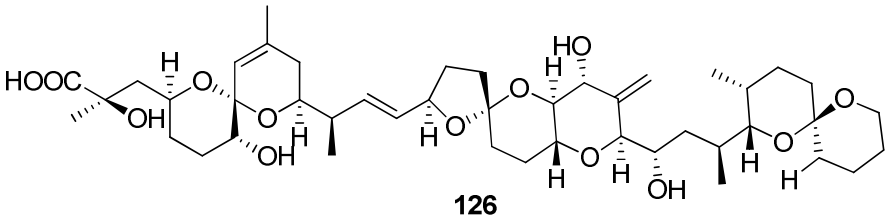
Figure 3.7

3.1.2.4. Spiroketals of marine origin

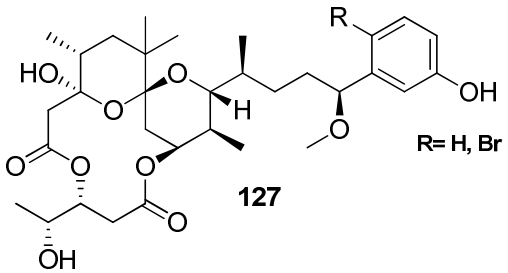
Most spiroketals from the marine environment exhibit some form of toxicity and the first spiroketals of this class to be described were the polyether carboxylic acids, acanthafolicin **125**[65] and okadaic acid **126**, shown in **Figure 3.8**.[66] These compounds were initially isolated from sponges, however, these compounds are believed to be produced by symbiotic microorganisms and cause diarrhetic shellfish poisoning. Other toxic metabolites such as **127** from blue-green algae have shown carcinogenic activity while other members of this class are responsible for contact dermatitis affecting swimmers of the Pacific Islands.



125



126



127

Figure 3.8

3.1.3. Aromatic spiroketals of interest

Spiroketal containing compounds more closely related to the compounds of interest to us are the aromatic spiroketals. These spiroketals include the griseusins and the rubromycins.[67]

The griseusins, specifically griseusin A **128** and B **129**, shown in **Figure 3.9**, are members of the class of pyranonaphthoquinones discussed in Chapter 1. Griseusin A and B have been isolated from a soil sample inoculated with *Streptomyces griseusis*.[68] They are synthetically attractive as they contain a 1,7-dioxaspiro[5.5]undecane ring fused to a juglone moiety. In addition, the same γ-lactone ring found in kalafungin **9** is evident. As discussed earlier, these compounds act as bioreductive alkylating agents, and are active against gram positive bacteria, pathogenic fungi and yeasts, thus making them attractive synthetic targets.

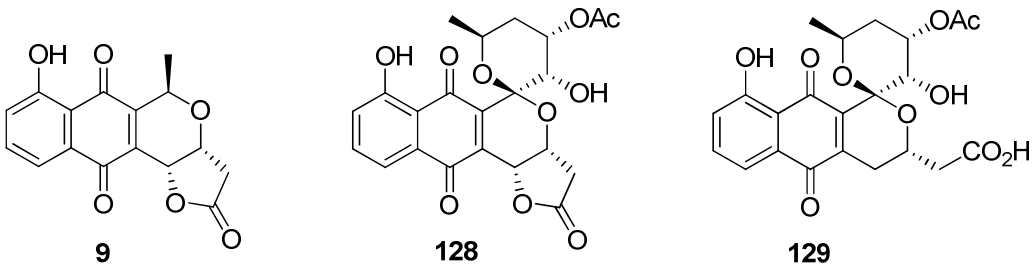
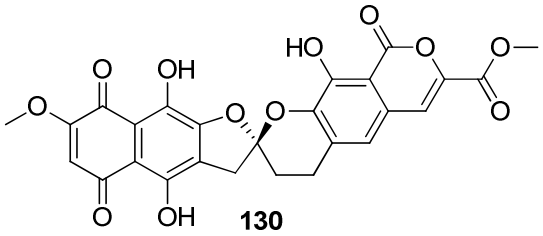


Figure 3.9

Other compounds of interest to us are the rubromycins.[67] The rubromycins are typified by an aliphatic 5,6-spiroketal core **130** fused to an aromatic naphthoquinone and isocoumarin moieties as for **130**. These compounds were initially isolated by Brockmann and co-workers as a red-coloured dye produced by *Streptomyces collinus*.[69,70] The rubromycins are considered potent antimicrobial agents and more importantly, as anticancer agents they suppress telomerase enzyme activity leading to cell death.[71]



130

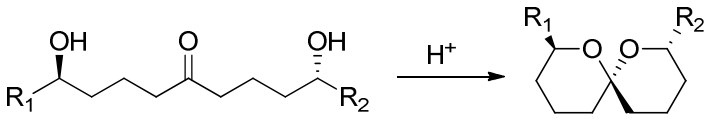
Figure 3.10

3.2. Selected synthetic strategies to spiroketals

A number of synthetic strategies have been developed for the preparation of spiroketal-containing compounds. A few selected strategies will be discussed below, with the emphasis on the preparation of the griseusin skeleton.

3.2.1. Acid catalysed approaches

The most widely used method for spiroketal formation is the acid-catalysed dehydration of dihydroxy ketones, shown in general **Scheme 3.1**.[72] This method results in the formation of the lowest energy spiroketal stereoisomers. This method is highly effective for the preparation of anomeric spiroketals and therefore appropriate for most natural products possessing this structural feature. This method is not without serious drawbacks, including the intolerance of acid-labile functional groups. Furthermore, the synthesis of nonanomeric or contrathermodynamic spiroketals using this methodology is more challenging.[73]

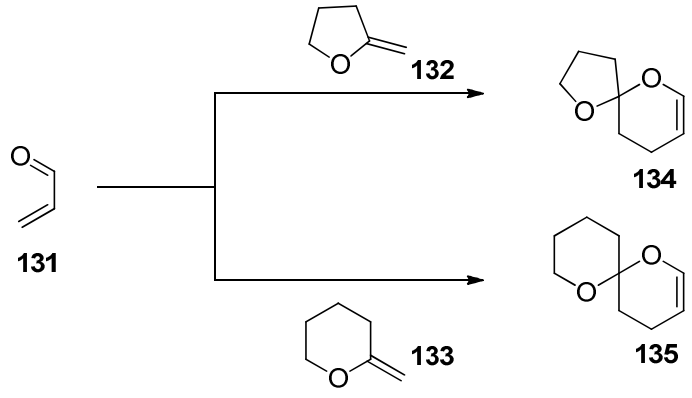


Scheme 3.1

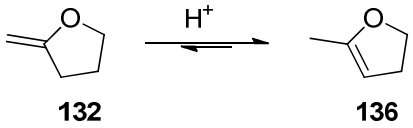
The past 30 years has seen the development of transition-metal-catalysed methods as an alternative to the acidic conditions used previously. The use of these types of methods has allowed for different strategies to be employed which enable different modes of reactivity. These methods have also provided new classes of compounds which can serve as spiroketal synthons which have allowed for new advanced strategies to be adopted. A few selected strategies of this approach will be highlighted. For a more comprehensive view, review articles by Perron and Palmes should be consulted.[51,73]

3.2.2. Hetero-Diels-Alder reaction methodology

The use of the hetero-Diels-Alder (HDA) reaction methodology has proven to be an efficient strategy for accessing the spiroketal functionality. The HDA method is versatile as it allows for the modification of the prepared spiroketal system. A general outline is shown in **Scheme 3.2**, where the [4+2] cycloaddition reaction between enone/enal **131** and α-methylenefuran **132** or α-pyran **133** will result in the construction of [6,5] and [6,6]-spiroketals **134** and **135**, respectively. The only challenge that this method presents is the isomerisation of the exo-vinyl ether **132** to the thermodynamically more stable endo-vinyl ether **136** which readily occurs under mild acidic conditions (**Scheme 3.3**).[74]

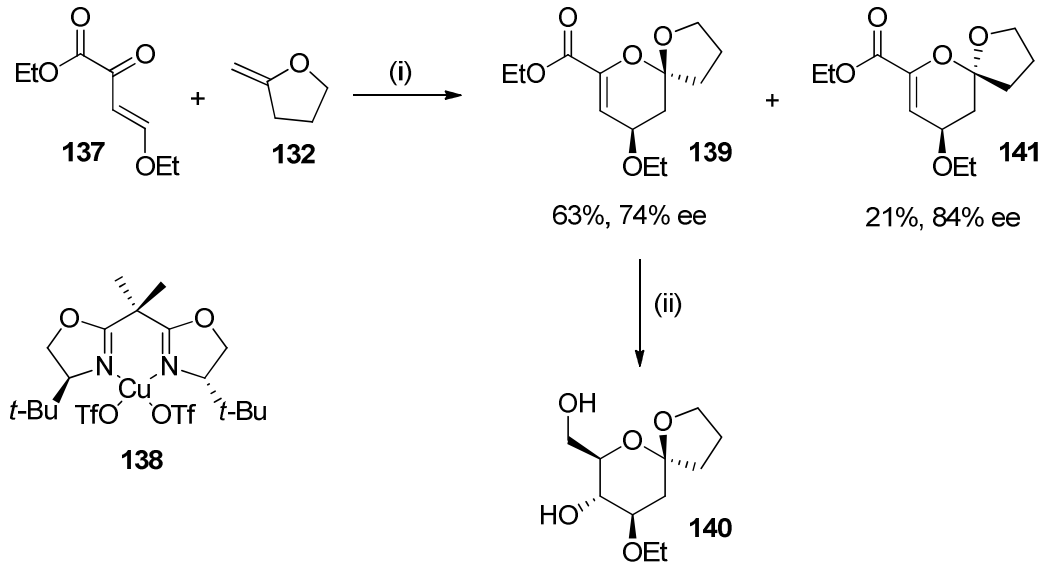


Scheme 3.2: The Hetreo-Diels-Alder (HDA) reaction for the synthesis of spiroketals.



Scheme 3.3: Undesired isomerisation of the methylene protons

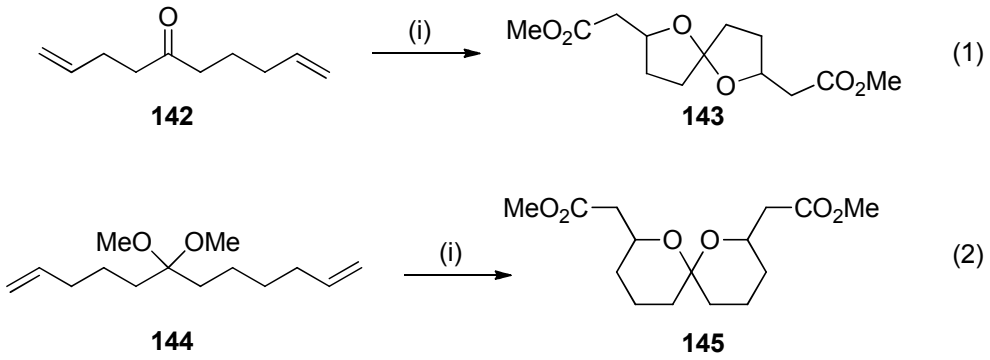
The preparation of optically active spiro-carbohydrates was achieved by Jorgensen and co-workers using an enantioselective HDA approach (**Scheme 3.4**). In their approach, *β*,*γ*-unstaturated *α*-ketone ester **137** was reacted with *α*-methylenefuran **132** in the presence of the transition metal catalyst **138**. This transition-metal mediated approach afforded the *endo*-spiroketal **139** as the major diastereomer in 74% *ee*. The carbohydrate derivative **140** was obtained by functionalisation of the alkene. The hydroxyl group was introduced in an *anti*-Markovnikov sense.[75]



Scheme 3.4: *Reagents and conditions*: (i) 20 mol% **138**, THF, –78°C, 63% (for **139**, 74% ee), 21% (for **141**, 84% ee); (ii) a. $LiAlH_4$, b. BH_3-SMe_2, c. NaOH, H_2O_2, 40%, 100% de.

3.2.3. Oxycarbonylation of dienones

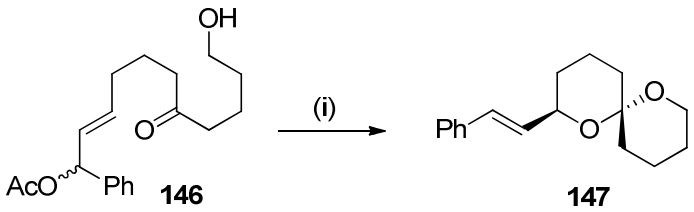
The use of alkenes in spiroketal formation via π-bond activation has been extensively employed. During their construction of bifunctional spiroketals, Yadav and co-workers utilised a transition metal palladium-catalysed double cyclisation of dienones.[76] Dienone **142** was converted to spiroketal **143**, with the concomitant introduction of two side chains. This was achieved using catalytic palladium(II) chloride in the presence of copper(II) chloride, carbon monoxide and trimethylorthoformate. The reaction is presumed to proceed through a dimethyl ketal intermediate which was formed *in situ*. To substantiate this claim, a control experiment was conducted where ketal **144** was treated with the same reaction conditions to furnish spiroketal **145** (**Scheme 3.5**).



Scheme 3.5: *Reagents and conditions*: (i) cat. $PdCl_2$, $CuCl_2$, CO, MeOH, trimethylorthoformate, 50% (for **143**), 85% (for **145**).

3.2.4. Monoacetylated ketodiol cyclisation

The diastereoselective construction of tetrahyropyrans from allylic acetates was reported by Cossy and co-workers, shown in **Scheme 3.6**. This type of cyclisation reaction was facilitated by an iron(III) catalyst which was used to cyclise hydroxy ketone **146** to afford spiroketal **147** where a carbocation intermediate was proposed through which the cyclisation had occurred. [77]

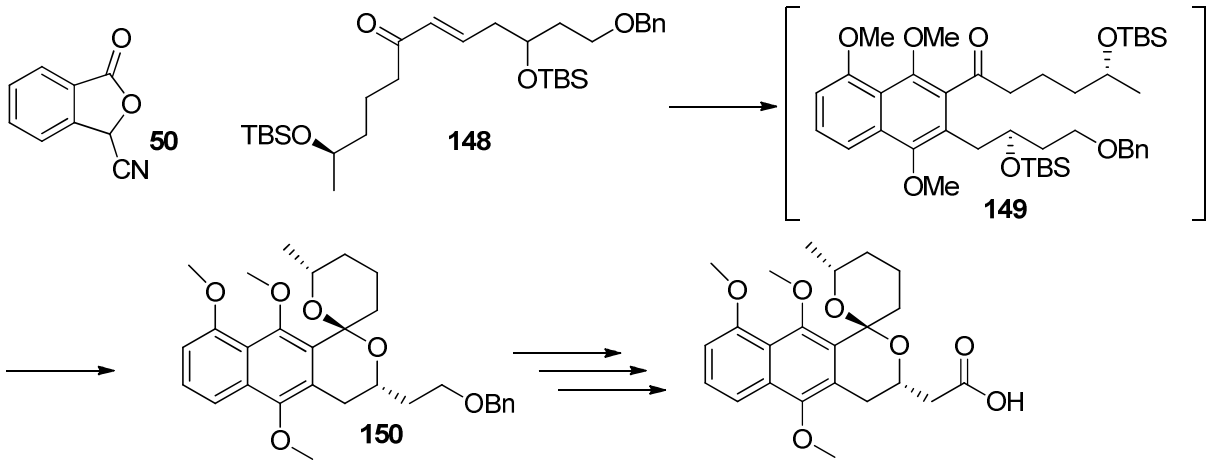


Scheme 3.6: *Reagents and conditions*: (i) 5 mol % $FeCl_3.6H_2O$, CH_2Cl_2, RT, 85 min, 76%.

3.2.5. Synthesis of aromatic spiroketals: griseusin A and B

Of direct interest to this section of the PhD thesis are the griseusin spiroketals that display interesting biological activity. Only one total synthesis of the griseusins has been reported. This synthesis by Yoshii and co-workers constructed the spiroketal ring system using the traditional intramolecular cyclisation reaction of a *δ,δ'*-dihydroxyketone. However, a number of other approaches to the core spiroketal system of the griseusins have been reported. In this section we will briefly look at a synthesis pertaining to the construction of the griseusin spiroketal core.

In their study, Naysmith and Brimble reported the synthesis of the framework of griseusin from advanced precursors using a one-pot reaction (**Scheme 3.7**). The synthesis employed a Hauser-Kraus annulation (discussed in **Section 1.5.2.**) between phthalide **50** and enone **148** to afford the hydroquinone dimethyl ether **149**. The crude material was then subjected to a reductive methylation reaction to afford the spiroketal **150** as the sole product.[78]



Scheme 3.7: *Reagents and conditions*: Bu^{t}OK, NaOH, Me_2SO_4, 49%.

3.2.6. The nitroalkane approach to spiroketals

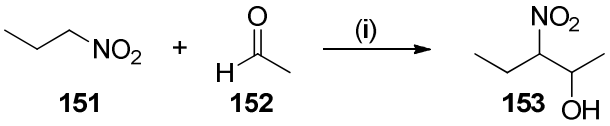
The use of nitroalkanes as carbanionic precursors has become a widely used route for the preparation of spiroketals via the assembly of dihydroxy ketone frameworks. These nitroalkanes are usually accessed through Henry condensation or nitroaldol reactions and Michael additions. The Nef reaction then facilitates the conversion of the nitro group to a carbonyl group, thus introducing the keto functionality. The following sections will highlight the use of the Henry condensation reaction and Nef reaction to assemble the spiroketal framework.[79]

3.2.6.1. Henry condensation reactions

The introduction of a nitro group is quite a challenging obstacle to overcome. An easily recognizable manner in which to introduce the nitro group is using a Henry or nitroaldol reaction. This reaction is essentially a coupling of a carbonyl compound with an alkylnitro compound. This reaction process results in the formation of a new carbon-carbon bond and the concomitant introduction of a new functional group, namely the β-nitroalcohol.[80]

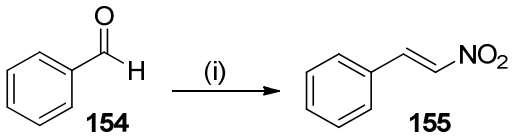
The nitroaldol reaction is often promoted by the use of protic or aprotic solvents, quaternary ammonium salts and organic bases. The reaction conditions are usually determined by other functional conditions present within the substrates as well as the solubility of the substrates.[80]

The use of alumina to facilitate the nitroaldol reaction has been reported by Rosini and co-workers.[81] During their study, they described a simple and efficient method for the preparation of nitroalcohols using alumina as a catalyst in the absence of solvent. Using these conditions, the nitroalkane **151** and aldehyde **152** afforded nitroalkanol **153** in an excellent yield (**Scheme 3.10**).



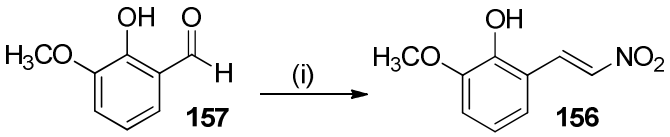
Scheme 3.10: *Reagents and conditions*: (i) Alumina, 0°C-RT, 80%.

Microwave assisted nitroaldol reactions have been shown to afford high yields of the nitroalkene compounds without the isolation of the intermediate nitroalcohol. This procedure circumvents the dehydration of the nitroalcohol to the nitroalkene. Varma and co-workers demonstrated the use of this method in the synthesis of nitroalkenes, shown in **Scheme 3.11**,[82] where benzaldehyde **154** was reacted with nitromethane in the presence of catalytic ammonium acetate to furnish nitroalkene **155** in a yield of 80%.



Scheme 3.11: *Reagents and conditions*: (i) CH_3NO_2, NH_4OAc, μν, 80%.

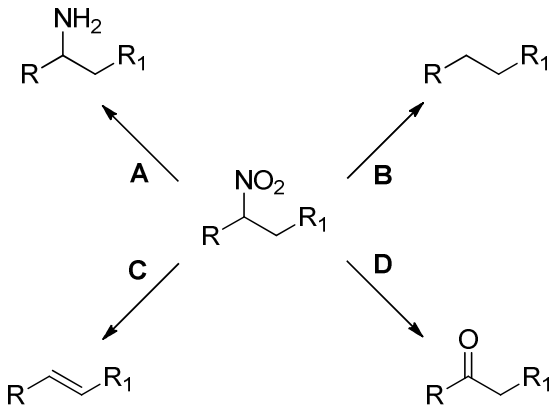
One of the early key reactions used in the synthesis of morphine alkaloid, (*d,l*)-thebainone A was a nitroaldol reaction. Tius and Kerr showed the formation of nitroalkene **156** from the acid-catalysed condensation of *o*-vanillin **157** with nitromethane as shown in **Scheme 3.12**.[83] The use of aromatic aldehydes allows for the formation of the nitroalkene directly as this affords a stable, conjugated alkene.



Scheme 3.12: *Reagents and conditions*: (i) CH_3NO_2, NH_4OAc, HOAc, 93%.

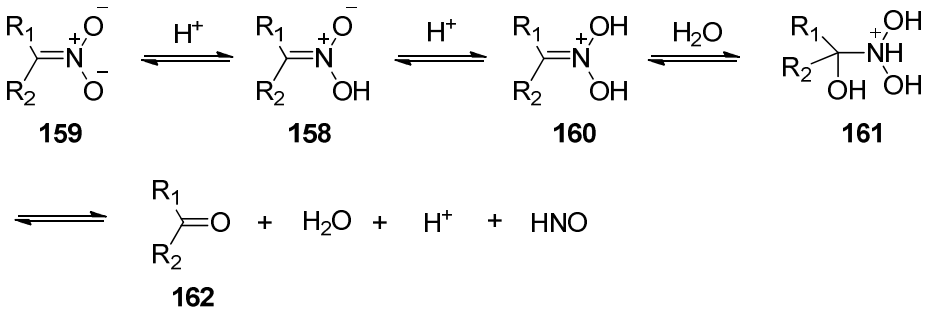
3.2.6.2. The Nef reaction

As outlined in **Section 3.2.6**, nitroalkanes have proven an efficient route to access the spiroketal skeleton. The nitro group has often been used as it can undergo a Nef reaction to the corresponding carbonyl group which undergoes nucleophilic addition with alcohols resulting in the spiroketal core. The nitro group is a very versatile functional group as it can undergo further nucleophilic addition or it can be transformed into other useful functional groups. **Scheme 3.13** outlines some of the different functional group transformations that the nitro group can undergo. Of interest to us, is the conversion of the nitro group into a carbonyl group, **step D**.[84] This transformation is known as a Nef reaction.



Scheme 3.13

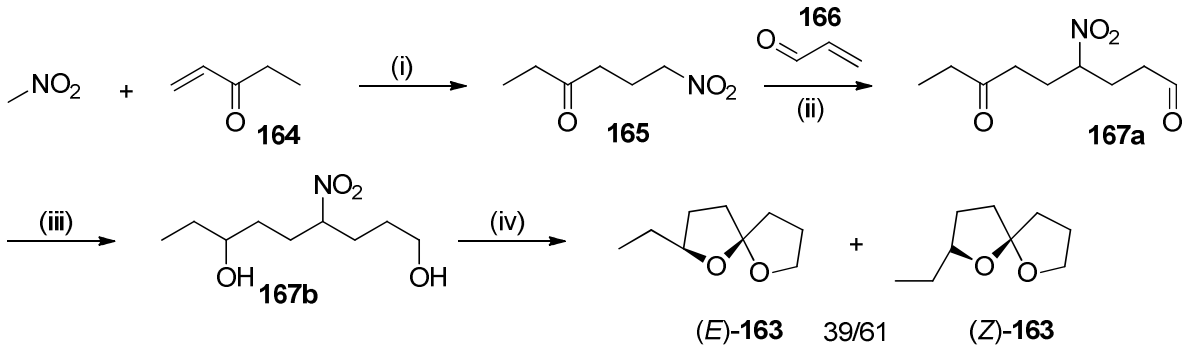
The Nef reaction was originally described as a strong acidic hydrolysis of a nitronate salt **158** which is produced from nitroalkane **159**. The general mechanism is shown in **Scheme 3.14**, where nitronic acid **158** is protonated resulting in **160**. Hydrolysis occurs on **160** producing intermediate **161** which undergoes a dehydration and loss of hyponitrous acid to afford carbonyl compound **162**.



Scheme 3.14

3.2.6.3. Nitroalkanes as precursors to spiroketals

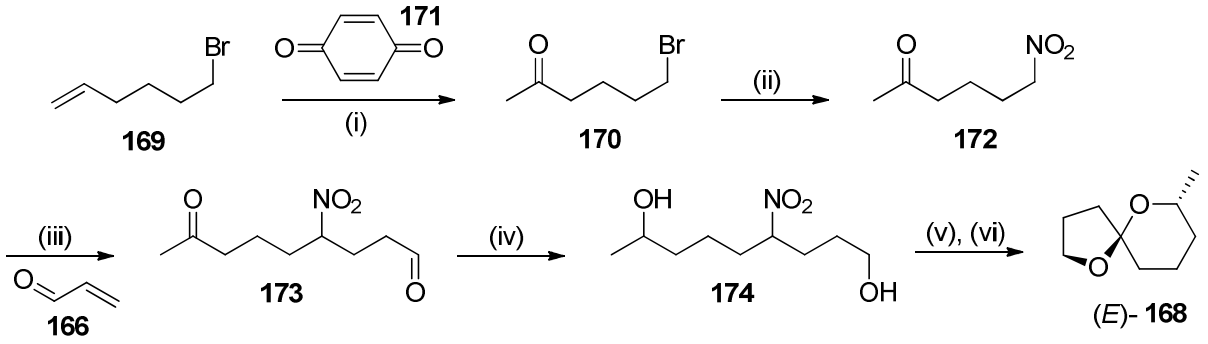
The preparation of chalcogran **163**, the main component of the aggregation pheromone of the bark beetle was achieved using a double Michael addition of nitromethane to different *α,β*-unsaturated carbonyl derivatives. As outlined in **Scheme 3.8**, nitromethane was added to 1-penten-3-one **164** to afford the corresponding 4-nitro ketone **165**. This newly formed ketone **165** undergoes a 1,4-addition to acrolein **166** resulting in nitro diketone **167a**. The carbonyl groups were reduced using sodium borohydride furnishing diol **167b**. With the diol in place, a Nef reaction was conducted using titanium trichloride which facilitated the conversion of the nitro group to the carbonyl group followed by the spontaneous spiroketalisation to afford chalcogran **163**.[85,86]



Scheme 3.8 *Reagents and conditions*: (i) Al_2O_3, 62%; (ii) acrolein, Al_2O_3, 53%; (iii) $NaBH_4$, EtOH, 85%; (iv) $TiCl_3$, H_2O, 65%.

Spiroketal (*E*)-7-methyl-1,6-dioxaspiro[4.5]decane **168**, a component of odours of the wasp *Paravespula vulgaris* was efficiently prepared using nitroalkanes as spiroketal precursors. Starting from 1-bromo-5-hexene **169**, Rosinidy and co-workers prepared ketone **170** using a Wacker-type oxidation with benzoquinone **171** (**Scheme 3.9**). A functional group interconversion by nucleophilic displacement of the bromine with sodium nitrite resulted in nitro ketone **172**. A Michael addition of **172** with acrylaldehyde **166** then afforded nitro diketone **173**. In order to form the spiroketal skeleton, nitro diketone **173** was reduced to the nitro diol **174**

using sodium borohydride. The synthesis of **168** was completed with the Nef reaction of nitro diol **174**, which exclusively resulted in the formation of the *E* stereoisomer.[87]



Scheme 3.9 *Reagents and conditions*: (i) $PdCl_2$, $CuCl_2$, DMF, 87%; (ii) $NaNO_2$, DMF, 75%; (iii) acrylaldehyde, amberlyst A21, 78%; (iv) $NaBH_4$, MeOH, 85%, (v) NaOH, EtOH; (vi) H_2SO_4, n-C_5H_{12}, 74%.

3.3. Proposed project aims

Synthesis of The spiroketal functionality presents both an interesting and challenging task to perform, and as such, one of the themes in our laboratory has been the synthesis and assembly of benzannelated spiroketals such as compound **175**, a precursor of γ-rubromycin **130** (**Figure 3.11**). Spiroketal **175** was successfully prepared in our laboratories by Cappechi, using the nitroalkane approach.

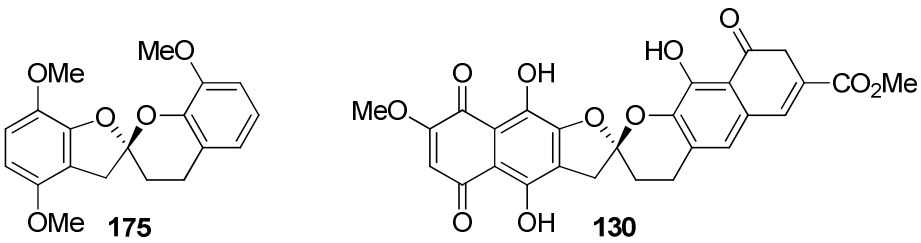
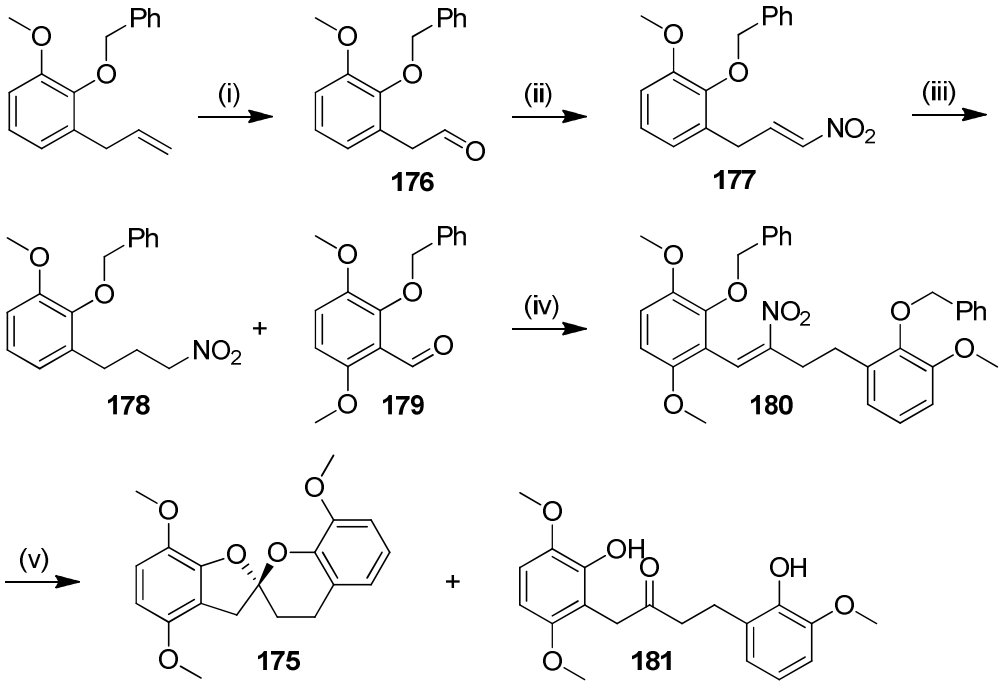


Figure 3.11

In her PhD studies, Cappechi reported the use of Pearlman's catalyst in the presence of a catalytic amount of concentrated hydrochloric acid and cyclohexene to facilitate the spiroketalisation.[88] The synthesis commenced with the preparation of aldehyde **176** followed by a Henry condensation reaction of **176** with nitromethane to afford nitroalkene **177** and subsequent reduction of the alkene to give nitroalkane **178**. A second Henry condensation of **178** with aldehyde **179** afforded nitroalkene **180** which was subjected to a modified Nef reaction to furnish spiroketal **175**, shown in **Scheme 3.10**. Ketone **181** was also isolated from the reaction.

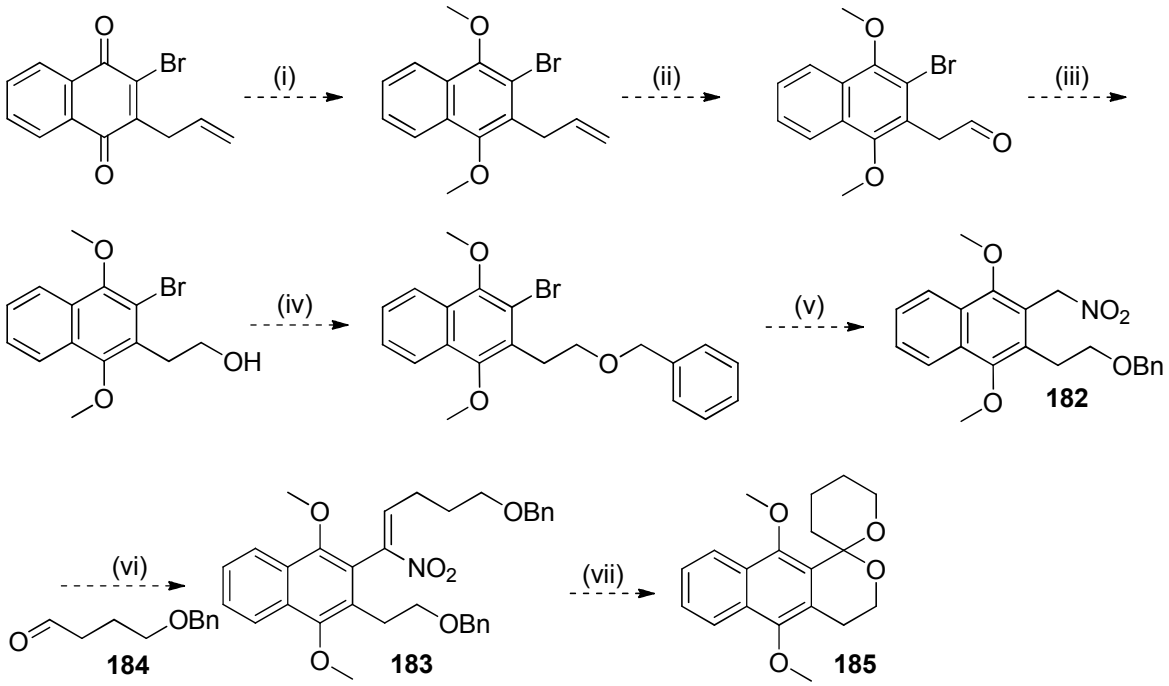


Scheme 3.10 *Reagents and conditions*: (i) (a) O_3, –40°C, (b) Zn, AcOH, 84%; (ii) (a) $MeNO_2$, cetyltrimethylammonium bromide (CTABr), 0.025 M NaOH, 100%; (b) MsCl, Pr^i_2NEt, CH_2Cl_2, 96%; (iii) $NaBH_4$, MeOH-THF, 70%; (iv) NH_4OAc, AcOH, 57%; (v) cat. $Pd(OH)_2/C$, EtOH, conc. HCl, cyclohexene, H_2(g) (1atm), RT, 64% (for **175**) and 18% (for **181**).

Our central aim for this PhD thesis stems from the work earlier conducted by Capecchi as the mechanism of this modified Nef reaction is not known. Identification of the reaction intermediates of this Nef reaction may allow for the elucidation of the mechanism of this novel reaction. In order to conduct this investigation we envisaged that we required substrates which lacked a phenol that could be liberated under the reaction conditions as this would be required to facilitate the spiroketalisation reaction. A more detailed reasoning for the omission of the free phenols will be discussed in **Section 4.1**.

We also plan to synthesise the spiroketal framework of griseusin A. We envisaged that we could achieve this by using methodology developed some time ago at Wits University, i.e., the nitroalkane approach.

A proposed synthetic route is outlined in **Scheme 3.11** which shows the formation of nitroalkane precursor **182** from readily prepared starting materials. This would allow the formation of nitroalkene **183** from the reaction of **182** and aldehyde **184**. The synthesis of the aromatic core of griseusin A would then be accomplished through a Nef reaction of nitroalkene **183** to give spiroketal **185**.



Scheme 3.11

Chapter 4: Mechanistic studies of the Nef reaction

4.1. Introduction

4.1.1. Background to project

As discussed in the previous chapter, Capecchi, during her PhD studies observed what appeared to be a novel Nef-type reaction during the preparation of the bisbenzannelated spiroketal core **175** of the γ-rubromycins **130**, shown in **Figure 4.1**.[88,89]

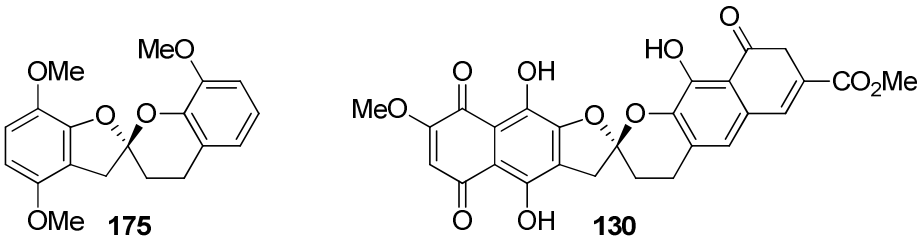
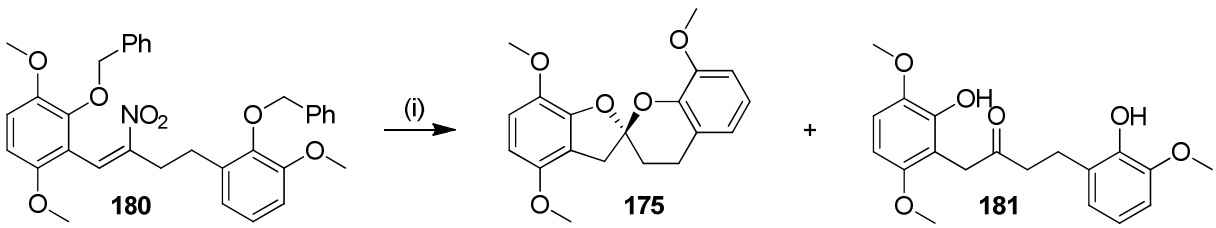


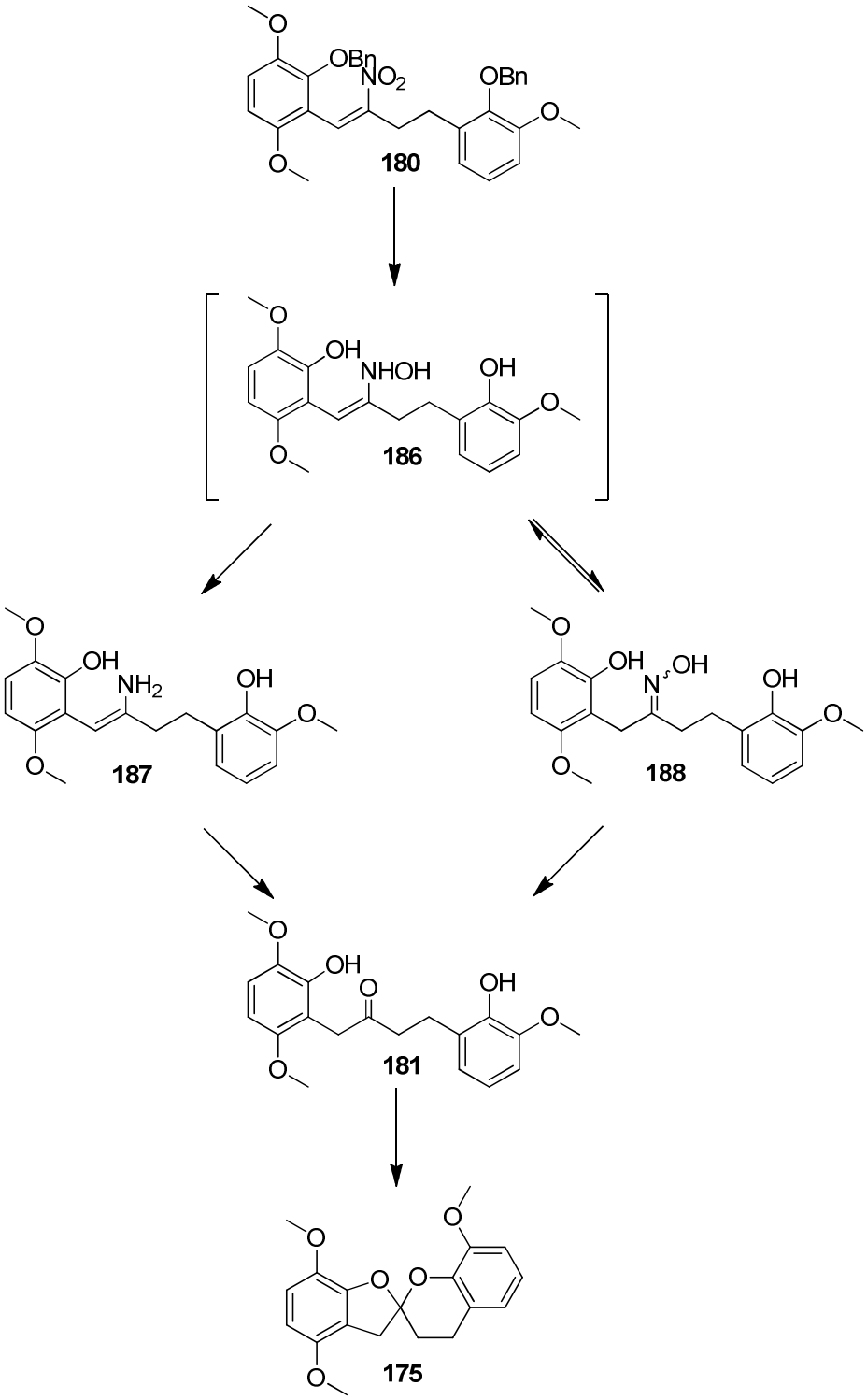
Figure 4.1

In particular, Capecchi found that when nitroalkene **180** was exposed to Pearlman's catalyst [$Pd(OH)_2/C$] in ethanol with a catalytic amount of hydrochloric acid and cyclohexene under an atmosphere of hydrogen, spiroketal **175** and the "open" ketone **181** were formed and isolated in yields of 64% and 18%, respectively (**Scheme 4.1**).



Scheme 4.1 *Reagents and conditions*: (i) cat. $Pd(OH)_2/C$, EtOH, conc. HCl, cyclohexene, $H_2(g)$ (1atm), rt, 64% (for **175**) and 18% (for **181**).

Two possible mechanisms for this transformation have been proposed and are shown in **Scheme 4.2**. The first mechanism involves initial reduction of the nitro group **180** to the hydroxylamine **186** followed by conversion to the enamine **187** which would hydrolyse to the carbonyl **181** under aqueous acidic conditions. This would then pave the way for the cyclisation to the spiroketal product **175**. An alternative mechanism involves the reduction of the nitro group **180** to the hydroxylamine **186** which would then tautomerise to the oxime **188** and this would be followed by hydrolysis to the carbonyl **181** and once again as before converted to the spiroketal **175**. Related literature precedence for the latter mechanism identified oximes as intermediates and they were indeed produced when nitro groups were reduced using palladium on carbon.[90]



Scheme 4.2: Proposed mechanism of the Nef reaction

Our research will therefore build on this as we hope to confidently elucidate the mechanism of this modified Nef reaction. Our main aim for this work is to try and identify stable and characterisable intermediates, if any, that are involved in our Nef reaction and thereby elucidate the mechanism of the reaction. As shown in **Scheme 4.2**, the formation of the carbonyl group of **181** as well as the removal of the benzyl protecting groups is required for the formation of the spiroketal **175**. In order to determine the intermediates involved in this transformation, we chose substrates that may afford stable, isolable intermediates that could not be converted further to the spiroketal functional group. We therefore decided to use three substrates lacking substituents that would furnish *o*-phenols, namely piperonal, anisaldehyde and vanillin, and convert them into aromatic conjugated nitro systems of the general structure shown in **Figure 4.3**. Compounds of this general structure, when subjected to Pearlman's catalyst would then not be able to form spiroketals.



Figure 4.2

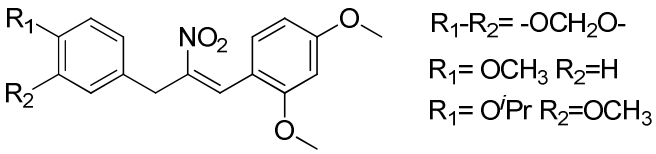
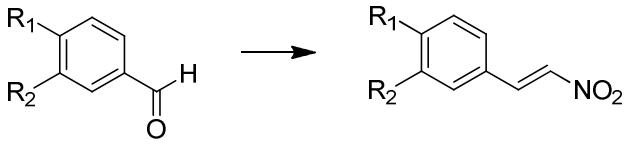


Figure 4.3

4.2. Preparation of nitroalkenes

The following section describes the preparation of our initial nitroalkenes by a Henry condensation reaction. Methodology described by Merchant and Mountwala was employed to successfully prepare the desired nitroalkenes **189**, **190** and **191**. [91]



189: $R_1 = R_2 = -OCH_2O-$

190: $R_1 = OMe$ $R_2 = H$

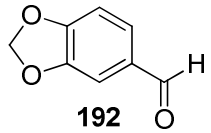
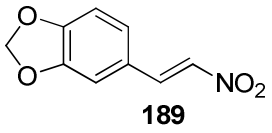
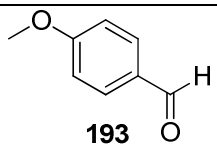
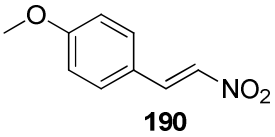
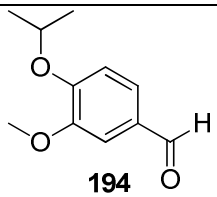
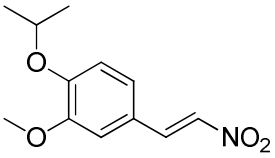
191: $R_1 = O^iPr$ $R_2 = OMe$

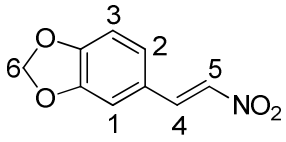
Scheme 4.3: General reaction scheme for the formation of nitroalkenes.

Commercially available aldehydes piperonal **192**, anisaldehyde **193**, and *O*-isopropyl protected vanillin, (4-isopropoxy-3-methoxybenzaldehyde) **194**, were added to freshly distilled nitromethane in the presence of ammonium acetate in glacial acetic acid. The reactions were then stirred under reflux for 6 hours resulting in deep red solutions. The reactions were cooled and after workup and purification by recrystallisation from a diethyl ether and hexane mixture, the corresponding nitroalkene products **189**, **190** and **191** were furnished as yellow solids. The yields obtained for these reactions were determined after recrystallisation. The general reaction is shown in **Scheme 4.3**.

Table 4.1 shown below shows a summary of each the nitroalkenes prepared and their isolated yields after recrystallization.

Table 4.1: Synthetic yields for the nitroalkenes prepared

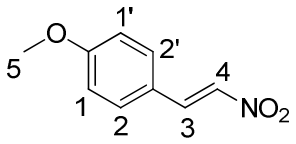
Substrate	Product	Yield (%)
 **192**	 **189**	43
 **193**	 **190**	51
 **194**	 **191**	44



It was evident from the ^{1}H NMR spectrum of **189** that the aldehyde proton was absent. Also noted on the spectrum were two downfield doublets at δ 7.92 and δ 7.47 ppm due to H_5 and H_4, respectively. Each of these doublets showed coupling of 13.6 Hz confirming the formation of the *trans* isomer of the conjugated alkene **189**. The aromatic region shows three distinct signals indicating three different environments. A doublet at δ 7.00 ppm due to H_1 which shows *meta* coupling to the multiplet found at δ 7.08 ppm due to H_2 with a coupling constant of 1.5 Hz, and doublet at δ 6.87 ppm due to H_3 showing *ortho* coupling of 8.0 Hz to H_2. The only remaining signal at δ 6.06 ppm, observed as a singlet integrating for two protons was therefore due to H_6. The ^{13}C NMR spectrum further attested to the success of the reaction as no signal above δ 160 ppm characteristic of a carbonyl group was observed. Instead, two new signals were present at δ 139.1 and δ 135.4 ppm due to the newly introduced alkene carbons C4 and C5 respectively. The presence of the newly introduced nitro group was confirmed by IR

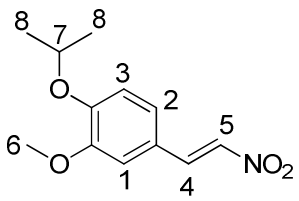
spectroscopy which showed absorption bands at 1500 and 1368 cm^{-1} which are characteristic of the nitro functional group. The *trans* geometry of the alkene was also confirmed by the presence of a $CH_{Ealkene}$ stretch at 965 cm^{-1} in the IR spectrum. The experimental melting point was determined to be 161–162°C and correlated well with the expected melting point of 164–165°C.[92]

(*E*)-1-Methoxy-4-(2-nitrovinyl)benzene **190** was prepared using *p*-anisaldehyde as our starting material. The *para* substitution pattern observed on the aromatic ring results in a simplified NMR spectrum compared to the previously examined nitroalkene **189**.[93]



The most distinctive feature of the ^{13}C NMR spectrum of **190** is the absence of a downfield signal above δ 160 ppm indicating that we no longer had our aldehyde functional group. Instead, we again observed signals in the alkene region at δ 139.03 and δ 135.07 ppm which are due to C3 and C4 respectively. In the ^{1}H NMR spectrum, the presence of the alkene was confirmed by the observation of a doublet at δ 7.97 ppm due to H_3, showing *trans* coupling of 13.6 Hz to the multiplet at δ 7.51 ppm due to overlapping of the signals from H_4, H_2 and $H_{2'}$.

(*E*)-1-Isopropoxy-2-methoxy-4-(2-nitrovinyl)benzene **191** was prepared from 4-isopropoxy-3-methoxybenzaldehyde.[94] This substrate was prepared by reacting vanillin dissolved in DMF with isopropyl bromide in the presence of sodium hydride. The most notable difference between nitroalkenes **189** and **191** was the presence of this isopropyloxy group as observed in the ^{1}H and ^{13}C NMR spectra.

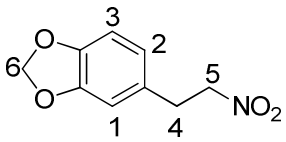


The ^{1}H NMR spectrum was characterized by the presence of an upfield doublet at δ 1.41 ppm integrating for six protons. This signal was due to H_8 and showed coupling of 6.1 Hz to H_7. The remaining differences between nitroalkene **189** and **191** were the presence of a singlet at δ 3.90 ppm integrating for three protons and a septet at δ 4.65 ppm integrating for one proton corresponding to H_6 and H_7 respectively. These features were also observed in the ^{13}C NMR

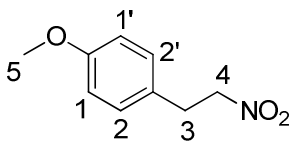
spectrum with three upfield signals at δ 71.45, δ 56.12 and δ 21.93 ppm due to C7, C6 and C8 respectively.

4.3. Synthesis of nitroalkanes

The reduction of the conjugated double bond present in each of the nitroalkenes was the next step in our synthesis. This was accomplished by the slow addition of sodium borohydride to a stirred slurry of the chosen nitroalkene and silica gel in a mixture of isopropanol and chloroform. The mixture of protic and aprotic solvents in the presence of an insoluble protic phase is believed to prevent the formation of dimeric products. These mild experimental conditions provide for a rapid reaction and more importantly, afford pure products in near quantitative yields.[95] A visual indication that the reaction was progressing was the change in colour from bright yellow to colourless. Once completed, as indicated by TLC analysis, the reactions were filtered through celite and purified by column chromatography to yield the nitroalkane compounds **195**, **196** and **197** as pale yellow oils.

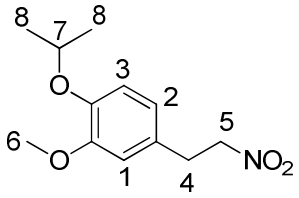


5-(2-Nitroethyl)benzo[*d*][1,3]dioxole **195** was isolated in 71% yield and characterised by NMR spectroscopy. The ^{1}H NMR spectrum confirmed the successful reduction of the double bond of nitroalkene **189**, with the loss of signals previously associated with the alkene protons and the presence of two new triplets at δ 4.55 and δ 3.21 ppm for H_5 and H_4 respectively. The ^{13}C NMR spectrum further attested to this with the upfield shift of the carbons associated with C4 and C5 from δ 139.08 and δ 135.44 to δ 33.20 and δ 101.15 ppm respectively. A singlet integrating for two protons due to H_6 was observed at δ 5.92 ppm in the ^{1}H NMR spectrum. The remaining signals were due to the aromatic protons and were observed at δ 6.74 ppm due to H_3, and at δ 6.68–6.62 ppm due to overlapping of the signals from protons H_2 and H_1.



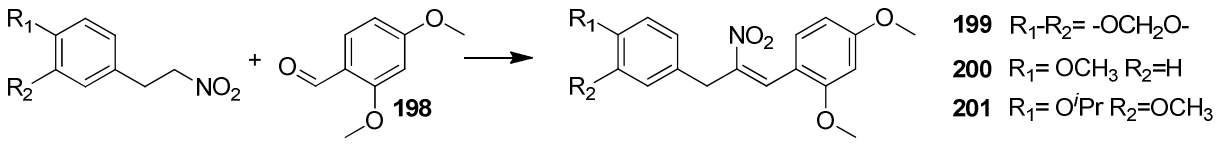
Analysis of the ^{1}H NMR spectrum of **196** once again provided us with evidence that the reduction of the double bond of nitroalkene **190** was successful. We were pleased to observe the disappearance of signals arising from the alkene protons and the concomitant appearance of the expected triplets as

observed for nitroalkane **195**. These triplets each integrated for two protons and were found at δ 4.55 and δ 3.24 ppm for H_4 and H_3 respectively. All other spectroscopic data, including ^{13}C NMR and IR spectroscopic data, confirmed the formation of **196**.



The last reduction we attempted was performed on nitroalkene **191** which resulted in the formation of nitroalkane **197**. Pleasingly, when we examined the ^{13}C NMR spectrum of **197**, we noticed the unmistakable upfield shift of the carbon signals previously found at δ 139.41 and δ124.45 ppm due to the alkene protons, to δ 33.18 and δ 76.53 ppm, respectively. This therefore confirmed the change in the nature of these carbons from being sp^2 hybridised to now being sp^3 hybridised.

4.4. Synthesis of nitroalkenes 199, 200 and 201 using Henry condensation reactions

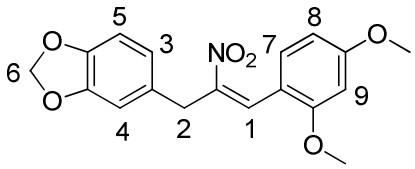


Scheme 4.4: General scheme for the preparation of nitroalkenes

Having successfully prepared our nitroalkanes **195**, **196** and **197**, all that remained was to couple each of these nitroalkanes with a suitably substituted aldehyde. We chose 2,4-dimethoxybenzaldehyde **198** as this would afford substrates that mimic the precursor **180** which contained two *ortho*-*O*-benzyl substituents as closely as possible. To this end, we attempted the Henry condensation reactions using the same method we employed in **Section 4.2**. However, following several attempts using TLC analysis to determine the progress of the reactions, we suspected that our product and starting nitroalkane had similar R_f values. This was confirmed by NMR spectroscopy. We therefore decided to adapt our method to drive the reactions to completion. The formation of nitroalkenes and not nitroalcohols as observed in some cases

indicates that spontaneous dehydration occurs forming the nitroalkene. We therefore employed a Dean-Stark set up for our subsequent Henry condensation reactions in order to facilitate dehydration of the intermediate nitroalcohol. Thus, nitroalkane **195**, **196** or **197** was stirred in toluene under reflux with 2,4-dimethoxybenzaldehyde **198** in the presence of ammonium acetate. After six hours, the reactions were cooled and purification by recrystallization from a diethyl ether and hexane mixture afforded the desired conjugated nitroalkene compounds **199**, **200** and **201** as bright yellow solids (**Scheme 4.4**).

Nitroalkane **195** was used as the precursor in the formation of (*Z*)-5-(3-(2,4-dimethoxyphenyl)-2-nitroallyl)benzo[*d*][1,3]dioxole **199**. TLC analysis of the reaction showed a bright yellow spot appearing which was visible to the naked eye and was a promising sign that we were forming a nitroalkene. The product was isolated and purified by silica gel column chromatography to yield what we expected to be our nitroalkene **199**. However, the ^{1}H NMR spectrum showed that our product was contaminated with the starting aldehyde. Recrystallization to remove the unreacted and unwanted starting material afforded pure (*Z*)-5-(3-(2,4-dimethoxyphenyl)-2-nitroallyl)benzo[*d*][1,3]dioxole **199** in a good yield of 71%.



Interpretation of the ^{1}H NMR spectrum confirmed that the desired nitroalkene **199** had indeed formed. This was indicated by the presence of two singlets at δ 8.52 and δ 4.14 ppm corresponding to H_1 and H_2 respectively. Interestingly, the alkene proton H_1 was significantly deshielded giving rise to a signal at δ 8.52 ppm, owing to the alkene being conjugated to both the nitro group and an aromatic ring. A singlet integrating for two protons was observed at δ 4.14 ppm, due to benzylic protons H_2, slightly downfield compared to that of the starting nitroalkane **195**. The ^{13}C NMR spectrum showed the presence of an alkene carbon, C1, at δ 131.38 ppm and a CH correlation spectrum was used to unambiguously assign the remaining carbons of nitroalkene **199**. The results of the mass spectral analysis afforded an accurate mass of 344.1129 which was in good agreement with the expected mass of 344.1129 for a compound of the formula $C_{18}H_{17}NO_6$.

Table 4.2 shows a comparison of NMR spectroscopic data of nitroalkene products **200** and **201**, and the recently discussed nitroalkene **199** (shown in **Figure 4.3**). It is evident from the table that the benzylic alkene proton occurs at a similar chemical shift and is significantly deshielded in each product. The benzylic methylene protons also occur at similar chemical shifts across all three products. The same trend is observed for the carbons associated with these protons as well as for the carbons attached to the nitro group. The yields obtained from these Henry condensation reactions were also considerably higher than those obtained for the nitroalkenes prepared in **Section 4.2**. The removal of water by use of a Dean-stark trap is clearly an advantage. All spectroscopic data including IR spectroscopy and mass spectrometry confirmed the identity of these aromatic nitroalkenes.

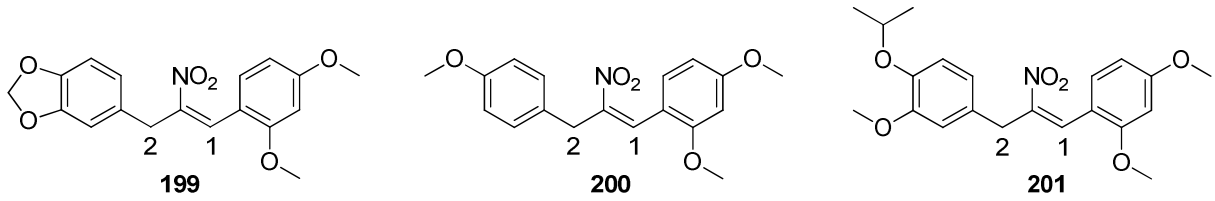


Figure 4.3

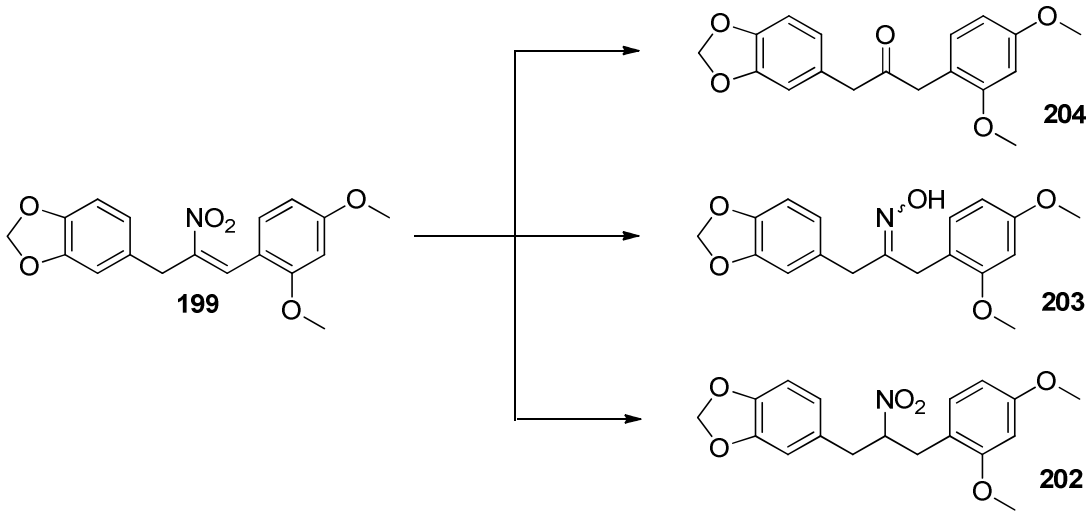
Table 4.2: Trends in the ^{1}H and ^{13}C NMR spectroscopic data of the nitroalkene products prepared and data comparison

Signal	199(ppm)	200(ppm)	201(ppm)
^{1}H NMR spectrum			
H_1	8.52 (s)	8.52 (s)	8.53 (s)
H_2	4.14 (s)	4.16 (s)	4.17 (s)
^{13}C NMR spectrum			
C1	131.38	131.11	131.27
C2	32.98	32.43	32.82
C-NO_2	146.44	147.75	147.66
Yield (%)	71	87	72

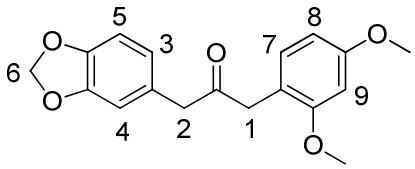
4.5. Application of our Novel Nef reaction conditions

With nitroalkenes **199**, **200** and **201** in hand, we turned our attention to the determination of the intermediates involved during what we considered to be a novel Nef reaction. To achieve this, we would subject each of our nitroalkenes **199–201** to Pearlman's catalyst in ethanol in the presence of catalytic concentrated hydrochloric acid and cyclohexene under an atmosphere of hydrogen.[96]

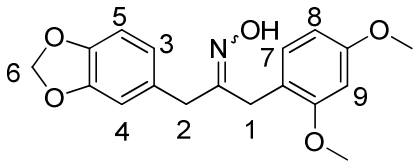
We first attempted these reaction conditions on nitroalkene **199**, as shown in **Scheme 4.4**. Upon completion of the reaction as monitored by TLC, the reaction mixture was filtered to remove the Pearlman's catalyst. The resulting filtrate, assumed to contain our reaction intermediates, was subjected to an aqueous work-up, and the crude reaction mixture was purified by column chromatography. This process yielded three products as yellow oils. Review and analysis of these three isolated products showed the formation of a reduced nitroalkane **202**, an oxime **203** and finally a carbonyl containing compound **204** (**Scheme 4.4**).



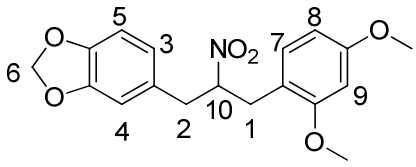
Scheme 4.4 *Reagents and conditions*: cat. $Pd(OH)_2/C$, EtOH, conc. HCl, cyclohexene, H_2 (1atm), RT, 29% (for **204**), 37% (for **203**) and 5% (for **202**).



Compound **204** was isolated as a yellow oil in 29% yield with an R_f of 0.39 in a 30% ethyl acetate: hexane mixture. Analysis of the ^{1}H NMR spectrum showed the loss of the alkene proton previously observed at δ 8.52 ppm, and the appearance of a singlet at δ 3.61 ppm. The only downfield signals we observed were due to the aromatic protons. The most downfield signal, observed as a doublet at δ 6.98 ppm showed *ortho* coupling of 8.7 Hz and was assigned as H_8 as confirmed by NOE experiments. This showed coupling to H_7 which was found within overlapping signals at δ 6.44 ppm. The doublet at δ 6.74 ppm was assigned as H_5 as it only showed *ortho* coupling of 7.9 Hz. A slight upfield shift of proton H_2 was observed from δ 4.14 to δ 3.59 ppm, which is an indication that this proton is now less deshielded. The most notable feature in the ^{13}C NMR spectrum was the presence of a downfield signal at δ 206.71 ppm, which unequivocally confirmed the presence of a carbonyl group. This result was corroborated by the IR spectrum which showed a stretch at 1715 cm^{-1} due to the carbonyl group. Furthermore, the signals associated with the alkene carbons at δ 146.44 and 131.38 ppm were no longer present.

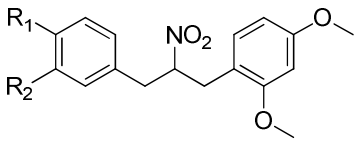


The most polar product isolated, with an R_f of 0.25 in a 30% ethyl acetate: hexane mixture and in 37% yield, was determined to be an oxime containing compound. Analysis of both the ^{1}H and ^{13}C NMR spectra showed the doubling of signals and therefore led us to believe that an inseparable mixture of both the *E* and *Z*-isomers of oxime **203** were formed from nitroalkene **199**. The ^{13}C NMR spectrum showed the presence of signals at δ 158.42 and δ 158.31 ppm which were assigned to the *E*- and *Z*-isomers of the carbon of the oxime functionality. A defining aspect of the ^{1}H NMR spectrum was the presence of a broad singlet at δ 9.47 ppm which is due to the hydroxyl group of the oxime. This was also observed when analyzing the IR spectrum which showed a broad stretch at 3220 cm^{-1}, characteristic of a hydroxyl group.

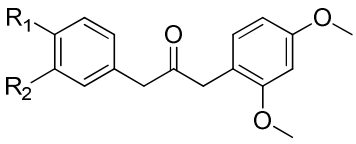


The final product isolated from the reaction mixture in 5% yield was nitroalkane **202** which was the least polar and was found at an R_f of 0.61 in a 30% ethyl acetate: hexane mixture. In the analysis of the ^{1}H NMR spectrum, the most evident features were the loss of the alkene proton in the starting material found at δ 8.52 ppm, and the appearance of a multiplet integrating for one proton at δ 5.03–4.87 ppm. We therefore assigned this signal to H_{10}. Using a COSY NMR spectrum, we confirmed that this signal coupled to the most upfield signal found at δ 3.24–2.86 ppm which integrated for four protons and was therefore due to protons H_1 and H_2. Under the reaction conditions used, it could be expected that the nitro group would also be reduced to the amine, however, no evidence of this was found. The ^{1}H NMR spectrum did not show the presence of a broad singlet integrating for two protons as would be expected. Furthermore, the IR spectrum showed stretches at 1591 and 1288 cm^{-1} which are characteristic of a nitro group.

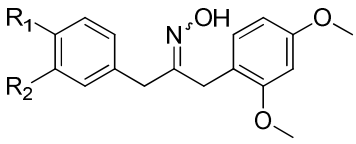
We then performed the reaction on nitroalkenes **200** and **201**, and observed similar intermediates being formed to those isolated in our initial reaction with nitroalkene **199**. Nitroalkene **200** afforded carbonyl **205**, oxime **206** and nitroalkane **207** when subjected to the novel Nef reaction. A similar trend was observed for the Nef reaction of nitroalkene **201** where we again isolated carbonyl **208**, oxime **209** and nitroalkane **210**. As shown in **Table 4.3**, the chemical shifts in the NMR spectra observed for **202**, **203** and **204** were similar to those of **207** and **210**, **206** and **209**, and **205** and **208** (**Figure 4.5**).



202: R_1-R_2= -OCH_2O-
207: R_1= OCH_3 R_2=H
210: R_1= O^{i}Pr R_2=OCH_3



204: R_1-R_2= -OCH_2O-
205: R_1= OCH_3 R_2=H
208: R_1= O^{i}Pr R_2=OCH_3



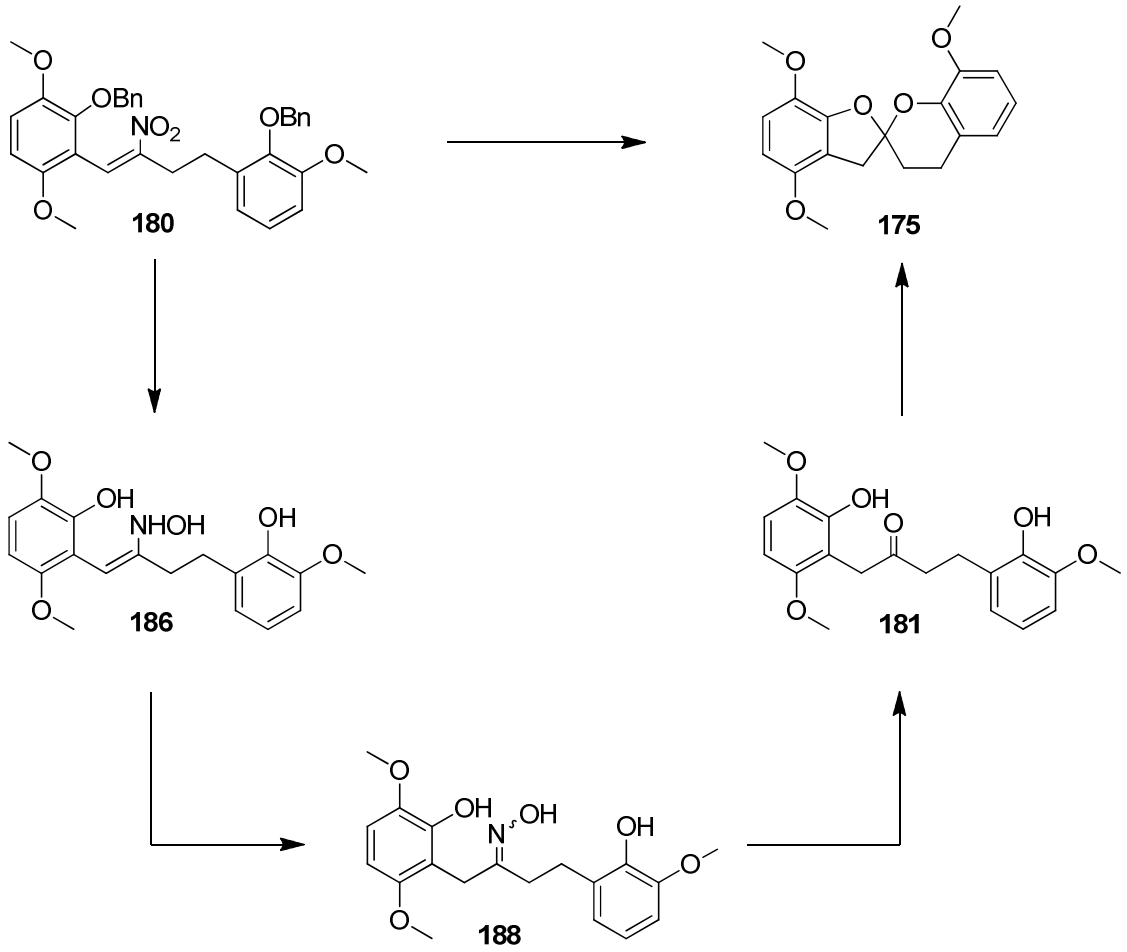
203: R_1-R_2= -OCH_2O-
206: R_1= OCH_3 R_2=H
209: R_1= O^{i}Pr R_2=OCH_3

Figure 4.5

Table 4.3: A summary of the NMR spectroscopic data of products of our novel Nef reaction

Compound	^{1}H NMR shift (ppm)		^{13}C NMR shift (ppm)			Yield (%)
	H_1	H_2	C=O	C=N	C–NO_2	
204	3.61	3.59	206.71	–	–	29
203	3.60/3.55	3.41/3.32	–	158.42/158.31	–	37
202	3.24-2.86		–	–	89.73	5
205	3.62	3.60	206.97	–	–	24
206	3.73/3.59	3.40/3.55	–	158.30/158.12	–	25
207	3.26-2.95		–	–	89.90	47
208	3.62	3.61	206.97	–	–	30
209	3.62/3.59	3.43/3.35	–	158.43/158.35	–	17
210	3.11	2.99	–	–	89.64	7.4

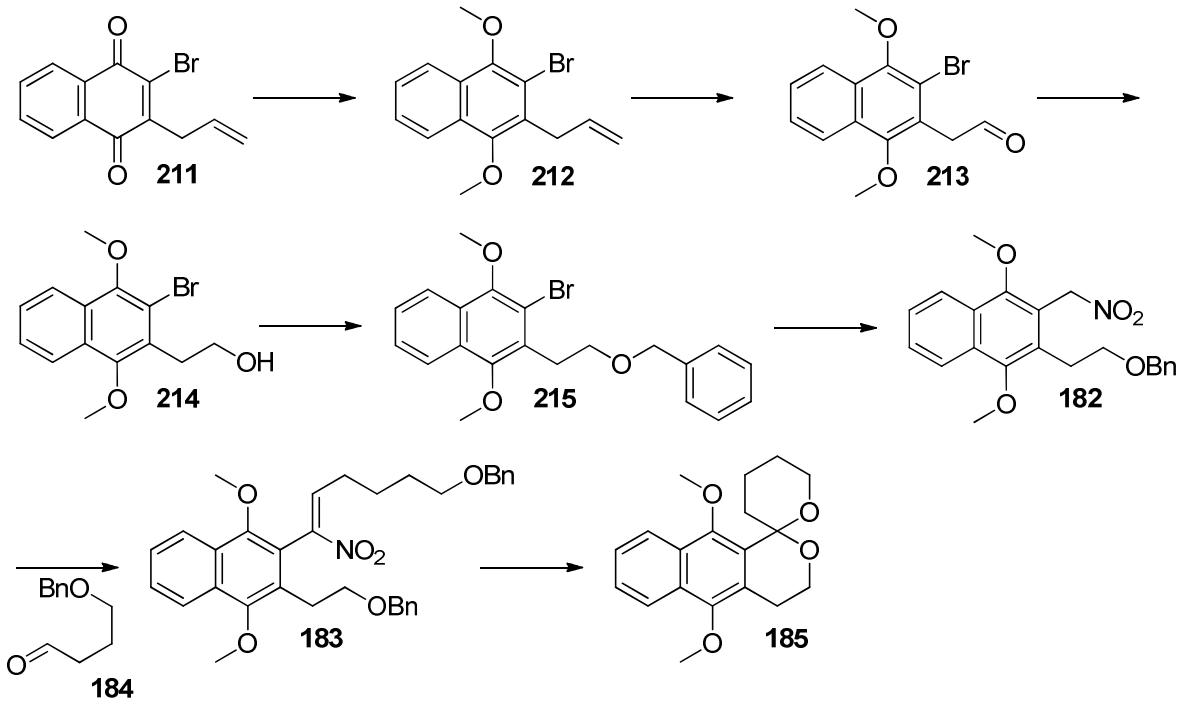
Having successfully isolated what we assumed to be the intermediates involved in the Nef reaction, we were in a position to propose a mechanism by which this particular Nef reaction operates. Based on the intermediates isolated, we propose that nitroalkene **180** is reduced to the hydroxylamine **186** and at the same time removal of the benzyl groups occurs (**Scheme 4.5**). This hydroxylamine **186** tautomerises to the more stable oxime **188** which in turn gets hydrolysed to the carbonyl **181**. This carbonyl **181** is attacked by the free phenols which result in the formation of the spiroketal **175**. This mechanism corroborates the earlier proposal by Capecchi.[88,89]



Scheme 4.5: Mechanism of the Nef reaction

4.6. Attempts towards the spiroketal core

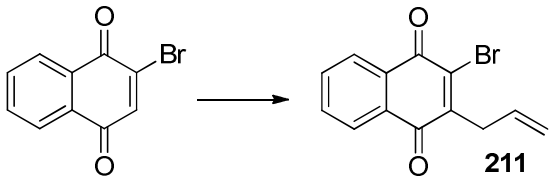
Having elucidated the mechanism of the novel Nef reaction, we could now turn our focus to the preparation of the spiroketal **185** (**Scheme 4.6**).



Scheme 4.6

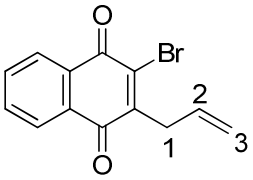
The next section of this chapter of the PhD thesis will therefore focus on our attempts towards the assembly of the spiroketal **185**. We aimed to use the methodology developed during our mechanistic studies where our key steps were a Henry condensation and our novel Nef reaction (**Scheme 4.6**).

We envisaged that spiroketal **185** could be prepared over several steps starting from commercially available 2-bromonaphthoquinone. The first step in the synthesis would employ a Hunsdiecker reaction to introduce the allyl group followed by protection of the quinone as the aromatic ether **212**. The alkene could then be oxidised to the aldehyde followed by reduction and subsequent protection of the alcohol as the benzyl ether **215**. Nitroalkane **182** could then be prepared using a palladium mediated cross coupling reaction with nitromethane which could be subjected to a Henry condensation reaction with **184** to afford nitroalkene **183**. If successful, the more complex aromatic conjugated nitro containing compound could then be subjected to our novel Nef reaction conditions to give the desired spiroketal **185**, as shown in **Scheme 4.6**.



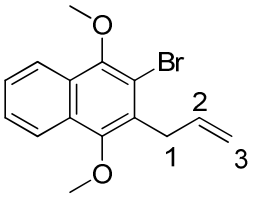
Scheme 4.7 *Reagents and conditions*: Vinyl acetic acid, $AgNO_3$, ammonium persulfate, MeCN, 60–70°C, 24 h, 79%.

To this end, a modified Hunsdiecker reaction was employed where ammonium persulphate in water was added to a solution of vinyl acetic acid, silver nitrate and 2-bromonaphthoquinone in acetonitrile. The reaction was heated to 60–70°C for 24 hours before purification by column chromatography yielded 2-allyl-3-bromonaphthalene-1,4-dione **211** as a yellow solid in 79% yield (**Scheme 4.7**).[29] This product proved unstable and decomposed on standing even at low temperatures (–20°C). As **211** is a known product, we decided to only obtain a ^{1}H NMR spectrum to confirm the identity of the product, and to use the material in the subsequent step immediately to avoid decomposition.



In the analysis of the ^{1}H NMR spectrum of **211** the presence of signals in the mid-region of the spectrum was a positive sign that the product had indeed been formed. The most upfield signal at δ 3.64 ppm integrating for two protons was observed as a doublet of triplets, and was assigned to the methylene protons at H_1. This signal showed coupling to three other signals: ^{3}J coupling of 6.6 Hz to the protons at δ 5.87 ppm which we assigned to H_2, and coupling of 1.4 Hz to the signals at δ 5.27 and δ 5.22–5.10 ppm which were due to alkene protons H_{3a} and H_{3b}. H_2 also showed both *trans* and *cis* coupling to H_{3a} and H_{3b} of 16.6 and 10.0 Hz respectively. The only remaining signals were due to our aromatic protons and were found as multiplets at δ 8.21–8.11 and δ 7.82–7.72 ppm each integrating for two protons.

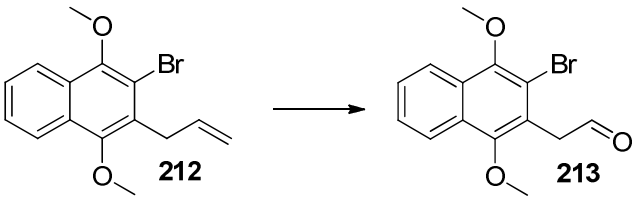
The next step was to protect our unstable quinone **211** as an aromatic ether. This was achieved by initially stirring quinone **211** with phase transfer catalyst tetrabutylammonium iodide in tetrahydrofuran with sodium dithionite in water to facilitate the reduction of the quinone to the hydroquinone. An aqueous solution of potassium hydroxide was then added to deprotonate the intermediate hydroquinone followed by the addition of dimethyl sulfate to furnish the dimethyl aromatic ether **211**. Column chromatography yielded the product, 2-allyl-3-bromo-1,4-dimethoxynaphthalene as a yellow solid in 75% yield over the two steps. [97]



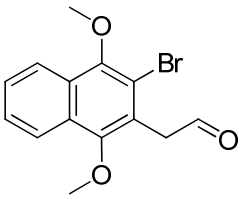
Evidence that the reaction was successful was obtained by examination of both the ^{1}H and ^{13}C NMR spectra. The most distinctive feature in the ^{1}H NMR spectrum was the presence of two signals at δ 3.92 and δ 3.98 ppm each integrating for three protons. This confirmed that we had in fact introduced aromatic methoxy groups. This was validated by the ^{13}C NMR spectrum with the presence of downfield signals at δ 150.17 and δ 150.95 ppm due to the two quaternary aromatic carbons attached to the methoxy groups. Similarly, the methoxy group carbons were found upfield in the expected region at δ 61.36 and δ 62.69 ppm. When the ^{1}H NMR spectrum was examined we noticed a shifting of the methylene proton, H_1 from δ 3.64 to δ 3.79 ppm indicating that these protons are more deshielded. A similar observation was made for the alkene protons where H_2 was previously found at δ 5.87 ppm and was now observed at δ 6.07 ppm while H_{3a} and H_{3b} were now observed as one multiplet signal at δ 5.12–4.98 ppm. The IR spectrum agreed

with this finding as no carbonyl stretches of the quinone were observed. We could therefore confidently say that we had formed **212**.

Keeping our focus on the preparation of nitroalkane **182**, as shown in **Scheme 4.6**, we now turned our attention to the conversion of the allyl substituent of **212** into the 2-carbon chain alcohol protected with a benzyl protecting group. In order to do this, bromoalkene **212** was first oxidised to aldehyde **213** using ozone as shown is **Scheme 4.8**. This was achieved by stirring **212** in dicholoromethane in the presence of Sudan III as our indicator. The reaction was cooled to –78°C and ozone gas was passed through the reaction mixture. Upon completion of the reaction, as noted by the colour change from pink to colourless, dimethyl sulfide was added to quench the reaction and purification after work-up afforded aldehyde **213** in 63% yield as a pink solid.[17]

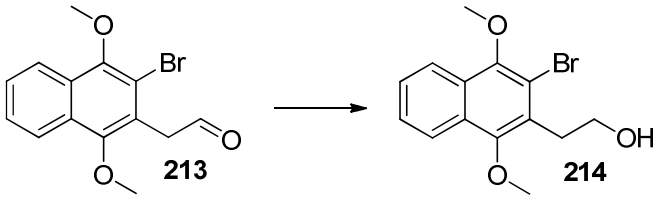


Scheme 4.8: (i) Sudan III, O_3, dimethyl sulfide, CH_2Cl_2, 63%.

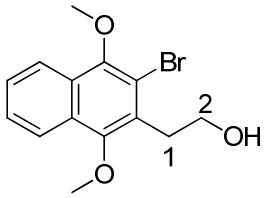


The ^{1}H NMR spectrum confirmed the formation of aldehyde **213** with the presence of a downfield signal at δ 9.86 ppm which is characteristic of an aldehyde functional group. Also noted was a downfield shift in the methylene proton signals from δ 3.79 to δ 4.13 ppm indicative of these protons being more deshielded due to the newly introduced aldehyde. These observations were verified by the ^{13}C NMR spectrum, with the presence of a signal at δ 198.54 ppm indicating that the carbon of the aldehyde was present. Once again, the downfield shift observed for the methylene protons in the ^{1}H NMR spectrum was supported by the ^{13}C NMR spectroscopic data with the shift from δ 34.36 to δ 45.20 ppm. The IR spectrum further attested to the formation of the aldehyde showing a stretch at 1717 cm^{-1} due to the carbonyl functional group.

Reduction of aldehyde **213** was accomplished using sodium borohydride in methanol (**Scheme 4.9**). A change in the R_f value from 0.33 to 0.23 in a 20% ethyl acetate: hexane mixture suggested that the reduction of the aldehyde to the primary alcohol **214** had taken place. The product **214** was isolated as a white solid in 73% yield.



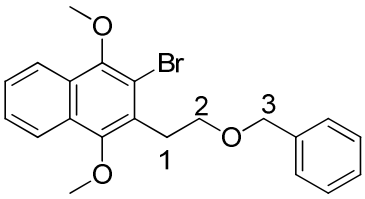
Scheme 4.9: $NaBH_4$, MeOH, RT, 73%.



Examination of the IR spectrum of **214** provided the first piece of evidence of the success of the reaction, showing a broad stretch at 3364 cm^{-1} due to the hydroxyl group. We also noticed the loss of the carbonyl stretch which was previously found at 1717 cm^{-1}. The ^1H NMR spectrum confirmed this as the only downfield signals we now observed were due to the aromatic protons. We observed a triplet at δ 1.91 ppm which showed coupling of 5.5 Hz to H_2. H_2 was observed at δ 3.92 ppm as a doublet of doublets with coupling of 12.5 and 6.7 Hz to the protons at H_1, found as a signal at δ 3.31 ppm due to it being deshielded by the hydroxyl group. H_1 coupled to the equivalent protons at H_2 and was therefore observed as a triplet with a coupling constant 6.8 Hz. Formation of the alcohol was further confirmed by the ^{13}C NMR spectrum. The most explicit indication was the loss of the carbonyl signal at δ 198.54 ppm. Instead, we now witnessed the presence of a signal at δ 61.36 ppm which was assigned as C2, as this was characteristic of a carbon attached to an oxygen atom. All other carbon signals were assigned using a CH correlation spectrum.

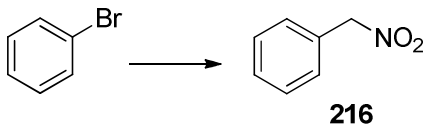
All that remained to do before we attempted the formation of nitroalkane **182** was the protection of alcohol **214**. We chose a benzyl protecting group as we knew that this would easily be removed if we subjected it to the Nef reaction conditions to form our desired spiroketal **185**, shown in **Scheme 4.6**. Therefore, alcohol **214** was dissolved in dimethyl formamide. Sodium

hydride followed by benzyl bromide were added and the reaction mixture was stirred overnight. Column chromatography afforded our protected alcohol **215** as a white solid in 61% yield.



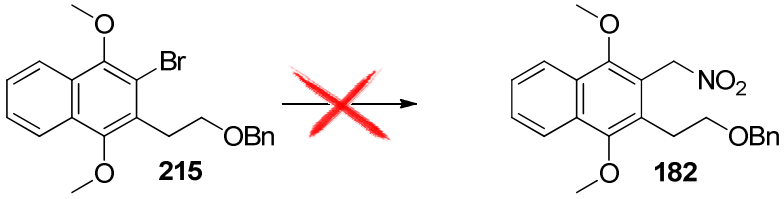
As expected, we no longer observed the triplet at δ 1.91 ppm previously seen for the alcohol. A clear singlet at δ 4.58 ppm integrating for two protons had appeared which we expected to be due to the methylene protons, H_3, of the newly introduced benzyl group. Additional signals were also observed for the aromatic protons of the benzyl group in the region δ 8.11–7.21 ppm. These protons overlapped with those of the naphthalene moiety and thus were not individually assigned. The ^{13}C NMR spectrum also showed the appearance of more carbon signals, the most important being the methylene carbon of the benzyl group, C3 which we observed at δ 72.90 ppm. The other signals which had appeared were found in the aromatic region as expected. Mass determination by HRMS of the product **215** showed the relevant increase in mass compared to the precursor **214**.

With **215** in hand we could move our efforts toward the formation of the aromatic nitroalkane **182**, realizing that this would be the most challenging step in our synthesis. However, a number of studies, in particular by Kozlowski, have been conducted describing the Pd-catalyzed coupling of aryl halides with nitromethane to furnish arylnitromethanes.[98,99] In these studies, bromoaryl substrates were converted to the corresponding arylnitromethanes using nitromethane, an appropriate base and ligand as well as a palladium catalyst. A range of arylnitromethanes were prepared using these methods where the most appropriate base was determined to be caesium carbonate, the ligand chosen was XPhos, while the palladium catalyst used was Pd_2dba_3. We therefore decided to test the reaction on simple bromobenzene as was conducted in the reference articles (**Scheme 4.10**),[98,99] and were pleased to observe the consumption of our starting material to afford the expected arylnitromethane **216** as confirmed by NMR spectroscopic analysis.



216

Scheme 4.10

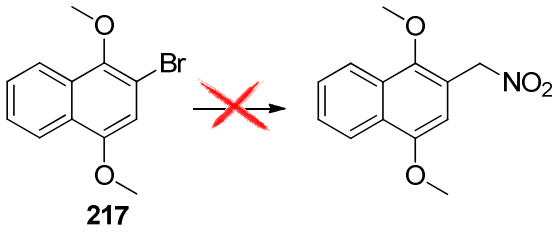


215 **182**

Scheme 4.11

Therefore, using this methodology we dissolved bromonaphthalene **215** in nitromethane under an atmosphere of argon. 4Å Molecular sieves were added to ensure that the reaction was kept moisture free. Xphos ligand, caesium carbonate and Pd_2dba_3 were then added and the reaction mixture stirred at 50°C.[99] The reaction progress was monitored by TLC and after stirring for 24 hours no consumption of the starting aromatic halide **215** was observed. Work-up of the reaction resulted in the recovery of starting material (**Scheme 4.11**). At this stage, we proposed that a likely reason that the reaction may not be progressing could be owing to steric hindrance or the electron rich nature of the substrate not allowing the oxidative addition of the palladium(0) to take place on the aromatic bromide.

We then decided that the reaction would be attempted on a substrate which lacked the alkyl side chain. To this end, we subjected 2-bromo-1,4-dimethoxynaphthalene **217** to the reaction conditions described above to determine whether the side chain was influencing the reaction (**Scheme 4.12**). To our disappointment we once again isolated only starting material.



Scheme 4.12

We could therefore assume that our starting arylbromide **215** was overly electron rich due to the electron donating methoxy substituents and it was this electronic effect that was preventing our palladium-coupling reaction from proceeding. Reviewing the literature, we found another article by Kozlowski where she described a similar coupling reaction in which nitroacetates were used instead of nitromethane.[100] The ethyl-2-nitroacetate was assumed to work more effectively due to the higher acidity (pKa 5.8) as compared to nitroalkanes (pKa 10). We therefore attempted the coupling reaction between our arylhalide **215** and ethyl-2-nitroacetate instead of nitromethane while keeping the palladium source and base the same as that of our earlier experiments (**Section 4.6**). However, once again TLC analysis of the reaction mixture showed no consumption of our starting material and crude NMR spectroscopic analysis showed the presence of our starting arylhalide **215**.

4.7. Concluding remarks pertaining to Chapter 4.

The central theme in this chapter was the elucidation of the intermediates, and thus the mechanism, of our novel Nef reaction. The key reactions involved in the preparation of these intermediates were a Henry condensation reaction as well as a modified Nef reaction. Our second aim was to develop methodology toward the preparation of the spiroketal core of Griseusin.

With respect to the elucidation of the mechanism of our modified Nef reaction, we envisaged that we would need to begin this investigation with substrates which did not contain any *ortho*-phenolic groups (described in **Section 4.1**). To this end we used three different substrates, namely piperanal, anisaldehyde and vanillin in our synthesis of nitroalkene precursors. A Henry condensation reaction was performed on each of our initial substrates to yield nitroalkenes **189**, **190** and **191**, as shown in **Figure 4.5**.

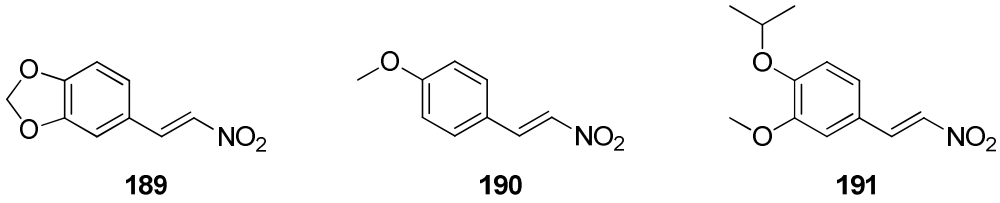


Figure 4.5

In order to obtain the *bis*-aromatic system, we envisaged that a second Henry condensation would be necessary. This was achieved by the reduction of the double bond in nitroalkenes **189**, **190** and **191** followed by a second Henry reaction with 2,4-dimethoxybenzaldehyde to form nitroalkenes **199**, **200** and **201**, shown in **Figure 4.6**.

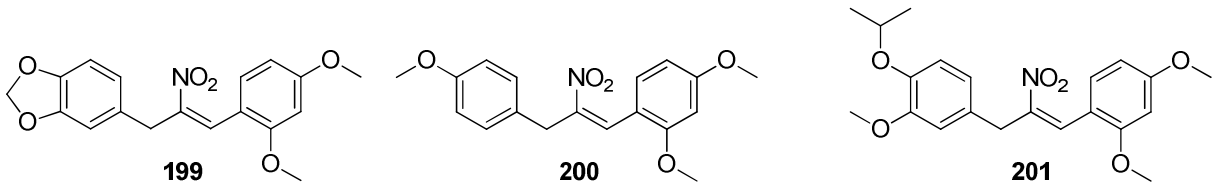
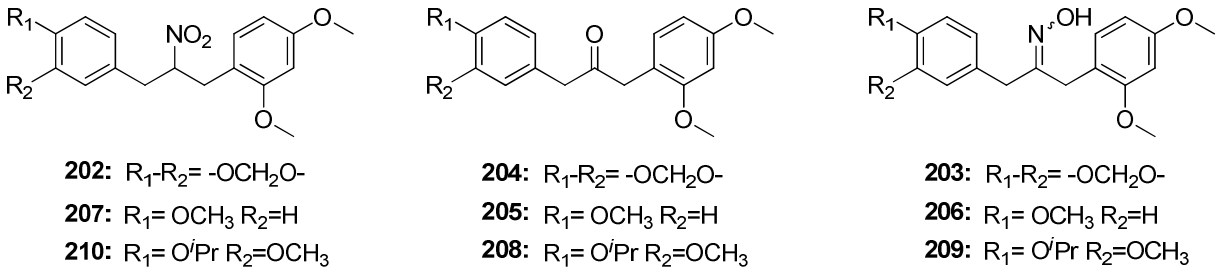


Figure 4.6

Having successfully prepared the nitroalkenes illustrated in **Figure 4.6**, we performed our modified novel Nef reaction to determine which intermediates were involved. Isolation of the products from each reaction confirmed the presence of three different intermediates. These intermediates were classed as nitroalkanes, carbonyl-containing compounds and oximes.

Figure 4.7 shows these intermediates using the nitroalkenes **199**, **200** and **201** as substrates in the Nef reaction.



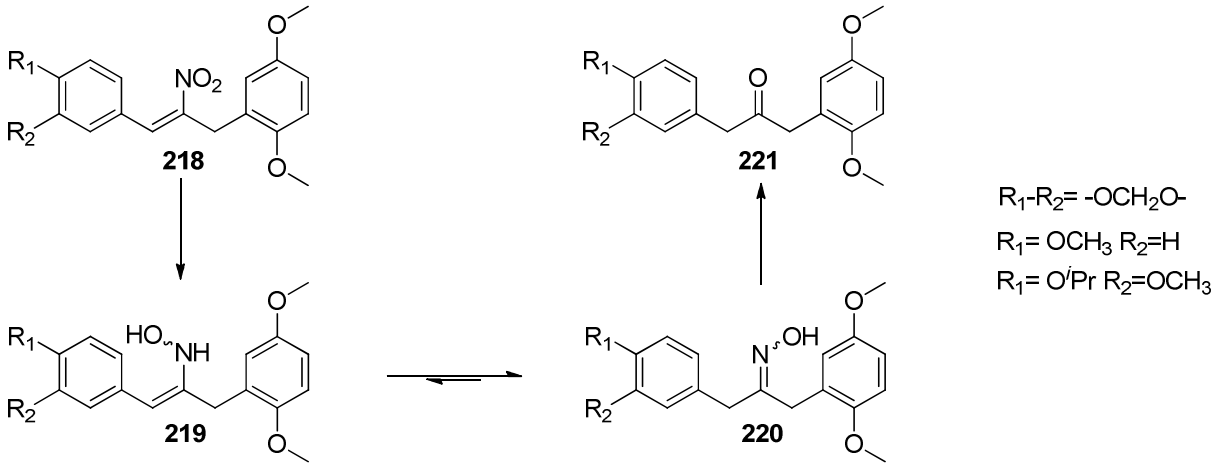
202: R_1-R_2= -OCH_2O-
207: R_1= OCH_3 R_2=H
210: R_1= O^{i}Pr R_2=OCH_3

204: R_1-R_2= -OCH_2O-
205: R_1= OCH_3 R_2=H
208: R_1= O^{i}Pr R_2=OCH_3

203: R_1-R_2= -OCH_2O-
206: R_1= OCH_3 R_2=H
209: R_1= O^{i}Pr R_2=OCH_3

Figure 4.7

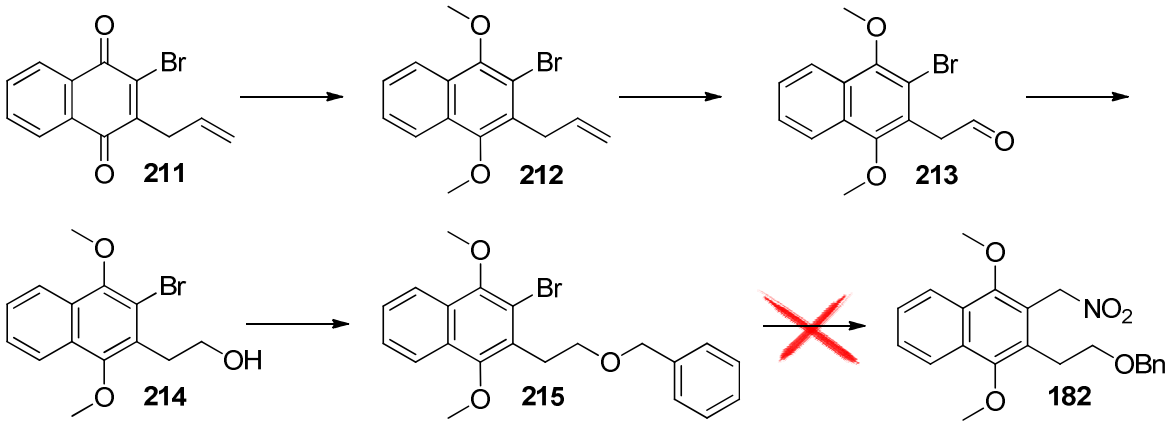
Literature precedent by Varma and co-workers [90] confirms that oxime formation occurs from unsaturated nitroalkenes, while Monti and coworkers[101] confirmed the rapid hydrogenolytic–hydrolytic conversion of oximes to carbonyl containing compounds. Based on these results, we propose that the novel Nef reaction proceeds by the general mechanism shown in **Scheme 4.13**. Nitroalkene **218** is reduced to the hydroxylamine **219**. This hydroxylamine tautomerises to the more stable oxime **220** which eventually undergoes a hydrolysis reaction to the carbonyl compound **221**. Our substrates lack the *ortho*-phenolic groups and therefore cannot continue toward the formation of the spiroketal functionality. It was also pleasing that the intermediates themselves could be converted to the carbonyl intermediate which we postulate to be the precursor to the spiroketal moiety.



Scheme 4.13: Elucidated reaction mechanism of our Nef reaction

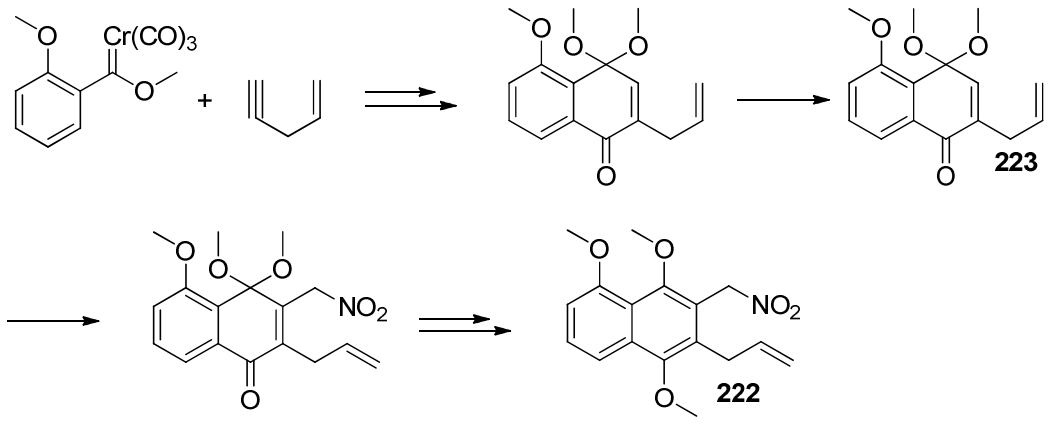
Unfortunately, the preparation of the spiroketal core of griseusin proved less fruitful than the mechanistic studies. Although this was the case, we have made some progress towards the spiroketal core and we were able to propose synthetic routes which may prove less challenging. We initially envisaged that we could prepare the spiroketal core using the methodology developed in the mechanistic studies. We therefore aimed to prepare aromatic halide **182** from commercially available 2-bromo-naphthoquinone. This was successfully achieved in four steps, as shown in **Scheme 4.14**.

Review of the literature provided evidence that we could couple arylbromides with nitroalkyl compounds using a palladium catalyst to provide arylnitromethane compounds. However, when we attempted this reaction on our substrate, we only isolated our starting bromide **215**. We then tried the reaction on simpler systems such as bromobenzene and 2-bromo-1,4-dimethoxynaphthalene **217** and found that the former reaction was successful while the latter yielded only starting bromide **217**. As discussed earlier, the lack of success of this reaction may be due to the electron donating effect of the methoxy substituents inhibiting the oxidative addition of palladium(0) to arylbromides **215** and **217**.



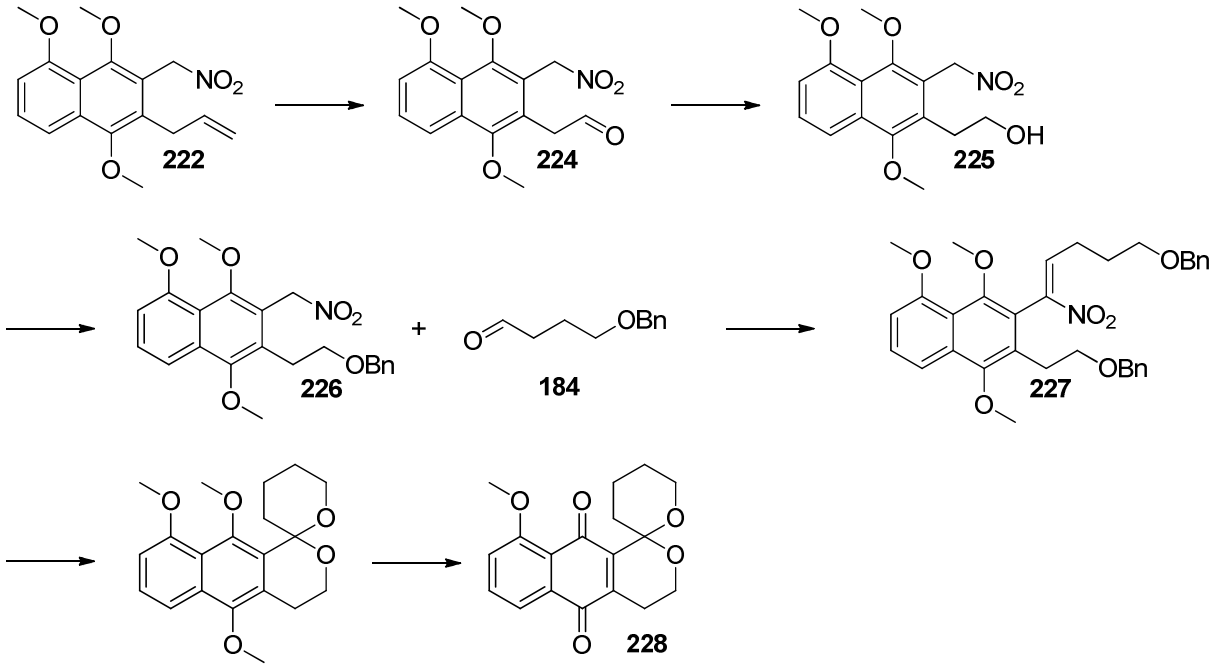
Scheme 4.14

Even though our efforts to form the arylnitromethanes did not meet with much success, there are literature reports which provide alternative avenues to preparing these compounds. Looking into the future, we could employ the strategy used by Semmelhack for the preparation of **222**.[102] In their study they used chromium complexation to form allyl quinone type compounds. A conjugate addition of nitromethane to compound **223** was then performed followed by the reduction of the quinone system and subsequent protection to yield arylnitromethane **222**, as shown in **Scheme 4.15**.



Scheme 4.15

Once the arylnitromethane **222** is successfully formed, the alkene could be oxidised to the aldehyde **224** followed by reduction to yield alcohol **225** (**Scheme 4.16**). This alcohol **225** could then be protected using benzyl bromide to afford arylnitromethane **226**. If these transformations were successful, a Henry condensation reaction between arylnitromethane **226** and 4-(benzyloxy)butanal **184** would provide us with nitroalkene **227** on which we could perform our modified Nef reaction. This would hopefully result in the formation of our expected spiroketal core **228**.

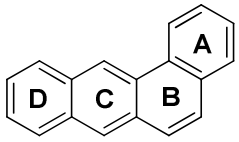


Scheme 4.16

Chapter 5: The angucycline antibiotics

5.1. Background and Introduction

A large number of secondary metabolites of microbial origin, called the angucycline antibiotics, exist in nature. This group of metabolites receive their name from their characteristic four-ring frame (labelled A, B, C and D) of the aglycone moiety where an angular assembly is observed and is related to the aromatic tetracyclic benz[*a*]anthracene system **229** shown in **Figure 5.1**.[103,104]



229

Figure 5.1

The angucycline antibiotics have been shown to possess a range of biological activities which include antibacterial and antiviral activity and cytostatic and enzyme inhibitory effects. Tetrangomycin **230** and tetrangulol **231** were the first isolated members of the angucycline antibiotics and to date more than one hundred members have been described.[103] The earliest antibiotics were considered simple sugarless angucyclines, such as tetrangulol **231** with relatively low molecular weights of slightly more than 300. However, recent examples of these compounds have molecular weights in excess of 1000, such as landomycin A **232** and urdamycin **233**, owing to their attached carbohydrate moieties (**Figure 5.2**).

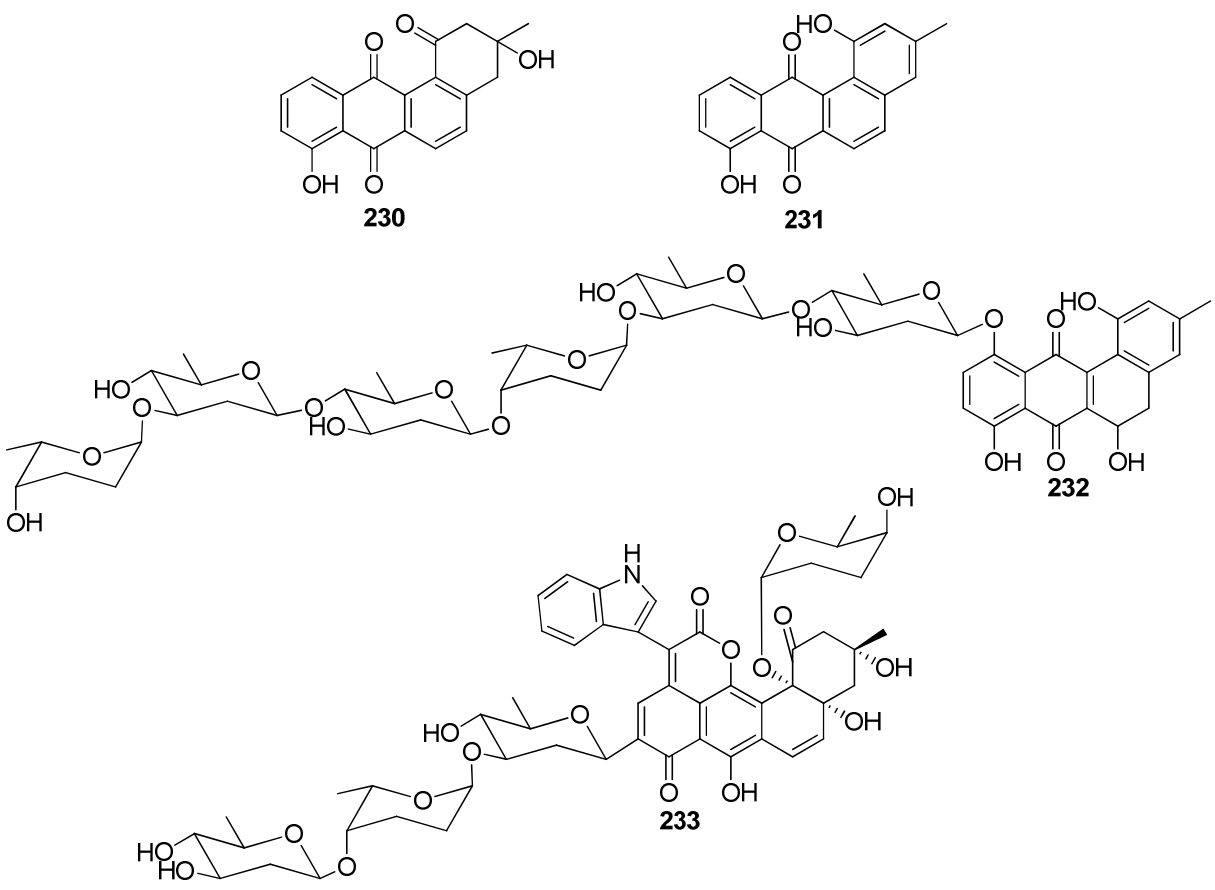
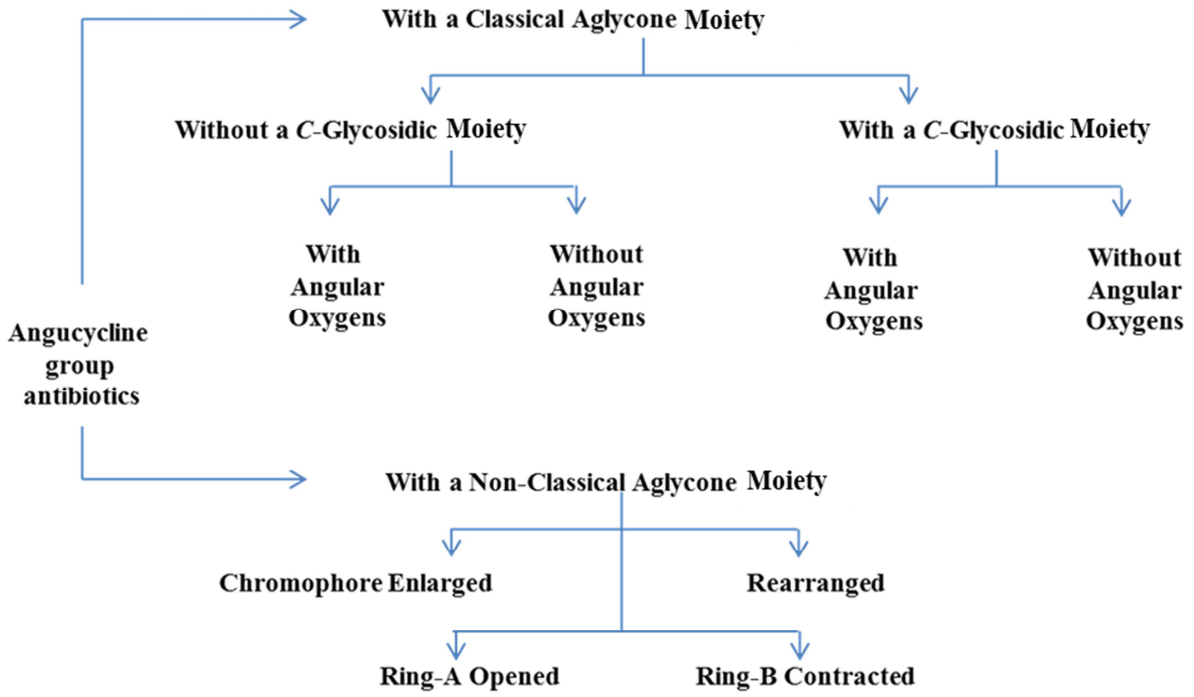


Figure 5.2

The anguclycline secondary metabolites have all been isolated from various soil samples or shallow sea mud.[105] In the classification of these compounds, it was found that they all belong exclusively to the *Actinomycetes* group where the majority of the organisms were classified by various species of *Streptomycetes*.[103]

5.2. Classification of angucyclines

The angucyclines are divided into two broad classes: classical and non-classical aglycone moieties (**Scheme 5.1**). The classical angucyclines are subdivided into two types, while the non-classical angucyclines are subdivided into four types. This classification is based on structural features which arise from either the C-glycosylation or the 12b-mono-oxygenase reactions which are key biosynthetic reactions involved early in the synthesis of these antibiotics.[106] Each of these classes and subclasses will briefly be discussed in the next few sections.



Scheme 5.1

5.2.1. Classical angucyclines

5.2.1.1. Angucyclines without C-glycoside moiety

This type of angucycline system is most commonly found and considered the simplest based on the biosynthetic pathway. Most compounds of this class are angucyclinones, which are compounds lacking a sugar functionality, with the landomycins family being the exception.

5.2.1.1.1. Metabolites with angular oxygen

Metabolites of this class contain angular oxygen, which originates from acetate (4a–O) and from air (12b–O) early in their biosynthesis through introduction by a mono-oxygenase. The antibiotic SS-228Y **234**[105,107] and the sakyomicin family **235**[108] typify this class of metabolites (**Figure 5.3**). The initial proposal for the structure of SS-228Y **234** was revised after biosynthetic studies on the vineomycins. Other antibiotics which fall into this class of metabolites are the sulfur-containing antibiotics, an example of a sulfur-containing antibiotic is sakyomicin E **236** which contains a sulfide group believed to originate from methionine.[103]

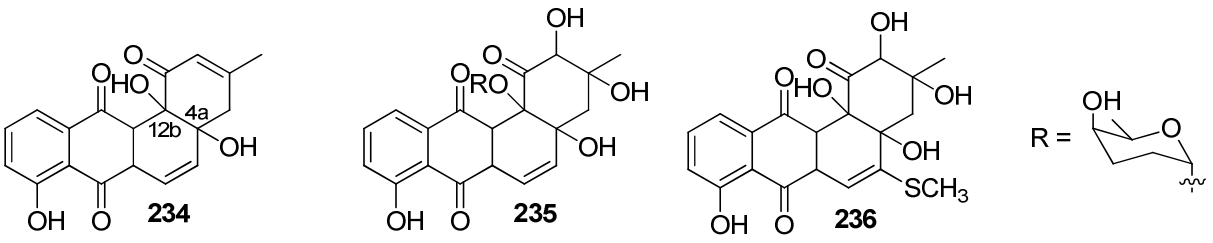
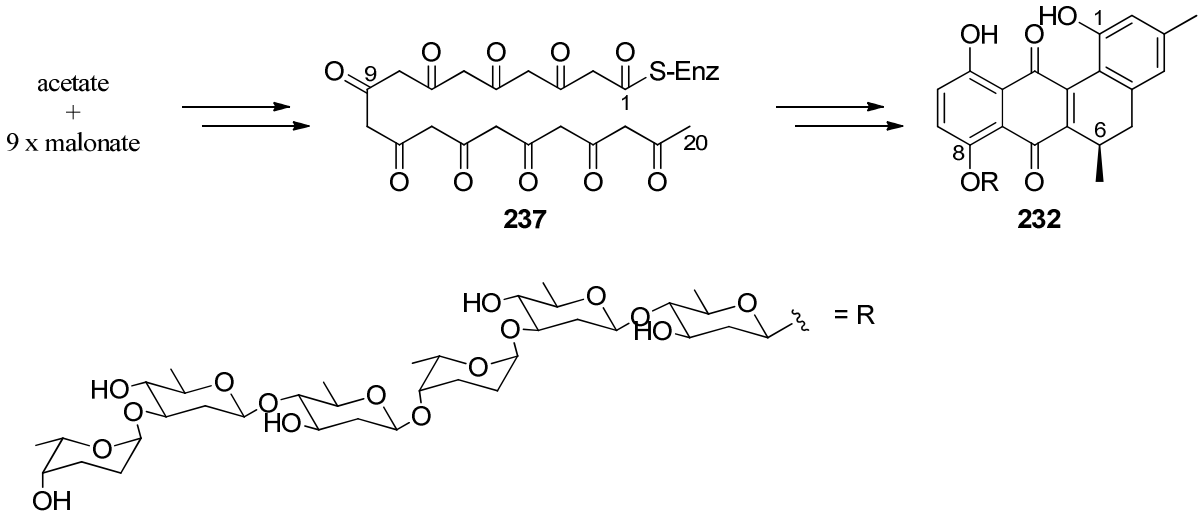


Figure 5.3

Specifically related to this project are the landomycin antibiotics such as **232**. This group of compounds was discovered in 1990 and is considered the best known family of the angucycline antibiotics. The landomycins were isolated from *Streptomyces sp.* and were found to comprise *tri-*, *penta-* or *hexa*-saccharidal chains. Feeding experiments have shown that the backbone of the landomycins arise from acetate and malonate where the biosynthesis involves a decaketide

intermediate **237** which undergoes cyclisation and aromatization to give landomycin **232** as shown in **Scheme 5.2**.[109]



Scheme 5.2

5.2.1.1.2. Metabolites without angular oxygen

This subgroup of metabolites contains a variety of structurally related compounds that possess an anthraquinone chromophore and vary with respect to the number and positions of free or methylated hydroxyl groups present such as in X-14881 **238** (**Figure 5.4**).[110] A rarity of this group is the presence of *O*-glycosidically bonded sugar moieties. The angucyclinones possess a saturated angular ring and a keto-group at C1. Reduction of this keto-group to the secondary alcohol is observed in metabolites such as rubiginone A_1 **239**. Other structural features observed in this class include the presence of the hydroxyl groups in unusual positions, such as in X-14881 D **240** which arise as a result of the oxygenase activity of the producing organisms.[111]

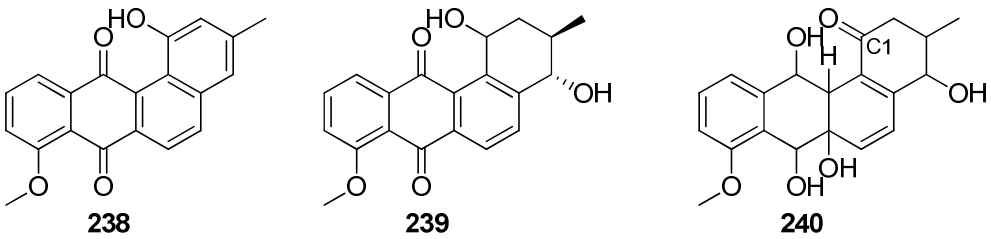


Figure 5.4

5.2.1.2. Angucyclines with a C-glycosidic moiety

In this section, we will describe all angucyclines which possess a C-glycosidic moiety. A large number of angucycline antibiotics possess this characteristic and structural feature and therefore constitute the largest group of C-glycosidic antibiotics. The C-glycosidic containing angucyclines can also be divided into two classes: those containing metabolites with angular oxygen and those without angular oxygen. These two classes will be discussed below.

5.2.1.1.1. Metabolites without angular oxygen

These metabolites are the least common of the angucyclines. The first examples of these antibiotics include the benzanthrins A **241** and B **242** which exhibit a C-glycosidic moiety linked to ring A as well as an O-glycosidically bonded carbohydrate at C1 (**Figure 5.5**).[112,113] A unique aspect of these carbohydrates is that they are amino sugars.

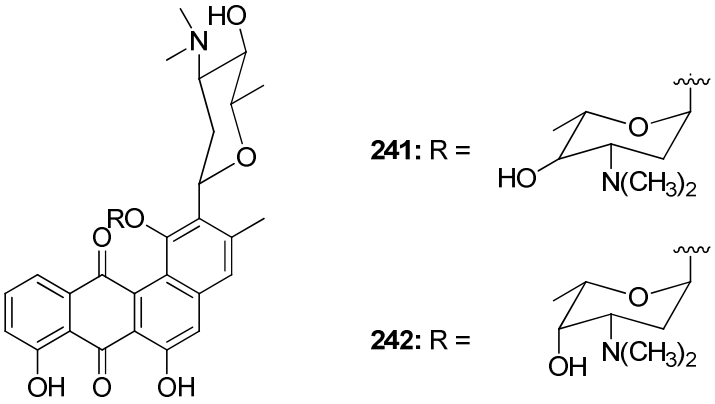


Figure 5.5

5.2.1.1.2. Metabolites with angular oxygen

The earliest example of this class of metabolites was aquayamycin **243**.[114-116] A number of structurally related angucyclines, such as urdamycinone E **244** and F **245**, are often called the "aquayamycin-type" antibiotics and have also been described. Variation in this class of antibiotics occurs in the form of deoxy sugar units attached to C3, C4', C5' and C12b, as shown in **Figure 5.6**.[103]

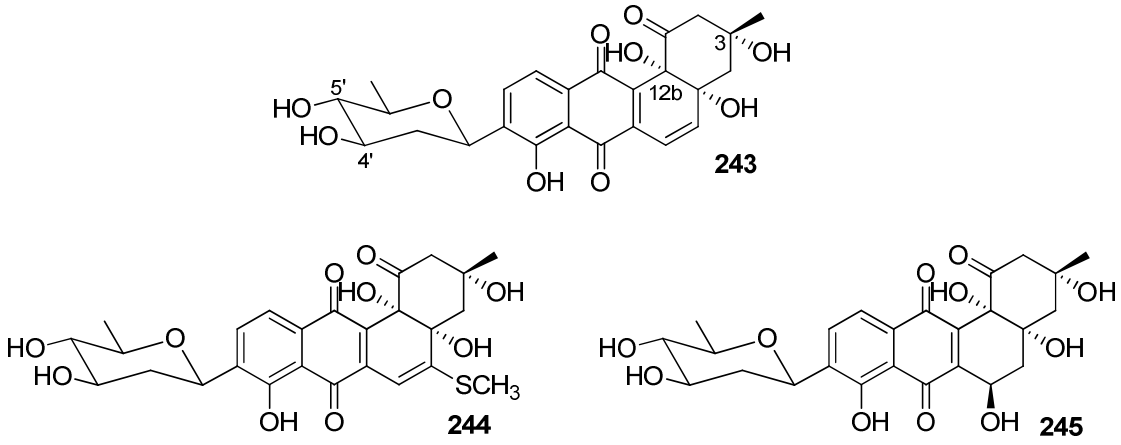


Figure 5.6

5.2.2. Non-classical angucycline antibiotics

The class of non-classical angucycline antibiotics is not as structurally diverse as the classical angucyclines and the inclusion of these compounds as angucyclines is based on the chemical and biosynthetic approaches. This class of compounds is subdivided into four categories two of which will briefly be discussed.

Linearly annelated naphthacenequinone antibiotics have been described as containing galtamycinone **246** as their aglycone moiety (**Figure 5.7**).[117] It is thought that these compounds are derived from classical angucyclines based on their oxygen atom substitution pattern, as well as the presence of the C-glycosidic moiety. Both enzymatic and non-enzymatic reactions are thought to allow this conversion to take place. An example of this class is galtamycin **246**[118,119] which possess a linear fused ring system.

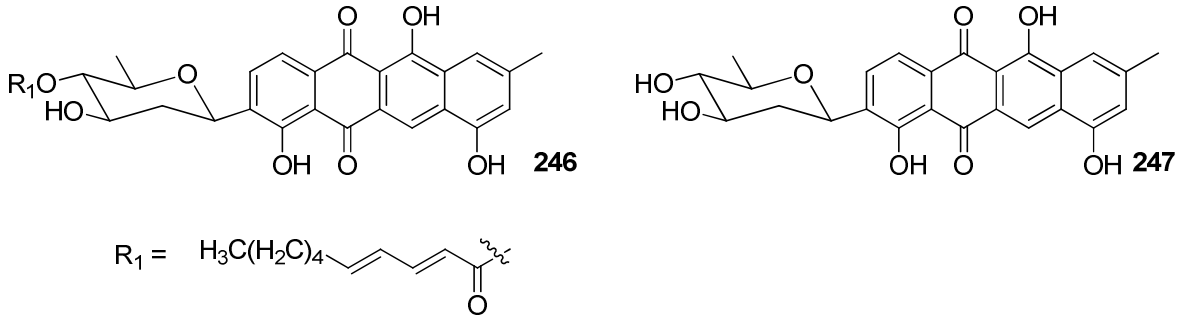
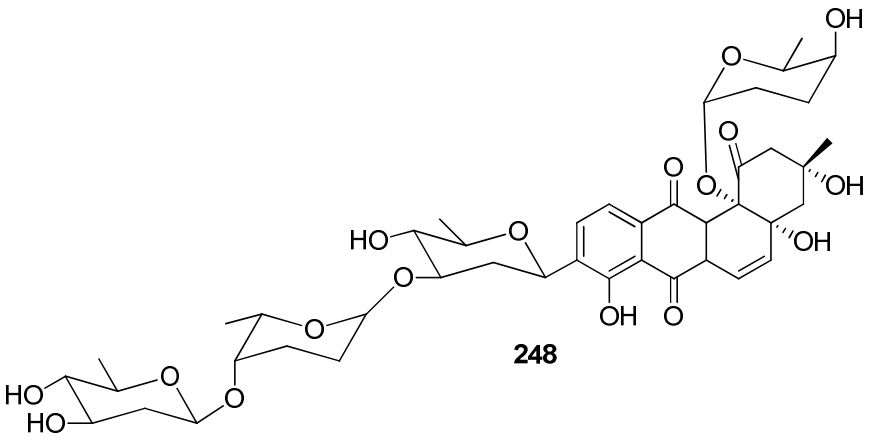


Figure 5.7

The chromophore enlarged angucycline antibiotics, named due to their conspicuous darker colour, were first found to occur within the urdamycin family. Studies on the biosynthesis of this class of compounds showed that the urdamycins are derived from the classical angucycline urdamycin A **248** and different amino acids.[103] In **Figure 5.8** we can see that the tetracyclic angular ring system is present in the chromophore enlarged angucycline antibiotics.

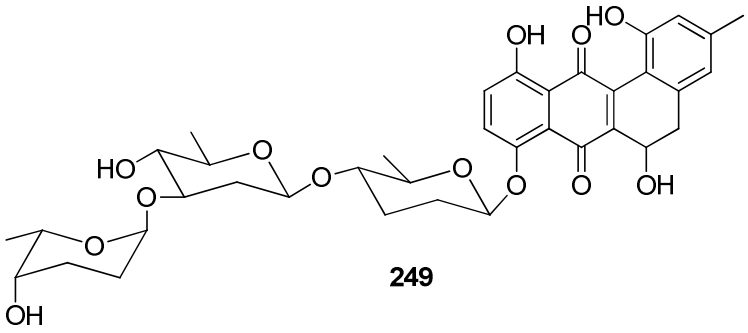


248

Figure 5.8

5.3. Biological activity of landomycin

The angucycline antibiotics, and in particular the landomycins, have been shown to possess a diverse range of biological activities such as anticancer, antibacterial and enzyme inhibitory activity. The biological activity of landomycin A has been extensively explored and it has been found to possess bioactivity against 60 cancer cell lines, including potent activity against prostate cancer cell lines.[120] It has been shown to inhibit thymidine uptake in murine smooth muscle,[121] and also inhibits cell cycle progression. Its unusual activity is attributed to its long oligosaccharide chain, as landomycins which possess shorter oligosaccharide chains have expressed weaker activity.[122] The angucycline antibiotic, landomycin E **249** (**Figure 5.9**), has exhibited anticancer activity *in vitro* and *in vivo* and has been suggested to act by inducing apoptosis.[123]



249

Figure 5.9

5.4. Synthetic strategies towards the landomycin core

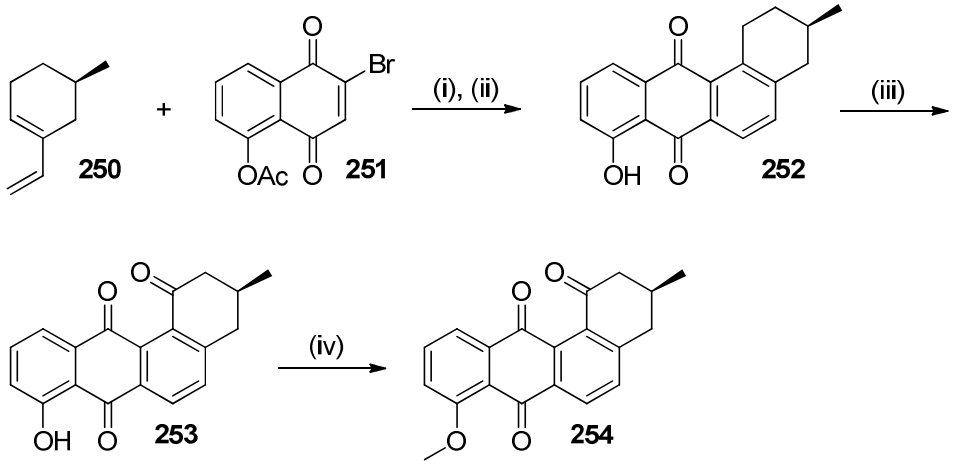
A number of synthetic strategies have been developed for the synthesis of the angucycline antibiotics due to their diverse biological activities as well as the attractive structural features they possess. There are several reviews which describe the synthesis of these antibiotics where most of the earlier reported syntheses utilised classical reactions, such as the Diels-Alder reaction or nucleophilic or electrophilic addition, as the key step. In recent years, a number of additional reactions were used as key reactions in the synthesis of the angucyclines such as transition metal catalyzed cross coupling and intramolecular cyclization strategies. We will briefly discuss these classical and newer reaction methodologies for the synthesis of the landomycins.

5.4.1. Diels-Alder reactions

The tetracyclic core of the angucycline antibiotics has been widely accessed via a Diels-Alder reaction of a suitably substituted diene and dienophile. This method allows for the formation of a range of angucyclines due to the structural diversity of the dienes and dienophiles.

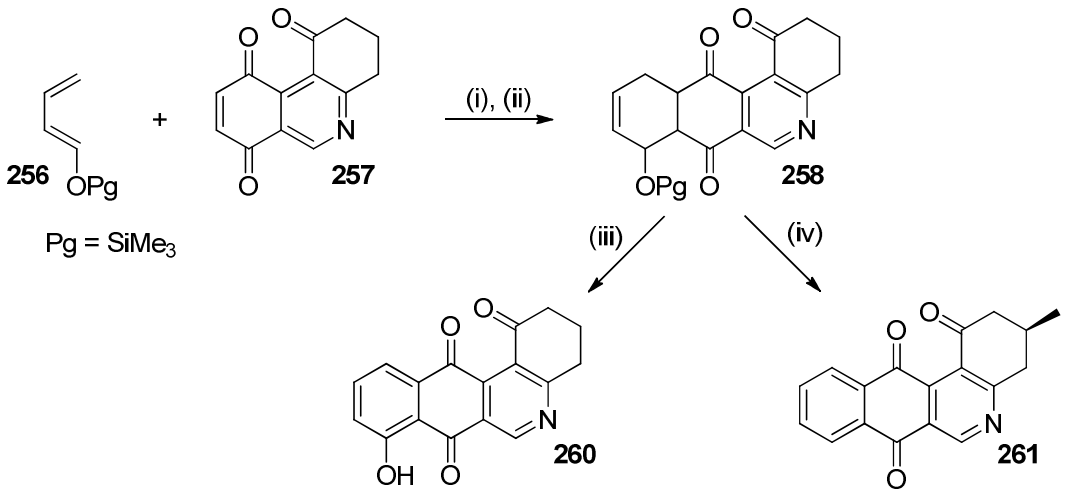
The enantioselective synthesis of five closely related natural products has recently been achieved by Kaliappan and co-workers using this methodology, as shown in **Scheme 5.3**.[124] A Diels-Alder reaction between 1,3-diene **250** and 5-acetoxy-2-bromo-1,4-naphthoquinone **251** in toluene at 80°C afforded an intermediate Diels-Alder adduct. The debromination of this adduct followed by

aromatisation yielded tetracycle **252**. A photooxygenation reaction of **252** afforded natural product, (+)-ochromycinone **253**. A methylation reaction of (+)-ochromycinone **253**, afforded a second natural product, (+)-rubiginone **254**.



Scheme 5.3 *Reagents and conditions*: (i) Toluene, 80°C, 16 h; (ii) K_2CO_3, MeOH, 45% over two steps; (iii) *hv*, O_2, benzene, 20 h, 82%; (iv) Ag_2O, MeI, CH_2Cl_2, RT, 5 h, 82%.

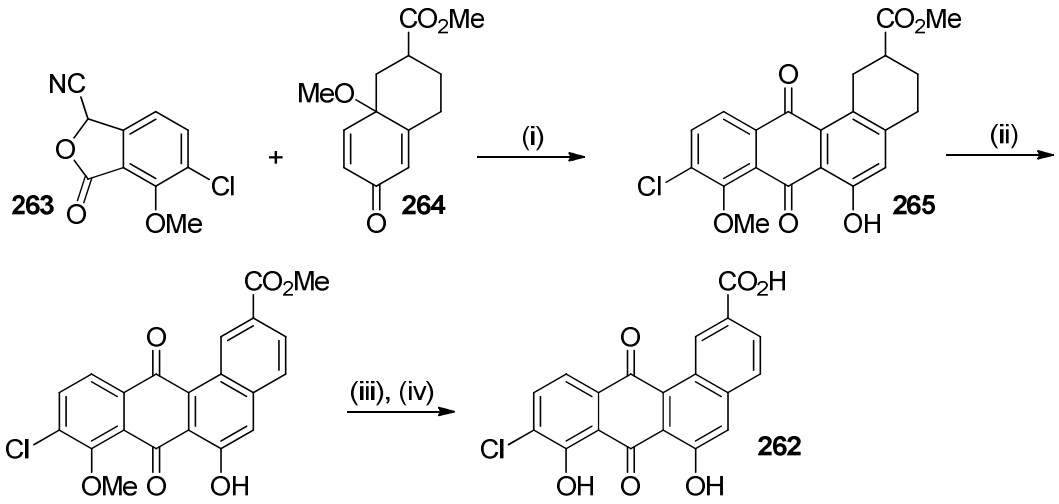
The aza anoalgues of the angucyclines have also been prepared using a key Diels-Alder reaction. Valderrama and co-workers illustrated this in the preparation of 5-aza-angucyclinone analogues.[125] In their synthesis, 1,3-diene **256** was subjected to a Diels-Alder reaction with a substituted 7,10-phenanthrenedione **257**, which furnished the nitrogen containing angucyclinone skeleton **258**. Using a selective deprotection-oxidation technique, analogue **258** could be converted to either the corresponding 8-hydroxy angucyclinone analogue **260** or the 8-non-hydroxy analogue **261** (**Scheme 5.4**).



Scheme 5.4: *Reagents and conditions*: (i) DCM, RT, 82%; (ii) HCl, THF-H_2O; (iii) PCC, 63%; (iv) HCl, THF-H_2O, 66%.

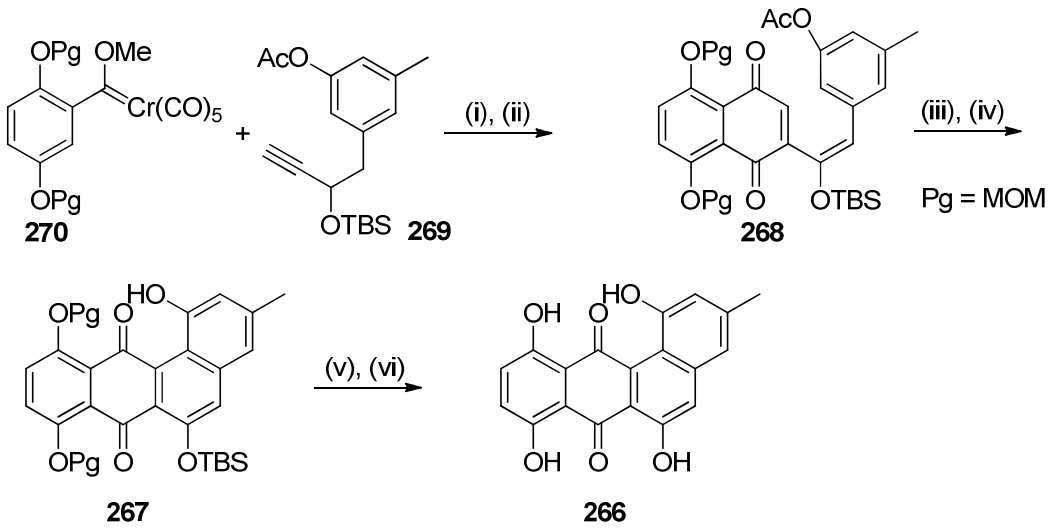
5.4.2. Nucleophilic addition strategies

Inter- and intra-molecular nucleophilic addition cyclisation reactions have been widely used since the first synthesis of tetrangulol **231**. This reaction methodology has been used in the regioselective assembly of the tetracyclic core of angucycline antibiotics. The most widely used version of this type of reaction is the anionic [4+2] cycloaddition reaction. This is better known as the Hauser[126] or the phthalide[127] annulation. The nucleophilic reaction can be described as an intermolecular Michael addition which is followed by a cyclisation reaction between α,β-unsturated carbonyls and an anion. This synthetic strategy, shown in **Scheme 5.5**, has been illustrated by Mal and Dey in the total synthesis of BE-23254 **262**.[128] In their synthesis, lithium *tert*-butoxide was used to generate an anion of **263** which was used in the key reaction with quinone monoketal **264**. This reaction afforded the preliminary angucyclone backbone **265**. Aromatization using DDQ, followed by demethylation and subsequent ester hydrolysis furnished the natural product **262**.



Scheme 5.5: *Reagents and conditions*: (i) Bu^{t}OLi, THF, –60°C to RT, 71%; (ii) DDQ, 49%; (iii) $AlCl_3$, 78%; (iv) aq. NaOH, 92%.

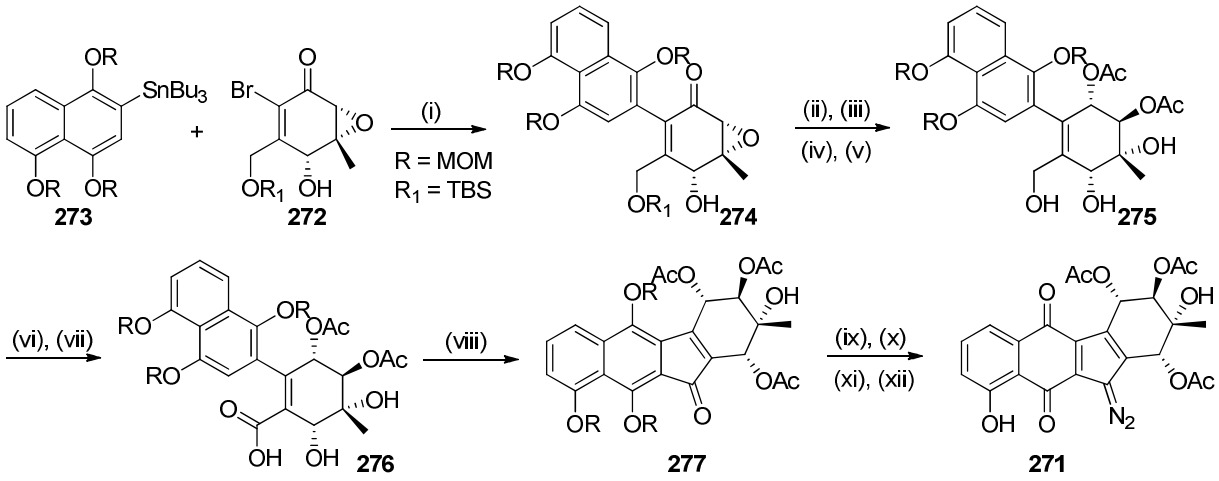
Another example in which a nucleophilic addition cyclisation reaction is used as a key step is in the total synthesis of landomycin **266**. As shown in **Scheme 5.6**, Roush and Neitz constructed the tetracyclic angucyclinone skeleton **267**, using a base mediated intramolecular nucleophilic addition cyclisation reaction of **268**.[129] The synthesis commenced with the construction of naphthoquinone **268** using a Dotz benzannulation reaction between alkyne **269** and chromium carbene **270**. The key cyclization reaction of **268** was initiated by sodium ethoxide followed by the aerial oxidation of the unstable hydroquinone resulting in the formation of **267**. Landomycin **266** was afforded after the removal of the protecting groups.



Scheme 5.6: *Reagents and conditions*: (i) heptane, 55°C; (ii) CAN, CH_3CN, 35-40%; (iii) NaOEt, EtOH, 0°C, 87%; (iv) NaOEt, EtOH, air, 55°C, 45%; (v) 0.05 M HCl, MeOH, 0°C, 1.5 h; (vi) $MgBr_2$, THF, 0°C, 65% over two steps.

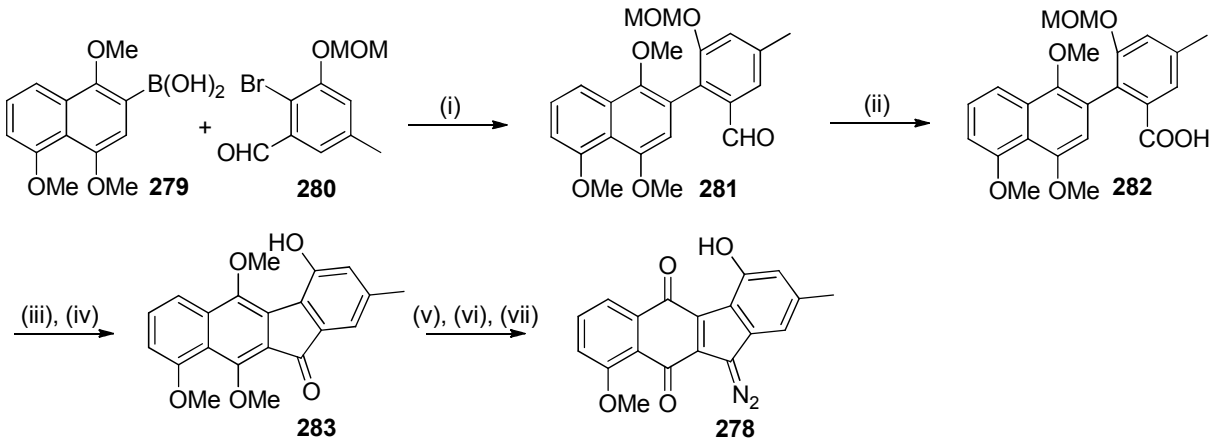
5.4.3. Electrophilic addition strategies

The synthesis of the angucyclinone skeleton using electrophilic addition or Friedel-Crafts type reactions has been widely reported. The first enantioselective total synthesis of kanamycin C **271** has been achieved by Lei and Porco using this synthetic methodology, shown in **Scheme 5.7**.[130] The synthesis commenced with a Pd-catalysed Stille cross coupling between vinyl bromide **272** and stannane **273** to afford biaryl compound **274**. A diastereoselective reduction of the carbonyl group of **274**, using Super-hydride, followed by the ring opening of the epoxide, acetyl protection and TBS deprotection afforded alcohol **275**. The secondary alcohol **275** was oxidised to the carboxylic acid **276** before being subjected to a Friedel-Crafts cyclisation with trifluoroacetic anhydride to provide the tetracyclic core **277**. The synthesis was completed to yield **271** after the oxidation of the hydroquinone and introduction of the diazo functionality.



Scheme 5.7: *Reagents and conditions*: (i) $Pd_2(dba)_3$, $AsPH_3$, CuCl, DIEA, CH_3CN, 70°C, 4 h, 70%; (ii) Super-Hydride, THF, –78°C, 1 h, 80% (dr> 10:1); (iii) $Ti(O^iPr)_4$, Bu_4^nNOAc, CH_2Cl_2, RT, 10 h, 60%; (iv) Ac_2O, pyridine, RT, 2 h; (v) Et_3N-3HF, CH_3CN, RT, 12 h, 67% over two steps; (vi) TPAP, NMO, CH_2Cl_2, RT, 20 min; (vii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, Bu^tOH-H_2O, RT, 12 h, 88% over two steps; (viii) TFAA, DCE, RT, 1 h, 90%; (ix) CBr_4, Pr^iOH, 84°C, 1 h; (x) Pd/C, air, EtOAc, RT, 30 min, 70% over two steps; (xi) TBSNHNHTBS, $Sc(OTf)_3$, CH_2Cl_2 (xii) $PhIF_2$, 2-chloropyridine, CH_2Cl_2, 35% over two steps.

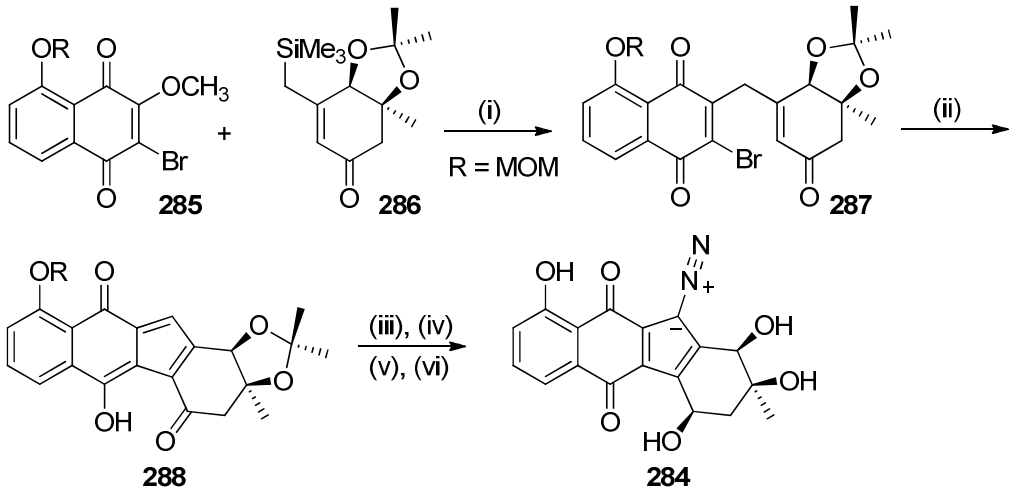
Another example in which a Friedel-Crafts cyclisation reaction was used as a key step was in the synthesis of prekinamycin **278**. In their synthesis, Kimura and co-workers performed a Suzuki cross coupling reaction between boronic acid **279** and bromide **280** to furnish biaryl **281**.[131] The aldehyde was then oxidised to the carboxylic acid **282**. The conversion to the acid chloride followed by the intramolecular Friedel-Crafts cyclisation reaction provided the tetracyclic compound **283**. Deprotection with BBr_3 followed by hydrazone formation and subsequent oxidation afforded prekinamycin **278** (**Scheme 5.8**).



Scheme 5.8: *Reagents and conditions*: (i) $Pd(PPh_3)_4$, 2M Na_2CO_3,DME, 90°C, 48 h, 97%; (ii) 15% NaOH, 30% H_2O_2, MeOH, 120°C, 1 h, 80%; (iii) $(COCl)_2$, CH_3CN, 80°C, 10 min; (iv) $AlCl_3$, CH_2Cl_2, RT, 2.5 h, 81% over two steps; (v) BBr_3, CH_2Cl_2, –40°C, 24 h; (vi) $TsNHNH_2$, 1M HCl, EtOH, 90°C, 2 h; (vii) Fetizon's reagent, Et_3N, CH_3CN, RT, 30 min, 47% over three steps.

5.4.4. Transition metal catalyzed strategies

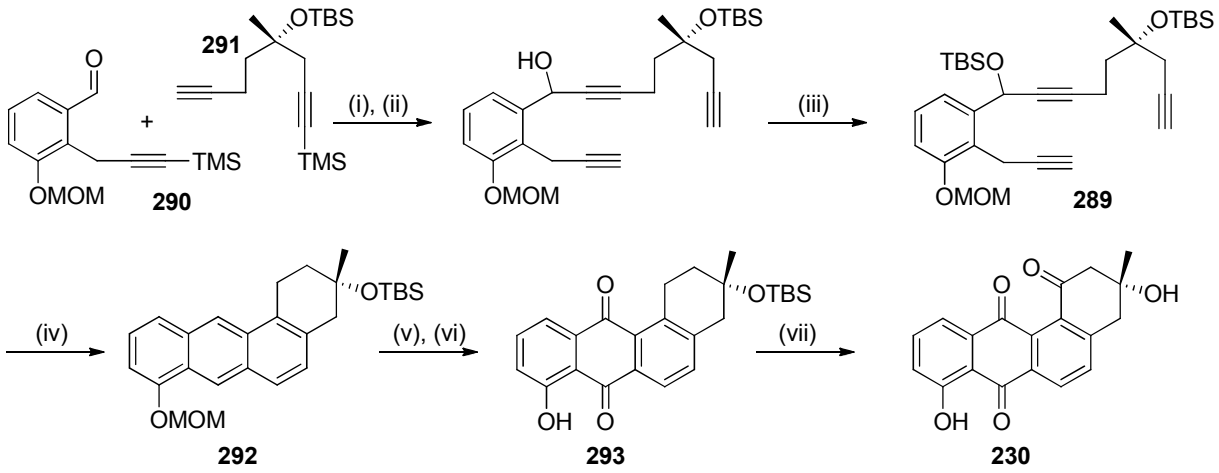
Transition metal catalysed C-C bond formation strategies have become a useful tool for organic chemists in recent years. A recent example involving a Michael addition, elimination and Heck coupling was described by Herzon and co-workers in the synthesis of kanamycin F **284**.[132] The construction of kanamycin F **284** commenced with a *tris*(diethylamino)sulfonium trimethyldifluorosilicate [TASF(Et)] mediated Michael addition reaction between quinone **285** and hexenone **286** to afford intermediate **287**. Intermediate **287** was then subjected to a Heck cross coupling reaction to afford benzofluorene **288**. A diazo functionality was introduced followed by oxidation to the quinone. Reduction of the carbonyl group followed by deprotection yielded kanamycin F **284** (**Scheme 5.9**).



Scheme 5.9: *Reagents and conditions*: (i) TASF(Et), CH_2Cl_2, –78°C, 79%; (ii) $Pd(OAc)_2$, polymer-supported PPh_3, Ag_2CO_3, toluene, 80°C, 66%; (iii) TfN_3, DIPEA, CH_3CN, 24°C, 99%; (iv) TIPSOTf, CH_2Cl_2, 0°C, DMDO, CH_2Cl_2-CH_3OH, –40°C, 76%; (v) BH_3.THF, THF, –20°C, 58%; (vi) AcCl, CH_3OH, –12° to 0°C, 65%.

5.4.5. Intramolecular cyclisation reaction strategies

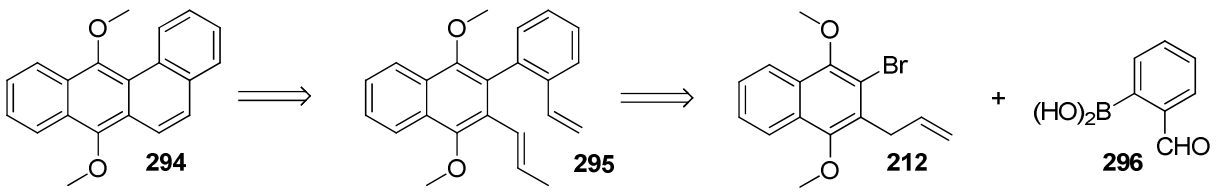
[4+2] Cycloaddition or [2+2+2] intramolecular reactions have also been used for the one-step synthesis of the angucylinone skeleton. Transition metals like cobalt or gold have generally been used to facilitate these reactions. The stereoselective synthesis of (-)-tetrangomycin **230**, shown in **Scheme 5.10**, by Groth and co-workers involved a cobalt mediated cycloaddition as the key step.[133] Chiral triyne **289** was prepared from the initial addition of lithiated octadiyne **290** to benzaldehyde **291** followed by a base mediated TMS removal and subsequent TBS protection of the newly formed secondary alcohol to afford intermediate **289**. Cyclisation of intermediate **289** affforded intermediate **292**, which was oxidised followed by MOM deprotection to furnish angucyclinone compound **293**. A TBS deprotection and regioselective photooxidation completed the synthesis of **230**.



Scheme 5.10: *Reagents and conditions*: (i) K_2CO_3, MeOH, RT, 16h, 96%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C to RT, 12h, 91%; (iii) $CpCo(C_2H_4)_2$, Et_2O, –60°C to 0°C, 4h, 93%; (iv) $Ag(py)_2MnO_4$, SiO_2, CH_2Cl_2, RT, 8h, 48%; (v) AcCl, MeOH, RT, 2h, 96%; (vi) aq. HF, CH_3CN, 50°C, 5h, 86%; (vii) air, hν, $CHCl_3$, RT, 48h, 60%.

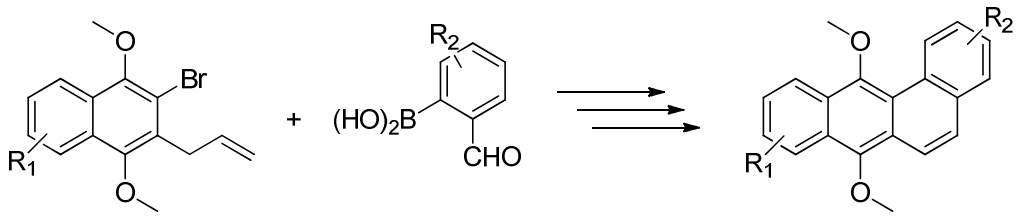
5.5. Proposed Aims of the project

Due to the biological activities and diverse structures of these landomycin antibiotics, our first aim for this section of the PhD project was the development of novel synthetic methodology for the preparation of this tetracyclic skeleton. Using a retrosynthetic approach, (**Scheme 5.11**) tetracyclic skeleton **294** can be obtained from an intramolecular cross metathesis reaction of diene **295**. We envisaged that diene **295** could be prepared using a Suzuki cross coupling reaction of an appropriately substituted boronic acid **296** and arylbromide **212**. This specific brominated naphthalene precursor was available as it had been synthesised by us in **Chapter 4**.



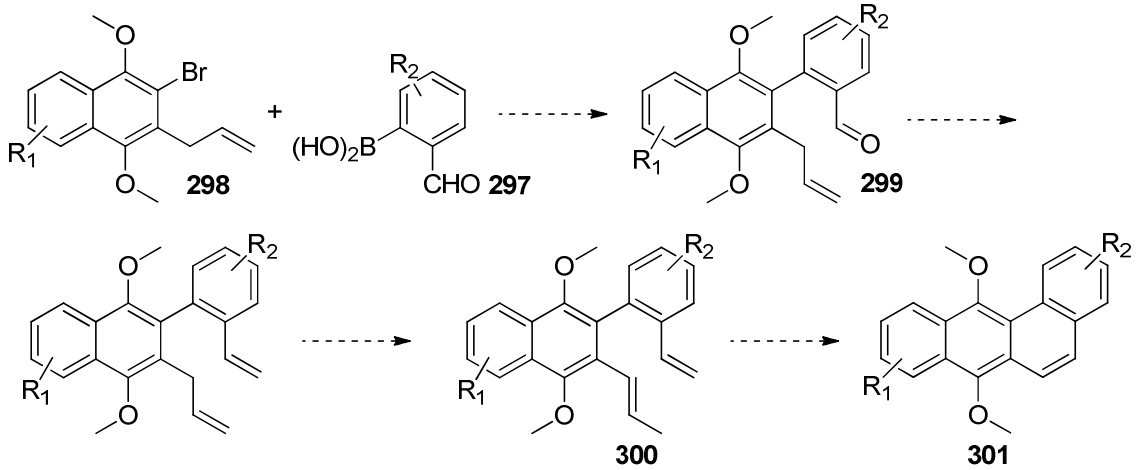
Scheme 5.12

The success of this initial synthetic route will allow us to build a mini-library of tetracyclic compounds which resemble the landomycin antibiotics. The variation in these compounds can arise from different substituents in either the aryl bromide or boronic acid. A general synthetic route is shown in **Scheme 5.12**.



Scheme 5.12

Our second aim would be to use this developed methodology to prepare the natural product, tetrangulol. We envisage that we would need to prepare an appropriate boronic acid **297** as well as the aryl bromide **298**. Once prepared, a Suzuki reaction between **297** and **298** would afford our biaryl compound **299** which would then undergo a Wittig reaction followed by an isomerisation reaction to afford a diene **300** which we can subject to a cross metathesis reaction to afford our tetracyclic tetrangulol analogue **301**, as shown in **Scheme 5.13**.



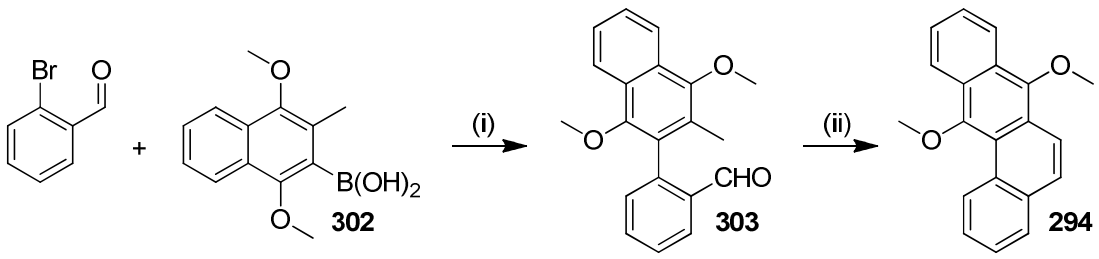
Scheme 5.13

Chapter 6: Synthetic strategies towards the angucycline antibiotics

6.1. Introduction and background

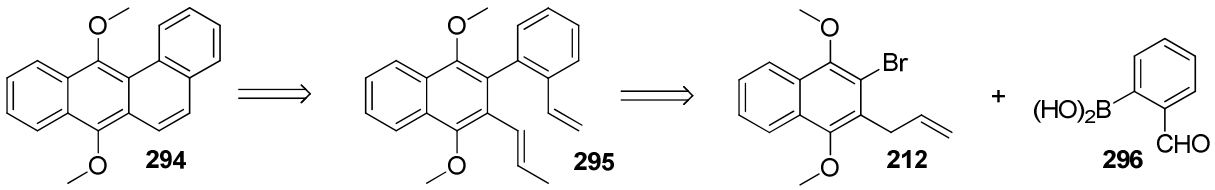
In this section, we will discuss our research conducted towards developing a synthetic strategy to access the angucycline antibiotics. This discussion will entail firstly, the development of the synthetic methodology and secondly, our attempts at synthesizing the natural product, terangulol **231**. Finally, some suggestions for future work will follow.

This project builds on previous studies conducted in our research group at Wits University.[134] The key steps in the previous study were a Suzuki cross coupling reaction followed by a ring closure reaction using potassium *tert*-butoxide in DMF at 80°C, which ultimately yielded analogues of the angucycline antibiotics. **Scheme 6.1** shows this reaction sequence where a Suzuki coupling between 2-bromobenzaldehyde and boronic acid **302** afforded the biaryl aromatic compound **303**. This biaryl aromatic compound **303** was subjected to the conditions of our novel aromatic ring closing reaction to form the final tetracyclic compound **294**.



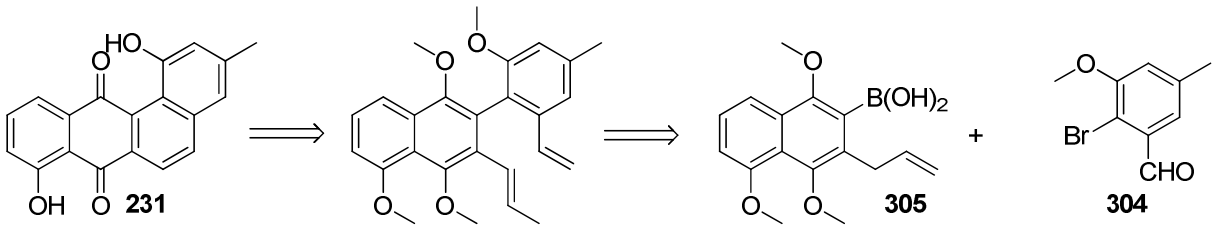
Scheme 6.1: *Reagents and conditions*: (i) $Pd(PPh_3)_4$, Na_2CO_3, DME-EtOH, 100%, $KOBu^t$, DMF, 80°C, *hv*, 87%.

We planned to synthesise the model benz[*a*]anthracene **294** again by utilising the key Suzuki coupling step already developed, but using ring closing metathesis as the final step to construct the last aromatic ring. Retrosynthetic analysis of **294**, shown in **Scheme 6.2**, led to the biaryl precursor **295**. This biaryl precursor **295** obtained via a Suzuki coupling reaction could be further disconnected to aromatic halide **212** and boronic acid **296**.



Scheme 6.2

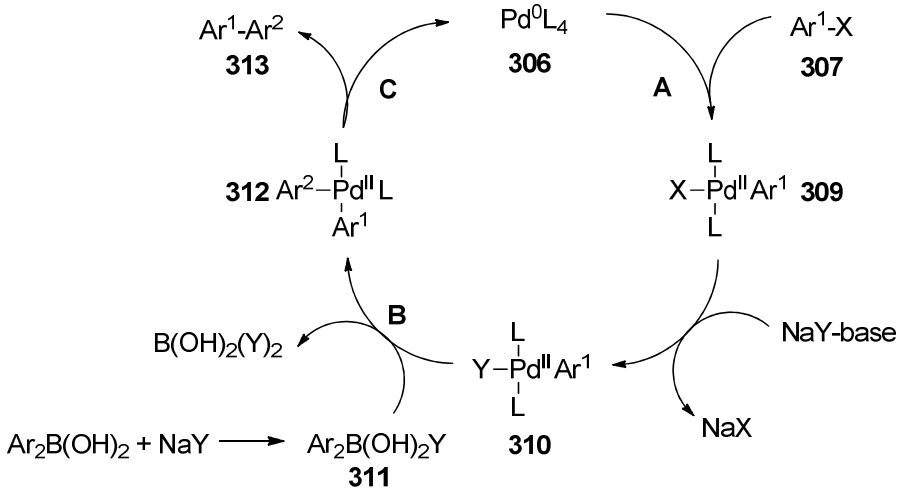
If successful, this synthetic scheme could be utilized in the preparation of the more substituted natural product tetrangulol **231**, which can be disconnected to aromatic halide **304** and the naphthalene boronic acid **305**. The proposed retrosynthesis of tetrangulol **231** is shown in **Scheme 6.3**.



Scheme 6.3

6.2. A brief look at the key steps in our synthesis: Suzuki-Miyaura reaction and RCM

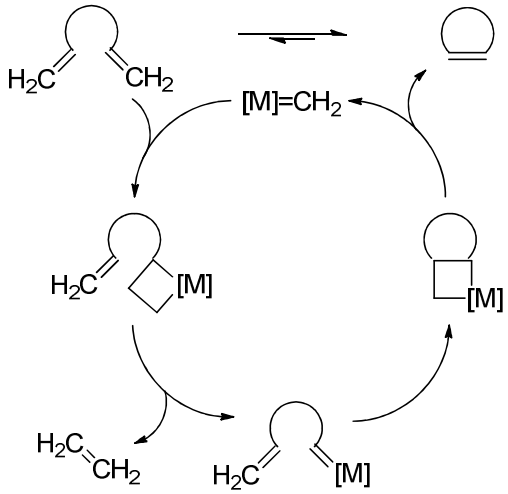
Since its publication in 1979, the Suzuki coupling reaction has been used extensively as one of the most important cross-coupling reactions in organic synthesis, which resulted in Suzuki being jointly awarded the 2010 Nobel Prize in Chemistry. The key aspect of the Suzuki reaction is the coupling of a boronic acid with an aromatic halide or triflate in the presence of a palladium catalyst. The catalytic cycle is outlined in **Scheme 6.4**. The cycle commences with the oxidative addition of Pd^0 **306** to the aryl halide **307**. This results in the formation of the *trans* σ-palladium complex **309** (**Step A**).[135] Complex **309** undergoes reaction with a base producing intermediate **310**. This is followed by transmetallation with the boron-ate complex **311** (produced from the corresponding boronic acid) resulting in intermediate **312** (**Step B**). The desired biaryl product **313** is obtained by reductive elimination of palladium regenerating the palladium (0) catalyst (**Step C**).



Scheme 6.4

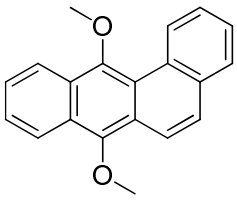
As mentioned above, the Suzuki coupling reaction is a powerful tool for carbon-carbon bond formation in organic synthesis. The inorganic by-product which is formed is non-toxic and is easily removed from the reaction mixture making the process suitable for both research laboratories and large scale industrial processes.

The second key step involves the use of RCM to facilitate the formation of the desired tetracyclic compound. The catalytic cycle of RCM was earlier discussed in **Section 2.3** and is briefly shown in **Scheme 6.5**.

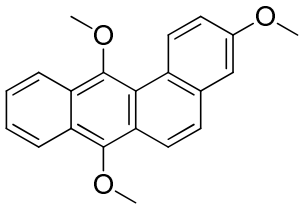


Scheme 6.5

6.3. Synthesis of angucycline analogues 7,12-dimethoxytetraphene 294 and 3,7,12-trimethoxytetraphene 314



294



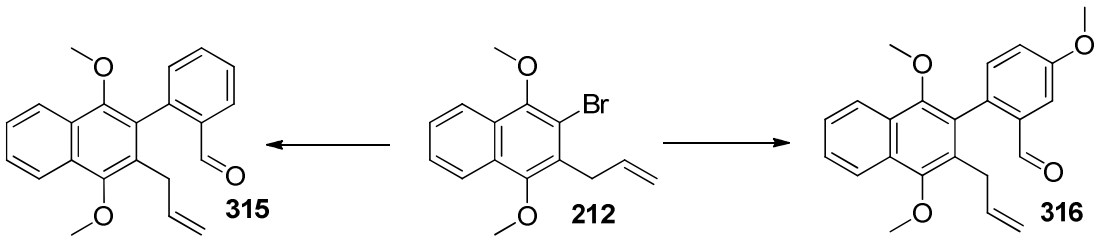
314

Figure 6.1

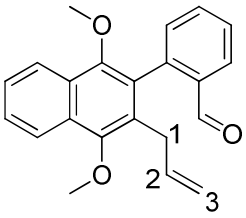
The first step in the synthesis of **294** and **314** (**Figure 6.1**) was to subject arylhalide **212**, prepared earlier in our attempted synthesis of **185**, to a Suzuki cross coupling reaction. Our first attempt at the Suzuki reaction involved conventional heating using an oil bath, palladium catalyst, tetrakis(triphenylphosphine)palladium(0) as catalyst and aqueous sodium carbonate

solution as base. However, under these reaction conditions, only starting material was recovered. By comparison, the use of microwave radiation proved successful in facilitating our Suzuki cross coupling reaction in the presence of cesium fluoride as base.

Thus, a microwave tube was charged with aromatic halide **212**, cesium fluoride, a commercially available boronic acid and tetrakis(triphenylphosphine)palladium(0). DME was then added to the reaction vessel and the mixture was subjected to microwave irradiation (150W, 150°C, 20 min). Purification of the crude reaction mixture yielded the biaryl compounds **315** and **316** as yellow oils and in mediocre yields, as shown is **Scheme 6.6**.

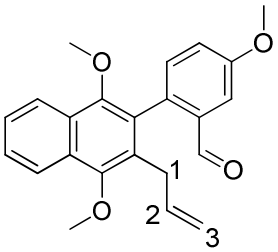


Scheme 6.6 *Reagents and conditions*: $Pd(PPh_3)_4$, BA, CsF, 150W, 150°C, 20 min, 50% (for **315**) and 43% (for **316**).



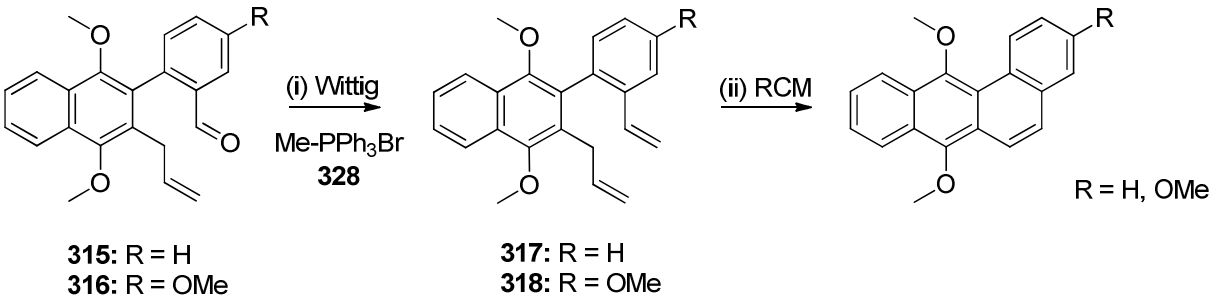
A moderate yield of 50% was obtained for **315** and attempts to improve this yield were not successful. We suspect that the steric interference provided by the allyl chain contributes to this moderate yield. However, we were pleased by the appearance of a deshielded singlet at δ 9.74 ppm in the ^{1}H NMR spectrum corresponding to the aldehyde proton, which was the initial indicator to the success of the coupling reaction. The protons corresponding to the allyl chain all showed an upfield shift. Methylene protons H_1 were now observed at δ 3.39 ppm as a doublet of triplets showing coupling to H_2 and H_3 with coupling constants of 5.8 and 1.7 Hz, respectively. We could therefore assign the signal at δ 5.68 ppm to H_2, while the signals at δ 4.56 and δ 4.81 ppm were assigned to H_3. Due to overlapping of the aromatic signals, this region of the ^{1}H NMR spectrum was not unambiguously assigned. Nonetheless, the overall integration for this region accounted for all the aromatic protons. In the ^{13}C NMR spectrum, the clear presence

of the deshielded carbonyl carbon was observed at δ 192.20 ppm. The presence of the carbonyl group was further confirmed by an absorption at 1664 cm^{-1} in the IR spectrum. Finally, the mass determination by high resolution mass spectrometry correlated well with the expected value (Found M^+ + H of 333.1496 amu, expected 333.1479).



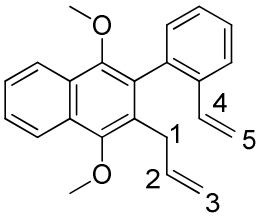
Similarly, a low yield of 43% was obtained for **316**. In the analysis of the ^{1}H NMR spectrum of this product, the deshielded aldehyde proton at δ 9.67 ppm was clearly present. This was corroborated by the analysis of the ^{13}C NMR spectrum which showed the deshielded carbonyl carbon at δ 192.08 ppm as well as by IR spectroscopy where an absorption at 1688 cm^{-1} was observed. Once again, the results of the mass spectral analysis afforded an accurate mass of 363.1588 amu, which was in good agreement with the expected mass of 363.1579 amu for $C_{23}H_{22}O_4$.

Satisfied by the success of the Suzuki cross coupling reaction, we were now able to continue with the preparation of **294**. In order to form the last aromatic ring by ring closing metathesis, we required two styrene moieties. To achieve this, we envisaged that we could perform a Wittig reaction on our newly formed biaryl aldehyde containing products **315** and **316** which would furnish the dialkene substrates on which we could perform an isomerization reaction followed a ring closing metathesis (RCM) reaction. **Scheme 6.7** illustrates the proposed route including the Witting and RCM reactions.

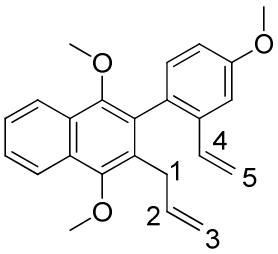


Scheme 6.7: Reagents and conditions: (i) MTPPBr, Bu^{n}Li, THF, 0°C–RT; (ii) Grubbs II, toluene, Δ.

To this end, conversion of both aldehydes **315** and **316** to alkenes **317** and **318** was achieved using traditional Wittig conditions. Methyltriphenylphosphonium bromide **319** was added to dry THF, followed by the dropwise addition of *n*-butyllithium resulting in the dissolution of **319** and the appearance of a yellow colour. After thirty minutes, the reaction was cooled to 0°C before the addition of our starting aldehydes **315** or **316**, which were dissolved in dry THF. Purification of the two crude reaction mixtures afforded alkenes **317** and **318** in excellent yields of 88 and 84%, respectively.



A positive sign that we had formed alkene **317** was the loss of the aldehyde proton previously observed at δ 9.74 ppm and the concominant appearance of new signals in the mid region of the ^{1}H NMR spectrum. The first of these new signals was observed as a doublet of doublets at δ 6.41 ppm integrating for one proton. This signal showed *cis* and *trans* coupling of 11.0 and 17.6 Hz respectively and was therefore assigned to H_4. Using a COSY spectrum we observed that H_4 coupled to two other signals, those being a multiplet at δ 5.76–5.59 ppm which integrated for two protons, and a doublet of doublets integrating for one proton at δ 5.07 ppm. The former multiplet contains two overlapping signals where one proton corresponds to H_{5a} while the other proton corresponds to H_2. The signal for the remaining proton corresponding to H_{5b} was seen at δ 5.07 ppm. The ^{13}C NMR spectrum confirmed the presence of our newly formed alkene with two signals observed at δ 135.12 and δ 114.55 ppm, corresponding to C4 and C5, respectively. The carbonyl carbon was also noticeably absent. The final piece of evidence was obtained from the IR spectrum where we no longer observed an absorption characteristic of a carbonyl group.

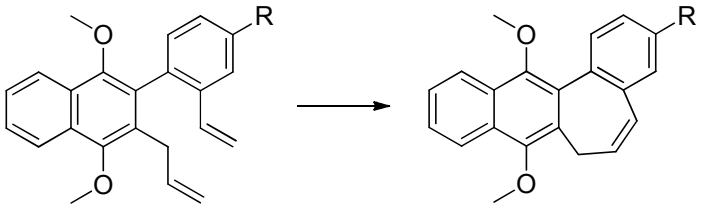


We observed similar changes in the ^{1}H and ^{13}C NMR spectra as well as the IR spectrum of **318**. In the ^{1}H NMR spectrum, the aldehyde proton was unmistakably absent. We again noticed the appearance of a new signal at δ 6.37 ppm corresponding to H_4 as well as signals at δ 5.76–5.61 ppm and δ 5.07 ppm due to H_5. The ^{13}C NMR spectrum further

confirmed this observation by the lack of a downfield deshielded carbonyl carbon signal. A molecular ion peak was observed at 361.1799 amu (100%) for **318** which correlated with the expected mass of 361.1779 amu for $C_{23}H_{22}O_2$.

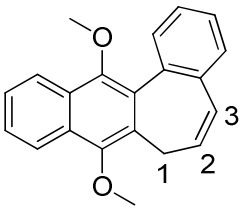
Having prepared our dienes **317** and **318**, we could now turn our attention to the formation of the final aromatic ring of the tetracyclic skeleton. In order to achieve this, we would need to isomerise the allyl chain before attempting the ring closure to allow for the formation of an aromatic six-membered ring. To this end, we subjected our dienes **317** and **318** individually to heating at 70°C in the presence of Grubb's first generation catalyst. This we hoped, would result in the isomerisation of the allyl chain in each diene as literature indicates that this was possible.[136] TLC analysis in both cases showed the formation of a new spot which we assumed was our desired product containing an isomerised double bond. After stirring for 2 hours, we added Grubbs second generation catalyst and toluene to each reaction mixture, to facilitate the ring closing metathesis reaction. These reaction mixtures were then heated under reflux for 18 hours. Purification of the reaction mixtures afforded pale yellow solids, which we expected to be our tetracyclic aromatic products.

However, during the analysis of the spectroscopic data of the isolated products, we discovered that we had formed a seven-membered ring instead of the desired six-membered ring system, as shown in **Scheme 6.8**. TLC analysis of the products showed no change to that seen when TLC analysis was conducted before the addition of Grubbs II. We therefore assumed that a tetracyclic compound containing a seven-membered ring had been formed under the Grubbs I conditions. When the reaction was repeated on diene **317** using only Grubbs I as catalyst, once again the undesired seven-membered ring containing compound **320** had been formed.

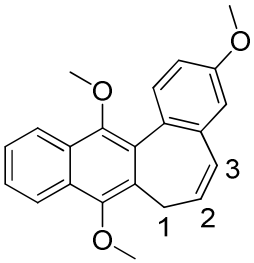


320: R= H
321: R= OMe

Scheme 6.8 *Reagents and conditions*: Grubbs I, Grubbs II, toluene, Δ, 18h, 98% (for **320**) and 87% (for **321**).

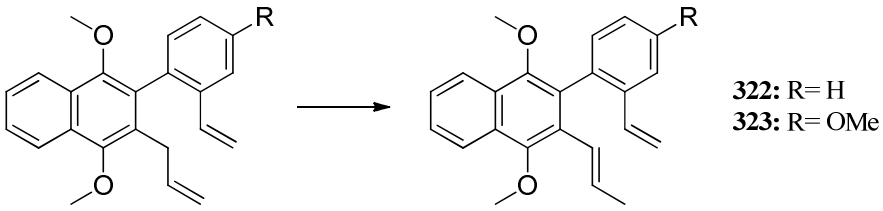


The tetracyclic compound, 8,13-dimethoxy-7*H*-benzo[3,4]cyclohepta[1,2-*b*]naphthalene **320** was isolated in 98% yield as a pale yellow solid. In the ^{1}H NMR spectrum, we noticed the presence of upfield signals at δ 3.87 and δ 2.70 ppm each integrating for one proton. Using a COSY spectrum, we observed that these signals coupled to each other as well as to two other protons. Owing to the upfield position of these signals we assigned these to H_1 where each of the protons at H_1 couple to H_2 and H_3. We could therefore assign the signals at δ 6.31 and δ 6.61 ppm to H_2 and H_3 respectively. The only remaining non-aromatic signals were two singlets each integrating for three protons at δ 3.26 and δ 3.97 ppm which corresponded to each of the methoxy groups. The signals found in the aromatic region integrated for eight protons as was expected. The ^{13}C NMR spectrum confirmed the presence of the methylene protons with a signal at δ 25.52 ppm being observed. The HRMS showed a molecular ion at 303.1387 amu which was in good agreement with the expected molecular formula, $C_{21}H_{18}O_2$ (requires 303.1379 amu).

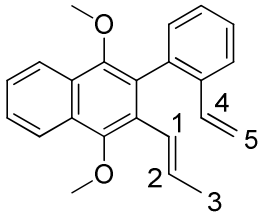


Similarly, 3,8,13-trimethoxy-7*H*-benzo[3,4]cyclohepta[1,2-*b*]naphthalene **321** was isolated as a pale yellow solid in a yield of 87%. As observed in the spectroscopic data for **320**, we observed two upfield signals integrating for one proton each and assigned these signals to the methylene protons H_1. This was corroborated by the ^{13}C NMR spectrum with the presence of an upfield signal at δ 25.57 ppm corresponding to C1.

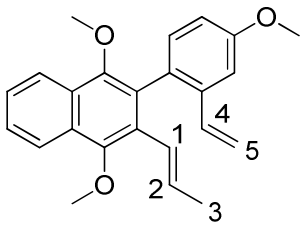
Our initial aim when attempting the ring closure was to obtain a six membered aromatic ring as this would resemble the angucycline antibiotics more closely. In order to achieve this, we needed to isomerise the allyl chains in diene **317** and **318** before attempting the ring closure. We subjected each of our dienes to potassium *tert*-butoxide in THF while stirring at ambient temperature. Upon completion of the reaction, as monitored by TLC, purification of the crude mixtures led to the isolation of the isomerised dienes **322** and **323** (Shown in **Scheme 6.9**).



Scheme 6.9 *Reagents and conditions*: KOBu^t, THF, RT, 94% (for **322**) and 84% (for **323**).



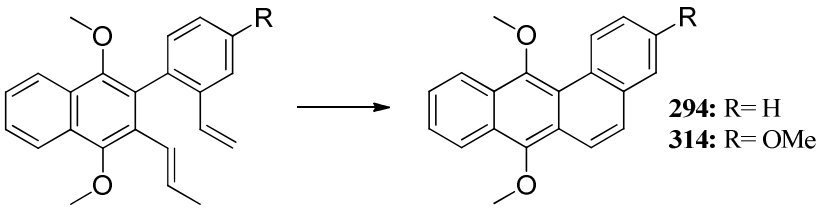
The most distinctive feature in the ^{1}H NMR spectrum of (*E*)-1,4-dimethoxy-2-(prop-1-en-1-yl)-3-(2-vinylphenyl)naphthalene **322** was the presence of a downfield signal at δ 1.65 ppm which integrated for three protons and corresponded to H_3. This signal was observed as a doublet of doublets and showed coupling of 6.2 Hz and 0.9 Hz to H_2 and H_1 respectively. We could therefore assign the multiplet at δ 6.07–5.93 ppm and doublet at δ 6.13 ppm to H_2 and H_1 respectively. A C-H correlation spectrum was used to assign all the remaining carbon signals.



As observed for **322**, in the analysis of the ^{1}H NMR spectrum of (*E*)-1,4-dimethoxy-2-(4-methoxy-2-vinylphenyl)-3-(prop-1-en-1-yl) naphthalene **323**, we observed an upfield signal at δ 1.69 ppm which integrated for three protons and which we assigned to H_3. We also observed the presence of three singlets at δ 3.47, δ 3.84 and δ 3.89 ppm each integrating for three protons, and these signals were assigned to the protons of the methoxy groups. The remaining signals were found downfield and corresponded to the

aromatic and alkene protons. Mass determination by high resolution mass spectrometry was in good agreement with the expected value (361.1804 amu, for $C_{24}H_{24}O_3$).

Having successfully prepared our isomerised dienes **322** and **323**, we were now in a position to perform the ring closing metathesis which we hoped would result in the formation of our desired six membered ring containing compound. To this end, we dissolved dienes **322** and **323** seperately in toluene under an atmosphere of argon. A catalytic amount of Grubbs second generation catalyst was added to each reaction and the reaction mixtures were stirred under reflux for 18 hours. Satisfyingly, our tetracyclic products **294** and **314** were obtained as yellow solids in 85% and 43% yield respectively, as shown in **Scheme 6.10**.



Scheme 6.10 *Reagents and conditions*: Grubbs II, toluene, Δ, 18 h, 85% (for **294**) and 43% (for **314**).

The ^{1}H NMR spectrum of 7,12-dimethoxytetraphene **294** confirmed the formation of the last aromatic six membered ring. In the ^{1}H NMR spectrum, we observed two singlets at δ 3.97 and δ 4.12 ppm each integrating for three protons. These signals were assigned to the methoxy group protons. The only other signals present in the spectrum were found downfield in the aromatic region. These signals integrated for ten protons which was expected for **294**. The ^{13}C NMR spectrum further confirmed this as we no longer observed any downfield signals besides those owing to the carbons of the methoxy groups which were found at δ 60.89 and δ 63.15 ppm. The spectroscopic data obtained compared well with that found in the literature.[134]

The formation of tetraphene **314** was similarly confirmed by both the ^{1}H and ^{13}C NMR spectra as we only observed signals in the aromatic region of both spectra, apart from the three methoxy groups. These were observed as signals at δ 3.96, δ 3.98 and δ 4.11 ppm in the ^{1}H NMR spectrum, and at δ 55.38, δ 60.72 and δ 63.18 ppm in the corresponding ^{13}C NMR spectrum.

6.4. Attempted synthesis of tetrangulol 231

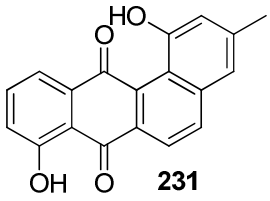
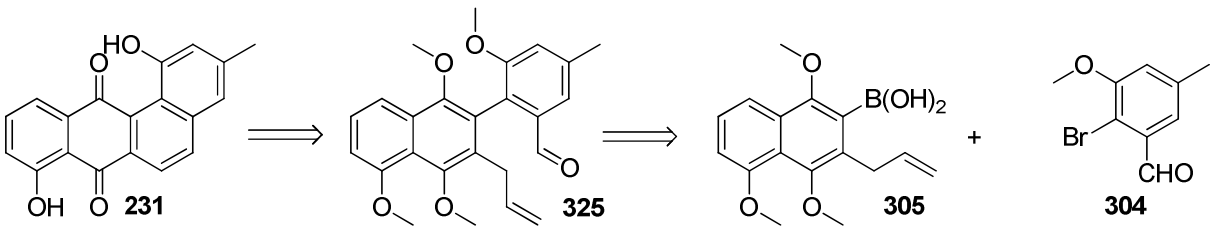


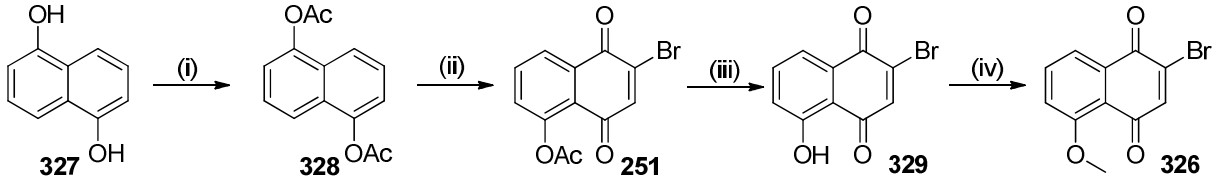
Figure 6.2

Having developed a feasible synthetic scheme that was used to prepare tetraphenes **294** and **314**, we could now turn our attention to the preparation of tetrangulol **231** (**Figure 6.2**). We envisaged that in order to utilize our developed methodology, we would require the aryl bromide **304**. This aryl halide could then be used in a Suzuki coupling reaction with an appropriate boronic acid **305** to afford our biaryl intermediate **325** which could be converted into tetrangulol **231** over several steps**. Scheme 6.11** shows the proposed retrosynthetic route resulting in two moieties **305** and **304**, which would need to be synthesised. The first precursor **305**, closely resembles **212** used in our model study but contains an extra methoxy substituent on the naphthalene nucleus.



Scheme 6.11

6.4.1. Preparation of 3-allyl-2-bromo-1,4,5-trimethoxynaphthalene 330[137]

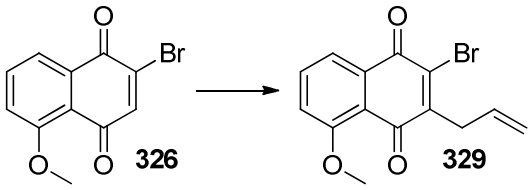


Scheme 6.12 *Reagents and conditions*: (i) pyridine, Ac_2O, RT, 18h, 81%; (ii) NBS, AcOH–H_2O, 65°C, 45 min, 95%; (iii) 3 N HCl, EtOH, Δ, 90 min, 69%; (iv) AgO, MeI, CH_2Cl_2, RT, 24 h, 43%.

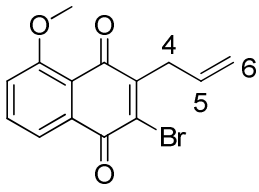
Using methodology described by Jung,[137] the preparation of 2-bromo-5-methoxy-1,4-naphthoquinone **326** was achieved over five steps from commercially available 1,5-dimethoxynaphthalene **327** (**Scheme 6.12**). The synthesis commenced with the acetylation of 1,5-dihydroxynaphthalene **327** using pyridine and acetic anhydride to afford 1,5-diacetoxynaphthalene **328** in 81% yield, which was an improvement on the yield of 44% reported in the literature. The identity of **328** was confirmed by the presence of a downfield signal at δ 169.26 ppm in the ^{13}C NMR spectrum which corresponds to the carbonyl carbon of the acetate group. Treatment of **328** with *N*-bromosuccinimide in aqueous acetic acid furnished 2-bromojuglone acetate **251** in a 95% yield. The structure of the product was confirmed by the ^{13}C NMR spectrum which showed a signal at δ 134.03 ppm owing to the carbon bonded to the bromine. This newly formed 2-bromojuglone acetate **251** was subjected to an acidic hydrolysis resulting in the formation of 2-bromojuglone **329** in a moderate yield of 69%. A downfield signal at δ 11.81 ppm in the ^{1}H NMR spectrum attested to the presence of a phenolic proton. The unprotected 2-bromojuglone **329** was then protected using methyl iodide in dichloromethane in the presence of silver oxide to afford the product, 2-bromo-5-methoxy-1,4-naphthoquinone **326**, as a yellow solid in 43% yield. In the ^{1}H NMR spectrum we clearly observed a singlet at δ 4.02 ppm which unambiguously proved the formation of the *O*-methylated product.

The next step in our synthesis involved the introduction of the allyl chain to the quinone **326**. To achieve this, we again employed a modified Hunsdiecker reaction, by reacting **326** with vinyl acetic acid and ammonium persulfate in the presence of silver nitrate in aqueous acetonitrile.

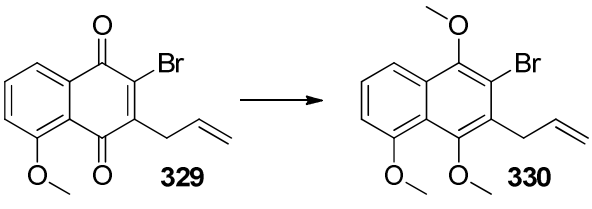
This gave the allyl containing quinone **329** as a yellow solid in a yield of 79% (shown in **Scheme 6.13**).[138]



Scheme 6.13 *Regeants and conditions*: vinyl acetic acid, ammonium persulfate, $AgNO_3$, H_2O-MeCN, 60°C, 79%.

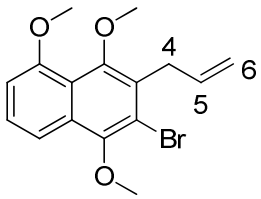


Interpretation of the ^1H NMR spectrum showed the unmistakable presence of new signals in the mid- and up-field regions of the spectrum. The most upfield signal which integrated for two protons was observed as a doublet of triplets at δ 3.60 ppm and was assigned to H_4. Using a COSY spectrum we noted that H_4 coupled to a signal integrating for one proton at δ 5.86 ppm corresponding to H_5. H_4 was also seen to couple to signals at δ 5.27 and δ 5.13 ppm which were the protons due to H_6. Each of these protons showed different coupling constants to H_5 and H_4. The ^{13}C NMR spectrum further confirmed the presence of the allyl chain with three additional signals appearing in the spectrum. The first of these signals was found at δ 35.76 ppm corresponding to C4. The two other additional signals were found at δ 118.8 and δ 134.94 ppm and corresponded to C6 and C5 respectively. All the remaining spectroscopic data compared well with literature.[138]



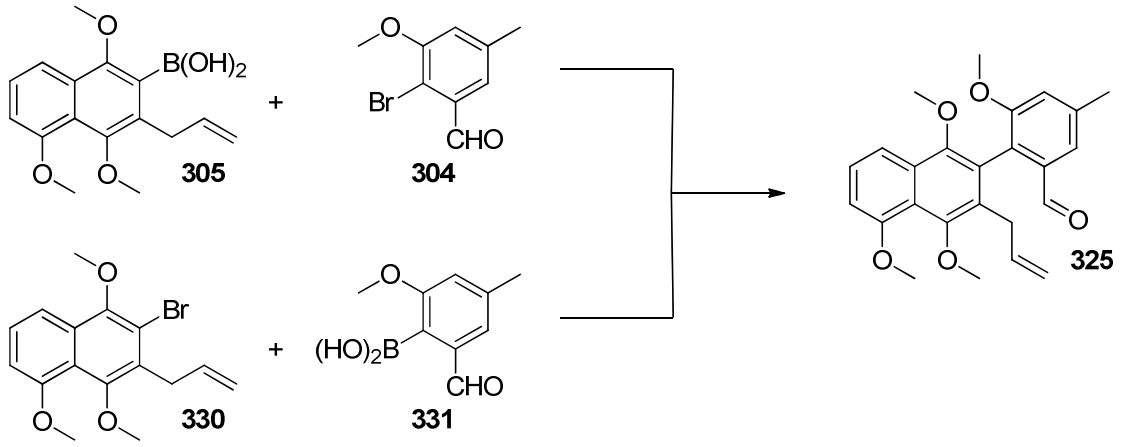
Scheme 6.14 *Reagents and conditions*: sodium dithionite, TBAI, aq. KOH, Me_2SO_4, THF, 18 h, RT, 75%.

With naphthoquinone **329** in hand, all that remained was the protection of the quinone moiety **329** using dimethyl sulfate to afford the aromatic ether **330**. To this end, shown in **Scheme 6.14**, naphthoquinone **329** was dissolved in THF and was allowed to stir under an atmosphere of argon. Sodium dithionite and *tetra*-butylammonium iodide in water were then added to the reaction flask to reduce the quinone to the hydroquinone. After one hour, aqueous potassium hydroxide solution was added to the reaction mixture to facilitate the deprotonation of the hydroquinone. After the addition of dimethyl sulfate the reaction mixture was allowed to stir at room temperature for 18 hours. Purification of the crude reaction mixture afforded naphthalene **330** in 75% yield.



The first indication of the success of the reaction was the loss of the carbonyl carbon signals in the ^{13}C NMR spectrum, and the concomitant appearance of four new signals. These newly introduced signals corresponded to the methoxy groups and appeared at δ 62.86 and δ 61.08 ppm and two signals at δ 151.19 and δ 149.69 ppm were observed for the aromatic carbons attached to the methoxy groups. The IR spectrum corroborated this observation as no stretches owing to the carbonyl groups of the quinone of the starting material were present.

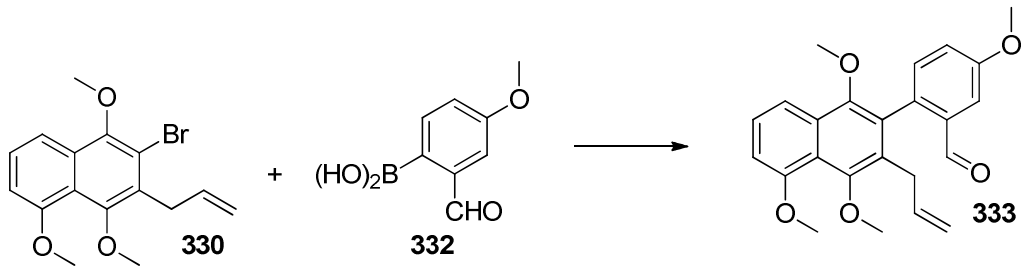
In our initial retrosynthesis we proposed that we would need to prepare naphthalene boronic acid **305** before we could perform the Suzuki coupling with the appropriately substituted aromatic bromide **304**, as shown in **Scheme 6.15**. However, aromatic bromide **330** could also be used in a Suzuki coupling reaction with boronic acid **331** to afford the desired biaryl compound **325**.



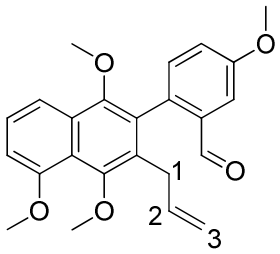
Scheme 6.15

6.4.2. Preparation of tetrangulol analogue 336.

With aromatic bromide **330** in hand, we decided to prepare an analogue of tetrangulol to test the methodology developed in the earlier sections of this chapter on a more highly oxygenated naphthalene precursor. To achieve this, we subjected aromatic bromide **330**, (preparation discussed in **Section 6.4.1**) to a Suzuki cross coupling reaction with commercially available 4-methoxy-2-formylphenyl boronic acid **332** using the conditions described in **Section 7.4.1**. The product, 2-(3-allyl-1,4,5-trimethoxynaphthalen-2-yl)-5-methoxybenzaldehyde **333**, was isolated as a yellow solid in a moderate yield of 46%, as shown in **Scheme 6.16**. However, we were pleased that the reaction was successful as the more electron-rich naphthalene precursor may have hindered the oxidative addition step.

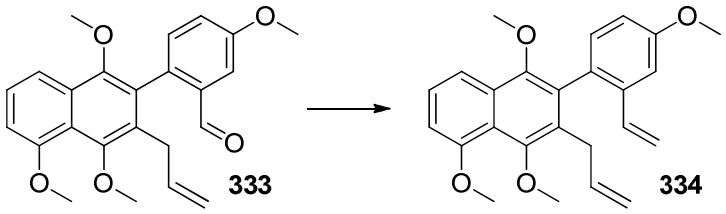


Scheme 6.16 *Reagents and conditions*: $Pd(PPh_3)_4$, 150W, 150°C, 20 min, 46%.

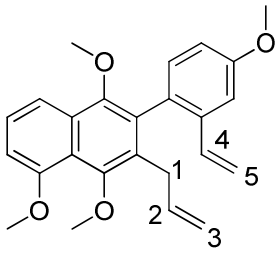


The ^{13}C NMR spectrum of the product **333** unequivocally proved that the desired coupling reaction had occurred due to the presence of both a signal at δ 192.11 ppm, which was characteristic of an aldehyde carbon, and signals from the methoxy groups and the allyl chains of the starting material. The presence of the carbonyl was further confirmed by the ^{1}H NMR spectrum which showed a deshielded singlet at δ 9.65 ppm corresponding to the aldehyde proton. Finally, the IR spectrum showed a stretch at 1686 cm^{-1} owing to the carbonyl group. An increase in the molecular mass was observed where mass spectrometry afforded an accurate mass of 393.1699 amu, which was in agreement with the expected mass of 393.1679 amu for $C_{24}H_{24}O_5$.

Pleased that our Suzuki coupling reaction had been successful, we continued with our synthesis. We subjected aldehyde **333** to a Wittig reaction using TMPPBr and *n*-BuLi which afforded the diene **334** in a 69% yield as a yellow oil (**Scheme 6.17**).



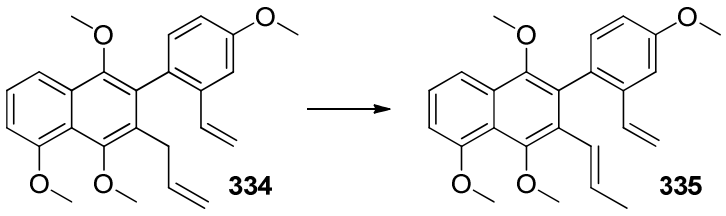
Scheme 6.17: Reagents and conditions: (i) MTPPBr, Bu^{n}Li, THF, 0°C–RT, 69%.



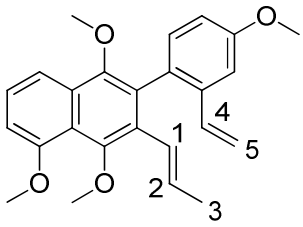
As before, in the analysis of the ^{1}H NMR spectrum of **334**, the unmistakable loss of the aldehyde proton confirmed the success of the Wittig reaction. In the ^{1}H NMR spectrum, we now observed newly formed signals in the mid-region of the spectrum. A mutiplet integrating for one proton was observed at δ 6.41–6.30 ppm which corresponded to H_4. This signal showed coupling to two other signals found at δ 5.66 ppm (which showed *trans* coupling of 17.5 Hz to H_4) and δ 5.06 (which showed *cis* coupling of 11.2 Hz to H_4). These

signals were therefore assigned to H_5. The ^{13}C NMR spectrum confirmed the loss of the aldehyde functional group with the loss of the signal previously observed at δ 192.11 ppm.

As we wanted to form the six membered ring system in the subsequent RCM reaction, we subjected our diene **334** to an isomerization reaction using potassium *tert*-butoxide in THF. TLC analysis of the reaction showed a downward shift in the R_f of the product indicating formation of the isomerized diene **335**. Purification of the reaction mixture afforded the isomerised diene **335** as a yellow oil in an excellent yield of 73%.

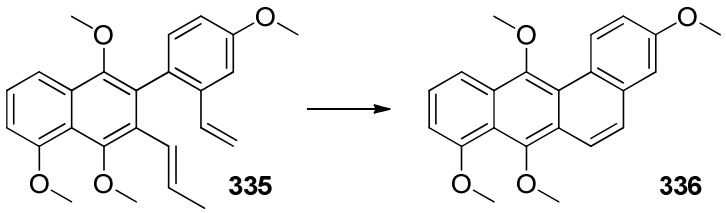


Scheme 6.18 *Reagents and conditions*: KOBu^t, THF, RT, 73%.

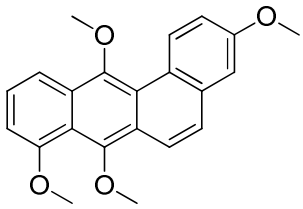


The interpretation of the ^1H NMR spectrum of the product **335** showed the disappearance of the methylene protons previously observed at δ 3.11 ppm in starting material **334** and the concomitant appearance of a multiplet at δ 1.65–1.62 integrating for three protons. This multiplet was found significantly upfield and can therefore not be due to the methoxy group protons. We could therefore assign this signal as H_3. The mid-region of the spectrum was characterised by a multiplet at δ 6.09–6.22 which was assigned to H_1 as well as doublet of quartets (dq) which was found at δ 5.84 as was assigned to H_2. The latter signal showed coupling of 15.9 Hz and 6.5 Hz to H_1 and H_3, respectively. In the aromatic region of the spectrum, we observed five different signals which collectively integrated for six protons as expected. The remaining signals which integrated for three protons each were found at δ 4.02, δ 3.89, δ 3.75 and δ 3.42 ppm and corresponded to the methoxy groups. All the carbon signals were assigned using a C-H correlation spectrum.

With the isomerised diene **335** in place, we could perform our ring closure using Grubb's II as catalyst. This catalyst was chosen owing to it being the known catalyst to facilitate RCM and moreover, we anticipated that the reaction would require harsher conditions as diene **335** was now more electron rich due to the added methoxy group on the naphthalene nucleus. To achieve the ring closure, we stirred diene **335** in the presence of Grubbs II catalyst, in toluene. The reaction was heated under reflux for 18 hours. After this time the reaction was purified using column chromatography to afford our tetraphene **336** as a yellow solid in an excellent yield of 84%.



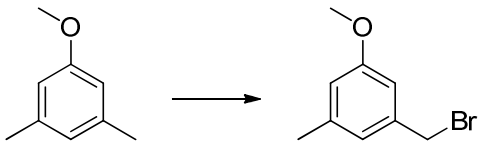
Scheme 6.19 *Reagents and conditions*: Grubbs II, toluene, Δ, 18 h, 84%.



The most distinctive aspect of the ^{1}H NMR spectrum was the presence of signals mainly in the aromatic region. In the ^{1}H NMR spectrum, four singlets were observed at δ 4.09, δ 4.00, δ 3.98 and δ 3.91 ppm. Each of these singlets integrated for three protons and were assigned as the methoxy group protons. The aromatic region contained seven signals which collectively integrated for eight protons as was expected for the product **336**. In the analysis of both the ^{1}H NMR and ^{13}C NMR spectra of the product we noticed the loss of the methyl protons previously observed at δ 1.62–1.65 ppm. Also absent were the alkene protons previously found in the mid-region of the ^{1}H NMR spectrum of the starting material. The results of the mass spectral analysis gave an accurate mass for $C_{25}H_{26}O_4$ of 391.1426 amu, which was in good agreement with the expected mass of 391.1479 amu..

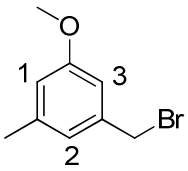
6.4.3. Attempted synthesis of 2-bromo-3-methoxy-5-methylbenzaldehyde 304

Having completed the synthesis of the tetrangulol analogue **336**, we continued with the synthesis of tetrangulol itself. The required bromide **304**, was not commercially available and therefore needed to be prepared. A study by Koyama has described the preparation of the desired bromide[139] and we therefore adopted this methodology for the formation of bromide **304**. Our synthesis commenced with the benzylic bromination of 3,5-dimethyl anisole **337** using NBS and a catalytic amount of benzoyl peroxide in refluxing carbon tetrachloride to furnish 3-bromomethyl-5-methylanisole **338** in 75% yield (**Scheme 6.20**).



337 **338**

Scheme 6.20 *Reagents and conditions:* NBS, benzoyl peroxide, CCl_4, Δ, 4 h, 75%.



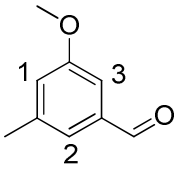
The ^{1}H NMR spectrum confirmed that the reaction was a success. The ^{1}H NMR spectrum was characterized by six singlets indicating the loss of symmetry in the molecule which was present in the starting material **337**. The most downfield signals at δ 6.78, δ 6.72 and δ 6.64 ppm each integrated for one proton and corresponded to the aromatic protons of the product. The singlet observed in the mid-region of the spectrum found at δ 4.40 ppm integrating for two protons was assigned as the benzylic protons. The remaining signals each integrating for three protons were due to the methoxy protons and the methyl protons and were found at δ 3.76 and δ 2.29 ppm respectively. The IR spectrum confirmed the addition of the bromine with the presence of an absorption at 644 cm^{-1} which is characteristic of a C–Br stretch.

Using the procedure developed by Koyama, 3-bromomethyl-5-methylanisole **338** was oxidised to 3-methoxy-5-methylbenzaldehyde using 2-nitropropane and sodium ethoxide. The product **339** was furnished as a pale yellow oil, however always in a consistently low yield of 30% (**Scheme 6.21**).



338 **339**

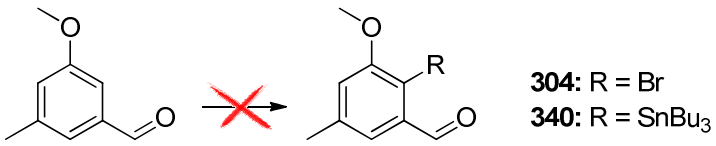
Scheme 6.21 *Reagents and conditions:* 2-Nitropropane, NaOEt, EtOH, RT, 30%.



The ^{13}C NMR spectrum unequivocally proved the formation of the aldehyde with the presence of a downfield signal at δ 192.30 ppm indicating the presence of a carbonyl group. The signal previously observed owing to the benzylic carbons was also noticeably absent, further attesting to the formation of the aldehyde. Analysis of the ^{1}H NMR and IR spectra explicitly confirmed the formation of the aldehyde with the presence of a singlet at δ 9.92 ppm in the ^{1}H NMR spectrum and an absorption at 1697 cm^{-1} in the IR spectrum.

We then attempted the bromination of 3-methoxy-5-methylbenzaldehyde **339**, employing the *ortho*-directed metallation methodolgy described by Comins,[140] but using a different source of bromine. Unfortunately, treatment of the lithium *α*-amino alkoxide, which was formed using lithium *N*,*N*,*N'*-trimethylethylene diamine, with 1,1,2,2-tetrabromoethane did not result in the formation of the expected bromide. The electrophilic source of bromine employed by Koyama was 1,2-dibromotetrafluoroethane, which is not readily available commercially in South Africa. Review of the literature[139,141] led us to believe that this bromination was indeed challenging as the best yield obtained was 69% when 1,2-dibromotetrafluoroethane was used as the electrophilic source of bromine. We attempted this reaction using various other sources of bromine, including NBS, bromine as well as 1,2-dibromotetrachloroethane, but these too met with disappointing results. At this stage, we decided to prepare the stannane **340** which would

allow us to perform a Stille coupling reaction to access the natural product tetrangulol.[141] To achieve this, we prepared the lithium α-amino alkoxide as described earlier and reacted it with tributyltin chloride. Unfortunately, purification of the reaction mixture again resulted in the isolation of our starting aldehyde **339** (**Scheme 6.22**).

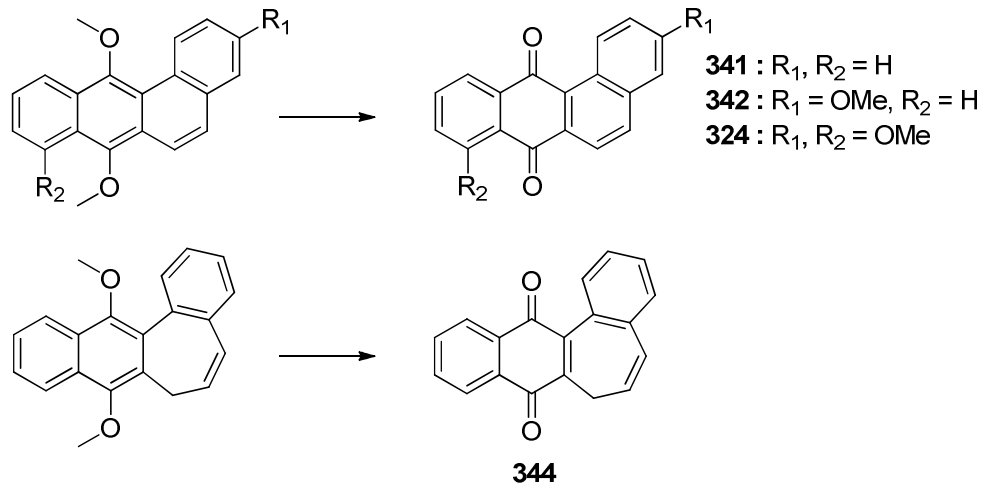


Scheme 6.22

Owing to time constraints, we were not able to prepare the required coupling partner for the synthesis of tetrangulol. This is an area for further development in our laboratories.

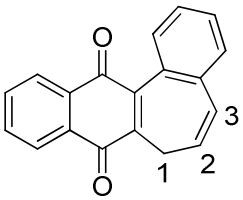
6.5. Oxidation of tetraphenes

With the tetraphenes **294**, **314** and **336** in hand, we decided to oxidise the six memebered compounds to the corresponding quinone systems as this motif is commonly found in natural products of this class. We also decided to oxidise one of the seven-membered rings to test the oxidation reaction on this class of compounds. The oxidation reactions were achieved by individually dissolving our ring closure products in acetonitrile. Ceric ammonium nitrate in water was then added to each reaction flask and the reaction mixtures were allowed to stir at room temperature for ten minutes. Work-up and purification of each reaction resulted in the formation of the oxidised products **341**, **342**, **343** and **344** in good overall yields (**Scheme 6.23**).



Scheme 6.23 *Reagents and conditions*: CAN, CH_3CN–H_2O, RT, 76% (for **341**), 87% (for **342**), 84% (for **343**), 70% (for **344**).

In the analysis of the ^{1}H NMR spectra of **341**, **342** and **343**, the loss of two signals corresponding to methoxy groups was observed for each analogue. The ^{13}C NMR spectra further confirmed that the oxidation was successful with the appearance of downfield signals in the region δ 180–185 ppm which were characteristic of carbonyl carbons. Furthermore, the IR spectra contained stretches at 1728 and 1661 cm^{-1}, 1734 and 1657 cm^{-1} and 1654 and 1618 cm^{-1} for **341**, **342** and **343** respectively, also indicating the presence of the carbonyl groups. We were therefore confident that our oxidation reactions were a success.



When we analysed the product isolated from the oxidation reaction of **344**, the NMR spectroscopic data was not as clear as we would have expected. In the analysis of **344**, the ^{1}H NMR spectrum clearly showed the loss of the methoxy protecting groups as we no longer observed singlets at δ 3.26 and δ 3.97 ppm. The spectrum also showed signals in the alkene region which indicated that our seven membered ring system was still intact, with a doublet showing *cis* coupling of 9.6 Hz visible at δ 6.74 ppm. This doublet was assigned as H_3 and coupled to H_2 which was observed as a signal at δ 6.18 ppm. Upon closer inspection of the spectrum we observed that H_2 coupled to another signal as it showed a second coupling constant of 6.9 Hz. It can be assumed that this coupling occurred with the methylene protons at H_1. However, we could not find any resolved

signals which would account for our methylene protons in the ^{1}H NMR spectrum. What we in fact observed were two broad signals at δ 4.26–3.70 and δ 2.81–1.62 ppm each integrating for one proton. We therefore assigned these two signals as H_1 as the methylene protons at H_1 would be non-equivalent in this system. In the analysis of the ^{13}C NMR spectrum we observed two clear signals at δ 184.14 and δ 183.51 ppm corresponding to the carbonyl carbons of our quinone. We also observed a signal at δ 23.70 ppm which was assigned as C1 using a DEPT135 NMR spectrum. Finally the structure of quinone **344** was unequivocally confirmed by X-ray crystallography. **Figure 6.3** clearly shows the presence of the quinone and as well as evidence that the methylene protons are indeed present.

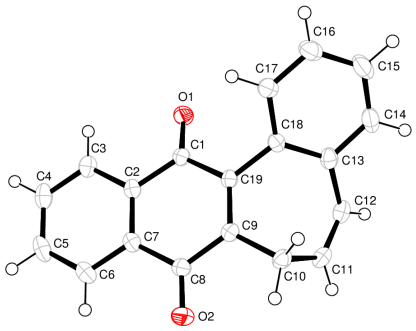
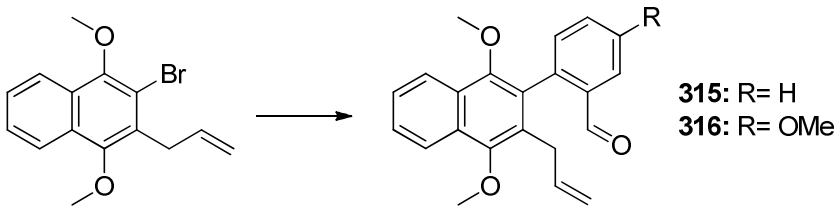


Figure 6.3

6.6. Conclusions and future work pertaining to Chapter 6

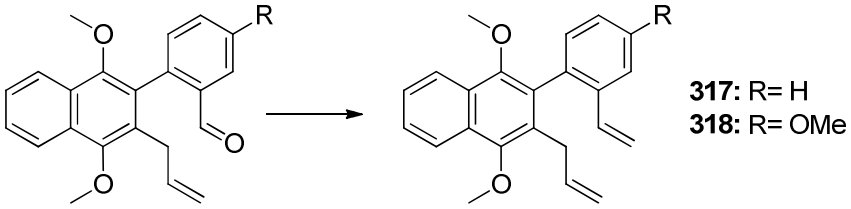
Our main aim in this section of the PhD thesis was the development of novel methodology for the preparation of angucycline antibiotics and their analogues. This synthetic route involved the use of Suzuki cross coupling chemistry to afford an aromatic compound containing a biaryl axis which allowed for a ring closure achieved using metathesis. We also attempted the preparation of a naturally occurring angucycline, tetrangulol **231**.

Our synthesis commenced with the preparation of arylbromide **212**, which we subjected to Suzuki reactions to afford aldehydes **315** and **316**, shown in **Scheme 6.24**. The yields of these reactions were mediocre which may have been as a result of steric effects provided by the allyl substituent.



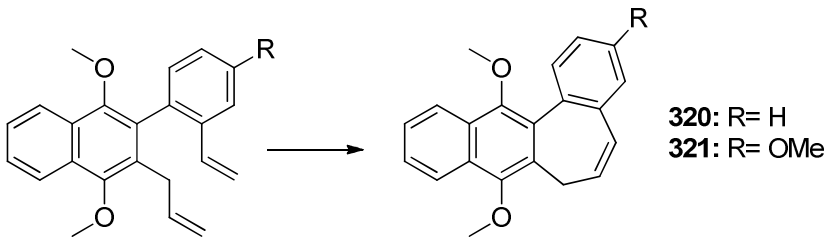
Scheme 6.24

The formation of the biaryl aldehydes was followed by a well-known Wittig reaction, which provided us with dienes **317** and **318** in excellent yields on which we could perform our ring closing metathesis reaction. (**Scheme 6.25**)



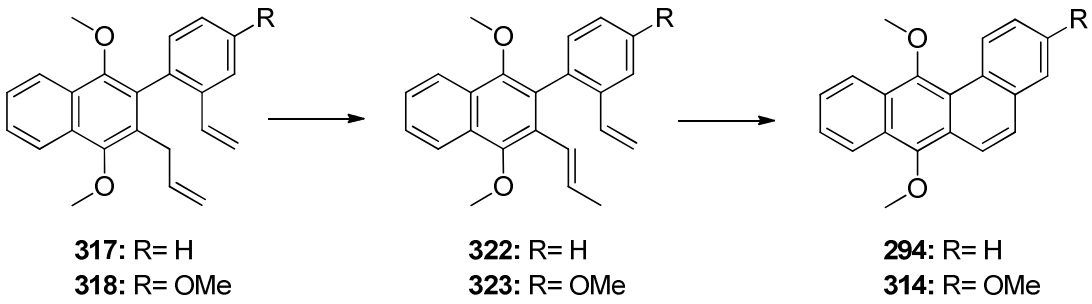
Scheme 6.25

Our final steps involved the use of ruthenium based catalysts to facilitate isomerization and RCM. Grubb's I catalyst was initially utilized to hopefully accomplish the isomerisation of the allyl double bond, and then Grubb's catalyst II we hoped would facilitate the ring closure. However, isolation of our initial ring closure products yielded compounds **320** and **321** containing seven membered rings (**Scheme 6.26**). Not unexpectedly, Grubbs I facilitated the RCM before isomerization of the allyl chain.



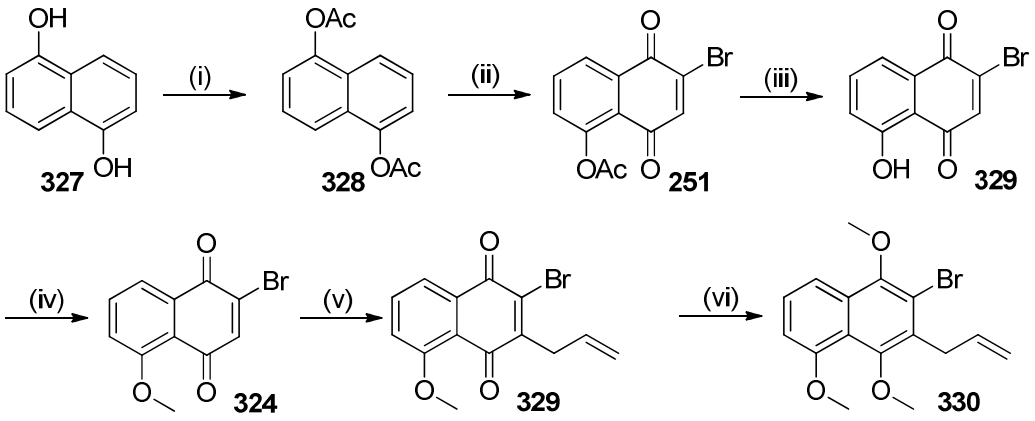
Scheme 6.26

In order to achieve the desired six membered ring containing compounds, we subjected dienes **317** and **318** to an isomerisation reaction using potassium *tert*-butoxide in THF. This resulted in the formation of dienes **322** and **323** which, when reacted with Grubbs II, formed our desired six membered ring compounds **294** and **314** (**Scheme 6.27**).



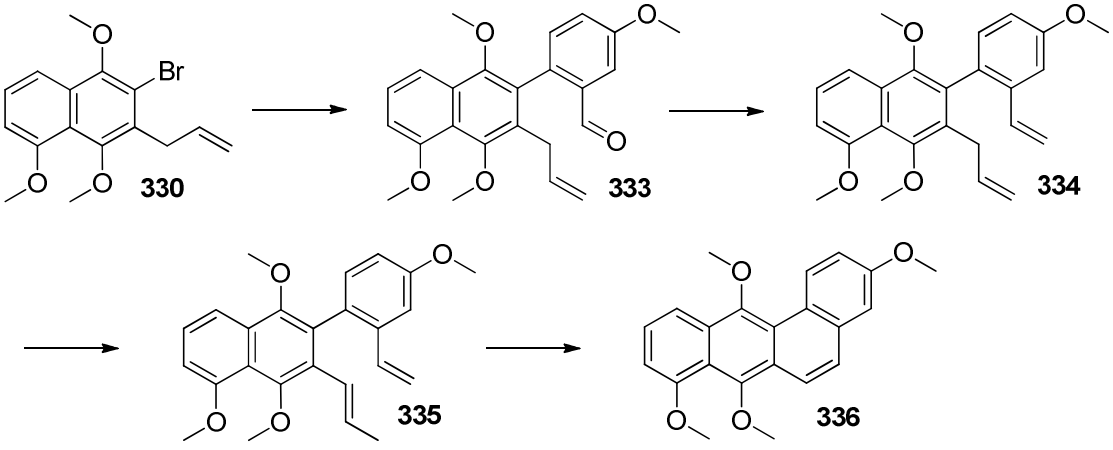
Scheme 6.27

Confident that we had developed feasible methodology for the preparation of analogues of angucycline, we turned our attention to the preparation of tetrangulol. We proposed that we would require two moieties **305** and **304** which could be coupled together using a Suzuki coupling reaction. Preparation of arylbromide **330** progressed smoothly using the methodology described by Jung and Sato (**Scheme 6.28**).[138]



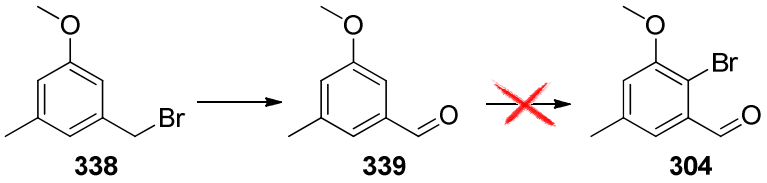
Scheme 6.28

To test the reaction methodology, the prepared arylbromide **330** was reacted with commercially available 4-methoxy-2-formylphenyl boronic acid **332** under Suzuki reaction conditions which afforded biaryl aldehyde **333**. Subjecting aldehyde **333** to a Wittig reaction yielded diene **334** which, after isomerisation with potassium *tert*-butoxide, afforded diene **335**. Our final step was the formation of the tetraphene **336** using Grubbs II to facilitate the ring closure in a yield of 84% (**Scheme 6.29**).



Scheme 6.29

The preparation of bromoaldehyde **304** proved less successful. After numerous attempts at synthesising this aldehyde we were convinced that the proposed electrophilic source of bromine used by Koyama was needed to facilitate the formation of the desired bromoaldehyde **304** (**Scheme 6.30**).



Scheme 6.30

For completeness, we oxidised our prepared tetraphenes using CAN to the corresponding quinones. Analysis of the isolated products yielded quinones **341**, **342** and **343** in excellent yields of 76%, 87% and 84% respectively (**Figure 6. 4**).

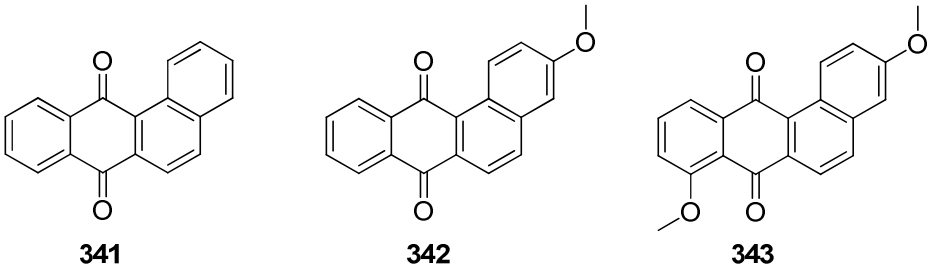
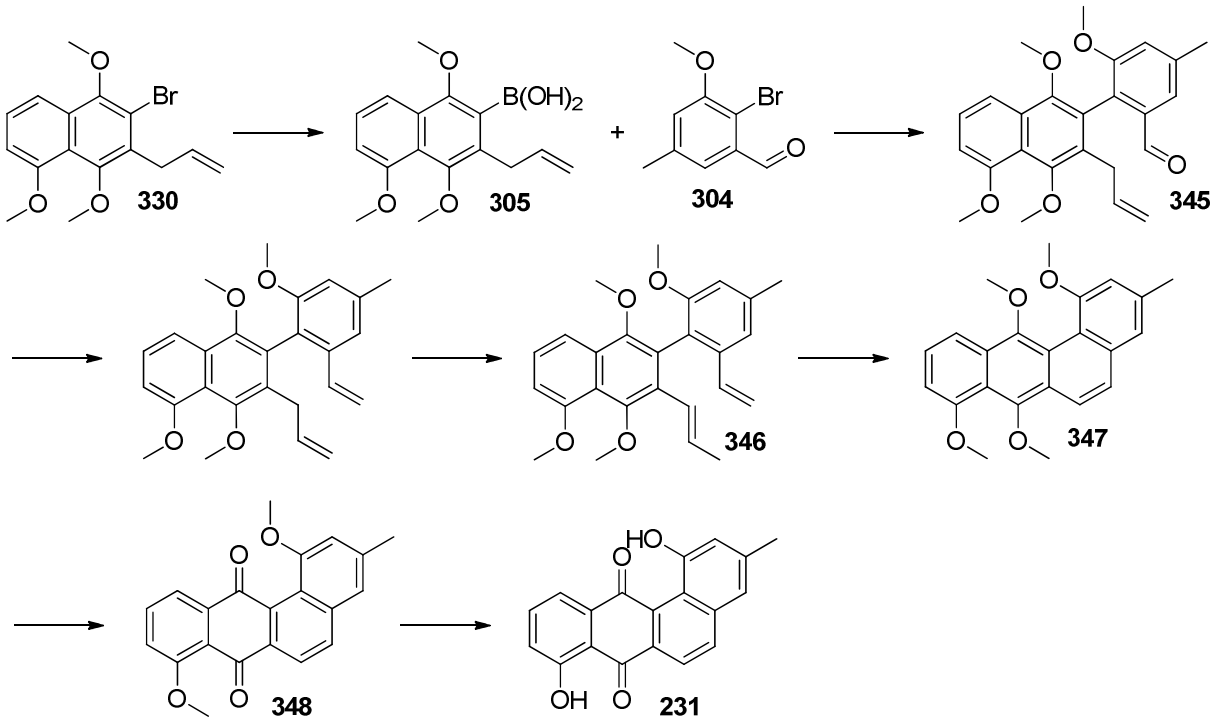


Figure 6.4

The seven membered ring systems were not as discernible using NMR spectroscopy. Hence, we obtained a crystal structure of **344** which unambiguously confirmed the oxidation of **320** to quinone **344**.

Future work for the preparation of tetrangulol **231** would involve the preparation of bromoaldehyde **304** which will provide us with the correct substitution pattern required for this natural product A review of the literature showed that we require a specific electrophilic source

of bromine, 1,2-dibromo-tetrafluroroethane, which will need to be sourced, to allow for the preparation of bromoaldehyde **304**. With bromoaldehyde **304** in hand we could continue with the synthesis of **231** by preparing the boronic acid **305** of arylbromide **330**. A Suzuki reaction of this boronic acid **305** and bromoaldehyde **304** would provide us with biaryl aldehyde **345**. A Wittig reaction followed by an isomerisation reaction would furnish diene **346**. Ring closing metathesis of diene **346** would afford tetraphene **347**. All that would remain would be the oxidation to the quinone **348** followed by the final deprotection of the phenolic groups to afford the naturally occurring tetrangulol **231** (**Scheme 6.31**).



Scheme 6.31

Chapter 7: Experimental procedures

7.1. General Procedures

7.1.1. Purification of solvents and reagents

All solvents used for chromatographic purposes were distilled prior to use by conventional distillation procedure. Solvents used for reaction purposes were dried over an appropriate drying agent and then distilled under a nitrogen atmosphere. Tetrahydofuran and diethyl ether were distilled from sodium wire using benzophenone as the indicator. Toluene was distilled from sodium metal. Acetonitrile, dichloromethane, dimethylformamide, ethanol and methanol were distilled from calcium hydride. Triethylamine was distilled from and stored over potassium hydroxide. Pyridine was distilled from potassium hydroxide. All reagents were obtained from commercial sources and used without further purification and when necessary purified by standard methods as recommended by Armarego *et al*.[142]

7.1.2. Chromatography

Macherey-Nagel Kieselgel 60, Sigma-Aldrich or Fluka silica-gel (particle size 0.063-0.200 mm) was used for standard column chromatography, while silica gel (particle size 0.035-0.070 mm) was used when performing flash column chromatography. R_f values quoted were obtained using TLC on aluminium-backed Macherey-Nagel ALUGRAM Sil G/UV_{254} plates pre-coated with 0.25 mm silica gel 60. Compounds were detected by viewing the absorbed compounds under UV light or by dipping or staining plates with various TLC staining solutions.

7.1.3. Spectroscopic and physical data

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 at 300.132 MHz for ^{1}H and 75.473 for ^{13}C or on a Bruker AVANCE III 500 at 500.13 MHz for ^{1}H and 125.75 for ^{13}C. Spectra were recorded in deuterated chloroform unless otherwise stated. The chemical shift values for all spectra obtained are reported in parts per million and referenced against the internal standard, TMS, which occurs at zero parts per million for ^{1}H NMR and relative to the central solvent signal taken as δ77.00 for ^{13}C NMR spectra. Coupling constants quoted are given in Hertz.

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

High resolution mass spectra were recorded on a Waters Synapt G2. All data was quoted in relative abundance (*m/z*).

Melting points of all solid compounds were obtained using a JM 626 meting-point apparatus with a microscope and digital thermometer, and are uncorrected.

For X-ray crystallography, intensity data were collected on a Bruker Apex II CCD area detector diffractometer with graphite monochromated Mo Kα radiation (50 kV, 30 mA) using the APEX 2 data collection software. The collection method involved ω-scans of width 0.5° and 512X512 bit data frames. Data reduction was carried out using the program *SAINT+* and face indexed absorption corrections were made using the program *XPREP*. The crystal structure was solved by direct methods using *SHELXTL*. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using *SHELXTL*, *PLATON* and *ORTEP*-3.

7.1.4. High pressure liquid chromatography

High pressure liquid chromatography (HPLC) was performed on a Dionex HPLC at a flow rate of 1.0 ml.min^{-1}. A C18 column Luna 5µ 150 x 4.6 mm was used to monitor reactions using mobile phases consisting of acetonitrile and water. A Chiralcel OJ 10µ 250 x 4.6 or Chiral column Lux 5µ Cellulose-1 250 x 4.6 mm was used to monitor reactions using mobile phases consisting of isopropyl alcohol and hexane. Detection of the eluted analytes was achieved using a TSP variable wavelength UV detector at 215 nM. All calculations were based on peak area.

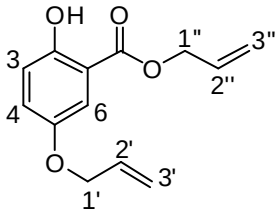
7.1.5. Additional experimental procedures and techiniques

Unless otherwise stated, all reactions were carried out under an argon atmosphere. All reaction vessels were either flame dried or dried in an oven. Microwave reactions were performed using a CEM Discovery microwave reactor (see relevant experimental sections). The term "*in vacuo*" refers to the removal of solvent by rotary evaporation followed by the removal of residual solvent using a high vacuum pump at *ca.* 1 mm Hg..

7.2. Experimental procedures pertaining to Chapter 2

7.2.1. Preparation of allyl 5-(allyloxy)-2-hydroxybenzoate 76

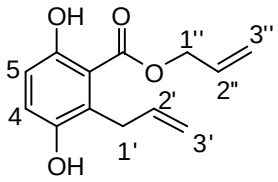
In a 1000 cm^3 (1 litre) RB flask equipped with a reflux condenser, potassium carbonate (11.95 g, 86.3 mmol, 2.2 equiv.) was added to a clear yellow solution of 2,5 dihydroxybenzoic acid **64** (6.05 g, 39.25 mmol) in dry acetone (600 cm^3). The resulting mixture was heated to 30°C while stirring under Ar(g). Allyl bromide (7.45 cm^3, 10.45 g, 86.36 mmol, 2.2 equiv.) was added to the solution using a dropping funnel. The reaction mixture was then heated at reflux overnight, during which time it became a cream paste. The reaction was then cooled, filtered through celite and the acetone removed *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc /Hexane) to yield the diallylated product **76** as white needle-like crystals (7.52 g, 82%).



R_f = 0.61 (20% EtOAc /Hexane); **mp.** 42–45°C, (lit 43.5–44.5°C)[143]; **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3567 (OH), 1672 (C=O), 1650 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.36 (1H, s, O*H*), 7.36 (1H, d, *J* = 3.1 Hz, H_6), 7.11 (1H, dd, *J* = 9.1, 3.1 Hz, H_4), 6.92 (1H, d, *J* = 9.1 Hz, H_3), 6.11–5.97 (2H, m, $H_{2'}$ and $H_{2''}$ overlapped), 5.48–5.24 (4H, m, $H_{3'}$ and $H_{3''}$ overlapped), 4.85 (1H, dt, *J* = 5.7, 1.3 Hz, $H_{1'}$), 4.50 (2H, dt, *J* = 5.3, 1.4 Hz, $H_{1''}$); **^{13}C NMR** (75 MHz): δ_C = 169.51 (C=O), 156.30 (C-2), 150.95 (C-5) , 133.19 (C-2''), 131.57 (C-2'), 124.68 (C-6), 118.51 (C-4), 117.81 (C-3''), 113.51 (C-3'), 111.92 (C-1), 69.66 (C-1''), 65.87 (C-1').

7.2.2. Preparation of allyl 2-allyl-3,6-dihydroxybenzoate 77

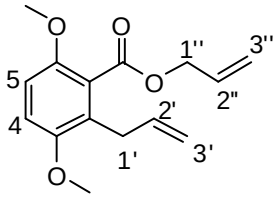
In a 100 cm^3 RB flask equipped with a reflux condenser, neat allyl 5-(allyloxy)-2-hydroxybenzoate **76** (6.85 g, 19.4 mmol) was heated at 170°C for 18 h, under an argon atmosphere. The white powder melted to first form a yellow oil and then turned to a dark orange liquid that became a black viscous oil. This was allowed to cool before purifying by silica gel column chromatography (5→10% EtOAc /Hexane) to yield 2-allyl-3,6-dihydroxybenzoate **77** as a viscous orange oil (5.53 g, 78%).



R_f = 0.28 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3412 (OH), 1662 (C=O), 1611 and 1461 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.40 (1H, s, 2-O*H*), 6.99 (1H, d, *J* = 8.9 Hz, H_5), 6.81 (1H, d, *J* = 8.9 Hz, H_4), 6.09–5.93 (2H, m, $H_{2'}$ and $H_{2''}$ overlapped), 5.47–5.28 (2H, m, $H_{3'}$), 5.12–5.00 (2H, m, $H_{3''}$), 4.86 (2H, ddd, *J* = 9.0, 5.1, 1.3 Hz, $H_{1'}$), 3.73 (2H, dt, *J* = 5.7, 1.6 Hz, $H_{1''}$); **^{13}C NMR** (75 MHz): δ_C = 170.57 (C=O), 156.21 (C-2), 147.33 (C-5), 136.29 (C-2′), 131.22 (C-2″), 126.36 (C-6), 123.52 (C-4), 119.75 (C-3), 116.63 (C-3′), 115.61 (C-3″), 112.96 (C-1), 66.54 (C-1′), 32.47 (C-1″).

7.2.3. Preparation of allyl 2-allyl-3,6-dimethoxybenzoate 78

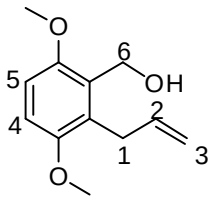
In a 250 cm^3 RB flask equipped with a reflux condenser, potassium carbonate (6.97 g, 50.0 mmol, 2.5 equiv.) was added to a clear yellow solution of allyl 2-allyl-3,6-dihydroxybenzoate **77** (4.67 g, 20.0 mmol) in acetone (100 cm^3). The solution was stirred at RT until it turned brown. Dimethyl sulfate (5 cm^3, 6.34 g, 52.6 mmol, 2.6 equiv.) was then added and the resulting mixture was refluxed for 24 h. The crude reaction mixture which was light brown in colour was filtered through celite and the solvent removed *in vacuo*. Once the residue was cooled, diethyl ether (65 cm^3) was added. The ether layer was washed with 10% aqueous ammonia solution (65 cm^3) until frothing stopped. The aqueous layer was thoroughly extracted with diethyl ether and dichloromethane. The organic extracts were combined and dried with anhydrous $MgSO_4$ before filtering through celite. The solvent was then removed *in vacuo*. The residue was purified by silica gel column chromatography (20% EtOAc /Hexane) to afford 2-allyl-3,6-dimethoxybenzoate **78** as an orange oil (4.98 g, 95%).



R_f = 0.50 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 1728 (C=O), 1638 and 1481 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.84 (1H, d, *J* = 9.0 Hz, H_5), 6.75 (1H, d, *J* = 9.0 Hz, H_4), 6.12–5.74 (2H, m, $H_{2'}$ and $H_{2''}$ overlapped), 5.45–5.35 (2H, m, $H_{3'}$), 5.27–4.90 (2H, m, $H_{3''}$), 4.81 (2H, dt, *J* = 5.8, 1.3 Hz, $H_{1'}$), 3.78 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 3.35 (2H, dt, *J* = 6.3, 1.4 Hz, $H_{1''}$); **^{13}C NMR** (75 MHz): δ_C = 167.46 (C=O), 151.63 (C-2), 150.26 (C-5), 135.91 (C-2′), 131.95 (C-2″), 127.08 (C-6), 125.11 (C-4), 118.70 (C-3), 115.35 (C-3′), 112.35 (C-3″), 109.81 (C-1), 65.87 (C-1′), 56.38 (OCH_3), 56.26 (OCH_3) 31.77 (C-1″).

7.2.4. Preparation of (2-allyl-3,6-dimethoxyphenyl)methanol 65

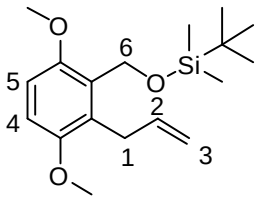
In a 500 cm^3 RB flask fitted with a reflux condenser, 2-allyl-3,6-dimethoxybenzoate **78** (5.23 g, 19.9 mmol) was dissolved in THF (250 cm^3). The solution was cooled to 0°C and lithium aluminium hydride (1.51 g, 39.8 mmol, 2 equiv.) was added slowly. The resulting suspension was heated to 40°C and stirred for 2 h. The mixture was cooled to 0°C again before a 10% aqueous hydrochloric acid solution (10%, 15cm^3) was added slowly. THF was removed *in vacuo* before the remaining aqueous layer was extracted with diethyl ether (4 × 30 cm^3) and dichloromethane (3 × 30 cm^3). The organic extracts were combined and dried with anhydrous $MgSO_4$ before filtering through celite. The solvent was then removed *in vacuo*. The residue was purified by silica gel column chromatography (20% EtOAc /Hexane) to afford (2-allyl-3,6-dimethoxyphenyl) methanol **65** as a light yellow oil (3.17 g, 77%).



R_f = 0.21 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3424 (OH), 1638 and 1478 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.82 (1H, d, *J* = 8.9 Hz, H_5), 6.77 (1H, d, *J* = 8.9 Hz, H_4), 6.04–6.91 (1H, ddt, *J* = 17.0, 10.2, 5.8 Hz, $H_{2'}$) , 5.00–4.88 (2H, m, $H_{3'}$), 4.71 (2H, s, Ar-C*H*$_2$-O-), 3.85 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 3.54 (2H, m, H1′), 2.36 (1H, s, O*H*); **^{13}C NMR** (75 MHz): δ_C = 152.33 (C-6), 151.79 (C-3), 137.41 (C-2′) , 128.82 (C-1), 128.26 (C-2), 114.74 (C-3′), 110.66 (C-4), 108.78 (C-5), 57.45 (OCH_3), 56.27 (OCH_3), 55.81 (Ar-CH_2-O-), 29.91 (C-1′).

7.2.5. Preparation of (2-allyl-3,6-dimethoxybenzyloxy)(*tert*-butyl)dimethylsilane 79

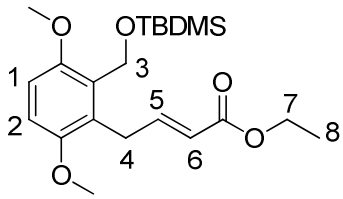
In a 250 cm^3 RB flask fitted with a reflux condenser, (2-allyl-3,6-dimethoxyphenyl)methanol **65** (1.97 g, 9.52 mmol) and TBDMSCl (1,7363 g, 11.52 mmol, 1.2 equiv.) were dissolved in THF (100 cm^3). Sodium hydride (60% in oil, 1.14 g, 28.5 mmol, ca. 3.0 equiv.) was added and the solution was refluxed for 24 h under an argon atmosphere, while stirring. The reaction was worked up by adding distilled water (20 cm^3) and then extracting the material with ethyl acetate (4 × 20 cm^3). The organic extracts were combined and dried with anhydrous $MgSO_4$ before filtering through celite and the solvent removed *in vacuo*. The residue was purified by silica gel column chromatography by using hexane as the initial eluent to remove the sodium hydride oil from the column and then 20% EtOAc /Hexane to afford (2-allyl-3,6-dimethoxybenzyloxy)(*tert*-butyl)dimethylsilane **79** as a light yellow oil (2.71 g, 90%).



R_f = 0.72 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 1638 (C=C), 834 (Si-C); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.81 (1H, d, *J* = 8.9 Hz, H_5), 6.74 (1H, d, *J* = 8.9 Hz, H_4), 6.01 (1H, ddt, *J* = 16.6, 10.7, 6.0 Hz, H_2), 4.99–4.97 (1H, m, H_3), 4.94 (1H, dq, *J* = 8.9, 1.7 Hz, H_3), 4.77 (2H, s, H_6), 3.80 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.59 (2H, dt, *J* = 5.9, 1.6 Hz, H_1), 0.93 (9H, s, $C(CH_3)_3$), 0.10 (4H, s, $Si(CH_3)_2$); **^{13}C NMR** (75 MHz): δ_C = 152.0 (ArCO), 151.9 (ArCO), 137.3 (C-2) , 129.9 (ArC), 128.8 (ArC), 114.3 (C-3), 110.8 (C-4), 109.4 (C-5), 56.2 (OCH_3), 56.1 (OCH_3), 30.9 (C-1), 25.9 ($C(CH_3)_3$), 18.5 ($C(CH_3)_3$), -5.3 ($Si(CH_3)_2$); **HRMS** (ESI+): Found M^+ + Na 345.1866, $C_{18}H_{30}O_3Si$ (M^+ + Na) requires 345.1864, m/z 345.1866 (M^+ + Na, 17%).

7.2.6. Preparation of (*E*)-ethyl 4-(2-((*tert*-butyldimethylsilyloxy) methyl)-3,6-dimethoxyphenyl)but-2-enoate 94

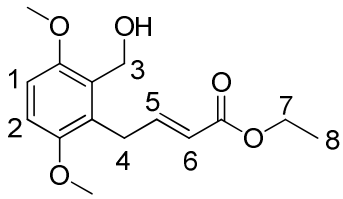
A 100cm^3 RB flask fitted with a reflux condenser was set under an argon atmosphere. Neat (2-allyl-3,6-dimethoxybenzyloxy)(*tert*-butyl)dimethylsilane **79** (1.71 g, 5.32 mmol) and ethyl acrylate (1.5 cm^3, 1.38 g, 13.78 mmol, 2.6 equiv.) was dissolved in dry toluene (50 cm^3) with stirring. Second generation Grubbs catalyst (67.8 mg, 7.99 × 10^{-5} mol, 5 mol%) was then added to the flask and the solution was heated at 90°C and left at this temperature for 18 h. The crude product was dried onto silica while removing the solvent *in vacuo*. The material was purified by silica gel column chromatography (10% EtOAc /Hexane) to afford (*E*)-ethyl 4-(2-((*tert*-butyldimethylsilyloxy)methyl)-3,6-dimethoxyphenyl)but-2-enoate **94** as a clear oil (1.63 g, 78%).



R$_f$ = 0.31 (10% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 1716 (C=O), 1602 (C=C), 1243 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.13 (1H, dt, *J* = 15.6, 6.1 Hz, H_5), 6.80 (1H, d, *J* = 9.0 Hz, H_1), 6.75 (1H, d, *J* = 9.0 Hz, H_2), 5.68 (1H, dt, *J* = 15.6, 1.6 Hz, H_6), 4.74 (2H, s, H_3), 4.15 (2H, q, *J* = 7.1 Hz, H_7), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.71 (2H, dd, *J* = 6.1, 1.7 Hz, H_4), 1.26 (3H, t, *J* = 7.1 Hz, H_8), 0.90 (9H, s, C(CH_3)$_3$), 0.07 (6H, s, Si(CH_3)$_2$) ; **^{13}C NMR** (75MHz): δ_C = 166.9(C=O), 151.9 (Ar*C*O), 151.7 (Ar*C*O), 148.0 (C-5), 133.6 (Ar*C*), 128.9 (Ar*C*), 121.1 (C-6), 110.5 (Ar*C*H), 109.9 (Ar*C*H), 61.3 (C-7), 56.2 (OCH_3), 56.1 (OCH_3), 55.9 (Ar*C*H_2OSi), 29.0 (C-4), 26.0 (C(*C*H_3)$_3$), 18.4 (*C*(CH$_3$)$_3$), 14.2 (C-8), -5.3 (Si(*C*H_3)$_2$); **HRMS** (ESI+): Found M$^+$ – ^{t}Bu 338.1490, $C_{17}H_{26}O_5Si$ (M$^+$ – ^{t}Bu) requires 338.4744, *m/z* 338.1490 (M$^+$ – ^{t}Bu, 25%).

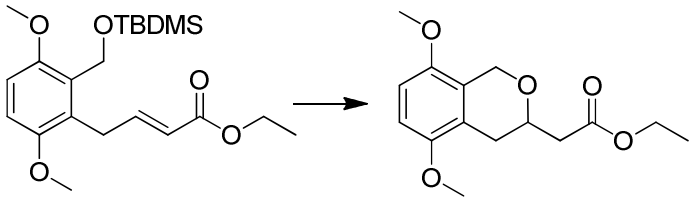
7.2.7. Preparation of (*E*)-methyl 4-(2-(hydroxymethyl)-3,6-dimethoxyphenyl)but-2-enoate 66

In a 100cm^3 RB flask fitted with a reflux condenser was set under an argon atmosphere. Neat (2-allyl-3,6-dimethoxyphenyl)methanol **65** (1.03 g, 4.97 mmol) and ethyl acrylate (1.50 cm^3, 1.34 g, 13.38 mmol, 2.7 equiv.) was dissolved in dry CH_2Cl_2 (30 cm^3) with stirring. Second generation Grubbs catalyst (211.1 mg, 2.49 × 10^{-4} mol, 5 mol%) was then added to the flask and the solution was heated at reflux and left at this temperature for 4 h. The crude product was dried onto silica while removing the solvent *in vacuo*. The material was purified by silica gel column chromatography (5% EtOAc /Hexane) to afford (*E*)-methyl 4-(2-(hydroxymethyl)-3,6-dimethoxyphenyl)but-2-enoate **66** (1.19 g, 86%).

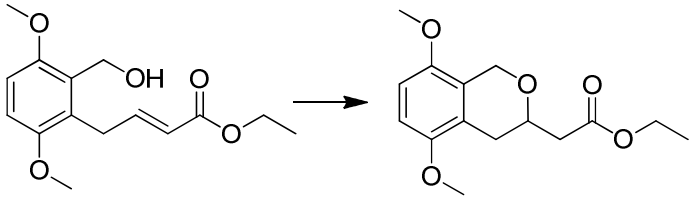


R_f = 0.52 (50% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3428 (OH), 1714 (C=O), 1599 and 1468 (C=C); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.10 (1H, dt, *J* = 15.6, 5.9 Hz, H_5), 6.81 (1H, d, *J* = 9.0 Hz, H_1), 6.77 (1H, d, *J* = 9.1 Hz, H_2), 5.63 (1H, dt, *J* = 15.6, 1.7 Hz, H_6), 4.66 (2H, s, H_3), 4.14 (2H, q, *J* = 7.1 Hz, H_7), 3.84 (3H, s, O*CH*$_3$), 3.78 (1H, s, O*CH*$_3$), 3.68 (2H, dd, *J* = 5.9, 1.8 Hz, H_4), 2.26 (1H, s, O*H*), 1.26 (3H, t, *J* = 7.1 Hz, H_8); **^{13}C NMR** (75MHz) δ_C = 171.2 (C=O), 152.2 (ArCO), 151.7 (ArCO), 147.4 (C-5), 128.8 (ArC), 126.2 (ArC), 121.4 (C-6), 110.5 (ArCH), 109.3 (ArCH), 61.3 (C-7), 57.4 (C-3), 56.1 (OCH_3), 56.0 (OCH_3), 28.6 (C-4), 14.2 (C-8); **HRMS** (ESI+): Found M$^+$ + Na 303.1198, $C_{15}H_{20}O_5$ (M$^+$ + Na) requires 303.1211, *m/z* 303.1198 (M$^+$ + Na, 60%) 263.1279 (55).

7.2.8. Preparation of ethyl 2-(5,8-dimethoxyisochroman-3-yl)acetate 67

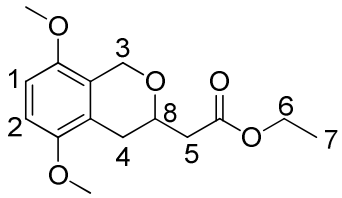


(*E*)-ethyl 4-(2-((*tert*-butyldimethylsilyloxy)methyl)-3,6-dimethoxyphenyl)but-2-enoate **94** (1.17 g, 2.96 mmol) was dissolved in dry THF (100 cm^3) containing acetic acid (0.20 cm^3, 3.49 mmol, 1.2 equiv.) in a dry two neck round bottom flask under argon. The reaction mixture was cooled to 0°C and TBAF solution (0.5 M in THF, 30 cm^3, 15.0 mmol, 5 equiv.) was added to the reaction mixture in one portion. The reaction mixture was allowed to warm up to room temperature and was stirred for 18 hours under argon. The reaction mixture was then extracted into EtOAc (4 × 50 cm^3). The organic layers were then combined, dried with anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The crude material was purified by flash silica gel column chromatography (10% EtOAc/Hexane) to yield the product **67** as a clear oil (0.73 g, 88%).



In a 50 cm^3 RB flask, the (*E*)-methyl 4-(2-(hydroxymethyl)-3,6-dimethoxyphenyl)but-2-enoate **66** (2.40 g, 8.56 mmol) was dissolved in dry THF (50 cm^3). The reaction mixture was cooled to 0°C and sodium hydride (60% in oil, 0.70 g, 17.5 mmol, 2.0 equiv.) was slowly added to the reaction mixture. The reaction mixture was allowed to stir for 30 minutes at room temperature under argon. The reaction mixture was then quenched with H_2O and diluted with EtOAc. The organic material was then extracted into EtOAc (4 × 50 cm^3) before being washed with brine (20 cm^3). The organic extracts were combined, dried with anhydrous $MgSO_4$, filtered through

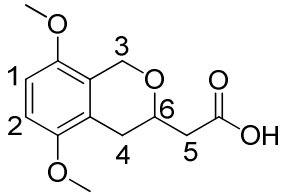
celite and the solvent removed *in vacuo*. The crude material was purified by flash silica gel column chromatography (10% EtOAc/Hexane) to yield the product **67** as a clear oil (2.06 mg, 86%).



R_f = 0.17 (10% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2940 (C-H), 1734 (C=O), 1607 and 1435 (C=C), 1254 and 1121 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.65 (1H, d, *J* = 9.0 Hz, H_1), 6.61 (1H, d, *J* = 9.0 Hz, H_2), 4.91 (1H, d, *J* = 15.9 Hz, H_{3a}), 4.62 (1H, d, *J* = 16.0 Hz, H_{3b}), 4.19 (1H, dq, *J* = 7.1, 2.0 Hz, H_6), 4.11–3.99 (1H, m H_8), 3.77 (1H, s, OCH_3), 3.75 (1H, s, OCH_3), 2.83 (1H, dd, *J* = 16.9, 1.8 Hz,, H_{4a}), 2.71 (1H, dd, *J* = 15.5, 7.8 Hz, H_{5a}), 2.60 (1H, dd, *J* = 15.5, 5.2 Hz, H_{5b}), 2.44 (1H, dd, *J* = 16.9, 10.9 Hz, H_{4b}), 1.28 (3H, t, *J* = 7.2 Hz, H_7); **^{13}C NMR** (75 MHz): δ_C = 171.1 (C=O), 150.9 (ArCO), 149.4 (ArCO) , 124.4 (ArC), 123.1 (ArC), 107.5 (ArCH), 107.0 (ArCH), 70.7 (C-8), 64.7 (C-3), 60.5 (C-6), 56.5 (OCH_3), 55.4 (OCH_3), 41.1 (C-5), 28.2 (C-4), 14.2 (C-7); **HRMS** (ESI+): Found M^+ + H 281.1381, $C_{15}H_{20}O_5$ (M^+ + H) requires 281.13904, m/z 281.1381 (M^+ + H, 100%) 279.1220 (25), 235.0958 (22).

7.2.9. Preparation of 2-(5,8-dimethoxyisochroman-3-yl)acetic acid 71

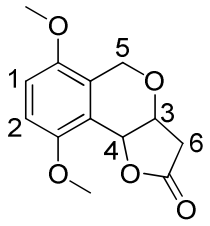
In a 25 cm^3 RB flask, the acetate **67** (1.03 g, 3.68 mmol) was dissolved in dry methanol (5 cm^3) and to this was added potassium hydroxide (1.51 g, 26.9 mmol, 7.2 equiv.). The reaction mixture was stirred for 3 hours at room temperature under an argon atmosphere. Upon completion the reaction mixture was quenched with H_2O and diluted with EtOAc. The aqueous layer was washed with EtOAc (2 × 20 cm^3) to remove any unreacted starting material. The aqueous phase was acidified to pH 2 using 6N HCl which resulted in a white precipitate. The organic material was extracted into EtOAc (4 × 50 cm^3) and the organic extracts combined and dried with anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo* to afford the acid **71** as a white powder (0.88 mg, 95%).



R_f = 0.46 (50% EtOAc /Hexane); **mp.** 155–157°C; **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3015 (OH), 1694 (C=O), 1488 (C=C), 1326 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 11.00 (1H, s, O*H*), 6.67 (1H, d, *J* = 8.9 Hz, H_1), 6.63 (1H, d, *J* = 8.9 Hz, H_2), 4.96 (1H, d, *J* = 15.9 Hz, H_{3a}), 4.65 (1H, d, *J* = 15.9 Hz, H_{3b}), 4.05 (1H, ddt, *J* = 7.8, 5.1, 3.3 Hz, H_6), 3.78 (1H, s, OCH_3), 3.76 (1H, s, OCH_3), 2.86 (1H, dd, *J* = 16.9, 1.9 Hz, H_{4a}), 2.77 (2H, dd, *J* = 15.2, 7.0 Hz, H_{5a}), 2.70 (2H, dd, *J* = 15.2, 4.6 Hz, H_{5b}), 2.48 (2H, dd, *J* = 16.9, 10.9, H_{4b}); **^{13}C NMR** (75 MHz): δ_C = 176.2 (C=O), 150.9 (Ar*C*O), 149.4 (Ar*C*O) , 124.4 (Ar*C*), 122.8 (Ar*C*), 107.7 (Ar*C*H), 107.2 (Ar*C*H), 70.5 (C-6), 64.7 (C-3), 56.6 (OCH_3), 55.5 (OCH_3), 40.8 (C-5), 28.2 (C-4); **HRMS** (ESI+): Found M^+ + H 253.1087, $C_{13}H_{16}O_5$ (M^+ + H) requires 253.1077, *m/z* 253.1087 (M^+ + H, 40%) 236.1021 (15).

7.2.10. Preparation of 6,9-dimethoxy-3,3a,5,9b-tetrahydro-2*H*-furo[3,2*c*]isochromen-2-one 72

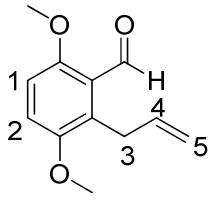
In a 50 cm^3 RB flask, the 2-(5,8-dimethoxyisochroman-3-yl)acetic acid **71** (0.20 g, 0.80 mmol) and KBr (0.11 g, 0.88 mmol, 1.1 equiv.) were suspended in dry CH_2Cl_2 (8 cm^3), to this was added p-anisiodine diacetate (0.34 g, 0.96 mmol, 1.2 equiv.) and the resulting reaction mixture was allowed to stir at room temperature for 18 hours. Sat. aq. $NaHCO_3$ (5 cm^3) was then added to the reaction mixture and stirred for an additional 5 minutes. The organic layer was then separated and washed sequentially with sat. aq. $NaHCO_3$ (5 cm^3) and dilute aq. sodium thiosulfate (5 cm^3). The organic extracts were combined and dried with anhydrous $MgSO_4$ before being filtered through celite and the solvent removed *in vacuo*. The crude material was purified by flash silica gel column chromatography (10% EtOAc/Hexane) to yield the product **72** as a white solid (58.5 mg, 29%).



R_f = 0.31 (50% EtOAc /Hexane); **mp.** 173–175°C (lit 162–165°C)[42]; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 1767 (C=O), 1605 and 1489 (C=C), 1326 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.84 (1H, d, *J* = 8.9 Hz, H_1), 6.77 (1H, d, *J* = 9.0 Hz, H_2), 5.33 (1H, d, *J* = 2.4 Hz, H_4), 4.98 (1H, d, *J* = 16.1 Hz, H_{5a}), 4.47 (1H, d, *J* = 16.1 Hz, H_{5b}), 4.34 (1H, dd, *J* = 4.7, 2.8 Hz, H_3), 3.84 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.91 (1H, dd, *J* = 17.5, 4.9 Hz, H_{6a}), 2.71 (1H, d, *J* = 17.5 Hz, H_{6b}); **^{13}C NMR** (75 MHz): δ_C = 175.2 (C=O), 152.8 (ArCO), 148.9 (ArCO) , 125.2 (ArC), 117.7 (ArC), 111.2 (ArCH), 109.0 (ArCH), 72.7 (C-5), 71.8 (C-4), 62.6 (C-3), 56.1 (OCH_3), 55.7 (OCH_3), 37.6 (C-6).

7.2.11. Preparation of 2-allyl-3,6-dimethoxybenzaldehyde 97

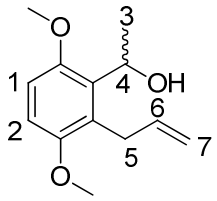
PCC (4.57 g, 21.17 mmol, 2.1 equiv.) was dissolved in MeCN (30 cm^3) and adsorbed onto neutral Al_2O_3 (50 g). This solid was then added to a solution of the (2-allyl-3,6-dimethoxyphenyl)methanol **65** (2.09 g, 10.08 mmol) in dry CH_2Cl_2 (150 cm^3). The reaction mixture was allowed to stir at room temperature for 18 hours under argon. Upon completion of the reaction, the mixture was filtered through celite and the solvent removed *in vacuo*. The crude material was purified by silica gel column chromatography (20–30% EtOAc/Hexane) to yield the product **97** as a clear yellow oil (1.86 g, 90%).



R_f = 0.41 (250% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 2940 (C-H), 1680 (C=O) ; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.57 (1H, s, C*H*O), 7.06 (1H, d, *J* = 9.0 Hz, H_1), 6.83 (1H, d, *J* = 9.0 Hz, H_2), 5.97 (1H, ddt, *J* = 16.2, 10.1, 6.1 Hz, H_4), 4.96 (2H, ddq, *J* = 9.9, 6.3, 1.7 Hz, H_5), 3.85 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.78 (2H, dt, *J* = 6.1, 1.6 Hz, H_3); **^{13}C NMR** (75 MHz): δ_C = 192.5 (C=O), 156.9 (ArCO), 151.7 (ArCO), 136.7 (C-4), 131.5 (ArC), 124.0 (ArC), 117.2 (ArCH), 114.8 (C-5), 109.8 (ArCH), 56.6 (OCH_3), 56.1 (OCH_3), 29.4 (C-3); **HRMS** (ESI+): Found M^+ + H 207.1026, $C_{12}H_{14}O_3$ (M^+ + H) requires 207.1022, *m/z* 207.1026 (M^+ + H, 100%) 191.1075 (15), 189.0923 (72).

7.2.12. Preparation of *rac*-1-(2-allyl-3,6-dimethoxyphenyl)ethanol ±68

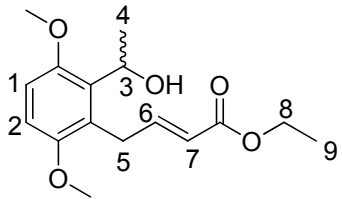
Under an argon atmosphere, Mg metal (0.70g, 28.90 mmol, 1.8 equiv.) was placed in an oven dried 250 cm^3 two-necked RB flask fitted with a condenser and dropping funnel. Dry E_2O (60 cm^3) followed by MeI (3.42g, 1.5 cm^3, 24.10 mmol, 1.5 equiv.) was added to the reaction flask. The reaction mixture became cloudy with a temperature increase. Once all the Mg metal was consumed, the dropping funnel was charged with a solution containing 2-allyl-3,6-dimethoxybenzaldehyde **97** (3.31g, 16.05 mmol) in dry THF (65 cm^3). This solution was added dropwise to the newly formed Grignard reagent. The solution was allowed to stir at room temperature for 18 hours after which time it was placed in an ice-bath and H_2O was added dropwise to quench any excess Grignard reagent. The reaction mixture was diluted with EtOAc (2 × 100 cm^3) and the organic material was washed with brine (100 cm^3). The organic extracts were combined, dried with anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The crude material was purified by silica gel column chromatography (20% EtOAc/Hexane) to yield the product **±68** as a clear oil (2.83 g, 84%).



R_f = 0.26 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3549 (OH); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.79 (2H, dd, *J* = 9.0 Hz, H_1), 6.74 (2H, dd, *J* = 9.0 Hz, H_2), 5.94 (1H, ddt, *J* = 16.2, 10.2, 5.8 Hz, H_6), 5.12-4.88 (3H, m, H_7 and H_4 overlapping), 4.07 (1H, d, *J* = 11.2 Hz, O*H*), 3.84 (3H, s, OCH_3), 3.76 (1H, s, OCH_3), 3.46 (2H, m, H_5), 1.53 (3H, d, *J* = 6.7 Hz, H_3); **^{13}C NMR** (75 MHz): δ_C = 152.0 (ArCO), 151.9 (ArCO), 136.6 (C-6), 132.7 (ArC), 126.1 (ArC), 115.0 (C-7), 109.5 (ArCH), 109.4 (ArCH), 67.3 (C-4), 56.2 (OCH_3), 55.6 (OCH_3), 29.8 (C-5), 23.7 (C-3).

7.2.13. Preparation of (*E*)-methyl-4-(2-(1-hydroxyethyl)-3,6-dimethoxyphenyl)but-2-enoate ±69

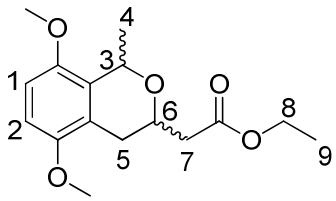
In a 50 cm^3 RB flasked fitted with a condenser was added the alkene **±68** (0.90 g, 4.268 mmol) and ethyl acrylate (1.07 g, 1.2 cm^3, 10.67 mmol, 2.5 equiv.) dissolved in dry CH_2Cl_2 (20 cm^3). Grubbs II catalyst (0.18 g, 0.213 mmol, 5 mol%) was then added to this solution and the mixture was allowed to stir at 90°C for 18 h under an argon atmosphere. After this time, the mixture was cooled to room temperature and the solvent removed *in vacuo*. The residue was purified by flash silica column chromatography (10–20% EtOAc/ Hexane) to yield the product **±69** as a brown oil (1.18 g, 94%).



R_f = 0.59 (50% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3538 (OH), 1712 (C=O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.05 (1H, dt, *J* = 15.6, 6.0 Hz, H_6), 6.77 (2H, 2 x d, *J* = 9.0 Hz, H_1 and H_2 overlapping signals), 5.66 (1H, dt, *J* = 15.6, 1.8 Hz, H_7), 4.95 (1H, dq, *J* = 11.1, 6.7 Hz, H_3), 4.13 (2H, q, *J* = 7.1 Hz, H_8), 3.97 (1H, d, *J* = 10.9 Hz, O*H*), 3.85 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.60 (2H, ddd, *J* = 7.7, 6.0, 1.8 Hz, H_5), 1.51 (3H, d, *J* = 6.7 Hz, H_4), 1.24 (3H, t, *J* = 7.1 Hz, H_9); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 166.66 (C=O), 151.90 (ArCO), 151.76 (ArCO), 147.03 (C-6), 132.77 (ArC), 124.08 (ArC), 121.62 (C-7), 110.09 (ArCH), 109.27 (ArCH), 67.26 (C-3), 60.15 (C-8), 56.02 (OCH_3), 55.65 (OCH_3), 28.50 (C-5), 23.75 (C-4), 14.24 (C-9); **HRMS** (ESI+): Found M^+ + Na 317.1360, $C_{16}H_{22}O_5$ (M^+ + Na) requires 317.1367, *m/z* 317.1360 (M^+ + Na, 35%) 312.1810 (18), 277.1437 (100), 203.1070 (72).

7.2.14. Preparation of *cis* and *trans* ethyl 2-(5,8-dimethoxy-1-methylisochroma-3-yl)acetate *rac*-70

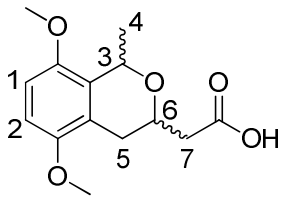
In a 50 cm^3 RB flask, the acetate **±69** (6.04 g, 20.51 mmol) was dissolved in dry THF (150 cm^3). The reaction mixture was cooled to 0°C and sodium hydride (60% in oil, 1.66 g, 41.03 mmol, 2.0 equiv.) was slowly added to the reaction mixture. The reaction mixture was allowed to warm up to room temperature and was stirred for 16 hours under argon. The reaction mixture was quenched with H_20 and diluted with EtOAc. The organic material was extracted into EtOAc (4 × 50 cm^3) before being washed with brine (20 cm^3). The organic extracts were combined, dried with anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The crude material was purified by flash silica gel column chromatography (10% EtOAc/Hexane) to yield the product ***rac*-70** as a clear oil (5.13 g, 85%).



R_f = 0.76 (50% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 2937 (C-H), 1732 (C=O), 1603 and 1437 (C=C), 1254 and 1114 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.66 (4H, m, 2 × ArC*H*, H_1 and H_2), 5.08 (2H, 2 × q, *J* = 6.6 Hz, 2 x H_3), 4.99 (1H, dt, *J* = 6.3, 1.5 Hz, H_3), 4.44–4.34 (1H, m, H_6), 4.25–4.10 (4H, m, 2 × H_8), 4.00–3.88 (1H, m, H_6), 3.78–3.76 (12H, m, 2 × (2 × OCH_3)), 2.90–2.31 (8H, m, 2 × H_5 and 2 × H_7), 1.53 (3H, d, *J* = 1.3 Hz, H_4), 1.50 (3H, d, *J* = 1.0 Hz, H_4), 1.28 (6H, dt, *J* = 7.1, 5.8 Hz, 2 × H_9); **^{13}C NMR** (75 MHz): δ_C = 171.27 (C=O), 171.23 (C=O), 150.86 (ArCO), 150.67 (ArCO), 150.25 (ArCO), 149.44 (ArCO), 129.22 (ArC), 129.03 (ArC), 124.53 (ArC), 122.71 (ArC), 108.09 (ArCH), 107.73 (ArCH), 107.55 (ArCH), 107.40 (ArCH), 71.18 (C-6), 69.78 (C-6), 68.50 (C-3), 63.42 (C-3), 60.52 (C-8), 60.42 (C-8), 55.69 (OCH_3), 55.58 (OCH_3), 55.43 (OCH_3), 55.40 (OCH_3), 41.44 (C-7), 41.21 (C-7), 29.23 (C-5), 28.26 (C-5), 21.63 (C-4), 19.23 (C-4), 14.24 (C-9); **HRMS** (ESI+): Found M^+ + H 295.1545, $C_{16}H_{22}O_5$ (M^+ + H) requires 295.1505, *m/z* 295.1545 (M^+ + H, 100%) 293.1384 (40), 251.1282 (85), 205.0858 (25).

7.2.15. Preparation of 2-(5,8-dimethoxyisochroman-3-yl)acetic acid *rac*-98

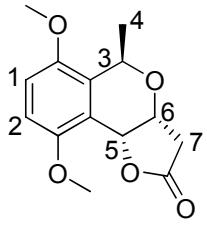
In a 50cm^3 RB flask, the ester ***rac*-70** (0.27 g, 0.91 mmol) was dissolved in dry THF (3 cm^3). Potassium hydroxide (0.39 g, 6.35 mmol, 7.0 equiv.) was slowly added to the reaction mixture. The reaction mixture was allowed stir at room temperature for 2 hours under argon The aqueous phase was acidified to pH 2 using 6N HCl which resulted and the organic material extracted into EtOAc (4 × 50 cm^3). The organic extracts were combined and dried with anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo* to afford the acid ***rac*-98** as a light brown oil (0.18 g, 73%).



R_f = 0.64 (50% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2974 (OH), 1703 (C=O), 1603 and 1482 (C=C), 1339 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 10.42 (2H, s, O*H*), 6.75–6.55 (4H, m, 2 x H_1 and 2 x H_2), 5.12 (1H, q, *J* = 6.5 Hz, H_3), 5.03 (1H, q, *J* = 6.2 Hz, H_3), 4.39 (1H, m, H_6), 3.94 (1H, dddd, *J* = 10.7, 7.5, 5.2, 2.1 Hz, H_6), 3.81–3.72 (6H, m, OCH_3), 2.93–2.34 (8H, m, 2 × H_5 and 2 × H_7), 1.53 (6H, dd, *J* = 6.5, 1.3 Hz, 2 × H_4); **^{13}C NMR** (75 MHz): δ_C = 176.10 (C=O), 175.78 (C=O), 150.85 (ArCO), 150.63 (ArCO), 150.19 (ArCO), 149.38 (ArCO), 128.73 (ArC), 128.65 (ArC), 124.00 (ArC), 122.25 (ArC), 108.26 (ArCH), 107.91 (ArCH), 107.69 (ArCH), 107.55 (ArCH), 71.36 (C-6), 69.53 (C-6), 68.74 (C-3), 63.30 (C-3), 55.58 (OCH_3), 55.44 (OCH_3), 41.02 (C-7), 40.78 (C-7), 29.10 (C-5), 28.19 (C-5), 21.69 (C-4), 19.24 (C-4); **HRMS** (ESI+): Found M^+ + H 267.1223, $C_{14}H_{18}O_5$ (M^+ + H) requires 267.1279, *m/z* 267.1223 (M^+ + H, 45%) 223.0967.1384 (50), 205.0862 (100), 177.0904 (30).

7.2.16. Preparation of (3a*R*, 5*R*, 9b*R*)-6,9-dimethoxy-5-methyl-3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*]isochromen-2-one *rac*-75

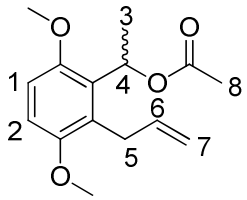
In a 50 cm^3 RB flask, p-anisiodine diacetate (0.80 g, 2.27 mmol, 1.2 equiv.) was added to a stirred suspension of the acid ***rac*-98** (0.50g, 1.89 mmol) and KBr (0.23, 1.91 mmol, 1.0 equiv.) in dry CH_2Cl_2 (20 cm^3). The reaction mixture was stirred at room temperature for 18 hours. After this time, sat. aq. $NaHCO_3$ (10 cm^3) was added and the reaction mixture stirred for an additional 5 minutes. The organic layer was separated and washed sequentially with another portion of sat. aq. $NaHCO_3$ (10 cm^3) and dilute aq. sodium thiosulfate (10 cm^3). The organic extracts were combined, dried with anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The crude material was purified by flash silica gel column chromatography (10% EtOAc/Hexane) to yield the product ***rac*-75** as a white solid (0.13 g, 26%).



R_f = 0.49 (50% EtOAc /Hexane); **mp.** 131–133°C; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 1768 (C=O), 1604 and 1487 (C=C), 1321 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.84 (1H, d, *J* = 8.9 Hz, H_1), 6.77 (1H, d, *J* = 8.9 Hz, H_2), 5.34 (1H, d, *J* = 2.8 Hz, H_5), 5.15 (1H, q, *J* = 6.7 Hz, H_3), 4.69 (1H, dd, *J* = 4.9, 2.9 Hz, H_6), 3.84 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.92 (1H, dd, *J* = 17.5, 5.0 Hz, H_{7a}), 2.65 (1H, d, *J* = 17.5 Hz, H_{7b}), 1.47 (3H, d, *J* = 6.7 Hz, H_4); **^{13}C NMR** (75 MHz): δ_C = 175.48 (C=O), 152.64 (ArCO), 148.66 (ArCO), 130.13 (ArC), 116.98 (ArC), 111.51 (ArCH), 109.05 (ArCH), 71.52 (C-5), 67.36 (C-3), 65.99 (C-6), 56.12 (OCH_3), 55.70 (OCH_3), 37.69 (C-7), 18.45 (C-4).

7.2.17. Preparation of 1-(2-allyl-3,6-dimethoxyphenyl)ethyl acetate ±102

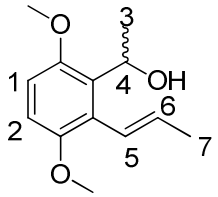
1-(2-allyl-3,6-dimethoxyphenyl)ethanol **±68** dissolved in dry THF (25 cm^3) was placed in a 50 cm^3 two necked RB flask fiited with a rubber septum. To this was added 4-dimethylaminopyridine (DMAP) (0.03 g, 0.24 mmol, 5 mol%) followed by aectic anhydride (1.95 g, 1.8 cm^3, 18.82 mmol, 4 equiv.) and triethylamine (4.83 g, 6.7 cm^3, 47.05 mmol, 10 equiv.). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then quenched with H_2O and the organic material extracted with EtOAc (3 × 50 cm^3). The organic extracts were combined, dried with anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The residue was purified by flash silica gel column chromatography (10% EtOAc/Hexane) to yield the product **±102** as a clear oil (0.89 g, 75%).



R_f = 0.59 (50% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2938 and 2836 (C–H stretch), 1732 (C=O), 1597 and 1478 (C=C), 1239 (C–O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.81–6.71 (2H, m, H_1 and H_2 overlapping), 6.39 (1H, q, *J* = 6.8 Hz, H_4), 5.97 (1H, ddt, *J* = 17.1, 10.3, 5.6 Hz, H_6), 4.92 (2H, ddq, *J* = 33.5, 17.2, 1.8 Hz, H_7), 3.81 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.65 (2H, ddd, *J* = 7.5, 4.3, 1.7 Hz, H_5), 2.02 (3H, s, H_8), 1.56 (3H, d, *J* = 6.8 Hz, H_3); **^{13}C NMR** (75 MHz): δ_C = 170.57 (C=O), 152.28 (ArCO), 151.95 (ArCO), 137.41 (C-6), 129.37, 128.21, 114.46 (C-7), 110.62 (ArCH), 110.33 (ArCH), 67.53 (C-3), 56.49, 30.93, 30.54, 21.52 (C-3), 20.18.

7.2.18. Preparation of (*E*)-1-(3,6-dimethoxy-2-(prop-1-en-yl)phenyl)ethanol ±104

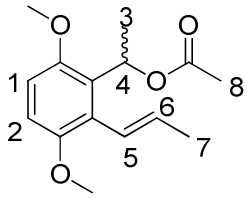
A 50 cm^3 RB flask, potassium tert-butoxide (1.38 g, 12.05 mmol, 4 equiv.) was added to a clear solution of 1-(2-allyl-3,6-dimethoxyphenyl)ethanol **±68** (0.63 g, 3.012 mmnol) dry THF (20 cm^3). The resulting reaction mixture was allowed to stir at room temperature for 2 h, under argon. The mixture was poured into sat. aq. ammonium chloride (20 cm^3) and the organic material extracted into EtOAc (4 × 50 cm^3). The organic extracts were combined, dried over $MgSO_4$ and filtered through celite. The solvent was removed *in vacuo* and the residue purified by flash silica gel column chromatography (10% EtOAc/Hexane) to yield the product **±104** as a clear oil (0.89 g, 75%).



R_f = 0.20 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3535 (OH), 2962 and 2836 (C-H), 1598 and 1447 and 927 (C=C), 1366 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.73 (2H, q, *J* = 9.0 Hz, H_1 and H_2 overlapping), 6.35 (1H, dd, *J* = 16.1, 1.7 Hz, H_5), 5.74 (1H, dq, *J* = 16.0, 6.5 Hz, H_6), 5.16 (1H, dq, *J* = 13.4, 6.7 Hz, H_4), 3.96 (1H, d, *J* = 11.6 Hz, O*H*), 3.86 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 1.91 (3H, dd, *J* = 6.5, 1.7 Hz, H_7), 1.55 (3H, d, *J* = 6.7 Hz, H_3); **^{13}C NMR** (75 MHz): δ_C = 151.91 (ArCO), 151.70 (ArCO), 131.97 (C-6), 127.22 (ArC), 124.32 (C-5), 109.59 (ArCH), 109.10 (ArCH), 67.60 (C-4), 56.08 (OCH_3), 55.60 (OCH_3), 23.84 (C-3), 19.07 (C-7).

7.2.19. Preparation of (*E*)-1-(3,6-dimethoxy-2-(prop-1-en-yl)phenyl)ethyl acetate ±103

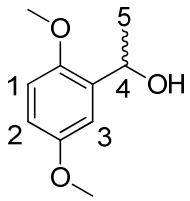
In a 25 cm^3 RB flask was added (*E*)-1-(3,6-dimethoxy-2-(prop-1-en-yl)phenyl)ethanol **±104** (0.35 g, 1.56 mmol) followed by pyridine (0.31 g, 0.35 cm^3, 3.94 mmol, 2.5 equiv.) and acetic anhydride (0.40 g, 0.37 cm^3, 3.94 mmol, 2.5 equiv.). the reaction was allowed to stir at room temperature for 18 h. After this time, H_2O (50 cm^3) was added to quench the reaction and the organic material extracted into EtOAc (3 × 50 cm^3). The organic extracts were combined and washed with brine (50 cm^3) before being dried over $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The resulting residue was purified by flash silica gel column chromatography (10% EtOAc/Hexane) to yield the product **±103** as a clear oil (0.28 g, 68%).



R_f = 0.31 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2938 and 2837 (C–H stretch), 1727 (C=O), 1594 and 1478 (C=C), 1241 (C–O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.76 (2H, s, H_1 and H_2 overlapping), 6.53 (1H, dd, *J* = 16.0, 1.7 Hz, H_5), 6.36 (1H, q, *J* = 6.8 Hz, H_4), 5.86 (2H, dq, *J* = 16.0, 6.5 Hz, H_6), , 3.86 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 2.01 (3H, s, H_8), 1.93 (3H, dd, *J* = 6.5, 1.7 Hz, H_7), 1.60 (3H, d, *J* = 6.8 Hz, H_3); **^{13}C NMR** (75 MHz): δ_C = 170.40 (C=O), 152.35 (ArCO), 151.63 (ArCO), 131.66 (C-6), 128.45 (ArC), 128.37 (ArC), 124.64 (C-5), 110.90 (ArCH), 110.82 (ArCH), 68.45 (C-4), 56.59 (OCH_3), 56.15 (OCH_3), 21.33 (C-8), 19.66 (C-3), 19.27 (C-7).

7.2.20. Preparation of 1-(2,5-dimethoxyphenyl)ethanol ±106

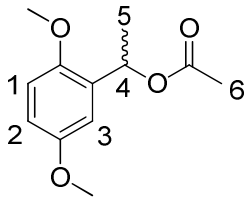
In a 250 cm^3 RB flask, 2,5-dimethoxyphenylacetophenone **105** (5.70 g 5.0 cm^3, 31.60 mmnol) was dissolved in dry THF (100 cm^3). The solution was cooled to 0°C and lithium aluminium hydride (2.97 g, 78.20 mmol, 2.5 equiv.) was slowly added. The reaction mixture was stirred at 40°C for 2 h, under argon. After completion, the reaction was cooled to 0°C before the slow addition of aq. NaOH solution (2M, 20 cm^3). The aqueous layer was extracted with diethyl ether (4 × 40cm^3) and dichloromethane (4 × 40cm^3). The organic extracts were combined, dried over $MgSO_4$ and filtered through celite. The solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc/Hexane) to yield the product **±106** as an orange oil (5.99 g, 99%).



R_f = 0.14 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3410 (OH), 2967 and 2834 (C–H), 1592 and 1493 (C=C), 1242 (C-O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.94 (1H, d, *J* = 2.8 Hz, H_3), 6.81–6.70 (2H, m, H_1 and H_3 overlapping), 5.05 (1H, d, *J* = 6.5 Hz, H_4), 3.79 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.01 (1H, s, O*H*), 1.46 (3H, d, *J* = 6.5 Hz, H_5); **^{13}C NMR** (126 MHz): δ_C = 153.81 (ArCO), 150.62 (ArCO), 134.84 (ArC), 112.43 (ArCH), 112.31 (ArCH), 111.44 (ArCH), 67.28 (C-4), 65.99 (C-6), 55.79 (OCH_3), 55.71 (OCH_3), 23.06 (C-5).

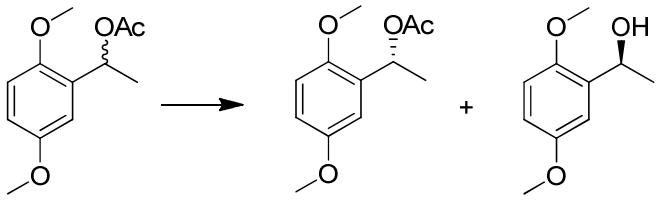
7.2.21. Preparation of 1-(2,5-dimethoxyphenyl)ethyl acetate ±99

In a 25 cm^3 RB flask, 1-(2,5-dimethoxyphenyl)ethanol **±106** (2.05 g, 11.23 mmol) was dissolved in dry THF (100 cm^3). To this stirred solution was added a catalytic amount of 4-dimethylaminopyridine (DMAP) (0.14 g, 1.12 mmol, 10 molar %), followed by acetic anhydride (4.58 g, 4.30 cm^3, 44.97 mmol, 4 equiv.) and triethylamine (11.35 g, 15.7 cm^3, 112.25 mmol, 10 equiv.). The reaction mixture was allowed to stir at room temperature for 2 h, under argon. The mixture was then quenched with distilled H_2O (30 cm^3) and the organic material extracted into EtOAc (4 × 50 cm^3). The organic extracts were combined and dried over $MgSO_4$ before being filtered through celite. The solvent was removed *in vacuo* and the residue purified by flash silica gel column chromatography (20% EtOAc/Hexane) to yield the product **±99** as a clear oil (2.46 g, 98%).



R_f = 0.40 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2937 and 2836 (C–H stretch), 1736 (C=O), 1592 and 1498 (C=C), 1234 (C–O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.94 (1H, d, *J* = 2.7 Hz, H_3), 6.83–6.71 (2H, m, H_1 and H_5 overlapping), 6.20 (1H, d, *J* = 6.5 Hz, H_4), 3.79 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 2.09 (3H, s, H_6), 1.46 (3H, d, *J* = 6.5 Hz, H_5); **^{13}C NMR** (75 MHz): δ_C = 170.07 (C=O), 153.72 (ArCO), 150.17 (ArCO), 131.75 (ArC), 112.42 (ArCH), 112.36 (ArCH), 111.64 (ArCH) 67.14 (C-4), 56.03 (OCH_3), 55.67 (OCH_3), 21.30 (C-6), 21.25 (C-5).

7.2.22. General procedure for the kinetic resolution of racemic alcohols using CALB



To a stirred solution of racemic alcohol **±99** in toluene (5 cm^3/200 mg) was added a buffer solution of tris(hydroxymethyl)amino methane (0.1 M, pH 7.5, 40 cm^3/200 mg). to this reaction mixture was added the lipase enzyme CALB (100 µl/200 mg) and the reaction was allowed to stir at 30°C. Completion of the reaction was determined by HPLC on a C18 column (70% acetonitrile/water) which showed a 50% conversion of the racemic acetate to the alcohol. The organic material was extracted into EtOAc (4 × 50 cm^3). The organic extracts were combined and dried with anhydrous MgSO4, filtered through celite and the solvent removed *in vacuo*. The crude material was purified silica gel chromatography (10% EtOAc/Hexane) to give the unreacted acetate (0.42 g, 56%) and enantioselectively hydroylsed alcohol (0.26 g, 43%). The enantiomeric excess for each product was determined by HPLC analysis on a Chiralcel OD colum (200 × 46 mm) using 7.5% isopropyl alcohol in hexane as the mobile phase. Both products were analysed spectroscopically and characterized as described above.

7.3. Experimental procedures pertaining to Chapter 4

7.3.1. Preparation nitroalkene via a Henry reaction

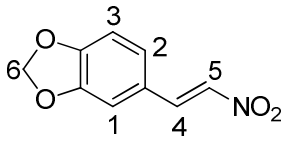
Method A

In a 100cm^3 RB flask equipped with a reflux condenser, aldehyde (33.90 mmol) and ammonium acetate (3 equiv.) was added to glacial acetic acid (60cm^3). Nitromethane (1.7 equiv.) was then added to the reaction, and the reaction mixture stirred at reflux for 6 hours under argon during which time it became a deep red solution. The reaction was then cooled and diluted with EtOAc before being transferred to a separating funnel. The organic layer was then washed with water (3 × 100cm^3), dried over anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The resulting residue was the recrystallized from diethyl ether-hexane to afford the nitro compounds as bright yellow solids.

Method B

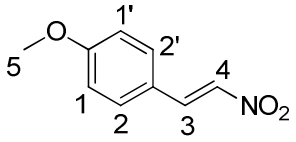
In a 100cm^3 RB flask equipped with a dean stark trap and reflux condenser, aldehyde (39.28 mmol) and ammonium acetate (3 equiv.) was added to dry toluene (65cm^3). Nitrocompound (1.7 equiv.) was then added to the reaction, and the reaction mixture stirred at reflux for 6 hours under argon during which time it became a deep red solution. The reaction was then cooled and diluted with EtOAc before being transferred to a separating funnel. The organic layer was then washed with water (3 × 100cm^3), dried over anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The resulting residue was the recrystallized from diethyl ether-hexane to afford the nitro compounds as bright yellow solids.

7.3.1.1. Preparation of (*E*)-5-(2-nitrovinyl)benzo[*d*][1,3]dioxole 189



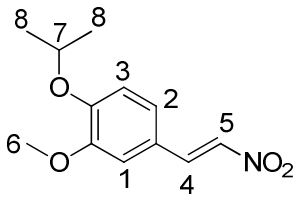
Method A: Yellow solid (2.81g, 43%); **R_f** = 0.45 (20% EtOAc /Hexane); **mp.** 161–162°C, (lit 164–165°C)[92]; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3118 and 2919 (C–H), 1602, 1487 and 965 (C=C), 1500 and 1368 (NO_2), 1240 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.92 (1H, d, *J* = 13.6 Hz, H_5), 7.47 (1H, d, *J* = 13.6 Hz, H_4), 7.08 (1H, dd, *J* = 8.0, 1.4 Hz, H_2), 7.00 (1H, d, *J* = 1.5 Hz, H_1), 6.87 (1H, d, *J* = 8.0 Hz, H_3), 6.06 (2H, s, H_6); **^{13}C NMR** (126MHz) δ_C = 151.40 (Ar*C*O), 148.80 (Ar*C*O), 139.08 (C-4) , 135.44 (C-5), 126.61 (Ar*C*), 124.23 (C-2), 109.09 (C-3), 107.03 (C-1), 102.07 (C-6).

7.3.1.2. Preparation of (*E*)-1-methoxy-4-(2-nitrovinyl)benzene 190



Method A:Yellow solid (3.77g, 51%); **R_f** = 0.39 (20% EtOAc /Hexane); **mp.** 86–88°C, (lit 46–48°C)[93]; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3017 (C–H), 1601 and 1493 (C=C), 1571 and 1324 (NO_2), 1248 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.97 (1H, d, *J* = 13.6 Hz, H_4), 7.51 (3H, dd, *J* = 11.1, 7.3 Hz, H_5, H_2 and $H_{2'}$ overlapping), 6.95 (2H, d, *J* = 8.8 Hz, H_1 and $H_{1'}$), 3.87 (3H, s, OCH_3); **^{13}C NMR** (126MHz) δ_C = 162.99 (Ar*C*O), 139.03 (C-3), 135.07 (C-4) , 131.18 (C-2 and C-2'), 122.58 (Ar*C*), 114.96 (C-1 and C-1'), 55.54 (C-5).

7.3.1.3. Preparation of (*E*)-1-isopropoxy-2-methoxy-4-(2-nitrovinyl)benzene 191

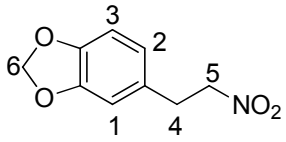


Method A: Yellow solid (4.19g, 44%); **R_f** = 0.45 (20% EtOAc /Hexane); **mp.** 84–86, (lit 82–83)[144]; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3120 and 2977 (C–H), 1624 and 1489 (C=C), 1596 and 1330 (NO_2), 1259 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.96 (1H, d, *J* = 13.5 Hz, H_5), 7.52 (1H, d, *J* = 13.5 Hz, H_4), 7.14 (1H, dd, *J* = 8.3, 1.9 Hz, H_2), 7.01 (1H, d, J = 1.8 Hz, H*1*), 6.91 (1H, d, *J* = 8.4 Hz, H*3*), 4.65 (1H, sept, *J* = 6.1 Hz, H_7), 3.90 (3H, s, OCH_3), 1.41 (6H, d, *J* = 6.1 Hz, H_8); **^{13}C NMR** (126MHz) δ_C = 151.49 (Ar*C*O), 150.48 (Ar*C*O), 139.41 (C-4) , 135.05 (C-2), 124.45 (C-5), 122.56 (Ar*C*), 111.12 (C-1), 71.45 (C-7), 56.12 (C-6), 21.93 (C-8).

7.3.2. Preparation of nitroalkane compounds

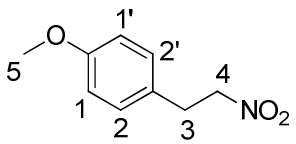
In a 250cm^3 RB flask, nitroalkene (14.55 mmol) was dissolved in dry chloroform (160 cm^3) and dry isopropanol (30 cm^3). To this solution was added silica gel (20 g) followed by the addition of sodium borohydride (2 equiv.). The reaction mixture was then stirred for 2 hours under argon at room temperature. Upon completion, as monitored by TLC, the reaction mixture was filtered through celite aand washed with EtOAc (100 cm^3). The organic phase was then washed with water (2 × 100cm^3) followed by brine (100cm^3), dried over anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The resulting residue was the purified by flash column chromatography (10% EtOAc/Hexane) to afford the pale yellow nitroalkane compounds.

7.3.2.1. Preparation of 5-(2-nitroethyl)benzo[*d*][1,3]dioxole 195



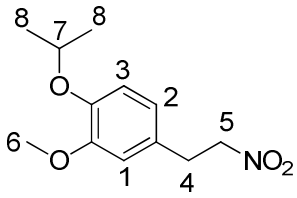
Yellow soild (2.02 g, 71%); **R_f** = 0.41 (20% EtOAc /Hexane); **mp.** 55–57, (lit 43.5-44.5)[94]; **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2897 (C–H), 1609 and 1499 (C=C), 1543 and 1362 (NO_2), 1243 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 6.74 (1H, d, *J* = 7.9 Hz, H_3), 6.68–6.62 (2H, m, H_1 and H_2 overlapping), 5.92 (2H, s, H_6), 4.55 (2H, t, *J* = 7.3 Hz, H_5), 3.21 (2H, t, *J* = 7.3 Hz, H_4); **^{13}C NMR** (126 MHz): δ_C 148.05 (Ar*C*O), 146.93 (Ar*C*O), 129.29 (Ar*C*) , 121.73 (C-3), 108.91 (C-1), 108.62 (C-6), 101.15 (C-5), 33.20 (C-4).

7.3.2.2. Preparation of 1-methoxy-4-(2-nitroethyl)benzene 196



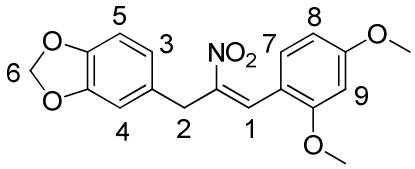
Yellow oil (2.96 g, 76%); **R_f** = 0.48 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2937 and 2837 (C–H), 1612 and 1512 (C=C), 1546 and 1342 (NO_2), 1245 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.11 (2H, d, *J* = 8.6 Hz, H_2 and H_2'), 6.85 (2H, d, *J* = 8.6 Hz, H_1 and $H_{1'}$), 4.55 (2H, t, *J* = 7.4 Hz, H_4), 3.78 (3H, s, O*C*H_3), 3.24 (2H, t, *J* = 7.4 Hz, H_3); **^{13}C NMR** (126 MHz) δ_C = 158.92 (Ar*C*O), 129.63 (C-2 and C-2'), 127.62 (Ar*C*), 114.36 (C-1 and C-1') , 76.59 (C-4), 55.26 (O*C*H_3), 32.69 (C-3).

7.3.2.3. Preparation of 1-isopropoxy-2-methoxy-4-(2-nitroethyl)benzene 197



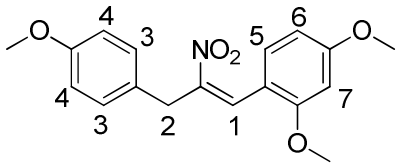
Yellow oil (3.03g, 72%); **R_f** = 0.35 (20% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 2976 and 2935 (C–H), 1588 and 1510 (C=C), 1548 and 1376 (NO_2), 1231 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 6.85–6.82 (1H, m, H_3), 6.72-6.69 (2H, m, H_1, H_2 overlapping), 4.58 (2H, t, *J* = 7.4 Hz, H_5), 4.48 (1H, hept, *J* = 6.1 Hz, H_7), 3.84 (3H, s, OCH_3), 3.25 (2H, t, *J* = 7.4 Hz, H_4), 1.35 (6H, d, *J* = 6.1 Hz, H_8); **^{13}C NMR** (126 MHz) δ_C = 150.67 (Ar*C*O), 146.69 (Ar*C*O), 128.53 (Ar*C*), 120.66 (C-2), 116.22 (C-3) , 112.55 (C-1), 76.53 (C-5), 71.56 (C-7), 56.01 (OCH_3), 33.18 (C-4), 22.09 (C-8).

7.3.3. Preparation of (Z)-5-(3-(2,4-dimethoxyphenyl)-2-nitroallyl)benzo[*d*][1,3]dioxole 199



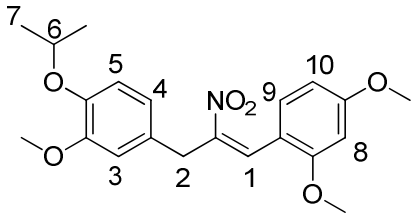
Method B: Yellow solid (2.02 g, 71%); **R_f** = 0.25 (50% CH_2Cl_2 /Hexane); **mp.** 80–82; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 2902 and 2838 (C–H), 1601, 1490 and 696 (C=C), 1574 and 1317 (NO_2), 1258 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 8.52 (1H, s, H_1), 7.25 (2H, d, *J* = 7.8 Hz, Ar*H*), 6.78-6.59 (3H, m, Ar*H*), 6.52-6.39 (2H, m, Ar*H*), 5.93 (2H, s, H_6), 4.14 (2H, s, H_2), 3.88 (3H, s, OCH_3), 3.83 (3H, s, OCH_3); **^{13}C NMR** (126 MHz): δ_C 163.36 (ArCO), 160.09 (ArCO), 148.10 (ArCO), 147.46 (ArCO), 146.44 (C-NO_2), 131.38 (C-1), 130.51 (ArCH), 130.47 (ArC), 120.42 (ArCH), 113.92 (ArC), 108.55 (ArCH), 108.25 (ArCH), 105.24 (ArCH), 101.04 (C-6), 98.50 (ArCH), 55.71 (OCH_3), 55.53 (OCH_3), 32.93 (C-2); **HRMS** (ESI+): Found M^+ + H 344.1129, $C_{18}H_{17}NO_6$ (M^+ + H) requires 344.1179, m/z 344.1129 (M^+ + H, 35%), 297.1132 (85), 233.0061 (75), 206.0470 (100), 191.5347 (95).

7.3.4. Preparation of (Z)-2,4-dimethoxy-1-(3-(4-methoxyphenyl)-2-nitroprop-1-en-1-yl)benzene 200



Method B: Yellow solid (3.45 g, 87%); $\mathbf{R_f}$ = 0.39 (30% EtOAc /Hexane); **mp.** 78–79; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3020 and 2950 (C–H), 1605 and 1499 (C=C), 1570 and 1297 (NO_2), 1247 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 8.52 (1H, s, H_1), 7.27-7.23 (1H, m, H_5), 7.12 (2H, d, *J* = 8.3 Hz, H_3), 6.85 (2H, d, *J* = 8.5 Hz, H_4), 6.49 (1H, d, *J* = 2.2 Hz, H_7), 6.44 (1H, dd, *J* = 8.7, 2.2 Hz, H_6), 4.16 (2H, s, H_2), 3.87 (3H, s, OCH_3), 3.82 (2H, s, OCH_3), 3.78 (3H, s, OCH_3); **^{13}C NMR** (126 MHz) δ_C = 163.29 (Ar*C*O), 160.06 (Ar*C*O), 158.45 (Ar*C*O), 147.75 (C-NO_2), 131.11 (C-1), 130.48 (C-5), 128.60 (Ar*C*), 128.60 (C-3), 114.29 (Ar*C*), 114.02 (C-4), 105.20 (C-6), 98.47 (C-7), 55.70 (O*C*H_3), 55.52 (O*C*H_3), 55.28 (O*C*H_3), 32.43 (C-2); **HRMS** (ESI+): Found M^+ + H 330.1346, $C_{18}H_{19}NO_5$ (M^+ + H) requires 330.1379, m/z 330.1346 (M^+ + H, 100%)

7.3.5. Preparation of (Z)-2,4-dimethoxy-1-(3-(4-methoxyphenyl)-2-nitroprop-1-en-1-yl)benzene 201

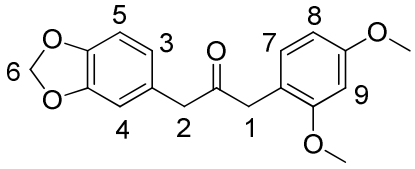


Method B: Yellow oil (4.24 g, 72%); $\mathbf{R_f}$ = 0.35 (CH_2Cl_2); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 2974 (C–H), 1604, 1502 and 827 (C=C), 1553 and 1294 (NO_2), 1232 (C–O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.54 (1H, s, H_1), 7.27 (1H, d, *J* = 7.7 Hz, ArH), 6.87–6.64 (3H, m, ArH), 6.45 (2H, ddd, *J* = 8.0, 6.8, 2.5 Hz, ArH), 4.54–4.40 (1H, m, H_6), 4.17 (2H, s, H_2), 3.87 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 1.35 (6H, d, *J* = 6.1 Hz, H_7); **^{13}C NMR** (75 MHz): δ_C = 163.33 (ArCO), 160.05 (ArCO), 150.68 (ArCO), 147.62 (ArCO), 146.19 (C-NO_2), 131.26 (C-1), 130.53 (ArCH), 129.69 (ArC), 119.32 (ArCH), 116.20 (ArCH), 114.00 (ArC), 111.81 (ArCH), 105.22 (ArCH), 98.45 (ArCH), 71.51 (C-6), 55.96 (OCH_3), 55.69 (OCH_3), 55.52 (OCH_3), 32.81 (C-2), 22.13 (C-7).

7.3.6. Novel Nef reaction experimental conditions

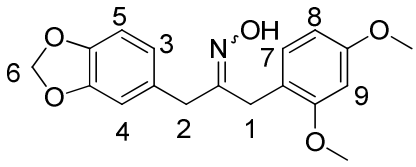
In a 100cm^3 RB flask, nitroalkene (3.000 mmol) was dissolved in 96% ethanol (65 cm^3). To this solution was added cyclohexene (1.2 equiv.). Palladium hydroxide on carbon (10 mol %), and one drop of conc. HCl. The reaction mixture was exposed to a hydrogen atmosphere (1atm) using a balloon. Upon completion, as monitored by TLC, the reaction mixture was filtered through celite and washed with EtOAc (100 cm^3). The organic phase was dried over anhydrous $MgSO_4$, filtered through celite. The solvent was removed *in vacuo* and flash column chromatography with a 10% EtOAc/Hexane solution afforded three products, oximes, carbonyl compounds and the reduced nitroalkane compounds.

7.3.6.1. Preparation of 1-(benzo[d][1,3]dioxol-5-yl)-3-(2,4-dimethoxyphenyl)propan-2-one 204



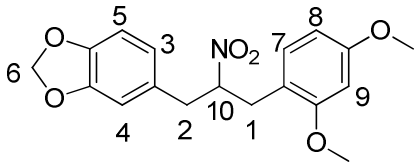
Yellow oil (0.27 g, 29%); **R_f** = 0.39 (30% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2901 (C–H), 1715 C=O), 1612 and 1488 (C=C), 1244 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 6.98 (1H, d, *J* = 8.7 Hz, H_8), 6.74 (1H, d, J = 7.9 Hz, H_5), 6.64-6.56 (2H, m, H_3 and H_4), 6.44 (2H, dd, *J* = 7.2, 1.7 Hz, H_7 and H_9), 5.93 (2H, s, H_6), 3.80 (3H, s, OC*H*$_3$), 3.76 (2H, s, OC*H*$_3$), 3.61 (2H, s, H_1), 3.59 (2H, s, H_2); **^{13}C NMR** (126MHz) δ_C = 206.71 (C=O), 160.30 (Ar*C*O), 158.25 (Ar*C*O), 147.72 (Ar*C*O), 146.49 (Ar*C*O), 131.50 (C-7), 128.13 (Ar*C*), 122.61 (Ar*C*H), 115.76 (Ar*C*), 109.94 (Ar*C*H), 108.28 (C-5), 104.30 (Ar*C*H), 100.95 (C-6), 98.65 (ArCH), 55.39 (OCH_3), 55.32 (OCH_3), 48.33 (C-2), 43.30 (C-1); **HRMS** (ESI+): Found M^+ + H 315.1232, $C_{18}H_{18}O_5$ (M^+ + H) requires 315.1279, m/z 315.1232 (M^+ + H, 100%), 297.1136 (15).

7.3.6.2. Preparation of 1-(benzo[d][1,3]dioxol-5-yl)-3-(2,4-dimethoxyphenyl)propan-2-one oxime 203



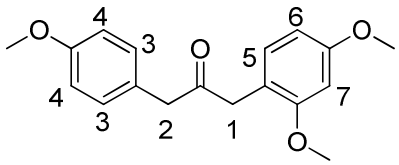
Yellow oil (0.36 g, 37%); **R_f** = 0.25 (30% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3220 (OH), 2999 and 2934 (C–H), 1610 (C=N), 1587 and 1462 (C=C), 1244 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 9.47 (2H, s, N-O*H*), 7.02 (2H, d, *J* = 8.7 Hz, 2 × H_7), 6.65 (6H, m, 2 × (H_3, H_4 and H_5)), 6.44–6.36 (4H, m, 2 × (H_8 and H_9)), 5.89 (4H, s, 2 × H_6), 3.76 (12H, m, 4 × OC*H*$_3$), 3.60 (2H, s, 2 × H_1), 3.55 (2H, s, 2 × H_1), 3.41 (2H, s, 2 × H_2), 3.32 (2H, s, 2 × H_2); **^{13}C NMR** (126 MHz, $CDCl_3$): δ = 159.93 and 159.72 (ArCO), 159.60 and 158.93 (ArCO), 158.42 and 158.31 (C=N), 147.58 and 147.52 (ArCO), 146.17 and 145.97 (ArCO), 131.31 and 131.08 (C-7), 130.73 and 130.49 (ArC), 122.22 and 122.18 (ArCH), 117.38 and 117.03 (ArC), 109.84 and 109.61 (ArCH), 108.04 and 108.01 (ArCH), 104.28 and 104.20 (ArCH), 100.80 and 100.78 (C-6), 98.56 and 98.34 (ArCH), 55.35 and 55.34 (OCH_3), 55.24 and 55.20 (OCH_3), 39.36 and 33.00 (C-2), 32.52 and 26.50 (C-1).

7.3.7. Preparation of 5-(3-(2,4-dimethoxyphenyl)2-nitropropyl)benzo[d][1,3]dioxole 202



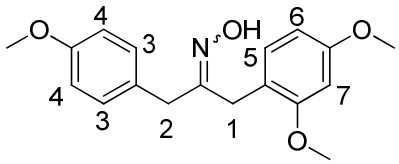
Yellow solid (0.05 g, 5%); **R_f** = 0.61 (30% EtOAc /Hexane); **mp.** 59–61, (lit 43.5-44.5); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2997 and 2929 (C–H), 1610 and 1503 (C=C), 1591 and 1288 (NO_2), 1245 (C–O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 6.95 (1H, d, *J* = 8.2 Hz, H_7), 6.74–6.51 (3H, m, ArH), 6.45–6.29 (2H, m, ArH), 5.90 (2H, s, -OCH_2O-), 5.03–4.87 (1H, m, H_{10}), 3.78 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.24–2.86 (4H, m, H_1 and H_2 overlapping).; **^{13}C NMR** (75 MHz) δ_C = 160.51 (ArCO), 158.33 (ArCO), 147.85 (ArCO), 146.79 (ArCO), 131.24 (ArCH), 129.49(ArC), 122.03 (ArCH), 116.11(ArC), 109.13 (ArCH), 108.43 (ArCH), 104.03 (ArCH), 101.03 (C-6), 98.65 (ArCH), 89.73 (C-10), 55.33 (OCH_3), 55.32 (OCH_3), 39.47 (C-2)*, 34.67(C-1)*; **HRMS** (ESI+): Found M^+ + H 346.1296, $C_{18}H_{19}NO_6$ (M^+ + H) requires 346.1279, m/z 346.1296 (M^+ + H, 100%), 299.1307 (15).

7.3.8. Preparation of 1-(2,4-dimethoxyphenyl)-3-(4-dimethoxyphenyl)propan-2-one 205



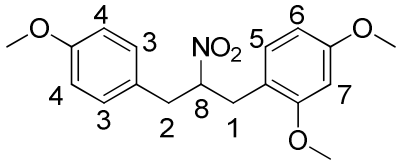
Yellow oil (0.22 g, 24%); **R_f** = 0.41 (30% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2936 and 2836 (C–H), 1716 C=O), 1612 and 1463 (C=C), 1246 (C–O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 7.06 (2H, d, *J* = 8.7 Hz, H_3), 7.00–6.92 (1H, m, ArH), 6.83 (2H, d, *J* = 8.7 Hz, H_4), 6.47–6.39 (2H, m, ArH), 3.78 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.62 (2H, s, H_1), 3.60 (2H, s, H_2); **^{13}C NMR** (75 MHz): δ_C = 206.97 (C=O), 160.26 (ArCO), 158.53 (ArCO), 158.28 (ArCO), 131.52 (C-3), 130.52 (ArCH), 126.59 (ArC), 115.87 (ArC), 113.96 (C-4), 104.28 (ArCH), 98.60 (ArCH), 55.39 (OCH_3), 55.27 (OCH_3), 55.22 (OCH_3), 47.92 (C-2), 43.27 (C-1); **HRMS** (ESI+): Found M^+ + H 301.1443, $C_{18}H_{20}O_4$ (M^+ + H) requires 301.1479, m/z 301.1443(M^+ + H, 100%).

7.3.9. Preparation of 1-(2,4-dimethoxyphenyl)-3-(4-dimethoxyphenyl)propan-2-one oxime 206



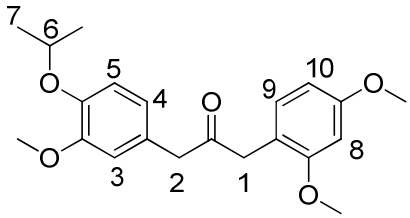
Yellow oil (0.24 g, 25%); **R_f** = 0.28 (30% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3226 (OH), 2999 and 2934 (C–H), 1610 (C=N), 1587 and 1462 (C=C), 1244 (C–O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 9.17 (2H, s, N-O*H*), 7.13 (2H, d, *J* = 8.7 Hz, ArH), 7.06–6.94 (4H, m, ArH), 6.86–6.71 (4H, m, ArH), 6.42 (4H, dd, *J* = 4.1, 2.0 Hz, ArH), 3.77 (18H, m, 6 × OC*H*$_3$), 3.73 (2H, s, 2 × H_1), 3.59 (2H, s, 2 × H_1), 3.40 (2H, s, 2 × H_2), 3.35 (2H, s, 2 × H_2); **^{13}C NMR** (75 MHz) δ_C = 159.90 and 159.81 (ArCO), 159.70 and 159.25 (ArCO), 158.46 and 158.35 (ArCO), 158.30 and 158.12 (C=N), 131.31 and 131.09 (ArCH), 130.27 and 130.16 (ArCH), 129.07 and 128.86 (ArC), 117.49 and 117.09 (ArC), 113.79 and 113.73 (ArCH), 104.21 and 104.15 (ArCH), 98.55 and 98.33 (ArCH), 55.35, 55.28 and 55.24 (OCH_3), 38.85 and 33.04 (C-2), 32.03 and 26.54 (C-1); **HRMS** (ESI+): Found M^+ + H 316.1555, $C_{18}H_{21}NO_4$ (M^+ + H) requires 316.1579, m/z 316.1555(M^+ + H, 100%).

7.3.10. Preparation of 2,4-dimethoxy-1-(3-(4-methoxyphenyl)-2-nitropropyl)benzene 207



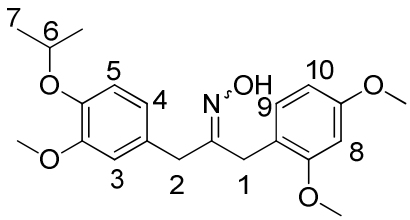
Yellow solid (0.48 g, 47%); **R_f** = 0.50 (30% EtOAc /Hexane); **mp.** 75–77, (lit 43.5-44.5); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 2934 and 2836 (C–H), 1613 and 1505 (C=C), 1585 and 1284 (NO_2), 1247 (C–O); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.06 (2H, d, *J* = 8.6 Hz, H_3), 6.96 (1H, d, *J* = 8.2 Hz, H_5), 6.82 (2H, d, *J* = 8.6 Hz, H_4), 6.45–6.34 (2H, m, H_6 and H_7 overlapping), 5.03–4.91 (1H, m, H_8), 3.78 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.26–2.95 (4H, m, H_1 and H_2 overlapping); **^{13}C NMR** (75 MHz): δ_C = 160.49 (ArCO), 158.81 (ArCO), 158.36 (ArCO), 131.26 (ArC), 129.89 (C-5), 127.87(C-3) , 116.25 (ArC), 114.13 (C-4), 104.15 (C-6), 98.65 (C-7), 89.80 (C-8), 55.33 (OCH_3), 55.26 (OCH_3), 55.21 (OCH_3), 39.01 (C-1), 34.65 (C-1); **HRMS** (ESI+): Found M^+ + H 332.1506, $C_{18}H_{21}NO_5$ (M^+ + H) requires 332.1479, m/z 332.1506 (M^+ + H, 35%), 285.1495 (25), 151.0764 (100).

7.3.11. Preparation of 1-(2,4-dimethoxyphenyl)-3-(4-isopropoxy-3-methoxyphenyl)propan-2-one 208



Yellow solid (0.31 g, 30%); **R_f** = 0.29 (30% EtOAc /Hexane); **mp.** 67–69, (lit 43.5-44.5); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2974 and 2936 (C–H), 1714 (C=O), 1612 and 1464 (C=C), 1259 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 6.96 (1H, d, *J* = 8.9 Hz, Ar*H*), 6.82 (1H, d, *J* = 8.9 Hz, Ar*H*), 6.68-6.64 (2H, m, H_5), 6.45-6.41 (2H, m, Ar*H*), 4.48 (1H, hept, *J* = 6.1Hz, H_6), 3.80 (3H, s, OCH_3), 3.78 (2H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.62 (4H, d, *J* = 1.8 Hz, H_1 and H_2), 1.35 (6H, d, *J* = 6.1 Hz, H_7); **^{13}C NMR** (126 MHz) δ_C = 206.97 (C=O), 160.26 (ArCO), 158.29 (ArCO), 150.38 (ArCO), 146.22 (ArCO), 131.54 (ArCH), 127.48 (ArC), 121.66 (ArCH), 116.05 (ArCH), 115.79 (ArC), 113.34 (ArCH), 104.27 (ArCH), 98.58 (ArCH), 71.53 (C-6), 55.89 (OCH_3), 55.35 (OCH_3), 55.29 (OCH_3), 47.43 (C-2), 43.26 (C-1), 22.12 (C-7); **HRMS** (ESI+): Found M^+ + H 359.1860, $C_{21}H_{26}O_5$ (M^+ + H) requires 359.1879, m/z 359.1860 (M^+ + H, 100%), 317.1388 (25).

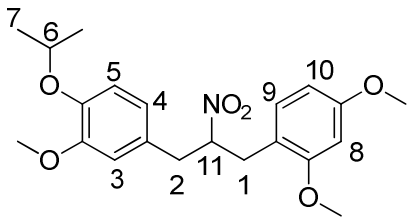
7.3.12. Preparation of 1-(2,4-dimethoxyphenyl)-3-(4-isopropoxy-3-methoxyphenyl)propan-2-one oxime 209



Yellow oil (0.19 g, 17%); **R_f** = 0.20 (30% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3233 (OH), 2974 and 2935 (C–H), 1611 (C=N), 1587 and 1463 (C=C), 1260 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 9.37 (2H, s, N-O*H*), 7.00 (2H, dd, *J* = 14.3, 8.6 Hz, ArH), 6.80–6.57 (6H, m, ArH), 6.40 (4H, tt, *J* = 8.3, 4.2 Hz, ArH), 4.50–4.40 (2H, m, 2 × H_6), 3.78–3.71 (9H , m, 6 × OCH_3), 3.62 (2H, s, 2 × H_1), 3.59 (2H, s, 2 × H_1), 3.43 (2H, s, 2 × H_2), 3.35 (2H, s, 2 × H_2), 1.34 (24H , t, *J* = 6.5 Hz, 2 × H_7); **^{13}C NMR** (126 MHz) δ_C = 159.88 and 159.68, (ArCO), 159.12 (ArCO), 158.43 and 158.35 (C=N), 150.31 and 150.28 (ArCO), 145.85 and 145.73 (ArCO), 131.33 and 131.02 (ArCH), 130.11 and 129.86 (ArC), 121.38 and 121.21 (ArCH), 117.48 and 117.06 (ArCH), 116.17 and 116.08 (ArC), 113.36 and 113.12 (ArCH), 104.20 and 104.09 (ArCH), 98.49 and 98.28 (ArCH), 71.61 and 71.56 (2 X C-6), 55.83, 55.80 and 55.32 (OCH_3), 55.26 and 55.22 (OCH_3), 33.01 and

32.53 (C-7), 22.14 and 22.12 (C-7), 39.35 (C-2) and 26.71 (C-1).; **HRMS** (ESI+): Found M^+ + H 374.1978, $C_{21}H_{27}NO_5$ (M^+ + H) requires 374.1979, m/z 374.1978(M^+ + H, 100%).

7.3.13. Preparation of 4-(3-(2,4-dimethoxyphenyl)-2-nitropropyl)-1-isopropoxy-2-methoxybenzene 210

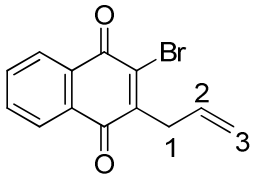


Yellow oil (0.08 g, 7.4%); $\mathbf{R_f}$ = 0.46 (30% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2968 and 2904 (C–H), 1614 and 1508 (C=C), 1588 and 1286 (NO_2), 1255 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 6.96 (1H, d, *J* = 8.2 Hz, H_9), 6.80 (1H, d, *J* = 7.9 Hz, H_5), 6.68-6.64 (2H, m, H_3 and H_4), 6.44-6.36 (2H, m, H_8 and H_{10}), 4.99 (1H, dq, *J* = 8.8, 7.0 Hz, H_{11}), 4.47 (1H, hept, *J* = 6.1 Hz, H_6), 3.81 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 3.76 (3H, s, OC*H*$_3$), 3.21 (1H, dd, *J* = 14.4, 9.1 Hz, H_2), 3.11 (2H, d, *J* = 7.0 Hz, H_1), 2.99 (1H, dd, *J* = 14.4, 5.2 Hz, H_2), 1.33 (6H, d, *J* = 6.1 Hz, H_7), ; **^{13}C NMR** (126MHz) δ_C = 160.48 (Ar*C*O), 158.34 (Ar*C*O), 150.45 (Ar*C*O), 146.53 (Ar*C*O), 131.23 (C-9), 128.80 (Ar*C*), 121.02 (Ar*C*H), 116.21 (Ar*C*), 116.03 (C-5), 112.82 (Ar*C*H), 104.16 (Ar*C*H), 98.62 (Ar*C*H), 89.64 (C-11), 71.47 (C-6), 55.99 (O*C*H$_3$), 55.31 (O*C*H$_3$), 55.29 (O*C*H$_3$), 39.43 (C-2), 34.63 (C-1), 22.09 (C-7); **HRMS** (ESI+): Found M^+ + H 390.1911, $C_{21}H_{27}NO_6$ (M^+ + H) requires 390.1879, m/z 390.1911 (M^+ + H, 100%), 348.1457 (20), 301.1439 (20).

7.3.14. Preparation of 2-allyl-3-bromonaphthalene-1,4-dione 211

In a 1000 cm^3 RB flask, 2-bromo-naphthaquinone (1.03g, 4.35 mmol), vinyl acetic acid (0.61 g, 0.60 cm^3, 7.06 mmol, 1.6 equiv.) and silver nitrate (0.37 g, 2.19 mmol, 0.5 equiv.) was added to dry MeCN (100 cm^3). The reaction mixture was heated to 65 °C and ammonium persulphate (1.79 g, 15.42 mmol, 1.8 equiv.) in distilled water (50 cm^3) was added dropwise to the reaction mixture. The reaction mixture was maintained at 65°C with stirring for 16 hours under argon. The reaction mixture was quenched with H_2O (100 cm^3) and extracted into EtOAc (4 × 100 cm^3). The combined organic phase was washed sequentially with $NaHCO_3$ (2 × 100 cm^3) followed by brine (100 cm^3). The organic extract was dried with MgSO4, filtered through celite

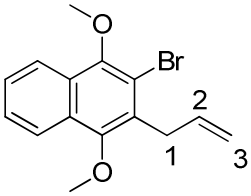
and the solvent removed *in vacuo*. The crude material was purified by flash silica gel chromatography (4% EtOAc/Hexane) to yield the product **211** as a yellow solid (0.95 g, 79%).



R_f = 0.50 (20% EtOAc /Hexane); **mp.** 78–80 (lit 79°C)[29]; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.21 – 8.11 (2H, m, ArH), 7.82 – 7.72 (2H, m, ArH), 5.87 (1H, ddt, *J* = 16.6, 10.0, 6.6 Hz, H_2), 5.27 (1H, ddd, *J* = 17.1, 2.9, 1.4 Hz, H_{3a}), 5.22 – 5.10 (1H, m, H_{3b}), 3.64 (2H, dt, *J* = 6.6, 1.4 Hz, H_1).

7.3.15. Preparation of 2-allyl-3-bromo-1,4-dimethoxynaphthalene 212

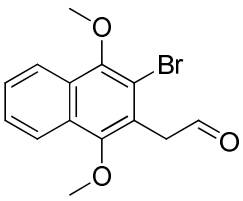
In a 500 cm^3 RB flask, sodium dithionite (21.72 g, 71.85 mmol, 6 equiv.) in H_2O (100 cm^3) and TBAI (0.40 g, 1.08 mmol, 0.09 equiv.) were added to a clear solution of 2-allyl-3-bromonaphthalene-1,4-dione **211** (3.13 g, 11.98 mmol) in dry THF (250 cm^3). The reaction was stirred at room temperature under argon for 30 minutes. Potassium hydroxide (26.16 g, 0.275 mol, 23 equiv.) in H_2O (100 cm^3) was added and the reaction was stirred for 1 hour. Finally, diemethyl sulfate (31.72 g, 24 cm^3, 0.252 mol, 21 equiv.) was added and the reaction mixture was stirred for 18 hours. 25% ammonia (100 cm^3) was added to the reaction and the organic material was extracted into EtOAc (3 × 100 cm^3). The organic layer was consecutively washed with distilled water (100 cm^3), 10% HCl (100 cm^3), brine (100 cm^3) and distilled water (100 cm^3) and was dried over $MgSO_4$ and filtered through celite. The solvent was removed in vacuo and the residue purified by silica gel chromatography (5% EtOAc/Hexane) to afford the product **212** as a yellow solid (1.2836g, 75%).



R_f = 0.67 (50% EtOAc /Hexane); **mp.** 56–58 (lit 57°C) [97];**IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3067 (C–H stretch), 1636 (C=C), 1258 (C–O), 993 and 913 (C–H bend); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.13 – 8.02 (2H, m, Ar*H*), 7.57 – 7.47 (2H, m, ArI), 6.07 (1H, ddt, *J* = 16.0, 10.2, 5.8 Hz, H2), 5.12 – 4.98 (2H, m, H3), 3.98 (3H, s, OC*H*$_3$), 3.92 (3H, s, OC*H*$_3$), 3.79 (2H, dt, *J* = 5.8, 1.7 Hz, H1); **^{13}C NMR** (75 MHz): δ_C = 150.95 (ArCO), 150.17 (ArCO), 135.73 (C2), 128.89 (ArC), 128.06 (ArC), 127.93 (ArC), 126.56 (ArCH), 126.50 (ArCH), 122.65 (ArCH), 122.55 (ArCH), 116.66 (ArCBr), 115.88 (C3), 62.69 (OCH_3), 61.36 (OCH_3), 34.36 (C1).

7.3.16. Preparation of 2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)acetaldehyde 213

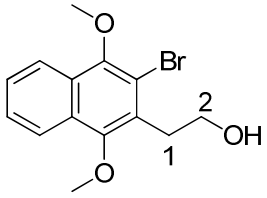
To a stirred solution of 2-allyl-3-bromo-1,4-dimethoxynaphthalene **212** (2.86 g, 9.32 mmol) in dry CH_2Cl_2 (400 cm^3) under argon was added 0.1% solution of Sudan III (3 drops) in CH_2Cl_2 and the reaction cooled to –78°C. Ozone gas was bubbled into the reaction until the colour changed from pink to colourless. Argon gas was then passed into the reaction for 10 min and dimethyl sulfide (8.86 g, 10.5 cm^3, 0.143, 13 equiv.) was added to the reaction at –78°C. The reaction was then warmed to room temperature and stirred at room temperature for 1 h. The reaction was then concentrated in vacuo and the residue purified by column chromatography (15% EtOAc/Hexane) to afford the product **213** as a pale pink solid (1.81g, 63%).



R_f = 0.33 (20% EtOAc /Hexane); **mp.** 68–70 (lit. 68–70)[17]; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 2942 and 2829 (C–H), 1717 (C=O), 1574 and 1492 (C=C), 687 (C–Br); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 9.86 (1H, s, C*H*O), 8.16–7.98 (2H, m, ArH), 7.59–7.52 (2H, m, ArH), 4.13 (2H, d, *J* = 1.3 Hz, CH_2), 3.97 (3H, s, OCH_3), 3.85 (3H, s, OCH_3); **^{13}C NMR** (126 MHz) δ_C = 198.54 (C=O), 151.95 (ArCO), 150.44 (ArCO), 128.81 (ArC), 127.73 (ArC), 127.16 (ArCH), 126.95 (ArCH), 122.98 (ArC), 122.65 (ArCH), 115.86 (ArCBr), 62.45 (OCH_3), 61.41 (OCH_3), 45.20 (CH_2).

7.3.17. Preparation of 2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)ethanol 214

In a 100 cm^3 RB flask, 2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)acetaldehyde **213** (1.81 g, 5.85 mmol) was dissolved in dry methanol (60 cm^3). The reaction was cooled to 0°C and sodium borohydride (0.45 g, 11.7 mmol, 2.2 equiv.) was added portion wise. The reaction was then warmed to room temperature and stirres at this temperature for 30 min. The reaction was quenched with H_2O (100 cm^3) and extracted into EtOAc (2 × 100 cm^3) and washed with H_2O (100 cm^3) and brine (100 cm^3). The organic phase was dried over anhydrous $MgSO_4$ and filtered through celite. The solvent was removed *in vacuo* and flash column chromatography with a 10% EtOAc/Hexane solution afforded the alcohol **214** as a white solid (1.32g, 73%).

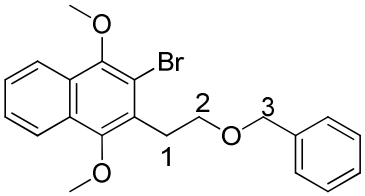


R_f = 0.23 (20% EtOAc /Hexane); **mp.** 107–109; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3364 (OH), 2936 (C–H), 1572 and 1454 (C=C), 1356 (C–O), 559 (C–Br); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 8.12–8.01 (2H, m, ArH), 7.58–7.48 (2H, m, ArH), 3.97 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 3.92 (2H, dd, *J* = 12.5, 6.7 Hz, H_2), 3.31 (2H, t, *J* = 6.8 Hz, H_1), 1.91 (1H, t, *J* = 5.5 Hz, O*H*); **^{13}C NMR** (126 MHz) δ_C 151.35 (ArCO), 150.36 (ArCO), 128.27 (ArC), 127.71 (ArC), 127.39 (ArC), 126.75 (ArCH), 126.67 (ArCH), 122.63 (ArCH), 116.42 (ArCBr), 62.37 (OCH_3), 62.25 (OCH_3), 61.36 (C-2), 33.80 (C-1); **HRMS** (ESI+): Found M^+ + H 374.1978, $C_{21}H_{27}NO_5$ (M^+ + H) requires 374.4479, m/z 374.1978(M^+ + H, 100%).

7.3.18. Preparation of 2-(2-(benzyloxy)ethyl)-3-bromo-1,4-dimethoxynaphthalene 215

In a 100 cm^3 RB flask, 2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)ethanol **214** (1.25 g, 4.01 mmol) was dissolved in dry N,N-dimethylformamide (40 cm^3). The reaction was cooled to 0°C and sodium hydride (60% in oil, 0.18 g, 4.41 mmol, 1.1 equiv.) was slowly added followed by benzyl bromide (0.76 g, 0.55 cm^3, 4.41 mmol, 1.1 equiv.). The reaction was warmed to room temperature and stirred at this temperature for 18 h. The reaction was quenched with H_2O (100 cm^3) and the organic material extracted into diethyl ether (2 × 100 cm^3). The organic extract was washed with H_2O (100 cm^3) and brine (100 cm^3), dried over $MgSO_4$, filtered through celite and

the solvent removed *in vacuo*. Column chromatography with a 10% EtOAc/Hexane solution afforded the product **215** as a white solid (0.98g, 61%).



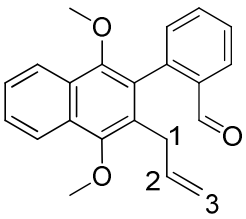
R_f = 0.66 (20% EtOAc /Hexane); **mp.** 63–65; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 2941, 2887 and 2864 (C–H), 1567 and 1496 (C=C), 1355 (C–O), 689(C–Br) ; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.11–8.00 (2H, m, ArH), 7.57–7.44 (2H, m, ArH), 7.37–7.21 (5H, m, ArH), 4.58 (2H, s, H_3), 3.95 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.75 (2H, t, *J* = 7.6 Hz, H_2), 3.36 (2H, t, *J* = 7.7 Hz, H_1); **^{13}C NMR** (75 MHz) δ_C = 151.43 (ArCO), 150.09 (ArCO), 138.45 (ArC), 128.31 (ArC), 128.13 (ArCH), 127.82 (ArCH), 127.64 (ArCH), 127.50 (ArCH), 127.41 (ArCH), 126.59 (ArC), 126.53 (ArC), 122.66 (ArCH), 122.55 (ArCH), 116.59 (ArCBr), 72.90 (C-3), 69.11 (C-2), 62.62 (OCH_3), 61.31 (OCH_3), 30.94 (C-1); **HRMS** (ESI+): Found M^+ + H 374.1978, $C_{21}H_{27}NO_5$ (M^+ + H) requires 374.4479, m/z 374.1978(M^+ + H, 100%).

7.4. Experimental prodecures pertaining to Chapter 6

7.4.1. Preparation of Suzuki products

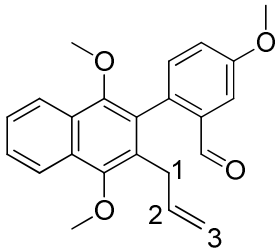
To a sealed microwave vessel was added 2-allyl-3-bromo-1,4-dimethoxynaphthalene (1.0 equiv.), boronic acid (1.6 equiv.), cesium fluoride (2 equiv.) and tetrakis(triphenylphosphine)palladium(0) (10% mol equiv.) in dimethoxyethane (2 cm^3/mmol of bromo-compound). The reaction mixture was irradiated at 150W at 150°C ofr 15 min by microwave reactor. The reaction was allowed to cool, diluted with H_2O (20 cm^3) and extracted into EtOAc (2 × 40 cm^3). The organic layer was consecutively washed with distilled water (40 cm^3) and brine (40 cm^3) before being dried over $MgSO_4$ and filtered through celite. The solvent was removed in vacuo and the residue purified by flash silica gel chromatography (5% EtOAc/Hexane) to afford the products as a yellow compounds.

7.4.1.1. Preparation of 2-(3-allyl-1,4-dimethoxynaphthalen-2-yl)benzaldehyde 315



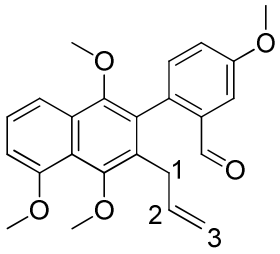
Yellow oil (0.85 g, 50%); **R_f** = 0.47 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3072, 2841 and 2747 (C–H stretch), 1664 (C=O), 1597 and 1482 (C=C), 1222 (C–O), 1000 and 923 (C–H bend); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 9.74 (1H, s, C*H*O), 8.18–8.05 (3H, m, Ar*H*), 7.67 (1H, m, ArH), 7.63–7.49 (3H, m, ArH), 7.38 (1H, ddd, *J* = 7.6, 1.3, 0.5 Hz, ArH), 5.68 (1H, ddt, *J* = 16.2, 10.1, 6.0 Hz, H_2), 4.81 (1H, dd, *J* = 10.1, 1.6 Hz, H_3), 4.56 (1H, dd, *J* = 17.1, 1.7 Hz, H_3), 3.97 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 3.39 (2H, dt, *J* = 5.8, 1.7 Hz, H_1); **^{13}C NMR** (126 MHz): δ_C = 192.20 (C=O), 150.78 (ArCO), 150.11 (ArCO), 140.21 (ArC), 136.09 (C-2), 134.40 (ArC), 133.23 (ArCH), 131.72 (ArCH), 128.92 (ArC), 128.15 (ArCH), 127.62 (ArC), 127.54 (ArC), 127.11 (ArCH), 126.77 (ArCH), 126.28 (ArCH), 122.89 (ArCH), 122.57 (ArCH), 115.81 (C-3), 62.45 (OCH_3), 61.22 (OCH_3), 31.84 (C-1); **HRMS** (ESI+): Found M^+ + H 333.1496, $C_{22}H_{20}O_3$ (M^+ + H) requires 333.1479, m/z 333.1496 (M^+ + H, 100%), 301.1233 (35), 289.1239 (50).

7.4.1.2. Preparation of 2-(3-allyl-1,4-dimethoxynaphthalen-2-yl)-5-methoxybenzaldehyde 316



Yellow oil (0.95 g, 43%); $\mathbf{R_f}$ = 0.67 (50% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3078, 2840 and 2765 (C–H stretch), 1688 (C=O), 1601 and 1498 (C=C), 1233 (C–O), 1000 and 923 (C–H bend); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 9.67 (1H, s, C*H*O), 7.62–7.49 (3H, m, ArH), 7.33–7.18 (2H, m, ArH), 5.69 (1H, ddt, *J* = 16.1, 10.1, 6.0 Hz, H_2), 4.83 (1H, dd,, *J* = 10.1, 1.5 Hz, H_3), 4.59 (1H, dd,, *J* = 17.1, 1.6 Hz, H_3), 3.97 (3H, s, OC*H*$_3$), 3.93 (3H, s, OC*H*$_3$), 3.46 (3H, s, OC*H*$_3$), 3.40 (2H, dt, J = 5.9, 1.5 Hz, H1); **^{13}C NMR** (75 MHz): δ_C = 192.08 (C=O), 159.39 (ArCO), 150.74 (ArCO), 150.47 (ArCO), 136.21 (C-2), 132.88 (ArCH), 128.86 (ArC), 127.98 (ArC), 127.82 (ArC), 127.62 (ArC), 126.71 (ArCH), 126.24 (ArCH), 122.90 (ArCH), 122.53 (ArCH), 120.96 (ArCH). 115.77 (C-3), 109.60 (ArCH), 62.43 (OCH_3), 61.15 (OCH_3), 55.55 (OCH_3), 31.86 (C-1); **HRMS** (ESI+): Found M^+ + H 363.1588, $C_{23}H_{22}O_4$ (M^+ + H) requires 363.1579, m/z 363.1588 (M^+ + H, 100%), 319.1336 (30).

7.4.1.3. Preparation of 2-(3-allyl-1,4,5-trimethoxynaphthalen-2-yl)-5-methoxybenzaldehyde 333

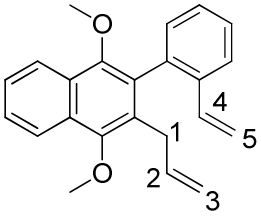


Yellow solid (0.68 g, 46%); $\mathbf{R_f}$ = 0.36 (20% EtOAc /Hexane); **mp.** 125–127; **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3094, 2931 and 2839 (C–H stretch), 1686 (C=O), 1602 and 1499 (C=C), 1265 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = δ 9.65 (1H, s, C*H*O), 7.71 (1H, d, *J* = 8.4 Hz, ArH), 7.56 (1H, dd, *J* = 10.0, 2.8 Hz, ArH), 7.43 (1H, t, *J* = 8.1 Hz, ArH), 7.25 (2H, ddd, *J* = 13.0, 12.5, 6.5 Hz, ArH), 6.94 (1H, d, *J* = 7.7 Hz, ArH), 5.73 (1H, ddt, *J* = 16.2, 10.2, 6.1 Hz, H_2), 4.81 (1H, dd, *J* = 10.1, 1.5 Hz, H_3), 4.57 (1H, dd, *J* = 17.1, 1.6 Hz, H_3), 4.04 (s, 3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.40–3.36 (2H, m, H_1); **^{13}C NMR** (126 MHz): δ_C = 192.11 (C=O), 159.36 (ArCO), 156.05 (ArCO), 150.92 (ArCO), 150.03 (ArCO), 136.67 (C-2), 135.17 (ArC), 132.93 (ArC), 132.80 (ArCH), 129.99 (ArC), 128.93 (ArC), 128.58 (ArCH), 126.41 (ArCH), 120.94 (ArCH), 115.56 (C-3), 115.26 (ArCH), 109.49 (ArCH), 106.76 (ArCH), 62.68 (OCH_3), 60.95 (OCH_3), 56.22 (OCH_3), 55.54 (OCH_3), 31.89 (C-1); **HRMS** (ESI+): Found M^+ + H 393.1699, $C_{24}H_{24}O_5$ (M^+ + H) requires 393.1679, m/z 393.1679 (M^+ + H, 100%).

7.4.2. Preparation of Wittig products

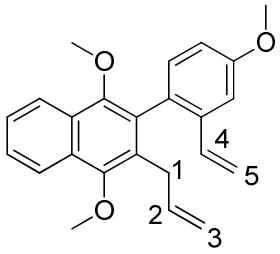
In a 50 cm^3 two necked RB flask fitted with a rubber septum, n-butyllithium (1.5 M, 1.6 cm3, 2.37 mmol, 2.5 equiv.) was added dropwise at room temperature to a suspension of methyltriphenylphosphonium bromide (0.85 g, 2.37 mmol, 2.5 equiv.) in dry THF (10 cm^3). The resulting orange solution was stirred for a further 30 minutes before being cooled to 0°C using an ice-bath. Aldehyde (0.95 mmol) in dry THF (5 cm^3) was added dropwise at 0°C to the resulting ylide. The reaction was then warmed to room temperature and stirred at this temperature for 18 h. The reaction was diluted with diethyl ether (50cm^3) and washed with H_2O (50 cm^3). The organic extract was dried over $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The resulting residue was purified by silica gel chromatography (5% EtOAc/Hexane) to afford the products as yellow oils.

7.4.2.1. Preparation of 2-allyl-1,4-dimethoxy3-(2-vinylphenyl)naphthalene 317



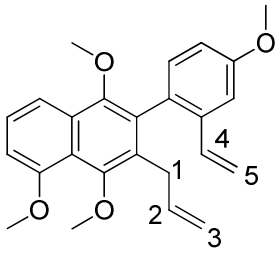
Yellow oil (0.28 g, 88%); $\mathbf{R_f}$ = 0.72 (20% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3072 and 2930 (C–H stretch), 1588, 1483 and (C=C), 1227 (C–O), 1006 and 910 (C–H bend); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.16–8.11 (2H, m, ArH), 7.72 (1H, dd, *J* = 7.7, 1.2 Hz, ArH), 7.58–7.47 (2H , m, ArH), 7.35 (2H, dtd, *J* = 20.7, 7.3, 1.2 Hz, ArH), 7.25–7.20 (1H, m, ArH), 6.41 (1H, dd, *J* = 17.6, 11.0 Hz, H_4), 5.76 – 5.59 (2H, m, H_2 and H_5 overlapping), 5.07 (1H, dd, *J* = 11.0, 1.1 Hz, H_5), 4.80 (dd, *J* = 17.0, 3.4, 1.6 Hz, H_3), 4.67 (1H, ddd, *J* = 10.1, 3.2, 1.5 Hz, H_3), 3.96 (3H, s, OCH_3), 3.55–3.44 (4H, m, OCH_3 and H_1 overlapping), 3.13 (1H, ddt, J = 14.9, 6.2, 1.5 Hz, H_1); **^{13}C NMR** (126 MHz): δ_C = 150.46 (ArCO), 149.79 (ArCO), 136.45 (C-2), 136.36 (ArC), 135.62 (ArC), 135.12 (C-4), 131.28 (ArCH), 131.17 (ArC), 128.57 (ArC), 128.39 (ArC), 127.95 (ArC), 127.79 (ArCH), 127.18 (ArCH), 126.23 (ArCH), 125.82 (ArCH), 124.60 (ArCH), 122.90 (ArCH), 122.41 (ArCH), 115.20 (C-3), 114.55 (C-5), 62.36 (OCH_3), 61.30 (OCH_3), 31.94 (C-1); **HRMS** (ESI+): Found M^+ + H 331.1698, $C_{23}H_{22}O_2$ (M^+ + H) requires 331.1679, m/z 331.1698 (M^+ + H, 95%), 289.1237 (50), 275.1073 (20).

7.4.2.2. Preparation of 2-allyl-1,4-dimethoxy-3-(4-methoxy-2-vinylphenyl)naphthalene 318



Yellow oil (0.23 g, 84%); $\mathbf{R_f}$ = 0.57 (20% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 2928 (C–H stretch), 1603 and 1490 (C=C), 1231 (C–O), 999 and 913 (C–H bend); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.12 (2H, dd, *J* = 7.2, 2.4 Hz, ArH), 7.57–7.47 (2H, m, ArH), 7.24 (2H, d, *J* = 3.4 Hz, ArH), 7.14 (1H, d, *J* = 8.4 Hz, ArH), 6.90 (1H, dd, *J* = 8.4, 2.6 Hz, ArH), 6.37 (1H, dd, *J* = 17.5, 11.0 Hz, H_4), 5.76–5.61 (2H, m, H_2 and H_5 overlapping), 5.07 (1H, dd, *J* = 11.0, 1.0 Hz, H_5), 4.81 (1H, dd, *J* = 10.1, 1.6 Hz, H_3), 4.69 (1H, dd, *J* = 17.1, 1.7 Hz, H_3), 3.96 (3H, s, OC*H*$_3$), 3.90 (3H, s, OC*H*$_3$), 3.51 (3H, s, OC*H*$_3$), 3.49–3.44 (1H, m, H_1), 3.14 (1H, dd, *J* = 14.9, 6.2, 1.6 Hz, H_1); **^{13}C NMR** (75 MHz): δ_C = 159.18 (ArCO), 150.40 (ArCO), 150.20 (ArCO), 137.48 (C-2), 136.57 (ArC), 135.19 (C-4), 132.29 (ArCH), 130.87 (ArCH), 128.86 (ArC), 128.53 (ArC), 128.26 (ArC), 127.95 (ArC), 126.20 (ArC), 125.79 (ArCH), 122.91, (ArCH), 122.40 (ArCH), 115.19 (C-3), 114.70 (C-5), 113.29 (ArCH), 109.48 (ArCH), 62.36 (OCH_3), 61.25 (OCH_3), 55.28 (OCH_3), 31.96 (C-1); **HRMS** (ESI+): Found M^+ + H 361.1799, $C_{24}H_{24}O_3$ (M^+ + H) requires 361.1779, m/z 361.1799 (M^+ + H, 100%), 279.0945 (75).

7.4.2.3. Preparation of 3-allyl-1,4,5-trimethoxy-2-(4-methoxy-2-vinylphenyl)naphthalene 334

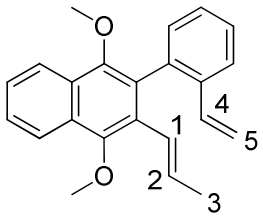


Yellow oil (0.41 g, 69%); $\mathbf{R_f}$ = 0.52 (20% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3078, 2932 and 2836 (C–H stretch), 1602 and 1493 (C=C), 1266 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.74 (1H, d, *J* = 8.4 Hz, ArH), 7.39 (1H, t, *J* = 8.1 Hz, ArH), 7.23 (1H, t, *J* = 6.5 Hz, ArH), 7.14 (1H, d, *J* = 8.4 Hz, ArH), 6.90 (2H, d, *J* = 6.8 Hz, ArH), 6.41–6.30 (1H, m, H_4), 5.73 (1H, ddt, *J* = 16.5, 10.2, 6.2 Hz, H_2), 5.66 (d, *J* = 17.5 Hz, H_5), 5.06 (1H, d, *J* = 11.2 Hz, H_5), 4.79 (1H, dd, *J* = 10.0, 1.3 Hz, H_3), 4.67 (1H, dd, *J* = 17.1, 1.5 Hz, H_3), 4.02 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.51 (1H, dd, *J* = 14.8, 6.1 Hz, H_1), 3.48 (3H, s, OCH_3), 3.11 (1H, dd, *J* = 14.7, 6.3 Hz, H_1); **^{13}C NMR** (126 MHz): δ_C = 159.14 (ArCO), 156.01 (ArCO), 150.60 (ArCO), 149.79 (ArCO), 137.35 (ArC), 137.00 (C-2), 135.20 (C-4), 132.17 (ArCH), 131.62 (ArC), 130.31 (ArC), 129.84 (ArC), 128.27 (ArC), 125.89 (ArCH), 120.59 (ArC), 115.33 (ArCH), 114.99 (C-3), 114.59 (C-5), 113.22 (ArCH), 109.45 (ArCH), 106.29 (ArCH), 62.60 (OCH_3), 61.03 (OCH_3), 56.16 (OCH_3), 55.22 (OCH_3), 31.92 (C-1);**HRMS** (ESI+): Found M^+ + H 391.1898, $C_{25}H_{26}O_4$ (M^+ + H) requires 391.1879, m/z 391.1898 (M^+ + H, 100%).

7.4.3. Preparation of Isomerisation products

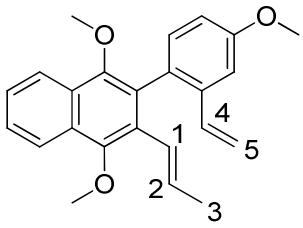
A 50 cm^3 RB flask, alkene (0.760 mmol) was dissolved in dry THF (10 cm^3). Potassium *tert*-butoxide (4 equiv.) in dry THF (10 cm^3) was slowly added and the resulting reaction mixture was stirred at room temperature for 4 h, under argon. The mixture was poured into sat. aq. ammonium chloride (20 cm^3) and the organic material extracted into EtOAc (4 × 50 cm^3). The organic extract was washed in succession with H_2O (100 cm^3) and brine (100 cm^3), dried over $MgSO_4$ and filtered through celite. The solvent was removed *in vacuo* and the residue purified by flash silica gel column chromatography (10% EtOAc/Hexane) to yield the products as clear oils

7.4.3.1. Preparation of (*E*)-1,4-dimethoxy-2-(prop-1-en-1yl)-3-(2vinylphenyl)naphthalene 322



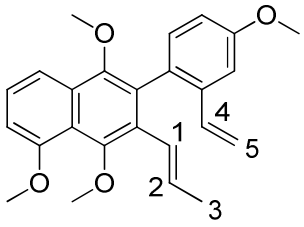
Yellow oil (0.38 g, 94%); **R_f** = 0.72 (20% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3066 (C–H stretch), 1626 and 1480 (C=C), 1269 (C–O), 967 and 910 (C–H bend); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.13 (2H, m, Ar*H*), 7.71–7.64 (1H, m, ArH), 7.55–7.41 (2H, m, ArH), 7.38–7.26 (2H, m, ArH), 7.21 (1H, dd, *J* = 7.3, 1.7 Hz, ArH), 6.46 (1H, dd, *J* = 17.5, 11.0 Hz, H_4), 6.13 (1H, d, *J* = 17.1 Hz, H_1), 6.07–5.93 (1H, m, H_2), 5.64 (1H, dd, *J* = 17.5, 0.9 Hz, H_5), 5.03 (1H, dd, *J* = 11.0, 0.9 Hz, H_5), 3.83 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 1.65 (3H, dd, *J* = 6.2, 0.9 Hz, H_3); **^{13}C NMR** (75 MHz): δ_C = 149.96 (ArCO), 149.60 (ArCO), 136.54 (ArC), 136.23 (ArC), 135.30 (C-4), 131.82 (C-2), 131.23 (ArCH), 130.11 (ArC), 128.92 (ArC), 127.76 (ArC), 127.56 (ArCH), 127.33 (ArCH), 126.79 (ArC), 126.32 (ArCH), 125.97 (ArCH), 124.77 (C-1), 124.61 (ArCH), 122.67 (ArCH), 122.58 (ArCH), 114.28 (C-5), 61.01 (OCH_3), 60.59 (OCH_3), 19.67 (C-3); **HRMS** (ESI+): Found M^+ + H 331.1693, $C_{23}H_{22}O_2$ (M^+ + H) requires 331.1679, m/z 331.1679 (M^+ + H, 45%), 317.1543 (85), 315.1390 (80), 289.1237 (50).

7.4.3.2. Preparation of (*E*)-1,4-dimethoxy-2-(4-methoxy-2vinylphenyl)-3-(prop-1-en-1yl)naphthalene 323



Yellow oil (0.23 g, 84%); **R_f** = 0.63 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2931 and 2837 (C–H stretch), 1602 and 1492 (C=C), 1228 (C–O), 967 and 908 (C–H bend); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.19–8.06 (2H, m, ArH), 7.55–7.45 (2H, m, ArH), 7.25–7.21 (1H, m, ArH), 7.13 (1H, dd, *J* = 8.4, 2.9 Hz, ArH), 6.92 (1H, dd, *J* =8.4, 2.4 Hz, ArH), 6.46–6.37 (1H, m, H_4), 6.12 (1H, dd, *J* = 15.9, 1.9 Hz, H_2), 6.08–5.98 (1H, m, H_1), 5.65 (1H, dd,, *J* = 17.5, 2.4 Hz, H_5), 5.06 (1H, dd,, *J* = 11.0, 1.0 Hz, H_5), 3.89 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.47 (3H, s, OCH_3), 1.69 (3H, dd, *J* = 4.8, 2.6 Hz, H_3); **^{13}C NMR** (126 MHz): δ_C = 159.02(ArCO), 149.95 (ArCO), 149.87 (ArCO), 137.65 (ArC), 135.39 (C-4), 132.26 (ArC), 131.77 (C-1), 129.82 (ArC), 128.86 (ArC), 128.80 (ArC), 127.72 (ArC), 127.18 (ArC), 126.26 (ArCH), 125.91 (ArCH), 124.86 (C-2), 122.67 (ArCH), 122.56 (ArCH), 114.37 (C-5), 113.42 (ArCH), 109.54 (ArCH), 61.02 (OCH_3), 60.63 (OCH_3), 55.24 (OCH_3), 19.76 (C-3); **HRMS** (ESI+): Found M^+ + H 361.1804, $C_{24}H_{24}O_3$ (M^+ + H) requires 361.1779, m/z 361.1804 (M^+ + H, 100%), 345.1495 (50), 319.1352 (35), 305.1188 (15).

7.4.3.3. Preparation of (*E*)-1,4-dimethoxy-2-(4-methoxy-2vinylphenyl)-3-(prop-1-en-1yl)naphthalene 335

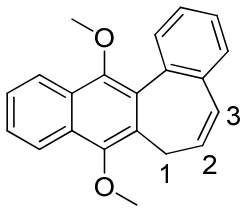


Yellow oil (86.3 mg, 73%); $\mathbf{R_f}$ = 0.34 (20% EtOAc /Hexane); **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 2993, 2934and 2837 (C–H stretch), 1605 and 1495 (C=C), 1244 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.71 (1H, d, *J* = 8.4 Hz, ArH), 7.42–7.32 (1H, m, ArH), 7.21 (1H, d, *J* = 2.6 Hz, ArH), 7.12 (1H, t, *J* = 6.6 Hz, ArH), 6.93–6.84 (2H, m, ArH), 6.40 (1H, dd, *J* = 17.5, 11.0 Hz, H_4), 6.22–6.09 (1H, m, H_1), 5.84 (1H, dqd, *J* = 15.9, 6.5, 1.0 Hz, H_2), 5.63 (1H, d, *J* = 17.5 Hz, H_5), 5.05 (1H, d, *J* = 11.2 Hz, H_5), 4.02 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 1.65–1.62 (3H, m, H3);**^{13}C NMR** (126 MHz): δ_C = 158.93 (ArCO), 156.50 (ArCO), 150.32 (ArCO), 149.70 (ArCO), 137.49 (ArC), 135.41 (C-4), 132.22 (ArCH), 131.64 (C-2), 130.48 (ArC), 130.14 (ArC), 128.87 (ArC), 128.77 (ArC), 126.02 (ArCH), 124.70 (C-1), 120.76 (ArC), 115.28 (ArCH), 114.31 (C-5), 113.35 (ArCH), 109.48 (ArCH), 106.51 (ArCH), 61.18 (OCH_3), 60.82 (OCH_3), 56.26 (OCH_3), 55.23 (OCH_3), 19.70 (C-3);); **HRMS** (ESI+): Found M^+ + H 391.1896, $C_{25}H_{26}O_4$ (M^+ + H) requires 391.1879, m/z 391.1896 (M^+ + H, 100%), 376.1648 (20), 375.1589 (35), 3.49.1436(35).

7.4.4. General Method for RCM ring closure

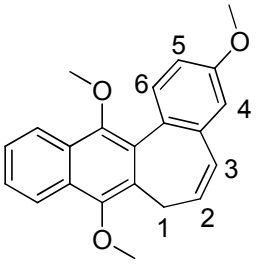
In a 50 cm^3 RB flasked fitted with a condenser was added the di-alkene (0.83 mmol) in dry CH_2Cl_2 (10 cm^3/ mmol of dialkene). To this was added Grubbs II catalyst (15% mol equiv.) and the reaction was heated under relux for 18 h under an argon atmosphere. The reaction was cooled to room temperature and the solvent removed *in vacuo*. The residue was purified by flash silica column chromatography (5% EtOAc/ Hexane) to yield the products as off white solids.

7.4.4.1. Preparation of 8,13-dimethoxy-7*H*-benzo[3,4]cyclohepta[1,2-*b*]naphthalene 320



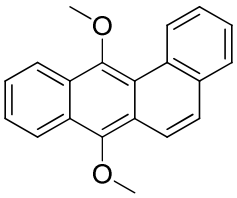
Pale yellow solid (0.23 g, 98%); $\mathbf{R_f}$ = 0.67 (20% EtOAc /Hexane); **mp.** 121–123;**IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$: 3019, 2994 (C–H aromatic stretch), 2928 and 2837 (CH_2 stretch), 1588 and 1496 (C=C), 1225 (C–O), 965 and 925 (C–H bend); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.23–8.17 (1H, m, ArH), 8.11 (1H, dd, *J* = 7.2, 1.9 Hz, ArH), 7.97 (1H, d, *J* = 8.0 Hz, ArH), 7.56–7.45 (2H, m, ArH), 7.43–7.29 (3H, m, ArH), 6.61 (1H, dd, *J* = 9.9, 1.5 Hz, H_3), 6.31 (1H, ddd, *J* = 9.9, 8.2, 5.8 Hz, H_2), 3.97 (3H, s, OCH_3), 3.87 (1H, ddd, *J* = 12.9, 8.2, 0.7 Hz, H_1), 3.26 (3H, s, OCH_3), 2.70 (1H, ddd, *J* = 12.9, 5.7, 2.1, H_1); **^{13}C NMR** (75 MHz): δ_C = 150.73 (ArCO), 146.40 (ArCO), 136.78 (ArC), 135.42 (ArC), 135.20 (ArC), 132.36 (ArCH),132.18 (C-2), 129.88 (C-3), 128.46 (ArCH), 128.35 (ArC), 127.94 (ArC), 127.83 (ArC), 127.08 (ArCH), 126.37 (ArCH), 125.57 (ArCH), 125.46 (ArCH), 122.91 (ArCH), 121.94 (ArCH), 62.55 (OCH_3), 60.50 (OCH_3), 25.52 (C-1); **HRMS** (ESI+): Found M^+ + H 303.1387, $C_{21}H_{18}O_2$ (M^+ + H) requires 303.1379, m/z 303.1387 (M^+ + H, 100%), 288.1122 (75), 247.1677 (50), 229.1394 (30).

7.4.4.2. Preparation of 3,8,13-trimethoxy-7H-benzo[3,4]cyclohepta[1,2-*b*]naphthalene 321



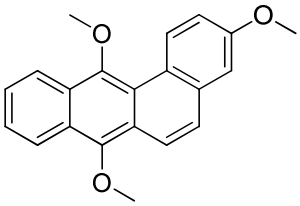
Pale yellow solid (0.12 g, 87%); **R_f** = 0.59 (20% EtOAc /Hexane); **mp.** 138–140; **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3073, 3024 (C–H aromatic stretch), 2929 and 2835 (CH_2 stretch), 1632 (C=C, conjugated), 1602 and 1494 (C=C), 1237 (C–O), 966 and 919 (C–H bend); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.22–8.07 (2H, m, ArH), 7.91 (1H, d, *J* = 8.7 Hz, H_6), 7.55–7.43 (2H, m, ArH), 6.91 (1H, dd, *J* = 8.7, 2.8 Hz, H_5), 6.85 (1H, d, *J* = 2.7 Hz, H_4), 6.57 (1H, dd, *J* = 9.7, 1.4 Hz, H_3), 6.30 (1H, ddd, *J* = 9.9, 8.2, 5.8 Hz, H_2), 3.96 (3H, s, OCH_3), 3.94–3.81 (4H, m, H_1 and OCH_3), 3.28 (3H, s, OCH_3), 2.70 (1H, ddd, *J* = 12.9, 5.7, 2.1 Hz, H_1); **^{13}C NMR** (75 MHz): δ_C = 158.37 (ArCO), 150.44 (ArCO), 146.45 (ArCO), 138.04, 134.71 (C-6), 133.69 (ArC), 132.23 (C-2), 129.85 (C-3), 128.20 (ArC), 128.08 (ArC), 127.81 (ArC), 127.66 (ArH), 126.11 (ArCH), 125.48 (ArCH), 122.78 (ArCH), 121.90 (ArCH), 112.28 (ArCH), 62.50 (OCH_3), 60.33 (OCH_3), 55.24 (OCH_3), 25.57 (C-1); **HRMS** (ESI+): Found M^+ + H 333.1485, $C_{22}H_{20}O_3$ (M^+ + H) requires 333.1479, m/z 333.1485 (M^+ + H, 100%), 332.1442 (50).

7.4.4.3. Preparation of 7,12-dimethoxytetraphene 294



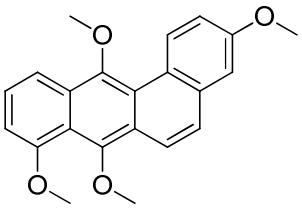
Yellow solid (0.13 g, 85%); **R_f** = 0.61 (20% EtOAc /Hexane); **mp.** 125–127 (lit 136–137)[134]; **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2931and 2837 (C–H aromatic stretch), 1593, 1495 and 1448 (C=C), 1252 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 9.67 (1H, d, *J* = 8.4 Hz, ArH), 8.50–8.41 (1H, m, ArH), 8.37–8.31 (1H, m, ArH), 8.14 (1H, d, *J* = 9.2 Hz, ArH), 7.84 (1H, d, *J* = 7.3 Hz, ArH), 7.71–7.65 (1H, m, ArH), 7.65–7.59 (4H, m, ArH), 4.12 (3H, s, OCH_3), 3.97 (3H, s, OCH_3);**^{13}C NMR** (125 MHz): δ_C = 151.14 (ArCO), 148.64 (ArCO), 132.67 (ArC), 130.00 (ArC), 128.42 (ArCH), 128.22 (ArCH), 127.62 (ArCH), 127.37 (ArC), 127.29 (ArCH), 127.02 (ArCH), 126.51 (ArC), 126.04 (ArCH), 125.93 (ArCH), 124.26 (ArC), 123.19 (ArCH), 122.29 (ArCH), 121.05 (ArCH), 120.76 (ArC), 63.15 (OCH_3), 60.89 (OCH_3); **HRMS** (ESI+): Found M^+ + H 289.1010, $C_{20}H_{16}O_2$ (M^+ + H) requires 289.1279, m/z 289.1010 (M^+ + H, 100%), 273.0919 (90).

7.4.4.4. Preparation of 3,7,12-trimethoxytetraphene 314



Yellow solid (0.030 g, 43%); **R_f** = 0.63 (20% EtOAc /Hexane); **mp.** 157–159 (lit 164–165)[145]; **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2933 (C–H aromatic stretch), 1606 and 1494 (C=C), 1267 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 9.58 (1H, d, *J* = 9.2 Hz, ArH), 8.43 (1H, dd, *J* = 7.4, 1.8 Hz, ArH), 8.32 (1H, dd, *J* = 7.3, 1.8 Hz, ArH), 8.13 (1H, d, *J* = 9.3 Hz, ArH), 7.64–7.53 (3H, m, ArH), 7.31–7.23 (2H, m, ArH), 4.11 (3H, s, OC*H*$_3$), 3.98 (3H, s, OC*H*$_3$), 3.96 (3H, s, OC*H*$_3$); **^{13}C NMR** (126 MHz): δ_C = 158.32 (ArCO), 150.08 (ArCO), 148.76 (ArCO), 134.39 (ArC), 129.86 (ArCH), 127.41 (ArC), 127.37 (ArCH), 125.91 (ArCH), 125.61 (ArCH), 125.44 (ArC), 123.74 (ArC), 123.72 (ArC), 122.98 (ArCH), 122.31 (ArCH), 121.72 (ArCH), 120.88 (ArC). 115.95 (ArCH), 110.03 (ArCH), 63.18 (OCH_3), 60.72 (OCH_3), 55.38 (OCH_3); **HRMS** (ESI+): Found M^+ + H 319.1259, $C_{21}H_{18}O_3$ (M^+) requires 319.1379, m/z 319.1259 (M^+, 90%), 318.1262 (100), 303.1032 (25).

7.4.4.5. Preparation of 3,7,8,12-tetramethoxytetraphene 336

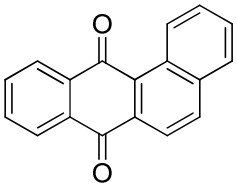


Yellow solid (53 mg, 84%); **R_f** = 0.41 (20% EtOAc /Hexane); **mp.** 176–178; **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3005, 2934 and 2834 (C–H), 1608 and 1499 (C=C), 1253 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 9.56 (1H, d, *J* = 9.1 Hz, ArH), 8.23 (1H, d, *J* = 9.3 Hz, ArH), 8.04 (1H, d, *J* = 8.6 Hz, ArH), 7.55 (1H, d, *J* = 9.3 Hz, ArH), 7.51–7.43 (1H, m, ArH), 7.28 (2H, dd, *J* = 9.2, 2.8 Hz, ArH), 6.90 (1H, d, *J* = 7.5 Hz, ArH), 4.09 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 3.91 (3H, s, OCH_3); **^{13}C NMR** (126 MHz): δ_C = 158.41 (ArCO), 156.35 (ArCO), 149.60 (ArCO), 149.14 (ArCO), 134.68 (ArC), 129.96 (ArCH), 129.65 (ArC), 127.09 (ArCH), 125.79 (ArCH), 124.78 (ArC), 123.38 (ArC), 122.24 (ArCH), 121.41 (ArC), 118.25 (ArC), 115.88 (ArCH), 115.34 (ArCH), 109.71 (ArCH), 104.60 (ArCH), 63.39 (OCH_3), 60.45 (OCH_3), 56.21 (OCH_3), 55.37 (OCH_3); **HRMS** (ESI+): Found M^+ + H 349.1426, $C_{22}H_{20}O_4$ (M^+) requires 349.1479, m/z 349.1479 (M^+, 100%), 334.1201 (30).

7.4.5. General Method for oxidation of naphthalenes

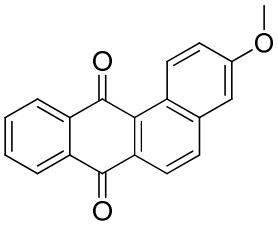
In a 50 cm^3 RB flasked arene (0.83 mmol) was dissolved in acetonitrile (10 cm^3/ mmol of arene). CAN (2.5 equiv.) was added and the reaction was stirred for 5 min. Sodium bicarbonate was added and the organic material extracted in EtOAc (3 × 10 cm^3). The organic layer was then dried over anhydrous $MgSO_4$ before being purified by silica column chromatography (10% EtOAc/ Hexane) to yield the products as yellow solids.

7.4.5.1. Preparation of tetraphene-7,12-dione 341



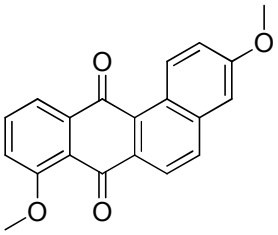
Yellow solid (19.1 mg, 76%); $\mathbf{R_f}$ = 0.61 (20% EtOAc /Hexane); **mp.** 166–169 (lit 168–169)[134]; **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2918 and 2850 (C–H), 1728 and 1661 (C=O), 1587 and 1507 (C=C), 1277 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 9.72 (1H, d, *J* = 8.8 Hz, ArH), 8.39 (1H, d, *J* = 8.5 Hz, ArH), 8.29 (2H, dd, *J* = 24.2, 7.3 Hz, ArH), 8.21 (1H, d, *J* = 8.5 Hz, ArH), 7.92 (1H, d, *J* = 8.1 Hz, ArH), 7.78 (3H, tdd, *J* = 9.4, 5.4, 4.3 Hz, ArH), 7.67 (1H, t, *J* = 7.3 Hz, ArH); **^{13}C NMR** (126 MHz): δ_C = 186.21 (C=O), 184.00 (C=O), 136.71 (ArC), 135.33 (ArCH), 135.09 (ArC), 134.22 (ArCH), 134.06 (ArC), 133.50 (ArCH), 132.25 (ArC), 130.55 (ArC), 129.95 (ArCH), 129.39 (ArC), 128.78 (ArCH), 128.73 (ArCH), 127.25 (ArCH), 126.49 (ArCH), 122.53 (ArCH); **HRMS** (ESI+): Found M^+ + H 259.0747, $C_{18}H_{10}O_2$ (M^+ + H) requires 259.0779, m/z 259.0747 (M^+ + H, 100%), 234.2048 (25), 224.1323 (10).

7.4.5.2. Preparation of 3-methoxytetraphene-7,12-dione 342



Yellow solid (0.023 g, 87%); **R_f** = 0.61 (20% EtOAc /Hexane); **mp.** 158–160 (lit 162–163)[146]; **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3010, 2917 and 2849 (C–H), 1734 and 1657 (C=O), 1610 and 1503 (C=C), 1264 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 9.61 (1H, d, *J* = 9.6 Hz, ArH), 8.34 (1H, d, *J* = 8.6 Hz, ArH), 8.30–8.21 (2H, m, ArH), 8.06 (1H, d, *J* = 8.6 Hz, ArH), 7.82–7.71 (2H, m, ArH), 7.38 (1H, dd, *J* = 9.6, 2.8 Hz, ArH), 7.18 (1H, t, *J* = 5.0 Hz, ArH), 3.97 (3H, s, OCH_3); **^{13}C NMR** (126 MHz): δ_C = 186.38 (C=O), 183.81 (C=O), 159.60 (ArCO), 138.88 (ArC), 135.04 (ArC), 134.01 (ArCH), 133.77 (ArCH), 133.46 (ArCH), 132.38 (ArC), 132.09 (ArC), 130.40 (ArCH), 129.45 (ArC), 127.17 (ArCH), 126.41 (ArCH), 125.69 (ArC), 123.35 (ArCH), 122.39 (ArCH), 106.74 (ArCH), 55.39 (OCH_3); **HRMS** (ESI+): Found M^+ + H 289.0805, $C_{19}H_{12}O_3$ (M^+ + H) requires 289.0879, m/z 289.0805 (M^+ + H, 100%).

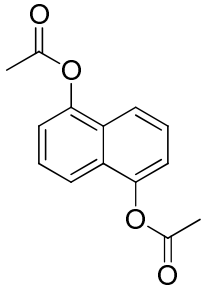
7.4.5.3. Preparation of 3,8-dimethoxytetraphene-7,12-dione 343



Yellow solid (53 mg, 84%); **R_f** = 0.61 (20% EtOAc /Hexane); **mp.** 202–204 (lit 206–207)[147]; **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 3089, 2925 and 2849 (C–H), 1654 and 1618 (C=O), 1587 and 1471 (C=C), 1268 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 9.52 (1H, d, *J* = 9.5 Hz, ArH), 8.32 (1H, d, *J* = 8.6 Hz, ArH), 8.06 (1H, d, *J* = 8.6 Hz, ArH), 7.93 (1H, d, *J* = 7.6 Hz, ArH), 7.72 (1H, t, *J* = 8.1 Hz, ArH), 7.38 (1H, dd, *J* = 9.5, 2.6 Hz, ArH), 7.31 (1H, d, *J* = 8.4 Hz, ArH), 7.19 (1H, d, *J* = 2.5 Hz, ArH), 4.06 (3H, s, OCH_3), 3.97 (3H, s, OCH_3); **^{13}C NMR** (126 MHz): δ_C = 186.50 (C=O), 183.20 (C=O), 159.64 (ArCO), 159.42 (ArCO), 138.22 (ArC), 137.46 (ArC), 134.90 (ArCH), 133.80 (ArCH), 130.11 (ArCH), 128.48 (ArC), 125.14 (ArC), 123.58 (ArCH), 122.21 (ArCH), 120.63 (ArC), 119.78 (ArCH), 117.15 (ArCH), 111.52 (ArC), 106.73 (ArCH), 56.57 (OCH_3), 55.39 (OCH_3); **HRMS** (ESI+): Found M^+ + H 319.0957, $C_{20}H_{14}O_4$ (M^+ + H) requires 319.0979, m/z 319.0957 (M^+ + H, 100%).

7.4.6. Preparation of 1,5-diacetoxynaphthalene 328

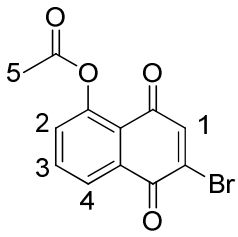
In a 250 cm^3 RB flask was placed 1,5-dihydroxynaphthalene **327** (10.77 g, 67.24 mmol) followed by pyridine (53.19 g, 55.0 cm^3, 0.672 mol, 10 equiv.) and acetic anhydride (61.78 g, 60.0 cm^3, 0.605 mol, 9.0 equiv.). The reaction was stirred at room temperature for 18 h. H_2O (100 cm^3) was added to quench the reaction causing the product to precipitate. The precipitate was filtered and washed with H_2O (5 × 100 cm^3) to afford the product **328** as a brown-red solid (12.18 g, 81%).[137]



R_f = 0.20 (20% EtOAc /Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.78 (2H, d, *J* = 8.1 Hz, ArH),7.51 (2H, t, *J* = 7. 6 Hz, ArH), 7.29 (2H, d, *J* = 7.1 Hz, ArH), 2.47 (6H, s, 2 X CH_3); **^{13}C NMR** (126 MHz): δ_C = 169.26 (C=O), 146.76 (ArCO), 128.17 (ArC), 126.05 (ArCH), 119.30 (ArCH), 118.81 (ArCH), 21.02 ($\underline{C}H_3$).

7.4.7. Preparation of 5-acetoxy-2-bromo-1,4-naphthalenedione 251

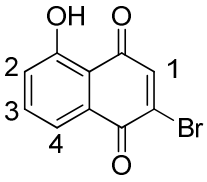
In a 1000 cm^3 RB flask fitted with a dropping funnel, N-bromosuccinamide (NBS) (14.64 g, 82.01 mmol) was dissolved in acetic acid (400 cm^3) and H_2O (200 cm^3) and the reaction heated to 65 °C. The dropping funnel was charged with 1,5-dihydroxynaphthalene **328** (5.01 g, 20.50 mmol) in warm acetic acid (200 cm^3) and this solution was added dropwise to the NBS solution. After complete addition, the reaction was maintained at 65 °C for a further 45 min. The cooled reaction was then extracted with chloroform (4 × 100cm^3) and the organic extracts combined. The organic phase was washed with H_2O (4 × 200cm^3) and brine (200cm^3) and dried over $MgSO_4$ before being concentrated *in vacuo*. Recrystallization from ethanol afforded the product **251** as yellow granules (5.75 g, 95%).[137]



R_f = 0.07 (20% EtOAc /Hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 8.09 (1H, dd, *J* = 7.6, 1.6 Hz, H_4), 7.96 (1H, s, H_1), 7.67 – 7.53 (2H, m, H_2 and H_3 overlapping), 2.52 (3H, s, H_5); **^{13}C NMR** (75 MHz): δ_C = 174.88 (C=O), 167.94 (C=O), 148.73 (ArCO), 134.03 (C–Br), 131.01(C-1), 129.96 (ArCH), 126.75 (ArC), 124.88 (ArCH), 119.97 (ArCH), 21.64 (C-5).

7.4.8. Preparation of 2-bromo-5-hydroxy-1,4-naphthalenedione 329

3 N HCl (60 cm^3) was added to a suspension of 5-acetoxy-2-bromo-1,4-naphthalenedione **251** (5.16 g, 17.48 mmol) in ethanol (200 cm^3). The suspension was heated gently under reflux for 90mins. The reaction mixture was concentrated *in vacuo* and the resulting residue extracted with chloroform (3 × 100cm^3). The organic extracts were combined and washed with H_2O (4 × 200cm^3) and brine (200 cm^3) before being dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Column chromatography (5% EtOAc/ Hexane) furnished the product as a yellow solid **329** (3.03 g, 69%).[137]

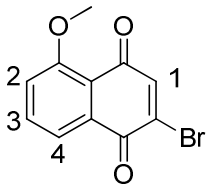


R_f = 0.47 (20% EtOAc /Hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H = 11.81 (1H, s, O*H*), 7.77–7.71 (1H, m, ArH), 7.65 (1H, t, *J* = 7.9 Hz, ArH), 7.50 (1H, s, H_1), 7.32 (1H, dd, J = 8.4, 1.0 Hz, ArH); **^{13}C NMR** (75 MHz): δ_C = 187.90 (C=O), 177.29 (C=O), 161.67 (C=O), 147.13 (ArCO), 136.50 (C-1), 135.86 (ArCH), 131.12 (ArC), 125.30 (ArCH), 120.70 (ArCH), 114.61 (ArC).

7.4.9. Preparation of 2-bromo-5-methoxy-1,4-naphthalenedione 326

In a 100 cm^3 RB flask, 2-bromo-5-hydroxy-1,4-naphthalenedione **329** (3.03 g, 11.98 mmol) was dissolved in dry CH_2Cl_2 (40 cm^3) followed by addition of silver oxide (10.01 g, 0.13 mol, 11 equiv.). To this suspension was added methyliodide (3.74 g, 1.7 cm^3, 26.35 mmol, 2.2 equiv.) and the reaction mixture was stirred for 24 h under argon at room temperature. The suspension was filtered through celite and the solvent removed *in vacuo*. The resulting residue was purified

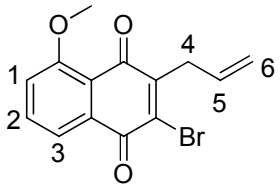
by column chromatography (20% EtOAc/ Hexane) to give the product as a yellow solid **326** (1.35 g, 43%).[137]



R_f = 0.07 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}):3043 and 2921 (C–H), 1674 and 1648 (C=O), 1342 (C-O), 666 (C–Br); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.84 (1H, dd, *J* = 7.7, 1.0 Hz, ArH), 7.72–7.67 (1H, m, ArH), 7.35 (1H, d, *J* = 8.5 Hz, ArH), 4.02 (3H, s, OCH_3); **^{13}C NMR** (126 MHz): δ_C = 181.50 (C=O), 178.30 (C=O), 160.02 (ArCO), 142.35 (C-1), 136.90 (ArC), 135.09 (C-3), 133.12 (ArC), 120.67 (C-4), 119.36 (C-2), 118.49 (ArCBr), 56.60 (OCH_3).

7.4.10. Preparation of 3-allyl-2-bromo-5-methoxy-1,4-naphthoquinone 329

To a mixture of 2-bromo-5-methoxy-1,4-naphthoquinone **326** (3.55g, 13.29 mmol) and silver nitrate (1.16 g, 6.64 mmol, 0.5 equiv.) in dry MeCN (220 cm^3) was added vinyl acetic acid (1.72 g, 2.0 cm^3, 19.93 mmol, 1.5 equiv.). The reaction mixture was heated to 65 °C and ammonium persulphate (6.04 g, 26.58 mmol, 2.0 equiv.) in distilled water (180 cm^3) was added dropwise to the reaction mixture over 30 min. After stirring for 16 hours at 65 °C under argon, the cooled reaction mixture was extracted into EtOAc (4 × 100 cm^3) washed sequentially with $NaHCO_3$ (2 × 100 cm^3) followed by brine (100 cm^3) and dried over MgSO4. After filtering through celite and the solvent was removed *in vacuo*, the crude product was purified by silica gel chromatography (20–30% EtOAc/Hexane) to yield the product as a yellow solid **329** (0.95 g, 79%).[138]

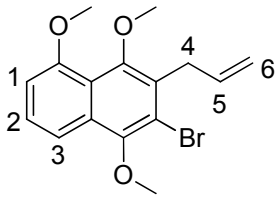


R_f = 0.31 (30% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2928 and 2841 (C–H), 1604 and 1468 (Ar-C=C), 1255 (C–O), 1007 and 909 (Allyl-C=C); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.82 (1H, dd, *J* = 7.7, 1.0 Hz, H_1), 7.67 (1H, dd, *J* = 10.2, 6.0 Hz, H_2), 7.32 (1H, d, *J* = 8.4, 0.6 Hz, H_3), 5.86 (1H, ddt, *J* = 16.7, 10.0, 6.6 Hz, H_5), 5.27 (1H, dq, *J* = 17.1, 1.5 Hz, H_6), 5.13 (1H, ddd, *J* = 10.0, 2.6, 1.3 Hz, H_6), 4.02 (3H, s, OCH_3), 3.60 (2H, dt, *J* = 6.6, 1.4 Hz, H_4); **^{13}C NMR** (126 MHz): δ_C = 180.29 (C=O), 178.14 (C=O), 160.08 (ArCO), 150.67 (ArC), 136.61 (ArCBr),

134.94 (C-5), 133.34 (ArC), 131.74 (C-2), 120.31 (C-3), 119.21 (ArC), 118.23 (C-1), 118.18 (C-6), 56.56 (OCH_3), 35.76 (C-4).

7.4.11. Preparation of 3-allyl-2-bromo-1,4,5-trimethoxynaphthalene 330

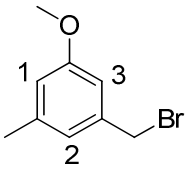
To a clear solution of 3-allyl-2-bromo-5-methoxy-1,4-naphthoquinone **329** (0.47 g, 1.53 mmol) in dry THF (25 cm^3) was added sodium dithionite (1.62 g, 9.19 mmol, 6 equiv.) in H_2O (10 cm^3) and TBAI (0.05 g, 0.14 mmol, 0.09 equiv.). The reaction was stirred at room temperature under argon for 30 minutes following addition of potassium hydroxide (2.02 g, 35.23 mmol, 23 equiv.) in H_2O (100 cm^3) was added. The reaction was stirred for 1 hour and dimethyl sulfate (4.06 g, 3.1 cm3, 32.17 mmol, 21 equiv.) was added. The reaction mixture was stirred for 18 hours before being quenched with 25% ammonia (50 cm^3) and the organic material extracted into EtOAc (3 × 100 cm^3). The organic layer was sequentially washed with distilled water (100 cm^3), 10% HCl (100 cm^3), brine (100 cm^3) and distilled water (100 cm^3). The organic extract was dried over $MgSO_4$, filtered through celite and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (5% EtOAc/Hexane) to afford the product as a yellow solid **330** (1.2836g, 75%).[138]



R_f = 0.67 (50% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2930 and 2835 (C–H), 1611 and 1494 (C=C), 1243 (C–O), 602 (C–Br); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 7.70 (1H, dd, *J* = 8.4, 0.6 Hz, H_1), 7.38 (1H, dd, *J* = 8.3, 7.9 Hz,, H_2), 6.87 (1H, dd, *J* = 7.7, 0.5 Hz, H_3), 6.06 (1H, ddt, *J* = 16.2, 10.3, 5.9 Hz, H_5), 5.05 (1H, ddq, *J* = 17.0, 15.4, 1.7 Hz, H_6) 3.97 (3H, s, OCH_3), 3.92 (2H, dt, *J* = 6.6, 1.4 Hz, H_4), 3.80–3.78 (5H, m, OCH_3 and H_4 overlapping); **^{13}C NMR** (126 MHz): δ_C = 156.05 (ArCO), 151.19 (ArCO), 149.69 (ArCO), 136.14 (C-5), 130.41 (ArC), 129.69 (ArC), 126.67 (ArCH), 120.02 (ArC), 117.46 (C-Br), 115.69 (C-6), 114.98 (ArCH), 106.62 (ArCH), 62.86 (OCH_3), 61.08 (OCH_3), 56.16 (OCH_3), 34.36 (C-4).

7.4.12. Preparation of 1-(bromomethyl)-3-methoxy-5-methylbenzene 338

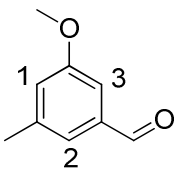
NBS (5.98 g, 33.59 mmol, 0.95 equiv.) was added to a solution of 3,5-dimethylanisole **337** (4.82 g, 5.0 cm^3, 35.36 mmol) and benzoyl peroxide (0.88 g, 3.54 mmol, 0.11 equiv.) in carbon tetrachloride (350cm^3). The reaction was heated gently under reflux for 4h. The reaction was then concentrated *in vacuo* and the resulting residue extracted into chloroform (3 × 100 cm^3), washed with H_2O (100 cm^3) and dried with $MgSO_4$. The organic phase was filtered and the solvent removed *in vacuo* to afford a yellow oil (5.74g, 75%). The crude product **338** was used without purification for the next step.[141]



R_f = 0.46 (50% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2914 and 2840 (C–H stretch), 1598 and 1455 (C=C), 1114 (C–O), 644 (C–Br); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H = 6.78 (1H, s, H), 6.72 (1H, s, H), 6.64 (1H, s, H), 4.40 (2H, s, –CH_2–), 3.76 (1H, s, OCH_3), 2.29 (3H, s, CH_3); **^{13}C NMR** (75MHz) δ_C = 159.76 (ArCO), 139.90 (ArC), 138.85 (ArC), 122.17 (ArCH), 115.02 (ArCH), 111.46 (ArCH), 55.18 (OCH_3), 33.66 (CH_2), 21.38 (CH_3).

7.4.13. Preparation of 3-methoxy-5-methylbenzaldehyde 339

1-(bromomethyl)-3-methoxy-5-methylbenzene **338** (5.74 g, 26.67 mmol) in ethanol (5 cm^3) and 2-nitropropane (3.92 g, 4.0cm^3, 44.0 mmol) were added to a solution of sodium ethoxide [prepared from ethanol (50 cm^3) and sodium (1.12 g, 48.8 mmol)] and the reaction mixture heated at 90 °C for 4 h under argon during which time it became a creamy paste. The solvent was then removed *in vacuo* and the residue was extracted into chloroform (3 × 50 cm^3). The combined extracts were combined and dried over $MgSO_4$, filtered through celite and evaporated under reduced pressure. The crude material was purified by column chromatography (5% EtOAc/Hexane) to yield the aldehyde **339** as a pale yellow oil (1.20 g, 30%).[141]



R_f = 0.49 (20% EtOAc /Hexane); **IR** ($CHCl_3$): ν_{max}(cm^{-1}): 2484 (C–H), 1697 (C=O), 1594 and 1465 (C=C), 1149 (C–O); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H =

9.92 (1H, s, C*H*O), 7.26 (1H, s, H_2), 7.19 (1H, s, H_3), 6.98 (1H, s, H_1), 3.84 (3H, s, OCH_3), 2.39 (3H, s, CH_3); **^{13}C NMR** (126 MHz): δ_C = 192.30 (C=O), 160.18 (ArCO), 140.35 (ArC), 137.78 (ArC), 124.33 (ArH), 122.12 (ArH), 109.54 (ArH), 55.43 (OCH_3), 21.20 (CH_3).

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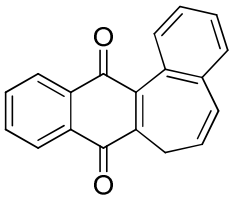
Appendix

X-ray chrystallography data for 7*H*-benzo[3,4]cyclohepta[1,2-*b*]naphthalene-8,13-dione



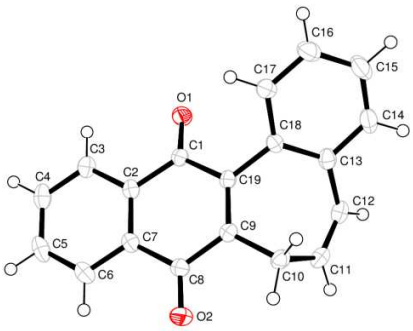


Table A1. Crystal data and structure refinement.

Identification code	MJ-535	
Empirical formula	C19 H12 O2	
Formula weight	272.29	
Temperature	173(2) K	
Wavelength	0.71069 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.5170(4) Å	a= 90°.
	b = 8.0460(4) Å	b= 90.091(2)°.
	c = 21.9940(10) Å	g = 90°.
Volume	1330.23(11) $Å^3$	
Z	4	
Density (calculated)	1.360 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	568	
Crystal size	0.41 x 0.40 x 0.04 mm^3	
Theta range for data collection	3.71 to 27.99°.	
Index ranges	-9<=h<=9, -10<=k<=10, -28<=l<=26	
Reflections collected	18565	
Independent reflections	3207 [R(int) = 0.0290]	

Completeness to theta = 27.99°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9969 and 0.9653
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3207 / 0 / 190
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R1 = 0.0408, wR2 = 0.1020
R indices (all data)	R1 = 0.0522, wR2 = 0.1096
Largest diff. peak and hole	0.369 and -0.161 e.$Å^{-3}$

Table A2. .Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5444(1)	3687(1)	5912(1)	19(1)
C(2)	6872(1)	2657(1)	5623(1)	20(1)
C(3)	6560(2)	2004(1)	4998(1)	21(1)
C(4)	7956(2)	1214(2)	4695(1)	26(1)
C(5)	7657(2)	517(2)	4127(1)	32(1)
C(6)	5983(2)	613(2)	3859(1)	33(1)
C(7)	4595(2)	1409(2)	4155(1)	28(1)
C(8)	4887(2)	2115(1)	4728(1)	22(1)
C(9)	3415(1)	2978(1)	5052(1)	22(1)
C(10)	3808(1)	3769(1)	5651(1)	20(1)
C(11)	2299(2)	4649(2)	5966(1)	25(1)
C(12)	1853(2)	3706(2)	6539(1)	27(1)
C(13)	2983(2)	3639(2)	7004(1)	28(1)
C(14)	4739(2)	4441(2)	7011(1)	25(1)
C(15)	5329(2)	5164(2)	7555(1)	34(1)
C(16)	6945(2)	5967(2)	7600(1)	39(1)
C(17)	8053(2)	6039(2)	7094(1)	33(1)
C(18)	7536(2)	5300(2)	6556(1)	25(1)
C(19)	5882(2)	4496(1)	6500(1)	20(1)
O(1)	8225(1)	2287(1)	5899(1)	29(1)
O(2)	1933(1)	3087(1)	4826(1)	34(1)

Table A3. Bond lengths [Å] and angles [°].

C(1)-C(10)	1.3582(15)
C(1)-C(19)	1.4833(15)
C(1)-C(2)	1.4984(15)
C(2)-O(1)	1.2205(13)
C(2)-C(3)	1.4892(15)
C(3)-C(8)	1.3933(15)
C(3)-C(4)	1.3969(16)
C(4)-C(5)	1.3873(17)
C(4)-H(4)	0.9500
C(5)-C(6)	1.391(2)
C(5)-H(5)	0.9500
C(6)-C(7)	1.3873(18)
C(6)-H(6)	0.9500
C(7)-C(8)	1.3996(16)
C(7)-H(7)	0.9500
C(8)-C(9)	1.4889(16)
C(9)-O(2)	1.2221(14)
C(9)-C(10)	1.4923(16)
C(10)-C(11)	1.5061(15)
C(11)-C(12)	1.5095(16)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.3299(18)
C(12)-H(12)	0.9500
C(13)-C(14)	1.4691(17)
C(13)-H(13)	0.9500
C(14)-C(15)	1.4027(17)
C(14)-C(19)	1.4171(16)
C(15)-C(16)	1.379(2)
C(15)-H(15)	0.9500
C(16)-C(17)	1.392(2)
C(16)-H(16)	0.9500
C(17)-C(18)	1.3799(17)

C(17)-H(17)	0.9500
C(18)-C(19)	1.4066(16)
C(18)-H(18)	0.9500

C(10)-C(1)-C(19)	123.14(10)
C(10)-C(1)-C(2)	119.76(10)
C(19)-C(1)-C(2)	117.00(9)
O(1)-C(2)-C(3)	120.19(10)
O(1)-C(2)-C(1)	121.38(10)
C(3)-C(2)-C(1)	118.34(10)
C(8)-C(3)-C(4)	120.24(10)
C(8)-C(3)-C(2)	120.80(10)
C(4)-C(3)-C(2)	118.91(10)
C(5)-C(4)-C(3)	119.52(11)
C(5)-C(4)-H(4)	120.2
C(3)-C(4)-H(4)	120.2
C(4)-C(5)-C(6)	120.34(12)
C(4)-C(5)-H(5)	119.8
C(6)-C(5)-H(5)	119.8
C(7)-C(6)-C(5)	120.45(11)
C(7)-C(6)-H(6)	119.8
C(5)-C(6)-H(6)	119.8
C(6)-C(7)-C(8)	119.55(12)
C(6)-C(7)-H(7)	120.2
C(8)-C(7)-H(7)	120.2
C(3)-C(8)-C(7)	119.89(11)
C(3)-C(8)-C(9)	119.78(10)
C(7)-C(8)-C(9)	120.33(11)
O(2)-C(9)-C(8)	121.07(11)
O(2)-C(9)-C(10)	120.52(10)
C(8)-C(9)-C(10)	118.36(10)
C(1)-C(10)-C(9)	122.05(10)
C(1)-C(10)-C(11)	120.70(10)
C(9)-C(10)-C(11)	117.24(9)
C(10)-C(11)-C(12)	108.42(9)

C(10)-C(11)-H(11A)	110.0
C(12)-C(11)-H(11A)	110.0
C(10)-C(11)-H(11B)	110.0
C(12)-C(11)-H(11B)	110.0
H(11A)-C(11)-H(11B)	108.4
C(13)-C(12)-C(11)	121.32(11)
C(13)-C(12)-H(12)	119.3
C(11)-C(12)-H(12)	119.3
C(12)-C(13)-C(14)	124.29(11)
C(12)-C(13)-H(13)	117.9
C(14)-C(13)-H(13)	117.9
C(15)-C(14)-C(19)	118.23(11)
C(15)-C(14)-C(13)	118.32(11)
C(19)-C(14)-C(13)	123.44(10)
C(16)-C(15)-C(14)	122.16(12)
C(16)-C(15)-H(15)	118.9
C(14)-C(15)-H(15)	118.9
C(15)-C(16)-C(17)	119.38(12)
C(15)-C(16)-H(16)	120.3
C(17)-C(16)-H(16)	120.3
C(18)-C(17)-C(16)	119.98(12)
C(18)-C(17)-H(17)	120.0
C(16)-C(17)-H(17)	120.0
C(17)-C(18)-C(19)	121.40(11)
C(17)-C(18)-H(18)	119.3
C(19)-C(18)-H(18)	119.3
C(18)-C(19)-C(14)	118.81(10)
C(18)-C(19)-C(1)	118.24(10)
C(14)-C(19)-C(1)	122.91(10)

Symmetry transformations used to generate equivalent atoms.

Table A4. Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(1)	18(1)	18(1)	2(1)	2(1)	0(1)
C(2)	21(1)	19(1)	20(1)	2(1)	1(1)	-1(1)
C(3)	26(1)	17(1)	19(1)	2(1)	2(1)	-1(1)
C(4)	30(1)	22(1)	25(1)	1(1)	4(1)	2(1)
C(5)	44(1)	25(1)	26(1)	-2(1)	9(1)	4(1)
C(6)	53(1)	25(1)	20(1)	-4(1)	2(1)	-2(1)
C(7)	38(1)	23(1)	22(1)	1(1)	-4(1)	-5(1)
C(8)	28(1)	18(1)	19(1)	2(1)	1(1)	-3(1)
C(9)	23(1)	23(1)	21(1)	5(1)	-1(1)	-4(1)
C(10)	21(1)	18(1)	21(1)	3(1)	2(1)	-1(1)
C(11)	21(1)	27(1)	27(1)	1(1)	1(1)	5(1)
C(12)	22(1)	26(1)	32(1)	0(1)	7(1)	1(1)
C(13)	30(1)	28(1)	25(1)	1(1)	9(1)	2(1)
C(14)	29(1)	23(1)	23(1)	-1(1)	2(1)	5(1)
C(15)	41(1)	38(1)	23(1)	-7(1)	3(1)	7(1)
C(16)	45(1)	40(1)	31(1)	-16(1)	-8(1)	5(1)
C(17)	31(1)	30(1)	38(1)	-10(1)	-8(1)	0(1)
C(18)	25(1)	23(1)	27(1)	-1(1)	-2(1)	2(1)
C(19)	23(1)	18(1)	20(1)	-1(1)	-2(1)	4(1)
O(1)	23(1)	36(1)	27(1)	-5(1)	-4(1)	8(1)
O(2)	24(1)	49(1)	28(1)	1(1)	-5(1)	-2(1)

Table A5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3).

x	y	z	U(eq)	
H(4)	9102	1155	4877	31
H(5)	8600	-27	3921	38
H(6)	5789	129	3470	39
H(7)	3455	1474	3970	33
H(11A)	1247	4694	5695	30
H(11B)	2652	5801	6067	30
H(12)	742	3149	6568	32
H(13)	2633	3032	7354	33
H(15)	4592	5098	7905	40
H(16)	7299	6466	7972	46
H(17)	9165	6596	7119	40
H(18)	8314	5335	6216	30

Table A6. Torsion angles [°].

C(10)-C(1)-C(2)-O(1)	-165.32(11)
C(19)-C(1)-C(2)-O(1)	11.17(16)
C(10)-C(1)-C(2)-C(3)	11.07(15)
C(19)-C(1)-C(2)-C(3)	-172.44(9)
O(1)-C(2)-C(3)-C(8)	166.27(11)
C(1)-C(2)-C(3)-C(8)	-10.16(15)
O(1)-C(2)-C(3)-C(4)	-11.14(16)
C(1)-C(2)-C(3)-C(4)	172.43(10)
C(8)-C(3)-C(4)-C(5)	-1.03(17)
C(2)-C(3)-C(4)-C(5)	176.40(11)
C(3)-C(4)-C(5)-C(6)	0.42(18)
C(4)-C(5)-C(6)-C(7)	0.18(19)
C(5)-C(6)-C(7)-C(8)	-0.18(19)
C(4)-C(3)-C(8)-C(7)	1.03(17)
C(2)-C(3)-C(8)-C(7)	-176.35(10)
C(4)-C(3)-C(8)-C(9)	-179.25(10)
C(2)-C(3)-C(8)-C(9)	3.37(16)
C(6)-C(7)-C(8)-C(3)	-0.43(17)
C(6)-C(7)-C(8)-C(9)	179.86(11)
C(3)-C(8)-C(9)-O(2)	-179.76(11)
C(7)-C(8)-C(9)-O(2)	-0.04(17)
C(3)-C(8)-C(9)-C(10)	2.66(16)
C(7)-C(8)-C(9)-C(10)	-177.63(10)
C(19)-C(1)-C(10)-C(9)	178.48(10)
C(2)-C(1)-C(10)-C(9)	-5.25(16)
C(19)-C(1)-C(10)-C(11)	-2.60(16)
C(2)-C(1)-C(10)-C(11)	173.67(10)
O(2)-C(9)-C(10)-C(1)	-179.27(11)
C(8)-C(9)-C(10)-C(1)	-1.68(16)
O(2)-C(9)-C(10)-C(11)	1.77(16)
C(8)-C(9)-C(10)-C(11)	179.37(10)
C(1)-C(10)-C(11)-C(12)	-65.64(14)
C(9)-C(10)-C(11)-C(12)	113.33(11)

C(10)-C(11)-C(12)-C(13)	67.46(14)
C(11)-C(12)-C(13)-C(14)	-0.29(19)
C(12)-C(13)-C(14)-C(15)	142.06(13)
C(12)-C(13)-C(14)-C(19)	-39.21(18)
C(19)-C(14)-C(15)-C(16)	2.32(19)
C(13)-C(14)-C(15)-C(16)	-178.89(12)
C(14)-C(15)-C(16)-C(17)	-1.4(2)
C(15)-C(16)-C(17)-C(18)	-0.5(2)
C(16)-C(17)-C(18)-C(19)	1.4(2)
C(17)-C(18)-C(19)-C(14)	-0.44(17)
C(17)-C(18)-C(19)-C(1)	-178.17(11)
C(15)-C(14)-C(19)-C(18)	-1.36(17)
C(13)-C(14)-C(19)-C(18)	179.91(11)
C(15)-C(14)-C(19)-C(1)	176.26(11)
C(13)-C(14)-C(19)-C(1)	-2.47(18)
C(10)-C(1)-C(19)-C(18)	-138.88(11)
C(2)-C(1)-C(19)-C(18)	44.76(14)
C(10)-C(1)-C(19)-C(14)	43.49(16)
C(2)-C(1)-C(19)-C(14)	-132.87(11)

Symmetry transformations used to generate equivalent atoms.