# *Novel Methods for the Synthesis of Naturally Occurring Oxygen and Nitrogen Heterocycles*

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

*August 2009*

# Declaration

I declare that the work presented in this thesis was carried out exclusively by myself under the supervision of Professor C.B. de Koning. 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.

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7th day of August, 2009

# Abstract

Pyranonaphthoquinones are a class of naturally occurring compounds that exhibit a wide range of biological properties ranging from antibiotic to anti-cancer activities. These compounds and their non-natural analogues are therefore of synthetic interest. This PhD describes the first total synthesis of cardinalin 3, previously isolated from the New Zealand toadstool *Dermocybe cardinalis*. We then proceeded to investigate possible novel stereoselective syntheses of 1,3-dimethylated pyranonaphthoquinones using arene tricarbonylchromium chemistry as well as the synthesis of other 1,3-disubstituted pyranonaphthoquinones using cross metathesis as a key step.

The racemic total synthesis of cardinalin 3 was achieved in 15 steps using a bidirectional approach. Starting from commercially available 1,3-dimethoxybenzene, the biaryl axis was introduced using an Ullmann coupling reaction to afford 2,2′,6,6′-tetramethoxy-1,1′-biphenyl. Further elaboration of the biphenyl to form the *bis*-naphthalene ring system diethyl [4,4′-diacetoxy-6,6′,8,8′-tetramethoxy-7,7′-binaphthalene]-2,2′-dicarboxylate was achieved with a Stobbe condensation and Friedel-Crafts acylative cyclisation. A Wacker oxidation was then employed to construct the pyran ring onto either side of the appropriately substituted naphthalene dimer to form (±)-5,5'-bis(benzyloxy)-7,7',9,9'-tetramethoxy-1,1',3,3'-tetramethyl-1*H*,1'*H*-8,8'-bibenzo[*g*]isochromene. The remaining transformations included hydrogenation to (±)-7,7',9,9'-tetramethoxy-*cis*-1,3-*cis*-1',3'-tetramethyl-3,3',4,4'-tetrahydro-1*H*,1'*H*-8,8'-bibenzo[*g*]isochromene-5,5'-diol, followed by oxidation to the quinone (±)-7,7',9,9'-tetramethoxy-*cis*-1,3-*cis*-1',3'-tetramethyl-3,3',4,4',6,9-hexahydro-1*H*, 1'*H*-8,8'-bibenzo[*g*]-isochromene-5,5',10,10'-tetrone and a selective *O*-demethylation reaction to furnish cardinalin 3, in an overall yield of 2.2%.

In a study on the usefulness of arene chromiumtricarbonyl chemistry to construct 1,3-dimethylisochromane systems, an arene chromiumtricarbonyl system was made from (*R*)-5,8-dimethoxyisochroman-4-ol. Unexpectedly, this complexation occurred without diastereoselectively forming both the *syn* and *anti* diastereomers which fortuitously could be separated. Despite several attempts we were unsuccessful in performing the required oxidation of the complexed isochromanol to (5,8-dimethoxyisochroman-4-one)tricarbonylchromium (0).

In another model study, cross metathesis of ethyl acrylate and silyl protected (2-allyl-3,6-dimethoxyphenyl)methanol successfully produced the α,β-unsaturated ester (*E*)-ethyl 4-(2-((*tert*-butyldimethylsilyloxy)methyl)-3,6-dimethoxyphenyl)but-2-enoate which subsequently underwent a spontaneous intramolecular Michael addition to produce ethyl 2-

(5,8-dimethoxyisochroman-3-yl)acetate. A similar strategy was employed to produce ethyl 2-(5,8-dimethoxy-1-methylisochroman-3-yl)acetate.

In the last part of this PhD we attempted the stereoselective synthesis of a chiral indoline ring system wherein we utilise a Trost asymmetric allylic alkylation reaction. The specific indoline moiety synthesised, 1-methyl-2-(prop-1-en-2-yl)indoline, is found embedded in many biologically useful compounds including the nodulisporanes which display potent insecticidal properties. The synthesis began from commercially available *N*-methyl aniline which was suitably functionalised and subjected to a Horner-Wadsworth-Emmons reaction to furnish (*E*)-ethyl 4-(2-(tert-butoxycarbonyl)phenyl)-2-methylbut-2-enoate to begin the construction of the dihydro pyrrole ring system. The asymmetric allylic alkylation was carried out on (*E*)-methyl-2-methyl-4-(2-(methylamino)phenyl)but-2-enyl carbonate using a palladium catalyst in the presence of the chiral Trost ligand to afford 1-methyl-2-(prop-1-en-2-yl)indoline. An enantiomeric excess of 32% was achieved suggesting that this reaction has potential scope for future investigation.

# Acknowledgements

I would like to express my sincere gratitude to Professor Charles de Koning. You have been a wonderful inspiration to me throughout my time at Wits, first as a lecturer and then later as my supervisor. Your patience and guidance throughout this project were invaluable and highly appreciated. Thank you also for always having an open door and making my concerns a priority no matter how insignificant they may have been and no matter how busy you were!
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Finally to my amazing husband Stephen, I would like to thank you firstly on a professional level for all your assistance and advice throughout this project and the writing of this thesis. You were always extremely particular about good lab technique and I'm proud to say that I learnt from the best! On a more personal level, thank you for being the most wonderful husband! I feel truly blessed to have you in my life and I look forward to our wonderful journey together.

# Chapter 1: An Introduction to Pyranonaphthoquinones

## 1.1 Pyranonaphthoquinone Based Natural Products

Pyranonaphthoquinone antibiotics are a vast and interesting class of naturally occurring compounds that have been isolated from various strains of bacteria, microbial fungi and plant species. They exhibit a wide range of anti-fungal, antibiotic as well as anti-cancer activity. This family of molecules, which are also referred to as benzoisochromane quinones, exist as the monomeric, dimeric and carbohydrate derivatives as illustrated in Figure 1.[1]

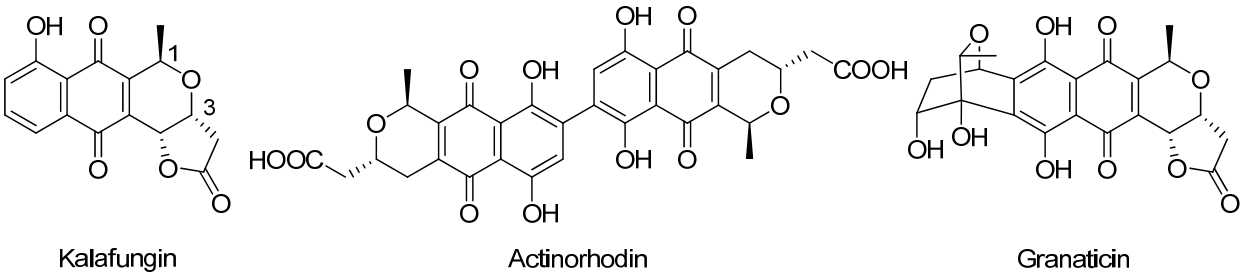
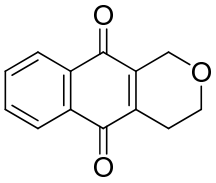



**Figure 1**: Monomeric, dimeric and carbohydrate-derived pyranonaphthoquinones

These pyranonaphthoquinones often contain substituents at the C1 and C3 positions of the pyran ring. These substituents may be quite diverse, ranging from simple methyl groups to more complex systems such as a γ-lactone ring fused to the dihydropyran moiety.[2] Furthermore, a carboxylic acid side chain may be obtained by ring opening of the γ-lactone ring. Central to this class however is the basic 2,3-dihydro-1*H*-naptho[2,3-*c*]pyran-5,10-dione skeleton **1** (Figure 2).



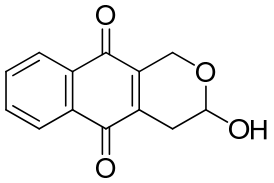
**1**

**Figure 2**

Of particular interest to us are the monomeric and dimeric forms of the pyranonaphthoquinones, and these two classes are briefly discussed in the following sections, paying particular attention to their structure, isolation and biological activity.

### 1.1.1 Interesting monomeric pyranonaphthoquinones

The simplest naturally occurring monomeric form of this class of compounds is psychorubin **2 (**Figure 3), which contains a hydroxyl group at the C3 position of the pyran ring of the basic naphthopyrandione skeleton, making it a hemiacetal. It was isolated from the chloroform extracts of *Psychorutria rubra*, known as "Chiu Chieh Mu" in Chinese folk medicine.[3] The extracts showed significant reproducible inhibitory activity against KB cells with an $ED_{50}$ = 3.0 μg.ml$^{-1}$.




**2**

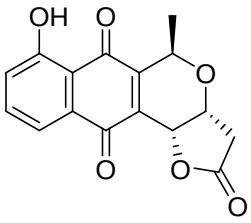
**Figure 3**

Other well known examples of monomeric pyranonaphthoquinones with simple substituents are kalafungin**,** eleutherin, the ventiloquinones and the nanaomycins, some of which are depicted in Figure 4, Figure 5 and Figure 6.

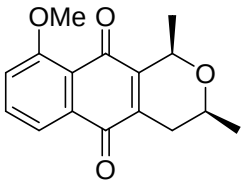
Kalafungin **3** (Figure 4) was first isolated in 1968 from the fermentation broth of *Streptomyces tanashiensis* strain Kala. It contains three stereogenic centres and is dextrorotary in chloroform ($[\alpha]_D^{25}$ +159).[4] This weakly acidic orange compound was shown to exhibit *in vitro* anti-bacterial activity against Gram-positive and Gram-negative bacteria, as well as inhibition activity against a wide spectrum of human pathogenic fungi, protozoa and yeasts.[5]

Eleutherin **4** was first isolated in 1955 from the tubers of *Eleutherine bulbosa* (Iridaceae),[6] and crystallised as yellow rods. The stereochemistry of the methyl group at C1 was shown to adopt the more stable pseudo-equatorial position as it is further removed from its adjacent carbonyl group.[7] Eleutherin **4** exhibits activity against the bacterial strains

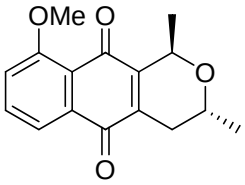
*Pycoccus aureus* and *Streptococcus haemolyticus A*. Extracts of *Eleutherine americana* containing eleutherin **4** and its C3 epimer isoeleutherin **5**, were used to treat heart diseases such as angina pectoris.[1]



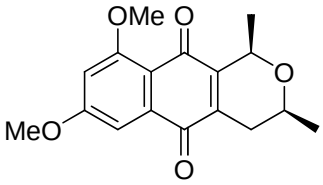

Kalafungin **3**




Eleutherin **4**



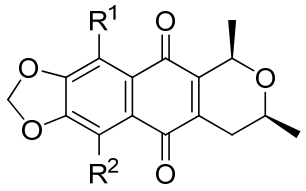

Isoeleutherin **5**



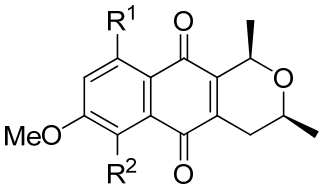

7-methoxyeleutherin **6**

**Figure 4**

The series of compounds known as the ventiloquinones **7-11** (Figure 5) are structurally related to the eleutherins. They also possess the naphthoquinone skeleton and 1,3-dimethylpyran ring system, but vary according to the oxygenated substituents on the aromatic ring. The ventiloquinone family consists of 15 members and five of those are shown in Figure 5. Ventiloquinones A **7**, B **8** and E **10** are from the acetone extracts of the root bark of the *Ventilago* species, *V. maderaspatana* and *V. calyculata*.[8] Ventiloquinones L **11** and M **9** were isolated from *V. goughii*.[9] The aromatic rings of ventiloquinones A, B and M, **7-9** are fused to a 1,3-dioxolane ring. Regarding the other aromatic substituents however, there still remains some ambiguity as to the positions of the methoxy and hydroxy substituents in ventiloquinone A **7** whereas in ventiloquinone B **8**, both of these oxygen substituents are methylated. In ventiloquinone M **9** they are found as the free phenols. Ventiloquinone E **10** bears three methoxy substituents on its aromatic ring and ventiloquinone L **11** contains one phenol and one methoxy substituent in an *ortho* arrangement. The position of the methoxy in ventiloquinone L **11** was found to be identical to a variant of eleutherin, 7-methoxyeleutherin **6** (Figure 4).[10]



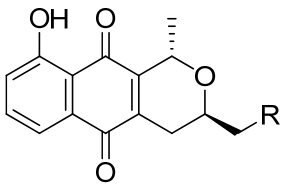
Ventiloquinone A **7**: $R^1$ = OH(OMe); $R^2$ = OMe(OH)
Ventiloquinone B **8**: $R^1$ = OMe; $R^2$ = OMe
Ventiloquinone M **9**: $R^1$ = OH; $R^2$ = OH



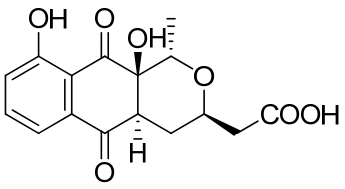
Ventiloquinone E **10**: $R^1$ = $R^2$ = OMe
Ventiloquinone L **11**: $R^1$ = OH; $R^2$ = H

**Figure 5**

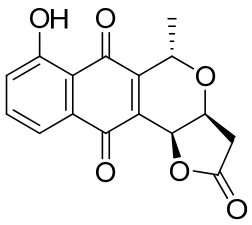
Another large family of antibiotic pyranonaphthoquinones are the nanaomycins **12-15**. The first four members shown in Figure 6 were isolated from *Streptomyces rosa*.[11, 12] Nanaomycin D **15** is the enantiomer of kalafungin **3**. Based on comparisons of the $^1$H NMR spectral data of nanaomycin A **12** with those of isoeleutherin **5**, it was shown that the substituent at C1 adopts a pseudo-axial orientation while that at C3 is equatorial.[13] Nanaomycin A **12** and B **14** exhibited inhibitory activity against mycoplasma, fungi and Gram-positive bacteria. Furthermore, nanaomycin A **12** was also found to inhibit the platelet aggregation agent, adenosine diphosphate.[11] Nanaomycin C **13** shows comparable activity against gram-positive bacteria but its activity against mycoplasmas and fungi is somewhat less pronounced.[13] In terms of the structure-activity relationship for these compounds, it was found that the naphthoquinone and the lactone portions of the molecule were required for antibacterial activity.



Nanaomycin A **12**: R = COOH
Nanaomycin C **13**: R = $CONH_2$



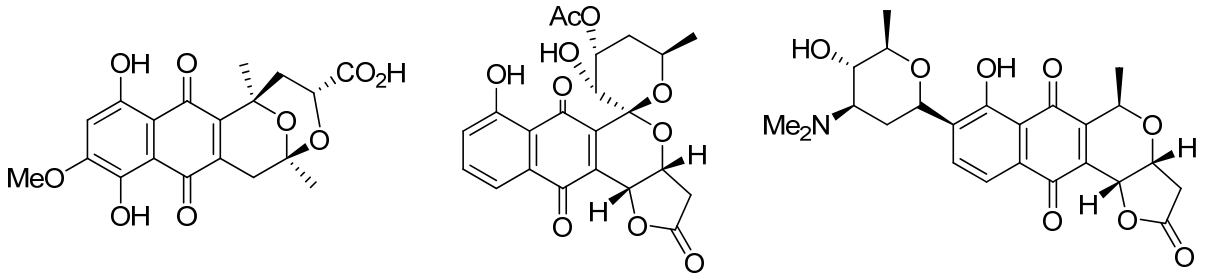
Nanaomycin B **14**



Nanaomycin D **15**

**Figure 6**

The examples discussed thus far represent some of the simpler members which exhibit antibiotic activity. There are more complex members which include marticin **16**, griseusin A **17** and medermycin **18** (Figure 7).[2] These representative examples of antibiotics include the presence of highly oxygenated sugar derived heterocyclic rings attached to their basic pyranonaphthoquinone skeleton and are thus classed as carbohydrate derived pyranonaphthoquinones.



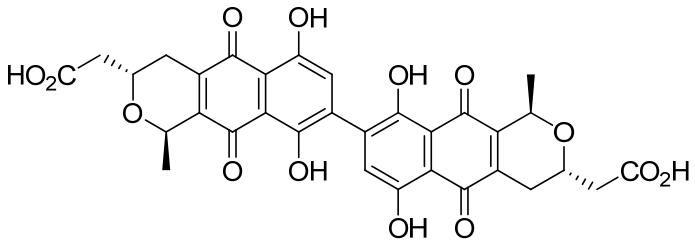

Marticin **16** Griseusin A **17** Medermycin **18**

**Figure 7**

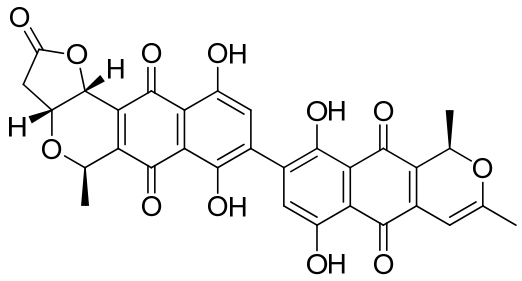
The next class in this vast family of antibiotics of interest to us are the "dimeric" pyranonaphthoquinones. The dimeric forms of these compounds contain similar structural features for each half of the molecule as well as a biaryl point of attachment linking the two halves. Some well known examples will be briefly discussed below.

### 1.1.2 Interesting dimeric pyranonaphthoquinones

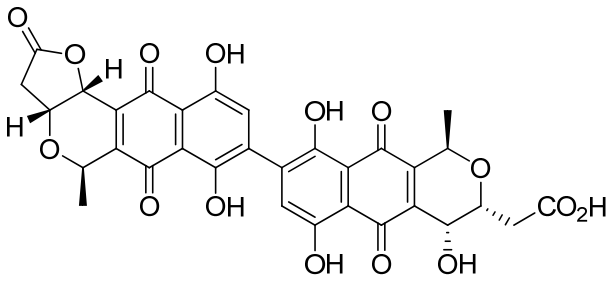
The actinorhodins **19-21** are a series of dimeric pyranonaphthoquinone pigments that were isolated from *Streptomyces coelicolor* [14] Three of the six naturally occurring compounds are shown in Figure 8.




Actinorhodin **19**



α–Actinorhodin **20**




ε–Actinorhodin **21**

**Figure 8**

The first to be isolated, actinorhodin **19**, displayed litmus like properties, appearing bright blue in alkali and red in acid. According to $^1$H NMR spectral studies, the two halves of actinorhodin **19** are identical and are linked in a symmetrical fashion by a C8-C8′ linkage.[15] α-Actinorhodin **20** is unsymmetrical with a monolactone coupled to an unsaturated moiety, while ε-actinorhodin **21** comprises of a lactone monomer and an acid monomer coupled to each other. Activity against *Staphylococcus aureus* has been reported for actinorhodin **19** itself,[14] however the activity of the other dimers is relatively unexplored.

The microorganism *Micromonospora purpureochromogenes*, obtained from a mud sample in the Philippines, produces an antibiotic complex, the major component of which was isolated and identified as crisamycin A **22** (Figure 9).[16]

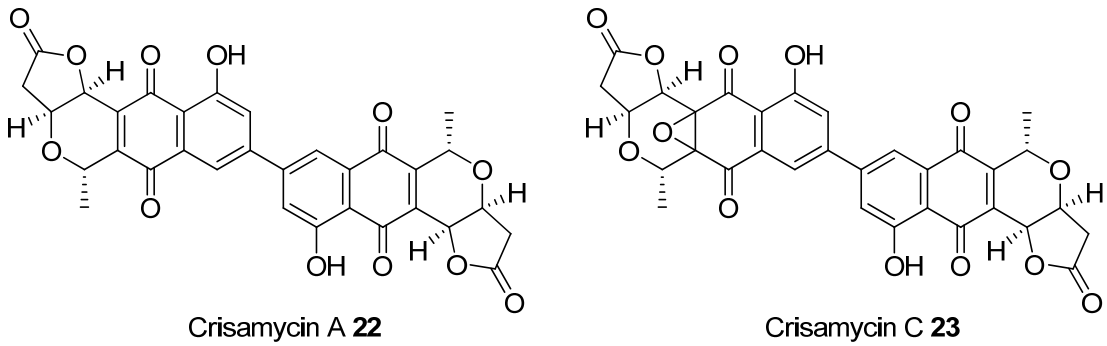
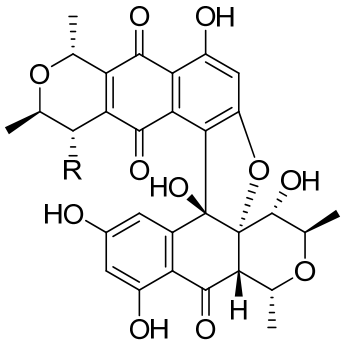



**Figure 9**

Similar to actinorhodin **19**, it was found to display litmus like properties, imparting a yellow colour in acid solution and purple colour in alkaline solution. The position of the biaryl axis is also at the C8-C8′ position. Of somewhat more interest is that crisamycin A **22** also displayed excellent activity against Gram-positive bacteria[16] and also showed *in vitro* activity against B16 murine melanoma cells, herpes simplex virus and vesicular stomatitis virus.[17] Shortly after the discovery of crisamycin A **22**, an epoxide derivative of the molecule was isolated and named crisamycin C **23**. Not surprisingly this compound also exhibited antimicrobial activity and in fact was found to be more potent than crisamycin A **22**.[18]

The novel pyranonaphthoquinones uroleuconaphins $A_1$ and $B_1$ **24-25** (Figure 10) were obtained from the ethereal extracts of the aphid *Uroleucon nigrotuberculatum* (Olive).[19]

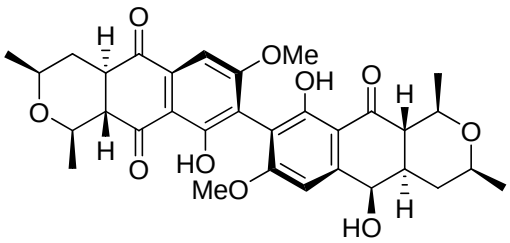


Uroleuconaphin $A_1$ **24**, R =H
Uroleuconaphin $B_1$ **25**, R =OH

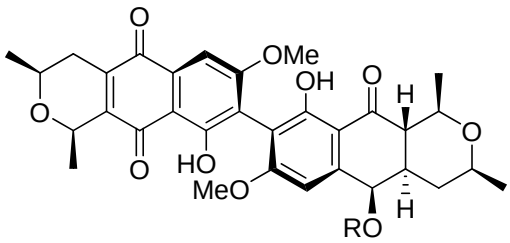
**Figure 10**

The two "monomeric halves" of the compound are connected by a dihydrofuran linkage. These compounds, responsible for the red pigment in the aphid, were found to exhibit cytotoxic activity against human promyelocytic leukaemia HL-60 cells with $ED_{50}$ values of 45 μM and 20 μM respectively. These values suggest that these pigments are important to the aphids in their defence against viral infections.

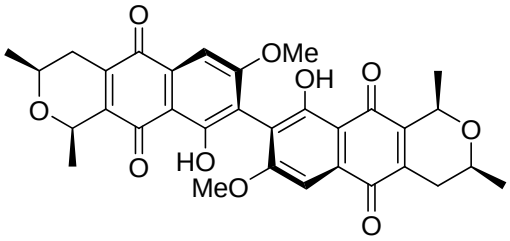
The distinctive purple and orange fruit bodies of *Dermocybe cardinalis* are among the most spectacular toadstools found in the *Nothofagus* forests of New Zealand. A new class of compounds, the cardinalins, were isolated from the ethanolic extracts of specimens of these fruit bodies.[20] Several members of this class of compounds are shown in Figure 11.



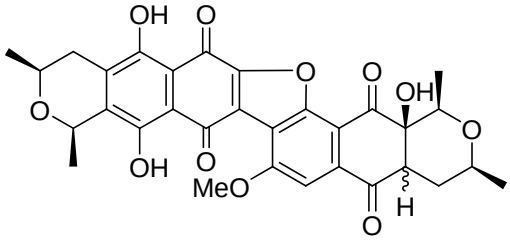
Cardinalin 1 **26**



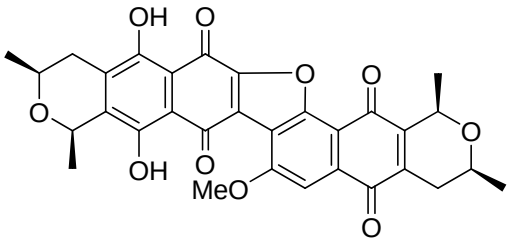
Cardinalin 2 **27**: R = H
Cardinalin 13 **28**: R = CHO



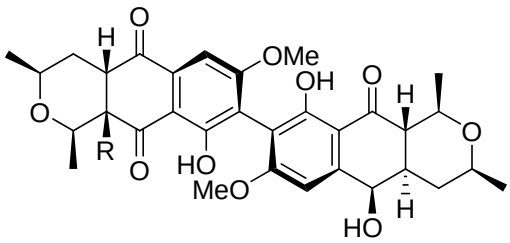
Cardinalin 3 **29**



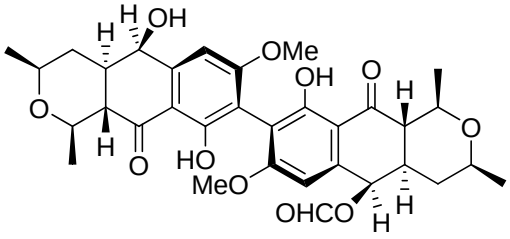
Cardinalin 4 **30** : αH
Cardinalin 5 **31** : βH



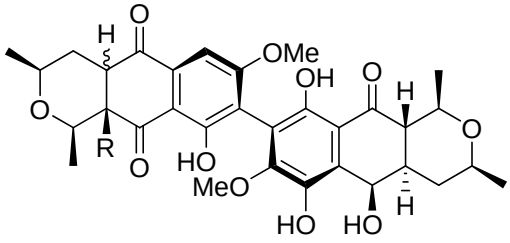
Cardinalin 6 **32**



Cardinalin 9 **33** : R = OH
Cardinalin 12 **34** : R = H



Cardinalin 14 **35**



Cardinalin 15 **36**: αH, R = H
Cardinalin 16 **37**: βH, R = OH

**Figure 11**

The cardinalins belong to the family of pyranonaphthoquinones and are the first quinones of this type to be isolated from higher fungi.[20] The deep red ethanolic extracts exhibited potent inhibition of the growth of P388 murine leukaemia cells ($IC_{50}$ 0.47 $\mu g.cm^{-3}$) and due to this significant cytotoxic activity, the individual components of the complex mixture were examined. Initial analysis led to the isolation and characterisation of a colourless quinone - cardinalin 1 **26**, two yellow quinones - cardinalins 2 **27** & 3 **29** and three red-

purple pigments - cardinalins 4 **30**, 5 **31** and 6 **32**. Further analysis showed the presence of a series of colourless compounds which were identified as cardinalins 8-12 (cardinalins 9 **33** and 12 **34** are shown in Figure 11), as well as four others, cardinalins 13-16 **28**, and **35-37**, which are believed to be artefacts of the purification procedure.[21] The most complex of these dimeric pyranonaphthoquinones is cardinalin 1 **26**, bearing 9 stereogenic centres in addition to its axis of chirality. The simplest in this series is cardinalin 3 **29**, devoid of much of the stereochemistry which is seen in cardinalin 1 **26**. Cardinalin 3 **29** is in fact the dimer of another naturally occurring pyranonaphthoquinone, ventiloquinone L **11** (Figure 5).

As shown in these examples, the pyranonaphthoquinone class of compounds consists of a vast variety of structurally diverse compounds, with new compounds constantly being discovered. Their usefulness as potential medicinal scaffolds has been proven through their wide range of biological activities. Among these uses, the most important to us is perhaps their ability to act as anti-cancer agents. In fact in the 1980's quinones formed the second largest class of cytotoxins used as anticancer drugs in the United States.[22] Their proposed mechanism of action for this remarkable ability will be further elaborated on in the subsequent sections.

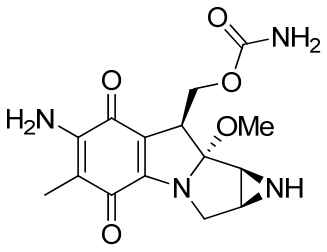
## 1.2 Mechanism of Biological Action

The cytotoxic and growth inhibitory properties of quinones are thought to be due to their ability to covalently bind to various proteins and peptides, as well as DNA and RNA.[22] One mode of action responsible for this binding, proposed by Moore,[23] is that they are able to act as bioreductive alkylating agents. A variety of other studies have shown that some quinones inhibit the catalytic activity of topoisomerase II.[24-26]

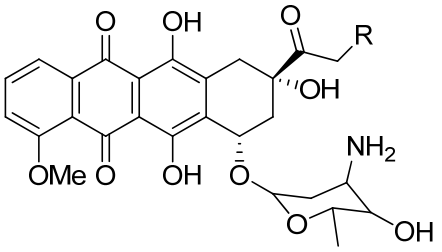
### 1.2.1 Bioreductive alkylating agents

Well known chemotherapeutic drugs, such as mitomycin C **38** (Figure 12), are first required to be biologically activated by means of an initial reduction to their active 'quinone methide' forms. Other quinone drugs proposed to act this way are the anthracyclines, daunomycin **39** and adriamycin **40**.[27] It is known that this reduction takes place preferentially under anaerobic conditions.[28, 29] Furthermore, it is also known that

tumour tissue has a significantly lower oxidation-reduction potential than most normal tissues.[30] This may be due to the fact that cancer cells grow extremely rapidly compared to healthy cells, and as a result of this rapid rate of growth, solid tumours tend to have poor vascularity, leading to a hypoxic (oxygen-deficient) environment at the inner parts of the tumours. Since this is a more favourable environment for the reduction of these quinones, there is an accumulation of the cytotoxic quinone methide in the tumours as compared to healthy cells.



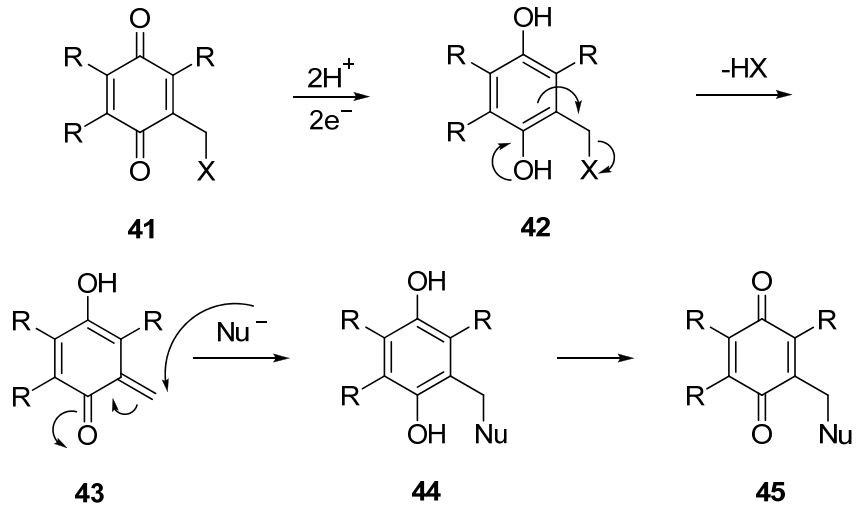

Mitomycin C **38**




Daunomycin **39** : R= H
Adriamycin **40** : R = OH

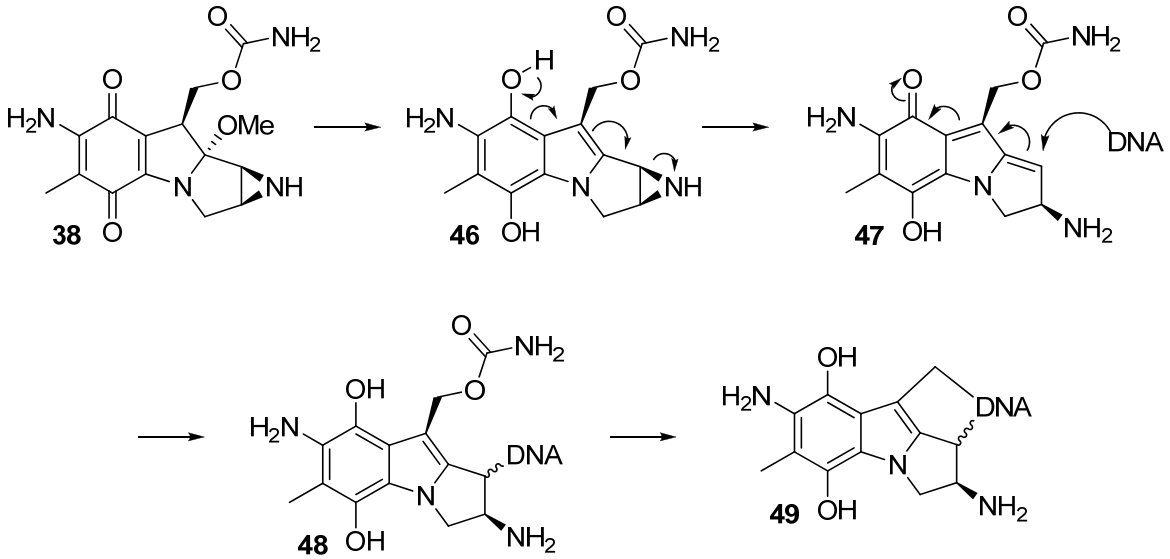
**Figure 12**

In a generalised reaction scheme (Scheme 1), *in vivo* bioreduction of the quinone **41** results in the hydroquinone **42**. The cleavage of a benzylic substituent on the hydroquinone by the mesomerically assisted loss of a suitable leaving group results in the formation of a quinone methide **43**. This active form of the drug can now form covalent adducts **44** with biological nucleophiles such as DNA, proteins or carbohydrates through a Michael addition to the reactive enone system. The formation of the covalent adduct renders the cell incapable of carrying out its normal functions, thus leading to apoptosis. Once this cytotoxic activity of the quinone has been carried out, the adduct can be oxidised, resulting in its biologically inactive form **45**.




**Scheme 1**

Mitomycin C **38** (Scheme 2) is reduced *in vivo* by a non-specific NADPH-dependant enzyme system.[28] It was found to be stable under aerobic conditions, and rapidly reacted in an anaerobic environment.[31] It is able to cross link DNA initially through the loss of a methoxy group forming **46** and then subsequent opening of the aziridine ring forming the toxic Michael acceptor **47**. Addition of DNA in a similar mechanism to that depicted in Scheme 1 provides the first linkage in **48**, which is followed by the displacement of a carbamate group providing the second DNA linkage of **49**.[32]




**Scheme 2**

It has been recently been reported that the naturally occurring pyranonaphthoquinones lactoquinomycin (medermycin) **18**, kalafungin **3** and frenolicin B **50** (Figure 13) possess significant inhibitory properties against the serine-threonine kinase AKT, which has been found in a wide variety of human tumour types.[33] Lactoquinomycin **18** was found to inhibit AKT1 with an $IC_{50}$ of 149 nM. The mechanism proposed for this inhibition was a bioreductive activation of the quinone to the active methide, as exemplified in the above schemes, which then forms an adduct with the cysteine residues of AKT.[34]

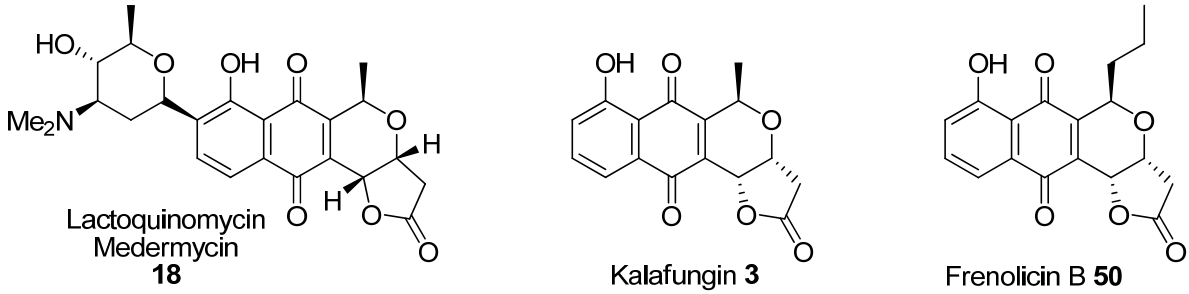


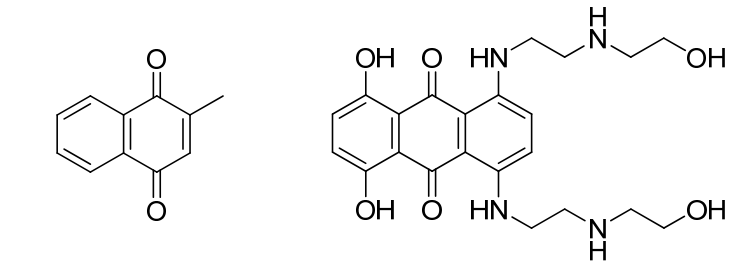

**Figure 13**

The pyranonaphthoquinones daunomycin **39** and its oxygenated relative adriamycin **40** are proposed to also undergo bioreductive activation, with the leaving group in their case being the sugar moiety. There is some speculation however regarding their precise mode of action, and an alternative suggestion is an intercalation-based pathway involving DNA topoisomerase.[24-26]

### 1.2.2 Topoisomerase II inhibition

Topoisomerase II enzymes are important for many vital functions of DNA during cell growth. They alter DNA topology by catalysing the passing of an intact DNA double helix through a transient double stranded break made in a second helix and are critical for relieving torsional stress that occurs during replication and transcription. They are also vital for daughter strand separation during mitosis. On the other hand, these useful proteins are highly vulnerable to stresses, such as for example exposure to topoisomerase poisons, which then drastically alters their function and may convert them into DNA cleaving nucleases, often leading to cell death.[35] A number of studies have shown that a variety of quinones (Figure 14 shows two such examples **51** and **52**) interact with and inhibit the useful activity of topoisomerase II. The mechanism by which this occurs is believed to be

related to the fact that topoisomerase II is cysteine-rich. The electrophilic reaction of the quinone with critical sulfhydryl groups on topoisomerase II is thought to be responsible for its inhibition.[26, 36]




Menadione, vitamin K3 **51** Mitoxantrone **52**

**Figure 14**

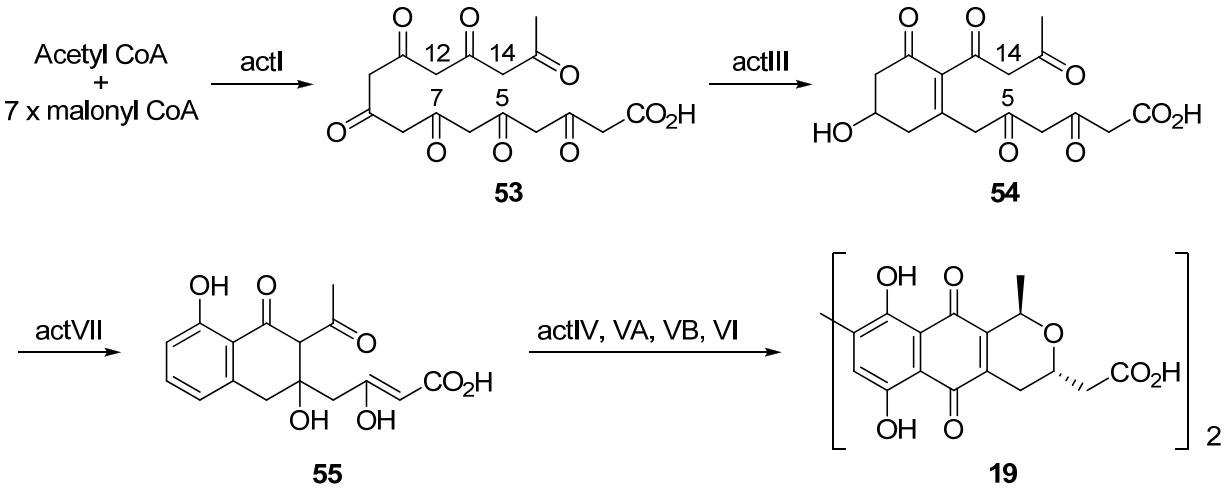
The properties of the pyranonaphthoquinone antibiotics have made them worthwhile synthetic targets and in the next few sections we will discuss some of the classic and novel approaches to these compounds. To begin this section a brief overview of the biosynthetic pathway is presented.

## 1.3 Biosynthesis of Pyranonaphthoquinones

The biosynthesis of pyranonaphthoquinone antibiotics has been comprehensively reviewed by O'Hagan.[37] The metabolites of bacteria, fungi and plants, are essentially polyketides and while there is a vast diversity of polyketide structural classes, their underlying biosynthetic mechanism is universal.[38] It involves a series of decarboxylative condensation reactions with residues of a single, simple carboxylic acid subunit (acetate or propionate) or a mixture of subunits (acetate, propionate, butyrate residues) and malonates using multi protein/enzyme complexes called polyketide synthases (PKSs). The intermediate produced is then further processed through a series of unique intramolecular cyclisation, elimination, redox and functional group transfer reactions to generate the highly functionalised natural products.

The biosynthesis of actinorhodin **19** was elucidated by means of a study involving the use of synthetic oligonucleotides (Scheme 3).[38] The biosynthesis involves gene clusters,[39] which control the starter unit, the nature and number of chain extender units and specify the reductive cycle and the pattern of cyclisation. The actinorhodin polyketide carbon

backbone **53** formed, is derived from an acetyl CoA starter unit as well as seven malonyl CoA extender units. It then undergoes a regiospecific intramolecular aldol condensation between C7 and C12, providing the intermediate **54**. Next a bond between C5 and C14 is formed producing **55**, to eventually lead to actinorhodin **19**, controlled by the specific gene clusters.




**Scheme 3**

The structurally diverse pyranonaphthoquinones are similarly biosynthesised according to their gene clusters. For example, the carbohydrate derived quinones will require additional enzymes for the attachment of their sugar moieties.

The next few chapters will touch on a few synthetic strategies that have been employed to generate these naturally occurring compounds.

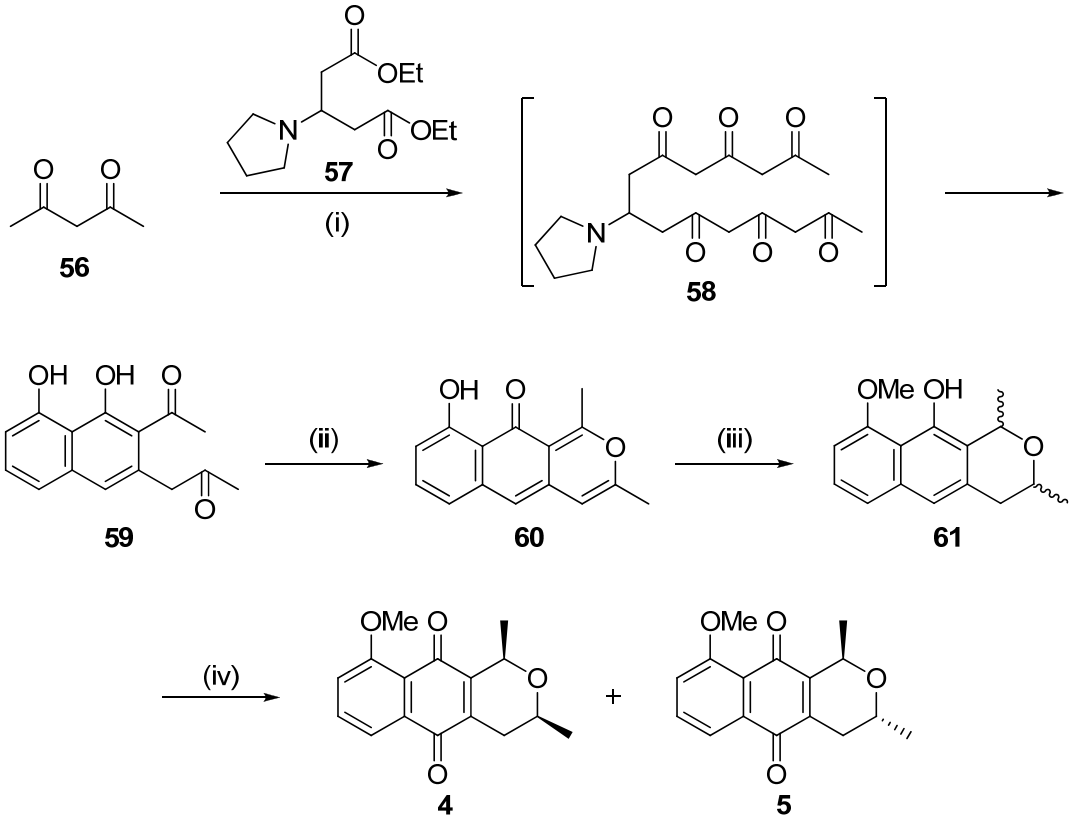
## 1.4 Selected Syntheses of Pyranonaphthoquinones

The various strategies that have been employed over the years has been comprehensively reviewed[2, 40] and this chapter will therefore only comprise of a few key examples.

### 1.4.1 Biomimetic approaches

The synthesis of eleutherin **4** and isoeleutherin **5** was achieved by Webb and Harris by adopting a biomimetic strategy.[41] In this approach, Webb and Harris constructed the key intermediate β-poly-carbonyl chain (Scheme 4). Starting from the 2-pyrrolidinyl glutarate diester **57**, tandem attacks of two equivalents of the dianion of acetyl acetone **56** provided

the heptaketide **58** which underwent spontaneous cyclisation furnishing the naphthyl diketone **59**. Given the many potential cyclisation products possible, the cyclisation of the polyketide precursor showed a high degree of regiospecificity. Cyclisation to form the third ring was accomplished by treatment with a catalytic amount of trifluoroacetic acid to produce **60**. Catalytic hydrogenation followed immediately by monomethylation in the absence of light furnished a 9:1 mixture of *cis*- and *trans*- **61**. The mixture was then oxidised using Fremy's salt, $(KSO_3)_2NO$ to afford the quinones **4** and **5** in a yield of 56%. The mixture could be converted exclusively into the *trans*-**5** by isomerisation in phosphoric acid.

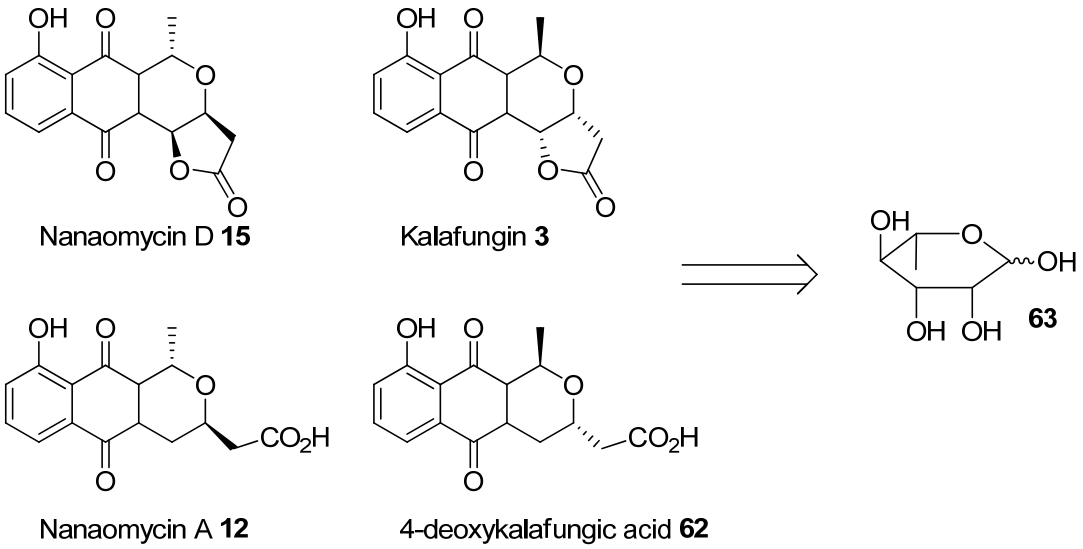



**Scheme 4:** *Reagents and conditions*: (i) LDA, THF, –78 °C, then **55**, –35 °C; (ii) EtOH, $CF_3CO_2H$ (cat), at reflux, quant. yield; (iii) 5% Pd/C, EtOH, $H_2$, rt, then $CH_2N_2$, $Et_2O$, 87%; (iv) $(KSO_3)_2NO$, 56%.

### 1.4.2 An enantiodivergent synthesis using a carbohydrate based Michael acceptor and phthalide annulation

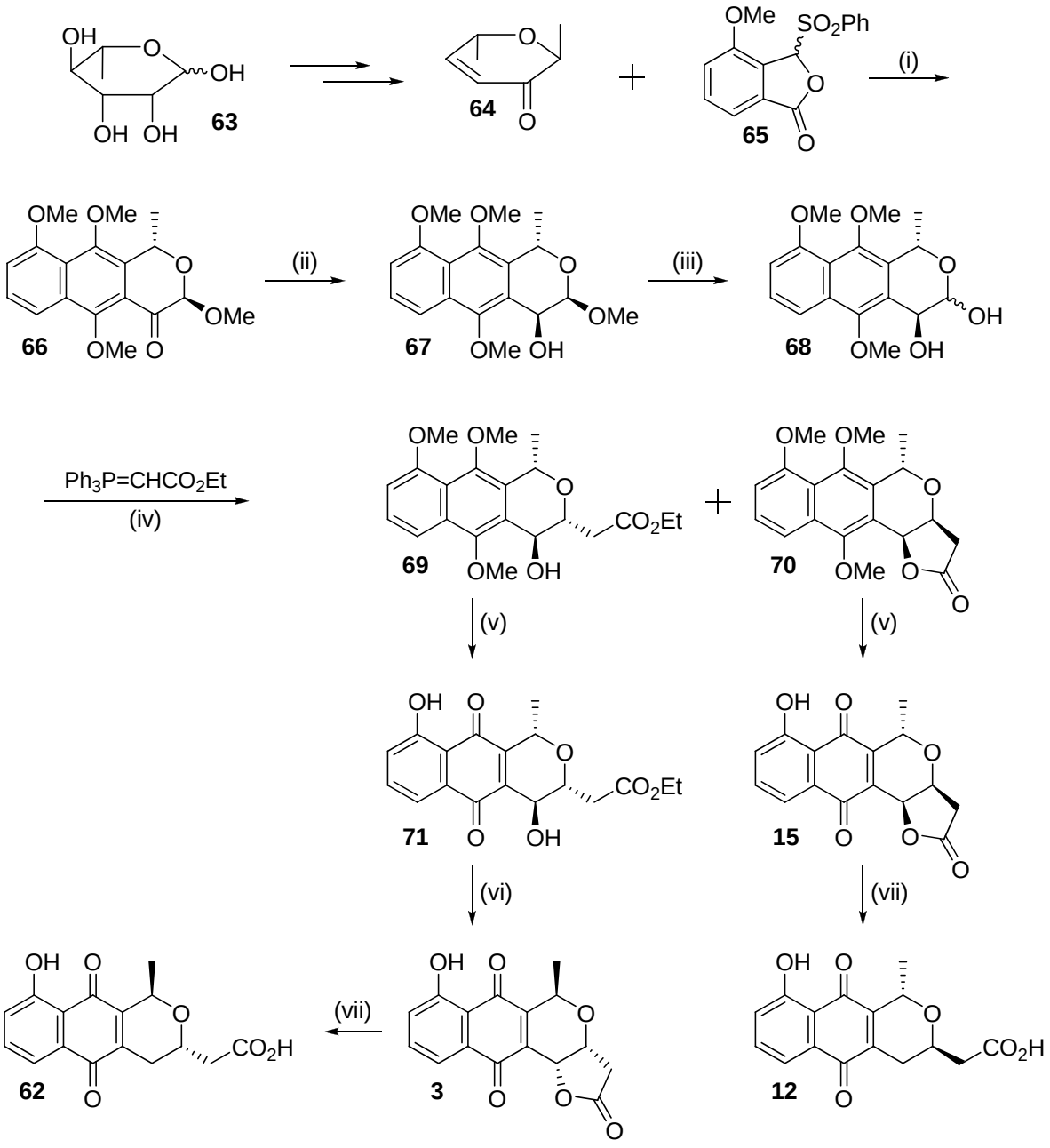
The first enantiospecific total syntheses of the optically active antibiotics nanaomycin A **12** and nanaomycin D **15** as well as their enantiomers kalafungin **3** and 4-deoxykalafunginic

acid **62**, were achieved by Tatsuta and co-workers using an enantiodivergent approach starting from optically active L-rhamnose **63** (Scheme 5).[42]




**Scheme 5**

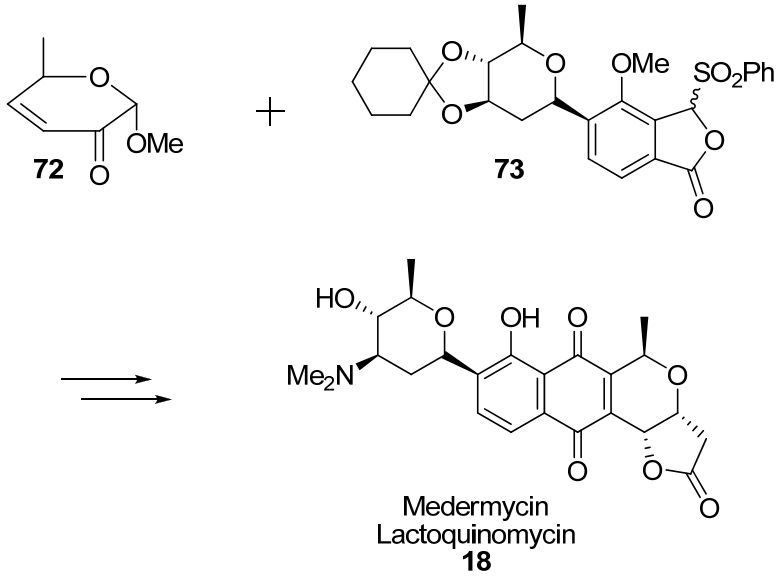
Summarised in Scheme 6, the enone **64,** from which the stereochemistry of the products are derived was synthesised from L-rhamnose, **63**. The enone was then condensed with the lithium *tert*-butoxide generated anion of the phthalide **65** and methylated to produce the pyranonaphthalene **66**. Subsequent reduction of the ketone **66** produced the alcohol **67** exclusively. Acid hydrolysis of the hemiacetal produced the key compound **68**, which was subjected to a Wittig olefination with carbonylmethylenetriphenylphosphorane, producing the ester **69** and the lactone **70**. The ester **69** results from an intramolecular Michael cyclisation of the intermediate α,β-unsaturated ester and the reaction ceases at this point for the *anti*-product but for the *syn*-product the benzylic alcohol and the just-formed ethyl ester are in close enough proximity to react and lactonisation takes place, to give **70** from *syn*-**69**, effectively resolving the diastereomers produced during step iv (Scheme 6). Oxidation and demethylation of the lactone **70** produced nanaomycin D **15**, which upon hydrogenolysis afforded nanaomycin A **12**. Similarly the ester **69** was converted into the quinone **71**, which was then epimerised at C1 and C4 to the preferred 1,3-*trans* configuration and lactonised to kalafungin **3**. Finally hydrogenolysis of **3** provided 4-deoxykalafunginic acid **62**.




**Scheme 6:** *Reagents and conditions*: (i) a: $^{t}$BuOLi, THF, −78 °C to rt, b: $Me_2SO_4$, $K_2CO_3$, $Me_2CO$, 40 °C, 80% over two steps; (ii) $NaBH_4$, MeOH, rt, 90%; (iii) 0.5 M HCl, AcOH, 75 °C, quant. yield; (iv) PhMe, heated to reflux, **69**: 53% and **70**: 41% ; (v) a: aq. CAN, MeCN, rt, b: $AlCl_3$, $CH_2Cl_2$, 0 °C to rt, **70**: 84%, **15**: 87%; (vi) $C_6H_6$, conc. $H_2SO_4$, 0 °C to rt, 92%; (vii) $PtO_2$, $H_2$, EtOH, **12**: 98%, **62**: 97%.

Five years later the same group utilised a similar strategy to accomplish the synthesis of another naturally occurring compound, medermycin **18** (Scheme 7).[43] In this case starting from D-rhamnal **72** as well as a carbohydrate derived phthalide **73** they completed the

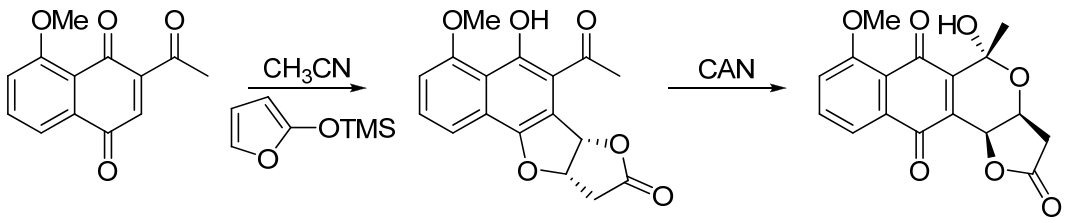
synthesis of medermycin **18** in 20 steps. The usefulness of this stereoselective synthesis was that it allowed for confirmation of its structural identity, which proved to be identical to the isolated medermycin as well as to the compound lactoquinomycin, putting to rest the debate that these two natural products were initially believed to be enantiomers of each other (both natural products were not compared to each other!)




**Scheme 7**

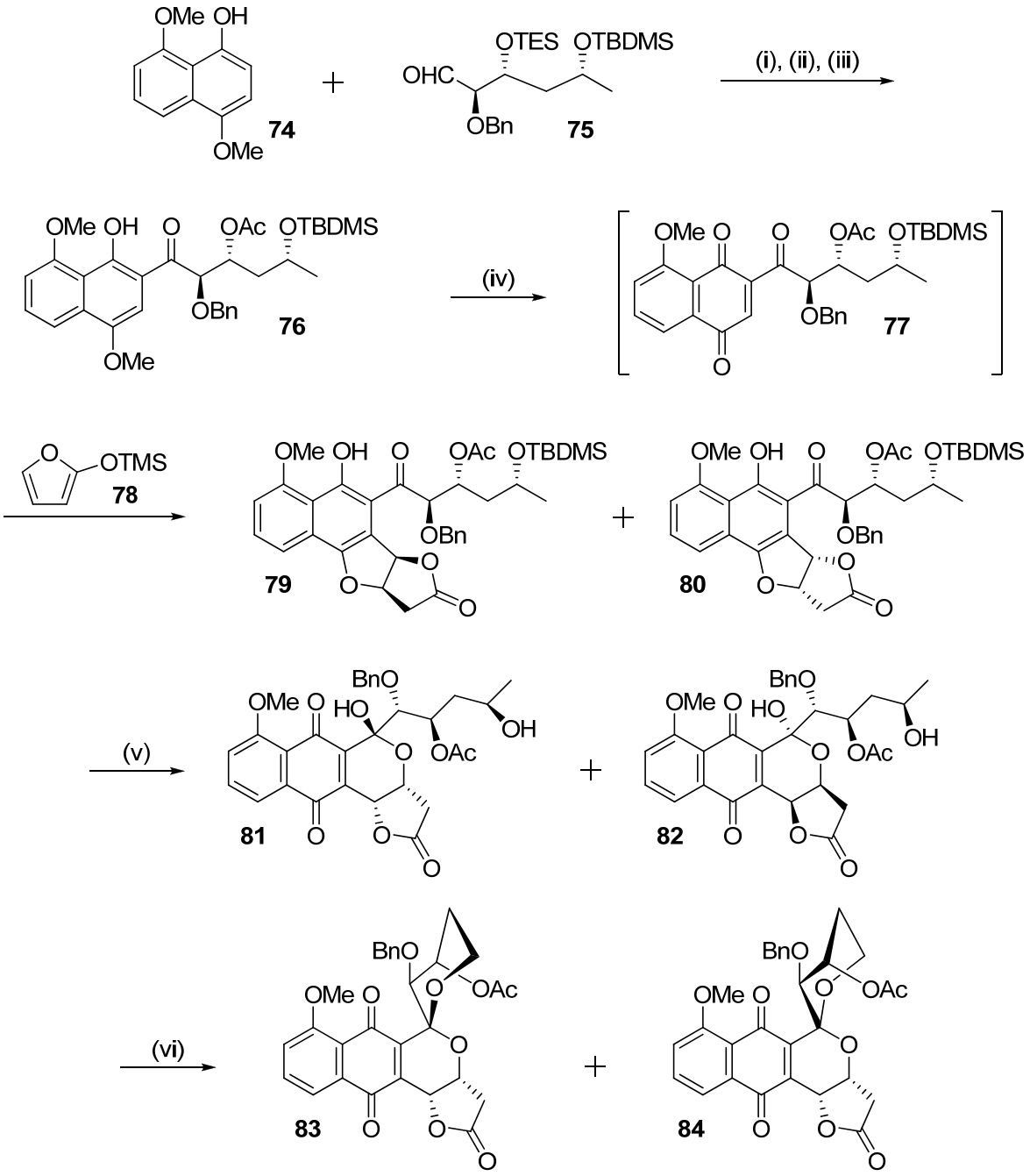
### 1.4.3 Furofuran annulations oxidative rearrangement

Another annulation strategy that has proven to be highly useful in the synthesis of pyranonaphthoquinones is the annulation of naphthoquinones with furans, followed by an oxidative rearrangement on treatment with ceric ammonium nitrate as shown in Scheme 8. The versatility of this procedure has been demonstrated extensively by Brimble and co-workers in the synthesis of analogues of griseusin A **17**,[44] medermycin **18**,[45] (see Figure 7) and kalafungin **3**.[46]




**Scheme 8**

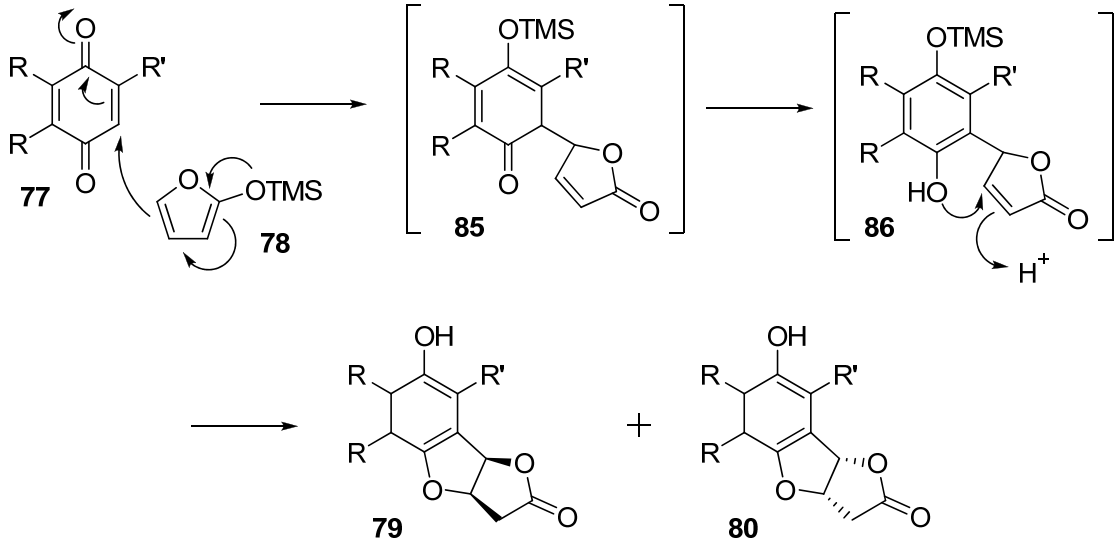
The synthesis of the analogues of griseusin A **83** and **84** is shown in Scheme 9 as an example of the application of this type of methodology.[44] The naphthol **74** and the chiral aldehyde **75** were combined with the use of a Lewis acid, followed by oxidation and acetylation to afford the ketone **76** as a single diastereomer. The key naphthoquinone **77** was then formed through an oxidative demethylation and immediately subjected to the furofuran annulation with 2-(trimethylsilyloxy)furan **78** to furnish a 1:1 mixture of furonaphthofurans **79** and **80**. Deprotection of this mixture followed by oxidative rearrangement with ceric ammonium nitrate afforded the isomeric lactols **81** and **82**. Finally acid-promoted spiroketalization produced an inseparable mixture of epimerised griseusin A analogues **83** and **84** in a 3:1 ratio.




**Scheme 9:** *Reagents and conditions*: (i) $TiCl_3(O^iPr)$, $CH_2Cl_2$, 0 °C, 9 min, 44%; (ii) $MnO_2$, $CH_2Cl_2$, 62%; (iii) $Ac_2O$, $CH_2Cl_2$, $Et_3N$, 41%; (iv) CAN, MeCN, $H_2O$ then **78**, 42% (1:1); (v) CAN, MeCN, $H_2O$, 5% HF, 48% (1:1); (vi) CSA, $CH_2Cl_2$, at reflux, 52% (3.2:1).

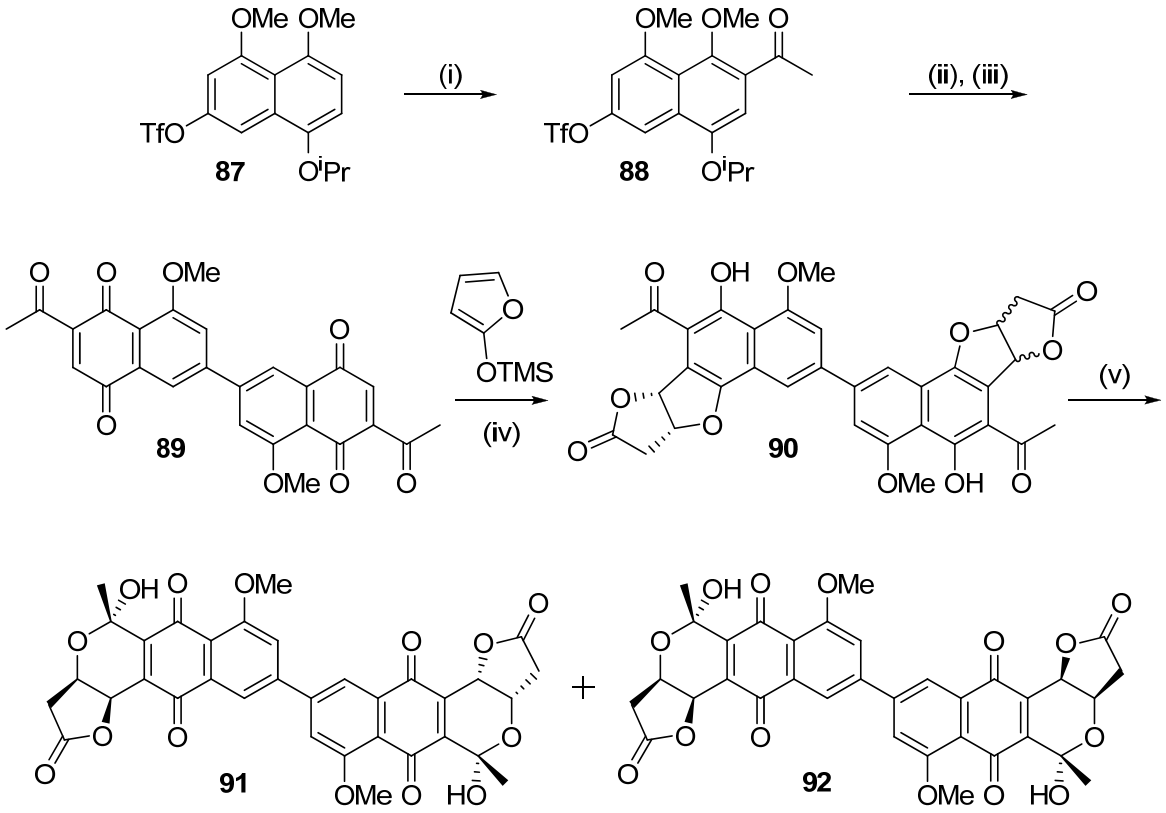
For the envisaged annulation reaction, the 2-trimethylsilyloxyfuran **78** adds *ortho* to the activating group on the quinone ring **77** through a 1,4 addition forming **85** (Scheme 10). This is followed by aromatisation and a second 1,4 addition of the resulting phenoxy group

of **86** onto the neighbouring butenolide moiety, providing the desired heterocycles **79** and **80**.




**Scheme 10**

The usefulness of this methodology was further exemplified in the 'bidirectional' synthesis of the regioisomeric analogues **91** and **92** of crisamicin A, a dimeric pyranonaphthoquinone (Scheme 11).[47] This strategy made use of a double furofuran annulation of *bis*-naphthoquinone **89**, previously obtained from a Suzuki-Miyaura homocoupling of the triflate **88**, obtained from **87**. Uncatalysed treatment of the *bis*-naphthoquinone **89** with an excess of 2-(trimethylsiloxy)furan produced the epimeric *bis*-furonaphthofurans **90** in a 1:1 ratio. Ceric ammonium nitrate mediated oxidative rearrangement effected the conversion to the pyranonaphthoquinones **91** and **92** as regiomeric analogues of naturally occurring crisamycin A **22** (see Figure 9).

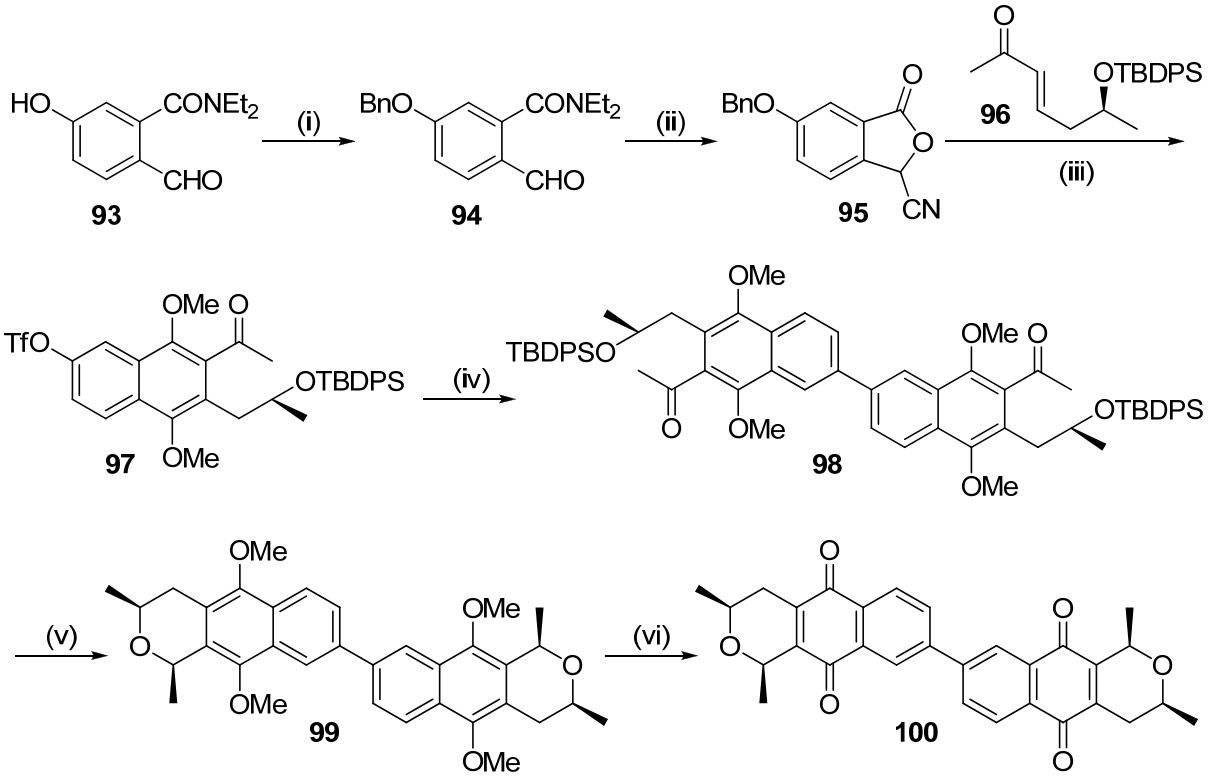



**Scheme 11:** *Reagents and conditions*: (i) AcOH, TFAA, rt, 5h, 32%; (ii) bis(pinacolato)diboron, $PdCl_2$(dppf), dppf, KOAc, dioxane, at reflux, 1.75 h, then triflate **88**, $PdCl_2$(dppf), $K_3PO_4$, dioxane, heated at reflux, 2.5 h 58%; (iii) AgO, $HNO_3$, dioxane, 10 min, 91%; (iv) MeCN, 0 °C, 1 h, 41% (1:1); (v) CAN, MeCN, $H_2O$, 15 min, 28%, (1:1).

### 1.4.4 Hauser-Kraus annulation

Expanding on this 'bidirectional' approach, Brimble and co-workers made use of a Hauser-Kraus annulation reaction to assemble a naphthoquinone monomer, which was subjected to a late stage homocoupling Suzuki-Miyaura reaction in order to achieve the enantioselective synthesis of the dimeric core of cardinalin 3 (Scheme 12).[48] The synthesis was achieved using the phenol **93**, obtained from commercially available *meta*-anisic acid, which was converted to the benzyl ether **94**. Ring closure and formation of the cyanophthalide annulation precursor **95** was then achieved using trimethylsilyl cyanide in the presence of catalytic potassium cyanide and 18-crown-6. Reaction of the cyanophthalide **95** and the enone **96** in the key Hauser-Kraus annulation reaction, followed immediately by reductive methylation, resulted in the production of a functionalised naphthalene, which was subsequently converted to the triflate **97** by initial removal of the benzyl protecting group and replacement with the triflate group. The homocoupling of the triflate **97** was achieved

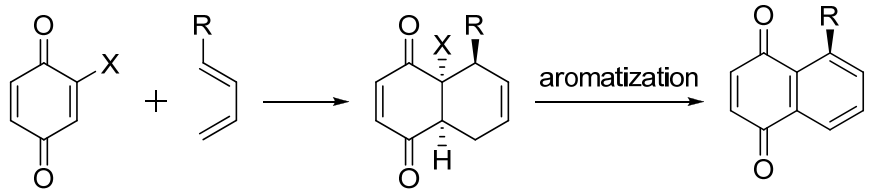
using palladium catalysis under microwave irradiation, the yield of which was found to be dependant of the addition of extra phosphine ligand. The newly formed biaryl **98** was then treated with TBAF to remove the silyl protecting groups and this was followed by a concomitant *in situ* cyclisation. The resulting lactol was immediately reduced to the more stable 1,3-dimethylpyran **99**. The 1,3-*cis* stereochemistry of **99** was unequivocally confirmed using NOE correlation as well as X-ray crystallographic analysis. Finally ceric ammonium nitrate mediated oxidative demethylation provided the model dimer **100**.




**Scheme 12:** *Reagents and conditions*: (i) BnBr, $K_2CO_3$, DMF, rt, 12 h; (ii) TMS-CN, KCN, 18-c-6, $CH_2Cl_2$, 0 °C, 2 h then AcOH, rt, 16 h, 90% from **93**; (iii) (a) $^tBuOK$, DMSO, rt, 15 min then NaOH, $Me_2SO_4$, TBAB, $Na_2S_2O_4$, THF/$H_2O$, rt, 16 h, 87%; (b) $H_2$, Pd/C, MeOH, rt, 16 h, 97%; (c) $PhN(Tf)_2$, DMAP, $NEt_3$, $CH_2Cl_2$, rt, 1 h, 95%; (iv) $PdCl_2$(dppf), dppf, bis(pinacolato)diboron, $K_2CO_3$, dioxane, microwave, 300 W, 150 °C, 1 h, 51%; (v) TBAF, THF then $CH_2Cl_2$, −78 °C, TFA, $Et_3Si$, rt, 16 h, 70%; (vi) CAN, $CH_3CN/H_2O$, rt, 45 min, 63%.

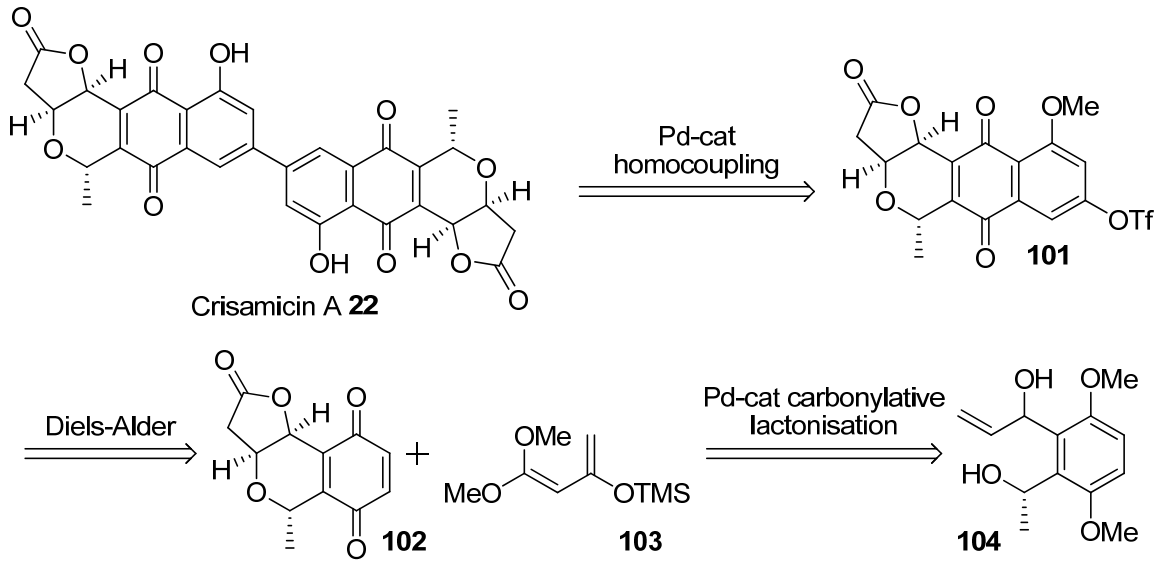
### 1.4.5 Cyclisation reactions – Diels-Alder methodology

One of the most general methods for the regiospecific syntheses of substituted quinones, used in the formation of the pyranonaphthoquinone unit,[2] involves the Diels-Alder reaction, pioneered by Rapoport and co-workers (Scheme 13).[49]




**Scheme 13**

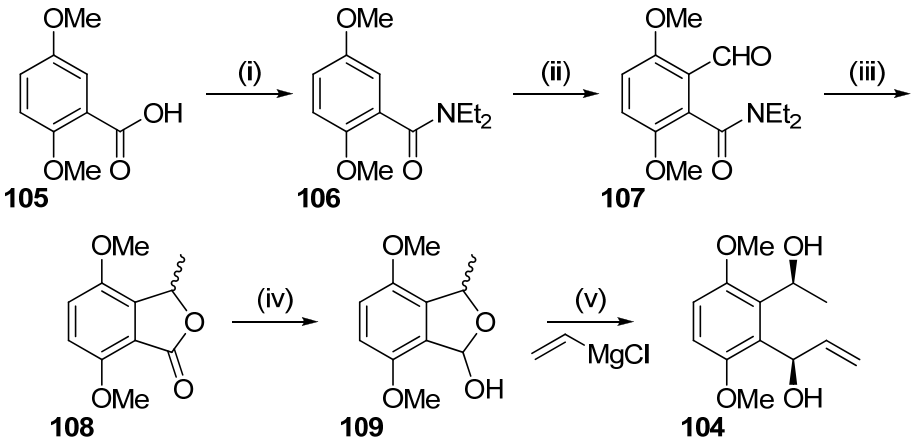
We now turn our attention to the first stereoselective synthesis of crisamicin A **22** by Yang *et al*. (Scheme 14) using Diels-Alder reaction methodology,[50] as well as a palladium catalysed alkoxycarbonylative lactonisation and a palladium catalysed homocoupling reaction.




**Scheme 14**

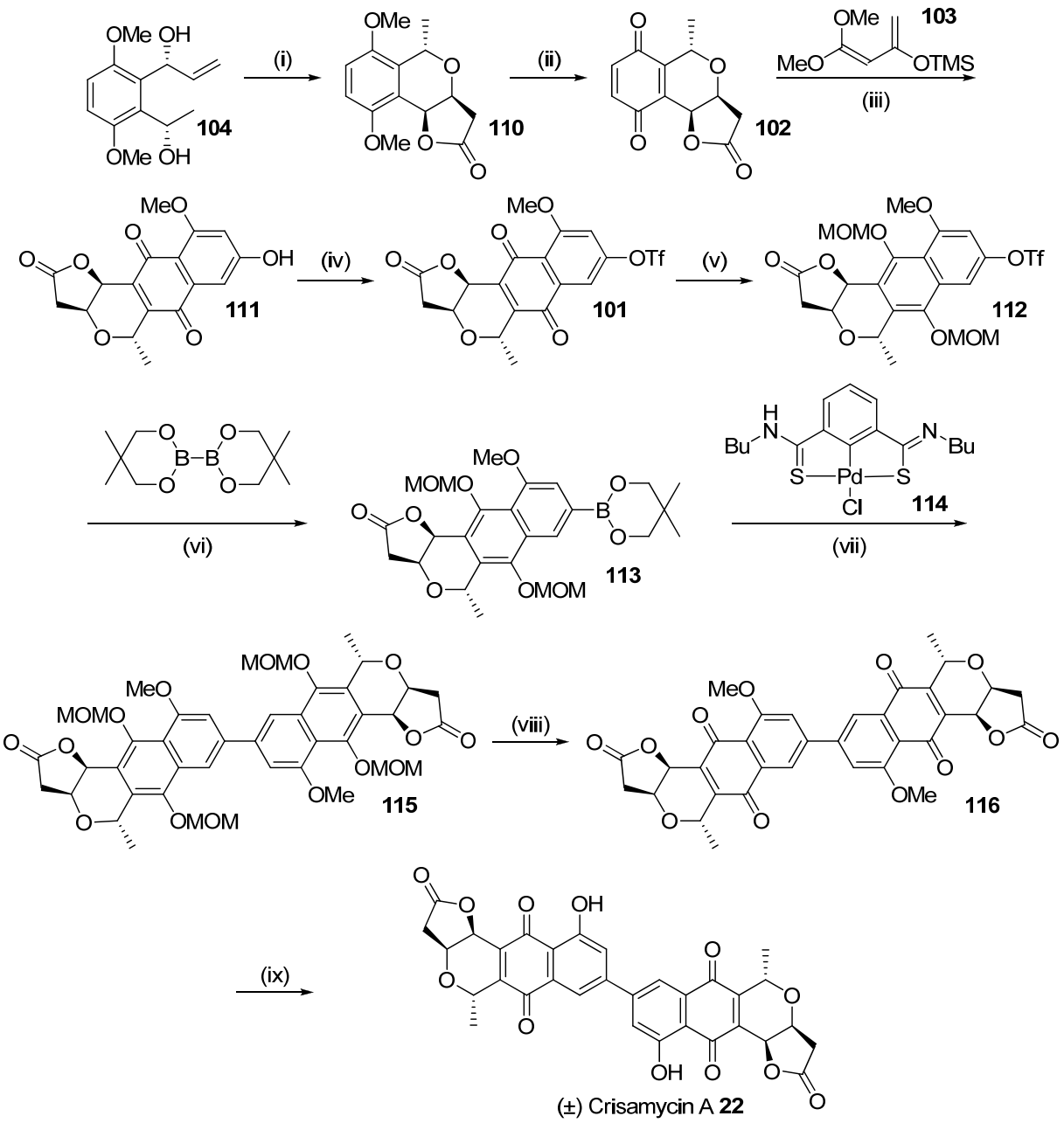
The synthesis of the key precursor **104** was achieved from the commercially available carboxylic acid **105** (Scheme 15), which was transformed to the amide **106** via the corresponding acid chloride. The amide facilitated a directed *ortho* metalation allowing for the instalment of the formyl functionality **107**. Subsequent Grignard addition to this aldehyde **107** formed the benzylic alcohol which could be lactonised under acid catalysed conditions to deliver the lactone **108**. Reduction of the lactone to form the hemiacetal **109**

paved the way for diastereoselective ring opening using vinyl magnesium chloride, affording the key diol **104**.




**Scheme 15:** *Reagents and conditions*: (i) $SOCl_2$, at reflux, $NHEt_2$, $CH_2Cl_2$, 93%; (ii) a: $^tBuLi$, TMEDA, THF, –78 °C, b: DMF, –78 °C to rt, 92%; (iii) a: MeMgCl, THF, rt, b: PTSA, toluene, at reflux, 89%; (iv) a: $LiAlH_4$, THF, 0 °C to rt; b: TEMPO, BAIB, $CH_2Cl_2$, rt, 79%; (v) THF, 40 °C, 59%.

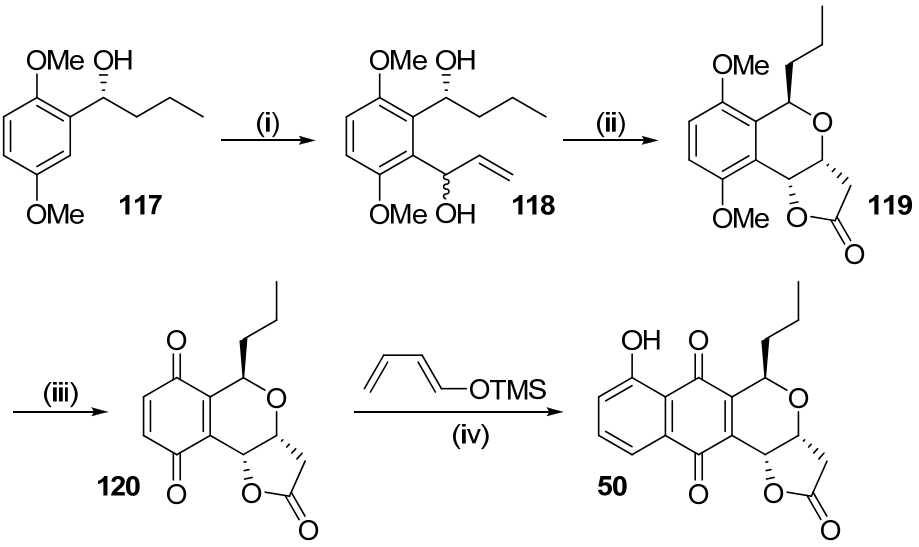
For the carbonylative annulation of the diol **104**, a palladium-thiourea catalyst system was identified to construct the pyran fused lactone ring system **110** (Scheme 16). A ceric ammonium nitrate oxidation of **110** produced the quinone **102** which was then subjected to a Diels-Alder cyclisation under Jones' conditions with the diene **103** to furnish the phenol **111**. The regioselectivity of the cyclisation was remarkably high (>20:1) presumably due to the stereoelectronic difference between the two quinone carbonyls that was dictated by the pyran fused moiety.[50] The phenol was then converted into the triflate **101** and subjected to a reductive protection forming **112**. The triflate **112** was then converted into the boronic ester **113** using a palladium catalysed boronylation and treated directly with a novel palladium-thiourea pincher complex **114** to give the homocoupled biaryl **115**. Deprotection of the hydroquinone moiety and subsequent air oxidation yielded the *bis*-quinone **116**. Finally, boron trichloride mediated demethylation gave crisamicin A **22** in an overall yield of 10% over 19 steps.




**Scheme 16:** *Reagents and conditions*: (i) $Pd(OAc)_2$/TMTU, $CuCl_2$, CO, THF, $NH_4OAc$, propylene oxide, 50 °C, 88%; (ii) CAN, MeCN, $H_2O$, −10 °C, 89%; (iii) Jones' reagent, 85%; (iv) $Tf_2O$, Pyr, DMAP, 78%; (v) a: $Na_2S_2O_4$, $Bu_4NBr$, THF, $H_2O$, b: MOMCl, DIPEA, DMAP, $CH_2Cl_2$; (vi) $PdCl_2$(dppf), dppf, KOAc, dioxane, 85°C, 76%; (vii) $Ag_2CO_3$, DMSO, $H_2O$, 87%; (viii) a: TMSBr, $CH_2Cl_2$, –78 °C to –40 °C, b: silica gel, air, rt, 93%; (ix) $BCl_3$, $CH_2Cl_2$, –78 °C to –40 °C, 91%.

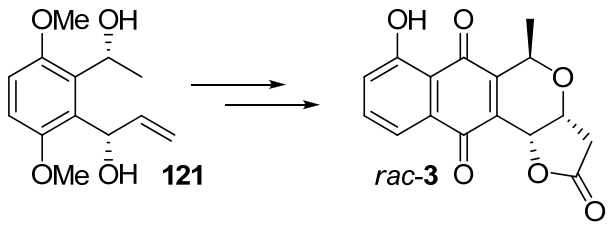
In the total syntheses of frenolicin **50** and racemic kalafungin *rac*-**3** (Scheme 17), Kraus *et al*. also make use of a highly regioselective Diels-Alder reaction.[51] For the synthesis of frenolicin, the starting alcohol **117** was derived from the stereoselective reduction of the

corresponding ketone. *Ortho* directed metalation of **117** using two equivalents of *n*-BuLi, followed by reaction with acrolein afforded the diol **118** as a mixture of diastereomers in a yield of 56%. The desired diastereomer (*R*,*S*)-**118** was isolated by flash chromatography. Cyclisation of **118** was then effected using palladium acetate and carbon monoxide to produce the lactone **119**, which was oxidised with silver(II) oxide forming the quinone **120**. A Diels-Alder reaction was carried out on **120** with 1-[(trimethyl)silyloxy]-butadiene and the Diels-Alder adduct was immediately treated with an excess of Jones' reagent to provide frenolicin B **50**.




**Scheme 17:** *Reagents and conditions*: (i) 2 equiv. *n*-BuLi, 0 °C to rt, acrolein, –78 °C; 56%; (ii) $Pd(OAc)_2$, CO, 65%; (iii) AgO, $HNO_3$, 95%; (iv) a: diene, $CH_2Cl_2$, –78 °C, b: Jones' reagent, 80%.

In the synthesis of racemic kalafungin *rac*-**3**, the same conditions were utilised, however in this case starting with the diol **121** (Scheme 18).




**Scheme 18**

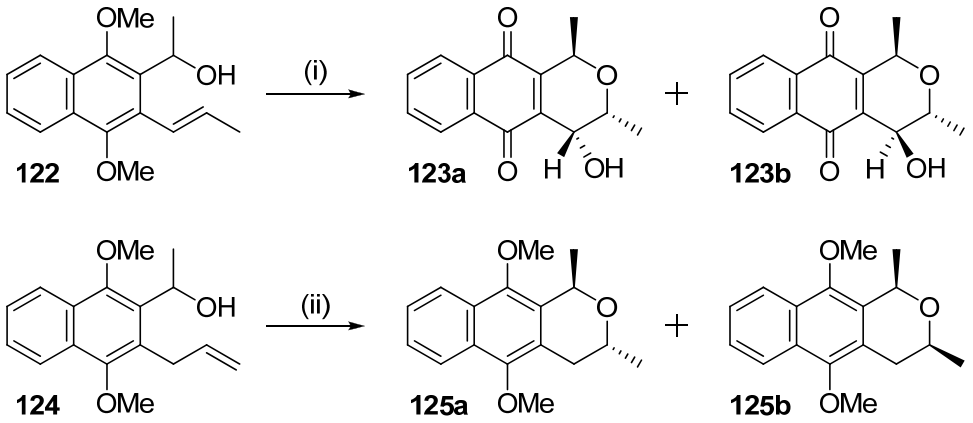
Various other pyranonaphthoquinones have been synthesised using this cycloaddition methodology whereby appropriately functionalised dienes and dienophiles are reacted to furnish the required oxygenation pattern.[2, 40]

### 1.4.6 Approaches to the formation of the pyran ring

In the above two examples, although not highlighted, the syntheses involved the formation of the pyran ring of the molecule using a palladium catalysed alkoxy carbonylation reaction. In this next section, syntheses of selected pyranonaphthoquinones and some analogues which also focus on the formation of the pyran ring system will be highlighted.

#### 1.4.6.1 Ring closure using potassium *tert* butoxide in dimethylformamide

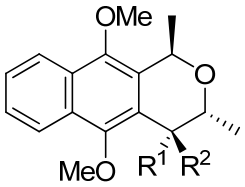
Having achieved the oxidative cyclisation of the naphthalene dimethyl ether **122** with ceric ammonium nitrate to the isomeric pyranoquinones **123** (Scheme 19),[52] Giles and co-workers discovered a novel cyclisation whilst attempting to isomerise the double bond into conjugation of the allylated naphthalene **124**, obtaining instead the pyranonaphthalenes **125**.[53]




**Scheme 19:** *Reagents and conditions*: (i) CAN, MeCN/$H_2O$, **123a**: 59%, **123b**: 20%; (ii) $^{t}$BuOK, DMF, 60 °C.

The interesting feature in this novel cyclisation is that the existing methods for the formation of naphthopyrans produce either a mixture of stereo-isomers or favour the *cis* isomer,[54, 55] whereas in this case the initial and major product of the reaction produces the *trans* isomer, with the *cis* isomer forming only on extended reaction time. Moreover, while **125a** and **125b** were formed when the reaction was performed in an inert atmosphere,

when the reaction mixture was exposed to air, products with the C4 position oxygenated **126** were also formed (Figure 15).

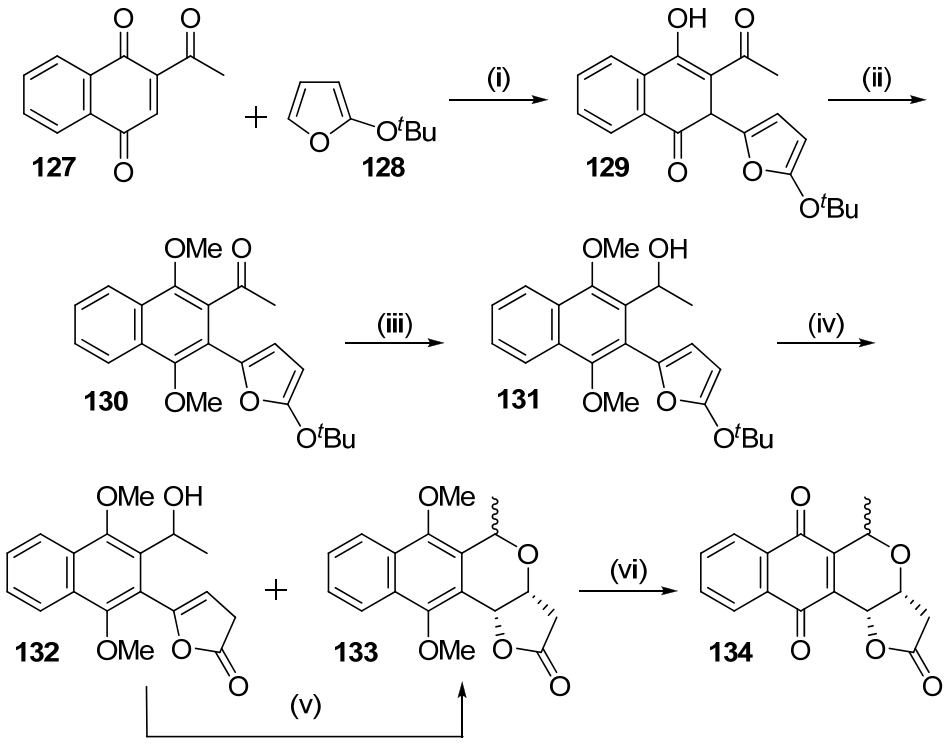



**126a** : $R^1$ = H and $R^2$ = OH
**126b** : $R^1$ = OH and $R^2$ = H

**Figure 15**

### 1.4.6.2 Michael additions

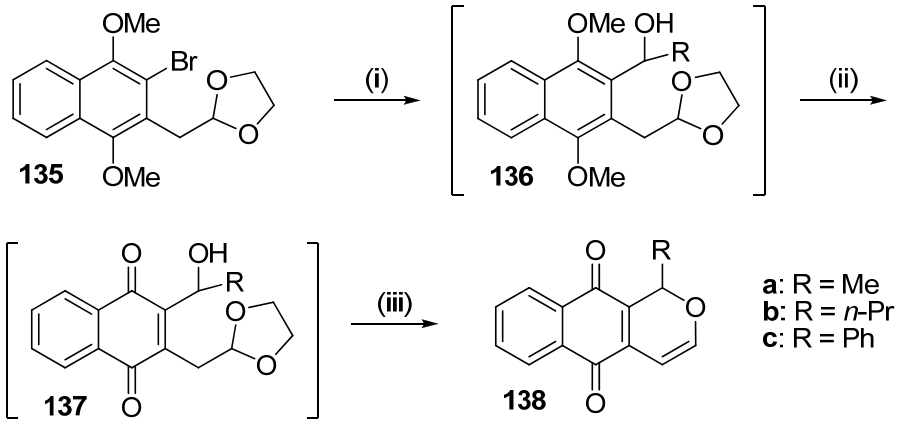
In 1978 Kraus and Roth completed the synthesis of 9-deoxykalafungin **134** (Scheme 20).[56] The assembly of the carbon framework was achieved by the slow addition of the alkoxy furan **128** to readily available 2-acetyl-1,4-naphthoquinone **127** at –78 °C, thereby forming the Michael adduct **129** without tautomerism to the hydroquinone. Compound **129** was then methylated to afford protected **130**, reduced to the secondary alcohol **131**, and then treated with trifluoroacetic acid to give a mixture of unsaturated β,γ-butenolide **132** as well as the desired the cyclised product **133**. Fortunately, the butenolide **132** was readily isomerised to the α,β-isomer and cyclised *in situ* to **133** by treatment with diazabicyclononene. Oxidative demethylation produced the target molecule **134** as a mixture of C1 epimers.




**Scheme 20:** *Reagents and conditions*: (i) toluene, −78 °C; (ii) $(CH_3)_2SO_4$, $K_2CO_3$, $Me_2CO$, at reflux, 62% over two steps; (iii) $LiAlH_4$, $Et_2O$, −10 °C, 95%; (iv) $CF_3CO_2H$, $CH_2Cl_2$, rt; (v) DBN, $C_6H_6$, 32% over the two steps; (vi) AgO, 95%.

### 1.4.6.3 Acid catalysed condensation

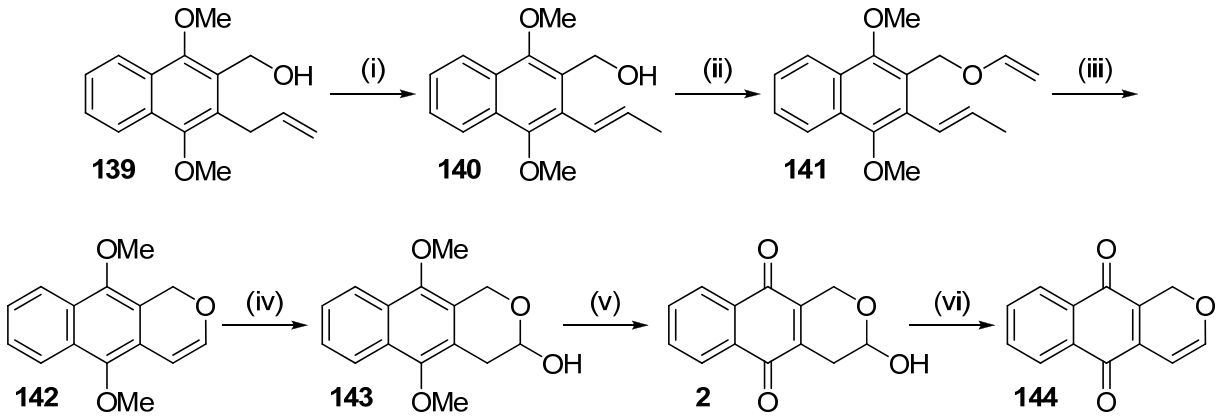
In their synthesis of several 1*H*-naphtho[2,3-*c*]pyran-5,10-diones **138** as analogues of pentalongin **144**, De Kimpe and co-workers employed an acid catalysed condensation.[57] In this procedure (Scheme 21), the synthesis begins with the acetal **135**, which undergoes a bromine–lithium exchange and subsequent condensation with several aldehydes to afford the alcohols **136a-c**. The alcohols were not purified and were immediately subjected to an oxidative demethylation forming the intermediate quinones **137a-c** which were cyclised using acid catalysis with concomitant loss of water, thereby producing the desired 1-alkyl or 1-phenyl-pyranonaphthoquinones **138a-c**.




**Scheme 21:** *Reagents and conditions*: (i) a: *n*-BuLi, THF, −78 °C, 10 min, b: RCHO, THF, −78 °C, 30 min, rt, 2 h, c: $H_3O^+$, (ii) CAN, $CH_3CN$, $H_2O$, rt, 30 min; (iii) TsOH (cat), $C_6H_6$, at reflux, 1 h, **138a**: 42%, **138b**: 34%, **138c**: 7%.

### 1.4.6.4 Ring closing metathesis

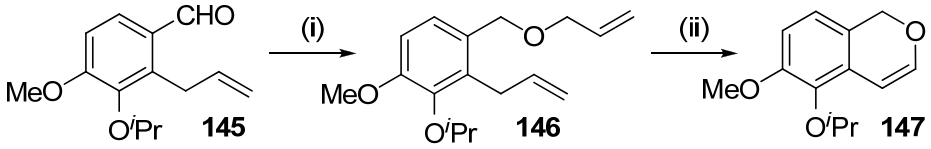
In 2004 De Kimpe and co-workers, completed the synthesis of psychorubin **2** and pentalongin **144** (this time without the C1 substituent), using ring closing metathesis as a key step (Scheme 22).[58] Starting from the allyl-naphthalene **139**, isomerisation of the double bond to the internal position using potassium *tert*-butoxide smoothly furnished the *E* isomer **140** exclusively. The benzylic alcohol was then *O*-vinylated affording **141**. With the required diene in hand, ring closing metathesis using the ruthenium Grubbs first generation catalyst afforded the benzoisochromene **142**. Hydration of the double bond under acidic conditions produced the hemiacetal **143**, paving the way for an oxidation using ceric ammonium nitrate affording the quinone psychorubin **2**. Finally, dehydration of **2** yielded pentalongin **144**.




**Scheme 22:** *Reagents and conditions*: (i) $^t$BuOK, THF, rt, 3 h, 95%; (ii) vinyl acetate, $Na_2CO_3$, $[IrCl(cod)]_2$, 100 °C, 12 h, 96%; (iii) Grubbs I, toluene, rt, 12 h, $N_2$, then 100 °C, 12 h, 86%; (iv) *p*-

TsOH, $CH_3CN$, $H_2O$, 100 °C, 3 h, 75%; (v) CAN, $CH_3CN$, $H_2O$, rt, 30 min, 91%; (vi) *p*-TsOH (cat), $C_6H_6$, 80 °C, 20 min, 72%.

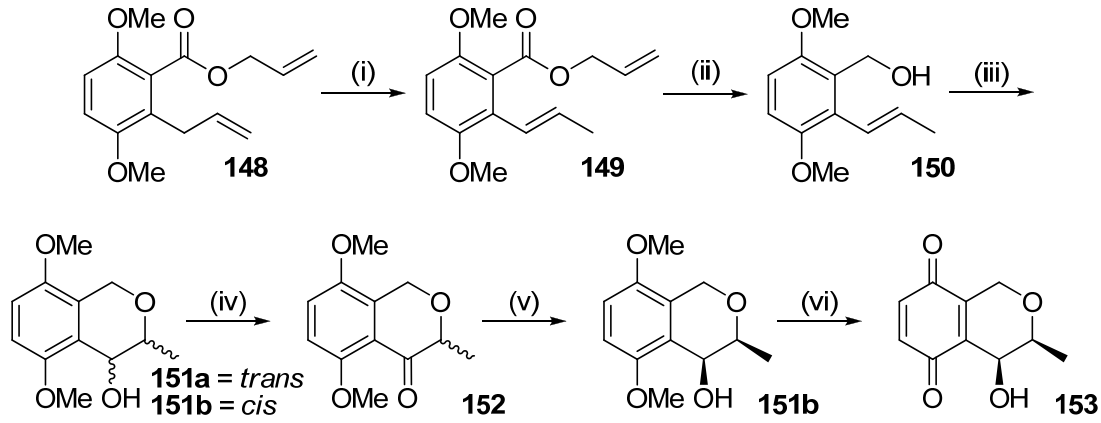
A similar strategy was used by van Otterlo *et al*. in their syntheses of benzo-fused heterocycles.[59-61] By employing a one-pot tandem isomerisation and subsequent ring closing metathesis reaction of **146** with the aid of two ruthenium catalysts, they synthesised the isochromene skeleton **147** ( Scheme 23).




**Scheme 23:** *Reagents and conditions*: (i) a: $LiAlH_4$, THF, 40 °C, 12 h, 86%, b: Allyl bromide, NaH, THF, at reflux, 20 h, 77%; (ii) a: $[RuClH(CO)(PPh_3)_3]$, toluene, 80 °C, b: Grubbs II (cat), toluene, 60 °C, 83% over two steps.

### 1.4.6.5 Oxidative mercury mediated ring closure

In their synthesis of isochroman-4-ol **153** as a model for naturally occurring pyranonaphthoquinones with C4 oxygen substituents, de Koning *et al*. made use of an oxidative mercury mediated ring closure method (Scheme 24).[62] After synthesising the required ester **148**, isomerisation using potassium *tert*-butoxide gave exclusively the *trans* isomer **149**. The ester functionality was then reduced with lithium aluminium hydride and the resulting alcohol **150** was treated with mercury(II) acetate, followed by reduction of the intermediate acetoxymercuri-isochromane using sodium borohydride in an oxygenated solution of DMF to afford the mixture of diastereomers **151a** and **151b** in a 1:1 ratio. Oxidation of the mixture to the corresponding racemic ketone **152** was achieved using pyridinium chlorochromate, facilitating a stereoselective reduction using lithium aluminium hydride to re-introduce the alcohol as exclusively the *cis* diastereomer **151b**. Treatment with silver(II) oxide finally afforded the desired quinone **153**.



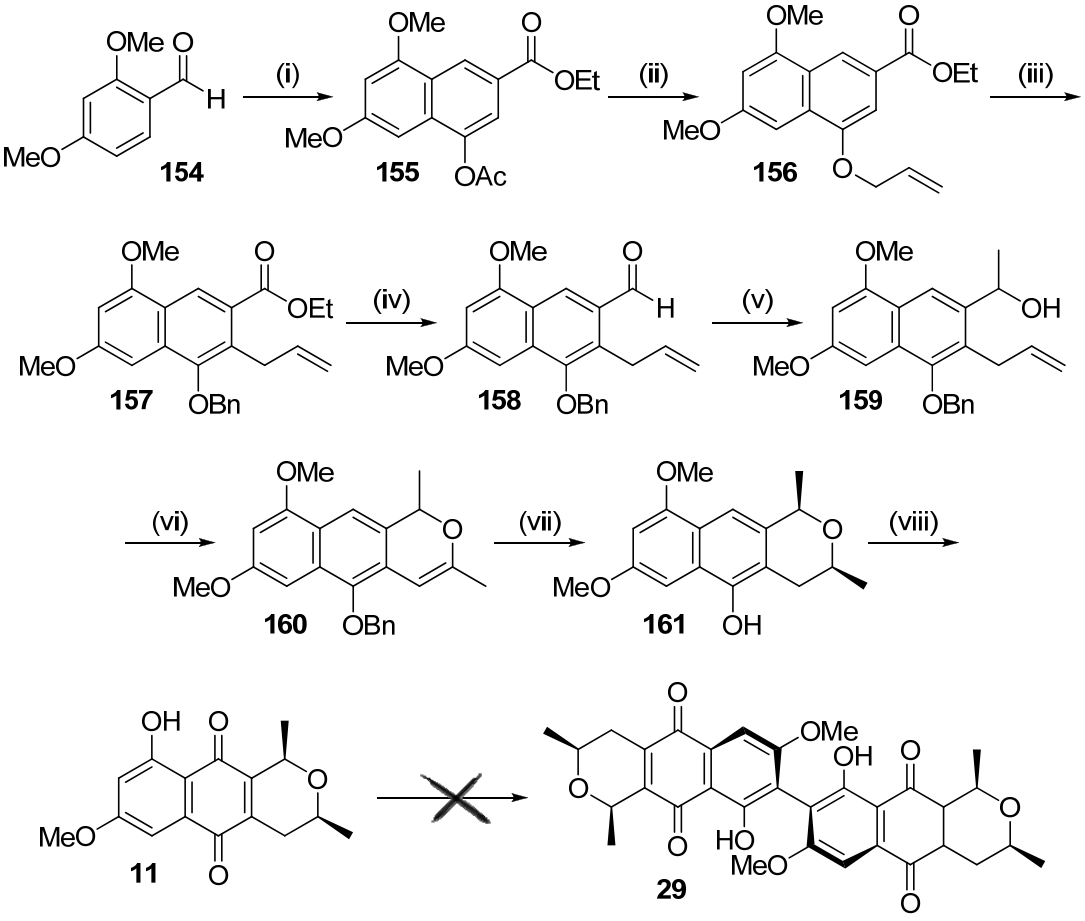

**Scheme 24:** *Reagents and conditions*: (i) $^{t}$BuOK, DMF, rt 15 min, 99%; (ii) $LiAlH_4$, $Et_2O$, 12 h, 98%; (iii) a: $Hg(OAc)_2$, THF, 15 min, b: $NaBH_4$, DMF, $O_2$, 86%; (iv) PCC, $CH_2Cl_2$, 74%; (v) $LiAlH_4$, $Et_2O$, 80%; (vi) AgO, $HNO_3$, dioxane, 89%.

## 1.5 Aims of this Project

Ongoing research in our laboratories has focused on developing efficient and novel methodology to synthesise pyranonaphthoquinones. This research has involved model studies on suitable precursors,[62-64] and then utilising this newly gained expertise to synthesise naturally occurring pyranonaphthoquinones.[65, 66]

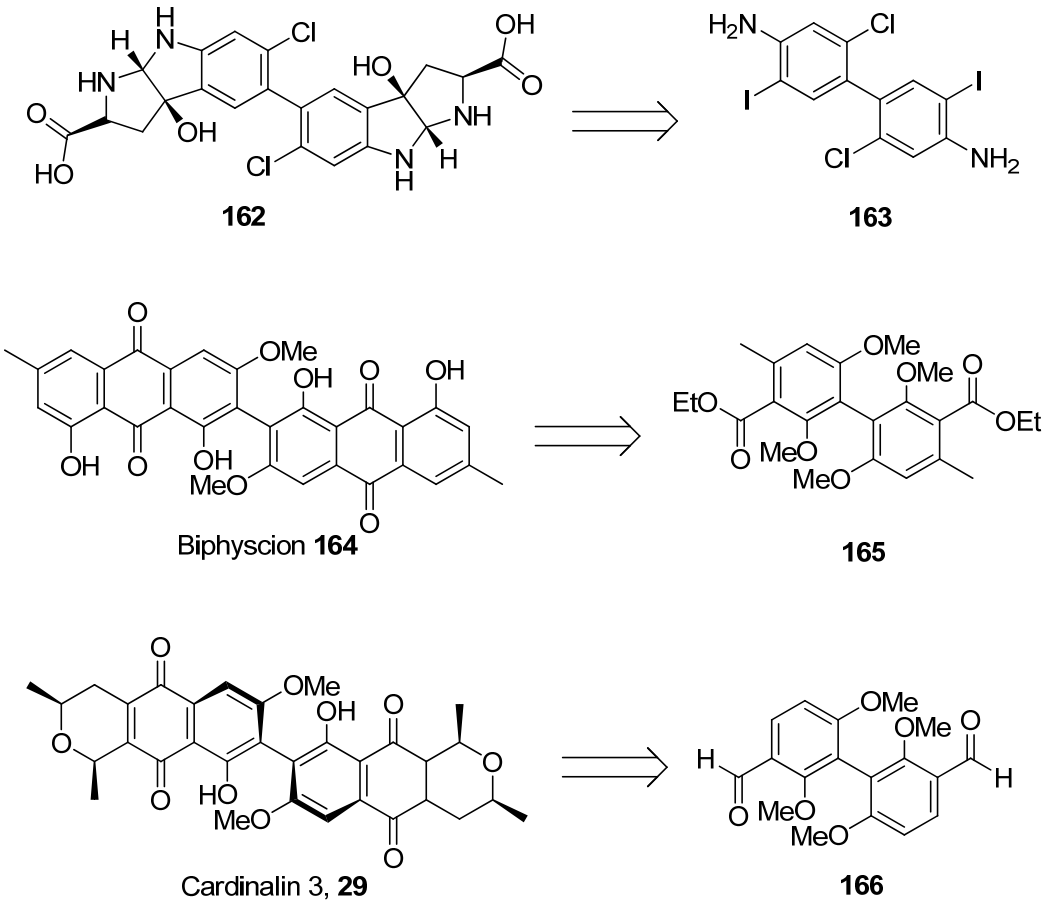
In 2006 our research group successfully completed the synthesis of the naturally occurring pyranonaphthoquinone ventiloquinone L **11**, which is in fact, as mentioned previously, also the monomer of another naturally occurring compound, cardinalin 3 **29**.[65, 66] The synthesis was achieved in 13 steps, starting from dimethoxy benzaldehyde **154** and in an overall yield of 7.7% (Scheme 25). Construction of the naphthalene ring system **155** was accomplished by subjecting the aldehyde **154** to a Stobbe condensation with diethyl succinate. This was followed by the removal of the acetate protecting group and the introduction of an allyl side chain onto the resulting phenol, affording **156**. A Claisen rearrangement reaction facilitated the rearrangement of the allyl group to the C2 position, and the resulting phenol was once again protected, this time as the benzyl ether **157**. The ester functionality was then converted into an aldehyde **158** by reduction with lithium aluminium hydride and subsequent oxidation with pyridinium chlorochromate. Grignard addition to the aldehyde by employing methyl magnesium iodide produced the racemic **159**, setting the stage for a Wacker oxidation, which proceeded in excellent yield thereby constructing the required pyran ring pyranonaphthoquinone **160**. Hydrogenation using

palladium on carbon performed the double task of reducing the double bond and removing the benzyl protecting group as planned, and in fact produced the desired *cis* isomer **161** as the major product albeit in a mediocre yield. The phenolic ring system was oxidised to the corresponding quinone and finally removal of the methyl protecting group afforded the naturally occurring target molecule, ventiloquinone L **11**. Unfortunately all attempts to 'dimerise' this molecule to produce the naturally occurring cardinalin 3 **29** proved unsuccessful.




**Scheme 25:** *Reagents and conditions*: (i) a: diethyl succinate, $^{t}$BuOK, $^{t}$BuOH, at reflux, 2h, b: NaOAc, $Ac_2O$, 140 °C, 2 h, 77%; (ii) a: guanidine-HCl, EtOH, $CH_2Cl_2$, rt 1 h, 95%, b: allyl bromide, $K_2CO_3$, $Me_2CO$, at reflux, 16 h, 99%; (iii) a: DMF, 170 °C, 12 h, 75%, b: BnCl, $K_2CO_3$, KI, $Me_2CO$, boiled at reflux, 18 h, 100%; (iv) a: $LiAlH_4$, THF, 0 °C to rt, 18 h, 95%, b: PCC-$Al_2O_3$, $CH_2Cl_2$, rt, 8 h, 78%; (v) MeMgI, $Et_2O$, THF, 0 °C to rt, 8 h, 95%; (vi) $PdCl_2$(cat), $CuCl_2$, $H_2O$, DMF, rt, $O_2$, 3 h, 92%; (vii) Pd/C (cat), $H_2$, $CH_2Cl_2$ (500KPa), $CH_2Cl_2$, dioxane, rt 48 h, 45%, (3:1 *cis*:*trans*); (viii) a: salcomine , DMF, $O_2$, rt, 18 h, 90%, b: $BCl_3$, $CH_2Cl_2$, –78 °C, 70%.

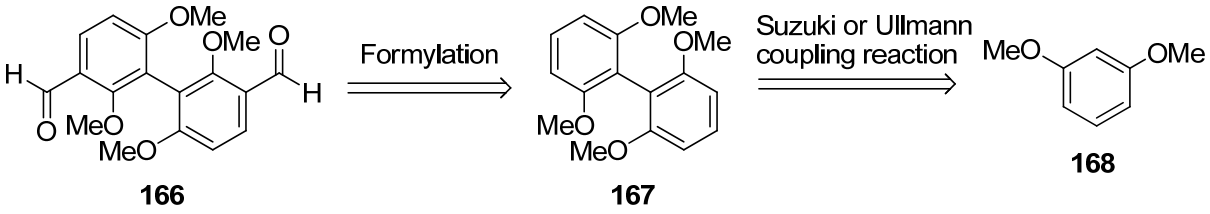
Having discovered that coupling of the fully functionalised monomer units was not feasible for the synthesis of the dimeric cardinalin 3 **29**, our aim for this project was to attempt the formation of the biaryl axis at an earlier stage, and then build onto both sides of this dimeric scaffold in a symmetrical fashion in order to achieve the synthesis of cardinalin 3 in a 'bidirectional manner'. This type of methodology has been used successfully for a number of compounds which contain a $C_2$ axis of symmetry.[67, 68] For example, for the synthesis of the central amino acid of chloptosin **162**, the bidirectional approach was employed starting from the biaryl diamine **163**.[69] As a second example synthesis of the *bis*-anthraquinone, biphyscion **164** was achieved starting from the symmetrical functionalised resorcinol derivative **165** (Scheme 26). Therefore we envisage that the synthesis of our target molecule, cardinalin 3 **29** could be realised through this 'bidirectional approach', by initially constructing the key biaryl resorcinol derivative **166**.




**Scheme 26**

Since the diformylated resorcinol derivative **166** shown above is really the biaryl version of the dimethoxy benzaldehyde **154**, which led to the successful synthesis of the

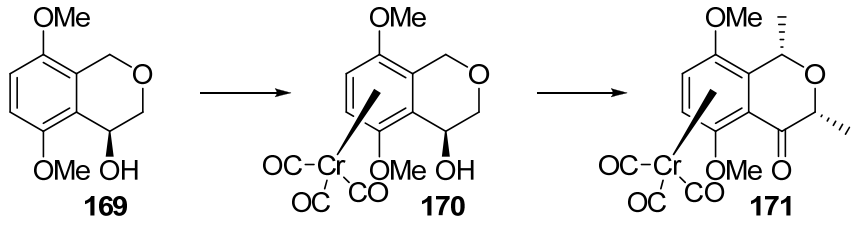
monomeric ventiloquinone L **11** (See Scheme 25), we envisage that similar methodology applied to **166** may lead to cardinalin 3 **29**. Therefore, this desired precursor **166** can be disconnected to tetramethoxy benzene **167**, through a retro formylation. For the formation of **167**, we can take advantage of various coupling reactions on commercially available 1,3-dimethoxybenzene **168** to facilitate the C8-C8′ biaryl linkage (Scheme 27).




**166** **167** **168**

**Scheme 27**

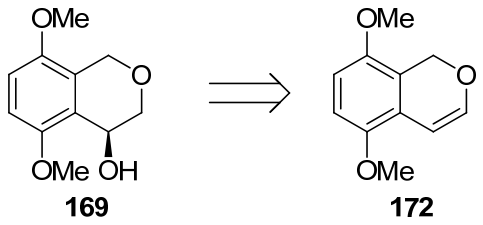
Another aspect of interest to us was the stereoselective addition of the methyl substituents to the C1 and C3 positions of the pyran ring, required for cardinalin 3 **29**. We envisaged that this could be achieved through the use of arene chromium tricarbonyl chemistry (Scheme 28). If a chromium tricarbonyl moiety can be attached selectively to one face of the arene ring of **169**, effectively blocking this face forming **170**, it could thereby sterically direct subsequent reactions to the opposite face affording **171**, provided the benzylic alcohol **170** could initially be oxidised to give its related ketone. We have successfully developed the methodology for the enantiomeric synthesis of the isochromanol *ent*-**169**,[70] which is a suitable subunit of the pyranonaphthoquinone molecule for our model study.




**169** **170** **171**

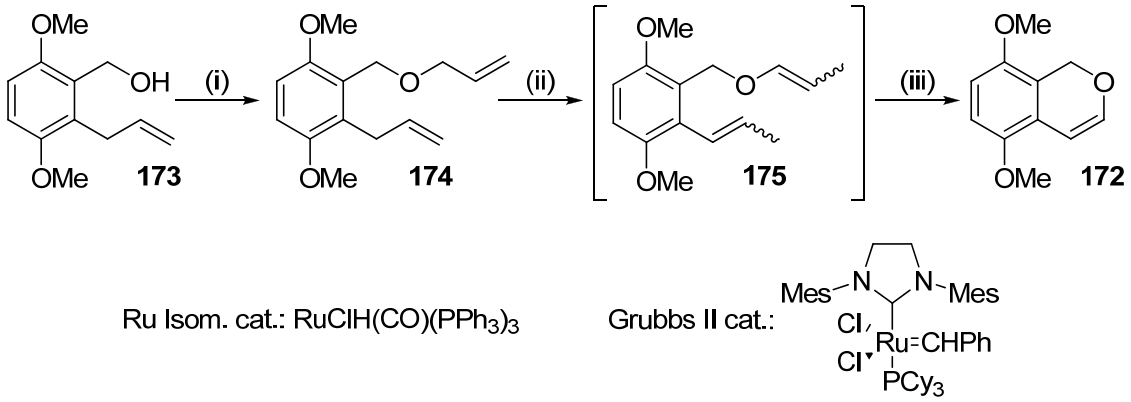
**Scheme 28**

The synthesis of isochromanol **169** was achieved from the isochromene **172** (Scheme 29), by means of a hydroboration-oxidation reaction.



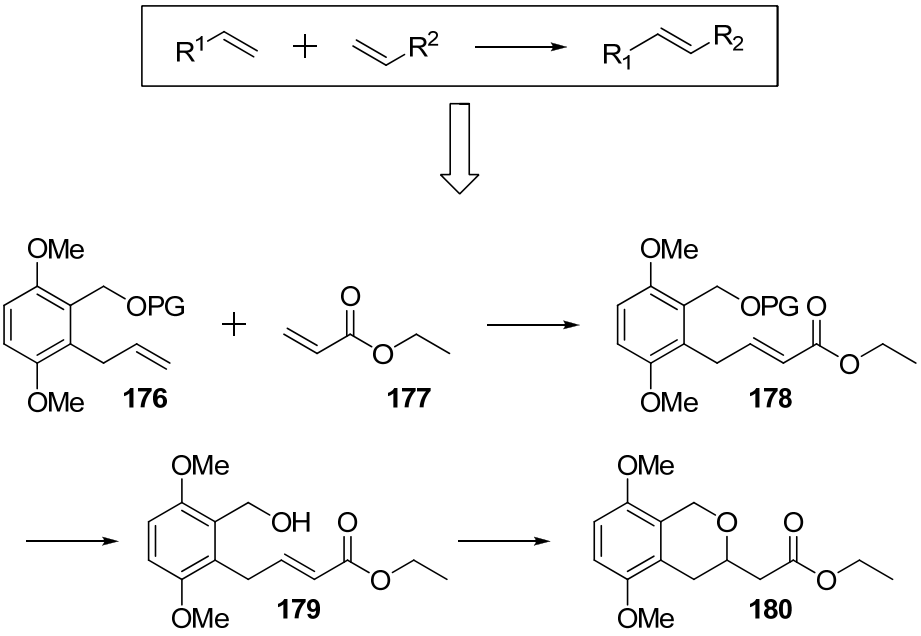

**Scheme 29**

The synthesis of the isochromene **172** was achieved through the ring closing metathesis of the intermediate **175** derived from the isomerisation of **174**, which was in turn synthesised from the benzylic alcohol **173** (Scheme 30).



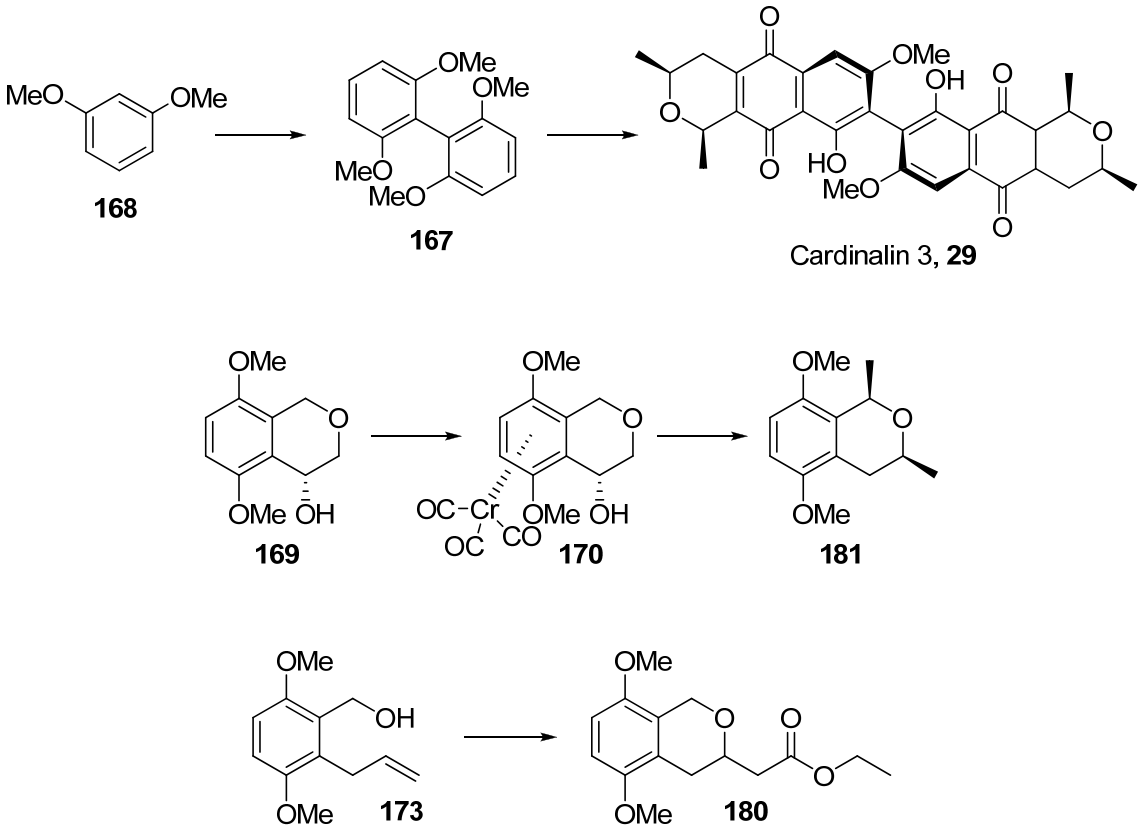

**Scheme 30:** *Reagents and conditions*: (i) allyl bromide, NaH, THF, 24 h, 91%; (ii) Ru isom. cat., 90 °C, 3h; (iii) Grubbs II (cat), toluene, 70 °C, 24 h, 85%.

Since ring closing metathesis had proven to be useful in deriving these compounds, we were also interested in investigating whether cross metathesis may be useful (Scheme 31). We envisaged that cross metathesis of **176** and **177** may prove useful to introduce an α,β-unsaturated ester moiety **178** in the *ortho* position to the benzylic alcohol **176**. Following this, we could then construct the pyran ring system **180** using an intramolecular Michael addition.




**Scheme 31**

Thus the aims of this project were firstly, to synthesis the naturally occurring pyranonaphthoquinone cardinalin 3 **29**, employing a bidirectional approach. Next we were interested in making use of arene chromium tricarbonyl chemistry for the stereoselective addition of substituents to the C1 and C3 positions of the pyran ring, using the isochromanol molecule **168** as a suitable model system. Finally, we intended investigating the use of cross metathesis as a new method for generating suitable precursors to C3 substituted pyranonaphthoquinones e.g. **179** from the benzylic alcohol **172** (Scheme 32).

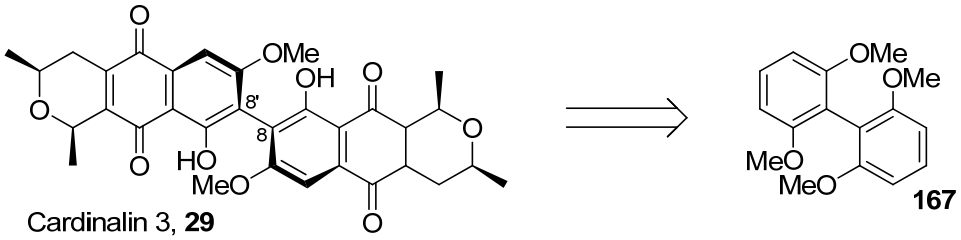

MeO
OMe
168
OMe
OMe
MeO
MeO
167
O
OMe
OH
O
O
O
HO
MeO
O
O
Cardinalin 3, 29
OMe
O
OMe OH
169
OMe
O
OC
Cr
CO
OC
OMe OH
170
OMe
O
OMe
181
OMe
OH
OMe
173
OMe
O
O
O
OMe
180

**Scheme 32**

# Chapter 2: The Synthesis of Cardinalin 3 and Novel Syntheses of Isochromanes

## 2.1 The Synthesis of Cardinalin 3: A Bidirectional Approach

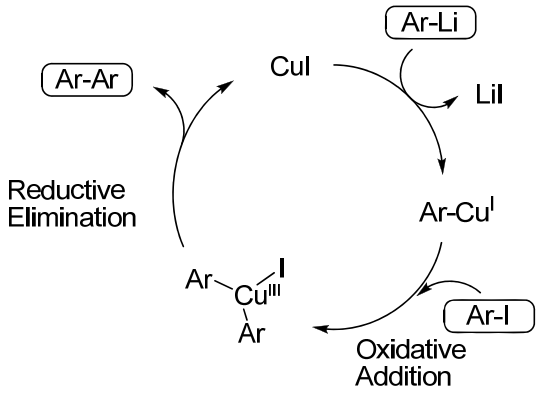
Our interest in the synthesis of the naturally occurring pyranonaphthoquinone cardinalin 3 **29** stemmed from the idea where we envisioned that a 'bidirectional approach' may in fact prove to be very effective. In line with this, we sought to create the C8-C8′ linkage between the two pyranonaphthoquinone monomers early in the synthesis, thereby generating a simple, but useful biaryl, such as for instance **167** (Scheme 33). We envisaged that this key step could be accomplished by transition metal mediated reactions, utilising the Suzuki coupling reaction or the Ullmann coupling reaction.[71, 72]




**Scheme 33**

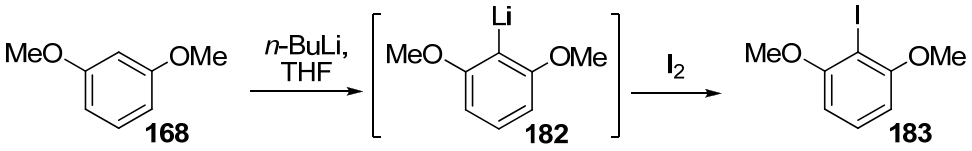
### 2.1.1 Formation of the biaryl axis

The use of transition metal mediated reactions for the formation of biaryl axes is an area which has received a significant amount of attention over the last two decades. However this methodology actually dates back to nearly a century ago where Fritz Ullmann employed copper to facilitate the coupling of two aryl halides in a reaction which now bears his name.[73] The generally accepted mode of coupling in this type of reaction is believed to be the interaction of an aryl copper species with an aryl halide, although, given the many oxidation and coordination states of copper, the actual mechanism of biaryl formation is controversial. One proposed mechanism involves a copper(I) intermediate,[74] which undergoes oxidative addition to form a copper(III) complex, and subsequently undergoes reductive elimination to release the biaryl product (Scheme 34).




**Scheme 34**

We envisaged that the dimeric scaffold **167** (See Scheme 33) would be an appropriate starting point for the bidirectional synthesis of cardinalin 3, and its synthesis could be accomplished using an Ullmann coupling reaction. We would therefore require the corresponding halogenated 1,3-dimethoxy benzene and the analogous copper substituted 1,3-dimethoxy benzene as the coupling partners for the reaction. Since the ease of displacement of the halogen from the aromatic ring is generally in the order: I>Br>Cl>F,[75] we envisaged that the most effective substrate for the halide portion would be 2-iodo-1,3-dimethoxy benzene **183** (Scheme 35). This molecule was easily attained by way of *ortho* directed lithiation of commercially available 1,3-dimethoxy benzene **168** at 0 °C, followed by treatment with iodine. Pleasingly, the progress of the reaction was easy to follow as the lithiated dimethoxy benzene **182** reacted rapidly with the iodine solution as it was added, resulting in a rapid disappearance of the brown colour associated with the iodine. The first persistence of the brown colour indicated that the lithiated 1,3-dimethoxy benzene had been completely consumed. Fortuitously, the 1,3 dispositions of the *ortho* directing methoxy groups rendered the C2 position by far the most reactive, resulting in selective iodination at this position.

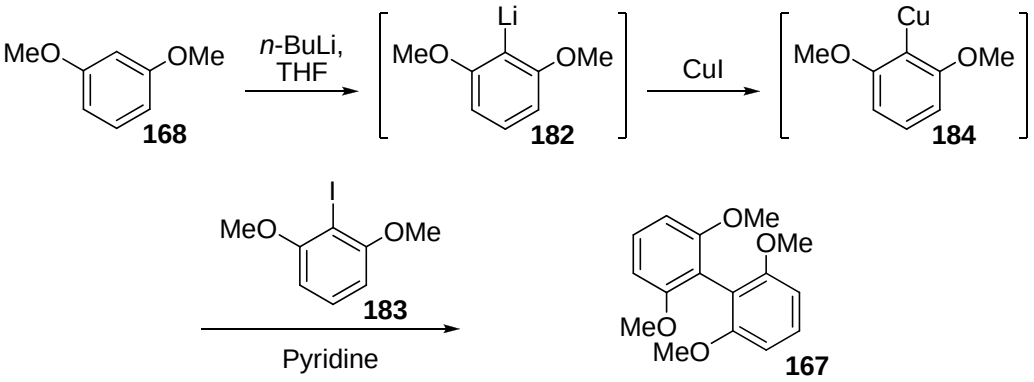



**Scheme 35**

The formation of the halide aryl **183** was confirmed spectroscopically, using $^{1}H$ and $^{13}C$ NMR spectra – the presence of an internal mirror plane resulting in an uncomplicated

spectrum. Therefore the $^{1}$H NMR spectrum contained just two signals, namely a triplet at 7.26 ppm and doublet at 6.50 ppm, integrating for 1 and 2 protons respectively and coupling to each other with a coupling constant of 8.3 Hz, indicative of $J^{3}$ coupling for this system. Furthermore, the lack of a proton signal for the C2 position, which would have shown *meta* coupling further attested to the formation of the correct product. The $^{13}$C NMR spectrum contained only five signals, namely a large upfield signal at 56.1 ppm attesting to the presence of the methoxy groups, a slightly more downfield quaternary signal at 112.6 ppm for the C2 carbon, and the remaining three signals at 158.4 ppm, 128.7 ppm and 104.5 ppm, as would be expected given the symmetry of the molecule. The mass spectrum of the molecule showed a molecular ion in good agreement with the expected mass of the molecule. The data obtained compared well with that reported in the literature for compound **183**.[76]

With our desired halide **183** in hand, it was now possible to attempt the Ullmann coupling reaction with its copper partner **184**, which would be generated *in situ* (Scheme 36).



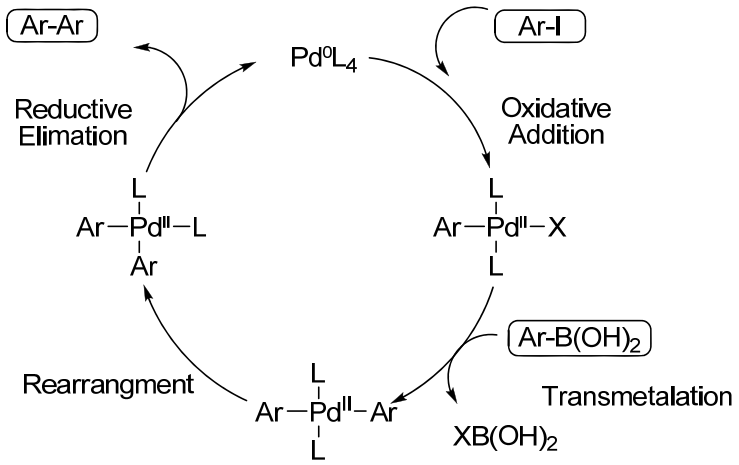

**Scheme 36**

In the generation of the required copper intermediate **184**, we once again capitalised on the 1,3-relationship of the methoxy groups to lithiate at the C2 position. We then employed a transmetalation reaction using copper(I) iodide to furnish the cuprate, **184** *in situ*, which was reacted with the iodated aryl **183**. After three days of heating at reflux, the mixture in pyridine, the desired tetra-substituted biphenyl **167** was obtained in an excellent yield of 93%.

NMR spectroscopic characterisation of the molecule compared well with literature.[77] However, this information was not conclusive to the assignment of the structure of the

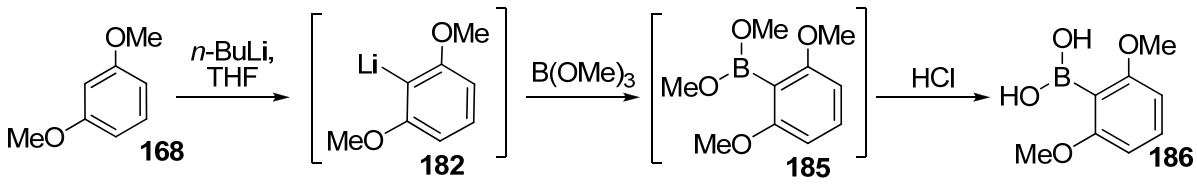
dimer **167** as both the $^{1}H$ and the $^{13}C$ NMR spectra were almost identical to that of its precursor **183**, with just slight shifts in the δ values, owing to the similar substitution pattern of both the molecules. The biphenyl **167** has two $C_2$ axes of symmetry, resulting in a reduction of the number of signals in both the spectra, similar to compound **183**. Conclusive proof for the formation of **167** was thus obtained from the mass spectrum of the product, which showed a molecular ion at 274.1198 amu, confirming a molecular formula of $C_{16}H_{18}O_4$. The precursor **183** had a molecular ion 263.9647 amu matching its formula of $C_8H_9IO_2$, thereby putting aside any doubt regarding the structure of the obtained product. Our precursor for our bidirectional synthesis was thus achieved in these two steps from two equivalents of the commercially available 1,3-dimethoxy benzene in 87% over the two steps.

As an alternative procedure, we investigated another well known transition metal biaryl axis forming reaction - the palladium catalysed Suzuki reaction. This reaction has been found to be useful for coupling many different aryl substrates and typically involves coupling an aryl boronic acid (or a borate ester) to an aryl halide (typically an iodide or bromide). The mechanism of the reaction is shown in the formal catalytic cycle, depicting the cross coupling between an aryl halide and an aryl boronic acid (Scheme 37).[71] The cycle begins with the oxidative addition of a Pd(0) complex to the aryl halide, forming a Pd(II) complex. Next the transmetalation of an aryl boronic acid to the Pd(II) complex takes place. The palladium maintains its +2 oxidation state by forming a bond to the organic component of the boronic acid with a concomitant loss of the halide acquired in the oxidative addition step. Rearrangement of the two organic moieties occurs, placing them *cis* to each other. Finally, reductive elimination, whereby a bond is formed between the two aryl groups takes place and the palladium is reduced back to Pd(0) and then re-enters the catalytic cycle.




**Scheme 37**

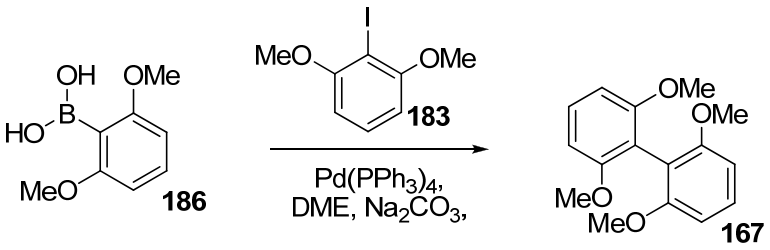
In order to perform the Suzuki coupling reaction for our desired system, it was only necessary for us to form the boronic acid **186** (Scheme 38) as we already had the aryl halide **183** in hand. The desired dimethoxy phenyl boronic acid **186** was readily synthesised from dimethoxy benzene **168**, through, once again a directed *ortho*- lithiation followed by reaction with trimethyl borate. The newly formed borate ester **185** was then hydrolysed with dilute hydrochloric acid to deliver the desired boronic acid **186** in a yield of 71%.




**Scheme 38**

Confirmation of the successful synthesis of the boronic acid **186** was obtained from the $^1$H NMR spectrum, which, although similar to the iodated aryl **183** as well as the biphenyl **167**, had in addition to the three expected signals another singlet at 7.22 ppm, integrating for two protons - indicative of the two new hydroxyl groups on the boron. The $^{13}$C NMR spectrum was also very similar to that obtained for **183** and **167**, with the exception of the C2 signal, now shifted much further upfield (55.8 ppm vs. 112.6 ppm). This is no doubt due to reduced deshielding by the electropositive boron in comparison to the high deshielding effect of the electronegative iodine.

For the Suzuki coupling reaction, we made use of a biphasic system with tetrakis(triphenylphosphine)palladium(0), as our source of palladium(0) and aqueous sodium carbonate as a base in DME as a solvent (Scheme 39).



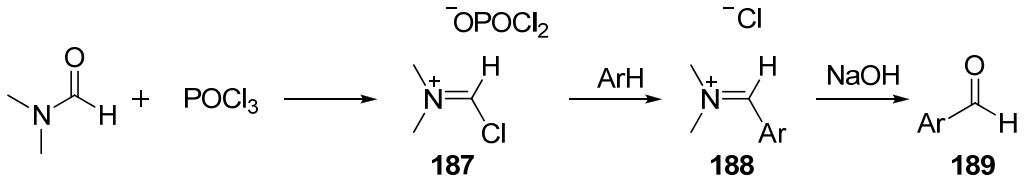

**Scheme 39**

Great care needed to be taken in order to exclude air from the reaction vessel in order to prevent the oxidation of the palladium catalyst. The reaction was completed much sooner than that of the Ullmann coupling reaction (1 day compared to 3 days), however the yield of the palladium catalysed reaction was much lower (54%). Isolation and purification of the product was also more challenging as the product had to be carefully separated from various uncharacterisable side products by column chromatography. In the Ullmann coupling reaction, the dimer was simply recrystallised from the crude reaction mixture with a dichloromethane:ethanol mixture. It is possible that the lower yield may be due to the fact that the Suzuki reaction when compared to the Ullmann reaction is more sensitive to steric hindrance,[78] and we were synthesising a *tetra*-substituted biaryl axis. Another option available to us for the formation of the biaryl axis was a procedure employed by Falck and co-workers. They were able to achieve the homocoupling of the boronic acid **186** with the use of a $CrCl_2$ catalysed reaction.[79] However, given that their yield was only 75%, the Ullmann coupling reaction was still the preferred option as we had obtained a 93% yield.

With our dimeric building block **167** in hand, we were now at the stage to commence our planned bidirectional synthesis. The first step of this planned route was to introduce an aldehyde functionality onto each aromatic ring, *ortho* to a methoxy group.

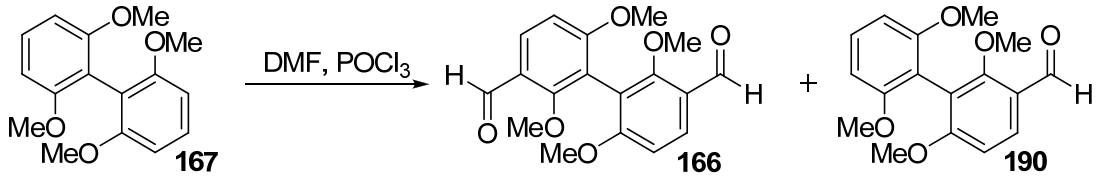
### 2.1.2 Formation of the di-carbaldehyde

The classic formylation reaction published in 1927 by Vilsmeier and Haack makes use of a substituted amide (e.g. dimethylformamide) and phosphorus oxychloride in order to formylate aromatic compounds.[80] The so-called Vilsmeier salt **187** resulting from the reaction of these two reagents is highly electrophilic and undergoes a substitution reaction with an aromatic substrate to form an iminium salt **188** (Scheme 40). This salt is then easily hydrolysed in the presence of a base, producing an aldehyde **189**.



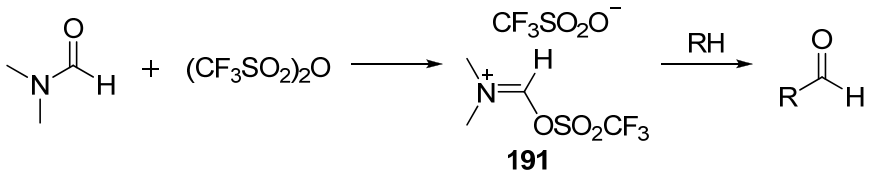

**Scheme 40**

This reaction was our first choice for the synthesis of our desired diformylated biphenyl **166**. However, disappointingly, this reaction proved to be troublesome on our system, (Scheme 41) producing a mixture of the mono-formylated biphenyl **190** in a yield of 21% and diformylated product **166** in a 5% yield. Even after allowing the reaction to proceed for several days the yield of the desired **166** did not improve.



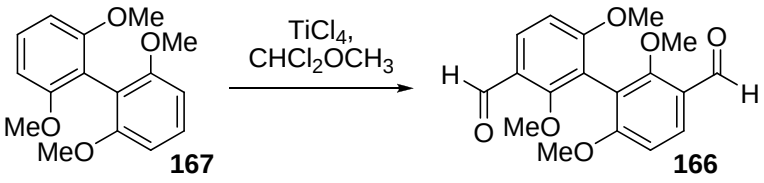

**Scheme 41**

An alternative formylation, developed by Martinez *et al.* utilises trifluoromethanesulphonic anhydride instead of phosphorus oxychloride (Scheme 42). This combination produces a more reactive iminium salt **191**, which is therefore a more effective formylation reagent.[81]




**Scheme 42**

Unfortunately, when we attempted to use this methodology no products were isolated from the reaction. It is possible that this more reactive formylation reagent was simply too reactive for our electron rich aromatic system. Therefore we once again turned our attention to the literature and discovered a procedure first reported by Gross *et al.* which described the formylation of sterically hindered aromatic compounds using dichloromethyl methyl ether in the presence of titanium(IV) chloride.[82] In fact this procedure had been utilised for the formylation of electron rich phenols and was found to be high yielding with good regioselectivity, and therefore seemed to be a better match for our systems.[83] Substrate **167** was therefore dissolved in freshly distilled dichloromethane, and reacted with titanium tetrachloride (Scheme 43). The reaction mixture immediately changed to a bright orange colour. Once cooled down to −78 °C and reacted with the dichloromethyl methyl ether, the colour changed to brown. Naturally, given our intention to perform a double formylation, the recommended amount of each reagent was doubled. After allowing the reaction to proceed for one hour followed by work up and purification, we pleasingly obtained our desired diformylated biphenyl **166** in an excellent yield of 95%.

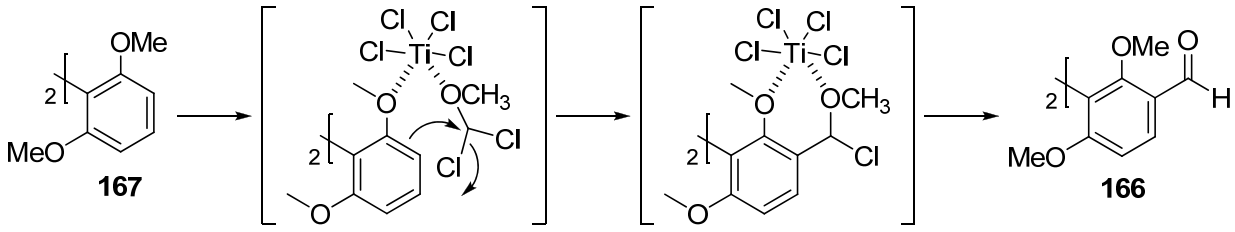



**Scheme 43**

The fact that a successful formylation had occurred was immediately confirmed upon scrutinising the $^{1}$H NMR spectrum. The presence of a new downfield singlet at 10.17 ppm signalling the presence of two aldehyde protons was very distinctive. There was of course only one signal for both new aldehyde groups as the molecule maintained its symmetry about the biaryl axis, with a single formylation having occurred at the desired *ortho* position on each ring. In fact, regarding the NMR spectral interpretations from this point forward: as we will be continuing in this bidirectional manner, it is far more convenient to discuss the spectroscopic evidence pertaining to the relevant products with respect to only one half of the dimeric system, as though it were an entity. Naturally, at the point where the introduction of stereochemistry results in non-equivalent diastereomeric moieties, this will be specifically pointed out in the text. Returning to the analysis of our product **166**: The multiplicities of the aromatic protons' signals were in line with our expectations,

having changed from a triplet and doublet to two doublets, while maintaining a coupling constant of 8 Hz, indicative of their *ortho* relationship. At this stage of the synthesis, the methoxy peaks, now in different environments, separated to two singlets one at 3.76 ppm and the other at 3.52 ppm. The $^{13}C$ NMR spectrum had a new downfield peak at 188.8 ppm signalling the presence of a new carbonyl carbon of the aldehyde. The increase in the number of signals in the carbon spectrum can be accounted for by the fact that one of the $C_2$ axes of symmetry has now been removed due to the introduction of the aldehyde functionality, placing all the carbons in unique environments. A noteworthy addition to the IR spectrum was a sharp band at 1677 $cm^{-1}$, further confirming the presence of our new carbonyl group. The mass spectrum of the molecule was also in good agreement with expected mass of 330.1103 amu.

The mechanism postulated for the *ortho* directing regioselectivity of this formylation reaction is explained in terms of the coordination of the titanium with the oxygen atoms (Scheme 44).[83] The coordination favours the regioselectivity by bringing the dichloromethyl methyl ether in close proximity to the methoxy group resulting in the substitution occurring in the desired *ortho* position. It also increases the electrophilicity of the dichloromethyl methyl ether and thus enhances the reaction rate.




**Scheme 44**

We were fortunate at this stage of the synthesis to obtain a crystal structure of our product (Figure 16), enabling us to unambiguously confirm our structure. Structural features worth mentioning are the orientation of the two rings, aligned perpendicular to each other. Due to the fact that the biaryl axis is tetra-substituted, with four bulky methoxy groups, this orientation minimises steric interactions. The methoxy functionalities *para* to the aldehyde functionalities are in the same plane as the rings they are attached to. The *ortho* methoxy groups are orientated such that they are pointing out of the plane of the ring. Owing to the

restricted rotation about the biaryl bond, **166** now possesses axial chirality because of the introduction of the formyl groups.

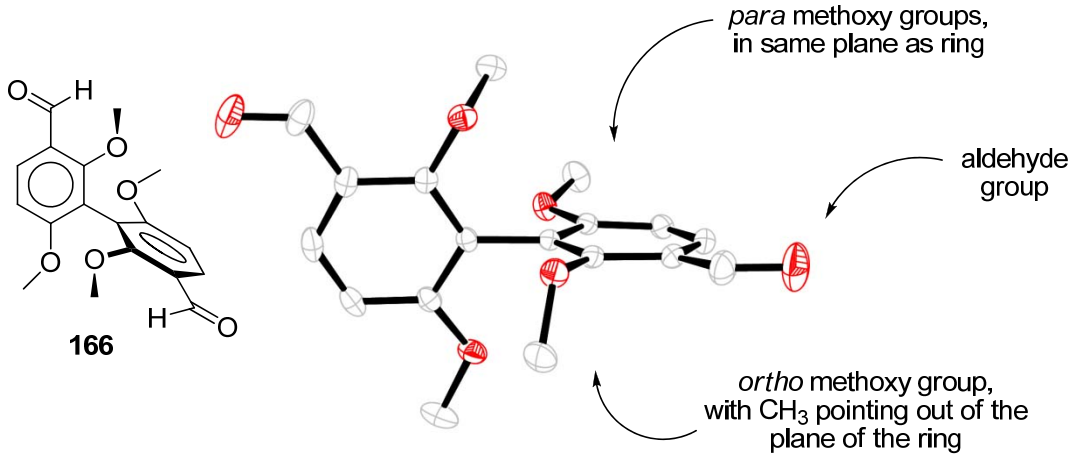



**Figure 16**

At this stage of our synthesis, we now had in hand the dimeric version of **154**, namely **166**, which was the starting material for our synthesis of ventiloquinone L (Figure 17).

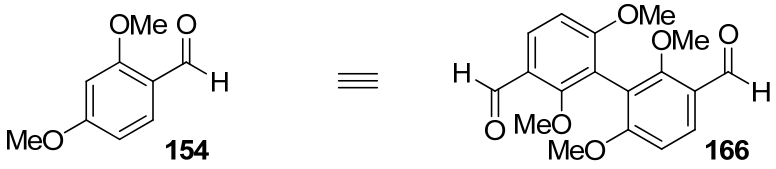
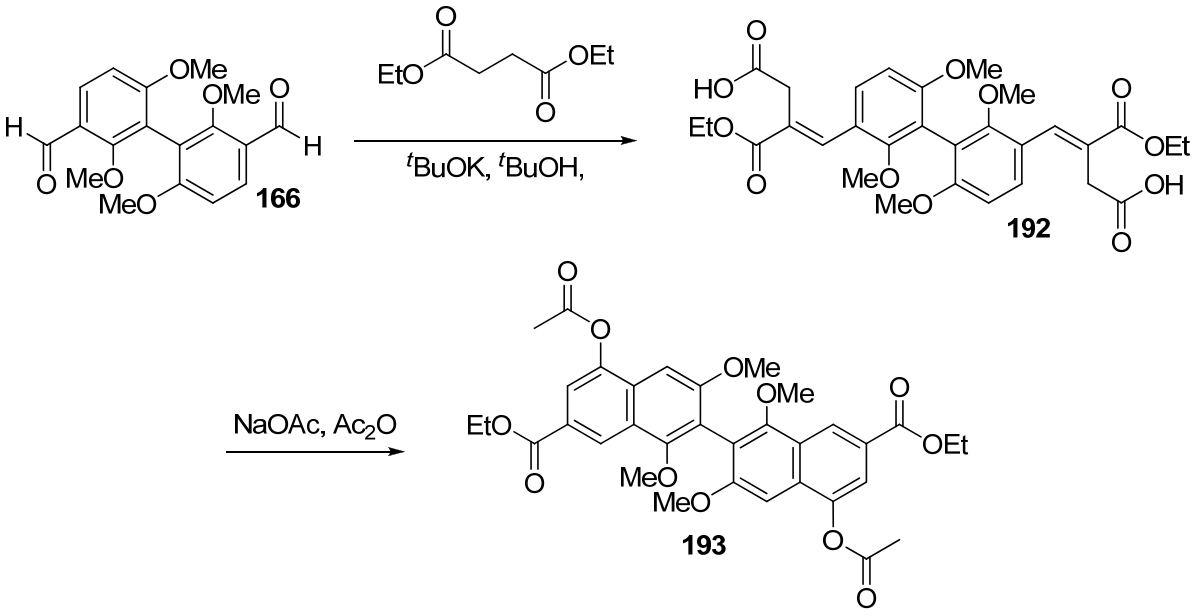



**Figure 17**

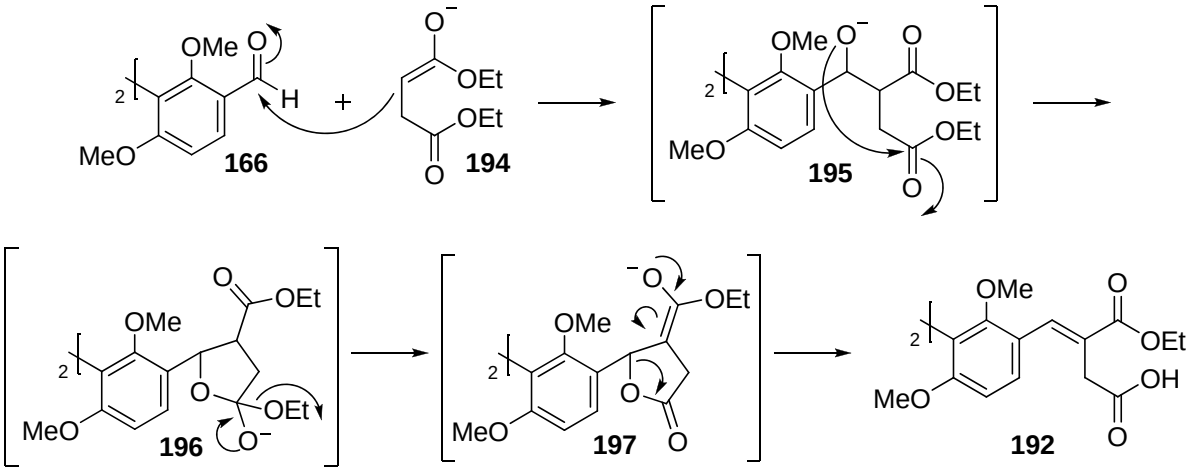
### 2.1.3 Construction of the *bis*-naphthalene skeleton

The next crucial phase in our synthesis would be the construction of our naphthalene ring system. We envisaged that this could be achieved using a Stobbe condensation, followed by a Friedel Crafts acylative cyclisation reaction (Scheme 45).




**Scheme 45**

The Stobbe condensation reaction involves the nucleophilic attack of the enolate derived from a succinate ester to aldehydes or ketones, resulting in the formation of the corresponding alkylidenesuccinic acids.[84] The reaction mechanism of our particular system is depicted below (Scheme 46).

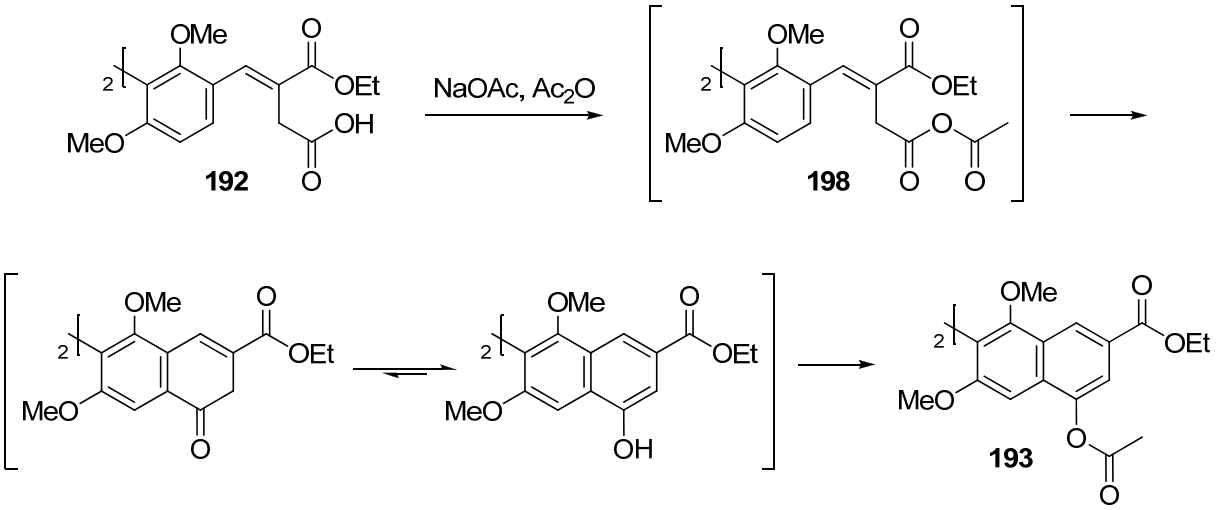



**Scheme 46**

For our desired purposes, we made use of diethyl succinate, and employed potassium *tert*-butoxide as our base to generate the enolate. The reaction was carried out in boiling *tert*-butyl alcohol for 2 hours. The specificity and success of the reaction is as a result of the

succinate ester attack placing the carbethoxyl group in a suitable position to allow for the formation of the lactone intermediate **197**. The reaction proceeds via the enolate **197**, facilitating ring opening of the lactone and subsequent formation of the *cis*-alkylidene acid **192**.

The acid **192** was isolated and reacted without further purification with sodium acetate in acetic anhydride at 140 °C, effectively forming the mixed anhydride **198** and inducing an intramolecular Friedel-Crafts acylative cyclisation leading to the formation of **193**



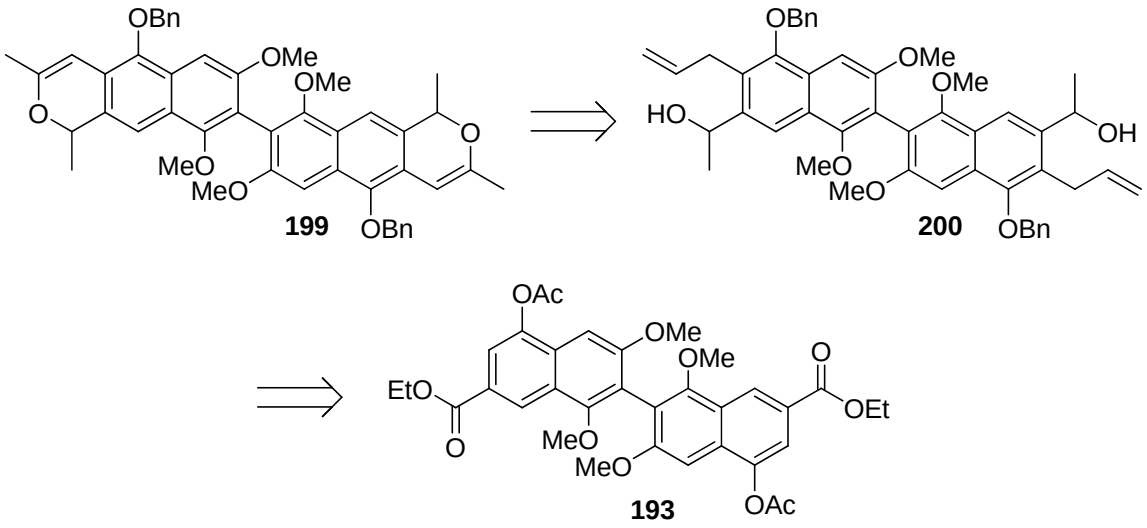

**Scheme 47**

Using this procedure, our desired *bis*-naphthalene **193** was obtained in yield of 60% over the two steps. The significantly different $^{1}$H NMR spectrum in comparison with that for the starting material **166** was a pleasing sign. Confirmation of the desired product was indicated firstly by the absence of the distinctive singlet at 10.17 ppm, previously indicative of the aldehyde proton. A change in the aromatic signals from two doublets to three singlets provided further evidence of the formation of **193**. There was also the characteristic quartet at 4.43 ppm and a triplet at 1.42 ppm in the $^{1}$H NMR spectrum, integrating for two and three protons respectively, representing the ethyl side chain. A new singlet at 2.51 ppm indicated the presence of the acetate group. The $^{13}$C NMR spectrum was significantly different in that there were now two carbonyl peaks, one at 169.4 ppm and the other at 166.2 ppm, indicative of the acetate and ethyl ester carbonyls respectively. The number of carbon signals in the aromatic region increased from 6 to 10 signals. The upfield region of the $^{13}$C NMR spectrum, now also contained, in addition to the two

methoxy signals, three new signals. These signals corresponded to the methyl group of the acetate, found at 21.0 ppm and the two carbons of the ethyl chain of the ester functionality at 61.1 ppm and 14.4 ppm. The IR spectrum contained a C=O absorption peak at 1770 $cm^{-1}$ and an additional peak at 1716 $cm^{-1}$. The molecular weight of 634.2038 amu obtained from mass spectral analysis was in good agreement with our expected molecular weight of 634.2050 amu. We had no doubt therefore that we had successfully constructed our *bis*-naphthalene scaffold **193**.

### 2.1.4 Formation of the pyran ring system

At this stage it was necessary to introduce and modify existing functionalities on our naphthalene **193** in order to set the stage for the formation of the final ring, the 1,3 dimethyl pyran ring system. The required isochromene system **199** can be disconnected to the secondary alcohol **200** via an envisaged Wacker oxidation reaction (Scheme 48), and **200** should be attainable from our *bis*-naphthalene **193** by the introduction of an allyl chain *ortho* to the ester functionality followed by the conversion of the ester group into a secondary alcohol, via the corresponding aldehyde.

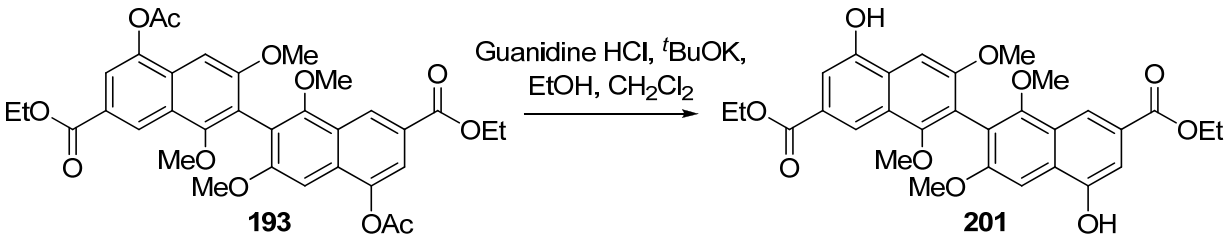



**Scheme 48**

#### 2.1.4.1 Introduction of the allyl moiety

Since our envisaged route to the substituted naphthalene **200** involved an allylation followed by a Claisen rearrangement, the first step required the selective removal of the acetate functionality to expose the free naphthol at position C4, thereby forming **201**

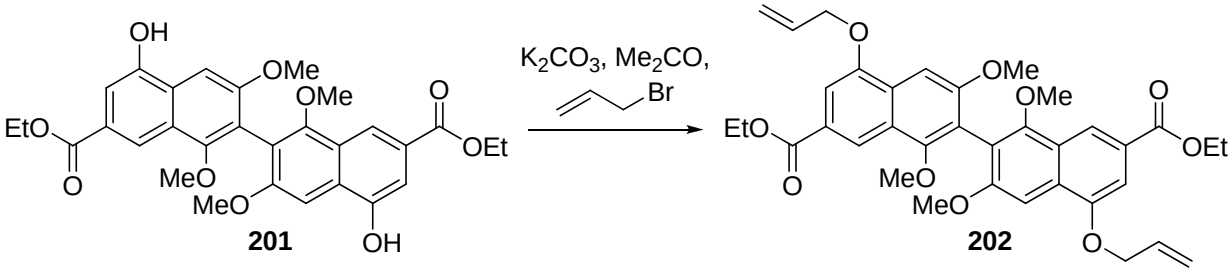
(Scheme 49). Fortunately this can be achieved without affecting the ester groups using the mild base, guanidine[85] as was established in our group's synthesis of ventiloquinone L.[66]




**Scheme 49**

The naphthalene **193** was therefore reacted with a solution of the guanidine hydrochloride and potassium *tert*-butoxide in ethanol to produce the naphthol **201** in a 78% yield after column chromatography. The product was insoluble in $CDCl_3$ and the $^1H$ NMR spectrum was thus obtained in deuterated DMSO. The most distinctive change of the product spectrum was a new broad singlet at 10.51 ppm, indicative of the new free hydroxyl group. Moreover, the characteristic singlet previously occurring at 2.51 ppm in the $^1H$ NMR spectrum of the starting material was absent indicating that the acetate group was no longer present. In the $^{13}C$ NMR spectrum, the carbonyl peak at 169.4 ppm was no longer present and the $CH_3$ peak at 21.0 ppm was also not evident, further attesting to the fact that we had selectively removed the acetate group. The IR spectrum also contained a distinctive broad band at 3413 $cm^{-1}$ signalling the presence of an OH group. Only one C=O stretching absorption was observed in the carbonyl region of the spectrum, at 1640 $cm^{-1}$. The mass spectrum of the ion of the sodium salt matched the expected mass of 573.174 amu.

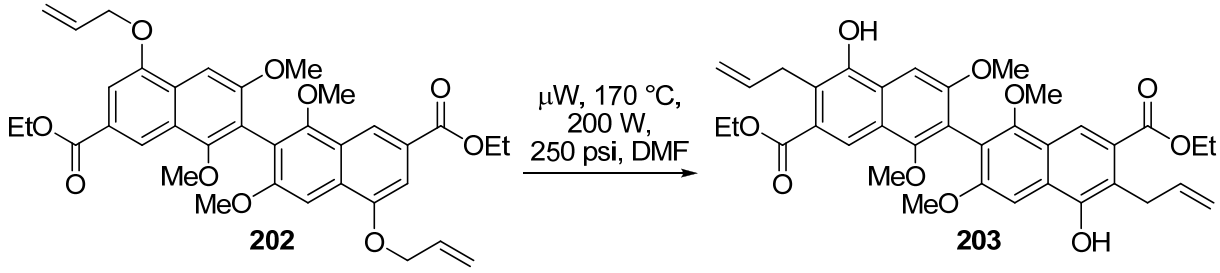
The next step in the synthesis was a routine allylation of the free naphthol of **201**, employing allyl bromide and potassium carbonate in boiling acetone to produce **202** (Scheme 50).




**Scheme 50**

As expected, the introduction of the allyl group resulted in a decrease in the polarity of the product **202**. The $^{1}$H NMR spectrum of **202** contained four distinct new signals and the broad signal at 10.51 ppm previously attributed to the naphtholic hydrogen was no longer present. A multiplet at 6.23 ppm could be assigned to the allylic CH group. The signals for the vinylic $CH_2$ protons appeared slightly further upfield as two double doublets, one at 5.57 ppm and the other at 5.38 ppm, with coupling constants indicating geminal coupling to each other ($J$ = 1.3 Hz) and coupling to the adjacent CH as well. Finally, the protons on the methylene attached to the oxygen atom produced broad doublet at 4.84 ppm, resulting from coupling to the neighbouring CH group. In the $^{13}$C NMR spectrum, there were three new signals confirming the presence of the allyl moiety. The allylic CH was located at 133.2 ppm and the vinylic $CH_2$ was further upfield at 118.8 ppm. The methylene carbon attached to the oxygen produced a signal somewhat further upfield at 69.3 ppm. As expected, the IR spectrum no longer contained the distinctive broad OH absorption band.

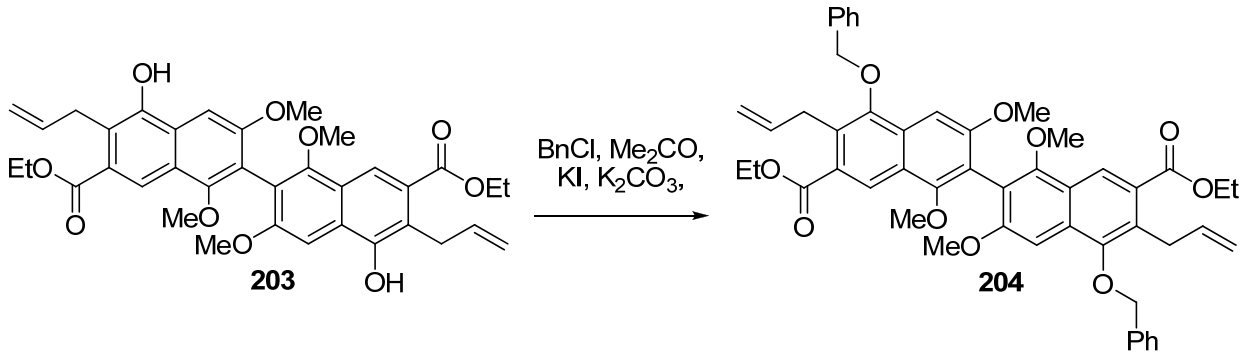
The relocation of the allyl side chain to the desired position was accomplished with the use of a Claisen rearrangement reaction. In order to effect this rearrangement, we initially employed the more conventional conditions, of heating the reaction mixture at 180 °C in dimethylformamide for 16 hours. However, using this methodology the yields were found to be irregular, ranging from values as low as 20% to the highest value of 68%. Therefore, as an alternative procedure, we decided to attempt this reaction using microwave radiation as an energy source (Scheme 51).[86] The results from this new procedure were extremely pleasing as subjecting our *O*-allylated naphthalene **202** to variable power microwave irradiation maintaining a constant temperature of 170 °C in dimethylformamide afforded our rearranged *C*-allylated naphthalene **203** in 98% yield in just 25 minutes!




**Scheme 51**

The accompanying changes in the $^{1}H$ NMR spectrum of **203** included the disappearance of an aromatic proton signal, and the appearance of a new singlet at 5.84 ppm, indicating the presence of the free naphtholic hydrogen on the naphthalene ring. The $^{13}C$ NMR spectrum remained largely unaltered except for a change in the chemical shift of the allyl $CH_2$ group, moving upfield from 69.3 ppm to 31.8 ppm as a result of it no longer being bonded directly to oxygen. Not surprisingly, a broad OH stretching absorption at 3420 $cm^{-1}$ was observed in the IR spectrum, attesting to the presence of the alcohol. The mass spectrum value remained unchanged from that of its precursor, in line with our expectations.

The next phase towards the synthesis of the pyran precursor **200** would be to begin modifying the ester functionality. However, the free hydroxyl group on the naphthol would first need to be protected. To this end, we envisaged that a benzyl ether would serve the purpose adequately as it would not only be unreactive in the subsequently planned steps, but its removal would coincide with the planned reduction of a future double bond, thereby eliminating the need for a dedicated protecting group cleavage step. Since we only had the somewhat less reactive benzyl chloride on hand, and not benzyl bromide, the introduction of the benzyl group was carried out under Finkelstein conditions, with benzyl chloride, potassium iodide and potassium carbonate in boiling acetone thereby affording the protected naphthol **204** in an excellent yield of 90% (Scheme 52).



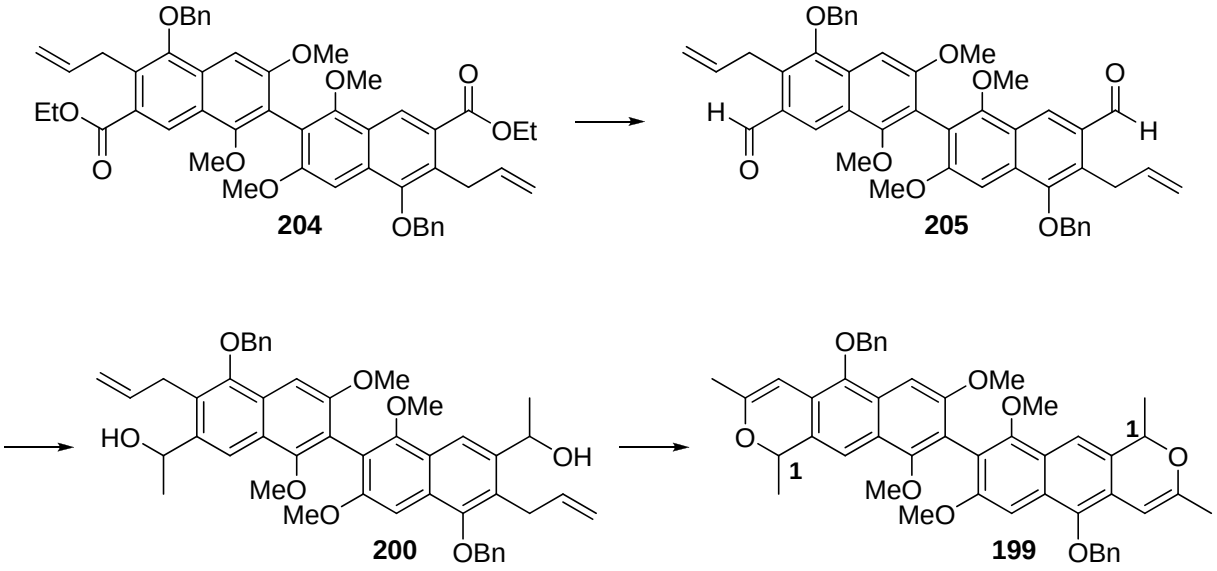

**Scheme 52**

The presence of a new multiplet in the aromatic region of the $^{1}H$ NMR spectrum provided the first evidence that the attachment of the benzyl group had been successful. Furthermore, a new singlet was observed in the region of 5.10 ppm, overlapping with the allylic $CH_2$ group, indicative of the benzylic $CH_2$ group. The $^{13}C$ NMR spectrum was distinctly different with the addition of five new signals, four in the aromatic region and a

new signal at 76.1 ppm, signalling the presence of the *O*-benzyl methylene carbon. The distinctive OH stretch in the IR spectrum was no longer present and the mass spectrum confirmed a significant increase in mass, corresponding well with the expected mass for the benzylated product **204**.

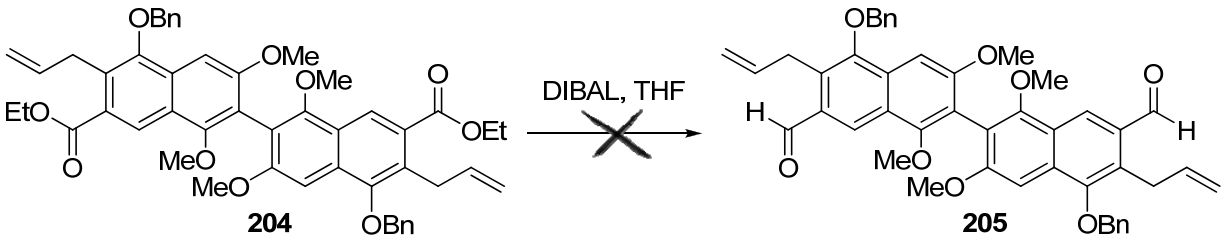
### 2.1.4.2 Conversion to the secondary alcohol

With the allyl functionality correctly installed, and the free OH group suitably protected, we were now in a position to modify the ester functionality to afford the desired secondary alcohol, a requirement for the forthcoming Wacker oxidation ring closure step. We envisaged that the required methyl group at the benzylic C1 position could be introduced using a Grignard reaction, (Scheme 53) producing the desired alcohol **200**, if the ester **204** was first converted into the corresponding aldehyde **205**.



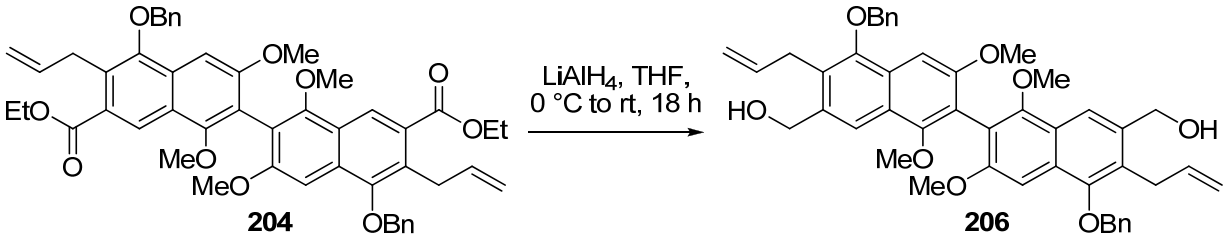

**Scheme 53**

Our first intention was to convert the ester directly to the aldehyde using DIBAL, however unfortunately this method proved unsuccessful resulting in the recovery of mainly starting material and some uncharacterisable material (Scheme 54).




**Scheme 54**

Therefore, we opted to carry out this conversion over two steps by firstly complete reduction of the ester to the primary alcohol **206** (Scheme 55), followed by a selective oxidation to aldehyde **205**.




**Scheme 55**

As a first attempt at the reduction, we employed lithium aluminium hydride in THF. However, the highest yield we obtained for this reaction was a disappointingly low 42%. Following this, several other reduction procedures were attempted on the ester and the results are summarised in Table 1. Clearly, these procedures turned out to be even less effective than using $LiAlH_4$.

**Table 1**: Reaction conditions of attempted reduction reactions

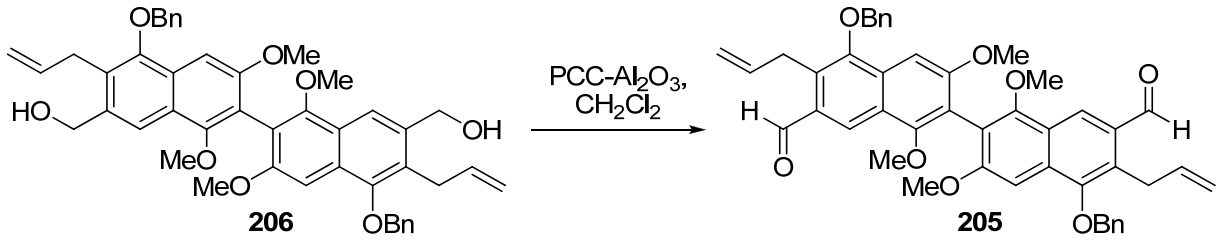
| **Conditions** | **Yield** |
|---|---|
| $LiBH_4$-Methanol[87] | No reaction |
| $NaBH_4$-Methanol[88] | No reaction |
| Na-Ethanol[89] | No reaction |
| $LiBH_4$-toluene[90] | No reaction |
| L-Selectride-THF[91] | 25% |

Having had little success with alternative reducing agents we then turned our attention back to optimising the $LiAlH_4$ reduction. To this end we investigated the influence of solvent, reaction time and temperature. Unfortunately however, we were unable to

optimise the reaction any further, and therefore had to settle for the moderate yield of the benzyl alcohol **206** in order to push forward with the synthesis. The conditions thus employed for a reproducible albeit low yield were the addition of the $LiAlH_4$ to a solution of the ester in freshly distilled THF, cooled down to 0 °C by means of an ice bath, and then allowing the reaction to slowly warm up to room temperature overnight. If the reaction was maintained at 0 °C, even lower yields were obtained. This step in the synthesis appeared to be trivial but ultimately proved to be the lowest yielding step in the synthesis.

In the $^{1}H$ NMR spectrum, the absence of the characteristic quartet and triplet corresponding to the ethyl side chain was immediately evident. The appearance of a new singlet at 4.84 ppm, indicative of a benzylic $CH_2$ provided further confirmation of the correct product, as did a broad singlet at 1.84 ppm signalling the presence of the proton of the newly formed alcohol functionality. In the $^{13}C$ NMR spectrum the peaks at 61.7 ppm and 14.3 ppm, previously arising from the ethyl side chain were no longer present. The downfield carbonyl signal, previously found at 168.0 ppm in the starting compound, was now shifted significantly upfield to 64.1 ppm in line with what we would expect for the benzylic methylene carbon also attached to an oxygen. In the IR spectrum, a broad OH stretching band at 3417 $cm^{-1}$ was noticeably present. The mass spectrum was in line with our expectations showing a molecular ion at 727.327 amu, which corresponded well with the calculated value of 727.3271 amu for our molecular formula of $C_{46}H_{47}O_8$.

Therefore with the benzylic alcohol **206** in hand, we could now complete the synthesis of the desired aldehyde **205** with a selective oxidation using pyridinium chlorochromate (**Scheme 56**).



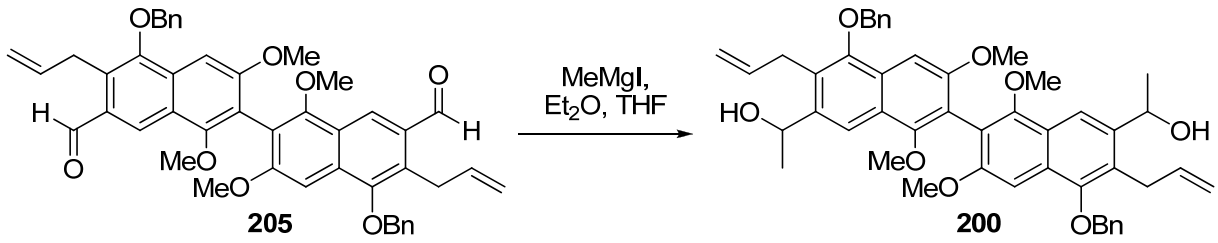

**Scheme 56**

In our hands, the most effective procedure for this oxidation required first adsorbing pyridinium chlorochromate onto neutral alumina, and then adding this to a solution of the

alcohol **206** in dry dichloromethane. This procedure proved to be quite convenient as on completion, the reaction mixture was simply filtered through celite effectively removing the oxidant. Purification of the crude material was nevertheless still necessary but was easily achieved using column chromatography, affording the aldehyde **205** in an excellent yield of 90%.

Convincing evidence for the formation of the aldehyde was the presence of a new singlet in the downfield region of the $^{1}$H NMR spectrum at 10.24 ppm, characteristic of an aldehyde proton. The disappearance of two notable signals, namely the singlet depicting the methylene group as well as the broad singlet indicative of an alcohol proton, was observed. In the $^{13}$C NMR spectrum, a distinctive deshielded signal was observed at 192.4 ppm, clearly that of the aldehyde carbon. The IR spectrum no longer contained the broad OH band, but did now display a C=O stretching band at 1691 cm$^{-1}$. Mass spectral analysis showed an $M^{+}$ ion of 723.295, corresponding well to the calculated value of 723.2958 amu.

The final conversion necessary to prepare the precursor for the forthcoming Wacker oxidation was the introduction of a methyl group to the aldehyde **205**. This reaction would simultaneously deliver the methyl functionality desired at the benzylic position of the final product as well as produce the required secondary alcohol, forming **200** (**Scheme 57**).




**Scheme 57**

To accomplish this addition we employed a Grignard reaction, using methyl magnesium iodide, prepared *in situ*. We found that the use of two solvents for this reaction was necessary due to the Grignard reagent's solubility in THF. Therefore, for the initial formation of the methyl magnesium iodide we employed dry diethyl ether over dried magnesium metal turnings. It should be mentioned that the formation of the Grignard proved to be quite exothermic and therefore we found it necessary to attenuate the reaction

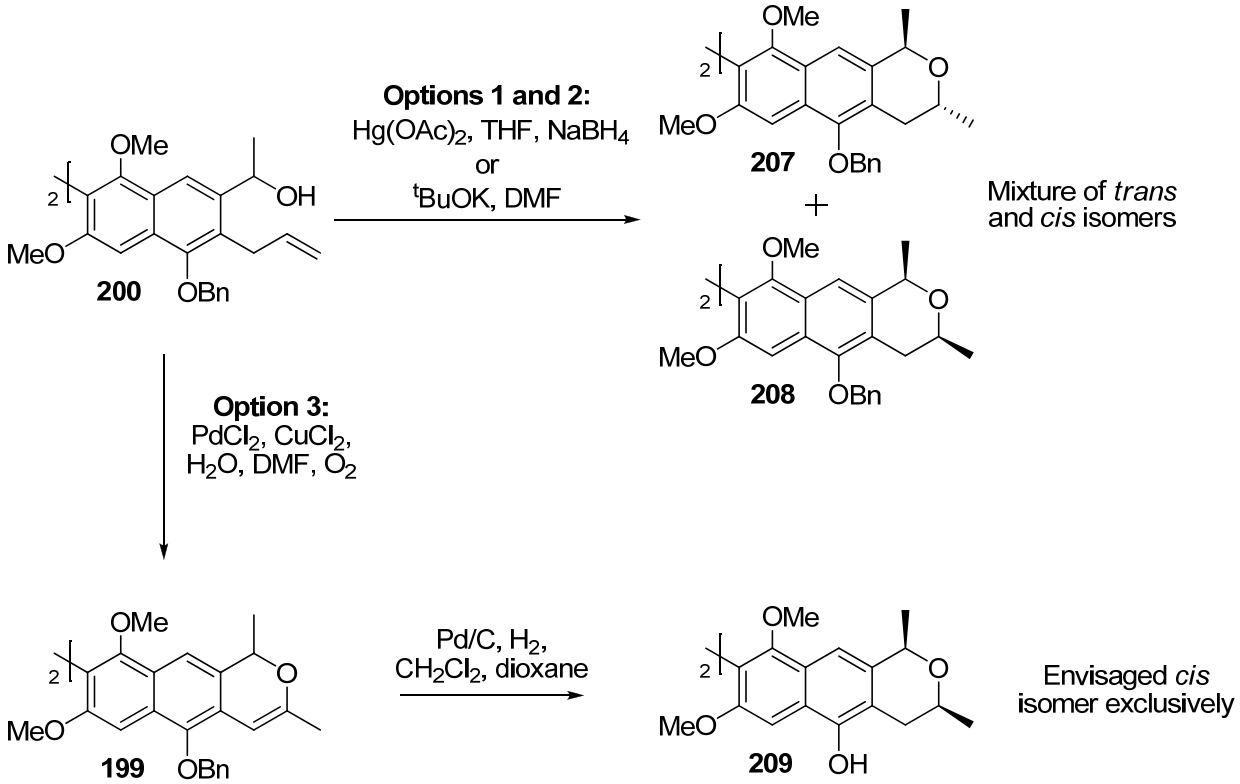
rate by cooling the solution. Once the Grignard reagent had formed, a solution of the aldehyde **205** in dry THF was then added drop-wise to the cloudy reaction mixture, resulting in an immediate colour change to milky yellow, which became progressively darker as the reaction proceeded. Interestingly, for the first time thin layer chromatography revealed that two new products had formed, having $R_f$ values of 0.33 and 0.27 in a solvent system of 40% ethyl acetate in hexane. This was in line with our expectations as the creation of a two stereogenic carbons now meant that we had formed a mixture of diastereomers, taking into account the fact that hindered rotation about the biaryl axis creates rotameric isomers. Our desired secondary alcohol **200** was easily purified by column chromatography and obtained in a pleasing yield of 79% as a mixture of diastereomers.

Spectroscopic analysis of the mixture confirmed that the addition of the methyl group to the aldehyde had been successful, forming the secondary alcohol **200**. In the $^{1}$H NMR spectrum the disappearance of the aldehyde proton's singlet at 10.24 ppm was evident. New features in the spectrum included a quartet at 5.25 ppm, formed as a result of the benzylic CH coupling to the added methyl group, itself producing a doublet at 1.60 ppm. Confirmation that these groups were indeed adjacent to each other was derived by their corresponding integration values, multiplicity and coupling constants. A broad singlet at 1.88 ppm indicated the presence of the proton of the OH group. Since we had a mixture of diastereomers, some additional peaks were observed. Noticeably, one of the methoxy groups on each of the diastereomers resulted in two singlets, one at 3.63 ppm and the other at 3.62 ppm. In the $^{13}$C NMR spectrum, the absence of the downfield signal in the region of 190 ppm and the presence of a new upfield signal at 24.5 ppm corresponded to the reduction of the aldehyde and the presence of a new $CH_3$ group. The IR spectrum regained its broad OH stretching band at 3415 $cm^{-1}$, indicating the alcohol functional group.

#### 2.1.4.3 The Wacker Oxidation procedure

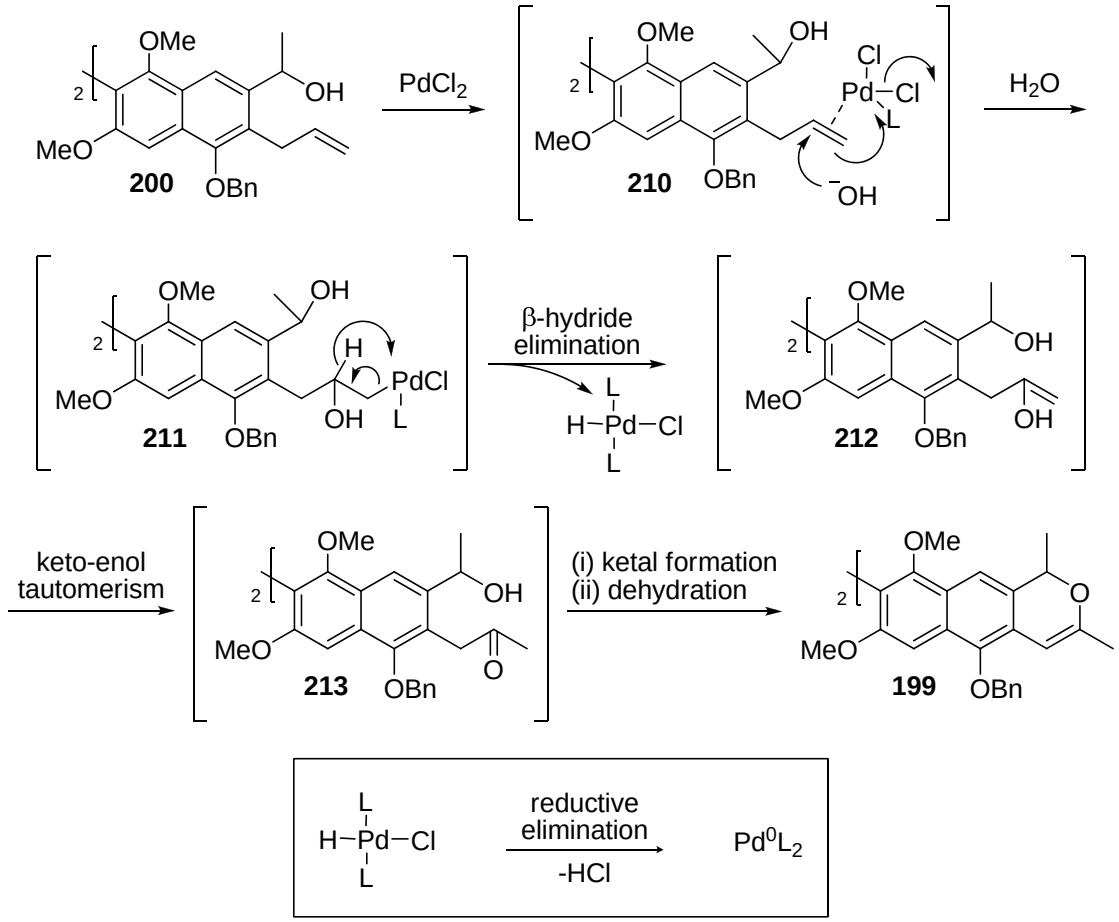
Having set the stage for the formation of the pyran ring, we now had a number of options on hand for this ring closure. Some of these include methods previously used in our laboratories, namely: a potassium *tert*-butoxide mediated ring closure,[65] an oxidative mercury mediated ring closure,[62] and a Wacker oxidation procedure,[63] (Scheme 58). We opted to steer clear of the first method as it leads to the production of the *trans* isomer **207**

exclusively or over extended periods tends to produce a mixture of *cis* and *trans* 1,3-dimethyl pyran rings **207** and **208** due to epimerization because of the strongly basic conditions,[53] and we require exclusively the *cis* stereochemical relationship between the two methyl groups. The second procedure, being the oxymercuration reaction, was also found to generate a mixture of *cis* and *trans* isomers in equal proportions, and so we decided to avoid this procedure as well - not to mention the fact that we would generate undesirable mercury waste. Finally, considering the third option, we envisaged that a palladium catalysed Wacker oxidation procedure would generate a slightly different product, namely the unsaturated 1,3-dimethyl isochromene system **199**. The presence of the alkene may then provide us with the opportunity to effect a simple sterically controlled reduction, leading hopefully to the desired *cis* dimethyl pyran **209**.



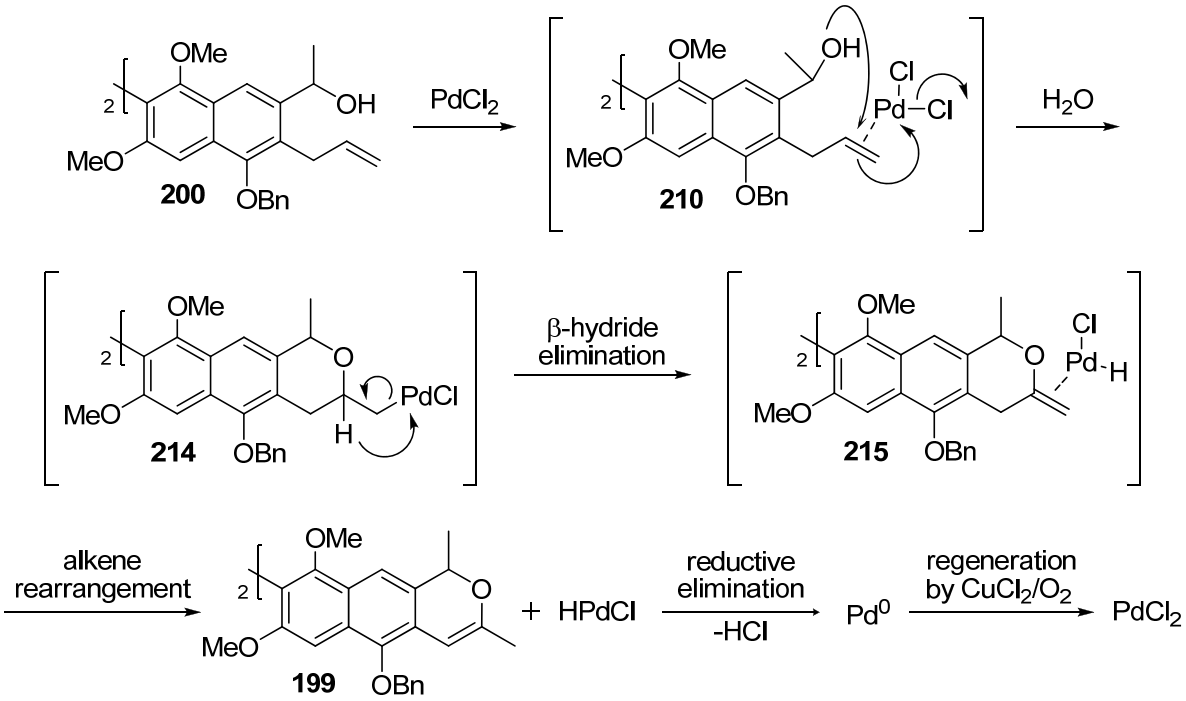

**Scheme 58**

In the generally accepted mechanism of the Wacker oxidation reaction, the overall ring closure is facilitated by the action of the palladium catalyst, which activates the alkene for reactivity with a nucleophile.[92] The catalyst does this by coordinating to the double bond drawing electron density away from the π orbitals of the alkene (depicted in **210** of **Scheme 59**). Attack by a suitable nucleophile, in this case water, takes place at the more substituted end and this is believed to be governed by the need of the palladium to be in the less hindered position **211**.[92] The palladium(II) species then decomposes by a β-hydride elimination releasing the substituted enol **212**, which of course immediately tautomerises to the corresponding ketone **213**. With the benzylic alcohol favourably positioned to form a six membered ring, the ketone **213** is expected to readily ketalise. A concomitant dehydration produces the isochromene **199**. Recycling of the palladium catalyst is achieved by reductive elimination of a proton and a leaving group, generating palladium(0). The catalyst now requires an external source of oxidation back to palladium(II) in order to re-enter the catalytic cycle. Copper(II) chloride is used to oxidize the palladium(0) to palladium(II) and is itself regenerated to copper(II) in the presence of oxygen.




**Scheme 59**

Our Wacker oxidation reaction, carried out using 10 mol% $PdCl_2$ catalyst as well as one equivalent of $CuCl_2$, smoothly delivered our isochromene **199** as a mixture of diastereomers in an overall yield of 78%. Typically, in a Wacker oxidation process it is the ketalisation step that is relatively slow and often requires the azeotropic removal of water to shift the equilibrium in favour of the product. However, in our specific case, given that only the isochromene **199** was isolated from the reaction, with no indication of the intermediate ketone, it is more likely that even in the presence of water the reaction follows a slightly different path, with the intramolecular attack of the benzylic alcohol onto the electron deficient alkene **210** occurring rapidly leading to **214** (**Scheme 60**). Then a β-elimination, followed by rearrangement of the alkene **215** leads to the desired isochromene **199**. The palladium catalyst, regenerated by copper(II) chloride and oxygen can then re-enter the catalytic cycle.



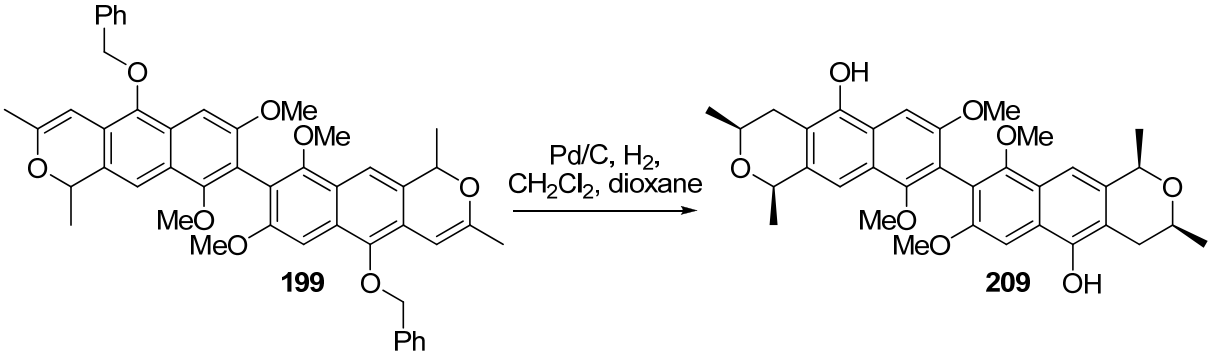

**Scheme 60**

Confirmation of the desired product **199** was evident in the $^{1}$H NMR spectrum with the disappearance of the characteristic peak pattern representing the allyl chain which had become a familiar feature over the last few compounds. Now, the C4 proton, located on the isochromene produced a singlet at 6.05 ppm. The signals for the methyl groups located at positions C1 and C3 were quite distinct, each integrating for three protons. The signal at 2.00 ppm could be assigned to the C3 methyl substituent in light of the fact that it is a singlet, and similarly the doublet at 1.70 ppm could be assigned to the C1 methyl group, coupling to its adjacent benzylic proton. Once again, since we had a mixture of diastereomers, one of the methoxy groups on each of the diastereomers resulted in two well resolved singlets at 3.56 ppm and 3.54 ppm. The presence of additional signals was even more noticeable in the $^{13}$C NMR spectrum. Supplementary proof for the formation of the isochromene **199** was received from the IR spectrum as the familiar OH stretching band was absent.

### 2.1.4.4 Hydrogenation as a means to the *cis* substituted naphthopyran system

Having successfully synthesised the isochromene **199**, the final step to form the pyran ring required the reduction of the double bond. We envisaged that by using hydrogen and palladium on carbon we could achieve these two goals in one step, as these reaction

conditions would also bring about the removal of the benzyl ether protecting group (Scheme 61). As mentioned previously, we also anticipated that the existing stereogenic carbon C1 would have an influence on the stereochemistry of the reduction, hopefully influencing the approach of the reductant, directing it to the less hindered face of the molecule thereby forming the *cis* 1,3 dimethyl substituted pyran ring.

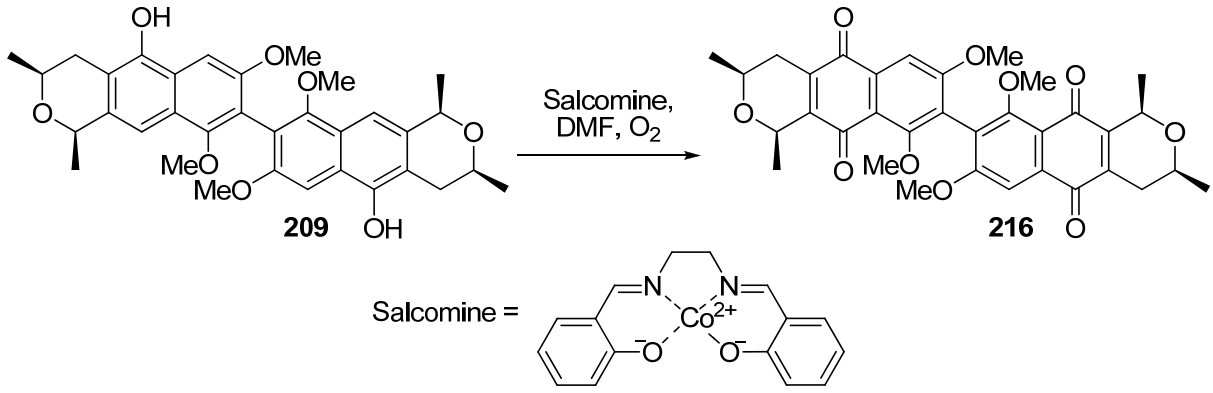



**Scheme 61**

After some experimentation, we found that the optimum reaction conditions required a mixture of solvents (namely 3:1, $CH_2Cl_2$: dioxane), carried out at room temperature and 1 atm of $H_2$ over Pd on carbon for 18 hours. Under these conditions we accomplished both the reduction of the alkene as well as the removal of the benzyl protecting group and the product **209** was obtained after routine purification as a white solid in quantitative yield. In the $^1$H NMR spectrum, a most pleasing feature was the signal at around 3.8 ppm for H3, overlapping with the methoxy peak. Since it has been shown previously that for *trans*-1,3-dimethyl aromatic-fused pyrans, the signal for H3 appears between δ 4.0-4.2, while for the corresponding *cis*-compound the signal for H3 appears between δ 3.5-3.9,[52, 93] we were confident that we had in fact formed the desired *cis* isomer as the major component. There appeared to be a small amount of the opposite isomer, however at this stage it was not possible to ascertain the ratio of the isomers due to the overlapping of peaks. The OH peak was found as a broad singlet at 8.54 ppm. In the $^{13}$C NMR spectrum, the methyl groups at C1 and C3 were found at 21.7 ppm and 21.9 ppm respectively. While the stereochemical relationship between the methyl groups was *cis*, the product was nevertheless still a mixture of diastereomers, and therefore some of the signals were duplicated. The $^{13}$C NMR spectrum also contained fewer aromatic signals.

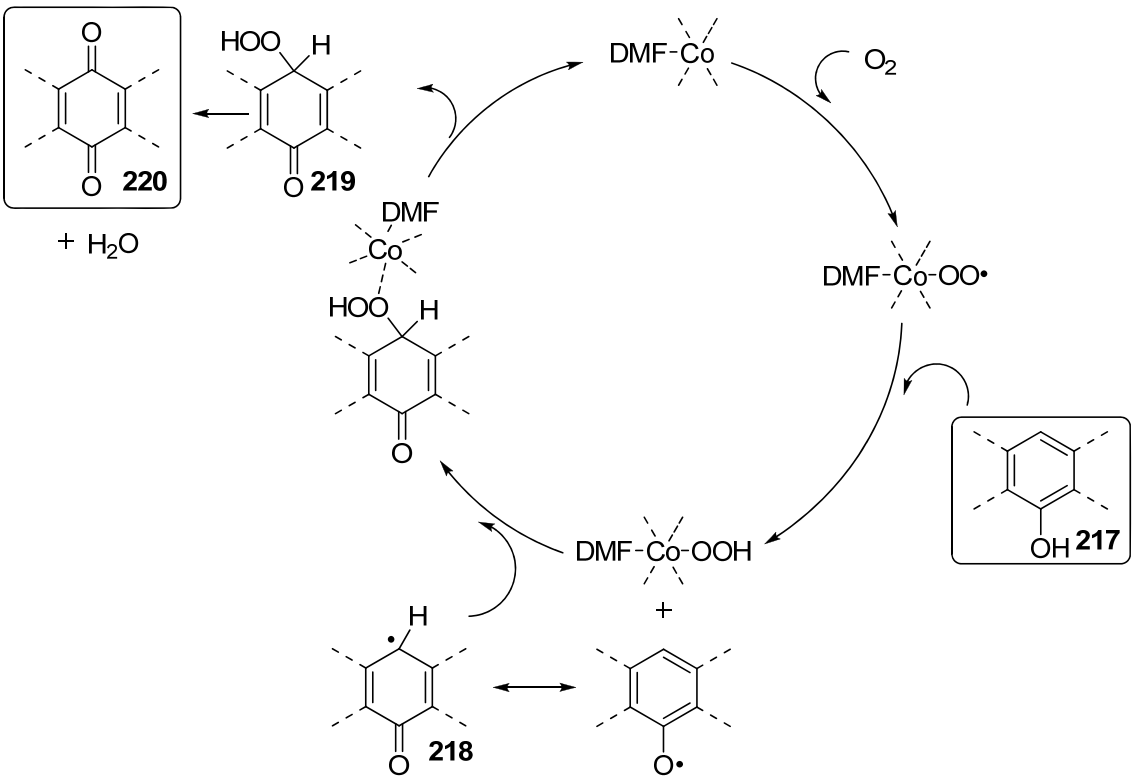
### 2.1.5 Quinone oxidation and completion of the synthesis of cardinalin 3

With our pyran ring formed and the benzyl protecting group removed, all that remained to complete our synthesis was the oxidation of the naphthol and selective *O*-demethylation of the methyl ether at position C9. To achieve this, we envisaged that the oxidation of the phenol to the quinone would most appropriately be achieved with the use of a salcomine catalyst, *N*, *N*′-*bis*-(salicylidene)ethylenediaminocobalt(II) (Scheme 62).




**Scheme 62**

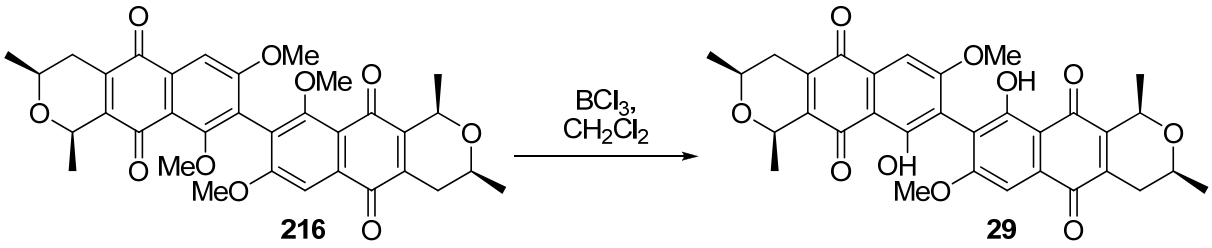
Salcomine complexes, related to the natural oxygen carrier haemoglobin, are known oxygen carriers that bind reversibly to molecular oxygen. The mechanism of oxidation proposed by Kothari *et al.* involves a four step procedure in which the solvent plays a key role.[94] Dimethylformamide has the ability to function as a ligand, coordinating with the cobalt catalyst, thereby solubilising it. In the reaction scheme shown below (**Scheme 63**), the salcomine:oxygen adduct abstracts a hydrogen from a hindered phenol e.g. **217** (representing **209**). The rearranged aryloxy radical **218** then interacts with the hydrogen peroxide ligand of the catalyst giving rise to a hydroperoxide intermediate **219**, which rearranges to the benzoquinone compound **220** (representing **216**).




**Scheme 63**

The oxidation of our phenol **209** proceeded in the presence of salcomine and 1 atm of oxygen, affording the quinone **216** in a 51% yield as a dark orange powder. This transformation was immediately confirmed upon scrutinising the $^{1}$H NMR spectrum. As the first indication, the broad singlet previously obtained for the naphthol was no longer present. The aromatic region, which previously contained signals for two aromatic protons, now only signalled the presence of one proton, as we would expect for our desired product **216**. The $^{13}$C NMR spectrum provided perhaps the most convincing evidence of the quinone formation, with the appearance of new peaks downfield at 183.7 ppm and 182.7 ppm. The OH band in the IR spectrum was absent and there were distinctive carbonyl stretching bands at 1659 cm$^{-1}$ and 1573 cm$^{-1}$.

The final transformation remaining in our synthetic route was the selective deprotection of the C9 methyl ether group. This was easily achieved with the use of the Lewis acid, boron trichloride (Scheme 64).




**Scheme 64**

Based on literature precedence,[66] we envisaged that we would be able to selectively cleave the methyl of the methoxy group at the C9 position using $BCl_3$. This selectivity is achieved due to the coordination of the boron to the adjacent carbonyl oxygen on the quinone moiety. Treatment of our quinone **216** with $BCl_3$ resulted in an immediate colour change of the solution from yellow to bright red. The reaction was complete in a few minutes, as determined by TLC, which revealed a new bright yellow compound at a slightly higher $R_f$ value. This increase in the retention factor is somewhat surprising given the change to a more polar phenol group on the aromatic system. However this can possibly be explained by the likelihood of a significant hydrogen bonding interaction between the naphthol and the adjacent quinone carbonyl, reducing the possible hydrogen bonding interactions between the phenolic hydrogen and the silica gel. Purification of the crude product and subsequent spectroscopic analysis showed conclusively that we has successfully synthesised racemic cardinalin 3 **29**. The $^{1}H$ and $^{13}C$ NMR spectra matched that reported in the literature for the natural product,[20] although the presence of additional peaks once again was observed due to the fact that we had a mixture of diastereomers. In the $^{1}H$ NMR spectrum, the signal for the previously mentioned hydrogen bonded phenolic hydrogen appeared in the downfield region of 12.3 ppm, with signals for the *S* atropisomer closer to 12.35 ppm and the other diastereomer at 12.31 ppm. Similarly, for the aromatic protons attached to C6, two signals were found very close to each other at 7.331 ppm and 7.329 ppm. The diagnostic signals for H3 of the 1,3-*cis* dimethyl benzopyrans could be seen 3.67 ppm and 3.47 ppm while expansion of the NMR spectrum revealed signals for 1,3-*trans* dimethyl benzopyrans between 3.96 ppm and 4.04 ppm. However, the ratio of this peak relative to that of the *cis* isomer amounted to less than 5% of the mixture. Presumably epimerisation had taken place in the presence of $BCl_3$. The IR spectrum also closely resembled that reported in literature, with an OH stretching band at 3450 $cm^{-1}$ and carbonyl stretching bands at 1636 $cm^{-1}$ and 1603 $cm^{-1}$. Although the literature reported a melting point in the range 213-220 °C, we noticed darkening of the crystals above 145 °C

and melting only took place between 236 and 241 °C. It is possible that these deviations in the melting point characteristics are due to the fact that we have a mixture of diastereomers, which would of course not only act as 'contaminants' for each other, but would of course themselves have different melting points, accounting for the observed physical change at 145 °C.

This represents the first synthesis of cardinalin 3, albeit in a racemic manner. Our concluding remarks and approaches to the enantiopure compound will be described in Section 2.3.

## 2.2 Studies towards Novel Methodology for the Synthesis of 1,3 Substituted Isochromanes

In our pursuit of novel and efficient methods for the synthesis of pyranonaphthoquinones, we decided to explore two additional routes. The first of these options involved the use of arene tricarbonylchromium chemistry, envisaged to be an interesting method for the enantioselective synthesis of 1,3 substituted isochromanes. The second method we investigated involved the use of cross metathesis as a means of introducing a suitable Michael acceptor for the ring closure to afford the pyran ring containing substituents other than a methyl at the C3 position. The results of these two methods will be discussed in the following two sections.

### 2.2.1 Arene tricarbonylchromium chemistry as a means to a stereoselective pyranonaphthoquinone synthesis

The complexation of the chromium tricarbonyl group, $Cr(CO)_3$ onto an arene ring, activates the complexed arene in many ways in order to facilitate transformations that would not be possible with the free arene.[95] The additional attraction of these arene tricarbonylchromium complexes is their relative stability to air and water once they are isolated as a solid, promoting their ease of handling. They are also diamagnetic, a feature which allows for NMR spectroscopic studies. Decomplexation of the chromium tripod can easily be achieved by exposure of the solution of the complex to light and air, or by the addition of oxidants such as iodine.

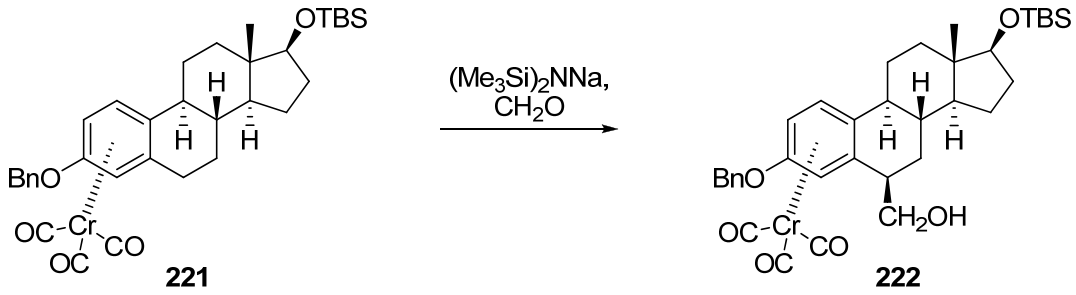
The key properties of arene tricarbonylchromium complexes which are useful in organic synthesis are:

(a) enhancement of the acidity of the benzylic protons
(b) steric hindrance provided by the $Cr(CO)_3$ group to the approaching reactants
(c) easier nucleophilic substitution on the arene ring
(d) enhancement of the acidity of the aromatic protons

The first two properties were used to good effect by Jaouen *et al.* in new syntheses of estrogen hormones (

**Scheme 65**).[96] The chromium tripod was complexed onto the suitably protected estradiol to form a mixture of diastereomers which could be separated by column chromatography facilitating the isolation of pure **221**, which was then subjected to a benzylic deprotonation

in the presence of a suitable electrophile, producing the *exo* substituted product **222** exclusively in a 56% yield.



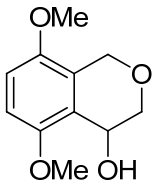

**Scheme 65**

We believed that we could also capitalise on these same properties of the chromium tripod complex to facilitate a stereoselective synthesis of substituted pyranonaphthoquinones. Our efforts towards this study are presented in the following section.

### 2.2.1.1 Chromium complexation onto the chiral alcohol

As a model system for studying the usefulness of arene chromiumtricarbonyl chemistry in the synthesis of 1,3-substituted pyranonaphthoquinones, we made use of the isochromanol **169** which we could easily synthesise (

**Figure 18**).

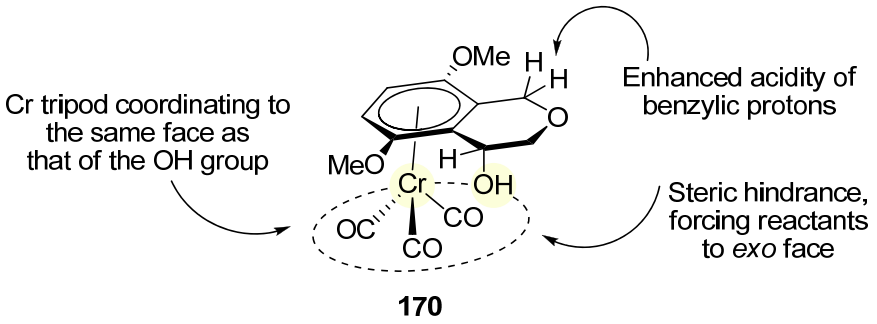



**169**

**Figure 18**

One of the key features of this model compound which we can use to our advantage is the stereochemistry of the existing benzylic alcohol. A chirally pure benzylic alcohol **169** should provide us with a handle to direct the chromium complexation (Figure 19). This stereocontrol is achieved by virtue of the fact that the chromium moiety will initially coordinate with the oxygen of this alcohol, directing it to the same face as it complexes to the arene.[97] Thereafter, enhancement of the acidity of the benzylic protons will allow us to

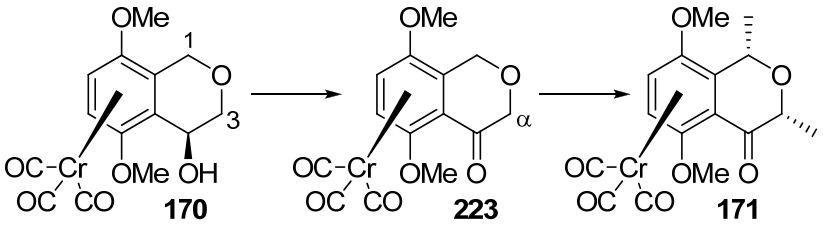
add electrophiles stereospecifically to the *exo* face of the chromium complexed isochromanol **170**, since these electrophiles will approach from the opposite face to the chromium tricarbonyl for steric reasons.




**170**

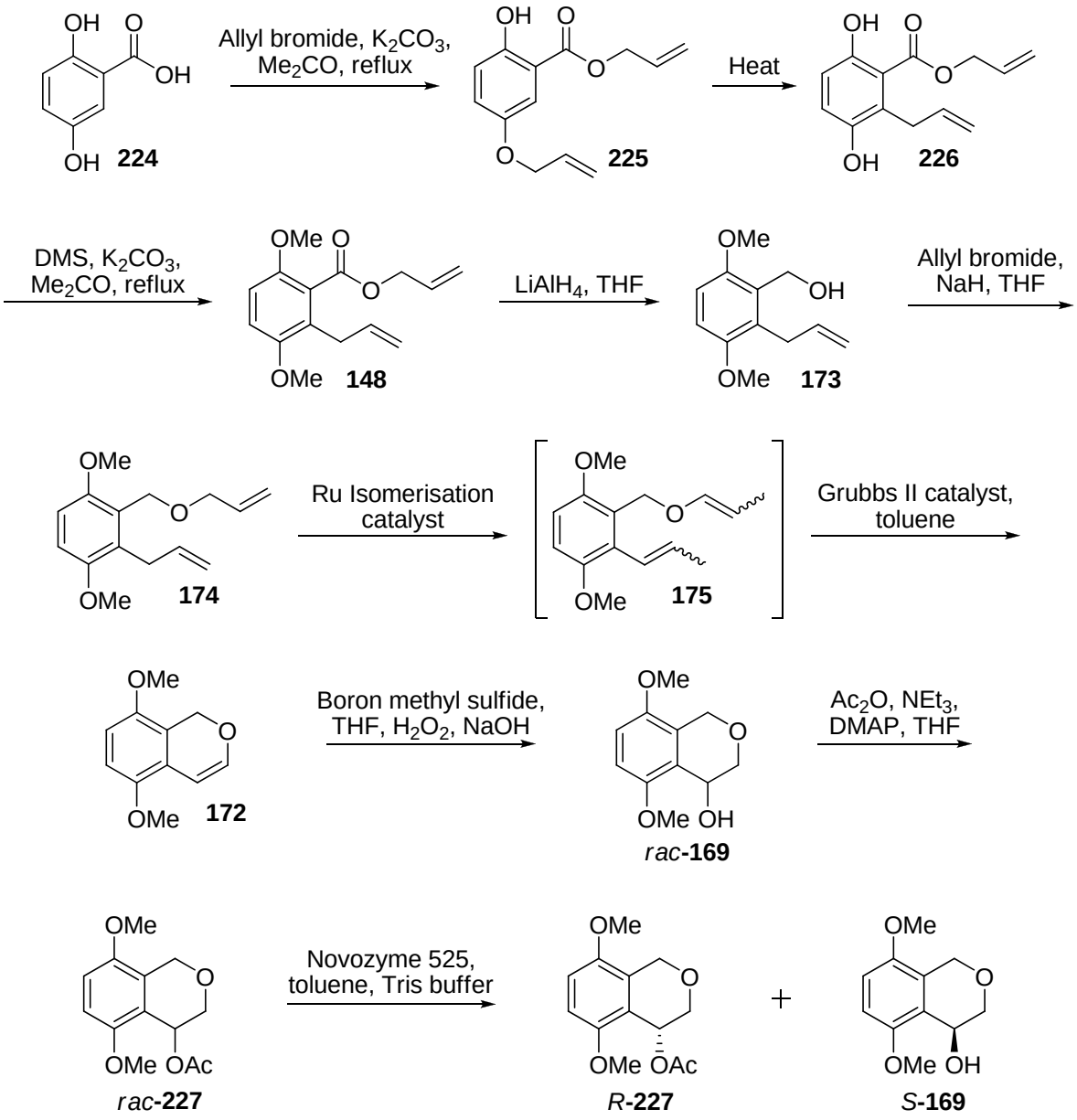
**Figure 19**

Furthermore, in our model system whilst the C1 position is easily accessible due to the enhanced acidity of the benzylic protons, in order to access the C3 position we will require a functional group interconversion. Fortunately, the presence of the benzylic OH group provides us with just the handle we need as it can be oxidized to the corresponding ketone **223**, thereby rendering the α-protons acidic (at the C3 position). A suitable base can then be employed to abstract the protons from both the C1 and the C3 positions in order to effect the stereoselective addition of electrophiles to both these positions (Scheme 66), once again directed to the opposite face as the chromium complex.




**Scheme 66**

Of course, if we wish to capitalise on the OH group of the isochromanol to direct the complexation of the chromium tripod, we need to start with the chiral isochromanol **169**, and as it turns out, we have already successfully completed this synthesis in previous work.[70] In this MSc project, we made use of an enzyme mediated chiral resolution procedure, which necessitated the synthesis of the racemic acetate **227** (Scheme 67).




**Scheme 67**

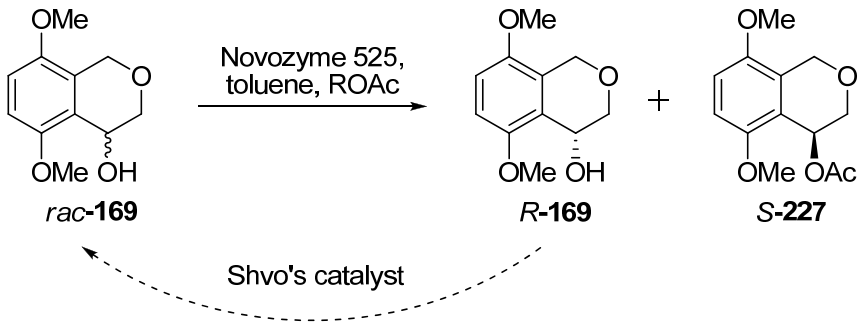
Since this work had been discussed before, we will only briefly run through the synthesis here. The synthesis of the required racemic acetate **227** was achieved in nine steps starting from commercially available 2,5 dihydroxybenzoic acid **224**, which was subjected to a selective allylation procedure. In this process, the carboxylic acid and the 5-OH were selectively allylated in the presence of allyl bromide to produce **225** in a 92% yield. However, the phenol at C2 was not allylated as this position is both sterically hindered and significantly less reactive due to hydrogen bonding of the phenolic hydrogen to the adjacent carbonyl group. Claisen rearrangement of this carefully prepared product under

thermal conditions produced **226** in 86% yield. Methylation of the phenolic groups using dimethyl sulphate produced **148** in 82% yield. With the hydroquinone protected, the ester functionality was reduced to the primary alcohol using lithium aluminium hydride in THF, affording **173** in 93% yield. We once again required an allylation to take place, this time reacting the benzylic alcohol **173** with allyl bromide and sodium hydride to produce **174** in a 91% yield. Both allyl substituents were then subjected to a one-pot, two-step ruthenium mediated isomerisation, followed by a ring closing metathesis reaction to form the isochromene **172** in an 85% yield over the two steps. The conveniently located alkene on **172** facilitated a hydroboration-oxidation reaction to produce the isochromanol **169** in 84% yield. Finally the alcohol was acetylated with acetic anhydride to produce the desired racemic acetate **227** in 70% yield.

The chiral resolution of the racemic acetate **227** was achieved utilising an enzyme mediated chiral resolution procedure, employing the commercially available lipase enzyme - Novozyme 525. Under the appropriate conditions, this enzyme is capable of enantioselectively acetylating or de-acetylating suitable substrates. This served our purposes well, as we were able to carry out the selective de-acetylation of one enantiomer of a racemic mixture of the acetylated isochromanol **227**. Then, with the different compounds in hand (i.e. acetylated *R*-**227** and de-acetylated *S*-**169**) we were then able to separate the enantiomers using conventional column chromatography. This procedure turned out to be very effective, affording the *S*-isochromanol *S*-**169** in an excellent enantiomeric excess of 98% as determined by chiral HPLC. Nevertheless, pleased as we were with this result, there remained a down side in that because the enzyme reacts selectively with one enantiomer, even under ideal conditions we would of course never be able to obtain our desired enantiomer in a yield that would be greater than 50%.

In this PhD study we therefore attempted to remedy this problem by improving our procedure, using a more complicated dynamic kinetic resolution technique. However, in this procedure we opted to utilise the reverse enzymatic reaction for our resolution purposes – i.e. acetylation of the isochromanol, which is possible using once again Novozyme 525, this time in the presence of a suitable acetylating agent. We now have a procedure to acetylate one enantiomer of racemic isochromanol **169** to form the acetate *S*-**227**, while leaving the other enantiomer unreacted as the free alcohol (Scheme 68). The

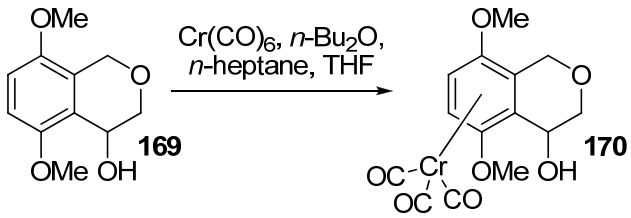
reason for this reversal in tactics is because we also wished to employ the use of another catalyst which should racemise the unreacted chiral alcohol, ***R*-169** *in situ*, thereby effectively continuously providing more *S*-substrate for the enzyme to acetylate. Such a racemisation catalyst has indeed been previously employed to racemise alcohols for this purpose (though not on this substrate) and is known as Shvo's catalyst.[98-100] This interesting method of continuously racemising an unwanted enantiomer *in situ* is known as dynamic kinetic resolution, and in theory, should allow one to obtain 100% conversion of a racemic mixture to a single desired enantiomer.




**Scheme 68**

Unfortunately however, when this procedure was attempted on our substrate we found that we were still recovering a significant amount of our benzylic alcohol, indicating that the racemising catalyst was in fact not working effectively and we were not able to optimise the process. It may simply be that the catalyst is ineffective on our substrate. Wishing to push forward with the synthesis to investigate the chromium chemistry, we therefore had to be satisfied with the less complicated lower yielding, though highly stereoselective, direct enzymatic conversion, in other words the kinetic resolution procedure.

Returning to the arene chromiumtricarbonyl chemistry with the chiral isochromanol **169** in hand, we were in a good position to attempt the complexation reaction. This attachment of the chromium tripod can be achieved by reacting the arene with $[Cr(CO)_3L_3]$, where L is most commonly CO, but can also be other donor ligands like acetonitrile, ammonia and pyridine - all of which have an influence over the rate and the reaction temperature of the coordination reaction.[101] For the formation of our arene tricarbonylchromium tripod **170** we made use of chromium hexacarbonyl $Cr(CO)_6$ since we had it on hand (Scheme 69).

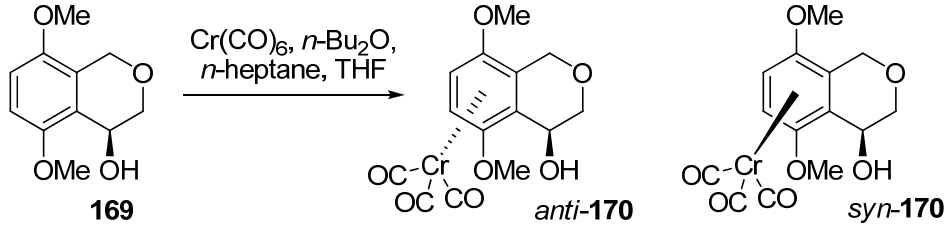



**Scheme 69**

The process of co-ordinating the chromium tripod onto the arene system was somewhat lengthy and we found that we needed to boil the arene and chromium hexacarbonyl in a mixture of *n*-dibutyl ether, THF and heptane for 72 hours at reflux to react most of the starting material. The choice of solvents is crucial when using the $Cr(CO)_6$ ligand, and it has been found that this mixture gives optimum results with respect to the diastereoselectivity of the reaction, arising from coordination of the approaching chromium to the benzylic alcohol (as previously discussed).[97] The reaction is also extremely sensitive to the presence of oxygen and great care needed to be taken to ensure that the solvent was thoroughly degassed and the reaction was carried out under an Ar(g) atmosphere. Although the use of the $Cr(CO)_6$ compared to the other chromium reagents (e.g. $\eta^6$-naphthalene$Cr(CO)_3$) has the attraction of being cost effective, the down side is that there are associated technical problems. One of these is the sublimation of the chromium hexacarbonyl on the condenser during the reaction. Fortunately, this can be overcome with the use of either a specially designed heated condenser, or the more convenient method which involves the use of solvents like THF and dibutyl ether, which at the reflux temperature constantly wash down the sublimed $Cr(CO)_6$.[101] Another important role played by the THF in the solvent mixture is as a weak donor ligand. It assists in the dissociation of one or more of the CO ligands during complexation and it also prevents the oligomerisation of the coordinatively unsaturated $Cr(CO)_3$ species.[102] Further degassing of the reaction mixture also facilitates the removal of CO gas.

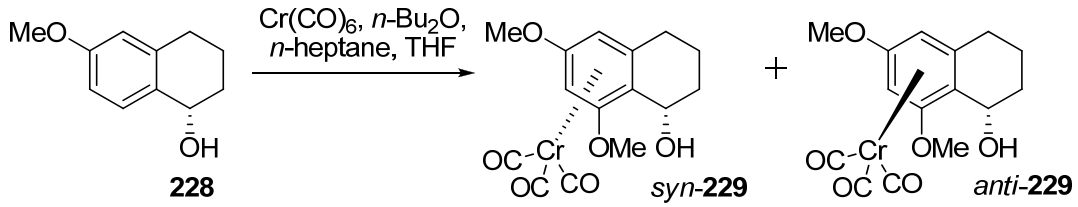
Great care had to be taken in order to exclude oxygen from the reaction mixture as this would oxidise the chromium source and prevent the complexation. The reaction was also conducted in the absence of light as this could also result in decomplexation of the chromium tripod. Further adding to these difficulties in terms of oxygen and light sensitivity is that the reaction proceeded slowly and needed 72 hours at reflux temperatures (~120 ºC) under an Ar(g) atmosphere. Over this time however, the reaction changed from a

colourless solution to bright yellow. A clear sign of an unsuccessful reaction was the unwelcomed green colour, which forms as a result of failed co-ordination and oxidation of the chromium to $Cr_2O_3$ instead, driven by oxygen leaching into the system. On completion of our reaction, the mixture was checked by TLC in order to confirm that we had in fact converted all of our starting material into the desired product. We were surprised on analysis of the TLC plate to discover that most of the starting material had been consumed, but there were now two new compounds present! However, on the TLC these compounds were both bright yellow in colour, indicating that they were both chromium complexes. Although rather close to each other on TLC, these compounds were easily separated by the use of flash chromatography (Scheme 70). To our dismay, and against literature precedent,[97] while we had expected the benzylic hydroxyl of the highly enantiomerically enriched isochromanol *S*-**169** to direct the chromium complexation to the same face as itself, this had not occurred, and we had in fact formed a mixture of diastereomers! The *anti*- and *syn*-complexed **170** had formed in a ratio of 2.6:1.




**Scheme 70**

As it turns out, this phenomenon of the oxygen substituent *not* directing the approaching chromium has been observed before. Schmalz *et al.* discovered this switching of the $Cr(CO)_3$ to the opposite face of the arene ring resulting in a decrease of the *syn*/*anti* ratio while working on a similar system **228** (Scheme 71).[103] Based on their studies, this loss of selectivity was found to become more pronounced as the number of methoxy substituents on the arene ring is increased. Consistent with this observation, our substrate **169** which has two methoxy substituents on the arene ring also exhibits poor diastereoselectivity during the complexation process.




**Scheme 71**

Nevertheless, the spectroscopic evidence unambiguously confirmed that we had indeed synthesised the chromium complexes, albeit without any selectivity thereby forming the compounds *syn*- and *anti*-**170**. Since the only change on our molecule **169** was the complexation of the $Cr(CO)_3$ moiety, we first turned our attention to the $^{13}C$ NMR spectrum, looking for evidence of the C≡O signals. Indeed we were pleased to discover this desired key feature in the spectrum, a signal in the far downfield region at 232.9 ppm typical of the C≡O groups on the chromium tripod. In addition to this, the remaining signals for the aromatic carbons were now all shifted upfield relative to the signals for the uncomplexed alcohol **169** (by approximately 25 ppm each). Similarly, in the $^{1}H$ NMR spectrum the signals for the aromatic protons were shifted slightly upfield in comparison to that of the uncomplexed starting material **169**. The signals for the two aromatic protons of the uncomplexed **169** for example were found overlapping at 6.72 ppm, whereas in the spectrum for the chromium complexed alcohol **170**, the signals were found as doublets at 5.16 ppm and 4.99 ppm. This observation is in keeping with the fact that the chromium tripod acts as an electron sink withdrawing electron density from the aromatic ring. This disruption in the usual aromaticity is observed by the slight upfield shift in the position of the aromatic protons' signals. Furthermore, the signals in the $^{1}H$ NMR spectrum of **170** were broader than that observed for the uncomplexed alcohol **169** – another characteristic feature of chromium complexes. In the IR spectrum a distinctive sharp C≡O stretching band at 1841 $cm^{-1}$ could be attributed to the presence of the CO groups. Unfortunately, upon attempting to determine the melting point of **170**, we discovered that at 140 ºC the bright yellow solid became green then black, indicating decomplexation and decomposition. Fortunately, due to the fact that we were able to separate the diastereomers using chromatography, we were able to crystallise and obtain suitable crystals of each diastereomer. These results showed conclusively that the products of our reaction were certainly the chromiumtricarbonyl complexed isochromanols, *syn*-**170** and *anti*-**170** (Figure 20).

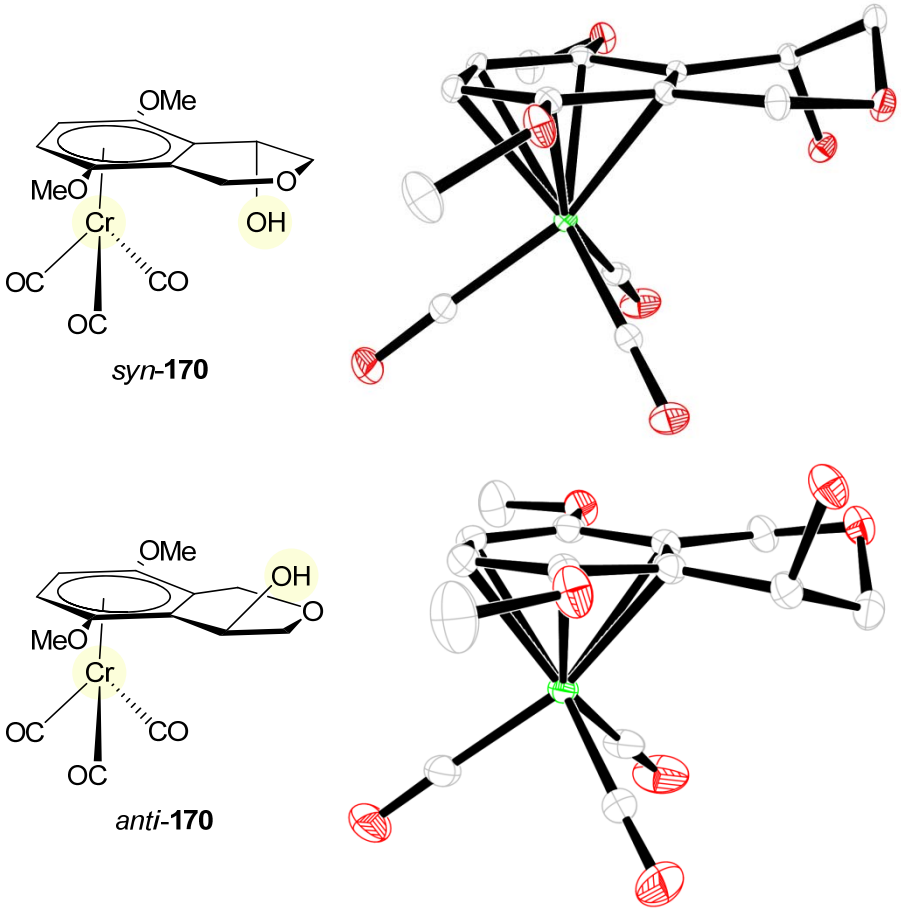
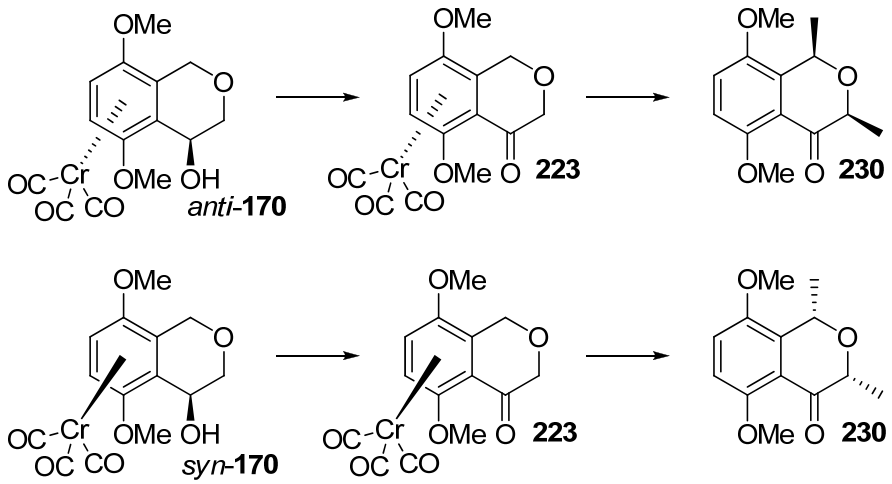



**Figure 20**

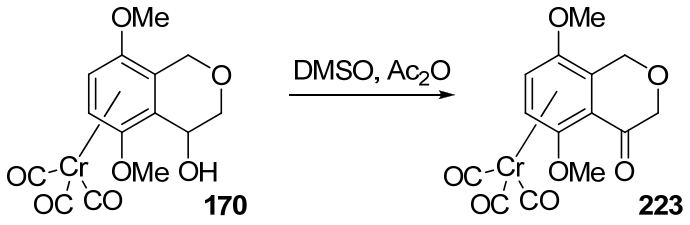
### 2.2.1.2 Oxidation of the complexed benzylic alcohol

With our diastereomers **170** in hand, the next step of our reaction sequence required the oxidation of the alcohol functionality to the ketone. Fortunately, since we were able to separate the chromium complexed diastereomers, we would be able to perform this reaction on the *anti*- and *syn*-**170** complexes separately, leading to the separate isochromanone enantiomers **223**, thereby giving us access to what we hoped would be both *R*,*S* and *S*,*R*-**230** (Scheme 72).




**Scheme 72**

We envisaged however that the oxidation of the benzylic alcohol **170** to the ketone **223** may be problematic since oxidative conditions are also employed as a method to remove the chromium tripod. The reagents for this transformation would therefore need to be carefully selected in order to achieve this conversion without a concomitant decomplexation of the chromium tricarbonyl. Mild oxidants, such as magnesium dioxide have been reported to oxidise similar systems in the presence of the chromium tricarbonyl group, however the yields reported were disappointing at only 20%.[104] Another more efficient procedure has been reported by Levine *et al.*[105] which is a modification of a Swern oxidation utilising a mixture of acetic anhydride and DMSO. We decided to attempt this more favourable option and to this end our complexed alcohol **170** was dissolved in a mixture of acetic anhydride and DMSO and allowed to react at ambient temperature (Scheme 73).

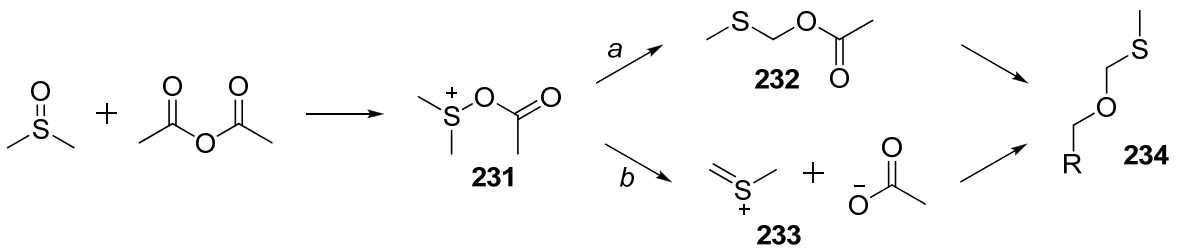



**Scheme 73**

Since our substrate **170** was similar in structure to the systems investigated by Levine *et al*. we were encouraged by the observed colour change of our reaction mixture from yellow to orange, the same as that reported by Levine.[105] However on completion of the reaction we

were disappointed to discover that we had in fact only formed trace amounts of our desired product and possibly another chromium complex which we unable to characterise. Worse still, we were subsequently unable to reproduce these disappointing results. Nevertheless we were able to obtain enough of the ketone for spectroscopic analysis. The formation of the desired ketone was confirmed by the $^{1}$H NMR spectrum which no longer contained the signal for the alcohol proton at 2.77 ppm. The doublet for the proton attached to position C4 at 4.81 ppm was also conspicuously absent. All the remaining signals were accounted for in the product. Unfortunately we were unable to obtain a $^{13}$C NMR spectrum due to the limited amount of material in hand. The IR spectrum however showed a new C=O stretching absorption at 1691 cm$^{-1}$, a feature not present in the alcohol precursor **170** which had instead a broad OH stretching band at 3251 cm$^{-1}$.

The use of acetic anhydride and DMSO as an oxidising agent behaves in much the same way as an "activated dimethyl sulfoxide" similar to that employed in the Swern oxidation.[92] A possible side product of the reaction is an addition of a methyl thiomethoxy group to the alcohol to form **234** (Scheme 74).[106] This reaction can occur via two pathways. In path *a*, the acyloxysulfonium salt **231** generated from the acetic anhydride and DMSO, undergoes a Pummerer rearrangement[92] to form the acetoxy methylmethyl sulphide **232** and acetic acid. In this pathway the acetate anion is no longer available for the formation of the ylide and this then leads to the formation of **234**. In path *b* there is an independent competitive rearrangement of the salt **231** forming the intermediate **233** which leads to the ether **234**.[106]




**Scheme 74**

Although we were unable to fully characterise the side product of our reaction, due once again to insufficient quantities, this could be a possible explanation for the failure of our reaction under the conditions employed.

Having encountered some difficulties with the modified Swern oxidation we then turned our attention to other oxidation procedures. In fact, we tried various methods which were reported in the literature and these conditions are listed in Table 2. Unfortunately, most of these reaction conditions proved completely unreactive and we simply recovered our starting material **170**. Worse still, in some instances the decomplexed yet otherwise unreacted alcohol **169** was obtained. Finally due to time constraints, we were aggrieved to resign ourselves to the fact that we would be unable to pursue this troublesome oxidation any further.

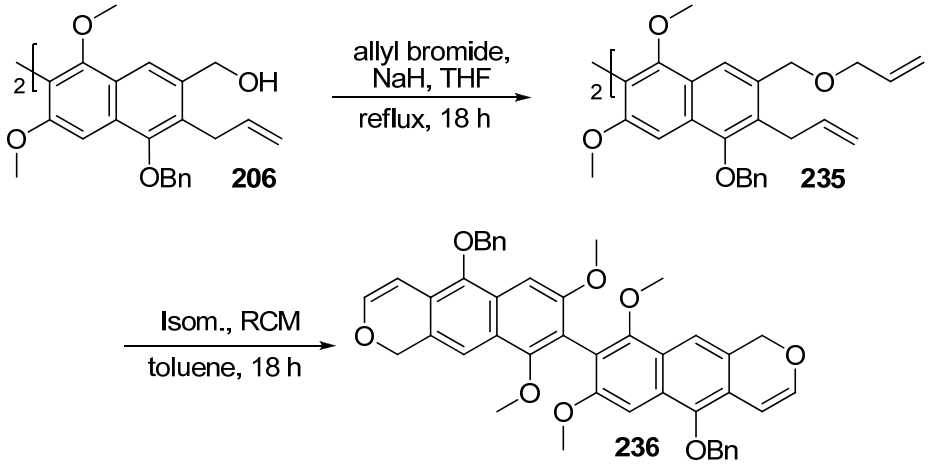
**Table 2**: Reaction conditions of attempted oxidation reactions

| **Conditions** | **Result** |
|---|---|
| $MnO_2$[104] | no reaction |
| $Ag_2O$, $MgSO_4$[107] | no reaction |
| $KMnO_4$, $MnO_2$[108] | decomplexed alcohol |
| PCC, $Al_2O_3$[109] | decomplexed alcohol |
| IBX[110] | decomplexed alcohol |

Nevertheless it has to be said that having overcome the hurdles of the tricky complexation of the chromium tripod onto our isochromanol **169**, we still believe given more time this work has much scope and many as yet unexplored options. These options will be discussed in the next chapter in our vision towards future work in this area.

In the meanwhile, not having anticipated these various problems associated with the use of arene chromiumtricarbonyl chemistry we had already optimistically begun steps towards the synthesis of a suitable chromium complex precursor of our actual target dimeric molecule (Scheme 75). Of course, all the chromium work being undertaken on the simpler model compounds ultimately was leading to the development of methodology for the stereoselective introduction of the C1 and C3 methyl groups, for a stereoselective bidirectional synthesis of cardinalin 3. To this end, the precursor we had in mind for chromium complexation was the benzoisochromene **236**. This compound was obtained by the initial allylation of the benzylic alcohol of **206** to form the diene **235** in an unoptimised yield of 68%. In order to construct the pyran ring system, **235** was subjected to a one-pot, two-step isomerisation and ring closing metathesis reaction to form the benzoisochromene

ring system **236** in an unoptimised yield of 51%. At this point, having incurred a roadblock with regard to the chromium chemistry on the model system **169**, we decided to halt the synthesis on the dimeric precursor **236** until such time as we were confident that we could in fact use the chemistry of the complexed chromium tripod to our advantage in the stereoselective synthesis of the cardinalin 3.




**Scheme 75**

The $^{1}$H NMR spectrum of the **235** clearly showed the addition of a new allyl substituent with its signals slightly overlapping with those of the existing allyl chain at the C3 position. The protons of the CH groups on both alkenes were found as two multiplets in the range 6.21 ppm to 5.88 ppm. The protons of the $CH_2$ group of one alkene produced a multiplet ranging from 5.40 ppm to 5.16 ppm, while the protons of the $CH_2$ group of the other alkene produced a multiplet in the region of 5.15 ppm to 4.93 ppm, overlapping with the signal for the protons attached to the benzylic group at C2. The protons of the methylene group on the allyl chain attached to C3 produced a doublet at 3.79 ppm, whilst the methylene group on the *O*-allyl chain produced a doublet at 4.07 ppm. The signal indicating the proton of the benzylic OH was no longer present. The $^{13}$C NMR spectrum of the molecule **235** similarly indicated three additional signals compared to the spectrum of the free alcohol **206** confirming the addition of the allyl substituent.

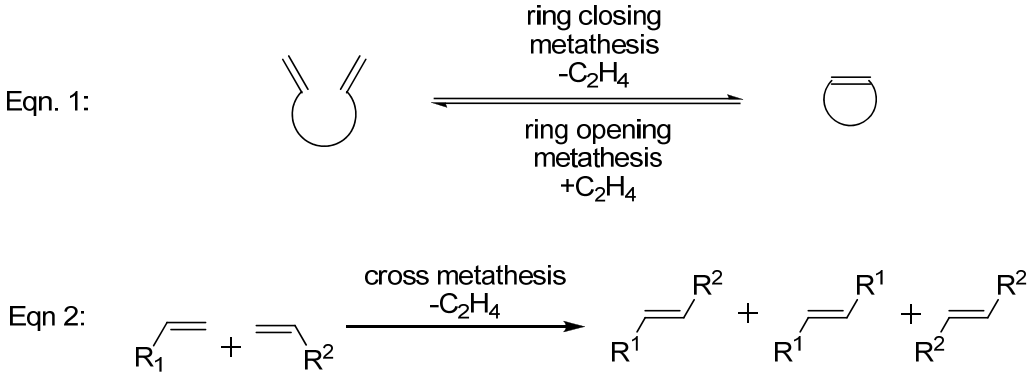
After converting **235** to **236**, the $^{1}$H NMR spectrum of the molecule was somewhat simplified, a welcome sign of the success of the reaction. Replacing the complicated multiplets of the protons of the allyl side chains was a doublet at 6.63 ppm representing the alkene proton at the C3 position of the pyran ring coupling to its neighbouring alkene

proton at C4, also appearing as a doublet at 6.16 ppm. The signal for the benzylic methylene protons at the C1 position of the system was found as a doublet at 5.02 ppm. The $^{13}C$ NMR spectrum correspondingly became slightly simpler, having lost four signals.

At this point we decided to move on to our next study where we would investigate the use of cross metathesis to form C3 substituted isochromanes.

### 2.2.2 A novel cross metathesis route to access substituted isochromanes

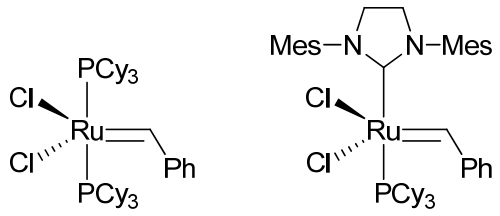
The valuable discovery by Karl Ziegler that certain transition metal catalysts promote the polymerisation of olefins under mild conditions has had a tremendous impact on synthetic chemistry.[111] It was soon discovered that not only do these catalysts promote addition polymerisation of alkenes, but can also induce a mutual alkylidene exchange. These transformations, which involve the cleavage and formation of relocated double bonds became referred to as "alkene metathesis". The term "metathesis" is a composite of the two Greek words *meta* (change) and *tithemi* (place). Some of the most useful metathesis reactions are illustrated in Scheme 76. In the case of tethered terminal alkenes, metathesis can result in the closing or opening of ring structures (Eqn 1), whereas individual alkenes are able to exchange partners forming novel unsaturated compounds (Eqn 2).




**Scheme 76**

The first generation of metathesis catalysts were unattractive for applications in organic synthesis as they were poorly compatible with polar functional groups, due to for instance their alkylating characteristics. Fortunately, significant progress in organometallic chemistry research has changed this situation, with the generation of new highly effective catalysts which are not only more tolerant of various functional groups but are also more stable. The ruthenium carbene complexes **237** and **238** are among the most popular and

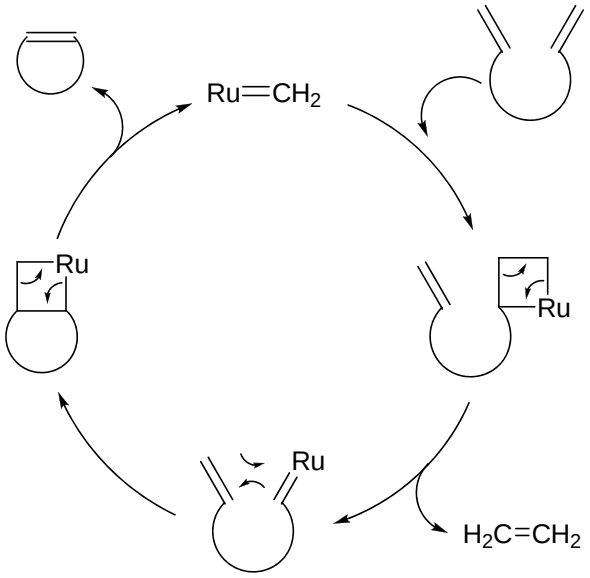
versatile catalysts used today, developed by Grubbs and co-workers (Figure 21),[112] a feat which earned Grubbs, Schrock and Chauvin a chemistry Nobel Prize in 2005.




**237** **238**

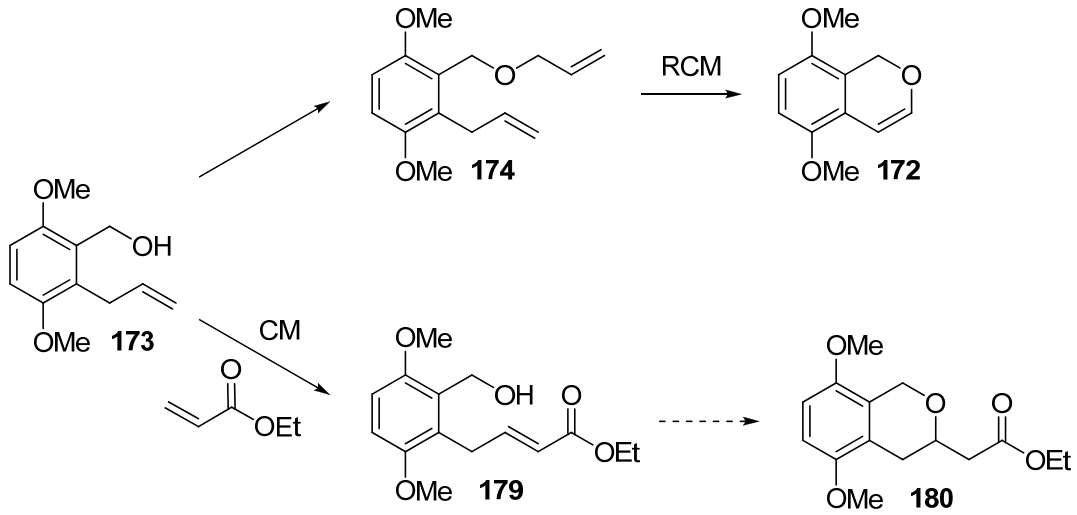
**Figure 21**

The generally accepted mechanism for the metathesis reaction referred to as the "Chauvin mechanism" consists of a sequence of formal [2+2] cycloaddition/cycloreversion reactions involving alkenes, metal carbenes and metallocyclobutane intermediates.[113] Since the individual steps are reversible, it is necessary for the equilibrium mixture of the alkenes to be pushed in the forward direction for a productive reaction. This shift in the equilibrium toward the products can be achieved in ring closing metathesis as one product is now cut into two, driving the reaction forward entropically. Additionally for terminal or short chain alkenes one of the products may be volatile for example ethene, which evaporates, further promoting the forward reaction (Scheme 77).[113]




**Scheme 77**

In our endeavours towards novel methods for the synthesis of pyranonaphthoquinones, we have successfully made use of ring closing metathesis (RCM) for the formation of the isochromene nucleus **172** as discussed in Section 1.5. This method could also be applied to the dimeric system of **206** shown in Scheme 75. Encouraged by these results we were prompted to further investigate the usefulness of this reaction in the synthesis of the isochromane skeleton **180** by employing, in this case, a cross metathesis on the scaffold of **173**, thereby providing access to the C3 substituted isochromanes (Scheme 78).




**Scheme 78**

Some well-known examples of C3 substituted pyranonaphthoquinones include kalafungin **3** and nanaomycin A **12** (Figure 22). Both the fused γ-lactone ring and the carboxylic acid side chain of these molecules can be derived from an ethyl ester chain at the C3 position.

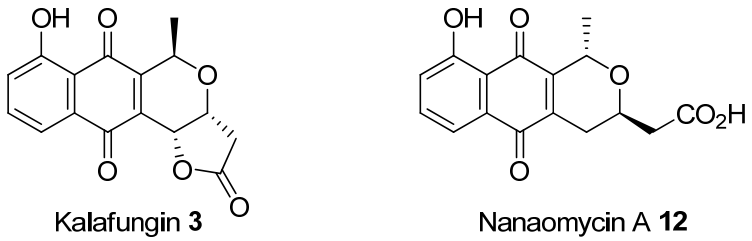
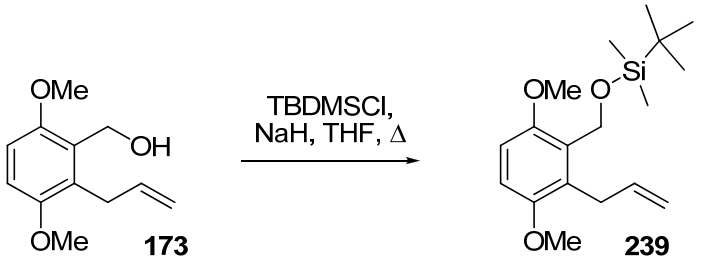



**Figure 22**

The required cross metathesis partners for this study would in fact be the protected derivative of the previously synthesised benzylic alcohol **173**, (containing an appropriate protecting group on the OH functionality), and commercially available ethyl acrylate. For the protection of the alcohol, we envisaged that a suitable silyl ether would be most

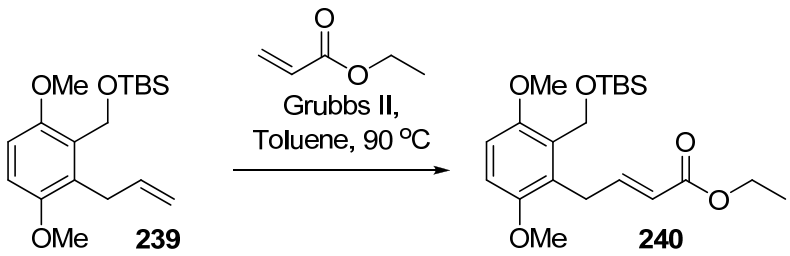
appropriate as it would be compatible with future planned reactions and could be easy to remove under mild conditions when required (Scheme 79).




**Scheme 79**

To this end, the benzyl alcohol **173** was treated with *tert*-butyldimethylsilyl chloride in the presence of sodium hydride. Interestingly, the reaction would not proceed at room temperature, perhaps due to difficulties encountered by the bulky silyl group in approaching the sterically crowded benzylic alkoxide, flanked by the methoxy group on one side and the allyl chain on the other. Fortunately however, with the increased energy provided under reflux conditions, the protected alcohol **239** was obtained in an excellent yield of 86% as a clear oil. Verification of the desired product was immediately evident in the $^{1}$H NMR spectrum. There were now two distinct up field singlets, one at 0.92 ppm and the other at 0.09 ppm, integrating for 9 and 6 protons respectively. The signal for the proton of the alcohol functionality was no longer present. The $^{13}$C NMR spectrum also contained 3 new upfield carbon signals. One of these belonged to the three equivalent methyl groups of the tertiary butyl group at 26.0 ppm; the other was attributed to the quaternary carbon located at 18.5 ppm. Finally the signal at −5.3 ppm could be assigned to the equivalent methyl groups attached directly to the silicon. The mass spectrum of the molecule was in agreement with the expected mass of **239**.

With the required alkene quickly in hand, we were in a position to investigate our cross metathesis reaction (Scheme 80).

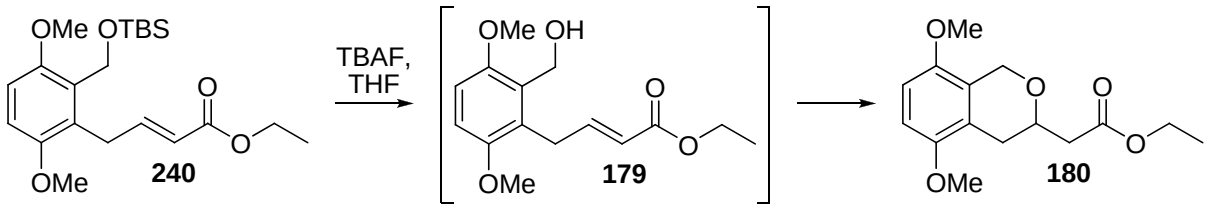



**Scheme 80**

Although there are several metathesis catalysts available, the catalyst that we employed for our reaction was the Grubbs second generation catalyst **238**, as it was on hand and we knew it was active as it was successfully being employed in other research projects. Therefore the alkene **239** and ethyl acrylate, were dissolved in dry, degassed toluene and blanketed with Ar(g). The ruthenium catalyst was then added to this oxygen free environment. After 18 h, TLC analysis of the reaction mixture revealed that the starting material **239** had been completely consumed and a new compound at a lower $R_f$ had formed. The reaction mixture, after purification by column chromatography afforded the new alkene **240** in a moderate yield of 62%. Although the yield was slightly disappointing, we were delighted to discover that this was the only product of the reaction and surprisingly none of the homo-coupled product was isolated.

The spectroscopic analysis of the product **240** was in line with our expectations and confirmed the successful cross metathesis of the two alkenes. In the $^{1}$H NMR spectrum, the signals previously observed for the alkene protons were now distinctly different. On the α,β-unsaturated system, the signal for the proton on the β-carbon was shifted downfield to 7.12 ppm, and the signal for the proton on the α-carbon was shifted upfield to 5.66 ppm. The most pleasing result of the reaction was that the coupling constant for the alkene protons indicated that we had formed the *trans* isomer exclusively, with a large *J* value of 15.6 Hz. The characteristic mid-range and upfield quartet and triplet pattern integrating for two and three protons respectively, provided a clear indication that the ethyl ester functionality was now present. In the $^{13}$C NMR spectrum, there was a new carbonyl peak at 166.9 ppm indicative of an ester carbonyl, as well as two new peaks at 60.0 ppm and 14.2 ppm indicating the new secondary and primary carbons of the ethyl chain respectively. The IR spectrum contained the expected carbonyl stretching frequency at 1719 $cm^{-1}$. The mass spectrum once again matched the expected value for the parent ion (394.21714 amu).

Having successfully formed the cross metathesis product **240**, all that remained was the ring closure by internal Michael addition to afford the pyran ring system **180,** which would of course bear the useful ester functionality at the C3 position. Firstly however, the benzylic alcohol would need to be unmasked by removing the silyl protecting group. In fact, we anticipated that by employing tetrabutylammonium fluoride as the deprotection reagent, the ring closure would be spontaneous, resulting in concomitant formation of our desired molecule **180** (Scheme 81). To this end, the silyl ether **240** was treated with TBAF in THF, and using TLC, the reaction was deemed to be complete within an hour, with only one new product observed at a much lower $R_f$. After extraction, purification, and analysis by NMR, we were indeed pleased to obtain the deprotected and cyclised isochromane **180** in 55% yield.

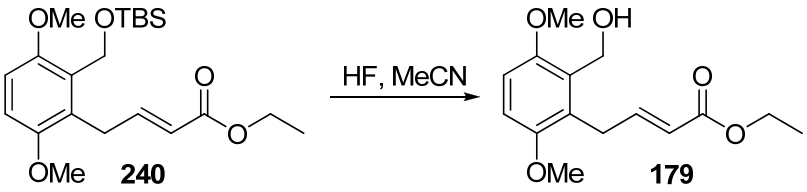



**Scheme 81**

In the $^1$H NMR spectrum, the first clear indication that the deprotection had indeed occurred was the absence of the two distinct singlets belonging to the TBS group in the upfield region of the spectrum at 0.88 ppm and 0.06 ppm. Furthermore, the absence of the alkene α-proton signal at 5.66 ppm provided the first suggestion that the intermediate **179** had indeed gone on to cyclise to the isochromane **180**. In fact, the only signals present in the downfield region of the spectrum were those belonging to the two aromatic protons. The C1 benzylic $CH_2$ group, now bearing non-equivalent protons produced doublets at 4.62 ppm and 4.19 ppm, whereas in the precursor **240**, these were observed as a singlet. The signal for the C3 proton now appeared as a multiplet in the range 4.11 ppm to 3.99 ppm, coupling to the methylene groups on either side. The remaining protons of the benzylic $CH_2$ group (at C4) also produced separate signals for each proton, being adjacent to a stereogenic centre, each producing a doublet of doublets, one at 2.83 ppm and the other 2.45 ppm. The signal for the $CH_2$ group *alpha* to the carbonyl appeared as a two double doublets at 2.65 ppm. In the $^{13}$C NMR spectrum the most significant change was the upfield shift of the two signals previously associated with the alkene carbons, now

present at 70.7 ppm and 41.2 ppm. The three upfield signals associated with the TBS protecting group were no longer present.

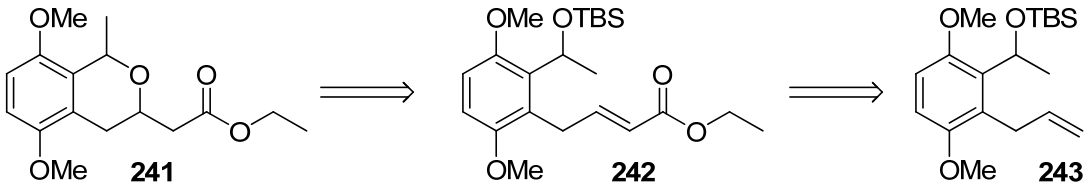
Although the spontaneous ring closure directly afforded the desired isochromane **180** from the silyl ether **240**, it unfortunately left two questions unanswered. Firstly, the yield was moderate overall – was this a problem with the actual deprotection step or the cyclisation step. Secondly, the construction of the Michael acceptor **179** actually puts us in a wonderful position to investigate possible enantioselective cyclisation procedures – but for this we would need to prevent the concomitant cyclisation of the benzylic alcohol onto the α,β-unsaturated system. Therefore, we opted for an acidic deprotection of the silylated alcohol **239**, which we hoped would suppress the concomitant cyclisation, affording **179**. To this end, the silyl ether **240** was treated with hydrofluoric acid and as before, the reaction was complete within an hour. Initially we were disappointed as TLC analysis indicated the formation of a product with the same $R_f$ as that observed previously for the already formed isochromane **180**. However, to our pleasant surprise, once purified and characterised, this product was indeed found not to be the same as the isochromane **180**. Scrutiny of the NMR spectra indicated that we had in fact isolated the benzylic alcohol **179** in a yield of 72% (Scheme 82).




**Scheme 82**

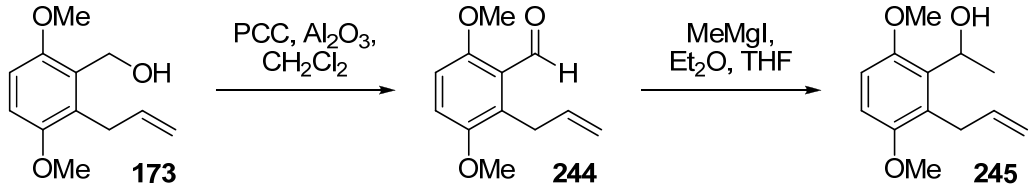
In the $^{1}H$ NMR spectrum, while the two signals indicating the *tert*-butyldimethylsilyl protecting group were conspicuously absent, the signals for the alkene protons were definitely still present at 7.07 ppm and 5.59 ppm! The benzylic C*H*$_2$OTBS signal that was previously observed as a singlet at 4.72 ppm was now a doublet at 4.39 ppm. A new singlet at 5.84 ppm attested to the presence of the proton of the benzyl alcohol. The $^{13}C$ NMR spectrum of **179** was very similar to its precursor **240** save for the conspicuously absent signals associated with the TBS group. This product, unlike its precursors or **180**, was a white solid with a melting point of 100-103 ºC.

Having had this much success using the cross metathesis methodology to synthesise the isochromane **180**, we now wished to extend it further by synthesising the C1 methyl substituted isochromane **241**. We envisaged that by starting with the precursor **243**, we could similarly arrive at **241**, probably as a mixture of *cis* and *trans* diastereomers (Scheme 83).




**Scheme 83**

Since the precursor **243**, contains the additional methyl group, we needed to consider how this could be most effectively introduced. We envisaged that this could in fact be achieved using a very similar route, with just two additional steps. In this approach, the benzylic alcohol **173** could first be oxidised to the aldehyde **244** and then, introduction of the required methyl by way of a Grignard reaction would also simultaneously reform the required alcohol **245** (Scheme 84).



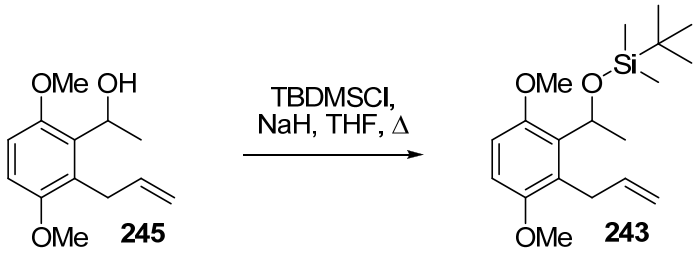

**Scheme 84**

Having had success with the oxidation of the benzylic alcohol in our cardinalin synthesis using pyridinium chlorochromate, we employed the same procedure in this case for the synthesis of the aldehyde **244**. To this end, the oxidant was adsorbed onto neutral alumina and added to a solution of the alcohol **173** in dry dichloromethane. Reliably, on completion of the reaction the aldehyde **244** was obtained in an excellent yield of 96%. Confirmation for the success of the reaction was immediately evident from the characteristic singlet at 10.57 ppm in the $^{1}$H NMR spectrum, indicative of the aldehyde proton. As anticipated there were no longer signals present for the benzylic $CH_2$ protons or the OH proton. In the $^{13}$C NMR spectrum a downfield signal at 192.4 ppm further attested to the newly

introduced carbonyl functionality. The IR spectrum showed a strong C=O absorption band at 1683 $cm^{-1}$ and no OH stretch was observed. The mass spectral analysis of the molecule **244** showed a molecular ion at 206.09311 amu which matched the molecular formula of our molecule ($C_{12}H_{14}O_3$).

We now prepared ourselves for the Grignard reaction. To this end, methyl magnesium iodide was first generated from magnesium metal and methyl iodide in dry diethyl ether and then reacted immediately with the aldehyde **244** dry THF. The reaction was monitored by TLC and once the aldehyde had been completely consumed the excess of the Grignard reagent was quenched by the slow addition of water. After chromatography, this straightforward procedure delivered our racemic secondary alcohol **245** in an excellent yield of 98%. On scrutinising the $^1H$ NMR spectrum, the absence of the downfield aldehyde signal was the first good sign. Instead, a new benzylic proton signal was observed between 5.09 ppm and 4.90 ppm, overlapping with the signals for the $CH_2$ alkene protons. There was also a new signal for the benzylic alcohol proton at 4.03 ppm. It is interesting to note that instead of the typical broad singlet we were accustomed to, this signal appeared as a doublet, coupling to its benzylic proton neighbour. A new upfield doublet at 1.52 ppm integrating for 3 protons confirmed the presence of the newly introduced methyl group. In the $^{13}C$ NMR spectrum, the previously observed signal for the aldehyde carbon in the downfield region was conspicuously absent. Instead, this carbon was now indicated by a new somewhat upfield signal at 67.3 ppm. There was also a new signal at 23.7 ppm, indicating the methyl group. In the IR spectrum, a broad band at 3547 $cm^{-1}$ unambiguously confirmed the presence of the hydroxyl group.

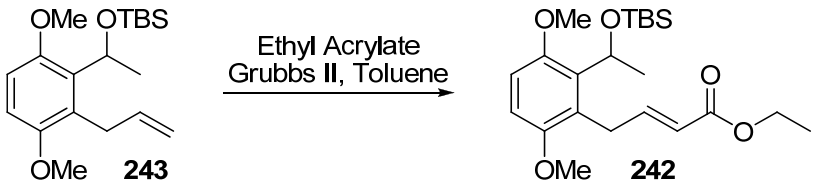
Having finally synthesised the desired precursor **245**, we could now continue in a similar fashion to that employed for the benzyl alcohol **173**. To achieve this, we would thus need to once again protect the free alcohol **245** as its silyl ether (Scheme 85). Treatment of the alcohol **245** with *tert*-butyldimethylsilyl chloride and sodium hydride smoothly furnished the silylated secondary alcohol **243** as a clear oil in 93% yield.




**Scheme 85**

The first sign of a successful silylation was the large change in the $R_f$ of the product, indicating a decrease in polarity. More definitive proof was obtained from the $^1$H NMR spectrum of compound **243**. At 0.85 ppm there was a distinct singlet integrating for 9 protons, belonging to the tertiary butyl peak. Interestingly, the two methyl groups attached to the silicon atom were non-equivalent and produced separate singlets at 0.01 ppm and –0.13 ppm, most likely brought about by their close proximity to the chiral benzylic carbon. In the $^{13}$C NMR spectrum we observed a similar phenomenon, as the methyl carbons attached to the silicon produced separate signals at –4.9 ppm and –5.1 ppm. The signal at 25.9 ppm could be assigned to the three equivalent methyl groups of the tertiary butyl group and that at 18.2 ppm to the quaternary carbon. The broad OH stretching band of the starting material was no longer present in the IR spectrum of the product **243**.

We were now once again in a position to try a cross metathesis reaction (Scheme 86). To this end, the new alkene **243** and ethyl acrylate were dissolved in toluene and reacted with the Grubbs II catalyst.

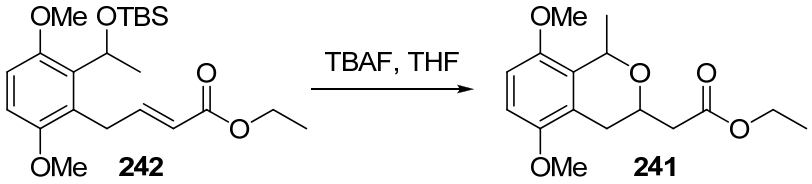



**Scheme 86**

Pleasingly, the reaction proceeded smoothly and we obtained the α,β-unsaturated ester **242** as the sole product in a yield of 83%. The $^1$H NMR spectrum of **242** contained distinctive peaks clearly indicating this transformation. At 7.13 ppm the presence of a doublet of triplets was indicative of the β-alkene proton coupling to its neighbouring α-alkene proton as well as the benzylic $CH_2$. The signal for the other alkene proton at the α-position was

overlapping with the benzylic CH proton signal in the range 5.69 ppm to 5.59 ppm. The signal for the $CH_2$ group of the ethyl ester was found overlapping with one of the protons of the benzylic $CH_2$ group, in the range 4.21 ppm to 4.09 ppm. Its neighbour, the $CH_3$ group of the ethyl side chain produced a triplet at 1.25 ppm. Once again a coupling constant of 15.7 Hz for the alkene protons indicated that we had formed the *trans* isomer exclusively and there was no sign of the *cis* isomer in the $^1$H NMR spectrum. The $^{13}$C NMR spectrum contained a new carbonyl signal at 167.1 ppm indicative of the newly introduced ester functionality. New signals for the ethyl group of the ester were found at 60.0 ppm and 14.3 ppm for the $CH_2$ and $CH_3$ components respectively. In the IR spectrum a sharp C=O stretching band at 1715 $cm^{-1}$ was observed.

All that remained was the deprotection of the alcohol to effect the ring closure in order to obtain the isochromane nucleus **241**, with a methyl substituent at the C1 position. To this end the newly formed alkene **242** was reacted with tetrabutyl ammonium fluoride in THF (Scheme 87).

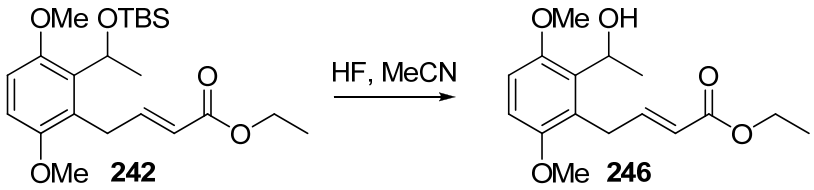



**Scheme 87**

Once again we were pleased to discover that under these conditions, the molecule deprotected and underwent a spontaneous Michael addition to afford the 1,3-substituted isochromane **241**. In the $^1$H NMR spectrum, the presence of the additional methyl substituent complicated matters as we now had a mixture of diastereomers. For some signals this was clearly evident as for instance, there were two distinct quartets for the C1 benzylic proton of each diastereomer. Similarly, the protons at C3 appeared as doublet of triplets at 4.39 ppm and 3.49 ppm, each corresponding to the different diastereomers. The cluster of signals located in the 2.29 ppm to 2.92 ppm range, although complicated by the mixture of isomers were characteristic of the neighbouring $CH_2$ groups alpha to their respective carbonyls and the $CH_2$ groups at the C4 position. There were no longer signals present for the silyl protecting group. The $^{13}$C NMR spectrum similarly, showed additional signals in line with the nature of the product mixture. The upfield carbons of the silyl ether

group were absent. The downfield region of the spectrum only contained signals for the aromatic protons as there were no longer any signals representing alkene carbons. The mass spectral analysis was in keeping with expectations, matching the calculated value for the parent ion of **241**.

For the same reasons as described previously, the deprotection of the silyl ether **242** was also attempted under acidic conditions using hydrofluoric acid (Scheme 88).

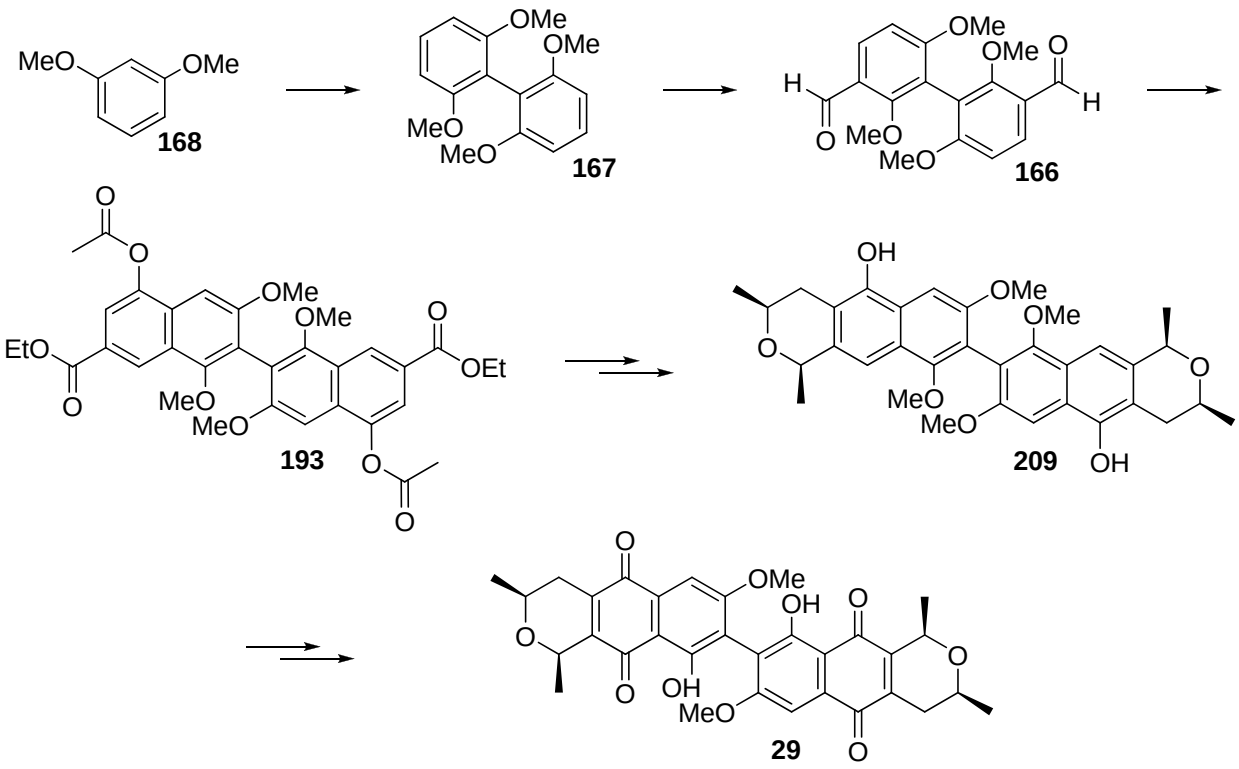



**Scheme 88**

To this end, the silyl ether **242** was treated with an excess of HF, thereby forming the alcohol **246** which was isolated as a white solid in 86% yield. Spectroscopic evidence for the formation of the product was obtained from the $^{1}$H NMR spectrum which although very similar to its starting precursor, lacked the highly shielded signals corresponding to the *tert*-butyldimethylsilyl ether group. The alkene protons were still present at 7.08 ppm and between 6.87 ppm and 6.66 ppm, overlapping with the aromatic protons. There was a new signal at 5.63 ppm representing the proton of the OH functionality. As observed for the primary alcohol **179**, the signal for the alcohol proton of **246** was split into a doublet, coupling to its neighbouring benzylic proton. The $^{13}$C NMR spectrum was in line with our expectations, displaying similar features to that present in the starting material **242**, except of course for the absence of the highly deshielded signals representing the carbons attached to the silyl ether group. The most notable change in the IR spectrum of the molecule **246** was a broad band at 3256 cm$^{-1}$, indicative of the now free OH group.

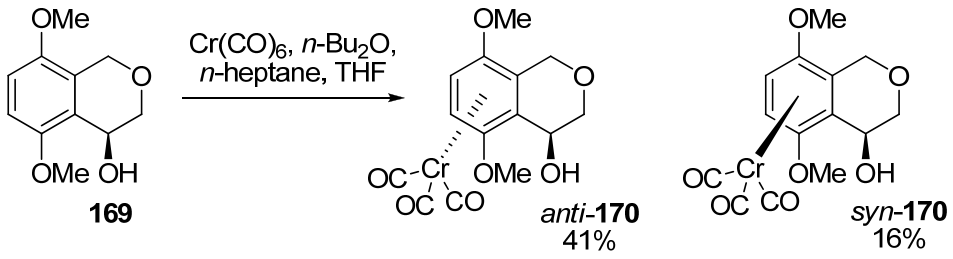
## 2.3 Concluding Remarks Pertaining to the Synthesis of Cardinalin 3

Using a bidirectional approach, we have successfully synthesised cardinalin 3 **29** in 15 steps starting from commercially available 1,3-dimethoxy benzene **168** in an overall yield of 2.2% (Scheme 89).



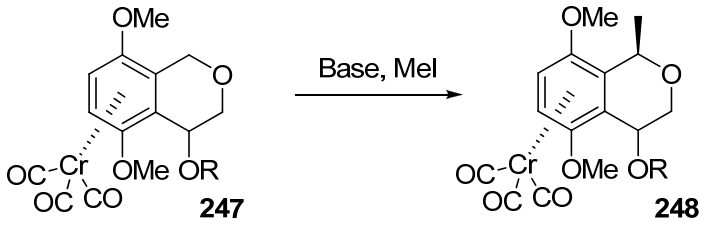

**Scheme 89**

In this synthesis, although we had formed the naturally occurring *cis* isomer as the major product, the synthesis was nevertheless racemic and not diastereoselective producing various matched and mismatched combinations of *R* and *S* configurations in the two halves of the molecule. As a vision for the future we would therefore be interested in the stereoselective synthesis of this naturally occurring molecule. To this end we put in motion an investigation pertaining to the feasibility of using arene chromium tricarbonyl chemistry on the model isochromanol nucleus **169**. Unfortunately, this route posed some severe and unexpected obstacles. Right up front, we ran into difficulties with the complexation of the chromium tripod in that we expected a *facio*-selective complexation, directed by the presence of a carefully created chiral benzyl alcohol functionality. Unfortunately, this reaction produced an almost equal ratio of *syn*- and *anti*-diastereomers **170**, as no *facio*-selectivity was observed and we suspect that the presence of the methoxy groups of the aromatic ring were responsible for this discouraging result, as this has indeed been observed before (Scheme 90).[103]



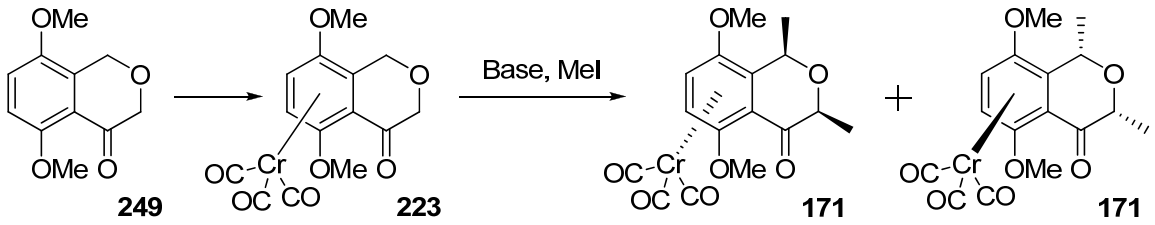

**Scheme 90**

Nevertheless, we were fortunate in that the *syn*- and *anti*-diastereomers **170** were separable, allowing us push ahead with our synthesis. In fact, this unexpected result may even turn out to be serendipitous in the future, providing access to more than one enantiomerically synthesised product. Moving forward, we once again stumbled into trouble when our efforts to oxidise the benzylic alcohol **170** to the corresponding ketone **223** were thwarted. In fact, this stopped further progress in the synthesis as without the carbonyl functionality, we were unable to generate the required enolate to facilitate the addition of the methyl groups to the isochromanone nucleus **223** (see Scheme 72). However with the complexed alcohol **170** in hand it is still possible that the stereoselective addition to the C1 position can take place. This would require a suitable protection of the alcohol functionality to form **247** and thereby produce **248** (Scheme 91).



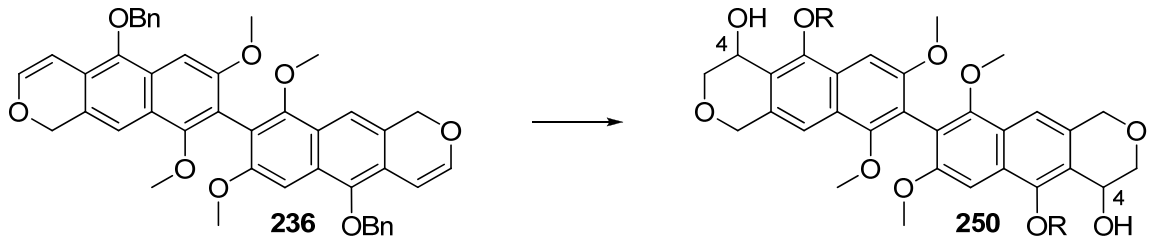

**Scheme 91**

Another viable option would be to attempt the complexation directly onto the ketone **249** (Scheme 92). Although this would no doubt produce an inseparable mixture of the enantiomers **223**, the subsequent addition of electrophiles should generate the enantiomers **171**, which on removal of the chromium tripod should produce separable diastereomers.




**Scheme 92**

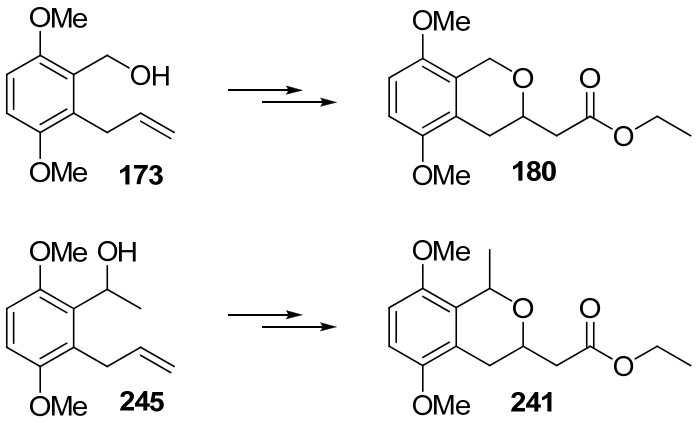
As we mentioned, whilst working on the model chromium complex system we had already begun the synthesis of a suitable chromium-complex precursor for the stereoselective synthesis of cardinalin 3. Once the chromium chemistry on the simpler system **169** is achieved it would then be necessary to further modify the dimeric system of **236** forming **250** in order attempt similar methodology (Scheme 93).




**Scheme 93**

In order to effect the complexation of the chromium onto this dimer **250** we would need to consider the usefulness of introducing the alcohol functionality at the C4 position. In the model study using **169**, the equivalent alcohol functionality did not in fact direct the incoming chromium group, resulting in poor diastereoselectivity of the resultant chromium complex, and we attributed this unusual phenomenon to the presence of the methoxy groups – as had been reported in the literature. Now, the actual precursor **250** also has two methoxy groups as well as an additional oxygen at the C5 position. Given what we now know about the selectivity problems in the presence of these additional groups, perhaps introducing the C1 and C3 methyl groups stereoselectively by way of chromium chemistry is indeed not a feasible option. Furthermore, for the actual compound **250**, there is the additional complication of two possible aromatic rings to which the chromium tripod could complex.

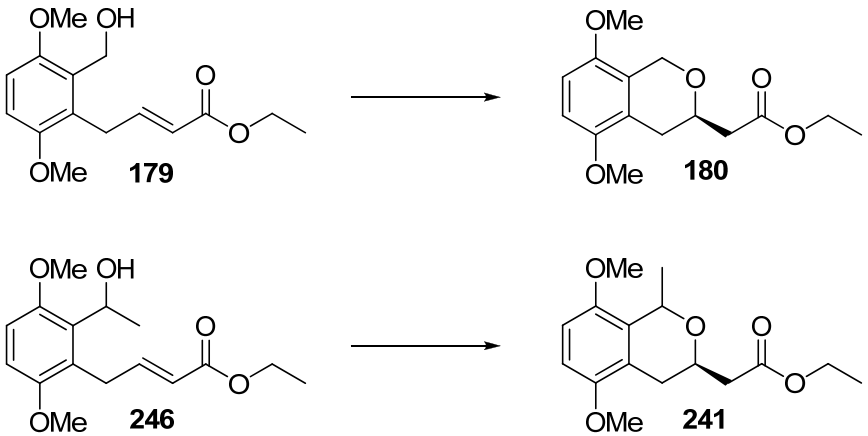
A far more productive model study was our investigation into the use of cross metathesis as a means to access substituted pyranonaphthoquinones (Scheme 94).




**Scheme 94**

These reactions pave the way for a variety of C1 and C3 substituted variants of the isochromane depending on the choice of the starting alkene partners.

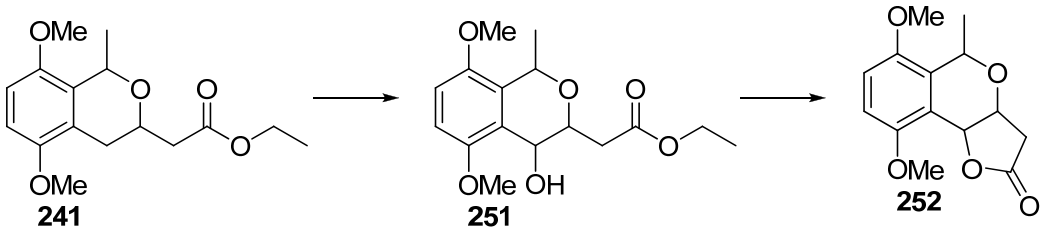
Interesting to note as well is the fact that the deprotection step was also conducted using hydrofluoric acid which prevented the concomitant Michael addition. We were thus able to isolate the alcohols **179** and **246** in yields of 79% and 86% respectively. This bodes well for future research as it provides room for stereoselective intramolecular Michael addition reactions, mediated perhaps with chiral Lewis acid reagents (Scheme 95).




**Scheme 95**

Looking even further to the future, the usefulness of this metathesis approach is that we now have access to isochromanes containing a fused lactone ring **252**, which are found in many of the naturally occurring pyranonaphthoquinone examples that were previously discussed in the introductory section of this thesis. Of course, to achieve this, we would

need to also perform an oxidation at the benzylic position to form **251**, which would then lactonise to **252** (Scheme 96).



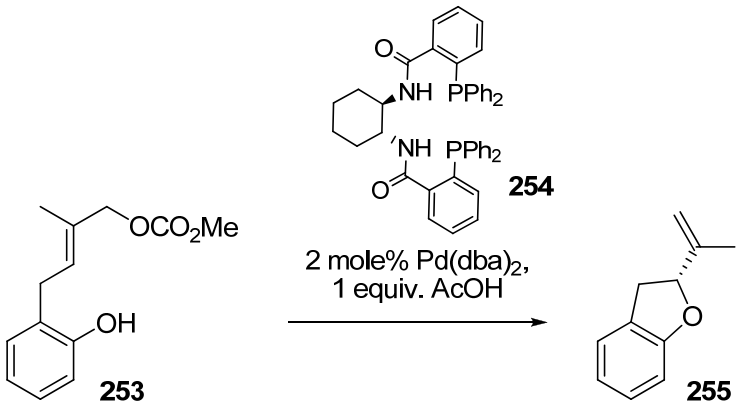

**Scheme 96**

This completes the pyranonaphthoquinone section of this PhD thesis. The next section will concentrate on our efforts towards the synthesis of dihydroindoles.

# Chapter 3: An Introduction to Indolines

## 3.1 The Indoline Subunit

In 2007 the Wits organic group successfully completed the stereoselective synthesis of the 2-isopropenyl-2,3-dihydrobenzofuran nucleus **255** (Scheme 97).[114] The key step for the synthesis of this compound was a palladium mediated cyclisation reaction of the carbonate **253** in the presence of the commercially available chiral Trost ligand **254**, thereby producing the benzofuran **255** in 98% yield and 93% enantiomeric excess.




**Scheme 97**

In light of this successful work we decided to extend the scope of this methodology by exploring the use of the same palladium catalysed reaction for the synthesis of the nitrogen variant of this compound, namely the dihydroindole skeleton **256**, otherwise known as an indoline (Figure 23). Indeed, although this compound has been synthesised previously,[115] it has never been accomplished enantioselectively.

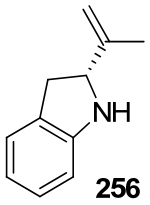
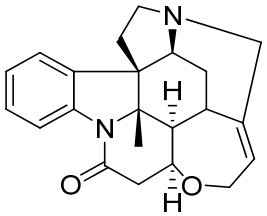



**Figure 23**

The indole ring system is the most ubiquitous heterocycle in nature.[116] Indole and its saturated relative, the indoline moiety such as **256**, are embedded in a wide range of natural products as well as designed synthetic analogues with varying biological activities. Some selected examples are shown below.

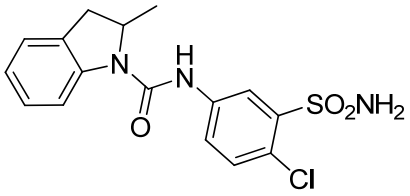
Strychnine **257** (Figure 24) was one of the first alkaloids to be isolated in its pure state in 1818 by Pelletier and Caventou. Perhaps this compound is most infamous as a poison, as it acts as an antagonist at the inhibitory glycine receptor in the spinal cord and the brain, causing muscular convulsions and asphyxia which eventually leads to death.[117] Strangely, strychnine was also among the most valuable and widely prescribed drugs where it was used for many applications, not the least of which was as a central nervous system stimulant.[118] It was first synthesised by Woodward in 1954, an outstanding achievement at that time given the complexity of this molecule.[119]




Strychnine **257**

**Figure 24**

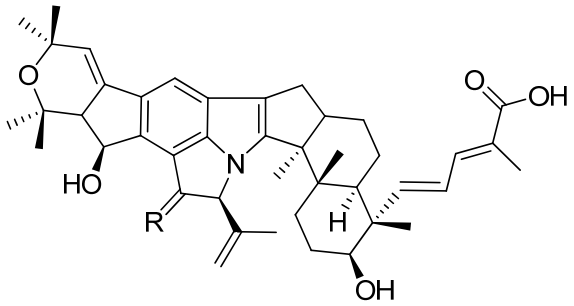
The indoline containing compound indapamine **258** shown in Figure 25 is a known diuretic agent.[120] Diuretics are drugs which elevate urination by blocking the reabsorbtion of $Na^+$ and $Cl^-$ ions thereby increasing the excretion of water from the body. This class of drugs is commonly used to treat hypertension (high blood pressure). However unfortunately, most diuretics also tend to increase one's risk of developing osteoporosis, a disease of the bone leading to an increased risk of fractures. Indapamine **258** in comparison to other diuretics, was found to reduce urinary $Ca^{2+}$ ion excretion thereby increasing bone formation and in so doing decrease the risk of fractures.[120]



Indapamine **258**

**Figure 25**

The nodulisporanes **259** and **260** are a novel class of indoline diterpene alkaloids (Figure 26).[121] They display potent insecticidal properties particularly against tick and flea infections in cats and dogs, while exhibiting little or no mammalian toxicity. This is attributed to their mode of action, which is the modulation of the invertebrate specific glutamate gated chloride ion channels.[122]



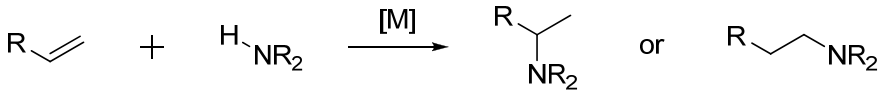
R = O, (+)-Nodulisporic acid A **259**
R = $H_2$, (+)-Nodulisporic acid B **260**

**Figure 26**

Both of these acids **259** and **260** contain the 2-isopropenyl indoline subunit. We envisage that by employing an asymmetric allylic alkylation reaction, not only will we form the indoline moiety, but we will also be able to control the stereochemistry at the C2 position. Other variants of this moiety, that is with different substituents on the C2 position, as well as a variety of protecting groups on the nitrogen have appeared widely in literature and in the next section of this introduction, we will highlight some of the methods used in their synthesis.

## 3.2 The Use of Hydroamination as a Route towards Nitrogen Heterocycles

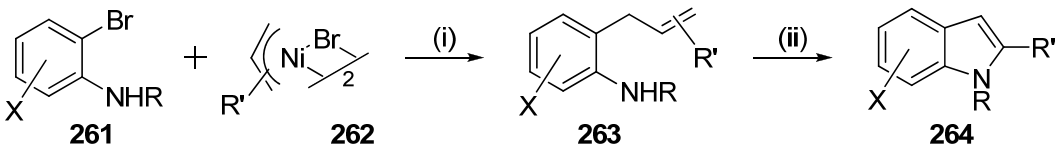
The direct addition of NH across alkene and alkyne bonds, known as hydroamination offers an attractive route for the formation of carbon-nitrogen bonds (Scheme 98). The activation of the alkene is normally accomplished using transition metal catalysts, which render the olefin more susceptible to attack by the amine nucleophile. This methodology has been used to synthesise a variety of important classes of nitrogen containing heterocycles.[123]




**Scheme 98**

### 3.2.1 Cyclisations involving the use of palladium: the Wacker approach

In 1978 Hegedus *et al*. employed palladium chloride for the conversion of *o*-allyl anilines into indoles **264** (Scheme 99).[124] The synthesis of the *o*-allyl aniline **263** was achieved by the reaction of the aromatic halide **261** and the π-allyl nickel halide **262** in a radical chain process. Although this reaction was found to be sluggish requiring 2 to 4 days to reach completion, it was tolerant to a wide variety of functional groups on both the allyl and aromatic moieties.

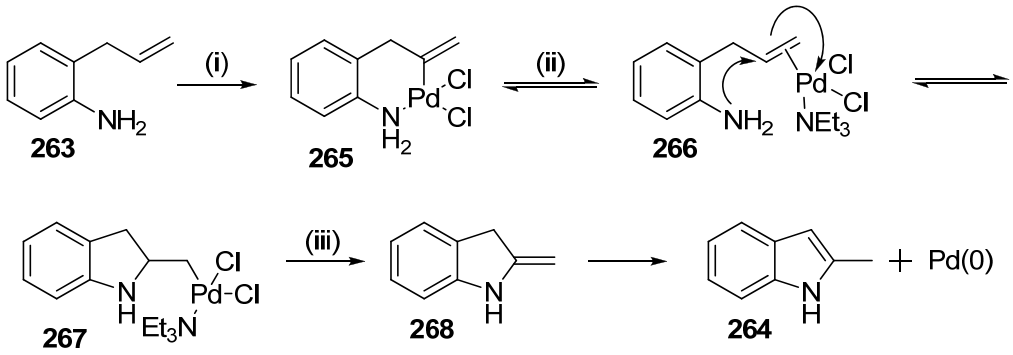



X = H, Me, $CO_2Et$ or $CO_2Me$
R = H, Me or $CH_3CO$
R' = H, Me or Et

**Scheme 99:** *Reagents and conditions:* (i) DMF, 50 ºC; (ii) $PdCl_2(CH_3CN)_2$, $Et_3N$.

The cyclisation reaction was performed under both stoichiometric and catalytic conditions. In the stoichiometric reaction (Scheme 100), the *o*-allyl aniline **263** reacts with $PdCl_2(CH_3CN)_2$ to produce compound **265**, in which both the amine and the olefin are coordinated in a chelating fashion. With the amino group coordinated, it cannot attack the olefin. The addition of triethylamine, which is a better ligand than the weakly basic aromatic amine, generates the π-alkene palladium complex **266**, facilitating attack of the

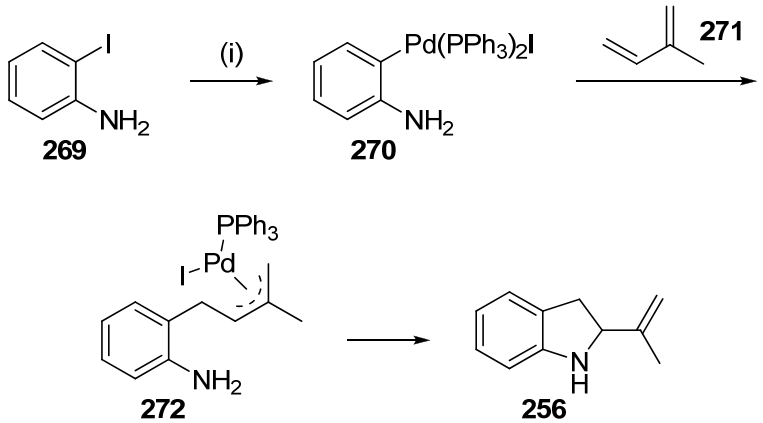
amine leading to **267**. This compound then undergoes loss of HCl and a β-hydride elimination of "Pd-H" to produce the indoline **268** which spontaneously rearranges to **264**.




**Scheme 100:** *Reagents and conditions*: (i) $PdCl_2(CH_3CN)_2$, THF; (ii) $NEt_3$; (iii) –HCl, –"Pd-H".

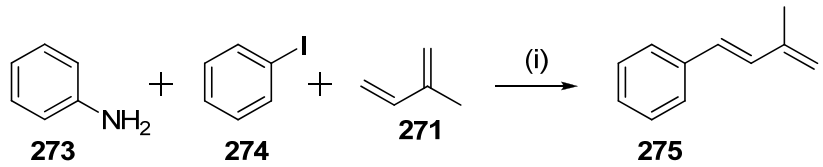
This procedure unfortunately does not recycle the Pd(II) reagent, as it is reduced to palladium metal and hence it is used stoichiometrically. In order to use this precious metal catalytically, a method would have to be found which would re-oxidise the Pd(0) *in situ*. Fortunately, benzoquinone was found to be a suitable oxidising agent for this purpose. Moreover, the resulting hydroquinone was easily separated from the indole products.[124]

O'Connor *et al*. achieved the synthesis of substituted indoline **256** by reaction of *o*-iodo aniline **269** with isoprene **271** in the presence of a phosphine-$Pd(OAc)_2$ catalyst (Scheme 101).[115] The aryl halide **269** initially undergoes an oxidative addition with the resulting Pd(0) species to form **270**.



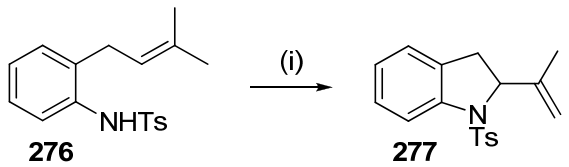

**Scheme 101:** *Reagents and conditions*: (i) $Pd(OAc)_2$, $PPh_3$, $NEt_3$, 72%.

This synthesis was presumed possible because of the proximity of the amino group to the π-allylic moiety in the intermediate complex **272**. This was confirmed by the reaction of aniline **273** with iodo-benzene **274** and isoprene **271**, which produced (*E*)-1-phenyl-3-methyl-1,3-butadiene **275** and no amine products (Scheme 102).



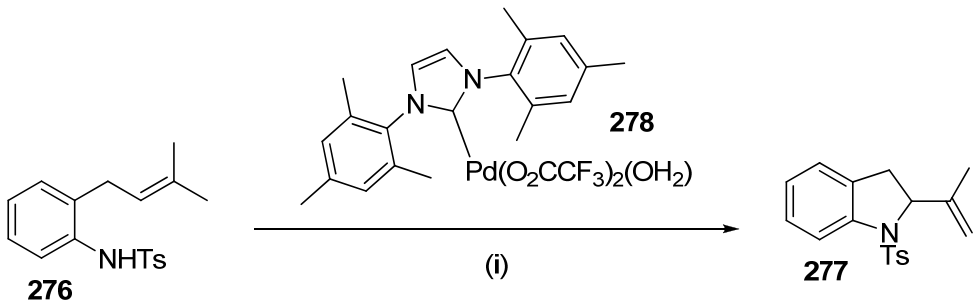

**Scheme 102:** *Reagents and conditions*: (i) $Pd(OAc)_2$, $PPh_3$, $NEt_3$.

The *N*-tosyl 2-isopropenyl indoline **277** was synthesised in a 62% yield from **276** using a catalyst system consisting of 5 mole% $Pd(OAc)_2$ in an oxygen atmosphere using DMSO as a solvent (Scheme 103).[125] Under these conditions there is no need for a re-oxidant as oxygen itself will reoxidise the Pd(0) to Pd(II).



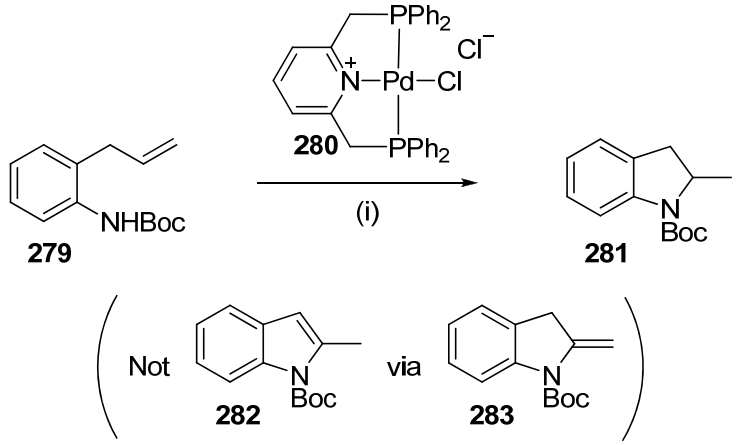

**Scheme 103:** *Reagents and conditions*: (i) $Pd(OAc)_2$, DMSO, $O_2$, 62%.

The formation of the tosylated indoline **277** has also been achieved in 56% yield by Stahl and co-workers. In their reaction they made use of a Pd(II) complex bearing an *N*-heterocyclic carbene ligand **278** (Scheme 104).[126]



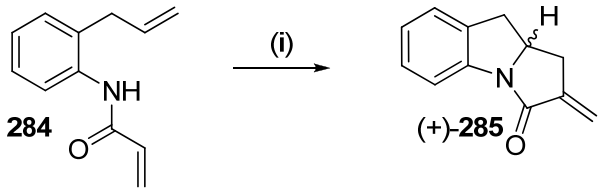

**Scheme 104:** *Reagents and conditions*: (i) toluene, 1 atm $O_2$, NaOAc, 56%.

One of the steps in these "Wacker-type" palladium catalysed cyclisation reactions involves the elimination of the palladium complex through a β-hydride elimination, as shown in Scheme 100. In order to avoid this step, Michael *et al*. made use of a tridentate ligand **280**, which blocks open coordination sites on the Pd catalyst (Scheme 105).[127] The hydroamination of **279** thus produces the compound **281** instead of the usual **282**. The reaction tolerates a variety of substituents on the nitrogen.




**Scheme 105:** *Reagents and conditions*: (i) 5 mol% of cat **280**, 10 mol% of $AgBF_4$, 10 mol% of $Cu(OTf)_2$, $MgSO_4$, 32%.

The first enantioselective cyclisation using Pd(II) catalysis was reported by Yang and co-workers in 2006 (Scheme 106). A tandem cyclisation on **284** produced the product (+)-**285** in a good enantiomeric excess of 86% and a yield of 76% using (–)-sparteine as a chiral ligand. A variety of other structurally diverse indolines were also obtained.[128]

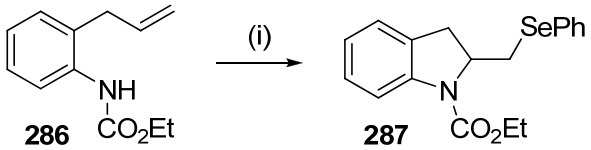



**Scheme 106:** *Reagents and conditions*: (i) 5 mol% $Pd(TFA)_2$, 20 mol% (–)-sparteine, 2 equiv. DIPEA, 3 Å MS, toluene, 1 atm $O_2$, 80 °C, 78%, 86% ee.

### 3.2.2 Cyclisation using phenylselanyl chloride

One year after the Hegedus group reported the use of palladium chemistry for the formation of nitrogen heterocycles, Clive *et al*. demonstrated a similar ring closure reaction

using phenylselanyl chloride in the presence of silica gel.[129] Phenylselanyl chloride is known to effect ring closure to give products carrying the phenylseleno group and it has been used in the formation of functionalised benzopyrans and benzofurans in good yield under mild conditions.[130] Clive and co-workers in pursuit of nitrogen analogues for the synthesis of useful alkaloids initially applied this methodology to *o*-allyl aniline, but found it did not produce a clean reaction. They discovered that in the case of simple anilines, the presence of the free amine results in direct attack on the nitrogen or alternatively the aniline undergoes an electrophilic *para* substitution of the aromatic ring when reacted with aryl selanyl halides. When however, the amine was protected as the carbamate such as **286** it successfully underwent the desired transformation to produce the functionalised indoline **287** (Scheme 107).

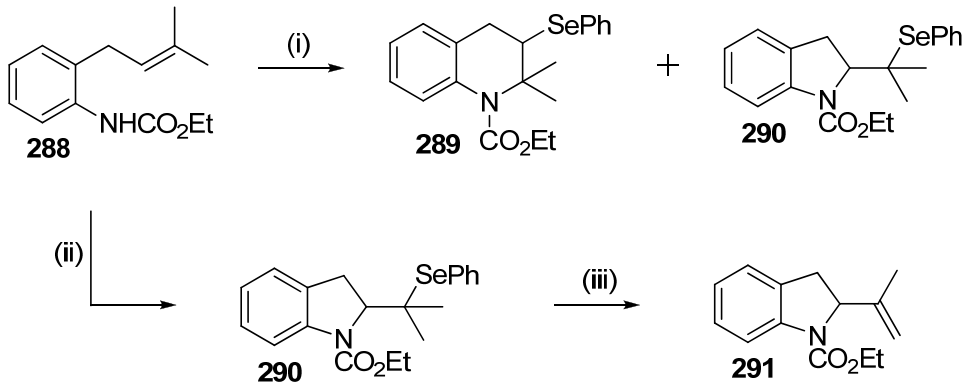



**286** **287**

**Scheme 107:** *Reagents and conditions*: (i) PhSeCl, $SiO_2$, $CH_2Cl_2$, −78 ºC, 84%.

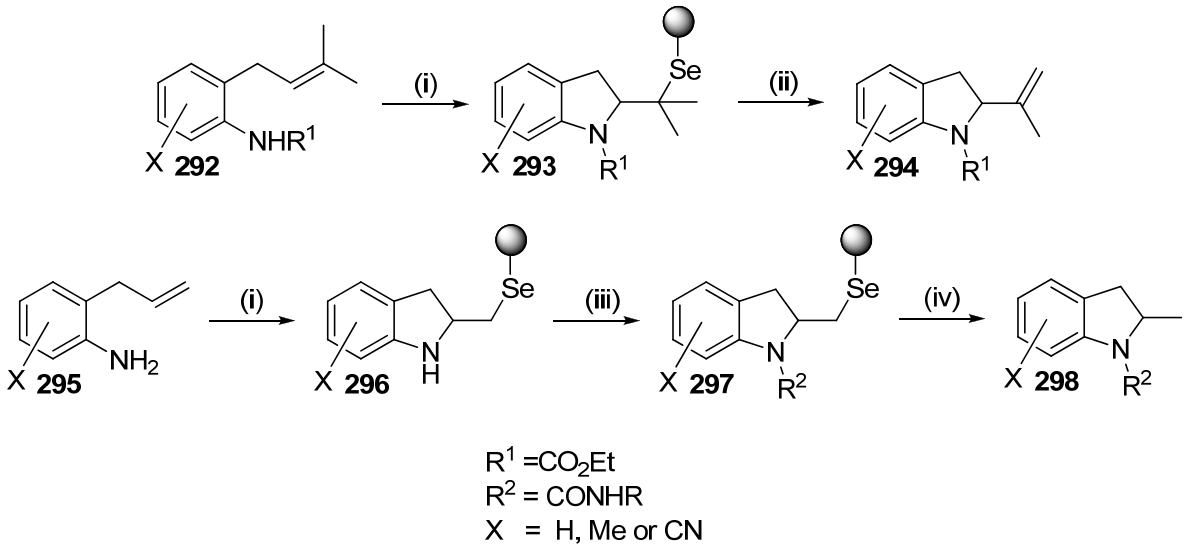
The reactions were found to be high yielding, and to complement the previously reported palladium assisted cyclisation reaction as these products were produced at a different oxidation level (dihydroindoles vs. indoles).

Cooper *et al*. also made use of this electrophilically-initiated cyclisation reaction for the ring closure of the prenyl alanine derivative **288** (Scheme 108).[131] Interestingly, when phenylselanyl chloride was used, the tetrahydroquinoline **289** was also formed in equal ratio to the indoline **290** and proved difficult to separate from the desired product. When changing the selanyl reagent to the bromide derivative, the indoline **290** was formed exclusively. It could then be converted into **291** via the selenoxide.




**Scheme 108:** *Reagents and conditions*: (i) PhSeCl, $K_2CO_3$, $SiO_2$, $CH_2Cl_2$, −78 ºC, 91%; (ii) PhSeBr, $K_2CO_3$, $SiO_2$, $CHCl_3$, −78 ºC; (ii) $H_2O_2$, $CH_2Cl_2$, 4 h, rt.

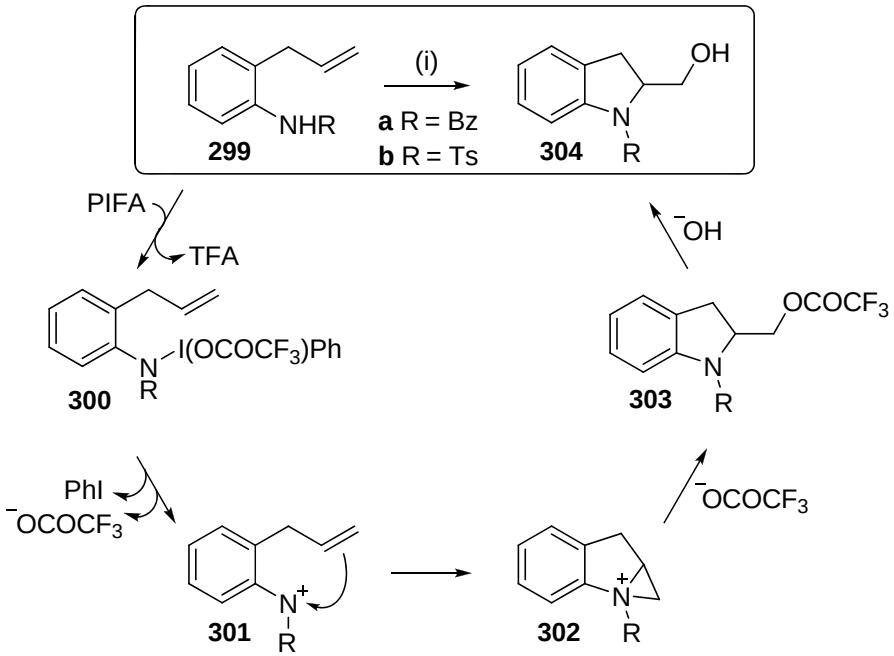
A library of indole and indoline templates were synthesised by Nicolaou and co workers by making use of a solid phase organic synthesis approach (Scheme 109).[132] Using a polystyrene based selanyl bromide resin, the group were able to synthesise a range of resin bound indoline scaffolds (**293** and **297**). Removal of the selenium under oxidative conditions produced the corresponding isopropenyl compounds **294**, or under reductive conditions produced the 2-methyl indolines **298**.




**Scheme 109:** *Reagents and conditions*: (i) SeBr resin, $CH_2Cl_2$, $SnCl_4$, –20 ºC, $NEt_3$; (ii) $H_2O_2$, THF, 1 h; (iii) $COCl_2$, $CH_2Cl_2$, 0 ºC, 1 h; $RNH_2$, $NEt_3$, $CH_2Cl_2$, 25 ºC, 12 h, (iv) *n*-$Bu_3SnH$, AIBN, toluene, 90 ºC, 2 h.

### 3.2.3 A metal free approach to cyclisation reactions

The hypervalent iodine reagent phenyliodine(III)bistrifluoroacetate (PIFA) was used to form the hydroxylated indoline **304** from an *o*-allylated aniline **299** (Scheme 110).[133] The transformation can be rationalised by the formation of the *N*-acylnitrenium ion **301**, which is generated by the action of PIFA on the allylated aniline **299** through the formation of **300**. The ion **301** is then trapped intramolecularly by the olefin moiety through a 5-*exo*-trig cyclisation. The primary carbocation species, stabilised as the aziridinium ion **302** is subsequently opened by the nucleophilic attack of a free trifluoroacetate group from the iodine reagent. The resulting ester **303** is not isolated but directly hydrolysed during the basic workup of the reaction to afford the final indoline derivative **304**.

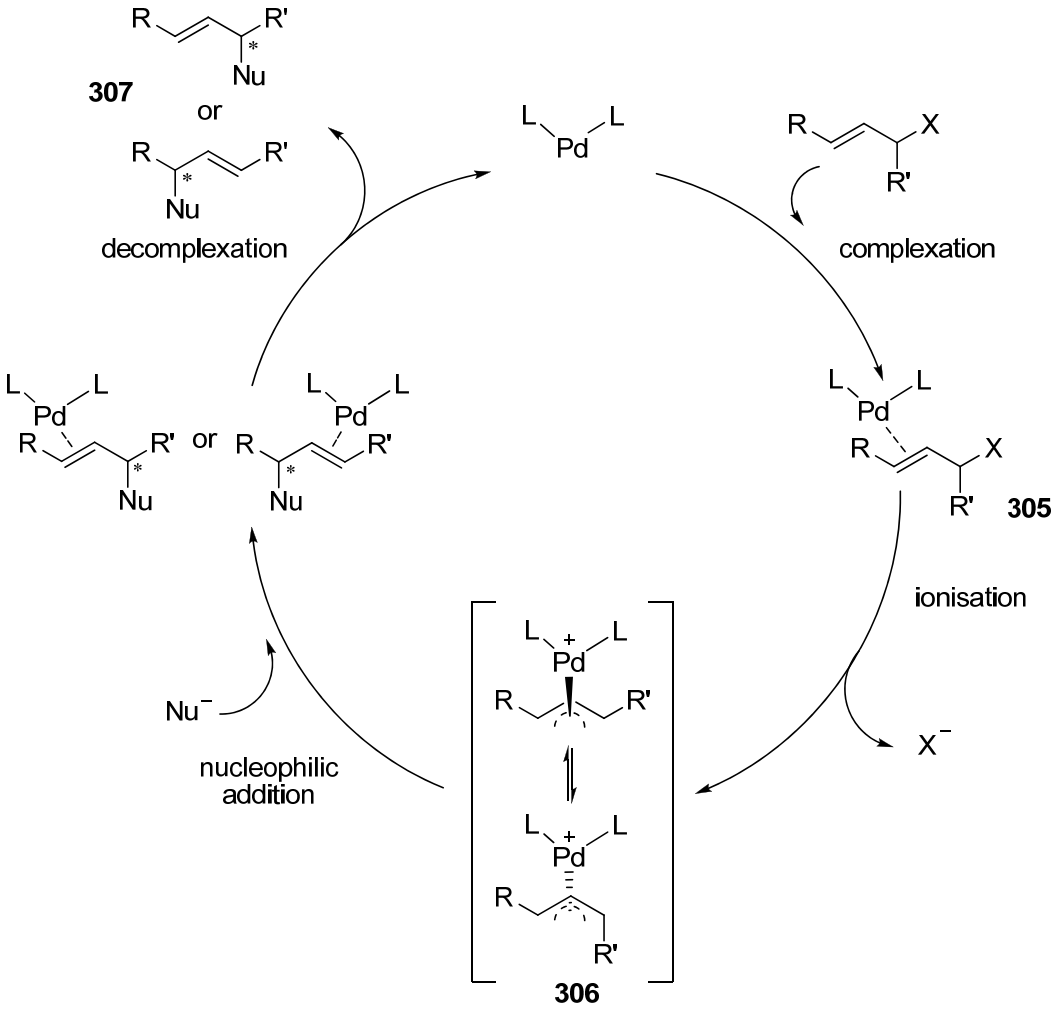



**Scheme 110**: *Reagents and conditions*: (i) PIFA, trifluoroethanol, rt, 3 h, **304a**: 71%, **304b**: 41%.

As mentioned at the beginning of this chapter, for our purpose, that is the enantioselective cyclisation to afford the indoline moiety **256**, we planned on using a similar approach to that employed for the successful stereoselective synthesis of benzofuran moieties. This approach known as asymmetric allylic alkylation will be further elaborated on in the following section.

## 3.3 Asymmetric Allylic Alkylation

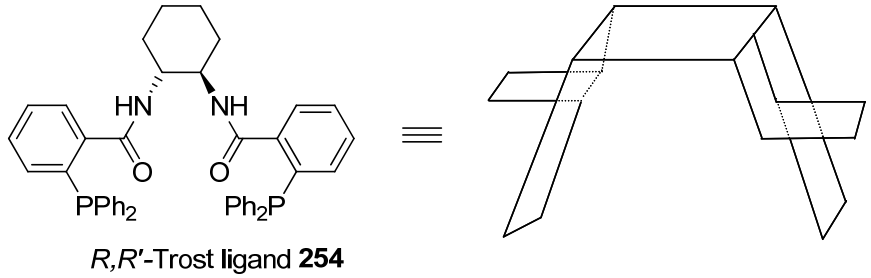
Seeing the advantages of the activation of the α-position of carbonyl groups to form new carbon-carbon bonds, Trost *et al*. believed that the olefin functional group could be used to the same end by taking advantage of its α (allylic) position.[134] Asymmetric allylic alkylation substitution reactions were developed as a direct method to add nucleophiles to alkenes containing a suitable leaving group. The process involves activation of the allylic position by the complexation of palladium onto the olefin forming an alkenylpalladium complex **305**. The subsequent ionisation of a leaving group forms **306**. Decomplexation of the palladium then leads to the production of **307** (Scheme 111).[135]




**Scheme 111**

Unlike the previously discussed Wacker type reactions, which make use of Pd(II) as the source of the catalyst, these allylic alkylations use Pd(0). Asymmetric allylic alkylations (AAA) are unique metal catalysed reactions as they have the ability to transform achiral,

prochiral and racemic material to enantiopure products. There are a number of potential sources for enantiodiscrimination in transition metal catalysed allylic alkylations. These include the complexation of the metal on the olefin and enantiofacial discrimination of the π allyl complex as well as the attack of the nucleophile at enantiotopic termini. The only step that is not enantiodiscriminating is the decomplexation of the metal complex. Of particular interest to us was the enantiotopic complexation of the metal onto the olefin, to allow for suitable ionisation of the leaving group and then attack of the nucleophile to the resulting π-Pd intermediate. The ligand we would be utilising for our envisaged cyclisation was the Trost ligand **254** as it was used successfully in our labs to synthesise chiral 2-isopropenyl-2,3-dihydrobenzofuran derivatives. The ligand can be spatially represented by the chiral scaffold shown in Figure 27. The walls and the flaps of the schematic representation are spatially equivalent to the phenyl groups of the triarylphoshine moieties of the ligand and using this diagram, Trost *et al.* were able to rationalise the stereochemical outcome of their reactions.[136]

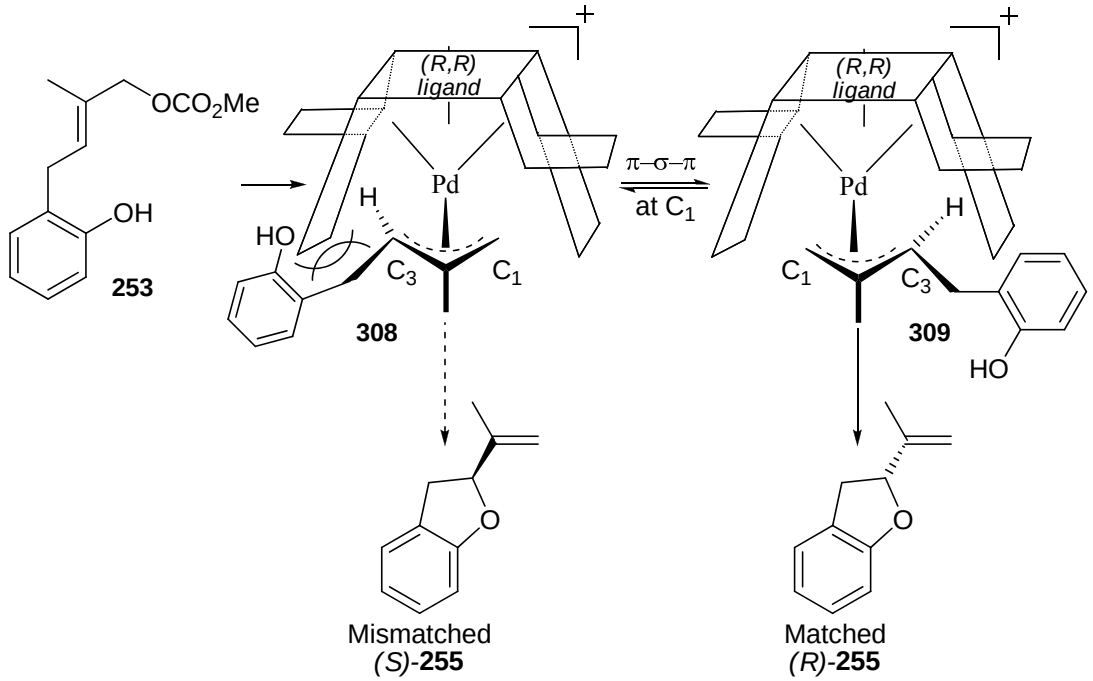



*R,R'*-Trost ligand **254**

**Figure 27**

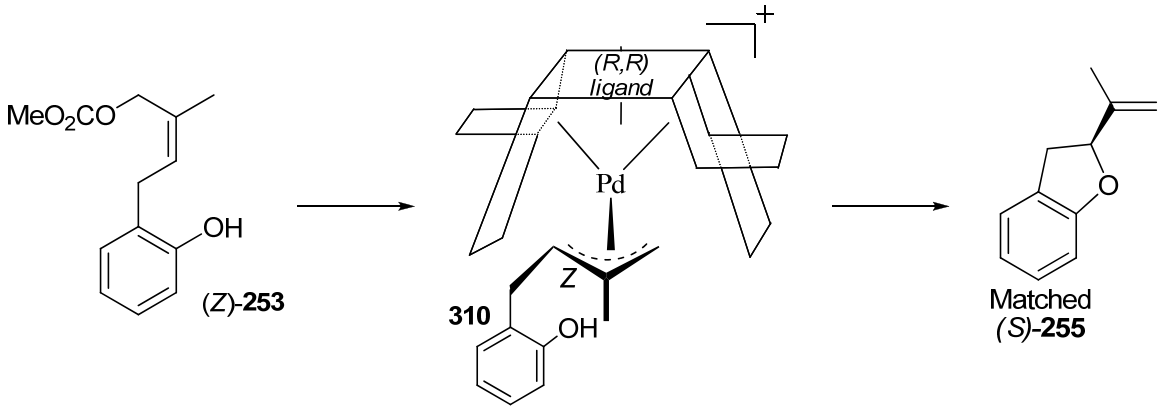
Using this same model and rationale de Koning and co-workers were also able to explain the results of their benzofuran cyclisation reaction (Scheme 112). The initial complexation of the allylic phenol **253** onto the chiral ligand forms complex **308**. This arrangement is favoured as the ionisation of the carbamate leaving group is able to occur from under the right flap of the ligand. Once this has occurred, the complex **308** is no longer in the most favourable steric arrangement with regard to the shape of the ligand. Attack of the nucleophilic OH group in this 'mismatched' scenario will lead to the formation of the *S* enantiomer of **255**. However if the π-allyl Pd complex is allowed to undergo a π-σ-π rearrangement to the thermodynamically more favoured complex **309**, attack of the OH group at this point leads to the formation of 'matched' *R* enantiomer **255**. It is possible for this rearrangement to occur if the attack by the phenol does not occur too quickly. This

slowing down of the reaction is facilitated by the addition of acetic acid, which decreases the nucleophilicity of the OH group,[136] thus allowing the required time for the rearrangement of **308** to **309**. In line with this underlying principle, the use of the *R*,*R* Trost ligand in the cyclisation of **253** produced (*R*)-**255** in 93% enantiomeric access.[114]




**Scheme 112**

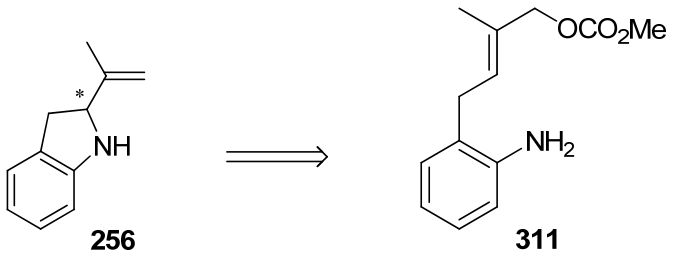
A key feature for the successful stereochemical outcome of the reaction is obviously the use of the single geometric isomer of the alkene **253** which will have an impact on the formation of the π-allyl palladium complex. As shown in the above scheme, complexation of the *E* isomer (*E*)-**253** results in the 'matched' complex **309** which leads to the formation of (*R*)-**255**. If however, the opposite isomer (*Z*)-**253** was used instead, a different 'matched' complex **310** would be formed (Scheme 113). In this case the initial complex **310** would be the most favourable for the ionisation of the carbamate leaving group and due to the shape of the isomer it would not require a rearrangement to facilitate the ensuing reaction. The result of this arrangement should result in the formation of the opposite enantiomer (*S*)-**255**. Thus a mixture of *E* and *Z* isomers will lead to the formation of different 'matched' complexes **309** and **310**, which will in turn result in the opposite enantiomers forming, thereby diminishing the enantioselectivity of the reaction.




**Scheme 113**

## 3.4 Aims of this Project

Our aim for this PhD was to undertake the synthesis of 2-isopropenyl-indoline **256** in a stereoselective manner, utilising the asymmetric allylic alkylation reaction. To accomplish this, a suitable allylic precursor such as **311**, would be required for the cyclisation reaction (Scheme 114).

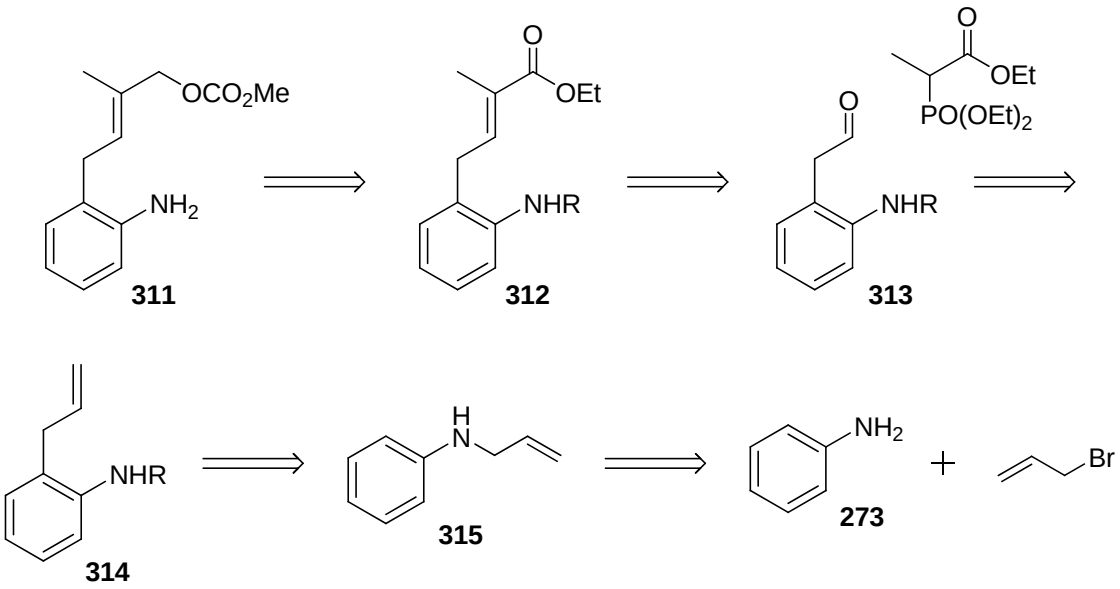



**Scheme 114**

In order to replicate the enantioselectivity demonstrated in the benzofuran work, a key requirement of the precursor **311** would be the exclusivity of the double bond arrangement as explained above. The carbonate was chosen as a suitable leaving group, as opposed to an acetate leaving group which showed diminished yields in the benzofuran work.[114]

In our envisaged plan for the synthesis of the allylic precursor, the olefin **311** could be disconnected to the ester **312** through a reduction to a primary alcohol and reaction with methyl chloroformate (Scheme 115). The ester **312** can in turn be disconnected to the aldehyde **313** through a Horner-Wadsworth-Emmons reaction, which should theoretically furnish exclusively the *E*-isomer, a requirement essential for the enantioselectivity of the final step. The aldehyde **313** can be obtained from the oxidation of the suitably protected 2-

allyl aniline **314** and this molecule can be accessed in a variety of ways as seen in the earlier section of this introduction. Our choice would be the formation of *N*-allylaniline **315** which is commercially available and also inexpensively synthesised by reaction of aniline **273** with allyl bromide.

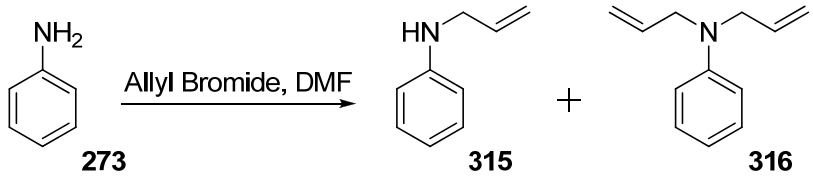



**Scheme 115**

# Chapter 4: Towards the Stereoselective Synthesis of Indolines

## 4.1 Attempted Synthesis of 2-isopropenylindoline

With a feasible synthetic strategy in mind, we set about the enantioselective syntheses of (*S*)- and (*R*)-2-isopropenyl indoline **256**. The first step in this endeavour was to obtain sufficient quantities of the required precursor, *N*-allyl aniline **315**. This was achieved through a routine allylation of readily available aniline **273** (Scheme 116), which was simply dissolved in dimethylformamide and reacted with allyl bromide. As expected, in order to minimise the formation of the di-allylated compound **316**, two equivalents of aniline were employed in this reaction.[137] Our desired product **315** was obtained in a satisfactory yield of 58% (based on the amount of allyl bromide) with 19% of di-allylated derivative **316** also being obtained . The desired product **315** was easily separated from the di-allylated aniline **316** using column chromatography.

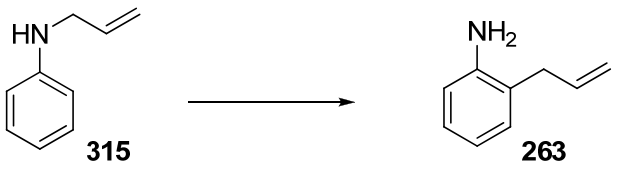



**Scheme 116**

Confirmation for the successful allylation was obtained from the $^1$H NMR spectra of the eluted oils. The singly allylated aniline **315** contained three distinct environments of aromatic protons in the range of 6.60 ppm to 7.16 ppm. Firstly a triplet at 7.16 ppm integrating for two hydrogens indicated the equivalent protons in the *meta* position of the ring. A triplet at 6.69 ppm integrating for one hydrogen could clearly be attributed to the aromatic proton in the *para* position. Finally a doublet at 6.60 ppm integrating for two protons signalled the presence of the two equivalent protons in the *ortho* position of the ring. The presence of the allyl chain was of course quite distinct in the $^1$H NMR spectrum. At 5.63 ppm there was a multiplet signalling the CH proton of the double bond. The signal for the protons of the alkene $CH_2$ could be found at 5.20 ppm as a doublet of doublets and the protons of the methylene $CH_2$ were found at 3.74 ppm as a doublet overlapping with the signal arising from the NH proton. In contrast to this, the $^1$H NMR spectrum for the di-allylated analogue **316** did not contain a signal for an NH proton. In this spectrum a similar

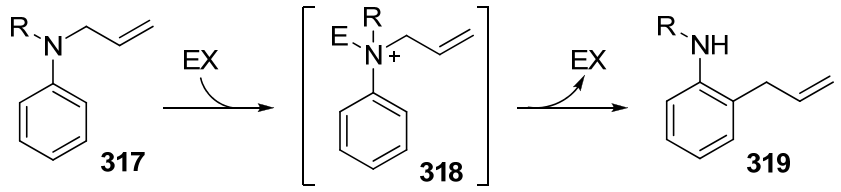
pattern of signals was observed for the allyl side chains given the symmetry of the molecule, but of course the integration of the signals accounted for twice as many protons in comparison to the mono-allyl compound **315**. The aromatic protons' signals were all quite similar to **315** and warrant no further mention. The $^{13}C$ NMR spectrum of both compounds **315** and **316** were quite similar, showing all the expected signals for the aromatic and alkene carbons in the downfield region, as well as one signal for the methylene carbon high upfield, at 46.5 ppm for the mono-allylated aniline **315** and at 52.7 ppm for the di-allylated aniline **316**.

The next step of the synthesis was to rearrange the allyl chain from the nitrogen to the *ortho* position of the aromatic ring (Scheme 117).




**Scheme 117**

The Claisen rearrangement or [3,3]-sigmatropic shift of vinyl and aryl allyl ethers has been extensively studied.[138] This reaction was in fact used to good effect in the other projects of this PhD.[139] The amino-Claisen rearrangement, the nitrogen analogue of the Claisen rearrangement on the other hand has received much less attention in synthetic chemistry due to several limitations including slow reaction rates, the need for high temperatures (200-350 ºC) and the subsequently low yields.[124, 137, 140] The approaches to overcoming these barriers have focused mainly on charge acceleration of the rearrangement process by reaction of the *N*-allylaniline derivative with electrophilic reagents to generate a quaternary intermediate (Scheme 118).[140]




R= H or alkyl

**Scheme 118**

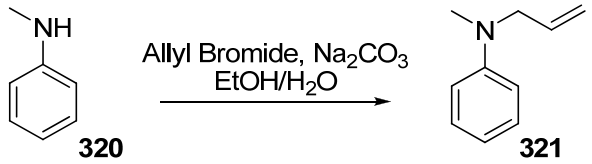
Initially the electrophilic sources used were protic acids, however the sigmatropic shift was accompanied by the formation of indole and indoline products, thus reducing the overall effectiveness of the reaction.[141] A promising alternative to protic acids was the use of Lewis acids and to this end zinc chloride and boron trifluoride-diethyl ether were found to be effective in facilitating the transformation of the type **317** to **319**. Hurd *et al.* made use of zinc chloride in xylene boiled at its reflux temperatuefor the amino-Claisen rearrangement of *N*-allylaniline **315** to produce *o*-allylaniline **263** in 42% yield.[142] Anderson and Lai demonstrated the use of $BF_3.OEt_2$ on various other allylated aromatic amines in moderate yields.[137]

For our synthesis of *o*-allylaniline **263**, we therefore attempted the amino-Claisen rearrangement experimenting with the use of both of these reagents. To this end, *N*-allylaniline **315** was dissolved in xylene along with each of the aforementioned Lewis acids. The reaction was heated at 140 ºC for 8 hours and after routine column chromatography of the crude product we isolated our rearranged 2-allylaniline **263** from each of the reactions, as confirmed by NMR spectroscopy. Confirmation for the rearrangement was obtained from the $^1H$ NMR spectrum which clearly showed the presence of the $NH_2$ protons as a broad singlet somewhat further downfield in comparison to the precursor, at 3.61 ppm integrating for 2 protons. The $^{13}C$ NMR spectrum contained six non equivalent signals for aromatic carbons due to the loss of symmetry in the molecule **263**.

Disappointingly however, the reaction utilising $ZnCl_2$ produced the desired product **263** in a yield of only 38%, and the yield for the reaction utilising the $BF_3.OEt_2$ was even lower. In an attempt to increase the reaction yield we switched to $AlCl_3$ and employed the conditions of Beholz and Stille.[140] We also attempted to use microwave radiation as a heat source as well as sealed tube conditions,[143,144] but all to no avail. However, a definite trend in the literature seemed to imply that the aza-Claisen reaction proceeded in a higher yield with an additional alkyl group present on the nitrogen atom. We therefore decided to modify our current route and explore this notion, opting for the simplest alkyl derivative - an additional methyl group on the nitrogen.

## 4.2 Synthesis of the 2-Allyl-*N*-methylaniline

For the synthesis of methyl derivative of the 2-allylaniline we were fortunate in that the required *N*-methyl aniline **320** is commercially available. For the allylation, we modified a procedure originally used by Tweedie *et al.* (Scheme 119).[145] To this end, allyl bromide and sodium carbonate were added to a 0.5 M solution of *N*-methylaniline **320** in a mixture of ethanol and water and allowed to react for 14 hours. The product **321** was obtained in a satisfactory yield of 66%.




**Scheme 119**

Spectroscopic analysis of the oil confirmed the successful addition of the allyl side chain. The $^{1}$H NMR spectrum was similar to that obtained for the unsubstituted allylated aniline **315** with respect to the five aromatic protons and the five protons of the allyl substituent. However, there was an additional singlet at 2.92 ppm integrating for three protons, arising due to the protons on the methyl attached to the nitrogen atom in **321**. The $^{13}$C NMR spectrum accordingly contained a new upfield signal at 37.9 ppm for the carbon of the *N*-methyl group, in addition to the expected signals.

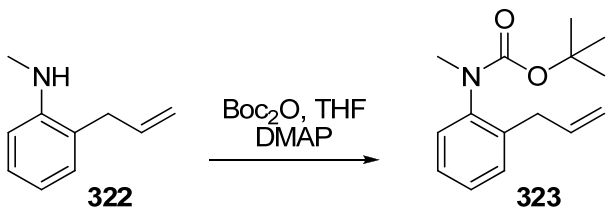
We were now in a position to attempt the tricky aza-Claisen on this new substrate **321** (Scheme 120). Using similar a similar approach to that utilised for the unsubstituted derivative **315**, the *N*-allyl-*N*-methyl aniline **321** was dissolved in xylene and heated to the reflux temperature in the presence of aluminium trichloride.[140] We were pleased to discover that rearrangement took place in a more acceptable yield of 61%.


**Scheme 120**

The $^{1}H$ and $^{13}C$ NMR spectra of **322** were in line with our expectations and matched that reported in the literature.[140] In the $^{1}H$ NMR spectrum there were now only four aromatic protons present, their signals appearing in the range of 7.18 ppm to 6.69 ppm. A broad signal at 3.72 ppm integrating for one proton confirmed the presence of the NH functionality. The protons of the allyl moiety were all accounted for at their expected chemical shift values. The signal for the benzylic methylene protons showed an upfield shift from 3.90 ppm to 3.28 ppm, which is not unexpected given the fact that this group is no longer attached to the more electronegative nitrogen atom. The $^{13}C$ NMR spectrum of **322** showed an increase in the number of aromatic carbon signals due to the fact that the molecule was no longer symmetrical. The shift of the signal for the methylene carbon from 55.2 ppm to 30.7 ppm, once again indicated a successful rearrangement.

### 4.2.1 Protection of the amine and oxidation of the olefin

At this point of the synthesis we envisaged that it would be necessary to protect the NH group of the aniline **322** in order to prevent undesired reactions in the subsequent steps. For this purpose we chose the *tert*-butyl carbamate group (Boc), which would not only be compatible with our future planned steps but would also render the amine non-basic by converting it to the carbamate. To this end, the 2-allyl-*N*-methylaniline **322** was dissolved in dry THF and reacted with the Boc anhydride and a catalytic amount of dimethylaminopyridine (Scheme 121), affording the carbamate **323** as a light yellow oil in 72% yield after purification.

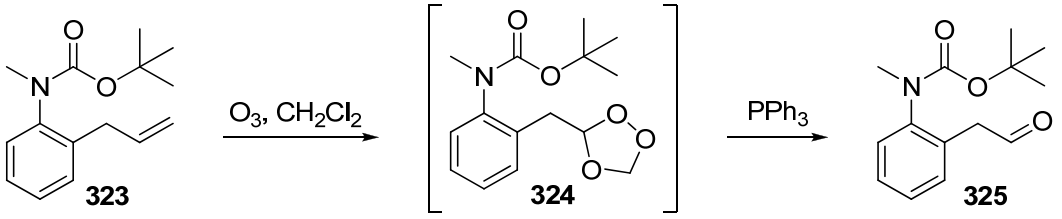



**Scheme 121**

The formation of compound **323** was immediately evident from analysis of its $^{1}H$ NMR spectrum. At 1.52 ppm and 1.33 ppm there were two new singlets integrating for 3 and 6 protons respectively indicating presence of the tertiary butyl group on the carbamate. It is interesting to note the *tert*-butyl group produces two singlets, as one would expect the three methyl groups to be equivalent. No doubt this is due to restricted rotation about the

carbamate group, causing two possible conformations of this group, which places the *tert*-butyl group in two different chemical environments; in fact this effectively produces two different compounds. Interestingly the signal for the *N*-methyl substituent is not similarly resolved and only produces one singlet at 3.13 ppm, although some distortion in the signal shape is observable. Unfortunately, we were not able to run higher temperature $^{1}$H NMR experiments at this time, which would of course provide enough activation energy to allow the two compounds to interconvert freely, leading to a simplified spectrum. The signals for the aromatic protons were grouped together as a multiplet around the 7.0 ppm range. The well recognised patterns of signals representing the allyl chain were present at their respective chemical shift values. A multiplet at 5.98 ppm to 5.95 ppm integrating for one hydrogen representing the proton of the alkene CH group, a multiplet at 5.10 ppm to 5.05 ppm representing the alkene $CH_2$ protons and finally a doublet at 3.32 ppm indicating the protons of the methylene group. In fact it should be mentioned that these multiplets may indeed have been well resolved signals if we could record the $^{1}$H NMR spectrum at a higher temperature. In the $^{13}$C NMR spectrum the three methyl groups now appeared as one signal at 28.2 ppm. The quaternary carbon of the *tert* butyl group was found at 79.6 ppm. There was also a new signal at 155.0 ppm, indicating the carbonyl functionality. The broadened signals of the $^{13}$C NMR spectrum further attested to the presence of the two geometric isomers about the carbamate group. The IR spectrum of the compound **323** showed a C=O stretching frequency at 1696 cm$^{-1}$.

With the Boc protecting group in place, we could now carry out the required conversion of the alkene **323** to the aldehyde **325.** The oxidation of the alkene was carried out using an ozonolysis reaction, as we had easy access to an ozone generator as well as previous experience with this type of reaction (Scheme 122).

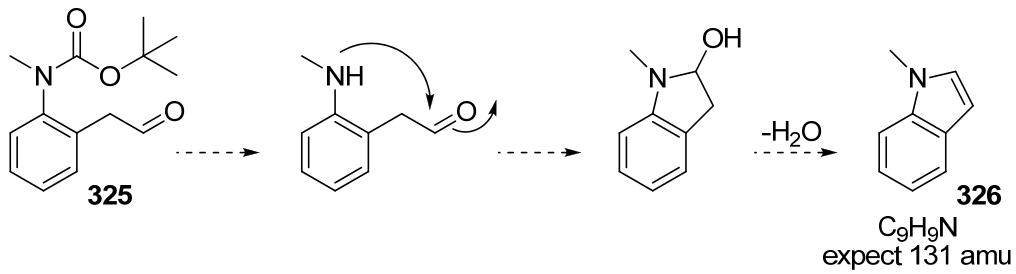



**Scheme 122**

To this end the alkene **323** was treated with ozone whilst maintaining the reaction temperature at –78 ºC in order to prevent over oxidation of aromatic ring system. For this

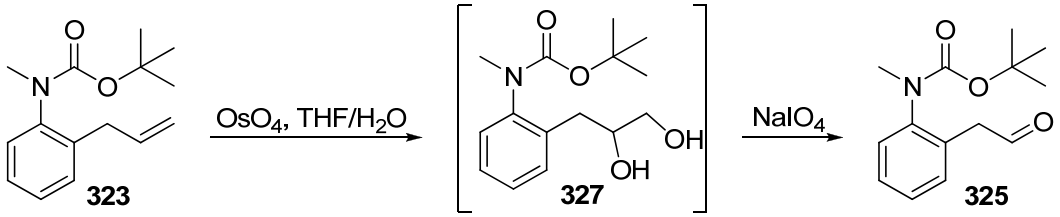
same reason, the addition of ozone was carefully controlled by bubbling it into the reaction mixture for short periods of time. After each short burst, the residual ozone was quickly displaced by bubbling oxygen into the reaction mixture and then the progress of the reaction was monitored by TLC analysis. Once all the starting material had reacted, triphenylphosphine was added and the solution was warmed up to 0 °C in order to reduce the resulting ozonide **324** to the aldehyde **325**. On work up and purification of the crude reaction mixture, the newly formed aldehyde **325** was obtained as a yellow oil in a disappointingly low yield of 30%.

The $^{1}$H NMR spectrum of the newly formed aldehyde **325** was greatly simplified in comparison to the precursor **323**. The first distinctive change was a new downfield singlet at 9.96 ppm characteristic of the aldehyde proton. The aromatic proton signals were still grouped together as a multiplet in the range 7.33 ppm to 7.26 ppm. Present at 3.63 ppm was a singlet indicative of the benzylic $CH_2$ protons. The singlet for the protons of the methyl group attached to the nitrogen atom could be found at 3.14 ppm and two singlets representing the protons of the *tert*-butyl functionality in two different environments were observed, one at 1.50 ppm and the other at 1.32 ppm. The $^{13}$C NMR spectrum contained two highly deshielded signals, one at 199.8 ppm and the other at 198.8 ppm, representing the carbons of the carbonyl functionalities present in the molecule **325**. There was also one less signal in the downfield region of the spectrum corresponding to the loss of one of the alkene carbons. In addition to the two carbonyl peaks, there were now six other signals representing the carbons on the aromatic ring. This compound proved to be rather unstable if not stored in a refrigerator and would decompose overnight forming a dark brown oil. The mass spectrum of the compound (low resolution) showed a fragment at 131 amu, but no signal representing the parent ion. The value could possibly be explained by the loss of the Boc group and subsequent attack of the nitrogen onto the aldehyde followed by the loss of water to produce **326** (Scheme 123).




**Scheme 123**

Although we were pleased with the success of the reaction, the yield was unsatisfactory for a linear synthesis and therefore we considered an alternative procedure for the formation of the aldehyde. Using osmium tetroxide, the alkene **323** could be converted into the corresponding 1,2-diol **327**, and then oxidative cleavage of this diol with sodium periodate should afford the corresponding aldehyde **325** (Scheme 124).



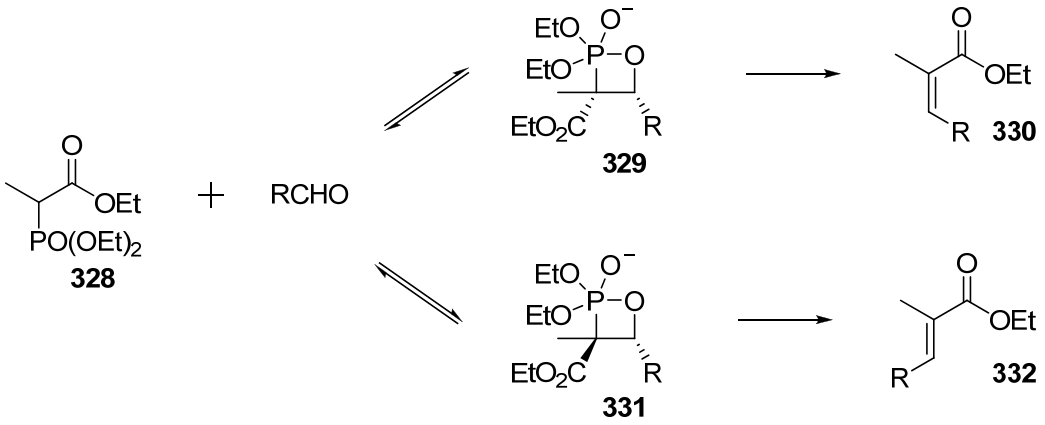

**Scheme 124**

To this end, osmium tetroxide was added to a solution of the alkene **323** in a mixture of water and THF resulting in an immediate colour change of the solution from clear to black. The sodium periodate was then added portion wise. The product obtained in this reaction matched that obtained in the ozonolysis reaction with respect to spectroscopic analysis and stability. The yield of this reaction was still rather low but slightly improved at 55%.

### 4.2.2 Exclusive formation of the (*E*)-alkene

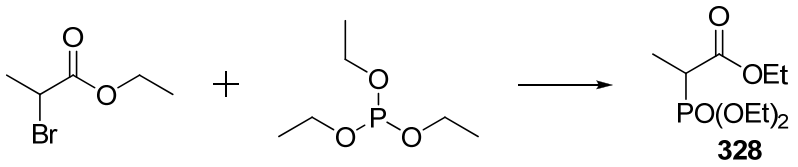
With our aldehyde **311** in hand we could now begin constructing the required functionality that would be necessary to facilitate the Pd-π allyl cyclisation reaction. We envisaged introducing this functionality by making use of a Horner-Wadsworth-Emmons reaction, a modified version of the Wittig reaction which generally forms *E* alkenes selectively. The reason for this is because the reaction involves the use of stabilised ylides e.g. **328** (Scheme 125). On attack of an ylide on an aldehyde, the kinetically controlled formation of the oxaphosphetane will occur to produce a *syn* compound **329**. The *syn* compound leads

to the formation of a *Z* alkene **330**. If however the ylide is stabilised, the reaction leading to the formation of the oxaphosphetane is reversible, and the stereochemical outcome in this step is now thermodynamically controlled and it is now possible for the formation of more stable *anti* oxaphosphetane **331**, which leads to the formation of the *E* alkene **332**.[92] The synthesis of the *E* isomer exclusively is essential for the stereoselective π-allyl Pd cyclisation reaction to follow as a mixture of *E* and *Z* alkenes would lead to the formation of different enantiomers in the presence of a single chiral ligand.



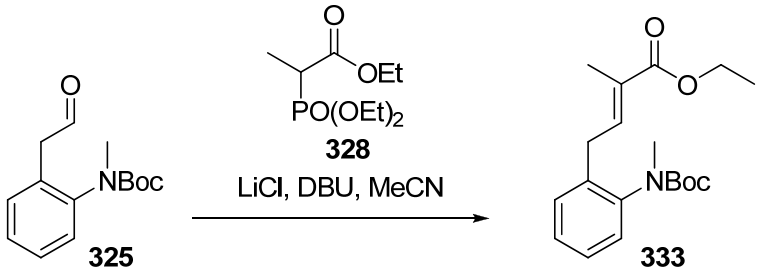

**Scheme 125**

The required diethyl phosphorylpropionate **328** although commercially available, could be easily synthesised by boiling triethylphosphite with a two-fold excess of ethyl 2-bromopropionate in the absence of a solvent for 72 hours (Scheme 126). The large excess of the propionate was required in order to ensure that all of the triethylphosphite reacted as its boiling point was very similar to that of the desired product, and therefore unreacted triethylphosphite caused problems in the purification step. The ethyl 2-bromopropanoate on the other hand has a significantly lower boiling point, and an excess of this material could be easily separated from the desired phosphorylpropionate **328**.




**Scheme 126**

For the purposes of the Horner-Wadsworth-Emmons reaction, the carbamate **325** was dissolved in dry acetonitrile and cooled to 0 ºC. The phosphorylated enolate was then generated in the dropping funnel by adding DBU to a solution of **328** in acetonitrile. Furthermore, in this process of generating the anion, care was taken to ensure that the phosphonate was in an excess and would therefore react with all the added DBU. Having formed the phosphorylated enolate in the dropping funnel, it was then added to the flask containing the carbamate **325** very slowly over a period of one hour. This elaborate procedure was found to be necessary as in previous work on a very similar compound,[114] it was found that any residual DBU is able to isomerise the alkene of the desired product **333** to be in conjugation with the phenyl ring, no doubt initiated by the DBU abstracting a benzylic proton on the product **333**. Interestingly, the anion itself seemingly is not basic enough to do so. The progress of the reaction could be monitored by TLC and once all the starting material had reacted, the reaction was quenched with water and the organic product extracted and purified, affording the desired α,β-unsaturated compound **333** in 80% yield (Scheme 127).




**Scheme 127**

In the now vastly different $^{1}$H NMR spectrum, an immediately obvious sign of a successful reaction was the absence of the signal for the aldehyde proton. In the downfield region a triplet at 6.84 ppm integrating for one hydrogen was a new feature, and could be attributed to alkene proton of **333** coupling to the neighbouring benzylic $CH_2$ protons. The characteristic pattern of a quartet at 4.18 ppm integrating for two protons and triplet at 1.27 ppm integrating for three protons indicated the presence of the ethyl side chain on the ester moiety. A new upfield singlet at 1.93 ppm could be assigned to the allylic $CH_3$ group. The accompanying $^{13}$C NMR spectrum contained five new signals confirming the addition of the ethyl propionate moiety. The downfield region which contained the signals for the aromatic carbons as well as the carbonyl carbon, now also displayed signals for the two

carbons on the alkene functionality at 154.8 ppm and 139.4 ppm. The upfield region contained signals for the carbons of the ethyl side chain at 60.3 ppm and 14.1 ppm (methylene and methyl respectively) as well as the allylic methyl at 12.4 ppm. The IR spectrum was in line with expectations as was the mass spectral analysis of the product **333** which showed a parent molecular ion at 333.1935 amu corresponding to the molecular formula of $C_{19}H_{27}NO_4$ which required a value of 333.1940 amu. An important feature in this reaction was that we required the exclusive construction of the *E* double bond. In the $^1$H NMR spectrum, it was clear that we had indeed formed a majority of one product, but we needed to confirm the geometry before continuing. To this end, an *NOE* spectrum of the molecule was obtained. In this spectrum irradiation of the benzylic $CH_2$ at 3.43 ppm showed a positive response from the new allylic $CH_3$ group at 1.93 ppm. If we had the Z-isomer, the allylic $CH_3$ would be too far away from the irradiated benzylic $CH_2$ to produce a response, thereby clarifying that the geometry around the double bond was indeed *E* (Figure 28).

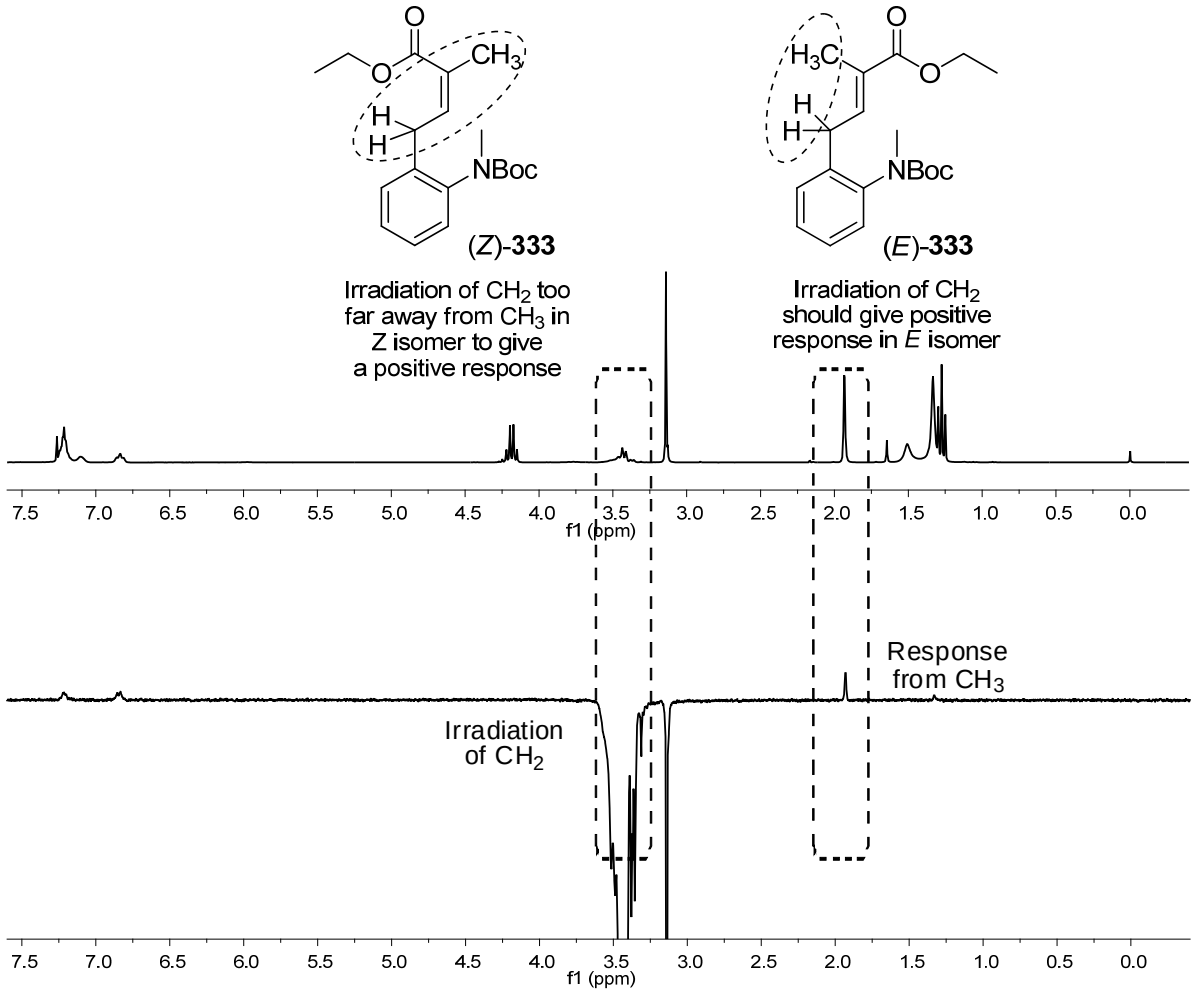



**Figure 28**

However, we did observe some small signals in the $^{1}$H NMR spectrum and magnification revealed a small triplet at 5.95 ppm. A triplet at this chemical shift could not be possible if we had any of the isomerised product contaminating our desired product **333**, however, the formation of any of the *Z*-isomer would certainly account for such a signal and therefore we attributed this triplet to the alkene proton of a small amount of (*Z*)-**333** contaminating our product (Figure 29). Integration of this signal relative to that of the *E*-isomer indicated that our *E*-alkene product was contaminated with about 5% of the *Z*-product. This of course may erode our enantiomeric excess at the end of the synthesis, but we could not eliminate all traces of the *Z*-isomer and therefore eagerly pushed forward in our synthesis.

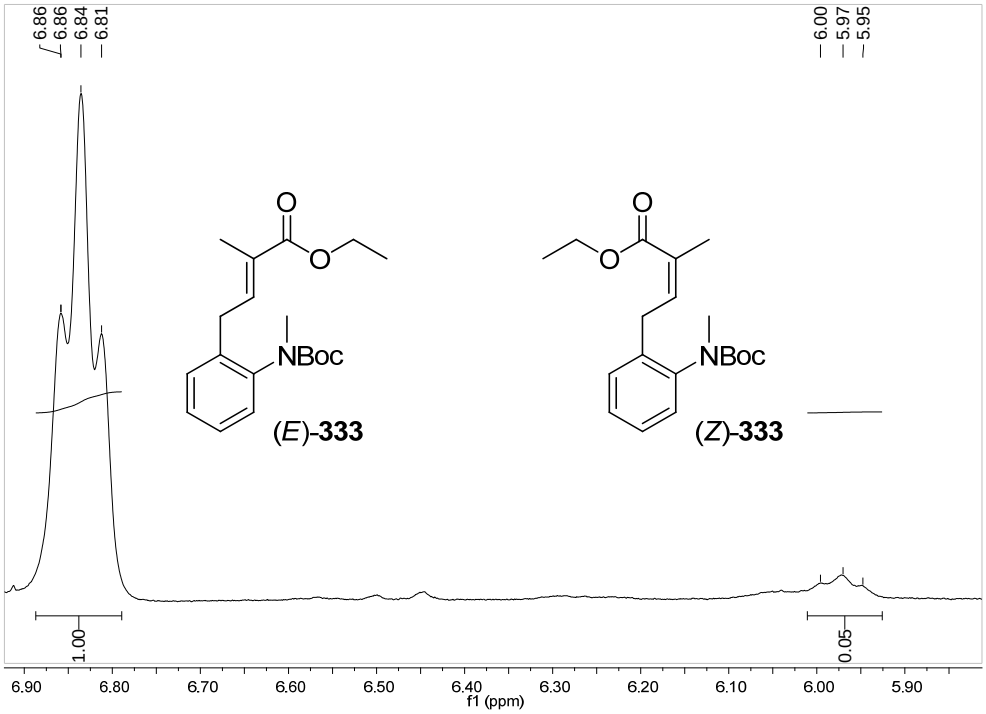
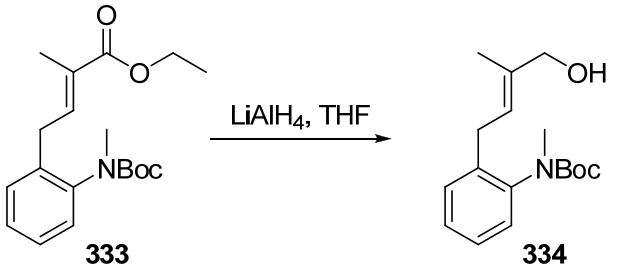



**Figure 29**

### 4.2.3 Preparation of the precursor required for Pd-mediated cyclisation

At this stage we were set for the attachment of a suitable leaving group on the allyl moiety. The best choice for a leaving group, as demonstrated in earlier work was a carbonate group.[146] In order to achieve this it would be necessary to reduce the ester **333** to the primary alcohol **334** (Scheme 128). To this end, the ester **333** was treated with $LiAlH_4$ in THF at 0 ºC and following the work up and purification we obtained the desired alcohol **334** in a 70% yield.

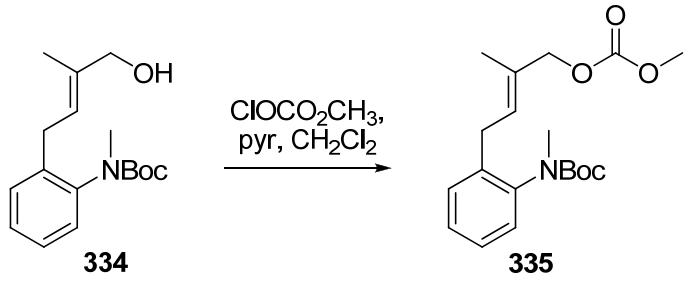



**Scheme 128**

The conversion was clearly evident from the changes observed in the $^1$H NMR spectrum of the product **334**. The signal for the alkene proton had shifted upfield from 6.84 ppm to 5.54 ppm, due to the fact that reduction of the carbonyl no longer resulted in delocalisation

of the alkene electrons which previously resulted in deshielding of this proton. Furthermore, the quartet and triplet representing the protons of the ethyl side chain were no longer present in the spectrum of the product **334**. The signal for the protons of the $CH_2$ group α to the alcohol functionality was a singlet located at 4.03 ppm and the benzylic $CH_2$ protons produced a doublet at 3.32 ppm. The methyl group attached to the nitrogen atom produced a singlet at 3.12 ppm, slightly downfield of the allylic methyl signal, 1.76 ppm (overlapping with the OH signal). The aromatic protons as well as the protons from the *tert* -butyl group were unchanged. The accompanying $^{13}C$ NMR spectrum now only contained one signal in the downfield region at 155.2 ppm, representing the carbonyl carbon. There were also two less signals present in the upfield region, due to the removal of the ethyl group. In the IR spectrum a clear OH stretching band was observed at 3412 $cm^{-1}$. The mass spectral analysis delivered a molecular ion matching the calculated value for the parent ion of the molecule (291.18274 amu).

The carbonate functionality could now be easily constructed by treatment of **334** with methyl chloroformate and pyridine (Scheme 129). This reaction proceeded uneventfully producing the carbonate **335** as a light yellow oil in 88% yield after workup and purification.



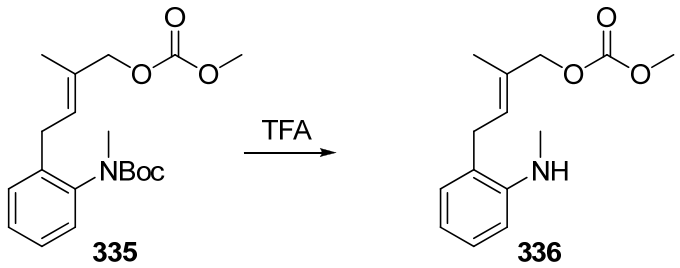

**334** **335**

**Scheme 129**

In the $^{1}H$ NMR spectrum of the product **335**, a new signal at 3.78 ppm integrating for three protons attested to the presence of the methyl group of the carbonate. A slight downfield shift in the singlet for the methylene α to the oxygen was also observed and otherwise the spectrum remained largely unchanged. The $^{13}C$ NMR spectrum displayed a new downfield signal at 142.3 ppm, corresponding to the carbonyl group of the carbonate. Another new upfield signal could be found at 54.7 ppm indicating the methyl carbon of the carbonate group. The broad band indicating the OH functionality was no longer present in the IR

spectrum of the molecule and instead there were now two carbonyl absorption peaks present, one at 1747 $cm^{-1}$ corresponding to the carbonate, and one at 1696 $cm^{-1}$ corresponding to the carbamate.

All that remained in preparation for the cyclisation was the removal of the Boc protecting group. To this end, the carbonate **335** was exposed to trifluoroacetic acid in the absence of any solvent (Scheme 130). On routine workup and purification of the reaction, the amine **336** was obtained in an 87% yield.




**335** **336**

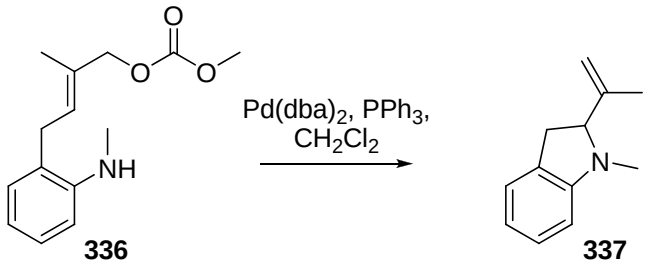
**Scheme 130**

The most distinctive change in the $^{1}H$ NMR spectrum of the product **336** was of course the absence of the two singlets representing the nine protons of the *tert*-butyl group. The signals for the aromatic protons of the molecule were now also more clearly laid out and existed as a triplet at 7.17 ppm, a doublet at 7.02 ppm and a multiplet at 6.74 ppm to 6.59 ppm. This clarification of the signals could be attributed to the fact that the molecule was no longer present as a mixture of conformations, previously resulting from restricted rotation within the carbamate functionality and subsequently the formation of different geometric isomers of the compound. The singlet at 1.27 ppm integrating for one proton was assigned to the NH hydrogen. The $^{13}C$ NMR spectrum of the product was largely unchanged compared to the starting material, save for the absence of the signals previously attributed to the Boc protecting group. The high resolution mass spectrum corresponded to the new molecular formula of the product, $C_{14}H_{19}NO_3$, displaying a parent ion of 249.13591 amu.

## 4.3 The Synthesis of 1-Methyl-2-isopropenyl Indoline

With our precursor **336** in hand, we were now in a position to investigate the π-allyl Pd cyclisation. The reaction was initially carried out in the absence of the chiral ligand to ascertain that the cyclisation would in fact occur (Scheme 131). To this end $Pd(PPh_3)_4$ was

used as the source of Pd(0). Although we had $Pd(PPh_3)_4$ on hand we intended to generate it *in situ* using $Pd(dba)_2$, as this would mimic the procedure we had in mind for generating the chiral Trost ligand-palladium complex.




**336** **337**

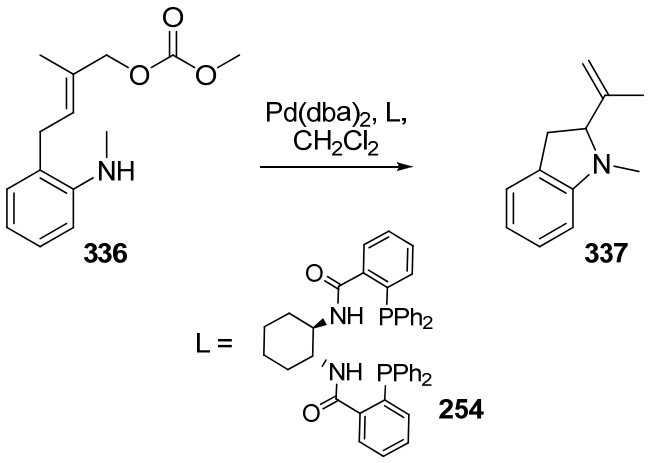
**Scheme 131**

For the formation of the $Pd(PPh_3)_4$ the pre-catalyst $Pd(dba)_2$ was dissolved in $CH_2Cl_2$ and the resulting deep wine red solution was thoroughly deoxygenated by bubbling Ar(g) into it. Once the solution was degassed and blanketed with Ar(g), triphenylphosphine was added against a flow of Ar(g), and immediately the colour of the solution began to change to yellow as the original dibenzylidene acetone ligand was displaced by the phosphine ligand, forming our desired $Pd(PPh_3)_4$ catalytic system, which is oxygen sensitive. The use of any solvent which may itself co-ordinate to the Pd(0) was specifically avoided. The reason for this is that although it would have no detrimental affect while we investigated this reaction achirally, when the chiral reaction is performed a coordinating solvent would compete with our chiral Trost ligand, producing a mixture of a chiral and non-chiral catalytic system, which would erode our enantiomeric excess. A slight excess of the phosphine ligand was added to ensure that all the dibenzylidene acetone was indeed displaced. The carbonate **336** was then added to the solution and left to react for 12 hours. After evaporation of the solvent and purification, we were pleased to discover that the cyclisation did indeed occur as expected, producing our racemic 2-isopropenyl indoline **337** in a moderate 55% yield.

The $^1H$ NMR spectrum was pleasingly quite different to the starting material. The aromatic protons were clearly present as four separate signals. The triplets at 7.08 ppm and 6.65 ppm represented the protons at the C6 and C7 position of the aromatic ring. The doublets at 7.04 ppm and 6.45 ppm accounted for the aromatic protons at positions C8 and C5. The protons of the alkene $CH_2$ group were split into two multiplets, one at 5.03 ppm to 5.01 ppm and the other at 4.95 ppm to 4.93 ppm. The multiplicity can be accounted for by

the fact that the alkene protons can couple to each other as well as display long range coupling to the ring proton at C2. The signal for the proton at the C2 position of the indoline ring could be found as a multiplet at 3.84 ppm to 3.77 ppm. The benzylic $CH_2$ group being adjacent to a stereogenic carbon, was split into two signals, one doublet of doublets at 3.04 ppm and another at 2.84 ppm, resulting from coupling to each other and to the proton at the C2 position. As for the remaining signals, a singlet at 2.62 ppm integrating for three protons could be assigned to the methyl attached to the nitrogen atom and similarly, another singlet at 1.74 ppm could be assigned to the protons of the methyl of the isopropenyl group. The most noteworthy change in the $^{13}C$ NMR spectrum of **337** was the fact that there was no longer a far down field signal representing the carbonyl functionality as well as the loss of a signal in the upfield region of the spectrum which would have accounted for the methyl group of the now absent carbonate group. All the remaining signals in the $^{13}C$ NMR spectrum were accounted for and could be assigned using a CH correlated spectrum. The mass spectral analysis showed a molecular ion at 173.11986 amu which confirmed the molecular formula $C_{12}H_{15}N$, corresponding to our product **337**.

Having carried out a successful non-stereoselective π-allyl Pd mediated cyclisation reaction, we now turned our attention to the enantioselective synthesis of the indoline **337**. Similarly to the previous experiment, we envisaged that the catalytic system could be generated *in situ* using $Pd(dba)_2$ as our pre-catalyst, followed by the addition of our phosphine ligand which would in this case be the chiral *R,R*-Trost ligand **254** (Scheme 132). To this end, the $Pd(dba)_2$ was dissolved into the dichloromethane, once again forming a deep wine red coloured solution which was thoroughly deoxygenated by bubbling Ar(g) into the solution. The chiral ligand was then added, and the colour of the solution began to change to yellow as the dibenzylidene acetone ligand was displaced by the chiral phosphine-based Trost ligand, forming our desired catalytic system. A slight excess of the chiral ligand was added to ensure that all the dibenzylidene acetone was indeed displaced, as any remaining $Pd(dba)_2$ would also catalyse the reaction, though non-stereospecifically, which would be detrimental to our enantiomeric excess. The carbonate was then added to the solution and left to react for 12 hours. After evaporation of the solvent and purification, we were pleased to obtain the desired 2-isopropenyl indoline **337** once again in the moderate yield of 45%.




**Scheme 132**

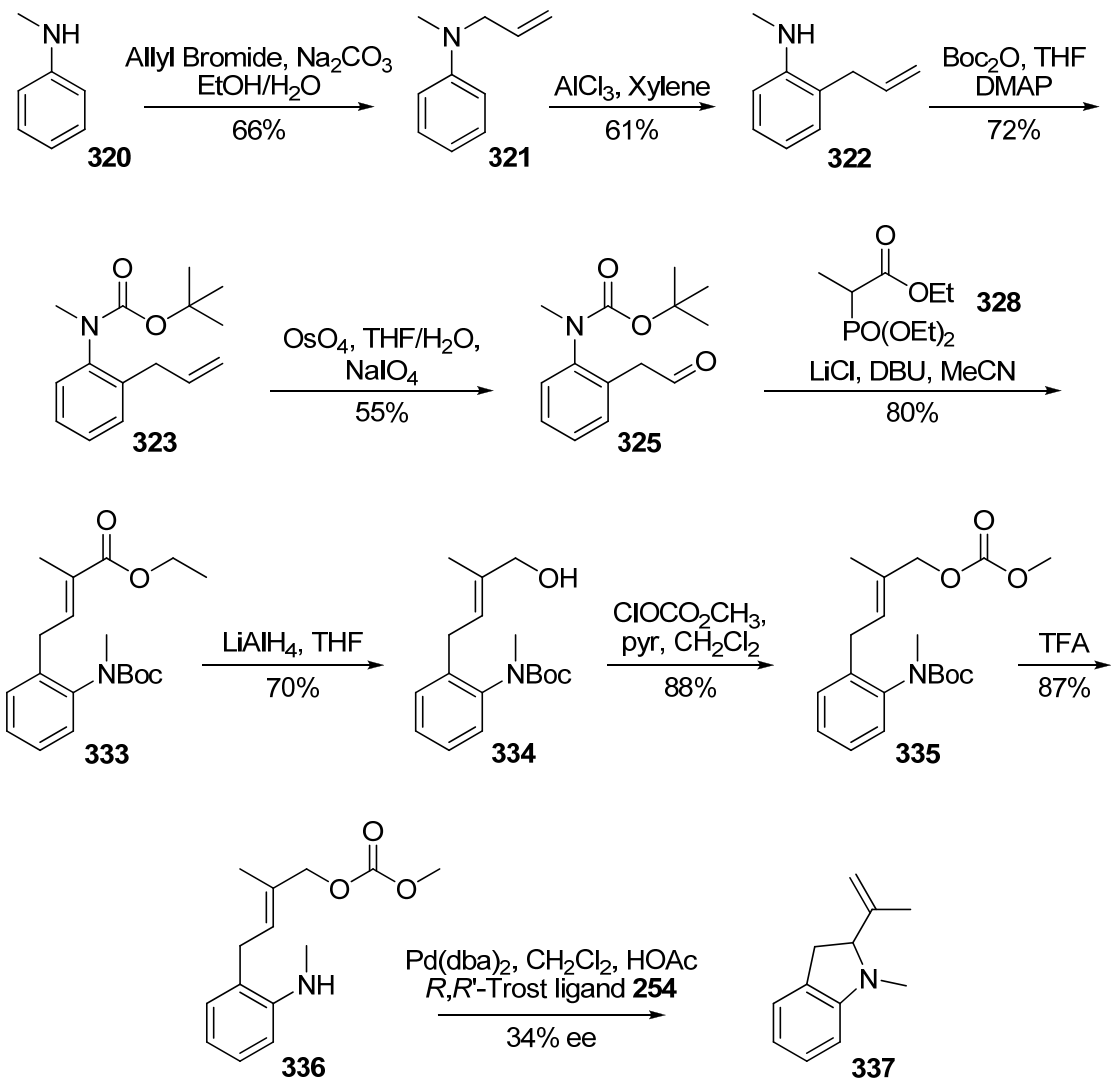
In order to determine our enantiomeric excess we made use of chiral HPLC. For the purposes of this exercise we first set about optimising the conditions using the racemic material in order to ensure that we could in fact separate the enantiomers on our Chiralcel OJ column. Fortunately, after some experimentation we found that by using a mobile phase consisting of a 20% solution of isopropyl alcohol in hexane we could obtain a baseline resolved separation of the two enantiomers. With this methodology in hand, we set about determining the enantiomeric excess of our first chiral cyclisation and to our bitter disappointment, two large peaks eluted! Clearly, our reaction had hardly been enantioselective as we obtained an equal ratio for the two enantiomers.

Trost reported that in his reactions they needed to slow down the cyclisation step to optimise their enantiomeric excesses.[136] As discussed earlier, the initial formation of the chiral π-allyl-Pd-$L_2^*$ system is not the most thermodynamically favoured arrangement, and requires some time to rearrange to the thermodynamically preferred face once the carbonate has been eliminated. Therefore, we decided to repeat the reaction, this time however in the presence of acetic acid which was intended to render the aniline substantially less nucleophilic, thereby slowing down its attack on the π-allyl-Pd-$L_2^*$ complex. Unfortunately, this change in procedure only mildly increased our reaction's enantioselectivity, affording the product in 32% ee. However, the reaction was also so detrimentally attenuated that even with boiling overnight, only trace amounts of the product were formed and most of the starting material was recovered! Clearly, another approach is required to decrease the nucleophilicity of the aniline, perhaps not by forming

an ammonium ion as this retards the reaction too significantly, but perhaps by forming a sulphonamide instead, and this will be discussed in the next section.

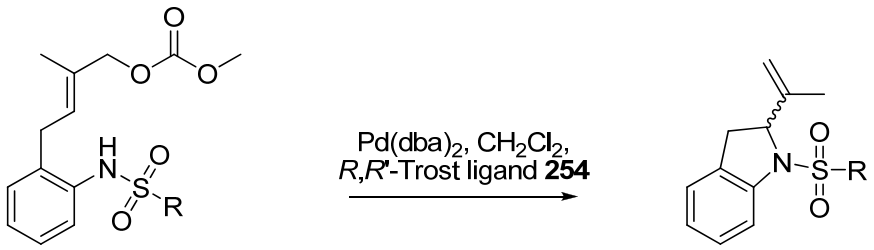
## 4.4 Concluding Remarks Regarding the Synthesis of the Indoline Subunit

The synthesis of the *N*-methyl indoline **337** was accomplished in nine steps from commercially available *N*-methyl aniline **320** in an overall yield of 3.1% (Scheme 133). While we were pleased at having completed the planned synthetic route towards the methylated indoline subunit **337**, the key step of the reaction sequence, the asymmetric allylic alkylation of carbonate **336**, did not proceed as per our expectations, delivering the product in a moderate yield without any enantioselectivity, or in a poor yield with only poor enantioselectivity when we attempted to decrease the nucleophilicity of the amine.




**Scheme 133**

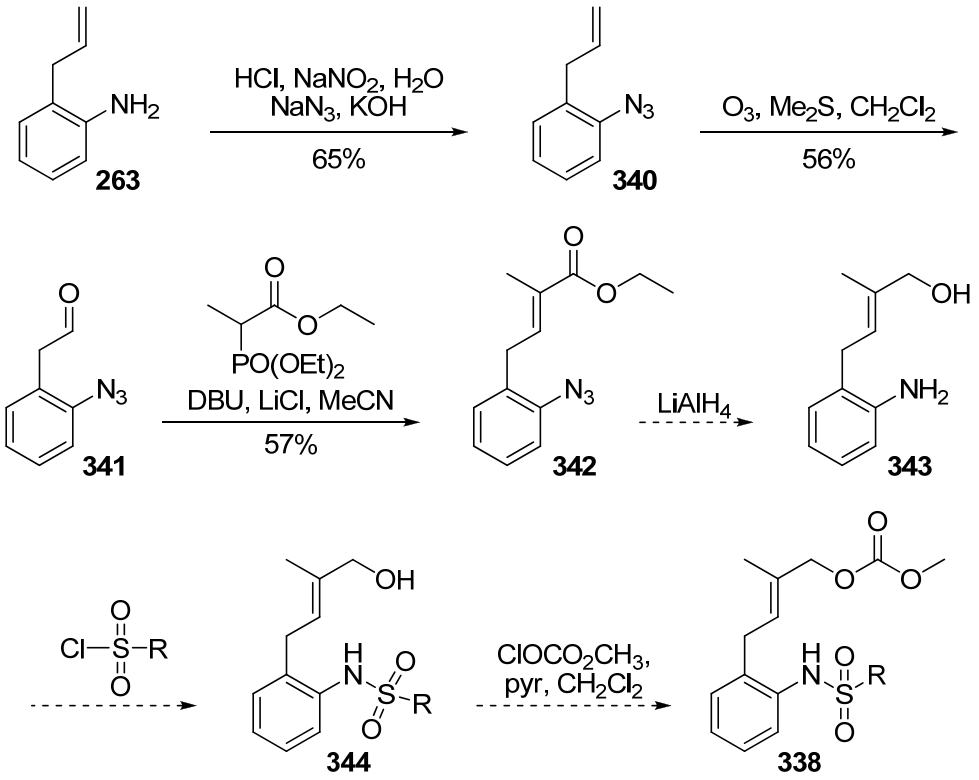
The cyclisation of **336** to **337** using the *R,R'*-π-allyl-Pd catalytic system did not show any enantioselectivity. The most plausible explanation for this is the fact that the reaction may have been proceeding too quickly. Unfortunately, when we attempted to slow down the rate of the reaction by the addition of acetic acid this only succeeded in raising the enantiomeric excess slightly. That the reaction requires attenuation to optimise the enantiomeric excess is without doubt, however, exactly how this is to be achieved without completely stopping the reaction is an area that requires further investigation. Perhaps, instead of forming the ammonium ion by adding acetic acid, one could investigate other methods to reduce the nucleophilicity of the amine, perhaps by converting it into a sulphonamide **338** for example (Scheme 134). Moreover, converting the amine to the sulphonamide **338** early on in the synthesis may obviate the need to methylate it.




**338** **339**

**Scheme 134**

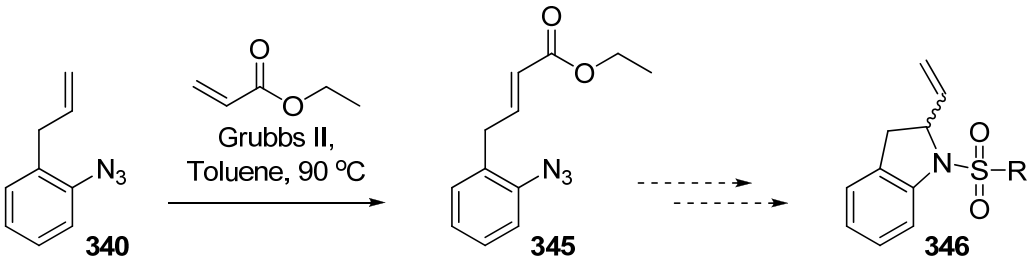
As a protection strategy, the allyl aniline **263** can be converted into the azide **340** (Scheme 135). Then the reaction sequence can proceed as planned until the Horner-Wadsworth-Emmons reaction has taken place. At this stage the reduction of the ester functionality of **342** should also result in the conversion of the azide to the amine **343**. The amine can then be converted into the sulphonamide **344**. In the absence of a base we hope the amine would react immediately with the sulphonyl chloride while leaving the alcohol functionality unreacted. The carbonate group can then be added to prepare the precursor **338** for the cyclisation reaction. Some preliminary work has been done in this regard, proving this to be a feasible strategy.




**Scheme 135**

In order for this route to be feasible, the formation of the *o*-allylaniline **263** will of course need to be optimised. In this regard an alternative method for the introduction of the allyl chain to the *ortho* position may need to be investigated.

Once this work is more established it would be interesting to ascertain the use of cross metathesis for the introduction of alternative unsaturated chains on the aromatic chain such as **345** and perhaps reduce the number of steps towards the asymmetric allylic alkylation reaction forming compounds such as **346** (Scheme 136).




**Scheme 136**

# Chapter 5: Experimental Procedures

## 5.1 General Procedures

### 5.1.1 Purification of solvents and reagents

The solvents used for chromatography were distilled prior to use by means of conventional distillation procedures. Solvents used for reactions were dried over the appropriate drying agent and then distilled under nitrogen gas. Tetrahydrofuran and diethyl ether were distilled over sodium using benzophenone as an indicator. Toluene and *n*-butyl ether were distilled from sodium metal. Dichloromethane and acetonitrile were distilled from calcium hydride. When necessary, solvents were stored over activated molecular sieves (4 Å) under an Ar(g) atmosphere. Reagents were obtained from commercial sources and used without further purification or purified by standard methods as recommended by Perrin *et al.*[147]

### 5.1.2 Chromatography

The $R_f$ values quoted are for analytical thin layer chromatography (TLC) on aluminium-backed Macherey-Nagel Alugram Sil G/$UV_{254}$ plates pre-coated 0.25 mm silica gel 60. Detection was carried out by viewing the adsorbed compounds under UV light. Purification of compounds by column chromatography was carried using Macherey-Nagel silica gel 60 (particle size 0.063 mm to 0.200 mm) as the adsorbent. When performing flash chromatography, silica gel of particle size 0.035 mm to 0.070 mm was used. Mixtures of ethyl acetate and hexane were used as the mobile phase.

### 5.1.3 High pressure liquid chromatography

High pressure liquid chromatography (HPLC) was performed on a TSP HPLC using a Chiralcel OJ 10µ 250 × 4.6 mm chiral column. Mobile phases consisting of isopropyl alcohol and hexane mixtures were used. Detection of the eluted compounds was achieved by using a TSP variable wavelength UV detector at 215 nM. Calculations were based on the area under the peak.

### 5.1.4 Spectroscopic and physical data

$^{1}$H NMR spectra were recorded on a Bruker AVANCE 300 (300.13 MHz) or a Bruker 400 (400.13 MHz) spectrophotometer. $^{13}$C NMR ($^{1}$H decoupled) spectra were recorded on a Bruker AVANCE 300 (75.47 MHz) or Bruker DRX 400 (100.63 MHz) spectrometer. Spectra were recorded in deuterated chloroform ($CDCl_3$) unless otherwise stated and chemical shifts are reported in parts per million downfield from tetramethylsilane for $^{1}$H NMR spectra and relative to the central signal of deuterated chloroform, taken as δ 77.00 for $^{13}$C NMR spectra. Coupling constants are given in Hertz.

Infra-red spectra were recorded using a Bruker IFS-25 Fourier Transform spectrometer or on a Bruker Vector-22 Fourier Transform spectrometer. Measurements were made using either a solution in chloroform between sodium chloride plates or by loading the sample directly onto a diamond cell. The signals are reported on the wavenumber scale ($\nu/cm^{-1}$).

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

High resolution mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer.

Intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo $K_\alpha$ radiation (50 kV, 30 mA) using the APEX 2[148] data collection software. The collection method involved ω-scans of width 0.5° and 512×512 bit data frames. Data reduction was carried out using the program *SAINT+* and face indexed absorption corrections were made using *XPREP*.[149]
The crystal structure was solved by direct methods using *SHELXTL*.[150] 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[151] and ORTEP-3.[152]

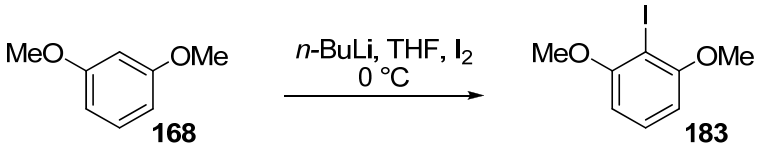
### 5.1.5 Other general procedures

All reactions, unless otherwise stated, were carried out under an Ar(g) atmosphere and the reaction vessels were dried in an oven. The term "*in vacuo*" refers to the removal of

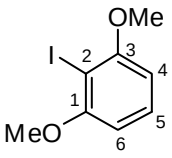
solvent by rotary evaporation. For purified products this is followed by removal of the residual solvent using a high vacuum pump (*ca.*0.1 mm Hg) at ambient temperature until constant mass was achieved.

## 5.2 Experimental Work Pertaining to the Synthesis of Cardinalin 3

### 5.2.1 Synthesis of 2-iodo-1,3-dimethoxybenzene 183

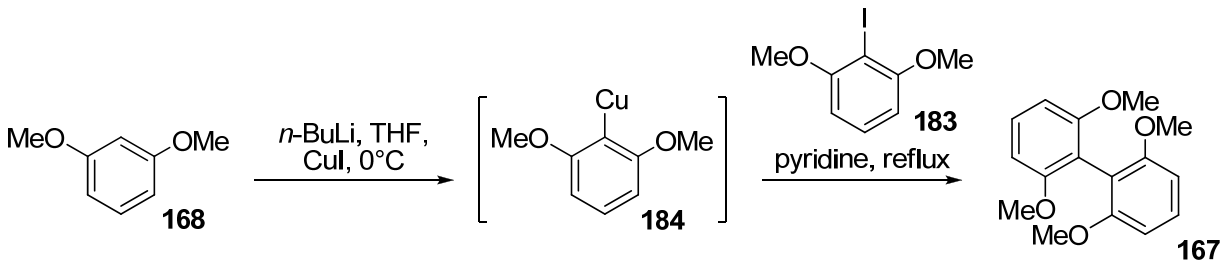



A solution of 1,3-dimethoxybenzene **168** (4.74 ml, 5.00 g, 36.2 mmol) in dry THF (50 ml) was placed in a flame dried 250 ml round bottom flask fitted with a dropping funnel. The solution was cooled down to 0 °C by means of an ice bath and the dropping funnel was charged with *n*-BuLi (1.40 M in hexane, 28.4 ml, 39.8 mmol, 1.1 equiv.). Once the solution was cooled, the *n*-BuLi was added dropwise. The reaction mixture was then stirred at 0 °C for 1 h. The dropping funnel was next charged with a solution of $I_2$ (10.1 g, 39.8 mmol, 1.1 equiv.) in THF (70 ml). The halogen solution was then added dropwise to the milky white reaction mixture. The end point of the reaction was observed at the appearance of the light brown halogen colour. The reaction mixture was stirred for an additional 1 h at rt. $H_2O$ was then added to the solution and the product extracted with $CH_2Cl_2$ (3 × 50 ml). The solvent was removed using a rotary evaporator and the crude product was recrystallised from $CH_2Cl_2$:EtOH to give large white crystals of iodo-1,3-dimethoxybenzene **183** (8.84 g, 93%).

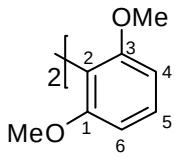



**$R_f$** = 0.70 (30% EtOAc/hexane). **Mp.** = 105-106 °C ($CH_2Cl_2$:EtOH), (lit[76] 104 °C). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.26 (1H, t, *J* = 8.3 Hz, H5); 6.50 (2H, d, *J* = 8.3 Hz, H4 and H6); 3.89 (6H, s, 2 × OMe). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 158.4 (C1 and C3), 128.7 (C5), 112.6 (C2), 104.5 (C4 and C6), 56.1 (2 × OMe). **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1587 and 1470 (Ar C=C), 1255 (Ar C-O). **HRMS**: Found $M^+$ 263.9654. $C_8H_9IO_2$ requires *M* 263.9647 amu, (EI) 264 ($M^+$, 100%), 249 (6), 221 (18), 206 (7), 122 (8), 107 (11), 92 (9), 77 (10), 51 (8).[70]

### 5.2.2 Synthesis of 2,2′,6,6′-tetramethoxy-1,1′-biphenyl 167

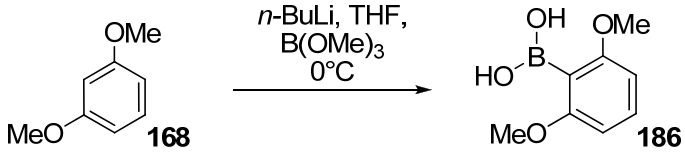



Into a flame dried 250 ml round bottom flask fitted with a dropping funnel was placed dry THF (50 ml), followed by 1,3-dimethoxybenzene **168** (3.47 ml, 3.66 g, 26.5 mmol, 1.1 equiv.). The solution was cooled down to 0 °C. Once cooled, *n*-BuLi (1.60 M in hexane, 16.6 ml, 26.5 mmol, 1.1 equiv.) was slowly added using the dropping funnel. The solution was stirred at 0 °C for 1 h. CuI (5.05 g, 26.5 mmol, 1.1 equiv.), dried overnight in an oven at 110 °C, was added in portions and the mixture was stirred at rt for another 2 h. The dropping funnel was then charged with a solution of 2-iodo-1,3-dimethoxybenzene **183** (6.36 g, 24.0 mmol) in dry pyridine (50 ml). Once the solution of the halide was added, the dropping funnel was replaced with a condenser, and the mixture was heated under reflux for 72 h. The product mixture was then poured onto ice and made acidic with concentrated aqueous HCl (*ca.* 25 ml). The product was then extracted with $CH_2Cl_2$ (3 × 80 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The crude product was recrystallised from $CH_2Cl_2$:EtOH to give 2,2′,6,6′-tetramethoxy-1,1′-biphenyl **167** (6.12 g, 93%).

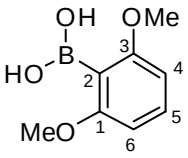



**$R_f$** = 0.47 (30% EtOAc/hexane). **Mp.** = 175-177 °C ($CH_2Cl_2$:EtOH), (lit[153] 175-176 °C). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.28 (2H, t, *J* = 8.3 Hz, H5 and H5′); 6.65 (4H, d, *J* = 8.3 Hz, H4, H4′, H6 and H6′); 3.71 (12H, s, 4 × OMe). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 158.4 (C1, C1′, C3 and C3′), 128.7 (C5 and C5′), 112.5 (C2 and C24′), 104.4 (C4, C4′, C6 and C6′), 56.1 (4 × OMe). **IR** ($CHCl_3$): $\nu_{max}$($cm^{-1}$) = 1587, 1451 (ArC=C), 1246 (Ar C-O). **HRMS**: Found $M^+$ 274.1198. $C_{16}H_{18}O_4$ requires *M* 274.1205 amu (EI) 274 ($M^+$, 100%), 243 (7), 228 (11), 155 (5), 151 (20), 114 (6), 91 (6).[70]

### 5.2.3 Synthesis of 2,6-dimethoxyphenylboronic acid 186

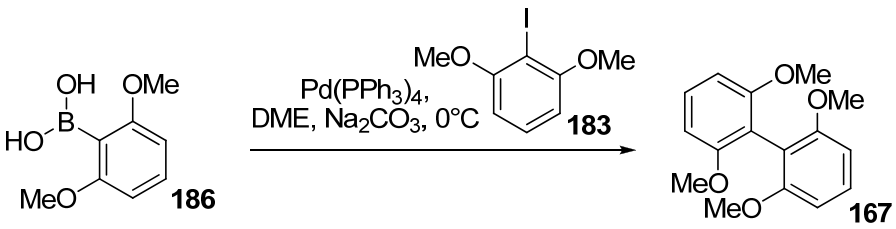



Into a flame dried 250 ml round bottom flask fitted with a dropping funnel was placed dry THF (100 ml), followed by 1,3-dimethoxybenzene **168** (4.74 ml, 5.00 g, 36.2 mmol). The solution was cooled down to 0 °C. Once cooled *n*-BuLi (1.40 M in hexane, 31.1 ml, 43.4 mmol, 1.2 equiv.) was slowly added via the dropping funnel. The solution was stirred at 0 °C for 1 h. The $B(OMe)_3$ (16.2 ml, 15.0 g, 144 mmol, 4 equiv.) was then added slowly using a syringe. The reaction was stirred for 18 h over which time it was allowed to warm up to rt. After this time the mixture was poured into a large beaker equipped with a stirrer bar. $H_2O$ (100 ml) and $Et_2O$ (50 ml) were added to the mixture which was then stirred vigorously. The initial pH was checked and found to be basic. Additions of a 1 M solution of aqueous HCl was then carried out while stirring, and the pH checked after each addition. This was continued until the mixture had become acidic. The organic layer was then extracted using $Et_2O$ (3 × 100 ml). The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$ and filtered. The solution was then concentrated (*ca*. 20 ml) by removing the solvent *in vacuo*. Hexane (*ca*. 100 ml) was then added to this, resulting in the precipitation of the boronic acid. The solution was cooled in an ice bath and the crystals were then collected by filtration, and washed with cold hexane to afford 2-ethyl-6-methoxyphenylboronic acid **186** (4.65 g, 71%).[70]




**$R_f$** = 0.27 (30% EtOAc/hexane). **Mp.** = 92-96 °C (lit[154] 100-115 °C). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.39 (1H, t, *J* = 8.4 Hz, H5); 7.22 (2H, s, Ar-B(O*H*)$_2$); 6.64 (2H, d, *J* = 8.4 Hz, H4 and H6); 3.91 (6H, s, 2 × OC*H*$_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 165.4 (2 × Ar*C*O), 132.9 (C5), 104.4 (C4 and C6), 56.0 (2 × O*C*H$_3$), 55.8 (Ar*C*B(OH)$_2$). **IR** ($CHCl_3$): $\nu_{max}$(cm$^{-1}$) = 3474 (br s, OH), 1650, 1586 (ArC=C). **HRMS**: Found M+ 182.0761. $C_8H_{11}BO_4$ requires M 182.0750 amu. (EI) 182 (M+, 100%), 181 (26), 164 (24), 138 (11), 109 (10), 78 (10), 76 (34).[70]

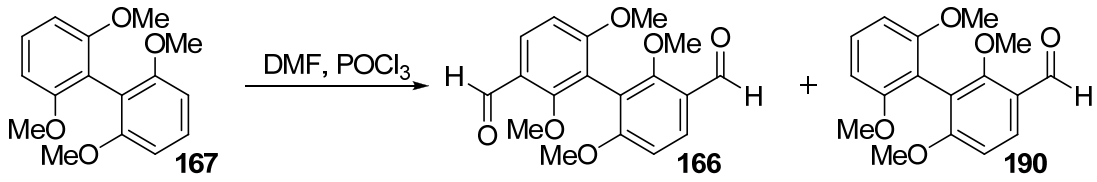
### 5.2.4 Synthesis of 2,2′,6,6′-tetramethoxy-1,1′-biphenyl 167



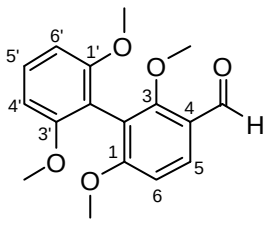

Into a two neck round bottom flask fitted with a dropping funnel and a condenser (oven dried and under Ar(g)) was placed $Pd(PPh_3)_4$ (0.87 g, 0.76 mmol, 10 mol%) and 2,6-dimethoxyphenylboronic acid **186** (2.07 g, 11.4 mmol, 1.5 equiv.). The reaction vessel was degassed and purged with Ar(g). The dropping funnel was then charged with DME (21.0 ml) and 2-iodo-1,3-dimethoxybenzene **183** (2.00 g, 7.57 mmol). Ar(g) was then bubbled into the dropping funnel by means of a Pasteur pipette and the solution was quickly added to the reaction flask. The dropping funnel was recharged with an aqueous $Na_2CO_3$ solution (1.80 M, 4.01 g, 21.0 ml, 5 equiv.). This solution was similarly degassed for 5 min and then discharged into the reaction vessel. The two phase mixture was heated to reflux and the yellow reaction mixture was left to react for 18 h. During this time the solution became homogenous as the catalyst fully dissolved and a colour change from yellow to pale brown occurred. The reaction mixture was cooled and decanted into a separating funnel. The flask was washed out with EtOAc (*ca* 100 ml) and $H_2O$ (*ca* 100 ml). After thorough mixing, the organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 80 ml). The combined organic fractions were then washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent *in vacuo* the crude material was purified by column chromatography (5%→10%→20% EtOAc/hexane)

to afford the desired 2,2′,6,6′-tetramethoxy-1,1′-biphenyl **167** (1.41 g, 54%), in an unoptimised yield.[70] The product was characterised as described above.

### 5.2.5 Attempted synthesis of 2,2',6,6'-tetramethoxy[1,1′-biphenyl]-3,3′-dicarbaldehyde 166 using the Vilsmeier-Haack formylation

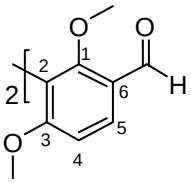



Into a two neck round bottom flask (dried, under Ar), fitted with a dropping funnel, was placed DMF (5.25 ml, 67.8 mmol, 10 equiv.) and the flask cooled by means of an ice bath. $POCl_3$ (6.32 ml, 67.8 mmol, 10 equiv.) was added using a syringe and the reaction was left to proceed for 10 min at 0 °C. $CHCl_3$ (20 ml) was then added to the newly formed reagent by means of the dropping funnel, and this solution was allowed to cool to 0 °C for 10 min. The dropping funnel was then charged with the tetramethoxybiphenyl **167** (1.86 g, 6.78 mmol) in dry $CHCl_3$ (30 ml) and this was added dropwise over a period of 5 min. The reaction was left to proceed and analysed by TLC. As the reaction showed no significant progress after several days ice cold $H_2O$ was carefully added (40 ml) and the reaction mixture was transferred to a beaker. $CH_2Cl_2$ was added (50 ml) followed by $H_2O$ (50 ml) and the two phase mixture was stirred vigorously. A 2 M NaOH solution was slowly added until the pH of the solution remained slightly basic. The organic phase was then separated and the aqueous phase extracted with $CH_2Cl_2$ (3 × 100 ml). The combined organic fractions were washed with brine (100 ml) and dried over anhydrous $MgSO_4$. Purification by column chromatography (40% EtOAc/hexane) afforded the monoformylated biphenyl **190** in 21% yield and the diformylated biphenyl **166** in 5% yield.



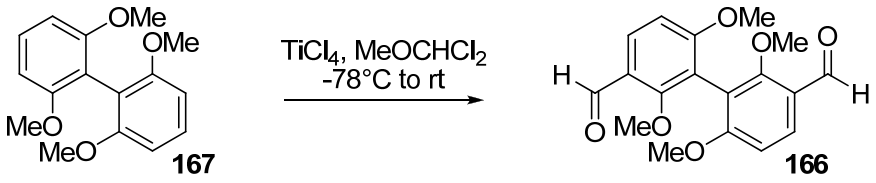

**$R_f$** = 0.53 (30% EtOAc/hexane). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 10.27 (1H, s, C*H*O); 7.90 (1H, d, *J* = 8.7 Hz, H6); 7.35 (1H, d, *J* = 8.3 Hz, H5'); 6.83 (1H, d, *J* = 8.8 Hz, H5); 6.67 (2H, d, *J* = 8.3 Hz, H4' and H6'); 3.78 (3H, s, OMe); 3.73 (6H, s, 2 × OMe); 3.53 (3H, s, OMe). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 189.2 (*C*HO),

163.8 (C1 or C3), 163.1 (C1 or C3), 158.2 (C1′ and C3'), 129.5 (C2 and C2'), 122.9 (C6), 117.6 (C5), 110.9 (C4), 107.1 (C5′), 104.3 (C4′ and C6′), 62.5 (OMe), 56.1 (OMe), 55.9 (2 × OMe).[70]



**$R_f$**= 0.36 (30% EtOAc/hexane). **Mp.** = 147-149 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 10.17 (2H, s, 2 × C*H*O); 7.91 (2H, d, *J* = 8.8 Hz, H4 and H4′); 6.83 (2H, d, *J* = 8.8 Hz, H5 and H5'); 3.76 (6H, s, 2 × OMe); 3.52 (3H, s, 2 × OMe). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 188.8 (2 × *C*HO), 163.5 (C2 and C2'), 162.7 (C6 and C6'), 130.6 (C5 and C5'), 123.1 (C3 and C3'), 116.4 (C1 and C1'), 107.1 (C4 and C4'), 63.0 (2 × OMe), 56.1 (2 × OMe). **IR** ($CHCl_3$): $\nu_{max}$($cm^{-1}$) = 1677 (Ar C=O), 1586, 1463 (ArC=C), 1248 (ArC-O). **HRMS**: Found $M^+$, 330.1093, $C_{18}H_{18}O_6$ requires *M* 330.1103 amu. (EI) 330 ($M^+$, 79%), 299 (100), 283 (16), 255 (28), 239 (66), 219 (17), 179 (28), 155 (10), 142 (9), 115 (10), 91 (5), 69 (19), 51 (5).[70]

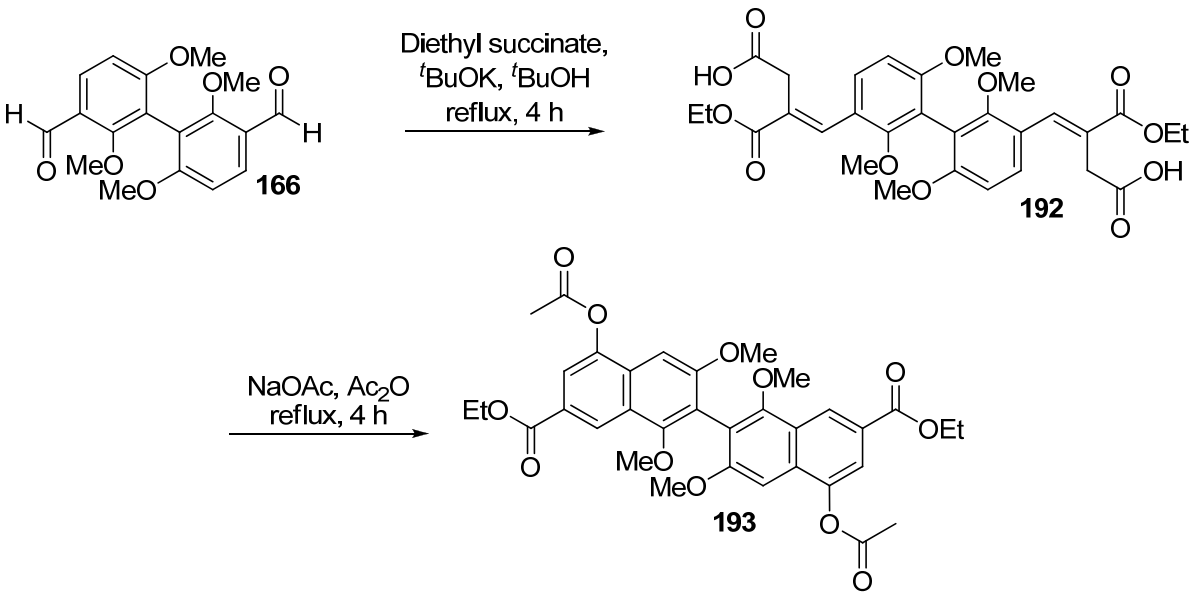
### 5.2.6 Synthesis of 2,2’,6,6’-tetramethoxy[1,1′-biphenyl]-3,3′-dicarbaldehyde 166 using the Rieche formylation




Into a two neck round bottom flask under Ar(g), fitted with a rubber septum, was added 2,2′,6,6′-tetramethoxy-1,1′-biphenyl **167** (0.70 g, 2.6 mmol) in dry $CH_2Cl_2$ (50 ml). To this solution was added $TiCl_4$ (1.12 ml, 1.93 g, 10.2 mmol, 4 equiv.) through the septum using a syringe. The solution immediately changed to an orange colour. The reaction mixture was then cooled down to −78 °C and $MeOCHCl_2$ (0.64 ml, 0.82 g, 7.1 mmol, 2.8 equiv.) was then added. The solution changed to a dark brown colour. Stirring at this temperature continued for 30 min. The resulting solution was then warmed up to 0 °C over 1 h and stirred at this temperature for an additional 15 min. The product mixture was then poured into a separating funnel containing crushed ice (*ca* 10 g) and aqueous conc. HCl (*ca* 8 ml) and shaken vigorously. The organic layer was then separated, washed with $H_2O$ (*ca* 50 ml)

and brine (*ca.* 50 ml). It was then dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by silica gel column chromatography (40% EtOAc/hexane) to give 2,2',6,6'-tetramethoxy[1,1′-biphenyl]-3,3′-dicarbaldehyde **166** as a white solid (0.80 g, 95%).[70] The diformylated product was isolated exclusively and characterised as described above.

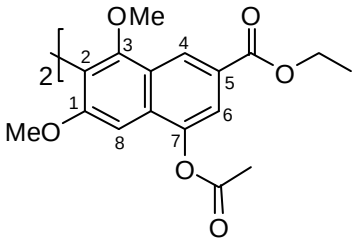
### 5.2.7 Synthesis of diethyl [4,4′-diacetoxy-6,6′,8,8′-tetramethoxy-7,7′-binaphthalene]-2,2′-dicarboxylate 193




In a two neck round bottom flask, fitted with a condenser, under Ar(g), 2,2',6,6'-tetramethoxy[1,1′-biphenyl]-3,3′-dicarbaldehyde **166** (1.53 g, 4.63 mmol) and diethyl succinate (2.31 ml, 2.42 g, 13.9 mmol, 3 equiv.) were dissolved in dry *t*-BuOH (20 ml). To this mixture was slowly added *t*-BuOK (1.56 g, 13.9 mmol, 3 equiv.). The resulting solution was heated under reflux for 2 h and then allowed to cool down to rt, poured into a separating funnel containing ice and adjusted to pH 3 with aqueous conc. HCl. The product was then extracted with EtOAc (3 × 50 ml). The combined organic extracts were then dried over anhydrous $MgSO_4$, filtered, and the solvent removed *in vacuo*. The resultant oil was not purified or characterised, but used immediately in the next step.

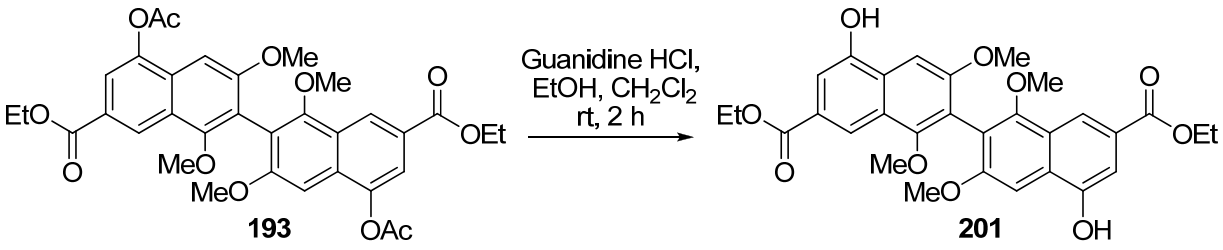
In a two neck round bottom flask, fitted with a condenser, under Ar(g), the Stobbe condensation product **192** from above was dissolved in $Ac_2O$ (80 ml). To this was added

anhydrous NaOAc (1.89 g, 23.2 mmol, 5 equiv.). The mixture was heated at 140 °C for 2 h and then allowed to cool. The $Ac_2O$ was removed *in vacuo*, $H_2O$ (*ca* 100 ml) was added, and the product extracted with $CH_2Cl_2$ (3 × 100 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by silica gel column chromatography (30% EtOAc/hexane) to yield diethyl [4,4′-diacetoxy-6,6′,8,8′-tetramethoxy-7,7′-binaphthalene]-2,2′-dicarboxylate **193** as a bright yellow solid (1.78 g, 60% over two steps).

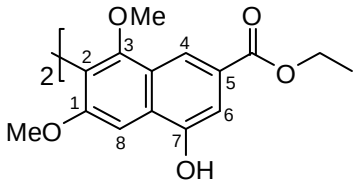



**$R_f$** = 0.17 (30% EtOAc/hexane). **Mp.** = 243-265 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 8.77 (2H, s, H8 and H8'); 7.87 (2H, s, H6 and H6'); 7.01 (2H, s, H4 and H4'); 4.43 (4H, q, *J* = 7.1 Hz, 2 × C*H*$_2$CH$_3$); 3.84 (6H, s, 2 × OMe); 3.64 (6H, s, 2 × OMe); 2.51 (6H, s, 2 × OAc) and 1.42 (6H, t, *J* = 7.1 Hz, 2 × CH$_2$C*H*$_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 169.4 (2 × OAc), 166.2 (2 × *C*O$_2$Et), 159.2 (2 × Ar*C*O), 156.5 (2 × Ar*C*O), 145.7 (2 × Ar*C*, C7), 130.9 (2 × Ar*C*), 125.2 (2 × Ar*C*), 124.7 (2 × Ar*C*), 123.9 (C8 and C8'), 118.9 (C6 and C6'), 117.8 (2 × Ar*C*), 94.9 (C4 and C4'), 61.9 (2 × OMe), 61.1 (2 × *C*H$_2$CH$_3$), 55.8 (2 × OMe), 21.0 (2 × OAc), 14.4 (2 × CH$_2$*C*H$_3$). **IR** ($CHCl_3$): $\nu_{max}$(cm$^{-1}$) =1770, 1716, (C=O), 1627, 1498, 1459 (ArC=C), 1253 (ArC-O), 1197 (alkyl CH). **HRMS**: Found $M^+$, 634.2038, $C_{34}H_{34}O_{12}$ requires *M* 634.2050 amu. (EI) 634 ($M^+$, 2%), 512 (32), 470 (27), 428 (73), 382 (5), 54 (26), 43 (18).[70]

### 5.2.8 Synthesis of diethyl (5,5'-dihydroxy-1,1',3,3'-tetramethoxy-2,2'-binaphthalene-7,7'-dicarboxylate) 201

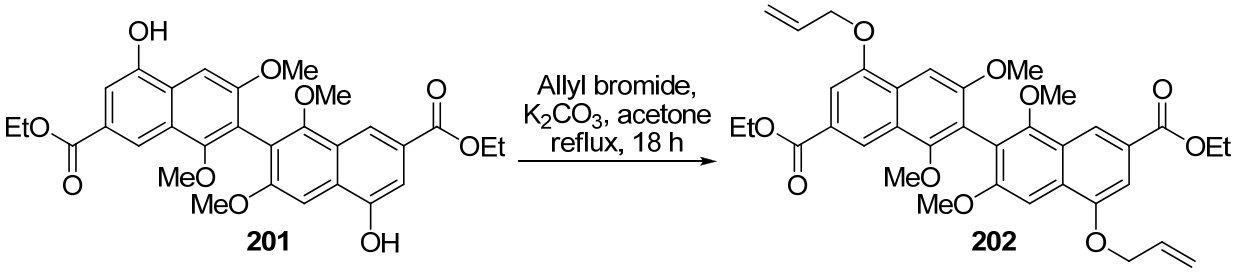



To a solution of guanidine HCl (0.93 g, 9.8 mmol, 2.2 equiv.) in dry EtOH (70 ml), stirring at rt under Ar(g) was added *t*-BuOK (1.1 g, 9.8 mmol, 2.2 equiv.) and the resulting suspension stirred for 30 min. To this mixture was added the diacetate ester **193** (2.8 g, 4.4 mmol) dissolved in $CH_2Cl_2$ (70 ml) and stirring was continued for 1.5 h. The reaction mixture was then poured into a beaker containing $H_2O$ (100 ml) and was adjusted to pH 4 with conc. HCl. The solution was then extracted with EtOAc (3 × 100 ml). The organic extracts were combined and dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography to yield **201** as a yellow solid (1.89 g, 78%).

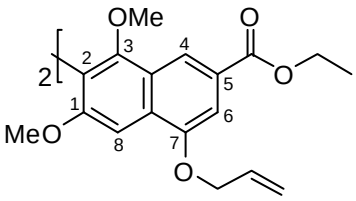



**$R_f$** = 0.33 (50% EtOAc/hexane). **Mp.** = 266-280 °C. **$^1$H NMR** (300 MHz, DMSO): $\delta_H$ = 10.51 (2H, s, 2 × OH); 8.15 (2H, br s, H8 and H8'); 7.45 (2H, d, *J* = 1.3 Hz, H6 and H6'); 7.42 (2H, s, H4 and H4'); 4.35 (4H, q, *J* = 7.0 Hz, 2 × C*H*$_2$CH$_3$); 3.81 (6H, s, 2 × OMe); 3.57 (6H, s, 2 × OMe) and 1.35 (6H, t, *J* = 7.0 Hz, 2 × CH$_2$C*H*$_3$). **$^{13}$C NMR** (75 MHz, DMSO): $\delta_C$ = 166.0 (2 × *C*O$_2$Et), 157.5 (2 × Ar*C*), 155.2 (2 × Ar*C*), 152.7 (2 × Ar*C*), 128.4 (2 × Ar*C*), 125.1 (2 × Ar*C*), 123.4 (2 × Ar*C*), 117.6 (2 × Ar*C*), 115.5 (2 × Ar*C*), 107.4 (2 × Ar*C*), 96.2 (C4 and C4'), 61.1 (2 × OMe), 60.5 (2 × *C*H$_2$CH$_3$), 55.7 (2 × OMe), 14.2 (2 × CH$_2$*C*H$_3$). **IR** ($CHCl_3$): $\nu_{max}$(cm$^{-1}$) = 3413 (O-H), 1640 (Ar C=O). **HRMS**: Found [M + Na]$^+$ 573.174,. $C_{30}H_{30}O_{10}Na$ requires *M* 573.1736 amu. (EI) 551 ($M^+$ + 1, 32%), 550 ($M^+$ 100), 505 (13), 504 (18), 275 (30) and (28).

### 5.2.9 Synthesis of (±)-diethyl 5,5'-*bis*(allyloxy)-1,1',3,3'-tetramethoxy-2,2'-binaphthalene-7,7'-dicarboxylate 202

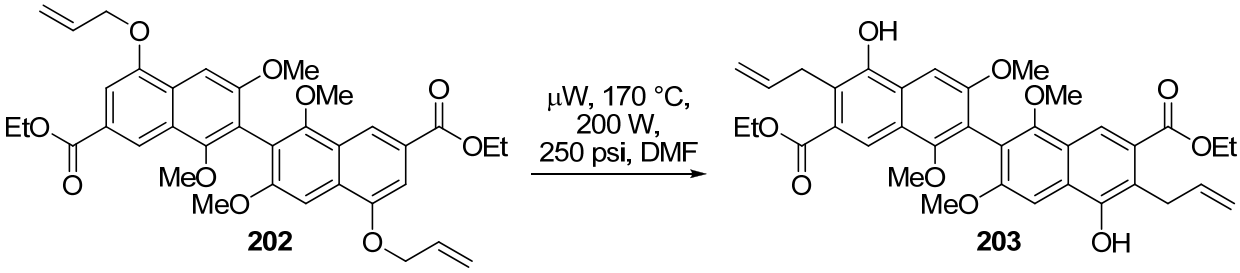



Allyl bromide (0.96 ml, 1.3 g, 11 mmol, 3 equiv.) and $K_2CO_3$ (1.53 g, 11.1 mmol, 3 equiv.) were added to a solution of the di-naphthol **201** (2.03 g, 3.69 mmol) in $Me_2CO$ (100 ml) in a round bottom flask fitted with a condenser. The mixture was stirred at reflux for 18 h. After this time it was allowed to cool to rt and filtered through celite. The $Me_2CO$ was then removed *in vacuo* and the light brown oil was purified using silica gel column chromatography (30% EtOAc/hexane) to yield the allylated product **202** as a light yellow solid (1.95 g, 84%).

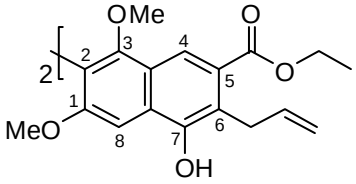



**$R_f$** = 0.30 (20% EtOAc/hexane). **Mp.** = 74-78 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 8.51 (2H, brd s, H8 and H8'); 7.54 (2H, s, H4 and H4'); 7.48 (2H, s, H6 and H6'); 6.23 (2H, m, 2 × $CH_2CH$=$CH_2$); 5.57 (2H, dd, *J*=17.3 Hz and 1.5 Hz, *trans*-$CH_2CH$=$CH_2$); 5.38 (2H, dd, *J* = 10.5 Hz and 1.3 Hz, 2 × *cis*-$CH_2CH$=$CH_2$); 4.84 (4H, br d, *J* = 5.2 Hz, 2 × $CH_2CH$=$CH_2$); 4.50-4.37 (4H, m, 2 × $CH_2CH_3$); 3.88 (6H, s, 2 × OMe); 3.64 (6H, s, 2 × OMe) and 1.43 (6H, t, *J* = 7.1 Hz, 2 × $CH_2CH_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 167.1 (2 × $CO_2$Et), 158.4 (2 × Ar*C*), 156.1 (2 × Ar*C*), 153.5 (2 × Ar*C*), 133.2 (2 × $CH_2CH$=$CH_2$), 129.7 (2 × Ar*C*), 125.3 (2 × Ar*C*), 124.0 (2 × Ar*C*), 118.8 (2 × $CH_2CH$=$CH_2$), 117.8 (2 × Ar*C*), 117.6 (C8 and C8'), 105.2 (C4 and C4'), 96.2 (C6 and C6'), 69.3 (2 × $CH_2CH$=$CH_2$), 61.7 (2 × OMe), 60.9 (2 × $CH_2CH_3$), 55.9 (2 × OMe), 14.4 (2 × $CH_2CH_3$). **IR** ($CHCl_3$): $\nu_{max}$($cm^{-1}$) = 1713 (ArC=O), 1622 (alkene C=C), 1495, 1461 (ArC=C), 1254 (ArCO). **HRMS**: Found $[M + Na]^+$ 653,236, $C_{36}H_{38}O_{10}Na$ requires *M* 653.2363 amu. (EI) 631 ($M^+$ + 1, 22%), 630 ($M^+$, 54), 590 (40), 589 (100), 561 (20), 548 (41), 315 (22) and 295 (26).

### 5.2.10 Synthesis of (±)-diethyl 6,6'-diallyl-5,5'-*bis*(hydroxy)-1,1',3,3'-tetramethoxy-2,2'-binaphthalene-7,7'-dicarboxylate 203

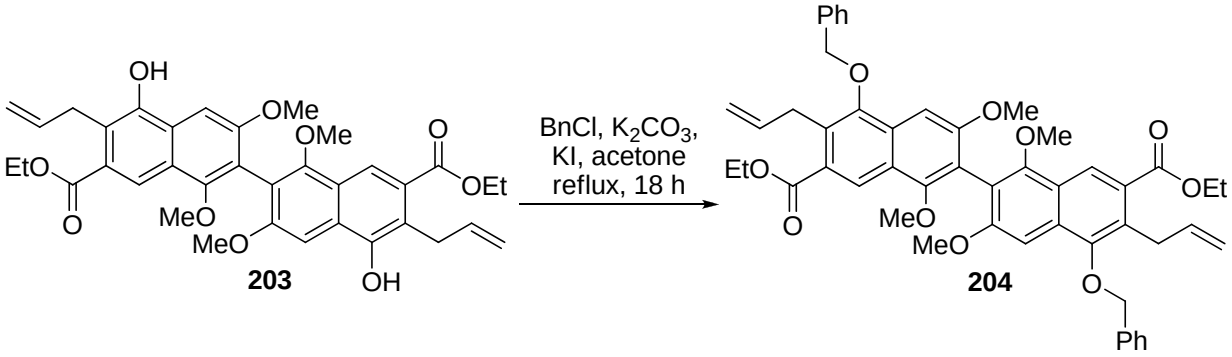



The allylated phenol **202** (1.92 g, 3.04 mmol) was dissolved in DMF (3 ml) and the solution transferred to a microwave vessel. The reaction mixture was then subjected to microwave radiation at a temperature of 170 °C and pressure of 250 psi with 200 W of power for a period of 25 min with stirring. The light yellow solution which changed to a dark brown colour was transferred to a separating funnel and washed with $H_2O$ (100 ml) and the organic product extracted with $CH_2Cl_2$ (2 × 20 ml). The extracts were dried over anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The dark brown viscous oil was purified by column chromatography (40% EtOAc/hexane) to yield **203** as a yellow foam (1.89 g, 98%).

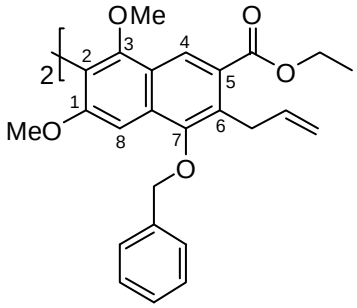



**$R_f$** = 0.63 (50% EtOAc/hexane). **Mp.** = 93-98 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 8.36 (2H, s, H8 and H8'); 7.41 (2H, s, H4 and H4'); 6.25-6.07 (2H, m, 2 × $CH_2CH$=$CH_2$); 5.84 (2H, s, 2 × O*H*); 5.25 (4H, m, 2 × $CH_2CH$=C$H_2$); 4.45-4.34 (4H, m, 2 × C$H_2CH_3$); 3.96 (4H, br d, *J* = 5.2 Hz, 2 × C$H_2CH$=$CH_2$); 3.86 (6H, s, 2 × OMe); 3.62 (6H, s, 2 × OMe) and 1.41 (6H, t, *J* = 7.1 Hz, 2 × $CH_2CH_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 168.2 (2 × *C*$O_2$Et), 158.4 (2 × Ar*C*), 155.7 (2 × Ar*C*), 150.1 (2 × Ar*C*), 136.4 (2 × $CH_2CH$=$CH_2$), 128.1 (2 × Ar*C*), 126.4 (2 × Ar*C*), 122.6 (2 × Ar*C*), 119.2 (C8 and C8'), 118.3 (2 × Ar*C*), 117.4 (2 × Ar*C*), 116.2 (2 × $CH_2CH$=$CH_2$), 95.6 (C4 and C4'), 61.6 (2 × $CH_2CH_3$), 60.9 (2 × OMe), 55.8 (2 × OMe), 31.8 (2 × $CH_2CH$=$CH_2$), 14.3 (2 × $CH_2CH_3$). **IR** ($CHCl_3$): $\nu_{max}$($cm^{-1}$) = 3420 (OH), 1713 (ArC=O), 1461 (ArC=C), 1238 (ArC-O). **HRMS:** Found $[M + Na]^+$ 653.235, $C_{36}H_{38}O_{10}Na$ requires *M* 653.2363 amu. (EI) 631 ($M^+$ + 1, 32%), 630 ($M^+$, 100), 585(8), 584 (10), 315 (17), 255 (30), 87 (62) and 55 (75).

### 5.2.11 Synthesis of (±)-diethyl 6,6'-diallyl-5,5'-*bis*(benzyloxy)-1,1',3,3'-tetramethoxy-2,2'-binaphthalene-7,7'-dicarboxylate 204



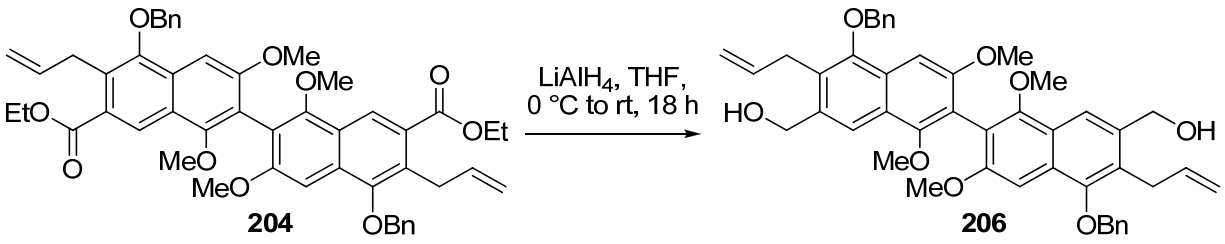

In a two neck round bottom flask fitted with a condenser was placed a solution of the phenol **203** (1.10 g, 1.75 mmol) in $Me_2CO$ (70 ml). To this yellow solution was added BnCl (0.40 ml, 0.46 g, 3.7 mmol, 2.1 equiv.), $K_2CO_3$ (0.51 g, 3.7 mmol, 2.1 equiv.) and KI (0.61 g, 3.7 mmol, 2.1 equiv.). The mixture was stirred under reflux for 18 h. After cooling to rt, the mixture was filtered through celite and the filtrate concentrated on a rotary evaporator. The resultant oil was purified by silica gel column chromatography (10% EtOAc/hexane) to produce the product **204** as a yellow foam (1.28 g, 90%).



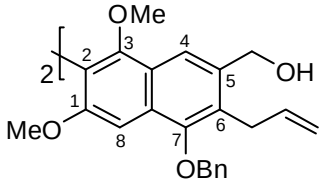

**$R_f$** = 0.63 (30% EtOAc/hexane). **Mp.** = 55-57 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 8.52 (2H, s, H8 and H8'); 7.60-7.58 (4H, m, 4 × ArH); 7.47-7.38 (8H, m, 6 ×Ar*H* and H4 and H4'); 6.18-6.03 (2H, m, 2 × $CH_2CH$=$CH_2$); 5.12-4.91 (8H, m, 2 × $CH_2CH$=C$H_2$ and 2 × C$H_2$Ph); 4.39 (4H, q, *J* = 6.3 Hz, 2 × C$H_2CH_3$); 4.07 (4H, br d, *J* = 5.6 Hz, 2 × C$H_2CH$=$CH_2$); 3.72 (6H, s, 2 × OMe); 3.62 (6H, s, 2 × OMe) and 1.41 (6H, t, *J* = 7.1 Hz, 2 × $CH_2CH_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 168.0 (2 × *C*$O_2$Et), 158.8 (2 × Ar*C*), 156.2 (2 × Ar*C*), 152.7 (2 × Ar*C*), 137.9 (2 × $CH_2CH$=$CH_2$), 137.6 (2 × Ar*C*), 131.7 (2 × Ar*C*), 129.4 (2 × Ar*C*), 128.7 (4 × Ar*C*H), 128.1 (2 × Ar*C*H), 127.6 (4 × Ar*C*H), 127.0 (2 × Ar*C*), 123.0 (2 × Ar*C*), 122.9 (2 × Ar*C*), 117.0 (C8 and C8'), 115.0 (2 × $CH_2CH$=*C*$H_2$), 96.2 (C4 and C4'), 76.1 (2 × *C*$H_2$Ph), 61.7 (2 × *C*$H_2CH_3$), 60.9 (2 × OMe), 55.7 (2 × OMe), 31.0 (2 × *C*$H_2CH$=$CH_2$) and 14.3 (2 × $CH_2$*C*$H_3$). **IR** ($CHCl_3$): $\nu_{max}$($cm^{-1}$) = 2981 (terminal alkene CH), 1736 (ArC=O), 1456 (ArC=C), 753, 700 (monosub. benzene). **HRMS:** Found

$[M + H]^+$ 811.347, $C_{50}H_{51}O_{10}$ requires *M* 811.3481 amu. (EI) 8180 ($M^+$, 3%), 721 (2), 720 (5), 719 (13), 555 (4), 92 (5), 91 (100) and 65 (6).

### 5.2.12 Synthesis of (±)-[6,6'-diallyl-5,5'-*bis*(benzyloxy)-1,1',3,3'-tetramethoxy-2,2'-binaphthalene-7,7'-diyl]dimethanol 206



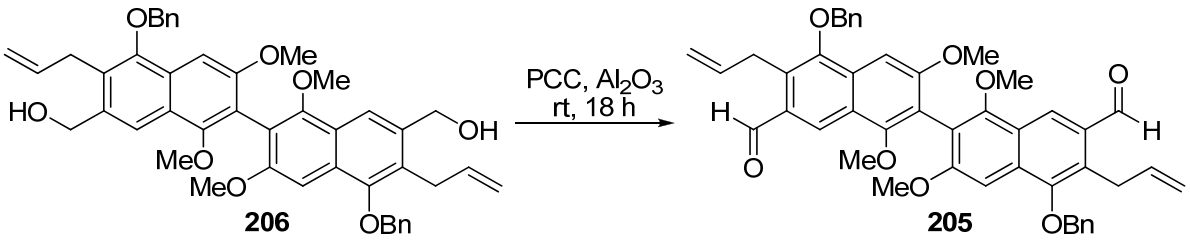

The ester **204** (0.70 g, 0.86 mmol) dissolved in dry THF (150 ml) was placed into a flame-dried two neck round bottom flask under Ar(g). The solution was cooled to 0 °C by means of an ice bath and once cooled $LiAlH_4$ (0.13 g, 3.5 mmol, 4 equiv.) was added portionwise resulting in effervescence of the solution. The reaction mixture was analysed by TLC at 1 h intervals for the first few hours and still showed starting material present. It was left to proceed at rt. After 18 h the TLC revealed that the reaction was still not complete however at this stage it was worked up by recooling to the mixture to 0 °C and adding $H_2O$ dropwise (approx. 10 ml) until the evolution of gas had stopped. The emulsion formed was broken by adding a 10% solution of aqueous HCl (approx. 5 ml). The mixture was transferred to a separating funnel and the product was extracted using EtOAc (2 × 25 ml) and $CH_2Cl_2$ (2 × 25 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered through celite and the solvent finally removed *in vacuo*. The crude oil was purified by silica gel column chromatography (50% EtOAc/hexane) to give the benzylic alcohol **206** (0.26 g, 42%).



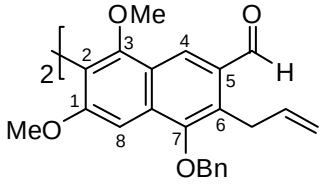

**$R_f$** = 0.40 (50% EtOAc/hexane). **Mp.** = 86-91 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.96 (2H, s, H8 and H8'); 7.60-7.56 (4H, m, 2 × Ar*H*); 7.47-7.30 (6H, m, 6 × Ar*H*); 7.26 (2H, s, H4 and H4'); 6.20-6.08 (2H, m, 2 × $CH_2CH$=$CH_2$); 5.14-4.99 (4H, m, 2 × $CH_2CH$=C$H_2$); 5.10 (4H, s, 2 × C$H_2$Ph); 4.84 (4H, s, 2 × C$H_2$OH); 3.86-3.69 (4H, br m, 2 × C$H_2$CH=$CH_2$); 3.70 (6H, s, 2 × OMe); 3.61 (6H, s, 2 × OMe) and 1.84 (2H, s,

2 × O*H*). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 157.2 (2 × Ar*C*), 155.4 (2 × Ar*C*), 152.6 (2 × Ar*C*), 137.8 (2 × Ar*C*), 137.7 (2 × $CH_2$*C*H=$CH_2$), 135.7 (2 × Ar*C*), 129.4 (2 × Ar*C*), 128.6 (4 × Ar*C*H), 128.0 (2 × Ar*C*H), 127.5 (4 × Ar*C*H), 124.0 (2 × Ar*C*), 118.7 (2 × $CH_2$CH=*C*$H_2$), 117.0 (2 × Ar*C*), 115.5 (C8 and C8'), 96.3 (C4 and C4'), 76.0 (2 × *C*$H_2$Ph), 64.1 (2 × *C*$H_2$OH), 61.4 (2 × OMe) and 55.6 (2 × OMe) and 30.4 (2 × *C*$H_2$CH=$CH_2$). **IR** ($CHCl_3$): $\nu_{max}$($cm^{-1}$) = 3417 (OH), 1600, 1496, 1455 (ArC=C), 1094 (primary alcohol C-O), 737, 699. **HRMS:** Found $[M + H]^+$ 727.327, $C_{46}H_{47}O_8$ requires *M* 727.3271 amu. (EI) 726 ($M^+$, 2%), 637 (2), 636 (7), 635 (15), 92 (10), 91 (100) and 65 (12).

### 5.2.13 Synthesis of (±)-6,6'-diallyl-5,5'-*bis*(benzyloxy)-1,1',3,3'-tetramethoxy-2,2'-binaphthalene-7,7'-dicarbaldehyde 205



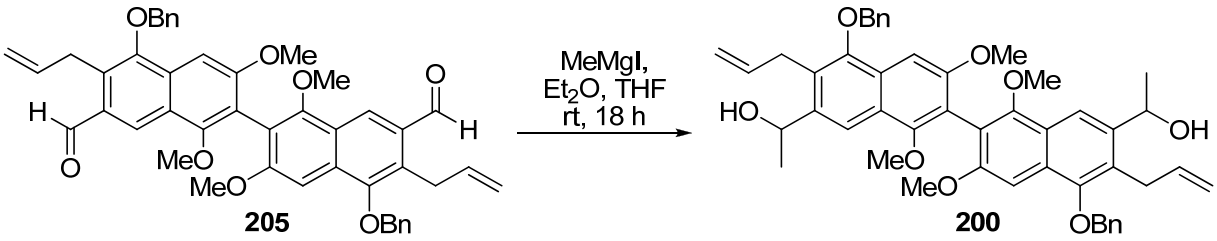

PCC (0.81 g, 3.7 mmol, 4 equiv.) was dissolved in MeCN (20 ml) and dried onto neutral $Al_2O_3$ (8 g) using a rotary evaporator. This bright orange solid was then added to a solution of the benzylic alcohol **206** (0.68 g, 0.94 mmol) dissolved in $CH_2Cl_2$ (50 ml). The now dark reaction mixture was allowed to stir at rt for 18 h. This was followed by filtration of the mixture through celite and concentration of the filtrate on a rotary evaporator. The crude oil was purified by silica gel column chromatography (20% EtOAc/hexane) to yield the aldehyde **205** (0.61 g, 90%).



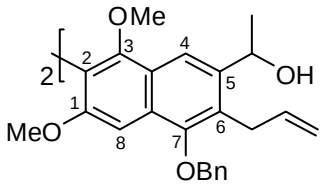

**$R_f$** = 0.50 (30% EtOAc/hexane). **Mp.** = 67-71 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 10.24 (2H, s, 2 × C*H*O); 8.47 (2H, s, H8 and H8'); 7.60-7.57 (4H, m, 4 × Ar*H*); 7.48-7.39 (6H, m, 6 × Ar*H*); 7.28 (2H, s, H4 and H4'); 6.24-6.11 (2H, m, 2 × $CH_2$C*H*=$CH_2$); 5.15-4.98 (4H, m, 2 × $CH_2$CH=C$H_2$); 5.11 (4H, s, 2 × C$H_2$Ph); 4.12

(4H, br d, $J$ = 5.5 Hz, 2 × C$H_2$CH=C$H_2$); 3.73 (6H, s, 2 × OMe) and 3.66 (6H, s, 2 × OMe). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 192.4 (2 × *C*HO), 159.8 (2 × Ar*C*), 156.8 (2 × Ar*C*), 152.9 (2 × Ar*C*), 137.6 (2 × C), 137.4 (2 × C), 133.1 (2 × C), 131.0 (2 × C), 129.2 (4 × Ar*C*H), 128.7 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 127.6 (4 × Ar*C*H), 123.3 (2 × C), 117.0 (2 × C), 115.7 (C8 and C8'), 96.6 (C4 and C4'), 76.3 (2 × *C*$H_2$Ph), 61.9 (2 × OMe), 55.8 (2 × OMe) and 29.7 (2 × *C*$H_2$CH=C$H_2$); one carbon signal not observed. **IR** ($CHCl_3$): $\nu_{max}$($cm^{-1}$) = 1691 (C=O), 1614, 1455 (ArC=C), 1257 (ArC-O), 751, 699 (monosub.benzene). **HRMS:** Found $[M + H]^+$ 723,295. $C_{46}H_{43}O_8$ requires *M* 723.2958 amu. (EI) 722 ($M^+$, 2%), 633 (4), 632 (10), 631 (22), 92 (7), 91 (100)and 65 (12).

### 5.2.14 Synthesis of (±)-1,1'-[6,6'-diallyl-5,5'-*bis*(benzyloxy)-1,1',3,3'-tetramethoxy-2,2'-binaphthalene-7,7'-diyl]diethanol 200

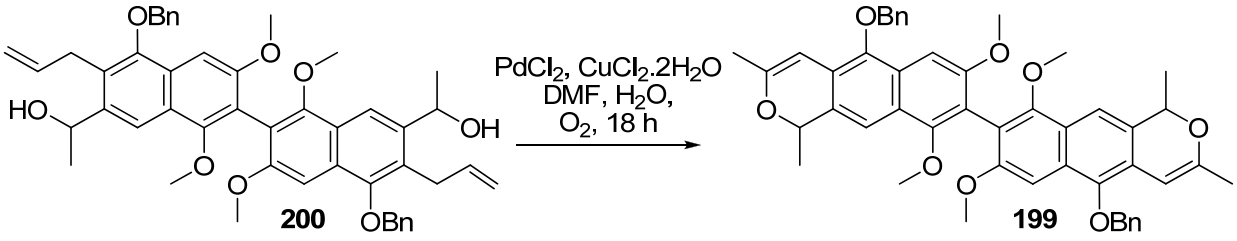



Into a flame-dried two neck round bottom flask fitted with a condenser, under Ar(g) was placed oven dried Mg turnings (0.034 g, 1.4 mmol, 3.2 equiv.) and dry $Et_2O$ (10 ml). To this suspension was added MeI (0.082 ml, 0.19 g, 1.3 mmol, 3 equiv.). The reaction mixture immediately became cloudy. It was slowly stirred to allow the formation of the Grignard reagent. Once most the Mg metal had reacted, the aldehyde **205** (0.32 g, 0.44 mmol) dissolved in dry THF (10 ml) was added dropwise to the cloudy reaction mixture. The now yellow solution was allowed to stir at rt under Ar(g) for a further 18 h. At this point it had become milky orange in colour. $H_2O$ (~5 ml) was carefully added to the reaction to quench the excess of Grignard reagent. The mixture was then transferred to a separating funnel and the organic product extracted with EtOAc (3 × 50 ml) and $CH_2Cl_2$ (3 × 50 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$ and filtered through celite. The solvent was removed *in vacuo* and the yellow oil residue was purified by silica gel column chromatography (30% EtOAc/hexane) to give the secondary alcohol **200** (0.26 g, 79%).



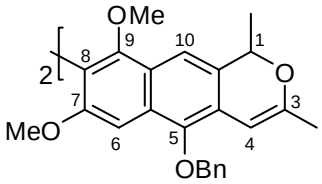

**$R_f$** = 0.33 and 0.27 (two diastereomers) (40% EtOAc/hexane). **Mp.** = 85-90 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 8.14 (2H, s, H8 and H8'); 7.60-7.24 (10H, m, 2 × Ph); 7.25 (2H, s, H4 and H4'); 6.22-6.09 (2H, m, 2 × $CH_2CH$=$CH_2$); 5.25 (2H, q, $J$ = 6.1 Hz, 2 × $CH_3$(C*H*)OH); 5.12-4.97 (8H, m, 2 × $CH_2CH$=C$H_2$ and 2 × $CH_2$Ph, overlapping signals); 3.92-3.79 (2H, m, 2 × C$H_2$CH=$CH_2$); 3.71 (6H, s, 2 × OMe); 3.63 and 3.62 (6H, s, 2 × OMe); 1.88 (1H, s, 2 × OH) and 1.60 (6H, d, $J$ = 6.2 Hz, 2 × C$H_3$(CH)OH). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 157.1 (2 × Ar*C*), 155.4 (2 × Ar*C*), 152.3 (2 × Ar*C*), 140.6 (2 × Ar*C*), 137.9 (2 × C), 137.8 (2 × C), 137.8 (2 × C), 128.9 (2 × C), 128.6 (4 × Ar*C*H), 128.0 (2 × Ar*C*H), 127.5 (4 × Ar*C*H), 127.1 (2 × C), 124.2 (2 × C), 117.0 (2 × C), 115.5 (C8 and C8'), 96.1 (C4 and C4'), 75.9 (2 × *C*$H_2$Ph), 66.7 (2 × $CH_3$(*C*H)OH), 61.4 (2 × OMe), 55.6 (2 × OMe), 30.2 (2 × *C*$H_2CH$=$CH_2$) and 24.5 (2 × *C*$H_3$(CH)OH). **IR** ($CHCl_3$): $\nu_{max}$($cm^{-1}$) = 3415 (OH), 1627, 1596, 1496, 1455 (ArC=C), 1096 (secondary alcohol C-O), 738, 699 (monosub. benzene). **HRMS:** Found $[M + Na]^+$ 777.340. $C_{48}H_{50}O_8Na$ requires *M* 777.3403 amu. (EI) 754 ($M^+$, 1%), 665 (2), 664 (6), 663 (11), 92 (8), 91 (100) and 65 (10).

### 5.2.15 Synthesis of (±)-5,5'-*bis*(benzyloxy)-7,7',9,9'-tetramethoxy-1,1',3,3'-tetramethyl-1*H*,1'*H*-8,8'-bibenzo[*g*]isochromene 199



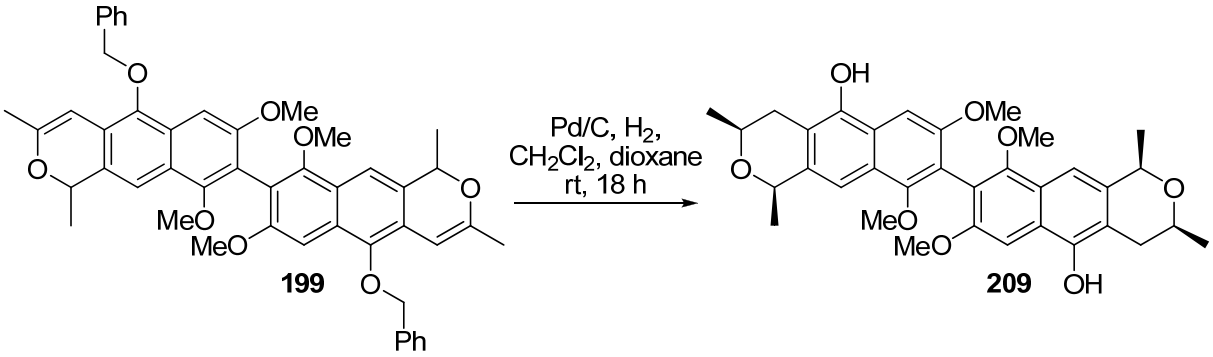

To a solution of the secondary alcohol **200** (0.06 g, 0.08 mmol) in DMF (5 ml), stirred at rt under $O_2$(g) (balloon) in a two neck round bottom flask, was added $CuCl_2.2H_2O$ (0.014 g, 0.080 mmol, 1 equiv.) and $PdCl_2$ (1.4 mg, 8.1 × $10^{-3}$ mmol, 10 mol%) in $H_2O$ (5 ml). The resultant suspension slowly changed from light yellow to dark orange in colour and was left to stir at rt for 18 h. Work-up of the reaction was accomplished by adding a 10% solution of aqueous HCl (10 ml) and the mixture was transferred to separating funnel. The

organic product was extracted with EtOAc (3 × 30 ml) and $CH_2Cl_2$ (1 × 30 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The crude yellow residue was purified by silica gel column chromatography (30% EtOAc/hexane) to yield the benzoisochromene **199** (0.048 g, 78%).

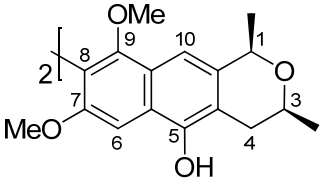



**$R_f$** = 0.67 (30% EtOAc/hexane). **Mp.** = 87-90 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.60-7.57 and 7.46-7.35 (12H, m, overlapping signals H6 and H 6'and 2 × Ph); 7.21 (2H, s, H10 and H10'); 6.05 (2H, s, H4 and H4'); 5.36-5.28 (2H, m, H1 and H1'); 5.11 (2H, d, *J* = 11.8 Hz, 2 × one of C*H*$_2$Ph); 5.06 (2H, d, *J* = 11.8 Hz, 2 × one of C*H*$_2$Ph); 3.71 (6H, s, 2 × OMe); 3.56 and 3.54 (6H, 2 × s, 2 × OMe); 2.00 (6H, s, 3-Me and 3'-Me); 1.70 (6H, d, *J* = 6.5 Hz, 1-Me and 1'-Me). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 157.1 (2 × C), 155.4 and 154.6 (2 × C), 154.4 (2 × C), 145.7 (2 × C), 137.9 (2 × C), 130.0 (2 × C), 129.5 (2 × C), 128.6 (2 × Ar*C*H), 128.0 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 127.8 (2 × Ar*C*H), 123.4 (2 × C), 121.6 and 121.5 (2 × C), 116.1 and 116.0 (2 × C), 113.2 and 113.1 (C10 and C10'), 96.1 (C6 and C6'), 95.9 and 95.8 (C4 and C4'), 75.7 (C5 and C5'), 74.3 and 74.2 (C1 and C1'), 61.3 and 61.2 (2 × OMe), 55.7 (2 × OMe), 20.5 (1-Me and 1'-Me), 20.0 (3-Me and 3'-Me). Some assignments were confirmed using CH correlation spectra. **IR** ($CHCl_3$): $\nu_{max}$($cm^{-1}$) = 1599, 1496 and 1455 (Ar C=C), 1128 (Ar C-O). **HRMS:** Found $[M + Na]^+$ 773.309. $C_{48}H_{46}O_8Na$ requires *M* 773.3090 amu. (EI) 750 ($M^+$, 2%), 661 (5), 660 (13), 659 (22), 571 (3), 570 (9), 569 (10), 285 (7), 289 (18), 92 (14), 91 (100) and 65 (19).

### 5.2.16 Synthesis of (±)-7,7',9,9'-tetramethoxy-*cis*-1,3-*cis*-1',3'-tetramethyl-3,3',4,4'-tetrahydro-1*H*,1'*H*-8,8'-bibenzo[*g*]isochromene-5,5'-diol 209 (mixture of diastereomers)



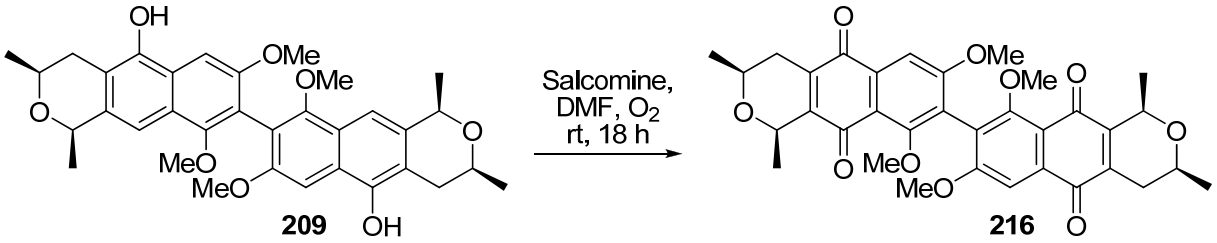

To a solution of the benzoisochromene **199** (0.16 g, 0.021 mmol) in a 3:1 $CH_2Cl_2$/dioxane mixture (40 ml), stirred at rt under $H_2$(g) (balloon) was added 10% w/w Pd/C (0.016 g) and stirring was continued for 18 h. The reaction mixture was then filtered through celite, the filtrate concentrated on a rotary evaporator and the resultant yellow oil purified by column chromatography (40% EtOAc/hexane) to give the unprotected benzoisochromane **209** (0.12 g, 100%) as a flaky off white solid.



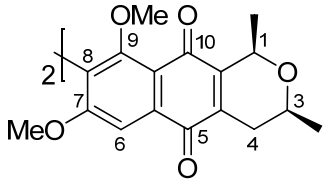

**$R_f$** = 0.30 (50% EtOAc/hexane). **Mp.** = 212-222 °C. **$^1$H NMR** (300 MHz, $CDCl_3$ + 4 drops DMSO-$d_6$): $\delta_H$ = 8.54 (2H, br s, 2 × O*H*); 7.46 (2H, s, H10 and H10'); 7.39 and 7.37 (2H, 2 × br s, H6 and H6'); 5.00-4.93 (2H, m, H1 and H1'); 3.89-3.83 (2H, m, H3 and H3'); 3.81, 3.80 and 3.80 (6H, 3 × s, 2 × OMe); 3.57, 3.54 and 3.53 (6H, 4 × s, 2 × OMe); 3.04 (2H, dd, *J* = 16.5 Hz and 2.5 Hz, H4$_\alpha$ and H4$_\alpha$'); 2.61 (2H, dd, *J* = 16.5 Hz and 11.3 Hz, H4$_\beta$ and H4$_\beta$'); 1.62 (6H, d, *J* = 6.3 Hz, 1-Me and 1'-Me); 1.42 (6H, d, *J* = 6.1 Hz, 3-Me and 3'-Me). **$^{13}$C NMR** (75 MHz, $CDCl_3$ + 4 drops DMSO-$d_6$): $\delta_C$ = 155.7 (2 × *C*), 154.3, 154.2 and 153.1 (2 × *C*), 147.9 and 147.8 (C5 and C5′), 135.5 and 135.4 (2 × *C*), 124.4, (2 × *C*), 122.8 and 122.7 (2 × *C*), 116.6 and 116.7 (2 × *C* and C10 and C10′), 109.0, 108.9 and 108.8 (2 × *C*), 95.5 (C6 and C6′), 73.3 and 73.3 (C1 and C1′), 70.2 (C3 and C3′), 60.6 and 60.7 (2 × C), 60.5 (2 × OMe), 55.5 (2 × OMe), 31.5 (C4 and C4′), 21.9 (3-Me and 3′-Me), 21.7 (1-Me and 1′-Me). **IR** ($CHCl_3$): $\nu_{max}$(cm$^{-1}$) = 3424 (O-H), 1601, 1495 and 1457 (Ar C=C). **HRMS:** Found $[M + Na]^+$ 597.247. $C_{34}H_{38}O_8Na$ requires

*M* 597.2465 amu (EI) 576 ($M^+$ + 2, 12%), 574 ($M^+$ + 1, 37), 574 ($M^+$, 100), 560 (7), 559 (32), 558 (93), 531 (4), 530 (11), 529 (17), 272 (37) and 258 (52).

### 5.2.17 Synthesis of (±)-7,7',9,9'-tetramethoxy- *cis*-1,3-*cis*-1',3'-tetramethyl-3,3',4,4',6,9-hexahydro-1*H*, 1'*H*-8,8'-bibenzo[*g*]isochromene-5,5',10,10'-tetrone 216



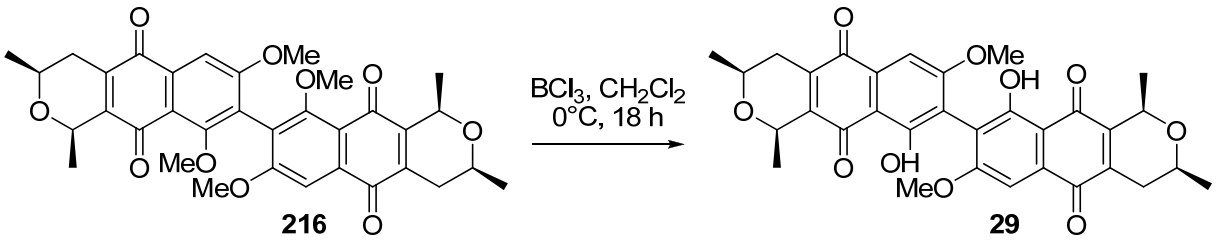

To a solution of the benzoisochromane **209** (0.10 g, 0.17 mmol) in DMF (10 ml), stirred at rt under an $O_2$(g) atmosphere (balloon) was added the salcomine complex *N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II) hydrate (0.062 g, 0.19 mmol, 1.1 equiv.). Stirring was continued at rt for 18 h. The reaction mixture was then poured into a beaker containing ice $H_2O$ (100 ml) and was adjusted to pH 3 by the dropwise addition of conc. HCl. This mixture was transferred to a separating funnel and the organic product extracted with $CH_2Cl_2$ (3 × 50 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered through celite and the product purified by silica gel column chromatography (40% EtOAc/hexane) to yield the quinone **216** (0.54 g, 51%).



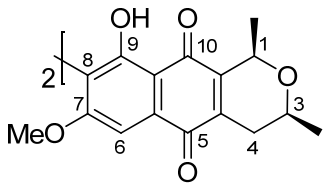

**$R_f$** = 0.73 (50% EtOAc/hexane). **Mp.** = 174-177 °C, darkens above 132 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.53 (2H, s, H6 and H6'); 4.9-4.82 (2H, m, H1 and H1'); 3.87 (6H, s, 2 × OMe); 3.64, 3.63, 3.62 and 3.61, (8H, 4 × s and overlapping m, 2 × OMe and H3 and H3'); 2.78 (2H, br d, *J* = 18.4 Hz, $H4_\alpha$ and $H4_\alpha$'); 2.22 (2H, ddd, *J* = 18.5 Hz, 10.3 Hz and 3.2 Hz, $H4_\beta$ and $H4_\beta$'); 1.54 (6H, d, *J* = 6.8 Hz, 1-Me and 1'-Me); 1.38 (6H, d, *J* = 6.0 Hz, 3-Me and 3'-Me). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 183.7 (2 × C=O), 182.7 (2 × C=O), 161.7, 161.6, 161.5 and 161.4, (C7 and C7')[a], 159.7, 159.6, 159.5 and 159.4 (C9 and C9')[a], 148.7 and 148.6 (C10a and C10a'), 140.0, 139.9 and 139.8, (C4a and C4a'), 135.3 and 135.2 (C5a and C5a'), 123.5, 123.4 and 123.3 (C8 and C8'),

119.1, 118.9, 118.8 and 118.7 (C9a and C9a'), 104.7 (C6 and C6'), 70.2 (C1 and C1'), 68.7 (C3 and C3'), 61.9, 61.8 and 61.7 (2 ×OMe), 56.3(×2) (2 × OMe), 30.0 (C4 and C4'), 21.2 (1-Me and 1'-Me), 20.9, 20.8 and 20.7 (3-Me and 3'-Me), assignments with the same superscript may be interchanged. **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1659 and 1573 (C=O). **HRMS:** Found $[M + Na]^+$, 625.205. $C_{34}H_{34}O_{10}Na$ requires *M* 625.2050 amu (EI) 604 ($M^+$ + 2, 12%), 603 ($M^+$ + 1, 33), 602 ($M^+$ 100), 544 (13), 543 (34), 497 (7), 469 (9), 286 (18), 279 (25), 264 (27) and 257 (37).

### 5.2.18 Synthesis of (±)-9,9'-dihydroxy-7,7'-dimethoxy- *cis*-1,3-*cis*-1',3'-tetramethyl-3,3',4,4',6,9-hexahydro-1*H*,1'*H*-8,8'-bibenzo[*g*]isochromene-5,5',10,10'-tetrone 3 (cardinalin 3) 29



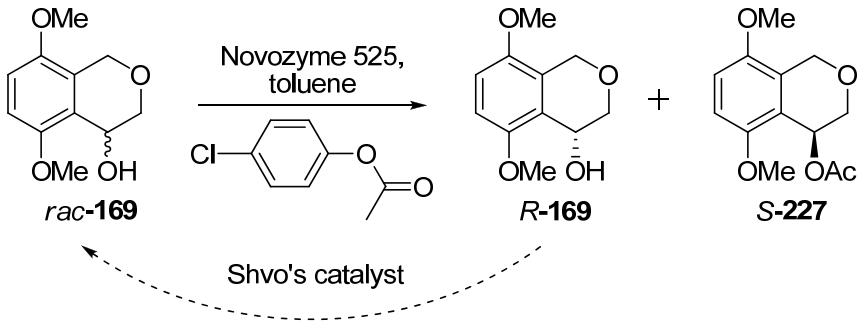

In a flame-dried two neck round bottom flask under Ar(g), a solution of the dimethoxy quinone **206** (40 mg, 0.066 mmol) in dry $CH_2Cl_2$ (10 ml) was cooled to 0 °C and to this was added the $BCl_3$ solution (0.27 ml, 1.00 M in $CH_2Cl_2$, 4 equiv.). The reaction mixture immediately changed from a light yellow colour to a dark red colour. Analysis of the reaction mixture by TLC after 15 min showed a new yellow spot at a slightly higher $R_f$ and the absence of the starting material. The reaction still at 0 °C was quenched with $H_2O$, transferred to a separating funnel and the organic product extracted with $CH_2Cl_2$ (3 × 20 ml). The solvent was dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was dried over silica and purified by silica gel column chromatography (30% EtOAc/hexane) to yield racemic cardinalin 3 **29** as a yellow powder (24 mg, 64%).



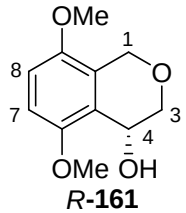

**$R_f$** = 0.83 (50% EtOAc/hexane). **Mp.** = 225-250 °C; (lit[20] 213-220 °C, S atropisomer). The product was obtained as a mixture of diastereomers. Assignments with the same chemical shift as the natural product were assigned according to the axial chirality as the natural product (*S*). **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 12.352 and 12.349 [2H, s, (*S*)-2 ×OH]; 12.31 and 12.30 [2H, s, 2 × OH]; 7.331 [2H, s, (*S*)-H6 and H6′]; 7.329 [2H, s, H6 and H6′]; 4.95-4.80 (2H, m, H1 and H1′); 3.91 [6H, s, (*S*)-2 × OMe]; 3.90 (6H, s, 2 × OMe); 3.67-3.47 (2H, m, H3 and H3′); 2.76 (2H, dt, *J* = 18.7 Hz and 2.4 Hz, $H4_\alpha$ and $H4_\alpha$′); 2.26 (2H, ddd, *J* = 18.6 Hz, 10.0 Hz and 3.9 Hz, $H4_\beta$ and $H4_\beta$′); 1.58 [6H, d, *J* = 6.5 Hz, (*S*)-1-Me and 1′Me); 1.57 (6H, d, *J* = 6.5 Hz, 1-Me and 1′-Me); 1.37 (6H, d, *J* = 6.1 Hz, 3-Me and 3′-Me). **$^{13}$C NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 187.9 (2 × C=O), 183.2 (2 × C=O), 163.2 (C7 and C7′), 161.0, 161.0 and 160.9 (C9 and C9′), 146.7 and 146.7 (C10a and C10a′), 143.1 and 143.0 (C4a and C4a′), 133.2 (C5a and C5a′), 114.5 (C8 and C8′), 110.2 (C9a and C9a′), 102.7 (C6 and C6′), 69.8 (C1 and C1′), 68.7 (C3 and C3′), 56.6 and 56,5 (2 × OMe), 30.6 and 30.6 (C4 and C4′), 21.3 (1-Me and 1′-Me) and 21.2 (3-Me and 3′-Me). **IR** ($CHCl_3$): $\nu_{max}$($cm^{-1}$) = 3450 (O-H), 1636 and 1603 (C=O). **HRMS:** Found [$M^+$ + Na], 597.174. $C_{32}H_{30}O_{10}$ requires *M* 597.1736 amu. (EI) 576 ($M^+$ + 2, 5%), 575 ($M^+$ + 1, 27), 574 ($M^+$, 100), 530 (12), 515 (35), 271 (35), 244 (37), 243 (91) and 98 (87).

## 5.3 Experimental Work Pertaining to the Synthesis of Chromium tricarbonyl Complexes

### 5.3.1 Attempted dynamic kinetic resolution of 5,8-dimethoxyisochroman-4-ol 169



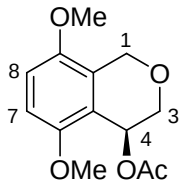

To a stirred solution of the racemic 5,8-dimethoxyisochroman-4-ol **169** (0.050 g, 0.23 mmol) and the acetylating agent 4-chlorophenyl acetate (0.12 g, 0.72 mmol, 3 equiv.) in toluene (2 ml) was added the lipase enzyme Novozyme 525 (6.0 mg). To this was added the ruthenium racemisation catalyst (5.2 mg, $4.7\times10^{-6}$ mol, 0.02 equiv.). The reaction mixture was allowed to stir at rt for 36 h. TLC analysis still showed the presence of the unreacted alcohol. The reaction mixture was then extracted with EtOAc (3 × 80 ml) to isolate the organic products. The organic layers were combined and dried over anhydrous $MgSO_4$, filtered through celite and the solvent removed *in vacuo*. The crude material was purified by silica gel column chromatography (30% EtOAc/hexane) to give the (*S*)-5,8-dimethoxy-3,4-dihydro-1*H*-isochromen-4-yl acetate **227** (18 mg, 31% ) and the unreacted (*R*)-5,8-dimethoxy-isochroman-4-ol **169** (18 mg, 36%).



*R*-**161**

**$R_f$** = 0.34 (50% EtOAc/hexane). **Mp.** = 96-98 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 6.72 (2H, m, H7 and H8, overlapping signals); 4.85 (1H, d, *J* = 16.0 Hz, $H1_a$); 4.79 (1H, m, H4); 4.51 (1H, d, *J* = 16.0 Hz, $H1_b$); 4.08 (1H, dd, *J* = 12.0 Hz and 2.8 Hz, $H3_a$), 3.85 (3H, s, $OCH_3$), 3.78 (1H, dd, *J* = 12.0 Hz and 3.1 Hz, $H3_b$), 3.76 (3H, s, $OCH_3$), 2.88 (1H, s, O*H*). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 151.5 (Ar*C*-O), 149.2 (Ar*C*-O), 125.1 (Ar*C*), 124.7 (Ar*C*), 109.1 (Ar*C*H), 108.3 (Ar*C*H), 70.3 (C3), 64.3 (C1), 60.3 (C4), 55.7 ($OCH_3$), 55.5 ($OCH_3$). **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 3447 (w, br, OH), 1606 (s, C=C). **HRMS**: Found $M^+$ 210.0904, $C_{11}H_{14}O_4$

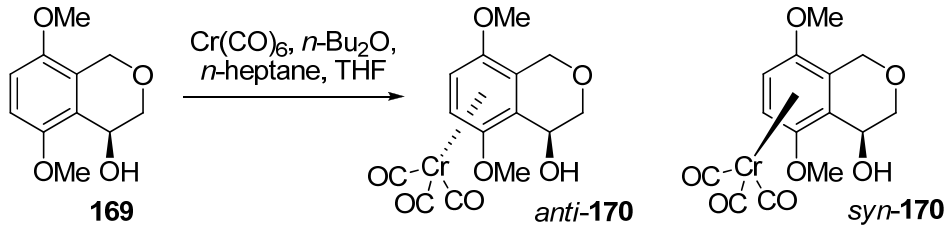
requires *M* 210.0892 amu. (EI) 210 ($M^+$, 94%), 180 (100), 165 (49), 151 (7), 134 (9), 120 (10), 107 (7), 91 (12), 77 (13), 65 (7), 51 (8).



*S*-**214**

**$R_f$** = 0.80 (50% EtOAc/hexane). **Mp.** = 119-121 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 6.79 and 6.72 (each 1H, d, *J* = 8.9 Hz, H7 and H8); 5.93 (1H, m, H4); 4.83 (1H, d, *J* = 16.1 Hz, $H1_a$); 4.48 (1H, d, *J* = 16.1 Hz, $H1_b$); 4.23 (1H, dd, *J* = 12.9 Hz and 0.9 Hz, $H3_a$); 3.78 (3H, s, $OCH_3$); 3.77 (3H, s, $OCH_3$); 3.73 (1H, dd, *J* = 12.9 Hz and 2.2 Hz, $H3_b$); 2.09 (3H, s, $COCH_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 170.6 (*C*=O), 151.9 (ArCO), 149.0 (ArCO), 126.2 (Ar*C*), 120.0 (Ar*C*), 110.2 (Ar*C*H), 108.5 (Ar*C*H), 68.7 (C3), 63.9 (C1), 62.5 (C4), 55.8 ($OCH_3$), 55.6 ($OCH_3$), 21.2 ($OCCH_3$). **IR** ($CHCl_3$): $\nu_{max}(cm^{-1})$ = 1729 (s, C=O), 1646 (s, C=C), 1263 (s, CO). **HRMS**: Found $M^+$ 252.0999 amu, $C_{13}H_{16}O_5$ requires *M* 252.0998 amu. (EI) 252 ($M^+$, 29%), 192 (100), 177 (23), 149 (9), 134 (7), 105 (10), 91 (10), 77 (7).

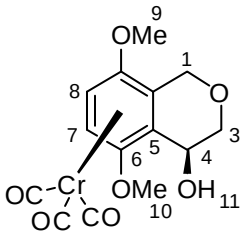
### 5.3.2 Synthesis of [(*S*)-5,8-dimethoxyisochroman-4-ol]tricarbonylchromium(0) 170



**169** *anti*-**170** *syn*-**170**

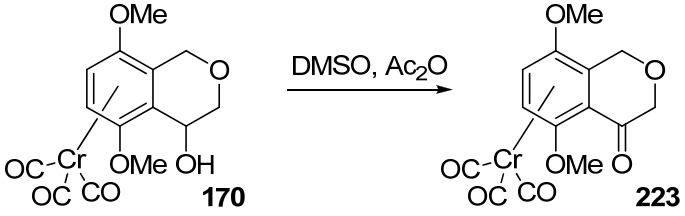
The synthesis of the (*S*)-5,8-dimethoxyisochroman-4-ol *S*-**169** used in this reaction has been discussed in Section 2.2.1.1 of this thesis. The alcohol **169** (0.50 g, 2.4 mmol) and chromium hexacarbonyl (0.79 g, 3.6 mmol, 1.5 equiv.) were placed in a three neck round bottom flask fitted with a condenser. To this was added *n*-$Bu_2O$ (10 ml) and *n*-heptane (10 ml). The solution was thoroughly deoxygenated by the repeated evacuation and purging with Ar(g). Freshly distilled THF (1 ml) was then added and the mixture deoxygenated once again. The reaction flask was then covered in foil, to protect the flask from exposure to light. The mixture was then stirred at reflux (120 °C) for 72 h. After this time the reaction was allowed to cool down and the now yellow-green solution was filtered through a cotton wool plug and the yellow solution that was eluted was adsorbed onto

silica gel and purified by flash chromatography (40% EtOAc/hexane) to elute the two diastereomers *syn*- and *anti*-**170** as yellow solids (0.14 g, 16% *syn* and 0.36 g, 41% *anti*).

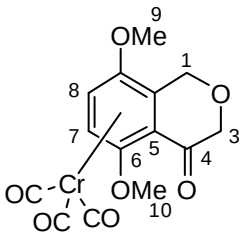



**$R_f$** = 0.27 (*syn*) and 0.13(*anti*) in 50% EtOAc/hexane. **Mp.:** decomposes at 140 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 5.16 (1H, d, *J* = 7.0 Hz, ArC*H*); 4.99 (1H, d, *J* = 7.1 Hz, ArC*H*); 4.92 (1H, d, *J* = 15.6 Hz, $H1_a$); 4.81 (1H, d, *J* = 6.7 Hz, H4); 4.65 (1H, d, *J* = 15.9 Hz, $H1_b$); 4.14 (1H, d, *J* = 12.3 Hz, $H3_a$); 3.95 (1H, d, *J* = 12.4 Hz, $H3_b$); 3.72 (3H, s, OMe); 3.65 (3H, s, OMe); 2.77 (1H, d, *J* = 6.8 Hz, O*H*). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 232.9 (3 × CO), 135.5(Ar*C*O), 131.6 (Ar*C*O), 99.0 (Ar*C*), 97.5 (Ar*C*), 73.5 (Ar*C*H), 72.3 (Ar*C*H), 69.5 (*C*O), 63.3 (*C*O), 61.2 (*C*O), 56.6 (2 × OMe).

### 5.3.3 Synthesis of (5,8-dimethoxyisochroman-4-one)tricarbonylchromium (0) 223

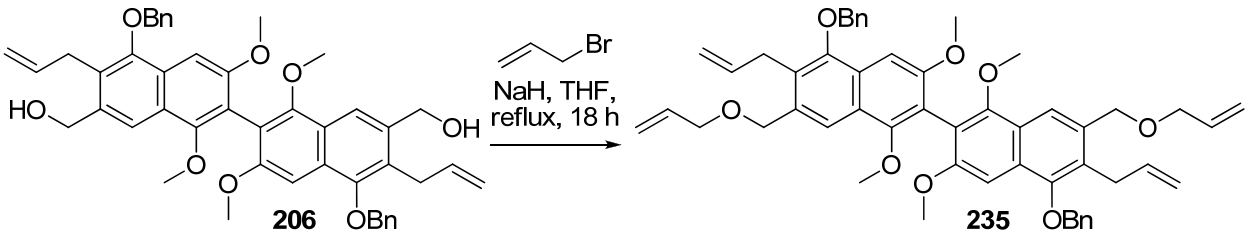



The alcohol **170** (0.020 g, 5.8 $\times 10^{-5}$ mol) was dissolved in a 3:1 mixture of degassed DMSO (0.9 ml) and $Ac_2O$ (0.6 ml). The yellow solution was stirred overnight at rt in a round bottom flask covered with foil. Disappearance of starting material was monitored by TLC. After 18 h the reaction mixture had become dark orange in colour. The reaction mixture was diluted with EtOAc and a 20% aqueous solution of NaOH was added to the dilute solution. The organic product was extracted with EtOAc (3 × 20 ml). The organic extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was dried over silica and purified by column chromatography to yield trace amounts of the product **223** as a dark orange solid.

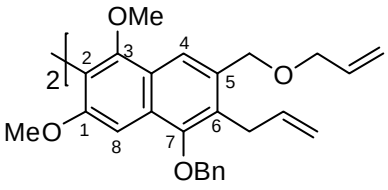



**$R_f$** = 0.13 (50% EtOAc/hexane). **Mp.**: decomposes at 150 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 5.57 (1H, d, *J* = 7.3 Hz, ArC*H*); 4.97 (1H, d, *J* = 15.3 Hz, H1$_a$); 4.89 (1H, d, *J* = 11.6 Hz, ArC*H*); 4.78 (1H, d, *J* = 15.0 Hz, H1$_b$); 4.40 (1H, d, *J* = 17.0 Hz, H3$_a$); 4.16 (1H, d, *J* = 16.8 Hz, H3$_b$); 3.75 (3H, s, OMe); 3.67 (3H, s, OMe).

### 5.3.4 Synthesis of (±)-[6,6'-diallyl-7,7′-*bis*(allyloxy)methyl-5,5'-*bis*(benzyloxy)-1,1',3,3'-tetramethoxy-2,2'-binaphthalene 235



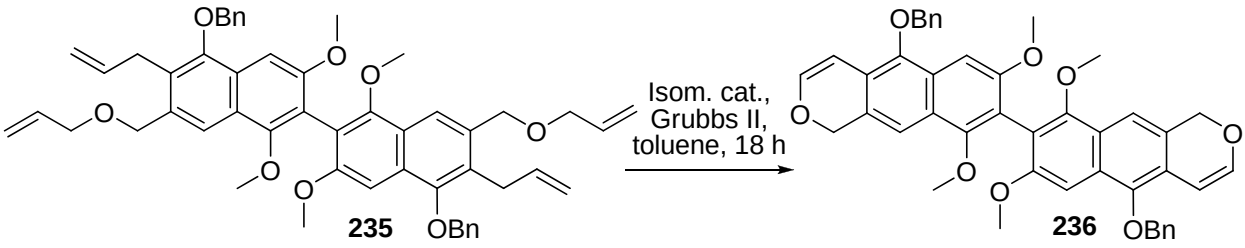

In a round bottom flask, fitted with a condenser, the benzylic alcohol **206** (0.12 g, 0.17 mmol) and allyl bromide (0.034 ml, 0.048 g, 0.4 mmol, 2.4 equiv.) were dissolved in dry THF (50 ml). Sodium hydride (50-55% in oil, 0.044 g, 0.99 mmol, *ca.* 6 equiv.) was added and the solution was boiled for 18 h under a nitrogen atmosphere. Workup was done by adding $H_2O$ (10 ml) and then extracting the material with $Et_2O$ (4 × 10 ml). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered 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 oil from the sodium hydride and then 20% EtOAc/hexane to afford the di-allylated ether **235** (0.086 g, 68%).



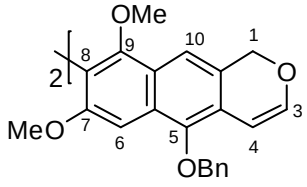

**$R_f$** = 0.50 (20% EtOAc/hexane). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.93 (2H, s,H8 and H8′); 7.59 (4H, d, *J* = 7.1 Hz, 4 × ArC*H*); 7.48–7.30 (6H, m, 6 × ArC*H*); 7.26 (2H, s, H4 and H4′); 6.21–5.88 (4H, m, 4 × $CH_2CH$=$CH_2$); 5.40–5.16 (4H, m, 2 × $CH_2CH$=C$H_2$); 5.15–4.93 (8H, m, 2 × $CH_2CH$=C$H_2$, 2 × Ar$CH_2$O, overlapping signals); 4.69 (4H, s, 2 × O$CH_2$Ph); 4.07 (4H d, *J* = 5.6 Hz, 2 × $CH_2CH$=$CH_2$); 3.79 (4H, d, *J* = 2.8 Hz, 2 × $CH_2CH$=$CH_2$); 3.70 (6H, s, 2 × OMe); 3.61 (6H, s, 2 × OMe). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 157.1 (2 × Ar*C*),

155.4 (2 × Ar*C*), 152.6 (2 × Ar*C*), 137.9 (2 × Ar*C*), 137.3 (2 × $CH_2CH{=}CH_2$), 134.9 (2 × Ar*C*), 132.8 (2 × $CH_2CH{=}CH_2$), 129.5 (2 × Ar*C*), 128.7 (4 × Ar*C*H), 127.9 (2 × Ar*C*H), 127.5 (4 × Ar*C*H), 123.8 (2 × Ar*C*), 119.8 (2 × $CH_2CH{=}CH_2$), 117.0 (2 × Ar*C*), 116.9 (2 × $CH_2CH{=}CH_2$), 115.2 (C8 and C8'), 96.2 (C4 and C4'), 75.8 (2 × $CH_2Ph$), 71.0 (2 × $CH_2O$), 61.3 (2 × $CH_2CH{=}CH_2$), 55.6 (2 × OMe), 55.6 (2 × OMe), 30.5 (2 × $CH_2CH{=}CH_2$).

### 5.3.5 Synthesis of (±)-5,5'-*bis*(benzyloxy)-7,7',9,9'-tetramethoxy-1*H*,1'*H*-8,8'-bibenzo[*g*]isochromene 236




A round bottom flask, equipped with a condenser, was set up under Ar(g). Neat diallyl ether **235** (0.080 g, $9.9 \times 10^{-5}$ mol) was placed in the flask and the isomerisation catalyst, [$RuClH(CO)(PPh_3)_3$] (5.0 mg, 5 mol%, $5.0 \times 10^{-6}$ mol) was added. The mixture was heated for 3 h at 90 °C. In this time the mixture went from light yellow to dark brown. Dry toluene (2 ml) and the second generation Grubbs catalyst (4.2 mg, 0.5 mol%, $5.0 \times 10^{-6}$ mol) were then added to the flask and the solution cooled slightly to 70 °C and left at this temperature for 18 h. The material was dried onto silica while removing the solvent *in vacuo*. The material was then purified by silica gel column chromatography (10% EtOAc/hexane) to afford the isochromene **236** (0.035 g, 51%).

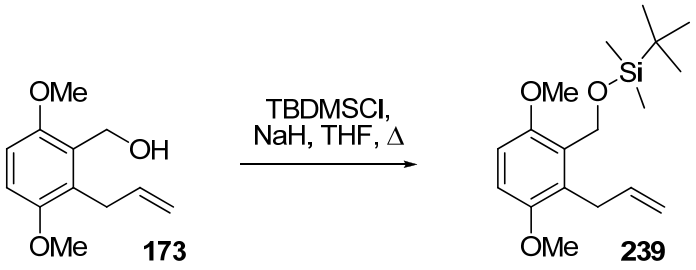



**$R_f$** = 0.37 (20% EtOAc/hexane). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.56–7.45 (6H, m, ArCH); 7.32 (6H, dt, *J* = 7.0 Hz, ArCH); 7.16 (2H, d, *J* = 2.6 Hz, ArCH); 6.63 (2H, d, *J* = 5.8 Hz, H3 and H3′); 6.16 (2H, d, *J* = 5.8 Hz, H4 and H4′); 5.11 (4H, s, 2 × OC$H_2$Ph); 5.02 (4H, d, *J* = 2.7 Hz, H1 and H1′); 3.64 (6H, s, 2 × OMe); 3.48 (6H, s, 2 × OMe). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 157.1 (2 ×ArC), 155.3 (2 ×ArC), 147.0 (2

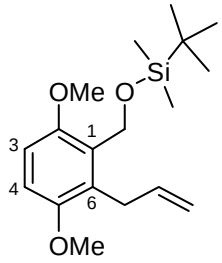
×ArC), 146.6 (2 ×ArC), 137.7 (2 ×ArC), 129.9 (2 × C), 128.6 (4 × Ar*C*H), 128.1 (2 × Ar*C*H), 128.0 (4 × Ar*C*H), 126.1 (2 × C), 123.9 (2 × C), 120.4 (2 × C), 116.6 (2 × C), 113.9 (2 × C), 100.4 (C10 and C10'), 96.3 (C6 and C6'), 76.1 (2 ×$OCH_2$Ph), 68.5 (C1 and C1'), 61.3 (2 × OMe), 55.7 (2 × OMe).

## 5.4 Experimental Work Pertaining to the Synthesis of Isochromanes using Cross Metathesis

### 5.4.1 Synthesis of (2-allyl-3,6-dimethoxybenzyloxy)(*tert*-butyl)dimethylsilane 239



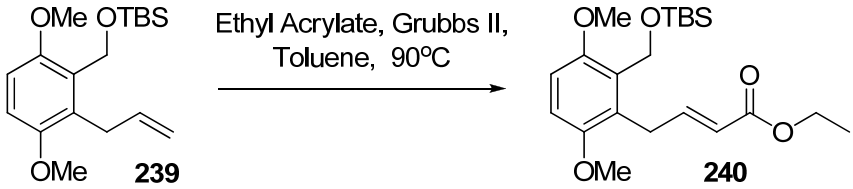

In a 100 ml two neck round bottom flask under Ar(g) and fitted with a condenser, the benzyl alcohol **173** (1.0 g, 4.8 mmol) and TBDMSCl (0.87 g, 5.8 mmol, 1.2 equiv.) were dissolved in dry THF (100 ml). NaH (0.63 g, 14 mmol, 3 equiv.) was then added and the solution was boiled for 14 h. The work up was done by adding $H_2O$ to quench the excess of NaH and the organic product was extracted with EtOAc (3 × 100 ml). The organic fractions were combined, washed with brine and dried over anhydrous $MgSO_4$. It was then filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography by using hexane as the initial eluent to remove the oil residue from the NaH suspension and then 10% EtOAc/hexane to yield the product **239** as a clear oil (1.33 g, 86%).



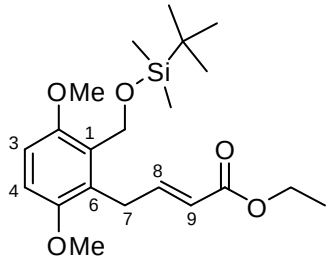

**$R_f$** = 0.73 (20% EtOAc/hexane). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 6.76 (2H, d, *J* = 8.9 Hz, H3 and H4, overlapping signals); 6.00 (1H, ddt, *J* = 17.7 Hz, 9.19 Hz and 6.0 Hz, $CH_2CH$=$CH_2$); 4.98 (1H, t, *J* = 1.6 Hz, $CH_2CH$=C$H_2$); 4.93 (1H, dq, *J* = 6.6 Hz, 1.9 Hz and 1.8 Hz, $CH_2CH$=C$H_2$); 4.77 (2H, s, C$H_2$OSi); 3.79 (3H, s, OC$H_3$); 3.78 (3H, s, OC$H_3$); 3.59 (2H, ddd, *J* = 6.0 Hz and 1.7 Hz, C$H_2$CH=$CH_2$); 0.92 (9H, s, C(C$H_3$)$_3$); 0.09 (6H, s, Si(C$H_3$)$_2$). **$^{13}$C NMR** (75 MHz, $CDCl_3$) $\delta_C$ = 152.0 (Ar*C*O), 152.0 (Ar*C*O), 137.3 ($CH_2$*C*H=$CH_2$), 129.9 (Ar*C*), 128.9 (Ar*C*), 114.3 ($CH_2CH$=*C*$H_2$), 110.8 (Ar*C*H), 109.5 (Ar*C*H), 56.2 (O*C*$H_3$), 56.2 (O*C*$H_3$), 56.1 (Ar*C*$H_2$OSi), 30.2 (*C*$H_2$CH=$CH_2$), 26.0 (C(*C*$H_3$)$_3$), 18.5 (*C*(CH$_3$)$_3$), –5.3 (Si(*C*$H_3$)$_2$). **IR**: $\nu_{max}$(cm$^{-1}$) = 2953, 1599 (C=C). **HRMS:**

Found $M^+$ 322.19649, $C_{18}H_{30}O_3Si$ requires *M* 322.19642 amu. (EI) 317 (4%), 323 (100), 329 (2)

### 5.4.2 Synthesis of (*E*)-ethyl 4-(2-((*tert*-butyldimethylsilyloxy)methyl)-3,6-dimethoxyphenyl)but-2-enoate 240

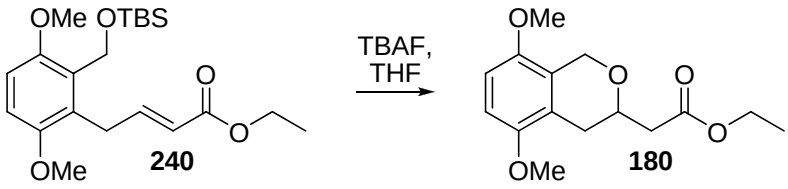



The alkene **239** (1.63 g, 5.07 mmol) and ethyl acrylate (1.27 g; 1.38 ml; 12.7 mmol; 2.5 equiv.) were dissolved in dry toluene (50 ml) in a two neck round bottom flask fitted with a condenser. The Grubbs II catalyst (0.065 g; $7.6 \times 10^{-5}$ mol; 1.5 mol%) was then added to this solution and the mixture was allowed to stir for 18 h at 90 °C. After this time the reaction was cooled down and the reaction mixture directly dried onto silica and purified by column chromatography with 10% EtOAc/hexane as the eluent to yield the product **240** as a clear oil (1.24 g, 62%).

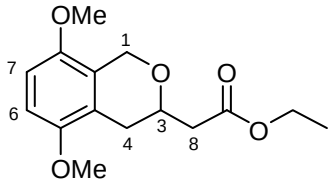



**$R_f$** = 0.37 (10% EtOAc/hexane). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.12 (1H, dt, *J* = 15.60 Hz and 6.12, Hz, H8); 6.76 (2H, dd, *J* = 8.99 Hz, H3 and H4); 5.66 (1H, d, *J* = 15.63 Hz, H9); 4.72 (2H, s, ArC*H*$_2$OSi); 4.13 (2H, q, *J* = 7.13 Hz, C*H*$_2$CH$_3$); 3.77 (3H, s, OC*H*$_3$); 3.76 (3H, s, OC*H*$_3$); 3.69 (2H, dd, *J* = 6.11 Hz and 1.32 Hz, H7); 1.24 (3H, t, *J* = 7.12 Hz, CH$_2$C*H*$_3$); 0.88 (9H, s, C(C*H*$_3$)$_3$); 0.06 (6H, s, Si(C*H*$_3$)$_2$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 166.9 (C=O), 151.9 (Ar*C*O), 151.6 (Ar*C*O), 148.0 (C8), 128.8 (Ar*C*), 127.7 (Ar*C*), 121.1 (C9), 110.5 (Ar*C*H), 109.8 (Ar*C*H), 60.0 (*C*H$_2$CH$_3$), 56.2 (O*C*H$_3$), 56.1 (O*C*H$_3$), 55.9 (Ar*C*H$_2$OSi), 28.9 (C7), 26.0 (C(*C*H$_3$)$_3$), 18.4 (*C*(CH$_3$)$_3$), 14.2 (CH$_2$*C*H$_3$), –5.3 (Si(*C*H$_3$)$_2$). **IR**: $\nu_{max}$(cm$^{-1}$) = 2932, 1483, 1719 (C=O). **HRMS:** Found $M^+$ 394.21714, $C_{21}H_{34}O_5Si$ requires *M* 394.21755 amu.

### 5.4.3 Synthesis of ethyl 2-(5,8-dimethoxyisochroman-3-yl)acetate 180

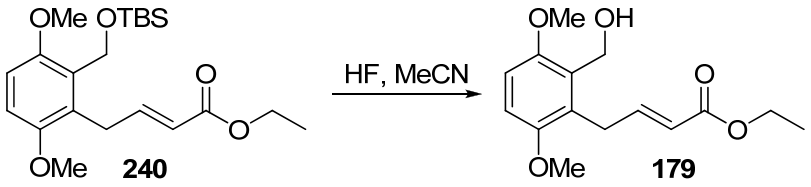



The ester **240** (0.095 g, 0.24 mmol) was dissolved in freshly distilled THF (30 ml) containing acetic acid (0.015 ml, 0.027 mmol, 1.1 equiv.) in a dry two neck round bottom flask under Ar(g). The reaction mixture was cooled to 0 °C by means of an ice bath and once cooled, the TBAF solution (1 M in THF, 0.72 ml, 0.72 mmol, 3 equiv.) was added in one portion. The reaction mixture was allowed to warm up to rt. Completion of the reaction was monitored by TLC (approx. 1 h). The reaction mixture was then transferred to a separating funnel and diluted with EtOAc and $H_2O$. After thorough mixing, the organic phase was separated and the aqueous phase further extracted with EtOAc (3 × 50 ml). The organic fractions were combined, dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography (50% EtOAc/hexane) to yield the product **180** as a clear oil (0.051 g, 55% yield).

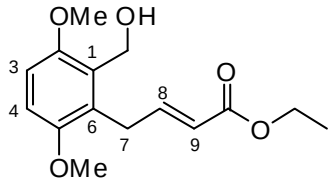



**$R_f$** = 0.27 (10% EtOAc/hexane). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 6.66 (1H, d, *J* = 8.91 Hz, ArC*H*); 6.61 (1H, d, *J* = 8.91 Hz, ArC*H*); 4.91 (1H, d, *J* = 15.95 Hz, $H1_a$); 4.62 (1H, d, *J* = 15.95 Hz, $H1_b$); 4.19 (2H, dq, *J* = 7.16 Hz and 2.00 Hz, $CH_2CH_3$); 4.11-3.99 (1H, m, H3); 3.78 (3H, s, $OCH_3$); 3.75 (3H, s, $OCH_3$); 2.83 (1H, dd, *J* = 16.86 Hz and 1.79 Hz, $H4_a$); 2.65 (2H, 2 × dd, *J* = 15.46 Hz and 6.51 Hz, H8); 2.45 (1H, dd, *J* = 16.82 Hz and 10.87 Hz, $H4_b$); 1.28 (3H, t, *J* = 7.15 Hz, $CH_2CH_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 171.1 (C=O), 150.9 (Ar*C*O), 149.4 (Ar*C*O), 124.4 (Ar*C*), 123.1 (Ar*C*), 107.5 (Ar*C*H), 107.0 (Ar*C*H), 70.7 (C3), 64.7 (C1), 60.6 ($CH_2CH_3$), 55.6 ($OCH_3$), 55.4 ($OCH_3$), 41.2 (C8), 28.2 (C4), 14.2 ($CH_2CH_3$). **IR**: $\nu_{max}$($cm^{-1}$) = 2937, 1732 (C=O). **HRMS:** Found $M^+$ 280.12993, $C_{15}H_{20}O_5$ requires *M* 280.13107 amu. (EI) 227 (10%), 274 (1).

### 5.4.4 Synthesis of (*E*)-ethyl 4-(2-(hydroxymethyl)-3,6-dimethoxyphenyl)but-2-enoate 179

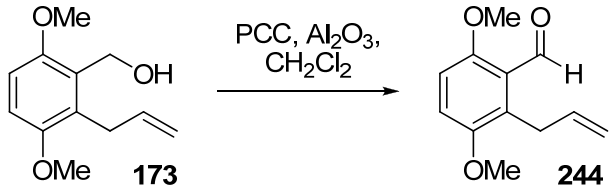



The protected alcohol **240** (0.050 g, 0.13 mmol) was placed in two neck round bottom flask containing MeCN (10 ml). HF (48%, 9.1 μl, 0.25 mmol, 2 equiv.) was to this solution at rt and the reaction monitored by TLC. Once the reaction was complete, saturated $NaHCO_3$ was added to the reaction mixture and the organic products were extracted with EtOAc (3 × 20 ml). The organic products were combined, dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography (50% EtOAc/hexane) to yield the benzylic alcohol **179** (0.025 g, 72%).



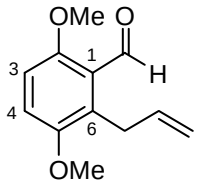

**$R_f$** = 0.10 (50% EtOAc/hexane). **Mp.**: 100-103 °C. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.07 (1H, dt, *J* = 15.64 Hz and 5.91 Hz, H8); 6.78 (1H, d, *J* = 8.99 Hz, ArC*H*); 6.74 (1H, d, *J* = 8.98 Hz, ArC*H*); 5.84 (1H, m, O*H*); 5.59 (1H, dd, *J* = 15.62 Hz and 1.59 Hz, H9); 4.39 (2H, d, *J* = 5.68 Hz, ArC$H_2$O); 4.11 (2H, q, *J* = 7.12 Hz, C$H_2$CH$_3$); 3.80 (3H, s, OC$H_3$); 3.75 (3H, s, OC$H_3$); 3.73-3.70 (2H, m, H7); 1.23 (3H, t, *J* = 7.13 Hz, CH$_2$C$H_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 166.6 (C=O), 152.3 (Ar*C*O), 151.7 (Ar*C*O), 147.4 (C8), 128.8 (Ar*C*), 126.2 (Ar*C*), 121.4 (C9), 110.5 (Ar*C*H), 109.4 (Ar*C*H), 60.1 (*C*H$_2$CH$_3$), 57.4 (Ar*C*H$_2$O), 56.0 (O*C*H$_3$), 55.8 (O*C*H$_3$), 28.6 (C7), 14.2 (CH$_2$*C*H$_3$). **IR**: $\nu_{max}$(cm$^{-1}$) = 3255 (OH), 1714 (C=O).

### 5.4.5 Synthesis of 2-allyl-3,6-dimethoxybenzyldehyde 244



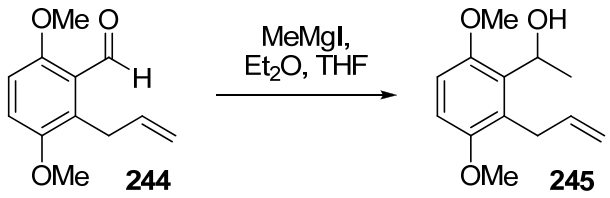

PCC (4.35 g, 20.0 mmol, 2.1 equiv.) dissolved in MeCN (30 ml) was dried onto neutral $Al_2O_3$ (50 g) with a rotary evaporator. This solid was then added to a solution of the alcohol **173** (2.0 g, 9.6 mmol) in dry $CH_2Cl_2$ (150 ml). The reaction mixture became progressively darker and was allowed to stir for 18 h under Ar(g).

Once the reaction was complete (as monitored by TLC), the reaction mixture was filtered through celite and concentrated on a rotary evaporator. The crude material was purified by column chromatography (20% to 30% EtOAc/hexane) to yield the product **244** as a clear oil (1.89 g, 96%).



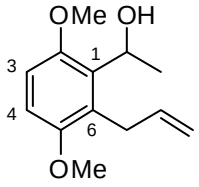

**$R_f$** = 0.43 (20% EtOAc/hexane). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 10.57 (1H, s, C*H*O); 7.05 (1H, d, *J* = 9.04 Hz, ArC*H*, H3 or H4); 6.82 (1H, d, *J* = 9.04 Hz, ArC*H*, H3 or H4); 5.96 (1H, ddt, *J* = 16.24 Hz, 10.09 Hz and 6.14 Hz, $CH_2CH$=$CH_2$); 5.02-4.92 (2H, m, $CH_2CH$=C$H_2$); 3.85 (3H, s, OC$H_3$); 3.80 (3H, s, OC$H_3$); 3.78 (2H, dt, *J* = 6.13 Hz and 1.58 Hz, C$H_2$CH=$CH_2$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 192.4 (*C*HO), 156.9 (Ar*C*O), 151.8 (Ar*C*O), 136.7 ($CH_2$*C*H=$CH_2$), 131.5 (Ar*C*), 124.1 (Ar*C*), 117.2 (Ar*C*H), 114.8 ($CH_2CH$=*C*$H_2$), 109.8 (Ar*C*H), 56.6 (O*C*$H_3$), 56.1 (O*C*$H_3$), 29.4 (*C*$H_2$CH=$CH_2$). **IR**: $\nu_{max}$($cm^{-1}$) = 2941, 1684 (C=O). **HRMS:** Found $M^+$ 206.09311, $C_{12}H_{14}O_3$ requires *M* 206.09429 amu. (EI) 191 (100%), 193 (12), 198 (4), 201 (2), 206 (40).

### 5.4.6 Synthesis of 1-(2-allyl-3,6-dimethoxyphenyl)ethanol 245



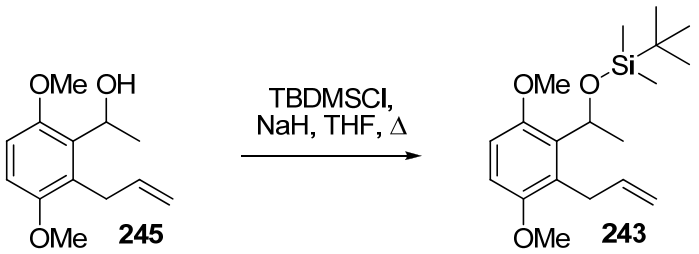

Mg metal (0.23 g, 9.6 mmol, 1.6 equiv.) was placed in a dry two neck round bottom flask fitted with a dropping funnel and a condenser, all under Ar(g). Dry $Et_2O$ (20 ml) was then placed in the flask, followed by MeI (1.3 g, 0.56 ml, 9.0 mmol, 1.5 equiv.). The mixture quickly became cloudy with an increase in the temperature. Once all the Mg metal had reacted, the dropping funnel was charged with a solution of the aldehyde **244** (1.0 g, 6.0 mmol) in THF (25 ml), and this solution was added dropwise to the cloudy Grignard suspension.

The solution was allowed to stir for 18 h at rt. Once complete the reaction mixture was cooled on an ice bath and $H_2O$ was added to quench the excess of the Grignard reagent. The mixture was then transferred to a separating funnel and the organic product was extracted with EtOAc (3 × 50 ml) and $CH_2Cl_2$ (2 × 30 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (20% to 30% EtOAc/hexane) to yield the pure product **245** as a clear oil (1.07 g, 98%).



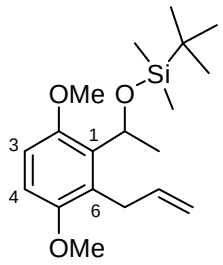

**$R_f$** = 0.33 (30% EtOAc/hexane). **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 6.75 (1H each, d, *J* = 8.9 Hz, H3 and H4, overlapping signals); 5.92 (1H, ddt, *J* = 17.06 Hz, 10.17 Hz and 5.83 Hz, $CH_2CH$=$CH_2$); 5.09-4.90 (3H, m, $CH_2CH$=$CH_2$ and Ar$CH(CH_3)$, overlapping signals); 4.03 (1H, d, *J* = 11.22 Hz, O*H*); 3.85 (3H, s, $OCH_3$); 3.77 (3H s, $OCH_3$); 3.45 (2H, m, $CH_2CH$=$CH_2$); 1.52 (3H, d, *J* = 6.69 Hz, ArCH($CH_3$)). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 151.9 (Ar*C*O), 151.8 (Ar*C*O), 136.5 ($CH_2CH$=$CH_2$), 132.7 (Ar*C*), 126.2 (Ar*C*), 114.9 ($CH_2CH$=$CH_2$), 109.5 (Ar*C*H), 109.4 (Ar*C*H), 67.3 (Ar*C*H($CH_3$)), 56.2 ($OCH_3$), 55.5 ($OCH_3$), 29.8 ($CH_2CH$=$CH_2$), 23.6 (ArCH($CH_3$)). **IR**: $\nu_{max}$($cm^{-1}$) = 3547 (OH).

### 5.4.7 Synthesis of (1-(2-allyl-3,6-dimethoxyphenyl)ethoxy)(*tert*-butyl)-dimethylsilane 243



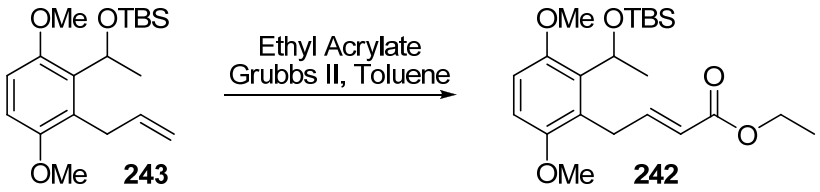

The alcohol **245** (1.79 g, 8.05 mmol) and TBDMSCl (1.46 g, 9.67 mmol, 1.2 equiv.) were placed in a dry two neck round bottom flask containing freshly distilled THF (100 ml). NaH (55% suspension in oil, 1.05 g, 24.2 mmol, 3 equiv.) was then added to this clear solution and the now cloudy mixture was boiled at reflux for 14 h under an Ar(g) atmosphere.

The reaction was quenched by the addition of $H_2O$ and the organic product was extracted with EtOAc (3 × 100 ml). The organic fractions were combined, dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was then purified by column chromatography by using hexane as the initial eluent to remove the oil from the NaH and then 5% EtOAc/hexane to produce the protected alcohol **243** in 93% yield (2.53 g).

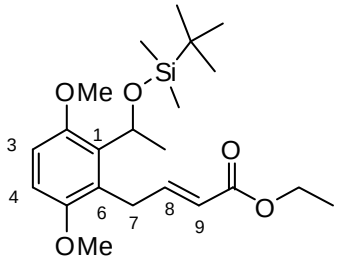



**$R_f$** = 0.70 (20% EtOAc/hexane). **$^1$H NMR** (300 MHz, CDCl3): $\delta_H$ = 6.70 (1H each, d, *J* = 8.93 Hz, H3 and H4, overlapping signals); 5.98 (1H, ddd, *J* = 22.34 Hz, 10.91 Hz and 5.81 Hz, $CH_2CH$=$CH_2$); 5.60 (1H, q, *J* = 6.6 Hz, Ar$CH(CH_3)$); 4.96-4.86 (2H, m, $CH_2CH$=$CH_2$); 4.04 (1H, dd, *J* = 15.13 Hz and 6.20 Hz, $CH_2CH$=$CH_2$); 3.76 (3H, s, $OCH_3$), 3.76 (3H, s, $OCH_3$); 3.57 (1H, dd, *J* = 15.21 Hz and 5.31 Hz, $CH_2CH$=$CH_2$); 1.43 (3H, d, *J* = 6.6 Hz, Ar$CH(CH_3)$); 0.85 (9H, s, $C(CH_3)_3$); 0.01 (3H, s, $Si(CH_3)_2$); –0.13 (3H, s, $Si(CH_3)_2$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 152.8 (Ar*C*O), 150.5 (Ar*C*O), 138.5 ($CH_2CH$=$CH_2$), 133.6 (Ar*C*), 129.0 (Ar*C*), 114.0 ($CH_2CH$=$CH_2$), 109.5 (Ar*C*H, C3 or C4), 109.1 (Ar*C*H, C3 or C4), 64.4 (Ar*C*H($CH_3$)), 56.2 ($OCH_3$), 55.9 ($OCH_3$), 30.6 ($CH_2CH$=$CH_2$), 25.9 ($C(CH_3)_3$), 24.5 (ArCH($CH_3$)), 18.2 ($C(CH_3)_3$), –4.9 ($Si(CH_3)_2$), –5.1 ($Si(CH_3)_2$). **IR**: $\nu_{max}$($cm^{-1}$) = 2953, 1474 (C=C).

### 5.4.8 Synthesis of (*E*)-ethyl 4-(2-(1-(*tert*-butyldimethylsilyloxy)ethyl)-3,6-dimethoxyphenyl)but-2-enoate 242

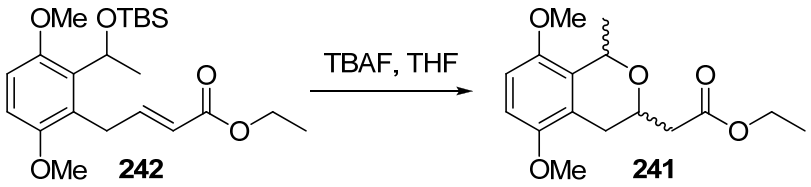



The alkene **243** (0.1 g, 0.3 mmol) and ethyl acrylate (0.074 g, 0.081 ml, 0.74 mmol, 2.5 equiv.) were dissolved in dry toluene (20 ml) in a two neck round bottom flask fitted with a condenser. The Grubbs II catalyst (3.78 mg, $4.46 \times 10^{-6}$ mol; 1.5 mol%) was then added to this solution and the mixture was allowed to stir for 18 h at 90 °C. After this time the reaction was cooled down and the reaction mixture directly dried onto silica and purified by silica gel chromatography with 10% EtOAc/hexane as the eluent to yield the product **242** as a clear oil (0.101 g, 83%).

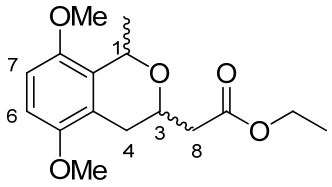



**$R_f$** = 0.37 (10% EtOAc/hexane). **Mp.:** 64-66 °C, **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.13 (1H, td, *J* = 15.65 Hz and 5.93 Hz, H8); 6.71 (2H, s, H3 and H4); 5.96-5.59 (2H, m, H9 and ArC*H*($CH_3$), overlapping signals); 4.21-4.09 (3H, m, $H7_a$ and $CH_2CH_3$, overlapping signals); 3.78 (1H, dd, *J* = 11.57 Hz and 6.53 Hz, $H7_b$); 3.76 (3H, s, $OCH_3$); 3.73 (3H, s, $OCH_3$); 1.39 (3H, d, *J* = 6.68 Hz, ArCH($CH_3$)); 1.25 (3H, t, *J* = 7.13 Hz, $CH_2CH_3$); 0.85 (9H, s, $C(CH_3)_3$); 0.03 (3H, s, $Si(CH_3)_2$); –0.10 (3H, s, $Si(CH_3)_2$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 167.1 (C=O), 152.7 (Ar*C*O), 150.1 (Ar*C*O), 149.7 (C8), 133.7 (Ar*C*), 126.7 (Ar*C*), 120.7 (C9), 109.4 (Ar*C*H), 109.2 (Ar*C*H), 64.2 (Ar*C*H($CH_3$)), 59.9 ($CH_2CH_3$), 56.2 ($OCH_3$), 55.7 ($OCH_3$), 29.4 (C7), 25.9 ($C(CH_3)_3$), 24.7 (ArCH($CH_3$)), 18.2 ($C(CH_3)_3$), 14.3 ($CH_2CH_3$), –4.9 ($Si(CH_3)_2$), –5.1 ($Si(CH_3)_2$). **IR**: $\nu_{max}$($cm^{-1}$) = 2860, 1715 (C=O).

### 5.4.9 Synthesis of *cis* and *trans* ethyl 2-(5,8-dimethoxy-1-methylisochroman-3-yl) acetate 241



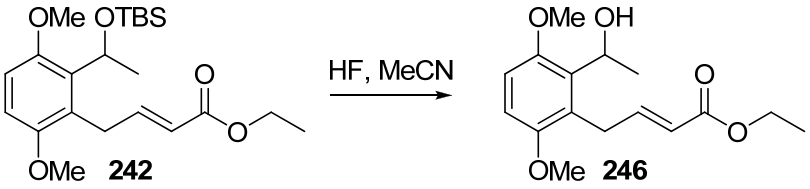

The ester **242** (0.091 g, 0.22 mmol) was dissolved in freshly distilled THF (30 ml) containing HOAc (0.014 ml, 2.5 $\times 10^{-5}$ mol, 1.1 equiv.) in a dry two neck round bottom flask under Ar(g). The reaction mixture was cooled to 0 °C by means of an ice bath and once cooled, the TBAF solution (1 M in THF, 0.67 ml, 0.67 mmol, 3 equiv.) was added in one portion. The reaction mixture was allowed to warm up to rt. Completion of the reaction was monitored by TLC (approx. 1 h). The reaction mixture was then transferred to a separating funnel and diluted with EtOAc and $H_2O$. After thorough mixing, the organic phase was separated and the aqueous phase further extracted with EtOAc (3 × 50 ml). The combined organic fractions were combined, dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography (50% EtOAc/hexane) to yield the product **241** as a clear oil (0.038 g, 58% yield).



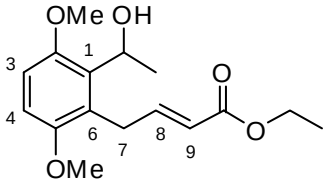

**$R_f$** = 0.20 (10% EtOAc/hexane). The molecule was isolated as an inseparable mixture of diastereomers (in a ratio of 1:0.9, *trans*: *cis*) and there were additional signals in the NMR spectrum. **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 6.74-6.57 (4H, m, 2 × Ar*C*H, H6 and H7); 5.11-4.96 (2H, 2 × q, *J* = 6.5 Hz, 2 × H1); 4.39 (1H, dt, *J* = 8.3 Hz, H3); 4.19 (4H, q, *J* = 6.31 Hz and 6.28 Hz, 2 × C$H_2$CH$_3$); 3.94 (1H, dt, *J* = 5.5 Hz, H3); 3.80-3.70 (12H, m, 2 × (2 × OC$H_3$)); 2.92-2.29 (8H, m, 2 ×H4 and 2 × H8); 1.51 (6H, d, *J* = 6.8 Hz, 2 × ArCH(C$H_3$)); 1.28 (6H, dd, *J* = 12.87 Hz and 6.99 Hz, 2 × CH$_2$C$H_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 171.3 (C=O), 150.8 and 150.6 (Ar*C*O), 150.2 and 149.4 (Ar*C*O), 129.2 and 129.0 (Ar*C*), 124.5 and 122.7 (Ar*C*), 108.1 and 107.7 (Ar*C*H), 107.5 and 107.4 (Ar*C*H), 71.2 and 69.8 (C3), 68.5 and 63.4 (C1), 60.5 and 60.4 (*C*H$_2$CH$_3$), 55.7 and 55.6 (OCH$_3$), 55.4 and 55.4 (OCH$_3$), 41.4 and 41.2 (C8), 29.2 and 28.2 (C4), 21.6 and 19.2 (ArCH(*C*H$_3$)), 14.2 (CH$_2$*C*H$_3$). **IR**: $\nu_{max}$(cm$^{-1}$) = 2976, 1733 (C=O). **HRMS:** Found

$M^+$ 294.00938, $C_{16}H_{22}O_5$ requires *M* 294.14672 amu. (EI), 279 (88%), 286 (100), 291 (66), 298 (80).

### 5.4.10 Synthesis of (*E*)-ethyl 4-(2-(1-hydroxyethyl)-3,6-dimethoxyphenyl)but-2-enoate 246



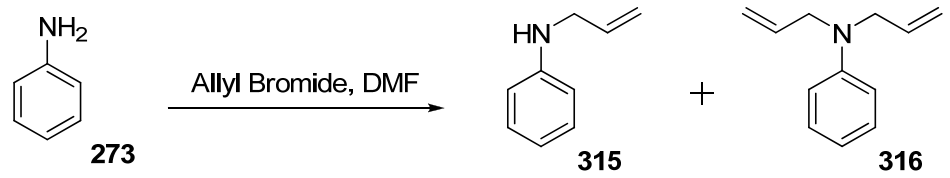

The protected alcohol **242** (0.050 g, 0.12 mmol) was placed in two neck round bottom flask containing MeCN (10 ml). HF (48%, 8.8 µl, 0.24 mmol, 2 equiv.) was added to this solution at rt and the reaction monitored by TLC. Once the reaction was complete, saturated $NaHCO_3$ was added to the reaction mixture and the organic products were extracted with EtOAc (3 × 20 ml). The organic products were combined, dried over anhydrous $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography (50% EtOAc/hexane) to yield the benzylic alcohol **246** (0.031 g, 86%).



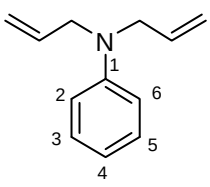

**$R_f$** = 0.13 (50% EtOAc/hexane). **Mp.:** 104-107 °C, **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.08 (1H, dt, *J* = 15.63 Hz and 5.95 Hz, H8); 6.87-6.66 (3H, m, H3, H4 and H9, overlapping signals); 5.63 (1H, d, *J* = 15.66 Hz, O*H*); 5.49-5.35 (1H, m, Ar(C*H*)$CH_3$); 4.12 (2H, q, *J* = 7.12 Hz, C$H_2$$CH_3$); 3.85 (3H, s, OC$H_3$); 3.76 (2H, dd, *J* = 5.96 Hz and 1.37 Hz, H7); 3.73 (3H, s, OC$H_3$); 1.38 (3H, d, *J* = 6.95 Hz, Ar(CH)C$H_3$); 1.23 (3H, t, *J* = 7.13 Hz, $CH_2$C$H_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 166.6 (C=O), 152.0 (Ar*C*O), 151.8 (Ar*C*O), 147.2 (C8), 130.9 (Ar*C*), 125.1 (Ar*C*), 121.4 (C9), 110.0 (Ar*C*H), 109.4 (Ar*C*H), 60.0 (Ar(*C*H)$CH_3$), 56.0 (O*C*$H_3$), 55.6 (O*C*$H_3$), 43.8 (*C*$H_2$$CH_3$), 28.7 (C7), 23.5 (ArCH(*C*$H_3$)), 14.1 ($CH_2$*C*$H_3$). **IR**: $\nu_{max}$($cm^{-1}$) = 3256 (OH), 1714 (C=O).

## 5.5 Experimental Work Pertaining to the Synthesis of Indolines

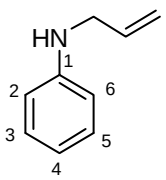
### 5.5.1 Synthesis of *N*-allyl aniline 315




Aniline **273** (7.70 g, 7.53 ml, 83.0 mmol, 2 equiv.) was dissolved in DMF (15 ml) in a two neck round bottom flask fitted with a dropping funnel. The solution was cooled to 0 ºC by means of an ice bath. Allyl bromide (5.0 g, 3.6 ml, 41 mmol) was placed in the dropping funnel and this was added dropwise to the above solution. The mixture was then stirred at 40 ºC for 18 h. Once the reaction was complete, the crude reaction mixture was poured into cold $H_2O$ and the solution made alkaline with a 2 M NaOH solution. The organic product was then extracted with EtOAc (3 × 100 ml). The combined organic layers were washed with $H_2O$ and dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The brown residue collected was purified by column chromatography (hexane) to yield the products **315** and **316** as yellow oils (4.31 g, 79% of monoallylated aniline **315**, 1.34 g, 19% of diallylated aniline **316**).

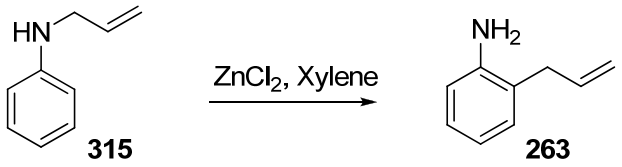



**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.18 (2H, t, *J* = 7.1 Hz, H2 and H6), 6.67 (3H, t, *J* = 9.4 Hz, H3, H4 and H5), 5.98–5.71 (2H, m, 2 × $CH_2CH$=$CH_2$), 5.29–5.04 (4H, m, 2 × $CH_2CH$=$CH_2$), 3.90 (4H, d, *J* = 3.0 Hz, 2 × $CH_2CH$=$CH_2$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 148.7 (ArCN), 134.0 (C2 and C6), 129.0 (C3 and C5), 116.3 (C4), 115.9 (2 × $CH_2CH$=$CH_2$), 112.3 (2 × $CH_2CH$=$CH_2$), 52.68 (2 × $CH_2CH$=$CH_2$).

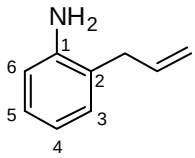



**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.16 (2H, t, *J* = 7.7 Hz, H3 and H5 ), 6.69 (1H, t, *J* = 7.3 Hz, H4), 6.60 (2H d, *J* = 8.4 Hz, H2 and H6), 5.93 (1H, m, $CH_2CH$=$CH_2$), 5.20 (1H dd, *J* = 35.8 Hz and 13.7 Hz, $CH_2CH$=$CH_2$), 3.74 (1H, d, *J* = 5.2 Hz, $CH_2CH$=$CH_2$ and N*H*, overlapping signals). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 148.0 (Ar*C*N), 135.4 ($CH_2CH$=$CH_2$), 129.1 (C2 and C4), 117.4 (C4), 116.1 ($CH_2CH$=$CH_2$), 112.9 (C3 and C5), 46.5 ($CH_2CH$=$CH_2$).

### 5.5.2 Synthesis of 2-allyl aniline 263

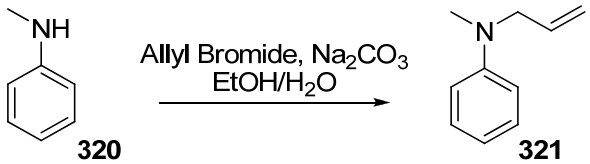



According to the procedure by Beholz *et al.*[140] in a two neck round bottom flask fitted with a condenser, *N*-allyl aniline **315** (5.9 g, 44 mmol) and $ZnCl_2$ (7.3 g, 1.2 equiv. 53 mmol) were added to dry xylene (89 ml, 0.5 M relative to aniline). The reaction was heated to 140 ºC and allowed to react for 8 h. The reaction was then cooled down to 0 ºC and quenched by the addition of a 15% solution of aqueous NaOH. The organic products were extracted with EtOAc (3 × 100 ml). The organic fractions were combined, dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The product was then purified by silica gel column chromatography (5% EtOAc/hexane) to yield the product **263** (2.22 g, 38%). The procedure was repeated with other Lewis acids: $BF_3.OEt_2$ and $AlCl_3$.



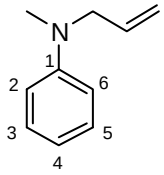

**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.11–6.97 (2H, m, H6 and H3), 6.73 (1H, t, *J* = 7.4 Hz, H4), 6.65 (1H, t, *J* = 6.5 Hz, H5), 5.93 (1H, ddt, *J* = 16.6 Hz, 10.4 Hz and 6.2 Hz, $CH_2CH$=$CH_2$), 5.16–4.98 (2H, m, $CH_2CH$=$CH_2$), 3.61 (2H, br s, $NH_2$), 3.27 (2H, d, *J* = 6.2 Hz, $CH_2CH$=$CH_2$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = δ144.7 (Ar*C*N), 135.8 ($CH_2CH$=$CH_2$), 130.0 (Ar*C*H), 127.4 (Ar*C*H), 123.9 (C2), 118.7 (Ar*C*H), 116.0 ($CH_2CH$=$CH_2$), 115.7 (Ar*C*H), 36.3 ($CH_2CH$=$CH_2$).

### 5.5.3 Synthesis of *N*-allyl-*N*-aniline 321



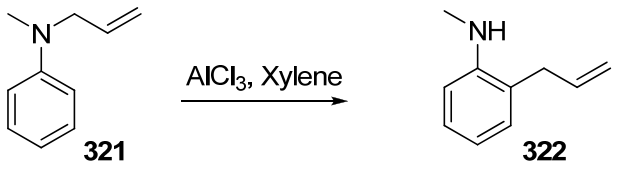

Allyl bromide (2.5 g, 1.8 ml, 0.020 ml, 1.1 equiv.) and $Na_2CO_3$ (1.2 g, 0.011 mol, 0.6 equiv.) were added to a 0.5 M solution of *N*-methyl aniline **320** (2.0 g, 2.0 ml,

0.019 mol) in a 4:1 mixture of ethanol to $H_2O$ (30 ml: 7.5 ml). This mixture was allowed to stir for 14 h at rt. The ethanol was then removed *in vacuo* and the organic product was extracted with EtOAc (3 × 50 ml). The organic extracts were combined, dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The crude oil was purified by column chromatography (5% EtOAc/hexane) to yield the product **321** as a yellow oil (1.85 g, 66%).

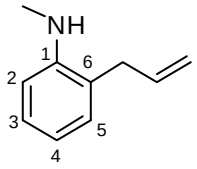



**$R_f$** = 0.77 (20% EtOAc/hexane). **$^1$H NMR** (300 MHz): $\delta_H$ = 7.24-7.18 (2H, m, H2 and H6); 6.70 (3H, dd, *J* = 7.3 Hz and 8.4 Hz, H3, H4 and H5); 5.83 (1H, tdd, *J* = 5.1 Hz, 10.2 Hz and 17.0 Hz, $CH_2CH$=$CH_2$); 5.19-5.12 (2H, m, $CH_2CH$=$CH_2$); 3.91-3.89 (2H, m, $CH_2CH$=$CH_2$); 2.92 (3H, s, $NCH_3$). **$^{13}$C NMR** (75 MHz): $\delta_C$ = 149.5 (Ar*C*N), 133.8 ($CH_2CH$=$CH_2$), 129.1 (C3 and C5), 116.4 (C4), 116.1 ($CH_2CH$=$CH_2$), 112.4 (C2 and C6), 55.2 ($CH_2CH$=$CH_2$), 37.9 ($NCH_3$). **IR**: $\nu_{max}$($cm^{-1}$) = 2893, 1642, 1503 (ArCH). **HRMS:** Found $M^+$ 147.1041, $C_{10}H_{13}N$ requires *M* 147.1048 amu. (EI) 142 (2%), 144 (4), 146 (36), 147 (100).

### 5.5.4 Synthesis of 2-Allyl-*N*-methylbenzenamine 322

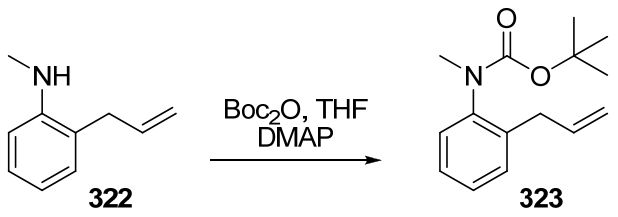



*N*-allyl-*N*-methylaniline **321** (13.6 g, 0.0920 mol) and $AlCl_3$ (16.7 g, 0.123 mol, 1.2 equiv.) were added to dry xylene (204 ml) to make up a 0.5 M solution in a two neck round bottom flask fitted with a condenser. The reaction was then heated to 140 °C and allowed to react for 8 h. The reaction was quenched at 0 °C by the addition of a 15% solution of aqueous NaOH solution. The organic product was extracted with EtOAc (3 × 100 ml) and the organic extracts were combined, dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The crude product was then purified by column chromatography (5% EtOAc/hexane) to yield **322** as a yellow oil (8.93 g, 61%).



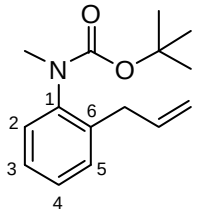
**$^{1}$H NMR** (300 MHz): $\delta_H$ = 7.18 (1H, dt, *J* = 7.8 Hz and 1.5 Hz, H2); 7.05-7.03 (1H, m, H4); 6.70 (1H, dt, *J* = 1.0 Hz, 7.4 Hz, H3); 6.69 (1H, d, *J* = 8.1 Hz, H5); 5.94 (1H, ddt, *J* = 16.62 Hz, 6.2 Hz and 10.4 Hz, $CH_2CH$=$CH_2$); 5.13-5.05 (2H, m, $CH_2CH$=$CH_2$); 3.72 (1H, br s, N*H*); 3.28 (2H, d, *J* = 6.1 Hz, $CH_2CH$=$CH_2$); 2.84 (3H, s, $NCH_3$).**$^{13}$C NMR** (75 MHz): $\delta_C$ = 147.3 (Ar*C*N), 136.0 ($CH_2CH$=$CH_2$), 129.6 (C4), 127.7 (C2), 123.5 (C6), 117.1 (C5), 116.1 ($CH_2CH$=$CH_2$), 109.9 (C3), 36.4 ($NCH_3$), 30.7 ($CH_2CH$=$CH_2$). **IR**: $\nu_{max}$(cm$^{-1}$) = 2812, 1604, 1509 (ArCH). **HRMS:** Found $M^+$ 147.1043. $C_{10}H_{13}N$ requires *M* 147.1408 amu. (EI) 142 (2%), 143 (10), 144 (38), 145 (22), 146 (36), 147 (100).

### 5.5.5 Synthesis of *tert*-butyl 2-allylphenyl(methyl)carbamate 323




**322** **323**

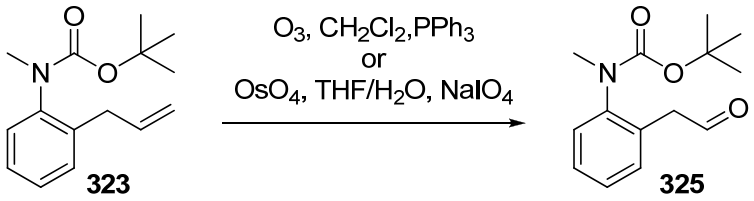
Into a two neck round bottom flask under Ar(g) was placed 2-allyl-*N*-methylbenzenamine **322** (0.50 g, 3.4 mmol) in dry THF (100 ml) followed by $Boc_2O$ (0.82 g, 0.86 ml, 1.1 equiv.) and a catalytic amount of DMAP. The reaction mixture was allowed to stir at rt for 18 h. The reaction was worked up by the addition of $H_2O$ and the organic material extracted with EtOAc (3 × 50 ml). The organic extracts were combined, dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The product was purified by column chromatography (5% EtOAc/hexane) to yield **323** as a light yellow oil (0.61 g, 72%).



**$R_f$** = 0.67 (20% EtOAc/hexane). **$^{1}$H NMR** (300 MHz): $\delta_H$ = 7.26-7-07 (4H, m, Ar*H*); 5.98-5.85 (1H, m, $CH_2CH$=$CH_2$); 5.10-5.05 (2H, m, $CH_2CH$=$CH_2$); 3.32 (2H, d, *J* = 5.9 Hz, $CH_2CH$=$CH_2$); 3.13 (3H, s, $NCH_3$); 1.52 and 1.33 (each 9H, s, $CO_2C(CH_3)_3$ in a respective ratio of 1:2 owing to rotational isomers). **$^{13}$C NMR** (75 MHz): $\delta_C$ = 155.1 (C=O), 142.2 (C1), 137.3 (C6), 136.5 ($CH_2CH$=$CH_2$), 129.9 (C5), 127.6 (C3), 127.2 (C4), 127.0 (C2), 116.1 ($CH_2CH$=$CH_2$), 79.6 ($OC(CH_3)_3$), 37.3 ($NCH_3$), 35.3 ($CH_2CH$=$CH_2$), 28.2 ($OC(CH_3)_3$).

**IR**: $\nu_{max}(cm^{-1}) = 2976$, 1492 (ArCH), 1697 (C=O). **HRMS:** Found $M^+$ 247.15670. $C_{15}H_{21}NO_2$ requires *M* 247.15723 amu. (EI) 244(2%), 247 (100).

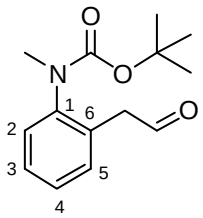
### 5.5.6 Synthesis of *tert*-butyl methyl(2-(2-oxoethyl)phenyl)carbamate 325




Procedure A: Into a two neck round bottom flask fitted with a glass rod connected by silicone tubing to the ozone generator, the *tert*-butyl 2-allylphenyl(methyl)carbamate **323** (0.32 g, 1.3 mmol) was dissolved in dry $CH_2Cl_2$ (50 ml) and the solution cooled to – 78 °C by means of an $Me_2CO$-dry ice bath. $O_3$ was bubbled through the solution and the conversion of the starting material to product was monitored by means of TLC at 5 min intervals. Once most of the starting material was used up, the solution had become a dark orange colour. $O_2$ was then bubbled through the solution to displace the $O_3$. The solution was then stirred at 0 °C and triphenylphosphine (0.68 g, 2.6 mmol, 2 equiv.) was added in one portion. The solution was allowed to stir at this temperature for 3 h. $H_2O$ was then added and the organic product extracted with $CH_2Cl_2$ (3 × 50 ml). The organic extracts were combined, dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (5% EtOAc/hexane) to yield the aldehyde **325** (0.097 g, 30%).

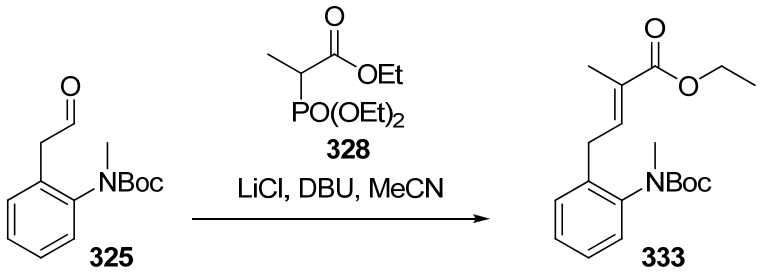
Procedure B: Into a two neck round bottom flask was placed *tert*-butyl 2 allylphenyl(methyl)carbamate **323** (1.0 g, 4.0 mmol) in a mixture of $H_2O$ (5 ml) and THF (15 ml). To this solution was added a 1% aqueous solution of $OsO_4$ (1 ml) over a period of 15 min. It was then allowed to stir for a further 30 min. During this time the yellow solution became black in colour. $NaIO_4$ (2.7 g, 3.1 equiv., 13 mmol) was then added portion wise over 15 min and the mixture was then allowed to stir at rt for a further 2 h. $H_2O$ was then added to the reaction mixture and the organic product was extracted with EtOAc (3 × 50 ml). The organic extracts were combined, dried over anhydrous $Na_2SO_4$,

filtered and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (5% EtOAc/hexane) to yield the aldehyde **325** (0.55 g, 55%).



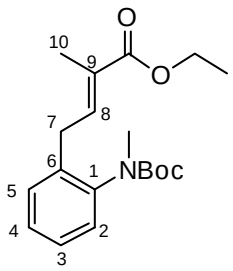
**$^{1}$H NMR** (300 MHz): $\delta_H$ = 9.69 (1H, s, C*H*O); 7.33-7.26 (4H, m, Ar*H*); 3.63 (2H, s, C$H_2$CHO); 3.14 (3H, s, NC$H_3$); 1.50 and 1.32 (each 9H, s, $CO_2C(CH_3)_3$ in a respective ratio of 1:2 owing to rotational isomers). **$^{13}$C NMR** (75 MHz): $\delta_C$ = 199.8 (*C*HO), 198.9 (*C*=O), 154.8 (C5), 143.1 (C4), 131.0 (Ar*C*N), 130.4 (C6), 128.7 (C2), 127.6 (C3), 80.5 (O*C*$(CH_3)_3$), 46.2 (N$CH_3$), 37.5 (Ar*C*$H_2$CHO), 28.2 (OC(*C*$H_3)_3$). **IR**: $\nu_{max}$(cm$^{-1}$) = 2977, 1496 (ArCH), 1695 (C=O). **LRMS:** Found $M^+$ 131.06 (possibly due to loss of the Boc group addition of N to aldehyde and $H_2O$), $C_{14}H_{19}NO_3$ requires *M* 249.13649 amu.

### 5.5.7 Synthesis of (*E*)-ethyl 4-(2-(*tert*-butoxycarbonyl)phenyl)-2-methylbut-2-enoate 333



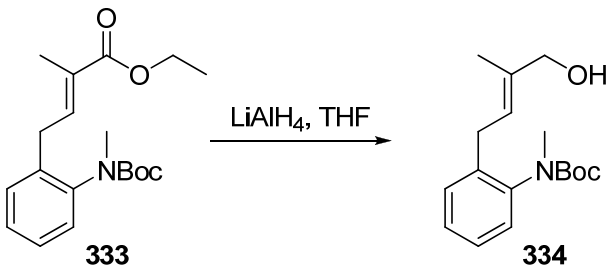

Into a dry two neck round bottom flask fitted with a dropping funnel under Ar(g) was placed dry MeCN (50 ml) followed by *tert*-butyl methyl(2-(2-oxoethyl)phenyl)carbamate **325** (0.1 g, 0.4 mmol) and LiCl (0.041 g, 0.96 mmol, 2.4 equiv.). The dropping funnel was charged with a mixture of DBU (0.055 g, 0.054 ml, 0.36 mmol, 0.9 equiv.) and ethyl 2-(diethoxyphosphoryl) propionate **328** (0.096 g, 0.086 ml, 1.0 equiv.) both dissolved in dry MeCN (20 ml). The solution in the round bottom flask was cooled to 0 °C by means of an ice bath and the solution in the dropping funnel was then added dropwise to this cooled solution over an hour. The reaction mixture was maintained at approximately 5 °C and monitored by TLC. Once the starting material was reduced to trace amounts, the reaction was transferred to a dropping funnel, diluted with EtOAc and $H_2O$ was added. After mixing the phases, the organic phase was separated and the aqueous phase extracted with

EtOAc (3 × 20 ml). The organic fractions were combined, dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography (10% EtOAc/hexane) to yield the product **333** (0.096 g, 80%).




**$^1$H NMR** (300 MHz): $\delta_H$ = 7.18 (4H, m, Ar*H*); 6.84 (1H, t, *J* = 6.9 Hz, H8); 4.18 (2H, q, *J* = 7.1 Hz, C$H_2$CH$_3$); 3.42 (2H, m, H7); 3.13 (3H, s, NC$H_3$); 1.93 (3H, s, C$H_3$C=C); 1.51 and 1.33 (each 9H, s, $CO_2C(CH_3)_3$ in a respective ratio of 1:2 owing to rotational isomers); 1.27 (3H, t, *J* = 7.1 Hz, $CH_2CH_3$) overlapping signals. **$^{13}$C NMR** (75 MHz): $\delta_C$ = 174.2 (*C*=O), 167.7 (N*C*=O), 154.8 (C9), 142.1 (Ar*C*N), 139.4 (C8), 136.4 (C6), 129.6 (C5), 128.5 (C3 ), 127.4 (C4), 126.4 (C2), 79.7 ($OC(CH_3)_3$), 60.3 ($CH_2CH_3$), 37.1 ($NCH_3$), 30.2 (C7), 28.1 ($OC(CH_3)_3$), 14.1 ($CH_2CH_3$), 12.4 (C10). **IR**: $\nu_{max}$(cm$^{-1}$) = 2977, 1494 (ArCH), 1696 and 1649 (C=O). **HRMS:** Found M$^+$ 333. 19349. $C_{19}H_{27}NO_4$ requires *M* 333.19401 amu. (EI) 330 (4%), 332 (16), 333 (100).

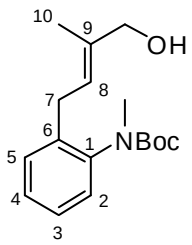
### 5.5.8 Synthesis of (*E*)-*tert*-butyl 2-(4-hydroxy-3-methylbut-2-enyl)phenyl(methyl)carbamate 334




**333** **334**

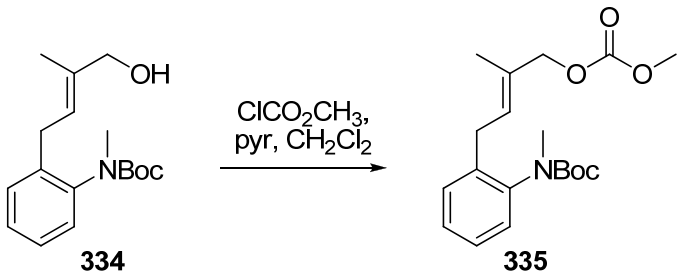
Into a flame-dried two neck round bottom flask under Ar(g) was placed (*E*)-ethyl 4-(2-(*tert*-butoxycarbonyl)phenyl)-2-methylbut-2-enoate **333** (0.10 g, 0.30 mmol) followed by dry THF (20 ml). The solution was cooled to 0 °C by means of an ice bath. $LiAlH_4$ (0.013 g, 0.33 mol, 1.1 equiv.) was added to the solution portionwise, resulting in effervescence of the solution. The solution changed to a bright green colour. It was left to stir overnight and the bright colour soon disappeared. After 18 h the solution was again cooled down to 0 °C and ice cold $H_2O$ was added to quench the reaction. It was diluted with EtOAc (on mixing the emulsion formed may be broken with the addition of a small

amount of aqueous HCl). The phases were separated and the aqueous phases further extracted with EtOAc (3 × 50 ml). The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (20% EtOAc/hexane) to yield **334** as a light yellow oil (0.06 g, 70%).




**$^1$H NMR** (300 MHz): $\delta_H$ = 7.15 (4H, m, Ar*H*); 5.54 (1H, t, *J* = 6.6 Hz, H8); 4.03 (2H, s, C$H_2$OH); 3.32 (2H, d, *J* = 7.0 Hz, H7); 3.12 (3H, s, NC$H_3$); 1.76 (4H, s, C$H_3$C=C and O*H*, overlapping signals); 1.52 and 1.34 (each 9H, s, $CO_2C(CH_3)_3$ in a respective ratio of 1:2 owing to rotational isomers). **$^{13}$C NMR** (75 MHz): $\delta_C$ = 155.2 (N*C*=O), 142.1 (C9), 138.1 (C8), 136.1 (Ar*C*N), 129.6 (C6), 127.6 (C5), 127.3 (C3), 126.9 (C4), 123.8 (C2), 79.8 (O*C*$(CH_3)_3$), 68.7 (*C*$H_2$OH), 37.1 (N*C*$H_3$), 29.5 (C7), 28.3 (OC(*C*$H_3)_3$), 13.8 (C10). **IR**: $\nu_{max}(cm^{-1})$ = 3412 (OH), 2977, 1678, 1494 (ArCH), 1698 (C=O). **HRMS:** Found $M^+$ 291.18274. $C_{17}H_{25}NO_3$ requires *M* 291.18344 amu. (EI) 289 (16%), 291 (100).

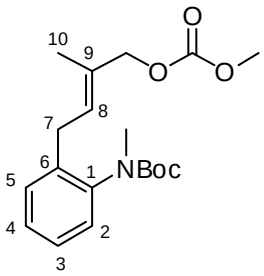
### 5.5.9 Synthesis of (*E*)-4-(2-(*tert*-butoxycarbonyl)phenyl)-2-methylbut-2-enyl methyl carbonate 335




**334** **335**

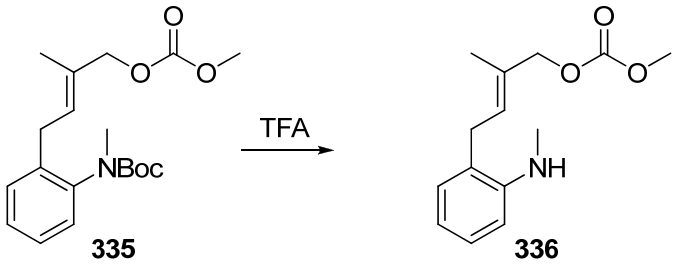
Into a two neck round bottom flask under Ar(g) was placed the (*E*)-*tert*-butyl 2-(4-hydroxy-3-methylbut-2-enyl)phenyl(methyl)carbamate **334** (0.19 g, 0.65 mmol) followed by dry $CH_2Cl_2$ (30 ml). The flask was placed into an ice bath and cooled to approximately 0 °C. Pyridine (0.21 g, 0.21 ml, 2.6 mmol, 4 equiv.) was added in one portion followed by the addition of the methyl chloroformate (0.12 g, 0.10 ml, 2 equiv.). The reaction was left to proceed at 0 °C for 30 min and then left to proceed at rt for a further 18 h. $H_2O$ was carefully added and the mixture decanted into a separating funnel. The mixture was diluted

with $CH_2Cl_2$ and $H_2O$. After thoroughly mixing, the phases were separated and the aqueous phase further extracted with $CH_2Cl_2$ (2 × 20 ml). The organic phases were combined, dried over anhydrous $Na_2SO_4$ and filtered. The solvent was removed *in vacuo* and the crude material purified by column chromatography (20% EtOAc/hexane) to give the product **335** as a light yellow oil (0.20 g, 88%).




**$^1$H NMR** (300 MHz): $\delta_H$ = 7.14 (4H, m, Ar*H*); 5.64 (1H, t, *J* = 6.9 Hz, H8); 4.57 (2H, s, C*H*$_2$OCO); 3.78 (3H, s, OC*H*$_3$); 3.30 (2H, m, H7); 3.13 (3H, s, NC*H*$_3$); 1.77 (3H, s, C*H*$_3$C=C); 1.51 and 1.33 (each 9H, s, $CO_2C(CH_3)_3$ in a respective ratio of 1:2 owing to rotational isomers). **$^{13}$C NMR** (75 MHz): $\delta_C$ = 155.7 (N*C*=O), 142.3 (C=O), 142.2 (C9), 137.6 (C8), 131.0 (Ar*C*N), 129.4 (C6), 127.8 (C5), 127.5 (C3), 127.4 (C4), 127.1 (C2), 79.7 (O*C*(CH$_3$)$_3$), 73.3 (*C*H$_2$OCO), 54.7 (OCH$_3$), 37.2 (NCH$_3$), 29.2 (C7), 28.3 (OC(*C*H$_3$)$_3$), 14.0 (C10). **IR**: $\nu_{max}$(cm$^{-1}$) = 2975, 1492, 1441 (ArCH), 1747, 1696 (C=O).

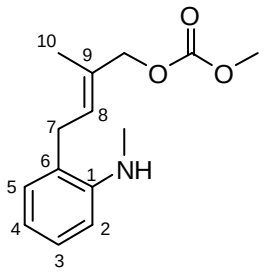
### 5.5.10 Synthesis of (*E*)-methyl-2-methyl-4-(2-(methylamino)phenyl)but-2-enyl carbonate 336




**335** **336**

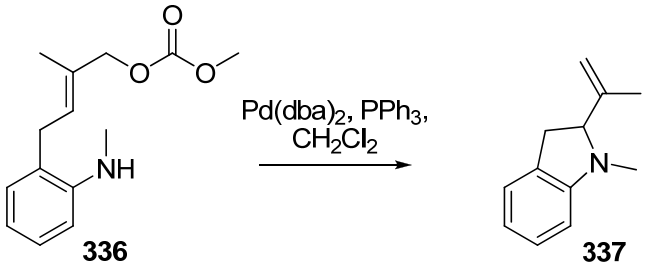
Neat (*E*)-4-(2-(*tert*-butoxycarbonyl)phenyl)-2-methylbut-2-enyl methyl carbonate **335** (0.30 g, 0.86 mmol) was placed in a round bottom flask followed by the addition of TFA (0.098 g, 0.066 ml, 0.86 mmol, 1 equiv.). The mixture was allowed to stir for 18 h at rt. $CH_2Cl_2$ was then added, followed by a saturated solution of $NaHCO_3$, to remove any unreacted acid. The organic product was separated and the aqueous phase further extracted with $CH_2Cl_2$ (2 × 20 ml). The organic extracts were combined, dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by

column chromatography (20% EtOAc/hexane) to yield the compound **336** as a light yellow oil (0.18 g, 87%).



**$^1$H NMR** (300 MHz): $\delta_H$ = 7.17 (1H, t, *J* = 7.7 Hz, H3); 7.02 (1H, d, *J* = 7.2 Hz, H5); 6.74-6.59 (2H, m, H4 and H2) 5.62 (1H, t, *J* = 6.7 Hz, H8); 4.57 (2H, s, C*H*$_2$OCO); 3.79 (3H, s, OC*H*$_3$); 3.24 (2H, d, *J* = 6.7 Hz, H7); 2.86 (3H, s, NC*H*$_3$); 1.80 (3H, s, C*H*$_3$C=C), 1.27 (1H, s, N*H*). **$^{13}$C NMR** (75 MHz): $\delta_C$ = 155.7 (C=O), 147.0 (C9), 131.6 (C8), 128.9 (C5), 127.6 (C3), 127.4 (Ar*C*N), 124.1 (C6), 117.1 (C4), 109.8 (C2), 73.3 (*C*H$_2$OCO), 54.8 (O*C*H$_3$), 30.8 (N*C*H$_3$), 30.1 (C7), 14.0 (C10). **IR**: $\nu_{max}$(cm$^{-1}$) = 2955 (NH), 1745 (C=O), 1695, 1511, 1440 (ArCH). **HRMS:** Found $M^+$ 249.13591. $C_{14}H_{19}NO_3$ requires *M* 249.13649 amu. (EI) 244 (4%), 248 (6), 249 (100).

### 5.5.11 Synthesis of 1-methyl-2-(prop-1-en-2-yl)indoline 337

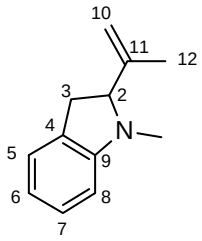



**336** **337**

For the racemic reaction: A solution of Pd(dba)$_2$ (2.8 mg, 2 mol%, 4.8 × 10$^{-6}$ mol) in dry degassed $CH_2Cl_2$ (5 ml) in a two neck round bottom flask was thoroughly degassed by bubbling Ar(g) through the solution with a Pasteur pipette. $PPh_3$ (6.4 mg, 10 mol%, 2.4 × 10$^{-5}$ mol) was then added to this red solution and the mixture further degassed and left to stir under Ar(g) until the solution changed in colour to yellow, indicating the formation of Pd($PPh_3$)$_4$ *in situ*. The carbonate **336** (60 mg, 0.24 mmol) was then introduced into the reaction flask against a flow of Ar(g). The reaction was left to stir at rt for 12 h. Once complete, the crude reaction mixture was adsorbed onto silica gel and purified by means of column chromatography (10% EtOAc/hexane) to yield the cyclised product **337** (0.023 g, 55%).

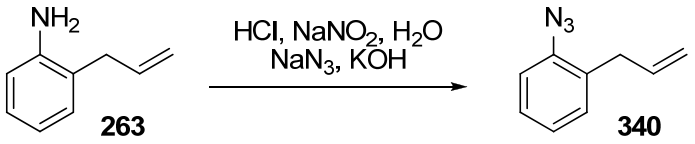
For the chiral reaction: $Pd(dba)_2$ (9.3 mg, 2 mol%, $1.6 \times 10^{-5}$ mol) and dry $CH_2Cl_2$ (5 ml) were introduced into a dry two neck round bottom flask under Ar (g). Argon was then further bubbled through the dark red solution by means of a Pasteur pipette for 5 min. The chiral Trost ligand (33.5 mg, 6 mol%, $4.90 \times 10^{-5}$ mol) was then introduced into the flask against a flow of Ar(g), and the reaction mixture stirred under Ar(g) for 10 min, during which time the solution changed from dark red to a light yellow colour indicating the ligand exchange. The carbonate **336** (0.20 g, 0.81 mmol) was then introduced to the flask and the reaction was left to stir for 12 h at 25 °C under an Ar(g) atmosphere. Once the reaction was complete the crude reaction mixture was dried onto silica gel and the product was purified by column chromatography (10% EtOAc/hexane) to yield the product **337** as a light yellow oil (0.066 g, 48%). The reaction showed no enantioselectivity.

Using acetic acid: $Pd(dba)_2$ (2.3 mg, 2 mol%, $4.0 \times 10^{-6}$ mol) and dry $CH_2Cl_2$ (5 ml) were introduced into a dry two neck round bottom flask equipped with a condenser. Ar(g) was then bubbled through the dark red solution by means of a Pasteur pipette for 5 min. The chiral Trost ligand (8.3 mg, 6 mol%, $1.2 \times 10^{-5}$ mol) was then introduced into the flask against a flow of Ar(g), and the reaction mixture stirred under Ar(g) for 10 min, during which time the solution changed from dark red to a light yellow colour indicating the ligand exchange. The carbonate **336** (50 mg, 0.20 mmol) followed by HOAc (12.0 mg, 11.6 μl, 0.20 mmol, 1.01 equiv.) was then introduced to the flask and the reaction was left to stir for 12 h at reflux under an Ar(g) atmosphere. Once the reaction was complete the crude reaction mixture was dried onto silica gel and the product was purified by column chromatography (10% EtOAc/hexane) to yield trace amounts of the product **337** showing 32% ee as determined by chiral HPLC (Chiralcel OJ 10μ 250 × 4.6 mm, 20% IPA/hexane).

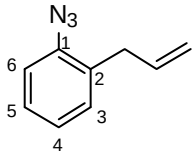



**$^1$H NMR** (400 MHz): $\delta_H$ = 7.08 (1H, t, *J* = 7.7 Hz, H6), 7.04 (1H, d, *J* = 7.2 Hz, H8), 6.65 (1H, t, *J* = 7.2 Hz, H7), 6.45 (1H, d, *J* = 7.8 Hz, H5), 5.03–5.01 (1H, m, H10$_a$), 4.95–4.93 (1H, m, H10$_b$), 3.84–3.77 (1H, m, H2), 3.04 (1H, dd, *J* = 15.6 Hz and 8.9 Hz, H3$_a$), 2.84 (1H, dd, *J* = 15.6 Hz and 10.9 Hz, H3$_b$), 2.62 (3H, s, NC*H*$_3$), 1.74 (3H, s, C*H*$_3$CH=CH$_2$). **$^{13}$C NMR** (100 MHz): $\delta_C$ = 153.4 (C9), 144.8 (C11), 128.7 (C4), 127.5 (C6), 124.0 (C8), 117.6 (C7), 113.4 (C10), 106.9 (C5), 73.5 (C2), 34.5 (C3), 33.7 (NCH$_3$), 17.5 (C12). **IR**: $\nu_{max}$(cm$^{-1}$) = 2948, 1606, 1484 (ArCH). **HRMS:** Found M$^+$ 173.11986. $C_{12}H_{15}N$ requires *M* 173.12045 amu. (EI) 186 (20%), 169 (28), 170 (36) 173 (100).

### 5.5.12 Synthesis of 1-allyl-2-azidobenzene 340

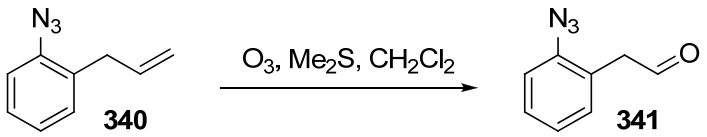



To a solution of 2-allylaniline **263** (2.25 g, 16.9 mmol) in 2 M HCl (100 ml) cooled to –5 ºC, was added dropwise a solution of $NaNO_2$ (1.3 g, 1.1 equiv., 18 mmol) in $H_2O$ (5 ml), while the temperature of the reaction was kept between –5 ºC and 0 ºC. After 30 min of stirring, a solution of $NaN_3$ (1.3 g, 1.2 equiv., 20 mmol) in $H_2O$ (5 ml) was added and stirring was continued for 1 h. After this time the reaction was saturated with KOH and then extracted with $CH_2Cl_2$ (3 × 50 ml). The extracts were washed with $H_2O$, then dried with anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography to produce **340** as a light yellow oil. (1.75 g, 65%)

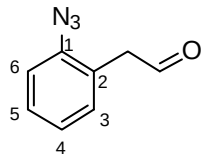



**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.32–7.00 (4H, m, ArC*H*), 6.05–5.82 (1H, m, CH$_2$C*H*=CH$_2$), 5.04 (2H, dd, *J* = 13.4 and 9.5 Hz, CH$_2$CH=C*H*$_2$), 3.34 (2H, d, *J* = 6.3 Hz, C*H*$_2$CH=CH$_2$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 138.0 (Ar*C*N), 136.3 (CH$_2$*C*H=CH$_2$), 131.5 (Ar*C*), 130.5 (Ar*C*H), 127.6 (Ar*C*H), 124.8 (Ar*C*H), 118.1 (Ar*C*H), 115.9 (CH$_2$CH=*C*H$_2$), 35.1 (*C*H$_2$CH=CH$_2$).

### 5.5.13 Synthesis of 2-(2-azidophenyl)acetaldehyde 341

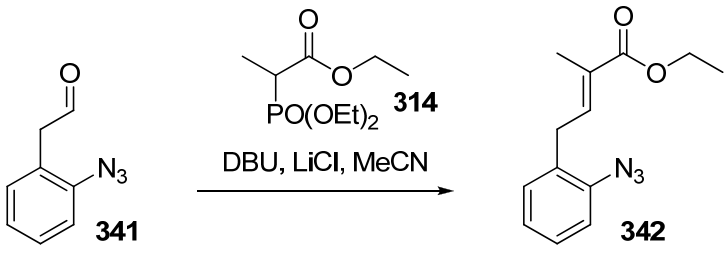



In a two neck round bottom flask fitted with a glass rod connected by silicon tubing to the $O_3$ generator, the azide **340** (1.8 g, 11 mmol) was dissolved in dry $CH_2Cl_2$ (50 ml). The solution was cooled down to − 78 ºC by means of a $Me_2CO$-dry ice bath. $O_3$ gas was bubbled through the solution and the conversion of the starting material was monitored by TLC. Once the starting material was used up the solution became blue in colour. $O_2$ gas was then used to displace the $O_3$. The solution was then stirred at 0 ºC and $Me_2S$ (6.8 g, 8.1 ml, 10 equiv., 0.11 mol) was added to it. The reaction was left to stir at rt for 18 h. After this time $H_2O$ was added and the organic phase was extracted with $CH_2Cl_2$ (3 × 50 ml). The organic fractions were combined, dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The crude material was columned through silica gel to yield **341** as a yellow oil. (0.99 g, 56%)



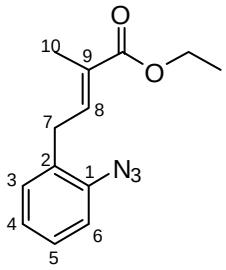

**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 9.69 (1H, s, C*H*O), 7.39–7.10 (4H, m, 4 × ArC*H*), 3.66 (2H, d, *J* = 1.2 Hz, ArC$H_2$CHO).

### 5.5.14 Synthesis of ethyl 4-(2-azidophenyl)-2-methylbut-2-enoate 342




Into a 2 neck round bottom flask under Ar (g) was placed dry MeCN (10 ml), LiCl (0.053 g, 1.2 mmol, 2.4 equiv.), phosphoryl propionate **341** (0.14 g, 0.12 ml, 5.7 mmol, 1.1 equiv.) and the aldehyde **327** (0.10 g, , 0.62 mmol, 1.2 equiv.). The solution was cooled to around 5 ºC. A solution of DBU (0.079 g, 0.077 ml, 0.51 mmol) in dry MeCN (5 ml)

was then very slowly added to the reaction mixture by means of a syringe pump, (added dropwise over 20 h). The aldehyde solution changed from yellow to orange. The reaction was maintained at 5 ºC and monitored by TLC. Once the starting material was reduced to trace amounts, the reaction was transferred to a dropping funnel and diluted with EtOAc (20 ml) and $H_2O$ (40 ml). After mixing the phases, the organic phase was extracted with more EtOAc (3 × 20 ml). The combined organic fractions were then dried over anhydrous $Na_2SO_4$, filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography (5% EtOAc/hexane) to yield the product **342** as a yellow oil (0.07 g, 57%).




**$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.31–7.20 (2H, m, ArC*H*), 7.17–7.03 (2H, m, ArC*H*), 5.99 (1H, td, *J* = 7.4 and 1.4 Hz, H8), 4.25 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 3.82–3.73 (2H, m, H7), 1.92 (3H, d, *J* = 1.4 Hz, C*H*$_3$C=C), 1.33 (3H, t, *J* = 6.95 Hz, CH$_2$C*H*$_3$). **$^{13}$C NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 167.9 (C=O), 139.6 (Ar*C*H), 138.0 (Ar*C*), 131.7 (Ar*C*), 130.6 (Ar*C*H), 128.0 (C9), 127.7 (Ar*C*H), 124.9 (Ar*C*H), 118.1 (C8), 60.3 (C7), 31.2 (*C*H$_2$CH$_3$), 20.6 (C10), 14.3 (CH$_2$*C*H$_3$).

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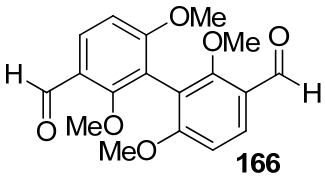
# Appendices

## A1 X-ray crystallographic data

Intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo $K_\alpha$ radiation (50kV, 30mA) using the APEX 2[155] data collection software. The collection method involved ω-scans of width 0.5° and 512×512 bit data frames. Data reduction was carried out using the program *SAINT+* and face indexed absorption corrections were made using *XPREP*.[156]

The crystal structure was solved by direct methods using *SHELXTL*.[157] 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[151] and ORTEP-3.[152]

### A1.1 X-Ray crystallographic data for 2,2',6,6'-Tetramethoxy[1,1′-biphenyl]-3,3′-dicarbaldehyde 166




166

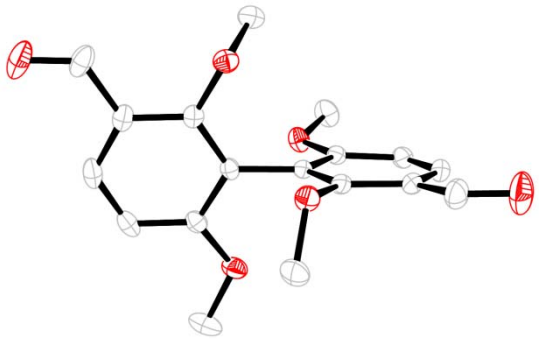


**Table A1.1.1 Crystal Data and Structure Refinement for 166**

| | | |
|---|---|---|
| Empirical formula | $C_{18}H_{18}O_6$ | |
| Formula weight | 330.32 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 8.0686(13) Å | α= 90°. |
| | b = 15.634(3) Å | β= 102.238(8)°. |
| | c = 13.592(2) Å | γ = 90°. |
| Volume | 1675.5(5) Å3 | |
| Z | 4 | |
| Density (calculated) | 1.309 Mg/m3 | |
| Absorption coefficient | 0.099 $mm^{-1}$ | |
| F(000) | 696 | |
| Crystal size | 0.43 x 0.18 x 0.18 $mm^3$ | |
| Theta range for data collection | 2.01 to 27.99°. | |
| Index ranges | -10<=h<=10, -16<=k<=20, -17<=l<=17 | |
| Reflections collected | 10745 | |
| Independent reflections | 4048 [R(int) = 0.0588] | |
| Completeness to theta = 27.99° | 100.0% | |

| | |
|---|---|
| Absorption correction | None |
| Max. and min. transmission | 0.9825 and 0.9588 |
| Refinement method | Full-matrix least-squares on F2 |
| Data / restraints / parameters | 4048 / 0 / 221 |
| Goodness-of-fit on F2 | 0.974 |
| Final R indices [I>2sigma(I)] | R1 = 0.0440, wR2 = 0.1133 |
| R indices (all data) | R1 = 0.0795, wR2 = 0.1272 |
| Largest diff. peak and hole | 0.211 and -0.224 e.Å-3 |

**Table A1.1.2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 166. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 1215(2) | 2687(1) | 4161(1) | 29(1) |
| C(1') | 1820(2) | 3591(1) | 4189(1) | 29(1) |
| C(2) | 2355(2) | 2010(1) | 4352(1) | 31(1) |
| C(2') | 2463(2) | 3937(1) | 3403(1) | 31(1) |
| C(3) | 1806(2) | 1155(1) | 4313(1) | 36(1) |
| C(3') | 3107(2) | 4777(1) | 3458(1) | 37(1) |
| C(4') | 3055(2) | 5261(1) | 4314(2) | 45(1) |
| C(4) | 72(2) | 1001(1) | 4122(1) | 40(1) |
| C(5) | -1103(2) | 1652(1) | 3947(1) | 37(1) |
| C(5') | 2391(2) | 4943(1) | 5092(1) | 43(1) |
| C(6') | 1778(2) | 4104(1) | 5034(1) | 34(1) |
| C(6) | -532(2) | 2496(1) | 3937(1) | 31(1) |
| C(7') | 952(2) | 3363(1) | 1856(1) | 48(1) |
| C(7) | 4820(2) | 2258(1) | 5607(1) | 54(1) |
| C(8') | 3826(2) | 5135(1) | 2635(2) | 51(1) |
| C(8) | 3030(3) | 451(1) | 4421(2) | 52(1) |
| C(9') | 1200(2) | 4161(1) | 6702(1) | 58(1) |
| C(9) | -3317(2) | 3036(1) | 3254(2) | 51(1) |
| O(1) | 4069(1) | 2186(1) | 4551(1) | 39(1) |
| O(1') | 2540(1) | 3445(1) | 2571(1) | 39(1) |
| O(2') | 4459(2) | 5841(1) | 2648(1) | 69(1) |
| O(2) | 2645(2) | -305(1) | 4383(1) | 77(1) |
| O(3') | 1129(1) | 3716(1) | 5764(1) | 44(1) |
| O(3) | -1574(1) | 3183(1) | 3710(1) | 38(1) |

**Table A1.1.3 Bond lengths [Å] and bond angles [°] for 166**

| | |
|---|---|
| C(1)-C(2) | 1.389(2) |
| C(1)-C(6) | 1.410(2) |
| C(1)-C(1') | 1.492(2) |
| C(1')-C(2') | 1.392(2) |
| C(1')-C(6') | 1.408(2) |
| C(2)-O(1) | 1.3795(18) |
| C(2)-C(3) | 1.406(2) |
| C(2')-O(1') | 1.3804(19) |
| C(2')-C(3') | 1.409(2) |
| C(3)-C(4) | 1.389(2) |
| C(3)-C(8) | 1.465(2) |
| C(3')-C(4') | 1.397(3) |
| C(3')-C(8') | 1.475(3) |
| C(4')-C(5') | 1.374(3) |
| C(4')-H(4') | 0.9500 |
| C(4)-C(5) | 1.376(2) |
| C(4)-H(4) | 0.9500 |
| C(5)-C(6) | 1.399(2) |
| C(5)-H(5) | 0.9500 |

| | |
|---|---|
| C(5')-C(6') | 1.399(2) |
| C(5')-H(5') | 0.9500 |
| C(6')-O(3') | 1.3595(19) |
| C(6)-O(3) | 1.3588(18) |
| C(7')-O(1') | 1.440(2) |
| C(7')-H(7'1) | 0.9800 |
| C(7')-H(7'2) | 0.9800 |
| C(7')-H(7'3) | 0.9800 |
| C(7)-O(1) | 1.439(2) |
| C(7)-H(7A) | 0.9800 |
| C(7)-H(7B) | 0.9800 |
| C(7)-H(7C) | 0.9800 |
| C(8')-O(2') | 1.215(2) |
| C(8')-H(8') | 0.9500 |
| C(8)-O(2) | 1.220(2) |
| C(8)-H(8) | 0.9500 |
| C(9')-O(3') | 1.442(2) |
| C(9')-H(9'1) | 0.9800 |
| C(9')-H(9'2) | 0.9800 |
| C(9')-H(9'3) | 0.9800 |
| C(9)-O(3) | 1.4304(19) |
| C(9)-H(9A) | 0.9800 |
| C(9)-H(9B) | 0.9800 |
| C(9)-H(9C) | 0.9800 |
| C(2)-C(1)-C(6) | 118.10(13) |
| C(2)-C(1)-C(1') | 121.08(13) |
| C(6)-C(1)-C(1') | 120.83(13) |
| C(2')-C(1')-C(6') | 118.81(14) |
| C(2')-C(1')-C(1) | 121.46(13) |
| C(6')-C(1')-C(1) | 119.71(13) |
| O(1)-C(2)-C(1) | 118.77(13) |
| O(1)-C(2)-C(3) | 119.43(13) |
| C(1)-C(2)-C(3) | 121.77(14) |
| O(1')-C(2')-C(1') | 120.07(13) |
| O(1')-C(2')-C(3') | 118.88(14) |
| C(1')-C(2')-C(3') | 121.00(15) |
| C(4)-C(3)-C(2) | 117.92(14) |
| C(4)-C(3)-C(8) | 121.32(15) |
| C(2)-C(3)-C(8) | 120.68(15) |
| C(4')-C(3')-C(2') | 118.24(16) |
| C(4')-C(3')-C(8') | 120.88(16) |
| C(2')-C(3')-C(8') | 120.88(17) |
| C(5')-C(4')-C(3') | 122.09(15) |
| C(5')-C(4')-H(4') | 119.0 |
| C(3')-C(4')-H(4') | 119.0 |
| C(5)-C(4)-C(3) | 122.26(14) |
| C(5)-C(4)-H(4) | 118.9 |
| C(3)-C(4)-H(4) | 118.9 |
| C(4)-C(5)-C(6) | 118.90(15) |
| C(4)-C(5)-H(5) | 120.6 |
| C(6)-C(5)-H(5) | 120.6 |
| C(4')-C(5')-C(6') | 119.07(16) |
| C(4')-C(5')-H(5') | 120.5 |
| C(6')-C(5')-H(5') | 120.5 |
| O(3')-C(6')-C(5') | 124.31(15) |
| O(3')-C(6')-C(1') | 114.92(13) |
| C(5')-C(6')-C(1') | 120.76(15) |
| O(3)-C(6)-C(5) | 123.99(13) |
| O(3)-C(6)-C(1) | 115.08(12) |
| C(5)-C(6)-C(1) | 120.92(14) |
| O(1')-C(7')-H(7'1) | 109.5 |
| O(1')-C(7')-H(7'2) | 109.5 |

| | |
|---|---|
| H(7'1)-C(7')-H(7'2) | 109.5 |
| O(1')-C(7')-H(7'3) | 109.5 |
| H(7'1)-C(7')-H(7'3) | 109.5 |
| H(7'2)-C(7')-H(7'3) | 109.5 |
| O(1)-C(7)-H(7A) | 109.5 |
| O(1)-C(7)-H(7B) | 109.5 |
| H(7A)-C(7)-H(7B) | 109.5 |
| O(1)-C(7)-H(7C) | 109.5 |
| H(7A)-C(7)-H(7C) | 109.5 |
| H(7B)-C(7)-H(7C) | 109.5 |
| O(2')-C(8')-C(3') | 124.4(2) |
| O(2')-C(8')-H(8') | 117.8 |
| C(3')-C(8')-H(8') | 117.8 |
| O(2)-C(8)-C(3) | 124.27(18) |
| O(2)-C(8)-H(8) | 117.9 |
| C(3)-C(8)-H(8) | 117.9 |
| O(3')-C(9')-H(9'1) | 109.5 |
| O(3')-C(9')-H(9'2) | 109.5 |
| H(9'1)-C(9')-H(9'2) | 109.5 |
| O(3')-C(9')-H(9'3) | 109.5 |
| H(9'1)-C(9')-H(9'3) | 109.5 |
| H(9'2)-C(9')-H(9'3) | 109.5 |
| O(3)-C(9)-H(9A) | 109.5 |
| O(3)-C(9)-H(9B) | 109.5 |
| H(9A)-C(9)-H(9B) | 109.5 |
| O(3)-C(9)-H(9C) | 109.5 |
| H(9A)-C(9)-H(9C) | 109.5 |
| H(9B)-C(9)-H(9C) | 109.5 |
| C(2)-O(1)-C(7) | 113.87(13) |
| C(2')-O(1')-C(7') | 114.44(12) |
| C(6')-O(3')-C(9') | 118.78(14) |
| C(6)-O(3)-C(9) | 118.36(12) |

Symmetry transformations used to generate equivalent atoms

**Table A1.1.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 166. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$**

| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| C(1) | 31(1) | 30(1) | 24(1) | 1(1) | 3(1) | -3(1) |
| C(1') | 24(1) | 27(1) | 34(1) | -2(1) | 2(1) | 0(1) |
| C(2) | 31(1) | 33(1) | 27(1) | 2(1) | 2(1) | -2(1) |
| C(2') | 24(1) | 29(1) | 37(1) | 3(1) | 3(1) | 4(1) |
| C(3) | 44(1) | 31(1) | 31(1) | 4(1) | 2(1) | -1(1) |
| C(3') | 25(1) | 32(1) | 51(1) | 9(1) | 2(1) | 2(1) |
| C(4') | 33(1) | 27(1) | 68(1) | 0(1) | -5(1) | -3(1) |
| C(4) | 49(1) | 31(1) | 37(1) | 2(1) | 4(1) | -9(1) |
| C(5) | 35(1) | 39(1) | 35(1) | -1(1) | 3(1) | -10(1) |
| C(5') | 36(1) | 36(1) | 50(1) | -15(1) | -3(1) | 1(1) |
| C(6') | 26(1) | 37(1) | 36(1) | -3(1) | 1(1) | 0(1) |
| C(6) | 31(1) | 33(1) | 27(1) | -1(1) | 4(1) | -2(1) |
| C(7') | 53(1) | 53(1) | 36(1) | -2(1) | 6(1) | -3(1) |
| C(7) | 43(1) | 59(1) | 49(1) | -2(1) | -11(1) | -6(1) |
| C(8') | 34(1) | 48(1) | 68(1) | 26(1) | 3(1) | -1(1) |
| C(8) | 54(1) | 36(1) | 60(1) | 6(1) | 0(1) | 3(1) |
| C(9') | 44(1) | 91(2) | 38(1) | -22(1) | 6(1) | 0(1) |
| C(9) | 30(1) | 53(1) | 63(1) | -7(1) | -3(1) | 0(1) |
| O(1) | 31(1) | 41(1) | 42(1) | 4(1) | 0(1) | 0(1) |
| O(1') | 38(1) | 42(1) | 37(1) | 1(1) | 11(1) | 5(1) |
| O(2') | 47(1) | 56(1) | 96(1) | 39(1) | 0(1) | -11(1) |
| O(2) | 73(1) | 33(1) | 118(1) | 9(1) | 2(1) | 4(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| O(3') | 46(1) | 52(1) | 33(1) | -9(1) | 10(1) | -4(1) |
| O(3) | 26(1) | 37(1) | 49(1) | -5(1) | 2(1) | -1(1) |

**Table A1.1.5 Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for 166**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(4') | 3492 | 5827 | 4361 | 54 |
| H(4) | -317 | 427 | 4113 | 48 |
| H(5) | -2281 | 1530 | 3834 | 44 |
| H(5') | 2350 | 5289 | 5661 | 51 |
| H(7'1) | 85 | 3145 | 2199 | 72 |
| H(7'2) | 1087 | 2964 | 1322 | 72 |
| H(7'3) | 605 | 3923 | 1561 | 72 |
| H(7A) | 4312 | 2742 | 5893 | 80 |
| H(7B) | 6044 | 2351 | 5694 | 80 |
| H(7C) | 4617 | 1730 | 5952 | 80 |
| H(8') | 3793 | 4789 | 2056 | 61 |
| H(8) | 4199 | 592 | 4526 | 62 |
| H(9'1) | 2386 | 4254 | 7036 | 87 |
| H(9'2) | 638 | 3816 | 7139 | 87 |
| H(9'3) | 622 | 4713 | 6569 | 87 |
| H(9A) | -3393 | 2631 | 2696 | 76 |
| H(9B) | -3853 | 3577 | 3000 | 76 |
| H(9C) | -3900 | 2797 | 3756 | 76 |

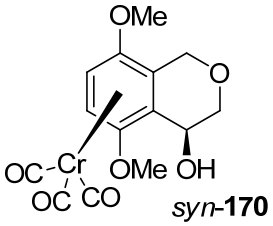
**Table A1.1.6 Torsion angles [°] for 166**

| | |
|---|---|
| C(2)-C(1)-C(1')-C(2') | 76.56(19) |
| C(6)-C(1)-C(1')-C(2') | -103.17(17) |
| C(2)-C(1)-C(1')-C(6') | -102.07(17) |
| C(6)-C(1)-C(1')-C(6') | 78.21(19) |
| C(6)-C(1)-C(2)-O(1) | 178.61(13) |
| C(1')-C(1)-C(2)-O(1) | -1.1(2) |
| C(6)-C(1)-C(2)-C(3) | 0.8(2) |
| C(1')-C(1)-C(2)-C(3) | -178.94(14) |
| C(6')-C(1')-C(2')-O(1') | 179.13(12) |
| C(1)-C(1')-C(2')-O(1') | 0.5(2) |
| C(6')-C(1')-C(2')-C(3') | 1.8(2) |
| C(1)-C(1')-C(2')-C(3') | -176.88(13) |
| O(1)-C(2)-C(3)-C(4) | 179.24(14) |
| C(1)-C(2)-C(3)-C(4) | -3.0(2) |
| O(1)-C(2)-C(3)-C(8) | -3.7(2) |
| C(1)-C(2)-C(3)-C(8) | 174.05(15) |
| O(1')-C(2')-C(3')-C(4') | -178.57(13) |
| C(1')-C(2')-C(3')-C(4') | -1.2(2) |
| O(1')-C(2')-C(3')-C(8') | 1.1(2) |
| C(1')-C(2')-C(3')-C(8') | 178.46(14) |
| C(2')-C(3')-C(4')-C(5') | -0.4(2) |
| C(8')-C(3')-C(4')-C(5') | 179.99(15) |
| C(2)-C(3)-C(4)-C(5) | 1.8(2) |
| C(8)-C(3)-C(4)-C(5) | -175.21(16) |
| C(3)-C(4)-C(5)-C(6) | 1.5(2) |
| C(3')-C(4')-C(5')-C(6') | 1.3(3) |
| C(4')-C(5')-C(6')-O(3') | 178.54(14) |
| C(4')-C(5')-C(6')-C(1') | -0.6(2) |
| C(2')-C(1')-C(6')-O(3') | 179.89(12) |
| C(1)-C(1')-C(6')-O(3') | -1.4(2) |
| C(2')-C(1')-C(6')-C(5') | -0.8(2) |
| C(1)-C(1')-C(6')-C(5') | 177.82(14) |

| | |
|---|---|
| C(4)-C(5)-C(6)-O(3) | 175.72(14) |
| C(4)-C(5)-C(6)-C(1) | -3.8(2) |
| C(2)-C(1)-C(6)-O(3) | -176.91(13) |
| C(1')-C(1)-C(6)-O(3) | 2.8(2) |
| C(2)-C(1)-C(6)-C(5) | 2.6(2) |
| C(1')-C(1)-C(6)-C(5) | -177.65(14) |
| C(4')-C(3')-C(8')-O(2') | 2.4(3) |
| C(2')-C(3')-C(8')-O(2') | -177.18(16) |
| C(4)-C(3)-C(8)-O(2) | -2.2(3) |
| C(2)-C(3)-C(8)-O(2) | -179.13(19) |
| C(1)-C(2)-O(1)-C(7) | 93.87(17) |
| C(3)-C(2)-O(1)-C(7) | -88.27(18) |
| C(1')-C(2')-O(1')-C(7') | 79.22(17) |
| C(3')-C(2')-O(1')-C(7') | -103.36(16) |
| C(5')-C(6')-O(3')-C(9') | -5.7(2) |
| C(1')-C(6')-O(3')-C(9') | 173.54(14) |
| C(5)-C(6)-O(3)-C(9) | -13.6(2) |
| C(1)-C(6)-O(3)-C(9) | 165.94(14) |

Symmetry transformations used to generate equivalent atoms:

## A1.2 X-Ray crystallographic data for [(*S*)-5,8-dimethoxyisochroman-4-ol]tricarbonylchromium (0): *syn*-170




*syn*-**170**

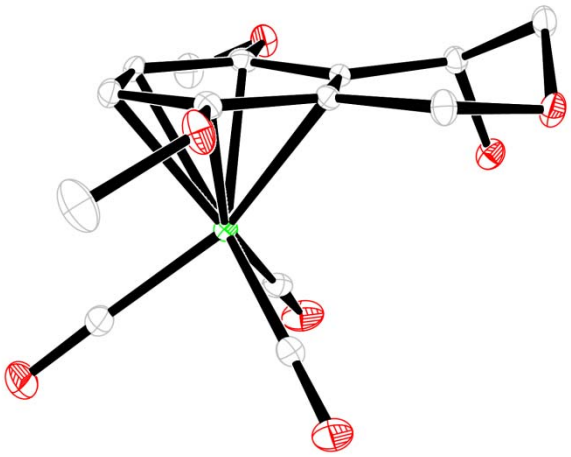


**Table A1.2.1 Crystal data and structure refinement for *syn*-170**

| | | |
|---|---|---|
| Empirical formula | $C_{14}H_{14}CrO_7$ | |
| Formula weight | 346.25 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | P2(1)2(1)2(1) | |
| Unit cell dimensions | a = 6.70100(10) Å | α= 90°. |
| | b = 12.7628(3) Å | β= 90°. |
| | c = 16.3036(4) Å | γ = 90°. |
| Volume | 1394.34(5) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.649 $Mg/m^3$ | |
| Absorption coefficient | 0.854 $mm^{-1}$ | |
| F(000) | 712 | |
| Crystal size | 0.48 x 0.10 x 0.09 $mm^3$ | |
| Theta range for data collection | 2.03 to 28.00°. | |
| Index ranges | -8<=h<=8, -15<=k<=16, -16<=l<=21 | |
| Reflections collected | 13196 | |
| Independent reflections | 3362 [R(int) = 0.0504] | |

| | |
|---|---|
| Completeness to theta = 28.00° | 100.0 % |
| Absorption correction | Integration |
| Max. and min. transmission | 0.9271 and 0.6846 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3362 / 0 / 202 |
| Goodness-of-fit on $F^2$ | 0.985 |
| Final R indices [I>2sigma(I)] | R1 = 0.0288, wR2 = 0.0641 |
| R indices (all data) | R1 = 0.0342, wR2 = 0.0657 |
| Absolute structure parameter | -0.003(16) |
| Largest diff. peak and hole | 0.313 and -0.241 e.$Å^{-3}$ |

**Table A1.2.2 Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for *syn*-170. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.**

| | X | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 5112(3) | 6492(2) - | 150(1) | 20(1) |
| C(2) | 6383(3) | 5530(2) | -39(1) | 18(1) |
| C(3) | 6466(3) | 5263(2) | 870(1) | 14(1) |
| C(4) | 6757(3) | 4220(2) | 1148(1) | 17(1) |
| C(5) | 6718(3) | 3985(2) | 1986(1) | 17(1) |
| C(6) | 6373(3) | 4796(2) | 2568(1) | 17(1) |
| C(7) | 6020(3) | 5818(2) | 2297(1) | 17(1) |
| C(8) | 6085(3) | 6057(2) | 1448(1) | 15(1) |
| C(9) | 5621(3) | 7165(2) | 1176(1) | 19(1) |
| C(10) | 8189(4) | 2571(2) | 781(1) | 27(1) |
| C(11) | 6458(4) | 6599(2) | 3614(1) | 33(1) |
| C(12) | 10878(3) | 4831(2) | 1056(1) | 21(1) |
| C(13) | 10626(3) | 4818(2) | 2625(1) | 25(1) |
| C(14) | 10114(3) | 6528(2) | 1902(1) | 20(1) |
| O(1) | 5925(2) | 7332(1) | 325(1) | 20(1) |
| O(2) | 8303(2) | 5663(1) | -399(1) | 22(1) |
| O(3) | 7066(2) | 3483(1) | 554(1) | 22(1) |
| O(4) | 5642(2) | 6650(1) | 2799(1) | 23(1) |
| O(5) | 12079(2) | 4532(1) | 609(1) | 35(1) |
| O(6) | 11693(2) | 4574(2) | 3149(1) | 43(1) |
| O(7) | 10807(3) | 7355(1) | 1999(1) | 33(1) |
| Cr(1) | 8958(1) | 5251(1) | 1796(1) | 15(1) |

**Table A1.2.3 Bond lengths [Å] and angles [°] for *syn*-170**

| | |
|---|---|
| C(1)-O(1) | 1.431(2) |
| C(1)-C(2) | 1.505(3) |
| C(1)-H(1A) | 0.9900 |
| C(1)-H(1B) | 0.9900 |
| C(2)-O(2) | 1.424(2) |
| C(2)-C(3) | 1.522(2) |
| C(2)-H(2) | 1.0000 |
| C(3)-C(8) | 1.406(3) |
| C(3)-C(4) | 1.420(3) |
| C(3)-Cr(1) | 2.2509(18) |
| C(4)-O(3) | 1.365(2) |
| C(4)-C(5) | 1.398(3) |
| C(4)-Cr(1) | 2.241(2) |
| C(5)-C(6) | 1.424(3) |
| C(5)-Cr(1) | 2.228(2) |
| C(5)-H(5) | 0.9500 |
| C(6)-C(7) | 1.396(3) |
| C(6)-Cr(1) | 2.2184(19) |

| | |
|---|---|
| C(6)-H(6) | 0.9500 |
| C(7)-O(4) | 1.364(2) |
| C(7)-C(8) | 1.419(2) |
| C(7)-Cr(1) | 2.251(2) |
| C(8)-C(9) | 1.514(3) |
| C(8)-Cr(1) | 2.255(2) |
| C(9)-O(1) | 1.419(2) |
| C(9)-H(9A) | 0.9900 |
| C(9)-H(9B) | 0.9900 |
| C(10)-O(3) | 1.435(3) |
| C(10)-H(10A) | 0.9800 |
| C(10)-H(10B) | 0.9800 |
| C(10)-H(10C) | 0.9800 |
| C(11)-O(4) | 1.439(2) |
| C(11)-H(11A) | 0.9800 |
| C(11)-H(11B) | 0.9800 |
| C(11)-H(11C) | 0.9800 |
| C(12)-O(5) | 1.151(2) |
| C(12)-Cr(1) | 1.843(2) |
| C(13)-O(6) | 1.158(3) |
| C(13)-Cr(1) | 1.838(2) |
| C(14)-O(7) | 1.164(2) |
| C(14)-Cr(1) | 1.813(2) |
| O(2)-H(2A) | 0.8400 |
| O(1)-C(1)-C(2) | 109.32(17) |
| O(1)-C(1)-H(1A) | 109.8 |
| C(2)-C(1)-H(1A) | 109.8 |
| O(1)-C(1)-H(1B) | 109.8 |
| C(2)-C(1)-H(1B) | 109.8 |
| H(1A)-C(1)-H(1B) | 108.3 |
| O(2)-C(2)-C(1) | 111.36(17) |
| O(2)-C(2)-C(3) | 113.26(16) |
| C(1)-C(2)-C(3) | 108.71(16) |
| O(2)-C(2)-H(2) | 107.8 |
| C(1)-C(2)-H(2) | 107.8 |
| C(3)-C(2)-H(2) | 107.8 |
| C(8)-C(3)-C(4) | 119.11(16) |
| C(8)-C(3)-C(2) | 118.97(18) |
| C(4)-C(3)-C(2) | 121.73(17) |
| C(8)-C(3)-Cr(1) | 71.98(11) |
| C(4)-C(3)-Cr(1) | 71.19(10) |
| C(2)-C(3)-Cr(1) | 132.95(13) |
| O(3)-C(4)-C(5) | 123.18(19) |
| O(3)-C(4)-C(3) | 116.10(16) |
| C(5)-C(4)-C(3) | 120.72(18) |
| O(3)-C(4)-Cr(1) | 129.67(15) |
| C(5)-C(4)-Cr(1) | 71.26(12) |
| C(3)-C(4)-Cr(1) | 71.96(11) |
| C(4)-C(5)-C(6) | 119.81(19) |
| C(4)-C(5)-Cr(1) | 72.27(12) |
| C(6)-C(5)-Cr(1) | 70.97(11) |
| C(4)-C(5)-H(5) | 120.1 |
| C(6)-C(5)-H(5) | 129.0 |
| C(7)-C(6)-C(5) | 119.77(17) |
| C(7)-C(6)-Cr(1) | 73.08(13) |
| C(5)-C(6)-Cr(1) | 71.68(11) |
| C(7)-C(6)-H(6) | 120.1 |
| C(5)-C(6)-H(6) | 120.1 |
| Cr(1)-C(6)-H(6) | 127.1 |
| O(4)-C(7)-C(6) | 124.68(17) |
| O(4)-C(7)-C(8) | 115.05(17) |
| C(6)-C(7)-C(8) | 120.26(18) |

| | |
|---|---|
| O(4)-C(7)-Cr(1) | 129.05(15) |
| C(6)-C(7)-Cr(1) | 70.53(13) |
| C(8)-C(7)-Cr(1) | 71.81(13) |
| C(3)-C(8)-C(7) | 120.28(18) |
| C(3)-C(8)-C(9) | 120.94(17) |
| C(7)-C(8)-C(9) | 118.69(17) |
| C(3)-C(8)-Cr(1) | 71.50(13) |
| C(9)-C(8)-Cr(1) | 132.42(15) |
| O(1)-C(9)-C(8) | 113.41(16) |
| O(1)-C(9)-H(9A) | 108.9 |
| C(8)-C(9)-H(9A) | 108.9 |
| O(1)-C(9)-H(9B) | 108.9 |
| C(8)-C(9)-H(9B) | 108.9 |
| H(9A)-C(9)-H(9B) | 107.7 |
| O(3)-C(10)-H(10A) | 109.5 |
| O(3)-C(10)-H(10B) | 109.5 |
| H(10A)-C(10)-H(10B) | 109.5 |
| O(3)-C(10)-H(10C) | 109.5 |
| H(10A)-C(10)-H(10C) | 109.5 |
| H(10B)-C(10)-H(10C) | 109.5 |
| O(4)-C(11)-H(11A) | 109.5 |
| O(4)-C(11)-H(11B) | 109.5 |
| H(11A)-C(11)-H(11B) | 109.5 |
| O(4)-C(11)-H(11C) | 109.5 |
| H(11A)-C(11)-H(11C) | 109.5 |
| H(11B)-C(11)-H(11C) | 109.5 |
| O(5)-C(12)-Cr(1) | 177.4(2) |
| O(6)-C(13)-Cr(1) | 178.1(2) |
| O(7)-C(14)-Cr(1) | 177.11(19) |
| C(9)-O(1)-C(1) | 111.22(15) |
| C(2)-O(2)-H(2A) | 109.5 |
| C(4)-O(3)-C(10) | 117.10(16) |
| C(7)-O(4)-C(11) | 116.63(16) |
| C(14)-Cr(1)-C(13) | 86.57(10) |
| C(14)-Cr(1)-C(12) | 91.50(9) |
| C(13)-Cr(1)-C(12) | 88.25(9) |
| C(14)-Cr(1)-C(6) | 120.97(9) |
| C(13)-Cr(1)-C(6) | 88.80(8) |
| C(12)-Cr(1)-C(6) | 147.14(9) |
| C(14)-Cr(1)-C(5) | 157.97(8) |
| C(13)-Cr(1)-C(5) | 95.12(9) |
| C(12)-Cr(1)-C(5) | 110.49(8) |
| C(6)-Cr(1)-C(5) | 37.35(7) |
| C(14)-Cr(1)-C(4) | 148.67(8) |
| C(13)-Cr(1)-C(4) | 124.74(9) |
| C(12)-Cr(1)-C(4) | 88.86(8) |
| C(6)-Cr(1)-C(4) | 66.39(7) |
| C(5)-Cr(1)-C(4) | 36.47(7) |
| C(14)-Cr(1)-C(7) | 92.88(8) |
| C(13)-Cr(1)-C(7) | 111.17(8) |
| C(12)-Cr(1)-C(7) | 160.30(8) |
| C(6)-Cr(1)-C(7) | 36.39(7) |
| C(5)-Cr(1)-C(7) | 65.99(7) |
| C(4)-Cr(1)-C(7) | 77.52(7) |
| C(14)-Cr(1)-C(3) | 112.03(8) |
| C(13)-Cr(1)-C(3) | 161.04(9) |
| C(12)-Cr(1)-C(3) | 94.64(8) |
| C(6)-Cr(1)-C(3) | 78.61(7) |
| C(5)-Cr(1)-C(3) | 66.30(7) |
| C(4)-Cr(1)-C(3) | 36.85(7) |
| C(7)-Cr(1)-C(3) | 65.94(7) |
| C(14)-Cr(1)-C(8) | 88.79(8) |

| | |
|---|---|
| C(13)-Cr(1)-C(8) | 147.22(8) |
| C(12)-Cr(1)-C(8) | 124.32(8) |
| C(6)-Cr(1)-C(8) | 66.12(7) |
| C(5)-Cr(1)-C(8) | 77.91(7) |
| C(4)-Cr(1)-C(8) | 65.62(7) |
| C(7)-Cr(1)-C(8) | 36.70(6) |
| C(3)-Cr(1)-C(8) | 36.37(7) |

Symmetry transformations used to generate equivalent atoms:

**Table A1.2.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$)for *syn*-170. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12} ]$**

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 26(1) | 18(1) | 16(1) | 3(1) | -4(1) | -2(1) |
| C(2) | 21(1) | 18(1) | 15(1) | 1(1) | -2(1) | 0(1) |
| C(3) | 13(1) | 15(1) | 15(1) | 2(1) | -2(1) | -1(1) |
| C(4) | 15(1) | 15(1) | 20(1) | -3(1) | -2(1) | -1(1) |
| C(5) | 17(1) | 14(1) | 20(1) | 6(1) | 0(1) | -2(1) |
| C(6) | 17(1) | 19(1) | 16(1) | 4(1) | 2(1) | 0(1) |
| C(7) | 15(1) | 21(1) | 16(1) | -1(1) | 0(1) | 1(1) |
| C(8) | 12(1) | 15(1) | 17(1) | 2(1) | 0(1) | 2(1) |
| C(9) | 23(1) | 16(1) | 18(1) | 1(1) | 1(1) | 5(1) |
| C(10) | 37(1) | 16(1) | 30(1) | -2(1) | 1(1) | 6(1) |
| C(11) | 43(2) | 36(1) | 19(1) | -8(1) | -6(1) | 14(1) |
| C(12) | 19(1) | 18(1) | 26(1) | -3(1) | -3(1) | -2(1) |
| C(13) | 21(1) | 30(1) | 26(1) | 8(1) | 0(1) | -2(1) |
| C(14) | 21(1) | 22(1) | 17(1) | 1(1) | -2(1) | 0(1) |
| O(1) | 28(1) | 16(1) | 18(1) | 3(1) | 0(1) | -2(1) |
| O(2) | 26(1) | 22(1) | 16(1) | -2(1) | 5(1) | -2(1) |
| O(3) | 32(1) | 14(1) | 20(1) | -2(1) | -3(1) | 1(1) |
| O(4) | 30(1) | 24(1) | 14(1) | -2(1) | -1(1) | 10(1) |
| O(5) | 22(1) | 42(1) | 41(1) | -10(1) | 11(1) | -1(1) |
| O(6) | 29(1) | 60(1) | 39(1) | 22(1) | -12(1) | -3(1) |
| O(7) | 37(1) | 25(1) | 37(1) | -2(1) | -9(1) | -11(1) |
| Cr(1) | 14(1) | 15(1) | 15(1) | 1(1) | -1(1) | -1(1) |

**Table A1.2.5 Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for *syn*-170**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 5079 | 6691 | -737 | 24 |
| H(1B) | 3729 | 6344 | 29 | 24 |
| H(2) | 5708 | 4936 | -327 | 21 |
| H(5) | 6921 | 3285 | 2166 | 20 |
| H(6) | 6383 | 4644 | 3138 | 21 |
| H(9A) | 4214 | 7326 | 1312 | 23 |
| H(9B) | 6475 | 7657 | 1488 | 23 |
| H(10A) | 9459 | 2786 | 1028 | 41 |
| H(10B) | 8450 | 2145 | 293 | 41 |
| H(10C) | 7425 | 2158 | 1179 | 41 |
| H(11A) | 5714 | 6083 | 3937 | 49 |
| H(11B) | 6353 | 7289 | 3875 | 49 |
| H(2A) | 8862 | 6189 | -192 | 32 |

**Table A1.2.6 Torsion angles [°] for *syn*-170**

| | |
|---|---|
| O(1)-C(1)-C(2)-O(2) | -67.9(2) |
| O(1)-C(1)-C(2)-C(3) | 57.6(2) |
| O(2)-C(2)-C(3)-C(8) | 101.7(2) |
| C(1)-C(2)-C(3)-C(8) | -22.7(2) |
| O(2)-C(2)-C(3)-C(4) | -83.5(2) |
| C(1)-C(2)-C(3)-C(4) | 152.17(18) |
| O(2)-C(2)-C(3)-Cr(1) | 9.8(3) |
| C(1)-C(2)-C(3)-Cr(1) | -114.5(2) |
| C(8)-C(3)-C(4)-O(3) | 178.28(18) |
| C(2)-C(3)-C(4)-O(3) | 3.4(3) |
| Cr(1)-C(3)-C(4)-O(3) | -126.02(18) |
| C(8)-C(3)-C(4)-C(5) | -1.6(3) |
| C(2)-C(3)-C(4)-C(5) | -176.44(18) |
| Cr(1)-C(3)-C(4)-C(5) | 54.09(17) |
| C(8)-C(3)-C(4)-Cr(1) | -55.69(16) |
| C(2)-C(3)-C(4)-Cr(1) | 129.47(17) |
| O(3)-C(4)-C(5)-C(6) | -179.58(19) |
| C(3)-C(4)-C(5)-C(6) | 0.3(3) |
| Cr(1)-C(4)-C(5)-C(6) | 54.71(16) |
| O(3)-C(4)-C(5)-Cr(1) | 125.7(2) |
| C(3)-C(4)-C(5)-Cr(1) | -54.41(17) |
| C(4)-C(5)-C(6)-C(7) | 1.8(3) |
| Cr(1)-C(5)-C(6)-C(7) | 57.14(18) |
| C(4)-C(5)-C(6)-Cr(1) | -55.33(17) |
| C(5)-C(6)-C(7)-O(4) | 178.94(19) |
| Cr(1)-C(6)-C(7)-O(4) | -124.6(2) |
| C(5)-C(6)-C(7)-C(8) | -2.6(3) |
| Cr(1)-C(6)-C(7)-C(8) | 53.9(2) |
| C(5)-C(6)-C(7)-Cr(1) | -56.46(17) |
| C(4)-C(3)-C(8)-C(7) | 0.8(3) |
| C(2)-C(3)-C(8)-C(7) | 175.8(2) |
| Cr(1)-C(3)-C(8)-C(7) | -54.5(2) |
| C(4)-C(3)-C(8)-C(9) | -175.66(18) |
| C(2)-C(3)-C(8)-C(9) | -0.7(3) |
| Cr(1)-C(3)-C(8)-C(9) | 129.0(2) |
| C(4)-C(3)-C(8)-Cr(1) | 55.30(16) |
| C(2)-C(3)-C(8)-Cr(1) | -129.72(17) |
| O(4)-C(7)-C(8)-C(3) | 179.89(18) |
| C(6)-C(7)-C(8)-C(3) | 1.3(4) |
| Cr(1)-C(7)-C(8)-C(3) | 54.56(19) |
| O(4)-C(7)-C(8)-C(9) | -3.5(3) |

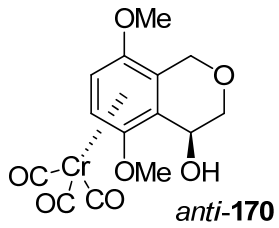
| | |
|---|---|
| C(6)-C(7)-C(8)-C(9) | 177.85(19) |
| Cr(1)-C(7)-C(8)-C(9) | -128.88(19) |
| O(4)-C(7)-C(8)-Cr(1) | 125.33(19) |
| C(6)-C(7)-C(8)-Cr(1) | -53.3(2) |
| C(3)-C(8)-C(9)-O(1) | -9.3(3) |
| C(7)-C(8)-C(9)-O(1) | 174.2(2) |
| Cr(1)-C(8)-C(9)-O(1) | 83.6(2) |
| C(8)-C(9)-O(1)-C(1) | 44.7(2) |
| C(2)-C(1)-O(1)-C(9) | -71.5(2) |
| C(5)-C(4)-O(3)-C(10) | -26.7(3) |
| C(3)-C(4)-O(3)-C(10) | 153.44(19) |
| Cr(1)-C(4)-O(3)-C(10) | 65.8(2) |
| C(6)-C(7)-O(4)-C(11) | 27.3(3) |
| C(8)-C(7)-O(4)-C(11) | -151.2(2) |
| Cr(1)-C(7)-O(4)-C(11) | -65.0(2) |
| O(7)-C(14)-Cr(1)-C(13) | -77(4) |
| O(7)-C(14)-Cr(1)-C(12) | -165(4) |
| O(7)-C(14)-Cr(1)-C(6) | 9(4) |
| O(7)-C(14)-Cr(1)-C(5) | 18(4) |
| O(7)-C(14)-Cr(1)-C(4) | 104(4) |
| O(7)-C(14)-Cr(1)-C(7) | 34(4) |
| O(7)-C(14)-Cr(1)-C(3) | 99(4) |
| O(7)-C(14)-Cr(1)-C(8) | 70(4) |
| O(6)-C(13)-Cr(1)-C(14) | 6(6) |
| O(6)-C(13)-Cr(1)-C(12) | 98(6) |
| O(6)-C(13)-Cr(1)-C(6) | -115(6) |
| O(6)-C(13)-Cr(1)-C(5) | -152(6) |
| O(6)-C(13)-Cr(1)-C(4) | -175(100) |
| O(6)-C(13)-Cr(1)-C(7) | -86(6) |
| O(6)-C(13)-Cr(1)-C(3) | -163(6) |
| O(6)-C(13)-Cr(1)-C(8) | -76(6) |
| O(5)-C(12)-Cr(1)-C(14) | 138(4) |
| O(5)-C(12)-Cr(1)-C(13) | 51(4) |
| O(5)-C(12)-Cr(1)-C(6) | -34(4) |
| O(5)-C(12)-Cr(1)-C(5) | -44(4) |
| O(5)-C(12)-Cr(1)-C(4) | -74(4) |
| O(5)-C(12)-Cr(1)-C(7) | -120(4) |
| O(5)-C(12)-Cr(1)-C(3) | -110(4) |
| O(5)-C(12)-Cr(1)-C(8) | -133(4) |
| C(7)-C(6)-Cr(1)-C(14) | 44.31(14) |
| C(5)-C(6)-Cr(1)-C(14) | 174.66(12) |
| C(7)-C(6)-Cr(1)-C(13) | 129.59(14) |
| C(5)-C(6)-Cr(1)-C(13) | -100.06(13) |
| C(7)-C(6)-Cr(1)-C(12) | -145.49(15) |
| C(5)-C(6)-Cr(1)-C(12) | -15.14(19) |
| C(7)-C(6)-Cr(1)-C(5) | -130.35(16) |
| C(7)-C(6)-Cr(1)-C(4) | -101.27(13) |
| C(5)-C(6)-Cr(1)-C(4) | 29.08(11) |
| C(5)-C(6)-Cr(1)-C(7) | 130.35(16) |
| C(7)-C(6)-Cr(1)-C(3) | -64.67(12) |
| C(5)-C(6)-Cr(1)-C(3) | 65.68(12) |
| C(7)-C(6)-Cr(1)-C(8) | -28.68(11) |
| C(5)-C(6)-Cr(1)-C(8) | 101.67(12) |
| C(4)-C(5)-Cr(1)-C(14) | 119.2(2) |
| C(6)-C(5)-Cr(1)-C(14) | -12.3(3) |
| C(4)-C(5)-Cr(1)-C(13) | -147.27(13) |
| C(6)-C(5)-Cr(1)-C(13) | 81.25(13) |
| C(4)-C(5)-Cr(1)-C(12) | -57.22(14) |
| C(6)-C(5)-Cr(1)-C(12) | 171.30(11) |
| C(4)-C(5)-Cr(1)-C(6) | 131.48(17) |
| C(6)-C(5)-Cr(1)-C(4) | -131.48(17) |
| C(4)-C(5)-Cr(1)-C(7) | 101.81(13) |

| | |
|---|---|
| C(6)-C(5)-Cr(1)-C(7) | -29.67(10) |
| C(4)-C(5)-Cr(1)-C(3) | 28.78(11) |
| C(6)-C(5)-Cr(1)-C(3) | -102.69(12) |
| C(4)-C(5)-Cr(1)-C(8) | 65.15(12) |
| C(6)-C(5)-Cr(1)-C(8) | -66.33(11) |
| O(3)-C(4)-Cr(1)-C(14) | 101.0(2) |
| C(5)-C(4)-Cr(1)-C(14) | -140.97(16) |
| C(3)-C(4)-Cr(1)-C(14) | -8.3(2) |
| O(3)-C(4)-Cr(1)-C(13) | -77.1(2) |
| C(5)-C(4)-Cr(1)-C(13) | 40.94(16) |
| C(3)-C(4)-Cr(1)-C(13) | 173.62(12) |
| O(3)-C(4)-Cr(1)-C(12) | 10.03(19) |
| C(5)-C(4)-Cr(1)-C(12) | 128.02(13) |
| C(3)-C(4)-Cr(1)-C(12) | -99.30(12) |
| O(3)-C(4)-Cr(1)-C(6) | -147.7(2) |
| C(5)-C(4)-Cr(1)-C(6) | -29.74(12) |
| C(3)-C(4)-Cr(1)-C(6) | 102.94(12) |
| O(3)-C(4)-Cr(1)-C(5) | -118.0(2) |
| C(3)-C(4)-Cr(1)-C(5) | 132.67(17) |
| O(3)-C(4)-Cr(1)-C(7) | 175.69(19) |
| C(5)-C(4)-Cr(1)-C(7) | -66.32(12) |
| C(3)-C(4)-Cr(1)-C(7) | 66.36(11) |
| O(3)-C(4)-Cr(1)-C(3) | 109.3(2) |
| C(5)-C(4)-Cr(1)-C(3) | -132.67(17) |
| O(3)-C(4)-Cr(1)-C(8) | 138.9(2) |
| C(5)-C(4)-Cr(1)-C(8) | -103.06(13) |
| C(3)-C(4)-Cr(1)-C(8) | 29.61(10) |
| O(4)-C(7)-Cr(1)-C(14) | -23.79(17) |
| C(6)-C(7)-Cr(1)-C(14) | -143.15(12) |
| C(8)-C(7)-Cr(1)-C(14) | 84.10(13) |
| O(4)-C(7)-Cr(1)-C(13) | 63.65(19) |
| C(6)-C(7)-Cr(1)-C(13) | -55.71(15) |
| C(8)-C(7)-Cr(1)-C(13) | 171.54(13) |
| O(4)-C(7)-Cr(1)-C(12) | -126.4(3) |
| C(6)-C(7)-Cr(1)-C(12) | 114.3(3) |
| C(8)-C(7)-Cr(1)-C(12) | -18.5(3) |
| O(4)-C(7)-Cr(1)-C(6) | 119.4(2) |
| C(8)-C(7)-Cr(1)-C(6) | -132.75(18) |
| O(4)-C(7)-Cr(1)-C(5) | 149.76(18) |
| C(6)-C(7)-Cr(1)-C(5) | 30.41(11) |
| C(8)-C(7)-Cr(1)-C(5) | -102.35(13) |
| O(4)-C(7)-Cr(1)-C(4) | -173.66(18) |
| C(6)-C(7)-Cr(1)-C(4) | 66.98(12) |
| C(8)-C(7)-Cr(1)-C(4) | -65.77(12) |
| O(4)-C(7)-Cr(1)-C(3) | -136.67(18) |
| C(6)-C(7)-Cr(1)-C(3) | 103.97(13) |
| C(8)-C(7)-Cr(1)-C(3) | -28.78(12) |
| O(4)-C(7)-Cr(1)-C(8) | -107.9(2) |
| C(6)-C(7)-Cr(1)-C(8) | 132.75(18) |
| C(8)-C(3)-Cr(1)-C(14) | -54.01(13) |
| C(4)-C(3)-Cr(1)-C(14) | 175.36(12) |
| C(2)-C(3)-Cr(1)-C(14) | 59.1(2) |
| C(8)-C(3)-Cr(1)-C(13) | 114.3(3) |
| C(4)-C(3)-Cr(1)-C(13) | -16.3(3) |
| C(2)-C(3)-Cr(1)-C(13) | -132.6(3) |
| C(8)-C(3)-Cr(1)-C(12) | -147.52(12) |
| C(4)-C(3)-Cr(1)-C(12) | 81.85(13) |
| C(2)-C(3)-Cr(1)-C(12) | -34.4(2) |
| C(8)-C(3)-Cr(1)-C(6) | 64.99(12) |
| C(4)-C(3)-Cr(1)-C(6) | -65.64(12) |
| C(2)-C(3)-Cr(1)-C(6) | 178.1(2) |
| C(8)-C(3)-Cr(1)-C(5) | 102.13(12) |

| | |
|---|---|
| C(4)-C(3)-Cr(1)-C(5) | -28.51(11) |
| C(2)-C(3)-Cr(1)-C(5) | -144.7(2) |
| C(8)-C(3)-Cr(1)-C(4) | 130.63(17) |
| C(2)-C(3)-Cr(1)-C(4) | -116.2(2) |
| C(8)-C(3)-Cr(1)-C(7) | 29.02(11) |
| C(4)-C(3)-Cr(1)-C(7) | -101.61(12) |
| C(2)-C(3)-Cr(1)-C(7) | 142.2(2) |
| C(4)-C(3)-Cr(1)-C(8) | -130.63(17) |
| C(2)-C(3)-Cr(1)-C(8) | 113.1(3) |
| C(3)-C(8)-Cr(1)-C(14) | 131.39(13) |
| C(7)-C(8)-Cr(1)-C(14) | -96.45(13) |
| C(9)-C(8)-Cr(1)-C(14) | 15.88(18) |
| C(3)-C(8)-Cr(1)-C(13) | -146.84(17) |
| C(7)-C(8)-Cr(1)-C(13) | -14.7(2) |
| C(9)-C(8)-Cr(1)-C(13) | 97.6(2) |
| C(3)-C(8)-Cr(1)-C(12) | 40.40(15) |
| C(7)-C(8)-Cr(1)-C(12) | 172.56(13) |
| C(9)-C(8)-Cr(1)-C(12) | -75.1(2) |
| C(3)-C(8)-Cr(1)-C(6) | -103.71(13) |
| C(7)-C(8)-Cr(1)-C(6) | 28.45(12) |
| C(9)-C(8)-Cr(1)-C(6) | 140.78(19) |
| C(3)-C(8)-Cr(1)-C(5) | -66.29(12) |
| C(7)-C(8)-Cr(1)-C(5) | 65.87(12) |
| C(9)-C(8)-Cr(1)-C(5) | 178.20(18) |
| C(3)-C(8)-Cr(1)-C(4) | -29.98(11) |
| C(7)-C(8)-Cr(1)-C(4) | 102.18(13) |
| C(9)-C(8)-Cr(1)-C(4) | -145.49(19) |
| C(3)-C(8)-Cr(1)-C(7) | -132.16(18) |
| C(9)-C(8)-Cr(1)-C(7) | 112.3(2) |
| C(7)-C(8)-Cr(1)-C(3) | 132.16(18) |
| C(9)-C(8)-Cr(1)-C(3) | -115.5(2) |

Symmetry transformations used to generate equivalent atoms

## A1.3 X-Ray crystallographic data for [(*S*)-5,8-dimethoxyisochroman-4-ol]tricarbonylchromium (0): *anti*-170




*anti*-**170**

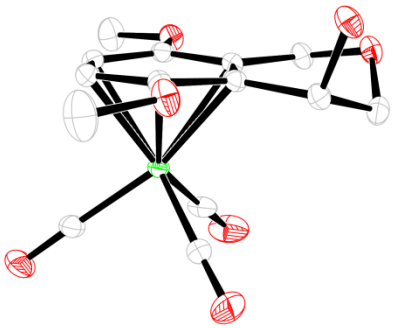


**Table A1.3.1 Crystal data and structure refinement for *anti*-170**

| | | |
|---|---|---|
| Empirical formula | $C_{18}H\ CrO_8$ | |
| Formula weight | 420.37 | |
| Temperature | 173(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | P2(1)2(1)2(1) | |
| Unit cell dimensions | a = 10.1491(3) Å | α= 90°. |
| | b = 13.7262(4) Å | β= 90°. |
| | c = 14.2451(5) Å | γ = 90°. |
| Volume | 1984.46(11) $Å^3$ | |
| Z | 4 | |

| | |
|---|---|
| Density (calculated) | 1.407 $Mg/m^3$ |
| Absorption coefficient | 0.617 $mm^{-1}$ |
| F(000) | 880 |
| Crystal size | 0.47 x 0.32 x 0.13 $mm^3$ |
| Theta range for data collection | 2.06 to 27.99°. |
| Index ranges | -13<=h<=13, -18<=k<=18, -18<=l<=18 |
| Reflections collected | 33866 |
| Independent reflections | 4790 [R(int) = 0.0449] |
| Completeness to theta = 27.99° | 100.0 % |
| Absorption correction | Integration |
| Max. and min. transmission | 0.9241 and 0.7602 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 4790 / 0 / 249 |
| Goodness-of-fit on $F^2$ | 1.082 |
| Final R indices [I>2sigma(I)] | R1 = 0.0264, wR2 = 0.0692 |
| R indices (all data) | R1 = 0.0285, wR2 = 0.0702 |
| Absolute structure parameter | -0.002(13) |
| Largest diff. peak and hole | 0.264 and -0.215 $e.Å^{-3}$ |

**Table A1.3.2 Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for *anti*-170. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 3258(2) | 3478(1) | 9093(1) | 34(1) |
| C(2) | 2835(2) | 2986(1) | 8198(1) | 29(1) |
| C(3) | 3853(2) | 2244(1) | 7906(1) | 26(1) |
| C(4) | 3559(2) | 1532(1) | 7209(1) | 28(1) |
| C(5) | 4469(2) | 803(1) | 7001(1) | 29(1) |
| C(6) | 5732(2) | 806(1) | 7435(1) | 30(1) |
| C(7) | 6068(2) | 1554(1) | 8053(1) | 29(1) |
| C(8) | 5114(2) | 2267(1) | 8310(1) | 26(1) |
| C(9) | 5491(2) | 3054(1) | 8997(1) | 33(1) |
| C(10) | 1909(2) | 841(2) | 6227(2) | 58(1) |
| C(11) | 8215(2) | 921(2) | 8327(2) | 53(1) |
| C(12) | 2510(2) | 770(1) | 8966(1) | 34(1) |
| C(13) | 4220(2) | -557(1) | 8584(1) | 34(1) |
| C(14) | 4755(2) | 833(2) | 9767(1) | 39(1) |
| O(1) | 4570(1) | 3831(1) | 9013(1) | 34(1) |
| O(2) | 2703(1) | 3721(1) | 7492(1) | 35(1) |
| O(3) | 2342(1) | 1613(1) | 6824(1) | 37(1) |
| O(4) | 7253(1) | 1665(1) | 8478(1) | 37(1) |
| O(5) | 1433(1) | 772(1) | 9225(1) | 59(1) |
| O(6) | 4190(2) | -1393(1) | 8613(1) | 54(1) |
| O(7) | 5095(2) | 880(2) | 10538(1) | 67(1) |
| Cr(1) | 4209(1) | 793(1) | 8549(1) | 23(1) |
| C(15) | 2618(5) | 3658(3) | 4951(2) | 106(1) |
| C(16) | 1226(5) | 3607(3) | 5089(2) | 99(1) |
| C(17) | -446(3) | 3379(3) | 6244(3) | 92(1) |
| C(18) | -732(4) | 3327(4) | 7219(3) | 125(2) |
| O(8) | 896(2) | 3512(1) | 6038(1) | 55(1) |

**Table A1.3.3 Bond lengths [Å] and angles [°] for *anti*-170**

| | |
|---|---|
| C(1)-O(1) | 1.421(2) |
| C(1)-C(2) | 1.506(2) |
| C(1)-H(1A) | 0.9900 |
| C(1)-H(1B) | 0.9900 |
| C(2)-O(2) | 1.430(2) |

| | |
|---|---|
| C(2)-C(3) | 1.510(2) |
| C(2)-H(2A) | 1.0000 |
| C(3)-C(8) | 1.403(2) |
| C(3)-C(4) | 1.426(2) |
| C(3)-Cr(1) | 2.2217(15) |
| C(4)-O(3) | 1.356(2) |
| C(4)-C(5) | 1.394(2) |
| C(4)-Cr(1) | 2.2599(16) |
| C(5)-C(6) | 1.422(2) |
| C(5)-Cr(1) | 2.2214(15) |
| C(5)-H(5) | 0.9500 |
| C(6)-C(7) | 1.395(2) |
| C(6)-Cr(1) | 2.2154(15) |
| C(6)-H(6) | 0.9500 |
| C(7)-O(4) | 1.355(2) |
| C(7)-C(8) | 1.425(2) |
| C(7)-Cr(1) | 2.2694(16) |
| C(8)-C(9) | 1.506(2) |
| C(8)-Cr(1) | 2.2480(15) |
| C(9)-O(1) | 1.419(2) |
| C(9)-H(9A) | 0.9900 |
| C(9)-H(9B) | 0.9900 |
| C(10)-O(3) | 1.428(2) |
| C(10)-H(10A) | 0.9800 |
| C(10)-H(10B) | 0.9800 |
| C(10)-H(10C) | 0.9800 |
| C(11)-O(4) | 1.430(2) |
| C(11)-H(11A) | 0.9800 |
| C(11)-H(11B) | 0.9800 |
| C(11)-H(11C) | 0.9800 |
| C(12)-O(5) | 1.154(2) |
| C(12)-Cr(1) | 1.8242(17) |
| C(13)-O(6) | 1.149(2) |
| C(13)-Cr(1) | 1.8536(16) |
| C(14)-O(7) | 1.153(2) |
| C(14)-Cr(1) | 1.8217(18) |
| O(2)-H(2) | 0.8400 |
| C(15)-C(16) | 1.429(6) |
| C(15)-H(15A) | 0.9800 |
| C(15)-H(15B) | 0.9800 |
| C(15)-H(15C) | 0.9800 |
| C(16)-O(8) | 1.399(4) |
| C(16)-H(16A) | 0.9900 |
| C(16)-H(16B) | 0.9900 |
| C(17)-O(8) | 1.405(4) |
| C(17)-C(18) | 1.420(6) |
| C(17)-H(17A) | 0.9900 |
| C(18)-H(18A) | 0.9800 |
| C(18)-H(18B) | 0.9800 |
| C(18)-H(18C) | 0.9800 |
| O(1)-C(1)-C(2) | 110.64(14) |
| O(1)-C(1)-H(1A) | 109.5 |
| C(2)-C(1)-H(1A) | 109.5 |
| O(1)-C(1)-H(1B) | 109.5 |
| C(2)-C(1)-H(1B) | 109.5 |
| H(1A)-C(1)-H(1B) | 108.1 |
| O(2)-C(2)-C(1) | 107.78(13) |
| O(2)-C(2)-C(3) | 110.30(14) |
| C(1)-C(2)-C(3) | 109.87(14) |
| O(2)-C(2)-H(2A) | 109.6 |
| C(1)-C(2)-H(2A) | 109.6 |
| C(3)-C(2)-H(2A) | 109.6 |

| | |
|---|---|
| C(8)-C(3)-C(4) | 119.49(14) |
| C(8)-C(3)-C(2) | 119.77(14) |
| C(4)-C(3)-C(2) | 120.72(14) |
| C(8)-C(3)-Cr(1) | 72.73(9) |
| C(4)-C(3)-Cr(1) | 72.92(9) |
| C(2)-C(3)-Cr(1) | 127.10(11) |
| O(3)-C(4)-C(5) | 125.26(15) |
| O(3)-C(4)-C(3) | 114.57(14) |
| C(5)-C(4)-C(3) | 120.11(15) |
| O(3)-C(4)-Cr(1) | 130.15(12) |
| C(5)-C(4)-Cr(1) | 70.38(9) |
| C(3)-C(4)-Cr(1) | 70.00(9) |
| C(4)-C(5)-C(6) | 120.18(15) |
| C(4)-C(5)-Cr(1) | 73.39(9) |
| C(6)-C(5)-Cr(1) | 71.07(8) |
| C(4)-C(5)-H(5) | 119.9 |
| C(6)-C(5)-H(5) | 119.9 |
| Cr(1)-C(5)-H(5) | 127.7 |
| C(7)-C(6)-C(5) | 119.78(15) |
| C(7)-C(6)-Cr(1) | 74.00(9) |
| C(5)-C(6)-Cr(1) | 71.53(9) |
| C(7)-C(6)-H(6) | 120.1 |
| C(5)-C(6)-H(6) | 120.1 |
| Cr(1)-C(6)-H(6) | 126.2 |
| O(4)-C(7)-C(6) | 125.65(15) |
| O(4)-C(7)-C(8) | 114.21(14) |
| C(6)-C(7)-C(8) | 120.11(15) |
| O(4)-C(7)-Cr(1) | 130.56(12) |
| C(6)-C(7)-Cr(1) | 69.78(9) |
| C(8)-C(7)-Cr(1) | 70.79(9) |
| C(3)-C(8)-C(7) | 119.91(14) |
| C(3)-C(8)-C(9) | 120.95(14) |
| C(7)-C(8)-C(9) | 119.13(15) |
| C(3)-C(8)-Cr(1) | 70.68(9) |
| C(7)-C(8)-Cr(1) | 72.43(9) |
| C(9)-C(8)-Cr(1) | 130.56(12) |
| O(1)-C(9)-C(8) | 112.44(14) |
| O(1)-C(9)-H(9A) | 109.1 |
| C(8)-C(9)-H(9A) | 109.1 |
| O(1)-C(9)-H(9B) | 109.1 |
| C(8)-C(9)-H(9B) | 109.1 |
| H(9A)-C(9)-H(9B) | 107.8 |
| O(3)-C(10)-H(10A) | 109.5 |
| O(3)-C(10)-H(10B) | 109.5 |
| H(10A)-C(10)-H(10B) | 109.5 |
| O(3)-C(10)-H(10C) | 109.5 |
| H(10A)-C(10)-H(10C) | 109.5 |
| H(10B)-C(10)-H(10C) | 109.5 |
| O(4)-C(11)-H(11A) | 109.5 |
| O(4)-C(11)-H(11B) | 109.5 |
| H(11A)-C(11)-H(11B) | 109.5 |
| O(4)-C(11)-H(11C) | 109.5 |
| H(11A)-C(11)-H(11C) | 109.5 |
| H(11B)-C(11)-H(11C) | 109.5 |
| O(5)-C(12)-Cr(1) | 178.73(18) |
| O(6)-C(13)-Cr(1) | 178.08(18) |
| O(7)-C(14)-Cr(1) | 178.6(2) |
| C(9)-O(1)-C(1) | 111.22(12) |
| C(2)-O(2)-H(2) | 109.5 |
| C(4)-O(3)-C(10) | 117.37(14) |
| C(7)-O(4)-C(11) | 117.25(15) |
| C(14)-Cr(1)-C(12) | 88.74(8) |

| | |
|---|---|
| C(14)-Cr(1)-C(13) | 90.18(9) |
| C(12)-Cr(1)-C(13) | 88.80(8) |
| C(14)-Cr(1)-C(6) | 118.03(7) |
| C(12)-Cr(1)-C(6) | 153.23(7) |
| C(13)-Cr(1)-C(6) | 91.32(7) |
| C(14)-Cr(1)-C(5) | 155.38(7) |
| C(12)-Cr(1)-C(5) | 115.84(7) |
| C(13)-Cr(1)-C(5) | 91.83(7) |
| C(6)-Cr(1)-C(5) | 37.40(6) |
| C(14)-Cr(1)-C(3) | 114.50(8) |
| C(12)-Cr(1)-C(3) | 89.79(7) |
| C(13)-Cr(1)-C(3) | 155.24(7) |
| C(6)-Cr(1)-C(3) | 79.11(6) |
| C(5)-Cr(1)-C(3) | 66.71(6) |
| C(14)-Cr(1)-C(8) | 89.58(7) |
| C(12)-Cr(1)-C(8) | 116.83(7) |
| C(13)-Cr(1)-C(8) | 154.35(7) |
| C(6)-Cr(1)-C(8) | 66.39(6) |
| C(5)-Cr(1)-C(8) | 78.21(6) |
| C(3)-Cr(1)-C(8) | 36.59(6) |
| C(14)-Cr(1)-C(4) | 151.58(8) |
| C(12)-Cr(1)-C(4) | 90.39(7) |
| C(13)-Cr(1)-C(4) | 118.21(7) |
| C(6)-Cr(1)-C(4) | 66.11(6) |
| C(5)-Cr(1)-C(4) | 36.23(6) |
| C(3)-Cr(1)-C(4) | 37.08(6) |
| C(8)-Cr(1)-C(4) | 65.65(6) |
| C(14)-Cr(1)-C(7) | 91.71(7) |
| C(12)-Cr(1)-C(7) | 153.58(7) |
| C(13)-Cr(1)-C(7) | 117.61(7) |
| C(6)-Cr(1)-C(7) | 36.22(6) |
| C(5)-Cr(1)-C(7) | 65.73(6) |
| C(3)-Cr(1)-C(7) | 66.07(6) |
| C(8)-Cr(1)-C(7) | 36.78(6) |
| C(4)-Cr(1)-C(7) | 76.90(6) |
| C(16)-C(15)-H(15A) | 109.5 |
| C(16)-C(15)-H(15B) | 109.5 |
| H(15A)-C(15)-H(15B) | 109.5 |
| C(16)-C(15)-H(15C) | 109.5 |
| H(15A)-C(15)-H(15C) | 109.5 |
| H(15B)-C(15)-H(15C) | 109.5 |
| O(8)-C(16)-C(15) | 112.0(3) |
| O(8)-C(16)-H(16A) | 109.2 |
| C(15)-C(16)-H(16A) | 109.2 |
| O(8)-C(16)-H(16B) | 109.2 |
| C(15)-C(16)-H(16B) | 109.2 |
| H(16A)-C(16)-H(16B) | 107.9 |
| O(8)-C(17)-C(18) | 114.2(3) |
| O(8)-C(17)-H(17A) | 108.7 |
| C(18)-C(17)-H(17A) | 108.7 |
| O(8)-C(17)-H(17B) | 108.7 |
| C(18)-C(17)-H(17B) | 108.7 |
| H(17A)-C(17)-H(17B) | 107.6 |
| C(17)-C(18)-H(18A) | 109.5 |
| C(17)-C(18)-H(18B) | 109.5 |
| H(18A)-C(18)-H(18B) | 109.5 |
| C(17)-C(18)-H(18C) | 109.5 |
| H(18A)-C(18)-H(18C) | 109.5 |
| H(18B)-C(18)-H(18C) | 109.5 |
| C(16)-O(8)-C(17) | 116.5(3) |

Symmetry transformations used to generate equivalent atoms

**Table A1.3.4 Anisotropic displacement parameters ($Å^2$x $10^3$)for *anti*-170. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12} ]$**

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 38(1) | 32(1) | 33(1) | -4(1) | 1(1) | 9(1) |
| C(2) | 30(1) | 25(1) | 32(1) | 1(1) | -2(1) | 3(1) |
| C(3) | 30(1) | 23(1) | 24(1) | 2(1) | 0(1) | 0(1) |
| C(4) | 34(1) | 25(1) | 24(1) | 1(1) | -2(1) | 0(1) |
| C(5) | 38(1) | 25(1) | 25(1) | 0(1) | 3(1) | 0(1) |
| C(6) | 32(1) | 26(1) | 31(1) | 2(1) | 9(1) | 1(1) |
| C(7) | 27(1) | 28(1) | 33(1) | 5(1) | 4(1) | -1(1) |
| C(8) | 28(1) | 23(1) | 28(1) | 2(1) | 2(1) | -2(1) |
| C(9) | 33(1) | 26(1) | 39(1) | -4(1) | -6(1) | -1(1) |
| C(10) | 53(1) | 56(1) | 65(1) | -23(1) | -27(1) | 2(1) |
| C(11) | 32(1) | 52(1) | 76(2) | -10(1) | -6(1) | 11(1) |
| C(12) | 34(1) | 30(1) | 39(1) | -2(1) | 8(1) | -1(1) |
| C(13) | 33(1) | 31(1) | 39(1) | 6(1) | 6(1) | 0(1) |
| C(14) | 39(1) | 44(1) | 33(1) | 8(1) | -1(1) | -13(1) |
| O(1) | 41(1) | 24(1) | 37(1) | -5(1) | -5(1) | 1(1) |
| O(2) | 41(1) | 25(1) | 38(1) | 3(1) | -12(1) | 2(1) |
| O(3) | 41(1) | 32(1) | 37(1) | -5(1) | -16(1) | 4(1) |
| O(4) | 24(1) | 35(1) | 53(1) | -3(1) | 0(1) | 0(1) |
| O(5) | 38(1) | 64(1) | 77(1) | -10(1) | 23(1) | -2(1) |
| O(6) | 63(1) | 27(1) | 72(1) | 9(1) | 14(1) | -1(1) |
| O(7) | 76(1) | 90(1) | 33(1) | 13(1) | -14(1) | -31(1) |
| Cr(1) | 24(1) | 22(1) | 24(1) | 2(1) | 2(1) | -1(1) |
| C(15) | 159(4) | 110(3) | 49(2) | 10(2) | 25(2) | 53(3) |
| C(16) | 138(4) | 107(3) | 51(2) | -14(2) | -42(2) | 15(2) |
| C(17) | 58(2) | 77(2) | 142(4) | 5(2) | -50(2) | -8(1) |
| C(18) | 54(2) | 205(5) | 115(3) | 48(3) | -12(2) | -19(3) |
| O(8) | 66(1) | 50(1) | 50(1) | 0(1) | -29(1) | 8(1) |

**Table A1.3.5 Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for *anti*-170**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 2657 | 4028 | 9231 | 41 |
| H(1B) | 3205 | 3009 | 9619 | 41 |
| H(2A) | 1967 | 2656 | 8296 | 35 |
| H(5) | 4246 | 303 | 6568 | 35 |
| H(6) | 6343 | 300 | 7304 | 35 |
| H(9A) | 5556 | 2767 | 9634 | 39 |
| H(9B) | 6370 | 3312 | 8828 | 39 |
| H(10A) | 2475 | 811 | 5670 | 87 |
| H(10B) | 997 | 962 | 6034 | 87 |
| H(10C) | 1958 | 222 | 6567 | 87 |
| H(11A) | 7876 | 297 | 8559 | 80 |
| H(11B) | 9026 | 1087 | 8665 | 80 |
| H(11C) | 8404 | 868 | 7654 | 80 |
| H(2) | 2241 | 3507 | 7049 | 52 |
| H(15A) | 2959 | 4258 | 5234 | 159 |
| H(15B) | 2812 | 3657 | 4277 | 159 |
| H(15C) | 3039 | 3093 | 5247 | 159 |
| H(16A) | 812 | 4205 | 4835 | 119 |
| H(16B) | 870 | 3044 | 4737 | 119 |
| H(17A) | -750 | 2770 | 5941 | 111 |
| H(17B) | -952 | 3924 | 5968 | 111 |
| H(18A) | -159 | 2842 | 7515 | 187 |
| H(18B) | -1656 | 3138 | 7306 | 187 |
| H(18C) | -581 | 3965 | 7507 | 187 |

**Table A1.3.6 Torsion angles [°] for *anti*-170**

| | |
|---|---|
| O(1)-C(1)-C(2)-O(2) | -69.16(17) |
| O(1)-C(1)-C(2)-C(3) | 51.05(17) |
| O(2)-C(2)-C(3)-C(8) | 103.12(16) |
| C(1)-C(2)-C(3)-C(8) | -15.6(2) |
| O(2)-C(2)-C(3)-C(4) | -75.45(18) |
| C(1)-C(2)-C(3)-C(4) | 165.87(15) |
| O(2)-C(2)-C(3)-Cr(1) | -166.66(11) |
| C(1)-C(2)-C(3)-Cr(1) | 74.66(17) |
| C(8)-C(3)-C(4)-O(3) | -176.02(14) |
| C(2)-C(3)-C(4)-O(3) | 2.6(2) |
| Cr(1)-C(3)-C(4)-O(3) | 126.03(14) |
| C(8)-C(3)-C(4)-C(5) | 6.6(2) |
| C(2)-C(3)-C(4)-C(5) | -174.85(15) |
| Cr(1)-C(3)-C(4)-C(5) | -51.38(14) |
| C(8)-C(3)-C(4)-Cr(1) | 57.95(13) |
| C(2)-C(3)-C(4)-Cr(1) | -123.47(14) |
| O(3)-C(4)-C(5)-C(6) | 178.51(15) |
| C(3)-C(4)-C(5)-C(6) | -4.4(2) |
| Cr(1)-C(4)-C(5)-C(6) | -55.59(13) |
| O(3)-C(4)-C(5)-Cr(1) | 51.21(14) |
| C(4)-C(5)-C(6)-C(7) | -1.6(2) |
| Cr(1)-C(5)-C(6)-C(7) | -58.26(13) |
| C(4)-C(5)-C(6)-Cr(1) | 56.70(13) |
| C(5)-C(6)-C(7)-O(4) | -176.90(15) |
| Cr(1)-C(6)-C(7)-O(4) | 126.05(16) |
| C(5)-C(6)-C(7)-C(8) | 5.3(2) |
| Cr(1)-C(6)-C(7)-C(8) | -51.77(13) |
| C(5)-C(6)-C(7)-Cr(1) | 57.05(13) |
| C(4)-C(3)-C(8)-C(7) | -2.8(2) |
| C(2)-C(3)-C(8)-C(7) | 178.56(14) |
| Cr(1)-C(3)-C(8)-C(7) | 55.20(13) |
| C(4)-C(3)-C(8)-C(9) | 175.57(15) |
| C(2)-C(3)-C(8)-C(9) | -3.0(2) |
| Cr(1)-C(3)-C(8)-C(9) | -126.39(15) |
| C(4)-C(3)-C(8)-Cr(1) | -58.04(13) |
| C(2)-C(3)-C(8)-Cr(1) | 123.36(14) |
| O(4)-C(7)-C(8)-C(3) | 178.88(14) |
| C(6)-C(7)-C(8)-C(3) | -3.1(2) |
| Cr(1)-C(7)-C(8)-C(3) | -54.37(13) |
| O(4)-C(7)-C(8)-C(9) | 0.4(2) |
| C(6)-C(7)-C(8)-C(9) | 178.49(15) |
| Cr(1)-C(7)-C(8)-C(9) | 127.18(14) |
| O(4)-C(7)-C(8)-Cr(1) | -126.75(14) |
| C(6)-C(7)-C(8)-Cr(1) | 51.31(13) |
| C(3)-C(8)-C(9)-O(1) | -12.6(2) |
| C(7)-C(8)-C(9)-O(1) | 165.79(14) |
| Cr(1)-C(8)-C(9)-O(1) | -102.96(16) |
| C(8)-C(9)-O(1)-C(1) | 48.74(19) |
| C(2)-C(1)-O(1)-C(9) | -70.57(17) |
| C(5)-C(4)-O(3)-C(10) | 6.4(3) |
| C(3)-C(4)-O(3)-C(10) | -170.84(18) |
| Cr(1)-C(4)-O(3)-C(10) | -86.9(2) |
| C(6)-C(7)-O(4)-C(11) | -4.1(3) |
| C(8)-C(7)-O(4)-C(11) | 173.85(17) |
| Cr(1)-C(7)-O(4)-C(11) | 89.0(2) |
| O(7)-C(14)-Cr(1)-C(12) | -79(7) |
| O(7)-C(14)-Cr(1)-C(13) | -168(7) |
| O(7)-C(14)-Cr(1)-C(6) | 101(7) |

| | |
|---|---|
| O(7)-C(14)-Cr(1)-C(5) | 98(7) |
| O(7)-C(14)-Cr(1)-C(3) | 10(7) |
| O(7)-C(14)-Cr(1)-C(8) | 38(7) |
| O(7)-C(14)-Cr(1)-C(4) | 10(7) |
| O(7)-C(14)-Cr(1)-C(7) | 75(7) |
| O(5)-C(12)-Cr(1)-C(14) | 106(8) |
| O(5)-C(12)-Cr(1)-C(13) | -164(8) |
| O(5)-C(12)-Cr(1)-C(6) | -74(8) |
| O(5)-C(12)-Cr(1)-C(5) | -73(8) |
| O(5)-C(12)-Cr(1)-C(3) | -9(8) |
| O(5)-C(12)-Cr(1)-C(8) | 17(8) |
| O(5)-C(12)-Cr(1)-C(4) | -46(8) |
| O(5)-C(12)-Cr(1)-C(7) | 14(8) |
| O(6)-C(13)-Cr(1)-C(14) | 93(6) |
| O(6)-C(13)-Cr(1)-C(12) | 4(6) |
| O(6)-C(13)-Cr(1)-C(6) | -149(6) |
| O(6)-C(13)-Cr(1)-C(5) | -112(6) |
| O(6)-C(13)-Cr(1)-C(3) | -83(6) |
| O(6)-C(13)-Cr(1)-C(8) | -178(100) |
| O(6)-C(13)-Cr(1)-C(4) | -86(6) |
| O(6)-C(13)-Cr(1)-C(7) | -175(100) |
| C(7)-C(6)-Cr(1)-C(14) | -47.96(13) |
| C(5)-C(6)-Cr(1)-C(14) | -177.80(10) |
| C(7)-C(6)-Cr(1)-C(12) | 131.19(16) |
| C(5)-C(6)-Cr(1)-C(12) | 1.4(2) |
| C(7)-C(6)-Cr(1)-C(13) | -138.87(11) |
| C(5)-C(6)-Cr(1)-C(13) | 91.29(11) |
| C(7)-C(6)-Cr(1)-C(5) | 129.84(14) |
| C(7)-C(6)-Cr(1)-C(3) | 64.12(10) |
| C(5)-C(6)-Cr(1)-C(3) | -65.72(10) |
| C(7)-C(6)-Cr(1)-C(8) | 28.05(9) |
| C(5)-C(6)-Cr(1)-C(8) | -101.79(10) |
| C(7)-C(6)-Cr(1)-C(4) | 100.67(10) |
| C(5)-C(6)-Cr(1)-C(4) | -29.17(9) |
| C(5)-C(6)-Cr(1)-C(7) | -129.84(14) |
| C(4)-C(5)-Cr(1)-C(14) | -126.40(19) |
| C(6)-C(5)-Cr(1)-C(14) | 4.7(2) |
| C(4)-C(5)-Cr(1)-C(12) | 49.61(12) |
| C(6)-C(5)-Cr(1)-C(12) | -179.32(10) |
| C(4)-C(5)-Cr(1)-C(13) | 139.16(11) |
| C(6)-C(5)-Cr(1)-C(13) | -89.77(11) |
| C(4)-C(5)-Cr(1)-C(6) | -131.07(14) |
| C(4)-C(5)-Cr(1)-C(3) | -28.10(9) |
| C(6)-C(5)-Cr(1)-C(3) | 102.97(10) |
| C(4)-C(5)-Cr(1)-C(8) | -64.67(10) |
| C(6)-C(5)-Cr(1)-C(8) | 66.40(9) |
| C(6)-C(5)-Cr(1)-C(4) | 131.07(14) |
| C(4)-C(5)-Cr(1)-C(7) | -101.22(11) |
| C(6)-C(5)-Cr(1)-C(7) | 29.85(9) |
| C(8)-C(3)-Cr(1)-C(14) | 51.14(11) |
| C(4)-C(3)-Cr(1)-C(14) | -179.45(10) |
| C(2)-C(3)-Cr(1)-C(14) | -63.49(16) |
| C(8)-C(3)-Cr(1)-C(12) | 139.66(10) |
| C(4)-C(3)-Cr(1)-C(12) | -90.93(11) |
| C(2)-C(3)-Cr(1)-C(12) | 25.03(15) |
| C(8)-C(3)-Cr(1)-C(13) | -133.67(17) |
| C(4)-C(3)-Cr(1)-C(13) | -4.3(2) |
| C(2)-C(3)-Cr(1)-C(13) | 111.70(19) |
| C(8)-C(3)-Cr(1)-C(6) | -64.85(10) |
| C(4)-C(3)-Cr(1)-C(6) | 64.56(10) |
| C(2)-C(3)-Cr(1)-C(6) | -179.48(15) |
| C(8)-C(3)-Cr(1)-C(5) | -101.91(10) |

| | |
|---|---|
| C(4)-C(3)-Cr(1)-C(5) | 27.49(9) |
| C(2)-C(3)-Cr(1)-C(5) | 143.45(15) |
| C(4)-C(3)-Cr(1)-C(8) | 129.41(14) |
| C(2)-C(3)-Cr(1)-C(8) | -114.63(17) |
| C(8)-C(3)-Cr(1)-C(4) | -129.41(14) |
| C(2)-C(3)-Cr(1)-C(4) | 115.96(18) |
| C(8)-C(3)-Cr(1)-C(7) | -29.28(9) |
| C(4)-C(3)-Cr(1)-C(7) | 100.13(11) |
| C(2)-C(3)-Cr(1)-C(7) | -143.91(15) |
| C(3)-C(8)-Cr(1)-C(14) | -134.87(11) |
| C(7)-C(8)-Cr(1)-C(14) | 93.42(11) |
| C(9)-C(8)-Cr(1)-C(14) | -20.21(16) |
| C(3)-C(8)-Cr(1)-C(12) | -46.51(11) |
| C(7)-C(8)-Cr(1)-C(12) | -178.21(10) |
| C(9)-C(8)-Cr(1)-C(12) | 68.16(16) |
| C(3)-C(8)-Cr(1)-C(13) | 135.59(17) |
| C(7)-C(8)-Cr(1)-C(13) | 3.9(2) |
| C(9)-C(8)-Cr(1)-C(13) | -109.8(2) |
| C(3)-C(8)-Cr(1)-C(6) | 104.05(10) |
| C(7)-C(8)-Cr(1)-C(6) | -27.65(9) |
| C(9)-C(8)-Cr(1)-C(6) | -141.29(16) |
| C(3)-C(8)-Cr(1)-C(5) | 66.65(9) |
| C(7)-C(8)-Cr(1)-C(5) | -65.05(10) |
| C(9)-C(8)-Cr(1)-C(5) | -178.68(16) |
| C(7)-C(8)-Cr(1)-C(3) | -131.70(14) |
| C(9)-C(8)-Cr(1)-C(3) | 114.66(18) |
| C(3)-C(8)-Cr(1)-C(4) | 30.75(9) |
| C(7)-C(8)-Cr(1)-C(4) | -100.95(11) |
| C(9)-C(8)-Cr(1)-C(4) | 145.42(16) |
| C(3)-C(8)-Cr(1)-C(7) | 131.70(14) |
| C(9)-C(8)-Cr(1)-C(7) | -113.64(19) |
| O(3)-C(4)-Cr(1)-C(14) | -104.72(19) |
| C(5)-C(4)-Cr(1)-C(14) | 135.21(16) |
| C(3)-C(4)-Cr(1)-C(14) | 1.1(2) |
| O(3)-C(4)-Cr(1)-C(12) | -16.65(15) |
| C(5)-C(4)-Cr(1)-C(12) | -136.72(11) |
| C(3)-C(4)-Cr(1)-C(12) | 89.13(11) |
| O(3)-C(4)-Cr(1)-C(13) | 72.20(16) |
| C(5)-C(4)-Cr(1)-C(13) | -47.87(12) |
| C(3)-C(4)-Cr(1)-C(13) | 177.98(10) |
| O(3)-C(4)-Cr(1)-C(6) | 150.13(16) |
| C(5)-C(4)-Cr(1)-C(6) | 30.06(10) |
| C(3)-C(4)-Cr(1)-C(6) | -104.09(10) |
| O(3)-C(4)-Cr(1)-C(5) | 120.07(18) |
| C(3)-C(4)-Cr(1)-C(5) | -134.15(15) |
| O(3)-C(4)-Cr(1)-C(3) | -105.78(18) |
| C(5)-C(4)-Cr(1)-C(3) | 134.15(15) |
| O(3)-C(4)-Cr(1)-C(8) | -136.15(16) |
| C(5)-C(4)-Cr(1)-C(8) | 103.78(11) |
| C(3)-C(4)-Cr(1)-C(8) | -30.37(9) |
| O(3)-C(4)-Cr(1)-C(7) | -173.27(15) |
| C(5)-C(4)-Cr(1)-C(7) | 66.66(10) |
| C(3)-C(4)-Cr(1)-C(7) | -67.49(10) |
| O(4)-C(7)-Cr(1)-C(14) | 18.87(16) |
| C(6)-C(7)-Cr(1)-C(14) | 139.02(12) |
| C(8)-C(7)-Cr(1)-C(14) | -87.00(11) |
| O(4)-C(7)-Cr(1)-C(12) | 109.47(19) |
| C(6)-C(7)-Cr(1)-C(12) | -130.38(16) |
| C(8)-C(7)-Cr(1)-C(12) | 3.6(2) |
| O(4)-C(7)-Cr(1)-C(13) | -72.23(17) |
| C(6)-C(7)-Cr(1)-C(13) | 47.92(12) |
| C(8)-C(7)-Cr(1)-C(13) | -178.10(10) |

| | |
|---|---|
| O(4)-C(7)-Cr(1)-C(6) | -120.15(19) |
| C(8)-C(7)-Cr(1)-C(6) | 133.98(14) |
| O(4)-C(7)-Cr(1)-C(5) | -150.91(17) |
| C(6)-C(7)-Cr(1)-C(5) | -30.77(9) |
| C(8)-C(7)-Cr(1)-C(5) | 103.21(10) |
| O(4)-C(7)-Cr(1)-C(3) | 135.01(16) |
| C(6)-C(7)-Cr(1)-C(3) | -104.84(11) |
| C(8)-C(7)-Cr(1)-C(3) | 29.14(9) |
| O(4)-C(7)-Cr(1)-C(8) | 105.87(18) |
| C(6)-C(7)-Cr(1)-C(8) | -133.98(14) |
| O(4)-C(7)-Cr(1)-C(4) | 172.56(16) |
| C(6)-C(7)-Cr(1)-C(4) | -67.29(10) |
| C(8)-C(7)-Cr(1)-C(4) | 66.69(10) |
| C(15)-C(16)-O(8)-C(17) | -175.1(3) |
| C(18)-C(17)-O(8)-C(16) | -177.5(4) |

Symmetry transformations used to generate equivalent atoms:

## A2 Literature Published during this PhD

The following paper was published in The Royal Society of Chemistry Journal, *Organic and Biomolecular Chemistry* in 2007.

### Bidirectional racemic synthesis of the biologically active quinone cardinalin 3

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Readily available 2,2,6,6-tetramethoxy-1,1-biphenyl was transformed in 14 synthetic steps into the natural product cardinalin 3 using a bidirectional approach. One of the key steps was the formation of the *cis*-1,3-dimethylnaphtho[2,3-*c*]pyran ring. (±)-1,1-[6,6-Diallyl-5,5-*bis*(benzyloxy)-1,1,3,3-tetramethoxy-2,2-binaphthalene-7,7-diyl]diethanol was treated with $O_2$ in the presence of $CuCl_2$ and catalytic $PdCl_2$ to afford 5,5-*bis*(benzyloxy)-7,7,9,9-tetramethoxy-1,1,3,3-tetramethyl-1*H*,1*H*-8,8-bibenzo[*g*]isochromene. Hydrogenation of this compound afforded 7,7,9,9-tetramethoxy-*cis*-1,3-*cis*-1,3-tetramethyl-3,3,4,4-tetrahydro-1*H*,1*H*-8,8-bibenzo[*g*]isochromene-5,5-diol in quantitative yield, which was converted in 3 steps to cardinalin 3.