Development of Novel Methodology for the Synthesis of the Angucycline Tetrangulol, Benzo[c]phenanthridines and Benzonaphthopyranones

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A thesis submitted to the Faculty of Science,
University of the Witwatersrand
Johannesburg

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

March 2017

Declaration

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

Kennedy John Ngwira

7th March, 2017

Abstract

In this PhD thesis, we report for the first time, new methodology for the synthesis of angucycline antibiotic natural products. In particular, for the synthesis of 1,8-dihydroxy-3-methyltetraphene-7,12-dione, commonly known as tetrangulol. We also report on the synthesis of 1,10,12-trimethoxy-8-methylbenzo[*c*]phenanthridine in our quest to synthesise phenanthroviridone from an intermediate product in the synthesis of tetrangulol.

The Suzuki-Miyaura coupling reaction between 1,4,5-(trimethoxynaphthalen-2-yl)boronic acid and 2-iodo-3-methoxy-5-methylbenzaldehyde afforded intermediate, 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde. Conversion of this benzaldehyde into the alkyne, 2-(2-ethynyl-6-methoxy-4-methylphenyl)-1,4,5-trimethoxynaphthalene was accomplished utilizing the Corey-Fuchs reaction. Exposure of the derived acetylene to a catalytic platinum(II)-mediated ring closure yielded the required tetracyclic aromatic product, 1,7,8,12-tetramethoxy-3-methyltetraphene which was converted into tetrangulol. Exposure of the related 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde *O*-phenyl oxime to microwave irradiation in an ionic liquid yielded 1,10,12-trimethoxy-8-methylbenzo[*c*]phenanthridine, instead of the desired natural product phenanthroviridone.

We also report on the unexpected synthesis of the benzonaphthopyranone core found in other classes of angucycline antibiotics from oxygen analogs of 2-naphthylbenzyl alcohols when exposed to *N*-bromosuccinimide. Treatment of (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol and related analogues with *N*-bromosuccinimide under an oxygen atmosphere afforded 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one, 2-Methoxy-6*H*-benzo[*c*]chromen-6-one and of 6*H*-benzo[*c*]chromen-6-one. An investigation into possible mechanisms for this transformation was also conducted.

Acknowledgements

First and foremost, I would like to thank the Almighty God for seeing me through this far. He was there for me during both the high and the low tides of this amazing journey.

Secondly, I am greatly indebted to an awesome team of Supervisors in Professor Charles de Koning, Dr. Amanda Rousseau and Dr. Myron Johnson without whose support, encouragement, advice, understanding and supervision, I would not have made it this far. I was truly privileged and honoured to work under their guidance.

I am grateful to Dr. Jean Dam, a great friend who was always there in both the good times as well as those difficult moments in the lab. She was a source of inspiration. In no small measure, I acknowledge the entire organic group for the support that they accorded me. More importantly, I am grateful to Jimmy Sumani, Donald Seanego, Peter Wanyama Juma, Charles Changunda, Memory Zimuwandei, Xolani Motloung and Hendrik Henning for teaching me new techniques when I was a novice in the group and for helping me to grow as a scientist. You were always an ear away when I faced obstacles.

I would like to acknowledge the support of my greatest friends in Priscilla, Thelma and Kelsey Ngwira. Thank you so much for your encouragement and most importantly, for your unceasing prayers. I drew a lot of inspiration from you and I could not have done it without you. A big thank you to William Khumbo Ngwira, for being the pillar in our family in my absence. Thank you to Monica, Mary, Takondwa, Grace, Chimwemwe and Richard.

I would not do myself justice if I do not recognise the support, encouragement and prayers of my dad Mr. William Cullen Ngwira and my mum, Mrs. Anne Nyagondwe Ngwira. Thank you for all your words of wisdom and for making me who I am today.

I am grateful to the Southern Africa Biochemistry and Informatics for Natural Products (SABINA) project for generous funding, from my Masters degree up to this PhD. A huge thank you to Prof. John Saka and Dr. John Becker (Academic Directors) of the project, Miss Ella Nyankunu, Mr. Frank Ngonda and Mrs. Jessika Naidoo (Project Managers), and SABINA fellows, some of whom we have been together during the last eight years of the Project. I also acknowledge the University of Malawi for the study leave.

And to many more than I could not list here, I say thank you!

Dedication

This PhD thesis is dedicated to Priscilla, Thelma and Kelsey Ngwira.

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CHAPTER 1: Angucycline Antibiotics – Introduction and Literature Review

1.1 Background and introduction on antibiotics

Antibiotics have been used for treatment of a number of diseases and ailments for more than 50 years and are regarded as one of the most successful forms of chemotherapy in the history of medicine.[1-2] They are defined as chemical substances of microbial origin that in low concentrations have the capacity to inhibit the growth of or kill other microorganisms.[3] Although the management of microbial infections is well documented in ancient Chinese, Greece and Egypt civilisations, the modern use of antibiotics mainly began with the serendipitous discovery of penicillin from the culture filtrate of a fungus by Sir Alexander Fleming in 1928.[4] Since this discovery, other more effective antimicrobials have been discovered and developed through better understanding of the drug target interactions.[5] As a result, they have changed the landscape of modern medicine and saved millions of lives across the globe.[6] Furthermore, they have played a critical role in achieving significant advances in surgery through prevention or treatment of infections in patients who have undergone complex surgical procedures like organ transplants or cardiac surgery.[7] In developing countries where infectious diseases are rampant due to poor sanitation, the morbidity and mortality rates due to food-borne and other poverty-related diseases, have been significantly decreased as a result of antibiotics.[8]

1.2 Classification and modes of action of antibiotics

Antibiotics are the only class of medical agents whose primary target is not the human tissue or its products.[7] They are classified on the basis of their cellular component or the systems they affect. Additionally, they are also categorised on the basis of the effect they have. Some antibiotics induce cell death (bactericidal) while others simply inhibit cell growth (bacteriostatic).[5] A variety of mechanisms of action have been postulated for antibiotics. Some antibiotics like β-lactams and glycopeptides interfere with the homeostatic cell wall biosynthesis.[5] Successful

inhibition of cell wall synthesis can result in changes to cell shape and size, leading to induced cellular stress responses. This eventually culminates in cell lysis.[9] Other antibiotics like tetracyclines, aminoglycosides and macrolides target the protein synthetic machinery through interaction with ribosomal subunits.[4] These antibiotics are also referred to as 50S or 30S ribosome inhibitors. 50S inhibitors include macrolide (erythromycin), amphenicol (chloramphenicol) and lincosamide (clindamycin). Examples of 30S ribosome inhibitors include the tetracycline and aminocyclitol families of antibiotics. [10-11] The 50S inhibitors physically block the initiation of protein translation or translocation of peptidyl-tRNAs.[12-13] On the other hand, 30S inhibitors work by blocking the access of the aminoacyl-tRNAs to the ribosome.[14] Another group of antibiotics, for example fluoroquinolone (ciprofloxacin) interfere with nucleic acid synthesis hence inhibiting DNA replication whereas rifamycin inhibits RNA replication. As a result of the inhibition of replication of nucleic acids, prokaryotic nucleic acid metabolism of the bacteria is affected inducing bacterial cell death.[15]

1.3 Antibiotic resistance

Although antibiotics largely enjoyed unprecedented successes since early 1940s, the successes however have been overshadowed by the emergence and dissemination of antimicrobial resistance (AMR) which is the greatest threat to human health world-wide.[16] Antibiotic resistance from a microbiological point of view can be defined as a phenotype which makes the microorganism less susceptible than other members of the same species, irrespective of any level of resistance. On the other hand, when the resistance reaches a certain critical level so as to interfere with the pharmacotherapy of a clinical problem caused by the bacterium, this is then referred to as clinical resistance.[17] Among Gram-positive pathogens, *Staphylococcus aureus* and *Enterococcus spp*. are the species which currently pose the biggest challenge in antibiotic resistance.[8] The accretion of resistance traits to multiple classes of antibiotics, resulting in strains with multidrug-resistance (MDR) phenotypes, has over time reduced the available treatment options for some pathogens.[8] More recently, the

emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) has been reported to kill more Americans every year than emphysema, HIV/AIDS, Parkinson's disease and homicides combined.[18] Furthermore, the mortality rates due to multidrug-resistant bacterial infections are on the increase. Each year, about 25,000 patients in the EU die from an infection with the selected multidrug-resistant bacteria.[19] Globally, 3.7% of new cases and 20% of previously treated cases of tuberculosis are estimated to be caused by strains that are resistant to isoniazid and rifampicin.[16] Furthermore, the emergence of drug resistance has led to an increase in health care costs. It is estimated that the direct cost to health care systems resulting from antibiotic resistance in Europe is €9 billion.[20] Smith and Coast further demonstrated that £20,000 could be the additional cost of resistance per patient episode in hospital. In the same study, they further reported that the highest cost of antimicrobial resistance in the US is $55 billion emanating from $20 billion health services cost and $35 billion from loss of productivity.[21]

1.4 Causes of multi-drug resistance of bacteria

One of the most likely causes of multi-drug resistant bacteria is over-prescription of antibiotics.[22] Epidemiological studies have indicated a direct relationship between consumption of antibiotics and development and dissemination of resistant strains.[23] Read *et al.* noted that antibiotics through a natural selective process remove drug-sensitive competitors, leaving behind drug-resistant ones. Typically, resistance develops through mutations.[24] The problem of over-use has been compounded by the fact that antibiotics are not regulated and are available over the counter without prescription in a number of countries.[25] Furthermore, it has been reported that inappropriate antibiotic prescriptions promote bacterial resistance.[6] Development of antibiotic resistance has also been attributed to extensive agricultural use of antibiotics.[22, 25] Antibiotics are used as growth supplements in animals both in the developed and developing world. It is further estimated that 80% of all antibiotics sold in the US are used in animals.[26-27] These antibiotics which bio-accumulate in the animals are eventually ingested by humans.[28] Thirdly, the limited availability of new

antibiotics has been observed to also contribute to the development of resistance.[22] The development of new antibiotics by the pharmaceutical industry has been hampered by both economic and regulatory obstacles.[27] The dwindling funding for academic research on antibiotics due to the economic crisis and mergers between pharmaceutical companies has led to fewer new antibiotics being developed and this resulted in less diversity to the range of antibiotics. Finally, stringent regulatory measures have acted as barriers in the development of new antibiotics.[22] For companies having an interest in development of new drugs, obtaining regulatory approval is often difficult leading to fewer drugs being developed.[29] **Figure 1** highlights the decline of new antibacterial drug approvals over the past three decades.[22] Additionally, changes made by the US Food and Drug Administration (FDA) on new standards for clinical trials design, have consequently made clinical trials more challenging. This has stifled progress towards development of new leads.

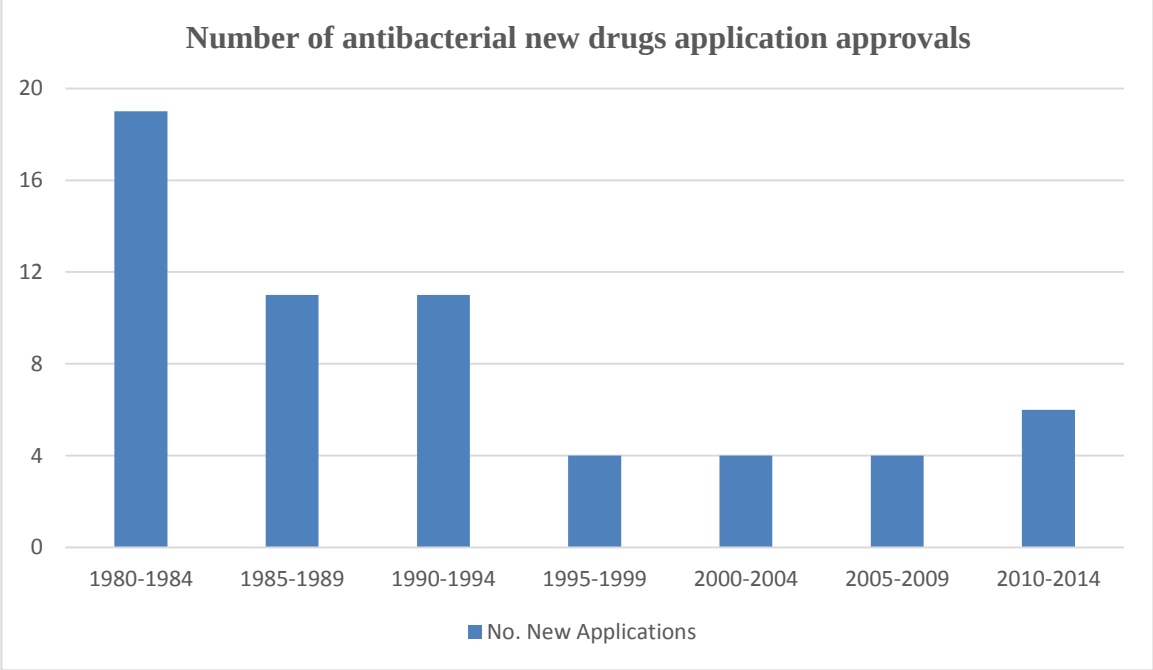


Figure 1: Trends in antibacterial new drugs application approvals

In view of these challenges with the current antibiotics, there is a need for the development of new and more effective antibiotic drug candidates. Traditionally,

natural products, i.e., genetically encoded small molecules produced by bacteria and fungi, have been the dominant source of clinically used antibiotics.[30] One class of such antibiotic natural products that has been reported to possess therapeutic properties is the angucycline antibiotics. Although this class of natural product belongs to the antibiotic family, their therapeutic potencies are not limited to antibacterial activities. As it will be demonstrated in the forthcoming sections, they are even more potent as anticancer agents.

1.5 Angucycline antibiotic natural products

Angucyclines belong to a relatively new and large group of antibiotic natural products featuring an angularly assembled carbotetracycle and have been isolated from the culture broths of different microorganisms.[31] In general, the angucyclines possess a benz[*a*]anthracene as a common structural framework (**Figure 2**) that bears oxygen functionalities at both C-1 and C-8, along with a single alkyl group or a combination of alkyl group and oxygen functionality at C-3. The main differences among them are found in the aromatic or hydro-aromatic nature of the A and/or B rings as well as the presence, in some cases, of oxygens at C-4, C-4a and/or C-12b. Glycosides are often found attached to some of the oxygen substituents and typically attached to C-3. However, *C*-glycosidic moieties can also be present at C-9 or C-2.[31] By definition, angucyclines include those compounds with hydrolysable carbohydrate moieties while angucyclinones are those without the carbohydrate moiety attached to the aromatic nucleus.

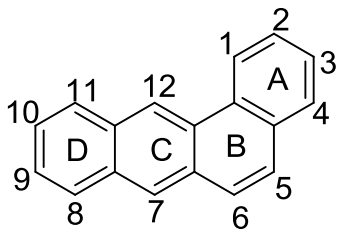
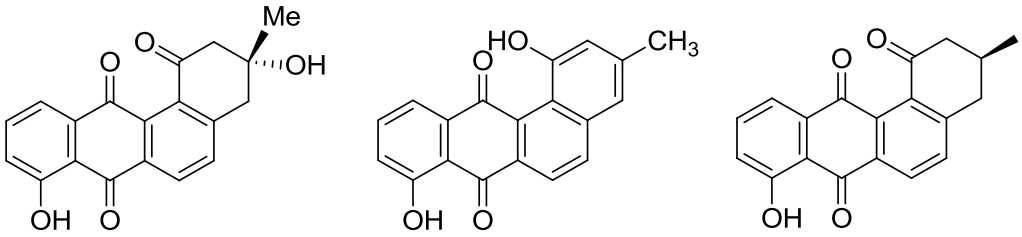


Figure 2: Carbon skeleton of angucycline antibiotics

The first members of this class of antibiotics, tetrangomycin **1** and tetrangulol **2** (**Figure 3**) were first isolated in 1965 and 1966 respectively.[32-33] Ochromycinone **3** was later isolated in 1967.[34] Since then, a number of other antibiotic natural products have been isolated with different therapeutic targets and potency.[35] The diverse biological activities include antibacterial, anticancer, enzyme inhibitory, antiviral and antifungal activity; as well as platelet aggregation inhibition.[36]



1 **2** **3**

Figure 3: First angucycline antibiotics to be isolated

1.6 Biological activities of natural angucycline antibiotics

Since the first angucycline antibiotics were isolated, biological activity evaluations of different classes of these natural products have been undertaken. The next section highlights the therapeutic potencies of some classes of angucyclines such as landomycins, urdamycins, kinamycins and other new isolates of angucycline antibiotics.

1.6.1 Landomycin antibiotics

Landomycins are a sub-group of the angucycline antibiotics. They are characterised by a linear oligosaccharide conjugated to the angular carbotetracyclic quinone on the C-8 oxygen[37] as shown in **Figure 4**.

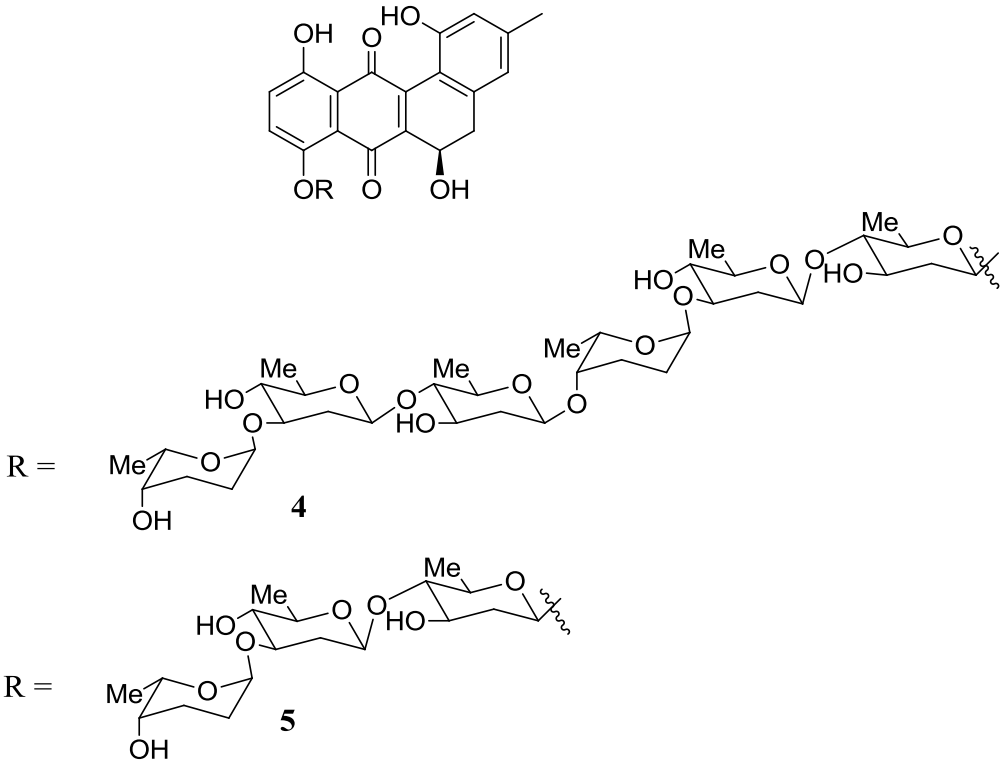
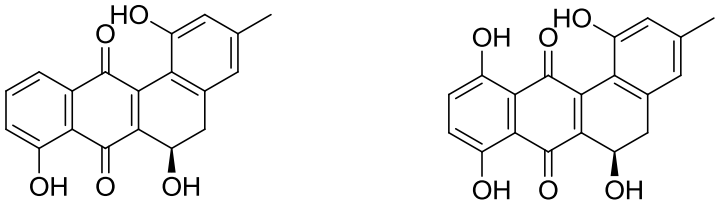


Figure 4: Structures of Landomycin Antibiotics

Landomycins have received a lot of interest and attention because of their antitumour activities, in particular against the NCI 60 human cancer cell line.[38] Landomycin A (LA) **4** was reported to exhibit activities against prostate cancer cell lines as well as cell cycle disruption activities. It was also reported to disrupt thymidine uptake in animal models.[39] Landomycin E (LE) **5** on the other hand, which was isolated from the *Streptomyces globisporus* strain,[40] showed promising activity in multiple drug resistant cell lines as an inducer of apoptosis (IC_{50} 0.76 mg/mL for MDA-MB-231 human breast cancer cell line, with mean GI_{50} at 1 mg/mL of 1 mM). This activity was still less than that of LA **4**. In a study by Korynevska *et al.* in understanding the mechanism of anticancer activities of LE **5** in human carcinoma cell model KB-3-1, they observed morphological signs of programmed cell death like cell shrinkage, chromatin condensation and formation of apoptotic bodies. Apoptotic cell death

induced by **5** was further characterised by caspase (substrate) cleavage and intense mitochondrial membrane depolarisation.[37] Interestingly, it was observed that landomycins with the hexasaccharide intact exhibited better activity in MCF-7 (estrogen responsive) and MDA-231(estrogen refractory) breast cancer cell lines than landomycins with shorter oligosaccharidal chains. Krohn and Rohr also reported that the cytostatic properties of particular members of the landomycin family were shown to depend on the length of the oligosaccharide chain.[41] Surprisingly though, 11-deoxy-landomycinone **6** and landomycinone **7** (**Figure 5**) demonstrated excellent activity in cancer cell lines as well, despite the absence of an oligosaccharide chain (IC_{50} 2.1 mM and 1.2 mM in MCF-7 and MDA-231cell lines respectively for **6** and IC_{50} 2.9 mM and 2.9 mM in MCF-7 and LL/2 murine cancer cell lines respectively for **7**).[38, 42]



6 **7**

Figure 5: Landomycins without an oligosaccharide chain

1.6.2 Urdamycin antibiotics

Urdamycins were first isolated in the mid-1980s from the culture broth of *Streptomyces fradiae* Tü2717.[43] While members in other classes of glycosidic antibiotics differ mainly in the amounts and kinds of sugar units attached, urdamycins differ with respect to their aglycones, as shown in **Figure 6** for urdamycin A **8**, C **10** and D**11**. On the other hand, urdamycin B **9** does not have hydroxy groups at the C-4a and C-12b positions.[43]

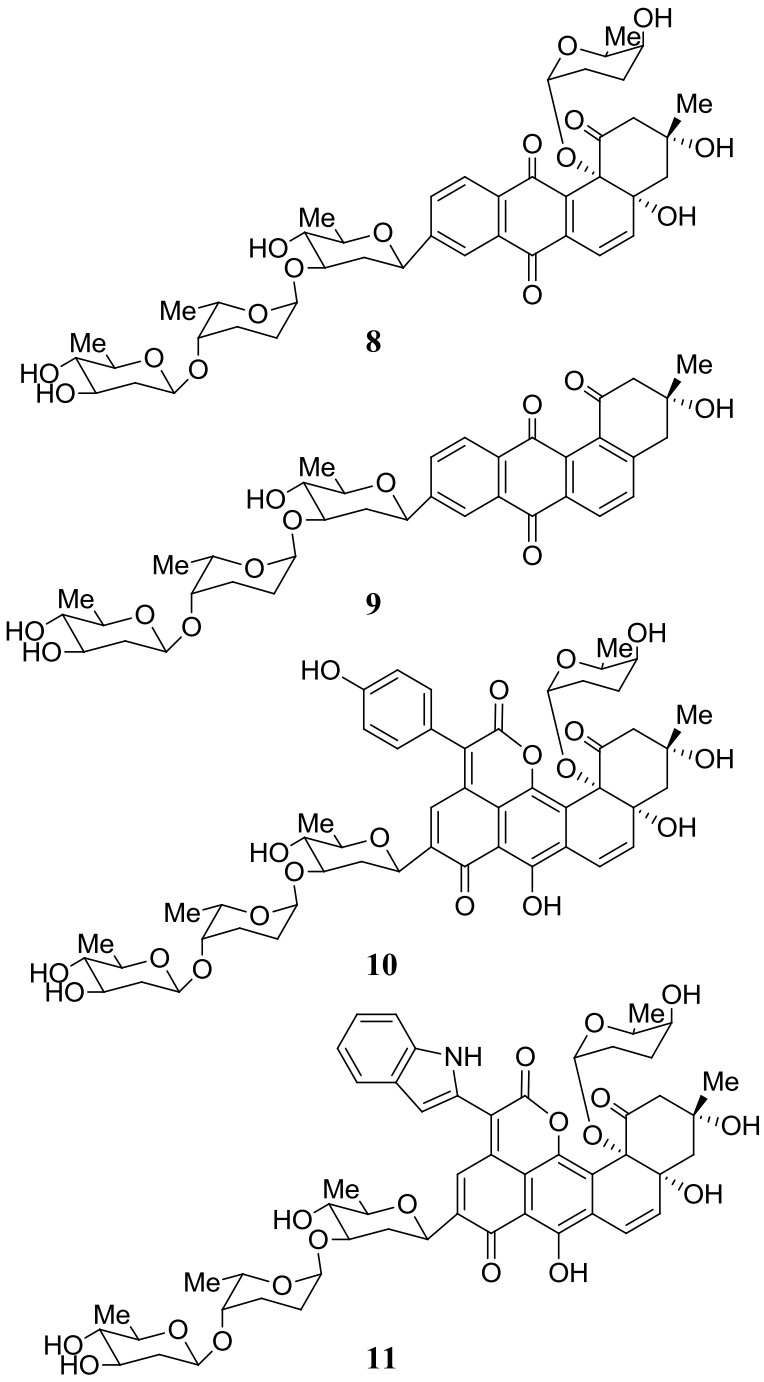
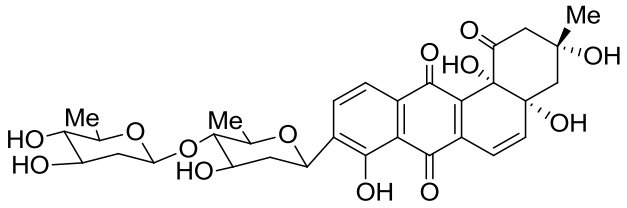


Figure 6: Examples of Urdamycins

Urdamycins were reported to exhibit strong antibacterial activities against both gram-positive and gram-negative bacteria equivalent to that of tetracenomycin and elloramycin. In the same study, urdamycin A **8** was reported to show activity against L1210 leukaemia cells.[44] Kirschning *et al.* also reported several new glycomodified urdamycin-type angucyclines such as **12** and **13** (**Figure 7**) with poor antitumour activity, but surprisingly having superior xanthine oxidase inhibition activities compared to allopurinol, one of the most potent inhibitors, with IC_{50} values of 0.42 µM for both **12** and **13**.[45]



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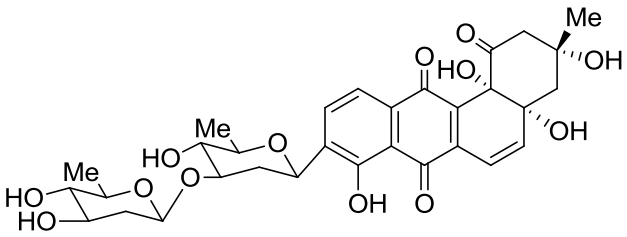

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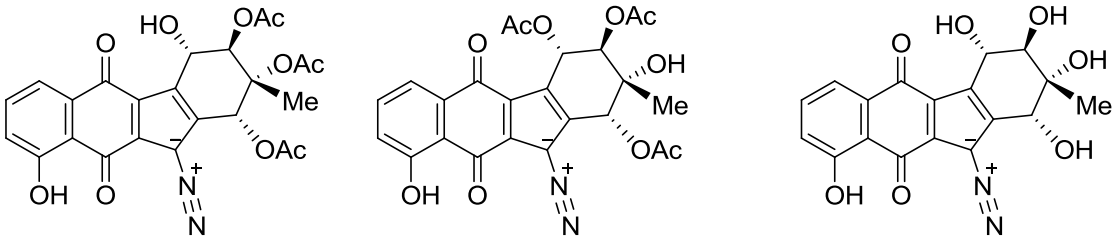
Figure 7: Glyco-modified urdamycins

1.6.3 Kinamycin antibiotics

Kinamycins were first isolated from *S. murayamaensis* and more recently, they have been isolated from the spiramycin producer *S. ambofaciens.*[46-47] This class of angucycline antibiotics contains a 6-6-5-6 ring system with a highly oxygenated cyclohexyl (ring D) moiety. Although this subunit has a different structural motif, they are related to the other angucycline antibiotics because they share the same

dehydrorabelomycin intermediate in their biosynthesis. Examples of compounds in this class include kinamycins A **14**, C **15** and F **16** which are given in **Figure 8.**



14 **15** **16**

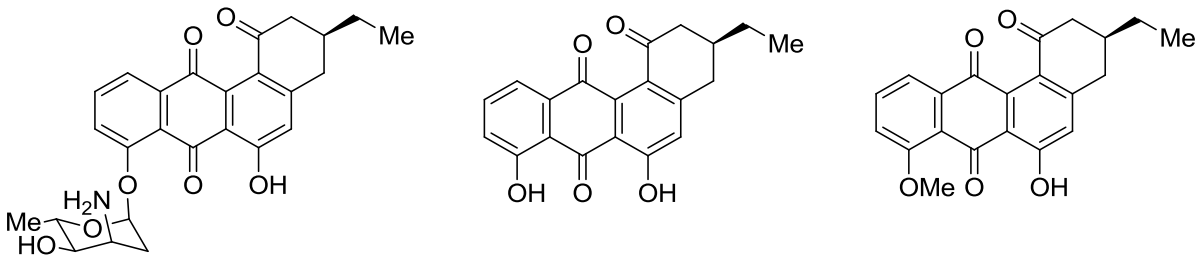
Figure 8: Examples of Kinamycin antibiotics

Kinamycins have recently attracted attention because of their antiproliferative activities. O'Hara *et al.* have recently reported that kinamycin F **16** downregulates cyclin D in human leukaemia K562 cells and it induced erythroid differentiation, a rapid apoptotic response.[48] Kinamycin C **15** was also reported by Omura *et al.* to exhibit antitumour activity *in vivo.*[47] Furthermore, kinamycins A **14** and C **15** also demonstrated K562 cell growth inhibition activities at submicromolar levels and they both induced apoptosis in Chinese hamster ovary (CHO) cancer cells with IC_{50} values in the ~10 nM range and 0.3 μM range, for **14** and **15** respectively.[49-50] Additionally, both antibiotics showed potency in abolishing topoisomerase IIα decatenation activity (IC_{50} value of 7.6 mmol/L for **14** and 9.2 mmol/L for **15**).[50]

1.6.4 Other new angucyclinone antibiotics

New angucyclinones in this context are antibiotics that have been discovered between 1997- 2010.[36] These compounds, just as those discovered earlier, have continued to show promising biological activities and could thus provide potential leads for drug development. In this section, some biological activities of selected new compounds are highlighted.

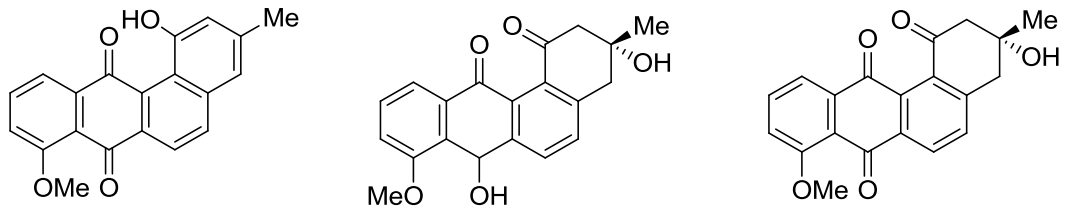
Brasiliquinone compounds A-C (**17-19**, **Figure 9**) were isolated from the actinomycete *Nocardia brasiliensis* IFM 0089.[51] These were shown to be potent against gram-positive bacteria including *Mycobacterium sp.* Furthermore, they also showed promising activities against multiple drug-resistant P388/ADR tumour cells.[52]



17 **18** **19**

Figure 9: Brasiliquinone angucyclinones

8-*O*-Methyltetrangulol **20**, 8-*O*-methyl-7-deoxo-7-hydroxytetrangomycin **21** and (-)-8-*O*-methyltetrangomycin **22** in **Figure 10** were isolated from *Streptomyces sp*. AC113.[53] These angucyclinones were reported to be active against *Bacillus cereus* and *Listeria monocytogenes*. When four cancer cell lines were subjected to these three natural products, compound **21** exhibited the most potent anticancer activity with an IC_{50} value of 0.054 mg/mL against a murine cancer cell line B16.[36]



20 **21** **22**

Figure 10: New Angucylinones

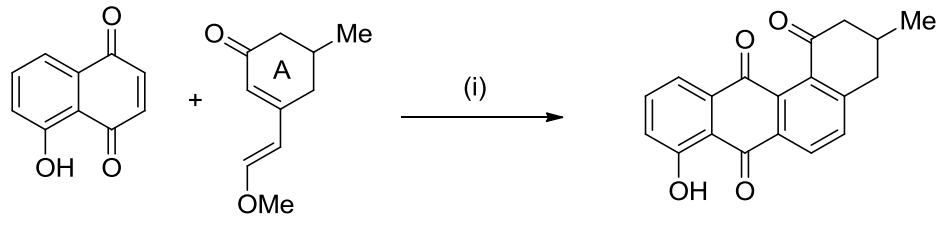
The wide range of biological activities and complex and challenging structures of some of these natural products have stimulated a lot of interest in developing synthetic methodologies for their formal synthesis, synthesis of their analogues and indeed the development of strategies to access the angular carbotetracyclic core of these antibiotics. The next section will highlight some of the strategies that have been developed for their synthesis.

1.7 Synthetic strategies towards angucycline antibiotics

Some of the strategies reported widely include, as a key step, the Diels-Alder reaction, the Friedel–Crafts reaction (electrophilic addition), nucleophilic additions, free radical annulations and more recently, transition metal catalysed cross coupling and intramolecular cyclisation strategies. Details of some of these strategies will be discussed in the subsequent sections.

1.7.1 Diels-Alder reaction

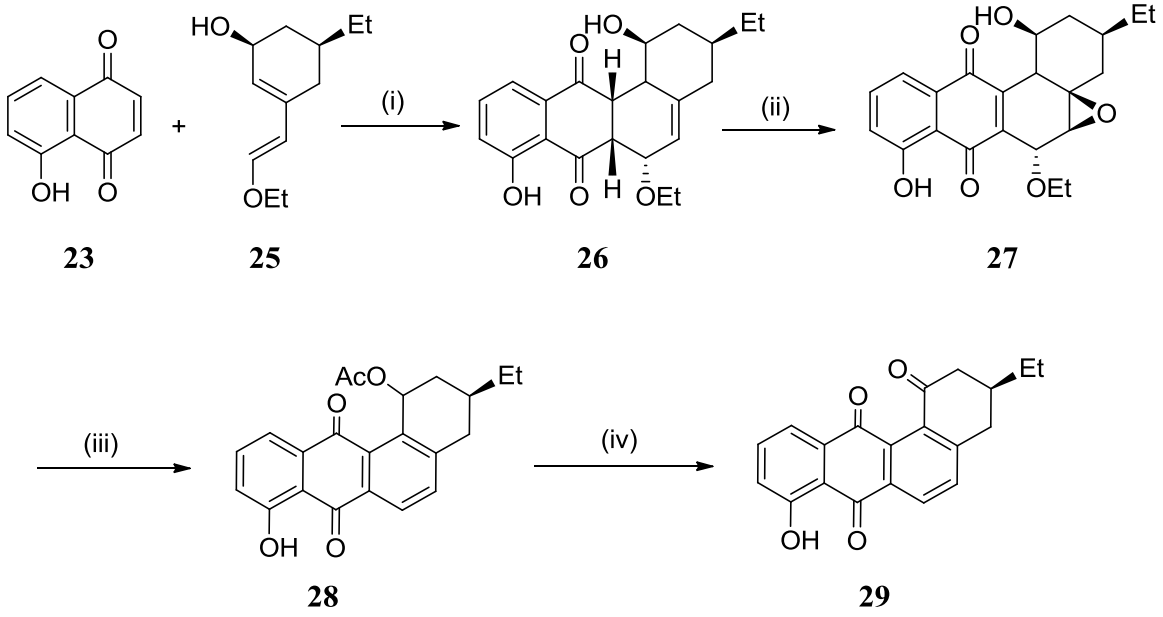
The synthesis of the tetracycline skeleton of angucycline antibiotics has been achieved using the Diels-Alder reaction as a key step. This reaction was pioneered by Guingant in the regioselective construction of the tetracycline skeleton of the racemic ochromycinone **3**.[54] This was accomplished by a boron triacetate-mediated Diels-Alder reaction between juglone **23** and methoxyvinylcyclohexenone **24** as shown in **Scheme 1**.



23 **24** **3**

***Scheme 1: Reagents and conditions**; (i) $B(OAc)_3$, CH_2Cl_2, 20 °C, 75%.*

This approach was also utilised by Krohn and co-workers in the synthesis of (±)-6-deoxybrasiliquinone **29**, a C-3 ethyl analogue of ochromycinone **3**.[55] In this synthesis illustrated in **Scheme 2**, juglone **23** was subjected to a Diels-Alder reaction with diene **25** to give the olefin product **26**, which was treated with dimethyldioxirane to afford the *cis*-epoxide **27** in good yield. Epoxide ring opening and rearomatisation gave acetate **28** albeit in a very modest yield. Saponification of the acetate followed by photooxidation of the resulting alcohol furnished the target compound **29.**



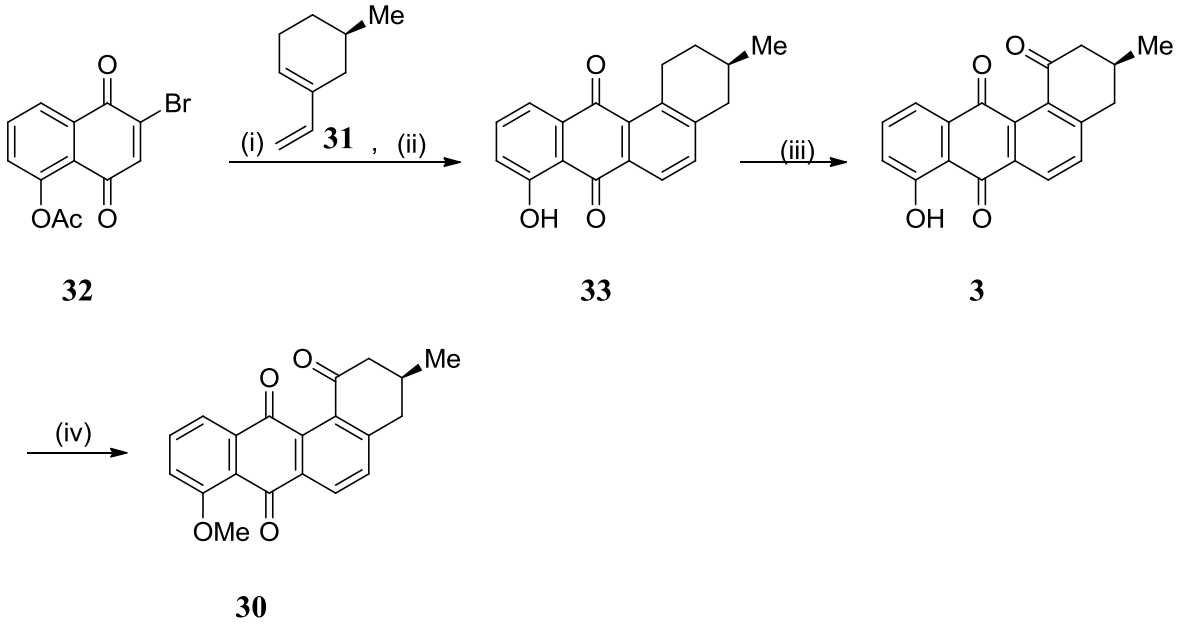
23 **25** **26** **27**

28 **29**

Scheme 2: Reagents and conditions*; (i) $B(OAc)_3$, CH_2Cl_2, 0 °C, 15 min, 71%; (ii) cat. 0.08 M dimethyldioxirane, CH_2Cl_2, Acetone, 0 °C, 15 h, 83%; (iii) $B(OAc)_3$, THF, 20 °C, 15 h, 23%; (iv) NaOMe, MeOH, THF, 20 °C, 15 min, then hv, 52%.*

The synthesis of enantiopure (+)-ochromycinone **3** and its structural analogue (+)-rubiginone **30** using a Diels-Alder promoted reaction as a key step was also reported by Kaliappan and Ravikumar.[56] This was realised by treating 1,3-diene **31** with 5-acetoxy-2-bromo-1,4-naphthoquinone **32** in toluene at 80 °C to yield a tetracyclic

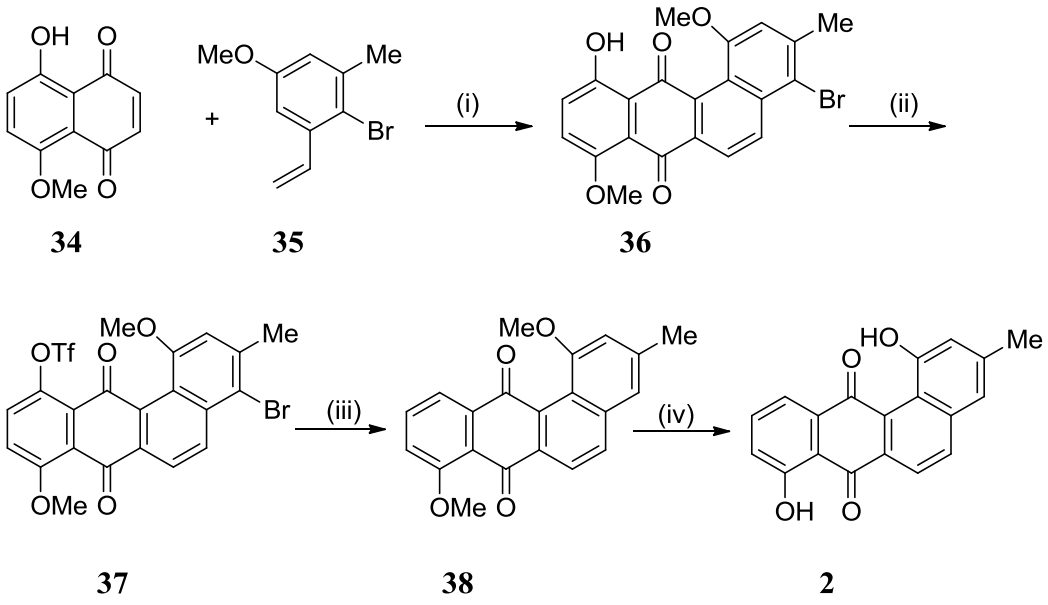
compound **33**. The irradiation of the tetracycle under positive pressure of oxygen afforded (+)-ochromycinone **3**, which was methylated under mild conditions to give (+)-rubiginone **30**. This is presented in **Scheme 3.**



Scheme 3: Reagents and conditions*; (i) Toluene, 80 °C, 16 h; (ii) K_2CO_3, MeOH, 45% over two steps; (iii) hv, O_2, benzene, 20 h, 82%; (iv) Ag_2O, MeI, CH_2Cl_2, rt, 5 h, 82%.*

Although the Diels-Alder reaction has been successfully used in the synthesis of angucycline antibiotics, Hsu and co-workers noted that these reactions require harsh conditions and a long time for completion, because styrenes typically act as dienophiles rather than dienes. In their work, a boron triacetate promoted Diels-Alder reaction of juglone adduct with a styrene in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone was successfully carried out at room temperature in the synthesis of tetrangulol **2**.[57] In their approach highlighted in **Scheme 4**, Diels-Alder reaction of *O*-methylnaphthazarin **34** and a substituted styrene **35** mediated by boron triacetate afforded the tetracyclic compound **36** where the C-11 hydroxy group was protected to give triflated tetracyclic compound **37** in excellent yield**.** Palladium

mediated debromination and deoxygenation of **37** gave quinone **38** which was deprotected by BBr_3 to afford tetrangulol **2**, thus completing the formal synthesis.

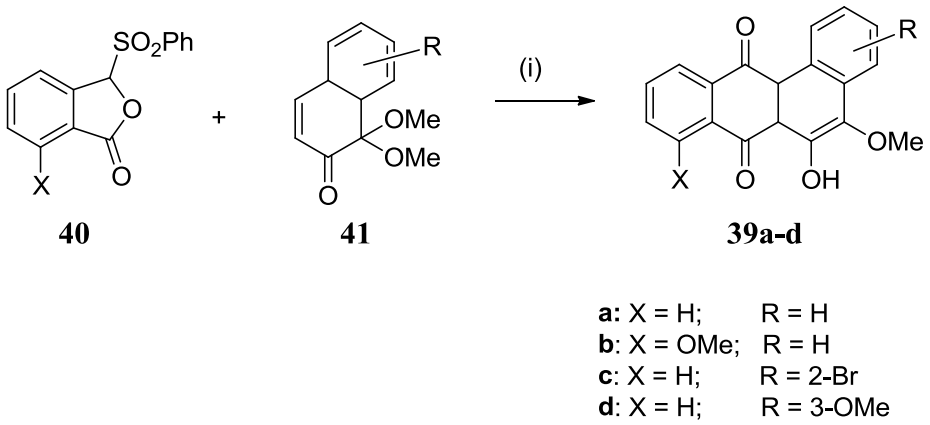


***Scheme 4: Reagents and conditions**; (i) $B(OAc)_3$, DDQ, CH_2Cl_2, rt, 72 h, 63%; (ii) Tf_2O, py, CH_2Cl_2, 0 °C, 1 h, 95%; (iii) $PdCl_2(PPh_3)_2$, HCOOH, i-$PrNEt_2$, DMF, 80 °C, 24 h, 86%; (iv) BBr_3, CH_2Cl_2, −78 °C, 3 h, 97%.*

1.7.2 Nucleophilic Addition strategies

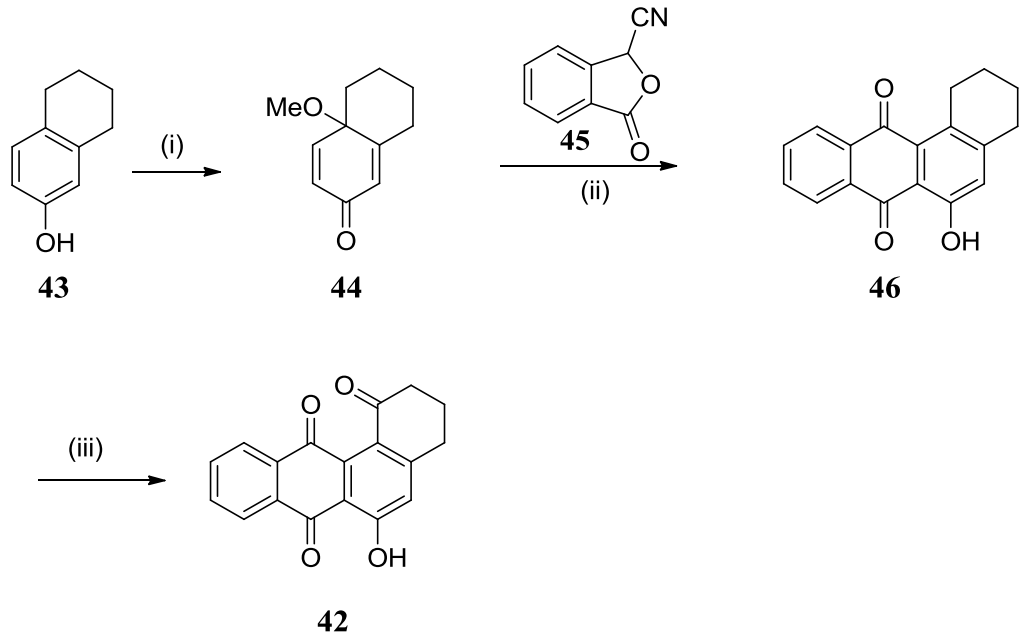
Intermolecular nucleophilic addition strategies are useful for the regioselective synthesis of the benz[*a*]anthraquinone core of angucyclines. This is then followed by the condensation of suitable components to effect the ring-closure to the tetracyclic framework.[58] The Hauser-Kraus or phthalide annulation reaction is the convenient method employed because of its regiochemical integrity and convergence. The reaction proceeds *via* an intermolecular Michael-type addition followed by cyclisation between a base-generated, stabilised anion from substituted phthalides with *α,β*-unsaturated carbonyl compounds.[36] The strategy was pioneered and successfully used by Mal and co-workers in the synthesis of benz[*a*]anthraquinones **39a-d**.[59] In this approach, reaction of a phthalide sulfone **40** with naphthoquinone

monoketals **41** under basic conditions resulted in the direct formation of benz[*a*]anthraquinone skeletons **39 a-d** as displayed in **Scheme 5**.



***Scheme 5: Reagents and conditions**; (i) t-BuOLi, −60 °C to rt, 12 h, **a**:77%, **b**: 66%, **c**: 88%, **d**: 43%*

This strategy was extended by the same authors to non-aromatic A ring angucycline **42**. To achieve this, an enone **44** prepared by phenyliodine diacetate (PIDA) oxidation of hydroxytetralin **43** was subjected to an annulation reaction with a cyano-phthalide (a Kraus phthalide) **45** in *t*-BuOLi to furnish the annulated product **46**. Introduction of a ketone function at C-1 was achieved by exposure to sunlight to give the angucycline **42**.[60] This is presented in **Scheme 6**.



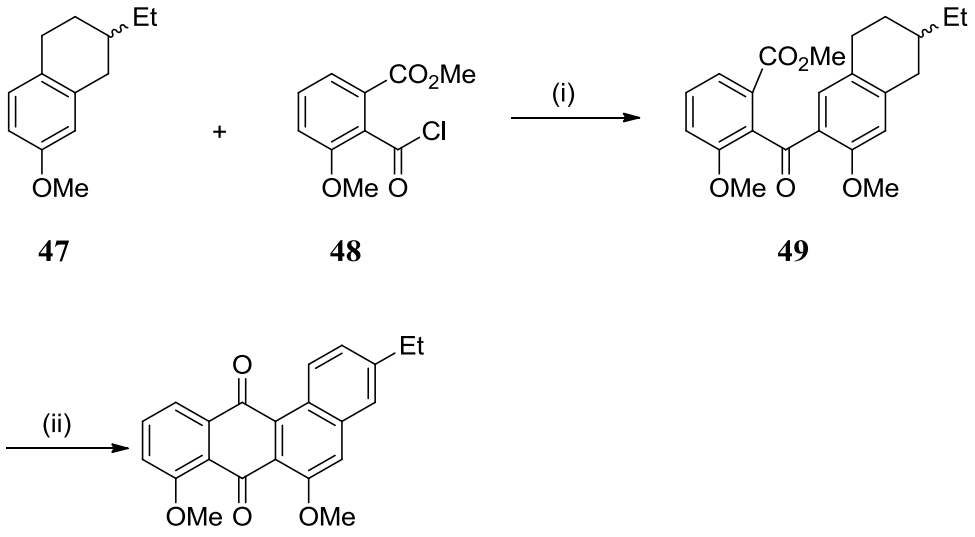
43 **44** **46**

42

***Scheme 6: Reagents and conditions**; (i) PIDA, MeOH, 67%; (ii) t-BuOLi, 85%; (iii) sunlight, $CHCl_3$, 88%.*

1.7.3 Friedel-Crafts acylation reactions

Friedel Crafts reactions have also been explored as a strategy in the synthesis of angucycline antibiotics. Use of Friedel-Crafts acylations, however, requires previous assembly of an appropriate tricyclic system and the tetracyclic skeleton is achieved through two successive acylation reactions.[58] This strategy was described by Deshpande and co-workers in the synthesis of a non-aromatic ring A brasiliquinone B **18**.[61] Using this synthetic route, previously assembled tetralin derivative **47** was subjected to an acylation reaction with benzoyl chloride **48** in the presence of aluminium chloride to furnish the acylated intermediate **49**. Attempted cyclisation of **49** using a combination of boric and sulfuric acids achieved the cyclisation, but equally so led to the undesired aromatisation of ring A to give the untargeted product **50**, as summarised in **Scheme 7**.

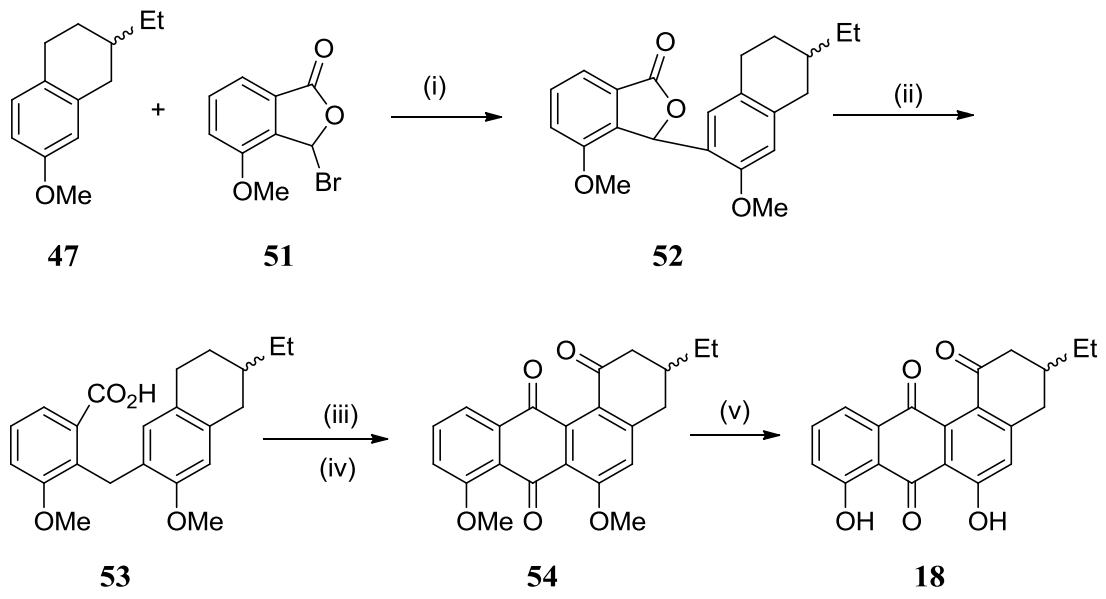


47 **48** **49**

50

Scheme 7: Reagents and conditions*; (i) $AlCl_3$, CH_2Cl_2, 0 °C to rt, overnight, 70%; (ii) $B(OH)_3$, H_2SO_4, 80 °C, 50 min, 45%.*

In order to synthesise the desired hydro-aromatic ring A angucycline, brasiliquinone B **18**, the same authors modified the sequence of **Scheme 7**. In this modification, initial Friedel Crafts alkylation between tetraline derivative **47** and 3-bromo-4-methoxy-phthalide **51** afforded the lactone intermediate **52** which underwent reductive ring opening with zinc (1 M in NaOH) and cupric sulfate to furnish the acid **53**. A second intramolecular Friedel-Crafts acylation reaction in the presence of TFAA followed by benzylic oxidation afforded **54**, which underwent demethylation in the presence of $AlCl_3$ to yield the desired natural product **18** (**Scheme 8**), albeit in a racemic manner.

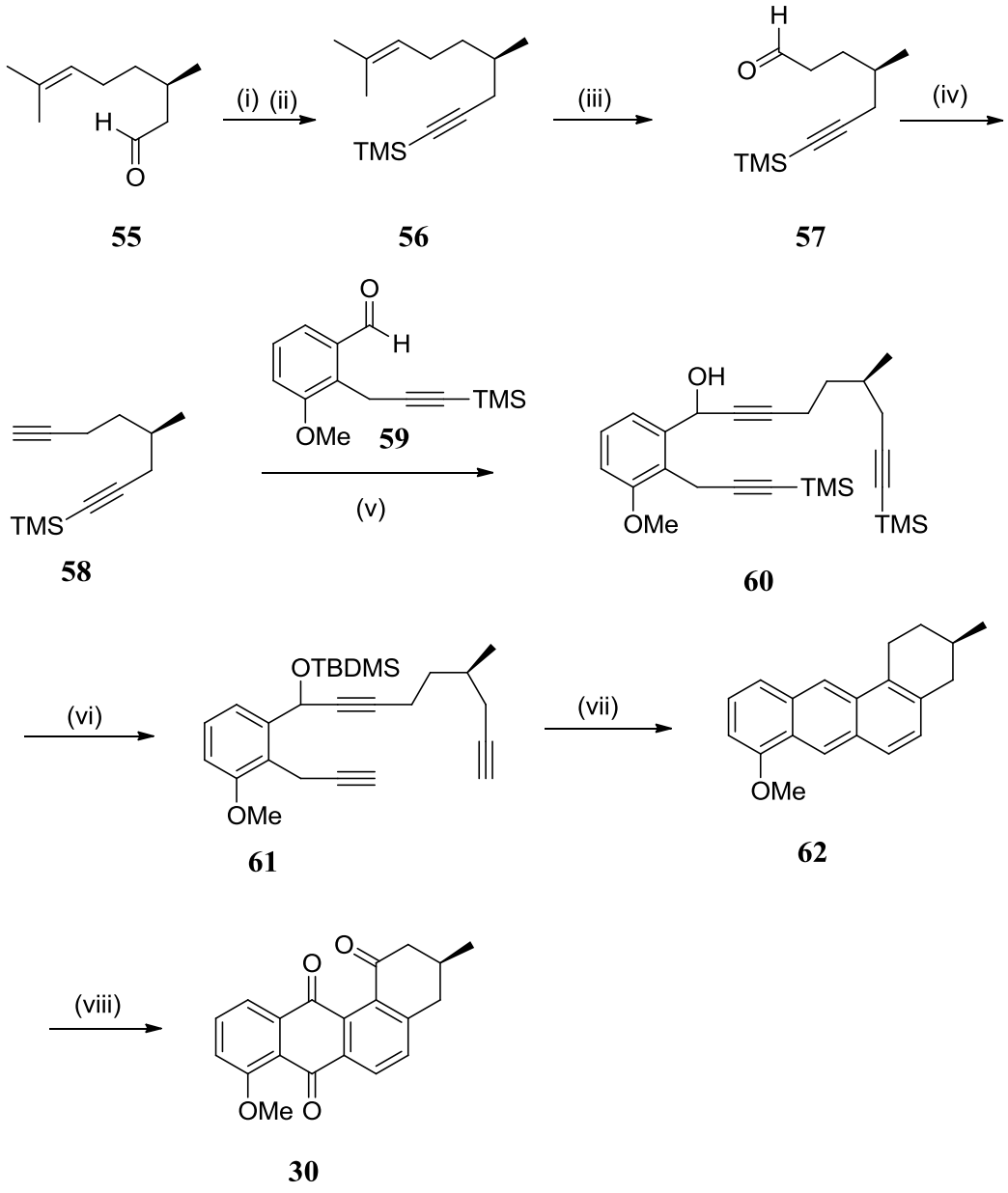


***Scheme 8: Reagents and conditions**; (i) $SnCl_2$, CH_2Cl_2, 0 °C, 84%; (ii) Zn, NaOH, pyridine, $CuSO_4$, reflux, 10 h, 85%; (iii) TFAA, CH_2Cl_2, 64%; (iv) CrO_3, HOAc, 0 °C to rt, 93%; (v) $AlCl_3$, CH_2Cl_2, −78 °C, 80%.*

1.7.4 Transition metal catalysed strategies

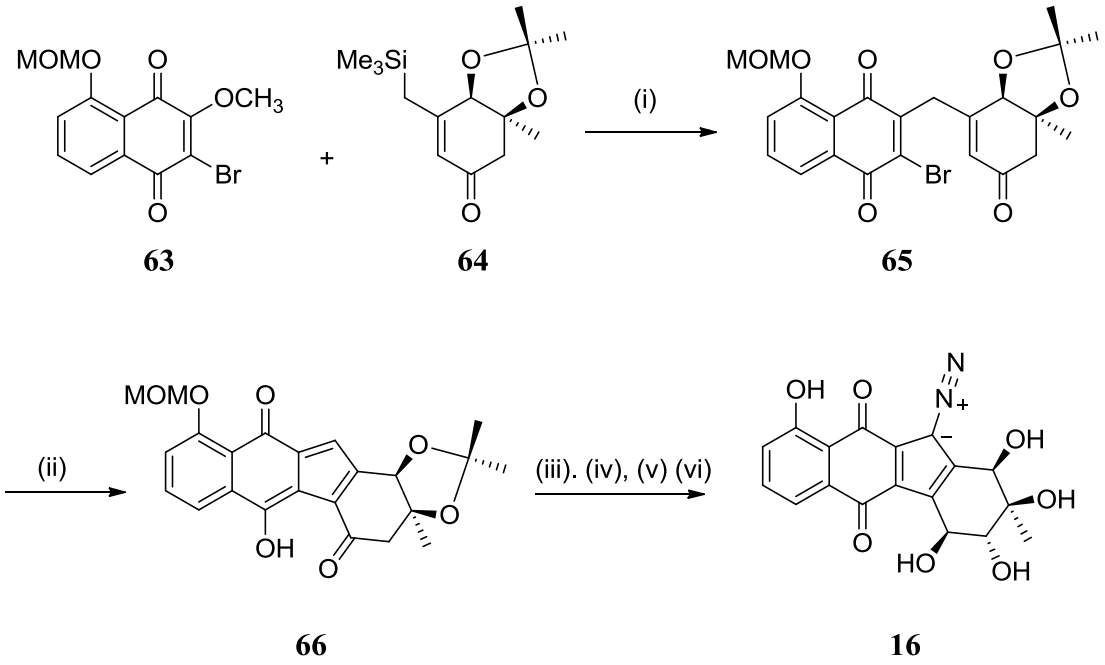
Transition metal mediated reactions have recently taken prominence in the synthesis of the benz[*a*]anthraquinone structure of the angucycline antibiotics. The use of this strategy was first reported by Groth and co-workers where the cobalt-mediated [2+2+2] cycloaddition of a triyne was employed.[62] This strategy was also reported in the asymmetric synthesis of (+)-rubiginone B_2 **30** starting from a commercially available (*R*)-(+)-citronella **55**,[63] as illustrated in **Scheme 9**. To achieve this, the aldehyde of citronella **55** was functionalised via the Corey-Fuchs olefination reaction to afford the TMS- protected alkyne **56**. Ozonolysis of the alkyne **56** followed by a second Corey-Fuchs olefination reaction of the resulting aldehyde **57** furnished the diyne **58**. Addition of the lithiated derivative of **58** to the substituted benzaldehyde **59** gave the triyne **60**. Deprotection of the triple bonds followed by TBDMS protection of the hydroxy group furnished the intermediate triyne **61.** Subjecting the triyne **61** to the cobalt mediated [2+2+2] cycloaddition as a key step in the synthesis

afforded the anthracene **62**, which was subjected to both metal and photooxidation to furnish the desired (+)-rubiginone B_2 **30**.



***Scheme 9: Reagents and conditions**; (i) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 30 min, then 25 °C, 2 h; (ii) a) n-BuLi, THF, −80 °C, 1 h; b) TMSCl, −80 °C to rt, 18 h, (76%, 2 steps); (iii) O_3, CH_2Cl_2, −80 °C, 15 min, Me_2S, AcOH, −80 °C to rt, 18 h; (iv) a) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 30 min, then 25 °C, 2 h; b) n-BuLi, THF, −80 °C, 1 h, (74%, 3 steps); (v) n-BuLi, THF, −80 °C to −30 °C, 4 h (93%); (vi) a) NH_4F, Bu_4NHSO_4, CH_2Cl_2, rt, 48 h (96%); b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 2 h, 95%; (vii) 10% $CpCo(CO)_2$, toluene, hv, reflux, 4 h, 74%; (viii) a) $[Ag(Py)_2]MnO_4$, CH_2Cl_2, 25 °C, 8 h, 62%; (b) hv, air, $CHCl_3$, 25 °C, 18 h, 67%.*

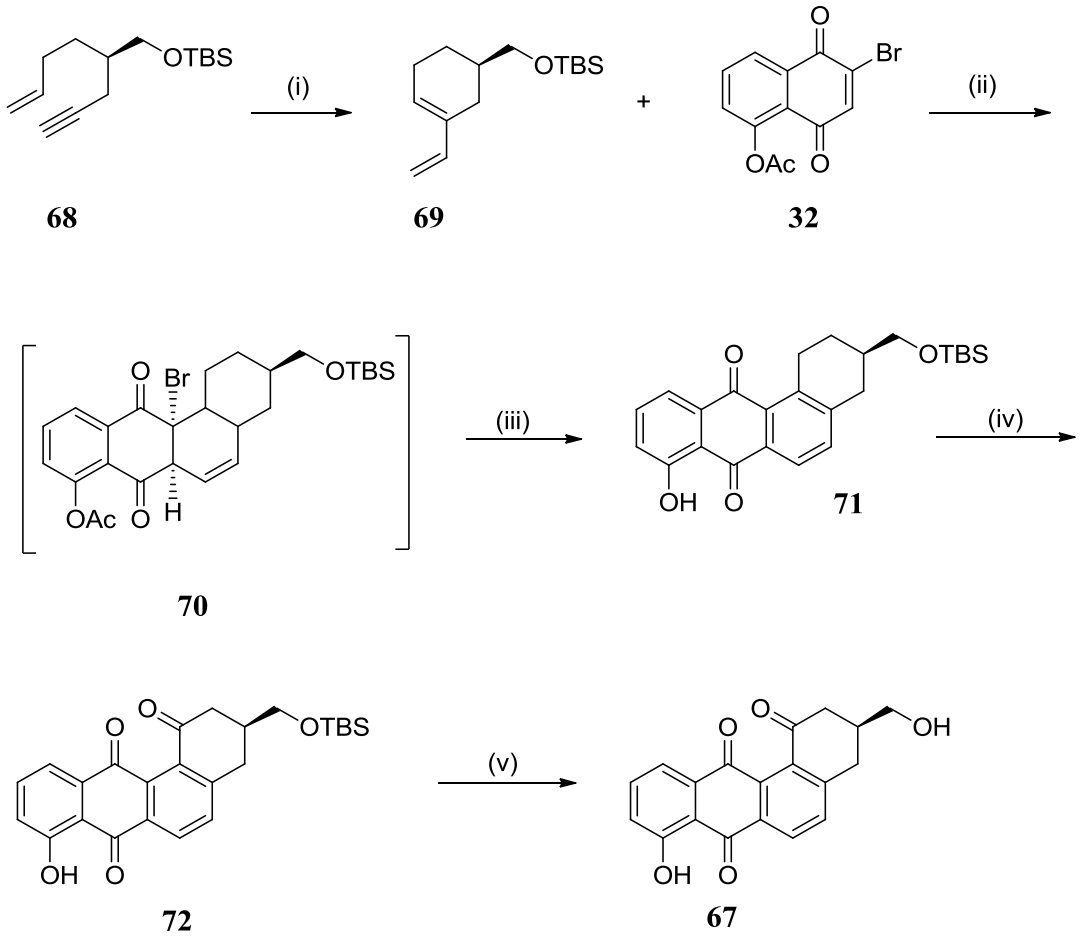
The palladium mediated Heck coupling reactions have also been used in the synthesis of angucycline antibiotics. Herzon and co-workers reported the use of this strategy for the assembly of the diazofluorene moiety during the convergent and enantioselective total synthesis of kinamycin F **16**.[64] This strategy commenced with the tris(diethylamino)sulfonium trimethyldifluorosilicate [TASF(Et)] promoted desilylative Michael addition reaction between naphthoquinone derivative **63** and β-(trimethylsilylmethyl)-cyclohexenone **64** to afford methylene bridged coupled intermediate **65**. The intermediate **65** was then subjected to palladium mediated Heck coupling reaction to furnish the tetracyclic benzofluorene **66**. Introduction of the diazo functionality with trifluoromethanesulfonyl azide, followed by α-oxidation, carbonyl reduction and global deprotection produced the desired target kinamycin F **16** as displayed in **Scheme 10**.



63 **64** **65** **66** **16**

Scheme 10: Reagents and conditions*; (i) TASF(Et), CH_2Cl_2, −78 °C, 79%; (ii) $Pd(OAc)_2$, polymer-supported PPh_3, Ag_2CO_3, toluene, 80 °C, 66%; (iii) TfN_3, DIPEA, CH_3CN, 24 °C, >99%; (iv) TIPSOTf, DIPEA, CH_2Cl_2, 0 °C; DMDO, CH_2Cl_2/CH_3OH, −40 °C, 76%; (v) BH_3•THF, THF, −20 °C, 58%; (vi) AcCl, CH_3OH, −12 to 0 °C, 65%.*

In recent times, olefin metathesis[65-67] has proven to be a versatile tool in organic synthesis due to the availability of air-stable metathesis catalysts.[68] Kaliappan and Ravikumar were the first to explore the use of sequential intramolecular enyne metathesis and intermolecular Diels-Alder reactions in the synthesis of YM-181741 (**67**).[56, 69] In this strategy (**Scheme 11**), enyne derivative **68** was subjected to intramolecular metathesis reaction catalysed by Grubbs second generation catalyst to afford the diene **69**.

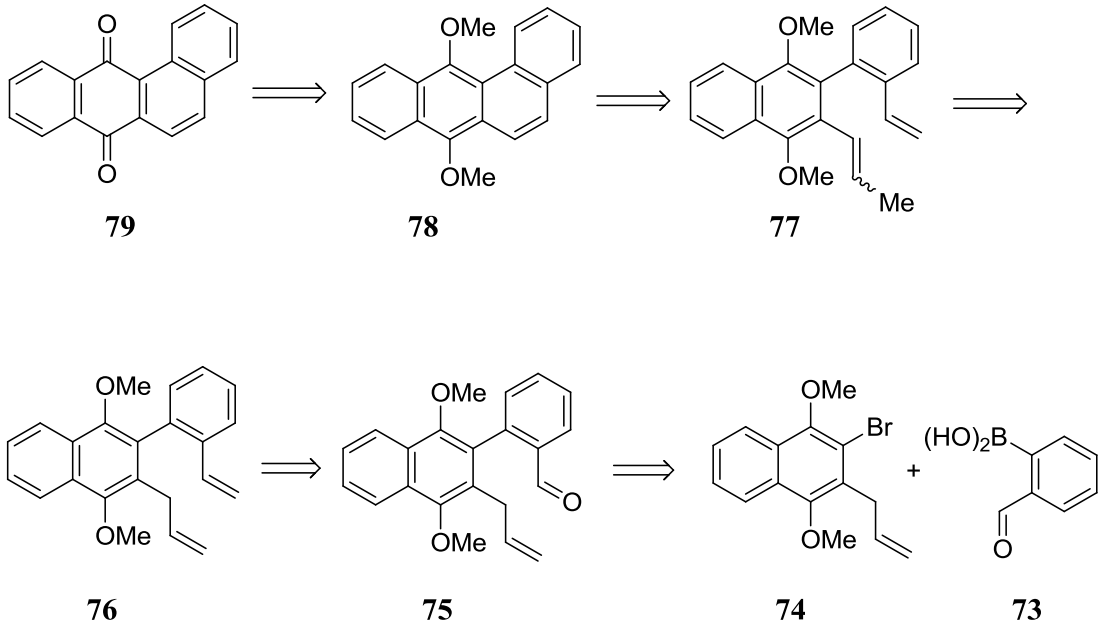


***Scheme 11: Reagents and conditions**; (i) Grubbs (II), ethylene, toluene, 80 °C, 12 h, 88%; (ii) toluene, 80 °C, 12 h; (iii) K_2CO_3, MeOH, 71% (over two steps); (iv) hv, O_2, benzene, 70%; (v) TBAF, THF, rt, 2 h, 68%.*

Diels-Alder reaction of the diene **69** with a naphthoquinone derivative **32** furnished the tetracyclic adduct **70** which was subsequently aromatised and deacetylated to give the intermediate tetracyclic compound **71**, albeit as a mixture with its regioisomer in 9:1 ratio. Photooxygenation of the inseparable mixture of **71** and the regioisomer afforded the ketone **72** and the other regioisomer which was separated by column chromatography. The ketone **72** was deprotected to furnish the desired natural product **67**.

1.7.5 Development of other transition metal catalysed strategies

The Organic Chemistry Research Group at Wits University became interested in developing new methods to access the angular tetracyclic skeleton of the angucycline antibiotic natural products by application of other transition metal mediated strategies. Dr. Myron Johnson, a former PhD student, pioneered these efforts. It was envisioned that Suzuki-Miyaura and ring closing metathesis (RCM) reactions could be key steps in assembling the carbotetracyclic skeletons of the natural products. The proposed retrosynthetic analysis is shown in **Scheme 12**.



79 **78** **77**

76 **75** **74** **73**

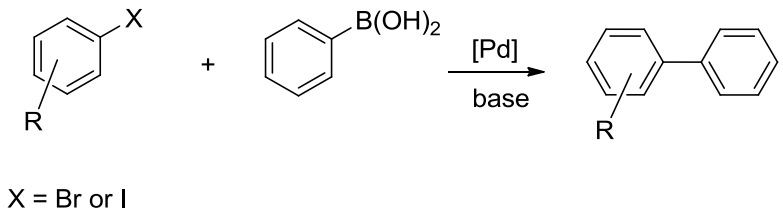
Scheme 12: Retrosynthetic analysis of benz[a]anthraquinone

It was envisaged that Suzuki-Miyaura cross coupling reaction of a boronic acid **73** and the bromonaphthalene **74** would furnish the biaryl benzaldehyde **75**. The aldehyde could then be functionalised to the alkene **76** through the Wittig reaction, followed by isomerisation of the allylic double bond to furnish the dialkene **77**. Subjecting the resulting dialkene to a ruthenium mediated ring closing metathesis allowing the construction of a new benzene ring could furnish the tetracyclic skeleton **78**, which, upon CAN oxidation, would give the desired quinone **79**.

The next sections give brief overviews of the two key reactions for the assembly of the carbotetracyclic skeleton of the angucyclines, i.e. the palladium mediated Suzuki-Miyaura cross coupling reaction and the ruthenium catalysed ring closing metathesis reaction. These reactions, and particularly the Suzuki-Miyaura cross coupling reactions, were extensively used in this PhD research project.

1.7.5.1 Palladium mediated Suzuki-Miyaura cross coupling reaction

The Suzuki-Miyaura (SM) reaction is one of the most versatile carbon-carbon bond forming reactions used in organic synthesis. The reaction involves palladium catalysed cross coupling of aryl halides or pseudohalides with boronic acids in the presence of a base, as shown in **Scheme 13**.



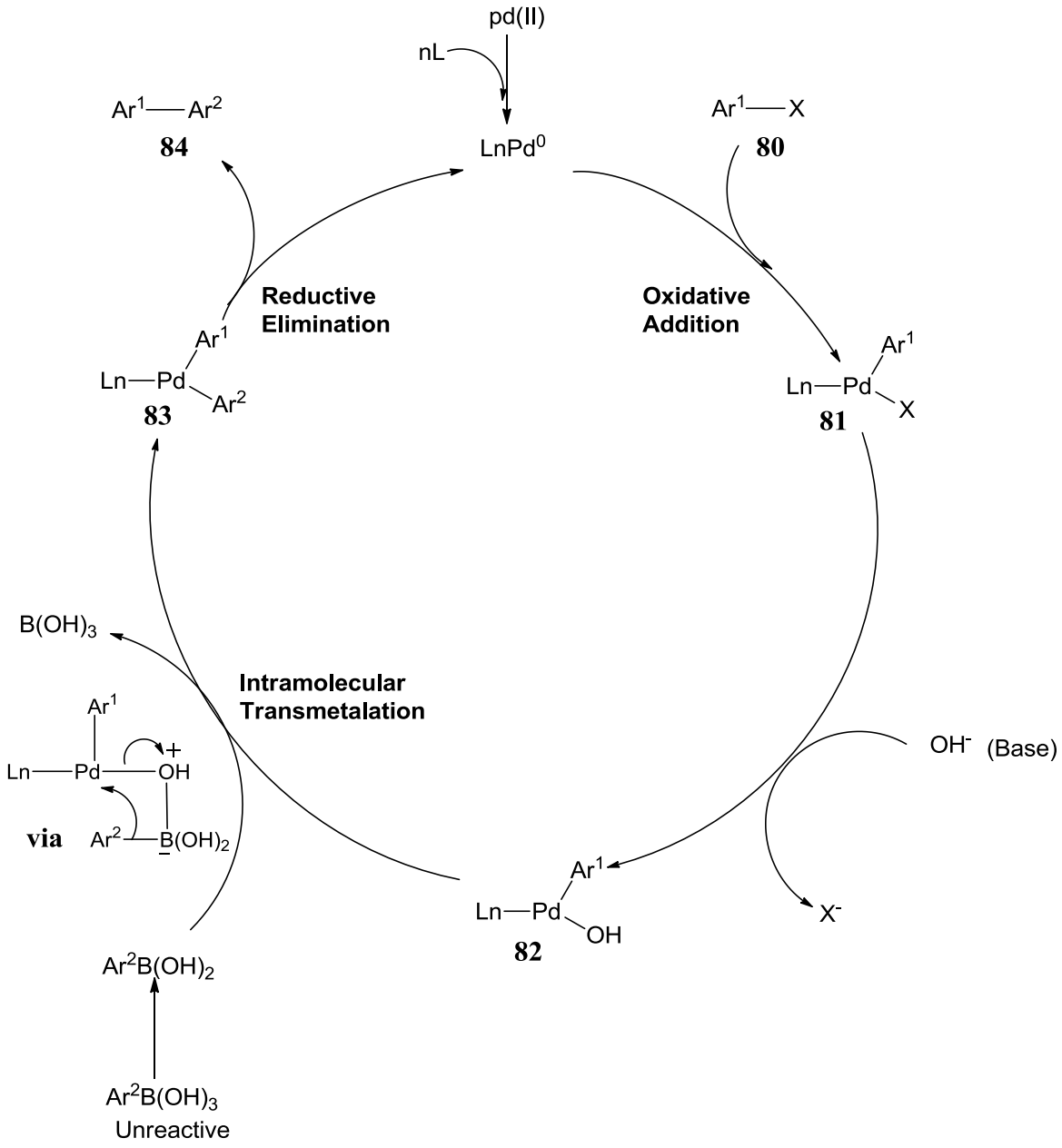
Scheme 13: General Suzuki-Miyaura reaction

This reaction is particularly useful for the assembly of biaryls.[70] The aryl-aryl bonds are found in numerous biologically active natural products. Although there are other metal mediated carbon-carbon bond forming coupling strategies like the Kumuda,

Negishi, Stille, Himaya and the Kharash reactions, the Suzuki-Miyaura reaction offers distinct advantages over the rest. Some of these include the mild reaction conditions and the commercial availability of a diversity of boronic acids that are environmentally safer than the other organometallic reagents. Furthermore, the handling and the subsequent removal of boron containing by-products is relatively easy. Finally, the reaction has a high tolerance towards functional groups and steric constraints.[71-73]

1.7.5.1.1 Mechanism of Suzuki-Miyaura cross coupling reaction

As exhibited in **Scheme 14**, the basic catalytic cycle of the palladium catalysed SM cross coupling reaction is thought to follow a sequence involving the oxidative addition of an aryl halide **80** to a Pd(0) complex to form an arylpalladium(II) halide intermediate **81**. This intermediate undergoes a base-halogen exchange to generate the oxo-palladium(II) complex **82**. If a carbonate base is used, the hydroxy base is generated *in situ* by reacting with water. The reactive oxo-palladium compound generated then complexes with an arylboronic acid before undergoing intramolecular transmetalation to form the diarylpalladium complex **83**. In the final step of the catalytic cycle, the diarylpalladium complex undergoes reductive elimination to afford the cross coupling product **84**, and the reactive palladium(0) species is regenerated.[74]



Scheme 14: Catalytic cycle of Suzuki-Miyaura Cross Coupling reaction

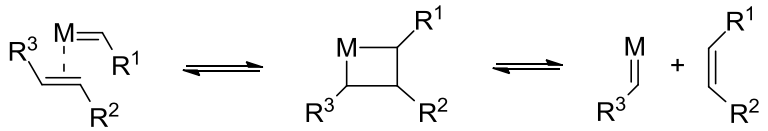
Sodium carbonate is a base commonly used in the SM cross coupling reaction although it is less effective with sterically demanding substrates where in such cases $Ba(OH)_2$ or K_3PO_4 are preferred. Other bases utilised include Cs_2CO_3, CsF, K_2CO_3, TlOH, KF and NaOH.[75]

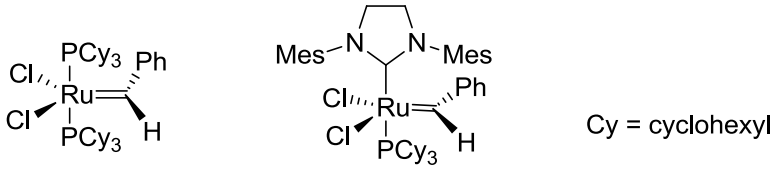
1.7.5.1.2 Supporting ligands

In the initial years of the SM reaction, triarylphosphines were used as supporting ligands. However, increased reactivity and stability of the metal catalysts by use of other more efficacious supporting ligands has led to improvements of the Suzuki-Miyaura coupling reactions.[76] The most common ligands used are monodentate, bulky, and electron-rich dialkylbiarylphosphine ligands, although others like *N*-heterocyclic carbenes (NHC) have also been utilised.[77] The ability to satisfy the diverse requirements of different SM cross coupling reactions with a single ligand, however, remains a challenge.[76]

1.7.5.2 Ruthenium catalysed ring closing metathesis (RCM) reactions

The application of carbon-carbon bond forming strategies to make ring systems remains a core theme in natural products synthesis. Cyclisation reactions are commonly used in this regard. The ring closing olefin metathesis reaction (RCM) is one such cyclisation strategy that has gained popularity because of its versatility.[78] Olefin metathesis is a unique carbon skeleton redistribution strategy that proceeds *via* carbene exchange between a metal carbene and an alkene through a metallocyclobutane (MCB) as exhibited in **Scheme 15**.[79] Grubbs (I and II) ruthenium based catalysts developed by Grubbs are commonly used, although other catalysts have also been developed.[80]



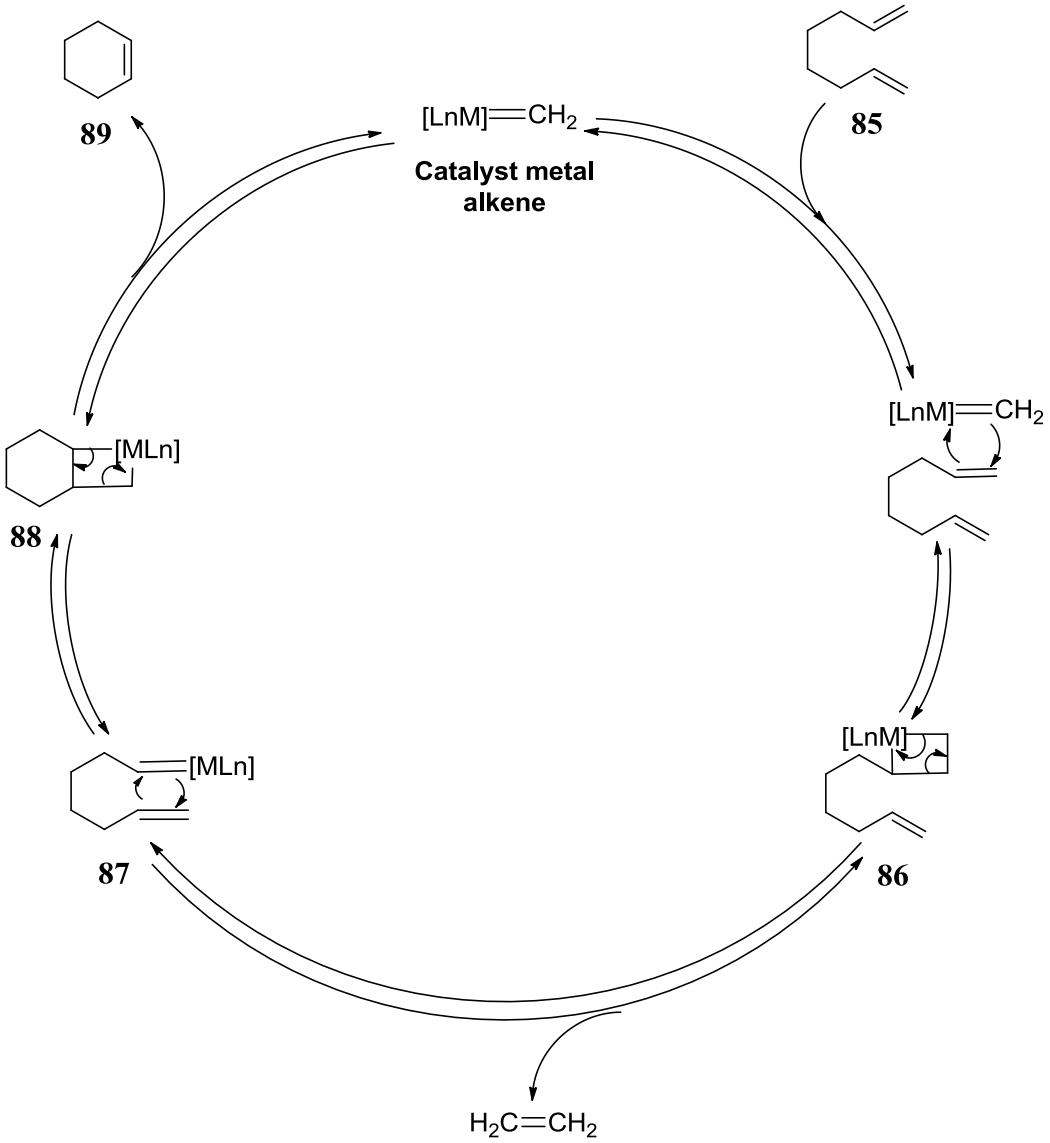


Grubbs 1 Grubbs II

Scheme 15: General [2+2] ring closing metathesis reaction and associated catalysts

1.7.5.2.1 Mechanism for ring closing olefin metathesis

In terms of the mechanism of the reaction, the commonly accepted view is that the metathesis reactions occur as postulated by Chauvin in 1971.[81] Essentially, the metathesis cascade is promulgated by way of a series of [2+2] cycloadditions and cycloreversions as depicted in **Scheme 16**.

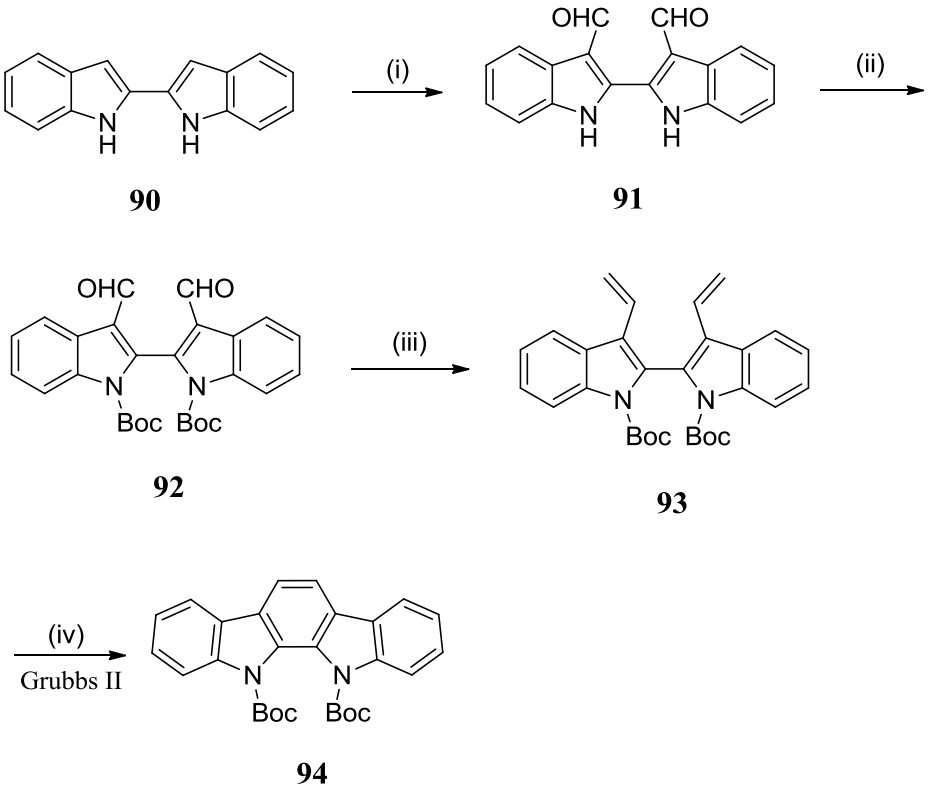


Scheme 16: Mechanism and catalytic cycle of ring closing metathesis

A diene e.g. **85** is treated with a catalyst metal alkene and undergoes a [2+2] cycloaddition reaction to give the metallocyclobutane **86**. The cyclobutane derivative **86** then undergoes cycloreversion to generate the metal alkylidine **87** which undergoes intramolecular [2+2] cycloaddition with the reactive terminal alkene on the same molecule to give a second metallocyclobutane intermediate **88**. Cycloreversion of this metallocyclobutane furnishes the RCM product, in this case, cyclohexene **89**, with the regeneration of the metal alkene catalyst.

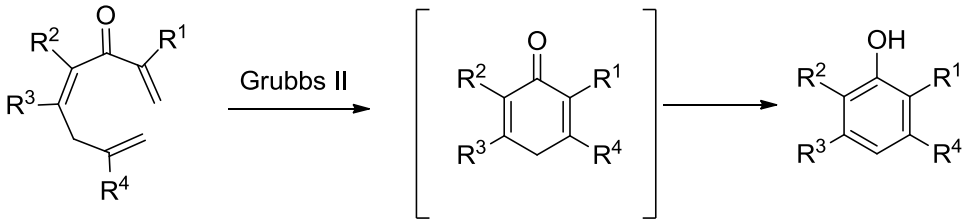
1.7.5.2.2 Applications of RCM in assembly of new benzene rings

The ring-closing metathesis reaction has been used in a number of synthetic transformations. We decided to use RCM as a key step in the synthesis of angucycline antibiotics by building on previous work done by our group on the construction of benzene rings using the RCM reaction. de Koning and co-workers have reported the use of RCM as a key step in the assembly of a new benzene ring in the synthesis of ring-fused carbazoles.[82] In the synthesis, previously assembled bis-indole **90** was formylated to give the dialdehyde **91**. Boc-protection of **91** afforded the biscarbamate **92**, which was then functionalised to the divinyl intermediate **93** using the Wittig reaction. Exposure of **93** to the Grubbs second generation catalyst afforded the desired fused-carbazoles **94** as shown in **Scheme 17**.



***Scheme 17: Reagents and conditions**; (i) $POCl_3$, DMF, 0 °C, 83%; (ii) Boc_2O, DMAP, 25 °C, 89%; (iii) $MePPh_2Br$, n-BuLi, 0 °C; (iv) 8% Grubbs II, toluene, 25 °C, 64% (over two steps).*

As a second example, Yoshida and Imamoto also demonstrated the versatility of the RCM in the synthesis of a range of phenol derivatives using Grubbs second generation catalyst as shown **Scheme 18**.[83]



Scheme 18: Yoshida's synthesis of phenol derivatives using RCM

The upcoming Chapter in this PhD thesis discusses our results on the development of new methodology for the synthesis of angucycline analogues, utilising the two key reactions outlined. Our attempted application of the methodology to synthesise a natural product and finally, the results of our formal synthesis of tetrangulol **2** are also discussed.

CHAPTER 2: Results and Discussion on Angucyclines

2.1 Overview

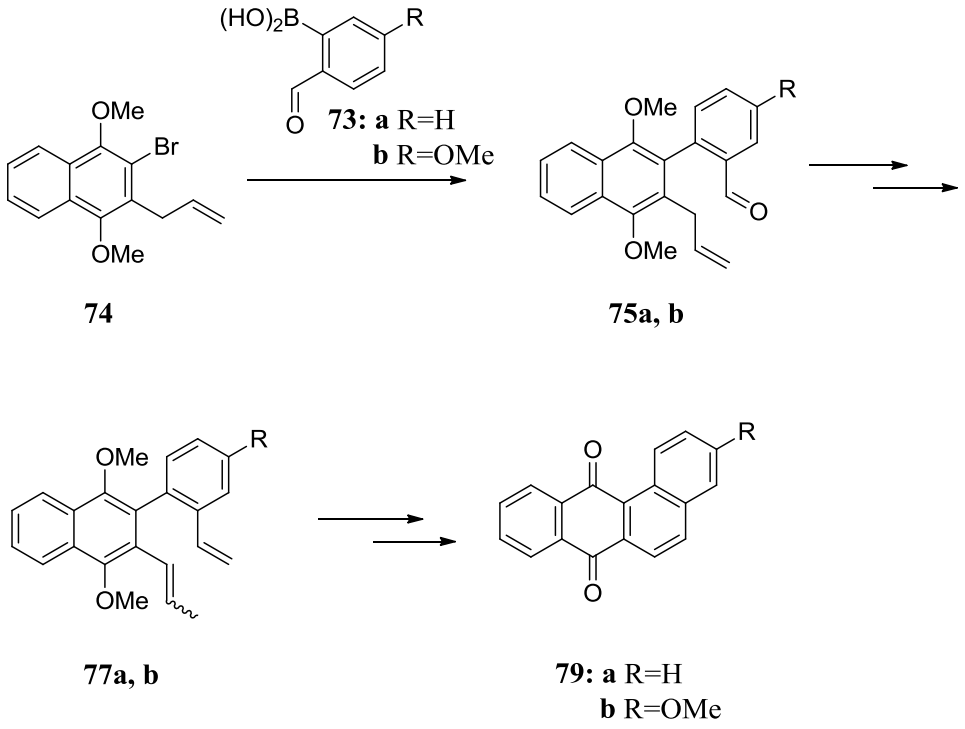
The starting point to this project was to revisit the model studies conducted by Dr. Myron Johnson, a former PhD student in our group, in using the palladium catalysed Suzuki-Miyaura cross coupling reaction and ruthenium catalysed ring closing metathesis as key steps in the synthesis of angucycline antibiotic analogues. Following this, application of the methodology used in the model studies to synthesise a natural product is presented. Finally, results of our novel method for the synthesis of the natural product tetrangulol **2** will be presented and discussed.

2.2 Model studies on the synthesis of angucycline antibiotic analogues

Two model studies were undertaken to synthesise the desired benz[*a*]anthraquinone skeleton of the angucyclines. These are discussed in the next section.

2.2.1 Synthesis of tetraphenes 79a and 79b

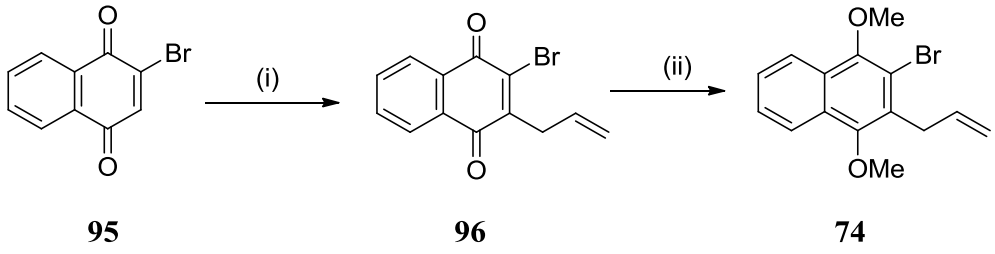
Model studies were done utilising the Suzuki-Miyaura cross coupling reaction and the ring closing metathesis reaction as key steps for the synthesis of tetraphene-7,12-dione **79a** and methoxytetraphene-7,12-dione **79b**. The synthetic scheme for the assembly of these two angucycline antibiotic analogues is illustrated in **Scheme 19**.



Scheme 19: Key synthetic steps for the assembly of angucycline analogues

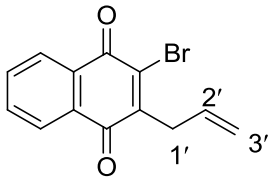
The synthesis commenced with the preparation of the bromonaphthalene precursor **74** that would subsequently be coupled utilising the Suzuki-Miyaura reaction to two different boronic acids, **73a** and **73b**, to give the biarylbenzaldehydes **75a** and **75b**.

2.2.1.1 Synthesis of 2-allyl-3-bromonaphthalene 74



***Scheme 20: Reagents and conditions**: (i) Vinyl acetic acid, $(NH_4)_2S_2O_8$, $AgNO_3$, H_2O-MeCN, 65 °C, 18 h, 71%; (ii) Me_2SO_4, $Na_2S_2O_4$, TBAI, aq. KOH, THF, rt, 70%.*

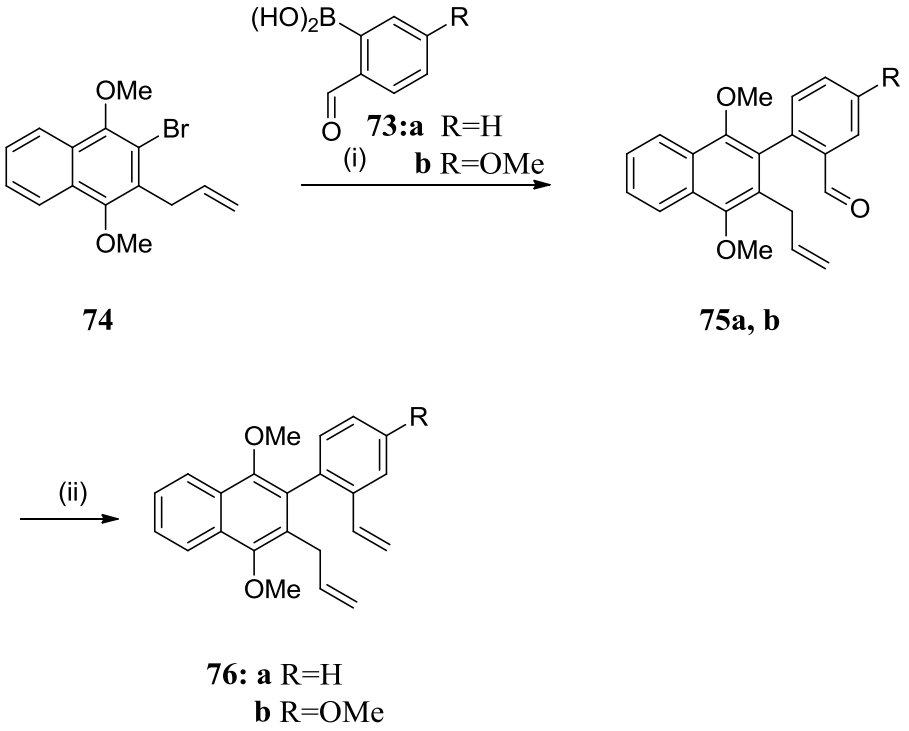
Our synthesis as shown in **Scheme 20** started with allylation of commercially available 2-bromo-1,4-naphthoquinone **95**. This was achieved by using a modified Minisci reaction where the allyl group is introduced *via* a radical process.[84] To the naphthoquinone **95** in acetonitrile was added vinyl acetic acid and silver nitrate, followed by the dropwise addition of ammonium persulfate in distilled water. The reaction mixture was maintained at 65 °C for 18 hours. Purification of the crude product on silica gel gave **96** as a yellow solid in 71% yield. The ^{1}H NMR spectrum unequivocally proved that we had formed the allylated product with the presence of 2 allylic protons at δ 3.64 ppm (H-1′), one vinylic proton at δ 5.87 ppm (H-2′) followed by a pair of vinylic protons between δ 5.27 and δ 5.22 ppm (H-3′). Analysis of the ^{13}C NMR spectrum showed the appearance of three additional carbon signals. The most upfield signal at δ 35.8 ppm corresponded to the allylic carbon C-1′ and the two signals at δ 118.8 and δ 134.9 ppm were consistent with the vinylic carbons C-3′ and C-2′ respectively.



96

Pleased with the successful synthesis of the allylated quinone **96**, our next step was to reduce and protect the quinone through methylation. To achieve this, sodium dithionite and tetrabutylammonium iodide (TBAI) were added to a clear solution of **96** in tetrahydrofuran. This was followed by the addition of an aqueous solution of potassium hydroxide and dimethyl sulfate and the reaction mixture was stirred for 18 hours. Chromatographic purification of the residue afforded **74** as a yellow, low melting solid in 70% yield. The presence of two methoxy protons signals at δ 3.98 and δ 3.92 ppm in the ^{1}H NMR spectrum clearly proved that product **74** was formed. This was further confirmed through ^{13}C NMR spectroscopy by the disappearance of the two carbonyl carbon signals and the appearance of four new signals at δ 160.0 and 150.2 ppm consistent with ArC-O and at δ 62.7 and 61.4 ppm which corresponded to the two methoxy group carbons.

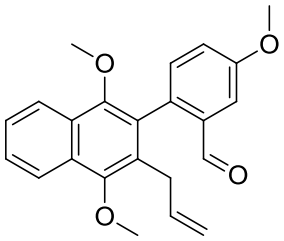
2.2.1.2 Synthesis of vinylphenylnaphthalene 76a and 76b



***Scheme 21: Reagents and conditions**; (i) **Method 1**: Pd(PPh$_3$)$_4$, CsF, DME, MW 150 °C, 150 W, 30 min,**75a**: 49%, **75b**: 45%; **Method 2**: (i) Pd(PPh$_3$)$_4$, aq. Na$_2$CO$_3$ (2 M), DME, reflux, 18 h, **75a**: 60%, **75b**: 65%; (ii) MePPh$_3$Br, n-BuLi, THF, **76a**: 81%, **76b**: 94%.*

With the reduced quinone **74** in hand, we then turned our attention to the first key step which was to use the palladium mediated Suzuki-Miyaura reaction to couple **74** to the commercially available boronic acids 2-formylphenyl boronic acid **73a** and 2-formyl-5-methoxyphenyl boronic acid **73b** (**Scheme 21**). Initially we explored the use of microwave irradiation to facilitate the coupling. Use of microwave conditions for Suzuki-Miyaura cross coupling reactions has been reported by Sharma *et al*. One advantage this method offers is the reduction of the reaction times from 24 hours in conventional methods to 20 minutes under microwave conditions due to the increase in the reaction rates.[85] Using this method, the allylated dimethoxynaphthalene **74**, boronic acid **73a** or **73b**, cesium fluoride, *tetrakis*(triphenylphosphine)palladium(0)

and dimethoxyethane were added in a sealed microwave tube. The reaction mixture was irradiated at 150 W and 150 °C for 30 minutes by a microwave reactor. Upon completion of this time, TLC confirmed that the starting material was consumed. The crude products were purified by column chromatography to furnish **75a** as a yellow compound in 49% and **75b** as an off-white solid in 45% yield. For **75a**, the presence of eight signals due to aromatic proton in the ^{1}H NMR spectrum unambiguously proved that the coupling had taken place, although specific assignment of the protons was difficult owing to most of the aromatic protons appearing in the same region of the spectrum. Additionally, the presence of the aldehydic proton at δ 9.74 ppm in the ^{1}H NMR spectrum was further evidence. The appearance of the aldehydic protons corresponded with the aldehyde carbonyl carbon signal at δ 192.2 ppm in the ^{13}C NMR spectrum. The biarylbenzaldehyde intermediate **75b** on the other hand was unmistakably verified to have been made owing to the presence of signals due to the three methoxy protons at δ 3.97, δ 3.93 and δ 3.46 ppm and, just as in compound **75a**, the presence of the aldehydic proton at δ 9.67 ppm in the ^{1}H NMR spectrum.

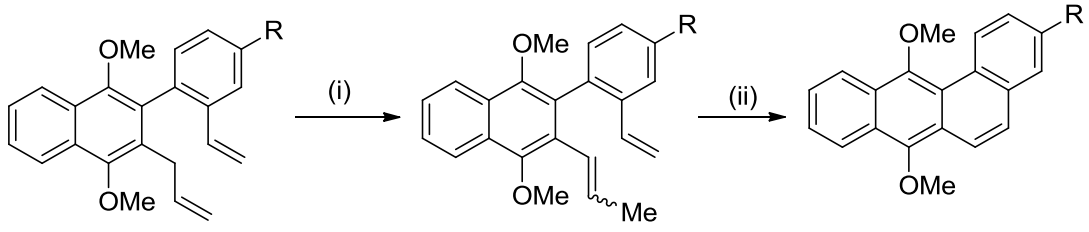


75b

Although the biarylbenzaldehydes **75a** and **75b** were assembled, the yields were moderate. All our attempts to optimise the microwave conditions did not improve the yields obtained. At this point, we then decided to explore the use of a conventional method for the Suzuki-Miyaura cross coupling reaction. In using this approach, *tetrakis*(triphenylphosphine)palladium(0) and boronic acids **73a** or **73b** were added to a deoxygenated solution of 2-allyl-3-bromo-1,4-dimethoxynaphthalene **74** in dimethoxyethane followed by the addition of a deoxygenated aqueous sodium carbonate solution and the reaction mixture was heated at reflux for 18 hours. Upon chromatographic purification, compound **75a** was obtained in 60% yield and compound **75b** in 65% yield. The moderate yields from microwave reactions were attributed to possible decomposition of the products. Going forward, we decided to adopt the conventional method for all the Suzuki-Miyaura cross coupling reactions.

Satisfied with the yields of the Suzuki product, our next step was to convert the aldehyde of **75a** and **75b** to an alkene. This was accomplished smoothly by subjecting the aldehydes to Wittig conditions using methyltriphenylphosphonium bromide as the ylide source to afford the vinyl adducts **76a** and **76b** in 81% yield and 94% yield respectively. The disappearance of the signals due to the aldehydic protons and the appearance of three new olefinic signals in the ^{1}H NMR spectrum at δ 6.41 ppm, δ 5.76–5.59 ppm (overlapping) and δ 5.07 ppm for **76a** and δ 6.37 ppm, δ 5.76–5.61 ppm (overlapping) and δ 5.05 ppm for **76b** undoubtedly confirmed the assembly of the alkenes. Analysis of the ^{13}C NMR spectra also showed the disappearance of the aldehyde carbon signals and the appearance of two olefinic carbon signals in each spectrum which provided further evidence for the synthesis of the alkenes.

2.2.1.3 Synthesis of dimethoxytetraphenes 78a and 78b



76a, b **77a, b** **78: a** R=H **b** R=OMe

Scheme 22: Reagents and conditions*: (i) KOtBu, THF, rt, 4 h,* ***77a****: 73%,* ***77b****: 88%; (ii) Grubbs (II), toluene, reflux, 18 h,* ***78a****: 92%,* ***78b****: 88%.*

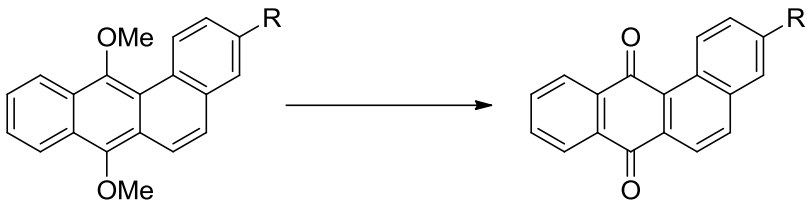
Pleased with the conversion of the aldehyde to the alkene using the Wittig reaction, the allylic double bond in both **76a** and **76b** was isomerised (**Scheme 22**). The idea in the subsequent step was to assemble a new benzene ring. If the allylic double bond was left unisomerised, a seven-membered ring would be formed. To isomerise the bonds, the alkenes **76a** and **76b** were subjected to potassium *tert*-butoxide in tetrahydrofuran at room temperature. Purification of the crude product by column

chromatography furnished the dialkenes **77a** and **77b** in 73% and 88% yields respectively. ^{1}H NMR spectroscopy unequivocally established the identity of the isomerised products by the appearance of a doublet of doublets at δ 1.65 ppm for **77a** and δ 1.69 ppm for **77b**, each integrating for 3 protons, which correlated with the appearance of a methyl substituent after isomerisation. The doublet of doublets signal arises from a *J*-3 coupling with the adjacent olefinic proton and a *J*-4 coupling with the other olefinic proton. The disappearance of the allylic protons signals at δ 3.13 ppm and δ 3.14 ppm for **77a** and **77b**, respectively, correlated to the shifting of the double bond.

Pleased with our isomerisation reaction, we then embarked on our next synthetic step of forming a new benzene ring using ruthenium catalysed ring closing metathesis. This reaction was key as it could lead to the assembly of a carbotetracyclic skeleton found in the angucycline antibiotic natural products. To achieve this, Grubbs II catalyst was added to each of the dialkenes **77a** and **77b** in toluene and the reaction mixtures were heated under reflux for 18 hours. Upon chromatographic purification of each of the reaction mixtures, products **78a** and **78b** were isolated as off-white solids in excellent yields of 92% and 88% respectively. ^{1}H NMR spectroscopy clearly established the identity of the tetraphenes formed by the disappearance of all signals due to the olefinic protons between δ 6.46 ppm and δ 5.03 ppm for **78a** and between δ 6.46 ppm and δ 5.06 ppm for **78b**. Additionally, the appearance of new signals in the aromatic region of the spectrum noted through the increase in total number of aromatic proton signals from eight to ten in **78a** and from seven to nine in **78b** further confirmed the assembly of a new benzene ring.

With the assembly of the benz[*a*]anthracene skeletons, we were able to demonstrate that the transition metal mediated methods of the Suzuki-Miyaura and the ring closing metathesis reactions could be used as key steps in the synthesis of angucycline antibiotic analogues. The last step was then to oxidise the benz[*a*]anthracene skeletons to the target benz[*a*]anthraquinone analogues.

2.2.1.4 Synthesis of angucycline analogues 79a and 79b



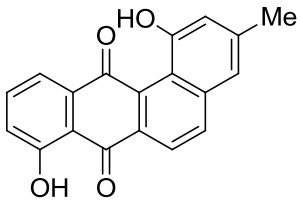
78: a R=H
b R=OMe

79a, b

Scheme 23: Reagents and conditions*; CAN, MeCN/H_2O, rt, 30 min,* ***79a****: 79%,* ***79b****: 81%.*

The oxidation was accomplished by subjecting the benz[*a*]anthracene derivatives **78a** and **78b** (**Scheme 23**) to the cerium ammonium nitrate (CAN) mediated oxidation reaction in acetonitrile and water at room temperature for 30 minutes to furnish the desired quinones **79a** and **79b** in 79% and 81% yield, respectively. The products were undoubtedly confirmed using ^{1}H NMR spectroscopy by the disappearance of the two signals due to the methoxy group at δ 4.12 and δ 3.97 ppm for **79a**, and the disappearance of two of the three methoxy group signals in **79b**. Further proof was provided by the appearance of two carbonyl carbon signals in the ^{13}C NMR spectra at δ 186.2, and δ 184.0 ppm for **79a** and δ 186.4 and δ 183.8 ppm for **79b**.

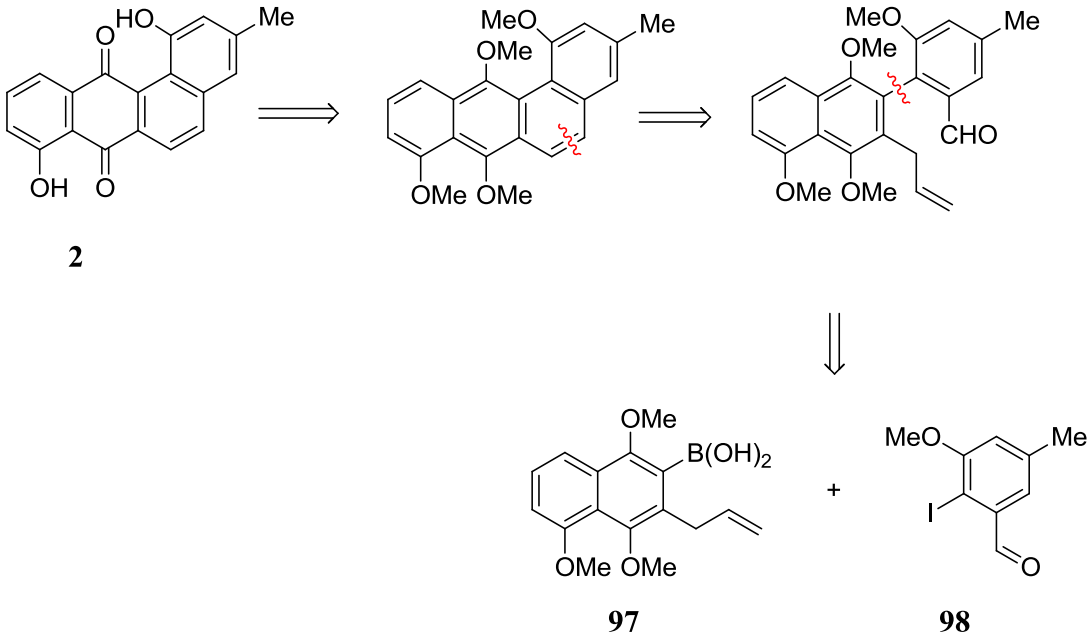
Having accomplished the synthesis of the benz[*a*]anthraquinone framework of angucycline natural products, we then decided to use this methodology for the synthesis of 1,8-dihydroxy-3-methyltetraphene-7,12-dione, commonly known as tetrangulol **2**, a natural product. This work will be discussed in the following section.



2

2.3 Attempted synthesis of tetrangulol using SM and RCM reactions

In order to synthesise the natural product tetrangulol **2**, we envisaged the following retrosynthetic pathway given in **Scheme 24**.



2 **97** **98**

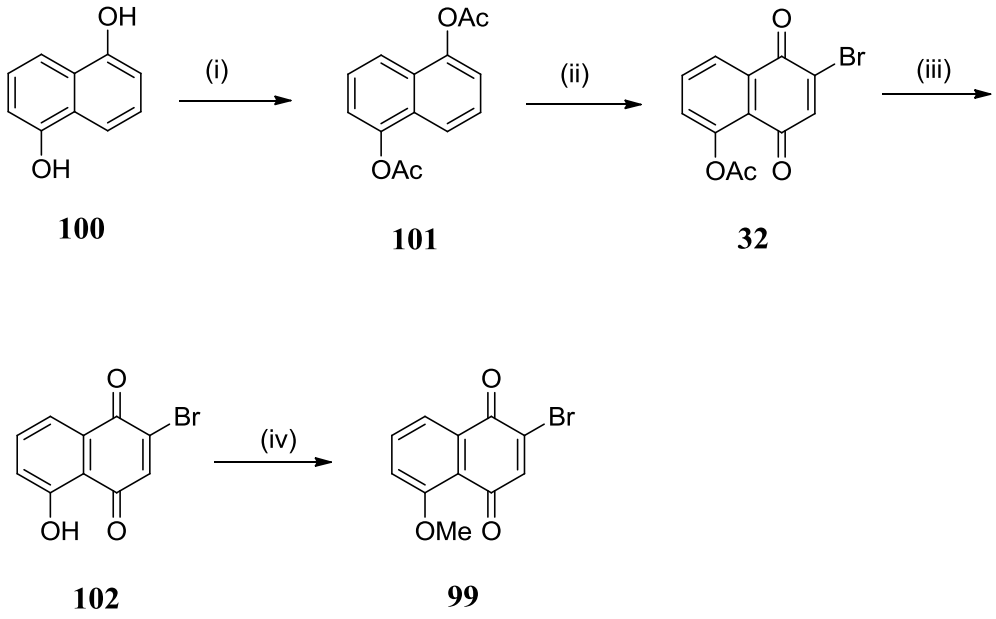
Scheme 24: Retrosynthetic Analysis for tetrangulol

It was evident from the retrosynthetic analysis that we needed to assemble the naphthalene boronic acid **97** and the substituted benzaldehyde **98** precursors. We envisioned that the boronic acid **97** could be assembled from juglone. Owing to the high price of juglone, we decided to synthesise the required juglone derivative. Its synthesis is described in the next section. It must be highlighted that although the boronic acid could be made on either precursor, we opted to place it on the naphthalene derivative, i.e. **97**, and place an iodine substituent on the benzaldehyde,

i.e. **98**. We foresaw some difficulties in carrying out the Suzuki-Miyaura cross coupling reaction with these precursors that necessitated this strategic decision. This will be further elaborated on in the relevant section.

2.3.1 Synthesis of the precursor boronic acid 97

There are some reports in the literature on the synthesis of bromo juglone derivatives, which in our case, could be functionalised to the desired boronic acid.[86-87] We decided to adopt the Jung approach to the synthesis of 2-bromo-5-methoxynaphthoquinone **99** from 1,5-dihydroxynaphthalene **100** as indicated in **Scheme 25**, with a few modifications.[87] Having synthesised the juglone derivative, we planned to use a modified Minisci reaction to introduce the allyl group as shown in **Scheme 26**.



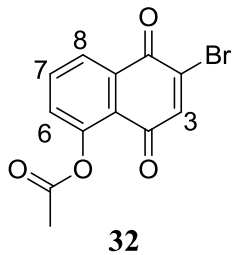
100 **101** **32**

102 **99**

***Scheme 25: Reagents and conditions**; (i) Ac_2O, pyridine, rt, 18 h, 97%; (ii) NBS, AcOH, H_2O, 65 °C, 1 h, 91%; (iii) 3 N aq. H_2SO_4, EtOH, reflux, 30 min, 81%; (iv) Ag_2O, MeI, CH_2Cl_2, rt, 24 h, 96%.*

2.3.1.1 Synthesis of 2-bromo-5-methoxy-1,4-naphthoquinone 102

The synthesis started from commercial 1,5-dihydroxynaphthalene **100**. Acetylation of **100** using acetic anhydride in pyridine at room temperature for 18 hours gave the desired acetoxynaphthalene **101** as a light brown solid in 97% yield. The ^{1}H NMR spectrum, through the appearance of a singlet at δ 2.45 ppm, unambiguously confirmed that the acetylated product was made. Additionally, the appearance of a signal due to an ester carbonyl at δ 169.3 ppm in the ^{13}C NMR spectrum further supported the synthesis of **101**. Pleased with the assembly of acetylated product **101**, our next step was to undertake an NBS mediated oxidative bromination of **101** to make the desired quinone **32**. To achieve this, *N*-bromo succinimide (NBS) was dissolved in a mixture of acetic acid and water and to this solution, the diacetoxynaphthalene **101** was added dropwise and the reaction was stirred at 65 °C for a further 1 hour. Chromatographic purification of the crude product furnished the quinone **32** as a yellow solid in 91% yield. The identity of the product **32** was confirmed by ^{1}H NMR spectroscopy which showed four aromatic signals. The doublet of doublets signal at δ 8.14 ppm was consistent with H-8. The *J* values of 7.8 and 1.3 Hz were consistent with both *ortho* coupling to H-7 and *meta* coupling to H-6. The triplet at δ 7.77 ppm was assigned to H-7 and the doublet of doublets at δ 7.42 ppm was assigned to H-6. Finally, the singlet at δ 7.39 ppm was indicative of the H-3 proton. It is worth noting that the reaction was carried out in high dilution to prevent potential multiple bromination. The initial acetylation step was equally important for the bromination reaction as the nucleophilicity of the powerful phenolic groups was masked, thereby preventing multiple brominations. One challenge we faced was the instability of the quinone **32**, which decomposes on exposure to air. To circumvent this challenge, the quinone was immediately subjected to the subsequent deacetylation step.



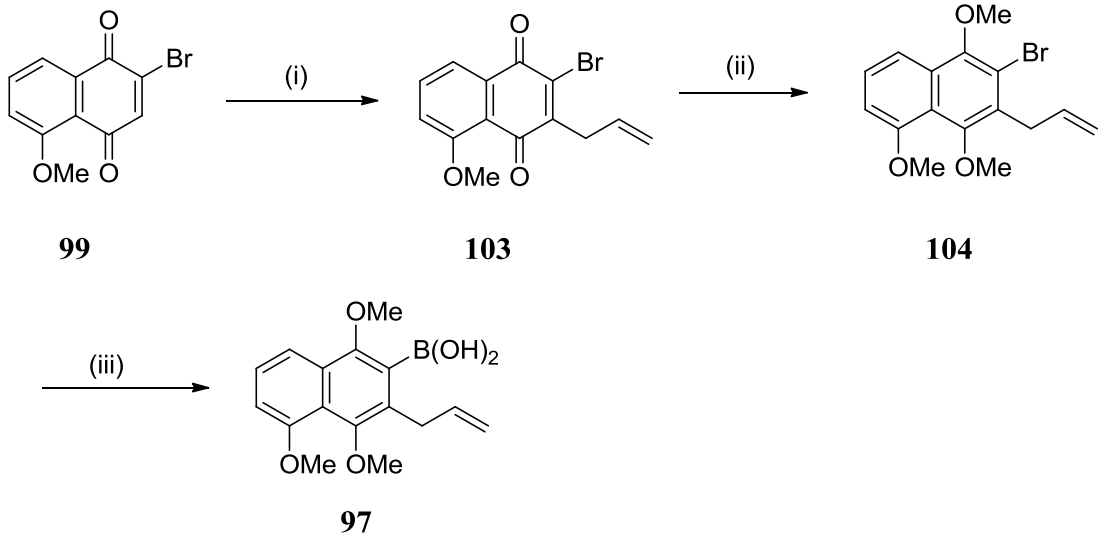
32

Deacetylation of **32** was smoothly accomplished by refluxing in 3 N aqueous sulfuric acid and ethanol for 30 minutes to furnish the hydroxyquinone **102** in an excellent yield of 91%. The identity of the quinone **102** was confirmed by the disappearance of

both the signal due to ester carbonyl in the ^{13}C NMR spectrum at δ 169.2 ppm and the singlet signal of the methyl protons at δ 2.44 ppm in the ^{1}H NMR spectrum. Furthermore, the appearance of a signal due to the phenolic proton at δ 11.77 ppm was additional evidence of the deacetylation. The phenolic group of the quinone was then protected as the *O*-methyl ether. To accomplish this, the quinone **102** was exposed to silver(I) oxide and methyl iodide and the mixture stirred at room temperature for 24 hours. Chromatographic purification afforded the desired methoxyquinone **99** in an excellent yield of 96%. The synthesis of **99** was unmistakably confirmed by the appearance in the ^{1}H NMR spectrum of a signal due to the methoxy protons at δ 4.02 ppm and the disappearance of the phenolic proton signal at δ 11.77 ppm.

2.3.1.2 Synthesis of allylated boronic acid 97

With the quinone **99** in hand, the insertion of the allyl group to assemble the allylated quinone adduct **103**, and subsequent reduction of the allylated quinone to furnish naphthalene **104** followed by the assembly of the boronic acid **97** were accomplished as highlighted in **Scheme 26**.



***Scheme 26: Reagents and conditions**; 3-butenoic acid, $(NH_4)_2S_2O_8$, $AgNO_3$, H_2O-MeCN, 60 °C, 18 h, 72%; (ii) Me_2SO_4, $Na_2S_2O_4$, TBAI, aq. KOH, THF, 75%; (iii) n-BuLi, $B(OiPr)_3$, −78 °C, 1 h, 94%.*

The protocols for the first two synthetic transformations above were similar to those discussed in the synthesis of benza[*a*]anthraquinone analogues in **Sections 2.1.1.1** and **2.1.1.2** and so will not be repeated in this section. The synthesis of the allylated bromonaphthoquinone **103** was accomplished in a very good yield of 72% and its subsequent reduction furnished the bromonaphthalene derivative **104** in 75% yield. Finally, we needed to convert the bromonaphthalene **104** into the boronic acid **97** for the palladium catalysed cross coupling reaction. To accomplish this, *n*-BuLi was added dropwise to a solution of bromonaphthalene **104** in tetrahydrofuran at −78 °C followed by the addition of triisopropylborate and stirred for 30 minutes. The reaction mixture was acidified with 10% aqueous hydrochloric acid solution and extracted with diethyl ether. The organic layer was then poured into hexane upon which a solid precipitated out of solution and the mixture was filtered to furnish the boronic acid **97** as an off-white crystalline solid in 94% yield. The boronic acid was used without further purification or characterization. It must be mentioned that there was a possibility for the isomerisation of the allyl substituent by *n*-BuLi and this could only be established in the next step.

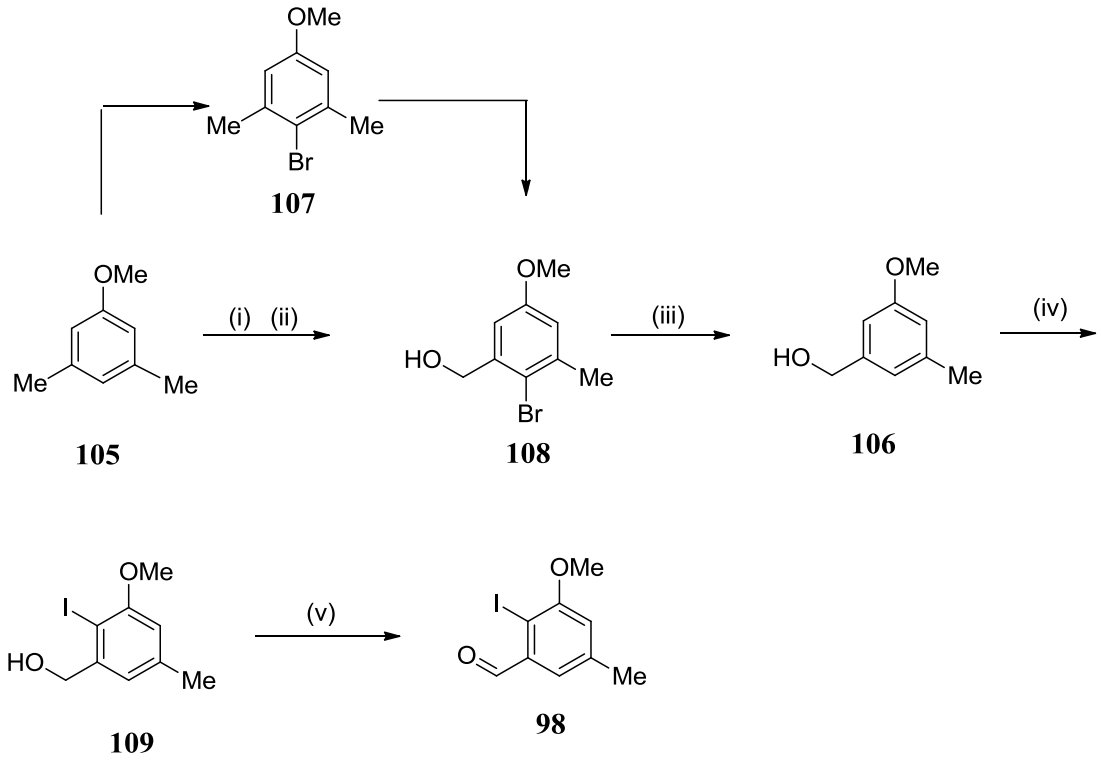
With the synthesis of the naphthalene boronic acid precursor **97** completed, we turned our attention to the synthesis of the second precursor for the Suzuki-Miyaura reaction, the substituted benzaldehyde **98.** The next section will highlight how the synthesis of **98** was accomplished.

2.3.2 Synthesis of 2-iodo-3-methoxy-5-methylbenzaldehyde 98.

One challenge we envisaged in our intended Suzuki-Miyaura reaction was steric hindrance, as we realised we would be forming a *tetra-ortho*-substituted biaryl axis intermediate. One of the halogens needed to be easily displaceable like iodine to facilitate the Suzuki-Miyaura reaction given the steric constraints. As a consequence, we opted to synthesise the required substituted benzaldehyde, containing an iodine in the appropriate position.

For the synthesis of the iodo substituted benzaldehyde precursor **98**, we adopted a method developed by Takahashi and co-workers where they synthesised the substituted benzaldehyde as an intermediate in the assembly of the landomycin antibiotics skeleton.[88] Owing to the difficulties we encountered in one of the steps, we decided to modify their method. This modified synthetic route is given in **Scheme 27**.

The synthesis commenced utilising an NBS mediated benzylic bromination of 3,5-dimethylanisole **105**. We initially applied Takahashi's conditions where 1 equivalent of NBS and a catalytic amount of benzoyl peroxide were added to the anisole **105** and the mixture refluxed for 4 hours. After this period, the reaction mixture was poured into diethyl ether and water and the aqueous layer was extracted with diethyl ether. The residue was used for the next reaction without further purification. To accomplish the next hydroxylation stage, calcium carbonate was added to a stirred solution of the residue in dioxane and water and the reaction mixture stirred at reflux for 12 hours. Chromatographic purification of the crude product furnished phenylmethanol **106** as a light-yellow oil in a very modest yield of only 19%. From the ^{1}H NMR spectrum, it was evident by the appearance of a singlet signal at δ 4.57 ppm integrating for two protons, that the product was formed. This signal is consistent with the two benzylic protons. Further evidence was provided by the appearance of a broad singlet at δ 2.28 ppm which was attributed to the OH group.



***Scheme 27: Reagents and conditions**; (i) **Method 1**: NBS, $(PhCO_2)_2$ or AIBN, CCl_4, reflux, 4 h; (ii) $CaCO_3$, 1,4-dioxane, reflux, 16 h; 70% (over two step); **Method 2**: NBS, AIBN or $(PhCO_2)_2$, EtOAc, MW 300 W, reflux, 1 h; (ii) $CaCO_3$, 1,4-dioxane, reflux, 16 h; 72% (over two step); (iii) n-BuLi, −78 °C, THF, 2 h, 94%; (iv) n-BuLi, Et_2O, −78 °C to rt, 4 h, then I_2, THF, 0 °C, 30 min, 70%; (v) MnO_2, CH_2Cl_2, rt, 18 h, 97%.*

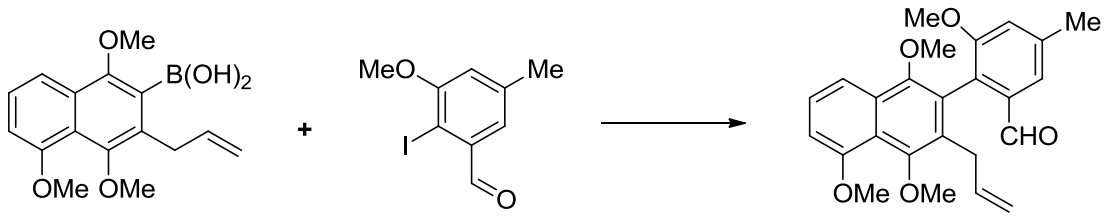
Although we had evidence that the desired phenylmethanol **106** had been synthesised, we were not satisfied with the yields and we decided to try and optimise the conditions. Takahashi using this protocol reported a 42% yield over the two steps. We undertook a number of initiatives, among them; increased reaction times, change in radical initiators, increased initiator loading from 1%-20%, changed reagents for the hydroxylation reaction to sodium bicarbonate in acetone instead of calcium carbonate, but none of these initiatives were helpful in improving the yields. We further explored the use of a microwave assisted green method of conducting the benzylic bromination in ethyl acetate which was reported by Jursic,[89] and the yields improved only marginally. Hence, we decided to isolate the initial product after the

NBS reaction to ascertain that we were indeed brominating the benzylic carbon atom. To our surprise, we isolated the *para* brominated anisole **107** in 77% yield. This was confirmed using ^{1}H NMR spectroscopy by the reduction in the number of aromatic proton signals from three to two. What was interesting about this reaction on this particular substrate was that even under radical conditions, nuclear bromination took preference over benzylic bromination. We searched the literature for precedence of this and discovered a report by Bickelhaupt. In the report, they analysed nuclear versus side chain bromination of a number of substituted anisoles, including our substrate **105**, on treatment with NBS. A key finding in their research was that when the two methyl substituents are in any position other than 3 and 5, benzylic bromination dominated. Nuclear bromination dominates when the two methyl substituents are in the 3 and 5 positions.[90] In their bromination of 3,5-dimethylanisole using NBS in carbon tetrachloride, they isolated the nuclear brominated product **107** in 75% yield and 25% of the side chain bromination product. Our findings, where we isolated the nuclear brominated product **107** in 77% yield were consistent with these reported results. Following this discovery, we then decided to modify Takahashi's protocol. To this end, we envisaged that adding another mole equivalent of NBS would facilitate benzylic bromination as the most reactive nuclear positon will have been occupied by initial bromination. This would be followed by the same hydroxylation conditions as before. When this was done, to our delight, we isolated the bromophenylmethanol derivative **108** as a white, low melting solid in 72% yield over two steps and 21% yield of the phenylmethanol adduct **106**. Formation of product **108** was unequivocally proved by the appearance of a broad singlet at δ 2.85 ppm and a signal due to the two benzylic protons at δ 4.64 ppm in the ^{1}H NMR spectrum. Aromatic debromination of **108** was smoothly accomplished by subjecting the compound **108** to *n*-BuLi in tetrahydrofuran −78°C for 2 hours to furnish the desired phenylmethanol derivative **106** in an excellent yield of 94%. Effectively using our modified procedure, we were able to synthesise the substituted phenylmethanol derivative **106** in 87% yield over three steps.

Pleased with the assembly of the phenylmethanol **106**, we then used the directed *ortho* metalation strategy to insert an iodine regioselectively at the C-6 position. We postulate that the oxygen on both the C-5 methoxy group and on the C-1 benzyl alcohol would coordinate to lithium, leading to directed lithiation and subsequent iodination at the C-6 position. To accomplish this, *n*-BuLi was added to a solution of **106** in diethyl ether at −78 °C. This was followed by the slow addition of iodine dissolved in tetrahydrofuran and the reaction being stirred for a further 30 minutes. The crude product was purified by chromatography on silica gel to afford iodophenylmethanol **109** as a white crystalline solid in 70% yield. The ^{1}H NMR spectrum clearly proved that the product **109** was formed by the disappearance of one aromatic proton signal. The position where the iodine substituent was placed was established by the HMBC spectrum where the methyl protons signal δ 2.31 ppm correlated to two aromatic carbon signals each carrying a proton three bonds away at δ 121.8 ppm and δ 111.2 ppm. This suggested that the protons on the two carbons were *ortho* to the methyl substituent. Consequently, this implied that the iodine substituent was placed *para* to the methyl substituent, which was the required position. Happy with this step, our final phase of the synthesis was to oxidise the benzyl alcohol to an aldehyde. This was easily accomplished by subjecting the alcohol **109** to manganese dioxide (MnO_2) in dichloromethane for 18 hours to furnish the desired benzaldehyde precursor **98** in 97% yield. The synthesis of **98** was unmistakably confirmed by the appearance of a signal due to the aldehydic proton at δ 10.16 ppm and the disappearance of both the signal due to the benzylic protons and the broad singlet in the ^{1}H NMR spectrum. The appearance of a signal due to the carbonyl carbon in the ^{13}C NMR spectrum at δ 196.6 ppm was further evidence of the synthesis of the benzaldehyde **98**.

Having assembled the two precursors **97** and **98**, the next step was to couple the two precursors using the palladium mediated Suzuki-Miyaura cross coupling reaction as shown in **Scheme 28**.

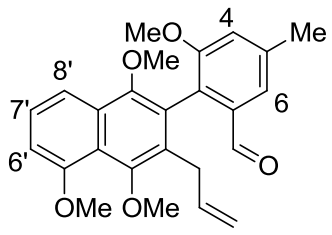
2.3.3 Synthesis of substituted benzaldehyde 110



97 **98** **110**

***Scheme 28: Reagents and conditions**: Pd(PPh$_3$)$_4$, aq. Na$_2$CO$_3$ (2 M), DME, reflux, 18 h, 12%.*

The critical step for us was to ascertain if we could utilize the Suzuki-Miyaura conditions we had used thus far for the coupling of the two precursors **97** and **98**. To this end, a deoxygenated solution of **97** and **98** in dimethoxyethane was added to *tetrakis*(triphenylphosphine)palladium(0) followed by the addition of deoxygenated aqueous sodium carbonate solution. The mixture was then heated at reflux for 18 hours. The crude product was purified by column chromatography on silica gel to afford the biarylaldehyde **110** as an off-white solid in a poor yield of 12%. Conclusive evidence for the formation of the compound was provided by both ^{1}H NMR and ^{13}C NMR spectroscopy. There were five signals due to aromatic protons in the ^{1}H NMR spectrum which were all assigned and were consistent with the 2-naphthylbenzaldehyde structure. The most deshielded singlet signal at δ 9.55 ppm was assigned to the aldehydic proton. One proton appearing as a doublet of doublets at δ 7.71 ppm was assigned to H-8′ with J = 8.4 Hz derived from *ortho* coupling with H-7′ and J = 1.0 Hz from *meta* coupling with H-6′. A triplet signal at δ 7.4 ppm with J = 8.4 Hz was assigned to H-7′. A doublet signal at δ 7.48 ppm with J = 0.8 Hz from *meta* coupling with H-4 was assigned to H-6, and similarly the doublet signal at δ 7.04 ppm with J = 0.9 Hz from coupling with H-6 was assigned to H-4. A doublet of doublets at δ 6.93 ppm with J = 7.8 and 1.0 Hz was assigned to H-



110

6'. The appearance of four signals due to the methoxy groups at δ 4.04, 3.86, 3.74 and 3.45 ppm unmistakably established the identity of the desired product **110**. The absence of another methyl proton signal and the presence of the benzylic protons signal at δ 3.86 ppm suggested that the allyl substituent was intact and had not isomerized in the process of preparing the boronic acid precursor **97**. The carbonyl carbon was clearly observed in the ^{13}C NMR spectrum as a signal at δ 192.7 ppm, and this functional group was further confirmed by FTIR with a C=O stretch at 1690.6 cm^{-1}. Upon examination of the HRMS, a molecular ion peak was observed at 406.1759 amu which was in good agreement with the expected mass of 406.1775 for $C_{25}H_{25}O_{5.}$

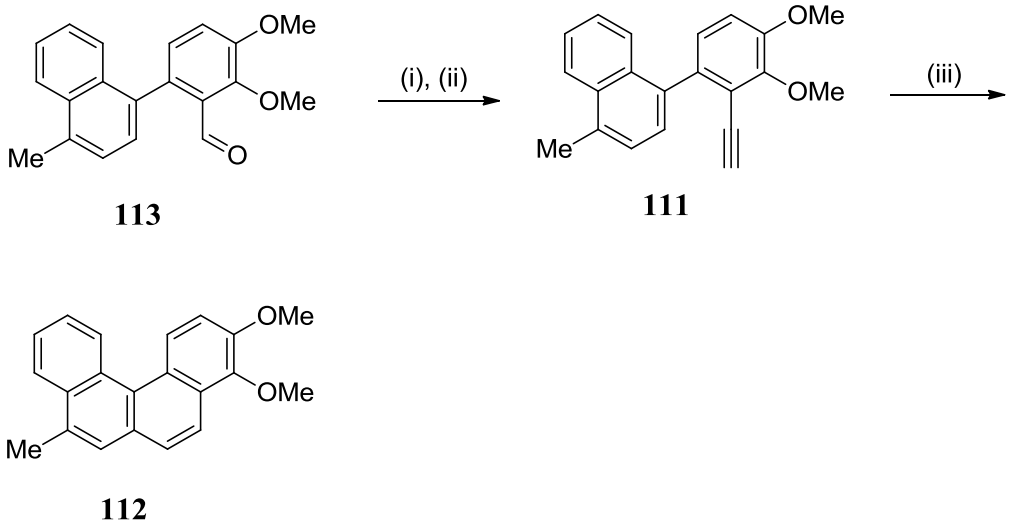
Although we were pleased that we had obtained our Suzuki product, the yield was a major concern. Hence, we spent a long time trying to optimise the reaction conditions. However, our attempts to improve the yields by varying conditions, preparing the palladium catalyst *in situ*, changing the supporting ligands from triphenyl phosphine to Xantphos, changing bases from Na_2CO_3 to CsF, K_3PO_4 and Cs_2CO_3, and finally using microwave conditions instead of the conventional method, were all unsuccessful. We rationalised the difficulty with this particular Suzuki-Miyaura reaction arises from the steric hindrance resulting from the four *ortho* substituents hindering the reaction in allowing for the formation of the *tetra-ortho* substituted biaryl axis intermediate **110**.

Over and above the difficulties encountered in coupling the two precursors, we also envisaged that the ruthenium mediated ring closing metathesis reaction to assemble a new benzene ring, would also pose a challenge. For that reaction to be successful in our case, we needed the dialkenes in the biaryl axis intermediate to align so that the orbitals can overlap for the [2+2] cycloaddition reactions as highlighted in **Section 1.7.5.2.1**. We hypothesised that the two rings forming the biaryl axis would not be flat to align the dialkenes, due to steric repulsions from the adjacent *ortho* groups on the rings. The lowest energy and most stable conformation would be achieved if the

groups are directed away from each other, implying that the alkenes on each side of the biaryl axis are not close enough for the necessary overlap of the orbitals to facilitate the [2+2] cycloaddition reactions. With this in mind, we decided to revisit our synthetic strategy.

2.4 Development of a new synthetic route

We needed to find a solution to the poor yields of our Suzuki-Miyaura coupling reaction and at the same time, in view of our hypothesis on the ring alignment, look at other metal mediated methods that could accommodate steric factors. In the literature we came across a report by Lakshman on platinum or gold mediated cycloisomerisation of alkynes to assemble fused polycyclic aromatic hydrocarbons.[91] In this approach, 1-(2-ethynylphenyl)naphthalene **111** was cycloisomerised to benzo[*c*]phenanthrene **112**. The 1-(2-ethynylphenyl)naphthalene was prepared from biarylaldehyde **113** using the Corey−Fuchs two-step alkynylation method.[92] The brief summary of the synthetic route is shown in **Scheme 29**.



113 **111** **112**

***Scheme 29: Reagents and conditions**: (i) PPh_3, CBr_4, CH_2Cl_2, 0 °C; (ii) n-BuLi, THF, −78 °C, 78% (over two steps); (iii) $PtCl_2$ or $AuCl_3$, PhMe, 80 °C, (Pt: 84%, Au:75%)*

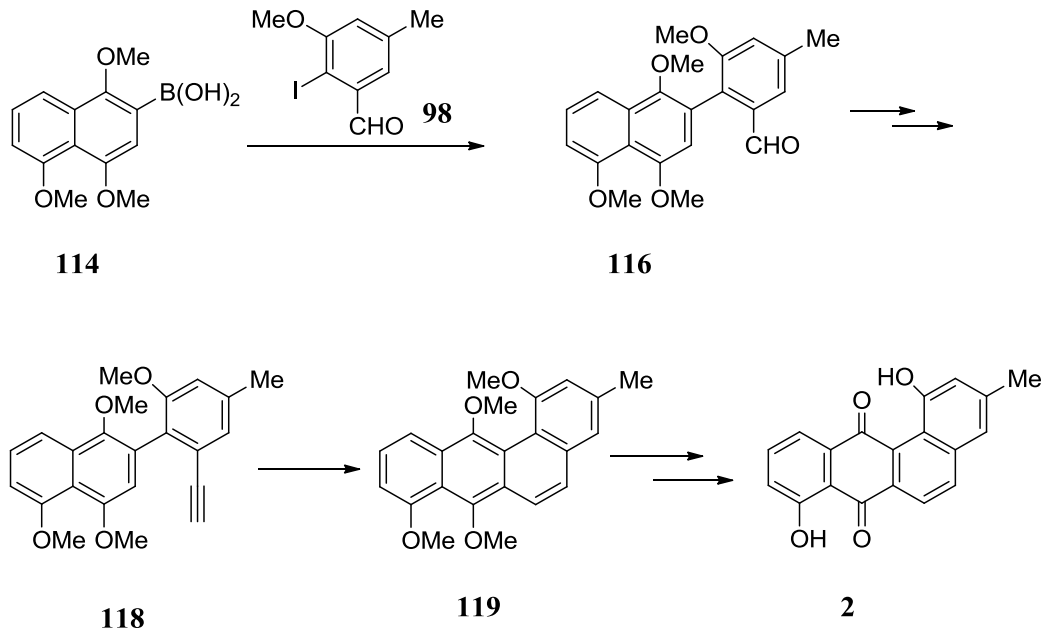
Although this strategy has never been used in the synthesis of benz[*a*]anthracene skeletons as found in angucycline cores, we thought we could adopt the $PtCl_2$ or $AuCl_3$ cycloisomerisation reaction to our substrates. The advantage of using this

approach was that the allyl substituent on naphthalene boronic acid **97** was no longer required, and as such, a *tetra-ortho* substituted biaryl axis intermediate would not be required. Hopefully, this would result in improving the yield of the Suzuki-Miyaura cross coupling reaction. Furthermore, our aldehyde precursor **98** could be utilised in this sequence to enable alkynylation and subsequent cycloisomerisation ring closure *via* a 6-*endo-dig* pathway.

In the next section, this new strategy towards the synthesis of tetrangulol will be discussed.

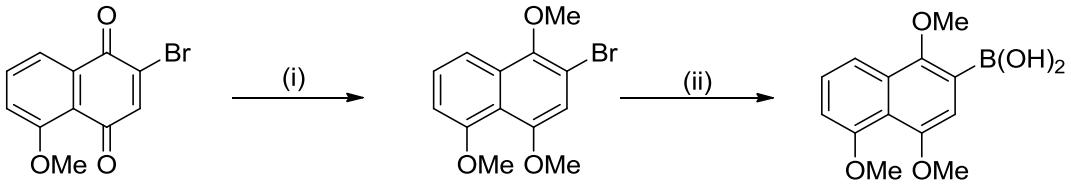
2.5 $PtCl_2$ or $AuCl_3$ mediated synthesis of tetrangulol

Our approach to the synthesis of tetrangulol using a $PtCl_2$ or $AuCl_3$ mediated cycloisomerisation reaction as a key step to assemble a new benzene ring is shown in **Scheme 30**.



Scheme 30: $PtCl_2$ and $AuCl_3$ mediated route to the synthesis of tetrangulol

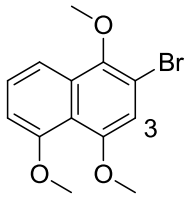
Our new synthetic route commenced with the assembly of a trimethoxynaphthalene boronic acid **114.** This was accomplished by the reduction of previously synthesised bromojuglone **99** to furnish the bromonaphthalene **115** which was subsequently functionalised to the desired boronic acid **114** as demonstrated in **Scheme 31**.



99 **115** **114**

Scheme 31: Reagents and conditions*; Me_2SO_4, $Na_2S_2O_4$, TBAI, aq. KOH, THF, 79%; (ii) n-BuLi, $B(OiPr)_3$, −78 °C, 1 h, 96%.*

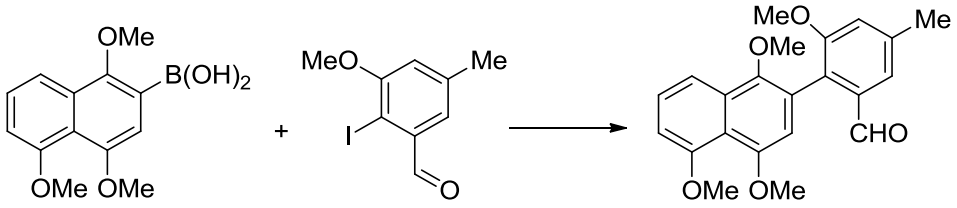
The quinone **99** was smoothly reductively methylated to the corresponding napthalene **115** as previously described in **Section 2.2.1.1** and in **Scheme 20**. The bromonaphthalene **115** was obtained in 79% yield. Analysis of the ^{1}H NMR spectrum showed the appearance of three methoxy group proton signals at δ 3.95, 3.93 and 3.92 ppm, which was consistent with the naphthalene. Furthermore, one singlet signal in the aromatic region of the ^{1}H NMR spectrum at δ 6.90 ppm was assigned to H-3 of the naphthalene structure.



115

Satisfied with the synthesis of the naphthalene derivative **115**, we now focused on the next step of making the naphthaleneboronic acid **114**. This synthesis was accomplished as described in **Section 2.3.1.2** and in **Scheme 26**. The boronic acid **114** was obtained as an off-white crystalline solid in 96% yield. This was then used in the subsequent step without further purification or characterization.

With the boronic acid **114** in hand, we now focused our attention on the palladium mediated Suzuki-Miyaura coupling reaction of the boronic acid **114** and the previously assembled substituted benzaldehyde **98** as illustrated in **Scheme 32**.

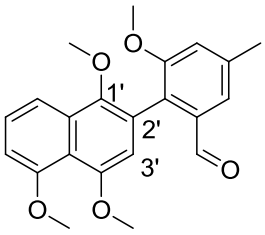


114 **98** **116**

***Scheme 32: Reagents and conditions**: Pd(PPh$_3$)$_4$, aq. Na$_2$CO$_3$ (2 M), DME, EtOH, reflux, 18 h, 80%.*

This reaction was very critical for us as we hoped the less sterically hindered boronic acid **114** would result in a successful Suzuki-Miyaura coupling reaction affording high yields of the biaryl product **116**.

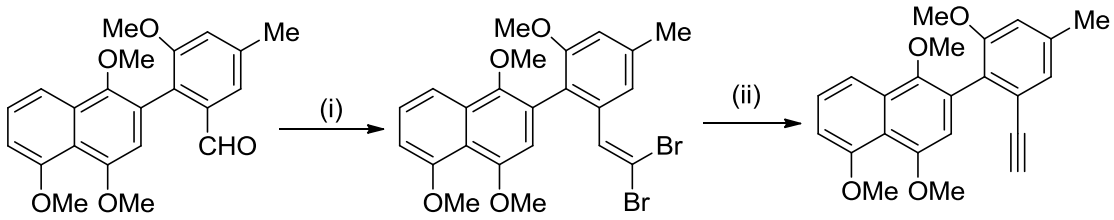
To accomplish this, a deoxygenated solution of boronic acid **114** and the benzaldehyde **98** in dimethoxyethane was added to *tetrakis*(triphenylphosphine)palladium(0) followed by the addition of deoxygenated aqueous sodium carbonate solution. The mixture was then heated at reflux for 18 hours. To our delight, chromatographic purification of the crude product furnished the 2-naphthylbenzaldehyde intermediate **116** in a very good yield of 80%. Analysis of the ^{1}H NMR spectrum showed the presence of four signals due to the methoxy group protons at δ 4.00, 3.92, 3.80 and 3.45 ppm with the most shielded of these being that for the C-1′ methoxy group. The most shielded aromatic singlet at δ 6.69 ppm was indicative of the proton H-3′. Furthermore, there were six signals in the aromatic region of the ^{1}H NMR spectrum which provided evidence that coupling of the precursors had occurred. Additionally, in the analysis of HRMS, a peak for the molecular ion was observed at



116

366.1452 amu (100%) which correlated with the expected mass of 366.1461 amu for $C_{22}H_{22}O_5$.

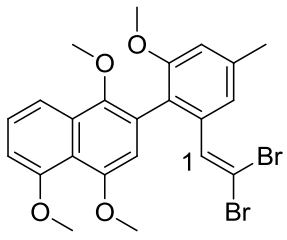
The successful assembly of the biarylbenzaldehyde **116** in very good yield proved that a *tetra-ortho* substituted biaryl axis intermediate **110** was simply too sterically hindered for the successful Suzuki-Miyaura coupling reaction as opposed to the *tri-ortho* substituted biaryl axis intermediate as noted by the increase in yields from 12% to 80%. With the successful synthesis of the biaryl compound **116** we then proceeded to convert the aldehyde to the dibromovinyl intermediate **117** and then subsequently to the acetylene **118** using the Corey-Fuchs method as shown in **Scheme 33**.



116 **117** **118**

***Scheme 33: Reagents and conditions**: (i) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 89% (ii) n-BuLi, THF, −78 °C, 88%.*

To achieve this, CBr_4 was added to a mixture of PPh_3 in dichloromethane followed by slow addition of the aldehyde **116** and the mixture was stirred for 4 hours. At the end of this period, TLC showed that all the starting material was consumed. Chromatographic purification of the crude product afforded the dibromovinyl intermediate **117** in 89% yield, as a foamy, yellow solid. The unmistakable disappearance of the signal due to the aldehyde proton in the ^{1}H NMR spectrum and the appearance of a new singlet signal integrating for one proton at δ 7.09 ppm which correlated to =C*H*- (H-1), was proof of its formation. Additionally, the HRMS showed a molecular ion peak at

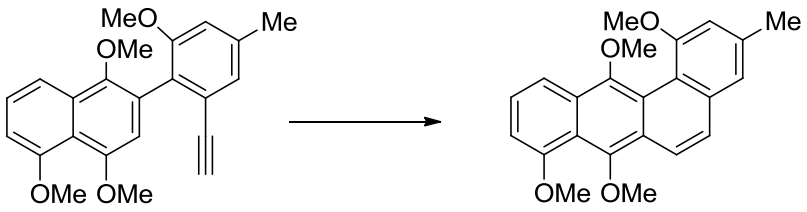


117

519.9881 amu which was in good agreement with the expected mass of 519.9879 amu for $C_{23}H_{22}O_4{}^{79}Br_2$.

The obtained dibromovinyl adduct **117** was then subjected to a debromination reaction by treating it with *n*-BuLi in tetrahydrofuran at −78 °C to smoothly furnish the acetylene **118** as a yellowish-brown solid in an excellent yield of 88%. The ^{1}H NMR spectrum unequivocally proved the formation of the product by the disappearance of a singlet signal at δ 7.09 ppm which correlated to =C*H*-, and the appearance of the singlet signal due to an acetylenic proton at δ 2.81 ppm. The acetylene functional group was also observed in the FTIR by a stretching band at 2370.8 cm^{-1}. Furthermore, analysis of the HRMS showed a molecular ion peak at 362.1522 amu (100%) which correlated with the expected mass of 362.1512 amu for $C_{23}H_{22}O_4$.

Pleased with the synthesis of acetylene **118**, we then focussed our attention on the $PtCl_2$ or $AuCl_3$ mediated cycloisomerisation reaction to assemble a new benzene ring. This was a key step for us as it would give us the desired benz[*a*]anthracene carbon skeleton of tetrangulol as illustrated in **Scheme 34**.

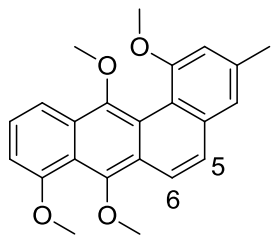


118 **119**

***Scheme 34: Reagents and conditions**: Cat. $PtCl_2$ or $AuCl_3$, PhMe, 90 °C, 24 h, (Pt: **119**-61%, Au: **119**-56%).*

Although $PtCl_2$ was alluded to as being a better catalyst in the assembly of substituted benzo[*c*]phenanthrenes, we decided to use both catalysts in order to compare their efficiency in the assembly of benz[*a*]anthracene skeletons. To accomplish this, $PtCl_2$

or $AuCl_3$ was added to acetylene **118** in toluene and the mixture was stirred at 90 °C for 24 hours. To our delight, chromatographic purification on silica gel furnished the desired tetramethoxy tetraphene **119** as a yellow solid in 61% yield for platinum and 56% for gold, along with an unknown product **120**. The identity of the tetraphene **119** was confirmed by ^{1}H NMR spectroscopy. The disappearance of the signal due to the acetylenic proton at δ 2.81 ppm and the most shielded aromatic singlet at δ 6.67 ppm, along with the increase in the number of signals in the aromatic region of the ^{1}H NMR spectrum from six to seven, clearly established the formation of the tetraphene **119**. The two *ortho* coupled doublet signals integrating as one proton each at 8.03 ppm (J = 9.2 Hz) and 7.36 ppm (J = 9.5 Hz) correlated to H-6 and H-5, respectively, in the structure. In addition, the HRMS showed a molecular ion peak at 362.1514 amu (100%) which was in good agreement with the expected mass of 362.1512 amu for $C_{23}H_{22}O_4$.

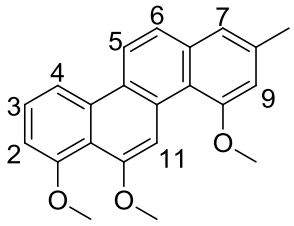


119

Satisfied that our cycloisomerisation ring closure step gave us our desired tetraphene **119** in good yields, we decided to examine in detail the identity of unknown compound **120**. Using both ^{1}H NMR and ^{13}C NMR spectroscopy, and in particular 2D experiments such as HMBC and HSQC spectroscopy, we were able to confirm the identity of the unknown compound. The disappearance of the acetylene proton signal at δ 2.81 ppm and the increase in the number of aromatic proton signals from six to eight clearly showed that this compound, just like the tetraphene **119** contained a new benzene ring. We therefore postulated that the unknown compound **120** arose by an alternative cycloisomerisation reaction. Two *ortho* coupled proton signals at δ 8.56 ppm and δ 7.69 ppm J = 9.1 Hz for both signals were assigned to H-5 and H-6 respectively. Detailed analysis of the HMBC spectrum showed that the triplet at δ 7.56 ppm and the doublet signal at δ 7.06 ppm both correlated to a methoxy carrying carbon three bonds and two bonds away respectively at δ 157.4 ppm assigned C-1. These two signals were indicative of H-2 and H-3 protons. The proton singlet signal at δ 9.20 ppm correlated to one methoxy carrying aromatic carbon signal at δ 154.9

ppm assigned C-12 and this was indicative of the H-11 proton. The doublet at δ 8.38 ppm, which using the HMBC spectrum, was correlating to an aromatic proton present as a triplet at δ 7.56 ppm two bonds away and another carbon carrying a doublet proton signal at δ 7.06 ppm three bonds away was consistent with H-4. Finally, the two *meta* coupled protons at δ 7.34 ppm and δ 6.92 ppm with J = 0.9 Hz were indicative of H-7 and H-9 respectively. Additionally, the proton signal at δ 6.92 ppm assigned to H-9 was correlating to a methoxy group carrying aromatic carbon two bonds away at δ 158.6 ppm assigned as C-10, and the methyl carrying aromatic carbon two bonds away at δ 136.5 ppm assigned C-8. Furthermore, in the HRMS, a molecular ion peak was observed at 332.1379 amu which was in good agreement with the expected mass of 332.1407 amu for $C_{22}H_{20}O_3$. Putting everything together, the identity of the unknown was established as the trimethoxychrysene derivative **120**.

From the results of the key step cycloisomerisation reaction, it was evident that $PtCl_2$ was a better catalyst than $AuCl_3$ for this reaction. These results were consistent with those found by Lakshman. Our combined yields of the two products in either platinum or gold catalysed transformations was above 80%. We were very pleased that our desired benz[*a*]anthracene **119** was formed in a better yield than the undesired chrysene derivative **120**. The rationale for the differences in the ratios of the products, and indeed why the chrysene was formed at all, has not been fully unravelled. However, we hypothesised that the steric interactions between the methoxy on C-1′ and that one on the C-3 position of the acetylene derivative **118** leads to the ring closure that proceeds *via* demethoxylation of the more sterically hindered methoxy at the C-1′ position.



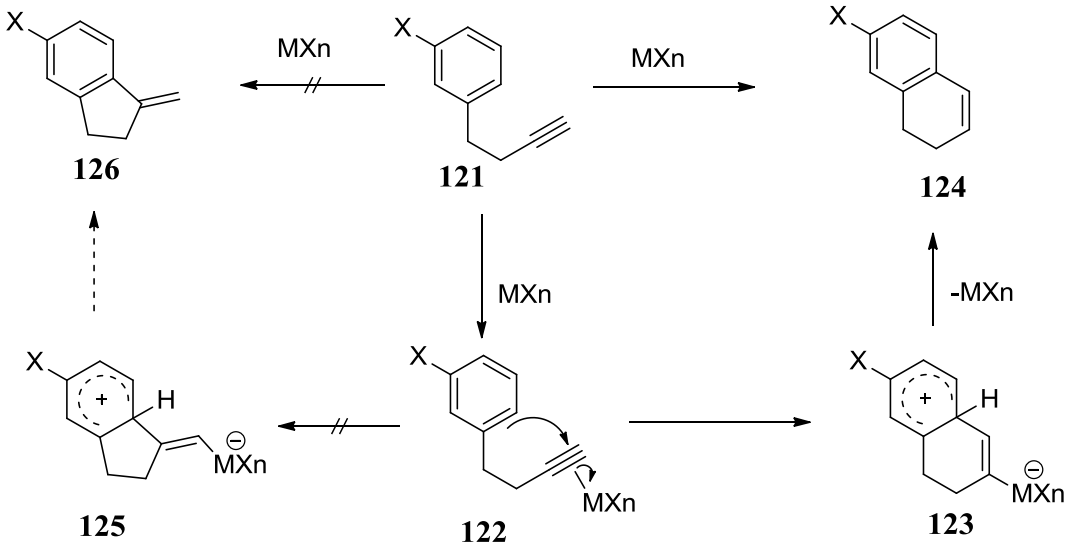
120

In both ring closing reactions to assemble the benz[*a*]anthracene and the benzo[*c*]anthracene frameworks, the preferred route was the 6-*endo*-*dig* pathway.

Echavarren reported on the mechanistic studies and the endo-selectivity of the intramolecular hydroarylation of alkynes by platinum and gold.[93] The next section will highlight the mechanistic pathways to the cycloisomerisation.

2.5.1 Intramolecular cycloisomerisation of alkynes.

The 6-*endo-dig* intramolecular hydroarylation pathway as proposed by Echavarren[93] is given in **Scheme 35**.

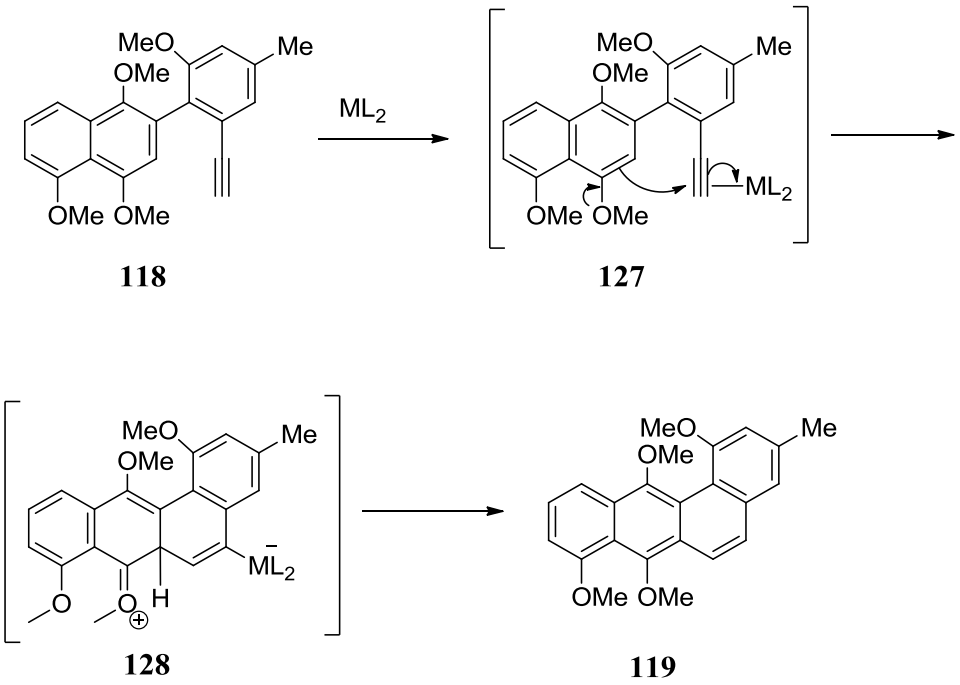


Scheme 35: Mechanism for cycloisomerisation

The postulated mechanistic pathway in this electrophilic aromatic substitution reaction is based on the Friedel-Crafts alkenylation reaction. In this pathway, the η^2-coordination of the MXn to **121** gives the organometallic compound **122** which undergoes an electrophilic aromatic substitution (EAS) reaction to furnish the Wheland type adduct **123** which upon a 1,3 H-shift affords the cycloisomerised product **124**. However, the 5-*exo-dig* pathway of electrophilic aromatic substitution reaction of **122** to give **125** does not take place hence substrate **121** does not furnish the 5-*exo-dig* product **126**.

In the case of intramolecular hydroarylation of the acetylene **118**, we have speculated two plausible mechanisms for the assembly of the tetramethoxytetraphene **119**. The

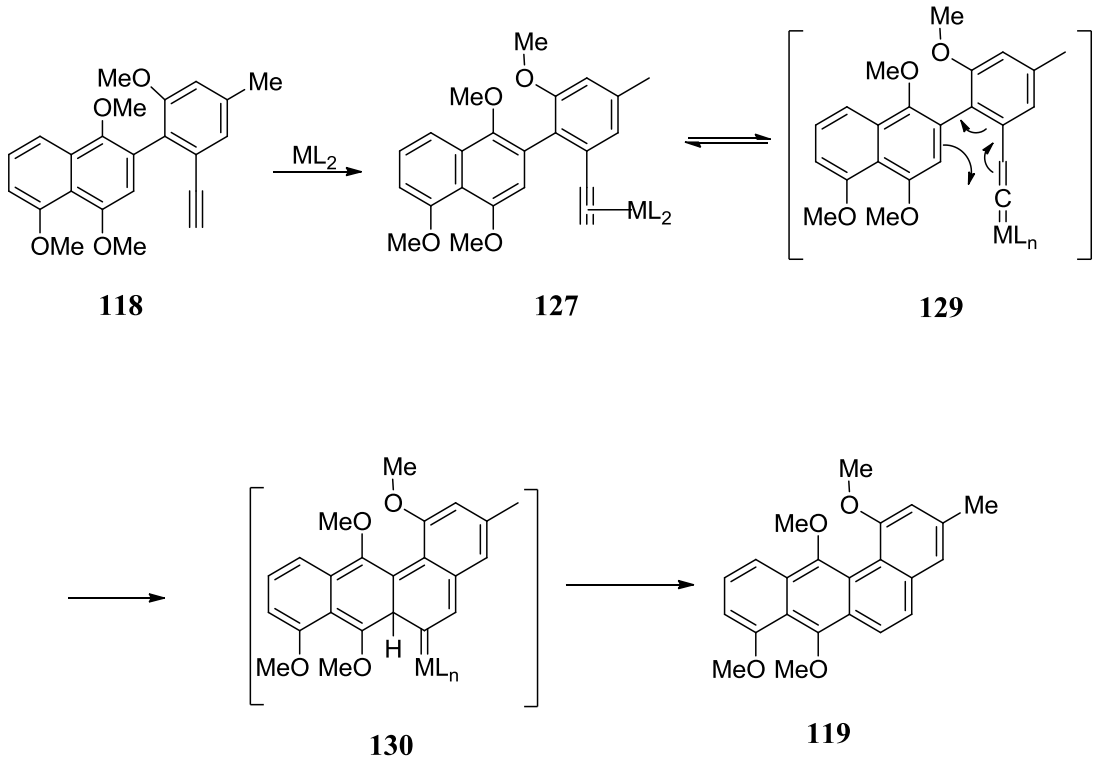
first mechanism proceeds *via* a Friedel-Crafts-type reaction by means of 6-*endo-dig* cyclisation as illustrated in **Scheme 36**.



Scheme 36: Proposed mechanism for cycloisomerisation via η^2- coordination

In this mechanism, the metal coordinates to the triple bond of the acetylene **118** to form the coordinated complex **127** which, upon an electrophilic aromatic substitution reaction driven by the lone pair of electrons on the oxygen of the C4-OMe group, affords the intermediate **128**. A concerted 1,3-H shift and rearomatisation furnish the tetraphene **119**. In our case, there are two factors that promote or drive this intramolecular cycloisomerisation reaction. Firstly, the naphthalene ring of the biaryl acetylene **118** is electronic rich due to electron donating methoxy groups that can facilitate the electrophilic aromatic substitution reaction. Secondly, the carbocation formed as a result of the EAS can be stabilised by the C8-OMe group, further promoting the cycloisomerisation reaction.

The alternative mechanism we have proposed proceeds *via* a vinylidene complex which then undergoes a π6–electrocyclisation to form the new aromatic ring as shown in **Scheme 37**.



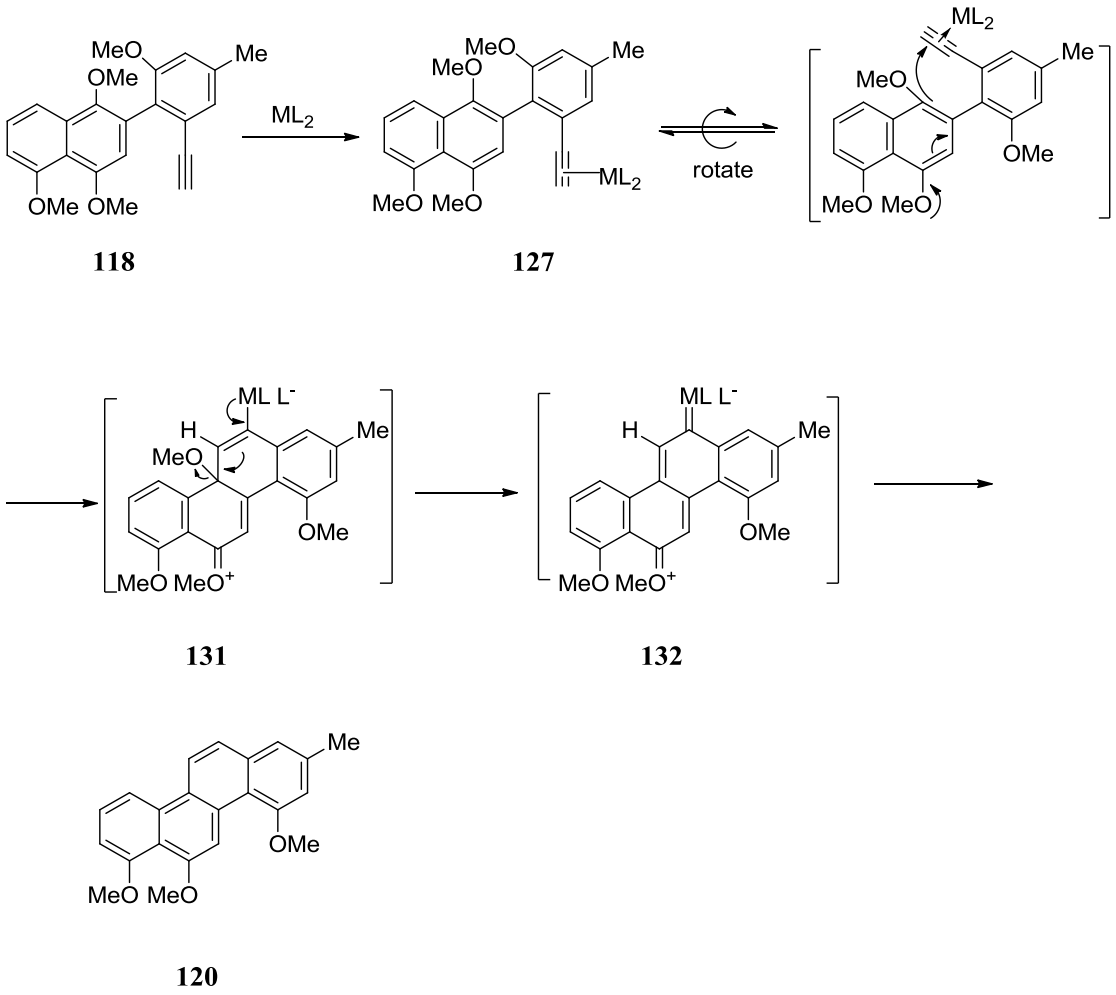
118 **127** **129**

130 **119**

Scheme 37: Proposed π6-electrocyclisation mechanism

In this mechanism, coordination of the metal to the triple bond of acetylene **118** gives the coordinated complex **127** which could form the vinylidine adduct **129**. The vinylidine undergoes the π6-electrocyclisation to assemble tetracyclic derivative **130** which upon rearomatisation furnish the tetraphene **119**.

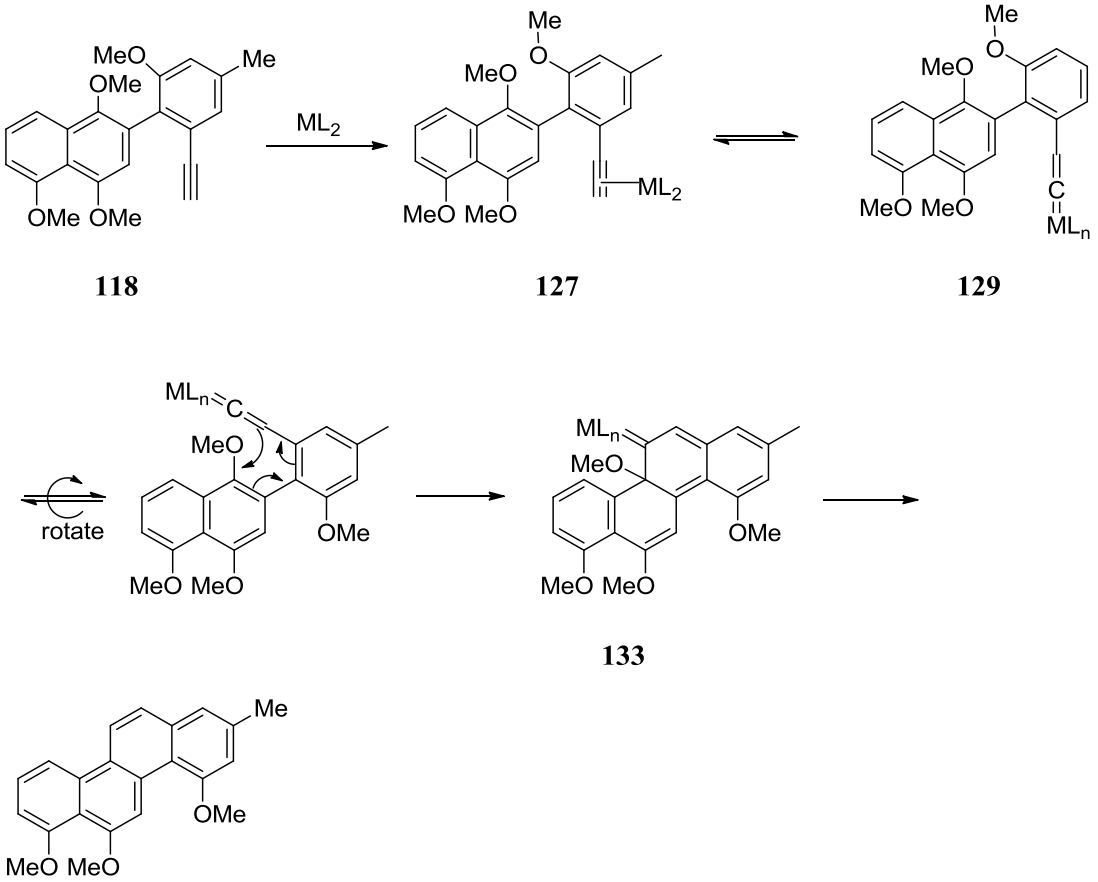
We also made an attempt to postulate the mechanism for the formation of the chrysene derivative **120** as illustrated in **Scheme 38**.



Scheme 38: Proposed mechanism for assembly of chrysene via η^2- coordination

Under this mechanism, the metal coordinates to the triple bond of the acetylene **118** to give the coordinated complex **127**, which upon electrophilic aromatic substitution reaction driven by the lone pair on oxygen affords the intermediate **131**. Demethoxylation of the intermediate **131** gives the benzo[*c*]phenanthridine adduct **132** which upon aromatisation furnishes the chrysene derivative **120**.

We also postulated that the chrysene derivative **120** could be assembled through the π6-electrocyclisation as illustrated in **Scheme 39**.

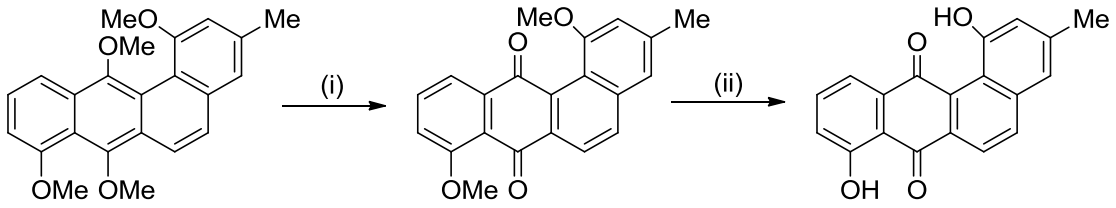


Scheme 39: Proposed π6-electrocyclisation mechanism for the assembly of chrysene

In this mechanism, coordination of the metal to the triple bond of acetylene **118** gives the coordinated complex **127** which could form the vinylidine adduct **129**. The vinylidine undergoes the π6-electrocyclisation to assemble the benzo[*c*]phenanthridine derivative **133** which, upon demethoxylation and rearomatisation, furnishes the tetraphene **120**.

Satisfied that we were able to assemble a benz[*a*]anthracene skeleton of tetrangulol in good yields using a $PtCl_2$ or $AuCl_3$ intramolecular cycloisomerisation reaction as a key step, we embarked on the final stages of the synthesis by oxidising the

tetramethoxytetraphene **119** into its corresponding quinone **38**, followed by demethylation, to furnish the targeted natural product **2** as shown in **Scheme 40**.



119 **38** **2**

Scheme 40: Reagents and conditions*: (i) CAN, MeCN/H_2O, 86%; (ii) BBr_3, CH_2Cl_2, −78 °C to rt, 93%.*

Tetramethoxytetraphene **119** was smoothly converted into its corresponding quinone **38**. To accomplish this, cerium ammonium nitrate (CAN) was added to the tetraphene **119** in acetonitrile and water and the mixture stirred for 30 minutes. The crude product was purified by column chromatography on silica gel to give the benza[*a*]anthraquinone derivative **38** in 86% yield as a yellow solid. The ^{1}H NMR spectrum unambiguously established the formation of the quinone by the distinct absence of two signals due to the methoxy group protons. Additionally, the ^{13}C NMR spectrum explicitly showed two signals due to carbonyl carbons at δ 186.6 and δ 182.3 ppm. The ^{1}H NMR spectrum and ^{13}C NMR spectrum signals were in good agreement with those found by Hsu and co-workers.[57]

To complete the formal synthesis of tetrangulol **2**, we needed to demethylate the quinone **38**. This was accomplished by subjecting the quinone **38** to BBr_3 in dichloromethane overnight. Chromatographic purification of the crude product furnished the dihydroxyquinone (tetrangulol) **2** in an excellent yield of 93% as a brown solid. As observed in the spectral data, the unmistakable disappearance of two signals due to the methoxy group protons at δ 4.03 ppm and δ 3.97 ppm and the

appearance of two signals arising from the phenolic protons at δ 12.24 ppm and 11.26 ppm proved that the dihydroxyquinone **2** was successfully synthesised. This spectroscopic data correlated well with that obtained by Hsu.[57]

2.6 Conclusion

In summary, we have successfully developed a novel convergent method for the synthesis of 1,8-dihydroxy-3-methyltetraphene-7,12-dione **2**, a natural angucycline antibiotic commonly known as tetrangulol in 16 steps and 19.5% overall yield. The palladium catalysed Suzuki-Miyaura cross coupling reaction and the platinum or gold mediated intramolecular cycloisomerisation were key steps in the synthesis. This method can be extended to the synthesis of other angucycline antibiotic natural products.

2.7 Future work arising from this novel synthesis

Having successfully developed a method for synthesising angucycline antibiotic natural products with a carbotetracyclic core, we wondered if we could extend this work to the synthesis of other natural products, particularly the nitrogen containing angucyclines and other alkaloids. One idea we were pondering on was; could we make nitrogen containing natural products or analogues of natural products from one of the intermediates that we used to synthesise tetrangulol?

The next chapter of this PhD thesis gives an introduction and background to nitrogen containing natural angucyclines and their related alkaloids. Following this introduction on nitrogen containing aromatic natural products, the subsequent chapter will detail the work that we did on developing a synthetic method for assembling nitrogen containing natural product analogues.

CHAPTER 3: Benzo[*b*]phenanthridines and Benzo[*c*]phenanthridines: Introduction and Literature Review

3.1 Background and Introduction

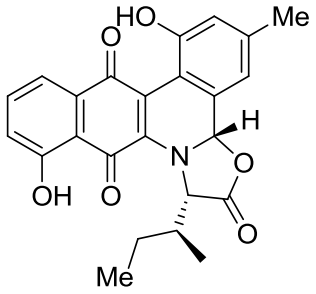
Naturally occurring nitrogen containing secondary metabolites are commonly distributed in plants, fungi, marine organisms, animals and others. These natural products with diverse and complex structures have been shown to exhibit potent therapeutic properties.[94] Some examples of aromatic natural products that incorporate nitrogen in their structures are the benzo[*b*]phenanthridines, jadomycins and benzo[*c*]phenanthridines.[95-96] On the basis of biosynthetic origins, whilst benzo[*b*]phenanthridines and jadomycins belong to the class of angucycline antibiotic natural products, benzo[*c*]phenanthridines, which are structural analogues of benzo[*b*]phenanthridines, are typically classified as alkaloids.[95, 97]The next sections will discuss each of these classes in detail.

3.2 Jadomycin antibiotics

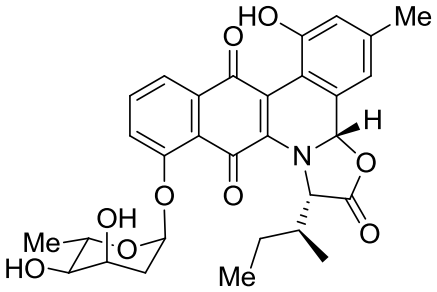
Jadomycins are unique members of the angucycline antibiotics and are one of the most studied subunits of the nitrogen containing angucyclines. The first compounds to be isolated from *Streptomyces venezuelae* ISP5230 were jadomycin A **134** and B **135**[98-99] (**Figure 11**).

3.2.1 Structure of jadomycins

Jadomycins contain an unusual 8*H*-benzo[*b*]oxazolo[3,3-*f*]-phenanthridine ring system.[100] Compounds in this class also exhibit two unique structural features as shown in **Figure 11**; a 2,6-dideoxysugar L-digitoxose and a five-membered oxazalone ring.[101-102] It is reported that the oxazolone ring is formed from the amino acid isoleucine with a biosynthetic aldehyde precursor.[97]



134

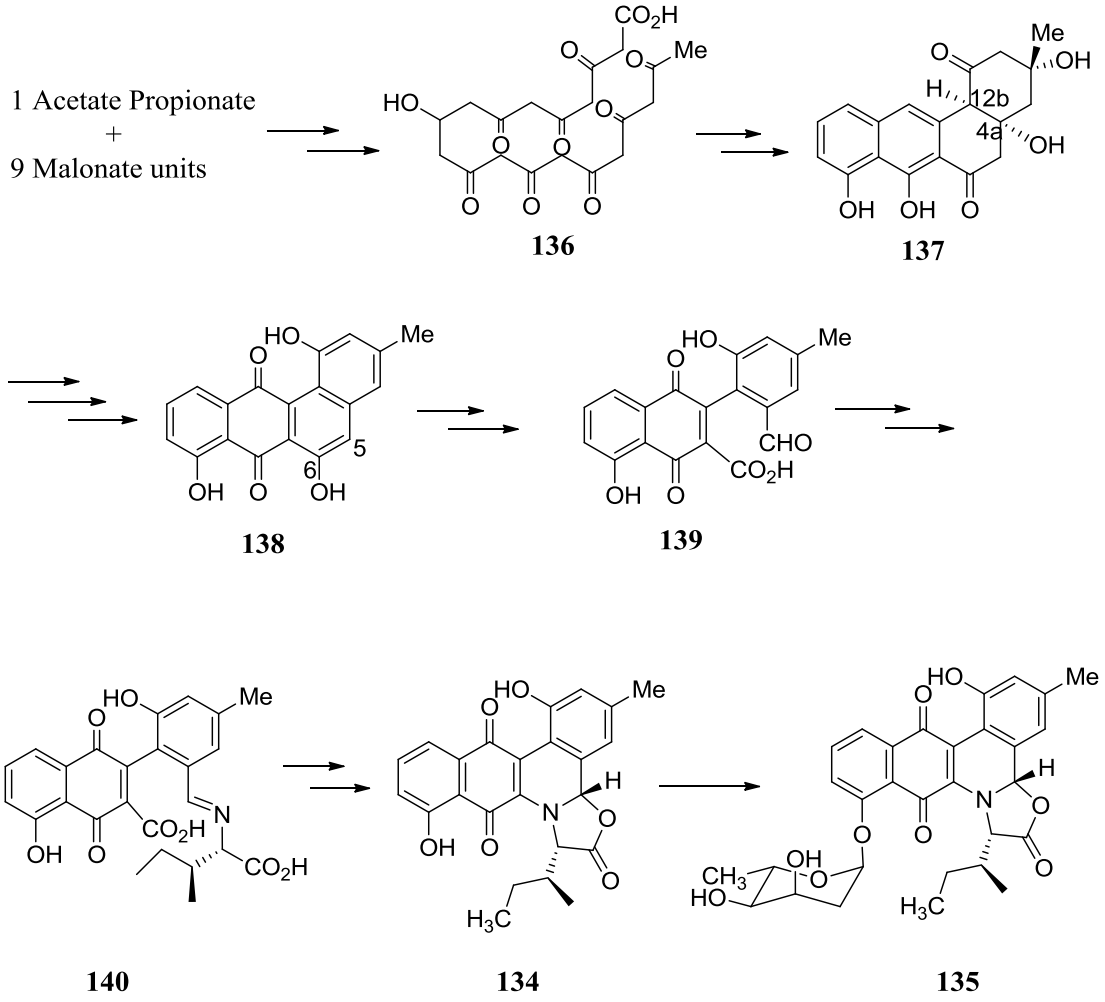


135

Figure 11: Jadomycin natural products

3.2.2 Biosynthesis of jadomycins

As with all angucycline antibiotics, the starting precursors for the jadomycin biosynthesis are an acetate propionate and nine malonate units, which combine through condensation to form the decaketide intermediate **136**. This subsequently cyclises to form the benzo[*b*]anthracene backbone **137** as shown in **Scheme 41**. Further oxidation, followed by dehydration across the C-4a and C-12b positions and subsequent aromatisation leads to the formation of the intermediate dehydrorabelomycin **138**. Oxidative cleavage of **138** at the C5-C6 bond gives the aldehyde/acid intermediate **139**. Non-enzymatic insertion of the L-isoleucine amino acid affords the aldimine moiety **140**. The non-enzymatic addition of an amino acid pathway has also been exploited synthetically to such an extent that almost all amino acids have been inserted in the jadomycin biosynthesis to create a library of analogues.[102] Cyclisation, oxidation of the intermediate hydroquinone and decarboxylation furnishes jadomycin A **134**, which, upon glycosylation, gives jadomycin B **135**.[101, 103]



Scheme 41: Biosynthesis of jadomycins

3.2.3 Biological activities

The jadomycin class of antibiotics has been reported to show potent therapeutic activities. Jadomycin B **135** and other analogues demonstrated potent antibacterial activities against *Staphylococcus aureus* C623, a methicillin resistant strain of bacteria (MIC < 2 µg/mL).[101] Currently, vancomycin is the only drug for the treatment of *Staphylococcus aureus* C623 infections.[101] These results illustrate the potential of the angucycline antibiotics as new drug candidates. Promising activities

were also exhibited by jadomycin B **135** and other analogues (**Figure 12**) against five cancer cell lines.

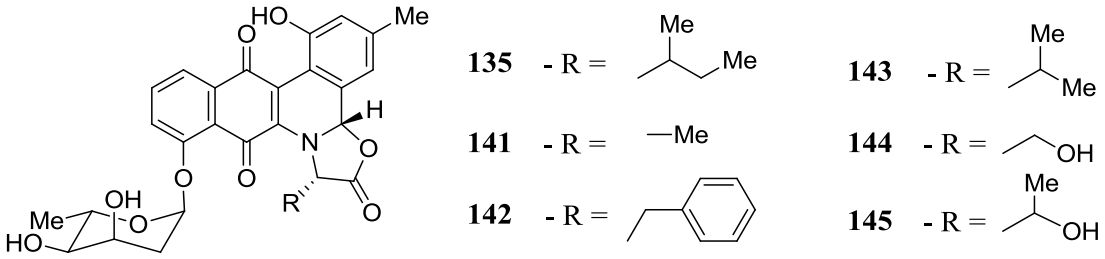


Figure 12: Biologically active jadomycins

Jadomycin **144** showed potent activity against HepG2, IM-9 and IM-9/Bcl-2 cell lines, whilst Jadomycin B 1**35** demonstrated activity against HepG2 and IM-9 cells. Additionally, Jadomycin F **142** exhibited excellent activity against the H460 cell line. Although all the compounds could supress the proliferation of tumour cell lines *in vitro*, jadomycins **141**, **143** and **145** were less active.[104] It was further demonstrated by the gel mobility assay that the jadomycin derivatives may also act as DNA cleaving agents.[101, 104]

3.3 Benzo[*b*]phenanthridines.

This is a small group of angucycline antibiotics that has been isolated from different *Streptomyces* species.

3.3.1 Structures of benzo[*b*]phenanthridines

The first naturally occurring benzo[*b*]phenanthridine, phenanthroviridone **146** and its glycoside, phenanthroviridine **147** (**Figure 13**) were isolated from *Streptomyces murayamaensis*.[105] This class of compounds possesses a nitrogen inserted at the C-6 position of the benzo[*b*]anthracene skeleton of the angucycline, tetrangulol. Very recently, L-digitoxosyl-phenanthroviridine **148** has been isolated from *Streptomyces venezuelae* ISP5230.[105]

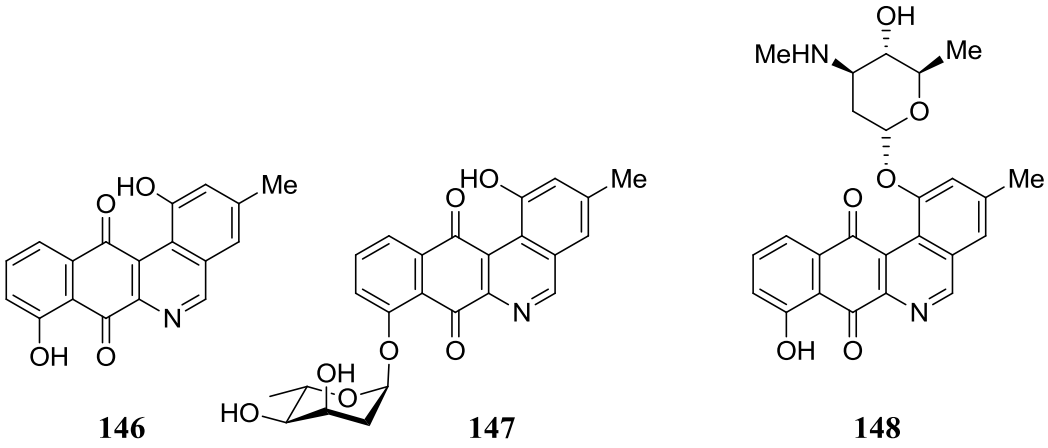
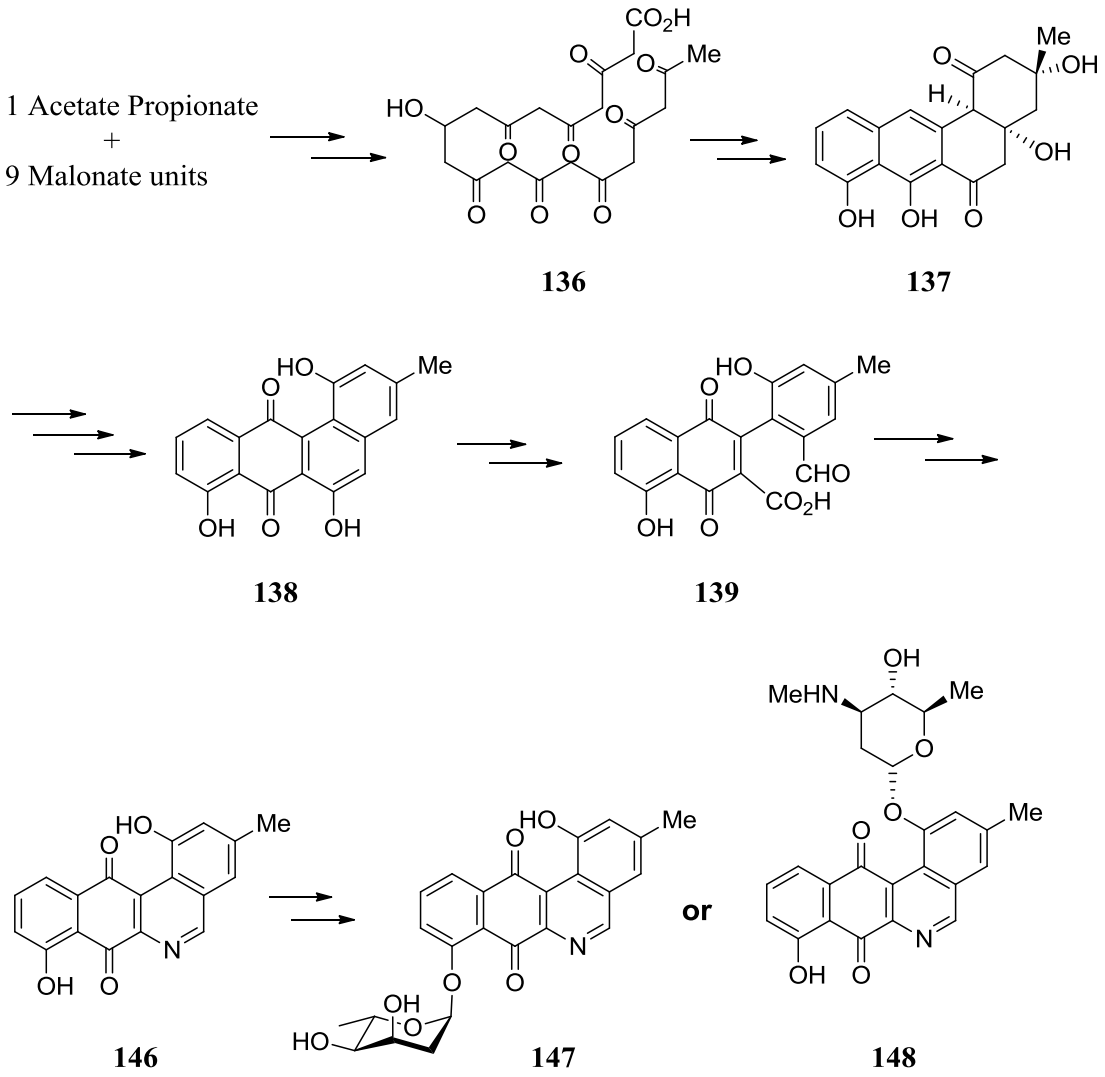


Figure 13: Common benzo[*b*]phenanthridine natural products

3.3.2 Biosynthesis of benzo[*b*]phenanthridines

Benzo[*b*]phenanthridines are believed to be intermediates in the transformation of dehydrorabelomycin **138** to the kinamycin class of antibiotics (**Section 1.6.3**) during their biosynthesis.[106] The biosynthetic pathway is summarised in **Scheme 42**. Just as in the biosynthesis of jadomycins described earlier, compounds in this class are also prepared from the condensation of Acetyl-CoA units, which affords the folded decaketide moiety **136**, which undergoes cyclisation to form the benzo[*b*]anthracene backbone **137**. Dehydration across C-12b and C-4a and subsequent oxidation affords the key intermediate, dehydrorabelomycin **138**. Oxidative cleavage results in the biaryl adduct **139**, which, upon nitrogen insertion, ring closure and decarboxylation, furnishes the phenanthroviridone **146**. Glycosylation of **146** affords phenanthroviridine **147**.[106-107] Alternatively, **148** can be prepared from **146** by glycosylation followed by amination of the sugar moiety.



***Scheme 42: Biosynthesis of phenanthroviridines* 146, 147 *and* 148**

3.3.3 Biological activities

Benzo[*b*]phenanthridines have been reported to exhibit a broad range of therapeutic activities. Phenanthroviridine **147** and its aglycone **146** showed potent activities against lung carcinoma cell line MBA9812 in a murine model.[108] Additionally, phenanthroviridone **146** demonstrated good antimicrobial activity against *Staphylococcus aureus ATCC 29213*, with an MIC value of 0.25 μg/mL and antibacterial activity against *Escherichia coli* ATCC 25922, *Bacillus thuringiensis*

SCSIO BT01, and *Bacillus subtilis* SCSIO BS01. When **146** was evaluated against three human cancer cell lines, it displayed significant *in vitro* cytotoxicity against SF-268 (IC_{50} 0.09 μM) and MCF-7 (IC_{50} 0.17 μM).[109] Recently isolated L-digitoxosyl-phenanthroviridine **148** demonstrated good activity against a number of human cancer cell lines (NCI 60). The median range values for all the cell lines were; GI_{50} = 2.14 μM for 56 cell lines, TGI = 5.75 μM for 56 cell lines and LC_{50} = 18.2 μM for 41 cell lines.

3.4 Benzo[*c*]phenanthridines

Benzo[*c*]phenanthridines are a class of natural products with a unique ring system. These alkaloids are targets for synthetic methodology development due to their diversity in nature and broad range of biological activities.[110-111] Unlike the previously discussed benzo[*b*]phenanthridine and jadomycin classes which are isolated from soil *Streptomyces sp.* of bacteria, benzo[*c*]phenanthridines on the other hand are secondary metabolites extracted and isolated from plant species.[97, 112]

3.4.1 Structures of benzo[*c*]phenanthridines

Members of this class of alkaloids are commonly isolated from Fumariacea, Papaveraceae and Rutaceae families of plants.[111] They are usually oxygenated at C-2, C-3, C-7 and C-8, although others with C-9 and C-10 oxygenation have also been isolated.[113] Some benzo[*c*]phenanthridines are quaternary alkaloids such as sanguinarine **149**, chelerythrine **150**, fagaronine **151** and nitidine **152**. Examples of non-quaternary natural products include decarine **153** and oxyterihanine **154** (**Figure 14**).

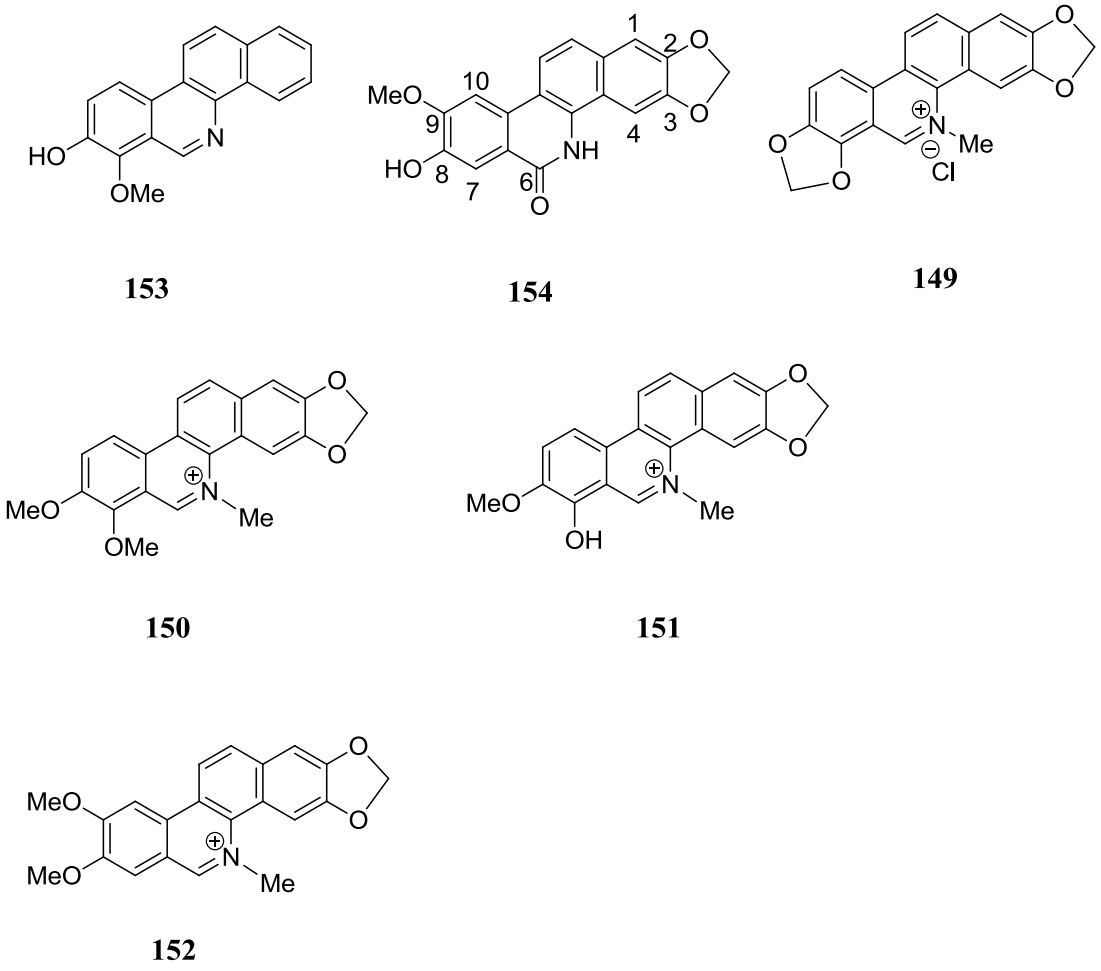


Figure 14: Examples of benzo[*c*]phenanthridines

These compounds have attracted attention because of their interesting biological activities which range from antileukemia activity, to inhibitors of DNA topoisomerases and both HIV-1 and HIV-2 reverse transcriptases.[114] The forthcoming section will highlight some of the biological activities displayed by these benzo[*c*]phenanthridines.

3.4.2 Biological activities

The biological activities of benzo[*c*]phenanthridines have been studied extensively. Fagaronine **151** and nitidine **152** were reported to show interesting antileukemic activities to the extent that they were the subject of preclinical studies at the National Cancer Institute in the early 1970s.[115] It has been suggested that the antitumour activity of **151** and **152** is due to the inhibition of DNA topoisomerase. This action is credited to their conformationally rigid structures.[114] Furthermore, chelerythrine **150**, sanguinarine **149**, nitidine **152** and fagaronine **151** also demonstrated excellent activities against cultured human cervical tumour cells (HeLa S3) *in vitro*, with reported IC_{50} values of 1.24, 0.16, 0.05 and 0.39 μg/Ml, respectively.[116] Additionally, **150** and **149** also inhibited protein kinase C (PKC).[117]

Sanguinarine **149** has also been reported to be a potent and selective inhibitor of mitogen-activated protein kinase phosphatase-1 (MKP-1). This phosphatase can protect cells from apoptosis caused by DNA-damaging agents or cellular stress through its overexpression in many human tumours. Sanguinarine **149** inhibited cellular MKP-1 with an IC_{50} value of 10 μM. It also exhibited selectivity for MKP-1 over MKP-3. Apart from the cellular MKP-1 inhibition, it inhibited both MKP-1 and the MKP-1-like phosphatase, MKP-L, *in vitro* with IC_{50} values of 17.3 and 12.5 μM, respectively.[118] More interestingly, the same compound was the most effective inhibitor of human choline acetyl-transferase (IC_{50} 284 nM) and was reported to further intercalate DNA, inhibiting DNA synthesis and HIV reverse transcriptase.[119]

The search for new synthetic methods for preparing these classes of natural products has been propelled by the toxicity of the most active members of these groups, and the consequent desire to study structure–activity relationships. The next section highlights the methodologies that have been developed for the synthesis of benzo[*b*]phenanthridine, jadomycin and benzo[*c*]phenanthridine classes of compounds.

3.5 Synthetic methodologies

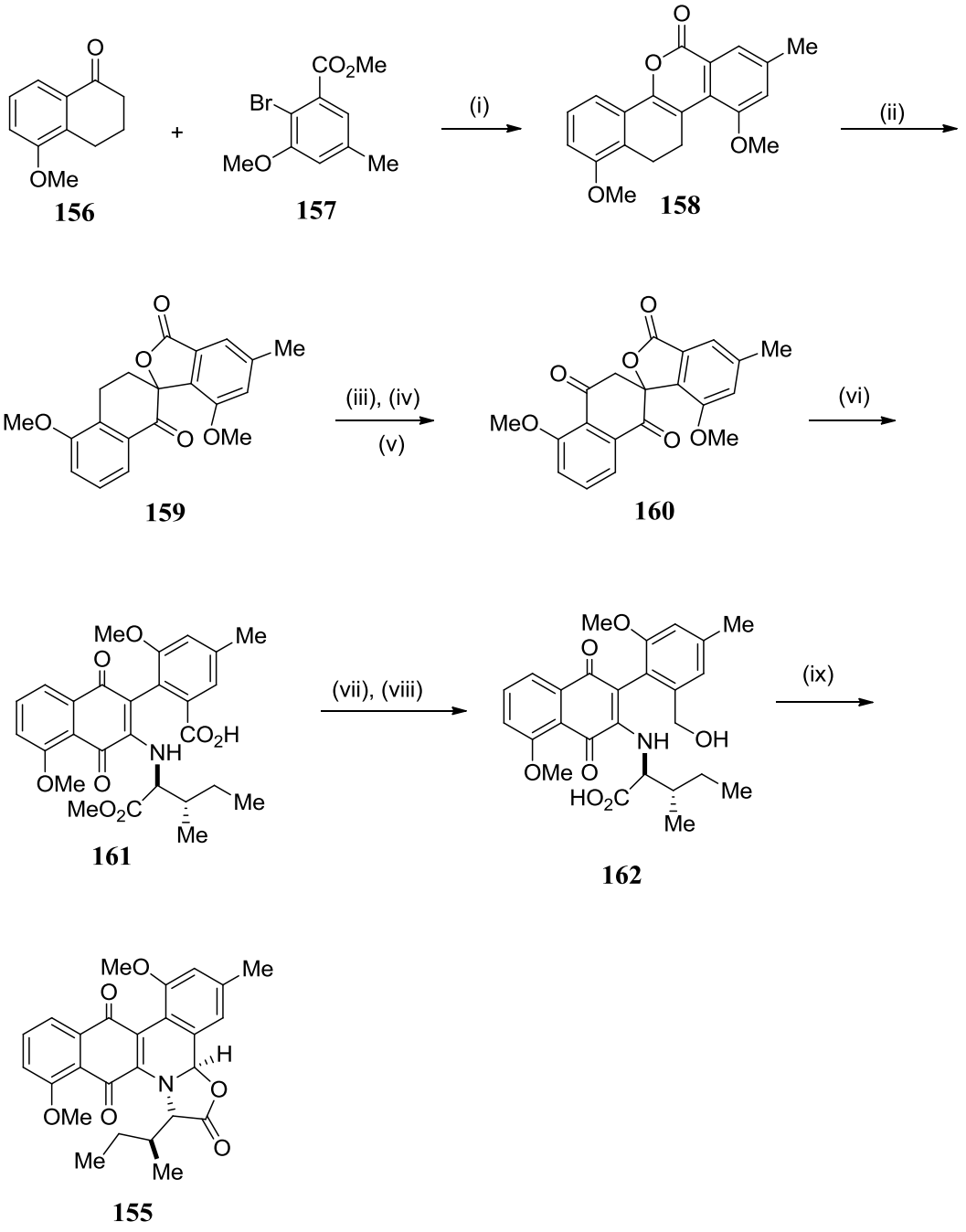
A number of approaches have been developed over the years to achieve the total synthesis of the natural products in these classes or for the assembly of the nitrogen incorporated tetracyclic cores.

3.5.1 Synthesis of jadomycins

There are only three recent reports in the literature on the total synthesis of jadomycins. These three synthetic strategies have been reported by O'Doherty's group, Ishikawa's group and finally by Yu and Young.[100, 120-121]

3.5.1.1 Ishikawas's jadomycin synthesis

Ishikawa and co-workers first reported the synthesis of dimethyl jadomycin A **155** as a proof of concept in constructing the 8*H*-benzo[*b*]oxazolo[3,2-*f*]phenanthridine skeleton.[120] In this strategy, they used an α-spiro-lactonedihydroquinone **160** as the key intermediate for the assembly of the jadomycin ring system (**Scheme 43**). Their synthesis commenced with a palladium catalysed enolate arylation coupling reaction of a tetralone derivative **156** and the bromobenzene derivative **157** followed by lactonization to assemble a benzo[*b*]naphthopyranone adduct **158**. Exposure of **158** to osmium tetraoxide afforded the α-spiro-lactone-tetralone derivative **159**, which, upon benzylic bromination, hydroxylation and subsequent 2-iodoxybenzoic acid (IBX) oxidation, gave the key intermediate α-spiro-lactonedihydroquinone **160**. Treatment of the diketone **160** with methyl isoleucinate furnished the acid **161**, which was subsequently reduced with the BH_3·THF complex, followed by the hydrolysis of the isoleucine methyl ester with LiOH, to give the biaryl amino intermediate **162**. Benzylic oxidation of the alcohol to facilitate condensation gave an iminium system, which was subsequently trapped by the carboxylate to furnish the pentacyclic oxazalone derivative **155**. Unfortunately, attempts to demethylate the intermediate to afford the target natural product jadomycin A **134** were unsuccessful.



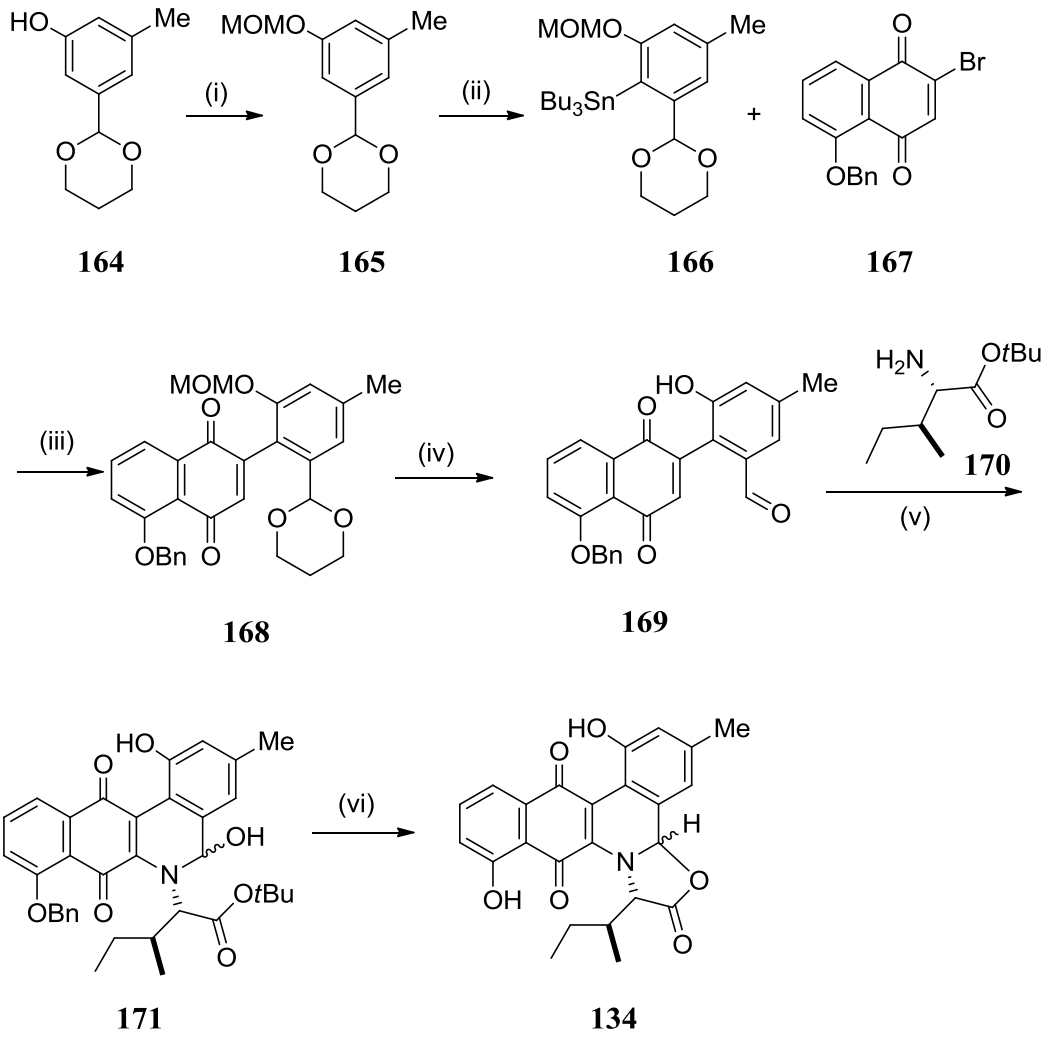
Scheme 43: Reagents and conditions; *(i) $Pd_2(dba)_3$, xantphos, K_3PO_4, $Na_2S_2O_5$, o-xylene, 130 °C, 5 h, 56%; (ii) OsO_4, NMO, acetone, CH_2Cl_2, H_2O, rt, 7 d, 95%; (iii) NBS, AIBN, benzene; (iv) TFH, H_2O; (v) IBX, DMSO 59% (over three steps); (vi) methyl isoleucinate, Et_3N, MeOH, H_2O, 60 °C, 2 d, 41%; (vii) BH_3.THF, 0 °C, 15 h, 36%; (viii) LiOH, THF, H_2O; (ix) MnO_2, CH_2Cl_2, rt, 40 h, 61%.*

3.5.1.2 O'Doherty's jadomycin synthesis

O'Doherty and co-workers recently reported the first ever synthesis of jadomycin A **134** and an analogue of jadomycin B **163**. The key step in the synthesis was a 6 π-electrocyclic ring closure reaction.[100] The synthesis exhibited in **Scheme 44** started with a commercially available phenol **164**, which was MOM protected to give the benzene derivative **165**. Directed *ortho*-metallation followed by exposure to tributyltin chloride afforded the stannane adduct **166**. Palladium mediated cross coupling between the stannane **166** and the benzyl-protected juglone moiety **167**, afforded the biaryl intermediate **168**, whose acetal protective group was subsequently cleaved to furnish an aldehyde in decent yield. Unfortunately, when this MOM protected aldehyde was subjected to a condensation reaction with the protected isoleucine amino acid **170** in the key step, the desired product was not formed owing to the negative *ortho-ortho* interactions between the quinone oxygen and the MOM group. The strategy was then modified by selective cleavage of the MOM protective group to give the phenolic aldehyde **169**, which, when subjected to the isoleucine **170** in the imine formation electrocyclic ring closure step, afforded the hemiaminal **171**. The phenolic group in this case contributed to the *ortho-ortho* positive-negative interaction through hydrogen bonding with the quinone. Acid hydrolysis of the *tert*-butyl ester to form the oxazalone pentacyclic ring, followed by benzyl deprotection, furnished the desired natural product jadomycin A **134**.

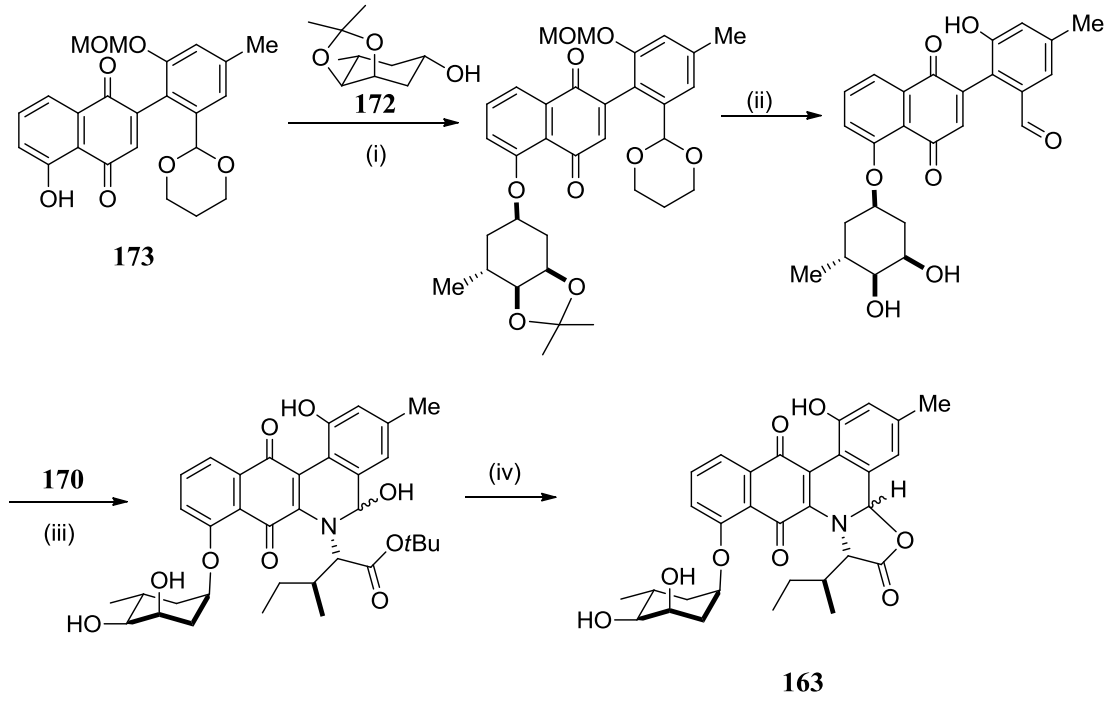
In the synthesis of an analogue of jadomycin B **163** (**Scheme 45**), an attempt to introduce the previously assembled cyclitol donor **172** to the synthesised jadomycin A **134** *via* the Mitsunobu cyclitolisation was not successful. Cyclitolisation was only successful on the debenzylated biaryl precursor **173**. Following the insertion of the carbasugar, the jadomycin B analogue **163** was synthesised by following the same scheme as used in the synthesis of jadomycin A.

a) Synthesis of jadomycin A



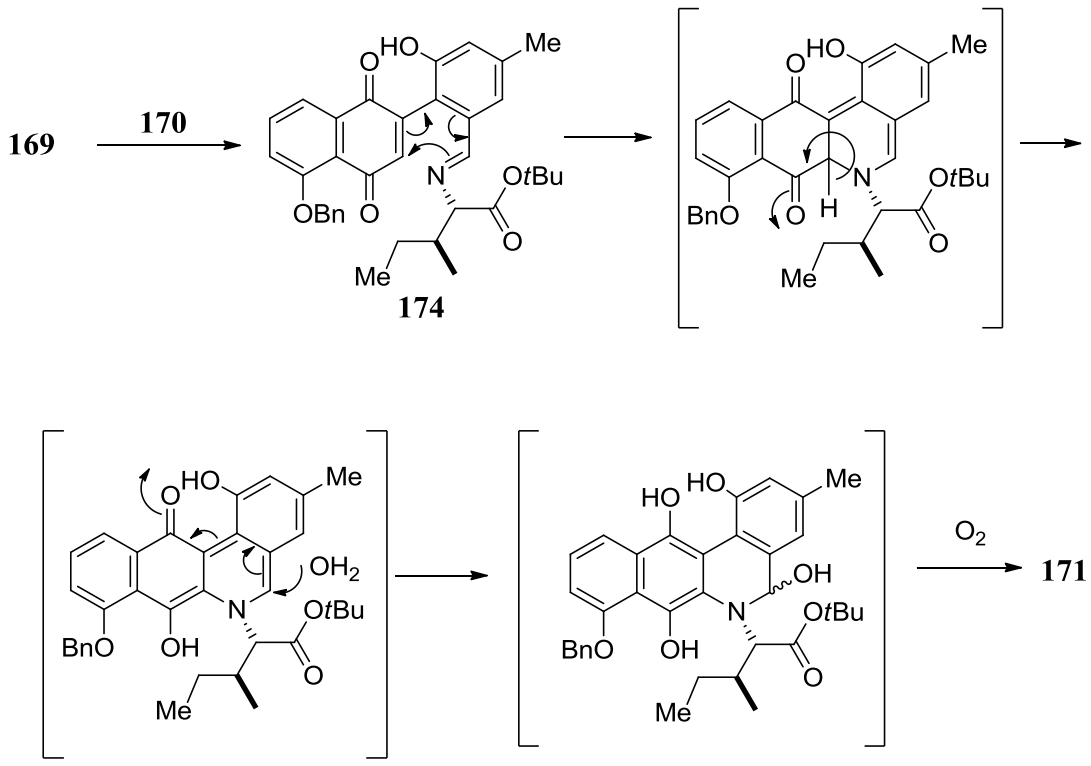
Scheme 44: Reagents and conditions*; (i) MOMCl, DIPEA, CH_2Cl_2, rt, 12 h, 68%; (ii) n-BuLi, Bu_3SnCl, hexane, 0 °C, 2 h, 68%; (iii) $Pd_2(dba)_3$, $CHCl_3$, PPh_3, CuI, THF, 75 °C, 12 h, 73%; (iv) HCl in MeCN, rt, 4-8 min, 77%; (v) isoleucine tert-butyl ester hydrochloride, toluene, rt, 24 h, 91%; (vi) TFA, rt, 2 d, 74%.*

b) Synthesis of jadomycin B analogue



***Scheme 45: Reagents and conditions**; (i) PPh_3, DIAD, THF, rt, 30 min, 91%; (ii) 2.4 M HCl/MeCN (1:5 v/v), 8 min, 59 %; (iii) isoleucine tert-butyl ester hydrochloride, toluene, rt, 24 h, 91%; (iv) TFA, rt, 2 h, 55%.*

The proposed mechanism for the 6 π-electrocyclic ring closure of the intermediate imine **174** is given in **Scheme 46**.

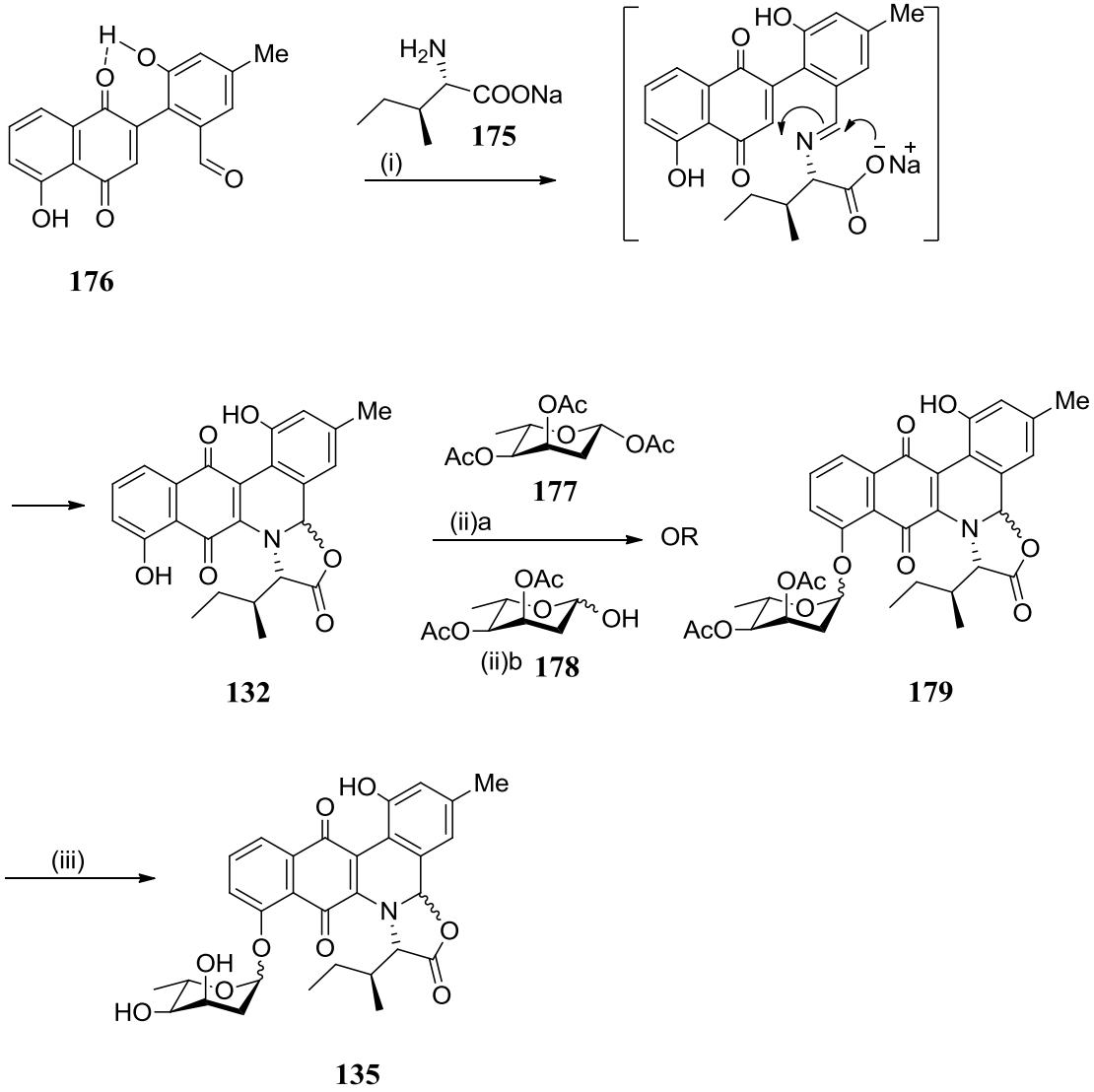


Scheme 46: Mechanism for a 6 π-electrocyclic ring closure

3.5.1.3 Yu's synthesis

Yu and Young have also reported a protective-group-free biomimetic synthesis of jadomycin A **134** which was then elaborated further to jadomycin B **135** .[121] Their strategy was a simple direct condensation of a naphthoquinone aldehyde with sodium L-isoleucinate as exhibited in **Scheme 47**. To accomplish this, isoleucinate **175** was added to a solution of naphthoquinone aldehyde **176** in tetrahydrofuran and the mixture stirred for 3 hours. Upon treatment with H^+ resin, the desired jadomycin A **132**, was isolated in a mediocre yield of 51%. Although other reaction conditions were tried, these conditions gave the best yield. Their initial glycosylation of **132** with 3,4-di-*O*-acetyl-L-digitoxosyl iodide prepared *in situ* from the acetate **177** was not successful due to the decomposition of the iodine adduct under the reaction conditions. To circumvent this, they opted to use the more stable glycosyl bromide which was also prepared *in situ* from the same acetate **177** using TMSBr and this

furnished the glycosyl coupled adduct **179** in a moderate yield of 25%, albeit with no α/β selectivity. The yield was improved to 64% with a 6:1 α/β ratio when the Mitsunobu conditions were applied and the amount of the donor was increased from 1.5 to 3.0 equivalents. In this case, the condensation of acetate **178** (3.0 equivalents) with **132** furnished the glycosyl adduct **179**. Base catalysed deacetylation of the glycosyl coupled adduct **179** afforded the desired jadomycin B **135** in very good yield.



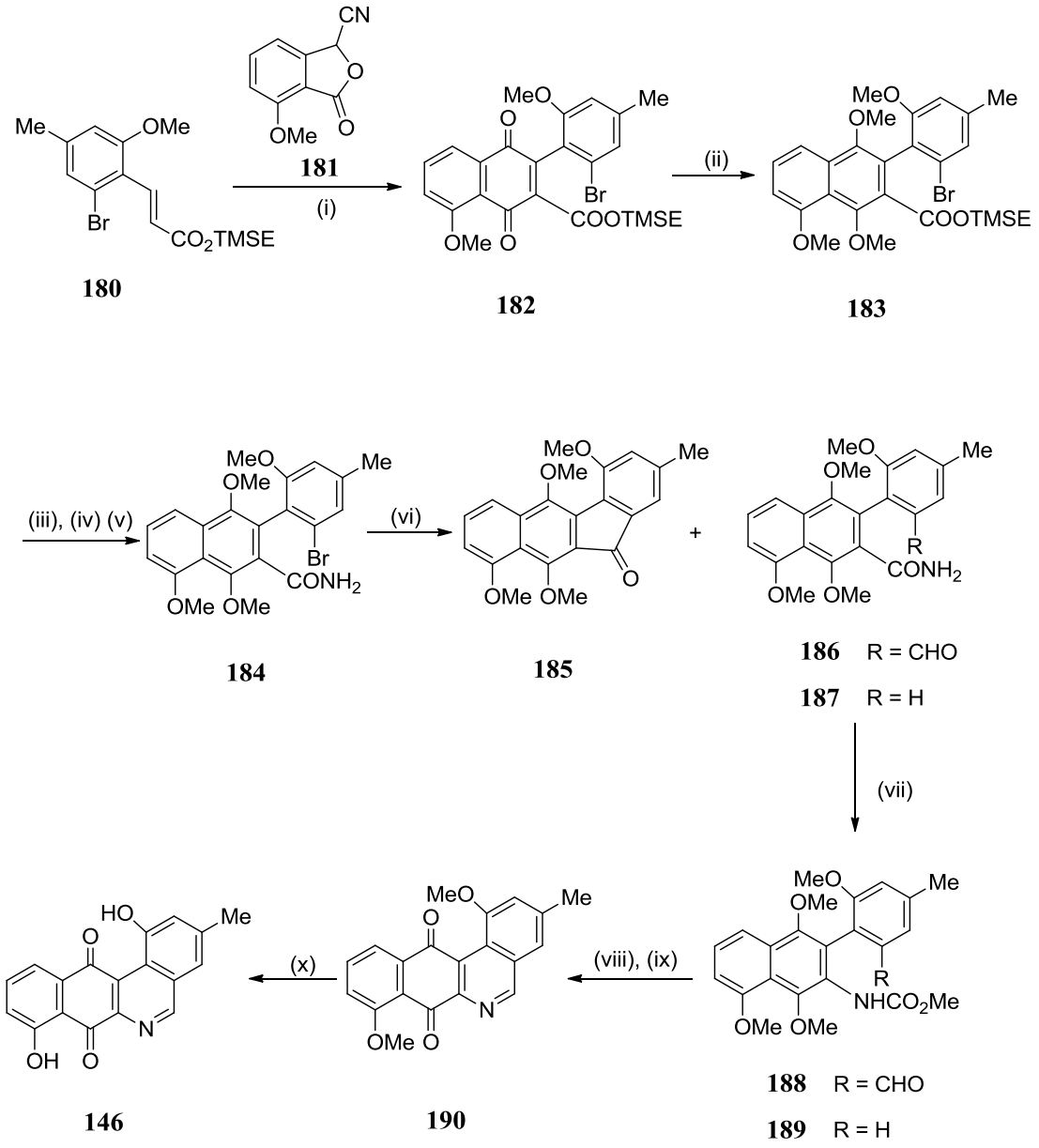
Scheme 47: Reagents and conditions*; (i) THF, rt, 3 h, then H^+ resin, 51%; (ii) a) TMSBr, CH_2Cl_2, 0 °C, then KHMDS, [18]C-6, 4 MS, THF, 0 °C, 25%; (ii) b) PPh_3, DEAD, 4 MS, toluene, -78 °C, 64%; (iii) 0.2 N NaOMe, MeOH/CH_2Cl_2, rt, 89%;*

3.5.2 Synthesis of Phenanthroviridone

Synthetic strategies for the assembly of the benzo[*b*]phenanthridine core of natural products have been reported in the literature, particularly in the total synthesis of phenanthroviridone **146**.[96, 122-124] The forthcoming sections will therefore give a synopsis of methods that have been developed, in particular highlighting Snieckus's, Gould's and Echavarren's synthesis of phenanthroviridone.

3.5.2.1 Gould's synthesis of phenanthroviridone

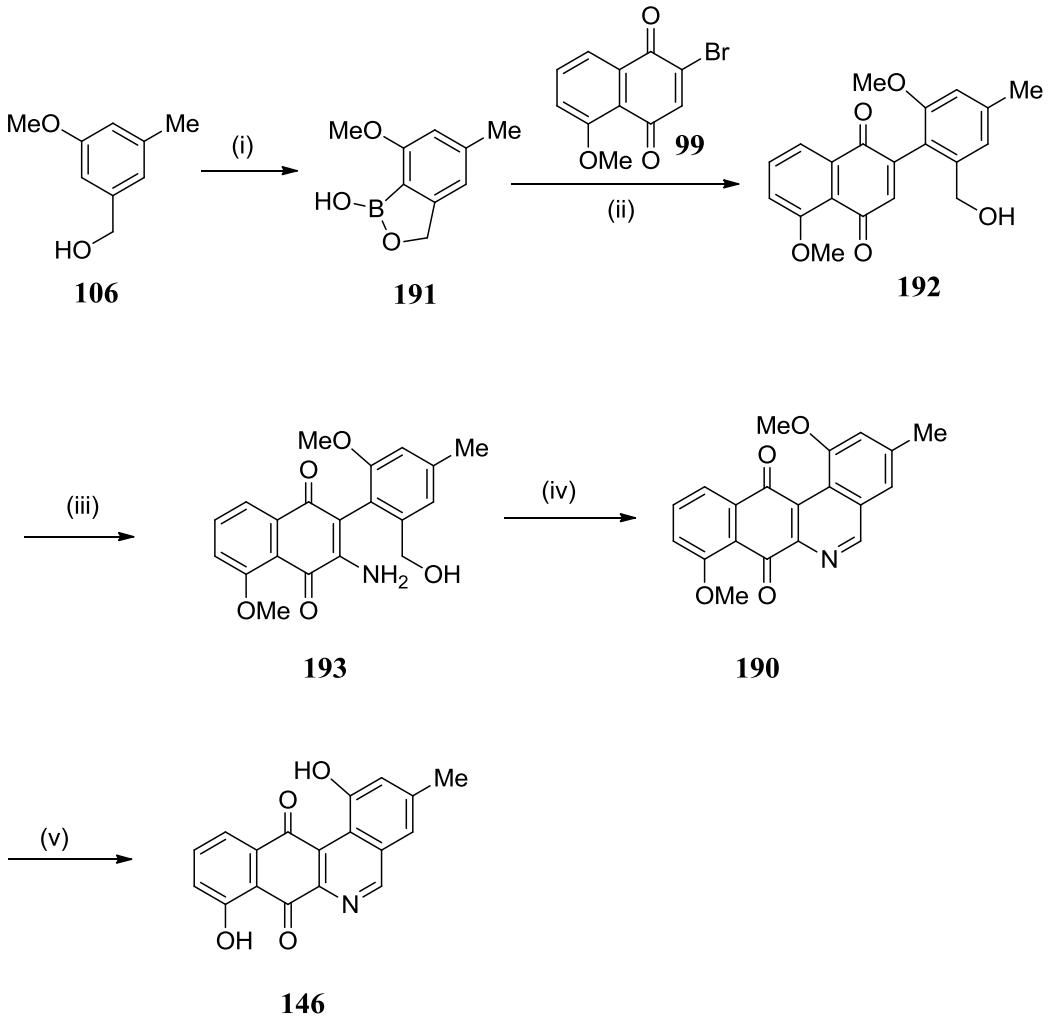
Gould and co-workers reported the first synthesis of phenanthroviridone **146**. The coupling reaction of a cyano phthalide and a bromo cinnamate was a key step in the synthesis.[122] To achieve this, a previously assembled bromo cinnamate **180** was treated with a cyano phthalide **181** to give an annulated product which was converted to the quinone **182** upon exposure to oxygen (**Scheme 48**). The quinone was then reduced to the corresponding biaryl naphthalene **183** and the ester substituent was then functionalised to give an amide **184** in 80% yield over three steps. Lithiation of the amide followed by a DMF quench afforded a chromatographically inseparable 1:1 mixture of the desired aldehyde **186** and the debrominated amide **187** along with traces of the fluorenone **185**. Subjecting the inseparable mixture to modified Hoffman rearrangement conditions gave a mixture of carbamates **188** and **189**, which, when quenched with water followed by reflux, led to the cyclisation of the carbamate **188** to afford the benzo[*b*]phenanthridine skeleton. This was then separated from **189** and oxidised to its corresponding quinone **190**. BBr_3 deprotection of the quinone furnished the desired phenanthroviridone **146** in quantitative yield.



Scheme 48: Reagents and conditions*; (i) t-BuOLi, THF, −78°C to rt, 20 h, then O_2, 68%; (ii) $Na_2S_2O_4$, Me_2SO4, K_2CO_3, acetone, reflux, 24 h, 77%; (iii) TBAF, THF; (iv) Tf_2O, pyridine; (v) aq. NH_3, 80 % (over three steps); (vi) t-BuLi, THF, −98 °C, then DMF; (vii) NaOMe, Br_2, MeOH,−54°C to 55°C; (viii) H_2O, NaOH, reflux; (ix) aq. NaOH, O_2; (x) BBr_3, CH_2Cl_2, −78°C, quant.*

3.5.2.2 Snieckus's synthesis of phenanthroviridone

Snieckus reported on a concise method for the synthesis of phenanthroviridine aglycone **146**. In the methodology, they used a combined Directed *Ortho*-Remote-Metallation (DORM) and Suzuki-Miyaura cross coupling strategy as a key step.[123] The synthesis commenced with the assembly of an oxaborole **191** from a benzyl alcohol **106** using a directed *ortho* metallation approach (**Scheme 49**).

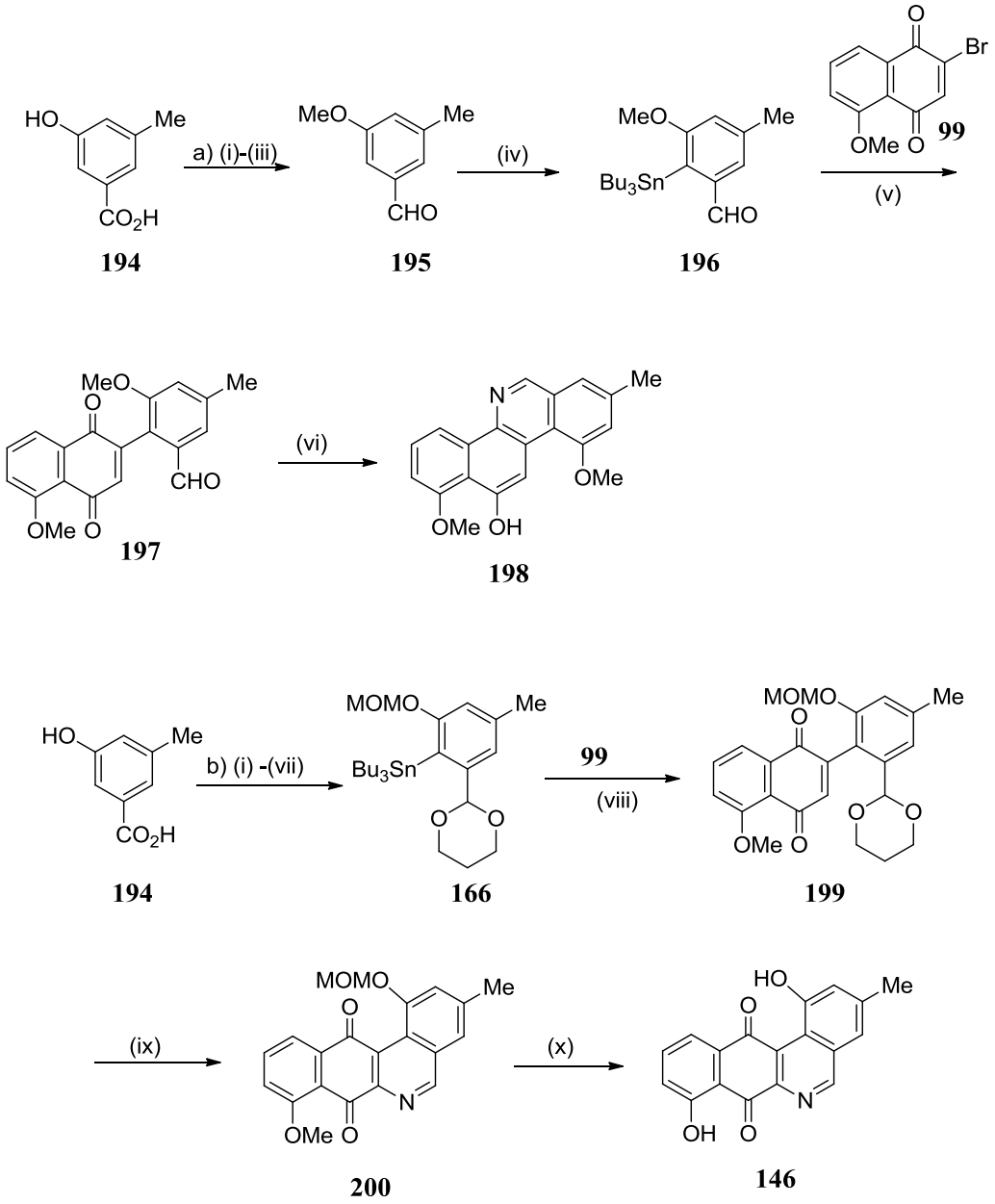


***Scheme 49: Reagents and conditions**; (i) n-BuLi, Et_2O, 0 to 25 °C, $B(OMe)_3$, 42%; (ii) $PdCl_2(dppf)$, K_3PO_4, DMF, rt, 62%; (iii) NH_3 (aq.), MeCN, 50%; (iv) MnO_2, CH_2Cl_2, rt, 78%; (v) BBr_3, CH_2Cl_2, −78 °C, quant.*

The oxaborole was then subjected to a Suzuki-Miyaura cross coupling with bromojuglone **99** to give the biaryl derivative **192**, which, upon exposure to aqueous ammonia, afforded the aminoquinone adduct **193**. Manganese dioxide mediated oxidation of the benzyl alcohol followed by imine condensation gave the benzo[*b*]phenanthridine skeleton **190** in good yield. BBr_3 deprotection furnished the target phenanthroviridine aglycone **146** in quantitative yield.

3.5.2.3 Echavarren's synthesis of phenanthroviridone

The synthesis of phenanthroviridone **146** has also been described by Echavarren. The use of palladium and copper catalysed coupling of organostannanes and bromo quinones was the key step in the synthesis.[96] This strategy was similar to the one used by O'Doherty and co-workers in the synthesis of jadomycin A **134** (**Scheme *50*44**).[100] Echavarren's synthesis, which is summarised in **Scheme 50**, started from the commercially available benzoic acid **194**. Methyl ether protection of the phenol group of **194**, reduction of the carboxylic acid to a benzyl alcohol followed by pyridinium chlorochromate (PCC) oxidation gave the aldehyde **195** in excellent yield. *Ortho*-metallation of the aldehyde was achieved using a protocol developed by Comins.[125] In this procedure, treatment of the aldehyde **195** with lithium amide of *N*,*N*,*N'*-trimethylethylenediamine, followed by addition of *n*-BuLi gave the aryllithium intermediate, which was subsequently quenched with *n*-Bu_3SnCl to afford the stannane derivative **196** in good yield. The Stille coupling of the aldehyde **196** with bromojuglone **99** gave the biaryl aldehyde **197**. Exposure of the aldehyde **197** to ammonia in a 1-4 Michael-type reaction with the quinone was not successful owing to the high reactivity of the exposed aldehyde. Instead, the benzo[*c*]phenanthridine **198** was isolated. To circumvent this challenge, the aldehyde was protected as an acetal **166** and the Stille coupling of this acetal **166** with bromojuglone **99** proceeded smoothly to yield the biaryl intermediate **199**. Exposure of this intermediate to ammonia gave a 2-aryl-3-aminoquinone which, when treated with aqueous acid, furnished the benzo[*b*]phenanthridine skeleton **200**. The formal synthesis of phenanthroviridone **146** was achieved by deprotection of **200**.



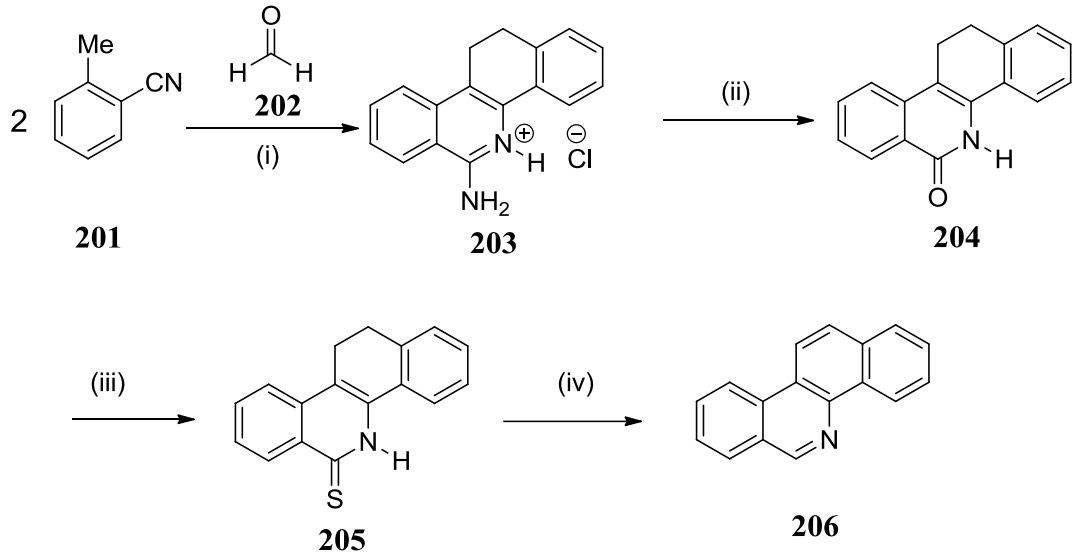
***Scheme 50: Reagents and conditions**; a) (i) MeI, K_2CO_3, acetone, 65 °C, 12 h, 86%; (ii) $LiAlH_4$, THF, 23 °C, 12 h, 90%; (iii) PCC, CH_2Cl_2, 23 °C, 2.5 h, 85%; (iv) N,N,N'-trimethylethylenediamine, n-BuLi, THF, −20 °C, 15 min; then n-BuLi, THF, −20 °C, 10 h; then n-Bu_3SnCl, −78 to 5 °C, 12 h, 85%; (v) $Pd(PPh_3)_4$, CuI, THF, 70 °C, 6 h, 65%; (vi) NH_4OAc, HOAc, 118 °C, 24 h, 21% b) (i) MeOH, H_2SO_4 (cat.), 23 °C, 14 h, 94%; (ii) DHP, PPTS (cat.), CH_2Cl_2, 23 °C, 48 h, 93%; (iii) $LiAlH_4$, THF, 23 °C, 13 h, 93%; (iv) PCC, NaOAc, CH_2Cl_2, 23 °C, 3 h, 81%; (v) 1,3-propanediol, TsOH, toluene, reflux, 3 h, 74%; (vi) MOMCl, iPr_2EtN, CH_2Cl_2, 40 °C, 24 h, 80%; (vii) n-BuLi, 0 °C; then n-Bu_3SnCl, 0 °C, 97%; (viii) $Pd(PPh_3)_4$, CuI, THF, 70 °C, 12 h, 85%; (ix) NH_4Cl, NaOAc, EtOH, 80 °C, 12 h; then aq. HCl, 1,4-dioxane, 23 °C, 3 h, 67%; (x) LiI, 2,6-lutidine, 140 °C, 6 h, 63%;*

3.5.3 Synthesis of benzo[*c*]phenanthridines

Having looked at the various methods that have been developed for the synthesis of jadomycins and benzo[*b*]phenanthridines in the preceding sections, this section will highlight some strategies that have been used for the assembly of benzo[*c*]phenanthridines. A number of synthetic strategies for this class of compounds have been reported in the literature.[95, 126-129] In the forthcoming sections, the Clement and Cho approaches will be discussed.

3.5.3.1 Clement's synthesis of the benzo[*c*]phenanthridine core

In this strategy, Kock and Clement explored the use of a potassium *t*-butoxide catalysed condensation reaction of 2 equivalents of a substituted benzonitrile and aliphatic aldehydes, to assemble the tetracyclic ring system.[95] The approach is summarised in **Scheme 51**. Subjecting paraformaldehyde **202** to a condensation reaction with 2 equivalents of 2-methylbenzonitrile **201** gave an amino substituted tetracyclic derivative **203** in moderate yields. Diazotisation of the amino group at the C-6 position with *t*-butylnitrite in dimethyl formamide afforded the 6-oxo derivative **204**, which, upon exposure to phosphorus pentasulfide, gave the 6-thio derivative **205** in very good yields. Desulfurisation of **205** by Raney nickel furnished the target benzo[*c*]phenanthridine **206**.

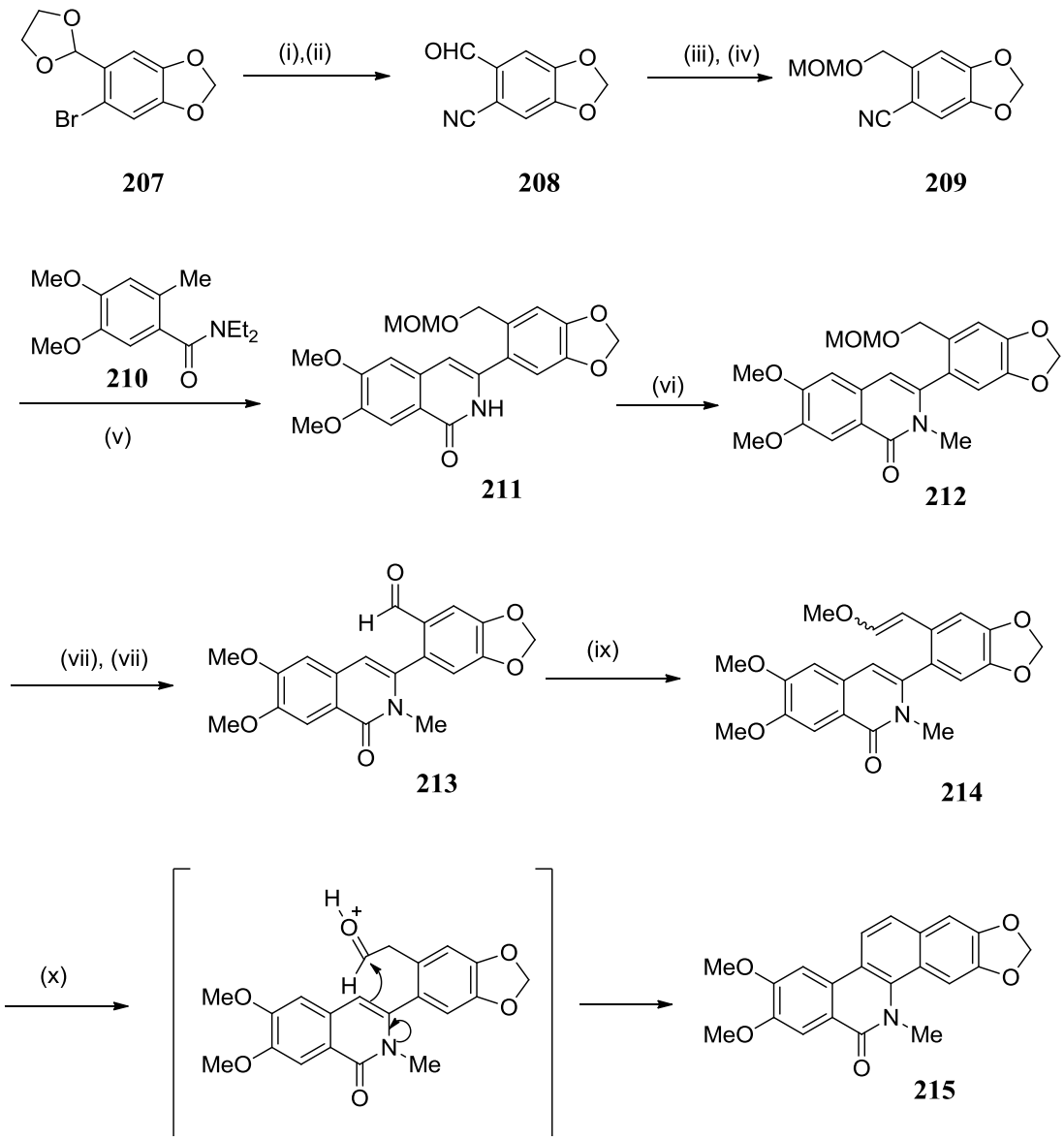


Scheme 51: Reagents and conditions*; (i) KO^{t}Bu, DMPU, 35-40 °C, 19%; (ii) t-butyl nitrile, DMF, 1 h, 55 °C, 72%; (iii) P_2S_5, pyridine, reflux, 2 h, 89%; (iv) Raney-Ni, DMF, EtOH, reflux, 1h, 44%.*

3.5.3.2 Cho's synthesis of oxynitidine and oxysanguinarine

Cho and co-workers also described the synthesis of benzo[*c*]phenanthridine analogues of the natural products nitidine **152** and sanguinarine **149**. Their approach involved the toluamide–benzonitrile cycloaddition reaction as a key step in the synthesis.[126] The synthesis began with the assembly of a substituted benzonitrile **208** from a bromobenzene adduct **207** (**Scheme 52**). The bromobenzene **207** was exposed to CuCN followed by acid catalysed deacetalisation to give the benzonitrile **208** in excellent yield. $NaBH_4$ reduction of the aldehyde followed by MOM protection of the resulting benzyl alcohol furnished the MOM protected benzonitrile precursor **209**. Exposure of **209** to *n*-BuLi deprotonated *N*-methyl-*O*-toluamide **210** gave the biaryl lactam derivative **211** in good yield. *N*- alkylation of the lactam with MeI gave the methylated derivative **212**. MOM deprotection of **212** followed by pyridinium dichromate (PDC) oxidation of the resulting alcohol gave the aldehyde **213**. Subjecting the aldehyde **213** to Wittig conditions afforded the olefin intermediate **214**, which, upon hydrolysis, furnished the desired oxynitidine **215**. The final

benzo[*c*]phenanthridine assembly is presumed to proceed via an enamide-aldehyde cyclisation as shown in **Scheme 52**.



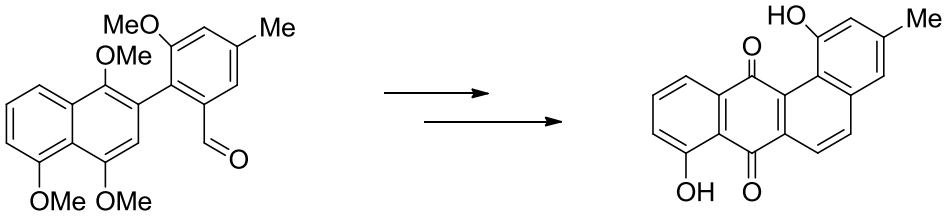
Scheme 52: Reagents and conditions*; (i) CuCN, DMF, reflux, 3h, 66%; (ii) 5% aq. HCl, MeOH, 50-60°C, 15 min, 100%; (iii) $NaBH_4$, AcOH, rt, 2 h, 78%; (iv) MOMCl, DIEA, CH_2Cl_2, 0 to 25 °C, 12 h, 92%; (v) n-BuLi, THF, −40°C, 4 h, 50%; (vi) NaH, THF, 0 °C, 1 h; then MeI, 0 to 60 °C, 78%; (vii) 10% aq. HCl, THF, reflux, 3 h; (viii) PDC, CH_2Cl_2, rt, 2 h, 85% (two steps); (ix) Ph_3PCH_2OMeI, n-BuLi, THF, 0 °C to rt, 4 h, 70%; (x) 10% aq. HCl, MeOH, reflux, 3 h, 88%.*

Having introduced nitrogen containing natural products and the synthetic routes that have been developed to access these aromatic natural products, the next chapter discusses our attempts to develop a method for constructing nitrogen containing aromatic compounds, and more specifically, to synthesise phenanthroviridone **146**.

Chapter 4: Results and Discussion benzo[*b*]phenanthridines and benzo[*c*]phenanthridines

4.1 Overview

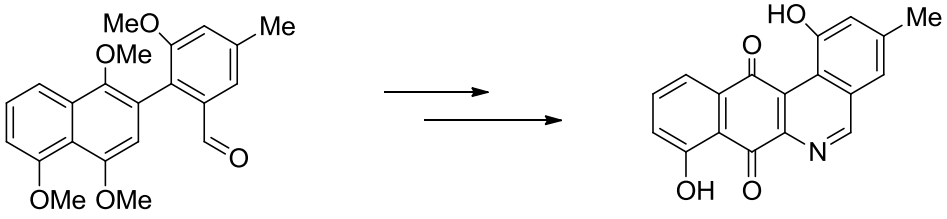
The work presented in this chapter draws on the results in Chapter 2 where we described the development of a new method for the assembly of tetrangulol, a natural angucycline antibiotic. We were able to synthesise the natural product tetrangulol from a key biarylbenzaldehyde intermediate **116**, as summarised in **Scheme 53**.



116 **2**

Scheme 53: Overview of tetrangulol synthesis

With the development of the above methodology, we were wondering if we could functionalise the same intermediate **116** to access aromatic nitrogen containing compounds, and particularly the phenanthroviridone **146**, as illustrated in **Scheme 54**.



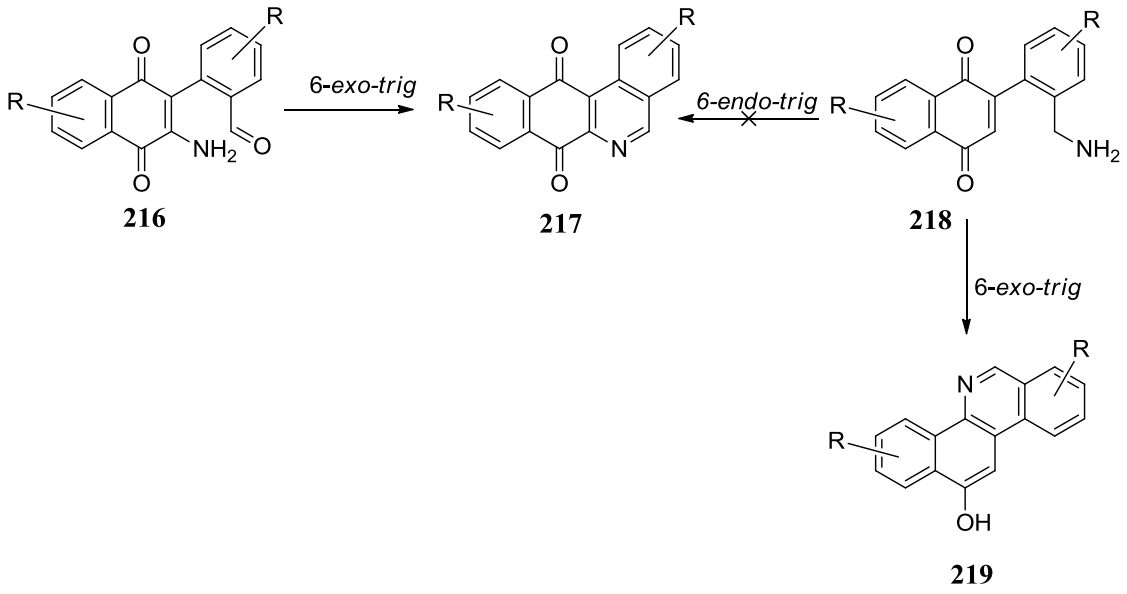
116 **146**

Scheme 54: Proposed overview of synthesis of phenanthroviridone

In order to accomplish the synthesis, we needed to add a nitrogen atom either on the naphthalene moiety or on the benzaldehyde substituent. The next section will discuss the development of a method for accessing phenanthroviridone **146**.

4.2 Development of a new synthetic method

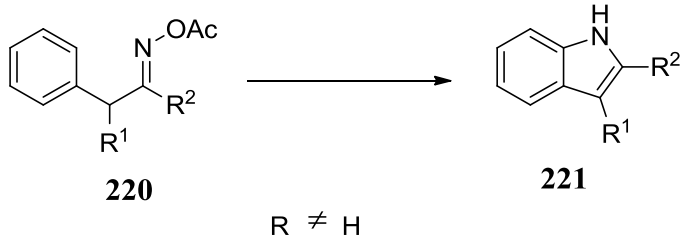
From previous studies on synthetic methodologies developed for the assembly of the benzo[*b*]phenanthridine-7,12-dione skeleton **217**, it could be concluded that for stereoelectronic reasons, ring B is best constructed by cyclisation of a 2-amino-3-phenylnaphthoquinone **216**, as opposed to an amine cyclisation onto the 3-position of the naphthoquinone **218**, which was observed to prefer a 1,2-addition at the C-1 positon of the quinone to give a benzo[*c*]phenanthridine skeleton **219**,[100] as displayed in **Scheme 55**.



Scheme 55: Regioselectivity of ring B formation

Since our intermediate compound **116** is a naphthalene as opposed to a naphthoquinone, we envisaged that the regioselectivity of 1,4- versus 1,2- additions might not be an issue. Hence we postulated that if we could convert the aldehyde of

116 to an oxime and use metal mediated amination methods to allow for the formation of a new nitrogen bond to an aromatic ring, this could facilitate the ring closure in constructing ring B. Examination of the literature for precedence in such protocols, we came across a report by Hartwig on the palladium catalysed amination of aromatic C-H bonds by oxime esters. Hartwig applied this procedure as a route to the synthesis of substituted indoles **221** from oxime esters **220**[130] as shown in **Scheme 56**.

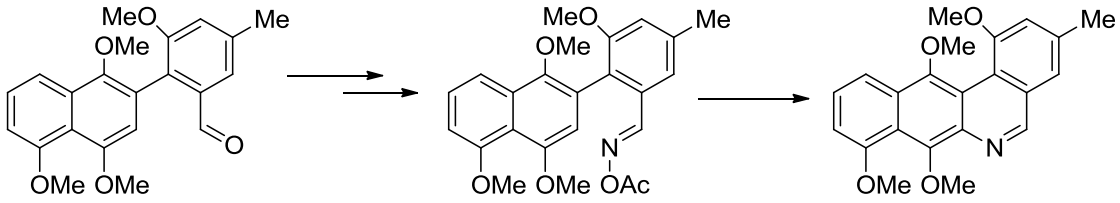


220 **221**

R ≠ H

Scheme 56: Reagents and conditions; *$Pd(dba)_2$, Cs_2CO_3, toluene, 150 °C, 24 h, 72%.*

With this idea in mind, we thought we could build on this method and apply it to the synthesis of the quinoline core which would give us the desired benzo[*b*]phenanthridine skeleton. To realise this, we planned converting the aldehyde **116** to an oxime ester **222** which, upon application of Hartwig's conditions, would furnish the desired benzo[*b*]phenanthridine skeleton **223**, as demonstrated in **Scheme 57**.

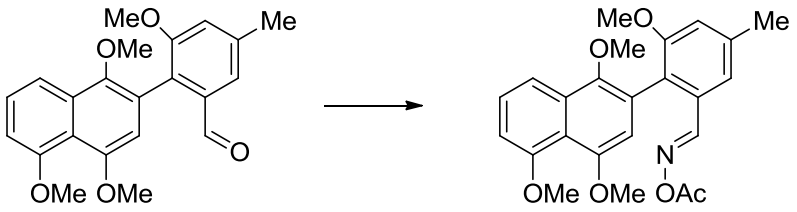


116 **222** **223**

Scheme 57: Proposed synthetic route for assembly of benzo[b]phenanthridine core

4.3 Synthesis of phenanthroviridone using the Hartwig approach.

Having developed our proposed synthetic pathway to access the targeted benzo[*b*]phenanthridine skeleton, we then embarked on the execution of this synthesis by converting the aldehyde **116** to the corresponding oxime ester as the first step (**Scheme 58**).

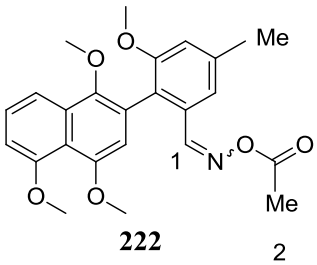


116 **222**

Scheme 58: Reagents and conditions*; $NH_2OH.HCl$, NaOAc, MeOH, reflux, 2 h, then TEA, AcCl, CH_2Cl_2, 0 °C to rt, 18 h, 86%.*

In order to accomplish the synthesis of the oxime ester **222**, benzaldehyde **116** in methanol was treated with hydroxylamine hydrochloride and sodium acetate. The reaction mixture was heated under reflux for 2 hours and then the solvent was removed *in vacuo.* To the residue in dichloromethane and triethylamine, acetyl chloride was then slowly added and the reaction mixture stirred at room temperature. Chromatographic purification of the crude product on silica gel furnished the acetyl oxime **222** as a yellow solid in 86% yield.

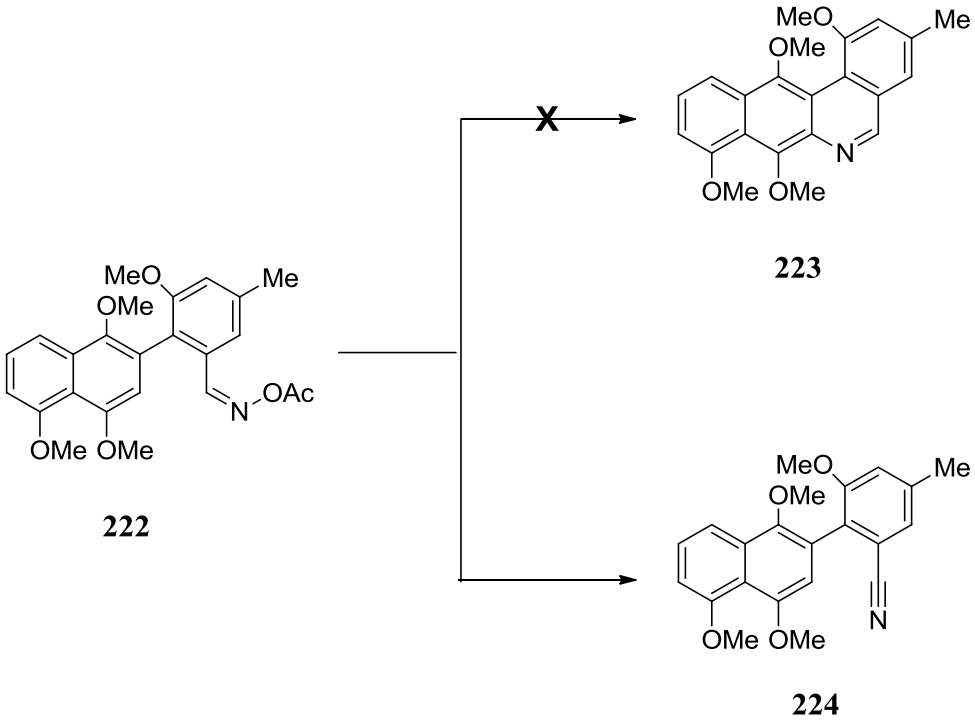
Examination of the ^{1}H NMR spectrum showed the unmistakable disappearance of the aldehydic proton and the appearance of two new singlet signals. The new singlet signal downfield integrating for one proton at δ 8.03 ppm corresponded to the imine proton H-1 and the other singlet signal integrating for three protons at δ 2.08 ppm was consistent with the acetyl methyl protons H-2. The ^{13}C NMR spectrum also showed the disappearance of the aldehyde carbonyl carbon signal and the appearance of an



222

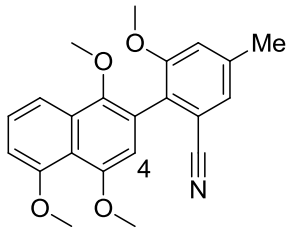
ester carbonyl signal at δ 168.6 ppm. Another new signal at δ 19.5 ppm collated well with the acetyl methyl carbon of the product. Additionally, in the analysis of HRMS, a molecular ion peak was observed at 423.1678 amu, which was in good agreement with the expected mass of 423.1676 amu for $C_{24}H_{25}NO_{6.}$

With our oxime ester in hand, the next step was to attempt the palladium mediated amination to assemble our desired nitrogen containing tetracyclic skeleton **223** of phenanthroviridone as illustrated in **Scheme 59**.



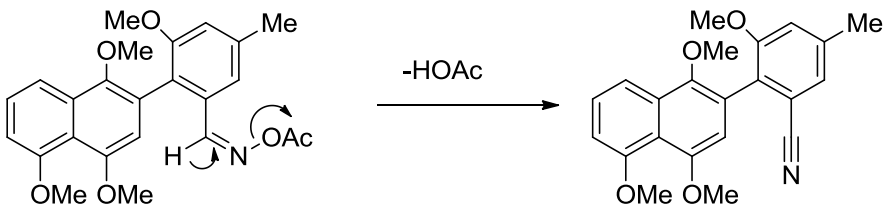
Scheme 59: Reagents and conditions; *$Pd(dba)_{2,}$ $Cs_2CO_{3,}$ toluene, 150 °C, 24 h, 62%.*

To this end, acetyl oxime **222** in toluene was treated with *bis*(dibenzylideneacetone)palladium(0) and cesium carbonate. The reaction was stirred at 150 °C for 24 hours. Upon purification of the crude product by column chromatography on silica gel, we isolated the benzonitrile **224** as a yellow solid in 62% yield, instead of the desired tetracyclic intermediate **223**. ^{1}H NMR spectroscopy unambiguously confirmed that the benzonitrile was formed by the distinctive disappearance of both the acetyl methyl proton signals at δ 2.08 ppm as well as the imine proton signal at δ 8.03 ppm. While the cleavage of the oxime ester was expected in the ring closure reaction, the disappearance of the imine proton was uncharacteristic. ^{13}C NMR spectroscopy also confirmed the disappearance of the ester carbonyl carbon signal and acetyl methyl carbon signal at δ 19.5 ppm and the appearance of the typical C≡N signal at δ 118.9 ppm. Furthermore, the presence of the nitrile was confirmed by the appearance of the C≡N stretch at 2364.7 cm^{-1} in the FTIR spectrum. Additionally, the HRMS showed a molecular ion peak at 363.1473 amu (100%), which correlated well with the expected mass of 363.1465 amu for $C_{22}H_{21}NO_4$.



224

Carefully examination of the oxime ester lead to the rational that the formation of benzonitrile **224** resulted from elimination of acetic acid from the oxime ester under the reaction conditions. The proposed mechanism is illustrated in **Scheme 60**.



222 **224**

Scheme 60: Mechanism for formation of benzonitrile

With these results, we revisited the model studies done by Hartwig in the synthesis of substituted indoles. We realised that these were conducted on ketones rather than aldehydes and hence the imine proton would be replaced with an alkyl substituent, which then made it impossible for any elimination reaction to take place. If our imine proton was replaced by an alkyl substituent, we believe our key reaction could have probably been successful. At this point, it therefore meant that the use of this methodology on our scaffold to access the benzo[*b*]phenanthridine skeleton was not viable and hence we needed to look at alternative strategies to construct the desired aromatic skeleton. We immediately embarked on the development of an alternative strategy. The following section will discuss the alternative synthetic route that we developed.

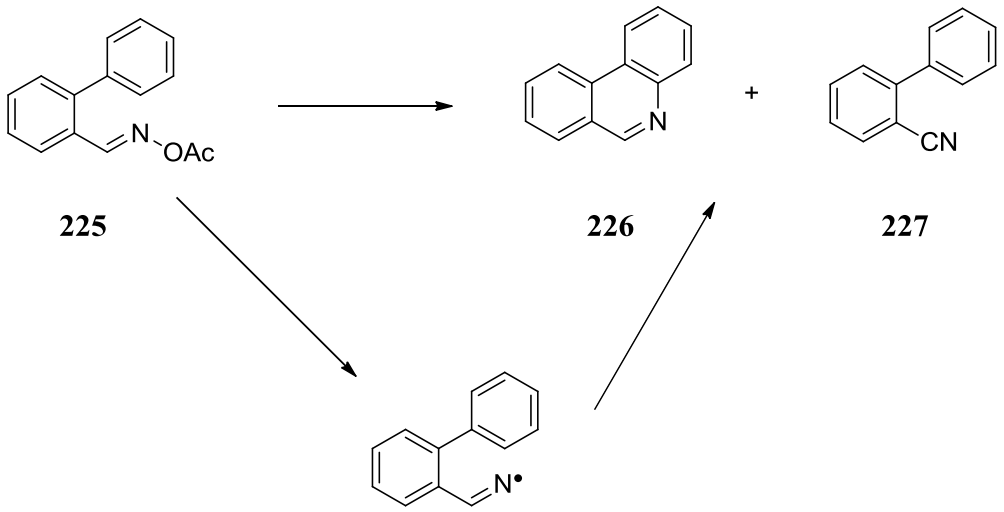
4.4 Development of an alternative synthetic route

With the failure of our strategy to use a palladium mediated amination method of an aromatic C-H bond, we went back to the literature to ascertain if other strategies for the construction of *N*-heterocycles from oximes existed. We came across two reports by Rodriguez and Walton where they used oxime esters and ethers respectively to assemble *N*-heterocycles *via* iminyl radicals.

4.4.1 Rodriguez assembly of *N*-heterocycles

Rodriguez and co-workers reported a light-induced iminyl radical cyclisation reaction of acyloximes derived from aldehydes to isoquinolines. Building on the principle that acyloximes can be used as photo initiators for UV curable coatings, they hypothesised that the iminyl radical so formed could cyclise to construct six membered heterocyclic compounds.[131] Iminyl radicals are easily generated owing to the ease of the cleavage of the N-O bond upon irradiation. Using light to induce

radicalisation, they successfully assembled *N*-heterocycles using this approach as illustrated in **Scheme 61**.



225 **226** **227**

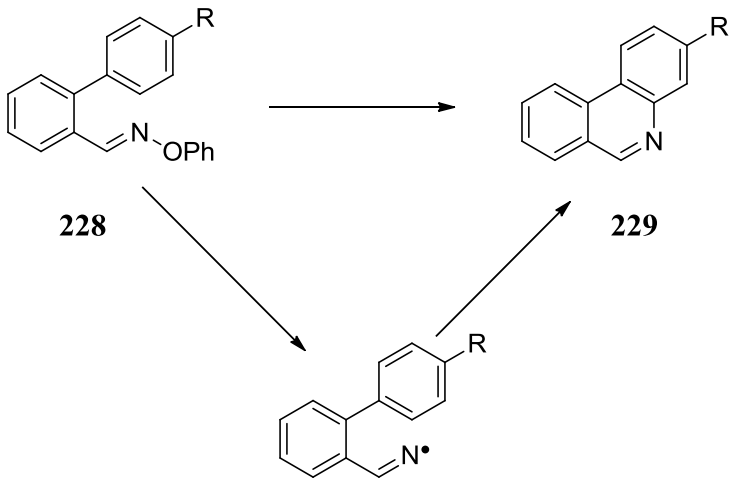
Scheme 61: Reagents and conditions*; hv, Pyrex, t-butanol,* ***226****-58%;* ***227****-28%.*

Utilising this synthetic methodology, they found that exposure of oxime ester **225** in *tert*-butanol to UV light through Pyrex gave the desired cyclised compound **226**, as well as the benzonitrile **227**, in an almost 2:1 ratio. Although a number of solvent systems were evaluated for the reaction, *tert*-butanol gave the best yield of the heterocyclic compound **226** (58%) versus the benzonitrile **227** (28%). This is due to *tert*-butanol being effective in breaking intramolecular H-bonding which facilitates elimination of acetic acid through a pericyclic type of reaction, leading to the formation of the benzonitrile. Although 2-propanol gave the lowest yield of the undesired benzonitrile **227** (8%), the yield for the phenanthridine was also very modest (25%). Use of non-polar solvents like hexane led to considerably higher yields of the benzonitrile **227** as compared to the desired tricyclic compound **226**.

4.4.2 Walton's approach to the synthesis of *N*-heterocycles

Apart from UV light induced formation of iminyl radicals, they can also be easily generated by thermolysis. Watson and co-workers reported on the microwave assisted

synthesis of *N*-heterocycles from *O*-phenyl oximes which proceeded *via* the same iminyl radical.[132] In their account, previously assembled oxime ether **228** was subjected to microwave irradiation in the presence of an ionic liquid and *tert*-butylbenzene to furnish the desired phenanthridine product **229** as exhibited in **Scheme 62**.



***Scheme 62: Reagents and conditions**; t-BuPh, EmimPF$_6$, MW 160 °C, 30 min, 78%.*

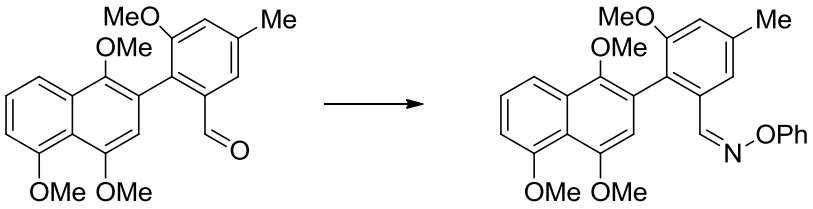
The ionic liquid EmimPF$_6$ was added to compensate for the dielectric loss factors of solvents and increase the microwave absorbance level of the medium.[132] In using this protocol, better yields of the phenanthridine products **229** were obtained as compared to the UV mediated protocol, and the elimination of the acetic acid was not observed. This was an interesting observation from our perspective.

We decided to assess the feasibility of both methodologies for the synthesis of our desired benzo[*b*]phenanthridine skeleton.

4.5 Microwave and UV assisted synthesis of benzo[*b*]phenanthridine

As a starting point, we decided to test the microwave assisted method for the intramolecular cyclisation of an oxime ether to furnish the desired nitrogen containing

tetracyclic derivative. To achieve this, we needed to convert our biarylbenzaldehyde **116** to an oxime ether derivative **230**, as demonstrated in **Scheme 63**.

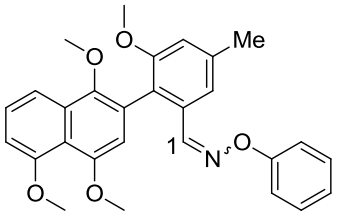


116 **230**

***Scheme 63: Reagents and conditions**; $NH_2OPh.HCl$, pyridine, rt, 18 h, 93%.*

O-Phenylhydroxylamine hydrochloride was therefore dissolved in anhydrous pyridine and the benzaldehyde **116** was added in one portion. The reaction was stirred at room temperature for 18 hours. The crude product was purified by column chromatography to furnish the *O*-phenyl oxime **230** as a yellowish-brown solid in 93% yield.

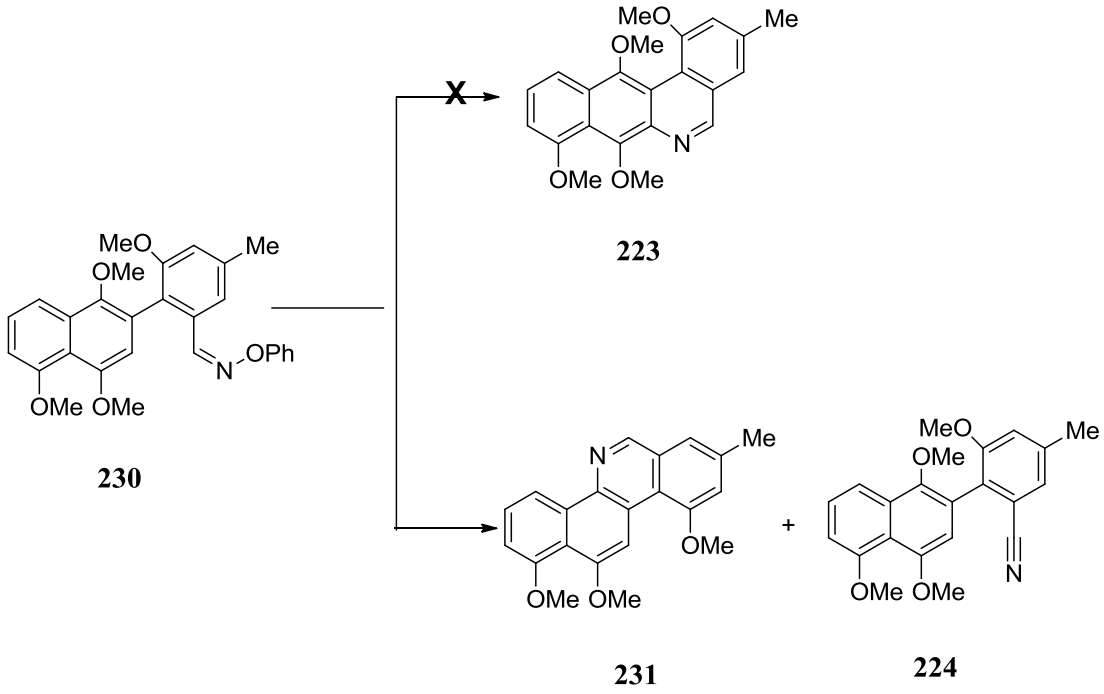
^{1}H NMR spectroscopy unequivocally proved the formation of the product by the unmistakable disappearance of the aldehyde proton signal and the appearance of a new singlet signal at δ 8.12 ppm, which correlated with the imine proton H-1. Furthermore, the increase in the number of aromatic proton signals from six to eleven confirmed the addition of the *O*-phenyl group. More evidence was provided by the ^{13}C NMR spectrum as it showed the disappearance of the aldehyde carbonyl signal and the appearance of new aromatic carbon signals. Additionally, analysis of the HRMS showed a molecular ion mass peak at 457.1890 amu which was in good agreement with the expected mass of 457.1883 amu for $C_{28}H_{27}NO_5$.



230

Although the oxime ether was synthesised as a mixture of E and Z isomers, no attempt was made to separate the two isomers as both of them should form the same iminyl radical in the first step of the cyclisation reaction. With our oxime ether in

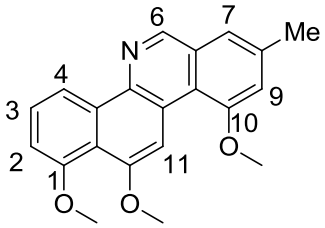
hand, we then embarked on the execution of the key step in our synthesis, which was the microwave promoted intramolecular cyclisation *via* an iminyl radical, as illustrated in **Scheme 64**.



Scheme 64: Reagents and conditions*; EmimPF$_6$, t-BuPh, MW 300 W, 160 °C, 20 min,* ***231*** *-58% and* ***224****-11%.*

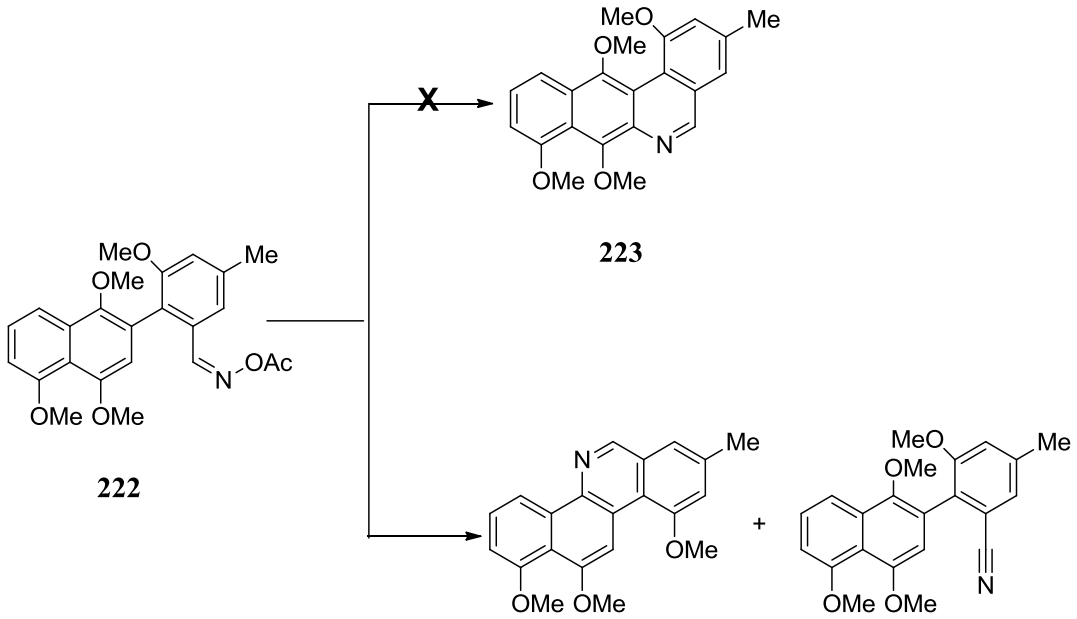
In order to achieve the intramolecular cyclisation, *O*-phenyl oxime **230** and EmimPF$_6$ were dissolved in *tert*-butylbenzene in a microwave reactor tube. The tube was sealed and the reaction mixture subjected to microwave irradiation. To our surprise, upon purification of the crude product by column chromatography, we isolated the benzo[*c*]phenanthridine **231** as a yellow solid in 58% yield, along with the benzonitrile **224** in 11% yield. We initially thought we had formed the benzo[*b*]phenanthridine, albeit with the loss of one methoxy group, but on detailed examination of the spectrum, it was evident that we had constructed the benzo[*c*]phenanthridine **231.** ^{1}H NMR spectroscopy proved that we had formed the benzo[*c*]phenanthridine skeleton. The most deshielded singlet signal integrating for one proton at δ 9.15 ppm correlated to H-6 and the doublet of doublet signal at δ 9.13

ppm (J = 8.4 and 0.7 Hz) was consistent with H-4. The singlet at δ 8.87 ppm was assigned to be due to H-11. In order to ascertain which methoxy group out of the four was no longer present and also to further confirm the assignments of the two singlet signals at δ 9.15 and 8.87 ppm, HSQC and HMBC spectroscopy were used. Using HMBC spectroscopy, both H-2 and H-3 were coupling to a methoxy carrying carbon signal at δ 156.8 ppm, which was assigned to be C-1. H-9 had strong correlation with another methoxy carrying carbon signal at δ 157.8 ppm, which was assigned to be C-10. The singlet at δ 8.87 ppm was strongly correlated to another methoxy carrying carbon signal at δ 155.4 ppm, which we assigned to be C-12. The proton H-7 was also observed to have a lower coupling correlation with a carbon at δ 149.0 ppm and from the HSQC spectrum, this carbon was carrying the most deshielded proton at δ 9.15 ppm and we consequently assigned that carbon to be C-6. Additionally, upon analysis of HRMS, a molecular ion peak was observed at 333.1368 amu which was in good agreement with the expected mass of 333.1361 amu for phenanthridine **231**.



231

Having obtained this unexpected result of assembling the benzo[*c*]phenanthridine skeleton as opposed to the benzo[*b*]phenanthridine core under microwave conditions, we then decided to attempt the UV mediated synthesis of *N*-heterocycles from oxime esters as shown in **Scheme 65**.



Scheme 65: Reagents and conditions*; t-butanol, UV (450 W),* ***231*** *- 46% and* ***224*** *- 18%.*

To accomplish this, previously prepared oxime ester **222** was introduced into a UV reactor with *tert*-butanol and the reaction mixture was subjected to UV irradiation. Purification of the crude product by column chromatography, once again furnished the same benzo[*c*]phenanthridine **231** in 46% yield and the benzonitrile **224** in 18% yield.

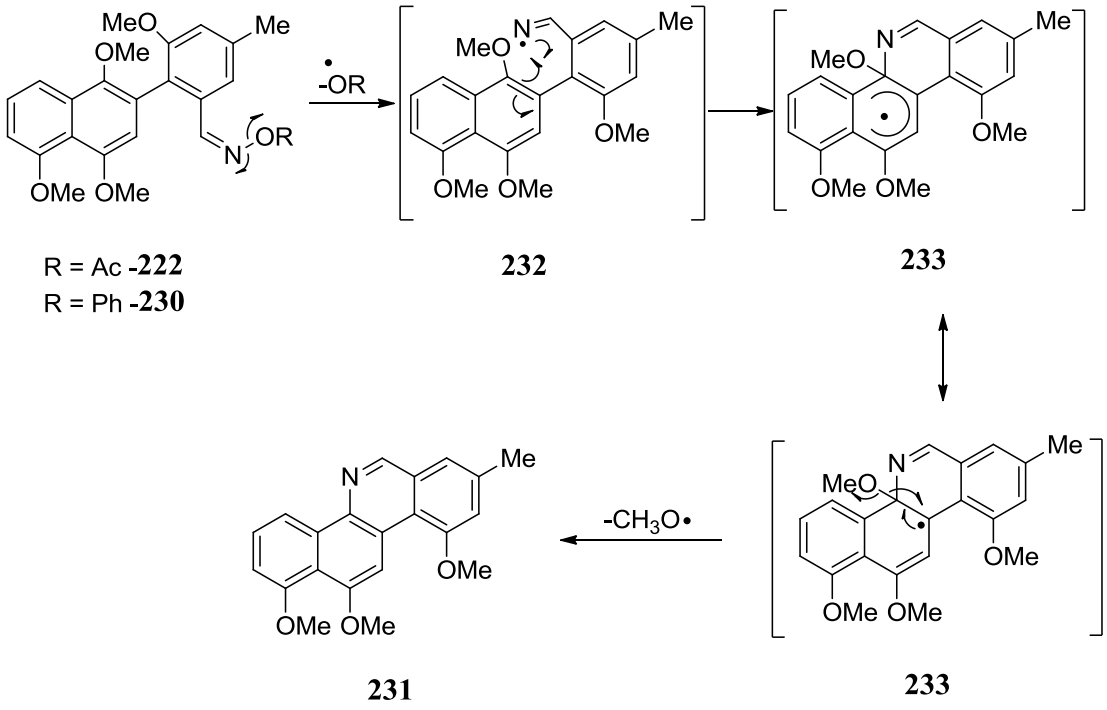
Both the microwave assisted and the UV mediated methods gave us the same products, albeit in different ratios. The microwave method gave a better yield of the benzo[*c*]phenanthridine compared to the UV mediated method.

Having obtained these unexpected results, we wanted to find out how the benzo[*c*]phenanthridine skeleton could be formed under the radical mechanism from an oxime ester or ether derivative. We hoped that by unravelling a possible

mechanism, we could rationalise why we were not forming the benzo[*b*]phenanthridine.

4.6 Mechanism for the assembly of benzo[*c*]phenanthridine skeleton

Since the reaction proceeds via an iminyl radical, we postulated that the first step involves the homolytic cleavage of the N-O bond in the ester **222** or ether **230** assisted by either thermolysis or UV irradiation to furnish the same iminyl radical **232** (**Scheme 66**).



Scheme 66: Mechanism for assembly of benzo[c]phenanthridine

The iminyl radical **232** could then cyclise by breaking the aromaticity of ring C to furnish the tetracyclic delocalised radical intermediate **233**. Homolytic cleavage of the ArC-OMe bond allows for the rearomatisation of ring C to furnish the benzo[*c*]phenanthridine **231**. We hypothesise that if the benzo[*b*]phenanthridine skeleton was formed, in the final rearomatisation step, it would be energetically

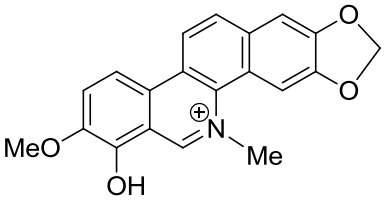
unfavorable to cleave an aromatic C6b-H bond homolytically as opposed to an ArC-O bond cleavage by homolysis to eliminate the methoxy radical in forming a benzo[*c]*phenanthridine skeleton. The presence of the methoxy group on the C-1 of the naphthalene ring afforded an easier and more energetically favored pathway to the cyclisation. Detailed mechanistic studies however need to be carried out to confirm this hypothesis.

4.7 Conclusion

In summary, we had planned to develop methodology for the synthesis of nitrogen containing phenanthroviridone **146** by functionalising a key intermediate which we used in the synthesis of tetrangulol **2**. Although we did not succeed in the synthesis of phenanthroviridone **146**, in this PhD we have serendipitously found a UV promoted or microwave assisted radical based strategy to assemble and access the biologically important benzo[*c*]phenanthridine alkaloids and other related natural products.

4.8 Future Work

Having found a method for making the benzo[*c*]phenanthridine skeleton, it could be worthwhile to apply this method to the synthesis of natural products that possess a benzo[*c*]phenanthridine core, for example, fagaronine **151**, nitidine **152** and decarine **153**. In this way, the limits and indeed the versatility of this method as a useful strategy could be unravelled.



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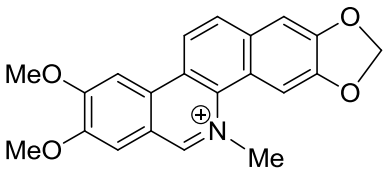

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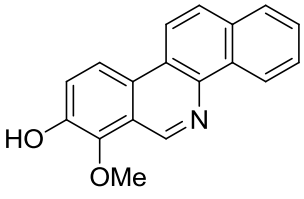
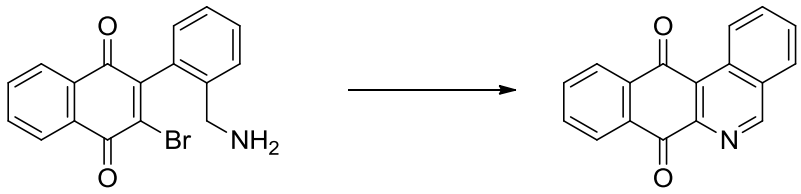


153

Secondly, detailed mechanistic studies to confirm the proposed mechanism need to be undertaken. A number of substituents could be varied on both the C-1 and C-3 positions of the naphthalene ring to decipher the effect of substituents on the *6-endo-trig* cyclisation that furnishes the benzo[*b*]phenanthridine versus the *6-exo-trig* cyclisation that gives the benzo[*c*]phenanthridine core.

4.9 Conception of a new project

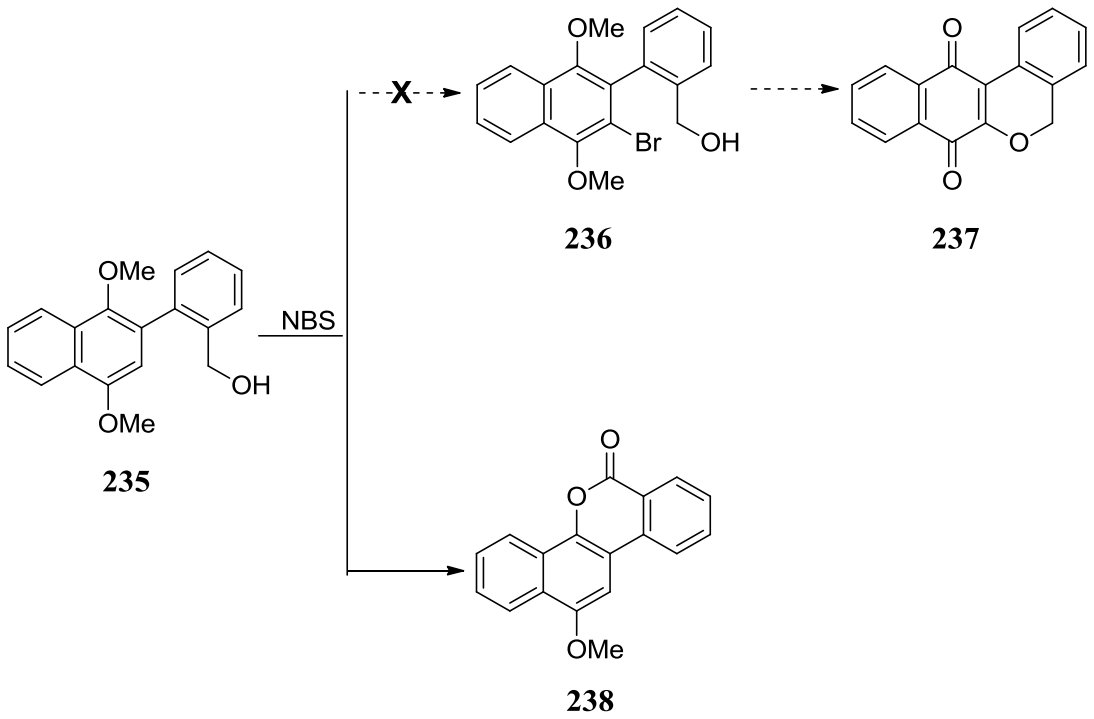
In **section 4.2**, it was highlighted during the discussion on regioselectivity of ring B formation that a *6-endo-trig* 1,4- addition type of cyclisation of a phenyl amine onto the C-3 position on a naphthoquinone does not occur, and instead a 1,2 addition-type *6-exo-trig* cyclisation onto the C-1 carbon of a quinone is preferred. However, if there is a halogen (e.g. bromine) on the C-3 position, then a 1,4- Michael-type *6-endo-trig* cyclisation furnishes the benzo[*b*]phenanthridine-7,12-dione skeleton as displayed in **Scheme 67**[133].



234 **217**

Scheme 67: Cyclisation of bromo quinone

This cyclisation was confirmed by Dr Priyamvada Pradeep, a former PhD student in our group at Wits University. In this project, we wanted to build on this strategy to synthesise oxygen containing analogues of natural products by cyclising a benzyl alcohol **236** onto the bromonaphthalene motif to give the cyclised oxygen containing skeleton **237** as exhibited in **Scheme 68**.



Scheme 68: NBS mediated synthesis of Benzo[b]naphthopyranone

Miss Chevonne Reynolds, then an MSc student in our group, pioneered this work. When the benzyl alcohol **235** was subjected to the NBS bromination, a benzo[*b*]naphthopyranone derivative **238** was isolated instead of the desired naphthylphenyl derivative **236**. On examination of the literature, we were pleased to notice that there are a number of natural products that contain a benzonaphthopyranone core. What was even more interesting was that three subclasses of such compounds, namely gilvocarcins, ravidomycins and chrysomycins, belong to the angucycline class of natural products.

Following this discovery, there were a number of questions for which we did not have answers. Could this discovery be a general method for the assembly of benzonaphthopyranone angucycline antibiotics? What would be the scope of such reactions? What could be the limitations of this strategy in the synthesis of

benzonaphthopyranone skeletons? These were some of the questions this PhD investigation aimed to unravel.

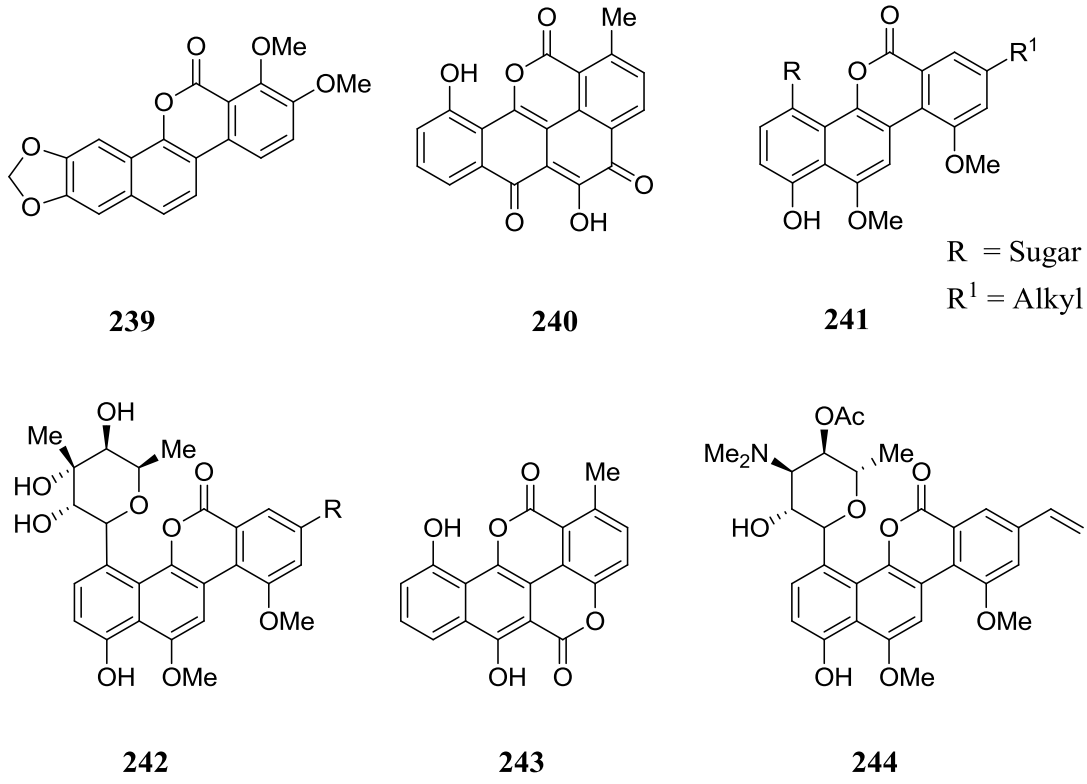
Building on this previous work, the forthcoming chapter of this PhD thesis (Chapter 5), will introduce the three sub classes of benzonaphthopyranone angucycline natural products and their associated biological activities. Furthermore, some selected synthetic strategies to these types of natural products are also highlighted. Following this introduction, results on the synthetic studies on the NBS mediated synthesis of benzonaphthopyranone skeletons are presented and discussed in Chapter 6.

CHAPTER 5: Benzonaphthopyranone Antibiotics: Introduction and Literature Review

5.1 Benzonaphthopyranone natural products

Nature is endowed with biologically active polyketide derived natural products that contain a benzonaphthopyranone core. These compounds are reported to exhibit antibacterial, antitumour and antiviral activities, among others.[134-135] Gilvocarcins, ravidomycins and chrysomycins are some of the classes of aromatic polyketide antibiotics that share a benzonaphthopyranone moiety and are characterised by their intense yellow colour.[136]

Examples of such antibiotics include arnottin I **239**, hayumicinone **240**, the gilvocarcins **241**, chrysomycins **242**, chartarin **243** and ravidomycin **244** (**Figure 15**). These families share the same biosynthetic origin.



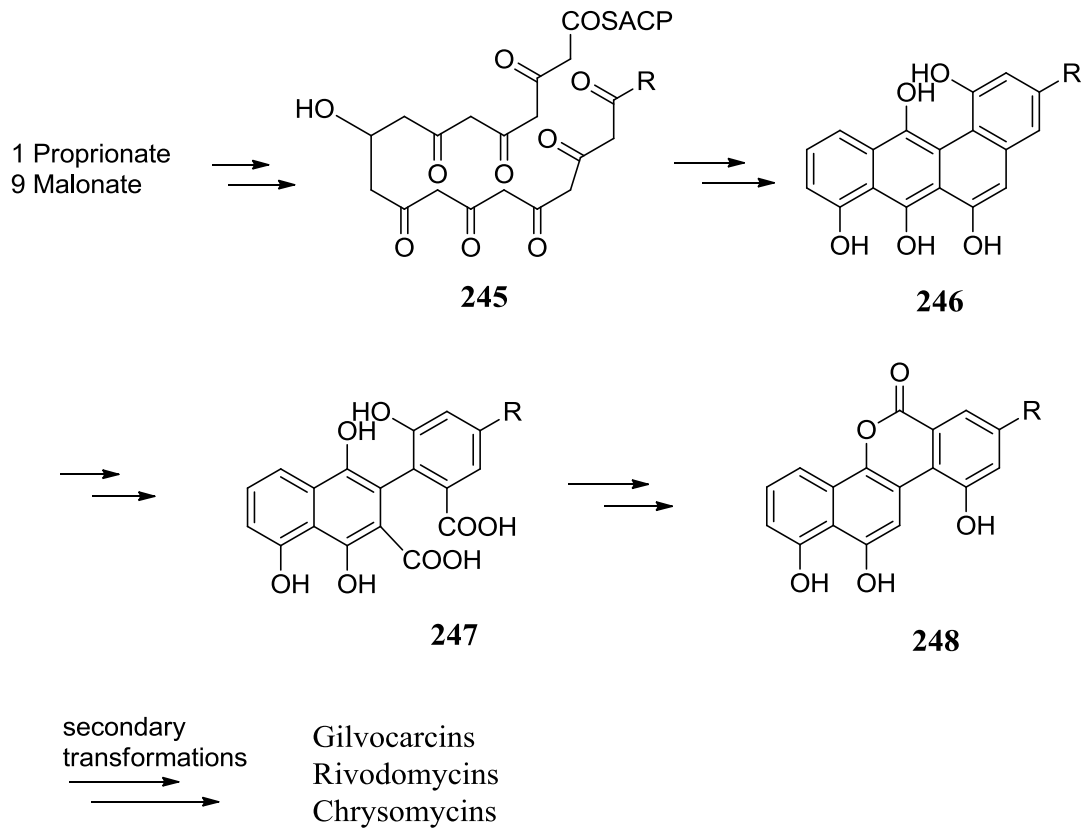
239 **240** **241**

242 **243** **244**

Figure 15: Examples of benzonaphthopyranone natural products

5.2 Biosynthesis of benzonaphthopyranones

The aryl-*C*-glycosidal linked classes of naphthocoumarins are believed to be biosynthesised from acetate units *via* the polyketide pathway.[137] This pathway is depicted in **Scheme 69**. Although it was initially hypothesised that the C-8 side chains found in these compounds resulted from secondary alkylation steps, this was disproved by labelling experiments done on ravidomycins and chrysomycins, which share the same chromophore.[134, 138]



Scheme 69: Biosynthesis of benzonaphthopyranone natural products

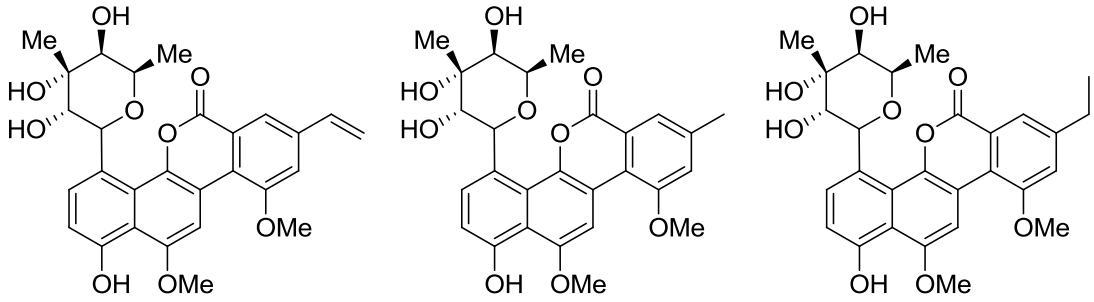
In the proposed pathway, the condensation of one proprionate and 9 malonate units gives the decaketide chain **245**, which cyclises to afford the tetracyclic intermediate **246**. Oxidative cleavage of **246** furnishes the dicarboxylic acid **247**, which, upon decarboxylation and lactonization, gives the benzonaphthopyranone core **248**. Secondary transformations of **248** like methylation, glycosidation, and dehydrogenation affords the various classes of the benzonaphthopyranone natural products.

These classes of antibiotic compounds have aroused considerable interest in view of the antibiotic and antitumour activity of their members.[139-141] The next sections highlight the biological potencies of these families.

5.3 Chrysomycins

5.3.1 Structure of chrysomycins

The yellow crystalline naphthocoumarin *C*-glycosidically linked chrysomycins A **249** and B **250** (**Figure 16**) were first isolated from *Streptomyces* A-419 species by Strelitz and co-workers[142] in 1955, but their structures were only elucidated by Weiss and co-workers in 1982.[143] Vishwakarma also isolated the two chrysomycins from *Streptomyces sporoverrucosus*,[144] together with a new compound chrysomycin C **251**.



249 **250** **251**

Figure 16: Structures of chrysomycin natural products

5.3.2 Biological activities of chrysomycins

The therapeutic potential of this class of antibiotics has been evaluated. The first isolate **249** was reported to have potent activity against *Bacillus cereus* with an MIC value of 0.01 µg/mL. It was also reported to inhibit the growth of the following fungi: *Aspergillus niger, Chaetomium globosum, Gliomasti convuluta, Myrotecium verrucaria, Penicillium nototum, Phycomyces blakesleeanus* and *Saccharomyces cerevisiae*.[142] Chrysomycins A **249** and B **250** also displayed potent activity against lymphocytic leukaemia P388 cells *in vivo*.[143] Additionally, the compounds **249-251** were tested against five cancer cell lines A549, Colo205, PC-3, MIAPaCa-2, and HL-60. They were all found to be potent, particularly against the human leukaemia HL-60 cells, with IC_{50} values of 0.9, 0.95 and 11 µM against this cell line, respectively.

Furthermore, evaluation of the mode of action studies show that **250** and **251**, at 1 μM concentration, distorted the morphology of the cell and nucleus with significant DNA damage and apoptosis in HL-60 cells.[144]

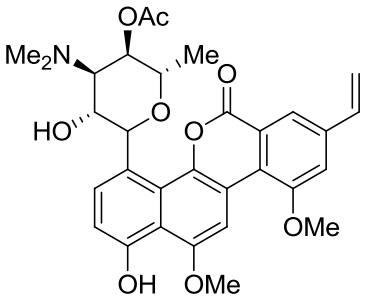
5.4 Ravidomycins

5.4.1 Structure of ravidomycins

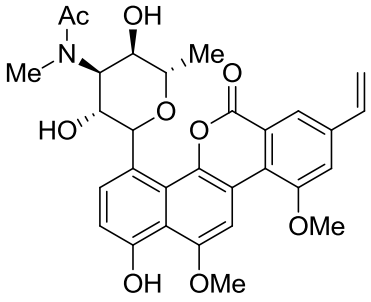
Ravidomycin **244** was isolated from Guatemalan soil bacteria *Streptomyces ravidus*.[139] This compound shares an identical chromophore with chrysomycin A **249** and differs only in the sugar attached at the C-4 position of their aglycon. Ravidomycin contains the amino pyranose sugar 4-*O*-acetyl-D-ravidosamine while chrysomycins contains the branched pyranose sugar D-virenose.[36]

5.4.2 Biological activities of ravidomycins

Ravidomycin **244** was reported to exhibit marked activity against Gram-positive bacteria, and particularly *Streptococcus faecalis* with an MIC value of < 0.2 μg/mL and *Mycobacterium fortuitum* with MIC value of 0.5 μg/mL.[139] In another study, **244** inhibited the growth of *Bacillus subtilis* at a concentration of 0.5 μg/mL with 100% inhibition at 1 μg/mL. It was further reported that the primary mode of action of **244** is to limit the synthesis of DNA in *Bacillus subtilis.*[141] Rakhit and co-workers also reported that the deacetyl analogue of ravidomycin **244** was more active against P388 leukaemia cells *in vivo* than **244** itself. Additionally, they postulated through structure-activity relationships that the vinyl group plays a role in retaining the inherent activity of ravidomycin.[140] Ravidomycin analogues **252** and **253** (**Figure 17**) were also reported to be cytotoxic against U937 histiocytic lymphoma cells in the low nanomolar range. Furthermore, they were postulated to induce caspase-3-like apoptosis at concentrations above 200 nM.[145]



244



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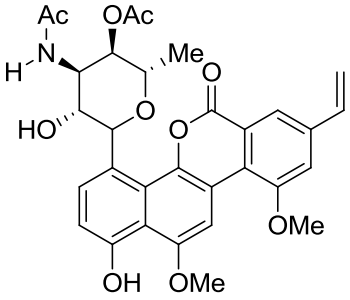


253

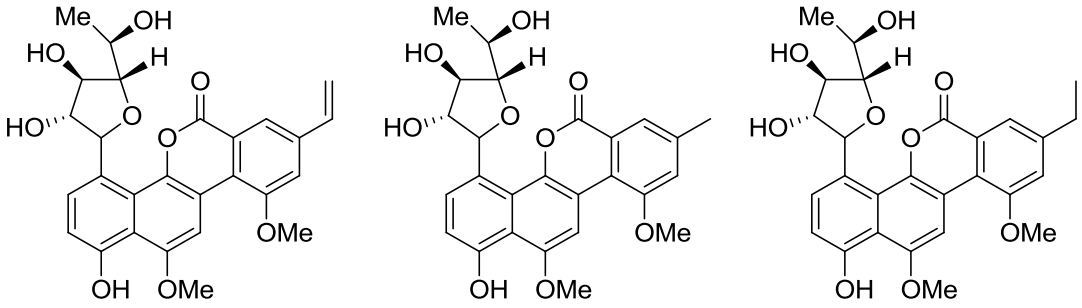
Figure 17: Bioactive ravidomycins

5.5 Gilvocarcins

5.5.1 Structure of gilvocarcins

Gilvocarcins are another class of angucycline antibiotic natural products and were isolated from different *Streptomyces sp.* Just like the chrysomycins and ravidomycins, th*e* members of this class contain a polyketide derived benzo[*d*]naphtho[1,2-*b*]pyran-6-one chromophore, but family members differ by the alkyl substituents at the C-8 position.[136] Although compounds in this class have an identical chromophore to chrysomycins and ravidomycins, they differ in the type of sugar at the C-4 position. Whilst ravidomycins have an amino sugar moiety, gilvocarcins have a fucose moiety, as shown in **Figure 18**.[146] Gilvocarcin V (GV) **254** is the major metabolite of *Streptomyces griseoflavus* Gö 3592 and other species and is produced with minor congeners gilvocarcin M (GM) **255** and gilvocarcin E (GE) **256**.[134] The names

gilvocarcin V, M and E are based on their structure in which vinyl, methyl and ethyl groups are borne, respectively.[147]



254 **255** **256**

Figure 18: Gilvocarcins Natural products

The three members of this family generally exhibit interesting biological activities as will be highlighted in the next section.

5.5.2 Biological activities of gilvocarcins

GV **254** was reported to have the most potent antitumour activities against both sarcoma180 induced as well as P388 lymphatic tumours *in vivo*, whilst GM **255** and GE **256** had moderate activities. GV **254** was also observed to be less toxic, with reported LD_{50} values of 1,000 mg/kg and 375 mg/kg for a single intraperitoneal and intravenous dose administration, respectively. GM **255** displayed an LD_{50} value of 450 mg/kg by a single intravenous administration.[148-149] The mode of action for the antitumour activities of these compounds appears to depend on several mechanisms. GV **254** has been shown to efficiently intercalate DNA strands, thus allowing UV mediated DNA cleavage by [2+2] cycloaddition with a thymine residue. It has also been reported that **254** is equally capable of cross linking between DNA and Histone H3.[150-152] Structure-activity relationship studies revealed that the vinyl group is an important functionality in the activity of GV **254**. The pivotal role of the vinyl group

is shown in the findings that GM **255** and GE **256**, which both carry aliphatic residues instead of the vinyl group, are not cytotoxic.[148, 152]

Gilvocarcins **254** and **255** also showed exceptional antibacterial activities against a number of organisms. GV **254** exhibited potent activities against *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Staphylococcus aureus* (penicillin resistant) and *Streptococcus faecalis* with MIC values of 0.13, 0.13 0.06, 0.25 and 0.016 µg/mL, respectively. For the same organisms, MIC values for GM **255** were 0.25, 0.5, 0.13, 0.5 and 0.13 µg/mL, respectively.[148]

As a result of their biological activities and interesting structures, a number of synthetic strategies have been developed for the total synthesis of these natural products or for the assembly of the benzo[*d*]naphtho[1,2-*b*]pyran-6-one core. The upcoming section will highlight some of the methodologies that have been developed for the synthesis of these compounds.

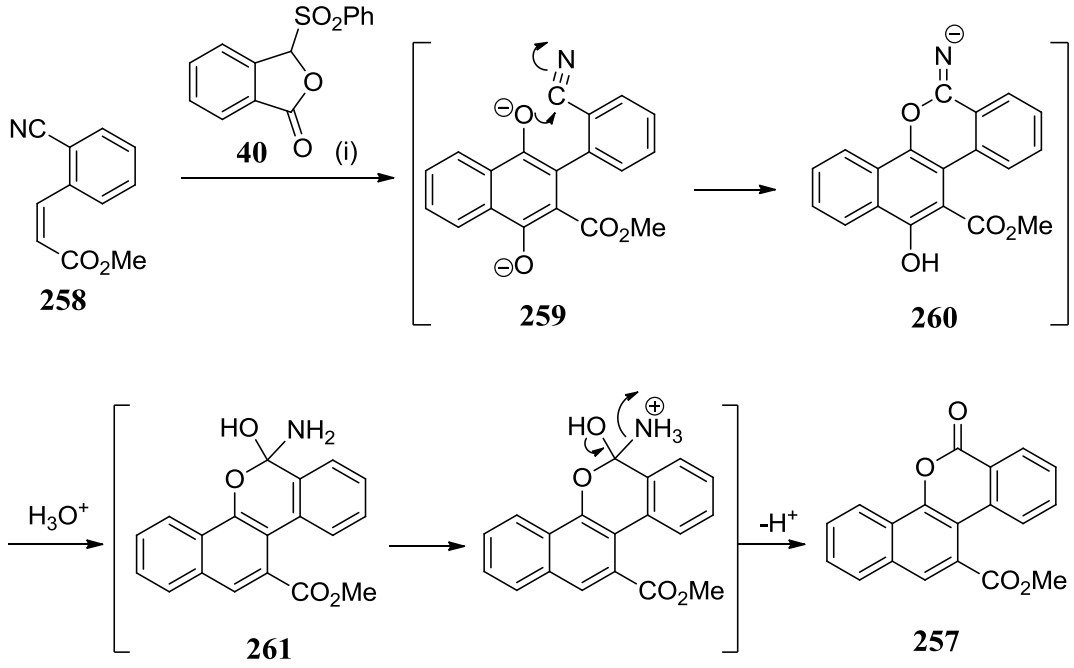
5.1 Synthetic strategies for benzonaphthopyranone type natural products.

Some of the strategies developed for the assembly of benzonaphthopyranone type natural products are highlighted, and these include among others, nucleophilic addition, transition metal catalysed as well as pericyclic or cycloaddition ([2+2], [4+2] and [2+2+2]) reactions.

5.6.1 Mal's Hauser-initiated tandem annulation synthesis of chartarin

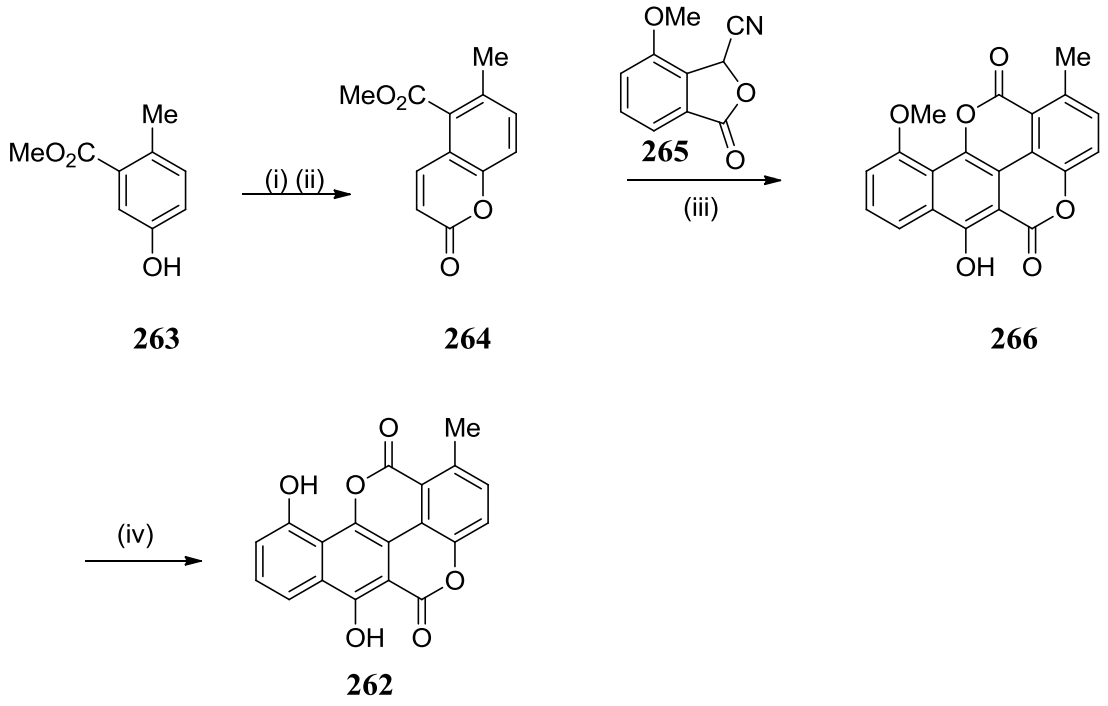
The Hauser-initiated tandem annulation was developed by Mai and co-workers to synthesise the benzonaphthopyranone core of these natural products. In principle, a Hauser Kraus donor is reacted with a Michael acceptor and the resulting intermediate undergoes intramolecular cyclisation to afford the target motif. This strategy was applied in a model study for the synthesis of a benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton **257** exhibited in **Scheme 70**.[136] The sulfone phthalide **40** was subjected to an annulation reaction with a Michael acceptor **258** to afford an aryloxy anion intermediate **259** which underwent intramolecular cyclisation through nucleophilic

attack of the oxygen anion onto the cyano group to give the intermediate **260**. During an acid work-up, the intermediate **260** was hydrolysed to amino compound **261**, which, upon protonation and elimination of ammonia, afforded the desired benzonaphthopyranone scaffold **257**.



***Scheme 70: Reagents and conditions**; t-BuOLi, −60 °C, THF then H^+/H_2O, 83%.*

Having successfully developed the method for the model study, this synthetic strategy was extended to the total synthesis of chartarin **262**[153] (**Scheme 71**). In this synthesis, 5-hydroxy-2-methylbenzoate **263** was subjected to a Wittig reaction-cyclisation sequence to give the coumarin derivative **264**. Exposure of the coumarin to an annulation reaction with a different phthalide, the Kraus cyanophthalide **265** afforded the methyl chartarin derivative **266**. Demethylation of **266** with a mixture of HBr and AcOH completed the formal synthesis of chartarin **262**.

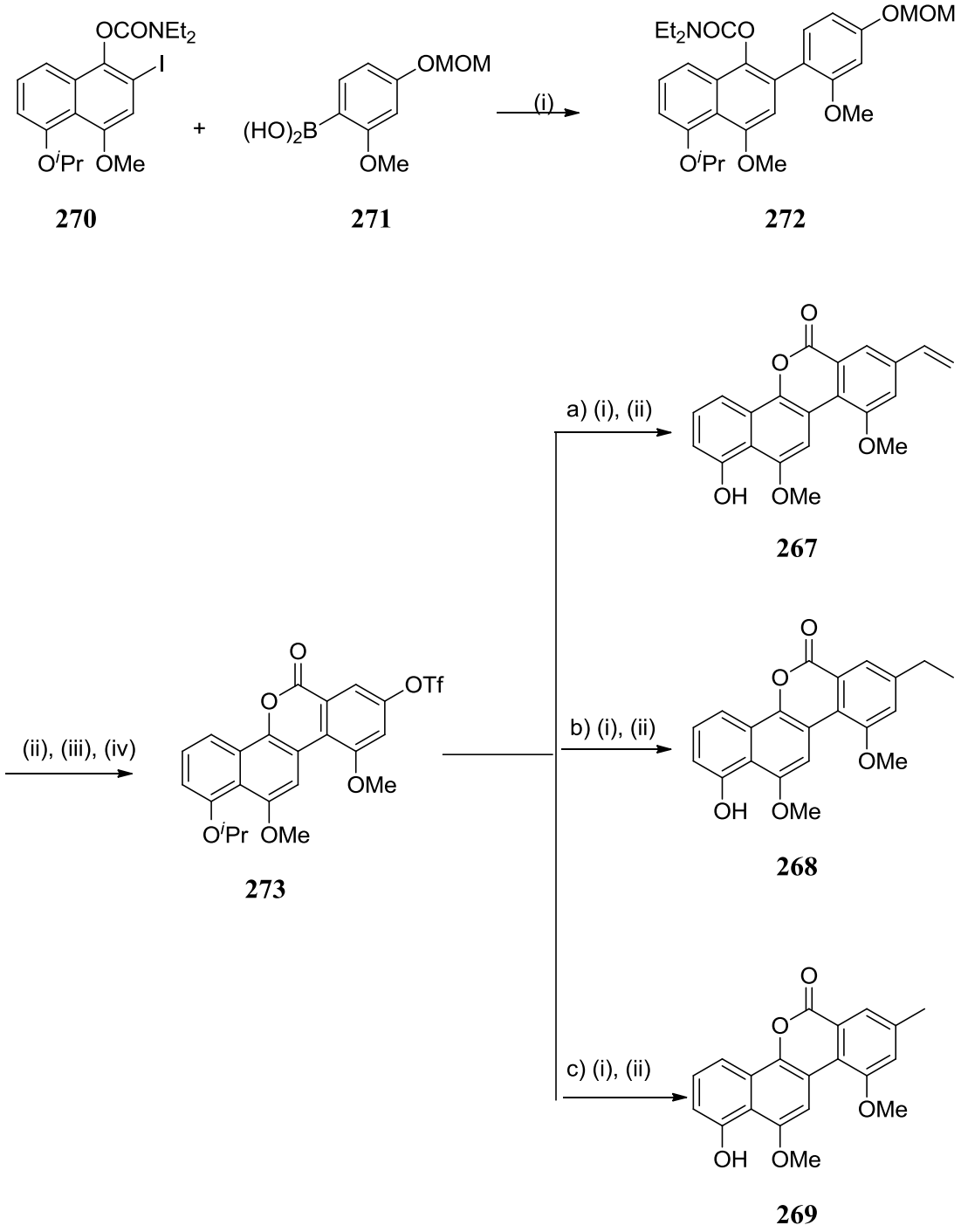


263 **264** **266** **262**

Scheme 71: Reagents and conditions*; (i) $(CH_2)_6N_4$, PPA, 100 °C, 30%; (ii) $Ph_3P{=}CHCO_2Et$, Et_2NPh, reflux, 95%; (iii) t-BuOLi, −60 °C, THF, 86%; (iv) HBr, AcOH, reflux, 81%.*

5.6.2 Snieckus's total synthesis of defucogilvocarcins

Snieckus has reported methodology for the total synthesis of defucogilvocarcins V **267**, E **268** and M **269**, aglycones of gilvocarcins. The key step in this synthesis was the directed remote metallation (DreM)-carbamoyl migration strategy. Transition metal catalysed cross coupling reaction strategies like Suzuki and Stille reactions were also used in key transformations in the synthesis.[154] The strategy is summarised in **Scheme 72**. The iodonaphthalene **270** was coupled to a boronic acid **271** using a palladium mediated Suzuki-Miyaura reaction to generate the biarylcarbamate **272**. The carbamate **272** was then subjected to the LDA induced directed remote metallation-carbamoyl migration. This was followed by acid hydrolysis and triflate protection to afford benzonaphthopyranone intermediate **273**.



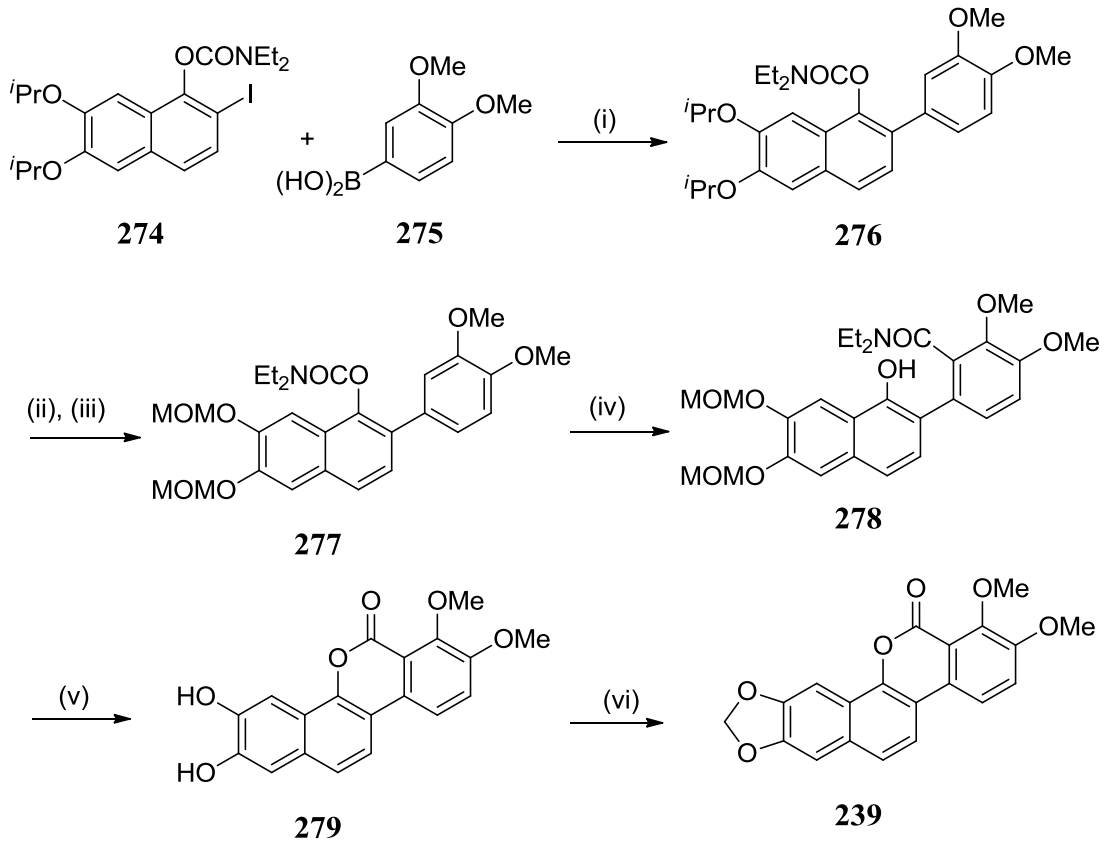
***Scheme 72: Reagents and conditions**; (i) $Pd(PPh_3)_4$, aq. $Ba(OH)_2$, reflux, 99%; (ii) LDA, THF, reflux; (iii) AcOH, H_2O, reflux, 54% (over two steps); (iv) Tf_2O, CH_2Cl_2, Et_3N, −78 °C, 81%; (**a**) (i) $C_2H_3SnBu_3$, Pd_2dba_3, NMP, LiCl, (2-furyl)$_3$P, 69%; (ii) BCl_3, CH_2Cl_2, 0 °C, 95%; (**b**) (i)BEt_3, $PdCl_2$(dppf), K_3PO_4, THF, reflux, 75%; (ii) BCl_3, CH_2Cl_2, 0 °C, 86%; (**c**) (i) MeZnCl, $NiCl_2$(dppf), THF, reflux, 59%; (ii) BCl_3, CH_2Cl_2, 0 °C, 83%.*

The C-8 triflate was introduced because it could easily be functionalised into the required vinyl, methyl and ethyl substituents. Palladium mediated modified Stille coupling reaction of **273** using tri-*n*-butyl vinylstannane, followed by BCl_3 demethylation, gave the desired defucogilvocarcin V **267**. Similarly, Suzuki coupling of **273** using BEt_3 followed by a similar demethylation strategy afforded defucogilvocarcin E **268**, while the Negishi-Quesnelle coupling conditions with MeZnCl followed by demethylation furnished defucogilvocarcin M **269**.

The authors extended this directed remote metallation (DreM)-carbamoyl migration methodology to the synthesis of arnottin I **239**.

5.6.3 Snieckus's total synthesis of arnottin I

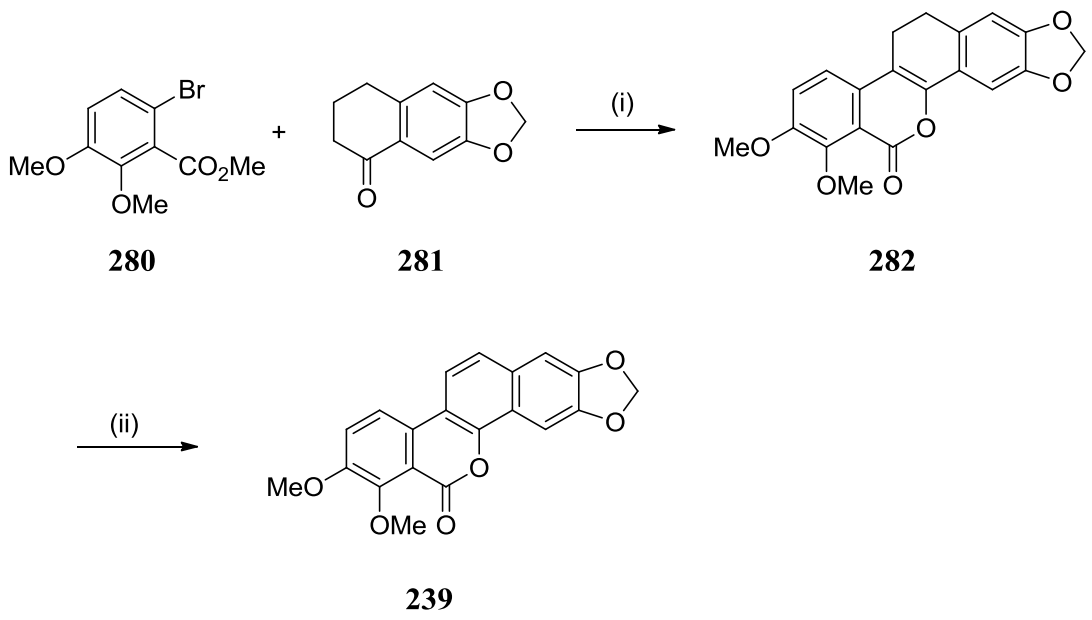
Following the strategy developed earlier, synthesis of **239**, illustrated in **Scheme 73** commenced with the Suzuki-Miyaura cross coupling reaction between a previously assembled iodonaphthalene **274** and the phenyl boronic acid **275** to give the biarlycarbamate **276**. Selective removal of the isopropyl protecting groups of **276** followed by the appropriate protection afforded the protected biaryl intermediate **277**. Subjecting the protected intermediate **277** to the key LDA mediated directed remote metallation-carbamoyl migration reaction furnished the benzonaphthopyranone derivative **278** in a modest yield. This was then subjected to acid hydrolysis to give the catechol derivative **279**. The formal synthesis of arnottin I **239** was achieved by the methylenation of the catechol moiety of **279**.[154]



***Scheme 73: Reagents and conditions**; (i) $Pd(PPh_3)_4$, aq. $Ba(OH)_2$, reflux, 95%; (ii) BCl_3, CH_2Cl_2, 0 °C, 89%; (iii) NaH, MOMCl, DMF, 95%; (iv) LDA, THF, reflux, 34%; (v) TsOH, MeOH, reflux; (vi) CH_2Cl_2, CsF, DMF, reflux, 39%.*

5.6.4 Ishikawa's synthesis of arnottin I

The synthesis of arnottin **239** has also been described by Ishikawa. The key strategy in this synthesis was the application of the Buchwald protocol on palladium mediated α-enolate arylation.[155] To accomplish this, the dimethoxy benzoate **280** and a tetralone derivative **281** were subjected to a palladium catalysed enolate arylation coupling reaction to afford the dihydroarnottin I **282**. DDQ mediated aromatisation of **282** furnished the desired arnottin I **239**, completing the formal synthesis (**Scheme 74**).



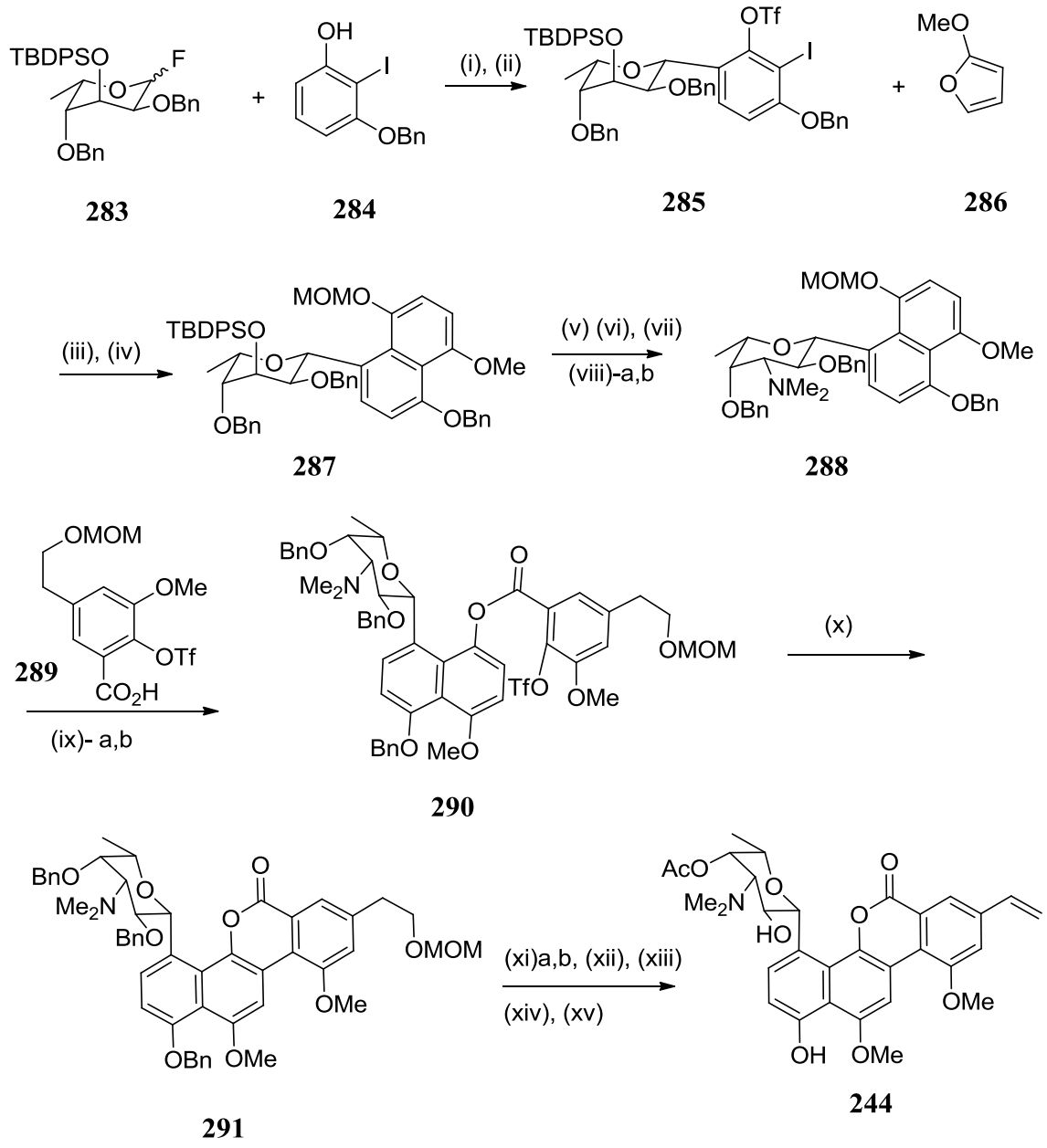
280 **281** **282**

239

***Scheme 74: Reagents and conditions**; (i) $Pd_2(dba)_3$, xantphos, CS_2CO_3, $Na_2S_2O_5$, Toluene, 105 °C, 48 h, 73 %; (ii) DDQ, benzene, 90 °C, 12 h, 94%.*

5.6.5 Suzuki's synthesis of ravidomycin V

The first total synthesis of ravidomycin **244** has been described by Suzuki. In this strategy exhibited in **Scheme 75**, the regioselective [4+2] cycloaddition of a benzyne and a furan derivative, followed by an intramolecular palladium catalysed cross coupling reaction, were key steps in the assembly of the benzonaphthopyranone skeleton.[156] Starting from the glycosyl donor **283** with a *t*-butyldiphenylsilyl substituent for stereocontrol, *C*-glycosylation with iodinated resorcinol derivative **284** gave a *C*-glycoside adduct **285** in a very good yield. A regioselective [4+2] cycloaddition of the derivative **285** with 2-methoxyfuran **286** followed by MOM protection of the resulting phenol afforded the naphthyl glycoside **287**. Introduction of an azide at the C-3′ position through an S_N2 type reaction followed by $LiAlH_4$ reduction and *N*, *N*-methylation furnished the amino-glycoside derivative **288**.

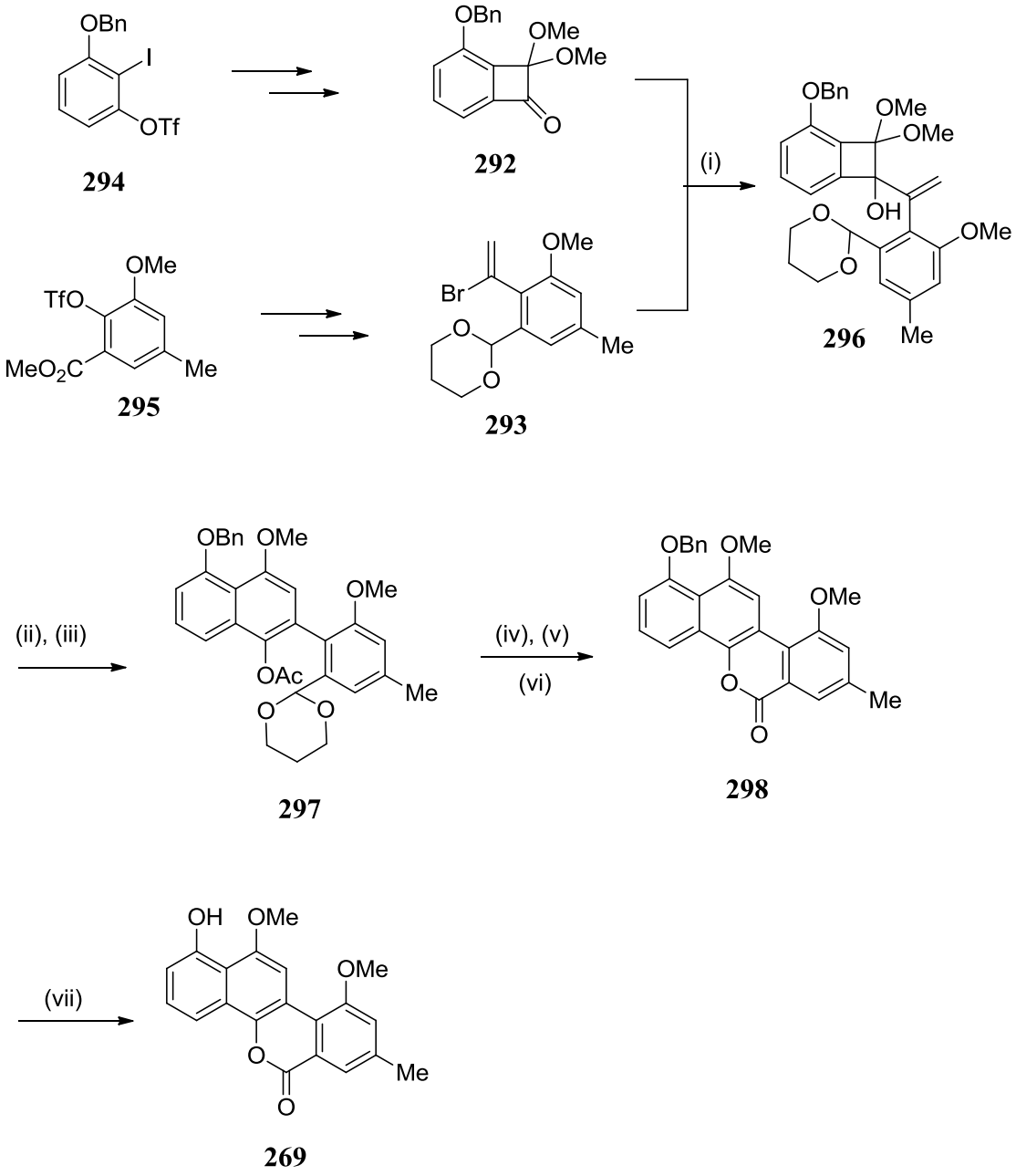


Scheme 75: Reagents and conditions*; (i) CP_2HfCl_2, $AgClO_4$, CH_2Cl_2, −78 °C to −10 °C, 83%; (ii) Tf_2O, i-Pr_2NEt/CH_2Cl_2, −78 °C, 20 min, 88% (iii) n-BuLi, THF, −78 °C, 0.5 h; (iv) MOMCl, NaH/DMF, 1 h (two steps, 77%); (v) CsF/DMF, 100 °C, 3 h, 90%; (vi) $(Imd)_2SO_2$, NaH/DMF, −40 to 0 °C, 0.5 h, 93%; (vii) NaN_3, $BnMe_3NCl$/DMF, 60 °C, 3 h, 57%; (viii) a) $LiAlH_4$/THF, 0 °C, 0.5 h; b) aq. HCHO, $NaBH_3(CN)/CH_3CN$, 0.5 h, 91% (over two steps); (ix) a) 1 M HCl/acetone, reflux, 3 h; b) EDCI, DMAP/CH_2Cl_2, 2 h, 98% (over two steps); (x) $Pd(OAc)_2$, DPPP, Bu_3P, Ag_2CO_3/DMF, 130 °C, 15 min, 70%; (xi) a) H_2, Pd black, 2 M HCl/MeOH, 0.5 h; b) Ac_2O, DMAP/pyridine, 45 min, 76% (two steps); (xii) H_2, Pd black, 2 M HCl/MeOH, 3 h, 86%; (xiii) TMSBr/CH_2Cl_2, −78 °C to −15 °C, 45 min, 59%; (xiv) MsCl /pyr, −20 °C, 0.5 h, quant.; (xv) DBN/CH_3CN, 80 °C, 0.5 h, 64%.*

Subjecting the derivative **288** to deprotection followed by a Mitsunobu reaction with the benzoic acid derivative **289** yielded ester-linked intermediate **290**. The benzonaphthopyranone skeleton **291** was assembled by an intramolecular palladium mediated cross coupling reaction of **290**. A series of protections and deprotections and finally elimination to construct the vinyl group furnished ravidomycin **244**.

5.6.6 Suzuki's synthesis of defucogilvocarcin M

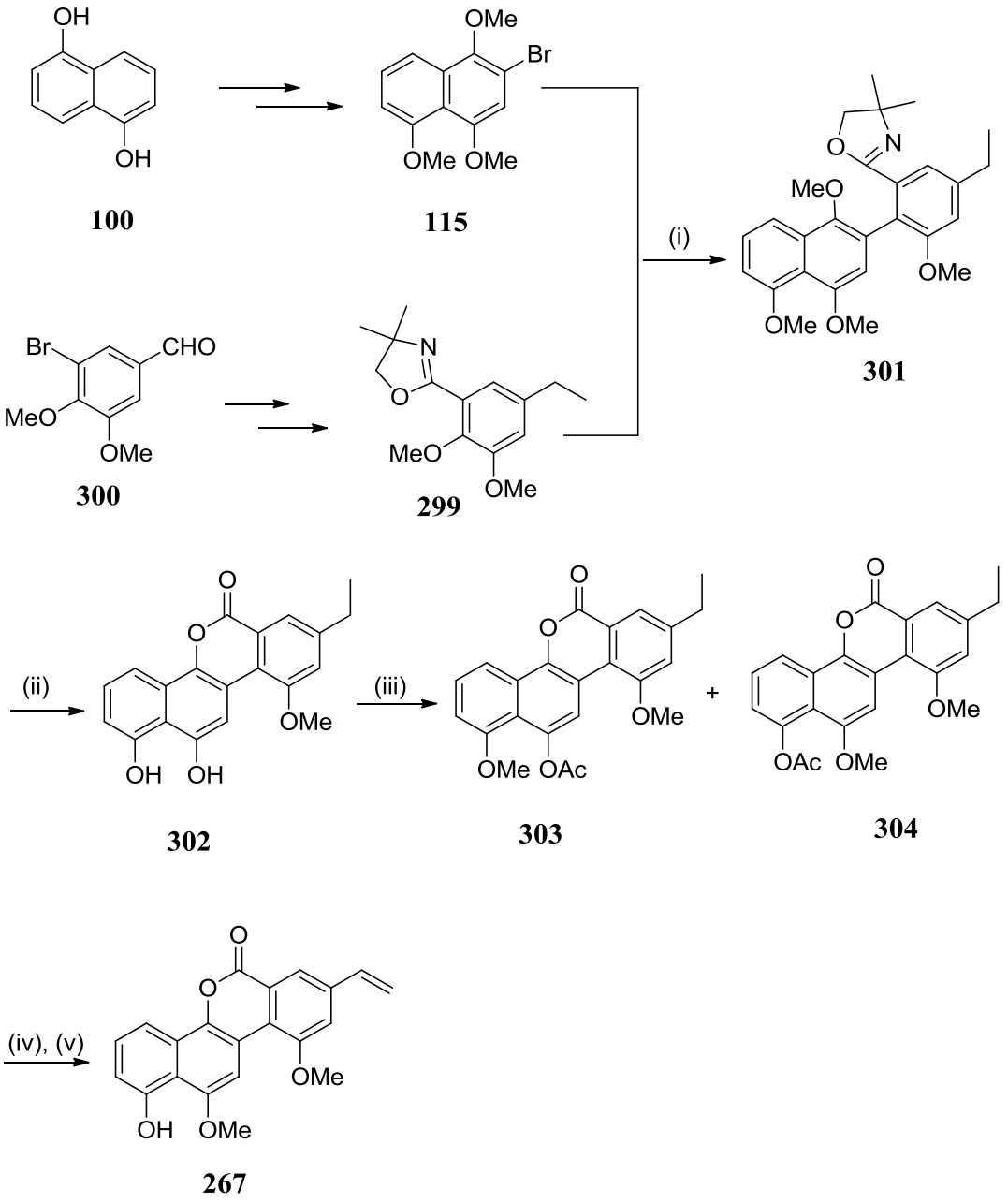
Suzuki and co-workers also used a strategy that exploits the use of a [2+2+2] cycloaddition reaction to synthesise defucogilvocarcin M **269**. The approach relies on the ready availability of various benzocyclobutene derivatives *via* regioselective [2+2] cycloaddition of α-alkoxybenzynes and ketenes.[157] This was a convergent synthesis of two advanced precursors, benzocyclobutenone **292** and styryl bromide **293** (**Scheme 76**). Benzocyclobutenone precursor **292** was prepared in four steps from the aromatic triflate **294**. On the other hand, the styryl bromide precursor **293** was prepared from a different aromatic triflate **295** in six steps. The convergent synthesis of the target compound commenced by coupling the two advanced precursors **292** and **293** to yield the cyclobutane intermediate compound **296**. Thermolysis and acetylation of the intermediate gave the biaryl adduct **297**. Hydrolysis of the acetal moiety in **297**, followed by oxidation of the resulting aldehyde and lactonization through methanolysis of the acetate and acidification, furnished the benzonaphthopyranone motif **298** in excellent yield. The synthesis was completed by debenzylation to give the target compound **269**.



Scheme 76: Reagents and conditions: *(i) t-BuLi, −78 °C, 10 min, quant.; (ii) toluene, 110 °C, 8.5 h; (iii) AC_2O, DMAP, pyridine, 95% (over two steps); (iv) AcOH aq., 25 °C, 4 h, 98%; (v) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, Acetone, H_2O, 25 °C, 15 min; (vi) K_2CO_3, MeOH, reflux, 4 h, then 2 M, HCl aq., 0 °C, 98% (two steps); (vii) H_2, 10% Pd/C, THF/DMF (12:1, v/v), 25 °C, 1 h, 85%.*

5.6.7 Findlay's synthesis of ravidomycin aglycone (defucogilvocarcin V)

Lastly in this section, synthesis of ravidomycin aglycone by Findlay and his group is highlighted. The synthetic approach, shown in **Scheme 77**, involves the joining of an appropriately functionalised Grignard reagent of naphthalene with the protected substituted benzoic acid derivatives *via* nucleophilic substitution reactions.[135] As discussed in the preceding section, this is also a convergent synthesis of the naphthalene and benzoic acid precursors. The Grignard naphthalene precursor **115** was synthesised from 1,5-dihydroxynaphalene **100** in four steps. The oxazoline precursor **299** was prepared in four steps from substituted benzaldehyde **300** derived from vanillin. Convergent coupling of the advanced precursors using conditions described by Meyers *et al.*[158] gave the biaryl phenylnaphthalene adduct **301**. Oxazoline deprotection of **301**, followed by demethylation at three sites and lactonization, furnished the benzonaphthopyranone skeleton **302** in good yield. Methylation of phenolic lactone gave a mixture of adducts **303** and **304**. Re-introduction of the vinyl group on **304** by NBS mediated benzylic bromination, followed by elimination and deacetylation, gave the target defucogilvocarcin V **267**.



***Scheme 77: Reagents and conditions**; (i) Mg, THF, cat. I_2, 15 h, rt, 81%; (ii) AcOH, 47% aq. HCl, reflux, 9 h, 77%; (iii) K_2CO_3, MeI, Acetone, DMSO, rt, 2 h, then Ac_2O, pyridine, cat. dimethylaminopyridine; (iv) NBS, CCl_4, dibenzoyl peroxide, reflux, 3 h, 75%; (v) $NaBH_4$, diphenyl diselenide, EtOH, THF, reflux, 2.5 h, then H_2O_2, 0 °C, 3 h, 40%.*

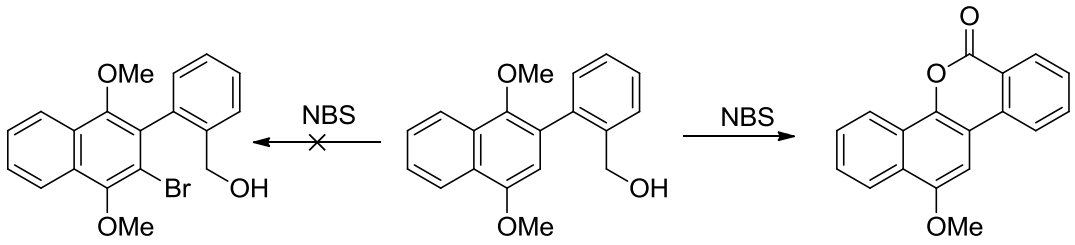
Having highlighted some of the synthetic strategies to access benzonaphthopyranones, the next chapter highlights a novel method that was

developed in our group for the synthesis of the benzonaphthopyranone core found in the gilvocarcins, ravidomycins and chrysomycin natural products. One aspect that will be dwelt on in the chapter is the evaluation of the versatility of the method to assemble different benzo-fused lactone rings systems.

CHAPTER 6: Results and Discussion on synthesis of fused lactone skeletons

6.1 Overview

As highlighted at the end of Chapter 4, our initial idea through the research of Miss Reynolds and Dr Pradeep in our research group was to conduct aromatic nuclear bromination of the benzylalcohol **235** using NBS, which serendipitously afforded the fused lactone system **238** as shown is **Scheme 78**, rather than the expected product **236**



236 **235** **238**

Scheme 78: NBS mediated synthesis of benzonaphthopyranone skeleton

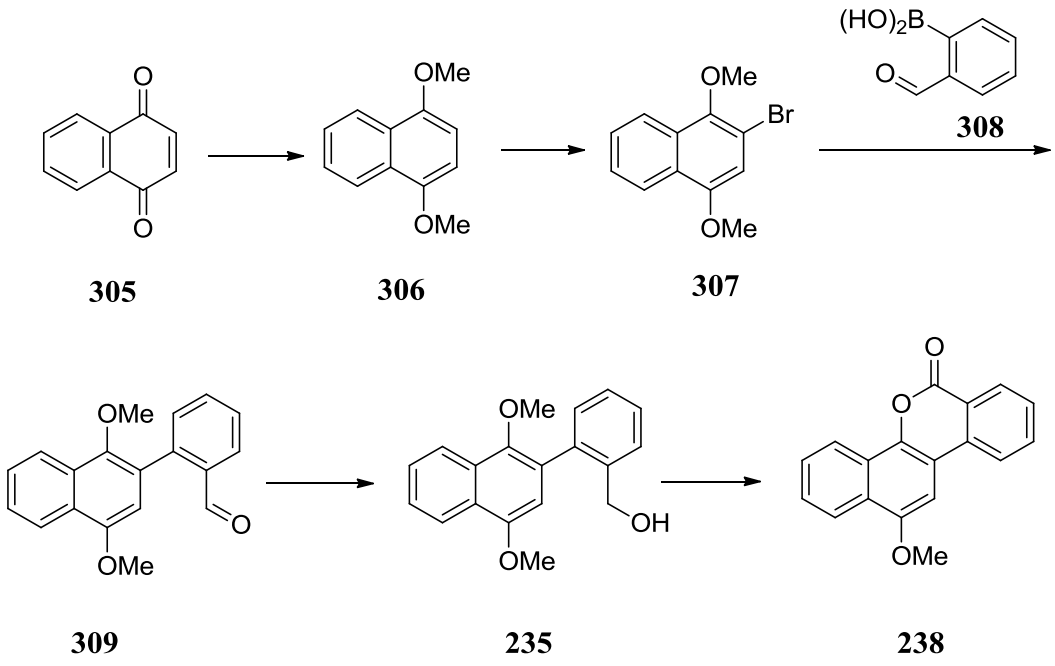
This finding was both unexpected and interesting. Although NBS has been used for a number of chemical transformations, this transformation was, however, unique. We needed to ascertain from the onset of this project whether this kind of reaction was reproducible and if so, we needed to determine if this could be a general reaction to access the benzonaphthopyranone skeleton which is found in natural products like the gilvocarcins, the ravidomycins and chrysomycins. For us to draw any conclusions on the generality of this methodology, we needed to understand and evaluate aspects such as the reproducibility, scope and conditions of this reaction. Additionally, we were also interested in unravelling the mechanism of this key step in the assembly of the fused aromatic lactone systems.

In the final chapter of this PhD thesis, results on the application of this new NBS mediated ring closure reaction for the synthesis of fused lactone systems are presented. Future aspects stemming from this work have also been highlighted.

This work has been peer reviewed and accepted for publication in the journal *Tetrahedron.*[133]

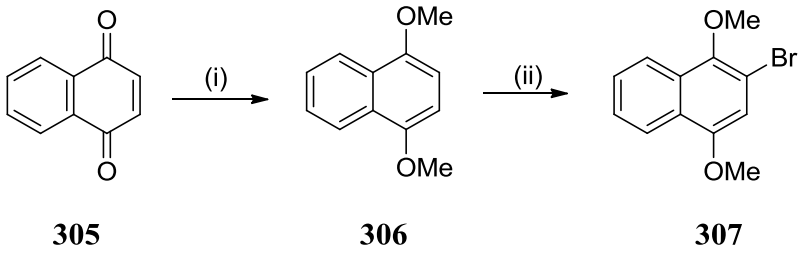
6.2 Reproducing the NBS mediated synthesis of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one

The starting point for this PhD was to repeat the NBS mediated reaction on the same substrate tested initially for the assembly of the benzonaphthopyranone skeleton, to ascertain if we could reproduce the results. The general synthetic approach is illustrated in **Scheme 79**. The strategy uses a Suzuki-Miyaura reaction as a key step to assemble the biaryl benzaldehyde **309** followed by reduction of the aldehyde to the alcohol **235** and finally the NBS mediated ring closure of the biaryl alcohol to furnish the desired product **238**.



Scheme 79: Synthetic pathway to access benzonaphthopyranone skeleton

In order to achieve this, we commenced our synthesis with the assembly of the bromonaphthalene **307** as shown in **Scheme 80**.



305 **306** **307**

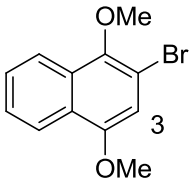
Scheme 80: Reagents and conditions*; (i) Me_2SO_4, $Na_2S_2O_4$, TBAI, aq. KOH, THF, 87%; (ii) NBS, CH_2Cl_2, reflux, 24 h, 81%.*

1,4-Naphthoquinone **305** in tetrahydrofuran was treated with sodium dithionite and tetrabutylammonium iodide (TBAI) followed by the addition of an aqueous solution of potassium hydroxide and dimethyl sulfate and the reaction mixture was stirred at room temperature. Chromatographic purification of the crude product on silica gel gave the commercially available 1,4-dimethoxynaphthalene **306** as a low melting, off-white crystalline solid in 87% yield.

The ^{1}H NMR spectrum undoubtedly established that the quinone was reduced by the appearance of a signal at δ 3.90 ppm due to the methoxy group protons and since the compound is symmetrical, one methoxy signal was observed as expected. Additionally, the ^{13}C NMR spectrum clearly showed the appearance of the characteristic aromatic ArC-O signal at δ 151.7 ppm and the corresponding methoxy carbon signal at δ 61.4 ppm.

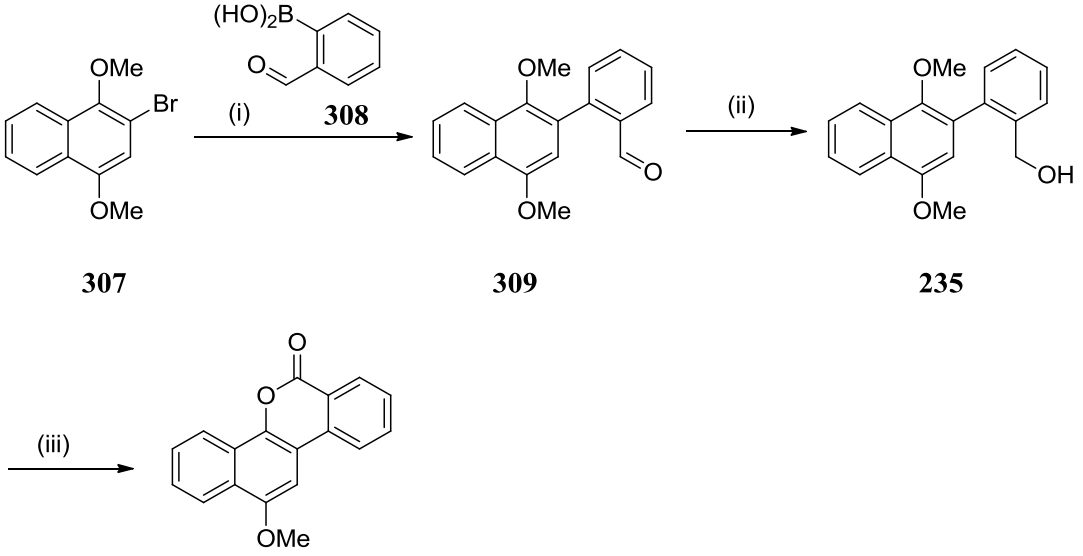
The obtained naphthalene **306** was smoothly brominated to furnish 2-bromo-1,4-dimethoxynaphthalene **307**. To accomplish this, NBS was added to a solution of the naphthalene **306** in dichloromethane and the resulting mixture refluxed for 30 minutes. The crude product was purified by column chromatography to isolate the brominated product **307** as a low melting off-white solid in 81% yield. Analysis of

the ^{1}H NMR spectrum showed the presence of a singlet signal integrating for one proton at δ 6.81 ppm which correlated with H-3. The appearance of two distinct signals at δ 3.90 and δ 3.84 ppm due to the methoxy protons implied that the original symmetry of the naphthalene was lost due to the bromination. Additionally, ^{13}C NMR spectroscopy supported the formation of the desired naphthalene by the appearance of twelve distinct carbon signals from only six carbon signals in the starting material. This was further evidence of the assembly of an asymmetrical naphthalene due to bromination.



307

With the bromonaphthalene **307** in hand, the next step was to subject it to an appropriate boronic acid under Suzuki-Miyaura reaction conditions and complete the synthesis of the benzonaphthopyranone framework as shown in **Scheme 81**.



***Scheme 81: Reagents and conditions**; (i) $Pd(PPh_3)_4$, aq. Na_2CO_3 (2 M), DME, reflux, 18 h, 90%; (ii) $LiAlH_4$, THF, rt, 2 h, 96%; (iii) NBS, CH_2Cl_2, air, 8 h, 34%.*

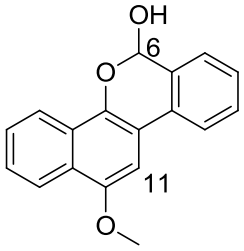
Tetrakis(triphenylphosphine)palladium(0) and 2-formylphenylboronic acid **308** were added to a deoxygenated solution of 2-bromo-1,4-dimethoxynaphthalene **307** in

dimethoxyethane. To this was added a deoxygenated aqueous sodium carbonate solution and the reaction mixture was refluxed for 18 hours. Upon chromatographic purification of the crude product, the biarylbenzaldehyde **309** was isolated as a yellow solid in 90% yield. The appearance of the aldehydic proton signal at δ 9.90 ppm and carbon signal at δ 192.4 ppm in the ^{1}H NMR spectrum and ^{13}C NMR spectrum, respectively, unmistakably confirmed the identity of the biaryl compound **309**. In addition, the presence of nine aromatic protons and nineteen carbon signals suggested the two precursors were successfully joined. The intermediate benzaldehyde **309** was smoothly reduced using lithium aluminium hydride to the corresponding 2-naphthylbenzyl alcohol **235** in an excellent yield of 96%. The successful reduction was confirmed through ^{1}H NMR spectroscopy by the disappearance of the aldehydic proton signal and the subsequent appearance of a broad singlet signal at δ 3.61 ppm and the benzylic methylene proton signal at δ 4.40 ppm. ^{13}C NMR spectroscopy also established the identity of the reduced product by the disappearance of the aldehyde carbonyl signal and the appearance of new signal at δ 64.1 ppm, which was consistent with a benzylic carbon signal.

Satisfied that we had obtained the desired benzyl alcohol **235**, the next step was to carry out the key NBS mediated ring closing reaction that furnished the lactone. To accomplish this, NBS was slowly added to a solution of the benzyl alcohol in dichloromethane and the reaction mixture was allowed to stir *open to the atmosphere* at room temperature. To our delight, chromatographic purification of the crude product furnished the desired lactone **238** as a light tan solid in a moderate yield of 34%, together with an unknown compound in 11% yield. The ^{1}H NMR spectrum unambiguously established that we had formed the lactone by the disappearance of the benzylic proton signals between δ 4.44 and 4.37 ppm, as well as the broad singlet signal was observed at δ 3.16 ppm. As expected, only one methoxy group proton signals at δ 4.12 ppm. The ^{13}C NMR spectrum also proved the formation of the dibenzochromenone core by the appearance of a typical lactone carbonyl signal at δ 161.4 ppm. The spectroscopic data was consistent with what was reported by Miss

Reynolds and Dr. Pradeep from our laboratory and was in good agreement with the data reported by Jones and Qabaja.[159]

Pleased that the NBS reaction gave the desired lactone **238**, albeit in a modest yield, we decided to take a closer look at the identity of the unknown compound. Using both ^{1}H NMR and ^{13}C NMR spectroscopy, the identity of the unknown compound was established to be a lactol, **310**. The aromatic proton signal at δ 7.12 ppm was indicative of H-11 and the other singlet at δ 7.08 was consistent with H-6 proton. Furthermore, one methoxy group proton signal at δ 4.04 ppm and a broad singlet at 1.54 ppm were also observed in the ^{1}H NMR spectrum. Further evidence was provided by the appearance of one methoxy carbon signal at δ 55.8 ppm and a signal at δ 92.8 ppm which correlated to C-6.

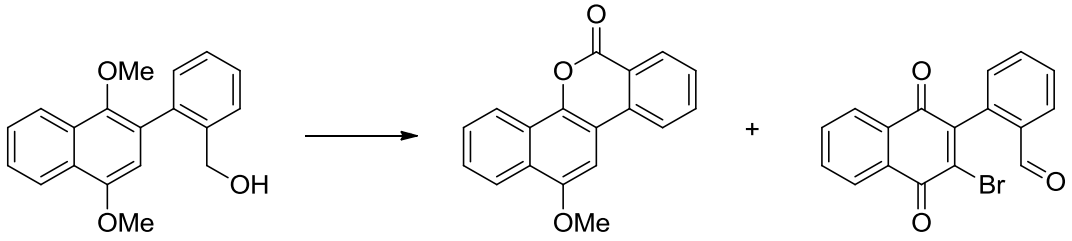


310

Although we were pleased with the results of the NBS mediated ring closure reaction, TLC evidence showed the presence of other products that we could not isolate, hence we decided to repeat the reaction to see if the results were reproducible. In addition, if the reaction was conducted on a large scale, we thought it might be possible to characterise other products formed in the reaction. Finally, as previous evidence has shown that the reaction needed to be conducted under atmospheric conditions, oxygen in the atmosphere could be playing a role in the reaction. Hence, we attempted the NBS mediated lactone forming reaction *under an oxygen atmosphere*.

As illustrated in **Scheme 82**, when the reaction was repeated under an atmosphere of oxygen, we isolated the desired lactone **238** in a yield of 42%, along with the quinone **311** in 36% yield. Not surprisingly though, we were unable to isolate the lactol **310** which we attributed to its instability as the hemiacetal should form the lactone **238** under these conditions. This could have been as a result of the reaction being conducted under oxygen. The ^{1}H NMR spectrum evidently established the formation of the quinone **311** by appearance of the distinct aldehydic proton signal at δ 9.94

ppm. Additionally, the distinct aromatic proton singlet signal between δ 6.50 and 6.70 ppm had disappeared. This suggested that aromatic nuclear bromination had taken place at this C'-3 position. Analysis of the ^{13}C NMR spectrum confirmed the appearance of the aldehyde carbonyl carbon signal at δ 191.3 ppm and two other carbonyl signals at δ 180.9 and 177.8 ppm. Furthermore, examination of the HRMS showed a molecular ion mass peak at 339.9720 amu, which was in good agreement with the expected mass of 339.9726 amu for $C_{17}H_9O_3{}^{79}Br$.



235 **238** **311**

***Scheme 82: Reagents and conditions**; NBS, CH_2Cl_2, O_2, rt, 8 h, **238**-42%; **311** -36%.*

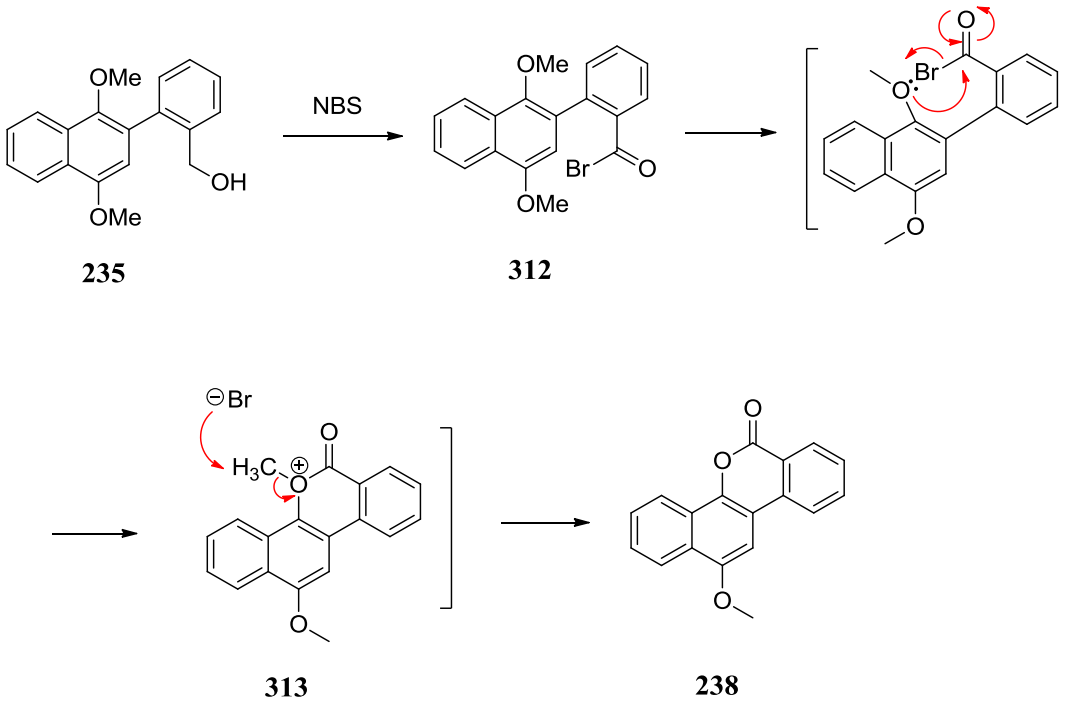
Satisfied that we had been able to reproduce this novel method for the synthesis of the dibenzochromenone motif **238**, albeit in mediocre yields, we were interested in unravelling the mechanism of the reaction. The upcoming sections will highlight our attempts to understand the mechanism of this reaction.

6.3 Mechanistic studies of the NBS catalysed ring closing reaction

The isolation of the quinone **311** from the preceding reaction suggested that NBS was oxidising both the benzyl alcohol of **235** to the corresponding aldehyde and also the naphthalene portion of **235** to the quinone **311**. It is not uncommon for NBS to oxidise benzylic alcohols to aldehydes and naphthalenes to corresponding quinones.[160-163]

6.3.1 Mechanist route *via* the benzoyl bromide intermediate

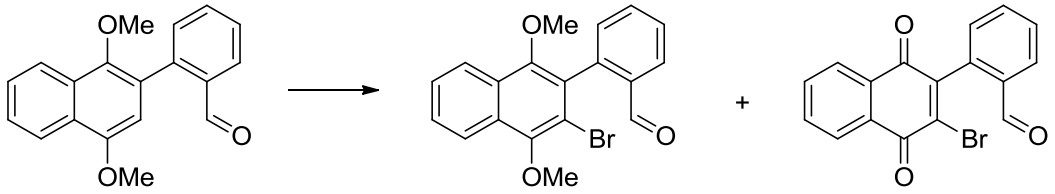
We therefore needed to determine whether the ring closure reaction proceeded *via* the benzoyl bromide intermediate **312**, as indicated in **Scheme 83**.



Scheme 83: Dibenzochromenone motif assembly via benzoyl bromine route

If the assembly of the dibenzochromenone **238** proceeded *via* this route, oxidation and subsequent bromination of the benzyl alcohol would have to give the benzoyl bromide **312** as an intermediate, which then would cyclise to furnish the lactone derivative **313**. *O*-Demethylation by formation of bromomethane would then afford the desired compound **238.** If this was the case, we expected that treating our initial 2-naphthylbenzaldehyde **309** with NBS should furnish the lactone **238**.

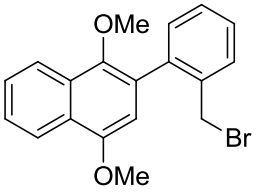
In order to verify if this was a possible mechanism for the synthesis of the lactone motif **238**, we subjected the 2-naphthylbenzaldehyde **309** to our NBS conditions as illustrated in **Scheme 84**.



309 **314** **311**

Scheme 84: Reagents and conditions*; NBS, CH_2Cl_2, O_2, rt, 8 h,* ***314****-57%;* ***311*** *-28%.*

When the biarylbenzaldehyde derivative **309** was subjected to the NBS reaction conditions, the desired lactone **238** was not obtained. Instead, the bromonaphthalene **314** and the quinone **311** were isolated in 57% and 28% yields respectively. The ^{1}H NMR spectrum confirmed the formation of the bromonaphthalene **314** by the disappearance of the most shielded proton singlet signal at δ 6.74 ppm at C'-3. This suggested that this was the position that was brominated, as it is also the most activated for electrophilic aromatic substitution. Further evidence was provided by HRMS where a molecular ion peak was observed at 370.0188 amu which correlated to the expected mass of 370.0199 amu for $C_{19}H_{15}O_3{}^{79}Br$. These results suggest that the ring closing reaction does not proceed *via* the acid bromide derivative **312.** A hypothesis that the reaction could proceed *via* the corresponding benzyl bromide intermediate **315** was also disproved by Dr. Pradeep in her PhD work.



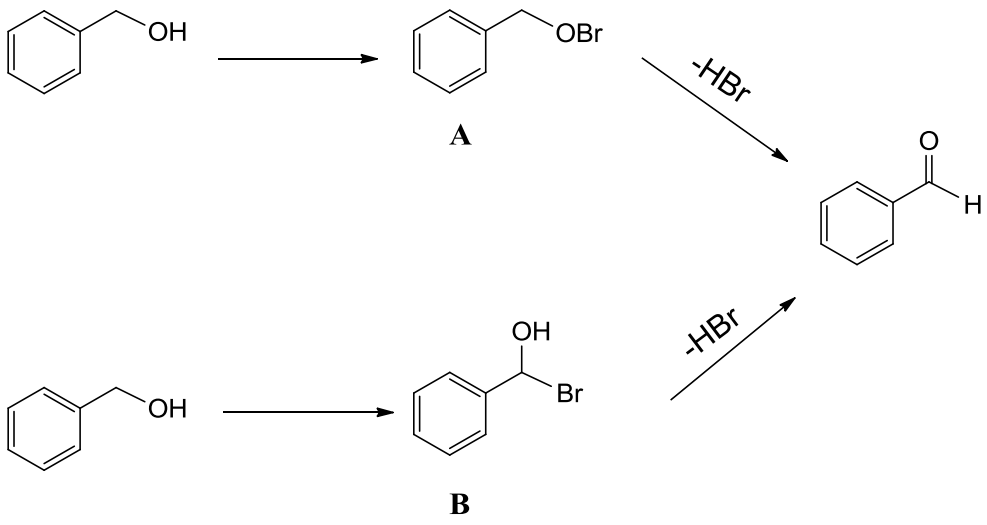
315

Although these results were disappointing from the point of view of our mechanistic study, they provided an unintended break-through in the initial project of assembling the oxygen containing analogues of angucycline antibiotics, as highlighted in **Scheme 68** at the end of Chapter 4.

During our initial attempt to reproduce the synthesis of the lactone **238**, we also isolated an unstable lactol **310** which we were unable to isolate again in the subsequent reactions we undertook. This led us to question whether this could be an important intermediate in the formation of the lactone **238**.

6.3.2 Proposed mechanistic route via a lactol derivative

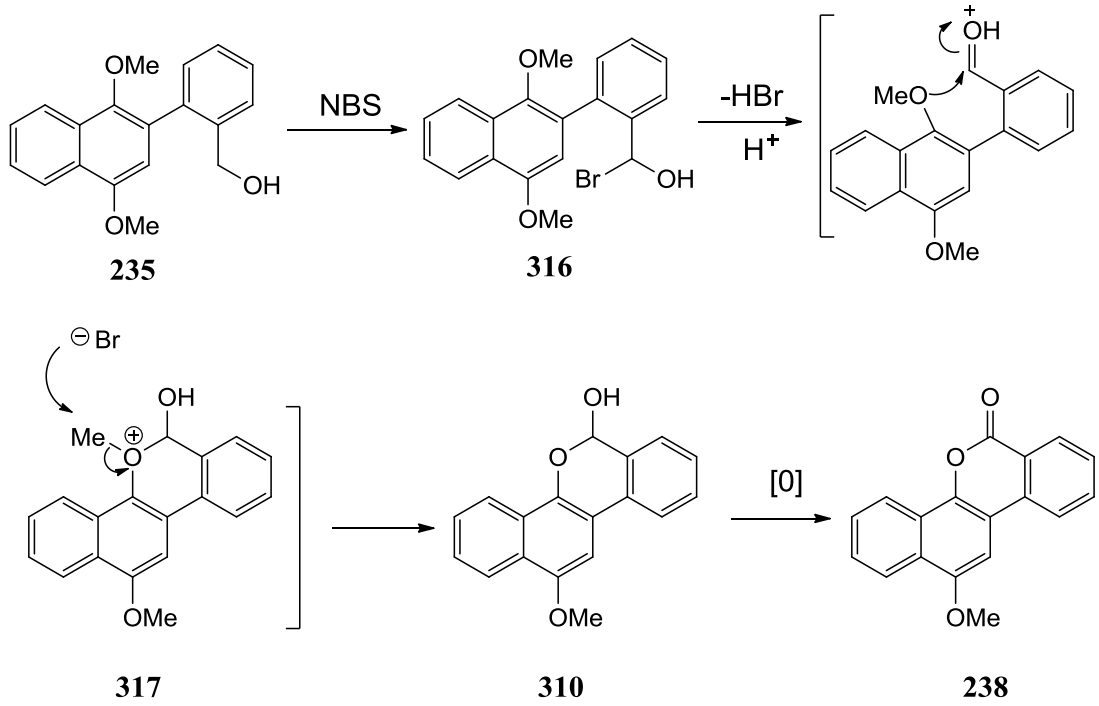
Examination of the literature on mechanisms for the oxidation of alcohols by NBS, shows that two potential mechanistic pathways have been advanced. In an experimental and theoretical study on the oxidation of alcohols to aldehydes and ketones with *N*-bromosuccinimide by Shang and co-workers,[163] they suggested that this oxidation possibly proceeds though either a reactive hypobromite species **A** or through substitution of a benzylic hydrogen by bromine to afford the intermediate **B**, presumably by means of a radical side chain bromination, as shown in **Scheme 85**.



Scheme 85: Plausible pathways to oxidation of alcohols by NBS

Using the benzyl alcohol as a model, the calculated free energy of the reactions for path **A** and **B** was found to be 1.18 kcal/mol and -30.8 kcal/mol respectively which suggested that path **B** was the more likely mechanism for the oxidation.

If this was a likely pathway for our reaction, we could indeed postulate that the unstable lactol **310** was an intermediate in the formation of the lactone **238**, as suggested in **Scheme 86**. In this proposed mechanism, the benzyl alcohol **235** is initially brominated on the benzylic carbon to give the bromomethanol derivative **316** which then cyclises to afford the methylated lactol derivative **317**. *O*-Demethylation of **317** through formation of bromomethane, gives the lactol intermediate **310**, which then easily oxidises to furnish the desired lactone **238**. This proposed mechanism correlated well with the results reported by Shang on the reaction proceeding *via* path A. However, more detailed mechanistic studies need to be undertaken to confirm this proposed mechanism.



Scheme 86: Proposed mechanism via a lactol intermediate

Having successfully improved on the methodology and proposed the mechanistic route for the NBS mediated synthesis of the benzonaphthopyranone skeleton, we then embarked on evaluating the scope and the limitations of this methodology for the

synthesis of lactones. We wanted to ascertain whether this could be a general and versatile method to access the lactone motif of natural products.

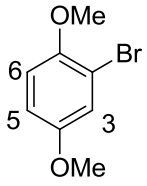
6.4 Expanding the scope and application of the NBS reaction

Having established that we could assemble the dibenzochromenone (benzonaphthopyranone) skeleton, we expanded the application of this new method to the assembly of smaller benzochromenone (dibenzopyranone) ring systems. We also wanted to evaluate the isoelectronic effects of the rings on the reaction by increasing or decreasing oxygen functionalities in the rings. The following section discusses our endeavours to expand the scope of the NBS reaction.

6.4.1 Synthesis of 2-methoxy-6*H*-benzo[*c*]chromen-6-one 322

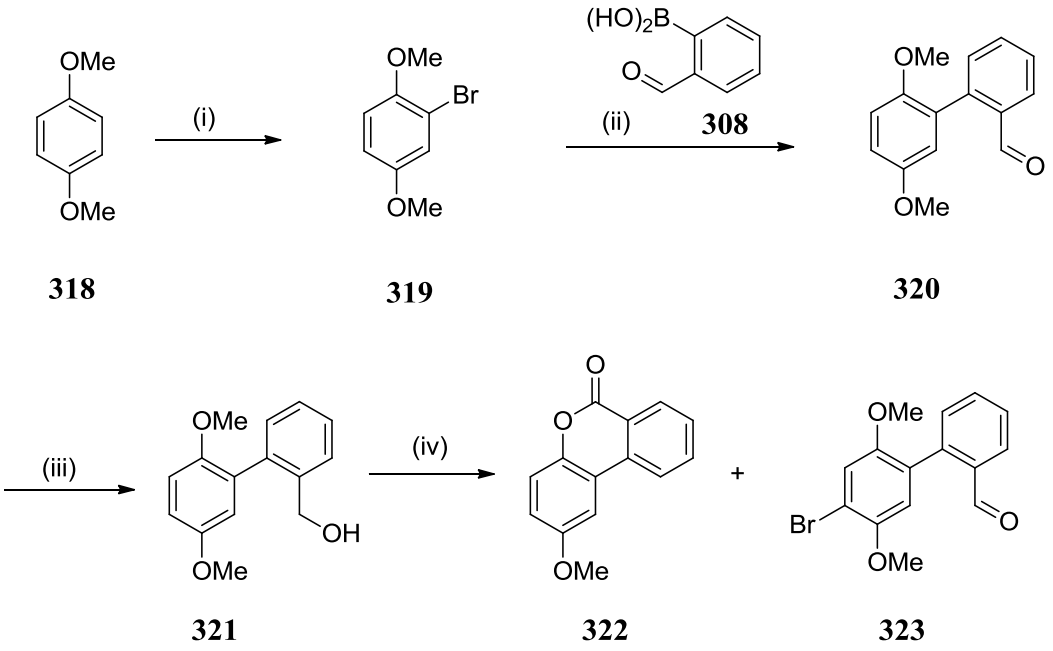
We commenced the general application of this methodology to the synthesis of 2-methoxy-6*H*-benzo[*c*]chromen-6-one by attempting the reaction on benzene precursors rather than naphthalene-containing substrates. Hence, in the previous reaction we started from a naphthoquinone, the starting point in this reaction was 1,4-dimethoxybenzene. This is illustrated in **Scheme 87**.

In this synthesis, the same protocols used in the model studies were adopted without significant variations. Commercially available 1,4-dimethoxy benzene **318** was subjected to NBS bromination to smoothly give the bromobenzene derivative **319** in 93% yield. The ^{1}H NMR spectrum established the formation of **319** by the appearance of three different aromatic signals, although two of them were overlapping. The doublet of doublet signal at δ 7.11 ppm J = 7.1, 0.8 Hz, correlated with H-5 and the overlapping signal between δ 6.82 - 6.79 ppm integrating for two protons was consistent with H-3 and H-6. Satisfied with the bromination reaction, we then subjected the bromobenzene derivative **319** to a palladium mediated cross coupling reaction with formylphenylboronic acid **308** to furnish the biarylbenzaldehyde **320** as an off-white solid in 88% yield (**Scheme 87**). Analysis of the ^{1}H NMR spectrum showed the presence of the aldehydic proton signal at δ 9.79 ppm. Additionally, there



319

were seven aromatic protons in total, which proved that the Suzuki-Miyaura coupling reaction was successful. From the ^{13}C NMR spectrum, the appearance of the aldehyde carbonyl signal at δ 192.5 ppm and six other new carbon signals established that we had formed the benzaldehyde **320.**

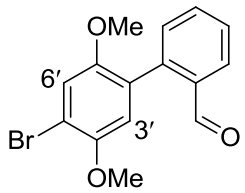


Scheme 87: Reagents and conditions*; (i) NBS, CH_2Cl_2, reflux, 36 hr, 93%; (ii) $Pd(PPh_3)_4$, aq. Na_2CO_3 (2 M), DME, reflux, 18 h, 88%; (iii) $LiAlH_4$, THF, rt, 2 h, 98%; (iv) NBS, CH_2Cl_2, O_2, 8 h,* ***322****-46%;* ***323*** *-36%.*

The benzaldehyde derivative **320** was then effortlessly reduced to the benzyl alcohol derivative **321** using lithium aluminium hydride in a quantitative yield. The reduction was confirmed by ^1H NMR spectroscopy through the unmistakable disappearance of the aldehyde proton signal at δ 9.79 ppm and the subsequent appearance of the broad singlet signal at δ 2.50 ppm and typical benzylic methylene signals at δ 4.41 ppm. The ^{13}C NMR spectrum also correlated with the ^1H NMR spectroscopy results by the disappearance of the aldehyde carbonyl signal δ 192.5 ppm and the subsequent appearance of a benzylic carbon signal at δ 63.8 ppm.

Satisfied with the reduction reaction and with the alcohol in hand, we then attempted the key step by exposing the alcohol **321** to our NBS reaction conditions. To our delight, the reaction furnished the desired benzochromenone **322** as a white solid in 46% yield along with the benzaldehyde **323** in 36% yield. The ^{13}C NMR spectrum unequivocally established the identity of the lactone **322** by the appearance of a typical lactone carbonyl signal at δ 161.3 ppm and only one methoxy carbon signal at δ 55.9 ppm. The ^{1}H NMR spectrum also showed the presence of only one methoxy group proton signal at δ 3.91 ppm. Analysis of HRMS showed a molecular ion peak at 226.0622 amu (100%) which correlated well with the expected mass of 226.0625 amu for $C_{14}H_{10}O_3$.

The formation of the benzaldehyde **323** was also supported by the spectroscopic data. The appearance of the aldehyde proton signal at δ 9.78 ppm and two aromatic proton singlet signals at δ 7.51 ppm (H-6′) and 7.18 ppm (H-3′) in the ^{1}H NMR spectrum signified that the C-5′ position was brominated. The confirmation of the aldehyde was also supported by the appearance of a typical aldehyde carbonyl signal in the ^{13}C NMR spectrum at δ 192.1 ppm and the subsequent disappearance of the benzylic carbon signal at δ 4.41 ppm. In the HRMS, a molecular ion peak was observed at 320.0041 amu, which was in good agreement with the expected mass of 320.0043 amu for $C_{15}H_{13}O_3{}^{79}Br$.



323

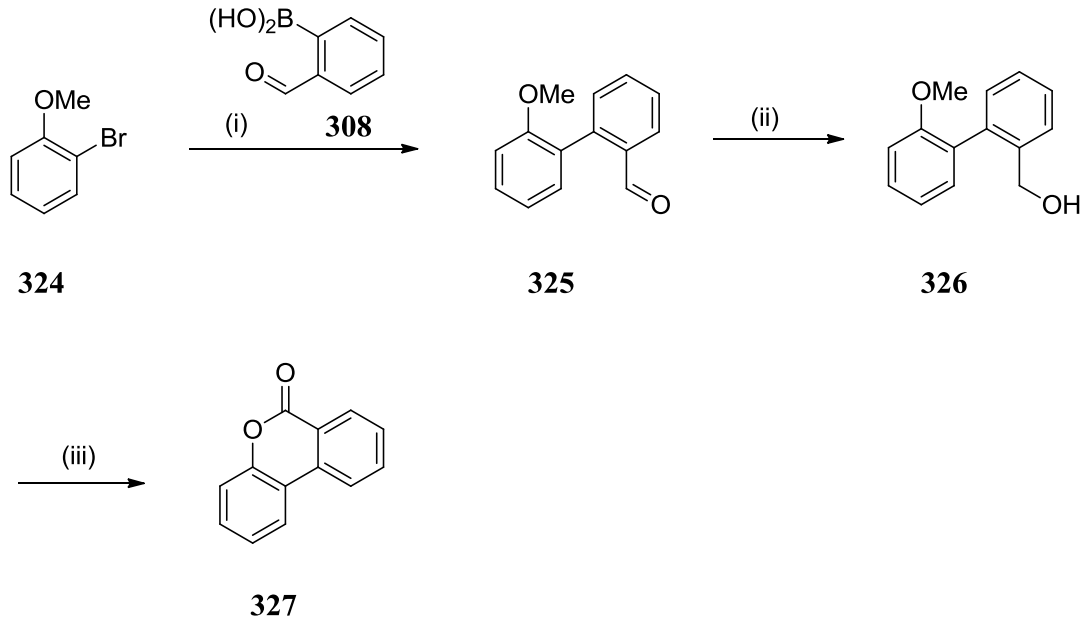
The results of the successful synthesis confirmed that the NBS methodology can be applied to the synthesis of the benzochromenone skeleton **322**. What was also significant in these results was that in conducting the reaction on (2',5'-dimethoxy-[1,1'-biphenyl]-2-yl)methanol **321** as compared to (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **235**, there was a slight improvement in the yield of the corresponding lactones from 42% to 46%, respectively.

Pleased with these results, we then decided to attempt the lactone forming reaction on a benzene substrate possessing one less methoxy substituent, making it less electron

rich. Hence, we wished to establish if the electronic effect of the ring has an impact on the assembly of the aromatic lactone. These results are highlighted in the next section.

6.4.2 Synthesis of 6*H*-benzo[*c*]chromen-6-one 327

In order to accomplish this, we decided to use commercially available 2-bromo anisole as a starting material in our synthesis. Using this starting material effectively reduces the electron density on the substrate in the final lactonisation reaction. The synthesis of 6*H*-benzo[*c*]chomen-6-one is shown in **Scheme 88**.



324 **325** **326**

327

Scheme 88: Reagents and conditions*; (i) $Pd(PPh_3)_4$, aq. Na_2CO_3 (2 M), DME, reflux, 18 h, 87%; (ii) $LiAlH_4$, THF, rt, 2 h, 98%; (iii) NBS, CH_2Cl_2, O_2, 8 h, 70%;*

The bromobenzene **324** was again coupled with formylphenylboronic acid **308** using a palladium catalysed Suzuki Miyaura cross coupling reaction to give the benzaldehyde **325** as an off-white solid in 87%. As before, the ^{1}H NMR spectrum confirmed the appearance of the aldehyde proton signal at δ 9.78 ppm. Furthermore, eight aromatic proton signals were also observed that suggested that the coupling was

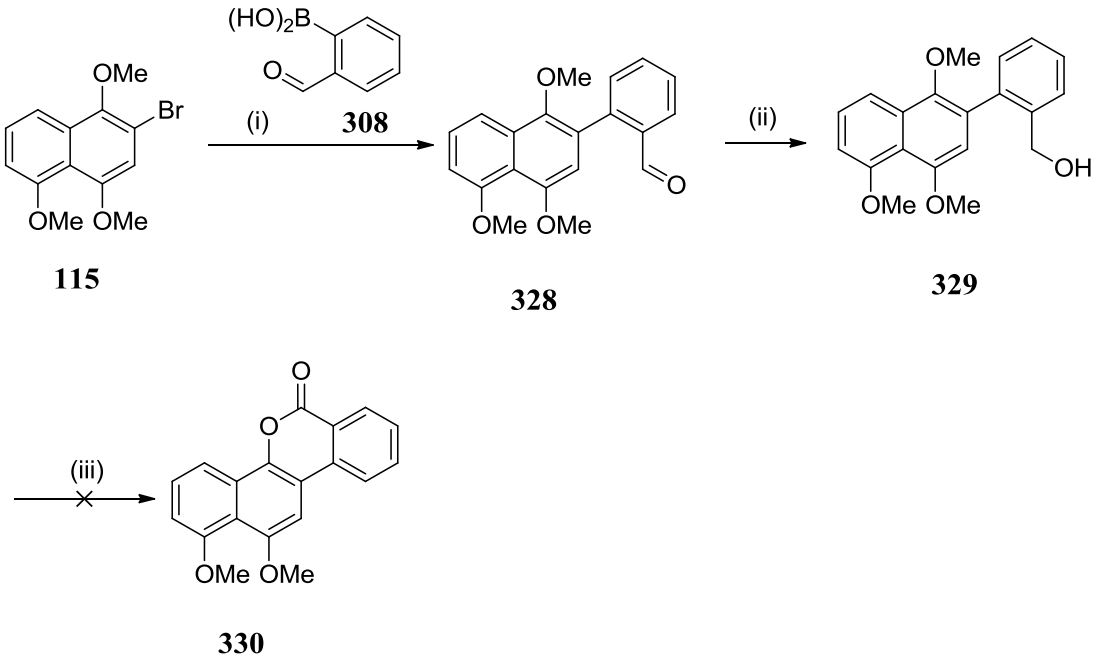
successful. The presence of the aldehyde carbonyl signal at δ 192.5 ppm was also confirmed by ^{13}C NMR spectroscopy. The benzaldehyde **325** was easily reduced using lithium aluminium hydride to the corresponding benzyl alcohol **326**, which was isolated as a clear oil in 92% yield. The identity of the alcohol was confirmed by the unmistakable disappearance of the aldehyde proton signal at δ 9.78 ppm in the ^{1}H NMR spectrum and the carbonyl signal at δ 192.5 ppm in the ^{13}C NMR spectrum. There was also the appearance of a broad singlet signal at δ 2.66 ppm consistent with the -OH proton, and a typical benzylic protons signal at δ 4.36 ppm in the ^{1}H NMR spectrum. The corresponding benzylic carbon signal was observed in the ^{13}C NMR spectrum at δ 63.3 ppm.

Satisfied with our reduction, we then subjected the benzyl alcohol **326** to our key NBS mediated ring closure reaction. To our delight, we smoothly isolated the desired benzochromenone **327** as a white crystalline solid in a good yield of 70%. The assembly of **327** was confirmed by the disappearance of the methoxy proton signal at δ 3.63 ppm in the ^{1}H NMR spectrum. The disappearance of the corresponding methoxy carbon signal was confirmed by ^{13}C NMR spectroscopy. Additionally, a typical lactone carbonyl signal was observed at δ 161.1 ppm.

The results thus far seemed to suggest two important points. Firstly, with the synthesis of three different lactone skeletons, the method could be described as a general method for the synthesis of benzonaphthopyranone ring systems. The second interesting observation was that the reactions appeared to favour less electron rich systems owing to the trend in the isolated yields. So far, the isolated yield for dibenzochromenone **238** was 42%, 2-methoxybenzochromenone **322** was 46% and finally benzochromenone **327** was 70%. This meant that there could be some limitations in the scope of the lactone scaffolds that could be synthesised by this new methodology. We decided to probe further this limitation by using a more oxygenated ring system such as a juglone derivative as a starting precursor.

6.4.3 Attempted synthesis of dibenzochromen-6-one 330

The synthesis commenced from our previously assembled bromonaphthalene derivative **115.** This precursor was chosen because it is highly oxygenated, and hence, an electron rich ring system. This afforded us the opportunity to further explore the limits of the NBS reaction. This synthesis is exhibited in **Scheme 89**.

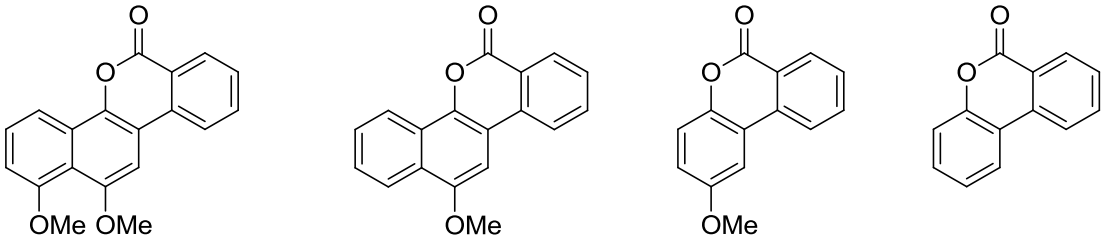


Scheme 89: Reagents and conditions: *(i) $Pd(PPh_3)_4$, aq. Na_2CO_3 (2 M), DME, reflux, 18 h, 81%; (ii) $LiAlH_4$, THF, rt, 2 h, 97%; (iii) NBS, CH_2Cl_2, O_2, 8 h.*

The Suzuki-Miyaura cross coupling reaction of the bromonaphthalene derivative **115** with a boronic acid **308** easily furnished the 2-naphthylbenzaldehyde derivative **328** as a yellow solid in 81% yield. The ^{1}H NMR spectrum undoubtedly proved that the coupling reaction was successful by the appearance of the aldehyde proton signal at δ 9.89 ppm and the corresponding carbonyl signal was observed in the ^{13}C NMR spectrum at δ 192.3 ppm. Reduction of the benzaldehyde **328** was accomplished by reacting with lithium aluminium hydride, affording the benzyl alcohol derivative **329**, which was obtained as a low melting solid in an excellent yield of 97%. As before, the disappearance of the aldehyde proton signal at δ 9.89 ppm and the appearance of a

methylene proton signal at δ 4.42 ppm in the ^{1}H NMR spectrum was evidence that the benzaldehyde was reduced. Additionally, ^{13}C NMR spectroscopy unambiguously established the formation of the alcohol by the disappearance of the aldehyde carbonyl signal at δ 192.3 ppm and the appearance of a typical benzylic carbon signal at δ 64.1 ppm.

The next step was the key NBS mediated ring closure reaction to furnish the lactone **330**. To accomplish this, the benzyl alcohol **329** was exposed to our NBS reaction conditions. Typically, upon addition of NBS, the reaction mixture is colourless and slowly turns light yellow after 4-6 hours, eventually turning a dark yellowish-brown colour when completed. To our surprise this time, when NBS was introduced, the reaction immediately turned brown and within a few minutes turned a deep purple colour. Examination of the TLC plate at this point showed a large number of spots. This suggested that decomposition of the reaction materials was possibly taking place. Our attempts to isolate and characterise any of these spots observed on the TLC plate were unsuccessful. This finding suggests that the NBS mediated lactonization reaction favours less electron rich ring systems although more detailed scientific study needs to be undertaken to confirm this. The overall trend is shown in **Figure 19**.



330	**238**	**322**	**327**
(decomposes)	**(42%)**	**(46%)**	**(70%)**

Figure 19: Yield comparisons in assembly of different ring systems

It would appear that this method would be useful in the synthesis of simpler and less oxygenated benzochromenone skeletons. We have not yet determined the reasons why electron rich systems are less favoured compared to less oxygenated ring systems in this NBS-mediated reaction.

6.5 Conclusion

Through the work presented in this chapter, we have established that the NBS mediated ring closing reaction is indeed a general method for the synthesis of benzonaphthopyranone ring systems. We have also established that the method has limitations in as far as the assembly of highly oxygenated or electron rich ring systems is concerned, and works best in electron deficient ring systems. Although the mechanism of the reaction has not been fully elucidated, we believe and have postulated that it proceeds *via* a lactol intermediate. Additionally, we hypothesised that the electronics in the rings play a role in the mechanism of the reaction and consequently in the formation of the products.

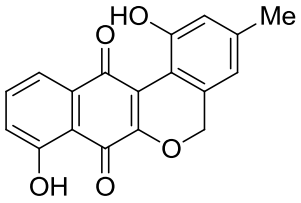
6.6 Future Work

This work has generated new scientific knowledge on the NBS mediated construction of benzonaphthopyranone ring systems, and at the same time, generated some unexpected results that could not be fully exploited due to time constraints of the PhD. One aspect that still needs to be studied is the mechanism of the reaction, along with rationalisation of the isoelectronic effect of the ring systems on the reaction.

Having established that the NBS reaction is a general method for the assembly of benzonaphthopyranone ring systems, it would be imperative to apply this methodology to the synthesis of natural products that possess the benzonaphthopyranone core like chrysomycins, ravidomycins and gilvocarcins.

Finally, one interesting aspect is that this reaction as highlighted in **Section 6.1** was serendipitously discovered in the process of brominating a naphthalene moiety at the C-3 position of a biaryl alcohol. In this study, we again serendipitously discovered that we were able to brominate that position of the ring on a 2-naphthylbenzaldehyde

scaffold as shown in **Scheme 84** in **Section 6.3.1.** With the bottleneck removed by this discovery, efforts to synthesise oxygen containing natural products such as lagumycin B **331** and WS-5995 A **332** could be explored.



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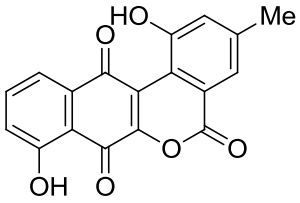


332

6.7 Overall conclusions from this PhD work

To sum up the work accomplished in this PhD, we undertook three projects, the first two of which were method development projects for the synthesis of natural angucycline antibiotics and the third project was based on synthetic studies in assembling benzonaphthopyranones using a novel reaction we discovered in our group.

In the first project, we have successfully developed a novel convergent method for the synthesis of 1,8-dihydroxy-3-methyltetraphene-7,12-dione **2**, a natural angucycline antibiotic commonly known as tetrangulol in 16 steps and 19.5% overall yield. In this strategy, the palladium catalysed Suzuki-Miyaura cross coupling reaction and the platinum or gold mediated intramolecular cycloisomerisation of a 2-naphthylphenylacetylene intermediate **118** were key steps. This method could now be extended to the synthesis of other angucycline antibiotic natural products.

Following this success, we then wanted to extend this work to the synthesis of other nitrogen containing aromatic natural products. More specifically, we wanted to develop a method for the synthesis of phenanthroviridone **146** from one of the intermediates that we used to synthesise tetrangulol. In our strategy, we sought to use microwave mediated or UV promoted intramolecular cyclisation of an advanced oxime ester or oxime ether precursor to give the nitrogen containing aromatic tetracyclic framework of phenanthroviridone. The intramolecular cyclisation instead furnished a benzo[*c*]phenanthridine skeleton. Although we did not succeed in the synthesis of phenanthroviridone **146**, we serendipitously found a UV promoted or microwave assisted radical based

strategy to assemble and access the biologically important benzo[*c*]phenanthridine alkaloids and other related natural products

The final project we undertook aimed at establishing the scope of NBS mediated cyclisation of 2-naphthylbenzylalcohol to assemble a fused chromenone skeletons. From this project, we established that the NBS mediated ring closing reaction is indeed a general method for the synthesis of benzonaphthopyranone ring systems. We further established that the method has limitations in as far as the assembly of highly oxygenated or electron rich ring systems is concerned, and works best in electron deficient ring systems.

Through this PhD, we believe we have contributed scientific knowledge in the area of total synthesis of angucycline antibiotic natural products and the assembly of benzonaphthopyranone motifs found in other classes of angucyclines. This is evidenced by our recent publication in the journal *Tetrahedron* based on our work on the NBS project. Additionally, a manuscript on the first two projects was submitted to *European Journal of Organic Chemistry* and is currently under review.

CHAPTER 7: Experimental Procedures

7.1 General Laboratory Procedures

7.1.1 Laboratory solvents

Solvents utilized for chromatographic techniques (ethyl acetate and *n*-hexane) were distilled preceding use by means of conventional distillation processes. The solvents employed in reactions were first dried over the suitable drying agent, followed by distillation under an inert atmosphere (argon or nitrogen gas). Acetonitrile and dichloromethane were distilled over calcium hydride, whereas tetrahydrofuran was distilled over sodium with benzophenone as an indicator. Toluene was distilled over sodium. All the required chemicals or reagents were obtained from FLUKA, SIGMA ALDRICH or MERCK and were used without further purification.

7.1.2 Chromatographic techniques

Normal chromatography was performed with silica gel 60 (Macherey-Nagel, particle size 0.063-0.200 mm) adsorbent, with both isocratic and gradient eluent systems being employed. Thin layer chromatography (TLC) of the compounds was executed on Macherey-Nagel Alugram Sil G/UV254 plates pre-coated with 0.25 mm silica gel 60. The TLC plates were viewed under UV light (254 nm and 366 nm).

7.1.3 Spectroscopic Analysis

7.1.3.1 Nuclear Magnetic Resonance (NMR)

Nuclear magnetic resonance (NMR) spectra were recorded on either a Bruker AVANCE 300 MHz or a Bruker AVANCE III 500 MHz spectrometer. All spectra were recorded in chloroform-*d*. All chemical shift values are reported in parts per million referenced against trimethylsilane which is given an assignment of zero parts per million. Coupling constants (*J*-values) are given in Hertz (Hz).

7.1.3.2 Infrared spectroscopy

The infra-red spectra were recorded on a Bruker Tensor 27 standard system spectrometer. Measurements were made by loading the sample directly onto a diamond cell. The measurements are reported on the wavenumber scale (/cm^{-1}).

7.1.3.3 High Resolution Mass Spectrometry

High resolution mass spectra were obtained with a Waters-LCT-Premier mass spectrometer. The sample was dissolved in methanol to a concentration of 2 ng/µl and introduced by direct infusion. The ionization mode was electrospray positive with a capillary voltage of 2500 V and a desolvation temperature of 250 °C using nitrogen gas at 250 L/hr. The intensity data was recorded on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K3 radiation (50 kV, 30 mA) with temperature of measurement at 173(2) K, using the APEX 2 data collection software. The collection method involved 4-scans of width 0.5 and 512×512 bit data frames. The data reduction was achieved by means of the program SAINT+ and face indexed absorption corrections were made using XPRE.

7.1.4 Melting points determination

Determination of melting points was done using a Reichert hot-stage microscope, and remain uncorrected. All crystalline compounds were recrystallized in the appropriate solvents prior to melting point determination.

7.1.5 Photochemical reactions

Photochemical reactions were done using a UV 450 W quartz mercury vapor Arc Lamp with an arc length of 5 inches, overall length 27 cm, overall diameter 13 inches, 430 mA operating current and UV output at principal wavelength of 254 nm. The lamp was inserted in a quartz immersion well 450 mm length. Reactions were undertaken in a 500 mL photochemical reaction vessel at a radiation distance of 1.5 cm.

7.1.6 Microwave reactions

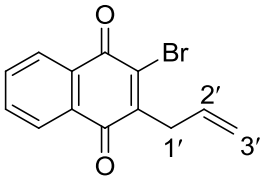
Microwave reactions were carried out in a CEM Discover microwave.

7.2 Experimental procedures pertaining to Chapter 2.

7.2.1 Experimental procedures for the synthesis of angucycline analogues

7.2.1.1 Preparation of 2-allyl-3-bromonaphthalene-1,4-dione 96

In a 1000 mL round-bottom flask, 2-bromo-naphthoquinone **95** (3.15 g, 13.29 mmol, 1.0 eq.), vinyl acetic acid (1.72 g, 1.70 mL, 19.98 mmol, 1.5 eq.) and silver nitrate (1.13 g, 6.65 mmol, 0.5 eq.) was added to dry MeCN (200 mL). The reaction mixture was heated to 65 °C and ammonium persulfate (6.07 g, 26.60 mmol, 2.0 eq.) in distilled water (150 mL) was added dropwise to the reaction mixture. The reaction mixture was maintained at 65 °C with stirring for 18 hrs under argon. Upon completion, the reaction mixture was quenched with H_2O (100 mL) and extracted into EtOAc (4 × 100 mL). The combined organic phase was washed sequentially with $NaHCO_3$ (2 × 100 mL) followed by brine (100 mL). The organic extract was dried over $MgSO_4$, filtered through Celite and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (20% EtOAc/Hexane) to yield 2-allyl-3-bromonaphthalene-1,4-dione **96** as a yellow solid (2.61 g, 9.44 mmol, 71%).

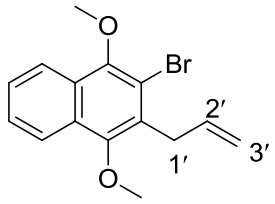


R_f = 0.50 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3114, 3018, 2911, 1688, 1677, 1591, 1484, 1457, 1126, 1051, 814; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.21 – 8.11 (2H, m, ArH), 7.82 – 7.72 (2H, m, ArH), 5.87 (1H, ddt, *J* = 16.6, 10.0, 6.6 Hz, H-2′), 5.27 (1H, ddd, *J* = 17.1, 2.9, 1.4 Hz, one of H-3′), 5.22 – 5.10 (1H, m, one of H-3′), 3.64 (2H, dt, *J* = 6.6, 1.4 Hz, H-1′); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 181.30, 177.66, 149.00, 139.40, 134.17, 133.92, 131.45, 131.40, 131.09, 127.48, 127.13, 118.27, 35.45.

7.2.1.2 Preparation of 2-allyl-3-bromo-1,4-dimethoxynaphthalene 74

In a 1000 mL round-bottom flask, sodium dithionite (7.85 g, 45.11 mmol, 5.0 eq.) in H_2O (50 mL) and TBAI (0.33 g, 0.90 mmol, 0.1 eq.) were added to a clear solution of

2-allyl-3-bromonaphthalene-1,4-dione **96** (2.50 g, 9.02 mmol, 1.0 eq.) in dry THF (100 mL). The reaction was stirred at rt under argon for 30 min and potassium hydroxide (5.05 g, 90.2 mmol, 10 eq.) in H_2O (150 mL) was then added and the reaction was stirred for a further 1 hr. Finally, dimethyl sulfate (11.35 g, 28.50 mL, 90.2 mmol, 10 eq.) was added and the reaction mixture was stirred for 18 hrs. Upon completion, the reaction was quenched with 25% aq. ammonia (100 mL) and the organic material was extracted into EtOAc (3 × 100 mL). The organic layer was consecutively washed with distilled water (100 mL), 10% aq. HCl (100 mL), brine (100 mL) and distilled water (100 mL) and was dried over $MgSO_4$ and filtered through Celite. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel chromatography (5% EtOAc/Hexane) to afford 2-allyl-3-bromo-1,4-dimethoxynaphthalene **74** as a yellow solid (1.94 g, 6.31 mmol, 70%).



R_f = 0.67 (50% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3067, 2988, 2812, 1636, 1258, 1058, 913; 817; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.13 – 8.02 (2H, m, ArH), 7.57 – 7.47 (2H, m, ArH), 6.07 (1H, ddt, *J* = 16.0, 10.2, 5.8 Hz, H-2′), 5.12 – 4.98 (2H, m, H-3′), 3.98 (3H, s, OMe), 3.92 (3H, s, OMe), 3.79 (2H, dt, *J* = 5.8, 1.7 Hz, H-1′); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 160.0, 150.2, 135.7, 128.9, 128.1, 127.9, 126.6, 126.5, 122.7, 122.6, 116.7, 115.9, 62.7, 61.4, 34.4.

7.2.1.3 General methods for preparation of Suzuki products

Method 1: Conventional method

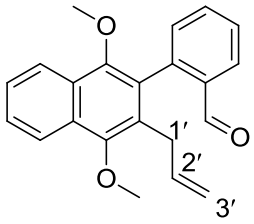
Tetrakis(triphenylphosphine)palladium(0) (10% mol) and boronic acid **73a** or **73b** (1.5 eq.) were added to a deoxygenated solution of 2-allyl-3-bromo-1,4-dimethoxynaphthalene (1.0 eq.) in DME (100 mL) under argon atmosphere with stirring. To this was added a deoxygenated aq. Na_2CO_3 solution (2 M, 4.0 eq.). The reaction mixture was then heated at reflux for 18 hrs. After this time, the mixture was

cooled to rt and reaction quenched with H_2O (50 mL). The organic material was extracted into EtOAc (3 × 100 mL), followed by a brine wash (100 mL). The combined extract was dried over $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (10-20% EtOAc/hexane) to afford the Suzuki products as yellow or off-white solids.

Method 2: Microwave assisted method

To a sealed microwave vessel was added 2-allyl-3-bromo-1,4-dimethoxynaphthalene (1.0 eq.), boronic acid **73a** or **73b** (1.6 eq.), cesium fluoride (2.0 eq.) and *tetrakis*(triphenylphosphine)palladium(0) (10 mol%) in dimethoxyethane (2 mL/mmol of bromo-compound). The reaction mixture was irradiated with 150 W at 150 °C for 15 min by microwave reactor. The reaction was allowed to cool, diluted with H_2O (20 mL) and extracted into EtOAc (2 × 40 mL). The organic layer was consecutively washed with distilled water (40 mL) and brine (40 mL) before being dried over $MgSO_4$ and filtered through Celite. The solvent was removed *in vacuo* and the residue purified by flash silica gel chromatography (5% EtOAc/Hexane) to afford the products as yellow compounds.

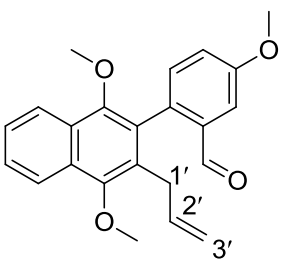
7.2.1.4 Preparation of 2-(3-allyl-1,4-dimethoxynaphthalen-2-yl)benzaldehyde 75a



Yellow solid (0.77 g, 60%); $\mathbf{R_f}$ = 0.45 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3072, 2841, 1676, 1597, 1482, 1201, 1126, 1007, 923; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.74 (1H, s, ArCHO), 8.18 – 8.05 (3H, m, ArH), 7.67 (1H, m, ArH), 7.63 – 7.49 (3H, m, ArH), 7.38 (1H, ddd, *J* = 7.6, 1.3, 0.5 Hz, ArH), 5.68 (1H, ddt, *J* = 16.2, 10.1, 6.0 Hz, H-2′), 4.81 (1H, dd, *J* = 10.1, 1.6 Hz, one of H-3′), 4.56 (1H, dd, *J* =17.1, 1.7 Hz, one of H-3′), 3.97 (3H, s, OMe), 3.46 (3H, s, OMe), 3.39 (2H, dt, *J* = 5.8, 1.7 Hz, H-1′); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 192.2, 150.8, 150.1, 140.2, 136.1, 134.4, 133.2, 131.7, 128.9, 128.2, 127.6, 127.5, 127.1,

126.8, 126.3, 122.9, 122.6, 115.9, 62.5, 61.2, 31.8; **HRMS** (ESI+): Found $(M + H)^+$ 333.1496, $C_{22}H_{20}O_3$ $(M + H)^+$ requires 333.1491, *m/z* 333.1496 [$(M + H)^+$, 100%], 301.1233 (35), 289.1239 (50).

7.2.1.5 Preparation of 2-(3-allyl-1,4-dimethoxynaphthalen-2-yl)-5-methoxybenzaldehyde 75b



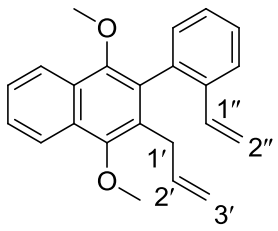
Yellow solid (1.15 g, 65%); $\mathbf{R_f}$ = 0.64 (50% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3078, 2840, 1682, 1601, 1498, 1233, 1102, 1008, 932; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.67 (1H, s, ArCHO), 7.62 – 7.49 (3H, m, ArH), 7.33 – 7.18 (2H, m, ArH), 5.69 (1H, ddt, *J* = 16.1, 10.1, 6.0 Hz, H-2′), 4.83 (1H, dd, *J* = 10.1, 1.5 Hz, one of H-3′), 4.59 (1H, dd, *J* = 17.1, 1.6 Hz, one of H-3′), 3.97 (3H, s, OMe), 3.93 (3H, s, OMe), 3.46 (3H, s, OMe), 3.40 (2H, dt, J = 5.9, 1.5 Hz, H-1′); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 192.1, 159.4, 150.7, 150.5, 136.2, 132.9, 128.9, 128.0, 127.8, 127.6, 126.7, 126.2, 122.9, 122.5, 121.0, 115.8, 109.6, 62.4, 61.1, 55.6, 31.9; **HRMS** (ESI+): Found $(M + H)^+$ 363.1588, $C_{23}H_{22}O_4$ $(M + H)^+$ requires 363.1574, *m/z* 363.1588 [$(M + H)^+$, 100%], 319.1336 (30).

7.2.1.6 General method for preparation of Wittig products

In a 50 mL two necked round-bottom flask fitted with a rubber septum, *n*-butyllithium (1.5 M, 2.5 eq.) was added dropwise at rt to a suspension of methyltriphenylphosphonium bromide (2.5 eq.) in dry THF (10 mL). The resulting orange solution was stirred for a further 30 min before being cooled to 0 °C using an ice-bath. Aldehyde **75a** or **75b** (1.0 eq.) in dry THF (5 mL) was added dropwise at 0 °C to the resulting ylide. The reaction was then warmed to rt and stirred at this temperature for 18 hrs. Upon completion, the reaction mixture was diluted with diethyl ether (50 mL) and washed with H_2O (50 mL). The organic extract was dried over $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. The resulting

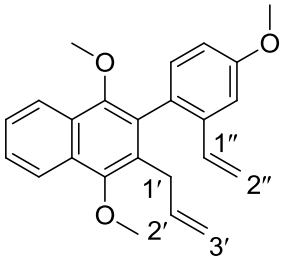
crude product was purified by column chromatography on silica gel (5% EtOAc/Hexane) to afford the products as yellow oils.

7.2.1.7 Preparation of 2-allyl-1,4-dimethoxy-3-(2-vinylphenyl)naphthalene 76a



Yellow oil (0.11 g, 81%); **R_f** = 0.70 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3108, 3072, 2930, 1588, 1483, 1227, 1124, 1006, 910; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.16 – 8.11 (2H, m, ArH), 7.72 (1H, dd, *J* = 7.7, 1.2 Hz, ArH), 7.58 – 7.47 (2H , m, ArH), 7.35 (2H, dtd, *J* = 20.7, 7.3, 1.2 Hz, ArH), 7.25 – 7.20 (1H, m, ArH), 6.41 (1H, dd, *J* = 17.6, 11.0 Hz, H-1″), 5.76 – 5.59 (2H, m, H-2′ and one of H-2″ overlapping), 5.07 (1H, dd, *J* = 11.0, 1.1 Hz, one of H-2″), 4.80 (1H, dd, *J* = 17.0, 3.4, 1.6 Hz, one of H-3′), 4.67 (1H, ddd, *J* = 10.1, 3.2, 1.5 Hz, one of H-3′), 3.96 (3H, s, OMe), 3.55–3.44 (4H, m, OMe and one of H-1′ overlapping), 3.13 (1H, ddt, *J* = 14.9, 6.2, 1.5 Hz, one of H-1′); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 150.5, 149.8, 136.5, 136.4, 135.6, 135.1, 131.3, 131.2, 128.6, 128.4, 128.0, 127.8, 127.2, 126.2, 125.8, 124.6, 122.9, 122.4, 115.2, 114.6, 62.4, 61.3, 31.9; **HRMS** (ESI+): Found $(M + H)^+$ 331.1698, $C_{23}H_{22}O_2$ $(M + H)^+$ requires 331.1674, *m/z* 331.1698 [$(M + H)^+$, 95%], 289.1237 (50), 275.1073 (20).

7.2.1.8 Preparation of 2-allyl-1,4-dimethoxy-3-(4-methoxy-2-vinylphenyl) naphthalene 76 b



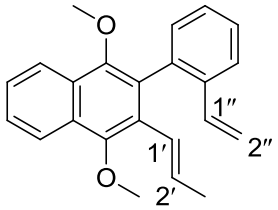
Yellow oil (0.88 g, 94%); **R_f** = 0.58 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3087, 3012, 2928, 1603, 1490, 1231, 1196, 1087, 913; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.12 (2H, dd, *J* = 7.2, 2.4 Hz, ArH), 7.57 – 7.47 (2H, m, ArH), 7.24 (2H, d, *J* = 3.4 Hz, ArH), 7.14 (1H, d, *J* = 8.4 Hz, ArH), 6.90 (1H, dd, *J* = 8.4, 2.6 Hz, ArH), 6.37 (1H, dd, *J* = 17.5, 11.0 Hz, H-1″), 5.76 – 5.61 (2H, m, H-2′ and one of H-2″ overlapping), 5.07 (1H, dd, *J* = 11.0, 1.0 Hz, one of H-2″), 4.81 (1H, dd, *J* = 10.1, 1.6 Hz, one of H-3′), 4.69 (1H, dd, *J* = 17.1, 1.7 Hz, one

of H-3′), 3.96 (3H, s, OMe), 3.90 (3H, s, OMe), 3.51 (3H, s, OMe), 3.49–3.44 (1H, m, one of H-1′), 3.14 (1H, dd, *J* = 14.9, 6.2, 1.6 Hz, one of H-1′); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 159.2, 150.4, 150.2, 137.5, 136.6, 135.2, 132.3, 130.9, 128.9, 128.5, 128.3, 128.0, 126.2, 125.8, 122.9, 122.4, 115.2, 114.7, 113.3, 109.5, 62.4, 61.3, 55.3, 32.0; **HRMS** (ESI+): Found $(M + H)^+$ 361.1799, $C_{24}H_{24}O_3$ $(M + H)^+$ requires 361.1773, *m/z* 361.1799 [$(M + H)^+$, 100%], 279.0945 (75).

7.2.1.9 General method for preparation of Isomerisation products

A 50 mL round-bottom flask, alkene **76a** or **76b** (1.0 eq.) was dissolved in dry THF (10 mL). Potassium *tert*-butoxide (4.0 eq.) in dry THF (10 mL) was slowly added and the resulting reaction mixture was stirred at rt for 4 hrs, under argon. The mixture was poured into saturated aq. ammonium chloride (20 mL) and the organic material extracted into EtOAc (4 × 50 mL). The organic extract was washed in succession with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$ and filtered through Celite. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (10% EtOAc/Hexane) to yield the products as clear oils.

7.2.1.10 Preparation of (*E*)-1,4-dimethoxy-2-(prop-1-en-1yl)-3-(2vinylphenyl)naphthalene 77a

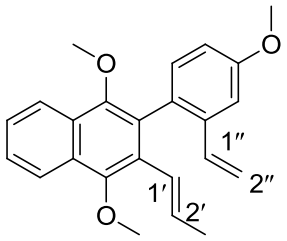


Clear oil (0.16 g, 73%); **R_f** = 0.72 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3066, 2984, 2813, 1626, 1480, 1269, 1190, 910; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.17 – 8.18 (2H, m, ArH), 7.71 – 7.64 (1H, m, ArH), 7.55 – 7.41 (2H, m, ArH), 7.38 – 7.26 (2H, m, ArH), 7.21 (1H, dd, *J* = 7.3, 1.7 Hz, ArH), 6.46 (1H, dd, *J* = 17.5, 11.0 Hz, H-1″), 6.13 (1H, d, *J* = 17.1 Hz, H-1′), 6.07 – 5.93 (1H, m, H-2′), 5.64 (1H, dd, *J* = 17.5, 0.9 Hz, one of H-2″), 5.03 (1H, dd, *J* = 11.0, 0.9 Hz, one of H-2″), 3.83 (3H, s, OMe), 3.45 (3H, s, OMe), 1.65 (3H, dd, *J*

= 6.2, 0.9 Hz, -Me); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.0, 149.6, 136.5, 136.2, 135.3, 131.8, 131.2, 130.1, 128.9, 127.8, 127.6, 127.3, 126.8, 126.3, 126.0, 124.8), 124.6, 122.7, 122.6, 114.3, 61.0, 60.6, 19.7; **HRMS** (ESI+): Found $(M + H)^+$ 331.1693, $C_{23}H_{22}O_2$ $(M + H)^+$ requires 331.1674, *m/z* 331.1679 [$(M + H)^+$, 45%], 317.1543 (85), 315.1390 (80), 289.1237 (50).

7.2.1.11 Preparation of (*E*)-1,4-dimethoxy-2-(4-methoxy-2vinylphenyl)-3-(prop-1-en-1-yl)naphthalene 77b

Clear oil (0.75 g, 88%); $\mathbf{R_f}$ = 0.63 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): , 3012, 2931, 2837, 1602, 1492, 1228, 1181, 1025, 908; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.19 – 8.06 (2H, m, ArH), 7.55 – 7.45 (2H, m, ArH), 7.25 – 7.21 (1H, m, ArH), 7.13 (1H, dd, *J* = 8.4, 2.9 Hz, ArH), 6.92 (1H, dd, *J* =8.4, 2.4 Hz, ArH), 6.46 – 6.37 (1H, m, H-1″), 6.12 (1H, dd, *J* = 15.9, 1.9 Hz, H-2′), 6.08 – 5.98 (1H, m, H-1′), 5.65 (1H, dd,, *J* = 17.5, 2.4 Hz, one of H-2″), 5.06 (1H, dd, *J* = 11.0, 1.0 Hz, one of H-2″), 3.89 (3H, s, OMe), 3.84 (3H, s, OMe), 3.47 (3H, s, OMe), 1.69 (3H, dd, *J* = 4.8, 2.6 Hz, -Me); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.0, 150.0, 149.9, 137.7, 135.4, 132.3, 131.8, 129.8, 128.9, 128.8, 127.7, 127.2, 126.3, 125.9, 124.9, 122.7, 122.6, 114.4, 113.4, 109.5, 61.0, 60.6, 55.2, 19.8; **HRMS** (ESI+): Found $(M + H)^+$ 361.1804, $C_{24}H_{24}O_3$ $(M + H)^+$ requires 361.1773, *m/z* 361.1804 [$(M + H)^+$, 100%], 345.1495 (50), 319.1352 (35), 305.1188 (15).

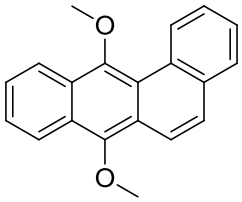


7.2.1.12 General Method for RCM ring closure

In a 50 mL round-bottom flask fitted with a condenser was added the di-alkene **77a** or **77b** (1.0 eq.) in dry CH_2Cl_2 (10 mL/mmol of dialkene). To this was added Grubbs II catalyst (15 mol%) and the reaction was heated under reflux for 18 hrs under an argon atmosphere. Upon completion, the reaction was cooled to rt and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (5% EtOAc/ Hexane) to yield the products as off white solids.

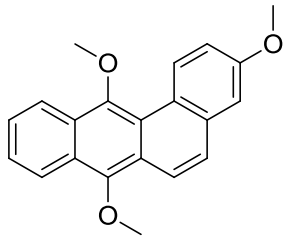
7.2.1.13 Preparation of 7,12-dimethoxytetraphene 78a

Yellow solid (0.11 g, 92%); **R_f** = 0.61 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3016, 2931, 2837, 1593, 1495, 1448, 1252, 1098; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.67 (1H, d, *J* = 8.4 Hz, ArH), 8.50 – 8.41 (1H, m, ArH), 8.37 – 8.31 (1H, m, ArH), 8.14 (1H, d, *J* = 9.2 Hz, ArH), 7.84 (1H, d, *J* = 7.3 Hz, ArH), 7.71 – 7.65 (1H, m, ArH), 7.65 – 7.59 (4H, m, ArH), 4.12 (3H, s, OMe), 3.97 (3H, s, OMe); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.1, 148.6, 132.7, 130.0, 128.4, 128.2, 127.6, 127.4, 127.3, 127.0, 126.5, 126.0, 125.9, 124.3, 123.2, 122.3, 121.1, 120.8, 63.2, 60.9; **HRMS** (ESI+): Found $(M + H)^+$ 289.1010, $C_{20}H_{16}O_2$ $(M + H)^+$ requires 289.1274, *m/z* 289.1010 [$(M + H)^+$, 100%], 273.0919 (90).



7.2.1.14 Preparation of 3,7,12-trimethoxytetraphene 78b

Yellow solid (0.38 g, 88%); **R_f** = 0.61 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3012, 2933, 2843, 1606, 1494, 1267, 1201, 1109; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.58 (1H, d, *J* = 9.2 Hz, ArH), 8.43 (1H, dd, *J* = 7.4, 1.8 Hz, ArH), 8.32 (1H, dd, *J* = 7.3, 1.8 Hz, ArH), 8.13 (1H, d, *J* = 9.3 Hz, ArH), 7.64 – 7.53 (3H, m, ArH), 7.31 – 7.23 (2H, m, ArH), 4.11 (3H, s, OMe), 3.98 (3H, s, OMe), 3.96 (3H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 158.3, 150.1, 148.8, 134.4, 129.9, 127.4, 127.4, 125.9, 125.6, 125.4, 123.7, 123.7, 123.0, 122.3, 121.7, 120.9, 116.0, 110.0, 63.2, 60.7, 55.4; **HRMS** (ESI+): Found $(M + H)^+$ 319.1259, $C_{21}H_{18}O_3$ $(M + H)^+$ requires 319.1379, *m/z* 319.1259 [$(M + H)^+$, 90%], 318.1262 (100), 303.1032 (25).

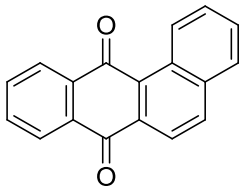


7.2.1.15 General Method for oxidation of naphthalenes

In a 50 mL round-bottom flask, the arene **78a** or **78b** (1.0 eq.) was dissolved in acetonitrile (10 mL/mmol of arene). CAN (2.5 eq.) in H_2O volume equivalent to acetonitrile was added and the reaction was stirred for 30 min. $NaHCO_3$ was added

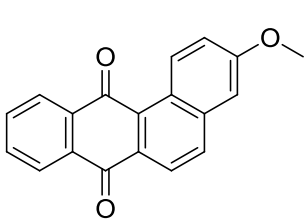
and the organic material extracted in EtOAc (3 × 10 mL). The combined organic layer was then dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (20% EtOAc/ Hexane) to yield the products as yellow solids.

7.2.1.16 Preparation of tetraphene-7,12-dione 79a



Yellow solid (71 mg, 79%); $\mathbf{R_f}$ = 0.63 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3011, 2918, 1682, 1675, 1587, 1507, 1277; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.72 (1H, d, *J* = 8.8 Hz, ArH), 8.39 (1H, d, *J* = 8.5 Hz, ArH), 8.29 (2H, dd, *J* = 24.2, 7.3 Hz, ArH), 8.21 (1H, d, *J* = 8.5 Hz, ArH), 7.92 (1H, d, *J* = 8.1 Hz, ArH), 7.78 (3H, tdd, *J* = 9.4, 5.4, 4.3 Hz, ArH), 7.67 (1H, t, *J* = 7.3 Hz, ArH); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 186.2, 184.0, 136.7, 135.3, 135.1, 134.2, 134.1, 133.5, 132.3, 130.6, 130.0, 129.4, 128.8, 128.7, 127.3, 126.5, 122.5; **HRMS** (ESI+): Found $(M + H)^+$ 259.0747, $C_{18}H_{10}O_2$ $(M + H)^+$ requires 259.0779, *m/z* 259.0742 [$(M + H)^+$, 100%], 234.2048 (25), 224.1323 (10).

7.2.1.17 Preparation of 3-methoxytetraphene-7,12-dione 79b



Yellow solid (0.103 g, 81%); $\mathbf{R_f}$ = 0.61 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3010, 2917, 2849, 1689, 1670, 1610, 1503, 1264, 1201; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.61 (1H, d, *J* = 9.6 Hz, ArH), 8.34 (1H, d, *J* = 8.6 Hz, ArH), 8.30 – 8.21 (2H, m, ArH), 8.06 (1H, d, *J* = 8.6 Hz, ArH), 7.82 – 7.71 (2H, m, ArH), 7.38 (1H, dd, *J* = 9.6, 2.8 Hz, ArH), 7.18 (1H, t, *J* = 5.0 Hz, ArH), 3.97 (3H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 186.4 183.8, 159.6, 138.9, 135.0, 134.0, 133.8, 133.5, 132.4, 132.1, 130.4, 129.5, 127.2, 126.4, 125.7, 123.4, 122.4, 106.7, 55.4; **HRMS** (ESI+): Found $(M + H)^+$ 289.0805, $C_{19}H_{12}O_3$ $(M + H)^+$ requires 289.0874, *m/z* 289.0805 [$(M + H)^+$, 100%].

7.2.2 Experimental procedures for the synthesis of tetrangulol

7.2.2.1 Preparation of (2-bromo-5-methoxy-3-methylphenyl)methanol 108

Method 1: Green Chemistry

To an ethyl acetate (15 mL) solution of 3,5-dimethylanisole **105** (900 mg, 6.61 mmol, 1.0 eq.), was added benzoyl peroxide (8 mg; 0.033 mmol, 0.5 mol%) and *N*-bromosuccinimide (2.47 g, 13.88 mmol, 2.1 eq.). The reaction mixture was refluxed for 60 min under microwave heating (magnetron power of 300 W). The crude product was washed with 30 mL each of 10% aq. HCl, saturated aq. $NaHCO_3$, H_2O and brine. The crude product was used for the next reaction without further purification.

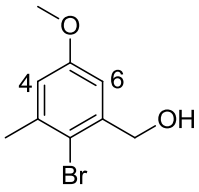
To a stirred solution of the above residue in dioxane (30.0 mL) and H_2O (30.0 mL), $CaCO_3$ (1.32 g, 13.22 mmol, 2.0 eq.) was added at rt under argon. The reaction mixture was stirred at reflux for 18 hrs and then cooled to rt and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (30% EtOAc/hexane) to afford (2-bromo-5-methoxy-3-methylphenyl)methanol **108** as an off-white solid (1.10 g, 4.76 mmol, 72%).

Method 2: Carbon tetrachloride method

To a stirred solution of 3,5-dimethylanisole **105** (2.07 ml, 14.68 mmol, 1.0 eq.) in CCl_4 (30.0 mL), NBS (2.62 g, 14.68 mmol, 1.0 eq.) and benzoyl peroxide (356 mg, 1.47 mmol) were added at rt under argon. The reaction mixture was refluxed for 4 hrs and the succinimide was filtered off and the filtrate was successively washed with 100 mL each of 10% aq. HCl, saturated aq. $NaHCO_3$, H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the above residue in dioxane (30 mL) and H_2O (30 mL), $CaCO_3$ (2.94 g, 29.36 mmol, 2.0 eq.) were added at rt under argon. The reaction

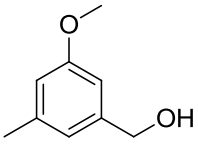
mixture was stirred at reflux for 12 hrs and then cooled to rt and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (100 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by chromatography (30% EtOAc/hexane) to afford (2-bromo-5-methoxy-3-methylphenyl)methanol **108** as an off-white solid (2.37 g, 10.28 mmol, 70%).



R_f = 0.42 (20% EtOAc/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.86 (1H, d, *J* = 3.2 Hz, H-6), 6.69 (1H, d, *J* = 3.1 Hz, H-4), 4.64 (2H, s, -C*H*$_2$OH), 3.75 (3H, s, OMe), 2.85 (1H, br-s, OH), 2.34 (3H, s, ArMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 158.6, 141.0, 139.2, 115.5, 115.1, 111.3, 65.3, 55.4, 23.4 (Me).

7.2.2.2 Preparation of (3-methoxy-5-methylphenyl)methanol 106

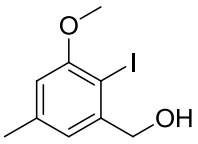
In an oven-dried 250 mL two-neck round-bottom flask equipped with a magnetic stirring bar was placed (2-bromo-5-methoxy-3-methylphenyl)methanol **108** (7.62 g, 33.0 mmol) in dry THF (150 mL) under argon atmosphere. The mixture was cooled to −78 °C and a 1.3 M solution of *n*-BuLi in hexanes (38.08 mL, 49.50 mmol) was added dropwise. The mixture was stirred at −78 °C for 2 hrs and was then slowly warmed to rt. The reaction was quenched with water (50 mL) and then extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (20-30% EtOAc/hexane) to give 3-methoxy-5-methylphenyl)methanol **106** as a yellowish oil (4.72 g, 31.02 mmol, 94%).



R_f = 0.27 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3377, 2979, 1612, 1443, 1297, 1166, 1042; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.74 (1H, d, *J* = 0.7 Hz, ArH), 6.69 (1H, d, *J* = 0.8 Hz, ArH), 6.63 (1H, d, *J* = 0.7 Hz, ArH), 4.57 (2H, s, -C*H*$_2$OH), 3.76 (3H, s, OMe), 2.31 (3H, s, ArMe), 2.28 (1H, br-s, OH); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 159.8, 142.4, 139.7, 120.0, 114.0, 109.3, 65.2, 55.2, 21.5.

7.2.2.3 Preparation of (2-iodo-3-methoxy-5-methylphenyl)methanol 109

In an oven-dried 50 mL three-neck round-bottom flask equipped with a magnetic stirring bar was placed (3-methoxy-5-methylphenyl)methanol **106** (500 mg, 3.29 mmol) in dry Et_2O (17 mL) under argon atmosphere. The mixture was cooled to −78 °C and a 1.2 M solution of *n*-BuLi in hexanes (6.05 mL, 7.26 mmol) was added dropwise. The mixture was the slowly warmed to rt and stirred for 4 hrs. The solution was cooled to 0 °C and THF (9 mL) was then added to the solution and the mixture further stirred for 1 hr followed by the slow addition of I_2 (1.00 g, 3.95 mmol) dissolved in THF (4.0 mL). After being stirred at 0 °C for 30 min, the reaction mixture was poured into aq. $Na_2S_2O_3$ and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (20% EtOAc/hexane) to afford (2-iodo-3-methoxy-5-methylphenyl)methanol **109** as a white crystalline solid (641 mg, 2.31 mmol, 70%).

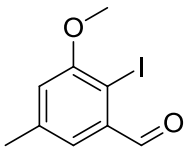


R_f = 0.39 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3193, 2912, 1576, 1449, 1302, 1171, 1041, 836; **H NMR** (500 MHz, $CDCl_3$): δ 6.90 (1H, d, *J* = 0.6 Hz, ArH), 6.58 (1H, d, *J* = 0.9 Hz, ArH), 4.65 (2H, s, -C*H*$_2$OH), 3.86 (3H, s, OMe), 2.34 (4H, s, ArMe and OH overlapping); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.8 (ArC-O), 144.0, 139.7, 121.8, 111.2, 85.4 (ArC-I), 69.6 (-*C*H_2OH), 56.5 (-OCH_3), 21.4 (Me).

7.2.2.4 Preparation of 2-iodo-3-methoxy-5-methylbenzaldehyde 98

In an oven-dried 10 mL round bottom flask equipped with a magnetic stirring bar was placed 2-iodo-3-methoxy-5-methylphenyl)methanol **109** (360 mg, 1.29 mmol) in dry CH_2Cl_2 (5.0 mL). To this solution, MnO_2 (450 mg, 5.2 mmol) was added and the reaction was stirred at rt for 24 hrs. The solution was then filtered through a pad of Celite and concentrated *in vacuo.* The crude product was purified by chromatography

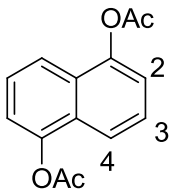
on silica gel (20 % EtOAc/hexane) to give 2-iodo-3-methoxy-5-methylbenzaldehyde **98** as an off-white solid (345 mg, 1.25 mmol, 97%).



R_f = 0.59 (20% EtOAc/Hexane)**; IR** (ν/cm^{-1}): 3174, 2912, 1703, 1576, 1457, 1309, 1116, 1041, 838; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.16 (1H, s, H-1), 7.31 (1H, s, H-2), 6.88 (1H, s, H-4), 3.93 (3H, s, OMe), 2.39 (3H, s, H-3); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 196.6, 158.2, 140.0, 136.2, 122.9, 117.2, 90.1, 56.8, 21.1.

7.2.2.5 Preparation of 1,5-diacetoxynaphthalene 101

In a 250 mL round-bottom flask equipped with a magnetic stirring bar was placed 1,5-dihydroxynaphthalene **100** (10.01 g, 62.5 mmol) followed by pyridine (50.4 mL, 0.625 mol) and acetic anhydride (53.2 mL, 0.563 mol). The mixture was stirred at rt for 18 hrs followed by the careful addition of H_2O to quench the reaction, causing the product to precipitate. The precipitate was filtered and washed with H_2O (5 × 100 mL) to afford the acetylated product **101** as a light brown solid (14.85 g, 60.6 mmol, 97 %).

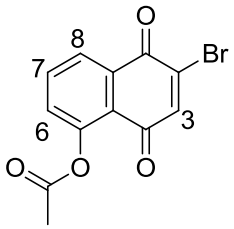


R_f = 0.21 (20% EtOAc/Hexane)**; IR** (ν/cm^{-1}): 3012, 2813, 1751, 1613, 1412, 1370, 1182, 1157, 1012, 950; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.78 (2H, d, *J* = 8.6 Hz, H-4), 7.50 (2H, t, *J* = 8.7 Hz, H-3), 7.29 (2H, dd, *J* = 7.4, 0.6 Hz, H-2), 2.45 (6H, s, -CO_2Me); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.3 (ArC-O), 146.8, 128.2, 126.0, 119.3, 118.8, 21.0.

7.2.2.6 Preparation of 5-acetoxy-2-bromo-1,4-naphthoquinone 32

In a 1000 mL round bottom flask equipped with a magnetic stirring bar and fitted with a dropping funnel, *N*-bromosuccinimide (NBS) (14.63 g, 82.01 mmol) was dissolved in AcOH (400 mL) and H_2O (200 mL) and the reaction heated to 65 °C. The dropping funnel was charged with 1,5-diacetoxynaphthalene **101** (5.01g, 20.50 mmol) in warm AcOH (200 mL) and this solution was added dropwise to the NBS

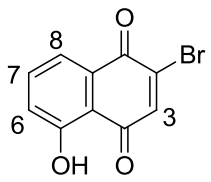
solution. After complete addition, the reaction was maintained at 65 °C for a further 1 hr. the cooled reaction mixture was then extracted with CH_3Cl (3 × 100 mL). The combined organic extract was sequentially washed with H_2O (4 × 200 mL) and brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (20 % EtOAc/hexane) to afford 5-acetoxy-2-bromo-1,4-naphthoquinone **32** as a yellow solid (5.50g, 18.7 mmol, 91%).



R_f = 0.40 (20% EtOAc/Hexane)**; IR** (ν/cm^{-1}): 3124, 2967, 1781, 1684, 1683, 1602, 1368, 1326, 1190; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.14 (1H, dd, *J* = 7.8, 1.3 Hz, H-8), 7.77 (1H, t, *J* = 7.9, Hz, H-7), 7.42 (1H, dd, *J* = 8.1, 1.3 Hz, H-6), 7.39 (1H, s, H-3), 2.44 (3H, s, -CO_2*Me*); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 180.9, 177.4, 169.2, 149.9, 141.4, 138.5, 134.9, 132.6, 130.3, 126.3, 21.0.

7.2.2.7 Preparation of 2-bromo-5-hydroxy-1,4-naphthoquinone 102

3 N H_2SO_4 (90 mL) was added to the suspension of 5-acetoxy-2-bromo-1,4-naphthoquinone **32** (8.20 g, 27.82 mmol) in EtOH (300 mL). the suspension was heated gently under reflux for 30 min. The solution was concentrated *in vacuo* to remove EtOH and the residue extracted with $CHCl_3$ (3 × 150 mL). The combined extracts were washed with H_2O (4 × 200 mL) and brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (15% EtOAc/hexane) to give 2-bromo-5-hydroxy-1,4-naphthoquinone **102** as a brown-orange solid (5.70 g, 22.5 mmol, 81%).

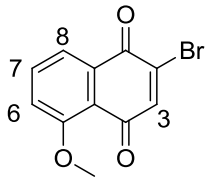


R_f = 0.68 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3326, 3190, 1681, 1674, 1596, 1460, 1310, 1097, 815; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.77 (1H, s, ArOH), 7.73 (1H, dd, *J* = 7.5, 1.2 Hz, H-8), 7.63 (1H, t, *J* = 8.4, 1.1

Hz, H-7), 7.49 (1H, s, H-3), 7.31 (1H, dd, *J* = 8.3, 1.3 Hz, H-6); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 187.5, 177.2, 161.7, 140.9, 140.3, 136.5, 130.7, 125.1, 121.0, 114.7.

7.2.2.8 Preparation of 2-bromo-5-methoxy-1,4-naphthoquinone 99

In a 100 mL round bottom flask equipped with a magnetic stirring bar was placed 2-bromo-5-hydroxy-1,4-naphthoquinone **102** (4.70 g, 18.60 mmol) dissolved in CH_2Cl_2 (60 mL) followed by Ag_2O (10.80 g, 46.63 mmol). To this suspension, MeI (7.92 g, 3.6 mL, 55.81 mmol) was added and the reaction mixture was stirred at rt for 24 hrs under argon. The suspension was filtered through a pad of Celite and the solvent removed *in vacuo.* The crude product was purified by column chromatography on silica gel (30% EtOAc/hexane) to give 2-bromo-5-methoxy-1,4-naphthoquinone **99** as a yellow solid (5.90 g, 17.9 mmol, 96 %).

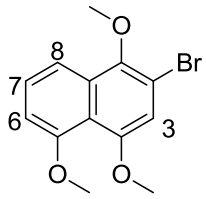


R_f = 0.16 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3013, 2915, 1680, 1672, 1595, 1475, 1457, 1298, 1047, 814; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.81 (1H, dd, *J* = 7.7, 1.2 Hz, H-8), 7.69 (1H, t, *J* = 8.4 Hz, H-7), 7.39 (1H, s, H-3), 7.35 (1H, dd, *J* = 8.5, 1.2 Hz, H-6), 4.02 (3H, s, OMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 181.4, 178.2, 160.0, 142.3, 136.8, 135.0, 133.0, 120.6, 119.3, 118.5, 56.6.

7.2.2.9 Preparation of 2-bromo-1,4,5-trimethoxynaphthalene 115

To a clear solution of 2-bromo-5-methoxy-1,4-naphthoquinone **99** (6.10 g, 22.85 mmol) in THF (380 mL) was added $Na_2S_2O_4$ (19.9 g, 114.30 mmol) in H_2O (100 mL) and TBAI (0.84 g, 2.28 mmol). The reaction was stirred at rt under argon for 30 min followed by the addition of KOH (12.8 g, 0.23 mol) in H_2O (300 mL). The reaction was stirred for 1 hr and Me_2SO_4 (28.8 g, 21.6 mL, 0.23 mol) was added. The reaction

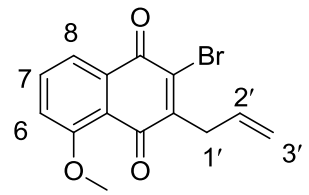
mixture was then stirred for 18 hrs before being quenched with 25% NH_4OH (150 mL) and the organic material extracted into EtOAc (3 × 200 mL). The combined organic extracts were washed sequentially with distilled water (200 mL), 10% aq. HCl (200 mL) and brine (200 mL). The organic extract was dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% EtOAc/hexane) to give 2-bromo-1,4,5-trimethoxynaphthalene **115** as a yellowish-brown solid (5.43 g, 18.1 mmol, 79%).



R_f = 0.57 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3094, 2921, 2910, 1605, 1465, 1385, 1270, 1156, 1092, 1054, 815; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.68 (1H, d, *J* = 8.4 Hz, H-8), 7.44 (1H, t, *J* = 8.0 Hz, H-7), 6.90 (1H, s, H-3), 6.88 (1H, dd, *J* = 7.8, 0.5 Hz, H-6), 3.95 (3H, s, OMe), 3.93 (3H, s, OMe), 3.92 (3H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.5, 153.9, 146.7, 131.7, 127.5, 117.6 114.6, 112,6, 109.8, 106.9, 61.1, 56.8, 56.4.

7.2.2.10 Preparation of 3-allyl-2-bromo-5-methoxy-1,4-naphthoquinone 103

To a mixture of 2-bromo-5-methoxy-1,4-naphthoquinone **99** (2.20 g, 8.24 mmol) and silver nitrate (0.71 g, 4.18 mmol) in dry MeCN (140 mL) was added vinyl acetic acid (1.42 g, 1.40 mL, 16.48 mmol). The reaction mixture was heated to 65 °C and $(NH_4)_2S_2O_8$ (3. 76 g, 16.48 mmol) in distilled water (120 mL) was added dropwise to the reaction mixture over 30 min. After stirring for 16 h at 65 °C under argon, the cooled reaction mixture was extracted with EtOAc (3 × 100 mL), washed with $NaHCO_3$ (2 × 100 mL) followed by brine (100 mL) and dried over $MgSO_4$. After filtering through Celite, the solvent was removed *in vacuo* and the crude product was purified by column chromatography on silica gel (20-30% EtOAc/hexane) to yield 3-allyl-2-bromo-5-methoxy-1,4-naphthoquinone **103** as a yellow solid (1.82 g, 5.93 mmol, 72%).

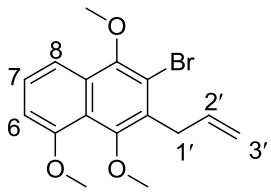


R_f = 0.28 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3109, 3008, 2917, 1684, 1675, 1591, 1496, 1126, 1108, 1051, 817; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.80 (IH, dd, *J* = 7.7, 1.1 Hz, H-8), 7.66 (1H, t, *J* = 8.4 Hz, H-7), 7.32 (1H, dd, *J* = 8.5, 0.9 Hz, H-6), 5.94 – 5.77 (1H, m, H-2′), 5.27 (1H, dd, *J* = 17.1, 1.5 Hz, H-3′), 5.12 (1H, dd, *J* = 10.0, 1.4 Hz, H-3′), 4.01 (3H, s, OMe), 3.60 (2H, d, *J* = 6.6 Hz, H-1′); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 180.2, 178.1, 160.1, 150.6, 136.6, 134.9, 133.3, 131.7, 120.3, 119.2, 118.2, 118.2, 56.6, 35.7.

7.2.2.11 Preparation of 3-allyl-2-bromo-1,4,5-trimethoxynaphthalene 104

To a clear solution of 3-allyl-2-bromo-5-methoxy-1,4-naphthoquinone **103** (1.40 g, 4.56 mmol) in THF (80 mL) was added $Na_2S_2O_4$ (3.97 g, 22.80 mmol) in H_2O (25 mL) and TBAI (0.17 g, 0.46 mmol). The reaction was stirred at rt under argon for 30 min followed by the addition of KOH (2.56 g, 45.60 mol) in H_2O (140 mL). The reaction was stirred for 1 hr and Me_2SO_4 (5.75 g, 4.32 mL, 45.6 mol) was added. The reaction mixture was then stirred for 18 hrs before being quenched with 25% NH_4OH (100 mL) and the organic material extracted into EtOAc (3 × 100 mL). The combined organic extracts were washed sequentially with distilled water (100 mL), 10% aq. HCl (100 mL) and brine (100 mL). The organic extract was dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% EtOAc/hexane) to give 3-allyl-2-bromo-1,4,5-trimethoxynaphthalene **104** as a yellowish-brown solid (1.12 g, 3.42 mmol, 75%).

R_f = 0.58 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3086, 2934, 2810, 1601, 1465, 1281, 1162, 1083, 812; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.71 (1H, d, *J* = 8.4 Hz, H-8), 7.41 (1H, t, *J* = 8.1 Hz, H-7), 6.90 (1H, d, *J* = 7.7 Hz, H-6), 6.16 – 5.93 (1H, m, H-2′), 5.20 – 4.83 (2H, m, H-3′), 4.00 (3H, s, OMe), 3.94 (3H, s, OMe), 3.80 (5H, m, OMe and H-1′ overlapping); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 156.1, 151.2, 149.7, 136.1, 130.4, 129.7, 126.7, 120.0, 117.5, 115.7, 115.0, 106.6, 62.9, 61.1, 56.2, 34.4.



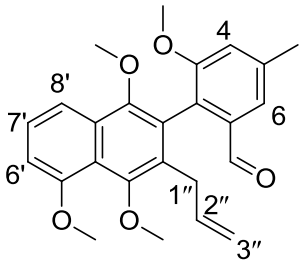
7.2.2.12 Preparation 3-allyl-1,4,5-trimethoxynaphthalen-2-yl-2-boronic acid 97

n-BuLi (1.2 M, 3.02 mL, 3.62 mmol, 2.0 eq.) was added dropwise to a solution of 3-allyl-2-bromo-1,4,5-trimethoxynaphthalene **104** (610 mg, 1.81 mmol, 1.0 eq.) in THF (15 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, then B(O*i*Pr)$_3$ (1.67 mL, 7.24 mmol, 4.0 eq.) was added. The resulting mixture was stirred at −78 °C for a further 30 min and then allowed to warm to rt. The reaction mixture was acidified with 10% aq. HCl solution and extracted with Et_2O (3 × 30 mL). The organic layer was then dried with $MgSO_4$ and concentrated under reduced pressure to afford 3-allyl-1,4,5-trimethoxynaphthalen-2-yl-2-boronic acid **97** as an off-white crystalline material (510 mg, 1.70 mmol, 94%), which was used without further purification or characterization.

7.2.2.13 Preparation of 2-(2-allyl-1,4,8-trimethoxynaphthalen-3-yl)-3-methoxy-5-methylbenzaldehyde 110

A deoxygenated solution of 3-allyl-1,4,5-trimethoxynaphthalen-2-yl-2-boronic acid **97** (310 mg, 1.03 mmol, 1.5 eq.) and 2-iodo-3-methoxy-5-methylbenzaldehyde **98** (185 mg, 0.67 mmol, 1.0 eq.) in DME (10 mL) was added to $Pd(PPh_3)_4$ (77 mg, 0.067 mmol, 0.1 eq.) under argon atmosphere with stirring. To this was added a deoxygenated aq. Na_2CO_3 (2 M, 1.34 mL, 2.68 mmol, 4.0 eq.). The mixture was then heated at reflux for 18 hrs. After this time, the mixture was cooled to rt and the

reaction quenched with H_2O (10 mL). The organic material was extracted into EtOAc (3 × 30 mL), the combined extract dried with $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (10-20% EtOAc/hexane) to afford 2-(2-allyl-1,4,8-trimethoxynaphthalen-3-yl)-3-methoxy-5-methylbenzaldehyde **110** as an off-white solid (33 mg, 0.08 mmol, 12%).



R_f = 0.32 (20% EtOAc/Hexane); **Mp**. 54-56 $CHCl_3$; **IR** (ν/cm^{-1}): 3018, 2944, 2835, 1691, 1604, 1567, 1446, 1232, 1187, 1055; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.55 (1H, s, ArCO), 7.71 (1H, dd, *J* = 8.4, 1.0 Hz, H-8′), 7.48 (1H, d, *J* = 0.8 Hz, H-6), 7.41 (1H, t, *J* = 8.4, H-7′), 7.04 (1H, d, *J* = 0.9 Hz, H-4), 6.93 (1H, dd, *J* = 7.8, 1.0 Hz, H-6′), 5.65 (1H, m, H-2″), 4.72 (1H, dd, *J* = 10.1, 1.6 Hz, H-3″), 4.50 (1H, dd, *J* = 17.1, 1.8 Hz, H-3″), 4.04 (3H, s, OMe), 3.86 (5H, m, OMe and H-1″), 3.74 (3H, s, OMe), 3.45 (3H, s, OMe), 2.49 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 192.7, 157.0, 156.1, 150.6, 150.1, 139.3, 136.6, 135.0, 130.1, 129.7, 126.7, 126.0, 125.0, 121.0, 119.2, 116.7, 115.3, 115.1, 106.6, 62.7, 60.7, 56.2, 55.6, 32.1, 21.7; **HRMS** (ESI+): Found $(M + Na)^+$ 429.1657 and $(M + H)^+$ 407.1838, $C_{25}H_{26}O_5$ $(M + Na)^+$ requires 429.1673 and $(M + H)^+$ requires 407.1854, *m/z* 429.1657 ($(M + Na)^+$, 100%), 407.1838 [$(M + H)^+$, 60%].

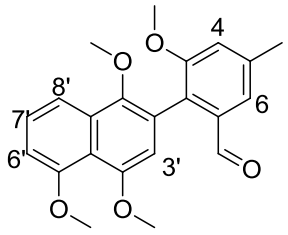
7.2.2.14 Preparation of (1,4,5-trimethoxynaphthalen-2-yl)boronic acid 114

n-BuLi (1.5 M, 8.53 mL, 12.80 mmol, 2.0 eq.) was added dropwise to a solution of 2-bromo-1,4,5-trimethoxynaphthalene **115** (1.90 g, 6.40 mmol, 1.0 eq.) in THF (50 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, then $B(OiPr)_3$ (3.61 g, 4.43 mL, 19.20 mmol, 4.0 eq.) was added. The resulting mixture was stirred at −78 °C for a further 30 min and then allowed to warm to rt. The reaction mixture was acidified with 10% aq. HCl solution and extracted with Et_2O (3 × 50 mL). The organic layer was then dried with $MgSO_4$ and concentrated under reduced pressure to afford (1,4,5-trimethoxynaphthalen-2-yl)boronic **114** acid as an off-white crystalline

solid (1.61 g, 6.14 mmol, 96%), which was used without further purification or characterization.

7.2.2.15 Preparation of 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde 116

A deoxygenated solution of (1,4,5-trimethoxynaphthalen-2-yl)boronic acid **114** (2.50 g, 9.51 mmol, 1.5 eq.) and 2-iodo-3-methoxy-5-methylbenzaldehyde **98** (1.75 g, 6.34 mmol, 1.0 eq.) in DME (80 mL) was added to $Pd(PPh_3)_4$ (10.73 g, 0.63 mmol, 10 mol %) under argon atmosphere with stirring. To this was added a deoxygenated aq. Na_2CO_3 (2 M, 2.69 g, 12.68 mL, 25.36 mmol, 4.0 eq.) solution. The mixture was then heated at reflux for 18 hrs. After this time, the mixture was cooled to rt and the reaction quenched with H_2O (100 mL). The organic material was extracted into EtOAc (3 × 100 mL), the combined extract dried with $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (10-20% EtOAc/hexane) to afford 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **116** as an off-white solid (1.70 g, 5.07 mmol, 80%).

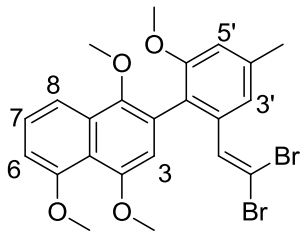


R_f = 0.24 (20% EtOAc/Hexane); **Mp**. 160-162 CH_2Cl_2; **IR** (ν/cm^{-1}): 3002, 2939, 1686, 1598, 1287, 1118, 1003, 849; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.70 (1H, s, ArCHO), 7.75 (1H, dd, *J* = 8.4, 1.0 Hz, H-8′), 7.50 (1H, d, *J* = 0.7 Hz, H-6), 7.44 (1H, t, *J* = 7.9 Hz, H-7′), 7.08 (1H, d, *J* = 0.8 Hz, H-4), 6.93 (1H, dd, *J* = 7.8, 0.7 Hz, H-6′), 6.69 (1H, s, H-3′), 4.00 (3H, s, 5′-OMe), 3.92 (3H, s, 4′-OMe), 3.80 (3H, s, 3-OMe), 3.45 (3H, s, 1′-OMe), 2.49 (3H, s, ArMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 192.8 (ArCO), 157.4 (C-5′), 157.2 (C-3), 152.8 (C-4′), 147.8 (C-1′), 139.3 (C-5), 134.7 (C-1), 131.2 (C-8b), 128.1 (C-2′), 126.9 (C-7′), 122.2 (C-2), 119.3 (C-6), 117.2 (C-4), 115.2 (C-8′), 109.7 (C-3′), 107.2 (C-6′), 60.8 (C1′-OMe), 56.9 (C4′-OMe), 56.6 (C5′-OMe), 56.0 (C3-OMe), 21.7 (ArMe); **HRMS**

(ESI+): Found $(M + H)^+$ 367.1531, $C_{22}H_{23}O_5$ $(M + H)^+$ requires 367.1540, *m/z* 367.1531 [$(M + H)^+$, 100%].

7.2.2.16 Preparation of 2-(2-(2,2-dibromovinyl)-6-methoxy-4-methylphenyl)-1,4,5-trimethoxynaphthalene 117

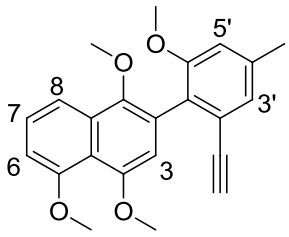
In an oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was placed PPh_3 (4.98 g, 19.0 mmol, 5.0 eq.) in dry CH_2Cl_2 (6 mL). The mixture was cooled to 0 °C and CBr_4 (3.15 g, 9.50 mmol) was added, and the mixture was stirred for 10 min at 0 °C. Aldehyde **116** (1.40 g, 3.81 mmol, 1.0 eq.) dissolved in dry CH_2Cl_2 (10 mL) was slowly added. The mixture was flushed with argon and allowed to stir at 0 °C for 4 hrs. The mixture was diluted with CH_2Cl_2 and washed with brine (2 × 30 mL) followed by H_2O (2 × 30 mL). The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layer was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product purified by column chromatography on silica gel (15-20% EtOAc/hexane) to afford the vinyl dibromide **117** as a foamy yellow solid (1.77 g, 3.40 mmol, 89%).



R_f = 0.47 (20% EtOAc/Hexane); **Mp**. 133-135 $(C_2H_5)_2O$; **IR** (ν/cm^{-1}): 3108, 2912, 1599, 1213, 1173, 1103, 630.0; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.78 (1H, dd, *J* = 8.4, 1,0 Hz, H-8), 7.43 (1H, t, *J* = 8.1 Hz, H-7), 7.14 (1H, d, *J* = 0.8 Hz, H-3′), 7.09 (1H, s, =C*H*-), 6.91 (1H, dd, *J* = 7.8, 1.1 Hz, H-6), 6.84 (1H, d, *J* = 0.9 Hz, H-5′), 6.55 (1H, s, H-3), 4.00 (3H, s, OMe), 3.92 (3H, s, OMe), 3.75 (3H, s, OMe), 3.52 (3H, s, OMe), 2.46 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 157.4, 157.0, 152.8, 147.3, 138.6, 137.1, 136.2, 131.6, 126.5, 124.7, 124.2, 121.7, 118.3, 115.3, 112.1, 109.6, 106.9, 90.6, 61.2, 56.9, 56.6, 55.9, 21.8; **HRMS** (ESI+): Found $(M + H)^+$ 520.9960, $C_{23}H_{23}O_4{}^{79}Br_2$ $(M + H)^+$ requires 520.9958, *m/z* 520.9960 [$(M + H)^+$, 50%], 522.9937 (100).

7.2.2.17 Preparation of 2-(2-ethynyl-6-methoxy-4-methylphenyl)-1,4,5-trimethoxynaphthalene 118

In an oven-dried 25 mL two-necked round bottom flask equipped with a magnetic stirring bar was placed the vinyl dibromide **117** (1.35 g, 2.59 mmol, 1.0 eq.) in dry THF (6 mL) under argon atmosphere. The mixture was cooled to −78 °C and a 1.2 M solution of *n*-BuLi in hexanes (5.40 mL, 6.48 mmol, 2.5 eq.) was added dropwise. The mixture was allowed to stir at −78 °C for 6 hrs and then for 1 hr at rt, at which time TLC showed the reaction to be complete. The mixture was quenched with water and extracted with Et_2O (3 × 30 mL). The combined organic layer was dried over $MgSO_4$ and solvent evaporated under reduced pressure. Chromatographic purification on silica gel (20% EtOAc/hexane) afforded the alkyne product **118** as a yellowish brown solid (0.83 g, 2.29 mmol, 88%).



R_f = 0.27 (20% EtOAc/Hexane); **Mp**. 135-137 $CHCl_3$; **IR** (ν/cm^{-1}): 3272, 3089, 2947, 2371, 1598, 1274, 1122, 1078; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.78 (1H, dd, *J* = 8.5, 1.0 Hz, H-8), 7.41 (1H, t, *J* = 8.2 Hz, H-7), 7.09 (1H, d, *J* = 0.9 Hz, H-3′), 6.89 (1H, dd, *J* = 8.5, 1,0 Hz, H-6), 6.84 (1H, d, *J* = 0.8 Hz, H-5′), 6.67 (1H, s, H-3), 3.98 (3H, s, OMe), 3.92 (3H, s, OMe), 3.73 (3H, s, OMe), 3.57 (3H, s, OMe), 2.81 (1H, s, ≡C*H*), 2.41 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 157.4, 157.1, 152.6, 147.7, 138.6, 131.4, 128.3, 126.2, 125.8, 125.6, 123.2, 118.3, 115.4, 113.0, 109.9, 106.7, 82.6, 79.9, 61.4, 56.9, 56.6, 56.0, 21.5; **HRMS** (ESI+): Found $(M + H)^+$ 363.1601, $C_{23}H_{23}O_4$ $(M + H)^+$ requires 363.1596, *m/z* 363.1601 [$(M + H)^+$, 100%], 348.1370 (30).

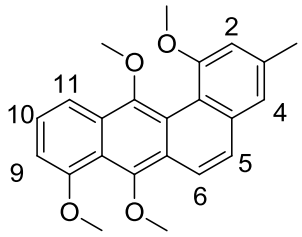
7.2.2.18 Preparation of 1,7,8,12-tetramethoxy-3-methyltetraphene 119 and 1,10,12-trimethoxy-8-methylchrysene 120

Method 1: Using platinum(II) chloride

In an oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was placed the alkyne **118** (810 mg, 2.24 mmol, 1.0 eq.) in dry PhMe (10 mL). $PtCl_2$ (0.089 mg, 0.34 mmol) was then added and the mixture was stirred at 90 °C for 24 hrs under argon atmosphere. The mixture was filtered through Celite and the residue was washed with CH_2Cl_2. Chromatographic purification on silica gel (15-20% EtOAc/hexane) afforded 1,7,8,12-tetramethoxy-3-methyltetraphene **119** as a yellow solid (495 mg, 1.37 mmol, 61 %) and 1,10,12-trimethoxy-8-methylchrysene **120** as a yellowish brown solid (171 mg, 0.515 mmol, 23%).

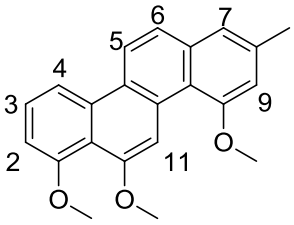
Method 2: Using gold(III) chloride

In an oven-dried 25 mL round-bottom flask equipped with a magnetic stirring bar was placed the alkyne **118** (820 mg, 2.27 mmol, 1.0 eq.) in dry PhMe (10 mL). $AuCl_3$ (0.103 mg. 0.34 mmol) was then added and the mixture was stirred at 90 °C for 24 h under argon atmosphere. The mixture was filtered through Celite and the residue was washed with CH_2Cl_2. Chromatographic purification on silica gel (15-20% EtOAc/hexane) afforded 1,7,8,12-tetramethoxy-3-methyltetraphene **119** as a yellow solid (0.460 mg, 1.27 mmol, 56 %) and 1,10,12-trimethoxy-8-methylchrysene **120** as a yellowish brown solid (234 mg, 0.704 mmol, 31%).



R_f = 0.48 (20% EtOAc/Hexane); **Mp**. 80-82 CH_2Cl_2; **IR** (ν/cm^{-1}): 3097, 2920, 1606, 1223, 1121, 1060, 832; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.11 (1H, dd, *J* = 8.6, 1.0 Hz, H-11), 8.03 (1H, d, *J* = 9.2 Hz, H-6), 7.44 (1H, t, *J* = 8.8 Hz, H-10), 7.36 (1H, d, *J* = 9.5 Hz, H-5), 7.17 (1H, d, *J* = 0.8 Hz, H-4), 6.92 (1H, d, *J* = 0.9 Hz, H-2), 6.89 (1H, d, *J* = 7.1 Hz, H-9), 4.07 (3H, s, OMe), 3.97 (6H, s, OMe), 3.51 (3H, s, OMe), 2.54 (3H, s, ArMe); **^{13}C NMR** (75

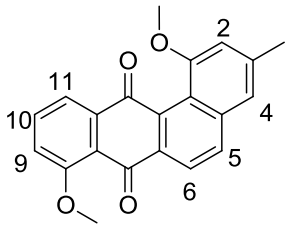
MHz, $CDCl_3$): δ 158.0, 156.2, 150.9, 147.1, 138.1, 134.6, 129.7, 126.2, 125.4, 125.1, 122.1, 119.6, 118.6, 117.4, 116.6, 115.8, 110.9, 105.2, 63.3, 60.4, 56.3, 56.2, 21.7; **HRMS** (ESI+): Found $(M + H)^+$ 363.1593, $C_{23}H_{23}O_4$ $(M + H)^+$ requires 363.1591, *m/z* 363.1593 [$(M + H)^+$, 100%], 362.1521 (55).



R_f = 0.29 (20% EtOAc/Hexane); **Mp.** 176-178 CH_2Cl_2; **IR** (ν/cm^{-1}): 3021, 2904, 1589, 1489, 1217, 1167, 1078, 742; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.20 (1H, s, H-11), 8.55 (1H, d, *J* = 9.1 Hz, H-5), 8.37 (1H, d, *J* = 8.5 Hz, H-4), 7.69 (1H, d, *J* = 9.1 Hz, H-6), 7.56 (1H, t, *J* = 8.2 Hz, H-3), 7.34 (1H, d, 0.9 Hz, H-7), 7.05 (1H, d, *J* = 7.8 Hz, H-2), 6.92 (1H, d, *J* = 0.9 Hz, H-9), 4.15 (3H, s, OMe), 4.11 (3H, s, OMe), 4.03 (3H, s, OMe), 2.54 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.6, 157.4, 154.9, 136.5, 135.3, 134.0, 130.0, 126.6, 124.8, 123.5, 122.4, 121.2, 118.9, 116.7, 116.2, 110.0, 107.8, 106.1, 56.8, 56.2, 56.1, 21.7. **HRMS** (ESI+): Found $(M + H)^+$ 333.1458, $C_{22}H_{21}O_3$ $(M + H)^+$ requires 333.1486, *m/z* 333.1458 [$(M + H)^+$, 100%].

7.2.2.19 Preparation of 1,8-dimethoxy-3-methyltetraphene-7,12-dione 38

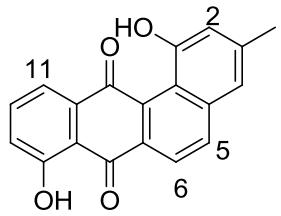
In a 25 mL round bottom flask equipped with a magnetic stirring bar was placed 1,7,8,12-tetramethoxy-3-methyltetraphene **119** (150 mg, 0.41 mmol, 1.0 eq.) in MeCN (5 mL). CAN (0.66 mg, 1.20 mmol, 3.0 eq.) in H_2O (5 mL) was then added and the mixture stirred for 30 min. $NaHCO_3$ was then added and the organic material was extracted into EtOAc (3 × 10 mL). The combined organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (50% EtOAc/hexane) to give 1,8-dimethoxy-3-methyltetraphene-7,12-dione **38** as a yellow solid (117 mg, 0.353 mmol, 86%)



R_f = 0.16 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3011, 2984, 1660, 1656, 1588, 1470, 1442, 1137, 1009, 947, 754; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.22 (1H, d, *J* = 8.6 Hz, H-5), 7.91 (1H, d, *J* = 8.6 Hz, H-6), 7.67 (2H, dd, *J* = 4.8, 0.7 Hz, ArH), 7.27 – 7.22 (2H, m, ArH), 6.89 (1H, d, *J* = 1.4 Hz, H-2), 4.03 (3H, s, OMe), 3.97 (3H, s, OMe), 2.52 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 186.6, 182.3, 159.4, 156.9, 140.3, 139.3, 137.8, 135.2, 135.0, 133.9, 132.5, 122.7, 120.7, 120.1, 119.1, 118.5, 116.2, 111.2, 56.5, 56.0, 22.1.

7.2.2.20 Preparation of 1,8-dihydroxy-3-methyltetraphene-7,12-dione 2

In an oven-dried 25 mL two-necked round bottom flask equipped with a magnetic stirring bar was placed 1,8,-dimethoxy-3-methyltetraphene-7,12-dione **38** (40 mg, 0.120 mmol. 1.0 eq.) in CH_2Cl_2 (5 mL) under argon atmosphere. The mixture was cooled to −78 °C and BBr_3 (1.20 mL, 1.20 mmol, 10.0 eq.) was added dropwise. The reaction was then slowly warmed to RT and stirred for a further 18hrs before being cooled to 0 °C and quenched with water. The organic material was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (5% EtOAc/hexane) to afford 1,8-dihydroxy-3-methyltetraphene-7,12-dione **2** as a brown solid (37.1 mg, 0.111 mmol, 93%)

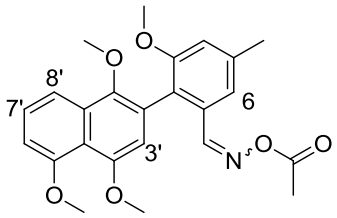


R_f = 0.58 (20% EtOAc/Hexane); **IR** ($CHCl_3$): (ν/cm^{-1}): 3002, 2996, 1677, 1656, 1578, 1543, 1499, 1477, 1371, 1292, 1157, 1080, 793; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 12.24 (1H, s, ArOH), 11.26 (1H, s, ArOH), 8.31 (1H, d, *J* = 8.6 Hz, H-5), 8.13 (1H, d, *J* = 8.6 Hz, H-6), 7.85 (1H, d, *J* = 7.6 Hz, H-11), 7.73 – 7.63 (2H, m, ArH), 7.36 – 7.30 (2H, m, ArH), 7.14 (1H, d, *J* = 1.4 Hz, H-2), 2.49 (3H, s, ArMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 189.7, 187.9, 161.7, 155.3, 142.0, 139.1, 137.7, 136.9, 134.8, 132.4, 124.8, 123.2, 121.9, 121.3, 121.2, 120.2, 120.0, 114.7, 21.3.

7.3 Experimental Procedures pertaining to Chapter 4

7.3.1 Preparation of 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde *O*-acetyl oxime 222

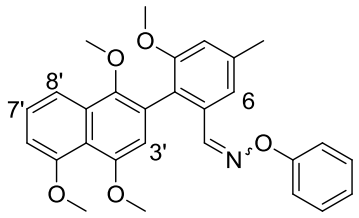
To a solution of 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **116** (0.505 g, 1.38 mmol, 1.0 eq.) in MeOH (5 mL) was added hydroxylamine hydrochloride (0.19 g, 2.75 mmol, 2.0 eq.) and NaOAc (0.170 g, 2.07 mmol, 1.5 eq.). The reaction mixture was heated at reflux for 2 hrs and the solvent was removed *in vacuo.* To the residue, dry CH_2Cl_2 (3 mL) and triethylamine (0.38 mL, 0.28 g, 2.75 mmol, 2.0 eq.) were added at 0 °C. To this cooled solution was slowly added a solution of acetyl chloride (0.2 mL, 0.22 g, 2.75 mmol, 2.0 eq.) in dry CH_2Cl_2 (1 mL). The reaction mixture was stirred at rt for 18 hrs. Upon completion, the reaction was quenched with water (5 mL) and the mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL) and dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel (30 % EtOAc/hexane) to afford the acetyl oxime **222** as a yellow solid (0.5 g, 1.18 mmol, 86%).



R_f = 0.17 (20% EtOAc/Hexane); **Mp**. 136-138 CH_2Cl_2; **IR** (ν/cm^{-1}): 3004, 2945, 1764, 1581, 1449, 1374, 1201, 1172, 752; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.03 (1H, s, -N=C*H*-), 7.77 (1H, dd, *J* = 8.4, 0.8 Hz, H-8′), 7.67 (1H, s, H-6), 7.46 (1H, t, *J* = 8.1 Hz, H-7′), 6.97 – 6.92 (2H, m, ArH), 6.57 (1H, s, H-3′), 4.00 (3H, s, OMe), 3.90 (3H, s, OMe), 3.77 (3H, s, OMe), 3.48 (3H, s, OMe), 2.46 (3H, s, ArMe), 2.08 (3H, s, -CO_2Me); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6, 157.5, 157.1, 155.3, 155.3, 152.9, 147.4, 139.4, 131.5, 129.6, 126.8, 126.4, 123.5, 119.1, 115.3, 114.7, 109.6, 107.2, 61.0, 56.9, 56.6, 55.9, 21.6, 19.5; **HRMS** (ESI+): Found $(M + H)^+$ 424.1757, $C_{24}H_{26}NO_6$ $(M + H)^+$ requires 424.1755, *m/z* 424.1757 [$(M + H)^+$, 7%], 364.1542 (100), 333.1357 (30).

7.3.2 Preparation of 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde *O*-phenyl oxime 230

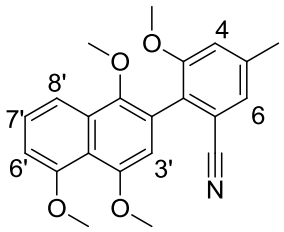
O-phenylhydroxylamine hydrochloride (0.240 g, 1.63 mmol, 1.0 eq.) was dissolved in anhydrous pyridine (10 mL) under argon at rt and 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **116** (0.60 g, 1.63 mmol, 1.0 eq.) was added in one portion. The reaction was stirred at rt for 18 hrs. On completion, the reaction was quenched with water and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed three times with $CuSO_4$ to removed traces of pyridine followed by brine and then dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by column chromatography (20% EtOAc/hexane) to give the *O*-phenyl oxime **230** as a yellowish brown solid (0.70 g, 1.53 mmol, 93%).



R_f = 0.35 (20% EtOAc/Hexane); **Mp**. 134-136 CH_2Cl_2; **IR** (ν/cm^{-1}): 3036, 2939, 1578, 1455, 1374, 1298, 1075, 749; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.12 (1H, s, -N=C*H*-), 7.78 (1H, dd, *J* = 8.4, 0.9 Hz, H-8′), 7.63 (1H, d, *J* = 0.8 Hz, H-6), 7.43 (1H, t, *J* = 8.1 Hz, H-7′), 7.28 – 7.11 (4H, m, ArH), 7.00 – 6.86 (3H, m, ArH), 6.59 (1H, s, H-3′), 3.97 (3H, s, OMe), 3.89 (3H, s, OMe), 3.74 (3H, s, OMe), 3.52 (3H, s, OMe), 2.47 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 159.40, 157.47, 157.20, 152.91, 150.84, 147.52, 139.04, 131.51, 130.92, 129.18, 126.76, 125.86, 123.90, 122.05, 118.45, 115.27, 114.41, 113.70, 109.67, 107.11, 60.97, 56.84, 56.58, 55.82, 21.76; **HRMS** (ESI+): Found $(M + H)^+$ 458.1969, $C_{28}H_{28}NO_5$ $(M + H)^+$ requires 458.1962, *m/z* 458.1969 [$(M + H)^+$, 60%], 364.1548 (100), 334.1434 (30).

7.3.3 Preparation of 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzonitrile 224

To a solution of the acetyl oxime **222** (0.32g, 0.76 mmol, 1.0 eq.) in toluene (10 mL) was added $Pd(dba)_2$ (44 mg, 0.076 mmol, 10 mol %) and Cs_2CO_3 (0.248 g, 0.76 mmol, 1.0 eq.). The reaction was stirred at 150 °C for 24 hrs. On completion, the reaction mixture was cooled to rt followed by the addition of EtOAc (15 mL) and water (15 mL). The organic layer was separated and subsequently washed with saturated NH_4Cl solution (10 mL), water (10 mL) and brine (10 mL) and dried over $MgSO_4$. The crude product was purified using column chromatography on silica gel (30% EtOAc/hexane) to afford the benzonitrile **224** as a yellow solid (0.17g, 0.471 mmol, 62%)



R_f = 0.13 (20% EtOAc/Hexane); **Mp.** 184-186 $CHCl_3$; **IR** (ν/cm^{-1}): 3043, 2991, 2365, 1597, 1455, 1227, 1176, 1076, 847; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.78 (1H, dd, *J* = 8.4, 1.0 Hz, H-8′), 7.43 (1H, t, *J* = 8.2 Hz, H-7′), 7.19 (1H, s, H-6), 7.03 (1H, s, H-4), 6.92 (1H, d, *J* = 7.8 Hz, H-6′), 6.63 (1H, s, H-3′), 3.98 (3H, s, OMe), 3.93 (3H, s, OMe), 3.77 (3H, s, OMe), 3.55 (3H, s, OMe), 2.44 (3H, s, ArMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 157.5, 157.3, 153.2, 147.9, 139.9, 131.5, 128.9, 126.8, 125.0, 123.6, 118.9, 118.1, 116.5, 115.4, 114.5, 108.7, 107.4, 61.6, 57.0, 56.7, 56.1, 21.5; **HRMS** (ESI+): Found $(M + H)^+$ 364.1552, $C_{22}H_{22}NO_4$ $(M + H)^+$ requires 364.1544, *m/z* 364.1552 [$(M + H)^+$, 100%].

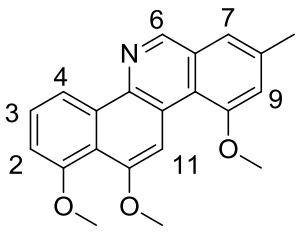
7.3.4 Preparation of 1,10,12-trimethoxy-8-methylbenzo[*c*]phenanthridine 231

Method 1: Microwave assisted method

O-phenyl oxime **230** (110 mg, 0.24 mmol, 1.0 eq.) and $EmimPF_6$ (60 mg, 0.24 mmol) were dissolved in *tert*-butylbenzene (3 mL) in a microwave reactor tube. The reaction mixture was subjected to microwave irradiation (300 W, 160 °C) for 20 min. After cooling, the ionic liquid was filtered off and the crude product was purified by column chromatography (20% EtOAc/hexane) to afford the phenanthridine **231** (46 mg, 0.14 mmol, 58%) and the benzonitrile **224** (9.60 mg, 0.026 mmol, 11%) as yellow solids.

Method 2: UV-induced photochemical method

O- acetyl oxime **222** (80 mg, 0.17 mmol, 1.0 eq.) was introduced into a UV reactor and tert-butanol (5 mL) was added and the reaction mixture was degassed with argon. The solution was then subjected to UV radiation (450 W) for 20 min. After cooling, the crude product was purified by column chromatography (20% EtOAc/hexane) to afford the phenanthridine **231** (26 mg, 0.078 mmol, 46%) and the benzonitrile **224** (11 mg, 0.031 mmol, 18%)



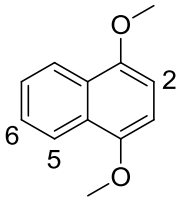
R_f = 0.17 (20% EtOAc/Hexane); **Mp**. 211-213 $CHCl_3$); **IR** (ν/cm^{-1}): 3067, 2914, 1589, 1447, 1364, 1256, 1195, 1076, 752; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.15 (1H, s, H-11), 9.13 (1H, dd, *J* = 8.4, 0.7 Hz, H-4), 8.87 (1H, s, H-6), 7.64 (1H, t, *J* = 8.1 Hz, H-3), 7.45 (1H, s, H-7), 7.12 (1H, d, *J* = 7.7 Hz, H-2), 7.03 (1H, s, H-9), 4.15 (3H, s, OMe), 4.11 (3H, s, OMe), 4.04 (3H, s, OMe), 2.56 (3H, s, ArMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.8, 156.8, 155.4, 149.0, 137.7, 137.2, 135.4, 129.6, 127.0, 122.6, 121.0, 120.6, 117.9, 117.4, 112.7, 108.7, 103.7, 56.8, 56.1, 56.0, 21.8; **HRMS** (ESI+): Found $(M + H)^+$

334.1447, $C_{21}H_{20}NO_3$ $(M + H)^+$ requires 334.1440, *m/z* 334.1447 [$(M + H)^+$, 100%], 335.1479 (25), 240.9883 (60).

7.4 Experimental procedures pertaining to Chapter 6

7.4.1 Preparation of 1,4-dimethoxynaphthalene 306

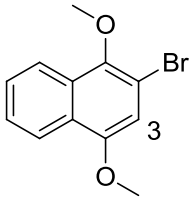
To a clear solution of 1,4-naphthoquinone **305** (5.00 g, 31.63 mmol, 1.0 eq.) in THF (200 mL) was added TBAI (1.17 g, 1.69 mmol, 10 mol %) and $Na_2S_2O_4$ (27.5 g, 158.1 mmol, 5.0 eq.) in H_2O (150 mL). The reaction was stirred at rt under argon for 30 min followed by the addition of KOH (17.7 g, 0.316 mol, 10.0 eq.) in H_2O (300 mL). The reaction was stirred for a further 1 hr followed by the addition of Me_2SO_4 (39.88 g, 30.0 mL, 0.316 mol, 10.0 eq.). The reaction mixture was then stirred for 18 hrs before being quenched with 25% NH_4OH (100 mL) and the organic material extracted into EtOAc (3 × 200 mL). The combined organic extracts were washed sequentially with distilled water (200 mL), 10% aq. HCl (200 mL) and brine (200 mL) then dried over $MgSO_4$, filtered through Celite and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10% EtOAc/hexane) to give the naphthalene **306** (5.18 g, 27.51 mmol, 87%) as a low melting off-white solid.



R_f = 0.67 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): = 3078, 2947, 2849, 1614, 1489, 1464, 1238, 1163, 1088, 837, 812, 787; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.32 – 8.10 (2H, m, H-5), 7.56 – 7.40 (2H, m, H-6), 6.63 (2H, s, H-2), 3.90 (6H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 149.5, 126.4, 125.8, 121.8, 103.2, 55.7.

7.4.2 Preparation of 2-bromo-1,4-dimethoxynaphthalene 307

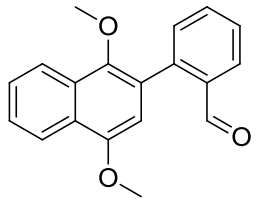
To a solution of 1,4-dimethoxynaphthalene **306** (6.50 g, 34.57 mmol, 1.0 eq.) in CH_2Cl_2 was added NBS (6.15 g, 34.57 mmol, 1.0 eq.) and the reaction mixture was stirred under reflux for 2 hrs. On completion, the reaction was quenched with a saturated solution of aq. sodium sulfite (50 mL). The organic layer was collected and washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and the organic solvent was removed under reduced pressure. The crude product was purified by column chromatography (10% EtOAc/Hexane) to furnish 2-bromo-1,4-dimethoxynaphthalene **307** as a low melting white solid (7.48 g, 28.0 mmol, 81 %).



R_f = 0.76 (20% EtOAc/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.17 (1H, dd, *J* = 7.8, 0.7 Hz, ArH), 8.03 (1H, dd, dd, *J* = 7.8, 0.7 Hz, ArH), 7.52 (1H, ddd, *J* = 8.3, 6.9, 1.3 Hz, ArH), 7.46 (1H, ddd, *J* = 8.2, 6.9, 1.3 Hz, ArH), 6.84 (1H, s, H-3), 3.92 (3H, s, OMe), 3.90 (3H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 152.2, 146.7, 129.0, 127.3, 125.8, 125.6, 122.57, 121.8, 111.9, 107.7, 61.4, 55.8.

7.4.3 Preparation of 2-(1,4-dimethoxynaphthalen-2-yl)benzaldehyde 309

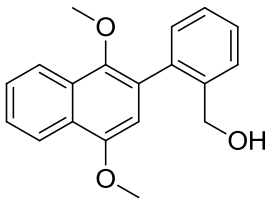
Tetrakis(triphenylphosphine)palladium(0) (2.08 g, 1.80 mmol, 0.1 eq.) and 2-formylphenylboronic acid **308** (4.05 g, 27.02 mmol, 1.5 eq.) were added to a deoxygenated solution of 2-bromo-1,4-dimethoxynaphthalene (4.8 g, 17.98 mmol, 1.0 eq.) in DME (100 mL) under argon atmosphere with stirring. To this was added a deoxygenated aq. Na_2CO_3 solution (2 M, 36 mL, 72.0 mmol, 4.0 eq.). The reaction mixture was then heated at reflux for 18 hrs. After this time, the mixture was cooled to rt and the reaction quenched with H_2O (100 mL). The organic material was extracted into EtOAc (3 × 00 mL), followed by a brine wash (100 mL). The combined extract was dried over $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (10 % EtOAc/hexane) to afford 2-(1,4-dimethoxynaphthalen-2-yl)benzaldehyde **309** as a yellow solid (4.25 g, 14.56 mmol, 90%).



R_f = 0.59 (20% EtOAc/Hexane); **Mp**. 190–192 °C $(C_2H_5)_2O$; **IR** (ν/cm^{-1}): 2935, 1723, 1625, 1591, 1506, 1464, 1263, 1223; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.90 (IH, s, CHO), 8.34 – 8.25 (1H, m, ArH), 8.17 – 8.04 (2H, m, ArH), 7.75 – 7.65 (1H, m, ArH), 7.63 – 7.50 (4H, m, ArH), 6.74 (s, 1H), 4.01 (3H, s. OMe), 3.40 (3H, s, OMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 192.4, 152.1, 147.0, 142.0, 133.8, 133.6, 131.0, 128.4, 127.9, 127.2, 127.1, 126.7, 126.2, 125.4, 122.4, 122.4, 105.9, 60.9, 55.8; **HRMS** (ESI+): Found $(M + H)^+$ 293.1169, $C_{19}H_{17}O_3$ $(M + H)^+$ requires 293.1173, *m/z* 293.1169 [$(M + H)^+$, 100%], 292.1092 (50%).

7.4.4 Preparation of (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol 235

2-(1,4-Dimethoxynaphthalen-2-yl)benzaldehyde **309** (2.97 g, 10.17 mmol, 1.0 eq.) was dissolved in 100 mL of freshly distilled dry THF under inert conditions. $LiAlH_4$ (1.15 g, 30.5 mmol, 3.0 eq.) was added carefully to the mixture at 0 °C under inert conditions. The reaction mixture was allowed to warm to rt and the reaction was stirred for 2 hrs. When completed, the reaction was cooled to 0 °C, a 2% aq. NaOH (50 mL) solution was added dropwise to quench the unreacted $LiAlH_4$ and then the mixture was diluted with ice-cold water (50 mL). The organic material was then extracted into EtOAc (3 × 100 mL) and combined organic phases were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude product was then subjected to column chromatography on silica gel (30% EtOAc/Hexane) to obtain (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **235** as a white solid (2.81 g, 9.56 mmol, 94%).

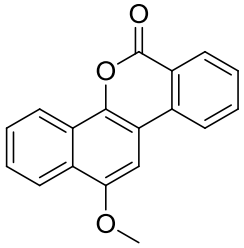


R_f = 0.36 (20% EtOAc/Hexane); **Mp**. 114-115 °C $(C_2H_5)_2O$; **IR** (ν/cm^{-1}): 3442, 2931, 1626, 1593, 1505, 1491, 1455, 1274, 1230; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.28 (1H, d, *J* = 7.8 Hz, ArH), 8.10 (1H, d, *J* = 7.8 Hz, ArH), 7.65 – 7.32 (6H, m, ArH), 6.62 (1H, s, ArH-3′), 4.44 (1H, d, *J* = 11.1

Hz, one of C*H*$_2$OH), 4.37 (1H, d, *J* = 11.1 Hz, one of C*H*$_2$OH), 3.93 (3H, s, OMe), 3.61 (1H, s, OH), 3.47 (3H, s, OMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 152.0, 146.2, 139.5, 137.9, 130.1, 129.9, 129.1, 128.4, 128.3, 127.8, 127.1, 126.2, 125.8, 122.4, 122.1, 106.4, 64.1, 61.6, 55.7; **HRMS** (ESI+): Found M^+ 294.1244, $C_{19}H_{17}O_2$ M^+ requires 294.1251, *m/z* 277.1240 (100%), 294.1244 (M^+, 30%).

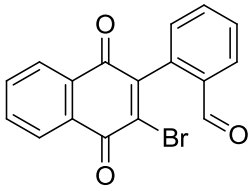
7.4.5 Preparation of 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one 238, 3-bromo-1,4-naphthoquinone)benzaldehyde 311 and 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-ol 310

A solution of (2-(1,4-dimethoxynaphthalen-2-yl)phenyl)methanol **235** (900 mg, 3.06 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL) was oxygenated and to this solution, NBS (1090 mg, 6.12 mmol) was slowly added under oxygen atmosphere and the reaction mixture was allowed to stir under oxygen at rt for 8 hrs. On completion, the reaction was quenched with a saturated solution of aq. sodium sulfite (30 mL). The organic layer was collected and washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and the organic solvent was removed under reduced pressure. The crude product was purified by column chromatography (10% EtOAc/Hexane) to isolate 12-methoxy-6*H*-dibenzo[*c,h*]chromen-6-one **238** as a light tan solid (356 mg, 1.29 mmol, 42%) and 2-(3-bromo-1,4-naphthoquinone)benzaldehyde **311** as a yellow solid (324 mg, 0.949 mmol 36%). The spectroscopic data for **238** was found to be in agreement with that of Jones and Qabaja.[159]



R_f = 0.88 (20% EtOAc/Hexane); **Mp**. 228-230 °C $(C_2H_5)_2O$; **IR** (ν/cm^{-1}): 2935, 2814, 1683, 1616, 1418, 1277, 1275, 938; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.58-8.43 (2H, m, ArH), 8.26 (1H, d, *J* = 7.7 Hz, ArH), 8.12 (1H, d, *J* = 8.1 Hz, ArH), 7.95-7.82 (1H, m, ArH), 7.69-7.55 (3H, m, ArH), 7.24 (1H, s, ArH-11), 4.12 (3H, s, OMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 161.4,

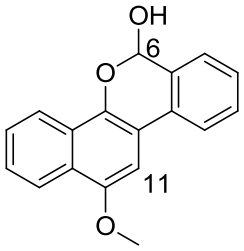
152.4, 141.8, 135.5, 134.7, 130.7, 128.4, 127.7, 127.3, 126.8, 124.8, 122.1, 122.1, 121.8, 121.4, 112.6, 95.7, 55.8; **HRMS** (ESI+): Found $(M + H)^+$ 277.0865, $C_{18}H_{12}O_3$ $(M + H)^+$ requires 277.0860, *m/z* 277.0865 [$(M + H)^+$, 100%], 278.0694 (20%).



R_f = 0.29 (20% EtOAc/Hexane); **Mp**. 114-116 °C $(C_2H_5)_2O$; **IR** (ν/cm^{-1}): 3069, 2759, 1693, 1667, 1591, 1578, 1268, 1246, 1129, 759; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.94 (1H, d, *J* = 0.7 Hz, CHO), 8.26-8.24 (1H, m, ArH), 8.12-8.10 (1H, m, ArH), 7.97 (1H, dd, *J* = 8.4, 1.3 Hz, ArH), 7.80 – 7.78 (2H, m, ArH), 7.75 (1H, td, *J* = 7.5, 1.4 Hz, ArH), 7.70 (1H, td, *J* = 7.6, 1.3 Hz, ArH), 7.38 (1H, dd, *J* = 8.4, 1.4 Hz, ArH); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 191.3, 180.9, 177.8, 150.9, 136.8, 135.1, 134.3, 134.1, 134.0, 133.9, 133.6, 131.9, 131.3, 130.2, 129.8, 127.7, 127.3; **HRMS** (ESI+): Found $(M + H)^+$ 340.9799, $C_{17}H_{10}O_3{}^{79}Br$ $(M + H)^+$ requires 340.9810.

Note: *The lactol **310** was isolated when the same reaction was done under atmospheric condition.*

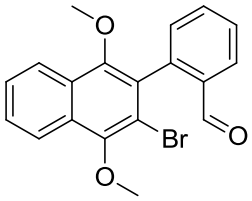
R_f = 0.48 (20% EtOAc/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.59 (1H, d, *J* = 8.3 Hz, ArH), 8.30 (1H, d, *J* = 8.4 Hz, ArH), 7.72 – 7.68 (2H, m, ArH), 7.60 (1H, d, *J* = 6.9, 7.0 Hz, ArH), 7.31 (1H, td, *J* = 7.6, 1.3 Hz, ArH), 7.12 (1H, s, ArH), 7.08 (1H, s, CH), 7.01 (1H, td, *J* = 7.5, 7.5, 1.1 Hz, ArH), 6.70 (1H, d, *J* = 7.6 Hz, ArH), 4.04 (3H, s, OMe), 1.54 (1H, s, OH); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 150.9, 139.5, 129.4, 129.3, 128.9, 127.5, 127.0, 126.8, 126.7, 126.5, 126.1, 122.3, 121.7, 121.5, 115.4, 98.3, 92.8, 55.8.



7.4.6 Preparation of 2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)benzaldehyde 314

A solution of 2-(1,4-dimethoxynaphthalen-2-yl)benzaldehyde **309** (410 mg, 1.42 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) was oxygenated and to this solution, NBS (504

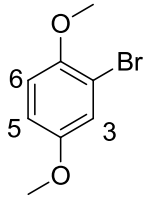
mg, 2.83 mmol, 2.0 eq.) was slowly added under oxygen atmosphere and the reaction mixture was allowed to stir under oxygen over 18 hrs at rt. On completion, the reaction was quenched with saturated solution of aq. sodium sulfite (15 mL). The organic layer was collected and washed with water (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered and the organic solvent was removed under reduced pressure. The crude product was purified by column chromatography (15% EtOAc/Hexane) to isolate 2-(3-bromo-1,4-dimethoxynaphthalen-2-yl)benzaldehyde **314** (301 mg, 0.809 mmol, 57 %) as an off-white low melting solid and 2-(3-bromo-1,4-naphthoquinone)benzaldehyde **311** as a yellow solid (136 mg, 0.397 mmol 28%).



R_f = 0.59 (20% EtOAc/Hexane); **Mp**. 89-91 °C CH_2Cl_2; **IR** (ν/cm^{-1}): 3070, 2933, 2844, 2745, 1694, 1596, 1576, 1491, 1351, 1146, 1080, 1040; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.82 (1H, d, *J* = 0.6 Hz), 8.20 – 8.17 (1H, m, ArH), 8.13 – 8.11 (1H, m, ArH), 8.10 (1H, dd, *J* = 7.8, 1.4 Hz), 7.72 (1H, td, *J* = 7.5, 1.4 Hz, ArH), 7.62 – 7.60 (3H, m, ArH), 7.42 (1H, dd, *J* = 7.7, 1.7 Hz, ArH), 4.03 (3H, s, OMe), 3.48 (3H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 191.6, 150.8, 150.4, 140.4, 134.1, 133.5, 132.0, 129.2, 128.7, 128.2, 128.0, 127.7, 127.6, 127.2, 123.1, 122.6, 114.7, 61.6, 61.5; **HRMS** (ESI+): Found $(M + H)^+$ 371.0267, $C_{19}H_{16}O_3{}^{79}Br$ $(M + H)^+$ requires 371.0278.

7.4.7 Preparation of 2-bromo-1,4-dimethoxybenzene 319

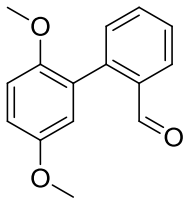
To a solution of 1,4-dimethoxybenzene **318** (5.00 g, 36.19 mmol, 1.0 eq.) in CH_2Cl_2 was added NBS (6.40 g, 36.19 mmol, 1.0 eq.) and the reaction mixture was stirred under reflux for 72 hrs. On completion, the reaction was quenched with a saturated solution of aq. sodium sulfite (50 mL). The organic layer was collected and washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and the organic solvent was removed under reduced pressure. The crude product was purified by column chromatography (10% EtOAc/Hexane) to furnish 2-bromo-1,4-dimethoxybenzene **319** as a light brown oil (7.31 g, 33.66 mmol, 93 %).



R_f = 0.59 (20% EtOAc/Hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.11 (1H, dd, *J* = 7.1, 0.8 Hz, H-5), 6.82 – 6.79 (2H, m, H-3 and H-6 overlapping), 3.81 (3H, s, OMe), 3.73 (3H, s, OMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.3, 119.0, 114.6, 113.6, 112.9, 111.9, 56.8, 55.1.

7.4.8 Preparation of 2',5'-dimethoxybiphenyl-2-carbaldehyde 320

To a deoxygenated solution of 2-bromo-1,4-dimethoxybenzene **319** (4.25 g, 19.66 mmol, 1.0 eq.) and 2-formylphenylboronic acid **308** (4.42 g, 29.49 mmol, 1.5 eq.) in DME (160 mL) was added $Pd(PPh_3)_4$ (1.82 g, 1.57 mmol, 8 mol %) under argon atmosphere with stirring. To this mixture was added a deoxygenated aq. Na_2CO_3 solution (2 M, 39.3 mL, 78.64 mmol, 4.0 eq.). The mixture was then heated at reflux for 18 hrs. After this time, the mixture was cooled to rt and the reaction quenched with H_2O (100 mL). The organic material was extracted into EtOAc (3 × 100 mL), the combined extract dried with $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (5-10% EtOAc/hexane) to afford 2',5'-dimethoxybiphenyl-2-carbaldehyde **320** as an off-white solid (4.19 g, 17.30 mmol, 88%).

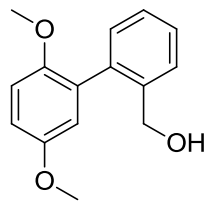


R_f = 0.48 (20% EtOAc/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.79 (1H, s, CHO), 8.01 – 7.97 (1H, m, ArH), 7.64 (1H, td, *J* = 7.5, 1.2 Hz, ArH), 7.48 (1H, t, *J* = 7.6 Hz, ArH), 7.38 – 7.34 (1H, m, ArH), 6.94 (1H, dd, *J* = 8.9, 3.0 Hz, ArH), 6.90 (1H, d, *J* = 8.9 Hz, ArH), 6.87 (1H, d, *J* = 3.0 Hz, ArH), 3.81 (3H, s, OMe), 3.67 (3H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 192.5, 153.8, 150.7, 141.6, 134.0, 133.7, 131.0, 127.8, 127.7, 126.6, 117.3, 114.4, 111.8, 55.9, 55.8.

7.4.9 Preparation of (2',5'-dimethoxybiphenyl-2-yl)methanol 321

2',5'-Dimethoxybiphenyl-2-carbaldehyde **320** (3.37 g, 13.92 mmol, 1.0 eq.) was dissolved in freshly distilled THF (140mL) and $LiAlH_4$ (1.58 g, 41.75 mmol, 3.0 eq.) was added to it at 0 °C under inert conditions. The reaction mixture was allowed to warm up to rt and was stirred for 2 hrs. When completed, the reaction was cooled to 0 °C, a 2% aq. NaOH (50 mL) solution was added dropwise to quench the unreacted $LiAlH_4$ and then the mixture was diluted with ice-cold water (50 mL). The organic material was then extracted into EtOAc (3 × 100 mL) and combined organic phases were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude product was purified using column chromatography on silica gel (20% EtOAc/Hexane) to isolate (2',5'-dimethoxybiphenyl-2-yl)methanol **321** as a clear oil (3.33 g, 13.64 mmol, 98%).

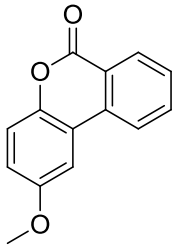
R_f = 0.37 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3422, 2999, 2836, 1600, 1499, 1483, 1460, 1447, 1440, 1274, 1211; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.53 (1H, dd, *J* = 7.5, 1.2 Hz, ArH), 7.36 (2H, dtd, *J* = 7.4, 7.4, 1.4 Hz, ArH), 7.26 – 7.15 (1H, m, ArH), 6.89 (2H, dt, *J* = 8.9, 5.9 Hz, ArH), 6.74 (1H, d, *J* = 2.9 Hz, ArH), 4.41 (2H, d, *J* = 10.6 Hz, C*H*$_2$OH), 3.77 (3H, s, OMe), 3.66 (3H, s, OMe), 2.50 (t, *J* = 6.2 Hz, OH); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 153.9, 150.6, 139.3, 137.4, 131.1, 130.1, 128.8, 128.1, 127.7, 117.0, 113.6, 112.8, 63.8, 56.7, 55.7; **HRMS** (ESI+): Found M^+ 244.1091, $C_{15}H_{16}O_3$ M^+ requires 244.1086, *m/z* 244.1091 (M^+, 15%), 227.1065 (100%).



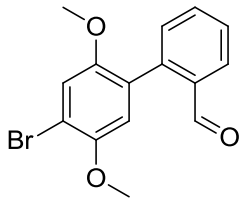
7.4.10 Preparation of 2-methoxy-6*H*-benzo[*c*]chromen-6-one 322 and (4′-bromo-2′,5′-dimethoxybiphenyl-2-yl)benzaldehyde 323

NBS (1.28 g, 7.21 mmol, 2.0 eq.) was slowly added under an oxygen atmosphere to an oxygenated solution of (2',5'-dimethoxybiphenyl-2-yl)methanol **321** (0.88 g, 3.60 mmol, 1.0 eq.) in CH_2Cl_2 (40 mL). The reaction mixture was allowed to stir under oxygen at rt for 8 hrs. On completion, the reaction was quenched with saturated

solution of aq. sodium sulfite (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered and the organic solvent was removed under reduced pressure. The crude product was purified by column chromatography (5% EtOAc/Hexane) to afford 2-methoxy-6*H*-benzo[*c*]chromen-6-one **322** as a white solid (0.37 g, 1.65 mmol, 46%) and (4′-bromo-2′,5′-dimethoxybiphenyl-2-yl)benzaldehyde **323** (0.42 g, 1.29 mmol 36%).



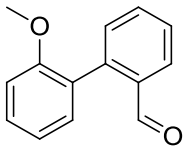
R_f = 0.45 (20% EtOAc/Hexane); **Mp** 117-119 °C CH_2Cl_2; **IR** (ν/cm^{-1}) 2938, 2812, 1679, 1609, 1420, 1278, 1224, 1003; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.41 (1H, dd, *J* = 7.9, 1.0 Hz, ArH), 8.07 (1H, d, *J* = 8.1 Hz, ArH), 7.83 (1H, td, *J* = 7.8, 1.4 Hz, ArH), 7.64 – 7.55 (1H, m, ArH), 7.50 (1H, d, *J* = 2.9 Hz, ArH), 7.31 (1H, d, *J* = 9.0 Hz, ArH), 7.05 (1H, dd, *J* = 9.0, 2.9 Hz, ArH), 3.91 (3H, s, OMe); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 161.3, 156.4, 145.7, 134.7, 134.7, 130.7, 129.0, 121.7, 121.4, 118.7, 118.6, 117.1, 106.4, 55.9; **HRMS** (ESI+): Found $(M + H)^+$ 227.0701, $C_{14}H_{11}O_3$ $(M + H)^+$ requires 227.0704, *m/z* 227.0701 [$(M + H)^+$, 100%], 226.0625 (30%).



R_f = 0.61 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 2976, 2847, 1691, 1596, 1206, 1198, 938, 656; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.78 (1H, s, CHO), 8.02-7.97 (1H, m, ArH), 7.65 (1H, d, *J* = 1.2 Hz, ArH), 7.51 (1H, s, ArH), 7.34 (1H, d, *J* = 7.6 Hz, ArH), 7.18 (1H, s, ArH), 6.86 (1H, s, ArH), 3.88 (3H, s, OMe), 3.69 (3H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 192.1, 150.8, 150.4, 140.7, 134.0, 133.7, 130.9, 128.2, 126.9, 126.7, 116.3, 115.2, 112.1, 57.0, 56.2; **HRMS** (ESI+): Found $(M + H)^+$ 321.0120, $C_{15}H_{14}{}^{79}BrO_3$ $(M + H)^+$ requires 321.0122, *m/z* 320.0043 (100%), 322.0043 (97%).

7.4.11 Preparation of 2′-methoxybiphenyl-2-carbaldehyde 325

To a deoxygenated solution of 2-bromoanisole **324** (4.00 g, 21.34 mmol, 1.0 eq.) and 2-formylphenylboronic acid **308** (4.80 g, 32.09 mmol, 1.5 eq.) in DME (160 mL) was added $Pd(PPh_3)_4$ (2.46 g, 2.13 mmol, 10 mol%) under argon atmosphere with stirring. To this mixture was added a deoxygenated aq. Na_2CO_3 (2 M, 42.7 mL, 85.36 mmol, 4.0 eq.). The mixture was then heated at reflux for 18 hrs. After this time, the mixture was cooled to rt and reaction quenched with H_2O (100 mL). The organic material was extracted into EtOAc (3 × 100 mL), the combined extract dried with $MgSO_4$, and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (5-10% EtOAc/hexane) to afford 2′-methoxybiphenyl-2-carbaldehyde **325** as an off-white solid (3.95 g, 18.63 mmol, 87%).

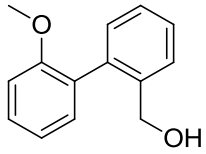


R_f = 0.52 (20% EtOAc/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.78 (1H, d, *J* = 0.9 Hz, CHO), 7.98 (1H, dd, *J* = 7.8, 1.5 Hz, ArH), 7.60 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 7.44 (1H, t, *J* = 7.6 Hz, ArH), 7.39 (1H, td, *J* = 7.5, 1.8 Hz, ArH), 7.33 (1H, dd, *J* = 7.7, 1.2 Hz, ArH), 7.26 (1H, dd, *J* = 7.5, 1.8 Hz, ArH), 7.06 (1H, td, *J* = 7.5, 1.1 Hz, ArH), 6.95 (1H, dd, *J* = 8.3, 1.0 Hz, ArH), 3.70 (3H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 192.5, 156.5, 141.8, 134.0, 133.6, 131.4, 131.2, 130.0, 127.7, 126.8, 126.5, 121.0, 110.6, 55.3.

7.4.12 Preparation of (2'-methoxybiphenyl-2-yl)methanol 326

2'-Methoxybiphenyl-2-carbaldehyde **325** (3.20 g, 15.09 mmol, 1.0 eq.) was dissolved in 140 mL of freshly distilled dry THF under inert conditions. $LiAlH_4$ (1.71 g, 45.28 mmol, 3.0 eq.) was added to the mixture carefully at 0 °C. The reaction was warmed to rt and allowed to stir at rt under inert conditions for 2 hrs. When completed, the reaction was cooled to 0 °C, a 2% aq. NaOH (50 mL) solution was added dropwise to quench the unreacted $LiAlH_4$ and then the mixture was diluted with ice-cold water (100 mL). The organic material was then extracted into EtOAc (3 × 100 mL) and the

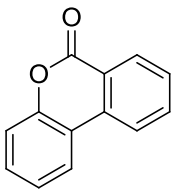
combined organic phases were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was then subjected to column chromatography (20% EtOAc/Hexane) to obtain (2'-methoxybiphenyl-2-yl)methanol **326** as a clear oil (3.17 g, 14.78 mmol, 98%).



R_f = 0.48 (20% EtOAc/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.49 (1H, dd, *J* = 7.4, 1.6 Hz, ArH), 7.35 – 7.27 (3H, m, ArH), 7.16 (1H, dd, *J* = 7.4, 1.6 Hz, ArH), 7.11 (1H, dd, *J* = 7.4, 1.8 Hz, ArH), 6.98 (1H, td, *J* = 7.5, 1.1 Hz, ArH), 6.92 (1H, dd, *J* = 8.4, 1.0 Hz, ArH), 4.36 (2H, d, *J* = 11.9 Hz, -C*H*$_2$-), 3.64 (3H, s, OMe), 2.66 (1H, s, OH); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.3, 139.3, 137.3, 131.2, 130.2, 129.0, 128.0, 127.8, 127.4, 126.8, 120.9, 111.0, 63.3, 55.6.

7.4.13 Preparation of 6*H*-benzo[*c*]chromen-6-one 327

NBS (1.10 g, 6.17 mmol, 1.5 eq.) was slowly added under an oxygen atmosphere to an oxygenated solution of (2'-methoxybiphenyl-2-yl)methanol **326** (880 mg, 4.11 mmol, 1.0 eq.) in CCl_4 (100 mL). The reaction mixture was allowed to stir under reflux for 18 hrs. On completion, the reaction was quenched with a saturated solution of aq. sodium sulfite (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were washed with water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered and the organic solvent was removed under reduced pressure. The crude product was purified by column chromatography (5 - 10% EtOAc/Hexane) to isolate 6*H*-benzo[*c*]chromen-6-one **327** as a white crystalline solid (0.57 g, 2.91 mmol, 70%).

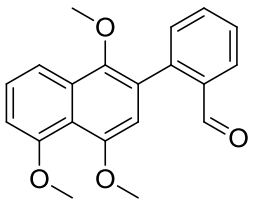


R_f = 0.57 (20% EtOAc/Hexane); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.39 (1H, d, *J* = 8.0 Hz, ArH), 8.10 (1H, d, *J* = 8.1 Hz, ArH), 8.04 (1H, d, *J* = 7.9 Hz, ArH), 7.81 (1H, t, *J* = 8.7, ArH), 7.57 (1H, t, *J* = 7.1, ArH), 7.42 – 7.51 (1H, m, ArH), 7.39-7.28 (2H, m, ArH);

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 151.3, 134.8, 134.7, 130.6, 130.4, 128.9, 124.5, 122.8, 121.7, 121.3, 118.0, 117.8.

7.4.14 Preparation of 2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde 328

Tetrakis(triphenylphosphine)palladium(0) (0.47 g, 0.404 mmol, 10 mol %) and 2-formylphenylboronic acid **308** (0.91 g, 6.06 mmol, 1.5 eq.) were added to a deoxygenated solution of 2-bromo-1,4,5-trimethoxynaphthalene **115** (1.20 g, 4.04 mmol, 1.0 eq.) in DME (40 mL) under argon atmosphere with stirring. To this, was added a deoxygenated aq. Na_2CO_3 solution (2 M, 8.1 mL, 16.16 mmol, 4.0 eq.). The reaction mixture was then heated at reflux for 18 hrs. After this time, the mixture was cooled to rt and reaction quenched with H_2O (50 mL). The organic material was extracted into EtOAc (3 × 50 mL), followed by a brine wash (50 mL). The combined extract dried over $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (10% EtOAc/hexane) to afford 2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde **328** as yellow solid (1.05 g, 3.27 mmol, 81%).

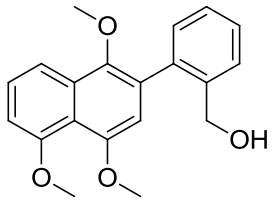


R_f = 0.45 (20% EtOAc/Hexane); **Mp**. 98-100 °C $CHCl_3$; **IR** (ν/cm^{-1}): 3002, 2837, 1687, 1583, 1413, 1263, 1183, 987; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.89 (1H, s, C*H*O), 8.07 (1H, d, *J* = 9.4, ArH), 7.78 (1H, dd, *J* = 8.4, 1.0 Hz, ArH), 7.70 (1H, dt, *J* = 8.5, 1.4 Hz, ArH), 7.55 (2H, d, *J* = 7.7 Hz, ArH), 7.48 (1H, t, *J* = 8.0 Hz, ArH), 6.95 (1H, dd, *J* = 7.8, 0.6 Hz, ArH), 6.78 (1H, s, ArH), 4.00 (3H, s, OMe), 3.97 (3H, s, OMe), 3.37 (3H, s, OMe); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 192.3, 157.5 153.7, 147.0, 141.6, 133.7, 133.5, 131.3, 130.9, 128.0, 127.4, 127.1, 126.1, 118.5, 115.2, 108.2, 107.4, 60.7, 56.9, 56.6; **HRMS** (ESI+): Found $(M + H)^+$ 323.1268, $C_{20}H_{18}O_4$ $(M + H)^+$ requires 323.1279, *m/z* 323.1268 [$(M + H)^+$, 100%], 322.1193 (40%).

7.4.15 Preparation of (2-(1,4,5-trimethoxynaphthalen-2-yl)phenyl)methanol 329

2-(1,4,5-Trimethoxynaphthalen-2-yl)benzaldehyde **328** (0.70 g, 2.17 mmol, 1.0 eq.) was dissolved in freshly distilled THF (30 mL) and $LiAlH_4$ (0.25 g, 6.52 mmol, 3.0 eq.) was added to it at 0 °C under inert conditions. The reaction mixture was allowed to warm to rt and was stirred for 2 hrs. When completed, the reaction was cooled to 0 °C, a 2% aq. NaOH (20 mL) solution was added dropwise to quench the unreacted $LiAlH_4$ and then the mixture was diluted with ice-cold water (20 mL). The organic material was then extracted into EtOAc (3 × 50 mL) and the combined organic phases were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude product was purified using column chromatography on silica gel (30% EtOAc/Hexane) to isolate (2-(1,4,5-trimethoxynaphthalen-2-yl)phenyl)methanol **329** as an off-white solid (0.68 g, 2.10 mmol, 97%).

R_f = 0.11 (20% EtOAc/Hexane); **IR** (ν/cm^{-1}): 3384, 3012, 2930, 1584, 1417, 1237, 1196, 1117, 1043; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.74 (1H, dd, *J* = 8.4, 1.0 Hz, ArH), 7.60 (1H, dd, *J* = 7.4, 1.4 Hz, ArH), 7.48 – 7.40 (1H, m, ArH), 7.37 (1H, dd, *J* = 7.4, 1.5 Hz, ArH), 6.92 (1H, dd, *J* = 7.8, 0.7 Hz, ArH), 6.66 (1H, s, ArH), 4.42 (2H, s, C*H*$_2$OH), 3.99 (3H, s, OMe), 3.93 (3H, s, OMe), 3.46 (4H, s, OMe and OH overlapping); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 157.5, 153.6, 146.2, 139.4, 137.6, 131.2, 130.0, 129.9, 129.8, 128.3, 127.8, 127.2, 118.0, 114.9, 108.5, 107.0, 64.1, 61.4, 56.8, 56.5.



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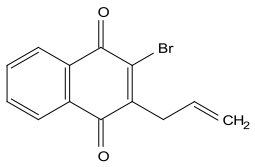
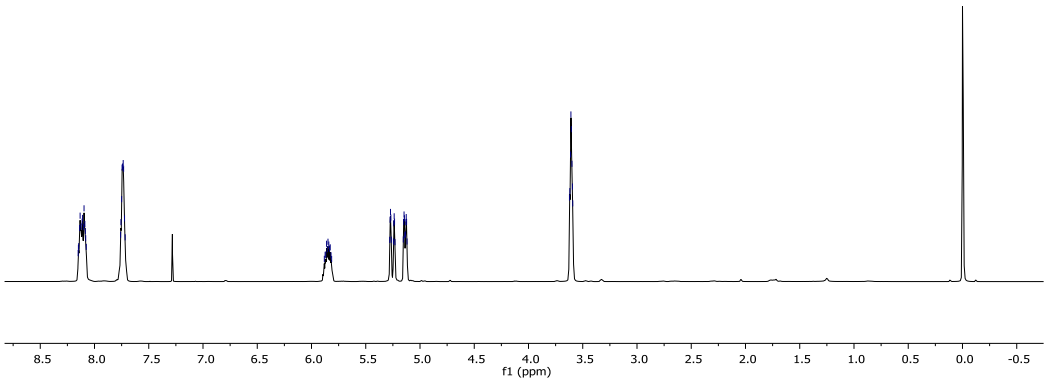
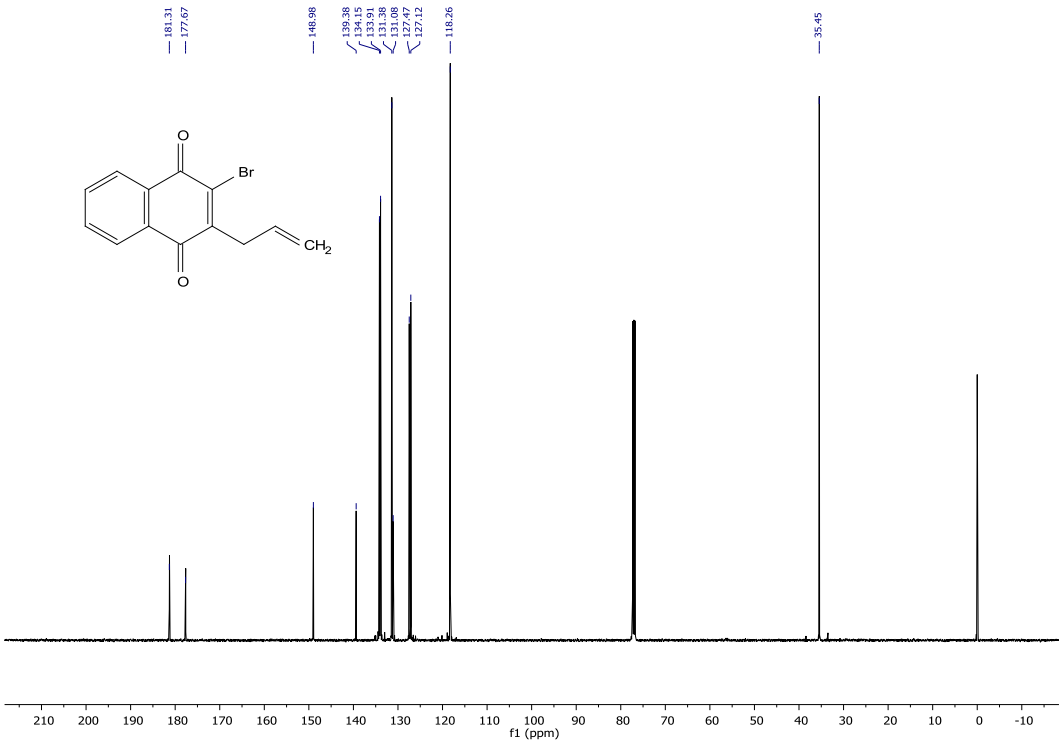
Appendices:

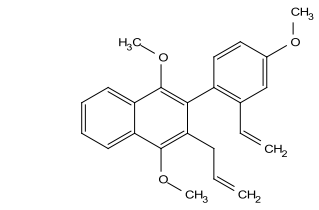
^{1}H and ^{13}C NMR spectra for compound 96

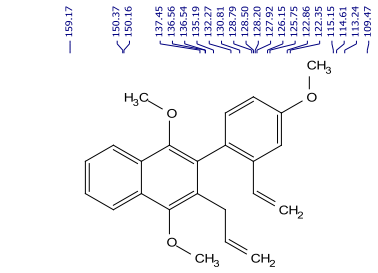






^{1}H and ^{13}C NMR spectra for compound 76b





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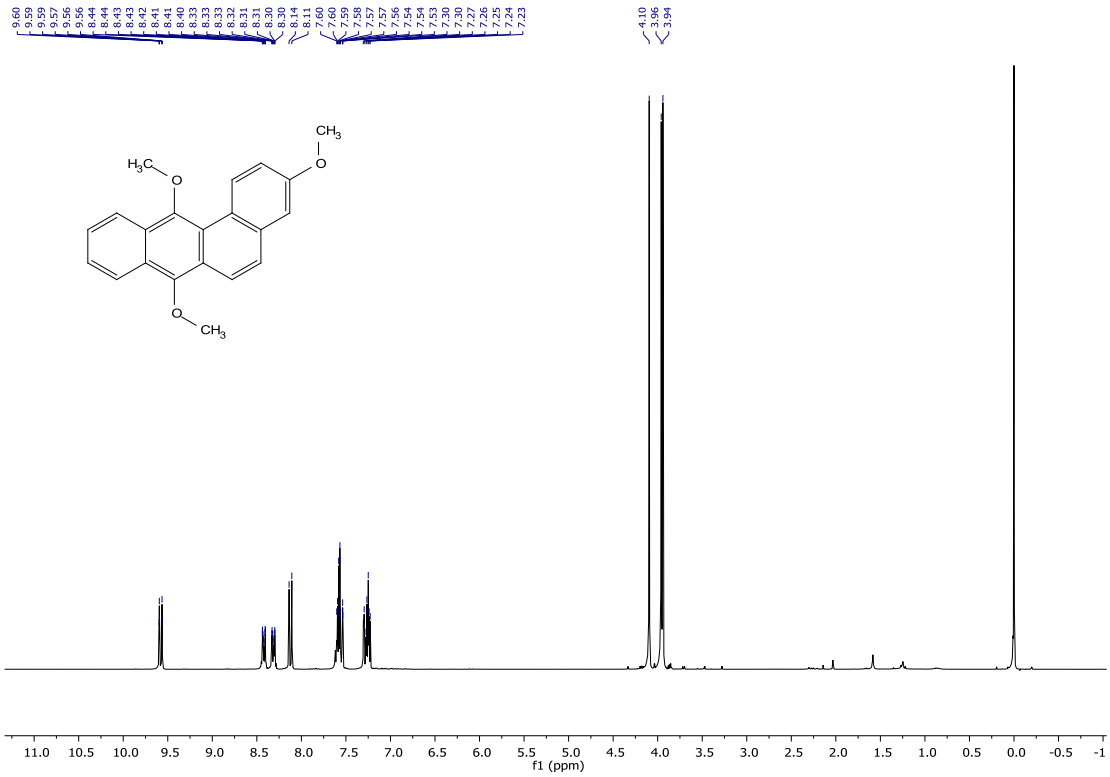

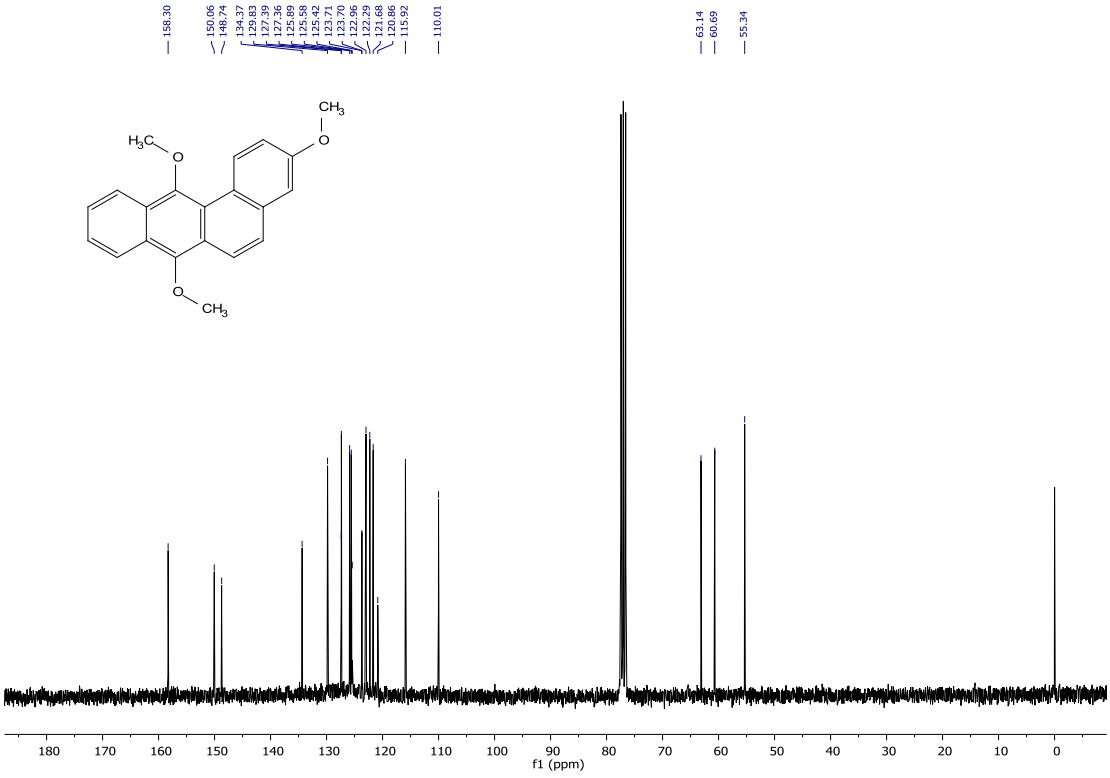

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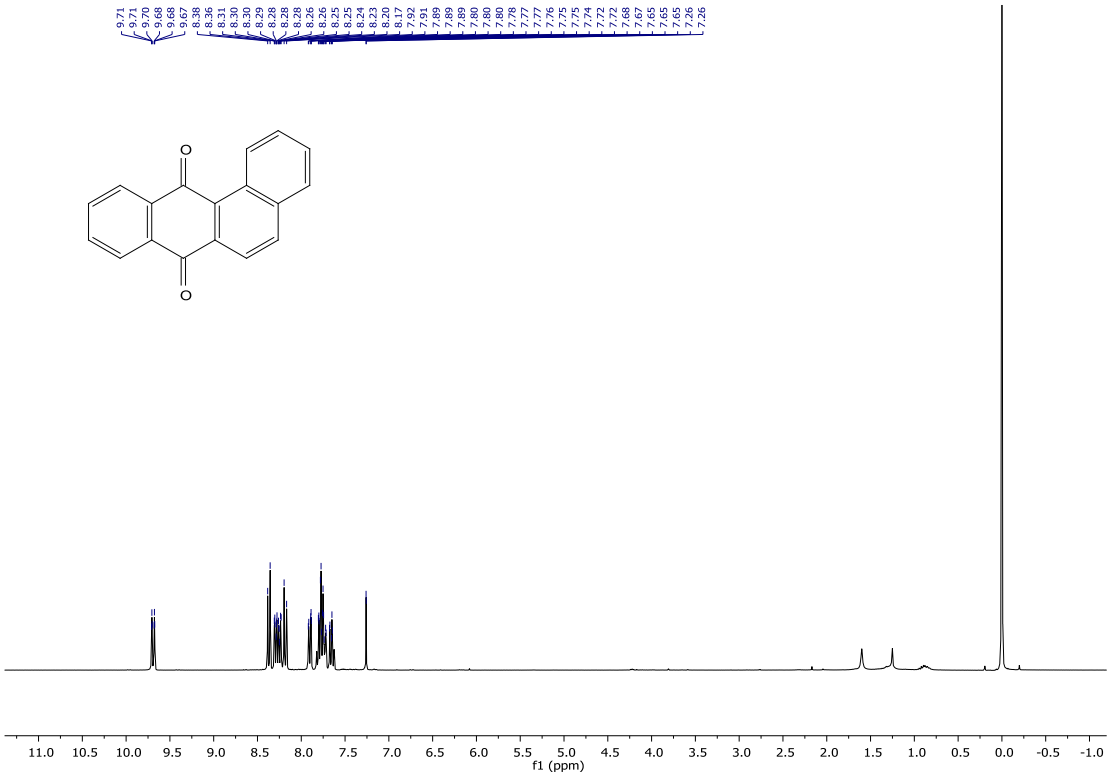

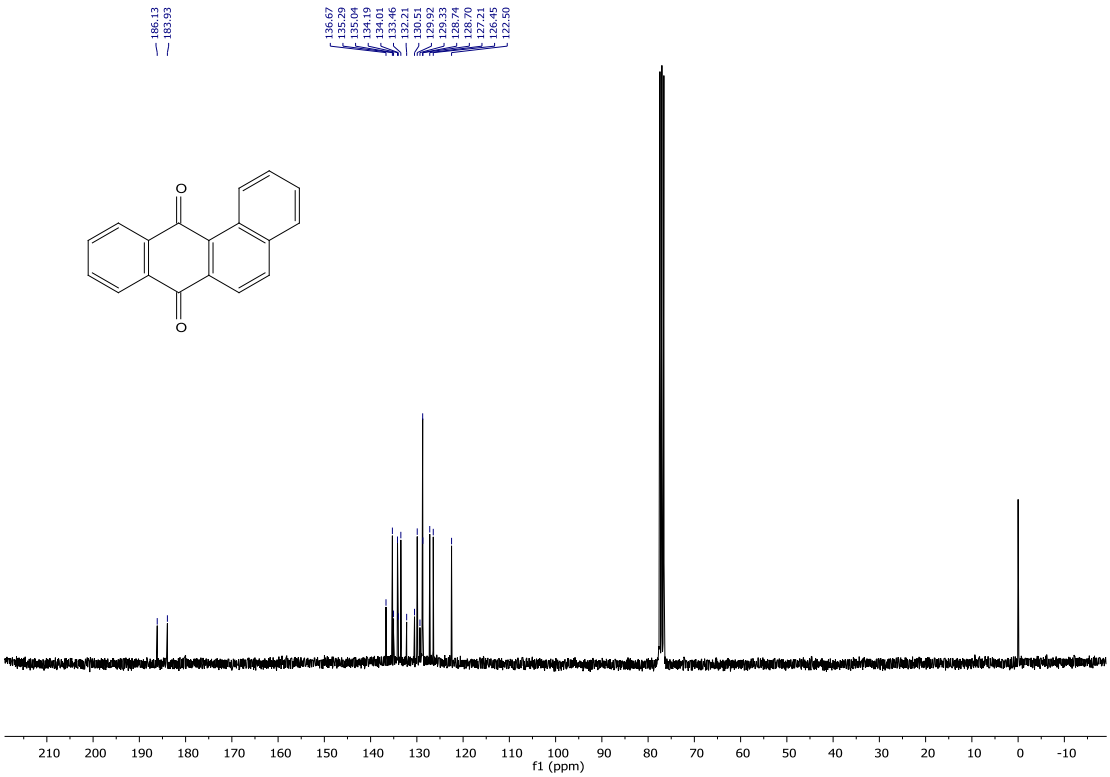

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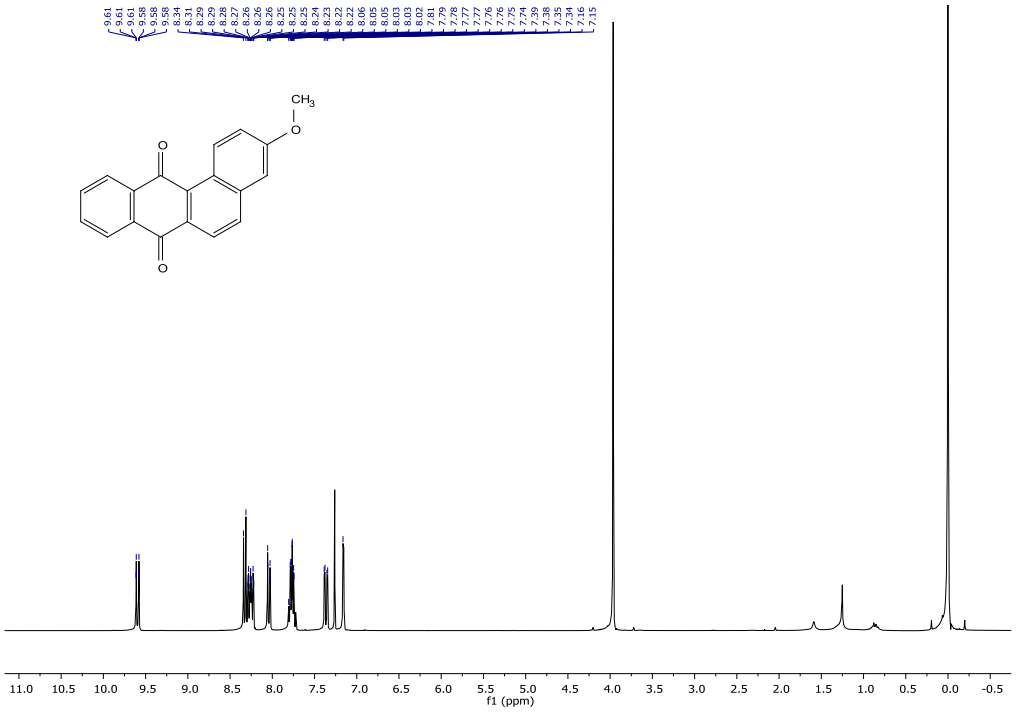

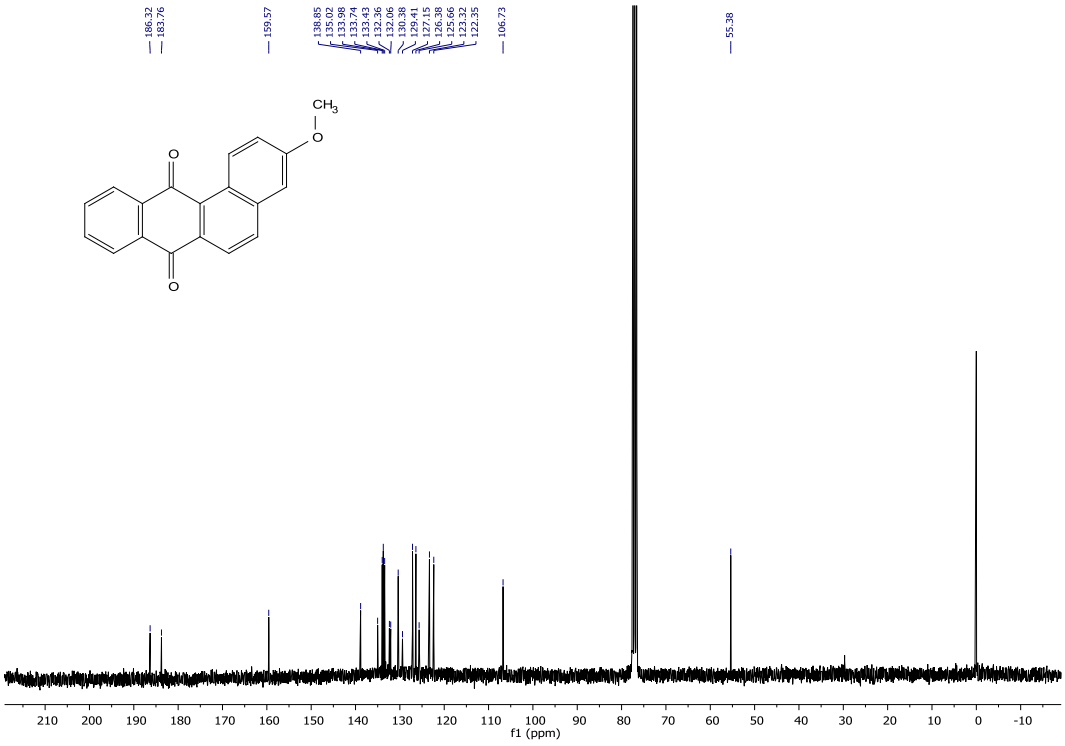

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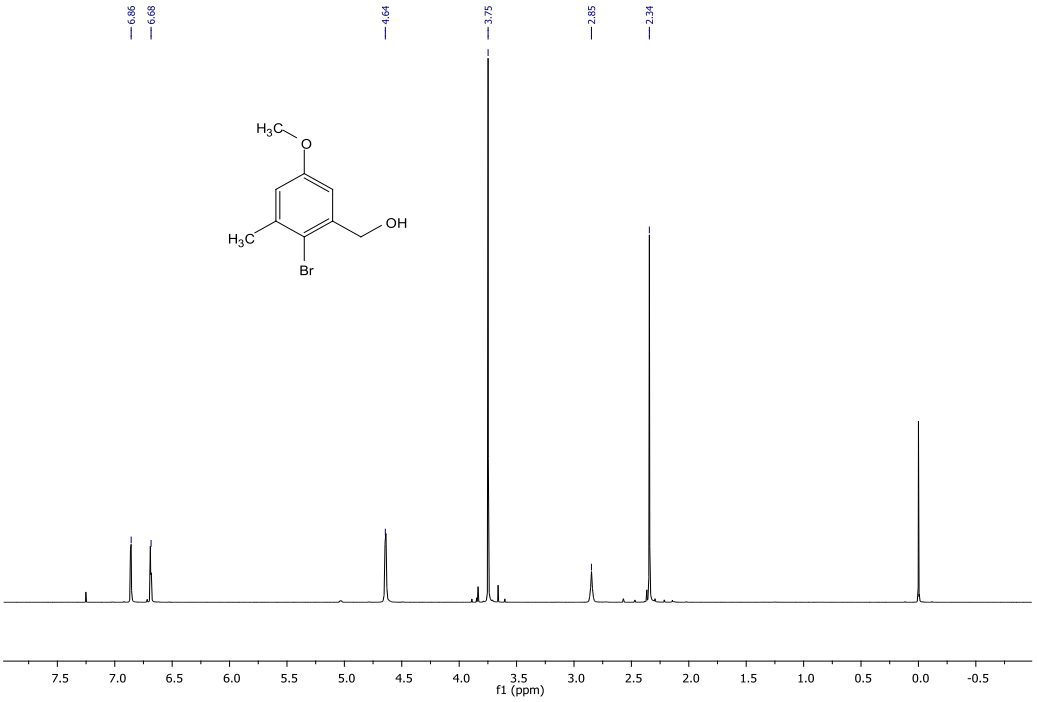

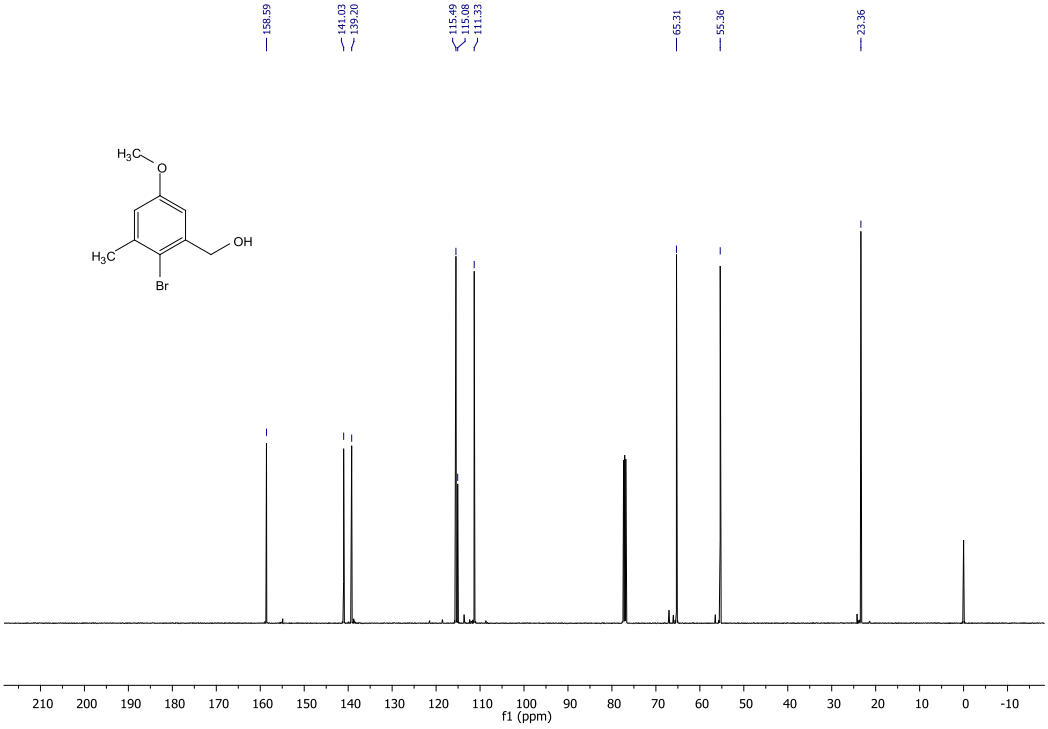

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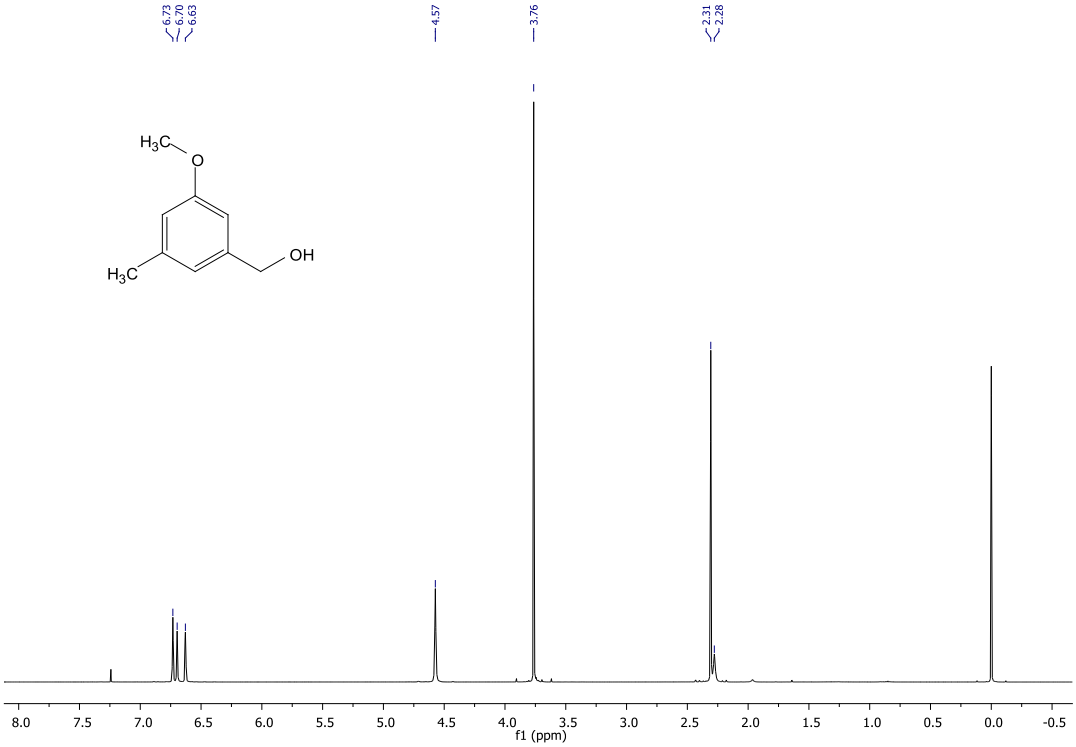

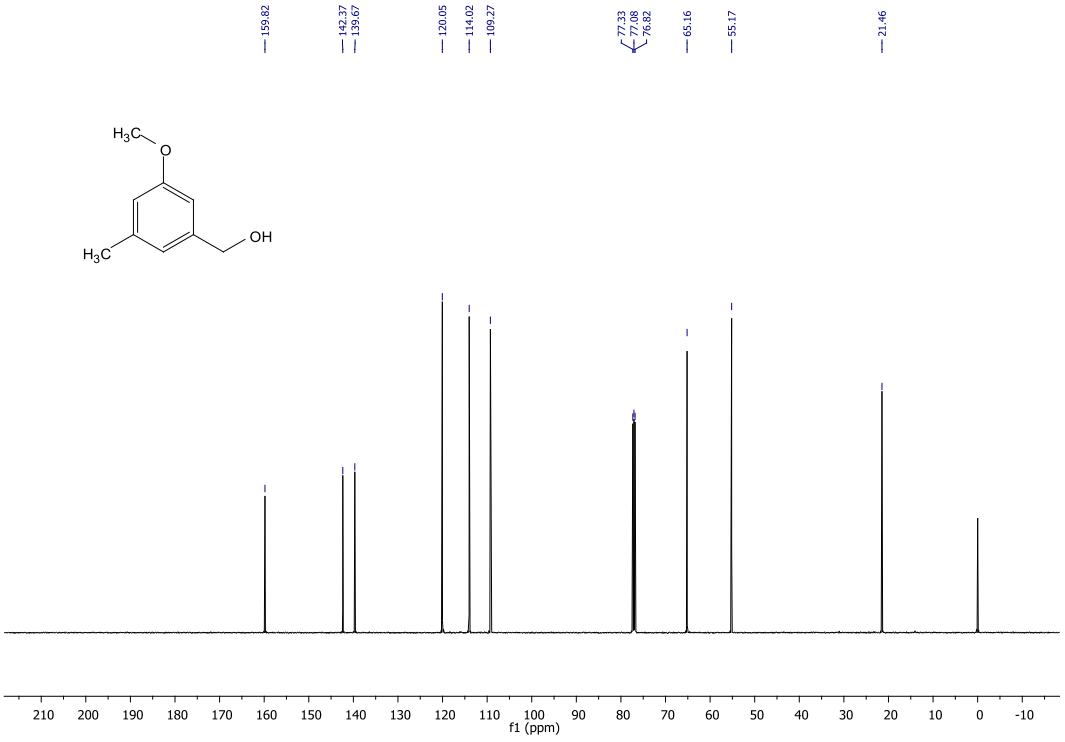

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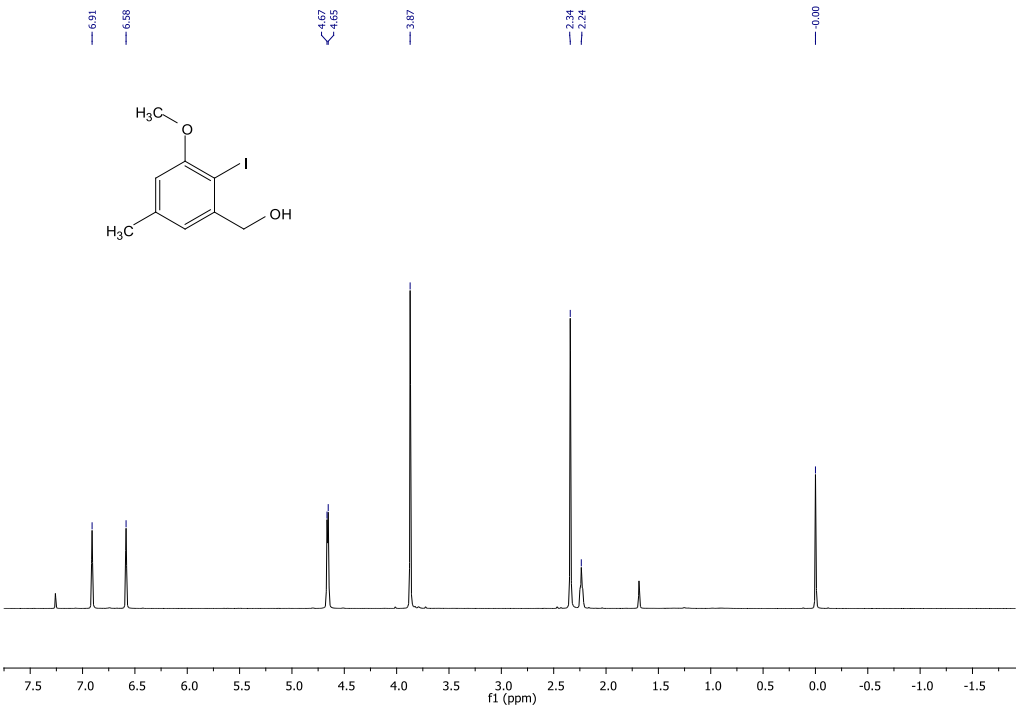

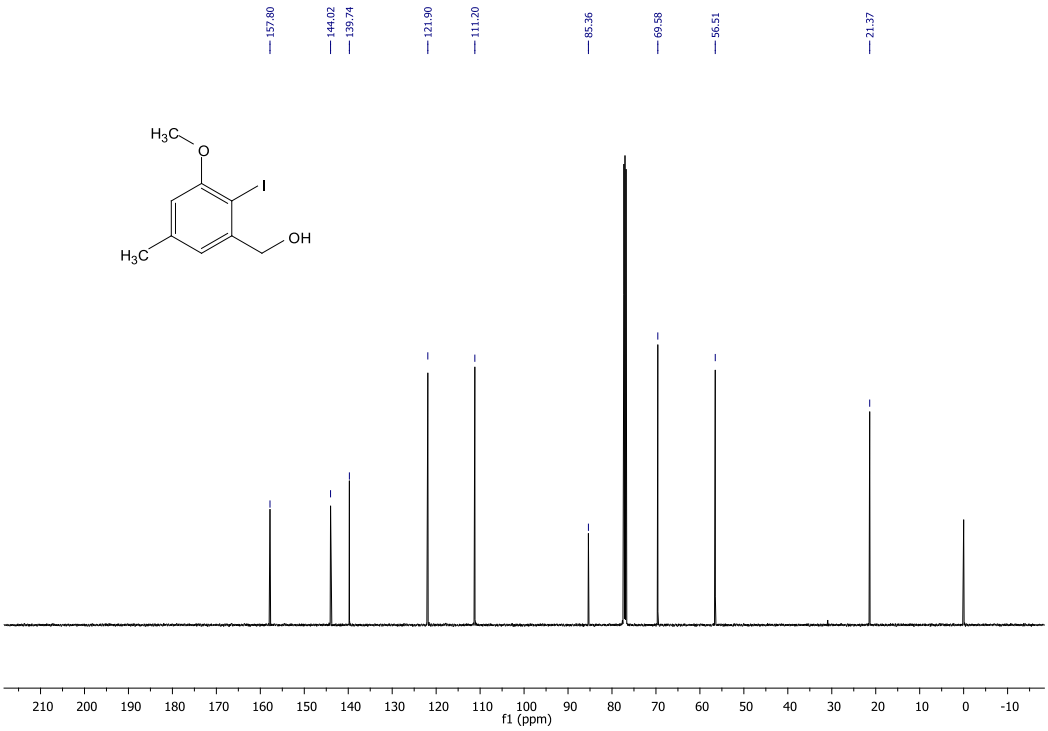

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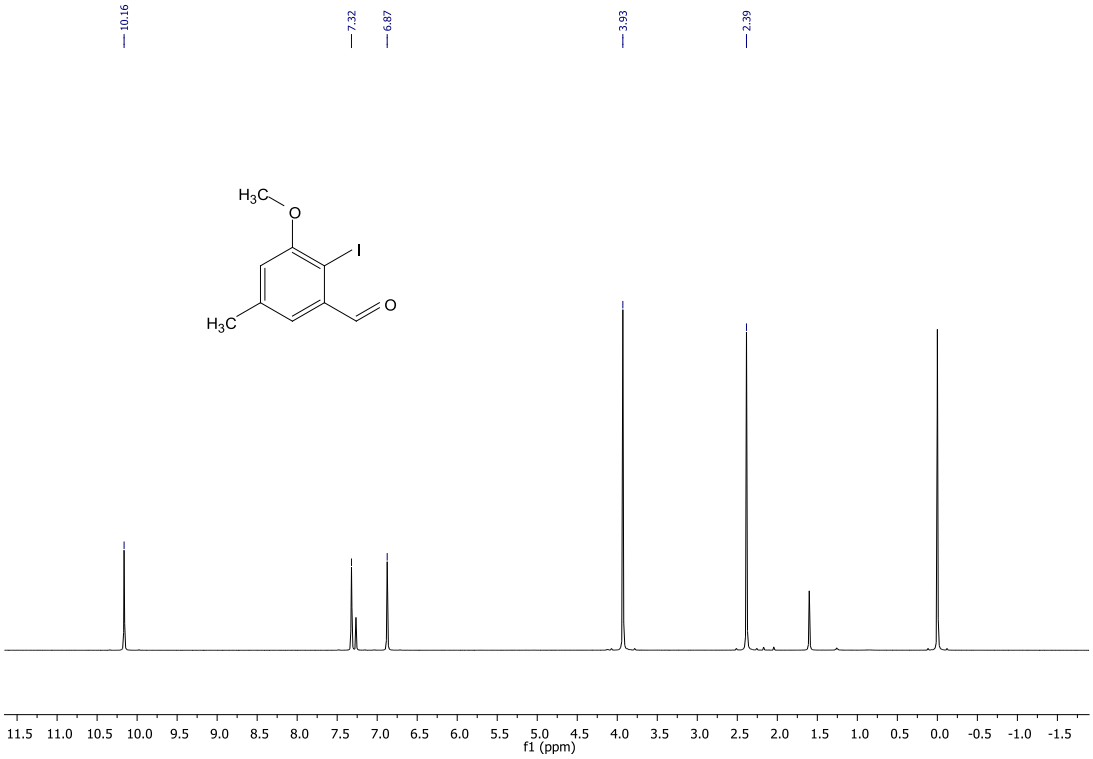

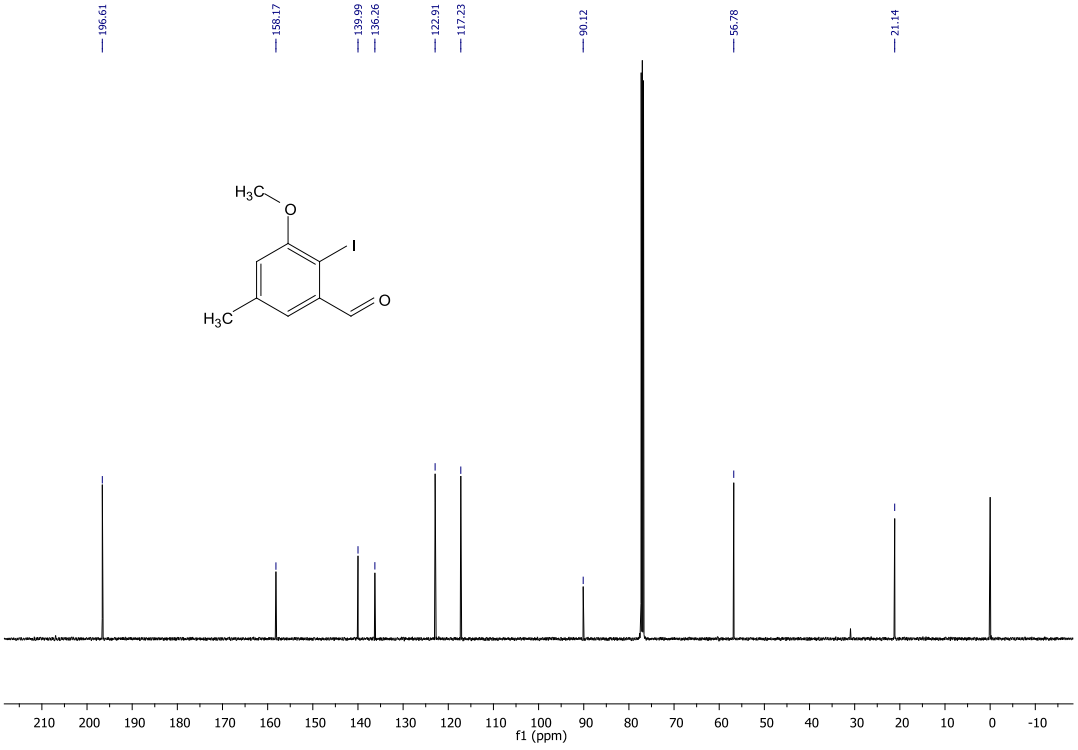

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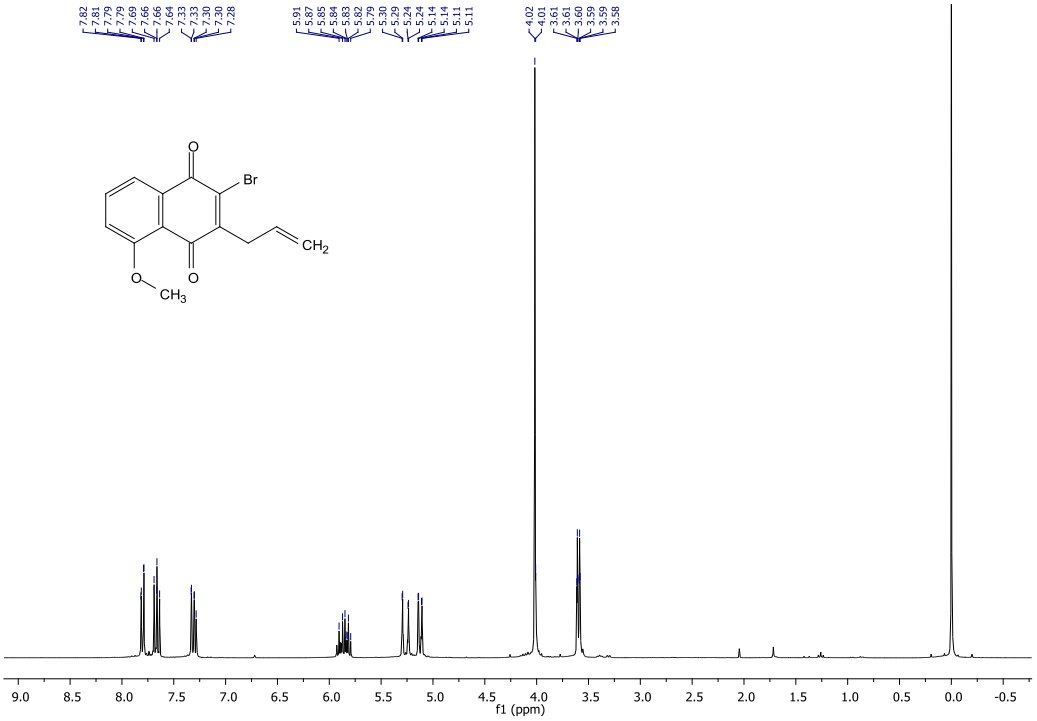

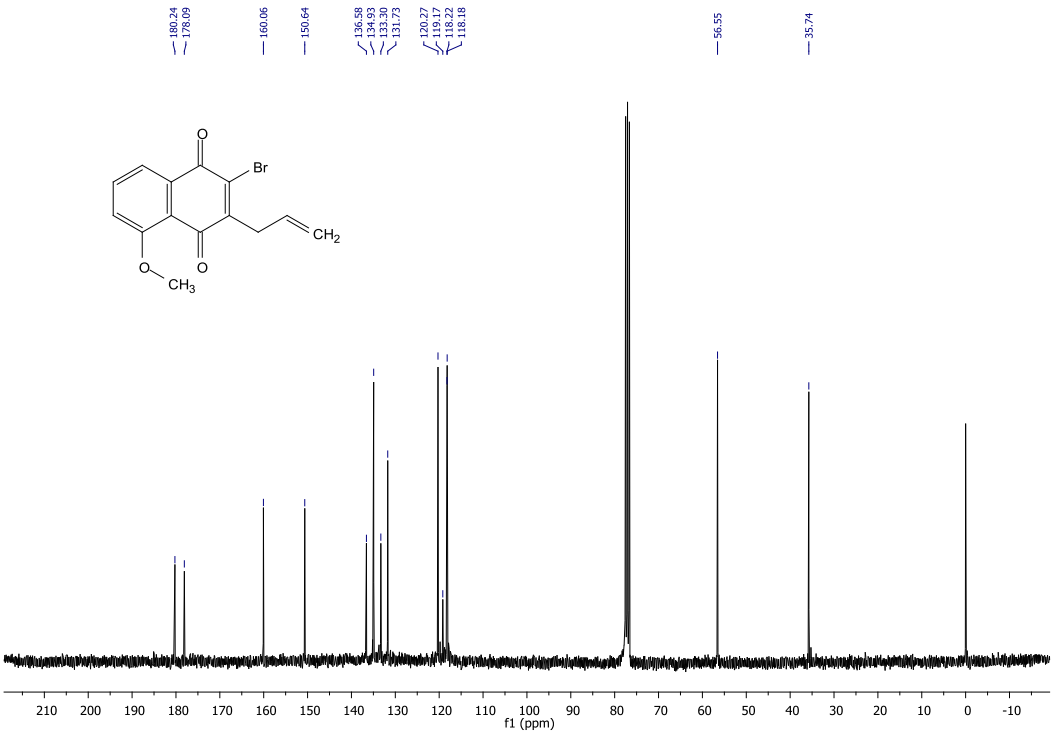

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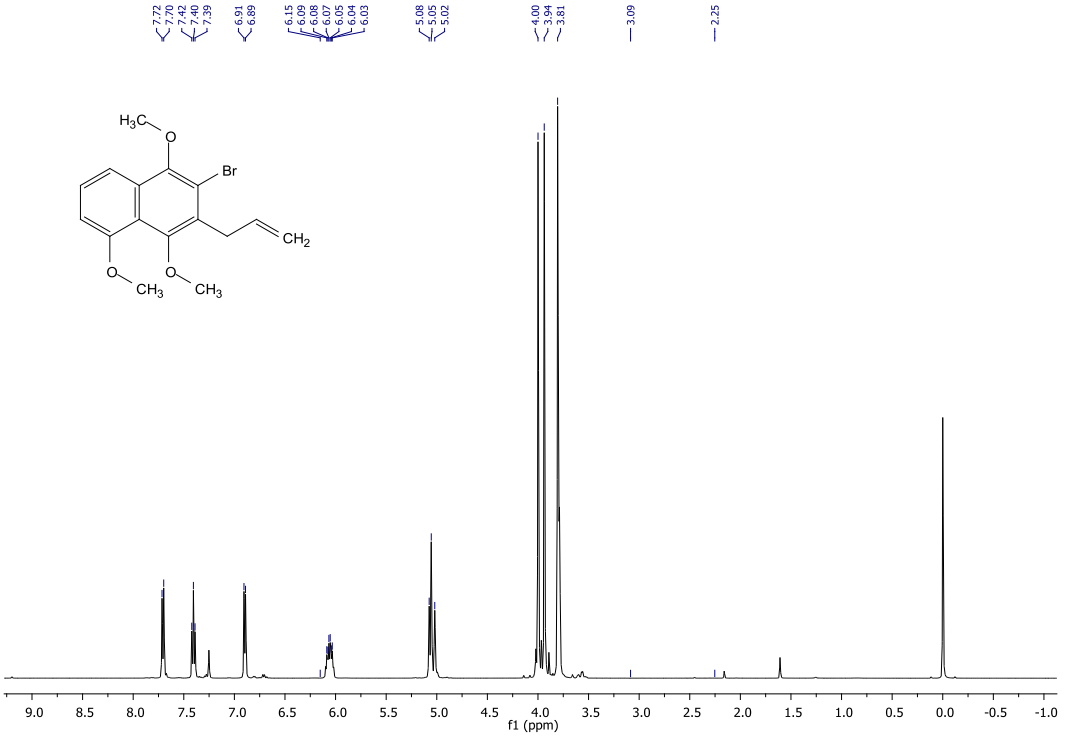
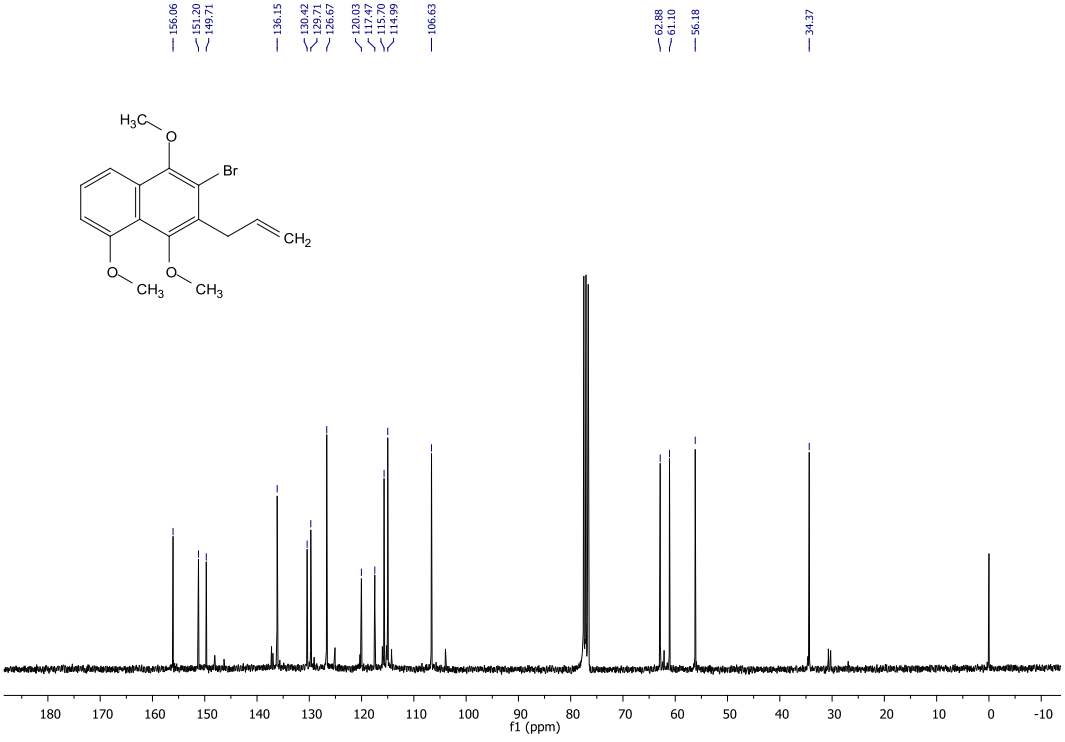
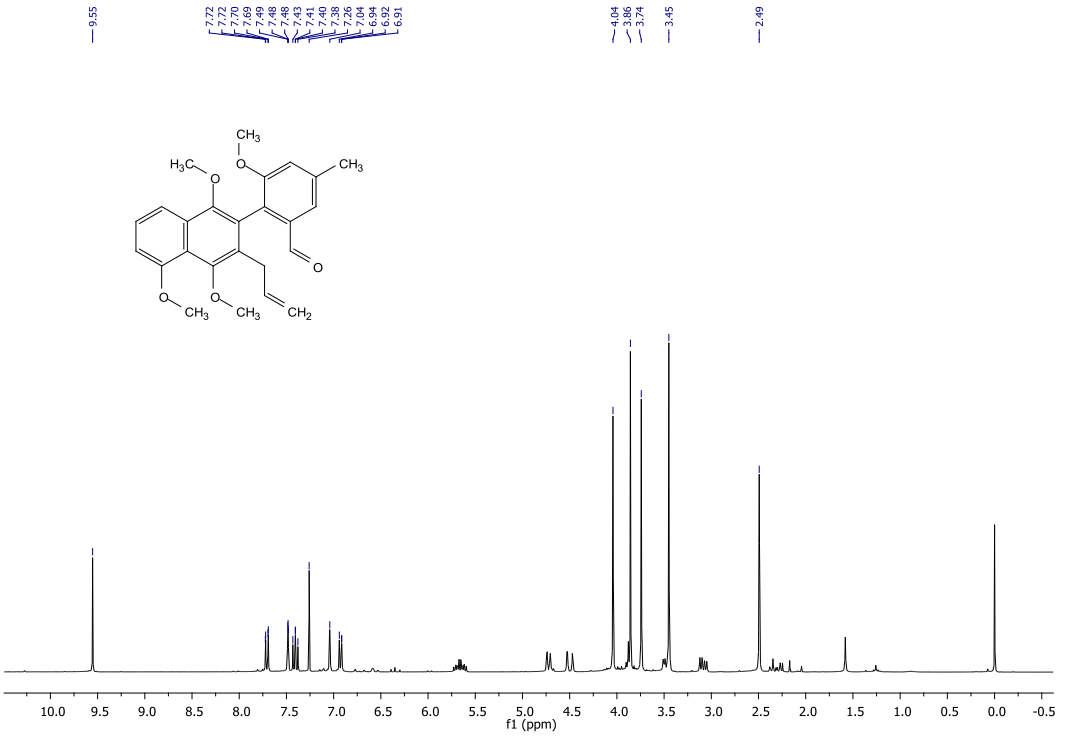
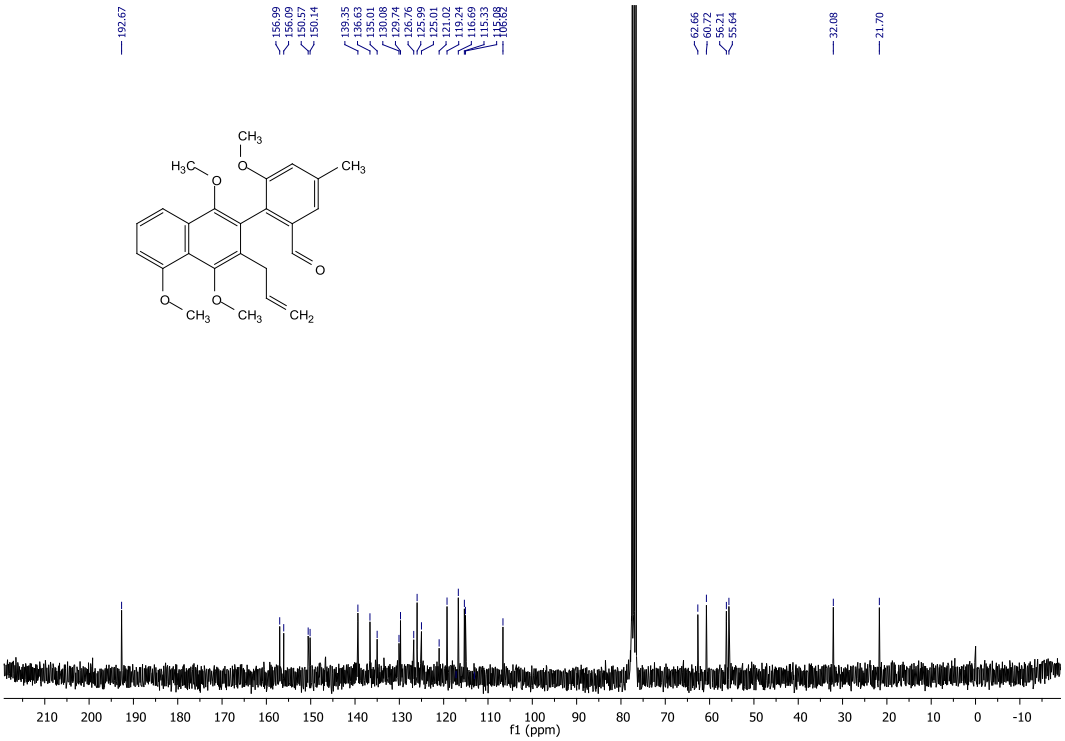


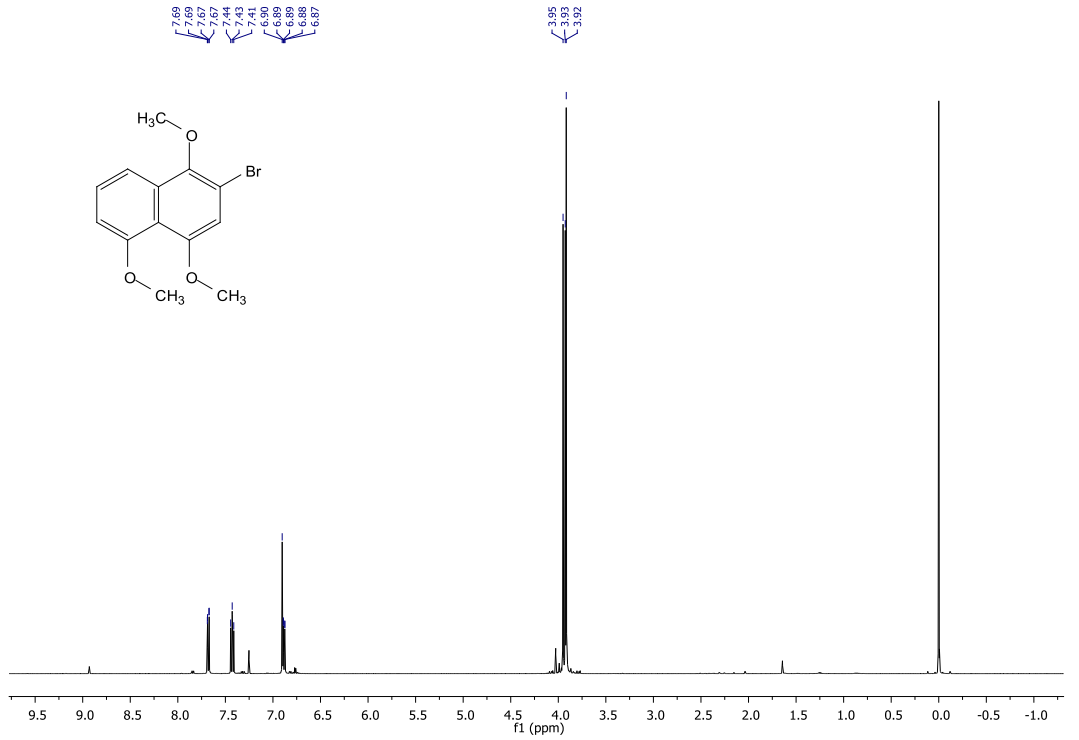


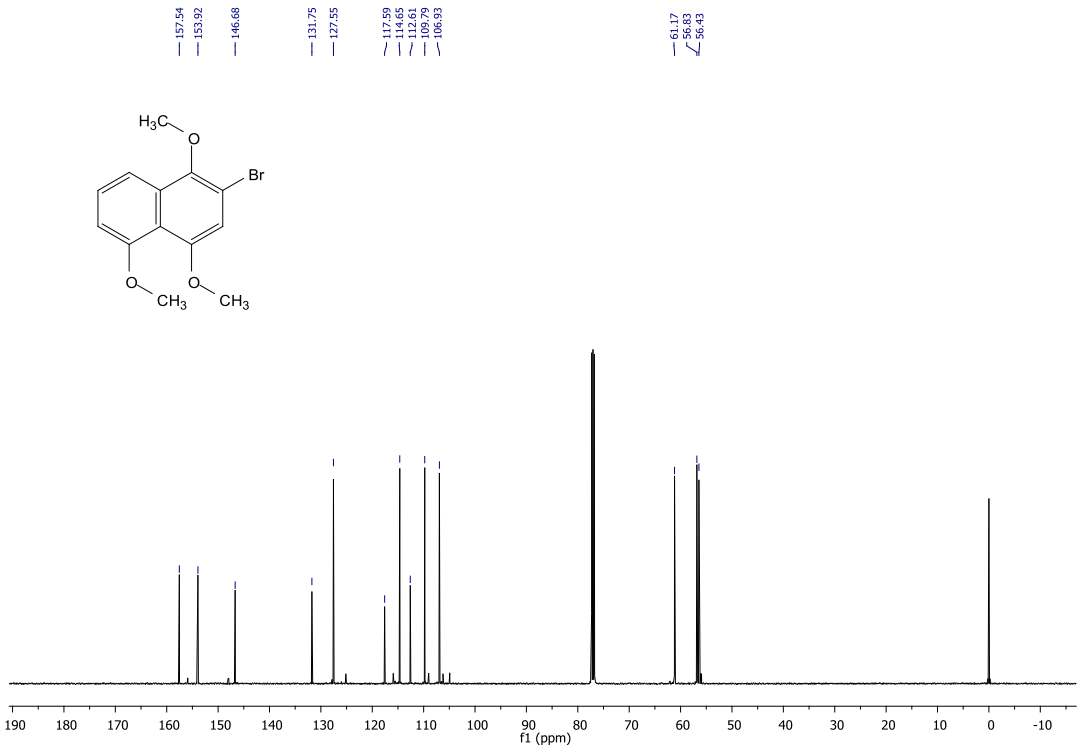
^{1}H and ^{13}C NMR spectra for Compound 110



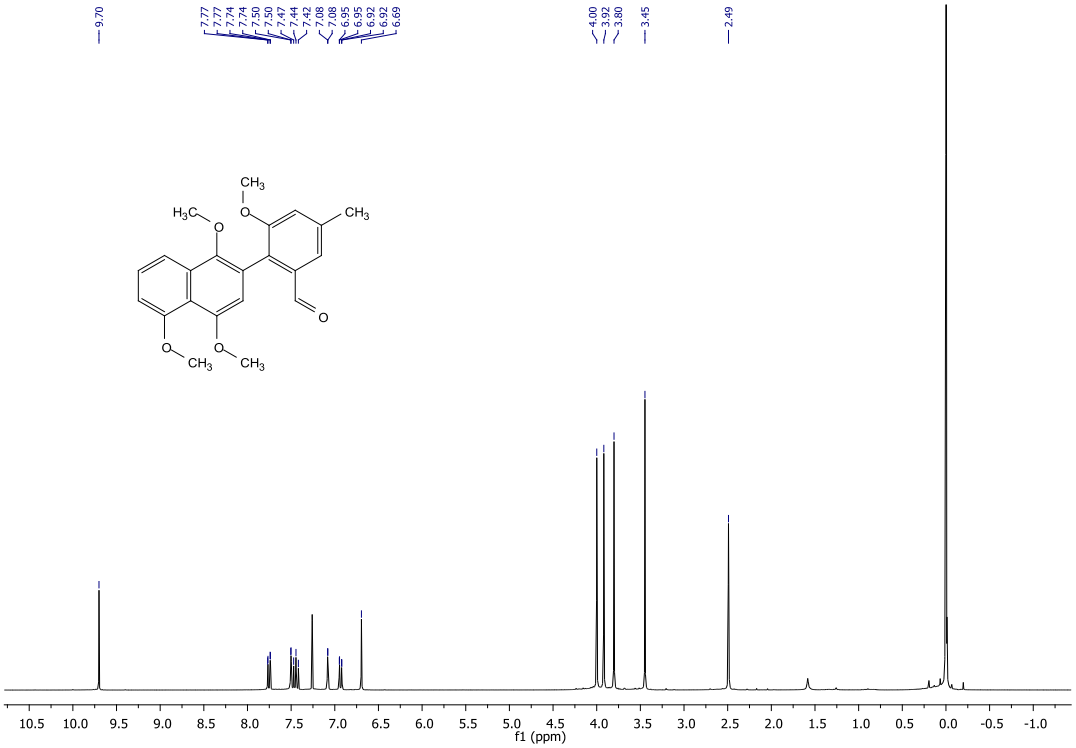


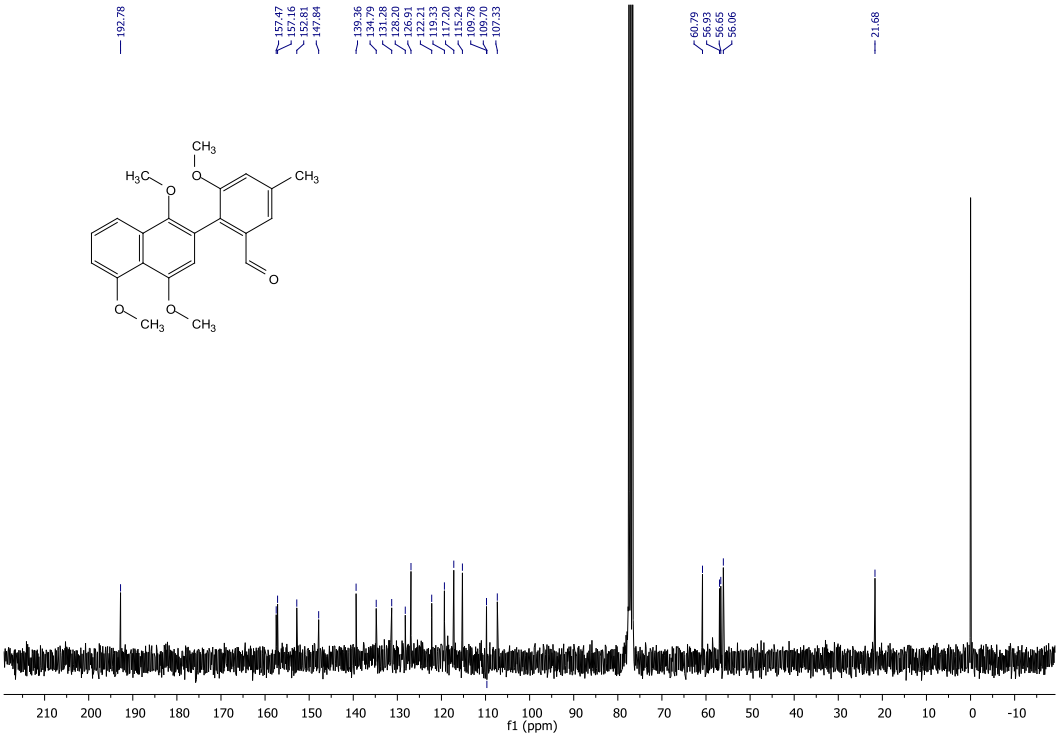
^{1}H and ^{13}C NMR spectra for Compound 115



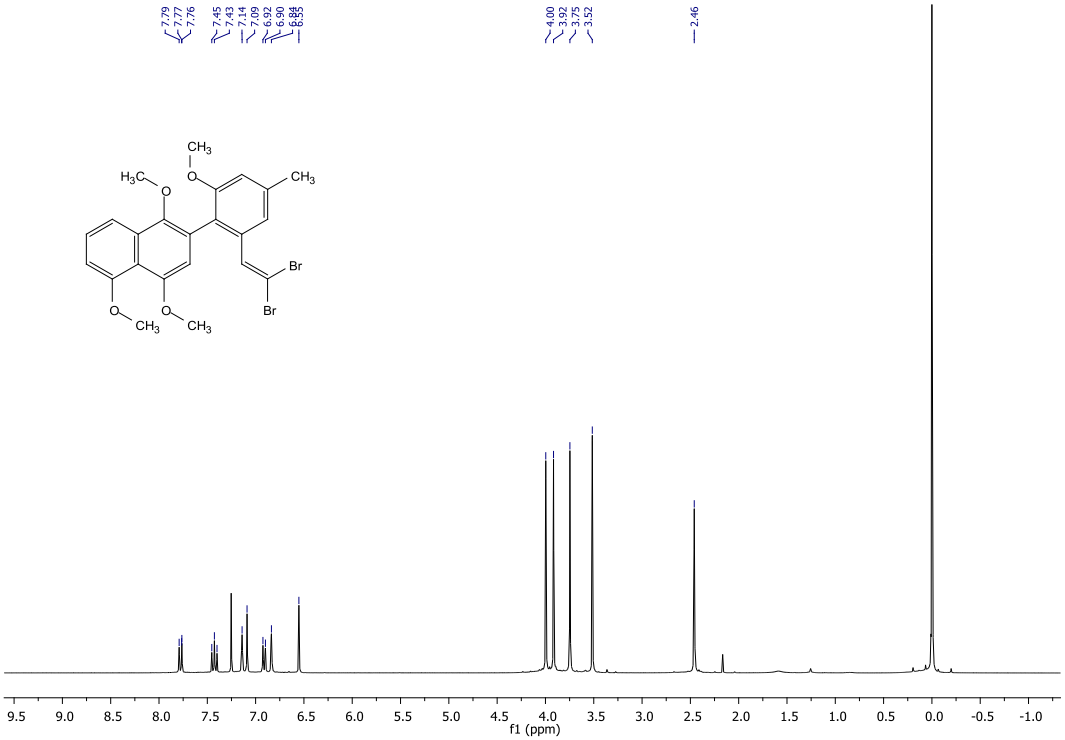


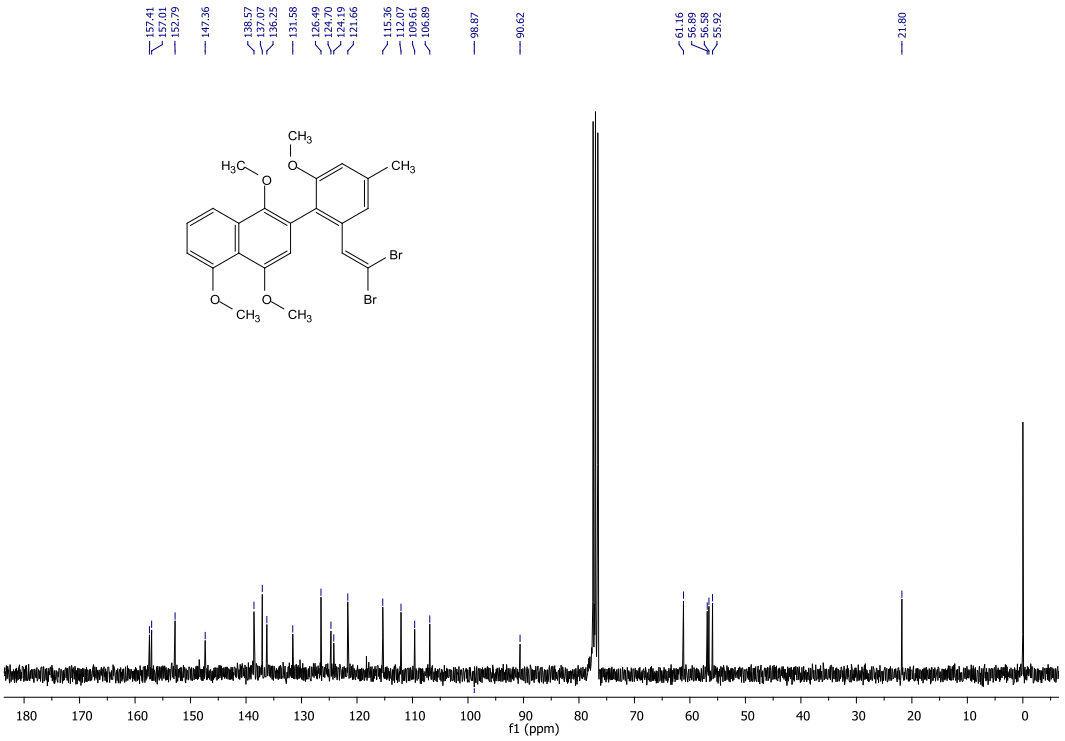
^{1}H and ^{13}C NMR spectra for Compound 116



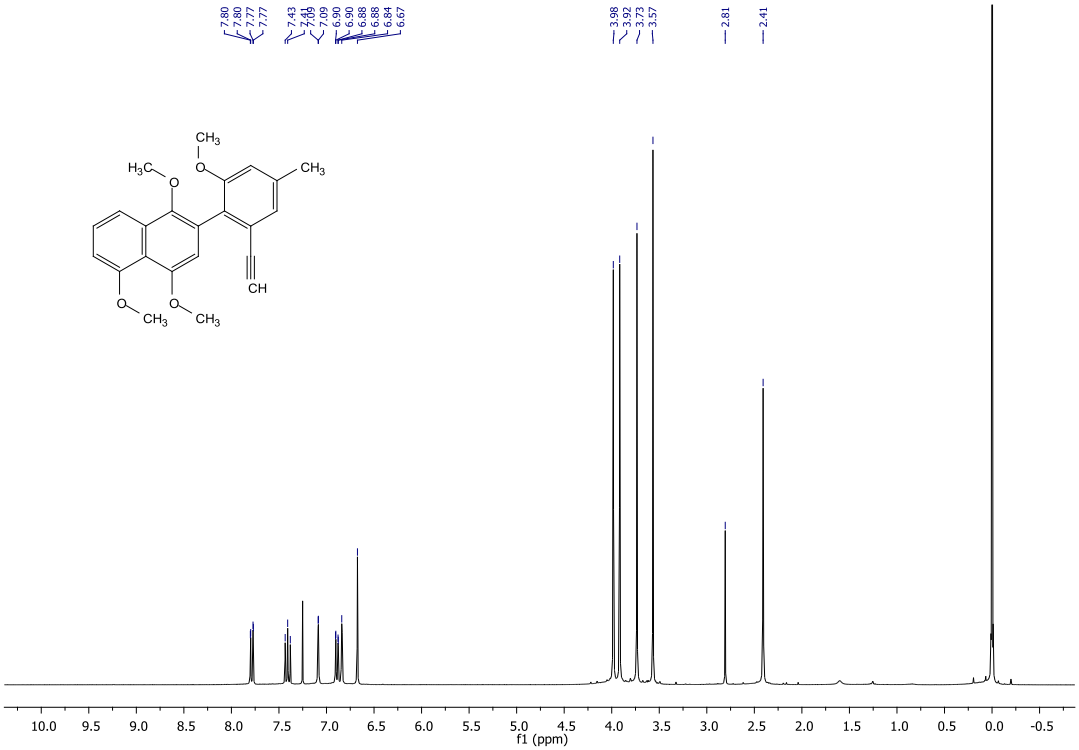


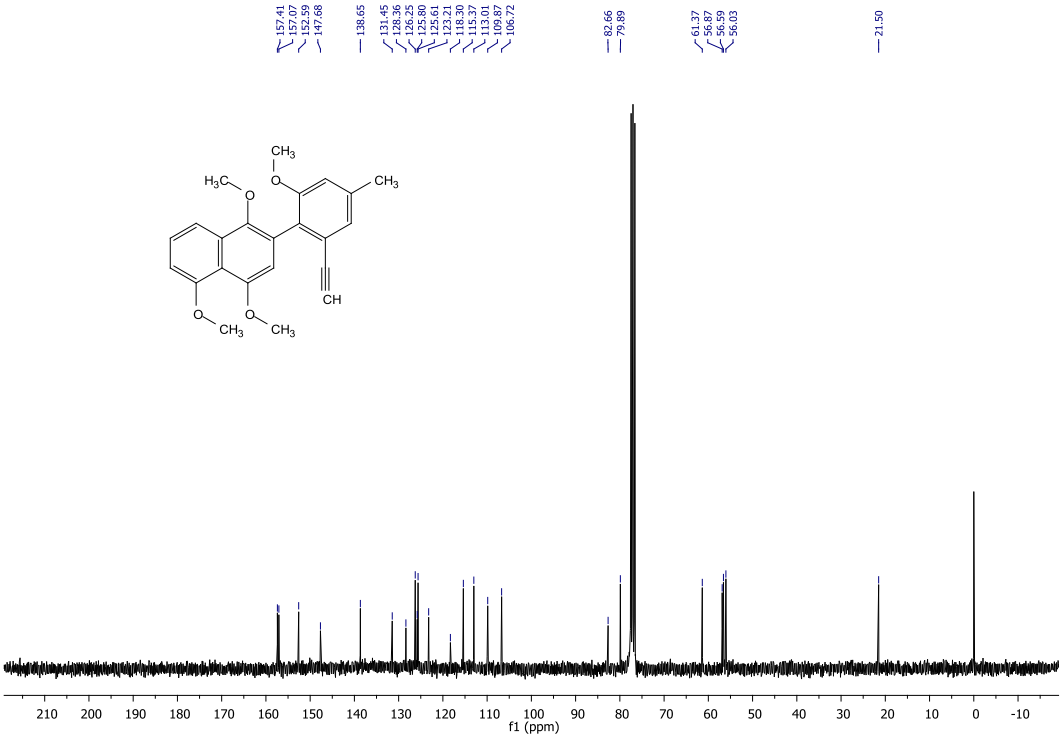
^{1}H and ^{13}C NMR spectra for Compound 117



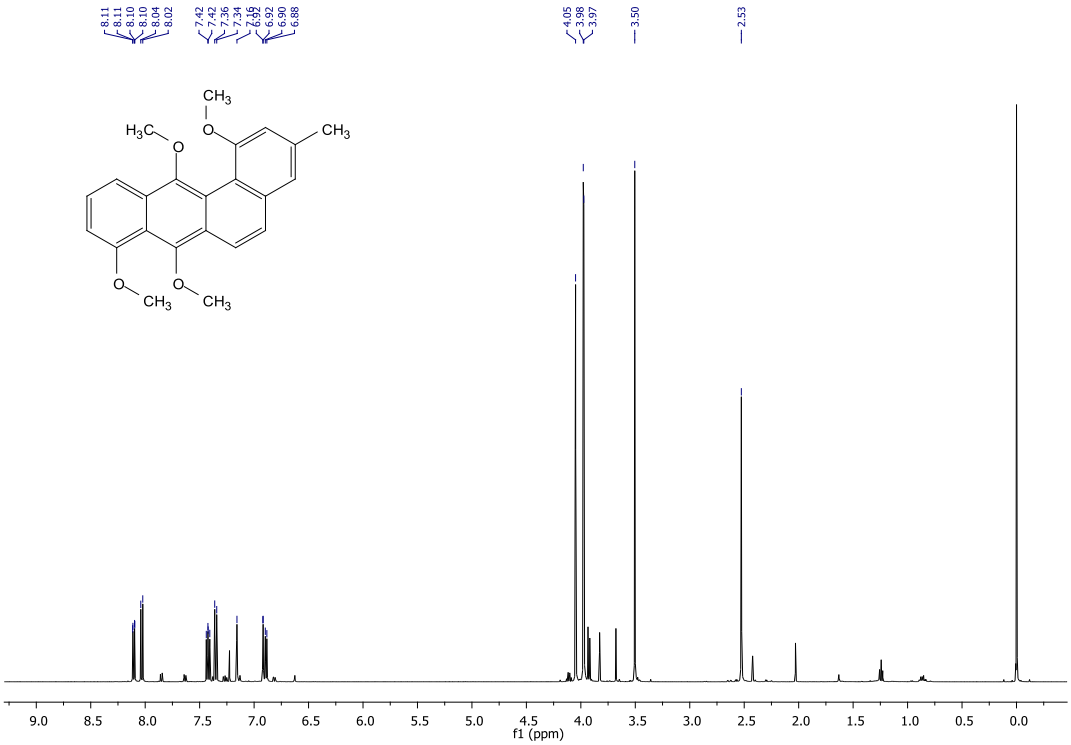


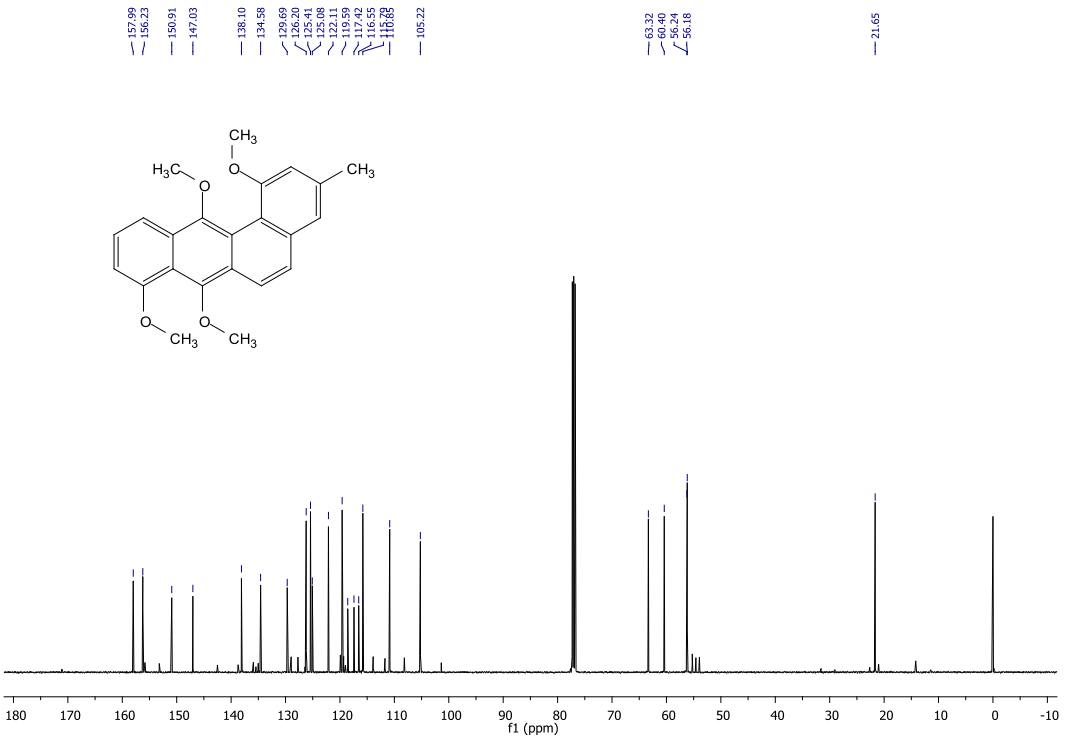
^{1}H and ^{13}C NMR spectra for Compound 118



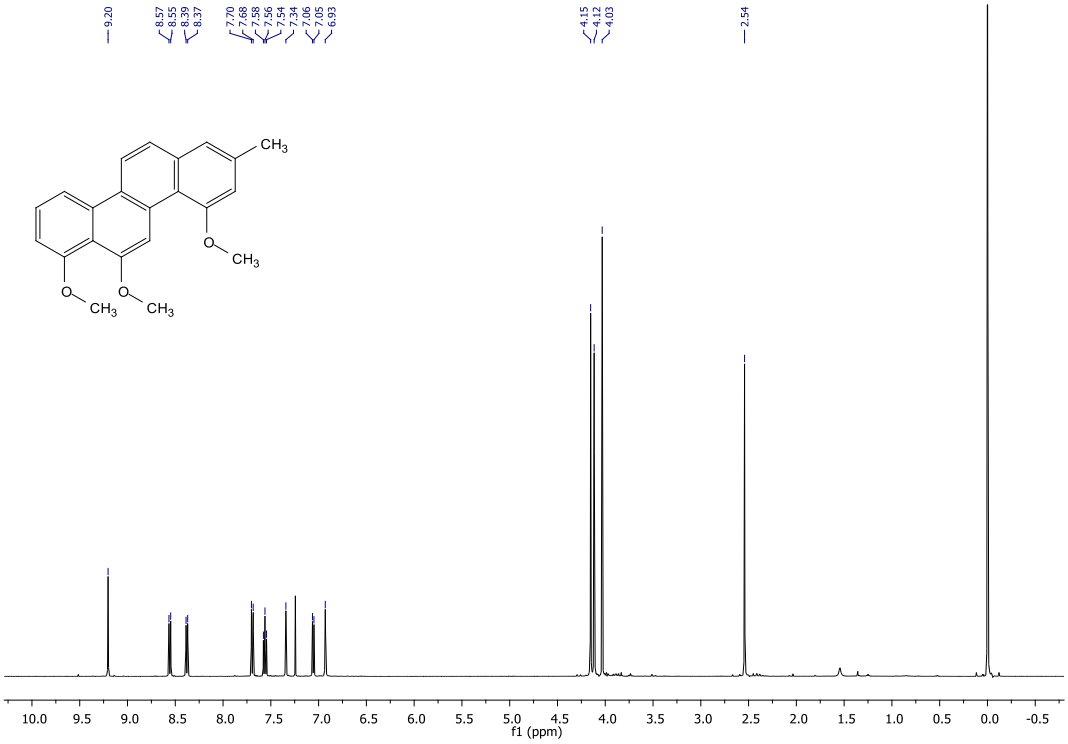


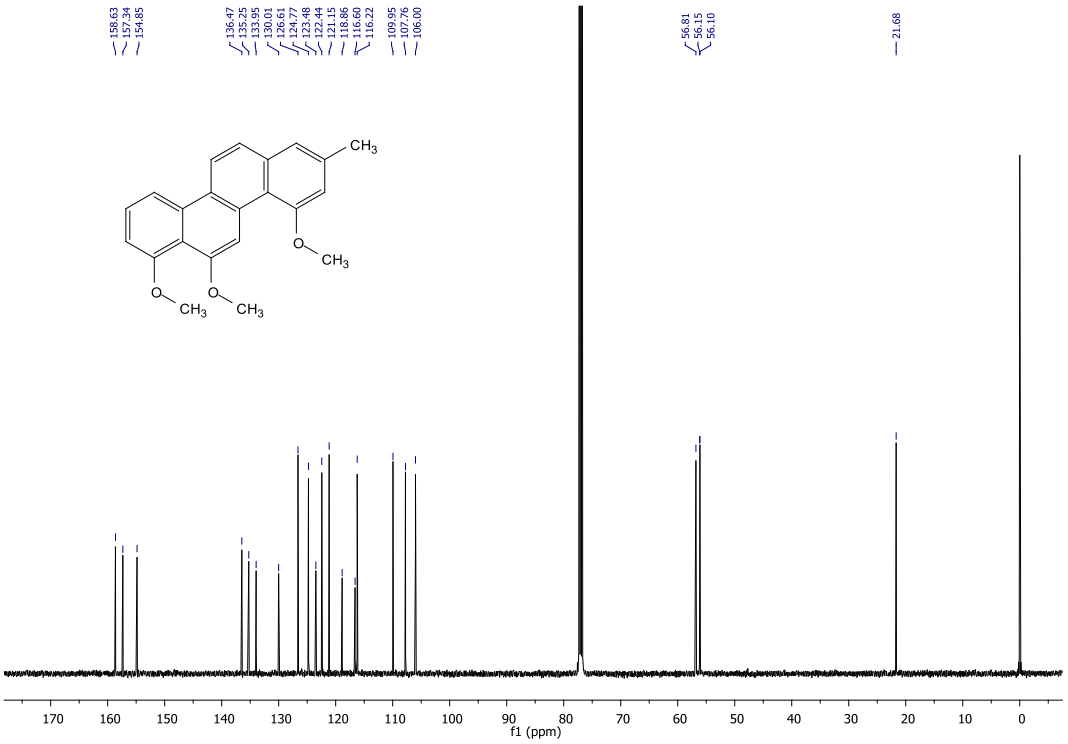
^{1}H and ^{13}C NMR spectra for Compound 119

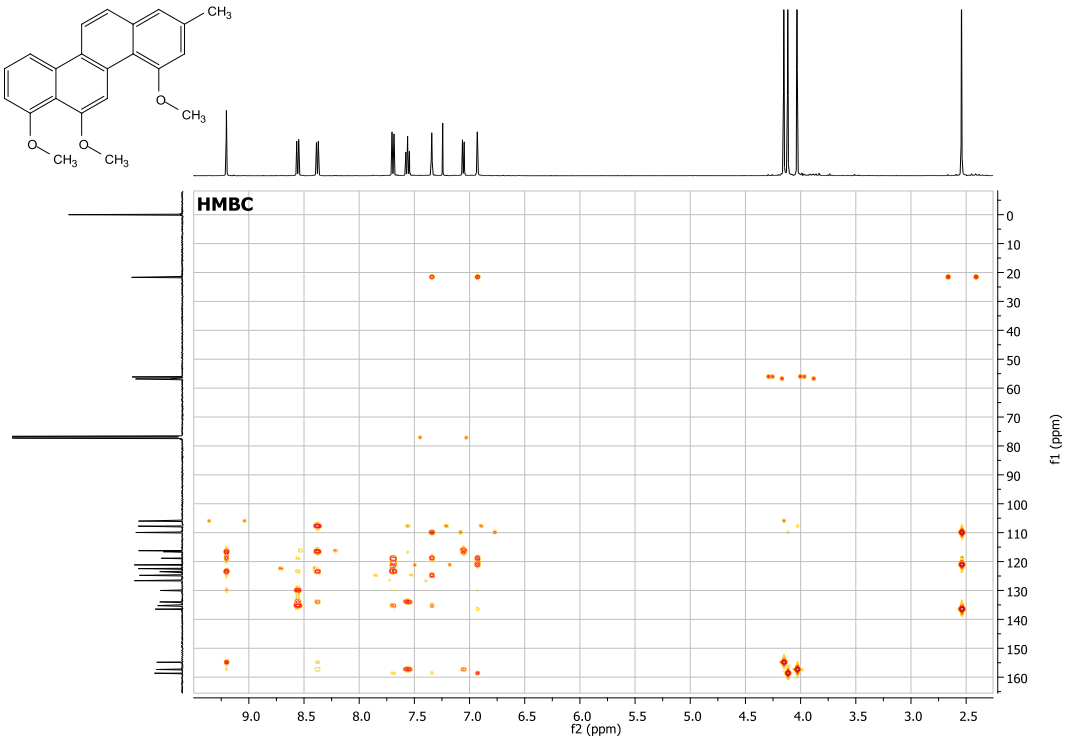


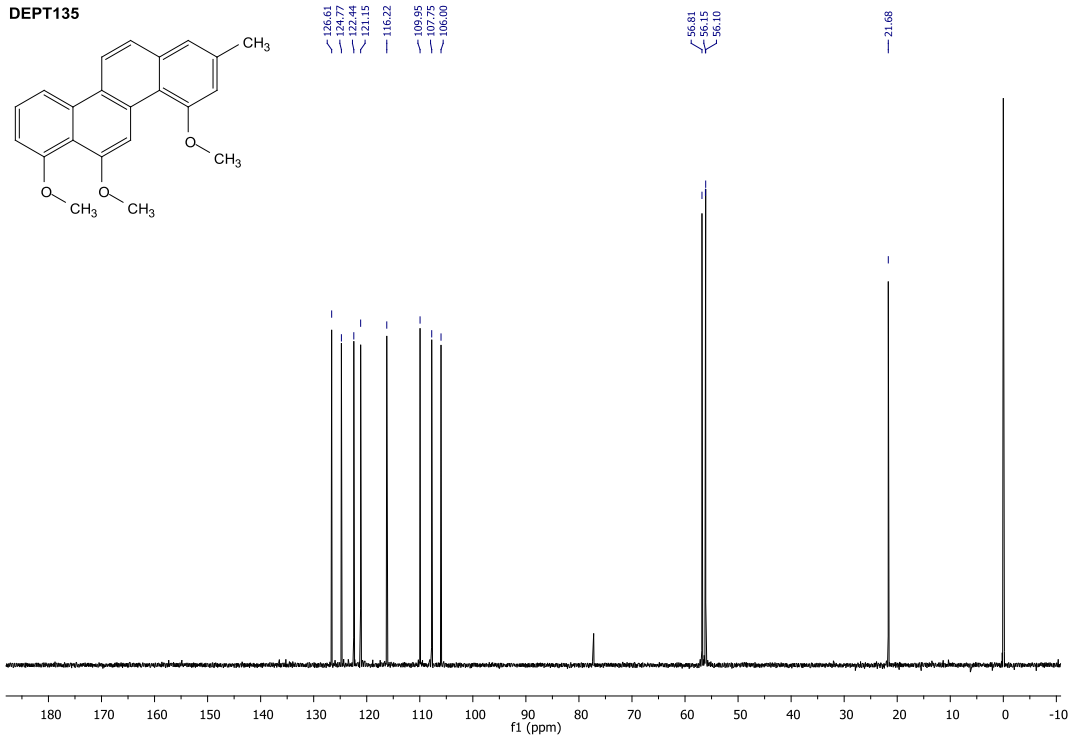


^{1}H , ^{13}C, DEPT 135 and HMBC NMR spectra for Compound 120

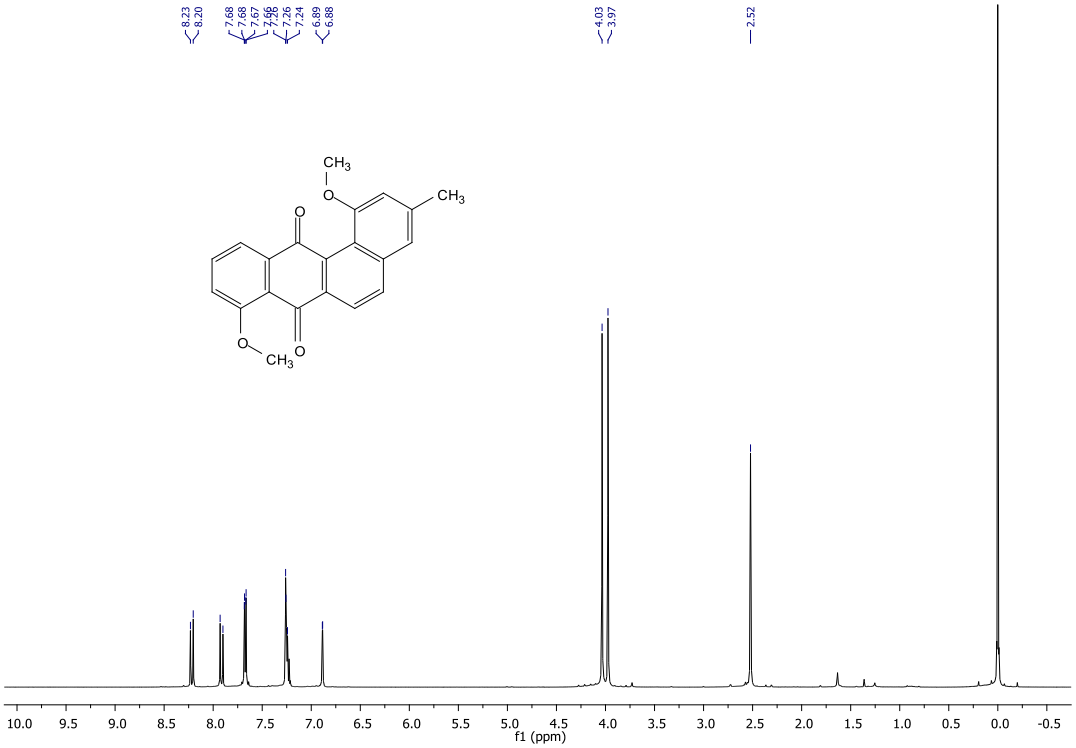


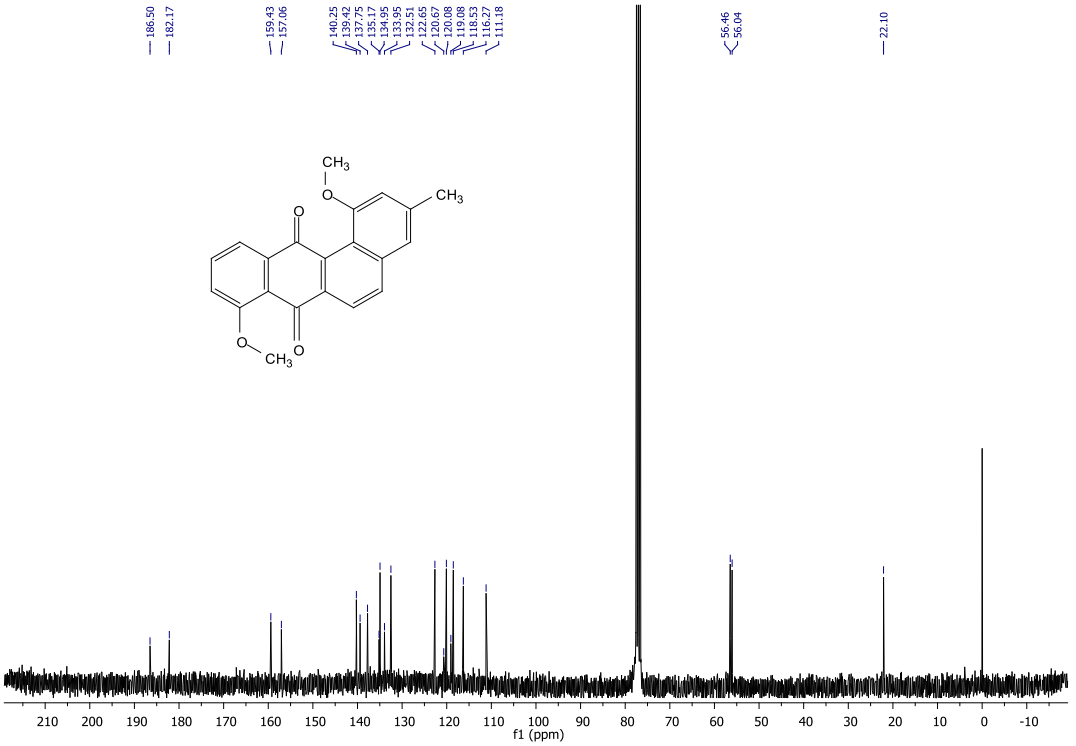



HMBC
f2 (ppm)
f1 (ppm)

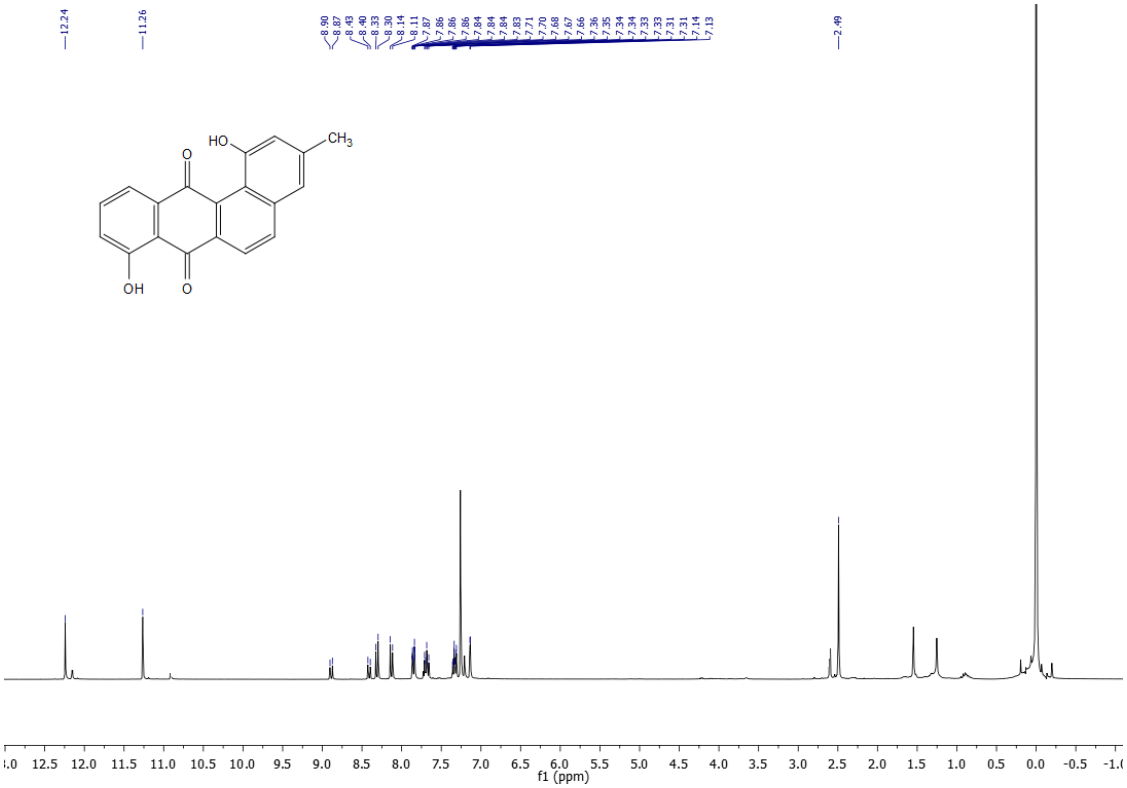

DEPT135
126.61
124.77
122.44
121.15
116.22
109.95
107.75
106.00
56.81
56.15
56.10
21.68
f1 (ppm)

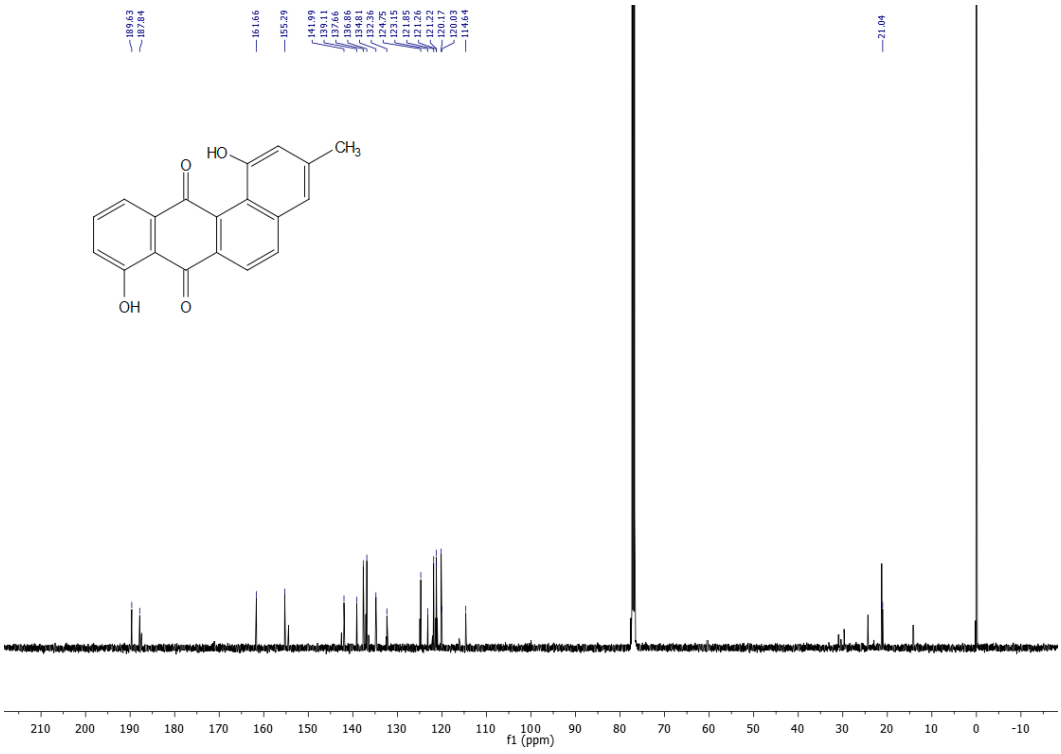
^{1}H and ^{13}C NMR spectra for Compound 38



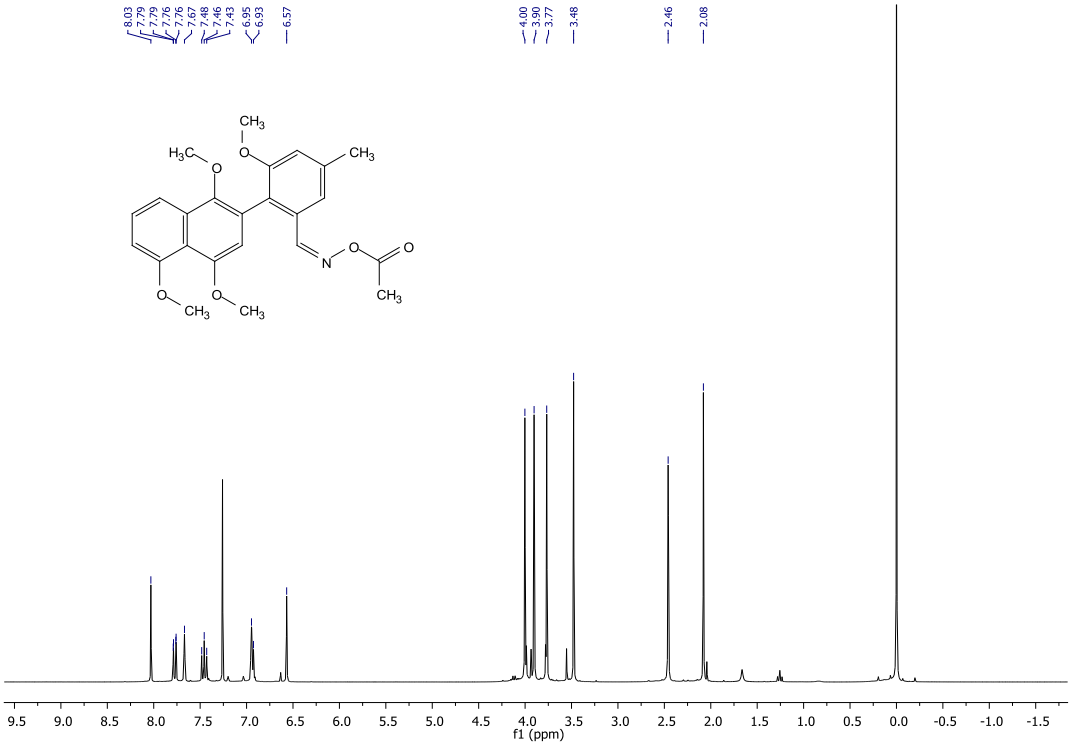


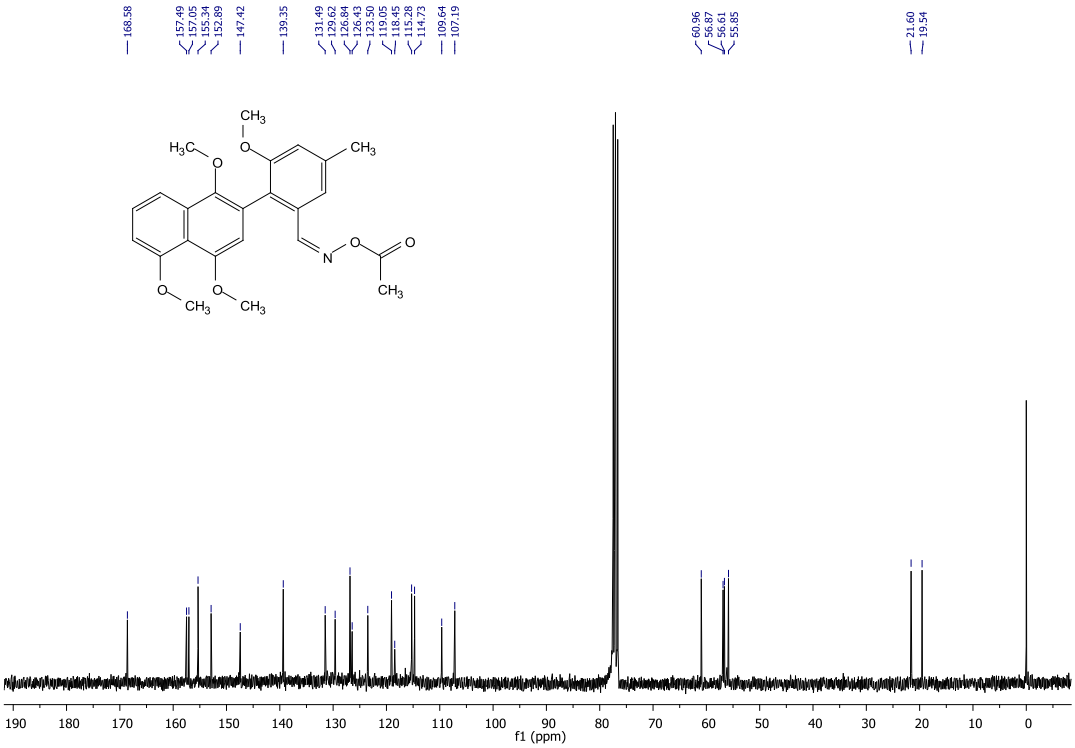
^{1}H and ^{13}C NMR spectra for Compound 2



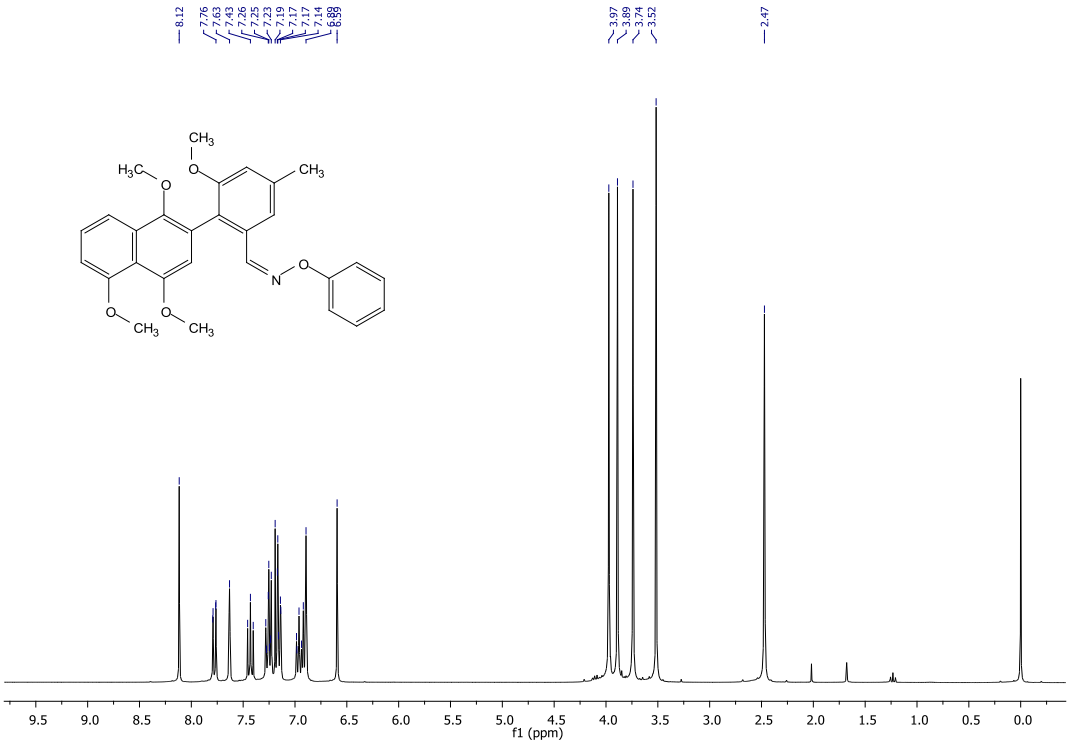


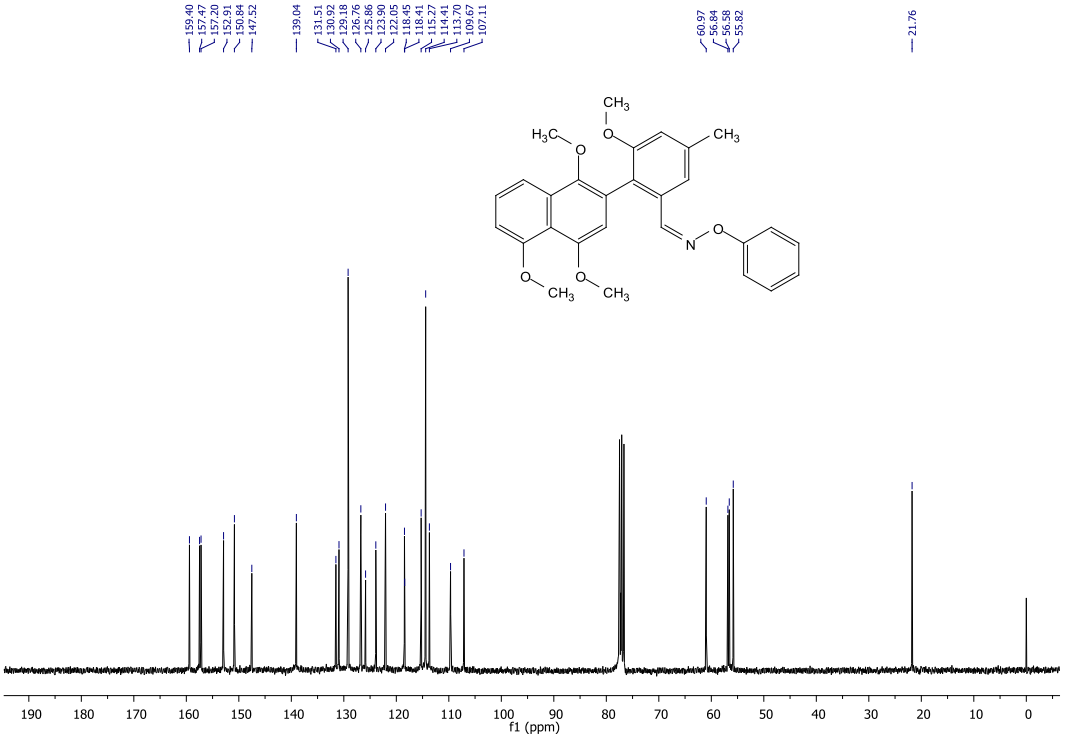
^{1}H and ^{13}C NMR spectra for Compound 222



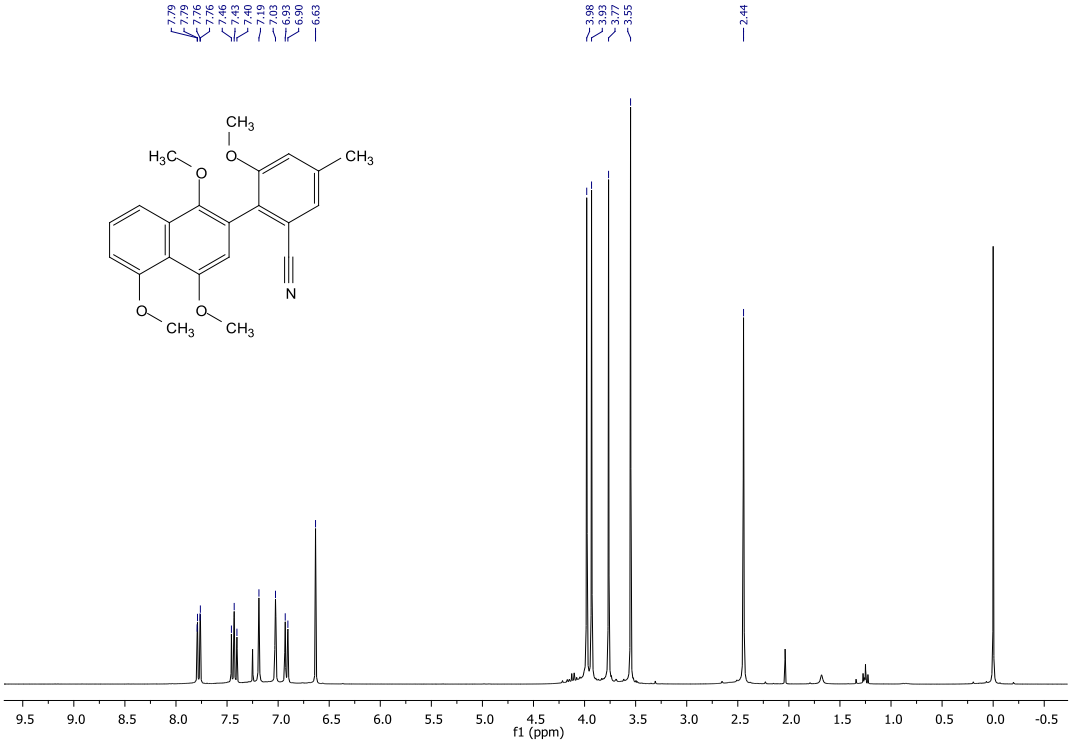


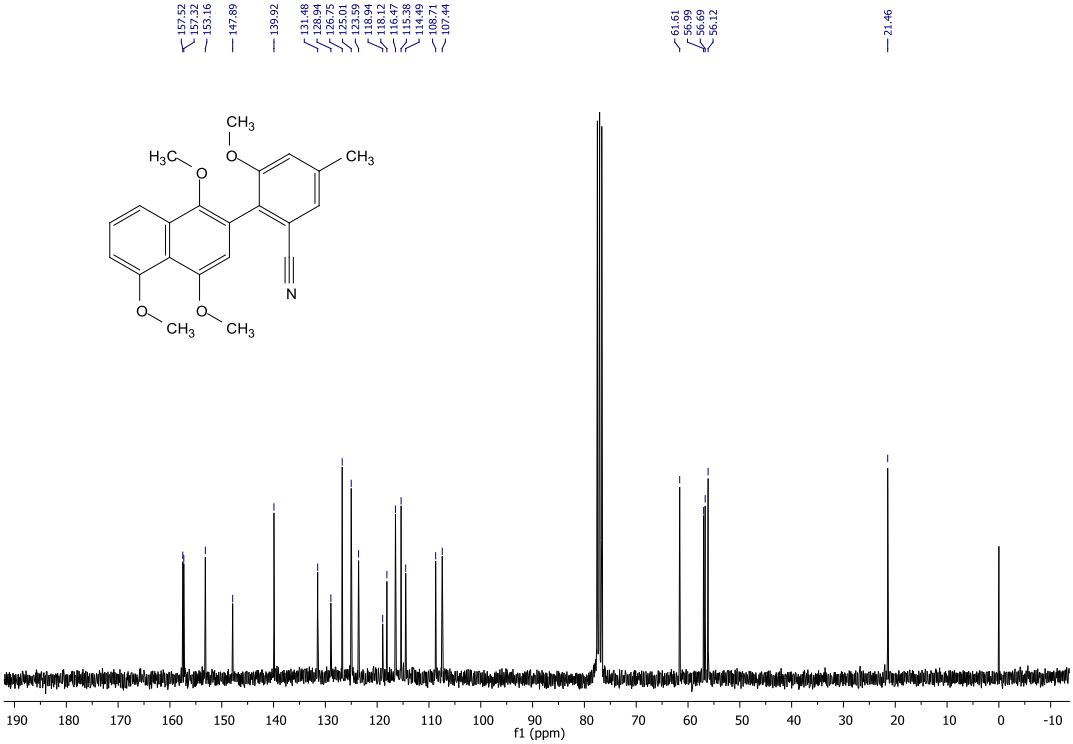
^{1}H and ^{13}C NMR spectra for Compound 230



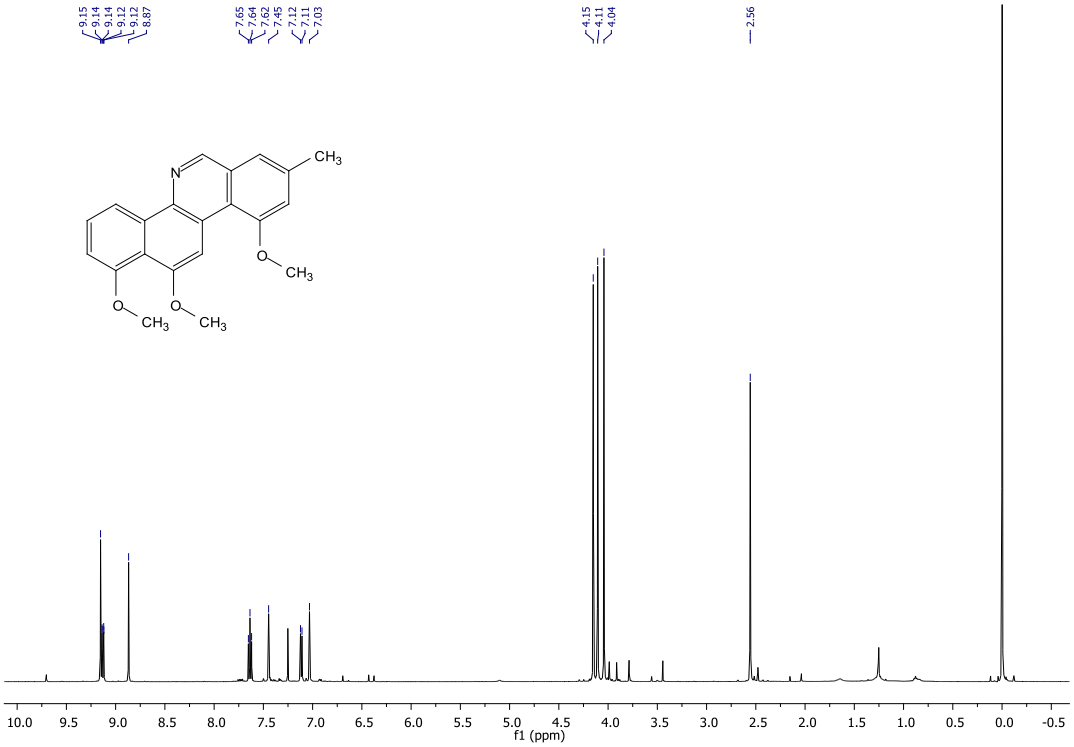


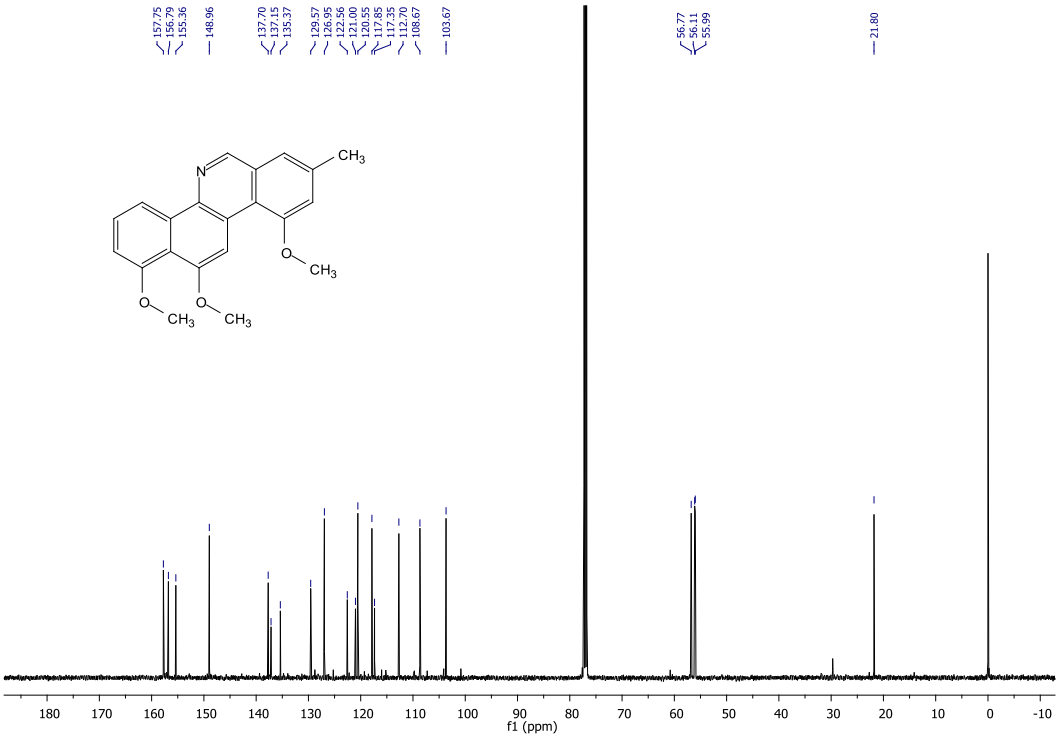
^{1}H and ^{13}C NMR spectra for Compound 224

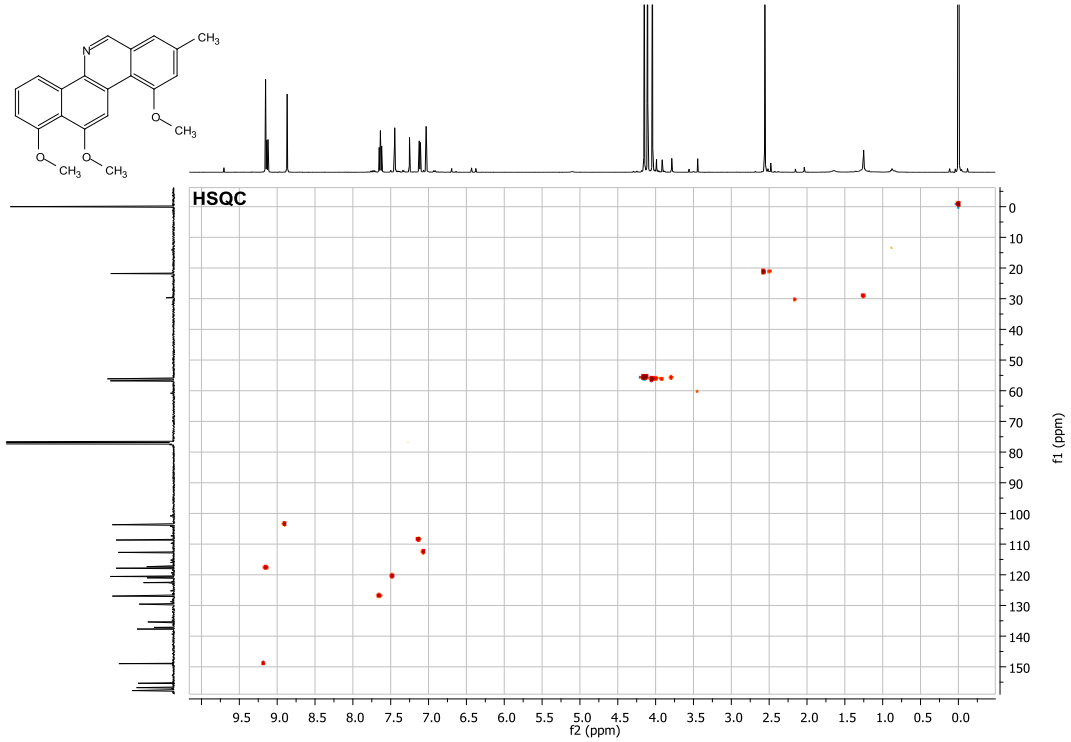


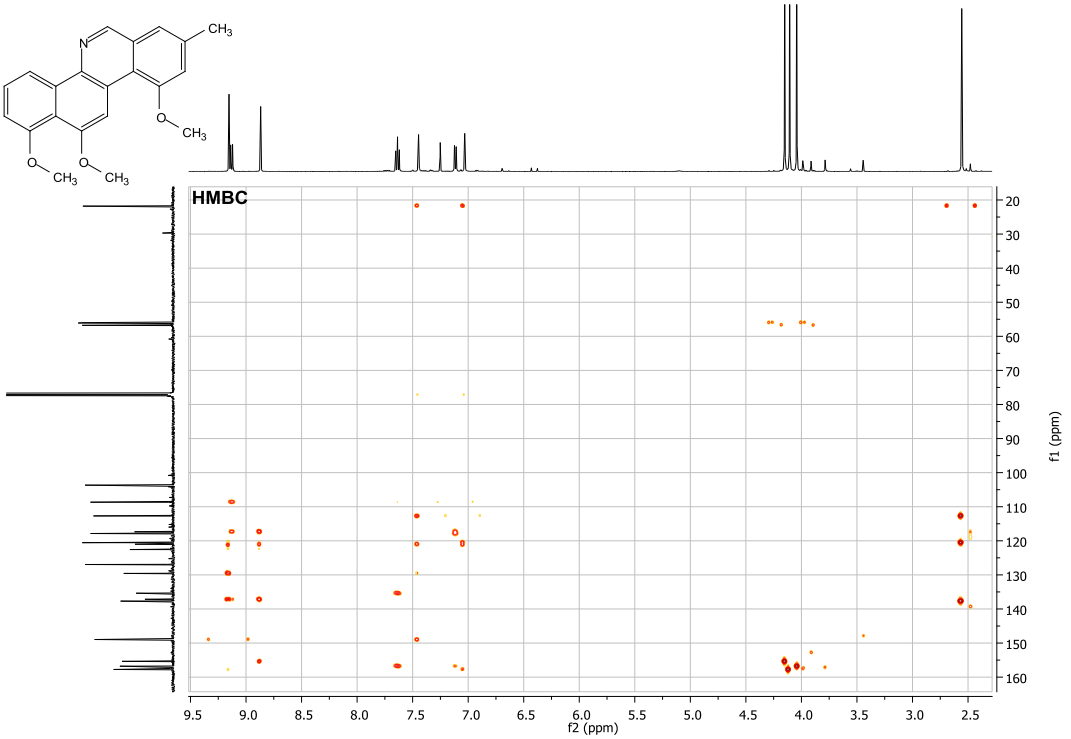


^{1}H, ^{13}C, HMBC and HMQC NMR spectra for Compound 231

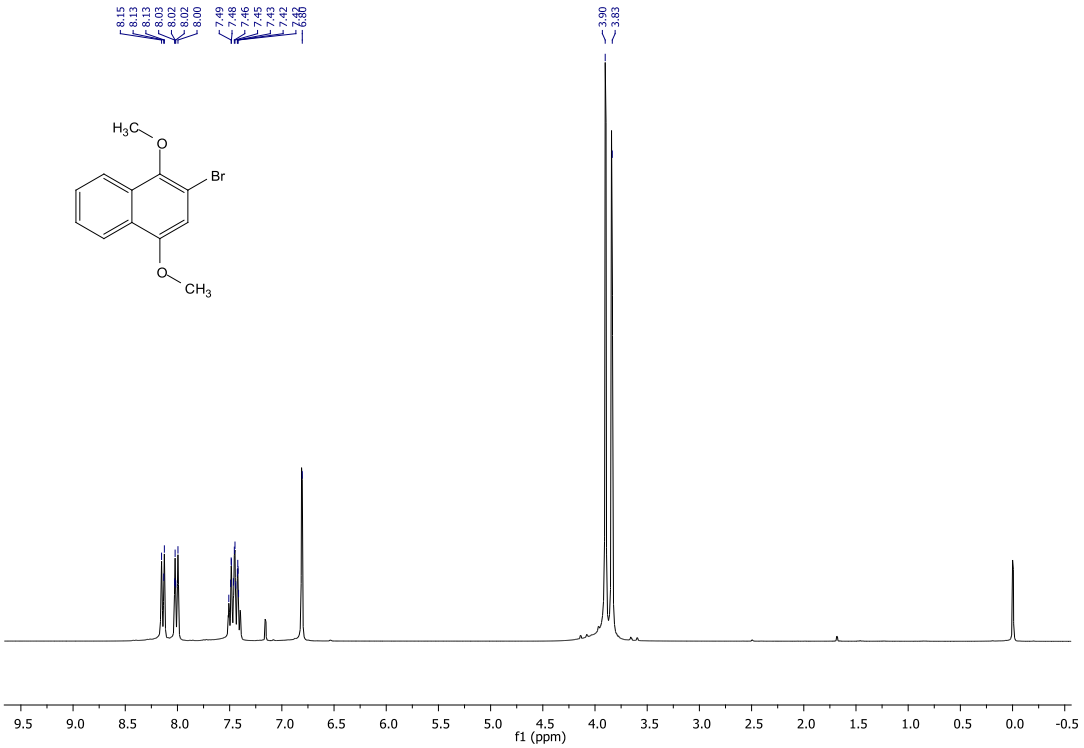


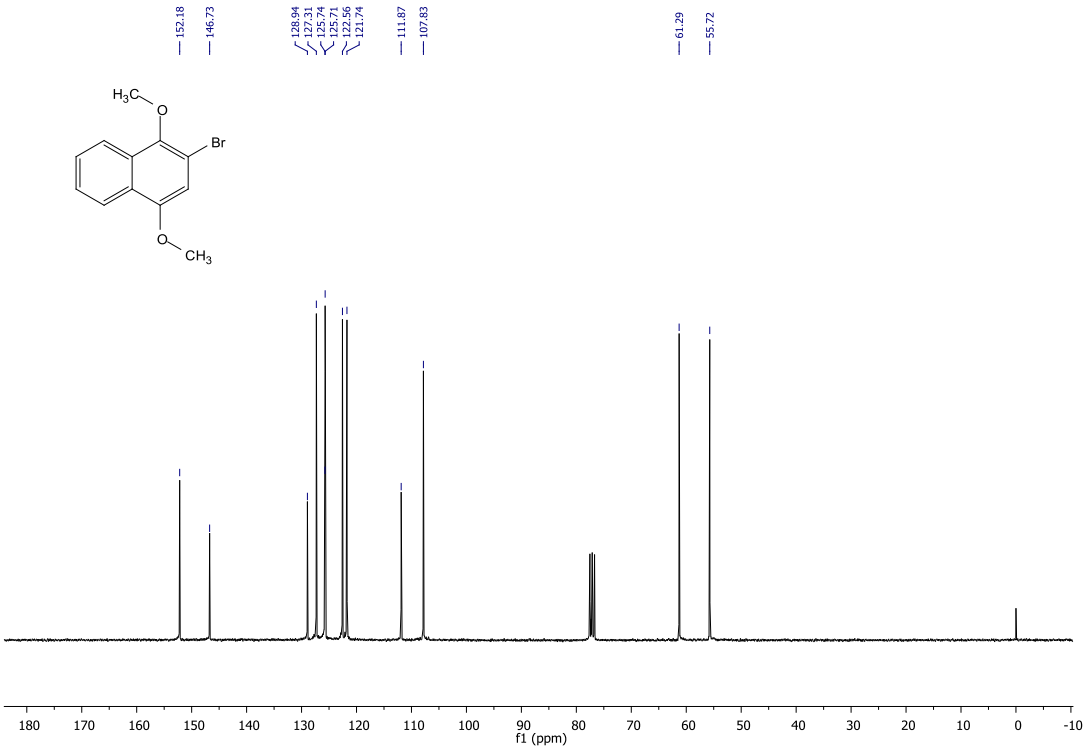



HSQC
f2 (ppm)
f1 (ppm)

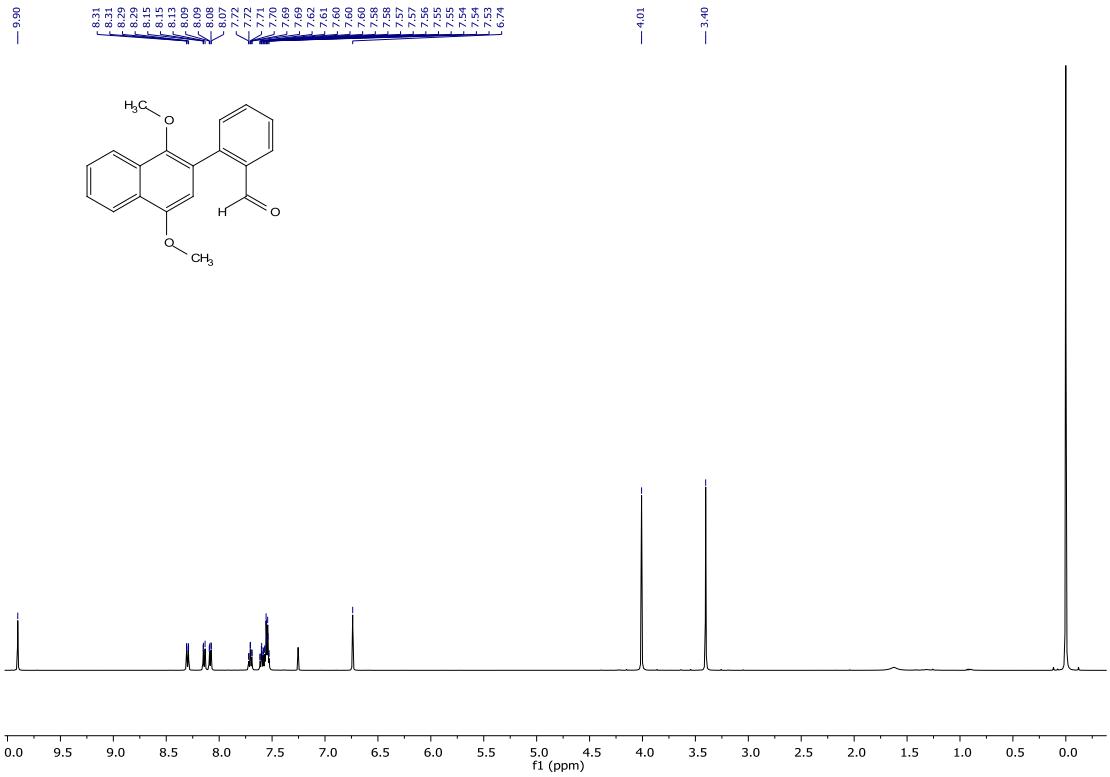

HMBC
f2 (ppm)
f1 (ppm)

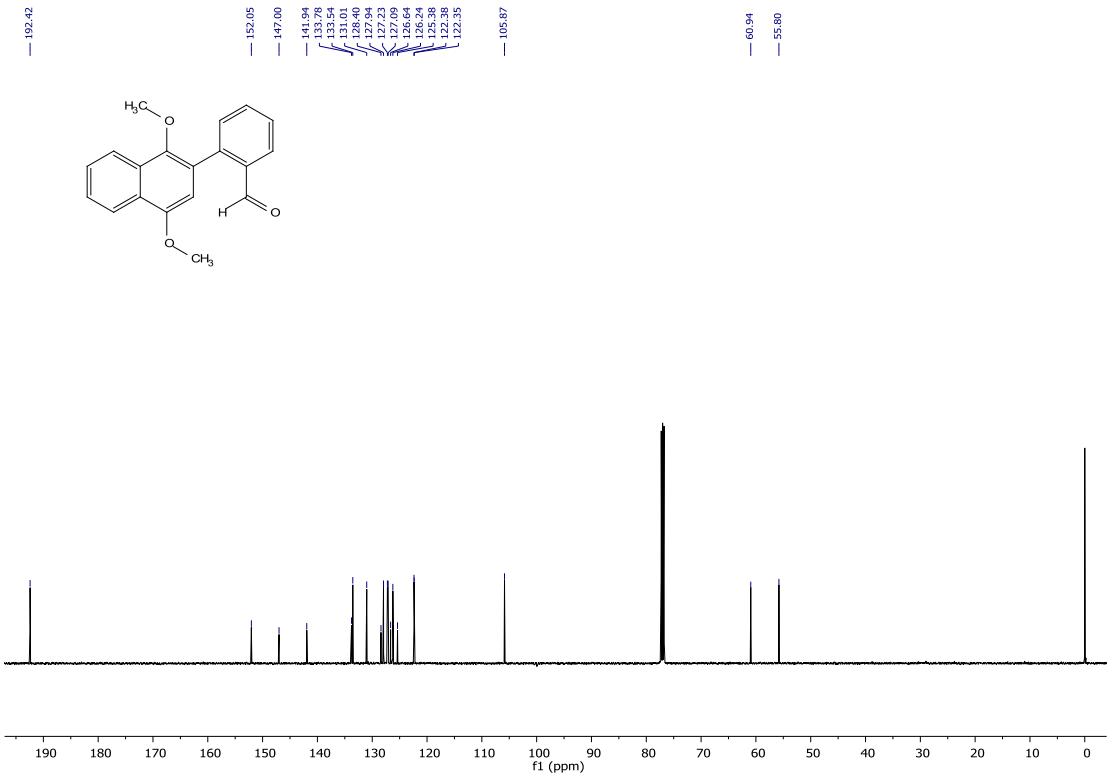
^{1}H and ^{13}C NMR spectra for Compound 307



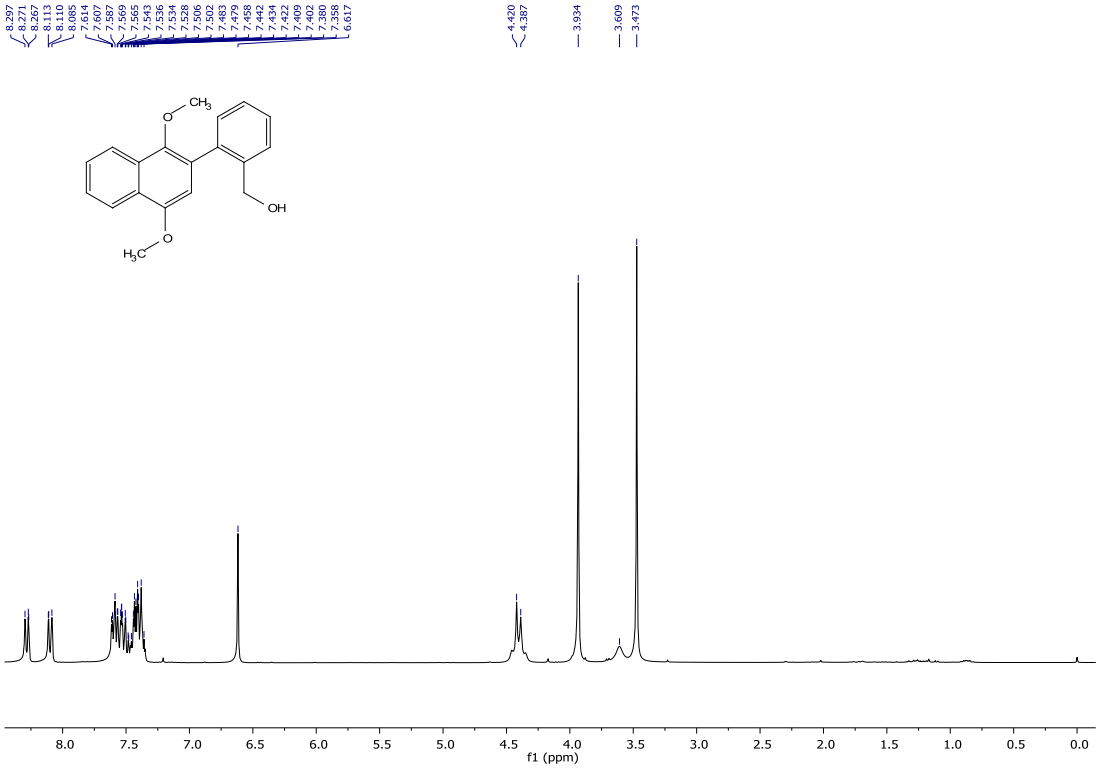


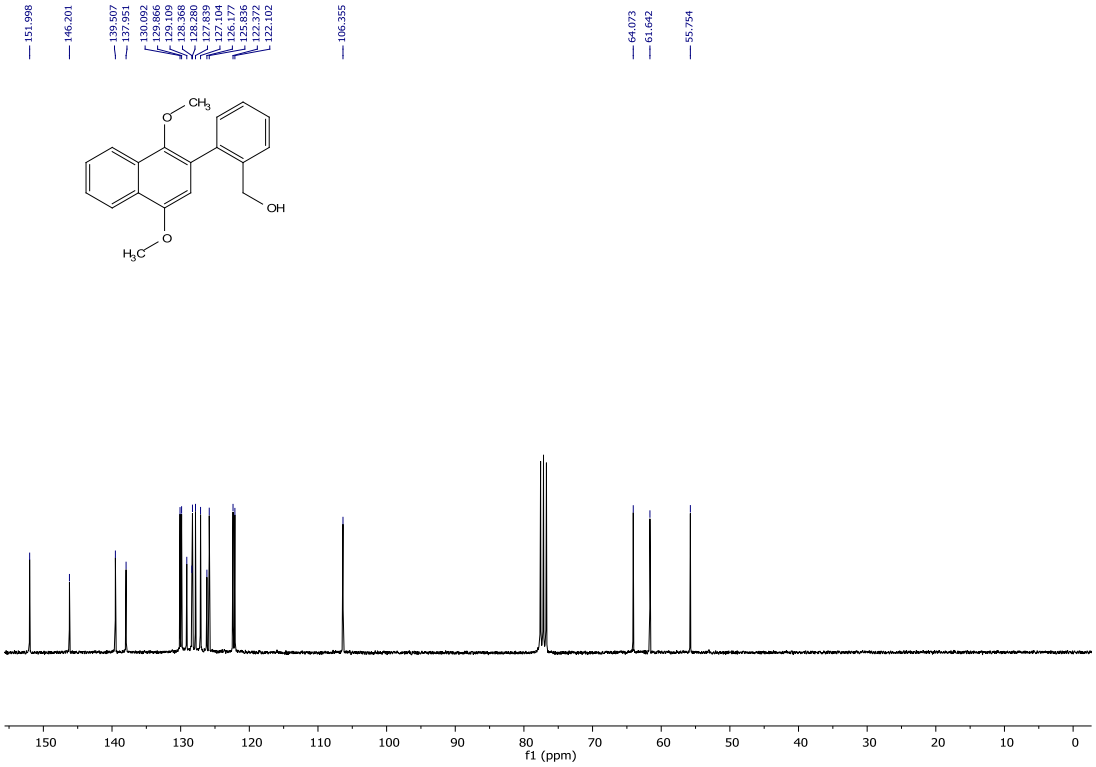
^{1}H and ^{13}C NMR spectra for Compound 309



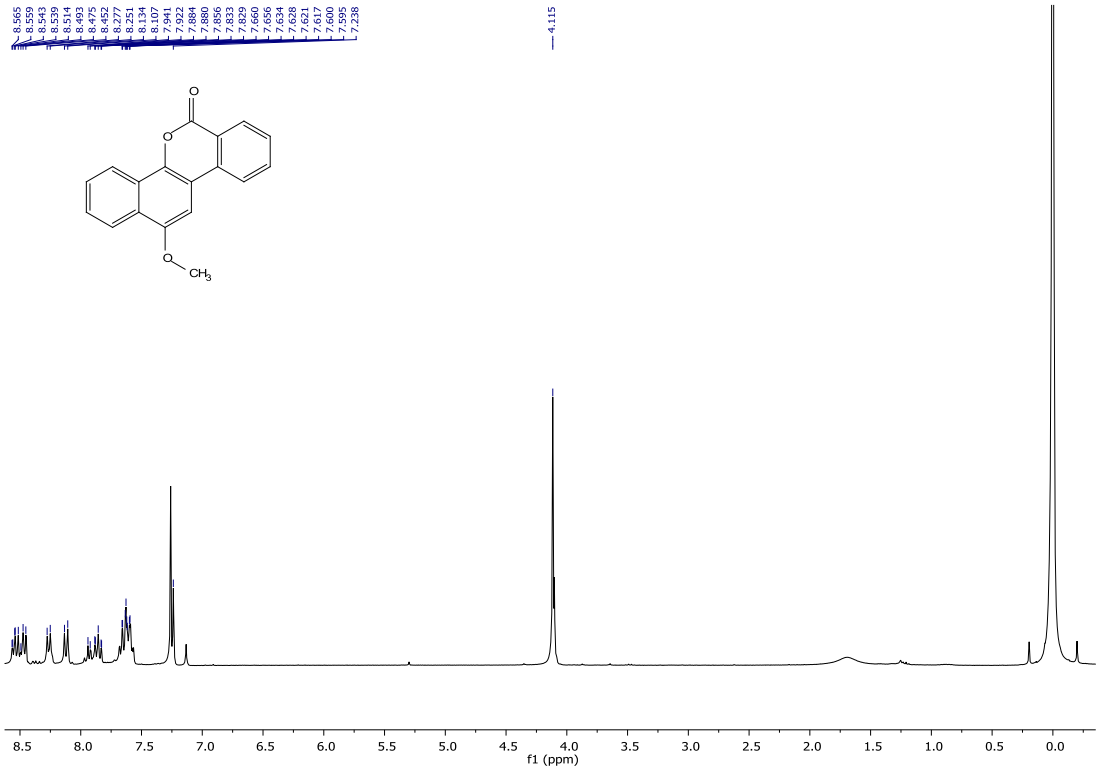


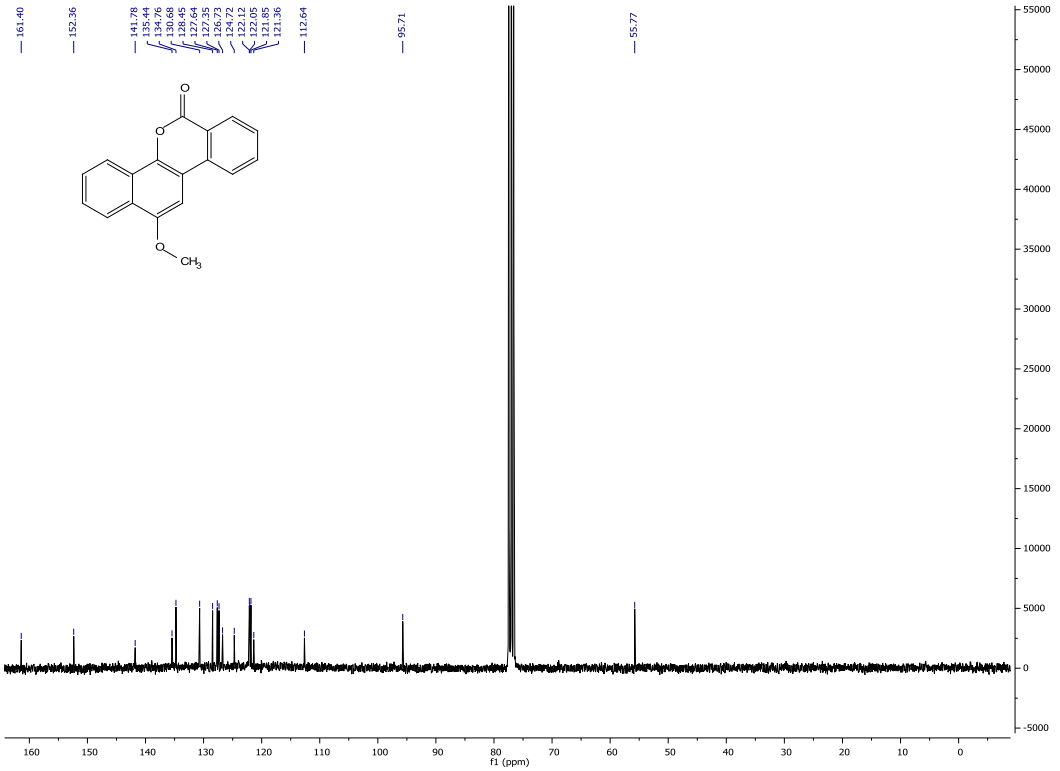
^{1}H and ^{13}C NMR spectra for Compound 235



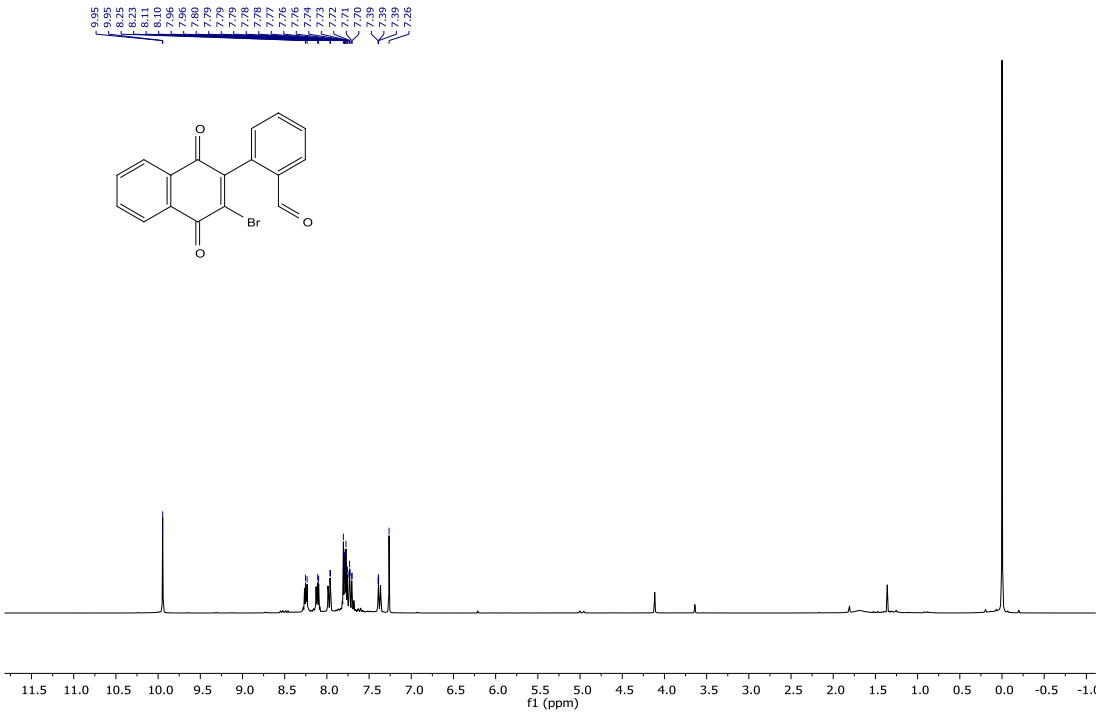


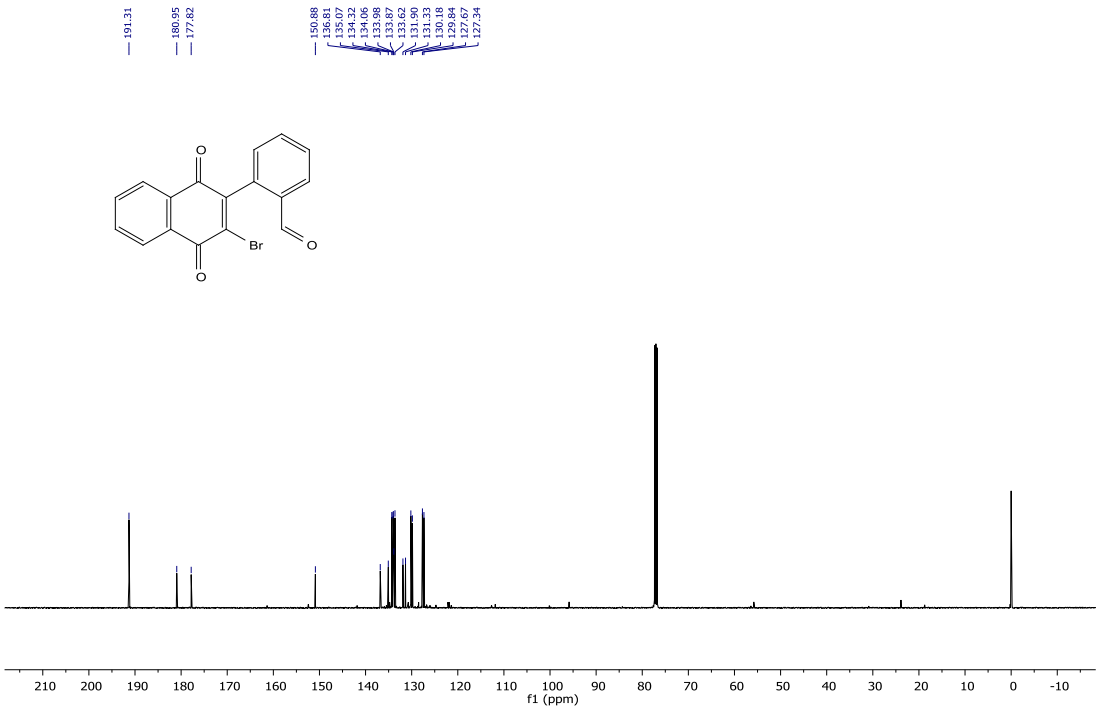
^{1}H and ^{13}C NMR spectra for Compound 238



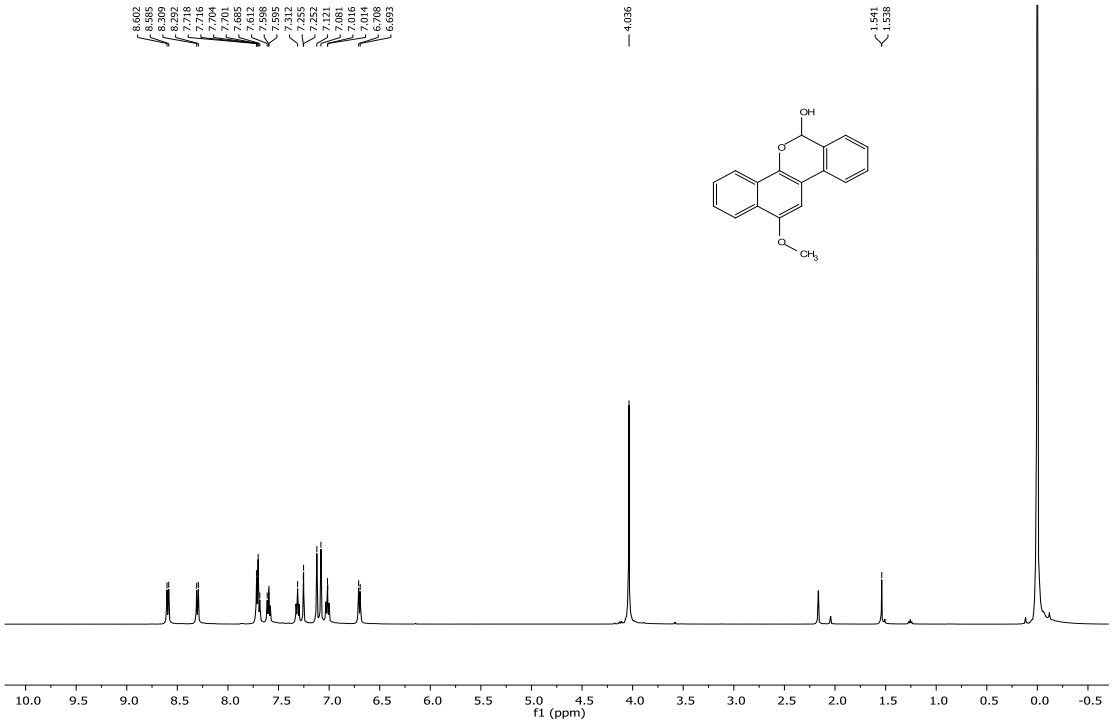


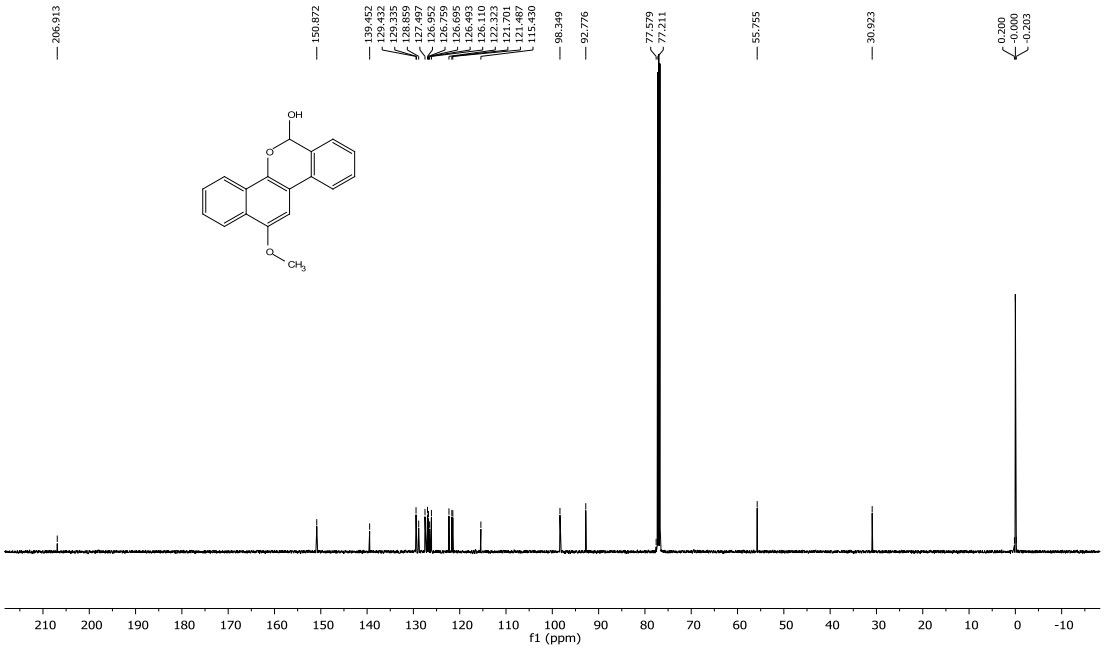
^{1}H and ^{13}C NMR spectra for Compound 231



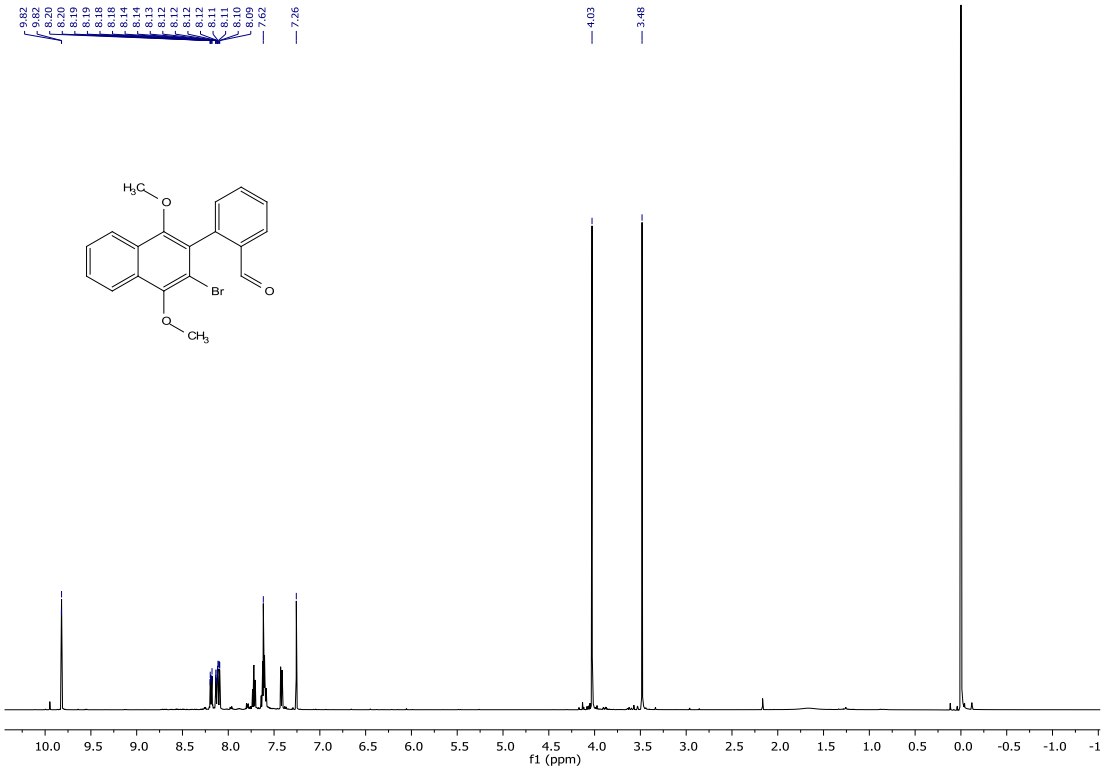


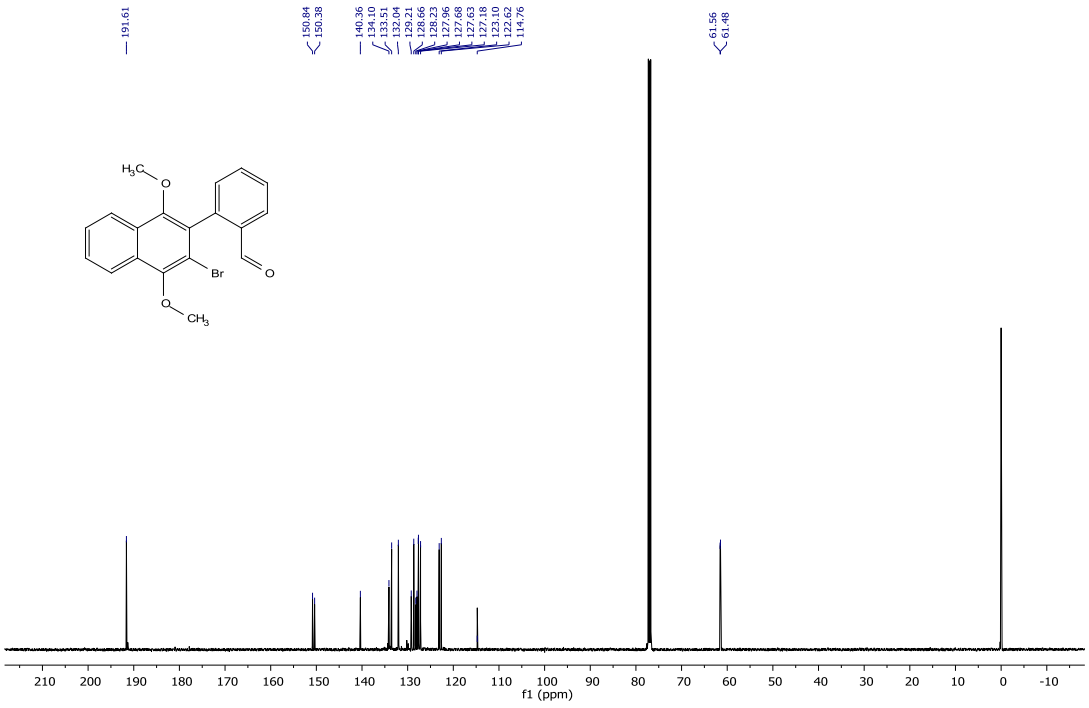
^{1}H and ^{13}C NMR spectra for Compound 310



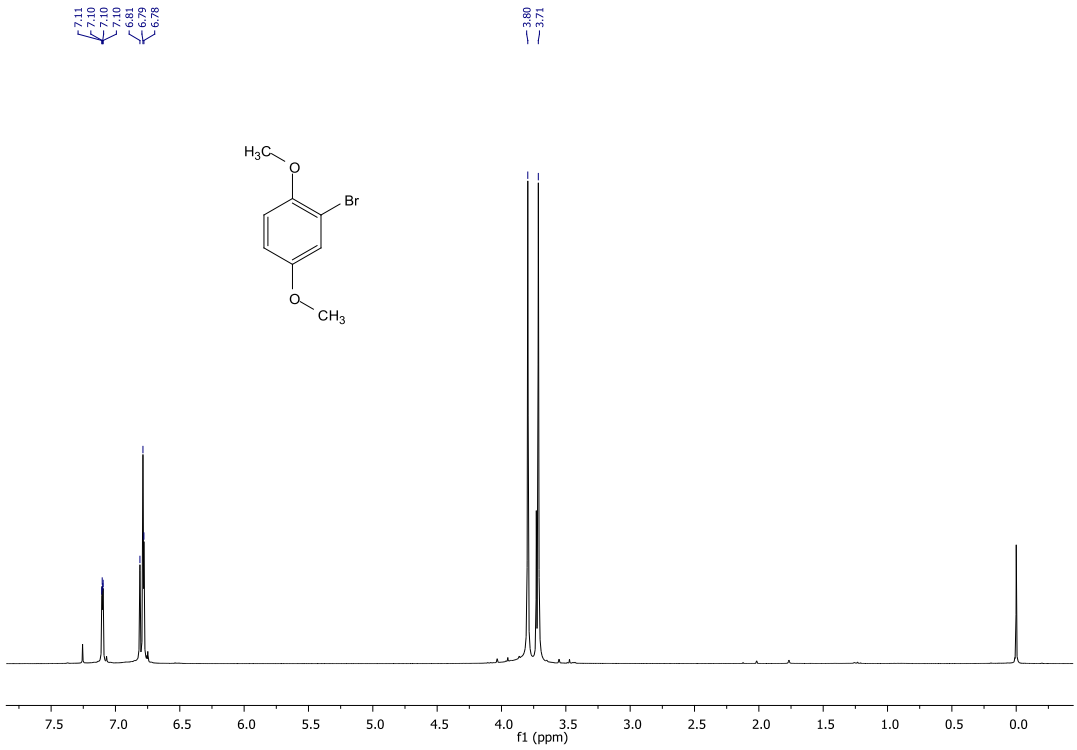


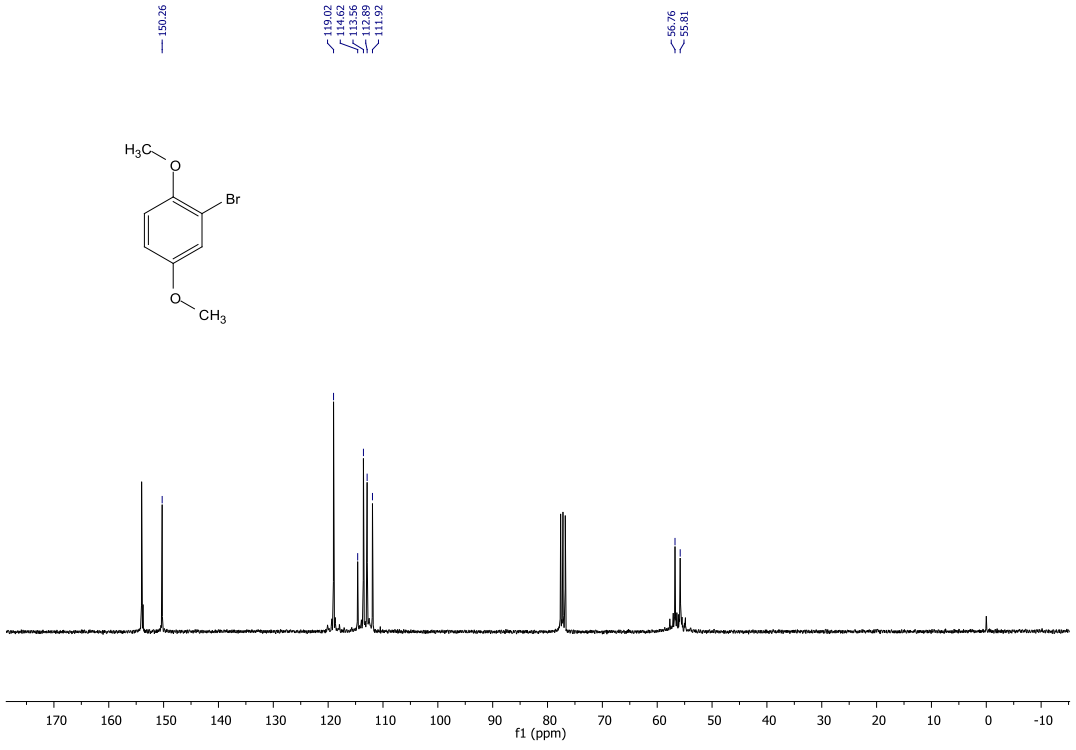
^{1}H and ^{13}C NMR spectra for Compound 314



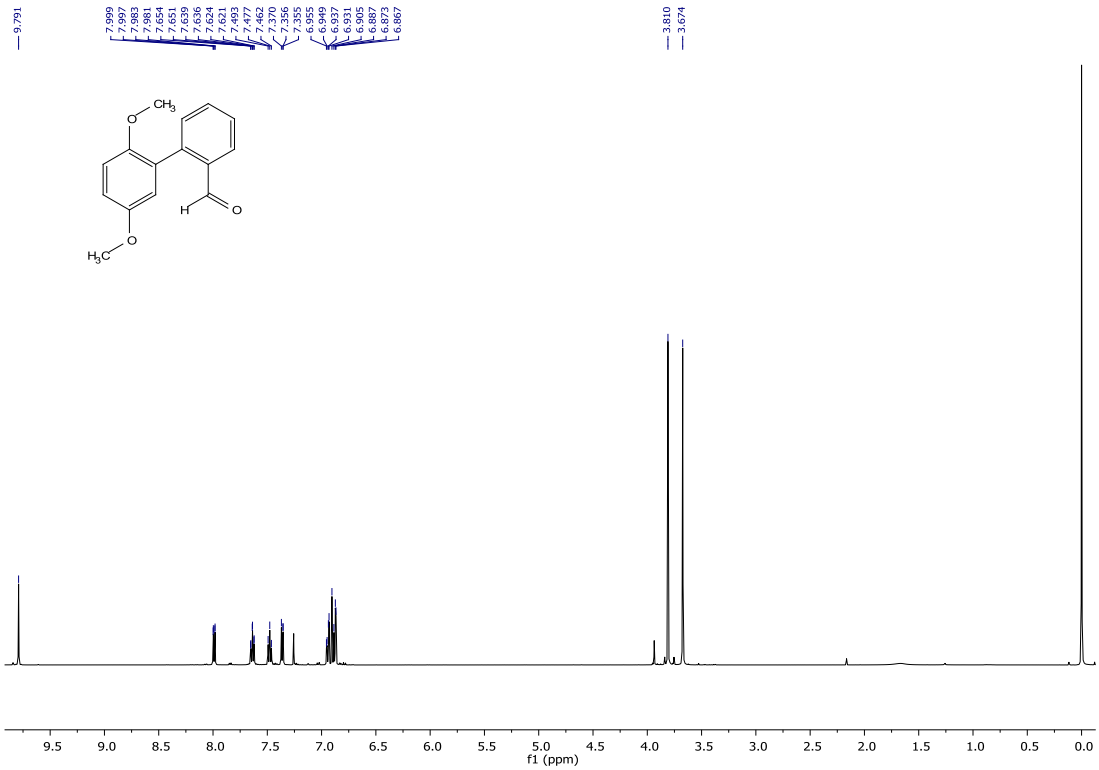


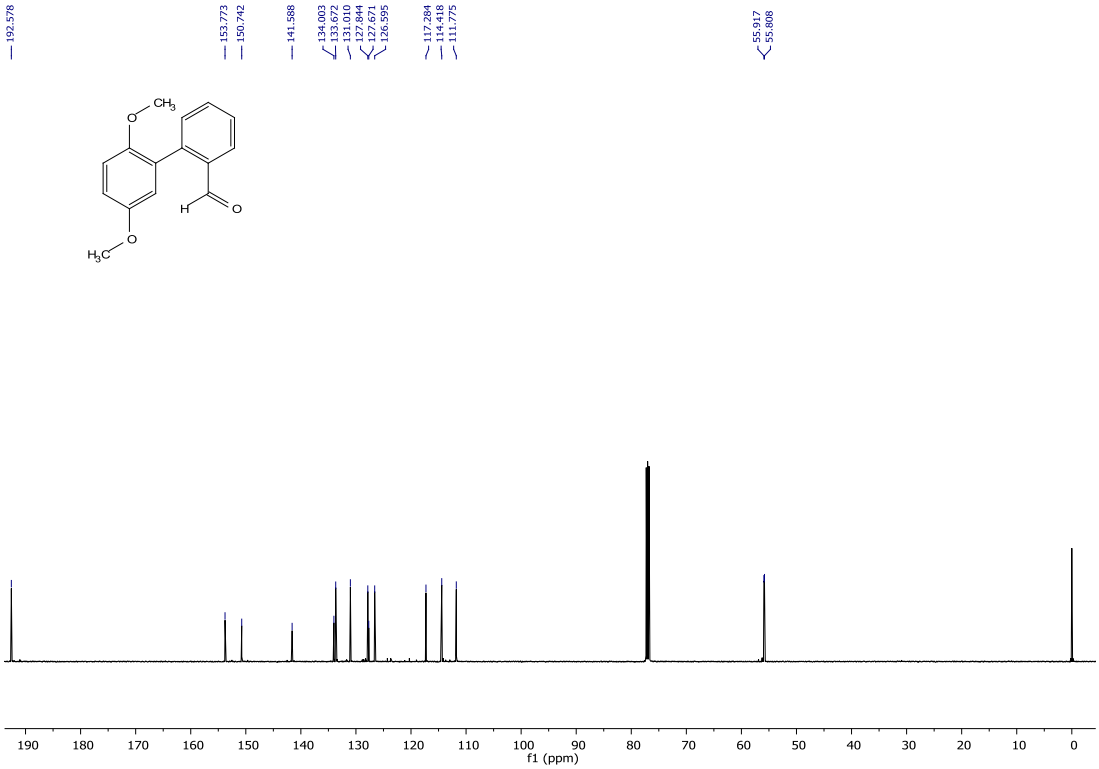
^{1}H and ^{13}C NMR spectra for Compound 319



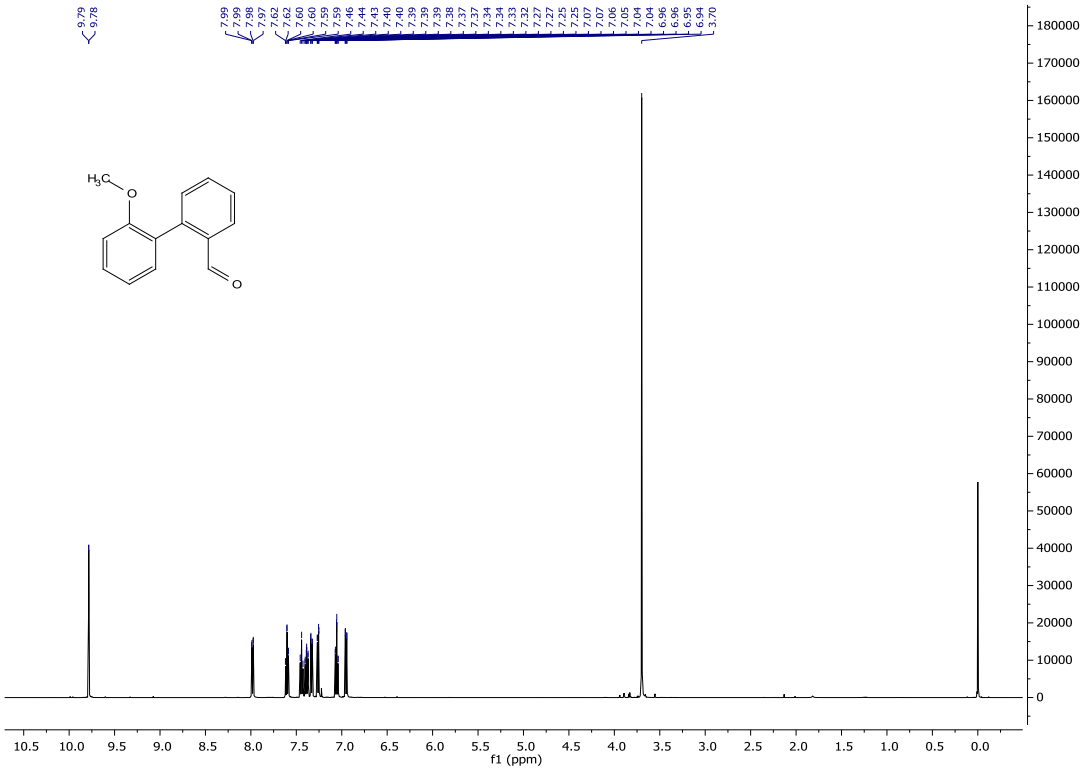


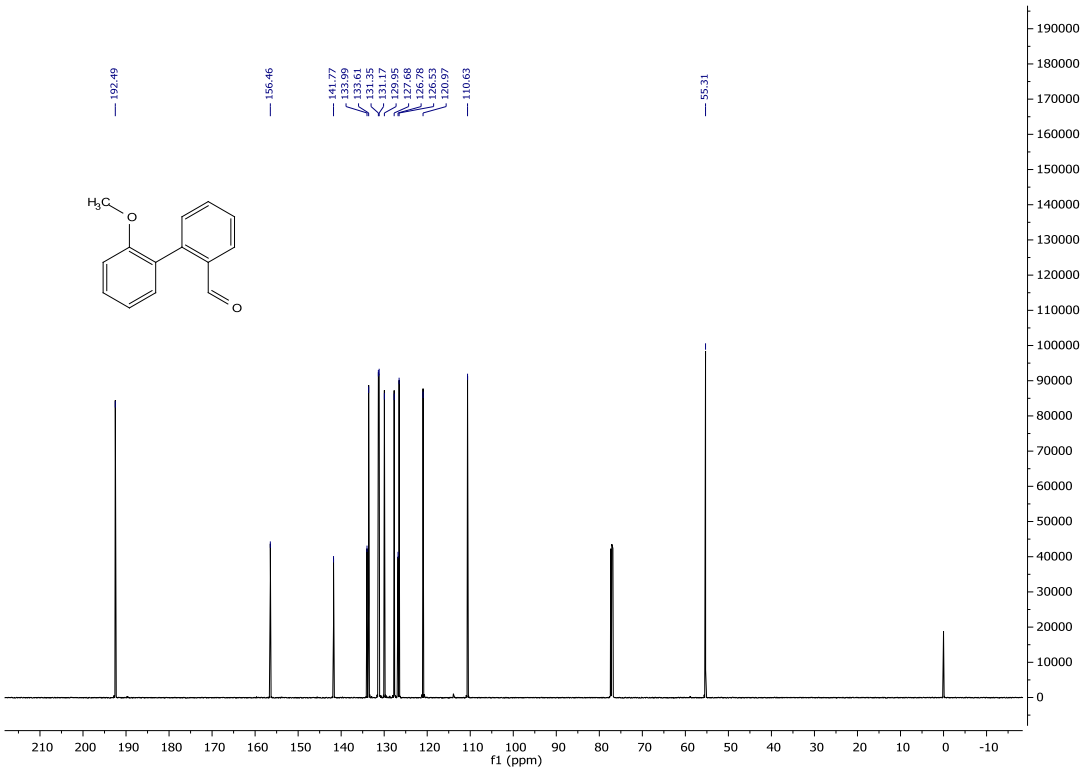
^{1}H and ^{13}C NMR spectra for Compound 320



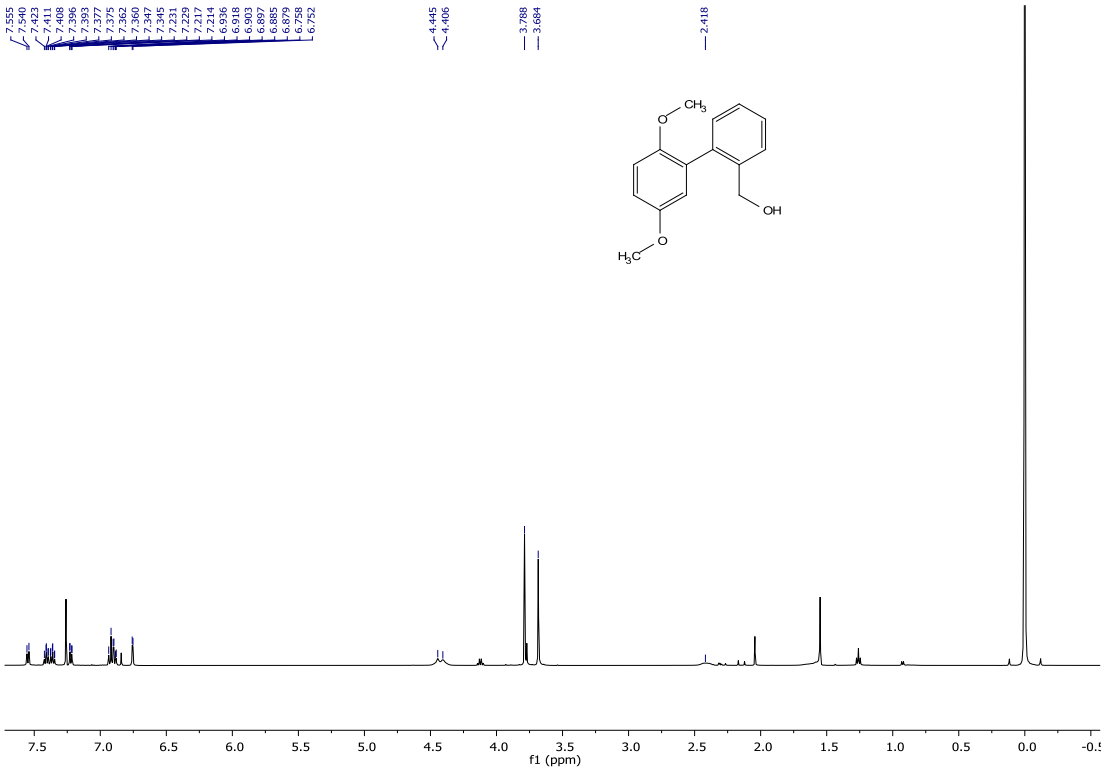


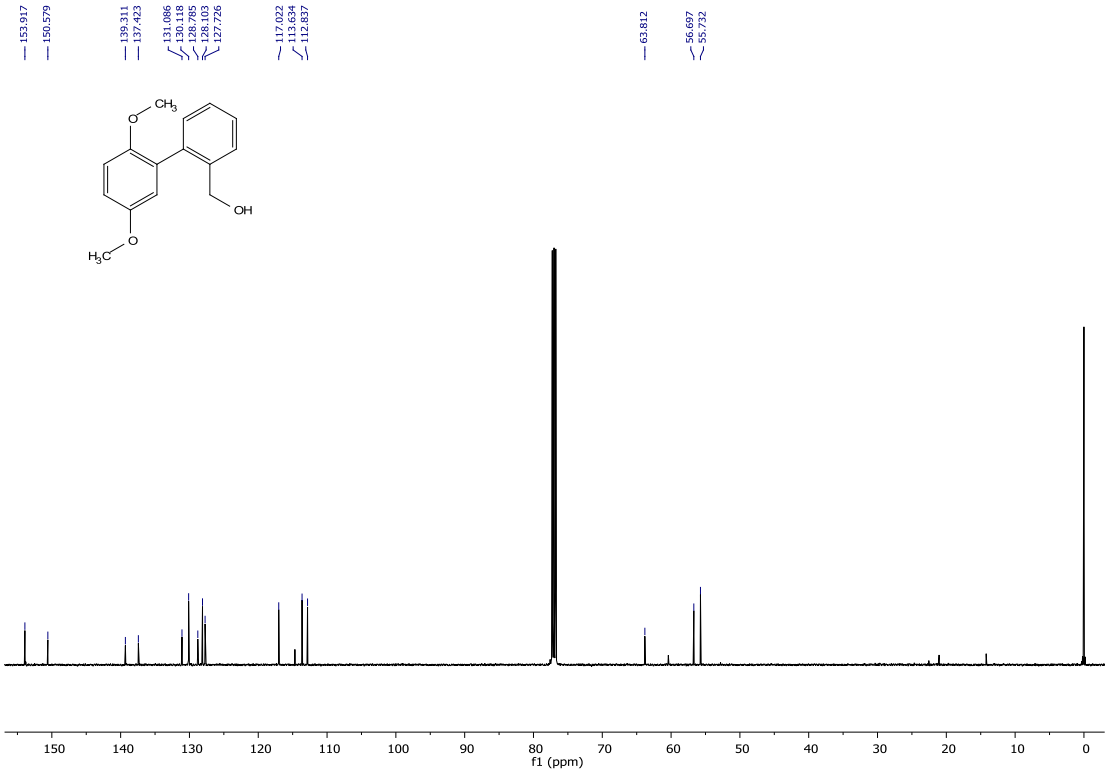
^{1}H and ^{13}C NMR spectra for Compound 325



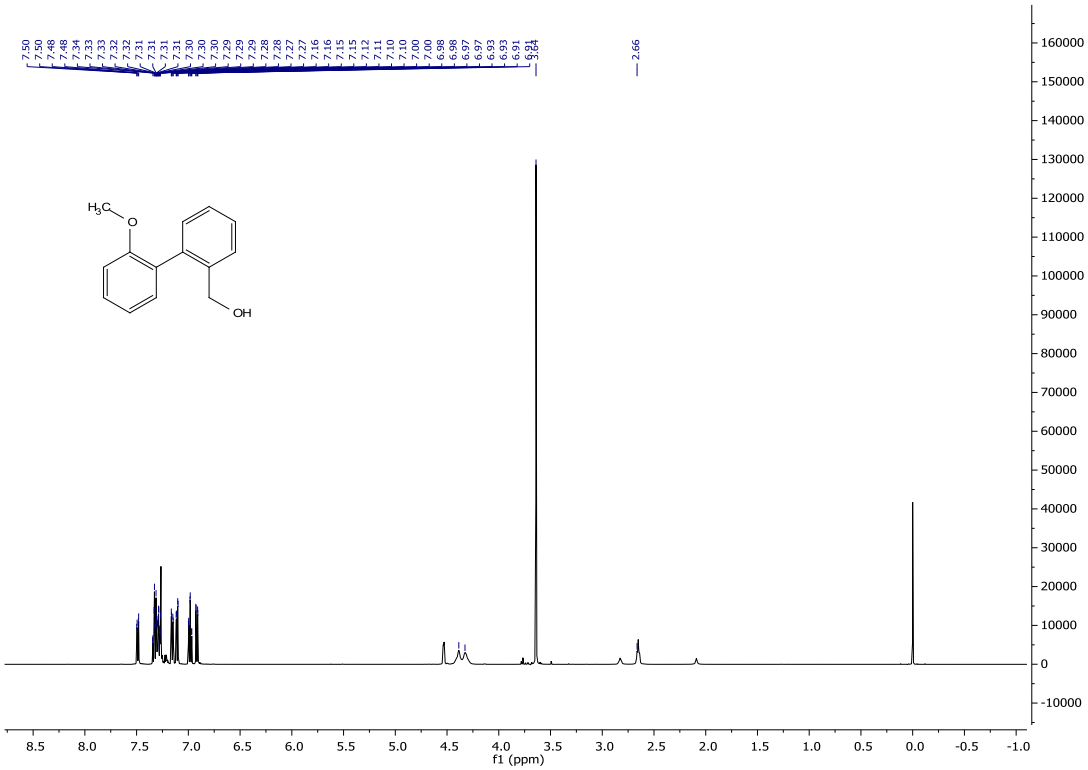


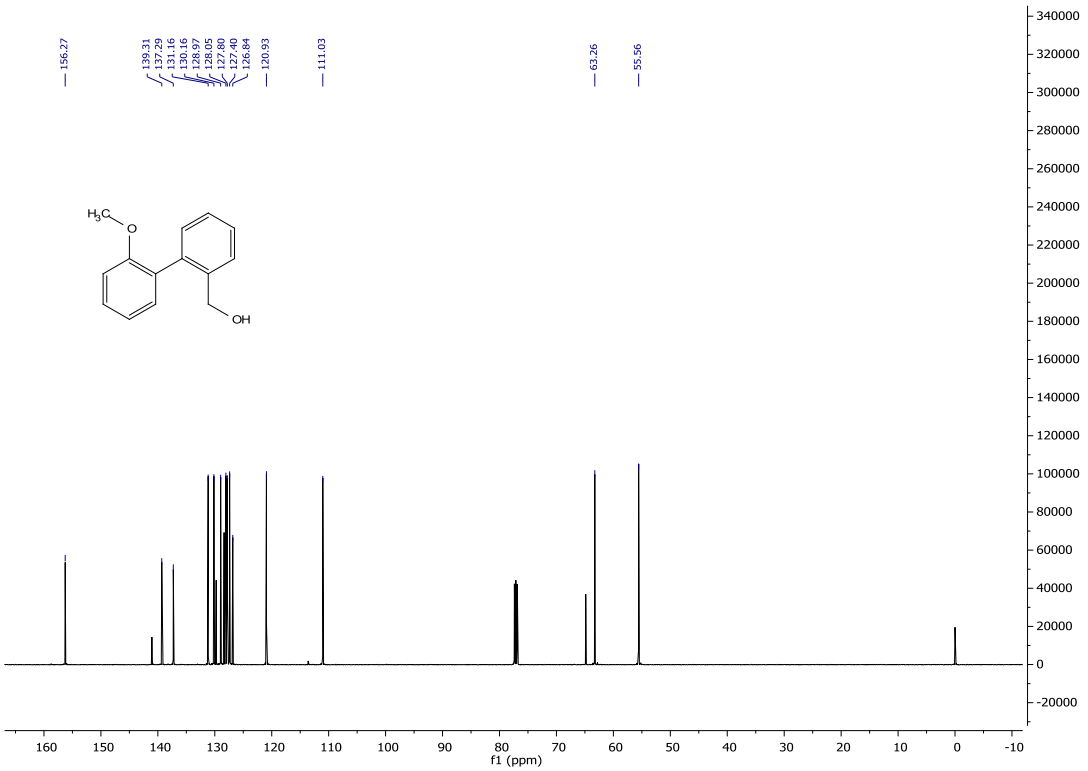
^{1}H and ^{13}C spectra NMR for Compound 321



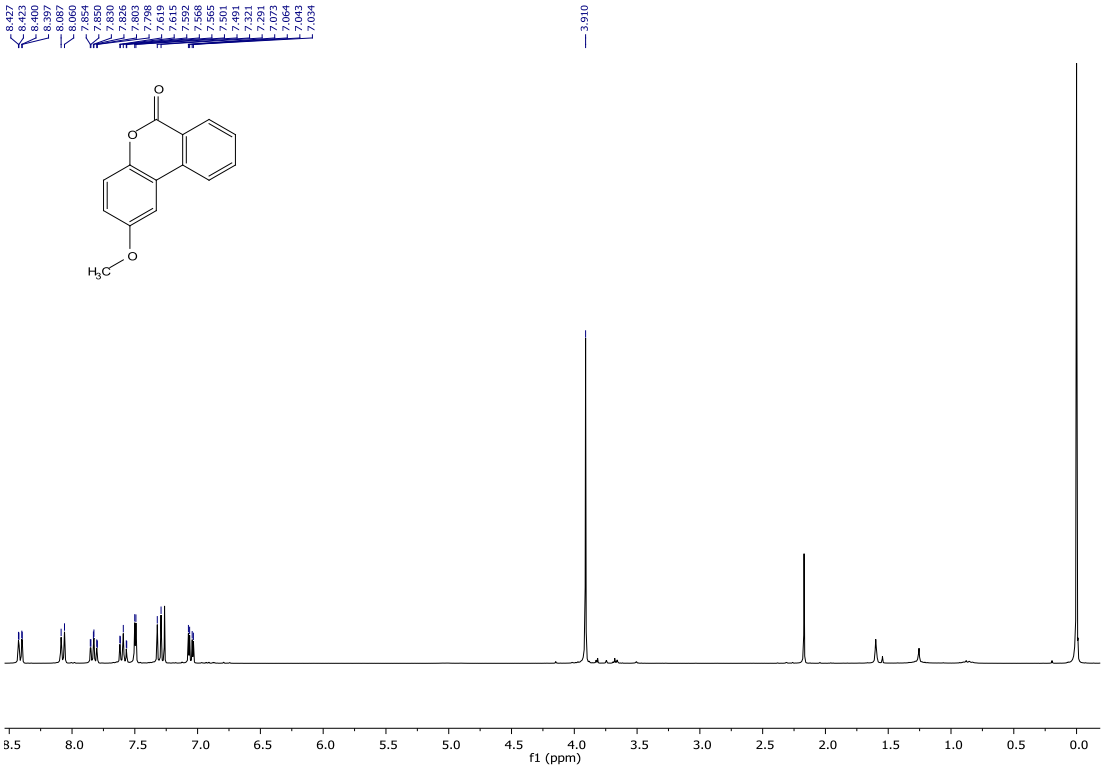


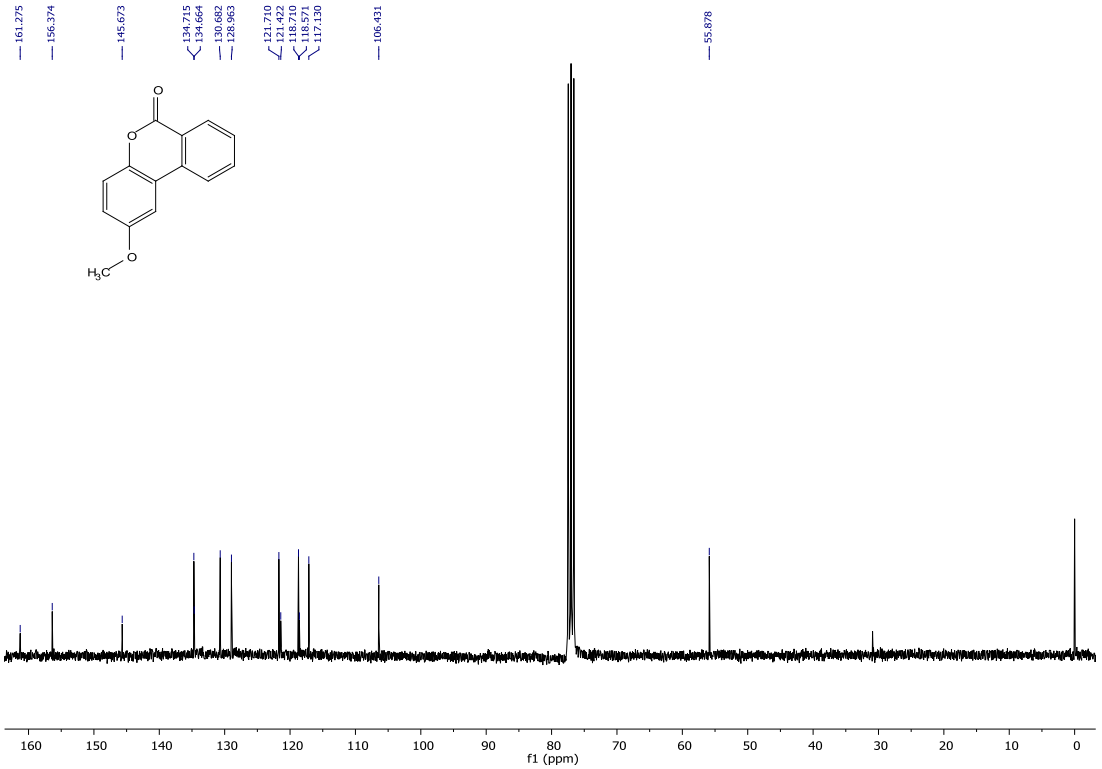
^{1}H and ^{13}C NMR spectra for Compound 326



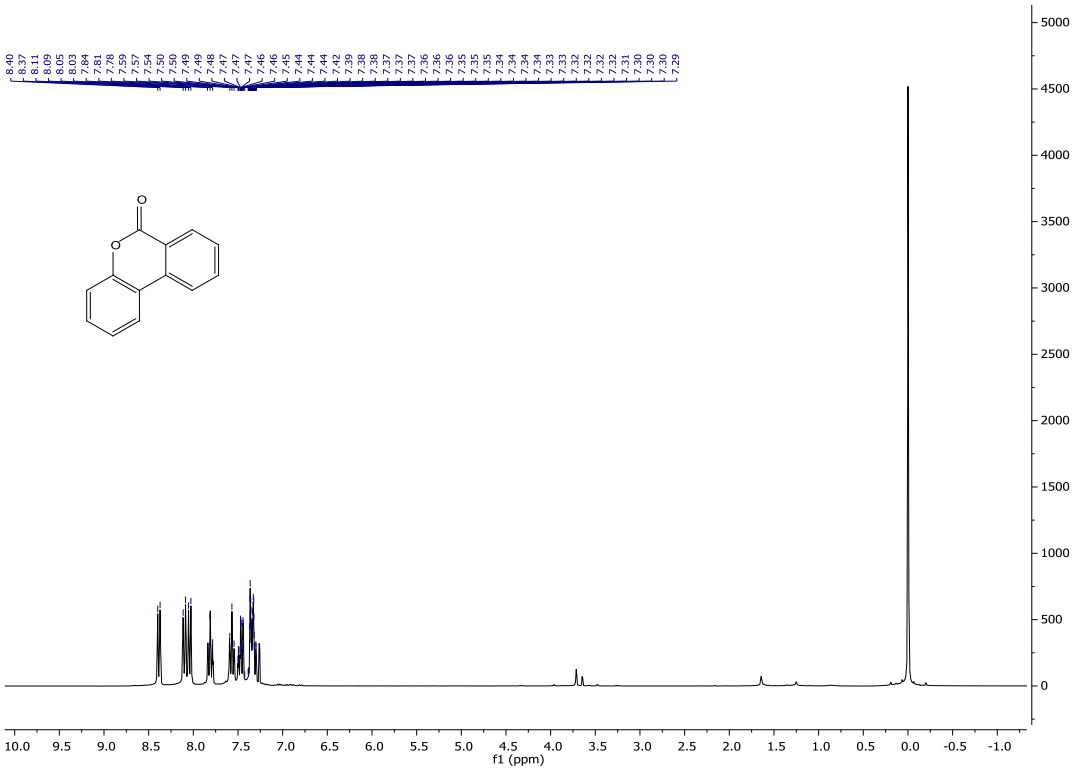


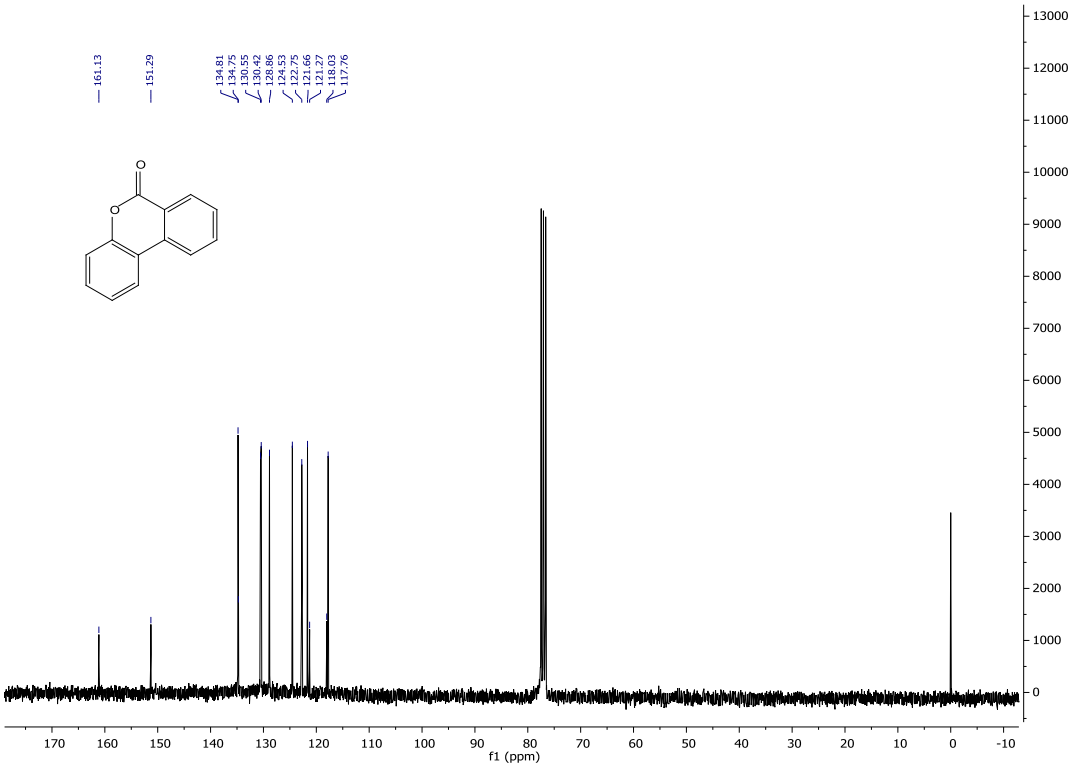
^{1}H and ^{13}C NMR spectra for Compound 322





^{1}H and ^{13}C NMR spectra for Compound 327





^{1}H and ^{13}C NMR spectra for Compound 323