SYNTHESIS OF PRENYLATED BENZOQUINONES

Thesis submitted in fulfillment of the requirements for the degree

Master of Science

School of Chemistry
Faculty of Science and Agriculture
University of KwaZulu-Natal
Pietermaritzburg

By

N. Mlondi Ngcobo

Supervisor:
Prof. F. R. van Heerden

ABSTRACT

The research presented in this study demonstrates the critical role that organic synthesis plays in natural product chemistry. The biological activity demonstrated by 2-methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone prompted an investigation into the synthesis of this compound. This natural product showed significant activity against *Staphylococcus epidermidis*. Therefore the aim of this study was to synthesise 2-methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone and structural analogues.

The regioselective synthetic route formulated for the synthesis of 2-methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone involved five steps. Different strategies towards the synthesis of this compound were investigated. The regioselective *C*-alkylation step was proving to be the most challenging. The synthetic strategies investigated included carbon alkylation of a phenoxide, directed-*o*-metallation, metal-halogen exchange and copper(II) Grignard-type metal halogen exchange.

Problems were encountered with regioselectivity when carbon alkylation of a phenoxide was employed for the *o*-prenylation of *o*-cresol. The *C*-prenylated isomer was formed along with the *O*-prenylated isomer. When the reaction temperature was lowered, the yield of the desired *C*-prenylated isomer improved, whereas the yield of *O*-prenylated isomer declined. Although the reaction was performed under different conditions, the formation of the *O*-prenylated isomer could not be prevented.

Therefore, another synthetic strategy was considered. The directed-*o*-metallation reaction was subsequently employed because of the associated regioselectivity. Unfortunately the desired product was not obtained when this method was employed. The reaction was attempted using different conditions, but the product could not be isolated.

Since the directed-*o*-metallation protocol did not yield the desired results, another method was considered. Therefore, a metal-halogen exchange reaction was employed. The metal-halogen exchange transformation was preceded by the preparation of the *o*-brominated precursor.

Regioselectivity-related problems were initially encountered during the synthesis of the *o*-brominated precursor. The *o*-brominated isomer was formed in a 1:1 ratio with the *p*-brominated isomer. Further investigation led to a synthetic protocol that afforded the desired *o*-brominated isomer in a better yield. The metal-halogen exchange transformation was subsequently attempted, but the product was obtained in an unsatisfactory yield.

Therefore, another method was employed in an effort to achieve regioselective *C*-alkylation with a better yield. Copper(II) Grignard-type metal-halogen exchange was successfully employed to achieve regioselective *C*-alkylation in good yield. The subsequent step was the deprotection, although problems were encountered, it was eventually achieved. The final step was the oxidation to obtain the desired compound, 2-methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone. The same procedure was successfully applied in the synthesis of structural analogues 2-isopentyl-6-methylbenzo-1,4-quinone, 2-(3,7-dimethylocta-2,6-dienyl)-6-methyl-1,4-benzoquinone and 2-(3,7-dimethyl-octyl)-6-methyl-1,4-benzoquinone.

PREFACE

The experiment work described in this dissertation was carried out in the School of Chemistry, Faculty of Science and Agriculture, University of KwaZulu-Natal, Pietermaritzburg, under the supervision of Professor Fanie van Heerden.

I thereby declare that these studies represent original work by the author and have not otherwise been submitted in any form for any degree or diploma to any tertiary institution. Where use has been made of the work of others it is duly acknowledged in the text.

Signed……
N. Mlondi Ngcobo

I hereby certify that the above statement is true and correct.

Signed……
Professor F. R. van Heerden

PLAGARISM DECLARATION

I, ……., declare that

1. The research reported in this thesis, except where otherwise indicated, is my original research.

2. This thesis has not been submitted for any degree or examination at any other university.

3. This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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Signed

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ACKNOWLEDGEMENTS

I would like to thank my supervisor, Professor Fanie van Heerden for her guidance, patience, and support throughout this project. I would also like to express thanks to Professor Siegfried Drewes for useful discussions.

Recognition is also due to the following without who this work would have never been completed:

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I would like to thank my late grandmother Cornelia Cabangani Ngcobo for raising me, I couldn't have asked for a better Guardian. I am indebted to my family for all the love and support they have offered; they are the source of my inspiration. I would like to thank all my friends and every single soul that has made a contribution in my life.

To my late parents Mjabulelwa and Jalisile Ngcobo, you have a special place in my heart even though you did not have the chance to guide me through the vagaries of life.

I also acknowledge the NRF for financial support

I like to thank God for giving life and for all the great things he has done for me.

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LIST OF ABBREVIATIONS

^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
^{1}H NMR	Proton Nuclear Magnetic Resonance
br	Broad
BuLi	Butyllithium
Calc	Calculated
C-alkylation	Carbon alkylation
Conc.	Concentrated
DMF	Dimethylformamide
d	Doublet
dd	Doublet of doublets
DMG	Directing metallating group
DoM	Directed ortho-metallation
eq	Equivalents
g	Grams
h	Hours
IR	Infrared
J	Scalar coupling constant
M	Molarity
m	Multiplet
m/z	Mass to charge ratio
MeCN	Acetonitrile
MeI	Methyl iodide
MHE	Metal-halogen exchange
MHz	Megahertz
min	Minutes
ml	Milliliter
mmol	Millimole
mol	Mole

m	multiplet
MS	Mass spectrometry
NMR	Nuclear Magnetic Resonance
Obsd	Observed
RT	Room temperature
s	Singlet
t	Triplet
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin-Layer Chromatography
TMEDA	Tetramethylethylenediamine

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CHAPTER ONE

General Introduction to Natural Product Chemistry

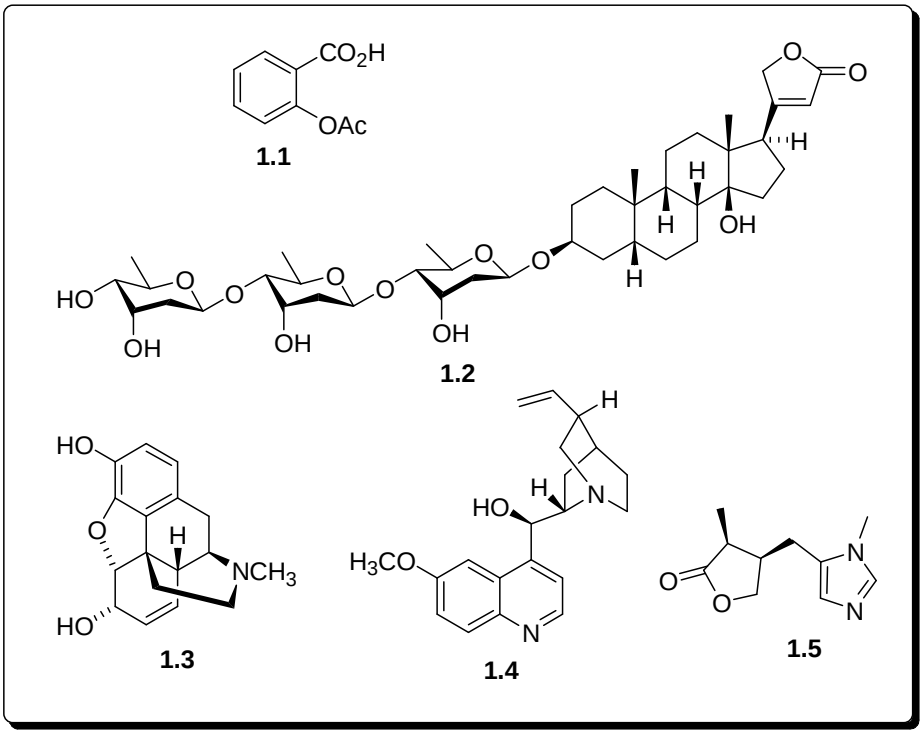
1.1 Natural Product Chemistry in Drug Discovery

Natural product chemistry has played, and continues to play, a major role in drug discovery. Drug discovery is a complex, interdisciplinary pursuit of chemistry, pharmacology, and clinical science, which has benefited humankind greatly over the last century.[1] Chemists and biologists have attempted to explain the mystery of why so many compounds in nature have biological effects on humans and other species. The generally accepted explanation is based on the long-term co-evolution within biological communities; interacting organisms that evolved in close proximity to one another developed compounds that could influence biological processes of neighbouring species.[2] The secondary metabolites of diverse living organisms have potent biological activities and have afforded lead compounds in drug discovery for the treatment of cancer, microbial infections, inflammation, and hypercholesteremia and tissue rejection in organ transplantation. They have also provided several useful tools to pharmacologists and cell biologists.[3]

Drugs of natural origin have been classified as original natural products, products derived semisynthetically from natural products or synthetic products based on natural product models.[4] Although secondary metabolites are not produced by all organisms, the diversity of nature has translated into a wide variety of biological active compounds. The origins of these invaluable compounds are mainly plants, marine invertebrates and microbes. Significant strides have been made since the isolation of the first commercial drug (morphine) and the use of microbial products as medicine (penicillin).

Natural products and medicine have been closely linked through the use of traditional medicines and natural poisons.[1] Approximately 60% of the world's population largely relies on plants for medication.[5] In developing countries such as South Africa, plants are still the most widely used and accessible source of primary medicine.

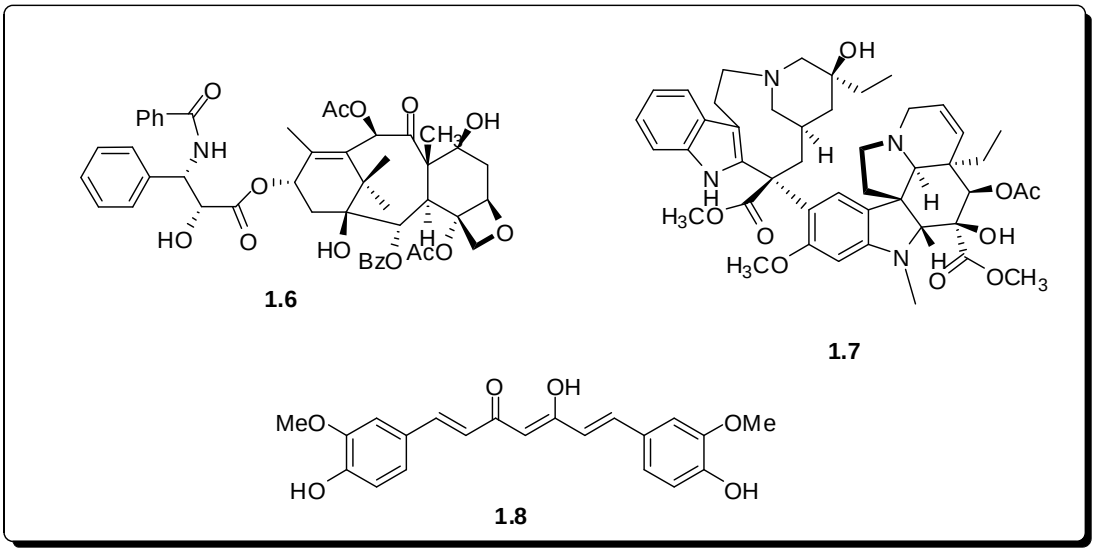
Clinical, pharmacological and chemical studies of traditional medicine derived from plants lead to the discovery of early medicinal compounds such as aspirin (**1.1**), digitoxin (**1.2**), morphine (**1.3**), quinine (**1.4**), and pilocarpine (**1.5**).[1] Drug discovery was subsequently revolutionised by the commercialisation of synthetic penicillin, which was serendipitously discovered by Fleming in 1928 when he realized that a fungus of a *Penicillium* family produced a substance with great antimicrobial activity. Florey and Chain followed up on Fleming's findings and their studies resulted in the successful application of penicillin to humans.[1,6]



The library of drugs derived from natural products has increased immensely from the first medicinal compounds. The pharmaceutical industry has benefited greatly from natural products. Natural products are well represented in the top 35 worldwide selling prescription drugs.[1] Proudfoot also reported that 8 out of 20 of the small molecule drugs launched in year 2000 were derived from natural products or hormones.[7] A study by Newman, Cragg, and Snader analyzing the number of natural products derived drugs present in the total drug launches from 1981 to 2002 demonstrated that natural products are

a significant source of new drugs.[8] They also concluded that natural products were more prevalent in the anticancer and antihypertensive therapeutic areas.[4,8]

Cancer is the leading cause of human death after cardiovascular diseases.[6] Currently a substantial number of anticancer agents used are either natural or derived from natural products.[9] The natural product-derived drugs paclitaxel (Taxol) (**1.6**) and vinblastine (Velban) (**1.7**) are two of the leading drugs in cancer treatment. Paclitaxel was originally isolated from the bark of *Taxus brevifolia* (yew tree), while vinblastine from the periwinkle plant of Madagascar (*Catharanthus roseus*).[6] Curcumin (**1.8**) is another natural product drug involved in chemoprevention, a promising anticancer approach. Extracted from the rhizome of *Curcuma longa* L, it causes suppression, retardation and inversion of carcinogenesis.[10]



1.6 **1.7** **1.8**

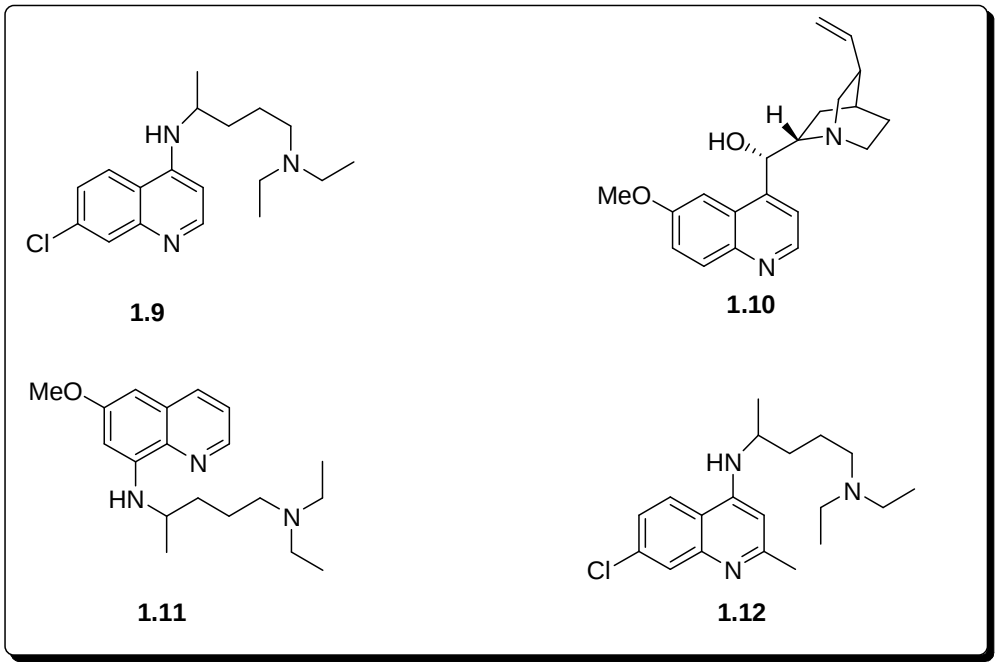
Although natural products are an unparalleled source of drugs, the advent of alternative, promising drug discovery methods has placed great pressure on natural product drug discovery programmes. In the last 10-15 years the interest in natural products by major pharmaceutical companies has diminished in favour of new technologies such as combinatorial chemistry and rational drug design. Lately the interest in drug discovery from natural products has been greatly resuscitated by the failure of these technologies in delivering the promised number, novel and cheaper drug candidates. The recent developments have also demonstrated that combining natural products with some of the

new technologies furnishes a powerful tool for drug discovery. Therefore, modern natural products chemistry has re-emerged as a promising supplier of adequately sophisticated lead structures for drug discovery.[3,11,12] Since only a small portion of the world's biodiversity has been tested for biological activity, it can be assumed that natural products will continue to provide novel leads for new therapeutic agents.[13]

1.2 Role of Total Synthesis in Natural Product Chemistry

Total synthesis has played a pivotal role in natural product chemistry. Natural products have furnished simple and complex molecules with biological activity, while total synthesis has been employed in the preparation of these medicinally important molecules. A clearly defined synthetic strategy for making a particular natural product means that there is an everlasting source of that compound, even when the original natural source is extinct. The symbiosis between total synthesis and natural product chemistry has contributed greatly in the evolution and advancement of total synthesis. Novel natural products have coincided with the discovery of new synthetic methods.[14]

Total synthesis has not only been used to conceive reported natural products, but has also been used to develop new compounds with biological activity. It has played a critical role in the synthesis of structural derivatives of biologically active compounds, thus furnishing compounds with possible higher or lower biological activity. Some of the synthesised derivatives have afforded synergistic effects when administered with the original natural product. For example, the total synthesis of quinine (**1.4)** has been subsequently followed by the synthesis of various derivatives, including chloroquine (**1.9)**, quinidine (**1.10)**, pamaquine (**1.11)** and sontoquine (**1.12)**. They all possess antimalarial activity like the parent compound, quinine (**1.4**). The combination of quinine (**1.4**) and pamaquine (**1.11**) rendered a powerful therapeutic tool. Quinine (**1.4**) on its own right affects the malaria parasite at the stage of its life cycle when it inhabits the bloodstream, whereas pamaquine (**1.11**) affects the parasite in the liver. The combination effectively clears an infection from both the liver and the blood.[6]



1.3 Aim of the Study

The only South African *Gunnera* species is *Gunnera perpensa* L., known as *uGobho* in isiZulu and river pumpkin in English. *Gunnera perpensa* has been utilised by South African people in the treatment of menstrual pain, psoriasis and female infertility. The leaves have been used as a dressing for wounds.[15]

The aims of the study:

- The synthesis of 2-methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone isolated from leaves and stem of *Gunnera perpensa*.
- The synthesis of structural derivatives.

In the next chapter we will present a literature review on some the biological important naturally occurring 1,4-benzoquinones. We will also outline some of the synthetic strategies which are normally employed during the synthesis of these natural products.

1.4 References

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CHAPTER TWO

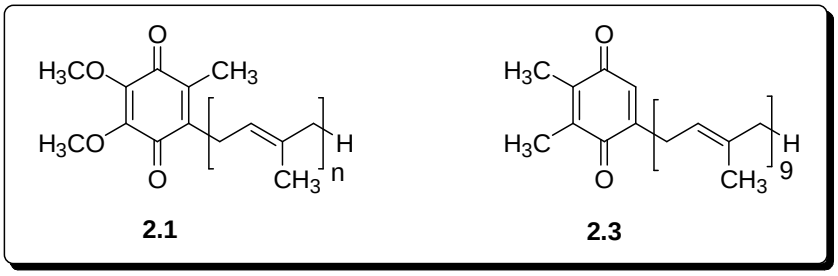
Biologically Active Quinones and Synthesis of Naturally Occurring 1,4-Benzoquinones

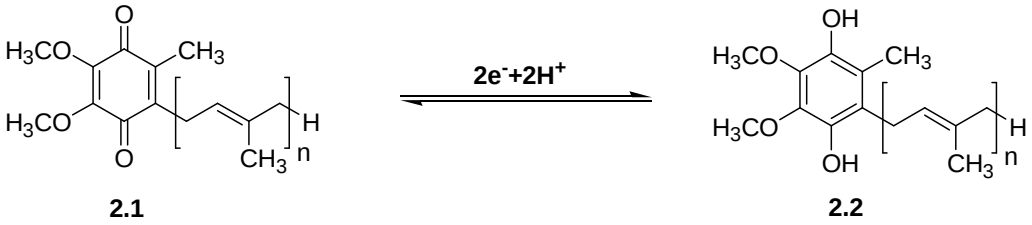
2.1 Biologically Active Naturally Occurring Quinones

In this chapter we will discuss the importance of naturally occurring 1,4-benzoquinones. It will be illustrated by looking at the role they play in metabolic processes and their therapeutic value. The other objective is to briefly discuss the general synthesis of these compounds. There will also be a discussion on some of the most widely used synthetic strategies.

Naturally occurring quinones are widespread in nature. They represent an important class of biological molecules possessing wide-ranging properties, and participate in various bioenergetic processes as important transport agents.[1] Quinones are the largest group of natural pigments, but they play a relatively small role in natural colouring and their major contribution is in biological redox processes.[2-4] Their importance and usefulness is not only limited to metabolic processes, but they also represent a clinically valuable entity for therapeutic agents with various applications.[5] They are widely used as anticancer, antimicrobial, antitumour and antimalarial drugs as well as fungicides.

Ubiquinones (Coenzymes Q) (**2.1**) are an example of quinones playing a critical role in biological redox processes. Ubiquinones are situated mainly in the mitochondria where they play a pivotal role in electron transport in the respiratory chain. Ubiquinones (CoQn) have different side chain lengths indicated by the number *n* after the name, which can range from 2 and 10 isoprene units. In a biological redox system, they can exist as either *p*-benzoquinones (**2.1**) (ubiquinones, CoQn) or *p*-hydroquinones (**2.2**) (ubiquinonols, $CoQnH_2$) (Scheme 2.1).[6-9] The structurally similar pastoquinones are also involved in electron transport. Plastoquinone-9 (**2.3**), which is found in the chloroplast of green plants, functions in the electron transport pathways in photosynthesis.[10] The involvement of quinones in biological processes is not only limited to electron transfer, but they are also involved in oxidative phosphorylation.[1]



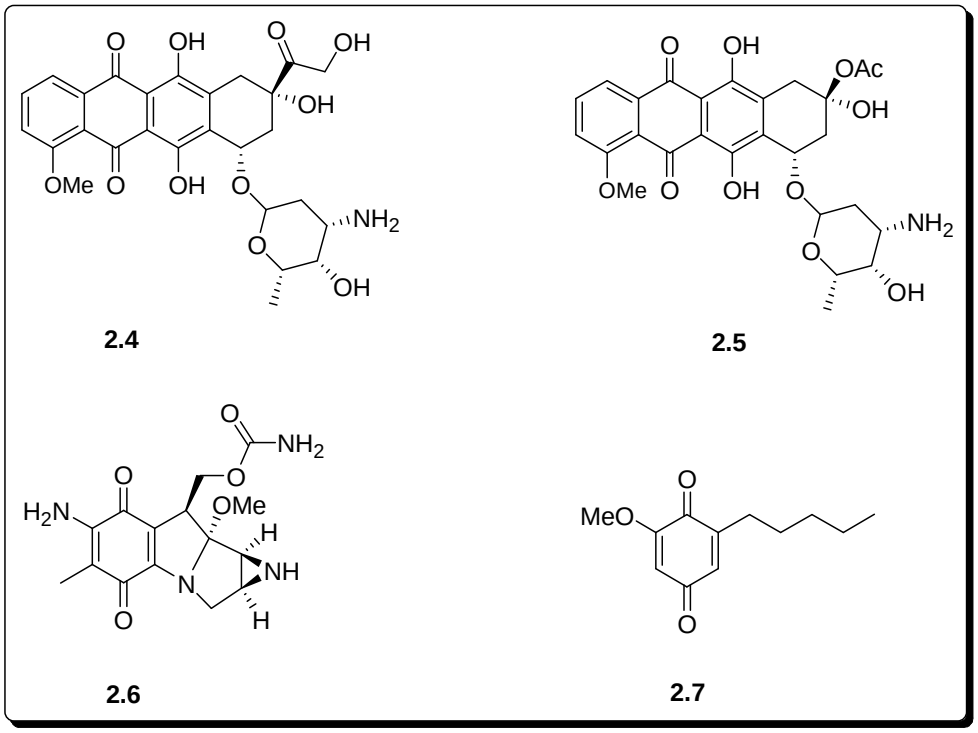


Scheme 2.1: Redox equilibrium of ubiquinones.

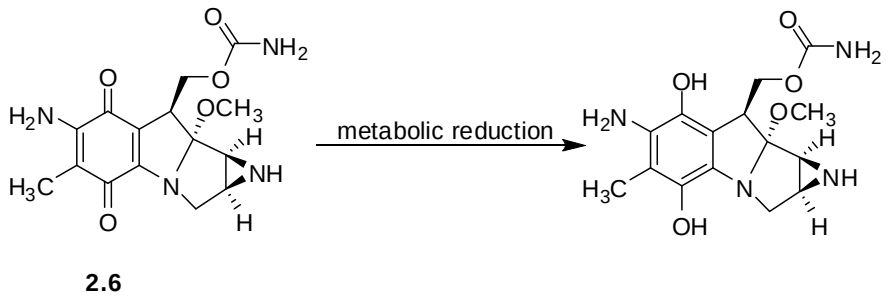
2.2 Quinones with Anticancer Activity

Quinones have demonstrated cytotoxic effects against various cancer cell lines. As a result, many quinone compounds have been screened for antitumour activity. The cytotoxic effect of quinones is predominantly due to their inhibition of DNA topoisomerase-II.[5] In chemotherapy, the most significant property of quinones is their ability to undergo redox cycling to produce reactive oxygen species which can curtail tumour cells.

Naturally occurring quinones are present in many drugs, such as the anthracyclines daunorubicin (**2.4**) and doxorubicin (**2.5**) and mitomycin (**2.6**), which are used clinically in solid cancer therapies.[11] Although these quinones are structurally complex, even relatively simple benzoquinones exhibit significant biological activity; primin (**2.7**), for example, has demonstrated significant antitumor activity.[12] Doxorubicin (**2.4**) is the most widely used anthracycline anticancer antibiotic. It was first isolated in 1967 from the fungus *Streptomyces peucetius*, it is active against several types of lymphoma, leukaemia, breast, ovary, bladder, stomach and thyroid gland cancer.[13]



Mitomycin (**2.6**) is another naturally occurring quinone that has received considerable attention because of its chemotherapeutic value. It is in the class of anticancer compounds that are termed archetypal bioreductive drugs. These anticancer compounds are inactive on their own, but upon metabolic reduction are transformed into cytotoxic species (Scheme 2.2).[10] Mitomycin is an alkylating agent, after metabolic reduction it forms crosslinks between DNA strands, thereby blocking DNA synthesis.[13] The contribution made by quinones in cancer treatment encourages further study and exploration of quinones in order to discover novel anticancer drugs.

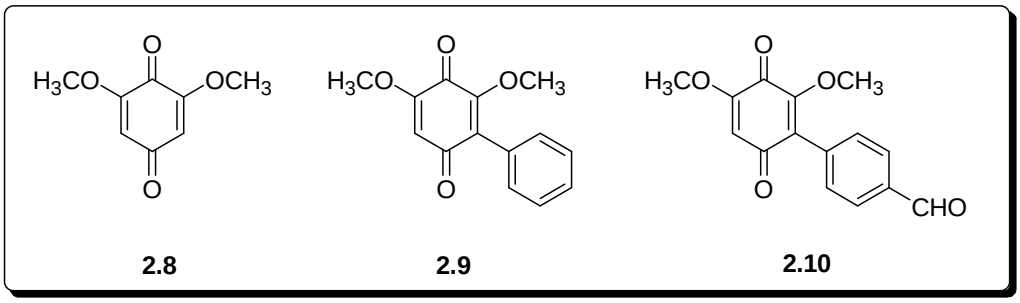


2.6

Scheme 2.2: Metabolic reduction of mitomycin.

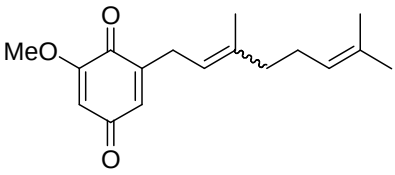
2.3 Quinones with Antimicrobial Activity

There is a great demand for new antimicrobial agents with the ability to cure frequently occurring bacterial illnesses. Bacterial resistance to some of the antibiotics currently available, is another more prevalent reason for the search of novel antimicrobial agents.[14] The challenge became more apparent when it was discovered that, shortly after introduction of the various classes of antibiotics, new pathogenic strains emerged that were no longer susceptible to the antibiotics.[13] Therefore, a concerted effort has been made to discover new antimicrobial agents to combat bacterial resistance. Quinones are amongst the large array of compounds that have been studied in order to discover new antimicrobial agents. 2,6-Dimethoxy-1,4-benzoquinone (**2.8)**, 3,5-dimethoxy-2-phenyl-1,4-benzoquinone (**2.9**) and 3,5-dimethoxy-2-(4-formylphenyl)-1,4-benzoquinone (**2.10**) are some of the structurally simple quinones that have demonstrated antimicrobial activity.[14]



2.4 Naturally Occurring Prenylated Benzoquinones

Natural occurring quinones, especially prenylated benzoquinones, play a critical role in several metabolic processes and possess significant biological activities. The ubiquinones (**2.1**) are a primary example of prenylated benzoquinones with biological importance. Besides their role in metabolic processes, its arsenal of biological activity includes termiticidal activity against *Coptotermes formosanus*.[15] Prenylated benzoquinones are ubiquitous in nature, where they possess wide-ranging biological activities. Verapliquinone A and B (*cis* or *trans* isomer) (**2.11**), atrovirinone (**2.12**) and 2-(3-methylbut-2-enyl)-5-(2-methylbut-3-en-2-yl)-1,4-benzoquinone (**2.13**) are some of the naturally occurring bioactive prenylated benzoquinones.[16-18]



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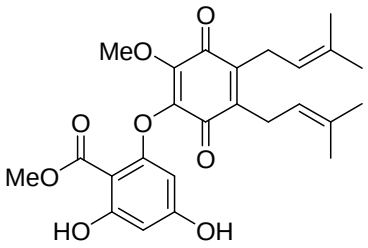

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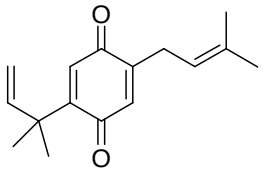


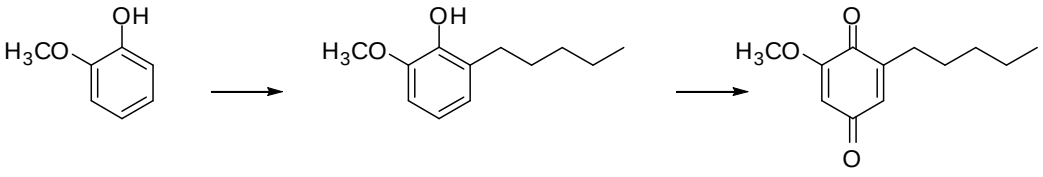
2.13

antiflammatory

2.5 Synthesis of Naturally Occurring Alkyl-1,4-benzoquinones

Naturally occurring 1,4-benzoquinones have received considerable attention from synthetic chemists. The synthesis of these natural products has been stimulated by the associated biological activity. Several synthetic approaches have been formulated to permit the synthesis of these bioactive natural products. The structural diversity within this class of compounds has facilitated constant improvement and development of new synthetic routes. Because of the diverse structure, there is no general synthetic route towards natural occurring 1,4-benzoquinones.[19,20]

The reported naturally occurring 1,4-benzoquinones are predominantly alkyl-1,4-benzoquinones. Therefore, several synthetic routes that have been formulated are based on the requirements of simple alkyl-1,4-benzoquinones. Primin (**2.7**) is the most studied alkyl-1,4-benzoquinone, this can be attributed to its biological properties. Consequently, several synthetic routes have been developed based on the synthesis of primin (**2.7**). The general synthesis of primin (**2.7**) normally involves two critical steps. The *C*-alkylation of the phenol **2.14** and the oxidation of the alkylated phenol **2.15** to the product, primin (**2.7**)[19] (Scheme 2.3).



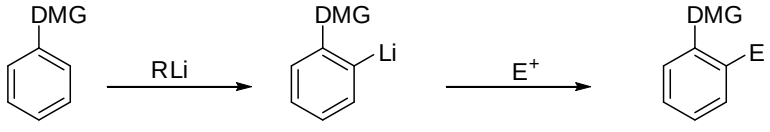
2.14 **2.15** **2.7**

Scheme 2.3: Outline of the general synthetic route towards primin

Besides, primin (**2.7**), there are several simple alkyl-1,4-benzoquinones that have been synthesised. Variable synthetic strategies have been employed in the synthesis of these natural products. The *C*-alkylation, specifically *ortho*-alkylation, of the corresponding phenol has proven to be a challenging task. Consequently, there has been a concerted effort to improve conventional methods and also discover simple and more efficient methods. Directed *ortho*-metallation (D*o*M), Claisen rearrangement and metal-halogen exchange reactions are some of the synthetic strategies that have received considerable attention.

2.5.1 Directed *ortho*-Metallation (D*o*M)

Directed *ortho*-metallation (D*o*M) is one of the strategies employed in the regiospecific preparation of substituted aromatic compounds. The D*o*M reaction involves deprotonation by a strong base at the *ortho* position of an aromatic compound containing a directed metallation group (DMG) (**2.16**). Alkyllithium reagents are normally used as the base to furnish an *ortho*-lithiated product (**2.17**) which subsequently reacts with electrophilic reagents to yield a 1,2-disubstituted product (**2.18**) (Scheme 2.4).[21-24]

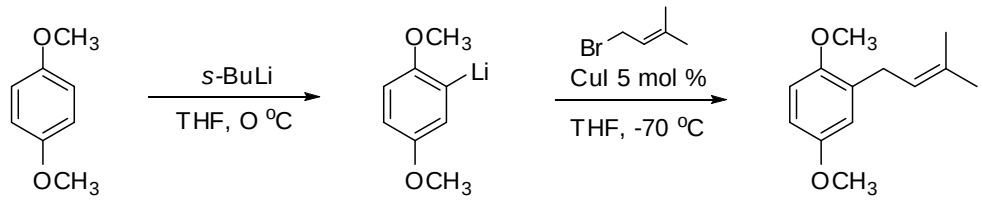


2.16 **2.17** **2.18**

Scheme 2.4: *Ortho*-alkylation using simple D*o*M reaction.

Although D*o*M has been successfully employed in the synthesis of naturally occurring 1,4-benzoquinones, it has also demonstrated significant limitations.[12] The success of a D*o*M reaction largely depends on the aromatic compound, base and DMG used. Limitations have been experienced during deprotonation of aromatic compounds with two or more oxygen substituents, due to proton transfer from the *ortho* groups (DMG) such as –OBn or -OMOM that quenches the aryl anion. Although acetals and carbamate can be employed as DMGs to avoid this complication, they also have their own limitations. The carbamate has the ability to migrate to the *ortho* lithiated aryl carbon atom at temperatures greater than 60 ^{o}C, generating the corresponding salicylicamide.[25]

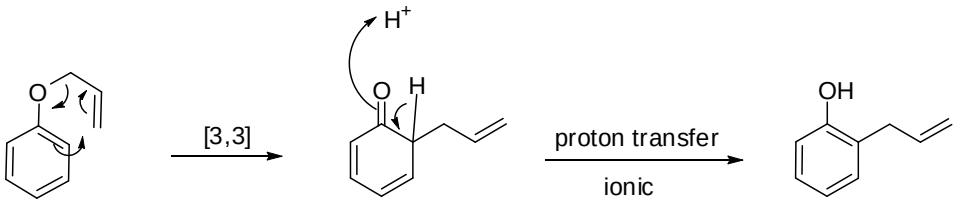
The strong alkyllithium bases that are preferred for D*o*M reactions, are also not without limitations. They form aggregates of defined structures in organic solvents. They normally form hexamers in hydrocarbon solvents and tetramers and dimers in Lewis basic solvents. The formation of the alkyllithium aggregates significantly decreases the basicity. This limitation has been addressed by the use of bidentate ligands, such as TMEDA. It breaks down the aggregates, producing monomers and dimers in solution and consequently increasing basicity.[22] This promotes formation of the lithiated species, which have also demonstrated poor reactivity, to achieve coupling they have been activated by formation of cuprate intermediates (Scheme 2.5).[26] Although the D*o*M reaction encompasses numerous limitations, it is still one of the preferred strategies in the preparation of alkyl-1,4-benzoquinones.



Scheme 2.5: D*o*M reaction activated by cuprate formation.

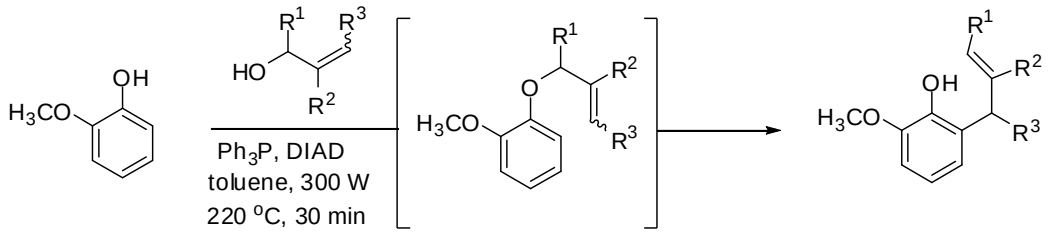
2.5.2 Claisen Rearrangement

The Claisen rearrangement was first reported almost a century ago, by Ludwig Claisen.[27] Since its discovery it has been regarded as a useful tool in synthetic organic chemistry. It was the first sigmatropic rearrangement to be discovered. It occurs when an aryl allyl ether (**2.19**) is heated without solvent and an *ortho*-allyl phenol (**2.20**) results (Scheme 2.6).[28] Over the years, it has been translated into an indispensable tool for synthetic chemists.



Scheme 2.6: Mechanism of a [3,3] sigmatropic rearrangement.

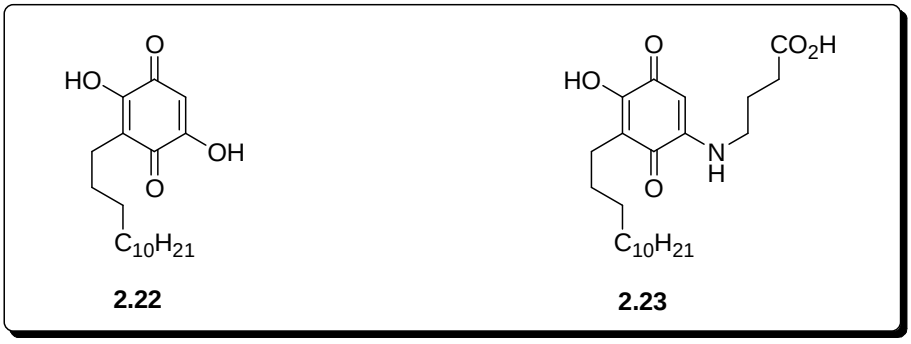
The usefulness of this reaction has prompted substantial development and improvement of the constituting parameters. Through technology the efficiency of the Claisen rearrangement has been greatly improved by microwave irradiation. The long reaction times associated with conventional Claisen rearrangement conditions are significantly reduced under microwave conditions.[29] The transformation of the Claisen rearrangement from a simple thermal process into a microwave-assisted reaction has enhanced its application. Consequently, microwave-assisted aromatic Claisen rearrangement has emerged as a key step in the synthesis of various naturally occurring 1,4-benzoquinones. It has demonstrated simplicity and versatility during the synthesis of these natural products. The versatility of microwave-assisted aromatic Claisen rearrangement has been confirmed by its successful combination with the Mitsunobu reaction in a one-pot operation. The Mitsunobu reaction is one of the methods that are employed in the synthesis of aryl allyl ethers (**2.21**), which are precursors for the Claisen rearrangement (Scheme 2.7). The Mitsunobu reaction-Claisen rearrangement protocol has become a preferred strategy in the synthesis of naturally occurring 1,4-benzoquinones. It was successfully employed by McErlean and Moody in the synthesis of two naturally occurring alkyl-1,4-benzoquinones, raponone (**2.22**) and *N*-(3-carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone (**2.23**).[20]



2.21

R^1, R^3 = H
R^2 = CH_3

Scheme 2.7: Synthesis of *ortho*-alkylated phenyls using the Mitsunobu reaction-Claisen rearrangement protocol.

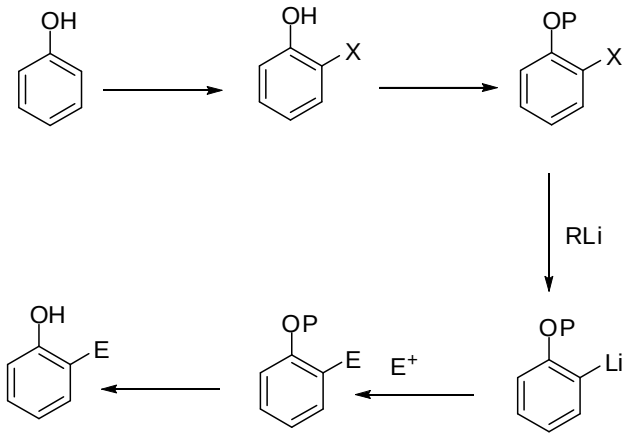


2.22 **2.23**

2.5.3 Metal-Halogen Exchange (MHE)

The reaction of organometallic compounds with organic halides is an extensively studied reaction in organic chemistry. Metal-halogen exchange reactions can be employed during the synthesis of *ortho*-alkylated aromatic species. It has received considerable attention in the synthesis of alkyl-1,4-benzoquinones, because it provides high control of regioselectivity. The first step in the metal-halogen exchange reaction is normally the *ortho*-halogenation, followed by protection with a corresponding protecting group. The next step is the displacement of the halogen with an appropriate metal. The organometallic species is subsequently reacted with an electrophile. The resulting compound is then deprotected to afford an *ortho*-alkylated phenol (Scheme 2.8). The efficiency and effectiveness of this reaction mostly depends on the halogen species employed. For

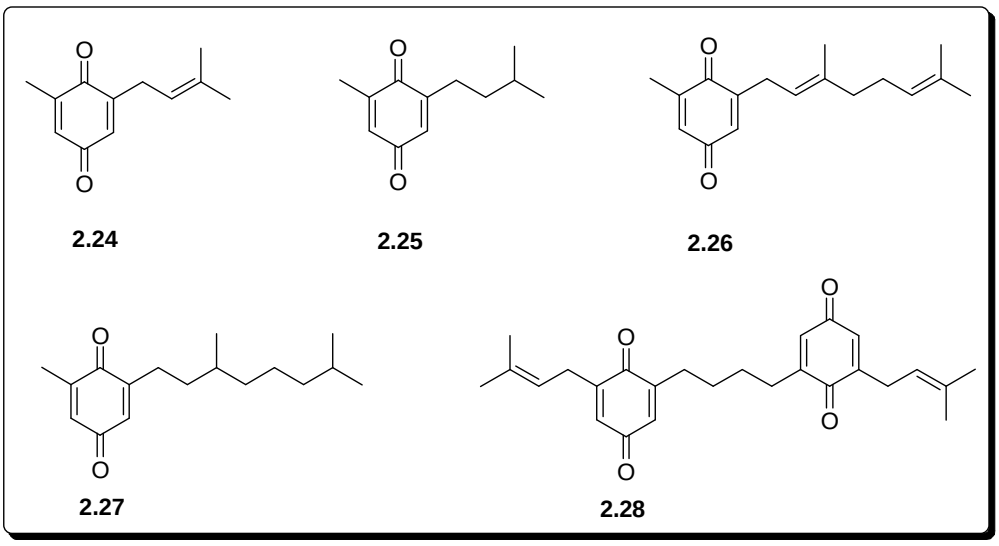
example, iodobenzene derivatives are preferred for high chemoselectivity and mild conditions.[21,30-32]



Scheme 2.8: Synthesis of *ortho*-alkylated phenol using a metal-halogen exchange reaction.

In this chapter the importance of natural occurring 1,4-benzoquinones has been demonstrated by the role they play in chemotherapy. It has also affirmed the critical and challenging role that organic synthesis plays in natural product chemistry. The synthesis of alkyl-1,4-benzoquinones was also introduced, with a brief discussion on the challenging *ortho*-alkylation process.

Therefore, some of the most employed synthetic strategies in the manifestation of this process were outlined. The subsequent chapter will discuss the synthesis of 5-(3-methyl-2-butenyl)-2-methylbenzo-1,4-quinone (**2.24**) and associated structural derivatives **2.25 - 2.28**. The discussion will be based on the synthetic strategies and various techniques that were employed during the synthesis of these compounds.


O
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2.28

2.6 Reference

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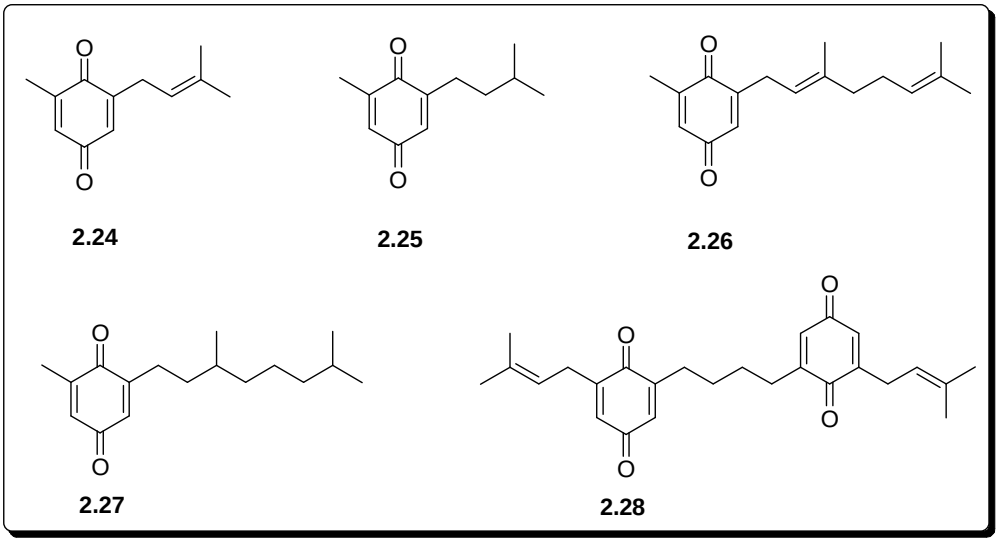
CHAPTER THREE

Synthesis of a Naturally Occurring 1,4-Benzoquinone and Structural Analogues

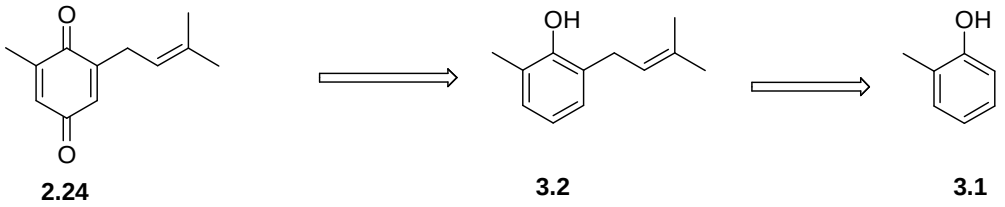
3.1 Synthetic Approach

This chapter will discuss the synthesis of 2-methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone (**2.24**) and its structural analogues **2.25-2.28**. 2-Methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone (**2.24**) is a 1,4-benzoquinone derivative isolated from the dichloromethane extract of the leaves and stem of *Gunnera perpensa*. It showed significant activity against *Staphylococcus epidermidis*.[1] *S. epidermidis* are gram-positive pathogenic bacteria that occur in microscopic clusters resembling grapes and are common in medical device-associated infections.[1,2]



As highlighted in Chapter 1, Section 1.3, the aim of this study was the synthesis of 2-methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone (**2.24**) and its structural analogues **2.25-2.28**. The antimicrobial activity of **2.24** prompted us to synthesise this compound and the related analogues. Furthermore, the development of versatile and flexible routes towards prenylated quinones is a matter of interest for synthetic chemists, due to the role they play in biological processes and their pharmacological properties.[3-5] The objective was to

prepare **2.24** and a number of derivatives to investigate the contribution made by different substituents on the biological activity of the compounds. Consequently, analogues with extended side chains and saturated side chains were synthesised in order to investigate the effect of the side chain on the associated biological activity. A retrosynthesis analysis of **2.24** suggested that **2.24** might be obtained from a prenylated phenol derivative, which can be prepared from *o*-cresol (**3.1**) (Scheme 3.1).



2.24 **3.2** **3.1**

Scheme 3.1: Retrosynthetic analysis of parent compound **2.24**.

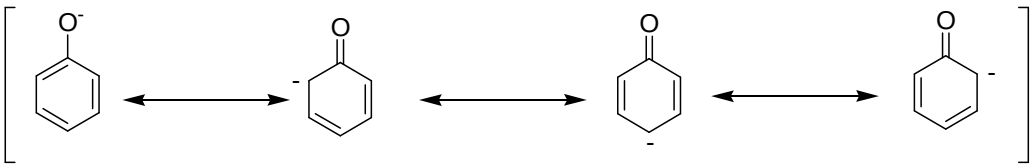
The proposed analogues **2.25-2.28** are structurally similar to the parent compound **2.24**. Therefore, it was envisaged that the synthetic strategy employed in the synthesis of **2.24** could also be employed in the preparation of analogues **2.25-2.28**. It was critical to develop a reliable synthetic approach characterised by consistency, wide applicability and mild conditions. The first synthetic approach to **2.24** involved carbon alkylation of a phenoxide.

3.2 Carbon Alkylation of a Phenoxide

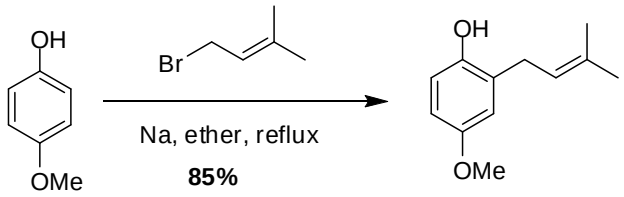
A retrosynthetic analysis suggested that carbon alkylation of a phenoxide could be employed in the synthesis of 2-methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone (**2.24**). The first step in the preparation of the parent **2.24** was *ortho*-prenylation of *o*-cresol (**3.1**), forming the *ortho*-prenylated phenol (**3.2**). This step can be achieved through carbon alkylation of a phenoxide. Phenoxide carbon-alkylation has been widely employed in the preparation of *ortho*-prenylated phenols.[6] The synthesis of **3.2** using carbon alkylation of a phenoxide has been reported by Yamada *et al*. The results obtained by Yamada *et al*. were motivating since the desired compound **3.2** was obtained in 76% yield.[7,8]

However, it has also been reported that *ortho*-prenylation by carbon alkylation of the phenoxide is associated with low yields.[6] The low yields have been attributed to the occurrence of side reactions. The competing reactions are normally *para*-carbon

prenylation, *bis*-prenylation and oxygen-prenylation. This is because the phenoxide ion is capable of coupling at the oxygen or at the *ortho* and *para*-positions on the ring (Scheme 3.2). Therefore, blocking of the *para*-position is one of the methods that have been implemented to circumvent the formation of side products (Scheme 3.3).[9-11]

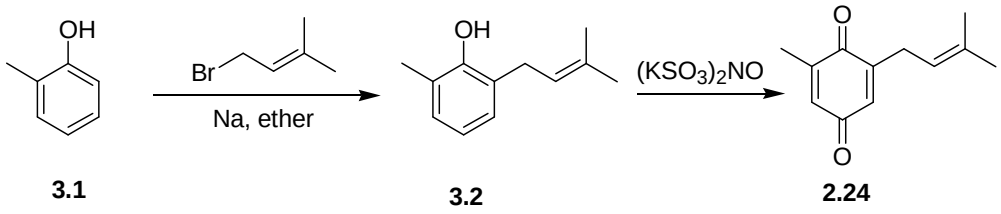


Scheme 3.2: Resonance forms, showing the possible coupling position.



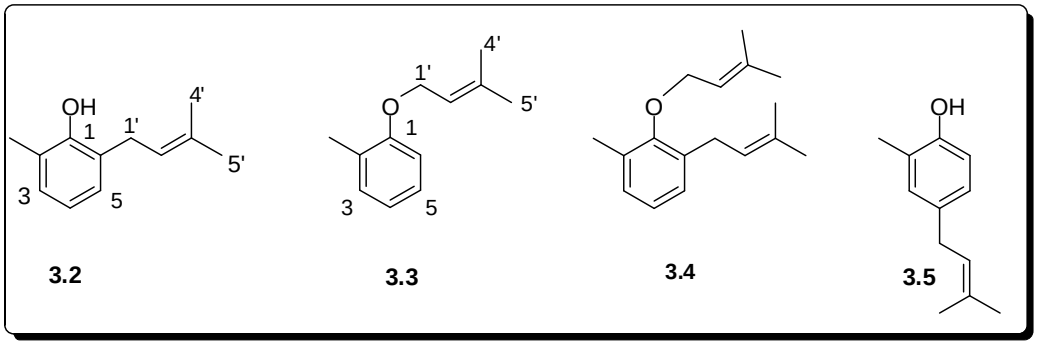
Scheme 3.3: *ortho*-Prenylation of a phenol with a blocked *para*-position.

In this investigation, the first proposed synthetic approach to **3.2** did not include the blocking of the *para*-position, since a good yield was reported by Yamada *et al*. without blocking the *para*-position.[7,8,12] The first step in the proposed synthetic route towards **2.24** was thus *C*-alkylation using the Yamada *et al*.[7,8] protocol. The second step was the oxidation of the *ortho*-prenylated phenol using $(KSO_3)_2NO$ (Fremy's salt) (Scheme 3.4).



Scheme 3.4: Proposed synthesis of **2.24**, after Yamada *et al*.[7,8]

Therefore, metallic sodium was added slowly to a solution of diethyl ether and *o*-cresol (**3.1**). The resulting mixture was stirred for 1 h, the prenyl bromide was added slowly and the mixture was subsequently refluxed for 10 h. Two products were isolated and identified as **3.2** (39%) and **3.3** (36%). The ^{1}H NMR assignments for **3.2** correlated well with those reported by Yamada *at al*.[7] The ^{1}H NMR spectrum (Fig. 3.1) of **3.2** was characterised by the broad singlet of a phenolic proton at δ_H 5.11; the presence of the phenolic proton was also confirmed by a broad IR absorption band at 3564 cm^{-1}. The observed signals in the aromatic region of the ^{1}H NMR spectrum of **3.2** also confirmed *ortho*-prenylation; the expected two doublet signals of H-3 and H-5 were observed at δ_H 6.97 (*d*, *J* = 7.4 Hz) and δ_H 6.93 (*d*, *J* = 7.2 Hz), and a triplet for H-4 was observed at δ_H 6.74 (*t*, *J* = 7.4 Hz). On the other hand, the *O*-prenylated product **3.3** was indicated by the absence of a signal due to the phenolic proton in the ^{1}H NMR spectrum (Fig. 3.2). The downfield shift of the methylene protons 2H-1' was also diagnostic of *O*-prenylation. Due to oxygen-associated deshielding, the signal was observed at δ_H 4.51 in **3.3,** whereas in **3.2** it was observed at δ_H 3.33. The *bis*-prenylated (**3.4**) and *para*-prenylated (**3.5**) products were not observed.



3.2 **3.3** **3.4** **3.5**

Although the desired **3.2** was obtained, we were not satisfied with the associated yields. The reaction was repeated several times in an effort to reproduced the results obtained by Yamada *et al*.[7] The highest yields that were obtained under these conditions were 40% for the desired product **3.2** along with the side product **3.3** at 32%. Consequently, we decided to explore other reaction conditions. Kornblum *et al*. reported that solvation plays a significant role in the carbon alkylation of phenoxide ions.[13,14] According to Kornblum *et al*., the solvent used can be the deciding factor on whether *C*-alkylation or *O*-alkylation is observed.[13,14] Therefore, the solvent was changed; THF was used instead of diethyl ether. Unfortunately, the *O*-alkylated side product **3.3** was obtained as the major product, there was only a trace of the desired product **3.2**.

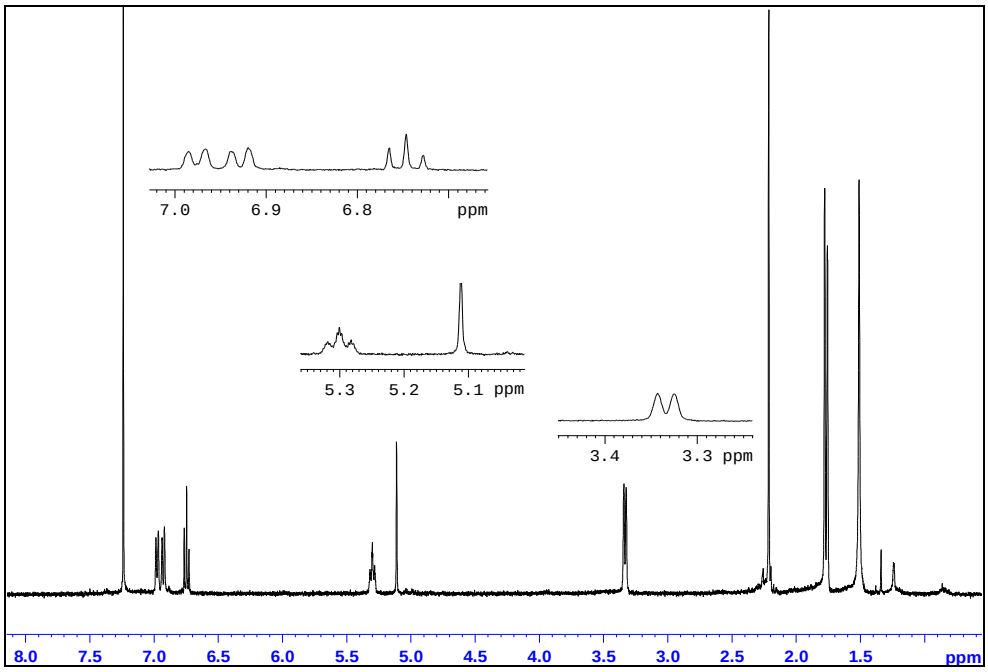


Figure 3.1: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **3.2**.

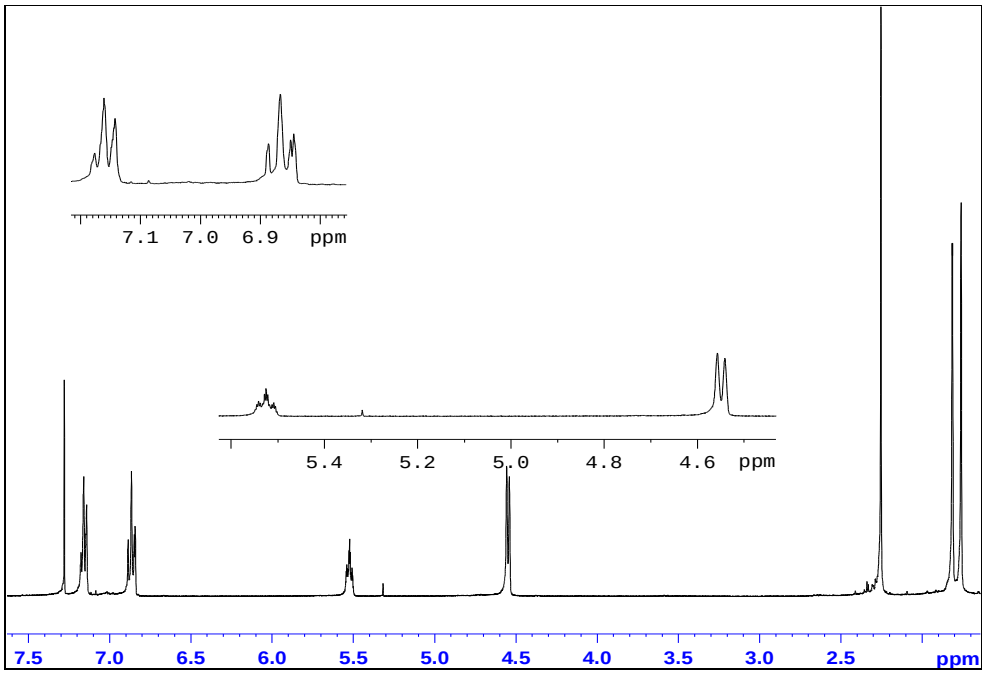
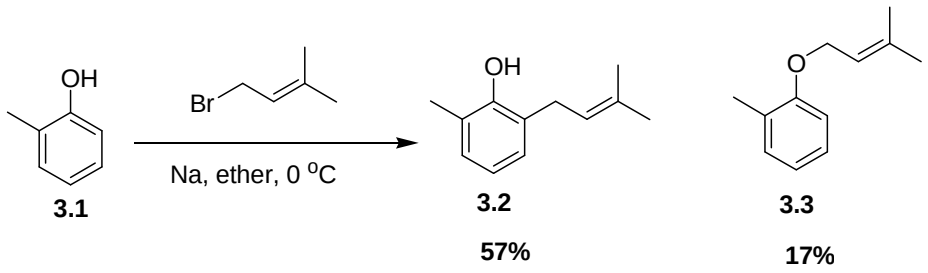


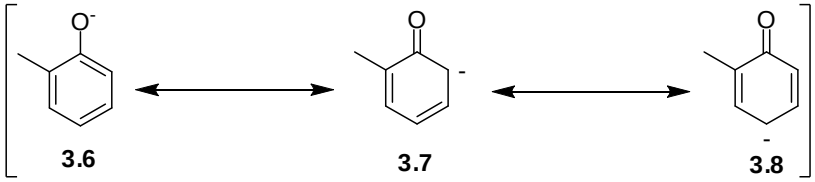
Figure 3.2: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **3.3**.

Since better results were obtained when using diethyl ether, it was decided to retain this solvent and manipulate other reaction conditions. The effect of heat was investigated by lowering the temperature. Therefore, the reaction was repeated with the initial temperature at 0 ^{o}C. The temperature was subsequently allowed to rise to room temperature and the reaction was stirred overnight. When the reaction was analysed, the desired product **3.2** was obtained as the major product (Scheme 3.5).



Scheme 3.5: *ortho*-Prenylation following the Yamada *et al*. protocol at 0 ^{o}C.[7,8]

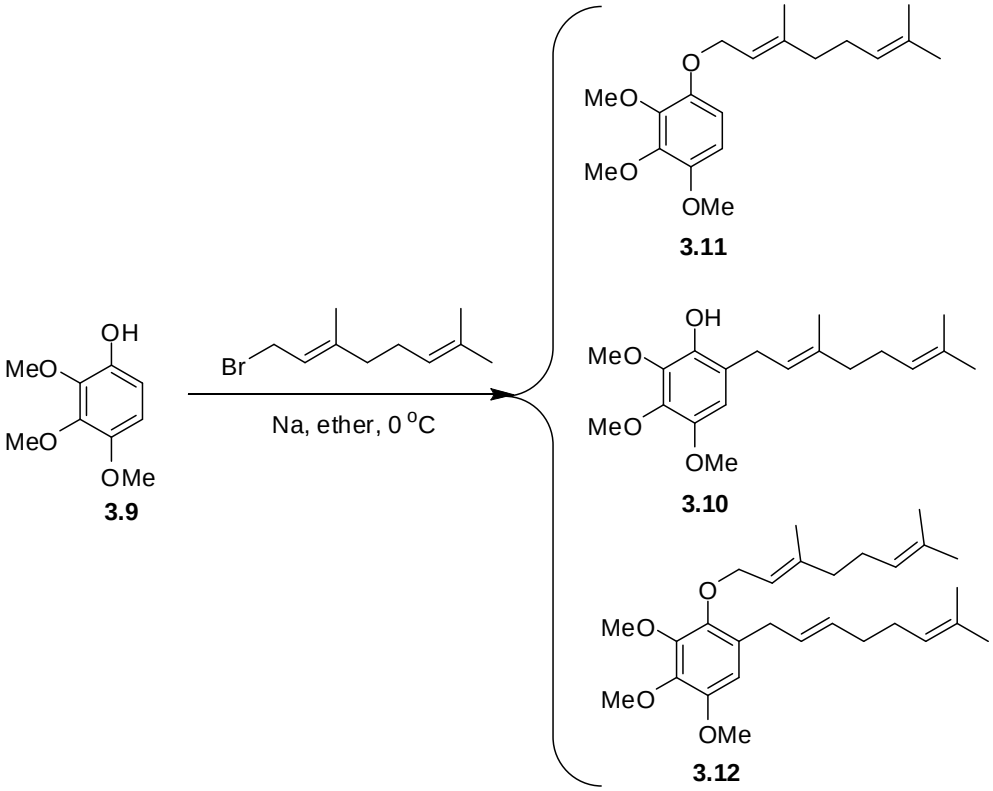
Since these results were consistent and reproducible, it suggested that *ortho*-prenylation of *ortho*-cresol is favoured by lower temperatures. The results obtained indicated that performing the reaction under these conditions promotes the formation of the *ortho*-carbanion **3.7**, while suppressing the emergence of the phenoxide ion **3.6** and para-carbanion **3.8** (Scheme 3.6). We then decided to explore temperatures below 0 ^{o}C, unfortunately there was no significant change in the yields.



Scheme 3.6: Intermediate carbanions that could be formed from *o*-cresol (**3.1**).

Since the formation of the *O*-alkylated product **3.3** could not be prevented, alternative methods were considered. Our decision was vindicated by the results reported by Shubina *et al*.[15], which came to our attention while still we were investigating the Yamada[7] protocol. Shubina *et al*.[15] performed *C*-alkylation of **3.9** with geranyl bromide using Yamada's *et al*.[7] protocol; the desired product **3.10** was obtained in low yields. When the reaction conditions were changed, the yield of the product did not increase. Instead **3.11**

and **3.12** emerged as products (Scheme 3.7).[16] Therefore, it was suspected that similar challenges would be encountered during the synthesis of analogues. Consequently, alternative synthetic strategies were considered.

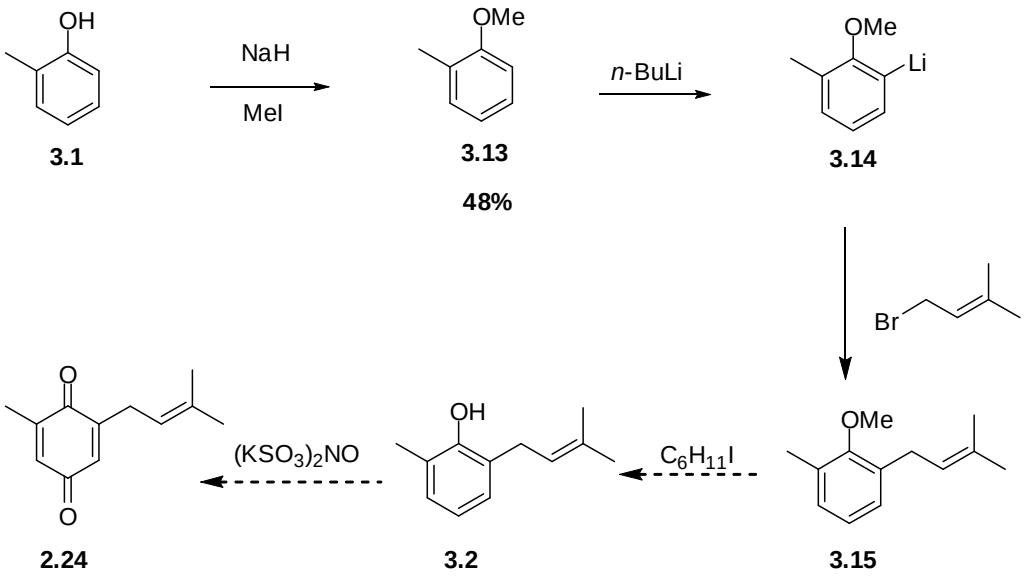


Scheme 3.7: Attempted synthesis of compound **3.10** by Shubina *et al***.** using the Yamada protocol.

3.3 Directed *ortho*-Metallation (D*o*M)

During the search for a new synthetic strategy, we targeted a synthetic approach that is characterised by regioselectivity and wide application. Subsequently, a directed *ortho*-metallation (D*o*M) reaction was considered because of the associated regioselectivity. Although the D*o*M transformation provided regiospecificity, it also increased the number of step involved in the proposed synthetic sequence (Scheme 3.8). The first step was the introduction of the directed metallation group (DMG). We decided to employ a methoxy (-OCH_3) group as the DMG since it has been widely used in D*o*M reactions. Amongst all

substrates available for investigation under the D*o*M protocol, anisole has been the preferred candidate.[17-21] Therefore, the first step was the methylation of *o*-cresol (**3.1**) and this transformation was first attempted with NaH and MeI. The product **3.13** was identified by the presence of the OCH_3 signal at δ_H 3.81 (3H, s) in the ^1H NMR spectrum. The presence of the OCH_3 was also supported by the signal at δ_C 63.9 (OCH_3) in the ^{13}C NMR spectrum. The product **3.13** was unfortunately obtained in an unsatisfactory yield of 48%. Therefore, an alternative method was considered and we decided to employ dimethyl sulfate (Me_2SO_4) as the methylating electrophile and Na_2CO_3 as the base to form the relevant phenoxide ion.[22] The product was successfully obtained in a yield of 96%.



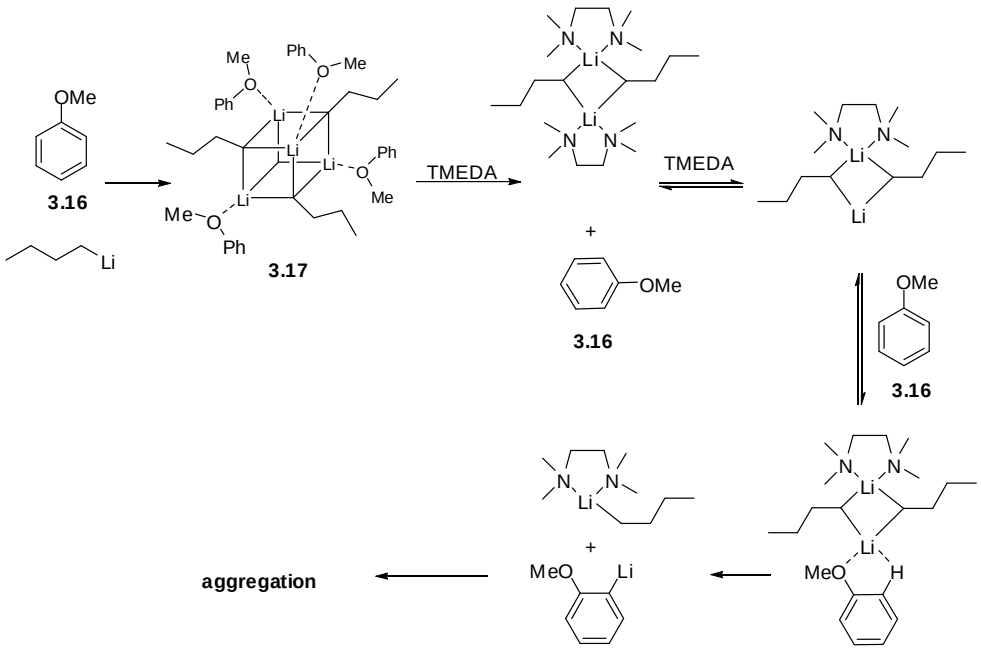
Scheme 3.8: Proposed synthetic sequence for **2.24** based on the D*o*M protocol.

The successful synthesis of **3.13** was subsequently followed by the attempted synthesis of **3.15**. Although the transformation from **3.13** to **3.15** was going to be achieved through a single reaction, it was envisaged to be a three-step process. The first step is the coordination of *n*-butyllithium dimer to the electron-rich anisole (**3.13**), followed by metal-proton exchange to give **3.14** by a simple D*o*M reaction. The last step is the coupling of the prenyl bromide.[17,18,23,24] The reaction was performed under anhydrous conditions in a N_2 atmosphere, since the presence of water would prevent the formation of the aryl organolithium product **3.14**. The first step was the deprotonation of compound **3.13** using the strong base *n*-BuLi (1 eq) to form **3.14**. This reaction was performed in dry diethyl

ether at -78 ^{o}C, it was subsequently followed by the *in situ ortho*-prenylation using the electrophilic prenyl bromide. Unfortunately, the desired product was not obtained.

The reaction was repeated several times, but product **3.15** was not obtained. Different amounts of *n*-BuLi were employed, but to no avail. Since there was uncertainty on whether it was the deprotonation step or the coupling step that was not working, limitations associated with the D*o*M reaction were considered. Some of the limitations were highlighted in the previous Chapter. One of the problems that could prevent the formation of compound **3.14** is the ability of organolithium reagents to form aggregates in organic solvents. As mentioned in Chapter Two, alkyllithium reagents have a tendency to form electron-deficient tetrameric aggregates (**3.17**) in Lewis base solvents such as diethyl ether. The formation of these aggregates (**3.17**) greatly decreases the basicity of alkyllithium species thus suppressing the metal-proton exchange process. In addition, a study of the structure of 2-lithioanisole indicated that the possible internal coordination between the lithium and the oxygen from the methoxy group highly reduces the nucleophilicity of anisole (**3.16**), thus making it almost unreactive to electrophiles.[25] Since a methoxy group was employed as a DMG, it was suspected that limitations relating to aggregate formation could be preventing the formation of the product **3.15**.

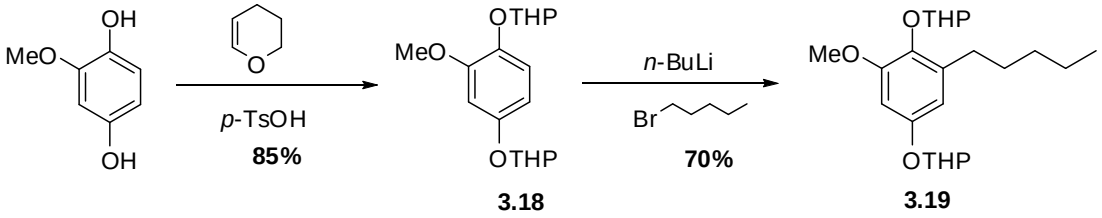
The formation of aggregates can be prevented by the use of bidentate ligands, such as TMEDA. It breaks down the aggregates, producing monomers and dimers in solution and consequently increasing basicity (Scheme 3.9). This subsequently increases the rate and the extent of metallation.[20,21,24] Therefore, we decided to repeat the reaction in the presence of TMEDA (1 *eq*.). Unfortunately, the use of TMEDA did not yield better results, as the coupled product was still not observed. Different amounts of TMEDA were employed, but the results were still the same, no product. Because the nature of the resulting aggregates is determined by the solvent employed, we decided to change the solvent from diethyl ether to THF. This strategy also did not yield the desired results.



Scheme 3.9: Dissociation of the tetrameric organolithium with TMEDA.

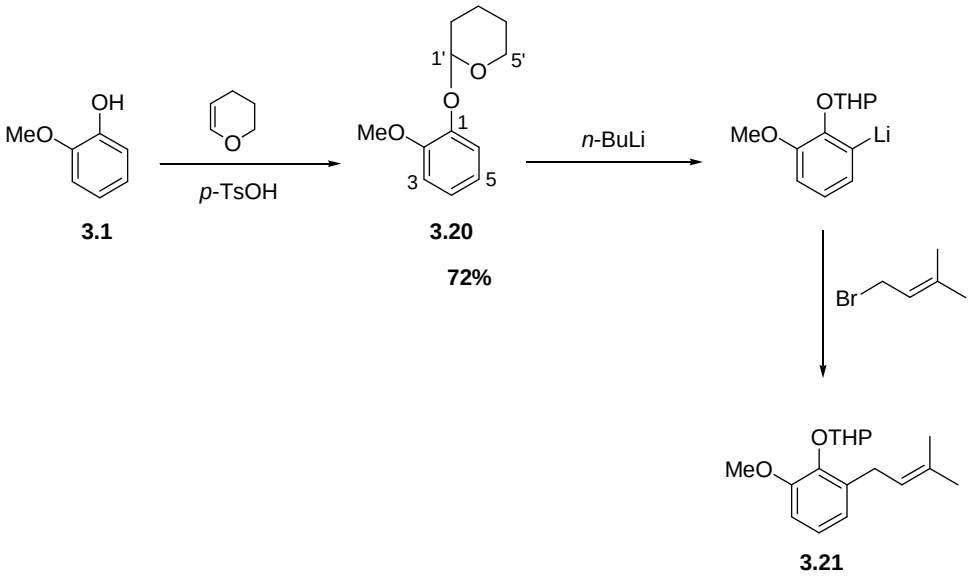
Since the employed strategies did not yield positive results, alternative methods were considered. As it was mentioned in the previous Chapter, sometimes, in order to attain coupling, the lithiated species need be activated. Subsequently, a method by Bouzbouz and Kirschleger was adopted, where they activated the lithiated species by the formation of a cuprate intermediate.[9,26] The reaction was repeated using similar conditions to those reported by Bouzbouz and Kirschleger, but instead of *sec*-BuLi, *n*-BuLi was used (Scheme 2.5).[9] Unfortunately, despite several attempts, product **3.15** was not obtained.

Although positive results were not obtained with the D*o*M protocol, a different DMG was considered, since some of the complications that were encountered could be associated with the use of methoxy as DMG. Guided by the results reported by Brondani *et al*., THP was employed as the DMG.[27] These authors employed a D*o*M protocol to obtain **3.19** from **3.18** in a yield of 70% (Scheme 3.10).[6,27,28]



Scheme 3.10: Brondani's synthesis of **3.19** from **3.18** using the D*o*M strategy.[27]

The first step was the protection of the phenolic hydroxy group using dihydropyran in the presence of a catalytic amount of anhydrous *p*-toluenesulfonic acid (*p*-TsOH) (Scheme 3.11). The product **3.20** was successfully obtained in a yield of 72%. The ^{1}H NMR spectroscopic analysis confirmed the formation of **3.20** by the absence of the broad singlet due to the phenolic proton. The expected downfield 1H triplet signal due to the anomeric proton (H-1') was also observed at δ_H 5.45 (t, J = 3.1 Hz,), it integrated for one proton. The signals due to the THP carbon atoms were also observed in the ^{13}C NMR at δ_C 96.1 (C-1'), 62.0 (C-5'), 30.6 (C-2'), 25.3 (C-4'), 19.0 (C-3'). The HRMS (ESI$^+$) analysis confirmed the molecular formula of **3.20** ([M+Na]$^+$ obsd. 215.1048, calc. for $C_{12}H_{16}O_2Na$ 215.1047). The subsequent step was the D*o*M protocol, where *n*-BuLi was employed as the base. Unfortunately, despite several attempts, the desired product could not be isolated. The reaction conditions were subsequently manipulated by adding TMEDA and CuI, unfortunately no product was observed.

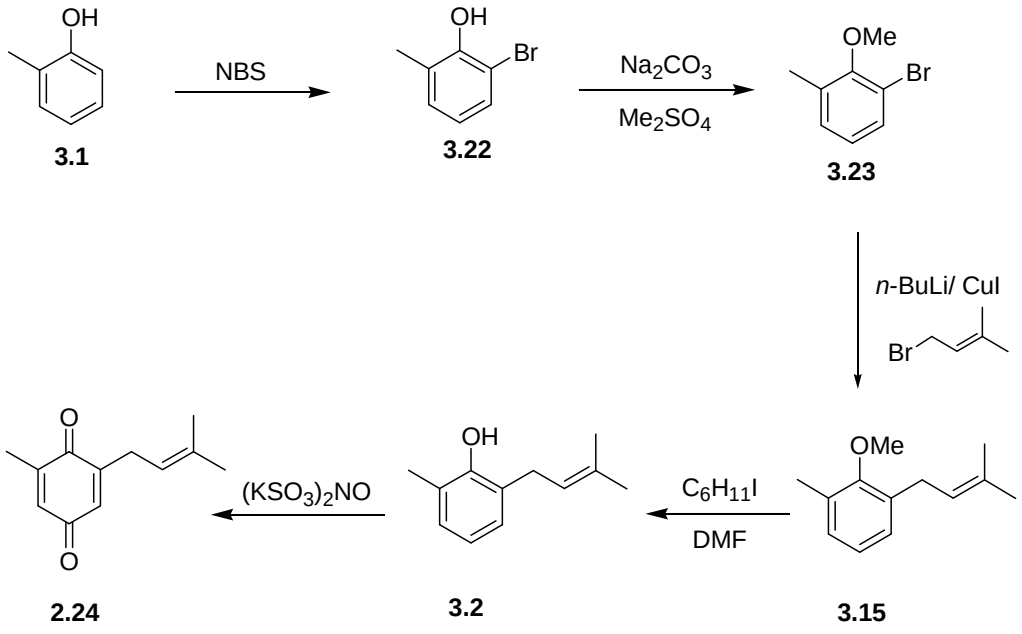


Scheme 3.11: The proposed synthetic strategy to **3.21**.[27]

Due to the discouraging results that were recorded with all attempted coupling using the D*o*M protocol, the use of this protocol was suspended. Therefore, a different synthetic route towards 2-methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone (**2.24**) was formulated.

3.4 Metal-Halogen Exchange (MHE) Mediated Transformation.

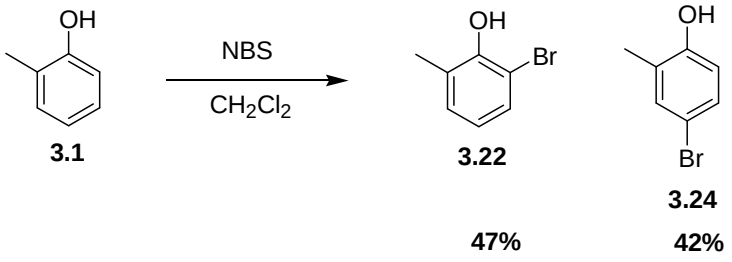
Guided by the requirement for a synthetic approach that permitted *C*-alkylation without the formation of regioisomers, metal-halogen exchange became a plausible option. In a MHE-mediated *C*-alkylation, the issue of regiocontrol is reassigned to the preparation of the *ortho*-halogenated species.[6] Terashima *et al.* successfully employed MHE mediated transformation to achieve regioselective *C*-alkylation.[29] The reported successful synthesis of prenylated aromatic compounds by Odejinmi and Wiemer further confirmed MHE-mediated transformation as a pragmatic option.[30] Therefore, a synthetic route based on MHE was formulated for the synthesis of **2.24** (Scheme 3.12).



Scheme 3.12: Proposed MHE-based synthesis of **2.24**

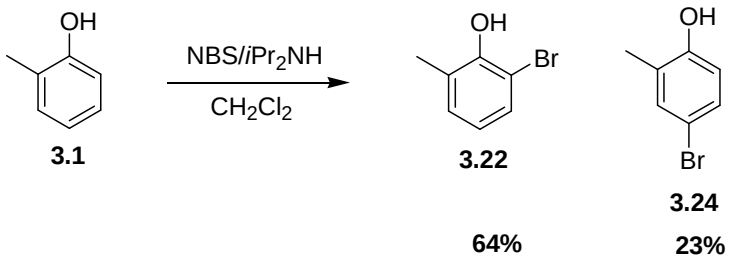
The first step was the synthesis of the *o*-brominated **3.22**. There are a variety of methods that have been employed to achieve bromination of phenols.[31-36] The most prominent one has been the treatment with bromine in different solvents, but the formation of a mixture of regioisomers sometimes emerge; thus decreasing the yield of the desired product.[32]

Therefore, this method could not be employed in the synthesis of **3.22**, since regioselective *o*-bromination was the target. Carreño *et al*. reported that regioselective *o*-bromination of *o*-cresol (**3.1**) can be achieved with *N*-bromosuccinimide (NBS) in CH_2Cl_2.[32] Consequently, this synthetic sequence was employed in the synthesis of **3.22**, unfortunately the results obtained did not correspond with the results reported by Carreño *et al*.[32] The desired product **3.22** was obtained in an unsatisfactory yield along with the *para*-brominated regioisomer **3.24** in almost the same amount (Scheme 3.13). The two products were identified and differentiated by ^{1}H NMR analysis. As expected, the ^{1}H NMR spectrum of **3.22** was characterised by the presence of the triplet at δ_H 6.69 (1H, t, J = 7.7 Hz) and two doublets at 7.27 (1H, d, J = 7.9 Hz) and 7.04 (1H, d, J = 7.5 Hz).



Scheme 3.13: Bromination of *o*-cresol (**3.1**) using NBS in CH_2Cl_2, after Carreño *et al*.[32]

Since the formation of the *para*-regioisomer **3.24** could not be prevented with this approach, a different synthetic route was considered. Subsequently, a method reported by Fugisaki *et al.* came to our attention.[37,38] A phenol was treated with NBS in the presence of a secondary amine (*i*-Pr_2NH) at room temperature in CH_2Cl_2 and afforded the *o*-brominated regioisomer as a major product. The *para*-brominated regioisomer and polybrominated species were recorded in very low yields. There are also earlier reports on the application of amines during *o*-bromination, but the method by Fugisaki *et al*. was preferred since it uses mild conditions. Therefore, *o*-bromination of *o*-cresol was performed using these conditions and the desired **3.22** was obtained as a major product with a yield of 64%. The *para*-brominated regioisomer **3.24** was isolated in a yield of 23% (Scheme 3.14). When the temperature was decreased to 0 ^{o}C, the desired product **3.22** was obtained in a better yield of 73%.



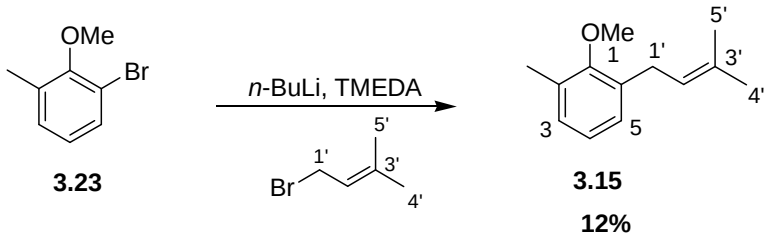
Scheme 3.14: Bromination of *o*-cresol (**3.1**) using NBS in the presence of *i*-Pr_2NH.

It was also interesting to note that the presence of undissolved NBS in the reaction mixture promoted the formation of the *para*-regioisomer, even in the presence of *i*-Pr_2NH. This indicated that the reaction between solid NBS and *o*-cresol superseded the reaction that should first take place between *i*-Pr_2NH and NBS. In order to promote *o*-bromination, the *N*-bromoamine (*i*-Pr_2NBr) should be generated, which first forms a strong hydrogen bond with *o*-cresol (**3.1**) to afford bromination at the *ortho*-position. Therefore, in order to promote the formation the *i*-Pr_2NBr, NBS should be completely dissolved in CH_2Cl_2 before mixing it with *o*-cresol (**3.1**) and *i*-Pr_2NH.

The successful preparation of 2-bromo-6-methylphenol (**3.22**) was subsequently followed by the synthesis of 2-bromo-6-methylanisole (**3.23**). The method that was used to synthesise 2-methylanisole (**3.13**) was also employed in the synthesis of **3.23**.[22] The product **3.23** was obtained in a good yield of 95%. The presence of a signal at δ_H 3.85 (3H, s) and δ_C 60.1 in the ^1H and ^{13}C NMR spectra confirmed the presence of the methoxy group. The HRMS (ESI^+) analysis also confirmed the molecular formula of **3.23** (obsd. *m/z* 200.9841, calc. for $C_8H_{10}O^{77}Br$ *m/z* 200.9842).

The successful synthesis of the two precursors **3.22** and **3.23** created the platform for the exploration of the MHE-facilitated transformation. The reaction was first attempted without the addition of CuI, but TMEDA was added to prevent the formation of aggregates (Scheme 3.9). The reaction was performed at various temperatures, while the solvent, diethyl ether, and n-BuLi were fixed. When the reaction was performed at temperatures between -20 ^oC and -78 ^oC, there was no product observed, even when CuI was added.[29] The product **3.15** was only observed at temperatures between 0 ^oC and -10 ^oC, but in low yields. A disappointing yield of 12% was recorded as the highest yield obtained when the

reaction was performed at 0 ^{o}C (Scheme 3.15). The addition of CuI unfortunately did not improve the yield. The structure of **3.15** was elucidated using NMR spectroscopy. The presence of a signal at δ_H 3.35 (2H, d, J = 7.2 Hz) in the ^{1}H NMR spectrum indicated successful coupling (Fig. 3.3). The methylene protons (2H-1') signal which was recorded at δ_H 3.35 had the expected upfield shift from δ_H 4.02 that was observed for the starting material, prenyl bromide. The molecular formula of **3.15** was also confirmed by HRMS (ESI$^+$) analysis (obsd. *m/z* 191.1432, calc. for $C_{13}H_{19}O$ *m/z* 191.1433).



Scheme 3.15: Synthesis of **3.15** using the MHE protocol at 0 ^{o}C

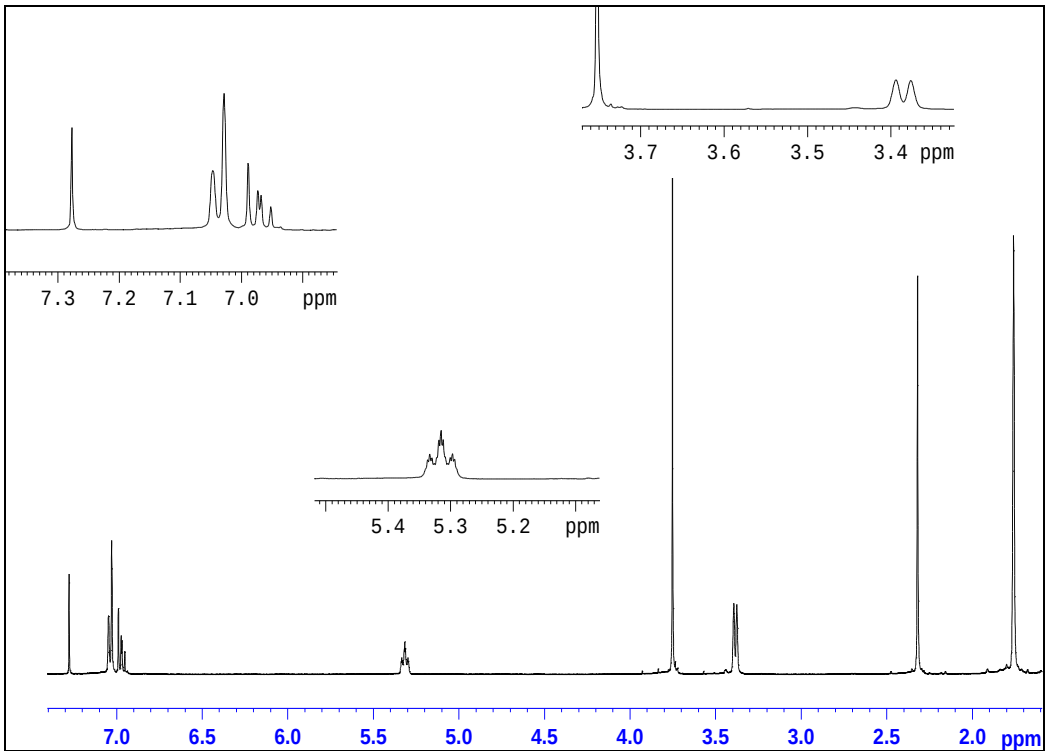
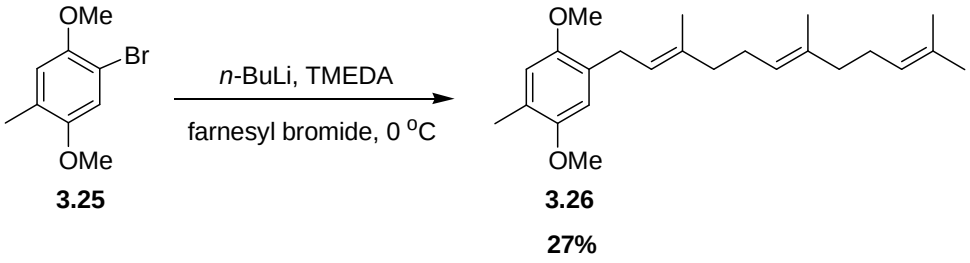


Figure 3.3: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **3.15**.

Although MHE-mediated transformation delivered the correct regioselectivity, the yield obtained was very discouraging. While attempting to repeat the reaction using a benzylated precursor as reported by Odejinmi and Wiemer, the results recorded by Scheepers *et al*. were discouraging.[30,39] Scheepers *et al*. reported that the attempted MHE reaction using a benzylated precursor was unsuccessful. Although Scheepers *et al*. subsequently synthesised **3.26** from a methylated precursor (**3.25**), the reported yield was low (Scheme 3.16).[39] Therefore, it became apparent that a different synthetic sequence had to be followed in order to obtain better yields.

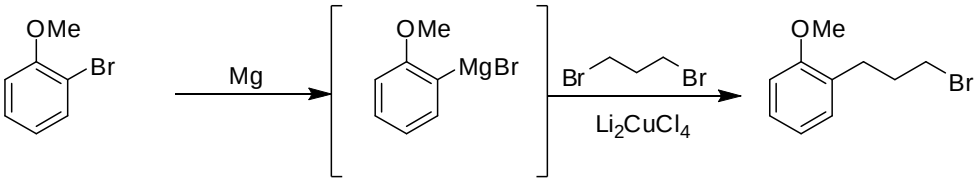


Scheme 3.16: Synthesis of **3.26** using a MHE-mediated transformation as reported by Scheepers *et al*.[39]

Unfortunately, when our MHE reaction was performed, Klein *et al*. had not yet published their work on factors influencing prenylation of an aromatic organolithium compound. Klein *et al*. established that the formation of aggregates persist even in the presence of TMEDA. They also discovered that alteration of the sequence in which the reactants are added significantly improves the yield. Although the reaction was performed under strictly anhydrous conditions, they decided that to test the role that is played by traces of water that could be present. Therefore, the sequence of adding reactants was reversed; excess *n*-BuLi and TMEDA were initially combined with diethyl ether, in order to quench traces of water and to prevent protonation of the organolithium intermediate that forms through metal-halogen exchange. Consequently, the yields of the reaction improved from a variable 5-40% to a consistent 65%.[40]

3.5 Copper (II)-Mediated Regioselective Alkylation

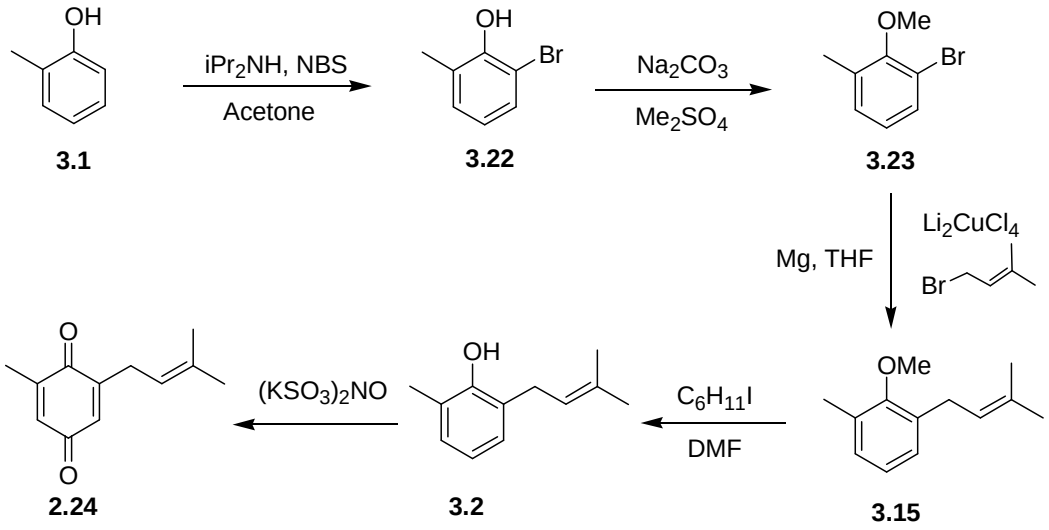
Although the *o*-alkylation step was proving to be challenging, the work by Burns *et al*. was very encouraging.[41] These authors achieved *o*-alkylation of anisole with 1,3-dibromopropane in 70-80% yields. *o*-Bromoanisole (**3.27**) was first reacted with magnesium to form a Grignard reagent, (2-methoxyphenyl)magnesium bromide (**3.28**), which was subsequently reacted with 1,3-dibromopropane in the presence of catalytic amounts of Li_2CuCl_4 to obtain 2-(3-bromopropyl)anisole **3.29** (Scheme 3.17).[41]



3.27 **3.28** **3.29**

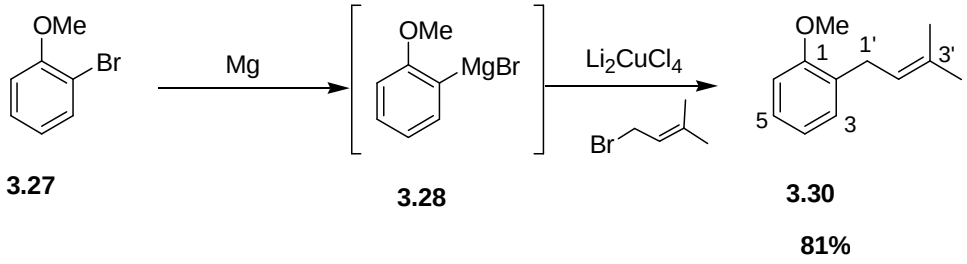
Scheme 3.17: Burns *et al.* regioselective *o*-alkylation.[41]

It was also interesting to note that Li *et al*. successfully employed the Burns copper-mediated transformation in order to synthesise **3.29** in a yield of 71%.[42,43] These results demonstrated a significant improvement when compared with the results by Scheepers *et al*. performing the same transformation using a lithium-halogen exchange reaction (Scheme 3.15).[39] Consequently, a synthetic route towards **3.15** was formulated based on Burns' copper-mediated transformation. (Scheme 3.18).



Scheme 3.18: Proposed synthetic route towards **2.24** based on Burns *et al.* protocol.[41]

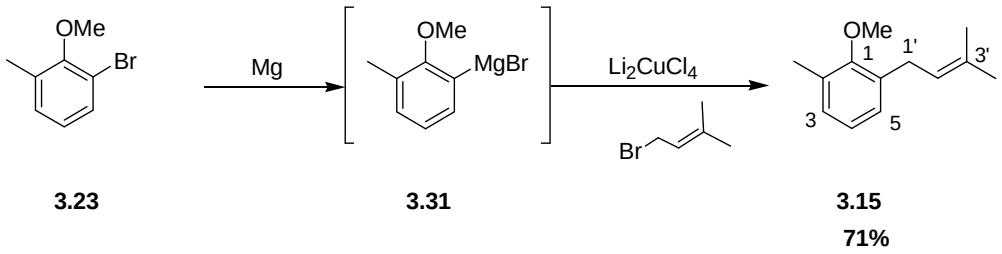
A model reaction was formulated in order to verify the prenyl bromide coupling using Burns's protocol (Scheme 3.15). *o*-Bromoanisole (**3.27**) was reacted with magnesium in order to form a Grignard-type reagent (**3.28**) (Scheme 3.16). The resulting Grignard reagent (**3.28**) was cannulated into a solution of Li_2CuCl_4 and prenyl bromide in order to achieve transmetallation. Subsequent coupling lead to the product **3.30** which was obtained in a yield of 81% (Scheme 3.19).[41,42]



Scheme 3.19: Synthesis of model product **3.30**.

Successful coupling was first indicated by a signal at δ_H 3.34 (2H, d, J = 7.7 Hz) due to the methylene protons (2H-1') observed in the ^{1}H NMR spectrum of **3.30**. The downfield aromatic region integrated for four protons. The molecular formula of **3.30** was also confirmed by HRMS (ESI$^+$) analysis ([M+H]$^+$ obsd. *m/z* 177.1276, calc. for $C_{12}H_{17}O$ 177.1275). The successful synthesis of **3.30** was subsequently followed by the synthesis of

3.15. The synthesised 2-bromo-6-methylanisole (**3.23**) was reacted with Mg to form **3.31** and was subsequently coupled with prenyl bromide. The product **3.15** was obtained with a reproducible yield of 71% (Scheme 3.20), which was much better than the 12% yield that was obtained by the lithium MHE-mediated transformation.



3.23 **3.31** **3.15**
71%

Scheme 3.20: Synthesis of **3.15** using Burns' protocol.[41]

The subsequent step was the deprotection of the aryl methyl ether **3.15**. Aryl methyl ethers can tolerate a variety of reagents and experimental conditions, but their high stability creates a problem when removing the protecting group.[44] Harsh conditions such as strong acids or bases, alkali metals, or oxidising reagents and reducing reagents are generally employed in the cleavage of methyl ethers.[44-51] These conditions often result in undesirable products and low reaction yields. Therefore, there has been a great desire amongst chemists for the development of a synthetic protocol characterised by chemoselectivity and regioselectivity. The use of Lewis acids such as BBr_3 as a demethylation reagent has been prevalent because of the associated relatively mild conditions, but this method has been characterised by long reaction times.[47]

Consequently Zou *et al*. developed a demethylation protocol characterised by relative mild reaction conditions and shorter reaction times.[44] Zou *et al*. employed iodocyclohexane in DMF under reflux to achieve the demethylation of 5,7-dimethoxy-4-methylphthalide (**3.32**) over 14 h in 91% yield. [52] The results obtained by these authors demonstrated significant improvement when compared with the results obtained by Canonica *et al*. while performing the same transformation using different synthetic protocols (Scheme 3.21).[44,52]

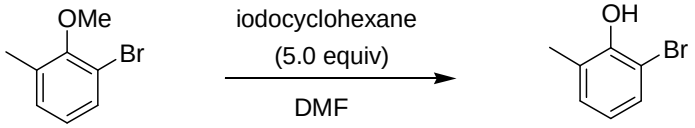
3.32

Method A: BBr_3, rt, 8 d, 70% yield.

Method B: 57% HI, anhyd P, Ac_2O, reflux, 12 h, 49% yield.

Scheme 3.21: Canonica *et al*. approach to the demethylation of **3.32**.[52]

Therefore, Zou's approach was adopted for the demethylation of **3.15**. In order to probe this protocol, a model reaction was performed. Demethylation of 2-bromo-6-methylanisole (**3.23**) was undertaken as the model reaction using the Zou conditions.[44] The demethylated product **3.22** was successfully obtained in a yield of 86% (Scheme 3.22). Successful demethylation was confirmed by the presence of a broad singlet at δ_H 5.54 which coincided with the disappearence of the signal due to OCH_3 in the ^1H NMR spectrum of **3.22**. Therefore, the same procedure was employed in the demethylation of **3.15**. The desired product was not obtained, although the reaction was repeated several times. The product was also not obtained even when the reaction was performed using different equivalents of iodocyclohexane.



3.23 **3.22**

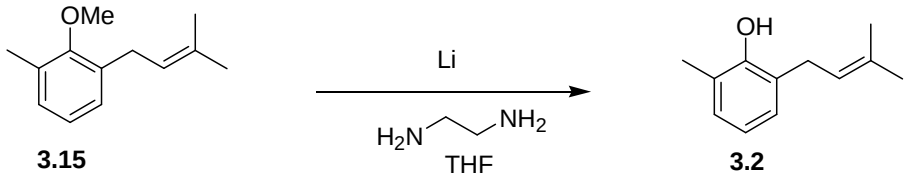
86%

Scheme 3.22: Demethylation of 2-bromo-6-methylanisole (**3.23**).

Since the desired product **3.2** was not obtained, alternative methods were considered in order to achieve the cleavage of the aryl methyl ether **3.15**. A synthetic approach by Fang *et al*. was considered. The cleavage of the aryl methyl ether was performed by Fang *et al*. using LiCl in DMF under microwave irradiation.[45] Using microwave irradiation significantly improved the reaction efficiency. Fang's approach was subsequently

employed in an attempt to demethylate **3.15.** Unfortunately product **3.2** was not formed. Prolonging the reaction time and also changing the microwave parameters such as temperature did not yield the required results.

The search for a demethylation procedure led us to a paper by Shindo *et al*.[53] These authors reported successful demethylation of aryl methyl ethers, using lithium and ethylenediamine in THF under mild conditions.[53,54] Although there is no generally accepted mechanism for this reaction, the yields obtained were very encouraging.[53] As a result Shindo's method was the subsequent synthetic strategy that was employed in order to obtain demethylation of **3.15** (Scheme 3.23).



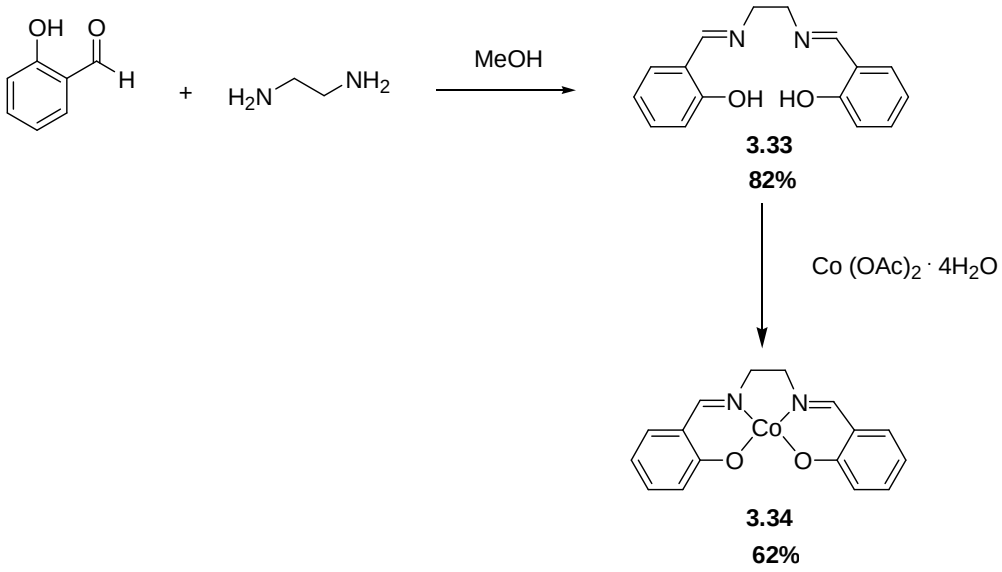
3.15 **3.2**

84%

Scheme 3.23: Demethylation of **3.15** using Shindo *et al*. approach.[53]

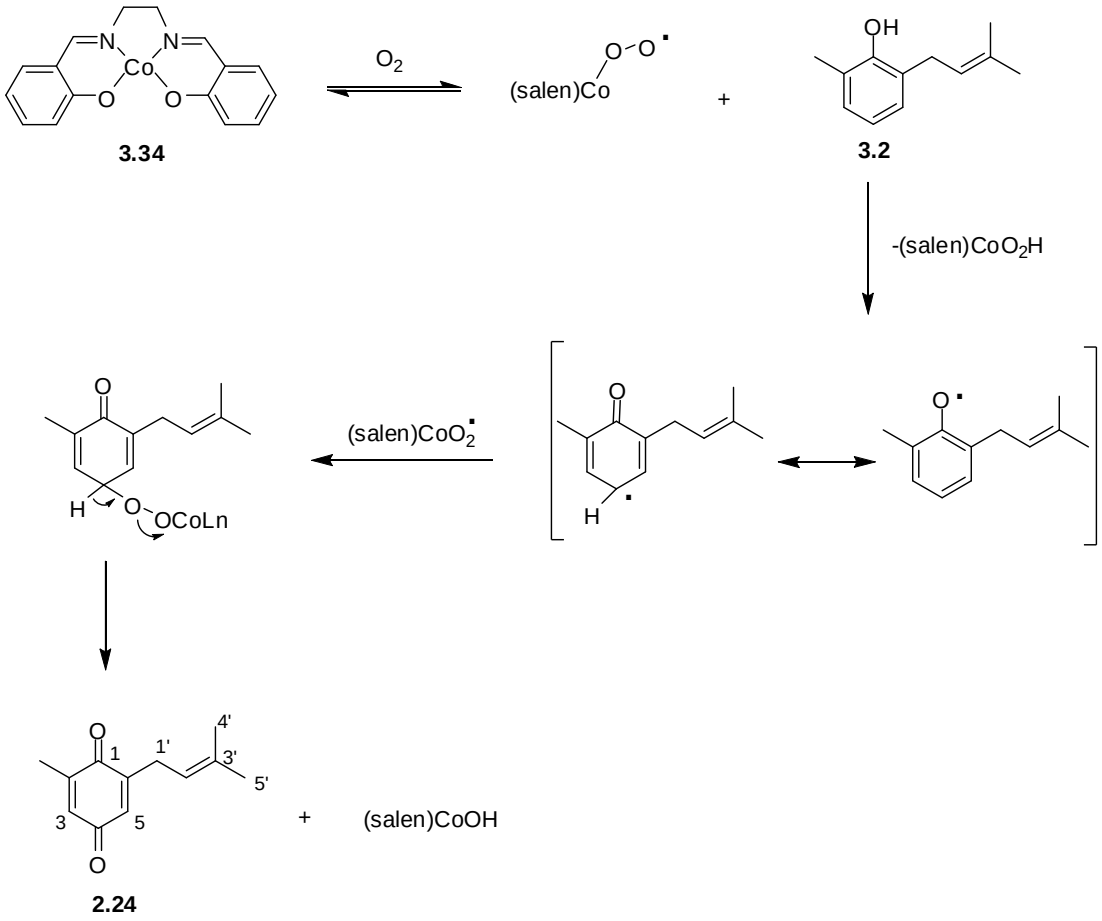
A solution of lithium (5 eq) and ethylenediamine (7 eq) in THF under N_2 at 0 ^oC was added **3.15** (1 eq). The addition of the reagents was preceded by degassing in order to remove traces of oxygen, since oxygen was reported to prevent formation of the desired product.[53] This has also been regarded as an indication that the demethylation occurs by an electron transfer reaction mechanism. The reaction mixture was allowed to stir at 0 ^oC for 2 h to give a deep blue reaction mixture. The reaction products were purified by silica column chromatography to give 2-methyl-6-(3-methyl-2-butenyl)phenol (**3.2**) in 84% yield. The product **3.2** was confirmed by the presence of a broad singlet in the ^1H NMR spectrum (Fig. 3.1) at δ_H 5.11 due to the phenolic proton. The observed IR absorption band at 3564 cm^{-1} also indicated the presence of OH functionality. The molecular formula of **3.2** was also confirmed by HRMS (ESI$^-$) analysis ([M-H]$^-$ obsd. *m/z* 175.1118, calc. for $C_{12}H_{15}O$ 175.1123).

The successful synthesis of **3.2** was subsequently followed by oxidation to afford the target compound **2.24** (Scheme 3.16). Fremy's salt $(KSO_3)_2NO$ was used as the oxidant to obtain the product in a yield of 49%.[4,55] The moderate yield obtained prompted a search for another method that would afford better yields. The cobalt-Schiff base complex, [bis-(salicylidene)ethylenediamine]cobalt (salcomine) (**3.34**), prevailed as the oxidant that would probably give better yields.[56-64] Therefore salcomine [(salen)Co] (**3.34**) was synthesised using a two-step synthetic protocol (Scheme 3.24).



Scheme 3.24: Synthesis of salcomine (**3.34**).

The first step was the synthesis of the Schiff base ligand, *N,N'*-ethylene-bis-salicylidenimine (**3.33**). The product **3.33** was obtained in a yield of 82%. The Schiff base ligand **3.33** was subsequently reacted with $Co(OAc)_2{\cdot}4H_2O$ to form salcomine (**3.34**).[57] The successfully prepared salcomine was subsequently used to synthesise **2.24.** The reaction was performed in CH_3CN while exposed to atmospheric oxygen. The use of pure oxygen did not institute a significant change on the yield. Scheme 3.25 shows a proposed mechanism for the oxidation of **3.2** using salcomine in the presence of O_2.[65]



Scheme 3.25: Mechanism for the oxidation of **3.2** to afford the 1,4-benzoquinone **2.24**.

The target compound **2.24** was obtained in a yield of 65%. The ^{1}H NMR spectrum of **2.24** was characterised by the presence of two downfield singlets at δ_H 6.50 and 6.42 due to H-3 and H-5 (Fig. 3.4). The presence of a signal due C-1 and C-4 at δ_C 188.0 in the ^{13}C NMR spectrum confirmed the presence of the benzoquinone moiety (Fig. 3.5). This was further confirmed by the IR absorption band at 1615 cm^{-1}. The ^{1}H and ^{13}C NMR data for synthetic **2.24** are identical with those reported for the natural product isolated from *Gunnera perpensa.*[1]

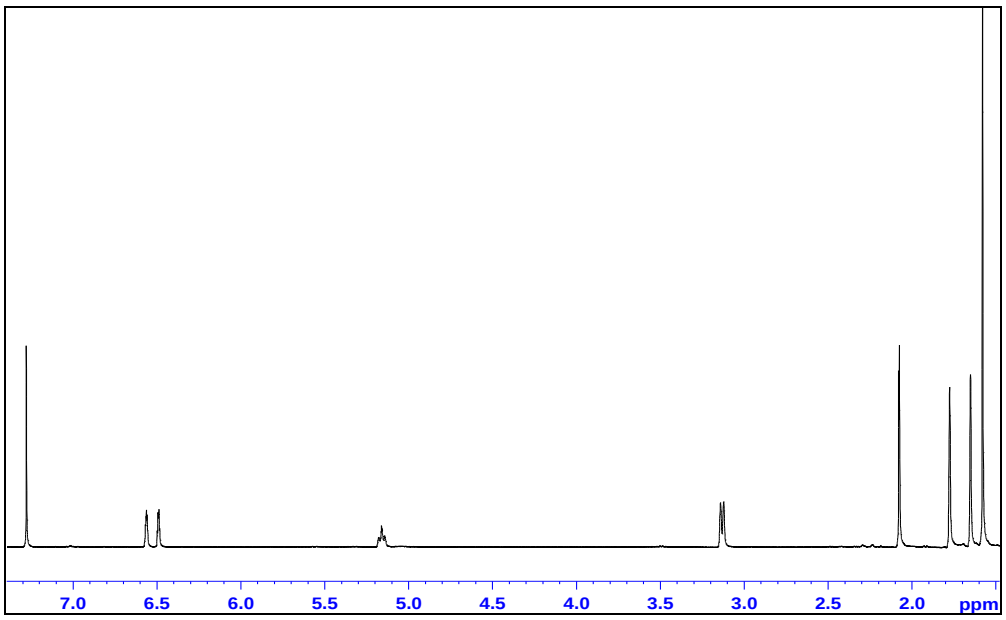


Figure 3.4: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **2.24**.

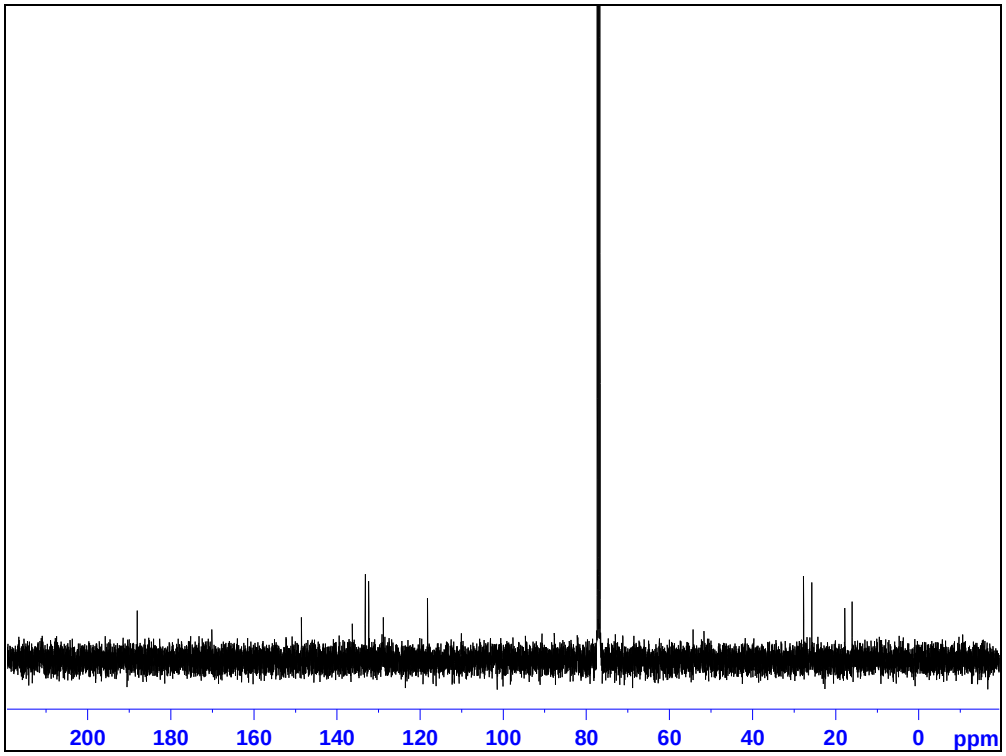
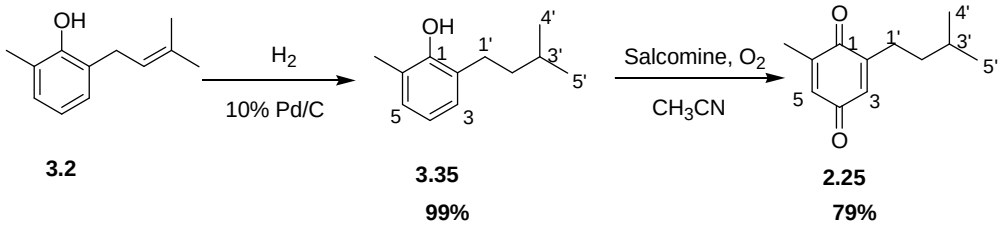


Figure 3.5: ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **2.24**.

3.6 Synthesis of 2-isopentyl-6-methylbenzo-1,4-quinone (2.25)

The synthesis of 2-isopentyl-6-methylbenzo-1,4-quinone (**2.25**) was achieved in a two-step process (Scheme 3.23) . The first was the Pd/C catalysed hydrogenation of **3.2** to obtain 2-isopentyl-6-methylphenol (**3.35**). The product **3.35** was obtained in a quantitative yield. ^{1}H NMR was used to confirm successful reduction, an upfield shift of signals due to H-1' and H-2' was observed with the expected splitting pattern. The signals for H-1' and H-2' were observed at δ_H 2.61 (2H, br t, J = 8.0 Hz) and 1.52 (2H, m) in the ^{1}H NMR spectrum of **3.35** confirming successful reduction of the double bond. The molecular formula of **3.35** was confirmed by HRMS (ESI$^-$) **(**[M-H]$^-$ obsd. *m/z* 177.1275, calc. for $C_{12}H_{17}O$ 177.1279). The final product was synthesised by oxidising **3.35** with salcomine to obtain a 1,4-benzoquinone **2.25** in a yield of 79%**.** The ^{1}H NMR spectrum (Fig. 3.6) of 2.25 was characterised by the presence of two downfield singlets at δ_H 6.56 (1H, s) and 6.51 (1H, s) due to H-3 and H-5. The IR absorption band at 1648 cm^{-1} confirms the presence of the benzoquinone moiety. This was further confirmed by the presence of the signal due to C-1 and C-4 at δ_C 188.1 in the ^{13}C NMR spectrum (Fig. 3.7).



Scheme 3.26: Synthesis of 2-isopentyl-6-methylbenzo-1,4-quinone (**2.25**).

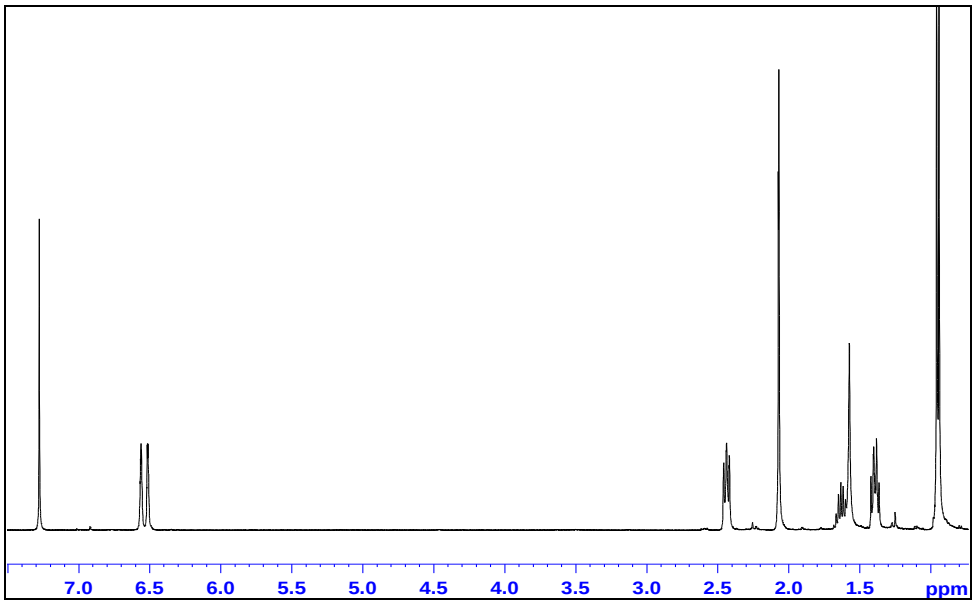


Figure 3.6: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **2.25**.

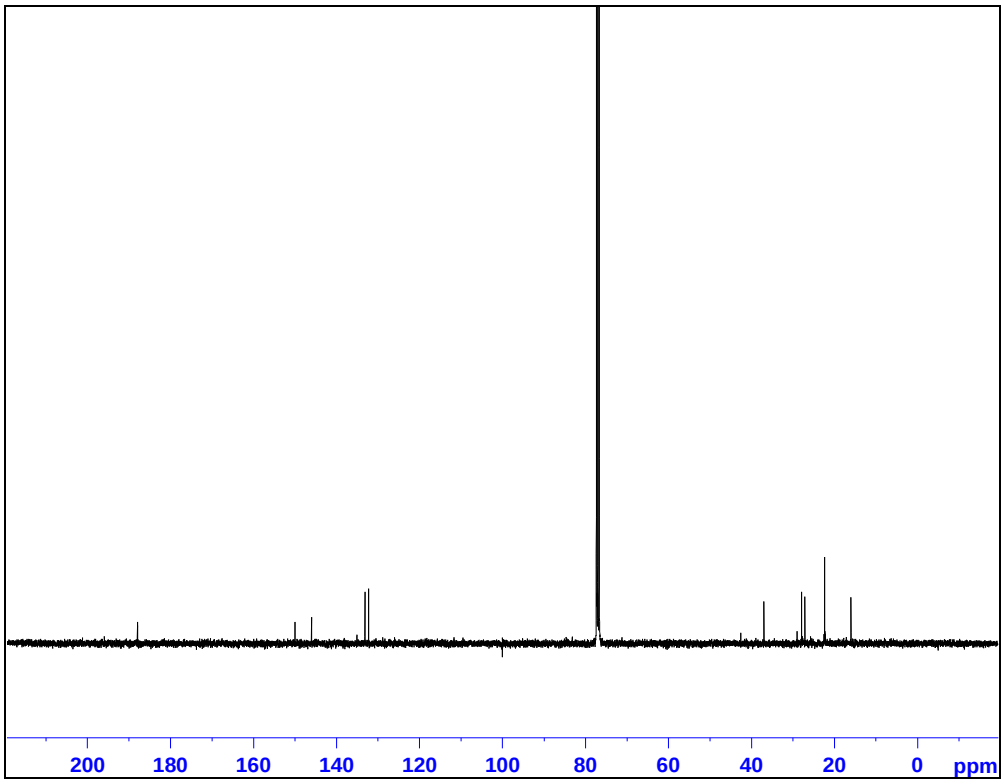
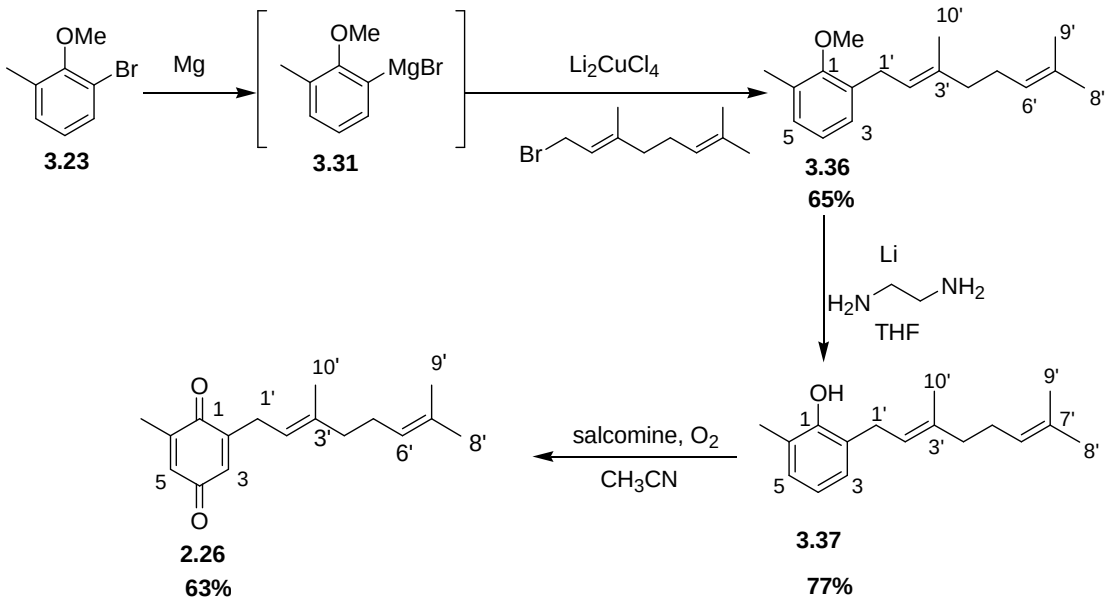


Figure 3.7: ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **2.25**.

3.7 Synthesis of 2-(3,7-dimethylocta-2,6-dienyl)-6-methyl-1,4-benzoquinone (2.26).

The synthetic route towards the synthesis of 2-(3,7-dimethyl-octa-2,6-dienyl)-6-methyl-1,4-benzoquinone (**2.26**), was similar to the one followed during the synthesis of 2-methyl-6-(3-methyl-2-butenyl)benzo-1,4-quinone. The only difference was the use of geranyl bromide instead of prenyl bromide for the regioselective *o*-alkylation step. Therefore, the previously synthesised **3.23** was reacted with Mg to form a Grignard type reagent **3.31**. The Grignard reagent was subsequently transmetallated with Li_2CuCl_4 and finally coupled with geranyl bromide to give **3.36** in 65% yield (Scheme 3.27).[41,42]



Scheme 3.27: Synthesis of 2-(3,7-dimethylocta-2,6-dienyl)-6-methyl-1,4-benzoquinone (**2.26**).

^{1}H NMR analysis confirmed successful coupling by the presence of the signal at δ_H 3.39 (2H, d, J = 7.1 Hz), due to the methylene protons (2H-1'). The signal demonstrated the expected upfield shift since the signal was observed at δ_H 4.00 in the starting material (geranyl bromide) ^{1}H NMR spectrum. The successful synthesis of **3.36** was subsequently

followed by demethylation using Shindo *et al.*'s approach.[53] The product **3.37** was obtained in a yield of 77%. The ^{1}H NMR spectrum of **3.37** demonstrated the expected absence of signal due to the OMe group and the presence of a broad singlet at δ_H 5.18 due to the phenolic proton (Fig. 3.8). The presence of the phenolic moiety was also confirmed by the IR absorption band observed at 3536.2 cm^{-1}. The molecular formula of **3.37** was confirmed by HRMS (ESI^{+}) ([M+Na]$^{+}$ obsd. *m/z* 267.1726, calc. for $C_{17}H_{24}ONa$ 267.1725).

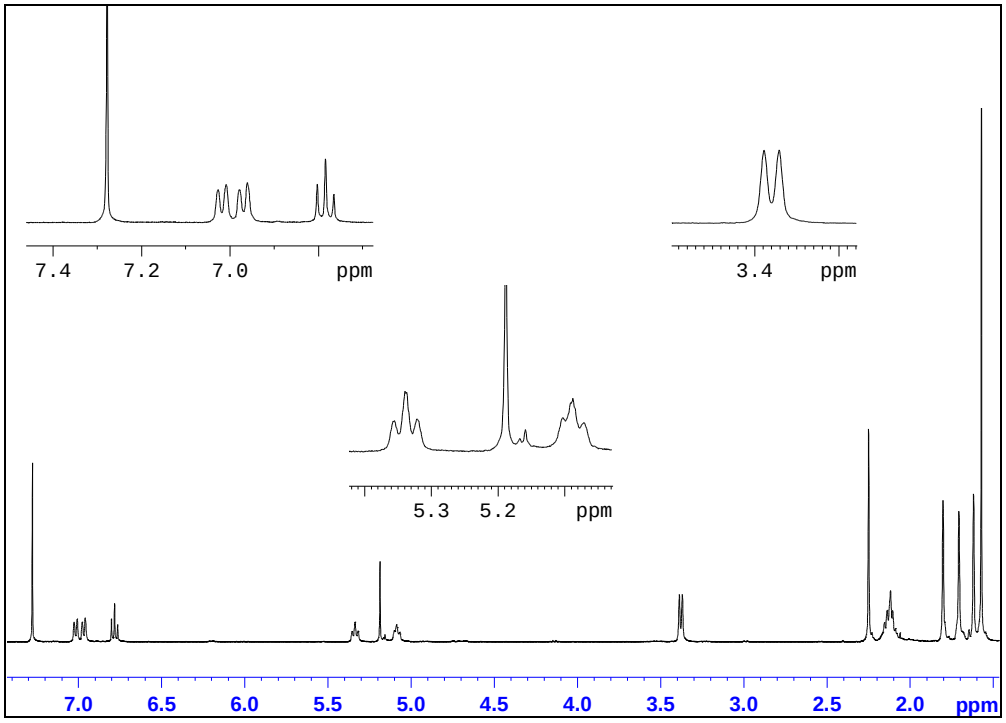


Figure 3.8: ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of **3.37**.

The synthesis of **3.37** was subsequently followed by an oxidation reaction with salcomine in the presence of oxygen. The product **2.26** was obtained in a yield of 63%. The ^{1}H NMR spectrum of **2.26** was characterised by the two downfield singlets at δ_H 6.56 and 6.48 due to H-3 and H-5 (Fig. 3.9). The acquired ^{13}C NMR spectrum of **2.26** demonstrated two signals at δ_C 188.0 and 187.9 due to C-4 and C-1, which confirmed the presence of the benzoquinone moiety. The observed IR absorption bands at 1651, 1614 cm^{-1} also confirm the presence of a benzoquinone moiety. The ^{1}H and ^{13}C NMR data for synthetic **2.26**

correlated with those reported for the natural product isolated from brown alga, *Cystophora harveyi*.[66]

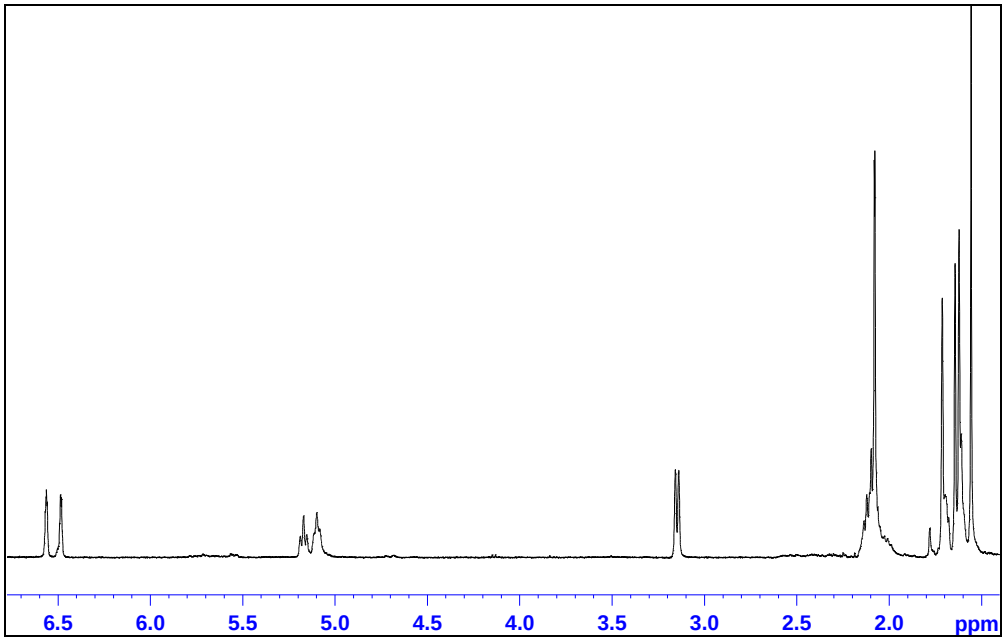
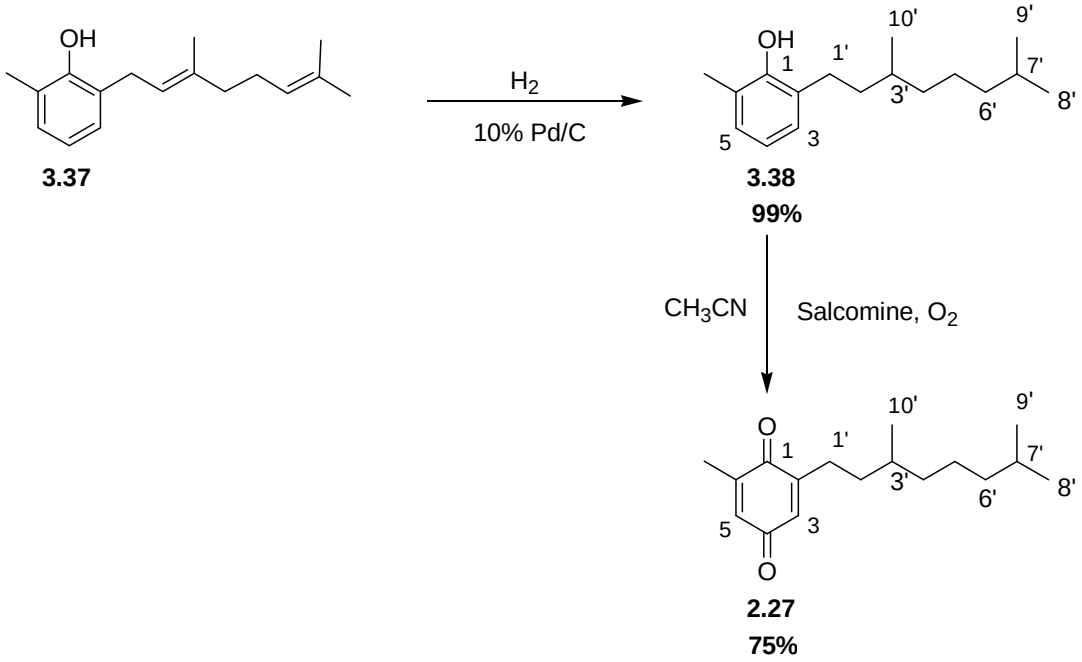


Figure 3.9: ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of **2.26**.

3.8 Synthesis of 2-(3,7-dimethyloctyl)-6-methyl-1,4-benzoquinone (2.27).

The successful synthesis of **2.26** provided the relevant foundation for the synthesis of **2.27**. Like the synthesis of **2.25,** the synthesis of **2.27** involved two steps. The first step was the reductive hydrogenation, while the second step was the oxidation using salcomine (Scheme 3.28). The synthesised **3.37** was reduced using H_2 in the presence of 10% Pd/C. The product was obtained in a quantitative yield. The structure of **2.27** was confirmed using NMR. The characteristic triplet signals at δ_H 5.34 (H-2') and 5.09 (H-6') in the ^{1}H NMR spectrum of **3.37** had disappeared which was an indication that the double bonds had been reduced (Fig. 3.10). The ^{13}C NMR spectrum of **3.38** demonstrated an upfield shift of C-2' and C-6', the signals were observed at δ_C 120.3 and 123.8 respectively (Fig. 3.11). The molecular formula of **3.38** was confirmed by **HRMS (ESI$^-$)** ($[M-H]^-$ obsd. *m/z* 247.2217, calc. for $C_{17}H_{27}O$ 247.2215). The synthesis of **3.38** was subsequently followed by an oxidation step. The product **2.27** was obtained in a yield of 75%. The structure of **2.27** was confirmed using NMR spectroscopy. The resonances at δ_C 187.9 and 187.8 in the ^{13}C NMR

spectrum were diagnostic of a benzoquinone moiety. The IR spectrum of **2.27** showed absorption band at 1651 cm^{-1} that also confirmed the presence of a benzoquinone moiety. The molecular formula of **2.27** was confirmed by HRMS (ESI^+) **(**$[M+H]^+$ obsd. *m/z* 263.2012, calc. for $C_{17}H_{27}O_2$ 263.2013).



Scheme 3.28: Synthetic route towards 2-(3,7-dimethyloctyl)-6-methyl-1,4-benzoquinone (**2.27**).

3.9 Approaches Towards the Synthesis of Analogue 2.28.

Since the synthesis of **2.28** also involved regioselective alkyl coupling, demethylation, regioselective bromination and methylation and oxidation, the formulated synthetic strategy was based on the synthetic strategies that were used in the synthesis of **2.24-2.27.**[22,37,41,53] In addition the synthesis of **2.28** was also used as a yardstick to test the flexibility of the developed synthetic approach (Scheme 3.29).

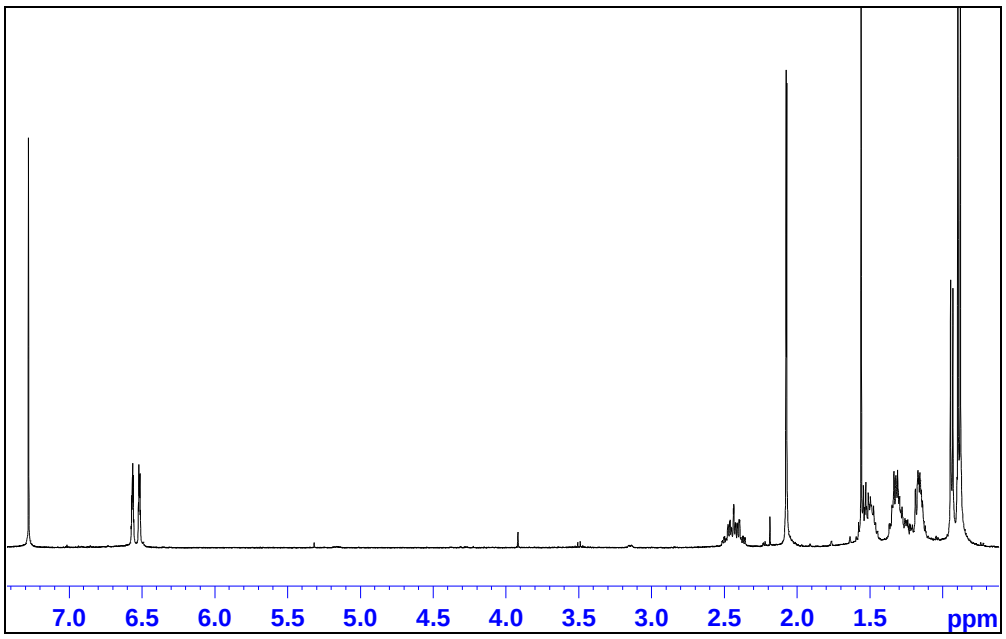


Figure 3.10: ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **2.27**.

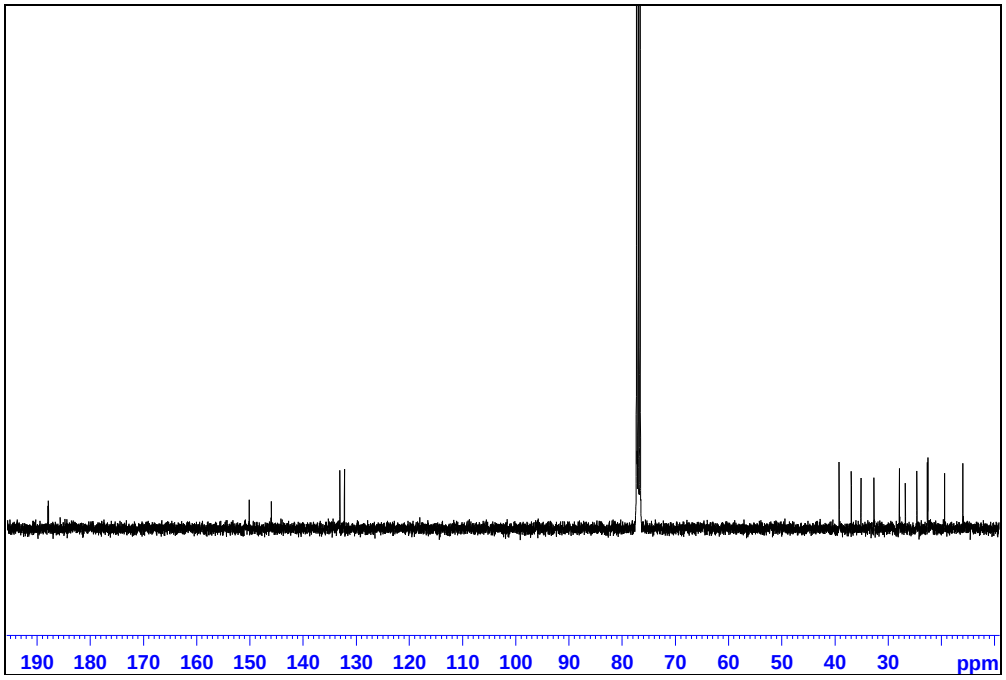
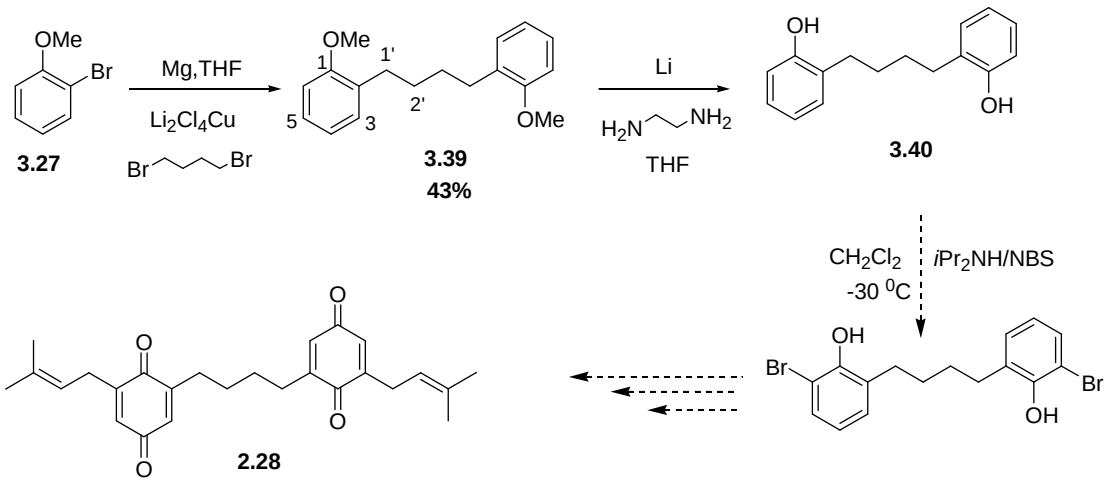
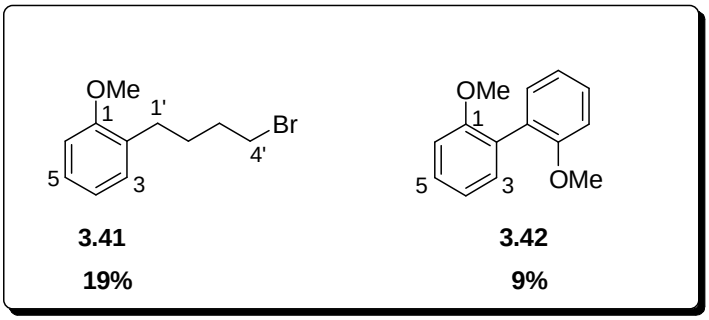


Figure 3.11: ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **2.27**.



Scheme 3.29: Proposed synthetic route towards **2.28.**

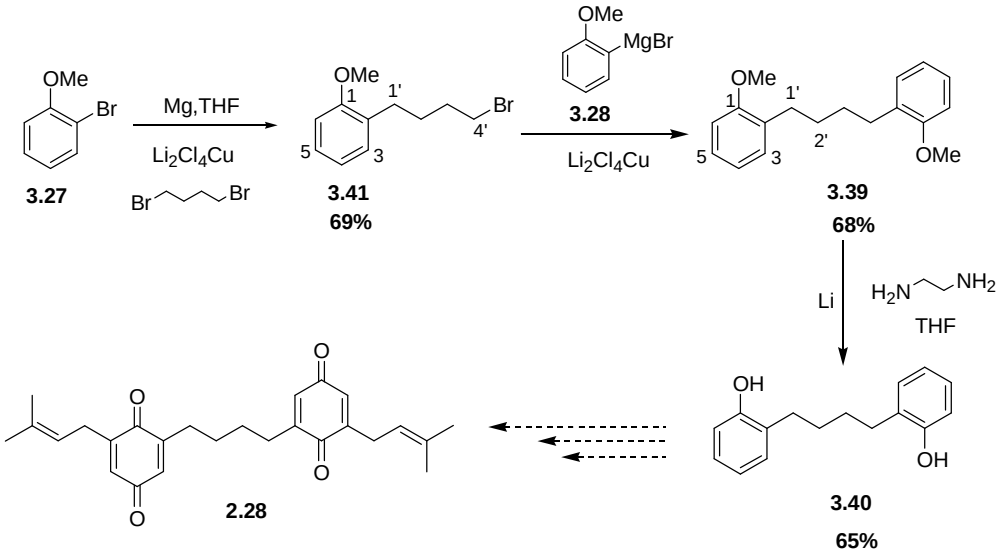
The synthesis of **2.28** started with the synthesis of **3.39** from 1.4-dibromobutane (1 eq) and *o*-bromoanisole (2 eq) (**3.27**) using Burns's approach.[41] Unfortunately the product was obtained along with side products **3.41** and **3.42**, consequently a low yield of 43% was obtained. The upfield shift of H-1' in the ^{1}H NMR spectrum was the first indication of successful coupling. The successful coupling was indicated by the presence of a triplet resonance at δ_C 2.65 due to H-1', which integrated for four protons in the ^{1}H NMR spectrum of **3.39**. The presence of only two resonances at δ_C 2.65 (4H, t, J = 7.5 Hz) and 1.64 (4H, qt) confirmed the successful synthesis of the symmetric **3.39**.



Since an unsatisfactory yield was obtained in the synthesis of **3.39**, another synthetic route was formulated. Instead of reacting *o*-bromoanisole (2 eq) (**3.27**) and 1,4-dibromobutane (1 eq), equimolar amounts were used in order to form **3.41** as the major product. The product **3.41** was obtained in a yield of 69%. It was subsequently reacted with **3.28** to obtain **3.39**

with an improved yield of 68%. Therefore, the subsequent step was the demethylation of **3.39** employing the approach described by Shindo *et al.*[53] The product **3.40** was successfully obtained in a yield of 65%. The absence of the characteristic resonance at δ_C 3.83 (6H, s) due to OCH_3 in the ^1H NMR spectrum was the first indication of successful demethylation. The IR absorption band at 3487 cm^{-1} confirms the presence of the phenolic moiety.

The synthesis of **2.28** could not be completed. Progress in this synthesis was retarded by the challenges that were experience during the attempted bromination of **3.40**. Therefore, due to time constraints the synthesis of **2.28** could be completed.



Scheme 3.30: Approaches towards the total synthesis of **2.28**.

In conclusion, the naturally occurring, 2-methyl-6-(3-methyl-2-butenyl)-benzo-1,4-quinone (**2.24**) was synthesised in five steps. The synthetic protocol employed in the synthesis of 2-methyl-6-(3-methyl-2-butenyl)-benzo-1,4-quinone (**2.24**) was subsequently employed in the synthesis of the analogues **2.25-2.27**. The three analogues were distinguishable from **2.24** only by the nature of the side chain. The analogue 2-(3,7-dimethylocta-2,6-dienyl)-6-methyl-1,4-benzoquinone (**2.26**) with a longer side was synthesised with the same synthetic strategy. The applicability of the formulated synthetic strategy in the synthesis of **2.26-26.8**, suggest that a reliable synthetic approach characterised by consistency, wide applicability and mild conditions has been developed. The results obtained also signify that

copper-mediated transformation is a potent synthetic strategy for regioselective *ortho*-prenylation of a phenol.

The synthesis of 2-methyl-6-(3-methyl-2-butenyl)-benzo-1,4-quinone (**2.24**) has been reported by other groups. Khanna and Singh prepared the compound by direct prenylation of 2-methyl-1,4-benzoquinone.[67] However this method leads to the formation of 1:1 mixtures of the 2-methyl-5-(3-methyl-2-butenyl)-benzo-1,4-quinone and 2-methyl-6-(3-methyl-2-butenyl)-benzo-1,4-quinone (**2.24**) isomer and is not suitable for large scale preparation or the synthesis of analogues.

During the cause of our investigation, we also became aware of a paper by Shaojun.[68] However this paper was not accessible to us and the abstract did not give a clear indication of their synthetic methods.

3.10 References

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CHAPTER FOUR

Conclusion

4.1 Conclusion and Future Work

The research presented in this dissertation demonstrated the pivotal role that organic synthesis plays in natural product chemistry. The naturally occurring biologically active, 2-methyl-6-(3-methyl-2-butenyl)-benzo-1,4-quinone (**2.24**) was synthesised in five steps. The synthesis of **2.24** has been reported previously by Shaojun and also by Khanna and Singh.[1,2] They employed different strategies and both of these methods are different to the method we employed. This further demonstrates that there is no general route towards the synthesis of naturally occurring benzoquinones. Our synthetic route also represents the first regioselective synthesis of **2.24**. Therefore, the synthetic strategy we have developed is a significant addition to the arsenal of simple, versatile and regioselective routes towards benzoquinones, which have been dominated by synthetic strategies based on the Claisen rearrangement.[3,4]

Versatility was demonstrated by our synthetic approach during the synthesis of analogues **2.25-2.28**. The critical *o*-prenylation step was achieved in reproducible good yields. Therefore, the same transformation can be employed in the synthesis of bioactive prenylated aromatic compounds. Prenylated aromatic natural products have been reported to exhibit antimicrobial and antifungal properties.[5-7] Consequently, chemists have demonstrated an interest in the synthesis of prenylated aromatic compounds.

Although the synthesis of analogues **2.25-2.27** was successfully achieved, the synthesis of analogue **2.28** was not completed. Therefore future work would include the completion of the synthesis of **2.28**.

One of our aims was to test the compounds for antimicrobial and anticancer activity. This was to be done in collaboration with biologists from another Department. However, due to time

constraints, the results of the assays could not be included in this dissertation. Future work will include evaluating of the activity of synthesised compounds in order to ascertain the structure-activity relationship of the various groups present in compounds **2.24**-**2.28**, and hence to determine whether further investigation is necessary.

4.2 References

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CHAPTER FIVE

Methods and Materials

5.1 Experimental

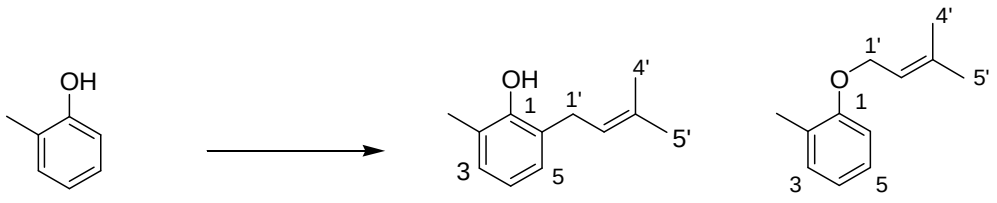
The NMR spectra were obtained in deuterated solvents using a Bruker Avance 400 MHz spectrometer. ^{1}H spectra were obtained at 400 MHz and referenced against the residual $CHCl_3$ singlet at 7.24 ppm. ^{13}C spectra were obtained at 100 MHz and were referenced against the central line of the $CDCl_3$ triplet at 77.0 ppm. Abbreviation used: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet. Mass spectra were obtained on a Waters-LCT Premier mass spectrometer. Infrared spectra were obtained as thin films (neat) / thin films (chloroform) or as nujol mixes using a Perkin-Elmer Spectrum One Spectrometer with a scan window of 4000 - 400 cm^{-1}. The spectrum resolution was 1.0 cm^{-1} and the average from 3 scans was taken.

Column chromatography was performed using Merck silica gel 60 PF_{254} and thin-layer chromatography (TLC) was performed using Merck silica gel 60 PF_{254} supported on aluminum backing. Visualisation of compounds on TLC was achieved under UV light (254/365 nm) and/or by exposure to iodine vapour or staining with an anisaldehyde staining solution. All moisture and air-sensitive reactions were performed under dry conditions under nitrogen pressure.

All microwave reactions were conducted on a CEM Focused MicrowaveTM Synthesis system which uses an infrared sensor located below the microwave cavity floor to measure temperature.

5.2 Phenoxide Carbon Alkylation

5.2.1 Preparation of 2-methyl-6-(3-methyl-2-butenyl)phenol (3.2)



3.1 **3.2** **3.3**

Method A

To a solution of dry diethyl ether (50 ml) and *o*-cresol (**3.1**) (0.279 g, 2.58 mmol) was slowly added small pieces of metallic sodium (0.237 g, 10.3 mmol). The mixture was stirred for 2 h. Allylic bromide (0.384 g, 2.58 mmol) was added dropwise, after which the mixture was refluxed for 10 h. The unreacted metallic sodium metal was quenched using methanol. The reaction mixture was acidified with 0.1 M aq HCl. The residue was extracted with diethyl ether (3 x 50 ml). The combined extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (9:1 hexane-ethyl acetate) to yield compound **3.2** (0.182 g, 1.03 mmol, 40%) as a yellowish oil and compound **3.3** (0.146 g, 0.825 mmol, 32%) as a colourless oil.

Method B

Procedure A was repeated with all the parameters the same except temperature and reaction time. The diethyl ether and *o*-cresol solution was prepared and kept at 0 ^{o}C, subsequently allylic bromide was added slowly at this temperature. The temperature of the resulting mixture was allowed to rise to room temperature. The reaction mixture was stirred overnight. The reaction yielded compound **3.2** (0.259 g, 1.47 mmol, 57%) as a yellowish oil and compound **3.3** (0.077 g, 0.439 mmol, 17%) as a colourless oil.

Compound 3.2

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.97 (1H, d, *J* = 7.4 Hz, H-3), 6.93 (1H, d, *J* = 7.2 Hz, H-5), 6.74 (1H, t, *J* = 7.4 Hz, H-4), 5.30 (1H, t, *J* = 7.2 Hz, H-2'), 5.11 (1H, br s, OH), 3.33 (2H, d, *J* = 7.0 Hz, H-1'), 2.21 (3H, s, CH_3), 1.78 (3H, s, H-4'), 1.76 (3H, s, H-5').

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 152.9 (C-1), 135.0 (C-3'), 129.0 (C-5), 127.6 (C-3), 126.1 (C-6), 124.2 (C-2), 122.0 (C-4), 120.2 (C-2'), 30.3 (C-5'), 25.7 (C-1'), 17.9 (C-4'), 15.8 (6-CH_3).

HRMS (ESI⁻) $[M-H]^-$ obsd. *m/z* 175.1118 (calc. for $C_{12}H_{15}O$ 175.1123).

IR ν_{max}: 3564, 2919, 1594, 1467, 1377, 1257, 1190, 765 cm^{-1}.

Compound 3.3

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.12 (2H, m, H-3, 5), 6.83 (2H, m, H-4, 6), 5.49 (1H, t, *J* = 6.52 Hz, H-2'), 4.51 (2H, d, *J* = 6.5 Hz, H-1'), 2.22 (3H, s, H-7), 1.78 (3H, s, H-4'), 1.72 (3H, s, H-5').

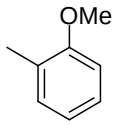
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.1 (C-1), 137.1 (C-3'). 130.6 (C-3), 127.1 (C-5), 126.6 (C-2), 120.4 (C-2'), 120.2 (C-4), 111.5 (C-6), 65.1 (C-1'), 25.8 (C-5'), 18.2 (C-4'), 16.3 (2-CH_3).

HRMS (ESI⁺) $[M+H]^+$obsd. *m/z* 177.1283 (calc. for $C_{12}H_{17}O$ 177.1284).

IR ν_{max}: 2917, 1603, 1493, 1237, 1119, 1006, 746, 713 cm^{-1}.

5.3 Directed *ortho*-Metalation

5.3.1 Preparation of 2-methylanisole (3.13)



3.13

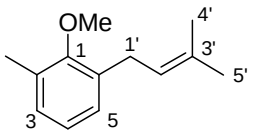
A solution of Na_2CO_3 (0.624 g, 5.89 mmol) and *o*-cresol (**3.1**) (1.00 g, 5.43 mmol) in dry acetone (20 ml) was refluxed under nitrogen for 1 h. To the mixture Me_2SO_4 (0.685 g, 5.43 mmol) was added and the mixture was refluxed for a further 3 h. The reaction mixture was quenched in water and extracted with ether (3 x 20 ml). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (hexane) to yield compound **3.13** (0.636 g, 5.12 mmol, 96%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.12 (2H, m, H-3,5), 6.82 (2H, m, H-4,6), 3.81 (3H, s, OCH_3), 2.20 (3H, s, CH_3),

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.3 (C-1), 130.6 (C-3), 128.1 (C-5), 120.3 (C-2), 119.3 (C-4), 110.7 (C-6), 63.9 (OCH_3), 14.1 (CH_3).

IR ν_{max}: 2920, 2851, 1459 1375, 906 cm^{-1}.

5.3.2 Attempted synthesis of 2-methyl-6-(3-methyl-2-butenyl)anisole (3.15)

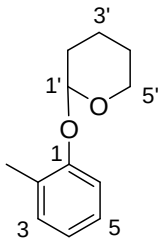


3.15

To a solution 2-methylanisole (**3.13**) **(**0.500 g, 4.09 mmol) in dry THF, *n*-BuLi (6.5 ml, 4.09 mmol) was added at -78 ^{o}C. The resulting solution was stirred for 1.5 h after which prenyl bromide (0.609 g, 4.09 mmol) was added. The solution was allowed to warm to room temperature. The reaction was quenched with saturated aqueuous NH_4Cl, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The material obtained subjected to silica column chromatography (1:4, diethyl ether-hexane). Unfortunately the product **3.15** was not obtained.

The same procedure was repeated several times manipulating the different variables. This included changing the solvent from diethyl ether to THF, addition of TMEDA and CuI and varying of the temperature. Each experiment was repeated several times but there was no product obtained.

5.3.3 Preparation of tetrahydropyran ether (3.20)



3.20

To a solution of o-cresol (**3.1**) (2.50 g, 23.1 mmol) in 20 mL THF, 3,4-dihydro-2*H*-pyran (4.86 g, 57.8 mmol) and anhydrous *p*-toluenesulfonic acid was added at 0 ^{o}C. The resulting mixture was stirred for 12 h at 5 ^{o}C. The reaction was quenched by basifying with 10% NaOH. The residue was extracted with dichloromethane (3 x 50 ml). The combined extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The

reaction product was purified using silica column chromatography (1:4, diethyl ether-hexane) to yield compound **3.20** (3.20 g, 16.6 mmol, 72%) as a colourless oil.

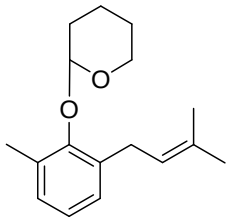
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.16 (2H, t, *J* = 6.5 Hz, H-3,5), 7.09 (1H, d, *J* = 7.71 Hz, H-6), 6.91 (1H, t, *J* = 7.7 Hz, H-4), 5.45 (1H, t, *J* = 3.1 Hz, H-1'), 3.93 (1H, td, *J* = 10.1, 2.8 Hz, H_{ax}-5') 3.63 (1H, m, H_{eq}-5'), 2.30 (3H, s, CH_3), 1.71-2.06 (6H, m, H-2',3',4')

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 155.1 (C-1), 130.6 (C-3), 127.3 (C-5), 126.7 (C-2), 121.2 (C-4), 114.2 (C-6), 96.1 (C-1'), 62.0 (C-5'), 30.6 (C-2'), 25.3 (C-4'), 19.0 (C-3'), 16.2 (2-CH_3).

HRMS (ESI$^+$) $[M+Na]^+$ obsd. *m/z* 215.1048 (calc. for $C_{12}H_{16}O_2Na$ 215.1047).

IR ν_{max}: 2940, 1492, 1235, 1035, 966, 746 cm^{-1}.

5.3.4 Attempted synthesis of compound 3.21



3.21

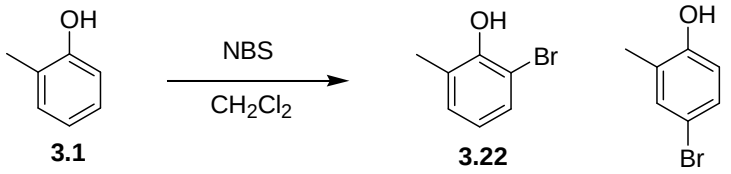
To a solution of compound **3.20 (**0.500 g, 2.60 mmol) in dry THF, *n*-BuLi (4.16 ml, 2.60 mmol) was added at -100 ^{o}C. The resulting solution was stirred for 1.5 h; prenyl bromide (0.387 g, 2.60 mmol) was added. The solution was allowed to warm up to room temperature. The reaction was quenched by the addition of water and the products extracted with diethyl ether (3 x 20 ml). The combined extracts were washed with 10% NaOH, water, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction product was subjected to silica column chromatography (1:4, diethyl ether-hexane). Unfortunately the product **3.21** was not obtained.

The same procedure was repeated several times manipulating the different variables. This included changing the solvent from diethyl ether to THF, addition of TMEDA and CuI and

varying of the temperature. Each experiment was repeated several times but there was no product obtained.

5.4 Metal-Halogen Exchange

5.4.1 Preparation of 2-bromo-6–methylphenol (3.22)



3.1 **3.22** **3.24**

47% **42%**

Method A

To a solution of *o*-cresol (**3.1**) (1.00 g, 9.26 mmol) in CH_2Cl_2 (30 ml), was added NBS (1.61 g, 9.26 mmol) in CH_2Cl_2 (30 ml). The mixture was stirred at room temperature for 2 h. The reaction mixture was acidified with HCl and the aqueous solution was extracted with CH_2Cl_2 (3 x 20 ml). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (1:9; diethyl ether: hexane) to yield compound **3.22** (0.811 g, 4.33 mmol, 47%) and compound **3.24** (0.724 g, 3.88 mmol, 42%) as colourless oils.

Method B

A solution of diisopropylamine (0.0919 g, 0.926 mmol) in CH_2Cl_2 (2 ml) was added to a solution of *o*-cresol (1.00 g, 9.26 mmol) in CH_2Cl_2 (10 ml) at 0 ^oC. To the resulting mixture, a solution of NBS (1.61 g, 9.26 mmol) in CH_2Cl_2 (30 ml) was added over 1 h. The mixture was stirred for 2 h at 0 ^oC. The reaction mixture was acidified with HCl and the aqueous solution was extracted with CH_2Cl_2 (3 x 20 ml). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (1:9, diethyl ether-hexane) to yield compound **3.21** (1.26 g, 6.74 mmol, 73%) as a colourless oil.

Compound 3.22

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.27 (1H, d, *J* = 7.9 Hz, H-3), 7.04 (1H, d, *J* = 7.5 Hz, H-5), 6.69 (1H, t, *J* = 7.7 Hz, H-4), 5.54 (1H, br s, OH), 2.28 (3H, s, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 150.4 (C-1), 130.4 (C-3), 129.4 (C-5), 125.9 (C-6), 121.2 (C-4), 110.2 (C-2), 16.6 (CH_3).

HRMS (ESI⁻) $[M-H]^-$ obsd. *m/z* 184.9602 (calc. for $C_7H_6O^{77}Br$ 184.9602).

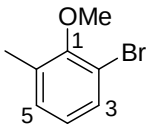
IR ν_{max} 3512, 1459, 1433, 1217, 1119, 1075, 758 cm^{-1}.

Compound 3.24

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.25 (1H, m, H-3), 7.18 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.66 (1H, d, *J* = 8.5 Hz, H-6), 4.82 (1H, br s, OH), 2.24 (3H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 152.9 (C-1), 133.5 (C-3), 129.7 (C-5), 126.2 (C-2), 116.5 (C-4), 112.5 (C-6), 15.6 (CH_3).

5.4.2 Preparation of 2-bromo-6-methylanisole (3.23)



3.23

A solution of Na_2CO_3 (0.678 g, 6.40 mmol) and compound **3.22** (1.00 g, 5.35 mmol) in dry acetone (20 ml) was refluxed under nitrogen for 1 h. To the mixture Me_2SO_4 (0.743g, 5.89 mmol) was added and the mixture was refluxed for a further 3 h. The reaction mixture was quenched with water and extracted with ether (3 x 20 ml). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (hexane) to yield compound **3.23** (1.02 g, 5.08 mmol, 95%) as a yellowish oil.

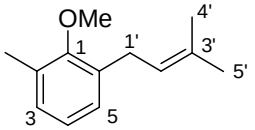
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 (1H, d, *J* = 7.9 Hz, H-3), 7.09 (1H, d, *J* = 7.6 Hz, H-5), 6.86 (1H, t, *J* = 7.8 Hz, H-4), 3.85 (3H, s, OCH_3), 2.35 (3H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 155.4 (C-1), 131.0 (C-3), 130.3 (C-5), 128.0 (C-6), 125.1 (C-4),117.3 (C-2), 60.1 (OCH_3), 16.5 (CH_3).

HRMS (ESI$^+$) $[M+H]^+$ obsd. *m/z* 200.9841 (calc. for $C_8H_{10}O^{77}Br$ 200.9842).

IR ν_{max}: 2930, 1467, 1415, 1228, 1004, 1083, 843, 769 cm^{-1}.

5.4.3 Preparation of 2-methyl-6-(3-methyl-2-butenyl)anisole (3.15)



3.15

2-Bromo-6-methylanisole **3.23** (0.500 g, 2.49 mmol) was dissolved in dry diethyl ether (10 ml), under nitrogen. The resulting solution was cooled to 0 ^{o}C before adding TMEDA (0.53 ml, 3.55 mmol) subsequently followed by the addition of *n*-BuLi (2.1 ml, 3.55 mmol). The mixture was allowed to stir for 20 min before adding prenyl bromide. The reaction was allowed to stir overnight and subsequently quenched using saturated aqueous NH_4Cl (10 ml) and extracted with diethyl ether (3 x 10 ml). The combined extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (1:4 diethyl ether-hexane) to yield compound **3.15** (0.057 g, 0.299 mmol, 12%) as a yellowish oil,

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.00 (2H, d, *J* = 7.4 Hz, H-3,5), 6.93 (1H, dd, *J* = 7.5, 6.4 Hz, H-4), 5.27 (1H, t, *J* = 7.2 Hz, H-2'), 3.72 (3H, s, OCH_3), 3.35 (2H, d, *J* = 7.2 Hz, H-1'), 2.28 (3H, s, CH_3), 1.72 (6H, s, H-4', 5').

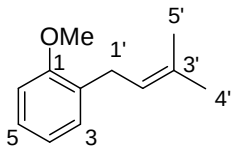
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.6 (C-1), 134.6 (C-3'), 132.2 (C-3), 130.9 (C-5), 129.0 (C-6), 127.7 (C-2), 124.0 (C-4), 123.3 (C-2'), 60.2 (OCH_3), 29.7 (C-1'), 25.7 (C-5'), 17.8 (C-4'), 16.1 (CH_3).

HRMS (ESI$^+$) $[M+H]^+$ obsd. *m/z* 191.1432 (calc. for $C_{13}H_{19}O$ 191.1433).

IR ν_{max}: 2926, 1713, 1511, 1467, 1377, 1254, 1015, 769 cm^{-1}.

5.5 Copper (II)-Mediated Regioselective Alkylation

5.5.1 Preparation of 2-(3-methylbut-2-enyl)anisole (3.30)



3.30

Compound **3.27** (1.50 g, 8.02 mmol) was added slowly to a mixture of Mg (0.220 g, 9.05 mmol) turnings and 20 ml of dry THF under nitrogen. The resulting mixture was allowed to reflux for 3 h. The mixture was cannulated into a solution of prenyl bromide (1.19 g, 8.02 mmol) and 1.5 ml of 0.1 M Li_2CuCl_4/THF solution, stirring at 0 ^oC under nitrogen. The reaction mixture was allowed to warm to room temperature and after 3 h another 1.5 ml of 0.1 M Li_2CuCl_4/THF was added. After 6 h, the last portion of 1.5 ml of 0.1 M Li_2CuCl_4/THF was added. After 24 h the reaction was quenched with distilled water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with dilute HCl, water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (hexane) to yield compound **3.30** (1.15 g, 6.50 mmol, 81%) as colourless oil.

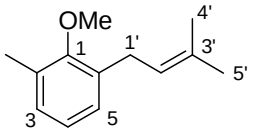
^1H NMR (400 MHz, $CDCl_3$) δ_H 7.17 (2H, m, H-3,5), 6.90 (1H, t, *J* = 7.4 Hz, H-4), 6.86 (1H, d, *J* = 8.1 Hz, H-3), 5.33 (1H, t, *J* = 7.2 Hz, H-2'), 3.86 (3H, s, OCH_3), 3.34 (2H, d, *J* = 7.7 Hz, H-1'), 1.76 (3H, s, H-4'), 1.73 (3H, s, H-5').

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.3 (C-1), 132.4 (C-3'), 130.1 (C-3), 129.3 (C-5), 126.8 (C-2), 122.6 (C-4), 120.4 (C-2'), 110.2 (C-6), 55.3 (OCH_3), 28.4 (C-1'), 25.8 (C-5'), 17.7 (C-4').

HRMS (ESI$^+$) $[M+H]^+$ obsd. *m/z* 177.1276 (calc. for $C_{12}H_{17}O$ 177.1275).

IR ν_{max}: 2968, 1599, 1462, 1240, 1028, 750. cm^{-1}.

5.5.2 Preparation of 2-methyl-6-(3-methyl-2-butenyl)anisole (3.15)



3.15

2-Bromo-6-methylanisole(**3.23**) (0.500 g, 2.49 mmol) was added slowly to a mixture of Mg turnings and 15 ml of dry THF under nitrogen. The resulting mixture was allowed to reflux for 5 h. The mixture was cannulated into a solution of allylic bromide (0.371 g, 2.49 mmol) and 1.5 ml of 0.1 M Li_2CuCl_4/THF solution, stirring at 0 ^oC under nitrogen. The reaction mixture was allowed to warm to room temperature and after 3 h another 1.5 ml of 0.1 M Li_2CuCl_4/THF was added. After 6 h, the last portion of 1.5 ml of 0.1 M Li_2CuCl_4/THF was added. After 24 h the reaction was quenched with distilled water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with dilute HCl, water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products was purified using silica column chromatography (1:4, diethyl ether-hexane) to yield compound **3.15** (0.336 g, 1.77 mmol, 71%) as yellowish oil;

^1H NMR (400 MHz, $CDCl_3$) δ_H 7.00 (2H, d, *J* = 7.4 Hz, H-3,5), 6.93 (1H, dd, *J* = 7.5, 6.4 Hz, H-4), 5.27 (1H, t, *J* = 7.2 Hz, H-2'), 3.72 (3H, s, OCH_3), 3.35 (2H, d, *J* = 7.2 Hz, H-1'), 2.28 (3H, s, CH_3), 1.72 (6H, s, H-4', 5').

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.6 (C-1), 134.6 (C-3'), 132.2 (C-3), 130.9 (C-5), 129.0 (C-6), 127.7 (C-2), 124.0 (C-4), 123.3 (C-2'), 60.2 (OCH_3), 29.7 (C-1'), 25.7 (C-5'), 17.8 (C-4'), 16.1 (CH_3).

HRMS (ESI$^+$) $[M+H]^+$ obsd. *m/z* 191.1432 (calc. for $C_{13}H_{19}O$ 191.1433).

IR ν_{max}: 2926, 1713, 1511, 1467, 1377, 1254, 1015, 769 cm^{-1}.

5.5.3 Demethylation of 2-bromo-6-methylanisole (3.23)

2-Bromo-6-methylanisole (**3.23**) (0.100 g, 0.500mmol) was dissolved in DMF (5 ml), to the resulting solution iodocyclohexane (1.05 g, 5 mmol) was added. The reaction mixture was subsequently refluxed for 8 h under nitrogen. The obtained reaction mixture was cooled and mixed with water (25 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with $NaHSO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (1:9, diethyl ether-hexane) to yield compound **3.22** (0.0804 g, 0.430 mmol, 86%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.27 (1H, d, J = 7.9 Hz, H-3), 7.04 (1H, d, J = 7.5 Hz, H-5), 6.69 (1H, t, J = 7.7 Hz, H-4), 5.54 (1H, br s, OH), 2.28 (3H, s, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 150.4 (C-1), 130.4 (C-3), 129.4 (C-5), 125.9 (C-6), 121.2 (C-4), 110.2 (C-2), 16.6 (CH_3).

HRMS (ESI⁻) $[M-H]^-$ obsd. *m/z* 184.9602 (calc. for $C_7H_6O^{77}Br$ 184.9602).

IR ν_{max} 3512, 1459, 1433, 1217, 1119, 1075, 758 cm^{-1}.

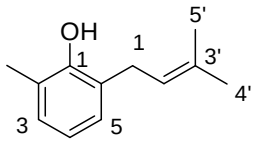
5.5.4 Attempted demethylation of 3.15 using Zuo's approach

2-Methyl-6-(3-methyl-2-butenyl)anisole (**3.15**) (0.190 g, 1.00 mmol) was dissolved in DMF (5 ml), to the resulting solution iodocyclohexane (2.10 g, 10 mmol) was added. The reaction mixture was subsequently refluxed for 10 h under nitrogen. The obtained reaction mixture was cooled and mixed with water (25 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with $NaHSO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The material obtained subjected to silica column chromatography (1:4, diethyl ether-hexane). Unfortunately the product **3.2** was not obtained.

5.5.5 Attempted demethylation of 3.15 using Fang's approach

To a solution of 2-methyl-6-(3-methyl-2-butenyl)anisole (**3.15**) (0.100 g, 0.526 mmol) in dry DMF (0.10 ml, 1.58 mmol), was added LiCl (0.0669 g, 1.58 mmol). The mixture was irradiated under microwave (300 W, 300 ^{o}C) for 5-30 min. The resulting mixture was quenched with dilute HCl, and extracted with ethyl acetate (3 x 20 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The material obtained subjected to silica column chromatography (1:4, diethyl ether-hexane). Unfortunately the product **3.2** was not obtained.

5.5.6 Preparation of 2-methyl-6-(3-methyl-2-butenyl)phenol (3.2)



3.2

To a mixture of 10 ml dry THF and metallic lithium (0.039 g, 5.68 mmol), stirring at 0 ^{o}C under nitrogen, was added ethylenediamine (0.478 g, 7.95 mmol). Compound **3.15** (0.200 g, 1.05 mmol) was added and the solution was allowed to stir at 0 ^{o}C for 2 h. The remaining lithium was separated from the resulting deep blue solution and quenched with methanol. The pink reaction mixture was quenched with distilled water (10 ml) and extracted with diethyl ether (3 x 20 ml). The organic layer was washed with dilute HCl, water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (1:4; diethyl ether-hexane) to yield compound **3.2** (0.154 g, 0.874 mmol, 84%) as a yellowish oil.

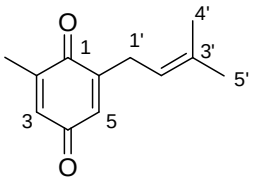
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.97 (1H, d, *J* = 7.4 Hz, H-3), 6.93 (1H, d, *J* = 7.2 Hz, H-5), 6.74 (1H, t, *J* = 7.4 Hz, H-4), 5.30 (1H, t, *J* = 7.2 Hz, H-2'), 5.11 (1H, br s, OH) 3.33 (2H, d, *J* = 7.0 Hz, H-1'), 2.21 (3H, s, CH_3), 1.78 (3H, s, H-4'), 1.76 (3H, s, H-5').

^{13}C NMR (100 MHz, $CDCl_3$) δ_C, 152.9 (C-1), 135.0 (C-3'), 129.0 (C-5), 127.6 (C-3), 126.1 (C-6), 124.2 (C-2), 122.0 (C-2'), 120.2 (C-4), 30.3 (C-1'), 25.7 (C-5'), 17.9 (C-4'), 15.8 (CH_3).

HRMS (ESI⁻) $[M-H]^-$ obsd. *m/z* 175.1118 (calc. for $C_{12}H_{15}O$ 175.1123).

IR ν_{max}: 3564, 2919, 1594, 1467, 1377, 1257, 1190, 765 cm^{-1}.

5.5.7 Preparation of 2-methyl-6-(3-methyl-2-butenyl)-benzo-1,4-quinone (2.24)



2.24

Method A

To a purple solution of $(KSO_3)_2NO$ (0.060 g, 0.222 mmol) and $KH_2PO_4 \cdot 3H_2O$ (0.080 g 0.420 mmol) in 10 ml water was added a solution of 2-methyl-6-(3-methyl-2-butenyl)phenol (**3.2**) (0.020 g, 0.114 mmol) in 10 ml methanol. The resulting mixture was vigorously stirred overnight. The reaction mixture was extracted with CH_2Cl_2 (2 x 20 ml). The combined extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction product was purified using silica column chromatography (1:4, diethylether-hexane) to yield compound **2.24** as a yellowish oil (0.021 g, 0.110 mmol, 49%) as yellowish oil.

Method B

2-Methyl-6-(methyl-2-butenyl)phenol (**3.2**) (0.100 g, 0.569 mmol) was dissolved in dry CH_3CN (20 ml) and salcomine (0.244 g, 0.750 mmol) was added to the resulting solution and the reaction mixture was allowed to stir for 24 h at room temperature. The resulting solution was filtered, the solids were discarded, quenched with water and extracted with diethyl ether (3 x 20 ml). The combined extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction product was purified using silica column chromatography (1:4, diethylether-hexane) to yield compound **2.24** as a yellowish oil (0.0704 g, 0.370 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.50 (1H, s, H-3), 6.42 (1H, s, H-5), 5.01 (1H, bt, *J* = 7.5 Hz, H-2'), 3.07 (2H, d, *J* = 7.6 Hz, H-1'), 2.07 (3H, s, CH_3), 1.71 (3H, s, H-4'), 1.59 (3H, s, H-5').

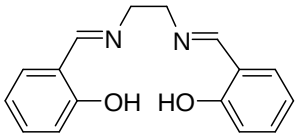
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 188.0 (C-1, 4), 148.5 (C-6), 145.9 (C-2), 136.2 (C-3'), 132.3 (C-3, 5), 118.1 (C-2'), 27.7 (C-1'), 25.7 (C-4'), 17.7 (C-5'), 16.0 (CH_3).

HRMS (ESI$^+$) $[M+Na+MeOH]^+$ obsd. *m/z* 245.1153 (calc. for $C_{13}H_{18}O_3Na$ 245.1154).

IR ν_{max}: 2919, 1651, 1613, 1437, 1291, 1172, 911 cm^{-1}.

5.6 Synthesis of [bis-(salicylidene)ethylenediamine]colbalt (Salcomine) (3.34)

5.6.1 Preparation of *N,N'*-ethylene-bis-salicylidenimine (3.33)



3.33

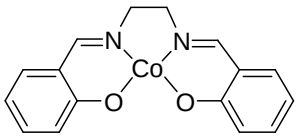
To a solution of salicylaldehyde (4.00 g, 32.7 mmol) in boiling ethanol (150 ml), athylenediamine (0.982g, 16.4 mmol) was added. The mixture was allowed to stand; within 2 min the formation of bright yellow crystals material was observed. The mixture was allowed to cool to temperature and subsequently filtered. The crystalline material was allowed to dry. The bright yellow crystals were recrystallized from ethanol to yield compound **3.33** (3.74g, 13.9 mmol, 82%), the melting point was measured to be 119-121 ^{o}C (literature value 123 ^{o}C)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.37 (2H, s, H-1'), 7.31 (2H, dt, *J* = 8.8, 1.7 Hz, H-4), 7.24 (2H, dd, *J* = 8.5, 1.6 Hz, H-6), 6.96 (2H, d, *J* = 8.29 Hz, H-3), 6.87 (2H, t, *J* = 7.45, H-5), 3.96 (1H, s, H-3),

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.5 (C-1'), 161.0 (C-2), 132.3 (C-4), 131.5 (C-6), 118.8 (C-1), 118.7 (C-5), 116.7 (C-3), 59.9 (C-3').

IR ν_{max}: 3545, 2967, 2853, 1548, 1653 cm^{-1}.

5.6.2 Preparation of Salcomine (34)

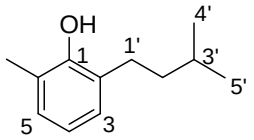


3.34

To a solution of **3.33** (3.5 g, 13.0 mmol) in 35 ml methanol at 40 ^{o}C under nitrogen was added NaOH (1 *eq*) (to dissolved all the crystals). $Co(OAc)_2 \cdot 4H_20$ (3.24 g, 13.0 mmol) dissolved in 5 ml distilled water was subsequently added dropwise. The complexs immediately started to precipitate. The mixture was further stirred at 40 ^{o}C for 2 h. After allowing the solution to cool down to room temperature, the precipitate was filtered and washed successively with water and absolute ethanol. The precipitate was dried to yield cobalt complex **3.34** (2.66g, 8.18 mmol, 62%) as a brownish solid. **HRMS (ESI^{+})** $[M+H]^{+}$ obsd. *m/z* 326.0478 (calc. for $C_{16}H_{15}O_2N_2Co$ 326.0476)

5.7 Synthesis of Analogue 2.25.

5.7.1 Preparation of 2-isopentyl-6-methylphenol (3.35)



3.35

2-Methyl-6-(3-methyl-2-butenyl)phenol (**3.2**) (0.200 g, 1.13 mmol) was dissolved in dry MeOH (15 ml) and to the resulting solution 10% Pd/C as a catalyst was added. The reaction mixture was stirred for 1 h at room temperature under a hydrogen pressure. The product, compound **3.35,** was obtained (0.199 g, 1.12 mmol, 99%) as a yellowish oil.

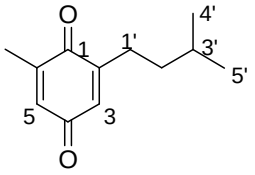
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.99 (2H, d, *J* = 7.2 Hz, H-3, 5), 6.79 (1H, t, *J* = 7.3, H-4), 4.60 (1H, br s, OH), 2.61 (2H, br t, *J* = 8.0 Hz, H-1'), 2.27 (3H, s, CH_3), 1.65 (1H, m, H-3'), 1.52 (2H, m, H-2') 0.97 (6H, d, *J* = 6.5 Hz, H-4',5').

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 151.9 (C-1), 128.4 (C-5), 128.1 (C-3), 127.6 (C-2) 123.0 (C-6), 120.3 (C-4), 39.3 (C-2'), 28.0 (C-3'), 27.9 (C-1'), 22,5 (C-4', 5'), 15.8 (CH_3).

HRMS (ESI⁻) $[M-H]^-$ obsd. *m/z* 177.1275 (calc. for $C_{12}H_{17}O$ 177.1279)

IR ν_{max}: 3585, 2954, 1594, 1467, 1187, 827, 741 cm^{-1}.

5.7.2 Preparation of 2-isopentyl-6-methylbenzo-1,4-quinone (2.25)



2.25

Compound **3.35** (0.100 g, 0.560 mmol) was dissolved in dry CH_3CN (20 ml) and to the resulting solution salcomine (0.243 g, 0.747 mmol) was added. The reaction mixture was allowed to stir for 24 h at room temperature. The resulting solution was filtered, the solids were discarded, quenched with water and extracted with diethyl ether (3 x 20 ml). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction product was purified using silica column chromatography (1:4, ethyl acetate-hexane) to yield compound **2.25** (0.085 g, 0.442 mmol, 79%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.56 (1H, s, H-3), 6.51 (1H, s, H-5), 2.43 (2H, t, *J* = 7.8 Hz, H-1') 2.07 (3H, s, CH_3), 1.63 (1H, m, H-3'), 1,39 (2H, q, *J* = 6.8 Hz, H-2'), 0.95 (6H, d, *J* = 6.5 Hz, H-4',5').

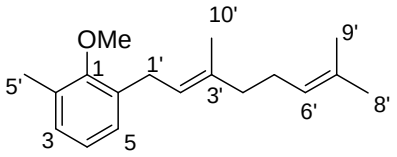
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 188.1 (C-1, 4), 150.1 (C-2), 146.1 (C-6), 133.2 (C-5), 132.4 (C-3) 37.2 (C-2'), 28.0 (C-3'), 27.2 (C-1'), 22.5 (C-4', 5'), 16.2 (CH_3).

HRMS (ESI$^+$) $[M+Na]^+$ obsd. *m/z* 215.1048 (calc. for $C_{12}H_{16}O_2Na$ 215.1047).

IR ν_{max}: 2954, 1648, 1467, 1366, 1291, 1034, 1190, 910 cm^{-1}.

5.8 Preparation of Analogue 2.26

5.8.1 Preparation of 2-(3,7-dimethylocta-2,6-dienyl)-6-methylanisole (3.36)



3.36

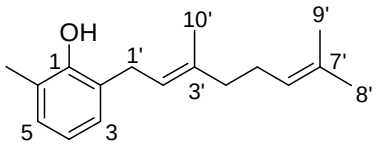
2-Bromo-6-methylanisole (**3.23**) (0.800 g, 3.98 mmol) was added slowly to a mixture of Mg (0.109 g, 4.50 mmol) turnings and 20 ml of dry THF under nitrogen. The resulting mixture was allowed to reflux for 5 h. The mixture was cannulated into a solution of geranyl bromide (0.864 g, 3.98 mmol) and 1.5 ml of 0.1 M Li_2CuCl_4/THF solution, stirring at 0 ^oC under nitrogen. The mixture was allowed to warm to room temperature and after 3 h another 1.5 ml of 0.1 M Li_2CuCl_4/THF was added. After 6 h, the last portion of 1.5 ml of 0.1 M Li_2CuCl_4/THF was added. After 24 h the reaction was quenched with distilled water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with dilute HCl, water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The reaction product was purified using silica column chromatography (1:4 diethyl ether: hexane) to yield compound **3.36** (0.669 g, 2.59 mmol, 65%) as a colourless oil.

^1H NMR (400 MHz, $CDCl_3$) δ_H ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.05 (2H, d, *J* = 7.5 Hz, H-3, 5), 6.99 (1H, t, *J* = 7.4 Hz, H-4), 5.28 (1H, t, *J* = 7.0 Hz, H-2'), 5.08 (1H, t, *J* = 6.8 Hz, H-6'), 3.71 (3H, s, OCH_3), 3.36 (2H, d, 7.2 Hz, H-1') 2.27 (3H, s, CH_3), 2.06 (2 x 2H, m, H-4', 5'), 1.74 (3H, s, H-10'), 1.69 (3H, s, H-8'), 1.61 (3H, s, H-9').

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.7 (C-1), 135.9 (C-3'), 131.3 (C-7'), 128.9 (C-5), 128.2 (C-3), 127.6 (C-2), 124.3 (C-6), 123.9 (C-6'), 123.0 (C-2'), 120.3 (C-4), 61.1 (OCH_3), 39.7 (C-4'), 30.6 (C-1'), 26.6 (C-5'), 25.6 (C-8'), 17.6 (C-9'), 16.2 (C-10), 16.0 (CH_3).

IR ν_{max}: 2932, 1715, 1518, 1452, 1372, 1257, 1153, 913 cm^{-1}.

5.8.2 Preparation of 2-(3,7-dimethylocta-2,6-dienyl)-6-methylphenol (3.37)



3.37

To a mixture of 10 ml dry THF and metallic lithium (0.0729 g, 10.5 mmol), stirring at 0 ^oC under nitrogen, was added ethylenediamine (0.883 g, 14.7 mmol). Compound **3.36** (0.500 g, 1.94 mmol) was added and the solution was allowed to stir at 0 ^oC for 3 h. The remaining lithium was separated from the resulting deep blue solution and quenched with methanol. The pink reaction mixture was quenched with distilled water (10 ml) and extracted with diethyl ether (3 x 20 ml). The organic layer was washed with dilute HCl, water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction product was purified using silica column chromatography (1:4, diethyl ether-hexane) to yield compound **3.37** (0.364 g, 1.49 mmol, 77%) as a yellowish oil.

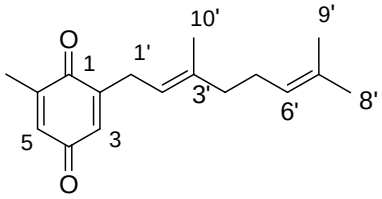
^1H NMR (400 MHz, $CDCl_3$) δ_H 7.02 (1H, d, *J* = 7.4 Hz, H-3), 6.97 (1H, d, *J* = 7.4 Hz, H-5), 6.78 (1H, t, *J* = 7.4 Hz, H-4), 5.34 (1H, t, *J* = 7.2 Hz, H-2'), 5.17 (1H, br s, OH), 5.09 (1H, t, *J* = 7.6 Hz, H-6'), 3.38 (2H, d, *J* = 7.4 Hz, H-1'), 2.25 (3H, s, CH_3), 2.12 (2 x 2H, m, H-4', 5'), 1.80 (3H, s, H-10'), 1.71 (3H, s, H-8'), 1.62 (3H, s, H-9').

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 152.9 (C-1), 138.7 (C-3'), 132.0 (C-7'), 129.0 (C-5), 127.5 (C-3), 126.1 (C-2), 124.4 (C-6), 123.8 (C-6'), 121.9 (C-2'), 120.3 (C-4), 39.7 (C-4'), 30.3 (C-1'), 26.3 (C-5'), 25.7 (C-8'), 17.7 (C-9'), 16.1 (C-10), 15.8 (CH_3)

HRMS (ESI$^+$) $[M+Na]^+$ obsd. *m/z* 267.1726 (calc. for $C_{17}H_{24}ONa$ 267.1725).

IR ν_{max}: 3536, 2918, 1651, 1614, 1438, 1375, 1291, 912 cm^{-1}.

5.8.3 Preparation of 2-(3,7-dimethylocta-2,6-dienyl)-6-methyl-1,4-benzoquinone (2.26)



2.26

Compound **3.37** (0.150 g, 0.614 mmol) was dissolved in dry CH_3CN (20 ml) and salcomine (0.262 g, 0.805 mmol) was added to the resulting solution and the reaction mixture was allowed to stir for 24 h at room temperature. The resulting solution was filtered, the solids discarded, and the filtratequenched with water and extracted with diethyl ether (3 x 20 ml). The combined extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction product was purified using silica column chromatography (1:9, ethyl acetate-hexane) to yield compound **2.26** (0.100 g, 0.387 mmol, 63%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.56 (1H, s, H-3), 6.48 (1H, s, H-5), 5.16 (1H, bt, *J* = 7.5 Hz, H-2'), 5.09 (1H, t, *J* = 6.9 Hz, H-6'), 3.14 (2H, d, *J* = 7.6 Hz, H-1'), 2.10 (1H, m, H-4', 5'), 2.07 (3H, d, *J* = 1.72, CH_3), 1.70 (3H, s, H-10'), 1.63 (3H, s, H-8'), 1.61 (3H, s, H-9).

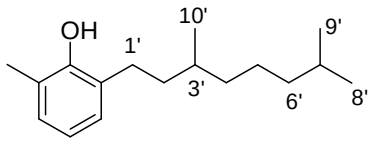
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 188.0 (C-4), 187.9 (C-1), 148.5 (C-2), 145.8 (C-6), 139.8 (C-3'), 133.2 (C-5), 132.2 (C-3), 131.8 (C-7'), 123.9 (C-6'), 118.0 (C-2'), 39.6 (C-4'), 27.5 (C-1'), 26.4 (C-5'), 25.6 (C-8'), 17.6 (C-9'), 16.1 (C-10'), 15.9 (CH_3).

HRMS (ESI$^+$) $[M+H]^+$ obsd. *m/z* 259.1696 (calc. for $C_{17}H_{23}O_2$ 259.1695).

IR ν_{max}: 2918, 1651, 1614, 1438, 1375, 1291, 912 cm^{-1}.

5.9 Syntheis of Analogue 2.27

5.9.1 Preparation of 2-(3,7-dimethyloctyl)-6-methylphenol (3.38)



3.38

Compound **3.37** (0.200 g, 0.818 mmol was dissolved in dry MeOH (15 ml) and to the resulting solution 10% Pd/C as a catalyst was added. The reaction mixture was stirred for 1 h at room temperature under a hydrogen atmosphere. The product **3.38** was obtained (0.199 g, 0.801 mmol, 99%) as a yellowish oil.

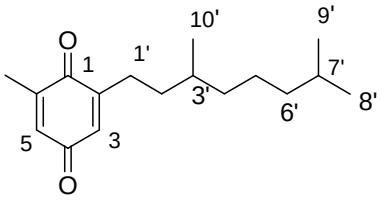
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.99 (2H, d, *J* = 7.5 Hz, H-3, 5), 6.79 (1H, t, *J* = 7.5 Hz, H-4), 4.60 (1H, br s, OH), 2.61 (2H, m, H-1'), 2.77 (3H, s, CH_3), 1.69-1.11 (10H, m, H-2', 3', 4', 5', 6', 7'), 0.97 (3H, d, *J* = 6.4 Hz, H-10'), 0.89 (6H, d, *J* = 6.6 Hz, H-8', 9').

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 151.7 (C-1), 128.4 (C-3), 128.2 (C-5), 127.6 (C-2), 123.0 (C-6), 120.2 (C-4), 39.3 (C-6'), 37.1 (C-2', 4'), 32.8 (C-3'), 27.9 (C-7'), 27.6 (C-5'), 24.6 (C-1'), 22.6(C-8', 9), 19.6 (C-10'), 15.8 (CH_3).

HRMS (ESI⁻) $[M-H]^-$ obsd. *m/z* 247.2217 (calc. for $C_{17}H_{27}O$ 247.2215).

IR ν_{max}: 3528.5, 2923,9 1466.6, 1190.5, 770.6, 746.6 cm^{-1}.

5.9.2 Preparation of 2-(3,7-dimethyl-octyl)-6-methyl-1,4-benzoquinone (2.27)



2.27

Compound **3.38** (0.100 g, 0.402 mmol) was dissolved in dry CH_3CN (20 ml) and salcomine (0.196 g, 0.604 mmol) was added to the resulting solution and the reaction mixture was allowed to stir for 24 h at room temperature. The resulting solution was filtered, the solids were discarded, quenched with water and extracted with diethyl ether (3 x 20 ml). The combined extracts were dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction product was purified using silica column chromatography (1:4-diethylether: hexane) to yield compound **2.27** (0.0792 g, 0.301 mmol, 75%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.56 (1H, s, H-3), 6.51 (1H, s, H-5), 2.43 (2H, m, H-1'), 2.07 (3H, s, CH_3), 1.56-1.12 (10H, m, H-2', 3', 4', 5', 6', 7'), 0.93 (3H, d, J= 6.5, H-10'), 0.88 (6H, d, 6.5 Hz, H-8', 9').

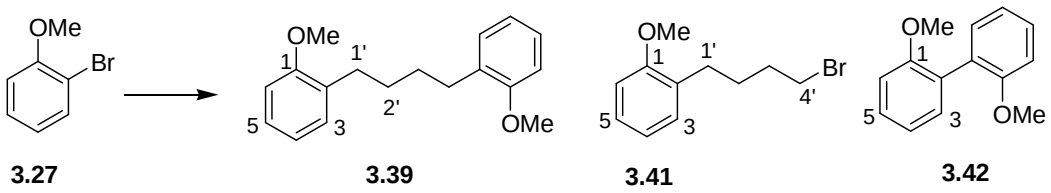
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 187.9 (C-4), 187.8 (C-1), 150.1 (C-2), 145.9 (C-6), 133.0 (C-5), 132.2 (C-3), 39.2 (C-6'), 36.9 (C-2'), 35.1 (C-4'), 32.6 (C-3'), 27.9 (C-7'), 26.8 (C-5'), 24.6 (C-1'), 22.6 (C-8'), 22.5 (C-9'), 19.4 (C-10'), 16.0 (CH_3).

HRMS (ESI$^+$) $[M+H]^+$ obsd. *m/z* 263.2012 (calc. for $C_{17}H_{27}O_2$ 263.2013).

IR ν_{max}: 2925.8, 1651.4, 1614.0, 1402.9, 1391.2, 1196.8, 1031.9, 912.4 cm^{-1}.

5.10 Approach towards synthesis of bis-benzoquinone (2.28)

5.11.1 Synthesis of 3.39



3.27 **3.39** **3.41** **3.42**

Compound **3.27** (1.50 g, 8.02 mmol) was added slowly to a mixture of Mg (0.220 g, 9.05 mmol) turnings and 20 ml of dry THF under nitrogen. The resulting mixture was allowed to reflux for 3h. The mixture was cannulated into a solution of 1,4-dibromobutane (0.866 g, 4.01 mmol) and 1.5 ml of 0.1 M Li_2CuCl_4/THF solution, stirring at 0 ^oC under nitrogen. The reaction mixture was allowed to warm to room temperature and after 3 h another 1.5 ml of 0.1 M Li_2CuCl_4/THF was added. After 6 h, the last portion of 1.5 ml of 0.1 M Li_2CuCl_4/THF was added. After 24 h the reaction was quenched with distilled water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with dilute HCl, water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The solid residure was purified using silica column chromatography (hexane) to yield three compounds.

Compound 3.39 (0.466 g, 1.72 mmol, 43%) was isolated as colourless solid.

^1H NMR (400 MHz, $CDCl_3$) δ_H 7.15 (4H, m, H-3', 5'), 6.86 (4H, m, H-4', 6'), 3.83 (6H, s, OCH_3), 2.65 (4H, t, J = 7.5 Hz, H-1'), 1.64 (4H, qr, H-2'),

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.5 (C-1), 131.3 (C-3) 129.8 (C-5), 126.7 (C-2), 120.3 (C-4), 110.3 (C-6), 55.3 (OCH_3), 30.0 (C-1'), 29.7 (C-2').

IR ν_{max}: 2938, 2856, 1589, 1492, 1455, 1237, 1022, 735, 731 cm^{-1}.

2-(4-bromo-butyl)anisole (**3.41**) (0.185 g, 0.762 mmol, 19%) was isolated as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.20 (1H, t, *J* = 7.5 Hz , H-3), 7.14 (1H, d, *J* = 8.4 Hz, H-5), 6.89 (2H, m, H-4, 6), 3.84 (3H, s, OCH_3), 3.45 (2H, t, *J* = 7.1 Hz, H-4'), 2.67 (2H, t, *J* = 7.5 Hz, H-1'), 1.92 (2H, qr, H-3'), 1.76 (2H, qr, H-2'),

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.4 (C-1), 130.2 (C-3), 129.8 (C-5), 127.1 (C-2), 124.4 (C-4), 110.3 (C-6), 55.2 (OCH_3), 33.7 (C-3'), 32.5 (C-4'), 29.2 (C-2'), 28.3 (C-1').

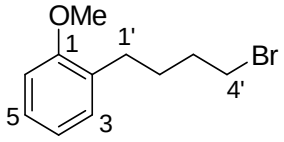
IR ν_{max}: 2935, 1599, 1492, 1239, 1031, 750 cm^{-1}.

2,2'-Dimethoxy-biphenyl (3.42) (0.077 g, 0.361 mmol, 9.0%) was isolated as colourless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31 (2H, td, *J* = 8.7, 1.8 Hz, H-5), 7.28 (2H, d, J = 7.2 Hz, H-3), 6.98 (4H, m, H-4, 6), 3.75 (3H, s, OCH_3),

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.1 (C-1), 131.4 (C-5), 128.5 (C-3), 127.9 (C-2), 120.3 (C-4), 111.2 (C-6), 55.7 (OCH_3).

5.10.2 Preparation of 2-(4-bromo-butyl)anisole (3.41)



3.41

o-Bromoanisole (**3.27**) (3.00 g, 16.0 mmol) was added slowly to a mixture of Mg (0.440 g, 18.1 mmol) turnings and 20 ml of dry THF under nitrogen. The resulting mixture was allowed to reflux for 2 h. The mixture was cannulated into a solution of 1,4-dibromobutane (3.45 g, 16.0 mmol) and 1.5 ml of 0.1 M Li_2CuCl_4/THF solution, stirring at 0 ^{o}C under nitrogen. The reaction mixture was allowed to warm to room temperature and after 3 h another 1.5 ml of 0.1 M Li_2CuCl_4/THF was added. After 6 h, the last portion of 1.5 ml of

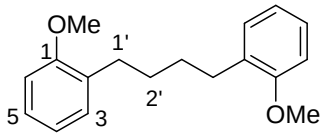
0.1 M Li_2CuCl_4/THF was added. After 24 h the reaction was quenched with distilled water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with dilute HCl, water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (hexane) to yield compound **3.41** (2.68 g, 11.0 mmol, 69%) as a colourless oil,

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.20 (1H, t, *J* = 7.5 Hz , H-3), 7.14 (1H, d, *J* = 8.4 Hz, H-5), 6.89 (2H, m, H-4, 6), 3.84 (3H, s, OCH_3), 3.45 (2H, t, *J* = 7.1 Hz, H-4'), 2.67 (2H, t, *J* = 7.5 Hz, H-1'), 1.92 (2H, qr, H-3'), 1.76 (2H, qr, H-2'),

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.4 (C-1), 130.2 (C-3), 129.8 (C-5), 127.1 (C-2), 124.4 (C-4), 110.3 (C-6), 55.2 (OCH_3), 33.7 (C-3'), 32.5 (C-4'), 29.2 (C-2'), 28.3 (C-1').

IR ν_{max}: 2935, 1599, 1492, 1239, 1031, 750 cm^{-1}.

5.10.3 Synthesis of Compound 3.39



3.39

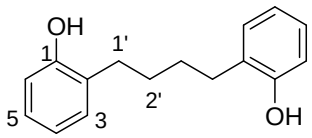
o-Bromoanisole (**3.27**) (1.87 g, 10.0 mmol) was added slowly to a mixture of Mg (0.292 g, 12.0 mmol) turnings and 20 ml of dry THF under nitrogen. The resulting mixture was allowed to reflux for 3h. The mixture was cannulated into a solution of 1-(4-bromobutyl)anisole (**3.41**) (2.43 g, 10.0 mmol) and 1.2 ml of 0.1 M Li_2CuCl_4/THF solution, stirring at 0 ^oC under nitrogen. The reaction mixture was allowed to warm to room temperature and after 3 h another 1.2 ml of 0.1 M Li_2CuCl_4/THF was added. After 6 h, the last portion of 1.2 ml of 0.1 M Li_2CuCl_4/THF was added. After 24 h the reaction was quenched with distilled water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with dilute HCl, water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (hexane) to yield **3.39** (1.83 g, 6.80 mmol, 68%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.15 (4H, m, H-3', 5'), 6.86 (4H, m, H-4', 6'), 3.83 (6H, s, OCH_3), 2.65 (4H, t, *J* = 7.5 Hz, H-1'), 1.64 (4H, qr, H-2'),

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 157.5 (C-1), 131.3 (C-3) 129.8 (C-5), 126.7 (C-2), 120.3 (C-4), 110.3 (C-6), 55.3 (OCH_3), 30.0 (C-1'), 29.7 (C-2').

IR ν_{max}: 2938, 2856, 1589, 1492, 1455, 1237, 1022, 735, 731 cm^{-1}.

5.10.4 Synthesis of Compound 3.40



4.40

To the mixture of 10 ml dry THF and metallic lithium (0.277 g, 39.9 mmol), stirring at 0 ^{o}C under nitrogen, was added ethylenediamine (3.68 g, 53.9 mmol). Compound **3.39** (2.00 g, 7.40 mmol) was added and the solution was allowed to stir at 0 ^{o}C for 6 h. The remaining lithium was separated from the resulting deep blue solution and quenched with methanol. The pink reaction mixture was quenched with distilled water (15 ml) and extracted with diethyl ether (3 x 20 ml). The organic layer was washed with dilute HCl, water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction products were purified using silica column chromatography (1:4, diethyl ether-hexane) to yield compound **3.40** (1.17 g, 4.81 mmol, 65%) as a whitish solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.10 (4H, m, H-3, 5), 6.87 (2H, t, *J* = 7.6 Hz, H-4), 6.77 (2H, d, *J* = 7.9 Hz, H-6), 2.68 (4H, t, *J* = 7.1 Hz, H-1'), 1.71 (4H, qr, H-2'),

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 153.4 (C-1), 130.3 (C-3), 128.4 (C-5), 127.1(C-2), 120.8 (C-4), 115.3 (C-6), 29.5 (C-1', 2').

IR ν_{max}: 3487, 2938, 2856, 1587, 1500, 1448, 1168, 761, 733 cm^{-1}.