THE SYNTHESIS OF ANALOGUES OF THE ANTI-TB (AGENT: DIOSPYRIN)

by

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A thesis submitted in partial fulfillment of the requirements for the degree of Magister Scientiae in the Department of Chemistry, University of the Western Cape.

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ABSTRACT

Diospyrin, a bisnaphthyl quinone molecule with proven anti-TB activity can be retrosynthetically formulated into two halves. In this work, the analogue chosen to be synthesized was similarly retrosynthesized into two halves. The one half, 2-bromo-5-methoxy-1,4-naphthoquinone was synthesized successfully starting from 1,5-diacetoxynaphthalene which was oxidized and brominated with N-bromosuccimide to the corresponding 5-acetoxy-2-bromo-1,4-naphthoquinone. Hydrolysis of the acetoxy group was effected with methanolic potassium hydroxide followed by methylation of the phenolic group by methyl iodide and silver (II) oxide.

The second half of the analogue, 7-bromo-1,4,6-trimethoxynaphthalene was attempted to be synthesized in the following way. Condensation between benzoquinone and Danishefsky's diene afforded an adduct which after much investigation was converted into 1,4,6-triacetoxynaphthalene. Through the process of transformations viz., oxidation, hydrolysis and phenol protection, the triacetoxynaphthalene was converted into 6-hydroxy-1,4-dimethoxynaphthalene. Attempts to brominate both this latter phenol as well as the original Diels-Alder adduct at C-7 proved to be problematic but gave some interesting results. Finally, by converting the 6-hydroxy-1,4-dimethoxynaphthalene into the corresponding carbamate, it could be transformed into the C-7 boronic acid albeit in low yield.

In two reference Suzuki coupling experiments, the boronic acid derived from the carbamate of phenol was condensed with 2-bromo-1,4-dimethoxybenzene and 6-methoxynaphthyl-2-boronic acid was coupled with 2-bromo-5-methoxy-1,4-naphthoquinone.

Finally, Suzuki coupling between 2-bromo-5-methoxy-1,4-naphthoquinone and C-7 boronic acid of 6-(N,N-diethylcarbamyloxy)-1,4-dimethoxynaphthalene proved to be problematic with a very low yield of biaryl product being detected.

Keywords

Diospyrin

Mycobacterium tuberculosis

2,5-Dibromobenzoquinone

2-Bromo-5-methoxynaphthoquinone

6-Hydroxy-1,4-dimethoxynaphthalene

Bromination of 6-hydroxy-1,4-dimethoxynaphthalene

6-N,N-Diethylcarbamyloxy-1,4-dimethoxynaphthalene

6-N,N-diethylcarbamyloxy-1,4-dimethoxy-7-naphthylboronic acid

5-Methoxy-2-(6'-methoxynaphth-2-yl)-1,4-naphthoquinone

5-Methoxy-2-[7'-(6'-N,N-diethylcarbamyloxy)-1',4'-dimethoxynaphthyl]-1,4-naphthoquinone

ABBREVIATIONS

CAN	cerium (IV) ammonium nitrate
atm	atmosphere
Br_2	bromine
THF	tetrahydrofuran
KOAc	potassium acetate
K_3PO_4	potassium phosphate
Ac_2O	acetic anhydride
Pyr	pyridine
HCl	hydrochloric acid
$Pd(PPh_3)_2Cl_2$	bis(triphenylphosphine)palladium(II) chloride
$Na_2S_2O_4$	sodium dithionite
MeOH	methanol
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
s-BuLi	secondary butyllithium
$B(OMe)_3$	trimethoxy borane
$(C_2H5)_2OMgBr_2$	magnesium bromide diethyl etherate
Ag_2O	silver (I) oxide
AgO	silver (II) oxide
HNO_3	nitric acid
Na_2SO_4	sodium sulphate
MnO_2	manganese oxide
KOH	potassium hydroxide
H_2SO_4	sulfuric acid
AcOH	acetic acid
LDA	lithium diisopropylamide
$FeCl_3$	iron (III) chloride
$PdCl_2$	palladium chloride
DCM	dichloromethane

TMSCl	trimethylsilylchloride
DMF	dimethyl formamide
H_2	hydrogen
CH_3CN	acetonitrile
DBU	1,8-diazabicyclo[5.4.0]undecene-7
rt	room temperature
Sn_2Bu_6	hexabutylditin
Tf_2O	trifluoromethanesulfonic anhydride
NaOAc	sodium acetate
H_2O	water
n-BuLi	n-butyllithium
NBS	N-bromosuccinamide
Zn	Zinc
BnI	benzyl iodide
HRMS	High Resolution Mass Spectroscopy
'M'	molar
'h'	hour
's'	singlet
'd'	doublet
'dd'	doublet of a doublet
't'	triplet
'm'	multiplet
'q'	quartet
'bs'	broad singlet

DECLARATION

I declare *The Synthesis of Analogues of the Anti-TB Agent*: *Diospyrin* to be my own work, that it has not been submitted before for any degree or examination at any other institution, and all the sources I have used or quoted have been indicated and acknowledged by complete references.

MLULEKI SITOZA Sign. .....

NOVEMBER 2005

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CHAPTER 1

INTRODUCTION

The prevalence of tuberculosis (TB) as a major disease in many areas of the world has promoted the search for novel compounds that are active against the resistant strains of *Mycobacterium tuberculosis*. It is estimated that TB claims between 2 and 3 million lives a year and shows every sign of spiraling out of control. According to the World Health Organization (WHO), there were 8.4 million new TB cases in 1999 up from 8 million in 1997. If there is no improvement in reducing this giant killer, 10.2 million new cases are expected in 2005 and Africa is expected to have more cases than any other WHO region.[1] The increase in the prevalence of multi-drug-resistant strains of this organism and the emergence of AIDS-related TB are the main reasons why TB is the disease with the fifth highest fatality rate in the world.[2]

Tuberculosis (TB) remains a serious health problem in many areas of the world more especially in the developing countries. It is the kind of disease that spreads by contact with an infected person and is thus highly contagious. It is estimated that about 30-60% of adults in the developing countries are infected with *Mycobacterium tuberculosis*. It is also postulated that between now and the year 2020, nearly 1 billion people will be newly infected and 200 million will become sick and 70 million will die from TB if it is not controlled.[3] The World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease (IUATLD) in 1989 have estimated that approximately 8-10 million people develop TB and 3 million die because of TB each year.[3] In South

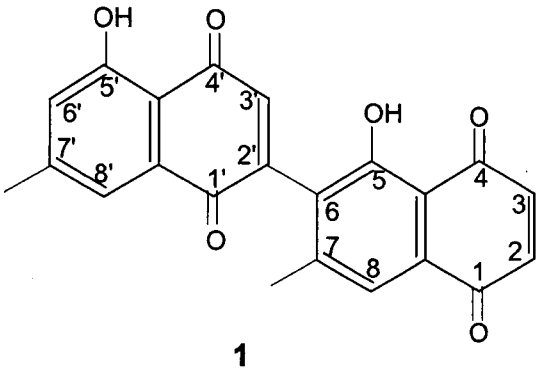
Africa, over 3 in every one thousand people die because of TB, which is the highest rate in the world.[3] TB is the most commonly notifiable disease in South Africa and the fifth largest cause of death among the black population. People who are infected by the Human Immunodeficiency Virus (HIV) are likely to be affected by TB. They often develop this disease before other manifestations of AIDS become visible.[4] It is said that the two diseases, TB and AIDS have an "evil collaboration".

TB therapy has been improved in the recent past and the current treatment regimes for TB are based on multi-drug therapy with usually 3 or 4 anti-tuberculosis drugs being administered. The problem of multi-drug resistant tubercle bacilli appears for various drugs, for instance, isoniazid, rifampin, streptomycin and ethambutol.[5] *Mycobacterium tuberculosis* that is resistant to the drugs is very difficult to treat and requires more and different medications for a longer period of treatment. Due to the increasing resistant strains of *mycobacteria*, the need for new anti-tuberculosis agents is urgent. The WHO recently reported that, globally, 2% of all cases of TB are multi-drug resistant. In the United States of America (USA) and other high resource regions these however, can be treated at great costs (> US$ 250 000 per case). They are using very long courses of toxic drugs that have raised serious problems of compliance [5] and South Africa is witnessing an outbreak in the number of cases of drug-resistant tuberculosis. In some areas of South Africa 1 in 10 cases of TB reported is ascribed as being resistant to the treatment. It is important to have new drugs that can cure TB and ideally be produced from local sources.

The use of some drugs derived from natural vegetation had a great impact in curing this "giant killer" in many developing countries. Herbal medicines have been used for centuries in rural areas by traditional healers and have been improved in developed countries. About twenty South African medicinal plants used to treat pulmonary diseases[5] have been screened for activity against drug-resistant strains of *Mycobacterium tuberculosis*. People used plants accidentally for hundreds of years, but now plants are enjoying a renaissance of interest and are used all over the world again. A preliminary screening of acetone and water plant extracts against a drug-sensitive strain of *Mycobacterium tuberculosis* viz., $H_{37}Rv$, was done by the agar plate method. Fourteen of the twenty plant acetone extracts showed inhibitory activity at a concentration of 0.5 mg/ml. Acetone and water extracts of *Euclea natalensis*, such as *Helicrysum melanaome*, *Thymus vulgaris* were also found to inhibit the growth of *M. tuberculosis*. [5] The important activity of the extracts of *Euclea natalensis* (*Ebecnaceae*) and that of the bisnaphthoquinonoid diospyrin **1**, isolated from this plant was observed against drug-susceptible and drug-resistant strains of *M. tuberculosis*.[5] Three derivatives viz., diospyrin dimethylether **1.2**, diospyrin dimethylether hydroquinone **1.3** and diospyrin diethylether hydroquinone **1.4** [5,6] and have also been investigated for their inhibitory activity against *Mycobacterium tuberculosis in vitro*. In South Africa, medicinal plant species that were traditionally used in the treatment of tuberculosis have also been investigated.

Drug resistance is shown to complicate the treatment of tuberculosis. Treatment of people or patients with multi-drug resistance which is defined as resistance to at least isoniazid and rifampicin, is long, costly and requires the use of drugs which frequently have a negative impact.[7] The outcome of treatment of multi-drug resistant tuberculosis is poor with low cure and increased fatality ratios.[8] Patients that are easily attacked by multi-drug resistant disease (MDR-TB) are those being infected by the human immunodeficiency virus (HIV).[9] The quality of tuberculosis treatment is a key element of tuberculosis control because effective treatment quickly renders the patient noncontagious and therefore stops the transmission of the virus to the community.[10]

Diospyrin **1** is an orange-red naphthoquinonylnaphthoquinone that is present in the heartwood of many species of diospyros trees.[11] Various workers [11] have investigated the potent anti-mycobacterial properties of diospyrin **1** and its analogues. Diospyrin **1** was first isolated in 1961 by Kapil and Dhar [12] as an orange-red constituent of *Diospyros montana*, a small to medium-sized tree found throughout India. The structure of **1** was firstly proposed by Ganguly and Govindachari [13] in 1966 as a dimer of 7-methyljuglone **1.1** linked between C-2' and C-3, which implied the two naphthoquinone halves are linked through quinone-quinone sides. Later, Sidhu and Pardhasaradhi [14] proposed the correct structure of diospyrin as **1**.



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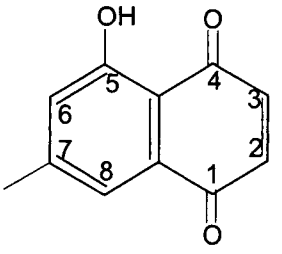

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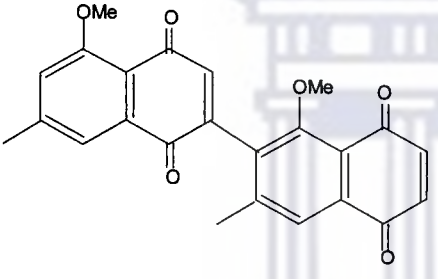

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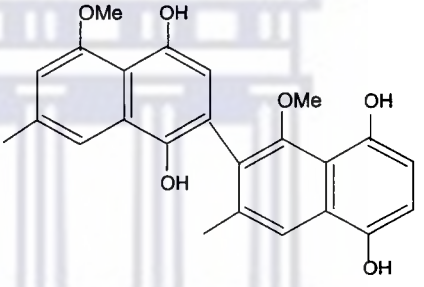

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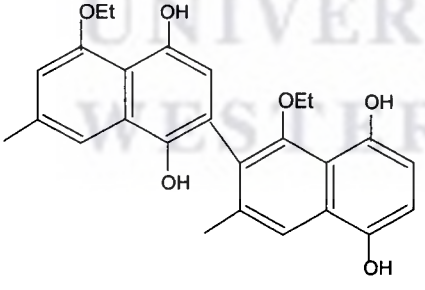


1.4

In this case the two halves of the binaphthoquinone are linked through the C-2' and C-6 C-atoms. Diospyrin **1** is optically inactive, which implies that there is no restricted rotation around the connecting bond between C-2' and C-6. In 2000 Yoshida and Mori [11] synthesized diospyrin **1** to support the findings by Sidhu and Pardhasaradhi.[14,15] The two OH groups of diospyrin participate in bifurcated intra and intermolecular hydrogen bonds to C=O acceptors. The intramolecular O-H…O bonds are much shorter and stronger than the intermolecular links. Recent studies have demonstrated that this drug kill tumor cells through apoptosis, and thus, has been recognized as a target for cancer therapy.[16] Diospyrin **1** has also been isolated from other species of Euclea such as *E. pseudebenus* [17], *E. schimperi and E.divinorum.* [18] The antifungal, antibacterial and termite resistant properties of Diospyros and Euclea species have all been attributed to the occurrence of the naphthoquinones. There is ample evidence from various studies done earlier that the strong antibacterial action of the roots of *E. natalensis* is due to naphthoquinones.[19,20,21] Diospyros belongs to the family Ebeneceae, a family consisting of seven genera containing about 500 species of tropical and subtropical trees and shrubs. The family is represented in Nigeria by 26 species of the genus *Diospyros*.

In a recent communication [22], it has been demonstrated that diospyrin **1** was isolated from *Euclea natalesis* found in Maputaland in KwaZulu Natal, South Africa which was very active against strains of drug-sensitive and drug resistant *M. tuberculosis*. The traditional use of *E. natalensis* extract against sores, purulent lesions and skin infections, cough-cold could possibly be attributed to the activity of diospyrin against *S. aureus* and *M. tuberculosis*. This might explain the plant's use in traditional remedies against TB and the credibility of earlier reports of the beneficial *anti-microbial*, *anti-protozoal*, *anti-tryponosomal* and *anti-schistiomiasic* effect of this naphthoquinone. The *anti-microbial* properties of the root extract provide the reason for its use in folk medicine also to treat

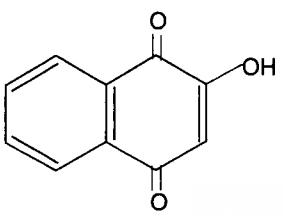
leprosy, which is caused by another mycobacterial species. The isolation of the active principle from the root extract of *E. natalensis* was initiated by a preliminary bioassay using *S. aureus*.[22] A recent synthesis has been published in which diospyrin **1** was to be tested against parasitic protozoan diseases.[11] In 1995 Hazra *et al.*[23] reported the *in vitro* antiplasmodial effects of diospyrin **1**, suggesting it to be a useful model for the development of anti-malarial drugs. In 1996 Hazra *et al.*[24] reported *in vitro* activity of diospyrin **1** and its derivatives **1.2**, **1.3**,**1.4** against *Leishmania donovani, Trypanosoma cruzi and T. brucei*. These are the causative agents of the protozoan diseases *leishmaniasis* and *trypanosomiasis*. The minimum inhibitory concentration (MIC) of diospyrin **1** was found to be 0.1mg/ml for many antibiotic resistant including antibiotic susceptible strains of *M. tuberculosis*. This MIC was also found reasonable for the treatment of *M. tuberculosis strains* that were resistant to seven major drugs. The validity of diospyrin **1** as an anti-tuberculosis agent is being investigated *in vivo* in mice infected with antibiotic sensitive and antibiotic strains of *M. tuberculosis*. [6]

Diospyrin **1** and its derivatives, **1.2**, **1.3**, **1.4** have been found to have antitumor properties against *Ehrlich ascites carcinoma* and *sarcoma 180* [25] and exhibit antiprotozoal activities towards *L. donovani, T. brucei, T. cruzi and P. falciparum* in *vitro*.[26] It has been shown that diospyrin **1** is a potent inhibitor of type I DNA topoisomerase of *L. donovani*; like camptothecin.[27] Diospyrin **1** selectively inhibits topoisomerase I and does not inhibit topoisomerase II of *L. donovani*, as detemined by decatenation of *L. donovani* kDNA, which contains large interlocked, 830-bp catenated DNA circles. Diospyrin **1** does not show any inhibition of topoisomerase II of *L. donovani* even at concentrations of up to 50μg/ml, which is 10 times higher than the concentration that inhibits topoisomerase I of *L. donovani*. Topoisomerase I introduces a single-strand nick in the phosphodiester bond of the DNA, allowing an intact strand to

pass through the nick and rejoins the nicked strand of the DNA. A covalent bond is formed between the 3'-OH group of the DNA backbone and the tyrosine group at the active site of topoisomerase I. After 100 minutes of incubation of *L. donovani* cells in 1 μg/ml of diospyrin **1**, the respiration with respect to the control was inhibited by about 42%, while the glucose-stimulated respiration was inhibited by 36%. This was also done for 2.5 μg/ml of diospyrin **1**; the respiration with respect to the control was inhibited by 80%, while the glucose-stimulated respiration was inhibited by 67% with respect to the control.[28] At a concentration of 5μg/ml, there was no consumption of oxygen by the *L. donovani* cells with only 60 minutes of contact with diospyrin.[28]

The inhibition by diospyrin is relatively specific, since a 10-fold higher concentration is required to inhibit DNA topoisomerase I from calf thymus. DNA topoisomerases are essential enzymes that regulate the conformational changes in DNA topology by catalyzing the concerted breakage and rejoining of DNA strands during normal cellular growth. Over the past few years there has been considerable pharmacological interest in these enzymes because inhibitors of DNA topoisomerases represent a major class of anticancer drugs. Diospyrin **1** is similar to β-lapachone **1.6**, a naphthoquinone and also a novel inhibitor of type I DNA topoisomerase with respect to its binding with enzyme and inhibition of catalytic activity of the enzymes.[29] The advantage of diospyrin **1** is that, it can also induce the formation of a stable cleavage complex of which β-lapachone **1.6** cannot do. It also stabilizes the cleavable complex of *L. donovani* as camptothecin **1.7** does, but it differs from camptothecin **1.7** with respect to its mode of action. Diospyrin **1** alone can bind with the enzymes unlike camptothecin **1.7**. Simultaneous incubation of large molar excess of enzyme DNA and diospyrin at inhibitory concentrations (5 μg/ml

and above) leads to stabilization of enzyme DNA complex. Therefore, diospyrin is a novel topoisomerase I poison.[27]



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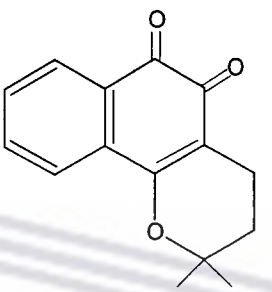

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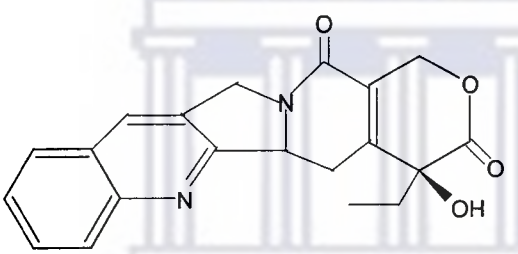

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Quinonoid compounds are widely distributed in nature, mainly in respiratory organisms, animal and plant cells. Some of these quinones act in an important role in linking the electron transport chains in the biochemistry of energy of their hosts.[16] Some of them act as "defensive weapons" in the sense that the organism carrying the kind of quinoid fluid would defend itself from the predator or invading pathogens. A number of quinonoids e.g. daunomycin group of drugs based on anturacyclin antibiotics and their synthetic analogues have been found to possess significant antitumor activity by virtue of their facile redox cycling capacity.[28] The prospective antimycobacterial activity of quinonoid compounds, more especially those extracted from natural sources, need to be investigated

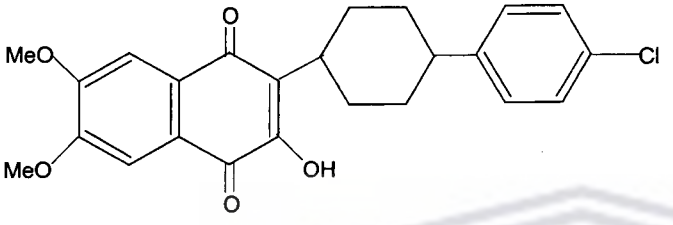
more intensively. The *Lawsonia inermis Linn.* has been reported to be active against *Mycobacteria tuberculosis*.[5] This suggests the involvement of lawsone, i.e. 2-hydroxynaphthoquinone **1.5** known to be the major bioactive component found in this herb. In addition, the dimeric form of lawsone has been found to be inactive. This shows the influence that structural modification may have on the biological activity of the bisnaphthoquinonoids e.g. diospyrin **1** a bisnaphthoquinone that has been reported to be active against *Mycobacterium tuberculosis*.[23,26]

In recent times, the synthesis of some diospyrin analogues led to the provision of more potent inhibitors against murine tumors.[24] The semi-synthetic derivatives such as diospyrin dimethylether **1.2** and diospyrin dimethylether hydroquinone **1.3** exhibited stronger inhibition than diospyrin **1** itself. This might be attributed to the effect that structural modification has on the remarkably versatile electron transfer mechanism operating in the quinonoid compounds. The cytotoxity of many quinonoid compounds involves oxidative stress. The quinonoid compounds can act as pro-drugs through bio-reductive alkylation that involves a two-electron reduction to the corresponding hydroquinones that would react with biologically significant nucleophiles like DNA and protein. A single electron reduction of a quinonoid compound can give rise to a semi-quinone radical, which in turn would generate reactive oxygen species. In their studies Sutapta Chakrabarty *et al.*[16], described the cytotoxic activity of diospyrin **1** vis-à-vis some of these analogues **1.2**,**1.3** and **1.4** on four human cancer cell lines *in vitro*. The studies were carried out to evaluate the potential of each of these compounds for the time taken to induce apoptotic death to these transformed cells. Thus cytotoxic effects of diospyrin **1** and three analogues, **1.2**, **1.3** and **1.4** were examined in four human tumor cell lines:[16] *acute myeloblastic leukemia* (HL-60), *chronic myelogenic leukemia* (K-562), *breast adenocarrcinoma* (MCF-7) and *cervical epithelial carcinoma* (HeLa). In screening

studies, diospyrin diethylether hydroquinone **1.4** was found to be more active than the parent compound, diospyrin **1** and its other analogues **1.2** and **1.3**. Morphological characterization of the treated cells revealed that the mode of action of the cell death induced by the diethylether derivative **1.4** was mediated through apoptosis. This means that the chromatin condensation and nuclear fragmentation of the treated cells were clearly evident and the apoptotic index was positively correlated with the treatment dose. The diospyrin analogue **1.4**, exhibited enhanced cytotoxicity in all parameters employed in the study. The results clearly suggest its antitumor potential. Its action seemed to be specific for tumor cells since normal human lymphocytes are not susceptible. From the results presented here, it is evident that diospyrin analogue **1.4** is capable of eliminating human tumor cells of diverse origin through induction of apoptosis. This gives an indication of the potential therapeutic role this compound may have even though not as strong as other quinonoid antitumor agents.

Diospyrin **1** is an antitumor compound [25] capable of inhibiting *L. donovani* promastigotes.[26] Diospyrin **1**, isolated from the stem-bark of *diospyros Montana Robx.*, was found in another study to show important tumor inhibitory effects against Ehrlich ascites carcinoma *in vivo*. Diospyrin **1**, diospyrin dimethylether **1.2** and diospyrin dimethylether hydroquinone **1.3** were found to be much less effective than atovaquone **1.8** in reducing ATP levels in *P. carinii* after 24 hours of exposure.[30] The exposure of the organism to each of the three compounds **1**, **1.2**, **1.3** at 10μg/ml for 48 hours was reasonable and the results were comparable to those of the effects of atovaquone **1.8** at the same concentration for the same period of exposure. The inhibitory effects of the diospyrin compounds increased over time even at lower concentration. This means that diospyrin **1** has a longer life span than atovaquone. The inhibitory concentrations used for diospyrin **1**, diospyrin dimethylether **1.2** and diospyrin dimethylether hydroquinone **1.3** at

48 hours were 2.09, 1.67 and 2.59μg/ml respectively, were slightly greater than that of atovaquone **1.8** but were considered to indicate moderate activity on the efficacy scale. Atovaquone **1.8** was more efficacious than diospyrin compounds at 48 hours, but after 72 hours of exposure, the ICs for the same three compounds were markedly reduced to 0.69, 0.31 and 0.34μg/ml, respectively.



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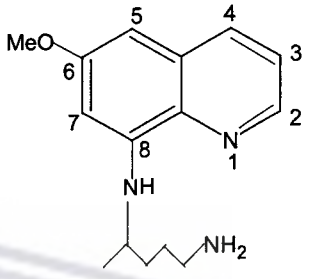

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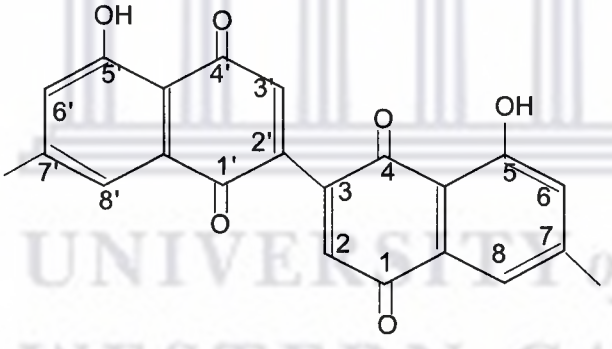
Other quinoid drugs with antiparasitic activity, as well as quinoid metabolites of other drugs e.g. primaquine **1.9** were suggested to block electron transport by functioning as analogs of ubiquinone. Atovaquone **1.8** was found to be the most effective drug in reducing ATP levels after 24 hours.[30] The disadvantage of atovaquone **1.8** is that, the inhibitory effect remains constant through the duration of the 3-day study, due to the fact that even though atovaquone **1.8** is available, it's no longer interacting with ATP. The diospyrin-based drugs, when considered individually demonstrate that the diospyrin dimethylether **1.2** exhibited greater activity against *P. carinii* than other quinoid compounds at 48 and 72 hours of exposure.

Leishmaniasis is a group of tropical diseases caused by a number of species of protozoan parasites belonging to the genus *leishmania*. These diseases range from benign cutaneous lesions through metastasizing mucocutaneous forms to the often-fatal visceralizing form.[27] In the present regime, sodium stibogluconate and meglumine antimonite have

that, it can help to reduce ATP levels at lower concentrations something that atovaquone **1.8** cannot do.[30] The exposure of *P. carinii* to pentamidine or diospyrin **1** and diospyrin analogues **1.2** and **1.3** causes a continual decrease in ATP levels over time.[30] It has been found that diospyrin **1** itself was slightly active at a dose of 5μg/ml causing only 22% inhibition of the parasite growth.

Diospyrin derivatives **1.2** and **1.3** produced more than 98% inhibition under comparable conditions. This means that structural modification of diospyrin could produce marked enhancement of its anti-leishmanial activity. The dimeric naphthoquinonoid analogue **1.10** did not show any inhibitory effect up to 5μg/ml concentration. The difference between diospyrin, **1** and dimer, **1.10**, is that the diospyrin linkage in the former is between quinone and the non-quinone sides of naphthoquinone halves, whereas in the case of **1.10** both quinones are linked through the quinone sides.



1.10

This finding explains the need to introduce appropriate structural changes in diospyrin leading to the antiparasitic activity. The dimethylether **1.2** and its hydroquinonoid analogue **1.3** were found to be the most active compounds, effecting almost 98% inhibition at a dose of 2.5μg/ml. The enhancement of the anti-leishmanial property in diospyrin itself has been feasible through the conversion of its phenolic –OH groups into methylethers, leaving the quinonoid groups free to take part in the redox cycling process, which generally gives rise to the biological activity of quinonoids.[26] A *L. donovani* cell-

suspension treated with 5μg/ml of diospyrin **1** was observed microscopically within 2-3 hours of drug contact.[28] These cells had been found to be distorted, showing no distinct boundary. This means that they were all swollen, non-motile and without any flagellum. Most of the cells were lysed after the 3rd hour. The untreated cells were found to be mostly motile, long and slender with their moving flagella projecting.[28] The growth of the cells in liquid media was totally stopped in the presence of diospyrin **1** at a low concentration viz., 1μg/ml. The total inhibition of respiration was observed with 5μg/ml of diospyrin. [28] Therefore, the *in vitro* susceptibility of cultured *L. donovani* towards diospyrin **1** is quite important.

One of the major therapeutic areas where natural products have played a significant role on longevity and an improvement to the quality of life is chemotherapy. Many anticancer drugs are sourced from natural products, plants or microorganisms. For the past few decades, anticancer compounds isolated from natural sources have gained in their significance due to their large chemical diversity. *Diospyros montana Robx.* was found to possess significant tumor inhibitory activity [25] during the exploration of indigenous medicinal plants for anticancer activity. *D. Montana* is a poisonous tree widely found in the tropics. This type of tree is commonly known as Tamala in Sanskrit and Bistendu in Hindi. The fruit of the tree is traditionally used to heal skin sores. The crushed leaves and fruit are used to stupefy fish. The paste of the stem bark in China is used to treat tumors. Through the process of extraction and other relevant techniques, diospyrin **1**, isolated from the stem bark was found to be the active principle responsible for antitumor activity.[25]

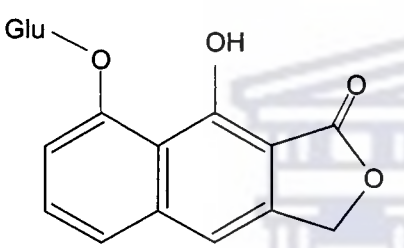
been used to treat the above-mentioned diseases but they do have side effects [27]. Amphotericin B and pentamides, even though used clinically are often of limited efficacy and are very toxic [31]. Because of side effects shown by the above-mentioned drugs, there is a need to improve the already existing drugs and find new molecular targets on which to base the future treatment strategies. Leishmaniasis affects about 12 million people in 80 countries. It is estimated that there are about two to three million new cases reported each year. It is also estimated that there are about 3 million people under risk of infection. Diospyrin **1** isolated from *D. montana* was reported to have leishmanicidal activity.[28] Diospyrin **1** is reported to be active against promastigotes of *L. donovani* even at low concentrations (1μg/ml). [28] It has been reported that diospyrin **1** exerts its leishmanicidal action against *L. donovani* by binding to the parasite's topoisomerase I, thus inhibiting the catalytic effect of the enzyme or by stabilizing the topoisomerase I-DNA binary complex. [32] The hydroxylated derivative **1.3** of diospyrin eliminates 73.8% of amastigotes in infected macophages at a concentration of 3 μM.

The mechanism of action of the hydroxylated diospyrin derivative **1.3** is based on its ability to perturb the electron transport chain in the mitochondria of the parasite or in the generation of free radicals during the interaction between the metabolite and the respiratory chain of the parasite.[32]

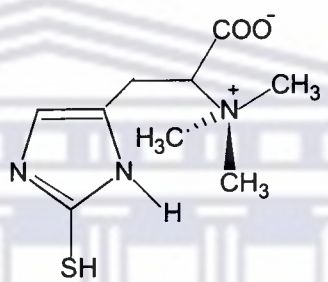
Diospyrin-based drugs were also tested against *L. donovani, T. cruzi* and *T. brucei* using enumeration of parasites after 5 days in culture to determine the 50% effective doses. [26] Diospyrin **1** itself and the dimethyl ether derivative **1.2** were ineffective in inhibiting the replication of *L. donovani* but both were able to reduce the growth of trypanosome species at 27 to 50μM concentration of diospyrin and at 2 to 17μM for the dimethylether derivative **1.2**. The hydroxyquinoid derivative **1.3** was found to be effective against *L. donovani* at 2.2μM and against *T. brucei* at 0.7μM. [30] The advantage of diospyrin **1** is

Diospyrin **1**, geshoidin **1.11** and ergothioneine **1.12** were investigated as potential inhibitors and inactivators of human glutathione transferases (GSTs).[33]

Ergothioneine **1.12**, because of its thiol group was investigated to determine whether it would play a protective role similar to glutathione (GSH) and dithiotheriol (DTT) towards GST P1-1. GST P1-1 contains a cysteine 47 residue that is highly reactive and susceptible to attack leading to inactivation of the enzyme.[34] Diospyrin **1** and geshiodin **1.11** inhibited the three GST isoforms, A1-1, M1-1 and P1-1, tested with inhibitory concentrations ranging from 0.1-0.5 μM.



1.11



1.12

Diospyrin **1** and geshoidin **1.11** are both hydrophobic but neither seemed to interact with the H-site as evident by the lack of competitive inhibition with respect to 1-chloro-2,4-dinitrobenzene (CDNB). This suggests that diospyrin **1** and geshoidin **1.11** are unlikely to be substrates of the GSTs. Other quinoid compounds have been found to inactivate GSTs by covalent modification of an essential amino acid.[35] This implies that, diospyrin **1** as a naphthoquinone, may inactivate P1-1 by covalent binding to the highly reactive cysteine 47 residue.[33] This interaction may arise from the redox activity of diospyrin **1** as a result of its quinoid structure.[34] Ergothioneine **1.12** had no effect on the GSTs at these concentrations. The effect of diospyrin **1** and geshoidin **1.11** on the kinetics of the GSTs was also determined. The trend changes $K_m^{GSH/CDNB}$ and $V_{max}^{GSH/CDNB}$ values with increase in the concentration of the natural products administered were used to determine

the type of inhibition that resulted. The inhibition was non-competitive with respect to both glutathione (GST) and 1-chloro-2,4-dinitrobenzene (CDNB). However, diospyrin **1** competitively inhibited A1-1 and M1-1 with respect to GST. Geshiodin **1.11** displayed mixed inhibition toward A1-1 with respect to GST. The k_i values for diospyrin **1** with respect to both GST and CDNB were in the range of 0.08-0.6 μM. These values were generally lower than those obtained with geshoidin **1.11**. These results indicate that diospyrin is a potent inhibitor of GSTs A1-1, M1-1 and P1-1. Diospyrin **1** was found to be a potent in-activator and inactivated P1-1.[33] In-activation of P1-1 by ergothioneine **1.12** may have implications for the anti-oxidant roles of P1-1 and ergothioneine **1.12** *in vivo*.[33]

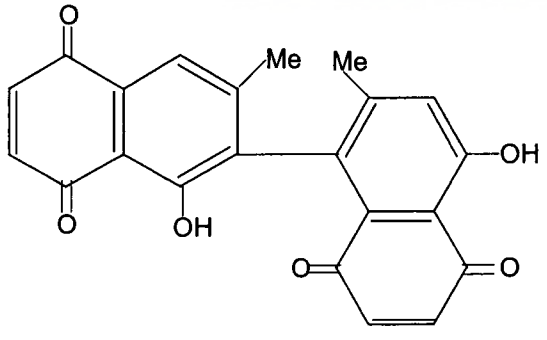
Diospyrin **1**, due to its inhibitory potency, would be worthy to be investigated as a possible chemomodular in anticancer drug resistance due to its inhibition of GST over expression.[35] It would also be worthy to investigate whether the competitive inhibition of A1-1 and M1-1 by diospyrin with respect to GSH could be used in conjuction with buthionine sulphoximine (BSO) in cancer therapy. BSO reduces GSH levels in cancer cells.[36] The reduction of GSH by BSO coupled with competitive inhibition of GSTs by diospyrin **1** could be used to prevent detoxification of anti-cancer drugs by GSTs. The disadvantage of this suggestion may be the lack of specificity of diospyrin **1** with respect to the isoforms inhibition. Since diospyrin **1** is capable of inhibiting GSTs and possesses antitumor activity, it may then act as a double-edged sword in cancer therapy. GST P1-1 has been found recently to be involved in regulation of cell proliferation and apoptosis by regulation of stress kinases.[37] Since diospyrin **1** is capable of inactivating P1-1, this could be the mechanism for the induction of the observed apoptosis.

In vitro studies have indicated the significant effect that small doses of diospyrin **1** has on Elrlich Ascites Carcinoma (E.A.C.) cell surfaces. This led to agglutination and exocytosis.[38] Higher doses caused disruption of the whole cell resulting in expulsion of intracellular material leading to total lyses. This means that diospyrin **1** acts primarily on the cell envelopes of E.A.C. cells. The respiratory inhibition of E.A.C. cells by diospyrin **1** is quite significant in its effect. The pathological importance of diospyrin **1** in the treatment of E.A.C.-bearing mice was clearly evident from the haematogical outcomes. The haemoglobin content of the control group of mice was lower by 46% than compared to normal. Treatment with diospyrin **1** resulted in substantial recovery. In order to broaden the results obtained from various studies carried out on the biological activity of diospyrin **1** and its derivatives towards tumor strains, it appears that they deserve further investigation to explore their potential as probable anti-tumor agents.

Diospyrin **1** has also been isolated together with another dimeric naphthoquinone, isodiospyrin **1.13** from the roots *Diospyros piscatorial* (Gurke), a common ingredient in several medicines.[39] The ethnopharmacological claims for the *Diospyros* species include the use of a leaf decoction for whooping cough and the root extracts as worm expellants. The leaves were also used as haemostatic agents for cuts and wounds. The decoction of the leaves and bark are used in the control of leprosy, dysentery, diarrhoea and oral infections.[40] The alcohol extracts of *Diospyros bateri* and *Diospyros monbutensis* were reported by Odedola and Okorosobo[41] to show strong antibacterial activity against a wide range of bacteria.

Diospyrin **1** and isodiospyrin **1.13** from this family have been shown to possess a broad spectrum of antibacterial activity. The MICs of diospyrin **1** against *Streptococcus pyogenes* ATCC 12344 and *Streptococcus pneumoniae* ATCC 33400 ranged from 1.56 to 50μg/ml. The MICs of diospyrin **1** against *Salmonella choleraesuis serotype typhi (S. typhi)*, ATCC 6539 and *Mycobacterium chelonae* ATCC 19977 were between 25 and 100 μg/ml.[39] Isodiospyrin **1.13** had been found to be more active than diospyrin **1**. The MICs against Gram-positive bacteria ranged from 0.78 to 50 μg/ml.[39]

The MICs of isodiospyrin **1.13** against *Pseudomonas aeruginosa* ATCC 15443 and *S. typhi* ranged from 50 to 100 μg/ml. The MICs of isodiospyrin **1.13** for a selection of eight Gram-positive organisms ranged between 0.78 to 50μg/ml, while those against a selection of four Gram-negative organisms ranged between 50 μg/ml and above 100 μg/ml. [39] The MICs of diospyrin **1** for the same eight Gram-positive bacteria ranged between 1.56 to above 100 μg/ml.[39] The two compounds, diospyrin **1** and isodiospyrin **1.13** were both found to be effective against *M. Chelonae*, an acid-fast bacillus with isodiospyrin **1.13** being more effective at MICs of 6.26 to 25 μg/ml compared to the MICs of diospyrin **1** of 25 to 100 μg/ml.[39]



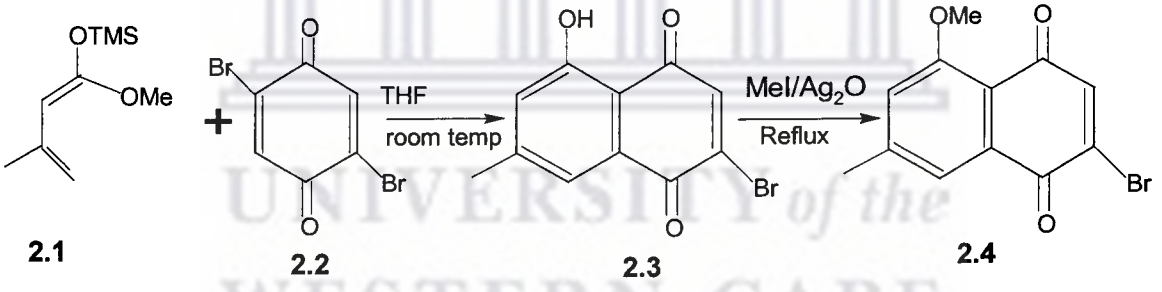
1.13

CHAPTER 2

2.1Synthesis of Diospyrin

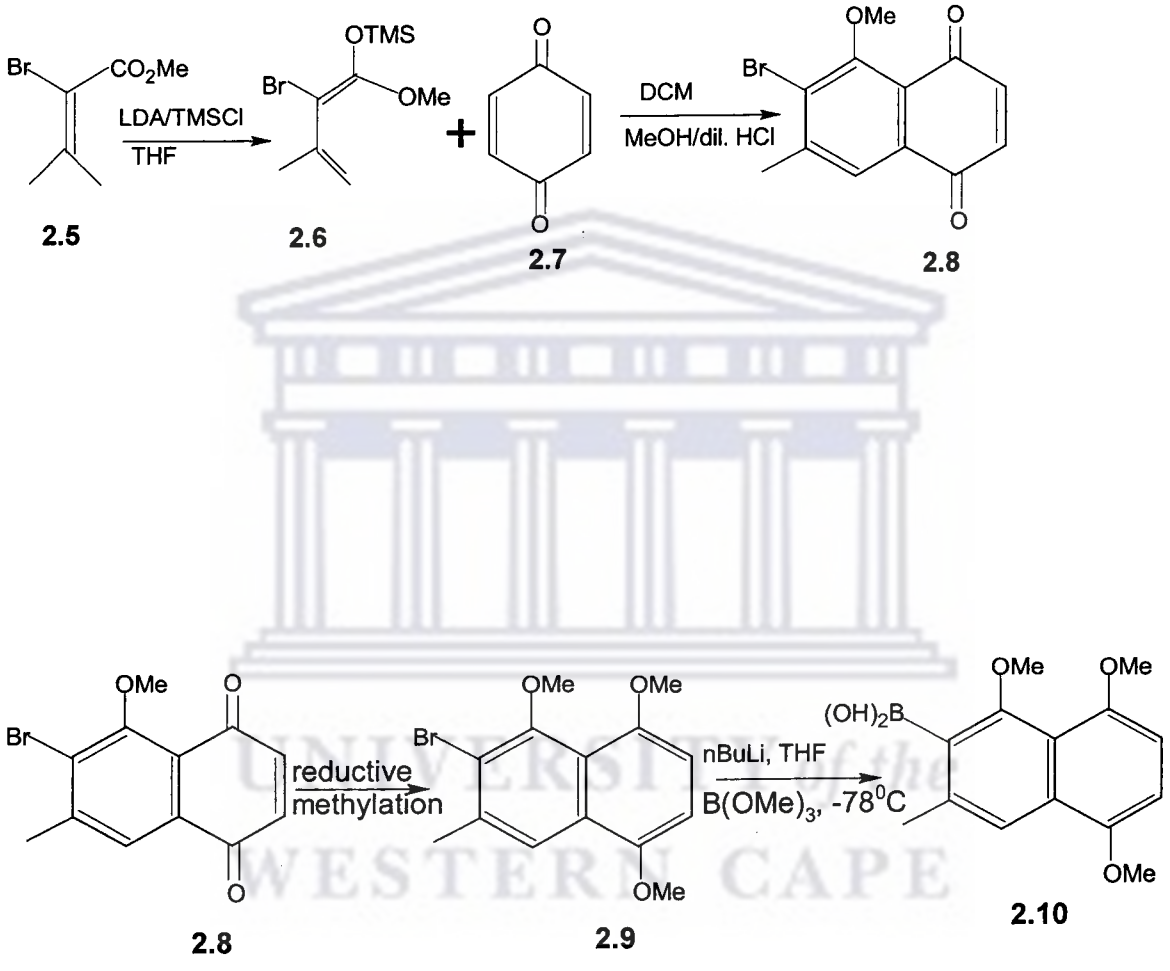
In 2000, Masao Yoshida and Kenji Mori [11] reported the synthesis of diospyrin **1** according to Schemes **2.1**, **2.2** and **2.3** shown below.

Quinone **2.4** represents the quinone half of the binaphthoquinone with the bromine atom in the regiochemical position shown. Thus, 1-methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene **2.1** in THF was reacted with 2,5-dibromo-1,4-benzoquinone **2.2**, to yield phenol **2.3** after chromatographic passage through a column. Phenol **2.3** was then treated with methyl iodide in the presence silver(II)oxide under reflux to afford 2-bromo-5-methoxy-7-methyl-1,4-naphthoquinone **2.4**.

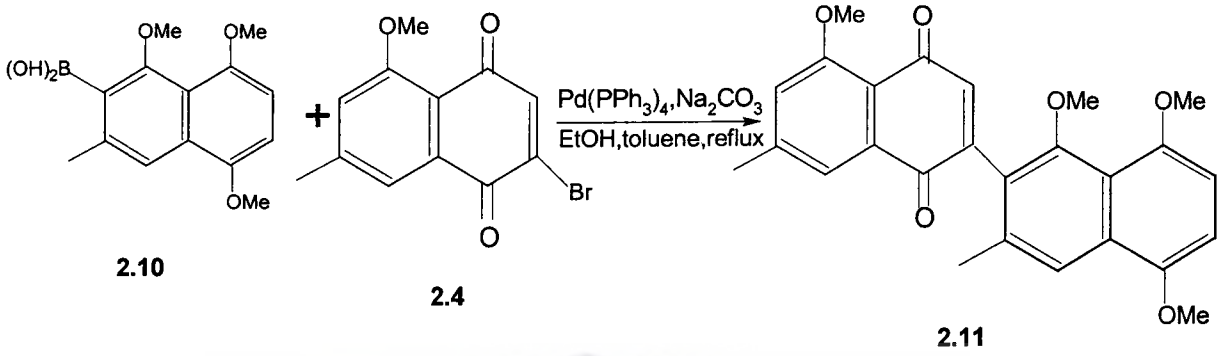


2.1 **2.2** **2.3** **2.4**

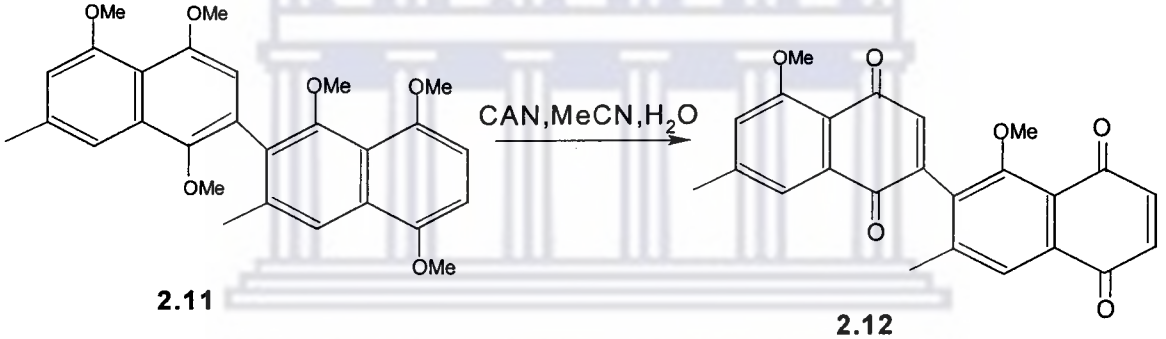
Scheme 2.1



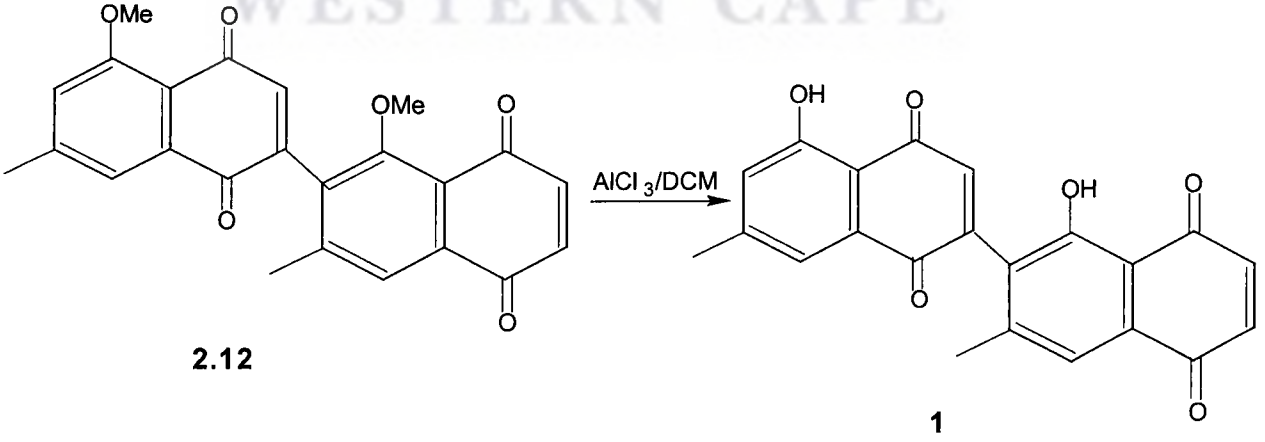
Scheme 2.2



2.10 2.4 2.11



2.11 2.12



2.12 1

Scheme 2.3

Synthesis of the other half of the molecule is illustrated in Schemes 2.2 and 2.3. Ester **2.5** in dry THF was treated with LDA and TMSCl to yield compound **2.6**, which was condensed with 1,4-benzoquinone **2.7** in dichloromethane and the adduct was then treated with methanol and 1M HCl to yield 6-bromo-5-methoxy-7-methyl-1,4-naphthoquinone **2.8**. Quinone **2.8** in ethanol was reduced with tin chloride and hydrochloric acid and the corresponding quinol was treated with methyl iodide in DMF in the presence of sodium hydride to yield the corresponding methoxynaphthalene **2.9**. This latter compound in THF was treated with n-butyllithium at -78^0C, followed by $B(OMe)_3$ and dilute hydrochloric acid to yield the naphthyl borate **2.10**.

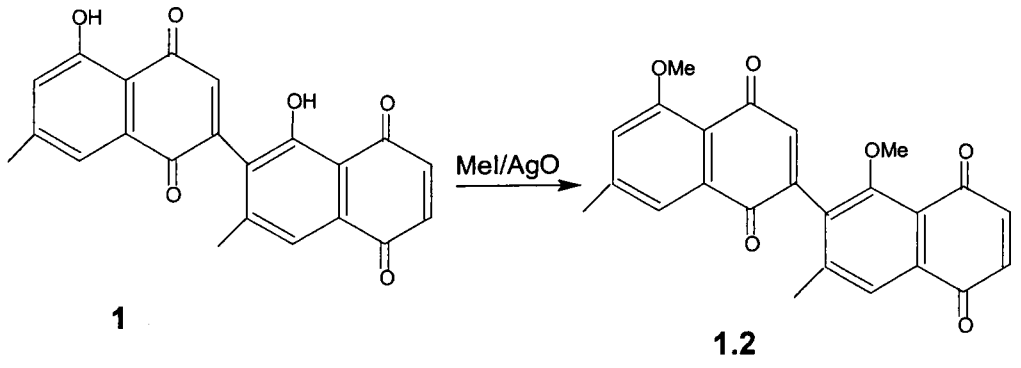
The cross coupling between the two halves is illustrated in Scheme **2.3**. Suzuki cross coupling between naphthalene **2.10** and 2-bromo-5-methoxy-7-methyl-1,4-naphthoquinone **2.4** in methanol and toluene was done in the presence of the base, sodium carbonate and tetrakis(triphenylphosphine)palladium(0), under reflux. The bisnaphthyl product **2.11** was then oxidized using ceric ammonium nitrate (CAN) to afford naphthoquinone **2.12**, which in turn was demethylated by treatment with $AlCl_3$ in dichloromethane to afford diospyrin **1**.

2.2 Synthesis of some diospyrin related compounds

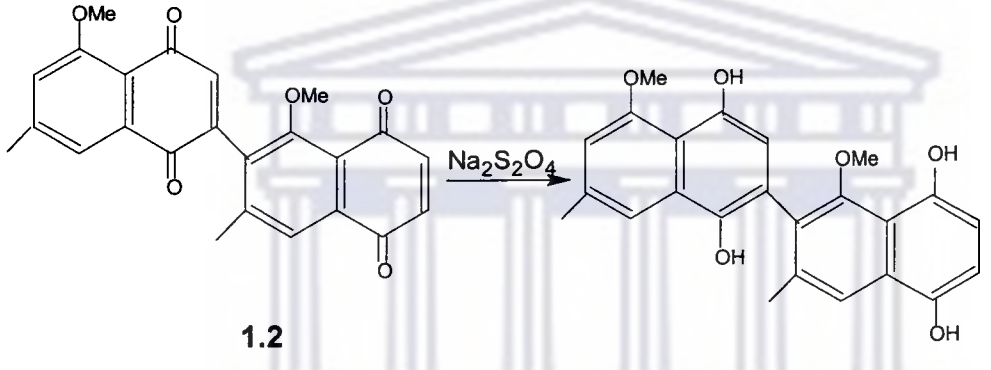
2.2.1 Diospyrin analogues

B. Hazra *et al.* [6,23,24] synthesized diospyrin analogues **1.2**, **1.3** and **1.4** mentioned in Chapter 1 from diospyrin **1**. These analogues were synthesized according to Scheme 2.4 shown below.

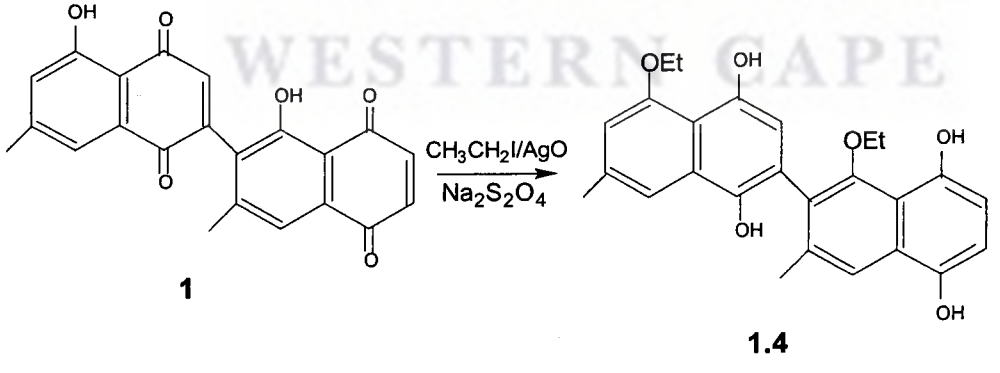
Diospyrin dimethylether **1.2** was synthesized by treating diospyrin **1** with methyl iodide and silver oxide. Diospyrin dimethylether hydroquinone **1.3** was synthesized from the diospyrin dimethyl ether derivative **1.2** by reduction with sodium dithionite to yield **1.3**. Diospyrin diethyl ether hydroquinone **1.4** was prepared from diospyrin **1** by treatment with ethyl iodide and silver oxide followed by reduction with sodium dithionite.



1 1.2



1.2 1.3

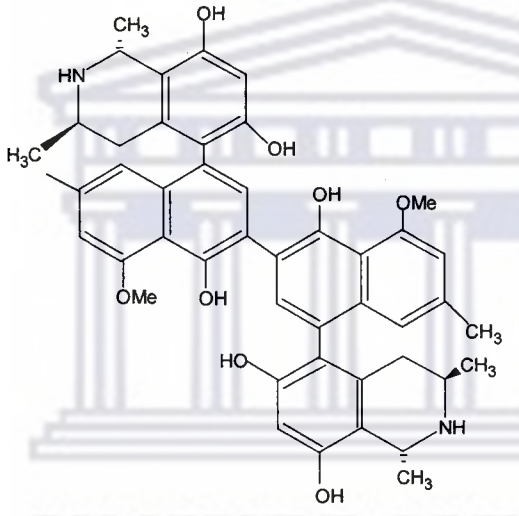


1 1.4

Scheme 2.4

2.2.2 Synthesis of Michellamine 2.13

Since TB is related to HIV,[5] it is necessary to consider other compounds that can be used to treat HIV, together with those that would work for the treatment of *M. tuberculosis*. An example of such a compound is the Michellamine **2.13**. This compound has similar features to those of diospyrin **1**. G. Bringmann *et al.* [42] synthesized Michellamine **2.13** according to Schemes 2.5, 2.6 and 2.7 respectively.



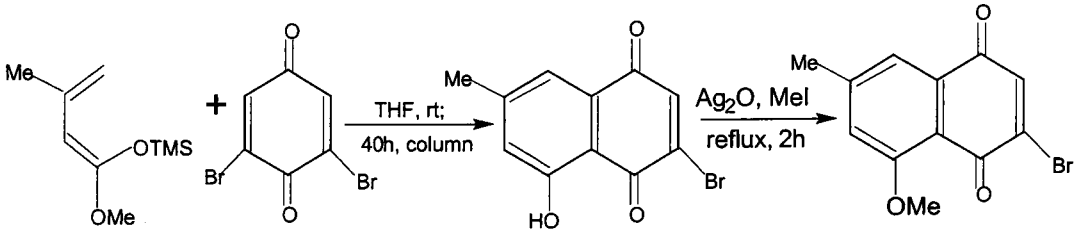
2.13

Ditriflate **2.22** was synthesized as illustrated in Scheme 2.5 below. The bromo naphthoquinone **2.16** was prepared by reacting diene **2.14** with 2,6-dibromo-1,4-benzoquinone **2.15** in tetrahydrofuran for 40 hours followed by chromatography. The bromo naphthoquinone **2.16** was subsequently treated with methyliodide in the presence of silver(I)oxide under reflux for 2h to yield the methylated analogue **2.17**, which in dioxane, was reacted with Sn_2Bu_6 in the presence of $(PPh_3)_2PdCl_2$ at 100^0C for an hour to afford the tin tributyl analogue **2.18**. This was then treated with 2-bromoquinone **2.17** in dioxane in the presence of $Pd(PPh_3)_2Cl_2$ for 12 hours to afford dimer **2.19**, which was

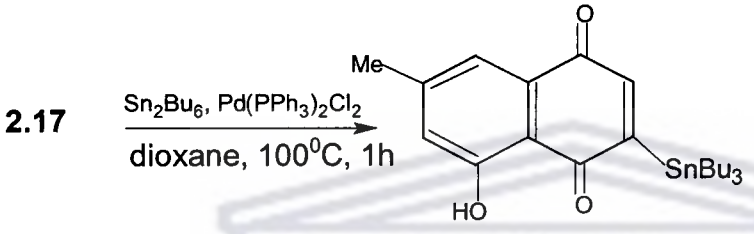
later converted to the corresponding tetra-acetoxynaphthalene dimer **2.20** using Zn, sodium acetate and Ac_2O followed by dimethylamino pyridine (DMAP) in dichloromethane at room temperature for 12 hours. The dimer **2.20** in methanol and dichloromethane was then treated with DBU at room temperature for 10 minutes to afford the corresponding dimer **2.21**. This was then treated with Tf_2O followed by 2,6-lutidine in DCM at room temperature for 10 minutes to afford naphthalene **2.22**. (Scheme 2.5)

In the synthesis of the second half of the Michellamine molecule, the bromo compound **2.23** in dry THF was treated with n-BuLi at -78^0C followed by trimethoxy borane and aqueous workup to afford the desired boronic acid **2.24**. (Scheme 2.6)

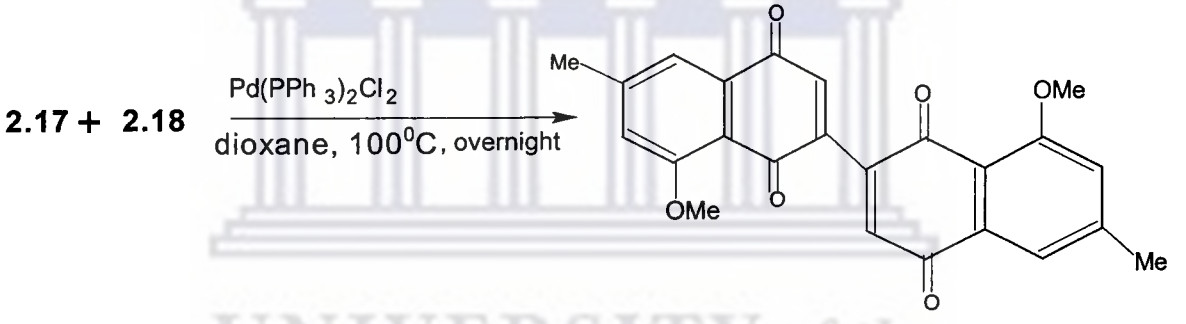
Finally, Suzuki cross-coupling was carried out according to Scheme 2.7 whereby the ditriflate **2.22** in toluene was treated with boronic acid **2.24** in the presence of tetrakis(triphenylphosphine)palladium(0) and barium hydroxide, $Ba(OH)_2$ to afford compound **2.25**, which was later debenzylated by treatment with H_2 in ethanol in the presence of palladium catalyst for 14 hours at a pressure of 1atm to afford the michellamine **2.13** as the major product.



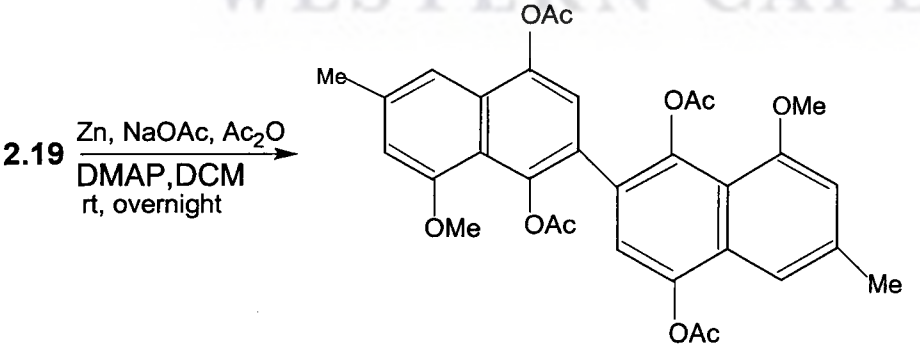
2.14 **2.15** **2.16** **2.17**



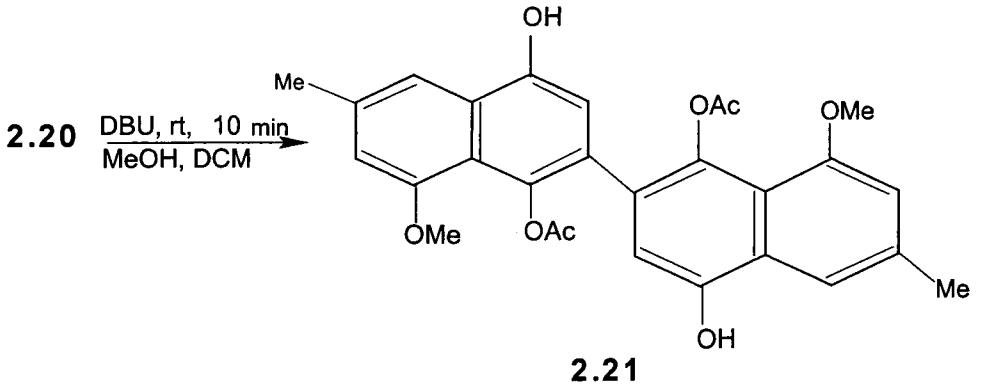
2.18



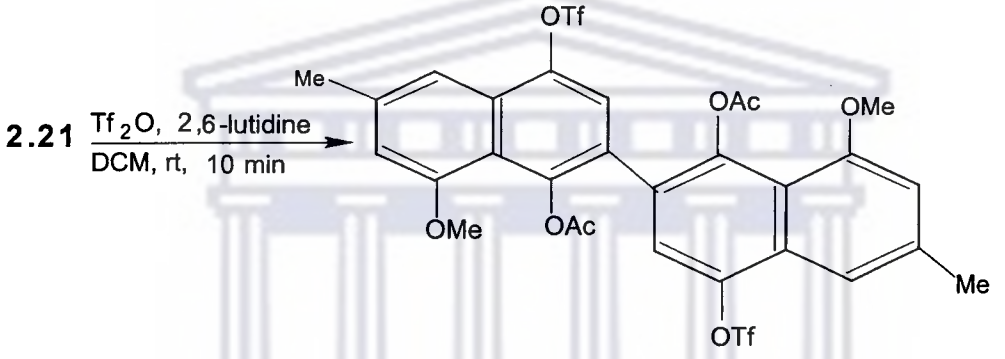
2.19



2.20

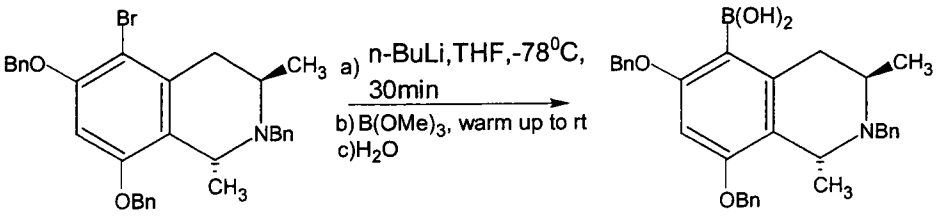


2.21



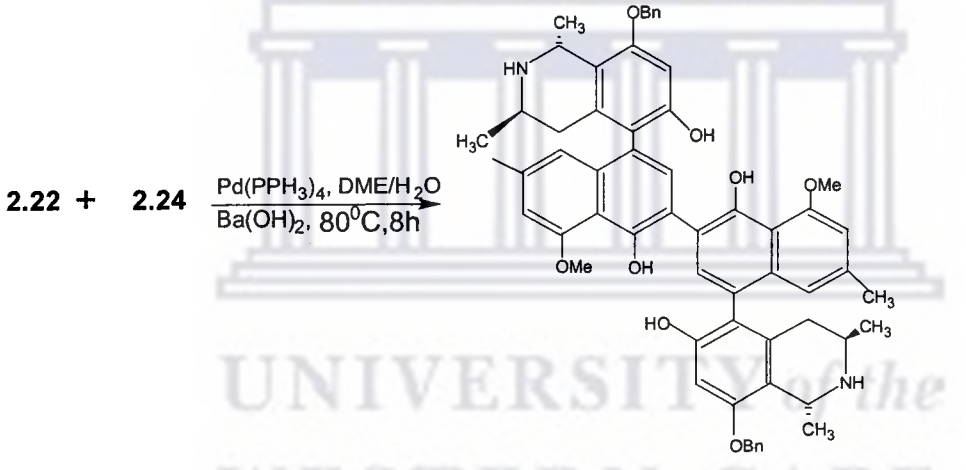
2.22

Scheme 2.5

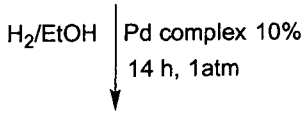


2.23 **2.24**

Scheme 2.6



2.25



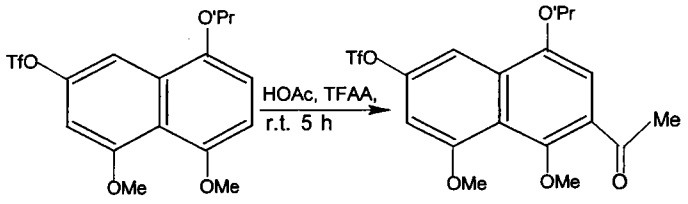
2.13

Scheme 2.7

2.2.3 Synthesis of analogues of crisamicin 2.33 and 2.34

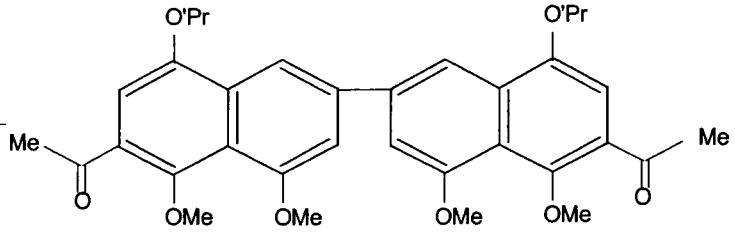
The pyranonaphthoquinone family exhibits activity against many types of Gram-positive bacteria and yeasts and have been proposed to act as bioreductive alkylating agents.[43] Crisamicins **2.33** and **2.34** were isolated from the microorganism *Micromonospora purpureochrmogenes* [44] and have been synthesized according to Scheme 2.8 below.

Triflate **2.26** was treated with trifluoroacetic anhydride in acetic acid at room temperature for 5h to afford triflate **2.27**, which in turn was treated with bis(pinacolato)diboron in the presence of palladium chloride followed by potassium acetate in dioxane and reflux for 2h. The product of this process was then treated with potassium phosphate in the presence of $PdCl_2$ in dioxane under reflux for 3h to yield dimer **2.28**, which was then oxidized with 6M nitric acid in the presence of silver oxide in dioxane to afford the corresponding naphthoquinone **2.29**, which was in turn condensed with diene **2.30** in acetonitrile at 0^0C for 1 hour to afford two isomers viz., bis-furonaphthofurans **2.31** and **2.32**. These were treated with cerium ammonium nitrate in acetonitrile for 15 minutes to furnish the desired bis-furonaphthopyrans **2.33** and **2.34**.



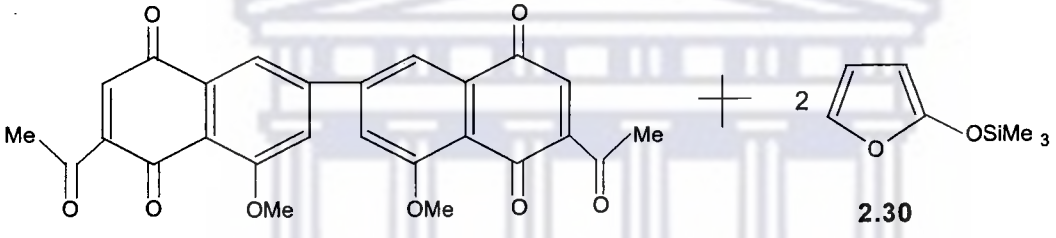
2.26 **2.27**

bis(pinacolato)diboron, $PdCl_2$, KOAc, dioxane, reflux, 2h, 2.27, $PdCl_2$, K_3PO_4, dioxane, reflux, 3h



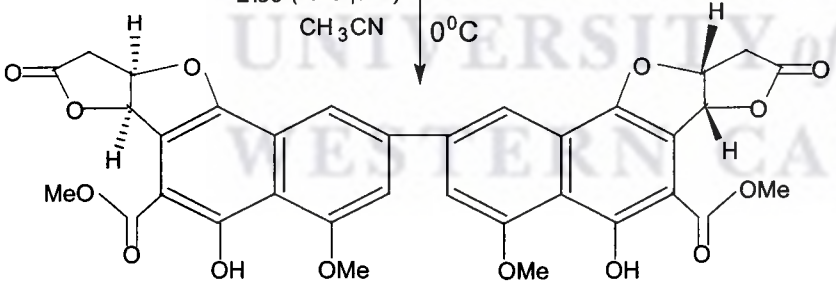
2.28

2.29 ← AgO, 6M HNO_3

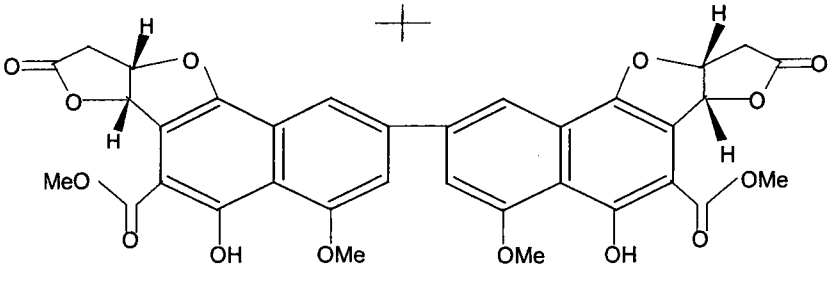


2.29 **2.30**

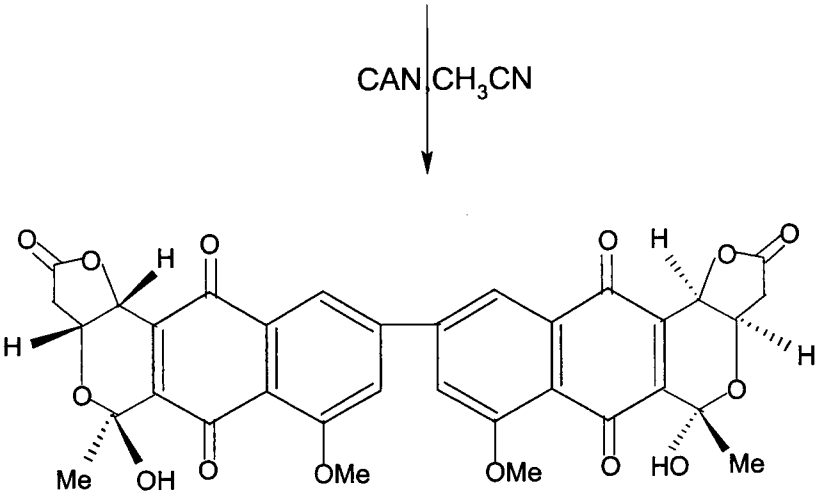
2.30 (3 equiv.), CH_3CN, 1 h, 0^0C



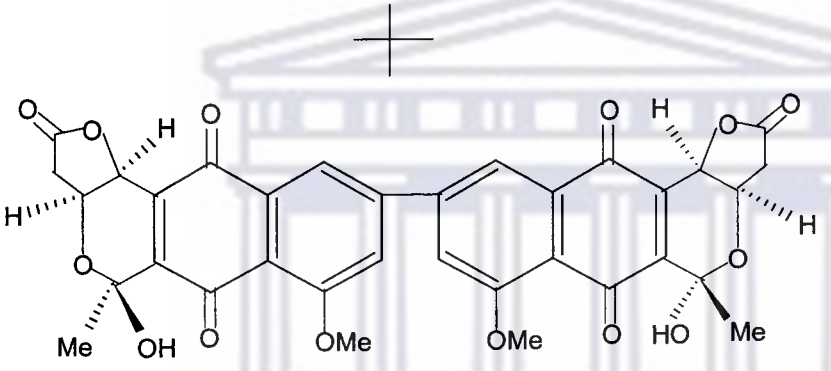
2.31



2.32



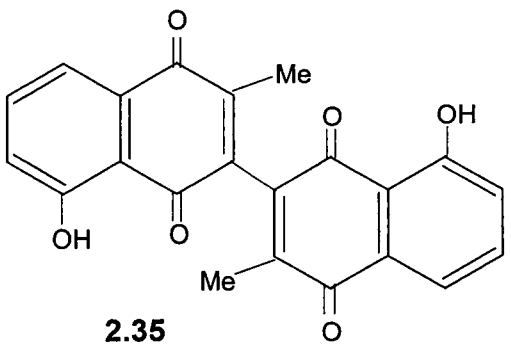
2.33



2.34

Scheme 2.8

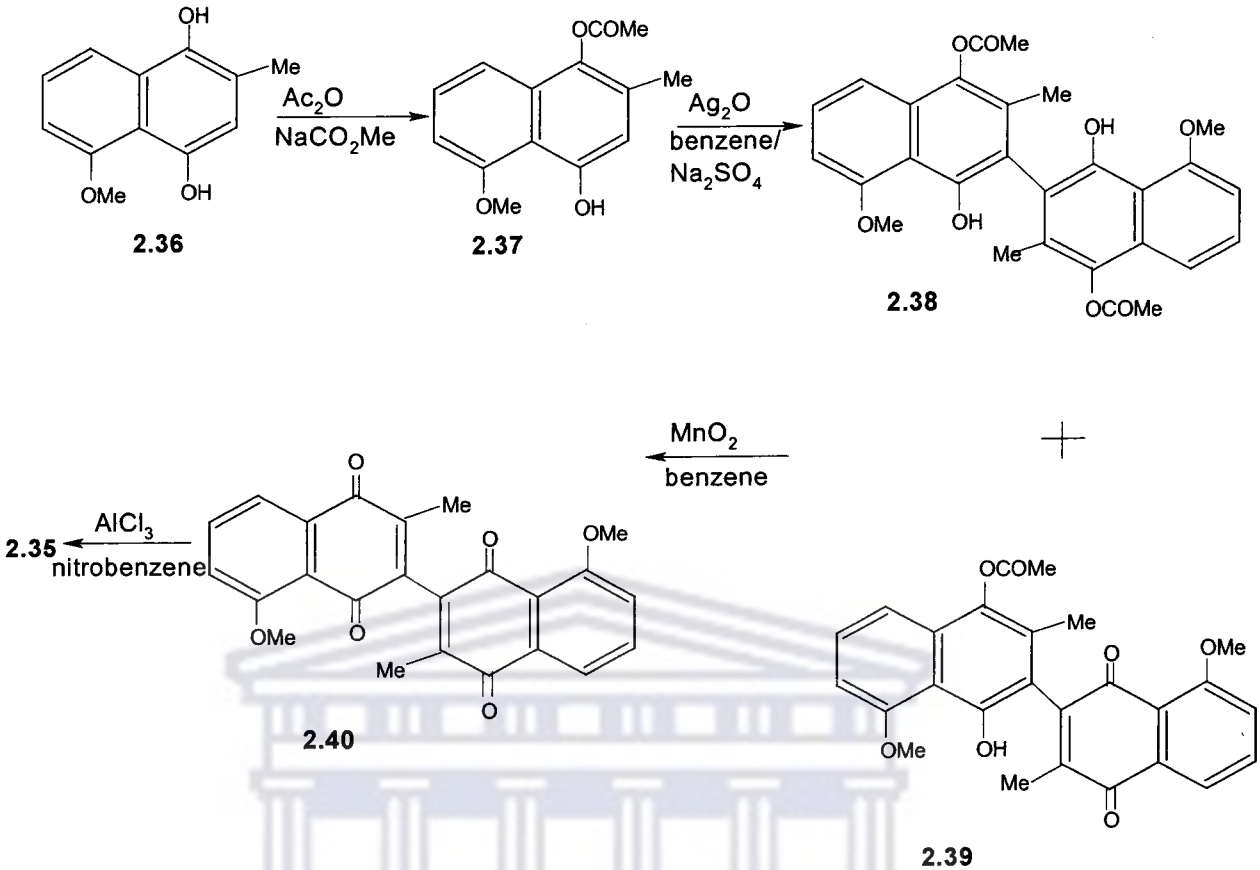
2.2.4 Synthesis of 3,3'-Biplumbagin 2.35



2.35

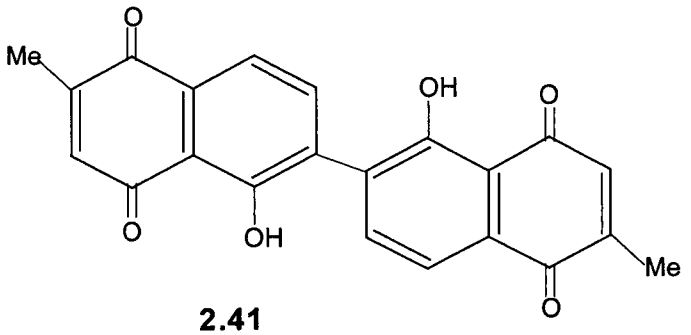
3,3'-Biplumbagin **2.35** was isolated from the roots of *Plumbago zeylanica* by Sankram and Sidhu [45], who later were the first people to publish the synthesis of 3,3'-biplumbagin **2.35**.[46] This bisnaphthoquinone **2.35** was synthesized according to Scheme 2.9 shown below.

Quinol **2.36** was treated with acetic anhydride and sodium acetate to yield two products viz., a diacetate and a mono-acetate. The major product was the mono-acetate, which was formulated as 1-acetoxy-4-hydroxy-2-methyl-5-methoxynaphthalene **2.37**. The oxidative coupling of mono-acetate **2.37** using Ag_2O in dry benzene in the presence of anhydrous sodium sulphate yielded products **2.38** and **2.39**. The two being separated through column chromatography were both treated separetely with manganese oxide, MnO_2, in dry benzene to yield the desired precursor product **2.40** as yellow crystalline material, which was then demethylated to the desired biplumbagin **2.35** with anhydrous $AlCl_3$ in nitrobenzene.



Scheme 2.9

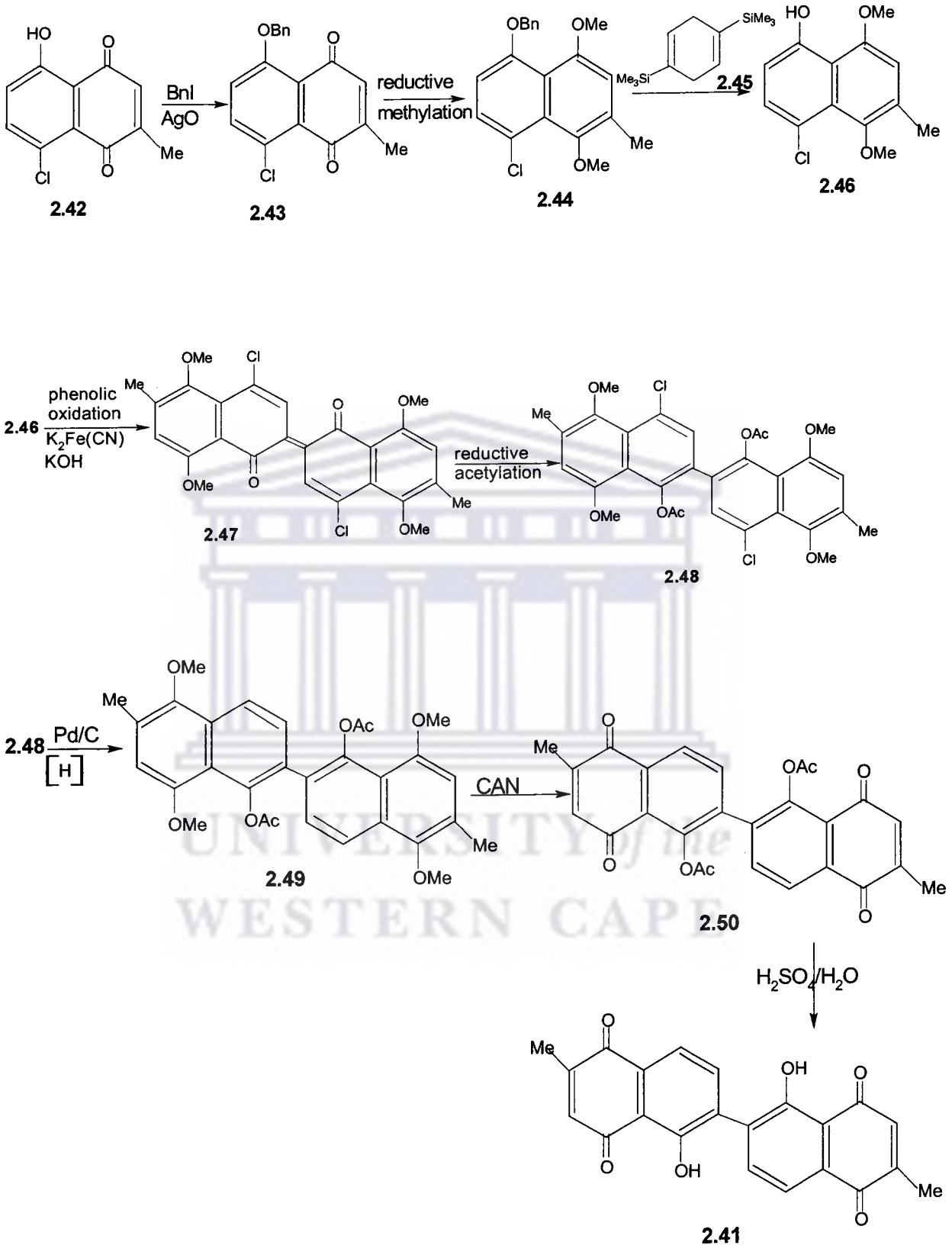
2.2.5 Synthesis of 6,6'-biplumbagin 2.41



2.41

6,6'-Biplumbagin **2.41** commonly known as elliptinone has been synthesized by H. Laatsch *et al.*[47] according to Scheme 2.10 below.

Treatment of 8-chloroplumbagin **2.42** with benzyl iodide in the presence of silver oxide yielded quinone **2.43**, which was subsequently reductively methylated to afford naphthalene **2.44**. This in turn was chemoselectively debenzylated using diene **2.45** to afford naphthol **2.46**. Phenol oxidation of naphthol **2.46** using potassium ferricyanide in the presence of potassium hydroxide afforded dimer **2.47**, which was then reductively acetylated to afford the corresponding dimer **2.48**. Treatment of this latter dimer **2.48** with palladium catalyst in the presence of hydrogen gas removed the chlorine atoms to afford the dechlorinated dimer **2.49**, which was oxidized using cerium ammonium nitrate to yield the corresponding quinone **2.50**. Finally, deacetylation with sulphuric acid afforded the desired dimer 6,6'-biplumbagin **2.41**.

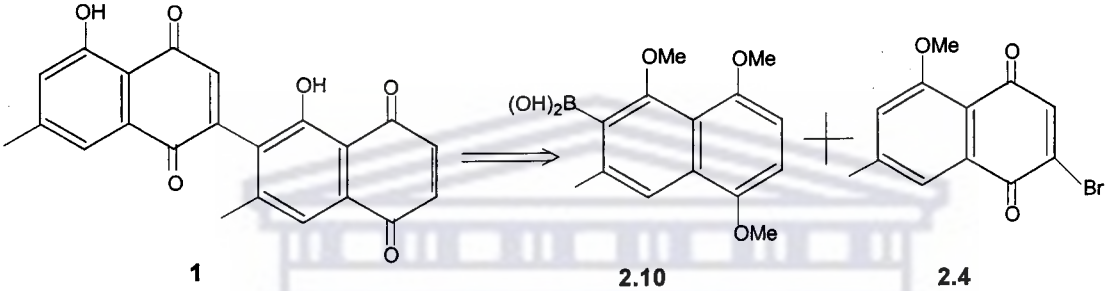


Scheme 2.10

CHAPTER 3

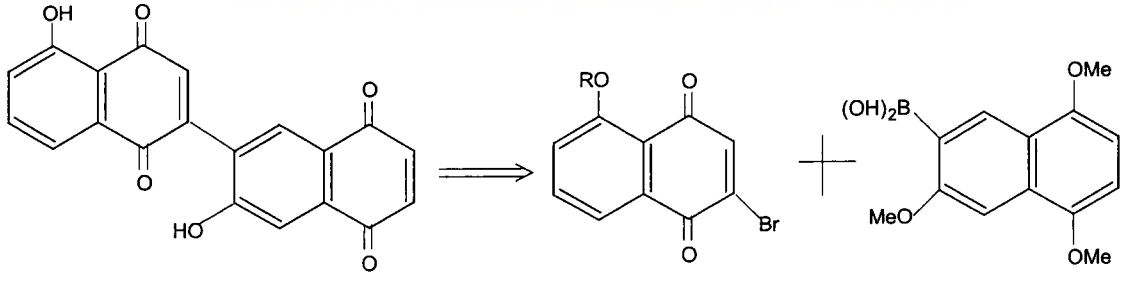
RESULTS AND DISCUSSIONS

The structure of diospyrin **1** is as described in Chapter 1. The retrosynthesis of diospyrin is as follows with its synthesis already being presented in Chapter 2.



1 **2.10** **2.4**

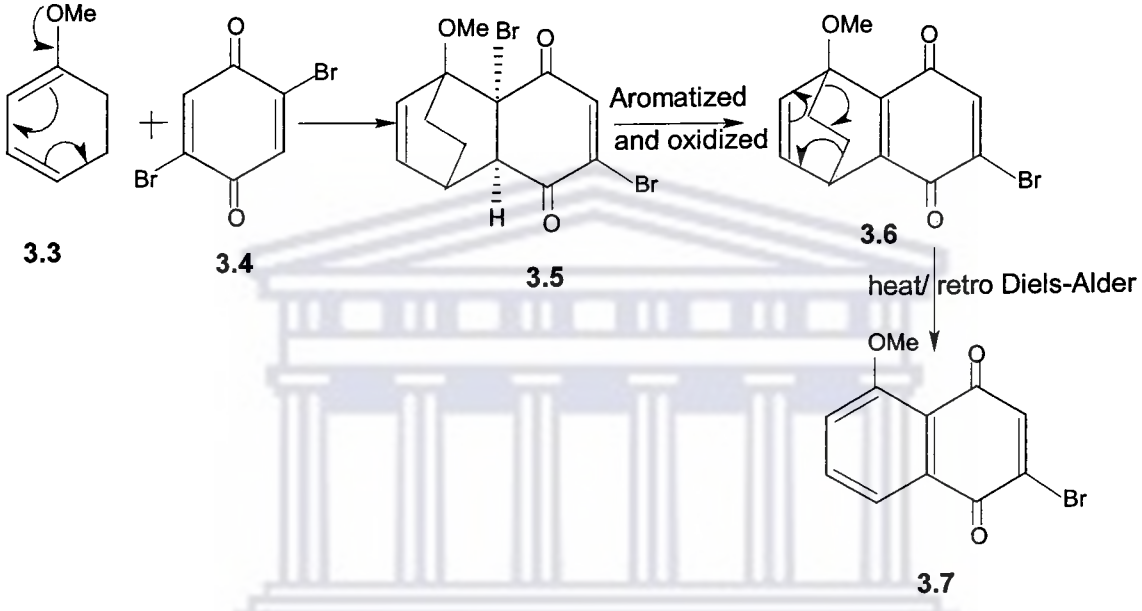
In considering analogues of diospyrin **1**, we opted for the one we considered the most convenient from the point of view of easily accessible diene starting materials and procedures. The molecule that we decided to attempt to synthesize was binaphthylquinone **3.19** in which the two retro synthons were quinone **3.1** and boronic acid **3.2** as shown in the retro synthesis below. The aims of the thesis were to synthesize the quinone **3.1** and a boronic acid similar to **3.2** and to attempt to cross couple these two entities.



3.19 **3.1** **3.2**

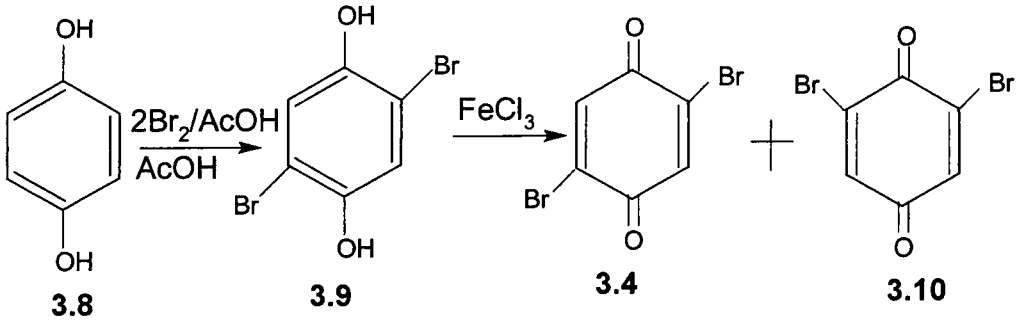
3.1.1 Synthesis of 2-bromo-5-methoxy-7-demethylnaphthoquinone 3.7

The proposed synthetic protocol of the target naphthoquinone **3.7** is illustrated on Scheme 3.1 below.



Scheme 3.1

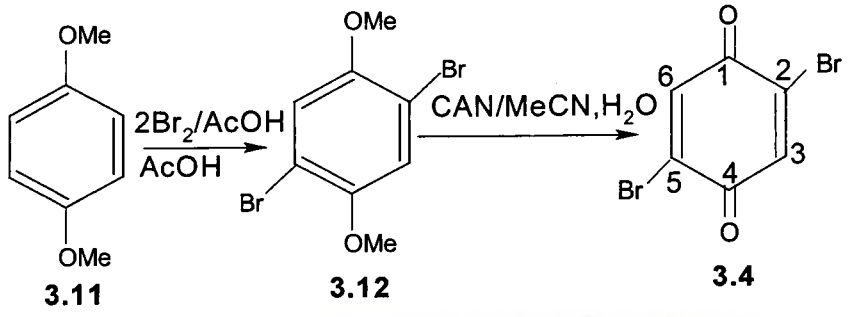
The first challenge was the synthesis of sufficient quantities of 2,5-dibromobenzoquinone **3.4**. The first attempt is illustrated in Scheme 3.2 shown below.



Scheme 3.2

Thus 1,4-dihydroxybenzene **3.8** in acetic acid was treated with bromine (2 molar equiv) to yield dibromobenzene **3.9** together with the corresponding 2,6-isomer which were then treated with $FeCl_3$ to yield a mixture of the 2,5-dibromobenzoquinone **3.4** and 2,6-dibromobenzoquinone **3.10**. The problem we faced in this process was the separation of the two compounds in order to get pure dibromobenzoquinone **3.4**. The mixture was not easy to separate since the solvent systems we used as eluents afforded a poor 20% yield of pure **3.4**. It is unclear as to why the selectivity of **3.4**:**3.10** is 1:1.

Due to the poor yield and difficulties in separating the two compounds, an alternative route for the synthesis of dibromobenzoquinone **3.4** was adopted in which the procedure by P.L. Alvarado *et al.*[48] was followed and is illustrated in Scheme 3.3 below.

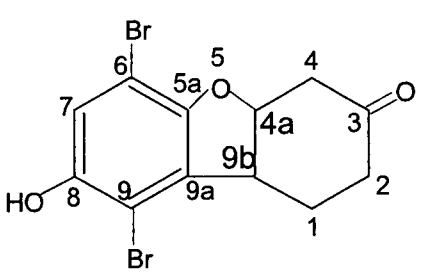


3.11 **3.12** **3.4**

Scheme 3.3

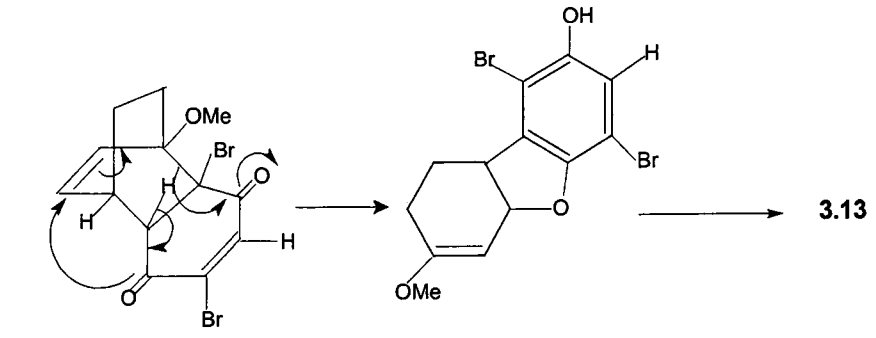
Thus 1,4-dimethoxybenzene **3.11** in acetic acid was treated with 2 equivalents of bromine in acetic acid to afford the corresponding 2,5-dibromobenzene **3.12**, which in acetonitrile and water was then oxidized with cerium ammonium nitrate to yield the corresponding 2,5-dibromobenzoquinone **3.4**, in 97% yield for the last step. The resulting material was assigned the structure **3.4** based on the following spectral evidence: The M^+ of 266 demonstrated a molecular formula of $C_6H_2Br_2O_2$ while the infrared spectrum showed the carbonyl frequencies in the range 1722-1728 cm^{-1}. In the ^1H n.m.r spectrum, the proton signal at 7.48ppm is due to the two symmetrical aryl hydrogens. In the ^{13}C n.m.r spectrum, the signal at 177.0 ppm is due to the carbonyl carbons, the signal at 137.9 ppm is due to the C-2/5 while the signal at 137.2 ppm is due to the C-3/6, the latter being more intense than the former.

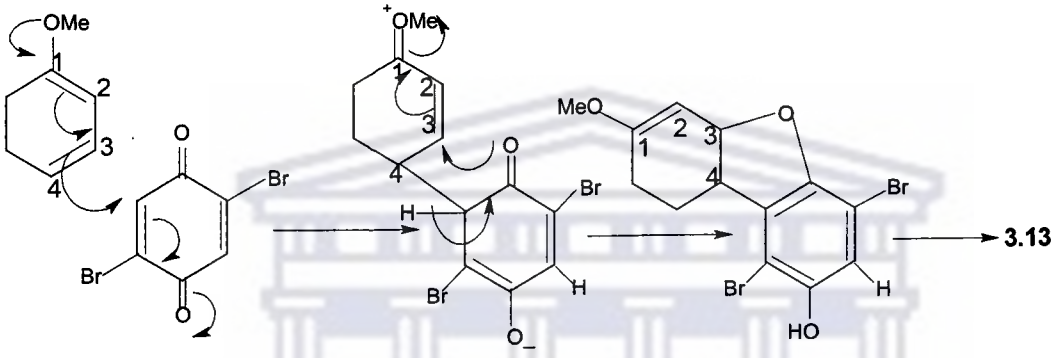
Diels-Alder addition between benzoquinone **3.4** and commercially available diene **3.3** was attempted as shown earlier in Scheme 3.1. Thus diene **3.3** in benzene was treated at room temperature with dibromobenzene **3.4** to initially yield the bridged bromoquinone **3.5** but which subsequently undergoes a rearrangemnt to form the keto-furan **3.13**. Assignment of structure **3.13** to the product isolated is based on the following spectral evidence. A HRMS of 359.8994 confirmed the molecular formula of $C_{12}H_{10}Br_2O_3$ (Required 359.8997), while the infrared spectrum showed absorption frequencies at 3290 (OH) and 1703 (C=O) cm^{-1}. A 4-proton multiplet in the ^1H n.m.r spectrum at 2.20 is assigned to H-1 and H-2; a 1-proton dd at 2.78ppm is assigned to H-4axial with (*J* 17.2 and 3.6 Hz), while the H-4equatorial appears as a dd at 3.03ppm (*J* 17.2 and 3.6 Hz); a 1-proton multiplet at 3.80ppm is assigned to H-9b; a D_2O exchangeable singlet at 5.20ppm is assigned to the 8-OH; a 1-proton dt at 5.32ppm (J 8.8 and 3.6 Hz) is assigned to H-4a, while H-7 appears as a singlet at 7.05ppm. In the ^{13}C n.m.r spectrum, the signal at 23.8 ppm is due to C-1, while signals at 36.0 and 41.3 ppm are assigned to C-2 and C-4 respectively. The signal at 42.7 ppm is due to C-9b, while the signal at 81.4ppm is due to C-4a. The signals at 102.2 and 106.3 ppm are due to $(C\text{-}6)^a$ and $(C\text{-}9)^a$. The signal at 118.9 ppm is assigned to C-7. The signal at 130.3ppm is assigned to C-9a. The signals at 147.5 and 151.2 ppm are due to $(C\text{-}5a)^b$ and $(C\text{-}8)^b$. Lastly, the signal at 207.9 ppm is due to the carbonyl carbon, C-3.



3.13

3.1.1.1 Suggested possible mechanisms for the formation of the furan product:



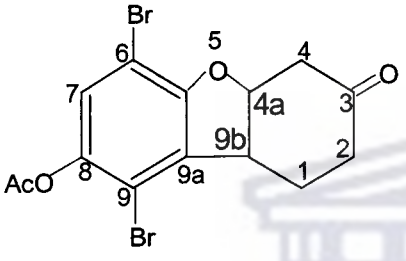


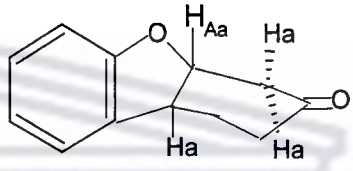
According to Birch *et al.*[49] the reaction between benzoquinone and diene **3.3** lead to the formation of furans similar to **3.13**.

Furan **3.13** was then treated with acetic anhydride in the presence of pyridine. This was done to verify the presence of hydroxyl group at C-8. Thus furan **3.13** in acetic anhydride and pyridine was stirred at room temperature for 12h and the reaction mixture was thrown into water and extracted with ethyl acetate. The organic layer was washed with dilute hydrochloric acid, water and a 10% solution of sodium hydrogen carbonate to afford a residue that was purified by column chromatography to afford acetoxy furan **3.14**, 88% yield. A HRMS of 401.9100 supported the molecular formula of $C_{14}H_{12}Br_2O_4$ (Requires: 401.9102). In the ^1H n.m.r spectrum a 4-proton multiplet at 2.23ppm is assigned to H-1 and H-2; a 3-proton singlet at 2.37ppm is assigned to the methyl of the C-8 acetoxy group; a 2-proton multiplet at 2.60ppm is assigned to H-4; a 1-proton multiplet at 4.50ppm is

assigned to H-9b; a 1-proton dd (*J* 10.2 and 3.0 Hz) at 6.10ppm is assigned to H-4a and finally a 1-proton singlet at 7.39ppm is assigned to H-7.

In the ^{13}C n.m.r spectrum some signals have been assigned viz., 20.8ppm to the methyl carbon of the acetoxy group; 28.4 and 38.1 (x2)ppm to C-1, C-2 and C-4; 42.4ppm to C-9b; 77.1ppm for C-4a; 117.5ppm for (C-9a)[a]; 126.9ppm to C-7; 128.6ppm to (C-6)[a]; 137.7ppm (C-9)[a]; 146.8ppm to (C-5a)[b]; 152.0ppm to (C-8)[b], 168.1ppm to the carbonyl of the acetoxy group and 198.1ppm to C-3 carbonyl.





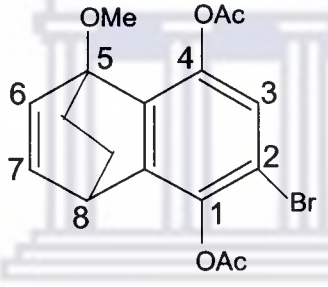
3.14

The reaction was repeated at 0^0C in THF since benzene (usual solvent) is of course a solid at 4^0C. After 12 hrs of stirring at 25^0C the reaction mixture was chromatographed to afford an initial reddish-band, which comprised of the product **3.5** together with diene **3.3**. The yield of the product was estimated to be 20% from the ^1H n.m.r spectrum.

A portion of the product **3.5** was chromatographed during whish process HBr was lost to afford the quinone **3.6**, which upon heating to above its melting point of 124-125^0C underwent a retro Diels-Alder reaction by rapid gas evolution to yield quinone **3.7** similar to the material synthesized later.

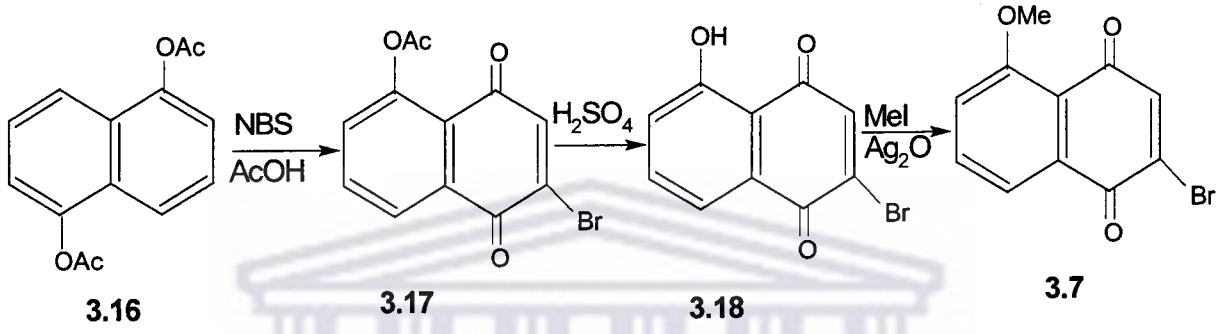
Another portion of the product **3.5** was treated with Ac_2O and pyridine, which lead to the formation of the bridged diacetate **3.15**. The structure **3.15** assigned to the diacetate is based on the following evidence. A HMRS at M^+ of 380.0256 demonstrated the molecular

formula $C_{17}H_{17}BrO_5$ (requires M^+ 380.0259), while the infrared spectrum showed an absorption frequency at 1735 cm^{-1}. In the ^1H n.m.r spectrum, the following signals have been assigned; two 2-proton triplets (*J* 6.8) at 1.5 and 1.7ppm for the ethano bridge; 3-proton singlets at 2.29 and 2.40ppm for the two acetoxy groups; a 3-proton singlet at 3.58ppm is assigned to the methoxy group; a 1-proton multiplet at 3.80ppm is assigned to H-8; a 1-proton dd at 6.46ppm (*J* 8.2 and 8.0) is assigned to H-7; a 1-proton d at 6.65ppm (*J* 8.2) is assigned to H-6 and finally a 1-proton singlet at 7.02 ppm is assigned to H-3. In the ^{13}C n.m.r spectrum some signals have been assigned viz., 20.6 and 20.8 ppm to the acetyl CH_3 groups; 25.4 and 28.5 ppm to the ethano CH_2 groups; 34.8ppm (C-8) and 53.7 ppm (CH_3O). The two carbonyl signals appear at 168.4 and 169.8 ppm.



3.15

Due to the poor yield of the adduct and subsequent product, an additional alternative route was then adopted and is shown in Scheme 3.4 below. The procedure published by S.W. Heinzman *et al.*[50] was then followed.



3.16 **3.17** **3.18** **3.7**

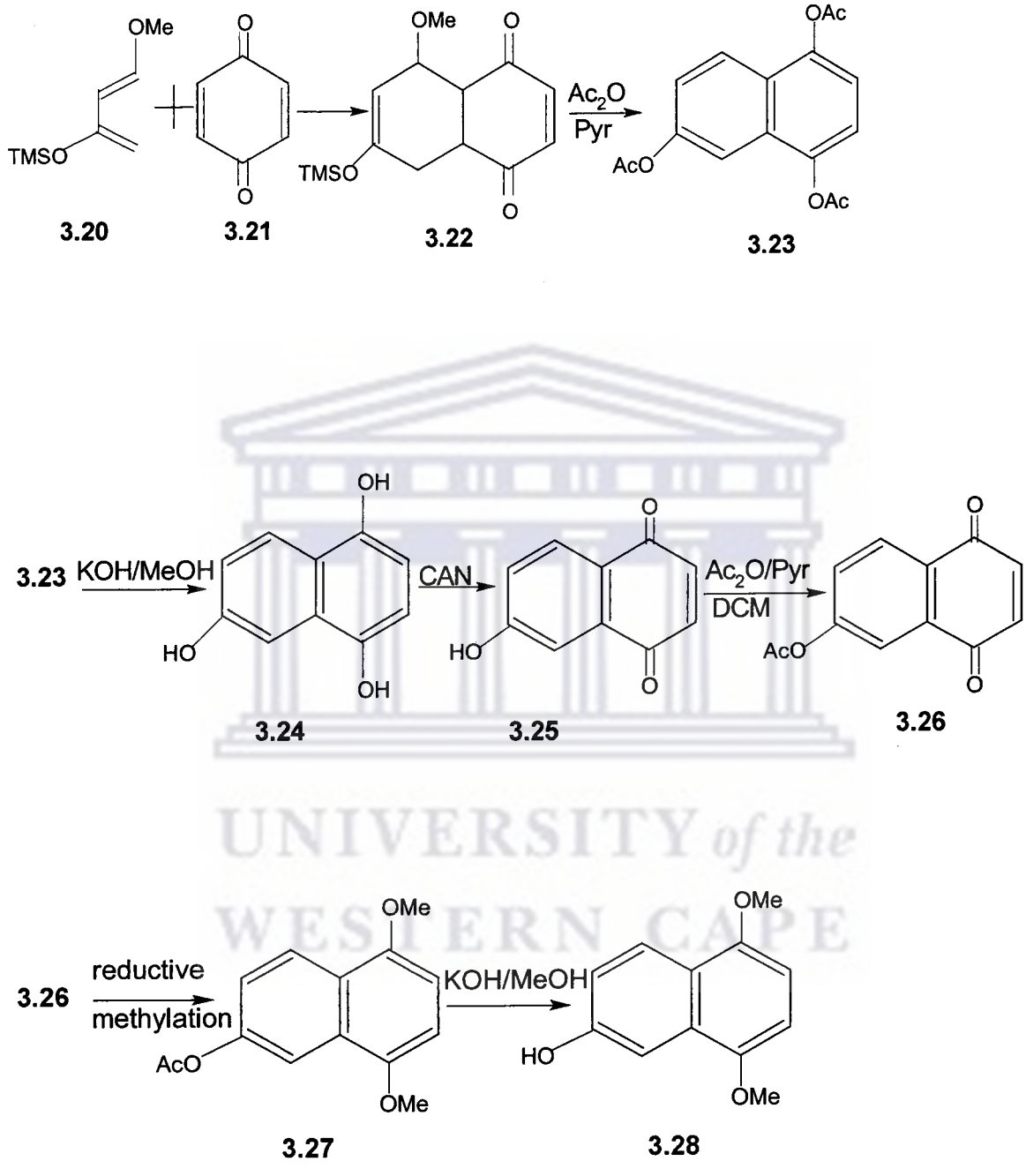
Scheme 3.4

Thus 1,5-diacetoxynaphthalene **3.16** in acetic acid was treated with N-bromosuccinamide to afford 2-bromo-5-acetoxy-1,4-naphthoquinone **3.17** in 71% yield, which was then hydrolysed with sulfuric acid to yield the corresponding phenol **3.18**. Phenol **3.18** was treated with methyliodide, in the presence of silver oxide, Ag_2O, to afford the desired bromoquinone **3.7** in 91% yield. The material produced was assigned structure **3.7** based on the following spectral evidence. The M^+ of 267 supported the molecular formula of $C_{11}H_7BrO_3$ while the infrared spectrum showed the absorption frequency at 1670 cm^{-1} for the quinone carbonyl system. A 3-proton singlet at 3.99 ppm in the ^1H n.m.r spectrum is assigned to the methoxy group. The dd at 7.38 ppm (*J* 8.0 and 2.0) is assigned to H-6, while a 1-proton singlet at 7.40 ppm is assigned to H-3. A deshielded 1-proton dd at 7.68ppm (*J* 8.4 and 2.0) is assigned to H-8. A 1-proton dd at 7.80ppm (*J* 8.4 and 8.0) is assigned to H-7.

Thus, this molecule represents one of the two halves of the synthetic target **3.19** we have set for this project.

3.1.2 Synthesis of 6-hydroxy-1,4-dimethoxynaphthalene 3.28

The next challenge was the synthesis of 6-hydroxy-1,4-dimethoxynaphthalene **3.28**, which in turn would be converted to an ortho bromo analogue.[50] The envisaged route to 6-hydroxy-1,4-dimethoxynaphthalene **3.28** was expected to proceed according to Scheme 3.5 below, whereby Danishefsky's diene **3.20** could be reacted with 1,4-benzoquinone **3.21** to afford **3.22**,[51] which should best be handled by treatment with pyridine and acetic anhydride to produce triacetoxy naphthalene **3.23**.[51] Hydrolysis of this latter product would then afford the trihydroxy naphthalene **3.24**. The trihydroxy naphthalene **3.24** in acetonitrile and water could be oxidized with CAN to afford 6-hydroxynaphthoquinone **3.25**, which in dichloromethane if treated with pyridine and Ac_2O would produce the 6-acetoxynaphthoquinone **3.26**, and this in turn could be subjected to reductive methylation to afford 6-acetoxy-1,4-dimethoxynaphthalene **3.27**.[52] Finally, naphthalene **3.27** upon hydrolysis with potassium hydroxide in methanol should yield phenol **3.28**, (Scheme 3.5).

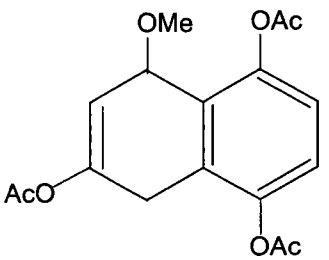


Scheme 3.5

Thus reaction between Danishefsky's diene **3.20** and benzoquinone **3.21** in benzene under reflux yielded an oil after removal of solvent. The oil was repeatedly chromatographed to afford quinone **3.25** in 25% yield.

Due to the poor yield of quinone **3.25** following this protocol, it was decided to follow an alternative route. The reaction was repeated and the product oil was treated with Pyr/Ac_2O at 25^0C for 12 hrs to give a white product, which was chromatographed to afford two products viz., the triacetoxy naphthalene **3.23** (8%) and a new product (92%), to which the structure **3.29** has been assigned according to the spectral evidence. A HRMS of 334.1050 confirmed the molecular formula of $C_{17}H_{18}O_7$, (Requires: 334.1053) while the infrared spectrum showed absorption frequencies at $1760cm^{-1}$. In the ^1H n.m.r spectrum three 3-proton sharp singlets at 2.20, 2.32 and 2.33ppm are assigned to the three acetoxy groups; a 1-proton dd (*J* 17.8 and 2.0 Hz) at 2.60ppm is assigned to H-8a; a 1-proton ddd at 2.80 ppm dd (*J* 17.8, 5.0 and 2.0 Hz) is assigned to H-8e; a 3-proton singlet at 3.35ppm is assigned to the methoxy group; a 1-proton dd (*J* 5.0 and 2.0 Hz) at 4.57 ppm is assigned to H-5; a 1-proton doublet (*J* 2.0 Hz) at 6.39ppm is assigned to H-6; a 1-proton doublet (*J* 8.8 Hz) at 6.99ppm is assigned to H-2 and a 1-proton doublet (*J* 8.8 Hz) at 7.10ppm is assigned to H-3. In the ^{13}C n.m.r spectrum, the signals at 20.9, 21.0 and 21.2 ppm are assigned to the three methyl carbons of the acetoxy groups, while the signal at 32.4ppm is assigned to C-8; a signal at 55.5 ppm is assigned to carbon of the methoxy group; a signal at 70.0ppm is assigned to C-5, a signal at 106.8 ppm is assigned to C-6. The signals at 121.3, 123.5, 123.9 and 127.2 ppm are assigned to C-2, C-3, C-8a and C-4a respectively. The signal at 144.1 ppm is assigned to C-1, a signal at 146.5 ppm is assigned to C-4; a

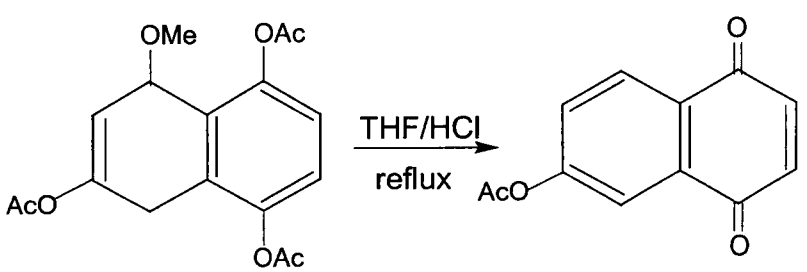
signal at 150.2 ppm is assigned to C-7 and finally the signals at 168.5, 168.9 and 169.0 ppm are assigned to the carbonyl carbons of the three acetoxy groups.



3.29

Thus the problem, which represented itself, was the conversion of product **3.29** into triacetate **3.23**. The conversion of **3.29** into **3.23** was attempted according to the three protocols discussed below and illustrated in Schemes 3.7, 3.8 and 3.9 respectively.

The adduct **3.29** in THF was treated with hydrochloric acid under reflux for 12h to afford 6-acetoxynaphthoquinone **3.26**, similar to the material synthesized later, but in a disappointing yield of 25%, (Scheme 3.6). No doubt, aromatization occurred but the 1,4-diacetoxy system also hydrolyzed and during the work-up the p-quinol system auto-oxidized to the corresponding quinone.



3.29 **3.26**

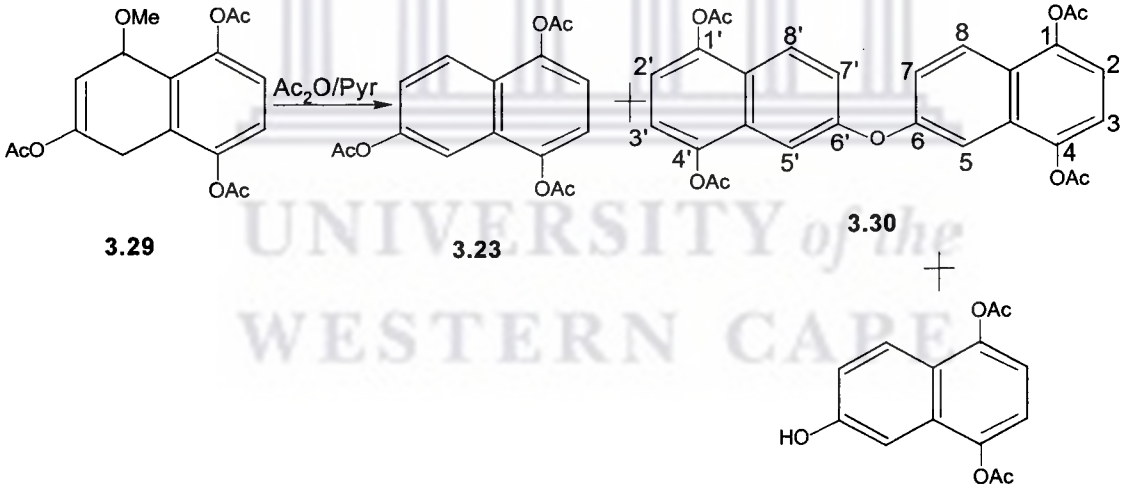
Scheme 3.6

Because of the poor yield of quinone **3.26**, an alternative protocol was adopted whereby triacetate **3.29** was stirred in a mixture of Ac_2O/Pyr under reflux for 2h to yield an oil, which was chromatographed to afford three fractions, (Scheme 3.7).

The first fraction was shown to be the triacetoxy naphthalene **3.23** (32%) by comparison of spectral data. The second fraction to elute (11%) was assigned the dimeric structure **3.30** based on the following evidence: A HMRS indicated a molecular formula of $C_{28}H_{22}O_9$ (Found: 502.1260; requires 502.1264) while the infrared spectrum showed the ester carbonyl frequencies at 1726 cm^{-1}. In the ^1H n.m.r spectrum, two 6-proton signals at 2.36 and 2.44ppm are assigned to the four acetate groups; a 1-proton doublet (J 8.5 Hz) at 6.44 ppm is due to H-2', while 1-proton doublet (J 8.2 Hz) at 6.94ppm is assigned to H-2; a 1-proton dd (*J* 9.0 and 2.2 Hz) at 7.16ppm is assigned to H-7, while 1-proton dd (*J* 8.8 and 2.4 Hz) at 7.22ppm is assigned to H-7'; a 1-proton doublet (J 8.2) at 6.85ppm is assigned to H-3 while H-3' appears as a doublet at 6.40 ppm (J 8.5 Hz) and H-5 appears as a doublet (*J* 2.2 Hz) at 7.42ppm while H-5' appears as doublet (*J* 2.2 Hz) at 7.75ppm. In all cases the same proton designation with the prime may be interchanged. By observing the ^{13}C-n.m.r spectrum C-6 and C-6' appear at 139.4 and 139.7 ppm while C-1, C-4, C-1' and C4' appear at 148.2, 149.5, 149.8 and 150.2 ppm. The signals at 169.9, 170.2, 170.6 and 170.7ppm are assigned to the four carbonyl carbons. In the ^{13}C signals, it is clear that the two naphthalene rings both have the 1,4,6-trisubtituted patterns and the fact that the four acetate methyl signals overlap in the proton spectrum and the four carbonyl carbon signals are so close in the ^{13}C-n.m.r spectrum supports the fact that the link between the two naphthalene rings is via the 6-6' ether bond. Since both the proton and C-13 signals are non-identical, it would appear that the molecule is non-symmetric, i.e. that there is

restricted rotation about the 6-6' bond as this would cause each of the two sets of similar protons and the C-13 atoms to be different.

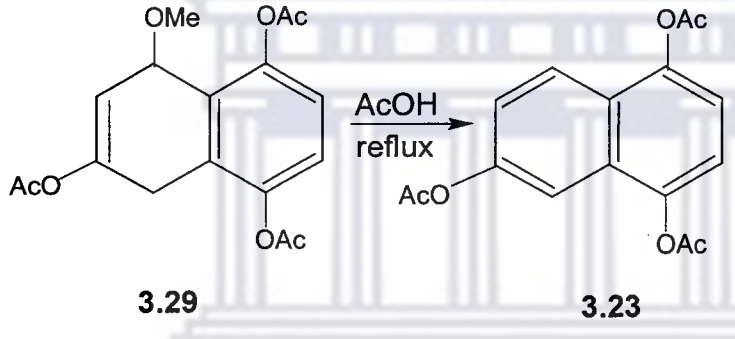
The third fraction to elute (21%) was assigned the structure 1,4-diaceotxy-6-hydroxynaphthalene **3.31** according to the following spectral evidence: A HMRS supported the molecular formula of $C_{14}H_{12}O_5$ (Found: 260.0681. Requires: 260.0685), while the infrared spectrum showed the OH frequency at 3350 cm^{-1} and ester carbonyl frequencies at 1729 cm^{-1}. In the ^1H n.m.r spectrum the two 3-proton singlets at 2.41 and 2.45ppm are assigned to the protons of the acetate groups. These are slightly different due to the influence that the hydroxyl group at C-6 might have. A broad D_2O exchangeable peak at 5.60ppm is due to the hydroxyl group.



3.29 **3.23** **3.30** **3.31**

Scheme 3.7

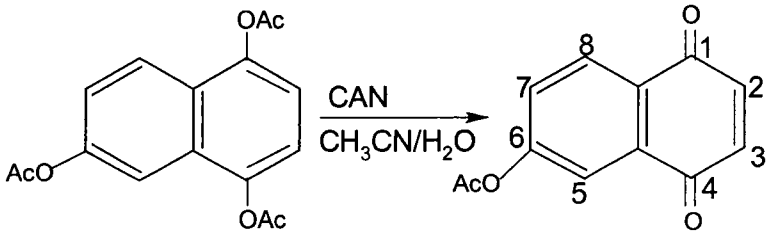
Due to the poor yield of the desired product **3.23**, an alternative route was adopted, whereby the adduct **3.29** was boiled in acetic acid under reflux for 5h to afford the triacetate **3.23** in quantitative yield (Scheme 3.8). The material produced was similar to the material synthesized earlier and thus was the route to follow for the production of triacetoxynaphthalene **3.23**.



3.29 **3.23**

Scheme 3.8

The triacetate **3.23** in acetonitrile was then oxidized with cerium ammonium nitrate in water, according to Scheme 3.9 shown below. This represented a shorter route to **3.26**.

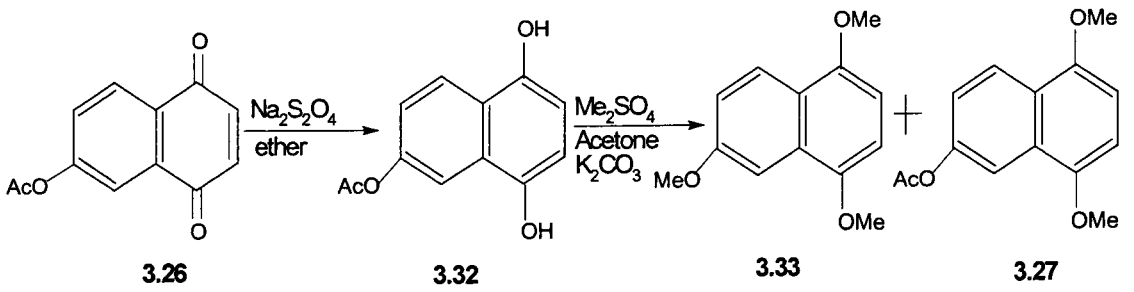


3.23 **3.26**

Scheme 3.9

The triacetate **3.23** in acetonitrile and water was treated with cerium ammonium nitrate at room temperature for 1h to yield the corresponding quinone **3.26** (93%). The resulting material was assigned structure **3.26** according to the following spectral evidence. A HRMS supported a molecular formula of $C_{12}H_8O_4$ (Found: 216.0429. Requires: 216.0423), while the infrared spectrum showed frequencies at 1727 (ester C=O) and 1668 (quinine C=O) cm^{-1}. In the ^1H n.m.r spectrum a 3-proton singlet at 2.36ppm is assigned to methyl of the acetoxy group; a 2-proton singlet at 6.99ppm is assigned to H-2 and H-3; a 1-proton dd (*J* 8.4 and 2.5 Hz) at 7.48ppm is assigned to H-7; a 1-proton doublet (*J* 2.5 Hz) at 7.80ppm is due to H-5 and a 1-proton doublet (*J* 8.4 Hz) at 8.13ppm is assigned to H-8. In the ^{13}C n.m.r spectrum, a signal at 21.1ppm is assigned to the methyl carbon of the acetoxy group; a signal at 119.6ppm is assigned to C-7. The signals at 127.3, 128.6 and 129.6ppm are assigned to C-5, C-8 and C-4a respectively. The signals at 133.7, 138.7 and 138.9ppm are assigned to C-8a, C-2 and C-3 respectively; a signal at 155.2ppm is assigned to C-6; a signal at 168.5ppm is assigned to the carbonyl carbon of an ester, while the signals at 184.1 and 184.2ppm are assigned to the carbonyl carbons of the quinone.

Treatment of 6-hydroxynaphthalene **3.31** in dichloromethane with pyridine and acetic anhydride at 24^0C under nitrogen atmosphere for 1h, followed by washing with water, 0.5M HCl, sodium hydrogen carbonate and chromatographic purification of the product, afforded the same quinone **3.26** (79%) with identical spectral properties to the product synthesized earlier.



3.26 **3.32** **3.33** **3.27**

Scheme 3.10

The 6-acetoxyquinone **3.26** in ether was reduced with aqueous $Na_2S_2O_4$ to give phenol **3.32**,[52] which was immediately treated with dimethylsulphate in dry acetone in the presence of potassium carbonate under reflux and vigorous stirring in the expectation to form 6-acetoxy-1,4-dimethoxynaphthalene **3.27** after chromatographic purification. As it turned out, two products were produced which were separated chromatographically.

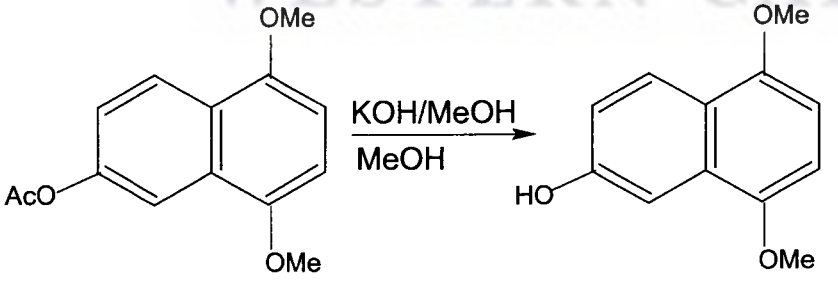
Indeed the first fraction to elute was the trimethoxy-naphthalene **3.33** (71%). The material produced was assigned the structure **3.33** according to the following evidence: A M^+ of 218 supported the molecular formula $C_{13}H_{14}O_3$ (requires 218). In the ^1H n.m.r spectrum a 9-proton peak at 3.99ppm is due to the three methoxy groups. A 1-proton doublet (*J* 8.4 Hz) at 6.57ppm is assigned to H-2, while a 1-proton doublet (*J* 8.4 Hz) at 6.70ppm is assigned to H-3. A 1-proton dd at 7.17ppm (*J* 9.2 and 2.6 Hz) is assigned to H-7, while a 1-proton doublet (*J* 2.6 Hz) at 7.51ppm is assigned to H-5. Finally, a 1-proton doublet (*J* 9.2 Hz) at 8.12ppm is assigned to H-8.

The second fraction to elute was the expected 6-acetoxy-1,4-dimethoxynaphthalene **3.27** (22%). The material produced was assigned the structure **3.27** based on the following

spectral evidence. A M^+ of 246 demonstrated the molecular formula of $C_{14}H_{14}O_4$, while the infrared spectrum showed a frequency at 1726cm^{-1}. In the ^{1}H n.m.r spectrum a 3-proton singlet at 2.35ppm is assigned to the acetoxy group; a 6-proton signal at 3.93ppm is assigned to the two methoxy groups; two 1-proton doublets (*J* 9.2 Hz) at 6.66 and 6.68ppm are assigned to H-2 and H-3; a 1-proton dd (J 9.2 and 2.6 Hz) at 7.30ppm is assigned to H-7; a 1-proton doublet (*J* 2.6 Hz) at 7.95ppm is assigned to H-5 and finally a 1-proton doublet (*J* 9.2 Hz) at 8.25ppm is due to H-8.

In order to improve the yield of the desired 6-acetoxynaphthalene **3.27** the following alternative synthetic protocol was adopted. After the ethereal reduction of quinone **3.26** with $Na_2S_2O_4$, the crude quinol **3.32** was methylated under neutral conditions with methyl iodide in the presence of silver (I) oxide in benzene and in this way the acetoxydimethoxynaphthalene **3.27** was produced in an 83% isolated yield.

With the 6-acetoxy-1,4-dimethoxynaphthalene **3.27** in hand, we turned our attention to hydrolyzing the 6-acetoxy group to transform it into the desired phenol **3.28** (Scheme 3.11).



3.27 **3.28**

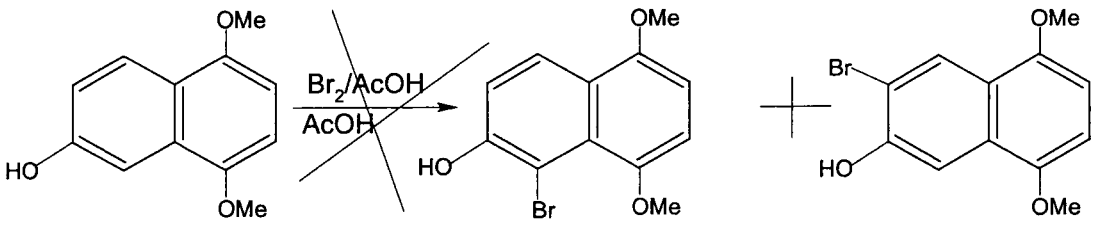
Scheme 3.11

Thus naphthalene **3.27** in methanol was treated with 1% potassium hydroxide in methanol to afford phenol **3.28** (78%). The material produced was assigned structure **3.28** based on

the following spectral evidence. A M^+ of 204 supported the molecular formula of $C_{12}H_{12}O_3$, while the infrared spectrum showed a strong absorption at 3368 cm^{-1}. In the ^1H n.m.r spectrum a 6-proton singlet at 3.93ppm is assigned to the two methoxy groups, a 1-proton D_2O exchangeable single peak at 5.34ppm is assigned to the C-6 hydroxyl group, a 1-proton doublet (J 8.0 Hz) at 6.55ppm is assigned to H-2, a 1-proton doublet (*J* 8.0 Hz) at 6.70ppm is assigned to H-3, a 1-proton dd (*J* 9.2 and 2.4 Hz) at 7.20ppm is assigned to H-7, a 1-proton doublet (J 2.4Hz) at 7.51ppm is assigned to H-5. Finally, a 1-proton doublet (J 9.2 Hz) at 8.25ppm is assigned to H-8.

3.1.3 Bromination of 6-hydroxy-1,4-dimethoxynaphthalene 3.28

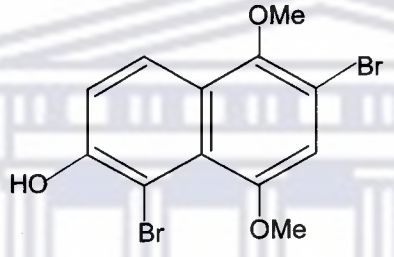
With the 6-hydroxy-1,4-dimethoxynaphthalene **3.28** successfully prepared, attempts to brominate it were made in order to introduce bromine ortho to the 6-hydroxyl group,[53] and is illustrated on Scheme 3.12 below. Thus phenol **3.28** in acetic acid was treated with 1 equivalent of bromine in acetic acid at 23^0C with the hope of producing compounds **3.34** and **3.35**. Indeed, two products of bromination were produced but unfortunately were not the ones that were hoped for. The mixture of products was chromatographed and eluted with ethyl acetate and hexane.



3.28 **3.34** **3.35**

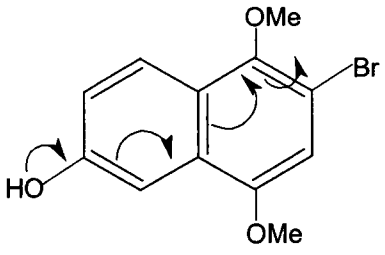
Scheme 3.12

The first fraction to elute (13%) was assigned the dibrominated structure **3.36** based on the following spectral evidence. The HMRS indicated a molecular formula of $C_{12}H_{10}Br_2O_3$, (Found: 359.8994. Requires 359.8997), while the infrared spectrum showed the OH frequency at 3350 cm^{-1}. The ^1H n.m.r spectrum had the following signals; a 6-proton peak at 3.90ppm assigned to the two methoxy groups; a 1-proton D_2O exchangeable signal at 6.51ppm assigned to the 6-OH group; a 1-proton singlet at 6.96ppm assigned to H-3; a 1-proton doublet (*J* 9.0 Hz) at 7.30ppm assigned to H-7. Finally, a 1-proton doublet (*J* 9.0 Hz) at 8.00ppm assigned to H-8.



3.36

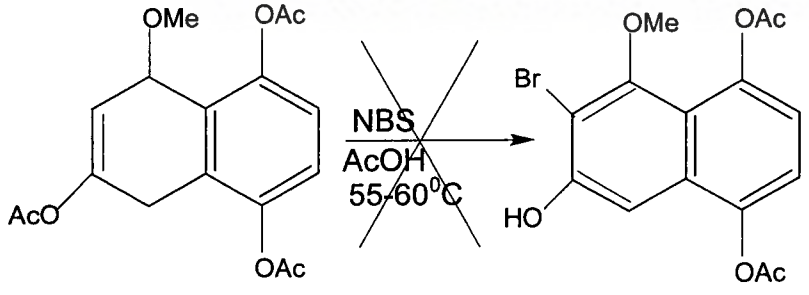
Further elution afforded a second fraction (16%) to which structure **3.37** of a monobrominated product was assigned based on the following spectral evidence. A M^+ of 283 supported the molecular formula of $C_{12}H_{11}BrO_3$, while the infrared spectrum showed the presence of the OH group at 3350cm^{-1}. The ^1H n.m.r spectrum had the following signals; a 6-proton peak at 3.93ppm assigned to the two methoxy groups; a broad D_2O exchangeable signal at 5.25ppm assigned to the 6-OH group; a 1-proton singlet at 6.84 assigned to H-3; 1-proton dd (*J* 8.4 and 2.6 Hz) at 7.15ppm assigned to H-7; a 1-proton doublet (J 2.4 Hz) at 7.48ppm assigned to H-5. Finally, a 1-proton doublet (*J* 8.4 Hz) at 7.99ppm is assigned to H-8.



3.37

On reflection, it was not too surprising that the more electron–rich ring viz., the 1,4-dimethoxy moiety was brominated and at C-2 due to the electron-donating ability of the 6-OH group making the amphi position to it also more electron-rich for the formation of bromophenol **3.37**. In the case of the dibromophenol **3.36**, the fact that the second bromine atom attacked at C-5 is due to the higher activity of the α-position of naphthalenes and thus C-7 was not brominated although also *ortho* to the OH group.

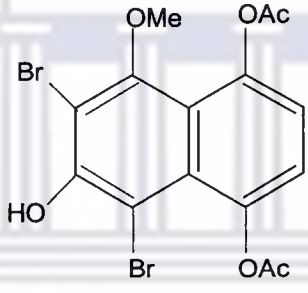
Since the bromination of phenol **3.28** failed to produce the desired products **3.34** and **3.35**, alternative routes were investigated, one of which is illustrated in Scheme 3.13, whereby adduct **3.29** was brominated in the hope of introducing bromine at C-6 only due to the double bond between C-6 and C-7.



3.29 **3.38**

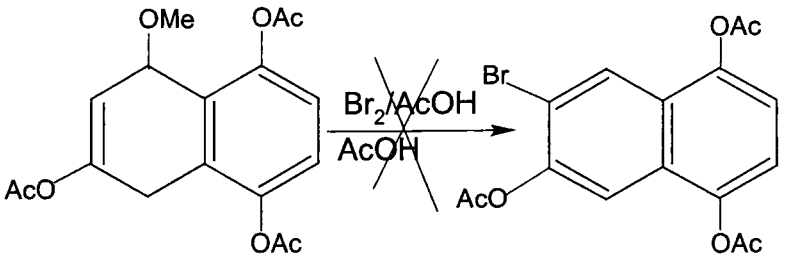
Scheme 3.13

Thus 1,4,7-triacetoxy-5-methoxynaphthalene **3.29** in acetic acid was treated with 1.5molar equivalents of N-bromosuccinimide in acetic acid at 55-60^{0}C in the hope of directing bromine to C-6. After 45min of stirring, the reaction mixture was poured onto water and the resulting precipitate was filtered. The resulting product (71%) was assigned structure **3.39** based on the following spectral evidence. The HRMS confimed the molecular formula of $C_{15}H_{12}Br_2O_6$ (Found: 445.9089. Requires: 445.9001) while the infrared spectrum showed frequencies at 3380 and 1740-1728 cm^{-1}. In the ^{1}H n.m.r the two 3-proton singlets at 2.44 and 2.49ppm are assigned to the two acetoxy groups; a 3-proton singlet at 3.33ppm is assigned to the methoxy group; a 1-proton D_2O exchangeable peak at 5.09ppm is assigned to the hydroxy group and finally two 1-proton doublets (*J* 8.4 Hz) at 7.29 and 7.35ppm are assigned to H-2 and H-3.



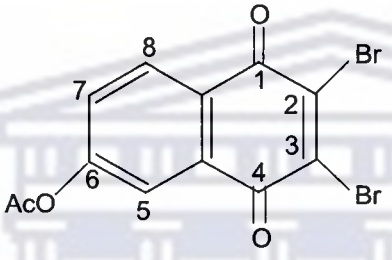
3.39

Since the treatement of adduct **3.29** with NBS did not afford the desired product **3.38**, the use of bromine to effect this instead of NBS was then considered. Thus adduct **3.29** in acetic acid was treated with 1molar equivalent of bromine in acetic acid at 24^{0}C in the hope of producing bromo-analogue **3.40**, Scheme 3.14. After 45min of stirring, the reaction mixture was poured onto water and extracted with dichloromethane and the residue obtained was then purified by column chromatography to afford two products viz., **3.41** and **3.23** respectively.



3.29 **3.40**

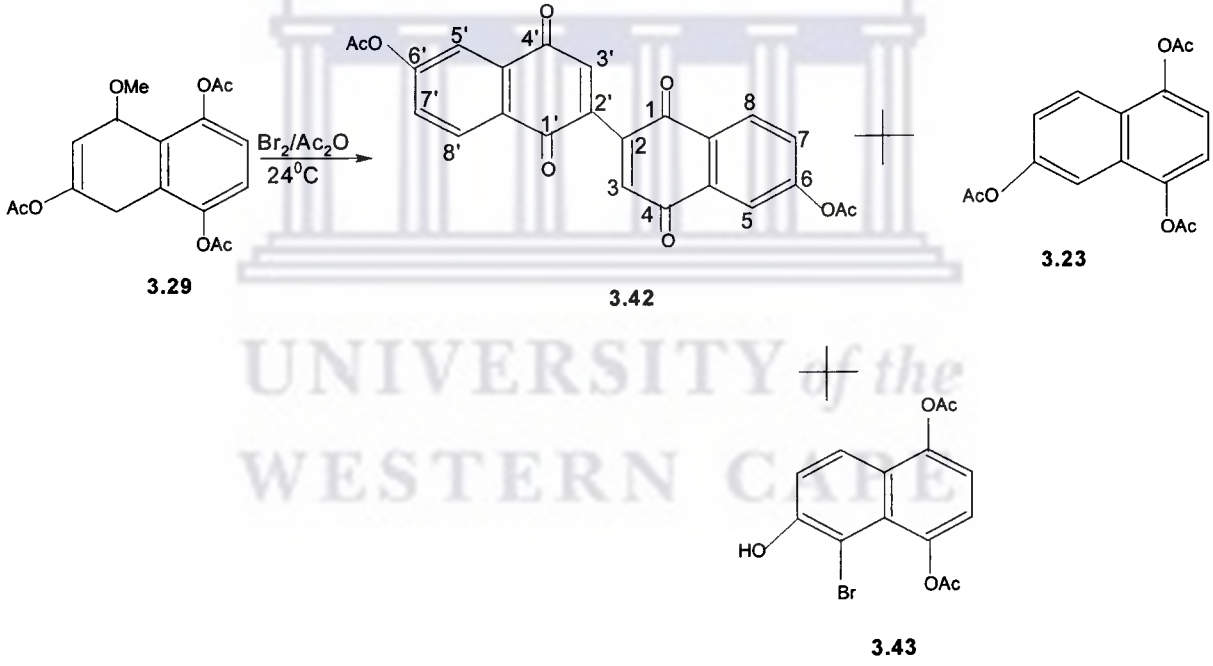
Scheme 3.14



3.41

The first fraction eluted (11%) was assigned structure **3.41** based on the following spectral evidence. A M^+ of 372/374/376 supported the molecular formula of $C_{12}H_6Br_2O_4$, while the infrared spectrum showed frequencies at 1754 (ester C=O) and 1665 (quinine C=O) cm^{-1} In the ^1H n.m.r spectrum a 3-proton singlet at 2.37ppm is assigned to the acetoxy group; a 1-proton dd (*J* 8.4 and 2.2 Hz) at 7.52ppm is assigned to H-7; a 1-proton doublet (*J* 2.2 Hz) at 7.90ppm is assigned to H-5; and finally, a 1-proton doublet (*J* 8.4Hz) at 8.23ppm is assigned to H-8. The second molecule to elute was 1,4,6-triacetoxynaphthalene **3.23** (65%) which had identical spectroscopic properties to the same material synthesized earlier.

In yet another variation of conditions, the reaction was repeated using acetic anhydride as solvent and this lead to the formation of three products illustrated on Scheme 3.15 below.



3.29 3.42 3.23 3.43

Scheme 3.15

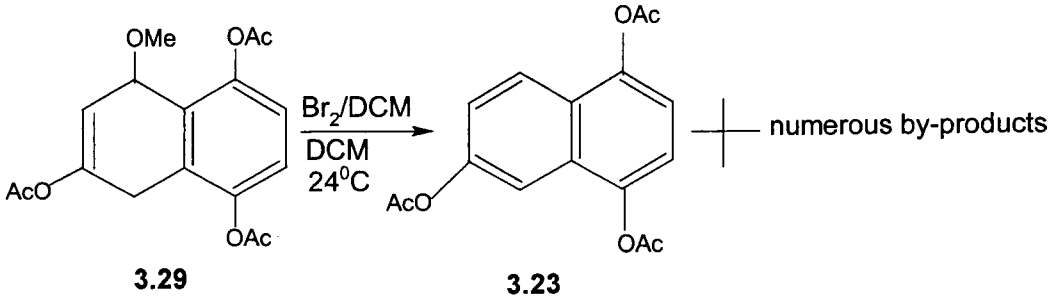
Thus adduct **3.29** was treated under the same conditions as described *vide supra* but with acetic anhydride used as a solvent. Upon work-up, the residue was purified by column chromatography using EtOAc:hex (3:7) as an eluent.

The first molecule to elute (4%) was assigned the structure **3.42** based on the following spectral evidence. A HRMS confirmed the molecular formula of $C_{24}H_{14}O_8$ (Found: 430.0687; Requires: 430.0689), while the infrared spectrum showed frequencies at 1728 (ester C=O) and 1660 (quinine C=O) cm^{-1}. In the ^1H n.m.r spectrum a 6-proton singlet at 2.36ppm is assigned to hydrogens of the two acetoxy groups; a 4-proton multiplet at 7.50ppm is assigned to H-3, H-3', H-7 and H-7'; two 1-proton doublets (*J* 2.2 Hz) at 7.79 and 7.87ppm are assigned to H-5 and H-5'and finally, two 1-proton doublets (*J* 8.4 Hz) at 8.11 and 8.20ppm are assigned to H-8 and H-8'. Assignments of the same protons may be interchanged.

Further elution afforded 1,4,6-triacetoxynaphthalene **3.23** (60%) spectroscopically identical to the material synthesized previously. The third compound to elute was identified as the bromophenol **3.43** (11%) based on the following spectral evidence. A M^+ of 338/340 supported the molecular formula of $C_{14}H_{11}BrO_5$ while the infrared spectrum showed frequencies at 3350 and 1740cm^{-1}. In the ^1H n.m.r spectrum a 6-proton singlet at 2.46ppm is assigned to the hydrogens of the two acetoxy groups; a 1-proton D_2O exchangeable signal at 6.48ppm is assigned to the 6-OH; a 1-proton doublet (*J* 8.2 Hz) at 7.15ppm is assigned to H-2; a 1-proton doublet (*J* 8.2 Hz) at 7.21ppm is assigned to H-3; a 1-proton doublet (*J* 9.2 Hz) at 7.28ppm is assigned to H-7 and finally, a 1-proton doublet (*J* 9.2 Hz) at 7.83ppm is assigned to H-8.

The dimerised product **3.42** was of interest since it in effect by default produced a quinone-quinone linked binaphthoquinone for evaluation. Apart from the aromatized product **3.23**, which was anticipated due to its greater thermodynamic stability, the only other product and indeed one representing monobromination of the more electron-rich ring was bromophenol **3.43** of α-bromination and none of the alternative C-7 bromination was observed.

The reaction was repeated with dichloromethane as solvent and is illustrated in scheme 3.16 shown below.



3.29 **3.23**

Scheme 3.16

Treatment of adduct **3.29** in dichloromethane with 1molar equivalent of bromine in dichloromethane at 24^{0}C afforded a residue which was chromatographed to give the triacetoxynaphthalene **3.23** as the major product (68%) identical to the material synthesized earlier with an array of minor components being present which were not analyzed.

Since the bromination at 24^{0}C lead to aromatization, the reaction was repeated at 10^{0}C. In this instance the residue found upon workup was chromatographed to afford the dimeric material **3.42** (4%) identical to the material synthesized earlier and further elution afforded the triacetoxynaphthalene **3.23** (68%) as the major product with identical spectral data to the material synthesized earlier. Bromonaphthalene **3.43** was eluted last in a yield of 10%.

Repeating the reaction at 4^{0}C afforded a residue, which was purified by column chromatography to afford three products. The first molecule to elute was identified as dimer **3.42** (3%) identical to the material synthesized earlier. The second fraction to elute was the triacetoxynaphthalene **3.23** (44%) identical in all spectral aspects to the molecule

synthesized before. Further elution produced bromonaphthalene **3.43** (9%), which was spectroscopically identical to the material synthesized before.

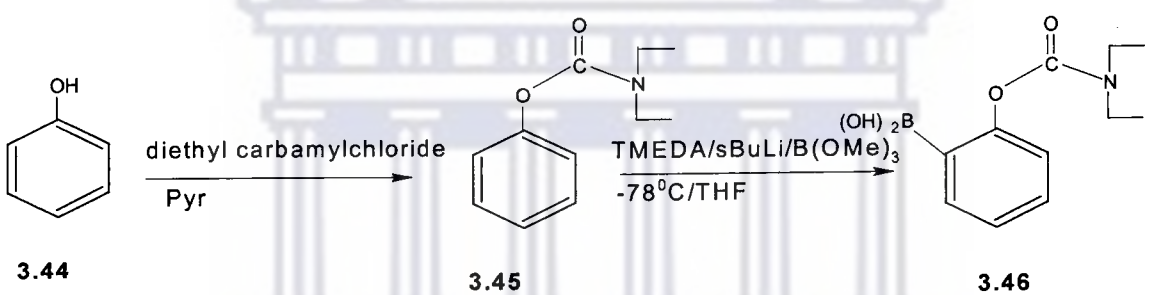
As a consequence of limited success to a viable synthetic route to the desired *ortho*-brominated naphthols **3.34** and **3.35** to be transformed into suitable boronic acids for Suzuki coupling with the earlier prepared bromoquinone **3.7** for the synthesis of an analogue of diospyrin 1 viz., **3.19**, we extended the search for alternative intermediates to this end.

3.1.4 Development of strategies for the synthesis of suitable boronic acids to coupling protocols

Due to the fact that the bromination of phenol **3.28** and adduct **3.29** failed to produce the expected *ortho*-brominated hydroxynaphthalenes, it was considered that the phenol **3.28** could be transformed into a carbamate which would undergo ortho-lithiation in order to obviate the necessity of a bromination step.[54,55] The synthesis of a representative boronic acid was carried out starting from a known carbamate of phenol in order to develop suitable reaction conditions for the synthesis of the target molecules.

This is illustrated in Scheme 3.17 shown below. Phenol **3.44** was treated with *N,N*-diethyl carbamylchloride in pyridine at 110^0C to yield the corresponding carbamate **3.45** (77%).[56,57] The product was assigned the structure **3.45** based on the following spectral evidence. A M^+ of 193 supported the molecular formula of $C_{11}H_{15}NO_2$. In the ^{1}H n.m.r spectrum, a 6-proton multiplet at 1.22ppm is assigned to the methyl groups of the ethyl moiety; 4-proton multiplet at 3.40ppm is assigned to the two methylene groups and finally the signals at the region of 7.0 to 7.5ppm is assigned to protons of the aromatic ring.

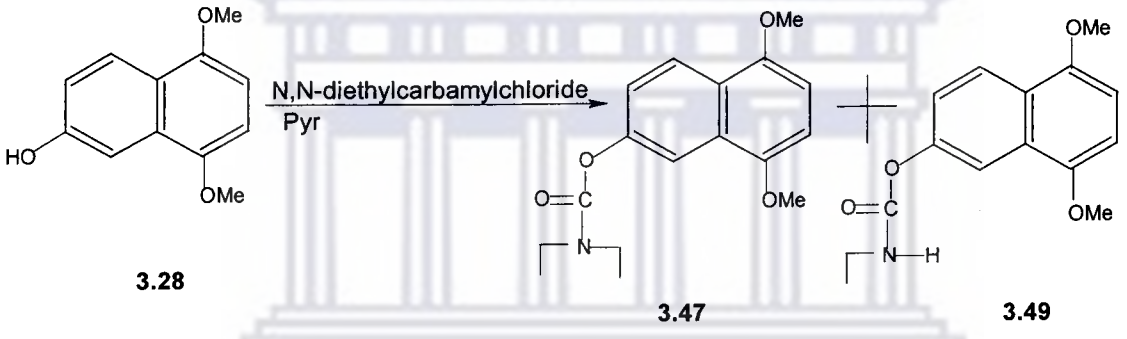
The carbamate **3.45** was then treated with TMEDA, sec-butyllithium and trimethoxyborane in THF at -78^{0}C to yield the corresponding boronic acid **3.46** (73%). The resulting compound was assigned structure **3.46** based on the following spectral evidence. A M^+ of 237 supported the molecular formula of $C_{11}H_{16}BNO_4$. In the ^{1}H n.m.r spectrum a 6-proton multiplet at 1.15ppm is assigned to the two methyl groups of the ethyl side chain; a 4-proton multiplet at 3.25ppm is assigned to the two methylene groups; a 3-proton multiplet in the range of 7.10 and 7.50ppm is assigned to the H-4, H-5 and H-6 and finally a dd (*J* 9.2 and 2.6 Hz) at 7.85ppm is assigned to H-3 due to the fact that the boronic group *ortho* to H-3 deshields this proton.



Scheme 3.17

Our attention was next directed towards the synthesis of boronic acid **3.48** in which case phenol **3.28** was the starting material [58] and is illustrated in Schemes 3.18 and 3.19 below. Thus 6-hydroxy-1,4-dimethoxynaphthalene **3.28** in pyridine was treated with *N,N*-diethylcarbamylchloride at 110^{0}C to afford the corresponding carbamate **3.47**in 79% yield after column chromatography. The first fraction to elute was assigned structure **3.47** based on the following spectral evidence. A HRMS supported the molecular formula of $C_{17}H_{21}NO_4$ (Found: 303.1466; Requires: 303.1471). In the ^{1}H n.m.r spectrum, a 6-proton multiplet at 1.26ppm is assigned to the two methyl groups of side chain; a 4-proton multiplet at 3.20ppm is assigned to the two methylene groups of the side chain; a 6-proton

peak at 3.93ppm is assigned to the two methoxy groups; a 1-proton doublet (*J* 9.2 Hz) at 6.66ppm is assigned to H-2; a 1-proton doublet (*J* 9.2 Hz) at 6.68ppm is assigned to H-3; a 1-proton dd (*J* 9.2 and 2.6 Hz) at 7.24ppm is assigned to H-7; a 1-proton doublet (*J* 2.6 Hz) at 7.91ppm is assigned to H-5 and finally, a 1-proton doublet (*J* 9.2 Hz) at 8.20ppm is assigned to H-8.



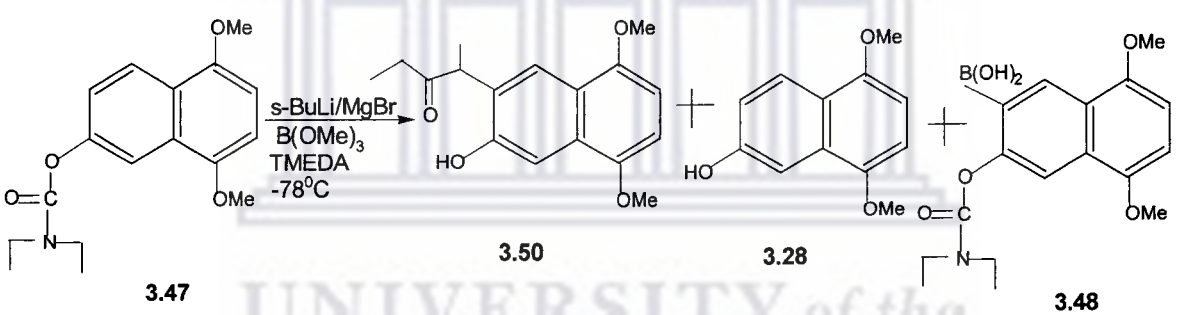
3.28 **3.47** **3.49**

Scheme 3.18

The second molecule to elute was assigned the structure **3.49** (16%) based on the following spectral evidence. A HRMS supported the molecular formula of $C_{15}H_{17}NO_4$ (Found: 275.1150. Calc.: 275.1158). In the ^1H n.m.r spectrum a 3-proton multiplet at 1.20ppm is assigned to the methyl group of the side chain; a 2-proton multiplet at 3.20ppm is assigned to the methylene group of the side chain; a 6-proton singlet at 3.93ppm is assigned to the two methoxy groups; a 1-proton singlet at 5.60ppm is assigned to N-H; a 1-proton doublet (*J* 8.4 Hz) at 6.54ppm is assigned to H-2; a 1-proton doublet (*J* 8.4 Hz) at 6.70ppm is assigned to H-3; a 1-proton dd (*J* 8.4 and 2.6 Hz) at 7.10ppm is assigned to H-7; a 1-proton

doublet (J 2.6 Hz) at 7.50ppm is assigned to H-5 and finally a 1-proton doublet (J 8.4 Hz) at 8.05ppm is assigned to H-8. Formation of the latter compound might be due to the presence of ethylamine as a contaminant in the commercial sample.

Further treatment of carbamate **3.47** with 1.5 molar equivalents of s-butyllithium in the presence of 1.5 molar equivalents of $MgBr_2$ etherate and TMEDA at -78^0C for 40min followed by treatment with 1.5 molar equivalents of methyl borate at -78^0C under nitrogen[54] and an aqueous work-up afforded essentially three identifiable products after column chromatography, Scheme 3.19.



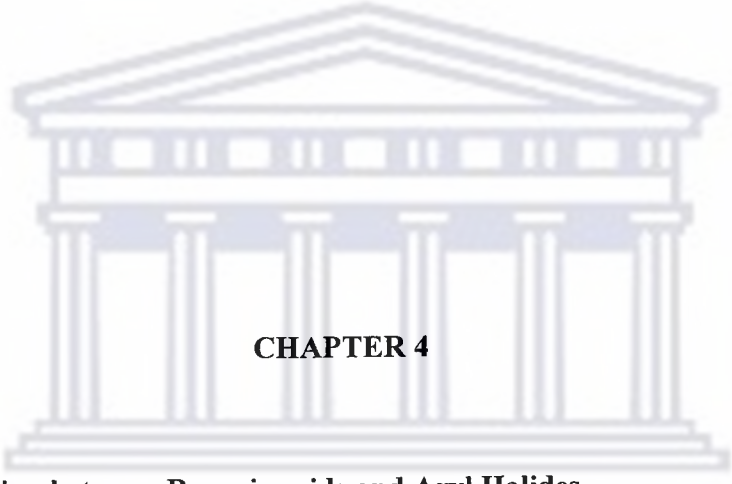
Scheme 3.19

The first fraction to elute (26%) was assigned the phenolic ketone structure **3.50** based on the following spectral evidence. The HRMS of 288.1346 indicated a molecular formula of $C_{17}H_{20}O_4$ (requires 288.1362), which clearly indicates that the carbamate **3.47** has undergone a rearrangement with the loss of nitrogen. The infrared spectrum had two diagnostic bands, one at 3383 and the other at 1650cm^{-1} for the hydroxyl and ketone groups respectively.

In the ^{1}H n.m.r spectrum, the following signals were observed; a 3-proton triplet at 0.97ppm (H-5') (*J* 7.4Hz) coupled to two 1-proton multiplets at 1.60 and 1.90ppm (H-4'); a 3-proton doublet at 1.29ppm (H-1') (*J* 7.0 Hz) coupled to a 1-proton quartet at 3.74ppm (H-2') (*J* 7.0). These connectivities were verified by a COSY spectrum and the methylene protons of the ethyl ketone side chain were diastereotopic due to the proximity of the chiral methine center. The two methoxy groups appeared as 3-proton singlets at 3.93 and 3.97ppm while the H-2 and H-3 appeared as two 1-proton doublets at 6.50 and 6.73ppm (*J* 8.0 Hz) respectively. Finally, three 1-proton singlets at 7.63, 8.80 and 12.00ppm are assigned to H-5, H-8 and OH respectively. In the ^{13}C n.m.r spectrum, the 2'-3'-oxapentyl side chain was demonstrated by signals at 11.9, 17.6, 27.2, 41.9 and 211.5ppm while C-1, C-4 and C-6 appeared at 148.2, 150.5 and 158.5ppm respectively. The four C-H carbons viz., C-2, C-3, C-5 and C-8 appeared at 100.6, 107.1, 107.8 and 126.8ppm while C-4a, C-8a and C-7 appeared at 119.8, 119.9 and 131.6ppm. The second fraction to elute (40%) was assigned to the naphthol **3.28** based on comparison of its ^{1}H n.m.r spectrum to the material synthesized earlier. The very last fraction to elute was assigned to the boronic acid **3.48** (29%), which was recrystallised and had the following features in the ^{1}H n.m.r spectrum; a 6-proton triplet at 1.33ppm (*J* 7.0 Hz) coupled to a 4-proton quartet at 3.58ppm (*J* 7.0Hz) for the N-Et_2; a 6-proton singlet at 3.93ppm for the C-1 and C-4 CH_3O groups; two 1-proton doublet at 6.53 and 6.70ppm (*J* 8.0 Hz) for H-2 and H-3 while two 1-proton singlets at 7.67 and 8.23ppm are assigned to H-8 and H-5 respectively. Broad D_2O exchangeable signals at 7.50 and 9.30ppm are ascribed to the two OH groups of the boronic acid. The ^{13}C n.m.r spectrum demonstrated the CH_3CH_2N group with signals at 13.5 and 42.6ppm respectively. The two CH_3CO groups had signals at 55.8 and 56.0ppm while the carbamate C=O group appeared at 171.5ppm. Three deshielded signals at 148.5, 150.1 and 155.1ppm are assigned to C-1, C-4 and C-6 while the intense signals at 101.0,

105.5, 107.2 and 122.5ppm are assigned to C-2, C-3, C-5 and C-8. The low intensity signals at 119.7, 120.0 and 129.0ppm are assigned to C-4a, C-8a and C-7.

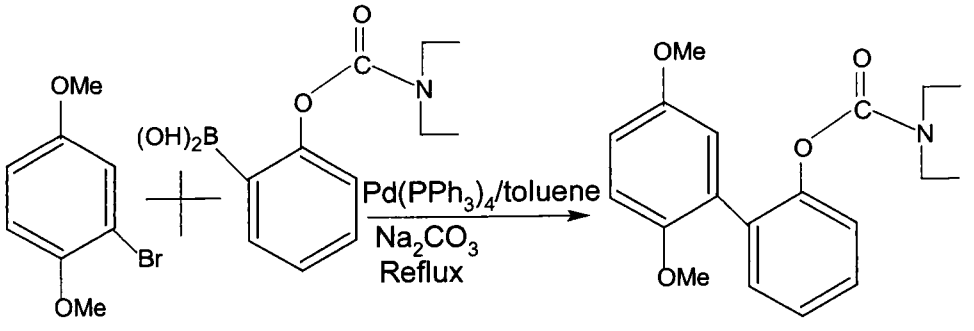
From the forgoing experiment, it would appear that under the conditions of generating the expected and desired boronic acid **3.48**, albeit in low yield, the working hypothesis that C-7 being sterically less crowded than C-5 would be the position of metallation as directed by the carbamate group [54,57], but that conditions would have to be found to improve the yield of boronic acid **3.48** while obviating formation of ketone **3.50** and hydrolysis of the carbamate **3.47** back into the phenol **3.28**.



CHAPTER 4

The Suzuki coupling between Boronic acids and Aryl Halides

In this section, the various Suzuki couplings, which were attempted, are discussed. With boronic acid **3.46** synthesized successfully, it was time to do Suzuki cross-coupling between **3.46** and 2-bromo-1,4-dimethoxybenzene **3.47** and is illustrated in Scheme 4.1 shown below.

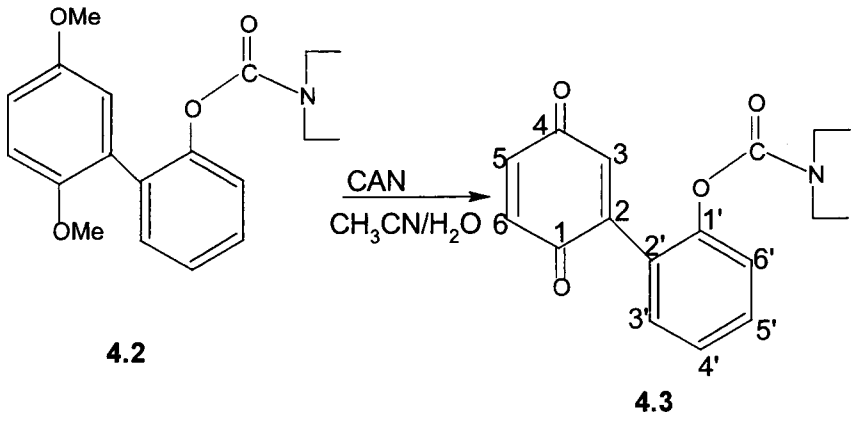


4.1 **3.46** **4.2**

Scheme 4.1

The mixture of 2-bromo-1,4-dimethoxybenzene **4.1** and Pd(0) in toluene was treated with aqueous Na_2CO_3 followed by boronic acid **3.46** with constant stirring under a N_2 atmoshere under reflux for 12h. [59,60,61] The residue recovered upon the removal of solvent was purified by column chromatography using ethyl acetate and hexane as eluent to afford the desired product **4.2** (84%). The resulting material was assigned the structure **4.2** based on the following spectral evidence. HRMS supported the molecular formula of $C_{19}H_{23}NO_4$ (Found: 329.1625; requires 329.1627). In the ^1H n.m.r spectrum the two 3-proton triplets (*J* 7.0 Hz) each at 0.87 and 1.05ppm are assigned to the two methyl groups of the side chains; a 4-proton multiplet at 3.20ppm is assigned to two methylene groups of the side chains; two 3-proton singlets at 3.65 and 3.74ppm are assigned to the two methoxy groups; a 3-proton sharp multiplet at 6.82ppm is assigned to H-3, H-5 and H-6 and finally a 4-proton multiplet at 7.26 is assigned to H-3', H-4', H-5' and H-6'.

As the final step, the biaryl system **4.2** was oxidized to the quinone **4.3** as illustrated in Scheme 4.2.

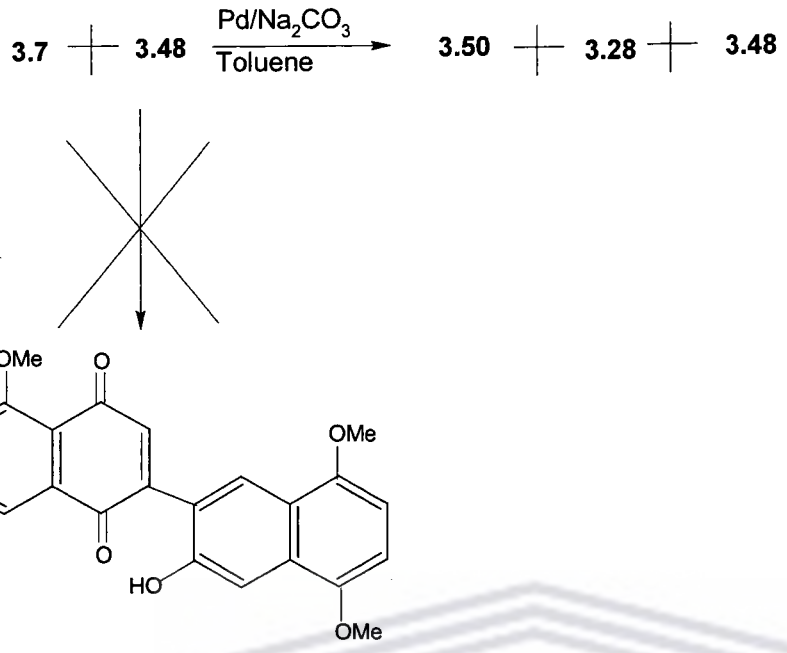


4.2 **4.3**

Scheme 4.2

The coupling product **4.2** in acetonitrile was oxidized with cerium ammonium nitrate in water to afford the corresponding quinone **4.3** (100%). The material produced was assigned the structure **4.3** based on the following spectral evidence. A HRMS demonstrated the molecular formula of $C_{17}H_{17}NO_4$ (Found: 299.1153; requires: 299.1158). In the ^1H n.m.r spectrum a 6-proton triplet (*J* 7.0 Hz) at 1.11ppm is assigned to the two methyl groups of the side chain; a 4-proton quartet (*J* 7.0Hz) at 3.28ppm is assigned to the methylene groups of the two side chains; a 3-proton multiplet at 6.82ppm is assigned to H-3, H-5 and H-6; a 3-proton multiplet at 7.26ppm is assigned to H-3', H-4' and H-5' and finally a 1-proton multiplet at 7.42ppm is assigned to H-6'.

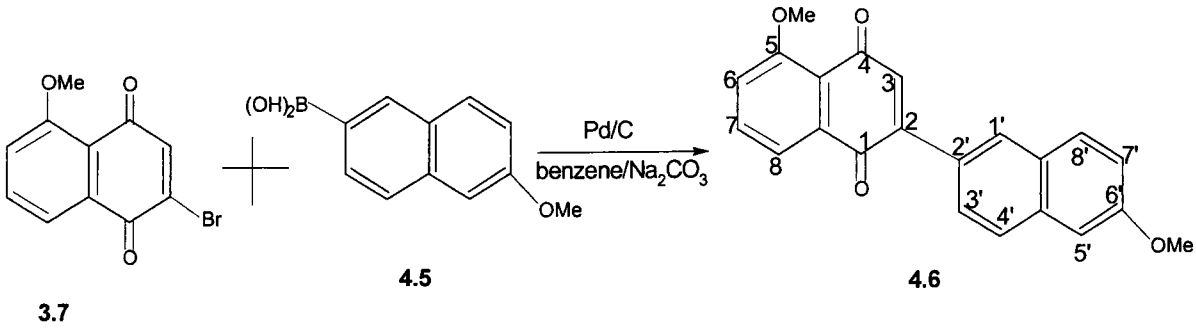
In one further experiment it was felt that since boronic acid **3.48** was indeed formed, the attempted Suzuki cross coupling with bromojuglone methyl ether **3.7** could be viable. However, in the attempted Suzuki cross coupling experiment, only products **3.50**, **3.28** and **3.48** were again formed and none of the desired coupling product **4.4** could be detected, Scheme 4.3. It was surmised that the Pd(0) catalyst has passed its shelf-life and that new catalyst is required.



4.4

Scheme 4.3

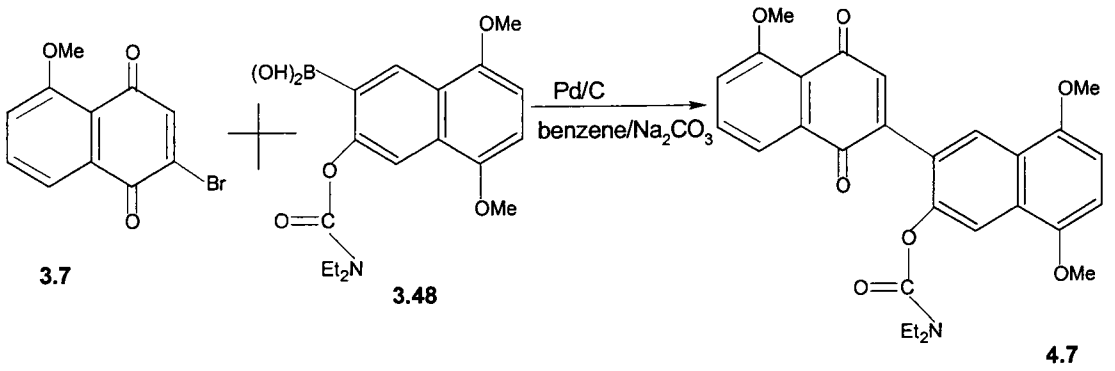
The third Suzuki coupling was performed on the previously synthesized bromoquinone **3.7** and a commercially available boronic acid viz., **4.5** with the freshly prepared catalyst and this is shown in Scheme 4.4.



Scheme 4.4

Thus condensation between quinone **3.7** and boronic acid **4.5** under the standard conditions of the Suzuki coupling protocol afforded the biaryl **4.6** in 63% yield. Assignment of the structure was based on the following signals in the ^{1}H n.m.r spectrum; two 3-proton singlets at 3.95 and 4.04ppm for the two methoxy groups; a 1-proton dd at 7.34ppm (*J* 8.2 and 0.8 Hz) for H-6; a 1-proton triplet at 7.72ppm (*J* 8.2 Hz) for H-7; a 1-proton dd at 7.87ppm (*J* 8.2 and 0.8 Hz) for H-8 and a downfield doublet at 8.08ppm (*J* 1.6 Hz) for H-1'. The ^{13}C n.m.r spectrum had supportive signals at *inter alia* 55.5 and 56.7ppm for C-5 and C-6' methoxy groups; 158.9 and 159.5ppm for C-5 and C-6' while the quinone carbonyl carbons appeared at 184.6 and 185.0ppm.

Finally, an attempt was made to perform the Suzuki coupling on the boronic acid **3.48** that we had synthesized previously and bromo analogue **3.7** using the freshly prepared catalyst and this is illustrated in Scheme 4.5.



Scheme 4.5

Subjecting the boronic acid **3.48** to the Suzuki coupling protocol as described above gave a residue, which was chromatographed to afford three fractions. The first fraction to elute was the starting material bromoquinone **3.7** (90%)*. The next fraction to elute was the boronic acid **3.48** (25%)* both confirmed by comparisons of spectral data to the pure compounds. The third fraction to elute (10%) demonstrated some peaks in the 1H n.m.r spectrum which could be ascribed to the product **4.7** and these are *inter alia* a triplet at 1.33ppm (*J* 7.0 Hz) and quatert at 3.58ppm (*J* 7.0 Hz) confirming the presence of N-CH_2CH_3 group; two signals at 3.87 and 3.94ppm with the former considerably larger than the latter are assigned to the three methoxy groups; a signal at 6.51ppm and what appears to be two doublets, one at 6.98ppm (*J* 7.0 Hz) and 7.10ppm (*J* 7.0 Hz). Two further sets of aromatic signals centered at 7.26 and 7.72ppm represented the last part of the spectrum. This later fraction could not be further purified.

* Given as a % of the unreacted recovered material relative to that put in.

CONCLUSIONS

It has been demonstrated that bromoquinone **3.7** is indeed able to undergo a cross-coupling condensation with an aryl boronic acid.

It has also been demonstrated that it is possible for an appropriate C-7-boronic acid of a 1,4,6-trioxygenated naphthalene system to be prepared. This was successfully done by not using the corresponding brominated derivative and performing a halogen metal exchange reaction but by using a carbamyloxy substituent on the C-6 oxygen and this gave the C-7 boronic acid with none of the C-5 isomer.

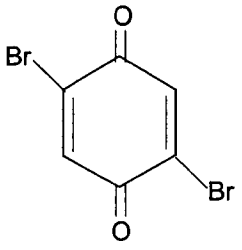
What still needs to be done is the improved coupling between bromoquinone **3.7** and boronic acid **3.48** by fine-tuning the reaction conditions since it is suspected that steric hindrance may be playing an inhibitory role.

CHAPTER 5

EXPERIMENTAL WORK

^{1}H and ^{13}C n.m.r spectra were recorded using a Varian 200MHz spectrometer at $20^{0}C$ in deuterochloroform and ***J*** values are given in Hz. Infrared spectra were measured as Nujol mulls on a Perkin Elmer FT-IR 1000PC spectrometer. Melting points were recorded using Fisher-Johns Melting Point Apparatus. Mass spectra were recorded on a Finnigan-Matt GCQ spectrometer. Column chromatography was carried out using Merck Kieselgel 60 (70-230 mesh) as dry columns. The residue obtained upon workup refers to material obtained from the dried (magnesium sulphate) organic extract after filtration and solvent removal. Hexane refers to that fraction of b.p. $70\text{-}75^{0}C$. In ^{13}C-spectra, assignments with the same superscript may be interchanged.

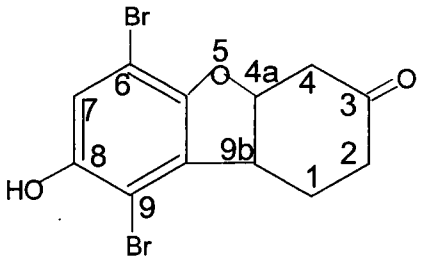
Synthesis of 2,5-dibromobenzoquinone **3.4**



3.4

To a solution of 1,4-dimethoxybenzene **3.3** (10.0g; 72.46mmol) in AcOH (20ml), was added bromine (7.44ml) in acetic acid (7ml) drop-wise at 24^{0}C. The reaction mixture was stirred for an additional 2h. The solution was then cooled to 8^{0}C and filtered. The filter cake was then dissolved in acetonitrile (140ml) in an Erlenmeyer flask in an oil bath at 100^{0}C. A solution of cerium ammonium nitrate (72g; 131.39mmol) in water (300ml) was added to the boiling solution of acetonitrile. The reaction mixture was left to cool to 24^{0}C while stirring for 30 minutes. The precipitate was filtered and washed with water (50 ml),[65] to afford quinone **3.4** (20.1g; 97%); m. p. 187-189^{0}C (from EtOAc-hexane), (lit.[65]188^{0}C). δ_H 7.48 (2H, s, H-3 and H-6). δ_C 137.2 (C-3/6), 137.9 (C-2/5), 177.0 (2x C=O).

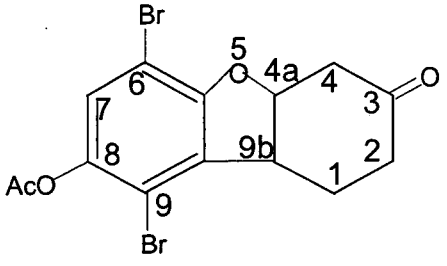
Trans 6,9-Dibromo -1,2,3,4,4a,9b-hexahydro-8-hydroxy-3-oxodibenzofuran **3.14**



3.14

Dibromobenzoquinone **3.4** (1750mg; 6.6mmol) in THF (50 ml) at 25^{0}C was treated with diene **3.13** (1530mg of a 65% isomeric mixture, 9.0mmol) over 10 minutes. During this time the solution turned dark and after 2 hours lightened up again. Removal of the solvent afforded a thick oil, which was passed through a column and eluted with ethyl acetate-hexane (3:7) to give the furan **3.14** (1700mg; 71%) as light brown crystals, m.p.197-198^{0}C (from ethanol); ν_{max} 3290 and 1705 cm^{-1}. δ_H 2.20 (4H, m, H-9 and H-10), 2.78 (1H, dd, *J* 17.2 and 3.6, H-4axial), 3.03 (1H, dd, *J* 17.2 and 3.6, H-4equatorial), 3.80 (1H, m, H-9b), 5.20 (1H, s, D_2O exchangeable, 8-OH), 5.32 (1H, dt, J 8.8 and 3.6, H-4a) and 7.05 (1H, s, H-7). δ_C 23.8 (C-1), 36.0 (C-2)[a], 41.3 (C-3)[a], 42.7 (C-9b), 81.4 (C-4a), 102.2 (C-6)[b], 106.3 (C-9)[b], 118.9 (C-7), 130.3 (C-9a)[c], 147.5 (C-5a)[c], 151.2 (C-8) and 207.9 (C-3). (Found: C, 39.6; H, 2.9%, M^+ 362 (100), 283 (80), 226 (68), 202(80), 174 (50). Cal for $C_{12}H_{10}Br_2O_3$: C, 39.8; H, 2.8%; M^+ 362).

***Trans 8-acetoxy-6,9-Dibromo-1,2,3,4,4a,9b-hexahydro-3-oxodibenzofuran* 3.15**

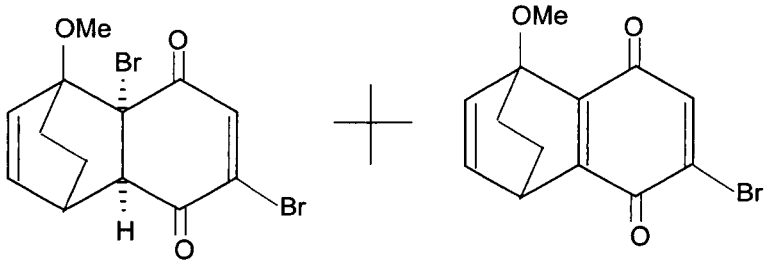


3.15

Phenol **3.14** (100mg; 0.28mmol) was stirred in acetic anhydride (10 ml) containing pyridine (2 ml) for 12h and thrown into water (50 ml) and extracted with ethyl acetate. The organic layer was washed with diluted hydrochloric acid (20 ml; 0.1 M), water (50ml) and sodium hydrogen carbonate (20ml; 10% solution) to afford a residue that was purified by chromatography using EtOAc:Hexane (3:7) as eluent to afford the acetate **3.15** (100 mg; 88%) as colorless needles; m.p. 152-154^{0}C (from isopropanol). ν_{max} 1728 and 1708 cm^{-1}; δ_H 2.23 (4H, m, H-1 and H-2), 2.37 (3H, s, 8-OCOCH$_3$), 2.60 (2H, m, H-4), 4.50 (1H, m, H-9b), 6.10 (1H, dd, *J* 10.2 and 3.0, H-4a) and 7.39 (1H, s, H-7). δ_C 20.8 (CH_3CO), 28.4 (C-4)^a, 38.1 (C-1 and C-2)^a, 42.4 (C-9b), 77.1 (C-4a), 117.5 (C-6)^b, 126.9 (C-7), 128.6 (C-9)^b, 137.7 (C-9a)^c, 146.8 C-5a)^c, 152.0 (C-8), 168.1 (CO_2Me) and 198.1 (C-3; C=O). (Found: C, 41.9; H, 3.2%. M^+ 402/404/406 (1:2:1). Calc. for $C_{14}H_{12}Br_2O_4$: C, 41.6, 3.0%; M^+ 402, 404, 406 (1:2:1)).

2,4a-Dibromo-5,8-ethano-5-methoxy-4a,5,8,8a-tetrahydro-1,4-naphthoquinone **3.5 and**

2-bromo-5,8-ethano-5-methoxy-5,8-dihydro-1,4-naphthoquinone **3.6**

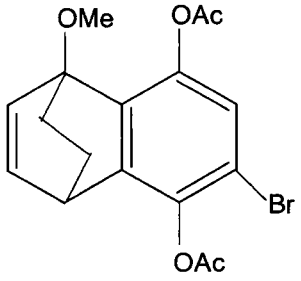


3.5 **3.6**

Dibromobenzoquinone **3.4** (500mg; 1.9mmol) in THF (20 ml) at 0^0C was treated drop-wise with diene **3.13** (350mg; 2.06mmol) in THF (5ml) over 5min. After 1h at 0^0C, the mixture was stirred at 20^0C for 12h. Removal of the solvent afforded a residue which was chromatographed using EtOAc:hexane (1:4) as eluent to afford red oil (100mg; 20%) of a mixture of product **3.5** and quinone **3.6** by ^{1}H-n.m.r. spectroscopy.

A portion of the mixture of **3.5** and **3.6** (25mg) was taken up in methanol (15ml) and treated with sodium hydrogen carbonate (5ml of a 10% solution) and stirred at 70^0C for 10 min. The cooled mixture was poured into water (100ml) and extracted with dichloromethane to afford a residue that was chromatographed using EtOAc: hexane (1:4) as eluent to afford pure quinone **3.6** (15mg; 30%) as yellow crystals; m.p. 124-125^{0}C (from ethanol) with gas evolution. δ_H 1.60 (4H, m, CH_2CH_2), 3.57 (3H, s, OCH_3), 4.37 (1H, m, H-8), 6.34 (1H, dd, *J* 7.6 and 6.2, H-7), 6.55 (1H, dd, *J* 7.6 and 1.4 Hz, H-6) and 7.05 (1H, s, H-3). δ_C 25.0 and 31.2 (-CH_2CH_2-), 33.4 (C-8), 56.4 (CH_3O), 84.9 (C-5), 104.9 (C-2), 131.2 (C-3), 135.5 (C-6)[a], 143.4 (C-8a)[b], 149.4 (C-7)[a], 158.9 (C-4a)[b], 177.3 (C-4)[c], 183.3 (C-1)[c]. (Found: C, 52.7; H, 3.9%; M^+ 294/296. Calc. for $C_{13}H_{11}BrO_3$ C, 52.9; H, 3.8%; M^+ 294/296).

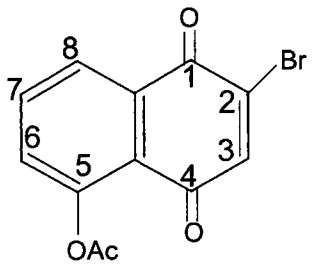
1,4-Diacetoxy-2-bromo-5,8-ethano-5-methoxy-5,8-dihydronaphthalene **3.15**



3.15

A mixture of **3.5** and **3.6** (50mg) was enolized as above and the crude extract was treated with acetic anhydride (10ml) and pyridine (2ml) at 25^{0}C for 8h, thrown into water and extracted with DCM to afford a residue which was chromatographed using EtOAc: hexane (3:7) as eluent to yield the diacetate **3.15** (25mg; 39%) as white crystals; m.p. 152-153^{0}C (from EtOAc-hexane); ν_{max} 1728 cm^{-1}; δ_H 1.62 (4H, m, -CH_2CH_2-), 2.29 and 2.40 (each 3H, each s, CH_3CO_2), 3.58 (3H, s, OCH_3), 3.89 (1H, m, H-8), 6.42 (1H, dd, *J* 8.0 and 6.2, H-7), 6.66 (1H, dd, *J* 8.0 and 1.4, H-6) and 7.02 (1H, s, H-3). δ_C 20.6 and 20.8 (CH_3CO_2-), 25.4 (-CH_2CH_2-), 28.5 (-CH_2CH_2-), 34.8 (C-8), 53.7 (CH_3O), 83.8 (C-5), 113.3 (C-2), 124.4 (C-6)[a], 132.7 (C-3)[a], 135.4 (C-7)[a], 136.0 (C-4a)[b], 138.5 (C-8a)[b], 140.2 (C-1)[c], 142.4 (C-4)[c], 168.4 and 169.8 (C=O). (Found: C, 53.4; H, 4.5% M^+ 380/382. Calc. for: $C_{17}H_{17}BrO_5$ C, 56.3; 4.20%; M^+ 380/382).

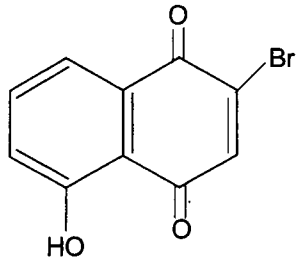
5-Acetoxy-2-bromo-1,4-naphthoquinone **3.17**



3.17

1,5-Diacetoxynaphthalene **3.16** (2000mg; 8.2mmol) in hot acetic acid (40ml) was added drop-wise over 5 min to N-bromosuccinimide (5840mg; 19.80mmol) in acetic acid (50ml) and water (80ml) at 55-65^{0}C and stirring was continued for an additional 45min. The reaction mixture was then poured onto water to afford a precipitate (1620.7mg; 67%) as pale yellow crystals, m.p.149-150^{0}C (from EtOH) (lit.[62] 158^{0}C); ν_{max} 1770 and 1662cm^{-1}; δ_H 2.44 (3H, s, CH_3CO_2), 7.38 (1H, s, H-3), 7.42 (1H, dd, *J* 8.0 and 1.0, H-6), 7.77 (1H, t, J 8.0, H-7) and 8.14 (1H, dd, *J* 8.0 and 1.4, H-8). δ_C 21.1 (CH_3CO_2), 121.1 (C-2), 126.4 (C-3), 130.4 (C-6)[a], 132.7 (C-4a)[b], 135.0 (C-7)[a], 138.6 (C-8a)[b], 141.5 (C-8), 150.0 (C-5), 169.3 (ester C=O), 177.5 and 181.0 (C=O).

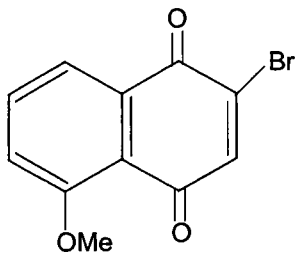
2-Bromo-5-hydroxy-1,4-naphthoquinone **3.18**



3.18

5-Acetoxy-2-bromo-1,4-naphthoquinone **3.17** (1.42g; 6.6mmol) in ethanol (50ml) was treated with an aqueous solution of concentrated sulfuric acid (3ml) in water (15ml) and heated under reflux for with constant stirring for 1h. The solution was cooled in ice/water for 30min to afford quinone **3.17** (1.14g; 68%) as orange brown crystals, m.p.129-130^{0}C (From EtOH), (lit.[62] 136^{0}C); ν_{max} 3350 and 1670cm^{-1}; δ_H 7.30 (1H, dd, *J* 8.0 and 1.4, H-6), 7.47 (1H, s, H-3), 7.63 (1H, t, *J* 8.0, H-7), 7.75 (1H, dd, *J* 8.0 and 1.4, H-8) and 11.75 (1H, s, D_2O exchangeable, 5-OH). δ_C 114.6 (C-2), 120.9 (C-3), 125.1 (C-6), 130.7 (C-4a)[a], 136.4 (C-7), 140.2 (C-8), 140.9 (C-8a)[a], 161.7 (C-5), 177.2 and 181.4 (C=O).

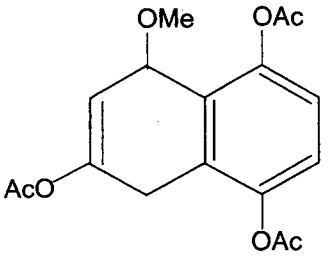
2-Bromo-5-methoxy-1,4-naphthoquinone **3.7**



3.7

To a mixture of 2-bromo-5-hydroxy-1,4-naphthoquinone **3.18** (960mg; 3.79mmol) and silver(II)oxide (0.96g; 4.14mmol) in dry benzene (50ml) was added dropwise methyl iodide (1.1g; 7.75mmol). The suspension was stirred at 24^{0}C for 20h and then filtered. The filtrate was concentrated under reduced pressure to yield the desired product **3.7** (769mg; 76%) as yellow crystals, m.p.128-129^{0}C (from EtOH), (lit.[62] 134^{0}C); ν_{max} 1670 cm^{-1}; δ_H 4.01 (3H, s, OCH_3), 7.34 (1H, dd, *J* 7.6 and 1.2, H-6), 7.40 (1H, s, H-3), 7.69 (1H, t, *J* 7.6, H-7), 7.82 (1H, dd, *J* 7.6 and 1.2, H-8). δ_C 56.7 (-OCH_3), 118.6 (C-2 and C-6), 120.7 (C-3), 133.2 (C-4a)[a], 135.1 (C-7), 137.0 (C-8a)[a], 142.4 (C-8), 160.1 (C-5), 178.3 and 181.5 (C=O).

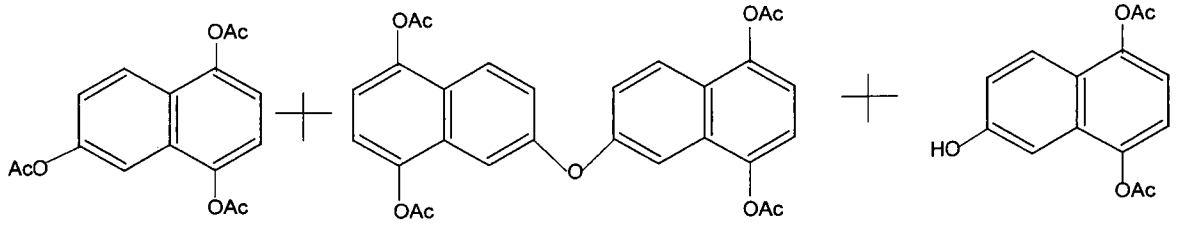
1,4,7-Triacetoxy-5-methoxy-5,8-dihydronaphthalene **3.29**



3.29

Benzoquinone **3.21** (3.0g; 27.8mmol) in benzene (60ml) was treated with 1-methoxy-3-trimethyl silyloxybutadiene **3.20** (5.0g; 29.2mmol) in benzene (10ml) at 24^0C and the resulting solution was gently heated at 60-70^0C for 1h and the residue obtained upon removal of the solvent was treated with acetic anhydride (80ml) and pyridine (40ml) at 25^0C for 12h and then poured into water to afford the triacetate **3.29** (8.11g; 87%) as white crystals, m.p. 146-147^0C (from EtOH); ν_{max} 1728cm^{-1}; δ_H 2.20, 2.32 and 2.33 (each 3H, each s, CH_3CO_2-), 2.66 (1H, dd, *J* 17.8 and 2.0, H-8a), 2.91 (1H, ddd, *J* 17.8, 5.0 and 2.4, H-8e), 3.23 (3H, s, 5-CH_3O), 4.57 (1H, dd, *J* 5.0 and 2.0, H-5), 6.39 (1H, d, *J* 2.4, H-6), 6.99 (1H, d, *J* 8.8, H-2) and 7.10 (1H, d, *J* 8.8, H-3). δ_C 20.9, 21.0 and 21.2 (3x CH_3CO), 32.4 (C-8), 55.5 (CH_3O), 69.9 (C-5), 106.8 (C-6), 121.3 (C-2)[a], 123.5 (C-3)[a], 123.9 (C-4a)[b], 127.2 (C-8a)[b], 144.1 (C-1)[c], 146.4 (C-7)[c], 150.2 (C-4)[c], 168.5, 168.9 and 169.0 (C=O). (Found: C, 61.3; H, 5.6%; M^+ 334. Calc. for: $C_{17}H_{18}O_7$ C, 61.1; H, 5.4%; M 334).

***1,4,6-Triacetoxynaphthalene* 3.23, *1,1'4,4'-tetraacetoxy-6,6'-oxobisnaphthalene* 3.30 and *1,4-diacetoxy-6-hydroxynaphthalene* 3.31**



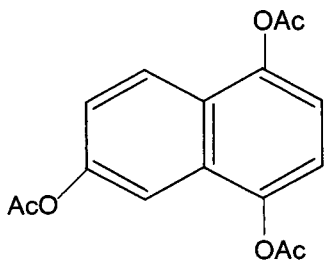
3.23 **3.30** **3.31**

Adduct **3.29** (480mg; 1.44mmol) in acetic anhydride (25ml) and pyridine (5ml) was heated and stirred under reflux for 2h, thrown into water (100ml) and extrated with dichloromethane, backwashed with water, 0.5M hydrochloric acid and finally 10% sodium hydrogen carbonate. The residue obtained upon workup was very carefully chromatographed using EtOAc:hexane (3:7) as eluent to afford in order of elution the 1,4,6-triacetoxynaphthalene **3.23** (140mg; 32%) as cream crystals, m.p. 106-107^{0}C, (from ethanol) (lit.[51] m.p. 94-95^{0}C); ν_{max} 1726cm^{-1}, δ_H 2.34 and 2.43 (x2) (9H, s, CH_3CO_2), 7.24 (1H, d, *J* 8.4, H-2), 7.25 (1H, d, *J* 8.4, H-3), 7.32 (1H, dd, *J* 9.2 and 2.2, H-7), 7.61 (1H, dd, *J* 2.2 and 0.8, H-5) and 7.91 (1H, dd, *J* 9.2 and 0.2, H-8). δ_C 21.1 (x2), 21.3 (CH_3CO_2), 112.9 (C-7)[a], 117.6 (C-5)[a], 118.7 (C-8)[a], 122.5 (C-2)[a], 123.5 (C-3)[a], 125.7 (C-4a)[b], 128.4 (C-8a)[b], 144.1 (C-1)[c], 144.4 (C-4)[c], 149.6 (C-1)[c], 169.1, 169.2 and 169.3 (C=O). (Found: C, 63.4; H, 4.5%; M^+ 302. Calc. for $C_{16}H_{14}O_6$: C, 63.4; H, 4.5%; M^+ 302). Further elution afforded a binaphthalene ether (80mg; 11%) to which the dimeric structure **3.30** has been assigned based on the following spectral evidence. A HRMS gave the M^+ at 502.1260 for a molecular formula of $C_{28}H_{22}O_9$ (Calculated: 502.1264), m.p. 123-124^{0}C; ν_{max} 1740-1750 cm^{-1}, δ_H 2.36 and 2.44 (each 6H, s, CH_3CO_2), 6.40 (1H, d, *J* 8.5, H-2')[a], 6.44 (1H, d, *J* 8.5, H-3')[a], 6.85 (d, *J* 8.2, H-2)[a], 6.94 (1H, d, *J* 8.2, H-3)[a], 7.16 (1H, dd, *J* 9.0 and 2.2, H-7)[b],

7.22 (1H, dd, *J* 8.8 and 2.4, H-7')[b], 7.42 (1H, d, *J* 2.2, H-5)[c], 7.74 (1H, d, *J* 8.8, H-8')[d], 7.75 (1H, d, *J* 2.4 H-5')[c] and 8.02 (1H, d, *J* 9.0, H-8)[d]. δ_C 21.0, 21.1, 21.2 and 21.3 (4x CH_3CO_2), 107.8, 108.6, 112.1, 114.1, 117.9, 119.1, 120.7, 122.0, 122.7 and 123.3 (C-H aryl), 124.6, 125.5, 125.9 and 128.1 (C-4a, C-8a, C-4a' and C-8a'), 139.4 and 139.7 (C-6 and C-6'), 148.2 149.5, 149.8 and 150.1 (C-1, C-4, C-1' and C-4'), 169.9, 170.2, 170.6 and 170.7 (C=O).

Further elution afforded a thick oil which solidified on standing to give 1,4-diacetoxy-6-hydroxynaphthalene **3.31** (80mg; 21%) as white needles, m.p. 141-142^{0}C (from EtOAc:hexane); ν_{max} 3350 and 1729cm^{-1}; δ_H 2.41 and 2.45 (each 3H, s, CH_3CO_2), 5.60 (1H, br s, D_2O exchangeable, 6-OH,), 7.02 (1H, dd, *J* 8.2 and 2.6, H-7), 7.06 (1H, dd, *J* 2.6 and 0.6, H-5), 7.06 (1H, d, *J* 8.2 , H-2) 7.19 (1H, d, *J* 8.2, H-3), and 7.71 (1H, dd, *J* 8.4 and 0.6, H-8). δ_C 21.0 and 21.1 (CH_3CO_2), 104.0 (C-7), 115.2 (C-5)[a], 118.5 (C-8)[a], 119.1 (C-2)[a], 123.1 (C-4a)[b], 123.9 (C-3)[a], 129.2 (C-8a)[b], 143.3 (C-1)[c], 144.7 (C-4)[c], 154.7 (C-6), 169.6 and 169.7 (C=O) (Found: C, 64.6; H, 4. 5%; M^+ 260. Calc. for: $C_{14}H_{12}O_5$ C, 64.4; H, 4.65%; M 260).

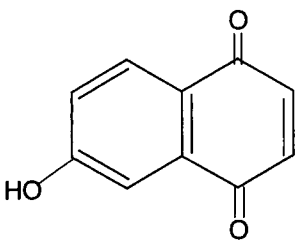
1,4,6-Triacetoxynaphthalene **3.23**



3.23

Adduct **3.29** (500mg; 1.5mmol) in acetic acid was heated under reflux for 2h, poured into water (200ml), cooled to 0^0C for 12h and the precipitate formed was filtered to afford 1,4,6-triacetoxynaphthalene **3.23** (453mg; 100%), spectroscopically identical to the material synthesized earlier.

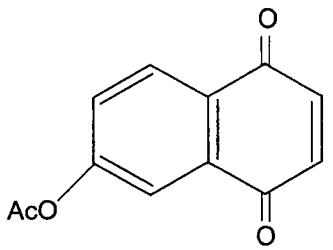
6-Hydroxy-1,4-naphthoquinone **3.25**



3.25

Treatment of benzoquinone **3.21** (3.0g; 27.8mmol) in benzene (60ml) with 1-methoxy-3-trimethyl silyloxybutadiene **3.20** (5.0g; 29.2mmol) in benzene (10ml) drop-wise over 5 minutes followed by heating under reflux for 3h and evaporation of solvent afforded a residue that was chromatographed using EtOAc: hexane (3:7) to afford quinone **3.25** after repeated chromatography of the dark-green residue (1.5g; 31%) as yellow crystals, m.p. 194-196^{0}C (from EtOAc: hexane); ν_{max} 3450 and 1666cm^{-1}; δ_H [$(CD_3)_2CO$] 6.96 (2H, s, H-2 and H-3), 7.25 (1H, dd, *J* 8.8 and 2.6, H-7), 7.42 (1H, d, *J* 2.6, H-5) and 7.94 (1H, d, *J* 8.8, H-8). δ_C 112.8 (C-7), 121.7 (C-5)^a, 125.9 (C-4a)^b, 129.9 (C-8)^a, 135.3 (C-8a)^b, 139.2 (C-2)^c, 140.0 (C-3)^c, 163.6 (C-6), 184.6 and 185.8 (C=O). (Found: C, 69.20; H, 3.3%; M^+ 174. Calc. for: $C_{10}H_6O_3$ C, 69.0; H, 3.5%; M^+ 174).

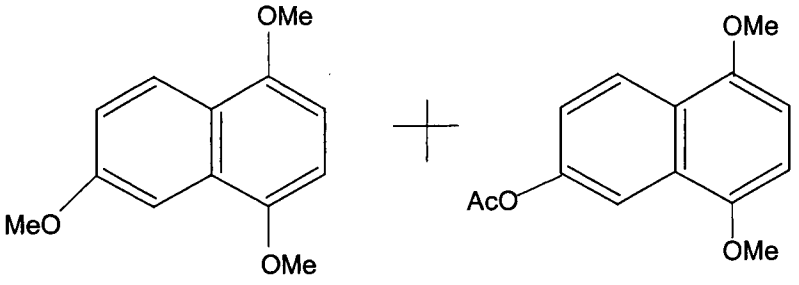
6-Acetoxy-1,4-naphthoquinone **3.26**



3.26

To the triacetoxynaphthalene **3.23** (520mg; 1.72mmol) in CH_3CN (30ml) and water (6ml) was added CAN (4.71g; 5mmol) in water (6ml) with rapid stirring at 24^0C and stirring was continued for 3h after which the reaction mixture was poured into water (100ml) to give a precipitate (372mg: 100%) as yellow needles, m.p. 98-99^0C (from EtOAc:hexane); ν_{max} 1727 and 1668cm^{-1}; δ_H 2.36 (3H, s, CH_3CO), 6.99 (2H, s, H-2 and H-3), 7.48 (1H, dd, *J* 8.4 and 2.5, H-7), 7.80 (1H, d, J 2.5, H-5) and 8.13 (1H, d, *J* 8.4, H-8). δ_C 21.1 (CH_3CO_2), 119.6 (C-7), 127.3 (C-5)[a], 128.6 (C-8)[a], 129.6 (C-8b)[b], 133.7 (C-4a)[b], 138.7 (C-2)[c], 138.9 (C-3)[c], 155.2 (C-6), 168.5 (C=O ester), 184.1 and 184.2 (C=O of quinone). (Found: C, 66.6; H, 3.5%; M^+ 216. Calc. for $C_{12}H_8O_4$: C, 66.7; H, 3.7%; M 216).

1,4,6-Trimethoxynaphthalene **3.33** and *6-Acetoxy-1,4-dimethoxynaphthalene* **3.27**

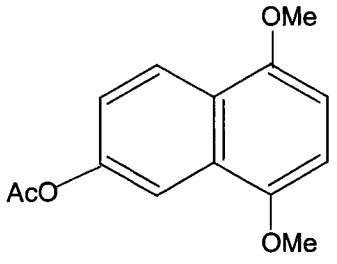


3.33 **3.27**

6-acetoxy-1,4-naphthoquinone **3.26** (300mg; 1.39mmol) in ether (200ml) was vigorously shaken with sodium dithionite solution (10g/100ml) which resulted in the ethereal solution losing its yellow color. The ether solution was dried ($MgSO_4$) and evaporated to yield a residue, which was immediately dissolved in acetone (20ml) and treated with Me_2SO_4 (700mg; 5.56mmol) in the presence of K_2CO_3 (770mg; 5.56mmol) and then vigorously stirred and heated under reflux under a N_2 atmosphere for 12h. The filtrate was concentrated under reduced pressure and purified by column chromatography using EtOAc:hexane (1:4) as eluent to afford the first fraction (213mg; 71%) as a yellow-brown oil and was assigned the structure **3.33** based on the following spectral evidence. δ_H 3.99 (9H, s, 3x OCH_3), 6.57 (1H, d, *J* 8.4, H-2), 6.70 (1H, d, *J* 8.4, H-3), 7.17 (1H, dd, *J* 8.4 and 2.6, H-7), 7.51 (1H, d, *J* 2.6, H-5), 8.12 (1H, d, *J* 8.4, H-8). δ_C 55.4, 55.7 and 55.8 (OCH_3), 100.5 (C-2)[a], 101.2 (C-3)[a], 104.2 (C-7)[a], 118.1 (C-5)[b], 121.6 (C-4a)[c], 123.7 (C-8)[b], 127.6 (C-8a)[c], 148.8 (C-1)[d], 149.9 (C-4)[d] and 158.1 (C-6). (Found: C, 71.3; H, 6.6%; M^+ 218. Calc. for $C_{13}H_{14}O_3$: C, 71.5; H, 6.5%; M 218).

Further elution afforded 6-acetoxy-1,4-dimethoxynaphthalene **3.27** (66mg; 22%) as a light yellow oil spectroscopically identical to the material synthesized later.

6-Acetoxy-1,4-dimethoxynaphthalene **3.27**

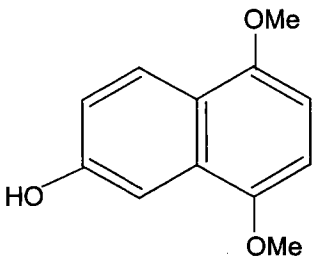


3.27

6-acetoxyquinone **3.26** (500mg; 2.3mmol) in ether 200ml was similarly reduced as just described to afford a residue, which was immediately treated with 5molar equivalents of methyl iodide (1.63g; 11.5mmol) in the presence of silver (II) oxide (1.45g; 11.69mmol) in dry acetone (40ml). This was then heated under reflux under a nitrogen atmosphere for 12h and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography using EtOAc:Hexane (1:4) as eluent, to afford the acetoxynaphthalene **3.27** (356mg; 63%) as a light yellow oil; ν_{max} 1726cm^{-1}. δ_H 2.35 (3H, s, $OCOCH_3$), 3.93 (6H, s, 2x OCH_3), 6.66 (1H, d, *J* 9.2, H-2), 6.68 (1H, d, *J* 9.2, H-3), 7.30 (1H, dd, *J* 9.2 and 2.6, H-7), 7.95 (1H, d, *J* 2.6, H-5) and 8.25 (1H, d, *J* 9.2, H-8). δ_C 21.1 (CH_3CO_2), 55.7 (OCH_3), 55.8 (OCH_3), 103.2 (C-2)[a], 104.2 (C-3)[a], 113.3 (C-7), 120.8 (C-5)[b], 123.7 (C-8)[b], 124.4 (C-4a)[c], 127.1 (C-8a)[c], 148.8 (C-4)[d], 149.2 (C-1)[d], 149.6 (C-6), 169.6 (C=O).

(Found: C, 68.6; H, 5.5%; M^+ 246. Calc. for $C_{14}H_{14}O_4$: C, 68.3, H, 5.7%; M 246).

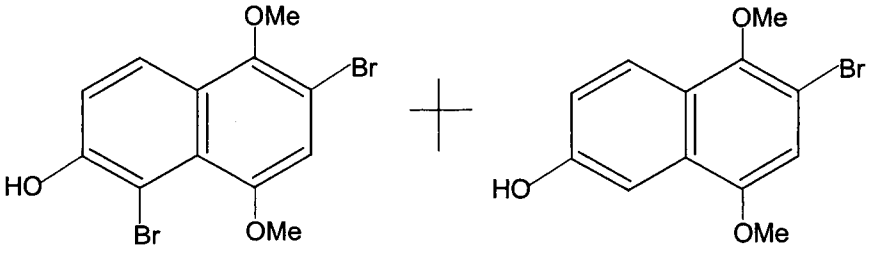
6-Hydroxy-1,4-dimethoxynaphthalene **3.28**



3.28

6-Acetoxy-1,4-dimethoxynaphthalene **3.27** (130mg; 0.53mmol) in MeOH (10ml) was treated with 1% KOH/MeOH (1.1ml) with constant stirring for 1h. The reaction mixture was then poured into water (100ml) and acidified with 0.1M HCl and the solution was extracted with dichloromethane to give naphthol **3.28** (95mg; 88%) as a greenish oil; ν_{max} 3368cm^{-1}. δ_H 3.93 (6H, s, 2x CH_3O), 5.34 (1H, s, D_2O exchangeable, 6-OH), 6.55 (1H, d, *J* 8.0, H-2), 6.70 (1H, d, *J* 8.0, H-3), 7.20 (1H, dd, *J* 8.0 and 2.4, H-7), 7.51 (1H, d, *J* 2.4, H-5) and 8.25 (1H, d, *J* 8.0, H-8). δ_C 55.8 (OCH_3), 55.9 (OCH_3), 101.1 (C-5)[a], 104.4 (C-2)[a], 104.5 (C-3)[a], 117.2 (C-7)[a], 121.7 (C-8a)[b], 124.2 (C-8), 127.8 (C-4a)[b], 148.6 (C-1)[c], 150.0 (C-4)[c], 154.0 (C-6). (Found: C, 70.7; H, 5.7%; M^+ 204. Calc. for $C_{12}H_{12}O_3$: C, 70.6; H, 5.9%; M 204).

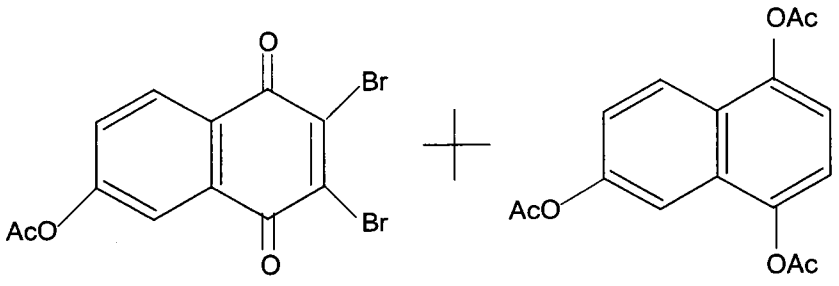
2,5-Dibromo-6-hydroxy-1,4-dimethoxynaphthalene **3.36** **and** ***2-bromo-6-hydroxy-1,4-dimethoxynaphthalene*** **3.37**



3.36 **3.37**

6-Hydroxy-1,4-dimethoxynaphthalene **3.28** (110mg; 0.54mmol) in AcOH (10ml) was treated with Br_2 (100mg; 0.54mmol) in AcOH (2ml) with constant stirring for 15minutes after which the reaction mixture was poured into water (100ml) and extrated with dichloromethane, back-washed with aqueous sodium hydrogen carbonate to afford a residue which was purified by column chromatography to give dibromonaphthol **3.36** (25mg; 13%) as yellow crystals, m.p.79-80^{0}C (dec.); ν_{max} 3350cm^{-1}; δ_H 3.90 (6H, s, CH_3O), 6.51 (1H, s, D_2O exchangeable, 6-OH), 6.96 (1H, s, H-3), 7.30 (1H, d, J 9.2, H-7), 8.00 (1H, d, J 9.2, H-8). δ_C 56.3 and 61.6 (CH_3O), 102.2 (C-2), 109.8 (C-5)[a], 112.3 (C-3)[a], 117.9 (C-7)[b], 123.9 (C-8)[b], 124.2 (C-8a)[c], 126.5 (C-4a)[c], 147.3 (C-6), 151.4 (C-1)[d], 151.8 (C-4)[d]. (Found: C, 40.0; H, 2.8%; M^+ 360/362/364) (1:2:1). Calc. for $C_{12}H_{10}Br_2O_3$: C, 39.8; H, 2.8%; M 360/362/364). Further elution afforded the 2-bromonaphthalene **3.37** (112mg: 72%) as light yellow needles, m.p. 108-109^{0}C (from EtOAc:hexane); ν_{max} 3350cm^{-1}; δ_H 3.93 (6H, s, CH_3O), 5.25 (1H, s, D_2O exchangeable, 6-OH), 6.84 (1H, s, H-3), 7.15 (1H, dd, *J* 9.2 and 2.6, H-7), 7.48 (1H, d, *J* 2.4, H-5), 7.99 (1H, d, *J* 8.4, H-8). δ_C 56.0 (OCH_3), 61.6 (OCH_3), 105.3 (C-3), 108.8 (C-7), 109.1 (C-4a)[a], 118.8 (C-5), 124.3 (C-8), 124.4 (C-8a)[a], 127.3 (C-2), 147.1 (C-6), 151.3 (C-1)[b], 153.9 (C-4)[b]. (Found: C, 50.7; H, 3.6%; M^+ 282/284. Calc. for $C_{12}H_{11}BrO_3$: C, 50.9; H, 3.9%; M 282/284).

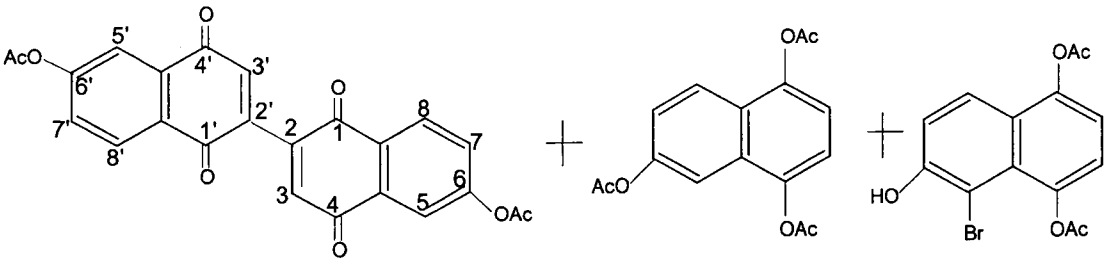
6-Acetoxy-2,3-dibromo-1,4-naphthoquinone **3.41** and *1,4,6-triacetoxynaphthalene* **3.23**



3.41 **3.23**

Bromine (268mg; 1.68mmol) in acetic acid (2ml) was dripped into a solution of adduct **3.29** (560mg; 1.68mmol) in acetic acid (8ml) at 24^{0}C over 3 minutes in a nitrogen atmosphere and thereafter stirring was continued for 3h. The reaction mixture was poured into water (200ml) and the organic material extracted into dichloromethane, which was back-washed with saturated sodium hydrogen bicarbonate to yield a residue which was then chromatographed using EtOAc: hexane (3:7) as eluent to yield 2,3-dibromo-6-acetoxy-1,4-naphthoquinone **3.41** (70mg; 11%) as bright yellow crystals, m.p. 181-182^{0}C (from EtOAc-hexane); ν_{max} 1754 and 1665cm^{-1}; δ_H 2.37 (3H, s, $OCOCH_3$), 7.52 (1H, dd, *J* 8.4 and 2.2, H-7), 7.90 (1H, d, *J* 2.2, H-5) and 8.23 (1H, d, *J* 8.8, H-8). δ_C 21.1 ($OCOCH_3$), 121.3 (C-7)[a], 127.9 (C-5)[a], 128.3 (C-4a)[b], 130.3 (C-8)[a], 132.5 (C-8a)[b], 142.4 (C-2)[c], 143.0 (C-3)[c], 155.6 (C-6), 168.3 (C=O of ester), 175.0 and 175.2 (C=O). (Found: C, 38.3; H, 1.5%; M^+ 372/374/376. Calc. for $C_{12}H_6Br_2O_4$: C, 38.5; H, 1.6%, M 372/374/376). Further elution afforded 1,4,6-triacetoxynaphthalene **3.23** (330mg; 65%), which had identical spectroscopic properties to the material synthesized previously.

***6,6'-Diacetoxy-2,2'-binaphthoquinone* 3.42, *1,4,6-triacetoxynaphthalene* 3.23 and *1,4-diacetoxy-5-bromo-6-hydroxynaphthalene* 3.43**

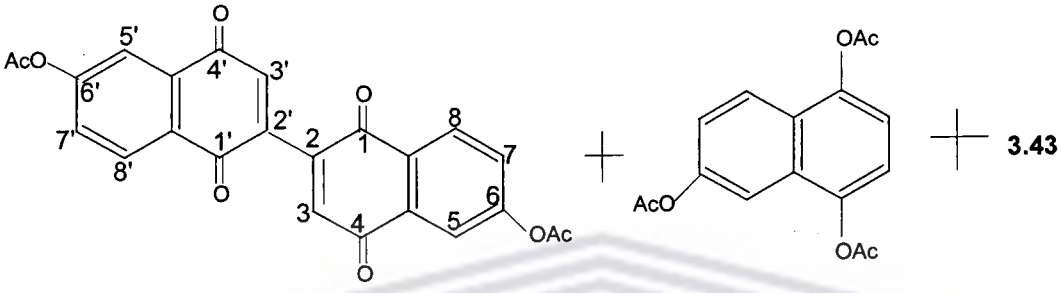


3.42 **3.23** **3.43**

A solution of bromine (321mg; 2.01mmol) in acetic anhydride (2ml) was dripped into a solution of the adduct **3.29** (670mg; 2.01mmol) in acetic anhydride under a nitrogen atmosphere at 10^0C over 5 minutes and stirring was continued for 2h. The reaction mixture was then poured into ice/water and extracted into dichloromethane. The residue obtained upon workup was chromatographed using EtOAc:hexane (3:7) to afford the dimer **3.42** (37mg; 4%) as yellow crystals, m.p. 112-114^{0}C (from EtOAc:Hexane); ν_{max} 1728 and 1660 cm^{-1}; δ_H 2.36 (6H, s, $OCOCH_3$), 7.5 (4H, m, H-3, H-3',H-7and H-7'), 7.79 and 7.87 (each 1H, each d, *J* 2.2, H-5and H-5'), 8.11 and 8.20 (each 1H, each d, *J* 8.4 H-8 and H-8'). δ_C 21.1 (2x $OCOCH_3$), 120.0 (C-3)^a, 121.0 (C-3')^a, 127.4 (C-7)^b, 127.4 (C-7')^b, 128.5 (C-2)^c, 129.0 (C-5)^d, 129.3 (C-2')^c, 130.0 (C-5')^d, 132.6 (C-4a)^e, 133.5 (C-4a')^e, 139.9 (C-8a)^e, 140.4 (C-8a')^e, 140.5 (C-8 and C-8')^e, 155.3 (C-6)^f, 155.6 (C-6')^f, 168.3 and 168.4 (C=O of the two ester groups), 177.0, 177.3, 181.4 and 181.6 (C=O of quinones). (Found: C, 66.9; H, 3.1%; HRMS 430.0687. Calc. for $C_{24}H_{14}O_8$: C, 67.0; H, 3.3% HRMS 430.0689). Further elution afforded 1,4,6-triacetoxynaphthalene **3.23** (413mg; 68%), which had identical spectroscopic properties to the material synthesized earlier. Finally a third compound to elute was the bromophenol **3.43** (68mg; 10%) as grayish crystals, m.p.

127-128^{0}C (from EtOAc-Hexane); ν_{max} 3350 and 1740 cm^{-1}; δ_H 2.46 (6-H, s, $OCOCH_3$), 6.48 (1H, s, D_2O exchangeable, 6-OH), 7.15 (1H, d, *J* 8.2, H-2), 7.21 (1H, d, *J* 8.2, H-3), 7.28 (1H, d, *J* 9.2, H-7) and 7.83 (1H, d, *J* 9.2, H-8). δ_C 21.1 ($OCOCH_3$), 22.0 ($OCOCH_3$), 100.4 (C-7), 116.5 (C-3)[a], 118.0 (C-5)[a], 122.1 (C-2)[a], 123.6 (C-8)[a], 124.8 (C-4a)[b], 126.1 (C-8a)[b] , 142.3 (C-1)[c], 144.8 (C-4)[c] , 152.4 (C-6), 169.1 (C=O) and 170.2 (C=O). (Found: C, 49.7; H, 3.3%; M^+ 338/340 (1:1). Calc. for $C_{14}H_{11}BrO_5$: C, 49.6, H, 3.3%; M^+338/340).

***6,6'-Diacetoxy-2,2'-binaphthoquinone* 3.42, *1,4,6-triacetoxynaphthalene* 3.23 and *1,4-diacetoxy-5-bromo-6-hydroxynaphthalene* 3.43**

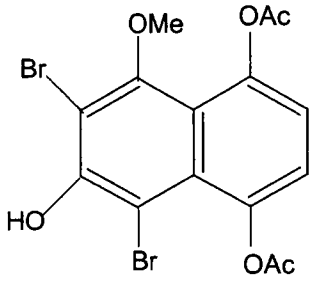


3.42 **3.23**

Bromine (238mg; 1.49mmol) in DCM (3ml) was dripped into a solution of the adduct **3.29** (496mg; 1.49mmol) in dichloromethane (10ml) at 4^0C over 2 minutes and stirring was continued for a further 5 minutes. The reaction mixture was worked-up as before to give a residue that was chromatographed using EtOAc:hexane (3:7) as eluent to yield solid material **3.42** (20mg; 3%) as yellow crystals, similar to the material synthesized earlier. Further elution afforded triacetoxynaphthalene **3.23** (200mg; 44%) identical in all spectral aspects to the material synthesized before.

The third fraction to elute was assigned the structure of the bromonaphthalene **3.43** (45mg; 9%) and was spectroscopically identical to the material synthesized earlier.

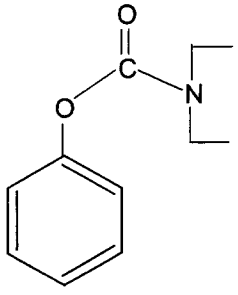
1,4-Diacetoxy-5,7-dibromo-8-methoxy naphthalene **3.39**



3.39

A solution of adduct **3.29** (500mg; 1.50mmol) dissolved in hot AcOH (30ml) was added over 5min to NBS (2200mg; 7.48mmol) in AcOH (30ml) and water (60ml) at 55-60^{0}C. The resulting solution was stirred at 55-60^{0}C for 30-45 min. The reaction mixture was then thrown onto water and the resulting precipitate was filtered to afford the dibromonaphthalene **3.39** (445mg; 71%) as yellow crystals, m.p. 202-203^{0}C (from EtOAc-hexane); ν_{max} 1738cm^{-1}; δ_H 2.44 and 2.50 (each 3H, s, $OCOCH_3$), 3.33 (3H, s, OCH_3), 5.09 (1H, s, D_2O exchangeable, 6-OH), 7.29 (1H, d, *J* 8.8, H-2), 7.35 (1H, d, *J* 8.8,H-3). δ_C 21.1 and 21.7 (CH_3CO), 58.7 (OCH_3), 123.2 (C-5)[a], 124.5 (C-7)[a], 125.1 (C-2), 127.0 (C-3), 142.6 (C-4a)[b], 144.6 (C-8a)[b], 152.1 (C-1)[c], 153.5 (C-4)[c], 158.1 (C-6), 165.3 and 168.4 (C=O). (Found: C, 40.0; H, 2.5%; M^+ 446/448/450. Calc. for $C_{15}H_{12}Br_2O_6$: C, 40.2; H, 2.7%; M 446/448/450).

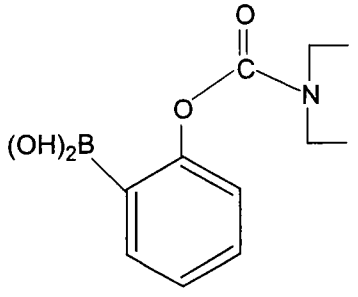
N,N-Diethylphenylcarbamate **3.45**



3.45

Phenol **3.44** (5g; 53.19mmol) in pyridine (10ml) was treated with N,N-diethylcarbamylchloride (7.2g; 53.10mmol) in a pressure-capped glass bottle. This was then heated for about 6h in an oil bath at 110^0C. The reaction mixture was then poured onto ice/water (200ml) and extracted with ether which was washed with 10% HCl followed by aqueous sodium hydrogen carbonate to afford the phenylcarbamate **3.45** [63] (9136.45mg; 89%) as light brown oil; δ_H 1.22 (6H, m, CH_3CH_2-), 3.40 (4H, m, -CH_2CH_3), 7.0 to 7.5 (5H, m, Aryl-H).

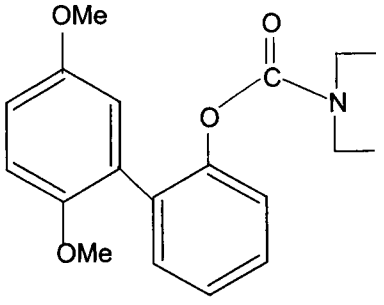
2-N,N-Diethylcarbamyloxyphenyl boronic acid **3.46**



3.46

Phenylcarbamate **3.45** (1g; 5.2mmol) in THF (20ml) was treated with TMEDA (600mg; 5.2mmol) followed by sec-butyllithium (5.5mmol) at -78^0C under a Nitrogen atmosphere for 1h and allowed to warm to room temperature for 2h. The reaction mixture was cooled again to -78^0C for 40min and treated with trimethylborane (540mg; 5.2mmol) and stirred for further 3h and then treated with saturated ammonium chloride (20ml) and extracted with dichloromethane to afford the boronic acid **3.46** [61,64] (1.01g; 82%) as a brown oil. δ_H 1.15 (6H, m, CH_3-), 3.25 (4H, m, -CH_2-), 7.10 to 7.50 (3H, m, H-4, H-5, H-6), 7.85 (1H, dd, *J* 9.2 and 2.6, H-3). (Found: C, 55.4; H, 6.5%; M^+ 237. Calc. for $C_{11}H_{16}BNO_4$: C, 55.7; H, 6.8%; M 237).

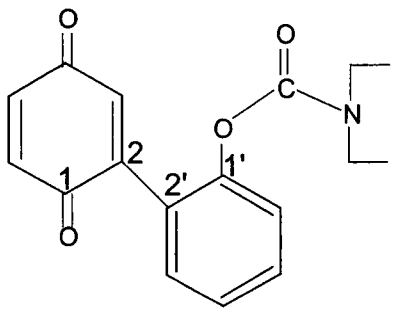
1,4-Dimethoxy-2-(2'-N,N-diethylcarbamyloxyphenyl)-benzene **4.2**



4.2

A solution of 2-bromo-1,4-dimethoxybenzene **4.1** (5g; 23.0mmol) and $Pd[P(Ph)_3]_4$ (100mg; 0.09mmol) in toluene (10ml) was treated with boronic acid **3.46** (720mg; 3.0mmol) in the presence of 2M sodium carbonate (2.1ml) as a base under reflux under N_2 atmosphere for 12h with vigorous stirring. This was then washed with brine and diluted with dichloromethane and concentrated under reduced pressure to afford a residue that was chromatographed using EtOAc:hexane (3:7) as eluent to produce the biaryl **4.2** [56,57,58,59] (563mg: 57%) as a brown oil; ν_{max} 1630cm^{-1}. δ_H 0.87 (3H, t, *J* 7.0, -CH_2CH_3), 1.05 (3H, t, *J* 7.0, -CH_2CH_3), 3.20 (4H, m, 2x –CH_2CH_3), 3.65 and 3.74 (each 3H, s, CH_3O), 6.82 (3H, sharp m, H-3, H-5 and H-6), 7.26 (4H, m, H-3', H-4', H-5' and H-6'). δ_C 13.3 and 13.7 (-CH_2CH_3), 55.8 and 56.2 (OCH_3), 112.0 (C-3)[a], 113.9 (C-5)[a], 117.0 (C-6)[a], 123.1 (C-6')[b], 125.0 (C-3')[b], 128.1 (C-2)[c], 128.3 (C-5')[b], 131.2 (C-4')[b], 131.5 (C-1')[b], 149.2 (C-2'), 151.3 (C-1)[c], 153.4 (C-4)[c] and 154.0 (C=O). (Found: C, 69.0; H, 7.0%; M^+ 329. Calc. for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.0%; M 329).

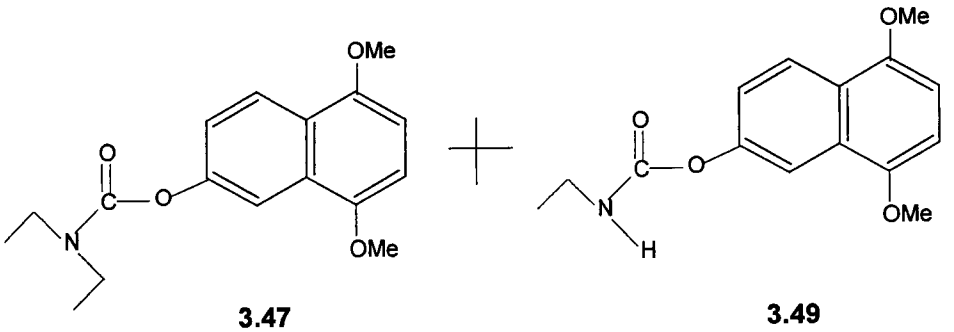
2-(2'-N,N-diethylcarbamyloxyphenyl)-1,4-benzoquinone **4.3**



4.3

To a solution of 1,4-dimethoxy-2-(2'-N,N-diethylcarbamyloxyphenyl)-benzene **4.2** (200mg; 0.61mmol) in CH_3CN (15ml) and H_2O (3ml) was added 2.5 molar equivalent of CAN (733mg; 1.34mmol) in water (3ml) drop-wise with constant stirring over 5min. Stirring was continued for 30min and water (200ml) was added and the aqueous solution was extracted with dichloromethane to afford quinone **4.3** (182mg; 100%) as yellow crystals, m.p. 93-94^{0}C (from hexane); ν_{max} 1670cm^{-1}; δ_H 1.11 (6H, t, *J* 7.0 $-CH_2CH_3$), 3.28 (4H, q, *J* 7.0, $-CH_2CH_3$), 6.82 (3H, m, H-3, H-5 and H-6), 7.26 (3H, m, H-3', H-4' and H-5') and 7.42 (1H, m, H-6'). δ_C 13.3 and 14.3 ($-CH_2CH_3$), 41.8 and 42.3 ($-CH_2CH_3$), 123.1 (C-3')[a], 125.2 (C-4')[a], 126.3 (C-2'), 130.6 (C-5')[a], 130.8 (C-6')[a], 134.6 (C-3)[b], 136.3 (C-5)[b], 136.9 (C-6)[b], 144.7 (C-2)[c], 149.1 (C-2')[c], 153.3 (C=O of carbonyl), 185.4 and 187.4 (C=O of quinone). (Found: C, 68.4; H, 5.5%; M^+ 299. Calc. for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7%; M 299).

***6-N,N-Diethylcarbamyloxy-1,4-dimethoxynaphthalene* 3.47 and *6-N-ethylcarbamyloxy-1,4-dimethoxynaphthalene* 3.49**



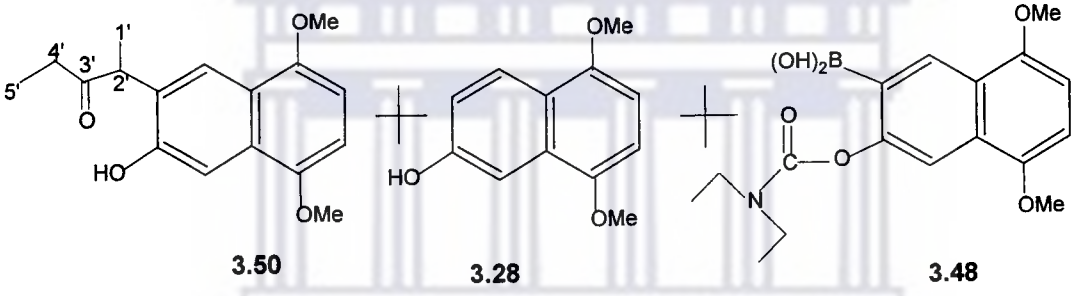
3.47 **3.49**

6-Hydroxy-1,4-dimethoxynaphthalene **3.28** (270mg; 1.33mmol) in pyridine (10ml) was treated with N,N-diethylcarbamylchloride (180mg; 1.33mmol) in a pressure-capped glass bottle heated in an oil bath at 110^{0}C for 3h. The cooled reaction mixture was then poured into ice/water and extracted with ether. The ether solution was washed with 10% aqueous hydrochloric acid (20ml), then aqueous sodium hydrogen carbonate and the residue thus obtained was purified by column chromatography using EtOAc:hexane (3:7) as eluent to afford two products. The first product to elute was **3.47** as an oil (334mg; 83%); ν_{max} 1716 cm^{-1}; δ_H 1.26 (6H, m, 2x CH_3CH_2-), 3.20 (4H, m, 2x -CH_2CH_3), 3.93 (6H, s, 2x OCH_3), 6.66 (1H, d, *J* 9.2, H-2), 6.68 (1H, d, *J* 9.2, H-3), 7.24 (1H, dd, *J* 9.2 and 2.4, H-7), 7.91 (1H, d, *J* 2.4, H-5), 8.20 (1H, d, *J* 9.2, H-8). δ_C 11.5 and 13.0 (CH_3CH_2-), 41.2 (-CH_2CH_3), 55.8 (2x OCH_3), 102.8 (C-2)[a], 104.0 (C-3)[a], 113.2 (C-7), 121.4 (C-8)[b], 123.4 (C-5)[b], 124.1 (C-4a)[c], 127.2 (C-8a)[c], 149.3 (C-6)[d], 149.7 (C-4)[d], 149.8 (C-1)[d], 154 (C=O). (Found: C, 67.1, H, 7.2%; M^+ 303. Calc. $C_{17}H_{21}NO_4$: C, 67.3; H, 7.0%; M 303). Further elution afforded **3.49** (58mg; 16%) as an oil; ν_{max} 3480 and 1670 cm^{-1}; δ_H 1.20 (3H, m, CH_3CH_2-), 3.20 (2H, m, -CH_2CH_3), 3.93 (6H, s, 2x OCH_3), 5.60 (1H, s, N-H), 6.54 (1H, d, *J* 8.4, H-2), 6.70 (1H, d, *J* 8.4, H-3), 7.10 (1H, dd, *J* 8.4 and 2.6, H-7), 7.50 (1H, d, *J* 2.6, H-5),

8.05 (1H, d, *J* 8.4, H-8). δ_C 13.1 (CH_3CH_2-), 30.0 (-CH_2CH_3), 55.8 and 55.9 (2x OCH_3), 101.0

(C-7)[a], 104.2 (C-2)[a], 104.5 (C-3)[a], 117.2 (C-5)[b], 121.7 (C-4a)[c], 124.2 (C-8)[b], 127.9 (C-8a)[c], 148.6 and 150.0 (C-1,C-4 and C-6), 154.2 (C=O). (Found: 275.1151. Calc. for $C_{15}H_{17}NO_4$: 275.1158).

***6-Hydroxy-7-(2'-3-oxapentyl)-1,4-dimethoxynaphthalene* 3.50, *6-hydroxy-1,4-dimethoxynaphthalene* 3.28 and *6-N,N-diethylcarbamyloxy-1,4-dimethoxy-7-naphthylboronic acid* 3.48**



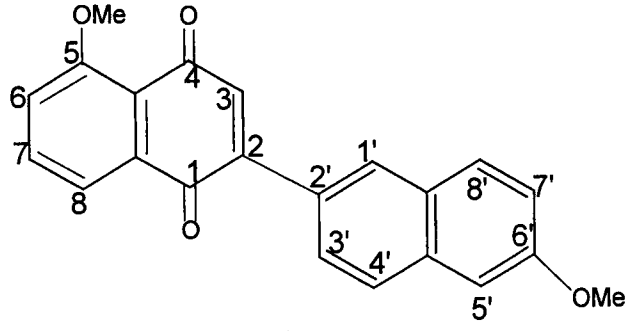
3.50 **3.28** **3.48**

To a stirred solution of sec-butyl lithium (3M equiv.), TMEDA (3M equiv.) in tetrahydrofuran (15ml) at -78^{0}C was added under nitrogen the carbamate **3.47** (300mg; 0.99mmol) in tetrahydrofuran (3ml). After 1h, $MgBrEt_2O$ (780mg; 3.03mmol) was added with vigorous stirring. The reaction mixture was allowed to warm to 24^{0}C and formed a clear solution, which was then cooled to -78^{0}C and then treated with methyl borate (310mg; 3mol) and stirred at this temperature for 10min and the allowed to reach 24^{0}C overnight. The resulting reaction mixture was poured into aqueous ammonium chloride and extracted with dichloromethane to yield an oily residue which was chromatographed using EtOAc:hexane (3:7) as eluent to give as the first fraction the ketonaphthalene **3.50** (74mg; 26%) as orange needles, m.p. 60-

61^{0}C (from EtOAc); ν_{max} 3383 and 1680 cm^{-1}; δ_H 0.97 (3H, t, *J* 7.4, H-5'), 1.29 (3H, d, *J* 7.4, H-1'), 1.60 (2H, m, H-4'), 1.90 (1H, m, H-4'), 3.74 (1H, q, *J* 7.4, H-2'), 3.93 and 3.97 (2x CH_3O), 6.50 (1H, dd, *J* 8.0, H-2), 6.73 (1H, dd, *J* 8.0, H-3), 7.63 (1H, s, H-5), 8.80 (1H, s, H-8), 12.00 (1H, s, D_2O exchangeable, 6-OH). δ_C 11.9, 17.6, 27.2, 41.9 (2'-3-oxapentyl side chain), 100.6 (C-2)[a], 107.1 (C-3)[a], 107.8 (C-5)[a], 119.8 (C-4a)[b], 119.9 (C-8a)[b],126.8 (C-8), 131.6 (C-7), 148.2 (C-1)[c], 150.5 (C-4)[c], 158.5 (C-6), 211.5 (C=O of 2'-3-oxapentyl side chain). (Found: C, 70.5; H, 7.2%; Calc. for $C_{17}H_{20}O_4$: C, 70.8; H, 7.0%; HRMS, 288.1362). Further elution afforded naphthol **3.28** (81mg; 40%) identical in all respects to material synthesized earlier.

Continued elution afforded boronic acid **3.48** (99mg; 29%) as yellow-brown crystals, m.p. 211-213^{0}C (from EtOAc-hexane); ν_{max} 3411 and 1627 cm^{-1}; δ_H 1.33 (6H, t, *J* 7.0, CH_3CH_2-), 3.58 (4H, q, *J* 7.0, CH_3CH_2-), 3.93 (6H, s, 2x OCH_3), 6.53 (1H, d, *J* 7.0, H-2) 6.70 (1H, d, *J* 7.0, H-3), 7.50 (1H, s, D_2O exchangeable OH of $B(OH)_2$), 7.67 (1H, s, H-8), 8.23 (1H, s, H-5), 9.30 (1H, s, D_2O exchangeable OH of $B(OH)_2$). δ_C 13.5 and 42.6 (CH_3CH_2-) respsctively, 55.8 and 56.0 (2x OCH_3), 101.0 (C-2)[a], 105.5 (C-3)[a], 107.2 (C-5), 119.7 (C-4a)[b], 120.0 (C-8a)[b],122.5 (C-8)[c], 129.0 (C-7)[c], 148.5 (C-1)[d], 150.1 (C-4)[d], 155.6 (C-6), 171.5 (C=O of the carbamate). (Found: C, 58.6; H, 6.2%; HRMS 347.1544. Calc. for $C_{17}H_{22}BNO_6$: C, 58.8; H, 6.4%; HRMS: 347.1540).

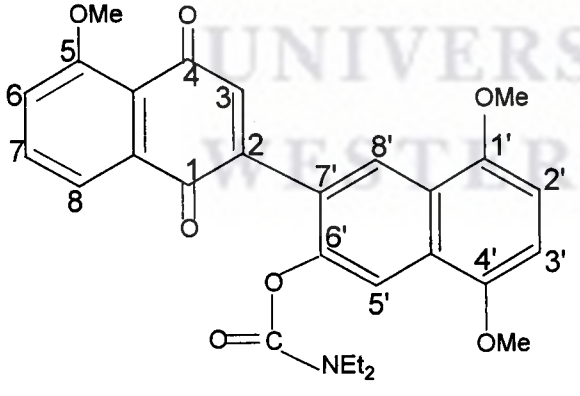
***5-Methoxy-2-(6'-methoxynaphth-2-yl)-1,4-naphthoquinone* 4.6**



4.6

To a solution of boronic acid **4.5** (60mg; 0.29mmol) in benzene (20ml) and $Pd(PPh_3)_4$ (13mg; 1.14mmol), 2M aqueous Na_2CO_3 (0.38ml) was added bromoquinone **3.7** (100mg; 0.38mmol) and this was kept under for 12h. This was then extracted with dichloromethane, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford biaryl system **4.6** (66.84mg; 67%) yield; m.p. 175-176^{0}C (from EtOAc-hexane); ν_{max} 1670cm^{-1}; δ_H 3.95 and 4.04 (each 3H, s, CH_3O), 7.16 (3H, m, aryl-H), 7.34 (1H, dd, *J* 8.2 and 0.8, H-6), 7.62 (1H, dd, *J* 8.8 and 1.8, H-3'), 7.72 (1H, t, *J* 8.2, H-7), 7.80 (2H, m, aryl-H), 7.87 (1H, dd, *J* 8.2 and 0.8, H-8), 8.08 (1H, d, *J* 1.6, H-1'). δC 55.5 and 56.7 (2x CH_3O), 105.8, 117.8, 119.5, 120.0, 120.2, 126.8, 127.0, 128.3, 128.6, 129.6, 130.4, 134.9, 135.1, 135.4, 137.0, 145.7, 158.9 (C-5)[a], 159.5 (C-6')[a], 184.6 and 185 (2x C=O). (Found: C, 76.4; H, 4.6%; M^+ 344. Calc. for $C_{22}H_{16}O_4$: C, 76.7; H, 4.7%; M 344).

5-Methoxy-2-[7'-(6'-N,N-diethylcarbamyloxy)-1',4'-dimethoxynaphthyl]-1,4-naphthoquinone **4.7**



4.7

To a mixture of 2-bromoquinone **3.7** (100mg; 0.37mmol) in toluene (10ml) and $Pd(PPh_3)_4$ (12.81mg; 0.01mmol) were added aqueous 2molar Na_2CO_3 (0.6ml) and boronic acid **3.48** (124mg; 0.37mmol) under N_2 atmosphere. The reaction mixture

was refluxed for 12h with vigorous stirring. The cooled solution was washed with brine and diluted with dichloromethane. The residue obtained upon workup was subjected to column chromatography using EtOAc:hexane (3:7) as eluent to afford three products in the following order: The first fraction to elute was the bromo quinone **3.7** (90%)* spectroscopically identical to the material synthesized earlier. The second fraction to elute was the boronic acid **3.48** (25%)* spectroscopically identical to the material synthesized earlier. The third fraction to elute was very crude **4.7** (10%), δ_H 1.33 (6H, t, *J* 7.0, N-CH_2CH_3), 3.58 (4H, q, *J* 7.0, N-CH_2CH_3), 3.87 (6H, s, 2x CH_3O), 3.94 (3H, s, CH_3O), 6.51 (H-3)[a], 6.98 (H-2')[a], 7.04 (H-3')[a], 7.26 and 7.72 (Aryl-Hs).

* Refers to the isolated yields relative to amounts put into the reaction.

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