THE SYNTHESIS OF METHOXY-2-HYDROXY-1,4-NAPHTHOQUINONES AND THEIR REACTION WITH ALIPHATIC ALDEHYDES UNDER BASIC CONDITIONS.

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

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Keywords

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Naphthoquinones

Naphthopyranquinones

Naphtho[2,3-b]pyranquinones

ABSTRACT

Although literature reports on the synthesis of variously substituted 2-hydroxy-1,4-naphthoquinones appeared to be reasonable; in our hands difficulty was experienced in duplicating much of the work.
In order to address this problem, two protocols were used with the one involving conversion of substituted α-tetralones into *hydroxyquinones* using a solution of the tetralones in an oxygenated solution of tertiary butyl alcohol containing potassium tertiary butoxide, and the other involving Diels-Alder Condensation, oxidation, pyrolysis and basic hydrolysis of a 2-methoxy-1,4-naphthoquinone **79** into the corresponding 2-hydroxy analogue **80**.

Condensation reaction between 2-hydroxyy-8-methoxy-1,4-naphthoquinone **80** and caproaldehyde **111**, produced the 3-alkenyl analogue **115** which was cyclised to the corresponding naphtho[2,3-b]pyrenquinone **116** and eventually reduced to 8-methoxynaphtho[2,3-b]pyran-5,10-dione **117**.

Condensation between 2-hydroxynaphthoquinone **80** and 4-dioxolanopentanal under basic conditions afforded the desired adduct which was cyclised with dichlorodicyanobenzoquinone, reduced and then hydrolysed with acid to produce 2-acetyl-3,4-dihydronaphtho[2,3-b]pyran-5,10-dione **125**. By the employment of an alternative sequence of events, the corresponding 4-hydroxy analogue of the above 2-acetylnaphthopyrandione **125** was also prepared for evaluations.

Finally condensation between 2-hydroxy-8-methoxy-1,4-naphthoquinone **80** and 5-dioxolanohexanal **128** under basic conditions afforded the 3-hexenyldioxolano **129** derivative, which was cyclised to the naphthopyrene **130** but the yields were disappointing in this instance.

ABBREVIATIONS

PPA Polyphosphoric acid

THF Tetrahydrofuran

DMF Dimethylformamide

PDC Pyridinium Dichromate

DDQ Dichlorodicyanobenzoquinone

CAN Cerium(IV) ammonium nitrate

DMS Dimethyl Sulphoxide

"s" singlet

"d" doublet

"t" triplet

"q" quartet

"m" multiplet

"dd" doublet of doublets

"ddd" doublet of doublet of doublets

"bs" broad singlet

DECLARATION

I declare that *The Synthesis of Methoxy-2-hydroxy-1,4-naphthoquinones and their Reaction with Aliphatic Aldehydes under Basic Conditions* is my own work, that it has not been submitted before for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

RENE' SIMON PEARCE

FEBRUARY 2003

SIGNED: .....

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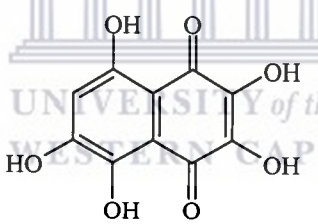
CHAPTER 1

Introduction

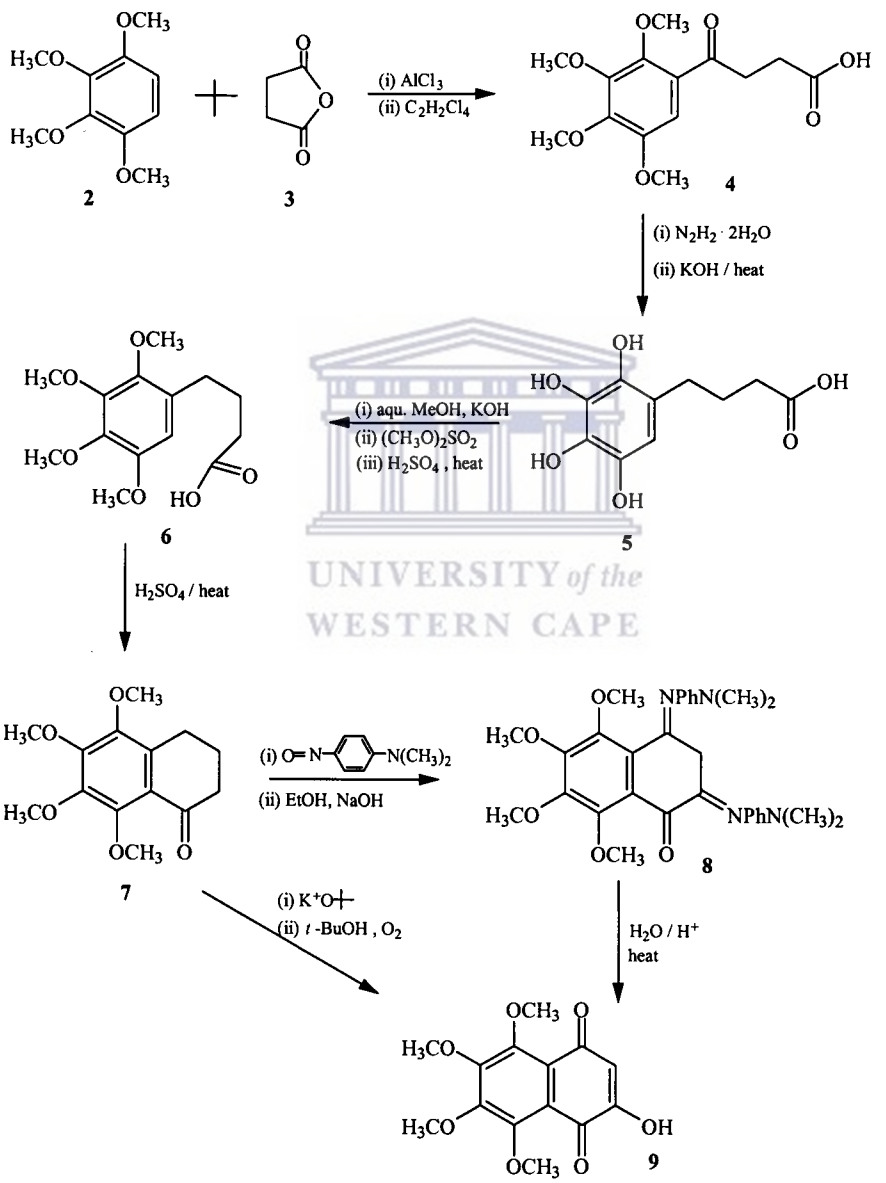
Naphthoquinones are found to occur widely in nature as well as in microorganisms and fungi e.g. *Spinochrome D* **1**; a pigment found in the spines of the sea urchin *Pseudocentrotus depressus* (Ag). Studies regarding their colour, structure and molecular activities were performed and results showed them to exhibit a number of interesting biological activities. *Naphthoquinones* also show physiological properties such as antitumor and antibiotic activities and these were proven by Isayama et al.[1] who reported the use of 5,8-dihydroxynaphthoquinones as drugs for thrombosis, delayed hypersensitivity, and the healing of wounds.



1

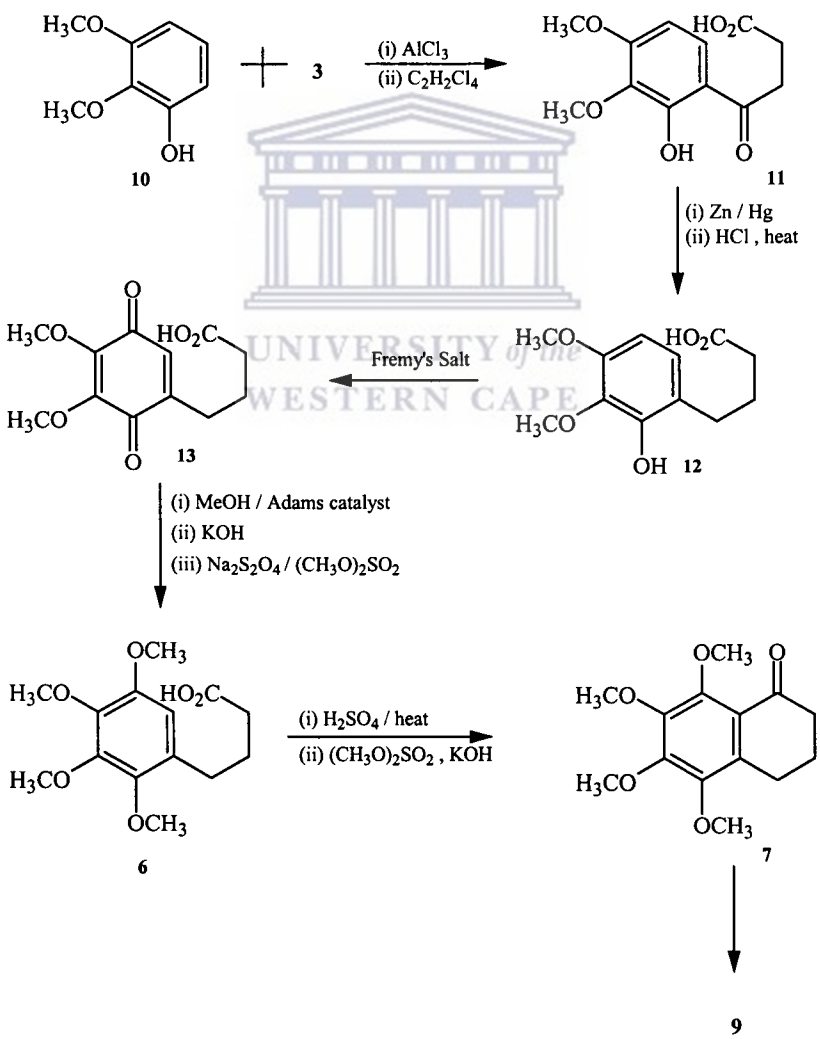
In their synthetic protocol towards Spinochrome D **1**, Anderson et al.[2] required the *2-hydroxynaphthoquinone* **9** as starting material in fair quantity. Thus a Friedel-Crafts acylation between 1,2,3,4-tetramethoxybenzene **2** and succinic anhydride **3** afforded the keto butyric acid **4**. The acid **4** was heated with hydrazine hydrate and potassium hydroxide pellets at 195°C for 1.5h; boiled under reflux for 3h, cooled and poured into ice containing hydrochloric acid. The mixture was extracted with ether and chloroform to give the hydroxylated butyric acid **5** which was re-methylated to give the acid **6**. Cyclisation of **6** into the tetralone **7** was effected by heating with sulphuric acid. Initial attempts to convert tetralone **7** into the desired *2-hydroxynaphthoquinone* **9** by condensation of the former with dimethyl-p-

nitrosoaniline to afford the dianil **8**, which upon aqueous hydrolysis afforded **9** proved to have limited success. Yields were extremely poor and thus it was subsequently found that treating tetralone **7** with potassium tert-butoxide under oxygen afforded quinone **9** in improved yields (see Scheme 1).



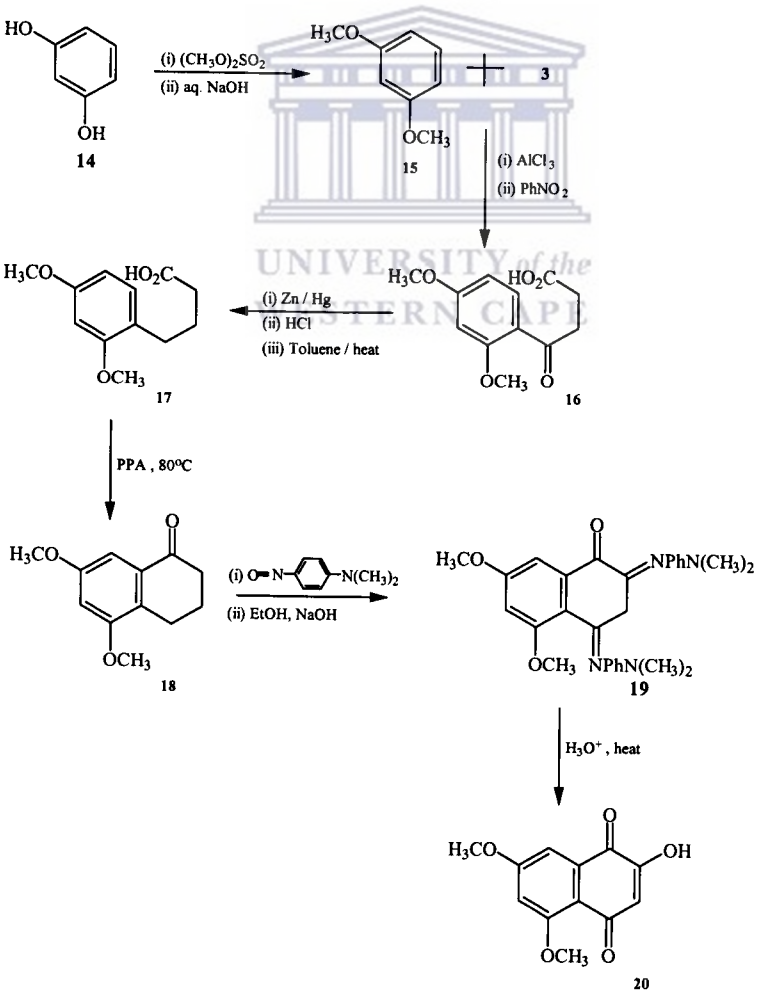
Scheme 1

In an alternative approach, Anderson et al.[2] employed methodology developed by Mitter et al.[3] Thus Friedel-Crafts acylation between phenol **10** and **3** afforded the keto acid **11** which was subsequently reduced via the Clemmenson Reduction protocol to afford the acid **12**. The phenol system of **12** was then oxidized to the quinone **13** with Fremy's salt and was then reductively dimethylated to afford butyric acid **6** which was cyclised to the tetralone **7** in sulphuric acid and subsequently methylated with dimethyl sulphate and potassium hydroxide. Conversion of tetralone **7** into quinone **9** was accomplished as described in Scheme 1 (Scheme 2).



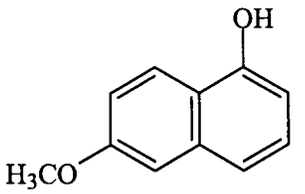
Scheme 2

In another approach, Davies et al.[4], converted resorcinol **14** using aqueous sodium hydroxide and dimethyl suphate into the corresponding dimethyl ether **15**, which was condensed under Friedel-Crafts conditions with succinic anhydride **3** to afford the keto butyric acid **16**, followed by Clemmensen Reduction to afford butyric acid **17**. Cyclisation of **17** into the tetralone **18** using polyphosphoric acid proved to be extremely low yielding in that at best only a 6% yield of **18** was obtained. Conversion of the tetralone **18** into the dianil **19** with dimethyl-p-nitrosoaniline was achieved in a 47% yield and final aqueous hydrolysis of **19** into the desired *2-hydroxynaphthoquinone* **20** was accomplished in a 24% yield. Again this methodology proved its inadequacies and is depicted in Scheme 3.



Scheme 3

In their endeavors in finding an alternative and easier method for the preparation of 6-methoxy-1-naphthol **21**, Kasturi et al.[5] followed the method of Crowshaw et al.[6] in which the latter reported obtaining phenol **23** from the unsaturated ketone **22** in the presence of potassium tert-butoxide in tert-butanol, under an atmosphere of oxygen (Scheme 4).



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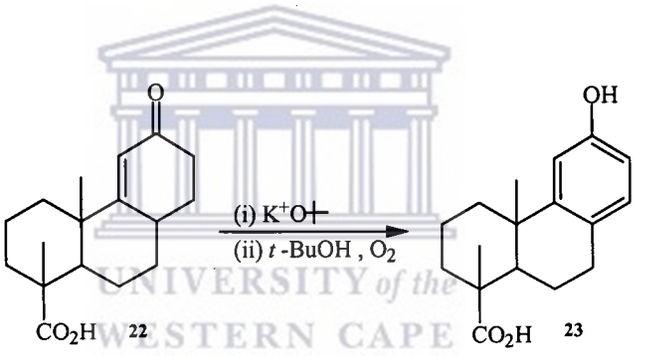
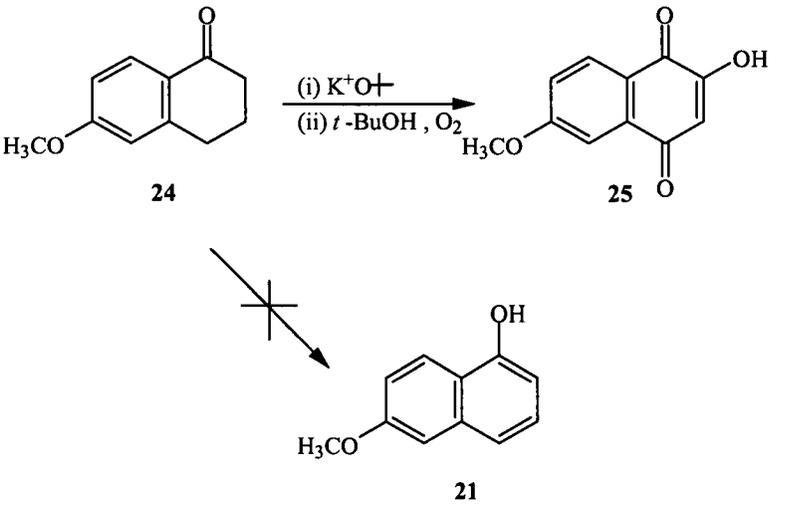


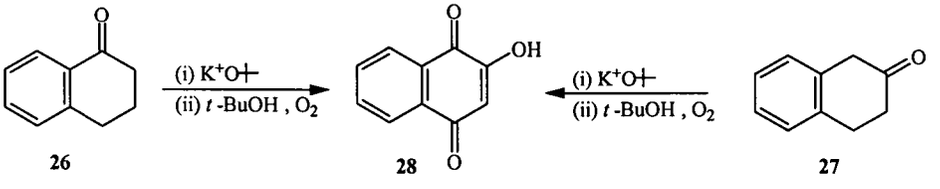
Scheme 4

Kasturi et al.[5] attempted to synthesize naphthol **21** from tetralone **24** using this method, but discovered that treatment of tetralone **24** with potassium tert-butoxide in tert-butanol, under an atmosphere of oxygen, resulted in rapid absorption of 2 moles of oxygen per mole of ketone to afford a high melting, yellow crystalline solid in 80% yield. This yellow solid was confirmed to be 2-hydroxy-6-methoxy-1,4-naphthoquinone **25** by analyses (Scheme 5).



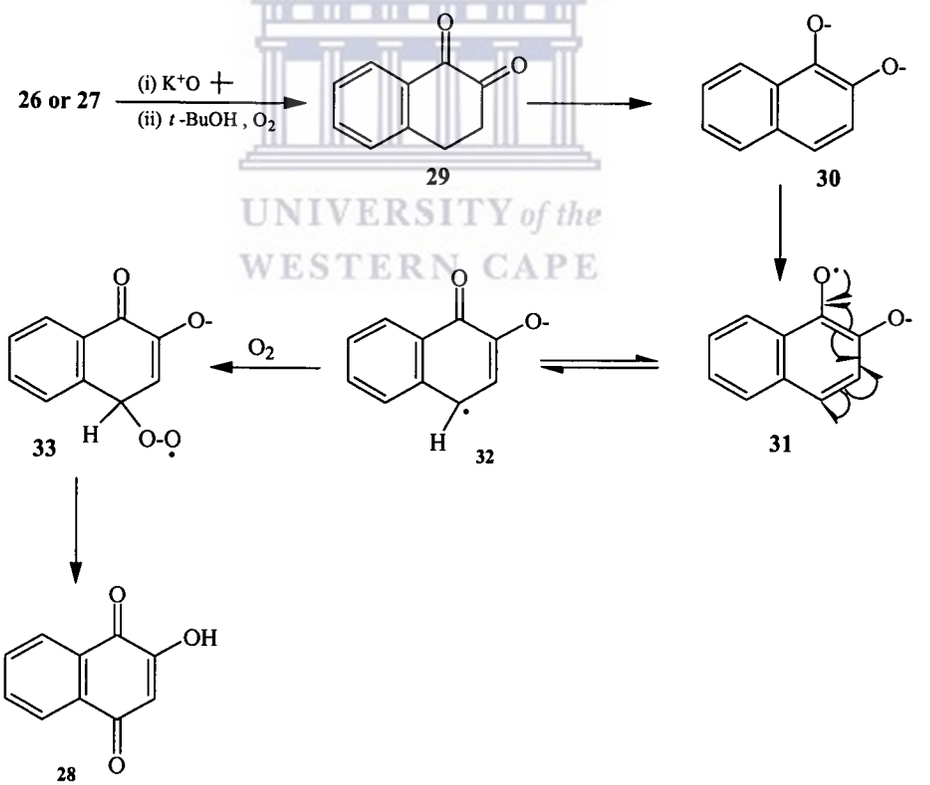
Scheme 5

In 1966, Baillie and Thomson[7] reported new routes for the synthesis of *2-hydroxy-1,4-naphthoquinones* via autoxidation reactions of ketones in basic solutions. Baillie and Thomson[7] discovered that autoxidation reactions involving both α- and β-tetralones resulted in oxygenation of the benzylic [C(4)] carbon atom thus resulting in the formation of *2-hydroxy-1,4-naphthoquinones*. They reported: "when shaken in t-butyl alcohol containing an excess of potassium tert-butoxide, saturated with oxygen, both α- and β-tetralones **26** and **27** absorb 2 moles of oxygen to form the *hydroxyquinone* **28**, the faster reaction of the β-isomers reflecting the enhanced activity of the benzyl position at C(1)." (Scheme 6)



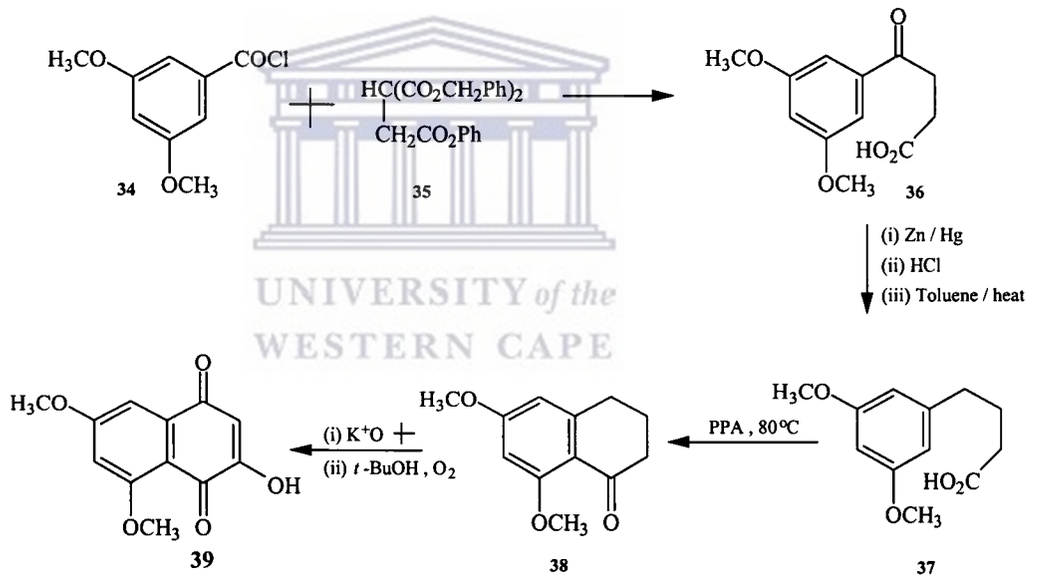
Scheme 6

Moderate yields of **28** were obtained by the conventional condensation of either **26** or **27** with 2 moles of dimethyl-p-nitrosoaniline, followed by acid hydrolysis. The former method proved to be much faster than the condensation reaction with dimethyl-p-nitrosoaniline. The mechanism by which α- and β-tetralones **26** and **27** are converted into *2-hydroxy-1,4-naphthoquinones* is shown in Scheme 7. According to Baillie and Thomson[7] : "Tetralones autoxidise normally and since both α- and β-tetralone give the same product, the common intermediate must be the α-diketone **29**. The latter would enolise in strongly basic solution giving **30** which is the di-anion of an *ortho*-quinol and therefore, in the presence of oxygen, would form the semiquinone anions **31** and **32** with subsequent oxidation by oxygen to afford **33** which then affords **28** (Scheme 7).



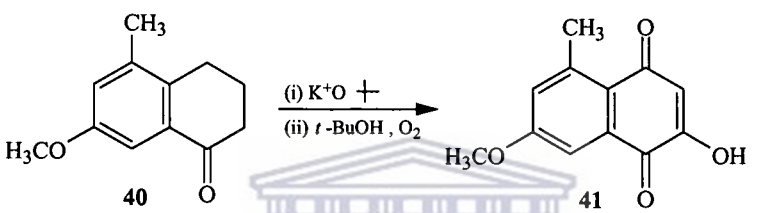
Scheme 7

Coombe[8] reported that similar yields of the keto butyric acid **36** could be obtained by following Davies's[3] procedures. Thus condensation between acid chloride **34** and the triester **35** in sodium and toluene, afforded keto butyric acid **36** in a 54% yield. Clemmensen Reduction of **36** afforded butyric acid **37** and cyclisation thereof with polyphosphoric acid at 80°C gave the α-tetralone **38** in good yield. Treatment of the tetralone **38** with oxygen in the presence of potassium tert-butoxide and tert-butyl alcohol, afforded the *hydroxyquinone* **39** directly and proved to be superior to the method employed by Davies et al.[3], see Scheme 5. (Note! Molecules in Scheme 8 are different to those in Scheme 3).



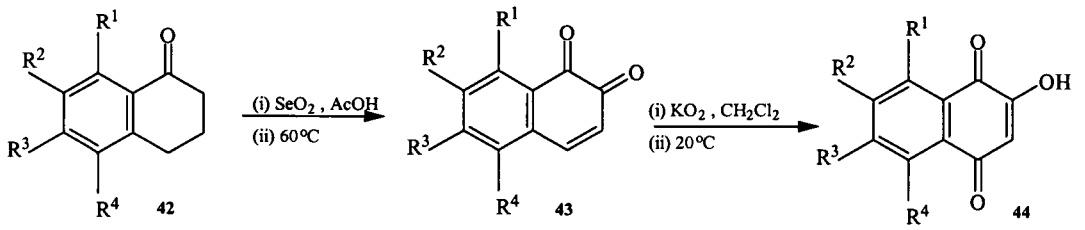
Scheme 8

In 1981, Cameron et al.[9] reported that " autoxidation of the tetralone **40** in potassium tert-butoxide solution according to the procedure of Baillie and Thomson[7] gave the naphthoquinone **41** in 60% yield. Such reactions are known to proceed by introduction of an oxygen substituent adjacent to the carbonyl group followed by conversion into the 1,4-quinone system." The ^{1}H NMR spectrum of **41** showed a singlet quinonoid peak (6.22ppm) together with the signals of the substituted benzonoid ring (Scheme 9).



Scheme 9

Bekaert et al.[10] reported a 98% yield and clean conversion of different methoxylated-1-tetralones **42a-d** into the corresponding *2-hydroxy-1,4-naphthoquinones* **44a-d** in two steps. In the first step, regiospecific oxidation of the tetralones **42** using selenium dioxide and acetic acid at 60°C afforded the corresponding 1,2-naphthoquininones **43** followed by heterogenous oxidation of **43** with potassium superoxide in dichloromethane to give the *2-hydroxy-1,4-naphthoquinones* **44**, in Scheme 10. In **Table 1**, the range of tetralones **42** and their products **44** are given.

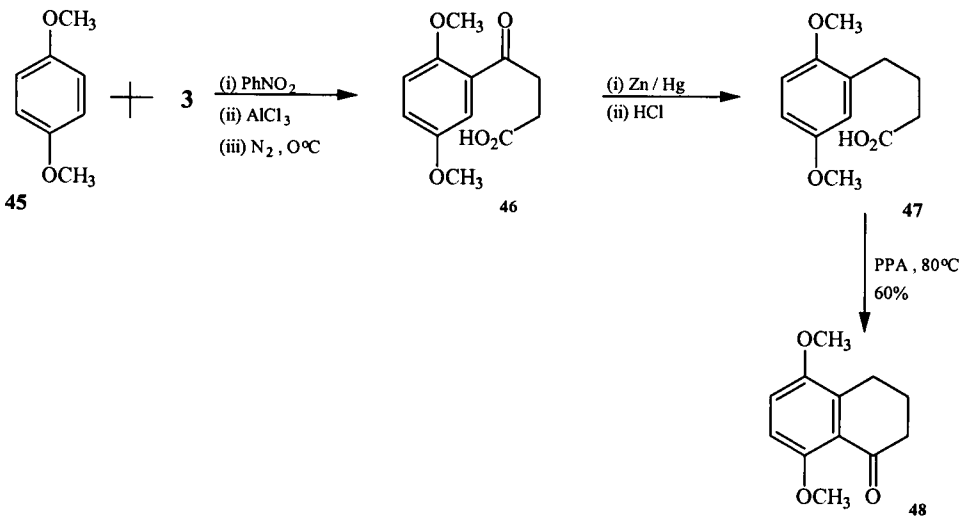


Scheme 10

Table 1

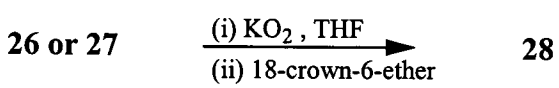
	42	43	44
42a	$R_1= R_2= R_3= H$, $R_4= OCH_3$	43a. 78%	44a. 95%
42b	$R_1= R_2= R_4= H$, $R_3= OCH_3$	43b. 72%	44b. 95%
42c	$R_1= R_3= R_4= H$, $R_2= OCH_3$	43c. 60%	44c. 97%
42d	$R_4= H$, $R_1= R_2= R_3= OCH_3$	43d. 60%	44d. 98%

Yang et al.[11] reported the synthesis of β-(2,5-dimethoxybenzoyl)-propionic acid **46** via a Friedel-Crafts acylation reaction between 1,4-dimethoxybenzene **45** and succinic anhydride **3**. Clemmensen Reduction of the keto acid **46** afforded the butyric acid **47** and cyclisation of **47** using polyphosphoric acid at 80°C afforded tetralone **48** in a 60% yield in the last step (Scheme 11).



Scheme 11

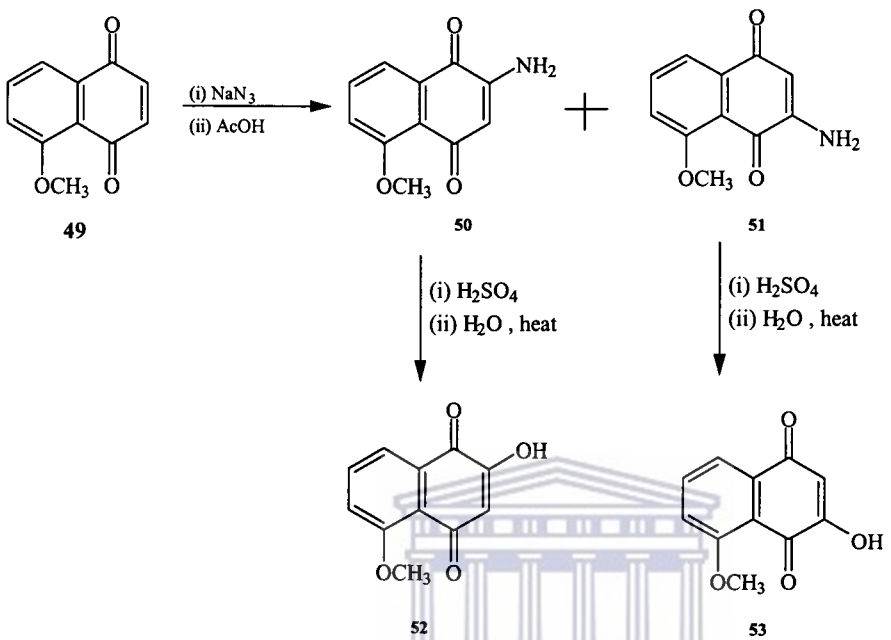
Hocquaux and Jaquet[12] focussed their attention on the potential oxidant behaviour of potassium superoxide in dry tetrahydrofuran, under nitrogen and solubilized by crown-ether on both the α- and β-tetralones **26** and **27**. The oxidation of tetralones **26** and **27** in positions 2 and 4, and 1 and 4 respectively, afforded the corresponding *2-hydroxy-1,4-naphthoquinone* **28** with yields of 75% being reported (Scheme 12).



Scheme 12

Spyroudis[13] recently reviewed various protocols towards the synthesis and reactivity of *hydroxyquinones* in general. Parker et al.[14] described the reaction of juglone methyl ether **49** in a solution of sodium azide and acetic acid, in which a mixture of two isomeric aminojuglone ethers **50** and **51** were obtained. The isomers **50** and **51**

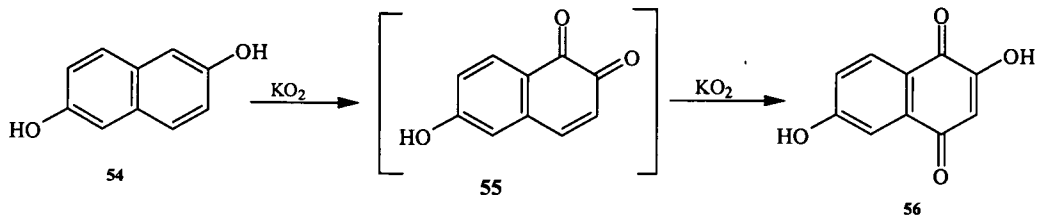
were converted into the corresponding *hydroxyquinones* **52** and **53** via acid hydrolysis (Scheme 13).



49 **50** **51** **52** **53**

Scheme 13

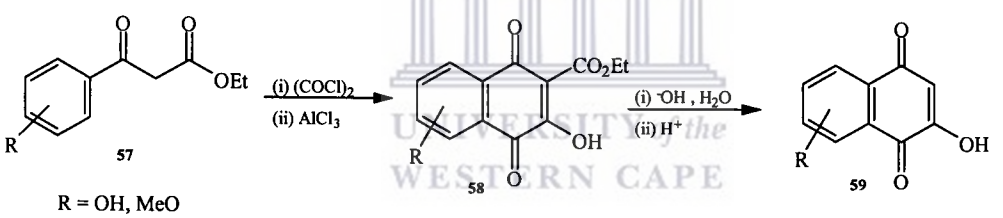
Spyroudis[13] also reported that "Oliveros et al.[15] used singlet oxygen for the conversion of a series of naphthalenediols into the corresponding *hydroxynaphthoquinone* derivatives." Oliveros et al.[16] were able to improve their yield of *hydroxyquinones* by employing solid potassium superoxide in the reaction. The oxidation of 2,6-naphthalenediol **54** to dihydroxynaphthoquinone **56** is a good example of Oliveros's et al.[16] work (Scheme 14).



54 55 56

Scheme 14

In 1993, Satori et al.[17] reported the synthesis of substituted *hydroxynaphthoquinones* via an intramolecular Friedel-Crafts cyclization, in which oxalyl chloride was added to a mixture of an aromatic keto-ester **57** and aluminium trichloride. This resulted in the formation of a 3-hydroxy-1,4-naphthoquinone-2-carboxylate **58** which was hydrolysed and decarboxylated to afford the corresponding substituted *2-hydroxy-1,4-naphthoquinone* **59** (Scheme 15).



57 58 59

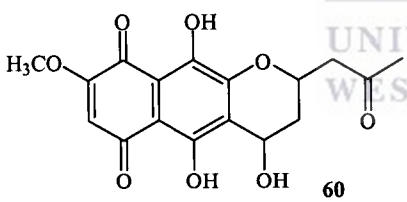
R = OH, MeO

Scheme 15

CHAPTER 2

Synthetic Methodology of 2-Hydroxy-n-methoxy-1,4-naphthoquinones.

Erythrostominone **60**[18], an antibacterial pigment, together with deoxyerythrostominone **61** and deoxyerythrostominol **62** were isolated from *Gnomonia Erythrostoma*. *G. Erythrostoma* is found on the bark of wallnut trees and when grown in an aerated stirred medium, it produces a deep red broth from which the above mentioned antibacterial pigments were extracted. *Erythrostominone* **60**[18] was found to have the molecular formula: $C_{17}H_{16}O_8$ and proved to be active against gram positive and gram negative bacteria, *in vitro*.



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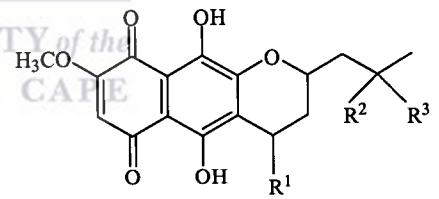
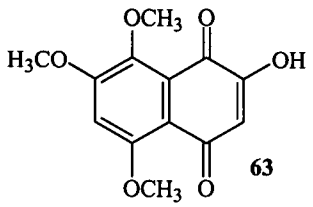


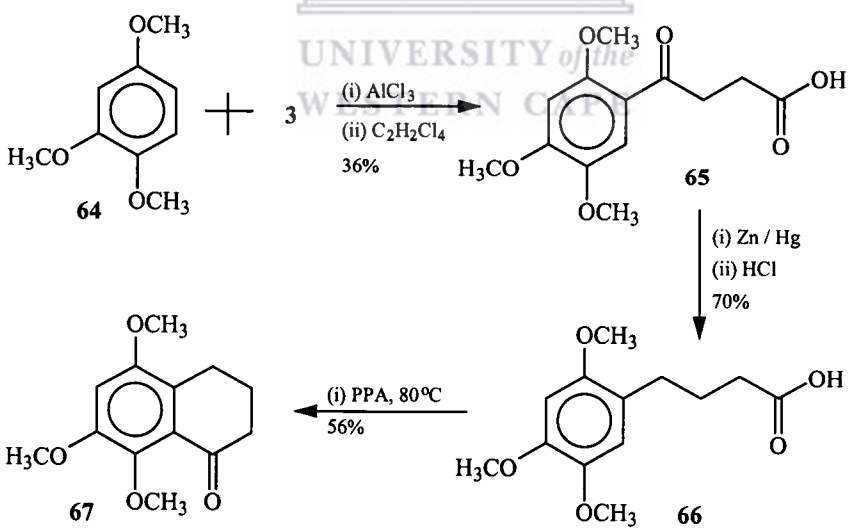
61 $R^1 = H$, $R^2 = R^3 = O$
62 $R^1 = R^2 = H$, $R^3 = OH$

Erythrostominone **60**[18] is also an example of one of the new series of *Napthazarin* antibiotics, as it contains a 5,8-dihydroxy-1,4-naphthoquinone nucleus, which is indicative of *naphthazarin*. In one of our envisaged routes towards *erythrostominone* **60**[18], the crucial intermediate viz., mompain trimethyl ether **63**, would be required and thus methods towards its synthesis in quantity would need to be established.



63

In this regard we attempted to repeat the claimed preparation by Bekaert et al.[10] and Jacquet et al.[12], but failed to reproduce their claimed results. In our hands a Friedel-Crafts acylation between 1,2,4-trimethoxybenzene **64** and succinic anhydride **3** afforded the keto butyric acid **65** in 36% yield. Clemmenson reduction of **65** afforded the butyric acid **66** (70%) and dehydrative cyclisation of **66** using polyphosphoric acid gave the corresponding 5,7,8-trimethoxy-1-tetralone **67** in a 56% yield (Scheme 16).



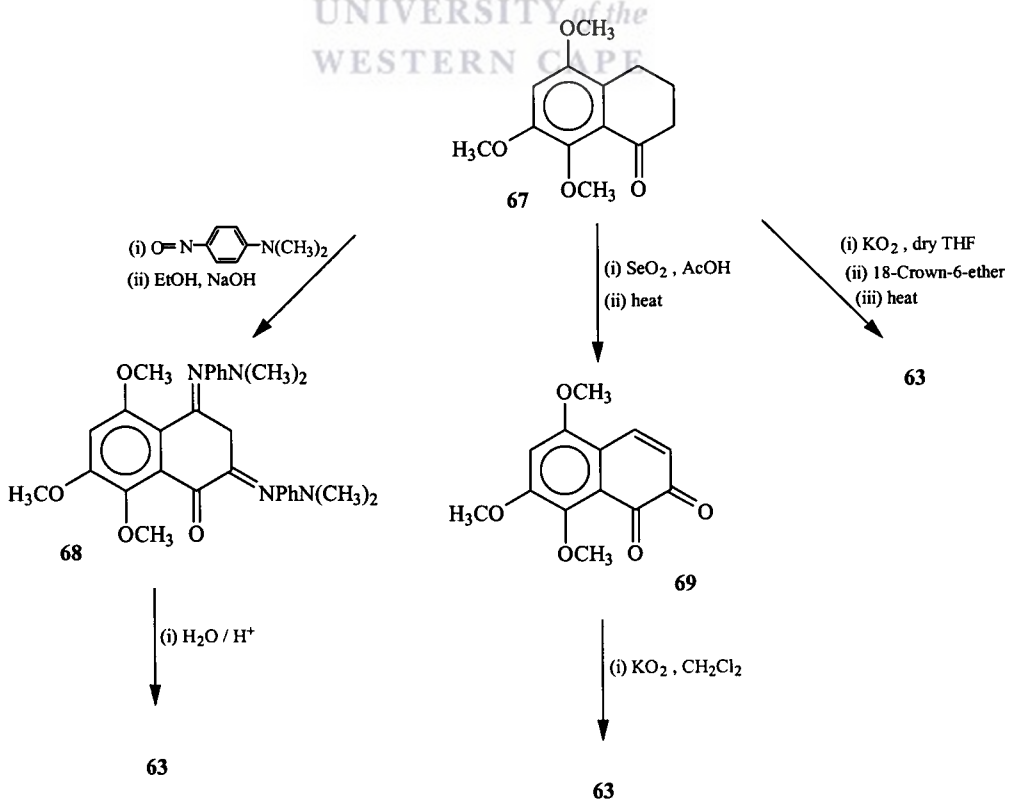
Scheme 16

Conversion of the tetralone **67** into the corresponding hydroxyquinone **63** proved to be problematic. Methods that we employed were as follows:

(i) following the same procedure described by Anderson et al.[2] in Scheme 1 the conversion of tetralone **67** into the dianil **68** was attempted followed by aqueuos hydrolysis to afford **63**.

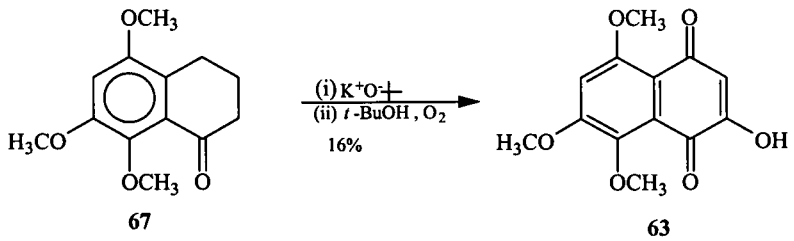
(ii) The procedure described by Bekaert et al.[10] in Scheme 10, whereby tetralone **67** was oxidized using selenium dioxide in acetic acid to afford the expected orthoquinone **69** which when further oxidized using potassium superoxide in dichloromethane should afford **63**.

(iii) The method employed by Hocquaux et al.[12] as depicted in Scheme 12, in which **67** should be oxidized to **63** using potassium superoxide in dry tetrahydrofuran, under nitrogen and solubilized by 18-crown-6-ether. These methods proved ineffective for the synthesis of 2-hydroxy-5,7,8-trimethoxy-1,4-naphthoquinone **63** (Scheme 17).



Scheme 17

The method employed by Baillie and Thomson[7] (i.e. the conversion of tetralones into the corresponding *hydroxyquinones* using molecular oxygen and potassium tert-butoxide) when applied to **67** resulted in the formation of 2-hydroxy-5,7,8-trimethoxy-1,4-naphthoquinones **63** but in a reported yield of 16% (Scheme 18).

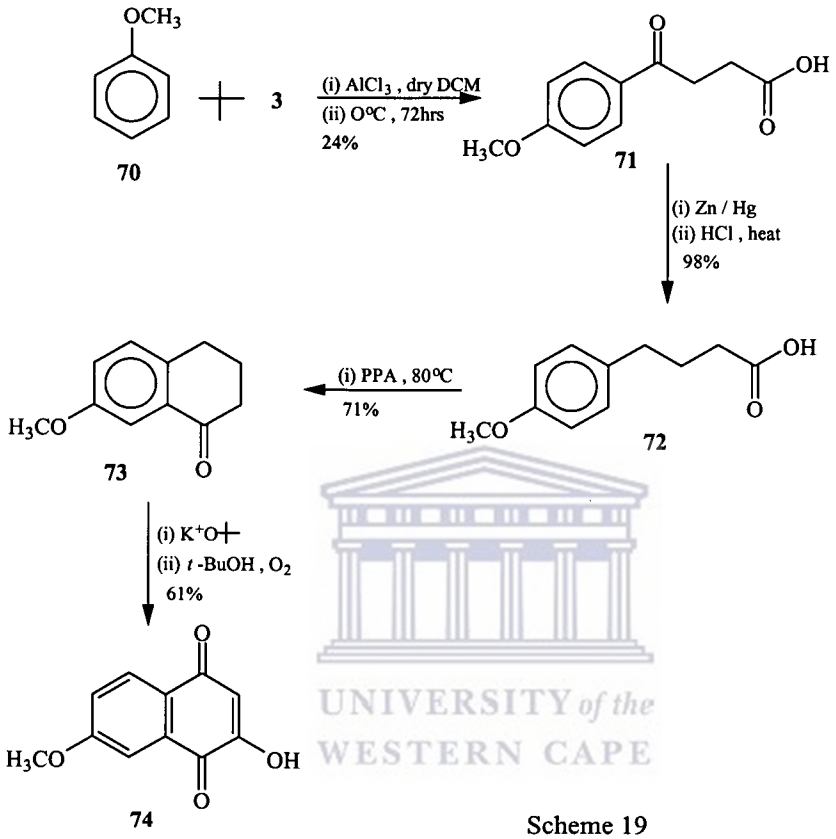


67 **63**

Scheme 18

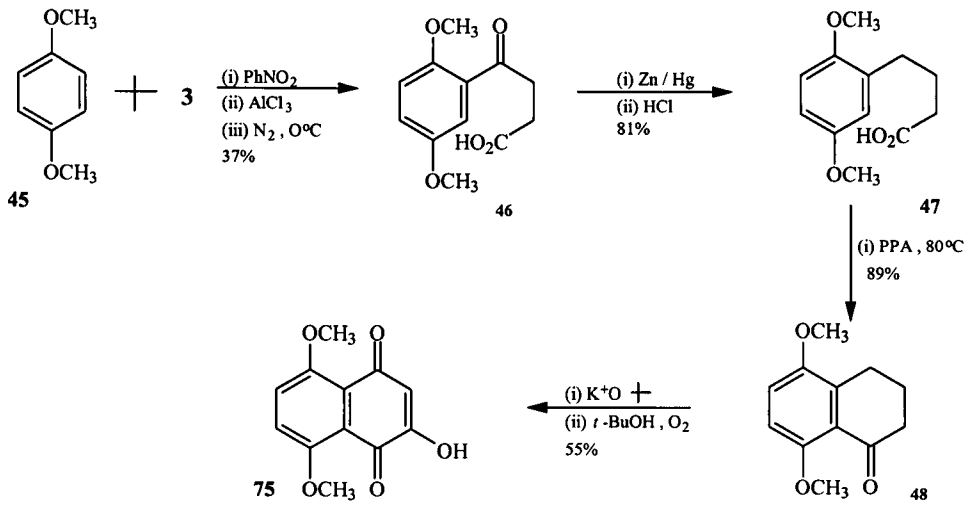
Since one of the objectives of the current research was to synthesize a variety of methoxylated 2-hydroxy-1,4-naphthoquinones, and due to the expensive synthetic procedure in procuring 1,2,4-trimethoxybenzene, attention was focussed on using two easily accessible starting materials viz. anisole **70** and 1,4-dimethoxybenzene **45**. In addition, these two ethers should provide access to two of the target molecules and allow some fine-tuning of reaction conditions. Using analogous reaction conditions shown in Scheme 16 (see experimental), anisole **70** was condensed with succinic anhydride **3** under Friedel-Crafts acylation conditions to afford the corresponding keto butyric acid **71** in 24%. Clemmensen reduction of the latter keto butyric acid **71** afforded the expected butyric acid **72** in 98% yield. This (i.e. reduction) is shown in the ^{1}H NMR spectrum where the side-chain protons namely: H-3 occurs as a multiplet at 2.06ppm (*J* 7.6); H-2 a triplet at 2.50ppm (*J* 7.4) and H-4 also a triplet at 2.75ppm (*J* 7.8). Finally heating the butyric acid **72** in freshly prepared polyphosphoric acid at 80°C for 1h lead to the formation of the desired tetralone **73** in 71% yield. Oxidation of tetralone **73** using Baillie and Thomson's[7] method depicted in Scheme 6 afforded 2-hydroxy-7-methoxy-1,4-naphthoquinone **74** in 61% yield for the final step. The ^{1}H-nmr spectrum of **74** showed a singlet peak at 6.29 ppm due to

the quinonoid proton, H-3; doublet of doublets at 7.25ppm (*J* 8.4 and 3.0) due to H-6; doublet at 7.55ppm (*J* 3.0) due to H-8 and a doublet at 8.05ppm (*J* 8.4) due to H-5 (see Scheme 19).



Scheme 19

Employing an analogous method as depicted in Scheme 16; the reactions were carried out successfully on 1,4 dimethoxybenzene **45** to the tetralone stage (**48**). Finally the oxidation method of Baillie and Thomson[7], when applied afforded the hydroxyquinone **75** in 55% yield for the last transformation (Scheme 20). The ^{1}H NMR spectrum of **75** showed a singlet peak at 6.21ppm due to the quinonoid proton, H-3; a doublet at 7.27ppm (*J* 9.4 Hz) due to H-7 and a doublet at 7.42ppm (*J* 9.4 Hz) due to the deshielded H-6.

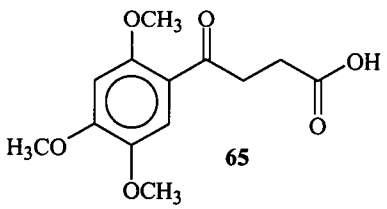


Scheme 20

Experimental

^{1}H and ^{13}C NMR spectra were recorded using a Varian 200MHz spectrometer at 20°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 on a Finnigan-Matt GCQ instrument. 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°-75°C. In ^{13}C-spectra, assignments with the same superscript may be interchanged.

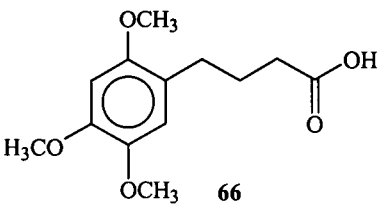
4-(2′,4′,5′-Trimethoxyphenyl)-4-keto-butyric acid (65)



65

Succinic anhydride **3** (18g; 0.18mol) in tetrachloroethane (100ml) was stirred at O°C for 30 min. 1,2,4-Trimethoxybenzene **64** (25g; 0.15mol), commercially available, in tetrachloroethane (20ml) was added to the reaction mixture, and allowed to stir for an additional 10min. Anhydrous aluminium trichloride (25g; 0.19mol) was added and the reaction mixture allowed to stir at O°C for 72h. The mixture was poured into ice/water (500ml) containing concentrated hydrochloric acid (20ml) and stirred well to obtain two distinct layers. The aqueous layer was extracted with dichloromethane (3×100ml) and combined with the organic layer, and this was extracted with saturated sodium hydrogen carbonate (3×100ml). The combined aqueous layer were acidified with dilute hydrochloric acid to a pH=2. This resulting solution was extracted with dichloromethane (4×100ml). The residue obtained upon workup afforded the keto butyric acid **65** (14.33g, 36%) as a white solid, m.p. 80-83°C (from hexane). ν_{max} 3400-2500 cm^{-1} (broad) OH and 1702 and 1695 cm^{-1} (C=O). δ_H 2.73 (2H, t, ***J*** 6.6, H-3), 3.31 (2H, t, ***J*** 6.6, H-2), 3.86, 3.93 and 3.95 (each 3H, s, OCH_3), 6.49 (1H, s, H-3′) and 7.47 (1H, s, H-6′). δ_C 28.8 (C-3), 38.8 (C-2), 56.2 (2×OCH_3), 56.3(OCH_3), 96.4 (C-3′), 112.8 (C-6′), 118.2 (C-1′), 143.3 (C-2′)[a], 154.3 (C-4′)[a], 155.9 (C-5′)[a], 178.7 and 197.3 (C=O). (Found: C, 58.0; H, 6.2%; M^+ 268(20), 195(100). Calc. For $C_{13}H_{16}O_6$: C, 58.2; H, 6.0%; M 268).

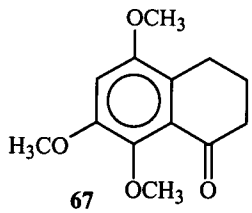
4-(2′,4′,5′-Trimethoxyphenyl)butyric acid (66)



66

Mossy zinc: Zinc (8.31g, 0.13mol) and mercuric chloride (3.45g, 0.013mol) were added to dilute hydrochloric acid (0.8ml conc. HCl, 20ml water) and stirred for 10min. The dilute hydrochloric acid was decanted and the mossy zinc washed with water (2×50ml). Aqueous hydrochloric acid (20ml conc. HCl, 10ml water) was added to the mossy zinc followed by a solution of compound **65** (6.4g, 0.024mol) in toluene (40ml). The reaction mixture was heated and stirred under reflux for 18h, cooled and poured into cold (10°C) water (100ml). The residue obtained upon workup afforded the butyric acid **66** (4.26g, 70.3%) as a brown solid, m.p. 76-82°C (from hexane). ν_{max} 3400-2500 cm^{-1} (broad) OH and 1700 cm^{-1} (C=O). δ_H 1.90 (2H, pentet, ***J*** 7.4, H-3), 2.37 (2H, t, ***J*** 7.4, H-2), 2.61 (2H, t, ***J*** 7.4, H-4), 3.79, 3.83 and 3.87 (each 3H, s, OCH_3), 6.51 (1H, s, H-3′), and 6.68 (1H, s, H-6′). δ_C 25.3 (C-3), 29.0 (C-2), 33.5 (C-4), 56.4 (2×OCH_3), 56.8 (OCH_3), 98.0 (C-3′), 114.5 (C-6′), 121.2 (C-1′), 143.0 (C-2′)[a], 148.0 (C-4′)[a], 151.7 (C-5′)[a] and 179.7 (C=O). (Found: C, 61.0; H, 7.3%; M^+ 254(30), 181(100), 151(20). Calc. For $C_{13}H_{18}O_5$: C, 61.4; H, 7.1%, M 254).

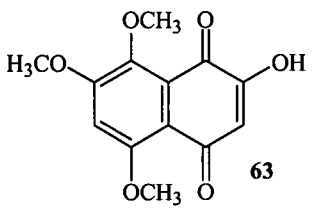
5,7,8-Trimethoxy-1-tetralone (67)



67

The acid **66** (4.0g, 0.016mol) and polyphosphoric acid (40g) were stirred together at 80°C for 45min, then poured into ice/water (50ml), and stirred vigorously until a yellow solid precipitate was obtained. The solution was extracted with ethyl acetate (3×50ml), and the organic layers combined and washed with brine. The residue obtained upon workup was purified by column chromatography using EtOAc: Hexane (3:7) as eluent. The tetralone **67** (2.08g, 56%) was obtained as a yellow solid, m.p. 105-107°C (from hexane). ν_{max} 1682 cm^{-1}; δ_H 2.04 (2H, m, H-3), 2.60 (2H, t, ***J*** 7.2, H-2), 2.80 (2H, t, ***J*** 6.4, H-4), 3.82, 3.84 and 3.89 (each 3H, s, OCH_3), and 6.70 (1H, s, H-6). δ_C 22.6 (C-3), 23.0 (C-2), 41.0 (C-4), 56.2 (2×OCH_3), 57.0 (OCH_3), 102.5 (C-6), 125.8 (C-4a)[a], 127.8 (C-8a)[a], 151.3 (C-5)[b], 152.3(C-7)[b], 152.8 (C-8)[b] and 186.3 (C=O). (Found: C, 66.4, H, 6.8%; M^+ 236(55), 207(100), 189(47). Calc. For $C_{13}H_{16}O_4$: C, 66.1, H, 6.8%, M 236)

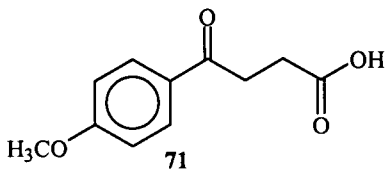
2-Hydroxy-5,7,8-trimethoxy-1,4-naphthoquinone (63)



63

To a stirred solution of tetralone **67** (0.2g, 0.847mmol) in tert-butyl alcohol (10ml), saturated with oxygen, was added potassium tert-butoxide (0.48g, 4.28mmol). The reaction mixture was stirred for 45min while dry oxygen was bubbled through, then acidified with dilute hydrochloric acid (0.5 M) and extracted with dichloromethane (3×50ml). The combined organic extract was washed with aqueous sodium bicarbonate (3×50ml) and this basic extract was acidified with dilute sulphuric acid, then extracted with dichloromethane (3×50ml). The residue obtained upon workup afforded the hydroxyquinone **63** (0.181g), which was chromatographed using EtOAc (100%) as the eluent. The product was recrystallised using aqueous methanol and afforded brown crystals (0.13g, 58.04%), m.p. 173-174°C, (lit.,[7] 174°C). ν_{max} 3300-2700 cm^{-1} (broad) OH, 1679 and 1735 cm^{-1} (C=O); δ_H 3.88 and 2×3.99 (each 3H, s, OCH_3), 6.18 (1H, s, H-6), 6.82 (1H, s, H-3). δ_C 56.4, 57.2 and 61.3 (OCH_3), 104.0 (C-6), 123.7 (C-3), 133.6 (C-4a)[a], 134.6 (C-8a)[a], 154.7 (C-2)[b], 158.8 (C-5)[b], 2×162.8 (C-8 and C-7)[b], 181.5 and 186.5 (C=O). (Found: C, 58.9; H, 4.7%; M^+ 264. Calc. for $C_{13}H_{12}O_6$: C, 59.2; H, 4.5%; M 264).

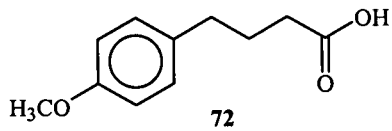
4-(4′-Methoxyphenyl)-4-keto butyric acid (71)



71

Anisole **70** (25.0g, 0.023mol) in dry dichloromethane (20ml) was added to a stirred solution containing succinic anhydride **3** (18.0g, 0.18mol) in dry dichloromethane (100ml) at 0°C. The reaction mixture was allowed to stir for a further 10min. at O°C, after which anhydrous aluminium trichloride (25.0g, 0.19mol) was added over a period of 30min. After stirring at O°C for 72h, the reaction mixture was worked up via a similar protocol described for compound **65**. The residue obtained upon workup afforded the keto butyric acid **71** (11.56g, 24%) as a cream solid, m.p. 148-150°C (from hexane). ν_{max} 3400-2500 cm^{-1} (broad) OH, 1697 and 1668 cm^{-1} (C=O). δ_H 2.82 (2H, t, ***J*** 6.6, H-2), 3.27 (2H, t, ***J*** 6.6, H-3), 3.88 (3H, s, OCH_3), 6.94 (2H, d, ***J*** 8.8,H-3′ and H-5′), 7.97 (2H, d, ***J*** 8.8, H-2′ and H-6′). δ_C 28.1 (C-3)[a], 33.0 (C-2)[a], 55.6 (OCH_3), 113.9 (C-3′ and C-5′), 129.7 (C-1′), 130.5 (C-2′ and C-6′), 163.8 (C-4′), 177.2 and 196.5 (C=O). (Found: C, 63.7; H, 5.6%; M^+ 208(10), 135(100), 77(18). Calc. for $C_{11}H_{12}O_4$: C, 63.5; H, 5.8; M 208).

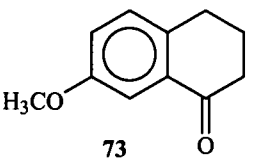
4-(4′-Methoxyphenyl)butyric acid (72)



72

Aqueous hydrochloric acid (25ml conc. HCl, 12.5ml water) was added to freshly prepared mossy zinc (see experimental procedure of compound **66** for preparation of mossy zinc), to which a solution of the keto acid **71** (8.0g, 0.038mol) in toluene (50ml) was then added. Similar reduction and workup procedure as described earlier afforded butyric acid **72** (7.2g, 98.4%) as a cream solid, m.p. 52-54°C (from hexane). ν_{max} 3400-2500 cm^{-1} (broad) OH and 1695 cm^{-1} (C=O). δ_H 2.06 (2H, m, ***J*** 7.6, H-3), 2.50 (2H, t, ***J*** 7.4, H-2), 2.75 (2H, t, ***J*** 7.8, H-4), 3.93 (3H, s, OCH_3), 6.94 (2H, d, ***J*** 8.0, H-3′ and H-5′) and 6.99 (2H, d, ***J*** 8.0, H-2′ and H-6′). δ_C 26.6 (C-3), 33.7 (C-2), 34.2 (C-4), 55.3 (OCH_3), 113.9 (C-3′ and C-5′), 129.4 (C-2′ and C-6′) 130.5 (C-1′), 133.4 (C-4′) and 158.0 (C=O). (Found: C, 68.3, H, 7.3%; M^+ 194(20), 176(100). Calc. For $C_{11}H_{14}O_3$: C, 68.0, H, 7.2%; M 194).

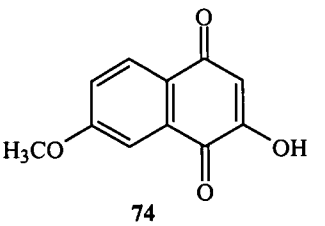
7-Methoxy-1-tetralone (73)



73

Treatment of the butyric acid **72** (5.0g, 25.8mmol) with polyphosphoric acid (50g) as described for the tetralone **67**, afforded a residue that was purified by column chromatography using EtOAc: Hexane (3:7) as eluent to afford tetralone **73** (3.21g, 70.8%) as pale yellow crystals, m.p. 56-59°C (from hexane). ν_{max} 1680 cm^{-1} (C=O); δ_H 2.09 (2H, m, H-3), 2.60 (2H, t, ***J*** 5.8, H-2), 2.88 (2H, t, ***J*** 5.8, H-4), 3.81 (3H, s, OCH_3), 7.03 (1H, dd, ***J*** 8.4 and 3.0, H-6), 7.15 (1H, d, ***J*** 8.4, H-5) and 7.49 (1H, d, ***J*** 3.0, H-8). δ_C 23.5 (C-3), 28.9 (C-2), 39.0 (C-4), 55.5 (OCH_3), 109.2 (C-6)[a], 121.7(C-5)[a], 129.9 (C-8)[a], 133.4 (C-4a)[b], 137.1 (C-8a)[b], 158.4 (C-7) and 198.3 (C=O). (Found: C, 75.3, H, 6.7%; M^+ 176(100), 120(50). Calc. for $C_{11}H_{12}O_2$: C, 75.0, H, 6.8%; M 176).

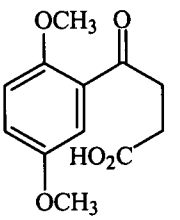
2-Hydroxy-7-methoxy-1,4-naphthoquinone (74)



74

Conversion of tetralone **73** (0.5g, 2.84mmol) into the corresponding hydroxyquinone **74** was achieved by following the same procedures as described for the synthesis of quinone **63**. The residue obtained upon workup afforded the hydroxyquinone **74** (0.621g) that was purified by column chromatography using EtOAc (100%) as the eluent. The quinone **74** (0.36g, 61%) was obtained as an orange solid, m.p. 160-163°C (from hexane). ν_{max} 3200-2700 cm^{-1} (broad) OH, 1672 and 1640 cm^{-1} (C=O), δ_H 3.95 (3H, s, OCH_3), 6.29 (1H, s, H-3), 7.25 (1H, dd, ***J*** 8.4 and 3.0, H-6), 7.55 (1H, d, ***J*** 3.0, H-8), and 8.05 (1H, d, ***J*** 8.4, H-5). δ_C 56.1 (OCH_3), 110.4 (C-5)[a], 110.7 (C-6)[a], 118.9 (C-8a)[b], 121.3 (C-8)[b], 129.1 (C-3)[b], 131.3 (C-4a)[b], 138.2 (C-2), 156.1 (C-7), 184.1 and 188.9 (C=O). (Found: C, 64.8, H 3.91%; M^+ 204(10), 176(60), 135(70). Calc, for $C_{11}H_8O_4$: C, 64.7, H, 3.94%; M 204).

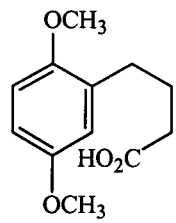
4-(2′,5′-Dimethoxyphenyl)-4-ketobutyric acid (46)



46

To a stirred solution of 1,4-dimethoxybenzene **45** (40g, 0.289mol) and succinic anhydride **3** (34.8g, 0.348mol) in nitrobenzene (240ml) was added anhydrous aluminium trichloride (92.6g, 0.695mol). The reaction mixture was stirred at O°C for 72h. After the usual workup as described for the keto acid **65**, the residue obtained upon workup afforded the crude acid **46** (56.33g), which was purified by column chromatography using EtOAc:Hexane (3:7) as the eluent to afford keto acid **46** (25.6g, 37%) as a light brown oil which later solidified and gave brown crystals, m.p. 98-100°C (from hexane), (lit.,[11] 101-101.5°C). ν_{max} 3300-2500 cm^{-1} (broad) OH, 1694 and 1657 cm^{-1} (C=O); δ_H 2.75 (2H, t, ***J*** 6.6, H-2), 3.34 (2H, t, ***J*** 6.6, H-3), 3.79 and 3.88 (each 3H, s, OCH_3), 6.91 (1H, d, ***J*** 9.2, H-3′), 7.05 (1, d, ***J*** 9.2 and 3.4, H-4′) and 7.34 (1H, d, ***J*** 3.4, H-6′). δ_C 28.6 (C-2), 38.7 (C-3), 55.9 and 56.2 (OCH_3), 113.3 (C-3′)[a], 114.0 (C-4′)[a], 120.9 (C-6′), 127.4 (C-1′), 153.6 (C-2′)[b], 153.7 (C-5′)[b], 178.1 and 199.3(C=O). (Found: C, 60.2, H 6.2%; M^+ 238(24), 165(100). Calc. for $C_{12}H_{14}O_5$: C, 60.5, H, 5.9%; M 238).

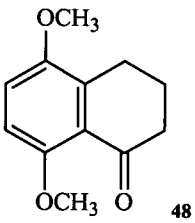
4-(2′,5′-Dimethoxyphenyl)butyric acid (47)



47

Clemmensen reduction of keto acid **46** (12.8g, 54mmol) with freshly prepared mossy zinc (28g, 0.428mol) in aqueous hydrochloric acid (40ml conc. HCl, 20ml water) and toluene (80ml) as described earlier, afforded the butyric acid **47** (9.70g, 81%) as brown crystals, m.p. 146-150°C (from hexane), (lit.,[11] 148-149°C). ν_{max} 3300-2500 cm^{-1} (broad) OH and 1708 cm^{-1} (C=O); δ_H 1.92 (2H, m, H-3), 2.37 (2H, t, ***J*** 7.2, H-2), 2.65 (2H, t, ***J*** 7.2, H-4), 3.76 and 3.77 (each 3H, s, OCH_3), 6.75 (3H, m, H-3′, H-4′ and H-6′). δ_C 24.8 (C-3), 29.6 (C-2), 33.5 (C-4), 55.8 and 55.9 (OCH_3), 111.3 (C-3′)[a], 111.4 (C-4′)[a], 116.5 (C-6′)[a], 130.9 (C-1′), 151.9 (C-2′)[b], 153.5 (C-5′)[b] and 179.8 (C=O). (Found: C, 64.1, H, 6.8%; M^+ 224(81), 164(100). Calc. for $C_{12}H_{16}O_4$: C, 64.3, H, 7.1%; M 224).

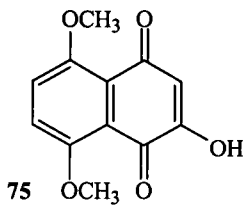
5,8-Dimethoxy-1-tetralone (48)



48

Treatment of butyric acid **47** (6.0g, 0.027mol) with polyphosphoric acid (60g) at 80°C for 1h, afforded after column chromatography using EtOAc:Hexane (3:7) as eluent, the tetralone **48** (4.89, 89%) as brown crystals, m.p. 50-54°C (from hexane), (lit.,[11] 53.5-54.5°C). ν_{max} 1732 cm^{-1} (C=O); δ_H 2.02 (2H, m, ***J*** 6.2, H-3), 2.59 (2H, t, ***J*** 6.2, H-2), 2.85 (2H, t, ***J*** 6.2, H-4), 3.79 and 3.84 (each 3H, s, OCH_3), 6.77 (1H, d, ***J*** 8.8, H-7), and 6.97 (1H, d, ***J*** 8.8, H-6). δ_C 22.3 (C-3), 23.7 (C-2), 40.8 (C-4), 56.1 and 56.4 (OCH_3), 110.1 (C-6)[a], 115.6 (C-7)[a], 123.2 (C-4a)[b], 135.4 (C-8a)[b], 150.3 (C-8)[c], 154.1 (C-5)[c], and 198.1 (C=O). (Found: C, 70.1, H, H, 8.2%; M^+ 206(90), 177(100), 163(32). Calc. for $C_{12}H_{16}O_3$: C, 69.9, H, 7.8%; M 206).

2-Hydroxy-5,8-dimethoxy-1,4-naphthoquinone (75)



75

Potassium tert-butoxide (0.872g, 7.77mmol) was added to a stirred solution of 5,8-dimethoxy-1-tetralone **48** (0.32g, 1.55mmol) and tert-butyl alcohol (16ml) saturated with oxygen, and the resulting solution was stirred for 45min while oxygen was bubbled through. The workup procedure is similar to that described for the synthesis of *hydroxyquinone* **63**. The residue obtained upon workup was purified by column chromatography using EtOAc (100%) as eluent to afford quinone **75** (0.20g, 55.1%) as orange crystals, m.p. >300°C (decomp.) (from ethanol). ν_{max} δ_H 3.96 and 4.00 (each 3H, s, OCH_3), 6.21 (1H, s, H-3), 7.27 (1H, d, ***J*** 9.4, H-7) and 7.42 (1H, d, ***J*** 9.4, H-6). δ_C 56.8 and 57.3 (OCH_3), 110.7 (C-6)[a], 119.0 (C-7)[a], 123.6 (C-3), 132.6 (C-4a)[b], 138.2 (C-8a)[b], 147.8 (C-2), 151.8 (C-8)[c], 153.9 (C-5)[c], 181.3 and 184.1 (C-1 and C-4). (Found: C, 61.8; H, 4.3%; M^+ 234. Calc. for $C_{12}H_{10}O_5$: C, 61.5; H, 4.1; M 234).

Results and Discussion

Clemmenson Reduction of **46**, **65** and **71**, resulted in the loss of the carbonyl groups and the appearance of a $-CH_2-$ group; this is evident in both the ^{1}H-nmr and infrared spectra of the butyric acids **47**, **66** and **72**. Similarly, a loss of 14 atomic mass units is found to occur in the mass spectra of the above mentioned butyric acids; this is indicative of the disappearance of an oxygen atom to be replaced by two hydrogen atoms. The appearance of sets of two-proton triplets in the region of 2.61 to 2.75ppm is the result of the methylene groups of the butyric acids. Cyclisation of **47**, **66**, and **72** using polyphosphoric acid, resulted in the loss of 18 atomic mass units; indicative of loss of a water molecule. Evidence thereof is found in the mass spectra of the corresponding tetralones **48**, **67** and **73**. Additionally the infrared spectra showed the absence of the hydroxyl groups of the butyric acids. Oxidation of tetralones **48**, **67** and **73** with potassium tertiary butoxide in tert-butyl alcohol, afforded the *hydroxynaphthoquinones* **63** (58%), **74** (61%) and **75** (55%). An increase of 28 atomic mass units for the molecules viz. $C_{12}H_{10}O_5$ requires 234; found 234; $C_{13}H_{12}O_6$ requires 264; found 264 and $C_{11}H_8O_4$ requires 204; found 204. The ^{1}H-nmr spectra of **63**, **74** and **75**, all indicated the disappearance of the unsaturated alkane ring and the appearance of a singlet quinonoid hydrogen atom in the region of 6.29 to 6.92 ppm.

Conclusion

The yields throughout the two synthetic procedures, scheme **19** and **20** were low. In order to improve the yields during the various stages of the synthetic protocol, the following modifications were introduced:

(i) Formation of the keto butyric acids **46** and **71** under Friedel-Crafts Acylation conditions: Instead of allowing the reaction mixture to stir at O°C for 3 days, it was allowed to stir at O°C for 24h followed by stirring at room temperature for 48h. Also an excess of 2 moles of succinic anhydride was added.

(ii) Formation of the butyric acids **47**, **66** and **72** using the Clemmenson Reduction protocol: The use of freshly prepared mossy zinc resulted in an increase in the yield of the butyric acids **47**, **66** and **72** (from an average of 45% to 86%).

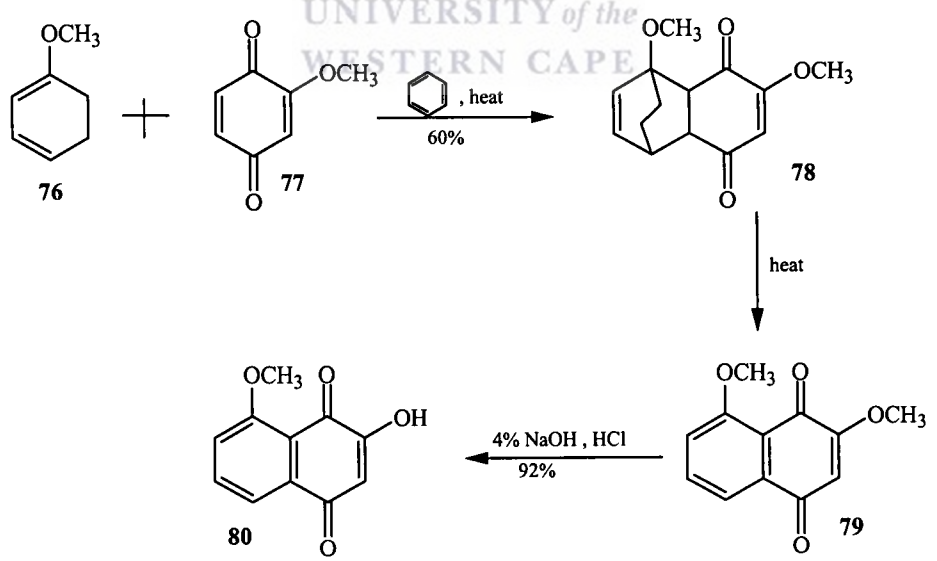
(iii) Preparation of tetralones **48**, **67** and **73**: The reaction mixture was allowed to stir for 45 to 50 min, instead of 30min at 80°C.

(iv) *Hydroxyquinones* **63**, **74** and **75**: Best results were obtained when doing the procedure in batches of 1.0g only.

CHAPTER 3

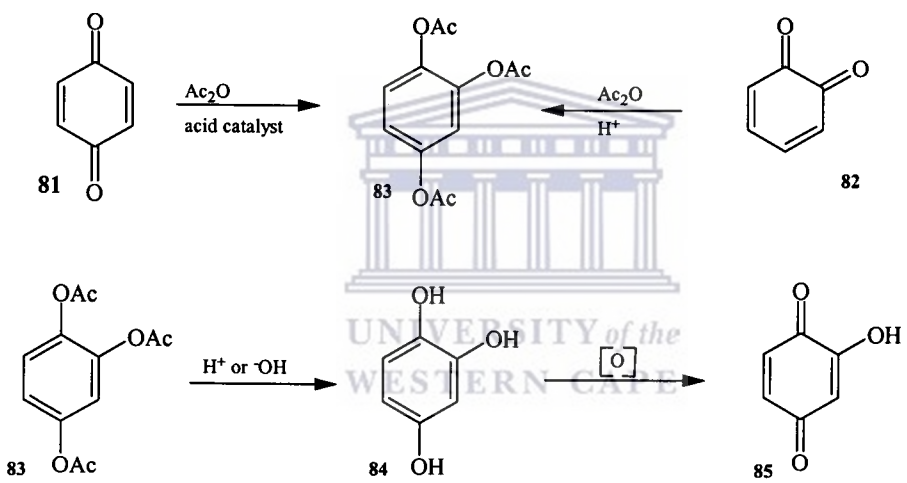
Synthesis of 2-Hydroxy-8-methoxy-1,4-naphthoquinone via a Diels-Alder reaction protocol.

Giles and Roos[19] reported the synthesis of the adduct **78** via Diels-Alder reaction involving the diene **76** and the quinone **77**. Enolization and oxidation of **78**, followed by pyrolysis resulted in the loss of the ethylene bridge to form the *naphthoquinone* **79**. Treatment of **79** with aqueous base resulted in the hydrolysis to afford the corresponding 2-hydroxy-8-methoxy-1,4-naphthoquinone **80** in a 92% yield for the last step (Scheme 21).



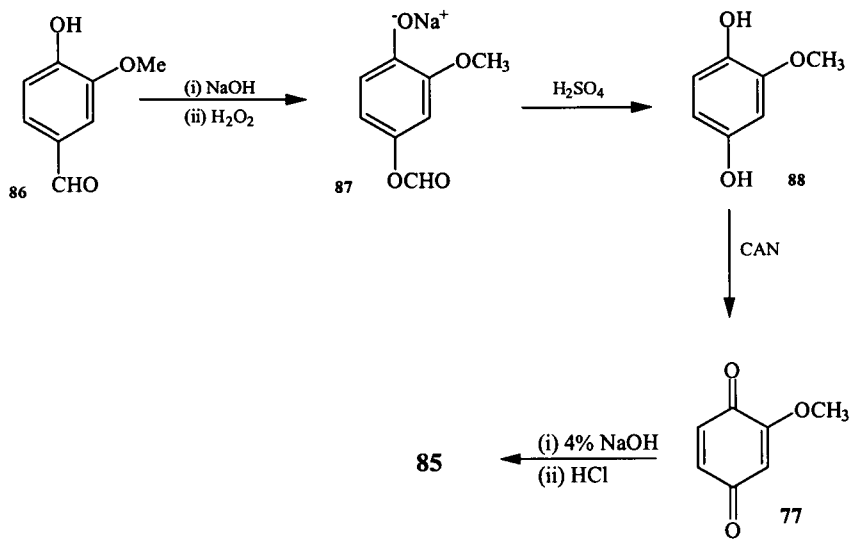
Scheme 21

In 1972, McOmie et al.[20] reported the synthesis of 2-hydroxy-1,4-benzoquinone **85** via the Thiele-Winter acetoxylation process, a reaction in which 1,4- or 1,2-benzoquinone **81** and **82** reacted with acetic anhydride, in the presence of an acid catalyst to afford a triacetoxy derivative **83**. The triacetoxy **83** was hydrolyzed under either basic or acidic conditions to yield the triol **84** that was oxidized to afford the desired *hydroxyquinone* **85** (Scheme 22). Best results were obtained when sulphuric acid and boron trifloroetherate were used as acid catalysts.[20,21] In 1997, Villemin et al.[22] reported that trifluorosulphonic acid proved to be a more effective catalyst compared to sulphuric acid and boron trifloroetherate.



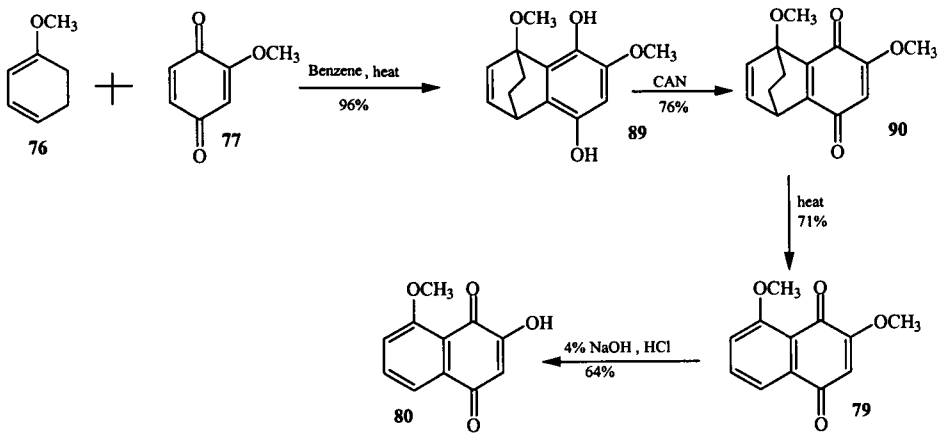
Scheme 22

Baeyer-Villiger[23] methodology has also been effectively used to synthesize precursors for conversion into *hydroxyquinones*. Thus Baeyer-Villiger[23] oxidation of vanillin **86** with alkaline hydrogen peroxide produced the intermediate formyl ester **87**, which upon acid hydrolysis afforded diol **88**. Cerium(IV) ammonium nitrate oxidation of this diol **88** produced the base labile 2-methoxybenzoquinone **77**. Removal of the methyl group was effected under basic conditions to yield 2-hydroxybenzoquinone **85** and is shown in Scheme 23.



Scheme 23

Having quinone **77** in hand, a Diels-Alder condensation between it and diene **76** was effected in boiling benzene and the crude product, presumably **78**, when passed through the column containing silica gel was enolized to afford the anthraquinol **89** in an overall yield of 96%. Evidence for the enolization was found in the infrared spectrum, showing a broad absorption at 3400-2500cm^{-1} for the hydroxyl groups; two D_2O exchangeable hydrogens in the ^{1}H-nmr spectrum at 4.48 and 8.69ppm and the absence of the C=O carbon atoms in the ^{13}C-nmr spectrum. Oxidation of the diol **89** was affected with cerium(IV) ammonium nitrate to afford the bridged quinone **90** in 76%. Pyrolysis of quinone **90** afforded quinone **79**, which was demethyated at C-2 under basic conditions to produce the desired *hydroxyquinone* **80** in an overall yield of 45% for the last two steps. In subsequent procedures, the crude product obtained from pyrolysis of **90** was treated with base to afford **80** in an improved yield of 64% (Scheme 24).

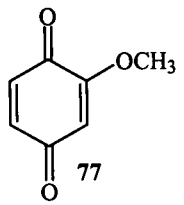


Scheme 24

Experimental

^{1}H and ^{13}C NMR spectra were recorded using a Varian 200MHz spectrometer at 20°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 on a Finnigan-Matt GCQ instrument. 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°-75°C. In ^{13}C-spectra, assignments with the same superscript may be interchanged.

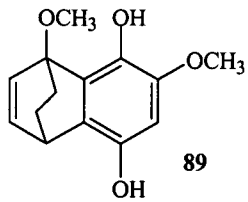
2-Methoxy-1,4-benzoquinone (77)



77

Vanillin, **86**, (1g; 6.58mmol) was dissolved in aqueous sodium hydroxide (15ml of a 4% solution). Hydrogen peroxide (3ml of a 30% solution in 15ml water) was slowly dripped in with stirring. The resulting solution was stirred for 1h and thereafter acidified with sulphuric acid (3.6ml of a 20% solution). The acidic solution was cooled and extracted with ether (3×50ml), which was evaporated to dryness and the resulting oil dissolved in water (10ml). To this solution, sulphuric acid (4ml of a 20% solution) was added, and the resulting mixture then added dropwise to a stirred solution of sodium dichromate (1.6g in 10ml water) at 5°C. After an addition of ice (20g), a yellow precipitate formed. Stirring was continued for 25min and the mixture then extracted with dichloromethane (3×60ml). The residue obtained upon workup afforded the quinone **77** (0.31g; 49%); as a brown solid, m.p. 140-143°C. ν_{max} 3200–2500 cm^{-1} (broad) OH, 1695 and 1745 cm^{-1} (C=O). δ_H 3.83 (3H, s, OCH_3), 5.94 (1H, d, ***J*** 14.4, H-2), 6.70 (2H, m, H-5 and H-6). (Found: C, 60.5; H, 4.3%; M^+ 138. Calc. for $C_7H_6O_3$: C, 60.9; H, 4.5%; M 138).

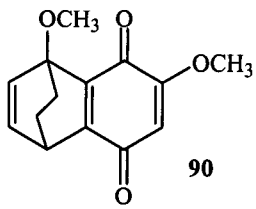
1,4-Dihydro-1,7-dimethoxy-1,4-ethanonaphthalene-5,8-diol (89)



89

1-Methoxycyclohex-1,3-diene **76** (6.4g; 58.2mmol) was heated under reflux in benzene (100ml), containing **77** (3.0g; 21.7mmol) for 1.5h, at which stage all the quinone was consumed. The solvent was evaporated off and the residue chromatographed using EtOAc: Hexane (3:7) as eluent to give the product **89**, as white crystals (2.8g; 96%), m.p. 108-110°C. ν_{max} 3400- 2500 cm^{-1} (broad) OH; δ_H 1.59 (4H, m, $-CH_2CH_2-$), 2.01 (1H, m, H-4), 3.67 and 3.77 (each 3H, s, OCH_3), 4.48 (1H, s, 5-OH), 6.22 (1H, s, H-6), 6.49 (1H, dd, ***J*** 8.2 and 5.8, H-3), 6.65 (1H, dd, ***J*** 8.2 and 1.4, H-2) and 8.69 (1H, s, 8-OH). δ_C 26.0 $(CH_2)^a$, 28.3 $(CH_2)^a$, 32.3 (C-4), 52.2 and 56.5 (OCH_3), 86.3 (C-1), 99.2 (C-6), 120.4 (C-4a)^b, 127.7 (C-8a)^b, 134.3 (C-2)^c, 134.8 (C-3)^c, 136.8 (C-8)^d, 141.1 (C-5)^d and 146.2 (C-7)^d. (Found: C, 68.0; H, 6.1%; M^+ 248 (2), 220 (100), 205 (70). Calc. for $C_{14}H_{16}O_4$: C, 67.7; H, 6.5%; M 248).

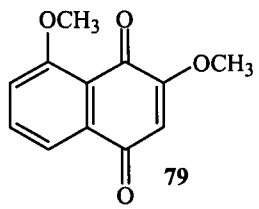
1,4-Dihydro-1,7-dimethoxy-1,4-etahnonaphthalene-5,8-dione (90)



90

To a stirred solution of adduct **89** (2.4g; 10mmol) in acetonitrile (60ml) and water (10ml), was added dropwise a solution of cerium(IV) ammonium nitrate (10.96g; 20mmol) in water (10ml). Stirring was continued for an additional 30min, followed by the addition of water (400ml) and then extraction with dichloromethane (3×50ml). The residue obtained upon workup afforded quinone **90** (1.8g; 76%), as an olive-green solid, m.p. 114-117°C (from ethanol); (lit.,[18] 117-119°C). ν_{max} 1668 and 1745 cm^{-1} (C=O), δ_H 1.60 (4H, m, $-CH_2CH_2-$), 2.02 (1H, m, H-4), 3.67 and 3.78 (each 3H, s, OCH_3), 6.22 (1H, s, H-6), 6.50 (1H, dd, ***J*** 8.2 and 5.8, H-3) and 6.65 (1H, dd, ***J*** 8.2 and 1.0, H-2). (Found: C, 68.3; H, 5.3%; M^+ 246 (60). Calc. for $C_{14}H_{14}O_4$: C, 68.5; H, 5.7%; M 246).

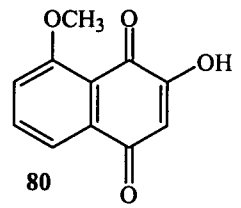
2,8-Dimethoxy-1,4-naphthoquinone (79)



79

The crude quinone **90** (1.8g; 8.25mmol), was pyrolysed at 140°C, under an atmosphere of nitrogen for 30min to afford the naphthoquinone **79** (1.13g; 71%) as green crystals; m.p. 198-201°C (from ethanol), (lit.,[18] 202-202.5°C). ν_{max} 1670 and 1695 cm^{-1} (C=O), δ_H 3.86 and 3.99 (each 3H, s, OCH_3), 6.08 (1H, s, H-3), 7.25 (1H, dd, ***J*** 8.0 and 1.8, H-7), 7.66 (1H, t, ***J***, 8.0, H-6) and 7.73 (1H, dd, ***J*** 8.0 and 1.8, H-5). δ_C 56.5 and 56.6 (OCH_3), 108.0 (C-7), 117.5 (C-3)[a], 119.0 (C-6)[a], 119.1 (C-5)[a], 134.5 (C-4a)[b], 135.4 (C-8a)[b], 160.3 (C-2)[c], 161.2 (C-8)[c], 178.6 and 184.8 (C=O). (Found: C, 59.3; H, 3.9%; M^+ 218 (80), 203 (100). Calc. for $C_{12}H_{10}O_4$: C, 59.5; H, 4.1%; M 218).

2-Hydroxy-8-methoxy-1,4-naphthoquinone (80)



80

The naphthoquinone **79** (1.0g; 4.6mmol) in aqueous 4% sodium hydroxide (20ml) was stirred until it had dissolved. The solution was washed with ether and then acidified with 5M hydrochloric acid. The resulting solution was extracted with dichloromethane (3×50ml), and the residue afforded the quinone **80** (0.6g; 64%) as a yellow solid; m.p. 211-214°C (decomp.), (from ethanol); [lit.,[18] 209-211°C (decomp.)]. ν_{max} 3200-2700 cm^{-1} (broad) OH, 1670 and1687 cm^{-1} (C=O). δ_H 4.05 (3H, s, OCH_3), 6.29 (1H, s, H-3), 7.27 (1H, dd, ***J*** 7.2 and 2.2, H-7), 7.73 (1H, t, ***J*** 7.2, H-6) and 7.79 (1H, dd, ***J*** 7.2 and 2.2, H-5). δ_C 56.6 (OCH_3), 108.6 (C-7), 117.0 (C-3)[a], 117.1 (C-6)[a], 119.7 (C-5)[a], 139.4 (C-4a)[b], 136.9 (C-8a)[b], 156.9 (C-2)[c], 160.5 (C-8)[c], 180.2 and 184.7 (C=O). (Found: C, 65.0; H, 3.9%; M^+ 204(60), 186(30). Calc. for $C_{11}H_8O_4$: C, 64.7; H, 3.95%; M 204).

Results and Discussion

Assignment of the adduct **89**, is based on the ^{1}H-nmr spectrum; a four-proton multiplet at δ1.59 for the ethylene bridge; a one-proton multiplet at δ2.01 for the H-4, two one-proton singlet peaks at δ4.48 and δ8.69 for the 5-OH and 8-OH respectively. Strong O-H stretching frequencies at ν_{max} 3305 and 2910 cm^{-1} can be seen in the infrared spectrum of **89**. Oxidation of **89** with cerium(IV) ammonium nitrate resulted in the formation of the quinone **90**, i.e. the disappearance of the hydroxyl groups in both ^{1}H-nmr and infrared spectra is evident. The appearance of strong carbonyl absorption bands at ν_{max} 1668 and 1745 cm^{-1} in the infrared spectrum, proved that oxidation of the diol **89** to the corresponding quinone **90** took place. Pyrolysis of **90** at 140°C under nitrogen, resulted in the loss of the ethylene bridge to afford quinone **79**. Evidence thereof is shown in the ^{1}H-nmr and mass spectra to confirm the molecular structure $C_{12}H_{10}O_4$. The disappearance of the ethylene bridge at δ1.59 together with the shift of the one-proton multiplet at δ2.01 to a dd at δ7.73 with ***J*** 8.0 and 1.8 Hz for H-5; proved to be sufficient evidence for the structure of quinone **79**. Demethylation of **79** using 4% sodium hydroxide afforded the hydroxyquinone **80**, in a 64% yield. The disappearance of one methoxy group at δ3.86 together with the appearance of a strong O-H group stretching frequency at ν_{max} 3200-2700 cm^{-1} lead to the confirmation of compound **80**.

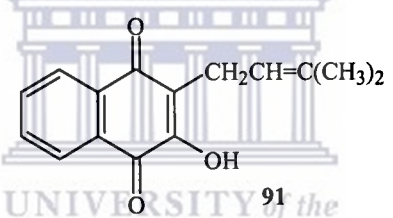
Conclusion

Employing the methods of Baeyer-Villiger[23] oxidation of vanillin **86**, together with Giles and Roos's[19] Diels-Alder methodology, proved to be effective for the synthesis of quinone **80**. An increase in the yield of quinone **78** (60 – 78%) was obtained before passing through the column containing silica gel, which resulted in the enolization of quinone **78** to form the diol **89** in a 96% yield. Compared to Giles and Roos's[19] 92% reported yield of quinone **80**, only a 64% yield of **80** was obtained.

CHAPTER 4

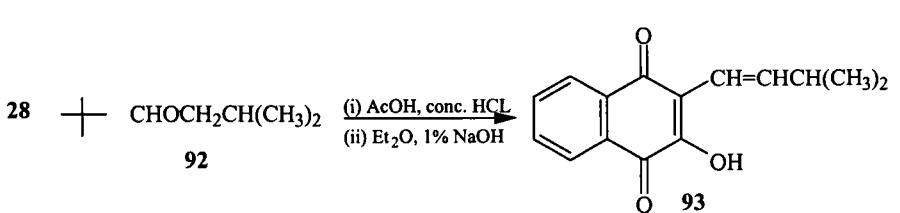
Condensation of aldehydes with 2-Hydroxy-1,4-naphthoquinones under acidic and basic conditions.

In investigating routes towards the synthesis of Lapachol, **91**, Hooker [24] in 1896 studied the acid catalyzed condensation reaction between isovaleraldehye **92**, and *2-hydroxy-1,4-naphthoquinone* **28**. He obtained a compound **93**, isomeric with Lapachol **91**, which he was able to convert into several substances, which he had previously obtained from Lapachol itself (Scheme 25).

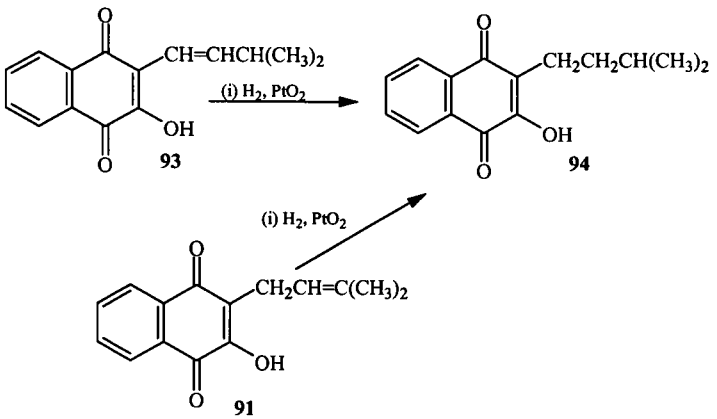


91

2-Hydroxy-1,4-naphthoquinone **28**, was treated with isovaleraldehyde **92** at 80°C to yield Isolapachol **93** (Scheme 25). Catalytic hydrogenation of **93** with Adam's catalyst, afforded hydrolapachol **94**; a product also obtained under the same conditions from the natural product, Lapachol **91** (Scheme 26).

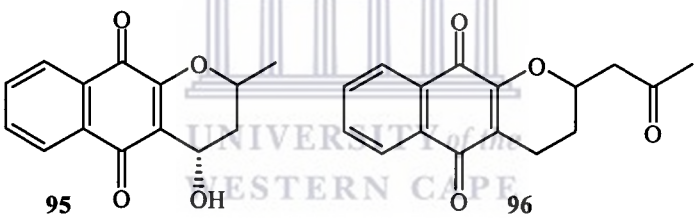


Scheme 25



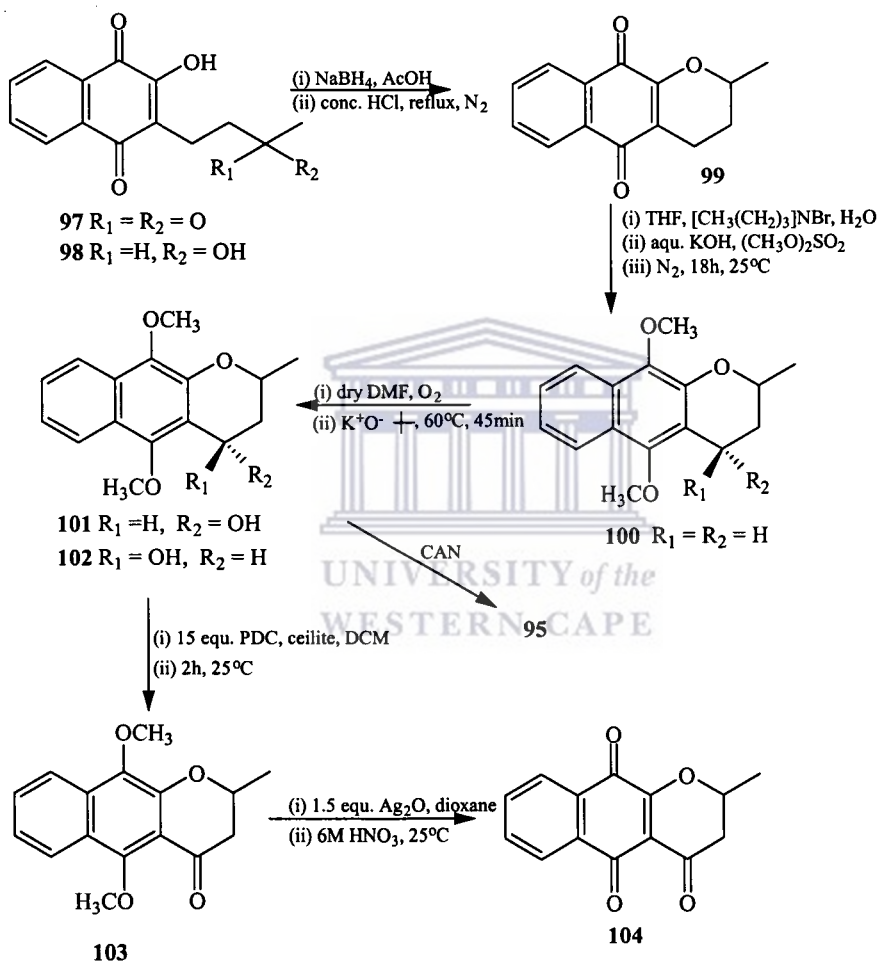
Scheme 26

In 1998, Joanne Ireland et al.[25] synthesized a number of *naphtho[2,3-b]pyranquinones* viz. **95**, **96** and **104** related to the antibiotic *Erythrostominone* **60**[18].



Ireland et al.[25] in their synthesis of **95** and **96,** reduced the hydroxyquinone **97**[26] with sodium borohydride in ethanol to afford the alcohol **98**, which was treated without purification, with concentrated hydrochloric acid and acetic acid under reflux to afford the quinone **99**. Reductive methylation of **99** with a phase transfer catalyst gave the dimethyl ether **100**. Treatment of **100** with potassium tert-butoxide in dry dimethylformamide under a stream of dry oxygen, resulted in the hydroxylation of C-4 of **100**, resulting in the formation of an inseparable mixture of the 4S- and 4R-hydroxynaphthopyrans **101** and **102**. Treatment of the 4-hydroxynaphthopyrans **101** and **102** with aqueous cerium(IV) ammonium nitrate afforded the quinone **95** (90%), in a ratio of (83:17) for the 4S and 4R isomers respectively. Similarly oxidation of the

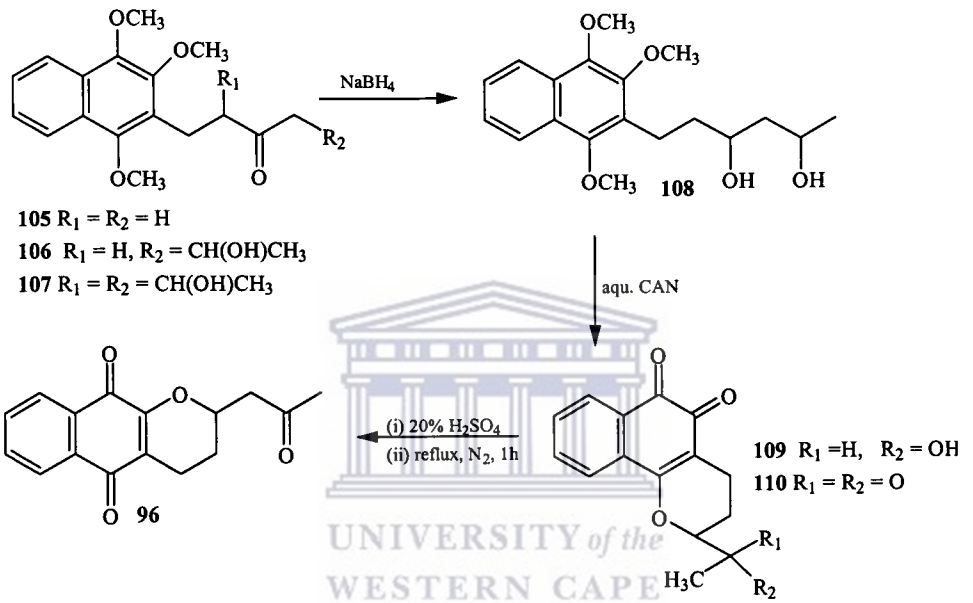
pyrans **101** and **102** with pyridium dichromate in dichloromethane afforded a mixture of the 4-oxonaphthopyran **103** and 4S-hydroxynaphthopyranquinone **101**. Treatment of **103** with silver oxide in 6M sulphuric acid, gave the desired quinone **104** (Scheme 27).



Scheme 27

On the other hand, addition of freshly prepared lithium diisopropyl amine to naphthalene **105**[27] at –78°C, followed by pre-cooled acetaldehyde resulted in the formation of a mixture of the hydroxyketone **106** and the bis-addition adduct **107** in a ratio of (73:27). Reduction of **106** with sodium borohydride in methanol-

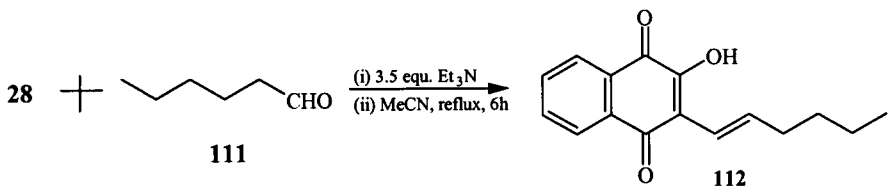
tetrahydrofuran afforded the diol **108**, which upon oxidation with cerium(IV) ammonium nitrate afforded the angular *ortho* quinone **109**. Oxidation of the secondary alcohol in the side chain of **109** with pyridinium dichromate gave the ketone **110**. Isomerisation of **110** into the pyran **96** was accomplished by heating under reflux in sulphuric acid (see Scheme 28).



Scheme 28

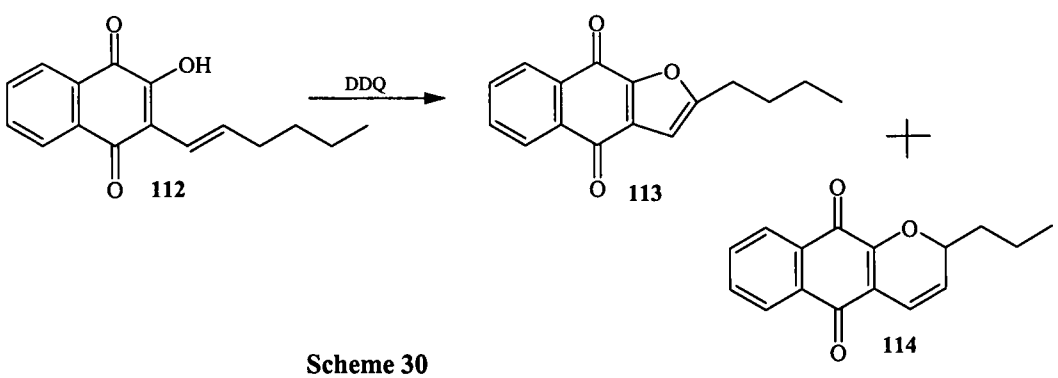
The condensation product formed between caproaldehyde **111** and *2-hydroxy-1,4-naphthoquinone* **28**, served as the starting material for Green et al.[28] in their research directed towards the synthesis of naphthopyrans related to *Erythrostominone* **60**[18], and their evaluation for biological activity. Base catalyzed conditions were employed since acid labile aldehyde diacetals were used in the research process. Condensation between **111** and **28** was carried out under both acidic and basic conditions and the results of the condensation product **112** were 38% for hydrochloric acid and 43% for triethylamine catalysis. Green et al.[28] reported: "Best yields of the desired product **112** were obtained when a solution containing 3.5 equivalents of triethylamine and 1.5 equivalents of caproaldehyde **111**, was dripped into a refluxing solution of 1

equivalent of the quinone **28** in acetonitrile and reflux maintained for a maximum of 6 hours." (Scheme 29)



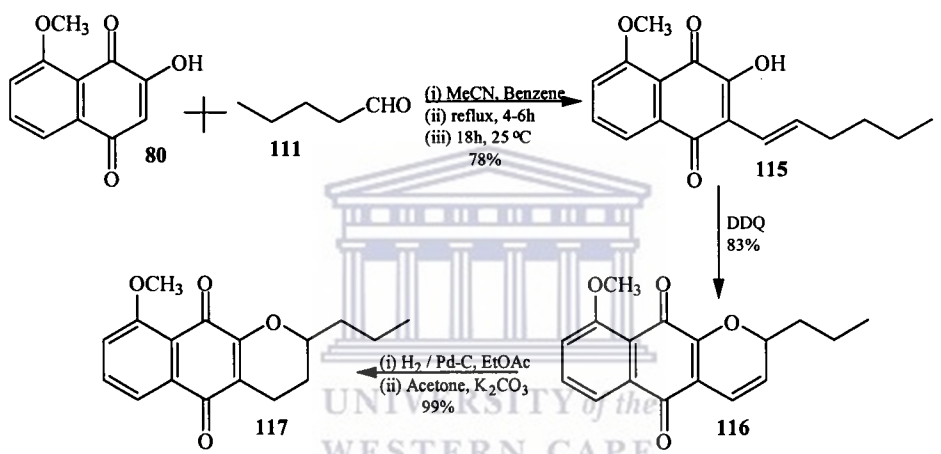
Scheme 29

In their endeavors to synthesize *naphthopyranquinones*, related to *Erythrostominone* **60**[18], Giles et al.[29] cyclised the alkenylnaphthoquinone **112**[28] using dichlorodicyanobenzoquinone. Thus, a mixture of quinone **112** and 1.2 mole equivalents of dichlorodicyanobenzoquinone in benzene at 60°C afforded two products viz. the naphthofuranquinone **113** (70%) and the *naphthopyranquinone* **114** (5%). Repeating the reaction at 25°C, lead to an increase in the desired product **114** (42%) and a decrease in the yield of **113** (43%). It was found that by lowering the temperature to 7°-8°C and extending the stirring period to 36h; formation of the desired *naphthopyranquinone* **114** was the sole product (78%) (Scheme 30).



Scheme 30

Aldehyde condensation reactions between quinone **80** and caproaldehyde **111** in acetonitrile and benzene, resulted in the formation of alkenylnaphthoquinone **115**, in a 78% yield. Cyclisation of **115** with 1.2 equivalents of dichlorodicyanobenzoquinone in benzene lead to the formation of *naphthopyranquinone* **116** (83%), as the sole product. Catalytic hydrogenation of **116** with palladium-charcoal in ethyl acetate afforded the pyran **117**, which was purified by column chromatography using EtOAc:Hexane (3:7) as eluent to afford quinone **117**, in a 99% yield (Scheme 31).

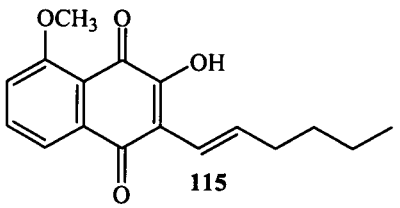


Scheme 31

Experimental

^{1}H and ^{13}C NMR spectra were recorded using a Varian 200MHz spectrometer at 20°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 on a Finnigan-Matt GCQ instrument. 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°-75°C. In ^{13}C-spectra, assignments with the same superscript may be interchanged.

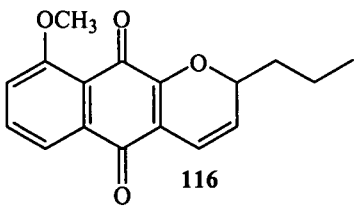
2-Hydroxy-8-methoxy-3-(1′-hexenyl)-1,4-naphthoquinone (115)



115

Caproaldehyde **111** (1.0g; 0.7ml; 10mmol) was added to a stirred mixture of quinone **80** (1.0g; 4.9mmol) in acetonitrile (25ml) over 3 min after which triethylamine (1.0g; 1.4ml; 10mmol) was added dropwise to the reaction mixture and allowed to stir for 4-6h under reflux in an atmosphere of nitrogen. After 12h stirring at 65°C the mixture was evaporated to obtain a dark red oil, which was taken up in acetonitrile (20ml) and ether (200ml) and washed with 0.5M sulphuric acid (±50ml). The residue obtained upon workup of the organic layer, was purified using column chromatography with EtOAc:Hexane (3:7) as eleuent. The quinone **115** (1.10g; 78%) was obtained as a dark red solid; m.p. 153°-155°C (from hexane-ethyl acetate). ν_{max} 3200-2500 cm^{-1} (broad) OH, 1685 and 1735 cm^{-1} (C=O). δ_H 0.92 (3H, t, ***J*** 7.0, H-6′), 1.42 (4H, m, H-4′ and H-5′), 2.30 (2H, m, H-3′), 4.03 (3H, s, OCH_3), 6.56 (1H, dt, ***J*** 16.6 and 1.4, H-1′), 7.02 (1H, dt, ***J*** 16.6 and 7.0, H-2′), 7.23 (1H, dd, ***J*** 7.6 and 1.4, H-7), 7.73 (1H, t, ***J*** 7.6, H-6), 7.80 (1H, dd, ***J*** 7.6 and 1.4, H-5) and 8.17 (1H, s, 2-OH). δ_C 14.0 (C-6′), 22.4 (C-5′), 31.4 (C-4′), 34.7 (C-3′), 56.6 (OCH_3), 116.8 (C-7)[a], 116.9 (C-3)[a], 118.5 (C-2′)[a], 120.0 (C-6)[a], 135.2 (C-4a)[b], 136.4 (C-8a)[b] and (C-1′)[b], 143.1 (C-5)[b], 151.9 (C-2), 159.9 (C-8), 180.0 and 184.2 (C=O). (Found: C, 71.3; H, 6.3%; M^+ 286(38), 229(100). Calc. for $C_{17}H_{18}O_4$: C, 71.0; H, 6.2%; M 286).

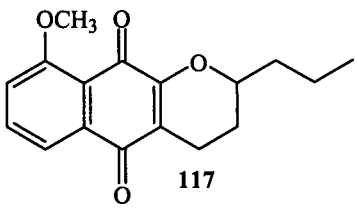
8-Methoxy-2-(1′-propyl)-3,4-dehydronaphtho[2,3-b]pyran-5,10-dione (116)



116

To a solution of quinone **115** (0.227g; 0.794mmol) in benzene (3ml), 1.2 equivalents of dichlorodicyanobenzoquinone (0.216g; 0.951mmol) in benzene (3ml) was added. Allow to stir at 25°C for 2h; filter and evaporate the filtrate to obtain a residue which was purified by column chromatography using EtOAc:Hexane (3:7) as eluent, to afford the pyranquinone **116** (0.187g; 83%) as an orange-brown solid; m.p. 45°-48°C. ν_{max} 1667cm^{-1} ; δ_H 0.94 (3H, t, ***J*** 7.0, H-3′), 1.50 (2H, m, H-2′), 1.65 (2H, m, H-1′), 3.99 (3H, s, OCH_3), 5.15 (1H, m, H-2), 5.74 (1H, dd, ***J*** 10.0 and 3.8, H-3), 6.66 (1H, dd, ***J*** 10.0 and 1.6, H-4), 7.24 (1H, dd, ***J*** 7.5 and 1.4, H-8), 7.64 (1H, t, ***J*** 7.5, H-7) and 7.75 (1H, dd, ***J*** 7.5 and 1.4, H-6).δ_C 13.9 (C-3′), 17.6 (C-2′), 37.8 (C-1′), 56.6 (OCH_3), 77.9 (C-2), 116.9 (C-8)[a], 117.6 (C-6)[a], 119.2 (C-3)[a], 124.2 (C-4a)[a], 2×125.4 (C-7and C-5a)[a], 134.0 (C-10a)[a], 135.2 (C-4)[a], 153.9 (C-9a)[a], 159.9 (C-9)[a], 178.6 and 181.7 (C=O). (Found: C, 71.8; H, 5.3%; M^+ 284. Calc. for $C_{17}H_{15}O_4$: C, 71.5; H, 5.6%; M 284).

8-Methoxy-2-(1′-propyl)naphtho [2,3-b]pyran-5,10-dione (117)



117

Quinone **116** (30mg; 0.106mmol) in ethyl acetate (20ml) and palladium-charcoal (10mg), was hydrogenated until 2 moles of hydrogen was absorbed. The solution was filtered and the solvent removed. The residue obtained upon workup was purified by column chromatography using EtOAc: Hexane (3:7) as eluent to afford the pyranquinone **117** (30mg; 99%); m.p. 78°-81°C. ν_{max} 1672 cm^{-1}; δ_H 0.96 (3H,t, ***J*** 7.0, H-3′), 1.64 (2H, m, H-2′), 2.04 (2H, m, H-1′), 2.42 (1H, ddd, ^{2}***J*** 18.8, ^{3}***J*** 9.6 and 6.4, 3-Ha), 2.49 (1H, ddd, ^{2}***J*** 18.8, ^{3}***J*** 9.6 and 6.2, 3-He), 2.63 (1H, ddd, ^{2}***J*** 18.4, ^{3}***J*** 6.2 and 4.4, 4-Ha), 2.68 (1H, ddd, ^{2}***J*** 18.2, ^{3}***J*** 5.8 and 4.4, 4-He), 3.97 (3H, s, OCH_3), 4.08 (1H, m, H-2), 7.21 (1H, dd, ***J*** 8.2 and 1.4, H-8), 7.61 (1H, t, ***J*** 8.4, H-7) and 7.73 (1H, dd, ***J*** 8.2 and 1.4, H-6). δ_C 14.0 (C-3′), 18.0 (C-2′), 18.6 (C-1′), 25.5 (C-3), 36.5 (C-4), 55.6 (OCH_3), 77.9 (C-2), 117.3 (C-8), 119.0 (C-7)[a], 2×119.2 (C-5a and C-4a)[a], 134.6 (C-9a)[a], 134.9 (C-6)[a], 156.3 (C-10a)[a], 159.9 (C-9), 178.6 and 184.4 (C=O). (Found: C, 71.7; H, 6.3%; M^+ 286(25), 216(100). Calc. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.5%; M 286).

Results and Discussion

The aldehyde condensation reaction between *hydroxyquinone* **80** and caproaldehyde **111** afforded the quinone **115** as a dark red oil, in a 45% yield. An increase of up to 78% was obtained by allowing the reaction mixture to stir overnight at ambient temperature after refluxing under nitrogen was completed. Cyclisation of quinone **115** with dichlorodicyanobenzoquinone in benzene afforded the naphthopyran **116**, in 83%. Apart from a decrease of two atomic mass units for the mass of the molecule viz. $C_{17}H_{16}O_4$ requires 284; found 284, compared to the starting material **115**, the ^{1}H-nmr spectrum indicated that cyclisation had occurred by the absence of the hydroxyl group at 8.19 ppm. A shift in the two one-proton signals at 6.56ppm (***J*** 16.6 and 1.4) and at 7.02ppm (***J*** 16.6 and 7.0) of the hexenyl side-chain to (a more shielded environment) of two one-proton signals as dd at 5.74ppm (***J*** 10.0 and 3.8) and 6.66ppm (***J*** 10.0 and 1.6) of H-3 and H-4 of the pyran ring also shows evidence that cyclisation had occurred. A 40% yield of the crude naphthopyran **116** was obtained. Allowing the reaction to stir and heat for 2h resulted in an increase in yield to 83% yield of **116**.

Catalytic hydrogenation of **116** afforded the reduced pyran **117** in a 99% yield. Reduction of the double bond is evident in the ^{1}H-nmr spectrum, in which a shift from 5.74ppm of H-3 and 6.66ppm of H-4 occurred to a more shielded region of the unsaturated alkanes where the chemical environment of the hydrogens of H-3 and H-4 became different i.e. pseudo-axial and pseudo-equatorial hydrogens. Thus, the change of a dd at 5.74ppm to a ddd at 2.50ppm (^{2}***J*** 18.8) and (^{3}***J*** 9.6 and 6.2) for 3-Ha and 3-He. Similarly a shift from a dd at 6.66ppm to a ddd at 2.42 (^{2}***J*** 18.2) and (^{3}***J*** 6.2, 5.8 and 4.4), for 4-Ha and 4-He respectively. A COSY spectrum also showed a clear connectivity between pseudo 3-H axial and 3-H equatorial hydrogens, as well as between the pseudo 4-H axial and 4-H equatorial hydrogens. Connectivity between the pseudo 3-Ha and 3-He hydrogens with the pseudo 4-Ha and 4-He was also shown. This confirmed the conformation of the structure, together with the mass

spectrum in which an increase of two atomic mass units of the molecule viz. $C_{17}H_{18}O_4$ requires 286; found 286.

Conclusion

The reaction containing caproaldehyde **111** and quinone **80** was monitored until completion by t.l.c. After 4h, an excess of starting material was still present, thus an excess of triethylamine was added and the reaction mixture stirred for an additional 2h under reflux in an atmosphere of nitrogen. The result; an increase in the yield from 30% to 78% of quinone **115** was observed.

Allowing the reaction mixture containing quinone **115** in benzene and dichlorodicyanobenzoquinone to stir at 55°C – 65°C for 2h, the pyranquinone **116** (83%) was obtained as the sole product. Catalytic hydrogenation of quinone**116** with palladium-charcoal in ethyl acetate afforded the pyran **117** (99%) after 12h of stirring at ambient temperature. The reaction was monitored by t.l.c. until hydrogenation of quinone **116** was completed.

Chapter 5

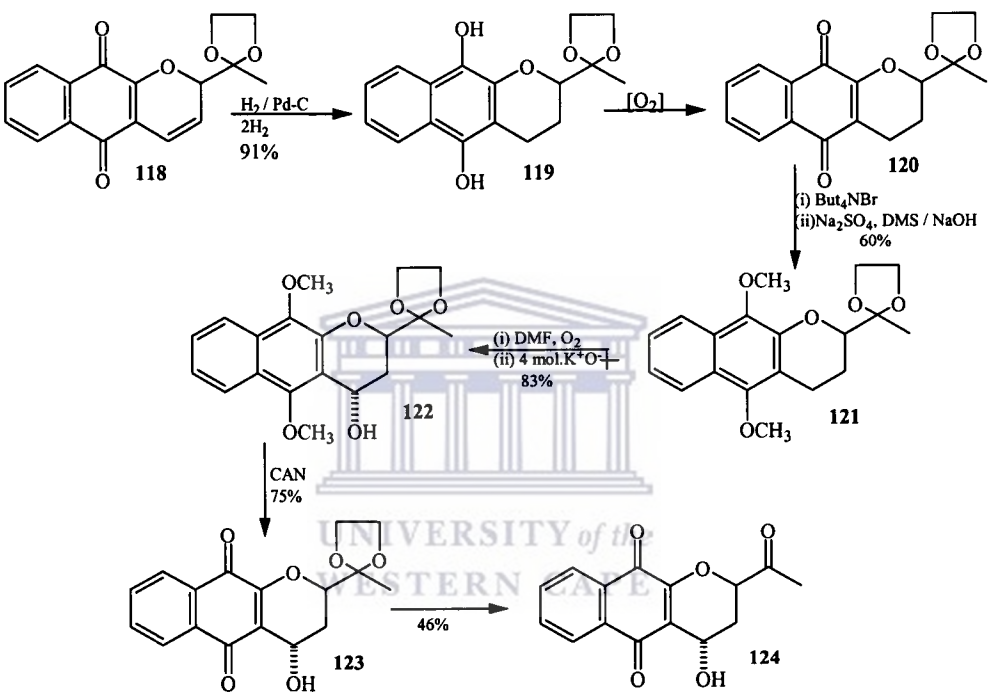
The synthesis of 2-acetyl-4-hydroxynaphtho[2,3-b]pyran-5,10-dione (124) and the 4-deoxy analogue (125).

Although *Erythrostominone* **60**[18] has a propan-2-one side chain at C-2 of the pyran ring, it was considered important to have an ethanone side chain analogue as well as to evaluate its biological activity. Thus the 6,8,9-trideoxy analogue **124** in which the 2-propan-2′-one side chain is replaced by a 2-1′-ethanone side chain was considered for synthesis.

The reduction of the known quinonedioxolane **118**[29] under catalytic conditions afforded the corresponding quinonedioxolane **120** in 91% yield. Apart from an increase of 2 atomic mass units for the mass of the molecule viz. $C_{17}H_{16}O_5$ requires 300; found 300, the ^{1}H- nmr spectrum indicated that reduction had occurred by the absence of the H-3 and H-4 pairs of doublets at 6.83 and 5.88ppm. A COSY spectrum showed a very clear connectivity between the multiplet at 4.19ppm for H-2a and the multiplet signals at 1.81 and 2.19ppm for the H-3 axial and H-3 equatorial hydrogens of the pyran ring. Additionally a ddd at 2.46ppm in the ^{1}H-nmr spectrum is assigned to 4-Ha showing geminal coupling of 18.4Hz to 4-He, diaxial coupling of 11.2Hz to H-3a and axial-equatorial coupling of 6.2Hz with H-3e. On the other hand a ddd at 2.85ppm is assigned to the pseudo 4-He and showed similar geminal coupling of 18.4Hz to 4-Ha, but due to the different dihedral angles of 4-Ha, the equatorial –axial coupling to 3-Ha was 5.4Hz, while the diequatorial coupling was 2.8Hz (Scheme 32).

Under the above conditions of catalytic hydrogenation, 2 mole equivalents of hydrogen were absorbed to yield the quinol **119**, which was observed as a colourless solution. However, even under nitrogen gas, some air inevitably is introduced and

oxidizes the quinol **119** to the quinone **120**. In order to reductively dimethylate quinone **120**, the phase transfer catalyst tetrabutyl ammonium bromide was employed together with aqueous sodium dithionite, followed by dimethylsulphate and aqueous sodium hydroxide. In this way quinone **120** was smoothly converted into the dimethoxy naphthalene **121** in a 60% yield after chromatography.



Scheme 32

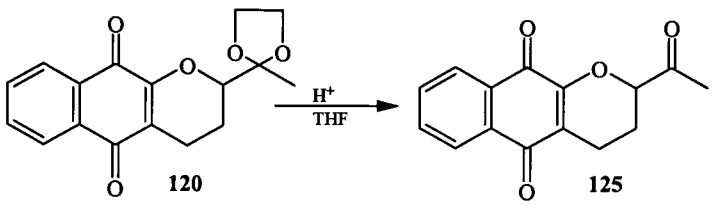
Again all four methylene hydrogens were clearly identified in the proton nmr spectrum with the H-3a appearing as a multiplet at 1.85ppm, the H-3e appearing as a multiplet at 2.22ppm. On the other hand a ddd at 2.83ppm (***J*** 16.8, 12.5 and 6.0) is assigned to H-4a, while a ddd at 3.24ppm (***J*** 16.8, 5.0 and 2.6) is assigned to H-4e. The splitting pattern has been explained for quinone **120**. Introduction of the hydroxy groups at C-4 of the pyran ring was effected by a method employed by Giles et.al.[29] In this way an 83% conversion was achieved. In the ^{1}H-nmr spectrum, pseudo 4-He appeared as a sharp dd at 5.30ppm demonstrating coupling of 2.2Hz with 3-Ha and 1.8Hz with 3-He. Thus the C-4 hydroxyl group is pseudoaxial. In the COSY

spectrum, very clear connectivity between this signal and the hydroxy signal at 2.36ppm, as well as the ddd of the H-3a at 1.98ppm (*J* 13.8,11.8 and 3.0) and the ddd of the H-3e at 2.27ppm (*J* 13.8, 2.2 and 1.8). Similarly the dd at 4.29ppm (*J* 11.8 and 2.2) has been assigned to the 2-Ha, since strong connectivity with 3-Ha and 3-He is also clearly indicated in the COSY spectrum.

Oxidation of the dimethoxypyran **122** into the corresponding quinone **123** was successfully achieved using aqueous cerium(IV) ammonium nitrate in the co-solvent acetonitrile to afford quinone **123** in a yield of 75%. In support of the structure, the 4-He appeared as a sharp dd at 5.00ppm in the ^{1}H-nmr spectrum with coupling of 4.0Hz to H-3a and 2.2Hz to H-3e. As expected H-3a appeared as a ddd at 1.85ppm (*J* 14.4, 12.4 and 4.0), while H-3e appeared as a ddd at 2.24ppm (*J* 14.4, 2.2 and 2.2) and finally H-2a appeared as a dd at 4.29ppm (*J* 12.4 and 2.2). The IR spectrum showed a ν_{max} at 3466 cm^{-1} for the hydroxyl group, while the strong peaks at 1651 and 1673 cm^{-1} demonstrated the quinone carbonyl groups.

In the final step of hydrolysis of the dioxolane **123** into ketone **124**, it was found that perchloric acid in tetrahydrofuran worked best. Transformation was achieved in a 46% yield after chromatography. In the IR spectrum, a strong band at 3474 cm^{-1} for the hydroxyl group was still present and in addition to the quinoidal carbonyl stretching frequencies at 1651 and 1679 cm^{-1}, a new ν_{max} at 1724 cm^{-1} was present for the ketone function. Of the two H-3 protons, only H-3a was observable in the ^{1}H-nmr spectrum as a ddd at 1.96ppm (*J* 14.5, 11.8 and 4.4). The signal due to the H-3e overlapped with that of the methyl group at 2.45ppm. In the absence of the dioxolane methylene signals, H-2a appeared as a clear dd at 4.73ppm showing transdiaxial coupling of 11.8Hz to H-3a and axial-equatorial coupling of 2.4Hz with 3-He. As expected 4-He appeared as a poorly defined dd at 4.98ppm (*J* 4.4 and 2.4). In order to discover the importance of the hydroxy group at C-4 of the pyran ring in the biological activity of these systems, the 4-deoxy analogue **125** was synthesized for comparative evaluation relative to the 4-hydroxy analogue **123**.

Consequently quinone **120** was treated with 70% perchloric acid in tetrahydrofuran to produce the desired quinone **125** in a moderate yield of 40% (Scheme 33).



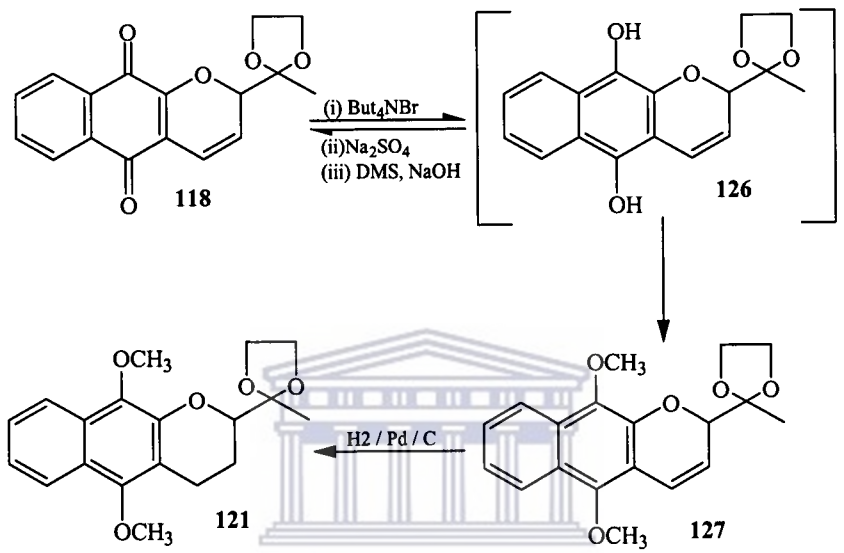
120 125

Scheme 33

The IR spectrum of **125** displayed the ketone carbonyl at 1722 cm^{-1}, while the quinone carbonyl appeared at 1672 cm^{-1}. In the ^{1}H-nmr spectrum, 2-Ha appeared as a ddd at 4.70ppm with diaxial coupling of 7.0Hz to 3-Ha, axial-equatorial coupling of 4.0Hz to 3-He and a four bond coupling of 0.8Hz with H-4a. The COSY spectrum established that 2-Ha was coupled to the multiplet signal centred at 2.58 ppm which allowed for the assignment of this signal to 4-Ha and 4-He.

In an alternative approach towards the synthesis of the dimethoxy-naphthopyran **121**, an attempt was made to reductively methylate quinone **118** into the dimethoxynaphthopyrene **127** employing analogous methodology of the phase transfer catalyst used in conversion of quinone **120** into the dimethoxy analogue **121**. Indeed the naphthopyrene **127** was isolated as a pale pink solid with a strong ν_{max} at 1180 cm^{-1}. From the ^{1}H-nmr spectrum it was clear that reduction of the quinone had occurred due to two 3-proton signals at 3.91 and 4.01ppm for the two methoxy groups. Retention of the pyrene nucleus was also obvious due to three 1-proton signals viz., a well defined dd at 4.91ppm with axial-equatorial coupling of 3.6 Hz with H-3 and axial-equatorial coupling of 1.8Hz with 4-H assigned to H-2a; a dd at 5.98ppm with ortho coupling of 10.2 Hz to 4-H and equatorial-axial coupling of 3.6Hz to 2-Ha and assigned to H-3 and finally H-4 appeared as a dd at 7.00ppm with

J 10.2 and 1.8Hz. However the yield was very poor being only 30% with starting material being isolated in 60%. It is believed that the intermediate quinol **126** under the conditions, in spite of attempting to perform the workup procedure under nitrogen, undergoes very rapid oxidation back to the quinone **118** (Scheme 34).



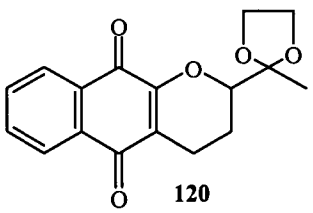
Scheme 34

Catalytic hydrogenation of pyrene **127** did in fact produce the desired pyran **121** in a yield of 93%. However, the poor yield obtained for the transformation of **118** into **124** persuaded us to follow the protocol sequence depicted in Scheme 32.

Experimental

^{1}H and ^{13}C NMR spectra were recorded using a Varian 200MHz spectrometer at 20°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 on a Finnigan-Matt GCQ instrument. 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°-75°C. In ^{13}C-spectra, assignments with the same superscript may be interchanged.

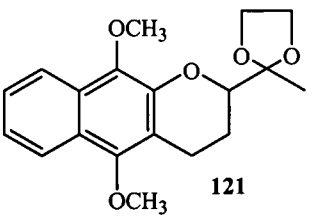
3,4-Dihydro-2-(1′-dioxolanoethyl)naphtho[2,3-b]pyran-5,10-dione (120)



120

Quinone **118**[29] (984mg; 3mmol) in ethyl acetate (50ml) containing Pd-C (10%) catalyst (15mg) was hydrogenated at 25°C at atmospheric pressure for 12h, filtered and the residue chromatographed using EtOAc: Hexane (3:7) as eluent to afford the naphthopyrandione **120** (821mg; 91%) as yellow crystals, m.p.153-154°C (from Hexane). ν_{max} 1676 and 1643 cm^{-1}; δ_H 1.47 (3H, s, H-2′), 1.81 (1H, m, H-3a), 2.19 (1H, m, H-3e), 2.46 (1H, ddd, ***J*** 18.4, 11.2 and 6.2, H-4a), 2.85 (1H, ddd, ***J*** 18.4, 5.4 and 2.8, H-4e), 4.06 (4H, m, OCH_2CH_2O), 4.19 (1H, m, H-2a), 7.64 (2H, m, H-7 and H-8), and 8.07 (2H, m, H-6 and H-9). δ_C 18.4 (C-2′), 20.9 (C-3), 21.3 (C-4), 65.9 and 66.1 (OCH_2CH_2O), 81.2 (C-2), 108.9 (C-1′), 2×121.5, 126.2 and 126.3 (C-8, C-7, C-6 and C-9), 132.2 (C-4a)[a], 133.1 (C-9a)[a], 133.9 (C-5a)[a], 155.4 (C-10a)[a], 179.2 and 184.3 (C=O). (Found: C, 68.2; H, 5.2%; M^+ 300. Calc. for $C_{17}H_{16}O_5$: C, 68.0; H, 5.3%; M 300).

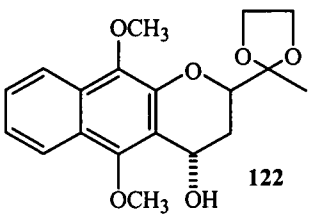
3,4-Dihydro-5,10-dimethoxy-2-(1′-dioxolanoethyl)naphtho[2,3-b]pyran (121)



121

To a solution of quinone **120** (751mg; 2.5mmol) in tetrahydrofuran (15ml), was added tetrabutyl ammonium bromide (200mg; 0.67mmol) in water (4ml) and sodium dithionite (3.04g; 17.5mmol) in water (8ml), and the resulting solution was stirred under nitrogen for 1.5h. Aqueous potassium hydroxide [2.1g; 38mmol in water (3ml)] was added, and after stirring for 10min, dimethyl sulphate (4.42g; 34mmol) was added and the reaction mixture was stirred at 25°C for 18h. To this solution, aqueous ammonia (concentrated) was added (10ml), followed by water (100ml) and the solution was then extracted with dichloromethane (4×50ml). The residue obtained upon workup was chromatographed using EtOAc: Hexane (3:7) as eluent to afford the dimethoxynaphthopyran **121** (495mg; 60%) as white crystals, m.p. 114-115°C (from Hexane). ν_{max} 1080 cm^{-1}; δ_H 1.46 (3H, s, H-2′), 1.85 (1H, m, H-3a), 2.22 (1H, m, H-3e), 2.83 (1H, m, H-4a), 3.24 (1H, m, H-4e), 3.89 and 3.98 (each 3H, s, OCH_3), 4.09 (5H, m, H-2a and OCH_2CH_2O), 7.37 (2H, m, H-7 and H-8), and 8.07 (2H, m, H-6 and H-9). δ_C 20.4 (C-2′), 21.2 (C-3), 22.8 (C-4), 61.0 and 61.3 (2×OCH_3), 65.6 and 65.9 (OCH_2CH_2O), 79.8 (C-2), 109.5(C-1′), 117.0(C-4a), 121.4 (C-7)[a], 121.7 (C-8)[a], 122.7 (C-5a)[b], 123.7 (C-6)[c], 125.7 (C-9)[c], 128.1 (C-9a)[b], 138.0 (C-10a)[b], 144.6 (C-5)[d] and 149.2 (C-10)[d]. (Found: C, 69.3; H, 6.5%; M^+ 330. Calc. for $C_{19}H_{22}O_5$: C, 69.1; H, 6.7%; M 330).

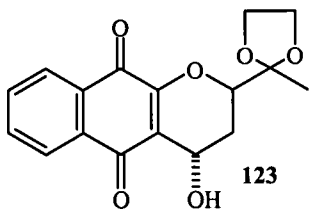
3,4-Dihydro-4-hydroxy-5,10-dimethoxy-2-(1′-dioxolanoethyl)-naphtho[2,3-b]pyran (122)



122

To an oxygen flushed solution of pyran **121** (396mg; 1.2mmol) in dry dimethylformamide (25ml) was added potassium tertiary butoxide (576mg; 5.1mmol) and stirring was continued while dry oxygen was passed into the solution at 25°C. After 30min, additional potassium tertiary butoxide was added (288mg; 2.4mmol) and stirring with oxygen bubbling into the mixture was continued until pyran **121** had been consumed as shown by the t.l.c. The reaction mixture was quenched by the addition of water (150ml) followed by extraction with diethyl ether which afforded a residue that was chromatographed using EtOAc: Hexane (2:3) as eluent to give the 4-hydroxynaphthol **122** (345mg; 83%) as a white solid, m.p. 134-135°C (from Hexane). ν_{max} 3466 cm^{-1}; δ_H 1.53 (3H, s, H-2′), 1.98 (1H, ddd, ***J*** 13.8, 11.8 and 3.0, H-3a), 2.27 (1H, ddd, ***J*** 13.8, 2.2 and 1.8, H-3e), 2.63 (1H, bs, D_2O exchangeable, 4-OH), 3.98 and 4.04 (each 3H, s, OCH_3), 4.10 (4H, m, OCH_2CH_2O), 4.29 (1H, dd, ***J*** 11.8 and 2.2, 2-Ha), 5.30 (1H, dd, ***J*** 2.2 and 1.8, pseudo 4-He), 7.35 and 7.46 (each 1H, each t, ***J*** 7.8, H-7 and H-8), 7.97 and 8.10 (each 1H, each d, ***J*** 7.8, H-6 and H-9). δ_C 21.2 (C-2′), 30.3 (C-3), 59.8 and 61.0 (OCH_3), 63.1 (C-4), 65.6 and 65.9 (OCH_2CH_2O), 74.7 (C-2), 109.3 (C-1′), 118.9 (C-4a)[a], 121.6 (C-7)[b], 122.1 (C-8)[b], 122.5 (C-5a)[a], 123.9 (C-6)[c], 126.2 (C-9)[c], 129.4 (C-9a)[a], 138.4 (C-10a), 143.5 (C-5)[d], 150.7 (C-10)[d]. (Found: C, 65.7; H, 6.6%; M^+ 346. Calc. for $C_{19}H_{22}O_6$: C, 65.9; H, 6.4%; M 346).

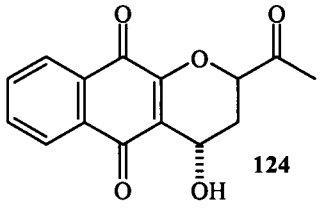
3,4-Dihydro-4-hydroxy-2-(1′-dioxolanoethyl)naphtho[2,3-b]pyran-5,10-dione (123)



123

To a solution of the alcohol **122** (100mg; 0.29mmol) in acetonitrile (10ml) containing water (1ml) was dripped in a solution of cerium(IV) ammonium nitrate (324mg; 0.59mmol) in water (3.0ml) over a period of 10min. After stirring an additional 15min, water (100ml) was added and the mixture exhaustively extracted with dichloromethane (5×25ml). The residue obtained on workup was chromatographed using EtOAc: Hexane (2:3) as eluent to afford the quinone **123** (67mg; 75%) as yellow crystals, m.p. 152-153°C (from Hexane). ν_{max} 3466, 1651 and1673 cm^{-1}; δ_H 1.48 (3H, s, H-2′), 1.85 (1H, ddd, ***J*** 14.4, 12.4 and 4.0, H-3a), 2.24 (1H, ddd, ***J*** 14.4, 2.2 and 2.2, H-3e), 2.92 (1H, bs, D_2O exchangeable, 4-OH), 4.07 (4H, m, OCH_2CH_2O), 4.29 (1H, dd, ***J*** 12.4 and 2.2, H-2a), 5.01 (1H, dd, ***J*** 4.0 and 2.2, H-4e), 7.21 (2H, m, H-7 and H-8) and 8.07 (2H, m, H-6 and H-9). δ_C 21.4 (C-2′), 29.2 (C-3), 58.1 (C-2), 65.9 and 66.2 (OCH_2CH_2O), 108.5 ×2 (C-4 and C-1′), 121.7 (C-4a), 126.3 (C-7)[a], 126.6 (C-8)[a], 131.3 (C-5a)[b], 131.9 (C-9a)[b], 133.6 (C-6)[c], 134.3 (C-9)[c], 155.6 (C-10a), 179.4 and 185.1 (C=O). (Found: C, 64.4; H, 4.8%; M^+ 316. Calc. for $C_{17}H_{16}O_6$: C, 64.6; H, 5.1%; M 316).

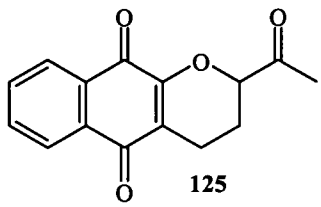
2-Acetyl-3,4-dihydro-4-hydroxynaphtho[2,3-b]pyran-5,10-dione (124)



124

To a solution of hydroxyquinone **123** (50mg; 16mmol) in tetrahydrofuran (10ml) was added 70% perchloric acid (0.1ml) at 10°C. The reaction mixture was stirred at10°C for 12h, after which water (20ml) was added and the solution extracted with ether (5×30ml). The residue obtained upon workup was chromatographed using EtOAc:Hexane (2:3) as eluent to afford the ketone **124** (20mg; 46%) as yellow crystals, m.p. 129-130°C (from Hexane). ν_{max} 3470,1723,1651 and 1679 cm^{-1}; δ_H 1.96 (1H, ddd, ***J*** 14.5, 11.8 and 4.4, 3-Ha), 2.45 (4H, single peak, H-2′ and 3-He), 3.12 (1H, bs, D_2O exchangeable, 4-OH), 4.73 (1H, dd, ***J*** 11.8 and 2.2, 2-Ha), 4.98 (1H, dd, ***J*** 4.4 and 2.4, H-4e), 7.75 (2H, m, H-7 and H-8), 8.11 (2H, m, H-6 and H-9). δ_C 26.5 (C-2′), 30.6 (C-3), 57.6 (C-2), 78.1 (C-4), 122.3 (C-4a), 126.4 (C-7)[a], 126.7 (C-8)[a] 131.1 (C-5a)[b], 131.8 (C-9a)[b], 133.8 (C-6)[c], 134.6 (C-9)[a], 154.3 (C-10a), 179.2, 184.9 and 204.7 (3×C=O). (Found: C, 66.4; H, 4.6%; M^+ 272. Calc. for $C_{15}H_{12}O_5$: C, 66.2; H 4.4%; M 272).

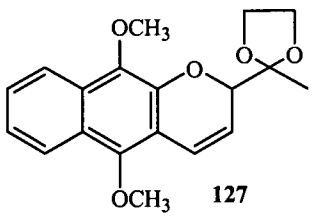
2-Acetyl-3,4-dihydronaphtho[2,3-b]pyran-5,10-dione (125)



125

To a solution of quinone **120** (50mg; 0.17mmol) in tetrahydrofuran (10ml) was added perchloric acid (0.1ml) at 10°C, and the mixture was stirred at this temperature for 12h and then quenched with water (20ml). Extraction of the solution with ether (5×40ml) afforded the residue that was chromatographed using EtOAc:Hexane (3:7) as eluent to afford the ketone **125** (20mg; 46%) as yellow crystals, m.p. 147-148°C (from Hexane). ν_{max} 1722, 1678 and 1653 cm^{-1}; δ_H 2.19 (2H, m, H-3a and H-3e), 2.34 (3H, s, H-2′), 2.58 (2H, m, H-4a and H-4e), 4.70 (1H, ddd, ***J*** 7.0, 4.0 and 0.8, H-2a), 7.72 (2H, m, H-7 and H-8), and 8.10 (2H, m, H-6 and H-9). δ_C 17.1 (C-2′), 21.9 (C-3), 26.2 (C-4), 81.0 (C-2), 121.9 (C-4a), 126.4 (C-7)[a], 126.5 (C-8)[a], 131.1 (C-5a)[b], 132.0 (C-9a)[b], 133.4 (C-6)[c], 134.2 (C-9)[c], 154.1 (C-10a), 179.1 , 184.0 and 205.6 (C=O). (Found: C, 70.2; H,4.5%; M^+ 256. Calc. for $C_{15}H_{12}O_4$: C, 70.3; H, 4.7%; M 256).

3,4-Dehydro-5,10-dimethoxy-2-(1′-dioxolanoethyl)naphtho[2,3-b]pyran (127)



127

Quinone **118**[29] (745mg; 2.5mmol) was subjected to the same conditions of reductive methylation described for the synthesis of pyran **121**. The residue was chromatographed using EtOAc:Hexane (3:7) as eluent to yield the pyrene **127** (246mg; 30%) as pale crystals, m.p. 93-94°C (from Hexane). ν_{max} 1180 cm^{-1}; δ_H 1.46 (3H, s, H-2′), 3.91 and 4.01 (each 3H, s, OCH_3), 4.02 (4H, m, OCH_2CH_2O), 4.91 (1H, dd, *J* 3.6 and 1.8, 2-Ha), 5.98 (1H, dd, *J* 10.2 and 3.6, H-3), 7.00 (1H, dd, *J* 10.2 and 1.8, H-4), 7.38 (2H, m, H-7 and H-8), 7.95 and 8.03 (each 1H, each d, *J* 7.8, H-6 and H-9). δ_C 20.8 (C-2′), 61.0 and 63.2 (OCH_3), 65.4 and 65.8 (OCH_2CH_2O), 78.3 (C-2), 110.1 (C-1′), 114.7 (C-4a), 120.7 (C-3), 121.6 (C-7)[a], 122.3 (C-8)[a], 123.5 (C-6)[b], 123.8 (C-9a)[c], 124.1 (C-9)[b], 126.5 (C-4), 129.8 (C-5a)[c], 137.2 (C-10a), 142.0 (C-5)[d], and 147.7 (C-10)[d]. (Found: C,69.4; H,6.3%; M^+ 328. Calc. for $C_{19}H_{20}O_5$: C, 69.5; H, 6.1%; M 328).

Conclusion

The process of hydrogenation of quinone **118** in ethyl acetate containing palladium-charcoal (10%) was monitored by t.l.c. until completion or the uptake of 2 moles of hydrogen (which afforded the pyran **120**) was observed. Reduction of the pyranquinone **120** to the dimethoxynaphthopyran **121** was successful due to the appearance of the methoxy groups in the ^{1}H nmr spectrum as singlets at 3.89ppm and 3.98ppm. By employing the method reported by Giles et al.[29] ; a hydroxyl group at position C-4 of the pyran ring of **121** was introduced; a yield of 83% was obtained.

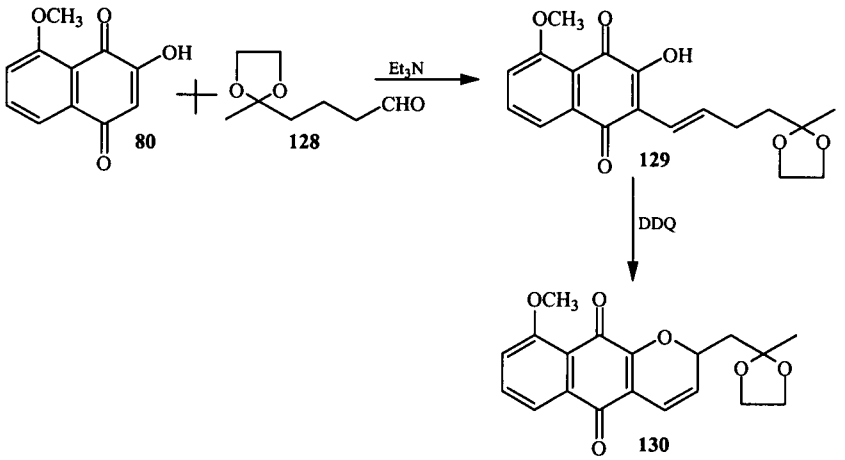
Demethylation of **122** via aqueous cerium(IV) ammonium nitrate afforded the quinone **123** (75%), which was acidified using 70% perchloric acid to afford the ketone **124** (46%). Similarly, acidification of quinone **120** using 70% perchloric acid afforded the ketone **125** in a 46% yield.

Chapter 6

Condensation products of 2-hydroxy-8-methoxy-1,4-naphthoquinone and various aldehydes.

Treatment of quinone **80** with aldehyde **128**[28] in the presence of triethylamine in acetonitrile afforded the expected condensation product **129**, but in a very modest yield of 16% as a deep red oil. The trans nature of the hexenyldioxolan side chain is clearly evident from the ^{1}H-nmr spectrum in which H-1′ appeared as a dt at 6.64ppm (***J*** 16.0 and 1.0), while H-2′ appeared as a dt at 7.03ppm (***J*** 16.0 and 6.8).

Subsequent treatment of **129** with 1.2 mole equivalents of dichlorodicyanobenzoquinone in benzene produced an array of products. In our hands a minor amount (10%) of the desired cyclised material **130** was obtained from preparative layer chromatography and clearly demonstrated the correct compound from an analysis of the ^{1}H-nmr spectrum (see Scheme 35). A dd at 6.65ppm is assigned to H-4 since it shows ortho coupling of 9.8Hz to H-3, and long range coupling of 1.8Hz to H-2a. In addition a dd at 5.81ppm is assigned to H-3 due to similar ortho coupling of 9.8Hz to H-4, but with a larger coupling of 3.6Hz to 2-Ha. A one-proton multiplet at 5.35ppm is assigned to 2-Ha. Unfortunately, due to the rather poor yields of products this venture was put on hold for the present.

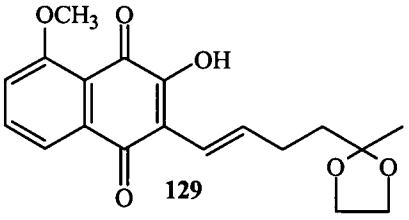


Scheme 35

Experimental

^{1}H and ^{13}C NMR spectra were recorded using a Varian 200MHz spectrometer at 20°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 on a Finnigan-Matt GCQ instrument. 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°-75°C. In ^{13}C-spectra, assignments with the same superscript may be interchanged.

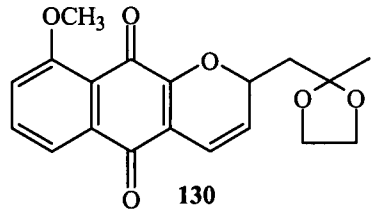
2-Hydroxy-8-methoxy-3-(5′-dioxolano-1′-hexenyl)-1,4-naphthoquinone (129)



129

Quinone **80** (1.0g; 6.4mmol) in acetonitrile (30ml) containing aldehyde **128**[28] (1.82g; 11.5mmol) was treated with triethylamine (5.0g; 49.5mmol), and the red solution was stirred under nitrogen at 60°C for 8h. After cooling the solution, water (150ml) was added and the resultant solution was extracted with ether (4×60ml). The ether extract was washed with sulphuric acid (40ml of a 0.5M solution) and the residue obtained upon workup was chromatographed using EtOAc:Hexane (2:3) as eluent to afford quinone **129** (346mg; 16%) as a red oil. ν_{max} 3468, 1670 and 1645 cm^{-1}; δ_H 1.36 (3H, s, H-6′), 1.84 (2H, m, H-4′), 2.39 (2H, m, H-3′), 3.96 (4H, sharp m, OCH_2CH_2O), 4.03 (3H, s, OCH_3), 6.64 (1H, dt, ***J*** 16.0 and 1.0, H-1′), 7.03 (1H, dt, ***J*** 16.0 and 6.8, H-2′), 7.23 (1H, dd, ***J*** 7.6 and 1.0, H-7), 7.69 (1H, t, ***J*** 7.6, H-6), 7.80 (1H, dd, ***J*** 7.6 and 1.0, H-5), and 8.16 (1H, s, D_2O exchangeable, 2-OH). δ_C 24.1 (C-6′), 29.6 (C-4′), 38.5 (C-3′), 56.6 (OCH_3), 64.8 ×2 (OCH_2CH_2O), 109.9 ×2 (C-5′ and C-7), 116.8 (C-2′)[a], 116.9 (C-3)[a], 118.6 (C-6)[a], 120.1 (C-5)[a], 135.2 (C-4a)[b], 136.4 (C-8a)[b], 142.3 (C-1′), 152.0 (C-2), 160.0 (C-8), 180.0 and 184.1 (C=O). Found: C, 66.7; H, 6.1%; M^+ 344. Calc. for $C_{19}H_{20}O_6$: C, 66.3; H, 5.8%; M 344).

9-Methoxy-2-(2′-dioxolanopropyl)-3,4-dehydronaphtho[2,3-b]pyran 5,10-dione (130)



130

To a solution of quinone **129** (200mg; 0.58mmol) in benzene (15ml), was added a solution of dichlorodicyanobenzoquinone (158mg; 0.70mmol) in benzene (15ml). And the resulting solution was stirred at 25°C under nitrogen for 12h; filtered and the residue was chromatographed by preparative layer chromatograpy using EtOAc:Hexane (3:7) to afford the pyranquinone **130** (20mg; 10%) as a thick red oil. ν_{max} 1690 and 1670 cm^{-1}; δ_H 1.26 (3H, s, H-3′), 2.17 (1H, m, H-1′), 2.38 (1H, m, H-1′), 3.98 (4H, sharp m, OCH_2CH_2O), 5.35 (1H, m, 2-Ha), 5.81 (1H, dd, ***J*** 9.8 and 3.6, H-3), 6.65 (1H, dd, ***J*** 9.8 and 1.8, H-4), 7.24 (1H, dd, ***J*** 8.0 and 1.2, H-8), 7.64 (1H, t, ***J*** 8.0, H-7), and 7.76 (1H, dd, ***J*** 8.0 and 1.2, H-6). (Found: C, 67.1; H, 4.8; M^+ 341. Calc. for $C_{19}H_{20}O_6$: C, 66.9; H, 5.0; M 341).

Conclusion

Aldehyde condensation reactions between quinone **80** and aldehyde **128**[28] in acetonitrile and triethylamine resulted in the formation of quinone **129**, but in a poor yield of 16%. Cyclisation of **129** using dichlorodicyanobenzoquinone resulted in the formation of the pyran **130** in a 10% yield.

Overall, the yields of both products i.e. quinone **129** and **130** were poor.

Conclusion

Aldehyde condensation reactions between quinone **80** and aldehyde **128**[28] in acetonitrile and triethylamine resulted in the formation of quinone **129**, but in a poor yield of 16%. Cyclisation of **129** using dichlorodicyanobenzoquinone resulted in the formation of the pyran **130** in a 10% yield. Overall, the yields of both products i.e. quinone **129** and **130** were poor.

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