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The Synthesis of Some Naphtho[2,3-b]pyran-5,10-Quinones as Preliminary Models for Biological Evaluations

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SYNTHETIC COMMUNICATIONS, 28(24), 4589-4604 (1998)

THE SYNTHESIS OF SOME NAPHTHO[2,3-*b*]PYRAN-5,10-QUINONES AS PRELIMINARY MODELS FOR BIOLOGICAL EVALUATIONS

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Abstract: Naphtho[2,3-*b*]pyran-5,10-quinones related to the known antibiotic, erythrostominone **5**, have been synthesized and demonstrate that biological activity is a function of the pyran ring as well as substituents at C-2 and C-4.

Many biologically active quinones found in Nature contain the naphtho[2,3-*b*]pyran ring system as part of their structure viz., α-lapachone **1**[1], rhinacanthin-A **2**, rhinacanthin-B **3**[2], lambertillin **4**[3] and erythrostominone **5**[4,5].

We have long suspected that the pyran ring plays an important role in the biological activity of naphthopyranquinones and have demonstrated this by synthesizing and testing a wide range of benzo[*c*]pyranquinones[6,7]. This was based on the concept of bioreductive alkylation as proposed by Moore[8] and earlier

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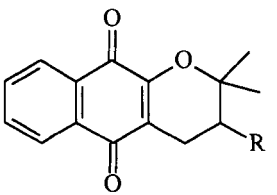
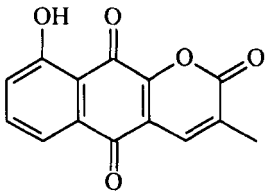


1 R=H
2 R=OH
3 R=OCOC=CHCH$_2$CH$_2$C=CHCH$_3$
CH$_3$ CH$_3$



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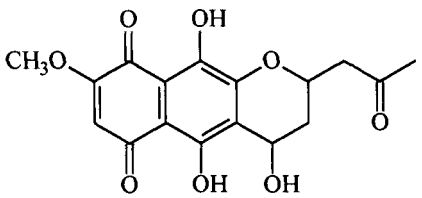

5

work by Sartorelli et. al.[9,10]. More recently Angle[11] has provided further insight into the inhibitory mechanism of antitumour antibiotics supporting the previous notions.

Since our previous work had focussed on the naphtho- and benzo[*c*]pyranquinone systems, it was decided to systemically investigate the biological activity of some naphtho[2,3-*b*]pyranquinones having the pyran oxygen in the benzilic position. In addition, the influence of substituents at the C-4 and C-2 positions of the pyran ring on biological activity were to be monitored since these positions are similar to those in erythrostominone **5**.

The initial target quinone chosen for meeting the criteria was **16** which could undergo an *in vivo* reduction to the quinol **6** followed by loss of the C-4 hydroxyl group leading to the quinone methide **7** and this would readily trap any nucleophic species as the quinol **8** which is shown in Scheme 1.

Reduction of the readily available hydroxyquinone **9**[12] with sodium borohydride in ethanol gave the expected alcohol **10** which was treated, without purification, with concentrated hydrochloric and acetic acid under reflux to yield the quinone **11** in a 70% yield. This is in stark contrast to a best yield of 18% employing similar

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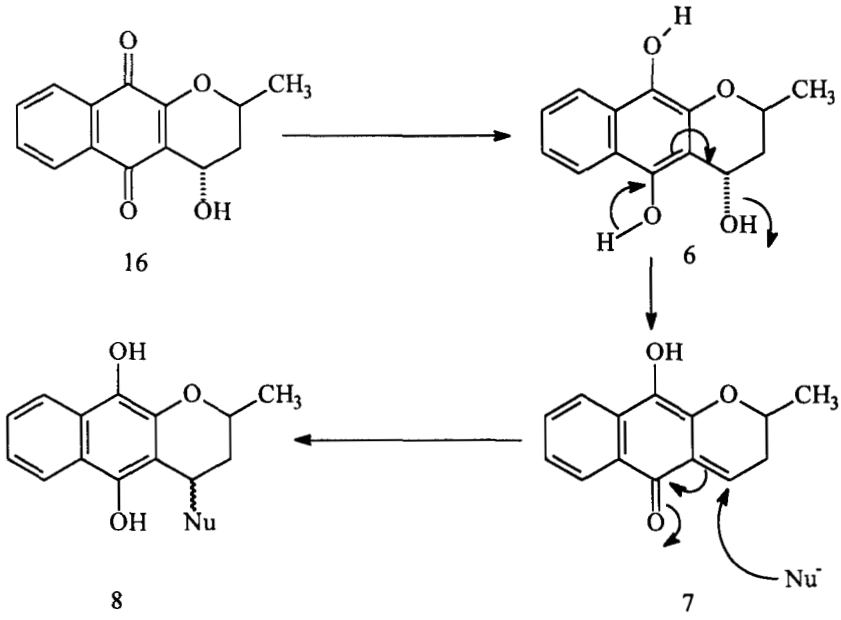
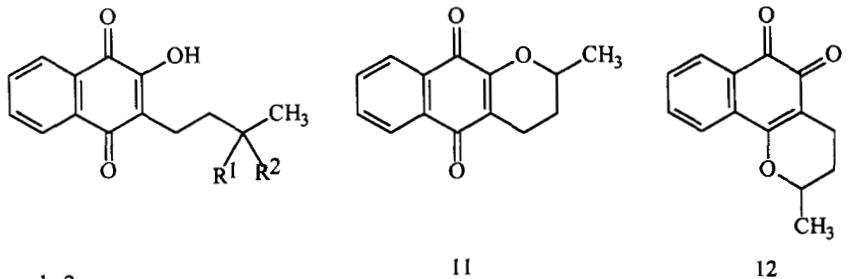


SCHEME 1

conditions reported by Valderrama et. al.[13]. When trifluoroacetic acid was used, the orange β-isomer **12** was obtained as the sole product in 41% yield. This latter quinone **12** could be isomerised into the linear quinone **11** in 82% yield under the same conditions of concentrated hydrochloric and acetic acid.



9 R^1R^2=O

10 R^1=H; R^2=OH

11

12

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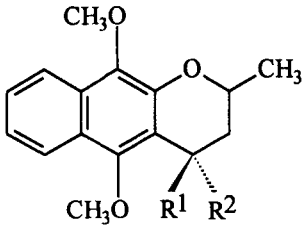
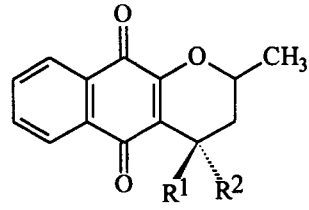
Reductive methylation of quinone **11** to the corresponding dimethyl ether **13** was best effected in a 96% yield employing a phase transfer catalyst similar to the protocol of Kraus[14]. Hydroxylation of C-4 was achieved by treating the dimethyl ether **13** with seven mol equivalents of potassium *tert*-butoxide in dry dimethylformamide while bubbling dry oxygen through the medium. In this way an inseparable mixture of the **4S**- and **4R**-hydroxynaphthopyrans **14** and **15** were obtained in a moderate yield of 65% in a ratio of 4:1 respectively as determined by H^1-n.m.r.





13 R^1=R^2=H

14 R^1=H; R^2=OH

15 R^1=OH; R^2=H

16 R^1=H; R^2=OH

17 R^1=OH; R^2=H

Consequently the mixture of 4-hydroxynaphthopyrans **14** and **15** were oxidised with aqueous cerium(IV) ammonium nitrate[15] to afford a 90% yield of the expected quinones which were separated into the **4S** diastereoisomer **16** and **4R** diastereoisomer **17** in a ratio of 83:17 respectively.

Assignments of the stereochemistry at C-4 were based on the H^1-n.m.r. spectra. In the case of the **4S** isomer **16** the 4e-H appeared as a doublet at δ 4.90 with *J* 2.2 Hz showing similar coupling to 3a- and 3e-H due to the similar dihedral angles. The signal for the 3a-H appeared as a ddd at δ 1.69 with geminal coupling of 15.6 Hz, transdiaxial coupling of 12.2 Hz to 2a-H and axial-equatorial coupling of 2.2 Hz to 4e-H. On the other hand the signal due to the 3e-H appeared as a dd at δ

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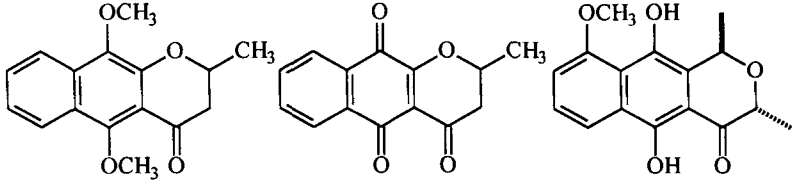
2.12 with geminal coupling of 15.6 Hz and a similar coupling of 2.2 Hz to 4e- and 2a-H resulting from similar dihedral angles.

This may by contrasted to the **4R** isomer **17** in which the signal assigned to the 4a-H appeared as a dd at δ 5.06 with transdiaxial coupling of 8.5 Hz to 3a-H and axial-equatorial coupling of 7.0 Hz to 3e-H. The signal assigned to 3a-H appeared as a ddd at δ 1.90 with geminal coupling of 13.9 Hz, transdiaxial couplings of 10.1 Hz to 2a-H and 8.5 Hz to 4a-H respectively. By contrast to pyran **16** the signal assigned to 3e-H of pyran **17** appeared as a ddd at δ 2.36 with geminal coupling of 13.9 Hz, axial-equatorial coupling of 7.0 Hz to 4a-H and a smaller coupling of 2.0 Hz to 2a-H most likely due to a more boat-like conformation. Indeed, whereas quinone **16** is crystalline and stable, quinone **17** is an oil and is rather unstable even as the C-4 acetate derivative.

Quinone **19** was best obtained by firstly oxidizing the mixture of alcohols **14** and **15** with pyridinium dichromate in methylene chloride[16] to afford a mixture of the 4-oxonaphthopyran **18** in a modest 52% yield together with a 31% yield of the 4S-hydroxynaphthopyranquinone **16**. Other oxidation methods were much less successful. It would appear that strong hydrogen bonding experienced in quinone **16** is the driving force for both its formation and lack of the 4-hydroxy group to oxidize to the 4-oxo group. Similar behaviour was noticed by us in our synthesis of racemic hongconin **20**[17]. Treatment of ketone **18** with silver(II) oxide in 6M nitric acid[18] afforded the desired quinone **19** in 82% yield.



18 19 20

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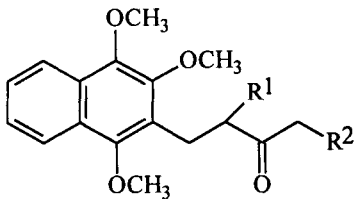
We next turned our attention to the synthesis of the 2-(2'-oxopropyl)naphtho-pyranquinone **27** having the same side chain at C-2 as in erythrostominone **5**. Although this target molecule has been reported[13] we were unable to reproduce the results and thus include this work together with our findings and changes. Freshly prepared lithium diisopropyl amine was added to naphthalene **21**[13] at –78°C followed by precooled acetaldehyde to give a best isolated yield of 57% of the hydroxyketone **22** and a 17% yield of the bis-addition adduct **23** based on its mass spectrum. Using sec-butyllithium and n-butyllithium did not improve the yields of product. Reduction of hydroxyketone **22** with sodium borohydride in a methanol-tetrahydrofuran mixed solvent[19] gave an excellent yield of 91% of diastereomeric mixture of diols **24**, which upon oxidation with aqueous cerium(IV) ammonium nitrate[15] afforded the angular *ortho*-quinone **25**. The secondary alcohol side chain of **25** was oxidized to the corresponding ketone **26** only after uitilizing more pyridinium chlorochromate with prior dispersion on celite. We were unable to isomerize the angular *ortho*-quinone **26** into the linear *para*-quinone **27** utilizing the conditions reported[13]. However, heating quinone **26** under reflux in sulphuric acid effected an 84% isomerisation of **26** into **27** while a 68% isomerisation was obtained using a mixture of concentrated hydrochloric and acetic acid under reflux.

Biological evaluations, which will be reported elsewhere, have demonstrated that activity is indeed a function of the 5,10-quinoidal system, both the hydroxyl and ketone groups at C-4 and the 2-oxopropyl side chain at C-2 of the pyran ring.

We are currently synthesizing molecules combining these functionalities in both simple systems as well as those close to erythrostominone **5**.

EXPERIMENTAL

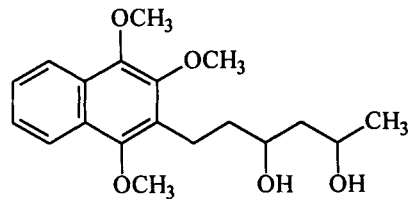
^{1}H NMR spectra were recorded on a Varian 200 MHz spectrometer at ambient temperature in deuterochloroform. Mass spectra were recorded on a modified AEI



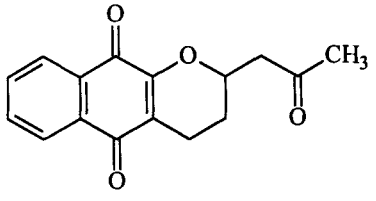
21 R^1=R^2=H

22 R^1=H; R^2=CH(OH)CH_3

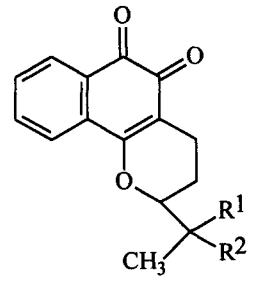
23 R^1=R^2=CH(OH)CH_3



24



27



25 R^1=H; R^2=OH

26 R^1R^2=O

analyser (902) at 70 eV and an ion source temperature of between 180°C and 220°C. Infrared spectra were measured for nujol mulls on a Beckman Acculab IR spectrophotometer, while melting points were determined on a Fischer-John melting point apparatus and are quoted uncorrected. Column chromatography was carried out on dry-packed columns with Merck Kieselgel 60 (70 – 230 mesh) as adsorbent, while thin-layer chromatography (TLC) was carried out on aluminium plates coated with Merck Kieselgel 60 F_{254}. Hexane refers to the fraction of boiling point 60-80°C derived from a petroleum ether raw material. Most organic solvents and liquid reagents were distilled prior to use. The phrase "residue obtained upon work-up" refers to the residue obtained when the organic layer was separated, backwashed with water, dried (using anhydrous magnesium sulphate) and the solvent (after filtration) evaporated under reduced pressure.

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(±)-3,4-Dihydro-2-methyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione 11

The hydroxyquinone **9**[12] (305 mg; 1.3 mmol) in ethanol (50 ml) was treated with sodium borohydride (307 mg; 6.5 equiv.) and stirred under reflux in a nitrogen atmosphere for 1 h. Removal of the ethanol on a rotatory evaporator left a residue which was treated with water (100 ml) and acidified to pH 4. The acidic solution was extracted with dichloromethane (4 x 40 ml) and the residue obtained upon work-up of the crude alcohol **10** was treated with a mixture of acetic acid (5 ml) and concentrated hydrochloric acid (30 ml) and stirred and heated under reflux under nitrogen for 1 h. The cooled solution was diluted with water (150 ml) and extracted with dichloromethane (4 x 40 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (3:7) as eluent to afford the quinone **11** (208 mg; 70%) as yellow crystals, m.p. 122-123°C (from hexane), lit.[12], m.p. 122-123°C; ν_{max} 1660 and 1640 cm^{-1}; δ_H 1.47(3H, d, *J* 6.4 Hz, 2-CH_3), 1.57-1.76 (1H, m, 3a-H), 1.99-2.12 (1H, m, 3e-H), 2.48 (1H, ddd, *J* 18.8, 9.9 and 6.3 Hz, 4a-H), 2.70 (1H, ddd, *J* 18.8, 6.3 and 3.9 Hz, 4e-H), 4.21-4.36 (1H, m, 2-H), 7.57-7.71 (2H, m, 7- and 8-H), and 7.94-8.13 (2H, m, 6- and 9-H) (Found: M^+, 228.0776. Calc. for $C_{14}H_{12}O_3$: *M*, 228.0786).

(±)-3,4-Dihydro-2-methyl-2*H*-naphtho[1,2-*b*]pyran-5,6-dione 12

The hydroxyquinone **9** (292 mg; 1.2 mmol) was reduced with sodium borohydride (295 mg; 6.5 equiv.) as described above. The crude residue of alcohol **10** was treated with trifluoroacetic acid (2 ml) and heated at 70°C (oil bath) under nitrogen for 4.5 h. The cooled reaction mixture was treated with saturated sodium bicarbonate and extracted with dichloromethane. The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:1) as eluent to afford the quinone **12** (112 mg; 41%) as red needles, m.p. 162-164°C (from ethanol-cyclohexane), lit.,[12] m.p. 164°C. δ_H 1.52(3H, d, *J* 6.4 Hz, 2-CH_3), 1.59-1.79 (1H, m, 3a-H), 2.02-2.15 (1H, m, 3e-H), 2.43 (1H, ddd, *J* 16.9, 10.6 and 6.1 Hz, 4a-H), 2.69 (1H, ddd, *J* 16.9, 6.1 and 3.4 Hz, 4e-H), 4.32-4.48 (1H, m 2-H), 7.48

(1H, dt, *J* 2 x 7.5 and 1.3 Hz, 8- or 9-H), 7.65 (1H, dt, *J* 2 x 7.5 and 1.5 Hz, 8- or 9-H), 7.79 (1H, dd, *J* 7.8 and 1.2 Hz, 10-H), and 8.04 (1H, dd, *J* 7.5 and 1.2 Hz, 7-H) (Found: C, 73.5; H, 5.3%; M^+, 228.0800. Calc. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3%; *M*, 228.0786).

(±)-3,4-Dihydro-5,10-dimethoxy-2-methyl-2*H*-naphtho[2,3-*b*]pyran 13

Quinone **11** (174 mg; 0.76 mmol) in tetrahydrofuran (2.6 ml) containing tetrabutyl ammonium bromide (29 mg; 0.12 equiv.), water (1.1 ml) and aqueous sodium dithionate [890 mg; 5 mmol in water (2.2 ml)] was stirred in a nitrogen atmosphere for 1 *h* at 25°C. Aqueous potassium hydroxide [980 mg; 17 mmol in water (1.1 ml)] was added and after 5 min dimethyl sulphate (1.0 g; 7.9 mmol) was added and the resulting mixture stirred under nitrogen for 18 h at 25°C. Concentrated ammonia solution (5 ml) and water (100 ml) were added and the solution was extracted with dichloromethane (4 x 40 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:4) as eluent to afford the dimethyl ether **13** (189 mg; 96%) was yellow plates m.p. 68.5-70.5°C (from hexane); ν_{max} 1235 cm^{-1}; δ_H 1.52 (3H, d, *J* 6.2 Hz, 2-CH_3), 1.64-1.86 (1H, m, 3a-H), 2.02-2.18 (1H, m, 3e-H), 2.90 (1H, ddd, *J* 17.1, 11.3 and 5.9 Hz, 4a-H), 3.16 (1H, ddd, *J* 17.1, 5.9 and 3.5 Hz, 4e-H), 3.91 and 3.96 (each 3H, s, OCH_3), 4.20-4.36 (1H, m, 2-H), 7.27-7.47 (2H, m, 7- and 8-H), and 7.95-8.10 (2H, m, 6- and 9-H) (Found: C, 74.2; H, 7.2%; M^+, 258.1248. Calc. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.0%; *M*, 258.1256).

(±)(4S)-3,4-Dihydro-4-hydroxy-5,10-dimethoxy-2-methyl-2*H*-naphtho[2,3-*b*] pyran 14 and the (4R) diastereoisomer 15

Naphthopyran **13** (242 mg; 0.94 mmol) was dissolved in dry dimethylformamide (20 ml) and flushed with dry oxygen for 15 min. Potassium *tert*-butoxide (420 mg; 3.75 mmol) was added at once and the resultant solution stirred and heated to 60°C (oil bath) with dry oxygen bubbling through for 45 min. A further quantity of potassium *tert*-butoxide (316 mg; 2.82 mmol) was added and stirring

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maintained for an additional 30 min. Water (100 ml) was added to the cooled solution which was then extracted with ether (5 x 30 ml) and the residue obtained upon work-up was chromatographed using ethyl acetate-hexane (3:7) as eluent. The first fraction was unchanged naphthopyran **13** (36 mg; 15%) followed by a mixture of the (**4S**)- and (**4R**)-hydroxypyrans **14** and **15** (167 mg; 65%) as a yellow oil; ν_{max} (neat) 3700-3100 cm^{-1}; δ_H 1.54 (3H, d, *J* 6.3 Hz, 2-CH_3), 1.90 (1H, ddd, *J* 14.8, 11.5 and 3.8 Hz, 3a-H), 2.19 (1H, dt, *J* 14.8 and 2.1 Hz, 3e-H), 2.72 (1H, br s, D_2O exchangeable, 4-OH), 3.97 and 4.04 (each 3H, s, OCH_3), 4.20-4.56 (1H, m, 2-H), 5.16-5.26 (1H, sharp m, 4-H), 7.30-7.51 (2H, m, 7- and 8-H), and 7.89-8.14 (2H, m, 6- and 9-H) (Found: C. 70.3; H, 6.7%; M^+, 274.1200. Calc. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6%; *M*, 274.1205).

(±)(4S)-3,4-Dihydro-4-hydroxy-2-methyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione 16 and the (4R) diastereoisomer 17

To a stirred solution of alcohols **14** and **15** (98 mg; 0.36 mmol) in acetonitrile (10 ml) and water (1 ml) was added dropwise an aqueous solution of cerium(IV) ammonium nitrate (431 mg; 2.2 equiv.) in distilled water (3 ml) over a period of 5 min at 25°C. After an additional 15 min water (100 ml) was added and the mixture extracted with dichloromethane (4 x 40 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (3:7) as eluent to afford the (**4R**)-hydroxyquinone **17** (13 mg; 15%) as a yellow oil; ν_{max} (neat) 3500 br, 1680 and 1640 cm^{-1}; δ_H 1.56 (3H, d, *J* 6.4 Hz, 2-CH_3), 1.90 (1H, ddd, *J* 13.9, 10.1 and 8.5 Hz, 3a-H), 2.36 (1H, ddd, *J* 13.9, 7.0 and 2.0 Hz, 3e-H), 4.21 (1H, br s, D_2O exchangeable, 4-OH), 4.37-4.44 (1H, m, 2-H), 5.06 (1H, dd, *J* 8.5 and 7.0 Hz, 4a-H), 7.60-7.84 (2H, m, 7- and 8-H), and 7.98-8.20 (2H, m, 6- and 9-H) (Found: M^+, 244.0748. Calc. for $C_{14}H_{12}O_4$: *M*, 244.0735). Further elution afforded the (**4S**)-hydroxyquinone **16** (65 mg; 75%) as yellow crystals, m.p. 127-128°C (from hexane); ν_{max} 3500 br, 1680 and 1640 cm^{-1}; δ_H 1.54 (3H, d, *J* 6.4 Hz, 2-CH_3), 1.69 (1H, ddd, *J* 15.6, 12.2 and 2.2 Hz, 3a-H), 2.12 (1H, dd, *J* 15.6 and 2.2 Hz, 3e-H), 3.10 (1H, br s, D_2O exchangeable, 4-OH), 4.35-4.49 (1H, m, 2-H),

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4.90 (1H, d, *J* 2.2 Hz, 4e-H), 7.60-7.75 (2H, m, 7- and 8-H), and 7.95-8.10 (2H, m, 6- and 9-H), (Found: C, 68.7; H, 5.1%; M^+, 244.0742. Calc. for $C_{14}H_{12}O_4$: C, 68.9; H, 4.9%; *M*, 244.0735).

(±)-3,4-Dihydro-5,10-dimethoxy-2-methyl-2*H*-4-oxonaphtho[2,3-*b*]pyran 18

To a stirred suspension of pyridinium dichromate (967mg; 15 equiv.) and celite (1 g) in dichloromethane (10 ml) was added dropwise a solution of the hydroxy-pyrans **14** and **15** (47 mg; 0.17 mmol) in dichloromethane (10 ml) over 5 min. The resulting mixture was stirred for 2 h and filtered and the residue obtained upon work-up was chromatographed using ethyl acetate-hexane (2:3) as eluent to afford the 4-oxopyran **18** (24 mg; 52%) as yellow plates, m.p. 111-112°C (from hexane); ν_{max} 1680 and 1620 cm^{-1}; δ_H 1.59 (3H, d, *J* 6.2 Hz, 2-CH_3), 2.78 (1H, d, *J* 3.6 Hz, 3a-H), 2.80 (1H, bs, 3e-H), 4.00 and 4.01 (each 3H, s, OCH_3), 4.56-4.72 (1H, m, 2-H), 7.35-7.61 (2H, m, 7- and 8-H), and 8.04-8.24 (2H, m, 6- and 9-H) (Found: C, 70.6; H, 6.1%; M^+, 272.1039. Calc. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9%; *M*, 272.1048). Further elution afforded the **4S**-hydroxyquinone **16** (13 mg; 31%) as yellow crystals, m.p. 127.5-128.5°C (from hexane) having identical spectral data to the compound prepared earlier.

(±)-3,4-Dihydro-2-methyl-2*H*-4-oxonaphtho[2,3-*b*]pyran-5,10-dione 19

A mixture of pyran **18** (22 mg; 0.08 mmol), silver(II) oxide (50 mg; 5 equiv.) in dioxane (5 ml) was stirred and treated dropwise with a 6 M solution of nitric acid at 25°C until all the silver(II) oxide had reacted as observed by its disappearance. After 15 min stirring, water (60 ml) was added and the yellow solution was extracted with dichloromethane (4 x 20 ml) to yield the quinone **19** (16 mg; 82%) as yellow crystals, m.p. 160-162°C (from hexane); ν_{max} 1710 and 1690 cm^{-1}; δ_H 1.67 (3H, d *J* 6.3 Hz, 2-CH_3), 2.71 (1H, d, *J* 4.4 Hz, 3a-H), 2.76 (1H, br s, 3e-H). 4.81-5.00 (1H, m, 2-H), 7.69-7.84 (2H, m, 7- and 8-H), and 8.08-8.18 (2H, m, 6- and 9-H) (Found: C, 69.2; H, 3.9%; M^+, 242.0565. Calc. for $C_{14}H_{12}O_4$: C, 69.4; H, 4.1%; *M*, 242.0579).

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3-(3'-Oxo-5'-hydroxyhexyl)-1,2,4-trimethoxynaphthalene 22 and the bis-addition adduct 23

To freshly distilled diisopropyl amine (0.31 ml; 2.2 mmol) in tetrahydrofuran (7.1 ml) at 0°C under nitrogen was added n-butyllithium (2.1 ml of a 1.4 M solution, 3.0 mmol). Stirring was continued for a further 30 min at 0°C after which the temperature was lowered to –78°C and a solution of ketone **21** (578 mg; 2.0 mmol) in tetrahydrofuran (5.7 ml) was slowly added. Thereafter the resultant solution was stirred at -78°C for 30 min. Precooled (0°C) acetaldehyde (0.2 ml; 3.3 mmol) was added to the enolate and stirring was continued for 30 min and thereafter allowed to reach 25°C over 1 h. The reaction mixture was quenched by the addition of aqueous hydrochloric acid (2.8 ml of a 5 M solution) and extracted with ether (5 x 10 ml) and the residue obtained upon work-up was chromatographed using ethyl acetate-hexane (2:3) as eluent to give unchanged ketone **21** (140 mg; 24%) followed by the keto alcohol **22** (288 mg; 43%; and 57% based on unrecovered starting material) as light yellow crystals, m.p. 74-76°C (from cyclohexane); lit.[13], m.p. 80.5-81.5°C); ν_{max} 4000-3000 and 1685 cm^{-1}; δ_H 1.20 (3H, d, *J* 6.4 Hz, 6'-CH_3), 2.59 (2H, d, *J* 8.36 H, 4'-CH_2), 2.75 (2H, dd, *J* 9.7 and 8.6 Hz, 2'-CH_2), 3.07 (2H, dd, *J* 9.7 and 8.6 Hz, 1'-CH_2), 3.17 (1H, d, *J* 3.1 Hz, D_2O exchangeable, 5'-OH), 3.89, 3.96 and 3.98 (each 3H, s, OCH_3), 4.10-4.40 (1H, m, 5'-H), 7.39-7.51 (2H, m, 6- and 7-H), and 7.94-8.13 (2H, m, 5- and 8-H) (Found: M^+, 332.1618. Calc. for $C_{19}H_{24}O_5$: *M*, 332.1624). Further elution afforded a semisolid material of the suspected bis-addition adduct **23** (131 mg; 17%) (Found: M^+, 376.1862. Calc. for $C_{21}H_{28}O_6$: *M*, 376.1886).

3-(3',5'-Dihydroxyhexyl)-1,2,4-trimethoxynaphthalene 24

The hydroxyketone **22** (314 mg; 0.95 mmol) in a mixture of methanol and tetrahydrofuran (1:10, v/v; 11 ml) at 0°C was treated with sodium borohydride (43 mg; 1.2 equiv.) in two portions and the mixture was stirred for 15 min at 0°C under a nitrogen atmosphere. Aqueous ammonium chloride (5 ml) and water (100 ml) were added and the resultant solution extracted with ether to give a residue

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which was chromatographed using ethyl acetate-hexane (2:3) as eluent to afford the diastereoisomeric mixture of diols **24** (290 mg; 91%) as a clear yellow oil; ν_{max} (neat) 3300 cm^{-1}; δ_H 1.12 and 1.17 (3H, d, *J* 6.2 Hz, 60% and 40% respectively, 6'-CH_3), 1.47-1.90 (4H, m, 2'- and 4'-CH_2), 2.96 (2H, t, *J* 6.1 Hz, 1'-CH_2), 3.52-4.20 (4H, m, 2 of the H's are D_2O exchangeable, 3'- and 5'-H; and 3'- and 5'-OH), 3.94, 3.96 and 4.01 (each 3H, s, OCH_3), 7.40-7.53 (2H, m, 6- and 7-H), and 7.93-8.15 (2H, m, 5- and 8-H) (Found: C, 68.3; H, 7.7%; M^+, 334.1770. Calc. for $C_{19}H_{26}O_5$: C, 68.3; H, 7.8%; *M*, 334.1780).

(±)2-(2'-Hydroxypropyl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran-5,6-dione 25

We employed a similar method to Valderrama et.al.[13] but using ethyl acetate-hexane (1:1) as eluent and obtained the *ortho* quinone **25** in a best yield of 57% as dark orange crystals, m.p. 109-110°C (from hexane); lit.[13], m.p. 122-123°C; ν_{max} 3400, 1690 and 1640 cm^{-1}, δ_H 1.36 (3H, d, *J* 6.0 Hz, 3'-CH_3), 1.60-2.80 (7H, m, 1'-, 3- and 4-CH_2 as well as 2'-OH which is D_2O exchangeable), 4.10-4.60 (2H, m, 2- and 2'-H), 7.40-7.80 (3H, m, 8-, 9- and 10-H), and 8.03 (1H, m, 7-H) (Found: M^+, 272.1056. Calc. for $C_{16}H_{16}O_4$: *M*, 272.1048).

(±)2-(2'-Oxopropyl)-3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran-5,6-dione 26

To a stirred suspension of pyridinium chlorochromate (553 mg; 4 equiv.) and celite (1 g) in dichloromethane (10 ml) was added dropwise a solution of the quinone **25** (175 mg; 0.64 mmol) in dichloromethane. After 18 h, ether (100 ml) was added and the mixture was filtered and the residue thus obtained from the filtrate was chromatographed on a short column using ethyl acetate as eluent to afford quinone **26** (122 mg; 71%) as orange needles, m.p. 150-152°C (from hexane) lit.[13], m.p. 162-164°C; ν_{max} 1780, 1752, 1690 and 1640 cm^{-1}; δ_H 2.26 (3H, s, 3'-CH_3), 1.67-2.47 (4H, m, 3- and 4-CH_2), 2.90-3.20 (2H, m 1'-CH_2), 4.52-4.80 (1H, m, 2-H), 7.38-7.68 (3H, m, 8-, 9- and 10-H), and 7.96 (1H, d, *J* 7.2 Hz, 7-H) (Found: C, 71.2; H, 5.5%; M^+, 270.0896. Calc. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.2%; *M*, 270.0892).

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(±)2-(2'-Oxopropyl)-3,4-dihydro-2*H*-naphtho[2,3-*b*]pyran-5,10-dione 27

Method A

Quinone **26** (70 mg; 0.26 mmol) in 20% aqueous sulphuric acid (30 ml) was heated under reflux under nitrogen for 1 h after which the solution was diluted with water (100 ml) and extracted with dichloromethane (4 x 40 ml). The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:1) as eluent to afford the linear quinone **27** (59 mg; 84%) as yellow crystals m.p. 121-122°C (from hexane); lit.[13], m.p. 117-118°C; ν_{max} 1710, 1685 and 1645 cm^{-1}; δ_H 1.56-1.78 (2H, m, 3-CH_2), 2.26 (3H, s, 3'-CH_3), 2.40-2.84 (3H, m, 1'-CH_2 and 4a-H), 3.14 (1H, dd, *J* 17.0 and 4.8 Hz, 4e-H), 4.40-4.65 (1H, m 2-H), 7.61-7.73 (2H, m, 7- and 8-H), and 8.03-8.07 (2H, m, 6- and 9-H) (Found: M^+, 270.0888. Calc. for $C_{16}H_{14}O_{14}$: *M*, 270.0892).

Method B

Quinone **26** (45 mg; 0.17 mmol) was added to a mixture of acetic acid (5 ml) and concentrated hydrochloric acid (30 ml) and the resulting mixture stirred and heated under reflux for 1 h under nitrogen. The work-up procedure was the same as described for quinone **11** but using a similar eluting phase as for Method A. In this way quinone **27** was isolated as yellow crystals (31 mg; 68%), m.p. 121-122°C (from hexane). Spectral data were similar to the quinone isolated via Method A.

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REFERENCES

1. Burnett, A.R., and Thomson, R.H., *J. Chem. Soc.* (*c*), 1967, 2100.

2. Wu, T.S., Tien, H.J., Yeh, M.Y., and Lee, K.H., *Photochemistry*, 1988, **27**, 3787.

3. Thomson, R.H., *Naturally Occurring Quinones*, 2nd Ed., 1971, Academic Press, London.

4. Cross, B.E., Edinberry, M.N., and Turner, W.B., *J. Chem. Soc. Perkin Trans.* 1, 1972, 380.

5. Cross, B.E., and Zammitt, L.J., *J. Chem. Soc. Perkin Trans.* 1, 1973, 2975.

6. Esterhuyser, A.J., Hugo, V.I., Pestana, J.A.X., Snijman, P.W., and Green, I.R., *S. Afr. J. Chem.*, 1993, **46**, 34.

7. Green, I.R., Hugo, V.I., Oosthuisen, F.J., van Eeden, N., and Giles, R.G.F., *S. Afr. J. Chem.*, 1995, **48**, 15.

8. Moore, H.W., Science, 1977, **197**, 527.

9. Lin, A.J., Cosby, L.A., and Sartorelli, A.C., *Cancer Chemother. Rep.*, 1974, **4**, 23.

10. Lin, A.J., Cosby, L.A., Shansky, C.W., and Sartorelli, A.C., *J. Med. Chem.*, 1972, **15**, 1247.

11. Angle, S.R., Rainier, J.D., Woytowicz, C., *J. Org. Chem.*, 1997, **62**, 5884.

12. Cassis, R., Tapia, R., and Valderrama, J.A., *J. Heterocyclic Chem.*, 1982, **19**, 381.

13. Saitz, B.C., Valderrama, J.A., and Tapia, R., *Synth. Commun.*, 1990, **20**, 3103.

14. Kraus, G.A., and On Man, T., *Synth. Commun.*, 1986, **16**, 1037.

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15. Jacob, P., Callery, P.S., Shulgin, A.T., and Castagnoli, N. (Jr)., *J. Org. Chem.*, 1976, **41**, 3627.

16. Corey, E.J., and Schmidt, G., *Tet. Letters*, 1979, **5**, 399.

17. Green, I.R., Hugo, V.I., Oosthuisen, F.J., and Giles, R.G.F., *Synth. Commun.*, 1996, **26**, 867.

18. Snyder, C.D., and Rapoport, H., *J. Am. Chem. Soc.*, 1972, **94**, 227.

19. Varma, R.S., and Kabalka, G.W., *Synth. Commun.*, 1985, **15**, 151.

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