Stereoselective Base-induced Conversion of Naphthalenic Precursors into Naphthopyrans related to the Aphin-derived Glucoside B

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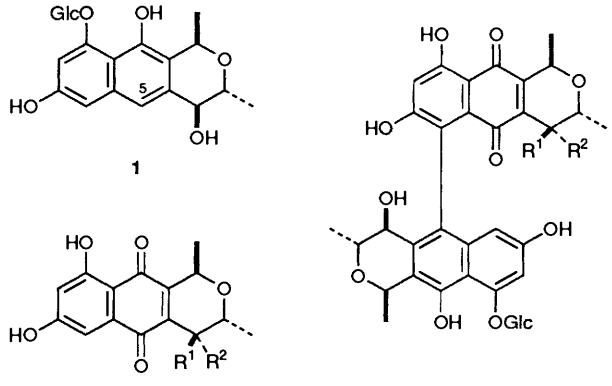
trans-5-Benzyloxy-3,4-dihydro-10-methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran **21** and *trans*-3,4-dihydro-10-isopropoxy-7,9-dimethoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran **34** are formed with complete stereoselectivity by reaction of, respectively, 2-allyl-1-benzyloxy-3-(1-hydroxyethyl)-4-methoxynaphthalene **20** and the mixture of (*E*)- and (*Z*)-3-(1-hydroxyethyl)-4-isopropoxy-5,7-dimethoxy-3-prop-2-enylnaphthalene **30** and **31** with potassium *tert*-butoxide in dimethylformamide under nitrogen. The benzyloxy substituent of compound **21** is removed in three steps to afford *trans*-3,4-dihydro-10-methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran **24**. Compounds **24** and **34** are also transformed with complete stereoselectivity into the corresponding pseudoequatorial 4-alcohols **25** and **35** with potassium *tert*-butoxide in oxygenated dimethyl sulfoxide and dimethylformamide, respectively.

Glucoside B **1** is the β-glycosidic naphthopyran obtained by reductive cleavage of each of the aphid pigments, the protoaphins.[1] A second naphthopyran is also isolated as the 5,10-quinone upon aerial reoxidation of each reaction mixture. Thus, in addition to **1**, this process also yields Quinone A **2** from protoaphin-fb **5**, Quinone A′ **3** from protoaphin-sl **6** and Deoxyquinone A **4** from deoxyprotoaphin **7**.[1]

Having synthesised the racemates of the three quinones **2**, **3** and **4**,[2] we wished to investigate the possibility of assembling Glucoside B. Since this compound **1** and Quinone A **2** possess the same substitution and stereochemistry about the pyran ring, it seemed reasonable to use the same novel stereoselective, base-induced cyclisation and hydroxylation procedures for the new target **1** as had been followed earlier for the quinonoid analogue **2**. This paper describes the application of these routes to appropriate models.



Results and Discussion

A major structural difference between compounds **1** and **2** is the lack of the C-5 oxygen in the former. Using the previously established methodology,[2,3] this would require either removal of the C-5 oxygen from a derived napthopyran **21** or proceeding with precursors without this aromatic oxygen substituent to form the naphthopyran **34**. Both routes had potential drawbacks; the former since cleavage of the aryl C-5 oxygen bond was likely to be more difficult than the benzylic C(1)–O(2) bond of the pyran ring, while for the latter process, the base-induced cyclisation to form the naphthopyran **34** might be much lower yielding. Preliminary experiments had shown that for the *para*-dioxygenated precursor **8**, this reaction proceeded in much higher yield (85%) to afford the pyran **11** than either of the monomethoxy substrates [**9**→**12** (25%) and **10**→**13** (0%)].[4]

For the first of these sequences, the target naphthalene chosen was **20**. The starting material **14**[5] was smoothly methylated to afford the methyl ether **15**. Hydrolysis of the acetate group of **15** yielded the naphthol **16** which was, in turn, allylated with allyl bromide, giving rise to the allyl ether **17**. This compound underwent a Claisen rearrangement at 160 °C to afford the *C*-allylnaphthol **18** as an unstable oil, a transformation which was confirmed *inter alia* by the expected corresponding upfield shift in the ^{1}H NMR spectrum of the allyl methylene protons from δ 4.72 in **17** to δ 3.42 in **18**. Naphthol **18** was immediately converted into the benzyl ether **19** which was, in turn, reduced to the corresponding alcohol **20** with lithium aluminium hydride. All six steps in the conversion of starting material **14** into target product **20** were of high yield, that for the overall process being 42%.

It is worth noting that the IR carbonyl stretch of the fully substituted acetophenone **19** at 1700 cm^{-1} appears at a significantly higher value than those for the less crowded precursors **15** and **17** at approximately 1670 cm^{-1}. This is ascribed to a sterically-induced loss of coplanarity of the acetyl and naphthyl moieties in **19**, which we have observed in other systems.[6] This observation is not inconsistent with the tentative suggestion[4] that the base-induced cyclisations of related alcohols, such as **20** arise, at least in part, through steric compression of the reacting centres.

The alcohol **20** was treated with an excess of potassium *tert*-butoxide in dry dimethylformamide under nitrogen at

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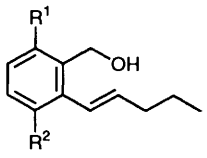
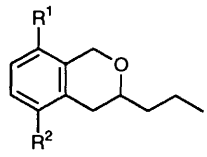
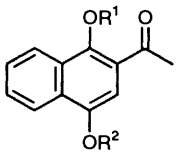
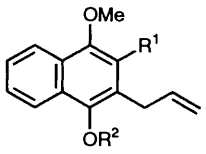




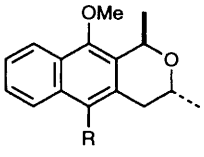
8 $R^1 = R^2 = OMe$ **11**
9 $R^1 = OMe, R^2 = H$ **12**
10 $R^1 = H, R^2 = OMe$ **13**

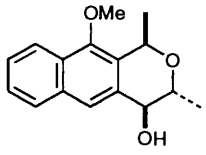




14 $R^1 = H, R^2 = Ac$
15 $R^1 = Me, R^2 = Ac$
16 $R^1 = Me, R^2 = H$
17 $R^1 = Me, R^2 = CH_2CH{=}CH_2$

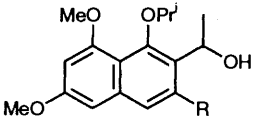
18 $R^1 = Ac, R^2 = H$
19 $R^1 = Ac, R^2 = CH_2Ph$
20 $R^1 = CH(OH)CH_3, R^2 = CH_2Ph$

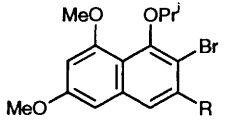




21 R = OCH_2Ph
22 R = OH
23 R = OSO_2Me
24 R = H

25





30 R = (*Z*)-CH=CHCH$_3$
31 R = (*E*)-CH=CHCH$_3$

26 R = CH_2OH
27 R = CHO
28 R = (*Z*)-CH=CHCH$_3$
29 R = (*E*)-CH=CHCH$_3$

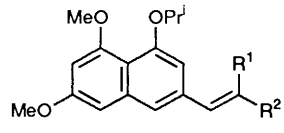
room temperature, whereupon the stereoselectively formed *trans*-naphthopyran **21** was obtained as a single product in good yield (72%). Characteristic signals in the ^{1}H NMR spectrum were the 3-H proton as a multiplet at δ 4.0–4.2 and the 1-H quartet at δ 5.34.[2,7] Removal of the benzyl group from compound **21** was achieved with 2 equiv. of boron trichloride, which afforded the unstable phenol **22**. This was, therefore, converted directly into the methanesulfonate ester **23** through reaction with methanesulfonyl chloride and pyridine. The structure of compound **23** was supported in the ^{1}H NMR spectrum by a new methyl singlet at δ 3.38 for the methanesulfonate group, and in its IR spectrum by two absorption bands at 1339 and 1167 cm^{-1}, characteristic for this substituent.

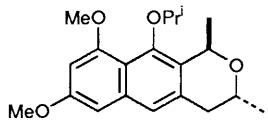
Selective cleavage of the aryl–oxygen bond of compound **23** was achieved with Raney nickel catalyst,[8] a process which left untouched the sensitive benzylic C–O bond, which is further activated in compounds **23** and **24** by the *peri*-methoxy substituent. A very reasonable yield of 66% was achieved for the conversion of **23** into **24** when the solvent used was in a ratio of three parts ethanol to one part water. In the ^{1}H NMR spectrum, the *trans* stereochemistry was confirmed by the characteristic appearance[2,7] of the new 3-H multiplet at δ 3.98–4.36 and the 1-H quartet at δ 5.34, while the presence of the derived C-5 proton was established by a one-proton singlet at δ 7.38.

The remaining step in the synthesis of target compound **25** proceeded smoothly with the required stereoselectivity. Thus, compound **24** dissolved in oxygenated dry dimethyl sulfoxide[2] was treated with potassium *tert*-butoxide at room temperature. Compound **25** was obtained as a single stereoisomer in a yield of 67%. The IR spectrum showed absorption at 3410 cm^{-1}, confirming the presence of an alcohol, while the molecular ion at *m*/*z* 258 in the mass spectrum supported the molecular formula corresponding to compound **25**. The stereochemistry about the pyran ring was confirmed by the ^{1}H NMR spectrum; the three pyran ring protons appeared as a doublet of quartets at δ 3.98 (*J* 8 and 7 Hz), a doublet (*J* 8 Hz) at δ 4.49, broadened by the adjacent hydroxy group, and a quartet (*J* 7 Hz) at δ 5.28 due, respectively, to 3-H, 4-H and 1-H. Significantly, the coupling constant of 8 Hz common to 3-H and 4-H indicated that these two protons are axial and pseudoaxial respectively, thereby confirming that the C-4 alcohol function is pseudoequatorial.[2]

Previous examples[2,7] of such oxygenations were carried out on substrates carrying 5-methoxy substituents and gave rise to both the corresponding pseudoequatorial and pseudoaxial C-4 epimeric alcohols. In the present case of the conversion of the naphthopyran **24** into the pseudoequatorial alcohol **25**, none of the alternative pseudoaxial alcohol was observed. This, presumably, reflects the less crowded reaction site, in the absence of the *peri*-methoxy group at C-5. This dichotomy in reactivity was invaluable since the C-5 methoxynaphthopyrans gave rise to the corresponding Quinones A **2** and A′ **3**, alcohols epimeric at C-4, whereas in the present case, the only alcohol obtained, **25**, was that with the stereochemistry required for Glucoside B. The same observation was made below in the conversion of naphthopyran **34** into the corresponding alcohol **35**.

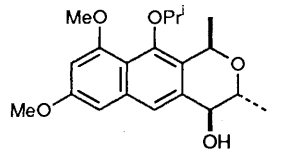
The second sequence investigated proceeded without oxygen at C-5 for the derived naphthopyran **34**. The target naphthalene to be investigated was the compound **31**. The starting material, alcohol **26**[9] was oxidised to the corresponding aldehyde **27**, and this was, in turn, subjected to a Wittig reaction with ethylidene(triphenyl)phosphorane to afford a mixture of the (*Z*)- and (*E*)-olefins **28** and **29**. This mixture was treated with butyllithium followed by acetaldehyde to yield the mixture of (*Z*)- and (*E*)-olefinic alcohols **30** and **31**, together with a mixture of the debrominated isomeric olefins **32** and **33** as minor by-products.[10]

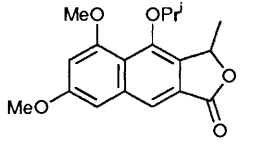




32 $R^1 = Me, R^2 = H$
33 $R^1 = H, R^2 = Me$

34





35 **36**

When the mixture of olefinic alcohols **30** and **31** was treated with potassium *tert*-butoxide in dimethylformamide under nitrogen, the naphthopyran **34** was isolated in high yield (83%) and as a single stereoisomer, thereby confirming that the stereochemistry of the product was not determined by that of the starting material. The *trans* stereochemistry was confirmed by the chemical shift of the 3-H proton at δ 4.01–4.20 and that of 1-H at δ 5.34 in the ^{1}H NMR spectrum; these values were very close indeed to those of the related naphthopyran **24**

described earlier, as well as to those of the oxygenated analogues **21** and **23**. The C-5 aromatic singlet appeared at δ 7.12.

No yield advantage was achieved on performing the ring closure to naphthopyran **34** using stereochemically pure (*E*)-olefinic precursors. These were obtained by conversion of the mixture of bromo olefins **28** and **29** into pure (*E*)-olefin **29** in high yield (90%) using bis(acetonitrile)dichloropalladium(II).[10] Pure bromo olefin **29** was converted into pure (*E*)-olefinic alcohol **31** together with pure compound **33** as a minor by-product. Compound **31** was, in turn, transformed into naphthopyran **34** in a yield of 83%, as before.

It is noteworthy that the naphthopyran **34** was obtained in high yield from its precursor(s), unlike the conversion of compound **9** into benzopyran **12**.[4] This may well be a reflection of the degree of steric hindrance in the reagents **30** and **31**.

The conversion of the naphthopyran **34** into the corresponding alcohol **35** was difficult to control, since over-oxidation to form the lactone **36** occurred readily. Optimum results were obtained using potassium *tert*-butoxide in oxygenated dimethylformamide (in spite of the fact that dimethyl sulfoxide was the solvent of choice when related systems carried alkoxy substituents at C-5 of the naphthopyran substrates) and by quenching the reaction before the consumption of all starting material. This procedure afforded the pseudoequatorial alcohol **35** in a yield of 46% based on unrecovered starting material. The stereochemical assignment was determined by the large coupling constant (*J* 7.8 Hz) between the vicinal protons 3-H and 4-H,[2] while the molecular formula was confirmed by a high-resolution mass-spectral determination of the molecular ion, and the presence of an alcohol by an IR absorption at 3413 cm^{-1}.

The experiments described in this paper define avenues and limitations to the assembly of compounds **25**, **35** and, ultimately, glucoside B **1**. An entirely different approach is described in the following paper.[11]

Experimental

^1H NMR spectra were recorded using a 200 MHz Varian VXR spectrometer unless otherwise stated. At 90 MHz, spectra were recorded on a Bruker WH-90 instrument. ^{13}C NMR spectra were recorded on the former at a frequency of 50.1 MHz. All these spectra were measured for solutions in [^2H]chloroform with tetramethylsilane as internal reference. *J* Values are given in Hz. For other general details, see preceding paper in this issue.

1-*Acetoxy*-3-*acetyl*-4-*methoxynaphthalene* **15**.—Naphthol **14**[5] (3.00 g, 12.3 mmol) was dissolved in dry acetone (50 cm^3) and potassium carbonate (4.4 g, 30.75 mmol) and dimethyl sulfate (3.87 g, 30.75 mmol) were added to the solution. The mixture was then stirred vigorously and boiled for 1.5 h under nitrogen. It was then cooled, filtered, and the solvent evaporated. The residue was taken up in ether and washed with water followed sequentially by 25% ammonia, water, then dilute hydrochloric acid. The residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate–light petroleum) to yield the *product* **15** (2.65 g, 84%) as white rhomboids, m.p. 92–93 °C (methanol) (Found: C, 69.7; H, 5.5. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4%); ν_{max}/cm^{-1} 1756 (OAc), 1671 (C=O) and 1602 (C=C); δ_H(90 MHz) 2.45 (3 H, s, $OCOCH_3$), 2.78 (3 H, s, $COCH_3$), 3.99 (3 H, s, OCH_3) 7.55 (1 H, s, 2-H), 7.55–7.66 (2 H, m, 6- and 7-H), 7.70–7.90 (1 H, m, 8-H) and 8.14–8.34 (1 H, m, 5-H); *m*/*z* 258 (M^+, 17%), 216 (100), 201 (68), 173 (28) and 160 (65).

3-*Acetyl*-4-*methoxy*-1-*naphthol* **16**.—Compound **15** (700 mg, 2.71 mmol) was dissolved in a 1% (w/v) methanolic solution of potassium hydroxide (227 mg, 4.0 mmol) and the solution was stirred at room temperature for 10 min before being quenched by addition of dilute hydrochloric acid. The organic material was extracted into methylene dichloride and the extract was washed with water. The residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate–light petroleum) to yield the naphthol **16** (510 mg, 87%) as pale yellow plates, m.p. 137–138 °C (methylene dichloride–light petroleum) (Found: C, 72.3; H, 5.65. $C_{13}H_{12}O_3$ requires C, 72.2; H, 5.55%); ν_{max}/cm^{-1} 3423 (OH), 1652 (C=O) and 1623 and 1595 (C=C); δ_H(90 MHz) 2.82 (3 H, s, $COCH_3$), 3.94 (3 H, s, OCH_3), 7.38 (1 H, s, 2-H), 7.41 (1 H, br s, OH, D_2O exchangeable), 7.48–7.67 (2 H, m, 6- and 7-H) and 8.04–8.36 (2 H, m, 5- and 8-H); *m*/*z* 216 (M^+, 100%), 201 (68), 186 (15) and 173 (42).

3-*Acetyl*-1-*allyloxy*-4-*methoxynaphthalene* **17**.—The naphthol **16** (500 mg, 2.31 mmol) was dissolved in dry acetone (50 cm^3) and treated with potassium carbonate (810 mg, 5.87 mmol) and allyl bromide (710 mg, 5.87 mmol). The mixture was boiled with vigorous stirring for 12 h under nitrogen after which it was cooled, filtered, and evaporated to give a residue which was dissolved in methylene dichloride and the solution washed with water. The residue obtained upon work-up was chromatographed (eluent 10% ethyl acetate–light petroleum) to yield the *product* **17** (510 mg, 86%) as a pale yellow oil (Found: C, 75.1; H, 6.3. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.25%); ν_{max}(film)/cm^{-1} 1669 (C=O) and 1622 and 1595 (C=C); δ_H(90 MHz) 2.58 (3 H, s, $COCH_3$), 3.92 (3 H, s, OCH_3), 4.72 (2 H, br d, *J* 5, OCH_2), 5.20–5.40 (2 H, m, vinyl CH_2), 5.64–6.38 (1 H, m, vinyl CH), 7.04 (1 H, s, 2-H), 7.44–7.68 (2 H, m, 6- and 7-H) and 8.02–8.38 (2 H, m, 5- and 8-H); *m*/*z* 256 (M^+, 25%), 215 (100), 183 (34) and 155 (30).

3-*Acetyl*-2-*allyl*-4-*methoxy*-1-*naphthol* **18**.—Compound **17** (143 mg, 0.56 mmol) was heated at 160–165 °C for 5 h as a neat oil under nitrogen to give a black gummy oil. This was chromatographed (eluent 10% ethyl acetate–light petroleum) to afford the unstable *naphthol* **18** (127 mg, 89%) as an oil; δ_H(90 MHz) 2.58 (3 H, s, $COCH_3$), 3.42 (2 H, br d, *J* 6, $ArCH_2$), 3.83 (3 H, s, OCH_3), 4.98–5.28 (2 H, m, vinyl CH_2), 5.60 (1 H, br s, OH, D_2O exchangeable), 5.78–6.20 (1 H, m, vinyl CH), 7.38–7.42 (2 H, m, 6- and 7-H) and 7.70–8.08 (2 H, m, 5- and 8-H). This oil was immediately converted into the benzyl derivative **19**.

3-*Acetyl*-2-*allyl*-1-*benzyloxy*-4-*methoxynaphthalene* **19**.—The naphthol **18** (2.28 g, 8.91 mmol) and benzyl bromide (3.85 g, 22.5 mmol) were dissolved in dry acetone (100 cm^3) and potassium carbonate (3.09 g, 22.5 mmol) was added to the solution. After being boiled under nitrogen for 18 h, the mixture was cooled, filtered and evaporated to dryness. The residue was chromatographed (eluent 10% ethyl acetate–light petroleum) to yield compound **19** (2.87 g, 93%) as white needles, m.p. 62–63 °C (methylene dichloride–light petroleum) (Found: C, 79.95; H, 6.45. $C_{23}H_{22}O_3$ requires C, 79.8; H, 6.4%); ν_{max}/cm^{-1} 1700 (C=O) and 1583 (C=C); δ_H(90 MHz) 2.60 (3 H, s, $COCH_3$), 3.62 (2 H, br d, *J* 5, $ArCH_2$), 3.88 (3 H, s, OCH_3), 4.80–5.14 (2 H, m, vinyl CH_2), 4.96 (2 H, s, OCH_2Ph), 5.70–6.14 (1 H, m, vinyl CH), 7.30–7.66 (7 H, m, OCH_2Ph, 6- and 7-H) and 7.96–8.18 (2 H, m, 5- and 8-H); *m*/*z* 346 (M^+, 40%), 255 (100), 240 (55), 213 (35) and 91 (84).

2-*Allyl*-1-*benzyloxy*-3-(1-*hydroxyethyl*)-4-*methoxynaphthalene* **20**.—The naphthalene **19** (2.91 g, 8.41 mmol) in dry ether (20 cm^3) was added to a stirred suspension of lithium aluminium hydride (1.12 g, 33.6 mmol) in dry ether (20 cm^3). After 20 min, TLC showed that all starting material had been consumed and the reaction was quenched by the addition of

saturated aqueous ammonium chloride followed by magnesium sulfate. Evaporation of the filtrate gave a residue which was chromatographed (eluent 20% ethyl acetate–light petroleum) to yield the *product* **20** (2.45 g, 83%) as pale yellow cubes, m.p. 45–46 °C (light petroleum) (Found: C, 79.5; H, 6.95. $C_{23}H_{24}O_3$ requires C, 79.3; H, 6.9%); ν_{max}(film)/cm^{-1} 3375 (OH) and 1586 (C=C); δ_H(90 MHz) 1.60 [3 H, d, *J* 8, CH(OH)CH_3], 3.59–4.03 [3 H, m, C*H*(OH)CH$_3$ and ArCH_2], 4.07 (3 H, s, OCH$_3$), 4.97 (2 H, s, OCH_2Ph), 4.81–5.43 (3 H, m, vinyl CH$_2$ and OH), 5.85–6.31 (1 H, m, vinyl CH), 7.35–7.65 (7 H, m, OCH$_2$*Ph*, 6- and 7-H) and 7.95–8.19 (2 H, m, 5- and 8-H): *m*/*z* 348 (M$^+$, 24%), 257 (100), 239 (20), 213 (20) and 91 (47).

trans-5-*Benzyloxy*-3,4-*dihydro*-10-*methoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-c]*pyran* **21**.—Compound **20** (50 mg, 0.14 mmol) was dissolved in dry dimethylformamide (3 cm^3) and dry nitrogen was passed through the solution for 10 min. Potassium *tert*-butoxide (96 mg, 0.86 mmol) was added to the solution which was then stirred under nitrogen at room temperature for 20 min. The mixture was then thrown into water and extracted exhaustively with ether. The residue obtained upon work-up was chromatographed (eluent 10% ethyl acetate–light petroleum) to afford the *naphthopyran* **21** (36 mg, 72%) as white needles, m.p. 106–107 °C (methylene dichloride–light petroleum) (Found: C, 79.5; H, 6.85. $C_{23}H_{24}O_3$ requires C, 79.3; H, 6.9%); ν_{max}/cm^{-1} 1592 (C=C); δ_H(90 MHz) 1.35 (3 H, d, *J* 6, 3-CH$_3$), 1.63 (3 H, d, *J* 6, 1-CH$_3$), 2.56 (1 H, dd, *J* 10 and 17, pseudoaxial 4-H), 3.10 (1 H, dd, *J* 3.5 and 17, pseudoequatorial 4-H), 3.92 (3 H, s, OCH$_3$), 4.01–4.20 (1 H, m, 3-H), 4.94 and 5.04 (each 1 H, d, *J* 10, OCH_2Ph), 5.35 (1 H, q, *J* 6, 1-H), 7.32–7.61 (7 H, m, OCH$_2$*Ph* and 7- and 8-H) and 7.98–8.15 (2 H, m, 6-and 9-H); *m*/*z* 348 (M$^+$, 10%), 257 (54), 213 (100) and 91 (30).

trans-3,4-*Dihydro*-10-*methoxy*-1,3-*dimethyl*-5-*methylsulfonyloxy*-1H-*naphtho*[2,3-c]*pyran* **23**.—Compound **21** (51 mg, 0.15 mmol) was dissolved in dry methylene dichloride (5 cm^3) at −78 °C and boron trichloride (35 mg, 0.30 mmol) in methylene dichloride was added to the solution. The mixture was then stirred at −78 °C for 10 min. The reaction was quenched by the addition of water to the mixture, and the organic layer was separated and washed with more water. The residue obtained upon work-up containing the naphthol **22** was immediately dissolved in dry pyridine (6 cm^3) and methanesulfonyl chloride (0.1 cm^3, 1.35 mmol) was added to the solution which was then stirred at room temperature for 3 h. Dilute hydrochloric acid was added to the mixture to quench the reaction and the organic material was extracted into methylene dichloride and the extract washed exhaustively with water. The residue obtained upon work-up was chromatographed (eluent 10% ethyl acetate–light petroleum) to afford the *product* **23** (41 mg, 81%) as white needles, m.p. 115–116 °C (methanol) (Found: C, 60.5; H, 5.95. $C_{17}H_{20}O_5S$ requires C, 60.7; H, 5.95%); ν_{max}/cm^{-1} 1594 (C=C) and 1339 and 1167 (OSO$_2$CH$_3$); δ_H(90 MHz) 1.36 (3 H, d, *J* 7, 3-CH$_3$), 1.62 (3 H, d, *J* 7, 1-CH$_3$), 2.74 (1 H, dd, *J* 11 and 18, pseudoaxial 4-H), 2.94 (1 H, dd, *J* 4 and 18 Hz, pseudoequatorial 4-H), 3.38 (3 H, s, OSO$_2$CH$_3$), 3.92 (3 H, s, OCH$_3$), 3.96–4.30 (1 H, m, 3-H), 5.33 (1 H, q, *J* 7, 1-H), 7.42–7.64 (2 H, m, 7- and 8-H) and 7.92–7.98 (2 H, m, 6- and 9-H); *m*/*z* 336 (M$^+$, 15%), 257 (32) and 213 (100).

trans-3,4-*Dihydro*-10-*methoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-c]*pyran* **24**.—Compound **23** (50 mg, 0.15 mmol) was dissolved in ethanol (7.5 cm^3) and water (2.5 cm^3) and the solution was boiled for 2 h with Raney nickel catalyst (50% in water; 400 mg). The catalyst was filtered off and washed exhaustively with methylene dichloride. The organic layer was washed with water. The residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate–light petroleum) to afford the *product* **24** (24 mg, 66%) as colourless rhomboids, m.p. 85–86 °C (methanol) (Found: C, 79.1; H, 7.45. $C_{16}H_{18}O_2$ requires C, 79.3; H, 7.4%); ν_{max}/cm^{-1} 1631 and 1559 (C=C); δ_H(90 MHz) 1.21 (3 H, d, *J* 7, 3-CH$_3$), 1.62 (3 H, d, *J* 7, 1-CH$_3$), 2.80 (1 H, dd, *J* 10.5 and 17, pseudoaxial 4-H), 2.94 (1 H, dd, *J* 5 and 17 Hz, pseudoequatorial 4-H), 3.90 (3 H, s, OCH$_3$), 3.98–4.36 (1 H, m, 3-H), 5.34 (1 H, q, *J* 7, 1-H), 7.30–7.50 (2 H, m, 7- and 8-H), 7.38 (1 H, s, 5-H), 7.60–7.80 (1 H, m, 6-H) and 7.90–8.06 (1 H, m, 9-H); *m*/*z* 242 (M$^+$, 25%), 227 (100) and 212 (30).

(1R,3R,4S)-3,4-*Dihydro*-4-*hydroxy*-10-*methoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-c]*pyran* **25** *and its Enantiomer*.—The napthopyran **24** (140 mg, 0.58 mmol) was dissolved in dry dimethyl sulfoxide (30 cm^3) and dry air passed through the solution for 15 min. Potassium *tert*-butoxide (250 mg, 2.23 mmol) was added to the solution which was then stirred at room temperature for 20 min under a stream of dry air. Further potassium *tert*-butoxide (130 mg, 1.16 mmol) was added to the mixture which was then stirred for a further 20 min. The reaction was quenched by the addition of water to the mixture which was then extracted exhaustively with ether. The combined ether layers were washed several times with water. The residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate–light petroleum) to yield the *product* **25** (100 mg, 67%) as white cubes, m.p. 141–142 °C (hexane) (Found: M$^+$, 258.1240. $C_{16}H_{18}O_3$ requires *M*, 258.1255); ν_{max}/cm^{-1} 3410 (OH) and 1631 and 1598 (C=C); δ 1.41 (3 H, d, *J* 6.5, 3-CH$_3$), 1.68 (3 H, d, *J* 6.6, 1-CH$_3$), 2.04 (1 H, br s, OH, D$_2$O exchangeable), 3.93 (3 H, s, OCH$_3$), 3.89–4.06 (1 H, m, partially obscured by OCH$_3$, 3-H), 4.50 (1 H, became sharp on D$_2$O exchange, br d, *J* 8, 4-H), 5.28 (1 H, q, *J* 6.6, 1-H), 7.48–7.52 (2 H, m, 7- and 8-H), 7.84 (1 H, s, 5-H) and 7.80–8.08 (2 H, m, 6- and 9-H); *m*/*z* 258 (M$^+$, 68%), 243 (100), 225 (18) and 214 (70).

3-*Bromo*-4-*isopropoxy*-5,7-*dimethoxy*-2-*naphthaldehyde* **27**.—Compound **26**[9] (330 mg, 0.93 mmol) was dissolved in dry benzene (40 cm^3) and boiled with activated manganese dioxide[12] (1.5 g) for 2 h. The solution was cooled, filtered and evaporated to yield a residue which was chromatographed (eluent 20% ethyl acetate–light petroleum) to afford the *aldehyde* **27** (290 mg, 88%) as yellow needles, m.p. 80–81 °C (light petroleum) (Found: C, 54.5; H, 4.7. $C_{16}H_{17}BRO_4$ requires C, 54.4; H, 4.8%); ν_{max}/cm^{-1} 1681 (C=O) and 1615 and 1573 (C=C); δ_H 1.33 (6 H, d, *J* 6.2, CHCH_3), 3.89 and 3.95 (each 3 H, s, OCH$_3$), 4.51 (1 H, septet, *J* 6.2, C*H*CH$_3$), 6.62 and 6.81 (each 1 H, d, *J* 2.2, 6- and 8-H), 8.01 (1 H, s, 1-H) and 10.50 (1 H, s, CHO); δ_C 21.91 (CH*C*H$_3$), 55.44 and 55.88 (2 × OCH$_3$), 77.64 (*C*HCH$_3$), 100.44 (C-6), 102.14 (C-1)[a], 114.16 (C-4a)[b], 120.47 (C-8a)[b], 125.28 (C-8)[a], 131.77 (C-2), 135.87 (C-3), 151.71 (C-4)[c], 156.49 (C-5)[c], 158.77 (C-7)[c] and 192.89 (CHO). Assignments with identical superscripts are interchangeable; *m*/*z* 354 (M$^+$, 19%), 352 (M$^+$, 19), 312 (100), 310 (100), 297 (9), 295 (9), 269 (25) and 267 (26).

(Z)- *and* (E)-3-*Bromo*-4-*isopropoxy*-5,7-*dimethoxy*-2-*prop*-1′-*enylnaphthalene* **28** *and* **29**.—Ethyltriphenylphosphonium bromide (673 mg, 1.81 mmol) was added to dry tetrahydrofuran (30 cm^3) under nitrogen at 0 °C followed by butyllithium (1.81 mmol, 1.6 mol equiv.). After the solution had been stirred at 0 °C for 15 min it was cooled to −78 °C and the aldehyde **27** (400 mg, 1.13 mmol) in dry tetrahydrofuran (5 cm^3) was added to it. The mixture was stirred at −78 °C for 15 min and then warmed to room temperature over 1 h. After this the reaction was quenched by the addition of water to the mixture which was then extracted with methylene dichloride. The extract was washed exhaustively with water. The residue obtained upon

work-up was chromatographed (eluent 5% ethyl acetate–light petroleum) to afford the *olefins* **28** and **29** (297 mg, 72%) as an oil; δ_H 1.32 and 1.34 (each 6 H, d, *J* 6.2, $CHCH_3$ of both isomers), 1.85 (3 H, dd, *J* 6.8 and 1.7, 3'-CH_3 of isomer **28**), 1.94 (3 H, dd, *J* 6.7 and 1.7, 3'-CH_3 of isomer **29**), 3.90 and 3.94 (each 6 H, s, OCH_3 of both isomers), 4.51 and 4.52 (each 1 H, septet, *J* 6.2, $CHCH_3$ of both isomers), 5.91 (1 H, dq, *J* 11.4 and 6.8, 2'-H of isomer **28**), 6.24 (1 H, dq, *J* 15.5 and 6.7, 2'-H of isomer **29**), 6.49 and 6.51 (each 1 H, d, *J* 2.2, 6-H of both isomers), 6.62 (1 H, dq, *J* 11.4 and 1.7, 1'-H of isomer **28**), 6.69 (2 H, d, *J* 2.2, 8-H of both isomers), 6.87 (1 H, dq, 15.5 and 1.7, 1'-H of isomer **29**), 7.37 (1 H, s, 1-H of isomer **28**) and 7.54 (1 H, s, 1-H of isomer **29**).

(E)-3-*Bromo*-4-*isopropoxy*-5,7-*dimethoxy*-2-*prop*-1'-*enylnaphthalene* **29**.—Bis(acetonitrile)dichloropalladium(II)[10] (20 mg) was added to a mixture of *Z*- and *E*-olefins **28** and **29** (100 mg, 0.27 mmol) dissolved in dry methylene dichloride (10 cm^3). This reaction mixture was stirred for 3 h at room temperature after which it was filtered. The residue obtained upon evaporation of the filtrate was chromatographed (eluent 5% ethyl acetate–light petroleum) to yield the *product* **29** (90 mg, 90%) as a yellow oil (Found: C, 59.4; H, 6.1. $C_{18}H_{21}BrO_3$ requires C, 59.2; H, 5.75%); ν_{max}(film)/cm^{-1} 1617 and 1571 (C=C); δ_H 1.32 (6 H, d, *J* 6.2, $CHCH_3$), 1.94 (3 H, dd, *J* 6.7 and 1.7, 3'-CH_3), 3.90 and 3.94 (each 3 H, s, OCH_3), 4.51 (1 H, septet, *J* 6.2, $CHCH_3$), 6.24 (1 H, dq, *J* 15.5 and 6.7, 2'-H), 6.49 and 6.69 (each 1 H, d, *J* 2.2, 6- and 8-H), 6.87 (1 H, dq, *J* 15.5 and 1.7, 1'-H) and 7.54 (1 H, s, 1-H); δ_C 18.65 (3'-CH_3), 21.95 ($CHCH_3$), 55.26 and 55.70 (2 × OCH_3), 76.36 ($CHCH_3$), 98.61 (C-6), 99.03 (C-1)[a], 115.55 (C-4a)[b], 120.02 (C-8)[a], 124.15 (C-8a)[b], 128.76 (C-1')[c], 130.92 (C-2')[c], 136.55 (C-2)[d], 137.35 (C-3)[d], 151.94 (C-4)[e], 156.63 (C-5)[e] and 158.13 (C-7)[e]; *m/z* 366 (M^+, 24%), 364 (M^+, 24), 324 (100), 322 (100), 281 (8), 279 (8) and 243 (15).

(E)-3-(1-*Hydroxyethyl*)-4-*isopropoxy*-5,7-*dimethoxy*-2-*prop*-1'-*enylnaphthalene* **31**.—The *E*-olefin **29** (80 mg, 0.22 mmol) was dissolved in dry tetrahydrofuran (15 cm^3) at −78 °C under nitrogen and butyllithium (0.31 mmol, 1.4 mol equiv.) was added to it. After the solution had been stirred for 30 min at this temperature under nitrogen an excess of acetaldehyde (0.5 cm^3) was added to it and the whole stirred for a further 15 min. The reaction was quenched by the addition of water to the mixture which was then extracted with ether. The residue obtained upon work-up was chromatographed (eluent 10% ethyl acetate–light petroleum) to afford the *product* **31** (42 mg, 58%) as an oil (Found: C, 72.3; H, 8.2. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%); ν_{max}(film)/cm^{-1} 3419 (OH) and 1618 and 1571 (C=C); δ_H 1.24 and 1.32 (each 3 H, d, *J* 6.1, $CHCH_3$), 1.58 (3 H, d, *J* 6.8, CH_3CHOH), 1.92 (3 H, dd, *J* 6.6 and 1.7, 3'-CH_3), 2.32 (1 H, br s, OH, D_2O exchangeable), 3.87 and 3.92 (each 3 H, s, OCH_3), 4.28 (1 H, septet, *J* 6.1, $CHCH_3$), 5.76 (1 H, q, *J* 6.8, CH_3CHOH), 6.13 (1 H, dq, *J* 15.5 and 6.6, 2'-H), 6.42 and 6.66 (each 1 H, d, *J* 2.2, 6- and 8-H), 7.24 (1 H, dq, *J* 15.5 and 1.7, 1'-H) and 7.47 (1 H, s, 1-H); δ_C 18.74, 21.55, 22.38 and 23.36 (4 × $CHCH_3$), 55.23 and 55.69 (2 × OCH_3), 65.16 and 77.00 (2 × $CHCH_3$), 98.54 (C-1)[a], 98.69 (C-6)[a], 114.69 (C-4a)[b], 121.49 (C-8)[a], 127.69 (C-1')[c], 130.29 (C-2')[c], 130.49 (C-8a)[b], 137.11 (C-2)[d], 137.40 (C-3)[d], 150.09 (C-4)[e], 157.09 (C-5)[e] and 157.93 (C-7)[e]; *m/z* 330 (M^+, 40%), 315 (37), 300 (35), 272 (55) and 254 (100). A further compound isolated from the mixture was the *E*-olefin **33** (6 mg, 10%), identical with authentic material.[10]

(Z)- *and* (E)-3-(1-*Hydroxyethyl*)-4-*isopropoxy*-5,7-*dimethoxy*-2-*prop*-1'-*enylnaphthalene* **30** *and* **31**.—A mixture of the *Z*-olefin **28** and *E*-olefin **29** (100 mg, 0.28 mmol) was dissolved in dry tetrahydrofuran (20 cm^3) at −78 °C under nitrogen. Butyllithium (0.39 mmol, 1.4 mol equiv.) was added to the solution which was then stirred for 30 min at this temperature. An excess of acetaldehyde (0.8 cm^3) was added to the solution which was then stirred for a further 15 min at −78 °C. The reaction was quenched by the addition of water to the mixture which was then extracted with ether. The residue obtained upon work-up was chromatographed (eluent 10% ethyl acetate–light petroleum) to yield the products **30** and **31** (53 mg, 57%) as an oil; δ_H 1.22 and 1.30 (each 3 H, d, *J* 6.1, $CHCH_3$ of isomer **30**), 1.24 and 1.32 (each 3 H, d, *J* 6.1, $CHCH_3$ of isomer **31**), 1.52 (3 H, d, *J* 6.8, CH_3CHOH of isomer **30**), 1.58 (3 H, d, *J* 6.8, CH_3CHOH of isomer **31**), 1.76 (3 H, dd, *J* 6.9 and 1.8, 3'-CH_3 of isomer **30**), 1.92 (3 H, dd, *J* 6.6 and 1.7, 3'-CH_3 of isomer **31**), 2.32 br (1 H, s, OH of isomer **31**), 2.71 br (1 H, s, OH of isomer **30**), 3.87, 3.90, 3.92 and 3.95 (each 3 H, s, OCH_3 of both isomers), 4.25 and 4.28 (each 1 H, septet, *J* 6.1, $CHCH_3$ of both isomers), 5.62 (1 H, q, *J* 6.8, CH_3CHOH of isomer **30**), 5.76 (1 H, q, *J* 6.8, CH_3CHOH of isomer **31**), 5.92 (1 H, dq, *J* 11.4 and 6.9, 2'-H of isomer **30**), 6.13 (1 H, dq, *J* 15.5 and 6.6, 2'-H of isomer **31**), 6.42 and 6.49 (each 1 H, d, *J* 2.2, 6-H of both isomers), 6.64 and 6.66 (each 1 H, d, *J* 2.2, 8-H of both isomers), 6.94 (1 H, dq, *J* 11.4 and 1.8, 1'-H of isomer **30**), 7.21 (1 H, s, 1-H of isomer **30**), 7.24 (1 H, dq, *J* 15.5 and 1.7, 1'-H of isomer **31**) and 7.47 (1 H, s, 1-H of isomer **31**). A mixture of olefins **32** and **33** (10 mg, 13%), identical with authentic material[10] was also isolated.

trans-3,4-*Dihydro*-10-*isopropoxy*-7,9-*dimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-c]*pyran* **34**.—Compound **31** (40 mg, 0.12 mmol) was dissolved in dry dimethylformamide (5 cm^3) and dry nitrogen was passed through the solution for 15 min. Potassium *tert*-butoxide (148 mg, 1.32 mmol) was added to the solution which was then stirred under nitrogen for 2 h at 75 °C. The reaction was quenched by the addition of water to the mixture which was then extracted exhaustively with ether. The residue obtained upon work-up was chromatographed (eluent 10% ethyl acetate–light petroleum) to yield the *product* **34** (33 mg, 83%) as white cubes, m.p. 133–134 °C (light petroleum) (Found: C, 72.7; H, 7.6. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%); ν_{max}/cm^{-1} 1626 and 1572 (C=C); δ_H 1.06 and 1.41 (each 3 H, d, *J* 6.1, $CHCH_3$), 1.30 (3 H, d, *J* 6.3, 3-CH_3), 1.55 (3 H, d, *J* 6.6, 1-CH_3), 2.72–2.84 (2 H, m, pseudoaxial and pseudoequatorial 4-H), 3.85 and 3.90 (each 3 H, s, OCH_3), 4.01–4.20 (1 H, m, 3-H), 4.28 (1 H, septet, *J* 6.1, $CHCH_3$), 5.34 (1 H, q, *J* 6.6, 1 H), 6.39 and 6.59 (each 1 H, d, *J* 2.3, 8- and 6-H) and 7.12 (1 H, s, 5-H); δ_C 20.51, 21.21, 21.78 and 22.95 (4 × $CHCH_3$), 36.15 (CH_2), 55.17 and 55.70 (2 × OCH_3), 62.56, 69.68 and 76.91 (3 × $CHCH_3$), 97.95 (C-5)[a], 98.03 (C-6)[a], 114.84 (C-4a)[b], 121.68 (C-8)[a], 128.89 (C-5a)[b], 133.29 (C-9a)[b], 136.57 (C-10a)[b], 149.06 (C-7)[c], 156.78 (C-9)[c] and 157.36 (C-10)[c]; *m/z* 330 (M^+, 20%), 315 (9) and 273 (100).

(1R,3R,4S)-3,4-*Dihydro*-4-*hydroxy*-10-*isopropoxy*-7,9-*dimethoxy*-1,3-*dimethyl*-1H-*naphtho*[2,3-c]*pyran* **35** *and its Enantiomer*.—The naphthopyran **34** (50 mg, 0.15 mmol) was dissolved in dry dimethylformamide (15 cm^3) and dry air was passed through the solution for 15 min. Potassium *tert*-butoxide (135 mg, 1.20 mmol) was added to the solution which was then stirred at room temperature with dry air bubbling through it. After 1 h, the reaction was quenched by the addition of water to the mixture and the organic material was extracted into ether. The extract was washed exhaustively with water. The residue obtained upon work-up was chromatographed (eluent 20% ethyl acetate–light petroleum) to afford the lactone **36** (3 mg, 8%) as an oil; ν_{max}(film)/cm^{-1} 1757 (C=O) and 1619 (C=C); δ_H 1.18 and 1.44 (each 3 H, d, *J* 6.1, $CHCH_3$), 1.74 (3 H, d, *J* 6.6, 3-CH_3), 3.94 and 3.99 (each 3 H, s, OCH_3), 4.44 (1 H, septet,

J 6.1, C*H*CH_3), 5.71 (1 H, q, *J* 6.6, 3-H), 6.65 and 6.88 (each 1 H, d, *J* 2.2, 6- and 8-H) and 8.02 (1 H, s, 9-H); * *m/z* 316 (M^+, 25%), 274 (59), 259 (100), 231 (38) and 203 (19). The second fraction afforded the *naphthopyran* **35** (17 mg, 33%) as a yellow oil (Found: M^+, 346.1799. $C_{20}H_{26}O_5$ requires *M*, 346.1780); ν_{max}(film)/cm^{-1} 3413 (OH), 1624 and 1575 (C=C); δ_H 1.07 and 1.44 (each 3 H, d, *J* 6.1, CHCH_3), 1.37 (3 H, d, *J* 6.1, 3-CH_3), 1.63 (3 H, d, *J* 6.5, 1-CH_3), 1.94 (1 H, br s, OH, D_2O exchangeable), 3.89 and 3.95 (each 3 H, s, OCH_3), 3.90 (1 H, dq, *J* 7.8 and 6.1, partially obscured by OCH_3, 3-H), 4.35 (1 H, septet, *J* 6.1, C*H*CH_3), 4.45 (1 H, br d, becomes sharp on D_2O exchange, *J* 7.8, 4-H), 5.27 (1 H, q, *J* 6.5, 1-H), 6.49 and 6.74 (each 1 H, d, *J* 2.3, 8- and 6-H) and 7.61 (1 H, s, 5-H); *m/z* 346 (M^+, 28%), 289 (100) and 271 (28). Starting material (15 mg, 30%) was recovered.

* Compound **36** is numbered from the lactone carbonyl in an anticlockwise manner and therefore differs markedly in this respect from the naphthopyrans reported in this paper.

Acknowledgements

Financial support from the South African Council for Scientific and Industrial Research and the Councils of the Universities of Cape Town and the Western Cape is gratefully acknowledged.

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Paper 3/05605H
Received 17*th September* 1993
Accepted 17*th November* 1993