Regioselective Bromination, Debromination and Bromine Migration in a 2-Acetoxymethyl-4,5,7-trialkoxynaphthalene

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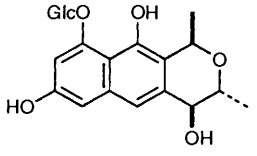
Dibromination of 2-acetoxymethyl-4-isopropoxy-5,7-dimethoxynaphthalene **10** in buffered solution afforded the 3,8-dibromo derivative **13**. Similar monobromination of compound **10** yielded the 8-bromo compound **15**, whereas monobromination in the absence of the buffer yielded the isomeric 1-bromonaphthalene **16**. Conversion of **15** into **16** was effected with trifluoroacetic acid. Selective monodebromination of the dibromo compound **13** gave rise to a third isomer, the 3-bromo compound **18**.

Following our recently reported synthesis of the racemates of the naphthoquinonoid halves of the aphid pigments, the protoaphins,[1,2] we wished to establish viable routes to glucoside B **1**, the remaining naphthalenic portion common to each of the three naturally occurring protoaphins.[3] This series of three publications describes different aspects of our investigations, and in this paper we report on the regioselective bromination of 2-acetoxymethyl-4-isopropoxy-5,7-dimethoxynaphthalene **10**,‡ as we believed these products of bromination would be useful intermediates in investigating routes to the target compound **1**.



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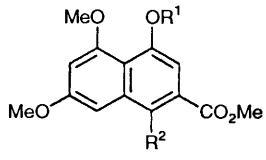
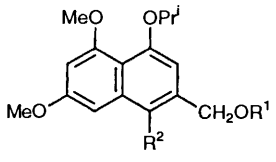
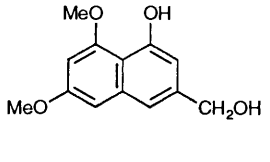


2 R^1 = Ac, R^2 = H
3 R^1 = Ac, R^2 = D
4 R^1 = R^2 = H
5 R^1 = H, R^2 = D
6 R^1 = Pr^i, R^2 = H
7 R^1 = Pr^i, R^2 = D



8 R^1 = R^2 = H
9 R^1 = H, R^2 = D
10 R^1 = Ac, R^2 = H
11 R^1 = Ac, R^2 = D



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Results and Discussion

The naphthyl acetate precursor **2** was available either through a standard Stobbe synthesis[4] or, in much better yield, through the more recently reported Sargent modification.[5] Selective hydrolysis of the acetate **2** afforded the naphthol **4**,[6] which was converted into the corresponding isopropyl ether **6**, in a yield of 81%, in order to provide for subsequent selective deprotection of the naphthalenic C-4 oxygen. Reduction of the ester function with lithium aluminium hydride afforded the alcohol **8**. This compound was also available through reduction of the acetate **2** with lithium aluminium hydride, which afforded the hydroxymethylnaphthol **12** in good yield, followed by selective isopropylation of its phenolic group. Since subsequent brominations of the naphthalene **8** with bromine in acetic acid afforded brominated products which were mixtures of alcohols and their derived acetates, the alcohol **8** was converted into the corresponding acetate **10**, whose reactions with bromine under various conditions were then explored. The ^{1}H NMR spectrum of compound **10** showed resonances at δ 6.45, 6.67, 6.74 and 7.24 for the protons 6-H, 8-H, 3-H and 1-H, respectively.

Treatment of the naphthalenic acetate **10** with 2 equiv. of both bromine and sodium acetate in acetic acid afforded a high yield of a dibromonaphthalene in which one bromine was attached to each of the two rings; this assignment was supported by a molecular ion cluster in the mass spectrum of the product at *m/z* 478, 476 and 474 with a relative signal intensity of *ca.* 1:2:1, as well as two singlets at δ 6.66 and 8.02 in the ^{1}H NMR spectrum. These chemical shifts suggested the assignment as the 3,8-dibromo derivative **13**, with 1-H being deshielded by the *peri*-bromine. However, these data did not rigorously exclude alternative structures. Unambiguous evidence for the assignment of structure **13** was obtained by replacement of 1-H by deuterium in the starting acetate **10** to afford the 1-deuterio derivative **11** by the method described below. Similar dibromination of **11**, as for **10** above, afforded the deuteriated analogue **14** of **13**, for which the ^{1}H NMR spectrum showed a lone aromatic singlet at δ 6.66. This confirmed the assignment of the structure **13** to the dibrominated product.

In the formation of the dibromonaphthalene **13** it is assumed that initial bromination occurs on the more electron-rich ring carrying the two methoxy groups, and at the kinetically favoured α-position. There are many precedents for similar general electrophilic substitution in other naphthalenes.[7] The second site of electrophilic attack is at C-3, a β-position on the naphthalenic system, as attack at C-1 would be prevented owing to unacceptable *peri* interactions between the two large bromine atoms.

That bromination had indeed occurred initially at C-8 under the reaction conditions described was confirmed by reaction of the naphthalenic acetate **10** with 1 equiv. each of bromine and sodium acetate in acetic acid. Under these buffered conditions, the 8-monobromo derivative **15** was obtained as the sole

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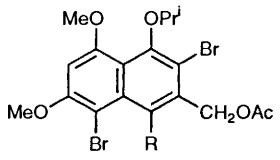
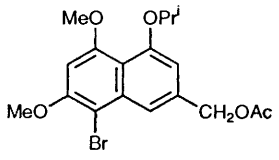
‡ The numbering used maintains consistency with related naphthalenes reported in earlier papers in this series; see references 1 and 2.

product. This assignment was supported in the mass spectrum by a molecular ion consisting of a pair of signals of approximately equal intensity at *m/z* 398 and 396, and a ^{1}H NMR spectrum which showed a singlet at δ 6.60 and two doublets (*J* 1.5 Hz) at δ 6.74 and 7.77 in the aromatic region. The latter doublets showed further minor broadening through long-range coupling to the adjacent benzylic methylene protons.

Bromination of the naphthalenic acetate **10** with 1 equiv. of bromine in acetic acid in the absence of the buffer sodium acetate afforded a new monobromo naphthalene, whose ^{1}H NMR spectrum showed a singlet in the aromatic region at δ 6.79 and a pair of doublets at δ 6.49 and 7.21. This new product was assigned the structure of the 1-bromonaphthalene **16** on account of the deshielding (0.54 ppm) of 8-H in this product relative to the starting material **10**. This value compared closely with the corresponding deshielding (0.53 ppm) of 1-H in the 8-monobromonaphthalene **15** relative to the same starting material **10**.



13 R = H
14 R = D



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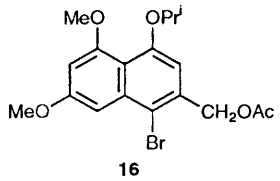

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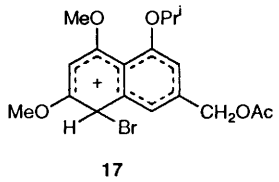

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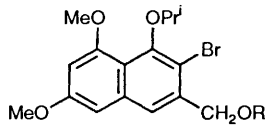
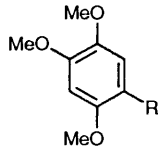
The fact that the 8-monobromonaphthalene **15** was formed in the presence of sodium acetate as buffer, whereas the 1-monobromonaphthalene **16** was obtained in the absence of that buffer suggested that the 8-bromo compound **15** is the kinetic product whereas the 1-bromo isomer **16** is the thermodynamic product. Furthermore, isomerisation of the former into the latter in the absence of buffer may occur through formation of hydrogen bromide in the latter case. Here, the presumably initially formed 8-monobromo derivative **15** is subjected to electrophilic attack at C-8 by hydrogen ions to give the intermediate cation **17**; this loses Br^+, which then attacks at C-1 to afford the thermodynamically favoured product **16**.

There is, of course, no evidence that the 8-monobromo compound **15** is actually derived in the absence of the buffer, as any σ-complex **17** formed from starting material may do so reversibly, and, indeed, the precise mechanism of the formation of the 1-bromonaphthalene is not relevant to this study. This notwithstanding, however, it was shown in a separate experiment that the 8-monobromo compound **15** could be converted into the 1-isomer **16** using trifluoroacetic acid in methylene dichloride, a transformation which did not occur when trifluoroacetic acid was replaced by the weaker analogue, acetic acid.

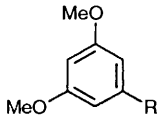
Since it was now established that bromine was indeed transferred from one site to another on the naphthalene nucleus, and since methods had now been formulated for preparing both the 8-monobromo compound **15** and the 1-monobromo compound **16**, the possibility was considered of establishing a route to the 3-monobromo isomer **18** from the 3,8-dibromonaphthalene **13** by selectively removing the bromine from C-8 of compound **13** in the presence of an acid. This would be possible if two conditions were met. The first of these was that the isomerisation of the 8-bromo compound **15** to the 1-bromo isomer **16** occurred *via* an intermolecular process involving free bromonium ions. The second condition was that a nucleophile more potent than the product **18** should be present to capture the free bromonium ion. Amongst the possibilities considered for the nucleophile, the first that was attempted proved to be highly successful. This was 1,2,4-trimethoxybenzene **20**, which is



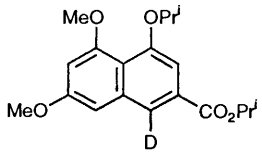
18 R = Ac
19 R = H



20 R = H
21 R = Br



22 R = CO$_2$Me
23 R = CD$_2$OH
24 R = CDO



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reported[8] to undergo extremely rapid bromination. When the 3,8-dibromonaphthalene **13** in methylene dichloride, containing 1 equiv. of the trimethoxybenzene **20**, was treated with trifluoroacetic acid, the desired products **18** and **21** were obtained as a two-component mixture which was difficult to separate other than by repeated preparative thin layer chromatography, a method not conducive to large scale synthesis. This was overcome by subjecting the reaction mixture to reduction with lithium aluminium hydride, which gave rise to the alcohol **19**, and this was readily separated from the trimethoxybromobenzene **21** by column chromatography. Compound **19** was reacetylated with acetic anhydride containing pyridine to afford **18**. This method provided a convenient route in very good yield for larger quantities of compound **18**, for which the aromatic protons appeared as a pair of doublets (*J* 2 Hz) at δ 6.49 and 6.68 due to 6-H and 8-H, respectively, and a singlet at δ 7.43 due to 1-H, which differentiated it from the regioisomers **15** and **16**.

Viable routes to the 1-, 3- and 8-monobromo derivatives of the naphthalene **10** have, therefore, been established, and the use of two of these, compounds **15** and **18**, will be reported in the following papers of this series.[9,10]

The 1-deuterionaphthalene **11** was prepared from methyl 3,5-dimethoxybenzoate **22** by reduction with lithium aluminium deuteride, followed by oxidation of the dideuteriated alcohol **23** with activated manganese dioxide to afford the deuteriated benzaldehyde **24**. This was, in turn, converted into the naphthyl acetate **3**, using Cameron's method[4] for the formation of the analogue **2**.

Methanolic sodium hydroxide hydrolysis of the deuteriated acetate **3**, to obtain the naphthol **5** related to **4**, provided a ^{1}H NMR spectrum which showed that deuterium had exchanged for hydrogen to the extent of approximately 50% under the protic conditions, giving rise to contamination of **5** by **4**. This was avoided by aprotic conversion of acetate **3** into the deuteriated isopropyl ether **7** using potassium *tert*-butoxide in dimethylformamide containing an excess of isopropyl bromide. In this reaction, the methyl deuterionaphthoate **7** was contaminated by the corresponding isopropyl ester **25**. This product, which had no doubt arisen through methyl ester alkyl-oxygen cleavage by butoxide (facilitated by the dipolar aprotic

solvent) and subsequent alkylation with isopropyl bromide, posed no difficulty as both esters **7** and **25** were reduced with lithium aluminium hydride to the same alcohol **9** which was, in turn, converted into the acetate **11**. Other examples of dealkylation by butoxide in a dipolar aprotic solvent have been known for some time.[11]

The structures of all deuteriated naphthalenes were assigned by comparison of their ^{1}H NMR and mass spectra with those of their non-deuteriated analogues. The NMR spectra showed the absence of the 1-H proton, while the mass spectra showed the molecular ion and appropriate fragments at one *m/z* value higher, for the deuteriated species.

Experimental

Unless otherwise stated, all ^{1}H NMR spectra were measured at 90 MHz on a Bruker WH-90 spectrometer for solutions in [^{2}H]chloroform with tetramethylsilane as internal reference, while that at 200 MHz was recorded on a Varian VXR instrument. *J* Values are given in Hz. IR spectra were measured for Nujol mulls using a Perkin-Elmer 237 spectrophotometer. Mass spectra were recorded on a VG Micromass 16 F mass spectrometer. Preparative layer chromatography (PLC) was performed on glass plates coated with Merck Kieselgel 60 F_{254}, while column chromatography refers to dry-packed columns using the same gel (70–230 mesh). Light petroleum refers to the fraction of b.p. 60–80 °C, and ether to diethyl ether. The phrase 'residue obtained upon work-up' refers to the residue when the organic layer was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure.

2-Hydroxymethyl-5,7-dimethoxy-4-naphthol **12**.—Compound **2** (249 mg, 0.82 mmol) was dissolved in dry ether (30 cm^3) and added dropwise to a suspension of an excess of lithium aluminium hydride in dry ether (20 cm^3) over a period of 30 min. Stirring was continued at room temperature for a further 2 h. Saturated aqueous ammonium chloride was added to the mixture followed by anhydrous magnesium sulfate. Removal of the ether under reduced pressure afforded the *product* (175 mg, 91%), m.p. 144–145 °C (ethanol–water) (Found: C, 66.4; H, 6.05. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.0%); ν_{max}/cm^{-1} 3350 (OH); δ 1.70 (1 H, s, CH_2OH), 3.92 and 3.98 (each 3 H, s, OCH_3), 4.70 (2 H, s, CH_2), 6.42 (1 H, d, *J* 2.5, 6-H), 6.67 (1 H, d, *J* 2.5, 8-H), 6.68 (1 H, d, *J* 1.5, 3-H), 7.14 (1 H, d, *J* 1.5, 1-H) and 9.08 (1 H, s, 4-OH).

Methyl 4-Isopropoxy-5,7-dimethoxy-2-naphthoate **6**.—A solution of naphthol **4**[4] (11.25 g, 37 mmol) in dimethylformamide (300 cm^3) was stirred at 90 °C for 18 h with isopropyl bromide (40.67 g, 330 mmol) and anhydrous potassium carbonate (45.63 g, 330 mmol). The residue was filtered off and the filtrate was dissolved in ether and the solution washed several times with water. The residue obtained upon work-up was chromatographed (eluent 10% ethyl acetate–light petroleum) to afford the *product* (10.65 g, 82%), m.p. 66–68 °C (ethanol) (Found: C, 66.8; H, 6.7. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%); ν_{max}/cm^{-1} 1725 (C=O); δ 1.40 (6 H, d, *J* 7, $CHCH_3$), 3.63, 3.87, and 3.91 (each 3 H, s, OCH_3), 4.61 (1 H, sept., *J* 7, $CHCH_3$), 6.53 (1 H, d, *J* 2, 6-H), 6.75 (1 H, d, *J* 2, 8-H), 7.31 (1 H, d, *J* 1.5, 3-H) and 8.00 (1 H, d, *J* 1.5, 1-H); *m/z* 304 (M$^+$, 37%), 262 (100), 219 (18), 208 (10) and 43 (12).

2-Hydroxymethyl-4-isopropoxy-5,7-dimethoxynaphthalene **8**.—The ester **6** (10.65 g, 35 mmol) in dry ether (300 cm^3) was added dropwise over 30 min to a stirred suspension of lithium aluminium hydride (2.10 g, 55 mmol) in dry ether (200 cm^3), and stirring was continued for 30 min. Work-up as for compound **12** above afforded a residue which was chromatographed (eluent 15% ethyl acetate–light petroleum) to give the *product* (8.89 g, 92%) as rods, m.p. 66–68 °C (light petroleum) (Found: C, 69.8; H, 7.2. $C_{16}H_{20}O_4$ requires C, 69.6; H, 7.3%); ν_{max}/cm^{-1} 3500 (OH); δ 1.36 (6 H, d, *J* 7, $CHCH_3$), 2.33 (1 H, t, *J* 6, OH, D_2O exchangeable), 3.81 and 3.86 (each 3 H, s, OCH_3), 4.49 (1 H, sept., *J* 7, $CHCH_3$), 4.65 (2 H, d, *J* 6, CH_2, collapses to singlet with D_2O), 6.41 (1 H, d, *J* 2, 6-H), 6.57 (1 H, d, *J* 2, 8-H), 6.67 (1 H, d, *J* 1.5, 3-H) and 7.13 (1 H, d, *J* 1.5, 1-H); *m/z* 276 (M$^+$, 38%), 234 (100), 219 (10) and 191 (18).

2-Acetoxymethyl-4-isopropoxy-5,7-dimethoxynaphthalene **10**.—The alcohol **8** (968 mg, 3.51 mmol) was dissolved in acetic anhydride (730 mg, 7.16 mmol) and pyridine (6 cm^3) and the solution was heated at 50 °C for 90 min. The mixture was thrown into water and extracted with ether. The organic layer was washed with saturated aqueous sodium hydrogen carbonate followed by dilute hydrochloric acid and then water. The residue obtained upon work-up was chromatographed (eluent 15% ethyl acetate–light petroleum) to afford the *product* (967 mg, 87%), m.p. 74–75 °C (light petroleum) (Found: C, 68.4; H, 6.7. $C_{18}H_{22}O_5$ requires C, 67.9; H, 6.95%); ν_{max}/cm^{-1} 1739 (C=O); δ 1.38 (6 H, d, *J* 7, $CHCH_3$) 2.10 (3 H, s, $COCH_3$), 3.85 and 3.87 (each 3 H, s, OCH_3), 4.52 (1 H, sept., *J* 7, $CHCH_3$), 5.13 (2 H, s, CH_2), 6.45 (1 H, d, *J* 2, 6-H), 6.67 (1 H, d, *J* 2, 8-H), 6.74 (1 H, d, *J* 1.5, 3-H) and 7.24 (1 H, d, *J* 1.5, 1-H); *m/z* 318 (M$^+$, 100%), 276 (19), 233 (57), 219 (32), 205 (71) and 43 (83).

2-Acetoxymethyl-3,8-dibromo-4-isopropoxy-5,7-dimethoxynaphthalene **13**.—A solution of bromine (171 mg, 1.07 mmol) in acetic acid (2 cm^3) was added dropwise to a solution of the acetate **10** (146 mg, 0.46 mmol) and anhydrous sodium acetate (95 mg, 1.16 mmol) in acetic acid (2 cm^3). After the mixture had been stirred for 15 min it was added to methylene dichloride, and the whole washed with saturated aqueous sodium hydrogen carbonate and then water. The residue obtained upon work-up was chromatographed (eluent 10% ethyl acetate–light petroleum) to obtain the *product* (187 mg, 85%), m.p. 119–122 °C (Found: C, 45.7; H, 4.35. $C_{18}H_{20}Br_2O_5$ requires C, 45.4; H, 4.2%); ν_{max}/cm^{-1} 1747 (C=O); δ 1.29 (6 H, d, *J* 2, $CHCH_3$), 2.18 (3 H, s, $COCH_3$), 3.96 and 3.98 (each 3 H, s, OCH_3), 4.48 (1 H, sept., *J* 7, $CHCH_3$), 5.30 (2 H, s, CH_2), 6.66 (1 H, s, 6-H) and 8.02 (1 H, s, 8-H); *m/z* 478 (M$^+$, 12%), 476 (M$^+$, 25), 474 (M$^+$, 13), 436 (47), 434 (88), 432 (45), 392 (18), 353 (28), 313 (100) and 311 (96).

2-Acetoxymethyl-8-bromo-4-isopropoxy-5,7-dimethoxynaphthalene **15**.—A solution of bromine (25 mg, 0.16 mmol) in acetic acid (1 cm^3) was added dropwise to a solution of the acetate **10** (50 mg, 0.16 mmol) and anhydrous sodium acetate (20 mg, 0.24 mmol) in methylene dichloride (5 cm^3). The mixture was stirred for 30 min and then washed with saturated aqueous sodium hydrogen carbonate followed by water. The residue obtained upon work-up was chromatographed (eluent 15% ethyl acetate–light petroleum) to obtain the *product* (44 mg, 80%), m.p. 119–121 °C (ethyl acetate–light petroleum) (Found: C, 54.2; H, 5.3. $C_{18}H_{21}BrO_5$ requires C, 54.4; H, 5.3%); δ 1.38 (6 H, d, *J* 7, $CHCH_3$), 2.10 (3 H, s, $COCH_3$), 3.92 and 3.97 (each 3 H, s, OCH_3), 4.56 (1 H, sept., *J* 7, $CHCH_3$), 5.18 (2 H, s, CH_2), 6.60 (1 H, s, 6-H), 6.74 (1 H, d, *J* 1.5, 3-H) and 7.77 (1 H, d, *J* 1.5, 1-H); *m/z* 398 (M$^+$, 58%), 396 (M$^+$, 57), 356 (71), 354 (72), 314 (21), 312 (23) and 233 (100).

2-Acetoxymethyl-1-bromo-4-isopropoxy-5,7-dimethoxynaphthalene **16**.—(a) A solution of bromine (69 mg, 0.41 mmol) in acetic acid (1 cm^3) was added dropwise to a stirred solution of the acetate **10** (132 mg, 0.41 mmol) in acetic acid (12 cm^3). The solution was stirred for 1.25 h at room temperature, after which methylene dichloride (10 cm^3) was added to it. The mixture

was then washed with saturated aqueous sodium hydrogen carbonate followed by water. The residue obtained upon work-up was chromatographed (eluent 5% ethyl acetate–light petroleum) to afford the *product* (140 mg, 86%), m.p. 96–97 °C (ethyl acetate–light petroleum) (Found: C, 54.5; H, 5.3. $C_{18}H_{21}BrO_5$ requires C, 54.4; H, 5.3%); ν_{max}/cm^{-1} 1733 (C=O); δ 1.37 (6 H, d, *J* 7, $CHCH_3$), 2.12 (3 H, s, $COCH_3$), 3.85 and 3.89 (each 3 H, s, OCH_3), 4.50 (1 H, sept., *J* 7, $CHCH_3$), 6.49 (1 H, d, *J* 2, 6-H), 6.79 (1 H, s, 3-H) and 7.21 (1 H, d, *J* 2, 8-H); *m/z* 398 (M^+, 23%), 396 (M^+, 26), 356 (13), 354 (13), 311 (13), 275 (16) and 233 (100).

(b) A solution of 8-bromonaphthalene **15** (45 mg, 0.11 mmol) in dry methylene dichloride (1 cm^3) was treated at 1.5 h intervals with a mixture of trifluoroacetic acid (8 mm^3, 13.3 mg, 0.11 mmol)* and acetic acid (6.3 mmol, 6.6 mg, 0.11 mmol) and stirred at room temperature. After three further additions of the acid mixture, the solution was neutralised with saturated aqueous sodium hydrogen carbonate (15 cm^3) and the whole was extracted with methylene dichloride (3 × 10 cm^3). The residue obtained upon work-up was chromatographed (10% ethyl acetate–light petroleum) to give the 1-bromo isomer **16** (44 mg, 98%) identical with that described in (a).

2-Acetoxymethyl-3-bromo-4-isopropoxy-5,7-dimethoxynaphthalene **18**.—(a) A solution of the 3,8-dibromonaphthalene **13** (151 mg, 0.32 mmol) and 1,2,4-trimethoxybenzene **20** (57 mg, 34 mmol) in methylene dichloride (4 cm^3) was stirred at room temperature in the presence of an excess of trifluoroacetic acid (0.12 cm^3, 1.6 mmol) for 12 h. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate and water. The residue obtained upon work-up was separated by PLC (eluent 5% ethyl acetate–light petroleum) to afford the required *product* **18** (113 mg, 90%), m.p. 95–97 °C (ethyl acetate–light petroleum) (Found: C, 54.5; H, 5.2. $C_{18}H_{21}BrO_5$, requires C, 54.4; H, 5.3%); ν_{max}/cm^{-1} 1737 (C=O); δ 1.31 (6 H, d, *J* 7, $CHCH_3$), 2.16 (3 H, s, $COCH_3$), 3.88 and 3.90 (each 3 H, s, OCH_3), 4.50 (1 H, sept., *J* 7, $CHCH_3$), 5.28 (2 H, s, CH_2), 6.49 (1 H, d, *J* 2, 6-H), 6.68 (1 H, d, *J* 2, 8-H) and 7.43 (1 H, s, 1-H); *m/z* 398 (M^+, 15%), 396 (M^+, 15), 356 (40), 354 (38), 275 (20) and 233 (100). An additional band afforded 2,4,5-trimethoxybromobenzene **21** (75 mg, 88%); δ 3.83, 3.86 and 3.88 (each 3 H, s, OCH_3), 6.58 (1 H, s, 3-H) and 7.03 (1 H, s, 6-H); *m/z* 248 (M^+, 100%), 246 (M^+, 100%), 233 (36), 231 (38), 205 (28) and 203 (30).

(b) Compound **19** (105 mg), was dissolved in acetic anhydride (2 cm^3) containing pyridine (1 cm^3) and the solution was warmed to 60 °C for 1 h and then cooled. Methylene dichloride was added to the solution which was then washed with saturated aqueous sodium hydrogen carbonate followed sequentially by water, dilute hydrochloric acid and then water. The residue obtained upon work-up was chromatographed (eluent 10% ethyl acetate–light petroleum) to afford the *product* **18** (112 mg, 95%) identical with material described in (a) above.

3-Bromo-2-hydroxymethyl-4-isopropoxy-5,7-dimethoxynaphthalene **19**.—(a) A solution of the 3,8-dibromonaphthalene **13** (151 mg, 0.32 mmol) and 1,2,4-trimethoxybenzene **20** (57 mg, 34 mmol) in methylene dichloride (4 cm^3) was stirred at room temperature in the presence of an excess of trifluoroacetic acid (0.12 cm^3, 1.6 mmol) for 12 h. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate and then water. The residue obtained upon work-up was dissolved in dry tetrahydrofuran (20 cm^3) and added to a stirred suspension of lithium aluminium hydride (36.5 mg, 0.96 mmol) in the same solvent (10 cm^3). The mixture was boiled under nitrogen for 1 h. Saturated aqueous ammonium chloride was carefully added to the cooled mixture, followed by anhydrous magnesium sulfate. The residue was filtered off and washed with methylene dichloride. Evaporation of the combined solutions afforded an oil which was chromatographed (eluent 10% ethyl acetate–light petroleum) to afford the by-product **21** (75 mg, 88%) followed by the *product* **19** (105 mg, 93%) as white grains, m.p. 126–127 °C (ethyl acetate–light petroleum) (Found: C, 54.4; H, 5.6. $C_{16}H_{19}BrO_4$ requires C, 54.1; H, 5.35%); ν_{max}/cm^{-1} 3467 (OH), 1621 and 1575 (C=C); δ_H(200 MHz) 1.29 (6 H, d, *J* 6.2, $CHCH_3$), 2.43 (1 H, br s, OH, D_2O exchangeable), 3.83 and 3.89 (each 3 H, s, OCH_3), 4.46 (1 H, sept., *J* 6.2, $CHCH_3$), 4.79 (2 H, s, CH_2), 6.46 and 6.61 (each 1 H, d, *J* 2.2, 6- and 8-H) and 7.47 (1 H, s, 1-H); δ_C 21.92 ($CHCH_3$), 55.25 and 55.66 (2 × OCH_3), 65.22 (CH_2), 77.82 ($CHCH_3$), 98.90 (C-6), 99.22 (C-1)[a], 113.76 (C-4a)[b], 116.64 (C-8a)[b], 121.59 (C-8)[a], 136.63 (C-3), 138.67 (C-2), 150.79 (C-4)[c], 156.54 (C-5)[c], and 158.21 (C-7)[c] (assignments with identical superscripts are interchangeable); *m/z* 356 (M^+, 18%), 354 (M^+, 18%), 314 (100), 312 (100), 271 (22), and 269 (22).

(b) The acetate **18** (100 mg, 0.25 mmol) was dissolved in a 1% w/v solution of potassium hydroxide (21 mg, 0.38 mmol) in methanol and the solution was stirred at room temperature for 10 min. The reaction was then quenched by the addition of dilute hydrochloric acid to the mixture. The organic material was extracted into ether and the solution washed with water. The residue obtained upon work-up was chromatographed (eluent 10% ethyl acetate–light petroleum) to yield the *product* **19** (82 mg, 92%) identical with material described in (a) above.

1-Deuterio-2-hydroxymethyl-4-isopropoxy-5,7-dimethoxynaphthalene **9**.—A solution of the acetate **3** (15 mg, 0.049 mmol) in dimethylformamide was treated with isopropyl bromide (0.6 cm^3, 6.4 mmol) and potassium *tert*-butoxide (55 mg, 0.49 mmol) and the mixture was then stirred for 2.5 h. The mixture was thrown into ether and the whole washed with water. The residue obtained upon work-up was chromatographed (PLC, eluent 30% ethyl acetate–light petroleum) to afford compound **7** (5.5 mg, 34%) and compound **25** (7 mg, 41%). For compound **25**, the ^1H NMR spectrum was as follows: δ 1.38 and 1.40 (each 6 H, d, *J* 7, $CHCH_3$), 3.88 and 3.89 (each 3 H, s, OCH_3), 4.64 and 5.26 (each 1 H, sept., *J* 7, $CHCH_3$), 6.53 (1 H, d, *J* 2, 6-H), 6.77 (1 H, d, *J* 2, 8-H) and 7.32 (1 H, s, 3-H). Compounds **7** and **25** were recombined and reduced with lithium aluminium hydride to afford the alcohol **9** (9 mg, 82%).

* 1 mm^3 ≡ 1 μl.

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