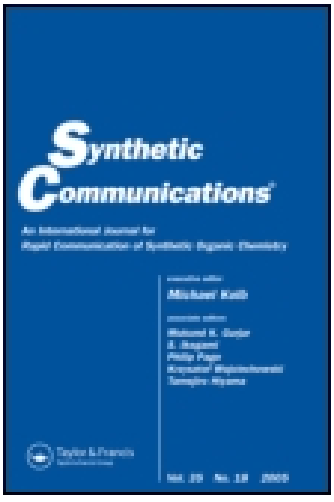

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Bromination Products of 2-Substituted 5,7-Dimethoxy-4-Naphthols

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Abstract: Bromination in acetic acid is favored at C-8 in 5,7-dimethoxy-4-naphthol when the C-2 substituent is methyl carboxylate, whereas C-1 is favored when the C-2 substituent is either acetoxymethylene or methyl.

Keywords: 2-Acetoxymethyl-5,7-dimethoxy-4-naphthol, brominations, 5,7-dimethoxy-2-methyl-4-napthol, methyl 5,7-dimethoxy-4-hydroxy-2-naphthoate

INTRODUCTION

In an earlier communication Giles et al.[1] described the treatment of naphthyl ester **1** with 2 mol of bromine and 2 mol of sodium acetate in acetic acid to afford the 3,8-dibromonaphthalene derivative **2**, whereas when the same ester was treated with one mol each of bromine and sodium acetate in acetic acid, only the 8-bromonaphthyl ester **3** was produced. (The same

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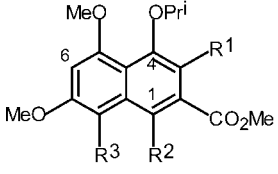
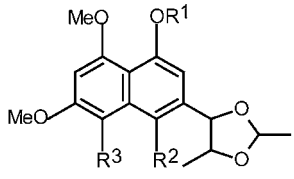
numbering system to that used by Giles et al.[1] will be adopted throughout the described work to maintain continuity.) Bromination in the absence of the buffer, on the other hand, afforded the 1-bromonaphthyl ester **4** as a single product. Treatment of a subsequent naphthyldioxolane **5** with titanium(IV) tetrachloride produced angular naphthopyrans **8** and **9**[2] in spite of the expectation that the presence of the bromine atom at C-8 would sterically discourage ring closure at C-1 and thus favor C-3 to produce the linear naphthopyran (viz., **10**) with C-10 having an isoproxy group (Figure 1).

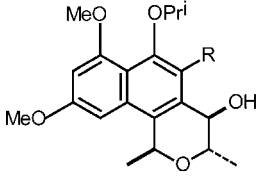
At the time it was suspected that the relatively large isopropoxy group at C-4 of naphthyl dioxolane **5** exhibited a sufficient steric effect to hinder



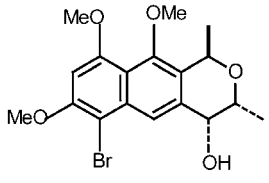
1 $R^1 = R^2 = R^3 = H$
2 $R^1 = R^3 = Br$; $R^2 = H$
3 $R^1 = R^2 = H$; $R^3 = Br$
4 $R^1 = R^3 = H$; $R^2 = Br$



5 $R^1 = Pr^i$; $R^2 = H$; $R^3 = Br$
6 $R^1 = Me$; $R^2 = H$; $R^3 = Br$
7 $R^1 = R^3 = H$; $R^2 = Br$



8 R = H
9 R = Br



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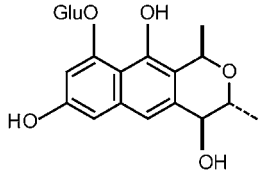

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Figure 1. Naphtholenes and naphthopyrans.

cyclization at C-3. Pursuant to this, Green et al.[3] treated naphthyl dioxolane **6** in which C-2 in the dioxolane ring was epimeric and the C-4 group was replaced by the smaller methoxy, to conditions similar to titanium(IV) tetrachloride,[4] and isolated the linear naphthopyran **10** as the C-4 acetate in 13% yield. These linear naphthopyrans are of great importance to our group because we have been investigating routes toward the synthesis of Glucoside B **11**.[5]

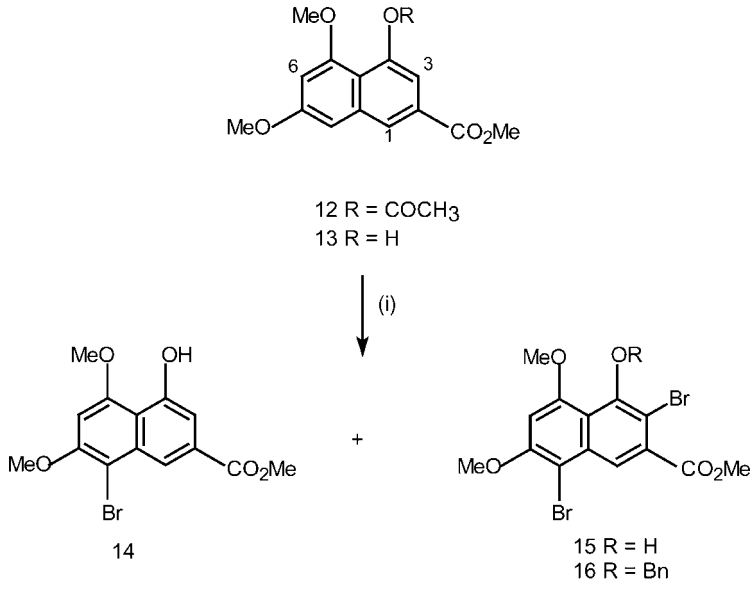
This latter finding was encouraging because it lent support to the hypothesis that reducing the steric size of the C-4 alkoxy group of naphthyl dioxolanes (viz., **6**) would favor attack at C-3, and thus it was decided to further improve this notion by blocking the C-1 position with bromine and replacing the C-4 alkoxy group with a stronger directing group (viz., an OH as in dioxolane **7**) because it was felt that this latter molecule would undergo the intramolecular Mukaiyama[4] reaction to afford a much higher yield of linear naphthopyran.

This article describes recent work relating to products obtained by treatment of C-2 substituted 5,7-dimethoxy-4-naphthols with bromine as a function of that substituent.

RESULTS AND DISCUSSIONS

Careful hydrolysis of naphthoate **12**[6] with sodium methoxide in methyl alcohol afforded the known naphthol **13**[7] in 94% yield, which represented the first naphthol to be investigated. Treatment of naphthol **13** with 1 molar equivalent of bromine in acetic acid produced two products (viz., 8-bromonaphthol **14** and 3,8-dibromonaphthol **15**) in yields of 57% and 21% respectively. We had earlier noted[1–3] that the ^4J value for naphthyl protons in the 5,7-dimethoxy ring is 2.2 Hz, whereas in the 2,4-disubstituted ring it is 1.4 Hz, and thus this fact is used inter alia for assigning structures to the various products of bromination throughout this study. The ^{1}H NMR spectrum of naphthol **14** displayed three 1-proton signals in the aromatic region; a singlet at 6.65 ppm for 6-H, a doublet (J 1.4) at 7.32 ppm for 3-H, and a doublet (J 1.4) at 8.42 ppm for 1-H. This latter deshielding (0.49 ppm) of 1-H is ascribed to the peri interaction of the C-8 bromine.[1] For the 3,8-dibromonaphthol **15** only two 1-proton singlets were observed in the ^{1}H NMR spectrum (viz., 6.62 ppm for 6-H and 8.00 ppm for 1-H). Treatment of naphthol **13** with 2 molar equivalents of bromine in acetic produced the 3,8-dibromonaphthol **15** in 90% yield as the sole product. In separate experiments it was found that adding 1 equivalent of sodium acetate to the reaction mixture when 1 equivalent of bromine was added had no effect on the outcome of the products nor their respective yields (Scheme 1).

These results suggest that the dimethoxy ring is sufficiently electron rich to override the C-4 hydroxy group's activating influence. A most likely reason for this is the electron-withdrawing ester group at C-2. In spite of this effect and the steric congestion, naphthol **15** was smoothly converted into the

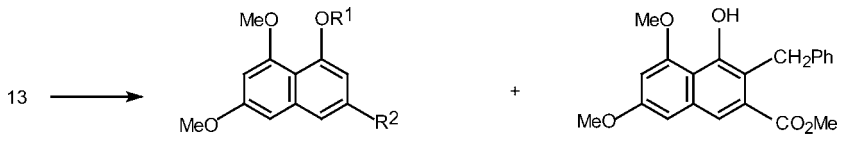


Scheme 1.

benzyloxy analogue **16** in 75% yield with benzyl bromide and potassium carbonate in boiling acetone.

As a consequence, 2-acetoxymethylnaphthol **21**, in which the deactivating ester group at C-2 has been transformed into a slightly electron-donating group, was investigated because this molecule was considered to be a pivotal precursor for the synthesis of dioxolane **7**. Thus large-scale benzylation of naphthol **13** with benzyl bromide and potassium carbonate in boiling acetone afforded the expected benzyloxynaphthalene **17** in 93% yield together with a trace amount (1%) of the 3-benzylnaphthol **18**. Assignment of the latter structure **18** to the minor product is based inter alia on the ^{1}H NMR spectrum in which two 1-proton doublets (J 2.2) at 6.58 and 6.80 ppm were assigned to 6- and 8-H respectively and a 1-proton singlet at 7.80 ppm that was assigned to 1-H. This latter product most likely arose from an electrophilic substitution reaction at the less congested C-3 position by a benzylic carbocation arising from ionization of benzyl bromide.

Ester **17** was subsequently reduced with lithium aluminium hydride in THF to produce alcohol **19** in 85% yield, which in turn was acetalated in acetic anhydride and pyridine to give acetate **20** in a yield of 97%. Finally, very careful catalytic hydrogenation of acetate **20** afforded the desired naphthol **21** in 91% yield (Scheme 2).



17 R^1 = Bn; R^2 = CO_2Me
19 R^1 = Bn; R^2 = CH_2OH
20 R^1 = Bn; R^2 = CH_2OAc
21 R^1 = H; R^2 = CH_2OAc
22 R^1 = H; R^2 = CH_2OH
23 R^1 = Ac; R^2 = CH_2OAc

18

Scheme 2.

Although the overall yield for the four transformation steps (13 → 17 → 19 → 20 → 21) was 70%, an alternative route was also investigated. Thus naphthol **13** was reduced to diol **22** in a yield of 90% with LAH in THF.[8] Acetalation of diol **22** as described previously produced the diacetate **23** in a yield of 85%. However, all attempts to chemoselectively mono-deacetalate **23** into naphthol **21** under basic conditions, even using 0.1 mol equivalent of potassium hydroxide per mol of **23** in methyl alcohol proved unsuccessful. In all cases diol **22** was the major product with minor quantities of naphthol **21** being produced (GC-MS). In some cases of low concentrations of base, the starting material was also observed.

Treatment of naphthol **21** with 1 mol equivalent of bromine in acetic acid afforded two monobrominated naphthols **24** and **25** in yields of 70% and 27% respectively. Assignment of the structures is based inter alia on the ^{1}H NMR spectra. In the case of 1-bromonaphthol **24**, three 1-proton signals were evident: namely, a doublet (*J* 2.2) at 6.51 ppm assigned to 6-H, a doublet (*J* 2.2) at 7.21 ppm assigned to 8-H deshielded by the peri 1-Br, and a singlet at 6.81 ppm for 3-H. On the other hand, 3-bromonaphthol **25** displayed three 1-proton signals as follows: a doublet (*J* 2.2) at 6.50 ppm assigned to 6-H, a doublet (*J* 2.2) at 6.69 ppm assigned to 8-H, and a singlet at 7.24 ppm assigned to 1-H.

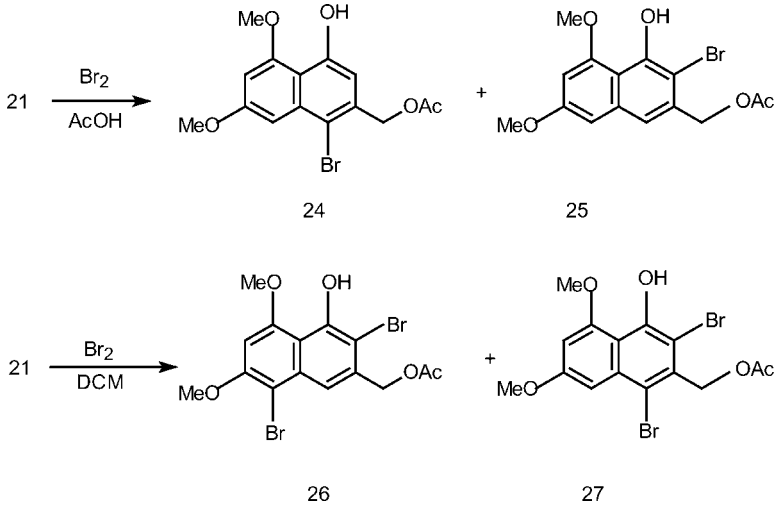
Repeating the bromination of naphthol **21** with 1 mol equivalent of bromine in acetic acid containing 1 and 2 mol equivalents of sodium acetate as buffer resulted in the recovery of starting material (80%) together with a mixture of 1-bromonaphthol **24** and 3,8-dibromonaphthol **26** (20%) in a ratio of 3 : 7 (by ^{1}H NMR).

On the other hand, treatment of naphthol **21** with 1 mol equivalent of bromine in a 1 : 1 ratio by volume of acetic acid and dichloromethane yielded the same two monobrominated naphthols (viz., **24** and **25**) in quantitative yield and in a 1 : 1 ratio by ^{1}H NMR. Finally, treatment of naphthol **21** with 2.7 mol equivalents of bromine in dichloromethane afforded two dibrominated naphthols (viz., 3,8-dibromonaphthol **26** and 1,3-dibromonaphthol

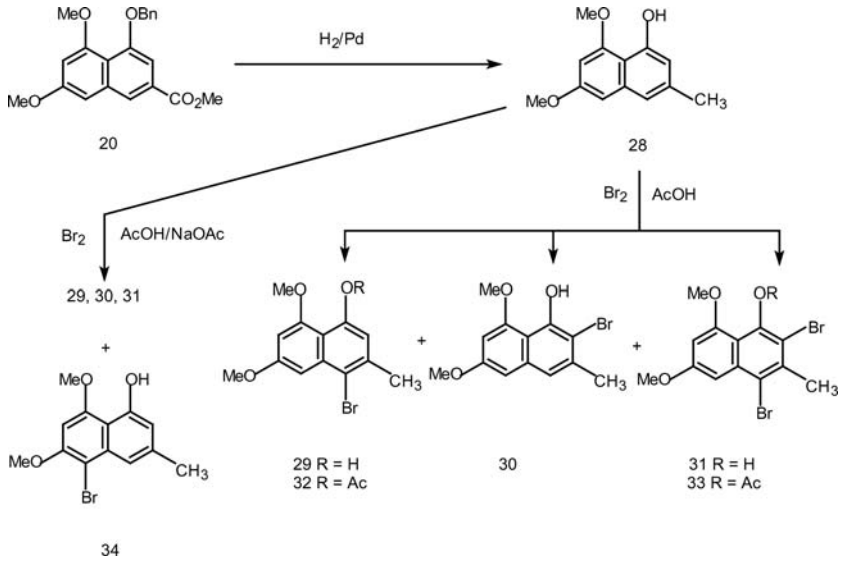
27) in yields of 70% and 25% respectively. The ^{1}H NMR spectrum of naphthol **26** exhibited two 1-proton signals in the aromatic region [viz., a singlet at 6.65 ppm assigned to 6-H and a doublet (J 0.6) at 7.77 ppm assigned to 1-H]. A similar ^4J of 0.6 was observed for the methylene protons at C-2, which appeared as a 2-proton doublet at 5.31 ppm. In the case of the minor product (viz., 1,3-dibromonaphthol **27**), two 1-proton doublets (J 2.2) appeared at 6.56 and 7.23 ppm and are assigned to 6- and 8-H respectively (Scheme 3).

During the catalytic hydrogenation of naphthyl ester **20** into naphthol **21**, a minor amount (5%) of 2-methylnaphthol **28** was produced. It occurred to us that this molecule presented itself as a further candidate for our investigations because it would be expected to enhance bromination at the phenolic side of naphthol **28**. Consequently, extended (48 h) hydrogenation of naphthyl ester **20** with Pd/C (5%) in ethyl acetate and a trace of conc. HCl produced the 2-methylnaphthol **28**[9,10] in 93% yield, typified by a 3-proton singlet at 2.39 ppm in the ^{1}H NMR spectrum.

Treatment of naphthol **28** with 1 mol equivalent of bromine in acetic acid afforded three products (viz., 1-bromonaphthol **29**, 3-bromonaphthol **30**, and 1,3-dibromonaphthol **31**) in the ratio 4 : 2 : 1 by ^{1}H NMR spectral analysis. Assignment of structures for the isolated and purified products was based inter alia on the ^{1}H NMR spectra, and just a few pertinent signals are a deshielded 1-proton doublet (J 2.2) at 7.21 ppm assigned to 8-H for naphthol **29**, a 1-proton doublet (J 0.6) at 7.08 ppm assigned to 1-H and a 3-proton doublet (J 0.6) at 2.49 ppm for the C-2 methyl group of naphthol **30**, and two 1-proton doublets (J 2.2) at 6.51 and 7.24 ppm for 6-and 8-H for naphthol **31** (Scheme 4). As a matter of course naphthols **29** and **31**



Scheme 3.



Scheme 4.

were transformed into the corresponding acetates **32** and **33** respectively to verify structural assignments. Finally, treatment of naphthol **28** with 1 mol equivalent of bromine in acetic acid in the presence of a 2 mol equivalent of sodium acetate buffer produced the same three brominated naphthols (viz., **29**, **30**, and **31**) in the same ratio as before (4 : 2 : 1) by ^{1}H NMR. However, in this case, a new monobrominated naphthol was isolated in 5% yield and eluted from the column after naphthol **31** and was assigned the structure **34** on the basis of inter alia the following ^{1}H NMR spectral data [viz., a 3-proton double (J 0.6) at 2.45 ppm assigned to the C-2 methyl group, a 1-proton singlet at 6.51 ppm for 6-H, a 1-proton doublet (J 1.4) at 6.66 pm for 3-H, and a 1-proton dd (J 1.4 and 0.6) at 7.49 ppm for the deshielded 1-H] (Scheme 4).

CONCLUSION

Thus an array of brominated products is produced upon treatment of 2-substituted, 5,7-dimethoxy-4-naphthols with the dimethoxy nucleus being favored when the C-2 group is electron withdrawing, whereas the phenol nucleus is favored when C-2 is electron donating. In all cases no single product is produced although as expected, α-bromination predominates over β-bromination in acetic acid. Bromination in the presence of a buffer (viz., sodium acetate) does not affect the outcome relative to the nonbuffered regime for the naphthols studied.

EXPERIMENTAL

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

Methyl 8-Bromo-4-hydroxy-5,7-dimethoxy-2-naphthoate 14 and Methyl 3,8-Dibromo-4-hydroxy-5,7-dimethoxy-2-naphthoate 15

Method A

Bromine (308 mg, 1.92 mmol) in AcOH (2 mL) was dripped into a solution of naphthol **13**[7] (500 mg; 1.91 mmol) in AcOH (10 mL) at 24 °C, and the resulting solution was stirred 15 min and then poured into water (150 mL) to form a precipitate, which was chromatographed using EtOAc–hexane (3 : 7) as eluent to produce the bromonaphthol **14** (371 mg; 57%) as light brown needles. Mp 190–191°C (from ethanol). ν_{max} 3360 and 1714 cm^{-1}; δ_H 3.96, 4.01, and 4.09 (each 3H, s, OCH_3), 6.65 (1H, s, 6-H), 7.32 (1H, d, *J* 1.4, 3-H), 8.42 (1H, d, *J* 1.4, 1-H), and 9.25 (1H, s, D_2O exchangeable, 4-OH). δ_C 52.4, 56.7, and 57.1 (OCH_3), 95.6 (C-6), 102.6 (C-8)[a], 108.9 (C-3)[a], 113.6 (C-2)[a], 119.9 (C-1)[a], 130.9 (C-4a)[6], 134.7 (C-8a)[b], 154.3 (C-4)[c], 155.1 (C-5)[c], 156.9 (C-7)[c], and 166.9 (C═O). [Found: C, 49.2; H, 3.6%; M^+ 341:343 (1 : 1). Calc. for $C_{14}H_{13}BrO_5$: C; 49.3; H, 3.8%; M 341:343 (1 : 1)]. Further elution afforded the dibromonaphthol **15** (168 mg; 21%) as light brown needles, mp 194–195 °C (from ethanol). ν_{max} 3340 and 1726 cm^{-1}; δ_H 3.99, 4.01, and 4.11 (each 3H, s, OCH_3), 6.62 (1H, s, 6-H), 8.00 (1H, s, 1-H), and 10.07 (1H, s, D_2O exchangeable, 4-OH). δ_H 52.8, 56.9, 57.2 (OCH_3), 95.8 (C-6), 100.9 (C-8)[a], 101.9 (C-2)[a], 112.3 (C-3)[a], 119.7 (C-1), 133.1 (C-4a)[b], 134.2 (C-8a)[b], 151.9 (C-4)[c], 154.6 (C-5)[c], 155.9 (C-7)[c], and 167.3 (C═O). [Found: C, 40.3; H, 3.0%; M^+ 420 : 422 : 424 (1 : 2 : 1). Calc. for $C_{14}H_{12}Br_2O_5$: C, 40.0; H, 2.9%. M 420 : 422 : 424 (1 : 2 : 1)].

Method B

Bromine (700 mg; 4.38 mmol) in AcOH (4 mL) was dripped into a solution of naphthol **13** (500 mg; 1.91 mmol) containing sodium acetate (410 mg;

5.0 mmol) at 24°C and after 30 min stirring, the reaction mixture was poured into water (150 mL) to yield a precipitate of the dibromonaphthol **15** (722 mg; 90%) identical to material prepared before, vide supra.

Methyl 4-Benzyloxy-3,8-dibromo-5,7-dimethoxy-2-naphthoate 16

A mixture of naphthol **15** (485 mg, 1.15 mmol) and benzyl bromide (983 mg, 5.75 mmol) in acetone (35 mL) containing potassium carbonate (794 mg, 5.75 mmol) was vigorously stirred and heated under reflux for 18 h. The cooled solution was filtered and evaporation of the solvent gave a residue, which was carefully chromatographed using EtOAc–hexane (1 : 4) as eluent to give the naphthoate **16** (440 mg, 75%) as white crystals. Mp 152–153 °C (from ethanol). ν_{max} 1725 cm^{-1}; δ_H 3.90 (3H, s, CO_2CH_3), 4.01 and 4.04 (each 3H, s, OCH_3), 5.00 (2H, s, CH_2Ph), 6.75 (1H, s, 6-H), 7.40 (3H, m, aryl-H), 7.61 (2H, m, aryl-H), and 8.41 (1H, s, 1-H). δ_C 52.9, 56.6, 57.1 (OCH_3), 75.9 (CH_2Ph), 97.5 (C-6), 100.7 (C-3)[a], 111.3 (C-8)[a], 118.9 (C-2)[a], 125.3 (C-1), 128.1 (C-2′/6′)[b], 128.5 (C-3′/6′)[b], 133.5 (C-4′)[c], 133.8 (C-4a)[c], 137.4 (C-8a)[c], 153.2 (C-4)[d], 155.1 (C-5)[d], 156.7 (C-7)[d], and 167.1 (C=O). [Found: C, 49.3; H, 3.6%; M^+ 510 : 512 : 514 (1 : 2 : 1). Calc. for $C_{21}H_{18}Br_2O_5$: C, 49.6; H, 3.6%; M 510 : 512 : 514 (1 : 2 : 1)].

Methyl 4-Benzyloxy-5,7-dimethoxy-2-naphthoate 17 and Methyl 2-Benzyl-4-hydroxy-5,7-dimethoxy-2-naphthoate 18

Benzyl bromide (6.72 g, 39.3 mmol) was added to a solution of naphthol **13** (4.11 g; 15.7 mmol) in acetone (50 mL) containing potassium carbonate (5.42 g; 39.3 mmol) and the resulting mixture was vigorously stirred under reflux for 18 h, cooled, and filtered. The residue obtained upon removal of solvent was chromatographed using EtOAc–hexane (3 : 7) as eluent to yield benzyloxynaphthalene **17** (5.14 g, 93%) as white needles. Mp 122–124 °C (from hexane). ν_{max} 1721 cm^{-1}; δ_H 3.91, 3.94, 3.94 (each 3H, s, OCH_3), 5.26 (2H, s, CH_2Ph), 6.61 (1H, d, *J* 2.2, 6-H), 6.82 (1H, d, *J* 2.2, 8-H), 7.37 (1H, d, *J* 1.4, 3-H), 7.40 (3H, m, aryl-H), 7.65 (2H, m, aryl-H), and 8.06 (1H, d, *J* 1.4, 1-H). δ_C 52.4, 55.4, 56.2 (OCH_3), 71.2 (CH_2Ph), 100.1 (C-6)[a], 101.1 (C-8)[a], 105.0 (C-3), 113.9 (C-2), 123.2 (C-4), 127.0 (C-3′/5′)[b], 127.6 (C-4′), 128.4 (C-2′/6′)[b], 128.5 (C-1′), 137.4 (C-4a)[c], 137.5 (C-8a)[c], 156.7 (C-4)[d], 158.5 (C-5)[d], 158.8 (C-7)[d], and 167.3 (C=O). (Found: C, 71.5; H, 5.6%; M^+ 352. Calc. for $C_{21}H_{20}O_5$: C, 71.6; H, 5.7%; M 352). Further elution afforded naphthol **18** (50 mg; 0.9%) as white crystals. Mp 137–138 °C (from hexane). ν_{max} 3310 and 1717 cm^{-1}; δ_H 3.88, 3.94, and 4.06 (each 3H, s, OCH_3), 4.50 (2H, s, CH_2Ph), 6.58 (1H, d, *J* 2.2, 6-H), 6.80 (1H, d, *J* 2.2, 8-H), 7.26 (5H, m, aryl-H), 7.80 (1H, s, 1-H), and 9.59 (1H, s, D_2O exchangeable, 4-OH). δ_C 31.6 (CH_2Ph), 51.2,

55.5, 56.4 (OCH_3), 99.7 (C-6), 100.2 (C-8), 112.3 (C-1)[a], 119.2 (C-2)[a], 120.6 (C-3)[a], 125.4 (C-4′), 128.1 (C-2′/6′)[b], 128.5 (C-3′/5′)[b], 131.6 (C-1′), 135.0 (C-4a)[c], 142.1 (C-8a)[c], 153.0 (C-4)[d], 156.8 (C-5), 157.9 (C-7), and 168.7 (C═O). (Found: C, 71.5; H, 5.8%; M^+ 352. Calc. for $C_{21}H_{20}O_5$: C, 71.6; H, 5.7%; M 352).

4-Benzyloxy-2-hydroxymethyl-5,7-dimethoxynaphthalene 19

A solution of ester **17** (360 mg, 1.02 mmol) in THF (15 mL) at 23 °C was dripped into a stirred slurry of LAH (100 mg, 2.6 mmol) in THF (10 mL) under N_2 and stirring was continued until reduction was complete (TLC). Saturated ammonium chloride was added (3 drops) to destroy the excess of LAH, and the residue obtained upon workup was chromatographed using EtOAc–hexane (2 : 3) as eluent to give the alcohol **19** (280 mg, 85%) as white needles. Mp 155–157 °C (from ethanol). ν_{max} 3420 cm^{-1}; δ_H 1.92 (1H, s, D_2O exchangeable, $-CH_2OH$), 3.89 and 3.92 (each 3H, s, OCH_3), 4.76 (2H, s, $-CH_2OH$), 5.18 (2H, s, $-CH_2Ph$), 6.50 (1H, d, *J* 2.2, 6-H), 6.69 (1H, d, *J* 2.2, 8-H), 6.79 (1H, d, *J* 1.4, 3-H), 7.26 (1H, d, *J* 1.4, 1-H), 7.42 (3H, m, aryl-H), and 7.60 (2H, m, aryl-H). δ_C 55.3 and 56.1 (OCH_3), 65.6 (CH_2OH), 71.3 (CH_2Ph), 98.9 (C-6), 99.0 (C-8), 105.2 (C-3), 113.2 (C-2), 117.9 (C-1), 127.0 (C-3′/5′)[a], 127.6 (C-4′), 128.4 (C-2′/6′)[a], 128.5 (C-1′), 137.7 (C-4a)[b], 138.3 (C-8a)[b], 156.8 (C-4)[b], 158.5 (C-5)[b] and 158.6 (C-7)[b]. (Found: C, 73.9; H, 6.1%; M^+ 324. Calc. for $C_{20}H_{20}O_4$: C, 74.1; H, 6.2%; M 324).

2-Acetoxymethyl-4-benzyloxy-5,7-dimethoxynaphthalene 20

Alcohol **19** (190 mg; 0.59 mmol) in acetic anhydride (2.0 mL) and pyridine (0.7 mL) was stirred at 23 °C for 24 h, after which water (80 mL) was added and the mixture extracted with ether. The extract was rinsed with 0.1 M hydrogen chloride followed by water, and the residue obtained upon workup was chromatographed using EtOAc–hexane (1 : 5) as eluent to give the acetate **20** (210 mg; 97%) as white crystals. Mp 102–103 °C (from hexane). ν_{max} 1744 cm^{-1}; δ_H 2.14 (3H, s, $COCH_3$), 3.90 and 3.92 (each 3H, s, OCH_3), 5.18 (2H, s, CH_2OAc), 5.20 (2H, s, CH_2Ph), 6.51 (1H, d, *J* 2.2, 6-H), 6.71 (1H, d, *J* 2.2, 8-H), 6.75 (1H, d, *J* 1.4, 3-H), 7.28 (1H, d, *J* 1.4, 1-H), 7.38 (3H, m, aryl-H), and 7.60 (2H, m, aryl-H). δ_C 21.1 ($COCH_3$), 55.4 and 56.2 (OCH_3), 66.5 (CH_2OAc), 71.4 (CH_2Ph), 99.1 (C-6), 99.4 (C-8), 106.3 (C-3), 113.6 (C-2), 119.8 (C-1), 127.1 (C-2′/6′)[a], 127.6 (C-4′), 128.4 (C-3′/5′)[a], 134.8 (C-1′), 138.2 (C-4a)[b], 138.8 (C-8a)[b], 156.1 (C-4)[c], 158.6 (C-5)[c], 158.7 (C-7)[c], and 171.0 (C═O). (Found: C, 72.0; H, 5.9%; M^+ 366. Calc. for $C_{22}H_{22}O_5$: C, 72.1; H, 6.0%; M 366).

2-Acetoxymethyl-5,7-dimethoxy-4-naphthol 21

A mixture of ester **20** (900 mg, 2.46 mmol) in EtOAc (35 mL) containing Pd/C (23 mg of a 10% mixture) and concentrated hydrogen chloride (1 drop) was hydrogenated at atmospheric pressure and 23 °C and monitored for the uptake of 1 mol equivalent of H_2. The filtered solution was evaporated, and the residue chromatographed to afford the naphthol **21** (620 mg, 91%) as white crystals. Mp 93–95 °C (from hexane). ν_{max} 3400 and 1739 cm^{-1}. δ_H 2.13 (3H, s, CO*C*H_3), 3.88 and 4.01 (each 3H, s, O*CH*$_3$), 5.14 (2H, s, *CH*$_2$OAc), 6.45 (1H, d, *J* 2.2, 6-H), 6.70 (2H, m, 8- and 3-H), 7.15 (1H, d, *J* 1.4, 1-H), and 9.14 (1H, s, D_2O exchangeable, 4-OH). δ_C 21.1 (CO*C*H$_3$), 55.5 and 56.3 (O*C*H$_3$), 66.2 (*C*H$_2$OAc), 98.1 (C-6), 99.7 (C-8), 108.1 (C-3), 110.6 (C-2), 117.1 (C-1), 136.3 (C-4a)[a], 137.4 (C-8a)[a], 155.0 (C-4)[b], 157.2 (C-5)[b], 158.1 (C-7)[b], and 170.9 (C═O). (Found: C, 65.0; H, 5.7%; M^+ 276. Calc. for $C_{15}H_{16}O_5$: C, 65.2; H, 5.8%; M 276).

2-Hydroxymethyl-5,7-dimethoxy-4-naphthol 22

A solution of ester **13** (830 mg, 3.16 mmol) in THF (40 mL) under nitrogen was dripped into a slurry of LAH (480 mg, 12.6 mmol) in THF (20 mL) After 1 h of stirring, saturated aqueous ammonium chloride was added dropwise to destroy the excess of LAH. The residue obtained upon workup was chromatographed using EtOAc–hexane (1 : 1) as eluent to produce the naphthol **22** (668 mg, 90%) as white crystals. Mp 142–143 °C (from hexane); lit. mp[1] 144–145 °C. ν_{max} 3450 and 3250 cm^{-1}. δ_H 1.80 (1H, s, D_2O exchangeable, CH$_2$O*H*), 3.88 and 4.02 (each 3H, s, O*CH*$_3$), 4.74 (1H, d, *J* 2.9, *CH*$_2$OH), 6.44 (1H, d, *J* 2.2, 6-H), 6.69 (1H, d, *J* 2.2, 8-H), 6.71 (1H, d, *J* 1.2, 3-H), 7.17 (1 h, D, *J* 1.2, 1-H), and 9.12 (1H, s, D_2O exchangeable, 4-OH). δ_C 55.4 and 56.2 (O*C*H$_3$), 65.4 (*C*H$_2$OH), 97.8 (C-6), 99.7 (C-8), 107.4 (C-3). 110.3 (C-2), 115.4 (C-1), 137.6 (C-4a)[a], 141.4 (C-8a)[a], 155.0 (C-4)[b], 157.3 (C-5)[b], and 158.1 (C-7)[b]. (Found: C; 66.6; H, 6.0%; M^+ 234. Calc. for $C_{13}H_{14}O_4$: C, 66.65; 6.0%; M 234.)

4-Acetoxy-2-acetoxymethyl-5,7-dimethoxynaphthalene 23

Naphthol **22** (240 mg, 1.03 mmol) was treated with acetic anhydride (4 mL) and pyridine (1.0 mL) and stirred under nitrogen for 18 h at 23 °C. Workup as described before (vide supra) afforded the diacetate **23** (280 mg, 85%) as white crystals. Mp 97–98 °C (from ethanol). ν_{max} 1740 cm^{-1}; δ_H 2.13 and 2.36 (each 3H, s, COC*H*$_3$), 3.89 (6H, s, O*CH*$_3$), 5.19 (2H, s, *CH*$_2$OAc), 6.50 (1H, d, *J* 2.6, 6-H), 6.74 (1H, d, *J* 2.6, 8-H), 6.91 (1H, d, *J* 1.4, 3-H), and 7.54 (1H, d, *J* 1.4, 1-H). δ_C 21.0 and 21.1 (COC*H*$_3$), 55.5 and 56.2 (O*C*H$_3$), 65.7 (*C*H$_2$OAc), 99.2 (C-6), 99.9 (C-8), 114.8 (C-2), 116.9 (C-3), 124.5

(C-1), 134.7 (C-4a)[a], 137.7 (C-8a)[a], 147.1 (C-4), 156.4 (C-5), 158.7 (C-7), 170.2 and 170.9 (C═O). (Found: C, 64.3; H, 5.6%; M^+ 318. Calc. for $C_{17}H_{18}O_6$: C, 64.2; H, 5.7%; M 318.)

2-Acetoxymethyl-1-bromo-5,7-dimethoxy-4-naphthol 24 and 2-Acetoxymethyl-3-bromo-5,7-dimethoxy-4-naphthol 25

Bromine (58 mg, 0.36 mmol) in acetic acid (1 mL) was added to a stirred solution of naphthol **21** (100 mg, 0.36 mmol) in acetic acid (10 mL), and stirring was maintained at 23 °C under nitrogen for 15 min, after which water (100 mL) was added and the products extracted into dichloromethane. The organic extract was rinsed with saturated sodium hydrogen carbonate, and the residue obtained upon workup was chromatographed using EtOAc–hexane (1 : 4) as eluent to afford the 1-bromonaphthol **24** (89 mg, 70%) as white needles. Mp 144–145 °C (from ethanol). ν_{max} 3340 and 1737 cm^{-1}; δ_H 2.18 (3H, s, COCH_3), 3.94 and 4.04 (each 3H, s, OCH_3), 5.31 (2H, s, CH_2OAc), 6.51 (1H, d, *J* 2.2, 6-H), 6.81 (1H, s, 3-H), 7.21 (1H, d, *J* 2.2, 8-H), and 9.28 (1H, s, D_2O exchangeable, 4-OH). δ_C 21.0 (CO*C*H_3), 55.6 and 56.6 (O*C*H_3), 66.6 (*C*H_2OAc), 98.5 (C-6), 99.6 (C-8), 108.9 (C-3), 110.6 (C-1)[a], 111.4 (C-2)[a], 135.6 (C-4a)[b], 136.1 (C-8a)[b], 154.6 (C-4)[c], 157.4 (C-5)[c], 159.1 (C-7)[c], and 170.7 (C═O). [Found: C, 50.8; H, 4.1%; M^+ 355 : 357 (1 : 1). Calc. for $C_{15}H_{15}BrO_5$: C, 50.85; H, 4.3%; M 355 : 357 (1 : 1)]. Further elution afforded the 3-bromonaphthol **25** (34 mg; 27%) as olive rosettes. Mp 138–139 °C (from ethanol). ν_{max} 3330 and 1735 cm^{-1}; δ_H 2.18 (3H, s, COCH_3), 3.88 and 4.03 (each 3H, s, OCH_3), 5.28 (2H, s, CH_2OAc), 6.50 (1H, d, *J* 2.2, 6-H), 6.69 (1H, d, *J* 2.2, 8-H), 7.24 (1H, s, 1-H), and 9.89 (1H, s, D_2O exchangeable, 4-OH). δ_C 21.1 (CO*C*H_3), 55.5 and 56.6 (O*C*H_3), 66.3 (*C*H_2OAc), 98.9 (C-6), 99.8 (C-8), 102.9 (C-3)[a], 110.8 (C-2)[a], 118.1 (C-1), 135.0 (C-4a)[b], 135.7 (C-8a)[b], 151.2 (C-4)[c], 156.3 (C-5)[c], 158.4 (C-7)[c], and 170.7 (C═O). [Found: C, 50.7; H, 4.0%; M^+ 355 : 357 (1 : 1). Calc. for $C_{15}H_{15}BrO_5$: C, 50.85; H, 4.3%; M 355 : 357 (1 : 1)].

2-Acetoxymethyl-3,8-dibromo-5,7-dimethoxy-4-naphthol 26 and 2-Acetoxymethyl-1,3-dibromo-5,7-dimethoxy-4-naphthol 27

A solution of bromine (320 mg; 2.0 mmol) in dichloromethane (10 mL) was added dropwise to a solution of naphthol **21** (202 mg; 0.73 mmol) in dichloromethane (10 mL), and after stirring an additional 10 min at 23 °C the solvent was removed to afford a residue that was chromatographed using EtOAc–hexane (3 : 7) as eluent to yield the 3,8-dibromonaphthol **26** (221 mg, 70%) as olive-colored needles. Mp 209–210 °C (from ethyl alcohol). ν_{max} 3310 and 1740 cm^{-1}; δ_H 2.21 (3H, s, COCH_3), 4.02 and 4.12 (each 3H, s, OCH_3), 5.31 (2H, d, *J* 0.6, CH_2OAc), 6.65 (1H, s, 6-H), 7.77 (1H, d, *J* 0.6, 1-H), and 10.01

(1H, s, D_2O exchangeable, 4-OH). δ_C 21.1 ($COCH_3$), 56.9 and 57.2 (OCH_3), 66.3 (CH_2OAc), 94.6 (C-6), 101.6 (C-3)[a], 104.0 (C-8)[a], 111.3 (C-2)[a], 117.6 (C-1), 133.5 (C-4a)[b], 136.5 (C-8a)[b], 151.2 (C-4)[c], 154.4 (C-5)[c], 156.1 (C-7)[c], and 170.7 (C═O). [Found: C, 41.6; H, 3.4%; M^+ 434 : 436 : 438 (1 : 2 : 1). Calc. for $C_{15}H_{14}Br_2O_5$: C, 41.5; H, 3.25%; M 434 : 436 : 438 (1 : 2 : 1)]. Further elution afforded the 1,3-dibromonaphthol **27** (80 mg, 25%) as olive crystals. Mp 174–175 °C (from ethanol). ν_{max} 3360 and 1732 cm^{-1}; δ_H 2.12 (3H, s, $COCH_3$), 3.94 and 4.06 (each 3H, s, OCH_3), 5.63 (2H, s, CH_2OAc), 6.56 (1H, d, *J* 2.2, 6-H), 7.23 (1H, d, *J* 2.2, 8-H), and 10.11 (1H, s, D_2O exchangeable, 4-OH). δ_C 20.8 ($COCH_3$), 55.6 and 56.9 (OCH_3), 68.3 (CH_2OAc), 99.8 (C-6), 100.5 (C-8), 105.6 (C-3)[a], 111.6 (C-1)[a], 115.1 (C-2)[a], 134.0 (C-4a)[b], 134.4 (C-8a)[b], 151.2 (C-4)[c], 156.4 (C-5)[c], 159.2 (C-7)[c], and 170.8 (C═O). [Found: C, 41.3; H, 3.4%; M^+ 434:436:438 (1:2:1). Calc. for $C_{15}H_{14}Br_2O_5$: C, 41.5; H, 3.25%; M 434 : 436 : 438 (1 : 2 : 1)].

5,7-Dimethoxy-2-methyl-4-naphthol 28

Benzyloxynaphthalene **20** (2.0 g, 5.50 mmol) in EtOAc (30 mL) containing Pd/C (5%) (40 mg) and concentrated hydrogen chloride (1 drop) was vigorously stirred under hydrogen (1 atm) for 48 h. The filtered solution was washed with water (30 mL), and the residue obtained upon workup was chromatographed using EtOAc–hexane (1 : 4) as eluent to afford the naphthol **28** (1.12 g, 93%) as tan-colored needles. Mp 83–84 °C (from hexane); lit. mp 83–84 °C[9]; 82 °C[10]. ν_{max} 3340 cm^{-1}; δ_H 2.39 (3H, s, 2-CH_3), 3.88 and 4.01 (each 3H, s, OCH_3), 6.38 (1H, d, *J* 2.2, 6-H), 6.58 (1H, d, *J* 1.4, 3-H), 6.63 (1H, d, *J* 2.2, 8-H), 6.97 (1H, d, *J* 1.4, 1-H), and 9.03 (1H, s, D_2O exchangeable, 4-OH). δ_C 21.7 (2-CH_3), 55.4 and 56.2 (OCH_3), 96.9 (C-6), 99.1 (C-8), 109.1 (C-2), 110.5 (C-3), 117.6 (C-1), 137.7 (C-4a)[a], 138.6 (C-8a)[a], 154.4 (C-4)[b], 157.3 (C-5)[b], and 157.9 (C-7)[b]. (Found: C, 71.4; H, 6.2%; M^+ 218. Calc. for $C_{13}H_{14}O_3$: C, 71.5; H, 6.5%; M 218).

1-Bromo-5,7-dimethoxy-2-methyl-4-naphthol 29, 3-Bromo-5,7-dimethoxy-2-methyl-4-naphthol 30, and 1,3-Dibromo-5,7-dimethoxy-2-methyl-4-naphthol 31

Bromine (320 mg, 2.0 mmol) in acetic acid (4 mL) was added to a stirred solution of naphthol **28** (436 mg, 2.0 mmol) in acetic acid (40 mL) dropwise at 23 °C under nitrogen. After stirring for 30 min, water (300 mL) was added, and the resulting emulsion was extracted with dichloromethane and backwashed with aqueous sodium hydrogen carbonate. The residue obtained upon workup (600 mg) was recrystallized from ethanol, and the crystalline product was chromatographed over a long column (1200 × 25 mm) using EtOAc–hexane (1 : 4) as eluent to afford the 1-bromonaphthol **29** (320 mg, 54%) as light brown

needles. (Masses given refer to the final masses of products obtained after pooling together.) Mp 144–145 °C (from ethyl alcohol). ν_{max} 3315 cm^{-1}; δ_H 2.51 (3H, s, 2-CH_3), 3.94 and 4.03 (each 3H, s, OCH_3), 6.46 (1H, d, *J* 2.2, 6-H), 6.67 (1H, s, 3-H), 7.21 (1H, d, *J* 2.2, 8-H) and 9.18 (1H, s, D_2O exchangeable, 4-OH). δ_C 24.4 (2-CH_3), 55.5 and 56.5 (OCH_3), 97.6 (C-6), 99.6 (C-8), 110.3 (C-1)[a], 111.5 (C-3), 112.4 (C-2)[a], 135.7 (C-4a)[b], 138.8 (C-8a)[b], 153.9 (C-4)[c], 157.5 (C-5)[c], and 158.9 (C-7)[c]. [Found: C, 52.4; H, 4.6%; M^+ 296:298 (1:1). Calc. for $C_{13}H_{13}BrO_3$: C, 52.7; H, 4.4%; M 296 : 298 (1 : 1)]. Further elution gave a slight mixture of **29**, **30**, and **31**, which was added to the mother liquor of the recrystallization. The next product to elute was the 1,3-dibromonaphthol **31** (74 mg, 9.9%) as light brown needles. (Masses given refer to the final masses of products obtained after pooling together.) Mp 175–177 °C (from ethanol). ν_{max} 3390 cm^{-1}; δ_H 2.79 (3H, s, 2-CH_3), 3.94 and 4.05 (each 3H, s, OCH_3), 6.51 (1H, d, *J* 2.2, 6-H), 7.24 (1H, d, *J* 2.2, 8-H) and 10.08 (1H, s, D_2O exchangeable, 4-OH). δ_C 25.7 (2-*C*H_3), 55.6 and 56.8 (OCH_3), 98.5 (C-6), 100.3 (C-8), 106.5 (C-1)[a], 110.0 (C-2)[a], 113.4 (C-3)[a], 134.4 (C-4a)[b], 137.9 (C-8a)[b], 150.5 (C-4)[c], 156.5 (C-5)[c], and 158.9 (C-7)[c]. [Found: C, 41.2; H; 3.0%; M^+ 374 : 376 : 378 (1 : 2 : 1). Calc. for $C_{13}H_{12}Br_2O_3$: C, 41.7; H, 3.2%; M 374 : 376 : 378 (1 : 2 : 1)].

The mother liquors from the recrystallization were evaporated to a residue, which was chromatographed on a similar column (1200 × 25 mm) to afford 1-bromo-naphthol **29**[11] followed by the 3-bromonaphthol **30** (118 mg, 19.9%) as olive needles. (Masses given refer to the final masses of products obtained after pooling together.) Mp 132–133 °C (from hexane). ν_{max} 3345 cm^{-1}; δ_H 2.49 (3H, d, *J* 0.6, 2-CH_3), 3.87 and 4.02 (each 3H, s, OCH_3), 6.43 (1H, d, *J* 2.2, 6-H), 6.61 (1H, d, *J* 2.2, 8-H), 7.08 (1H, d, *J* 0.6, 1-H), and 9.82 (1H, s, D_2O exchangeable, 4-OH). δ_C 23.7 (C-2 *C*H_3), 55.4 and 56.4 (O*C*H_3), 97.8 (C-6), 99.0 (C-8), 105.9 (C-2)[a], 109.6 (C-3)[a], 118.7 (C-1), 135.8 (C-4a)[b], 138.1 (C-8a)[b], 150.7 (C-4)[c], 156.3 (C-5)[c], 158.1 (C-7)[c]. [Found: C, 52.9; H, 4.6%; M^+ 296 : 298 (1 : 1). Calc. for $C_{13}H_{13}BrO_3$: C, 52.7; H, 4.4%; M 296 : 298 (1 : 1)].

4-Acetoxy-1-bromo-5,7-dimethoxy-2-methylnaphthalene 32

Naphthol **29** (20 mg, 0.07 mmol) was acetylated in acetic anhydride (0.5 mL) and pyridine (0.2 mL) as described earlier to give the corresponding acetate **32** (22 mg, 93%) as white needles. Mp 150–151 °C (from ethyl alcohol). ν_{max} 1740 cm^{-1}; δ_H 2.34 (3H, s, COCH_3), 2.55 (3H, s, 2-CH_3), 3.88 and 3.94 (each 3H, s, OCH_3), 6.50 (1H, d, *J* 2.2, 6-H), 6.83 (1H, s, 3-H), and 7.27 (1H, d, *J* 2.2, 8-H). δ_C 21.0 (CO*C*H_3), 24.3 (C-2 *C*H_3), 55.5 and 56.4 (O*C*H_3), 99.2 (C-6)[a], 99.3 (C-8)[a], 114.4 (C-2)[b], 119.7 (C-3), 120.7 (C-1)[b], 136.3 (C-4a)[c], 137.5 (C-8a)[c], 145.8 (C-4)[d], 156.7 (C-5)[d], 159.5 (C-7)[d], and 170.1 (C=O). [Found: C, 53.3; H, 4.2%; M^+ 338 : 340 (1 : 1). Calc. for $C_{15}H_{15}BrO_4$: C, 53.1; H, 4.5%; M 338 : 340 (1 : 1)].

4-Acetoxy-1,3-dibromo-5,7-dimethoxy-2-methylnaphthalene 33

Naphthol **31** (26 mg, 0.07 mmol) was transformed in a similar way as described previously into the acetate **33** (26 mg, 90%) as white needles. Mp 160–161 °C (from ethyl alcohol). ν_{max} 1737 cm^{-1}; δ_H 2.41 (3H, s, $COCH_3$), 2.82 (3H, s, 2-CH_3), 3.89 and 3.94 (each 3H, s, OCH_3), 6.52 (1H, d, *J* 2.2, 6-H), and 7.27 (1H, d, *J* 2.2, 8-H). δ_C 20.9 ($COCH_3$), 26.0 (C-2 CH_3), 55.5 and 56.5 (OCH_3), 99.6 (C-6), 100.3 (C-8), 115.1 (C-1)[a], 115.5 (C-2)[b], 121.3 (C-3)[a], 135.0 (C-4a)[b], 137.1 (C-8a)[b], 156.3 (C-4)[c], 159.6 (C-5 and C-7)[c], and 168.8 (C=O). [Found: C, 42.8; H, 3.1%; M^+ 416 : 418 : 420 (1 : 2 : 1). Calc. for $C_{15}H_{14}Br_2O_4$: C, 43.1; H, 3.4%; M 416 : 418 : 420 (1 : 2 : 1)].

8-Bromo-5,7-dimethoxy-2-methyl-4-naphthol 34

Bromine (160 mg, 1.0 mmol) in acetic acid (2 mL) was added to a stirred solution of naphthol **28** (218 mg, 1.0 mmol) in acetic acid (20 mL) containing sodium acetate (162 mg, 2 mmol) at 23 °C under nitrogen. After stirring for 75 min, water (150 mL) was added, and the resulting emulsion was worked up as described before. The ratio of brominated products **29**, **30**, and **31** that eluted were the same as found earlier. However, a fourth fraction to elute was assigned to the 8-bromonaphthol **34** (14 mg, 5%) as olive needles. Mp 137–138 °C (from ethyl alcohol). ν_{max} 3420 cm^{-1}; δ_H 2.45 (3H, d, *J* 0.6, 2-CH_3), 3.98 and 4.05 (each 3H, s, OCH_3), 6.51 (1H, s, 6-H), 6.66 (1H, d, *J* 1.4, 3-H), 7.49 (1H, dd, *J* 1.4 and 0.6, 1-H), and 9.14 (1H, s, D_2O exchangeable, 4-OH). δ_C 22.1 (C-2 CH_3), 56.4 and 57.2 (OCH_3), 93.1 (C-6), 100.9 (C-8)[a], 109.9 (C-2)[a], 113.3 (C-3), 117.1 (C-1), 135.2 (C-4a)[b], 140.1 (C-8a)[b], 153.8 (C-4)[c], 154.5 (C-5)[c], and 157.1 (C-8)[c]. [Found: C, 52.3; H, 4.5%; M^+ 296 : 298 (1 : 1). Calc. for $C_{13}H_{13}BrO_3$: C, 52.7; H, 4.4%; M 296 : 298 (1 : 1)].

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