A Convenient Synthesis of 1-Bromo-4,5-dimethoxy-7-methylnaphthalene, a Naphthol Derivative Useful for Construction of Naphthylisoquinoline Alkaloids

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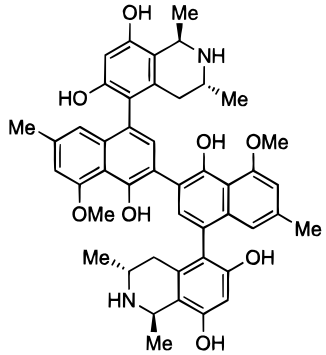
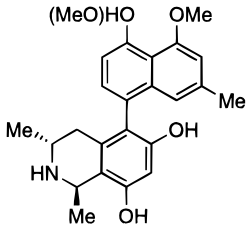
The anti-HIV agents, michellamines A, B, and C (cf. **1**),[1] as well as their presumed biosynthetic precursors, the monomeric korupensamines A and B (cf. **2**),[2] all contain a naphthalene ring bearing a 1,8-dioxygenated-4-aryl-6-methyl substitution pattern. We employed 1-bromo-4,5-dimethoxy-7-methylnaphthalene in our syntheses of korupensamine C and ancistrobrevine B.[3] This structural motif also is present in other members of this naphthylisoquinoline family of natural products.[4]



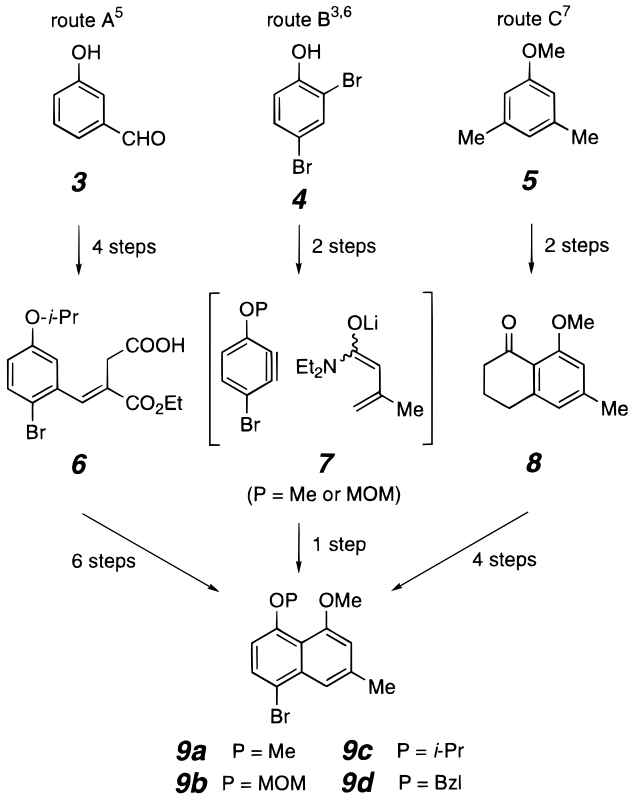
Michellamines
1



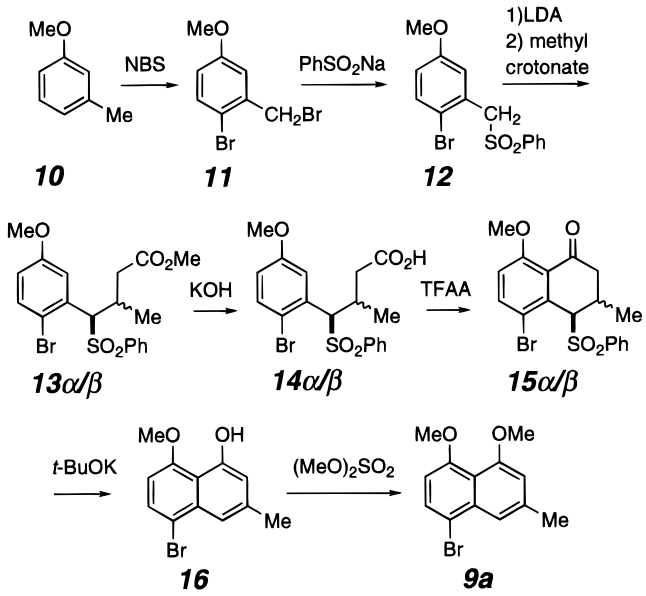
Korupensamines
2

In previous syntheses of various of these natural products, several strategies have evolved for construction of the naphthalene subunit. These are summarized in Scheme 1. The routes (A−C) begin with the commercially available benzene derivatives **3**−**5**, pass through the indicated intermediates **6**−**8**, and proceed on to the various protected 4-bromo-1-naphthols **9** in the indicated number of transformations. Bromonaphthols **9** can be converted into various arylmetal species (trialkylstannane, boronic acid, or zinc) in preparation for palladium-catalyzed biaryl cross-coupling reactions.

Scheme 1



Scheme 2



Even though our previous synthesis (route B) was quite short, the benzyne annulation reaction (cf. **7**) reproducibly proceeds in 20−25% yield. Chromatographic purification is cumbersome on a large scale (we have prepared up to multigram quantities of **9a** and **9b** by this method), and so we have developed another synthesis that is efficient (although longer), passes through many crystalline intermediates, and is amenable to implementation on a large scale.

The new synthesis is outlined in Scheme 2. Naphthalene **9a** was prepared by this seven-step sequence. A

(1) (a) Manfredi, K.; Blunt, J. W.; Cardellina, J. H., II; McMahon, J. B.; Pannell, L. L.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1991**, *34*, 3402. (b) Boyd, M. R.; Hallock, Y. H.; Cardellina, J. H., II; Manfredi, K. P.; Blunt, J. W.; McMahon, J. B.; Buckheit, R. W., Jr.; Bringmann, G.; Schäffer, M.; Cragg, G. M.; Thomas, D. W.; Jato, J. G. *J. Med. Chem.* **1994**, *37*, 1740.

(2) Hallock, Y. F.; Manfredi, K. P.; Blunt, J. W.; Cardellina, J. H., II; Schaffer, M.; Gulden, K.-P.; Bringmann, G.; Lee, A. Y.; Clardy, J.; Francois, G.; Boyd, M. R. *J. Org. Chem.* **1994**, *59*, 6349.

(3) Hoye, T. R.; Mi, L. *Tetrahedron Lett.* **1996**, *37*, 3097.

(4) (a) Bringmann, G. In *The Alkaloids;* Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 29, Chapter 3. (b) Bringmann, G.; Pokorny, F. In *The Alkaloids;* Cordell, G., Ed.; Academic Press: New York, 1995; Vol. 46, Chapter 4.

(5) (a) Bringmann, G.; Gotz, R.; Ketter, P. A.; Walter, R.; Henschel, P.; Schaffer, M.; Stablein, M.; Kelly, T. R.; Boyd, M. R. *Heterocycles* **1994**, *39* (2), 503. (b) Rizzacasa, M. A.; Sargent, M. V. *Aust. J. Chem.* **1987**, *40*, 1737.

(6) (a) Hoye, T. R.; Chen, M.; Mi, L.; Priest, O. P. *Tetrahedron Lett.* **1994**, *35*, 8747. (b) Hoye, T. R.; Chen, M. *Tetrahedron Lett.* **1996**, *37*, 3099.

(7) Hobbs, P. D.; Upender, V.; Liu, J.; Pollart, P. J.; Thomas, D. W.; Dawson, M. I. *J. Chem. Soc., Chem. Commun.* **1996**, 923.

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notable feature is the efficient bis-bromination of *m*-methylanisole (**10**) with NBS in methylene chloride (at reflux while irradiating with 100 W tungsten incandescent bulbs) to give the monoaryl monobenzyl dibromide **11**. It is critical to use irradiation sufficiently intense to minimize formation of the 4,6-dibrominated analogue, an event that competes with benzylic bromination if the latter is slow. The anion formed from the derived sulfone **12** (LDA, −78 °C) adds to methyl crotonate to generate the diastereomeric sulfones **13α**/**13*β*** (ratio = 4:1).[8] The diastereomeric methyl ethers **14** were separated one time, and the major isomer **14α** was cyclized (TFAA, 80 °C)[9] to **15α** with no loss of configurational control, but more often the diastereomeric mixture of **14α**/***β*** was ring-closed directly to a mixture of **15α**/***β***. Aromatization by elimination of sulfinate from the ketosulfones **15** with potassium *tert*-butoxide[10] was very efficient and the resulting naphthol **16** could readily be *O*-methylated to give the desired naphthalene. The overall yield for this sequence that converts **10** to **9a** was typically between 40 and 50%. Although the largest amount of material we have prepared at one time with this sequence is ∼3 g of **9a**, the reaction conditions and intermediates are all easy to handle. In most cases the crude product mixture is of sufficient purity for carrying into the next reaction, and if purification is necessary, recrystallization usually can be used.

In summary we have developed an alternative route for the preparation of brominated naphthalene derivatives useful for the synthesis of naphthylisoquinoline alkaloids.[11] The sequence presumably can be easily modified to access other ring-substitution patterns. We recommend the use of this method of naphthalene synthesis for instances where large quantities of **9a** or related derivatives may be required.

Experimental Section

General. Infrared and GC−MS (70 eV) data, obtained for every compound, are entirely consistent with the indicated structures but are ordinary. Only the carbonyl and OH stretches are reported; molecular ions were observed for all compounds except acids **14α**/***β***.

4-Bromo-3-(bromomethyl)-1-methoxybenzene (11). *N*-Bromosuccinimide (18.7 g, 105 mmol) was added to a solution of 3-methylanisole (**10**, 6.11 g, 50 mmol) in 250 mL of anhydrous methylene chloride. The mixture was refluxed for 4 h while exposed to light from two 100 W incandescent bulbs that were placed within 2 cm of the reaction vessel. The resulting mixture was filtered, and the filtrate was diluted with 200 mL of methylene chloride and washed with water. The organic layer was separated and concentrated. Recrystallization of the resulting residue in hexanes gave dibromide **11**[12] (11.9 g, 88%) as white crystals. Mp: 85−87 °C. ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.45 [d, *J* = 9.0 Hz, 1**H**], 6.99 [d, *J* = 3.0 Hz, 1**H**], 6.74 [dd, *J* = 9.0 and 3.0 Hz, 1**H**], 4.56 [s, 2**H**], and 3.80 [s, 3**H**]. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 159.1, 137.7, 133.9, 116.5, 116.1, 114.7, 55.5, and 33.5. Anal. Calcd for $C_8H_8Br_2O$: C, 34.32; H, 2.88. Found: C, 34.26; H, 3.04.

4-Bromo-1-methoxy-3-[(phenylsulfonyl)methyl]benzene (12). Dibromide **11** (6.16 g, 22.0 mmol) and sodium benzenesulfinite (4.69 g, 28.6 mmol) were suspended in 150 mL of DMF. The mixture, which became homogeneous upon being heated and stirred, was refluxed for 4 h. DMF was distilled from the mixture under reduced pressure. The resulting residue was dissolved in 250 mL of ether. The solution was washed with water and brine. The organic layer was separated, dried with sodium sulfate, and concentrated. The residue was recrystallized with hexanes/ethyl acetate to give sulfone **12** (7.80 g, 95%) as white crystals. Mp: 113−116 °C. ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.67 [dd, *J* = 7.5 and 1.0 Hz, 2**H**], 7.62 [tt, *J* = 7.5 and 1.0 Hz, 1**H**], 7.46 [t, *J* = 7.5 Hz, 2**H**], 7.30 [d, *J* = 9.0 Hz, 1**H**], 7.00 [d, *J* = 3.0 Hz, 1**H**], 6.75 [dd, *J* = 9.0 and 3.0 Hz, 1**H**], 4.54 [s, 2**H**], and 3.78 [s, 3**H**]. ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 158.8, 138.0, 133.9, 133.4, 129.0, 128.9, 128.8, 117.5, 117.0, 116.3, 61.7, and 55.5. Anal. Calcd for $C_{14}H_{13}BrO_3S$: C, 49.28; H, 3.84. Found: C, 49.67; H, 3.89.

(±)-(3*R,4*S**)- and (±)-(3*R**,4*R**)-Methyl 4-(2-Bromo-5-methoxyphenyl)-3-methyl-4-(phenylsulfonyl)butanoate (13α and 13*β*).** Diisopropylamine (435 mg, 4.3 mmol) in 10 mL of anhydrous THF was treated with *n*-butyllithium (1.7 mL, 4.2 mmol, 2.5 M in hexane) at −78 °C under nitrogen. A solution of sulfone **12** (1.36 g, 4.0 mmol) in 5 mL of THF was added. The mixture was stirred at −78 °C for 2 h, methyl crotonate (410 mg, 4.1 mmol) in 5 mL of THF was added, and the mixture was stirred at −78 °C for 4 h. The mixture was partitioned into saturated aqueous ammonium chloride and ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and concentrated. Filtration of the residue through a bed of silica gel with 3:1 hexanes/ethyl acetate gave esters **13α** and **13*β*** (4:1 mixture, 1.51 g, 86%) as a white solid. ^{1}H NMR of **13α** (300 MHz, $CDCl_3$, from the mixture): *δ* 7.59 [dd, *J* = 8.5 and 1.0 Hz, 2**H**], 7.47 [tt, *J* = 8.5 and 1.0 Hz, 1**H**], 7.33 [d, *J* = 3.0 Hz, 1**H**], 7.31 [t, *J* = 8.5 Hz, 2**H**], 7.14 [d, *J* = 9.0 Hz, 1**H**], 6.64 [dd, *J* = 9.0 and 3.0 Hz, 1**H**], 4.83 [d, *J* = 9.0 Hz, 1**H**], 3.84 [s, 3**H**], 3.62 [s, 3**H**], 3.20 [dddq, *J* = 9.0, 9.0, 3.5, and 6.5 Hz, 1**H**], 2.45 [dd, *J* = 15.5 and 3.5 Hz, 1**H**], 2.15 [dd, *J* = 15.5 and 9.0 Hz, 1**H**], and 1.44 [d, *J* = 6.5 Hz, 3**H**]. ^{13}C NMR of **13α** (125 MHz, $CDCl_3$, from the mixture): *δ* 172.0, 159.0, 138.6, 133.4, 133.3, 133.1, 128.5, 128.3, 117.3, 116.6, 115.1, 72.4, 55.7, 51.7, 38.9, 32.3, and 19.1. ^{1}H NMR of **13*β*** (300 MHz, $CDCl_3$, from the mixture): *δ* 7.58 [dd, *J* = 8.5 and 1.0 Hz, 2**H**], 7.48 [tt, *J* = 8.5 and 1.0 Hz, 1**H**], 7.37 [d, *J* = 3.0 Hz, 1**H**], 7.32 [t, *J* = 8.5 Hz, 2**H**], 7.15 [d, *J* = 9.0 Hz, 1**H**], 6.65 [dd, *J* = 9.0 and 3.0 Hz, 1**H**], 5.08 [d, *J* = 9.0 Hz, 1**H**], 3.84 [s, 3**H**], 3.72 [s, 3**H**], 3.18 [dddq, *J* = 9.0, 8.0, 4.0, and 7.0 Hz, 1**H**], 3.04 [dd, *J* = 16.0 and 4.0 Hz, 1**H**], 2.66 [dd, *J* = 16.0 and 8.0 Hz, 1**H**], and 1.01 [d, *J* = 7.0 Hz, 3**H**]. ^{13}C NMR of **13*β*** (75 MHz, $CDCl_3$, from the mixture): *δ* 172.2, 158.9, 138.4, 133.4, 133.2, 133.0, 128.6, 128.4, 117.4, 116.5, 115.4, 70.8, 55.6, 51.6, 38.8, 31.3, and 17.9. IR of the mixture (neat): 1735 cm^{-1}. Anal. Calcd for $C_{19}H_{21}BrO_5S$: C, 51.71; H, 4.80. Found: C, 51.58; H, 5.20.

(±)-(3*R,4*S**)- and (±)-(3*R**,4*R**)-4-(2-Bromo-5-methoxyphenyl)-3-methyl-4-(phenylsulfonyl)butanoic Acid (14α) and (14*β*).** The mixture of esters **13α** and **13*β*** (176 mg, 0.4 mmol) was dissolved in a solution of potassium hydroxide in methanol (10%, 10 mL) and stirred at room temperature until TLC showed that complete hydrolysis had occurred. The mixture was acidified (pH ∼5, 10% aqueous HCl). Most of the MeOH was removed under reduced pressure, and the residue was extracted with ethyl acetate. The combined organic layers were dried with sodium sulfate and concentrated to give acids **14α** and **14*β*** (4:1 mixture, 170 mg, 100%) as a white solid. Recrystallization of the mixture in hexanes/ethyl acetate gave acid **14α** as a white solid: Mp: 167−168 °C. ^{1}H NMR of **14α**

(8) The assignment of relative configuration rests on the observation of a lower field chemical shift for the C(3)-methyl doublet and higher field shift of the C(2)-methylene resonances in the ^{1}H NMR spectrum of the major α-isomer compared with the minor *β*-isomer. We presume that the 2-bromo-5-methoxyphenyl ring is differentially shielding those resonances in the dominant conformation about C(3)−C(4) in which the two methine protons are anti.

(9) Klix, R. C.; Cain, M. H.; Bhatia, A. V. *Tetrahedron Lett.* **1995**, *36*, 6413.

(10) On one occasion the ketone **15** was accompanied by some of its enol trifluoroacetate. This mixture in methylene chloride was stirred under a layer of aqueous NaOH at room temperature for 24 h to cleave the enol ester. During this treatment, smooth conversion of the entire sample to the naphthol **16** was observed, indicating that even mildly basic treatment is sufficient to eliminate sulfinate and promote the aromatization.

(11) We have also investigated the synthesis of the *O*-MOM analogue **9b** starting from 4-bromo-1-(methoxymethoxy)-3-methylbenzene by a route entirely analogous to that depicted in Scheme 2 for the anisole derivative. On one occasion it was equally successful, including the Friedel−Crafts cyclization of the *O*-MOM analogue of the 4-arylbutanoic acid **14α**/***β***. However, that acid-catalyzed cyclization (TFAA) to produce the *O*-MOM analogue of the tetralines **15α**/***β*** has proven to be irreproducible.

(12) Breslow, R.; Garratt, S.; Kaplan, L.; LaFollette, D. *J. Am. Chem. Soc.* **1968**, *90*, 4051.

(500 MHz, $CDCl_3$): δ 7.59 [dd, J = 8.0 and 1.0 Hz, 2**H**], 7.47 [tt, J = 8.0 and 1.0 Hz, 1**H**], 7.32 [t, J = 8.0 Hz, 2**H**], 7.32 [d, J = 3.0 Hz, 1**H**], 7.15 [d, J = 9.0 Hz, 1**H**], 6.64 [dd, J = 9.0 and 3.0 Hz, 1**H**], 4.84 [d, J = 9.0 Hz, 1**H**], 3.83 [s, 3**H**], 3.20 [dddq, J = 10.0, 9.0, 3.0, and 6.5 Hz, 1**H**], 2.53 [dd, J = 16.0 and 3.0 Hz, 1**H**], 2.18 [dd, J = 16.0 and 10.0 Hz, 1**H**], and 1.47 [d, J = 6.5 Hz, 3**H**]. ^{13}C NMR of **14α** (125 MHz, $CDCl_3$): δ 177.6, 159.1, 138.5, 133.4, 133.2, 132.9, 128.5, 128.4, 117.3, 116.6, 115.0, 72.2, 55.6, 38.7, 32.1, and 19.0. ^{1}H NMR of **14*β*** (500 MHz, $CDCl_3$ from the mixture): δ 7.56 [dd, J = 8.0 and 1.0 Hz, 2**H**], 7.48 [tt, J = 8.0 and 1.0 Hz, 1**H**], 7.32 [t, J = 8.0 Hz, 2**H**], 7.32 [d, J = 3.0 Hz, 1**H**], 7.16 [d, J = 9.0 Hz, 1**H**], 6.65 [dd, J = 9.0 and 3.0 Hz, 1**H**], 5.05 [d, J = 9.0 Hz, 1**H**], 3.83 [s, 3**H**], 3.20 [dddq, J = 9.0, 9.0, 4.0, and 6.5 Hz, 1**H**], 3.13 [dd, J = 18.0 and 4.0 Hz, 1**H**], 2.70 [dd, J = 18.0 and 9.0 Hz, 1**H**], and 1.26 [d, J = 6.5 Hz, 3**H**]. ^{13}C NMR of **14*β*** (125 MHz, $CDCl_3$, from the mixture): δ 177.4, 159.1, 138.3, 133.5, 133.2, 133.0, 128.6, 128.4, 177.4, 116.5, 115.4, 70.8, 55.7, 38.8, 31.1, and 17.9. IR of the mixture (KBr): 3420−2574 (br), 1709 cm^{-1}. Anal. Calcd for $C_{18}H_{19}BrO_5S$: C, 50.60; H, 4.48. Found: C, 51.07; H, 5.03.

(±)-(3*R,4*S**)- and (±)-(3*R**,4*R**)-5-Bromo-8-methoxy-3-methyl-4-(phenylsulfonyl)-1-tetralone (15α and 15*β*).** A mixture of acids **14α** and **14*β*** (427 mg, 1.0 mmol) was dissolved in 20 mL of 1,2-dichloroethane in a screw-capped culture tube, and trifluoroacetic anhydride (420 mg, 2.0 mmol) was added. The mixture was refluxed for 12 h and partitioned into saturated aqueous sodium bicarbonate and methylene chloride. The organic layer was washed with water and concentrated. Filtration of the residue through a bed of silica gel with 2:1 hexanes/ethyl acetate gave cyclized products **15α** and **15*β*** (356 mg, 87%) as a white solid. Pure compound **15α** was also obtained from a similar reaction of acid **14α**. Mp of **15α**: 181−184 °C. ^{1}H NMR of **15α** (500 MHz, $CDCl_3$): δ 7.64 (m, 3**H**], 7.54 [d, J = 9.0 Hz, 1**H**], 7.46 [m, 2**H**], 6.95 [d, J = 9.0 Hz, 1**H**], 4.80 [dd, J = 2.0 and 1.0 Hz, 1**H**], 3.93 [s, 3**H**], 3.41 [dd, J = 19.0 and 8.0 Hz, 1**H**], 3.26 [dddq, J = 8.0, 2.0, 1.0, and 7.5 Hz, 1**H**], 2.32 [ddd, J = 19.0, 1.0, and 1.0 Hz, 1**H**], and 1.03 [d, J = 7.5 Hz, 3**H**]. ^{13}C NMR of **15α** (75 MHz, $CDCl_3$): δ 193.0, 158.6, 137.4, 137.0, 134.1, 129.2, 129.0, 128.5, 124.6, 117.1, 124.8, 69.2, 56.4, 42.1, 26.5, and 21.6. ^{1}H NMR of **15*β*** (300 MHz, $CDCl_3$, as the minor component in a 4:1 mixture): δ 7.67−7.34 [m, 6**H**], 6.88 [d, J = 9.0 Hz, 1**H**], 4.91 [dd, J = 3.0 and 1.0 Hz, 1**H**], 3.92 [s, 3**H**], 3.19 [dd, J = 21.0 and 14.5 Hz, 1**H**], 2.70−2.80 [m, 2**H**], and 1.60 [d, J = 6.5 Hz, 3**H**]. ^{13}C NMR of **15*β*** (75 MHz, $CDCl_3$, from the mixture): δ 194.5, 158.8, 137.6, 137.1, 133.9, 129.2, 129.0, 128.7, 124.7, 115.5, 114.6, 68.6, 56.4, 42.7, 33.0, and 19.2. IR of the mixture (neat): 1687 cm^{-1}. FABMS: calcd for $C_{18}H_{18}BrO_4S$ 409.0111, found 409.0101.

5-Bromo-8-methoxy-3-methyl-1-naphthalenol (16). Potassium *tert*-butoxide (898 mg, 8.0 mmol) and sulfones **15α** and **15*β*** (818 mg, 2.0 mmol) were dissolved in 10 mL of anhydrous THF. The solution was stirred at room temperature for 12 h and partitioned with 10% aqueous HCl and ether. The organic layer was concentrated, and the residue was purified by flash chromatography (9:1 hexanes/ethyl acetate) to give naphthalenol **16** (491 mg, 92%) as a white solid. Mp: 152−153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.30 [s, 1**H**], 7.55 [d, J = 8.3 Hz, 1**H**], 7.47 [bs, 1**H**], 6.80 [bs, 1**H**], 6.53 [d, J = 8.3 Hz, 1**H**], 4.00 [s, 3**H**], and 2.47 [s, 3**H**]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 154.5, 139.6, 134.4, 129.5, 118.0, 114.5, 114.1, 113.5, 56.3, and 21.9. IR (neat): 3397 cm^{-1}. Anal. Calcd for $C_{12}H_{11}BrO_2$: C, 53.96; H, 4.28. Found: C, 53.78; H, 4.28.

1-Bromo-4,5-dimethoxy-7-methylnaphthalene (9a). A solution of dimethyl sulfate (945 mg, 7.5 mmol) in 20 mL of methylene chloride was added to a solution of tetrabutylammonium bromide (1.06 g, 3.3 mmol) and sodium hydroxide (250 mg, 6.2 mmol) in water (15 mL). A solution of naphthalenol **16** (668 mg, 2.5 mmol) in methylene chloride (10 mL) was added. The resulting two-phase mixture was stirred at room temperature for 18 h, separated, and extracted with additional methylene chloride. The combined organic layers were washed with water, dried with sodium sulfate, and concentrated. The residue was purified by silica gel flash chromatography (9:1 hexane/ethyl acetate) to give methylated naphthalene **9a** (660 mg, 94%) as a white solid. Mp: 105−106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 [d, J = 9.0 Hz, 1**H**], 7.61 [d, J = 1.5 Hz, 1**H**], 6.76 [d, J = 1.5 Hz, 1**H**], 6.64 [d, J = 9.0 Hz, 1**H**], 3.96 [s, 3**H**], 3.94 [s, 3**H**], and 2.51 [s, 3**H**]. ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 157.0, 137.9, 134.8, 130.5, 130.4, 119.3, 113.1, 109.1, 105.6, 56.6, 56.4, and 22.1. Anal. Calcd for $C_{13}H_{13}BrO_2$: C, 55.54; H, 4.66. Found: C, 55.76; H, 5.00.

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