Convenient AB-Ring Segments for Anthracyclinone Synthesis via Bishydroxylation of 2-Ethyl-5,8-dimethoxy-7-bromo-1-tetralone

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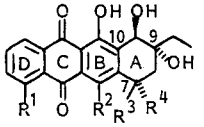
A convenient synthesis of bicyclic synthons having the proper relative stereochemistry of the A-ring substitution patterns of α- and β-rhodomycinone and α-citromycinone is reported. The key intermediate is a dihydroxy ketone obtained via bishydroxylation of an α-tetralone derivative.

The synthesis of tetracyclic anthraquinone derivatives has been of much interest because of the anticancer activity associated with the glycosides of such compounds.[2] A successful strategy for preparing these systems has involved the coupling of the AB and CD rings to form a fully



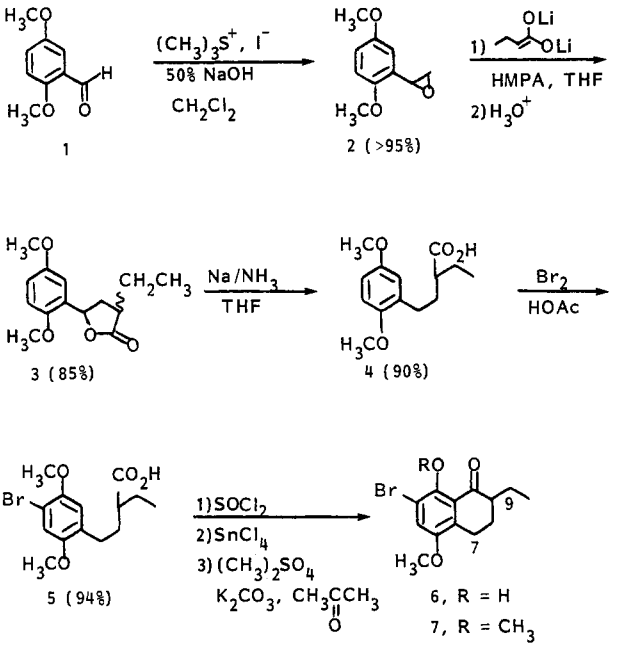
α-rhodomycinone R^1, R^2, R^3 = OH; R^4 = H
β-rhodomycinone R^1, R^2, R^4 = OH; R^3 = H
α-citromycinone R^1, R^4 = OH; R^2, R^3 = H

functionalized tetracyclic ring system.[3-5] Such routes are often more useful than reaction sequences wherein A-ring functionality is introduced after the tetracyclic ring system is formed. While synthetic routes are available for the AB-ring segment having the daunomycinone A-ring substitution pattern, no bicyclic compounds having the trihydroxyl and ethyl substituents characteristic of α- and β-rhodomycinones and α-citromycinones are known.[6,7] We report herein a convenient synthesis of such a bicyclic ring system employing as the key step a bishydroxylation of an α-tetralone derivative.[8]

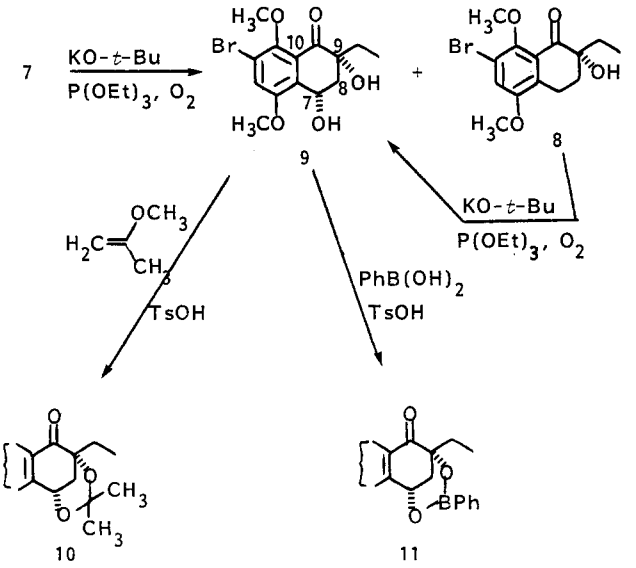
The synthesis of the α-tetralone **6**[9] from commercially available **1** is outlined in Scheme I. The conversion of **1** to the epoxide via sulfonium ylide chemistry never proved satisfactory under standard conditions; however, the phase-transfer procedure[10] gave an excellent yield of the labile epoxide **2**. The epoxide, which is stable for days at 0 °C but slowly decomposes at room temperature, was used without purification in the next step. The epoxide ring opening with the dilithium salt of butyric acid in tetrahydrofuran gave the lactone in only 55% yield. However, if an equivalent of hexamethylphosphoramide was added, the yield of the diasteriomeric mixture of lactones **3** was routinely 85%.

The reductive cleavage of the lactone **3** was especially troublesome. Catalytic hydrogenation under a variety of conditions or reduction with red phosphorus/iodine gave

Scheme I



Scheme II



low yields at best of the desired product. However, reduction of **3** with sodium in liquid ammonia/tetrahydrofuran (9:1) proved acceptable. Even in this case, the best yield was obtained by adding sodium to the reaction mixture until a blue color persisted.[11] While this corre-

(1) The Ohio State University Presidential fellow, 1981–1982.
(2) (a) El Khadem, E., Ed. "Anthracycline Antibiotics"; Academic Press: New York, 1982. (b) Arcamone, F. "Doxorubicin Anticancer Antibiotics"; Academic Press: New York, 1982.
(3) (a) Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989. (b) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825. (c) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263.
(4) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *J. Chem. Soc., Chem. Commun.* **1982**, 158.
(5) See also: (a) Kröhn, K.; Tolkien, K. *Tetrahedron Lett.* **1978**, 4023. (b) Garland, R. B.; Palmer, J. R.; Schulz, J. A.; Sollman, P. B.; Pappo, R. *Ibid.* **1978**, 3669.
(6) Brockmann, H. *Fortschr. Chem. Org. Naturst.* **1963**, *21*, 121–182.
(7) Thomson, R. H. "Naturally Occurring Quinones"; Academic Press: New York, 1971; Chapter 6.
(8) For a preliminary account of this work, see: Coburn, C. E.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1982**, 987.
(9) The synthesis of **6** via a different synthetic route was reported earlier by: Braun, M. *Tetrahedron Lett.* **1980**, *21*, 3871.
(10) Yang, N. C.; Chiang, W.; Leonov, D.; Leonov, E.; Bilyk, I.; Kim, B. *J. Org. Chem.* **1978**, *43*, 3425.
(11) Addition of the lactone in tetrahydrofuran to a solution of sodium in liquid ammonia also gave the reduction in ~80% yield (results of G. Morrow).

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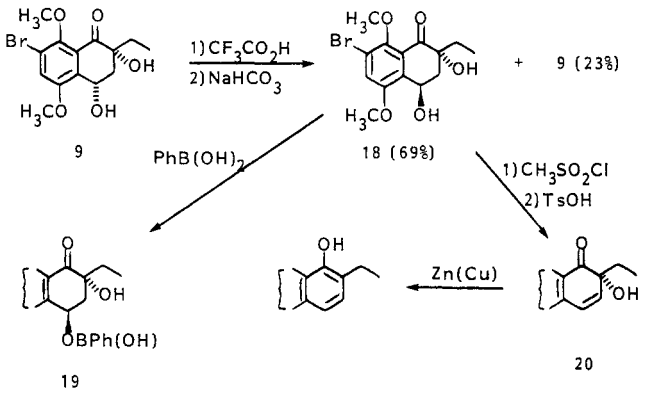
Scheme III



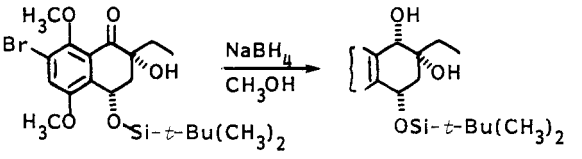
sponded to only 80% of the required sodium for the reduction, unreacted lactone was easily recovered from the neutral fraction of the reaction mixture.

Standard bromination of **4** gave **5** which was then cyclized with polyphosphoric acid. The major product isolated from the reaction was not **7** but the phenolic compound **6**.[12] This poses no problem since the reaction mixture from the cyclization can be methylated with dimethyl sulfate to convert **6** to **7**, with **7** being obtained in 80% yield from **5**. In scale-up work, it was more convenient to perform the cyclization on the acid chloride to afford a mixture of **6** and **7**. Methylation of this reaction mixture as above afforded a good overall yield of **7** from **5**.

While numerous multistep sequences can be envisioned for hydroxylation at what eventually will be C_7 and C_9 of the anthracyclinone, a single-step procedure is more desirable. When oxygenation of the enolate of **7** was performed, TLC analysis indicated the formation of a compound with a lower R_f than that of the starting material. On extended reaction, the first product was largely replaced by a lower R_f compound on TLC. Workup and chromatography on silica gel gave 60% of **9** and 8% of **8** (Scheme II). The structural assignment for **8** rests on the analogy with many similar oxygens α to carbonyl groups together with analytical and spectroscopic data given in the Experimental Section. When **8** was subjected to the same oxygenation conditions as **7**, **9** was formed in 67% yield.

The structural assignment for **9** is supported by the following data. Combustion analysis showed a formula of $C_{14}H_{17}O_5Br$, indicating two oxygen atoms had been introduced into **7**. To establish that no structural rearrangement had occurred under the basic oxygenation conditions,[13] we reduced **9** with zinc–copper couple to 7-bromo-5,8-dimethoxy-2-ethyl-1-naphthol. The ^1H NMR of **9** was especially diagnostic, showing, in addition to the aromatic, methoxy, ethyl, and two hydroxyl protons, a clear ABX pattern: δ 5.10 (dd with D_2O added, J = 6.8, 9.0 Hz), 2.70 (dd, J = 6.8, 13.5 Hz), 2.03 (dd, J = 9.0, 13.5 Hz). The broad band decoupled ^{13}C NMR showed 14 resonances, the signals at 76.4 and 62.5 ppm corresponding to the tertiary and secondary carbons, respectively, bearing hydroxyl groups. The stereochemical relationships of the hydroxyl groups was established by the high-yield formation of the cyclic derivatives **10**[14] and **11**[4] under mild conditions. This oxygenation not only introduced the two hydroxyl groups at C_7 and C_9 but also afforded the diol with the proper relative stereochemistry for the A ring of β-rhodomycinone and α-citromycinone.

The only remaining problem was to reduce the carbonyl group of **9** to give the correct stereochemistry at what will be C_{10} in the anthracyclinones. Initially, we examined the reduction of the protected derivative **12** with sodium bo-



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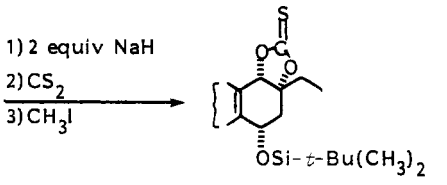

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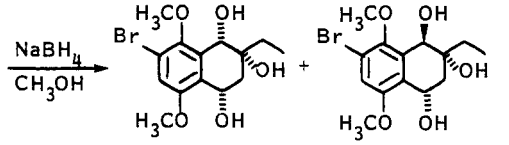
rohydride. While one diol, **13**, was formed stereospecifically in this reaction, it was established as the undesired cis-vicinal compound by conversion to the cyclic thiocarbonate **14**. However, reduction of the diol **9** gave a 1:1 mixture of these triols which were separated by flash chromatography. One of these triols could be reacted with



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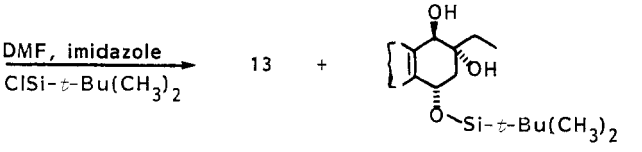

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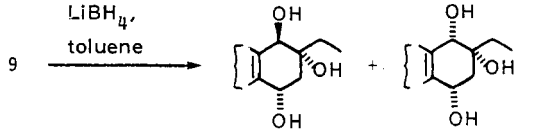
tert-butyldimethylsilyl chloride to give **13**. The silylation product of the second triol, **17**, did not form a cyclic thiocarbonate as in the **13** → **14** reaction but gave an intermediate under these reaction conditions which was converted back to **17** upon workup of the reaction. The triol **16** is then assigned the desired cis,trans stereochemistry.

Having had only marginal success with these reductions in protic media, it was hoped that one of the hydroxyl groups in aprotic media might act to direct the reduction. When **9** was reduced with lithium borohydride, the major product was the desired triol **16**, with only minor amounts



16 (78%) 15 (16%)

(12) The yield of **6** and **7** must be a function of reaction conditions since ref 9 did not mention a demethylation reaction accompanying the cyclization step.

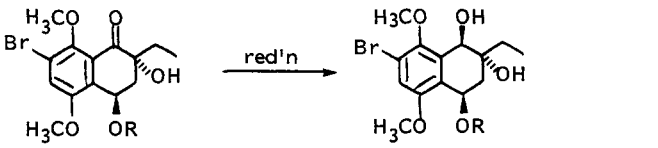
(13) Rearrangement reactions, presumably involving the α-hydroxy ketone moiety, have been observed in basic media at higher temperatures. However, the products from these reactions have not been rigorously identified.

(14) Fanton, E.; Gelas, J.; Horton, D. *J. Chem. Soc., Chem. Commun.* 1980, 21.

of **15** being formed. Thus, a bicyclic system possessing the proper relative stereochemistry of the A ring of β-rhodomycinone and α-citromycinone is available from 2,5-dimethoxybenzaldehyde in ~30% overall yield.

There remained a procedure for obtaining a bicyclic ring system with the relative stereochemistry of α-rhodomycinone (epimeric at C_7 with the other anthracyclinones). When **9** was stirred at −10 °C in trifluoroacetic acid followed by hydrolysis of the trifluoroacetate mixture with sodium bicarbonate, a new dihydroxyl ketone was formed in 69% yield with 23% of recovered **9** (Scheme III). This appears to be the thermodynamic mixture of trifluoroacetates since a similar mixture of **18** and **9** was obtained by starting with pure **18**. To establish that skeletal rearrangement had not occurred during the trifluoroacetolysis, we converted **18** to 7-bromo-5,8-dimethoxy-2-ethyl-1-naphthol. Treatment of **18** with zinc–copper couple gave the naphthol in very low yield.[15] However, dehydration of **18** to **20** followed by reduction of **20** gave the naphthol in a poor but reproducible overall yield of 40%. Compound **9** could also be converted to **20** in 45% yield via formation of the mesylate and then elimination. In contrast to **9**, **18** formed a quite labile compound, **19**, with phenylboronic acid and not the cyclic boronic ester. These chemical transformations together with the near-identical ^{13}C NMR spectra and mass spectral fragmentation data of **9** and **18** strongly support the structure assigned at **18**.

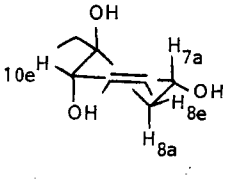
The one remaining problem was reduction of the carbonyl group of **18** to obtain the required *trans*-diol stereochemistry at what will be the C_9 and C_{10} positions of the eventual α-rhodomycinone. Reduction of **18** with sodium borohydride in methanol, lithium borohydride in toluene, or diborane in tetrahydrofuran gave in good yield the triol assigned as **22a**. Similarly, reduction of **21** gave **22b** in



18, R = H
21, R = Si-t-Bu(CH3)2

22a, R = H
b, R = Si-t-Bu(CH3)2

quantitative yield. All attempts to obtain the epimeric reduction product from **18** or **21** failed. The stereochemical assignment of **22b** is based on the inability to form a cyclic thiocarbonate derivative under the conditions used for **13**. Furthermore, the 200-MHz ^1H NMR spectrum of **22a** supports the stereochemical assignment [δ 1.05 (t, J = 7.5 Hz, 3 H), 1.86 (center of ABX_3, heptet, J = 7.5, 21.7 Hz, 2 H), 2.00 (dd, J = 8.6, 14.2 Hz, 1 H), 2.24 (ddd, J = 1.5, 7.3, 14.2 Hz, 1 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.62 (d, J = 1.5 Hz, 1 H), 5.09 (dd, J = 7.3, 8.6 Hz, 1 H), 7.06 (s, 1 H). Especially informative are the lower-field component of the AB portions and the X component of the ABX patterns of H_{10e}, H_{8a}, and H_{8e}. The lower-field signal at



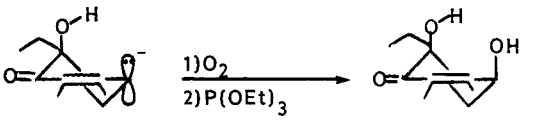
22a, half-chair conformation

δ 2.24 is assigned to the equatorial proton H_{8e} and shows coupling with H_{8a} (J = 14.2 Hz) and H_{7a} (J = 7.3 Hz) and a long-range coupling to H_{10} (J = 1.5 Hz). The hydrogen H_{10e} in turn shows long-range coupling to H_{8e}, appearing as a doublet (J = 1.5 Hz). This type of four-bond coupling is commonly observed in anthracyclinone A-ring systems only when the two protons (H_{10e} and H_{8e}) are both equatorial. While this NMR argument supports the stereochemistry assigned as **22a**, the critical assumption is that the preferred conformer of the ring is as shown above. Thus, the stereochemical assignment for **22a** and **22b** must be considered tentative. We plan to rigorously establish the stereochemistry when **22** is carried to α-rhodomycinone.

(15) Reductive aromatization of **9** and **18** under a variety of conditions never gave high yields of the corresponding naphthol.

Discussion

A convenient synthesis has been developed for the AB-ring segments of β-rhodomycinone and α-rhodomycinone, the key step being the bishydroxylation of the α-tetralone derivative **7**. The preferential formation of the *cis*-diol **9** is most simply viewed as arising from preferential axial attack on the vinylogous enolate ion **23**. However, par-



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ticipation of the oxygen linkage at C_9 in establishing the cis stereochemistry of the diol cannot be ruled out. Such an oxygenation may have utility in the benzylic oxygenation of other vinylogous enolate species.

Since a number of procedures are available for coupling AB-ring segments to the CD-ring part of anthracyclinones, the trihydroxylated derivatives reported here can be employed in a number of anthracyclinone synthetic strategies. The use of **9** and **18** in our synthetic approaches to anthracyclinones as well as the elaboration of **18** to the aklavinone A-ring substitution pattern is currently under study. Finally, we note that compounds analogous to **20**, with the ethyl side chain being replaced by a methyl group, could prove useful in the synthesis of the A ring of steffrimycin.[16]

Experimental Section[17]

2. To a mechanically stirred solution of 50.0 g (0.3 mol) of **1** in 750 mL of dichloromethane under a nitrogen atmosphere were added 5.0 g of tetrabutylammonium iodide, 80.0 g (0.39 mol, 1.3

(16) (a) Bergy, M. E.; Reusser, F. *Experientia* **1967**, *23*, 254. (b) Brodasky, T. F.; Reusser, F. *J. Antibiot.* **1974**, *27*, 809. (c) Kelly, R. C.; Schletter, I.; Koert, J. M.; MacKellar, F. A.; Wiley, P. F. *J. Org. Chem.* **1977**, *42*, 3591.

(17) All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Measurements of standard samples indicated that the observed melting points were probably 1–2 °C lower than the corrected value. Infrared spectra were recorded on a Perkin-Elmer Model 283B grating spectrometer and are reported in reciprocal centimeters. ^1H NMR spectra were taken at 90 MHz in $CDCl_3$ with a Varian EM-90 and are reported in δ units unless noted otherwise. Apparent multiplicities are reported, and in some cases, signals reported as triplets should in fact be closely spaced doublet of doublets. ^{13}C NMR spectra (Me_4Si reference) were recorded on a Bruker HX-90 instrument at 20 MHz in $CDCl_3$ by Mr. Carl Engelman. Multiplicities from the off-resonance spectra are reported in parentheses adjacent to the chemical shift when these measurements were determined. Mass spectra and exact mass measurements were obtained by Mr. C. R. Weisenberger on a Consolidated Electronic MS-9 double-focusing mass spectrometer. Analytical samples were determined by Scandinavian Microanalytical Laboratory. Aluminum oxide and silica gel were from E. Merck Co. The extractive workup consisted of extraction of the organic product into methylene chloride, drying over calcium sulfate, and concentration in vacuo. Solvent abbreviations are as follows: E = diethyl ether; H = hexanes.

equiv) of trimethylsulfonium iodide, and 750 mL of a 50% sodium hydroxide solution. The reaction mixture was heated to reflux for 4 days, and the reaction progress was monitored by TLC (40% E/H elution). The dichloromethane layer was removed, and the aqueous layer was extracted with dichloromethane (2 × 250 mL). The workup afforded a quantitative yield of the epoxide **2** as a light yellow oil: IR (CCl_4) 1505 (vs), 1465 (m), 1280 (m), 1255 (m), 1220 (vs), 1180 (m), 1050 (s); ^1H NMR (CCl_4) 2.50 (dd, J = 2.4, 6.0 Hz, 1 H), 2.97 (dd, J = 4.2, 6.0 Hz, 1 H), 3.60 (s, 3 H), 3.65 (s, 3 H), 4.05 (dd, J = 2.4, 4.0 Hz, 1 H), 6.63 (s, 3 H); ^{13}C NMR 48.3, 50.7, 55.8, 56.2, 110.7, 111.7, 113.8, 127.4, 152.5, 154.1 ppm; exact mass calcd for $C_{10}H_{12}O_3$ m/e 180.0786, obsd m/e 180.0792.

3. To a mechanically stirred solution of 167.5 mL (1.2 mol, 4 equiv) of diisopropylamine in 250 mL of tetrahydrofuran at −78 °C under nitrogen was slowly added 760 mL (1.2 mol, 4 equiv) of a 1.59 M solution of *n*-butyllithium in hexane. This solution was warmed to 0 °C, and 55.5 mL (0.60 mol, 2 equiv) of butyric acid was added. This was stirred for 0.5 h at ambient temperature, and 52.5 mL (0.30 mol, 1 equiv) of hexamethylphosphoramide was added. After 1 h, 54.2 g (0.30 mol, 1 equiv) of epoxide **2** was added in tetrahydrofuran. The reaction mixture was heated to 50 °C for 24 h during which time a gummy material precipitated and coated the wall of the flask. The reaction was quenched with 100 mL of water and partially concentrated, and then the basic aqueous phase was washed with dichloromethane. The basic aqueous phase was acidified to pH 1 and stirred at 45 °C for 12 h. The resulting lactone was extracted with dichloromethane and washed with a 5% sodium bicarbonate solution. The dichloromethane was removed, and the resulting yellow oil was dissolved in carbon tetrachloride. This was washed several times with water to remove residual hexamethylphosphoramide. The carbon tetrachloride solution was dried by passing it through sodium sulfate and concentrated in vacuo to yield 66.3 g (88%) of a viscous yellow oil: IR (CCl_4) 2970 (m), 1770 (br, s), 1505 (s), 1470 (m), 1285 (m), 1230 (m), 1200 (m), 1180 (s), 1170 (s), 1050 (s), 1030 (s); ^1H NMR (CCl_4) 0.95 (t, J = 6.5 Hz, 3 H), 1.10–3.00 (m, 5 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 5.23–5.68 (overlapping t, 1 H), 6.7–6.9 (s overlapping m, 3 H); exact mass calcd for $C_{14}H_{18}O_4$ m/e 250.1205, obsd m/e 250.1212.

4. To a three-necked, round-bottomed flask equipped with a magnetic stirrer and dry ice condenser was added 25 g (0.10 mol) of lactone **3** in 50 mL of tetrahydrofuran followed by 450 mL of liquid ammonia. Next, 4.33 g (0.19 mol, 1.88 equiv) of sodium was quickly added in six or seven portions until a blue color persisted for 3 min. The reaction was quenched by the cautious addition of 40 mL of a saturated ammonium chloride solution, and the solvents were allowed to evaporate overnight at ambient temperature. The resulting slurry was acidified, and the organics were extracted with dichloromethane. The acidic products were removed with a 5% sodium hydroxide solution, regenerated by a 20% hydrochloric solution, and stirred at pH 1 for 12 h to close the hydroxy acid back to the lactone. The organics were extracted with dichloromethane, and the product was removed by extraction with a 5% sodium hydroxide solution. The acid was regenerated with a 20% hydrochloric acid solution and then extracted with dichloromethane. Concentration in vacuo yielded 19.3 g (76%) of a yellow oil that crystallized with time; mp 50.3–51.3 °C. All organic layers after basic extractions were saved, combined, and stirred with a 5% sodium hydroxide solution for 12 h. The basic aqueous phase was washed with dichloromethane and acidified to pH 1, and the lactone **3** was extracted with dichloromethane. The solvent was dried through sodium sulfate and removed in vacuo to yield 4.5 g of recovered lactone (corrected yield for **4** is 93%). The acid **4** showed the following: IR (KBr) 3500–2400 (m, br), 2960 (m), 2940 (m), 1735 (w), 1705 (s), 1500 (s), 1460 (m), 1220 (s), 1045 (m); ^1H NMR (60 MHz, $CDCl_3$) 0.95 (t, J = 6.5 Hz, 3 H), 1.40–2.80 (m, 7 H), 3.7 (s, 6 H), 6.68 (s, 3 H), 11.23 (s, br); exact mass calcd for $C_{14}H_{20}O_4$ m/e 252.1362, obsd m/e 252.1354.

5. To a magnetically stirred solution of 58.2 g (0.23 mol) of acid **4**, 19.9 g (0.24 mol, 1.05 equiv) of sodium acetate, and 600 mL of acetic acid was added 12.4 mL (0.24 mol, 1.05 equiv) of bromine over a period of 20 min at 20 °C under nitrogen. After an additional 3 min, the orange reaction mixture was quenched by the addition of a 10% sodium bisulfite solution until a constant yellow color was observed. The solution was diluted with 50 mL of water, and the product was extracted with dichloromethane. This was washed with water, and the product was taken up with a 5% sodium hydroxide solution, regenerated by the addition of a 20% hydrochloric acid solution, and extracted with dichloromethane. Drying and concentration yielded 72.5 g (94%) of light brown crystals, mp 62–65 °C. Recrystallization from E/H yielded an analytical sample: mp 67.5–68.3 °C; IR (KBr) 3500–2400 (br), 2970 (m), 2940 (m), 1705 (s), 1495 (s), 1465 (m), 1385 (m), 1210 (s), 1055 (m), 1030 (m); ^1H NMR 0.93 (t, J = 7.0 Hz, 3 H), 1.20–2.80 (m, 5 H), 3.70 (s, 3 H), 3.80 (s, 3 H), 6.70 (s, 1 H), 6.93 (s, 1 H), 11.18 (br, s); ^{13}C NMR 11.6, 25.2, 28.2, 31.5, 46.5, 56.1, 57.0, 108.9, 114.8, 115.9, 130.3, 150.0, 152.0, 182.8 ppm; exact mass calcd for $C_{14}H_{19}O_4Br$ m/e 330.0467, obsd m/e 330.0475. Anal. Calcd for $C_{14}H_{19}O_4Br$: C, 50.76; H, 5.78. Found: C, 50.83; H, 5.79.

6 and 7. To 21.0 g (63.5 mmol) of the bromo acid **5** was added 50 g of polyphosphoric acid. This was magnetically stirred at 105 °C for 1 h. An additional 20 g of polyphosphoric acid was added, and the reaction mixture was stirred at 105 °C for another hour. The reaction was quenched with water, and the products were extracted with dichloromethane. The organic phase was washed with a 5% sodium hydroxide solution, dried, and concentrated to yield 18.2 g of a dark semicrystalline material. Chromatography on silica gel (1.5 in. × 10 in. column) proceeded as follows: 400 mL of H, nil; 800 mL of 2% E/H, 14.0 g of yellow phenolic product **6**, mp 58–64 °C, recrystallized from E/H to yield an analytical sample: mp 65.5–66.5 °C; IR (KBr) 2960 (strong absorption m) 1640 (s), 1450 (s), 1425 (s), 1285 (s), 1260 (s), 1245 (s), 1180 (s), 1055 (s); ^1H NMR (60 MHz, CCl_4) 0.95 (t, J = 7.5 Hz, 3 H), 1.20–3.10 (m, 7 H), 3.70 (s, 3 H), 7.00 (s, 1 H), 12.10 (s, 1 H); ^{13}C NMR 11.3, 21.8, 22.2, 26.3, 48.4, 56.4, 107.3, 117.4, 122.3, 132.5, 148.8, 152.9, 207.0 ppm; exact mass calcd for $C_{13}H_{15}O_3Br$ m/e 298.0205, obsd m/e 298.0213]. Anal. Calcd for $C_{13}H_{15}O_3Br$: C, 52.17; H, 5.20. Found: C, 52.17; H, 5.14.

Elution was continued with 700 mL of 4% E/H to give 1.27 g of a mixture of **6** and **7**. For convenience, the mixture of 15.27 g of **6** and **7** was combined, and **6** was remethylated by addition of 14.65 g (107 mmol) of anhydrous potassium carbonate, 10.2 mL (107 mmol, 2 equiv) of dimethyl sulfate, and 80 mL of dry acetone. This was heated at reflux with stirring under nitrogen for 24 h, 10 mL of 5% sodium hydroxide solution was added, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered and concentrated in vacuo. The residue was extracted with dichloromethane and worked up as usual to yield 15.9 g (80%) of an orange oil. This material was used as obtained. Pure **7** could be prepared by short-path distillation [bath temperature 120 °C (0.05 torr)]: mp 39–40 °C; IR (neat) 2960 (m), 2940 (m), 1695 (s), 1570 (m), 1465 (s), 1420 (s), 1385 (m), 1260 (m), 1240 (s), 1180 (m), 1050 (s), 970 (m); ^1H NMR (CCl_4) 0.93 (t, J = 7.5 Hz, 3 H), 1.10–3.10 (m, 7 H), 3.78 (s, 3 H), 3.83 (s, 3 H), 7.08 (s, 1 H); ^{13}C NMR 11.5, 22.5, 27.1, 50.0, 56.0, 61.8, 116.6, 118.2, 128.5, 133.6, 150.8, 153.1, 199.2 ppm; exact mass calcd for $C_{14}H_{17}O_3Br$ m/e 312.0361, obsd m/e 312.0353.

7 via Acid Chloride Route. To 11.4 mL (0.159 mol, 1.3 equiv) of thionyl chloride was added dropwise 40.6 g (0.123 mol) of **5** in 40 mL of dichloromethane over 0.5 h. The reaction was refluxed for 2 h, and the excess thionyl chloride and dichloromethane was removed in vacuo. The resulting residue was dissolved in 130 mL of dichloromethane, and 17.1 mL (0.148 mmol, 1.2 equiv) of stannic chloride was added. This was stirred at room temperature for 12 h and then refluxed for 2 h. The reaction mixture was poured onto ice, and the product was extracted with dichloromethane. After a 5% sodium bicarbonate wash and a workup as usual, distillation of the resulting oil at bp 165–175 °C (0.2 mm) resulted in a mixture of **6** and **7**. This mixture was remethylated as described above to yield 27.9 g (72.6%) of **7** as a yellow oil.

8 and 9.[18] To a two-necked, round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was added 5.19 g of 37% potassium hydride oil dispersion (48 mmol, 5 equiv). The potassium hydride was washed with hexane to remove the oil, and without stirring 20 mL of dimethylformamide was added. To this mixture at −15 °C was added 10.8 mL (0.12 mol, 12 equiv) of *tert*-butyl alcohol, and the reaction mixture was stirred and al-

(18) The reaction has been performed several times on a >10-g scale; however, in this case, the yields are more variable, ranging from 50% to 60% of **9** and 8% to 20% of **8**.

lowed to warm to avoid freezing the alcohol. When the hydrogen gas evolution was complete (ca. 0.5 h), the solution was cooled to −15 °C, and 55 mL of dimethylformamide and then 3.75 mL of triethyl phosphite (20.8 mmol, 2.2 equiv) were added. The nitrogen line was removed, and oxygen was bubbled through the solution (approximately 3 bubbles/s from a disposable pipet). Then 3.0 g (9.6 mmol) of **7** was added in a minimum amount of tetrahydrofuran. While the temperature was carefully maintained between −15 and −10 °C, the color of the reaction mixture changed from yellow to orange to red to dark red to dark blue-green. By taking small aliquots and quenching these in water, one can monitor the reaction by TLC (50% E/H eluant). After 1.25 h, the TLC showed little change, and the reaction was quenched by the addition of 20 mL of water. The crude reaction mixture was stirred for 3 h at ambient temperature, the color of the reaction mixture changing from dark blue-green to red-brown. The dimethylformamide was removed under vacuum, and the resulting slurry was dissolved in dichloromethane. The organic phase was then washed with water, filtered, and concentrated, and the triethylphosphate was removed at 50 °C (10^{-4} torr). The resulting 3.1 g of a red-brown oil was chromatographed on silica gel (2.5 × 20 cm column). Elution proceeded as follows: 450 mL of 10% E/H, nil; 150 mL of 10% E/H and 300 mL of 15% E/H, 0.14 g of C_9-monohydroxylated α-tetralone **8**, mp 119.3–120.0 °C (from E/H) [IR (KBr) 3460 (s), 1690 (s), 1570 (s), 1470 (s), 1420 (s), 1285 (s), 1265 (s), 1255 (s), 1205 (s), 1185 (s), 1060 (s), 980 (s), 845 (s), 750 (s); ^{1}H NMR 0.85 (t, J = 7 Hz, 3 H), 1.63 (q, J = 7 Hz, 2 H), 1.83–3.20 (high structured absorption of the two methylene groups, 4 H), 3.83 (overlapping s, 6 H), 4.03 (s, 1 H), 7.15 (s, 1 H); ^{13}C NMR 7.2 (q), 21.0 (t), 28.1 (t), 33.0 (t), 55.9 (q), 61.7 (q), 75.9 (s), 116.8 (s), 118.8 (d), 125.9 (s), 132.8 (s), 150.3 (s), 153.0 (s), 200.5 (s) ppm; exact mass calcd for $C_{14}H_{17}O_4Br$ m/e 328.0310, obsd m/e 328.0316].

Elution was continued as follows: 450 mL of 15% E/H, nil; 1000 mL of 20% E/H, nil; 600 mL of 20% E/H, 1.16 g of **9** as a foam; 1200 mL of 25% E/H, 1.22 g of **9** as a foam; 150 mL of 50% E/H, nil. The crude **9** fractions were combined and crystallized from E/H to yield 1.89 g (57.1%) of **9** as white crystals, mp 103.3–105.0 °C. A second crop yielded 0.14 g (4.2%) of slightly orange crystals. The analytical sample had the following: mp 107.5–110.0 °C; IR (KBr) 3550 (m), 3440 (w), 2930 (w), 1700 (vs), 1570 (m), 1470 (s), 1450 (m), 1280 (s), 1250 (s), 1060 (m), 980 (s), 750 (m); ^{1}H NMR ($CDCl_3$) 0.80 (t, J = 8 Hz, 3 H), 1.43–1.70 (m, 2 H), 2.03 (dd, J = 9.0, 13.5 Hz, 1 H), 2.70 (dd, J = 6.8, 13.5 Hz, 1 H), 3.8 (d, J = 1.5 Hz, 1 H, disappeared with D_2O), 3.90 (s, 3 H), 3.93 (s, 3 H), 4.03 (s, 1 H, disappeared with D_2O), 5.10 (m, 1 H, collapsed to dd with D_2O, J = 6.8, 9.0 Hz, 1 H), 7.28 (s, 1 H); ^{13}C NMR ($CDCl_3$) 7.1 (q), 29.7 (t), 40.8 (t), 56.1 (q), 62.0 (q), 62.5 (d), 76.4 (s), 119.0 (s), 119.8 (d), 125.2 (s), 132.9 (s), 149.7 (s), 153.2 (s), 199.1 (s) ppm; exact mass calcd for $C_{14}H_{17}O_5Br$ m/e 344.0259, obsd m/e 344.0269. Anal. Calcd for $C_{14}H_{17}O_5Br$: C, 48.71, H, 4.96. Found: C, 48.67; H, 5.06.

7-Bromo-5,8-dimethoxy-2-ethyl-1-naphthol from 9. A mixture of 0.050 g (0.145 mmol) of **9** and 0.028 g of zinc–copper couple in 0.8 mL of acetic acid, 0.1 mL of water, and 2 mL of tetrahydrofuran was stirred at 100 °C for 2.5 days. The reaction mixture was concentrated in vacuo, and the product was extracted with dichloromethane. Workup followed by preparative TLC on silica gel (30% E/H eluant) gave 0.015 g of the title α-naphthol as a yellow oil which showed spectroscopic properties identical with those of an authentic sample as prepared below.

A mixture of 250 mg (0.80 mmol) of **7**, 143 mg (0.80 mmol) of *N*-bromosuccinimide, and a catalytic amount of azobis(isobutrylnitrile) in 10 mL of carbon tetrachloride was irradiated with a 200-W unfrosted incandescent bulb for 1 h. The reaction mixture was filtered, and the resulting organic phase was washed with saturated sodium bicarbonate solution, dried by passing it through sodium sulfate, and concentrated in vacuo to yield the naphthol as an orange-yellow oil. This was purified by flash chromatography using a 5.5 in. × 0.75 in. silica gel column (1% E/H as the eluant) to give 174 mg of the pure naphthol as a light yellow oil. This yellow oil was recrystallized from E/H to afford white crystals: mp 45.8–46.8 °C; IR (KBr) 3350 (s), 2960 (m), 2930 (m), 1590 (s), 1510 (s), 1450 (m), 1425 (m), 1375 (vs), 1325 (s), 1100 (m), 1040 (vs), 955 (m), 815 (m); ^{1}H NMR (CCl_4) 1.23 (t, J = 7.5 Hz, 3 H), 2.70 (q, J = 7.5 Hz, 2 H), 3.88 (s, 3 H), 3.95 (s, 3 H), 6.60 (s, 1 H), 7.30 (AB, J = 8.3 Hz, $\Delta\nu$ = 28.5 Hz, 2 H), 9.33 (s, 1 H, disappeared with D_2O); ^{13}C NMR 14.1, 23.0, 55.9, 62.5, 107.4, 110.4, 113.2, 117.9, 126.1, 127.4, 128.6, 146.0, 149.7, 152.8 ppm; exact mass calcd for $C_{14}H_{15}O_3Br$ m/e 310.0205, obsd m/e 310.0214.

10. A solution of **9** (2 g, 5.8 mmol) and 2-methoxypropene (2 g, 27.6 mmol) in dry dimethylformamide (19 mL) was cooled to 0 °C under nitrogen with stirring and was treated with anhydrous *p*-toluenesulfonic acid (60 mg). After being stirred for 10 h at 0 °C, the solution was treated with an additional amount (1 g, 13.8 mmol) of 2-methoxypropene, and stirring was continued for 5 h at 0 °C. The reaction was quenched with saturated sodium bicarbonate (20 mL), allowed to warm to room temperature, and then extracted with methylene chloride (3 × 40 mL). The organic layer was washed with water (4 × 50 mL) until clear and brine (50 mL) and dried by passsage through a cone of calcium sulfate. Removal of the solvent yielded 2.7 g of a light yellow solid (still containing dimethylformamide). This material was placed under vacuum [56 °C (0.5 torr)] overnight to yield 2.26 g (quantitative) of **10**, mp 113–117 °C. Recrystallization from E/H yielded 1.97 g (88%) of very fine, white needles: mp 119–121 °C; IR (CCl_4) 2990 (m), 2970 (m), 2935 (m), 1715 (s), 1560 (m), 1465 (vs), 1425 (m), 1390 (m), 1380 (m), 1265 (s), 1240 (s), 1135 (s), 1115 (s), 1060 (s), 1035 (s); ^{1}H NMR (CCl_4, 90 MHz) 7.15 (s, 1 H), 5.3 (t, J = 3 Hz, 1 H), 3.87 (s, 3 H), 3.8 (s, 3 H), 2.57 (dd, J = 3.5, 13.5 Hz, 1 H), 2.1 (dd, J = 2, 13.5 Hz, 1 H), 1.85 (q, J = 7.5 Hz, 2 H), 1.4 (s, 3 H), 1.05 (s, 3 H, overlaps t), 0.95 (t, J = 7.5 Hz, 3 H); exact mass calcd for $C_{17}H_{21}O_5{}^{79}Br$ m/e 384.0573, obsd m/e 384.0582.

11. A mixture of 0.30 g (0.87 mmol) of **7**, 0.12 g (0.96 mmol) of phenyl boric acid, and 20 mg of anhydrous *p*-toluenesulfonic acid in 5 mL of toluene was stirred at 18 °C for 5 h. After addition of 2 mL of 5% sodium bicarbonate solution to the reaction mixture, the organic layer and dichloromethane washings were worked up to give a light yellow oil which crystallized when triturated with E/H to afford 0.36 g (96%) of white crystals, mp 88.7–90.0 °C. The analytically pure material recrystallized from E/H showed the following: mp 90.0–90.8 °C; IR (KBr) 1705 (s), 1465 (m), 1440 (m), 1390 (m), 1350 (m), 1325 (vs), 1290 (m), 1270 (m), 1250 (m), 1130 (s), 700 (m); ^{1}H NMR 1.00 (t, J = 7.5 Hz, 3 H), 1.9–2.3 (m, 2 H), 2.35 (3-line m, 2 H), 3.78 (s, 3 H), 3.85 (s, 3 H), 5.65 (t, apparent $J \simeq$ 3 Hz, 1 H), 7.10–7.4 (m, 4 H), 7.65–7.83 (m, 2 H); ^{13}C NMR 7.4, 28.1, 35.8, 56.8, 60.7, 61.5, 75.6, 120.7, 121.3, 124.3, 127.5, 131.0, 132.0, 134.0, 152.0, 152.9, 192.5 ppm; exact mass calcd for $C_{20}H_{20}O_5B^{79}Br$ m/e 430.0588, obsd m/e 430.0601.

12. A mixture of 0.10 g (0.29 mmol) of **9**, 0.22 g (1.46 mmol, 5 equiv) of *tert*-butyl dimethylsilyl chloride, and 0.20 g (2.8 mmol, 10 equiv) of imidazole was dissolved in 2 mL of dimethylformamide. The reaction mixture was stirred at ambient temperature for 24 h. The reaction was quenched (1 mL of saturated sodium bicarbonate solution). Extractive workup (methylene chloride) gave a quantitative yield of light yellow oil. This material was suitable for use without any further purification: IR (neat) 3480 (m, br), 2940 (s), 2860 (s), 1705 (s), 1570 (m), 1470 (s), 1430 (m), 1250 (m), 1060 (m, br), 980 (m), 830 (m), 780 (m); ^{1}H NMR 0.00 (s, 3 H), 0.20 (s, 3 H), 0.80 (s, 9 H), 0.85 (t, J = 7.5 Hz, 3 H), 1.45–1.7 (strong q, 2 H), 2.28 and 2.23 (2 s, 2 H), 3.80 (s, 3 H), 3.88 (s, 3 H), 5.28 (dd with center lines overlapping, $J \simeq$ 4 Hz, 1 H), 7.20 (s, 1 H); ^{13}C NMR −5.0, 7.3, 17.8, 25.6, 32.1, 42.2, 55.7, 61.7, 62.7, 75.9, 119.0, 119.3, 127.9, 133.2, 149.6, 151.9, 199.7 ppm.

13. A solution containing 0.53 g (1.15 mmol) of **12** in 10 mL of methanol was cooled to 0 °C, and 0.070 g (1.9 mmol) of sodium borohydride was added. After the mixture was stirred under nitrogen for 2 h, an additional 0.025 g (0.67 mmol, 0.6 equiv) of sodium borohydride was added, and the reaction was allowed to warm to ambient temperature over 0.5 h. The solution was quenched with acetone and was stirred for an additional 10 min. Next, 3 mL of 5% potassisum hydroxide solution was added, and the mixture was concentrated in vacuo with heating (ca. 50 °C). An extractive workup (methylene chloride) yielded 0.51 g (96%) of light tan crystals. This material was suitable for use without further purification. Recrystallization (E/H) gave 0.42 g (82%) of **13**: mp 110–112 °C; IR (KBr) 3490 (m), 3400 (m), 2950 (m), 2930 (m), 2860 (m), 1470 (s), 1435 (m), 1250 (m), 1235 (m), 1055 (s), 1030 (m), 1010 (m), 975 (m), 940 (m), 835 (m), 830 (s), 780 (m); ^{1}H NMR 0.03 (s, 3 H), 0.20 (s, 3 H), 0.88 (s, 9 H), 0.93 (t, J = 7.5 Hz, 3 H), 1.50 (q, J = 7.5 Hz, 2 H), 1.78 (dd, J = 3.8, 15

Hz, 1 H), 2.25 (dd, J = 2.6, 15 Hz, 1 H), 3.78 (s, 3 H), 3.93 (s, 3 H), 4.13–4.30 (m, 1 H), 4.50–4.80 (m, 2 H), 5.23 (dd, J = 2.6, 3.8 Hz, 1 H), 6.98 (s, 1 H). Anal. Calcd for $C_{20}H_{33}O_5SiBr$: C, 52.06; H, 5.52. Found: C, 52.16; H, 5.53.

14. To 7.3 mg (1.7 mmol, 2 equiv) of a 57% sodium hydride oil dispersion (washed with hexane) and 1 mL of tetrahydrofuran was added 0.040 g (0.087 mmol) of **13** as a solid. The mixture was stirred at ambient temperature for a couple of minutes and cooled to 0 °C, and 5.2 μL (0.087 mmol, 1 equiv) of carbon disulfide was syringed into the reaction mixture. TLC (1:1 E/H as the eluant) indicated completion of the reaction in 3 h. Then, 5.4 μL (0.087 mmol, 1 equiv) of iodomethane was added, and after an additional 2 h at 0 °C, TLC (1:1 E/H as the eluant) indicated that the reaction was complete. After 0.5 mL of a saturated solution of ammonium chloride was added, the tetrahydrofuran layer was separated from the aqueous phase, and the aqueous phase was extracted with dichloromethane. The combined organic layers were worked up to yield 0.048 g of a yellow oil. Preparative TLC on silica gel (20% E/H eluted twice) gave 0.026 g of a white foam that was recrystallized from E/H: mp 143.3–143.5 °C; IR (KBr) 2960 (m), 2860 (m), 1480 (m), 1350 (m), 1320 (s), 1270 (s), 1245 (s), 1210 (s), 1110 (m), 1080 (m), 1065 (m), 1015 (m), 975 (m), 945 (m), 835 (m); ^{1}H NMR 0.10 (s, 3 H), 0.18 (s, 3 H), 0.85 (s, 9 H), 1.05 (t, J = 7.5 Hz, 3 H), 1.60 (dd, J = 3.0, 12.8 Hz, 1 H), 1.88 (q, J = 7.5 Hz, 2 H), 2.48 (dd, J = 3.0, 12.8 Hz, 1 H), 3.78 (s, 3 H), 3.93 (s, 3 H), 5.33 (t, $J \simeq$ 3.0 Hz, 1 H), 5.90 (s, 1 H), 7.10 (s, 1 H). Anal. Calcd for $C_{21}H_{31}O_5SiSBr$: C, 50.09; H, 6.21. Found: C, 50.22; H, 6.32.

15 and 16 from Reduction of 9. To a round-bottomed flask equipped with a magnetic stirrer and nitrogen inlet was added 0.10 g (0.29 mmol) of **9** in 2 mL of methanol. The solution was cooled to 0 °C, and 0.016 g (0.45 mmol, 1.5 equiv) of sodium borohydride was added. After 2 h, 1 mL of acetone was added, the reaction mixture was warmed to ambient temperature, and then 2 mL of a 5% sodium hydroxide solution was added. Workup as described above gave 0.098 g (98%) of a white foam which was separated by flash chromatography as in the lithium borohydride reduction described below.

13 and 17 from 9. A stereoisomeric mixture of **15** and **16** (0.15 g, 0.43 mmol), imidazole (0.257 g, 3.76 mmol), and *tert*-butyl dimethylsilyl chloride (0.28 g, 1.83 mmol) was dissolved in 3 mL of dimethylformamide, and the reaction was run at ambient temperature. The reaction progress was monitored by TLC (20% E/H as eluant), and after 1.5 h the reaction appeared complete. Addition of 1 mL of sodium bicarbonate and an extractive workup (methylene chloride) gave 0.176 g of off-white crystals. The two isomers could be separated by preparative TLC on silica gel (20% E/H, eluted six times). The spectral data of compound **13** (mp 110–112 °C) matched the previously reported values. Compound **17**: mp 167.8–169.3 °C; IR (KBr) 3450 (m, br), 3380 (m, br), 2930 (s), 2860 (m), 1470 (s), 1250 (m), 1230 (m), 1065 (m), 1040 (s), 1010 (s), 970 (m), 950 (m), 830 (s), 780 (m); ^{1}H NMR 0.08 (s, 3 H), 0.23 (s, 3 H), 0.90 (s, 9 H), 1.10 (t, J = 7.5 Hz, 3 H), 1.78 (q, J = 7.5 Hz, 2 H), 2.00 (d, separation ~3 Hz, 2 H), 3.80 (s, 3 H), 3.93 (s, 3 H), 4.68 (s, 1 H), 4.80 (s, 1 H), 5.25 (t, $J \simeq$ 3.0 Hz, 1 H), 6.98 (s, 1 H). Anal. Calcd for $C_{20}H_{33}O_5SiBr$: C, 52.06; H, 7.21. Found: C, 51.86; H, 7.25.

16 and 15 from 9. To 1.0 g (2.9 mmol) of **9** were added 0.10 g (4.3 mmol) of lithium borohydride and 20 mL of toluene. This was stirred at room temperature under nitrogen for 12 h when TLC (100% E as the eluant) showed the reaction to be complete. The reaction was quenched by the addition of 2 mL of acetone and 10 mL of a 5% sodium hydroxide solution, and then the mixture was stirred for an additional 20 min. Concentration and extractive workup gave 0.99 g of a white foam which was purified by flash chromatography with 50:50 ethyl acetate/petroleum ether as the eluant. Elution proceeded as follows: 40 mL, nil; 110 mL, 0.78 g (78%) of **15** as a white solid, mp 128–129 °C [IR (KBr) 3600–3200 (br), 2940 (m), 1470 (s), 1440 (m), 1235 (s), 1010 (s), 960 (m), 760 (m); ^{1}H NMR 1.00 (t, J = 7.5 Hz, 3 H), 1.73 (q, J = 7.5 Hz, 2 H), 2.00 (d, J = 3.3 Hz, 2 H), 2.6–3.7 (br s, disappeared with D_2O, 3 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 4.55 (s, 1 H), 5.00 (formed t with D_2O, J = 3.3 Hz, 1 H), 6.98 (s, 1 H); ^{13}C NMR 7.2, 31.2, 40.0, 56.5, 62.0, 62.3, 75.9, 119.6, 120.3, 125.0, 132.4, 150.4, 153.4, 201.5 ppm; exact mass calcd for $C_{14}H_{19}O_5Br$ m/e 346.041 628, obsd m/e 346.042 474, difference 0.000 846]. Anal. Calcd for $C_{14}H_{19}O_5Br$: C, 48.43; H, 5.52. Found: C, 48.44; H, 5.60.

Elution was continued as follows: 40 mL, nil; 220 mL, 0.164 g (16%) of **15** as a clear oil which turns yellow when kept in solution at room temperature [IR (KBr) 3700–3100 (br s), 2960 (m), 2930 (m), 1465 (s), 1430 (m), 1375 (m), 1285 (m), 1225 (s), 1055 (s), 1000 (s), 970 (m); ^{1}H NMR 0.98 (t, J = 7.5 Hz, 3 H), 1.60 (7-line m, 2 H), 1.83 (dd, overlaps with m, J = 4.5, 14.3 Hz, 1 H), 2.30 (dd, J = 4.5, 14.3 Hz, 1 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 4.68 (s, 1 H), 4.90 (t, J = 4.5 Hz, 1 H), 7.03 (s, 1 H); ^{13}C NMR 7.6, 30.6, 35.3, 56.2, 61.6, 63.2, 69.6, 72.9, 115.1, 116.6, 127.4, 132.4, 149.8, 154.4 ppm; exact mass calcd for $C_{14}H_{19}O_5Br$ m/e 346.0416, obsd m/e 346.0425].

18 from 9. To 0.50 g (1.5 mmol) of **9** at −15 °C was added 6 mL of cold trifluoroacetic acid. This was allowed to stir at −15 °C until homogeneous and then kept at −20 °C for 24 h. The trifluoroacetic acid was removed from the yellow solution under reduced pressure, and 5 mL of a 5% sodium bicarbonate solution and 5 mL of acetone were added. After 12 h at room temperature, the hydrolysis was complete. Concentration in vacuo, extraction of the product with methylene chloride, and the workup gave 0.50 g of yellow foam. This mixture of **9** and **18** was partially separated by flash chromatography on silica gel (5.5 in. × 1.5 in. column with 80% E/H as the eluant). Elution proceeded as follows: 450 mL, nil; 75 mL, 0.28 g (56%) of **18**, mp 116.3–117.3 °C [IR (KBr) 3560 (s), 3470 (m), 2940 (m), 1690 (s), 1570 (m), 1470 (s), 1375 (m), 1295 (m), 1265 (s), 1255 (s), 1155 (m), 1105 (m), 1055 (s), 1000 (s); ^{1}H NMR 0.85 (t, J = 7.5 Hz, 3 H), 1.93 (q, J = 7.5 Hz, 2 H), 2.20 (dd, J = 6.0, 14.3 Hz, 1 H), 2.55 (dd, J = 2.0, 14.3 Hz, 1 H), 3.08 (s, disappeared with D_2O, 1 H), 3.85 (s, 3 H), 3.93 (s, 3 H), 5.15 (forms dd with D_2O, J = 2.0, 6.0 Hz, 1 H), 7.28 (s, 1 H); ^{13}C NMR 7.2, 31.2, 40.0, 56.5, 62.0, 62.3, 75.9, 119.7, 120.3, 125.0, 132.4, 150.4, 153.4, 201.5 ppm; exact mass calcd for $C_{14}H_{17}O_5Br$ m/e 344.0259 obsd m/e 344.0266.

Elution was continued as follows: 60 mL, 0.1 g (20%) of a mixture of **9** and **18**; 75 mL, 0.10 g (20%) of **9**. Complete separation of a similar mixture gave 69% of **18** and 23% of **9**.

12 and 21 Directly from 9. The separation of the epimerized diols described in the preceding experiment is much simpler if the diols are first silylated as described here. To 0.85 g (0.810 mmol) of the crude reaction mixture obtained from the epimerization reaction of compound **9** were added 0.605 g (3.47 mmol, 4.3 equiv) of *tert*-butyldimethylchlorosilylane and 0.551 g (8.10 mmol, 10 equiv) of imidazole. This was dissolved in 2 mL of dimethylformamide and stirred under nitrogen for 24 h, when TLC (eluted with ether) indicated the completion of the reaction. After the reaction was quenched with 1 mL of saturated sodium bicarbonate solution, an extractive workup with dichloromethane gave 0.381 g of a semicrystalline solid. Pure **21** [156 mg (42%); mp 135–136 °C] was obtained through a crystallization of the crude reaction mixture from E/H. The mother liquors were separated by preparative TLC (25% E/H, eluted twice) to yield 0.072 g (19%) of compound **21**: mp 135–136.5 °C; IR (KBr) 3500 (m), 2940 (m), 1695 (s), 1465 (s), 1295 (m), 1270 (m), 1255 (m), 1070 (s), 1020 (m), 1000 (m), 965 (m), 840 (m); ^{1}H NMR 0.18 (s, 3 H), 0.23 (s, 3 H), 0.88 (s overlapping t, 12 H), 1.73–2.35 (structured m, 3 H), 2.45 (dd, J = 1.9, 14.3, Hz, 1 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 5.18 (collapsed to dd with D_2O, J = 1.9, 4.9 Hz, 1 H), 7.23 (s, 1 H); ^{13}C NMR −5.2, −3.9, 7.4, 18.1, 25.7, 31.3, 42.9, 55.4, 62.1, 76.0, 119.3, 119.8, 125.7, 132.8, 150.1, 153.5, 201.7 ppm. Anal. Calcd for $C_{20}H_{31}O_5SiBr$: C, 52.28; H, 6.80. Found: C, 52.19; H, 6.83.

From preparative TLC there was obtained 0.072 g (19%) of **12**.

19. A mixture of 0.03 g (0.087 mmol) of **18**, 0.012 g (0.096 mmol) of phenyl boric acid, and ~5 mg of *p*-toluenesulfonic acid in 1.5 mL of toluene was stirred at room temperature for 24 h. After the yellow reaction mixture was quenched with 1 mL of 5% sodium bicarbonate solution, an extractive workup with methylene chloride gave 0.039 g of a yellow oil which was crystallized from E/H to give 0.024 g (61%) of **19** as white crystals: mp 126.5–127.5 °C; IR (KBr) 3480 (m), 1695 (s), 1470 (s), 1440 (s), 1375 (s), 1340 (s), 1320 (vs), 1290 (s), 1265 (s), 1250 (s), 1120 (s), 1060 (s), 980 (s), 700 (s); ^{1}H NMR ($CDCl_3$) 0.85 (t, J = 7.5 Hz, 3 H), 1.93 (q, J = 7.5 Hz, 2 H), 2.20 (dd, J = 6.0, 15.0 Hz, 1 H), 2.55 (dd, J = 1.5, 15.0 Hz, 1 H), 3.83 (s, 3 H), 3.88 (s, 3 H), 5.13 (dd, J = 1.5,

6.0 Hz, 1 H), 7.23–7.60 (m, 4 H), 8.15–8.30 (m, 2 H). This molecule is quite sensitive to handling, but an analytical sample could be obtained. Anal. Calcd for $C_{20}H_{22}O_6BBr$: C, 53.49; H, 4.94. Found: C, 53.17; H, 5.10.

22b. To a mixture of 0.118 g (0.256 mmol) of **21** and 0.039 g (1.03 mmol, 4 equiv) of sodium borohydride at 0 °C was added 2 mL of methanol. After 3 h the reaction was quenched by the addition of 2 mL of acetone and 1 mL of a 5% sodium hydroxide solution. The reaction mixture was concentrated in vacuo at ca. 50 °C. An extractive workup (dichloromethane) gave **22b** (99%) as white crystals: mp 86–87 °C; IR (KBr) 3430 (m), 3350 (m), 2960 (m), 2860 (m), 1470 (s), 1235 (m), 1065 (m), 1020 (vs), 995 (s), 935 (m), 835 (s), 820 (m), 790 (m); ^{1}H NMR −0.10 (s, 3 H), 0.10 (s, 3 H), 0.80 (s, 9 H), 1.00 (t, J = 7.5 Hz, 3 H), 1.50–1.70 (br s disappeared with D_2O, 1 H), 1.70–2.05 (highly structured m, 3 H), 2.15 (dd, J = 2.3, 15.3 Hz, 1 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 4.48 (center of AB, J = 12 Hz, $\Delta\nu_{AB}$ = 27 Hz, 2 H which collapsed to a s at 4.58 upon addition of D_2O), 5.30 (dd, J = 2.3, 5.5 Hz, 1 H), 6.98 (s, 1 H); ^{13}C NMR −5.1, −5.0, 7.0, 17.8, 25.3, 33.2, 44.3, 55.6, 61.9, 62.5, 69.0, 74.8, 115.0, 117.3, 127.0, 136.0, 149.7, 152.5 ppm. Anal. Calcd for $C_{20}H_{33}O_5SiBr$: C, 52.06; H, 7.21. Found: C, 52.30; H, 7.26.

20. To 0.050 g (0.14 mmol) of the *trans*-diol α-tetralone **18** were added 1.5 mL of dichloromethane, 60 μL (0.43 mmol, 3 equiv) of triethylamine, and 23 μL (0.29 mmol, 2 equiv) of methanesulfonyl chloride. The reaction mixture was stirred under nitrogen at room temperature for 0.5 h and then quenched by addition of 5% sodium bicarbonate solution. An extractive workup with methylene chloride gave a quantitative yield of crude mesylate which was used in the next step without purification. To the mesylate was added ca. 5 mg of *p*-toluenesulfonic acid and 1.5 mL of dimethylformamide, and the reaction was stirred at 60 °C under nitrogen for 18 h. The dimethylformamide was then removed at reduced pressure, and the residue was dissolved in dichloromethane. The workup yielded 0.055 g of a yellow oil which was purified by flash chromatography (5.5 in. × 0.5 in.). Elution proceeded as follows: 50 mL of 12% E/H, nil; 75 mL of 12% E/H, 0.026 g (57%) of **20** as a yellow oil [IR (neat) 2940 (w), 1695 (m), 1570 (w), 1465 (m), 1430 (w), 1395 (w), 1290 (m), 1260 (br, m), 1150 (m), 1050 (m), 1025 (w); ^{1}H NMR 0.88 (t, J = 7.5 Hz, 3 H), 1.40–2.10 (strong m, 2 H), 3.73 (s, 1 H, disappeared with D_2O), 3.80 (s, 3 H), 3.88 (s, 3 H), 6.48 (AB, J = 9.8 Hz, $\Delta\nu$ = 35.3 Hz, 2 H), 7.20 (s, 1 H); ^{13}C NMR 8.0, 33.7, 56.4, 62.3, 79.7, 118.1, 118.4, 121.1, 127.3, 136.5, 139.2, 150.2, 151.3, 203.6 ppm; exact mass calcd for $C_{11}H_{15}O_4Br$ m/e 326.0154, obsd m/e 326.0161.

When the cis isomer **9** was reacted as above, **20** was obtained in 43% yield.

7-Bromo-5,8-dimethoxy-2-ethyl-1-naphthol from 20. A mixture of 33 mg (0.10 mmol) of **20**, 13 mg (0.20 mmol, 2 equiv) of zinc–copper couple, 1.5 mL of tetrahydrofuran, 0.5 mL of acetic acid, and 0.1 mL of water was stirred at room temperature for 10 h. The reaction mixture was neutralized with a saturated sodium bicarbonate solution. Extractive workup with methylene chloride yielded a yellow oil which was purified by flash chromatography (5.5 in. × 0.5 in. silica gel column). Elution proceeded as follows: 25 mL of 1% E/H, nil; 50 mL of 1% E/H, 22 mg of the naphthol as a clear oil which crystallized with E/H to afford white crystals which showed spectroscopic properties identical with those reported earlier, mp 45.8–46.8 °C.

22a. A mixture of 0.10 g (0.29 mmol) of **18** and 0.023 g (1.58 mmol) of sodium borohydride in 2 mL of methanol was stirred at 0 °C for 1 h. The reaction was quenched by the addition of 1 mL of acetone and 1 mL of a 5% sodium hydroxide solution. The reaction mixture was partially concentrated at 50 °C, and the product was extracted with dichloromethane. The workup gave 0.093 g (92%) of the triol **22a** as a white foam. The product can be crystallized from chloroform to yield white needles, mp 145.8–146.8 °C. The crystals sometimes melt above 120 °C and then resolidify and melt at 145–147 °C: IR (KBr) 3510 (m), 3420 (s), 3360 (m), 2960 (m), 1470 (s), 1430 (m), 1375 (m), 1290 (m), 1235 (s), 1060 (m), 1030 (s), 990 (s); ^{1}H NMR (see text); ^{13}C NMR 6.5, 31.4, 35.8, 56.1, 62.2, 63.8, 68.1, 74.0, 115.1, 116.2, 127.9, 133.4, 150.2, 154.2 ppm; exact mass calcd for $C_{14}H_{19}O_5Br$ m/e 346.0416, obsd m/e 346.0424.

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Registry No. 1, 93-02-7; **2**, 83436-65-1; *cis*-**3**, 84944-53-6; *trans*-**3**, 84944-64-9; **4**, 84944-54-7; **5**, 84944-55-8; **6**, 84959-61-5; **7**, 83923-01-7; **8**, 83923-03-9; **9**, 83923-02-8; **10**, 83923-04-0; **11**, 83923-05-1; **12**, 84944-56-9; **13**, 83923-09-5; **14**, 83923-08-4; **15**, 83923-07-3; **16**, 83923-06-2; **17**, 83923-10-8; **18**, 84944-57-0; **19**, 84944-58-1; **20**, 84944-59-2; **21**, 84944-60-5; **22a**, 84944-61-6; **22b**, 84944-62-7; $H_2C{=}C(OCH_3)CH_3$, 116-11-0; $PhB(OH)_2$, 98-80-6; butyric acid, 107-92-6; 7-bromo-5,8-dimethoxy-2-ethyl-1-naphthol, 84944-63-8.

Metacyclophanes and Related Compounds. 8. Preparation and Reaction of 8,16-Diformyl[2.2]metacyclophanes[1]

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As key synthetic compounds, 8,16-diformyl[2.2]metacyclophanes **4a,b** were prepared from the corresponding 8,16-bis(bromomethyl)metacyclophanes **1a,b** by Kröhnke's procedure. From compounds **4**, [2.2]metacyclophanes having CN, COOH, CH(OH)R, or CH=CHR groups at the internal positions were easily prepared. Effects of ring current of the opposite aromatic rings on chemical shifts of protons of the internal groups of the metacyclophanes prepared in this work are also discussed.

Although some [2.2]metacyclophanes (MCP) having functions such as alkyl-,[2-5] halomethyl-,[5] alkoxy-,[6] and hydroxy groups[7] at their 8,16-positions have been reported, there are few reports concerning the preparation of [2.2]MCP having other functions at these internal positions.

We report the preparation of the title compounds **4**, which seem to be an important synthetic key compounds

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