Total Synthesis of the Biologically Active, Naturally Occurring 3,4-Dibromo-5-[2-bromo-3,4-dihydroxy-6-(methoxymethyl)benzyl]benzene-1,2-diol and Regioselective *O*-Demethylation of Aryl Methyl Ethers

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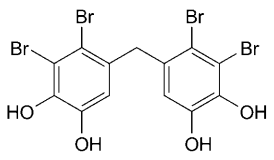
3,4-Dibromo-5-[2-bromo-3,4-dihydroxy-6-(methoxymethyl)benzyl]benzene-1,2-diol (**2**), a natural product, has been synthesized for the first time starting from (3-bromo-4,5-dimethoxyphenyl)methanol (**5**) in five steps and with an overall yield of 34%. The reaction of some methoxymethyl-substituted aryl methyl ethers with BBr_3, followed by the addition of MeOH, afforded the corresponding methoxymethyl-substituted arylphenols in high yields.

Introduction. – Marine life is one of the most important sources of biologically active natural products [1]. Halogenated metabolites with significant medicinal value are abundantly found in marine plants and animals [2]. Bromophenols, frequently isolated from red algae of the family Rhodomelaceae, are prominent biologically active compounds [2a–c][3]. The diarylmethane-type bromophenols 5,5′-methylenebis(3,4-dibromobenzene-1,2-diol) (**1**) and 3,4-dibromo-5-[2-bromo-3,4-dihydroxy-6-(methoxymethyl)benzyl]benzene-1,2-diol (**2**), were first isolated by *Kurata* and *Amiya* [4]. Recently, both of these compounds have been obtained from different sources [5–10]. Isolation of the title compound **2** was also reported by *Xu et al.* and *Suzuki et al.* [11]. Bromophenols, particularly **1** and **2**, exhibit enzyme inhibition [5], cytotoxicity [6], as well as feeding deterrent [7], microbial [8][9], and fungicidal [12] activities. On the other hand, 3,4,6-tribromo-5-(2,5-dibromo-3,4-dihydroxybenzyl)benzene-1,2-diol (**3**) and 5,5′-methylenebis(3,4,6-tribromobenzene-1,2-diol) (**4**) show aldose reductase inhibitory activity [13]. Furthermore, it is known that **4** exhibits antioxidant activity [14].



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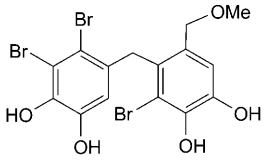

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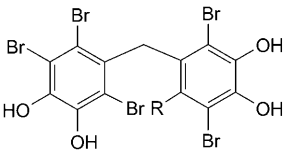


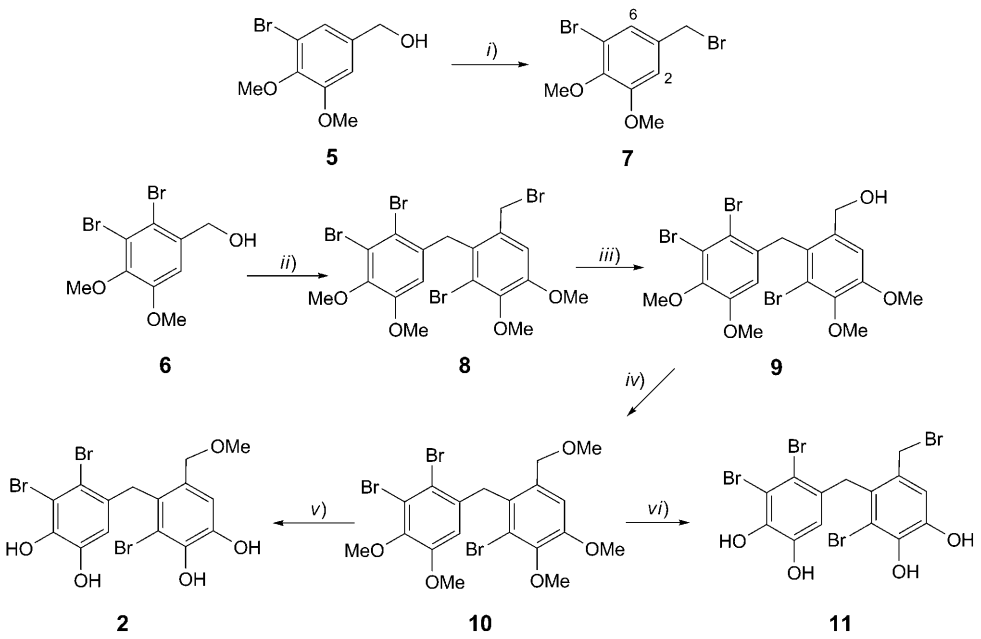
3 R = H
4 R = Br

Here, we report the first total and convenient synthesis of naturally occurring benzenediol **2** starting from (3-bromo-4,5-dimethoxyphenyl)methanol (**5**) and (2,3-

dibromo-4,5-dimethoxyphenyl)methanol (**6**) in five steps. We also investigated the regioselective *O*-demethylation of aryl methyl ethers containing a benzyl methyl ether moiety.

Results and Discussion. – (3-Bromo-4,5-dimethoxyphenyl)methanol (**5**) [15] and (2,3-dibromo-4,5-dimethoxyphenyl)methanol (**6**) [16] were synthesized according to the procedures described in the literature. For the synthesis of benzyl bromide **7**, **5** was reacted with PBr_3 in the presence of Et_3N at 0–25°. One of the most critical steps in the synthesis of **2** was the alkylation of compound **7** with alcohol **6**. Even though the alkylation or acylation of aromatic compounds with alcohols and carboxylic acids, respectively, in the presence of polyacids is well described in the literature [17], the reaction of **6** with **7** might fail by leading to polymerization because of the benzyl bromide **7**. Furthermore, alcohol **6** could have reacted with **7** at either C(2) or C(6). Fortunately, the reaction of **6** with **7** in the presence of polyphosphoric acid took place at C(6) to give **8** regioselectively in moderate yield (53%; *Scheme 1*).

Scheme 1



i) PBr_3/ Et_3N, CH_2Cl_2, 0–25°, 6 h; 84%. *ii*) H_3PO_4/P_2O_5 (polyphosphoric acid, PPA), then compound **7**, 80°, 30 min; 53%. *iii*) H_2O, dioxane, 110°, 3 d; 95%. *iv*) NaH/Me_2SO_4, THF, 0–25°, 24 h; 97%. *v*) BBr_3, CH_2Cl_2, 0–25°, 24 h, then MeOH, 0–60°; 82%. *vi*) BBr_3, CH_2Cl_2, 0–25°, 24 h, and then H_2O, 0°; 90%.

^{1}H- and ^{13}C-NMR analysis of **8** did not allow determination of its exact structure. Therefore, it was established by X-ray diffraction analysis. The structure and numbering scheme of **8** are illustrated in *Fig. 1*, and the packing in the crystal is shown in *Fig. 2*.

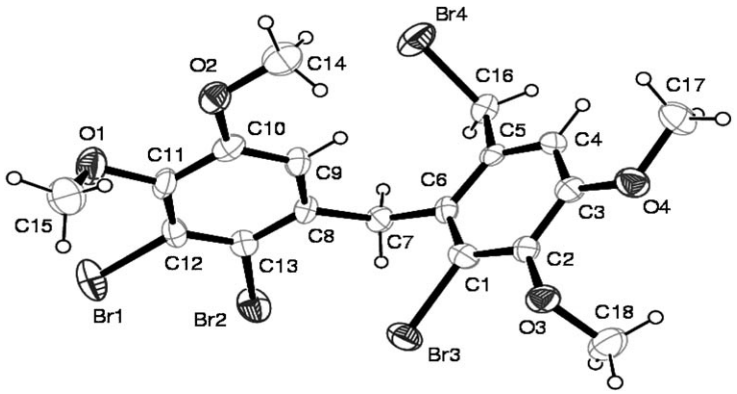


Fig. 1. *Molecular structure of compound* **8** *showing the atom-numbering scheme.* Thermal ellipsoids are drawn at the 40% probability level.

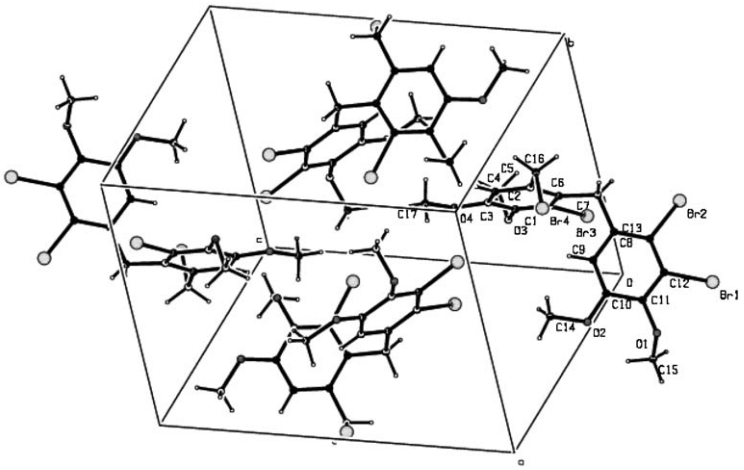


Fig. 2. *Packing diagram for* **8**, *viewed down the* a-*axis.*

The hydrolysis of **8** in dioxane at 110° gave the corresponding benzyl alcohol **9** in high yield. The reaction of **9** with NaH, followed by methylation with Me_2SO_4 at 0–25°, yielded the benzyl methyl ether **10** (*Scheme 1*).

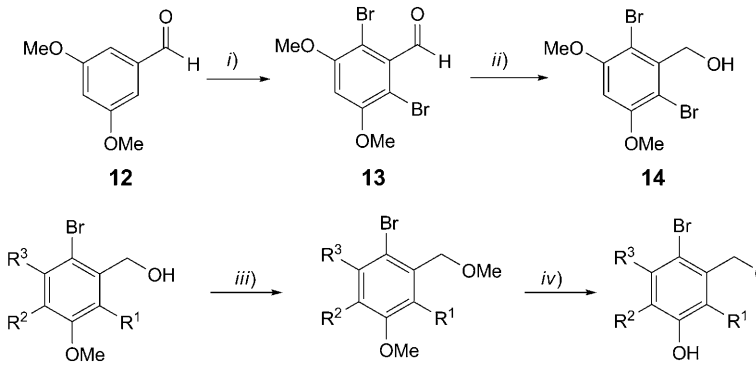
Deprotection of functional groups is often used in organic synthesis, *e.g.*, cleavage of ethers remains an integral functional group transformation, as it is important for the synthesis of natural products, pharmaceuticals, and fine chemicals. Although the procedures for the cleavage of alkyl aryl ethers with HBr [18], BBr_3 [19] or with other methods [20] are well-known, regioselective *O*-demethylation of methoxymethyl-substituted aryl methyl ethers remains unknown. Compound **10** contains a $MeOCH_2$ and four MeO groups as substituents. Demethylation of **10** with HBr or other cleaving reagents (such as HI, $AlCl_3$, BBr_3, BCl_3) was expected to lead to the ether cleavage at the benzylic position. Hence, demethylation of the methyl phenyl ether groups of **10** without cleavage of benzyl methyl ether was the most crucial step of the synthesis. For

this purpose, compound **10** was treated with BBr_3 at 0–25° under N_2 for 24 h. After the reaction was completed, quenching of excess BBr_3 with MeOH at 0–60° afforded the *O*-demethylation of the methyl phenyl ethers in a one-pot reaction under mild conditions to give the natural compound **2** (*Scheme 1*). ^{1}H- and ^{13}C-NMR analysis showed that no benzyl bromide was formed under these reaction conditions.

To gain more insight into the reaction course, treatment of **10** with BBr_3 was followed by direct addition of H_2O to deactivate BBr_3, without addition of MeOH, and the extraction of the organic layer with AcOEt gave the corresponding bromomethyl-benzenediol **11**. This result indicated that the reaction did not proceed regioselectively. Indeed, the benzyl methyl ether part of compound **10** was also cleaved, and then, addition of MeOH to the reaction mixture led to compound **2** (*Scheme 1*).

Although the reaction does not proceed as a regioselective *O*-demethylation, the method will be useful for the synthesis of this type of compounds. Therefore, we focused on the synthesis of some other $MeOCH_2$-substituted aryl methyl ethers, and their reactions with BBr_3 were investigated under the same conditions as those described above. For this purpose, 3,5-dimethoxybenzaldehyde (**12**) was brominated with Br_2 in CH_2Cl_2 at room temperature for 24 h to give the corresponding dibrominated aldehyde **13** [21]. Reduction of **13** with $NaBH_4$ in MeOH/THF gave benzyl alcohol **14**. The synthesis of **15** was performed according to the procedure described in [22]. Reaction of alcohols **6**, **14**, and **15** with Me_2SO_4 in the presence of NaH gave benzyl methyl ethers **16** [23], **17**, and **18** [22], respectively, in high yields (96, 96, and 94%, resp.). *O*-Demethylation of **16**, **17**, and **18** with BBr_3 in CH_2Cl_2 at 0–25° under N_2, followed by addition of MeOH for deactivation of excess BBr_3 at 0–60°, afforded $MeOCH_2$-substituted benzene-diols **19** [24], **20**, and **21** [25], respectively, in high yields in a one-pot reaction (*Scheme 2*).

Scheme 2



i) Br_2, CH_2Cl_2, 25°; 92%. *ii*) $NaBH_4$, THF/MeOH, 25°, 24 h, then H_2O; 95%. *iii*) NaH/Me_2SO_4, THF, 0–25°, 24 h, then H_2O. *iv*) BBr_3, CH_2Cl_2, 0–25°, 24 h, then MeOH, 0–60°.

Conclusions. – In summary, we have achieved the first and convenient synthesis of the naturally occurring bromophenol **2** starting from (3-bromo-4,5-dimethoxyphenyl)-methanol (**5**) and (2,3-dibromo-4,5-dimethoxyphenyl)methanol (**6**) in five steps with a yield of 34%.

Furthermore, we developed a method for a 'pseudo-selective' *O*-demethylation of methoxymethyl-substituted aryl methyl ethers. This method is the first one-pot synthesis of $MeOCH_2$-substituted benzene-diols. The effectiveness of the methodology was shown by the preparation of 3,4-dibromo-5-(methoxymethyl)benzene-1,2-diol (**19**), 4,6-dibromo-5-(methoxymethyl)benzene-1,3-diol (**20**), and 3,4,6-tribromo-5-(methoxymethyl)benzene-1,2-diol (**21**).

The authors are indebted to the *Scientific and Technological Research Council of Turkey* (*TÜBİTAK*, Grant No: TBAG-107T/348) and *Atatürk University* for their financial support of this work.

Experimental Part

General. All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Column chromatography (CC): silica gel (SiO_2, 60 mesh; *Merck*). Prep. thick-layer chromatography (PLC): 1 mm of SiO_2 60 PF (*Merck*) on glass plates. M.p.: cap. melting-point apparatus (*Thomas-Hoover*); uncorrected. IR Spectra: solns. in 0.1-mm cells; *Perkin-Elmer* spectrophotometer; in cm^{-1}. ^1H- and ^{13}C- NMR spectra: 200 (50) and 400 (100)-MHz *Varian* spectrometer; δ in ppm, J in Hz; Me_4Si as the internal standard. ESI-MS: *Bruker microTOF-Q*. Elemental analyses: *Leco* CHNS-932 apparatus.

1-Bromo-5-(bromomethyl)-2,3-dimethoxybenzene (**7**). To a stirred soln. of *(3-bromo-4,5-dimethoxyphenyl)methanol* (**5**; 13.0 g, 52.6 mmol) in CH_2Cl_2 (70 ml) was added Et_3N (5.8 g, 57.3 mmol) and a soln. of PBr_3 (15.5 g, 57.3 mmol) in CH_2Cl_2 (20 ml) dropwise at 0°. After the addition was complete, the mixture was stirred at the same temp. for 30 min. The mixture was warmed to r.t. and stirred for 6 h. After the evaporation of the solvent, ice (20 g) and HCl (1M, 20 ml) were added to the residue. Org. phase was extracted with AcOEt (2 × 50 ml). Drying of org. phase (Na_2SO_4) and evaporation of the solvent gave **7** (13.7 g, 84%). White solid. M.p. 91–93°. IR (CH_2Cl_2): 2937, 2829, 1596, 1568, 1489, 1463, 1428, 1413, 1310, 1277, 1238, 1217, 1144, 1047, 1000. ^1H-NMR (400 MHz, $CDCl_3$): 7.16 (*d*, $^4J = 2.02$, 1 arom. H); 6.88 (*d*, $^4J = 2.02$, 1 arom. H); 4.40 (*s*, CH_2); 3.87 (*s*, MeO); 3.85 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 153.95 (2 C); 134.90 (C); 125.42 (CH); 117.76 (C); 112.64 (CH); 60.84 (MeO); 56.36 (MeO); 32.77 (CH_2). Anal. calc. for $C_9H_{10}Br_2O_2$: C 34.87, H 3.25; found: C 34.89, H 3.18.

2,3-Dibromo-1-[2-bromo-6-(bromomethyl)-3,4-dimethoxybenzyl]-4,5-dimethoxybenzene (**8**). Polyphosphoric acid (PPA), prepared from conc. H_3PO_4 (5.1 ml) and P_2O_5 (15.71 g), was heated to 80° in a beaker (250 ml). To this mixture were added **6** (5.00 g, 15.3 mmol) and **7** (4.76 g, 15.3 mmol). The mixture was stirred with a glass stick at 80° for 30 min. The mixture was carefully poured onto 50 ml of ice/water. The org. phase was extracted with AcOEt (2 × 50 ml). The combined org. layers were dried (Na_2SO_4), and the solvent was evaporated. The resulting residue was purified by CC (SiO_2 (100 g); hexane/AcOEt 85:15) to afford **8** (5.12 g, 53% yield). Yellow needles. M.p. 149–151° (AcOEt/hexane). IR (CH_2Cl_2): 2937, 1594, 1549, 1485, 1464, 1422, 1372, 1318, 1283, 1212, 1192, 1162, 1121, 1100, 1039, 1006, 988. ^1H-NMR (400 MHz, $CDCl_3$): 6.95 (*s*, 1 arom. H); 6.16 (*s*, 1 arom. H); 4.35 (*s*, CH_2); 4.32 (*s*, CH_2); 3.92 (*s*, MeO); 3.88 (*s*, MeO); 3.81 (*s*, MeO); 3.57 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 152.69 (C); 152.65 (C); 147.44 (C); 146.44 (C); 135.71 (C); 133.79 (C); 130.79 (C); 123.13 (C); 122.13 (C); 117.79 (C); 113.97 (CH); 112.27 (CH); 60.80 (MeO); 60.74 (MeO); 56.37 (MeO); 56.33 (MeO); 39.93 (CH_2); 32.03 (CH_2). Anal. calc. for $C_{18}H_{18}Br_4O_4$: C 34.99, H 2.94; found: C 35.01, H 2.90.

[3-Bromo-2-(2,3-dibromo-4,5-dimethoxybenzyl)-4,5-dimethoxyphenyl]methanol (**9**). To a stirred soln. of **8** (1.0 g, 1.6 mmol) in dioxane (30 ml) was added H_2O (20 ml), and the mixture was stirred at 110° for 3 d. After the evaporation of the solvent, H_2O (50 ml) was added to the residue, and org. phase was extracted with AcOEt (3 × 30 ml). The combined org. layers were dried (Na_2SO_4). Evaporation of

the solvent and crystallization of the residue from AcOEt/hexane gave **9** (0.85 g, 95%). Yellow crystals. M.p. 155–157°. IR (CH_2Cl_2): 3495, 2937, 1595, 1549, 1465, 1422, 1372, 1310, 1282, 1192, 1161, 1103, 1038, 1006. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.10 (*s*, 1 arom. H); 6.16 (*s*, 1 arom. H); 4.54 (*s*, CH_2O); 4.24 (*s*, CH_2); 3.93 (*s*, MeO); 3.87 (*s*, MeO); 3.80 (*s*, MeO); 3.56 (*s*, MeO); 1.70 (br. *s*, OH). ^{13}C-NMR (100 MHz, $CDCl_3$): 152.71 (C); 152.65 (C); 146.32 (C); 146.16 (C); 136.84 (C); 136.11 (C); 128.92 (C); 122.79 (C); 122.04 (C); 117.65 (C); 112.02 (CH); 111.55 (CH); 63.36 (MeO); 60.74 (MeO); 60.72 (MeO); 56.31 (MeO); 56.28 (CH_2O); 39.50 (CH_2). Anal. calc. for $C_{18}H_{19}Br_3O_5$: C 38.95, H 3.45; found: C 38.85, H 3.51.

General Procedure (*GP*) *for Synthesis of Benzyl Methyl Ethers. 2,3-Dibromo-1-[2-bromo-3,4-dimethoxy-6-(methoxymethyl)benzyl]-4,5-dimethoxybenzene* (**10**). To a stirred soln. of **9** (0.40 g, 0.7 mmol) in THF (20 ml) were added NaH (0.04 g, 1.7 mmol) and Me_2SO_4 (0.11 g, 0.87 mmol) at 0°. The mixture was stirred at the same temp. for 1 h and then at r.t. for 24 h. After evaporation of the solvent, H_2O (30 ml) was added to the residue. The org. phase was extracted with AcOEt (3 × 30 ml). The combined org. phases were dried (Na_2SO_4). Evaporation of the solvent and crystallization of the residue from AcOEt/hexane afforded **10** (0.39 g, 97%). Yellow solid. M.p. 118–120°. IR (CH_2Cl_2): 2926, 2854, 1595, 1549, 1463, 1423, 1397, 1373, 1313, 1284, 1252, 1223, 1193, 1162, 1112, 1091, 1040, 1008. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.01 (*s*, 1 arom. H); 6.15 (*s*, 1 arom. H); 4.24 (*s*, CH_2); 4.20 (*s*, CH_2); 3.90 (*s*, MeO); 3.83 (*s*, MeO); 3.78 (*s*, MeO); 3.54 (*s*, MeO); 3.33 (*s*, CH_2O*Me*). ^{13}C-NMR (100 MHz, $CDCl_3$): 152.63 (C); 152.46 (C); 146.30 (C); 146.19 (C); 136.23 (CH); 134.21 (CH); 129.56 (C); 122.71 (C); 121.86 (C); 117.53 (C); 112.37 (C); 112.06 (C); 72.95 (CH_2O); 60.67 (MeO); 60.66 (MeO); 58.81 (MeO); 56.26 (MeO); 56.22 (MeO); 39.57 (CH_2). Anal. calc. for $C_{19}H_{21}Br_3O_5$: C 40.10, H 3.72; found: C 39.97, H 3.73.

General Procedure (*GP*) *for* O*-Demethylation of Aryl Methyl Ethers. 3,4-Dibromo-5-[2-bromo-3,4-dihydroxy-6-(methoxymethyl)benzyl]benzene-1,2-diol* (**2**). A soln. of **10** (0.40 g, 0.7 mmol) in CH_2Cl_2 (20 ml) was chilled to 0° under N_2. To this soln. was added a soln. of BBr_3 (0.5 ml, 1.32 g, 5.3 mmol) in CH_2Cl_2 (15 ml) at the same temp. under N_2. After the addition of BBr_3 was completed, the mixture was stirred at r.t. for 24 h. Then, it was cooled to 0°, and to this mixture was added MeOH (10 ml) dropwise for 10 min. The mixture was heated at 60° for 3 h. After evaporation of the solvent, AcOEt (40 ml) and H_2O (20 ml) were added to the residue. The org. layer was separated, and the H_2O phase was extracted with AcOEt (2 × 20 ml). The org. layers were combined and dried (Na_2SO_4). Evaporation of the solvent gave **2** (0.30 g, 82%). Brownish solid. M.p. > 300° ([4]: M.p. 540°). ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): 8.45 (*m*, 4 OH); 7.00 (*s*, 1 arom. H); 6.08 (*s*, 1 arom. H); 4.21 (*s*, CH_2); 4.12 (*s*, CH_2); 3.24 (*s*, MeO). ^{13}C-NMR (100 MHz, $(CD_3)_2CO$): 144.79 (C); 144.22 (C); 142.85 (C); 142.83 (C); 131.78 (C); 130.22 (C); 128.90 (C); 115.68 (CH); 115.63 (C); 114.39 (CH); 114.32 (C); 114.28 (C); 72.62 (CH_2); 57.42 (MeO); 38.70 (CH_2). Anal. calc. for $C_{15}H_{13}Br_3O_5$: C 35.12, H 2.55; found: C 35.18, H 2.60.

3,4-Dibromo-5-[2-bromo-3-(bromomethyl)-4,5-dihydroxybenzyl]benzene-1,2-diol (**11**). The *O*-demethylation method described for the synthesis of **2** was applied to **10** (0.40 g, 0.70 mmol); however, after the reaction was completed, H_2O instead of MeOH was added to the mixture at 0°. The org. layer was separated, and the H_2O layer was extracted with AcOEt (2 × 50 ml). Combined org. layers were dried ($MgSO_4$), and evaporation of the solvent gave **11** (0.36 g, 90%). Brownish solid. M.p. > 270° (dec.). IR (acetone): 3384, 2921, 2845, 1693, 1604, 1579, 1492, 1468, 1400, 1351, 1278, 1204, 1172, 1093. ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): 7.08 (*s*, 1 arom. H); 6.11 (*s*, 1 arom. H); 4.57 (*s*, CH_2Br); 4.24 (*s*, CH_2). ^{13}C-NMR (100 MHz, $(CD_3)_2CO$): 144.68 (C); 144.38 (C); 144.16 (C); 142.91 (C); 131.18 (C); 130.00 (C); 129.39 (C); 116.88 (CH); 115.79 (2 C); 114.29 (CH); 113.12 (C); 38.98 (CH_2); 32.99 (CH_2). Anal. calc. for $C_{14}H_{10}Br_4O_4$: C 29.93, H 1.79; found: C 29.98, H 1.71.

2,6-Dibromo-3,5-dimethoxybenzaldehyde (**13**). To a stirred soln. of **12** (1.0 g, 6.02 mmol) in $CHCl_3$ (30 ml) was added a soln. of Br_2 (2.023 g, 12.6 mmol) in $CHCl_3$ (10 ml) dropwise for 10 min at r.t. The mixture was stirred at r.t. for 24 h. The evaporation of excess Br_2 and solvent gave **13** (1.79 g, 92%). Brownish solid. M.p. 218–220° ([21]: M.p. 221–222°). ^{1}H-NMR (400 MHz, $CDCl_3$): 10.19 (*s*, CHO); 6.65 (*s*, 1 arom. H); 3.95 (*s*, 2 MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 191.80 (CO); 156.73 (2 C); 135.17 (C); 103.71 (2 C); 99.90 (CH); 57.08 (2 MeO).

(2,6-Dibromo-3,5-dimethoxyphenyl)methanol (**14**). To a stirred soln. of **13** (1.0 g, 3.09 mmol) in THF/MeOH 1:1 (40 ml) was added $NaBH_4$ (0.118 g, 3.12 mmol) in small pieces at 0°. The mixture was stirred at the same temp. for 30 min and then at r.t. for 24 h. After evaporation of the solvent, CH_2Cl_2 (50 ml) and H_2O (50 ml) were added to the residue. The org. layer was separated, and H_2O layer was

extracted with CH_2Cl_2 (2×40 ml). Combined org. layers were dried (Na_2SO_4). The evaporation of the solvent and the crystallization of the residue with AcOEt/hexane gave **14** (0.96 g, 95%). Brown crystals. M.p. 182–184°. IR (CH_2Cl_2): 3399, 3253, 2951, 2932, 1667, 1584, 1513, 1494, 1464, 1432, 1388, 1340, 1271, 1242, 1167, 1138, 1094, 1021. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.50 (*s*, 1 arom. H); 5.07 (*s*, CH_2); 3.91 (*s*, 2 MeO); 2.26 (br. *s*, OH). ^{13}C-NMR (100 MHz, $CDCl_3$): 156.43 (2 C); 140.19 (2 C); 106.13 (C); 97.19 (CH); 65.85 (CH_2); 56.92 (2 MeO). Anal. calc. for $C_9H_{10}Br_2O_3$: C 33.16, H 3.09; found: C 33.15, H 3.08.

2,3-Dibromo-4,5-dimethoxy-1-(methoxymethyl)benzene (**16**). The *GP* described for the synthesis of **10** was applied to **6** (1.00 g, 3.1 mmol) to give **16** (1.00 g, 96% yield). Yellow crystals. M.p. 73–75° ([23]: M.p. 71–72°). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.06 (*s*, 1 arom. H); 4.46 (*s*, CH_2); 3.87 (*s*, MeO); 3.82 (*s*, MeO); 3.47 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 152.87 (C); 146.85 (C); 135.54 (C); 121.85 (C); 115.02 (C); 111.42 (CH); 74.98 (CH_2O); 60.73 (MeO); 58.97 (MeO); 56.40 (MeO).

2,4-Dibromo-1,5-dimethoxy-3-(methoxymethyl)benzene (**17**). The *GP* described for the synthesis of **10** was applied to **14** (0.70 g, 3.1 mmol) to give **17** (0.67 g, 96% yield). Brownish crystals. M.p. 125–127°. IR (CH_2Cl_2): 3014, 2977, 2924, 1577, 1458, 1432, 1377, 1338, 1286, 1223, 1186, 1101, 1075, 944, 817. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.51 (*s*, 1 arom. H); 4.84 (*s*, CH_2); 3.90 (*s*, 2 MeO); 3.44 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 156.29 (2 C); 137.78 (C); 107.22 (2C); 97.33 (CH); 74.06 (CH_2O); 58.73 (MeO); 56.92 (2 MeO). Anal. calc. for $C_{10}H_{12}Br_2O_3$: C 35.32, H 3.56; found: C 35.19, H 3.54.

1,2,4-Tribromo-5,6-dimethoxy-3-(methoxymethyl)benzene (**18**). The *GP* described for the synthesis of **10** was applied to **15** (1.00 g, 2.47 mmol) to give **18** (0.98 g, 94%). Yellow crystals. M.p. 88–90° ([22]: M.p. 91–92°). ^{1}H-NMR (400 MHz, $CDCl_3$): 4.85 (*s*, CH_2); 3.89 (*s*, MeO); 3.88 (*s*, MeO); 3.46 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 152.32 (C); 150.92 (C); 134.36 (C); 124.15 (C); 122.10 (C); 121.99 (C); 75.70 (CH_2); 61.11 (MeO); 61.05 (MeO); 58.94 (MeO).

Synthesis of Benzendiols **19**, **20**, *and* **21**. The *GP* described above for the synthesis of **2** was applied to **16**, **17**, and **18** to give **19** (82% yield), **20** (79% yield), and **21** (95% yield), resp.

3,4-Dibromo-5-(methoxymethyl)benzene-1,2-diol (**19**). Brownish solid. M.p. 111–113° ([24]: M.p. 112–114°). ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): 8.88 (br. *s*, OH); 8.33 (br. *s*, OH); 7.05 (*s*, 1 arom. H); 4.40 (*s*, CH_2); 3.38 (*s*, MeO). ^{13}C-NMR (100 MHz, $(CD_3)_2CO$): 144.95 (C); 143.89 (C); 130.85 (C); 114.77 (CH); 113.91 (C); 113.09 (C); 74.48 (CH_2); 57.77 (MeO). Anal. calc. for $C_8H_8Br_2O_3$: C 30.80, H 2.58; found: C 30.76, H 2.59.

4,6-Dibromo-5-(methoxymethyl)benzene-1,3-diol (**20**). Brownish solid. M.p. 59–61°. IR (CH_2Cl_2): 3397, 2933, 1719, 1596, 1580, 1515, 1495, 1464, 1433, 1388, 1335, 1235, 1191, 1152, 1139, 1095, 1063, 1024, 949. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.74 (*s*, 1 arom. H); 5.83 (br. *s*, 2 OH); 4.74 (*s*, CH_2); 3.45 (*s*, MeO). ^{13}C-NMR (100 MHz, $CDCl_3$): 153.04 (2 C); 135.87 (C); 105.79 (2 C); 103.41 (CH); 74.40 (CH_2); 58.71 (MeO). Anal. calc. for $C_8H_8Br_2O_3$: C 30.80, H 2.58; found: C 30.69, H 2.66.

3,4,6-Tribromo-5-(methoxymethyl)benzene-1,2-diol (**21**). Brownish solid. M.p. 125–127° ([25b]: M.p. 124–125°). ^{1}H-NMR (400 MHz, $(CD_3)_2CO$): 6.04 (br. *s*, OH); 5.93 (br. *s*, OH); 4.81 (*s*, CH_2); 3.46 (*s*, MeO). ^{13}C-NMR (100 MHz, $(CD_3)_2CO$): 144.79 (C); 143.20 (C); 129.47 (C); 118.38 (C); 113.72 (C); 113.06 (C); 75.33 (CH_2); 57.57 (MeO). Anal. calc. for $C_8H_7Br_3O_3$: C 24.58, H 1.81; found: C 24.64, H 1.79.

X-Ray Structure Determination for **8**. For the crystal structure determination, the single-crystal of compound **8** was used for data collection on a four-circle *Rigaku R-AXIS RAPID-S* diffractometer (equipped with a two-dimensional area IP detector). The graphite-monochromatized MoK_α radiation (λ 0.71073 Å) and oscillation scans technique with $\Delta\omega = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares method on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for *Lorentz* and polarization effects, and cell refinement were performed using CrystalClear (*Rigaku*/MSC Inc., 2005) software [26]. The structures were solved by direct methods using SHELXS-97 [27] and refined by a full-matrix least-squares procedure using the program SHELXL-97 [27]. The H-atoms were positioned geometrically and refined using a riding model. The final difference *Fourier* maps showed no peaks of chemical significance. Thermal ellipsoids in ORTEP [28] plots represent a 40% probability.

Crystal Data for **8**. $C_{18}H_{18}O_4Br_4$, crystal system, space group: monoclinic, *P*21/*n*; (no. 14); unit cell dimensions: $a = 13.2050(2)$, $b = 10.4580(3)$, $c = 15.5470(4)$ Å, $\beta = 100.50(3)°$; volume: 2111.0(2) Å^3; $Z = 4$; calculated density: 1.94 mg/m^3; absorption coefficient: 7.645 mm^{-1}; $F(000)$: 1192; θ range for data collection 2.2–26.4°; refinement method: full-matrix least-square on F^2; data/parameters: 4317/239;

goodness-of-fit on F^2: 1.392; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.097$, $wR_2 = 0.152$; R indices (all data): $R_1 = 0.139$, $wR_2 = 0.160$; largest diff. peak and hole: 0.861 and -0.851 e Å^{-3}.

Compound **8** crystallizes in the monoclinic space group $P21/n$, with four molecules in the unit cell (*Fig. 2*). The C–Br bond lengths are within the expected range (1.892(5)–1.935(5) Å). The X-ray structure of **8** displayed the twisting of the two phenyl moieties with a dihedral angle of 86.9(2)°. The data (CCDC-719647) can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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