First and short syntheses of biologically active, naturally occurring brominated mono- and dibenzyl phenols

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Abstract
First and short syntheses of biologically active, naturally occurring 3,4,6-tribromo-5-(2,3-dibromo-4,5-dihydroxybenzyl)benzene-1,2-diol 3, 3,4,6-tribromo-5-(2,3,6-tribromo-4,5-dihydroxybenzyl)benzene-1,2-diol 4 and 3,4-dibromo-5-[3-bromo-2-(2,3-dibromo-4,5-dihydroxybenzyl)-4,5-dihydroxybenzyl]benzene-1,2-diol 5 from the red alga were carried out.

Keywords: Bromination, bromophenols, red algae, natural product, synthesis

Introduction
Naturally occurring bromophenols are found in marine life and frequently isolated from red algae of the family Rhodomelaceae. Most of these compounds have important biological activities. For example, bromophenols 1 and 2 (Figure 1) exhibit enzyme inhibition, cytotoxicity, feeding deterrent, and microbial activities. Protein tyrosine phosphatase inhibitory activity of bromophenol 1 was also reported. Monobenzylphenol derivatives 3 and 4, first isolated from the red alga Symphyocladia latiuscula in 2005 by Wang et al. (Figure 1), were reported to exhibit significant aldose reductase inhibitory activity. On the other hand, antioxidant activity of bromophenol 4 was also noted. In 2003, Fan et al. reported the first isolation of dibenzylphenol derivative 3,4-dibromo-5-[3-bromo-2-(2,3-dibromo-4,5-dihydroxybenzyl)-4,5-dihydroxybenzyl]benzene-1,2-diol 5 from red alga Rhodomela confervoides (Figure 1). The extracts of bromophenols including 5 from red alga were used for the treatment of rats with diabetes as an inhibitor of protein tyrosine phosphatase.
To our knowledge, biologically active natural products, bromophenols 3, 4 and 5, have not yet been synthesized. In the present study, we report on the first synthesis of these natural products 3, 4 and 5.

**Results and Discussion**

Bromophenols 3, 4 and 5 as biologically active natural products are highly brominated mono- and dibenzyl phenols (Figure 1). One ring of 3 and two rings of 5 are dibrominated pyrocatechol derivatives while both rings of 4, a symmetric molecule, are tri-brominated pyrocatechol derivatives. One ring of 3 and 4 is a tri-brominated pyrocatechol derivative and these rings are the same. For the synthesis of these compounds, our method is based on the preparation of aromatic rings with Br, followed by their connection. For these purposes, acetylation of (3,4-dimethoxyphenyl)methanol 6 with Ac₂O⁶(acetic anhydride)/pyridine was performed to give 3,4-dimethoxybenzyl acetate 7 in high yield. From this acetate 7, bromoalcohol 9 was synthesized via 8 (Scheme 1).⁶ On the other hand, tribromoveratrole 13⁷ was also obtained via 10-12 (Scheme 1) for the preparation of the other ring of 4. Methyl protection of starting materials is necessary to prevent side reactions and purification-characterization difficulties. Therefore, phenolic reagents were methylated or purchased as methylated.
Scheme 1. Synthesis of 9 and 13. a) Ac₂O/pyridine, 25 ºC, 97%; b)Br₂/Fe, AcOH, 18 %; c) dioxane/water, reflux, 90%; d) Br₂ (8 eq.)/AcOH, 120 ºC, quantitative; e)Zn/AcOH, 120 ºC, 20%; f) (CH₃)₂SO₄/K₂CO₃, THF, reflux, 98%.

Scheme 2. Synthesis of biologically active natural products 3 and 4.
Bromoalcohol 9 was reacted with both 13 to give 16, and 14 to give 15 in the PPA (polyphosphoric acid) at 80°C (Scheme 2). Monobenzyl phenol derivatives 15 and 16 were obtained in high yields in their reactions as a sole product. According to their NMR data, 15 is unsymmetrical while 16 is symmetric. Protons of 15 resonate at 6.48, 4.49, 3.96, 3.93 and 3.89 ppm as singlet (s) with relative intensities of 1:2:3:6:3, while protons of 16 resonate at 4.91, 3.90 and 3.87 ppm with relative intensities of 1:3:3 as s. NMR data of 15 and 16 are consistent with the proposed structures. They are precursor compounds of natural products 3 and 4, respectively.

Monobenzyl phenols 3, 4 were first synthesized from 15 and 16 by ether cleavage with BBr₃ (Scheme 2). Data such as NMR of 3 and 4 were consistent with the literature. Total yields of 3 and 4 are 13% starting from commercial product 6.


In the structure of bromophenol 5, brominated dibenzyl phenol derivative, there are two 2,3-dibromo-4,5-dihydroxybenzyl and one 3-bromo-catechol units. Firstly, (2,3-dibromo-4,5-dimethoxyphenyl)methanol 17 and 1-bromo-2,3-dimethoxybenzene 18 were synthesized for these units by following the procedures described in the literature. Secondly, reaction of 17 (2 equivalent) with 18 (1 equivalent) gave two isomeric pentabromides. Protons of one of them resonate at 6.61, 6.58, 6.36, 4.12, 4.01, 3.90, 3.85, 3.84, 3.82, 3.73 and 3.72 ppm as s with relative intensities of 1:1:1:2:2:3:3:3:3:3:3, while protons of the other resonate at 6.60, 6.45, 6.14, 4.20, 3.96, 3.88, 3.80, 3.79, 3.78, 3.71 and 3.57 ppm as s with relative intensities of
Tri-isomeric pentabromides may be formed as a result of this reaction because they are disubstituted products of 18.

Their formations should be a sequential dissubstitution to 18. Monosubstituted product(s) may provide information about these dissubstituted isomeric products. To this end, reaction of 17 with 18 in equimolar (1:1) was performed, and a monosubstituted product was obtained from this reaction as the sole product. The presence of an AB system in the 1H-NMR spectrum of this product shows that substitution may occur at C-4 or C-6 in 18. To be sure of the place of the monosubstitution in 18, bromination of 18 was performed and dibromoveratrole was obtained as the sole product. Dibromoveratrole should be 22 because other dibromides such as 14 do not give an AB-system in the aromatic region of their 1H-NMR spectra. Therefore, the monosubstitution product should be 21.

Substitution at C-5 or C-6 atoms in 21 may give two isomeric products. They will be disubstituted isomeric products obtained from the reaction of 17 with 18. According to the NMR spectra of disubstituted isomeric products, it is not easy to establish their exact configurations. Therefore, the exact structure of one of them was determined by X-ray crystallographic analysis (Figure 2).13 This isomer is pentabromide 19 which is a precursor compound for the natural compound 5. The other disubstituted product should be 20. NMR data of 19-22 are also consistent with the proposed structures.

The molecular structure of the pentabromide 19 was successfully determined using single-crystal X-ray diffraction analysis. The unit cell of pentabromide 19 comprises two centrosymmetric molecules (C_{26}H_{24}Br_{5}O_{6}) which, however, in spite of the considerable structural similarity, are structurally inequivalent to each other (see Figure 2). Therefore, X-ray structure determination of pentabromide 19 revealed that the asymmetric unit contains two independent conformational isomers, which are (conformers in 3-D) due to rotations about σ-bonds (the different rotation of methoxy about the C_{phenyl}–O2 and C_{phenyl}–O2' bonds). Moreover, in both conformers edge phenyl rings are considerably folded on each other. (distance between C5/C10 and C15/C20 phenyl ring centroid is 3.777(6) Å; C5'/C10' and C15'/C20' ring centroid is 3.781(6) Å) (Figure 3).
Figure 2. The molecular structure of pentabromide 19. The asymmetric unit contains half of the molecule. Displacement ellipsoids are shown at the 50% probability level.

Figure 3. Packing diagram of pentabromide 19 along the a-axis.
Conclusions

The first and short synthesis of brominated natural products 3 and 4 from the red alga *Symphyocladia latiuscula* as monobenzylphenol derivatives and 5 from the red alga *Rhodomela confervoides* as dibenzylphenol derivative were carried out.

Experimental Section

**General.** All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Melting points were determined on a capillary melting apparatus (Buchi530) and are uncorrected. IR spectra were obtained from solutions in 0.1 mm cells with a Perkin-Elmer spectrophotometer. The $^1$H- and $^{13}$C- NMR spectra were recorded on a 200 (50) and 400 (100)-MHz Varian spectrometer; δ in ppm, Me$_4$Si as the internal standard. Coupling constants are reported in Hz. Multiplicity is defined as s (singlet), d (doublet), t (triplet), br (broad), or m (multiplet). Elemental analyses were performed on a Leco CHNS-932 apparatus. All column chromatography was performed on silica gel (60-mesh, Merck). PLC is preparative thick-layer chromatography: 1 mm of silica gel 60 PF (Merck) on glass plates.

**Synthesis of 3,4-dimethoxybenzylacetate (7).** 3,4-Dimethoxybenzyl alcohol (6) (10.0 g, 60 mmol) was allowed to react at room temperature for 1 day with pyridine (15 mL) and Ac$_2$O (10 mL) by applying a known method. The reaction mixture was poured into dilute aqueous HCl (700 mL) with ice and checked with pH paper. It was extracted with CH$_2$Cl$_2$ (2 × 50 mL), the extract was washed with cold NaOH (0.5 %, 100 mL) and water (200 mL), and dried over CaCl$_2$. The solvent was evaporated and the 3,4-dimethoxybenzylacetate (7) (11.97 g, 97%) was obtained as colourless liquid. $^1$H-NMR (400 MHz, CDCl$_3$) δ 6.90 (d, $J = 1.5$ Hz, 1H), 6.87 (dd, $J = 8.4$, 1.5 Hz, 1H), 6.81 (d, $J = 8.1$ Hz, 1H), 5.00 (s, methylenic, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 2.04 (s, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 171.10 (CO), 149.34 (C), 149.21 (C), 128.66 (C), 121.52 (CH), 112.08 (CH), 111.26 (CH), 66.58 (CH$_2$), 56.09 (OCH$_3$), 56.06 (OCH$_3$), 21.23 (CH$_3$).

**Synthesis of 1,2,5-tribromo-3,4-dimethoxybenzene (13).** To a solution of 1,2-dihydroxybenzene 10 (5.0 g, 45.4 mmol) in acetic acid (HOAc, 100 mL) bromine (58.0 g, 363.2 mmol, 8 equivalent) was added at room temperature. After the reaction mixture was heated and refluxed for 18 h, the solvent and excess bromine were removed. Tetrabromocatechol 11 was obtained in quantitative yield.

To a mixture of glacial HOAc (15 ml), water (5 ml) and tetrabromocatechol 11 (5.0 g, 11.74 mmol) zinc dust were added and the mixture was refluxed for 4 minutes. The filtered liquid was precipitated in water as solid and then tribromocatechol 12 was crystallized from boiling water as thin needles (0.82 g, 20%).
A solution of tribromocatechol (0.9 g, 2.6 mmol) in tetrahydrofuran (THF, 10 mL) was heated at 80°C and then tetramethyl ammonium bromide (catalytic amount), a solution of dimethyl sulfate (0.95 g, 7.53 mmol) in THF (4.0 mL) and a solution of K2CO3 (1.2 g, 12.1 mmol) in water (3.0 mL) were added, respectively. After the reaction mixture was refluxed for 2 days, THF was removed and water was added to the reaction mixture (30 mL). The mixture was extracted with ethyl acetate (3x25 mL). After the combined organic layer was dried over Na2SO4, it was filtered and the solvent was evaporated, 1,2,5-tribromo-3,4-dimethoxybenzene (13) was obtained as 0.96 g (86%).

3,4,6-Tribromobenzene-1,2-diol (12). Mp 104-106°C (Lit. 7 106°C); 1H-NMR (400 MHz, CDCl3) δ 7.38 (s, 1H), 5.86 (s, 2OH); 13C-NMR (100 MHz, CDCl3) δ 142.60 (C), 140.84 (C), 127.08 (CH), 115.21 (C), 112.09 (C), 108.84 (C).

1,2,5-Tribromo-3,4-dimethoxybenzene (13). Mp 66-67°C (Lit. 7 69°C); 1H-NMR (400 MHz, CDCl3) δ 7.61 (s, 1H), 3.89 (s, methoxy, 3H), 3.88 (s, methoxy, 3H); 13C-NMR (100 MHz, CDCl3) δ 152.89 (C), 150.91 (C), 131.66 (CH), 120.91 (C), 120.17 (C), 117.45 (C), 61.17 (2 OCH3).

General procedure for coupling in PPA: synthesis of 1,2,4-tribromo-3-(2,3-dibromo-4,5-dimethoxybenzyl)-5,6-dimethoxybenzene (15)

Polyphosphoric acid (PPA), prepared from conc. H3PO4 (85%, 0.83 g) and P2O5 (1.49 g, 10.5 mmol), was heated to 80°C in a beaker (100 mL). To this mixture were added synthesized 9 (0.59 g, 1.45 mmol) and 14 (0.43 g, 1.45 mmol) quickly. The mixture was stirred with a glass stick at 80°C for 45 minutes and was then carefully poured onto 10 mL of ice/water. The organic phase was extracted with EtOAc (2x40 mL). The combined organic layers were dried over Na2SO4 and the solvent was evaporated. Pentabromide 15 (0.92 g, 92% ) was the sole product and was crystallized from ethyl acetate/hexane as white crystals. mp 159-162°C; 1H-NMR (CDCl3, 400 MHz) δ 6.48 (s, 1H), 4.49 (s, CH2, 2H), 3.96 (s, methoxy, 3H), 3.93 (s, methoxy, 6H), 3.89 (s, methoxy, 3H); 13C-NMR (100 MHz, CDCl3) δ 151.80 (C), 151.46 (C), 151.12 (C), 149.91 (C), 135.86 (C), 134.52 (C), 126.42 (CH), 123.73 (C), 122.16 (C), 121.66 (C), 119.70 (C), 116.92 (C), 61.16 (OCH3), 61.12 (OCH3), 61.08 (OCH3), 61.06 (OCH3), 44.94 (CH2); IR (CH2Cl2, cm⁻¹): 3855, 3445, 2939, 2857, 1639, 1453, 1419, 1386, 1370, 1301, 1155, 1134, 1062, 1034, 1001, 961, 926, 852, 796, 769, 738, 702, 642, 524; Anal. Calcd for C17H15Br5O4: C, 29.90; H, 2.21. Found: C, 29.89; H, 2.21.

Synthesis of 1,2,4-tribromo-5,6-dimethoxy-3-(2,3,6-tribromo-4,5-dimethoxybenzyl)benzene (16). The reaction was performed by following the standard procedure described above for the synthesis of 15. Bromoalcohol 9 (0.5 g, 1.25 mmol), tribromoveratrole 13 (0.46 g, 1.25 mmol), H3PO4 (85%, 0.70 g) and P2O5 (1.26 g) were used in the reaction. The reaction lasted for 1 hour. Hexabromide 16 (0.91 g, 97%) was the sole product and was crystallized from ethyl acetate as white crystals. mp 124-126°C; 1H-NMR (CDCl3, 400 MHz) δ 4.91 (s, CH2, 2H), 3.90 (s, methoxy, 6H), 3.87 (s, methoxy, 6H); 13C-NMR (100 MHz, CDCl3) δ 150.82 (C), 150.80 (C), 136.27 (C), 123.50 (C), 122.22 (C), 122.00 (C), 61.19 (OCH3), 61.02 (OCH3), 47.86 (CH2); IR
Reaction of (2,3-dibromo-4,5-dimethoxyphenyl)methanol (17) and 1-bromo-2,3-dimethoxybenzene (18). The reaction was carried out by following the standard procedure described above for the synthesis of 15. Bromoalcohol 17 (2.0 g, 6.13 mmol, 2.0 equivalent), 1-bromo-2,3-dimethoxybenzene 18 (0.67 g, 3.1 mmol, 1.0 equivalent), H3PO4 (85%, 3.50 g) and P2O5 (6.29 g) were used in the reaction. The reaction lasted for 1.0 h. The residue (2.71 g) was subjected to column chromatography on silica gel (150 g) using ethyl acetate/hexane (5:95) to give 19 (1.20 g, 1.44 mmol, 47%) and 20 (1.13 g, 1.35 mmol, 44%), respectively.

2,3-Dibromo-1-[3-bromo-2-(2,3-dibromo-4,5-dimethoxybenzyl)-4,5-dimethoxybenzyl]-4,5-dimethoxybenzene (19). It was crystallized from ethyl acetate/hexane; mp 132-135°C; 1H-NMR (400 MHz, CDCl3) δ 6.60 (s, aromatic, 1H), 6.45 (s, aromatic, 1H), 6.14 (s, aromatic, 1H), 4.20 (s, methylenic, 2H), 3.96 (s, methylenic, 2H), 3.88 (s, methoxy, 3H), 3.80 (s, methoxy, 3H), 3.79 (s, methoxy, 3H), 3.78 (s, methoxy, 3H), 3.70 (s, methoxy, 3H), 3.58 (s, methoxy, 3H); 13C-NMR (100 MHz, APT, CDCl3) δ 152.57 (C), 152.48 (C), 152.45 (C), 152.45 (C), 152.42 (C), 152.41 (C), 152.39 (C), 152.38 (C), 146.68 (C), 146.68 (C), 146.66 (C), 145.80 (C), 145.79 (C), 145.78 (C), 145.77 (C), 145.76 (C), 136.24 (C), 135.62 (C), 135.50 (C), 135.49 (C), 135.48 (C), 135.47 (C), 130.13 (C), 123.06 (CH), 122.33 (C), 121.88 (C), 118.23 (C), 117.70 (C), 114.16 (CH), 114.04 (CH), 112.13 (CH), 60.76 (OCH3), 60.71 (OCH3), 56.37 (OCH3), 56.36 (OCH3), 42.35 (CH2), 40.71 (CH2); IR (CH2Cl2, cm-1): 2995, 2962, 2934, 2854, 1741, 1519, 1452, 1393, 1369, 1311, 1281, 1213, 1156, 1058, 1039, 1011, 963, 943, 910, 878, 824, 776, 699, 527; Anal. Calcd for C17H14Br6O4: C, 26.81; H, 1.85. Found: C, 26.73; H, 1.86.

2,3-Dibromo-1-[4-bromo-5-(2,3-dibromo-4,5-dimethoxybenzyl)-2,3-dimethoxybenzyl]-4,5-dimethoxybenzene (20): It was crystallized from ethyl acetate/hexane; mp 164-166°C; 1H-NMR (400 MHz, CDCl3) δ 6.61 (s, aromatic, 1H), 6.58 (s, aromatic, 1H), 6.36 (s, aromatic, 1H), 4.12 (s, methylenic, 2H), 4.01 (s, methylenic, 2H), 3.90 (s, methoxy, 3H), 3.85 (s, methoxy, 3H), 3.84 (s, methoxy, 3H), 3.82 (s, methoxy, 3H), 3.73 (s, methoxy, 3H), 3.72 (s, methoxy, 3H); 13C-NMR (100 MHz, APT, CDCl3) δ 152.74 (C), 152.63 (C), 150.76 (C), 150.75 (C), 146.67 (C), 146.56 (C), 136.90 (C), 136.41 (C), 134.87 (C), 132.72 (C), 126.23 (CH), 122.19 (C), 122.14 (C), 118.79 (C), 118.22 (C), 118.94 (C), 114.02 (2CH), 104.28 (2CH2), 60.81 (2OCH3), 60.79 (OCH3), 60.65 (OCH3), 56.46 (OCH3), 56.44 (OCH3), 43.74 (CH2), 37.77 (CH2); IR (CH2Cl2, cm-1): 3000, 2962, 2934, 2841, 1593, 1549, 1469, 1373, 1310, 1283, 1193, 1162, 1101, 1057, 1039, 1006, 813, 736; Anal. Calcd for C26H25Br5O6: C, 37.49; H, 3.03. Found: C, 37.44; H, 2.99.

Synthesis of 2,3-dibromo-1-(2-bromo-3,4-dimethoxybenzyl)-4,5-dimethoxybenzene (21). The reaction was carried out by following the standard procedure described above for the synthesis of 8. Bromoalcohol 17 (0.50 g, 1.53 mmol, 1.0 equivalent), 1-bromo-2,3-dimethoxybenzene (18) (0.33 g, 1.53 mmol, 1.0 equivalent), H3PO4 (85%, 0.87 g) and P2O5 (1.57 g) were used in the reaction. The reaction lasted for 1 h. Monosubstituted product 21 (0.91 g, 96%) was the sole product and was crystallized from ethyl acetate/hexane as white crystals. mp 97-99°C; 1H-NMR (400 MHz, CDCl3) δ 6.80 (d, J = 8.4 Hz, A part of AB system, aromatic, 1H), 6.77 (d, J = 8.4 Hz, B part of AB system, aromatic, 1H), 6.57 (s, aromatic, 1H), 4.16 (s,
CH2, 2H), 3.87 (s, methoxy, 3H), 3.86 (s, methoxy, 3H), 3.84 (s, methoxy, 3H), 3.73 (s, methoxy, 3H); 13C-NMR (100 MHz, CDCl3), δ 152.74 (C), 152.47 (C), 147.00 (C), 146.52 (C), 136.88 (C), 131.72 (C), 125.37 (CH), 122.18 (C), 120.81 (C), 118.18 (C), 113.78 (CH), 111.54 (CH), 60.74 (OCH3), 60.68 (OCH3), 56.35 (OCH3), 56.30 (OCH3), 43.61 (CH2); IR (CH2Cl2, cm⁻¹): 3686, 2992, 2937, 2835, 1592, 1549, 1485, 1469, 1422, 1375, 1284, 1202, 1161, 1059, 1033, 1007, 814; Anal. Calcd for C17H17Br3O4: C, 38.89; H, 3.26.  

**Synthesis of 1,2-dibromo-3,4-dimethoxybenzene (22).** To a stirring solution of 1-bromo-2,3-dimethoxybenzene (18) (0.217 g, 1.0 mmol) in CHCl3 (20 mL) was added dropwise a solution of bromine (0.17 g, 1.1 mmol) in CHCl3 (10 mL) at room temperature (RT) in 1 minute. After the reaction mixture was stirred at RT for 1 day, the solvent was evaporated. The residue was subjected to column chromatography on silica gel (SiO2, 60 g) and eluted with EtOAc/hexane (1:40). 1,2,3-Tribromo-4,5-dimethoxybenzene (13)7 (147 mg, %4) and 1,2-dibromo-3,4-dimethoxybenzene (22) (0.27 g, %94) were isolated, consecutively. Liquid; 1H-NMR (400 MHz, CDCl3): δ 7.33 (d, J = 9.0 Hz, A part of AB system, aromatic, 1H), 6.77 (d, J = 9.0 Hz, B part of AB system, aromatic, 1H), 3.86 (s, methoxy, 3H), 3.84 (s, methoxy, 3H); 13C-NMR (100 MHz, CDCl3) δ 153.01 (C), 128.38 (CH and C), 121.37 (C), 115.99 (C), 112.78 (CH), 60.74 (OCH3), 56.48 (OCH3); IR (CH2Cl2, cm⁻¹): 3441, 3003, 2937, 2838, 2549, 2069, 1575, 1468, 1427, 1388, 1290, 1258, 1158, 1134, 1036, 1005, 861, 797, 748, 653, 620, 589, 507; Anal. Calcd (C8H8Br2O2): C 32.47, H 2.72; Found: C 32.49, H 2.69.

**Standard procedure for demethylation of compounds with OMe by ether cleavage.**

**Synthesis of 3,4,6-tribromo-5-(2,3-dibromo-4,5-dihydroxybenzyl)benzene-1,2-diol (3).** A solution of pentabromide 15 (0.52 g, 0.76 mmol) in CH2Cl2 (12 mL) was cooled to 0 oC and then a solution of BBr3 (0.5 mL) in CH2Cl2 (5.2 mL) was added dropwise under N2(g) over 5 minutes. After the cold bath was removed, the mixture was stirred at RT and under N2 for 1 day. Methanol (30 mL) was slowly added over 15 minutes and then the solvent was evaporated. After water (40 mL) and EtOAc (50 mL) were added, the mixture was shaken. The organic phase was separated and the water phase was extracted with EtOAc (2x30 mL). The combined organic phases were dried over Na2SO4 and the solvent was evaporated. The natural product bromophenol 3 (0.5 g, 96%) was obtained and crystallized from ethyl acetate/hexane as amorphous; mp 165-167°C (lit.3a 168-172°C); 1H-NMR (400 MHz, CD3COCD3) δ 8.65 (s, 4 OH), 6.25 (s, 1H), 4.42 (s, methylenic, 2H); 13C-NMR (100 MHz, CD3COCD3) δ 144.33 (C), 143.04 (C), 143.71 (C), 142.10 (C), 130.68 (C), 130.17 (C), 121.56 (CH), 117.82 (CH), 113.78 (C), 113.63 (C), 113.40 (2C), 108.97 (C), 44.04 (CH2).

**Synthesis of bromophenols 4, 5 and 23 from the corresponding compounds 16, 19 and 20, respectively.** The standard procedure described above for the synthesis of 3 with BBr3 was applied. From these reactions, bromophenols 4, 5 and 23 were obtained.

**3,4,6-Tri bromo-5-(2,3,6-tribromo-4,5-dihydroxybenzyl)benzene-1,2-diol (4).** Amorphous; (0.564 g, 94%); mp 164-168°C (lit.3a 168-172°C); 1H-NMR (400 MHz, CD3COCD3) δ 8.65 (s, 4 OH), 4.84 (s, CH2, 2H); 13C-NMR (100 MHz, CD3COCD3) δ 143.30 (2C), 131.15 (C), 117.82 (C), 113.78 (C), 113.63 (C), 46.94 (CH2).
3,4-Dibromo-5-[3-bromo-2-(2,3-dibromo-4,5-dihydroxybenzyl)-4,5-dihydroxybenzyl]benzene-1,2-diol (5). Pale brown amorphous solid; (0.40 g, 95%); mp 234-236°C (lit. 4 237-238°C) 

1H-NMR (400 MHz, CD3COCD3) δ 8.82 (s, OH, 1H), 8.71 (s, OH, 1H), 8.69 (s, OH, 1H), 8.27 (s, OH, 1H), 8.15 (s, OH, 1H), 8.00 (s, OH, 1H), 6.56 (s, aromatic, 1H), 6.50 (s, aromatic, 1H), 6.21 (s, aromatic, 1H), 4.05 (s, methylenic, 2H), 3.78 (s, methylenic, 2H); 13C-NMR (100 MHz, CD3COCD3) δ 144.97 (C), 144.87 (C), 144.51 (2C), 143.26 (C), 142.95 (C), 141.96 (C), 132.25 (C), 131.19 (2C), 128.65 (C), 116.30 (CH), 116.25 (CH), 114.83 (CH), 114.41 (C), 114.27 (CH), 113.34 (C), 113.15 (C), 40.34 (CH2), 39.48 (CH2); IR (CH3OH, cm⁻¹): 3571, 3325, 2967, 2918, 2863, 1594, 1480, 1405, 1267, 1206, 1033; Anal. Calcd for C20H13Br5O6: C, 32.08; H, 1.75. Found: C, 32.08; H, 1.77.

3,4-Dibromo-5-[4-bromo-5-(2,3-dibromo-4,5-dihydroxybenzyl)-2,3-dihydroxybenzyl]benzene-1,2-diol (23). Pale brown amorphous solid; (0.43 g, 95%); mp 99-103°C; 

1H-NMR (400 MHz, CDCl3) δ 8.70 (s, OH, 1H), 8.69 (s, OH, 1H), 8.16 (s, OH, 1H), 8.14 (s, OH, 1H), 8.05 (s, OH, 1H), 7.93 (s, OH, 1H), 6.60 (s, aromatic, 1H), 6.51 (s, aromatic, 1H), 6.43 (s, aromatic, 1H), 3.99 (s, methylenic, 2H), 3.97 (s, methylenic, 2H); 13C-NMR (100 MHz, CDCl3) δ 144.87 (2C), 144.84 (2C), 143.14 (C), 143.04 (C), 142.98 (C), 142.91 (C), 132.22 (C), 130.05 (C), 125.83 (C), 123.83 (C and CH), 115.98 (CH), 115.75 (CH), 114.00 (C), 113.15 (C), 111.18 (C), 42.84 (CH2), 36.95 (CH2); IR (CH3OH, cm⁻¹): 3571, 3467, 3391, 2973, 2918, 2863, 1594, 1480, 1403, 1276, 1206, 1033; Anal. Calcd for C20H13Br5O6: C, 32.08; H, 1.75. Found: C, 32.03; H, 1.79.

NMR spectra of natural products 3, 4 and 5 are consistent with data given in the literature.3a,4a

X-Ray structure determination

For the crystal structure determination, the single crystal of the compound pentabromide 19 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 Mo Kα radiation (λ=0.71073 Å) and oscillation scans technique with Δω=5° or one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with F2>2σ(F2). Integration of the intensities, correction for Lorentz and polarization effects and cell refinement were performed using CrystalClear (Rigaku/MSC Inc., 2005) software.13 The structures were solved by direct methods using SHELXS-9714 and refined by a full-matrix least-squares procedure using the program SHELXL-97.14 H atoms were positioned geometrically and refined using a riding model by fixing the aromatic C–H distances at 0.93 Å and methyl C–H distances at 0.96 Å [ Uiso(H)=1.2Ueq(C) and Uiso(H)=1.5Ueq(methyl C)]. The final difference Fourier maps showed no peaks of chemical significance. Crystal data for pentabromide 19: C26H25Br5O6, crystal system, space group: triclinic, P-1; (no:2); unit cell dimensions: a= 8.4083(2), b= 17.3134(4), c= 19.3196(5) Å, α=88.63(3) β= 89.37(4), γ=86.51(3)°; volume: 2806.3(2)Å³; Z=4; calculated density: 1.97 mg/m³; absorption coefficient: 7.200 mm⁻¹; F(000): 1616; θ range for data collection 2.4 –26.4°; refinement method: full-matrix least-square on F²; data/parameters: 11455/668; goodness-of-fit on F²: 1.278; final R indices
[I>2σ(I)]: R1= 0.098, wR2=0.157; R indices (all data): R1=0.227, wR2=0.178; largest diff. peak and hole: 0.609 and -0.582 e Å⁻³; CCDC- 743502.

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References


