Bromophenols from the Red Alga *Rhodomela confervoides*

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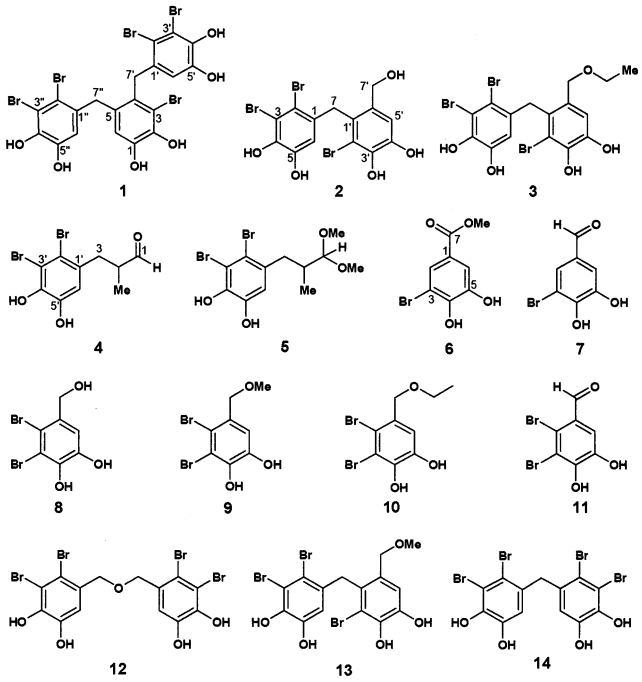
Six new bromophenols, 3-bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl)pyrocatechol (**1**), 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-hydroxymethyldiphenylmethane (**2**), 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-ethyloxymethyldiphenylmethane (**3**), (±)-2-methyl-3-(2,3-dibromo-4,5-dihydroxyphenyl)propylaldehyde (**4**), (±)-2-methyl-3-(2,3-dibromo-4,5-dihydroxyphenyl)propylaldehyde dimethyl acetal (**5**), and 3-bromo-4,5-dihydroxybenzoic acid methyl ester (**6**), together with eight known bromophenols, 3-bromo-4,5-dihydroxybenzaldehyde (**7**), 2,3-dibromo-4,5-dihydroxybenzyl alcohol (lanosol, **8**), 2,3-dibromo-4,5-dihydroxybenzyl methyl ether (**9**), 2,3-dibromo-4,5-dihydroxybenzyl ethyl ether (**10**), 2,3-dibromo-4,5-dihydroxybenzylaldehyde (**11**), bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (**12**), 3-bromo-4-(2,3-dibromo-4,5-dihydroxybenzyl)-5-methoxymethylpyrocatechol (**13**), and 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenyl methane (**14**), were isolated from the red alga *Rhodomela confervoides*. Their structures were elucidated by chemical and spectroscopic methods including IR, HRFABMS, and 1D and 2D NMR techniques.

A number of bromophenols have been previously isolated from red marine algae of the family Rhodomelaceae,[1−11] and some have shown feeding deterrent[8] and α-glucosidase inhibitory activities.[11] *Rhodomela confervoides* (Huds.) Lamour. is a red alga belonging to this family and is widely distributed in the Gulf of the Yellow Sea, China. 2,3-Dibromo-4,5-dihydroxybenzyl alcohol (**8**) and 3,5-dibromo-4-hydroxybenzyl alcohol have been reported from this alga,[12] while some chlorinated bromophenols and 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**14**) have been identified by stepwise extraction followed by GC−MS.[5] In our investigation of the chemical constituents of *R. confervoides* collected at the coast of Qingdao, China, six new bromophenols, 3-bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl)pyrocatechol (**1**), 2,2′,3-tribromo-3′,4,4′, 5-tetrahydroxy-6′-hydroxymethyldiphenylmethane (**2**), 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-ethyloxymethyldiphenylmethane (**3**), 2-methyl-3-(2,3-dibromo-4,5-dihydroxyphenyl)propylaldehyde (**4**), 2-methyl-3-(2,3-dibromo-4,5-dihydroxyphenyl)propylaldehyde dimethyl acetal (**5**), and 3-bromo-4,5-dihydroxybenzoic acid methyl ester (**6**), together with eight known bromophenols, 3-bromo-4,5-dihydroxybenzaldehyde (**7**),[3,6] 2,3-dibromo-4,5-dihydroxybenzyl alcohol (lanosol, **8**),[8] 2,3-dibromo-4,5-dihydroxybenzyl methyl ether (**9**),[1,8] 2,3-dibromo-4,5-dihydroxybenzyl ethyl ether (**10**),[8,10] 2,3-dibromo-4,5-dihydroxybenzylaldehyde (**11**),[1] bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (**12**),[11] 3-bromo-4-(2,3-dibromo-4,5-dihydroxybenzyl)-5-methoxymethylpyrocatechol (**13**),[4,8] and 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**14**),[4,8] were isolated from the ethanolic extract of this red alga. We report here the isolation and structural elucidation of these new bromophenols.

The air-dried and ground red alga *R. confervoides* was extracted with 95% EtOH, and the concentrated extract was suspended in water and then partitioned with EtOAc. The EtOAc extract was chromatographed over silica gel eluting with a gradient of increasing MeOH (0−100%) in $CHCl_3$. The subsequent fractions were further purified by a variety of chromatographic techniques to yield bromophenols **1**−**14**.



Compound **1** was obtained as white needles (Me_2CO), mp 237−238 °C. The IR spectrum showed a strong yet broadened absorption band for hydroxyl groups at 3410 cm^{-1} and characteristic absorption bands for aromatic rings at 1606 and 1489 cm^{-1}. The positive FABMS spectrum with glycol as a matrix exhibited a quasi-molecular ion peak cluster at *m/z* 744/746/748/750/752/754 (1: 5: 10: 10: 5: 1), which suggested the presence of five bromine atoms in compound **1**. The molecular formula was determined as $C_{20}H_{13}Br_5O_6$ by HRFABMS at *m/z* 743.6645 (calcd for $C_{20}H_{13}{}^{79}Br_5O_6$ 743.6629). The ^1H NMR spectrum of **1** in acetone-d_6 showed three singlets attributed to aromatic protons at δ 6.56 (1H, s, H-6″), 6.49 (1H, s, H-6), and 6.20 (1H, s, H-6′) and two singlets assigned to methylene protons at δ 4.04 (2H, s, H-7′) and 3.78 (2H, s, H-7″), as well as six exchangeable broadened singlets for the phenolic hydroxyl protons at δ

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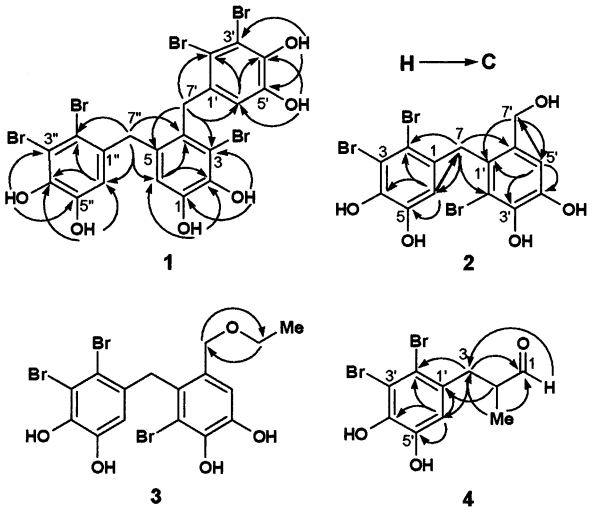

Figure 1. Key HMBC correlations of compounds **1**−**4**.

8.83 (1H, br s, OH-5″), 8.73 (1H, br s, OH-5′), 8.72 (1H, br s, OH-1), 8.35 (1H, br s, OH-4″), 8.19 (1H, br s, OH-4), and 8.03 (1H, br s, OH-4′). The ^{13}C NMR and DEPT spectra of **1** displayed 20 carbon signals attributed to three pentasubstituted benzene rings and a pair of methylene groups (see Experimental Section). The protonated carbons were assigned by the HMQC experiment of **1**, and the oxygenated quaternary carbons were recognized by their chemical shifts (δ > 140 ppm). All of the above spectral data indicated that **1** was a pentabrominated dibenzylphenol. In the HMBC spectrum (see Figure 1), cross-peaks from aromatic and phenolic protons to their correlated long-range carbons unambiguously established the substitution patterns of the three aromatic rings. Long-range correlations from H_2-7′ to C-3, C-5, C-2′, and C-6′ and from H_2-7″ to C-4, C-6, C-2″, and C-6″ unequivocally demonstrated that the 3-bromopyrocatechol unit was substituted at C-4 and C-5 by two 2,3-dibromo-4,5-dihydroxybenzyl groups. Accordingly, the structure of **1** was determined as 3-bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl)pyrocatechol.

Compound **2** was obtained as yellowish white needles (Me_2CO), mp 127−129 °C. The IR spectrum (KBr) of **2** showed characteristic absorption bands for hydroxyl groups at 3477 and 3425 cm^{-1} and for aromatic rings at 1608, 1577, 1491, and 1469 cm^{-1}. The EIMS spectrum gave the tribrominated molecular ion peak cluster at *m*/*z* 502/500/498/496 with a ratio of abundances 1: 3: 3: 1. The molecular formula was determined as $C_{14}H_{11}Br_3O_5$ by HREIMS at *m*/*z* 495.8134 (calcd for $C_{14}H_{11}{}^{79}Br_3O_5$ 495.8157). In addition to a very broadened exchangeable signal integrating for four protons at δ 8.52, the ^{1}H NMR spectrum of **2** (acetone-d_6) showed only four singlets attributed to aromatic protons at δ 7.09 (1H, s, H-5′), 6.08 (1H, s, H-6), and two methylenes at δ 4.42 (2H, s, H-7′) and 4.12 (2H, s, H-7). The ^{13}C NMR and DEPT spectra of **2** (see Experimental Section) displayed 14 carbons assignable to two methylenes and two pentasubstituted benzene rings with four oxygenated carbons (δ > 142 ppm). The above spectral data indicated that **2** possessed a tribrominated diarylmethane structure with four hydroxyl and one hydroxymethyl group. In the HMBC spectrum (see Figure 1), long-range correlations from H_2-7 to C-2, C-6, C-2′, and C-6′ confirmed the diarylmethane structure of **2**. The substituted patterns of the aromatic rings were unambiguously established by correlations from H-6 to C-2, C-4, C-5, and C-7, from H-5′ to C-1′, C-3′, C-4′, and C-7′, and from H_2-7′ to C-1′ and C-5′. Therefore, the structure of **2** was determined as 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-hydroxymethyldiphenylmethane.

Compound **3** was obtained as yellowish white needles (Me_2CO), mp 197−199 °C and showed the tribrominated molecular ion peak cluster at *m*/*z* 530/528/526/524 (1: 3: 3: 1) in its EIMS spectrum. The molecular formula was determined as $C_{16}H_{15}Br_3O_5$ by HREIMS at *m*/*z* 523.8466 (calcd for $C_{16}H_{15}{}^{79}Br_3O_5$ 523.8470). The IR and NMR spectra of **3** were very similar to those of **2** (see Experimental Section), except for appearances of characteristic signals attributed to an ethyloxyl group at δ_H 1.06 (3H, t, J = 7.0 Hz) and 3.40 (2H, q, J = 7.0 Hz) and δ_C 65.5 (t) and 14.7 (q) in the ^{1}H and ^{13}C NMR spectra of **3**. In addition, by comparing the NMR data of **3** with those of **2**, H_2-7′ was shifted upfield from δ 4.42 in **2** to δ 4.25 in **3**, and C-6′ and C-7′ were shifted respectively from δ 133.5 and 62.1 in **2** to 130.5 and 70.7 in **3**. Therefore, **3** is a 7′-ethyloxyl derivative of **2**. This assignment of signals was confirmed by an HMBC experiment (see Figure 1). Thus, the structure of **3** was assigned as 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-ethyloxymethyldiphenylmethane.

Compound **4** was obtained as a gum. The IR spectrum (KBr) showed absorption bands for hydroxyl (3386 cm^{-1}) and carbonyl (1712 cm^{-1}) groups and aromatic rings (1600, 1576, 1498, and 1469 cm^{-1}). Its EIMS spectrum gave characteristic dibrominated molecular ion peaks at *m*/*z* 339/337/335 (1: 2: 1). The molecular formula $C_{10}H_{10}Br_2O_3$ was determined by HREIMS at *m*/*z* 335.8982 (calcd for $C_{10}H_{10}{}^{79}Br_2O_3$ 335.8997). The ^{1}H NMR spectrum of **4** in acetone-d_6 showed a diagnostic signal at δ 9.70 (1H, d, J = 1.5 Hz, H-1) for an aldehyde proton and signals attributed to a aromatic proton at δ 6.88 (1H, s, H-6′) and a methyl group at δ 1.07 (3H, d, J = 7.0 Hz, H-4), as well as an ABX coupling system at δ 2.66 (1H, dd, J = 13.5 and 7.8 Hz, H-3a), 2.74 (1H, m, H-2), and 3.18 (1H, dd, J = 13.5 and 6.3 Hz, H-3b). The ^{1}H−^{1}H COSY spectrum of **4** confirmed that there was a 2-methylpropylaldehyde unit with substitution at C-3 in the structure. In addition to the carbon signals of this unit, the ^{13}C NMR and DEPT spectrum (see Experimental Section) exhibited six sp^2 carbon signals attributed to a pentasubstituted benzene ring with two oxygenated carbons (δ > 143 ppm). All of the above spectral data suggested that the structure of **4** was 2-methyl-3-phenylpropylaldehyde with substitution by two hydroxyl and two bromine groups on the phenyl moiety. In the HMBC spectrum of **4** (see Figure 1), long-range correlations from H_2-3 to C-2′ and C-6′ and from H-6′ to C-1′, C-2′, C-4′, and C-5′ unambiguously established the substitution pattern of the phenyl moiety. Therefore, the structure of **4** was determined as 2-methyl-3-(2,3-dibromo-4,5-dihydroxyphenyl)propylaldehyde. It was considered to be a racemate since no optical rotation was observed for **4**.

Compound **5** was obtained as a white amorphous powder (Me_2CO), mp 117−118 °C. Its IR spectrum (KBr) showed absorption bands for hydroxyl groups (3462 cm^{-1}) and aromatic rings (1599, 1581, and 1496 cm^{-1}). The EIMS spectrum exhibited dibrominated molecular ion peaks at *m*/*z* 382/384/386 (1: 2: 1). The molecular formula $C_{12}H_{16}Br_2O_4$ was determined by HREIMS at *m*/*z* 381.9425 (calcd for $C_{12}H_{16}{}^{79}Br_2O_4$ 381.9415). The ^{1}H NMR spectrum of **5** was very similar to that of **4** (see Experimental Section), except for loss of the signal attributed to the aldehyde proton and the appearance of proton signals at δ 4.11 (1H, d, J = 5.1 Hz, H-1), 3.35 (3H, s), and 3.34 (3H, s) and carbon signals δ 108.5 (d), 54.0 (q), and 53.9 (q), which were assigned to a dimethyl acetal moiety. Thus, the structure

of **5** was established as 2-methyl-3-(2,3-dibromo-4,5-dihydroxyphenyl)propylaldehyde dimethyl acetal. It was also isolated as a racemate, as it was optically inactive. An HMBC experiment confirmed the structural assignment of **5**.

Compound **6** was a white amorphous powder, mp 176−178 °C. Its IR spectrum showed absorption bands for hydroxyl (3425 cm^{-1}) and carbonyl (1685 cm^{-1}) groups and aromatic rings (1608 and 1496 cm^{-1}). The EIMS spectrum gave monobrominated molecular ion peaks at *m*/*z* 246/248 (1: 1), and the molecular formula $C_8H_7BrO_4$ was determined by HREIMS at *m*/*z* 245.9532 (calcd for $C_8H_7{}^{79}BrO_4$ 245.9528). The ^{1}H NMR spectrum showed only three signals at δ 7.70 (1H, d, J = 1.8 Hz, H-2), 7.56 (1H, d, J = 1.8 Hz, H-6), and 3.90 (3H, s, OCH_3) attributed to two *meta*-coupled aromatic protons and a methoxyl group, respectively. The ^{13}C NMR and DEPT spectra displayed eight carbon signals including a methoxyl, two sp^2 methines, and five quaternary carbons (one carbonyl and two oxygenated). These spectral data revealed a monobrominated dihydroxybenzoic acid methyl ester structure for **6**. The substitution pattern was established by long-range correlations from both aromatic protons to C-4 and C-7 and from the methoxyl protons to C-7. Consequently, the structure of **6** was assigned as 3-bromo-4,5-dihydroxybenzoic acid methyl ester. Although this structure had been previously synthesized, no spectral data were reported.[12]

Compounds **3** and **5** may be artifacts produced in the extraction and isolation procedures since, in separate experiments, **2** was refluxed with ethanol to yield **3**, and **4** with methanol to give **5**. The methyl ether derivative of **2**, 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-methoxymethyldiphenylmethane, was previously isolated from the methanolic extract of red alga *R. larix*[4] and may also be an artifact of extraction.

Experimental Section

General Experimental Procedures. Melting points were determined on an XT-4 micro melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter. IR spectra were recorded as KBr disks on a Nicolet Impact 400 FT-IR spectrophotometer. 1D and 2D NMR spectra were obtained at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, on an Inova 500 MHz spectrometer in acetone-d_6 with solvent peaks as references. EIMS, FABMS, HREIMS, and HRFABMS data were measured with a Micromass Autospec-Ultima ETOF spectrometer. Column chromatography was performed with silica gel (200−300 mesh), Bio-Beads SX3 (200−400 mesh), RP-18 reversed-phase silica gel (43−60 μm), and Sephadex LH-20. TLC was carried out with glass precoated silica gel GF_{254} plates. Spots were visualized under UV light or by spraying with 7% sulfuric acid in EtOH followed by heating. HPLC was performed using an Alltima C18 10 μm preparative column (22 × 250 mm).

Plant Material. The red alga *Rhodomela confervoides* was collected at the coast of Qingdao, China, in May 2001 and identified by Professor B.-M. Xia. A voucher specimen (No. 200102) was deposited at the Chemisty Department of Marine Algae, Institute of Oceanology, Chinese Academy of Sciences, Qingdao 266071.

Extraction and Isolation. Air-dried *R. confervoides* (14.4 kg) was extracted with EtOH at room temperature for 3 × 48 h. After the solvent was removed under reduced pressure at <40 °C, a dark residue was obtained. The residue was suspended in water and then partitioned with EtOAc. The EtOAc fraction (594.6 g) was chromatographed over silica gel (1200 g), eluting with a gradient increasing MeOH (0−100%) in $CHCl_3$, and separated into 24 fractions (I−XXIV) on the basis of TLC analyses. Fraction VII was purified by column chromatography over silica gel using $CHCl_3$−MeOH (40: 1) as the eluent to give 2,3-dibromo-4,5-dihydroxybenzyl ethyl ether (**10**) (174 mg). Stored in a mixed solvent of petroleum ether and acetone, fraction VIII yielded a precipitate, and filtration followed by recrystallization gave 2,3-dibromo-4,5-dihydroxybenzyl alcohol (lanosol) (**8**) (1.668 g). The filtrate was decolored by Sephadex LH-20 eluting with petroleum ether−$CHCl_3$−MeOH (5: 5: 1) and then purified by reversed-phase preparative HPLC using MeOH−H_2O−AcOH (87: 13: 0.1) as the mobile phase to yield bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (**12**) (31 mg) and 2,3-dibromo-4,5-dihydroxybenzyl methyl ether (**9**) (70 mg). Fraction IX was chromatographed over Sephadex LH-20 eluting with petroleum ether−$CHCl_3$−MeOH (5: 5: 1) to yield 2,3-dibromo-4,5-dihydroxybenzylaldehyde (**11**) (663 mg) and 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**14**) (46 mg). Fraction XI was separated into three subfractions by chromatography over Sephadex LH-20 eluting with petroleum ether−$CHCl_3$−MeOH (5: 5: 1). The last fraction was purified by reversed-phase preparative HPLC using MeOH−H_2O−AcOH (85: 15: 0.1) as the mobile phase to yield 3-bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl)pyrocatechol (**1**) (66 mg), 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-hydroxymethyldiphenyl methane (**2**) (60 mg), 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-ethyloxymethyldiphenylmethane (**3**) (28 mg), and 3-bromo-4-(2,3-dibromo-4,5-dihydroxybenzyl)-5-methoxymethylpyrocatechol (**13**) (148 mg). Fraction XII was decolored by column chromatography over Bio-Beads SX3 using $CHCl_3$−EtOAc (1: 1) and then separated by reversed-phase preparative HPLC using MeOH−H_2O−AcOH (8: 2: 0.01) as mobile phase to yield 2-methyl-3-(2,3-dibromo-4,5-dihydroxyphenyl)propylaldehyde (**4**) (220 mg), 2-methyl-3-(2,3-dibromo-4,5-dihydroxyphenyl)propylaldehyde dimethyl acetal (**5**) (21 mg), 3-bromo-4,5-dihydroxybenzoic acid methyl ester (**6**) (16 mg), and 3-bromo-4,5-dihydroxybenzaldehyde (**7**) (38 mg).

3-Bromo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl)pyrocatechol (1): white needles (Me_2CO); mp 237−238 °C; IR (KBr) ν_{max} 3410, 1666, 1606, 1577, 1489, 1406, 1325, 1277, 1165, 1088, 949, 858 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.83 (1H, br s, OH-5″), 8.73 (1H, br s, OH-5′), 8.72 (1H, br s, OH-1), 8.35 (1H, br s, OH-4″), 8.19 (1H, br s, OH-4), 8.03 (1H, br s, OH-4′), 6.56 (1H, s, H-6″), 6.49 (1H, s, H-6), 6.20 (1H, s, H-6′), 4.04 (2H, s, H-7′), 3.78 (2H, s, H-7″); ^{13}C NMR (acetone-d_6, 125 MHz) δ 145.0 (s, C-5′), 144.9 (s, C-5″), 144.5 (s, C-1), 143.3 (s, C-4″), 143.0 (s, C-4′), 142.0 (s, C-2), 132.2 (s, C-1″), 131.1 (s, C-5), 131.1 (s, C-1′), 128.6 (s, C-4), 116.3 (s, C-2″), 116.2 (d, C-6″), 115.8 (s, C-2′), 115.7 (d, C-6), 114.4 (s, C-3), 114.2 (d, C-6′), 113.3 (s, C-3″), 113.2 (s, C-3′), 40.4 (t, C-7″), 39.5 (t, C-7′); FABMS *m*/*z* 744, 746, 748, 750, 752, 754 [M + H]$^+$; HRFABMS *m*/*z* 743.6645 (calcd for $C_{20}H_{13}{}^{79}Br_5O_6$, 743.6629).

2,2′,3-Tribromo-3′,4,4′,5-tetrahydroxy-6′-hydroxymethyldiphenyl methane (2): white needles (Me_2CO); mp 127−129 °C; IR (KBr) ν_{max} 3477, 3425, 1684, 1608, 1577, 1491, 1469, 1439, 1402, 1277, 1190, 1093, 1016, 949, 858 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 8.52 (4H, br s, OH-4, OH-5, OH-3′, OH-4′), 7.09 (1H, s, H-5′), 6.08 (1H, s, H-6), 4.42 (2H, s, H-7′), 4.12 (2H, s, H-7); ^{13}C NMR (acetone-d_6, 125 MHz) δ 144.8 (s, C-5), 144.4 (s, C-4′), 142.9 (s, C-4), 142.3 (s, C-3′), 133.5 (s, C-6′), 131.7 (s, C-1), 127.7 (s, C-1′), 115.7 (s, C-2), 114.4 (d, C-5′), 114.2 (s, C-2′), 114.1 (d, C-6), 113.1 (s, C-3), 62.1 (t, C-7′), 38.6 (t, C-7); EIMS *m*/*z* 502, 500, 498, 496 [M]$^+$ (8, 23, 25, 6), 484 (12), 482 (27), 480 (32), 479 (14), 467 (16), 465 (46), 463 (48), 461 (18), 403 (3), 401 (11), 399 (4), 322 (15), 320 (15), 242 (10), 231 (13), 229 (14), 213 (8), 184 (6), 149 (8), 139 (13), 82 (96), 80 (100); HREIMS *m*/*z* 495.8134 (calcd for $C_{14}H_{11}{}^{79}Br_3O_5$, 495.8157).

2,2′,3-Tribromo-3′,4,4′,5-tetrahydroxy-6′-ethyloxymethyldiphenylmethane (3): yellowish white needles (Me_2CO); mp 197−199 °C; IR (KBr) ν_{max} 3527, 3415, 2978, 2875, 1610, 1585, 1568, 1487, 1469, 1406, 1348, 1302, 1271, 1097, 1076, 1003, 955, 872, 808 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.00 (1H, s, H-5′), 6.08 (1H, s, H-6), 4.25 (2H, s, H-7′), 4.13 (2H, s, H-7), 3.40 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 1.06 (3H, t, J = 7.0 Hz, OCH$_2$$CH_3$); ^{13}C NMR (acetone-$d_6$, 125 MHz) δ 144.7 (s, C-5), 144.1 (s, C-4′), 142.8 (s, C-4), 142.7 (s, C-3′), 131.8

(s, C-1), 130.5 (s, C-6′), 128.8 (s, C-1′), 115.6 (s, C-2), 114.3 (d, C-5′), 114.4 (s, C-2′), 114.3 (d, C-6), 112.9 (s, C-3), 70.7 (t, C-7′), 65.5 (t, O$CH_2$$CH_3$), 38.8 (t, C-7), 14.7 (q, OCH$_2$$CH_3$); EIMS *m*/*z* 530, 528, 526, 524 $[M]^+$ (4, 12, 12, 4), 484 (11), 482 (34), 480 (34), 478 (12), 467 (9), 645 (28), 463 (31), 461 (10), 403 (30), 401 (58), 399 (31), 384 (18), 357 (6), 355(17), 353 (7), 322 (100), 320 (97), 393 (15), 391 (15), 242 (56), 213 (33), 184 (24), 161 (32), 160 (35), 139 (25), 121 (51), 58 (80); HREIMS *m*/*z* 523.8466 (calcd for $C_{16}H_{15}{}^{79}Br_3O_5$, 523.8470).

Conversion of 2 into 3. 2 (21 mg) was dissolved in EtOH (5 mL) and refluxed at 60 °C for 72 h. The solution was dried by blowing nitrogen gas to give a residue, which was separated by reversed-phase HPLC using MeOH−H_2O (85: 15) as mobile phase to give a product (6 mg). The TLC, HPLC, and ^{1}H NMR spectral data proved the identity to be **3**.

(±)-2-Methyl-3-(2,3-dibromo-4,5-dihydroxyphenyl)propylaldehyde (4): yellowish gum; IR (KBr) ν_{max} 3386, 2968, 2931, 2873, 1712, 1600, 1576, 1498, 1469, 1406, 1273, 1188, 1014, 930, 856, 814 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 9.70 (1H, d, J = 1.5 Hz, H-1), 6.88 (1H, s, H-6′), 3.18 (1H, dd, J = 13.5, 6.3 Hz, H-3b), 2.74 (1H, m, H-2), 2.66 (1H, dd, J = 13.5, 7.8 Hz, H-3a), 1.07 (3H, d, J = 7.0 Hz, H-4); ^{13}C NMR (acetone-d_6, 125 MHz) δ 203.7 (d, C-1), 144.9 (s, C-5′), 143.4 (s, C-4′), 131.4 (s, C-1′), 117.0 (d, C-6′), 115.8 (s, C-2′), 113.3 (s, C-3′), 46.5 (d, C-2), 37.7 (t, C-3), 12.8 (q, C-4); EIMS *m*/*z* 339, 337, 335 $[M]^+$ (21, 43, 20), 282 (50), 280 (100), 278 (52), 258 (32), 256 (31), 230 (27), 228 (27), 202 (34), 200 (36), 177 (15), 148 (20), 132 (13), 130 (21), 102 (16), 101 (16), 74 (90); HREIMS *m*/*z* 335.8982 (calcd for $C_{10}H_{10}{}^{79}Br_2O_3$ 335.8997).

(±)-2-Methyl-3-(2,3-dibromo-4,5-dihydroxyphenyl)propylaldehyde dimethyl acetal (5): white amorphous powder (Me_2CO); mp 117−118 °C; IR (KBr) ν_{max} 3462, 3064, 2935, 2837, 1600, 1581, 1496, 1454, 1400, 1367, 1334, 1277, 1192, 1174, 1103, 1041, 985, 930, 872, 856, 843 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.83 (1H, s, H-6′), 4.11 (1H, d, J = 5.1 Hz, H-1), 3.35 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 2.96 (1H, dd, J = 13.5, 4.8, H-3b), 2.44 (1H, dd, J = 13.5, 3.6, H-3a), 2.15 (1H, m, H-2), 0.80 (3H, d, J = 6.6 Hz, H-4); ^{13}C NMR (acetone-d_6, 125 MHz) δ 108.5 (d, C-1), 144.7 (s, C-5′), 143.0 (s, C-4′), 133.0 (s, C-1′), 117.0 (d, C-6′), 115.9 (s, C-2′), 113.2 (s, C-3′), 54.0 (q, OCH_3), 53.9 (q, OCH_3), 36.3 (d, C-2), 39.2 (t, C-3), 13.3 (q, C-4); EIMS *m*/*z* 382, 384, 386 $[M]^+$ (23, 47, 24), 354 (4), 352 (10), 350 (5), 321(3), 283 (23), 281 (34), 279 (24), 273 (6), 271 (6), 241 (5), 203 (6), 201 (8), 160(6), 131 (8), 121 (5), 75 (100), 58 (25), 45 (53); HREIMS *m*/*z* 381.9425 (calcd for $C_{12}H_{16}{}^{79}Br_2O_4$ 381.9415).

Conversion of 4 into 5. 4 (12 mg) was dissolved in MeOH (5 mL) and refluxed at 40 °C for 8 h. The solution was dried by blowing nitrogen gas to give a residue, which was separated by reversed-phase HPLC using MeCN−H_2O (85: 15) as mobile phase to give a product (4 mg). The TLC, HPLC, and ^{1}H NMR data showed that it was identical to **5**.

3-Bromo-4,5-dihydroxybenzoic acid methyl ester (6): white amorphous powder (Me_2CO); mp 176−178 °C; IR (KBr) ν_{max} 3425, 3070, 2954, 1685, 1608, 1570, 1496, 1456, 1421, 1338, 1294, 1230, 1161, 1092, 984, 964, 887, 841, 768, 669 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.70 (1H, d, J = 1.8 Hz, H-2), 7.56 (1H, d, J = 1.8 Hz, H-6) and 3.90 (3H, s, OCH_3); ^{13}C NMR (acetone-d_6, 125 MHz) δ 165.5 (s, C-7), 151.2 (s, C-5), 149.1 (s, C-4), 128.0 (s, C-1), 125.3 (d, C-6), 117.5 (d, C-2), 116.8 (s, C-3), 60.2 (q, OCH_3); EIMS *m*/*z* 246, 248 $[M]^+$ (98, 100), 233 (74), 231 (72), 205 (10), 203 (10), 177 (18), 175 (18), 152 (5), 113 (12), 79 (8), 51 (26); HREIMS *m*/*z* 245.9532 (calcd for $C_8H_7{}^{79}BrO_4$ 245.9528).

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