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*.[1] Most of these compounds have important biological activities.[1-4] For example, bromophenols **1** and **2** (Figure 1) exhibit enzyme inhibition,[2a] cytotoxicity,[2b] feeding deterrent,[2c] and microbial[2d,e] activities. Protein tyrosine phosphatase inhibitory activity of bromophenol **1** was also reported.[2f,g]

Monobenzylphenol derivatives 3,4,6-tribromo-5-(2,3-dibromo-4,5-dihydroxybenzyl)benzene-1,2-diol **3** and 3,4,6-tribromo-5-(2,3,6-tribromo-4,5-dihydroxybenzyl)benzene-1,2-diol **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.[3a] On the other hand, antioxidant activity of bromophenol **4** was also noted.[3b] 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).[4] 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.[2f,g]

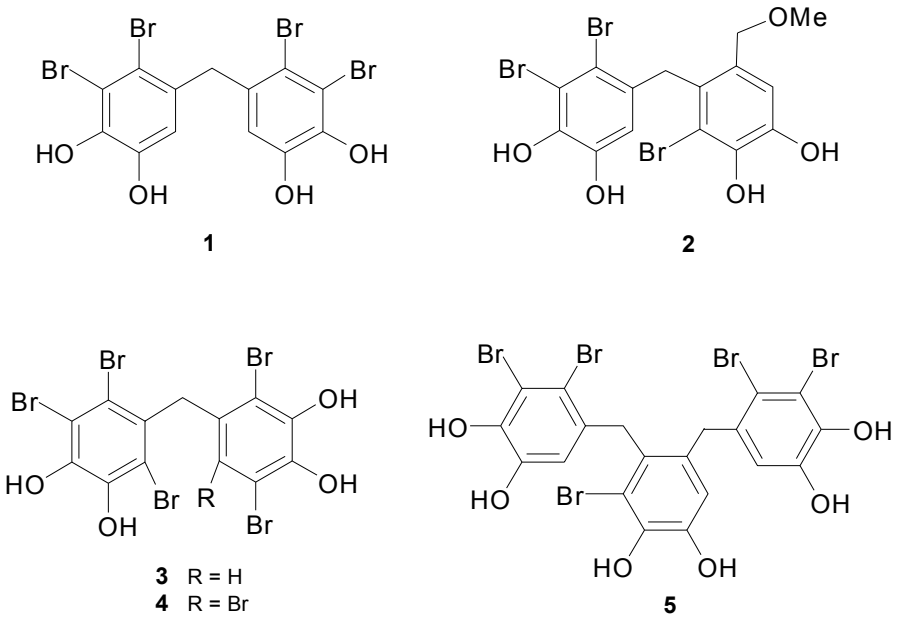
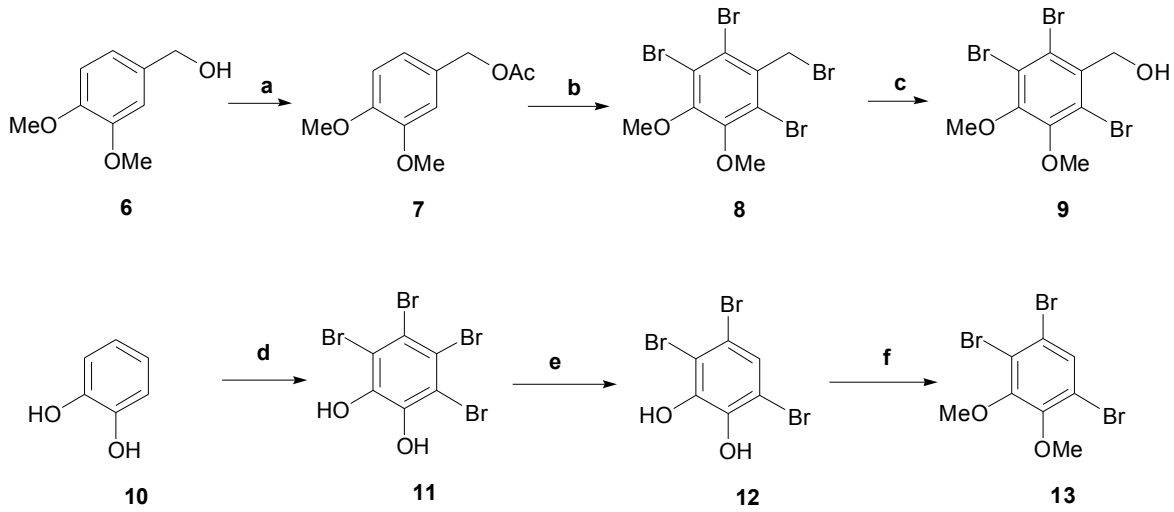


Figure 1. Biologically active natural products, bromophenols.

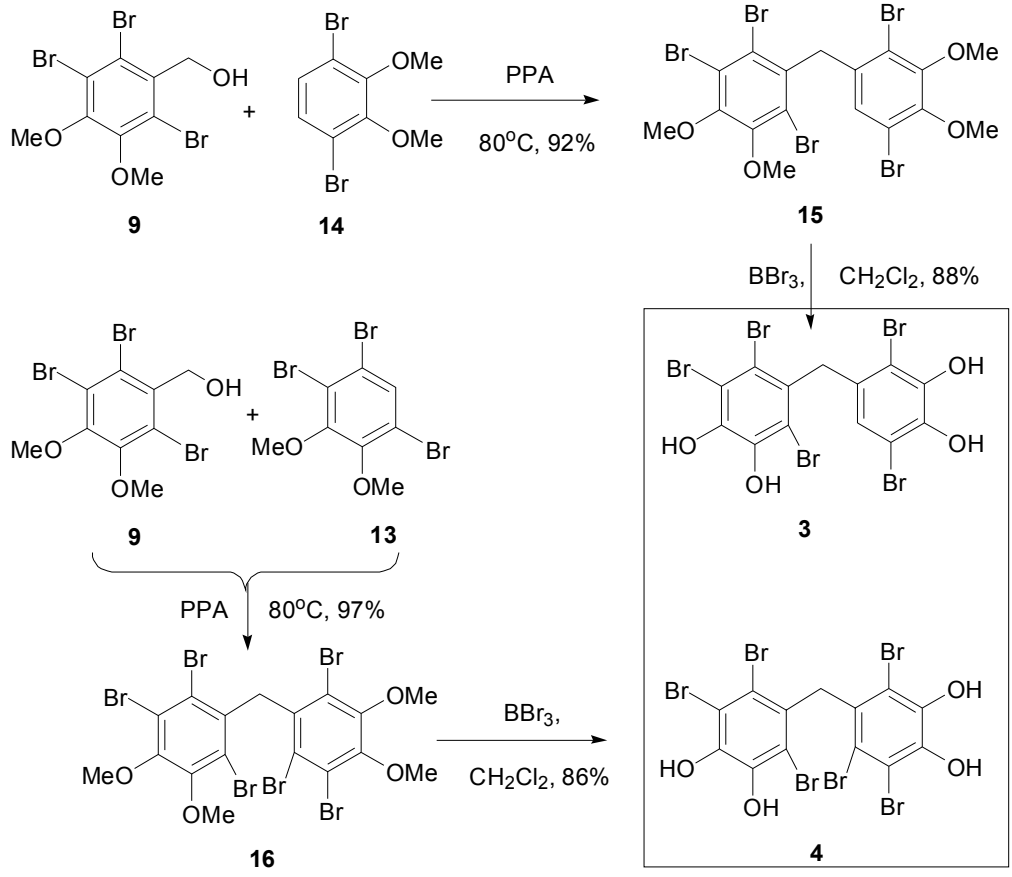
To our knowledge, biologically active natural products, bromophenols **3**, **4** and **5**, have not yet been synthesized. In the present study, we report on the first synthesis of these natural products **3**, **4** and **5**.

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 Ac_2O[5,6](acetic anhydride)/pyridine was performed to give 3,4-dimethoxybenzyl acetate **7** in in high yield. From this acetate **7**, bromoalcohol **9** was synthesized via **8** (Scheme 1).[6] On the other hand, tribromoveratrole **13**[7] 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.



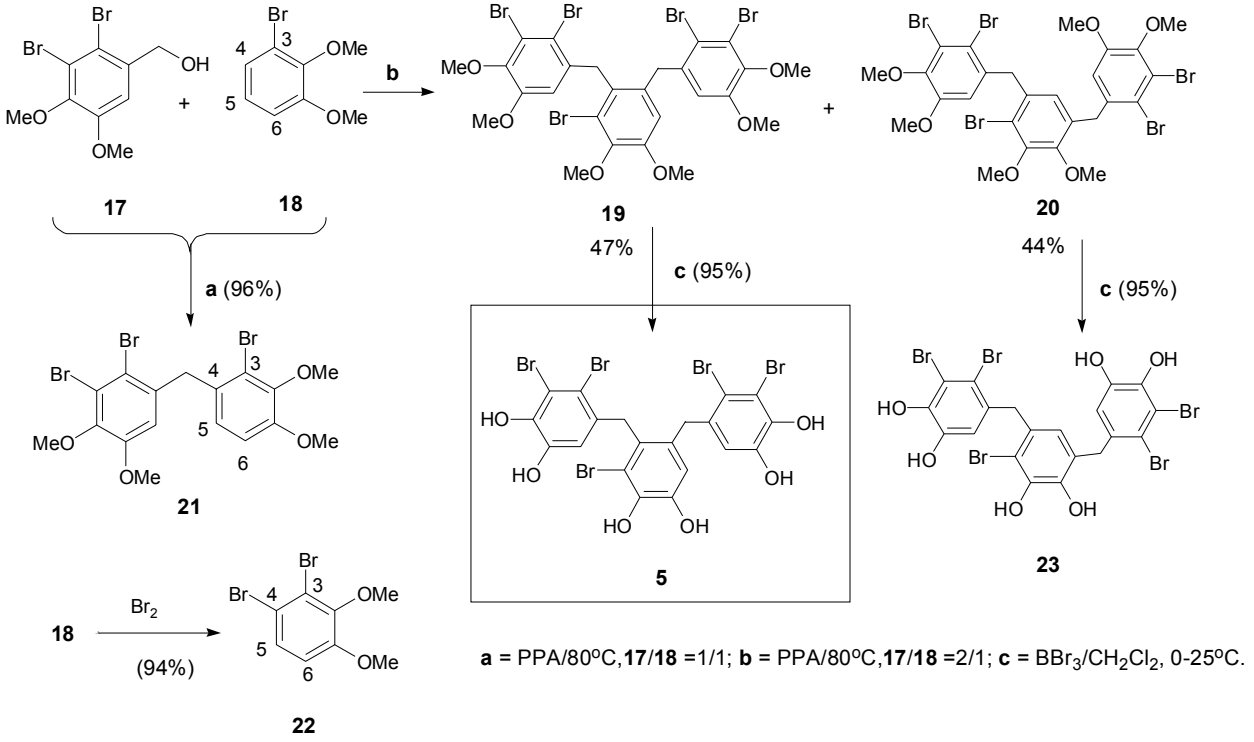
Scheme 1. Synthesis of **9** and **13.** a) Ac_2O/pyridine, 25 ºC, 97%; b)Br_2/Fe, AcOH, 18 %; c) dioxane/water, reflux, 90%; d) Br_2 (8 eq.)/AcOH, 120 ºC, quantitative; e)Zn/AcOH, 120 ºC, 20%; f) $(CH_3)_2SO_4/K_2CO_3$, THF, reflux, 98%.



Scheme 2. Synthesis of biologically active natural products **3** and **4**.

Bromoalcohol **9** was reacted with both **13** to give **16**, and **14**[8] to give **15** in the PPA[9] (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 BBr_3[10] (Scheme 2). Data such as NMR of **3** and **4** were consistent with the literature.[3a] Total yields of **3** and **4** are 13% starting from commercial product **6**.



Scheme 3. Synthesis of biologically active natural product **5** and its derivative **23**.

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**[11] and 1-bromo-2,3-dimethoxybenzene **18**[12] 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

1:1:1:2:2:3:3:3:3:3:3. 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 disubstitution to **18**. Monosubstituted product(s) may provide information about these disubstituted 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 ^{1}H-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 ^{1}H-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 ($C_{26}H_{24}Br_5O_6$) 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).

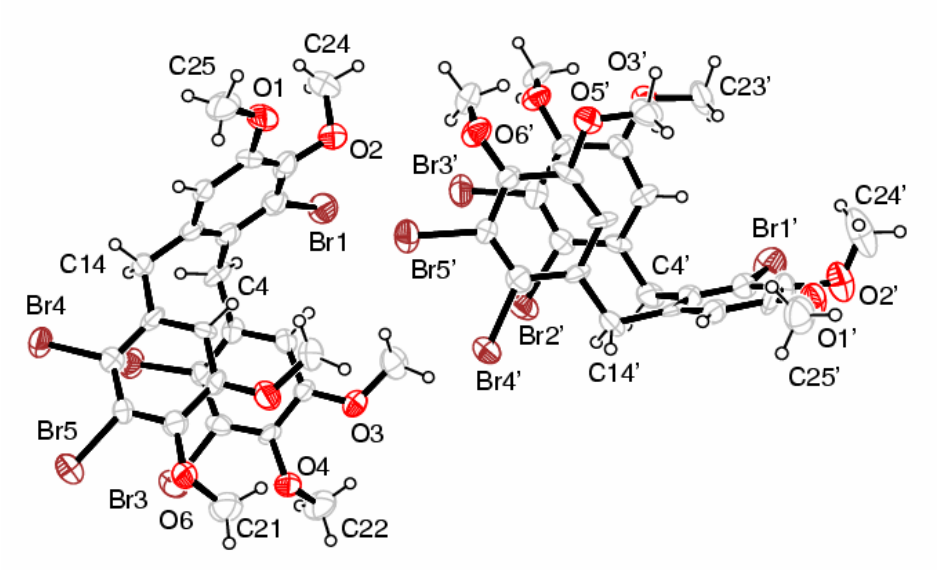


Figure 2. The molecular structure of pentabromide **19.** The asymmetric unit contains half of the molecule. Displacement ellipsoids are shown at the 50% probability level.

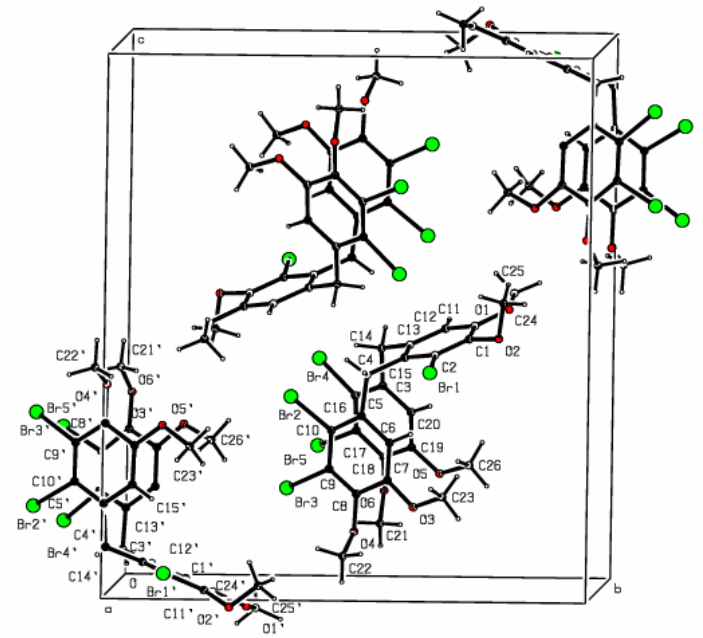


Figure 3. Packing diagram of pentabromide **19** along the *a*-axis.

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_4Si 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_2O (10 mL) by applying a known method.[5,6] The reaction mixture was poured into dilute aqueous HCl (700 mL) with ice and checked with pH paper. It was extracted with CH_2Cl_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**).[7] 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 K_2CO_3 (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 Na_2SO_4, it was filtered and the solvent was evaporated, 1,2,5-tribromo-3,4-dimethoxybenzene (**13**)[7] was obtained as 0.96 g (86%).

3,4,6-Tribromobenzene-1,2-diol (12). Mp 104-106°C (Lit.[7] 106°C); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.38 (s, 1H), 5.86 (s, 2OH); ^{13}C-NMR **(**100 MHz, $CDCl_3$**)** 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); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 3.89 (s, methoxy, 3H), 3.88 (s, methoxy, 3H); ^{13}C-NMR **(**100 MHz, $CDCl_3$**)** δ 152.89 (C), 150.91 (C), 131.66 (CH), 120.91 (C), 120.17 (C), 117.45 (C), 61.17 (2 OCH_3).

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. H_3PO_4 (85%, 0.83 g) and P_2O_5 (1.49 g, 10.5 mmol), was heated to 80°C in a beaker (100 mL). To this mixture were added synthesized **9**[6] (0.59 g, 1.45 mmol) and **14**[8] (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 Na_2SO_4 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; ^{1}H-NMR ($CDCL_3$, 400 MHz**)** δ 6.48 (s, 1H), 4.49 (s, CH_2, 2H), 3.96 (s, methoxy, 3H), 3.93 (s, methoxy, 6H), 3.89 (s, methoxy, 3H); ^{13}C-NMR (100 MHz, $CDCL_3$) 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 (OCH_3), 61.12 (OCH_3), 61.08 (OCH_3), 61.06 (OCH_3), 44.94 (CH_2); IR (CH_2Cl_2, cm^{-1}): 3855, 3445, 2939, 2857, 1639, 1453, 1419, 1386, 1370, 1311, 1282, 1155, 1134, 1062, 1034, 1001, 961, 926, 852, 796, 769, 738, 702, 642, 524; Anal. Calcd for $C_{17}H_{15}Br_5O_4$: 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**[6] (0.5 g, 1.25 mmol), tribromoveratrole **13**[7] (0.46 g, 1.25 mmol), H_3PO_4 (85%, 0.70 g) and P_2O_5 (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; ^{1}H-NMR ($CDCL_3$, 400 MHz**)** δ 4.91 (s, CH_2, 2H), 3.90 (s, methoxy, 6H), 3.87 (s, methoxy, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$), δ 150.82 (C), 150.80 (C), 136.27 (C), 123.50 (C), 122.22 (C), 122.00 (C), 61.19 (OCH_3), 61.02 (OCH_3), 47.86 (CH_2); IR

(CH_2Cl_2, cm^{-1}) 2934, 2854, 1741, 1519, 1452, 1393, 1369, 1311, 1281, 1213, 1156, 1058, 1039, 1011, 963, 943, 910, 878, 824, 766, 699, 527; Anal. Calcd for $C_{17}H_{14}Br_6O_4$: C, 26.81; H, 1.85. Found: C, 26.73; H, 1.86.

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**[11] (2.0 g, 6.13 mmol, 2.0 equivalent), 1-bromo-2,3-dimethoxybenzene **18**[12] (0.67 g, 3.1 mmol, 1.0 equivalent), H_3PO_4 (85%, 3.50 g) and P_2O_5 (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; ^{1}H-NMR **(**400 MHz, $CDCl_3$**)** 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); ^{13}C-NMR **(**100 MHz, APT, $CDCl_3$) δ 152.57 (C), 152.48 (C), 152.45 (C), 146.68 (C), 146.23 (C), 145.80 (C), 136.24 (C), 135.62 (C), 135.44 (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 (2 OCH_3), 60.71 (OCH_3), 56.37 (2 OCH_3), 56.29 (OCH_3), 42.35 (CH_2), 40.71 (CH_2); IR (CH_2Cl_2, cm^{-1}): 2995, 2962, 2936, 2842, 2824, 1583, 1549, 1468, 1422, 1397, 1375, 1309, 1262, 1200, 1057, 1008, 853, 822, 736, 616; Anal. Calcd for $C_{26}H_{25}Br_5O_6$: C, 37.49; H, 3.03. Found: C, 37.44; H, 2.99.

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; ^{1}H-NMR **(**400 MHz, $CDCl_3$**)** 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); ^{13}C-NMR **(**100 MHz, APT, $CDCl_3$**)** δ 152.74 (C), 152.63 (C), 150.76 (C), 150.68 (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), 117.94 (C), 114.02 (2CH), 60.81 (2OCH_3), 60.79 (OCH_3), 60.65 (OCH_3), 56.46 (OCH_3), 56.44 (OCH_3), 43.74 (CH_2), 37.77 (CH_2); IR (CH_2Cl_2, cm^{-1}): 3000, 2962, 293, 2841, 1593, 1549, 1469, 1373, 1310, 1283, 1193, 1162, 1101, 1057, 1039, 1006, 813, 736; Anal. Calcd for $C_{26}H_{25}Br_5O_6$: C, 37.49; H, 3.03. Found: C, 37.48; H, 3.02.

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**[11] (0.50 g, 1.53 mmol, 1.0 equivalent), 1-bromo-2,3-dimethoxybenzene (**18**)[12] (0.33 g, 1.53 mmol, 1.0 equivalent), H_3PO_4 (85%, 0.87 g) and P_2O_5 (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; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.80 (d, J = 8.4 Hz, A part of AB system, aromatic, 1H), 6.67 (d, *J=8.43 Hz*, B part of AB system, aromatic, 1H), 6.57 (s, aromatic, 1H), 4.16 (s,

CH_2, 2H), 3.87 (s, methoxy, 3H), 3.86 (s, methoxy, 3H), 3.84 (s, methoxy, 3H), 3.73 (s, methoxy, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$), 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 (OCH_3), 60.68 (OCH_3), 56.35 (OCH_3), 56.30 (OCH_3), 43.61 (CH_2); IR (CH_2Cl_2, cm^{-1}): 3686, 2992, 2937, 2835, 1592, 1549, 1485, 1469, 1422, 1375, 1284, 1202, 1161, 1059, 1033, 1007, 814; Anal. Calcd for $C_{17}H_{17}Br_3O_4$: C, 38.89; H, 3.26. Found: C, 38.79; H, 3.28.

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 $CHCl_3$ (20 mL) was added dropwise a solution of bromine (0.17 g, 1.1 mmol) in $CHCl_3$ (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 (SiO_2, 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; ^{1}H-NMR (400 MHz, $CDCl_3$): 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); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.01 (C), 128.38 (CH and C), 121.37 (C), 115.99 (C), 112.78 (CH), 60.74 (OCH_3), 56.48 (OCH_3); IR (CH_2Cl_2, cm^{-1}): 3441, 3003, 2937, 2838, 2549, 2069, 1575, 1468, 1427, 1388, 1290, 1258, 1224, 1158, 1134, 1036, 1005, 861, 797, 748, 653, 620, 589, 507; Anal. Calcd ($C_8H_8Br_2O_2$): 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 CH_2Cl_2 (12 mL) was cooled to 0^{o}C and then a solution of BBr_3 (0.5 mL) in CH_2Cl_2 (5.2 mL) was added dropwise under N_2(g) over 5 minutes. After the cold bath was removed, the mixture was stirred at RT and under N_2 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 Na_2SO_4 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^{o}C (lit.[3a] 168-172^{o}C); ^{1}H-NMR (400 MHz, CD_3COCD_3) δ 8.65 (s, 4 OH), 6.25 (s, 1H), 4.42 (s, methylenic, 2H); ^{13}C-NMR (100 MHz, CD_3COCD_3) δ 144.33 (C), 143.04 (C), 143.71 (C), 142.10 (C), 130.68 (C), 130.17 (C), 121.56 (CH), 117.75 (C), 113.40 (2C), 111.61 (C), 108.97 (C), 44.04 (CH_2).

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 BBr_3 was applied. From these reactions, bromophenols **4, 5** and **23** were obtained.

3,4,6-Tribromo-5-(2,3,6-tribromo-4,5-dihydroxybenzyl)benzene-1,2-diol (**4**). Amorphous; (0.564 g, 94%); mp 164-168^{o}C (lit.[3a] 168-172^{o}C); ^{1}H-NMR (400 MHz, CD_3COCD_3) δ 8.65 (s, 4 OH), 4.84 (s, CH_2, 2H); ^{13}C-NMR (100 MHz, CD_3COCD_3) δ 143.30 (2C), 131.15 (C), 117.82 (C), 113.78 (C), 113.63 (C), 46.94 (CH_2).

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) ^{1}H-NMR (400 MHz, CD_3COCD_3) 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); ^{13}C-NMR (100 MHz, CD_3COCD_3) 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 (C), 116.25 (CH), 115.83 (CH), 114.41 (C), 114.27 (CH), 113.34 (C), 113.15 (C), 40.34 (CH_2), 39.48 (CH_2); IR (CH_3OH, cm^{-1}): 3571, 3325, 2967, 2918, 2863, 1594, 1480, 1403, 1276, 1206, 1033; Anal. Calcd for $C_{20}H_{13}Br_5O_6$: 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; ^{1}H-NMR (400 MHz, $CDCl_3$) 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); ^{13}C-NMR (100 MHz, $CDCl_3$) 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 (CH_2), 36.95 (CH_2); IR (CH_3OH, cm^{-1}): 3571, 3467, 3391, 2973, 2918, 2863, 2835, 2313, 1594, 1472, 1405, 1273, 1183, 1055, 1033, 857; Anal. Calcd for $C_{20}H_{13}Br_5O_6$: 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 K_α radiation (λ=0.71073 Å) and oscillation scans technique with $\Delta\omega$=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 $F^2>2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement were performed using CrystalClear (Rigaku/MSC Inc., 2005) software.[13] The structures were solved by direct methods using SHELXS-97[14] 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 [U_{iso}(H)=1.2U_{eq}(C) and U_{iso}(H)=1.5U_{eq}(methyl C)]. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data for* pentabromide **19**: $C_{26}H_{25}Br_5O_6$, 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)Å^3; Z'=4; calculated density: 1.97 mg/m^3; 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 F^2; data/parameters: 11455/668; goodness-of-fit on F^2: 1.278; final R indices

[$I>2\sigma(I)$]: R_1= 0.098, wR_2=0.157; R indices (all data): R_1=0.227, wR_2=0.178; largest diff. peak and hole: 0.609 and -0.582 e $Å^{-3}$; CCDC- 743502.

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