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GRAPHICAL ABSTRACT

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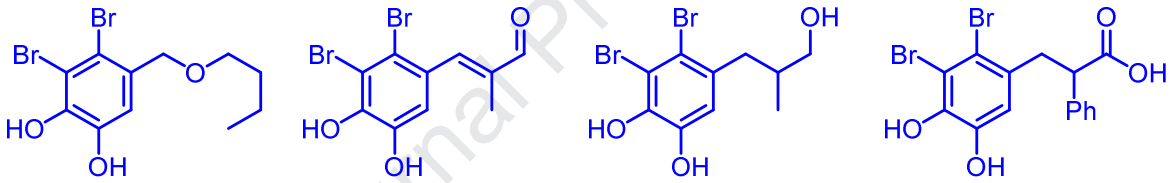

The first synthesis of phenylpropanoid derivative bromophenols including natural products: Formation of an indene derivative compound

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Abstract: ~~The first s~~ Synthesis of the natural bromophenols 3,4-dibromo-5-(butoxymethyl)benzene-1,2-diol, (E)-3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-methylacrylaldehyde (**7**), 3,4-dibromo-5-(3-hydroxy-2-methylpropyl)benzene-1,2-diol and 3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-phenylpropanoic acid is reported for the first time. An indene-derived compound (**12**) was formed during ~~the~~ attempts to synthesize ~~of~~ the bromophenol **7**. The formation of compound **12** is discussed.

Keywords: $AlCl_3$, bromination, condensation, indene-derived compound, natural bromophenol.

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1. Introduction

Many bromophenols including natural products exhibit important biological activities such as antioxidant[1-4], cytotoxicity[5], glucose 6-phosphate dehydrogenase[6], carbonic anhydrase[7-9], feeding deterrent[10], aldose reductase inhibitory[11], antiviral[12] and anticancer activities[13]. The natural bromophenol compounds **1-9** were isolated from marine life such as the red algae *Rhodomela confervoides* and *Symphyocladia latiuscula* (Figure 1)[1,3,5,6,14,15]

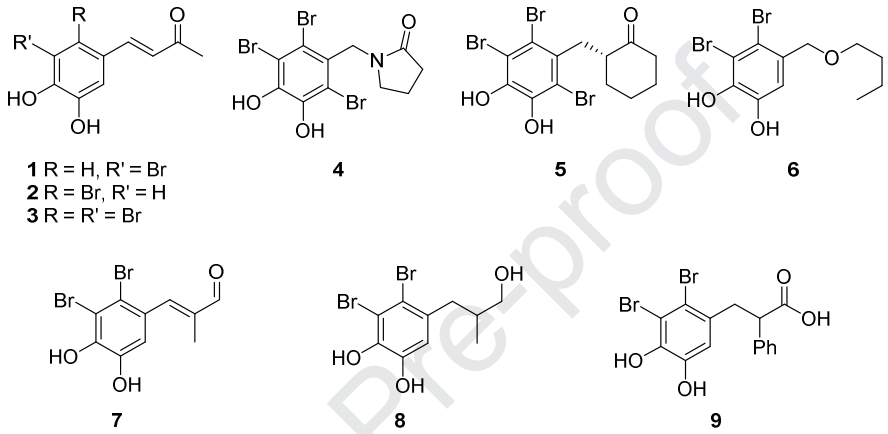


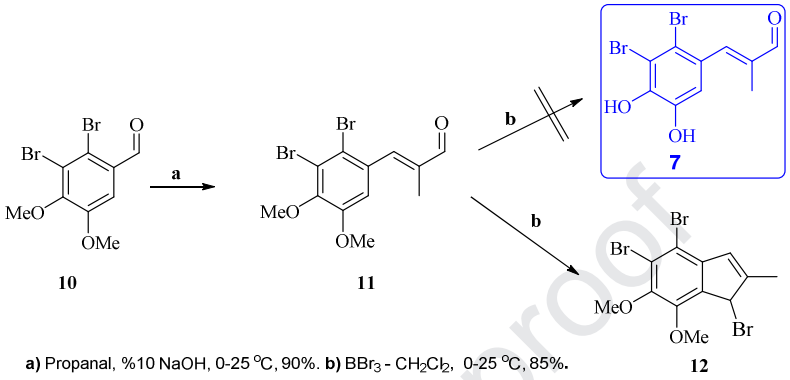
Figure 1. Some biologically active natural bromophenols.

We reported the first synthesis of many bromophenols including natural bromophenols[8,7,16-22]. To the best of our knowledge, there are no reports on the synthesis of the bromophenols **6-9** having biological activities[3,5,6,15] ~~have not yet been synthesized. In this work~~ Herein, the ~~first~~ synthesis of these natural products **6-9** is reported for the first time.

2. Results and Discussion

The groups on the benzene rings of natural bromophenols **6-9** are the same while other parts of them are different. For the synthesis of these bromophenols and their derivatives, our method involves the prepar~~ing~~ation of aromatic rings including the corresponding groups and then connecting them to the corresponding compounds. In addition to the synthesis of natural bromophenols, synthesis of their derivatives was also planned because they may have biological activities. Firstly, the aldehyde **10** was prepared from the starting material vanillin by the previously published methods[8,7,19-24]. Then condensation product **11** was obtained from the reaction of benzaldehyde derivative **10** with propanal at room temperature (RT) [25].

For the synthesis of the natural bromophenol **7**, a demethylation reaction with BBr_3 of compound **11** was performed because demethylation of the aryl methyl ethers was ~~done~~ previously achieved with BBr_3 [7,8,19-22] (Scheme 1). However, instead of the expected natural bromophenol **7**, a different product was obtained from this reaction (Scheme 1).

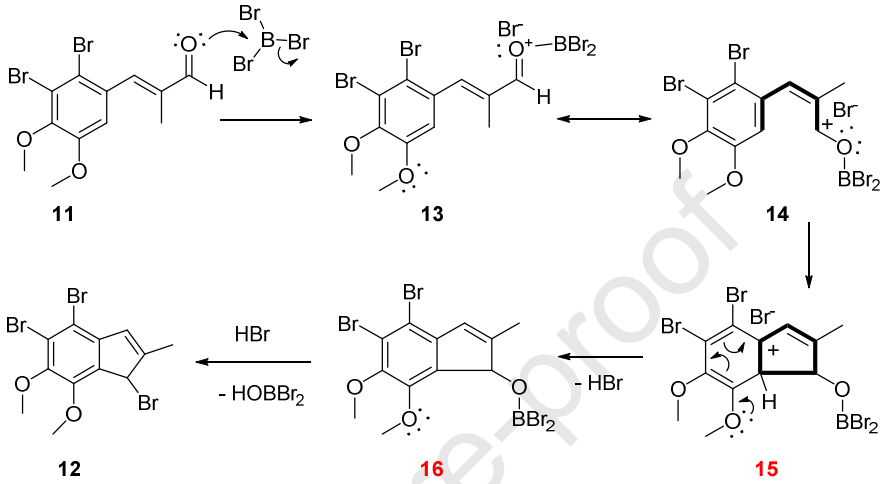


Scheme 1. An attempt to synthesize compound and the formation of indene derivative 12.

~~When~~ Examination of the ^{1}H-NMR spectrum of the product ~~was investigated~~, revealed five singlet peaks at 6.51, 5.29, 4.07, 3.85 and 2.13 ppm ~~were found~~. None of these singlets should belong to the hydrogen of the aldehyde group because they are present in the higher areas. The last three (at 4.07, 3.85 and 2.13 ppm) should belong to OMe, OMe and Me groups, respectively. The singlet peaks at 6.51 and 5.29 ppm in the ^{1}H-NMR spectrum should belong to CH, and these CH groups should resonate at 128.75 and 48.40 ppm in the ^{13}C-NMR spectrum. In the ~~^{1}H- and~~ ^{13}C-NMR spectrum, there is an aromatic or olefinic CH resonating at 128.75 ppm. ~~Therefore, the product should be indene derivative **12.**~~ The h~~H~~ydrogen ~~(CHBr)~~ resonating at 5.29 ppm should be CHBr because it is both benzylic and allylic. Therefore, the product should be indene derivative **12**. The Br in the CHBr may be a OH such as CHOH. However, the chemical shift of the CH ~~hydrogen~~ in this CHOH should be at a field lower than at 48.40 ppm in the ^{13}C-NMR spectrum. The HRMS spectrum of **12** also confirm the structure as (M-H) calcd. For $C_{12}H_{10}{}^{79}Br_3O_2$: 422.8231; Found: 422.8285.

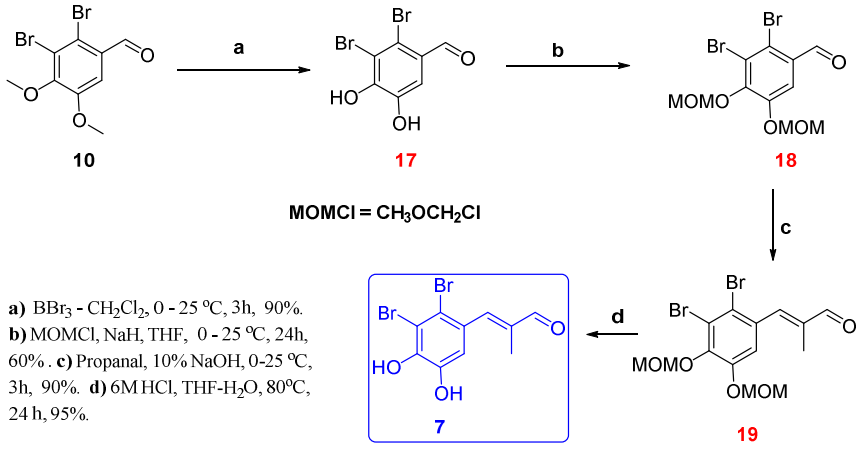
For the formation of indene derivative **12**, we can propose the mechanism in Scheme 2. The first interaction is between the oxygen atom of the aldehyde group in **11** and the Lewis acid BBr_3. Structure **14** is a resonance structure~~s~~ of the ~~formed~~ intermediate formed **13**. By electrophilic aromatic substitution, intermediate ~~**19**~~ **16** may be obtained from **14** ~~or **16**~~ via ~~**18**~~ **15**. Benzylic OH or its derivatives are converted to benzylic bromides in the reaction medium with BBr_3 [16-22]. The nucleophilic substitution reaction of intermediate ~~**19**~~ **16** with Br^- gives indene derivative **12**. ~~In~~ For the formation of indene derivative **12**, an electrocyclic ring closure reaction may also be considered as an alternative. ~~way~~[26] ~~(Sankararaman 2005)~~. When a part~~s~~ of ~~the~~ structure~~s~~ ~~**14** and **15**~~ is thought of as a pentadienyl cation (4nπ), it may be converted to ~~**17**~~ **15** ~~,~~

~~whose structure is the resonance structure of **18**~~ by conrotatory ring closure. It was reported that cinnamic aldehyde derivatives were converted into the corresponding indene derivatives in the presence of $BF_3.OEt_2/CH(OMe)_3$,[27] $FeCl_3/CH(OMe)_3$,[28] $FeCl_3/Ac_2O$[29] and $AlCl_3$[30] by electrophilic aromatic substitution.



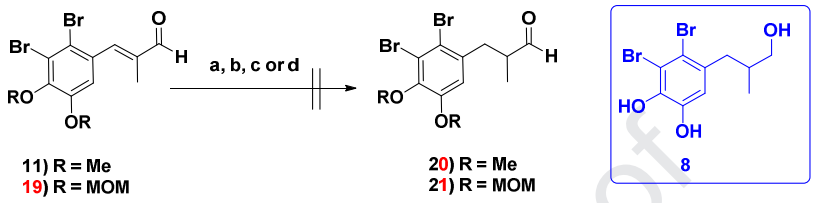
Scheme 2. The mechanism for the formation of compound 12.

Another way was considered for the synthesis of the natural product **7**. Aromatic OMOM groups such as aromatic OMe are stable in basic medium and they are obtained by reactions of OH groups with MOMCl (methoxymethylchloride). The known[31] aldehyde **18** was obtained from reactions of compound **10** with BBr_3 and MOMCl, consecutively, via **17**. After aldehyde **18** ~~with propanal~~ was allowed to react~~ed~~ with propanal in basic medium, hydrolysis of the product formed, ~~product~~ **19** in acidic medium afforded the natural bromophenol **7** (Scheme 3).



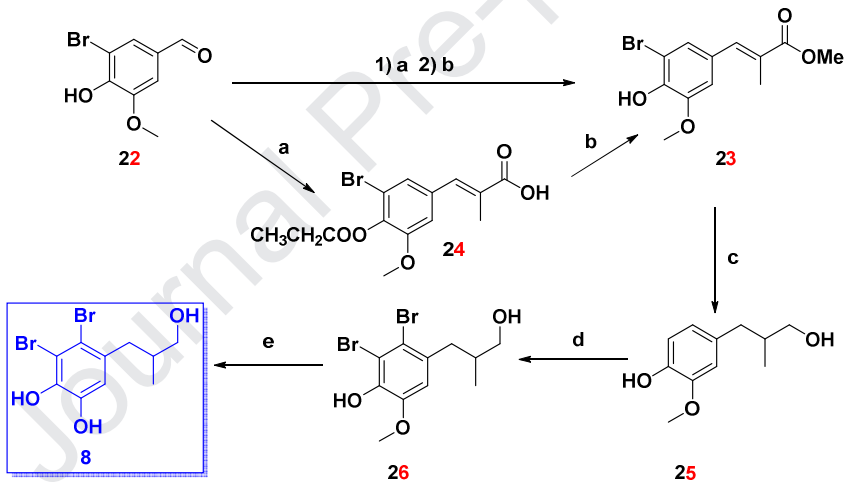
Scheme 3. Synthesis of the natural bromophenol 7.

In the synthesis of the other natural product compound **8**, reduction of the α,β-unsaturated aldehyde groups in compounds **11** or **19** to saturated aldehyde groups is important. Therefore, it was attempted to reduce ~~induce~~ compounds **11** or **19** using the reducing agents mentioned in the literature[32-34] (Scheme 4). However, neither compound **20** nor **21** was obtained from these reactions.



a) $NiCl_2$. 6 H_2O / $NaBH_4$ / H_2O / MeOH / 0-25 ° C. **b)** NH_2NH_2. H_2O / EtOH / Reflux. **c)** Me_3SiCl / NaI / H_2O / Hexane / rt or Reflux **d)** HCl or HBr / CH_2Cl_2 (or MeOH, HOAc) / RT. **e)** $LiAlH_4$ $AlCl_3$ / THF Reflux

Scheme 4. Attempts to synthesize the natural bromophenol 8.



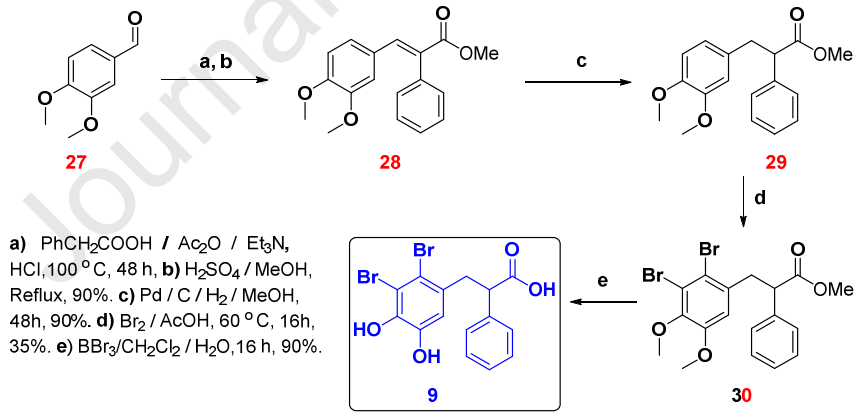
a) Et_3N, $(CH_3CH_2CO)_2O$, 24h, Reflux. **b)** MeOH / H_2SO_4, Reflux. 24 h, 92%. **c)** Na / t-BuOH-THF, 24h, Reflux, 77% **d)** Br_2/ $CHCl_3$, Darkness, rt, 24h, 83% **e)** BBr_3/ CH_2Cl_2, rt, 24h, 73%

Scheme 5. Synthesis of the natural bromophenol 8.

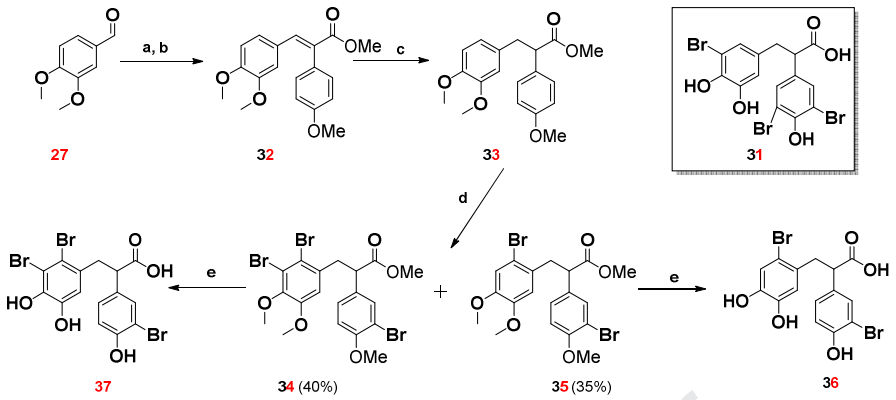
For the synthesis of the natural bromophenol **8**, another method was also considered. For this, aldehyde **22**, propionic anhydride and triethylamine (NEt_3) were mixed (at RT for 10 min), and then the mixture was refluxed (for 4h), cooled (0 °C) and refluxed with H_2SO_4 (catalytic) in MeOH. Ester **23** was obtained from these reactions via acid **24** because the corresponding acid such as intermediate **24** occurs ~~in~~ during these reactions ~~as an intermediate **20.** (Buckles and Bremer 1963)~~ (Scheme 5). Aldehyde **22** was used rather than vanillin in the reaction because of both the rate and yield of the reaction. Reduction of ester **23** with metallic Na and *tert*-butyl alcohol (*t*-BuOH) in tetrahydrofuran (THF) gave

product **25** having OMe, and two OH (aromatic and aliphatic) groups by Birch reduction[35-37]. Compound **25** was treated ~~reacted~~ with molecular bromine (Br_2) in $CHCl_3$ and compound **26** was obtained. Electron-rich benzene rings rapidly give an aromatic electrophilic substitution reaction with Br_2[16-24]. Reaction of the product **26** with BBr_3 in CH_2Cl_2 gave the natural bromophenol **8** (Scheme 5).

The natural bromophenol **9** is a saturated acid with two benzene rings, one of which has two OH and two Br groups. Reduction of the double bonds of the α,β-unsaturated carbonyl groups in **11** and **19** could not be carried out. Therefore, our method ~~is stated as (i), (ii), and (iii)~~ for the synthesis of **9** was as follows: (i) The s~~S~~tarting material ~~from~~ was a corresponding aromatic aldehyde including OMe groups in the case of OH groups; (ii) ~~C~~condensation of this aldehyde was performed with phenyl acetic acid ~~and~~ followed by esterification with MeOH; (iii) ~~C~~catalytic hydrogenation,[38]~~,~~ bromination, and demethylation of product formed were conducted consecutively. ~~(iv) Substitution of Br atoms into the aromatic ring; (v) Demethylation.~~ The condensation of **27** with phenyl acetic acid, conversion of intermediate acid to ester **28**, reduction of ester **28** with catalytic hydrogen, bromination of **29** with molecular bromine and demethylation of dibromide **30** with BBr_3 were carried out, consecutively (Scheme 6). The natural bromophenol **9** was synthesized as a result of these reactions.



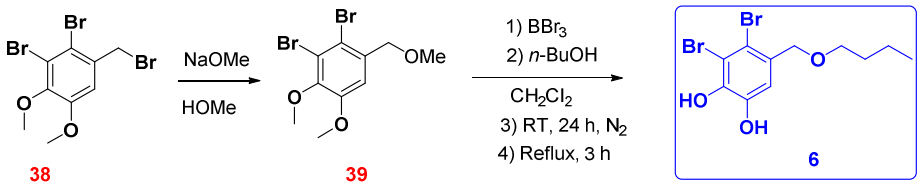
Scheme 6. Synthesis of the natural bromophenol 9.



a) *p*-OMe-PhCH$_2$COOH-Ac$_2$O/Et$_3$N, HCl, 100 °C, 56 h, **b)** H_2SO_4 / MeOH, Reflux, 85%. **c)** Pd/ C / H_2 - MeOH, 24 h, 94%. **d)** Br_2/ AcOH, 60 °C, Darkness, 24 h, 35-40%. **e)** BBr_3/ CH_2Cl_2-H_2O, 24 h, 86-90%.

Scheme 7. Synthesis of derivatives 36 and 37 ~~belonging to~~ of the natural bromophenol 31.

Synthesis of the antioxidant natural bromophenol **31**[39] and its derivatives is important because to the best of our knowledge it ~~is not known to the best of our knowledge~~ has not been reported. Similar to the synthesis of compound **29**, ester **33** was synthesized from the starting material aldehyde **27** via **32**. The reaction of ester **33** with molecular bromine (2.0 equiv.) in AcOH in darkness gave the products **34** and **35**. The presence of an AB system (as d and dd) in the aromatic regions of both products also indicates that there is a Br in the ortho position of OMe in rings with single OMe. Demethylation of compounds **34** and **35** with BBr_3 gave bromophenols in high yield as derivatives **36** and **37** of natural bromophenol **31**. In the bromination of ester **33** because of the directions of groups in the aromatic rings, compound **35** should be formed first, and then compound **34** should be formed from **35**. A precursor compound of natural bromophenol **31** should not occur in the bromination of ester **33** due to these reactions. A derivative whose structure has a *tert*-butyl (*t*-Bu) group at the para (p) position of OMe in the ring with two OMe groups as auxiliary groups of ester **33** may be synthesized. Probably, the precursor compound will occur in this bromination. However, we have not attempted to synthesize the precursor compound yet.



Scheme 8. Synthesis of the natural bromophenol 6.

The natural product **6**, an ether, is an inhibitor of glucose 6-phosphate dehydrogenase enzyme[6]. The synthesis of the natural product **6** may be planned from reactions of the benzyl bromide derivative **38** with n-butanol or n-buthoxide and BBr_3. This method was not used because benzyl ether is unstable in the reactions of BBr_3[19]. For the synthesis of natural bromophenol **6**, compound **39** was prepared (from the reaction of **38** with MeO) and reacted with BBr_3 in CH_2Cl_2 under N_2 for 10 min at 0 °C. Then the mixture was refluxed with *n*-BuOH for 3 h and the natural bromophenol **6** was purified by column chromatography (Scheme 8).

3. Conclusion

~~In conclusion, t~~The first synthesis of natural bromophenol compounds **6-9** ~~were~~ was successfully realized from the corresponding reactions. The reaction of α,β-unsaturated aldehyde compound **11** with BBr_3 gave the indene derivative **12**. ~~According t~~To the best of our knowledge, synthesis of an indene derivative from the reaction of α,β-unsaturated aldehyde such as **11** with BBr_3 ~~is~~ has not ~~known~~ be reported previously. The formation of an indene-derivative in the presence of BBr_3 is a new reaction. ~~This should be a new reaction.~~ ~~Also~~ Moreover, ~~the~~ compounds **36** and **37** which ~~is~~ are derivatives of natural product **31** were synthesized.

4. Experimental section

4.1. General Experimental Procedures

The solvents were purified and dried by known methods. For all compounds, values as well as M.p, IR spectra, ^1H and ^{13}C NMR spectra, chemical shift and elemental analyses were obtained as explained previously[22,40]. Preparative thick-layer chromatography was used with 1 mm of silica gel 60 PF (Merck, Darmstadt, Germany) on glass plates. HRMS data were obtained by LC-MS-TOF electrospray ionization (1200/6210, Agilent).

4.1.1. Experimental Text (E)-3-(2,3-Dibromo-4,5-dimethoxyphenyl)-2-methylacrylaldehyde (11).

A solution of the aldehyde **10** (3.0 g, 9.30 mmol) in a mixture of EtOH (50 mL) and THF (5 mL) was cooled at 0 °C using an ice-water bath, and cold propanal (0.64 g, 11.16 mmol, < 0 °C,) and solution of NaOH (10%, 0 °C, 10 mL) were slowly added. After the reaction mixture was stirred for 30 min at 0 °C, the cold bath was removed and the mixture was stirred for 24 h. The solvent was removed under vacuum and the crude product was extracted with EtOAc (2 × 30 mL). The combined extracts were dried over Na_2SO_4 and the solvent was removed in the evaporator. ~~under vacuum.~~ The residue was purified by column chromatography on silica gel (10 g) using EtOAc/hexane (2:8) eluent. Compound **11** (2.41 g, 90%) was obtained as a yellow solid. M.p: 110-113 °C; R_f = 0.32 EtOAc/Hexane (1:9); IR (CH_2Cl_2, v_{max} cm^{-1}): 2922, 1681, 1583, 1466, 1378, 1302, 1264, 1206, 1191, 1072; ^1H-NMR (400 MHz, $CDCl_3$): 9.66 (s, CHO, 1H), 7.40 (s, 1H), 6.92 (s, 1H), 3.89 (s, OCH_3, 3H), 3.88 (s, OCH_3, 3H), 1.93 (s, CH_3, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): 194.77 (CO), 152.62 (C), 148.86 (CH), 148.38 (C), 139.79 (C), 131.88 (C), 122.04 (C), 117.41 (C), 112.87 (CH), 60.61 (OCH_3), 55.96 (OCH_3), 10.56 (CH_3); Elemental Anal. Calcd (%) for $C_{12}H_{12}Br_2O_3$: C 39.59, H 3.32. Found: C 40.03, H 3.33.

4.1.2. (1R)-1,4,5-Tribromo-6,7-dimethoxy-2-methyl-1H-indene (12).*

A solution of compound **11** (1.0 g, 2.74 mmol) in CH_2Cl_2 (10 mL) under N_2 gas was cooled to 0 °C using an ice-water bath and BBr_3 (1.38 g, 5.49 mmol) was added by the aid of a syringe. The resulting mixture was allowed to stir under N_2 for 10 min at 0 °C. After removal of the cold bath, ~~was removed,~~ the mixture was stirred for 10 h at RT and cooled

again to 0 °C. MeOH (10 mL) was added dropwise and then the solvent was removed in the evaporator. ~~under vacuum.~~ The crude product was extracted with EtOAc (2 × 25 mL). The combined extracts were dried over Na_2SO_4 and the solvent was removed in the evaporator. ~~under vacuum.~~ Compound **12** (997 mg, 85%) was obtained as a black solid. M.p: 125-127 °C; R_f = 0.71 EtOAc/Hexane (1:9); IR (CH_2Cl_2, v_{max} cm^{-1}): 2923, 2848, 1459, 1398, 1320, 1266, 1199, 1116, 1042, 967; ^{1}H-NMR (400 MHz, $CDCl_3$): 6.51 (s, 1H), 5.29 (s, CHBr, 1H). 4.07 (s, OCH_3, 3H), 3.85 (s, OCH_3, 3H), 2.13 (s, CH_3, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): 149.64 (C), 148.10 (2 C), 140.75 (C), 135.55 (C), 128.75 (CH), 122.24 (C), 111.29 (C), 60.94 (OMe), 60.80 (OMe), 48.40 (CH_2Br) 14.52 (CH_3); Elemental Anal. Calcd (%) for $C_{12}H_{11}Br_3O_2$: C 33.76, H 2.60. Found: C 33.61, H 2.61. HRMS: m/z (M-H) calcd. For $C_{12}H_{10}{}^{79}Br_3O_2$: 422.8231; Found: 422.8285.

4.1.3. (E)-3-(2,3-Dibromo-4,5-bis(methoxymethoxy)phenyl)-2-methylacrylaldehyde (19).

The standard procedure described for the synthesis of **11** was performed for this reaction. ~~Prepared~~ [31] ~~t~~The ~~P~~prepared compound **18**[31] (2.0 g, 5.2 mmol), propanal (0.30 g, 5.2 mmol) and NaOH (10%, 0 °C, 10 mL) were used and the product **19** (2.0 g, 90%) was obtained as a white solid. M.p: 42-44 °C; R_f = 0.17 EtOAc/Hexane (1:9); IR (CH_2Cl_2, v_{max} cm^{-1}): 2916, 2824, 1686, 1541, 1455, 1369, 1285, 1156, 1092; ^{1}H-NMR (400 MHz, $CDCl_3$): 9.64 (s, CHO, 1H), 7.36 (s, 1H), 7.24 (s, 1H), 5.24 (s, OCH_2, 2H), 5.20 (s, OCH_2, 2H), 3.66 (s, OCH_3, 3H), 3.48 (s, OCH_3, 3H), 1.91 (s, CH_3, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): 195.42 (CO), 149.58 (C), 148.59 (CH), 145.97 (C), 139.85 (C), 132.72 (C), 122.81 (C), 119.73 (C), 116.93 (CH), 98.62 (OCH_2), 95.80 (OCH_2), 57.97 (OCH_3), 56.41 (OCH_3), 10.84 (CH_3); Elemental Anal. Calcd (%) for $C_{14}H_{16}Br_2O_5$: C 39.65, H 3.80. Found: C 39.49, H 3.79.

4.1.4. (E)-3-(2,3-Dibromo-4,5-dihydroxyphenyl)-2 methylacrylaldehyde (7): Standard procedure for the demethylation.

To a solution of compound **19** (0.5 g, 1.17 mmol) in THF (10 mL)~~,~~ was added HCl (3.0 M, 2.0 mL) ~~was added~~. After the solution was stirred ~~in~~ at 80 °C for 24 h, the reaction mixture was cooled to RT and the solvent was removed in the evaporator. ~~under vacuum.~~ H_2O (10 m~~l~~L) and EtOAc (10 mL) ~~was~~ were added and the mixture extracted with EtOAc (2 ×~~x~~ 25 mL). The combined extracts were dried over Na_2SO_4 and the solvent was removed in the evaporator. ~~under vacuum.~~ Natural product **7** (443 mg, 95%) was obtained as a yellow solid. M.p: 158-160 °C ~~[~~(138-140 °C) [41]~~]~~. ^{1}H-NMR (400 MHz, Acetone-d_6): 9.65 (s, CHO, 1H), 9.30 (bs, aromatic OH, 1H), 8.88 (bs, aromatic OH, 1H), 7.44 (s, 1H), 7.17 (s, 1H), 1.86 (s, CH_3, 3H); ^{13}C-NMR (100 MHz, Acetone-d_6): 195.41 (CO), 148.93 (CH), 145.70 (C), 144.61 (C), 139.11 (C), 127.52 (C), 116.59 (C), 115.75 (CH), 113.38 (C), 10.15 (CH_3); HRMS: m/z (M-H) calcd. For $C_{10}H_7{}^{79}Br^{81}BrO_3$: 334.8741; Found: 334.8750.

4.1.5. Methyl (E)-3-(3-bromo-4-hydroxy-5-methoxyphenyl)-2-methylacrylate (23): Standard procedure for methyl ester of condensed product.

A mixture of compound **22** (1.00 g, 4.33 mmol), NEt_3 (4.0 mL) and propionic anhydride (6.0 mL) was ~~added~~ prepared. After the mixture was stirred in 80 °C for 4 h and the reaction was stopped, the reaction mixture was cooled at 0 °C and HCl (18%, 8.0 mL) and H_2O (20 mL) were added. Then, the reaction mixture was stirred for 1h more at RT and extracted with CH_2Cl_2 (2 ×~~x~~ 50 mL). The combined extracts were dried over Na_2SO_4 and the solvent was removed under vacuum. After MeOH (10 mL) and a catalytic amount of p-toluene sulfonic acid (HOTs, 5.0 mg) were added, the mixture was refluxed for 24 h and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed in the evaporator. ~~under vacuum.~~ The residue was purified by column chromatography on silica gel (10 g) using EtOAc/hexane (4:6) as eluent. Compound **23** (1.05 g, 92%) was obtained as a white solid. M.p: 90-92 °C;

R_f = 0.39 EtOAc/Hexane (2:8); IR (CH_2Cl_2, v_{max} cm^{-1}): 2951, 2846, 1709, 1575, 1501, 1417, 1342, 1285, 1253, 1115; ^1H NMR (400 MHz, $CDCl_3$): 7.53 (s, 1H), 7.18 (s, 1H), 6.83 (s, 1H), 6.12 (s, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.23 (CO), 147.21 (C), 143.55 (C), 137.80 (CH), 129.07 (C), 127.73 (C), 126.59 (CH), 111.66 (CH), 108.52 (C), 56.59 (OMe), 52.37 (OMe), 14.34 (CH_3); HRMS: m/z (M-H) calcd. For $C_{12}H_{12}{}^{81}BrO_4$: 300.9898; Found: 300.9920.

~~After the mixture stirring at 80 ° C for 4 h and the reaction cooling at 0 °C,~~

4.1.6. (E)-3-(3-Bromo-5-methoxy-4-(propionyloxy)phenyl)-2-methylacrylic acid (24).

A mixture of compound **22** (0.6 g, 2.6 mmol), NEt_3 (4.0 mL) and propionic anhydride (6.0 mL) was ~~added~~ prepared. After the mixture was stirred at ~~in~~ 80 °~~e~~C for 4 h and ~~the reaction was~~ cooled ~~at~~ to 0 °~~e~~C, HCl (18%, 8.0 mL) and H_2O (20 mL) were added. Then~~,~~ the reaction mixture was stirred for 1 h more at RT ~~as addition~~ and extracted with CH_2Cl_2 (2 ×~~x~~ 30 mL). The combined extracts were dried over Na_2SO_4 and the solvent was removed in the evaporator.~~ under vacuum.~~ The compound **24** (0.81 g, 91%) was obtained as a white solid. M.p: 140-142 °~~e~~C; R_f = 0.33 EtOAc/Hexane (2:5); IR (CH_2Cl_2, v_{max} cm^{-1}): 3435, 2923, 1770, 1675, 1568, 1487, 1450, 1413, 1272, 1128, 1047, 952; ^1H NMR (400 MHz, $CDCl_3$): 7.71 (s, 1H), 6.92 (s, 1H), 3.84 (s, OMe, 3H), 2.68 (q, CH_2, J = 7.5 Hz, 2H), 2.15 (s, CH_3, 3H), 1.32 (t, CH_3, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.64 (CO), 171.34 (CO), 152.33 (C), 139.14 (CH), 138.12 (C), 134.87 (C), 128.91 (C), 125.63 (CH), 117.40 (C), 112.72 (CH), 56.31 (OMe), 27.30 (CH_2), 13.76 (CH_3), 9.16 (CH_3); Elemental Anal. Calcd (%) for $C_{14}H_{15}BrO_5$: C 49.00, H 4.41. Found: C 48.83, H 4.43.

4.1.7. (2R*)-4-(3-Hydroxy-2-methylpropyl)-2-methoxyphenol (25).

To a stirred solution of compound **23** (2.0 g, 6.64 mmol) in THF (50 mL) was added metallic Na (1.53 g, 66.42 mmol) in small ~~pieces~~ amounts over ~~a period of~~ 10 min~~ute~~ at RT, and then a solution of *t*-BuOH (4.~~,~~92 g, 66.~~,~~42 mmol) in THF (120 m~~l~~L) was slowly added. After the mixture was refluxed for 24 h, it was stopped, cooled at RT, and excess ~~of~~ sodium in the reaction mixture was filtered off. The mixture was cooled ~~at~~ to 0 °~~e~~C and EtOH (25 mL) was slowly and carefully added for neutralization. After the removal of solvent, ~~and then~~ solution of HCl (3%, 25 mL) was slowly added, the mixture was extracted with EtOAc (2 × 20 mL), the combined organic extracts were dried over Na_2SO_4 and the solvent was removed in the evaporator.~~ under vacuum.~~ Purification of the residue on silica gel (20 g) by column chromatography eluting with EtOAc/hexane (1/4) gave compound **25** (1.00 g, 77%) as a yellow solid. M.p: 70-72 °~~e~~C; R_f = 0.32 EtOAc/Hexane (2:5); IR (CH_2Cl_2, v_{max} cm^{-1}): 3434, 2075, 1516, 1463, 1376, 1271, 1126, 1033; ^1H NMR (400 MHz, $CDCl_3$): 6.81 (d, A part of AB system, J = 8.0 Hz, 1H), 6.69–6.58 (m, 2H, ArH), 6.03 (bs, OH, 1H), 3.81 (s, OCH_3, 3H), 3.51 (dd, A part of AB system J = 10.6, 6.0 Hz, 1H), 3.45 (dd, B part of AB system J = 10.6, 6.1 Hz, 1H), 2.67 (dd, A part of AB system, J = 13.6, 6.2 Hz, 1H), 2.32 (dd, B part of AB system J = 13.6, 8.1 Hz, 1H), 2.13–1.76 (m, 1H), 0.89 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 146.72 (C), 143.94 (C), 132.78 (C), 121.94 (CH), 114.53 (CH), 112.02 (CH), 67.80 (CH_2OH), 56.09 (OMe), 39.60, 38.11, 16.69 (CH_3); HRMS: m/z (M) calcd. For $C_{11}H_{16}O_3$: 196.1099; Found: 196.1102.

4.1.8. (2R*)-3-(2,3-Dibromo-4-hydroxy-5-methoxyphenyl)-2-methylpropanoic acid (26): Standard procedure for bromination.

To a solution of compound **25** (400 mg, 2.04 mmol) in $CHCl_3$ (15 mL) at RT~~,~~ was added molecular bromine (716.61 mg, 4.48 mmol) ~~was added in the lightless medium~~ darkness. After the reaction mixture was stirred ~~at~~ under the same

conditions for 24 h and volatile compounds ~~was~~ were removed in the evaporator ~~under vacuum.~~, the residue was purified by column chromatography on silica gel (10 g) using EtOAc/hexane (1:4) as eluent. Compound **26** (600 mg, 83%) was obtained as a brown liquid. R_f = 0.17 EtOAc/Hexane (2:5); IR (CH_2Cl_2, v_{max} cm^{-1}): 3434, 2083, 1487, 1396, 1270, 1193, 1059; ^{1}H NMR (400 MHz, $CDCl_3$): 6.68 (s, 1H), 3.83 (s, OCH_3, 3H), 3.53 (dd, A part of AB system, J = 10.7, 5.5 Hz, 1H), 3.48 (dd, B part of AB system J = 10.7, 5.8 Hz, 1H), 2.89 (dd, A part of AB system J = 13.6, 6.5 Hz, 1H), 2.52 (dd, B part of AB system, J = 13.6, 8.0 Hz, 1H), 2.06-1.93 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 146.08 (C), 142.89 (C), 133.13 (C), 118.03 (C), 112.55 (CH), 112.45 (C), 67.51 (CH_2O), 56.72 (OMe), 41.29, 36.69, 16.66 (CH_3); Elemental Anal. Calcd (%) for $C_{11}H_{14}Br_2O_3$: C 37.32, H 3.99. Found: C 37.16, H 3.97.

4.1.9. (2R*)-3,4-Dibromo-5-(3-hydroxy-2-methylpropyl)benzene-1,2-diol (8).

This reaction was performed according to the standard procedure described ~~in~~ for the synthesis of natural bromophenol **7**. In the reaction, compound **29** (0.20 g, 0.56 mmol), CH_2Cl_2 (10 mL) and BBr_3 (311.35 mg, 1.24 mmol) were used. The residue was purified by column chromatography on silica gel (10 g) using MeOH/CH_2CI_2 (3:97) as eluent. Natural product **8** (140 mg 73%) was obtained as a yellow gum ~~brown liquid~~; ~~[~~(~~G~~gummy) [41]~~]~~. ^{1}H NMR (400 MHz, Acetone-d_6): 9.05-7.98 (m, 2H), 6.86 (s, 1H), 3.77 (s, 1H), 3.58–3.31 (m, 2H), 2.87 (dd, A part of AB system, J = 13.4, 6.1 Hz, 1H), 2.49 (dd, B part of AB system J = 13.4, 8.0 Hz, 1H), 2.08-2.05 (m, 1H), 0.92 (d, CH_3, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, Acetone-d_6): 145.41 (C), 143.57 (C), 134.07 (C), 117.64 (CH), 116.62 (C), 113.89 (C), 67.11 (CH_2O), 41.45 (CH_2), 37.38 (CH), 16.85 (CH_3); HRMS: m/z (M-H) calcd. For $C_{10}H_{11}{}^{79}Br^{81}BrO_3$: 338.9054; Found: 338.9060.

4.1.10. Methyl (E)-3-(3,4-dimethoxyphenyl)-2-phenylacrylate (28).

The standard procedure described for the synthesis of **23** was performed for this reaction. Compound **27** (1.0 g, 12.04 mmol), NEt_3 (4.0 mL), acetic anhydride (6.0 mL) and phenyl acetic acid (1.64 g, 12.04 mmol) were used in this reaction~~s~~, and ~~the~~ compound **28** (2.75 g, 90%) was obtained as a yellow liquid; R_f = 0.60 EtOAc/Hexane (2:5); IR (CH_2Cl_2, v_{max} cm^{-1}): 2839, 2065, 1635, 1510, 1464, 1248, 1143, 1024; ^{1}H NMR (400 MHz, $CDCl_3$): 7.80 (s, olefinic, 1H), 7.44–7.38 (m, 2H), 7.36–7.31 (m, 1H), 7.28–7.23 (m, 2H), 6.83 (dd, A part of AB system, J = 8.4, 2.1 Hz, 1H), 6.71 (d, B part of AB system, J = 8.4 Hz, 1H), 6.39 (d, J = 2.1 Hz, 1H), 3.81 (s, OCH_3, 3H), 3.76 (s, OCH_3, 3H), 3.36 (s, OCH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.62 (CO), 150.24 (C), 148.40 (C), 140.74 (C) 140.68 (CH), 136.78 (C), 130.17 (CH), 129.05 (CH), 127.93 (CH), 127.57 (CH), 125.85 (C), 112.46 (CH), 110.70 (CH), 55.97 (OCH_3), 55.27 (OCH_3), 52.48 (OCH_3); Elemental Anal. Calcd (%) for $C_{18}H_{18}O_4$: C 72.47, H 6.08. Found: C 72.21, H 6.07.

4.1.11. (2R*)-Methyl 3-(3,4-dimethoxyphenyl)-2-phenylpropanoate (29).

To a solution of compound **28** (2.0 g, 6.7 mmol) in MeOH (60 mL) was added Pd-C (5.0 mg) ~~was added~~. After the air in the flask was evacuated under vacuum and hydrogen gas was sent into the flask,~~.~~ ~~T~~the reaction mixture was stirred for 48 h at RT. After the reaction was complete, the catalyst (Pd-C) was filtered off and the solvent was evaporated. Compound **29** (1.80 g, 90%) was obtained as a yellow liquid; R_f = 0.41 EtOAc/Hexane (1:5); IR (CH_2Cl_2, v_{max} cm^{-1}): 2953, 2928, 2852, 1735, 1516, 1465, 1264, 1238, 1157, 1029; ^{1}H NMR (400 MHz, $CDCl_3$): 7.33-7.28 (m, 5H), 6.74 (d, A part of AB system, J = 8.2 Hz, 1H), 6.67 (dd, B part of AB system, J = 8.2, 1.7 Hz, 1H, ArH), 6.56 (d, J = 1.7 Hz, 1H), 3.82 (s, OCH_3, 3H), 3.82–3.78 (m, CH, 1H). 3.76 (s, OCH_3, 3H), 3.61 (s, OCH_3, 3H), 3.35 (dd, A part of AB system, J = 13.7, 8.5 Hz, CH_2, 1H), 2.98 (dd, B part of AB system, J = 13.7, 7.0 Hz, CH_2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 174.13 (CO), 148.80 (C), 147.75 (C), 138.78 (C), 131.81 (C), 128.85 (CH), 128.26 (CH), 127.58 (CH), 121.12 (CH), 112.49 (CH),

111.32 (CH), 56.03 (OCH_3), 55.93 (OCH_3), 54.09 (OCH_3), 52.21 (CH), 39.71 (CH_2); Elemental Anal. Calcd (%) for $C_{18}H_{20}O_4$: C 71.98, H 6.71. Found: C 72.25, H 6.71.

4.1.12. (R*)-Methyl 3-(2,3-dibromo-4,5-dimethoxyphenyl)-2-phenylpropanoate (30).

To a solution of compound **29** (0.5 g, 1.66 mmol) in AcOH (10 mL) was added molecular bromine (665 mg, 4.16 mmol) ~~was added~~ in ~~the lightless medium~~ darkness. After the reaction mixture was stirred at 60 °~~e~~C for 16 h and was cooled to RT, H_2O (20 m~~l~~L) was added, and the mixture was extracted with EtOAc (2 × 30 m~~l~~L). The combined organic extracts were dried over Na_2SO_4, the solvent was removed in the evaporator. ~~under vacuum~~ and the residue was purified by column chromatography on silica gel (20 g) using EtOAc/hexane (1:9) as eluent. Compound **30** (265 mg, 35%) was obtained as yellow liquid; R_f = 0.35 EtOAc/Hexane (1:9); IR (CH_2Cl_2, v_{max} cm^{-1}): 2939, 2845, 1735, 1584, 1550, 1470, 1423, 1378, 1308, 1261, 1200, 1163, 1060, 1007; ^{1}H NMR (400 MHz, $CDCl_3$): 7.36–7.22 (m, 5H), 6.57 (s, 1H), 3.97 (dd, J = 8.5, 6.6 Hz, CH, 1H), 3.80 (s, OCH_3, 3H), 3.67 (s, OCH_3, 3H), 3.62 (s, OCH_3, 3H), 3.55 (dd, A part of AB system, J = 13.6, 8.5 Hz, 1H), 3.13 (dd, B part of AB system, J = 13.6, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.66 (CO), 152.21 (C), 146.54 (C), 138.51 (C), 135.72 (C), 128.98 (CH), 128.11 (CH), 127.75 (CH), 121.95 (C), 117.70 (C), 114.68 (CH), 60.70 (OCH_3), 56.27 (OCH_3), 52.34 (OCH_3), 51.19 (CH), 42.15 (CH2); Elemental Anal. Calcd (%) for $C_{18}H_{18}Br_2O_4$: C 47.19, H 3.96. Found: C 47.05, H 3.98.

4.1.13. (R*)-3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-phenylpropanoic acid (9).

This reaction was performed according to the standard procedure described ~~in~~ for the synthesis of natural bromophenol **7**. ~~The c~~Compound **30** (0.3 g, 0.65 mmol), BBr_3 (492 mg, 1.96 mmol) and CH_2Cl_2 (15 m~~l~~L) were used, and natural product **9** (245 mg, 90%) was obtained as a white solid. M.p: 122-124 °~~e~~C; ~~[~~(brown gum)[15] ~~(Zhao et al 2004)]~~; ^{1}H NMR (400 MHz, Acetone-d_6): 11.25-10.50 (m, OH, 1H), 8.74 (s, OH, 1H), 8.19 (s, OH, 1H), 7.47–7.20 (m, 5H), 6.78 (s, 1H), 3.99 (dd, J = 8.9, 6.1 Hz, CH, 1H), 3.44 (dd, A part of AB system, J = 13.8, 8.9 Hz, CH_2, 1H), 3.07 (dd, B part of AB system, J = 13.8, 6.1 Hz, CH_2, 1H); ^{13}C NMR (100 MHz, Acetone-d_6): 173.50 (CO), 144.63 (C), 143.38 (C), 139.35 (C), 131.36 (C), 128.79 (CH), 128.04 (CH), 127.47 (CH), 117.10 (CH), 117.02 (C), 115.97 (C), 51.29 (CH), 41.18 (CH_2); HRMS: m/z (M-H) calcd. For $C_{15}H_{11}{}^{79}Br_2O_4$: 412.9024; Found: 412.9042.

4.1.14. (E)-Methyl 3-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylate (32).

The standard procedure described for the synthesis of **23** and **24** was performed for this reaction. Compound **27** (1.0 g, 6.02 mmol), triethylamine (4.0 mL), acetic anhydride (6.0 mL), ~~and~~ *p*-methoxyphenylacetic acid (1.0 g, 6.02 mmol), and a catalytic amount of *p*-toluene sulfonic acid (HOTs, 5.0 mg) ~~was~~ were used and compound **32** (1.24 g, 85%) was obtained as a yellow solid. M.p: 68-70 °~~e~~C; R_f = 0.30 EtOAc/Hexane (1:5); IR (CH_2Cl_2, v_{max} cm^{-1}): 2952, 2835, 1705, 1643, 1512, 1427, 1337, 1248, 1146, 1090, 1025; ^{1}H NMR (400 MHz, $CDCl_3$): 7.75 (s, 1H), 7.16 (d, AA' part of AA'BB' system, J = 8.5 Hz, 2H), 6.93 (d, BB' part of AA'BB' system, J = 8.4 Hz, 2H), 6.81 (d, A part of AB system, J = 6.5 Hz, 1H), 6.70 (d, B part of AB system, J = 8.4 Hz, 1H), 6.47 (bs, 1H), 3.81 (s, OMe, 3H), 3.79 (s, OMe, 3H), 3.76 (s, OMe, 3H), 3.44 (s, OMe, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.85 (CO), 159.40 (C), 150.12 (C), 148.38 (C), 140.51 (CH), 131.38 (CH), 129.89 (C), 128.74 (C), 127.80 (C), 125.53 (CH), 114.50 (CH), 112.66 (CH), 110.73 (CH), 55.96 (OMe), 55.48 (OMe), 55.35 (OMe), 52.44 (OMe). HRMS: m/z (M) calcd. For $C_{19}H_{20}O_5$: 328.1311; found: 328.1312.

4.1.15. (R*)-Methyl 3-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)propanoate (33).

The standard procedure described for the synthesis of **29** was performed for this reaction. Compound **32** (0.4 g, 6.7 1.22 mmol), MeOH (50 mL), Pd-C (5.0 mg) and H_2 gas were used. Compound **33** (380 mg, 94%) was obtained as a white solid. M.p: 60-72 °°C; R_f = 0.32 EtOAc/hexane (1:5); IR (CH_2Cl_2, v_{max} cm^{-1}): 2999, 2952, 2836, 1735, 1610, 1513, 1465, 1259, 1157, 1030; ^{1}H NMR (400 MHz, $CDCl_3$): 7.20 (d, AA' part of AA'BB' system, J = 8.6 Hz, 2H), 6.82 (d, BB' part of AA'BB' system, J = 8.6 Hz, 2H), 6.72 (d, A part of AB system, J = 8.2 Hz, 1H), 6.64 (dd, B part of AB system J = 8.2, 1.7 Hz, 1H), 6.56 (bs, 1H), 3.90-3.75 (m, 1H), 3.80 (s, OMe, 3H), 3.76 (s, OMe, 3H), 3.74 (s, OMe, 3H), 3.58 (s, OMe, 3H), 3.31 (dd, A part of AB system, J = 13.7, 8.5 Hz, 1H), 2.93 (dd, B part of AB system, J = 13.7, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 174.36 (CO), 159.09 (C), 148.80 (C), 147.71 (C), 131.90 (C), 130.93 (C), 129.25 (CH), 121.13 (CH), 114.20 (CH), 112.49 (CH), 111.31 (CH), 56.00 (OMe), 55.92 (OMe), 55.40 (OMe), 53.17 (OMe), 52.10 (CH), 39.75 (CH_2); Elemental Anal. Calcd (%) for $C_{19}H_{22}O_5$: C 69.07, H 6.71. Found: C 69.05, H 6.70.

4.1.16. Bromination of compounds 33.

The standard procedure described for the synthesis of **30** was performed for this reaction. Compound **33** (0.4 g, 1.21 mmol), AcOH (15 mL) and Br_2 (619.15 mg, 3.87 mmol) were used, and compound **34** (279 mg, 40%) was obtained as a yellow solid ~~and~~ as well as compound **35** (208 mg, 35%)~~ were obtained~~.

4.1.17. (2R*)-Methyl 2-(3-bromo-4-methoxyphenyl)-3-(2,3-dibromo-4,5-dimethoxyphenyl)propanoate (34).

M.p: 86-88 °°C; R_f = 0.35 EtOAc / Hexane (1.5:8.5); IR (CH_2Cl_2, v_{max} cm^{-1}): 2082, 1639, 1497, 1470, 1284, 1258, 1163, 1056; ^{1}H NMR (400 MHz, $CDCl_3$): 7.51 (d, J = 2.2 Hz, 1H), 7.16 (dd, A part of AB system, J = 8.5, 2.2 Hz, 1H), 6.82 (d, B part of AB system, J = 8.5 Hz, 1H), 6.62 (s, 1H), 3.91 (dd, A part of AB system, J = 8.8, 6.5 Hz, 1H), 3.86 (s, OMe, 3H), 3.81 (s, OMe, 3H), 3.72 (s, OMe, 3H), 3.62 (s, OMe, 3H), 3.49 (dd, A part of AB system, J = 13.6, 8.8 Hz, 1H), 3.10 (dd, B part of AB system, J = 13.6, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.42 (CO), 155.53 (C), 152.28 (C), 146.64 (C), 135.53 (C), 132.69 (CH), 132.04 (C), 128.35 (CH), 121.95 (C), 117.71 (C), 114.65 (CH), 112.18 (CH), 112.04 (C), 60.73 (OMe), 56.51 (OMe), 56.33 (OMe), 52.50 (OMe), 49.97 (CH), 42.05 (CH_2); HRMS: m/z (M) calcd. For $C_{19}H_{19}{}^{79}Br_3O_5$: 563.8783; Found: 563.8773.

4.1.18. (2R*)-Methyl 3-(2-bromo-4,5-dimethoxyphenyl)-2-(3-bromo-4-methoxyphenyl)propanoate (35).

M.p: 97-99 °°C; R_f = 0.28 EtOAc/Hexane (1:5); IR (CH_2Cl_2, v_{max} cm^{-1}): 2925, 2850, 1734, 1602, 1498, 1463, 1440, 1384, 1260, 1219, 1056; ^{1}H NMR (400 MHz, $CDCl_3$): 7.54 (bs, 1H), 7.17 (dd, A part of AB system, J = 8.4, 1.9 Hz, 1H). 6.98 (s, 1H), 6.81 (d, B part of AB system J = 8.4 Hz, 1H), 6.55 (s, 1H), 3.91-385 (m, 1H), 3.86 (s, OMe, 3H), 3.83 (s, OMe, 3H), 3.73 (s, OMe, 3H), 3.62 (s, OMe, 3H), 3.37 (dd, A part of AB system, J = 13.7, 8.7 Hz, 1H), 3.02 (dd, B part of AB system J = 13.6, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.45 (CO), 155.23 (C), 148.30 (C), 147.98 (C), 132.55 (CH), 131.99 (C), 129.79 (C), 128.18 (CH), 115.47 (CH), 114.36 (C), 114.15 (CH), 111.90 (CH), 111.75 (C), 56.25 (OMe), 56.09 (OMe), 55.95 (OMe), 52.12, 50.22, 39.81 (s); Elemental Anal. Calcd (%) for $C_{19}H_{20}Br_2O_5$: C 46.75, H 4.13. Found: C 46.65, H 4.12.

4.1.19. (2R*)-Methyl 3-(2-bromo-4,5-dihydroxyphenyl)-2-(3-bromo-4-hydroxyphenyl)propanoate (36).

This reaction was performed according to the standard procedure described ~~in~~ for the synthesis of the natural bromophenol **7**. Compound **35** (0.2 g, 409.69 µmol), BBr_3 (410.55 mg, 1.64 mmol), and CH_2Cl_2 (15 m~~l~~L) were used and compound **36** (154 mg, 86%) ~~were~~ was obtained as a brown liquid; R_f = 0.57 CH_2Cl_2/MeOH (9:1); IR (CH_2Cl_2, v_{max} cm^{-1}):

3243, 2924, 1704, 1602, 1495, 1469, 1274, 1179; ^{1}H NMR (400 MHz, Acetone-d_6): 7.53 (d, J = 1.9 Hz, 1H), 7.20 (dd, A part of AB system, J = 8.4, 2.0 Hz, 1H), 7.04 (s, 1H), 6.98 (d, B part of AB system, J = 8.4 Hz, 1H), 6.75 (s, 1H), 3.94 – 3.89 (m, 1H), 3.31 (dd, A part of AB system, J = 13.8, 8.6 Hz, 1H), 2.98 (dd, B part of AB system J = 13.8, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, Acetone-d_6): 174.77 (CO), 154.10 (C), 145.70 (C), 145.41 (C), 133.12 (CH), 132.76 (C), 130.13 (C), 129.31 (CH), 119.94 (CH), 118.92 (CH), 117.34 (CH), 113.53 (C), 110.40 (C), 51.07, 39.93; Elemental Anal. Calcd (%) for $C_{15}H_{12}Br_2O_5$: C 41.70, H 2.80. Found: C 41.61, H 2.81; HRMS: m/z (M-H) calcd. For $C_{15}H_{11}{}^{79}Br_2O_5$: 428.8973; Found: 428.9009.

4.1.20. (2R*)-Methyl 3-(2-bromo-4,5-dihydroxyphenyl)-2-(2,3-dibromo-4-hydroxyphenyl)propanoate (37).

This reaction was performed according to the standard procedure described ~~in~~ for the synthesis of natural bromophenol **7**. Compound **34** (0.3 g, 529.~~,~~04 µmol), BBr_3 (530.~~,~~14 mg, 1.~~,~~12 mmol) and CH_2Cl_2 (15 m~~l~~L) were used and compound **37** (244 mg, 90%) was obtained as a brown liquid; R_f = 0.46 CH_2Cl_2/MeOH (9:1); IR (CH_2Cl_2, v_{max} cm^{-1}): 3373, 2928, 1705, 1603, 1578, 1495, 1471, 1407, 1358, 1275, 1180, 1045; ^{1}H NMR (400 MHz, Acetone-d_6): 8.87 (bs, 2H), 8.25 (bs, 1H), 7.52 (s, 1H), 7.18 (d, A part of AB system, J = 8.3 Hz, 1H), 6.96 (d, B part of AB system, J = 8.3 Hz, 1H), 6.77 (s, 1H), 3.96–3.80 (m, 1H), 3.40 (dd, A part of AB system, J = 13.8, 8.6 Hz, 1H), 3.04 (dd, B part of AB system, J = 13.8, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, Acetone-d6): 173.73 (CO), 153.48 (C), 144.70 (C), 143.37 (C), 132.38 (CH), 131.97 (C), 131.11 (C), 128.58 (CH), 117.06 (CH), 116.66 (CH), 116.01 (C), 113.20 (C), 109.73 (C), 50.10, 41.16; Elemental Anal. Calcd (%) for $C_{15}H_{11}Br_3O_5$: C 35.26, H 2.17. Found: C 35.17, H 2.15; HRMS: m/z (M-H) calcd. For $C_{15}H_{11}{}^{79}Br_3O_5$: 506.8078; Found: 506.8095.

4.1.21. Natural bromopheol 3,4-dibromo-5-(butoxymethyl)benzene-1,2-diol (6).

This reaction was performed according to the standard procedure described ~~in~~ for the synthesis of the natural bromophenol **7**. Compound **39** (0.4 g, 1.~~,~~18 mmol), BBr_3 (589.~~,~~44 mg, 2.~~,~~35 mmol), CH_2Cl_2 (15 m~~l~~L) and *n*-BuOH (5.0 mL) were used, and natural product **6** (130 mg 31%) was obtained as a pale brown liquid; ~~[~~(yellow liquid)[6]~~]~~; R_f = 0.45; MeOH / CH_2Cl_2 (2:98); ^{1}H NMR (400 MHz, $CDCl_3$): 6.97 (s, 1H,), 6.50-6.30 (m, OH, 1H), 6.10-5.90 (m, OH, 1H), 4.48 (s, benzyl CH_2, 2H), 3.56 (t, J = 6.7 Hz, CH_2, 2H), 1.69–1.58 (m, CH_2, 2H), 1.47–1.34 (m, CH_2, 2H), 0.92 (t, J = 7.4 Hz, CH_3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 143.67 (C), 141.65 (C), 131.53 (C), 115.64 (CH), 114.84 (C), 113.58 (C), 73.32 (OCH_2), 71.20 (OCH_2), 31.86 (CH_2), 19.57 (CH_2), 14.16 (CH_3); HRMS: m/z (M-H) calcd. For $C_{11}H_{13}{}^{79}Br_2O_3$: 350.9231; Found: 350.9231.

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Supplementary Material: Experimental and NMR spectra of synthesized compounds are available in the supplementary material, which are cited in the appropriate place in the text. https:

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Highlights

1- The first synthesis of biological active natural bromphenols by good yields were realized.

2- Inden-derivative **12** was synthesized from reaction of BBr_3 with benzne ring bearing OMe, Br and conjugated aldehyde moiety. Formation reaction of a indene derivative during demethylation with BBr_3 is new.

3- The first synthesis of bromophenols **36** and **37**, isomers of 3-(3-bromo-4,5-dihydroxyphenyl)-2-(3,5-dibromo-4-hydroxyphenyl)propanoic acid (**31**), were also realized.