Chemical and *In Vitro* Syntheses of Brominated and Chlorinated 3,4'-Dihydroxybibenzyls (Halogenated Lunularins)

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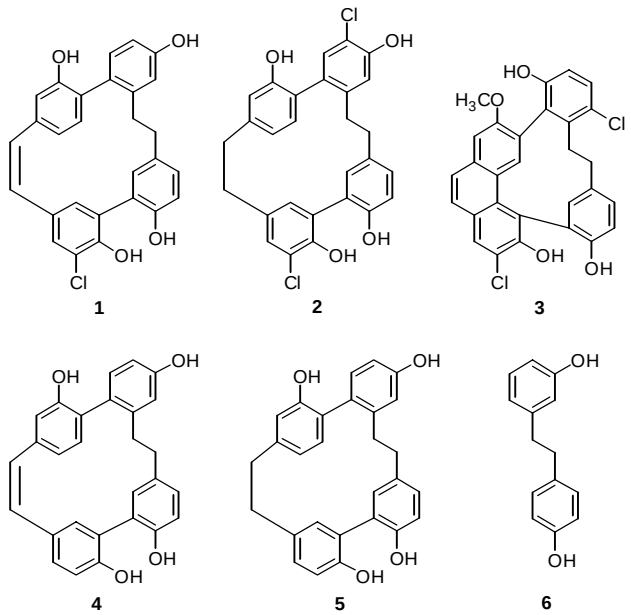
Abstract. Ten halogenated lunularins **16**, **17**, **26**, **27**, **30**, **31**, **36**, **37**, **42** and **43** as model substances for a new class of halometabolites isolated from bryophytes are prepared by chemical total syntheses according to a Wittig-protocol using halogenated aldehydes and phosphonium salts and/or by an *in vitro* halogenation of lunularin using potassium halide and hydrogen peroxide in the presence of a chloroperoxidase. The results confirm the need for a haloperoxidase in the *in vitro* chlorination of lunularin **6**.

The number of halogenated natural products isolated from different living beings has strongly increased during the last years [1]. Most of these metabolites with a broad structural diversity are found in marine organisms like algae and invertebrates (sponges, molluscs, worms) [2]. Halometabolites from bacteria (*e.g.* chloramphenicol, chlortetracyclin) [3] and fungi (*e.g.* griseofulvin) [4] exhibit high therapeutic significance. Halogenated compounds from higher plants are less numerous although they were detected in all plant divisions (ferns, lichen, flowering plants) [5]. Recently, chlorinated metabolites were isolated for the first time from mosses (bryophytes) [6, 7]. With the exception of two older compounds probably representing artefacts [8, 9] twenty chlorometabolites from the liverworts (hepaticae) *Plagiochila sp.* [6], *Bazzania trilobata* [7] and *Lepidozia incurvata* [10] like bazzanin A **1**, bazzanin J **2** or bazzanin K **3** are obviously derived from a isoplagiochin C **4** or isoplagiochin D **5** backbone chain (modified in the case of **3**) [11]. These cyclic bisbibenzyls [12] are biogenetically derived *via* oxidative coupling [13] from two units of lunularin **6** [14, 15], a typical metabolite from bryophytes. Because of the biological activities of **6** and of some of its derivatives [16] and the effects of activity enhancement by halogenation [5] we have synthesized brominated and chlorinated lunularins. Despite of recent studies on bacteria [17] enzymes of the haloperoxidase type are thought to be involved in the halogenating step in the biosynthesis of halometabolites [18]. Therefore, we studied the possibilities of the *in vitro* halogenation of lunularin **6** using this enzyme type.



Scheme 1 Structure and biogenetic relationship of chlorinated bryophyte constituents

Results and Discussion

Halogenated lunularins were unknown compounds up to now. We realized the construction of these bibenzyls [19, 20] by Wittig reactions between suitable substituted aldehydes and phosphonium building blocks followed by catalytic hydrogenation and – where necessary – removing of the phenolic protective groups. The 3-hydroxy fragments A ("*meta*-moiety") were introduced as phosphonium salts **7** (derived of 3-methylphenol **9**) whereas the 4-hydroxy fragments B ("*para*-moiety") were installed as aldehydes **8** starting from 4-hydroxybenzaldehyde **10** (scheme 2). The halogenation of these building blocks was performed by convenient methods partially used for the first time on these substrates.

We prepared monohalogenated (*para*-moiety) lunularins **16**/**17** by coupling 3-halo-4-benzyloxy benzalde-

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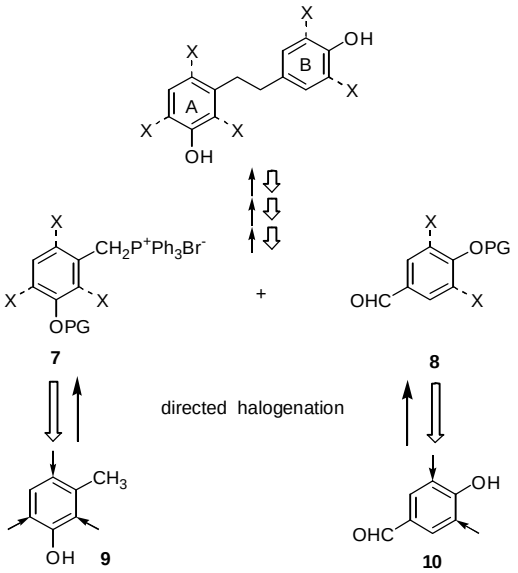
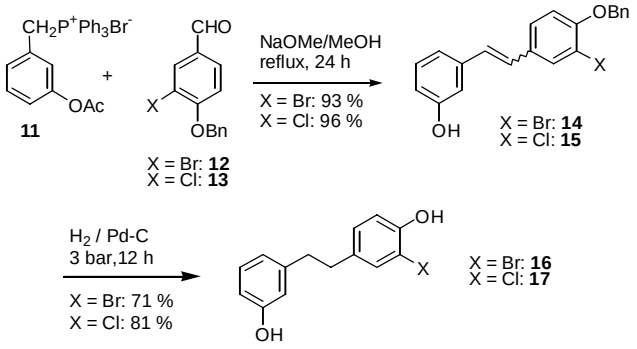


Scheme 2 Strategy of synthesis for halogenated lunularins (PG = protective group)

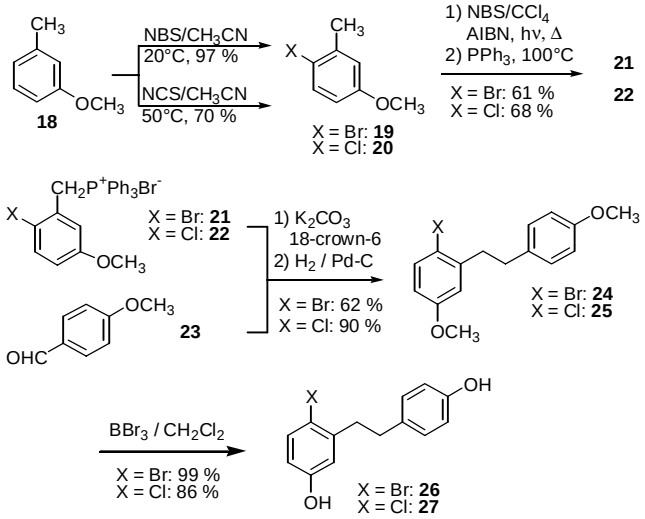
hydes **12**/**13** [21, 22] with the phosphonium bromide **11** [23] – also suitable for the synthesis of the unsubstituted lunularin – to the *E/Z*-stilbene mixtures **14**/**15** followed by catalytic hydrogenation (scheme 3).



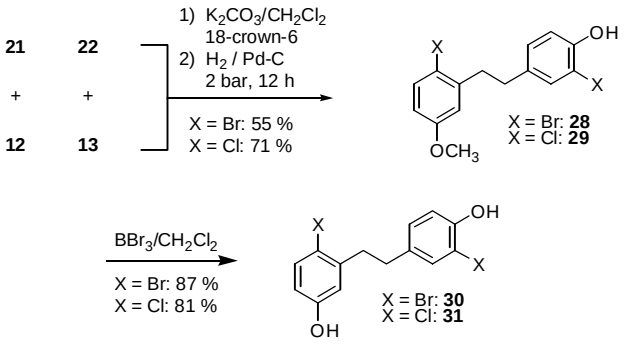
Scheme 3 Syntheses of monohalogenated lunularins (*para*-moiety) (Bn = Ph–CH_2)

The monohalogenation of 3-methylanisol **18** was achieved using *N*-bromosuccinimide [24] or *N*-chlorosuccinimide, respectively. The phosphonium salts **21**/**22** readily available from **19**/**20** were coupled with anisaldehyde **23**. Catalytic hydrogenation of the *E/Z*-products (to **24**/**25**) and boron tribromide induced cleavage of the methyl ethers yielded the monohalogenated lunularins (*meta*-moiety) **26**/**27** (scheme 4).

Dihalogenated lunularins **30**/**31** were prepared by Wittig reactions between the monohalogenated phosphonium salts **21**/**22** and the monohalogenated aldehydes **12**/**13** followed by catalytic hydrogenation to **28**/**29** and cleavage of the methylethers (scheme 5).



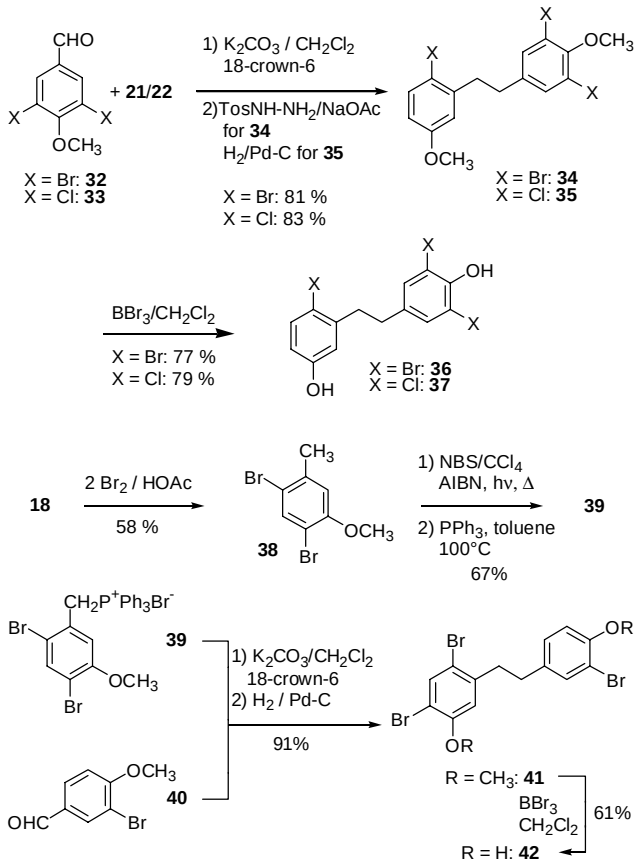
Scheme 4 Syntheses of monohalogenated lunularins (*meta*-moiety)



Scheme 5 Syntheses of dihalogenated lunularins

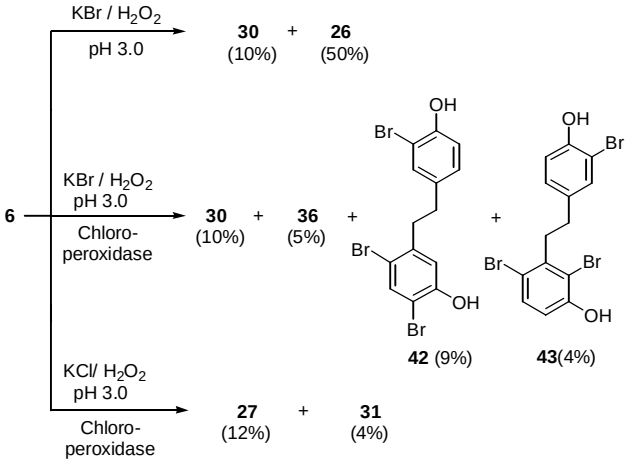
We synthesized trihalogenated lunularins **36**/**37** from 3,5-dibromo anisaldehyde **32** [25] or 3,5-dichloro anisaldehyde **33** [26], respectively and the phosphonium salts **21**/**22** following the improved procedure (Wittig coupling and reduction of the stilbenes to **34**/**35**). In the case of **34** *p*-toluenesulfonylhydrazine was used as diimin source in the stilbene reduction step because catalytic hydrogenation resulted in substantial debromination of the desired product (scheme 6). Dibromination of 3-methylanisol **18** to **38** [27] could result a phosphonium salt **39** which was further transformed with the commercially available 3-bromo-4-methoxybenzaldehyde **40** to an additional tribrominated lunularin **42** following the standard sequence (*via* **41**). Using the benzyl protected building block **12** instead of **40** resulted in a substantial dehalogenation during the more drastic hydrogenation conditions.

Haloperoxidases are enzymes which catalyse the incorporation of halogen atoms into organic molecules in the presence of a halide and hydrogen peroxide and which are thought to be involved in the biosynthesis of halometabolites [5, 17]. Numerous *in vitro* reactions are



Scheme 6 Syntheses of trihalogenated lunularins

described for the commercially available chloroperoxidase (CPO, EC 1.11.1.10) isolated first from the growing medium of the fungus *Caldariomyces fumago* [18]. We proved the suitability of lunularin **6** – base unit of isoplagiochins **4**/**5** and bazzanins – as a reactive substrate for a chemical transformation with KBr or KCl/H_2O_2 in the presence of CPO in a buffered aqueous medium (scheme 7). Four products **30**, **36**, **42** and **43** – double or triple halogenated – could be isolated in a brominating experiment. Mainly the monobrominated compound **26** was observed without adding any enzyme preparation. This means however that a haloperoxidase is obviously not always essential for the bromination of reactive arenes like lunularin **6** under these conditions. This must be considered in biogenetic studies or in common haloperoxidase assays [28]. A chlorination experiment in the presence of CPO yielded mono- and dihalogenated lunularins **27** and **31**. In this case no chlorination was observed without an enzyme activity. Control experiments with exclusive addition of H_2O_2 proved to be negative in all cases. The structures of the halolunularins obtained on this pathway could be spectroscopically confirmed by comparison with the synthetic products (the tribromide **43** was not synthesized). These results confirm the need for a haloperoxidase in the *in vitro* chlorination experiments for lunularin **6** under these conditions.



Scheme 7 *In vitro* halogenation of lunularin **6**

Experimental

Melting points (not corrected): Büchi melting point apparatus (Dr. Tottoli); Elemental analyses: Leco CHNS-932; FT-IR: Bio-Rad Excalibur FTS 3000; ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz): Bruker AM 400 (TMS as internal standard); MS: Finnigan MAT 90 (CI 120 eV); Analytical TLC: Merck aluminium roll 0.2 mm (silica gel 60 HF_{254}); preparative TLC: Macherey-Nagel DC-plates 20×20 cm SIL G-200 UV_{254}; Column chromatography (CC): J. T. Baker silica gel 60, 63–200 mm; Flash chromatography: Macherey-Nagel silica gel 60, 40–63 mm; analytical HPLC: Macherey-Nagel Nucleosil 100-5 (200 × 4mm); preparative HPLC: Macherey-Nagel Nucleosil 100-7 (250 × 21 mm); Catalytic hydrogenation: Parr hydrogenation apparatus. – Chloroperoxidase from *Caldariomyces fumago* (EC 1.11.1.10) was obtained from *Fluka, Buchs* (suspension in 0.1M sodium phosphat pH 4.0, 1717 U/mg, 8 mg protein/ml). – Solvents were commonly dried and purified by conventional methods prior to use. All air- or moisture-sensitive reactions were carried out by inert gas techniques under nitrogen.

Preparation of Phosphonium Salts from Methylarenes (General Procedure 1)

The methylarene in CCl_4 (5 ml / mmol) was heated to reflux for 4 h in the presence of 1 equiv. NBS and a trace of AIBN and with additional illuminating (daylight lamp 300 W). The mixture was cooled, the succinimide was filtered off and the solvent evaporated *in vacuo*. The residue was dissolved in toluene (5 ml/mmol) together with 1 equiv. of triphenylphosphane and heated to 100 °C for 15 h. The phosphonium salt was filtered off, washed with petroleum ether and dried. The spectroscopic data and elemental analyses (not given below) were in agreement with the desired structures.

Preparation of Stilbenes (by Wittig Reactions) (General Procedure 2)

a) Using K_2CO_3 /18-crown-6 in dichloromethane: The aldehyde and the phosphonium salt (1.05 equiv.) were dissolved in CH_2Cl_2 (10 ml/mmol), anhydrous K_2CO_3 (1.2 equiv.) and a small amount of 18-crown-6 were added and the mixture was refluxed for 24 h. The insoluble material was filtered off and the filtrate concentrated *in vacuo*. The crude material was purified by CC (silica gel/CH_2Cl_2).

b) Using $NaOCH_3$ in Methanol: To sodium methoxide (3 equiv.) in CH_3OH (1 ml/mmol aldehyde) the phosphonium salt (1.2 equiv.) was added followed by the aldehyde. The mixture was heated to reflux for 12 h. The solvent was removed *in vacuo*, the residue mixed with water and extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude material was purified by CC (silica gel/CH_2Cl_2). All stilbenes were obtained as *E/Z*-mixtures. The spectroscopic data and elemental analyses (not given below) were agreement with the desired structures.

Catalytic Hydrogenation of Stilbenes and Benzylethers (General Procedure 3)

The stilbene (benzylether) was dissolved in ethyl acetate (100–300 ml), palladium on activated carbon (5% Pd) was added (100 mg/mmol) and the hydrogenation performed at 3.5 bar hydrogen pressure. The catalyst was filtered off and the solvent removed *in vacuo*. The crude material was purified by CC (silica gel/CH_2Cl_2). Small amounts of (partial) dehalogenated products were detected during the hydrogenation of the bromine containing stilbenes.

Cleavage of Aryl Methyl Ethers (General Procedure 4)

To the aryl methyl ether in CH_2Cl_2 (2 ml/mmol) was added dropwise BBr_3 (1M solution in CH_2Cl_2, 2 equivalents per methyl ether to be cleaved) at –78 °C. Stirring was continued for 3 h at this temperature and the mixture allowed to warm up to 20 °C within 15 h. Ice cold water was added dropwise and the product isolated by extraction with CH_2Cl_2 and purified by CC (silica gel/CH_2Cl_2).

4-Chloro-3-methylanisol (**20**)

A solution of 12.2 g (0.10 mol) 3-methylanisole and 13.4 g (0.10 mol) *N*-chlorosuccinimide in 300 ml acetonitrile was stirred for 3 d at 50 °C (monitored by GC). The solvent was removed *in vacuo* and the residue was digested with 150 ml tetrachloromethane filtering off from succinimide. The filtrate was evaporated and the residue distilled *in vacuo*; yield 11.0 g (70%), colourless oil, $b.p._{.15}$ 95 °C. – ^{1}H NMR ($CDCl_3$): δ/ppm = 7.19 (d, ^3J = 8.8 Hz, 1H), 6.74 (d, ^4J = 3.1 Hz, 1H), 6.64 (dd, ^3J = 8.8 Hz, ^4J = 3.1 Hz 1H), 3.74 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3). – ^{13}C NMR: δ/ppm = 158.2, 136.9, 129.6, 125.8, 116.5, 112.5, 55.4, 20.2

3',5',6-Tribromo-3,4'-dimethoxybibenzyl **34**

To a refluxing mixture of 477 mg (1.00 mmol) of the stilbene obtained from **32** and **21** as *E/Z*-mixture and 2.79 g (15.0 mmol) *p*-toluenesulfonylhydrazine in 40 ml dimethoxyethane was added dropwise 2.05 g (25.0 mmol) NaOAc in 30 ml H_2O during a period of 24 h. After cooling the solution was extracted repeatedly with diethylether and the etheral extracts were washed with a 2 mol/l Na_2CO_3 solution and H_2O, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel/EtOAc-*n*-hexane 1:5).

In Vitro Halogenation of Lunularin

214 mg (1.00 mmol) of lunularine (pre-dissolved in 1 ml ethanol) was added to a solution of 5.00 mmol potassium bromide or chloride in 20 ml 0.1M potassium phosphate buffer (pH 3.0). The temperature of the mixture was kept constant to 30–35 °C and 40 mmol H_2O_2 (3% in H_2O) as well as 1500 units (for bromination) or 3000 units (for chlorination) of Chloroperoxidase were added in ten portions each during 10 h. After five portions of both an additional amount of the halide (5.00 mmol) was added. The mixture was extracted with ethyl acetate. The crude product mixture was purified and separated by preparative TLC (silica gel/CH_2Cl_2) and HPLC (EtOAc – *n*-hexane 1:1). Control experiments were performed without any addition of the enzyme preparation. The spectroscopical data of the synthesized halogenated bibenzyls derived from lunularin are given in table 1.

Table 1 Spectroscopical data of the halogenated bibenzyls

Compound (educt(s)/Procedure)	IR: ν/cm^{-1}	^{1}H NMR: δ/ppm	^{13}C NMR: δ/ppm	MS: *m/z* (%)
16: 3'-Bromo-3,4'-dihydroxybibenzyl (**11**,**12**/*2b*, *3*) *m.p.* 55 °C $C_{14}H_{13}BrO_2$ (293.16) Calcd.: C 57.36, H 4.47 Found: C 57.37, H 4.52	3363, 3033, 2926, 2857, 1705, 1588, 1493, 1453, 1416, 1338, 1211, 1155, 820, 776 (diffuse)	7.23 (d, ^4J = 2.2 Hz, 1H), 7.07–7.03 (m, 1H), 6.91 (dd, ^3J = 8.1 Hz,4 ^3J = 2.2 Hz, 1H), 6.78 (d, ^3J = 8.1 Hz, 1H), 6.63 – 6.59 (m, 3H), 4.83 (s_{br}, 2H, OH), 2.75 (s, 4H, CH_2–CH_2) (CD_3OD)	158.2, 153.2, 144.4, 135.9, 133.8, 130.2, 129.6, 120.9, 117.1, 116.4, 113.8, 110.5, 39.0, 37.6 (CD_3OD)	294 (22) [M^+], 292 (83), 260 (15), 258 (17), 187 (94), 185 (100), 121 (13), 120 (11), 107 (48)
17: 3'-Chloro-3,4'-dihydroxybibenzyl (**11**,**13**/*2b*, *3*) *m.p.* 57 °C $C_{14}H_{13}ClO_2$ (248.70) Calcd.: C 67.61, H 5.27 Found: C 67.67, H 5.29	3368, 3038, 2944, 2861, 1589, 1500, 1456, 1419, 1343, 1269, 1226, 1157, 1054, 950, 825, 779 (diffuse)	7.07–7.03 (m, 2 H), 6.86 (dd, ^3J = 8.1 Hz, ^4J = 2.0 Hz, 1H), 6.79 (d, ^3J = 8.1 Hz, 1H), 6.63–6.60 (m, 3 H), 4.92 (s_{br}, 2 H, OH), 2.73 (s, 4H, CH_2–CH_2) (CD_3OD)	158.2, 152.1, 144.3, 135.4, 130.6, 130.2, 128.9, 121.2, 120.9, 117.4, 116.4, 113.8, 38.9, 37.6 (CD_3OD)	251–247 (86) [M^+], 144–141 (100), 121 (22), 107 (51)

Table 1 (Continued)

Compound **(**educt(s)/Procedure)	IR: ν/cm^{-1}	^{1}H NMR: δ/ppm	^{13}C NMR: δ/ppm	MS: *m/z* (%)
24: 6-Bromo-3,4'-dimethoxybibenzyl (**21**,**23**/*2a, 3*); oil $C_{16}H_{17}BrO_2$ (321.21) Calcd.: C 59.83, H 5.33 Found: C 59.95, H 5.38	3000, 2934, 2834, 1610, 1573, 1510, 1470, 1239, 1175, 1034, 807 (ATR)	7.40 (d, ^3J = 8.8 Hz, 1H), 7.13 (d, ^3J = 8.0 Hz, 2H), 6.82 (d, ^3J = 8.0 Hz, 2 H), 6.69 (d, ^4J = 3.6 Hz, 1H), 6.61 (dd, ^3J = 8.8 Hz, ^4J = 3.6 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 3H, OCH_3), 2.95–2.80 (m, 4H, CH_2–CH_2) ($CDCl_3$)	158.9, 158.0, 142.0, 133.6, 133.3, 129.4, 116.2, 114.9, 113.9, 113.4, 55.4, 55.3, 38.9, 35.3 ($CDCl_3$)	322 (18), 320 (18)[M$^+$], 242 (12), 216 (5), 121 (100)
25: 6-Chloro-3,4'-dimethoxybibenzyl (**22**,**23**/*2a, 3*); oil, $C_{16}H_{17}ClO_2$ (276.76) Calcd.: C 69.44, H 6.19 Found: C 69.25, H 6.32	3001, 2934, 2835, 1608, 1581, 1511, 1475, 1302, 1240, 1163, 1130, 1063, 1031, 938, 806, 773, 723 (ATR)	7.21 (d, ^3J = 8.8 Hz, 1H), 7.09 (d, ^3J = 8.0 Hz, 2 H), 6.80 (d, ^3J = 8.0 Hz, 2H), 6.67 (d, ^4J = 2.0 Hz, 1H), 6.65 (dd, ^3J = 8.8 Hz, ^4J = 2.0 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H, OCH_3), 2.95–2.80 (m, 4H, CH_2–CH_2) ($CDCl_3$)	158.3, 158.0, 140.3, 133.6, 130.0, 129.4, 125.4, 116.0, 113.9, 112.9, 55.4, 55.2, 36.3, 35.1 ($CDCl_3$)	278 (4), 276 (13) [M$^+$], 208 (19), 158 (35), 156 (100), 141 (20), 135 (12), 121 (71), 113 (17), 91 (16)
26: 6-Bromo-3,4'-dihydroxybibenzyl (**24**/*4*) *m.p.* 124 °C $C_{14}H_{13}BrO_2$ (293.16) Calcd.: C 57.36, H 4.47 Found: C 57.50, H 4.61	3317, 3019, 2920, 2860, 1593, 1513, 1439, 1342, 1296, 1222, 1169, 1120, 1026, 824, 797 (diffuse)	7.35 (d, ^3J = 8.4 Hz, 1 H), 7.07 (d, ^3J = 8.4 Hz, 2H), 6.79 (d, ^4J = 2.6 Hz, 1H), 6.77 (d, ^3J = 8.4 Hz, 2H), 6.64 (dd, ^3J = 8.4 Hz, ^4J = 2.6 Hz, 1H), 2.90–2.75 (m, 4H, CH_2–CH_2) [d^6]-acetone	157.8, 156.4, 142.8, 134.0, 133.0, 130.1, 118.4, 116.0, 113.7, 39.4, 36.0 [d^6]-acetone	294 (15) [M$^+$] , 292 (15), 214 (8), 107 (100)
27: 6-Chloro-3,4'-dihydroxybibenzyl (**25**/*4*) *m.p.* 117 °C $C_{14}H_{13}ClO_2$ (248.70) Calcd.: C 67.61, H 5.27 Found: C 67.80, H 5.35	3312, 3020, 2923, 2860, 1596, 1513, 1440, 1344, 1297, 1222, 1170, 1123, 1049, 990, 823, 640 (diffuse)	7.12 (d, ^3J = 8.2 Hz, 1H), 6.98 (d, ^3J = 8.5 Hz, 2H), 6.70 (d, ^3J = 8.5 Hz, 2H), 6.62 (d, ^4J = 2.9 Hz, 1H), 6.60 (dd, ^3J = 8.8 Hz, ^4J = 2.0 Hz, 1H), 4.75 (s_{br}, 2H, OH), 2.95–2.80 (m, 4H, CH_2–CH_2) (CD_3OD)	157.3, 156.4, 141.5, 133.8, 130.9, 130.4, 124.9, 118.5, 116.2, 115.5 37.3, 36.2 (CD_3OD)	250 (12), 249 (10), 248 (36) [M$^+$], 220 (38), 205 (42), 175 (20), 152 (20), 142 (19), 135 (24), 115 (45), 107 (100), 105 (35)
28: 3',6-Dibromo-4'-hydroxy-3-methoxy-bibenzyl (**21**,**12**/*2a, 3*) oil, $C_{15}H_{14}Br_2O_2$ (386.08) Calcd.: C 46.66, H 3.65 Found: C 46.78, H 3.49	3010, 2932, 2839, 1615, 1578, 1505, 1472, 1237, 1170, 1031, 808 (ATR)	7.40 (d, ^3J = 8.4 Hz, 1H), 7.29 (d, ^4J = 2.2 Hz, 1H), 7.03 (dd, ^3J = 8.4 Hz, ^4J = 2.2 Hz, 1H), 6.92 (d, ^3J = 8.4 Hz, 1H), 6.66 (d, ^4J = 3.0 Hz, 1H), 6.63 (dd, ^3J = 8.4 Hz, ^4J = 3.0 Hz, 1H), 5.41 (s, 1H, OH), 3.73 (s, 3H, OCH_3), 2.95-2.75 (m, 4 H, CH_2–CH_2) ($CDCl_3$)	158.9, 150.5, 141.4, 135.1, 133.3, 131.7, 129.3, 116.2, 115.9, 114.8, 113.5, 109.9, 55.4, 38.6, 34.9 ($CDCl_3$)	387–383 (17–100) [M$^+$], 309–306 (10–62), 254 (8), 252 (18), 250 (8), 236 (11), 234 (9), 226 (21), 216 (10), 201 (14), 199 (13), 188–184 (14–90)
29: 3',6-Dichloro-4'-hydroxy-3-methoxy-bibenzyl (**22,13**/*2a, 3*) oil, $C_{15}H_{14}Cl_2O_2$ (297.18) Calcd.: C 60.62, H 4.75 Found: C 60.43, H 4.82	3472, 3025, 2935, 2862, 1598, 1501, 1419, 1332, 1241, 1180, 1052, 1026, 940, 899, 867, 857, 808 (diffuse)	7.22 (d, ^3J = 8.4 Hz, 1H), 7.12 (d, ^4J = 1.8 Hz, 1H), 6.97 (dd, ^3J = 8.4 Hz, ^4J = 1.8 Hz, 1H), 6.90 (d, ^3J = 8.0 Hz, 1H), 6.68 (dd, ^3J = 8.4 Hz, ^4J = 3.0 Hz, 1H), 6.65 (d, ^4J = 3.0 Hz, 1H), 5.50 (s_{br}, 1H, -OH), 3.71 (s, 3H, OCH_3), 2.95–2.75 (m, 4H, CH_2–CH_2) ($CDCl_3$)	158.3, 149.7, 139.8, 134.8, 134.7, 130.1, 128.8, 128.5, 125.3, 119.6, 116.1, 113.1, 55.5, 36.1, 34.9 ($CDCl_3$)	298–296 (6–27) [M$^+$], 262–260 (3–5), 155 (13), 143 (37), 140 (100), 125 (6), 107 (6), 105 (11)
30: 3',6-Dibromo-3,4'-dihydroxybibenzyl (**28**/*4*) *m.p.* 100 °C $C_{14}H_{12}Br_2O_2$ (372.05) Calcd.: C 45.20, H 3.25 Found: C 45.37, H 3.34	3381, 3065, 3032, 2927, 2897, 2865, 1578, 1492, 1435, 1343, 1288, 1219, 1164, 1122, 1029, 860, 811, 675 (diffuse)	8.67 (s_{br}, 1H, OH), 8.57 (s_{br}, 1H, OH), 7.37 (d, ^4J = 2.2 Hz, 1H), 7.34 (d, ^3J = 8.4 Hz, 1H), 7.06 (dd, ^3J = 8.0 Hz, ^4J = 2.2 Hz, 1H), 6.91 (d, ^3J = 8.0 Hz, 1H), 6.79 (d, ^4J = 3.1 Hz, 1H), 6.64 (dd, ^3J = 8.4 Hz, ^4J = 3.1 Hz, 1H), 2.95–2.75 (m, 4H, CH_2–CH_2) [d^6]-acetone	157.8, 153.0, 142.4, 135.2, 134.0, 133.5, 129.5, 118.5, 117.2, 116.1, 113.7, 110.2, 39.0, 35.4 [d^6]-acetone	375–370 (9–49) [M$^+$], 294–290 (5–16), 229 (17), 212 (12), 188–185 (19–100)
31: 3',6-Dichloro-3,4'-dihydroxybibenzyl (**29**/*4*) *m.p.* 119 °C $C_{14}H_{12}Cl_2O_2$ (283.15) Calcd.: C 59.39, H 4.27 Found: C 59.39, H 4.36	3390, 3035, 2932, 2901, 1587, 1581, 1498, 1438, 1346, 1290, 1221, 1168, 1128, 1052, 957, 861, 815, 689, 640 (diffuse)	7.12 (d, ^3J = 9.3 Hz, 1H), 7.08 (d, ^4J = 2.2 Hz, 1H), 6.89 (dd, ^3J = 8.4 Hz, ^4J = 2.2 Hz, 1H), 6.80 (d, ^3J = 8.0 Hz, 1H), 6.59–6.62 (comb. signals, 2H), 5.50 (s_{br}, 1H, -OH), 2.90–2.70 (m, 4H, CH_2–CH_2) (CD_3OD)	157.2, 152.2, 141.0, 135.1, 130.9, 130.7, 128.9, 124.8, 121.3, 118.4, 117.5, 115.6, 36.9, 35.8 (CD_3OD)	286–281 (6–42) [M$^+$], 250–245 (2-7), 215–210 (1–5), 144 (7), 143 (51), 142 (23), 141 (100)

Table 1 (Continued)

Compound (educt(s)/Procedure)	IR: ν/cm^{-1}	^{1}H NMR: δ/ppm	^{13}C NMR: δ/ppm	MS: *m/z* (%)
34: 3',5',6-Tribromo-3,4'-dimethoxy-bibenzyl (**21**,**32**/*2a*, *3*) *m.p.* 70 °C $C_{16}H_{15}Br_3O_2$ (479.00) Calcd.: C 40.12, H 3.16 Found: C 39.96, H 3.25	3005, 2928, 2863, 1594, 1574, 1543, 1470, 1421, 1397, 1259, 1164, 1125, 1056, 998, 867, 804 (ATR)	7.39 (d, ^3J = 8.8 Hz, 1H), 7.31 (s, 2H), 6.66 (d, ^4J = 3.1 Hz, 1H), 6.63 (dd, ^3J = 8.8 Hz, ^4J = 3.1 Hz, 1H), 3.88 (s, 3H), 3.72 (s, 3H, OCH_3), 2.93–2.71 (m, 4H, CH_2–CH_2) ($CDCl_3$)	159.0, 152.4, 140.9, 140.0, 133.4, 132.6, 117.8, 116.2, 114.7, 113.7, 60.5, 55.4, 38.2, 34.9 ($CDCl_3$)	479–475 (1–5) [M$^+$], 468–463 (2–8), 401–398 (1–5), 288–278 (18–100), 267–263 (5–119), 239–235 (8–13), 216–212 (4–14), 202–199 (6–24)
35: 3',5',6-Trichloro-3,4'-dimethoxy-bibenzyl (**22**,**33**/*2a*, *3*) *m.p.* 185 °C $C_{16}H_{15}Cl_3O_2$ (345.65) Calcd.: C 55.60, H 4.37 Found: C 55.76, H 4.51	3009, 2936, 2833, 1596, 1555, 1480, 1285, 1167, 1034, 996, 867, 804, 634 (diffuse)	7.24 (d, ^3J = 8.6 Hz, 1H), 7.11 (s, 2H), 6.70 (dd, ^3J = 8.6 Hz, ^4J = 3.0 Hz, 1H), 6.65 (d, ^4J = 3.0 Hz, 1H), 3.87 (s, 3H), 3.74 (s, 3H, OCH_3), 2.90–2.70 (m, 4H, CH_2–CH_2) ($CDCl_3$)	158.5, 150.7, 139.3, 138.9, 130.2, 129.0, 128.9, 125.3, 116.1, 113.3, 60.7, 55.5, 35.6, 34.9 ($CDCl_3$)	349–344 (8–88) [M$^+$], 313–309 (6–13), 191 (64), 189 (100)
36: 3',5',6-Tribromo-3,4'-dihydroxybibenzyl (**34**/*4*) *m.p.* 160 °C $C_{14}H_{11}Br_3O_2$ (450.95) Calcd.: C 37.29, H 2.46 Found: C 37.36, H 2.55	3514, 3466, 3062, 2955, 2933, 2897, 2867, 2599, 2567, 1602, 1574, 1470, 1406, 1319, 1292, 1270, 1237, 1165, 1123, 1021, 953, 875, 860 (diffuse)	7.30 (d, ^3J = 8.4 Hz, 1H), 7.25 (s, 2H), 6.62 (d, ^4J = 3.1 Hz, 1H), 6.55 (dd, ^3J = 8.4 Hz, ^4J = 3.1 Hz, 1H), 4.89 (s_{br}, 2H, OH), 2.90–2.70 (m, 4H, CH_2–CH_2) (CD_3OD) [a])	158.1, 150.4, 142.3, 136.9, 134.4, 133.3, 118.7, 116.3, 114.1, 112.1, 39.2, 35.6 (CD_3OD)	454–447 (5–66) [M$^+$], 373–368 (5–28), 293–290 (5–24), 267–263 (6–100), 214 (40), 187–185 (11–87)
37: 3',5',6-Trichloro-3,4'-dihydroxybibenzyl (**35**/*4*) *m.p.* 119 °C $C_{14}H_{11}Cl_3O_2$ (317.59) Calcd.: C 52.95, H 3.49 Found: C 52.81, H 3.69	3577, 3326, 2932, 2864, 1642, 1600, 1489, 1451, 1416, 1329, 1279, 1246, 1228, 1165, 865, 801, 712 (diffuse)	7.13 (dd, ^3J = 7.5 Hz, ^4J = 2.6 Hz, 1H), 7.03 (s, 2H), 6.63 (d, ^4J = 2.6 Hz, 1H), 6.61 (d, ^3J = 7.5 Hz, 1H), 4.89 (s_{br}, 2H, OH), 2.90–2.70 (m, 4H, CH_2–CH_2) (CD_3OD)	157.3, 148.6, 140.6, 135.4, 131.0, 129.4, 124.8, 123.1, 118.5, 115.8, 36.6, 35.6 (CD_3OD)	320–316 (8–50) [M$^+$], 285–281 (3–7), 177 (874), 175 (100), 141 (19)
41: 3',4,6-Tribromo-3,4'-dimethoxy-bibenzyl (**39**,**40**/*2a*,*3*) *m.p.* 11 2 °C $C_{16}H_{15}Br_3O_2$ (479.00) Calcd.: C 40.12, H 3.16 Found: C 40.21, H 3.09	3025, 2973, 2942, 2847, 1580, 1495, 1464, 1370, 1252, 1175, 1055, 1014, 877, 843, 817, 772, 727, 681, 645, 616 (diffuse)	7.67 (s, 1H), 7.39 (d, ^4J = 1.8 Hz, 1H), 7.01 (dd, ^3J = 8.0 Hz, ^4J = 1.8 Hz, 1H), 6.79 (d, ^3J = 8.0 Hz, 1H), 6.57 (s, 1H), 3.85 (s, 3H), 3.76 (s, 3H, OCH_3), 2.95– 2.70 (m, 4H, CH_2–CH_2) ($CDCl_3$)	155.3, 154.5, 140.9, 136.3, 134.7, 133.4, 128.6, 114.9, 114.0, 112.1, 110.0, 56.5, 56.4, 38.5, 34.8 ($CDCl_3$)	479–475 (1) [M$^+$], 468–463 (1), 401–398 (1), 288–278 (11–100), 267–263 (2–14), 239–235 (6–10), 216–212 (3–13), 202–199 (4–21)
42: 3',4,6-Tribromo-3,4'-dihydroxybibenzyl (**41**/*4*) *m.p.* 105 °C $C_{14}H_{11}Br_3O_2$ (450.95) Calcd.: C 37.29, H 2.46 Found: C 37.31, H 2.58	3528, 3433, 2929, 2862, 1611, 1583, 1505, 1451, 1408, 1339, 1292, 1252, 1212, 1053, 872, 820, 612 (diffuse)	7.63 (s, 1H), 7.28 (d, ^4J =1.8 Hz, 1H), 7.00 (dd, ^3J =7.9 Hz, ^4J = 1.8 Hz, 1H), 6.93 (d, ^3J = 7.9 Hz, 1H), 6.83 (s, 1H), 5.40 (s_{br}, 1H, OH), 2.90–2.70 (m, 4H, CH_2–CH_2) ($CDCl_3$)	151.7, 150.5, 141.5, 134.7, 134.4, 131.4, 129.0, 117.4, 115.8, 114.3, 109.8, 108.1, 37.8, 34.5 ($CDCl_3$)	454–447 (6–16) [M$^+$], 372–368 (5–14), 292–286 (6–16), 260 (18), 258 (21), 187 (33), 185 (36), 107 (17), 102 (100)
43: 2,3',6-Tribromo-3,4'-dihydroxybibenzyl **6**; oil $C_{14}H_{11}Br_3O_2$ (450.95) Calcd.: C 37.29, H 2.46 Found: C 37.39, H 2.37	3522, 3431, 2925, 2867, 1613, 1578, 1508, 1453, 1408, 1337, 1290, 1249, 1213, 1056, 874, 822 (ATR)	7.40 (d, ^3J = 8.8 Hz, 1H), 7.35 (d, ^4J = 2.2 Hz, 1H), 7.12 (dd, ^3J = 8.2 Hz, ^4J = 2.2 Hz, 1H), 6.94 (d, ^3J = 8.2 Hz, 1H), 6.80 (d, ^3J = 8.8 Hz, 1H), 5.63 (s_{br}, 1H, OH), 5.40 (s_{br}, 1H, OH), 3.20 (m_c, 2H), 2.75 (m_c, 2H, CH_2–CH_2) ($CDCl_3$) [a])	152.1, 150.8, 140.0, 134.8, 132.7, 131.7, 129.3, 116.1, 115.2, 114.9, 113.6, 110.1, 39.7, 33.0 ($CDCl_3$)	454–447 (4–49) [M$^+$], 374–368 (5–15), 292–286 (1–6), 187 (95), 185 (100)

[a]) The structure was confirmed using 2D NMR techniques (C–H-correlation, NOESY)

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