

## Supporting Information

### Regiocontrolled First Synthesis of Procyanidin B<sub>6</sub>, Catechin Dimer with Rare Connectivity: Halo-capping Strategy for Formation of 4,6-Interflavan Bond

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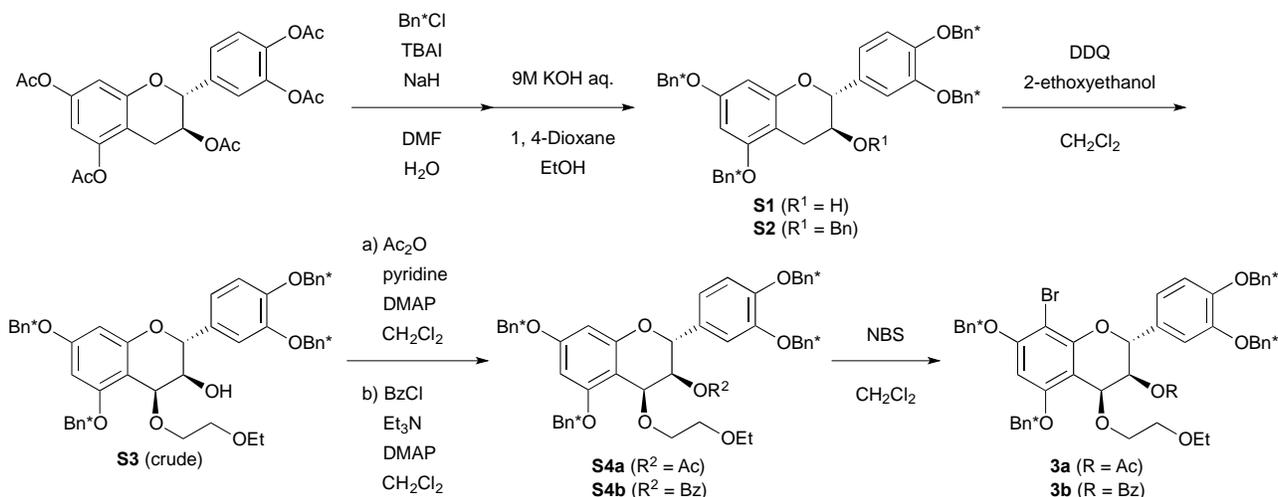
#### General Experimental Procedures

All reactions utilizing air- and moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry argon or nitrogen. Ethereal solvents (anhydrous; Kanto Chemical Co., Inc.) were used as received. *N,N*-Dimethylformamide (DMF) was distilled from CaH<sub>2</sub> under reduced pressure and stored over molecular sieves 4A.

For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (silica gel 60 F254, Art 5715, 0.25 mm). Preparative silica gel TLC (PTLC) was performed on Merck Silica gel 60 PF254 (Art 7747). For flash column chromatography, silica gel 60N (Spherical, neutral, 63–210 μm) from Kanto Chemical was used.

Melting point (mp) determinations were performed by using a Yanako MP-S3 or MP-500 instrument and are uncorrected. <sup>1</sup>H NMR and <sup>13</sup>C NMR were measured on a JEOL ECX-500 (500 MHz) spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from internal standard (tetramethylsilane, 0.00 ppm), and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 spectrometer. Elemental analyses were recorded on an Elementar vario MICRO cube analyzer. Optical rotations ([α]<sub>D</sub>) were measured on a JASCO P-2300 polarimeter. Low-resolution mass spectra (LRMS) were obtained on a Shimadzu MALDI-TOF Mass AXIMA<sup>®</sup> Confidence. High-resolution mass spectra (HRMS) were obtained with micrOTOF-Q II (Bruker Daltonics).

### Synthesis of **3a** and **3b**



### Preparation of **S1** and **S2**

To a suspension of NaH (63%, dispersion in mineral oil, washed with hexane, 8.4 g, 0.22 mol) in DMF (70 mL), was added (+)-catechin pentaacetate (10 g, 20 mmol),  $d_7$ -benzyl chloride<sup>[1]</sup> (10 mL, 90 mmol), and *n*-Bu<sub>4</sub>NI (1.5 g, 4.0 mmol). A solution of  $\text{H}_2\text{O}$  (1.4 mL, 80 mmol) in DMF (13 mL) was added dropwise over 25 min at 0 °C. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by adding  $\text{Et}_2\text{NH}$  (4.2 mL, 40 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The mixture was poured into 6 M HCl solution and the products were extracted with EtOAc ( $\times 3$ ). The combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo. The residue was dissolved in the mixed solvent of EtOH (40 mL) and 1,4-Dioxane (40 mL), and was added 9 M KOH solution (20 mL) at 0 °C. The reaction mixture was stirred for 4 h at room temperature. The reaction was quenched by adding 6 M HCl solution at 0 °C. The products were extracted with EtOAc ( $\times 3$ ). The combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc/ $\text{CHCl}_3 = 8/1/1$ ) to afford **S1** (7.5 g, 55%) as a white solid and **S2** (4.7 g, 31%) as a white solid.

**S1:** Rf 0.80 (hexane/EtOAc/CHCl<sub>3</sub> = 4/1/1); mp 128–130 °C;  $[\alpha]_{\text{D}}^{20} = -1.0^{\circ}$  (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.71 (brs, 1H, OH), 2.68 (dd, 1H, *J* = 16.6, 8.6 Hz), 3.13 (dd, 1H, *J* = 16.6, 5.7 Hz), 4.01 (ddd, 1H, *J* = 8.6, 8.1, 5.7 Hz), 4.65 (d, 1H, *J* = 8.1 Hz), 6.25 (d, 1H, *J* = 2.3 Hz), 6.31 (d, 1H, *J* = 2.3 Hz), 6.97 (d, 2H, *J* = 1.2 Hz), 7.06 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 27.8, 68.3, 68.9–71.2 (m), 81.7, 94.0, 94.5, 102.4, 114.1, 115.2, 120.7, 126.5–128.4 (m), 131.1, 136.7, 136.8, 136.9, 137.0, 149.2, 149.5, 155.4, 157.9, 159.0; IR (neat) 3012, 2905, 2277, 2191, 2119, 1616, 1616, 1592, 1511, 11493, 1442, 1428, 1380, 1328, 1272, 1233, 1203, 1184, 1155, 1122, 1087, 1054, 1033, 1000, 978, 839, 819, 755. 543 cm<sup>-1</sup>; Anal. calcd for C<sub>43</sub>H<sub>10</sub>D<sub>28</sub>O<sub>6</sub>: C 76.07, H(D) 5.64. Found: C 75.97, H(D) 5.85.

**S2:** 0.42 (hexane/EtOAc/CHCl<sub>3</sub> = 4/1/1);  $[\alpha]_{\text{D}}^{20} = +34.0$  (*c* 1.32, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.79 (dd, 1H, *J* = 16.6, 8.6 Hz), 3.14 (dd, 1H, *J* = 16.6, 5.6 Hz), 3.80 (ddd, 1H, *J* = 8.6, 8.0, 5.6 Hz), 4.86 (d, 1H, *J* = 8.0 Hz), 6.31 (d, 1H, *J* = 2.3 Hz), 6.34 (d, 1H, *J* = 2.3 Hz), 7.02 (s, 2H), 7.10 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 26.3, 68.9–71.3 (m), 74.7, 80.3, 93.9, 94.6, 102.5, 114.1, 115.2, 120.7, 126.7–128.5 (m), 132.6, 136.8, 136.9, 137.1, 137.2, 137.9, 149.0, 149.1, 155.6, 157.9, 159.0; IR (neat) 3452 (br), 3011, 2906 2277, 2203, 2120, 1617, 1592, 1509, 1493, 1428, 1327, 1271, 1204, 1185, 1154, 1116, 1086, 1053, 1000, 839, 819, 754, 545 cm<sup>-1</sup>; Anal. calcd for C<sub>50</sub>H<sub>9</sub>D<sub>35</sub>O<sub>6</sub>: C 77.38, H(D) 5.71. Found: C 77.63, H(D) 5.99.

#### *Preparation of S4a*

To a solution of alcohol **S1** (0.40 g, 0.59 mmol) and 2-ethoxyethanol (0.80 mL) in CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) was added portion wise DDQ (0.20 g, 0.88 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched by adding DMAP (0.16 g, 1.3 mmol). The reaction mixture was stirred for 1 h. The mixture was filtered through Celite<sup>®</sup> pad and washed with CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was washed successively with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was passed through a short column (hexane/EtOAc = 2/1) to afford crude material of **S3**, which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL), and was added pyridine (0.11 mL, 1.3 mmol), Ac<sub>2</sub>O (67 μL, 0.71 mmol) and DMAP (3.6 mg, 0.030 mmol). The reaction mixture was stirred for 11 h at room temperature. The reaction was quenched by adding 1 M HCl solution. The

mixture was extracted with EtOAc ( $\times 3$ ) and the combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 4/1) to afford **S4a** (0.45 g, 93% 2 steps) as a colorless amorphous foam.

**S4a**: Rf 0.33 (hexane/EtOAc = 3/1);  $[\alpha]_{\text{D}}^{20} = +65$  ( $c$  0.86,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.17 (t, 3H,  $J = 6.9$  Hz), 1.82 (s, 3H), 3.39–3.48 (m, 2H), 3.50 (t, 2H,  $J = 5.7$  Hz), 3.74–3.86 (m, 2H), 4.90 (d, 1H,  $J = 2.9$  Hz), 5.24 (dd, 1H,  $J = 10.9, 2.9$  Hz), 5.30 (d, 1H,  $J = 10.9$  Hz), 6.17 (d, 1H,  $J = 2.3$  Hz), 6.27 (d, 1H,  $J = 2.3$  Hz), 6.95 (d, 1H,  $J = 8.3$  Hz), 7.00 (dd, 1H,  $J = 8.3, 1.8$  Hz), 7.09 (d, 1H,  $J = 1.8$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  15.4, 20.8, 66.5, 68.4, 68.8–71.0 (m), 69.9, 70.9, 72.8, 74.4, 93.8, 94.4, 103.7, 114.6, 114.9, 121.4, 126.8–128.4 (m), 130.7, 136.3, 136.4, 137.0, 149.0, 149.3, 155.9, 158.6, 161.0, 169.8; IR (neat) 2973, 2928, 2869, 1741, 1614, 1592, 1512, 1489, 1432, 1372, 1328, 1272, 1232, 1204, 1160, 1109, 1085, 1053, 999, 961, 916, 839, 819, 755, 601, 546  $\text{cm}^{-1}$ ; Anal. calcd for  $\text{C}_{49}\text{H}_{20}\text{D}_{28}\text{O}_9$ : C 72.74, H(D) 5.98. Found: C 72.70, H(D) 5.85.

#### Preparation of **S4b**

To a solution of crude **S3** (1.5 g, ca. 2.0 mmol) and  $\text{Et}_3\text{N}$  (0.54 mL, 4.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) was added benzoyl chloride (0.34 mL, 2.9 mmol) and DMAP (24 mg, 0.20 mmol). The reaction mixture was stirred for 14 h at room temperature. The reaction was quenched by adding successively *N,N*-dimethyl-1,3-propanediamine (0.30 mL) and 1 M HCl solution. The mixture was extracted with EtOAc ( $\times 3$ ) and the combined organic extracts were washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc/ $\text{CHCl}_3$  = 3/1) to afford **S4b** (1.4 g, ca 82%) as a colorless amorphous foam.

**S4b**: Rf 0.60 (hexane/EtOAc = 3/1);  $[\alpha]_{\text{D}}^{20} = +93$  ( $c$  0.82,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.11 (t, 3H,  $J = 6.9$  Hz), 3.32–3.43 (m, 2H), 3.44–3.52 (m, 2H), 3.75–3.81 (m, 2H), 3.82–3.88 (m, 2H), 5.04 (d, 1H,  $J = 1.8$  Hz), 5.49 (brs, 2H), 6.22 (d, 1H,  $J = 2.3$  Hz), 6.30 (d, 1H,  $J = 2.3$  Hz), 6.90 (d, 1H,  $J = 8.6$  Hz), 6.92 (dd, 1H,  $J = 8.6, 2.3$  Hz), 7.15 (d, 1H,  $J = 2.3$  Hz), 7.38 (t, 2H,  $J = 8.1$  Hz), 7.53 (t, 1H,  $J = 7.5$  Hz), 7.94 (d, 2H,  $J = 8.6$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  15.3, 66.4, 68.7, 68.8–72.0 (m), 70.0, 71.3, 73.5, 74.5, 93.9, 94.4, 103.9, 114.7, 115.1, 121.4, 126.8–128.4 (m), 128.4,

129.78, 129.84, 130.8, 133.2, 136.3, 136.5, 136.97, 137.00, 149.1, 149.3, 155.9, 158.7, 161.1, 165.3; IR (neat) 3065, 2973, 2927, 2869, 2278, 2205, 2120, 1722, 1615, 1592, 1512, 1490, 1443, 1431, 1354, 1329, 1316, 1273, 1203, 1160, 1119, 1104, 1087, 1054, 1029, 999, 961, 839, 819, 754, 713, 543  $\text{cm}^{-1}$ ; Anal. calcd for  $\text{C}_{54}\text{H}_{22}\text{D}_{28}\text{O}_9$ : C 74.45, H(D) 5.79. Found: C 74.53, H(D) 6.06.

### Preparation of **3a**

To a solution of **S4a** (0.32 g, 0.40 mmol) in  $\text{CH}_2\text{Cl}_2$  (4.0 mL) was added *N*-bromosuccinimide (74 mg, 0.42 mmol) at 0 °C. The reaction mixture was stirred for 2 h at same temperature. The reaction was quenched by adding  $\text{Et}_3\text{N}$  and 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ . The mixture was extracted with EtOAc ( $\times 3$ ) and the combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 4/1) to afford **3a** (0.32 g, 89%) as a colorless amorphous foam.

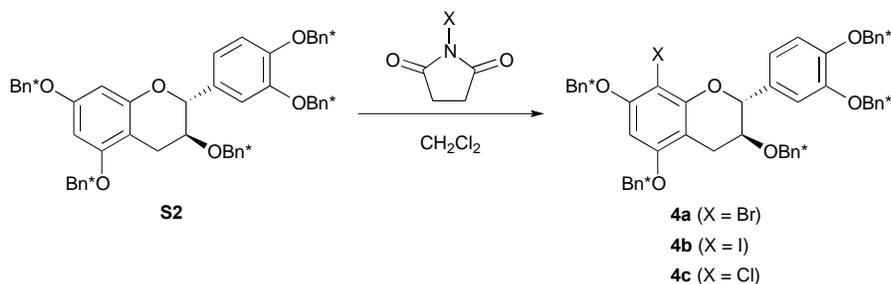
**3a**: Rf 0.27 (hexane/EtOAc = 3/1);  $[\alpha]_{\text{D}}^{20} = +22.7$  (*c* 1.08,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.19 (t, 3H,  $J = 6.9$  Hz), 1.87 (s, 3H), 3.42–3.51 (m 2H), 3.53 (t, 2H,  $J = 5.2$  Hz), 3.75–3.81 (m, 1H), 3.81–3.87 (m, 1H), 4.94 (d, 1H,  $J = 3.4$  Hz), 5.12 (dd, 1H,  $J = 10.3, 3.4$  Hz), 5.43 (d, 1H,  $J = 10.3$  Hz), 6.27 (s, 1H), 6.96 (d, 1H,  $J = 8.0$  Hz), 7.04 (dd, 1H,  $J = 8.0, 1.7$  Hz), 7.17 (d, 1H,  $J = 1.7$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  15.4, 20.9, 66.6, 68.2, 69.8–71.2 (m), 69.9, 70.8, 73.0, 74.6, 92.4, 92.7, 105.1, 114.3, 114.8, 121.1, 126.4–128.6 (m), 130.6, 136.0, 136.3, 137.06, 137.11, 148.9, 149.3, 152.4, 157.0, 157.2, 169.7; IR (neat) 2973, 2928, 2869, 2278, 2206, 2120, 1742, 1602, 1577, 1512, 1484, 1418, 1370, 1328, 1272, 1231, 1202, 1188, 1115, 1087, 1052, 1032, 1000, 840, 820, 754, 544  $\text{cm}^{-1}$ ; Anal. calcd for  $\text{C}_{49}\text{H}_{19}\text{D}_{28}\text{Br}_1\text{O}_9$ : C 66.28, H(D) 5.34. Found: C 66.37, H(D) 5.37.

### Preparation of **3b**

To a solution of **S4b** (1.0 g, 1.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (25 mL) was added *N*-bromosuccinimide (0.21 g, 1.2 mmol) at 0 °C. The reaction mixture was stirred for 3 h at same temperature. The reaction was quenched by adding  $\text{Et}_3\text{N}$  and 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ . The mixture was extracted with EtOAc ( $\times 3$ ) and the combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 4/1) to afford **3b** (1.1 g, 99%) as a colorless amorphous foam.

**3b**: Rf 0.55 (hexane/EtOAc = 3/1);  $[\alpha]_D^{20} = +73$  (*c* 0.99, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.14 (t, 3H, *J* = 6.9 Hz), 3.36–3.48 (m, 2H), 3.52 (t, 2H, *J* = 5.2 Hz), 3.77–3.82 (m, 2H), 3.85–3.91 (m, 2H), 5.08 (d, 1H, *J* = 3.5 Hz), 5.38 (dd, 1H, *J* = 10.9, 3.5 Hz), 5.62 (d, 1H, *J* = 10.9 Hz), 6.31 (s, 1H), 6.92 (d, 1H, *J* = 8.6 Hz), 7.15 (dd, 1H, *J* = 8.6, 1.7 Hz), 7.22 (d, 1H, *J* = 1.7 Hz), 7.42 (t, 2H, *J* = 8.0 Hz), 7.56 (t, 2H, *J* = 8.0 Hz), 8.00 (t, 2H, *J* = 8.1 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ; 15.4, 66.6, 68.4, 68.8–71.2 (m), 70.0, 71.3, 73.7, 74.7, 92.5, 92.8, 105.3, 114.4, 115.1, 121.0, 126.4–128.3 (m), 128.5, 129.7, 129.8, 130.6, 133.3, 136.0, 136.3, 137.0, 137.1, 149.0, 149.3, 152.4, 157.1, 157.3, 165.2; IR (neat) 3064, 2973, 2927, 2869, 2278, 2205, 2119, 1723, 1603, 1578, 1512, 1485, 1451, 1418, 1365, 1328, 1315, 1272, 1201, 1189, 1121, 1106, 1053, 1029, 1000, 840, 820, 755, 713, 544 cm<sup>-1</sup>; Anal. calcd for C<sub>54</sub>H<sub>21</sub>D<sub>28</sub>Br<sub>1</sub>O<sub>9</sub>: C 68.27, H(D) 5.20. Found: C 68.42, H(D) 5.30.

### Synthesis of **4a**, **4b** and **4c**



#### Preparation of **4a**

To a solution of **S2** (0.10 g, 0.13 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) was added *N*-bromosuccinimide (24 mg, 0.14 mmol) at 0 °C. The reaction mixture was stirred for 2 h at same temperature. The reaction was quenched by adding  $\text{Et}_3\text{N}$  and 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ . The mixture was extracted with EtOAc ( $\times 3$ ) and the combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 3/1) to afford **4a** (0.11 g, 99%) as a colorless amorphous foam.

**4a**: Rf 0.38 (hexane/EtOAc = 3/1);  $[\alpha]_{\text{D}}^{20} = -5.6$  ( $c$  0.81,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.79 (dd, 1H,  $J = 16.6, 7.5$  Hz), 2.94 (dd, 1H,  $J = 16.6, 5.2$  Hz), 3.76 (ddd, 1H,  $J = 7.5, 6.9, 5.2$  Hz), 5.04 (d, 1H,  $J = 7.5$  Hz), 6.27 (s, 1H), 6.96 (brs, 2H), 7.06 (s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  25.5, 69.2–71.4 (m), 74.2, 79.9, 92.9, 104.2, 113.7, 115.1, 120.0, 126.5–128.5 (m), 132.1, 136.55, 136.61, 137.0, 137.2, 137.8, 148.8, 148.9, 151.2, 154.9, 156.3; IR (neat) 3011, 2908, 2277, 2191, 2119, 1604, 1579, 1511, 1486, 1413, 1361, 1327, 1271, 1202, 1187, 1126, 1095, 1051, 1030, 1000, 839, 820, 756, 542  $\text{cm}^{-1}$ ; Anal. calcd for  $\text{C}_{50}\text{H}_8\text{D}_{35}\text{Br}_1\text{O}_6$ : C 70.24, H(D) 5.07. Found: C 70.07, H(D) 5.36.

#### Preparation of **4b**

To a solution of **S2** (0.10 g, 0.13 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) was added *N*-iodosuccinimide (58 mg, 0.26 mmol) at  $-78$  °C. The reaction mixture was stirred for 2 h at 0 °C. The reaction was quenched by adding  $\text{Et}_3\text{N}$  and 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ . The mixture was extracted with EtOAc ( $\times 3$ ) and the combined organic extracts were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo. The

residue was purified by PTLC (hexane/EtOAc = 3/1) to afford **4b** (0.11 mg, 98%) as a colorless amorphous foam.

**4b**: Rf 0.38 (hexane/EtOAc = 3/1);  $[\alpha]_D^{20} = -27$  (*c* 0.76, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.72 (dd, 1H, *J* = 16.6, 7.5 Hz), 2.87 (dd, 1H, *J* = 16.6, 5.2 Hz), 3.68 (ddd, 1H, *J* = 7.5, 6.9, 5.2 Hz), 4.98 (d, 1H, *J* = 6.9 Hz), 6.17 (s, 1H), 6.91 (brs, 2H), 7.03 (s, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 25.6, 69.1–71.4 (m), 67.6, 74.4, 80.1, 92.2, 103.7, 113.6, 114.9, 120.0, 126.5–128.5 (m), 132.1, 136.6, 137.0, 137.2, 137.8, 148.7, 148.9, 154.1, 157.3, 158.0; IR (neat) 3226, 3010, 2906, 2277, 2190, 2119, 1600, 1575, 1511, 1481, 1428, 1408, 1356, 1327, 1271, 1202, 1186, 1171, 1126, 1094, 1052, 1030, 1000, 960, 839, 820, 786, 756, 667, 543 cm<sup>-1</sup>; Anal. calcd for C<sub>50</sub>H<sub>8</sub>D<sub>35</sub>I<sub>1</sub>O<sub>6</sub>: C 66.58, H(D) 4.81. Found: C 66.60, H(D) 5.11.

#### *Preparation of 4c*

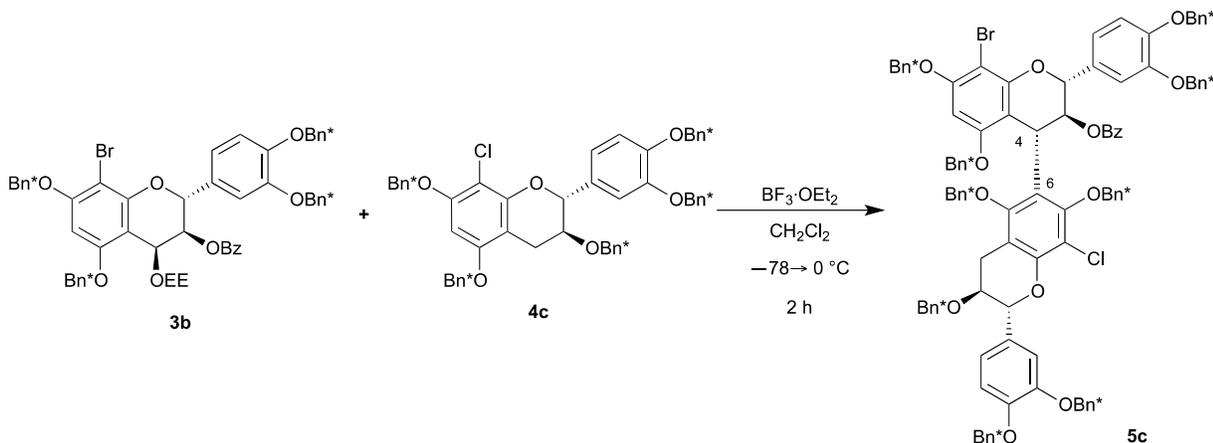
To a solution of **S2** (0.10 g, 0.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was added *N*-chlorosuccinimide (36 mg, 0.27 mmol) at 0 °C. The reaction mixture was stirred for 24 h at room temperature. The reaction was quenched by adding Et<sub>3</sub>N and 10% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The mixture was extracted with EtOAc (×3) and the combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 3/1) to afford C8-chlorinated **4c** (68 mg, 65%) as a light yellow amorphous foam and C6-chlorinated **4c'** (32 mg, 31%) as a light yellow amorphous foam.

**4c**: Rf 0.40 (hexane/EtOAc = 3/1);  $[\alpha]_D^{20} = +7.2$  (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.75 (dd, 1H, *J* = 16.6, 7.5 Hz), 2.92 (dd, 1H, *J* = 16.6, 5.2 Hz), 3.75 (ddd, 1H, *J* = 7.5, 7.5, 5.2 Hz), 5.00 (d, 1H, *J* = 7.5 Hz), 6.28 (s, 1H), 6.93 (brs, 2H), 7.02 (d, 1H, *J* = 1.7 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 25.5, 68.4–71.4 (m), 74.0, 79.9, 93.0, 103.5, 104.1, 113.6, 115.0, 120.0, 126.7–128.4 (m), 132.0, 136.5, 136.6, 137.0, 137.1, 137.7, 148.9, 151.0, 153.9, 155.3; IR (neat) 3012, 2908, 2277, 2202, 2119, 1606, 1586, 1511, 1489, 1418, 1364, 1328, 1271, 1202, 1127, 1107, 1052, 1030, 839, 820, 755, 542 cm<sup>-1</sup>; Anal. calcd for C<sub>50</sub>H<sub>8</sub>D<sub>35</sub>Cl<sub>1</sub>O<sub>6</sub>: C 74.09, H(D) 5.35. Found: C 74.03, H(D) 5.55.

**4c'**: Rf 0.43 (hexane/EtOAc = 3/1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.62 (dd, 1H, *J* = 16.3, 8.0 Hz), 2.85 (dd, 1H, *J* = 16.3, 5.2 Hz), 3.61 (ddd, 1H, *J* = 8.0, 7.5, 5.2 Hz), 4.76 (d, 1H, *J* = 7.5 Hz), 6.40 (s,

1H), 6.84 (dd, 1H,  $J = 8.3, 2.0$  Hz), 6.89–6.93 (m, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  26.2, 69.8–71.3 (m), 74.0, 80.2, 98.6, 108.5, 109.6, 113.8, 115.1, 120.4, 126.4–128.4 (m), 132.0, 136.3, 136.8, 137.0, 137.1, 149.0, 153.5, 154.2, 154.2; IR (neat) 3012, 2908, 2277, 2205, 2118, 1605, 1579, 1510, 1464, 1423, 1380, 1328, 1270, 1234, 1203, 1183, 1173, 1100, 1052, 1029, 1000, 840, 820, 755, 542  $\text{cm}^{-1}$ ;

General experimental procedure for the coupling reaction of 3 and 4  
(the formation of C4, 6-inter-flavan linkage)

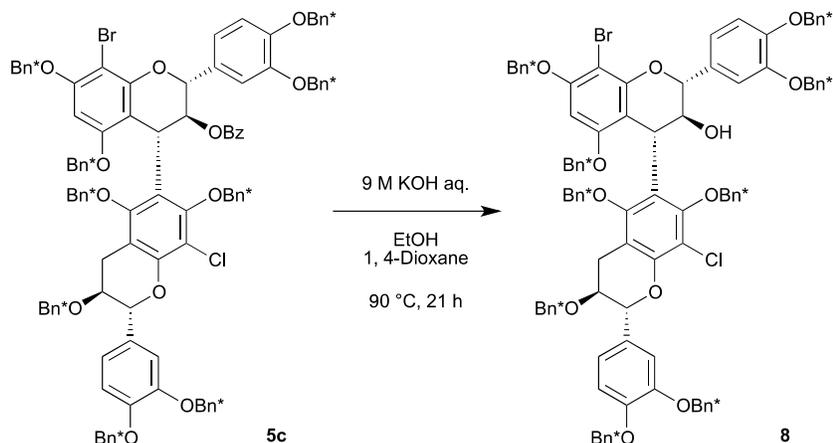


To a solution of bromo-capped benzoate **3b** (1.1 g, 1.2 mmol) and chloro-capped unit **4c** (1.5 g, 1.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60 mL) was added a solution of BF<sub>3</sub>·OEt<sub>2</sub> (0.26 g, 1.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6.0 mL) at -78 °C. The reaction gradually warmed to 5 °C during 2 h. The reaction was quenched by adding Et<sub>3</sub>N and saturated aqueous NaHCO<sub>3</sub>. The mixture was extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, toluene/EtOAc = 30/1) to afford the C4,6-dimer **5c** (1.9 g, 93%, as a colorless amorphous foam, α isomer only).

**5c**: R<sub>f</sub> 0.53 (toluene/EtOAc = 10/1); [α]<sub>D</sub><sup>20</sup> = -93.4 (*c* 1.17, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) the rotamer ratio = 65:35, δ 2.39 (dd, 0.35H, *J* = 16.4, 8.6 Hz), 2.50 (dd, 0.35H, *J* = 16.4, 5.2 Hz), 2.80 (dd, 0.65H, *J* = 15.5, 8.6 Hz), 3.11 (dd, 0.65H, *J* = 15.5, 5.2 Hz), 3.48 (ddd, 0.35H, *J* = 8.6, 8.0, 5.2 Hz), 3.63 (ddd, 0.65H, *J* = 8.6, 8.0, 5.2 Hz), 4.75 (d, 0.35H, *J* = 8.0 Hz), 4.844.93 (br, 1H), 4.95 (d, 0.65H, *J* = 8.0 Hz), 4.99 (d, 0.35H, *J* = 9.2 Hz), 5.03 (d, 0.65H, *J* = 8.6 Hz), 5.84–5.96 (m, 1H), 6.23 (s, 0.35H), 6.27 (s, 0.65H), 6.73 (d, 0.35H, *J* = 8.6 Hz), 6.79 (d, 0.65H, *J* = 8.1 Hz), 6.84–7.05 (m, 5H), 7.23–7.26 (m, 2H), 7.42–7.46 (m, 1H), 7.71 (t, 2H, *J* = 7.5 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, the signals of minor rotamer's are marked with an asterisk) δ 26.7\*, 28.0, 37.5, 37.6\*, 69.2–73.0 (m), 73.9\*, 74.7, 75.0\*, 80.2\*, 80.4, 80.7, 93.9, 94.0\*, 94.5, 109.5\*, 109.7, 111.1\*, 111.7, 111.8, 112.2\*, 113.6, 113.8, 114.2\*, 115.0, 115.1, 120.3\*, 120.4, 120.5, 120.7\*, 122.9\*, 123.3, 126.6–128.4 (m), 128.3, 129.2\*, 129.7, 130.0\*, 130.2, 130.4, 131.9, 132.0\*, 132.8, 132.9\*, 135.3,

135.9\*, 136.40, 136.44, 136.8, 136.9, 136.97, 137.01, 137.1, 137.2, 137.5, 137.6, 137.7, 137.9, 148.9, 149.00, 149.01, 149.06, 149.13, 150.1, 152.9\*, 153.5, 153.6, 154.3, 154.8, 154.9\*, 156.3, 156.4\*, 164.4\*, 164.8; IR (neat) 3010, 2912, 2277, 2205, 2120, 1727, 1560, 1571, 1511, 1483, 1428, 1359, 1328, 1315, 1269, 1235, 1201, 1182, 1112, 1051, 1028, 998, 960, 839, 820, 754, 711, 542  $\text{cm}^{-1}$ ; MS (MALDI-TOF, DHBA matrix)  $m/z$  1690.6 ( $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{100}\text{H}_{19}\text{D}_{63}\text{Br}_1\text{Cl}_1\text{O}_{13}\text{Na}_1$  : 1690.9); HRMS (ESI)  $m/z$  1690.8479 ( $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{93}\text{H}_{16}\text{D}_{63}\text{Cl}_1\text{O}_{12}\text{Na}_1$ : 1690.8630); Anal. Calcd for  $\text{C}_{100}\text{H}_{19}\text{D}_{63}\text{Br}_1\text{Cl}_1\text{O}_{13}$ : C, 71.90; H(D), 4.95. Found: C, 71.92; H(D), 5.13.

### Hydrogenolysis of Benzoyl group

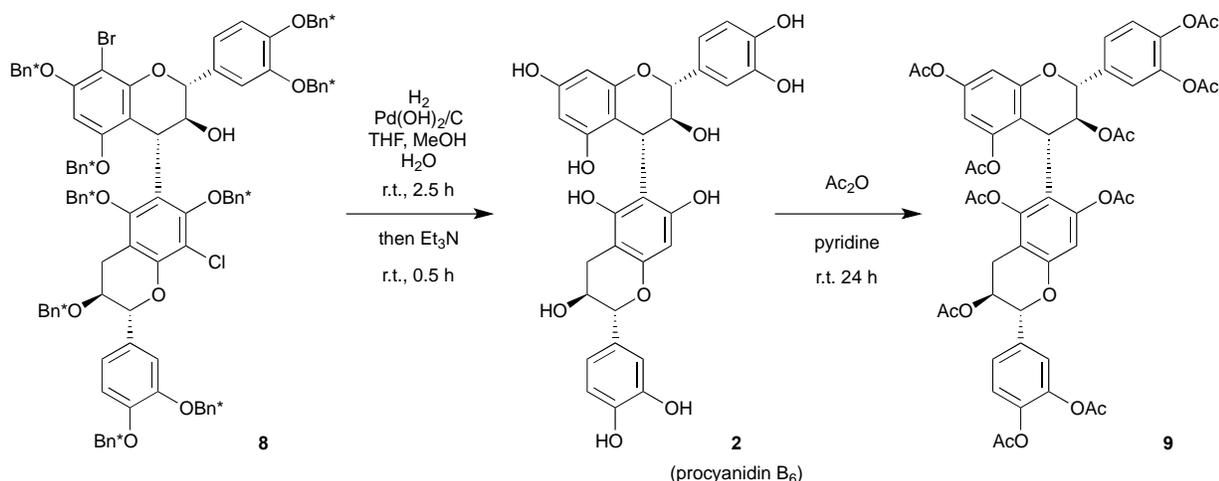


To a solution of C4,6-dimer **5c** (0.32 g, 0.19 mmol) in 1,4-Dioxane (4.0 mL) and EtOH (4.0 mL) was added a solution of 9 M KOH (2.0 mL, 18 mmol) at 0 °C. The reaction mixture was refluxed for 21 h. After cooling to room temperature, pH value of the mixture was adjusted to ca. 5 by addition of 6 M HCl solution. The mixture was extracted with EtOAc ( $\times 3$ ). The combined organic extracts were successively washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, toluene/EtOAc = 30/1) to afford dimer **8** (0.30 mg, 99%, as a colorless amorphous foam).

**8**: Rf 0.49 (toluene/EtOAc = 10/1);  $[\alpha]_{\text{D}}^{20} = -87.6$  ( $c$  1.14,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) the rotamer ratio = 50:50,  $\delta$  1.63 (brs, 0.5H, OH), 1.68 (brs, 0.5H, OH), 2.67 (dd, 0.5H,  $J = 16.1, 9.2$  Hz), 2.75–2.83 (m, 1H), 3.02 (dd, 0.5H,  $J = 16.1, 5.2$  Hz), 3.45–3.57 (m, 1H), 4.26–4.41 (m, 1H), 4.56 (d, 0.5H,  $J = 10.9$  Hz), 4.58 (d, 0.5H,  $J = 9.8$  Hz), 4.68 (d, 0.5H,  $J = 8.6$  Hz), 4.69 (d, 0.5H,  $J = 8.6$  Hz), 4.81 (d, 0.5H,  $J = 8.1$  Hz), 4.95 (d, 0.5H,  $J = 8.1$  Hz), 6.15 (s, 0.5H), 6.19 (s, 0.5H), 6.80–7.23 (m, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  72.9, 73.5, 74.7, 74.8, 80.4, 80.7, 82.4, 82.6, 93.9, 94.3, 94.4, 94.6, 110.1, 111.4, 111.6, 111.9, 112.0, 112.2, 113.7, 113.9, 114.1, 114.2, 114.8, 115.0, 115.1, 120.51, 120.54, 120.9, 121.0, 124.7, 124.8, 126.2–128.8 (m), 131.0, 131.1, 131.8, 132.0, 135.6, 136.1, 136.4, 136.7, 136.76, 136.82, 136.95, 137.00, 137.1, 137.2, 137.4, 137.7, 137.8, 149.0, 149.2, 149.3, 149.86, 149.89, 152.3, 153.6, 154.0, 154.6, 154.7, 155.6, 156.2, 156.5; IR (neat) 3573, 3430, 3011, 2913, 2277, 2206, 2120, 1596, 1570, 1510, 1481, 1427,

1359, 1328, 1272, 1230, 1200, 1184, 1119, 1100, 1051, 1030, 959, 942, 840, 820, 753, 541  $\text{cm}^{-1}$ ;  
HRMS (ESI)  $m/z$  1586.8217 ( $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{93}\text{H}_{16}\text{D}_{63}\text{Cl}_1\text{O}_{12}\text{Na}_1$ : 1586.8214); Anal. Calcd for  
 $\text{C}_{93}\text{H}_{15}\text{D}_{63}\text{Br}_1\text{Cl}_1\text{O}_{12}$ : C, 71.30; H(D), 5.02. Found: C, 71.12; H(D), 4.78.

### Sequential one-pot hydrogenolysis and Acylation



A mixture of **9** (50 mg, 0.037 mmol) and 5 %  $\text{Pd(OH)}_2/\text{C}$  (0.27 g) in MeOH (1.0 mL), THF (1.0 mL), and  $\text{H}_2\text{O}$  (0.5 mL) was hydrogenated under  $\text{H}_2$  atmosphere at room temperature for 2.5 h. Then  $\text{Et}_3\text{N}$  (23  $\mu\text{L}$ , 0.17 mmol) was added to the reaction mixture and was hydrogenated under  $\text{H}_2$  atmosphere again for 30 min. The mixture was filtrated through a glass fiber filter under Ar atmosphere. The filtrate was added  $\text{H}_2\text{O}$  and evaporated only partially so as to remove most of the organic solvents. The solution was lyophilized to afford procyanidin **B**<sub>6</sub> (**2**) (26 mg, quant.) as an off-white powder.

procyanidin **B**<sub>6</sub> (**2**): MS (MALDI-TOF, DHBA matrix)  $m/z$  578.9 ( $[\text{M}]^-$ ; calcd for  $\text{C}_{30}\text{H}_{26}\text{O}_{12}\text{Na}_1$ : 578.1); HRMS (ESI)  $m/z$  579.1496 ( $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{30}\text{H}_{27}\text{O}_{12}$ : 579.1497).

**2** (21 mg) was dissolved in pyridine/acetic anhydride (3.0 mL, 1:1 v/v) at 0 °C. The reaction mixture was stirred for 24 h at 0 °C. The reaction mixture was diluted  $\text{CH}_2\text{Cl}_2$ , and quenched by adding saturated  $\text{CuSO}_4$  solution at 0 °C. The products were extracted with  $\text{CH}_2\text{Cl}_2$  (x3). The combined organic extracts were washed successively with 10% aqueous  $\text{CuSO}_4$  solution, water and brine, dried ( $\text{MgSO}_4$ ), and concentrated in vacuo. The residue was purified by flash column chromatography (toluene/acetone = 8/1) to afford acetate **11** (24 mg, 2 steps 88%) as a white solid.

**11**: R<sub>f</sub> 0.50 (benzene/acetone = 4/1);  $[\alpha]_{\text{D}}^{20} = -70$  ( $c$  0.53,  $\text{CHCl}_3$ ); {lit.<sup>[2]</sup>  $[\alpha]_{\text{D}}^{20} = -20$  ( $c$  0.70,  $\text{CHCl}_3$ )};  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ) the rotamer ratio = 50:50,  $\delta$  1.68–2.35 (m, 30H), 2.48 (dd,

0.5H,  $J = 16.1, 9.8$  Hz), 2.60 (dd, 0.5H,  $J = 16.7, 8.6$  Hz), 2.90 (dd, 0.5H,  $J = 16.7, 5.2$  Hz), 2.93–3.01 (m, 0.5H), 4.39 (d, 0.5H,  $J = 9.2$  Hz), 4.48 (d, 0.5H,  $J = 9.2$  Hz), 4.83 (d, 0.5H,  $J = 9.8$  Hz), 4.85 (d, 0.5H,  $J = 9.7$  Hz), 4.91 (d, 0.5H,  $J = 8.6$  Hz), 5.03 (d, 0.5H,  $J = 8.0$  Hz), 5.05–5.10 (m, 0.5H), 5.10–5.17 (m, 0.5H), 5.67–5.74 (m, 0.5H), 5.74–5.81 (m, 0.5H), 6.46 (d, 0.5H,  $J = 1.7$  Hz), 6.50 (d, 0.5H,  $J = 2.3$  Hz), 6.60 (s, 0.5H), 6.68 (brs, 1.5H), 7.12–7.40 (m, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  20.0–21.1 (m), 29.4, 29.8, 36.7, 37.2, 68.6, 68.7, 71.7, 71.9, 77.8, 78.5, 79.8, 108.6, 109.7, 108.9, 110.4, 110.7, 110.9, 113.3, 113.4, 115.6, 115.8, 118.0, 118.1, 122.4, 122.8, 123.1, 123.5, 123.6, 125.0, 125.3, 125.5, 125.6, 134.7, 134.8, 135.7, 135.8, 141.9, 142.1, 142.3, 142.4, 142.6, 148.0, 148.1, 148.2, 148.3, 149.7, 150.0, 150.1, 150.2, 153.1, 153.4, 155.9, 166.6–170.0 (m); IR (neat) 3026 (br), 3025, 2937, 1722, 1629, 1592, 1507, 1481, 1430, 1371, 1260, 1207, 1186, 1125, 1111, 1050, 1014, 900, 840, 755  $\text{cm}^{-1}$ ; MS (MALDI–TOF, DHBA matrix)  $m/z$  1020.85 ( $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{50}\text{H}_{46}\text{O}_{13}\text{Na}_1$  : 1021.24); HRMS (ESI)  $m/z$  1021.2385 ( $[\text{M}+\text{Na}]^+$  calcd for  $\text{C}_{50}\text{H}_{46}\text{O}_{13}\text{Na}_1$  : 1021.2373).

[1] Furness, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; Longman Scientific & Technical, 1989.

[2] A. C. Fletcher, L. J. Porter, E. Haslam and R. K. Gupta, *J. Chem. Soc., Perkin Trans 1*, 1977, 1387.