

## Synthesis of ellagic acid and its 4,4'-di-*O*-alkyl derivatives from gallic acid

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Synthesis of ellagic acid and its 4,4'-di-*O*-alkyl derivatives from gallic acid is described. Ellagic acid is prepared by oxidative coupling of gallic acid with *o*-chloranil. Functionalized methyl bormogallate underwent Ullmann coupling to give the biphenyl that upon lactonization resulted in the ellagic acid and its alkoxy derivatives.

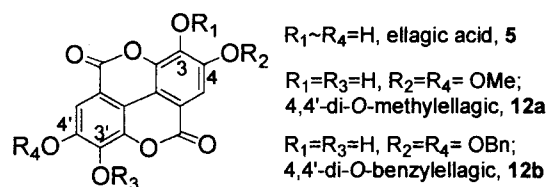
**Keywords:** *ellagic acid, 4,4'-di-O-alkylellagic acid, Ullmann coupling, oxidative coupling*

### Introduction

Ellagic acid and its derivatives are very potent for their various biological activities such as anti-tumor,<sup>1</sup> anti-HIV,<sup>2</sup> anti-cancer,<sup>3</sup> anti-hepatitis,<sup>4</sup> anti-oxidant<sup>5</sup> and anti-microbial<sup>6</sup> effects. Interestingly ellagic acid and its derivatives exhibit free radical scavenging activity and thus used in anti-aging supplements.<sup>7</sup> Takasaki<sup>8</sup> has reported the isolation of variety of ellagic acid derivatives and their inhibitory effects on Epstein-Barr virus action. They found the enhanced inhibitory activity of some ellagic acid derivatives than the parent compound ellagic acid. Other di- or trialkoxy derivatives (Fig. 1) also found to be much more active than the ellagic acid itself. Besides the wide biological activity of ellagic acid and its derivatives, these are used as

important ingredients for some supplements such as anti-aging, skin lightening and other skin care cosmetics.<sup>9</sup> Recent study revealed that the ellagic acid prevent the breast cancer and base on this, some oral medicines or medicated creams containing ellagic acid are commercially available.<sup>10</sup>

**Fig. 1** Ellagic acid and its 4,4'-di-*O*- derivatives.



High concentration of Ellagic acid occurs in raspberries, strawberries, cranberries, grapes, berries, nuts such as walnuts, pecans, etc and these are good sources for the dietary requirements of ellagic acid. In plants, it is present in the form of esters of glucose with hexahydroxydiphenic acid, called ellagitannin. When hydrolyzed, ellagitannin yields ellagic acid, and this method of hydrolysis is one of the major sources of ellagic acid. On the other hand all the

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ellagic acid derivatives investigated so far either has been isolated from the plants materials or derivatized from ellagic acid.<sup>4(b),8,11</sup> Commercial ellagic acid is provided by hydrolysis of natural ellagitannins. However, recently the synthesis of ellagic acid has been reported.<sup>12</sup>

Here we wish to report a simple method for the systematic synthesis of ellagic acid, 4,4'-di-*O*-methylellagic acid **12a** and 4,4'-di-*O*-benzylellagic acid **12b** from the cheap and commercially available gallic acid. This method can also be applied for the synthesis of other 4,4'-di-*O*-derivative as well as other tri-*O*-derivatives of ellagic acid.

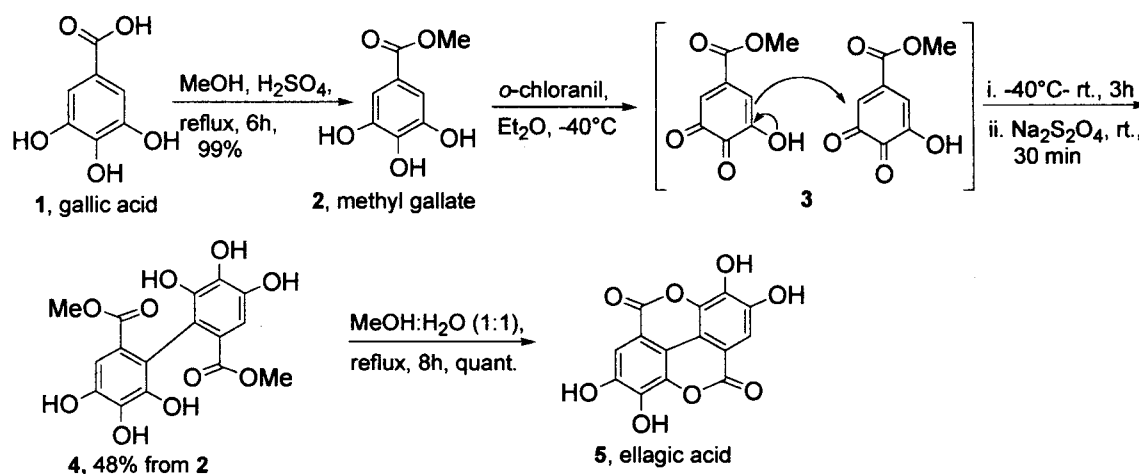
### Results and discussion

Commercially available gallic acid **1** was esterified to methyl gallate **2** by treating it with methanol in the presence of H<sub>2</sub>SO<sub>4</sub>. Methyl gallate **2** was treated with oxidizing agent *o*-chloranil at -40°C to room temperature followed by the reduction with Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> gave the hexahydroxy diphenyl **4**.<sup>13</sup> Compound **4** was

refluxed with MeOH/H<sub>2</sub>O (1:1) resulted in lactonization<sup>13</sup> and gave the desired ellagic acid **5** in high yield (Scheme 1).

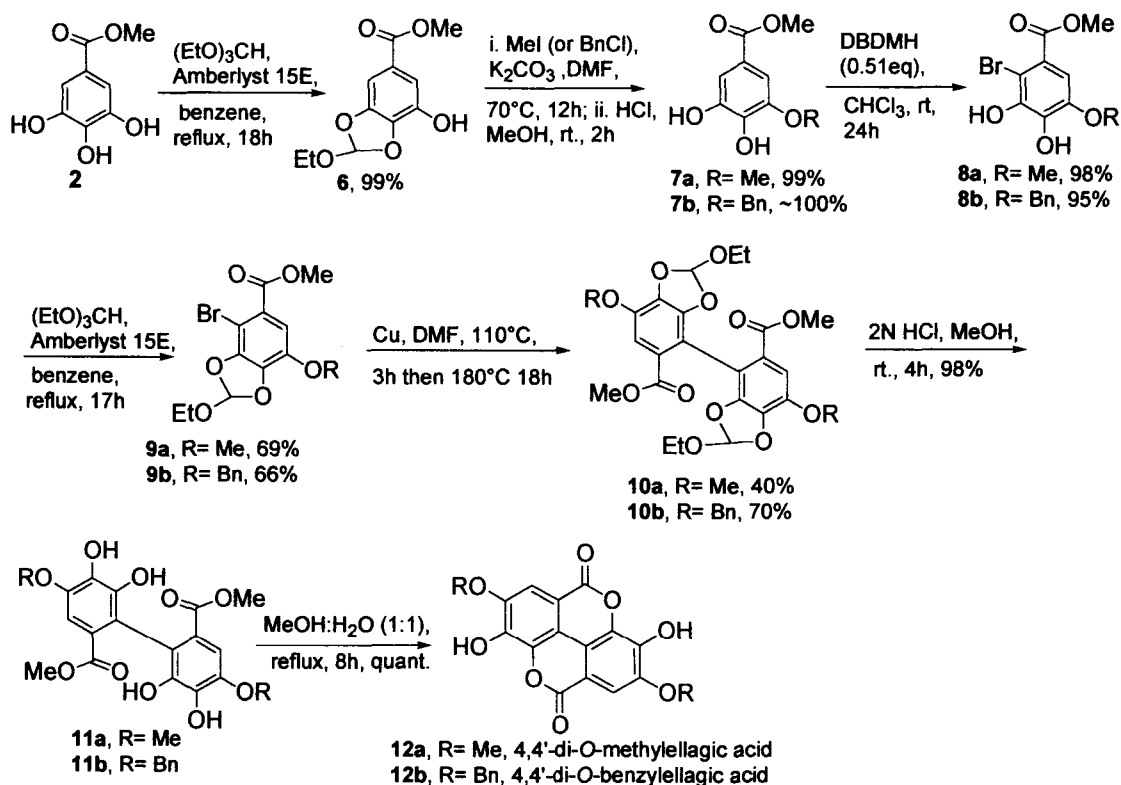
Unlike most of the reported methods mentioned before, we started the synthesis of 4,4'-di-*O*-alkylellagic acid from gallic acid **1** (Scheme 2). For this purpose methyl gallate **2** was converted to methyl 3-methoxy-4,5-dihydroxybenzoate **7a** via acetal **6** in 99% yield over 2 steps. Similarly, methyl 3-benzyloxy-4,5-dihydroxybenzoate **7b** was also prepared in almost 100% yield from **6**. Regioselective bromination of **7a** and **7b** at 6-position was done by our DBDMH method,<sup>14</sup> which gave the corresponding bromides **8a** and **8b** respectively. The hydroxy groups of **8a** and **8b** were protected as acetals **9a** and **9b** respectively. Then, the fully hydroxy protected methyl bromogallate **9a** and **9b** underwent the Ullmann coupling reaction to give the desired key intermediate **10a** and **10b** in 40 and 70% yield respectively. Deprotection of **10a** and **10b** gave the tetrahydroxybiphenyl **11a** and **11b** in 98% of yield.

**Scheme 1.** Preparation of ellagic acid by oxidative coupling of gallic acid



Lactonization of compounds **11a** and **11b** by refluxing with MeOH/H<sub>2</sub>O (1:1) gave the quantitative yield of desired ellagic acid derivatives 4,4'-di-*O*-methyl ellagic acid **12a** and 4,4'-di-*O*-benzyl ellagic acid **12b** respectively.

**Scheme 2.** Preparation of 4,4'-di-*O*-alkylellagic acid from gallic acid by Ullmann coupling



## Experimental

**General:** All moisture-sensitive reactions were carried out under nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agents. Reactions were monitored on TLC on silica gel 60 F<sub>254</sub> and visualized under UV light and/or 5% ethanolic solution of phosphomolybdic acid. Flash chromatography was performed on silica gel (Merck, 60N, spherical, neutral, 40-50 mash). Melting points were determined with a Mel-TEMP apparatus. IR was recorded on a

Thermo Nicolet Avatar 360T2 instrument using ATR. <sup>1</sup>H NMR (300 MHz) and <sup>13</sup>C NMR (75 MHz) were recorded by JEOL AL 300 instrument. GC-MS was studied with a SHIMADZU GCMS-QP5000 instrument.

**Methyl gallate (2):** To a 200 ml round bottom flask fitted with a condenser was added gallic acid **1** (6.00 g, 10.8 mmol), dry MeOH (120 ml) and conc. H<sub>2</sub>SO<sub>4</sub> (1.20 g), and then the mixture was heated at refluxing temperature for 6-8 h. After completion of the reaction, the solvent was

removed in vacuo and extracted with EtOAc followed by washing with sufficient amount of water. The organic layer was concentrated in vacuo giving the crude methyl gallate **2**. Recrystallization from hot water gave 6.36 g of pure methyl gallate (99%).

**Dimethyl 4,4',5,5',6,6'-hexahydroxybiphenyl-2,2'-dicarboxylate (4):** Solution of **2** (1.70 g, 9.24 mmol) in Et<sub>2</sub>O (90ml) was added dropwise under argon to a stirred cooled solution of *o*-chloranil (2.49 g, 10.1 mmol) in Et<sub>2</sub>O (20ml) at -40°C. After completion of the addition, the reaction mixture was allowed to warm slowly to rt. over 2 hour and an additional 1h and was stirred at rt. The yellow solid was appeared at the bottom of the flask and separated by filtration. The solid was washed extensively with cooled Et<sub>2</sub>O to give a yellow solid (1.28 g). The yellow solid was dissolved in THF and solution was cooled to 0°C and Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (1.22 g) was added. The solution was stirred at rt for 30 min, poured in ice-cooled water and the organic layer was extracted with Et<sub>2</sub>O. Removal of the solvent gave the crude hexahydroxydiphenyl **4**: mp 240-245°C(decomp.). <sup>1</sup>H NMR (CDCl<sub>3</sub>-CD<sub>3</sub>OD) δ 3.46 (s, 6H), 7.12 (s, 2H), 7.66 (bs, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>-CD<sub>3</sub>OD) δ 51.33, 110.70, 118.73, 122.55, 137.53, 144.52, 144.65.

**Ellagic acid (5):** Compound **4** (260 mg) was refluxed in MeOH:H<sub>2</sub>O (1:1, 5ml) for 18 h resulted in lactonization. Complete removal of the solvent yielded the crude ellagic acid **5** (218 mg, 100%) which was recrystallized from DMSO/CHCl<sub>3</sub> (1:1) to give a light brown solid: mp 350°C; IR: 3572, 3066, 1690, 1616, 1581, 1446, 1396, 1326, 1195, 1110, 1053, 922, 882,

756 cm<sup>-1</sup> (identical with the authentic ellagic acid). Anal. Calcd for C<sub>14</sub>H<sub>6</sub>O: C, 55.64; H, 2.00; Found: C, 55.52; H, 2.11.

**Methyl-3-hydroxy-4,5-(ethoxymethylenedioxy) benzoate (6):** A mixture of compound **2** (2.50 g, 13.6 mmol), (EtO)<sub>3</sub>CH (6.03 g, 40.7 mmol) and Amberlyst 15E (62 mg) in benzene (140 ml) was refluxed for 18 h with azeotropic removal of the EtOH:benzene mixture by using the Dean Stark trap. After completion, the reaction mixture was filtered over celite and the solvent was removed and directly put on a silica gel column eluted with 10-15% EtOAc in hexane yielded 3.21 g of **6** (99%) as a white solid: mp 91-92°C; IR: 3351, 1709, 1618, 1438, 1316, 1254, 1081, 1038, 765 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.28 (t, 3H, *J* = 7.1 Hz), 3.75 (q, 2H, *J* = 7.1 Hz), 3.88 (s, 3H), 5.56 (bs, 1H), 6.96(s, 1H), 7.19 (d, 1H, *J* = 1.5 Hz), 7.39 (d, 1H, *J* = 1.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.68, 52.38, 59.71, 102.71, 113.96, 120.04, 124.03, 137.08, 138.68, 147.14, 166.95.

**Methyl 3-methoxy-4,5-dihydroxybenzoate(7a):** Compound **6a** was treated with MeI (1.2 eq), K<sub>2</sub>CO<sub>3</sub> (2.0 eq.) in DMF at 55-60°C for 12 h. Then the crude was extracted with Et<sub>2</sub>O, washed with brine, dried over MgSO<sub>4</sub> and concentrated. The crude was treated with 2N aq.HCl at rt. for 2 h in MeOH gave **7a** (99% yield over 2 steps) as a colorless crystal: mp 115-119°C; IR: 3382, 1708, 1593, 1506, 1436, 1243, 1161, 1058, 1000, 964, 726 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.88 (s, 3H), 3.92 (s, 3H), 5.49 (s, 1H), 5.86 (s, 1H), 7.21 (d, 1H, *J* = 1.8 Hz), 7.34 (d, 1H, *J* = 1.8 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>-CD<sub>3</sub>OD) δ 51.85, 55.96, 104.94, 110.78, 120.38, 138.51, 144.21, 147.18, 167.56.

**Methyl 3-benzyloxy-4,5-dihydroxybenzoate (7b):** Using a similar procedure of **7a** with BnCl instead of MeI compound **7b** was obtained in ~100% yield as a colorless solid: mp 142-145°C; IR: 3412, 3342, 1686, 1434, 1326, 1239, 1055, 744 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.87 (s, 3H), 5.14 (s, 2H), 5.36 (s, 1H), 5.84 (s, 1H), 7.31 (d, 1H, *J* = 1.8 Hz), 7.35 (d, 1H, *J* = 1.8 Hz), 7.39-7.43 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>-CD<sub>3</sub>OD) δ 51.76, 71.03, 106.36, 110.92, 120.36, 127.71, 128.06, 128.38, 136.08, 138.62, 144.33, 167.33

**Methyl 2-bromo-3,4-dihydroxy-5-methoxybenzoate (8a):** Using the procedure of ref. 14, **8a** was prepared from **7a** in 98% yield as a slight yellow crystal: mp 140-142°C; IR: 3461, 3341, 1717, 1601, 1429, 1292, 1210, 1101, 1018, 923, 776 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.91 (s, 3H), 3.94 (s, 3H), 5.84 (s, 1H), 5.92 (s, 1H), 7.18 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 52.30, 56.42, 103.26, 107.06, 121.81, 136.68, 141.36, 145.67, 165.94.

**Methyl 2-bromo-3,4-dihydroxy-5-benzyloxybenzoate (8b):** Using the same procedure of **8a**, **8b** was prepared from **7b** in 95% yield as a light yellow crystal: mp 116-118°C; IR : 3370, 1712, 1342, 1222, 1000 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.90 (s, 3H), 5.14 (s, 2H), 5.91 (s, 1H), 5.92 (s, 1H), 7.27 (s, 1H), 7.38-7.52 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>- CD<sub>3</sub>OD) δ 52.14, 71.34, 103.24, 108.31, 121.44, 127.96, 128.45, 128.62, 133.74, 137.64, 142.61, 144.93, 167.37.

**Methyl 2-bromo-3,4-(ethoxymethylenedioxy)-5-methoxybenzoate (9a):** Using the similar procedure as compound **6**, compound **9a** was prepared in 69% yield from **8a** as a white solid: mp 80-81°C; IR: 1722, 1432, 1318, 1171, 1081,

1035, 938, 752, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.28 (t, 3H, *J* = 7.1 Hz), 3.73 (q, 2H, *J* = 7.1 Hz), 3.91 (s, 3H), 3.94 (s, 3H), 7.01 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 14.68, 52.28, 59.85, 71.79, 94.16, 114.41, 119.91, 124.17, 127.65, 128.32, 128.59, 135.90, 137.24, 140.43, 146.57, 165.41.

**Methyl 2-bromo-3,4-(ethoxymethylenedioxy)-5-benzyloxybenzoate (9b):** Using the similar procedure of **9a**, **9b** was prepared in 66% yield from **8b** as a light yellow crystal: mp 116-118°C; IR: 3370, 1712, 1342, 1222, 1000 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.90 (s, 3H), 5.14 (s, 2H), 5.91 (s, 1H), 5.92 (s, 1H), 7.27 (s, 1H), 7.38-7.52 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>-CD<sub>3</sub>OD) δ 52.14, 71.34, 103.24, 108.31, 121.44, 127.96, 128.45, 128.62, 133.74, 137.64, 142.61, 144.93, 167.37.

**Dimethyl 4,4'-dimethoxy-5,6,5',6'-bis(ethoxymethylenedioxy)biphenyl-2,2'-dicarboxylate (10a):** A mixture of compound **9a** (655 mg), Cu powder (655 mg) and DMF (1.5 ml) was stirred at 110°C for 3h. Then another 10 ml of DMF was added and the reaction mixture was stirred at 180°C for 18 h. After completion, crushed ice was added and extracted with CHCl<sub>3</sub>. The organic layer was washed with water and then brine, dried over MgSO<sub>4</sub> and concentrated in vacuo. Purification by silica gel column chromatography (eluted with 20% EtOAc in hexane and then 100% CHCl<sub>3</sub>) gave 155 mg of **10a** (40%). White solid, <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.28 (t, 6H, *J* = 7.1 Hz), 3.73 (q, 4H, *J* = 7.1 Hz), 3.84 (s, 6H), 4.00 (s, 3H), 4.03 (s, 3H), 6.89 (s, 2H).

**Dimethyl 4,4'-dibenzyloxy-5,6,5',6'-bis(ethoxymethylenedioxy)biphenyl-2,2'-dicarboxylate (10b):** Using the same procedure as **10a**, **10b** was

obtained in 70% from **9b** as gummy solid. IR: 2979, 1724, 1638, 1589, 1433, 1348, 1314, 1243, 1171, 1091, 1036, 906, 746, 698.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.28 (t, 6H,  $J=7.1$  Hz), 3.73 (q, 4H,  $J=7.1$  Hz), 3.60 (s, 6H), 5.24 (s, 4H), 7.34~7.49 (m, 12H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.13, 14.56, 14.65, 14.68, 51.76, 51.85, 58.27, 58.66, 58.72, 58.93, 71.48, 111.29, 111.61, 111.87, 112.59, 112.66, 112.71, 112.76, 119.63, 119.70, 119.73, 119.87, 123.05, 123.21, 123.41, 123.63, 127.73, 128.18, 128.54, 128.66, 128.68, 136.27, 136.97, 137.09, 137.14, 140.58, 140.69, 140.75, 140.82, 145.70, 145.75, 166.21, 166.23, 166.25.

**Dimethyl 5,5',6,6'-tetrahydroxy-4,4'-dimethoxy biphenyl-2,2'-dicarboxylate (11a):** Treatment of **10a** with 2N HCl in MeOH at room temperature for 4 h gave the hexahydroxy biphenyl **11a** in 98% yield. White solid,  $^1\text{H}$  NMR ( $\text{CDCl}_3\text{-CD}_3\text{OD}$ )  $\delta$  3.63 (s, 6H), 3.75 (s, 6H), 5.30 (s, 2H), 5.89 (s, 2H), 7.42 (s, 2H).

**Dimethyl 5,5',6,6'-tetrahydroxy-4,4'-dibenzoxy biphenyl-2,2'-dicarboxylate (11b):** Using the same procedure as **11a**, **11b** was also prepared in 98% yield from **10b**. IR: 3232, 1701, 1617, 1572, 1497, 1444, 1371, 1338, 1255, 1186, 1126, 1089, 810, 757, 740, 695.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.63 (s, 6H), 5.18 (s, 4H), 5.30 (s, 2H), 5.89 (s, 2H), 7.40~7.46 (s, 1H), 7.38~7.52 (m, 12H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  51.86, 71.26, 107.00, 119.09, 121.30, 128.22, 128.53, 128.74, 133.95, 136.58, 141.72, 144.97, 166.74.

**4,4'-Di-O-methylellagic acid (12a):** Compound **11a** was dissolved in MeOH/ $\text{H}_2\text{O}$  (1:1) and was refluxing at  $110^\circ\text{C}$  for 8 h gave the final product **12a** in almost quantitative yield. Light brown

solid; mp  $358\text{-}361^\circ\text{C}$ (decomp) (lit.<sup>15</sup> 360-363);  $^1\text{H}$  NMR ( $\text{CDCl}_3\text{-DMSO-}D_6$ )  $\delta$  4.00 (s, 6H), 7.57 (s, 2H), 7.85 (s, 2H).

**4,4'-Di-O-benzylellagic acid (12b):** Using the similar procedure as **12a**, **12b** was prepared in quantitative yield. Light yellow solid, mp  $280\text{-}285^\circ\text{C}$  (decomp);  $^1\text{H}$  NMR ( $\text{CDCl}_3\text{-DMSO-}D_6$ )  $\delta$  5.31 (s, 4H), 7.35~7.45 (m, 6H), 7.51~7.55 (m, 4H), 7.66 (s, 2H), 7.92 (s, 2H).

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