

HETEROCYCLES, Vol. 85, No. 9, 2012, pp. 2241 - 2250. © 2012 The Japan Institute of Heterocyclic Chemistry  
Received, 18th June, 2012, Accepted, 6th July, 2012, Published online, 11th July, 2012  
DOI: 10.3987/COM-12-12526

## SYNTHESIS OF PROCYANIDINS C2 AND C1 USING LEWIS ACID MEDIATED EQUIMOLAR CONDENSATION

Yukiko Oizumi,<sup>a</sup> Miyuki Katoh,<sup>a</sup> Yasunao Hattori,<sup>b</sup> Kazuya Toda,<sup>c</sup> Koichiro Kawaguchi,<sup>c</sup> Hiroshi Fujii,<sup>c</sup> and Hidefumi Makabe<sup>a\*</sup>

<sup>a</sup>Sciences of Functional Foods, Graduate School of Agriculture, Shinshu University, 8304 Minami-minowa, Kami-ina, Nagano 399-4598, Japan

<sup>b</sup>Department of Medicinal Chemistry, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8412, Japan

<sup>c</sup>Department of Bioscience and Biotechnology, Faculty of Agriculture, Shinshu University, 8304 Minami-minowa, Kami-ina, Nagano 399-4598, Japan

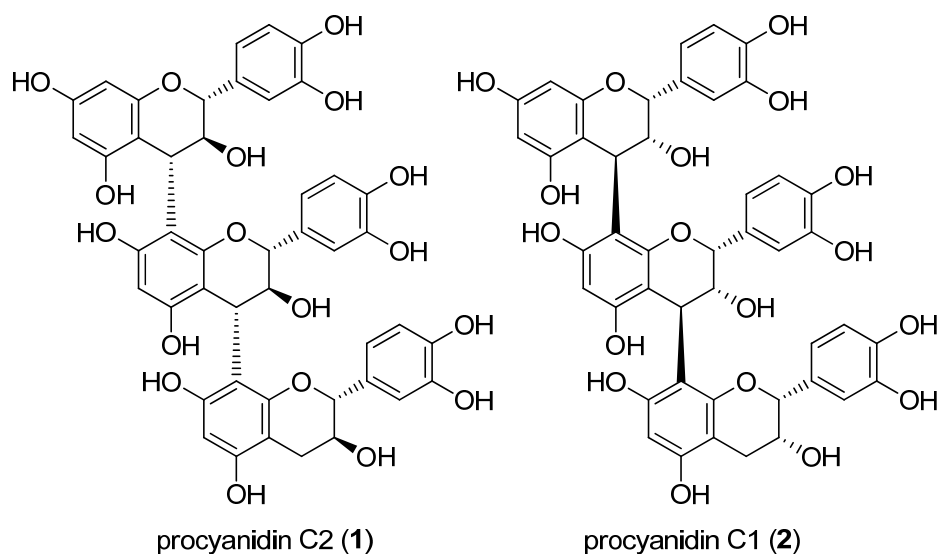
\*E-mail: makabeh@shinshu-u.ac.jp

**Abstract** – Synthesis of procyanidins C2 and C1 was achieved via a stereoselective intermolecular condensation of equimolar amount of dimeric catechin or epicatechin nucleophile and monomeric catechin or epicatechin electrophile using Lewis acid. In the case of synthesis of procyanidin C2, AgBF<sub>4</sub> and AgOTf afforded condensed product in excellent yield. As to the synthesis of procyanidin C1, Yb(OTf)<sub>3</sub> was effective for equimolar condensation.

## INTRODUCTION

Proanthocyanidins are known as condensed or non-hydrolysable tannins.<sup>1</sup> These tannins are widely found in the vegetables, fruits and the bark of trees.<sup>2</sup> Proanthocyanidins have been reported to exhibit strong free-radical scavenging and antioxidative activities.<sup>3</sup> Many biological activities such as antitumor,<sup>4</sup> antiviral,<sup>5</sup> anti-inflammatory,<sup>6</sup> and inhibition of DNA polymerase were reported.<sup>7</sup> Thus proanthocyanidins are increasingly recognized as possessing health beneficial effects for humans. Tannin extracts from the nature give various types of polyphenols. Because their identification as well as purification is extremely difficult, further investigation of biological activities, i. e. mechanism of action remains unsolved. In these days, in order to obtain procyanidin oligomers in pure state, synthetic efforts have been devoted.<sup>8</sup> As to

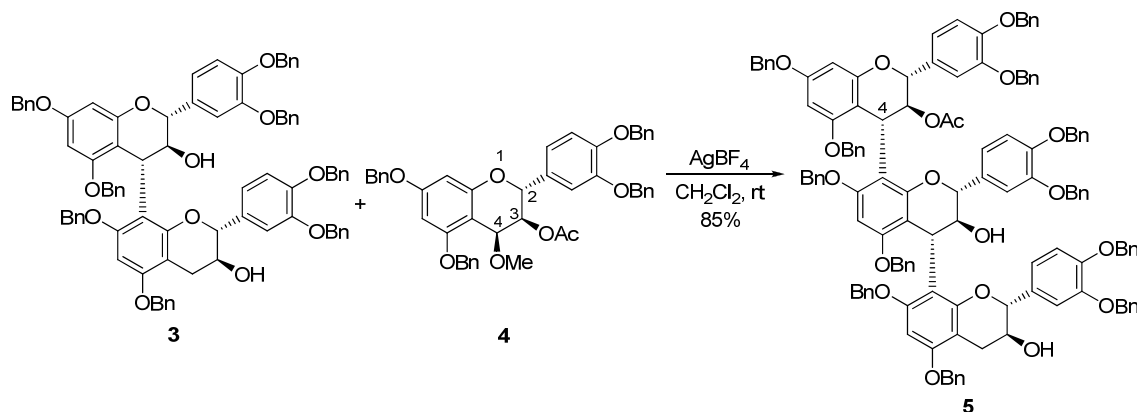
the synthesis of catechin and/or epicatechin trimers, several synthetic studies were reported. The typical synthetic methods are as follows. The first example is pioneering work of the synthesis of procyanidins reported by Saito et al.<sup>9</sup> This method requires to use nucleophilic partner in large excess (3.0 to 4.5 eq.) for condensation to prevent further oligomerization. The disadvantage of this procedure is that excess nucleophilic partner needs to be removed after condensation. The next one is use of C-8 bromide derivative to prevent forming further oligomerization.<sup>10</sup> Quite recent example is using C-8 bromide and C-8 metallated nucleophile for the selective synthesis of C-4 and C-8 bound catechin trimers.<sup>11</sup> So far, little attention has been paid to the screening of Lewis acids for *equimolar* condensation to construct the skeleton of procyanidin trimers. We have already reported a stereoselective synthesis of catechin trimer derivative using equimolar condensation.<sup>12</sup> However, synthesis of epicatechin trimer using equimolar condensation has not been reported yet. In this article, we wish to report total synthesis of procyanidin C2 (**1**) and the recent progress of the synthesis of procyanidin C1 (**2**) via equimolar condensation between dimeric catechin or epicatechin nucleophile and monomeric catechin or epicatechin electrophile (Figure 1).



**Figure 1.** The structures of procyanidin C2 (**1**) and C1 (**2**)

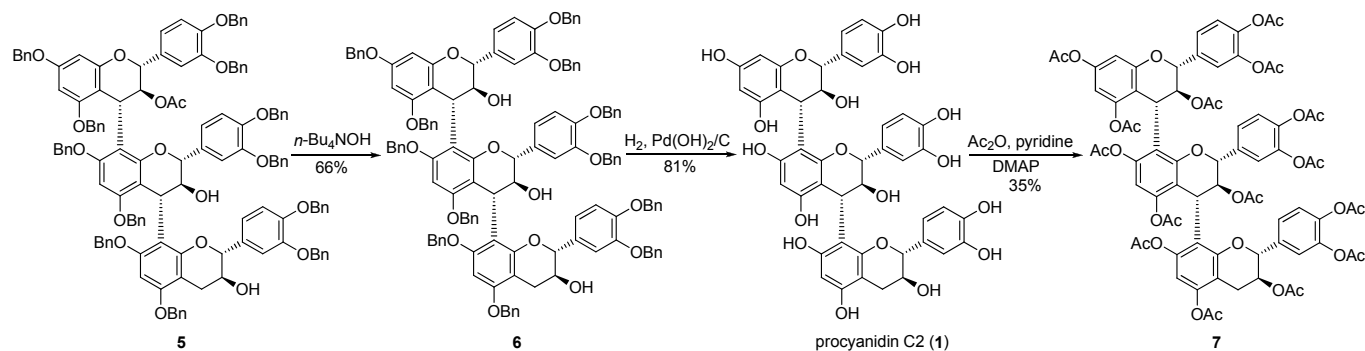
## RESULTS AND DISCUSSION

We have investigated various Lewis acids including Ag, Cu, and Yb for equimolar condensation between dimeric catechin nucleophile **3** and monomeric catechin electrophile **4**. Among these Lewis acids, we found that silver Lewis acids such as AgBF<sub>4</sub> and AgOTf gave condensed product in excellent yield (Scheme 1).<sup>12</sup>



**Scheme 1.** Equimolar condensation between dimeric catechin nucleophile **3** and monomeric catechin electrophile **4**

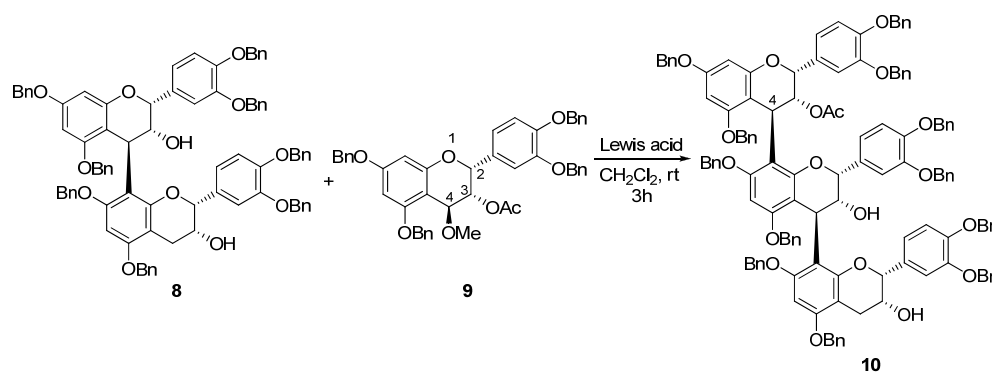
The condensed product **5** was obtained in high yield,<sup>9</sup> we next pursued to establish total synthesis of procyanidin C2 (**1**). Hydrolysis of the acetate of **5** using NaOMe under reflux did not furnish **6** although this reaction worked well in the case of procyanidin B1-B4.<sup>13</sup> Thus diol **5** was once acetylated using  $\text{Ac}_2\text{O}$  to give triacetate and subsequent reduction with DIBALH afforded **6** in 45% yield through 2 steps.<sup>9</sup> However, the yield of transformation from **5** to **6** was not high enough, we tried the Kozikowski's method using  $n\text{-Bu}_4\text{NOH}$  to afford **6** in 66% yield.<sup>14</sup> The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data of **6** were identical with those of the reported values.<sup>9</sup> The 3,4-*cis* trimer could not be detected. This result indicated that electrophile **4** reacted with nucleophile **3** at C-4 position in a stereoselective manner to afford 3,4-*trans* trimer **5**. The benzyl ether **6** was deprotected to yield procyanidin C2 (**1**) by hydrogenolysis over Pearlman's catalyst. As to the purification of **1**, when the crude products were directly evaporated, partially insoluble materials remained.<sup>14</sup> We met with some difficulty to purify **1** after debenzylation. We tried separation by ODS cartridge column chromatography and preparative HPLC, however, we could not obtain **1** in a satisfying yield. Kozikowski and colleagues reported that lyophilization is useful for purification of these type compounds.<sup>14</sup> Thus we used this method to afford procyanidin C2 (**1**) in good yield. We confirmed that lyophilized procyanidin C2 (**1**) was pure by HPLC analysis.<sup>15</sup> The optical rotation value and mass spectrum data of synthetic **1** were in good accordance with those of the reported values.<sup>9</sup> With regard to the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data of **1**, we could not find them in any reports to the best of our knowledge. In this article, we wish to supply these data in experimental section and supporting information for future reference. The  $^1\text{H}$  NMR spectral datum of peracetate **7** was in good agreement with that of the reported values (Scheme 2).<sup>16</sup>



**Scheme 2.** Synthesis of procyanidin C2 (**1**) and its peracetate **7**

As to the synthesis of procyanidin C1 (**2**), equimolar condensation of **8** with **9** was examined using transition metal Lewis acids and Yb(OTf)<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>. As shown in Table 1, AgBF<sub>4</sub> and AgOTf gave condensed product **10**<sup>9,14</sup> in poor yield although these silver Lewis acids gave good results in the condensation of **3** with **4**. The stereochemistry at C-3 position of **9** seemed to affect the reactivity, however, we could not explain the reason at this stage and further investigation is necessary. Next we used Yb(OTf)<sub>3</sub> and found that the yield of condensation was slightly improved (Table 1).

**Table 1.** Lewis acid mediated equimolar condensation between **8** and **9**

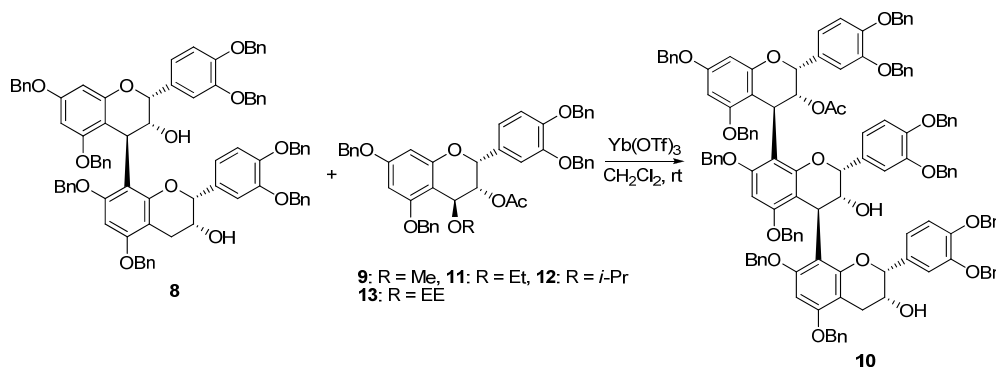


Entry	Lewis acid	Yield of <b>10</b> (%)
1	AgBF <sub>4</sub>	15
2	AgOTf	27
3	Cu(OTf) <sub>2</sub>	17
4	Yb(OTf) <sub>3</sub>	36

This result encouraged us to examine equimolar condensation of **8** with various 4-alkoxy epicatechin derivatives **11-13** using Yb(OTf)<sub>3</sub>. As shown in Table 2, 4-(2''-ethoxyethoxy) derivative **13** afforded condensed product **10** in 57% yield. Other 4-alkoxy derivatives gave **10** in low yield and both of the

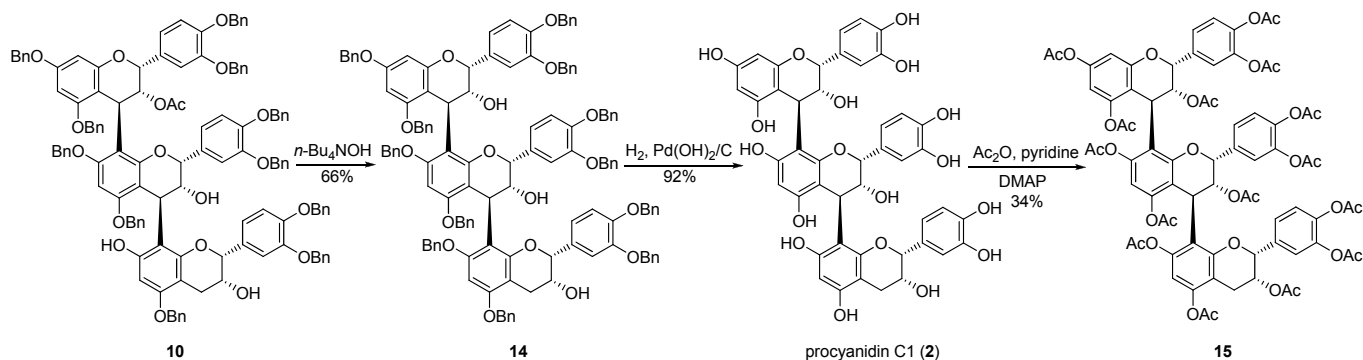
starting materials remained. We found that 4-(2''-ethoxyethoxy) group was suitable for Yb(OTf)<sub>3</sub> mediated activation at C-4 position of electrophile (Table 2).

**Table 2.** Equimolar condensation of 4-alkoxy epicatechin derivatives **9**, **11-13** with dimeric epicatechin nucleophile **8** by Yb(OTf)<sub>3</sub>



Entry	electrophile	Time (h)	Yield (%)
1	<b>9</b>	3	36
2	<b>11</b>	3	18
3	<b>12</b>	3	15
4	<b>13</b>	1	57

The condensed product **10** was transformed into triol **14** using *n*-Bu<sub>4</sub>NOH.<sup>14</sup> The <sup>1</sup>H and <sup>13</sup>C NMR spectral data of **14** were in good agreement with those of the reported values. The 3,4-*cis* diastereomer could not be detected.<sup>9,14</sup> Finally deprotection of the benzyl group of **14** subsequent lyophilization afforded procyanidin C1 (**2**) in good yield. We confirmed that lyophilized procyanidin C1 (**2**) was pure by HPLC analysis (Scheme 3).<sup>17</sup>



**Scheme 3.** Synthesis of procyanidin C1 (**2**) and its peracetate **15**

The optical rotation value and spectral data of synthetic **2** were in good accordance with those of the reported values.<sup>9,14</sup> The <sup>1</sup>H and <sup>13</sup>C NMR spectral data of peracetate **15** were in good agreement with those of the reported values.<sup>14</sup>

## CONCLUSION

Synthesis of procyanidin C2 (**1**) was achieved via AgBF<sub>4</sub> or AgOTf mediated intermolecular condensation using equimolar amount of dimeric catechin nucleophile **3** and monomeric catechin electrophile **4**. As to the synthesis of procyanidin C1 (**2**), dimeric epicatechin derivative **8** and 4-(2''-ethoxyethoxy) epicatechin electrophile **13** in the presence of Yb(OTf)<sub>3</sub> afforded condensed product **10** in moderate yield. For purifying procyanidin C2 (**1**) and C1 (**2**) after debenzoylation, we recognized that lyophilization was useful.

## EXPERIMENTAL

### General

<sup>1</sup>H and <sup>13</sup>C NMR spectra were measured with a Bruker Avance DRX 500 FT-NMR spectrometer in CDCl<sub>3</sub> or CD<sub>3</sub>OD at 500 and 125 MHz, respectively. Chemical shifts were relative to tetramethylsilane as an internal standard. The coupling constants were given in Hz. Mass spectra were obtained on Shimadzu LCMS-2010EV and Waters Xevo QTOF mass spectrometers. Optical rotations were measured with a JASCO DIP 1000 polarimeter. Merck silica gel 60 (70-230 mesh) was used for column chromatography unless otherwise noted. Solvents for reactions were distilled prior to use: THF from Na and benzophenone, CH<sub>2</sub>Cl<sub>2</sub> from CaH<sub>2</sub>.

**3-O-Acetyl-tris(5,7,3',4'-tetra-O-benzyl)catechin (4 $\alpha$ /8)<sub>2</sub>-trimer (5).** To a solution of nucleophile **3** (68 mg, 0.052 mmol) and electrophile **4** (38 mg, 0.052 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) under an argon atmosphere was added AgBF<sub>4</sub> (10 mg, 0.052 mmol). After the resulting mixture had been stirred for 3 h at room temperature, the reaction was quenched with water. The mixture was extracted with Et<sub>2</sub>O, and the combined organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified with silica gel column chromatography (hexane:AcOEt:CH<sub>2</sub>Cl<sub>2</sub> = 4:1:2) to give **5** (89 mg, 85%) as a colorless oil. [ $\alpha$ ]<sub>D</sub><sup>16</sup> -100 (*c* 3.20, CHCl<sub>3</sub>). ESIMS: *m/z* 2011.9 [M+Na]<sup>+</sup>.

**Tris(5,7,3',4'-tetra-O-benzyl)catechin (4 $\alpha$ /8)<sub>2</sub>-trimer (6).** To a solution of **5** (108 mg, 0.054 mmol) in THF (3 mL) was added 40% aqueous *n*-Bu<sub>4</sub>NOH (0.58 mL, 0.89 mmol). The reaction mixture was allowed to be stirred for 96 h at room temperature, then partially evaporated to remove THF. The residue was diluted with H<sub>2</sub>O (5 mL), and the product was extracted with EtOAc (2  $\times$  5 mL). The combined

organic layer was washed with brine and concentrated. The residue was purified with preparative TLC (hexane:AcOEt:CH<sub>2</sub>Cl<sub>2</sub> = 4:1:2) to afford **6** (70 mg, 66%) as a colorless foam.  $[\alpha]_{\text{D}}^{22}$   $-143$  ( $c$  0.850, CHCl<sub>3</sub>), {lit.,  $[\alpha]_{\text{D}}^{26}$   $-82.2$  ( $c$  0.12, CHCl<sub>3</sub>)}.<sup>9</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 0.82:0.18 mixture of rotational isomer, major isomer)  $\delta$  = 7.44-6.40 (69H, m), 6.17 (1H, d,  $J$  = 2.3 Hz), 6.16 (1H, d,  $J$  = 2.3 Hz), 6.09 (1H, d,  $J$  = 2.3 Hz), 6.08 (1H, s), 5.22-4.40 (26H, m), 4.25 (1H, d,  $J$  = 8.8 Hz), 4.05-3.95 (2H, m), 3.81-3.75 (1H, m), 3.60 (1H, d,  $J$  = 8.9 Hz), 3.10 (1H, dd,  $J$  = 16.0, 6.0 Hz), 2.96 (1H, d,  $J$  = 9.5 Hz), 2.37 (1H, dd,  $J$  = 16.5, 9.8 Hz), 1.36 (1H, d,  $J$  = 4.0 Hz, -OH), 1.33 (1H, d,  $J$  = 3.5 Hz, -OH), 1.14 (1H, d,  $J$  = 3.5 Hz), <sup>13</sup>C NMR (CDCl<sub>3</sub>, major isomer)  $\delta$  = 157.9, 157.8, 156.7, 155.5, 155.4, 155.2, 155.1, 155.0, 153.8, 149.2, 149.1, 148.8, 148.6, 137.7, 137.5, 137.4, 137.3, 137.2, 137.1, 136.0, 132.4, 131.7, 128.9-126.9, 121.1, 120.7, 120.6, 115.1, 114.9, 114.8, 114.6, 114.2, 113.8, 112.4, 109.4, 108.8, 102.4, 94.7, 93.8, 92.0, 91.8, 81.8, 81.0, 80.4, 73.1, 73.0, 71.9-69.8, 68.4, 37.6, 37.5, 28.5; ESIMS:  $m/z$  1969.8 [M+Na]<sup>+</sup>.

**Procyanidin C2 (1).** A solution of **6** (74 mg, 0.038 mmol) in THF/MeOH/H<sub>2</sub>O (20/20/1) (15 mL) was hydrogenated over 20% Pd(OH)<sub>2</sub>/C (65 mg) for 1 h at room temperature. The mixture was filtered and filtration residue was washed with MeOH (20 mL). The combined filtrates were evaporated, and the residue was taken up in distilled water (10 mL). The solution was filtered and lyophilized to give **1** (30 mg, 81%) as a fluffy amorphous solid.  $[\alpha]_{\text{D}}^{20}$   $-274$  ( $c$  0.110, EtOH), {lit.,  $[\alpha]_{\text{D}}^{20}$   $-233.7$  ( $c$  0.38, EtOH)}.<sup>9</sup> <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  = 7.05-6.50 (8H, m), 6.40-5.65 (5H, m), 4.80-4.05 (6H, m), 4.00-3.50 (1H, m), 2.90-2.10 (3H, m); <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  = 158.5, 158.0, 157.7, 157.3, 156.9, 156.1, 155.7, 154.5, 146.3, 146.2, 146.0, 145.9, 145.3, 145.2, 132.6, 132.4, 132.3, 132.1, 132.0, 131.6, 121.1, 120.5, 120.3, 120.2, 120.0, 117.3, 116.7, 116.6, 116.4, 116.1, 115.7, 115.3, 114.1, 113.1, 109.2, 108.8, 108.6, 107.4, 98.7, 97.5, 97.3, 96.8, 96.4, 96.0, 95.5, 85.6, 84.0, 83.7, 83.4, 83.0, 82.9, 80.0, 78.1, 74.9, 74.0, 73.7, 73.0, 72.8, 39.1, 38.8, 38.7, 28.5; HRESIMS calcd for C<sub>45</sub>H<sub>37</sub>O<sub>18</sub> [M-H]<sup>-</sup>; 865.1979; found 865.1955.

**Peracetate of 1 (7).** Acetylation of **1** (6 mg, 6.9  $\mu$ mol) using general procedure gave peracetate **7** (5 mg, 35%).  $[\alpha]_{\text{D}}^{19}$   $-205$  ( $c$  0.302, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 7.27 (2H, d,  $J$  = 8.5 Hz), 7.10-7.05 (5H, m), 6.86 (1H, d,  $J$  = 1.5 Hz), 6.80 (1H, d,  $J$  = 2.0 Hz), 6.67 (1H, s), 6.62 (1H, s), 6.54 (1H, d,  $J$  = 2.5 Hz), 6.55-6.50 (2H, m), 6.21 (1H, d,  $J$  = 2.5 Hz), 5.58 (1H, dd,  $J$  = 10.0, 9.0 Hz), 5.48 (1H, dd,  $J$  = 10.0, 8.5 Hz), 5.25 (1H, brs), 5.23 (2H, m), 4.74 (1H, d,  $J$  = 10.0 Hz), 4.62 (1H, d,  $J$  = 10.0 Hz), 4.57 (1H, d,  $J$  = 8.5 Hz), 4.12 (1H, d,  $J$  = 9.0 Hz), 2.60-2.55 (1H, m), 2.35 (3H, s), 2.34 (3H, s), 2.29 (3H, s), 2.272 (9H, s), 2.269 (3H, s), 2.25 (3H, s), 2.22 (3H, s), 2.14 (3H, s), 2.07 (3H, s), 1.96 (3H, s), 1.65 (3H, s), 1.64 (3H, s), 1.62 (3H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 171.4, 169.7, 169.4, 168.7, 168.6, 168.4, 168.1, 167.9, 167.6, 156.3, 154.8, 151.1, 150.0, 149.2, 148.0, 147.4, 147.2, 147.0, 142.5, 141.9, 141.6, 141.5, 141.1, 136.6, 135.1,

134.9, 125.6, 124.6, 123.7, 123.2, 122.9, 122.5, 122.4, 119.5, 118.7, 117.2, 116.7, 116.6, 110.4, 109.8, 109.0, 108.4, 108.3, 79.7, 78.5, 76.3, 72.1, 70.9, 66.6, 53.4, 36.7, 29.7, 21.2, 20.9, 20.7, 20.6, 20.5, 20.4, 20.3, 20.2.

**3-*O*-Acetyl-tris(5,7,3',4'-tetra-*O*-benzyl)epicatechin (4 $\beta$ /8)<sub>2</sub>-trimer (10).** To a solution of nucleophile **8** (58 mg, 0.045 mmol) and electrophile **13** (35 mg, 0.045 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) under an argon atmosphere was added Yb(OTf)<sub>3</sub> (28 mg, 0.045 mmol). After the resulting mixture had been stirred for 1 h at room temperature, the reaction was quenched with water. The mixture was extracted with Et<sub>2</sub>O, and the combined organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified with silica gel column chromatography (hexane:AcOEt:CH<sub>2</sub>Cl<sub>2</sub> = 4:1:2) to give **10** (51 mg, 57%) as a colorless oil.  $[\alpha]_D^{19} +129$  (*c* 0.901, CHCl<sub>3</sub>). ESIMS: *m/z* 2011.9 [M+Na]<sup>+</sup>.

**Tris(5,7,3',4'-tetra-*O*-benzyl)epicatechin (4 $\beta$ /8)<sub>2</sub>-trimer (14).** In the same manner as described the synthesis of **6**, compound **10** (42 mg, 0.021 mmol) afforded **14** (27 mg, 66%) as a colorless foam.  $[\alpha]_D^{18} +93.9$  (*c* 1.32, CHCl<sub>3</sub>), {lit.,  $[\alpha]_D^{25} +75.9$  (*c* 0.32, CHCl<sub>3</sub>)}.<sup>9</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 0.5:0.5 mixture of rotational isomer)  $\delta$  = 7.51-6.73 (67.5H, m), 6.45 (0.5H, d, *J* = 8.0 Hz), 6.39 (0.5H, d, *J* = 8.0 Hz), 6.35 (0.5H, s), 6.27 (0.5H, d, *J* = 2.5 Hz), 6.18 (0.5H, s), 6.13 (0.5H, dd, *J* = 8.5, 1.5 Hz), 6.06 (0.5H, d, *J* = 2.0 Hz), 5.95 (0.5H, d, *J* = 2.0 Hz), 5.90 (0.5H, s), 5.85 (0.5H, s), 5.73 (0.5H, s), 5.70 (0.5H, d, *J* = 2.0 Hz), 5.49 (0.5H, s), 5.18-4.05 (29.5H, m), 3.95 (0.5H, d, *J* = 5.5 Hz), 3.64 (0.5H, s), 2.97-2.80 (2H, m), 1.81 (0.5H, d, *J* = 5.5 Hz, -OH), 1.70 (0.5H, d, *J* = 6.5 Hz, -OH), 1.55 (1H, m), 1.45 (0.5H, brs), 1.20 (1H, brs); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  = 158.3, 158.1, 158.0, 157.4, 156.8, 156.5, 156.4, 156.2, 156.1, 155.7, 155.5, 155.3, 154.7, 137.3, 137.2, 137.0, 132.9, 132.6, 132.4, 132.3, 131.3, 128.6-126.2, 120.0, 119.7, 118.9, 118.8, 115.1, 115.0, 114.8, 114.2, 113.6, 113.5, 113.2, 113.0, 111.3, 111.1, 110.1, 106.0, 105.4, 104.7, 104.6, 101.4, 100.8, 94.4, 94.0, 93.8, 93.4, 92.6, 92.5, 92.3, 90.3, 72.7, 72.5, 71.4-69.3, 65.3, 64.9, 36.6, 36.2, 35.5, 28.6; ESIMS: *m/z* 1969.8 [M+Na]<sup>+</sup>.

**Procyanidin C1 (2).** In the same manner as described the synthesis of **1**, compound **14** (54 mg, 0.028 mmol) afforded **2** (25 mg, 92%) as a fluffy amorphous solid.  $[\alpha]_D^{19} +60.7$  (*c* 0.45, MeOH), {lit.,  $[\alpha]_D^{27} +59$  (*c* 0.30, MeOH),<sup>9</sup>  $[\alpha]_D +70.4$  (*c* 2.2, MeOH)<sup>14</sup>}. <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  = 7.13 (1H, s), 7.02 (1H, s), 6.92 (2H, s), 6.77-6.70 (5H, m), 6.02 (2H, d, *J* = 16.5 Hz), 5.93 (2H, s), 5.22 (1H, s), 5.07 (1H, s), 4.99 (1H, s), 4.71 (2H, brs), 4.33 (1H, s), 4.01 (2H, m), 2.95 (1H, d, *J* = 15.5 Hz), 2.81 (1H, d, *J* = 16.5 Hz); <sup>13</sup>C NMR (CD<sub>3</sub>OD)  $\delta$  = 158.6, 157.3, 156.9, 156.6, 154.6, 146.0, 145.8, 145.7, 132.7, 132.1, 119.3, 119.1, 118.9, 116.0, 115.3, 115.1, 107.2, 101.4, 100.6, 97.6, 96.6, 96.2, 79.7, 77.1, 73.5, 72.9, 66.8, 59.5, 39.1,

37.4, 33.1, 30.7, 30.6, 29.8, 24.8; HRESIMS calcd for C<sub>45</sub>H<sub>37</sub>O<sub>18</sub> [M-H]<sup>-</sup>; 865.1979; found 865.1984.

**Peracetate of 2 (15).** Acetylation of **2** (14 mg, 16 μmol) using general procedure gave peracetate **15** (11 mg, 34%). [α]<sub>D</sub><sup>17</sup> +56 (*c* 0.35, acetone), {lit., [α]<sub>D</sub> +55.3 (*c* 10.4, acetone)},<sup>14</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 2:1 mixture of rotational isomers) δ = 7.37 (0.33H, d, *J* = 2.0 Hz), 7.29 (0.67H, d, *J* = 1.5 Hz), 7.25 (0.33H, d, *J* = 1.5 Hz), 7.29-7.05 (1.65H, m), 7.20-7.05 (5.67H, m), 6.99 (0.33H, d, *J* = 2.0 Hz), 6.94 (0.33H, d, *J* = 8.5 Hz), 6.89 (0.33H, s), 6.79 (0.33H, dd, *J* = 8.5, 2.0 Hz), 6.76 (0.67H, d, *J* = 2.0 Hz), 6.72 (0.67H, s), 6.65 (0.67H, s), 6.60 (0.33H, s), 6.25 (0.33H, d, *J* = 2.0 Hz), 5.94 (0.33H, d, *J* = 2.0 Hz), 5.70 (0.33H, brs), 5.47 (0.67H, d, *J* = 4.5 Hz), 5.40 (1.67H, m), 5.36 (1.33H, m), 5.21 (0.67H, brs), 5.12 (0.33H, brs), 5.11 (0.33H, brs), 4.94 (0.33H, m), 4.78 (0.67H, brs), 4.70 (0.67H, brs), 4.67 (0.33H, brs), 4.66 (0.33H, brs), 4.49 (0.33H, d, *J* = 2.5 Hz), 3.07 (0.67H, dd, *J* = 18.0, 5.0 Hz), 3.02 (0.33H, dd, *J* = 18.0, 5.0 Hz), 2.97 (0.67H, m), 2.89 (0.33H, m), 2.38-1.38 (45H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ = 170.1, 169.9, 169.0, 168.8, 168.7, 168.5, 168.4, 168.3, 168.1, 168.0, 167.9, 167.8, 167.7, 167.6, 167.4, 154.9, 154.0, 151.8, 151.7, 149.9, 148.6, 148.5, 148.3, 147.9, 147.6, 147.2, 146.9, 142.1, 142.0, 141.9, 141.8, 141.6, 141.5, 136.5, 135.7, 135.4, 135.1, 133.1, 124.8, 124.2, 124.1, 123.9, 123.2, 123.1, 123.0, 122.7, 122.0, 121.6, 121.5, 121.3, 117.8, 117.7, 117.6, 117.2, 112.2, 111.6, 110.9, 110.6, 110.5, 110.0, 109.9, 109.3, 108.1, 107.5, 107.4, 76.1, 74.9, 74.7, 73.8, 71.4, 71.2, 70.9, 70.4, 66.6, 35.6, 35.0, 34.3, 32.9, 31.9, 29.7, 29.4, 22.7, 21.2, 21.0, 20.8, 20.7, 20.6, 20.5, 20.4, 20.2, 20.1, 20.0, 19.8, 19.7, 19.5.

## SUPPORTING INFORMATION

<sup>1</sup>H and <sup>13</sup>C NMR spectra of **1**, **2**, **7**, and **15**.

## ACKNOWLEDGEMENTS

We thank financial support from Japan Science and Technology Agency, Adaptable and Seamless Technology transfer Program through target-driven R&D (to HM (AS232Z00626E)).

## REFERENCES AND NOTES

1. D. Ferreira and X.-C. Li, *Nat. Prod. Rep.*, 2000, **17**, 193.
2. D. Ferreira and X.-C. Li, *Nat. Prod. Rep.*, 2002, **19**, 517.
3. N. Seeram, M. Aviram, Y. Zhang, S. M. Hennings, L. Feng, M. Dreher, and D. Heber, *J. Agric. Food Chem.*, 2008, **56**, 1415.
4. S. Mitsuhashi, A. Saito, N. Nakajima, H. Shima, and M. Ubukata, *Molecules*, 2008, **13**, 2998.
5. H. Y. Cheng, T. C. Lin, C. M. Yang, D. E. Shieh, and C. C. Lin, *J. Sci. Food Agric.*, 2005, **85**, 10.
6. X. Terra, J. Valls, X. Vitrac, J. M. Merrillon, L. Arola, A. Ardevol, C. Blade, J. Fernandez-Larrea, G.

- Pujadas, J. Salvado, and M. Blay, *J. Agric. Food Chem.*, 2007, **55**, 4357.
7. A. Saito, Y. Mizushina, H. Ikawa, H. Yoshida, Y. Doi, A. Tanaka, and N. Nakajima, *Bioorg. Med. Chem.*, 2005, **13**, 2759.
  8. D. Ferreira and C. M. Coleman, *Planta Med.*, 2011, **77**, 1071; K-i. Oyama, K. Yoshida, and T. Kondo, *Curr. Org. Chem.*, 2011, **15**, 2567; K. Ohmori and K. Suzuki, *Curr. Org. Chem.*, 2012, **16**, 566.
  9. A. Saito, A. Tanaka, M. Ubukata, and N. Nakajima, *Synlett*, 2004, 1069; A. Saito, Y. Doi, A. Tanaka, N. Matsuura, M. Ubukata, and N. Nakajima, *Bioorg. Med. Chem.*, 2004, **12**, 4783; A. Saito, Y. Mizushina, A. Tanaka, and N. Nakajima, *Tetrahedron*, 2009, **65**, 7422.
  10. K. Ohmori, N. Ushimaru, and K. Suzuki, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 12002; K. Ohmori, T. Shono, Y. Hatakoshi, T. Yano, and K. Suzuki, *Angew. Chem. Int. Ed.*, 2011, **50**, 4862.
  11. E. G. Dennis, D. W. Jeffery, M. R. Johnston, M. V. Perkins, and P. A. Smith, *Tetrahedron*, 2012, **68**, 340.
  12. Y. Oizumi, Y. Mohri, Y. Hattori, and H. Makabe, *Heterocycles*, 2011, **83**, 739.
  13. Y. Mohri, M. Sagehashi, T. Yamada, Y. Hattori, K. Morimura, T. Kamo, M. Hirota, and H. Makabe, *Tetrahedron Lett.*, 2007, **48**, 5891; Y. Mohri, M. Sagehashi, T. Yamada, Y. Hattori, K. Morimura, Y. Hamazu, T. Kamo, M. Hirota, and H. Makabe, *Heterocycles*, 2009, **79**, 549; Y. Oizumi, Y. Mohri, M. Hirota, and H. Makabe, *J. Org. Chem.*, 2010, **75**, 4884; M. Katoh, Y. Oizumi, Y. Mohri, M. Hirota, and H. Makabe, *Lett. Org. Chem.*, 2012, **9**, 233.
  14. A. P. Kozikowski, W. Tückmantel, G. Böttcher, and L. J. Romanczyk, Jr., *J. Org. Chem.*, 2003, **68**, 1641.
  15. HPLC measurement condition: column; Inertsil ODS-3 250 × 4.6 mm GL-Sciences, eluent MeOH-0.2%AcOH (5:95~25:75), flow rate: 0.8 mL/min, detection: UV 280 nm, retention time: 15.35 min.
  16. J. A. Delcour and S. A. R. Vercruyse, *J. Inst. Brew.*, 1986, **92**, 244.
  17. HPLC measurement condition: column; Inertsil ODS-3 250 × 4.6 mm GL-Sciences, eluent MeOH-0.2%AcOH (5:95~25:75), flow rate: 0.8 mL/min, detection: UV 280 nm, retention time: 23.60 min.