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# Systematic synthesis of four epicatechin series procyanidin trimers and their inhibitory activity on the Maillard reaction and antioxidant activity

Akiko Saito,[a,*] Yuki Doi,[b] Akira Tanaka,[c] Nobuyasu Matsuura,[d] Makoto Ubukata[e] and Noriyuki Nakajima[b,*]

[a] *Biotechnology Center, Toyama Prefecture, Kosugi, Toyama 939-0398, Japan*
[b] *Biotechnology Research Center, Toyama Prefectural University, Kosugi, Toyama 939-0398, Japan*
[c] *Department of Biosources Science, College of Technology, Toyama Prefectural University, Kosugi, Toyama 939-0398, Japan*
[d] *Department of Life Science, Faculty of Science, Okayama University of Science, Ridai-cho, Okayama 700-0005, Japan*
[e] *Graduate School of Agriculture, Hokkaido University, Kita-ku, Sapporo 060-8589, Japan*

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**Abstract**—A systematic synthesis of four natural epicatechin series procyanidin trimers {[4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*cis*-3″,4″-*trans*: 2⁗,3⁗-*trans*-(−)-epi-catechin-(−)-epicatechin-(+)-catechin, [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*cis*-3″,4″-*trans*: 2⁗,3⁗-*cis*-tri-(−)-epicatechin: procyanidin C1, [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*trans*-3″,4″-*trans*: 2⁗,3⁗-*trans*-(−)-epicatechin-(+)-catechin-(+)-catechin: procyanidin C4, and [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*trans*-3″,4″-*trans*: 2⁗,3⁗-*cis*-(−)-epicatechin-(+)-catechin-(−)-epicatechin} is described. Condensation of (2*R*,3*R*,4*S*)-5,7,3′4′-tetra-*O*-benzyl-4-(2″-ethoxyethyloxy)flavan derived from (−)-epicatechin as an electrophile with the dimeric nucleophiles in the presence of TMSOTf followed by deprotection yielded trimers. Inhibitory activities on the Maillard reaction and antioxidant activity on lipid peroxide of the synthesized oligomers were also investigated.

## 1. Introduction

Proanthocyanidins are known as condensed tannins and/or oligomeric flavonoids.[2,3] The investigation of proanthocyanidins is now increasingly important because of their various strong bioactivities such as antioxidant activity,[4] cardioprotection activity,[5] antiviral activity,[6] and antimicrobial activity.[7] However, the structure–activity relationship of proanthocyanidin oligomers has not been proved yet, because a large number of isomers in the plants makes it very difficult to purify and supply each pure compound for assay. There are many reports[8] about the isolation and semi-synthesis of procyanidin dimers and trimers, but no efficient method for the stereoselective synthesis of each oligomer has yet been reported. So we have undertook a stereoselective synthesis of procyanidin oligomers, and further investigated their bioactivities. We previously reported a stereoselective synthesis of procyanidin dimers[9–12] and trimers[1a] consisting of (+)-catechin **1** and (−)-epicatechin **2** and the Maillard reaction inhibitory activities of the synthesized procyanidin dimers,[10] procyanidin B1 **5**, B2 **7**, B3 **9**, and B4 **11**. The Maillard reaction is known as a nonenzymatic browning reaction caused by heating a mixture solution of sugar with protein or amino acid. This reaction occurs extensively in food systems and in vivo. The relationship of the Maillard reaction to diabetic complication has been noted in the field of sitology. There have been many studies of the Maillard reaction inhibitors, and aminoguanidine (AG),[13] aspirin,[14] vitamin B6,[15] taurine,[16] quercetin,[17] and components of tea extracts (catechin derivatives)[18] have been reported as important inhibitors. The strong antioxidant activity of proanthocyanidins is noteworthy because the inhibitory activity on the Maillard reaction is considered to be closely related to antioxidant activity.[19] Here we describe the details of stereoselective synthesis of four

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*Keywords*: Procyanidin trimers; Maillard reaction; Antioxidant activity; Stereoselective synthesis.

[*] Corresponding authors. Tel.: +81-766567500x568; fax: +81-766562498; e-mail: nori@pu-toyama.ac.jp

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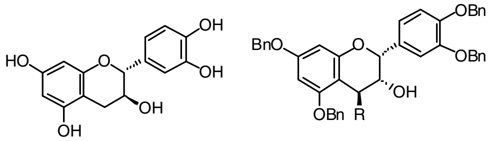
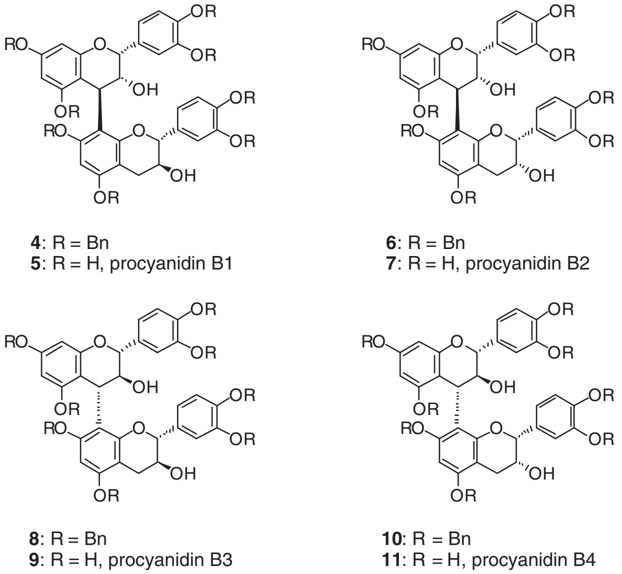


**1**: (+)-catechin

**2**: R = H,(–)-epicatechin
**3**: R = OEE, (–)-epicatechin electrophile

**Figure 1.** Structure of (+)-catechin, (–)-epicatechin, and its electrophile.



**4**: R = Bn
**5**: R = H, procyanidin B1

**6**: R = Bn
**7**: R = H, procyanidin B2

**8**: R = Bn
**9**: R = H, procyanidin B3

**10**: R = Bn
**11**: R = H, procyanidin B4

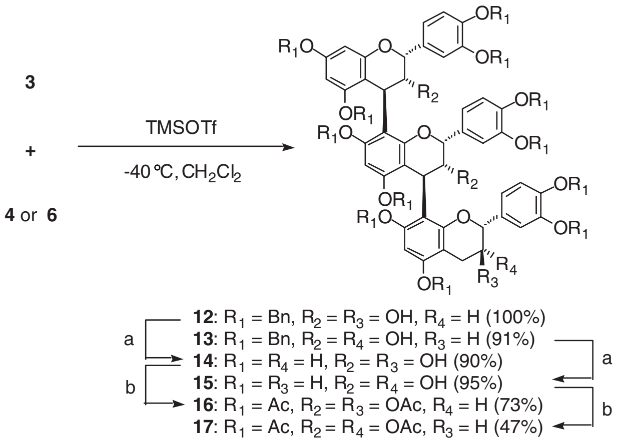
**Figure 2.** Structure of the dimeric nucleophiles.

protected procyanidin trimers, containing (–)-epicatechin as the upper part, by condensation of (2*R*,3*R*,4*S*)-5,7,3′4′-tetra-*O*-benzyl-4-(2″-ethoxyethyloxy)flavan **3** as an electrophile with four dimeric nucleophiles. And inhibitory activities on the Maillard reaction of the synthesized trimers and their peracetate and antioxidant activity of the synthesized dimers and trimers were investigated (Figs. 1 and 2).

## 2. Results and discussion

### 2.1. Synthesis of procyanidin trimers

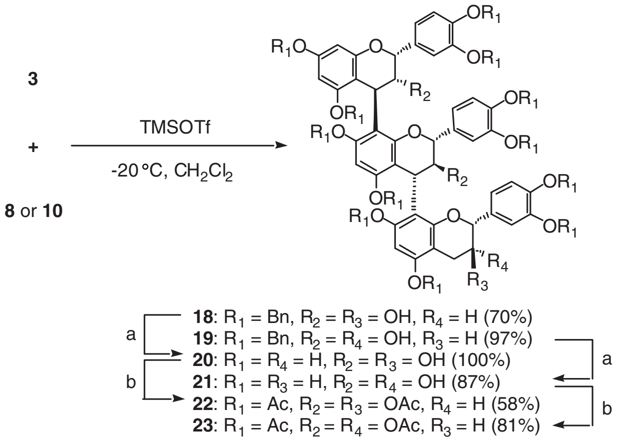
Decabenzyl protected procyanidin trimers containing (–)-epicatechin as the upper part were synthesized by condensation of the upper part of electrophile **3** with the central and bottom parts of dimeric nucleophiles (**4**, **6**, **8**, and **10**) in the presence of TMSOTf as a catalyst. We report here the synthesis of four trimers (**14**, **15**, **20**, and **21**) and their acetates (**16**, **17**, **22**, and **23**) in a similar manner. The procedure is described in Scheme 1; tandem epicatechin trimers, epicatechin-epicatechin-catechin **14** and epicatechin-epicatechin-epicatechin **15**, were synthesized by condensation of electrophile **3** with dimeric nucleophile **4** and **6**. These condensation reactions proceeded smoothly at −40 °C and afforded decabenzyl trimers **12** and **13**[20] in 100% and 91% yield, respectively. The high condensation yields were only attained at −40 °C, whereas either lowering or raising of the reaction temperature resulted in decreasing the product yields. Both protected trimers, **12** and **13**, were hydrogenated in the presence of cat. $Pd(OH)_2/C$ and purified with LH-20 short column and HPLC to give natural procyanidin trimers **14**[21] and **15**[20a,21c,d] in 90% and 95% yields, respectively. And acetylation of these trimers under the usual conditions afforded peracetate **16**[21c] and **17**[20a] in 73% and 47% yields, respectively.



**12**: $R_1$ = Bn, $R_2$ = $R_3$ = OH, $R_4$ = H (100%)
**13**: $R_1$ = Bn, $R_2$ = $R_4$ = OH, $R_3$ = H (91%)
**14**: $R_1$ = $R_4$ = H, $R_2$ = $R_3$ = OH (90%)
**15**: $R_1$ = $R_3$ = H, $R_2$ = $R_4$ = OH (95%)
**16**: $R_1$ = Ac, $R_2$ = $R_3$ = OAc, $R_4$ = H (73%)
**17**: $R_1$ = Ac, $R_2$ = $R_4$ = OAc, $R_3$ = H (47%)

**Scheme 1.** Synthesis of epicatechin trimers. Reagents: (a) $Pd(OH)_2/C$, $H_2$; (b) $Ac_2O$, DMAP, py.

Two other trimers that have a (+)-catechin unit in the central part were synthesized as shown in Scheme 2. The electrophile **3** was condensed with the nucleophile **8** or **10** at −20 °C to give trimers **18** and **19** in 70% and 97% yields, respectively. In a similar manner to that described above, the best yields were obtained at −20 °C, and lowering or raising the reaction temperature gave poor results. Natural procyanidin trimers **20**[22] and **21**[22] were given by hydrogenation with $Pd(OH)_2/C$ in 100% and 87% yields, and their peracetates **22** and **23** were also synthesized in 58% and 81% yields, respectively.



**18**: $R_1$ = Bn, $R_2$ = $R_3$ = OH, $R_4$ = H (70%)
**19**: $R_1$ = Bn, $R_2$ = $R_4$ = OH, $R_3$ = H (97%)
**20**: $R_1$ = $R_4$ = H, $R_2$ = $R_3$ = OH (100%)
**21**: $R_1$ = $R_3$ = H, $R_2$ = $R_4$ = OH (87%)
**22**: $R_1$ = Ac, $R_2$ = $R_3$ = OAc, $R_4$ = H (58%)
**23**: $R_1$ = Ac, $R_2$ = $R_4$ = OAc, $R_3$ = H (81%)

**Scheme 2.** Synthesis of epicatechin trimers. Reagents: (a) $Pd(OH)_2/C$, $H_2$; (b) $Ac_2O$, DMAP, py.

**2.1.1. Inhibitory activity on the Maillard reaction and antioxidant activity.** Inhibitory activity on the Maillard reaction of natural procyanidin trimers and their peracetates was assayed using our reported method.[23] The $IC_{50}$ values (concentration of 50% inhibitory activity) are shown in Table 1. The $IC_{50}$ value of procyanidin trimers (**14**, **15**, **20**, and **21**) and their acetyl derivatives (**16**, **17**, **22**, and **23**) showed at the range of 0.8–1.9 and 1.0–2.0 μM. In comparison with those of (+)-catechin **1** and (−)-epicatechin **2** at 5.0, and 24 μM, dimeric procyanidins at 30–72, and 7–40 μM for their peracetate, procyanidin trimers are effective so as to inhibit the Maillard reaction. It has also become apparent that the inhibitory activity on the Maillard reaction of procyanidin oligomers rises as the oligomer chain is lengthened, thus indicating that procyanidin trimers are powerful inhibitors against the Maillard reaction.

Antioxidant activity on UV-induced lipid peroxide using the TBA method[24] was subsequently investigated (Table 2). The $IC_{50}$ values of (+)-catechin **1** and (−)-epicatechin **2** were 37 and 40 μM, respectively, while those values of dimeric procyanidins, **5**, **7**, **9**, and **11** were 37, 29, 21, and 39 μM, respectively. The $IC_{50}$ values of trimeric procyanidins, **14**, **15**, **20**, and **21**, showed at 17, 15, 29, and 28 μM, respectively. Interestingly, their peracetates did not show antioxidant activity at all.

From the results of both inhibitory activity tests, it is apparent that (1) antioxidant activity was not influenced by the length of the oligomer chain, (2) the relationship between Maillard reaction inhibition and antioxidant activity was not parallel to each other. Further work to explain the mechanism of the Maillard reaction inhibition by procyanidins is now under way.

**Table 1.** Inhibitory activity on the Maillard reaction of synthetic procyanidins and their peracetates

| Entry | Compound | $IC_{50}$ (μM) |
|---|---|---|
| 1 | **1** | 5.0 |
| 2 | **2** | 24 |
| 3 | **14** | 1.1 |
| 4 | **15** | 0.8 |
| 5 | **20** | 1.9 |
| 6 | **21** | 1.4 |
| 7 | **16** (dodecaAc-**14**) | 1.5 |
| 8 | **17** (dodecaAc-**15**) | 1.0 |
| 9 | **22** (dodecaAc-**20**) | 1.4 |
| 10 | **23** (dodecaAc-**21**) | 2.0 |
| 11 | Aminoguanidine | 300 |

**Table 2.** Inhibitory activity of synthetic procyanidins on lipid peroxidation by TBA method

| Entry | Compound | $IC_{50}$ (μM) |
|---|---|---|
| 1 | **1** | 37 |
| 2 | **2** | 40 |
| 3 | **5** | 37 |
| 4 | **7** | 29 |
| 5 | **9** | 21 |
| 6 | **11** | 39 |
| 7 | **14** | 17 |
| 8 | **15** | 15 |
| 9 | **20** | 29 |
| 10 | **21** | 28 |
| 11 | DL-μ-Tocopherol | 580 |

## 3. Conclusion

We have synthesized four procyanidin trimers containing (−)-epicatechin as the upper part, and investigated the Maillard reaction inhibitory activity and antioxidant activity of the synthesized oligomers.

## 4. Experimental

### 4.1. Synthesis

Optical rotation was measured with a Horiba SEPA-300 spectrometer. $^1H$ NMR spectra were measured with JEOL JNMLA400 spectrometer, and MS spectra were recorded with a JEOL JMS-AX500 instrument. HPLC purification was carried out on a Mightysil RP-18 GP column (Kanto Chemical Co. Inc, Japan; 250 × 20 mm, 5 μm) using the solvents (A) 0.05% $CF_3CO_2H$ in $CH_3CN$ and (B) 0.05% $CF_3CO_2H$ in $H_2O$. Elusion was done with a linear gradient 5–100% A in 40 min (flow rate, 3.0 mL/min).

**4.1.1. [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*cis*-3″,4″-*trans*: 2″″,3″″-*trans*-Dodeca-*O*-benzyl-(−)-epicatechin-(−)-epicatechin-(+)-catechin (12).** To a solution of **3** (126 mg, 0.17 mmol) and **4** (886 mg, 0.68 mmol) in $CH_2Cl_2$ (100 mL) was added dropwise 0.5 M $CH_2Cl_2$ solution of TMSOTf (0.34 mL, 0.17 mmol) at −40°C. After stirring for 5 min, the pale yellow reaction mixture was quenched with satd sodium hydrogen carbonate. The aq solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried ($Na_2SO_4$). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 2/1) afforded 333 mg (0.17 mmol, 100%) of **12** as a colorless oil: $[\alpha]_D^{25}$ +92.0 (*c* 1.12, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, a 0.5:0.5 mixture of rotational isomers) 7.53–6.73 (67H, m), 6.74 (0.5H, d, $J = 8.3$ Hz), 3.45 (0.5H, dd, $J = 1.7$, 8.3 Hz), 6.40 (0.5H, d, $J = 8.3$ Hz), 6.35 (0.5H, s), 6.26 (0.5H, d, $J = 2.2$ Hz), 6.20 (0.5H, s), 6.13 (0.5H, dd, $J = 1.7$, 8.3 Hz), 6.06 (0.5H, d, $J = 2.2$ Hz), 6.00 (0.5H, d, $J = 2.2$ Hz), 5.91 (0.5H, s), 5.86 (0.5H, s), 5.72 (0.5H, br s), 5.69 (0.5H, d, $J = 2.2$ Hz), 5.52 (0.5H, br s), 5.51 (0.5H, br s), 5.17 (0.5H, d, $J = 7.5$ Hz), 5.14–4.20 (27.0H, m), 4.10–4.06 (0.5H, m), 4.01–3.97 (0.5H, m), 3.97–3.94 (0.5H, m), 3.58–3.56 (0.5H, m), 3.51–3.40 (1H, m), 3.05 (0.5H, dd, $J = 8.5$, 16.4 Hz), 3.04 (0.5H, dd, $J = 8.8$, 16.4 Hz), 2.61 (0.5H, dd, $J = 9.6$, 16.4 Hz), 2.52 (0.5H, dd, $J = 9.6$, 16.4 Hz), 1.84 (0.5H, d, $J = 6.1$ Hz, OH), 1.73 (0.5H, d, $J = 6.3$ Hz, OH), 1.59 (0.5H, d, $J = 3.4$ Hz, OH), 1.52–1.51 (0.5H, m, OH), 1.43–1.42 (0.5H, m, OH), 1.32 (0.5H, d, $J = 6.8$ Hz, OH); $^{13}C$ NMR (100 MHz, $CDCl_3$, a 0.5:0.5 mixture of rotational isomers) 158.3, 158.1, 158.0, 157.4, 156.7, 156.4, 156.0, 155.9, 155.73, 155.67, 155.58, 155.46, 155.36, 155.32, 154.8, 153.2, 152.9, 152.5, 149.2, 149.0 (×4), 148.9, 148.7 (×2), 148.6, 148.3, 148.1, 148.0, 138.2–136.7 (C×34), 132.9, 132.54, 132.48, 132.3, 131.3, 131.1, 128.5–126.1 (C×70), 120.21, 120.18, 120.07, 119.9, 119.7, 118.9, 115.1, 115.0 (×2), 114.7, 114.6, 114.1, 113.7 (×3), 113.3, 113.2, 113.1, 111.2, 110.8, 110.7, 110.2, 106.2, 105.6, 104.7, 104.6, 102.3, 101.9, 94.4, 94.3, 94.0, 93.4, 92.4, 92.1, 81.32, 81.25, 76.2, 75.8, 75.6 (×2), 72.6–68.2 (C×16), 36.5, 36.1, 35.5, 35.3, 27.5, 26.8; IR (neat, cm$^{-1}$) 3550 (m), 3450 (br m), 3088 (m), 3063 (m), 3032 (m), 2920 (m), 2880 (m), 1813 (w), 1736 (w), 1597 (s), 1510 (s), 1454 (s), 1421 (s), 1383 (s), 1325 (m), 1265 (s), 1217 (m), 1121 (s), 1028 (s), 910 (w), 856 (w), 735 (m); FAB-MS (*m/z*) 1974 (13.2), 1973 (22.4), 1972 (35.6), 1971 (52.4), 1970 ([M+Na]$^+$, 44), 1952 (15.2), 1951 (30.5), 1950 (53.9), 1948 ([M+H]$^+$, 100), 1511 (19.3), 1510 (46.2), 1509 (65.9), 1508 (68.0), 1506 (19.2); FAB-HRMS calcd for $C_{129}H_{110}O_{18}Na$ [M+Na]$^+$, 1969.7590; found: 1969.7609.

**4.1.2. [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*cis*-3″,4″-*trans*: 2⁗,3⁗-*trans*-(−)-Epi-catechin-(−)-epicatechin-(+)-catechin (14).** A solution of **12** (50mg, 0.026mmol) in a mixture of THF/MeOH/$H_2O$ (20/1/1) (11mL) was hydrogenated over 20% $Pd(OH)_2/C$ (5mg) for 1h at rt. Filtration and concentration afforded a pale brown oil, which was purified by Sephadex® LH-20 short column chromatography (EtOH–MeOH) and HPLC purification to give 20mg of pure **12** (90%) as an amorphous solid: $[\alpha]_D^{25}$ +56.9 (*c* 0.30, EtOH) (lit.[21b,25] $[\alpha]_D$ +76.9); $^1$H NMR (400MHz, $CD_3COCD_3/D_2O$, 15/1) 7.13–6.69 (9H, br), 6.10–5.83 (4H, br), 5.30–5.05 (1H, br), 5.04–5.03 (1H, br), 4.89–4.54 (3H, br), 4.16–3.95 (3H, br), 2.75–2.60 (1H, br), 2.58–2.51 (1H, br); $^{13}$C NMR (100MHz, $CD_3COCD_3/D_2O$, 15/1) 157.4–153.4 (C×9), 145.4, 145.21, 145.18 (×2), 145.0, 144.8, 132.03, 132.01, 131.97, 119.1–118.6 (×3), 115.7, 115.49, 115.45, 115.43, 114.8, 114.4, 110.9, 107.3, 104.8, 100.7, 96.91, 96.88, 96.5, 95.7 (×2), 81.6, 76.7, 76.6 (×2), 72.8, 71.4, 67.5, 36.8 (×2); FAB-MS (*m/z*) 890 (5.6), 889 ([M+Na]$^+$, 12.8), 888 (7.1), 887 (5.8), 868 (4), 867 ([M+H]$^+$, 9.0), 866 (6.7), 329 (100); FAB-HRMS calcd for $C_{45}H_{38}O_{18}Na$ [M+Na]$^+$, 889.1956; found: 889.1927.

**4.1.3. Peracetate of 14 (16).** Acetylation of **14** (8mg, 9.2µmol) with the general procedure gave 10mg of peracetate **16** (6.7µmol, 73%) as a colorless amorphous solid: $[\alpha]_D^{25}$ +113.3 (*c* 0.30, acetone) {lit.[8f] $[\alpha]_{578}$ +110 (*c* 0.16, acetone)}; $^1$H NMR (400MHz, $CDCl_3$, 0.4:0.4:0.2 mixture of rotational isomers) major isomers: 7.35–6.59 (6.8H, m), 6.92 (0.4H, d, $J$ = 8.3Hz), 6.74 (0.4H, dd, $J$ = 1.7, 8.3Hz), 6.70 (0.4H, d, $J$ = 8.3Hz), 6.64 (0.4H, d, $J$ = 8.3Hz), 6.30 (0.4H, dd, $J$ = 1.7, 8.3Hz), 6.26 (0.4H, d, $J$ = 2.2Hz), 5.96 (0.4H, d, $J$ = 2.2Hz), 5.91 (0.4H, d, $J$ = 2.2Hz), 5.83 (0.4H, d, $J$ = 2.2Hz), 5.69 (0.4H, br s), 5.62 (0.4H, br s), 5.41 (0.4H, br s), 5.41–4.59 (1.6H, m), 5.27 (0.4H, br s), 4.93 (0.4H, br s), 4.87 (0.4H, br s), 4.74 (0.4H, br s), 4.62 (0.4H, br s), 4.61 (0.4H, br s), 4.47 (0.4H, d, $J$ = 2.4Hz), 4.44 (0.4H, d, $J$ = 2.0Hz), 4.35 (0.4H, d, $J$ = 1.9Hz), 3.12 (0.4H, dd, $J$ = 5.6, 16.6Hz), 2.74 (0.4H, dd, $J$ = 8.1, 16.6Hz), 3.08–2.45 (0.8H, m), 2.36–1.25 (36H, m): minor isomer was not assigned; $^{13}$C NMR (100MHz, $CDCl_3$) 0.4:0.4:0.2 mixture of rotational isomers was observed. However, each rotational isomer was not assigned; IR (neat, cm$^{-1}$) 3065 (w), 2934 (w), 2855 (w), 2363 (w), 1779 (s), 1599 (m), 1507 (m), 1429 (m), 1371 (s), 1205 (s), 1109 (s), 1042 (s), 943 (w), 903 (m); FAB-MS (*m/z*) 1523 (42.5), 1522 (63.4), 1521 (98.5), 1520 (99.9), 1519 ([M+Na]$^+$, 100); FAB-HRMS calcd for $C_{75}H_{68}O_{33}Na$ [M+Na]$^+$, 1519.3541; found: 1519.3588.

**4.1.4. [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*cis*-3″,4″-*trans*: 2⁗,3⁗-*cis*-Dodeca-*O*-benzyl-tri-(−)-epicatechin (13).** To a solution of **3** (20.0mg, 0.027mmol) and **6** (140mg, 0.11mmol) in $CH_2Cl_2$ (30mL) was added dropwise TMSOTf (0.054mL, 0.027mmol, 0.5M solution in $CH_2Cl_2$) at −78°C. After stirring for 5min, the pale yellow reaction mixture was quenched with satd sodium hydrogen carbonate. The aq solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried ($Na_2SO_4$). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 2/1) afforded 48mg (0.025mmol, 91%) of **13** as a colorless oil: $[\alpha]_D^{25}$ +75.9 (*c* 0.32, $CHCl_3$) {lit.[20a] $[\alpha]_D$ +72.1 (*c* 6.9, EtOAc)}; $^1$H NMR (400MHz, $CDCl_3$, a 0.5:0.5 mixture of rotational isomers) 7.51–6.74 (66.5H, m), 6.83 (0.5H, dd, $J$ = 1.7, 8.3Hz), 6.75 (0.5H, d, $J$ = 8.3Hz), 6.45 (0.5H, dd, $J$ = 1.7, 8.3Hz), 6.39 (0.5H, d, $J$ = 8.3Hz), 6.35 (0.5H, s), 6.27 (0.5H, d, $J$ = 2.2Hz), 6.18 (0.5H, s), 6.14 (0.5H, dd, $J$ = 1.7, 8.3Hz), 6.07 (0.5H, d, $J$ = 2.2Hz), 5.95 (0.5H, d, $J$ = 2.2Hz), 5.90 (0.5H, s), 5.85 (0.5H, s), 5.73 (0.5H, br s), 5.70 (0.5H, d, $J$ = 2.2Hz), 5.49 (0.5H, br s), 5.22 (0.5H, br s), 5.18–4.16 (28.5H, m), 4.09 (0.5H, br s), 4.07 (0.5H, br s), 3.96 (0.5H, br s), 3.64 (0.5H, br s), 2.95–2.80 (2H, m), 1.85–1.80 (0.5H, br, OH), 1.76–1.69 (0.5H, br, OH), 1.60–1.55 (0.5H, m, OH), 1.50–1.45 (0.5H, br, OH), 1.25–1.17 (1H, br, OH); $^{13}$C NMR (100MHz, $CDCl_3$) 158.3, 158.1, 158.0, 157.4, 156.7, 156.44, 156.36, 156.2, 156.12, 156.08, 156.01, 156.7, 155.5, 155.3, 154.7, 153.1, 152.8, 152.4, 149.2, 149.00, 148.96, 148.93, 148.80, 148.75, 148.69, 148.4 (×2), 148.3, 148.2, 148.1, 138.2, 137.6–136.9 (C×24), 132.9, 132.5, 132.4, 132.3, 131.3, 131.2, 128.6–126.1 (C×69), 120.0, 119.9, 119.7, 118.9, 118.84, 118.76, 115.1, 115.0 (×2), 148.8 (×2), 114.2, 113.6 (×2), 113.5, 113.2 (×2), 113.0, 111.2, 111.1, 111.0, 110.1, 106.0, 105.4, 104.7, 104.6, 101.4, 100.8, 94.4 (×2), 94.0, 93.8, 93.4 (×2), 92.6, 92.5, 92.3, 90.3, 78.1, 78.0, 76.3, 75.8, 75.7, 75.6, 72.7, 72.5, 72.2, 71.5–69.6 (C×24), 69.3, 65.3, 64.9, 36.5, 36.2, 35.4 (×2), 28.63, 28.57; IR (neat, cm$^{-1}$) 3570 (m), 3520 (br), 3063 (m), 3032 (m), 2930 (m), 2872 (m), 2361 (w), 1954 (w), 1877 (w), 1813 (w), 1732 (m), 1597 (s), 1514 (s), 1454 (s), 1383 (s), 1265 (s), 1116 (s), 1026 (s), 910 (w), 852 (w), 735 (m); FAB-MS (*m/z*) 1974 (12.0), 1973 (25.2), 1970 ([M+Na]$^+$, 63.4), 1950 (26.0), 1949 (56.9), 1948 ([M+H]$^+$, 100), 1510 (43.9), 1509 (44.4), 1508 (74.7); FAB-HRMS calcd for $C_{129}H_{110}O_{18}Na$ [M+Na]$^+$, 1969.7590; found: 1969.7570.

**4.1.5. [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*cis*-3″,4″-*trans*: 2⁗,3⁗-*cis*-Tri-(−)-epicatechin, procyanidin C1 (15).** A solution of **13** (80mg, 0.041mmol) in a mixture of

THF/MeOH/$H_2O$ (20/1/1) (22mL) was hydrogenated over 20% $Pd(OH)_2/C$ (5mg) for 1h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 short column chromatography (EtOH–MeOH) and HPLC purification to give 34mg of pure **15** (0.039mmol, 95%) as a pale brown amorphous solid: $[\alpha]_D^{27}$ +59.3 (*c* 0.30, MeOH) {lit.[20a] $[\alpha]_D$ +70.4 (*c* 0.22, MeOH), lit.[21c] $[\alpha]_{578}$ +92 (*c* 0.19, water)}; $^1H$ NMR (400MHz, $CD_3OD$) 7.15–7.09 (1H, br), 7.08–6.98 (1H, br), 6.98–6.82 (2H, m), 6.80–6.63 (5H, m), 6.08–6.02 (1H, br), 6.02–5.98 (1H, br), 5.98–5.83 (2H, m), 5.26–5.18 (1H, br), 5.10–5.05 (1H, br), 5.02–4.95 (1H, br), 4.74–4.65 (1H, br), 4.61–4.57 (1H, br), 4.35–4.27 (1H, br), 4.05–3.95 (2H, m), 2.98–2.90 (1H, m), 2.85–2.77 (1H, m); FAB-MS (*m/z*) 890 (1.9), 889 ($[M+Na]^+$, 3.3), 888 (2.2), 887 (1.7), 868 (1.6), 867 ($[M+H]^+$, 3.3), 866 (2.5), 613 (8.3), 482 (25.5), 459 (45.8), 328 (100), 306 (100); FAB-HRMS calcd for $C_{45}H_{38}O_{18}Na$ $[M+Na]^+$, 889.1956; found: 889.2031.

**4.1.6. Peracetate of procyanidin C1 (17).** Acetylation of **15** (18mg, 0.021mmol) with general procedure gave 15mg of peracetate **17** (0.010mmol, 47%) as a colorless amorphous solid: $[\alpha]_D^{30}$ +48.6 (*c* 0.30, acetone) {lit.[20a] $[\alpha]_D$ +55.3 (*c* 1.04, acetone)}; $^1H$ NMR (400MHz, $CDCl_3$, 0.67:0.33 mixture of rotational isomers) major isomer: 7.22–7.00 (6.03H, m), 6.69 (0.67H, d, $J = 2.2$Hz), 6.64 (0.67H, s), 6.58 (0.67H, d, $J = 2.2$Hz), 6.57 (0.67H, s), 5.42–5.38 (0.67H, m), 5.35 (0.67H, br s), 5.34 (0.67H, br s), 5.32 (0.67H, br s), 5.29 (0.67H, br s), 5.14 (0.67H, br s), 4.71 (0.67H, br s), 4.63 (0.67H, br s), 3.02 (0.67H, dd, $J = 4.7$, 18.3Hz), 2.89 (0.67H, d, $J = 18.3$Hz), 2.25 (2.01H, s), 2.222 (2.01H, s), 2.216 (2.01H, s), 2.192 (2.01H, s), 2.188 (2.01H, s), 2.15 (2.01H, s), 2.14 (2.01H, s), 1.95 (2.01H, s), 1.88 (2.01H, s), 1.81 (4.02H, s), 1.75 (2.01H, s), 1.72 (2.01H, s), 1.48 (2.01H, s), 1.31 (2.01H, s); minor isomer: 7.30 (0.33H, d, $J = 1.7$Hz), 7.22–7.00 (1.65H, m), 6.93 (0.33H, d, $J = 1.7$Hz), 6.88 (0.33H, d, $J = 8.3$Hz), 6.81 (0.33H, s), 6.73 (0.33H, dd, $J = 1.7$, 8.3Hz), 6.53 (0.33H, s), 6.19 (0.33H, d, $J = 2.2$Hz), 5.87 (0.33H, d, $J = 2.2$Hz), 5.64 (0.33H, br s), 5.40–5.29 (0.33H, m), 5.05 (0.33H, br s), 5.04 (0.33H, br s), 4.89–4.87 (0.33H, m), 4.60 (0.33H, br s), 4.58 (0.33H, br s), 4.42 (0.33H, d, $J = 2.2$Hz), 2.97 (0.33H, dd, $J = 4.6$, 18.3Hz), 2.84 (0.33H, d, $J = 18.3$Hz), 2.30 (0.99H, s), 2.23 (0.99H, s), 2.22–2.19 (5.94H, m), 2.16 (0.99H, s), 2.09 (0.99H, s), 2.08 (0.99H, s), 1.88 (0.99H, s), 1.82 (0.99H, s), 1.64 (0.99H, s), 1.43 (0.99H, s); $^{13}C$ NMR (100MHz, $CDCl_3$) major isomer: 169.9, 169.1, 169.0, 168.8, 168.42, 168.40, 168.3, 168.1, 168.01, 167.98, 167.93, 167.88, 167.80, 167.7, 167.6, 154.9, 151.9, 151.7, 149.88, 149.87, 148.6, 148.5, 147.6, 147.2, 142.1, 142.02, 141.95, 141.86, 141.81, 141.7, 135.7, 135.4, 135.2, 124.15, 124.08, 123.9, 123.24, 123.16, 123.06, 122.7, 122.0, 121.6, 121.3, 117.7, 117.6, 112.2, 111.6, 111.0, 110.6, 110.0, 109.3, 108.1, 77.2, 74.7, 71.3, 70.5, 66.6, 34.9, 34.3, 26.4, 21.0, 20.73, 20.66–20.5 (C × 7), 20.4 (×2), 20.2, 20.0, 19.7, 19.5; minor isomer: 170.11, 170.06, 169.9, 169.1, 168.7, 168.6, 168.4, 168.1, 168.0, 167.93, 167.86, 167.76, 167.4, 166.2, 166.1, 155.8, 154.1, 151.7, 149.9, 148.8, 148.1, 148.0, 147.8, 146.9, 142.1, 142.02, 141.95, 141.93, 141.8, 141.5, 136.5, 135.7, 133.2, 125.2, 124.8, 124.2, 123.24, 123.16, 123.0, 122.74 (×2), 122.0, 121.5, 118.8, 117.8, 114.7, 113.3, 112.2, 110.6, 110.5, 107.5, 107.4, 75.1, 73.8, 71.4, 70.9, 66.6, 35.4, 34.3, 26.4, 21.1, 20.9, 20.7–20.6 (C × 7), 20.5, 20.2, 20.10 (×2), 20.08, 19.8; IR (neat, $cm^{-1}$) 3065 (w), 2973 (w), 2936 (w), 2361 (w), 1779 (s), 1601 (m), 1507 (m), 1429 (m), 1372 (s), 1206 (s), 1111 (s), 1043 (s), 902 (m), 735 (m); FAB-MS (*m/z*) 1522 (15.7), 1521 (38.5), 1520 (77.2), 1519 ($[M+Na]^+$, 100), 1498 (3.7), 1497 ($[M+H]^+$, 4.6), 1396 (9.1), 1395 (16.7), 1394 (29.9), 1393 (36.2); FAB-HRMS calcd for $C_{75}H_{68}O_{33}Na$ $[M+Na]^+$, 1519.3541; found: 1519.3574.

**4.1.7. [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*trans*-3″,4″-*trans*: 2⁗,3⁗-*trans*-Dodeca-*O*-benzyl-(−)-epicatechin-(+)-catechin-(+)-catechin (18).** To a solution of **3** (132mg, 0.18mmol) and **8** (1.04g, 0.80mmol) in $CH_2Cl_2$ (80mL) was added dropwise 0.5M $CH_2Cl_2$ solution of TMSOTf (0.36mL, 0.18mmol) at −20°C. After stirring for 5min, the pale yellow reaction mixture was quenched with satd sodium hydrogen carbonate. The aq solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried ($Na_2SO_4$). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 2/1) afforded a 244mg (0.13μmol, 70%) of **18** as a colorless oil: $[\alpha]_D^{25}$ −26.5 (*c* 0.60, $CHCl_3$); $^1H$ NMR (400MHz, $CDCl_3$, 0.82:0.18 mixture of rotational isomers) major isomer: 7.42–6.67 (55.76H, m), 6.54 (0.82H, dd, $J = 1.7$, 8.3Hz), 6.27 (0.82H, s), 6.02 (0.82H, d, $J = 2.2$Hz), 5.92 (0.82H, s), 5.52 (0.82H, d, $J = 2.2$Hz), 5.50 (0.82H, br s), 5.14–4.43 (22.14H, m), 4.04–3.90 (0.82H, m), 3.90–3.94 (0.82H, m), 3.73–3.68 (1.64H, m), 3.54 (0.82H, d, $J = 9.8$Hz), 2.98 (0.82H, dd, $J = 5.4$, 16.6Hz), 2.31 (0.82H, dd, $J = 9.1$, 16.6Hz), 1.68 (0.82H, d, $J = 5.8$Hz, OH), 1.44–1.36 (1.64H, m, OH); minor isomer was not identified. $^{13}C$ NMR (100MHz, $CDCl_3$) major isomer: 158.0, 156.8, 156.02, 155.99, 155.5, 155.2, 155.0, 154.6, 153.5, 149.2, 149.1 (×2), 149.0, 148.9, 148.3, 137.9, 137.53, 137.51, 137.46, 137.40, 137.38, 137.31, 137.29, 137.24, 137.17, 137.15, 136.9, 132.8, 131.9, 131.8, 130.9, 128.9–126.0 (C × 32), 120.4, 120.0, 119.1, 115.2, 115.1, 114.8, 114.4, 114.0, 113.4, 112.8, 112.23, 112.15, 112.0, 111.7, 111.2, 104.4, 102.0, 93.4, 93.0, 92.4, 91.4, 82.1, 80.6, 75.0, 74.4, 72.6, 71.5–69.1 (C × 12), 68.4, 37.4, 35.7, 28.9; IR (neat, $cm^{-1}$) 3800 (br), 3065 (m), 3032 (m), 2900 (m), 2361 (m), 1508 (s), 1456 (s), 1028 (m), 910 (w), 852 (w), 808 (w), 752 (s), 696 (s); FAB-MS (*m/z*) 1973 (20.4), 1972 (48), 1971 (50), 1970 ($[M+Na]^+$, 44), 1951 (27.0), 1950 (54.1), 1948 ($[M+H]^+$, 100), 1932 (23.3), 1931 (25.4), 1930 (43.2), 1840 (37.7), 1839 (53.6), 1509 (40.5), 1508 (49.3); FAB-HRMS calcd for $C_{129}H_{110}O_{18}Na$ $[M+Na]^+$, 1969.7590; found: 1969.7570.

**4.1.8. [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*trans*-3″,4″-*trans*: 2⁗,3⁗-*trans*-(−)-Epicatechin-(+)-catechin-(+)-catechin, procyanidin C4 (20).** A solution of **18** (55mg, 0.028mmol) in a mixture of THF/MeOH/$H_2O$ (20/1/1)

(22 mL) was hydrogenated over 20% $Pd(OH)_2/C$ (5 mg) for 2 h at rt. Filtration and concentration afforded a pale brown solid, which was purified by Sephadex® LH-20 short column chromatography (EtOH–MeOH) and HPLC purification to give 24 mg of pure **20** (0.028 mmol, 100%) as an amorphous solid: $[\alpha]_D^{23}$ −118.8 (*c* 0.20, EtOH); FAB-MS (*m*/*z*) 890 (8.3), 889 ([M+Na]$^+$, 14.0), 888 (9.1), 868 (4.3), 867 ([M+H]$^+$, 7.1), 866 (5.3), 679 (100); FAB-HRMS calcd for $C_{45}H_{38}O_{18}Na$ [M+Na]$^+$, 889.1956; found: 889.1913.

**4.1.9. Peracetate of 20 (22).** Acetylation of **20** (3.0 mg, 1.46 μmol) with the general procedure gave 3.0 mg of peracetate **22** (2.0 μmol, 58%) as a colorless amorphous solid: $[\alpha]_D^{23}$ −106.5 (*c* 0.20, acetone); $^1$H NMR (400 MHz, $CDCl_3$) 7.15 (1H, d, *J* = 2.0 Hz), 7.09 (1H, d, *J* = 8.5 Hz), 6.99 (2H, d, *J* = 8.5 Hz), 6.85 (1H, dd, *J* = 2.0, 8.5 Hz), 6.78 (1H, d, *J* = 2.0 Hz), 6.64 (1H, d, *J* = 2.0 Hz), 6.63 (1H, s), 6.59 (1H, s), 6.23 (1H, dd, *J* = 2.0, 8.5 Hz), 6.21 (1H, d, *J* = 2.2 Hz), 6.18 (1H, dd, *J* = 2.0, 8.5 Hz), 5.84 (1H, d, *J* = 2.2 Hz), 5.60 (1H, dd, *J* = 8.3, 10.2 Hz), 5.24 (1H, br s), 5.16 (1H, dd, *J* = 2.9, 3.9 Hz), 5.12 (1H, br s), 4.84 (1H, br s), 4.35 (1H, d, *J* = 8.3 Hz), 4.34 (1H, br s), 4.26 (1H, d, *J* = 10.2 Hz), 2.66 (1H, dd, *J* = 2.9, 17.1 Hz), 2.35 (1H, dd, *J* = 3.9, 17.1 Hz), 2.29 (6H, s), 2.22 (6H, s), 2.20 (3H, s), 2.19 (3H, s), 2.15 (3H, s), 2.13 (3H, s), 2.12 (3H, s), 2.11 (3H, s), 1.98 (3H, s), 1.93 (3H, s), 1.90 (3H, s), 1.73 (3H, s), 1.51 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) 171.0, 169.6, 169.3, 169.0, 168.8, 168.7, 168.6, 168.4, 168.1 (×2), 168.0, 167.71, 167.67 (×2), 167.6, 155.4, 155.1, 151.0, 149.2, 148.5, 148.0, 147.8, 147.7, 147.3, 142.2, 142.0, 141.91, 141.90, 141.53, 141.50, 136.0, 135.2, 134.5, 125.1, 124.5, 123.8, 123.2, 122.9, 122.8, 122.4, 122.2, 119.8, 117.9, 117.3, 116.8, 111.6, 111.5, 110.0, 108.9, 108.2, 107.0, 79.3, 77.2, 73.1, 70.7, 70.0, 67.1, 36.6, 33.5, 21.5–20.2 (C × 16); IR (neat, cm$^{-1}$) 3025 (w), 2926 (m), 2855 (w), 2361 (w), 1771 (s), 1669 (m), 1507 (m), 1437 (m), 1372 (s), 1209 (s), 1126 (s), 1068 (s), 945 (m), 758 (m); FAB-MS (*m*/*z*) 1523 (18), 1522 (34), 1521 (55), 1520 (85), 1519 ([M+Na]$^+$, 93), 1498 (10), 1497 ([M+H]$^+$, 7.9), 531 (100); FAB-HRMS calcd for $C_{75}H_{68}O_{33}Na$ [M+Na]$^+$, 1519.3541; found: 1519.3527.

**4.1.10. [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*trans*-3″,4″-*trans*: 2⁗,3⁗-*cis*-Dodeca-*O*-benzyl-(−)-epicatechin-(+)-catechin-(−)-epicatechin (19).** To a solution of **3** (42 mg, 0.057 mmol) and **10** (304 mg, 0.23 mmol) in $CH_2Cl_2$ (30 mL) was added dropwise 0.5 M $CH_2Cl_2$ solution of TMSOTf (0.11 mL, 0.057 mmol) at −20 °C. After stirring for 5 min, the pale yellow reaction mixture was quenched with satd sodium hydrogen carbonate. The aq solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried ($Na_2SO_4$). Filtration, concentration, and preparative silica gel TLC purification (hexane/EtOAc, 2/1) afforded 108 mg (0.055 mmol, 97%) of **19** as a colorless oil: $[\alpha]_D^{25}$ −46.8 (*c* 0.4, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) 7.35–6.88 (62H, m), 6.84 (1H, d, *J* = 8.3 Hz), 6.71 (1H, dd, *J* = 1.7, 8.3 Hz), 6.66 (1H, d, *J* = 1.7 Hz), 6.59 (1H, d, *J* = 8.3 Hz), 6.46 (1H, d, *J* = 8.3 Hz), 6.29 (1H, dd, *J* = 1.7, 8.3 Hz), 6.23 (1H, dd, *J* = 1.7, 8.3 Hz), 6.23 (1H, s), 5.95 (1H, d, *J* = 2.2 Hz), 5.82 (1H, s), 5.45 (1H, d, *J* = 2.2 Hz), 5.45 (1H, br s), 5.12–4.55 (22H, m), 4.64 (1H, d, *J* = 8.1 Hz), 4.54 (1H, d, *J* = 11.4 Hz), 4.48 (1H, d, *J* = 11.4 Hz), 4.29 (1H, d, *J* = 11.0 Hz), 3.97 (1H, dd, *J* = 8.1, 9.7 Hz), 3.92 (1H, br s), 3.78 (1H, br s), 3.75 (1H, br s), 3.52 (1H, d, *J* = 9.7 Hz), 2.75 (1H, d, *J* = 16.8 Hz), 2.44 (1H, dd, *J* = 4.1, 16.8 Hz), 1.60 (1H, br, OH), 1.60–1.20 (2H, m, OH); $^{13}$C NMR (100 MHz, $CDCl_3$) 158.0, 156.7, 156.10, 156.05, 155.8, 155.5, 155.0, 154.5, 153.3, 149.2, 149.0, 148.9, 148.24, 148.21 (×2), 137.9, 137.50, 137.47, 137.41 (×2), 137.37, 137.32 (×2), 137.2, 137.1, 136.8, 132.7, 132.3, 131.8, 128.6–126.0 (C × 37), 120.4, 119.0, 118.7, 115.2 (×2), 114.0, 112.9, 112.7, 112.3, 112.1, 111.7, 111.4, 104.4, 100.2, 93.4, 92.9, 92.4, 91.3, 82.1, 77.2, 75.0, 74.3, 72.5, 71.4 (×2), 71.3, 71.0, 70.8, 70.5, 70.3, 70.2, 69.8, 69.4, 69.1, 69.0, 66.0, 37.1, 35.8, 29.7; IR (neat, cm$^{-1}$) 3400 (br), 3065 (w), 3032 (w), 2936 (m), 2857 (w), 1603 (s), 1512 (s), 1454 (m), 1381 (m), 1267 (m), 1217 (m), 1117 (s), 1078 (m), 1028 (m), 910 (w), 851 (w), 756 (s), 696 (s); FAB-MS (*m*/*z*) 1972 (81.8), 1971 (100), 1970 ([M+Na]$^+$, 66.9), 1948 ([M+H]$^+$, 79.6), 1947 (83.6); FAB-HRMS calcd for $C_{129}H_{110}O_{18}Na$ [M+Na]$^+$, 1969.7590; found: 1969.7563.

**4.1.11. [4,8:4″,8″]-2,3-*cis*-3,4-*trans*: 2″,3″-*trans*-3″,4″-*trans*: 2⁗,3⁗-*cis*-(−)-Epicatechin-(+)-catechin-(−)-epicatechin (21).** A solution of **19** (80 mg, 0.041 mmol) in a mixture of THF/MeOH/$H_2O$ (20/1/1) (22 mL) was hydrogenated over 20% $Pd(OH)_2/C$ (5 mg) for 1 h at rt. Filtration and concentration afforded a pale brown oil, which was purified by Sephadex® LH-20 column chromatography (EtOH–MeOH) and HPLC purification to give 31 mg of pure **21** (87%) as a colorless amorphous solid: $[\alpha]_D^{24}$ −112.6 (*c* 0.40, MeOH) {lit.[22] $[\alpha]_D^{27}$ −97.6 (*c* 1.0, MeOH)}; $^1$H NMR (400 MHz, $CD_3OD$, 0.89: 0.11 mixture of rotational isomer) major isomer: 7.09–6.58 (8.01H, m), 6.10–5.80 (3.56H, m), 5.28 (0.89H, br), 5.20–4.40 (2.67H, m), 4.50 (0.89H, br), 4.24 (0.89H, br s), 3.84 (0.89H, br s), 3.21–3.18 (0.89H, m), 2.93 (0.89H, dd, *J* = 4.1, 16.3 Hz), 2.82 (0.89H, d, *J* = 16.3 Hz); minor isomer was not assigned: 7.09–6.58 (0.99H, m), 6.10–5.80 (0.44H, m), 5.70 (0.11H, br), 5.20–4.40 (0.33H, m), 4.41 (0.11H, br), 4.11 (0.11H, br), 3.72 (0.11H, br s), 3.50–3.20 (0.11H, m), 2.94–2.74 (0.22H, m); FAB-MS (*m*/*z*) 890 (2.2), 889 ([M+Na]$^+$, 4.0), 888 (3.3), 887 (2.1), 868 (2.2), 867 ([M+H]$^+$, 3.9), 866 (3.1), 613 (4.2), 483 (11.7), 482 (25.2), 460 (48.2), 328 (100), 306 (100); FAB-HRMS calcd for $C_{45}H_{38}O_{18}Na$ [M+Na]$^+$, 889.1956; found: 889.1882.

**4.1.12. Peracetate of 21 (23).** Acetylation of **21** (5 mg, 5.8 μmol) with the general procedure gave 7 mg of peracetate **23** (4.7 μmol, 81%) as a colorless amorphous solid: $[\alpha]_D^{23}$ −4.4 (*c* 0.25, acetone); $^1$H NMR (400 MHz, $CDCl_3$, a 0.46:0.46:0.08 mixture of rotational isomers) major isomers: 7.41 (0.46H, d, *J* = 2.2 Hz), 7.35 (0.46H, dd, *J* = 2.2, 8.6 Hz), 7.27 (0.46H, d, *J* = 8.6 Hz), 7.20 (0.46H, d, *J* = 8.6 Hz), 7.19 (0.46H, d, *J* = 2.2 Hz), 7.22–7.16 (1.38H, m), 7.10 (0.46H, d, *J* = 8.6 Hz), 7.09 (0.46H, d, *J* = 8.6 Hz), 7.04 (0.46H, dd, *J* = 2.2, 8.6 Hz), 6.97 (0.46H, d, $J = 8.6$ Hz), 6.93 (0.46H, d, $J = 2.2$ Hz), 6.89 (0.46H, d, $J = 2.2$ Hz), 6.85 (0.46H, dd, $J = 2.2$, 8.6 Hz), 6.78 (0.46H, d, $J = 2.2$ Hz), 6.74 (0.46H, s), 6.72 (0.46H, s), 6.71 (0.46H, s), 6.62 (0.46H, s), 6.52 (0.46H, dd, $J = 2.2$, 8.6 Hz), 6.32 (0.46H, d, $J = 1.7$ Hz), 6.29 (0.46H, d, $J = 1.7$ Hz), 6.26 (0.46H, dd, $J = 2.2$, 8.6 Hz), 5.92 (0.46H, d, $J = 1.7$ Hz), 5.86 (0.46H, d, $J = 1.7$ Hz), 5.64 (0.46H, br s), 5.54 (0.46H, dd, $J = 10.0$, 10.3 Hz), 5.51 (0.46H, dd, $J = 9.5$, 10.0 Hz), 5.49–5.48 (0.46H, m), 5.22 (0.46H, d, $J = 2.0$ Hz), 5.20 (0.46H, br s), 5.23–5.20 (0.46H, m), 5.16–5.13 (0.92H, m), 5.12 (0.46H, br s), 4.91 (0.46H, d, $J = 9.5$ Hz), 4.57 (0.46H, d, $J = 10.3$ Hz), 4.47 (0.46H, d, $J = 10.0$ Hz), 4.46 (0.46H, d, $J = 10.0$ Hz), 4.43 (0.46H, d, $J = 2.0$ Hz), 4.38 (0.46H, br s), 2.99–2.94 (0.92H, m), 2.88 (0.46H, d, $J = 16.6$ Hz), 2.77 (0.46H, dd, $J = 3.1$, 17.5 Hz), 2.354 (1.38H, s), 2.347 (1.38H, s), 2.32 (1.38H, s), 2.31 (1.38H, s), 2.30 (4.14H, s), 2.29 (1.38H, s), 2.285 (1.38H, s), 2.283 (1.38H, s), 2.263 (1.38H, s), 2.259 (1.38H, s), 2.23 (1.38H, s), 2.213 (1.38H, s), 2.211 (1.38H, s), 2.17 (1.38H, s), 2.10 (1.38H, s), 2.06 (1.38H, s), 1.97 (1.38H, s), 1.91 (1.38H, s), 1.902 (1.38H, s), 1.897 (1.38H, s), 1.88 (1.38H, s), 1.85 (1.38H, s), 1.79 (1.38H, s), 1.77 (1.38H, s), 1.76 (1.38H, s), 1.65 (1.38H, s), 1.58 (1.38H, s), 1.55 (1.38H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) 170.4, 170.2, 170.1, 169.8, 169.6, 169.4, 169.3, 168.91, 168.86, 168.80, 168.74, 168.72, 168.6 (×2), 168.23, 168.17, 168.13, 168.09, 168.05, 168.03, 167.99, 167.92, 167.90, 167.8, 167.7, 167.6 (×2), 167.5, 167.1, 167.0, 155.7, 155.4, 154.3, 153.8, 153.1, 152.0, 149.4, 149.1, 148.6, 148.5, 148.4, 148.3, 148.2, 147.9, 147.83, 147.78, 142.5, 142.4, 142.2, 142.1, 142.0, 141.9, 141.73, 141.69 (×2), 141.62, 141.59, 141.46, 136.1, 135.6, 135.3, 133.9, 133.8, 128.4, 125.2, 124.8, 124.2, 123.9, 123.8, 127.7, 123.6, 123.2, 123.1, 123.0, 122.9, 122.77, 122.75, 121.9, 121.7, 121.1, 117.6, 117.4, 117.1, 117.0, 116.5, 115.8, 111.7, 111.5, 111.4, 111.3, 110.5, 109.6, 109.5, 108.9, 108.7, 108.6, 107.20, 107.17, 79.6, 79.4, 77.6, 74.0, 73.4, 70.6, 70.5, 66.9, 66.4, 60.4, 37.4, 36.1, 34.6, 31.9, 29.71, 29.67, 29.4, 26.1, 25.6, 22.7, 21.2, 21.14, 21.13, 21.06, 21.04, 21.8, 20.8, 20.72 (×5), 20.68 (×3), 20.65 (×3), 20.55, 20.54, 20.51, 20.41 (×2), 20.37, 20.34, 20.26, 20.21, 20.17, 20.06, 20.03, 14.2, 14.1; IR (neat, cm$^{-1}$) 3027 (m), 2926 (m), 2855 (m), 2361 (w), 2089 (w), 1779 (s), 1747 (s), 1601 (m), 1506 (m), 1427 (m), 1422 (s), 1261 (s), 1261 (s), 1215 (s), 1109 (s), 1049 (s), 954 (w), 903 (m), 758 (s); FAB-MS (*m*/*z*) 1522 (15.2), 1521 (41.3), 1520 (78.0), 1519 ($[M+Na]^+$, 100), 1498 (1.7), 1497 ($[M+H]^+$, 2.4), 1396 (12.7), 1395 (21.7), 1394 (29.9); FAB-HRMS calcd for $C_{75}H_{68}O_{33}Na$ $[M+Na]^+$, 1519.3541; found: 1519.3574.

### 4.2. Maillard reaction inhibitory activity

Maillard reaction inhibitory activity was measured with our reported method.[10,23]

### 4.3. The measurement of antioxidant activity

Inhibitory activity of antioxidant activity was measured with the general procedure of the TBA method.[24]

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## References and notes

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25. There is no $[\alpha]_D$ data of neither concentration nor solvent.