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SYNTHETIC STUDIES OF PROANTHOCYANIDINS. PART 4.[1] THE SYNTHESIS OF PROCYANIDIN B1 AND B4: TMSOTf-CATALYZED CYCLIZATION OF CATECHIN AND EPICATECHIN CONDENSATION

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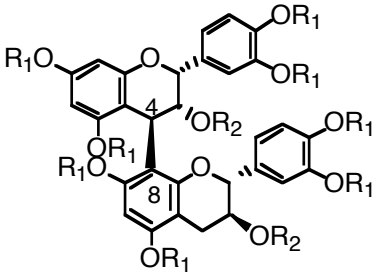
Abstract – Highly stereoselective synthesis of 3,4-*trans* series of (+)-catechin and (-)-epicatechin dimers under intramolecular condensation is described. Intramolecular condensation achieved an equimolar amount of coupling with 3,4-*trans* stereoselectivity and we succeeded in the synthesis of two 3,4-*trans* natural procyanidins, procyanidin-B1and B4.

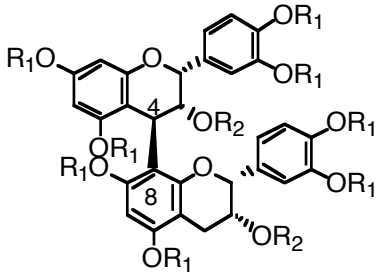
Introduction

Plant proanthocyanidin[2] and their dimers,[3,4] (-) procyanidin-B1 (**1**), B2 (**2**), B3 (**3**) and B4 (**4**) consist of (-)-epicatechin (**5**) and (+)-catechin (**6**) components with C(4)-C(8) linkage as shown in Figure 1. They possess various biological activities, powerful free-radical-scavenging activity[5] and an anti-tumor-promoting effect,[6] and investigation of these compounds is now increasingly important. In addition, absorption of procyanidin-B1 in rat[7] and procyanidin-B2 in human[8] has recently been reported.

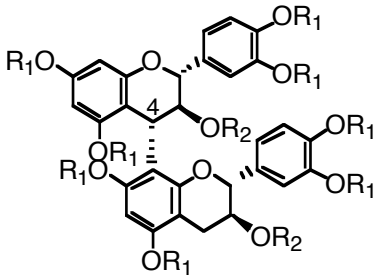
We have studied a synthetic method of proanthocyanidin oligomers. For the synthesis of the 3,4-*trans*-catechin-catechin dimer, procyanidin B3 (**3**),[9] a potential electrophile and a nucleophile were quantitatively condensed in the presence of TMSOTf at –78°C under intermolecular conditions. However, intermolecular condensation required 4.5 times excess of the nucleophile for the reaction. Therefore, we designed an intramolecular one-to-one coupling method. A potential electrophile and nucleophile units were connected with diester linkers and TMSOTf-catalyzed one-to-one catechin-catechin condensation was carried out.[1] Intramolecular condensation proceeded with reversed 3,4-*cis* selectivity in an excellent yield. The intramolecular condensation method is expected to promote a good oligomerization method. We next examined the intramolecular epicatechin-catechin and catechin-epicatechin condensation with a glutaryl linker.



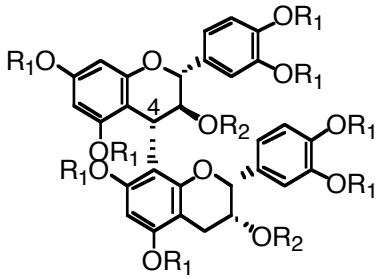
1: $R_1 = R_2$=H, procyanidin B1
[(-)-epicatechin-(+)-catechin]
Bn_8-**1**: R_1=Bn, R_2=H,
procyanidin B1 octabenzyl ether
Ac_{10}-**1**: $R_1 = R_2$=Ac,
procyanidin B1 decaacetyl ester



2: $R_1 = R_2$=H, procyanidin B2
[(-)-epicatechin-(-)-epicatechin]
Bn_8-**2**: R_1=Bn, R_2=H,
procyanidin B2 octabenzyl ether



3: $R_1 = R_2$=H,procyanidin B3
[(+)-catechin-(+)-catechin]
Bn_8-**3**: R_1=Bn, R_2=H,
procyanidin B3 octabenzyl ether



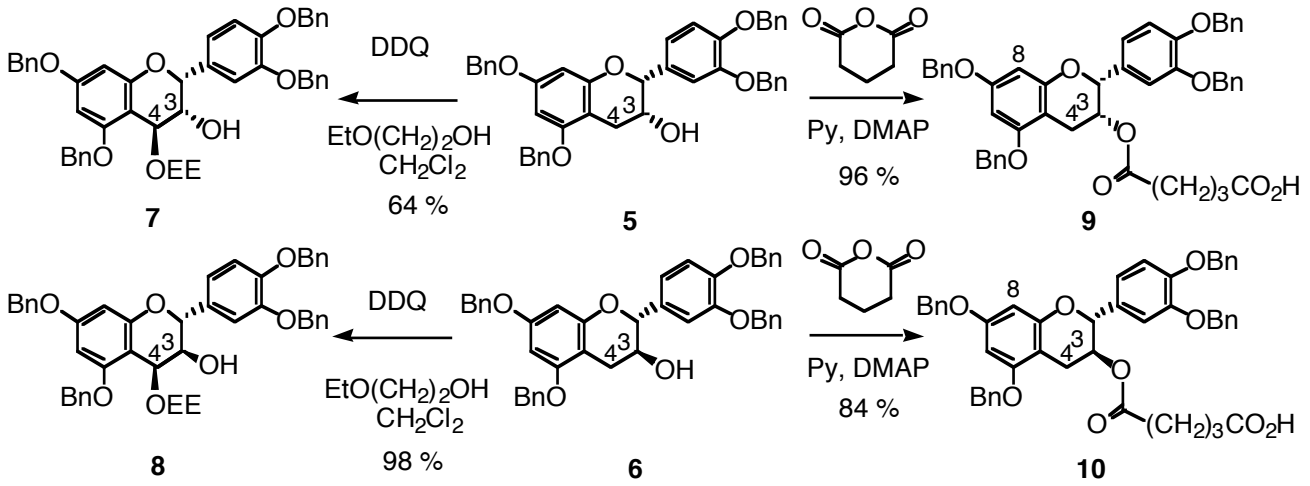
4: $R_1 = R_2$=H, procyanidin B4
[(+)-catechin-(-)-epicatechin]
Bn_8-**4**: R_1=Bn, R_2=H,
procyanidin B4 octabenzyl ether
Ac_{10}-**4**: $R_1 = R_2$=Ac,
procyanidin B4 decaacetyl ester

Figure 1

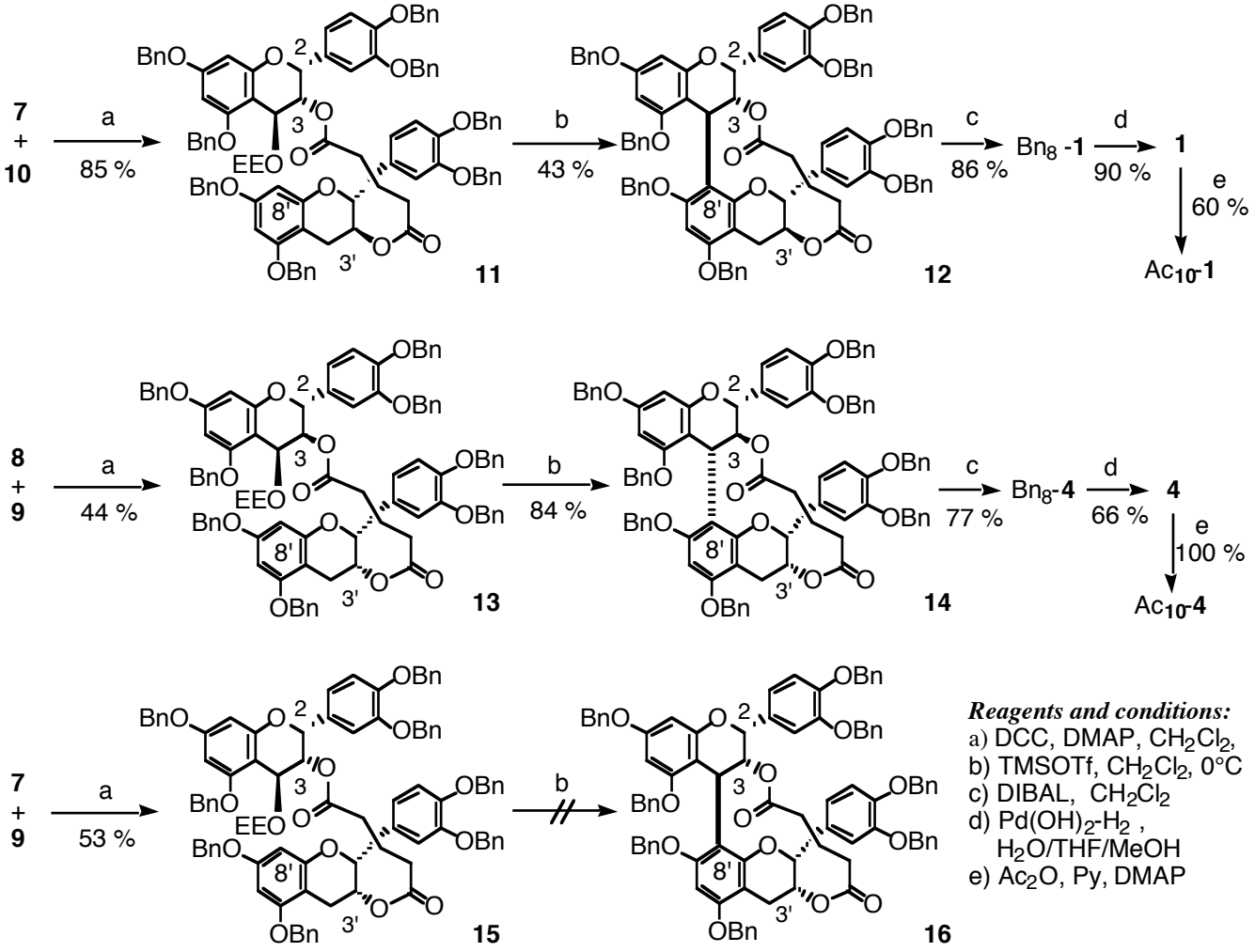
RESULTS AND DISCUSSION

Electrophile units were prepared by the introduction of an oxygen function[10] to the benzylic C-4 position. 4α-*O*-Ethoxyethyloxytetra-*O*-benzylated (-)-epicatechin (**7**) and 4β-*O*-ethoxyethyloxytetra-*O*-benzylated (+)-catechin (**8**)[9] were prepared by DDQ oxidation[11] from tetra-*O*-benzylated (-)-epicatechin (**5**) and (+)-catechin (**6**) in the presence of 2-ethoxyethanol in CH_2Cl_2 in 64% and 98% yields, respectively. The 3-hydroxy groups of the C-3 position of **5** and **6** were esterified with glutaric anhydride to give monoesters (**9** and **10**) in 96% and 84% yields, respectively. The resulting carboxylic monoesters were coupled with epicatechin electrophile (**7**) and catechin electrophile (**8**) by the DCC method to give diesters (**11** and **13**) in 85% and 44% yields, respectively. (-)-Epicatechin-(-)-epicatechin glutaryl diester (**15**) was also obtained from **7** and **9** in 53 % yield.

Intramolecular condensation for **11** and **13** was attempted by use of TMSOTf at 0°C for 5 min. The epicatechin electrophile was less reactive and 3,4-*trans*-octa-*O*-benzylated (-)-epicatechin-(4β→8)-(+)-catechin dimer (**12**) was obtained in 43 % yield. The more reactive catechin electrophile provided 3,4-*trans*-octa-*O*-benzylated (+)-catechin-(4β→8)-(-)-epicatechin dimer (**14**) in 84 % yield. Interestingly, intramolecular (-)-epicatechin and (-)-epicatechin condensation only provided a messy product. No amount of dimer **16** was detected in the reaction mixture.



Scheme 1



Scheme 2

Glutaryl linkers were removed by DIBAL reduction to furnish Bn_8-**1** and Bn_8-**4** in 86% and 77 % yields, respectively. All benzyl groups were finally removed by $Pd(OH)_2$–catalyzed hydrogenolysis to convert into 3,4-*trans*-(-)-epicatechin-(4→8)-(+)-catechin dimer, (**1**, procyanidin B1) in 90 % yield and 3,4-*trans*-(+)-catechin-(4→8)-(-)-epicatechin dimer, (**4**, procyanidin B4) in 66% yield. All the spectral data [NMR, IR, MS] for **1** and **4** were also collected as decaacetates (Ac_{10}-**1**[12] and Ac_{10}-**4**[13]) which were identical with those of authentic samples reported before.

In conclusion, we have synthesized 3,4-*trans*-natural procyanidin dimers, procyanidin-B1, and B4 based on a TMSOTf-catalyzed intramolecular condensation method. Study on the inhibitory activity of the Maillard reaction of the synthesized dimers and their acetates is now underway, and the structure and activity relationship will be reported in due course.

EXPERIMENTAL

All mp are uncorrected. Optical rotation was measured with a HORIBA SEPA-300 polarimeter. IR spectra were measured with a Shimadzu OR-8000 spectrophotometer. ^{1}H-NMR spectra were measured with a JEOL JNM-LA400 spectrometer, and MS spectra were recorded with a JEOL JMS-AX500 instrument or a JEOL JMS-700V instrument. Synthetic proanthocyanidin dimers (**1** and **4**) were analyzed on a Mightysil® RP-18 GP column (Kanto Chemical Co. Inc, Japan; 250 x 4.6 mm, 5 μm) using the solvents (A) 0.1% CF_3CO_2H in CH_3CN and (B) 0.1% CF_3CO_2H in H_2O. Elusion was done with a linear gradient 5 to 100% A in 40 min (flow rate, 0.5 mL/min).

(2*R*,3*R*)-5,7,3',4'-tetrabenzyloxyflavan-3-yl glutarate (9): (2*R*,3*R*)-5,7,3',4'-Tetrabenzyloxyflavan-3-ol (**5**) (710 mg, 1.09 mmol), glutaric anhydride (373 mg, 3.27 mmol) and DMAP (10 mg) in pyridine (30 mL) was stirred at 0°C for 1 h. After stirring for 48 h at rt, the reaction mixture was quenched with water, and extracted with EtOAc. The combined organic phases were washed with brine, and dried (Na_2SO_4). Filtration, concentration and short silica gel column chromatography (hexane/EtOAc, 1/1) gave 797 mg (96 %) of **9** as a white foam: $[\alpha]_D^{25}$ = -21.5° (*c* 1.10, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.46-7.21 (20H, m), 7.09 (1H, d, *J* = 1.7 Hz), 6.96 (1H, dd, *J* = 1.7, 8.5 Hz), 6.92 (1H, d, *J* = 8.5 Hz), 6.28 (2H, s), 5.46-5.42 (1H, m), 5.18 (1H, d, *J* = 11.9 Hz), 5.14 (2H, s), 5.13 (1H, d, *J* = 11.9 Hz), 5.01 (4H, s), 5.01-4.97 (1H, m), 3.02 (1H, dd, *J* = 4.4, 17.6 Hz), 2.94 (1H, d, *J* = 17.6 Hz), 2.26-2.05 (4H, m), 1.75-1.64 (2H, m) (The carboxyl proton was not detected.); ^{13}C-NMR (100 MHz, $CDCl_3$) 176.7, 172.1, 158.8, 157.9, 155.4, 149.1, 148.8, 137.2, 136.9, 136.6, 131.0, 128.6, 128.5, 128.45, 128.44, 128.0, 127.9, 127.79, 127.75, 127.6, 127.4, 127.3, 127.2, 123.9, 119.6, 114.7, 113.6, 100.7, 94.7, 93.9, 77.1, 71.5, 71.2, 70.1, 69.9, 67.8, 33.1, 32.5, 25.9, 19.7. IR (neat, cm^{-1}) 3320 (m), 3033 (m), 2930 (m), 1732 (s), 1709 (s), 1620 (s), 1593 (s), 1499 (m), 1454 (m), 1379 (m), 1269 (s), 1145 (s), 1119 (s), 1028 (m), 812 (w), 737 (m), 696 (m); FAB-MS (m/z) 788 (34), 787 ($[M+Na]^+$, 62), 767 (14), 766 (41), 765 ($[M+H]^+$, 75), 764 (28), 763 (15), 632 (100); FAB-HRMS calcd for $C_{48}H_{45}O_9$ $[M+H]^+$, 765.3064; found, 765.3041.

(2*R*,3*S*)-5,7,3',4'-Tetrabenzyloxyflavan-3-yl glutarate (10): Glutarate formation according to the general procedure using (2*R*,3*S*)-5,7,3',4'-tetrabenzyloxyflavan-3-ol (**6**) (1.00 g, 1.54 mmol), glutaric

anhydride (877 mg, 7.68 mmol) and DMAP (10 mg) in pyridine (20 mL) at 0°C afforded 992 mg (84 %) of **10**: $[\alpha]_D^{24}$ = +11.9° (*c* 1.08, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.42-7.20 (20H, m), 6.97 (1H, d, *J* = 1.2 Hz), 6.89 (1H, d, *J* = 8.3 Hz), 6.86 (1H, dd, *J* = 1.2, 8.3 Hz), 6.26 (1H, d, *J* = 2.2 Hz), 6.23 (1H, d, *J* = 2.2 Hz), 5.32 (1H, ddd, *J* = 5.6, 6.8, 6.8 Hz), 5.13 (2H, s), 5.10 (2H, s), 4.99 (4H, s), 4.95 (1H, d, *J* = 6.8 Hz), 2.90 (1H, dd, *J* = 5.6, 16.6 Hz), 2.70 (1H, dd, *J* = 6.8, 16.6 Hz), 2.29-2.12 (4H, m), 1.80-1.69 (2H, m) (The carboxyl proton was not detected.); ^{13}C-NMR (100 MHz, $CDCl_3$) 178.2, 171.8, 158.9, 157.6, 154.8, 149.0, 148.8, 137.1, 137.0, 136.81, 136.79, 130.8, 128.6, 128.5, 128.44, 128.43, 128.0, 127.9, 127.78, 127.77, 127.5, 127.4, 127.24, 127.23, 120.0, 114.7, 113.4, 101.3, 94.4, 93.8, 78.3, 71.2, 71.1, 70.1, 69.9, 69.1, 33.1, 32.5, 24.1, 19.6; IR (neat, cm^{-1}) 3750 (w), 3065 (w), 3032 (w), 1734 (s), 1700 (s), 1618 (s), 1593 (s), 1508 (s), 1456 (s), 1370 (m), 1261 (m), 1219 (m), 1145 (s), 1093 (w), 1026 (m), 812 (m), 738 (s), 690 (s); FAB-MS (m/z) 766 (49), 765 ($[M+H]^+$, 92), 632 (100); FAB-HRMS calcd for $C_{48}H_{45}O_9$ $[M+H]^+$, 765.3064; found, 765.3093.

(2*R*,3*R*,4*R*)-5,7,3',4'-Tetrabenzyloxy-4-ethoxyethyloxyflavan-3-yl (2*R*,3*S*)-5,7,3',4'-tetrabenzyloxyflavan-3-yl glutarate (11): A solution of (2*R*,3*R*,4*S*)-5,7,3',4'-tetrabenzyloxy-4-(2''-ethoxyethoxy)flavan-3-ol (**7**) (75 mg, 0.10 mmol), (2*R*,3*S*)-5,7,3',4'-tetrabenzyloxyflavan-3-yl glutarate (**10**) (153 mg, 0.20 mmol), DCC (41.3 mg, 0.20 mmol) and DMAP (5.00 mg) in CH_2Cl_2 (10 mL) was stirred at 0°C for 1 h. After stirring for 12 h at rt, the reaction mixture was quenched with water, and extracted with CH_2Cl_2. The combined organic phases were washed with brine, and dried (Na_2SO_4). Filtration, concentration and short silica gel column chromatography (hexane/EtOAc, 2/1) gave 126 mg (85 %) of **11** as a colorless amorphous solid: $[\alpha]_D^{24}$ = +2.57° (*c* 0.92, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.48-7.19 (40H, m), 7.11 (1H, d, *J* = 1.7 Hz), 6.99 (1H, dd, *J* = 1.7, 8.3 Hz), 6.92 (1H, d, *J* = 1.7 Hz), 6.91 (1H, d, *J* = 8.3 Hz), 6.79 (1H, d, *J* = 8.3 Hz), 6.74 (1H, dd, *J* = 1.7, 8.3 Hz), 6.24-6.23 (3H, m), 6.21 (1H, d, *J* = 2.2 Hz), 5.27 (1H, s), 5.27-5.22 (1H, m), 5.22 (1H, d, *J* = 2.4 Hz), 5.14 (1H, s), 5.13 (1H, s), 5.10 (2H, s), 5.07 (2H, s), 5.06 (2H, s), 4.96 (4H, s), 4.95 (4H, s), 4.87 (1H, d, *J* = 6.6 Hz), 4.47 (1H, d, *J* = 2.4 Hz), 3.96-3.92 (1H, m), 3.83-3.79 (1H, m), 3.54-3.52 (2H, m), 3.45 (2H, q, *J* = 7.1 Hz), 2.82 (1H, dd, *J* = 5.1, 16.5 Hz), 2.65 (1H, dd, *J* = 6.4, 16.5 Hz), 2.01-1.93 (4H, m), 1.58-1.53 (2H, m), 1.17 (3H, t, *J* = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 171.9, 171.8, 160.5, 159.4, 158.8, 157.6, 156.1, 154.8, 148.83, 148.76, 137.19, 137.17, 137.1, 137.0, 136.80, 136.76, 136.6, 130.8, 130.6, 128.5-127.2 (Cx28), 119.9, 119.8, 114.8, 114.6, 113.8, 113.2, 101.9, 101.2, 94.3, 94.0, 93.7, 78.0, 77.2, 73.6, 71.4, 71.1, 71.0, 70.2, 70.03, 69.96, 69.85, 69.6, 69.3, 69.2, 68.8, 68.2, 66.3, 32.8, 32.6, 23.8, 19.6, 15.2. IR (neat, cm^{-1}) 3065 (m), 3032 (m), 2932 (m), 2872 (m), 1736 (s), 1618 (s), 1593 (s), 1514 (s), 1454 (s), 1377 (s), 1265 (s), 1147 (s), 1028 (s), 814 (m), 737 (s), 698 (s); FAB-MS (m/z) 1486 ($[M+H]^+$, 2), 1485 (5), 1484 (7), 631 (100); FAB-HRMS calcd for $C_{95}H_{89}O_{16}$ $[M+H]^+$, 1485.6151; found, 1485.6167.

(2*R*,3*S*,4*S*)-5,7,3',4'-Tetrabenzyloxy-4-ethoxyethyloxyflavan-3-yl (2*R*,3*R*)-5,7,3',4'-tetrabenzyloxyflavan-3-yl glutarate (13): Ester formation according to the general procedure using (2*R*,3*S*,4*S*)-5,7,3',4'-tetrabenzyloxy-4-(2''-ethoxyethoxy)flavan-3-ol (**8**) (136 mg, 47 mmol), (2*R*,3*R*)-5,7,3',4'-tetrabenzyloxyflavan-3-yl glutarate (**9**) (178 mg, 0.23 mmol), DCC (47 mg, 0.17 mmol) and DMAP (5.00 mg) in CH_2Cl_2

(10 mL) afforded 119 mg (44 %) of **13** as a colorless amorphous solid: $[\alpha]_D^{24}$ = +21.9° (*c* 0.18, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.42-7.24 (40H, m), 7.19-6.79 (6H, m), 6.25 (2H, s), 6.23 (1H, d, *J* = 1.9Hz), 6.12 (1H, d, *J* = 1.9 Hz), 5.43-5.36 (1H, m), 5.21-5.19 (2H, m), 5.11-4.93 (17H, m), 4.81 (1H, d, *J* = 2.5 Hz), 3.75-3.67 (2H, m), 3.44-3.41 (2H, m), 3.38-3.31 (2H, m), 2.99 (1H, dd, *J* = 4.4, 17.8 Hz), 2.91 (1H, dd, *J* = 2.0, 17.8 Hz), 2.03-1.83 (4H, m), 1.48-1.39 (2H, m), 1.08 (3H, t, *J* = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 171.9, 171.4, 160.9, 158.8, 158.5, 157.9, 155.8, 155.4, 149.3, 148.83, 148.80, 137.3 (x2), 137.2, 136.9, 136.8, 136.6, 136.5, 131.0, 130.3, 128.6-127.2 (Cx26), 121.4, 119.7, 114.7, 114.42, 114.35, 113.63, 103.59, 100.8, 94.7, 94.2, 93.9, 93.8, 77.2, 74.3, 72.5, 71.4, 71.22, 71.17, 71.0, 70.8, 70.4, 70.10, 70.05, 69.9, 69.8, 68.4, 67.7, 66.3, 32.9, 32.7, 26.0, 19.5, 15.2. IR (neat, cm^{-1}) 3065 (m), 3032 (m), 2932 (m), 2872 (m), 1736 (s), 1616 (s), 1593 (s), 1514 (s), 1499 (s), 1454 (s), 1377 (s), 1267 (s), 1219 (s), 1188 (s), 1147 (s), 1116 (s), 1028 (s), 814 (m), 736 (s), 698 (s); FAB-MS (m/z) 1486 ($[M+H]^+$, 3), 1485 (5), 1484 (6), 1483 (5), 633 (87), 632 (100), 631 (92); FAB-HRMS calcd for $C_{95}H_{89}O_{16}$ $[M+H]^+$, 1485.6151; found, 1485.6123.

(2*R*,3*R*,4*S*)-5,7,3',4'-Tetrabenzyloxy-4-ethoxyethyloxyflavan-3-yl (2*R*,3*R*)-5,7,3',4'-tetrabenzyloxy-flavan-3-yl glutarate (15): Ester formation according to the general procedure using (2*R*,3*R*,4*S*)-5,7,3',4'-tetrabenzyloxy-4-(2''-ethoxyethoxy)flavan-3-ol (**7**), (121 mg, 0.16 mmol) (2*R*,3*R*)-5,7,3',4'-tetrabenzyloxyflavan-3-yl glutarate (**9**) (125 mg, 0.16 mmol), DCC (33.0 mg, 0.16 mmol) and DMAP (5.00 mg) in CH_2Cl_2 (10 mL) afforded 156 mg (53 %) of **15** as a white foam: $[\alpha]_D^{27}$ = -7.00° (*c* 0.70, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.43-7.23 (40H, m), 7.06 (1H, d, *J* = 1.7 Hz), 7.01 (1H, dd, *J* = 1.7, 8.3 Hz), 7.00 (1H, d, *J* = 1.7 Hz), 6.94 (1H, dd, *J* = 1.7, 8.3 Hz), 6.84 (1H, d, *J* = 8.3 Hz), 6.80 (1H, d, *J* = 8.3 Hz), 6.26-6.23 (4H, m), 5.39 (1H, br s), 5.25 (1H, s), 5.20 (1H, br s), 5.14-5.07 (2H, m), 5.14 (2H, s), 5.03 (4H, s), 4.98-4.95 (1H, m), 4.96-4.94 (1H, m), 4.95 (6H, s), 4.92 (1H, d, *J* = 12.0 Hz), 4.45 (1H, d, *J* = 2.2 Hz), 3.91 (1H, dt, *J* = 4.9, 11.0 Hz), 3.80 (1H, dt, *J* = 4.9, 11.0 Hz), 3.51 (2H, t, *J* = 4.9 Hz), 3.44 (2H, q, *J* = 6.8 Hz), 2.98 (1H, dd, *J* = 4.4, 17.8 Hz), 2.89 (1H, d, *J* = 17.8 Hz), 1.97-1.78 (4H, m), 1.51-1.47 (2H, m), 1.58 (3H, t, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 171.93, 171.87, 160.5, 159.4, 158.8, 157.9, 156.2, 155.4, 148.74, 148.67, 137.26, 137.23, 137.1, 136.84, 136.78, 136.67, 136.66, 130.8, 130.5, 128.6-127.16 (Cx27), 119.9, 119.6, 114.7, 114.6, 113.8, 113.5, 102.0, 100.7, 94.8, 94.4, 94.0, 93.9, 73.6, 71.43, 71.38, 70.99, 70.96, 70.2, 70.1, 70.0, 69.9, 69.6, 69.3, 69.2, 68.2, 67.7, 66.4, 60.4, 32.73, 32.70, 25.9, 19.5, 15.2; IR (neat, cm^{-1}) 3032 (m), 2930 (m), 2870 (m), 1736 (s), 1618 (s), 1593 (s), 1510 (s), 1454 (s), 1377 (s), 1267 (s), 1149 (s), 1028 (s), 814 (m), 736 (s), 696 (s); FAB-MS (m/z) 1486 ($[M+H]^+$, 2), 1485 (3), 1484 (4), 1483 (4), 1482 (3), 633 (85), 632 (100), 631 (87); FAB-HRMS calcd for $C_{95}H_{89}O_{16}$ $[M+H]^+$, 1485.6151; found, 1485.6156.

[4,8]-2,3-*cis*-3,4-*trans*:2,3-*trans*-Octa-*O*-benzyl-3,3'-*O*-glutaryl-(-)-epicatechin-(+)-catechin (12): To a solution of **11** (219 mg, 0.15 mmol) in CH_2Cl_2 (20 mL) was added dropwise TMSOTf (0.29 mL, 0.15 mmol, 0.5 M solution in CH_2Cl_2) at 0°C. After stirring for 5 min, the pale yellow reaction mixture was quenched with sat. 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 90 mg (43 %) of a mixture of **12** as a colorless oil: $[\alpha]_D^{27}$ = +64.7° (*c* 0.22, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.39-7.17 (33H, m), 7.08-6.98 (5H, m), 7.02 (1H, d, *J* = 1.7 Hz), 6.86 (1H, dd, *J* = 1.7, 8.3 Hz), 6.81 (1H, d, *J* = 1.7 Hz), 6.76 (1H, d, *J* = 8.3 Hz), 6.75-6.73 (2H, m), 6.43 (1H, dd, *J* = 1.7, 8.3 Hz), 6.25 (1H, s), 6.21 (1H, d, *J* = 8.3 Hz), 6.05 (1H, d, *J* = 2.2 Hz), 6.03 (1H, d, *J* = 2.2 Hz), 5.84 (1H, dd, *J* = 5.6, 10.0 Hz), 5.38 (1H, br s), 5.35 (1H, d, *J* = 5.6 Hz), 5.26-5.23 (1H, m), 5.07 (2H, s), 5.03 (1H, d, *J* = 11.8 Hz), 4.98 (2H, s), 4.97 (1H, d, *J* = 11.8 Hz), 4.95 (1H, d, *J* = 12.4 Hz), 4.910 (1H, d, *J* = 12.4 Hz), 4.908 (2H, s), 4.88 (1H, d, *J* = 11.5 Hz), 4.87 (1H, d, *J* = 13.2 Hz), 4.82 (1H, d, *J* = 11.5 Hz), 4.77 (1H, d, *J* = 10.0 Hz), 4.76 (1H, d, *J* = 11.7 Hz), 4.69 (1H, d, *J* = 13.2 Hz), 4.62 (1H, d, *J* = 11.7 Hz), 2.89 (1H, dt, *J* = 2.5, 16.8 Hz) 2.49-2.42 (1H, m), 2.32-2.21 (2H, m) 2.22 (1H, dd, *J* = 2.9, 16.8 Hz), 2.16-2.07 (1H, m), 1.86-1.71 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 172.04, 171.98, 158.2, 157.4, 156.5, 155.5, 154.5, 152.4, 148.5, 148.4, 148.3, 148.2, 137.3, 137.19, 137.17, 137.04, 136.98, 131.9, 130.8, 128.6-126.8 (Cx29), 120.6, 118.4, 114.6, 114.5, 114.3, 114.5, 110.4, 107.7, 100.7, 95.4, 94.2, 91.0, 77.2, 74.9, 72.3, 71.4, 71.0, 70.9, 70.2, 70.1, 69.93, 69.88, 69.3, 33.6, 32.8, 30.3, 19.6; IR (neat, cm^{-1}) 3065 (m), 3032 (m), 2930 (m), 2870 (m), 1732 (s), 1606 (s), 1508 (s), 1456 (s), 1417 (s), 1379 (s), 1265 (s), 1148 (s), 1138 (s), 1028 (s), 910 (w), 848 (w), 810 (m), 736 (s), 698 (s); FAB-MS (m/z) 1398 (34), 1397 (68), 1396 ($[M+H]^+$, 100), 1395 (79), 1394 (27); FAB-HRMS calcd for $C_{91}H_{79}O_{14}$ $[M+H]^+$, 1396.5504; found, 1395.5490.

[4,8]-2,3-*trans*-3,4-*trans*:2,3-*cis*-Octa-*O*-benzyl-3,3'-*O*-glutaryl-(+)-catechin-(-)-epicatechin (14): To a solution of **13** (80 mg, 0.054 mmol) in CH_2Cl_2 (40 mL) was added dropwise TMSOTf (0.11 mL, 0.054 mmol, 0.5 M solution in CH_2Cl_2) at 0°C. After stirring for 5 min, the pale yellow reaction mixture was quenched with sat. 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 63 mg (84 %) of **14** as a colorless oil: $[\alpha]_D^{24}$ = -64.1° (*c* 1.26, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.45-7.09 (40H, m), 6.94 (1H, d, *J* = 8.3 Hz), 6.94 (1H, d, *J* = 1.7Hz), 6.84-6.77 (2H, m), 6.74 (1H, d, *J* = 8.3Hz), 6.69 (1H, dd, *J* = 1.7, 8.3 Hz), 6.23 (1H, s), 6.23 (1H, d, *J* = 2.2 Hz), 6.21 (1H, d, *J* = 2.2 Hz), 5.79 (1H, dd, *J* = 9.5, 10.3 Hz), 5.34 (1H, br s), 5.21 (1H, d, *J* = 11.9 Hz), 5.15-4.87 (12H, m), 4.96-4.92 (1H, m), 4.84 (1H, d, *J* = 11.9 Hz), 4.73 (1H, d, *J* = 10.3 Hz), 4.65 (1H, d, *J* = 10.2 Hz), 4.54 (1H, d, *J* = 10.2 Hz), 4.05 (1H, br s), 2.91 (1H, d, *J* = 16.9 Hz), 2.61 (1H, dd, *J* = 3.1, 16.9 Hz), 2.41-2.35 (1H, m), 2.23-2.16 (1H, m), 1.89-1.79 (2H, m), 1.44-1.31 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 171.8, 171.3, 158.2, 157.7, 156.3, 156.1, 156.0, 152.7, 149.1, 149.0, 148.8, 148.0, 137.32, 137.30, 137.28, 137.22, 137.18, 137.09 (x2), 136.5, 131.9, 130.6, 128.60-127.09 (Cx25), 121.5, 118.5, 115.0, 114.6, 113.5, 112.4, 110.6, 108.2, 100.0, 94.9, 94.2, 91.1, 77.2, 76.0, 72.9, 71.4, 71.2, 71.0 (x2), 70.2, 70.1, 70.0 (x2), 68.0, 35.9, 32.9, 32.4, 26.8, 18.3; IR (neat, cm^{-1}) 3065 (w), 3032 (w), 2932 (w), 2870 (w), 1732 (s), 1609 (s), 1514 (m), 1454 (m), 1383 (s), 1265 (s), 1217 (s), 1142 (s), 1118 (s), 1028 (m), 737 (s), 698 (s); FAB-MS (m/z) 1397 (30), 1396 ($[M+H]^+$, 100); FAB-HRMS calcd for $C_{91}H_{79}O_{14}$ $[M+H]^+$, 1395.5470; found: 1395.5470.

[4,8]-2,3-*cis*-3,4-*trans*:2,3-*trans*-Octa-*O*-benzyl-(-)-epicatechin-(+)-catechin (Bn_8-1): To a solution

of **12** (48 mg, 0.034 mmol) in CH_2Cl_2 (20 mL) was added 1M solution of DIBAL (0.34 mL, 0.34 mmol) at –78°C. After 30 min at -78°C, the reaction mixture was warmed to rt and then the reaction was quenched with sat. aq. NH_4Cl solution. The reaction mixture was diluted with $CHCl_3$, and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. Purification of the residue was accomplished by silica gel preparative TLC (hexane/EtOAc, 2/1) to afford a 38 mg (86%) of Bn_8-**1** as a colorless amorphous solid: $[\square]_D^{30}$ = +53.4° (*c* 1.20, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, 0.74: 0.26 mixture of rotational isomers) major isomer: 7.46-6.73 (31.08H, m), 7.00 (0.74H, dd, *J* = 1.7, 8.3 Hz), 6.79 (0.74H, d, *J* = 8.3 Hz), 6.72 (0.74H, d, *J* = 1.7 Hz), 6.50 (0.74H, dd, *J* = 1.7, 8.3 Hz), 6.34 (0.74H, s), 6.02 (0.74H, d, *J* = 2.2 Hz), 5.54 (0.74H, d, *J* = 2.2 Hz), 5.40 (0.74H, br s), 5.12-4.78 (10.36H, m), 4.83 (0.74H, br s), 4.62 (0.74H, d, *J* = 11.2 Hz), 4.52 (0.74H, d, *J* = 11.2 Hz), 4.03 (0.74H, br s), 3.74 (0.74H, ddd, *J* = 6.3, 9.0, 9.3 Hz), 3.65 (0.74H, d, *J* = 9.0 Hz), 3.24 (0.74H, dd, *J* = 6.3, 16.8 Hz), 2.58 (0.74H, dd, *J* = 9.3, 16.8 Hz), 1.60 (0.74H, br s, OH), 1.41 (0.74H, br s, OH); minor isomer: 7.46-6.73 (11.96H, m), 6.21 (0.26H, d, *J* = 2.2 Hz), 6.17 (0.26H, s), 6.06 (0.26H, d, *J* = 2.2 Hz), 5.26 (0.26H, br s), 5.12-4.82 (3.64H, m), 4.68 (0.26H, br s), 4.62 (0.26H, d, *J* = 11.9 Hz), 4.62 (0.26H, br s), 4.40 (0.26H, d, *J* = 11.9 Hz), 3.87 (0.26H, br s), 3.65-3.62 (0.26H, m), 3.17 (0.26H, dd, *J* = 5.1, 16.6 Hz), 2.68 (0.26H, dd, *J* = 8.5, 16.6 Hz), 1.54 (0.26H, br s, OH), 1.68-1.21 (0.26H, m, OH); ^{13}C-NMR (100 MHz, $CDCl_3$, 0.74 : 0.26 mixture of rotational isomers) major isomer: 158.1, 157.0, 155.9, 155.8, 155.1, 154.4, 149.1, 148.9, 148.7, 148.6, 137.3, 137.2 (x2), 137.1, 137.04, 136.98, 132.6, 130.3, 128.6-126.7 (Cx26), 120.5, 119.6, 115.0, 113.9, 113.6, 112.1, 111.2, 104.3, 104.2, 93.5, 93.0, 91.5, 81.6, 75.4, 72.3, 71.4, 71.3, 71.2, 70.5, 70.2, 69.9, 69.5, 69.1, 68.5, 35.6, 29.1; minor isomer: 158.3, 157.7, 156.8, 155.9, 155.8, 155.6, 149.0, 148.9, 148.8, 148.5, 137.7, 137.6, 137.39, 137.38, 137.28, 137.0, 132.5, 131.0, 128.5-126.7 (Cx26), 120.1, 119.9, 114.5, 114.0, 113.0, 112.7, 109.3, 104.6, 102.7, 94.4, 93.2, 92.6, 81.3, 75.5, 71.7, 71.4, 71.2, 71.1, 71.0, 70.7, 69.8, 69.4, 69.2, 68.2, 35.7, 27.7; IR (neat, cm^{-1}) 3550 (m), 3450 (m), 3063 (m), 3032 (m), 2928 (m), 2872 (m), 1605 (s), 1598 (s), 1514 (s), 1454 (s), 1379 (s), 1329 (m), 1265 (s), 1215 (s), 1118 (s), 1072 (s), 1028 (s), 910 (w), 852 (w), 808 (m), 735 (s), 696 (s); FAB-MS (m/z) 1324 (12), 1323 (25), 1322 ($[M+Na]^+$, 27), 1302 (33), 1301 (74), 1300 ($[M+H]^+$, 100), 1299 (67); FAB-HRMS calcd for $C_{86}H_{75}O_{12}$ $[M+H]^+$, 1299.5259; found: 1299.5254.

[4,8]-2,3-*trans*-3,4-*trans*:2,3-*cis*-Octa-*O*-benzyl-(+)-catechin-(-)-epicatechin (Bn_8-4): To a solution of **14** (21 mg, 0.015 mmol) in CH_2Cl_2 (20 mL) was added 1M solution of DIBAL (0.15 mL, 0.15 mmol) at –78°C. After 30 min at -78°C, the reaction mixture was warmed to rt and then the reaction was quenched with sat. aq. NH_4Cl solution. The reaction mixture was diluted with $CHCl_3$, and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Purification of the residue was accomplished by silica gel preparative TLC (hexane/EtOAc, 2/1) to afford a 15 mg (77 %) of Bn_8-**4** as a colorless amorphous solid: $[\alpha]_D^{30}$ = -84.7° (*c* 0.72, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$, 0.67 : 0.33 mixture of rotational isomers) major isomer: 7.45-6.71 (29.48H, m), 6.91 (0.67H, d, *J* = 8.3 Hz), 6.78 (0.67H, d, *J* = 8.3 Hz), 6.22 (0.67H, s), 6.19 (0.67H, d, *J* = 2.2 Hz), 6.12 (0.67H, d, *J* = 2.2 Hz), 5.20-4.46 (10.72H, m), 4.79 (0.67H, d, *J* = 9.0 Hz), 4.50 (0.67H, d, *J* = 9.0 Hz), 4.29 (0.67H, t, *J* = 9.0 Hz), 3.90-3.83 (0.67H, m), 3.78-3.72 (0.67H, m), 2.86 (0.67H, d, *J* = 17.1 Hz),

2.58 (0.67H, dd, *J* = 4.4, 17.1 Hz), 1.67 (0.67H, br s, OH), 1.80-1.20 (0.67H, m, OH); minor isomer: 7.45-6.71 (14.85H, m), 6.47 (0.33H, dd, *J* = 1.7, 8.3 Hz), 6.17 (0.33H, d, *J* = 2.2 Hz), 6.10 (0.33H, d, *J* = 2.2 Hz), 5.99 (0.33H, s), 5.20-4.12 (6.27H, m), 4.49-4.47 (0.33H, m), 4.09-4.07 (0.33H, m), 3.02 (0.33H, d, *J* = 17.3 Hz), 2.89 (0.33H, dd, *J* = 4.4, 17.3 Hz), 1.54 (0.33H, br s, OH), 1.80-1.20 (0.33H, m, OH); ^{13}C-NMR (100 MHz, $CDCl_3$, 0.67 : 0.33 mixture of rotational isomers) major isomer: 157.9, 157.8, 156.8, 156.1, 155.4, 153.6, 149.1, 149.0, 148.9, 148.2, 137.4, 137.3, 137.21, 137.17, 137.07, 137.03, 136.6, 132.1, 131.7, 128.5-127.1 (Cx25), 121.2, 118.7, 114.9, 114.4, 113.8, 113.5, 111.6, 108.2, 100.8, 94.8, 94.1, 91.4, 82.1, 77.2, 73.1, 71.4, 71.2, 71.0, 70.9, 70.2, 70.1, 69.93, 69.90, 65.9, 37.0, 28.2; minor isomer: 158.1, 158.0, 156.9, 156.5, 156.0, 152.8, 150.0, 149.1, 148.9, 148.7, 137.6, 137.4, 137.2, 137.1, 137.0, 136.9, 136.8, 131.8, 131.0, 128.56-127.05 (Cx25), 120.9, 119.8, 114.9, 114.4, 113.8, 113.5, 111.6, 108.2, 102.1, 95.3, 94.4, 92.0, 81.8, 78.1, 72.4, 71.7, 71.1, 71.0, 70.9, 70.3, 69.93, 69.86, 69.6, 66.3, 37.3, 28.8; IR (neat, cm^{-1}) 3450 (m), 3065 (w), 3032 (w), 2870 (w), 1736 (m), 1608 (s), 1512 (s), 1454 (s), 1375 (s), 1265 (s), 1136 (s), 1109 (s), 1045 (s), 1028 (s), 910 (s), 735 (s), 698 (s); FAB-MS (m/z) 1324 (23), 1323 (46), 1322 ($[M+Na]^+$, 48), 1302 (32), 1301 (64), 1300 ($[M+H]^+$, 100), 1299 (71); FAB-HRMS calcd for $C_{86}H_{75}O_{12}$ $[M+H]^+$, 1299.5259; found: 1299.5289.

Procyanidin B1 (1): A solution of **14** (35 mg, 0.027 mmol) in THF/MeOH/H_2O, 20/1/1 (10 mL) was hydrogenated over 20% $Pd(OH)_2$/C (14 mg) for 12 h in a current of H_2 at rt. Filtration and concentration afforded a pale brown oil, which was purified by Sephadex® LH-20 column chromatography (EtOH) to give 14 mg of pure procyanidin-B1 (**1**) (90 %) as a pale brown powder: HPLC ^{t}R-**1**, 17.2 min; $[\alpha]_D^{24}$ = +19.6° (*c* 0.28, EtOH) [lit.,[3] $[\alpha]_{578}$ = +31° (*c* 0.8, EtOH)]; ^{1}H-NMR (400 MHz, CD_3OD, all the NMR peaks were broadened and discrimination of the rotational isomers were impossible) 6.92-6.88 (1H, m), 6.88-6.70 (1H, m), 6.70-6.65 (4H, m), 6.05-5.90 (3H, m), 5.12-5.08 (1H, m), 4.85-4.80 (1H, m), 4.63-4.57 (1H, m), 4.15-4.00 (1H, m), 3.92 (1H, m), 2.85-2.65 (1H, m), 2.65-2.55 (1H, m): FAB-MS (m/z) 602 (2), 601 ($[M+Na]^+$, 4), 176 (100); FAB-HRMS calcd for $C_{30}H_{26}O_{12}Na$ $[M+Na]^+$, 601.1322; found, 601.1309.

Decaacetylprocyanidin-B1 (Ac_{10}-1): Acetylation using **1** (15 mg, 0.026 mmol) with Ac_2O (49 μL, 0.52 mmol) and 4-(dimethylamino)pyridine (1 mg) in pyridine (5 mL) afforded 15 mg (60 %) of Ac_{10}-**1** as a colorless amorphous solid:$[\alpha]_D^{21}$ = +76.3° (*c* 0.16, $CHCl_3$) [lit.,[3] $[\alpha]_{578}$ = +110° (*c* 1.21, $CHCl_3$)]; ^{1}H-NMR (400 MHz, $CDCl_3$, 0.86 : 0.14 mixture of rotational isomers) major isomer: 7.29 (0.86H, d, *J* = 1.7 Hz), 7.24 (0.86H, dd, *J* = 1.7, 8.3 Hz), 7.16 (0.86H, d, *J* = 8.3 Hz), 7.09 (0.86H, d, *J* = 8.3 Hz), 6.94 (0.86H, dd, *J* = 1.7, 8.3 Hz), 6.88 (0.86H, d, *J* = 1.7 Hz), 6.68 (0.86H, s), 6.29 (0.86H, d, *J* = 2.2 Hz), 5.99 (0.86H, d, *J* = 2.2 Hz), 5.45 (0.86H, br s), 5.18-5.13 (0.86H, m), 5.05 (0.86H, ddd, *J* = 6.6, 9.3, 9.5 Hz), 4.42 (0.86H, d, *J* = 1.7 Hz), 4.33 (0.86H, d, *J* = 9.5 Hz), 3.21 (0.86H, dd, *J* = 6.6, 16.8 Hz), 2.56 (0.86H, dd, *J* = 9.3, 16.8 Hz), 2.35 (2.58H, s), 2.30 (2.58H, s), 2.28 (7.74H, s), 2.25 (2.58H, s), 2.15 (2.58H, s), 1.89 (2.58H, s), 1.86 (2.58H, s), 1.83 (2.58H, s); minor isomer: 7.29-7.14 (0.56H, m), 7.17 (0.14H, d, *J* = 8.5 Hz), 7.13 (0.14H, d, *J* = 8.5 Hz), 6.74 (0.14H, d, *J* = 2.2 Hz), 6.70 (0.14H, d, *J* = 2.2 Hz), 6.60 (0.14H, s), 5.33 (0.14H, br s), 5.29 (0.14H, br s), 5.21-5.19 (0.28H, m), 4.55 (0.14H, br s), 3.10-3.04 (0.14H, m),

2.78-2.69 (0.14H, m), 2.33-2.25 (1.26H, m), 2.26 (1.26H, s), 1.92 (0.42H, s), 1.95 (0.42H, s), 1.72 (0.42H, s), 1.63 (0.42H, s)**;** ^{13}C-NMR (100 MHz, $CDCl_3$, 0.86 : 0.14 mixture of rotational isomers) major isomer: 169.8 (x2), 169.7, 169.0, 168.9, 168.3, 168.2, 168.1, 167.83, 167.80, 155.5, 154.0, 149.3, 148.7, 147.94, 147.93, 142.3, 141.9, 141.7, 136.4, 134.6, 125.4, 124.5, 123.2, 123.1, 122.3, 122.1, 117.0, 113.6, 111.4, 110.7, 108.6, 107.2, 78.3, 77.2, 73.5, 70.9, 68.4, 34.0, 27.1, 21.2, 21.1, 20.8, 20.7, 20.66 (x3), 20.63, 20.41, 10.0; minor isomer couldn't been identified; IR (neat, cm^{-1}) 2936 (w), 2361 (w), 1770 (s), 1747 (s), 1622 (m), 1597 (m), 1508 (m), 1487 (m), 1425 (m), 1371 (s), 1209 (s), 1126 (m), 1111 (m), 1043 (m), 900 (m), 736 (m); FAB-MS (m/z) 1021 ([M+Na]$^+$, 100), 999 ([M+H]$^+$, 15); FAB-HRMS calcd for $C_{50}H_{46}O_{22}Na$ [M+Na]$^+$, 1021.2378; found, 1021.2358.

Procyanidin B4 (4): Hydrogenation according to the above procedure using 76 mg of **20** (0.058 mmol) in THF/MeOH/H_2O, 20/1/1 (1.0 mL) afforded 22 mg (66 %) of the procyanidin-B4 (**4**) as a colorless amorphous solid: HPLC ^{t}R-**4**, 19.4 min; $[\alpha]_D^{25}$ = -222° (*c* 0.36, EtOH) [lit.,[3] $[\alpha]_{578}$ = -193.5° (*c* 1.0, EtOH)]; ^{1}H-NMR (400 MHz, CD_3OD, 0.63 : 0.37 mixture of rotational isomers) major isomer: 6.99 (0.63H, d, *J* = 1.9 Hz, B2 or E2), 6.89 (0.63H, d, *J* = 1.9 Hz, B2 or E2), 6.77 (1.26H, dd, *J* = 1.9, 8.1 Hz, B6 and E6), 6.89 (0.63H, d, *J* = 8.1 Hz, B5 or E5), 6.68 (0.63H, d, *J* = 8.1 Hz, B5 or E5), 5.85 (0.63H, s, D6), 5.74 (0.63H, d, *J* = 2.3 Hz, A6 or A8), 5.69 (0.63H, d, *J* = 2.3 Hz, A6 or A8), 4.83 (0.63H, br s, F2), 4.53 (0.63H, d, *J* = 8.0 Hz, C2 or C4), 4.48 (0.63H, dd, *J* = 8.0, 9.5 Hz, C3), 4.32 (0.63H, d, *J* = 9.5 Hz, C2 or C4), 4.18-4.16 (0.63H, m, F3), 2.83 (0.63H, dd, *J* = 4.3, 16.8 Hz, F4), 2.72 (0.63H, dd, *J* = 1.5, 16.8 Hz, F4); minor isomer: 6.62 (0.37H, d, *J* = 8.0 Hz, B5 or E5), 6.59 (0.37H, d, *J* = 1.9 Hz, B2 or E2), 5.58 (0.37H, d, *J* = 1.9 Hz, B2 or E2), 6.51 (0.37H, d, *J* = 8.0 Hz, B5 or E5), 6.35 (0.37H, dd, *J* = 1.9, 8.0 Hz, B6 or E6), 6.31 (0.37H, dd, *J* = 1.9, 8.0 Hz, B6 or E6), 6.00 (0.37H, s, D6), 5.84 (0.37H, d, *J* = 2.5 Hz, A6 or A8), 5.79 (0.37H, d, *J* = 2.5 Hz, A6 or A8), 4.71 (0.37H, br s, F2), 4.36 (0.37H, dd, *J* = 2.2, 6.1 Hz, C3), 4.22 (0.37H, d, *J* = 6.1 Hz, C2 or C4), 4.21 (0.37H, d, *J* = 2.2 Hz, C2 or C4), 3.95-3.85 (0.37H, m, F3), 2.85-2.70 (0.37H, m, F4), 2.60 (0.37H, dd, *J* = 2.2, 17.3 Hz, F4); ^{13}C-NMR (100 MHz, CD_3OD, 0.63 : 0.37 mixture of rotational isomers) major isomer: 158.7, 157.5, 157.3, 156.4, 155.9, 155.4, 146.5, 146.1, 145.63, 145.60, 132.6, 132.3, 121.2, 119.1, 116.3, 116.0 (x2), 115.2, 107.4, 107.2, 99.4, 97.6, 97.5, 96.1, 83.8, 80.0, 73.8, 67.4, 38.9, 30.1; minor isomer: 158.5, 157.3, 157.2, 156.3, 155.8, 155.4, 146.0, 145.9, 145.58, 145.55, 132.5, 131.7, 120.5, 120.3, 116.4, 116.0, 115.9, 114.8, 108.7, 108.3, 101.5, 97.7, 97.1, 96.3, 84.0, 79.9, 73.8, 67.8, 38.7, 29.3; FAB-MS (m/z) 602 (1), 601 ([M+Na]$^+$, 4), 579 ([M+H]$^+$, 3), 176 (100); FAB-HRMS calcd for $C_{30}H_{26}O_{12}Na$ [M+Na]$^+$, 601.1322; found, 601.1307.

Decaacetylprocyanidin-B4 (Ac_{10}-4): Acetylation using **4** (10 mg, 0.017 mmol), Ac_2O (32 μL, 0.34 mmol) and 4-(dimethylamino)pyridine (1 mg) in pyridine (2 mL) afforded 17 mg (100 %) of Ac_{10}-**4** as a colorless amorphous solid: $[\alpha]_D^{25}$ = -120.8° (*c* 0.24, $CHCl_3$) [lit.,[3] $[\alpha]_{578}$ = -130.8° (*c* 2.0, $CHCl_3$)]; ^{1}H-NMR (400 MHz, $CDCl_3$, 0.78 : 0.22 mixture of rotational isomers) major isomer: 7.15 (0.78H, d, *J* = 8.3 Hz), 7.10 (0.78H, d, *J* = 8.3 Hz), 6.97 (0.78H, d, *J* = 2.2 Hz), 6.90 (0.78H, dd, *J* = 2.2, 8.3 Hz), 6.90 (0.78H, d, *J* = 2.2 Hz), 6.87 (0.78H, dd, *J* = 2.2, 8.3 Hz), 6.63 (0.78H, s), 6.58 (0.78H, d, *J* = 2.5 Hz), 6.53 (0.78H, d, *J* = 2.5 Hz), 5.72 (0.78H, t, *J* = 9.8 Hz), 5.23-5.21 (0.78H, m), 5.01 (0.78H, br s), 4.82 (0.78H, d, *J* = 9.8 Hz), 4.53 (0.78H, d, *J* = 9.8 Hz), 3.02 (0.78H, dd, *J* = 4.9, 17.8 Hz), 2.76 (0.78H, d, *J* = 17.8

Hz), 2.35 (2.34H, s), 2.30 (2.34H, s), 2.29 (2.34H, s), 2.28 (2.34H, s), 2.26 (2.34H, s), 2.25 (4.68H, s), 1.93 (2.34H, s), 1.86 (2.34H, s), 1.64 (2.34H, s); minor isomer: 7.46 (0.22H, d, *J* = 1.9 Hz), 7.40 (0.22H, dd, *J* = 1.9, 8.5 Hz), 7.35 (0.22H, dd, *J* = 1.9, 8.5 Hz), 7.29 (0.22H, d, *J* = 1.9 Hz), 7.26 (0.22H, d, *J* = 8.5 Hz), 7.24 (0.22H, d, *J* = 8.5 Hz), 6.73 (0.22H, s), 6.68 (0.22H, d, *J* = 2.2 Hz), 6.56 (0.22H, d, *J* = 2.2 Hz), 5.65 (0.22H, t, *J* = 9.8 Hz), 5.56-5.52 (0.22H, m), 5.18 (0.22H, br s), 5.06 (0.22H, d, *J* = 9.8 Hz), 5.02 (0.22H, d, *J* = 9.8 Hz), 2.97 (0.22H, dd, *J* = 3.9, 15.9 Hz), 2.90 (0.22H, d, *J* = 15.9 Hz), 2.32 (0.66H, s), 2.31 (0.66H, s), 2.30 (0.66H, s), 2.29 (0.66H, s), 2.25 (1.32H, s), 1.90 (0.66H, s), 1.83 (0.66H, s), 1.82 (0.66H, s), 1.72 (0.66H, s); ^{13}C-NMR (100 MHz, $CDCl_3$, 0.78 : 0.22 mixture of rotational isomers) major isomer: 170.9, 169.4, 168.7, 168.5, 168.4, 168.0, 167.98, 167.93, 167.88, 167.80, 155.7, 153.5, 149.5, 149.2, 148.3, 147.6, 142.1, 142.0, 141.7, 141.4, 135.22, 135.16, 125.0, 124.8, 123.6, 123.5, 123.0, 122.7, 121.8, 116.9, 115.0, 110.4, 110.1, 109.5, 108.1, 78.9, 77.2, 66.1, 36.7, 26.6, 21.1, 20.92, 20.86, 20.7, 20.60, 20.57 (x2), 20.50, 20.4, 20.2; minor isomer: 170.9, 170.3, 168.7, 168.19, 168.17, 168.0, 167.91, 167.88, 167.4, 167.3, 155.6, 152.0, 149.6, 149.1, 147.9, 145.4, 142.4, 142.2, 142.0, 141.8, 135.5, 135.0, 126.1, 125.5, 124.6, 123.9, 123.6, 123.4, 121.6, 117.1, 115.2, 110.2, 109.6, 108.8, 108.4, 67.0 (x2), 66.1, 35.6, 26.1, 21.0, 20.92, 20.86, 20.7, 20.61, 20.57 (x2), 20.49, 20.36, 20.27; IR (neat, cm^{-1}) 3067 (w), 2936 (w), 2361 (w), 1770 (s), 1616 (m), 1506 (m), 1429 (m), 1371 (s), 1240 (s), 1126 (s), 1105 (s), 1049 (s), 1014 (m), 900 (m), 736 (m); FAB-MS (m/z) 1021 ($[M+Na]^+$, 100), 999 ($[M+H]^+$, 8); FAB-HRMS calcd for $C_{50}H_{46}O_{22}Na$ $[M+Na]^+$, 1021.2378; found, 1021.2384.

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