Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Unified approach to catechin hetero-oligomers: first total synthesis of EZ-EG-CA isolated from *Ziziphus jujuba*

Takahisa Yano, Ken Ohmori, Haruko Takahashi, Takenori Kusumi and Keisuke Suzuki*

Department of Chemistry, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8551, Japan

ksuzuki@chem.titech.ac.jp

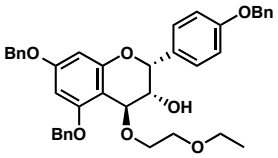
General Experimental Procedures

All reactions utilizing air- and moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry argon or nitrogen. Ethereal solvents (anhydrous; Kanto Chemical Co., Inc.) were used as received. Dichloromethane was distilled successively from P_2O_5 and CaH_2, and stored over 4A molecular sieves.

For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) or Yamazen diol-modified silica plates [TLC plates $(OH)_2$, Art 7519] were used. Preparative silica gel TLC (PTLC) was performed on Merck Silica gel 60 PF_{254} (Art 7747). For flash column chromatography, silica gel 60N (Spherical, neutral, 63–210 μm) from Kanto Chemical was used.

Melting point (mp) determinations were performed by using a Yanako MP-S3 or MP-500 instrument and are uncorrected. ^{1}H NMR and ^{13}C NMR were measured on a JEOL JNM AL-400 (400 MHz), a JEOL ECX-400 (400 MHz), a JEOL ECX-500 (500 MHz), a Bruker DRX-500 (500 MHz), or a Bruker Avance III 600 (600 MHz) spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from internal standard (tetramethylsilane, 0.00 ppm), and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 FTIR, a Horiba FT-710, or a Perkin Elmer Spectrum 100 spectrometer. Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) spectra were recorded on a Perkin Elmer 1600 FTIR. Elemental analyses were recorded on an Elementar vario MICRO cube analyzer. Optical rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 polarimeter. High-performance liquid chromatography (HPLC) analyses were performed by using a Jasco 880PU instrument with UV detection at 280 nm. Low-resolution mass spectra (LRMS) were obtained on a Shimadzu MALDI TOF Mass AXIMA® Confidence. High-resolution mass spectra (HRMS) were obtained with micrOTOF-Q II (Bruker Daltonics).

Preparation of H-(EZ)-OEE 11



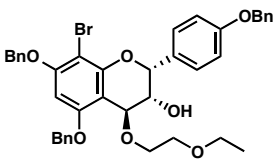
H-(EZ)-OEE **11**

To a solution of tri-*O*-benzyl-(–)-epiafzelechin[a] **10** (1.00 g, 1.83 mmol) in toluene (61 mL) was added 2-ethoxyethanol (1.0 mL, 10 mmol) and DDQ (1.25 g, 6.83 mmol) at 0 °C. After stirring for 23 h at ambient temperature, the reaction was stopped by adding DMAP (0.78 g, 6.4 mmol) at 0 °C. The resulting mixture was filtered through a Celite® pad (washed with EtOAc, 20 mL), and the filtrate was concentrated to half its volume (30 mL) in vacuo. The mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by Frorisil® column chromatography (hexane/EtOAc = 3/1) and flash column chromatography (silica gel, hexane/EtOAc = 4/1 to 3/1, gradient elution) to afford H-(EZ)-OEE **11** (0.85 g, 72%) as a colorless amorphous foam.

11: R_f 0.44 (hexane/EtOAc = 3/1); $[\alpha]_D^{28}$ +1.9 (*c* 2.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, 3H, *J* = 6.7 Hz), 1.61 (d, 1H, *J* = 6.3 Hz, OH), 3.43 (q, 2H, *J* = 6.7 Hz), 3.49–3.55 (m, 2H), 3.76–3.86 (m, 2H), 4.09 (dd, 1H, *J* = 6.3, 2.3 Hz), 4.61 (d, 1H, *J* = 2.3 Hz), 5.01 (s, 2H), 5.02 (d, 1H, *J* = 11.5 Hz), 5.07 (d, 1H, *J* = 11.5 Hz), 5.10 (s, 2H), 5.24 (s, 1H), 6.27 (d, 1H, *J* = 2.3 Hz), 6.29 (d, 1H, *J* = 2.3 Hz), 7.03 (d, 2H, *J* = 9.2 Hz), 7.30–7.61 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 66.6, 68.6, 69.1, 70.0, 70.17, 70.19, 70.4, 70.5, 74.9, 94.3, 94.6, 102.1, 115.1, 127.5, 127.6, 127.7, 128.0, 128.1, 128.6, 128.7, 130.4, 136.8, 136.9, 137.1, 156.3, 158.7, 160.0, 160.1; IR (film) 3432, 3064, 3032, 2973, 2870, 1615, 1592, 1513, 1498, 1454, 1444, 1376, 1311, 1243, 1220, 1197, 1175, 1151, 1109, 1027, 811, 737, 697 cm^{-1}; Anal. calcd for $C_{40}H_{40}O_7$: C, 75.93; H, 6.37. Found: C, 75.91; H, 6.08.

a) K. Ohmori, T. Yano and K. Suzuki, *Org. Biomol. Chem.*, 2010, **8**, 2693.

Preparation of Br-(EZ)-OEE 12



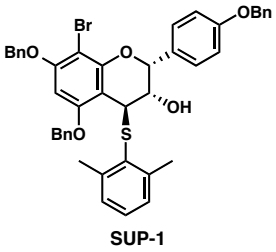
Br-(EZ)-OEE **12**

To a solution of H-(EZ)-OEE **11** (0.852 g, 1.34 mmol) in CH_2Cl_2 (9.0 mL) was added *N*-bromosuccinimide (NBS, 0.303 g, 1.70 mmol) at –15 °C. The reaction mixture was gradually warmed to –8 °C over 3 h. The reaction was stopped by adding Et_3N (0.3 mL) and 10% $Na_2S_2O_3$ aqueous solution

(10 mL) at –8 °C. The products were extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 4/1) to afford Br-(EZ)-OEE **12** (0.679 g, 71%) as colorless amorphous foam.

12: R_f 0.42 (hexane/EtOAc = 2/1); $[\alpha]_D^{26}$ –2.0 (*c* 1.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (t, 3H, *J* = 7.0 Hz), 1.53 (d, 1H, *J* = 5.5 Hz, OH), 3.44 (q, 2H, *J* = 7.0 Hz), 3.50 (t, 2H, *J* = 4.8 Hz), 3.74–3.84 (m, 2H), 4.10–4.20 (m, 1H), 4.64 (d, 1H, *J* = 2.9 Hz), 4.97 (d, 1H, *J* = 11.4 Hz), 5.03 (d, 1H, *J* = 11.4 Hz), 5.09 (s, 2H), 5.12 (s, 2H), 5.35 (s, 1H), 6.27 (s, 1H), 7.04 (d, 2H, *J* = 8.7 Hz), 7.29–7.50 (m, 15H), 7.52 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 66.6, 68.3, 69.3, 70.0, 70.1, 70.2, 70.7, 71.3, 75.4, 92.8, 92.9, 103.7, 115.2, 127.1, 127.5, 127.6, 127.7, 128.1, 128.3, 128.7, 129.7, 136.5, 136.6, 137.1, 152.5, 156.7, 158.6, 158.7; IR (film) 3560, 3428, 3064, 3032, 2927, 2926, 2870, 1604, 1578, 1513, 1498, 1454, 1429, 1417, 1380, 1351, 1310, 1243, 1223, 1200, 1178, 1126, 1027, 901, 843, 789, 738, 697 cm^{-1}; Anal. calcd for $C_{40}H_{39}BrO_7$: C, 67.51; H, 5.52. Found: C, 67.29; H, 5.27.

Preparation of bromo-sulfide SUP-1



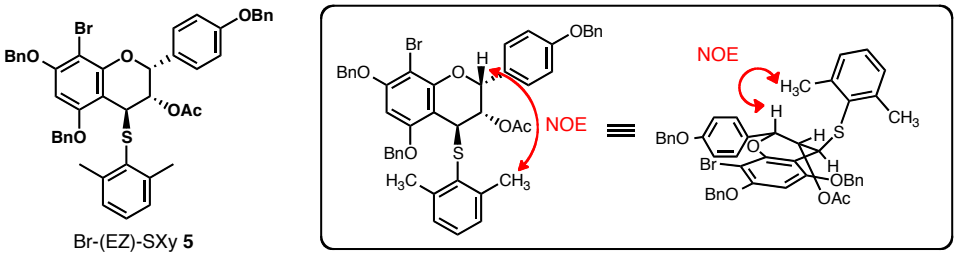
SUP-1

To a solution of Br-(EZ)-OEE **12** (679 mg, 0.954 mmol) in CH_2Cl_2 (20 mL) was added 2,6-dimethylbenzenethiol (2.8 mL, 21 mmol) and a solution of $BF_3{\cdot}OEt_2$ (215 mg, 1.51 mmol) in CH_2Cl_2 (2.0 mL) at –78 °C. The reaction mixture was gradually warmed to –55 °C over 3.5 h. The reaction was stopped by adding Et_3N (0.4 mL) and saturated aqueous $NaHCO_3$ (10 mL). The products were extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 5/1 to 2/1, gradient elution) to afford bromo-sulfide **SUP-1** (698 mg, 96%) as colorless amorphous foam.

SUP-1: R_f 0.64 (hexane/EtOAc = 3/1); $[\alpha]_D^{25}$ +2.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (brs, 1H, OH), 2.51 (s, 6H), 3.80 (brs, 1H), 4.55 (d, 1H, *J* = 2.4 Hz), 5.03 (d, 1H, *J* = 11.6 Hz), 5.06 (d, 1H, *J* = 11. 6 Hz), 5.07 (d, 1H, *J* = 12.5 Hz), 5.08 (s, 2H), 5.11 (d, 1H, *J* = 12.5 Hz), 6.01 (s, 1H), 6.25 (s, 1H), 7.01–7.20 (m, 5H), 7.28–7.50 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 43.5, 68.4, 70.2, 70.8, 71.2, 74.8, 92.85, 92.9, 102.0, 115.2, 127.1, 127.5, 127.6, 128.05, 128.08, 128.3, 128.4, 128.7, 129.8,

131.7, 136.4, 136.6, 137.0, 143.5, 152.1, 156.2, 157.9, 158.8; IR (film) 3554, 3063, 3032, 2925, 2875, 1602, 1575, 1513, 1455, 1415, 1378, 1348, 1244, 1220, 1175, 1121, 1074, 1027, 914, 816.7, 752, 737, 697 cm^{-1}; Anal. calcd for $C_{44}H_{39}BrO_5S$: C, 69.56; H, 5.17; S, 4.22. Found: C, 69.52; H, 5.22; S, 4.08.

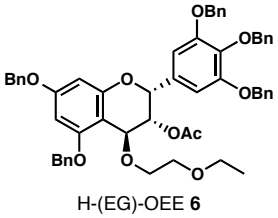
Preparation of Br-(EZ)-SXy 5



To a solution of **SUP-1** (655 mg, 0.862 mmol) in CH_2Cl_2 (5 mL) was added pyridine (3.3 mL), DMAP (48 mg, 0.39 mmol), and Ac_2O (1.5 mL, 16 mmol) at room temperature. After stirring for 2 h, the reaction mixture was slowly poured into dil. aq. HCl (20 mL) at 0 °C. The products were extracted with EtOAc (x3), and the combined organic extracts were washed with H_2O (x2), saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 4/1) to afford Br-(EZ)-SXy **5** (668 mg, 95%) as a colorless amorphous foam.

5: R_f 0.60 (hexane/EtOAc = 4/1); $[\alpha]_D^{26}$ –8.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 (s, 3H), 2.53 (s, 6H), 4.59 (s, 1H), 4.88 (brs, 1H), 5.02–5.16 (m, 6H), 6.05 (s, 1H), 6.27 (s, 1H), 6.97 (d, 2H, *J* = 8.0 Hz), 7.02–7.18 (m, 3H), 7.28–7.52 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 22.3, 40.9, 69.6, 70.1, 70.9, 71.2, 73.8, 92.7, 92.8, 102.1, 114.8, 127.1, 127.6, 127.8, 128.0, 128.05, 128.09, 128.3, 128.4, 128.68, 128.73, 128.9, 129.6, 130.9, 136.3, 136.6, 137.1, 143.4, 152.4, 156.2, 157.4, 158.7, 169.9; IR (film) 3033, 2926, 1744, 1602, 1575, 1514, 1455, 1416, 1372, 1344, 1223, 1177, 1126, 1069, 1029, 948, 892, 832, 751, 697 cm^{-1}; Anal. calcd for $C_{46}H_{41}BrO_6S$: C, 68.91; H, 5.15; S, 4.00. Found: C, 69.05; H, 5.30; S, 4.12.

Preparation of H-(EG)-OEE 6



H-(EG)-OEE **6**

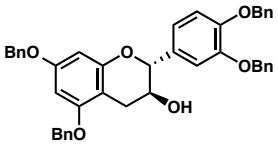
To a solution of penta-*O*-benzyl-(–)-epigallocatechin[a)] **14** (10.0 g, 13.2 mmol) in toluene (440 mL) was

added 2-ethoxyethanol (7.0 mL, 72 mmol) and DDQ (9.0 g, 40 mmol) at room temperature. After stirring for 12 h, the reaction was quenched by adding DMAP (5.1 g, 41 mmol) at 0 °C. The resulting mixture was filtered through a Celite® pad (washed with EtOAc, 30 mL), and the filtrate was concentrated to half its volume in vacuo. The mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with water, saturated aqueous $NaHCO_3$, brine (x2), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by Frorisil® column chromatography (hexane/EtOAc = 3/1) and flash column chromatography (silica gel, hexane/EtOAc = 3/1) to afford the ether. To a solution of the product in CH_2Cl_2 (30 mL) and pyridine (4.0 ml) was added DMAP (10 mg, 82 μmol) and Ac_2O (2.5 mL, 27 mmol) at room temperature. After stirring for 12 h, the reaction was quenched by pouring the solution slowly into dil. aq. HCl at 0 °C. The products were extracted with EtOAc (x3) and the combined organic extracts were washed with water (x2), saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 3/1) to afford H-(EG)-OEE **6** (7.3 g, 62%, from **14**) as colorless amorphous foam.

6: R_f 0.51 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ –3.8 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, 3H, *J* = 7.0 Hz), 1.80 (s, 3H), 3.48 (q, 2H, *J* = 7.0 Hz), 3.55 (t, 2H, *J* = 4.8 Hz), 3.83 (dt, 1H, *J* = 10.9, 4.8 Hz), 3.96 (dt, 1H, *J* = 10.9, 4.8 Hz), 4.48 (d, 1H, *J* = 2.4 Hz), 4.98–5.08 (m, 6H), 5.08 (d, 2H, *J* = 11.6 Hz), 5.14 (d, 2H, *J* = 11.6 Hz), 5.23 (brs, 1H), 5.24 (s, 1H), 6.29 (s, 2H), 6.82 (s, 2H), 7.20–7.50 (m, 25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5, 21.0, 66.5, 68.3, 69.42, 69.45, 69.8, 70.2, 70.5, 71.5, 74.1, 75.3, 94.3, 94.5, 102.3, 106.8, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.6, 128.69, 128.71, 128.8, 133.2, 136.8, 137.2, 138.0, 138.4, 153.0, 156.2, 159.6, 160.7, 170. 1; IR (film) 3063, 3039, 3032, 2929, 2869, 1744, 1618, 1592, 1498, 1454, 1436, 1371, 1226, 1155, 1118, 1029, 815, 736, 697 cm^{-1}; Anal. calcd for $C_{56}H_{54}O_{10}$: C, 75.83; H, 6.14. Found: C, 75.63; H, 6.35.

a) K. Ohmori, T. Yano and K. Suzuki, *Org. Biomol. Chem.*, 2010, **8**, 2693.

Preparation of tetra-*O*-benzyl-(+)-catechin H-(CA)-H 7



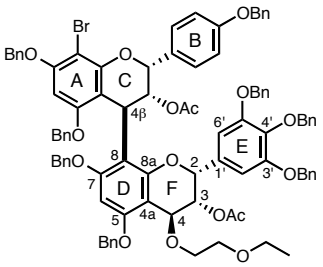
H-(CA)-H **7**

To a suspension of NaH (63% dispersion in mineral oil, 0.93 g, 23 mmol) in DMF (4.0 mL) was added penta-*O*-acetyl-(+)-catechin (1.00 g, 2.00 mmol), benzyl chloride (1.1 mL, 9.1 mmol) and *n*-Bu_4NI (146 mg, 0.395 mmol) at 0 °C. After stirring for 10 min, H_2O (160 mg, 8.88 mol) in DMF (4.0 mL) was slowly dropped over 15 min at 0 °C. After additional stirring for 10 min, the reaction temperature was raised to

16 °C. After stirrng for 16 h at the same temperature, the reaction was stopped by adding Et_2NH (0.21 mL, 2.0 mmol) and pouring the mixture into dil. aq. HCl (20 mL) at 0 °C. The mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. This crude material was dissolved in CH_2Cl_2 (5.0 mL), to which was added 28% NaOMe (MeOH, 2.5 mL, 2.0 mmol) at 0 °C. After stirring for 4 h at room temperature, the reaction was stopped by pouring the mixture into saturated aqueous NH_4Cl at 0 °C. The mixture was extracted with EtOAc (x3) and the combined organic extaracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (Silica gel, hexane/EtOAc/$CHCl_3$ = 7/1/12) to give tetra-*O*-benzyl-(+)-catechin H-(CA)-H **7** (1.07 g, 82%) as a white solid.

7: R_f 0.42 (hexane/EtOAc = 4/1x2); mp 128–130 ºC (hexane/Et_2O/EtOAc = 7/8/5); $[\alpha]_D^{28}$ –27 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (d, 1H, *J* = 3.6 Hz, OH), 2.64 (dd, 1H, *J* = 16.4, 8.6 Hz), 3.11 (dd, 1H, *J* = 16.4, 5.4 Hz), 3.92–4.00 (m, 1H), 4.62 (d, 1H, *J* = 8.0 Hz), 4.99–5.21 (m, 8H), 6.21 (d, 1H, *J* = 2.1 Hz), 6.27 (d, 1H, *J* = 2.1 Hz), 6.89–7.02 (m, 3H), 7.14–7.45 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 66.3, 69.9, 70.1, 71.3, 71.4, 78.3, 94.1, 94.7, 101.0, 113.5, 115.1, 119.5, 127.2, 127.3, 127.48, 127.52, 127.79, 127.84, 128.0, 128.47, 128.50, 128.6, 131.5, 136.9, 137.0, 137.1, 137.2, 148.8, 149.0, 155.2, 158.3, 158.8; IR (film) 3429 (br), 1618, 1593, 1510, 1499, 1454, 1377, 1263, 1217, 1143, 1116, 1049, 1028, 909, 810, 743, 696 cm^{-1}; Anal. calcd for $C_{43}H_{38}O_6$: C, 79.36; H, 5.89. Found: C, 79.31; H, 6.19.

Preparation of Br-(EZ)-(EG)-OEE 15



Br-(EZ)-(4ß-8)-(EG)-OEE **15**

rotamer ratio = 90/10

To a solution of Br-(EZ)-SXy **5** (433 mg, 0.540 mmol) and H-(EG)-OEE **6** (730 mg, 0.823 mmol) in CH_2Cl_2 (11 mL) was added MS4A (540 mg) at room temperature and *N*-iodosuccinimide (157 mg, 0.698 mmol) at –78 °C. The reaction mixture was gradually warmed to 0 °C over 25 min and the stirring was continued for 11 h at 0 °C. The reaction was stopped by adding 10% aq. $Na_2S_2O_3$ (10 mL) and sat. aq. $NaHCO_3$ (5 mL) at 0 °C. The resulting suspension was filtered through a Celite® pad (washed with EtOAc), and the filtrate was concentrated to half its volume in vacuo. The mixture was extracted with

EtOAc (x3) and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 4/1 to 3/1, gradient elution) to afford Br-(EZ)-(EG)-OEE **15** (766 mg, 91%) as colorless amorphous foam.

15: R_f 0.55 (hexane/EtOAc = 2/1); $[\alpha]_D^{32}$ +27 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the rotamer ratio = 90:10, the minor rotamer's signals are marked with an asterisk) δ 1.14 (t, 2.7H, *J* = 6.9 Hz, CH_3, OEE), 1.22* (t, 0.3H, *J* = 6.9, CH_3, OEE), 1.33* (s, 0.3H, Ac, EG), 1.41* (s, 0.3H, Ac, EZ), 1.75 (s, 2.7H, Ac, EZ), 1.82 (s, 2.7H, Ac, EG), 3.43 (q, 2H, *J* = 6.9 Hz, CH_2, OEE), 3.54 (t, 1.8H, *J* = 5.2 Hz, CH_2, OEE), 3.62* (t, 0.2H, *J* = 5.2 Hz, CH_2, OEE), 3.81 (dt, 0.9H, *J* = 10.9, 5.2 Hz, CH_2, OEE), 3.90* (dt, 0.1H, *J* = 10.5, 5.2 Hz, CH_2, OEE), 3.93 (dt, 0.9H, *J* = 10.9, 5.2 Hz, CH_2, OEE), 4.02* (dt, 0.1H, *J* = 10.5, 5.2 Hz, CH_2, OEE), 4.43* (d, 0.1H, *J* = 12.1 Hz, Bn), 4.46 (s, 0.9H, C4, EG), 4.58* (d, 0.1H, *J* = 12.1 Hz, Bn), 4.64* (s, 0.1H, C4, EG), 4.67–5.15 [m, 0.1+15.8H, C4*(EZ)+Bn], 4.69 (s, 0.9H, C2, EG), 4.80 (s, 0.9H, C4, EZ), 4.89 (s, 0.9H, C3, EG), 5.31* (s, 0.1H, C3, EG), 5.44* (s, 0.1H, C2, EG), 5.46* (s, 0.1H, C2, EZ), 5.48 (s, 0.9H, C3, EZ), 5.82 (brs, 0.9+0.1H, C2+C3*, EZ), 6.12 (s, 0.9H, C6, EZ), 6.14* (s, 0.1H, C6, EZ), 6.13* (s, 0.1H, C6, EG), 6.27 (s, 0.9H, C6, EG), 6.46 (s, 1.8H, C2'+C6', EG), 6.73* (d, 0.1H, *J* = 7.5 Hz, Bn), 6.78* (d, 0.1H, *J* = 6.3 Hz, Bn), 6.82* (s, 0.2H, C2'*+C6'*, EG), 6.89 (d, 1.8H, *J* = 8.6 Hz, C3'+C5', EZ), 6.94–7.56 [m, 42H, C2'+C2'*+C6'+C6*+C3'*+C5'*(EZ)+Bn]; ^{13}C NMR (125 MHz, $CDCl_3$, the minor signals were omitted) δ 15.4, 20.8, 21.0, 33.5, 66.4, 69.3, 69.5, 69.8, 69.9, 70.0, 70.1, 70.4, 70.5, 70.8, 71.3, 72.0, 72.7, 74.8, 75.0, 75.8, 91.2, 93.7, 94.2, 103.1, 106.1, 106.5, 107.1, 109.4, 114.7, 127.28, 127.36, 127.44, 127.5, 127.65, 127.70, 127.8, 128.07, 128.17, 128.22, 128.3, 128.47, 128.52, 128.7, 128.8, 130.7, 132.2, 136.9, 137.05, 137.09, 137.3, 138.4, 138.5, 152.1, 152.8, 154.4, 154.7, 155.5, 157.6, 158.5, 158.8, 169.3, 169.9; IR (film) 3063, 3032, 2973, 2870, 1744, 1604, 1587, 1512, 1498, 1454, 1430, 1371, 1218, 1177, 1124, 1029, 835, 736, 697 cm^{-1}; Anal. calcd for $C_{94}H_{85}BrO_{16}$: C, 72.81; H, 5.53. Found: C, 72.59; H, 5.57.

Determination of the regio- and stereochemistry of interflavan bond of dimer 15

The carbon and proton chemical shifts of dimer **15** are listed in Table I. On the HMBC spectrum, long-range correlations between the methine protons of the C3 and carbonyl carbons of acetyl groups were observed. The TOCSY, HMQC and HMBC correlations assigned the protons at the C4, C3, C2 of either the C or F ring. HMQC spectrum showed that the C4 carbon signals of C and F rings appeared at 33.5 ppm and 69.6 ppm, respectively. Therefore, all protons of the C and F ring are assigned. The aromatic protons of A and D rings were assigned by the HMBC long-range correlations between C4, C3, and aromatic protons and C4a carbons. Location of the interflavan linkage was determined by the HMBC correlations. On the HMBC spectrum, C4 proton, C(6 or 8) proton, and benzyl methylene protons of the

lower unit showed the long range correlations with C5 carbon of the lower unit. These correlations were incompatible with the C4–C6 linkage, so proving that dimer **15** has the C4–C8 linkage (Fig. A). The stereochemistry of the interflavan bond was determined by the ROESY spectrum. The coupling constant ($J_{3,4} \leq 0.5$ Hz) was useless, but the ROESY correlation between C2 methine proton of the C ring and the E ring proton proved that dimer **15** has the 4β→8 linkage (Fig. B).

Table I. ^{13}C and ^{1}H Chemical Shift Assingment[a)] of Dimer **15**

		^{13}C δ /ppm	^{1}H δ /ppm (mult, *J* Hz)			^{13}C δ /ppm	^{1}H δ /ppm (mult, *J* Hz)
A	4a	107.1	—	D	4a	103.1	—
	5	155.5	—		5	158.5	—
	6	93.7	6.12 (s), 6.14*(s)		6	91.2	6.27 (s), 6.13*(s)
	7	154.7	—		7	157.6	—
	8	94.2	—		8	109.4	—
	8a	152.1	—		8a	154.4	—
B	1'	130.7	—	E	1'	132.2	—
	2', 6'	overlapped (Bn)	overlapped (Bn)		2', 6'	106.5	6.46 (s), 6.82*(s)
	3', 5'	114.7	6.89 (d, 8.6), overlapped*(Bn)		3', 5'	152.8	—
	4'	158.8	—		4'	138.5	—
C	2	75.8	5.82 (s), 5.46*(s)	F	2	74.8	4.69 (s), 5.44*(s)
	3	72.0	5.48 (s), 5.82*(s)		3	overlapped (Bn)	4.89 (s), 5.31*(s)
	4	33.5	4.80 (s), overlapped*(Bn)		4	69.5	4.46 (s), 4.64*(s)
	3-Ac	169.3, 20.8 (Me)	1.75 (s), 1.41*(s)		3-Ac	169.9, 21.0 (Me)	1.82 (s), 1.33*(s)

a) Minor rotamer's signals were marked with asterisk and ethoxyethoxy group's signals were omitted.

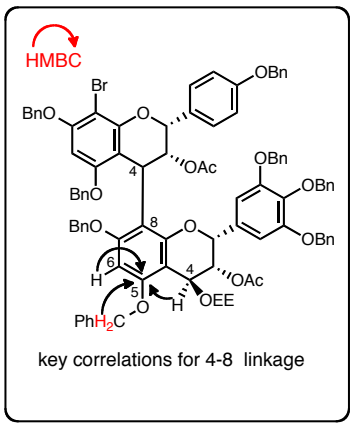


Figure A

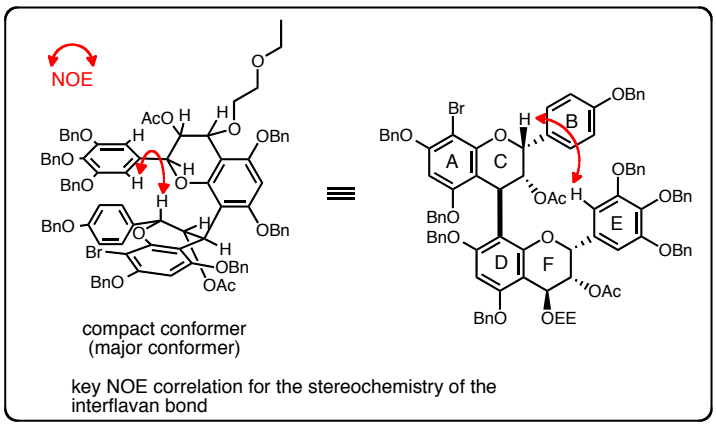
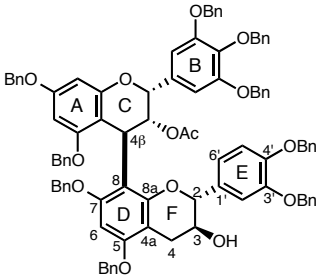


Figure B

Preparation of H-(EG)-(CA)-H 17



H-(EG)-(4β-8)-(CA)-H **17**
rotamer ratio = 77/23

To a solution of H-(EG)-OEE **6** (23 mg, 26 μmol) and H-(CA)-H **7** (50 mg, 77 μmol) in CH_2Cl_2 (1.5 mL) was added a solution of $BF_3{\cdot}OEt_2$ (10 mg, 71 μmol) in CH_2Cl_2 (0.5 mL) at –78 °C over 2 min. The reaction mixture was gradually warmed to –25 °C over 40 min and then stopped by adding Et_3N (0.1 mL) and saturated aqueous $NaHCO_3$ (5 mL). The products were extracted with EtOAc (x3), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 3/1) to afford H-(EG)-(CA)-H **17** (29 mg, 74%) as a colorless amorphous foam.

17: R_f 0.31 (hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ +29.5 (*c* 1.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, the rotamer ratio = 77:23, the minor rotamer's signals are marked with an asterisk) δ 1.29* (s, 0.69H, Ac, EG), 1.44* (brs, 0.23H, OH, CA), 1.54 (brs, 0.77H, OH, CA), 1.68 (s, 2.31H, Ac, EG), 2.60 (dd, 0.77H, *J* = 16.6, 9.8 Hz, C4ß, CA), 2.69* (dd, 0.23H, *J* = 16.6, 9.8 Hz, C4ß, CA), 3.18* (dd, 0.23H, *J* = 16.6, 5.7 Hz, C4α, CA), 3.25 (dd, 0.77H, *J* = 16.6, 6.6 Hz, C4α, CA), 3.57–3.68* (m, 0.23H, C3, CA), 3.64 (d, 0.77H, *J* = 9.2 Hz, C2, CA), 3.78 (ddd, 0.77H, *J* = 9.8, 9.2, 6.6 Hz, C3, CA), 4.57–5.25 (m, 18H, Bn), 4.61* (s, 0.23H, C4, EG), 4.63* (brs, 0.23H, C2, CA), 4.72 (s, 0.77H, C4, EG), 5.30* (s, 0.23H, C3, EG), 5.38* (s, 0.23H, C2, EG), 5.48 (s, 0.77H, C3, EG), 5.51 (s, 0.77H, C2, EG), 5.56 (d, 0.77H, *J* = 1.8 Hz, C6 or C8, EG), 6.04 (d, 0.77 H, *J* = 1.8 Hz, C6 or C8, EG), 6.15* (brs, 0.23H, C6 or C8, EG), 6.20* (s, 0.23H, C6, CA), 6.24* (brs, 0.23H, C6 or C8, EG), 6.32 (s, 0.77H, C6, CA), 6.49 (dd, 0.77H, *J* = 8.0, 1.8 Hz, C6', CA), 6.71* (s, 0.46H, C2'+C6', EG), 6.73 (d, 0.77H, *J* = 1.8 Hz, C2', CA), 6.77* (brs, 0.23H, C6', CA), 6.79 (d, 1H, *J* = 8.0 Hz, C5'+C5'*, CA), 6.80 (s, 1.54H, C2'+C6', EG), 6.84* (brs, 0.23H, C2', CA), 6.88–7.50 (m, 45H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$, the minor signals are marked with an asterisk) δ 20.4*, 20.9, 28.1*, 29.3, 33.4, 33.7*, 68.0*, 68.8, 69.4, 69.7, 70.1, 70.4, 70.8, 71.0, 71.2, 71.3, 71.4, 71.5, 72.1, 72.3*, 74.8, 75.2, 75.3*, 81.3*, 81.9, 91.7, 92.4*, 93.0, 93.4*, 93.7, 94.7*, 103.3*, 104.3, 104.5, 105.0*, 106.5, 106.7*, 110.8, 111.5*, 112.1, 113.6*, 114.3, 114.7*, 120.7, 120.9*, 127.21, 127.27, 127.30, 127.6, 127.9, 128.2, 128.45, 128.50, 128.6, 128.8, 130.5, 131.2*, 134.1*, 134.5, 137.0, 137.1, 137.29, 137.39, 137.41, 138.0*, 138.1, 138.2, 148.8*, 148.9, 149.5, 152.8*, 152.9, 154.6, 155.5, 155.6*,

156.0*, 156.2, 156.3, 156.55, 157.56*, 158.2, 158.4*, 168.7*, 169.0; IR (film) 3566, 3473, 3089, 3064, 3032, 2872, 1743, 1594, 1499, 1454, 1430, 1374, 1351, 1332, 1262, 1216, 1152, 1118, 1076, 1028, 736, 696 cm^{-1}; MS (MALDI–TOF, DHBA matrix) calcd for $C_{95}H_{82}O_{14}K$ ($[M+K]^+$) *m/z* 1486.54, found *m/z* 1486.65.

Structure determination of dimer 17

The carbon and proton chemical shifts of dimer **17** are listed in Table II. Location of the interflavan linkage was determined by the HMBC correlations. On the HMBC spectrum, C4 protons of the F ring, aromatic proton of the D ring, and benzyl methylene protons showed long-range correlations with C5 carbon of the D ring (Fig. C). This correlation proved that dimer **17** has the C4–C8 linkage. The stereochemistry of the interflavan bond was determined by ROESY. The ROESY correlation between C2 methine proton of the C ring and E ring proton was observed (Fig. D). This proved that dimer **17** has a 4ß→8 linkage.

Table II. ^{13}C and ^{1}H Chemical Shift Assingment of Dimer **17**

		^{13}C δ /ppm	^{1}H δ /ppm (mult, *J* Hz)			^{13}C δ /ppm	^{1}H δ /ppm (mult, *J* Hz)
A	4a	104.5, 105.0*	—	D	4a	104.3, 103.3*	—
	7	158.2, 158.4*	—		5, 7	156.2	—
	6, 8	93.7, 94.7*	5.56 (d, 1.8), 6.15* (brs)			156.3	—
		93.0, 93.4*	6.04 (d, 1.8), 6.24* (brs)		6	91.7, 92.4*	6.32 (s), 6.20* (s)
	5, 8a	155.5, 155.6*	—		8	110.8, 111.5*	—
		156.55	—		8a	154.6	—
B	1'	134.5, 134.1*	—	E	1'	130.5, 131.2*	—
	2', 6'	106.5, 106.7*	6.80 (s), 6.71* (s)		2'	112.1, 113.6*	6.73 (d, 1.8), 6.84* (brs)
	3', 5'	152.9, 152.8*	—		3'	149.5	—
	4'	138.2, 138.0*	—		4'	148.9, 148.8*	—
					5'	114.3, 114.7*	6.79 (d, 8.0)
					6'	120.7, 120.9*	6.49 (dd, 8.0, 1.8), 6.77* (brs)
C	2	74.8, 75.3*	5.51 (s), 5.38* (s)	F	2	81.9, 81.3*	3.64 (d, 9.2), 4.63* (brs)
	3	72.1, 72.3*	5.48 (s), 5.30* (s)		3	68.8, 68.0*	3.78 (ddd, 9.8, 9.2, 6.6), 3.57–3.68* (m)
	4	33.4, 33.7*	4.72 (s), 4.61* (s)		4β	29.3, 28.1*	2.60 (dd, 16.6, 9.8), 2.69* (dd, 16.6, 9.8)
	3-Ac	169.0, 168.7*	—		4α		3.25 (dd, 16.6, 6.6), 3.18* (dd, 16.6, 5.7)
	Ac(Me)	20.9, 20.4*	1.68 (s), 1.29* (s)		OH		1.54 (brs), 1.44* (brs)

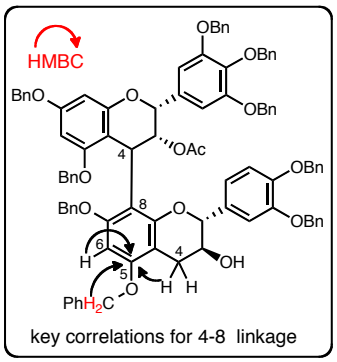


Figure C

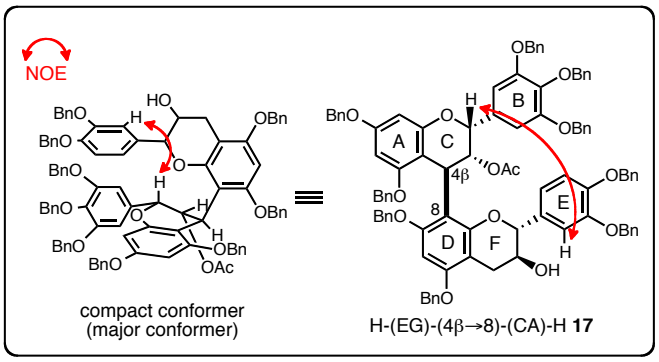
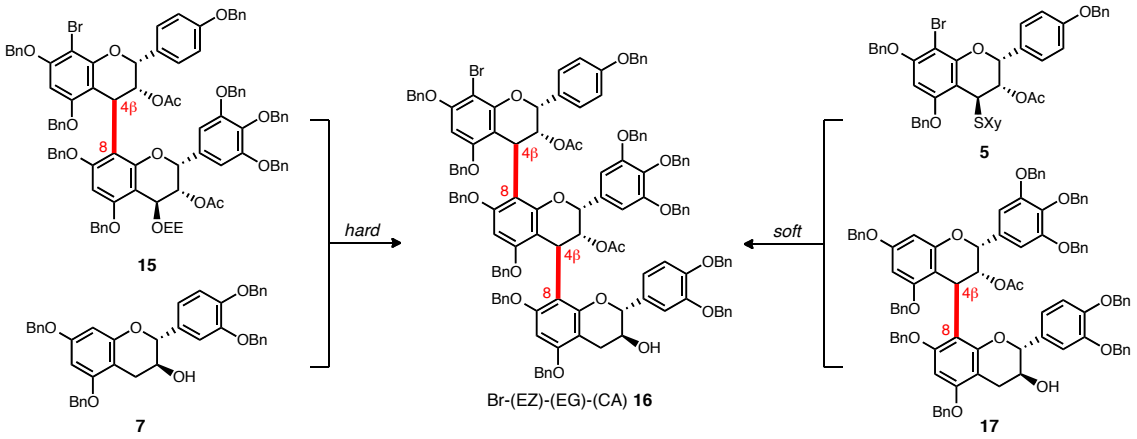


Figure D

Preparation and structure determination of Br-(EZ)-(EG)-(CA)-H 16



Route A, hard activation

To a solution of Br-(EZ)-|4β→8|-(EG)-OEE **15** (602 mg, 0.388 mmol) and tetra-*O*-benzyl catechin H-(CA)-H **7** (327 mg, 0.502 mmol) in CH_2Cl_2 (20 mL) was added a solution of $BF_3{\cdot}OEt_2$ (103 mg, 0.730 mmol) in CH_2Cl_2 (4.0 mL) at –78 °C over 10 min. The reaction was gradually warmed to –30 °C over 1.3 h, and the reaction was stopped by adding Et_3N (0.5 mL) and saturated aqueous $NaHCO_3$ (5 mL). Products were extracted with EtOAc (x3), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (Silica gel, hexane/EtOAc = 2/1) to afford Br-(EZ)-|4β→8|-(EG)-(CA)-H **16** (756 mg, 92%) as colorless amorphous foam.

Route B, soft activation

To a solution of Br-(EZ)-SXy **5** (11 mg, 13 μmol) and H-(EG)-|4β→8|-(CA)-H **17** (29 mg, 20 μmol) in CH_2Cl_2 (1.5 mL) was added MS4A (15 mg), Ag_2O (4.9 mg, 21μmol) at room temperature, and a solution of I_2 (11 mg, 42 μmol) in CH_2Cl_2 (0.5 mL) at –78 °C over 5 min. The reaction mixture was gradually

warmed to 0 °C over 3 h, and the reaction stopped by adding 10% aq. $Na_2S_2O_3$ (5 mL). Products were extracted with EtOAc (x3), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 1.5/1) to give trimer Br-(EZ)-(EG)-|4β→8|-(CA)-H **16** (21 mg, 76%) as colorless amorphous foam.

Structure determination of trimer 16

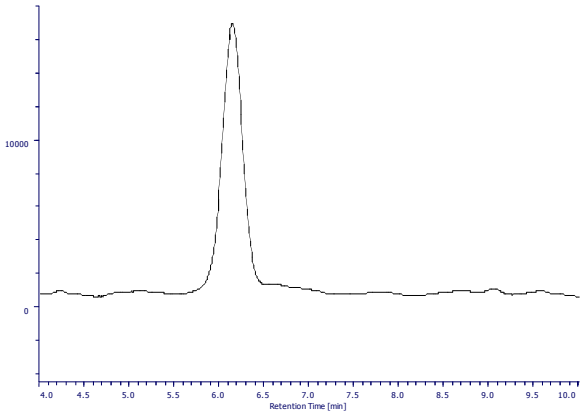
Two trimers synthesized by route A and B were identical by comparison with their physical data, proving two interflavan bond of trimer **16** must be both 4β→8.

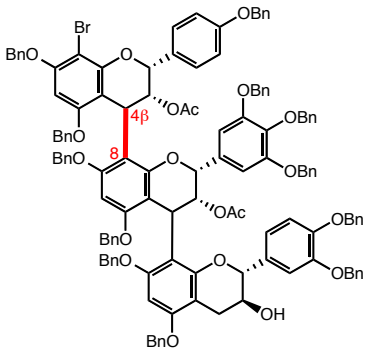
16: R_f 0.33 (hexane/EtOAc = 2/1), 0.30 (toluene/EtOAc = 10/1); HPLC [Mightysil® Si60 (0.46 cm ϕ x 25 cm, 5 μm), hexane/EtOAc = 3/2, flow rate 1.0 mL/min, 30 °C, t_R = 6.1 min for **16**]; $[\alpha]_D^{31}$ +95 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, rotamer ratio = 65:20:15:0) δ 0.95 (d, 0.15H, *J* = 6.8 Hz, OH), 1.16 (s, 0.60H), 1.36 (s, 0.60H), 1.40 (s, 1.95H), 1.60 (brs, 0.65+0.20H, OH, overlapped with H_2O), 1.71 (s, 0.45H), 1.73 (s, 0.45H), 1.77 (s, 1.95H), 2.05 (dd, 0.15H, *J* = 16.6, 3.5 Hz), 2.59 (dd, 0.65H, *J* = 16.0, 9.2 Hz), 2.62 (dd, 0.20+0.15H, *J* = 16.0, 9.2 Hz), 3.02 (dd, 0.20H, *J* = 16.0, 5.2 Hz), 3.07 (dd, 0.65H, *J* = 16.0, 5.7 Hz), 3.50–3.62 (m, 0.65+0.20H), 3.65 (brs, 0.15H), 4.22–5.36 [m, 24+5H, Bn+C2(CA)+C4(EZ)+C4(EG)+C2(EG or EZ)+C3(EG or EZ)], 5.42 (s, 0.20H), 5.52 (s, 0.15H), 5.58 (s, 0.65H), 5.76 (s, 0.20H), 5.85 (s, 0.15H), 5.88 (s, 0.65H), 5.96 (s, 0.15H), 6.02 (s, 0.65+0.65+0.20H), 6.11 (s, 0.15H), 6.14 (s, 0.20H), 6.18 (s, 0.20H), 6.28 (brs, 0.30H), 6.34 (s, 0.65+1.30H), 6.50–7.60 (m, 67.55H); ^{13}C NMR (125 MHz, $CDCl_3$, the major/minor signals were not distinguished) δ 20.3, 20.5, 20.9, 22.3, 27.7, 27.9, 32.8, 33.6, 33.7, 34.0, 34.2, 34.5, 67.9, 68.69, 69.70, 69.8, 69.87, 69.98, 70.04, 70.2, 70.3, 70.6, 70.7, 70.9, 71.0, 71.19, 71.24, 71.3, 71.4, 71.5, 71.7, 72.1, 72.2, 72.59, 72.63, 73.1, 73.3, 74.9, 75.0, 75.1, 75.6, 75.8, 75.9, 76.3, 79.3, 81.1, 81.2, 90.5, 90.8, 90.9, 91.3, 91.4, 92.0, 92.1, 92.8, 92.9, 93.9, 94.6, 102.3, 102.8, 106.3, 106.5, 107.8, 109.6, 110.1, 110.3, 110.9, 111.0, 111.1, 113.7, 113.9, 114.3, 114.8, 120.5, 120.7, 126.1, 126.4, 126.7, 126.88, 126.93, 127.0, 127.06, 127.13, 127.2, 127.3, 127.4, 127.5, 127.56, 127.63, 127.7, 127.8, 127.86, 127.94, 128.06, 128.12, 128.2, 128.4, 128.5, 128.56, 128.64, 128.7, 130.3, 130.4, 130.8, 130.9, 131.3, 131.6, 132.98, 133.05, 133.12, 134.8, 136.8, 137.2, 137.35, 137.40, 137.5, 138.0, 138.19, 138.22, 138.4, 138.5, 148.6, 148.8, 148.9, 152.45, 152.48, 152.8, 154.4, 154.6, 155.4, 155.5, 155.6, 155.7, 155.8, 155.9, 156.1, 156.3, 156.4, 156.5, 156.6, 158.0, 158.8, 168.2, 168.5, 168.8, 169.2, 169.3; IR (film) 3571, 3469 (br), 3062, 3030, 2869, 1742, 1599, 1511, 1497, 1453, 1424, 1372, 1329, 1217, 1122, 1028, 736, 696 cm^{-1}; Anal. calcd for $C_{133}H_{113}BrO_{20}$: C, 75.66; H, 5.39. Found: C, 75.52; H, 5.28.

HPLC analysis of trimer 16

[Mightysil® Si60 (0.46 cm ϕ x 25 cm, 5 μm), hexane/EtOAc = 3/2, flow rate 1.0 mL/min, 30 °C, t_R = 6.1 min for **16**]

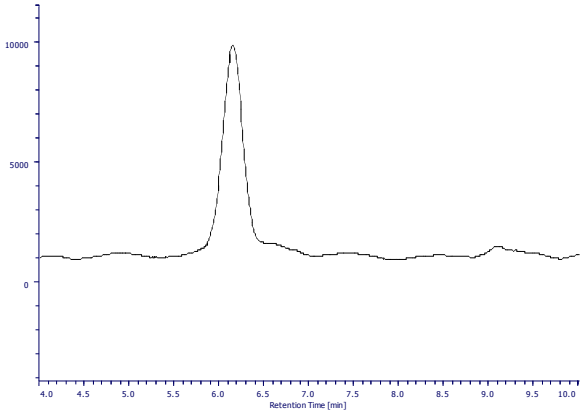
a) downward assembly

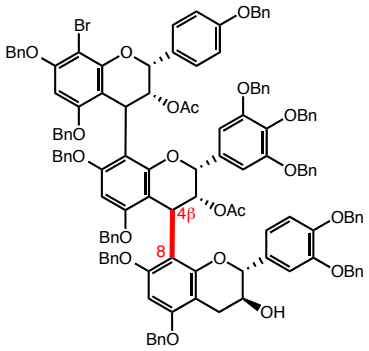




rotamer ratio = 65: 20: 15

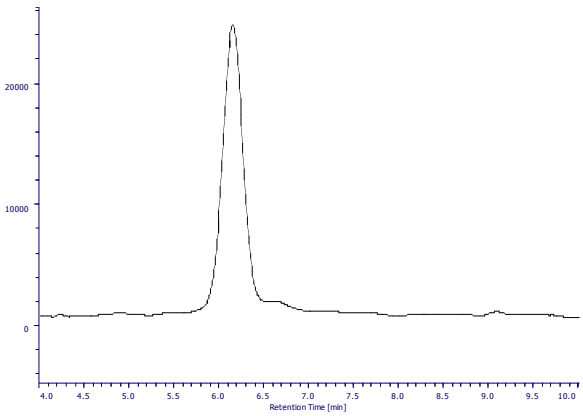
b) upward assembly



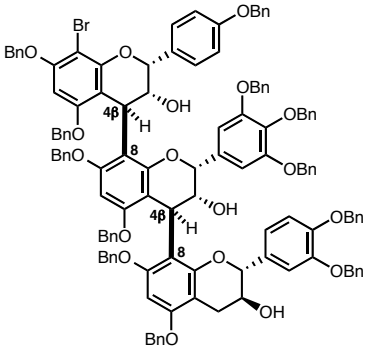


rotamer ratio = 65: 20: 15

c) coinjection of two trimers **16**



Preparation of Br-(EZ)-(EG)-(CA)-H 18



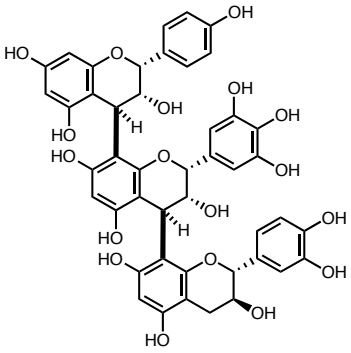
Br-(EZ)-(4β→8)-(EG)-(4β→8)-(CA)-H **18**

To a solution of Br-(EZ)-(EG)-(CA)-H **16** (278 mg, 132 μmol) in CH_2Cl_2 (8.0 mL) was added a solution of 28% NaOMe in MeOH (2.0 mL) at 0 °C. After stirring for 1 h at room temperature, the reaction was stopped by adding H_2O (10 mL) at 0 °C. Products were extracted with EtOAc (x3), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (Silica gel, hexane/EtOAc = 2/1) to afford trimer **18** (251 mg, 94%) as colorless amorphous foam.

18: R_f 0.34 (hexane/EtOAc = 2/1); $[\alpha]_D^{31}$ +72 (*c* 1.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, rotamer ratio = 45:45:5:5) δ 0.94 (d, 0.05H, *J* = 5.0 Hz, OH), 1.32 (d, 0.45H, *J* = 5.0 Hz, OH), 1.43 (brs, 0.10H, OH), 1.48 (d, 0.45H, *J* = 3.5 Hz, OH), 1.51 (d, 0.45H, *J* = 3.5 Hz, OH), 1.55 (d, 0.45H, *J* = 3.5 Hz, OH), 1.57 (d, 0.45H, *J* = 5.8 Hz, OH), 1.61 (d, 0.05H, *J* = 5.0 Hz, OH), 1.67 (d, 0.05H, *J* = 5.4 Hz, OH), 1.69 (d, 0.05H, *J* = 3.0 Hz, OH), 1.73 (d, 0.45H, *J* = 5.2 Hz, OH), 2.09 (dd, 0.05H, *J* = 16.8, 3.6 Hz), 2.55 (dd, 0.45H, *J* = 16.2, 9.6 Hz), 2.63 (dd, 0.45H, *J* = 16.2, 9.6 Hz), 2.67 (dd, 0.05H, *J* = 16.8, 3.6 Hz), 2.73 (dd, 0.05H, *J* = 16.8, 6.0 Hz), 2.79 (dd, 0.05H, *J* = 16.8, 4.2 Hz), 3.06 (dd, 0.45H, *J* = 16.2, 5.4 Hz), 3.09 (dd, 0.45H, *J* = 16.2, 5.4 Hz), 3.40–3.55 (m, 1.35H), 3.65 (brs, 0.05H), 3.78 (brs, 0.05H), 3.82 (brs, 0.05H), 3.97 (brd, 0.45H, *J* = 5.4 Hz), 4.05 (brd, 0.45H, *J* = 6.0 Hz), 4.13 (brd, 0.45H, *J* = 4.8 Hz), 4.21 (d, 0.45H, *J* = 13.8 Hz, Bn), 4.28 (d, 0.45H, *J* = 11.4 Hz, Bn), 4.38–5.20 [m, 26.65H, Bn+EZ(C4)+EG(C4)+CA(C2)+EG or EZ(C2)], 5.28 (s, 0.45H), 5.51 (s, 0.05H), 5.56 (s, 0.45H), 5.65 (s, 0.05H), 5.79 (s, 0.05H), 5.84 (s, 0.05H), 5.86 (s, 0.45H), 5.91 (s, 0.45H), 5.94 (s, 0.45H), 5.98 (s, 0.45H), 6.10 (s, 0.45H), 6.13 (s, 0.45H), 6.15 (s, 0.45H), 6.20 (s, 0.45H), 6.23 (s, 0.45H), 6.34 (s, 0.05H), 6.36 (s, 0.45H), 6.39 (s, 0.05H), 6.43 (s, 0.05H), 6.44 (s, 0.05H), 6.50 (brs, 0.90H), 663 (d, 0.90H, *J* = 9.0 Hz), 6.68–7.60 (m, 66H); ^{13}C NMR (150 MHz, $CDCl_3$, the major/minor rotamer's signals are not distinguished) δ 26.1, 27.6, 27.9, 29.7, 35.3, 35.6, 35.9, 36.2, 68.2, 68.4, 69.72, 69.76, 69.81, 69.9, 70.0, 70.1, 70.2, 70.7, 70.9, 71.09, 71.17, 71.23, 71.3, 71.4, 71.8, 72.3, 72.4, 72.5, 75.0, 75.2, 76.1, 76.2, 76.6, 81.3, 81.4, 90.3, 91.8, 92.2, 92.7, 93.3, 94.3, 94.4, 102.1, 102.5, 105.6, 105.9, 106.3, 106.4, 107.1, 107.7,

109.7, 110.67, 110.72, 113.2, 114.65, 114.74, 114.97, 120.0, 126.0, 126.3, 126.6, 126.8, 127.0, 127.07, 127.12, 127.17, 127.20, 127.35, 127.40, 127.47, 127.56, 127.58, 127.64, 127.7, 127.76, 127.79, 127.82, 127.87, 127.93, 128.0, 128.04, 128.1, 128.15, 128.20, 128.28, 128.37, 128.40, 128.47, 128.49, 128.55, 128.57, 128.65, 128.7, 130.8, 131.1, 131.4, 133.8, 134.6, 136.7, 136.8, 136.9, 137.0, 137.05, 137.09, 137.2, 137.3, 137.34, 137.41, 137.7, 137.8, 138.0, 138.35, 138.42, 138.5, 148.9, 149.0, 149.1, 152.1, 152.3, 152.76, 152.82, 152.9, 153.05, 153.13, 154.4, 154.6, 155.2, 155.5, 155.8, 156.1, 156.2, 156.3, 156.5, 156.60, 156.64, 158.1, 158.7; IR (film) 3568, 3461, 3062, 3030, 2929, 2870, 1599, 1509, 1497, 1453, 1420, 1377, 1331, 1243, 1219, 1120, 1027, 909, 734, 696 cm^{-1}; Anal. calcd for $C_{129}H_{109}BrO_{18}$: C, 76.43; H, 5.42. Found: C, 76.27; H, 5.41.

Preparation of (–)-epiafzelechin-(4β→8)-(–)-epigallocatechin-(4β→8)-(+)-catechin (1)



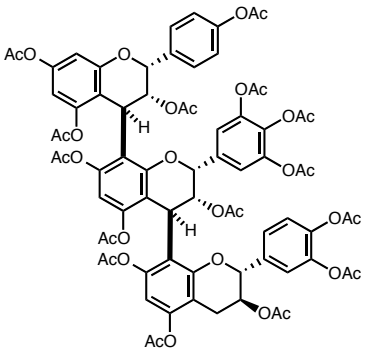
H-EZ-(4β→8)-EG-(4β→8)-CA-H **1**

A mixture of trimer **18** (24.0 mg, 11.8 μmol) and 5% $Pd(OH)_2$/C (87 mg) in THF (2.0 mL), MeOH (2.0 mL), and H_2O (0.5 mL) was stirred under a H_2 atmosphere for 40 min. The mixture was carefully filtered through a glass-fiber filter under an argon atmosphere, and roughly half volume of the filtrate was evaporated. The solution was lyophilized to give EZ-EG-CA **1** (7.1 mg, 70%) as off-white powder.

1: R_f 0.25 ($CHCl_3$/MeOH = 2/1, diol-TLC); mp 223–226 °C (decomp.); $[\alpha]_D^{30}$ +52 (*c* 1.3, H_2O/acetone = 1/1), *lit.* $[\alpha]_D^{22}$ +58 (*c* 1.0, H_2O/acetone = 1/1); ^{1}H NMR (600 MHz, D_2O/acetone-d_6 = 1/1, the minor rotamer's signals are omitted) δ 2.48 (dd, 1H, *J* = 16.7, 5.7 Hz), 2.56 (dd, 1H, *J* = 16.7, 5.0 Hz), 3.93 (brs, 1H), 4.00 (brs, 1H), 4.15 (brs, 1H), 4.58 (brs, 2H), 4.89 (brd, 1H, *J* = 3.6 Hz), 5.02 (brs, 1H), 5.06 (brs, 1H), 5.80–6.00 (m, 4H), 6.20–7.10 (m, 7H), 7.14 (brd, 2H, *J* = 7.1 Hz); ^{13}C NMR (150 MHz, D_2O/d_6-acetone = 1/1, the minor rotamer's signals were omitted) δ 27.2, 37.2, 37.3, 67.8, 71.8, 73.4, 76.9, 77.1, 81.7, 96.4, 96.9, 101.2, 107.4, 108.4, 115.3, 116.4, 117.0, 120.1, 129.3, 131.9, 132.6, 133.1, 145.6, 145.8, 146.5, 153.9, 155.3, 156.1, 156.7, 156.9, 157.0, 157.2, 157.8, 158.0; IR (ATR) 3323(br), 2924, 2615, 1602, 1515, 1433, 1415, 1358, 1248, 1143, 1104, 960, 821 cm^{-1}; LRMS (MALDI–TOF, DHBA matrix) calcd for $C_{45}H_{38}O_{18}Na$ ($[M+Na]^+$) *m/z* 889.20, found *m/z* 889.16; HRMS (ESI) calcd for

$C_{45}H_{37}O_{18}$ ([M-2H+H]$^+$) m/z 865.1974, found m/z 865.1980.

Preparation of per-acetylated hetero-trimer 19



O-acetyl-EZ-(4β→8)-EG-(4β→8)-CA-H **19**

A mixture of **18** (57 mg, 28 μmol) and 5% $Pd(OH)_2/C$ (213 mg) in THF (5.4 mL), MeOH (5.4 mL), and H_2O (2.5 mL) was stirred under H_2 atmosphere for 45 min. The mixture was carefully filtered through a glass fiber filter under an argon atmosphere, and roughly half volume of the solution was evaporated. The solution was lyophilized to afford trimer **1** as an off-white powder. To a solution of the product in pyridine (1.5 mL) was added DMAP (10 mg, 82 μmol) and acetic anhydride (0.50 mL, 5.3 mmol) at 0 °C. After stirring for 1 h, the reaction was stopped by slowly pouring the solution into aqueous dil. HCl (10 mL) at 0 °C. The products were extracted with EtOAc (x3), and the combined organic extracts were washed with H_2O (x2), saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 1/4) to afford per-acetylated trimer **19** (26 mg, 2 steps 63%) as a colorless amorphous foam.

19: R_f 0.58 (hexane/EtOAc = 1/4); $[\alpha]_D^{30}$ +76.4 (*c* 1.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, rotamer ratio = 46:34:17:3, the minor rotamer's signals were partially omitted) δ 1.38–2.40 (45H, Ac), 2.69 (dd, 0.34H, *J* = 16.6, 8,1 Hz), 2.73 (dd, 0.46H, *J* = 16.6, 8.1 Hz), 3.03 (dd, 0.34H, *J* = 16.6, 5.8 Hz), 3.10 (dd, 0.46H, *J* = 16.6, 5.2 Hz), 4.33 (d, 0.17H, *J* = 2.3 Hz), 4.46 (d, 0.17H, *J* = 2.3 Hz), 4.48 (d, 0.34H, *J* = 2.3 Hz), 4.53 (s, 0.03H), 4.58 (s, 0.34H), 4.59 (s, 0.34H), 4.61 (s, 0.03H), 4.63 (s, 0.46H), 4.70 (s, 0.46H), 4.87–5.20 (m, 2.36H), 5.23 (bs, 0.34H), 5.30 (s, 0.92H), 5.34 (s, 0.46H), 5.37 (s, 0.46H), 5.60 (s, 0.34H), 5.69 (s, 0.46H), 5.72 (s, 0.17H), 5.85 (d, 0.34H, *J* = 2.3 Hz), 5.88 (d, 0.34H, *J* = 2.3 Hz), 6.01 (d, 0.46H, *J* = 2.3 Hz), 6.26 (d, 0.46H, *J* = 2.3 Hz), 6.50–7.50 [m, 11.4H, Ar(EZ)+Ar(EG)+Ar(CA)]; ^{13}C NMR (125 MHz, $CDCl_3$, major and minor signals were not distinguished) δ 19.6, 19.77, 19.79, 20.06, 20.08, 20.16, 20.23, 20.3, 20.4, 20.55, 20.61, 20.65, 20.68, 20.8, 21.05, 21.10, 21.2, 21.3, 25.4, 25.6, 33.2, 33.8, 34.2, 34.6, 34.9, 35.2, 35.3, 35.7, 43.2, 67.7, 68.3, 68.4, 70.0, 70.9, 71.1, 74.0, 74.3, 74.9, 75.16, 75.24, 75.8, 75.9, 77.6, 77.9, 78.16, 78.24, 88.8, 107.3, 107.4, 107.6, 108.2, 108.3, 109.1, 109.3, 109.6, 110.1, 110.4,

110.6, 110.7, 110.8, 111.1, 111.2, 111.3, 111.76, 111.78, 112.8, 113.9, 116.0, 116.6, 116.7, 117.1, 117.4, 117.5, 117.7, 118.6, 118.8, 119.7, 120.2, 120.3, 121.4, 121.5, 121.7, 122.2, 122.7, 123.6, 123.7, 123.9, 124.3, 124.4, 124.7, 127.6, 128.0, 128.1, 128.2, 133.0, 133.5, 134.0, 134.2, 134.3, 134.6, 134.8, 135.0, 135.2, 135.4, 135.8, 135.9, 136.1, 136.9, 142.09, 142.16, 142.27, 142.33, 142.5, 142.7, 142.8, 143.1, 143.3, 147.3, 147.5, 147.6, 147.7, 147.8, 147.9, 148.0, 148.1, 148.2, 148.4, 148.5, 148.6, 148.9, 149.7, 149.9, 150.0, 150.1, 150.5, 150.6, 150.7, 150.8, 151.69, 151.74, 152.1, 153.8, 154.3, 155.2, 155.4, 156.0, 166.5, 166.6, 167.36, 167.41, 167.6, 167.75, 167.82, 168.0, 168.23, 168.29, 168.32, 168.38, 168.42, 168.5, 168.68, 168.72, 168.77, 168.82, 169.08, 169.11, 169.17, 169.22, 169.3, 169.5, 169.6, 169.9, 170.0, 170.1, 170.2, 171.0, 171.1; IR (film) 3026, 2939, 1772, 1600, 1507, 1436, 1421, 1371, 1201, 1128, 1109, 1054, 898, 755 cm^{-1}; Anal. calcd for $C_{75}H_{68}O_{33}$: C, 60.16; H, 4.58. Found: C, 60.07; H, 4.83.