Supporting Information

New Synthetic Strategy for Catechin-Class Ployphenols: Concise Synthesis of (–)-Epicatechin and its 3-*O*-Gallate

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General Experimental Procedures

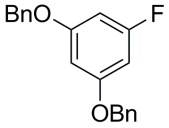
All manipulations of air- and moisture sensitive reagents were performed in dried glassware and under an argon atmosphere. Tetrahydrofuran (anhydrous; *Kanto Chemical Co., Inc.*) was used as received. Dichloromethane was distilled successively from P_2O_5 and CaH_2 and stored over molecular sieve 4A. *N*,*N*-Dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP) were distilled from CaH_2 under reduced pressure and stored over molecular sieve 4A.

For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (silica gel 60 F_{254}, Art 5715, 0.25 mm) were used. Silica-gel preparative TLC (PTLC) was performed on Merck Silica gel 60 PF_{254} (Art 7747).

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 ECX-500 (500 MHz), JEOL JNM AL-400 (400 MHz) or a JEOL JNM AL-300 (300 MHz) spectrometer. ^{19}F NMR was measured on a JEOL ECX-500 (500 MHz). Chemical shifts are expressed in parts per million (ppm) downfield from internal standard tetramethylsilane (0.00 ppm) for ^{1}H NMR and hexafluorobenzene (−162.2 ppm) for ^{19}F NMR 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. Optical rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 polarimeter.

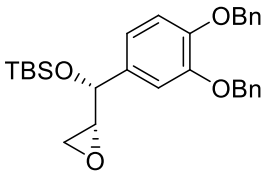
Preparation of 4



NaH (60% dispersion in mineral oil, 1.95 g, 49 mmol) was washed with hexane (×2), to which *N*-methylpyrrolidone (29 ml) was added. Benzyl alcohol (4.19 ml, 40.5 mmol) was slowly added at 0 ºC, and stirring was continued for 1 h. 1,3,5-Trifluorobenzene (5.00 g, 16.2 mmol) was added at 0 ºC. After stirring for 2 h at room temperature, the mixture was heated at 100 ºC for further 2 h. The reaction was quenched with water, and the products extracted with EtOAc (×3). The combined organic extracts were washed with brine (×1), dried over Na_2SO_4 and concentrated in vacuo. Recrystallization from hexane/EtOAc (1/1) afforded the product **4** (9.2 g, 79%) as a white solid.

4: R_f 0.59 (*n*-hexane /EtOAc = 5/1); mp 90–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (s, 4H), 6.32 (dd, J = 10.8, 2.4 Hz, 2H), 6.39–6.42 (m, 1H), 7.28–7.41 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.2, 95.3 (d, $J_{C–F}$ = 25.5 Hz), 97.9 (d, $J_{C–F}$ = 2.5 Hz), 127.4, 128.0, 128.5, 136.3, 160.5 (d, $J_{C–F}$ = 13.1 Hz), 164.1 (d, $J_{C–F}$ = 242 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ –106.4 (s, 1F); IR (ATR) 1620, 1600, 1500, 1455, 1425, 1390, 1330, 1250, 1170, 1125, 1040, 830, 810, 750, 700, 680 cm^{-1}; Anal. calcd. for $C_{20}H_{17}FO_2$: C, 77.90; H, 5.56. Found: C, 77.86; H, 5.60.

Preparation of 5

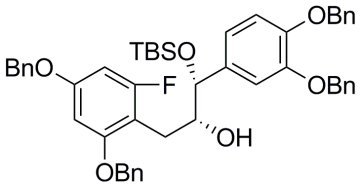


TBMDSCl (0.83 g, 5.5 mmol) in DMF (1.5 ml) was added to a solution of the epoxy alcohol (prepared according to T. Higuchi, K. Ohmori and K. Suzuki, *Chem. Lett.*, 2006, **35**, 1006) (1.00 g, 2.76 mmol) and imidazole (0.47 g, 6.9 mmol) in DMF (2.0 ml) at 0 °C. After stirring for further 2 h at 0 °C, the reaction was quenched with phosphate buffer solution (pH 7) and extracted with EtOAc (×3). The combined organic extracts were washed with brine (×1), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 5/1) to afford silyl ether **5** (1.31 g, 99%) as a colorless oil.

5: R_f 0.26 (*n*-hexane /EtOAc = 20/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.05 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 2.54 (dd, 1H, J = 4.9, 2.7 Hz), 2.67 (dd, 1H, J = 4.9, 4.2 Hz), 3.00 (ddd, 1H,

J = 6.2, 4.2, 2.7 Hz), 4.24 (d, 1H, *J* = 6.2 Hz), 5.15 (s, 2H), 5.16 (d, 1H, *J* = 12.5 Hz), 5.19 (d, 1H, *J* = 12.5 Hz), 6.81 (dd, 1H, *J* = 8.2, 2.0 Hz), 6.89 (d, 1H, *J* = 8.2 Hz), 6.98 (d, 1H, *J* = 2.0 Hz), 7.25–7.46 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 25.7, 25.8, 45.1, 56.9, 71.1, 71.2, 76.2, 76.3, 113.1, 113.2, 114.5, 119.1, 127.3, 127.7, 128.4, 128.4, 134.2, 137.2, 137.2, 137.3, 148.5, 148.6; IR (ATR) 3050, 3025, 2950, 2925, 2875, 2850, 1600, 1580, 1505, 1470, 1460, 1450, 1420, 1380, 1360, 1260, 1220, 1155, 1130, 1115, 1080, 1020, 940, 840, 780, 740, 695, 670, 630 cm^{-1}; $[\alpha]_D^{27}$ –5.83 (*c* 1.10, $CHCl_3$); Anal. calcd. for $C_{29}H_{36}O_4Si$: C, 73.07; H, 7.61. Found: C, 73.12; H, 7.64.

Preparation of 6

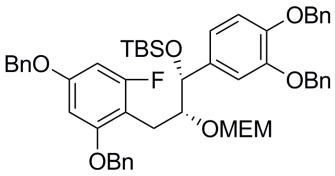


To a solution of fluorobenzene **4** (1.44 g, 4.66 mmol) in THF (20 ml) was slowly added *n*-BuLi (3.2 ml, 1.65 M hexane solution, 5.1 mmol) at –78 °C, and the resulting mixture was stirred for 1 h. A solution of epoxide **5** (1.04 g, 2.33 mmol) in THF (10 ml) was added at –78 °C followed by $BF_3{\cdot}OEt_2$ (0.66 g, 4.7 mmol) in THF (10 ml), and the stirring was continued for 15 min. The reaction was stopped by addition of methanol and brine. The mixture was extracted with EtOAc (×3), and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/ EtOAc = 5/1) to afford adduct **6** (1.60 g, 88%) as a white solid.

6: R_f 0.40 (*n*-hexane/EtOAc = 5/1); mp 96–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.26 (s, 3H), 0.00 (s, 3H), 0.85 (s, 9H), 2.51 (d, 1H, *J* = 5.1 Hz, OH), 2.55–2.66 (m, 2H), 3.81–3.86 (m, 1H), 4.43 (d, *J* = 5.6 Hz, 1H), 4.91 (s, 2H), 4.94 (s, 2H), 5.06 (s, 2H), 5.11 (s, 2H), 6.29 (dd, 1H, *J* = 11.7, 2.2 Hz), 6.31 (br, 1H), 6.76 (dd, 1H, *J* = 8.4, 1.6 Hz), 6.81 (d, 1H, *J* = 8.4 Hz), 6.92 (d, 1H, *J* = 1.6 Hz,), 7.20 –7.45 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.11, –4.47, 18.1, 25.8, 26.1, 69.9, 70.3, 75.4, 78.5, 94.3 (d, J_{C-F} = 30 Hz), 96.3, 107.6 (d, J_{C-F} = 16 Hz), 114.2, 127.2, 127.5, 127.8, 127.9, 128.1, 128.2, 128.2, 128.5, 128.5, 128.6, 133.9, 136.5, 136.5, 137.0, 158.2 (d, J_{C-F} = 8 Hz), 158.4 (d, J_{C-F} = 15 Hz), 162.6 (d, J_{C-F} = 248 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ –106.0 (s, 1F); IR (neat) 3550, 3050, 3025, 2950, 2925, 2875, 2850, 1950, 1875, 1800, 1620, 1590, 1500, 1450, 1430, 1380, 1260, 1220, 1180, 1140, 1100,

1070, 1040, 1025, 940, 910, 870, 840, 780, 735, 700, 670, 620 cm^{-1}; $[\alpha]_D^{23}$ –11.1 (*c* 2.18, $CHCl_3$); Anal. calcd. for $C_{42}H_{46}FO_5Si$: C, 74.41; H, 6.84. Found: C, 75.16; H, 6.89.

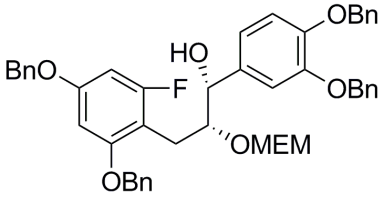
Preparation of 7



To a solution of alcohol **6** (1.60 g, 2.04 mmol) in CH_2Cl_2 (6.04 ml) and *i*-Pr_2NEt (4.16 ml, 24.5 mmol) was added methoxyethoxymethyl chloride (MEMCl) (1.38 ml, 12.2 mmol) and *n*-Bu_4NI (37.6 mg, 0.10 mmol) at 0 °C, and the mixture was stirred for 15 h at room temperature. The reaction was quenched by adding saturated aqueous $NaHCO_3$, and the products extracted with EtOAc (×3). The combined organic extracts were washed with brine (×1), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 5/1) to afford ether **7** (1.64 g, 92%) as a colorless oil.

7: R_f 0.42 (*n*-hexane /EtOAc = 4/1); ^1H NMR (300 MHz, $CDCl_3$) δ –0.23 (s, 3H), –0.02 (s, 3H), 0.82 (s, 9H), 2.40 (brd, 1H, *J* = 13.4 Hz), 2.62 (dd, 1H, *J* = 13.4, 10.5 Hz), 2.88–2.96 (m, 1H), 3.00–3.08 (m, 2H), 3.10–3.18 (m, 1H), 3.24 (s, 3H), 4.01–4.09 (m, 1H), 4.45 (d, 1H, *J* = 7.0 Hz), 4.56 (d, 1H, *J* = 6.0 Hz), 4.73 (d, 1H, *J* = 7.0 Hz), 4.94 (s, 4H), 5.06 (s, 2H), 5.11 (s, 2H), 6.23–6.29 (m, 2H), 6.73 (dd, 1H, *J* = 8.2, 1.6 Hz), 6.79 (d, 1H, *J* = 8.2 Hz), 6.94 (d, 1H, *J* = 1.6 Hz), 7.23–7.45 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.04, –4.76, 18.1, 25.0, 25.7, 25.8, 70.2, 70.3, 71.0–71.5 (m, 1C), 71.6, 78.6, 80.1, 94.1 (d, J_{C-F} = 24 Hz), 95.0, 96.2, 108.3 (d, J_{C-F} = 19 Hz), 114.3, 114.5, 120.3, 127.0, 127.1, 127.2, 127.3, 127.4, 127.6, 127.7, 128.1, 128.3, 128.4, 128.5, 128.6, 135.4, 136.7, 137.3, 137.4, 148.2, 148.3, 158.3 (d, J_{C-F} = 15 Hz), 158.6 (d, J_{C-F} = 15 Hz), 162.4 (d, J_{C-F} = 248 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ –109.7 (s, 1F); IR (neat) 3050, 3025, 2950, 2925, 2875, 2850, 1950, 1870, 1820, 1620, 1585, 1495, 1450, 1430, 1425, 1375, 1375, 1360, 1325, 1255, 1215, 1200, 1175, 1150, 1095, 1040, 1025, 940, cm^{-1}; $[\alpha]_D^{25}$ +5.3 (*c* 0.34, $CHCl_3$); Anal. calcd. for $C_{53}H_{61}FO_8Si$: C, 72.91; H, 7.04. Found: C, 72.80; H, 6.96.

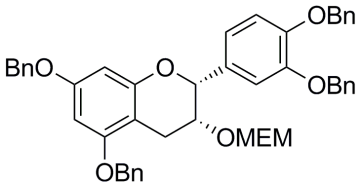
Preparation of 8



Tetrabutylammonium fluoride (1 M solution in THF, 2.76 ml, 2.8 mmol) was added to a stirred solution of **7** (1.85 g, 2.12 mmol) in THF (106 ml) at room temperature for 14 h. The reaction was quenched with phosphate buffer solution (pH 7) and the resulting mixture was extracted with EtOAc (×3). The combined organic extracts were washed with water (×1) and brine (×1), then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 1.5/1) to afford alcohol **8** (1.59 g, 99%) as a colorless oil.

8: R_f 0.36 (*n*-hexane/EtOAc = 1.5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60 (dd, 1H, *J* = 13.8, 4.5 Hz), 2.80 (dd, 1H, *J* = 13.8, 8.5 Hz), 3.31 (s, 3H), 3.31–3.35 (m, 2H), 3.40–3.44 (m, 2H), 3.50 (brd, 1H, J = 3.8 Hz, OH), 3.94–4.00 (m, 1H), 4.39 (d, 1H, *J* = 7.1 Hz), 4.44 (d, 1H, *J* = 7.1 Hz), 4.46 (dd, 1H, *J* = 5.3, 3.8 Hz), 4.93 (d, 1H, *J* = 11.9 Hz), 4.96 (s, 2H), 4.97 (d, 1H, *J* = 11.9 Hz), 5.03 (d, 1H, *J* = 12.1 Hz), 5.09 (d, 1H, *J* = 12.1 Hz), 5.10 (s, 2H), 6.30 (dd, 1H, *J* = 11.2 (C–F), 2.4 Hz), 6.34 (brs, 1H), 6.75 (dd, 1H, *J* = 8.1, 1.4 Hz), 6.79 (d, 1H, *J* = 8.1 Hz), 6.97 (d, 1H, *J* = 1.4 Hz), 7.24–7.45 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 58.9, 67.4, 70.3, 70.5, 71.1, 71.3, 71.5, 75.7, 82.5, 82.6, 94.3 (d, J_{C-F} = 24 Hz), 96.2, 96.3, 106.8 (d, J_{C-F} = 15 Hz), 113.7, 114.9, 119.8, 127.2, 127.3, 124.4, 127.5, 127.7, 128.1, 128.2, 128.3, 128.4, 128.5, 158.7, 162.3 (d, J_{C-F} = 240 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ –109.7 (s, 1F) ; IR (neat) 3450, 3050, 3025, 2925, 2875, 1950, 1870, 1810, 1620, 1585, 1505, 1500, 1450, 1435, 1430, 1380, 1330, 1280, 1220, 1200, 1170, 1140, 1095, 940, 925, 910, 850, 820, 740, 700 cm^{-1}; $[\alpha]_D^{25}$ –1.1 (*c* 0.10, $CHCl_3$); Anal. calcd. for $C_{47}H_{47}FO_8$: C, 74.39; H, 6.24. Found: C, 74.09; H, 6.23.

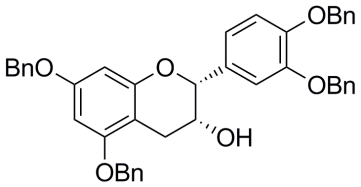
Preparation of 9



KH (30 wt% suspension in mineral oil, 8.6 mg, 64 μmol) was added to a solution of **8** (9.7 mg, 13 μmol) in DMF (1 ml) at 0 °C. The resulting reaction mixture was allowed to reach room temperature and stirred for further 2 h. Then the reaction was quenched with water and extracted with EtOAc (×3). The combined organic extracts were washed with water (×1) and brine (×1), then dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1.5/1) to afford pyran **9** (8.6 mg, 91%) as a white solid.

9: R_f 0.37 (*n*-hexane/EtOAc = 1.5/1); mp 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.83 (dd, 1H, *J* = 17.4, 4.3 Hz), 2.90–3.08 (m, 2H), 3.13–3.20 (m, 2H), 3.24 (s, 3H), 3.24–3.32 (m, 1H), 4.21–4.25 (br, 1H), 4.35 (d, 1H, *J* = 7.3 Hz), 4.63 (d, 1H, *J* = 7.3 Hz), 4.96 (brs, 1H), 5.00 (s, 2H), 5.03 (s, 2H), 5.16 (s, 2H), 5.18 (s, 2H), 6.25 (d, 1H, *J* = 2.3 Hz), 6.28 (d, 1H, *J* = 2.3 Hz), 6.93 (d, 1H, *J* = 8.3 Hz), 6.97 (dd, 1H, *J* = 8.3, 1.6 Hz), 7.21 (d, 1H, *J* = 1.6 Hz), 7.27–7.48 (m, 20H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 58.8, 66.5, 69.9, 70.1, 70.3, 71.2, 71.4, 78.1, 93.9, 94.8, 101.3, 113.6, 114.8, 119.5, 127.1, 127.2, 127.3, 127.5, 127.5, 127.7, 127.8, 127.9, 128.4, 128.5, 128.5, 132.3, 137.0, 137.1, 137.3, 137.3, 148.8, 155.5, 158.0, 158.7; IR (neat) 3050, 3025, 2925, 2875, 1950, 1880, 1820, 1625, 1595, 1505, 1495, 1450, 1440, 1420, 1375, 1310, 1260, 1220, 1195, 1180, 1140, 1110, 1075, 1040, 1020, 910, 850, 810, 735, 695 cm^{-1}; $[\alpha]_D^{25}$ –6.9 (*c* 0.83, $CHCl_3$); Anal. calcd. for $C_{47}H_{46}O_8$: C, 76.40; H, 6.28. Found: C, 76.14; H, 6.22.

Preparation of 10

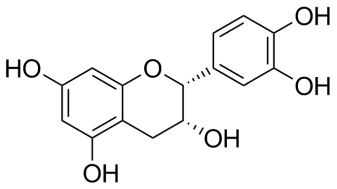


A mixture of **9** (118 mg, 0.159 mmol) and phloroglucinol (60 mg, 0.48 mmol) were suspended in CH_2Cl_2 (11.4 ml). Under vigorous stirring, *p*-TsOH·H_2O (60 mg, 0.80 mmol) was added at 0 °C, and the resulting mixture was stirred for 6 days at room temperature. Then, the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc (×3), and the combined organic extracts were washed with brine (×1), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1.5/1) to afford alcohol **10** (91 mg, 87%) as a white solid.

10: R_f 0.45 (*n*-hexane/EtOAc = 1.5/1); mp 130–131 °C (hexane/Et_2O/EtOAc); $[\alpha]_D^{25}$ –16.7 (*c* 3.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (d, 1H, *J* = 5.7 Hz), 2.88 (dd, 1H, *J* = 17.3, 4.5 Hz), 3.00 (dd, 1H, *J* = 17.3, 2.1 Hz), 4.17 (brs, 1H), 4.87 (s, 1H), 4.99 (s, 4H), 5.14 (s, 2H), 5.17 (s, 2H), 6.26 (s, 2H), 6.94 (d, 1H, *J* = 8.3 Hz), 6.98 (dd, 1H, *J* = 8.3, 1.2 Hz), 7.13 (d, 1H, *J* = 1.2 Hz), 7.20–7.50 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 66.5, 70.1, 70.3, 71.4, 71.5, 78.5, 94.2, 94.8, 101.2, 113.7, 115.2, 119.7, 127.3, 127.4, 127.6, 127.7, 127.9, 128.0, 128.2, 128.6, 128.7, 128.7, 128.8, 131.6, 137.1, 137.2, 137.3, 137.4, 149.0, 149.2, 155.4, 158.5, 158.9; IR (neat) 3564, 3089, 3064, 3032, 2932, 2906, 2871, 1618, 1592, 1512, 1499,

1454, 1442, 1425, 1377, 1265, 1218, 1144, 1112, 1078, 1027, 910, 812, 792, 737, 696, 623 cm^{-1}; Anal. calcd. for $C_{43}H_{38}O_6$: C, 79.36; H, 5.89. Found: C, 79.29; H, 6.06.

Preparation of (–)-EC (1)



A mixture of **10** (41.8 mg, 64.2 μmol) and 5 wt% $Pd(OH)_2$ (72.4 mg) in MeOH (1 ml), THF (1 ml), and H_2O (1 ml) was stirred under H_2 atmosphere for 2.5 h at room temperature. The mixture was filtered through a Celite pad under argon atmosphere, and half of the volume of the filtrate was evaporated. Then, H_2O was added and the remaining MeOH evaporated. The water phase was lyophilized to afford (–)-epicatechin (20.8 mg, *ca.* quant.) as a white powder. **1**: R_f 0.21 (*n*-hexane/EtOAc = 1/3); mp 139–142 °C (amorphous); ^{1}H NMR (400 MHz, CD_3OD) δ 2.63 (dd, 1H, *J* = 16.8, 2.8 Hz), 2.76 (dd, 1H, *J* = 16.8, 4.8 Hz), 4.05-4.15 (m, 1H), 4.71 (s, 1H), 5.81 (d, 1H, *J* = 2.2 Hz), 5.84 (d, 1H, *J* = 2.2 Hz), 6.66 (d, 1H, *J* = 8.4 Hz), 6.70 (dd, 1H, *J* = 8.4, 2.0 Hz), 6.87 (d, 1H, *J* = 2.0 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 29.3, 67.5, 79.9, 95.9, 96.4, 100.0, 115.3, 115.9, 119.4, 132.3, 145.8, 145.9, 157.4, 157.7, 158.0; IR (neat) 3212, 1627, 1607, 1519, 1466, 1353, 1266, 1144, 1116, 1095, 1059, 1014, 981, 823, 785 cm^{-1}; $[\alpha]_D^{24}$ –50 (*c* 0.69, MeOH) (lit.* –53.8, *c* 1.03, acetone/water 1/1 v/v); Anal. calcd. for $C_{15}H_{14}O_6 \cdot H_2O$: C, 58.44; H, 5.23. Found: C, 58.22; H, 5.23.

* K. Kamiya, C. Watanabe, H. Endang, M. Umar, and T. Satake, *Chem. Pharm. Bull.*, 2001, **49**, 551.