Electronic Supplementary Information (ESI)

Asymmetric total synthesis of talienbisflavan A

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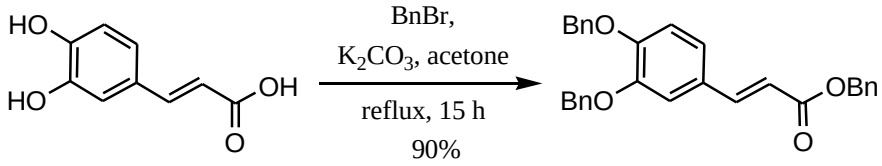
2. General Information

Common reagents and materials were purchased from commercial sources and were used without further purification. Organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under argon. All experiments were carried out under an argon atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents unless otherwise noted. Organic extracts were, in general, dried over anhydrous sodium sulfate (Na_2SO_4). TLC plates were visualized by exposure to ultra violet light (UV). IR spectra were recorded by using an Electrothemal Nicolet 380 spectrometer. High-resolution mass spectra (HRMS) were recorded by using an Electrothemal LTQ-Orbitrap mass spectrometer. Melting points were measured by using a Gongyi X-5 microscopy digital melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained by using a Bruker Avance III 400 MHz NMR spectrometer. Chemical shifts for protons are reported in parts per million (δ scale) and are referenced to residual protium in the NMR solvents [$CDCl_3$: δ 7.26; CD_3OD: δ 3.31; $(CD_3)_2CO$: δ 2.05]. Chemical shifts for carbon resonances are reported in parts per million (δ scale) and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.0; CD_3OD: δ 49.05). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constant in Hertz (Hz).

3. Experimental Procedures

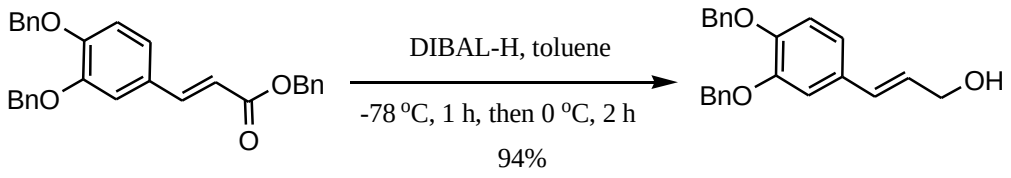
3.1 Synthesis of (*E*)-benzyl 3-(3,4-bis(benzyloxy)phenyl)acrylate (12)



11 **12**

To a solution of caffeic acid (**11**, 1.5 g, 8.3 mmol) in acetone (20 mL) were added potassium carbonate (3.45 g, 25 mmol) and benzyl bromide (3.95 mL, 33.3 mmol). The resulting mixture was stirred under reflux for 15 h, and was added with water (20 mL). The mixture was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The syrupy residue was purified by crystallization in ethanol to afford (*E*)-benzyl 3-(3,4-bis(benzyloxy)phenyl)acrylate (**12**) as a white solid (3.38 g). Yield: 90%; m.p. = 80–81 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.64 (d, 1H, *J* = 15.9 Hz), 7.48–7.34 (m, 15H), 7.15 (s, 1H), 7.09 (d, 1H, *J* = 8.3 Hz), 6.94 (d, 1H, *J* = 8.3 Hz), 6.32 (d, 1H, *J* = 15.9 Hz), 5.26 (s, 2H), 5.22 (s, 2H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 166.9, 151.1, 149.0, 144.9, 136.8, 136.7, 136.2, 128.5, 128.2, 128.2, 127.9, 127.8, 127.3, 127.1, 122.9, 115.8, 114.3, 113.8, 71.3, 71.0, 66.2; IR (film): ν_{max} = 3068, 3025, 2907, 2857, 1683, 1595, 1516, 1445, 1390, 1272, 1130, 1021, 946, 871, 840, 816 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{30}H_{27}O_4$ $[M+H]^+$: 451.1904, found: 451.1905.

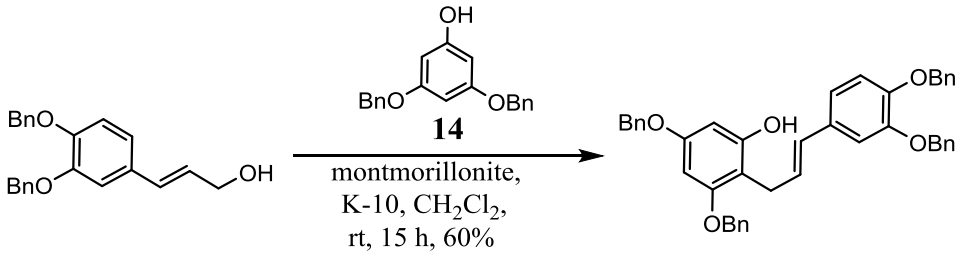
3.2 Synthesis of (*E*)-3-(3,4-bis(benzyloxy)phenyl)prop-2-en-1-ol (13)



12 **13**

To a solution of (*E*)-benzyl 3-(3,4-bis(benzyloxy)phenyl)acrylate (**12**, 1.0 g, 2.22 mmol) in toluene (10 mL) was added DIBAL-H (1.5 M in toluene, 3.7 mL, 5.55 mmol) at –78 ℃. The mixture was stirred at –78 ℃ for 1 h, warmed to 0 ℃ and stirred for 2 h at this temperature, and then water (5 mL) was added dropwise. The resulting reaction mixture was diluted with water (10 mL) and diethyl ether (10 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated. Recrystallization of the crude product from hexanes and dichloromethane provided (*E*)-3-(3,4-bis(benzyloxy)phenyl)prop-2-en-1-ol (**13**) as a white solid (0.72 g). Yield: 94%; m.p. = 77–78 ℃; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.49–7.33 (m, 10H), 7.05 (s, 1H), 6.92 (s, 2H), 6.52 (d, 1H, *J* = 15.9 Hz), 6.21 (td, 1H, *J* = 15.9, 5.9 Hz), 5.19 (s, 2H), 5.18 (s, 2H), 4.69 (s, 1 H, OH), 4.30 (dd, 2H, *J* = 5.8 Hz, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 149.1, 148.9, 137.2, 130.5, 128.5, 127.8, 127.3, 127.2, 126.9, 120.3, 115.0, 113.1, 71.4, 71.3, 63.7; IR (film): ν_{max} = 3294, 3063, 3033, 2924, 2861, 1653, 1599, 1581, 1510, 1454, 1425, 1380, 1342, 1318, 1260, 1235, 1221, 1163, 1134, 1197, 1080, 1043, 1007, 963 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{23}H_{23}O_3$ $[M + H]^+$: 347.1642, found: 347.1643.

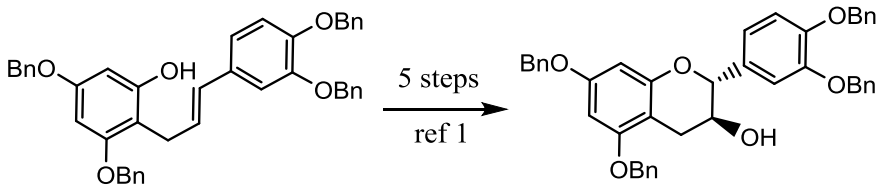
3.3 Synthesis of (*E*)-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]-1-[3,4-bis(benzyloxy)phenyl]propene (15)



13 **15**

To a well stirred mixture of 3,5-bis(benzyloxy)phenol (**14**, 480 mg, 1.57 mmol) in anhydrous dichloromethane (20 mL) under nitrogen atmosphere was added montmorillonite K-10 (480 mg) at room temperature. Then, a solution of (*E*)-3-(3,4-bis(benzyloxy)phenyl)prop-2-en-1-ol (**13**, 181 mg, 0.52 mmol) in anhydrous dichloromethane (10 mL) was added dropwise over 30 min. The resulting purple mixture was stirred at room temperature for 15 h and then filtered through a pad of Celite, which was rinsed with ethyl acetate (200 mL). After evaporation, the residue was purified by column chromatography (20% ethyl acetate in petroleum ether) over silica gel to afford (*E*)-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]-1-[3,4-bis(benzyloxy)phenyl]propene (**15**) as a white amorphous foam (198 mg). Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.43–7.32 (m, 20H), 6.95 (d, 1H, *J* = 1.2 Hz), 6.84–6.81 (m, 2H), 6.37 (d, 1H, *J* = 15.5 Hz), 6.27 (d, 1H, *J* = 1.7 Hz), 6.16 (d, 1H, *J* = 1.7 Hz), 6.14–6.10 (dd, 1H, *J* = 15.5, 5.8 Hz), 5.12 (s, 2H), 5.11 (s, 2H), 5.01 (s, 2H), 4.98 (s, 2H), 3.55 (d, 2H, *J* = 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 158.5, 157.6, 155.5, 148.7, 148.1, 137.0, 136.8, 136.6, 130.9, 129.8, 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 127.2, 127.1, 127.0, 126.4, 119.6, 114.8, 112.3, 106.7, 94.8, 93.4, 76.9, 71.1, 70.1, 69.8, 26.1; IR (film): ν_{max} = 3492, 3029, 1621, 1506, 1374, 1116, 997 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{43}H_{38}O_5Na$ $[M+Na]^+$: 657.2611, found: 657.2613.

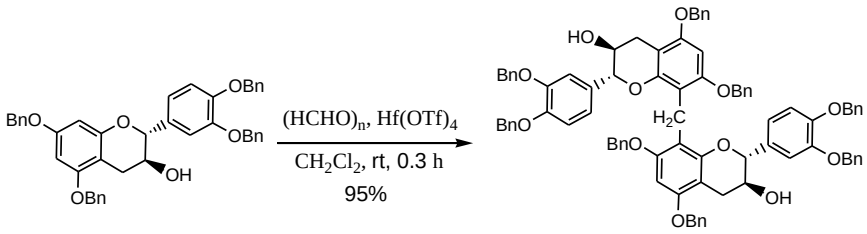
3.4 Synthesis of (2*R*,3*S*)-5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)chroman-3-ol (4)



15 **4**

(2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)chroman-3-ol (**4**) was synthesized from (*E*)-3-[2,4-bis(benzyloxy)-6-hydroxyphenyl]-1-[3,4-bis(benzyloxy)-phenyl]propene (**15**) according to the literature[1]. M.p. = 115–116 ℃; $[\alpha]_D^{25}$ +3 (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.54–7.38 (m, 20H), 7.14 (s, 1H), 7.02 (s, 2H), 6.38 (s, 1H), 6.34 (s, 1H), 5.23 (s, 4H), 5.18–5.02 (m, 4H), 4.70 (d, 1H, *J* = 8.1 Hz), 4.05 (dd, 1H, *J* = 14.0, 7.9 Hz), 3.19 (dd, 1H, *J* =16.4, 5.5 Hz), 2.74 (dd, 1H, *J* = 16.4, 8.7 Hz,); ^{13}C NMR (100 MHz,$CDCl_3$): δ/ppm = 158.7, 157.6, 155.2, 149.1, 148.9, 137.0, 136.9, 136.8, 136.8, 131.0, 128.7, 128.4, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.4, 127.1, 127.0, 120.4, 114.8, 113.8, 102.2, 94.3, 93.7, 81.4, 71.1, 71.0, 69.9, 69.7, 67.9, 27.5. IR (film): ν_{max} = 3030, 1613, 1593, 1512, 1497, 1453, 1377, 1263, 1215, 1139, 1116, 744, 690 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{43}H_{39}O_6$ $[M + H]^+$: 651.2741, found: 651.2744.

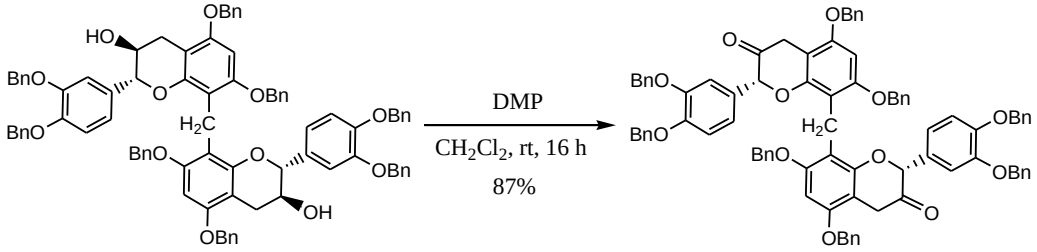
3.5 Synthesis of octa-*O*-benzyl bis-8,8´-catechinylmethane (10)



4 **10**

To a solution of (2*R*,3*S*)-5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)chroman-3-ol (**4**, 100 mg, 0.15 mmol) in anhydrous dichloromethane (0.15 mL) were added paraformaldehyde (4.5 mg, 0.15 mmol) and $Hf(OTf)_4$ (1.16 mg, 0.0015 mmol). The mixture was stirred at room temperature for 0.3 h. Water was poured into the solution, and the mixture was extracted with ethyl acetate (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% ethyl acetate in petroleum ether) over silica gel to afford octa-*O*-benzyl bis-8,8´-catechinylmethane (**10**) as a yellow oil (95.9 mg). Yield: 95%; $[\alpha]_D^{25}$ +5.0 (c = 1.0, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.47–7.17 (m, 40H), 6.79 (dd, 4H, *J* = 9.1, 4.9 Hz), 6.59 (dd, 2H, *J* = 8.2, 1.5 Hz), 6.13 (s, 2H), 5.16–4.98 (m, 14H), 4.73 (d, 2H, *J* = 11.8 Hz), 4.57 (d, 2H, *J* = 11.8 Hz), 4.14 (d, 2H, *J* = 8.5 Hz), 4.05 (s, 2H), 3.14 (dd, 2H, *J* = 16.2, 5.7 Hz), 2.60 (dd, 2H, *J* = 16.2, 9.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 156.1, 154.6, 153.5, 148.9, 148.8, 137.8, 137.3, 137.3, 137.0, 131.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.7, 127.6, 127.4, 127.3, 127.2, 127.1, 127.1, 120.6, 114.6, 113.8, 111.2, 102.2, 91.1, 80.9, 71.3, 71.0, 70.0, 69.9, 68.5, 26.9, 17.4; IR (film): ν_{max} = 3035, 1624, 1593, 1510, 1495, 1444, 1376, 1254, 1218, 1128, 1113, 742, 695 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{87}H_{77}O_{12}$ $[M + H]^+$: 1313.5410, found: 1313.5418.

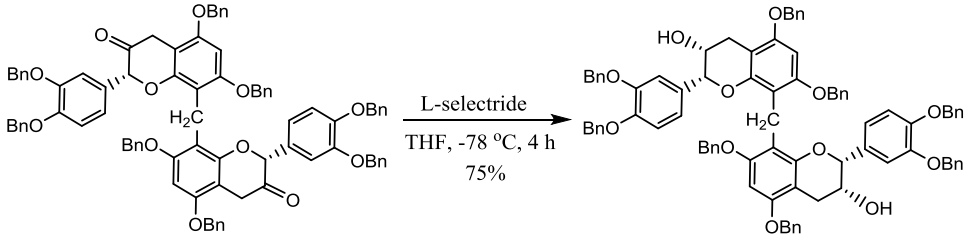
3.6 Synthesis of Ketone 16



10 **16**

To a solution of octa-*O*-benzyl bis-8,8´-catechinylmethane (**10**, 90 mg, 0.068 mmol) in anhydrous dichloromethane (0.5 mL) were added Dess–Martin periodinane (DMP，87.18 mg, 0.21 mmol) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for about 16 h until TLC showed the absence of starting material. Subsequently, saturated aqueous $NaHCO_3$ solution (1 mL) and 10% aqueous $Na_2S_2O_3$ solution (1 mL) were added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate in petroleum ether) over silica gel to afford ketone **16** as a yellow oil (78.06 mg). Yield: 87%; $[\alpha]_D^{25}$ +41 (c = 1.0, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.44–7.20 (m, 40H), 6.85 (s, 2H), 6.78 (d, 2H, *J* = 8.3 Hz), 6.67 (d, 2H, *J* = 8.2 Hz), 6.19 (s, 2H), 5.11 (s, 4H), 4.98 (s, 8H), 4.71 (d, 2H, *J* = 11.5 Hz), 4.60 (d, 2H, *J* = 11.4 Hz), 4.52 (s, 2H), 4.19 (s, 2H), 3.68 (d, 2H, *J* = 20.3 Hz), 3.33 (d, 2H, *J* = 20.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 206.5, 156.7, 154.1, 153.4, 149.0, 148.7, 137.2, 137.1, 137.0, 136.8, 128.6, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.7, 127.7, 127.6, 127.4, 127.2, 127.2, 120.3, 114.5, 113.6, 112.8, 102.9, 92.7, 83.0, 71.1, 70.3, 70.1, 67.9, 26.9, 17.6; IR (film): ν_{max} = 3035, 1723, 1620, 1594, 1515, 1503, 1380, 1160, 736, 696 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{87}H_{73}O_{12}$ $[M + H]^+$: 1309.5097, found: 1309.5099.

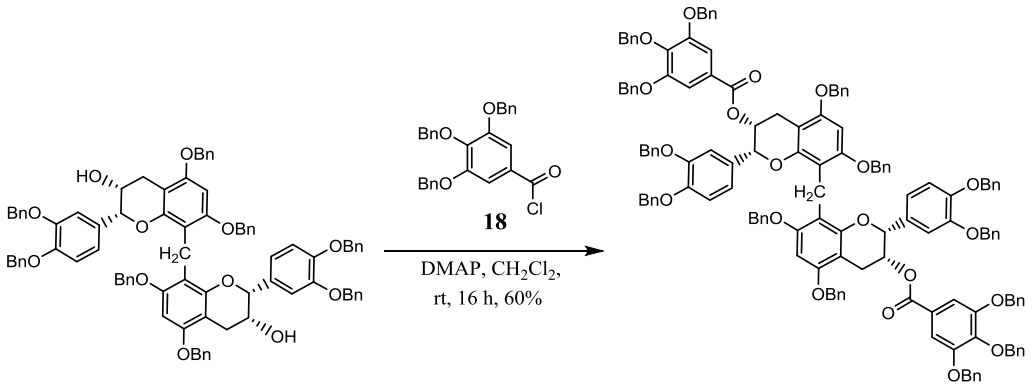
3.7 Synthesis of octa-*O*-benzyl bis-8,8′-epicatechinylmethane (17)



16 **17**

To a solution of ketone **16** (65 mg, 0.05 mmol) in dry THF (0.5 mL) was added dropwise L-selectride (0.1 mL, 1.0 M solution in THF, 0.1 mmol) at –78 ℃. The resulting solution was stirred at –78 ℃ for 4 h, and TLC showed the reaction was complete. Saturated aqueous $NaHCO_3$ (1 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (25% ethyl acetate in petroleum ether) over silica gel to afford octa-*O*-benzyl bis-8,8′-epicatechinylmethane (**17**) as colorless oil (48.9 mg). Yield: 75%; $[\alpha]_D^{25}$ -28.4 (c = 1.0, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.46–7.11 (m, 40H), 6.93 (s, 2H), 6.84 (d, 2H, *J* = 8.2 Hz), 6.63 (d, 2H, *J* = 8.1 Hz), 6.21 (s, 2H), 5.22–5.11 (m, 14H), 4.75 (d, 2H, *J* = 13.1 Hz), 4.33 (s, 2H), 4.17 (s, 2H), 4.00 (s, 2H), 3.01 (d, 2H, *J* = 17.0 Hz), 2.82 (dd, 2H, *J* = 17.3, 3.9 Hz); ^{13}C NMR (100 MHz,$CDCl_3$): δ/ppm = 156.2, 155.3, 153.4, 148.6, 148.4, 137.7, 137.4, 137.4, 137.2, 132.1, 128.5, 128.4, 128.2, 127.8, 127.4, 127.3, 127.3, 127.2, 119.6, 114.7, 113.6, 111.5, 101.0, 91.8, 77.8, 71.2, 71.1, 70.5, 70.0, 66.1, 26.9, 17.6; IR (film): ν_{max} = 3547, 1619, 1592, 1516, 1494, 1460, 1441, 1379, 1261, 1219, 1146, 1110, 753, 699 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{87}H_{77}O_{12}$ $[M + H]^+$: 1313.5410, found: 1313.5418.

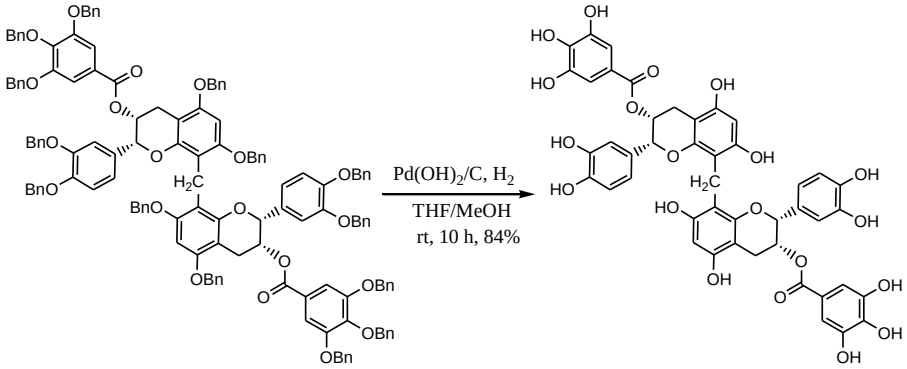
3.8 Synthesis of ester 19



17 **19**

To a suspension of tri-*O*-benzyl gallic acid (53.66 mg, 0.12 mmol) and one drop of DMF in anhydrous dichloromethane (1 mL) was slowly added oxalyl chloride (0.1 mL) in a nitrogen atmosphere. The resulting mixture was stirred under reflux for 3 h. The excess oxally chloride and solvent were removed by distillation and the residue was dried under vacuum for 3 h. To this mixture (3,4,5-tri-*O*-benzylgalloyl chloride, **18**) was added octa-*O*-benzyl bis-8,8´-epicatechinylmethane (**17**, 40 mg, 0.03 mmol) and 4-dimethylaminopyridine (7.44 mg, 0.06 mmol) in dichloromethane (0.5 mL) at 0 ℃. The mixture was stirred at room temperature for 16 h, and was then added with saturated aqueous $NaHCO_3$ (1 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate in petroleum ether) over silica gel to afford ester **19** as a colorless oil (39.4 mg). Yield: 60%; $[\alpha]_D^{25}$ -105.0 (c = 1.0, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.35–7.17 (m, 70H), 7.05 (d, 4H, *J* = 7.1 Hz), 6.84 (s, 2H), 6.69 (d, 2H, *J* = 8.1 Hz), 6.63 (d, 2H, *J* = 8.1 Hz), 6.19 (s, 2H), 5.38 (s, 2H), 5.08–4.94 (m, 26H), 4.73–4.65 (m, 4H), 4.24–4.21 (m, 2H), 3.04–2.93 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 165.2, 156.3, 154.9, 153.7, 152.3, 148.7, 148.5, 142.8, 137.4, 137.3, 137.1, 136.5, 131.8, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.3, 127.1, 119.9, 114.5, 113.7, 111.7, 109.5, 101.1, 91.6, 75.0, 71.2, 71.2, 70.6, 70.0, 68.6, 29.7, 17.4; IR (film): ν_{max} = 3065, 3028, 2934, 2870, 1718, 1614, 1590, 1499, 1446, 1428, 1371, 1322, 1269, 1119, 868, 813, 735, 694 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{143}H_{120}O_{20}Na$ $[M + Na]^+$: 2179.8265, found: 2179.8268.

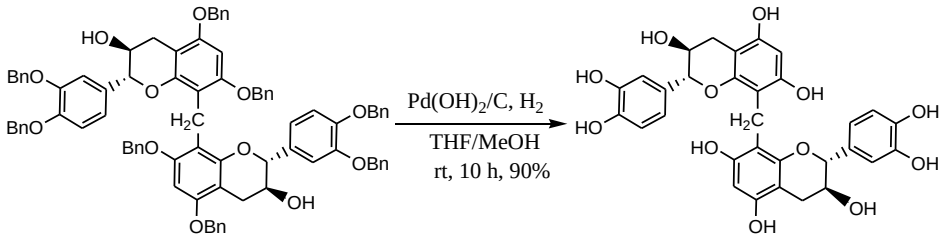
3.9 Synthesis of talienbisflavan A (1)



19 talienbisflavan A (**1**)

To a solution of ester **19** (21.6 mg, 0.01 mmol) in a solvent mixture of THF/MeOH (1:1, v/v, 1 mL) were added $Pd(OH)_2/C$ (5%, 40 mg) in an hydrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 10 h, and TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatography ($AcOH/MeOH/CH_2Cl_2$=1:5:50) over silica gel to afford talienbisflavan A (**1**) as a yellow amorphous powder (7.5 mg). Yield: 84%; $[\alpha]_D^{14}$ -105.4 (c = 0.1, methanol); ^{1}H NMR (400 MHz, CD_3OD): δ/ppm = 6.92 (s, 4H), 6.84 (s, 2H), 6.69–6.65 (m, 4H), 6.01 (s, 2H), 5.40 (s, br, 2H), 4.81 (s, br, 2H), 3.92 (s, 2H), 2.93 (dd, 2H, *J* = 17.9, 3.4 Hz), 2.77 (dd, 2H, *J* = 17.9, 3.4 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ/ppm = 167.6, 155.6, 155.3, 153.8, 146.2, 146.1, 145.8, 140.0, 130.3, 121.6, 120.0, 116.1, 115.0, 110.3, 106.7, 99.9, 96.8, 79.0, 69.4, 26.4, 16.6; IR (film): ν_{max} = 3407, 1695, 1615, 1451, 1229, 1038, 766 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{45}H_{35}O_{20}$ $[M - H]^-$: 895.1727, found: 895.1725. All spectral data match those of the natural talienbisflavan A[2].

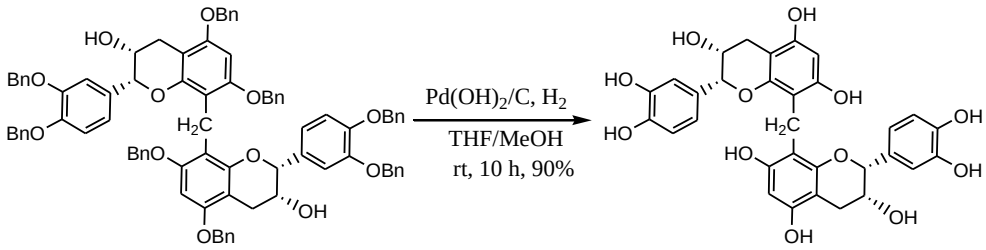
3.10 Synthesis of Bis-8,8′-catechinylmethane (2)



10 **2**

To a solution of octa-*O*-benzyl bis-8,8′-catechinylmethane (**10**, 13.1 mg, 0.01 mmol) in a solvent mixture of THF/MeOH (1:1, v/v, 1 mL) were added $Pd(OH)_2/C$ (5%, 40 mg) under hydrogen atmosphere. The resulting mixture was stirred at room temperature for 10 h, and TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatography ($AcOH/MeOH/CH_2Cl_2$ = 1:5:50) over silica gel to afford bis-8,8′-catechinylmethane (**2**) as a yellow amorphous powder (5.3 mg). Yield: 90%; $[\alpha]_D^{25}$ -104.7 (c = 1.5, MeOH); ^{1}H NMR [400 MHz, $(CD_3)_2CO$]: δ/ppm = 6.94 (s, 2H), 6.80 (s, 4H), 5.98 (s, 2H), 4.69 (d, 2H, *J* = 7.2 Hz), 4.10–3.98 (m, 2H), 3.61 (s, 2H), 2.91 (dd, 2H, *J* = 16.0, 8.1 Hz), 2.54 (dd, 2H, *J* = 16.0, 8.1 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ/ppm = 154.0, 153.8, 151.9, 145.0, 144.8, 130.2, 118.8, 114.8, 114.0, 105.1, 99.9, 95.5, 81.9, 67.0, 27.2, 15.4; IR (film): ν_{max} = 3057, 3031, 2932, 2878,1612, 760 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{31}H_{27}O_{12}$ $[M - H]^-$: 591.1508, found: 591.1507. All spectral data match those of the natural bis-8,8′-catechinylmethane[3].

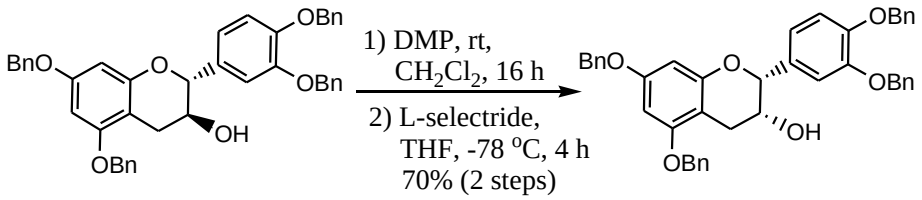
3.11 Synthesis of Bis-8,8′-epicatechinylmethane (3)



17 **3**

To a solution of octa-*O*-benzyl bis-8,8′-epicatechinylmethane (**17**, 13.1 mg, 0.01 mmol) in a solvent mixture of THF/MeOH (1:1, v/v, 1 mL) were added $Pd(OH)_2/C$ (5%, 40 mg) under hydrogen atmosphere. The resulting reaction mixture was stirred at room temperature for 10 h, and TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatography ($AcOH/MeOH/CH_2Cl_2$ = 1:5:50) over silica gel to afford bis-8,8′-epicatechinylmethane (**3**) as a white amorphous powder (5.3 mg). Yield: 90%; $[\alpha]_D^{25}$ -104.1 (c = 0.15, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ/ppm = 6.97 (s, br, 2H), 6.75 (s, br, 4H), 5.98 (s, 2H), 4.78 (s, br, 2H), 4.12 (s, br, 2H), 3.90 (s, 2H), 2.85 (dd, 2H, *J* = 16.6, 4.7 Hz), 2.70 (dd, 2H, *J* = 16.6, 4.7 Hz); ^{13}C NMR (100 MHz, CD_3OD): δ/ppm = 155.8, 155.2, 153.6, 145.8, 131.6, 119.6, 116.0, 115.4, 106.5, 100.4, 96.8, 80.4, 67.0, 29.0, 16.5; IR (film): ν_{max} = 3065, 3033, 2919, 2873, 1606, 763 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{31}H_{27}O_{12}$ $[M - H]^-$: 591.1508, found: 591.1507. All spectral data match those of the natural bis-8,8′-epicatechinylmethane[4].

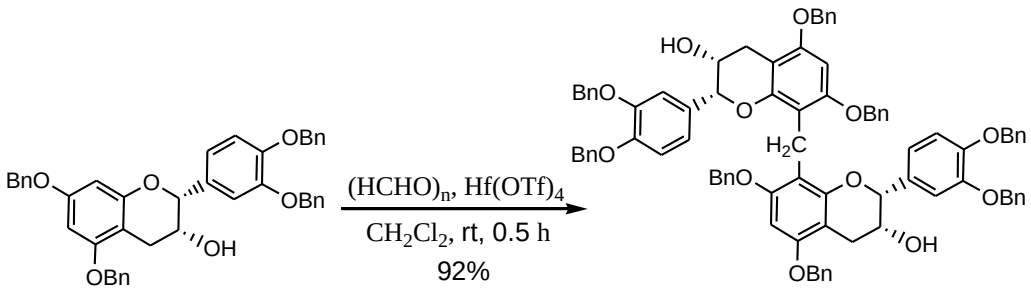
3.12 Synthesis of (2*R*,3*R*)-5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)chroman-3-ol (20)



4 **20**

To a solution of tetra-*O*-benzyl catechin (**4**, 325.4 mg, 0.5 mmol) in anhydrous dichloromethane (10 mL) were added Dess–Martin periodinane (318.1 mg, 0.75 mmol) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for about 16 h until TLC showed the absence of starting material. Subsequently, saturated aqueous $NaHCO_3$ solution (4.2 mL) and 10% aqueous $Na_2S_2O_3$ solution (4.2 mL) were added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15% ethyl acetate in petroleum ether) on silica gel to afford the ketone as a yellow oil. To a solution of the resulting ketone in dry THF (5 mL) was added dropwise L-selectride (0.6 mL, 1.0 M solution in THF, 0.60 mmol) at –78 ℃. The resulting solution was stirred at –78 ℃ for 4 h. When TLC showed the reaction was complete, saturated aqueous $NaHCO_3$ solution (5 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% Ethyl acetate in petroleum ether) over silica gel to afford tetra-*O*-benzyl epicatechin (**20**) as a white solid (244.1 mg). Yield: 70% (2 steps); m.p. = 129–130 °C; $[\alpha]_D^{25}$ -27.7 (c = 2.16, Ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.48–7.33 (m, 20H), 7.18 (s, 1H), 7.03–7.01 (m, 2H), 6.30 (s, 2H), 5.22 (s, 2H), 5.20 (s, 2H), 5.05 (s, 2H), 5.04 (s, 2H), 4.94 (s, 1H), 4.25 (s, br, 1H), 3.05–2.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 158.8, 158.3, 155.3, 149.1, 149.0, 137.3, 137.2, 137.0, 137.0, 128.5, 128.5, 128.4, 128.4, 127.9, 127.8, 127.5, 127.3, 127.2, 119.5, 115.3, 113.8, 101.0, 94.8, 94.1, 78.4, 71.5, 71.4, 70.2, 70.0, 66.3, 28.2; IR (film): ν_{max} = 3030, 1617, 1592, 1512, 1498, 1455, 1441, 1377, 1260, 1217, 1144, 1112, 750, 697 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{43}H_{39}O_6$ $[M + H]^+$: 651.2741, found: 651.2749.

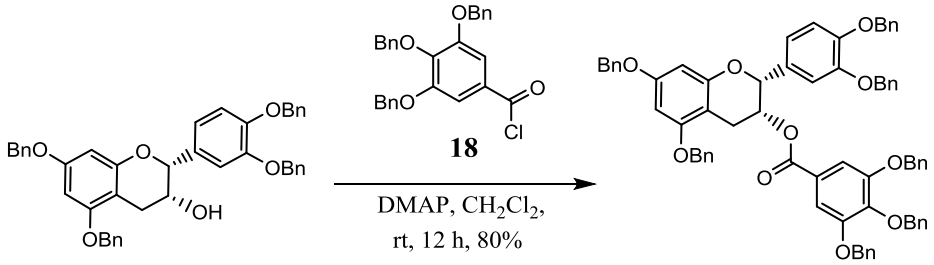
3.13 Synthesis of octa-*O*-benzyl bis-8,8´-epicatechinylmethane (17)



20 **17**

To a solution of tetra-*O*-benzyl epicatechin (**20**, 100 mg, 0.15 mmol) in anhydrous dichloromethane (0.15 mL) were added paraformaldehyde (4.5 mg, 0.15 mmol) and $Hf(OTf)_4$ (1.16 mg, 0.0015 mmol). The resulting mixture was stirred at room temperature for 0.5 h. Water was poured into the solution, and the mixture was extracted with ethyl acetate (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% ethyl acetate in petroleum ether) over silica gel to afford octa-*O*-benzyl bis-8,8´-epicatechinylmethane (**17**) as a colorless oil (92.9 mg). Yield: 92%; $[\alpha]_D^{25}$ -28.4 (c = 1.0, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.46–7.11 (m, 40H), 6.93 (s, 2H), 6.84 (d, 2H, *J* = 8.2 Hz), 6.63 (d, 2H, *J* = 8.1 Hz), 6.21 (s, 2H), 5.22–5.11 (m, 14H), 4.75 (d, 2H, *J* = 13.1 Hz), 4.33 (s, 2H), 4.17 (s, 2H), 4.00 (s, 2H), 3.01 (d, 2H, *J* = 17.0 Hz), 2.82 (dd, 2H, *J* = 17.3, 3.9 Hz); ^{13}C NMR (100 MHz,$CDCl_3$): δ/ppm = 156.2, 155.3, 153.4, 148.6, 148.4, 137.7, 137.4, 137.4, 137.2, 132.1, 128.5, 128.4, 128.2, 127.8, 127.4, 127.3, 127.3, 127.2, 119.6, 114.7, 113.6, 111.5, 101.0, 91.8, 77.8, 71.2, 71.1, 70.5, 70.0, 66.1, 26.9, 17.6; IR (film): ν_{max} = 3547, 1619, 1592, 1516, 1494, 1460, 1441, 1379, 1261, 1219, 1146, 1110, 753, 699 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{87}H_{77}O_{12}$ $[M + H]^+$: 1313.5410, found: 1313.5418.

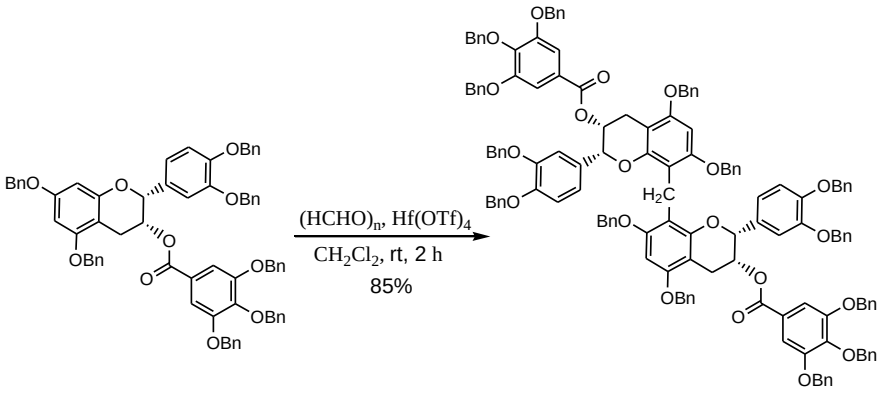
3.14 Synthesis of (2*R*,3*R*)-5,7-bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)chroman-3-yl-3,4,5-tris(benzyloxy)benzoate (21)



20 **21**

To a suspension of tri-*O*-benzyl gallic acid (135.38 mg, 0.31mol) and one drop of DMF in anhydrous dichloromethane (3 mL) was slowly added oxalyl chloride (0.5 mL) at room temperature with agitation under nitrogen atmosphere. The reaction mixture was stirred under reflux for 3 h. The excess oxalyl chloride and solvent were removed by distillation. The residue was dried under vacuum for 3 h, and was then added dropwise to a solution of tetra-*O*-benzyl epicatechin (**20**, 100 mg, 0.15 mmol) and 4-dimethylaminopyridine (18.77 mg, 0.015 mmol) in dichloromethane (2 mL) at zero temperature. The resulting mixture was stirred at room temperature for 12 h, and was then added with saturated aqueous $NaHCO_3$ (1 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (25% ethyl acetate in petroleum ether) over silica gel to afford ester **21** as a white solid (131.9 mg). Yield: 80%; m.p. = 45–47 ℃; $[\alpha]_D^{25}$ -87.0 (c = 3.45, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.55-7.15 (m, 37H), 7.08 (s, 1H), 6.95 (d, 1H, *J* = 8.0 Hz), 6.87 (d, 1H, *J* = 8.1 Hz), 6.41 (s, 1H), 6.37 (s, 1H), 5.65 (s, 1H), 5.12 (s, 4H), 5.05 (d, 8H, *J* = 11.4 Hz), 4.96 (s, 1H), 4.80 (d, 1H, *J* = 11.7 Hz), 4.69 (d, 1H, *J* = 11.7 Hz), 3.20-3.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 165.0, 158.8, 158.0, 155.7, 152.3, 149.0, 148.9, 137.2, 137.0, 136.8, 136.5, 131.1, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.9, 127.7, 127.5, 127.4, 120.0, 114.8, 113.7, 109.1, 100.9, 94.6, 93.9, 75.0, 71.2, 71.0, 70.2, 70.0, 68.5, 29.7; IR (film): ν_{max} = 3090, 3064, 3032, 2930, 2872, 1715, 1619, 1592, 1499, 1454, 1429, 1373, 1327, 1266, 1215, 1145, 1112, 1028, 910, 860, 812, 735, 696 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{71}H_{61}O_{10}$ $[M + H]^+$: 1073.4259, found: 1073.4266**.**

3.15 Synthesis of ester 19



21 **19**

To a solution of ester **21** (100 mg, 0.09 mmol) in anhydrous dichloromethane (0.09 mL) were added paraformaldehyde (2.7 mg, 0.09 mmol) and $Hf(OTf)_4$ (3.49 mg, 0.0045 mmol). The resulting mixture was stirred at room temperature for 2 h, added with water, extracted with ethyl acetate (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (30% ethyl acetate in petroleum ether) over silica gel to afford ester **19** as a colorless oil (87.2 mg). Yield: 85%; $[\alpha]_D^{25}$ -105.0 (c= 1.0, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.35–7.17 (m, 70H), 7.05 (d, 4H, *J* = 7.1 Hz), 6.84 (s, 2H), 6.69 (d, 2H, *J* = 8.1 Hz), 6.63 (d, 2H, *J* = 8.1 Hz), 6.19 (s, 2H), 5.38 (s, 2H), 5.08–4.94 (m, 26H), 4.73–4.65 (m, 4H), 4.24–4.21 (m, 2H), 3.04–2.93 (m, 4H); ^{13}C NMR(100 MHz, $CDCl_3$): δ/ppm = 165.2, 156.3, 154.9, 153.7, 152.3, 148.7, 148.5, 142.8, 137.4, 137.3, 137.1, 136.5, 131.8, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.3, 127.1, 119.9, 114.5, 113.7, 111.7, 109.5, 101.1, 91.6, 75.0, 71.2, 71.2, 70.6, 70.0, 68.6, 29.7, 17.4; IR (film): ν_{max} = 3065, 3028, 2934, 2870, 1718, 1614, 1590, 1499, 1446, 1428, 1371, 1322, 1269, 1119, 868, 813, 735, 694 cm^{-1}. HRMS (ESI) *m/z*: calcd for $C_{143}H_{120}O_{20}Na$ $[M + Na]^+$: 2179.8265, found: 2179.8268.

References

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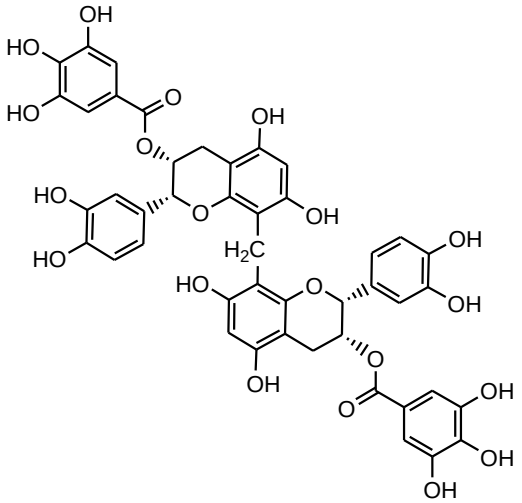
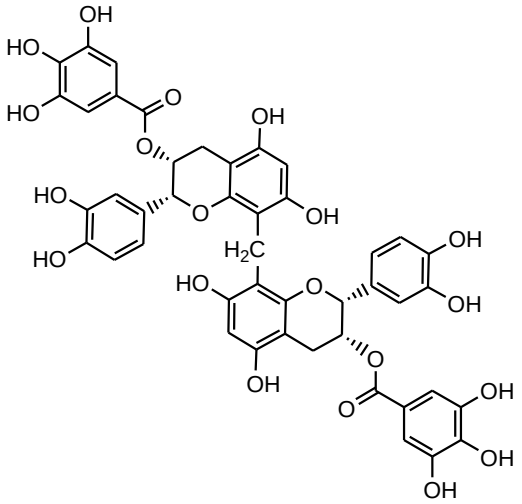
Supplementary Table S1. Comparison of ^{1}H NMR (400 MHz, CD_3OD) spectroscopic data of the natural and synthetic talienbisflavan A (1)



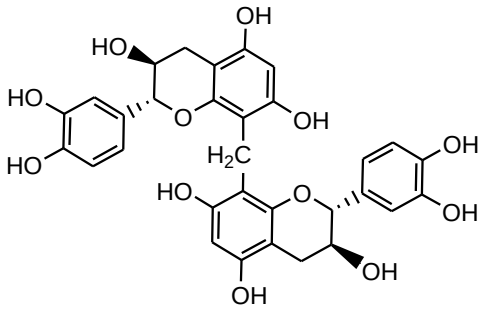
Natural δ_H [ppm, *J* (Hz), mult] 400 MHz	Synthetic δ_H [ppm, *J* (Hz), mult] 400 MHz	Err (Natural−Synthetic) $\Delta\delta_H$ (ppm)
6.91 (s, 4H)	6.92 (s, 4H)	0.01
6.84 (s, 2H)	6.84 (s, 2H)	0
6.67 (m, 4H)	6.69−6.65 (m, 4H)	0
6.01 (s, 2H)	6.01 (s, 2H)	0
5.40 (s, br, 2H)	5.40 (s, br, 2H)	0
4.81 (s, br, 2H)	4.81 (s, br, 2H)	0
3.92 (s, 2H)	3.92 (s, 2H)	0
2.93 (dd, 2H, *J* = 17.2, 4.4 Hz)	2.93 (dd, 2H, *J* = 17.9, 3.4 Hz)	0
2.77 (dd, 2H, *J* = 17.2, 2.2 Hz)	2.77 (dd, 2H, *J* = 17.9, 3.4 Hz)	0

Supplementary Table S2. Comparison of ^{13}C NMR (100 MHz, CD_3OD) spectroscopic data of the natural and synthetic talienbisflavan A (1)



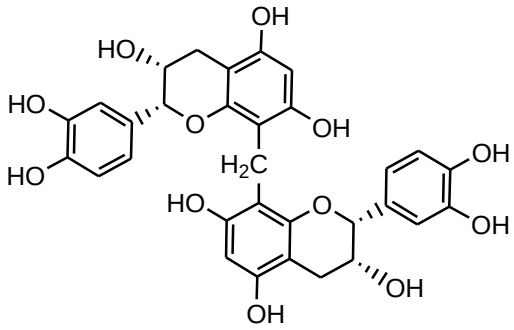
Natural $\delta_{C\ ppm,\ 100\ MHz}$	Synthetic $\delta_{C\ ppm,\ 100\ MHz}$	Err (Natural−Synthetic) $\Delta\delta_C$ (ppm)
167.5	167.6	0.1
155.7	155.6	0.1
155.3	155.3	0
153.7	153.8	0.1
146.2	146.2	0
146.1	146.1	0
145.9	145.8	0.1
139.8	140.0	0.2
130.3	130.3	0
121.4	121.6	0.2
119.7	120.0	0.3
116.1	116.1	0
115.2	115.0	0.2
110.3	110.3	0
106.6	106.7	0.1
99.9	99.9	0
96.9	96.8	0.1
79.0	79.0	0
69.5	69.4	0.1
26.7	26.4	0.3
16.7	16.6	0.1

Supplementary Table S3. Comparison of ^{1}H NMR [400 MHz, $(CD_3)_2CO$] spectroscopic data of the natural and synthetic bis-8,8´-catechinylmethane (2)



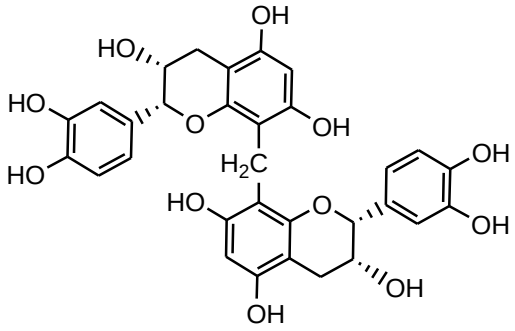
Natural δ_H [ppm, *J* (Hz), mult] 400 MHz	Synthetic δ_H [ppm, *J* (Hz), mult] 400 MHz	Err (Natural−Synthetic) $\Delta\delta_H$ (ppm)
6.94 (s, 2H)	6.94 (s, 2H)	0
6.79 (s, 4H)	6.80 (s, 4H)	0.01
5.98 (s, 2H)	5.98 (s, 2H)	0
4.69 (d, 2H, *J* = 8 Hz)	4.69 (d, 2H, *J* = 7.2 Hz)	0
4.07 (m, 2H)	4.10−3.98 (m, 2H)	0.03
3.60 (s, 2H)	3.61 (s, 2H)	0.01
2.92 (dd, 2H, *J* = 15, 5 Hz)	2.91 (dd, 2H, *J* = 16.0, 8.1 Hz)	0.01
2.54 (dd, 2H, *J* = 15, 8 Hz)	2.54 (dd, 2H, *J* = 16.0, 8.1 Hz)	0

Supplementary Table S4. Comparison of ^{1}H NMR (400 MHz, CD_3OD) spectroscopic data of the natural and synthetic bis-8,8´-epicatechinylmethane (3)



Natural δ_H [ppm, *J* (Hz), mult] 400 MHz	Synthetic δ_H [ppm, *J* (Hz), mult] 400 MHz	Err (Natural−Synthetic) $\Delta\delta_H$ (ppm)
6.96 (s, br, 2H)	6.97 (s, br, 2H)	0.01
6.73 (s, br, 4H)	6.75 (s, br, 4H)	0.02
5.96 (s, 2H)	5.98 (s, 2H)	0.02
4.76 (s, br, 2H)	4.78 (s, br, 2H)	0.02
4.10 (dd, br, 2H, *J* = 4.7, 3.7 Hz)	4.12 (s, br, 2H)	0.02
3.88 (s, 2H)	3.90 (s, 2H)	0.02
2.83 (dd, 2H, *J* = 16.6, 4.7 Hz)	2.85 (dd, 2H, *J* = 16.6, 4.7 Hz)	0.02
2.69 (dd, 2H, *J* = 16.6, 3.7 Hz)	2.70 (dd, 2H, *J* = 16.6, 4.7 Hz)	0.01

Supplementary Table S5. Comparison of ^{13}C NMR (100 MHz, CD_3OD) spectroscopic data of the natural and synthetic bis-8,8´-epicatechinylmethane (3)

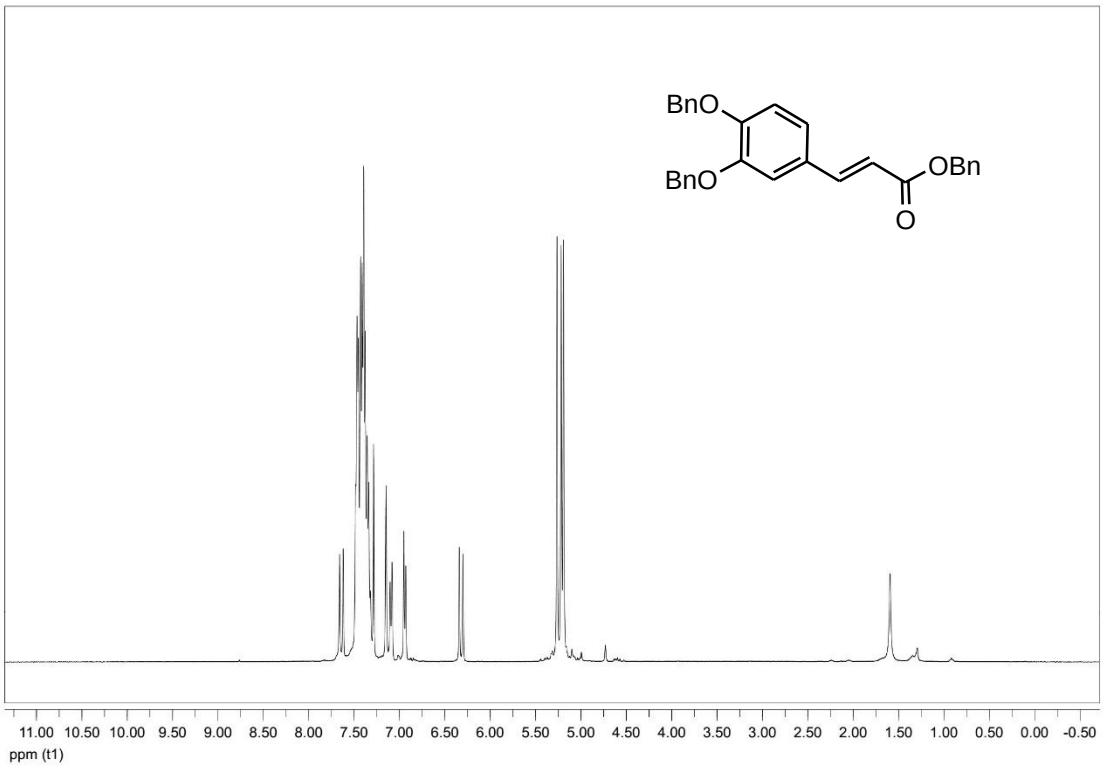


Natural $\delta_{C\ ppm,\ 100\ MHz}$	Synthetic $\delta_{C\ ppm,\ 100\ MHz}$	Err (Natural−Synthetic) $\Delta\delta_C$ (ppm)
155.8	155.8	0
155.2	155.2	0
153.6	153.6	0
145.9	145.8	0.1
131.7	131.6	0.1
119.7	119.6	0.1
116.0	116.0	0
115.4	115.4	0
106.7	106.5	0.2
100.5	100.4	0.1
96.8	96.8	0
80.4	80.4	0
67.2	67.0	0.2
29.0	29.0	0
16.8	16.5	0.3

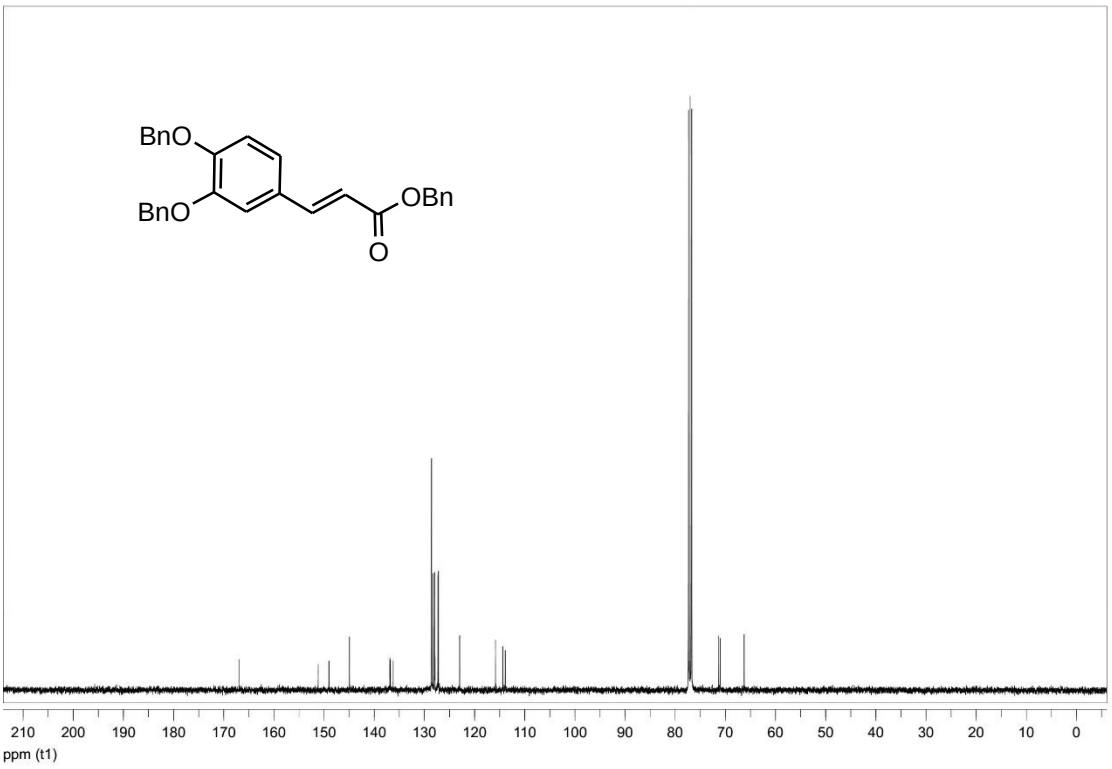
4. NMR Spectra of Compounds

(*E*)-Benzyl 3-(3,4-bis(benzyloxy)phenyl)acrylate (**12**)

^{1}H NMR (400 MHz, $CDCl_3$)

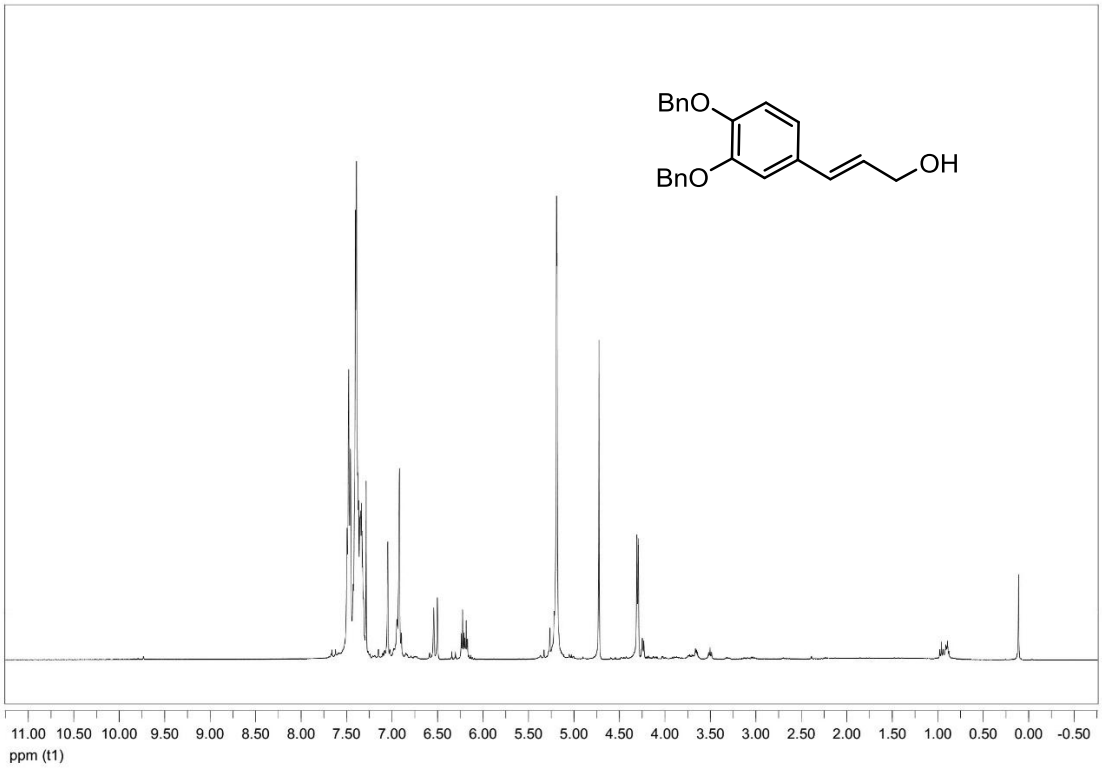


^{13}C NMR (100 MHz, $CDCl_3$)

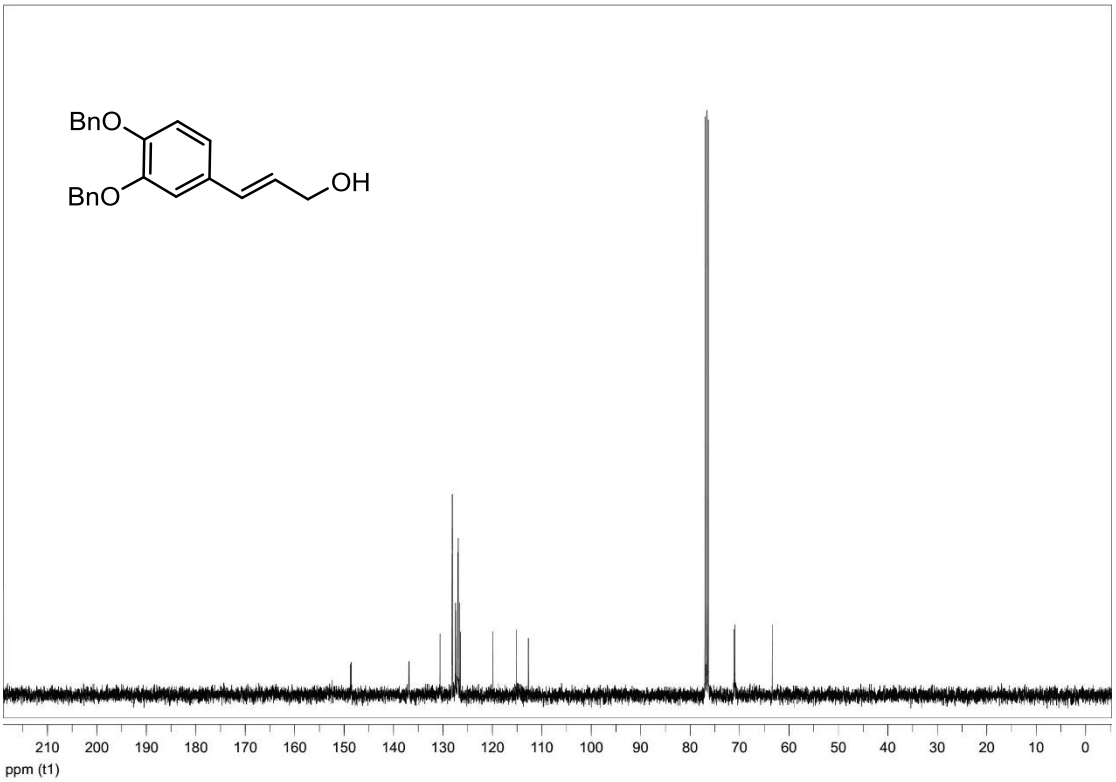


(*E*)-3-(3,4-Bis(benzyloxy)phenyl)prop-2-en-1-ol (**13**)

^{1}H NMR (400 MHz, $CDCl_3$)

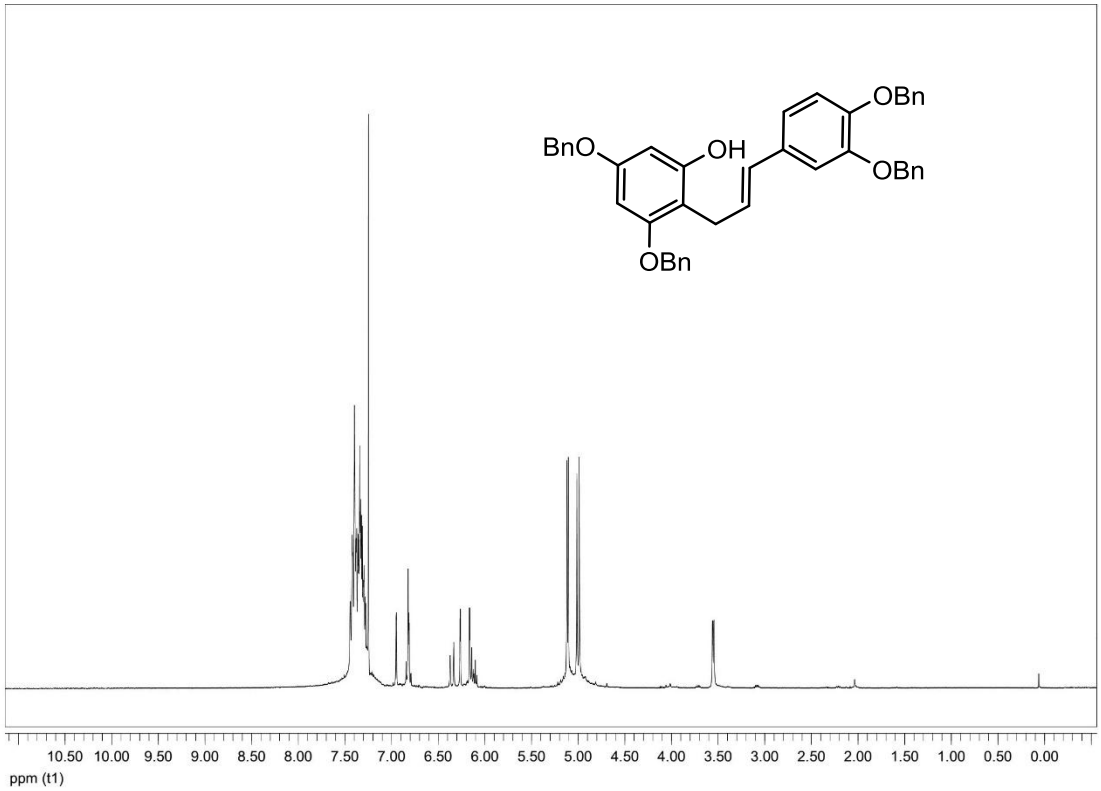


^{13}C NMR (100 MHz, $CDCl_3$)

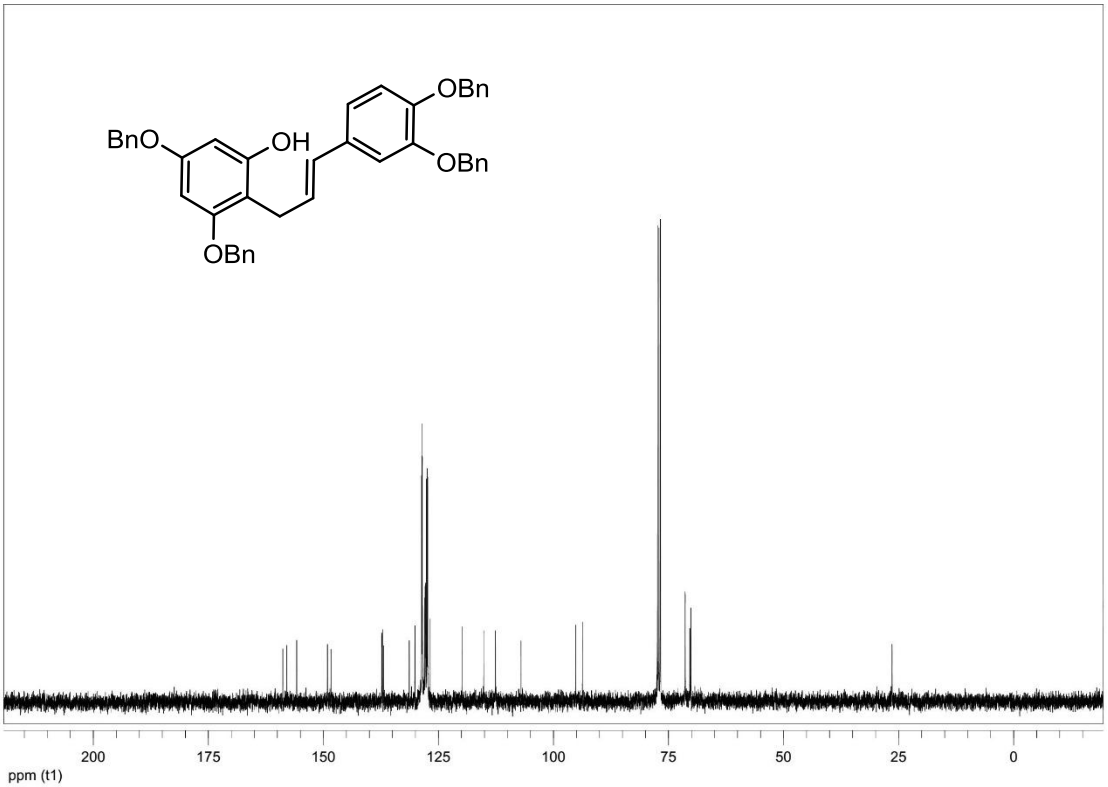


(*E*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-[3,4-bis(benzylo-xy)phenyl]propene (**15**)

^{1}H NMR (400 MHz, $CDCl_3$)

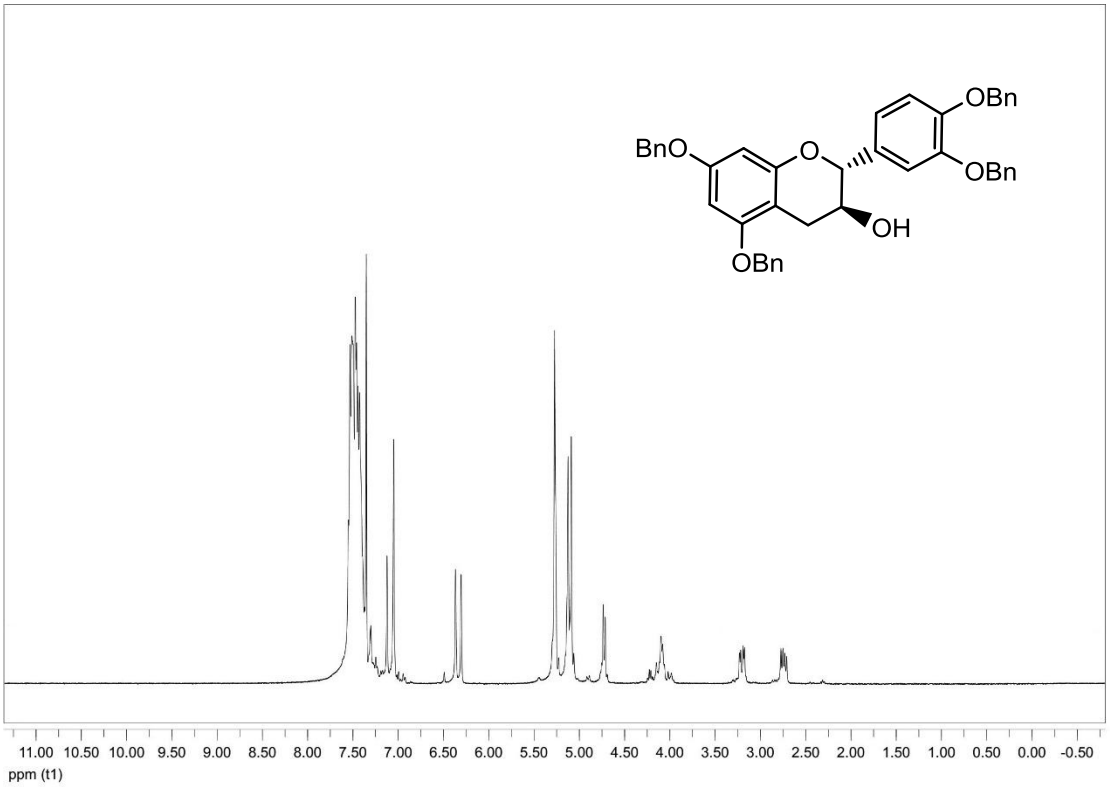


^{13}C NMR (100 MHz, $CDCl_3$)

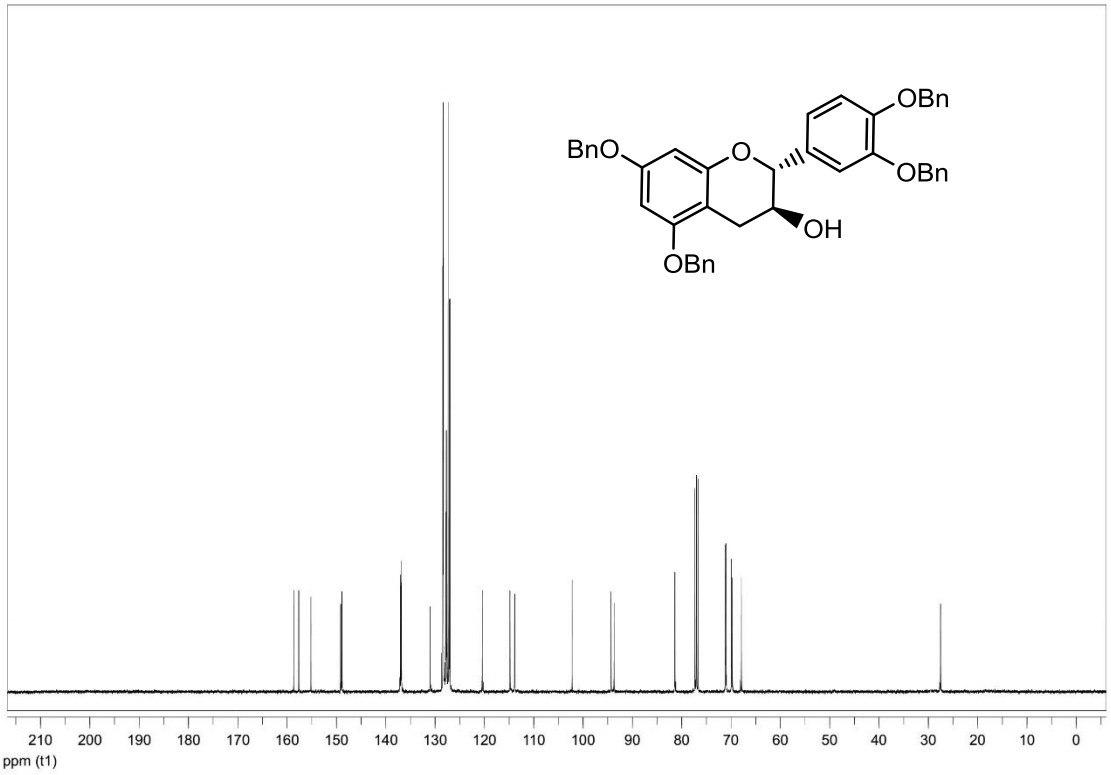


(2*R*,3*S*)-5,7-Bis(benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)chroman-3-ol (**4**)

^{1}H NMR (400 MHz, $CDCl_3$)

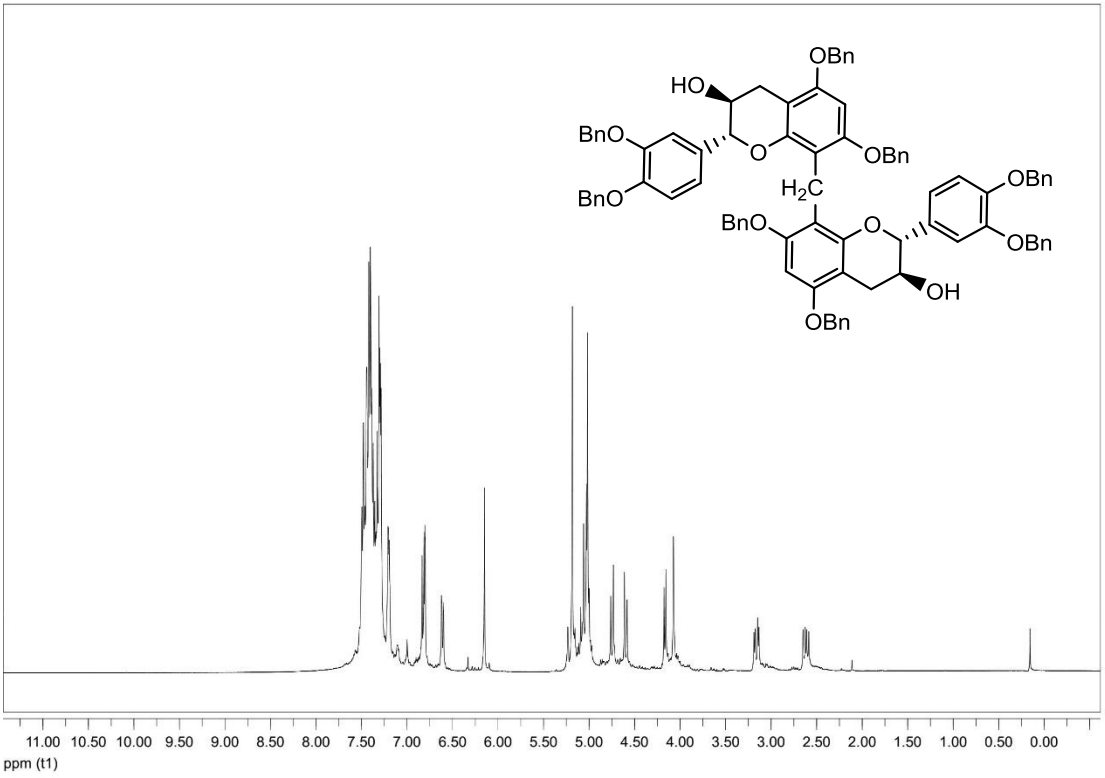


^{13}C NMR (100 MHz, $CDCl_3$)

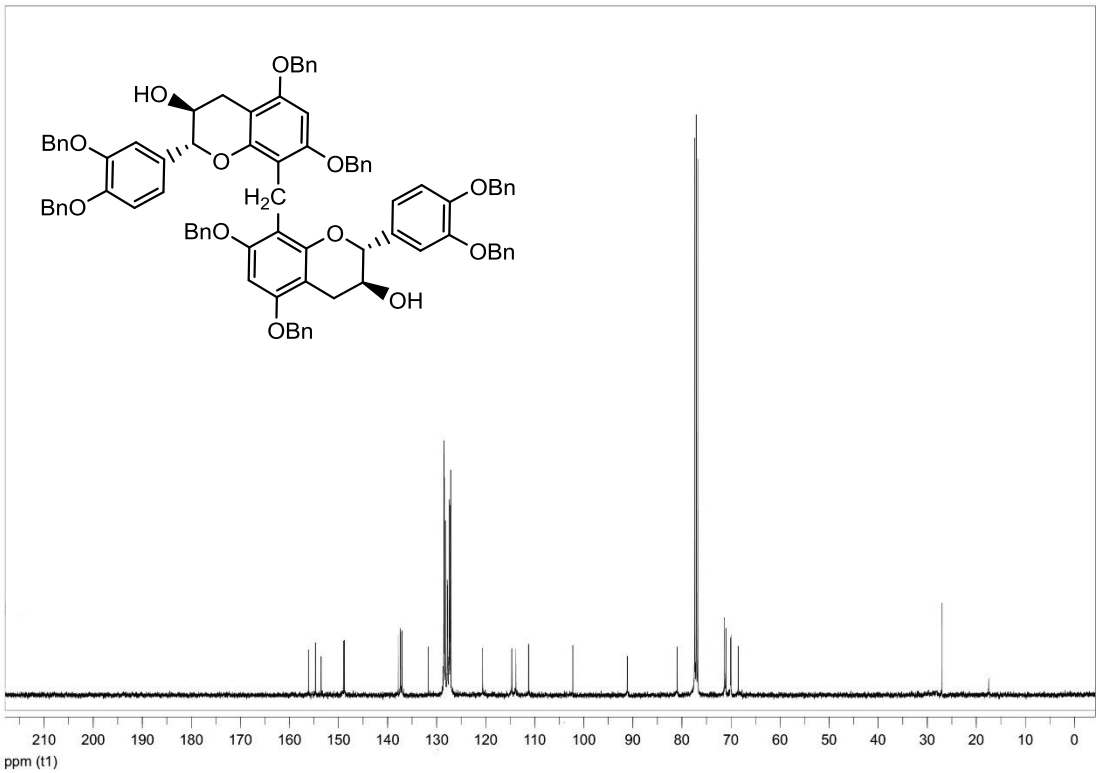


Octa-*O*-benzyl bis-8,8´-catechinylmethane (**10**)

^{1}H NMR (400 MHz, $CDCl_3$)

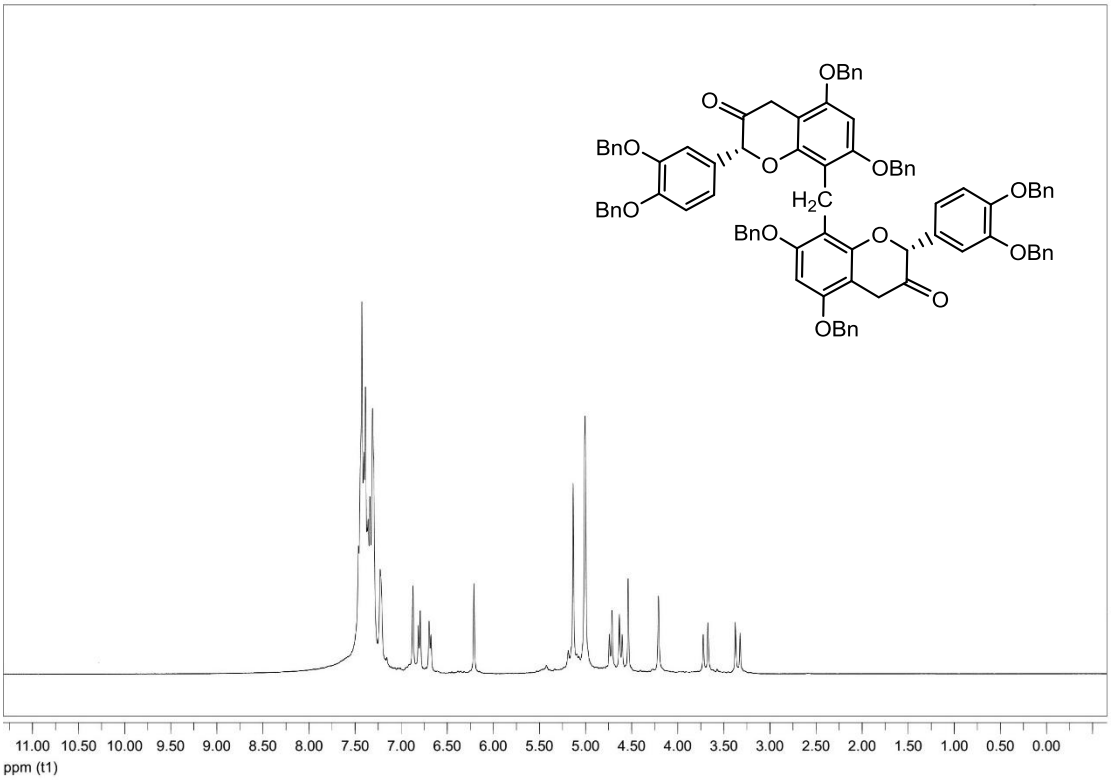


^{13}C NMR (100 MHz, $CDCl_3$)

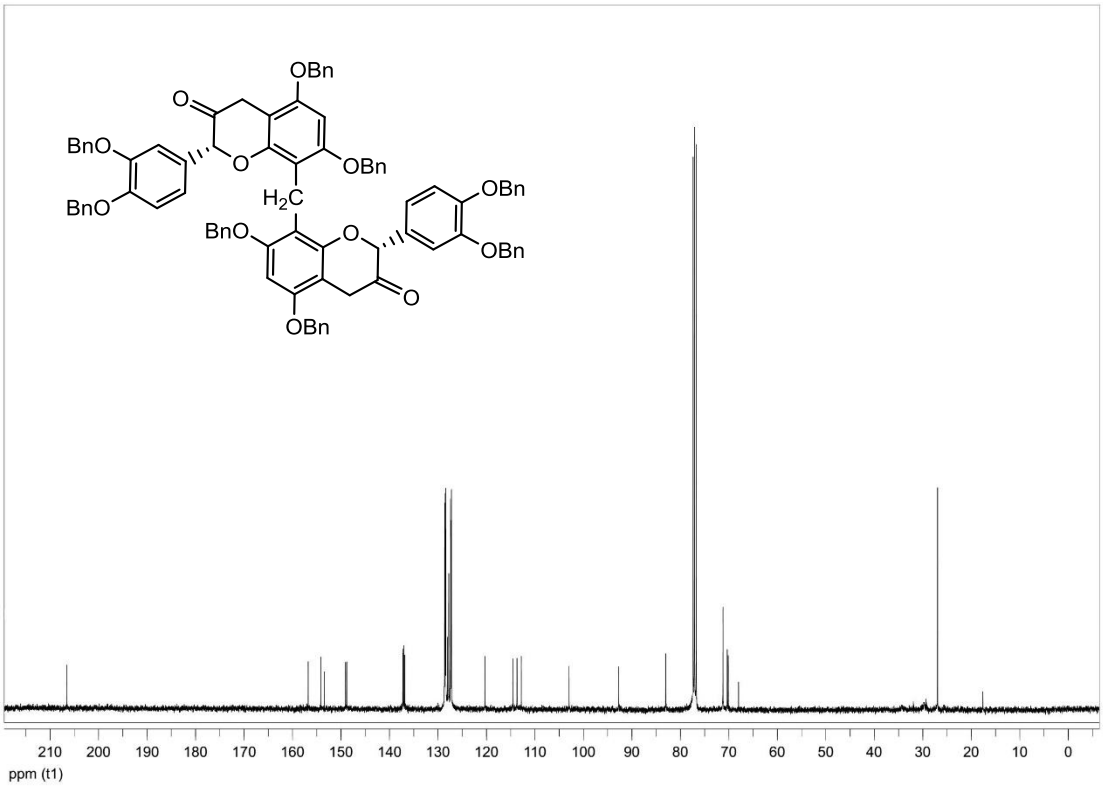


Ketone **16**

^{1}H NMR (400 MHz, $CDCl_3$)

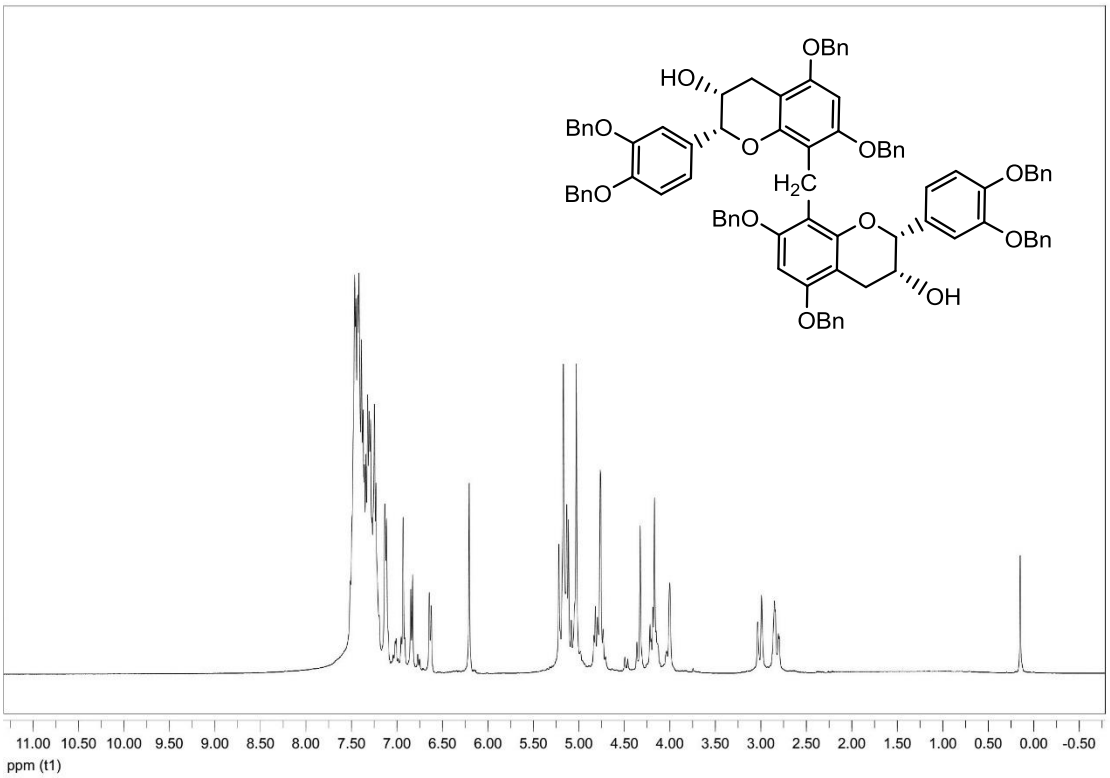


^{13}C NMR (100 MHz, $CDCl_3$)

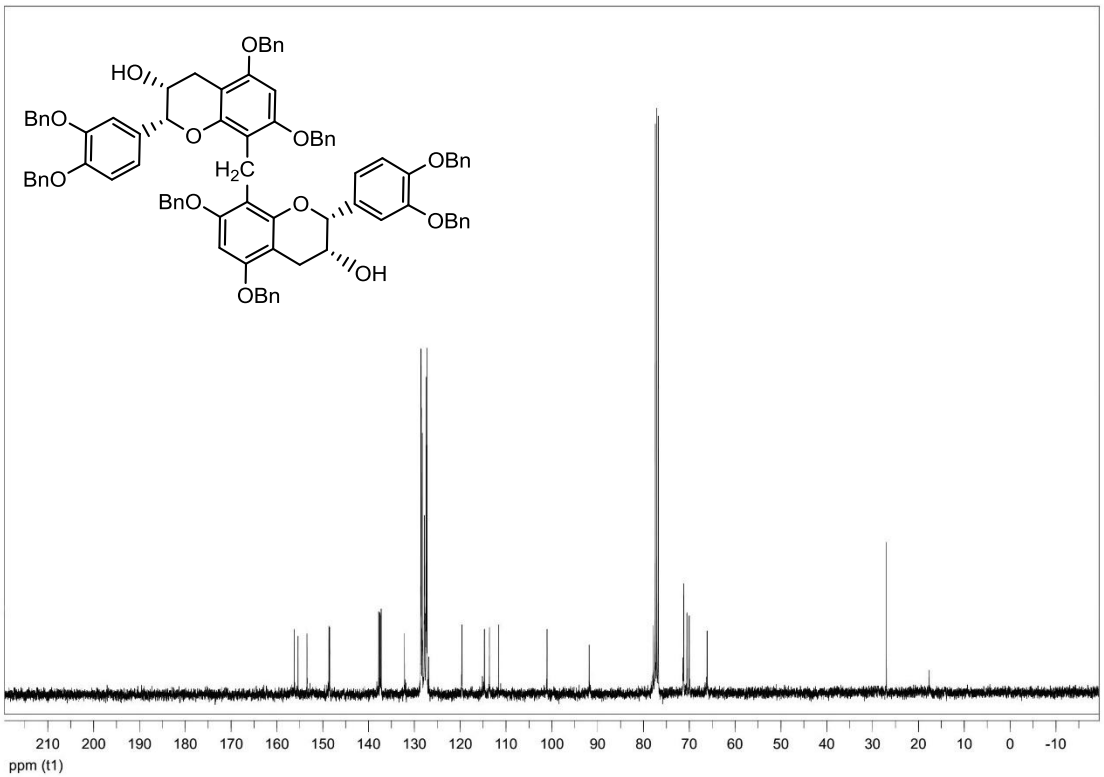


Octa-*O*-benzyl bis-8,8´-epicatechinylmethane (**17**)

^{1}H NMR (400 MHz, $CDCl_3$)

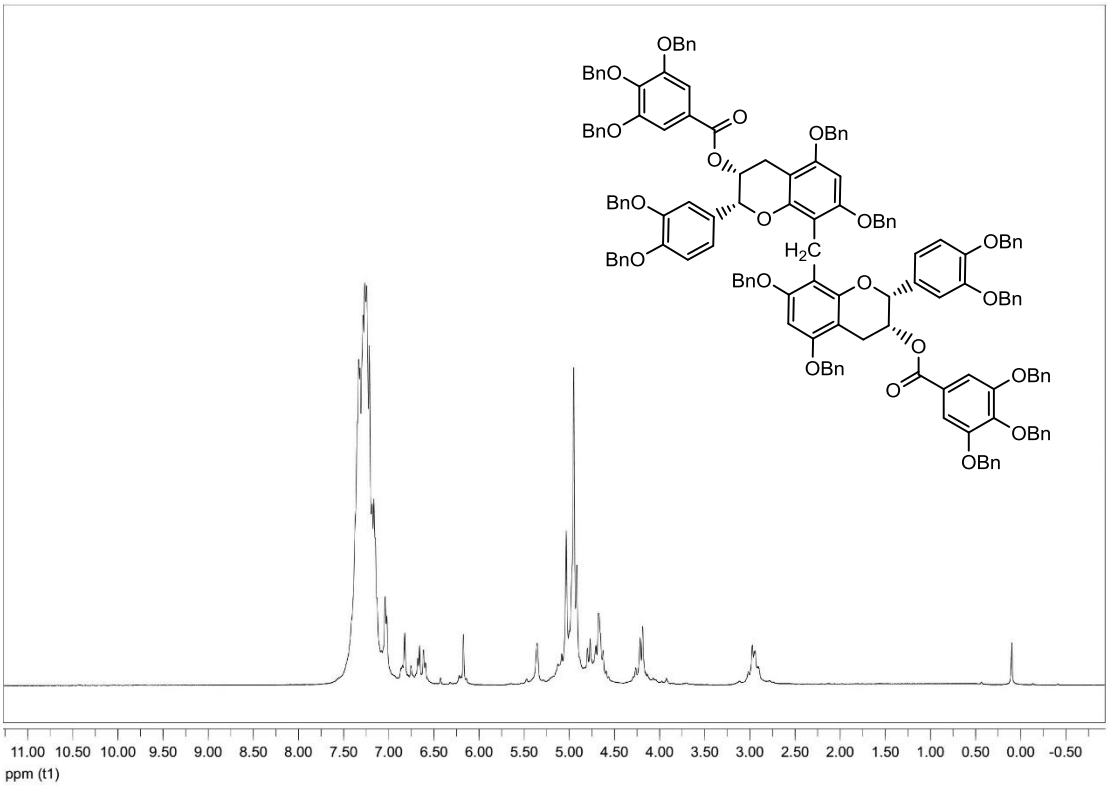


^{13}C NMR (100 MHz, $CDCl_3$)

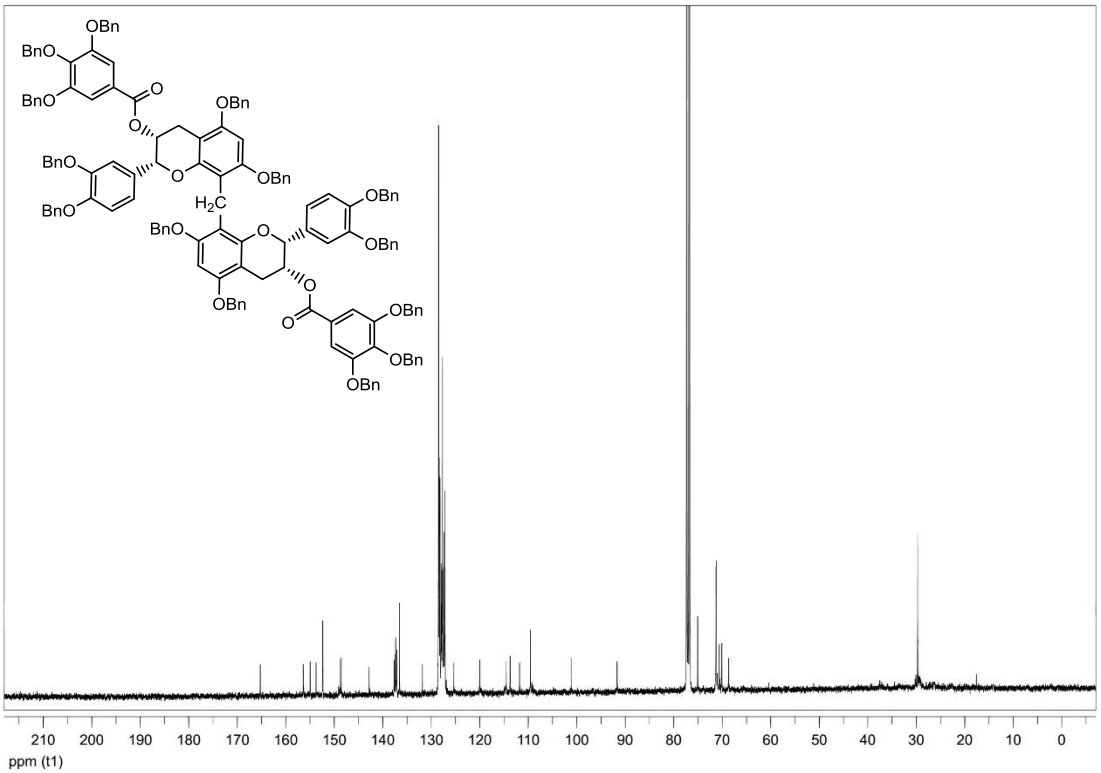


Ester **19**

^{1}H NMR (400 MHz, $CDCl_3$)

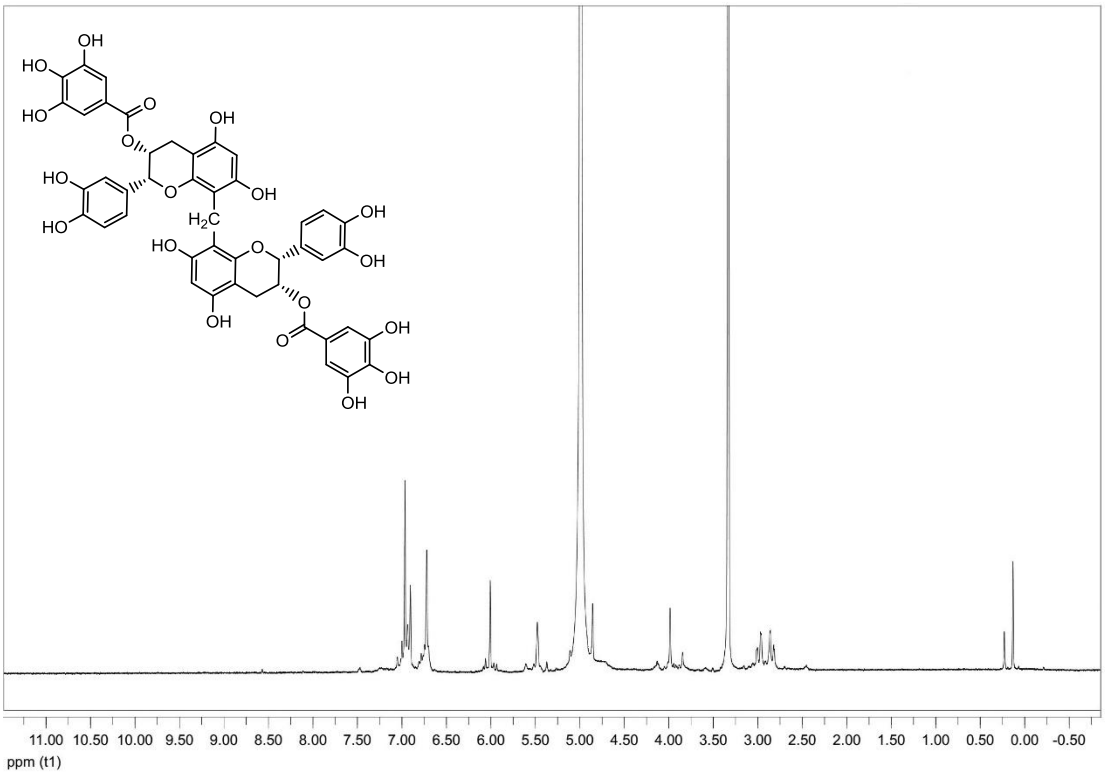


^{13}C NMR (100 MHz, $CDCl_3$)

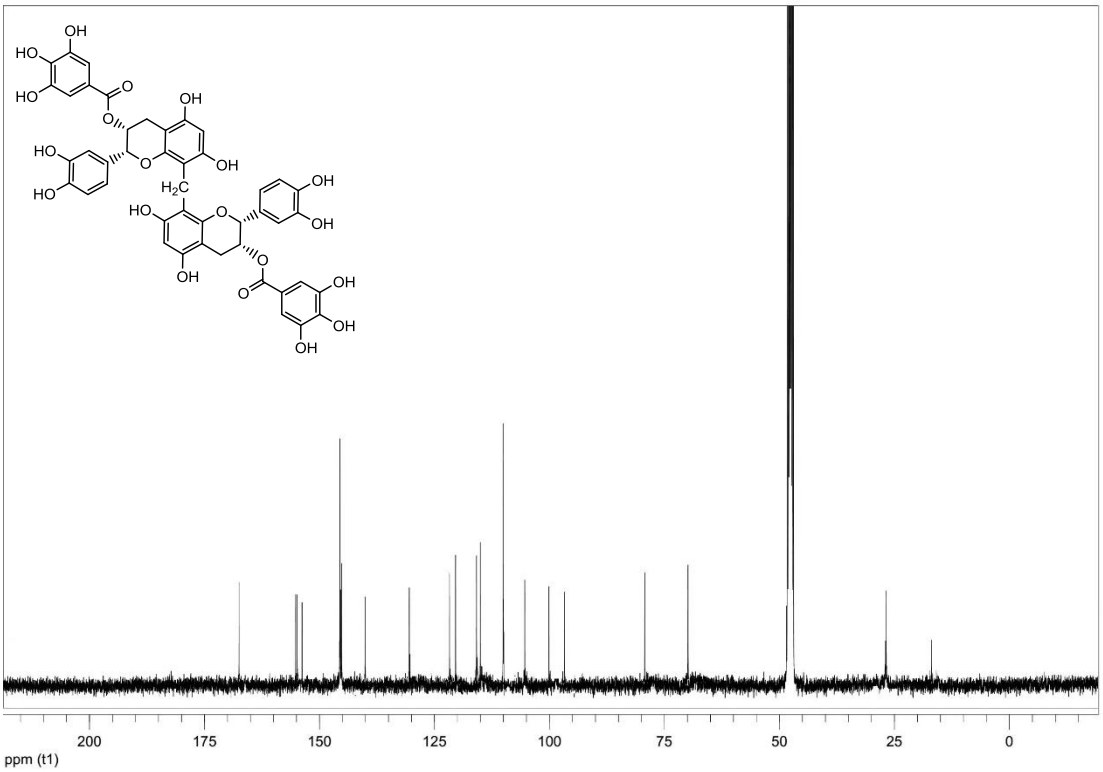


Talienbisflavan A (**1**)

^{1}H NMR (400 MHz, CD_3OD)

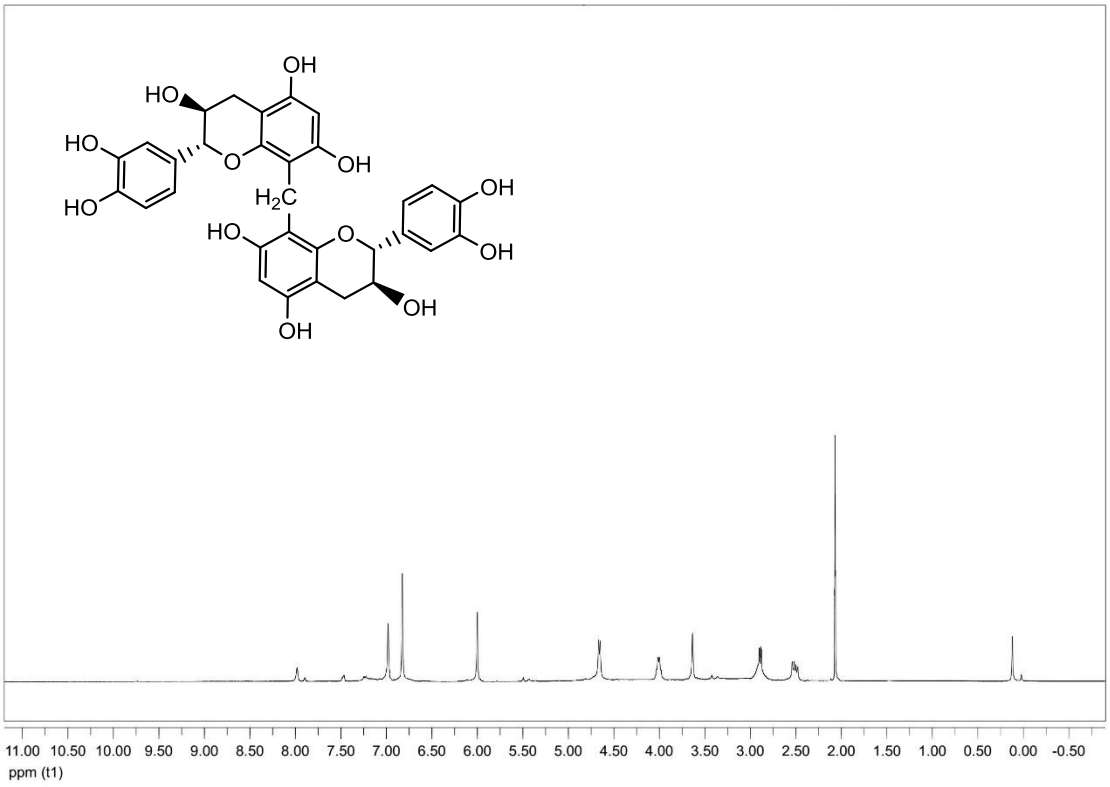


^{13}C NMR (100 MHz, CD_3OD)

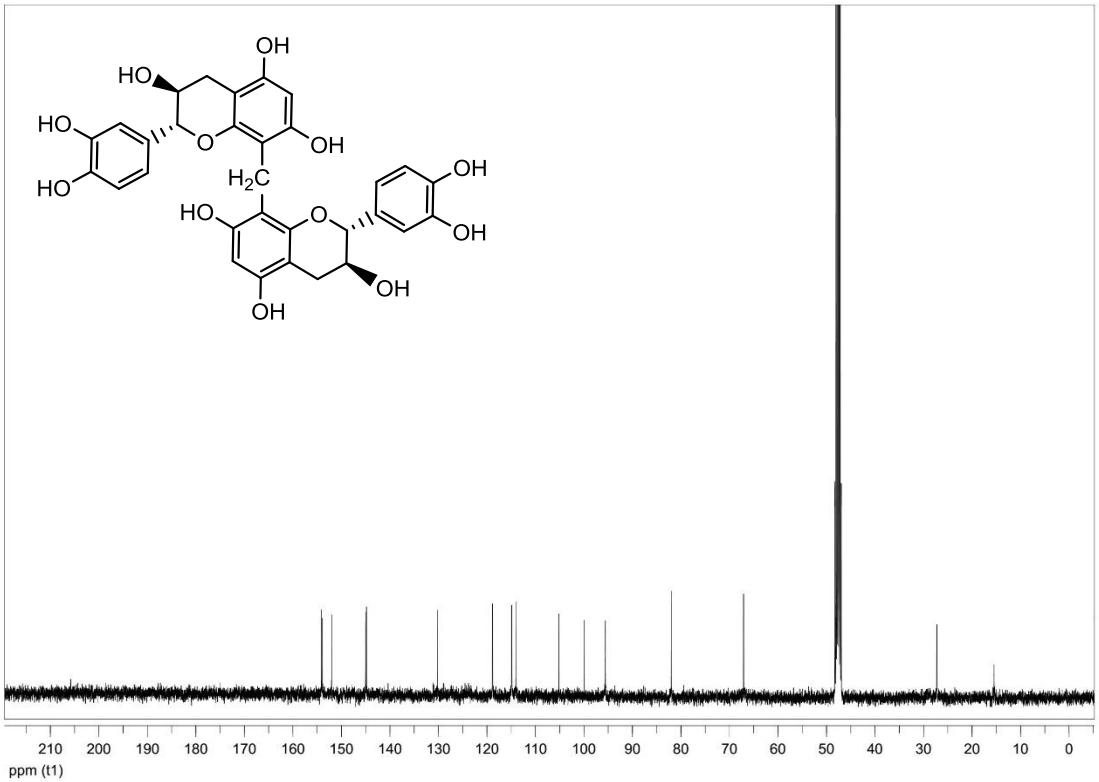


Bis-8,8 ´-catechinylmethane (**2**)

^{1}H NMR [400 MHz, $(CD_3)_2CO$]

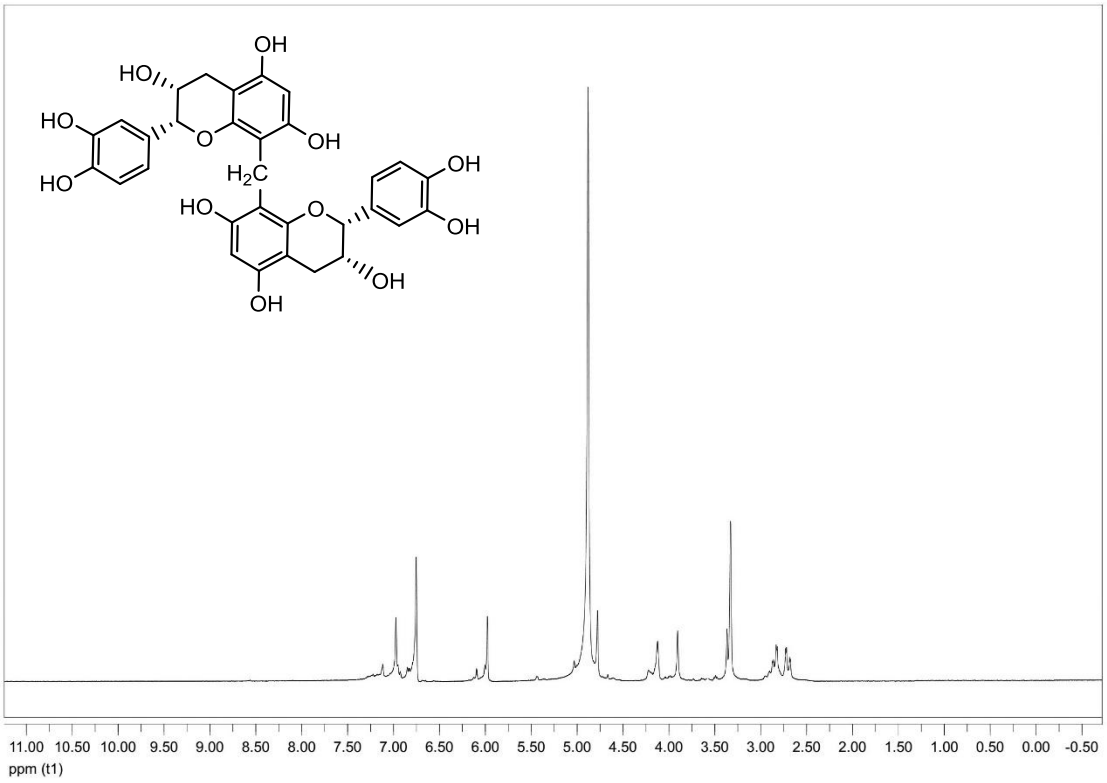


^{13}C NMR (100 MHz, CD_3OD)

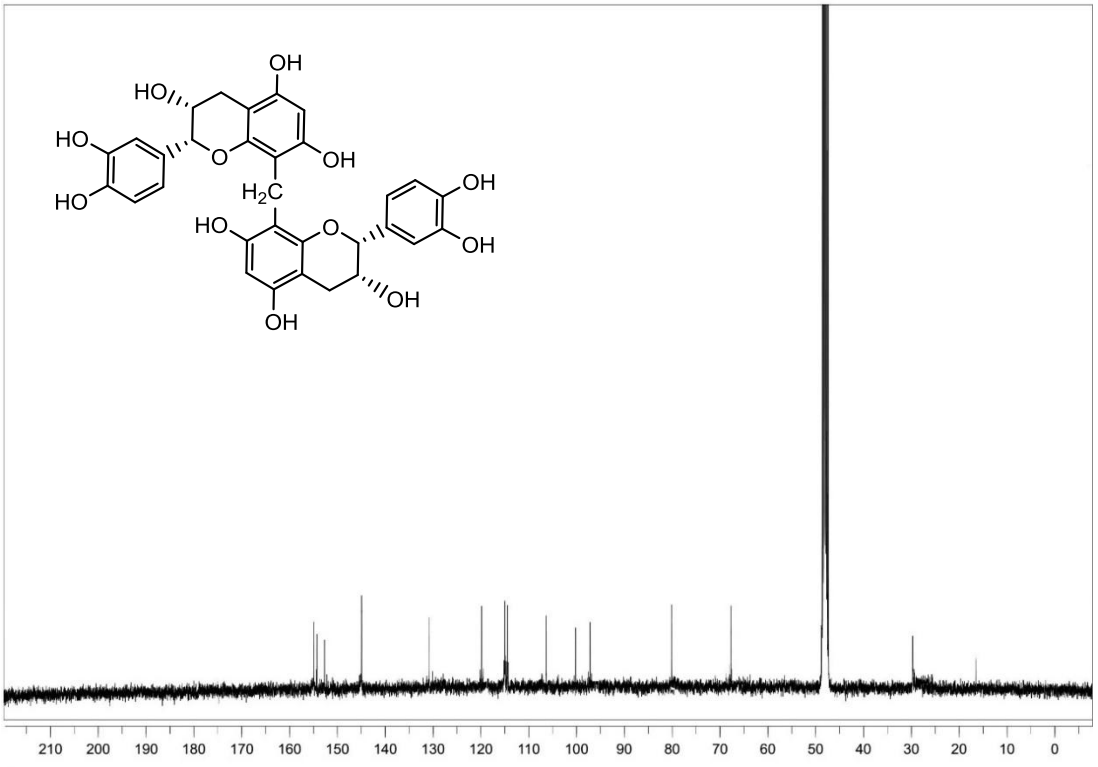


Bis-8,8´-epicatechinylmethane (**3**)

^{1}H NMR (400 MHz, CD_3OD)

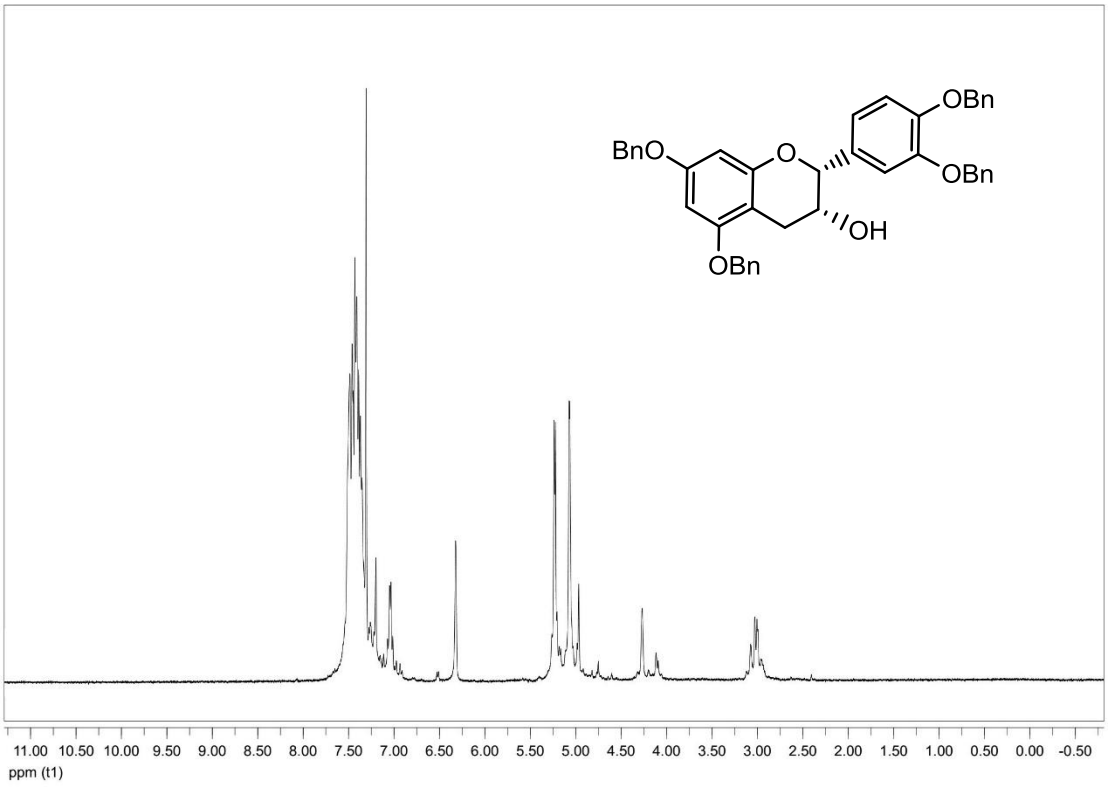


^{13}C NMR (100 MHz, CD_3OD)

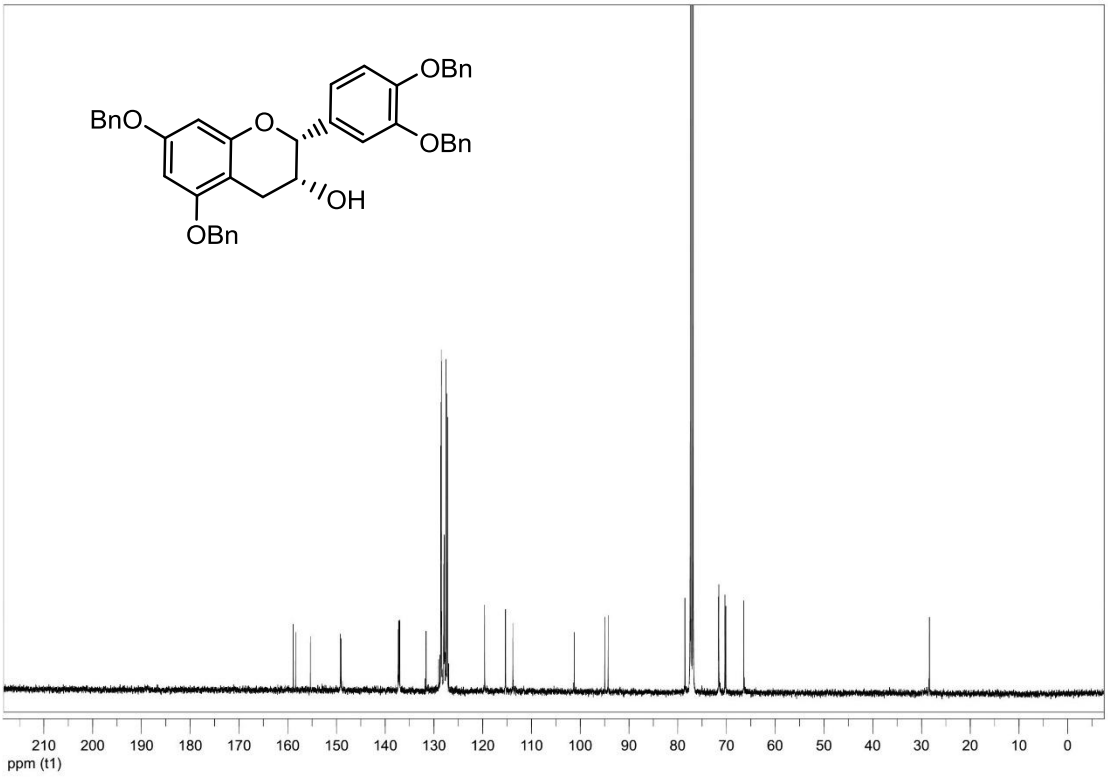


Tetra-*O*-benzyl epicatechin (**20**)

^{1}H NMR (400 MHz, $CDCl_3$)

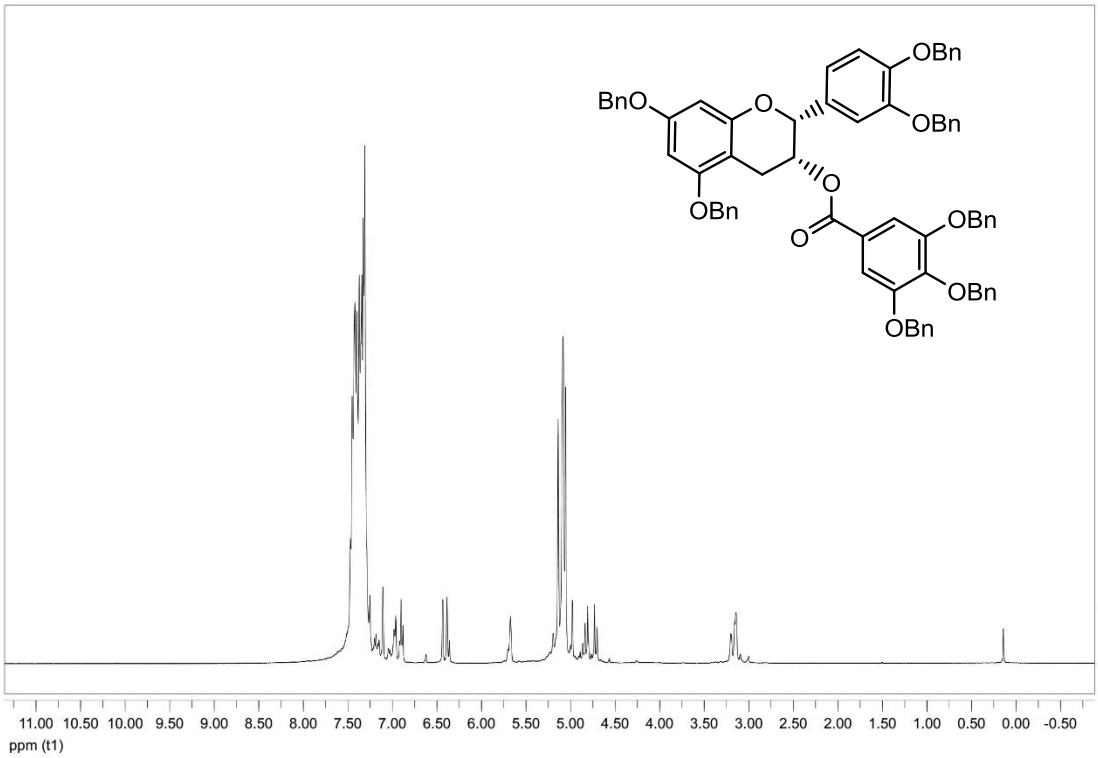


^{13}C NMR (100 MHz, $CDCl_3$)



Ester **21**

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)