
Supporting Information

Total synthesis of antiallergic bicyclic peptide seongsanamide A

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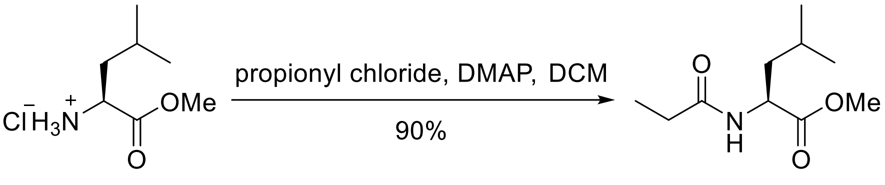
I. General Information

All reactions were conducted in flame-dried or oven-dried glassware under an atmosphere of dry nitrogen or argon. Oxygen and/or moisture sensitive solids and liquids were transferred appropriately. Concentration of solutions in *vacuo* was accomplished using a rotary evaporator fitted with a water aspirator. All reaction solvents were purified before use: Tetrahydrofuran was distilled from sodium. Toluene was distilled over molten sodium metal. Dichloromethane, dimethylformamide, diethylamine, triethylamine and diisoproylethylamine were distilled from CaH_2. Methanol was distilled from Mg/I_2. Flash chromatography was performed using the indicated solvents on E. Qingdao silica gel 60 (230 – 400 mesh ASTM). TLC was carried out using pre-coated sheets (Qingdao silica gel 60-F250, 0.2 mm). Compounds were visualized with UV light, iodine, *p*-anisaldehyde stain, ceric ammonium molybdate stain, or phosphomolybdic acid in EtOH. ^1H NMR spectra were recorded on Bruker Bruker Avance 300 MHz, Avance 400 MHz or Avance 500 MHz spectrometers. Chemical shifts were reported in parts per million (ppm), relative to either a tetramethylsilane (TMS) internal standard or the signals due to the solvent. The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets; other combinations are derived from those listed above. Coupling constants (*J*) are reported in Hertz. High resolution mass spectra were measured on ABI Q-star Elite. ^1H Nuclear magnetic resonance spectra were recorded using a 300 MHz, a 400 MHz or a 500 MHz spectrometer. Coupling constants are reported in Hertz (Hz) for corresponding solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm), Methonal-d_4 δ_H (3.31 ppm) and DMSO-d_6 δ_H (2.50 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using a 75 MHz, a 101 MHz or a 126 MHz spectrometer for corresponding solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CDCl_3$ δ_C (77.16 ppm), Methonal-d_4 δ_C (49.00 ppm) and DMSO-d_6 δ_C (39.52 ppm). Optical rotations were recorded on a Rudolph AutoPol-I polarimeter at 589 nm, 100 mm cell at 25 °C. Data were reported as follows: optical rotation (*c* (g/100 mL), solvent).

II. Experimental Details and Spectral Data



6 **7**

To a solution of **6** (10 g, 68.9, 1.0 eq.) in DCM (200 mL, 0.35 M) at 0 °C was added Et_3N (28.9 mL, 206.7 mmol, 3.0 eq.), followed by the consecutive addition of propionyl chloride (7.85 mL, 89.6 mmol, 1.3 eq.), and DMAP (843.0 mg, 6.9 mmol, 0.10 eq.). The mixture was stirred at room temperature for 8 h, quenched with saturated aqueous solution of NH_4Cl (300 mL) and then extracted with ethyl acetate (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:2 ethyl acetate/hexanes) to furnish the amide **7** in 90% yield (12.5 g, 62.0 mmol) as a white amorphous solid.

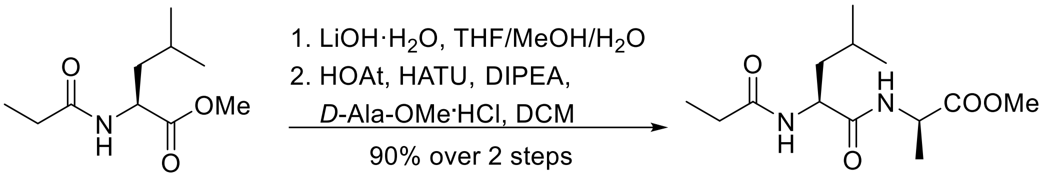
TLC: $R_f = 0.30$ (silica gel, ethyl acetate/hexanes = 1:2), PMA stain.

$[\alpha]_D^{25} = +1.30$ (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, *J* = 8.3 Hz, 1H), 4.58 – 4.44 (m, 1H), 3.60 (s, 3H), 2.14 (q, *J* = 7.6 Hz, 2H), 1.60 – 1.45 (m, 2H), 1.49 – 1.36 (m, 1H), 1.03 (t, *J* = 7.6 Hz, 3H), 0.82 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 173.7, 52.0, 50.5, 41.3, 29.2, 24.7, 22.7, 21.8, 9.6.

HRMS (ESI, *m/z*): calculated for $C_{10}H_{20}NO_3^+$ $[M + H]^+$: 202.1438, found 202.1435.



7 **8**

To a solution of **7** (4.2 g, 20.6 mmol, 1.0 eq.) in THF/H_2O/MeOH (50 mL/50 mL/50 mL, 0.14 M) was added $LiOH·H_2O$ (2.6 g, 61.0 mmol, 3.0 eq.) at 0 °C. After being stirred for 5 h at room temperature, the organic solvents were evaporated. The reaction mixture was diluted with water (20 mL), acidified to pH 1−2 with HCl (1.0 M in water), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo* to afford the crude acid, which was used directly in the next step without further purification.

To a solution of the crude acid in DCM (100 mL) at 0 °C was added *D*-Ala-OMe·HCl (3.2 g, 22.7 mmol, 1.1 eq.), followed by consecutive addition of DIPEA (21.6 mL, 124 mmol, 6.0 eq.), HATU (11.8 g, 31.0 mmol, 1.5 eq.) and HOAt (2.8 g, 20.7 mmol, 1.0 eq.). The reaction mixture was stirred overnight at room temperature, quenched with 4% citric acid aqueous solution (40 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:1 ethyl acetate/hexanes) to furnish dipeptide **8** in 90% yield over two steps (5.0 g, 18.5 mmol) as a white amorphous solid.

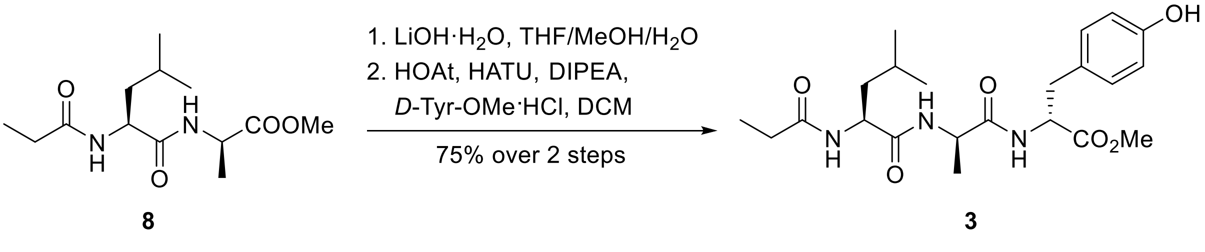
TLC: $R_f = 0.35$ (silica gel, ethyl acetate/hexanes = 3:1), PMA stain.

$[\alpha]_D^{27}$ = -57.50 (c 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.5 Hz, 1H), 6.45 (d, *J* = 8.3 Hz, 1H), 4.67 – 4.34 (m, 2H), 3.68 (s, 3H), 2.20 (q, *J* = 7.5 Hz, 2H), 1.68 – 1.56 (m, 2H), 1.55 – 1.46 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 173.2, 172.2, 52.4, 51.4, 48.1, 41.2, 29.5, 24.9, 23.0, 22.3, 18.1, 9.9.

HRMS (ESI, *m/z*): calculated for $C_{13}H_{24}N_2NaO_4^+$ $[M + H]^+$: 295.1628, found 295.1625.



To a solution of **8** (5.0 g, 18.5 mmol, 1.0 eq.) in THF/H_2O/MeOH (50 mL/50 mL/50 mL, 0.12 M) was added LiOH·H_2O (2.3 g, 55.5 mmol, 3.0 eq.) at 0 °C. After being stirred for 4 h at room temperature, the organic solvents were evaporated. The reaction mixture was diluted with water (30 mL), acidified to pH 1−2 with HCl (1.0 M in water), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo* to afford the crude acid, which was used directly in the next step without further purification.

To a solution of the crude acid in DCM (100 mL) at 0 °C was added *D*-Tyr-OMe·HCl (3.2 g, 20.4 mmol, 1.1 eq.), followed by consecutive addition of DIPEA (19.3 mL, 111 mmol, 6.0 eq.), HATU (10.6 g, 27.8 mmol, 1.5 eq.) and HOAt (2.5 g, 18.5 mmol, 1.0 eq.). The reaction mixture was stirred overnight at room temperature, quenched with 4% citric acid aqueous solution (40 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 4:1 ethyl acetate/hexanes) to furnish the tripeptide **3** in 75% yield over two steps (6.8 g, 15.7 mmol) as a white amorphous solid.

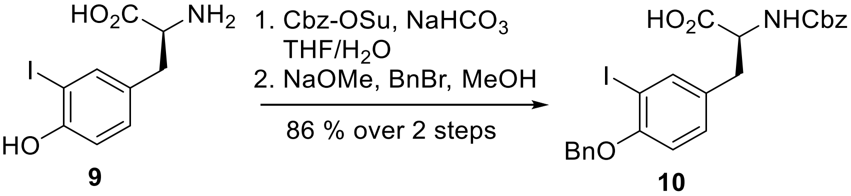
TLC: $R_f = 0.35$ (silica gel, ethyl acetate/hexanes = 4:1), PMA stain.

$[\alpha]_D^{27} = -1.85$ (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 6.1 Hz, 1H), 7.32 – 7.17 (m, 1H) 6.91 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 4.79 (td, *J* = 8.0, 4.8 Hz, 1H), 4.66 (q, *J* = 7.7 Hz, 1H), 4.63 – 4.51 (m, 1H), 3.69 (s, 3H), 3.06 (dd, *J* = 14.1, 4.7 Hz, 1H), 2.85 (dd, *J* = 13.9, 7.8 Hz, 1H), 2.53 (brs, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.61 – 1.56 (m, 2H), 1.56 – 1.50 (m, 1H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.6 Hz, 3H), 0.92 – 0.89 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 172.4, 172.2, 172.1, 155.9, 130.5, 127.1, 115.7, 53.7, 52.5, 51.7, 49.0, 42.0, 37.6, 29.5, 24.9, 23.1, 22.4, 18.3, 9.9.

HRMS (ESI, *m/z*): calculated for $C_{22}H_{33}N_3NaO_6^+$ $[M + Na]^+$: 458.2262, found 458.2258.



To a solution of **9** (4.0 g, 13.0 mmol, 1.0 eq.) in THF/H_2O (15 mL/45 mL, 0.22 M) was added $NaHCO_3$(s) (2.2 g, 26.0 mmol, 2.0 eq.), followed by addition of Cbz-OSu (3.2 g, 13.0 mmol, 1.0 eq.) at 0 °C. After being stirred for 10 h at room temperature, the organic solvent was evaporated. The reaction mixture was diluted with water (30 mL), acidified to pH 1−2 with HCl (1.0 M in water), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo* to afford the crude acid, which was used directly in the next step without further purification.

To a solution of the crude acid (5.4 g, 12.4 mmol, 1.0 eq.) in MeOH (100 mL, 0.12 M) was added NaOMe (24.8 mL, 24.8 mmol, 2.2 eq., 1 M in MeOH), followed by dropwise addition of BnBr (2.2 mL, 18.6 mmol, 1.5 eq.) at 0 °C. After being stirred for 12 h at room temperature, the organic solvent was evaporated. The reaction mixture was diluted with water (50 mL), acidified to pH 1−2 with HCl (1.0 M in water), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:2 ethyl acetate/hexanes) to furnish the titled compound **10** in 86% yield over two steps (5.4 g, 12.4 mmol) as a white solid.

TLC: $R_f = 0.30$ (silica gel, ethyl acetate/hexanes = 1:2), UV & PMA stain.

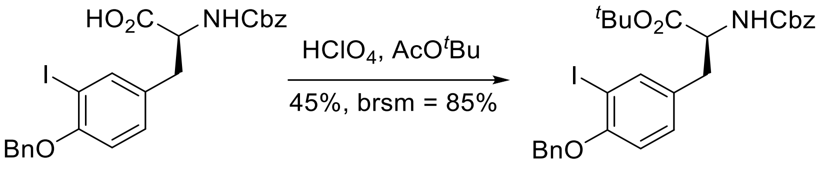
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = +9.07 (c 1.0, MeOH).

<u>^{1}H NMR</u> (500 MHz, $CDCl_3$) δ 10.16 (brs, 1H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.43 – 7.31 (m, 8H), 7.09 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.33 (d, *J* = 8.1 Hz, 1H), 5.24 – 4.92 (m, 4H), 4.69 – 4.66 (m, 1H), 3.15 (dd, *J* = 14.2, 5.4 Hz, 1H), 3.01 (dd, *J* = 14.2, 6.6 Hz, 1H).

<u>^{13}C NMR</u> (126 MHz, $CDCl_3$) δ 176.0, 156.6, 156.0, 140.4, 136.5, 136.1, 130.4, 130.2, 128.7, 128.7, 128.4, 128.2, 128.0, 127.1, 112.7, 87.0, 71.0, 67.4, 54.8, 36.6.

<u>M.P.</u> 108 °C - 110 °C.

<u>HRMS</u> (ESI, *m/z*): calculated for $C_{17}H_{16}INNaO_5^+$ $[M + Na]^+$: 554.0435, found 554.0428.



10 **11**

To a solution of **10** (5.4 g, 12.4 mmol, 1.0 eq.) in AcO*t*Bu (60 mL, 0.21 M) was added $HClO_4$ (2.5 mL, 18.6 mmol, 1.5 eq.) at 0 °C. After being stirred for 10 h at room temperature, the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:10 ethyl acetate/hexanes) to furnish ester **11** in 45% yield (3.3 g, 5.6 mmol) as a white solid.

TLC: $R_f = 0.30$ (silica gel, ethyl acetate/hexanes = 1:10), UV & PMA stain.

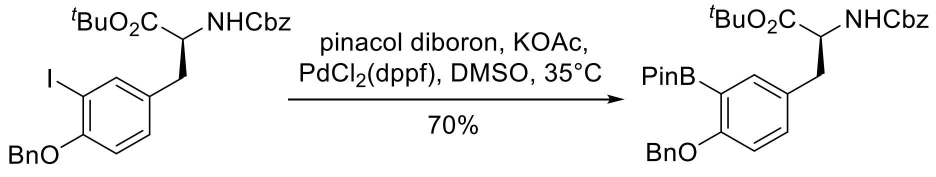
$[\alpha]_D^{25} = +5.20$ (c 1.0, $CHCl_3$).

<u>^{1}H NMR</u> (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.44 – 7.29 (m, 8H), 7.08 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 5.42 (d, *J* = 8.0 Hz, 1H), 5.19 – 5.06 (m, 4H), 4.65 – 4.36 (m, 1H), 3.01 (d, *J* = 6.0 Hz, 2H), 1.44 (s, 9H).

<u>^{13}C NMR</u> (126 MHz, $CDCl_3$) δ 170.3, 156.3, 155.6, 140.4, 136.5, 136.4, 130.7, 130.5, 128.5, 128.5, 128.1, 128.1, 127.9, 127.0, 112.5, 86.7, 82.5, 70.9, 66.9, 55.3, 37.0, 28.0.

<u>M.P.</u> 98 °C - 100 °C.

<u>HRMS</u> (ESI, *m/z*): calculated for $C_{28}H_{30}INNaO_5^+$ $[M + Na]^+$: 610.1061, found 610.1058.



11 **12**

To a solution of **11** (2.6 g, 5.6 mmol, 1.0 eq.) in DMSO (25 mL, 0.22 M) was added a suspension of potassium acetate (1.6 g, 16.8 mmol, 3.0 eq.) and bis(pinacolate) diboron (1.7 g, 6.7 mmol, 1.2 eq.) and $PdCl_2$(dppf) (327.6 mg, 0.448 mmol, 0.080 eq.) at room temperature. After being stirred for 12 h at 35 °C, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:10 ethyl acetate/hexanes) to furnish **12** in 70% yield (2.6 g, 4.5 mmol) as a colorless liquid.

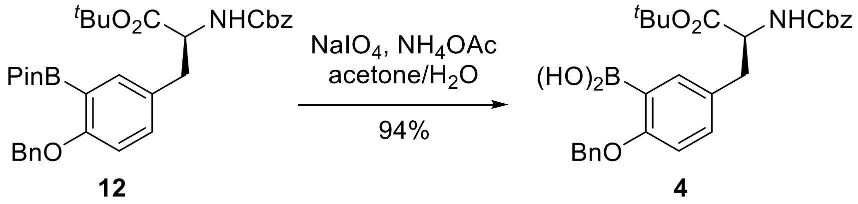
TLC: R_f = 0.30 (silica gel, ethyl acetate/hexanes = 1:10), UV & PMA stain.

$[\alpha]_D^{25}$ = +30.43 (c 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 6.7 Hz, 2H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.45 – 7.28 (m, 8H), 7.18 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 5.25 (d, *J* = 8.1 Hz, 1H), 5.10 (d, *J* = 3.1 Hz, 4H), 4.51 (dt, *J* = 8.1, 5.8 Hz, 1H), 3.14 – 2.88 (m, 2H), 1.42 (s, 9H), 1.35 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 162.5, 155.7, 138.0, 137.7, 136.5, 133.7, 128.6, 128.2, 128.1, 128.1, 127.9, 127.4, 126.8, 112.2, 83.5, 83.5, 82.3, 70.1, 66.9, 55.4, 37.5, 28.1, 25.0, 25.0.

HRMS (ESI, *m/z*): calculated for $C_{28}H_{30}INNaO_5^+$ $[M + Na]^+$: 610.2947, found 610.2951.



To a solution of **12** (2.6 g, 4.5 mmol, 1.0 eq.) in acetone/H_2O (20 mL/20 mL, 0.11 M) was added NH_4OAc (2.5 mL, 18.6 mmol, 1.5 eq.) and $NaIO_4$ at 0 °C. After being stirred at room temperature for 10 h, acetone was removed in *vacuo*, and the remaining solution was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:3 ethyl acetate/hexanes) to furnish arylboronic acid **4** in 94% yield (2.2 g, 4.3 mmol) as a white amorphous solid.

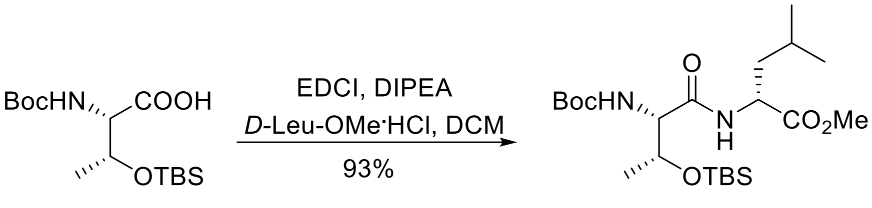
TLC: R_f = 0.35 (silica gel, ethyl acetate/hexanes = 1:2), UV & PMA stain.

$[\alpha]_D^{25}$ = +26.93 (c 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.4 Hz, 1H), 7.44 – 7.37 (m, 4H), 7.41 – 7.27 (m, 6H), 7.20 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.08 (s, 2H), 5.32 (d, *J* = 8.0 Hz, 1H), 5.10 (s, 4H), 4.62 – 4.40 (m, 1H), 3.07 –3.05 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 163.0, 155.8, 138.3, 136.6, 136.1, 133.9, 129.1, 129.0, 128.7, 128.6, 128.2, 128.2, 127.8, 111.4, 82.6, 70.9, 66.9, 55.4, 37.5, 28.1.

HRMS (ESI, *m/z*): calculated for $C_{28}H_{32}BNN_aO_7^+$ $[M + Na]^+$: 528.2164, found 528.2170.



13 **14**

To a solution of compound **13** (5.0 g, 15.0 mmol, 1.0 eq.) in DCM (100 mL, 0.15 M) at 0 °C was added *D*-Leu-OMe·HCl (2.4 g, 16.5 mmol, 1.1 eq.), followed by addition of DIPEA (15.7 mL, 90 mmol, 6.0 eq.), EDCI (3.5 g, 18 mmol, 1.2 eq.). The reaction mixture was stirred overnight at room temperature, quenched with 4% citric acid aqueous solution (20 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:10 ethyl acetate/hexanes) to furnish dipeptide **14** in 93% (6.4 g, 13.9 mmol) as a colorless oil.

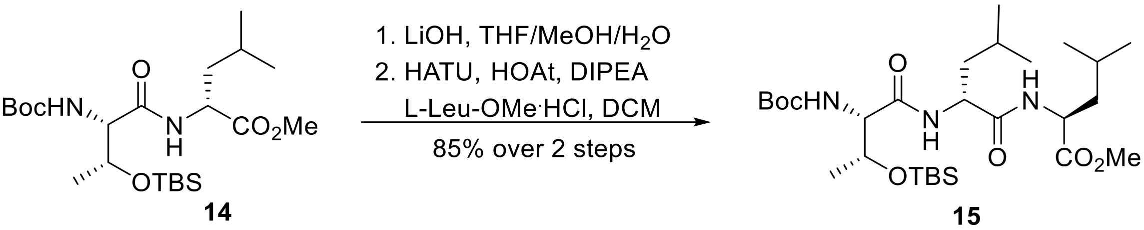
TLC: R_f = 0.30 (silica gel, ethyl acetate/hexanes = 1:10), PMA stain.

$[\alpha]_D^{24}$ = +12.70 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.3 Hz, 1H), 5.44 (d, *J* = 6.4 Hz, 1H), 4.62 (td, *J* = 8.7, 4.9 Hz, 1H), 4.31 (qd, *J* = 6.3, 3.0 Hz, 1H), 4.10 (dd, *J* = 6.9, 3.2 Hz, 1H), 3.68 (s, 3H), 1.71 – 1.57 (m, 2H), 1.56 – 1.46 (m, 1H), 1.42 (s, 9H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 2.6 Hz, 3H), 0.89 (d, *J* = 2.8 Hz, 3H), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 169.5, 155.7, 79.9, 68.3, 59.2, 52.3, 50.7, 41.8, 28.4, 25.8, 24.8, 22.9, 21.8, 18.6, 17.9, -4.7, -5.0.

HRMS (ESI, *m/z*): calculated for $C_{22}H_{44}N_2NaO_6Si^+$ $[M + Na]^+$: 483.2861, found 483.2868.



To a solution of **14** (6.4 g, 13.9 mmol, 1.0 eq.) in THF/H_2O/MeOH (30 mL/30 mL/30 mL, 0.15 M) was added LiOH·H_2O (1.7 g, 41.7 mmol, 3.0 eq.) at 0 °C. After being stirred for 4 h at room temperature, the organic solvents were evaporated. The reaction mixture was diluted with water (30 mL), acidified to pH 2−3 with HCl (1.0 M in water), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo* to afford the crude acid, which was used directly in the next step without further purification.

To a solution of the above crude acid in DCM (100 mL) at 0 °C was added *L*-Leu-OMe·HCl (2.8 g, 15.3 mmol, 1.1 eq.), followed by addition of DIPEA (14.5 mL, 83.4 mmol, 6.0 eq.), HATU (7.9 g, 20.8 mmol, 1.5 eq.) and HOAt (1.9 g, 13.9 mmol, 1.0 eq.). The reaction mixture was stirred overnight at room temperature, quenched with 4% citric acid aqueous solution (40 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:6 ethyl acetate/hexanes) to furnish tripeptide **15** in 85% yield over two steps (6.8 g, 11.8 mmol) as a white amorphous solid.

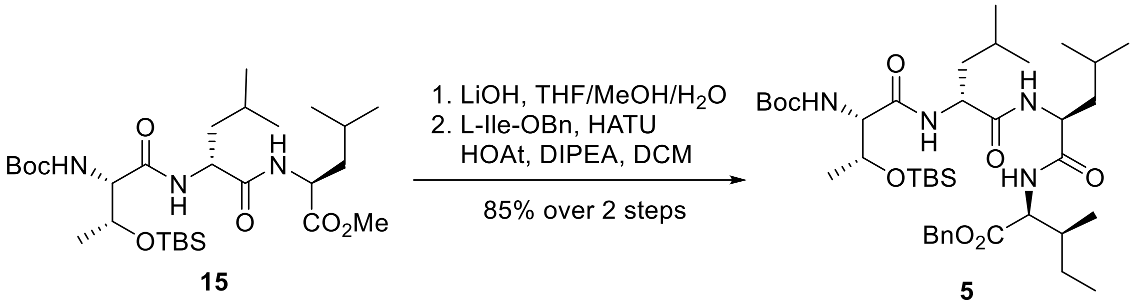
TLC: $R_f = 0.35$ (silica gel, ethyl acetate/hexanes = 1:6), PMA stain.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}} = +24.60$ (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 7.9 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 1H), 5.48 (d, *J* = 6.3 Hz, 1H), 4.60 (td, *J* = 8.4, 5.1 Hz, 1H), 4.50 (td, *J* = 8.3, 4.7 Hz, 1H), 4.31 (dt, *J* = 9.9, 4.8 Hz, 1H), 4.11 (dd, *J* = 6.5, 3.4 Hz, 1H), 3.72 (s, 3H), 1.74 – 1.52 (m, 6H), 1.46 (s, 9H), 1.10 (d, *J* = 6.3 Hz, 3H), 0.96 – 0.90 (m, 12H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 171.4, 169.9, 155.5, 79.8, 68.3, 59.4, 52.2, 51.6, 50.7, 41.5, 41.3, 28.3, 25.8, 24.9, 24.5, 23.0, 22.8, 21.9, 21.8, 18.7, 17.8, -4.8, -5.0.

HRMS (ESI, *m/z*): calculated for $C_{28}H_{55}N_3NaO_7Si^+$ $[M + Na]^+$: 596.3701, found 596.3768.



To a solution of **15** (6.8 g, 11.8 mmol, 1.0 eq.) in THF/H_2O/MeOH (30 mL/30 mL/30 mL, 0.13 M) was added LiOH·H_2O (1.5 g, 35.4 mmol, 3.0 eq.) at 0 °C. After being stirred for 5 h at room temperature, the organic solvents were evaporated. The reaction mixture was diluted with water (30 mL), acidified to pH 2−3 with HCl (1.0 M in water), and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo* to afford the crude acid, which was used directly in the next step without further purification.

To a solution of the crude acid in DCM (100 mL) at 0 °C was added *L*-Ile-OBn (2.9 g, 13 mmol, 1.1 eq.), followed by addition of DIPEA (12.3 mL, 70.8 mmol, 6.0 eq.), HATU (6.7 g, 17.7 mmol, 1.5 eq.) and HOAt (1.6 g, 11.8 mmol, 1.0 eq.). The reaction mixture was stirred overnight at room temperature, quenched with 4% citric acid aqueous solution (40 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (80 mL), brine (80 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:6 ethyl acetate/hexanes) to furnish tetrapeptide **5** in 85% yield over two steps (6.8 g, 11.8 mmol) as a white amorphous solid.

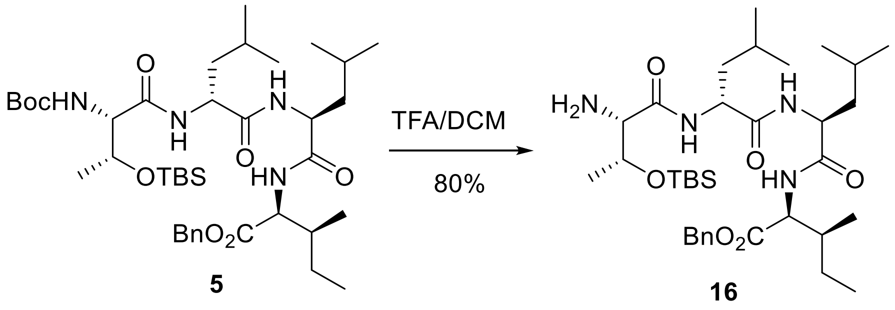
TLC: $R_f = 0.35$ (silica gel, ethyl acetate/hexanes = 1:6), UV & PMA stain.

$[\alpha]_D^{25}$ = +8.80 (c 1.0, $CHCl_3$).

<u>^{1}H NMR</u> (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 7.00 (d, *J* = 6.5 Hz, 1H), 6.71 (d, *J* = 6.9 Hz, 1H), 6.67 (d, *J* = 7.5 Hz, 1H), 5.50 (d, *J* = 5.8 Hz, 1H), 5.18 (d, *J* = 12.3 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 4.58 (dd, *J* = 8.6, 4.7 Hz, 1H), 4.42 (td, *J* = 8.8, 5.6 Hz, 2H), 4.23 (dt, *J* = 10.3, 5.0 Hz, 1H), 4.11 – 4.06 (m, 1H), 1.88 (dqt, *J* = 9.2, 6.8, 4.6 Hz, 1H), 1.74 – 1.48 (m, 6H), 1.43 (s, 9H), 1.37 – 1.29 (m, 1H), 1.16 – 1.09 (m, 1H), 1.06 (d, *J* = 6.3 Hz, 3H), 0.94 – 0.86 (m, 21H), 0.84 (d, *J* = 3.5 Hz, 3H), 0.82 (d, *J* = 3.0 Hz, 2H), 0.14 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 171.7, 171.5, 170.2, 155.5, 135.4, 128.7, 128.5, 128.4, 79.8, 68.4, 67.1, 59.2, 56.6, 52.1, 52.0, 40.8, 40.7, 37.9, 28.5, 25.9, 25.0, 24.9, 24.6, 23.1, 23.0, 22.1, 21.7, 18.3, 18.0, 15.6, 11.7, -4.7, -4.8.

HRMS (ESI, *m/z*): calculated for $C_{40}H_{70}N_4NaO_8Si^+$ [M + Na] $^+$: 785.4855, found 785.4874.



To a solution of compound **5** (3.0 g, 3.9 mmol, 1.0 eq.) in DCM (10 mL) was added TFA (10 mL, 34.5 eq.) dropwise at 0 °C. After being stirred at room temperature for 10 h, the reaction mixture was concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:4:6% ethyl acetate/hexanes/ triethylamine) to furnish the titled compound **16** in 80% yield (2.1 g, 3.12 mmol) as a yellow colorless oil.

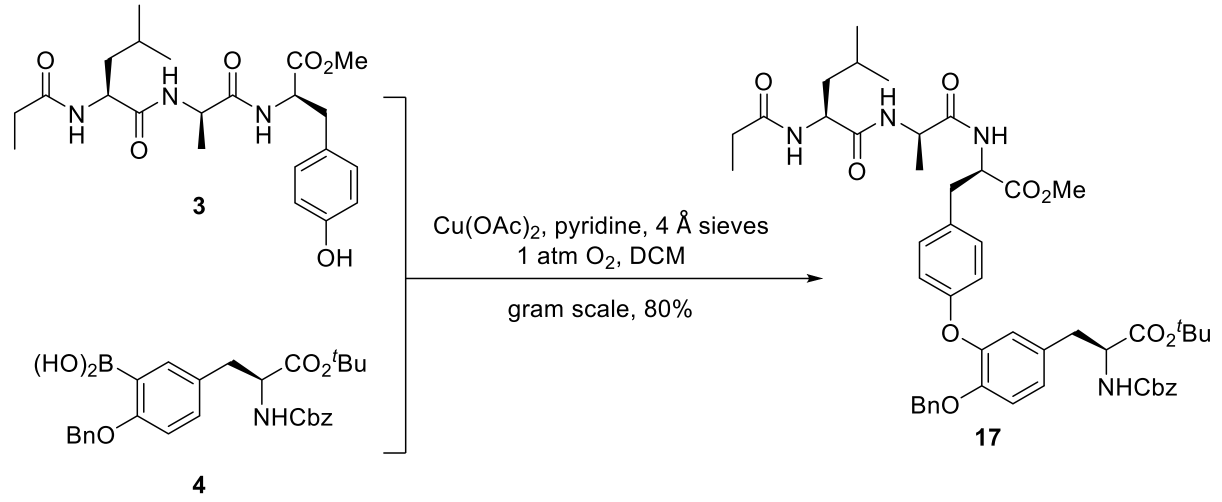
TLC: R_f = 0.35 (silica gel, 1:3:4% ethyl acetate/hexanes/ triethylamine), UV & PMA stain.

$[\alpha]_D^{26}$ = -4.00 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.7 Hz, 1H), 7.40 – 7.24 (m, 5H), 6.67 (d, *J* = 8.5 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 5.18 (d, *J* = 12.3 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 4.58 (dd, *J* = 8.6, 4.9 Hz, 1H), 4.48 – 4.37 (m, 2H), 4.19 (qd, *J* = 6.3, 3.6 Hz, 1H), 3.24 (d, *J* = 3.6 Hz, 1H), 1.89 (dqt, *J* = 9.3, 6.9, 4.7 Hz, 1H), 1.74 – 1.44 (m, 6H), 1.52 – 1.44 (m, 1H), 1.41 – 1.22 (m, 1H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.96 – 0.88 (m, 12H) 0.86 (s, 9H) ,0.84 (d, *J* = 6.6 Hz, 6H), 0.08 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 172.0, 171.6, 171.6, 135.4, 128.7, 128.6, 128.5, 69.9, 67.1, 60.1, 56.6, 52.1, 51.9, 41.2, 41.1, 38.0, 25.9, 25.1, 24.9, 24.8, 23.1, 23.0, 22.1, 21.9, 19.3, 18.0, 15.6, 11.7, -4.5, -4.8.

HRMS (ESI, *m/z*): calculated for $C_{35}H_{62}N_4NaO_6Si^+$ [M + Na]$^+$: 685.4331, found 685.4338.



To a solution of $Cu(OAc)_2$ (273.3 mg, 2.3 mmol, 1.0 eq.) in DCM (30 mL) was added pyridine (0.90 mL, 11.2 mmol, 5.0 eq.) dropwise at 0°C. The suspension was stirred at room temperature for 20 min under O_2 (1 atm). To this solution was added phenol **3** (1.03 g, 2.3 mmol, 1.0 eq.), powdered 4 Å MS (2.0 g), and a slow solution of boronic acid **4** (2.04 g, 4.03 mmol, 1.8 eq.) in DCM (10 mL) over 8 h. After being stirred for additional 12 h at room temperature, the reaction mixture was diluted with ethyl acetate and filtered through a pad of celite. The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 3:1 ethyl acetate/hexanes) to furnish **17** in 80% yield (1.6 g, 1.8 mmol) as a white amorphous solid.

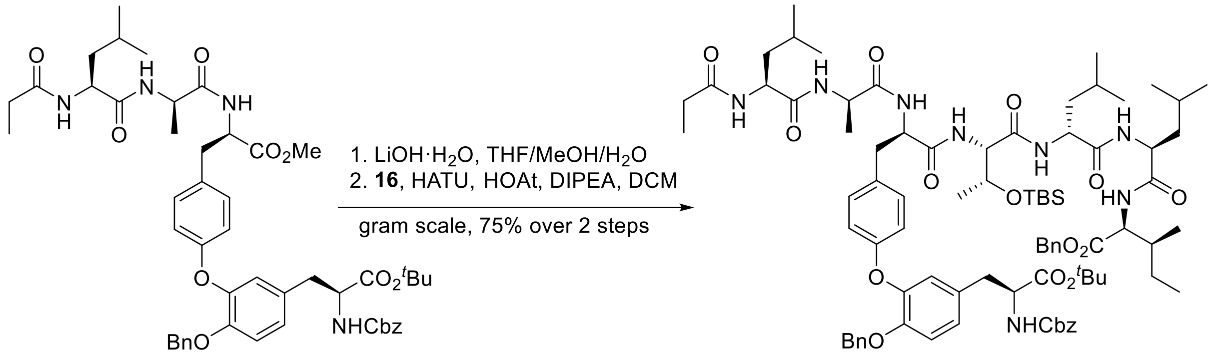
TLC: $R_f = 0.30$ (silica gel, ethyl acetate/hexanes = 3:1), UV & PMA stain.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -21.00 (c 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (d, *J* = 7.5 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.37 – 7.24 (m, 8H), 7.21 (d, *J* = 1.9 Hz, 1H), 7.19 (d, *J* = 1.6 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 1H), 7.04 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.00 (d, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.07 (s, 2H), 5.05 – 4.97 (m, 2H), 4.42 (q, *J* = 7.7 Hz, 1H), 4.33 – 4.23 (m, 2H), 4.19 – 4.05 (m, 1 H), 3.55 (s, 3H), 3.06 – 2.97 (m, 2H), 2.94 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.80 (dd, *J* = 13.9, 9.6 Hz, 1H), 2.14 (qd, *J* = 7.5, 4.8 Hz, 2H), 1.59 (dq, *J* = 7.9, 6.2 Hz, 1H), 1.49 – 1.38 (m, 2H), 1.34 (s, 9H), 1.18 (d, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 173.4, 172.3, 171.9, 171.6, 170.9, 156.8, 155.9, 148.9, 143.7, 137.0, 136.9, 130.8, 130.8, 130.2, 128.2, 128.2, 127.7, 127.6, 127.6, 127.2, 125.9, 122.8, 116.0, 114.8, 80.6, 69.8, 65.4, 56.2, 53.9, 51.6, 51.4, 47.8, 40.5, 35.9, 35.8, 28.2, 27.5, 24.2, 22.9, 21.8, 17.9, 9.7.

HRMS (ESI, *m/z*): calculated for $C_{50}H_{63}N_4O_{11}^+$ $[M + H]^+$: 895.4488, found 895.4479.



17 **2**

To a solution of **17** (1.6 g, 1.8 mmol, 1.0 eq.) in THF/MeOH/H_2O (4 mL/8 mL/4 mL, 0.11 M) was added LiOH·H_2O (226.6 mg, 5.4 mmol, 3.0 eq.) at 0 °C. After being stirred for 30 min at room temperature, the organic solvents were evaporated. The reaction mixture was diluted with water (10 mL), acidified to pH 4-5 with HCl (0.50 M in water), and extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo* to afford the crude acid, which was used directly in the next step without further purification.

To a solution of the above crude acid in DCM (20 mL) at 0 °C was sequentially added amine **16** (1.26 g, 1.9 mmol, 1.05 eq.), DIPEA (1.88 mL, 10.8 mmol, 6.0 eq.), HATU (1.03 g, 2.7 mmol, 1.5 eq.) and HOAt (244.0 mg, 1.8 mmol, 1.0 eq.). The reaction mixture was stirred overnight at room temperature, quenched with 4% citric acid aqueous solution (10 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:1 ethyl acetate/hexanes) to furnish **2** in 75% yield over two steps (2.05 g, 1.35 mmol) as a white amorphous solid.

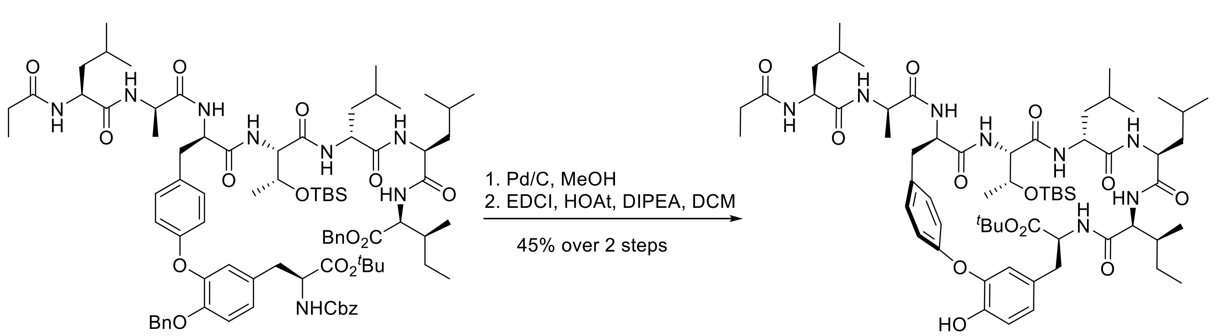
TLC: R_f = 0.35 (silica gel, ethyl acetate/hexanes = 1:1), UV & PMA stain.

$[\alpha]_D^{25}$ = +0.86 (c 1.0, CHCl$_3$).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (d, *J* = 8.0 Hz, 2H), 8.14 (d, *J* = 7.6 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.38 – 7.31 (m, 7H), 7.31 – 7.29 (m, 2H), 7.28 (d, *J* = 4.5 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.20 – 7.17 (m, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.01 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 2H), 5.13 (d, *J* = 12.5 Hz, 1H), 5.07 (d, *J* = 12.5 Hz, 1H), 5.05 (s, 2H), 5.03 – 4.93 (m, 2H), 4.58 (q, *J* = 7.6 Hz, 1H), 4.41 (dt, *J* = 14.7, 8.8 Hz, 2H), 4.26 (dt, *J* = 14.4, 7.6 Hz, 3H), 4.21 (dd, *J* = 7.7, 6.4 Hz, 1H), 4.06 (td, *J* = 8.7, 6.1 Hz, 1H), 3.91 (dd, *J* = 6.3, 3.4 Hz, 1H), 2.93 (dd, *J* = 13.9, 6.2 Hz, 1H), 2.88 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.84 (dd, *J* = 13.9, 8.7 Hz, 1H), 2.76 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.11 (q, *J* = 7.6 Hz, 2H), 1.82 – 1.73 (m, 1H), 1.63 – 1.48 (m, 3H), 1.45 – 1.35 (m, 6H), 1.31 (s, 9H), 1.25 – 1.19 (m, 1H), 1.21 – 1.17 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.89 – 0.73 (m, 36H), 0.01 (s, 3H), 0 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 173.2, 172.3, 172.0, 171.9, 171.4, 171.1, 170.9, 170.6, 168.1, 156.6, 155.9, 148.9, 143.8, 137.0, 136.9, 135.8, 131.2, 130.8, 130.3, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 127.7, 127.6, 127.1, 125.9, 122.7, 115.9, 114.9, 80.6, 69.8, 68.4, 65.8, 65.4, 57.5, 56.6, 56.2, 54.3, 51.2, 51.1, 50.5, 48.0, 41.9, 40.8, 40.7, 36.7, 36.2, 35.9, 28.2, 27.6, 25.7, 24.8, 24.3, 24.1, 24.0, 23.0, 23.0, 22.9, 21.8, 21.7, 21.5, 19.0, 18.1, 17.6, 15.4, 11.1, 9.8, -5.0, -5.1.

HRMS (ESI, *m/z*): calculated for $C_{84}H_{121}N_8O_{16}Si^+$ [M + H]$^+$ 1525.8664, found 1525.8654.



2 **18**

To a solution of compound **2** (100.5 mg, 0.066 mmol, 1.0 eq.) in MeOH (10 mL) was added palladium on charcoal (200.3 mg, 10% Pd, 0.19 mmol, 2.9 eq.) in one portion. The reaction flask was evacuated and purged with H$_2$ three times and then the reaction was stirred at ambient temperature under a hydrogen atmosphere for 10 h. The reaction flask was then evacuated and purged with nitrogen three times. The catalyst was removed by filtration through Celite. The filtrate was concentrated in *vacuo* to give the desired compound which was used directly in the next step without further purification.

To a solution of the above crude compound in DCM (10 mL) at 0 °C was added DIPEA (0.066 mL, 0.396 mmol, 6.0 eq.), EDCI (38.2 mg, 0.2 mmol, 3.0 eq.) and HOAt (27.2 mg, 0.2 mmol, 3.0 eq.). The mixture was stirred overnight at room temperature, quenched with 4% citric acid aqueous solution (5 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 2:1 ethyl acetate/hexanes) to furnish cyclopeptide **18** in 45% yield over two steps (35.4 mg, 0.030 mmol) as a white amorphous solid.

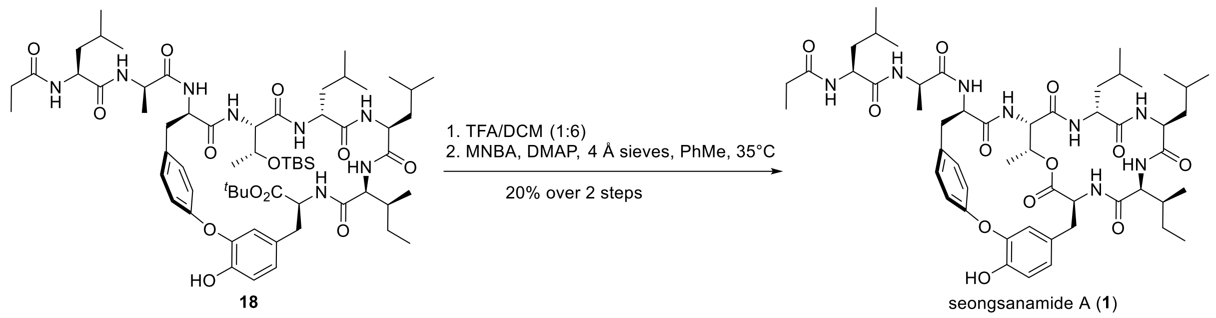
TLC: R_f = 0.35 (silica gel, ethyl acetate/hexanes = 1:1), UV & PMA stain.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{27}}$ = +7.50 (c 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, MeOD-*d*$_4$) δ 7.26 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.79 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.68 (d, *J* = 1.9 Hz, 1H), 4.56 (ddt, *J* = 14.7, 9.2, 4.9 Hz, 2H), 4.50 – 4.35 (m, 5H), 4.34 – 4.23 (m, 1H), 4.15 (d, *J* = 8.2 Hz, 1H), 3.20 (dd, *J* = 13.8, 5.1 Hz, 1H), 3.07 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.95 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.73 (dd, *J* = 14.1, 8.2 Hz, 1H), 2.31 (q, *J* = 7.6 Hz, 2H), 1.87 – 1.73 (m, 1H), 1.73 – 1.61 (m, 4H), 1.63 – 1.50 (m, 7H), 1.42 (s, 9H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.18 – 1.11 (m, 6H), 0.99 – 0.94 (m, 12H), 0.93 (s, 9H), 0.92 – 0.87 (m, 12H), 0.15 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (101 MHz, MeOD-*d*$_4$) δ 177.1, 174.9, 174.7, 173.9, 173.9, 173.3, 172.9, 172.1, 170.9, 157.6, 148.0, 146.3, 132.5, 132.1, 129.7, 125.6, 120.8, 120.6, 117.8, 82.8, 69.8, 59.7, 59.0, 57.0, 56.2, 53.4, 53.0, 52.9, 50.4, 42.3, 42.1, 37.9, 37.9, 37.5, 29.9, 28.3, 26.5, 26.4, 26.0, 26.0, 25.9, 25.8, 23.6, 23.4, 23.4, 22.3, 22.1, 22.0, 20.1, 18.9, 18.1, 16.0, 11.4, 10.5, -4.5, -4.5.

HRMS (ESI, *m/z*): calculated for $C_{62}H_{101}N_8O_{13}Si^+$ $[M + H]^+$ 1193.7252, found 1193.7265.



To a solution of **18** (35.4 mg, 0.030 mmol, 1.0 eq.) in DCM (4 mL) was added TFA (0.67 mL, 9.0 mmol, 300.0 mmol) dropwise at 0 ºC. After being stirred at room temperature for 3 h, the reaction mixture was concentrated in *vacuo* to afford the crude hydroxy acid which was used directly in the next step without further purification.

To a solution of 2-methyl-6-nitrobenzoic anhydride (MNBA, 20.7 mg, 0.060 mmol, 2.0 eq.), DMAP (22.0 mg, 0.18 mmol, 6.0 eq.) and MS 4Å (150 mg) in toluene (5 mL) was slowly added a solution of the above hydroxy acid in PhMe/THF (2.5 mL/2.5 mL) at 35 °C over 8 hours via a syringe pump. After being stirred for additional 12 h at 35 °C, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl (2 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 1:10 MeOH/DCM) to furnish seongsanamide A in 20% yield over two steps (6.0 mg, 0.0060 mmol) as a colorless oil.

TLC: R_f = 0.30 (silica gel, MeOH/DCM = 1:10), UV & PMA stain.

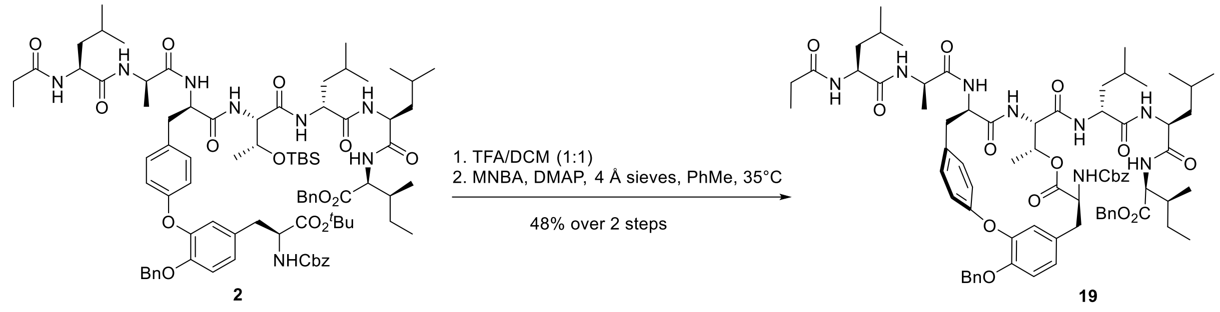
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -11.30 (c 0.1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.26 (d, *J* = 4.4 Hz, 1H), 8.18 (d, *J* = 5.9 Hz, 1H), 8.17 – 8.09 (m, 3H), 8.02 (d, *J* = 7.3 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.20 (brs, 2H), 6.97 (brs, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.65 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 5.14 (q, *J* = 6.1 Hz, 1H), 4.58 (dt, *J* = 10.4, 5.2 Hz, 1H), 4.54 – 4.44 (m, 1H), 4.30 – 4.13 (m, 3H), 3.98 (dt, *J* = 9.9, 6.0 Hz, 1H), 3.69 (t, *J* = 9.6 Hz, 1H), 3.07 – 2.89 (m, 2H), 2.84 – 2.70 (m, 2H), 2.14 (q, *J* = 7.5 Hz, 2H), 1.91 (s, 1H), 1.68 – 1.46 (m, 4H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.35 (td, *J* = 9.3, 8.9, 4.7 Hz, 4H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.6

Hz, 3H), 0.89 (d, *J* = 3.1 Hz, 3H), 0.87 (d, *J* = 3.1 Hz, 3H), 0.86 – 0.73 (m, 18H), 0.38 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 173.3, 172.1, 171.8, 171.7, 171.2, 171.1, 170.4, 169.8, 167.9, 155.7, 146.2, 145.7, 131.8, 130.7, 128.0, 124.4, 120.2, 116.8, 115.8, 69.9, 59.7, 55.8, 55.6, 52.9, 52.5, 51.5, 50.5, 47.3, 41.1, 40.3, 40.2, 37.2, 35.6, 35.2, 28.0, 24.3, 24.2, 24.2, 24.0, 22.8, 22.8, 22.6, 22.2, 21.7, 21.3, 17.8, 16.5, 15.3, 10.1, 9.7.

HRMS (ESI, *m/z*): calculated for $C_{52}H_{77}N_8O_{12}^+$ $[M + H]^+$ 1005.5655, found 1005.5663.



To a solution of compound **2** (100.7 mg, 0.066 mmol, 1.0 eq.) in DCM (2 mL) was added TFA (2.0 mL, 26.9 mmol, 407.0 eq.) dropwise at 0 °C. After being stirred at room temperature for 10 h, the reaction mixture was concentrated in *vacuo* to afford the crude hydroxy acid, which was used directly in the next step without further purification.

To a solution of 2-methyl-6-nitrobenzoic anhydride (MNBA, 45.4 mg, 0.13 mmol, 2.0 eq.), DMAP (48.9 mg, 0.40 mmol, 6.0 eq.) and MS 4Å (300 mg) in toluene (10 mL) was slowly added a solution of the above hydroxy acid in PhMe/THF (2.5 mL/2.5 mL) at 35 °C over 5 h via a syringe pump. After being stirred for 12 h at 35 °C, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (4 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 2:1 ethyl acetate/hexanes) to furnish lactone **19** in 48% yield over two steps (42.8.mg, 0.032 mmol) as a white amorphous solid.

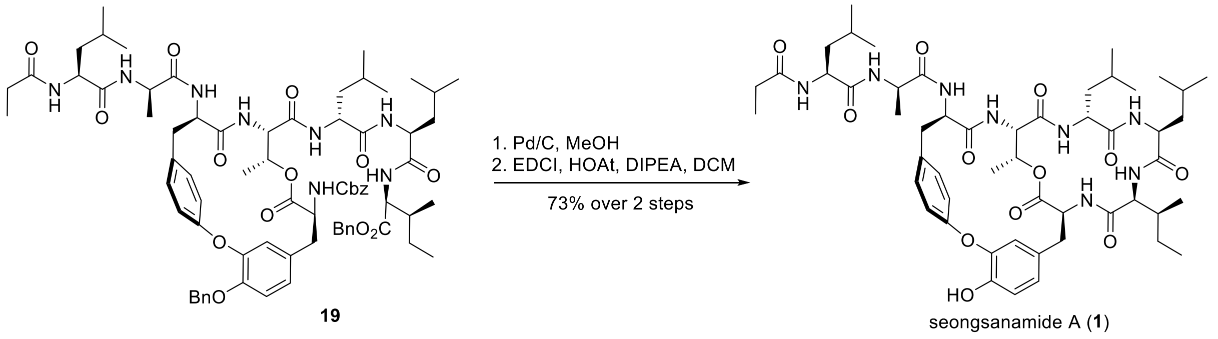
TLC: R$_f$ = 0.30 (silica gel, ethyl acetate/hexanes = 2:1), UV & PMA stain.

$[\alpha]_D^{27}$ = +12.77 (c 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, MeOD-d_4) δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.43 – 7.24 (m, 15H), 7.02 (brs, 2H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.65 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.36 (d, *J* = 2.1 Hz, 1H), 5.20 – 5.16 (m, 4H), 5.15 (d, *J* = 12.7 Hz, 1H), 5.06 (dd, *J* = 12.4, 3.8 Hz, 2H), 4.79 – 4.71 (m, 1H), 4.64 – 4.53 (m, 2H), 4.49 (q, *J* = 6.7 Hz, 1H), 4.45 – 4.32 (m, 4H), 3.17 (dd, *J* = 12.7, 4.1 Hz, 1H), 3.11 – 2.99 (m, 2H), 2.95 (dd, *J* = 14.2, 7.1 Hz, 1H), 2.28 (q, *J* = 7.6 Hz, 2H), 1.86 (dtd, *J* = 9.1, 6.7, 4.4 Hz, 1H), 1.76 – 1.53 (m, 9H), 1.49 – 1.40 (m, 1H), 1.34 (d, *J* = 7.0 Hz, 3H), 1.24 – 1.18 (m, 1H), 1.15 (t, *J* = 7.6 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.96 – 0.83 (m, 21H), 0.75 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, MeOD-d_4) δ 176.7, 175.0, 174.8, 174.3, 174.3, 173.5, 172.7, 171.9, 170.2, 157.7, 157.2, 150.7, 149.2, 138.7, 138.1, 137.2, 134.0, 132.2, 130.9, 129.6, 129.6, 129.5, 129.4, 129.4, 129.0, 129.0, 128.8, 128.8, 128.7, 125.6, 123.3, 119.1, 117.0, 72.7, 72.5, 67.8, 59.7, 58.7, 57.1, 55.6, 54.1, 53.5, 52.7, 49.5, 42.4, 42.1, 41.6, 38.2, 37.7, 37.2, 37.2, 29.8, 26.6, 26.1, 26.0 ,23.5, 23.4, 23.0, 22.7, 22.4, 22.3, 18.8, 17.5, 16.0, 11.8, 10.3.

HRMS (ESI, *m/z*): calculated for $C_{74}H_{97}N_8O_{15}^+$ [M + H]$^+$ 1337.7068, found 1337.7073.



19

seongsanamide A (**1**)

To a solution of lactone **19** (42.8 mg, 0.032 mmol, 1.0 eq.) in MeOH (5 mL, 0.0064 M) was added palladium on charcoal (85.6 mg, 10% Pd, 0.081 mmol, 2.5 eq.) in one portion. The reaction flask was evacuated and purged with H_2 three times and then the reaction was stirred at ambient temperature under a hydrogen atmosphere for 10 h. The reaction flask was then evacuated and purged with nitrogen three times. The catalyst was removed by filtration through Celite. The filtrate was concentrated in *vacuo* to give the desired compound which was used directly in the next step without further purification.

To a solution of crude compound in DCM (10 mL) at 0 °C was added DIPEA (0.032 mL, 0.192

mmol, 6.0 eq.), EDCI (18.5 mg, 0.096 mmol, 3.0 eq.) and HOAt (21.8 mg, 0.16 mmol, 5.0 eq.). The reaction mixture was stirred overnight at room temperature, quenched with 4% citric acid aqueous solution (5 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (5 mL), brine (5 mL), dried over anhydrous Na_2SO_4(s) and concentrated in *vacuo*. The residue was purified by flash chromatography (SiO_2, 2:1 ethyl acetate/hexanes) to furnish seongsanamide A in 73% yield over two steps (22.5 mg, 0.023mmol) as a colorless oil.

TLC: R_f = 0.35 (silica gel, ethyl acetate/hexanes = 1:1), UV & PMA stain.

$[\alpha]_D^{25}$ = -11.30 (c 0.1, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 8.26 (d, *J* = 4.4 Hz, 1H), 8.18 (d, *J* = 5.9 Hz, 1H), 8.17 – 8.09 (m, 3H), 8.02 (d, *J* = 7.3 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.20 (brs, 2H), 6.97 (brs, 2H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.65 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 5.14 (q, *J* = 6.1 Hz, 1H), 4.58 (dt, *J* = 10.4, 5.2 Hz, 1H), 4.54 – 4.44 (m, 1H), 4.30 – 4.13 (m, 3H), 3.98 (dt, *J* = 9.9, 6.0 Hz, 1H), 3.69 (t, *J* = 9.6 Hz, 1H), 3.07 – 2.89 (m, 2H), 2.84 – 2.70 (m, 2H), 2.14 (q, *J* = 7.5 Hz, 2H), 1.91 (s, 1H), 1.68 – 1.46 (m, 4H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.35 (td, *J* = 9.3, 8.9, 4.7 Hz, 4H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.89 (d, *J* = 3.1 Hz, 3H), 0.87 (d, *J* = 3.1 Hz, 3H), 0.86 – 0.73 (m, 18H), 0.38 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 173.3, 172.1, 171.8, 171.7, 171.2, 171.1, 170.4, 169.8, 167.9, 155.7, 146.2, 145.7, 131.8, 130.7, 128.0, 124.4, 120.2, 116.8, 115.8, 69.9, 59.7, 55.8, 55.6, 52.9, 52.5, 51.5, 50.5, 47.3, 41.1, 40.3, 40.2, 37.2, 35.6, 35.2, 28.0, 24.3, 24.2, 24.2, 24.0, 22.8, 22.8, 22.6, 22.2, 21.7, 21.3, 17.8, 16.5, 15.3, 10.1, 9.7.

HRMS (ESI, *m/z*): calculated for $C_{52}H_{77}N_8O_{12}^+$ $[M + H]^+$ 1005.5655, found 1005.5663.

III. Table: Comparison of ^{13}C NMR Data of Seongsanamide A

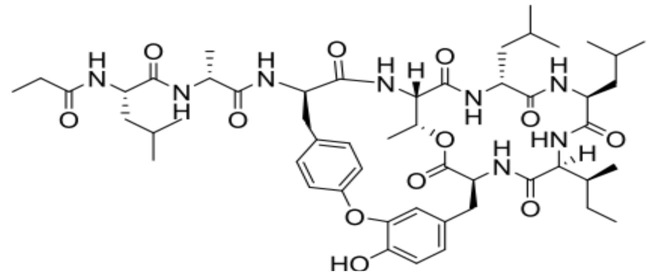
(Natural Product and Synthetic Sample)

Carbon No.	**Seongsanamide A**		
	Natural (δ_{A1})	**Synthetic (δ_{A2})**	**$\Delta_{\delta}=\delta_{A1}-\delta_{A2}$**
1	173.31	173.31	0.00
2	172.14	172.14	0.00
3	171.81	171.77	0.04
4	171.73	171.69	0.04
5	171.26	171.23	0.03
6	171.07	171.08	-0.01
7	170.45	170.40	0.05
8	169.83	169.81	0.02
9	167.87	167.88	-0.01
10	155.76	155.69	0.07
11	146.26	146.24	0.02
12	145.77	145.73	0.04
13	131.82	131.78	0.04
14	130.76	130.73	0.03
15	128.06	127.99	0.07
16	124.45	124.43	0.02
17	120.24	120.20	0.04
18	116.85	116.83	0.02
19	115.88	115.82	0.06
20	69.89	69.87	0.02
21	59.67	59.71	-0.04
22	55.75	55.76	-0.01
23	55.61	55.57	0.04
24	52.91	52.92	-0.01
25	52.54	52.53	0.01
26	51.47	51.48	-0.01
27	50.47	50.46	0.01
28	47.25	47.26	-0.01
29	41.16	41.13	0.03
30	40.30	40.28	0.02
31	40.20	40.16	0.04
32	37.20	37.17	0.03
33	35.65	35.59	0.06
34	35.23	35.21	0.02
35	28.06	28.04	0.02
36	24.27	24.33	-0.06
37	24.26	24.23	0.03
38	24.21	24.18	0.03
39	24.03	23.99	0.04
40	22.80	22.79	0.01
41	22.77	22.76	0.01
42	22.63	22.62	0.01
43	22.22	22.17	0.05

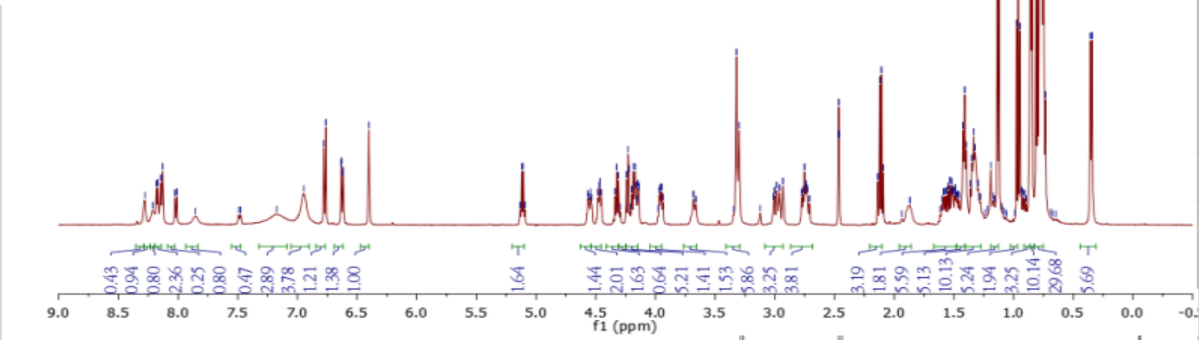
44	21.73	21.71	0.02
45	21.32	21.30	0.02
46	17.83	17.82	0.01
47	16.56	16.54	0.02
48	15.28	15.27	0.01
49	10.13	10.12	0.01
50	9.70	9.70	0

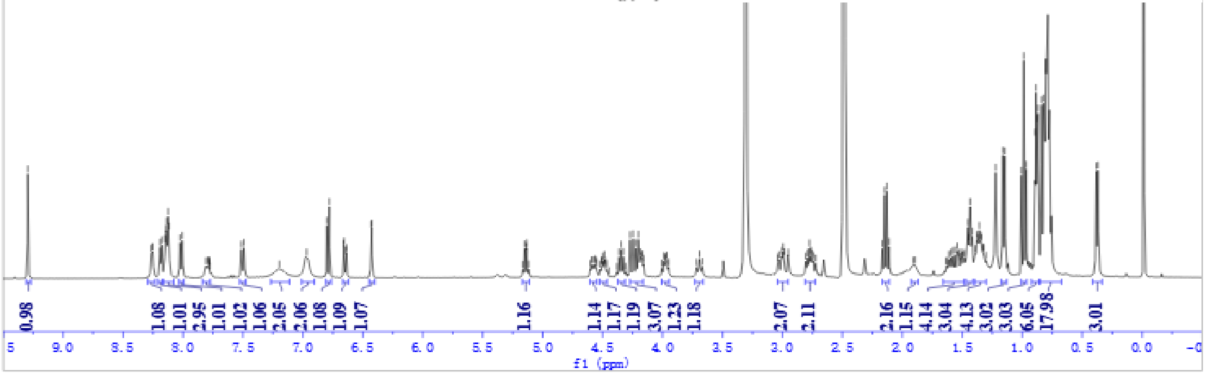
IV. Comparison of NMR Spectra of Natural and Synthetic Seongsanamide A.

^{1}H NMR (Natural Product, 500 MHz, DMSO-d_6)

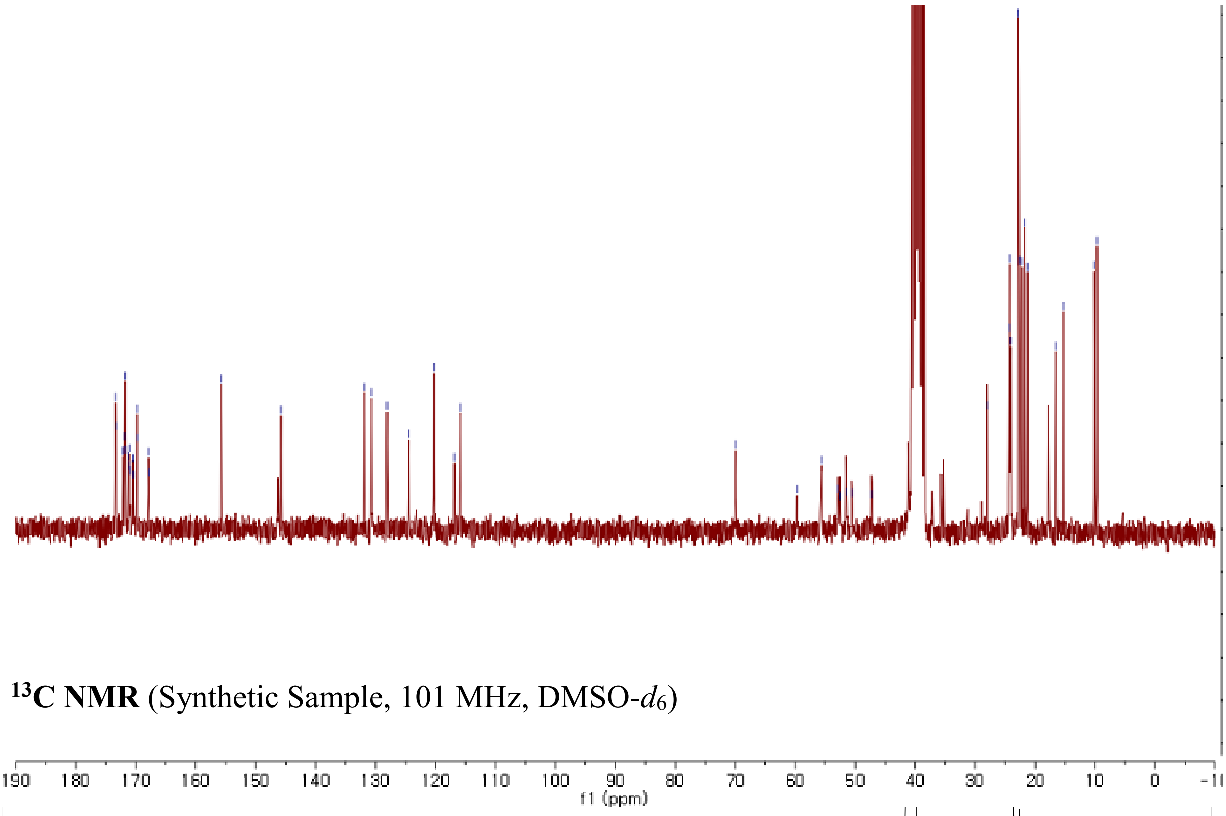


^{1}H NMR (Synthetic Sample, 400 MHz, DMSO-d_6)

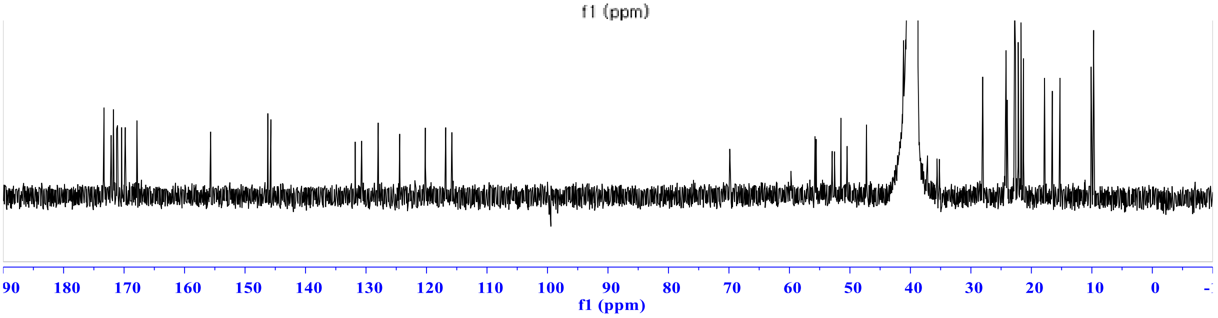




^{13}C **NMR** (Natural Product, 126 MHz, DMSO-d_6)

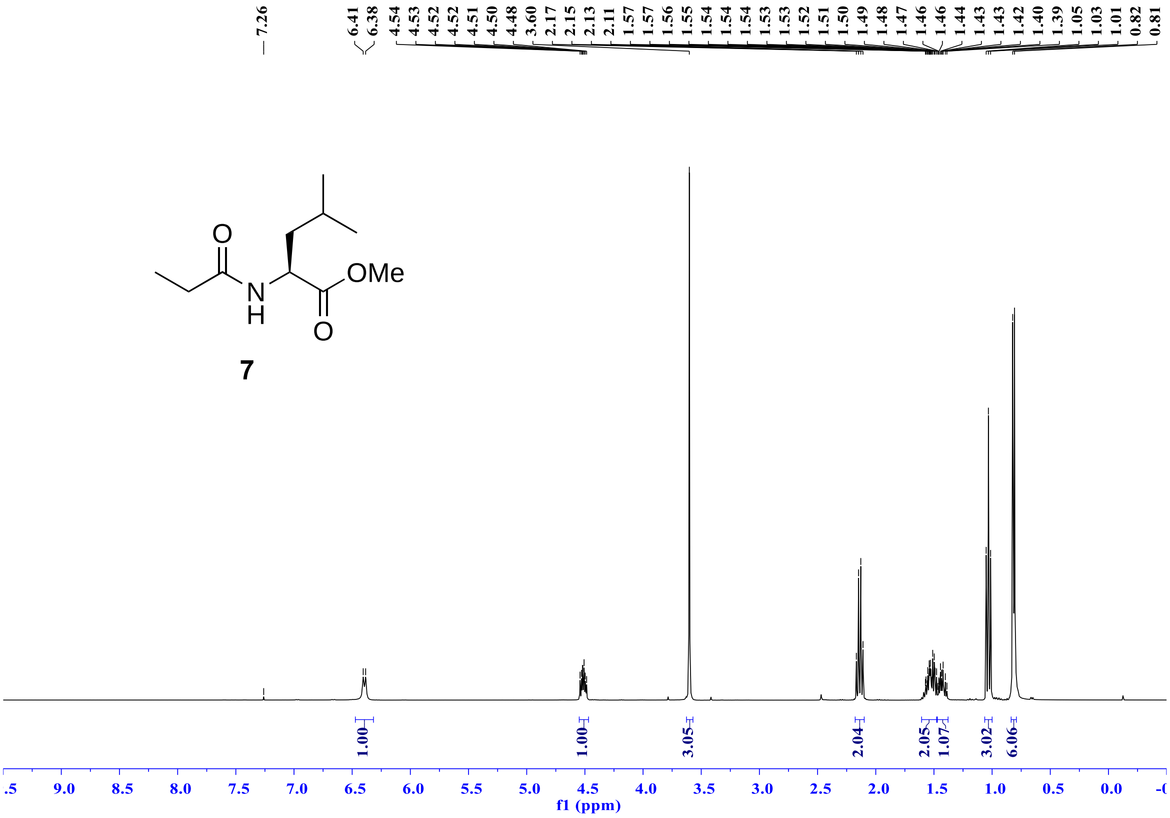


^{13}C **NMR** (Synthetic Sample, 101 MHz, DMSO-d_6)

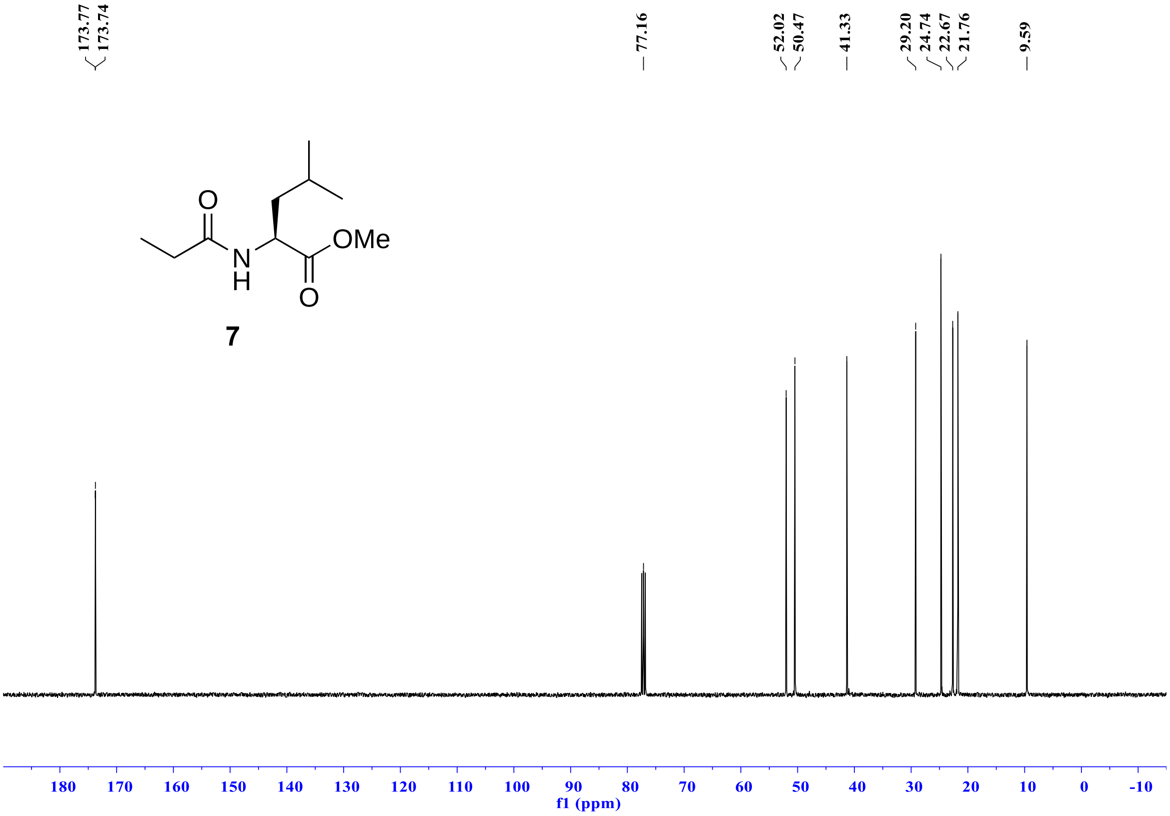


V. ^{1}H and ^{13}C NMR Spectra

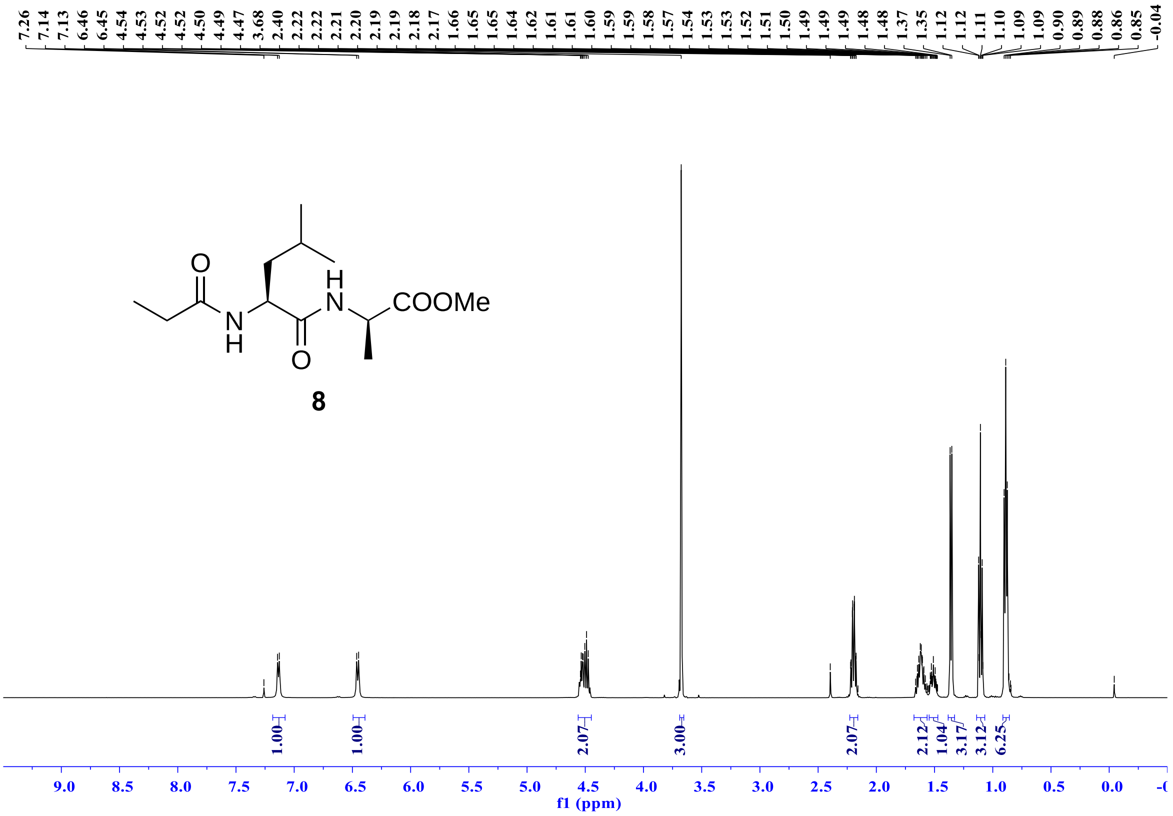
^{1}H NMR Spectra for 7 (CDCl$_3$)



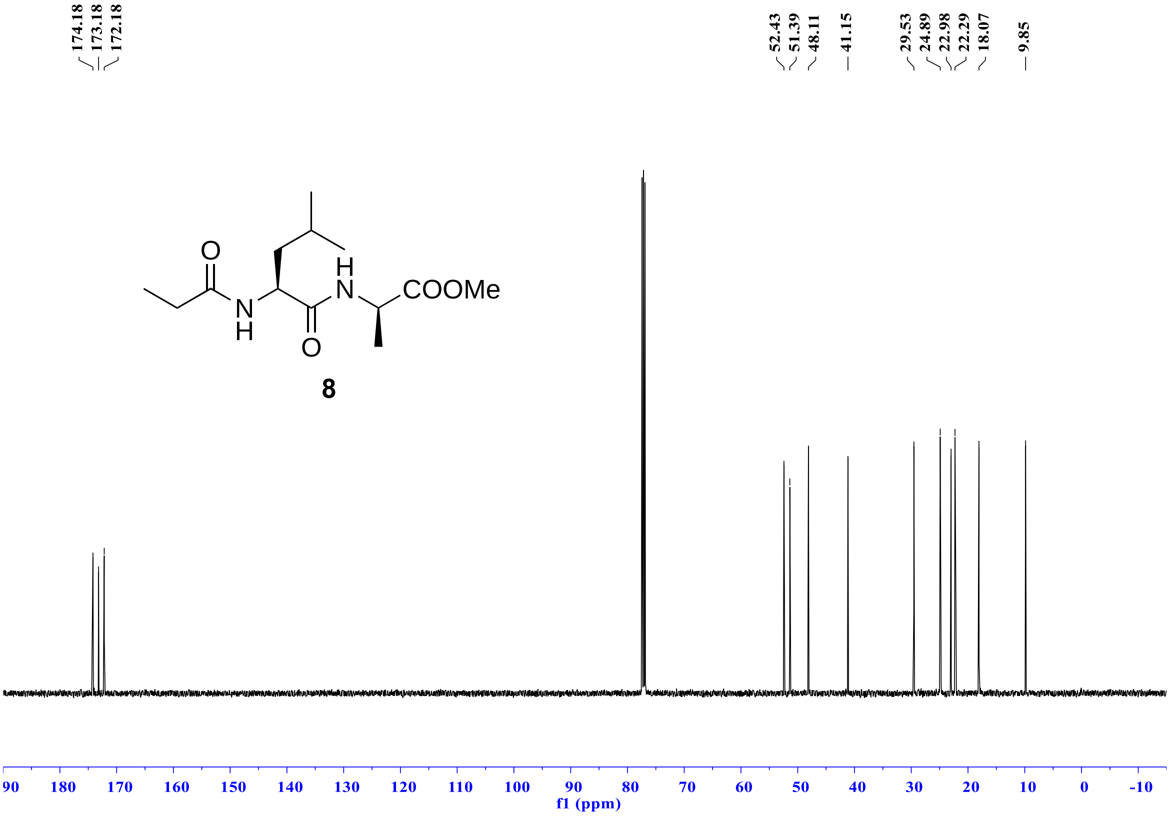
^{13}C NMR Spectra for 7 (CDCl$_3$)



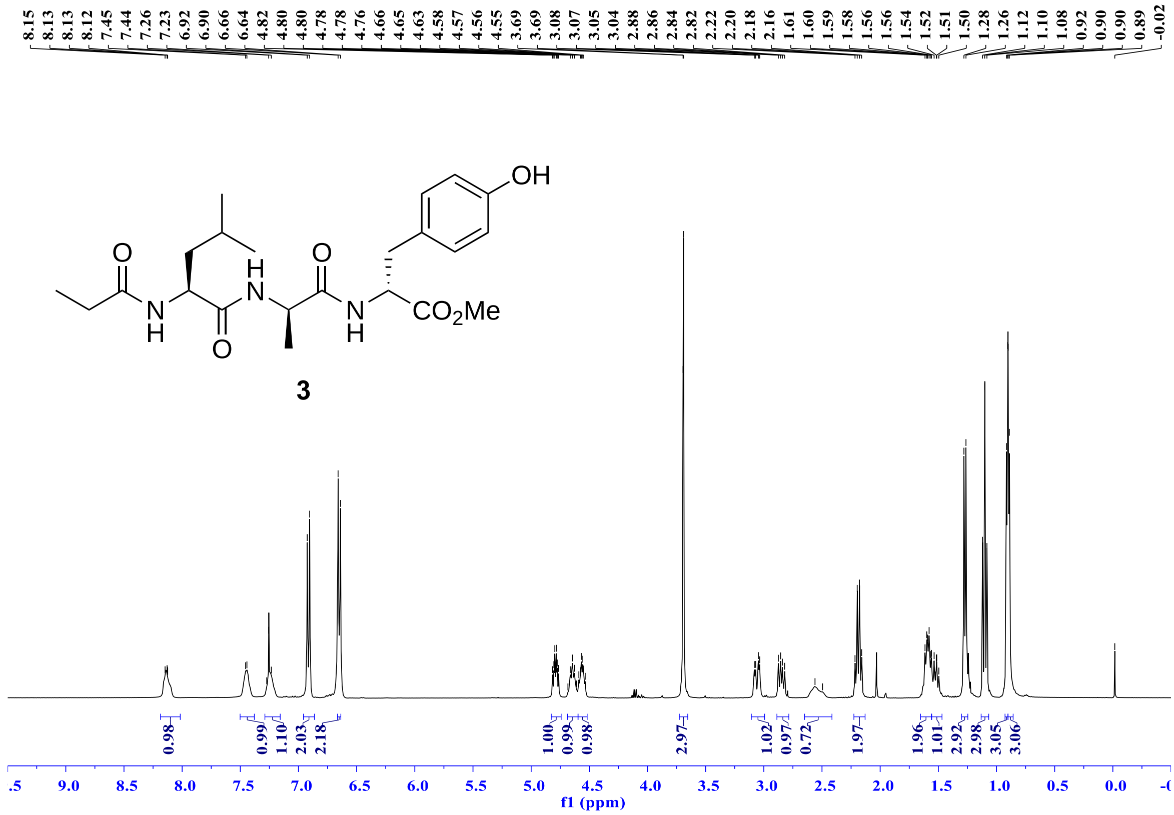
^{1}H NMR Spectra for 8 (CDCl$_3$)



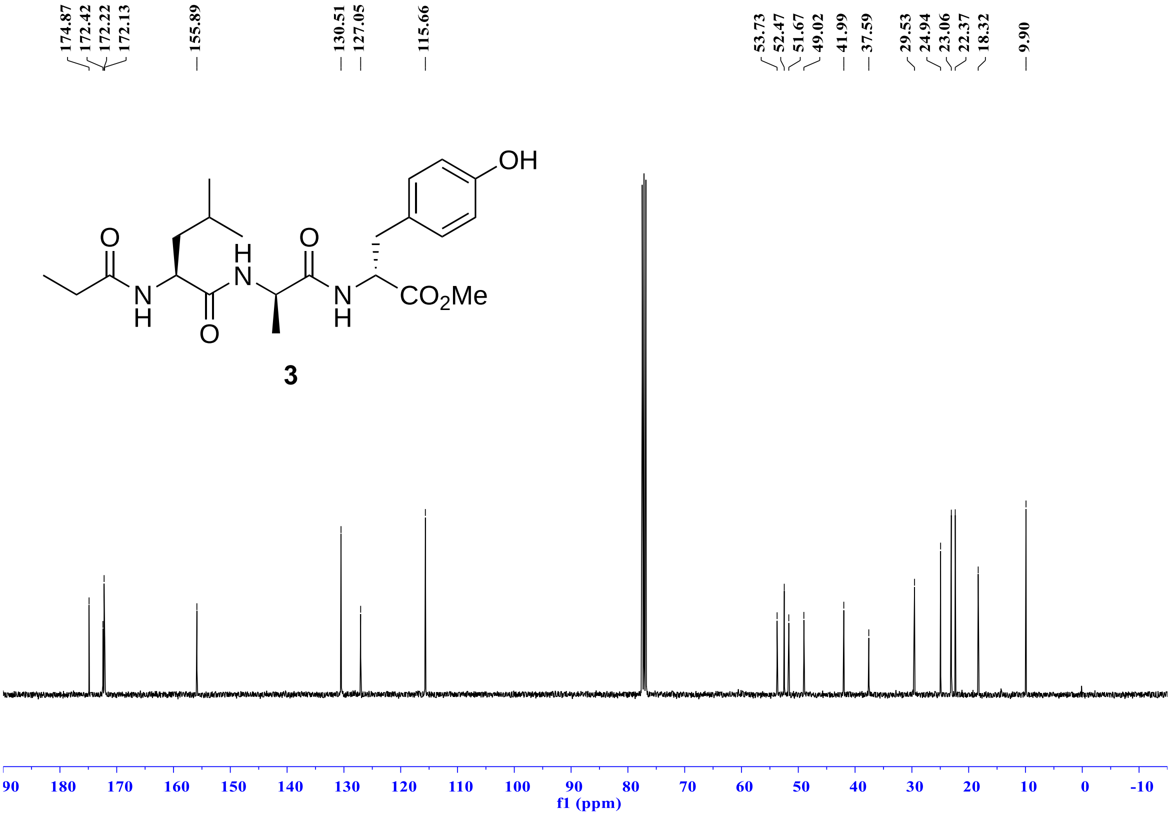
^{13}C NMR Spectra for 8 (CDCl$_3$)



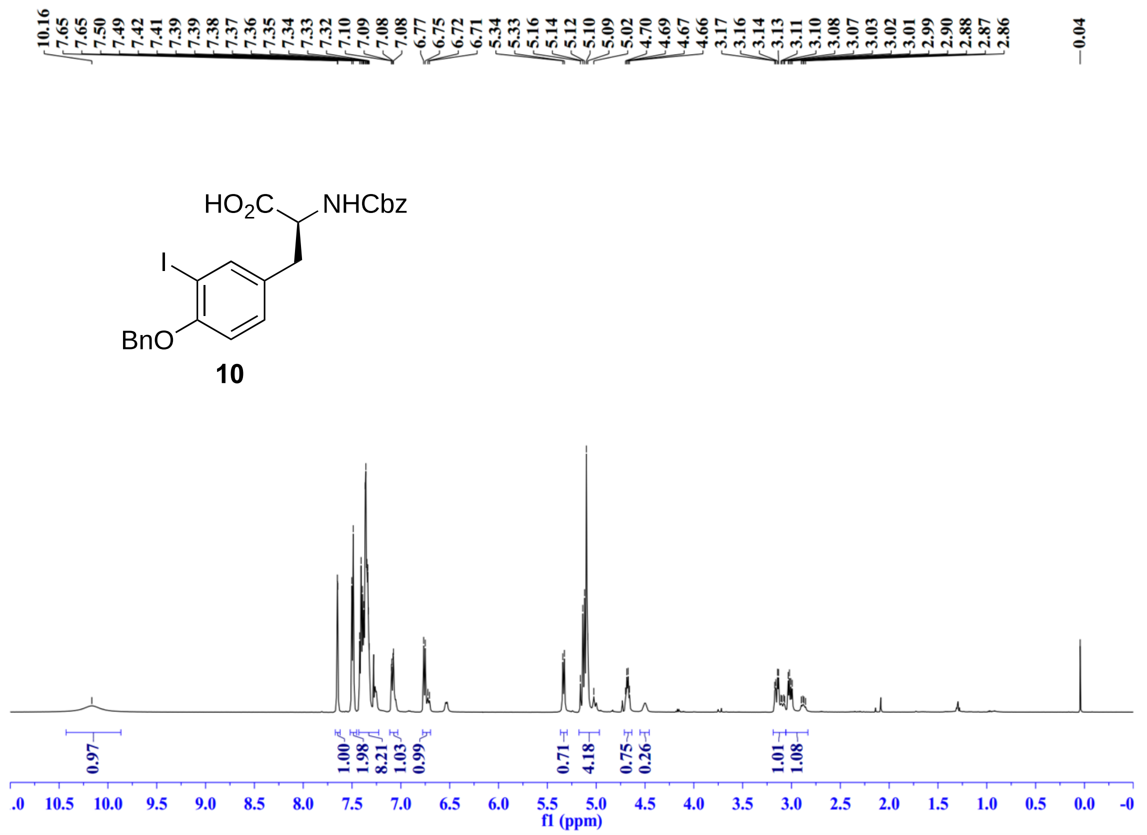
^{1}H NMR Spectra for 3 ($CDCl_3$)



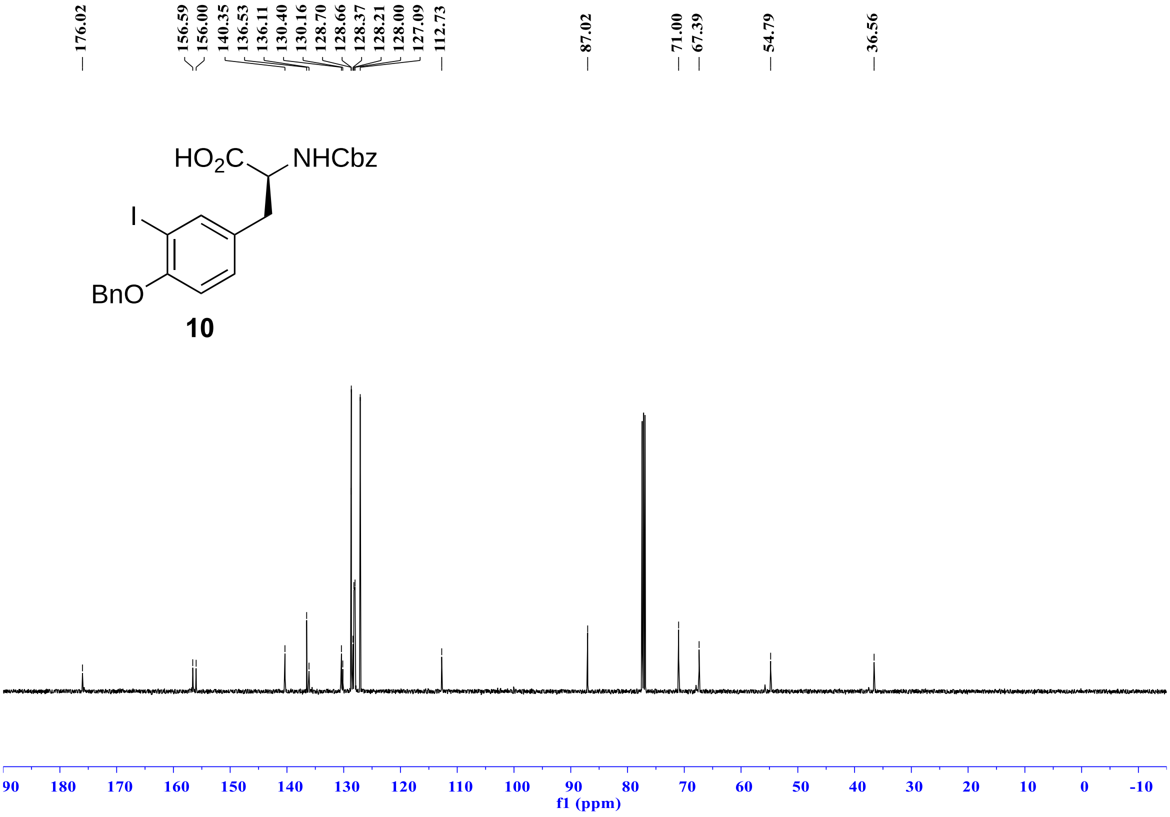
^{13}C NMR Spectra for 3 ($CDCl_3$)



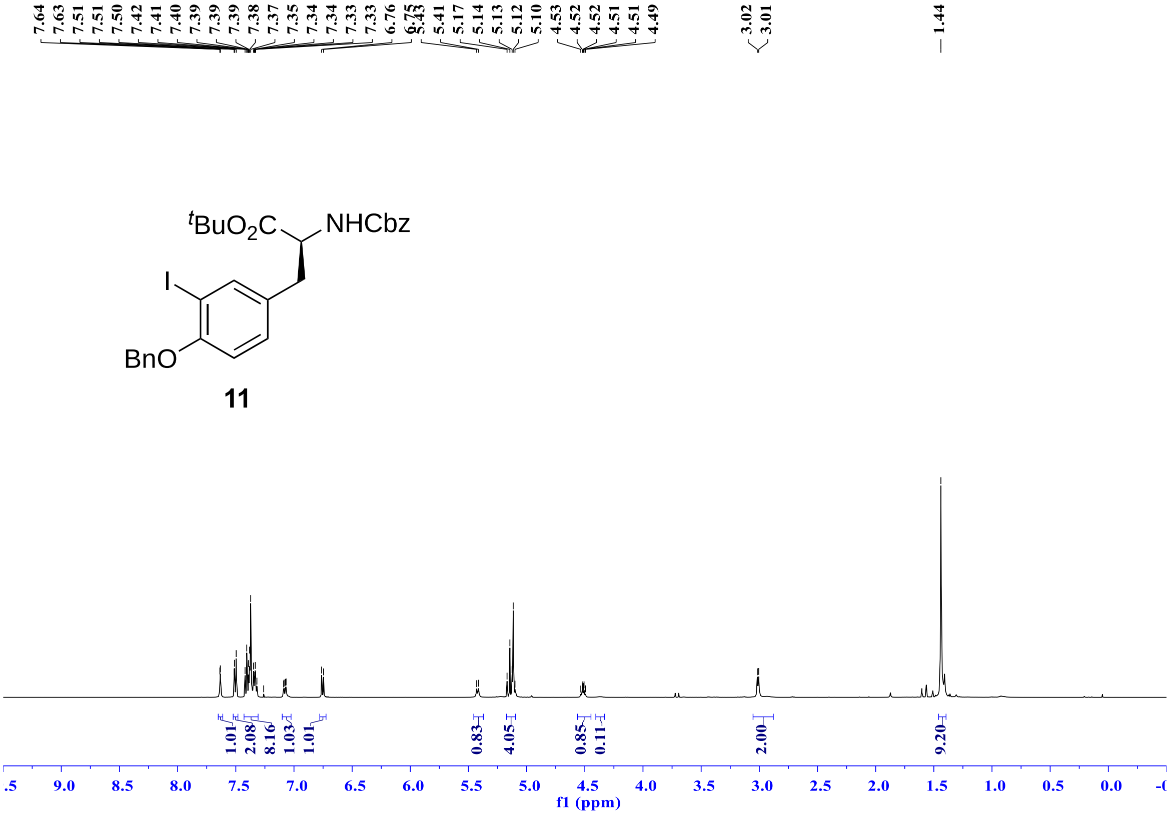
^{1}H NMR Spectra for 10 ($CDCl_3$)



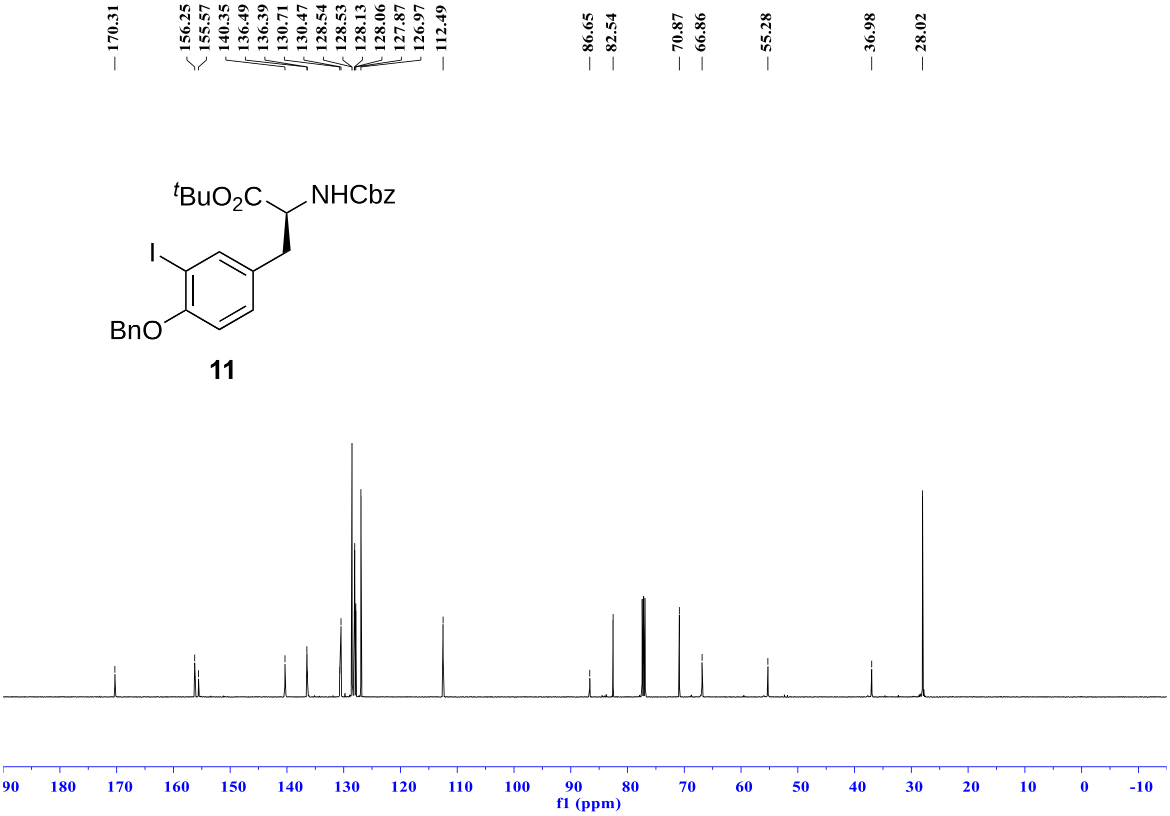
^{13}C NMR Spectra for 10 ($CDCl_3$)



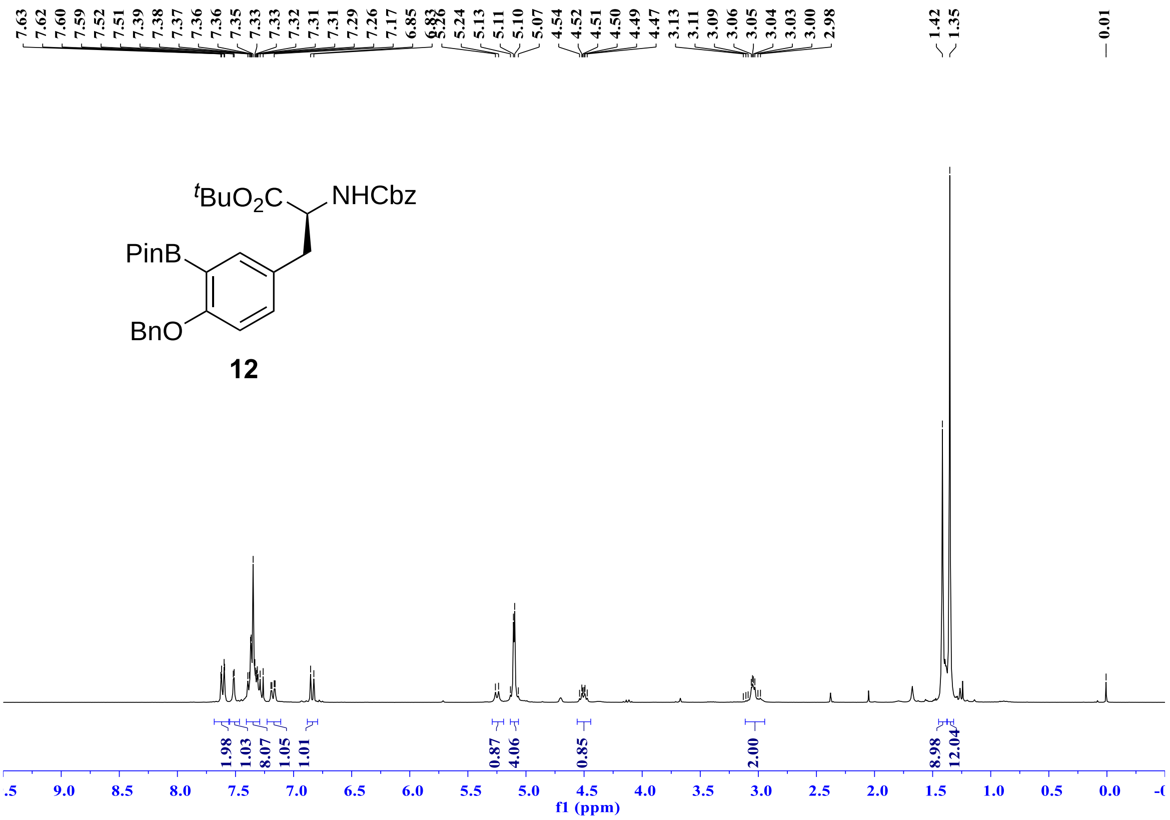
^{1}H NMR Spectra for 11 ($CDCl_3$)



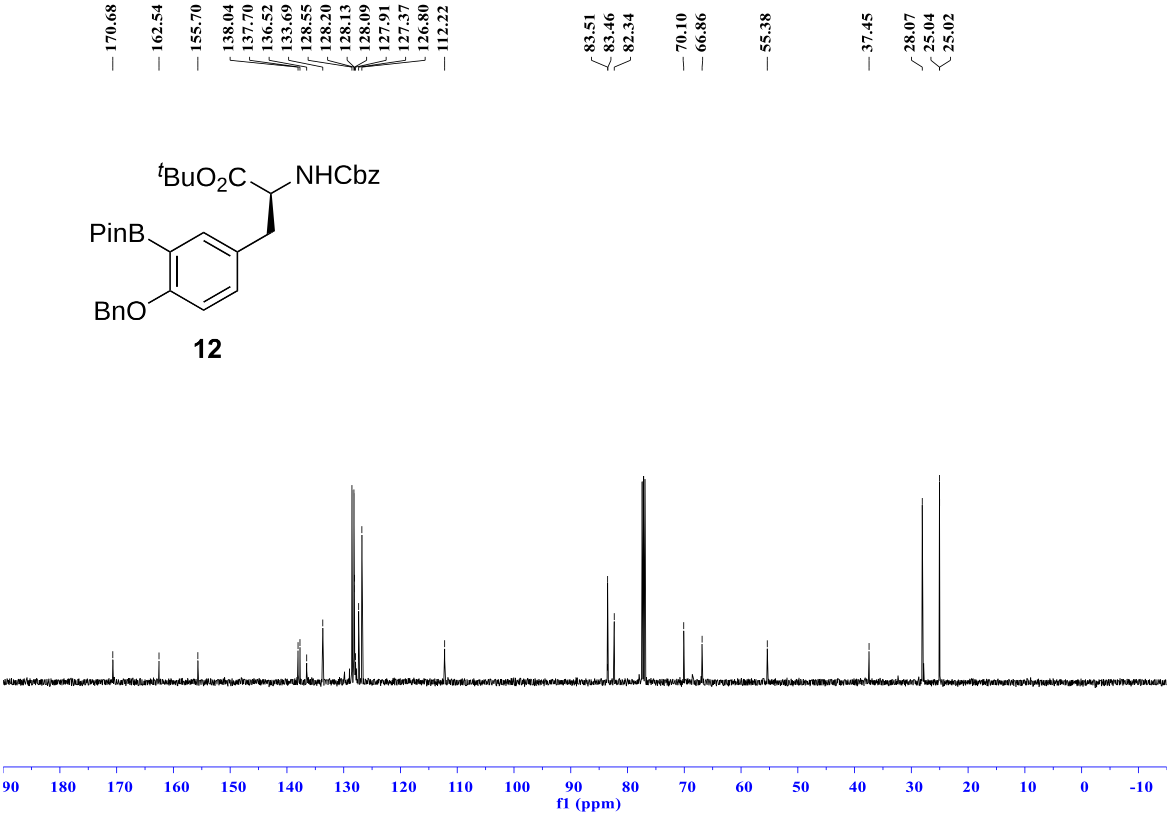
^{13}C NMR Spectra for 11 ($CDCl_3$)



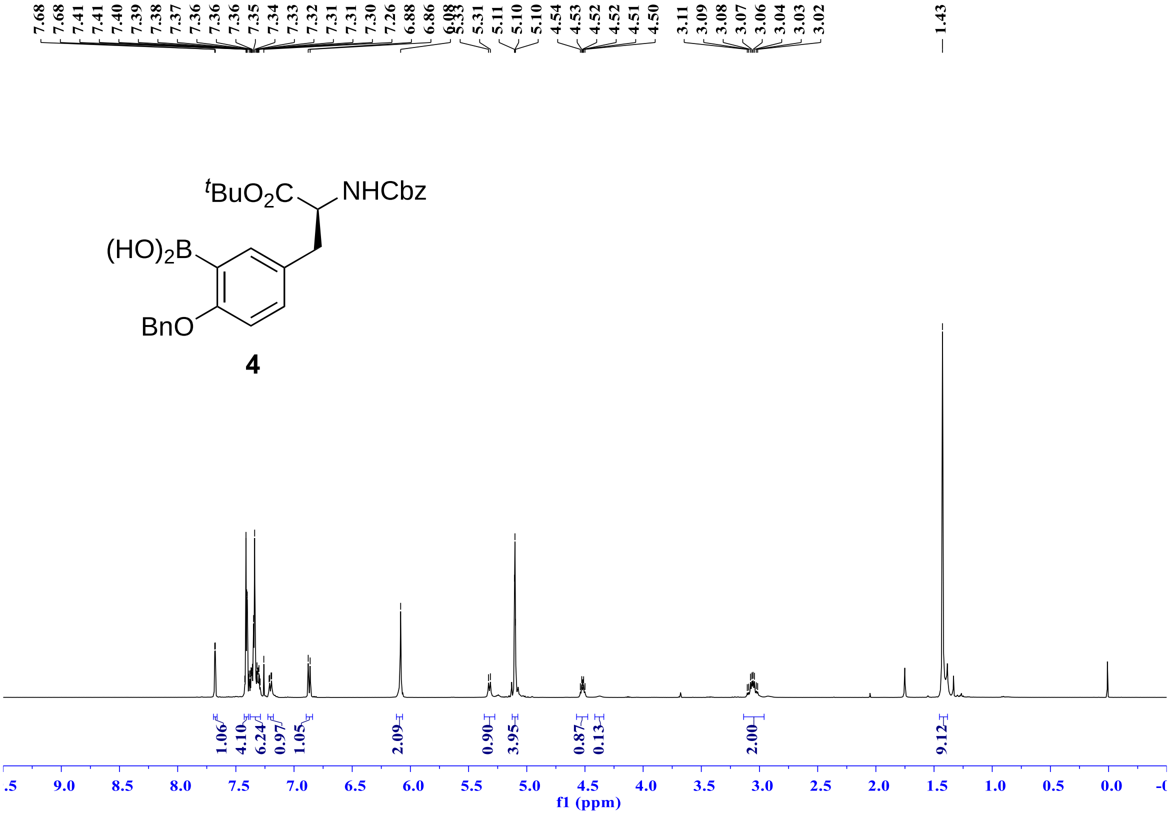
^{1}H NMR Spectra for 12 (CDCl$_3$)



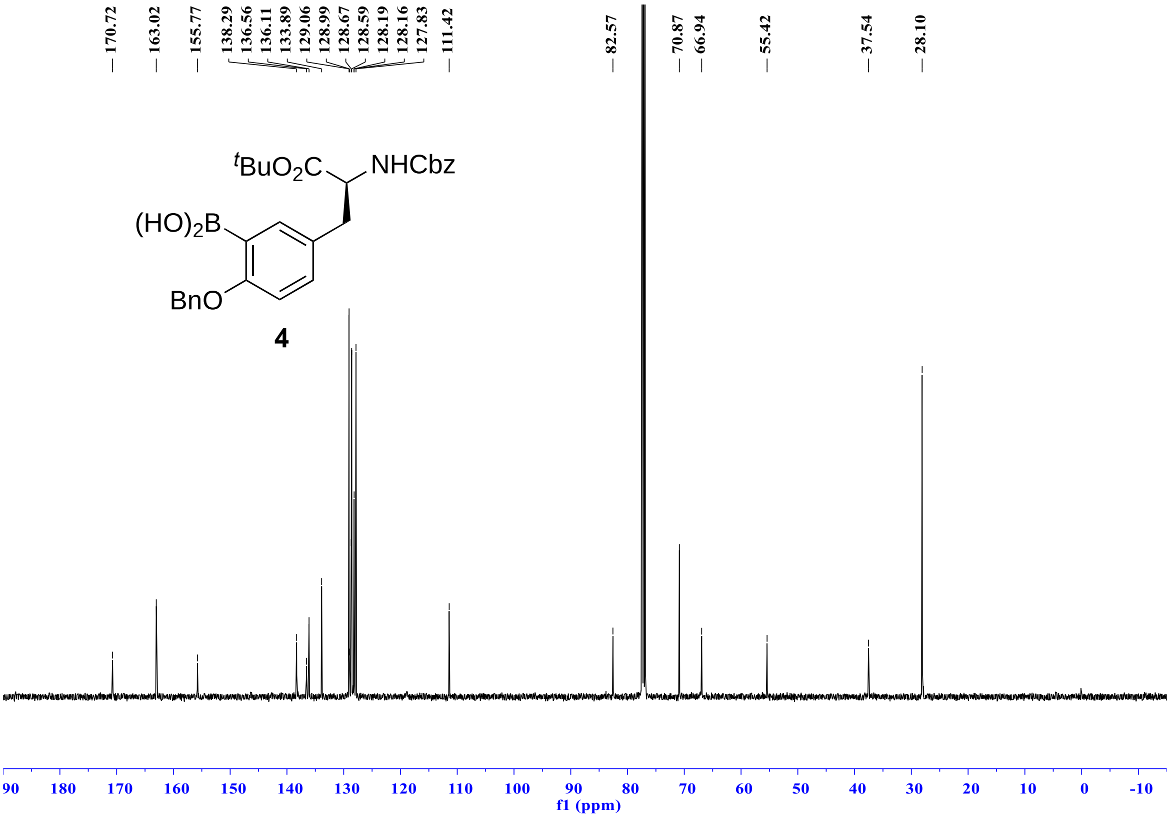
^{13}C NMR Spectra for 12 (CDCl$_3$)



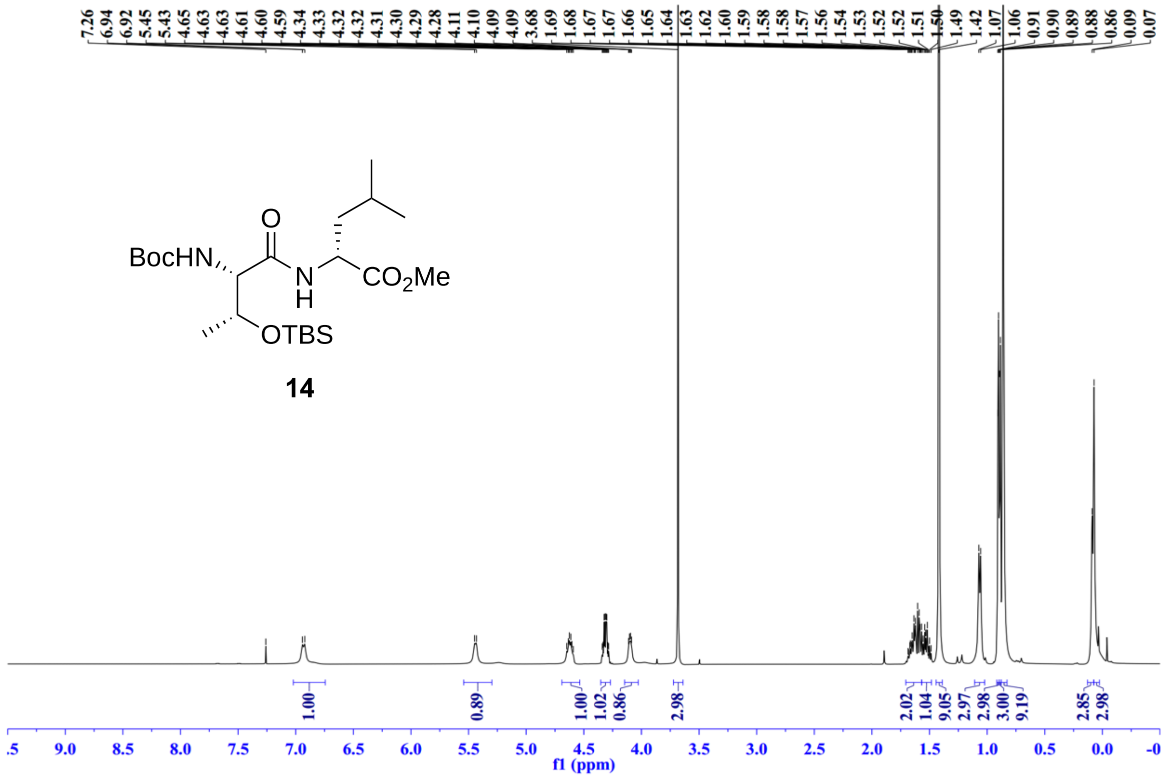
^{1}H NMR Spectra for 4 ($CDCl_3$)



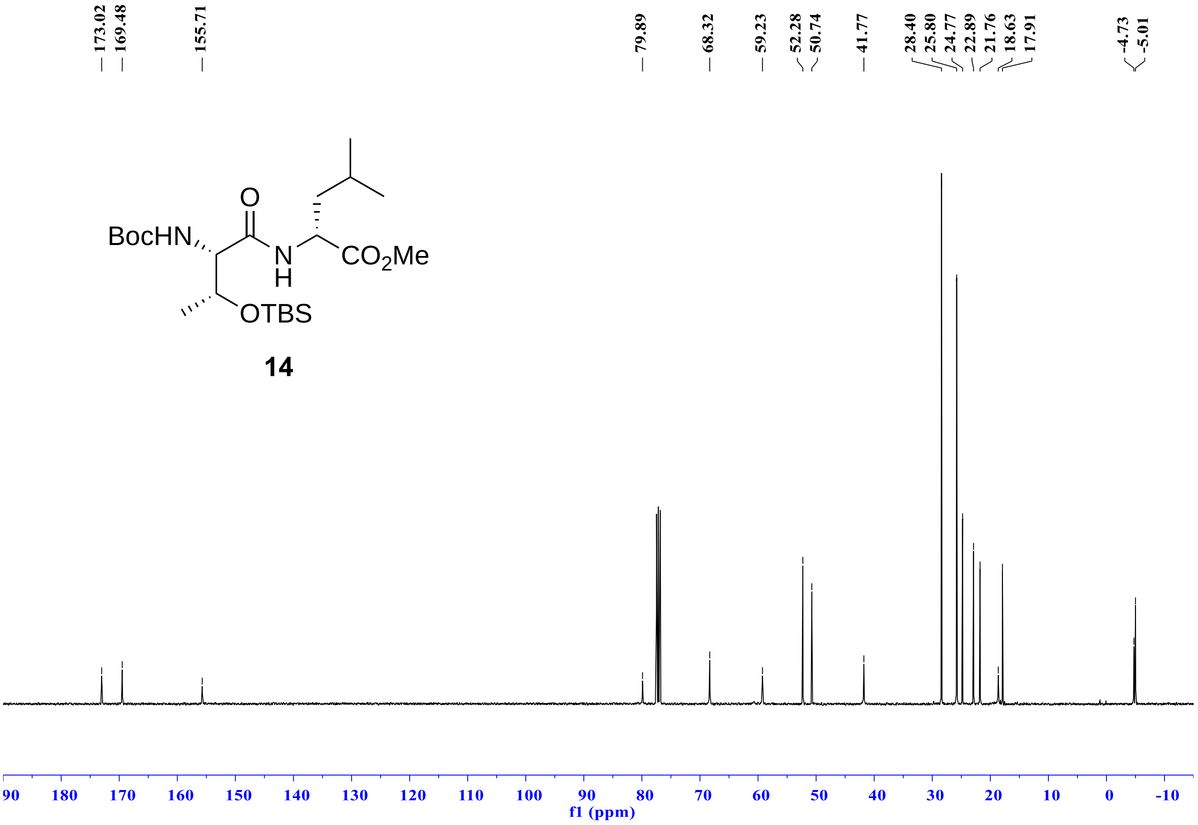
^{13}C NMR Spectra for 4 ($CDCl_3$)



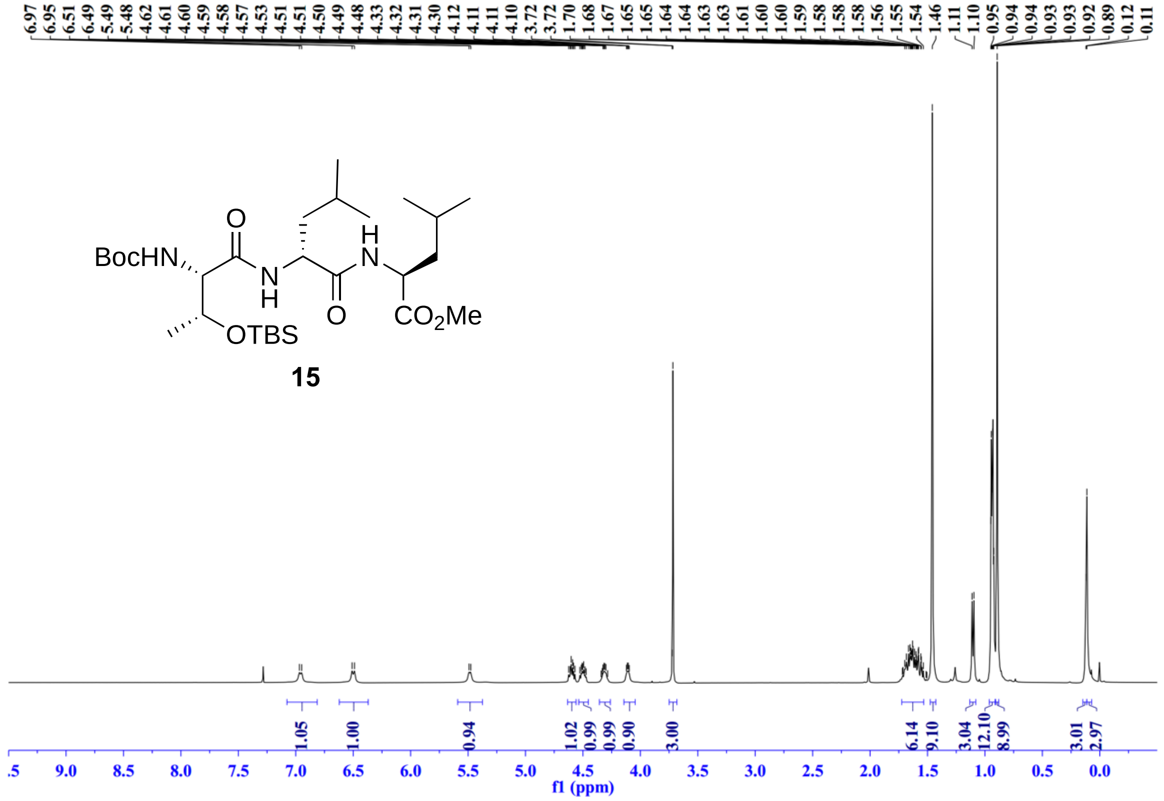
^{1}H NMR Spectra for 14 (CDCl$_3$)



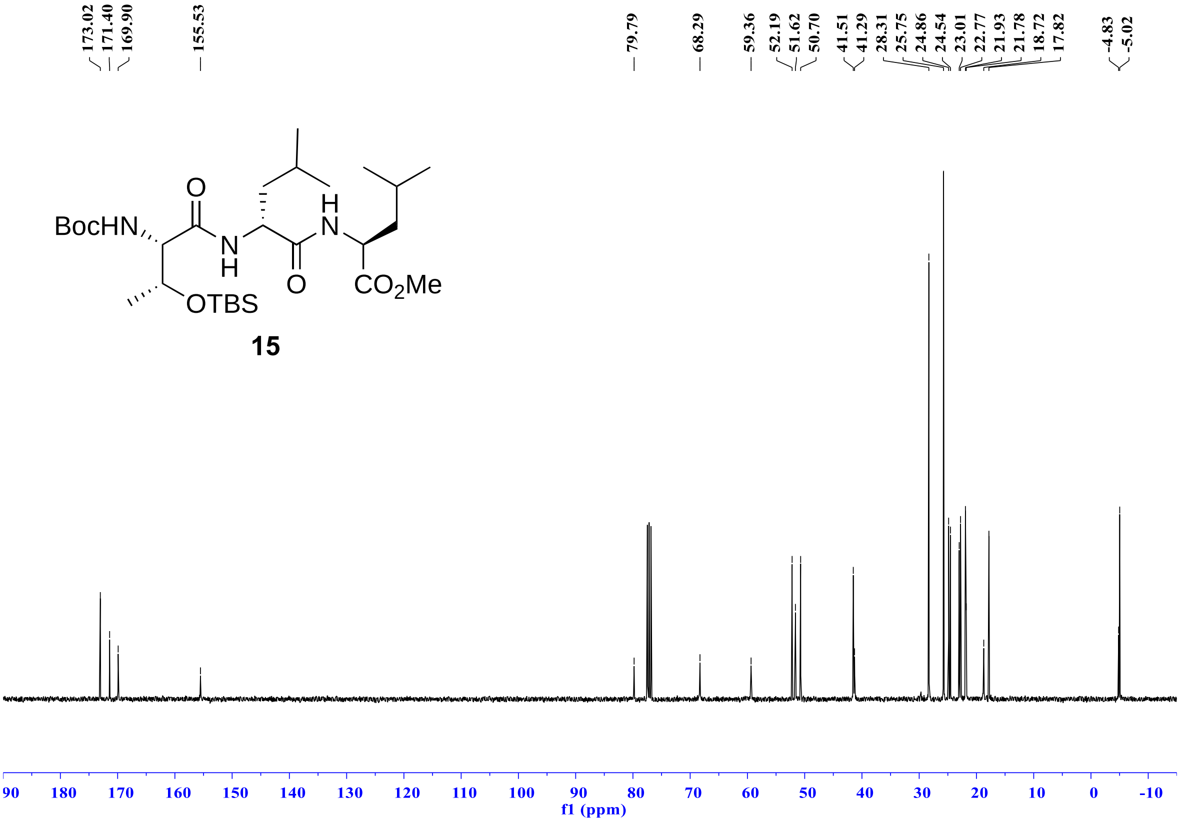
^{13}C NMR Spectra for 14 (CDCl$_3$)



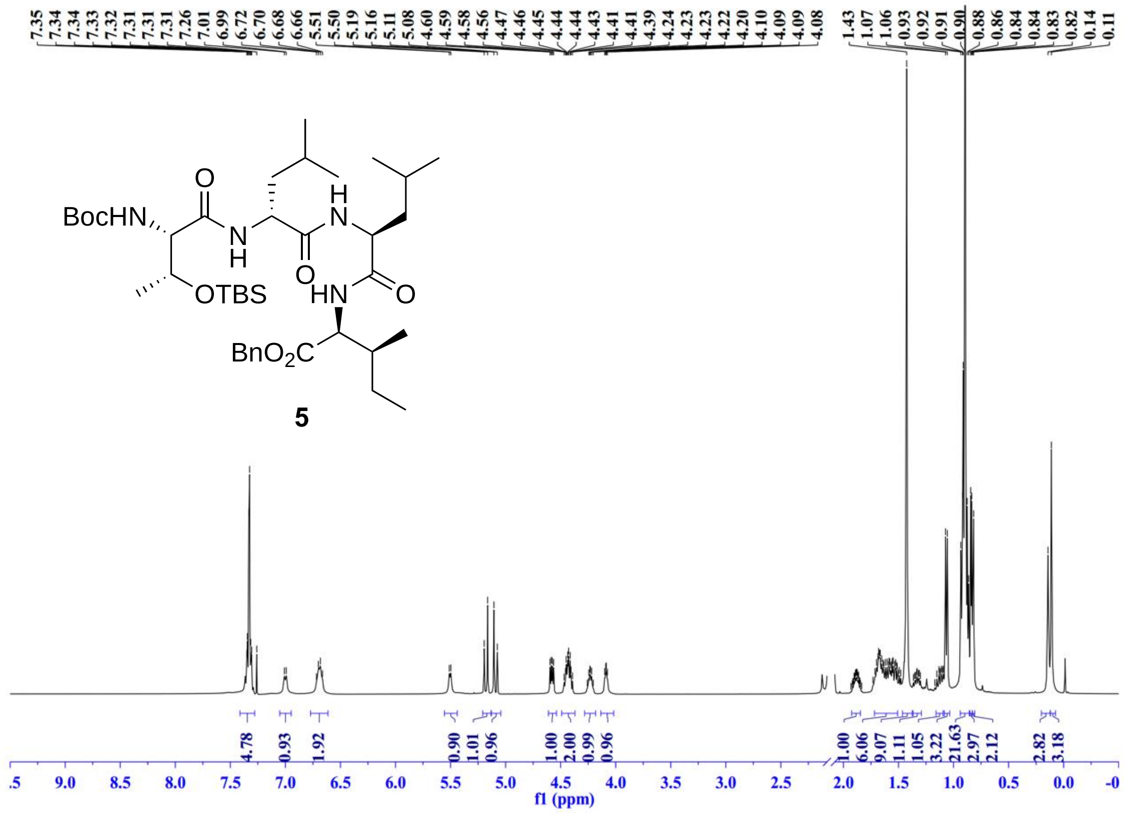
^{1}H NMR Spectra for 15 (CDCl$_3$)



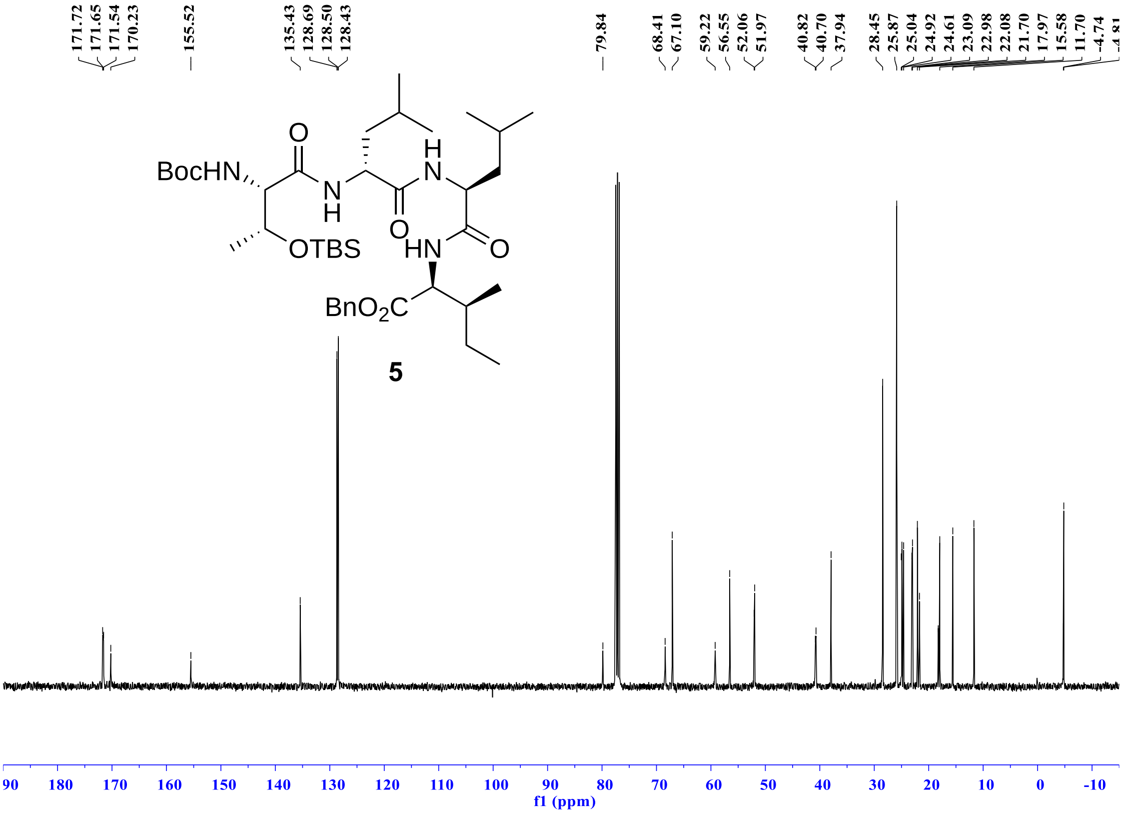
^{13}C NMR Spectra for 15 (CDCl$_3$)



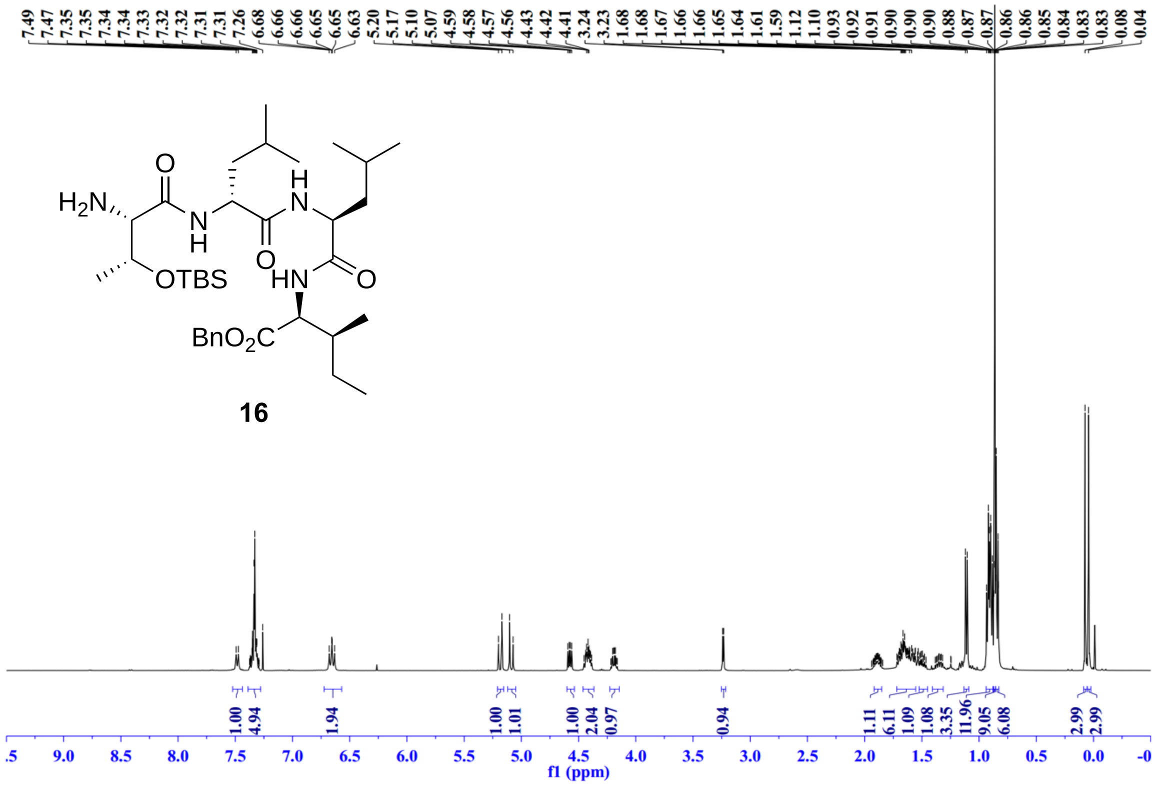
^{1}H NMR Spectra for 5 ($CDCl_3$)



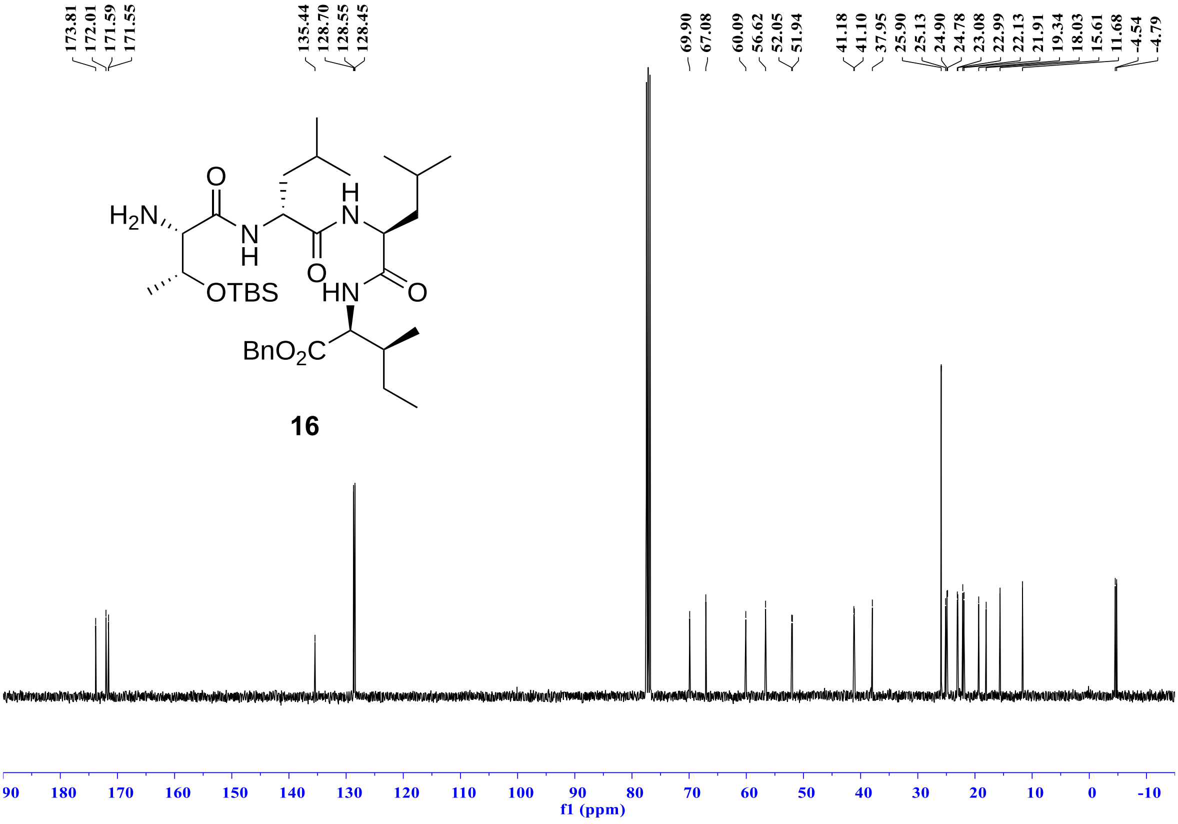
^{13}C NMR Spectra for 5 ($CDCl_3$)



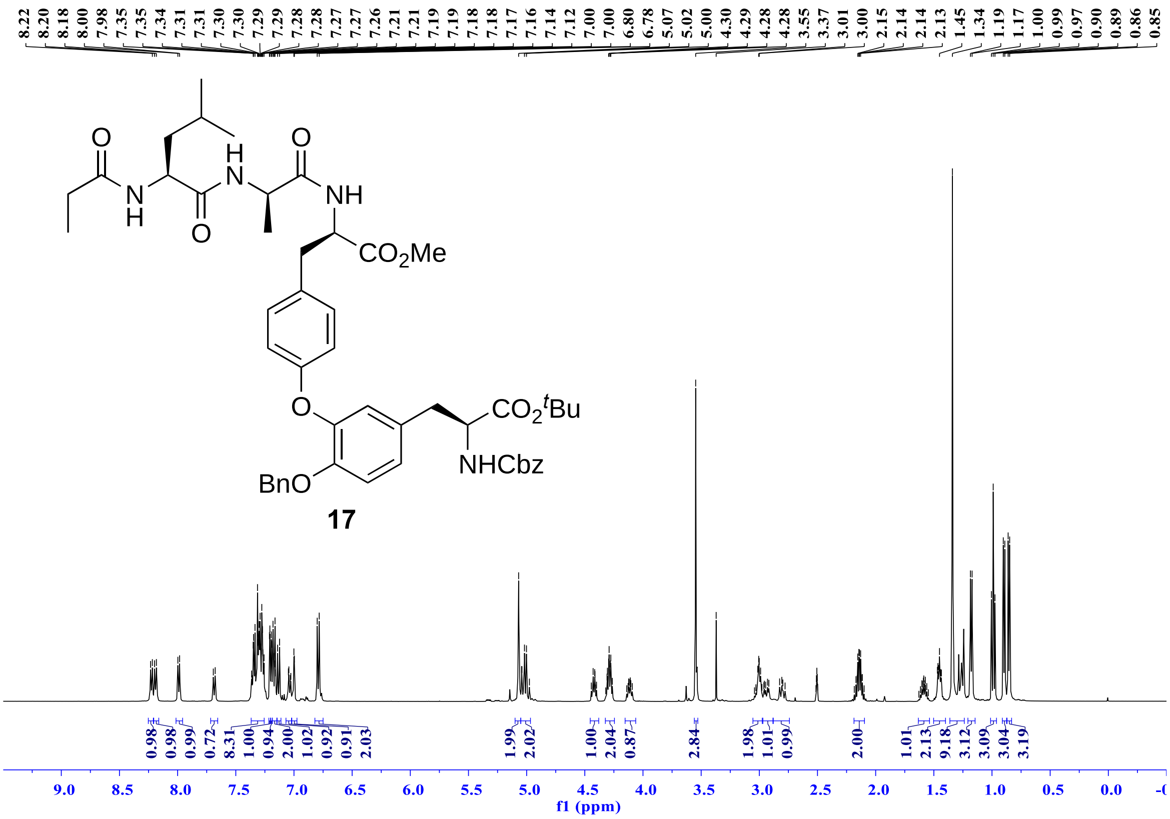
^{1}H NMR Spectra for 16 (CDCl$_3$)



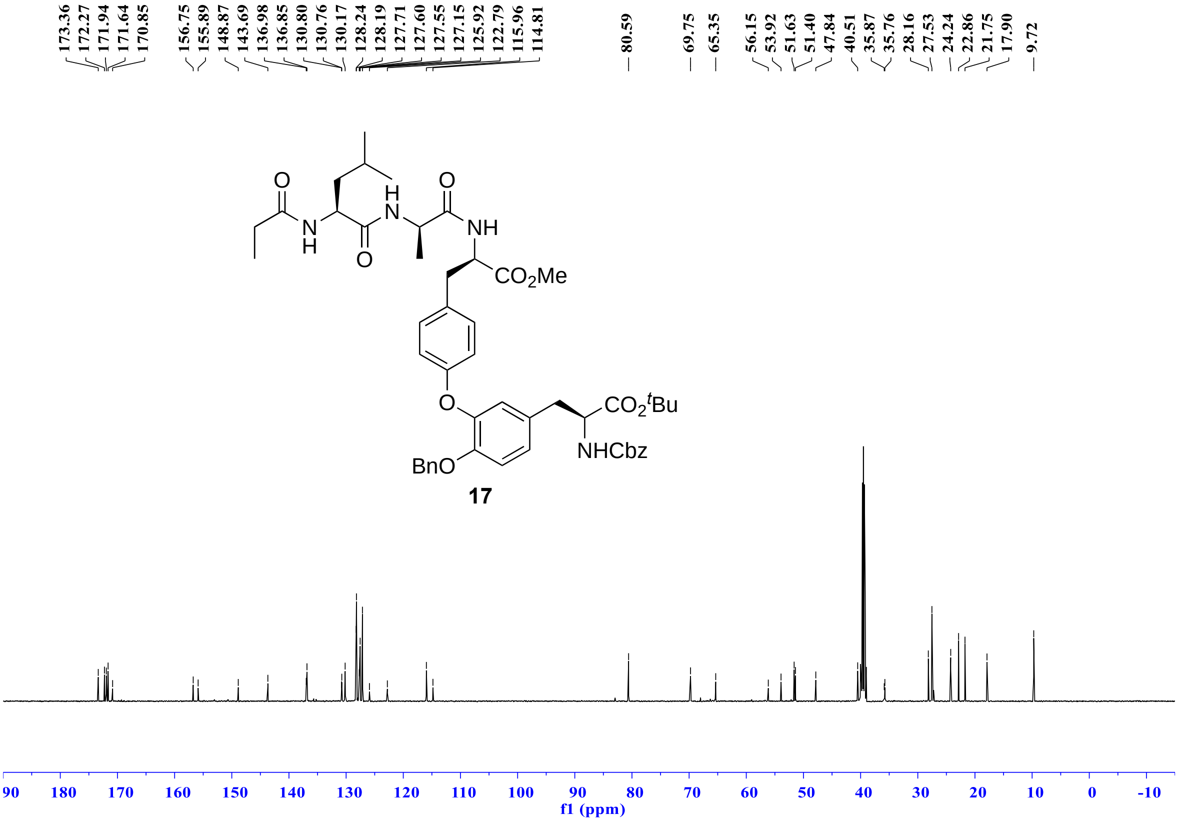
^{13}C NMR Spectra for 16 (CDCl$_3$)



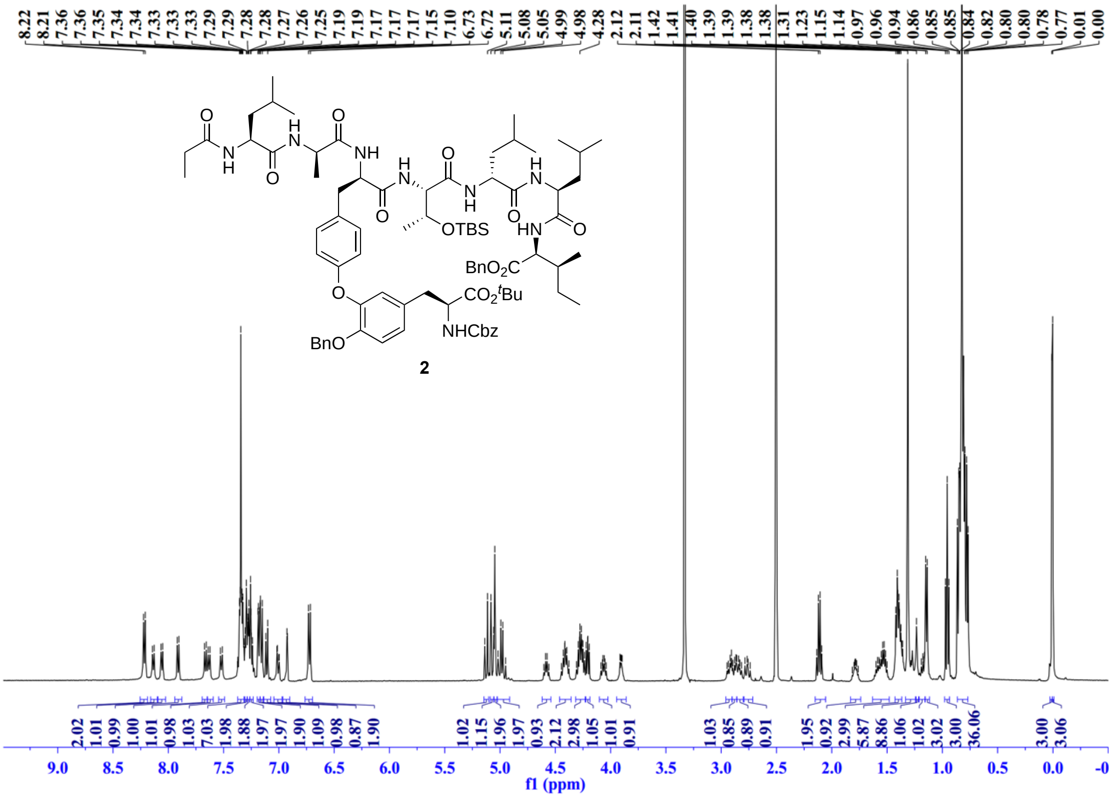
^{1}H NMR Spectra for 17 (DMSO-d_6)



^{13}C NMR Spectra for 17 (DMSO-d_6)

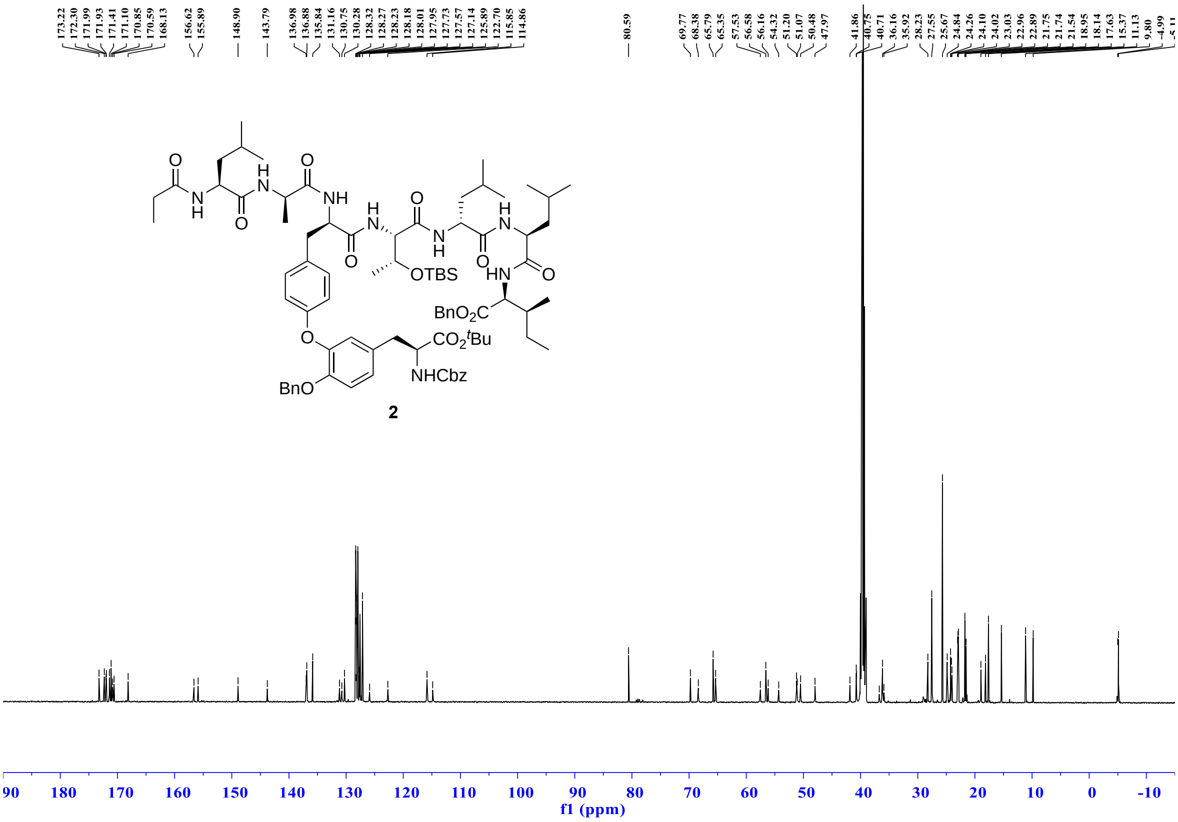


^{1}H NMR Spectra for 2 (DMSO-d_6)



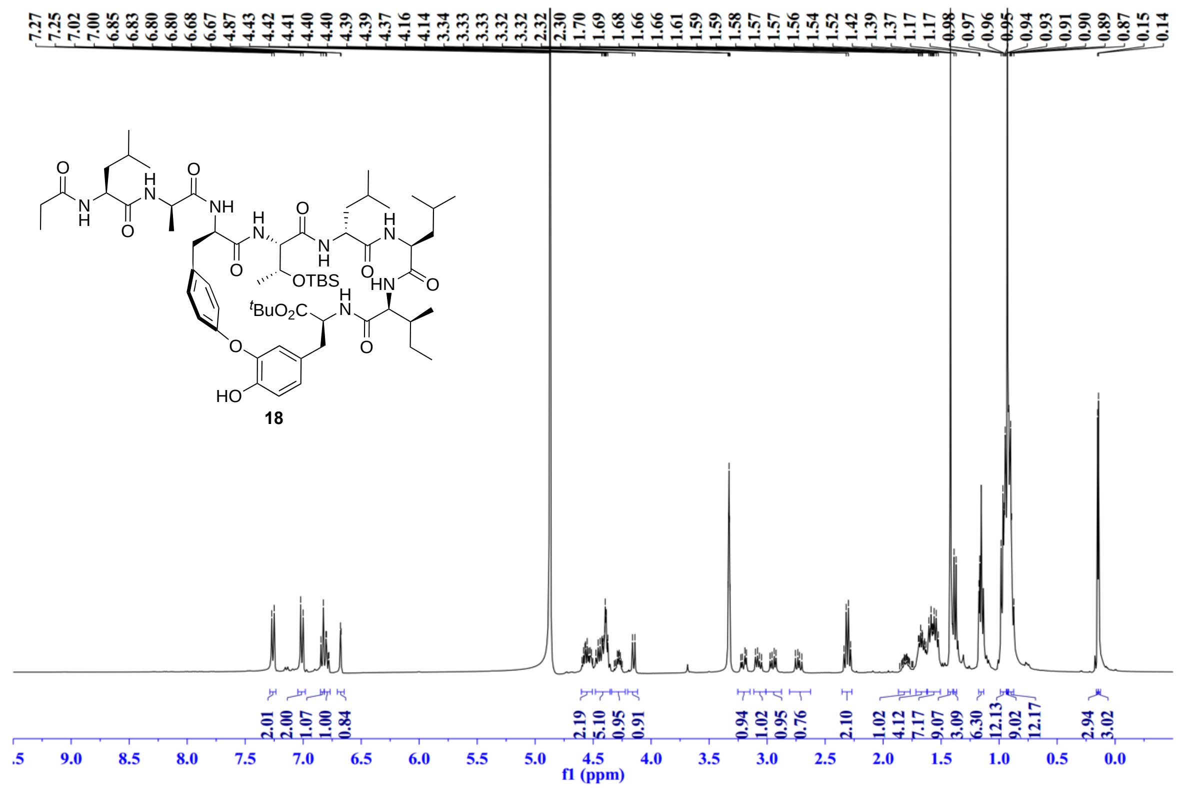
2

^{13}C NMR Spectra for 2 (DMSO-d_6)

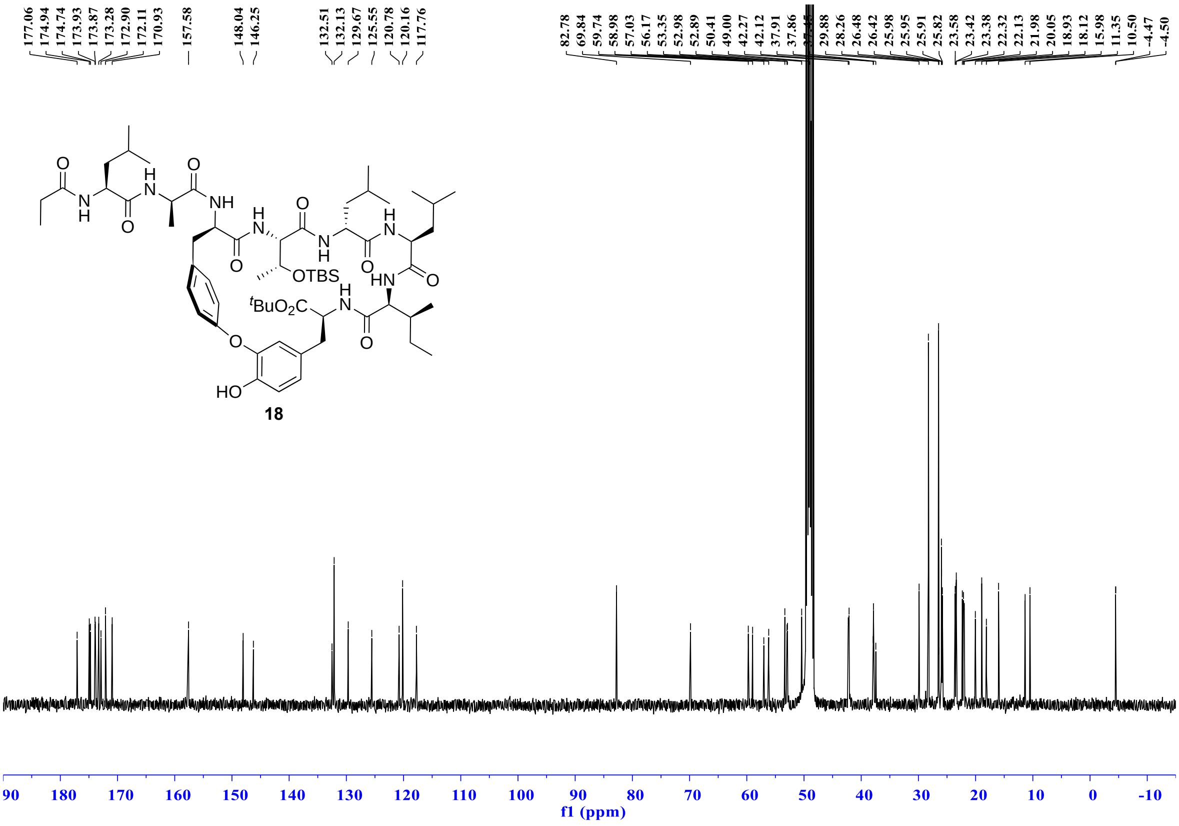


2

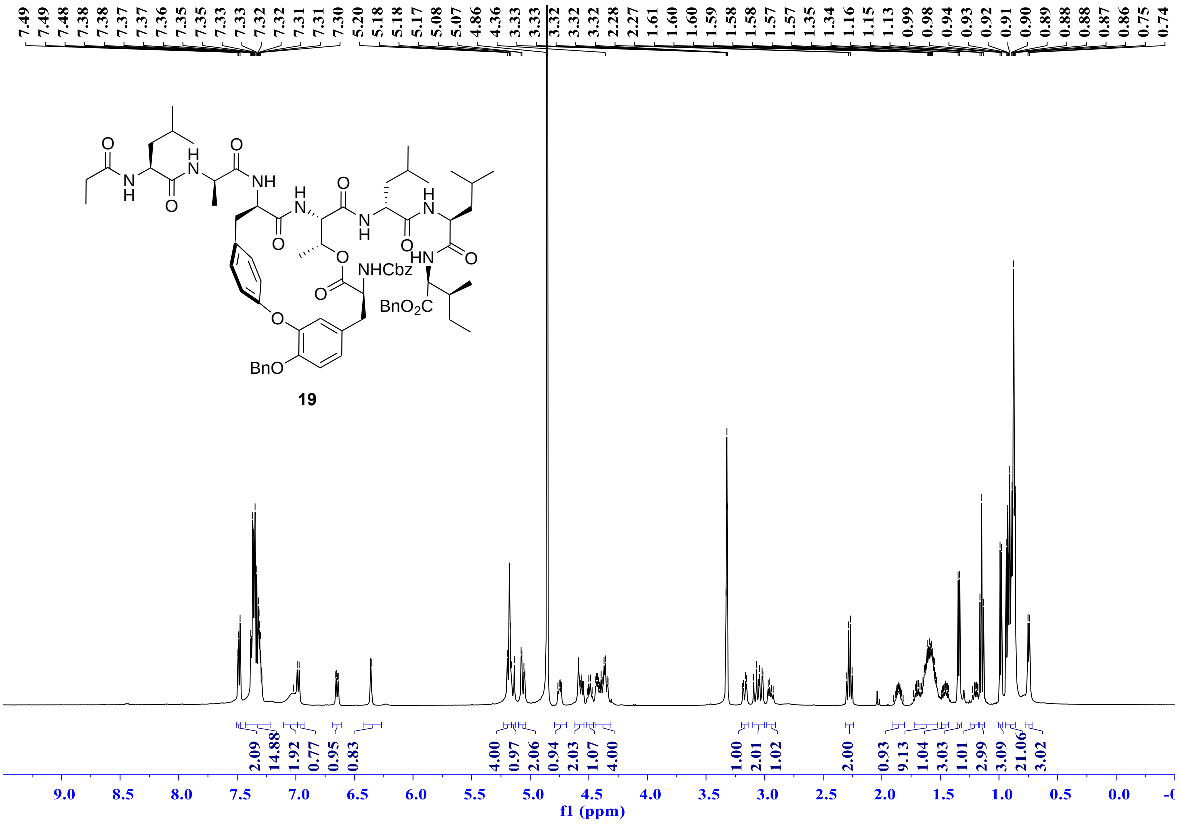
^{1}H NMR Spectra for 18 (CD_3OD)



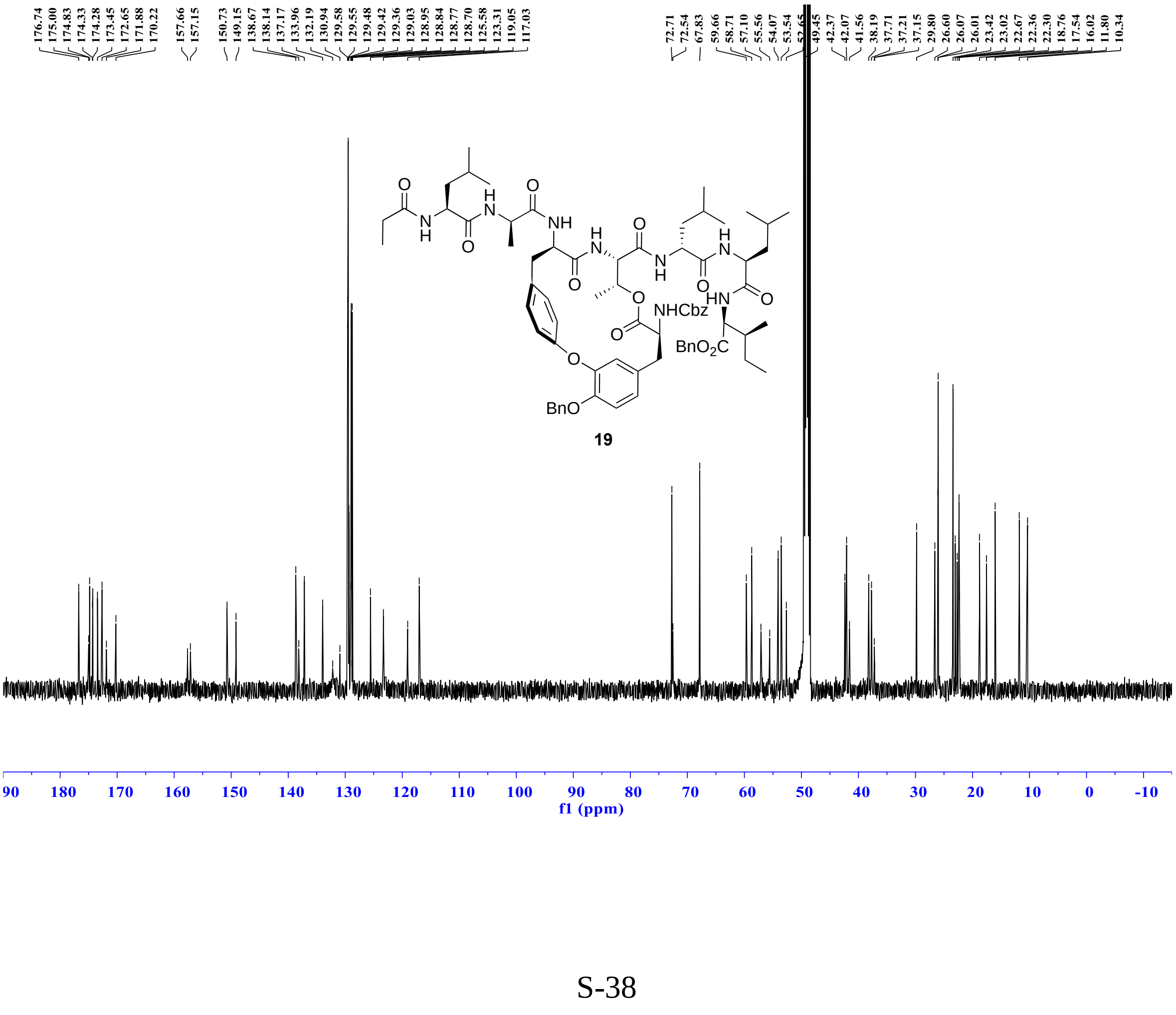
^{13}C NMR Spectra for 18 (CD_3OD)



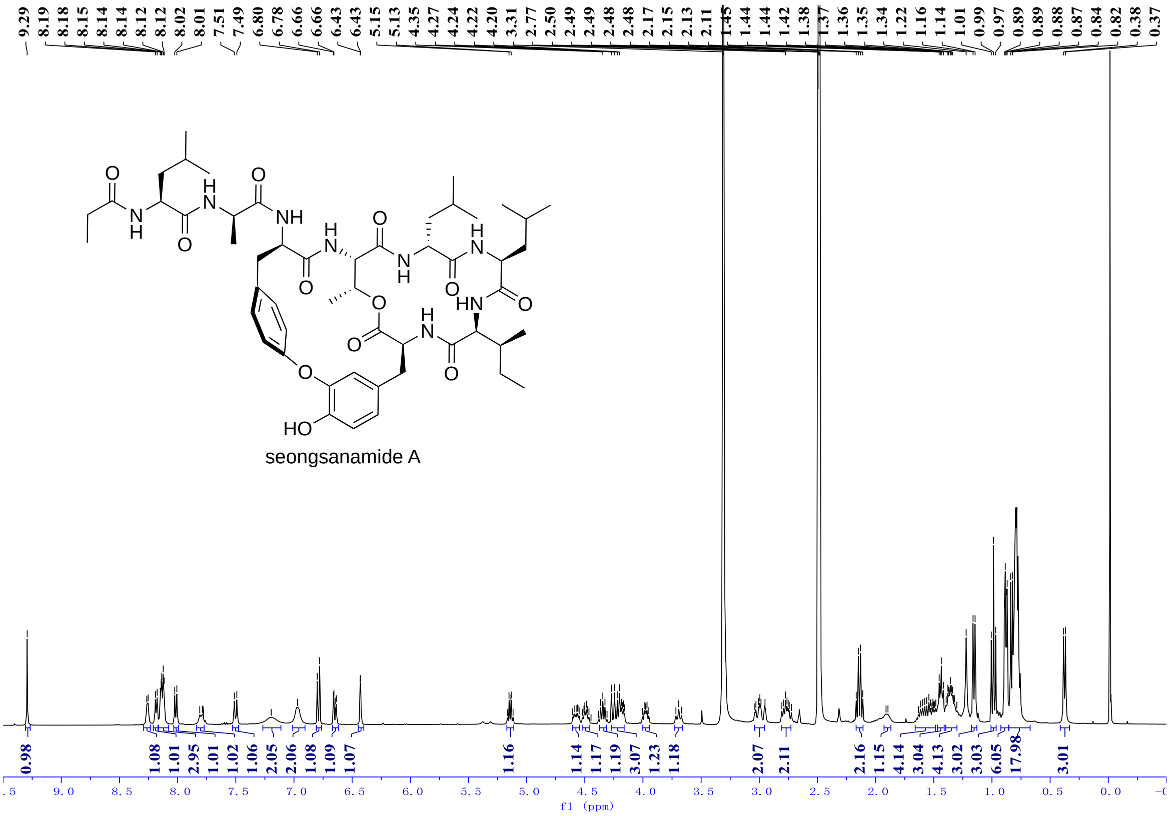
^{1}H NMR Spectra for 19 (CD_3OD)



^{13}C NMR Spectra for 19 (CD_3OD)



^{1}H NMR Spectra for Seongsanamide A (DMSO-d_6)



^{13}C NMR Spectra for Seongsanamide A (DMSO-d_6)