Supporting Information

Total Synthesis of Plusbacin A_3: A Depsipeptide Antibiotic Active Against Vancomycin-Resistant Bacteria

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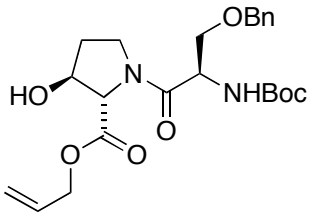
General. All reactions were carried out in flame-dried glassware under an atmosphere of dry nitrogen or argon. Unless otherwise mentioned, solvents were purified as follows. All solvents were dried over activated alumina using a Seca Solvent System (Glass Contour). All other commercially available reagents were used as received.

^{1}H NMR spectra were measured at 300 MHz on a Varian Mercury instrument, at 400 MHz on a Varian Gemini-400, or at 500 MHz on a Varian VXR-500 instrument. ^{13}C NMR spectra were measured at 100 MHz on a Varian Gemini spectrometer. Chemical shifts are reported relative to the central line of residual solvent. Infrared spectra were recorded using a Nicolet IR/42 spectrometer FT-IR (thin film, NaCl cells). High-resolution mass spectra were obtained via electrospray ionization on an Agilent ESI-TOF spectrometer. Optical rotations were measured on a Perkin–Elmer polarimeter (Model 241) using a 1 mL capacity quartz cell with a 10 cm path length.

Analytical thin layer chromatography (TLC) was performed using Whatman glass plates coated with a 0.25 mm thickness of silica gel containing PF 254 indicator, and compounds were visualized with UV light, potassium permanganate stain, cerium molybdate stain or ninhydrin stain. Analytical high performance liquid chromatography (HPLC) was performed on a Beckman-Coulter instrument (System Gold) with diode array detection. Analysis was carried out using Phenomenex Jupiter reverse-phase (C_{18}) column (10μ particle size, 300 Å pore size, 250 mm length x 4.6 mm diameter) with mobile phases consisting of 1% trifluoroacetic acid in water and acetonitrile. Preparatory HPLC purifications (Phenomenex Jupiter C_{18} reverse-phase column, 10μ particle size, 300 Å pore size, 250 mm length x 21.2 mm diameter) were performed with a Waters

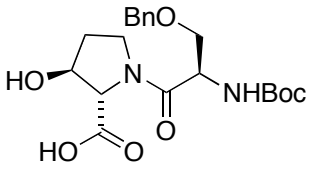
Millipore Model 510 System with a Model 2487 Dual Absorbance Detector. Flash chromatography purifications were performed using Silicycle 60 Å, 35-75 μm silica gel or Biotage purification system (SP1 HPFC system). All compounds purified by chromatography were sufficiently pure for use in further experiments, unless otherwise noted.

Experimental Section



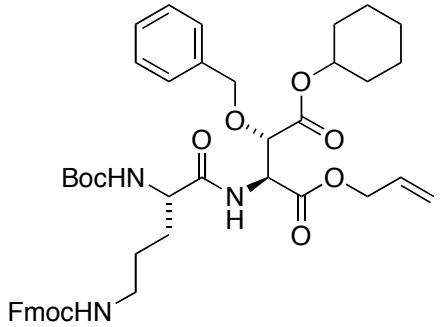
Boc-D-Ser(OBn)-β-OH-Pro-OAllyl. Boc-β-OH-Pro-OAllyl (0.457 g, 1.68 mmol) was treated with 4N HCl-Dioxane (3 mL) and the resulting mixture was stirred at room temperature for 90 minutes. The volatiles were removed in vacuo. The residual HCl was further removed by adding Et_2O (3 mL) to the hydrochloride salt followed by its removal in vacuo. This residue and Boc-D-Ser(OBn)-OH (0.500 g, 1.69 mmol) were dissolved in THF (5.11 mL). The mixture was then treated sequentially at 0^oC with DIEA (0.587 mL, 3.37 mmol), HOAt (0.298 g, 2.19 mmol), and EDCI (0.420 g, 2.19 mmol). The reaction mixture was stirred for 8 hrs while slowly warming to room temperature. The reaction was quenched with H_2O (2 mL) and the solvent was condensed. The residue was redissolved in EtOAc (30 mL), washed with 1N HCl (1 x 20 mL), saturated $NaHCO_3$ (1 x 20 mL), and brine (1x 20 mL), dried over Mg_2SO_4, filtered and concentrated in vacuo. Chromatography (10% EtOAc-Hexanes) provided Boc-D-Ser(OBn)-β-OH-Pro-OAllyl as a white hydroscopic foam (0.676 g, 1.506 mmol, 89%). $[\alpha]^{22}_D$ -34.8 (c 1.0, $CHCl_3$); ^1H

NMR (400 MHz, $CDCl_3$) δ 7.33-7.22 (m, 1H), 5.87 (tdd, *J* = 16.14, 10.56, 5.68, 5.68 Hz, 1H), 5.42 (d, *J* = 8.32 Hz, 1H), 5.34-5.26 (m, 1H), 5.22 (dd, *J* = 10.45, 1.23 Hz, 1H), 4.75 (dd, *J* = 13.51, 7.54 Hz, 1H), 4.60 (td, *J* = 5.64, 1.22, 1.22 Hz, 2H), 4.49 (d, *J* = 9.31 Hz, 2H), 4.45 (t, *J* = 4.47, 4.47 Hz, 1H), 4.41 (s, 1H), 3.90-3.77 (m, 2H), 3.68 (dd, *J* = 9.27, 5.41 Hz, 1H), 3.58 (dd, *J* = 9.24, 7.36 Hz, 1H), 2.11 (m 1H), 1.99-1.87 (m, 1H), 1.45-1.36 (m, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.8, 169.4, 155.0, 137.6, 131.5, 128.3, 127.6, 127.5, 118.6, 79.8, 73.2, 73.1, 70.5, 68.0, 65.9, 51.6, 45.0, 32.8, 28.3; IR (neat) ν_{max} 3409, 2980, 2934, 2873, 1745, 1707, 1645, 1507, 1454, 1362, 1247, 1170, 1108; ESI MS *m/z* 470.99 $[M+Na]^+$



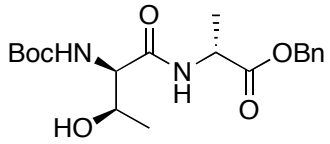
Boc-D-Ser(OBn)-β-OH-Pro-OH (2). $PdCl_2(PPh_3)_2$ (0.067 g, 0.096 mmol) and PPh_3(0.075 g, 0.287 mmol) were dissolved in dry CH_2Cl_2 (2 mL) and stirred under an atmosphere of argon for 15 minutes. This solution was transferred via syringe to a solution of Boc-D-Ser(OBn)- β-OH-Pro-OAllyl (1.716 g, 3.83 mmol) in dry CH_2Cl_2 (17.0 mL) under argon. $PhSiH_3$ (0.944 mL, 7.65 mmol) was added via syringe and the reaction was stirred at room temperature for 12 hours. The solvent was concentrated via rotary evaporation and the crude residue was loaded directly onto a silica gel column. Chromatography (1-30% MeOH-$CHCl_3$) afforded **2** (1.33 g, 3.26 mmol, 85%) as a white solid. mp 88-90 ^oC; $[\alpha]^{22}_D$ -12.6 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, 45 ^oC, DMSO-d_6) δ 7.35-7.25 (m, 5H), 4.60 (dd, *J* = 13.51, 6.58 Hz, 1H), 4.49 (d, *J* = 3.52 Hz, 1H), 4.47-

4.43 (m, 1H), 4.41-4.38 (m, 1H), 4.36 (d, J = 11.34 Hz, 1H), 4.28-4.23 (m, 1H), 4.14 (s, 1H), 3.71 (ddd, J = 27.00, 17.53, 9.09 Hz, 2H), 3.63-3.47 (m, 1H), 3.45-3.38 (m, 1H), 2.04-1.82 (m, 1H), 1.84-1.63 (m, 1H), 1.40-1.36 (m, 9H), 6.71 (d, J = 42.74 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.457, 169.946, 155.298, 137.626, 128.243, 127.484, 127.418, 79.771, 72.915, 69.872, 69.107, 64.481, 51.550, 45.490, 32.471, 28.249, IR (neat) ν_{max} 3386, 2983, 2928, 1717, 1631, 1515, 1452, 1367, 1165, 1103; ESI MS m/z 431.08 [M+Na]+



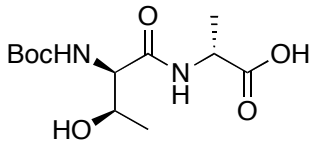
Boc-Orn(Fmoc)-β-OBn-D-*a*Asp(OCy)-OAllyl. Boc-β-OBn-D-*a*Asp(OCy)-OAllyl (0.447 g, 0.968 mmol) was treated with 4N HCl-Dioxane (3 mL) and the solution was stirred at ambient temperature for 90 min. The volatiles were removed in vacuo. The residual HCl was removed by the addition of Et_2O and its subsequent removal in vacuo. The hydrochloride salt was employed without any further purification. To a solution of Boc-Orn(Fmoc)-OH (0.660 g, 1.451 mmol) in THF (2.93 mL) was added HCl-βOBn-D-*a*Asp(OCy)-OAllyl (0.385 g, 0.968 mmol), DIEA (0.37 mL, 2.13 mmol), and HOBt (0.261 g, 1.935 mmol). The solution was cooled to 0^{O}C followed by the addition of EDCI (0.371 g, 1.935 mmol) and the resulting suspension was stirred overnight while slowly warming to room temperature. The reaction was quenched by the addition of EtOAc (1 mL). The THF was removed in vacuo and the residue was diluted with EtOAc

(30 mL). The solution was washed with 1N HCl (1 x 20 mL), sat. aq. $NaHCO_3$ (1 x 20 mL) and brine (1 x 20 mL). The EtOAc was dried over Mg_2SO_4, filtered and condensed. Chromatography (30% EtOAc-Hexanes) gave Boc-Orn(Fmoc)-βOBn-D-*a*Asp(OCy)-OAllyl (0.718 g, 0.900 mmol, 93%). mp 48-50 ^oC; $[\alpha]^{22}_D$ +11.6 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6) δ 8.12 (d, *J* = 8.69 Hz, 1H), 7.89 (d, *J* = 7.60 Hz, 1H), 7.68 (d, *J* = 8.02 Hz, 2H), 7.41 (m, 2H), 7.37-7.23 (m, 7H), 6.95 (d, *J* = 7.91 Hz, 1H), 5.91-5.72 (m, 1H), 5.29 (d, *J* = 17.26 Hz, 1H), 5.18 (d, *J* = 10.56 Hz, 1H), 4.94 (d, *J* = 8.68 Hz, 1H), 4.79-4.65 (m, 2H), 4.57 (s, 2H), 4.53-4.39 (m, 2H), 4.27 (s, 2H), 4.20 (d, *J* = 6.10 Hz, 1H), 4.09-3.99 (m, 1H), 2.93 (s, 1H), 1.85-1.50 (m, 6H), 1.48-1.15 (m, 17H); ^{13}C NMR(100MHz, $CDCl_3$) 171.779, 167.995, 156.375, 155.068, 143.789, 143.713, 140.953, 136.276, 131.033, 128.133, 127.924, 127.321, 126.728, 124.880, 119.651, 118.903, 79.725, 76.406, 74.373, 72.511, 66.403, 54.275, 53.453, 47.187, 40.170, 31.541, 31.217, 30.197, 28.285, 25.580, 25.168, 23.646, 23.607; IR (neat) ν_{max} 3425, 3340, 3068, 3014, 2936, 2858, 1748, 1717, 1700, 1684, 1522, 1452, 1367, 1250, 1212, 1165, 1103; ESI MS *m/z* 820.20 $[M+Na]^+$, 797.87 $[M+H]^+$



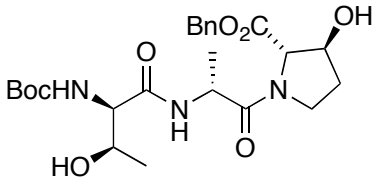
Boc-D-*a*Thr-DAla-OBn (9). Boc-D-Ala-OBn (7.08 g, 25.3 mmol) was treated with a solution of 20% TFA in CH_2Cl_2 (48.7 mL, 127 mmol) and stirred for 1 hr at room temperature. The solvent was removed in vacuo and the residue was diluted with sat. aq. $NaHCO_3$ (75 mL) and CH_2Cl_2 (75 mL). The aq. phase was extracted with CH_2Cl_2 (4 x 75 mL). The combined organic extracts were dried over Na_2SO_4, filtered and condensed

to afford H_2N-D-Ala-OBn as a colorless, viscous oil which was used without further purification. This residue, Boc-D-*a*Thr-OH (4.5 g, 20.53 mmol), HOBt (5.55 g, 41.1 mmol) and DIEA (3.60 mL, 20.53 mmol) were dissolved in THF (62 mL). The solution was cooled to 0^oC and EDCI (7.87 g, 41.1 mmol) was added. The reaction mixture was stirred 36 hrs and then quenched with H_2O (3 mL). The THF was removed in vacuo and to the residue was added EtOAc (100 mL). This solution was washed with 1N HCl (1 x 75 mL), sat. aq. $NaHCO_3$ (1 x 75 mL), and brine (1 x 75mL). The EtOAc was dried over Mg_2SO_4, filtered and condensed. Chromatography (35% EtOAc/Hexanes) provided **9** (6.815 g, 17.91 mmol, 87%) as a white solid. mp 79-81^oC; $[\alpha]^{22}_D$ +36.1 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 6.87 Hz, 1H), 7.41-7.29 (m, 5H), 6.58 (d, J = 8.95 Hz, 1H), 5.11 (s, 2H), 4.69 (d, J = 5.08 Hz, 1H), 4.34 (p, J = 7.17, 7.17, 7.09, 7.09 Hz, 1H), 3.98 (dd, J = 8.86, 5.82 Hz, 1H), 3.83 (dd, J = 11.61, 5.78 Hz, 1H), 1.38 (s, 9H), 1.30 (d, J = 7.26 Hz, 3H), 1.00 (d, J = 6.33 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) 172.7, 171.0, 156.0, 135.1, 128.5, 128.4, 128.1, 80.2, 69.3, 67.7, 58.6, 48.3, 28.2, 19.4, 17.4; IR (neat) ν_{max} 3308, 3072, 2981, 2933, 1713, 1658, 1522, 1456, 1394, 1367, 1293, 1247, 1204, 1161, 1049, 1017, 885, 750, 699; ESI MS *m/z* 403.04 $[M+Na]^+$, 380.85 $[M+H]^+$



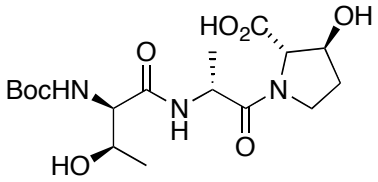
Boc-D-*a*Thr-D-Ala-OH. Boc-D-*a*Thr-D-Ala-OBn (6.51 g, 17.11 mmol) was dissolved in MeOH (115 mL). 10% palladium on carbon (0.651 g, 0.612 mmol) was added and the mixture was purged with H_2 three times. The reaction was stirred vigorously under an

atmosphere of H_2 for 5 hours. The mixture was then filtered through a pad of celite and the solvent was removed to afford Boc-D-*a*Thr-D-Ala-OH (4.91 g, 16.91 mmol, 99%) as a white solid. The crude product was used without further purification. mp 113-115 ^{o}C ; $[\alpha]^{22}_{D}$ -11.7 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) ppm 8.04 (d, J = 7.05 Hz, 1H), 6.64 (d, J = 8.90 Hz, 1H), 4.21 (p, J = 7.16, 7.16, 7.15, 7.15 Hz, 1H), 3.93 (dd, J = 8.70, 6.21 Hz, 1H), 3.82 (p, J = 6.05, 6.05, 6.01, 6.01 Hz, 1H), 3.35 (s, 1H), 1.38 (s, 9H), 1.26 (d, J = 7.27 Hz, 3H), 1.02 (d, J = 6.28 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 175.601, 171.213, 156.262, 80.520, 69.404, 59.273, 48.395, 28.254, 19.062, 17.202; IR (neat) ν_{max} 3308, 2984, 2933, 1697, 1654, 1530, 1456, 1394, 1367, 1297, 1243, 1161, 1041, 1017, 937, 870, 781; ESI MS *m/z* 288.86 $[M+Na]^+$



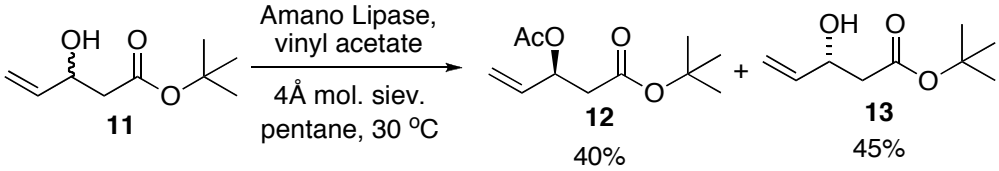
Boc-D-*a*Thr-D-Ala-β-OH-Pro-OBn (10). Boc-D-β-OH-Pro-OBn (6.455 g, 20.09 mmol) was treated with a solution of 4N HCl-Dioxane (25 mL 100mmol) and stirred for 1hr at room temperature. The solvent was condensed and hexanes (50 mL) was added then condensed in vacuo two times to remove any residual HCl. The white solid was left under high vacuum for several hours to afford HCl-β-OH-Pro-OBn (5.17 g, 20.06 mmol, 99%) which was used without further purification. To this solid, Boc-D-*a*Thr-D-Ala-OH (4.87 g, 16.78 mmol), HOBt (4.53 g, 33.6 mmol) and DIEA (4.34 mL, 33.6 mmol) in DMF (51mL) at 0 ^{o}C was added EDCI (6.43 g, 33.6 mmol). The reaction mixture was

stirred 36 hrs and then quenched with H_2O (2 mL). The DMF was removed in vacuo and to the residue was added EtOAc (100 mL). This solution was washed with 1N HCl (1 x 75 mL), sat. aq. $NaHCO_3$ (1 x 75 mL), and brine (1 x 75 mL). The EtOAc was dried over Mg_2SO_4, filtered and condensed. Chromatography (35% Acetone-CH_2Cl_2) provided **10** (7.41 g, 15.0 mmol, 90%) as a white solid. mp 71-73 ^oC; $[\alpha]^{22}_D$ -3.9 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.02 (d, J = 7.35 Hz, 1H), 7.86 (d, J = 7.61 Hz, 1H), 7.41-7.31 (m, 5H), 6.76 (d, J = 8.82 Hz, 1H), 5.57 (d, J = 3.61 Hz, 1H), 5.20 (s, 1H), 5.10 (dd, J = 30.20, 12.57 Hz, 2H), 4.79 (d, J = 4.82 Hz, 1H), 4.65 (p, J = 6.75, 6.75, 6.67, 6.67 Hz, 1H), 4.22 (s, 1H), 4.18 (s, 1H), 3.91 (dd, J = 8.45, 6.23 Hz, 1H), 3.86-3.74 (m, 2H), 3.63 (dd, J = 16.66, 9.63 Hz, 1H), 3.47 (m, 1H), 1.97 (dq, J = 9.22, 9.10, 9.10, 4.34 Hz, 1H), 1.91-1.73 (m, 1H), 1.37 (s, 9H), 1.20 (d, J = 6.79 Hz, 3H), 1.04-0.96 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.4, 172.0, 171.4, 170.8, 169.7, 169.5, 155.8, 155.8, 135.2, 134.9, 128.6, 128.5, 128.3, 128.3, 128.0, 80.0, 74.6, 72.7, 69.2, 68.7, 68.1, 68.1, 67.5, 67.1, 59.5, 58.8, 47.2, 47.1, 44.9, 32.6, 30.5, 28.2, 19.7, 19.3, 17.1, 16.9; IR (neat) ν_{max} 3312, 3070, 2976, 2929, 1740, 1694, 1632, 1519, 1454, 1255, 1170, 1102, 1044; ESI MS *m/z* 516.09 $[M+Na]^+$



Boc-D-*a*Thr-D-Ala-β-OH-Pro-OH (4). To a solution of Boc-D-*a*Thr-D-Ala-β-OH-Pro-OBn **(10)** (4.524 g, 9.17 mmol) in MeOH (45 mL) was added 5% Pd-C (0.500 g). The flask was purged with H_2 three times and stirred for 8hr under an H_2 atmosphere. The mixture was then filtered through a pad of celite and the solvent was removed to afford the carboxylic acid (**4**) (3.68 g, 9.12 mmol, 100%) as a white solid. The product was

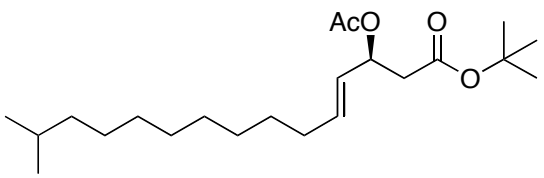
used without further purification. mp 92-95 ^{o}C; $[\alpha]^{22}_{D}$ +25.2 (c 1.00, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (d, J = 7.32 Hz, 1H), 7.84 (d, J = 7.61 Hz, 1H), 6.78 (d, J = 8.79 Hz, 1H), 5.49 (s, 1H), 4.84-4.72 (m, 1H), 4.62 (p, J = 6.58, 6.58, 6.58, 6.58 Hz, 1H), 4.52 (s, 1H), 4.39 (s, 1H), 4.31 (p, J = 7.33, 7.33, 7.15, 7.15 Hz, 1H), 4.22 (s, 1H), 4.08 (s, 1H), 3.94-3.86 (m, 1H), 3.85-3.69 (m, 2H), 3.60 (q, J = 9.23, 9.23, 9.00 Hz, 1H), 3.49-3.40 (m, 1H), 3.16 (s, 1H), 2.03-1.90 (m, 1H), 1.90-1.70 (m, 1H), 1.37 (s, 9H), 1.18 (d, J = 6.70 Hz, 2H), 1.11 (d, J = 6.67 Hz, 1H), 1.01 (d, J = 5.87 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 174.0, 173.2, 172.4, 157.7, 80.7, 76.0, 74.0, 68.8, 61.2, 48.2, 46.0, 33.8, 31.6, 28.7, 19.5, 17.4, IR (neat) ν_{max} 3351, 2984, 2929, 1692, 1633, 1529, 1464, 1393, 1367, 1250, 1156; ESI MS m/z 426.02 $[M+Na]^{+}$



(S)-tert-butyl 3-acetoxypent-4-enoate (12). To a solution of **11** (7.95 g, 46.2 mmol) and vinyl acetate(21.3 mL, 231 mmol) in pentane (230 mL) was added Amano Lipase PS (4.62 g) and 4 Angstrom molecular Sieves (7.62 g). The reaction was stirred at 30 ^{o}C for 10 hours and filtered through a short plug of silica rinsing with Ether. (Reaction times varied between 10–24 hrs. Conversion to the acetate was monitored following β-proton signals in ^{1}H NMR.) The mixture was condensed and column chromatography (PE-Et_2O,8:2) afforded the (*S*)-acetate product (3.88 g, 18.1 mmol, 40%) and (*R*)-alcohol (3.56 g, 20.7 mmol, 45%) as colorless oils. Analytical data for (*S*)-*tert*-butyl-3-acetoxypent-4-enoate (**12**): $[\alpha]^{22}_{D}$ -4.4 (c 1.0, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, J = 17.01, 10.50, 6.18 Hz, 1H), 5.59 (dd, J = 13.53, 6.35 Hz, 1H), 5.29 (d, J =

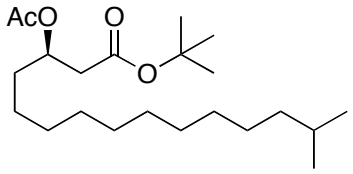
17.31 Hz, 1H), 5.19 (d, *J* = 10.21 Hz, 1H), 2.55 (ddd, *J* = 20.99, 15.25, 6.89 Hz, 2H), 2.04 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.5, 168.7, 135.0, 117.2, 81.0, 71.1.0, 40.7, 28.1.0, 21.1; IR (Neat) v_{max} 2976, 2937, 2367, 1741, 1366, 1233, 1155; ES MS *m/z* 236.90 $[M+Na]^+$

Analytical data for (*R*)-tert-butyl 3-hydroxypent-4-enoate (**13**): $[\alpha]^{22}_D$ +8.4 (c 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 17.16, 10.51, 5.48 Hz, 1H), 5.26 (td, *J* = 17.22, 1.43, 1.43 Hz, 1H), 5.09 (td, *J* = 10.52, 1.35, 1.35 Hz, 1H), 4.45 (s, 1H), 3.25 (s, 1H), 2.43 (dq, *J* = 16.07, 16.07, 16.07, 6.20 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 171.3, 138.7, 114.9, 81.3, 69.0, 42.2, 28.1; IR (Neat) v_{max} 3425, 2983, 2920, 2105, 1647, 1367, 1258, 1157; ES MS *m/z* 194.91 $[M+Na]^+$

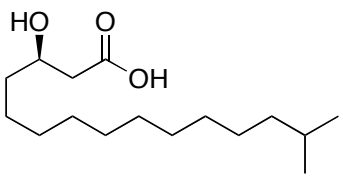


(***S*)-*tert*-butyl-3-acetoxy-14-methylpentadec-4-enoate.** To a stirring solution of the allylic acetate (**12**) (5.00 g, 23.3 mmol) and 11-methyl-1-dodecene (16.71g, 92.0 mmol) in dry CH_2Cl_2 (117 mL) was added Grubb's 2nd generation catalyst (0.992 g, 1.17 mmol. The flask was fitted with condenser and stirred at 50 ^{o}C under a steady stream of argon for 24 hours. The reaction mixture was then reduced in volume and loaded directly onto a silica gel column. Chromatography (0-10% EtOAc-Hexanes) afforded the hydroxy lipid (7.74g, 21.0mmol, 90%) as a pale yellow oil. The unreacted lipid was recovered quantitativly and recycled. $[\alpha]^{22}_D$ -23.9 (c 1.0, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.52 (dd, *J* = 13.78, 7.28 Hz, 1H), 5.37 (dd, *J* = 15.35, 7.28 Hz, 1H), 2.50 (ddd, *J* = 20.92, 15.08, 6.93 Hz, 2H), 1.98 (s, 3H), 1.54-1.41 (m, 3H), 1.39 (s, 9H), 1.35-

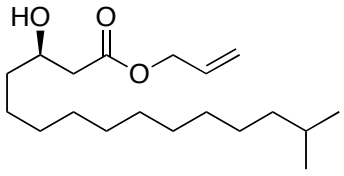
1.26 (m, 4H), 1.26-1.17 (m, 11H), 1.15-1.06 (m, 3H), 0.82 (d, J = 6.60 Hz, 6H) ^{13}C NMR (75MHz, $CDCl_3$) δ 169.7, 169.0, 135.2, 126.7, 80.7, 71.2, 41.1, 38.9, 32.1, 29.8, 29.5, 29.4, 29.0, 28.7, 27.9, 27.9, 27.3, 22.6, 21.1; IR (neat) v_{max} 3441, 2928, 2850, 2361, 2097, 1732, 1639, 1468, 11367, 1235, 1157, 1017, 963; ESI MS *m/z* 391.05 $[M+Na]^+$, 385.86 $[M+NH_4]^+$



(*R*)-*tert*-butyl-3-acetoxy-14-methylpentadecanoate (15). (*S*)-*tert*-butyl-3-acetoxy-14-methylpentadec-4-enoate (1.03g, 2.79mmol) was dissolved in ethanol (27 mL) and 10% Pd/C (0.155g) was added. The flask was sealed and purged with hydrogen. The mixture was stirred for 24 hours, and upon completion filtered through a celite pad. The solvent was removed and silica gel chromatography (10% EtOAc-Hexanes) afforded **15** (1.0181 g, 2.75 mmol, 98%) as a colorless oil. $[\alpha]^{22}_D$ +2.89 (c 1.625, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (m, 1H), 2.40 (dd, J = 6.56, 2.28 Hz, 2H), 1.96 (s, 3H), 1.57-1.41 (m, 6H), 1.37 (s, 1H), 1.24-1.16 (m, 15H), 0.80 (d, J = 6.61 Hz, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 170.1, 169.5, 80.5, 70.7, 40.5, 38.9, 33.9, 29.8, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 27.9, 27.3, 25.0, 22.5, 20.9; IR (neat) 2930, 2857, 1743, 1466, 1371, 1240, 1152; ESI MS *m/z* 393.09 $[M+Na]^+$

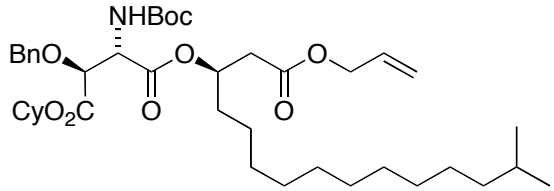


(*R*)-3-hydroxy-14-methylpentadecanoic acid. (*R*)-*tert*-butyl-3-acetoxy-14-methyl-pentadecanoate (9.25 g, 24.95 mmol) was treated with a solution of TFA/CH_2Cl_2 (1:1, 100 mL) and allowed to stir at room temperature overnight. The volatiles were removed in vacuo and the residue was left under high vacuum for several hours. The crude material was dissolved in MeOH (125 mL) and K_2CO_3 (17.3 g, 125 mmol) was added. The mixture was stirred for 12 hours and the solvent was removed. EtOAc (50 mL) was added followed by the careful addition of 1N HCl while stirring. The aq. phase was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (1x 50 mL), dried over Mg_2SO_4, filtered and condensed. Silica gel chromatography (EtOAc) afforded (*R*)-3-hydroxy-14-methylpentadecanoic acid (6.12 g, 22.47 mmol, 90%) as a white solid. mp 59-60 ^oC; $[\alpha]^{22}_D$ -13.6 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.03 (tt, *J* = 8.04, 8.04, 4.08, 4.08 Hz, 1H), 2.51 (ddd, *J* = 25.53, 16.54, 6.07 Hz, 2H), 1.59-1.38 (m, 4H), 1.34-1.19 (m, 15H), 1.14 (dd, *J* = 13.18, 6.47 Hz, 2H), 0.85 (d, *J* = 6.62 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 178.080, 68.323, 41.3, 39.3, 36.7, 30.2, 29.9, 29.9, 29.8, 29.8, 29.7, 28.2, 27.6, 25.7, 22.9; IR (neat) ν_{max} 3228, 2922, 2850, 2689, 2592, 1713, 1467, 1446, 1363, 1316, 1301, 1189; ESI MS *m/z* 271.16 $[M-H]^-$



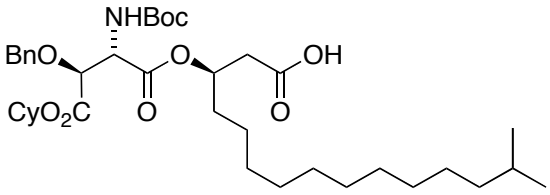
(*R*)-allyl-3-hydroxy-14-methylpentadecanoate (16). To a solution of (*R*)-3-hydroxy-14-methylpentadecanoic acid (1.50 g, 5.51 mmol) in MeOH (23 mL) was added Cs_2CO_3(1.83 g, 5.62 mmol) dissolved in H_2O (2.3 mL) drop wise. The mixture was stirred at room temperature for 15 minutes and the solvent was removed in vacuo. To the

residue was added DMF (5 mL). The solvent was removed in vacuo and placed under high vacuum for several hours. DMF (25 mL) was added followed by allyl bromide (4.76 mL, 55.1 mmol) and the mixture was stirred under argon for 12 hours. The DMF was removed and the crude residue was dissolved in EtOAc (30 mL) and washed with water (1 x 20mL) and brine (1 x 20 mL). The organic phase was dried over Mg_2SO_4, filtered and condensed. Column chromatography (10% EtOAc-Hexanes) afforded the allyl ester (**16**) (1.55 g, 4.96 mmol, 90%) as a colorless oil. $[\alpha]^{22}_D$ -13.7 (c 1.0); ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.85 (qd, *J* = 10.44, 5.73, 5.73, 5.73 Hz, 1H), 5.23 (m, 2H), 4.54 (dd, *J* = 5.75, 1.24 Hz, 1H), 3.95 (s, 1H), 3.13 (s, 1H), 2.42 (dq, *J* = 16.23, 16.19, 16.19, 6.13 Hz, 2H), 1.54-1.33 (m, 1H), 1.28-1.16 (m, 15H), 1.12-1.05 (m, 2H), 0.80 (dd, *J* = 6.63, 1.87 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 132.1, 118.8, 68.2, 65.5, 41.5, 39.270, 36.8, 30.2, 29.9, 29.9, 29.8, 29.8, 29.7, 28.2, 27.6, 25.7, 22.9; IR (neat) ν_{max} 3456, 2922, 2854, 2364, 1731, 1648, 1464, 1411, 1384, 1363, 1168; ESI MS *m/z* 313.00 $[M+H]^+$



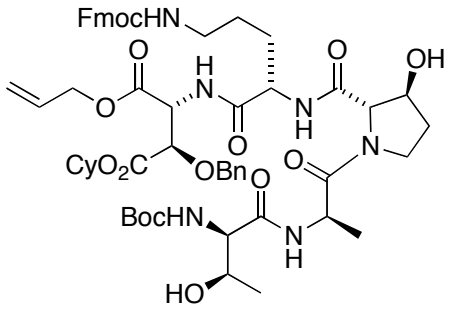
(2S,3S)-1-((*R*)-1-(allyloxy)-14-methyl-1-oxopentadecan-3-yl)-4-cyclohexyl-3-(benzyloxy)-2-(tert-butoxycarbonylamino)succinate. To a stirring solution of Boc-βOBn-Asp(OCy)-OH (0.141 g, 0.335 mmol), the alcohol (**16)** (0.209 g, 0.670 mmol), and DMAP (0.020 g, 0.168 mmol) dissolved in CH_2Cl_2 (1.1ml) at -15 ^{O}C was added EDCI (0.066 g, 0.342 mmol) in five portions over a period of 1 hour. The solution was stirred at this temperature under argon for 2 hours then slowly warmed to room temperature.

The reaction was stirred 12hr then quenched with EtOAc (1ml). The solvent was removed in vacuo and the residue was dissolved in EtOAc (20 mL) then washed with 1N HCl (1 x 10 mL) and brine (1 x 10 mL). The EtOAc was dried over Mg_2SO_4, filtered and condensed. Column chromatography (15% Pet. Ether-Ether) afforded (2*S*,3*S*)-1-((*R*)-1-(allyloxy)-14-methyl-1-oxopentadecan-3-yl) 4-cyclohexyl 3-(benzyloxy)-2-(tert-butoxycarbonylamino)succinate (0.201g, 0.280 mmol, 84%) as a colorless oil. $[\alpha]^{22}_{D}$ -16.0 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H), 5.88 (qd, *J* = 10.50, 5.75, 5.73, 5.73 Hz, 1H), 5.26 (q4 4H), 4.89-4.82 (m, 1H), 4.84-4.76 (m, 2H), 4.58-4.50 (m, 1H), 4.39 (d, *J* = 10.97 Hz, 1H), 2.59 (dq, *J* = 15.62, 15.54, 15.54, 6.24 Hz, 1H), 1.90-1.78 (m, 2H), 1.77-1.65 (m, 2H), 1.63-1.44 (m, 5H), 1.45-1.08 (m, 33H), 0.85 (d, *J* = 6.61 Hz, 1H); ^{13}C (100MHz, $CDCl_3$) δ 169.6, 168.8, 168.5, 155.1, 136.7, 131.8, 128.2, 127.8, 127.8, 118.5, 79.7, 77.7, 74.1, 72.9, 72.3, 65.3, 56.022, 38.9, 38.8, 33.7, 31.4, 31.1, 29.8, 29.5, 29.5, 29.5, 29.3, 29.2, 28.0, 27.8, 27.3, 25.1, 24.9, 23.5, 23.4, 22.6, IR (neat) ν_{max} 3450, 2926, 2857, 1741, 1501, 1456, 1390, 1365, 1336, 1258, 1208, 1163, 1126, 1064; ESI MS *m/z* 738.28 $[M+Na]^+$



(R)-3-((2S,3S)-3-(benzyloxy)-2-(tert-butoxycarbonylamino)-4-(cyclohexyloxy)-4-oxobutanoyloxy)-14-methylpentadecanoic acid (5). $PdCl_2(PPh_3)_2$ (0.013 g, 0.019 mmol) and PPh_3 (0.015 g, 0.057 mmol) were dissolved in dry CH_2Cl_2 (1 mL) and stirred under an atmosphere of argon for 15 min. This solution was transferred via syringe to a

solution of the allyl ester (0.542 g, 0.757 mmol) in dry CH_2Cl_2 (2.8 mL) under argon. $PhSiH_3$ (0.187 mL, 1.51 mmol) was added via syringe and the reaction was stirred at room temperature for 12 hours. The solvent was condensed and the crude residue was loaded directly onto a silica gel column. Chromatography (30% EtOAc-Hexanes) afforded the carboxylic acid (**5**) (0.501 g, 7.42 mmol, 98%) as a colorless oil. $[\alpha]^{22}_D$ -14.8 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 5.38-5.27 (m, 1H), 5.22 (p, *J* = 5.63, 5.63, 5.61, 5.61 Hz, 1H), 4.91-4.75 (m, 3H), 4.55 (s, 1H), 4.39 (d, *J* = 11.01 Hz, 1H), 2.65 (dd, *J* = 16.19, 6.32 Hz, 1H), 2.54 (dd, *J* = 16.13, 5.92 Hz, 1H), 1.90-1.79 (m, 2H), 1.79-1.65 (m, 2H), 1.64-1.45 (m, 5H), 1.44-1.10 (m, 33H), 0.86 (d, *J* = 6.56 Hz, 1H); ^{13}C (100MHz, $CDCl_3$) δ 175.5, 169.2, 168.8, 155.643, 137.0, 128.6, 128.2, 128.2, 80.3, 78.0, 74.6, 73.3, 72.5, 56.4, 39.3, 38.9, 34.0, 31.7, 31.4, 30.171, 29.9, 29.9, 29.7, 29.6, 28.4, 28.2, 27.7, 25.5, 25.3, 23.9, 23.7, 22.9; IR (neat) ν_{max} 3262, 2936, 2858, 1733, 1506, 1456, 1394, 1365, 1336, 1262, 1208, 1163, 1118, 1019; ESI MS *m/z* 628.25 $[M+Na]^+$

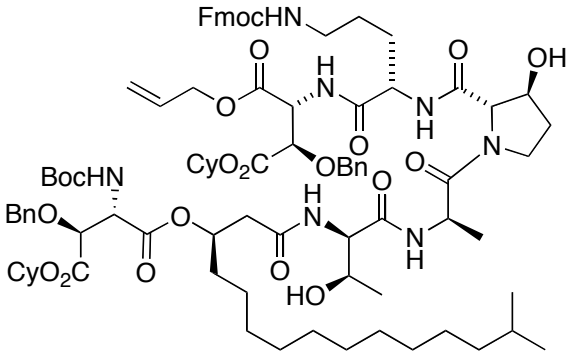


Boc-D-*a*Thr-D-Ala-β-OH-Pro-Orn(Fmoc)-β-OBn-D-*a*Asp(OCy)-OAllyl (17).

Boc-Orn(Fmoc)-β-OBn-D-*a*Asp(OCy)-OAllyl (5.87 g, 7.37 mmol) was treated with 4N HCl-dioxane (15 mL) and the resulting mixture was stirred at room temperature for 90min. The volatiles were removed in vacuo. The residual HCl was further removed by

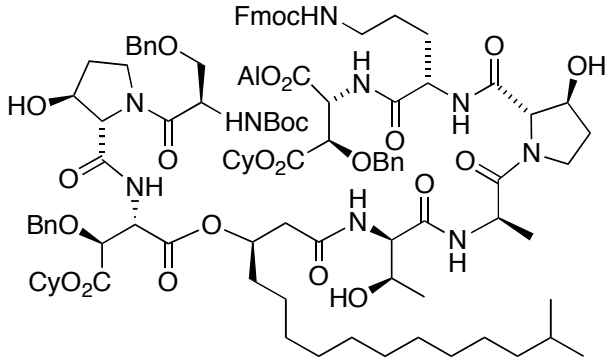
adding Et_2O (3 mL) to the hydrochloride salt followed by its removal in vacuo. This residue, Boc-D-*a*Thr-D-Ala-β-OH-Pro-OH (2.70 g, 6.70 mmol), and DIEA (1.4 mL, 8.04 mmol) were dissolved in THF (22 mL). The solution was cooled to 0 ^oC and EDCI (1.54 g, 8.04 mmol) was added. The reaction mixture was stirred under argon for 18hr and then quenched with H_2O (3 mL). The THF was removed in vacuo and to the residue was added EtOAc (100 mL). This solution was extracted with 1N HCl (1 x 50ml), sat. aq. $NaHCO_3$ (1 x 50 mL), and brine (1 x 50 mL). The EtOAc was dried over Mg_2SO_4, filtered and condensed. Chromatography (EtOAc) provided the pentapeptide (**17**) (6.60 g, 6.10 mmol, 91%) as a white solid. mp 84-86^oC, $[\alpha]^{22}$ -2.2 (c 1.0, $CHCl_3$) ^1H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, *J* = 7.53 Hz, 1H), 8.39 (d, *J* = 9.08 Hz, 1H), 8.23 (d, *J* = 9.37 Hz, 1H), 8.03 (d, *J* = 8.21 Hz, 1H), 7.94-7.86 (m, 4H), 7.71-7.64 (m, 2H), 7.41 (t, *J* = 7.46, 7.46 Hz, 1H), 7.36-7.22 (m, 13H), 6.73 (t, *J* = 9.32, 9.32 Hz, 1H), 5.81 (tdd, *J* = 16.00, 10.71, 5.49, 5.49 Hz, 1H), 5.32-5.15 (m, 3H), 4.99-4.89 (m, 1H), 4.79 (dd, *J* = 18.04, 4.81 Hz, 2H), 4.75-4.66 (m, 2H), 4.61-4.52 (m, 4H), 4.50 (m, 1H), 4.46 (m, , 1H), 4.43 (d, *J* = 11.85 Hz, 1H), 4.35 (dd, *J* = 13.78, 6.59 Hz, 1H), 4.31-4.25 (m, 3H), 4.24-4.15 (m, 4H), 3.90 (t, *J* = 7.56, 7.56 Hz, 1H), 3.83-3.75 (m, 1H), 3.74 (t, *J* = 10.02, 10.02 Hz, 1H), 3.57 (m , 1H), 3.46 (dd, *J* = 9.87, 4.17 Hz, 1H), 3.02-2.88 (m, 2H), 2.03-1.83 (m, 1H), 1.84-1.55 (m, 9H), 1.55-1.22 (m, 18H), 1.24-1.11 (m, 3H), 1.07-0.98 (m, 3H); ^{13}C (100MHz, $CDCl_3$) δ 172.5, 171.941, 171.3, 169.8, 168.3, 156.7, 155.7, 144.0, 143.9, 141.1, 136.3, 131.2, 128.3, 128.e, 128.1, 127.5, 126.9, 125.1, 119.8, 119.1, 79.8, 76.4, 74.5, 73.0, 72.7, 69.0, 68.9, 66.5, 59.2, 54.2, 52.8, 47.5, 47.2, 45.2, 40.3, 32.3, 31.4, 31.1, 30.5, 28.7, 28.2, 25.7, 25.1, 23.496, 19.7, 19.6, 16.4; IR (neat) ν_{max} 3306, 3068, 2981, 2937, 2859, 2364, 1743, 1699, 1650, 1527, 1454, 1393, 1367, 1163, 1104; ESI MS *m/z*

1105.27 $[M+Na]^+$



Septapeptide (18). Boc-D-*a*Thr-D-Ala-β-OH-Pro-Orn(Fmoc)-β-OBn-D-*a*Asp(OCy)-OAllyl (**17**) (0.860 g, 0.794 mmol) was treated with a solution of 4N HCl-dioxane (4.0 mL, 15.89 mmol) and stirred for 90 minutes. The volatiles were removed in vacuo. The residual HCl was further removed by adding Et_2O (5 mL) to the hydrochloride salt followed by its removal in vacuo. The residue was then dissolved in EtOAc (30ml) and washed with sat. aq. $NaHCO_3$ (2 x 20 mL). The EtOAc was dried over Mg_2SO_4, filtered and condensed. This residue, the carboxylic acid (**5**) (0.486g, 0.719 mmol), and HOBt (0.117 g, 0.863 mmol) were dissolved in THF (2.4 mL) and cooled to 0 ^oC. EDCI (0.165 g, 0.863 mmol) was added and the mixture was stirred under argon for 18 hrs while slowly warming to room temperature. The reaction was quenched with EtOAc (5 mL) and the THF removed in vacuo. This residue was dissolved in EtOAc (50 mL) and washed with 1N HCl (1 x 30 mL), saturated aq. $NaHCO_3$ (1 x 30 mL), and brine (1 x 30mL). The organic phase was dried over Mg_2SO_4, filtered and condensed. Column chromatography (EtOAc) afforded the septapeptide **18** (0.980 g, 0.597 mmol, 83%) as a white solid. mp 70-72 ^oC; $[\alpha]^{22}_D$ – 1.0 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-*d6)* δ 8.38 (d, *J* = 9.31 Hz, 1H), 8.23 (d, *J* = 9.13 Hz, 1H), 8.06 (d, *J* = 9.10 Hz, 1H), 8.04 (d, *J* = 9.65 Hz, 1H), 8.00 (d, *J* = 8.21 Hz, 1H), 7.86 (d, *J* = 7.47 Hz, 2H), 7.69-7.61 (m, 2H),

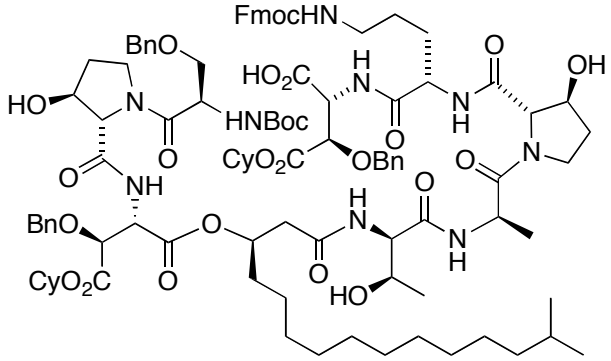
7.38 (t, *J* = 7.40, 7.40 Hz, 2H), 7.34-7.21 (m, 14H), 6.83 (dd, *J* = 17.39, 9.66 Hz, 1H), 5.79 (tdd, *J* = 16.10, 10.95, 5.47, 5.47 Hz, 1H), 5.21 (dd, *J* = 42.63, 13.72 Hz, 2H), 5.08 (m,1H), 4.97-4.87 (m, 1H), 4.82-4.60 (m, 6H), 4.60-4.32 (m, 9H), 4.24 (t, *J* = 6.66, 6.66 Hz, 3H), 4.22-4.13 (m, 3H), 3.75 (dd, *J* = 16.31, 7.92 Hz, 1H), 3.50 (dd, *J* = 46.41, 6.44 Hz, 1H), 3.01-2.86 (m, 1H), 2.47-2.35 (m, 1H), 1.82-1.53 (m, 11H), 1.52-1.25 (m, 29H), 1.25-1.02 (m, 31H), 0.99 (d, *J* = 5.66 Hz, 1H), 0.81 (d, *J* = 6.57 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 172.6, 172.2, 170.9, 170.1, 169.9, 169.2, 168.6, 157.6, 157.1, 155.7, 144.3, 141.5, 137.0, 136.7, 131.6, 128.636, 128.5, 128.2, 127.9, 127.8, 127.3, 125.4, 125.2, 120.1, 119.4, 78.0, 78.4, 78.2, 76.8, 74.7, 74.4, 73.7, 73.5, 73.2, 73.0, 69.0, 68.2, 67.5, 66.8, 58.8, 58.2, 56.4, 54.6, 53.1, 48.2, 47.9, 47.5, 45.5, 41.2, 40.7, 39.3, 34.1, 33.9, 32.6, 31.7, 31.4, 30.2, 29.9, 29.7, 28.4, 28.183, 27.635, 26.2, 25.4, 23.8, 22.9, 20.3, 20.1, 16.7, 15.9; IR (Neat) v_{max} 3300, 3069, 2932, 2857, 2361, 1749, 1731, 1713, 1655, 1634, 1540, 1522, 1507, 1456, 1367, 1339, 1257, 1206, 1160, 1104; ESI MS *m/z* 1662.55 $[M+Na]^+$



Linear Peptide (19). The septapeptide (**18**) (0.8759 g, 0.534 mmol) was treated with 4N HCl-dioxane (4 mL) and the resulting mixture was stirred at room temperature for 90 minutes. The volatiles were removed in vacuo. The residual HCl was further removed by adding Et_2O (5 mL) to the hydrochloride salt followed by its removal in vacuo. This

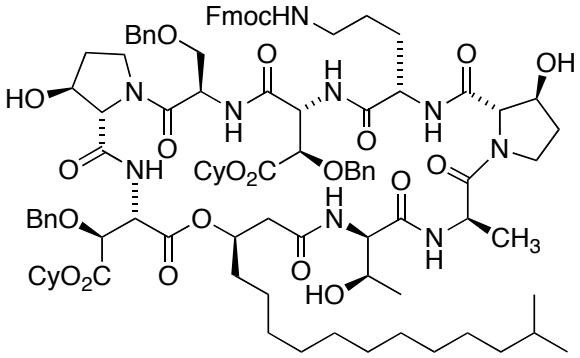
residue, Boc-D-Ser(OBn)-β-OH-Pro-OH (0.216 g, 0.529 mmol), HOBt (0.086 g, 0.634 mmol) and DIEA (0.110 mL, 0.634 mmol) were dissolved in THF(1.7 mL). The solution was cooled to 0 ^{o}C and EDCI (0.122 g, 0.634 mmol) was added. The reaction mixture was stirred under argon for 18 hrs and then quenched with EtOAc (1 mL). The THF was removed in vacuo and to the residue was added EtOAc (50 mL). This solution was extracted with 1N HCl (1 x 25 mL), sat. aq. $NaHCO_3$ (1 x 25 mL), and brine (1 x 25mL). The EtOAc was dried over Mg_2SO_4, filtered and condensed. Chromatography (10% acetone-EtOAc) provided the linear peptide **19** (0.736 g, 0.381 mmol, 72%) as a white solid. mp 78-81 ^{o}C; $[\alpha]^{22}_{D}$ +1.2 (c 1.0, $CHCl_3$) ^{1}H NMR (500 MHz DMSO-d_6, 45^{o}C) δ 8.29 (t, *J* = 9.97, 9.97 Hz, 1H), 8.14 (d, *J* = 8.96 Hz, 1H), 8.06-7.91 (m, 3H), 7.87 (d, *J* = 7.53 Hz, 2H), 7.69-7.64 (m, 2H), 7.40 (t, *J* = 7.43, 7.43 Hz, 2H), 7.36-7.23 (m, 19H), 5.88-5.76 (m, 1H), 5.29 (dd, *J* = 17.15, 1.22 Hz, 1H), 5.18 (dd, *J* = 10.52, 1.35 Hz, 1H), 5.12 (d, *J* = 3.86 Hz, 1H), 5.09 (d, *J* = 3.77 Hz, 1H), 5.00 (s, 1H), 4.98-4.85 (m, 1H), 4.76-4.66 (m, 6H), 4.63-4.40 (m, 11H), 4.36 (s, 2H), 4.34-4.15 (m, 8H), 3.86-3.64 (m, 1H), 3.65-3.38 (m, 2H), 3.02-2.91 (m, 2H), 2.47-2.39 (m, 1H), 2.07-1.86 (m, 2H), 1.85-1.56 (m, 11H), 1.55-1.05 (m, 57H), 1.03 (d, *J* = 6.01 Hz, 3H), 0.84 (d, *J* = 1.63 Hz, 1H), 0.83 (d, *J* = 1.64 Hz, 3H); ^{13}C(100 MHz, $CDCl_3$) δ 173.5, 172.8, 172.0, 171.8, 170.0, 169.5, 168.6, 168.5, 168.4, 168.2, 157.1, 156.896, 155.1, 144.2, 141.4, 138.2, 137.4, 136.9, 136.6, 131.5, 131.4, 130.0, 128.6, 128.5, 128.4, 128.2, 127.9, 127.8, 127.2, 125.2, 120.1, 119.4, 119.2, 79.6, 76.6, 76.1, 74.8, 74.6, 74.5, 74.1, 73.7, 73.5, 73.2, 72.9, 71.2, 70.6, 69.2, 68.7, 68.2, 66.8, 66.5, 58.3, 54.7, 53.0, 51.8, 51.1, 48.8, 48.4, 47.4, 46.2, 45.8, 41.6, 40.6, 39.2, 34.1, 33.1, 31.7, 31.5, 31.4, 31.3, 30.9, 30.1, 29.8, 29.7, 28.5, 28.1, 27.6, 26.0, 25.5, 25.3, 24.7, 23.8, 22.9, 19.9, 16.4; IR (neat) ν_{max} 3314, 3089, 3066, 3034, 2932,

2862, 1740, 1691, 1642, 1529, 1450, 1260, 1104; ESI MS *m/z* 1953.55 $[M+Na]^+$



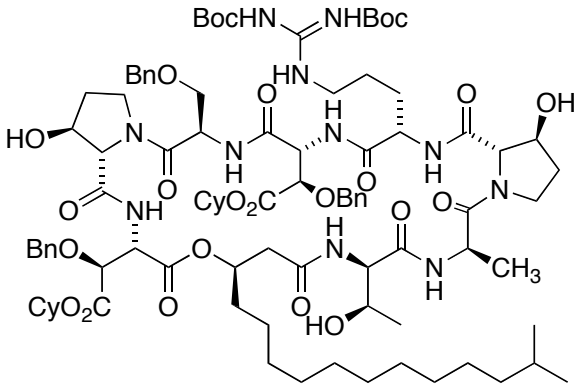
Carboxylic acid (20). $PdCl_2(PPh_3)_2$ (6.5 mg, 0.00921 mmol) and PPh_3 (7.25 mg, 0.028 mmol) were dissolved in dry CH_2Cl_2 (1.85 mL) and stirred under an atmosphere of argon for 15 min. This solution was then added to the allyl ester **19** (0.712 g, 0.368 mmol) via syringe and pheynylsilane (0.091 mL, 0.737 mmol) was added drop wise. The solution was stirred at room temperature under an atmosphere of argon for 6 hrs. The solvent was condensed and the crude material was loaded directly onto a silica gel column. Chromatography (1-15%EtOH-$CHCl_3$) afforded carboxylic acid **20** (0.664 g, 0.351 mmol, 95%) as a white solid. mp 109-111 ^oC; $[\alpha]^{22}_D$ -12.9 (c 1.0, $CHCl_3$) ^1H NMR (500 MHz, DMSO-d_6, 75^oC) δ 7.83 (d, *J* = 1.87 Hz, 1H) *)*, 7.43-7.15 (m, 19H), 7.64 (d, *J* = 1.87 Hz, 2H), 5.16 (d, *J* = 1.87 Hz, 1H) , 4.87 (d, *J* = 1.87 Hz, 1H), 4.72-4.61 (m, 3H), 4.60-4.39 (m, 9H) , 4.38-4.31 (m, 2H), 4.30-4.20 (m, 6H) , 4.18 (dd, *J* = 6.63, 1.87 Hz, 1H), 4.14 (s, 1H), 3.82-3.64 (m, 1H) , 3.64-3.50 (m, 1H), 2.96 (d, *J* = 1.87 Hz, 2H) , 2.44-2.34 (m, 1H) , 2.03-1.68 (m, 8H), 1.63 (s, 4H), 1.56-1.06 (m, 57H) , 1.03 (d, *J* = 1.87 Hz, 3H) 0.82 (d, *J* = 1.87 Hz, 1H) ^{13}C NMR(100 MHz, $CDCl_3$) δ 174.4, 173.69, 170.71, 170.9, 170.7, 170.2, 169.7, 168.7, 166.6, 163.0, 157.6, 156.8, 155.7, 155.3, 144.2, 141.5, 138.1, 136.9, 134.3, 133.2, 130.1, 128.2, 127.8, 127.3, 125.4, 120.2, 79.7, 76.05,

74.5, 73.3, 72.7, 71.7, 70.7, 69.7, 68.7, 68.4, 67. 8, 67.5, 66.8, 66.2, 66.0, 65.2, 63.9, 62.0, 61.2, 59.4, 58.9, 58.1, 56.4, 56.1, 55.9, 54.7, 53.2, 53.0, 51.9, 49.2, 48.1, 47.5, 45.7, 41.1, 40.8, 39.3, 36.7, 34.3, 32.7, 31.7, 30.1, 29.9, 28.6, 28.2, 27.6, 26.4, 25.5, 23.9, 22.9, 21.6, 20.9, 20.0, 17.8, 15.4, 14.2, 13.7; IR (neat) ν_{max} 3308, 3065, 2929, 2857, 1706, 1642, 1527, 1451, 1255, 1200, 1158; ESI MS *m/z* 1913.57 $[M+Na]^+$



Cyclic peptide (22). The linear peptide (0.276 g, 0.146 mmol) was treated with a 4N HCl-Dioxane solution (2.0 mL) and stirred under an atmosphere of argon for 1 hr. The volatiles were then removed in vacuo and to the residue was added CH_2Cl_2/hexanes (1:1, 10 mL). The solvent was condensed to remove any residual HCl and the crude residue was placed under high vacuum for several hours. The product was used without further purification. To this residue in dry DMF (73 mL) at 0 ^oC was added HOBt (0.099 g, 0.730 mmol), DIEA (0.51 mL, 0.292 mmol) and finally EDCI (0.140 g, 0.730 mmol). The mixture was stirred under and atmosphere of argon at this temperature for 48 hours. The solvent was then removed and the crude material was diluted with EtOAc (30 mL). The organic phase was washed with 1N HCl (1 x 20 mL), sat. aq. $NaHCO_3$ (1 x 20 mL) and brine (1 x 20 mL). The EtOAc was dried over Mg_2SO_4, filtered and condensed. Silica gel chromatography (1-10% EtOH-$CHCl_3$) afforded the cyclic peptide **(22)** as a

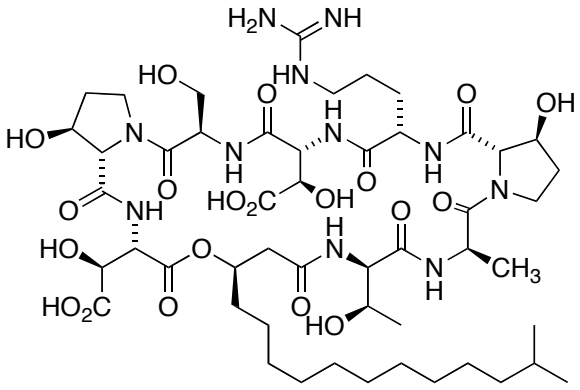
white solid. mp 93-95 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89-7.81 (m, 4H), 7.81-7.76 (m, 1H), 7.64 (d, J = 7.02 Hz, 2H), 7.60-7.53 (m, 2H), 7.39 (t, J = 7.45, 7.45 Hz, 3H), 7.36-7.18 (m, 17H), 5.23 (s, 1H), 5.05-4.89 (m, 1H), 4.86 (d, J = 7.85 Hz, 1H), 4.79-4.68 (m, 4H), 4.67-4.30 (m, 13H), 4.31-4.09 (m, 8H), 3.95-3.88 (m, 1H), 3.88-3.77 (m, 1H), 3.76-3.70 (m, 1H), 3.64 (dd, J = 9.45, 6.54 Hz, 1H), 3.61-3.52 (m, 2H), 2.93 (m, 2H), 2.61 (dd, J = 19.11, 11.29 Hz, 1H), 2.47-2.44 (m, 1H), 2.34 (dd, J = 14.25, 5.38 Hz, 2H), 2.00-1.87 (m, 1H), 1.85-1.56 (m, 14H), 1.57-0.99 (m, 51H), 0.88-0.76 (m, 6H); ^{13}C (100MHz, $CDCl_3$) δ 175.0, 173.4, 172.4, 171.5, 170.9, 170.5, 170.0, 169.6, 169.2, 168.3, 167.63, 157.0, 144.2, 141.5, 137.9, 137.2, 136.7, 128.7, 128.7, 128.6, 128.6, 128.4, 128.3, 128.1, 127.9, 127.2, 126.2, 125.7, 125.4, 120.1, 117.8 111.3, 74.6, 73.5, 73.4, 69.9, 68.9, 68.3, 67.4, 67.2, 66.8, 54.6, 54.1, 52.1, 47.5, 47.4, 45.5, 41.5, 40.9, 39.8, 34.5, 33.3, 32.0, 31.8, 31.7, 31.5, 31.2, 30.9, 30.3, 30.1, 29.9, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 28.2, 27.6, 26.4, 25.5, 25.3, 24.8, 24.0, 23.7, 23.7, 22.9, 20.2, 19.3, 16.8; IR (neat) ν_{max} 3303, 3066, 3035, 2926, 2855, 1741, 1650, 1546, 1528, 1467, 1450, 1260, 1202; ESI MS m/z 1795.65 $[M+Na]^{+}$.



Depsipeptide (23). Cyclic peptide **22** (0.117 g, 0.066 mmol) was treated with a 5% piperidine-DMF solution (0.5 mL) and stirred at room temperature for 15 minutes. The reaction was diluted with DMF 5ml and the solvent was removed in vacuo. To the

residue was added DMF (5 mL) and the solvent was again removed in vacuo. The crude material was then left under high vacuum for several hours (4-8). *N*,*N*'-diBoc-*N*"-triflylguanidine (0.387g, 0.990mmol) and DIEA (0.172 mL, 0.990 mmol) were added to a stirring solution of the deprotected amine in dry DMF (0.75 mL). The reaction was stirred at room temperature for 18h then the DMF was removed in vacuo. Column chromatography (1-20% EtOH - $CHCl_3$) afforded the guanidinylated peptide (**23**) (0.107 g, 0.060 mmol, 91%) as a pale yellow solid. mp 89-91 ^oC; $[\alpha]^{22}_D$ -36.8 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.23 (t, J = 4.84, 4.84 Hz, 1H), 8.10 (d, J = 12.10 Hz, 1H), 7.92 (d, J = 7.08 Hz, 1H), 7.86 (d, J = 5.39 Hz, 1H), 7.61 (d, J = 5.35 Hz, 1H), 7.38-7.17 (m, 1H), 5.33 (d, J = 6.32 Hz, 1H), 5.02 (s, 1H), 4.96-4.82 (m, 2H), 4.82-4.72 (m, 2H), 4.70 (dd, J = 15.65, 11.77 Hz, 3H), 4.65-4.08 (m, 12H), 3.85 (m,1H), 3.73 (ddd, J = 25.55, 14.57, 7.93 Hz, 1H), 3.62 (dd, J = 8.83, 6.00 Hz, 1H), 3.56 (dd, J = 10.73, 6.55 Hz, 1H), 2.58 (d, J = 4.73 Hz, 1H), 2.46 (d, J = 10.88 Hz, 1H), 2.35 (dd, J = 12.91, 5.83 Hz, 1H), 1.98-1.87 (m, 1H), 1.87-1.56 (m, 12H), 1.56-1.08 (m, 70H), 1.05 (d, J = 6.03 Hz, 1H), 0.99 (d, J = 6.17 Hz, 1H), 0.84 (d, J = 6.26 Hz, 1H), 0.83 (d, J = 6.58 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 173.7, 172.4, 170.9, 170.388, 170.0, 170.0, 169.6, 169.3, 168.4, 167.4, 167.7, 163.6, 163.2, 156.3, 153.3, 137.2, 136.5, 129.9, 128.849, 128.7, 128.6, 128.6, 128.5 128.3, 128.3, 128.2, 128.1, 127.8, 127.8, 121.3, 118.2, 115.0, 83.3, 79.6, 76.3, 74.6, 73.6, 73.4, 73.3, 73.3, 68.1, 54.3, 53.7, 52.9, 52.431, 52.3, 48.0, 45.7, 41.6, 40.9, 40.6, 39.2, 34.4, 33.0, 32.1, 31.6, 31.7, 31.4, 31.3, 30.9, 30.5, 30.108, 29.8, 29.7, 29.6, 29.6, 28.4, 28.2, 27.6, 25.7, 25.4, 25.4, 24.8, 23.8, 23.7, 23.6, 22.9, 22.7, 20.5, 19.6, 16.9, 14.3; IR (neat) ν_{max} 3337, 3068, 3028, 2930, 2853, 1740, 1642, 1452, 1415, 1386, 1365, 1328, 1258, 1233, 1196, 1155, 1134, 1101; ESI MS *m/z*

1814.26 $[M+Na]^+$

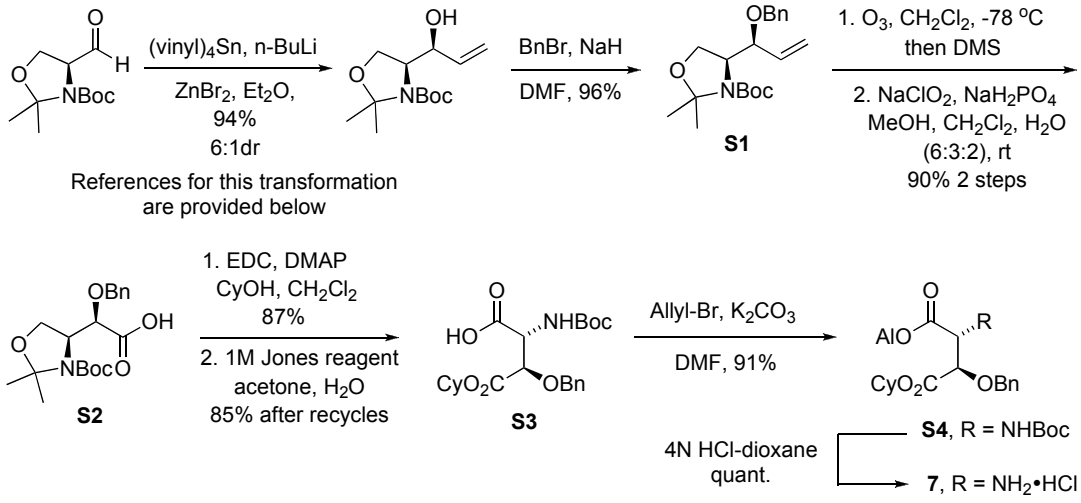


Plusbacin A_3 (1). The guanidinylated peptide (**23**) (0.091g, 0.051mmol) and anisole (1ml) in an HF reaction apparatus were purged with N_2 and cooled to -78 ^oC. HF gas was distilled into the reaction vessel to a total volume of approximately 5 mL. The reaction was warmed to 0 ^oC and stirred at this temperature for 3hrs. The HF was then evaporated under a steady stream of N_2 and the crude material was transferred to a round bottom flask using EtOH. The volatiles were removed in vacuo and the crude material was triturated with Et_2O and centrifuged. The crude material (0.059 g) was HPLC purified (35-65% CH_3CN/H_2O over 60 minutes) to afford (0.011 g, 0.0103 mmol, 20%) of Plusbacin A_3 as a white powder. mp >250 ^oC decomposition; $[\alpha]^{22}_D$ + 21.1 (c 0.052, EtOH); ^1H NMR (500 MHz, CD_3CN/D_2O/TFA, 500:500:1) δ 5.20-5.13 (m, 1H), 5.10 (t, *J* = 5.99, 5.99 Hz, 1H), 5.04 (d, *J* = 2.80 Hz, 1H), 4.92 (d, *J* = 2.31 Hz, 1H), 4.91 (m, 1H), 4.85 (d, *J* = 2.92 Hz, 1H), 4.78 (dd, *J* = 9.22, 2.04 Hz, 1H), 4.75 (d, *J* = 2.07 Hz, 1H), 4.73 (d, *J* = 2.25 Hz, 1H), 4.71-4.67 (m, 3H), 4.64 (d, *J* = 2.90 Hz, 1H), 4.61-4.57 (m, 3H), 4.49 (t, *J* = 7.16, 7.16 Hz, 1H), 4.41-4.36 (m, 1H), 4.34 (s, 1H), 4.33-4.30 (m, 1H), 4.28 (d, *J* = 2.13 Hz, 1H), 4.19-4.18 (m, 1H), 4.15-4.11 (m, 1H), 4.02-3.80 (m, 2H), 3.81-3.70 (m, 1H), 3.70-3.49 (m, 1H), 3.07 (dd, *J* = 14.19, 7.16 Hz, 2H), 2.64-2.41 (m,

2H), 2.12-1.99 (m, 1H), 1.90-1.85 (m, 1H), 1.82-1.77 (m, 1H), 1.66 (s, 1H), 1.55 (s, 3H), 1.44 (dd, J = 13.36, 6.72 Hz, 2H), 1.42-1.38 (m, 1H), 1.28-1.16 (m, 19H), 1.14 (d, J = 6.77 Hz, 1H), 1.12-1.07 (m, 3H), 1.03 (d, J = 6.43 Hz, 1H), 0.80 (d, J = 6.62 Hz, 6H); ^{13}C NMR (100MHz, CD_3CN/D_2O/TFA, 500:500:1) δ 175.2, 174.6, 174.1, 173.8, 173.3, 172.6, 172.2, 171.7, 171.4, 170.3, 169.7, 157.5, 76.3, 74.7, 74.3, 74.0, 70.7, 70.2, 69.7, 69.5, 68.7, 68.1, 61.2, 61.0, 56.2, 55.9, 54.8, 54.1, 53.8, 48.6, 46.2, 41.2, 40.8, 39.5, 34.5, 34.0, 33.2, 31.1, 30.3, 30.0, 29.1, 28.4, 27.8, 25.4, 25.2, 22.8, 19.5, 18.6, 16.8, 16.5; IR (KBr pellet) v_{max} 3432, 2959, 2926, 2860, 1735, 1674, 1535, 1441, 1204, 1186, 1127; HR ESI TOF *m/z* 1158.5873 $[M+H]^+$

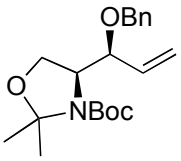
Scheme and Experimental Procedures for Preparation of Compound 7

Scheme S1. Synthetic route to H-β-OBn-D-Asp(OCy)-OH **(7)**



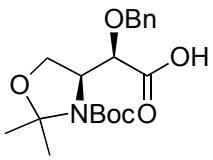
Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697-1700.
Shimamoto, K.; et. al. *Bioorg. Med. Chem. Lett.* **2000**, 2407-2410.
Zhang, X.; Ni, W., van der Donk, W. *J. Org. Chem.* **2005**, *70*, 6685-6692.

Compound **7** was used directly without purification or characterization in the coupling reaction illustrated in Scheme 1 of the manuscript.



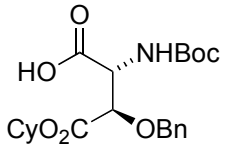
(*S*)-*tert*-butyl-4-((*S*)-1-(benzyloxy)allyl)-2,2-dimethyloxazolidine-3-carboxylate (S1). To a stirring solution of the alcohol (0.378 g, 1.4 7mmol) and benzyl bromide (0.21 mL, 1.76 mmol) in dry DMF at 0°C was added NaH (60% dispersion, 0.062 g, 1.16 mmol) in one portion. The solution was stirred under argon for 4 hours while slowly warming to room temperature. The reaction was quenched by the addition of H_2O (2 mL) and the solvent was removed in vacuo. The crude residue was partitioned between EtOAc (20 mL) and H_2O (20 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried over Mg_2SO_4. Column chromatography

(hexanes/EtOAc, 9.5:0.5) provided the benzyl ether (0.490 g, 1.41 mmol, 96%) as a colorles oil. $[\alpha]^{25}_{D}$ = -11.4 (c = 1.00, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H), 5.84 (td, *J* = 18.09, 9.18, 9.18 Hz, 1H), 5.41-5.21 (m, 2H), 4.61 (m, 1H), 4.44-4.31 (m, 1H), 4.23 (t, *J* = 5.04, 5.04 Hz, 1H), 4.20-4.06 (m, 1H), 4.02 (t, *J* = 5.29, 5.29 Hz, 1H), 3.97-3.86 (m, 1H), 1.65-1.30 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.48, 151.80, 138.52, 138.23, 134.87, 134.39, 128.30, 128.18, 127.57, 127.51, 127.45, 127.32, 120.29, 119.79, 94.23, 93.74, 80.11, 79.63, 79.43, 78.92, 70.75, 70.1, 63.61, 63.44, 59.53, 59.32, 28.29, 26.50, 25.65, 24.27, 22.83; IR (neat) ν_{max} 3369, 2982, 2935, 2880, 1704, 1452, 1389, 1263, 1168, 1089; ESI MS *m/z* 370.06 $[M+Na]^+$, 347.92 $[M+H]^+$



(*R*)-2-(benzyloxy)-2-((*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)acetic acid (S2). Ozone was gently bubbled through a solution stirring solution of the olefin (1.21g, 3.49 mmol) at -78^{o}C until a light blue color persisted (approximately 20 min). Nitrogen was then passed through the solution for 30 min followed by the addition of dimethylsulfide (7.3 ml, 82.0 mmol). The solution was stirred at this temperature for 15 min then slowly warmed to room temperature. After stirring for 2 hrs at this temperature the solvent was removed in vacuo. The residue was dissolved in MeOH/CH_2Cl_2/H_2O (115 ml, 6:3:2) followed by the addition of NaH_2PO_4-H_2O (1.93 g, 13.98 mmol) and $NaClO_2$ (0.790 g, 6.99 mmol). The reaction was stirred for 90 min and the volatiles were removed in vacuo. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 ml). The

combined CH_2Cl_2 was dried over Na_2SO_4, filtered and condensed. Silica gel chromatography (1-10% MeOH/$CHCl_3$) afforded the carboxylic acid (1.15 g, 3.14 mmol, 90%) as a hydroscopic foam. $[\alpha]^{22}_D$ +1.8 (c = 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.36-7.23 (m, 5H), 4.61 (t, *J* = 15.06, 15.06 Hz, 1H), 4.35 (t, *J* = 12.14, 12.14 Hz, 1H), 4.17-3.98 (m, 3H), 3.89 (m, 1H), 1.48-1.19 (m, 15H), ^{13}C NMR (100 MHz, $CDCl_3$) 175.607, 175.015 (rotamer), 152.528, 151.492 (rotamer), 137.150, 136.812 (rotamer), 128.212, 128.078, 127.793, 127.560, 94.463, 94.168 (rotamer), 80.825, 80.197 (rotamer), 77.204, 76.328 (rotamer), 72.723, 72.444 72.194, 64.188, 63.785 (rotamer), 58.826, 29.675, 28.363, 26.374, 25.768 (rotamer), 24.303, 22.849 (rotamer); IR (neat) ν_{max} 3432, 2975, 2927, 2359, 1704, 1389, 1263, 1168, 1097; ESI MS *m/z* 388.04 $[M+Na]^+$, 365.82 $[M+H]^+$

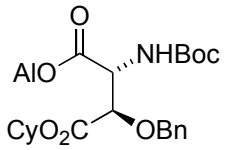


(2*R*,3*R*)-3-(benzyloxy)-2-(*tert*-butoxycarbonylamino)-4-(cyclohexyloxy)-4-oxobutanoic acid (S3). To a stirring solution of the carboxylic acid (4.846 g, 13.26 mmol), DMAP (0.810 g, 6.63 mmol) and cyclohexanol (4.25 mL, 39.8 mmol) in dry CH_2Cl_2 (44 mL) at 0^{o}C was added EDCI (2.80 g, 14.59 mmol) in one portion. The reaction was stirred under argon for 7 hours while slowly warming to room temperature. The solution was diluted with CH_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and condensed. Column chromatography (hexanes/EtOAc, 9:1)

afforded the ester (5.123 g, 11.45 mmol, 86%) as a colorless oil. $[\alpha]^{22}_{D}$ -14.4 (c = 2.43, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 6.42 Hz, 1H), 4.85 (m, 1H), 4.63 (dd, *J* = 29.85, 11.45 Hz, 1H), 4.47-4.41 (m, 1H), 4.39-4.23 (m, 2H), 4.04 (t, *J* = 5.26, 5.26 Hz, 1H), 3.90 (dd, *J* = 9.45, 6.61 Hz, 1H), 1.99-1.81 (m, 2H), 1.78-1.67 (m, 2H), 1.57-1.31 (m, 20H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 169.5, 169.3 (rotamer), 152.2, 151.4 (rotamer), 137.3, 136.8 (rotamer), 128.2, 128.0 (rotamer), 127.8, 127.7 (rotamer), 127.6, 127.5(rotamer), 94.2, 93.8(rotamer), 80.2, 79.8 (rotamer), 77.1, 76.7 (rotamer), 73.5, 73.3(rotamer), 72.3, 72.0 (rotamer), 63.4, 63.4(rotamer), 59.0, 58.7, 58.7(rotamer), 31.6, 31.5 (rotamer), 31.4, 28.3, 28.2 (rotamer), 26.506, 25.8 (rotamer), 25.3, 24.1, 23.7, 22.7 (rotamer); ; ESI m/z 470.09 $[M+Na]^+$

The cyclohexyl ester (6.302 g, 14.0 8mmol) was dissolved in dry acetone (280 mL) and cooled to 0^{o}C. To this solution was added a freshly prepared solution of 1M Jones reagent (43 mL) dropwise via addition funnel over a period of 30 min. The reaction was stirred vigorously at this temperature for 30 min then at room temperature for 12 hours. Isopropanol was added drop-wise until the solution turned dark green. The acetone was removed in vacuo and the mixture was diluted with EtOAc (200 mL) and water (100 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine (200 mL). The EtOAc was dried over Mg_2SO_4, filtered and condensed. Column chromatography (1-15% MeOH/$CHCl_3$) afforded the carboxylic acid (2.48 g, 5.89 mmol, 42%, 88% based on recovered starting material) as a white foam. The unreacted starting material (3.30 g, 7.37 mmol, 53%) was recovered and recycled. m.p. 55-58^{o}C, $[\alpha]^{22}_{D}$ +13.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 7.35-7.23 (m, 5H), 6.21 (s, 1H), 4.70 (m, 1H), 4.63 (d, *J* = 11.93 Hz, 1H), 4.52 (d, *J*

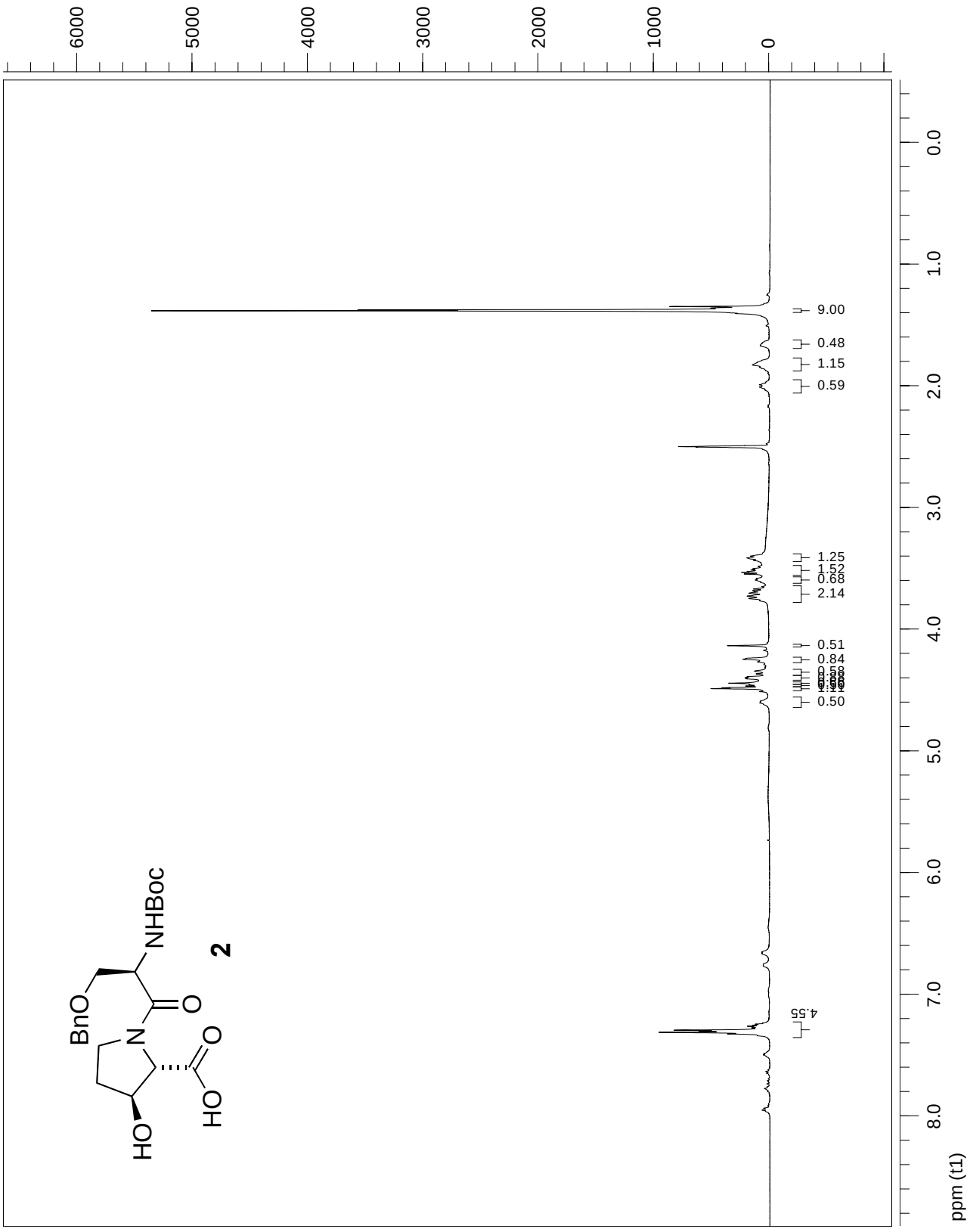
= 2.09 Hz, 1H), 4.41 (d, *J* = 11.03 Hz, 2H), 1.82-1.71 (m, 2H), 1.70-1.59 (m, 2H), 1.52-1.18 (m, 16H); ^{13}C NMR (100MHz, $CDCl_3$) δ 175.003, 169.258, 155.700, 136.677, 128.277, 127.941, 80.079, 77.246, 74.222, 73.017, 56.305, 31.356, 31.116, 28.143, 25.176, 23.562, 23.470, IR (neat) ν_{max} 3443, 2978, 2862, 1747, 1499, 1453, 1391, 1213, 1174, 1112; ESI *m/z* 444.03 $[M+Na]^+$



(2*R*,3*R*)-1-allyl-4-cyclohexyl-3-(benzyloxy)-2-(tert-butoxycarbonylamino)butane-dioate (S4). To a stirring solution of the carboxylic acid (5.00 g, 11.91 mmol) and allyl bromide (2.061 ml, 23.82 mmol) in dry DMF (60 ml) at 0°C was added K_2CO_3 (3.29 g, 23.82 mmol). The mixture was stirred under argon for 12 hours while slowly warming to room temperature. The solvent was then removed and to the crude residue was added H_2O (100 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (3 x 100 ml) and the combined organic extracts were dried over Mg_2SO_4, filtered and condensed. Silica gel chromatography (10% EtOAc/Hexanes) afforded Boc-β-OBn-D-Asp(OCy)-OAllyl (4.984g, 10.80mmol, 91%) as a colorless oil. $[\alpha]^{22}_D$ +29.5; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.40-7.25 (m, 1H), 7.05 (d, *J* = 9.71 Hz, 1H), 5.83 (tdd, *J* = 15.90, 10.58, 5.35, 5.35 Hz, 1H), 5.29 (dd, *J* = 17.24, 1.51 Hz, 1H), 5.19 (d, *J* = 10.43 Hz, 1H), 4.74 (m, 1H), 4.72-4.63 (m, 2H), 4.60 (d, *J* = 5.35 Hz, 1H), 4.55 (dd, *J* = 14.07, 5.28 Hz, 2H), 4.49 (d, *J* = 4.20 Hz, 1H), 4.43 (d, *J* = 11.77 Hz, 1H), 1.83-1.71 (m, 2H),

1.70-1.58 (m, 2H), 1.51-1.19 (m, 15H) ^{13}C NMR (100MHz, $CDCl_3$) δ 169.1, 168.5, 155.3, 136.6, 131.4, 128.3, 128.1, 128.0, 118.8, 79.9, 77.0, 74.2, 72.8, 66.2, 56.0, 31.4, 31.1, 28.1, 25.1, 23.5, 23.4; IR (neat) ν_{max} 3453, 2937, 2859, 1757, 1726, 1499, 1452, 1366, 1257, 1210, 1155, 1116, 1014; ESI *m/z* 484.03 $[M+Na]^+$.

Compound **S4** was then treated with 4N HCl-dioxane (15mL) and stirred at room temperature for 90 min. The volatiles were removed in vacuo and CH_2Cl_2/hexanes (1:1, 20 mL) was added to the residue. The solvent was removed in vacuo to drive off any residual HCl to afford **(7)** (4.30 g, 10.80 mmol, 100%) as white solid. The hydrochloride salt was left under high vacuum for several hours and then used without further purification.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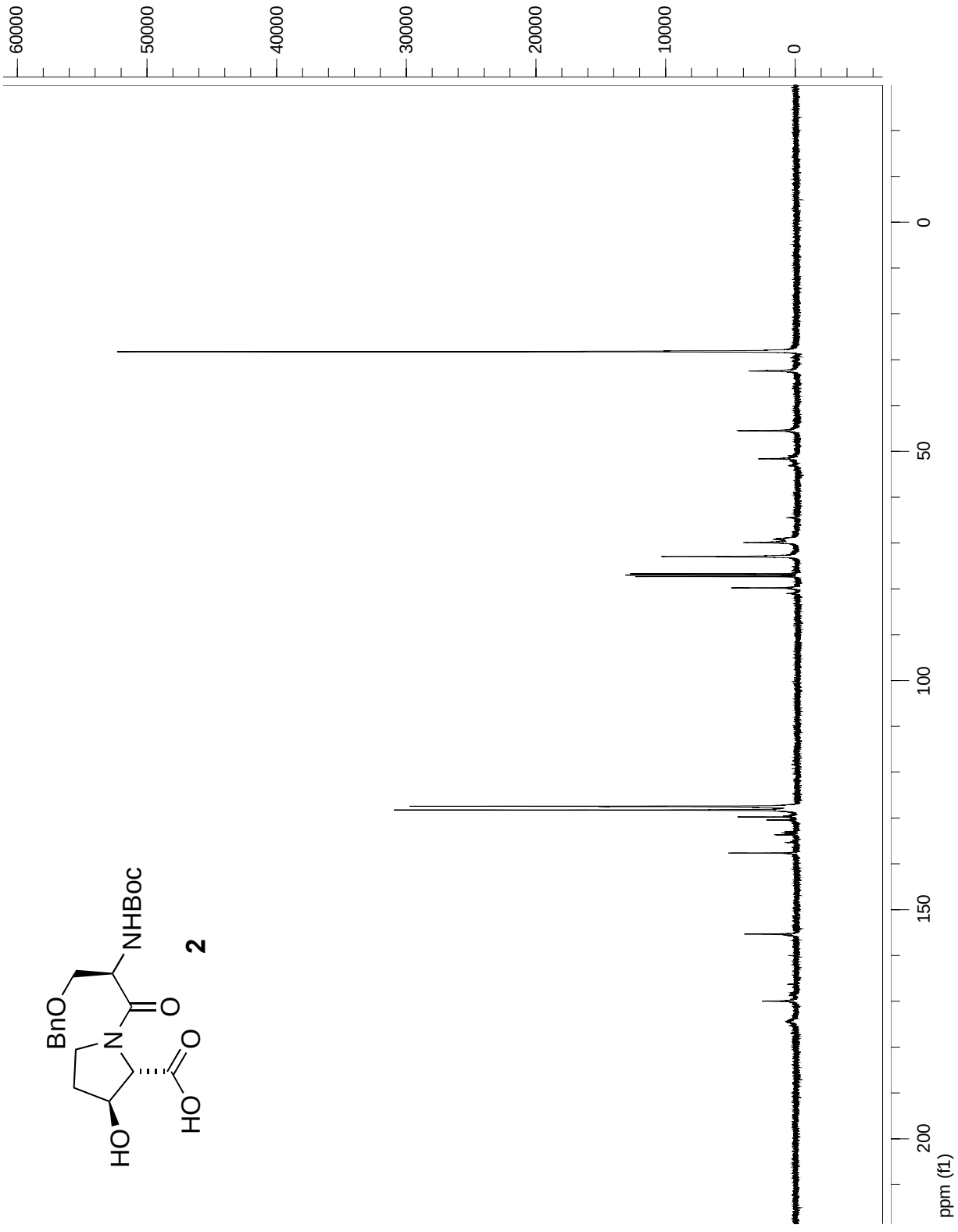
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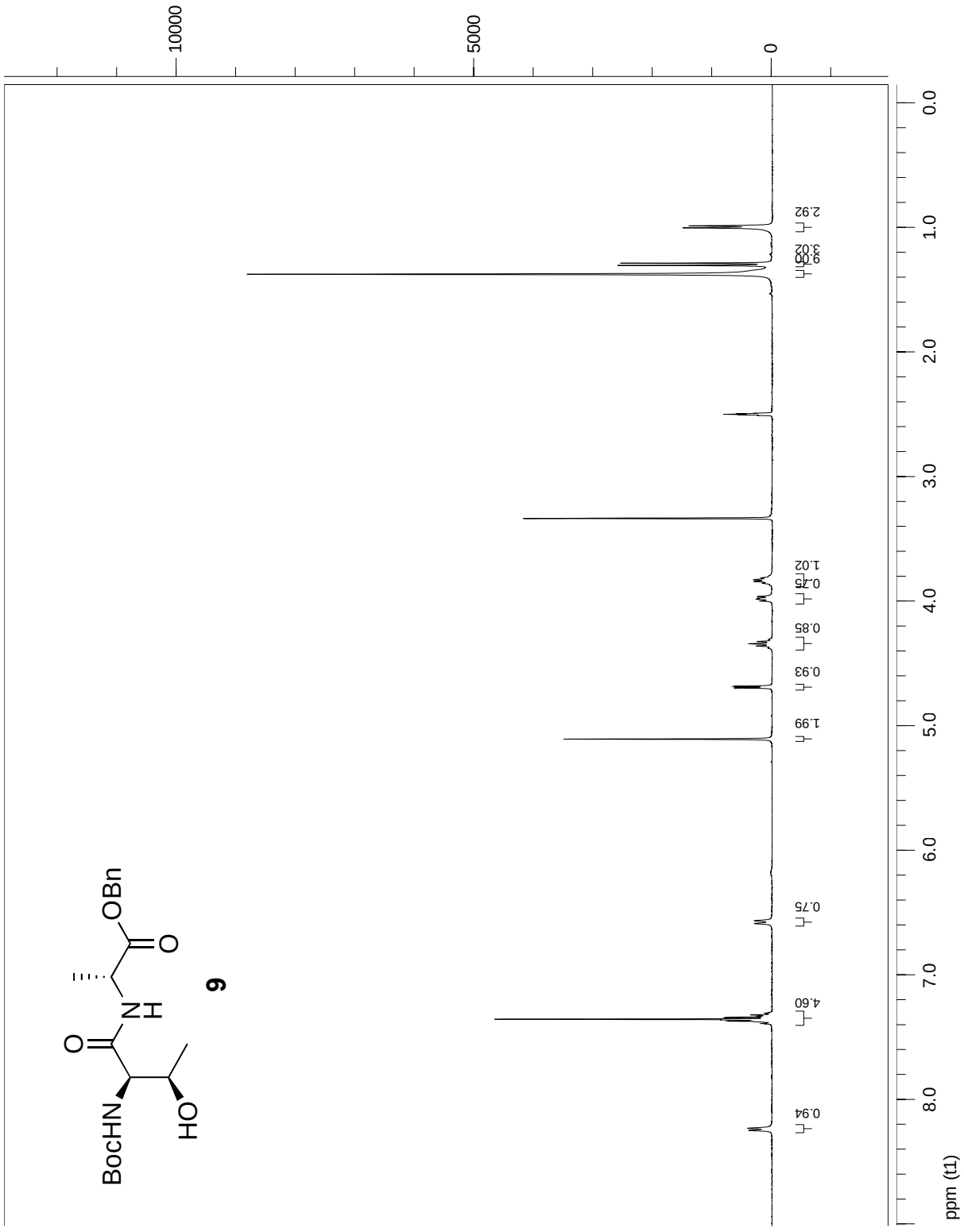
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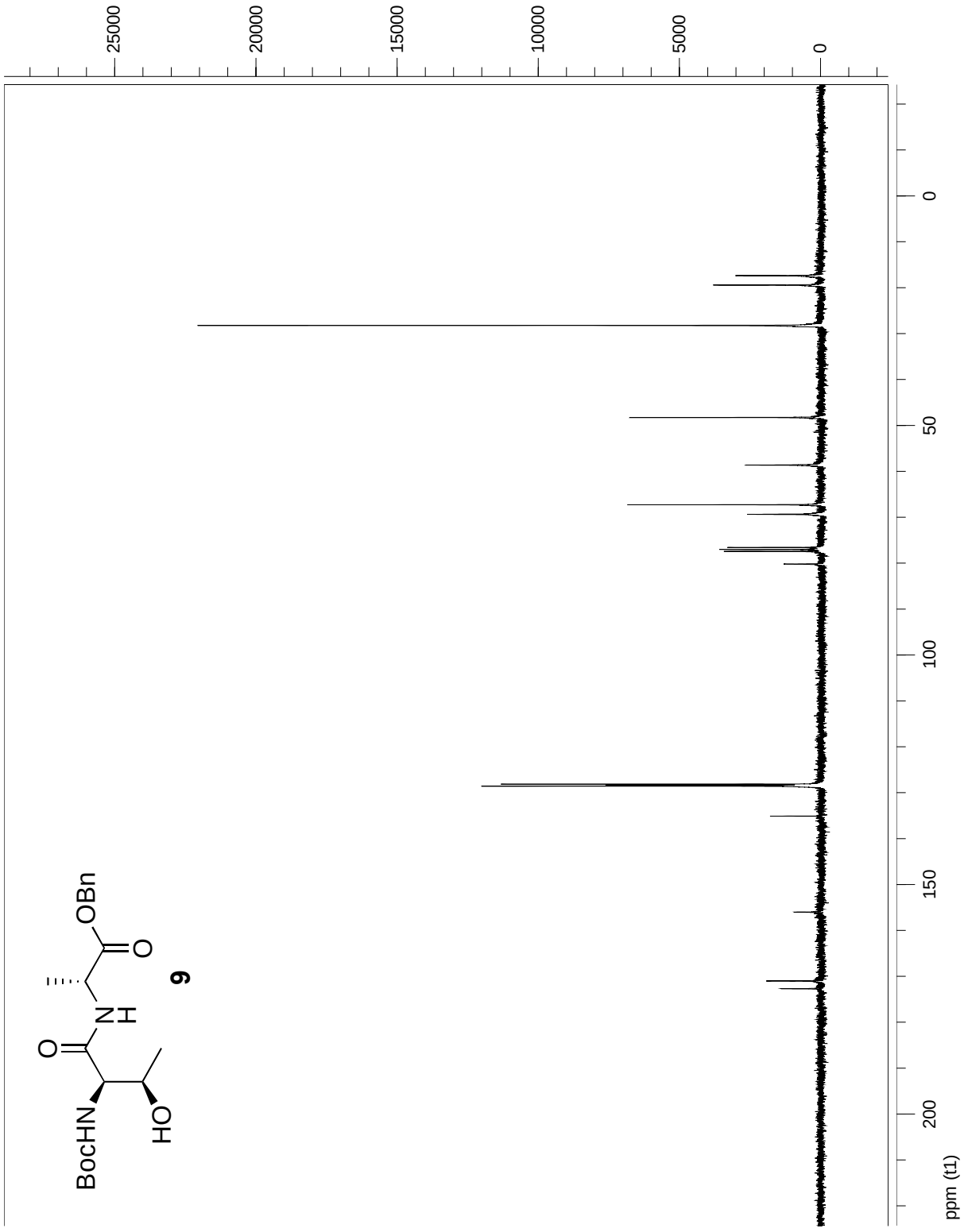
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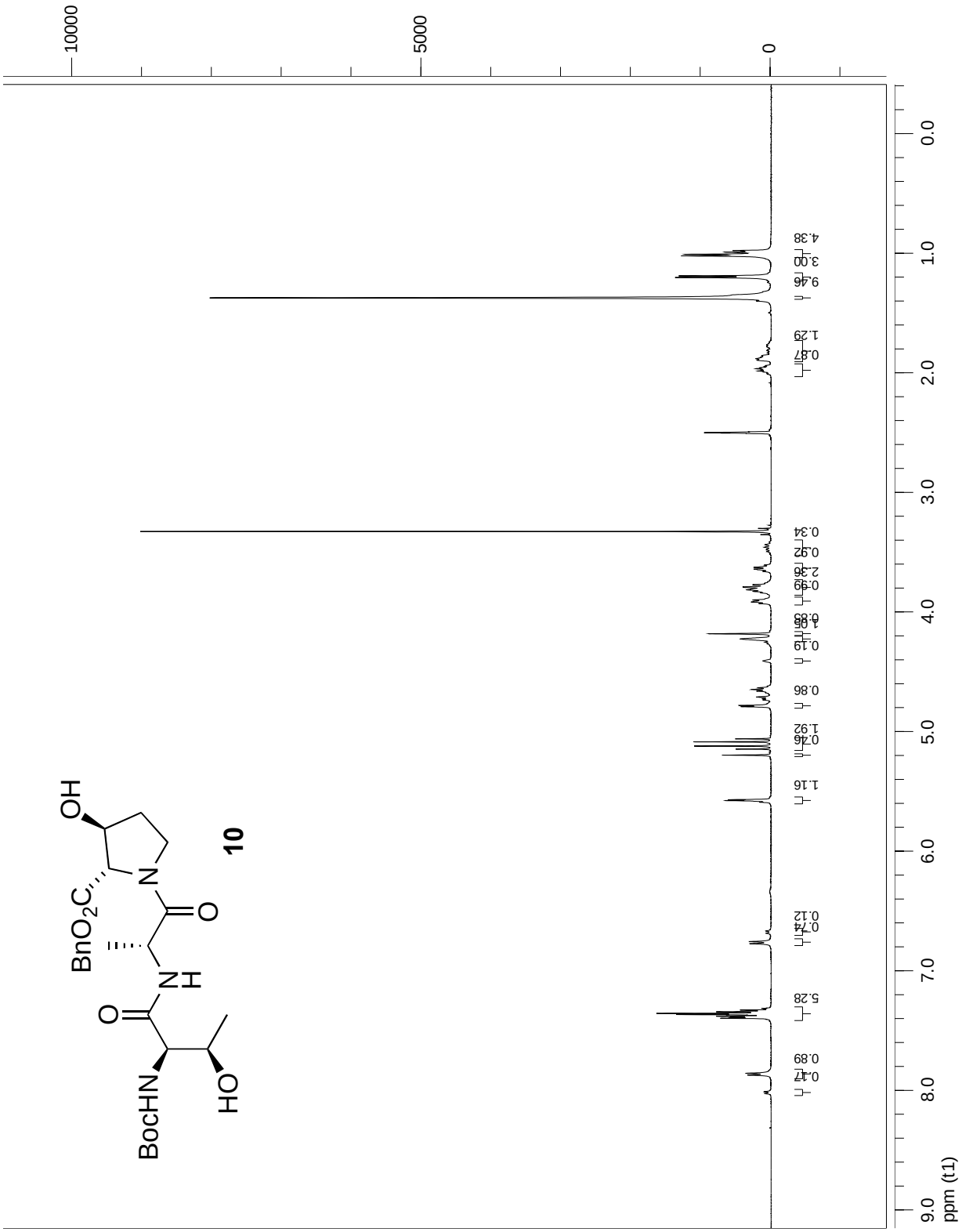
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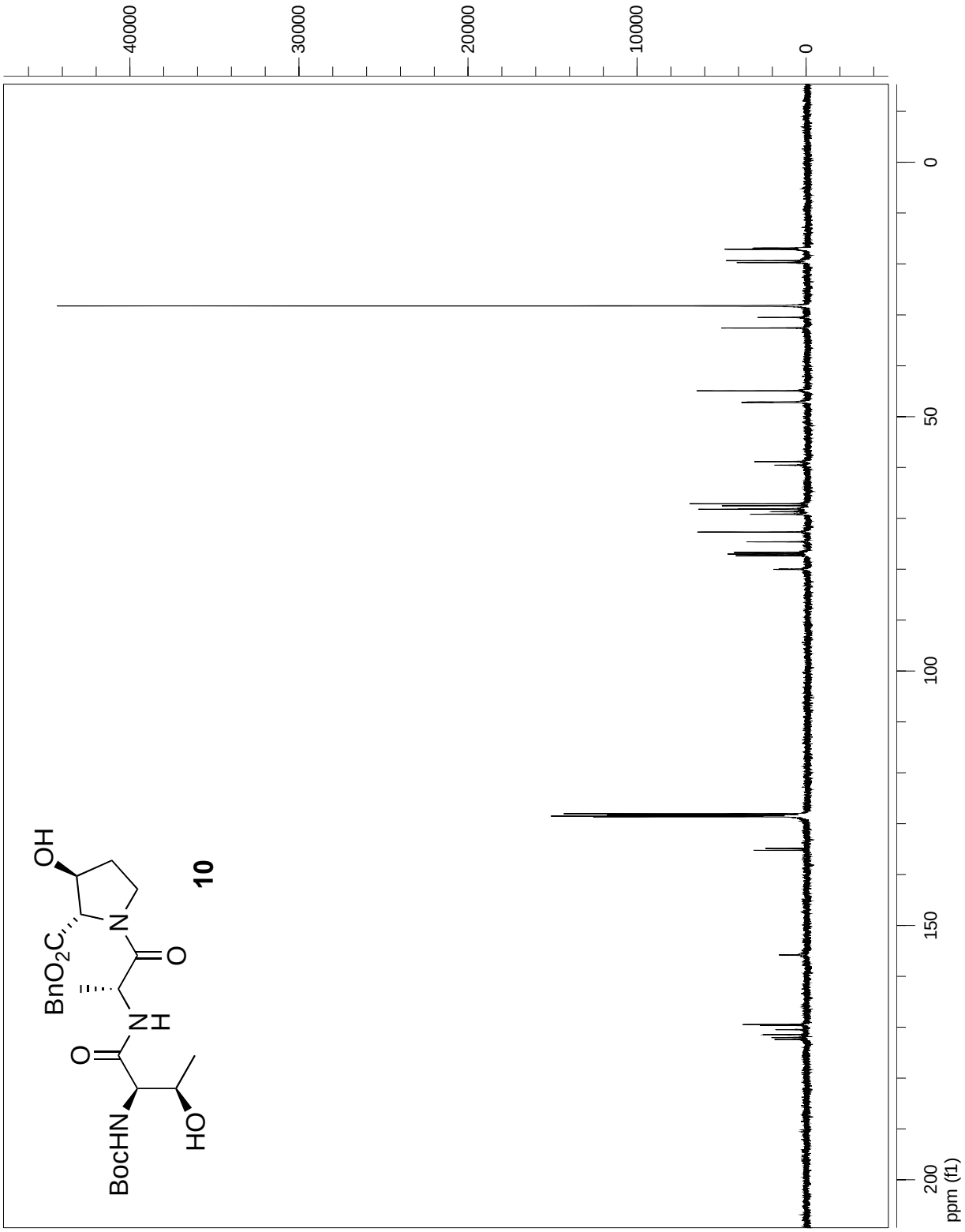
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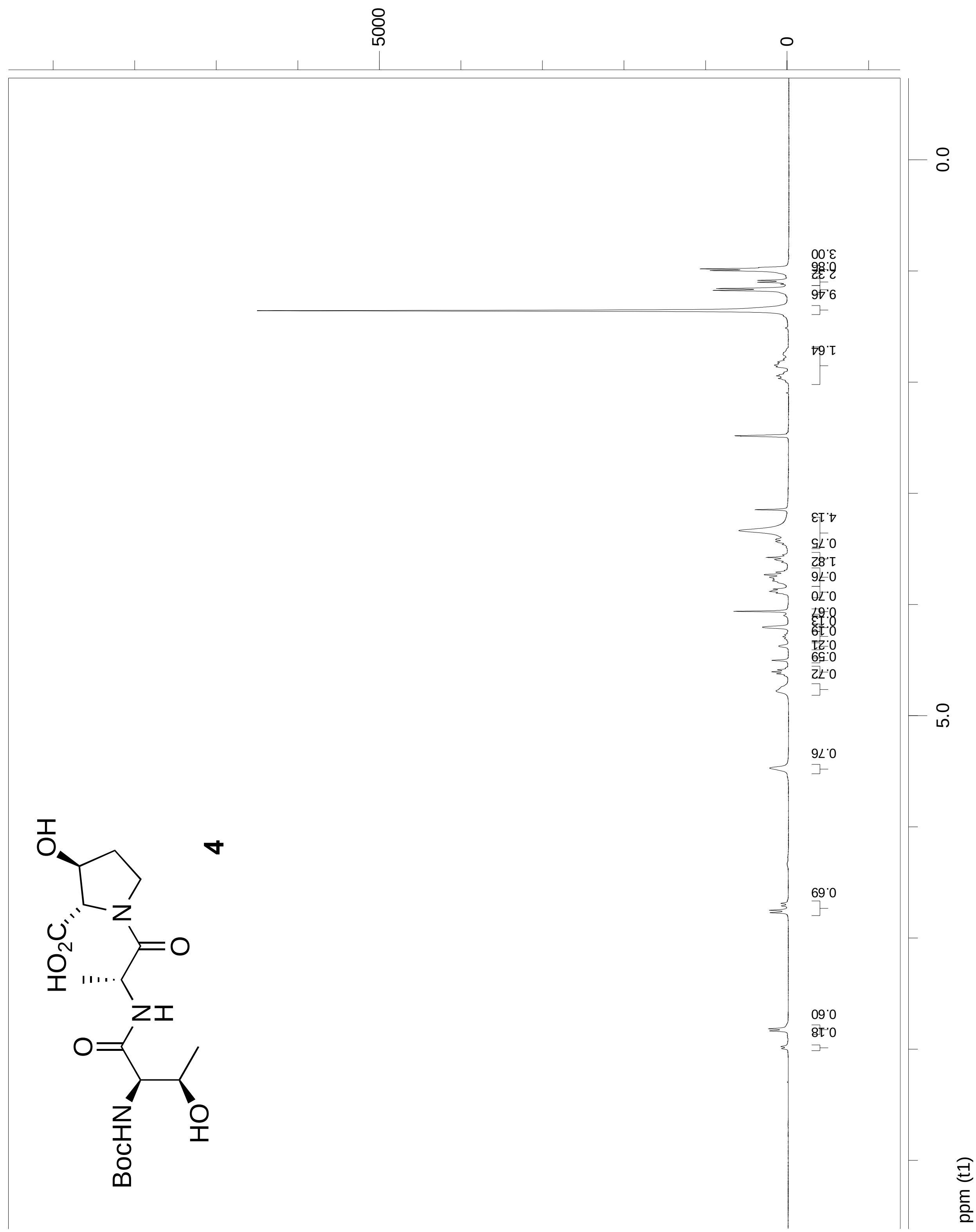
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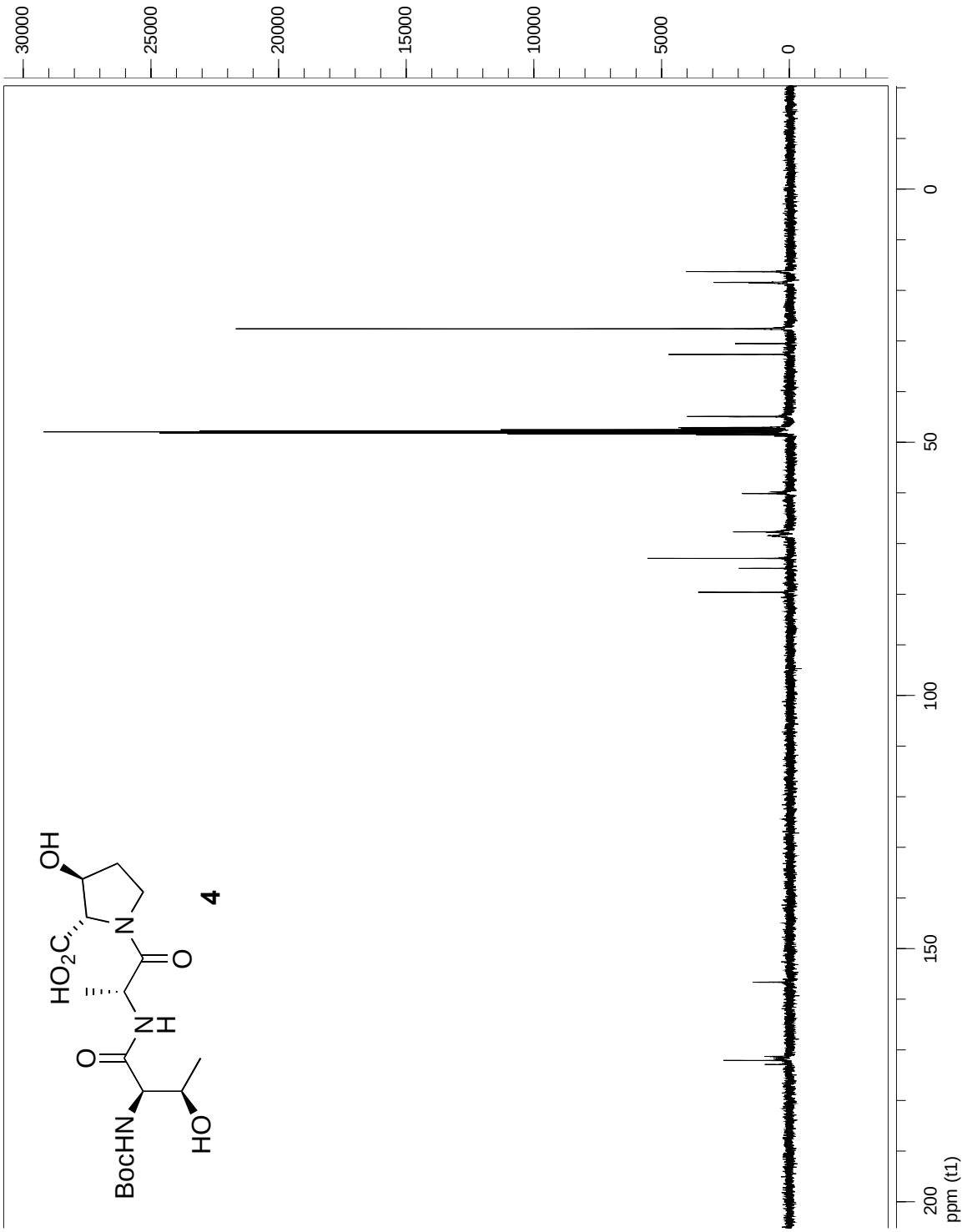
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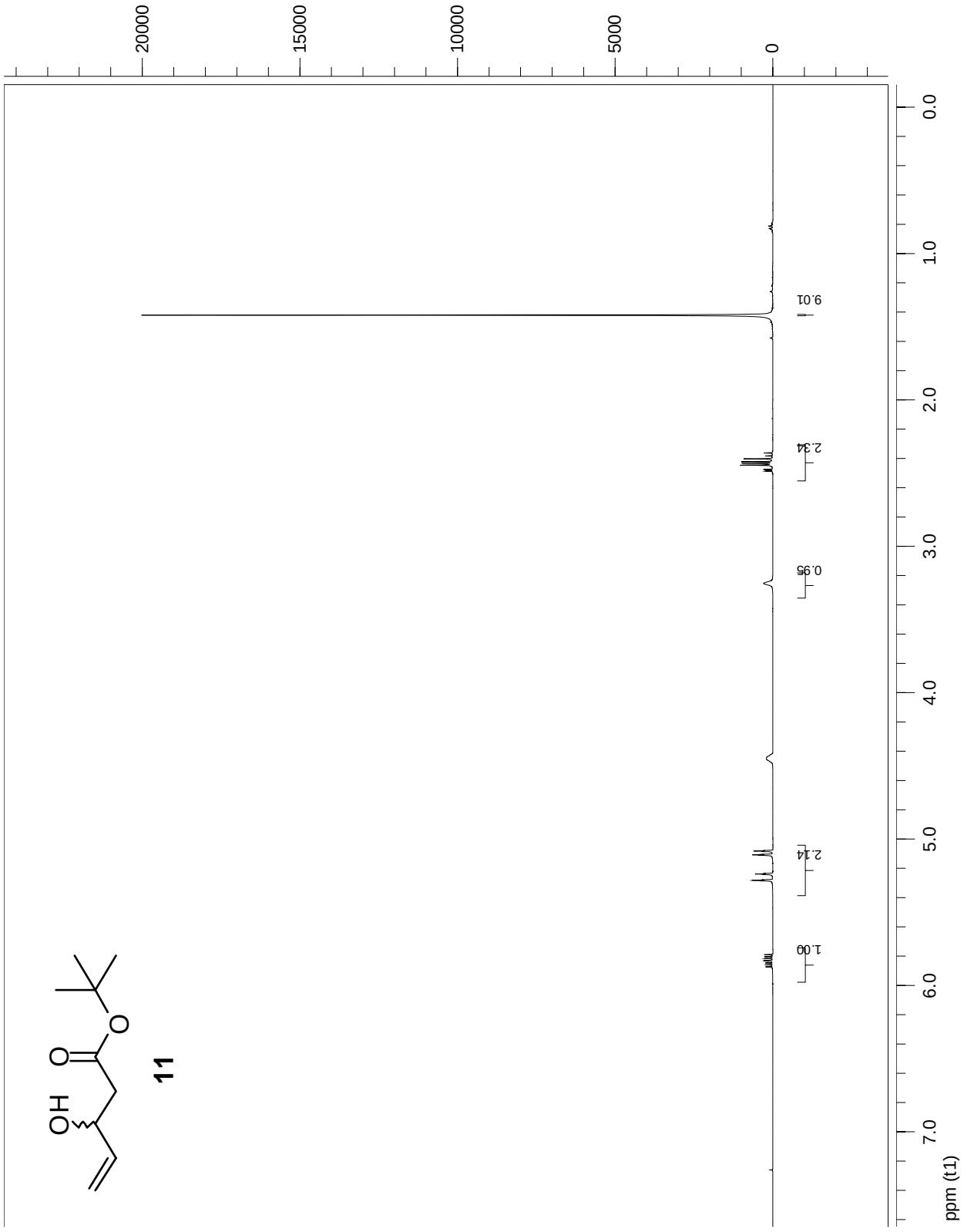
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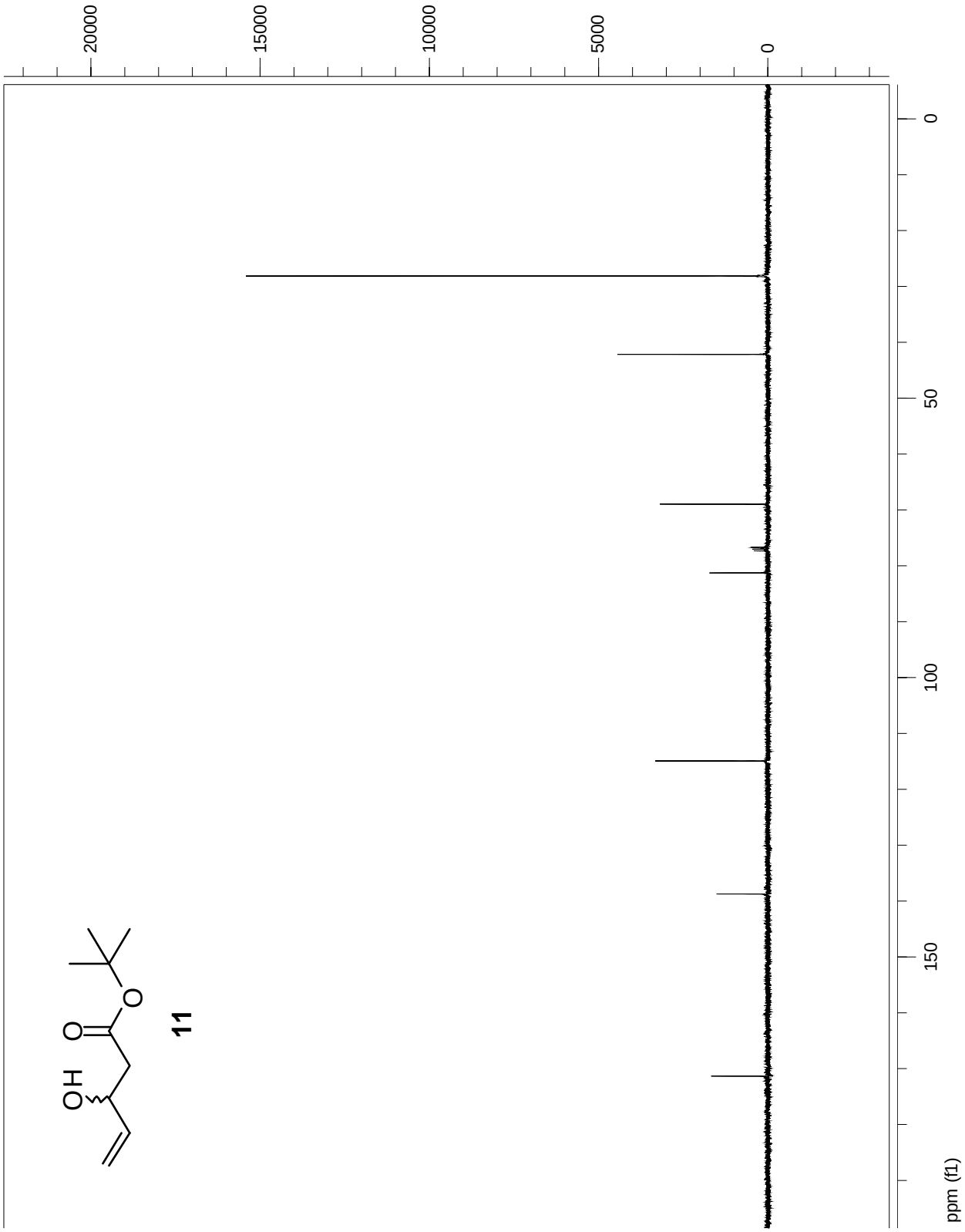

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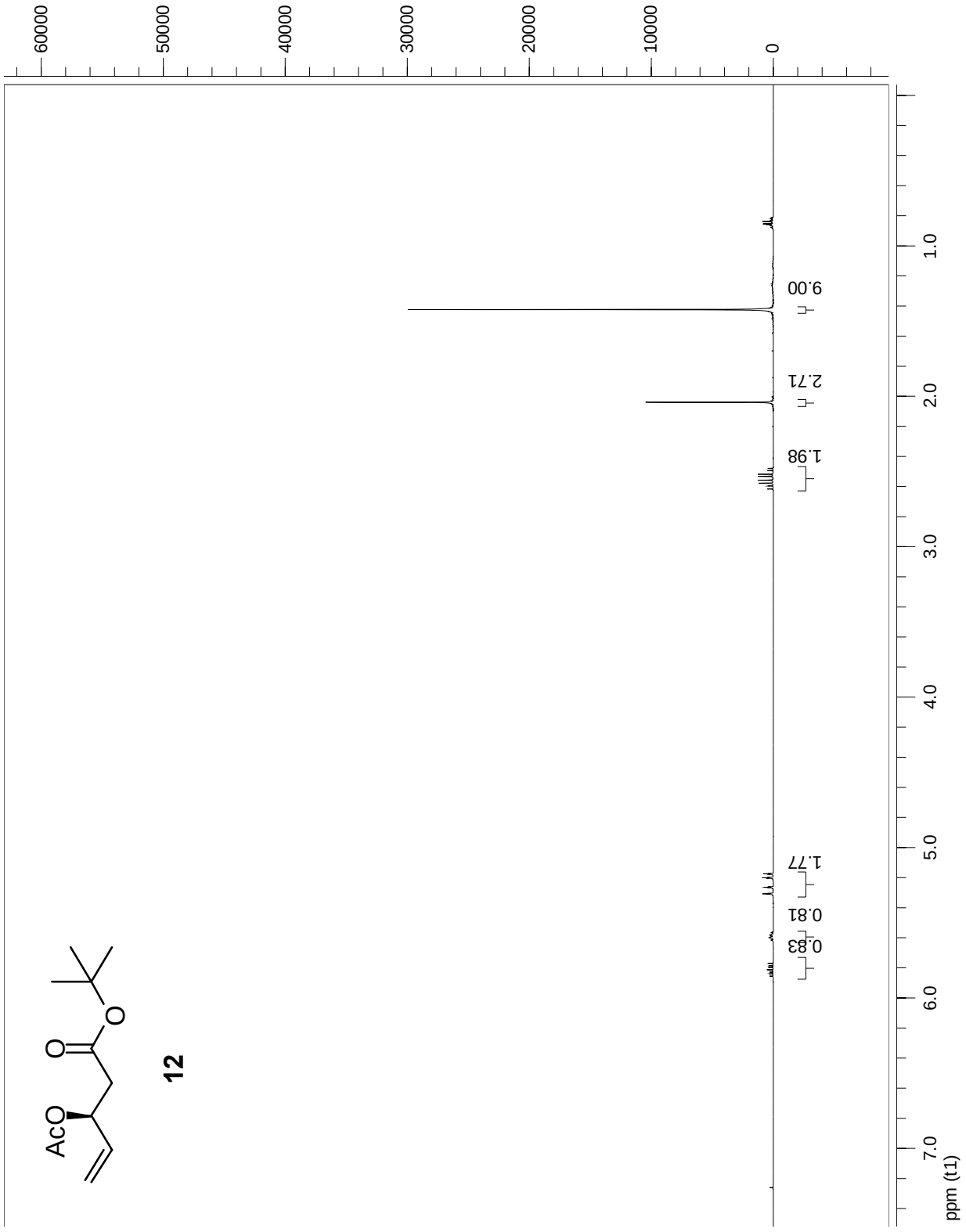
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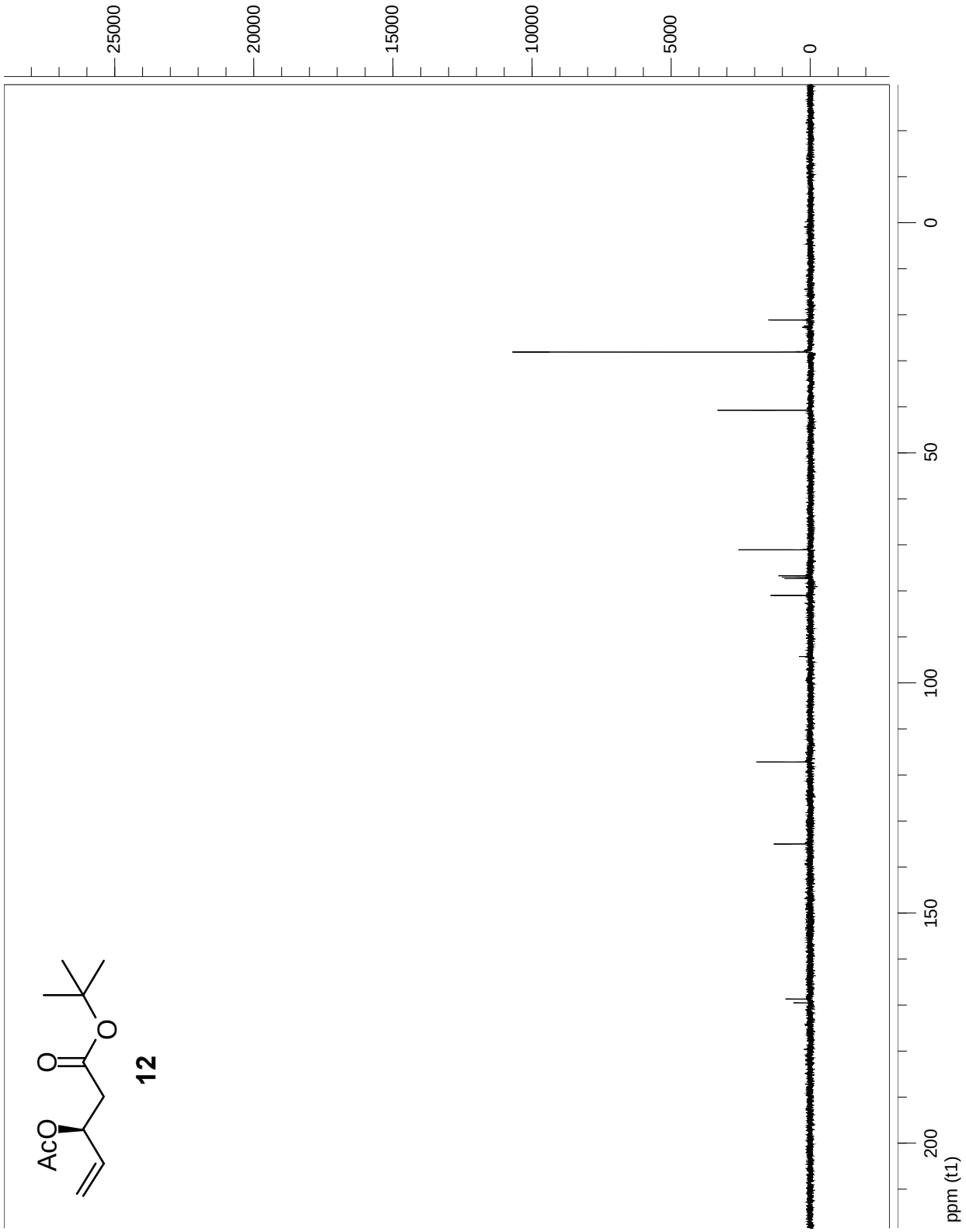
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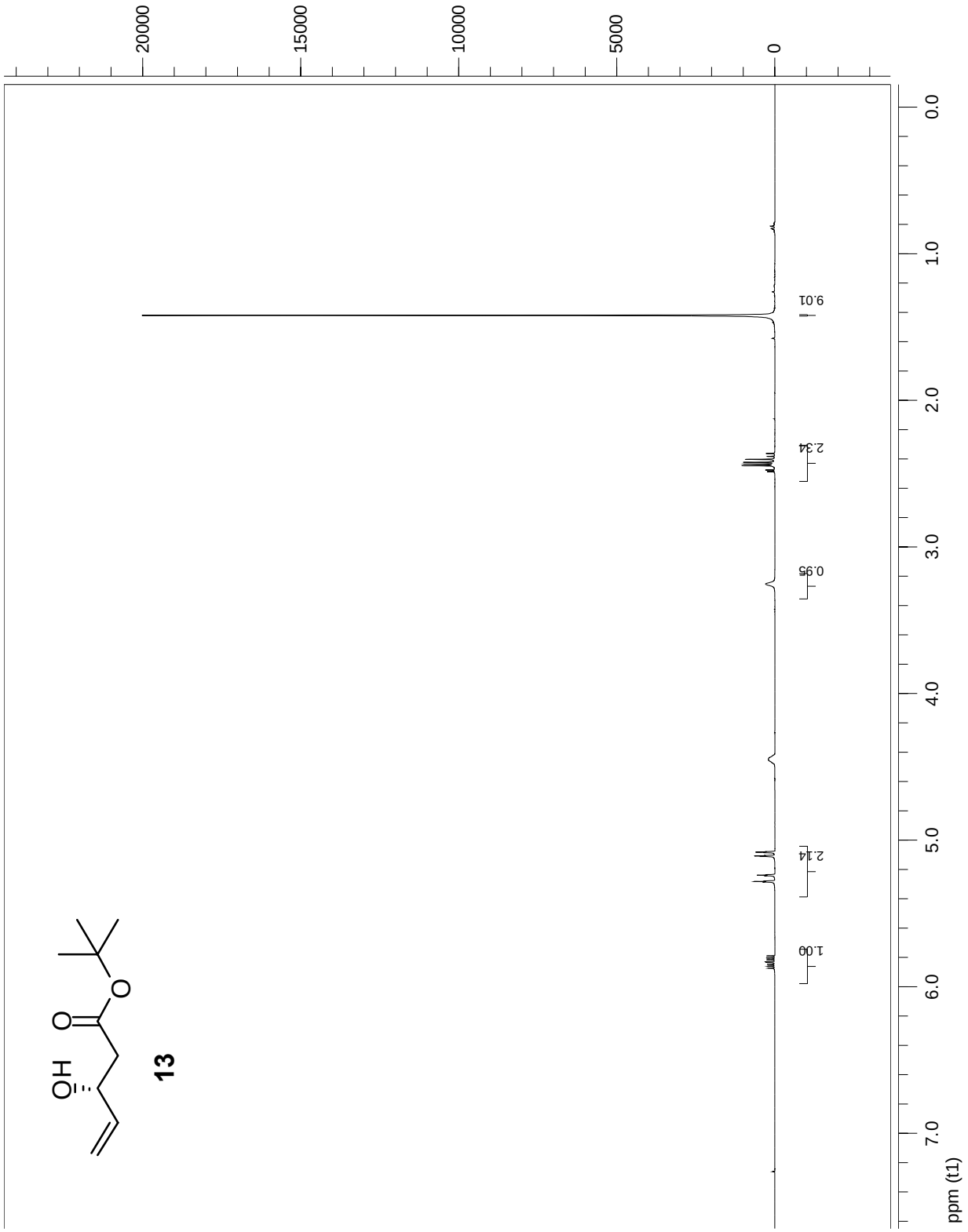
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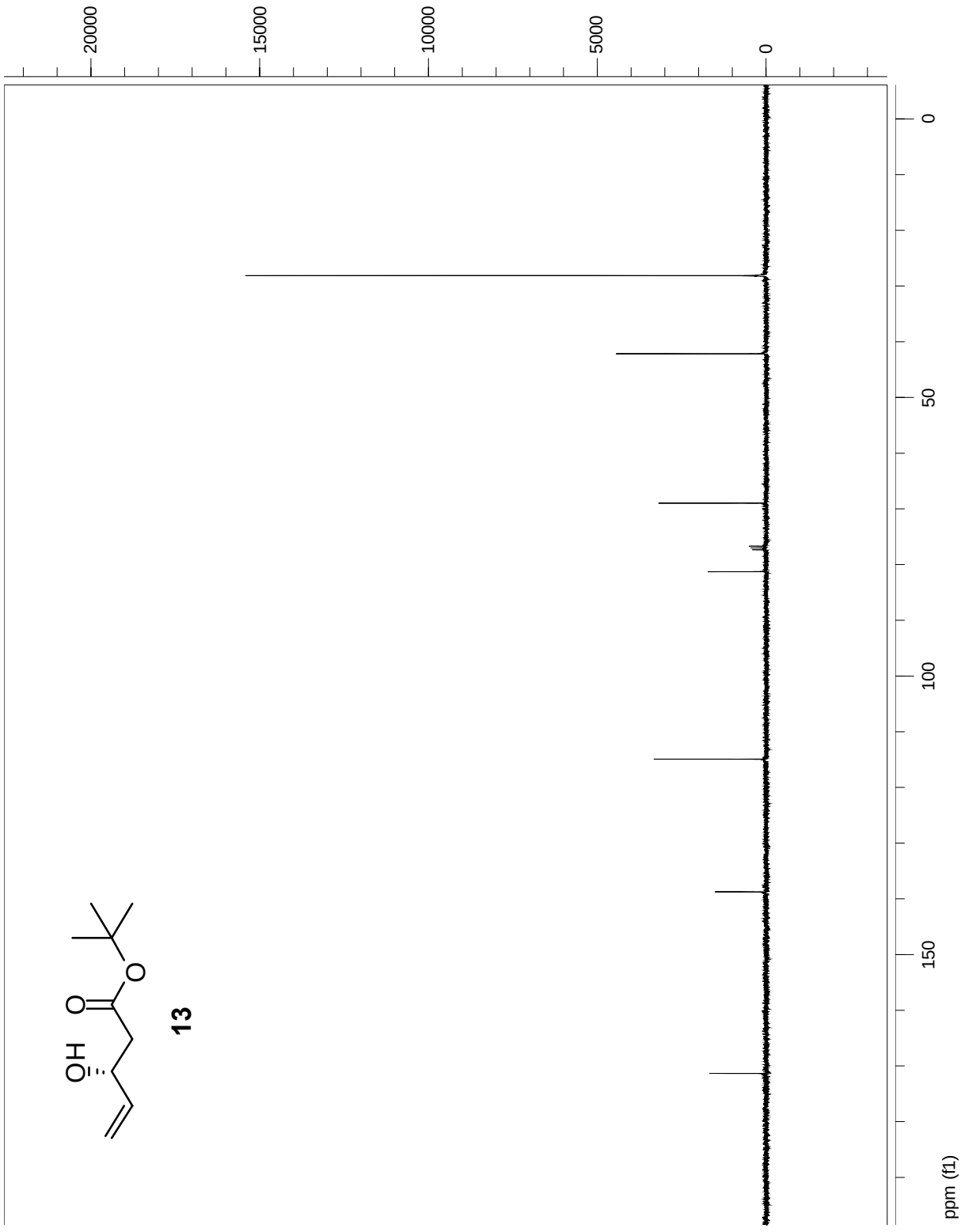

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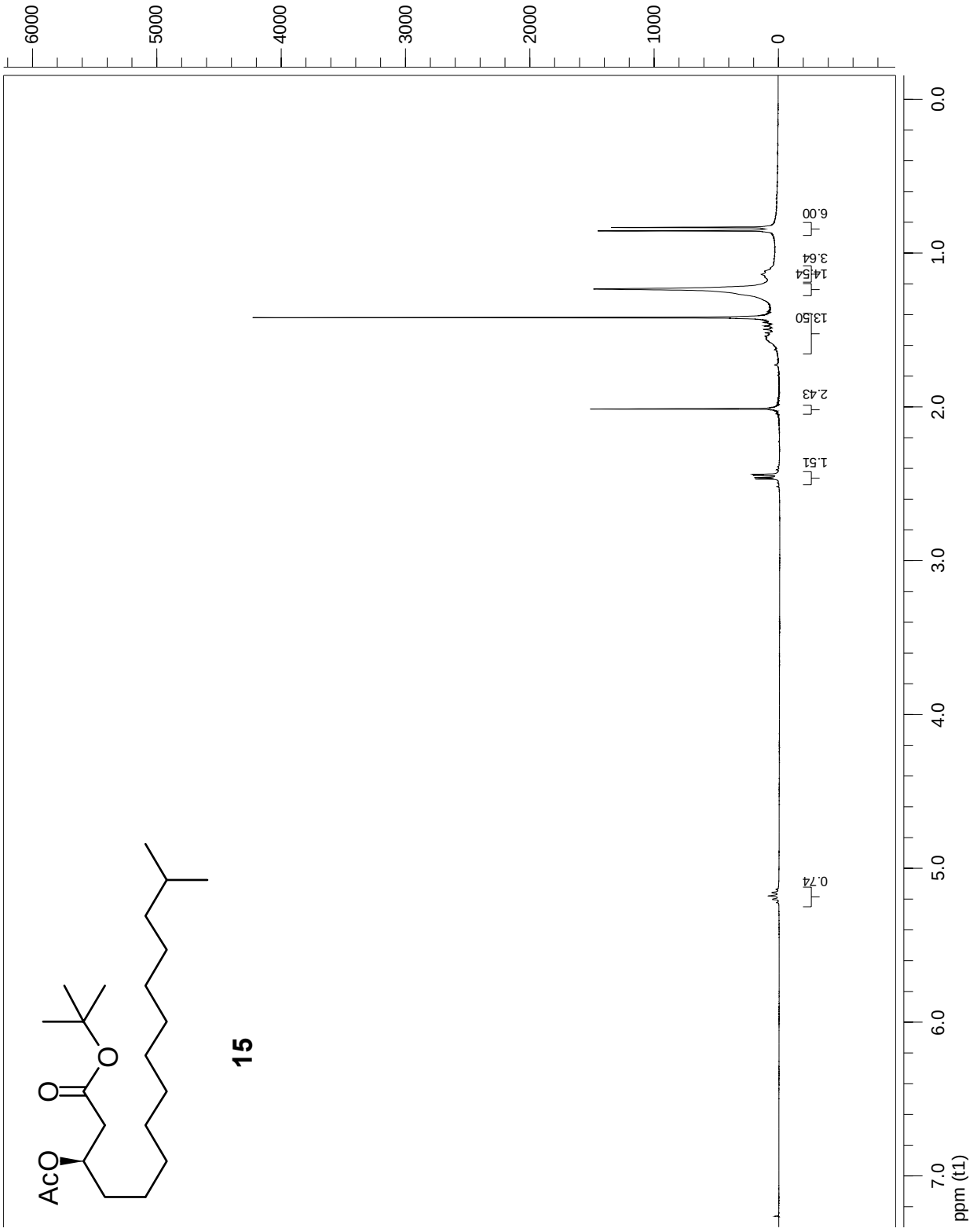
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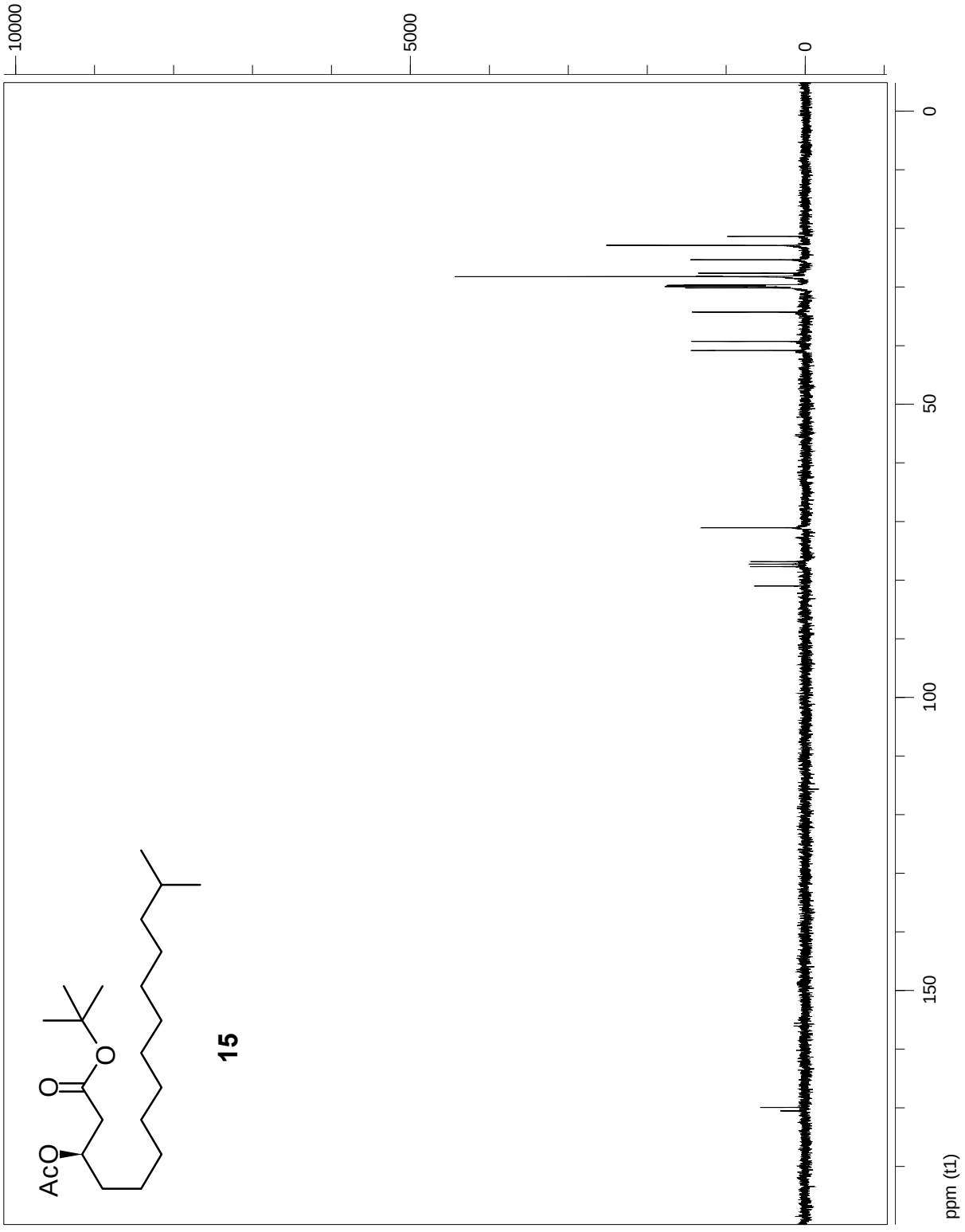
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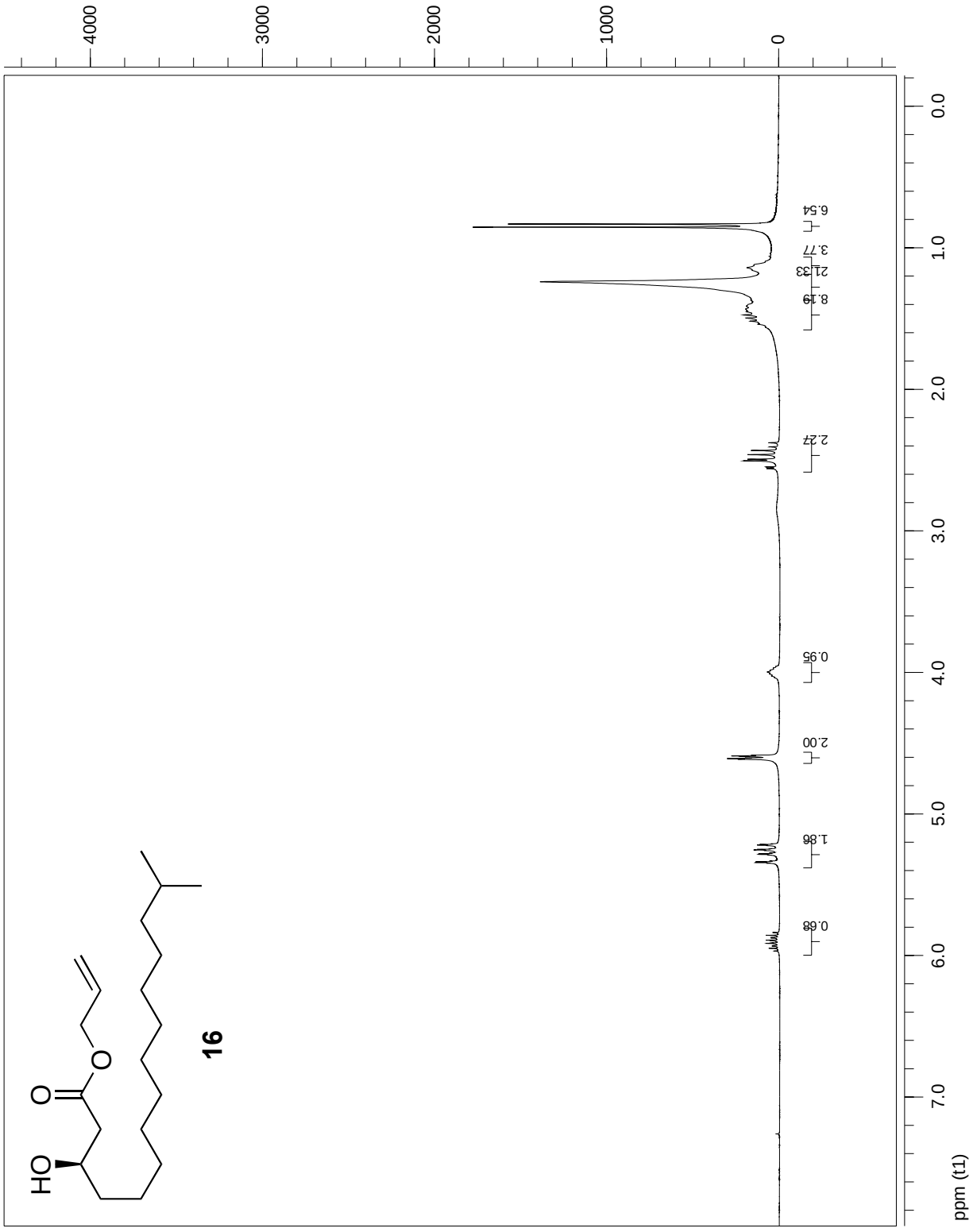
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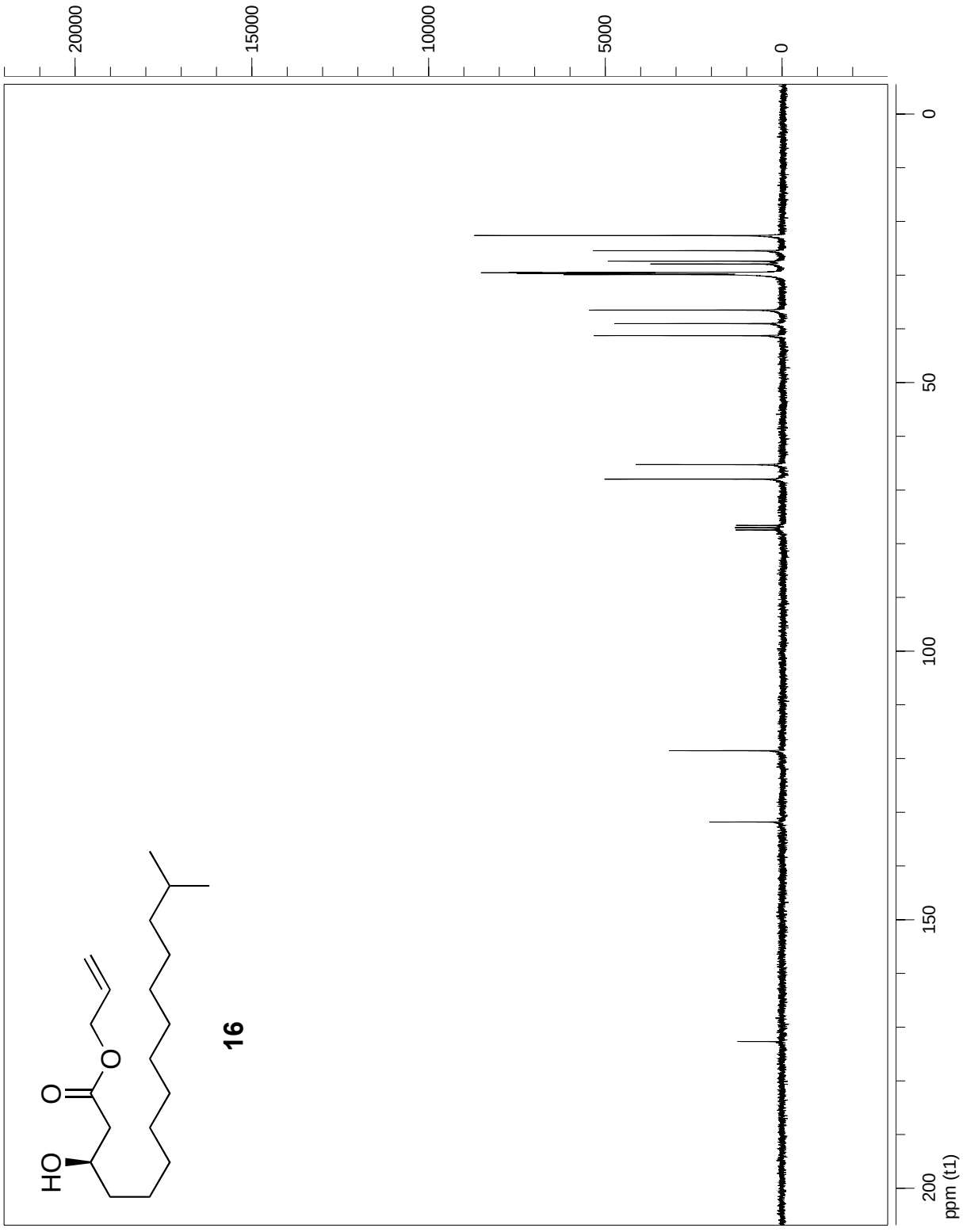

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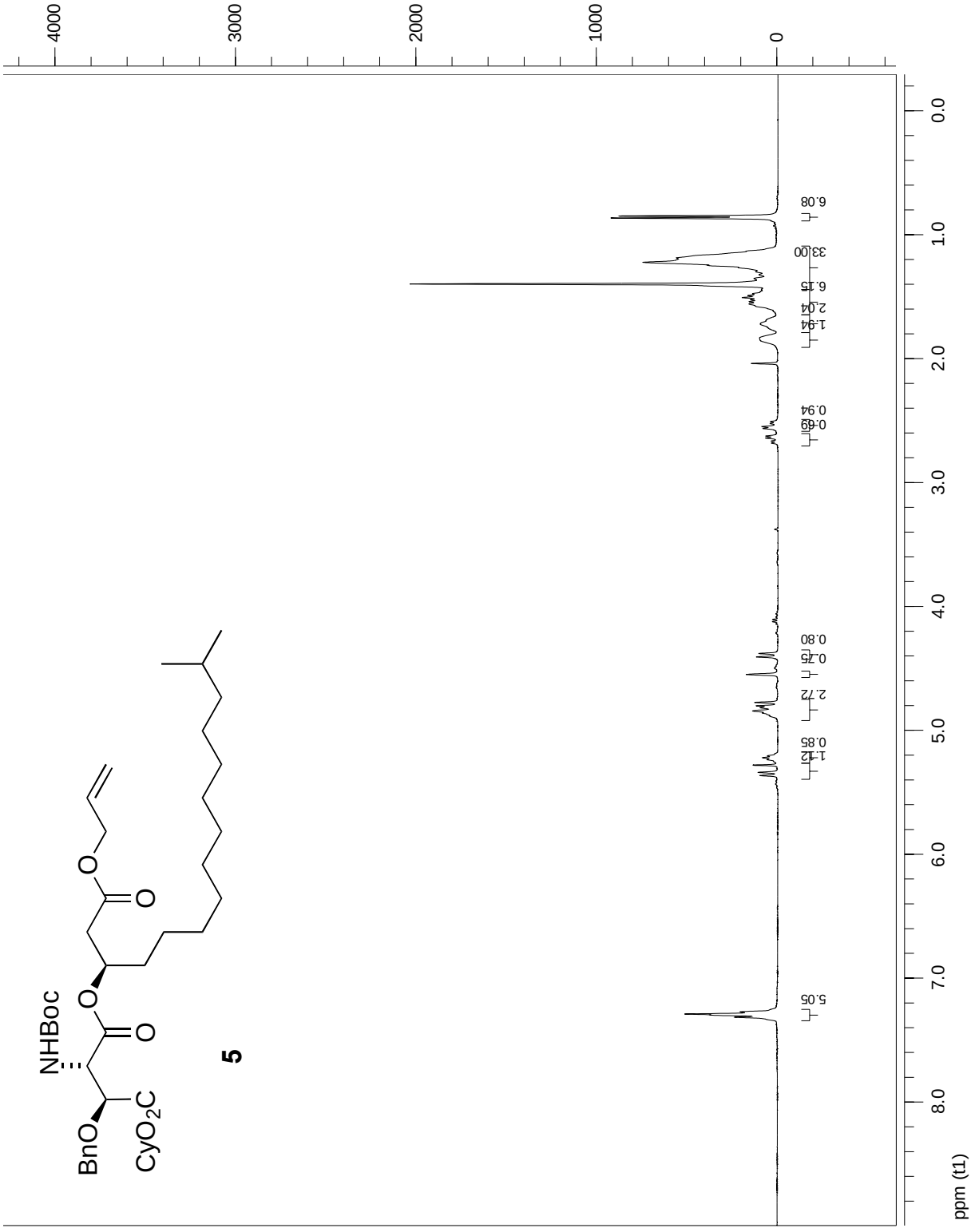
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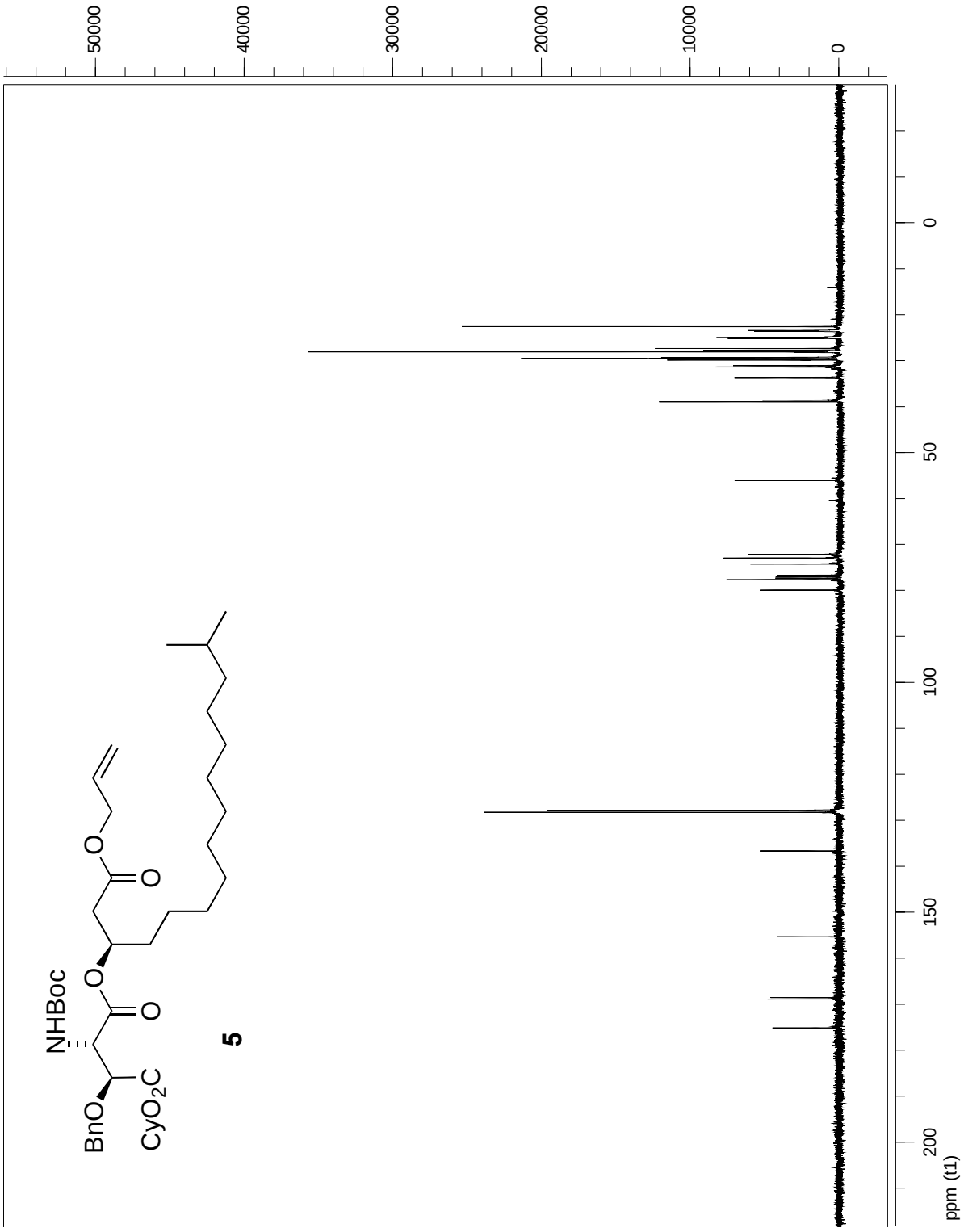
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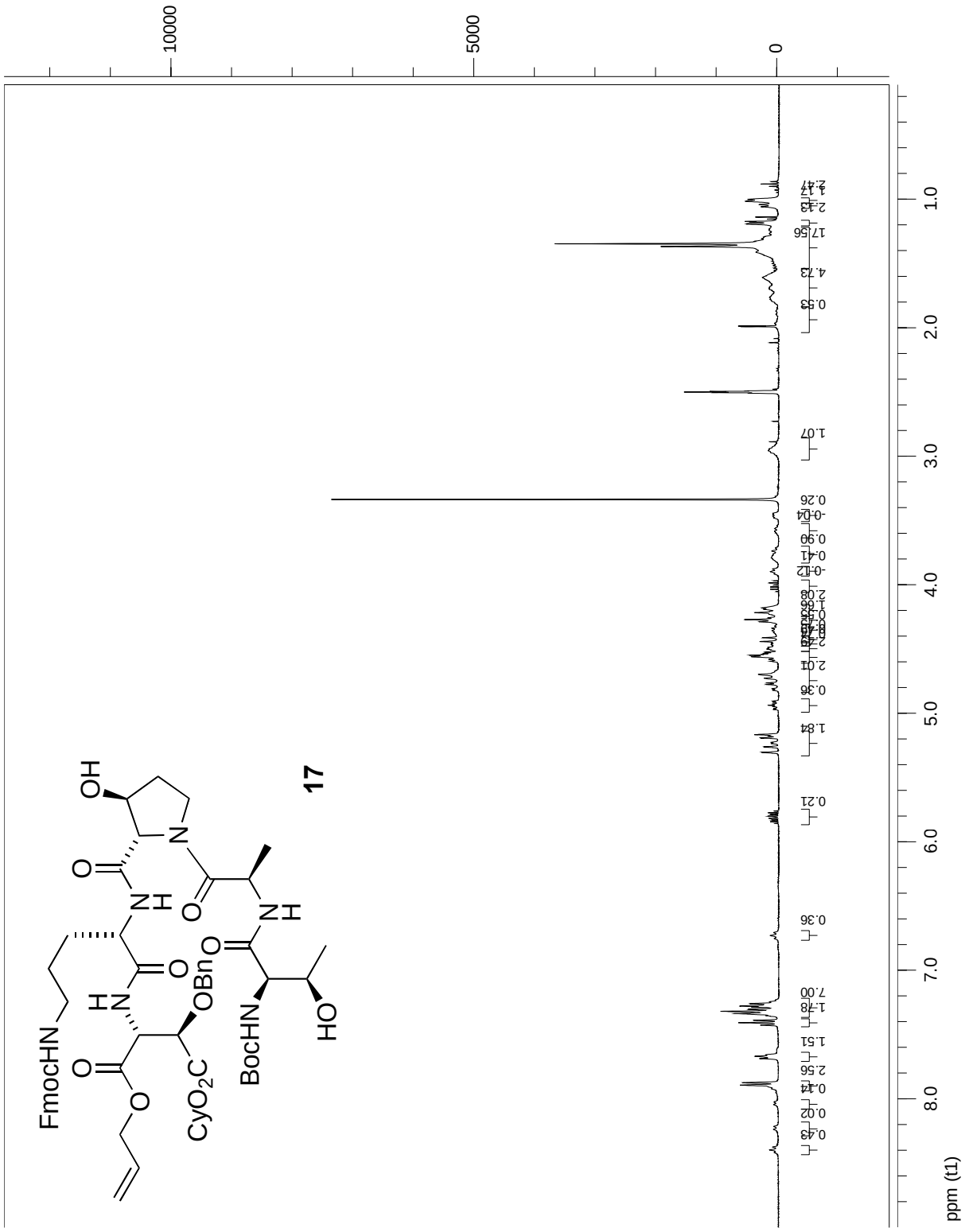
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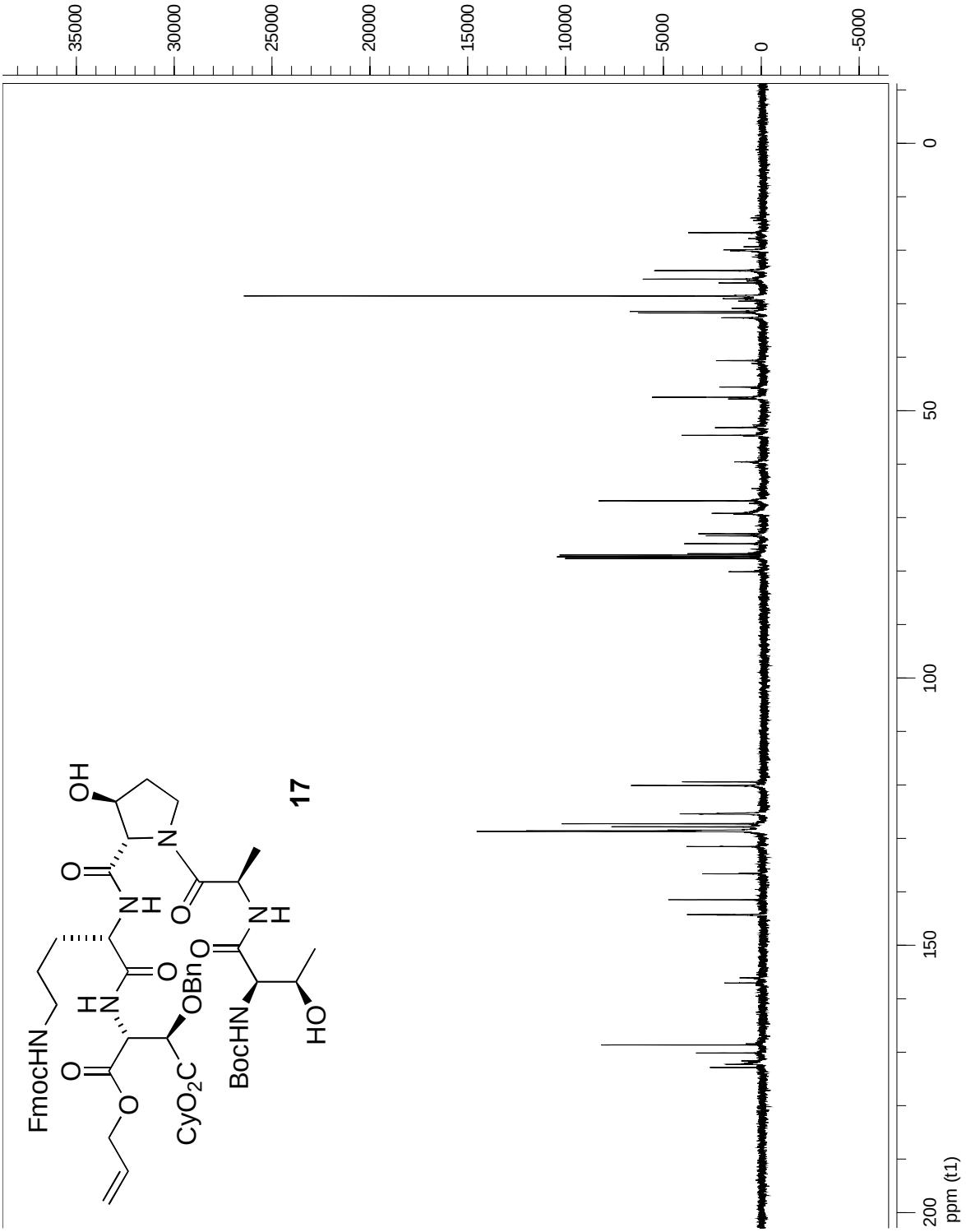
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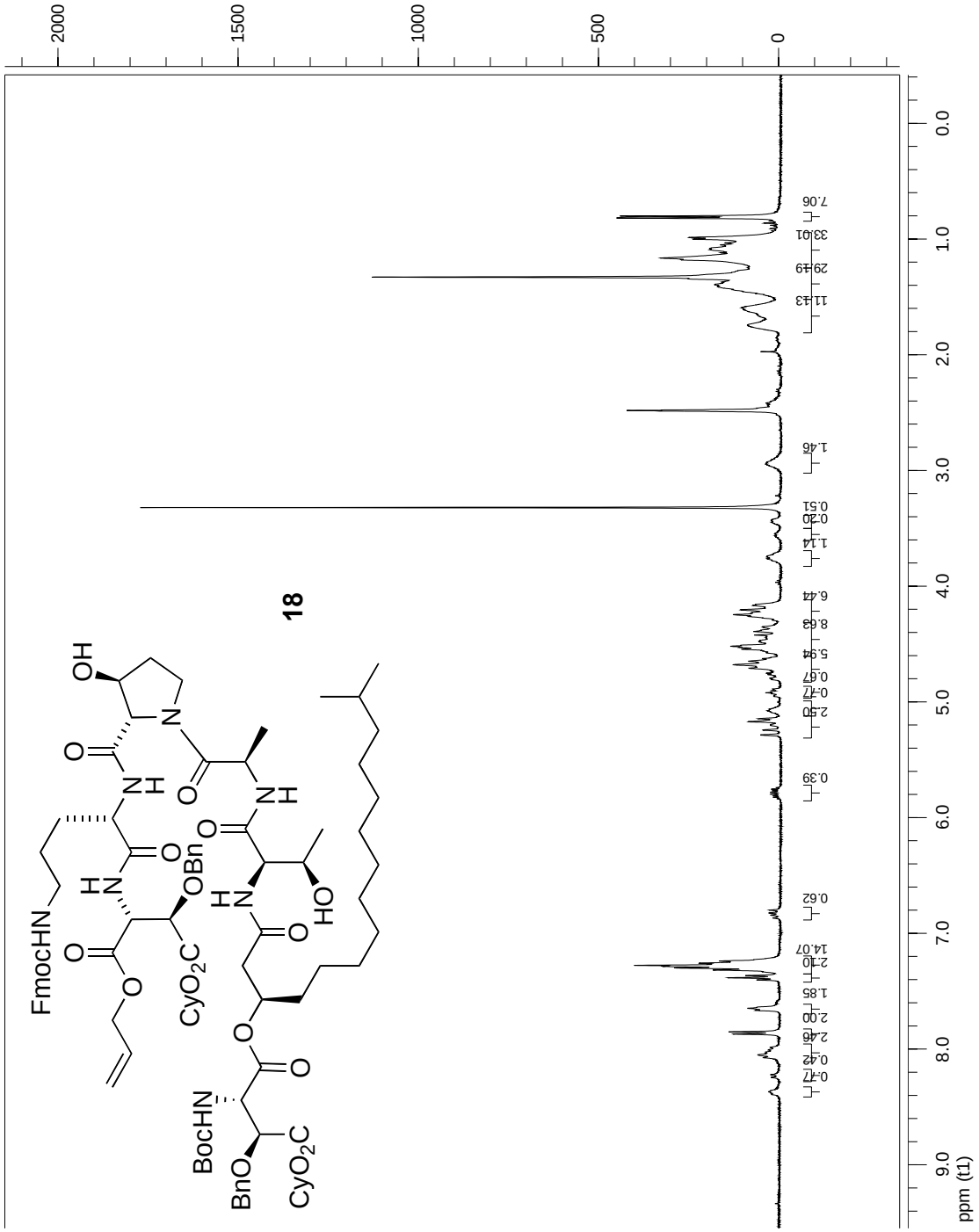
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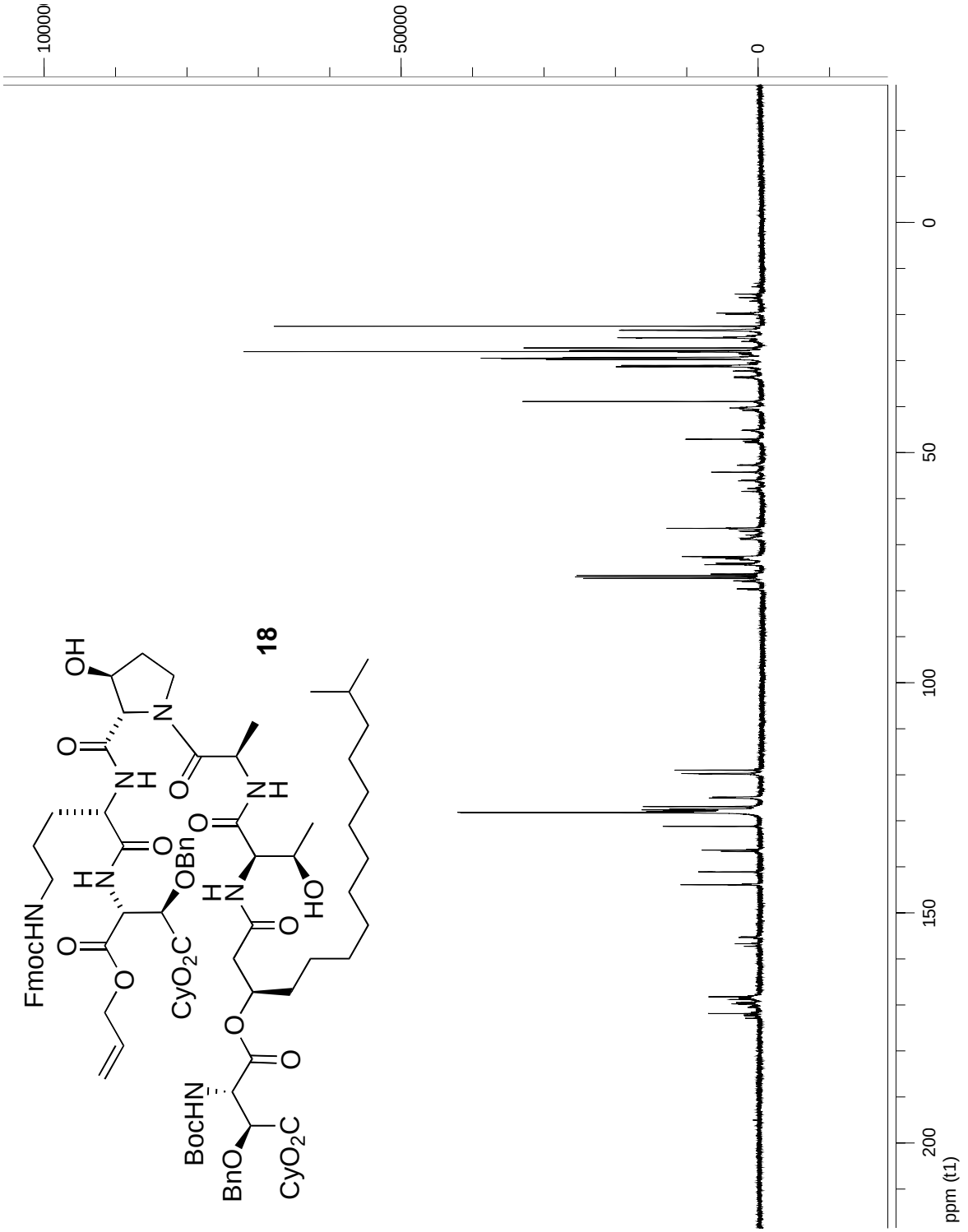
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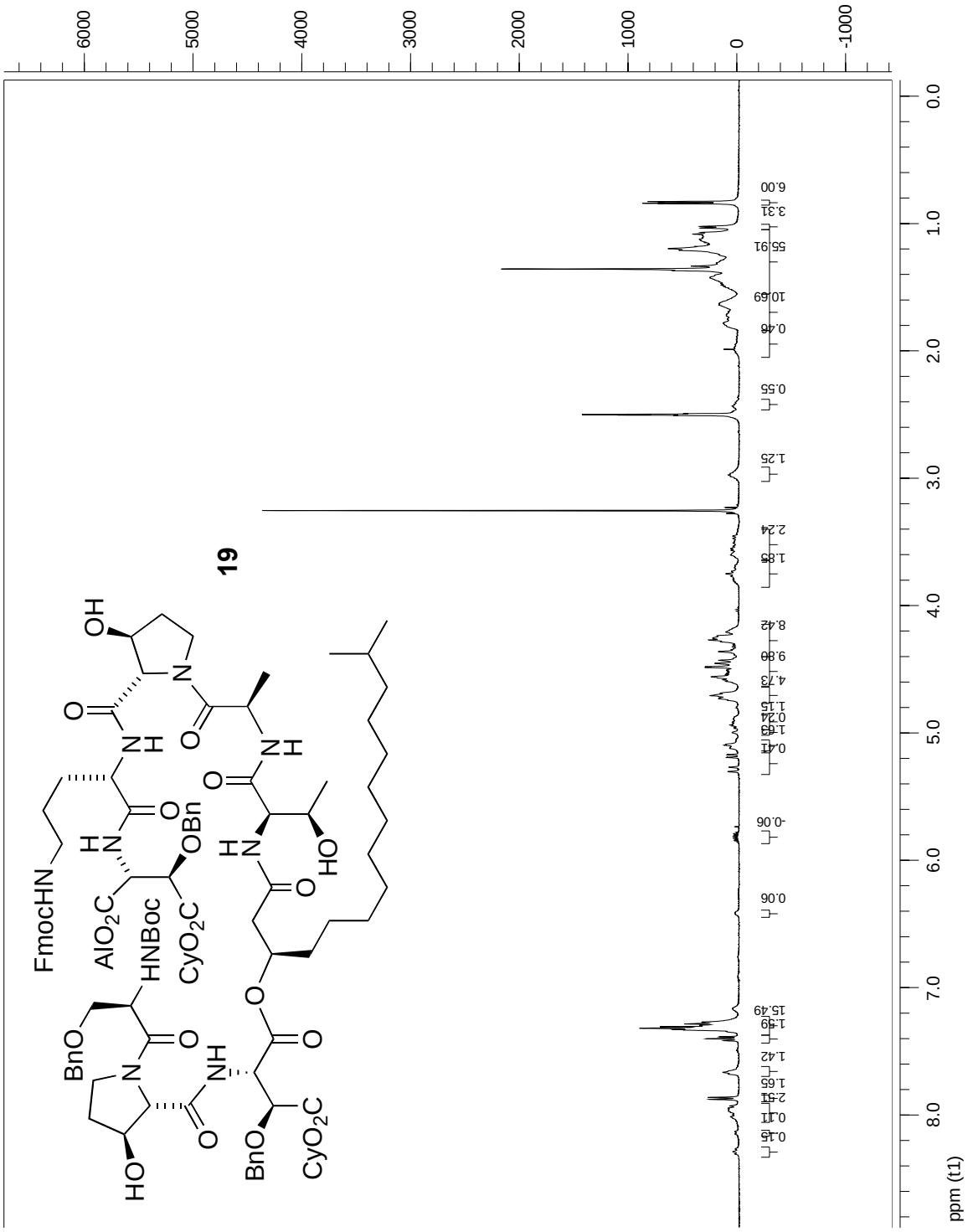
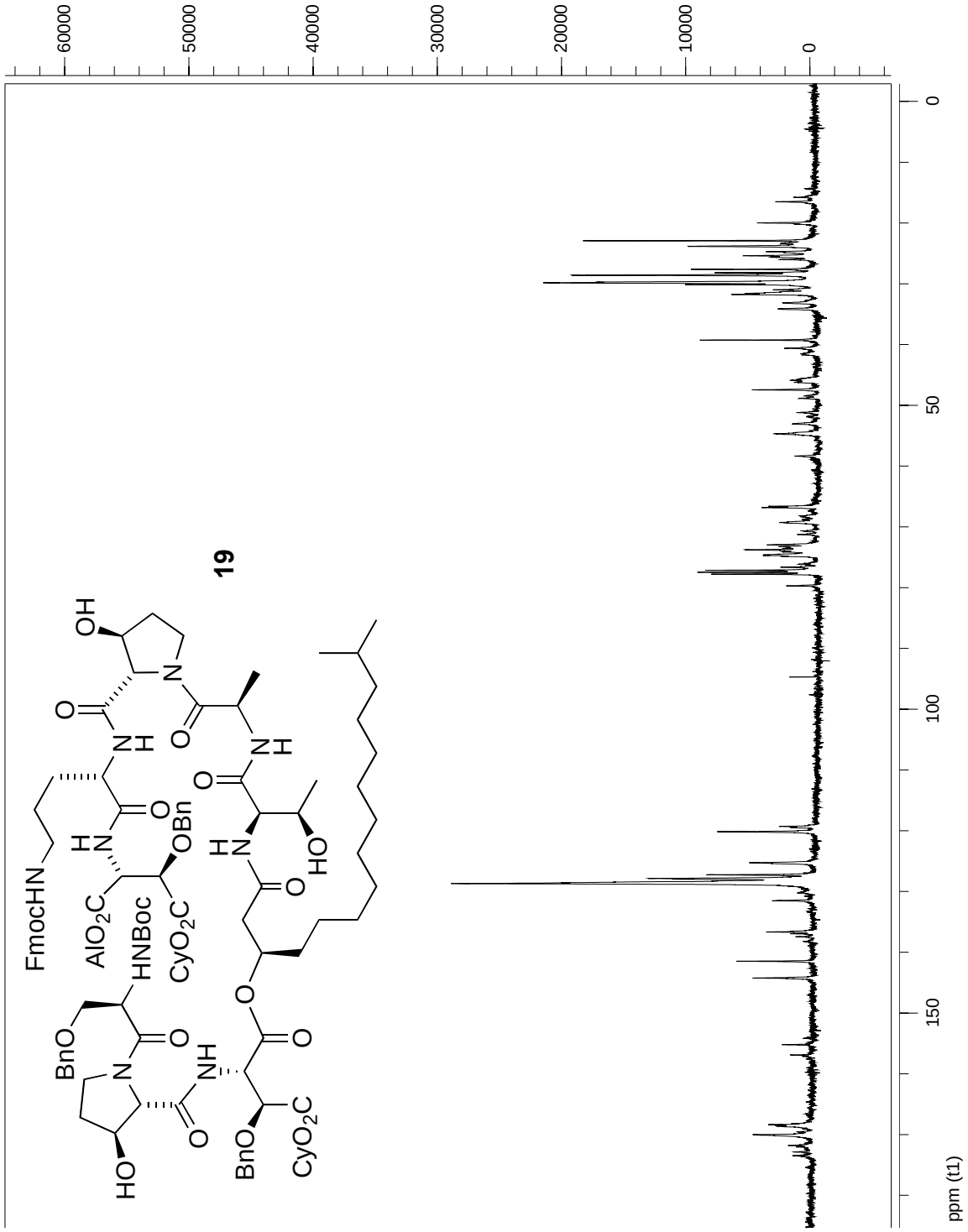
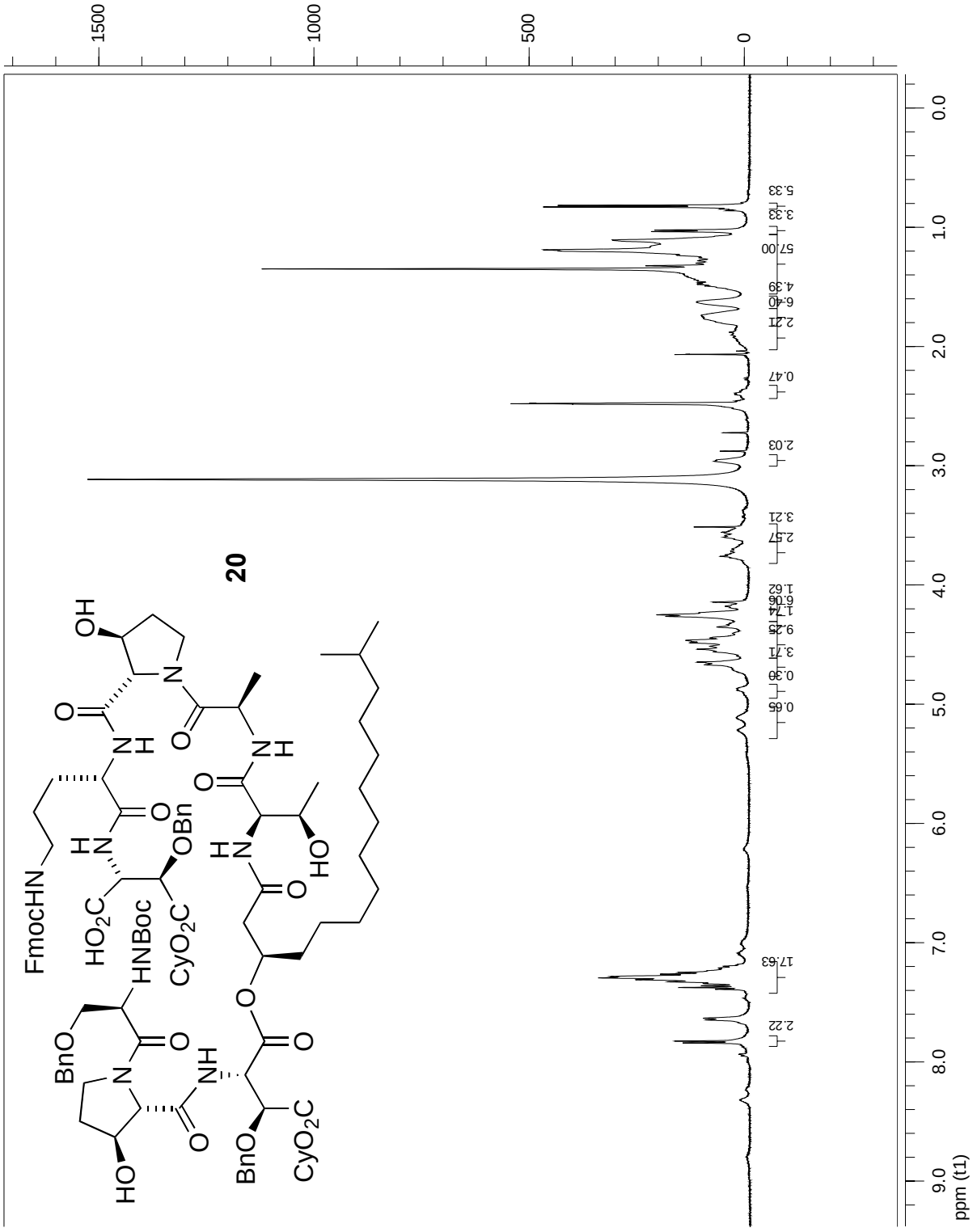
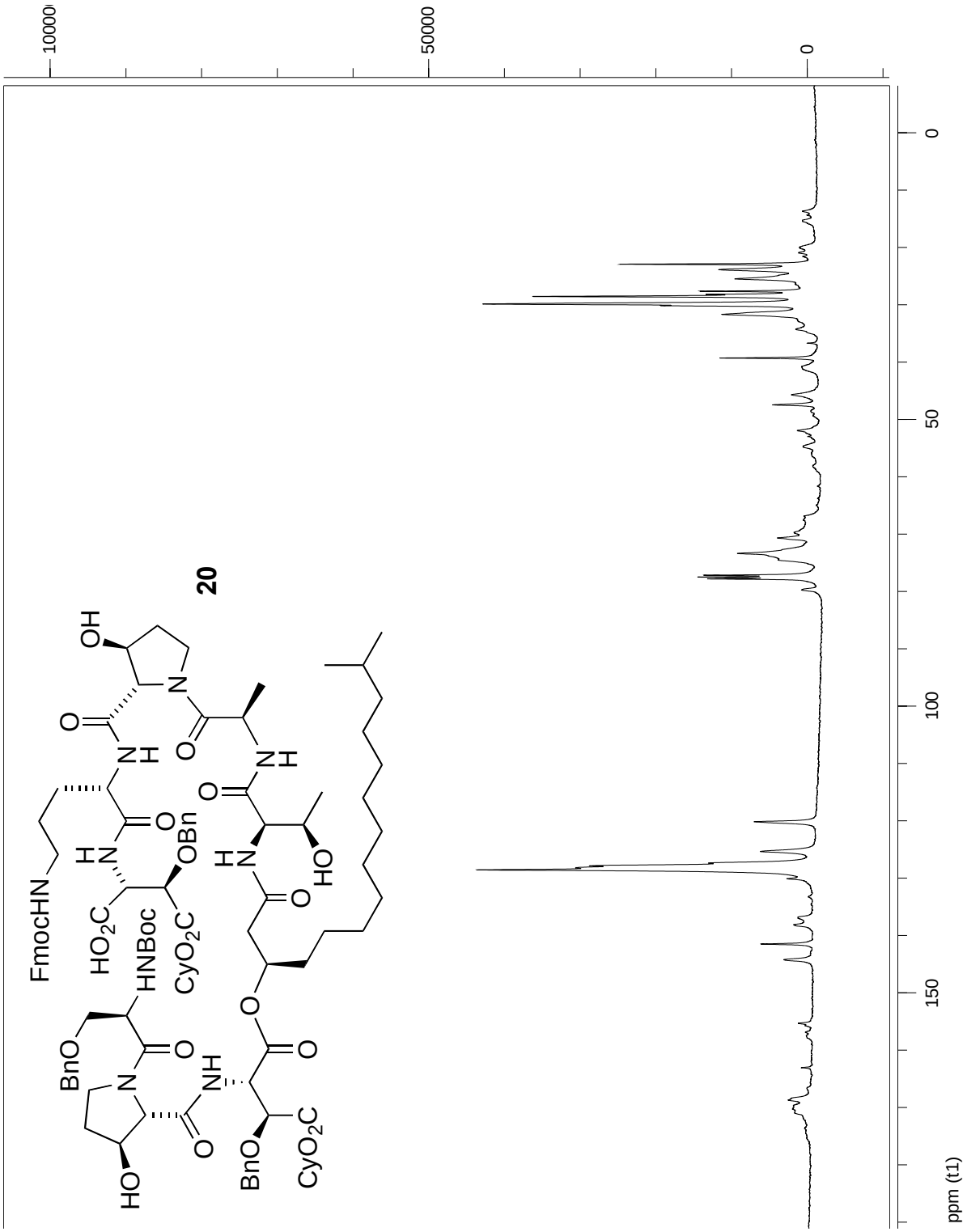
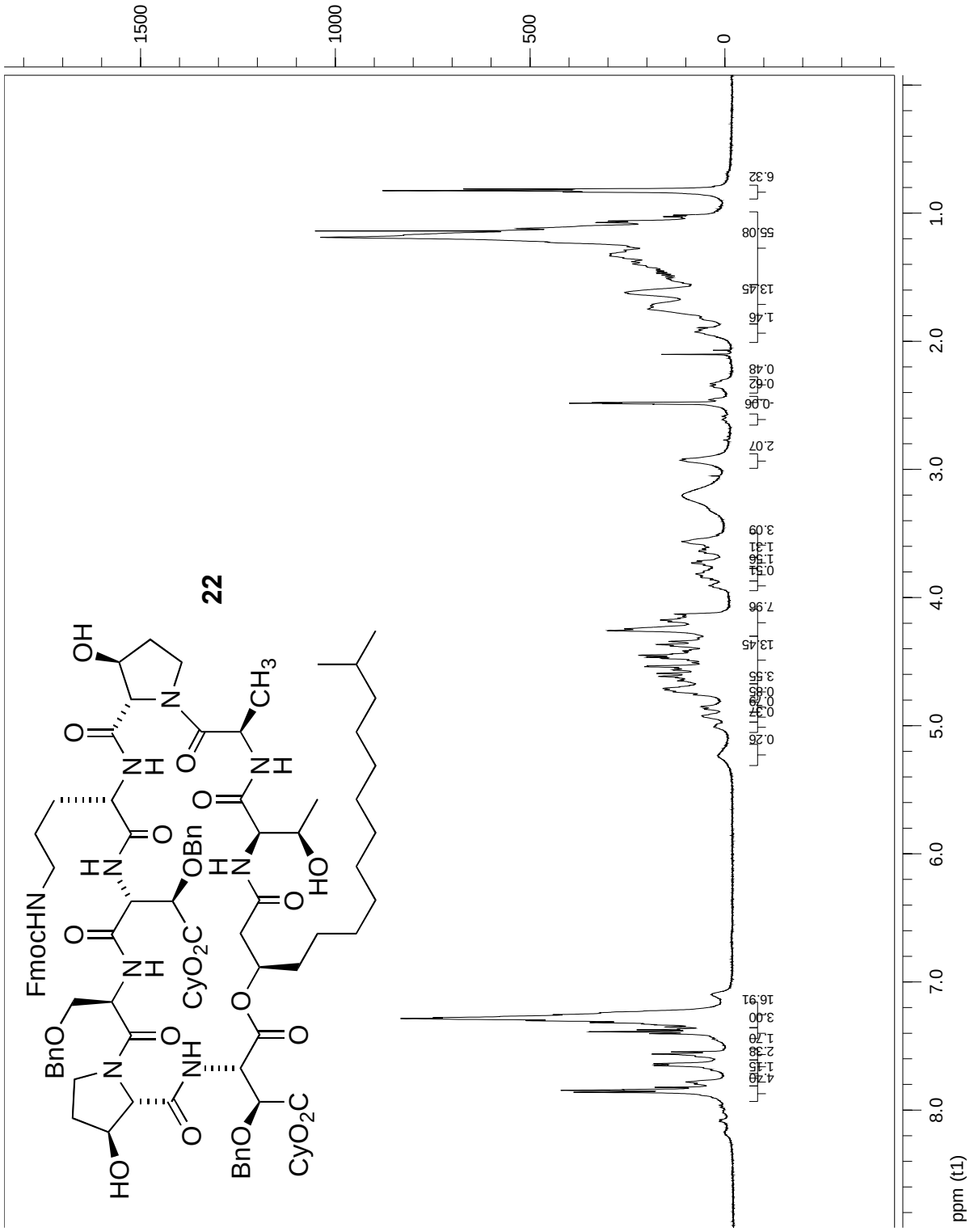
FmocHN
OH
BocHN
BnO
OBn
HO
CyO2C
CyO2C

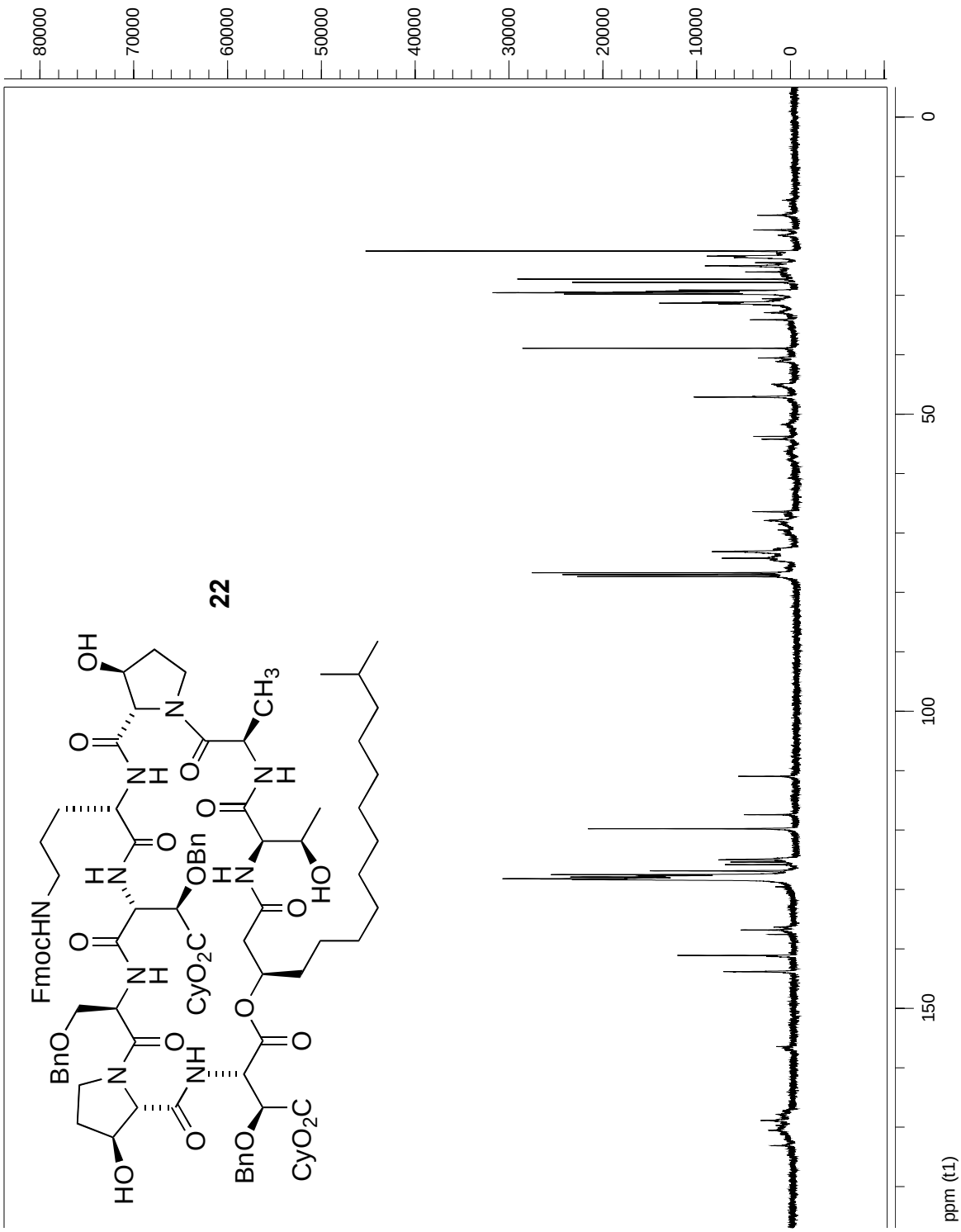

19
FmocHN
AlO2C
HNBoc
CyO2C
OBn
BnO
HO
BnO
CyO2C
OH
HO
6000
5000
4000
3000
2000
1000
0
-1000
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)

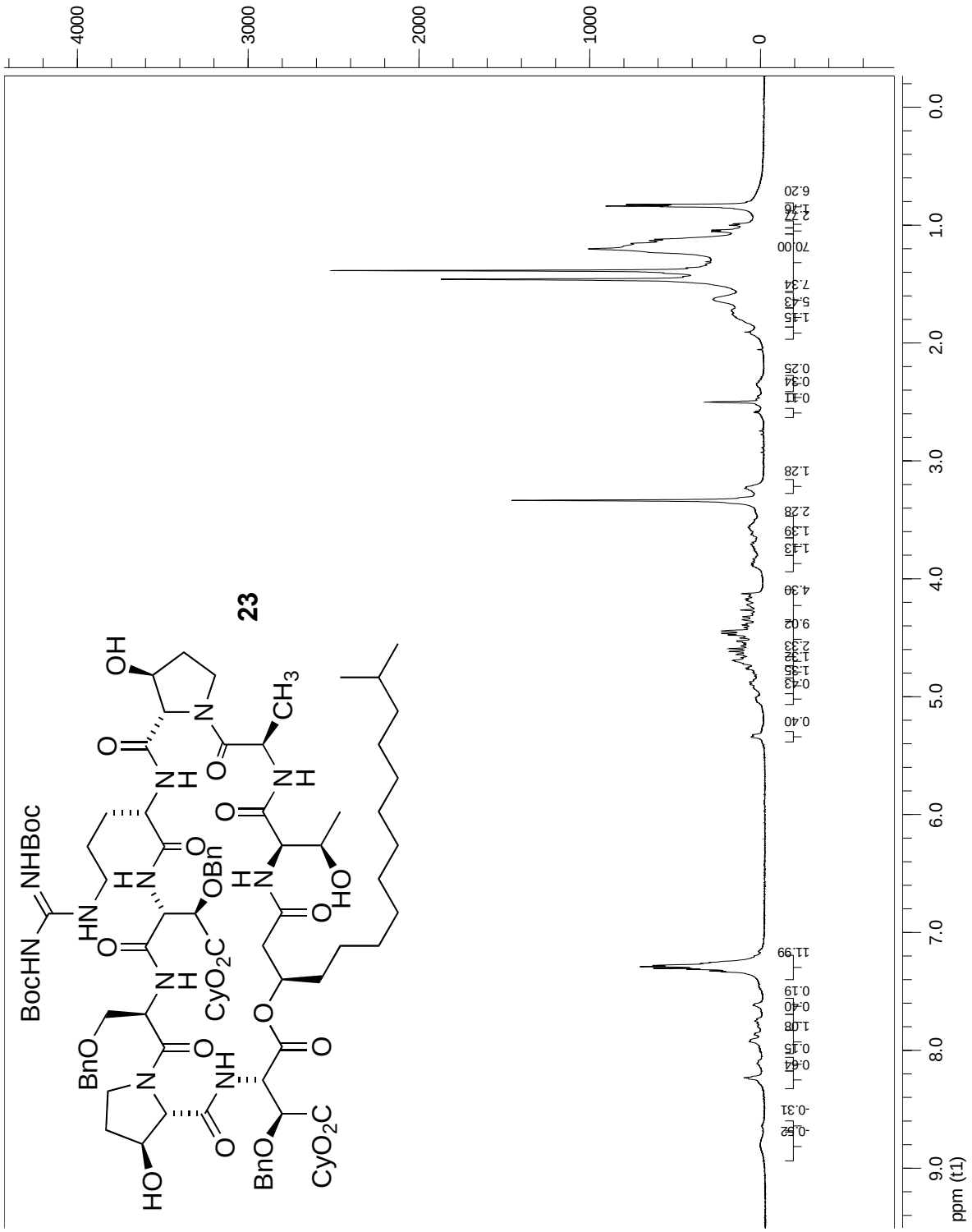

19
FmocHN
AlO2C
HNBoc
CyO2C
OBn
BnO
HO
BnO
CyO2C
OH
HO
60000
50000
40000
30000
20000
10000
0
0
50
100
150
ppm (t1)

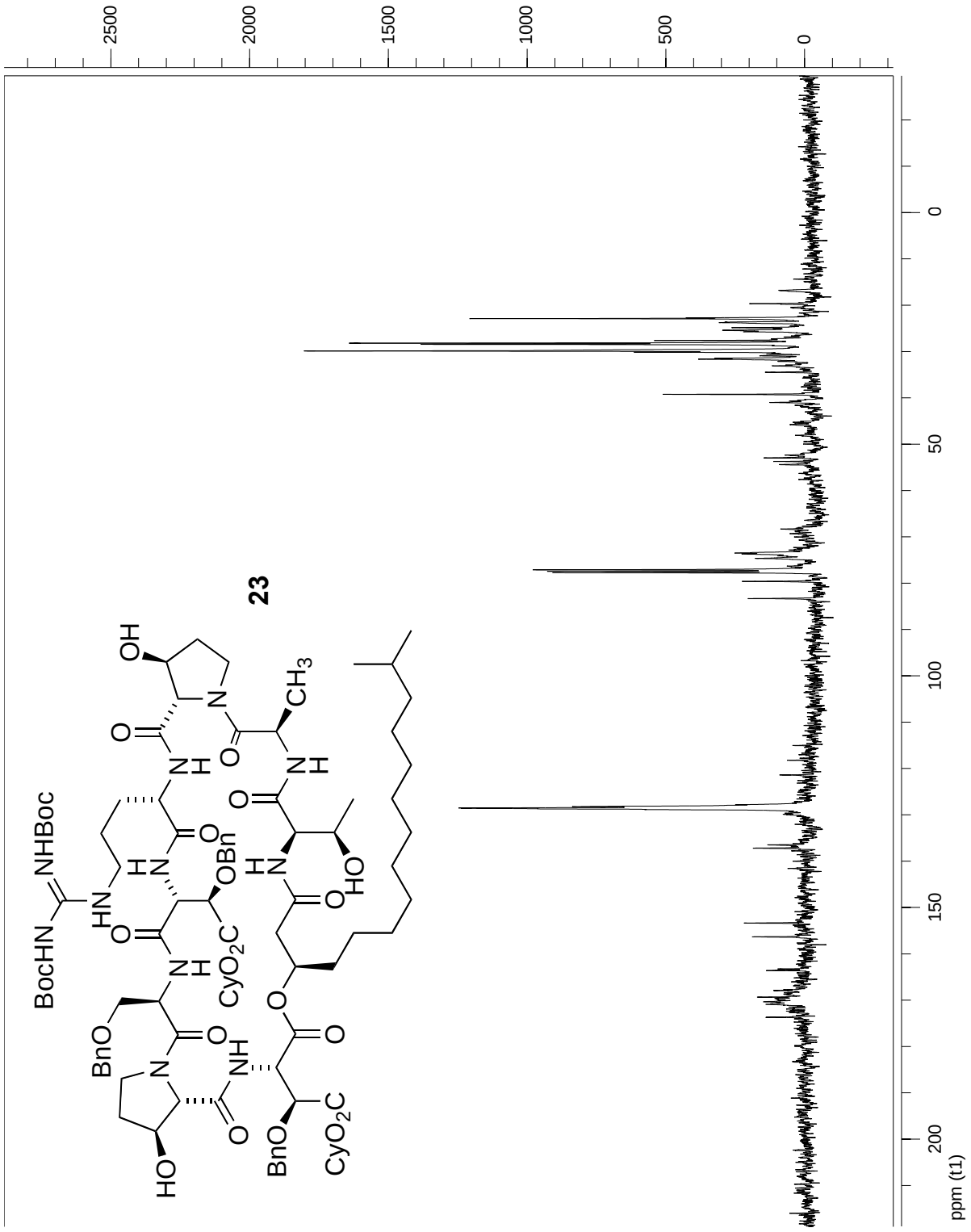

20
FmocHN
HNBoc
OBn
BnO
HO
OH
BnO
CyO2C
HO2C
CyO2C
ppm (t1)

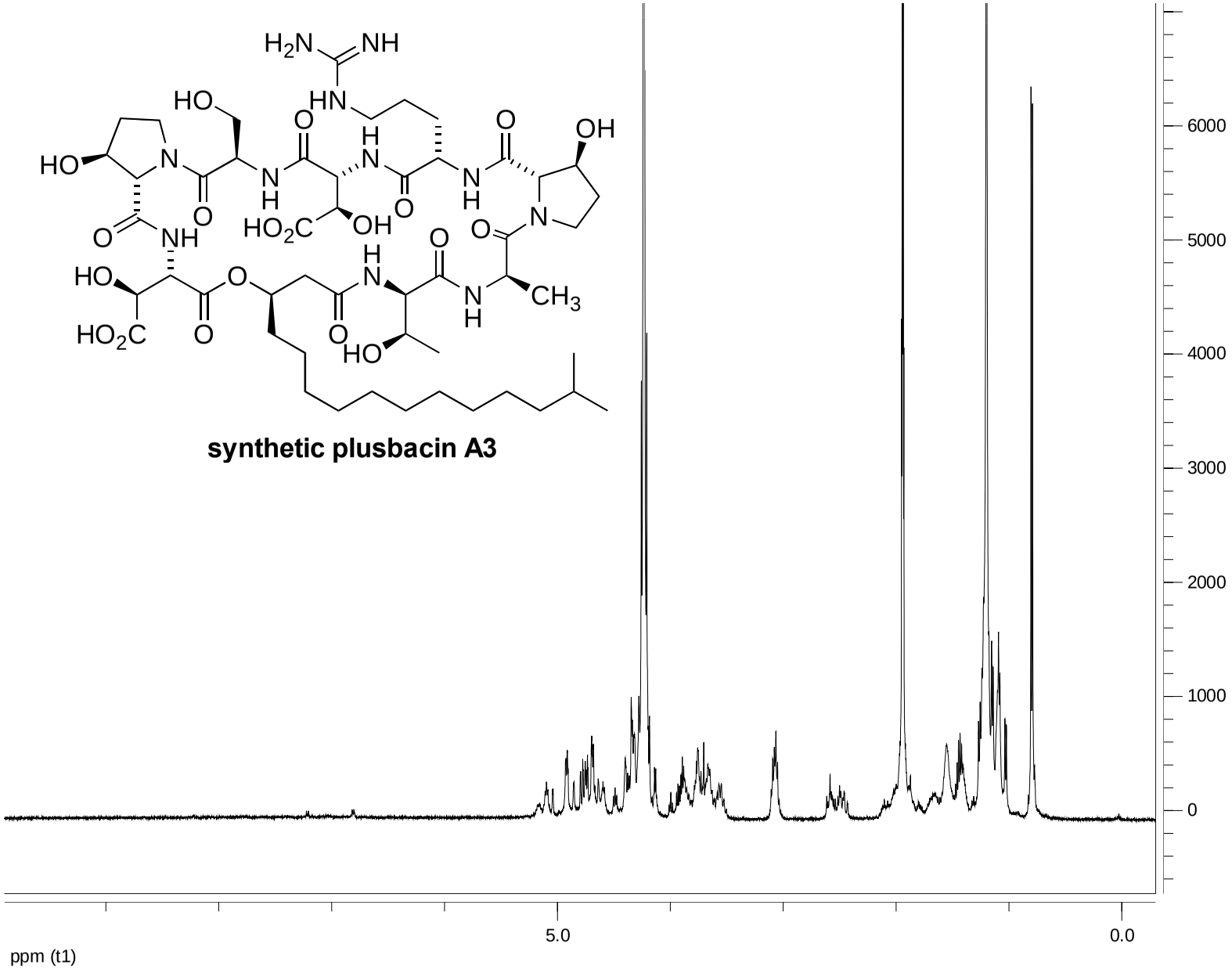

20
FmocHN
HO2C
HNBoc
CyO2C
OBn
BnO
HO
BnO
CyO2C
OH
HO
10000
50000
0
0
50
100
150
ppm (t1)

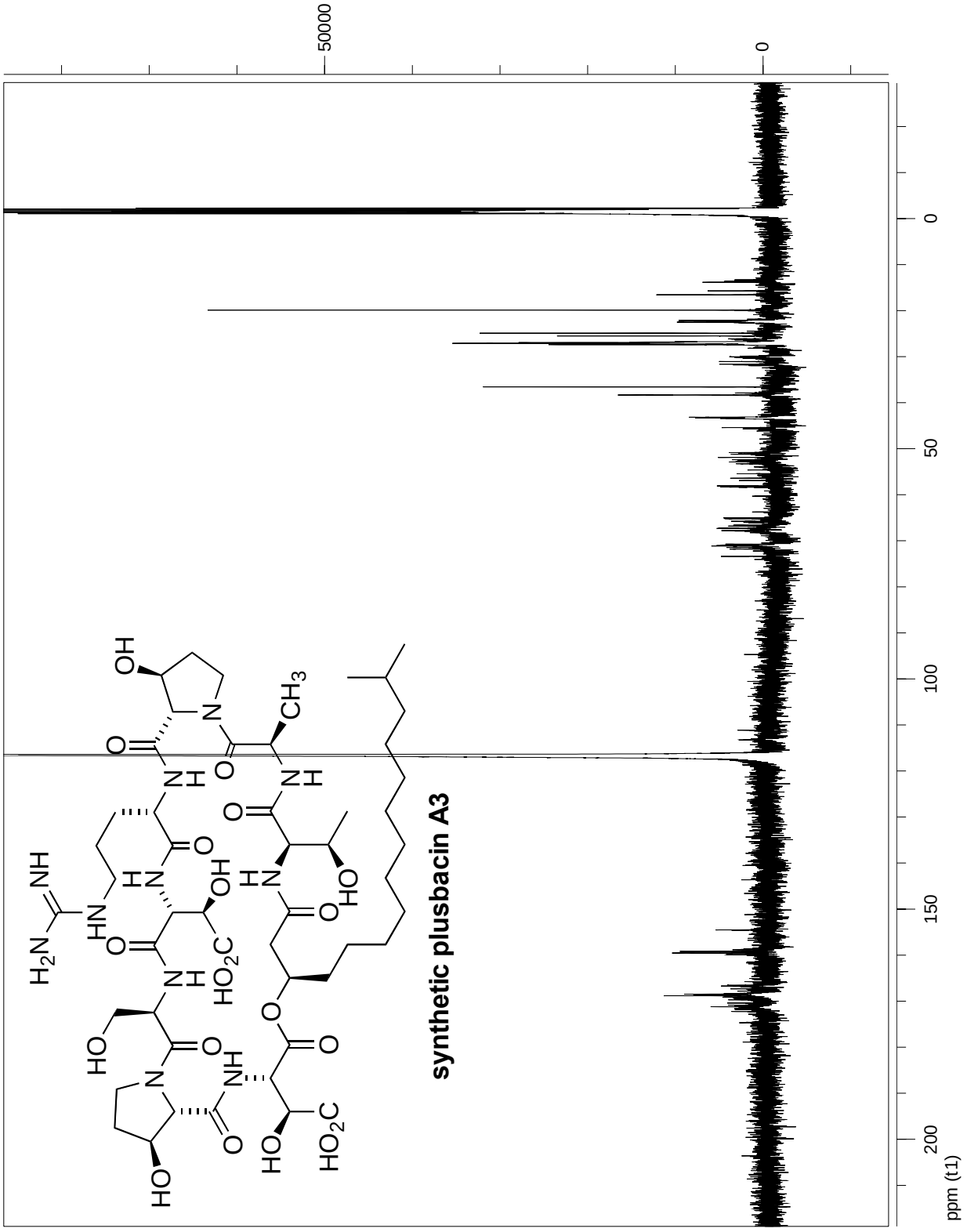

22
FmocHN
BnO
HO
OBn
BnO
CyO_2C
CyO_2C
CH_3
OH
HO
1500
1000
500
0
ppm (t1)
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
6.32
55.08
13.45
1.46
0.48
0.62
0.06
2.07
3.09
1.31
1.06
0.91
7.96
13.45
3.55
0.26
16.91
3.00
1.70
2.38
1.55
4.26

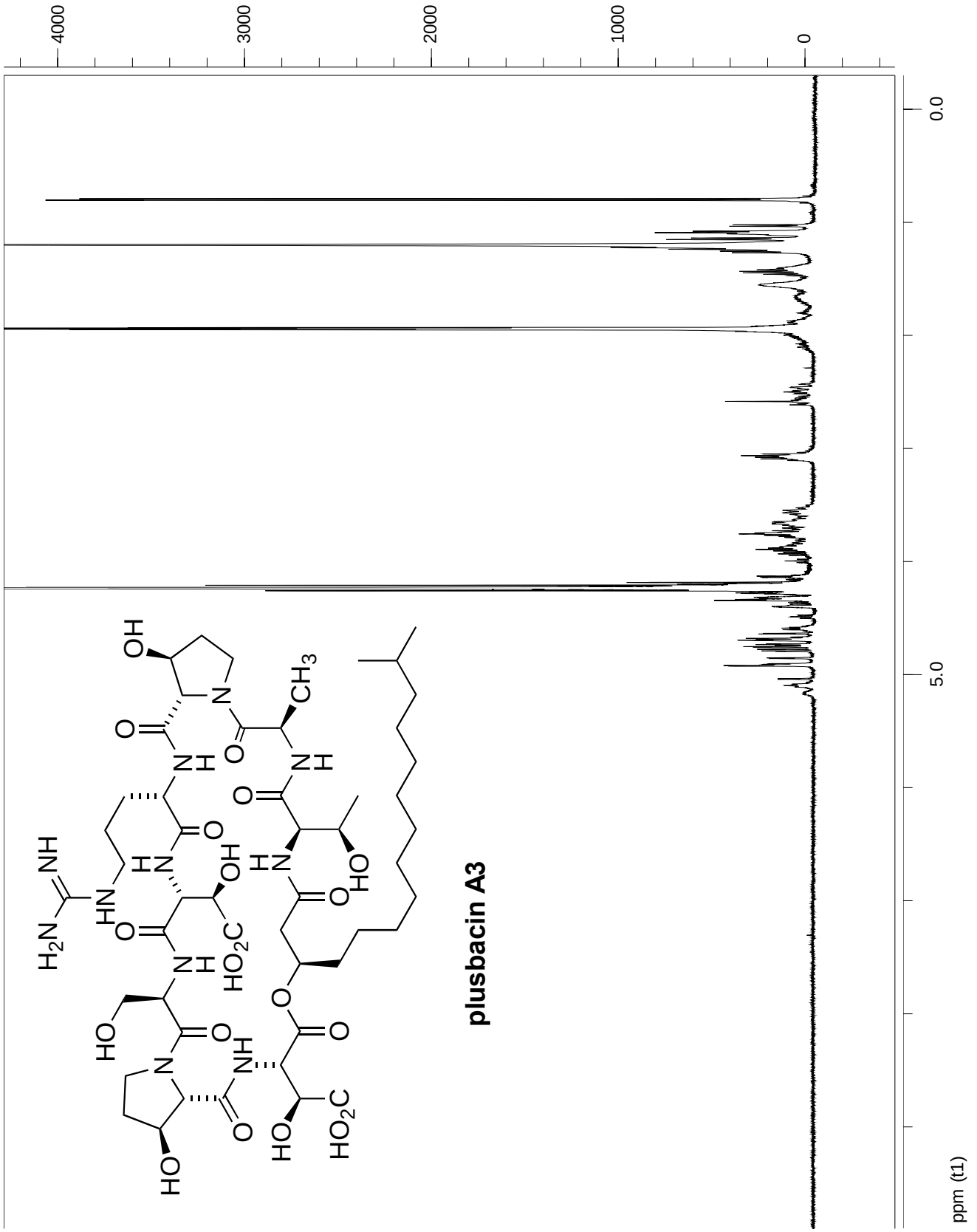

22
80000
70000
60000
50000
40000
30000
20000
10000
0
0
50
100
150
ppm (t1)

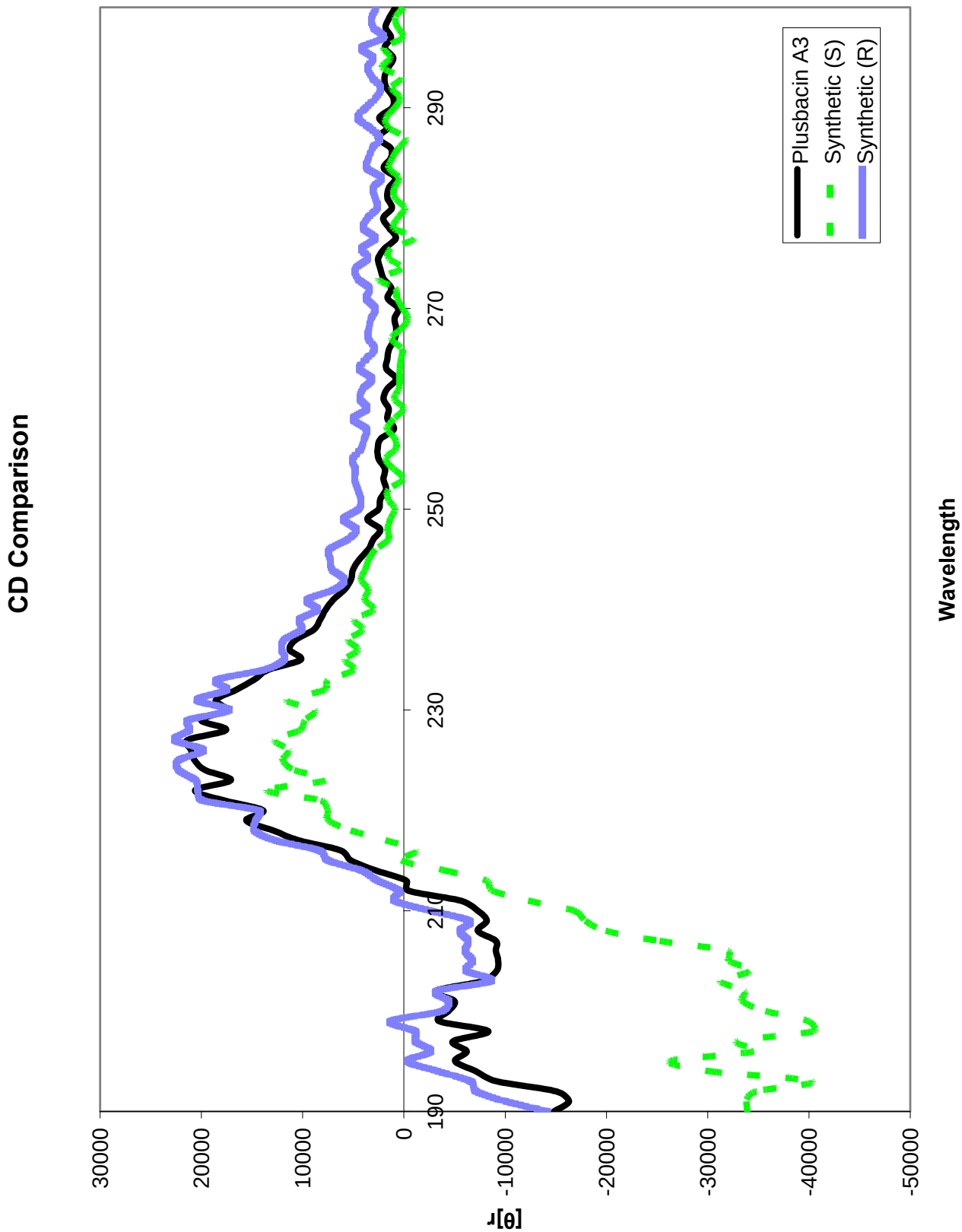

23
BocHN
NHBoc
BnO
CyO2C
OBn
BnO
CyO2C
OH
CH3
HO
HO
4000
3000
2000
1000
0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)

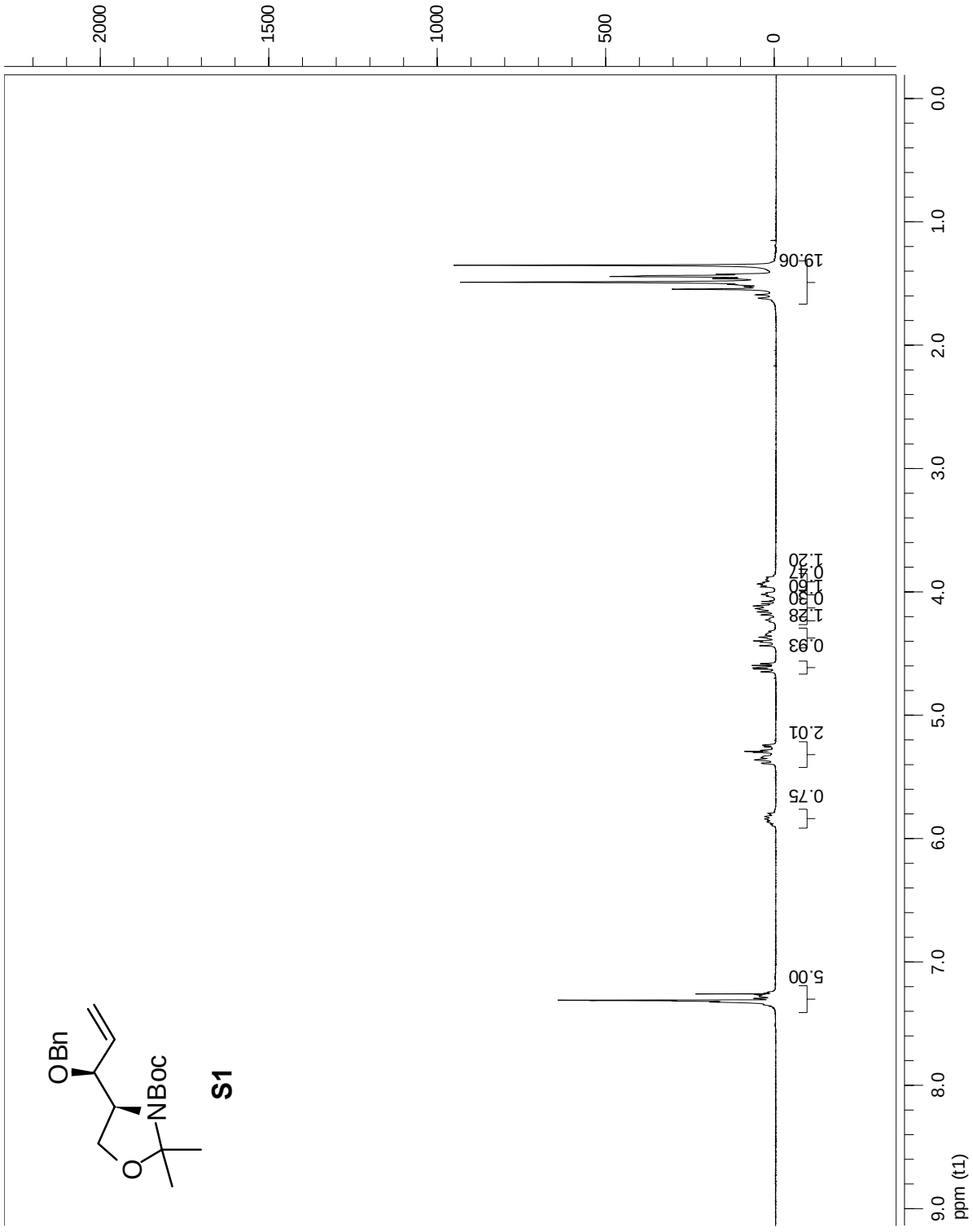

23
BocHN
NHBoc
HN
BnO
HO
OBn
CyO2C
BnO
CyO2C
OH
CH3
HO
2500
2000
1500
1000
500
0
0
50
100
150
200
ppm (t1)

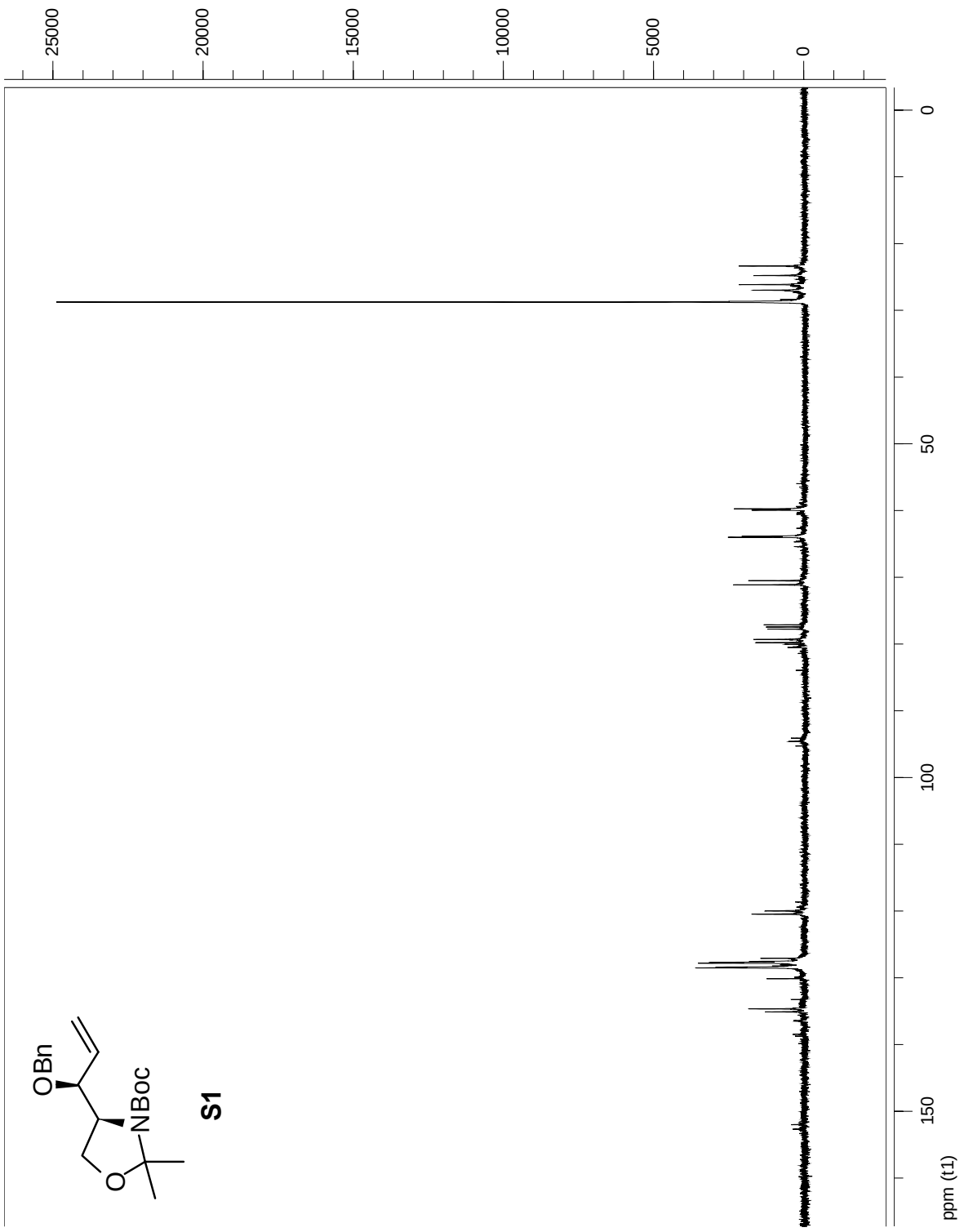

synthetic plusbacin A3
6000
5000
4000
3000
2000
1000
0
5.0
0.0
ppm (t1)

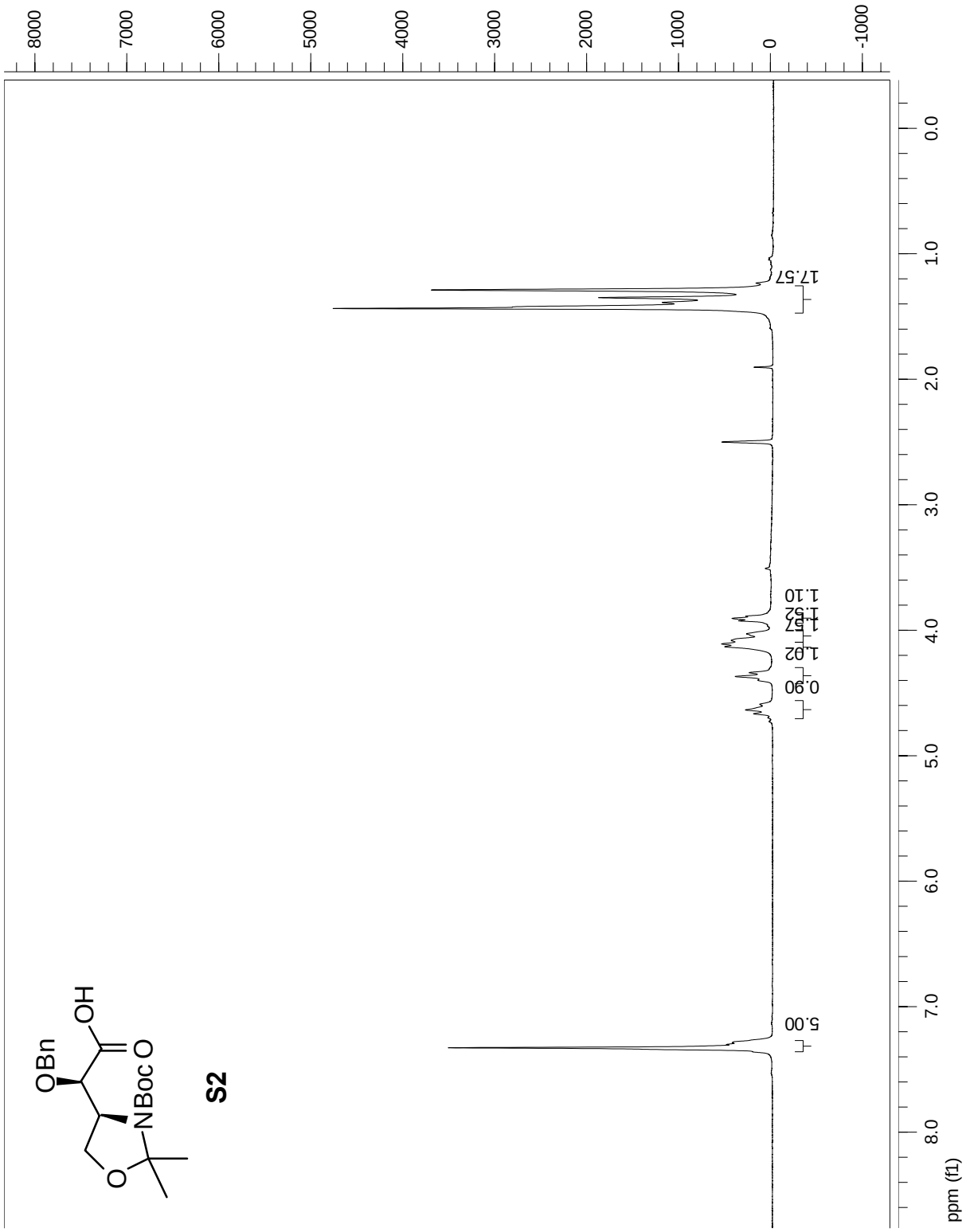

synthetic plusbacin A3
50000
0
0
50
100
150
200
ppm (t1)

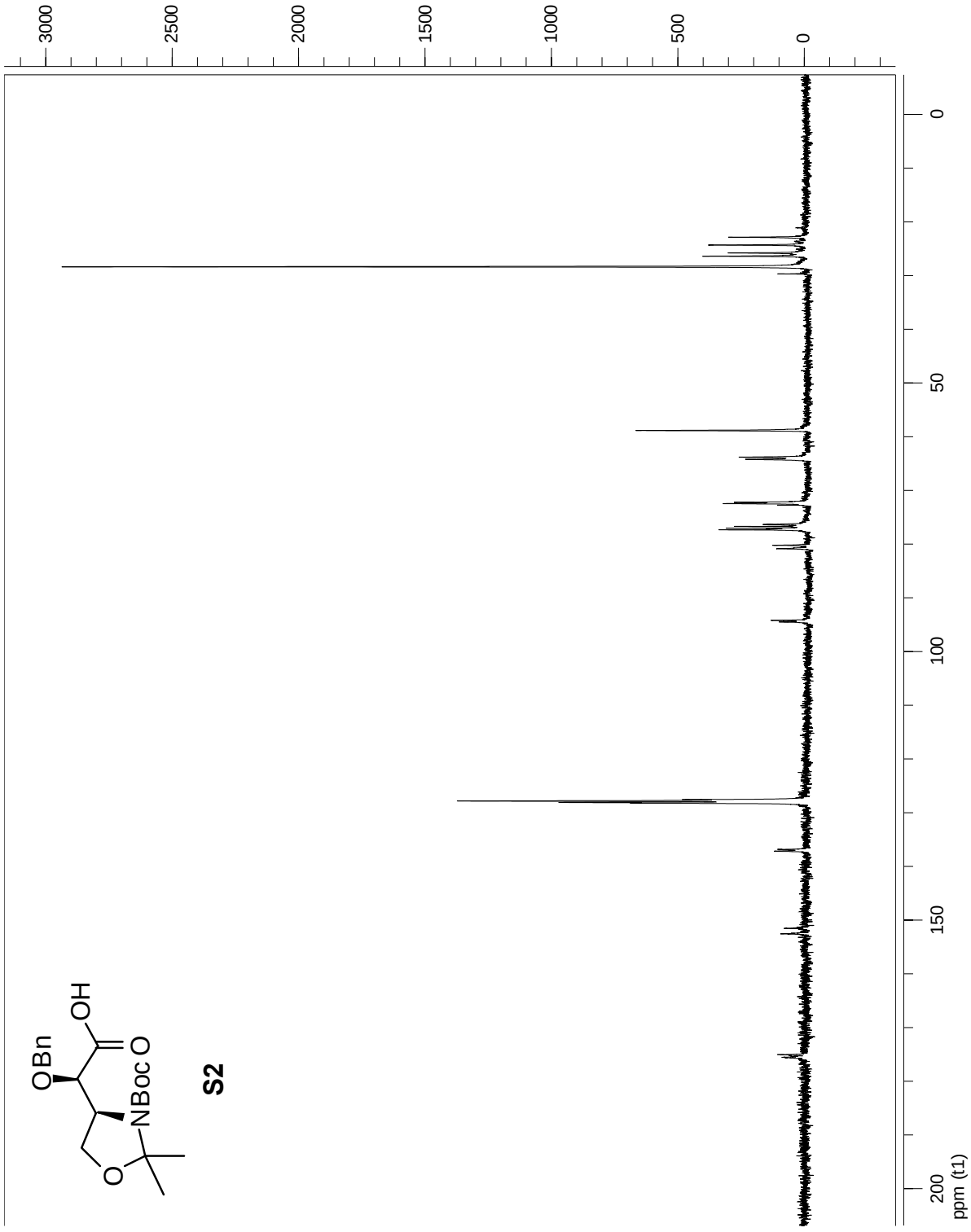

4000
3000
2000
1000
0
0.0
5.0
ppm (t1)
plusbacin A3


CD Comparison
Plusbacin A3
Synthetic (S)
Synthetic (R)
30000
20000
10000
0
-10000
-20000
-30000
-40000
-50000
190
210
230
250
270
290
[θ]r
Wavelength

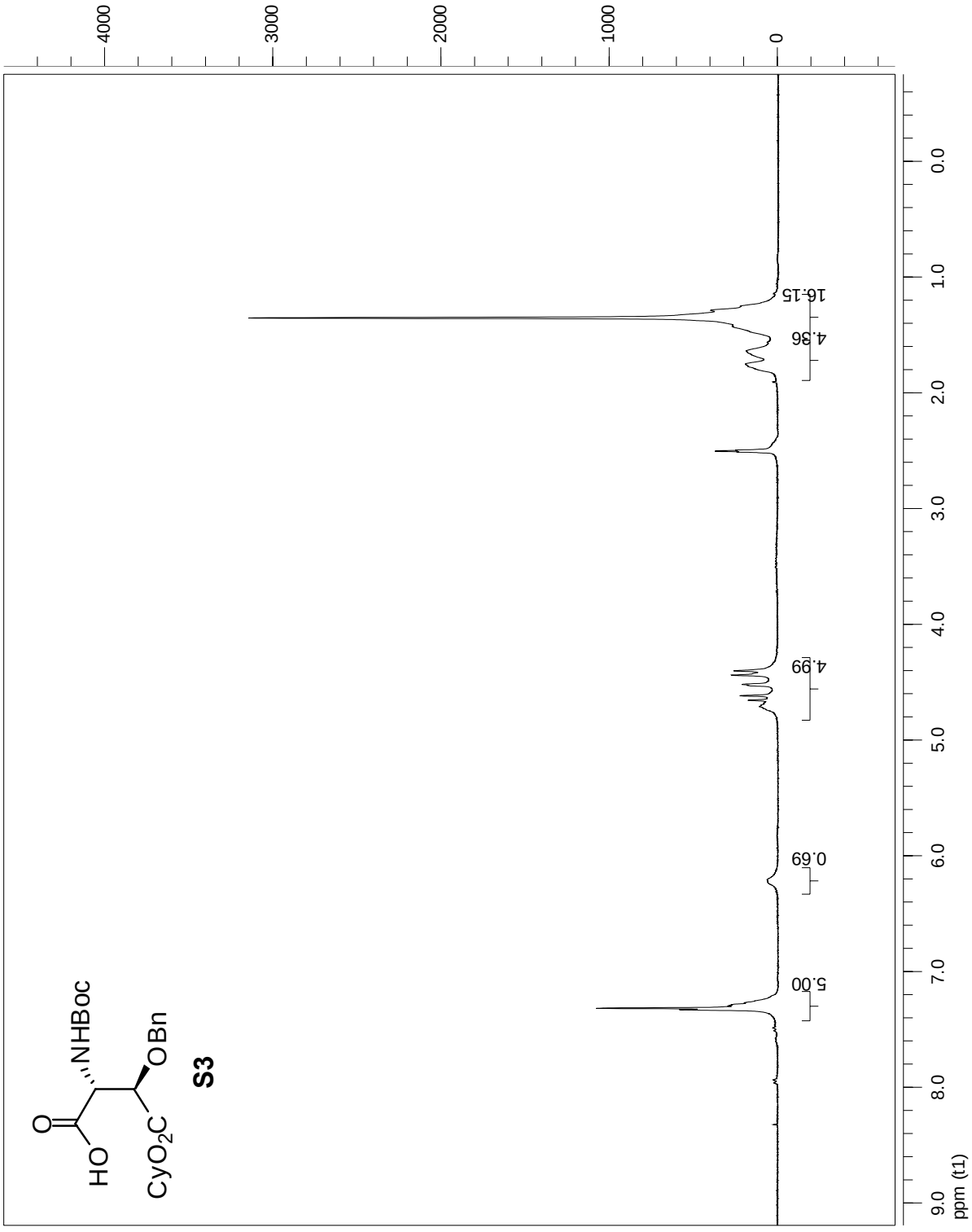

OBn
NBoc
O
S1
2000
1500
1000
500
0
19.06
5.00
0.75
2.01
0.93
1.28
0.30
1.60
0.47
1.20
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)

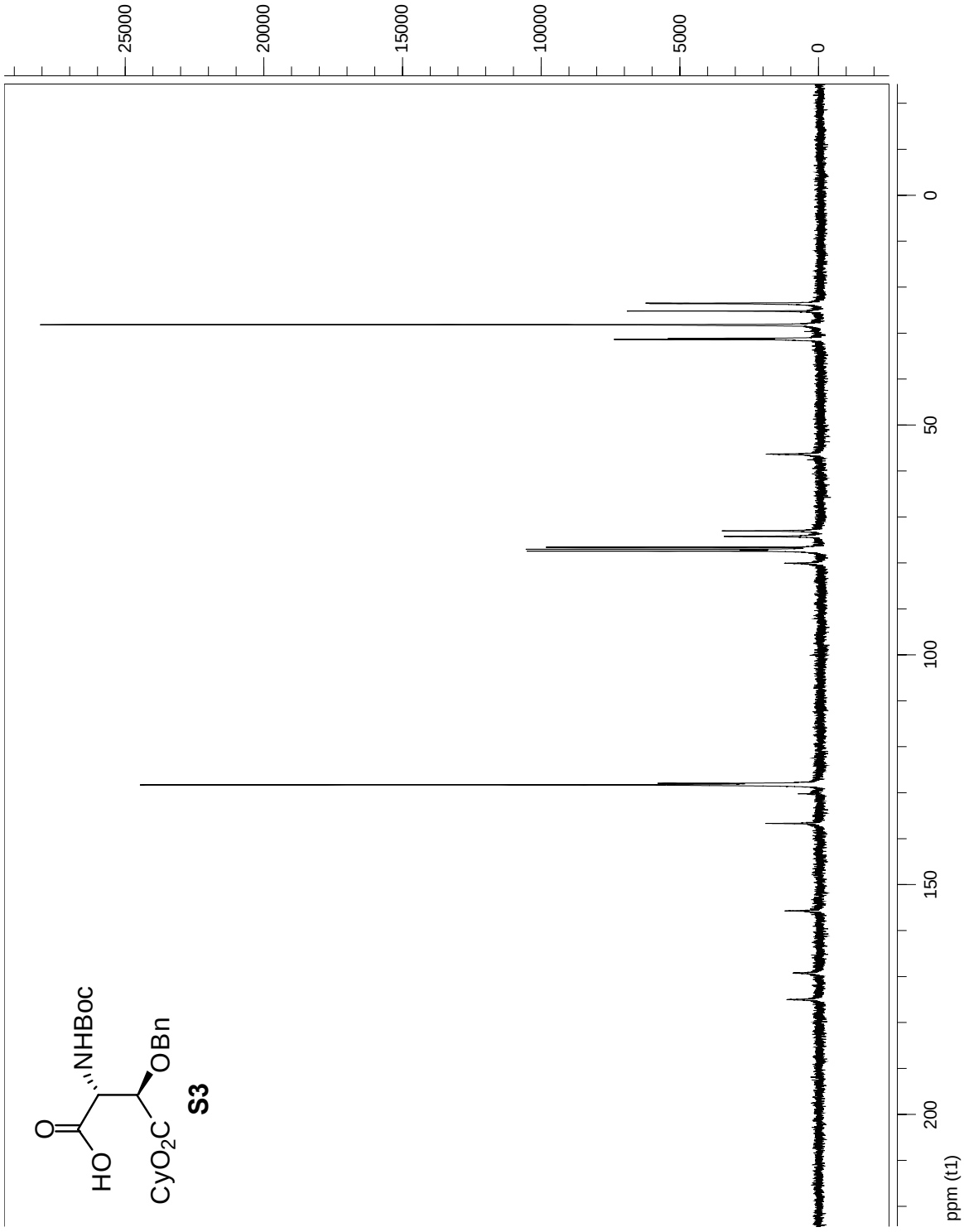

25000
20000
15000
10000
5000
0
0
50
100
150
ppm (t1)
OBn
NBoc
O
S1

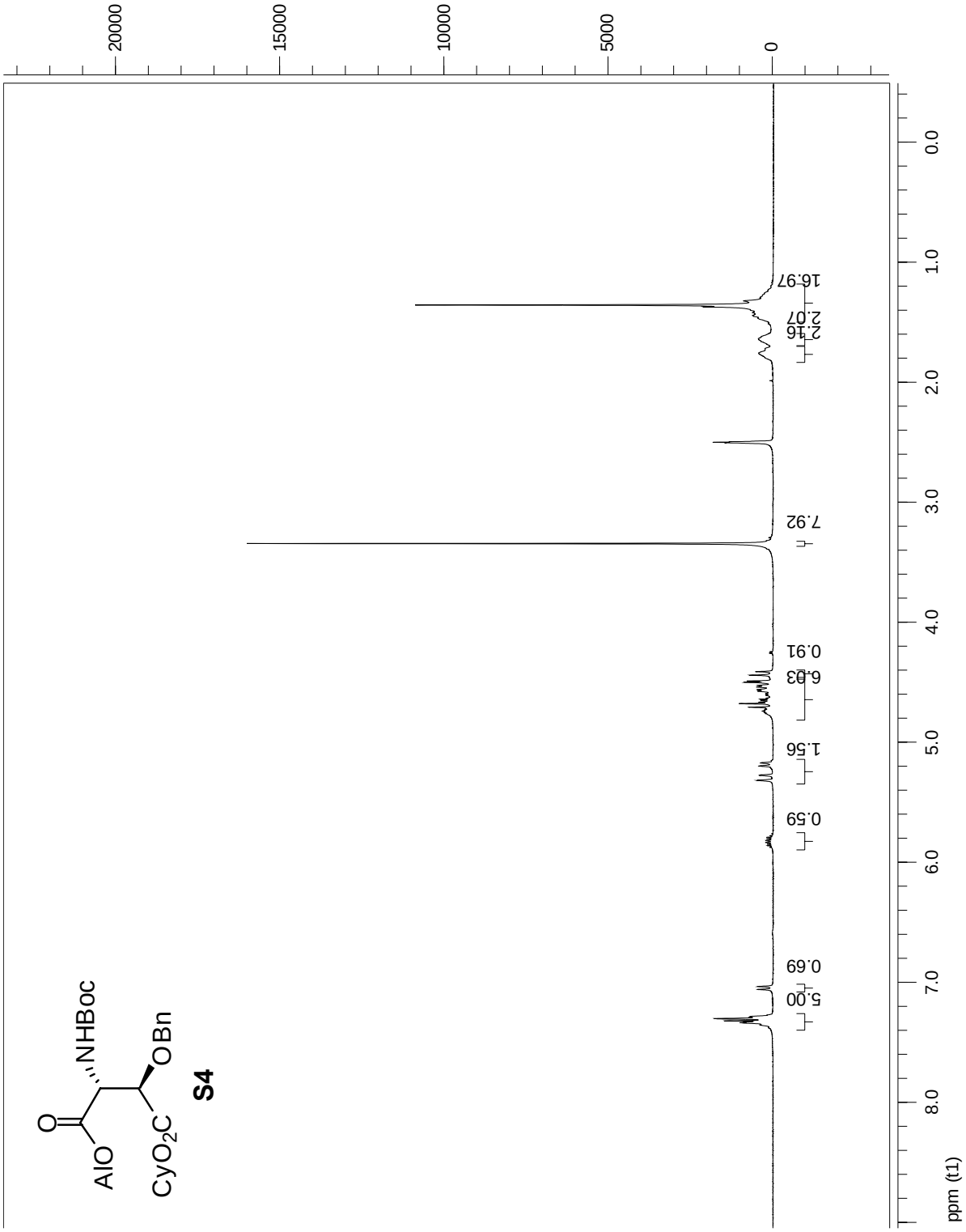

OBn
OH
NBoc
O
O
S2
17.57
5.00
1.10
1.52
1.57
1.02
0.90
ppm (f1)

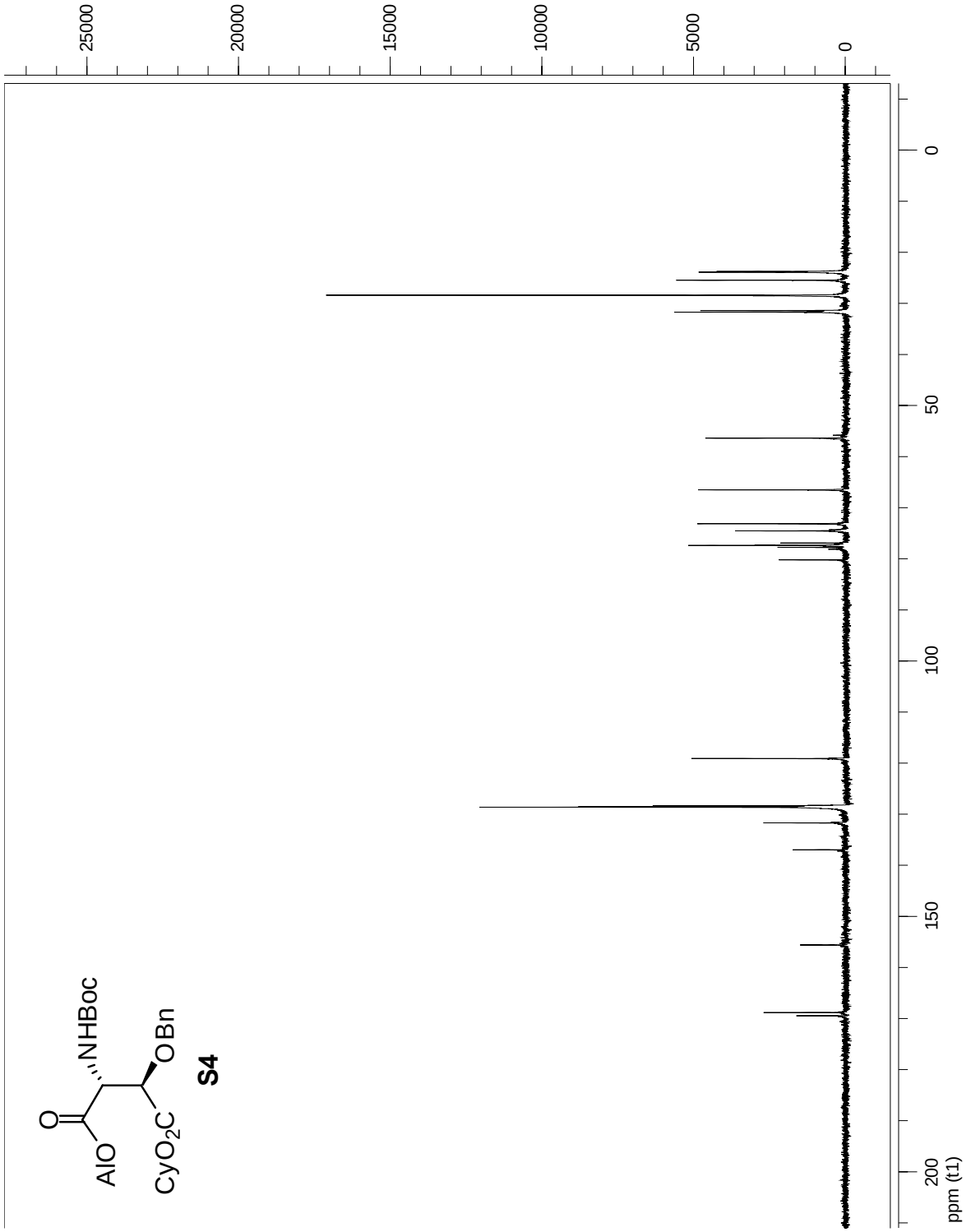

3000
2500
2000
1500
1000
500
0
0
50
100
150
200
ppm (t1)
OBn
OH
NBoc
O
O

S2


4000
3000
2000
1000
0
16.15
4.36
4.99
0.69
5.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)
NHBoc
OBn
HO
CyO2C
S3


25000
20000
15000
10000
5000
0
0
50
100
150
200
ppm (t1)
NHBoc
OBn
HO
O
CyO2C
S3


20000
15000
10000
5000
0
16.97
2.16
2.07
7.92
0.91
6.03
1.56
0.59
5.00
0.69
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)
AlO
NHBoc
CyO2C
OBn
S4


25000
20000
15000
10000
5000
0
0
50
100
150
200
ppm (t1)
NHBoc
OBn
AlO
CyO2C
S4