Supporting Information

Synthesis of the AviMeCys-Containing D-Ring of Mersacidin

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General Methods

Unless otherwise noted, all reactions were carried out in flame-dried glassware under an atmosphere of argon. Amino acids and coupling reagents were purchased from Nova Biochem, Chem Impex, and Bachem. Anhydrous solvents were purchased from Aldrich. Diisopropylethylenamine (DIEA) and triethylamine (TEA) were distilled from CaH_2 under dry air immediately before use. Tetrahydrofuran (THF) was degassed immediately before use. Polystyrene-supported triphenylphosphine was purchased from Aldrich: 200-400 mesh, 3.0 mmol/g loading, 2% cross-linked with divenylbenzene. DPPA (diphenylphosphoryl azide), DEPBT (3-(diethoxyphosphoryl)-1,2,3-benzotriazin-4(3H)-one), PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate), and all the other commercially available reagents were used as received.

Optical rotations were measured on a Perkin-Elmer polarimeter (Model 241) at 589 (sodium D line) using a 1 mL capacity quartz cell with a 10 cm path length. Concentrations © are given in g/100 mL. ^{1}H-NMR spectra were measured on a Varian VXR-400 (400 MHz), Varian INOVA-500 (500 MHz) or a Varian INOVA-400 (400 MHz). ^{13}C-NMR spectra were

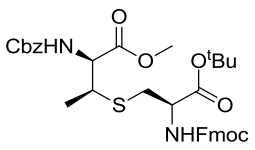
measured on a VXR-400 (101 MHz), INOVA-500 (125 MHz) or a INOVA-400 (101 MHz). Chemical shifts are reported relative to the central line of residual solvent. Infrared spectra were recorded using a Nicolet IR/42 spectrometer FT-IR (thin film, NaCl cells). Mass spectral data were recorded on a Waters LCT Classic Electrospray time of flight analyzer with Agilet 1100 capillary HPLC inlet, Sciex API III electrospray quadropole with direct infusion inlet, or a Finnigan MAT-95 by use of chemical ionization (CI) or electron impact (EI).

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, cerium molybdate stain or ninhydrin stain.

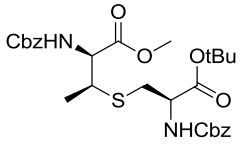
Analytical high performance liquid chromatography (HPLC) was performed on a Beckman-Coulter instrument (System Gold) with diode array detection. Analysis was carried out using Phenomenex Luna normal phase column (5µ particle size, 100 Å pore size, 150 mm length x 4.6 mm diameter) with mobile phases consisting of hexanes and ethyl acetate or dichloromethane and isopropanol. Preparatory HPLC purifications were performed with an Agilent 1100 Series HPLC purification system on a Phenomenex Luna normal phase column (10µ particle size, 100 Å pore size, 250 mm length x 22 mm diameter).

Flash column chromatography was performed using Silicycle 60 Å, 35-75 µm silica gel. All compounds purified by chromatography were sufficiently pure for use in further experiments, unless otherwise noted.

Experimental Section

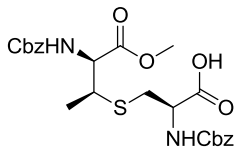


(2*S*,3*S*)-methyl 3-(((*R*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tert-butoxy)-3-oxopropyl)thio)-2-(((benzyloxy)carbonyl)amino)butanoate (4): Cesium carbonate solution (220 mL, pH = 13) was added to a solution of **5** (6.2 g, 22.2 mmol) and **6** (9.9 g, 22.2 mmol) in EtOAc (220 mL). Tetrabutyl ammonium bisulfate (30.19 g, 88.9 mmol) was added to the heterogeneous solution under vigorous stirring. The reaction was stirred overnight at room temperature under argon. Sat. aq. $NaHCO_3$ was added to the mixture and the aqueous phase was extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Silica gel flash column chromatography (30% EtOAc in hexanes) afforded a white foam (9.2 g, 65%). $[\alpha]_D^{26}$: – 14.8 (c 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.43-7.36 (m, 2H), 7.37-7.27 (m, 6H), 5.62 (dd, *J* = 14.9, 8.4 Hz, 2H), 5.11 (s, 2H), 4.53 (dd, *J* = 9.3, 2.9 Hz, 2H), 4.48-4.33 (m, 3H), 4.23 (t, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 3.44 (d, *J* = 4.3 Hz, 1H), 2.99 (dd, *J* = 13.4, 4.2 Hz, 1H), 2.88 (dd, *J* = 13.5, 5.2 Hz, 1H), 1.47 (s, 9H), 1.33 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 169.3, 156.5, 155.7, 143.8, 141.4, 136.2, 128.6, 128.3, 128.1, 127.8, 127.1, 125.1, 120.1, 83.1, 67.3, 67.2, 58.4, 54.2, 52.6, 47.2, 43.7, 34.0, 28.0, 19.7; IR (film) ν_{max}: 3339, 2977, 1722, 1509, 1451, 1342, 1216, 1154, 1082, 1049, 758, 741; CI MS *m/z* for $C_{35}H_{40}N_2O_8S$ $[M+Na]^+$: calculated 671.2403, found 671.2419.



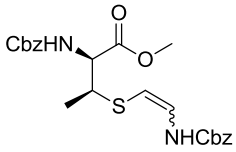
(2*S*,3*S*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-(((*R*)-2-(((benzyloxy)carbonyl)amino)-3-(tert-butoxy)-3-oxopropyl)thio)butanoate (7): A solution of **4** (0.47 g, 0.72 mmol) in 20% piperidine in DMF (5 mL) was stirred for 15 min. The solution was evaporated under reduced

pressure. Silica gel flash column chromatography (10% EtOAc in CH_2Cl_2) afforded a colorless oil. The free amine was dissolved in H_2O:EtOAc, 1:1.6 (1.6 mL). $NaHCO_3$ (0.078 g, 0.94 mmol) and benzylchloroformate (0.073 mL, 0.5 mmol) were added to the solution at room temperature. The solution was stirred for 2 h. The organic phase was extracted with more EtOAc, washed with brine, and dried over Na_2SO_4. The solution was filtered and evaporated under reduced pressure. Silica gel flash column chromatography (20% EtOAc in hexanes) afforded a colorless oil (0.19 g, 85%). $[\alpha]_D^{26}$: – 19.4 (c 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.31 (m, 10 H), 5.62-5.59 (m, 2H), 5.16-5.08 (m, 4H), 4.51 (dd, *J* = 9.6, 3.2 Hz, 1H), 4.44-4.43 (m, 1H), 3.74 (s, 3H), 3.41-3.40 (m, 1H), 2.96 (dd, *J* = 13.6, 4 Hz, 1H), 2.86 (dd, *J* = 13.2, 5.2 Hz, 1H), 1.45 (s, 9H), 1.29 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 169.4, 156.6, 155.8, 136.5, 136.3, 128.7, 128.4, 128.3, 128.3, 83.2, 67.4, 67.2, 58.5, 54.4, 52.7, 43.9, 34.1, 28.1, 19.8; IR (film) ν_{max}: 3347, 2978, 1732, 1505, 1455, 1344, 1215, 1155, 1049, 912, 735, 698; ESI MS *m/z* for $C_{28}H_{36}N_2O_8S$ $[M+Na]^+$: calculated 583.2090, found 583.2119.



(*R*)-2-(((benzyloxy)carbonyl)amino)-3-(((2*S*,3*S*)-3-(((benzyloxy)carbonyl)amino)-4-methoxy-4-oxobutan-2-yl)thio)propanoic acid (8): TFA (1mL) was added to a solution of **7** (0.19 g, 0.36 mmol) in CH_2Cl_2 (1 mL). The solution was stirred for 1 h at room temperature and the volatiles were evaporated under reduced pressure. The residue was dissolved in diethyl ether and the solvent was evaporated under reduced pressure. Silica gel flash column chromatography (30% acetone in CH_2Cl_2) afforded the product as a foam (0.16 g, 90%). $[\alpha]_D^{26}$: –2 (c 0.4,

$CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (bs, 1H), 7.38-7.24 (m, 10H), 5.76-5.68 (m, 2H), 5.20-5.01 (m, 4H), 4.68-4.47 (m, 2H), 3.73 (s, 3H), 3.38 (bs, 1H), 3.06 (d, *J* = 13.7 Hz, 1H), 2.90 (dd, *J* =13.8, 5.1 Hz, 1H), 1.28 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 171.2, 156.6, 156.1, 136.0, 128.6, 128.3, 128.2, 67.5, 67.4, 58.5, 53.6, 52.8, 43.7, 33.8, 19.4; IR (film) ν_{max}: 3329, 3034, 2955, 1723, 1715, 1515, 1343, 1215, 1050, 736, 698; ESI MS *m/z* for $C_{24}H_{28}N_2O_8S$ $[M+Na]^+$: calculated 527.1464, found 527.1487.



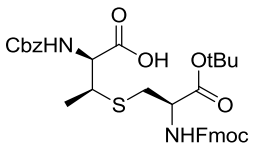
(2*S*,3*S*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-(((*Z*)-2-(((benzyloxy)carbonyl)amino)vinyl)thio)butanoate (9):

Method 1: DPPA (18 µL, 0.059 mmol) was added to a solution of **8** (0.015 g, 0.029 mmol) and TEA (11 µL, 0.059 mmol) in toluene (0.4 mL) at 0 °C under argon. The solution was heated at 94 °C overnight. The volatiles were removed under reduced pressure. Normal phase HPLC (5-30% EtOAc in hexanes over 30 min) afforded both isomers as oils (8.7 mg, 65%; *Z*:*E*, 2:1).

Method 2: $Pb(OAc)_4$ (0.068 g, 0.15 mmol) was added to a solution of **8** (70 mg, 0.14 mmol), $Cu(OAc)_2$ (0.028 g, 0.15 mmol) and pyridine (23 µL, 0.27 mmol) in THF (0.7 mL) at 0 °C under argon. The solution was allowed to warm to room temperature and stirred for 2.5 h. The solution was diluted with 8% TEA in EtOAc. The mixture was eluted through a pad containing silica gel, washed with 8% TEA in EtOAc, and concentrated in *vacuo*. Normal phase HPLC of the crude mixture (5-30% EtOAc in hexanes over 30 min) afforded both isomers as oils (22 mg, 35%; *Z*:*E*, 1:1).

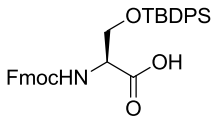
9*Z*: $[\alpha]_D^{26}$: – 3 (c 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.32 (m, 10H), 7.17 (d, *J* = 10.8 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 5.51 (d, *J* = 8.8 Hz, 1H), 5.17-5.08 (m, 5H), 4.55 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.70 (s, 3H), 3.44-3.38 (m, 1H), 1.34 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 156.2, 153.2, 136.0, 135.6, 130.9, 128.6, 128.5, 128.5, 128.3, 128.2, 128.1, 96.5, 67.6, 67.3, 58.1, 52.4, 46.0, 18.4; IR (film) ν_{max}: 3324, 2928, 1724, 1635, 1514, 1454, 1338, 1215, 1047; ESI MS *m/z* for $C_{23}H_{26}N_2O_6S$ $[M+Na]^+$: calculated 481.1409, found 481.1431.

9*E*: $[\alpha]_D^{26}$: – 6 (c 0.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.36 (m, 10H), 6.92 (t, *J* = 15 Hz, 1H), 6.80-6.70 (m, 1H), 5.62 (d, *J* = 5 Hz, 1H), 5.56 (d, *J* = 10 Hz, 1H), 5.25-5.11 (m, 4H), 4.50 (dd, *J* = 10, 5.0 Hz, 1H), 3.71 (s, 3H), 3.41-3.39 (m, 1H), 1.32 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 156.4, 152.8, 136.3, 135.7, 132.7, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 99.3, 67.8, 67.4, 58.1, 52.6, 45.5, 18.5; IR (film) ν_{max}: 3324, 2928, 1724, 1635, 1514, 1454, 1338, 1215, 1047; ESI MS *m/z* for $C_{23}H_{26}N_2O_6S$ $[M+Na]^+$: calculated 481.1409, found 481.1431.



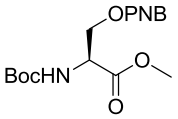
(2*S*,3*S*)-3-(((*R*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tert-butoxy)-3-oxopropyl)thio)-2-(((benzyloxy)carbonyl)amino)butanoic acid (12): Trimethyltinhydroxide (0.83 g, 4.6 mmol) was added to a solution of **4** (0.5 g, 0.77 mmol) in 1,2-dichloroethane (7.7 mL) under argon. The solution was stirred at 78 °C for 4 h. The volatiles were evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ and washed with 1M HCl. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated in *vacuo*. Silica gel

flash column chromatography (20% acetone in CH_2Cl_2) afforded a colorless oil (0.34 g, 70%). $[\alpha]_D^{26}$: –12.1 (c 1.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.04 (bs, 1H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.44-7.27 (m, 9H), 5.86 (d, *J* = 7.5 Hz, 1H), 5.71 (d, *J* = 9.1 Hz, 1H), 5.18-5.05 (m, 2H), 4.59 (dd, *J* = 9.1, 2.5 Hz, 1H), 4.49-4.32 (m, 3H), 4.20 (t, *J* = 6.9 Hz, 1H), 3.51 (d, *J* = 4.7 Hz, 1H), 3.10 (dd, *J* = 13.4, 4.0, 1H), 2.93 (dd, *J* = 13.4, 5.0 Hz, 1H), 1.45 (s, 9H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 169.5, 156.7, 156.0, 143.8, 143.7, 141.3, 136.0, 128.5, 128.2, 128.1, 127.8, 127.1, 125.1, 120.0, 83.3, 67.3, 58.3, 54.6, 47.1, 44.0, 34.3, 27.9, 19.8; IR (film) ν_{max}: 3322, 2979, 1722, 1515, 1451, 1338, 1247, 1154, 1047, 757, 741; CI MS *m/z* for $C_{34}H_{38}N_2O_8S$ $[M+H]^+$: calculated 635.2422, found 635.2426.

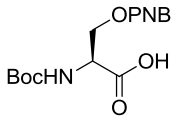


(*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-((tert-butyldiphenylsilyl)oxy)propanoic acid (13): ^{t}Butyl diphenyl silane chloride (3.9 mL, 0.014 mmol) was added to a solution of **18** (5 g, 0.013 mmol) and imidazole (1.85 g, 0.027 mmol) in THF (120 mL). The mixture was stirred overnight. The solids were removed by filtration and the filtrate was evaporated under reduced pressure. The product was employed without further purification. $Pd(OAc)_2$ (0.3 g, 1.3 mmol) and polymer supported PPh_3 (3.5 g, 10.5 mmol) were dissolved in CH_2Cl_2 (80 mL) and stirred under inert atmosphere for 15 min. The protected serine dissolved in CH_2Cl_2 (50 mL) was added to the catalyst mixture. Finally, $PhSiH_3$ (3.26 mL, 26 mmol) was added to the reaction mixture. After 3 hours the solution was filtered through a pad of celite and the volatiles were evaporated under reduced pressure. Silica gel flash column chromatography (20% acetone in CH_2Cl_2) afforded a colorless oil (4.3 g, 65% after 2 steps).

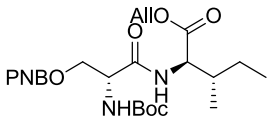
$[\alpha]_D^{26}$: + 10.2 (c 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.69 (bs, 1H), 7.81 (d, *J* = 7.5 Hz, 2H), 7.67 (dd, *J* = 15.1, 10.0, 6H), 7.50-7.29 (m, 10H), 5.78 (d, *J* = 8.5 Hz, 1H), 4.59 (dd, *J* = 8.4 Hz, 1H), 4.47 (dd, *J* = 10.2, 7.2 Hz, 1H), 4.41- 4.35 (m, 1H), 4.29 (t, *J* = 7.2 Hz, 1H), 4.24-4.20 (m, 1H), 4.01 (dd, *J* = 10.1, 2.7 Hz, 1H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.7, 156.0, 144.0, 143.7, 141.3, 135.6, 135.5, 132.8, 132.5, 130.0, 127.9, 127.9, 127.8, 127.2, 125.3, 125.2, 120.0, 67.5, 64.3, 55.8, 47.1, 26.8, 19.4; IR (film) ν_{max}: 3433, 3070, 2931, 2857, 1721, 1511, 1427, 1338, 1248, 1209, 1112, 738, 702; ESI MS *m/z* for $C_{34}H_{35}NO_5Si$ $[M+H]^+$: calculated 588.2182, found 588.2201.



(*S*)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl 4-nitrobenzoate (20): Silver (I) oxide (13.7 g, 59 mmol) and 3 Å MS (10 g) were added to a solution of ^{t}Boc-Ser-OMe (10g, 45 mmol) and *p*-nitrobenzylbromide (12.8 g, 59 mmol) in toluene (100 mL). The solution was stirred at room temperature for 3 days and filtered through a pad of celite. The filtrate was washed with 5% HCl, aq. sat. $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Silica gel flash column chromatography of the residue (20% EtOAc in CH_2Cl_2) afforded a yellow oil (9.6 g, 65%). $[\alpha]_D^{26}$: + 18.6 (c 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22-8.19 (m, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 5.43 (d, *J* = 8.2 Hz, 1H), 4.63 (q, *J* = 13.4 Hz, 2H), 4.54-4.48 (m, 1 H), 3.93 (dd, *J* = 9.4, 3.2 Hz, 1H), 3.78 (s, 3H), 3.76 (d, *J* = 3.2 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 155.36, 147.4, 145.1, 127.5, 123.6, 80.1, 71.9, 70.8, 53.9, 52.5, 28.2; IR (film) ν_{max}: 3416, 2977, 1750, 1713, 1606, 1522, 1346, 1164, 1107, 844, 738; ESI MS *m/z* for $C_{16}H_{22}N_2O_7$ $[M+Na]^+$: calculated 377.1325, found 377.1330.

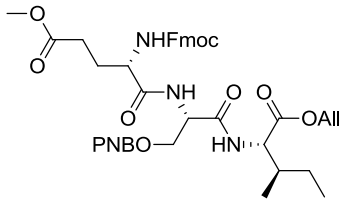


(*S*)-2-((tert-butoxycarbonyl)amino)-3-((4-nitrobenzoyl)oxy)propanoic acid (15): Lithium hydroxide (0.778 g, 32.5 mmol) was added to a solution of **20** (9.6 g, 27 mmol) in THF:H_2O (1:1) (260 mL). The solution was stirred at room temperature for 1 h. The aqueous layer was acidified with 5% HCl. The acid was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. A yellow oil was obtained (9.2 g, 99%). $[\alpha]_D^{26}$: + 15 (c 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (bs, 1H), 8.09 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 5.37 (d, *J* = 8.2 Hz, 1H), 4.56 (q, *J* = 13.3 Hz, 2H), 4.47 (d, *J* = 7.9 Hz, 1H), 3.91 (d, *J* = 7.4 Hz, 1H), 3.74-3.69 (m, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9, 155.7, 147.5, 145.1, 127.7, 123.7, 80.7, 72.1, 70.6, 53.9, 28.3; IR (film) ν_{max}: 3333.8, 2980, 2934, 1713, 1520, 1346, 1162, 1108, 738; ESI MS *m/z* for $C_{15}H_{20}N_2O_7$ $[M+H]^+$: calculated 363.1168, found 363.1163.



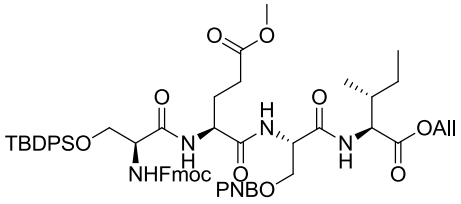
(*R*)-3-(((2*R*,3*S*)-1-(allyloxy)-3-methyl-1-oxopentan-2-yl)amino)-2-((tert-butoxycarbonyl)amino)-3-oxopropyl 4-nitrobenzoate (21): DEPBT (16.7 g, 55 mmol) was added to a solution of **15** (9.5 g, 27.9 mmol), H-Ile-OAll.HOTs (11.5 g, 33 mmol), and DIEA (9.72 mL, 55 mmol) in THF (111 mL) at 0 °C. The solution was stirred at room temperature overnight. The solution was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced

pressure. Silica gel flash column chromatography of the residue (40% EtOAc in hexanes) afforded the product as white solid (10.2 g, 75%). mp: 89-90 °C; $[\alpha]_D^{26}$: +27 (c 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, *J* = 8.4 Hz, 2H), 7.87 (bs, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.09 (bs, 1H), 5.94-5.84 (m, 1H), 5.50 (bs, 1H), 5.33 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.70-4.59 (m, 5H), 4.39 (bs, 1H), 3.97 (dd, *J* = 9.2, 4 Hz, 1H), 3.69-3.65 (m, 1H), 1.94-1.88 (m, 1H), 1.46 (s, 9H), 1.46-1.36 (m, 1H), 1.15-1.07 (m, 1H), 0.91-0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 170.4, 155.7, 147.6, 144.9, 131.5, 128.0, 127.8, 123.7, 119.2, 80.8, 72.3, 70.5, 66.0, 56.9, 53.9, 38.0, 28.3, 25.0, 15.5, 11.6; IR (film) ν_{max}: 3287, 2964, 1737, 1643, 1524, 1450, 1347, 1254, 1199, 738; EI/CI MS *m/z* for $C_{24}H_{36}O_8N_3$ $[M+H]^+$: calculated 494.2497, found 494.2488.



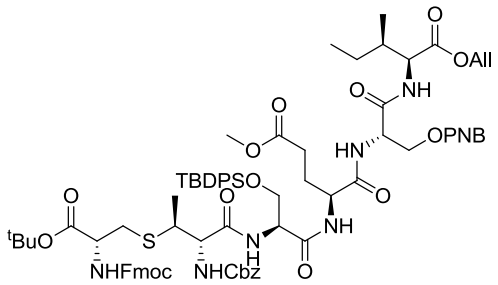
(*S*)-2-((*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-methoxy-5-oxopentanamido)-3-(((2*S*,3*R*)-1-(allyloxy)-3-methyl-1-oxopentan-2-yl)amino)-3-oxopropyl 4-nitrobenzoate (22): **21** (0.26 g, 0.42 mmol) was dissolved in a solution of 4M HCl in dioxane (3 mL) and the mixture was stirred for one hour. The volatiles were removed under reduced pressure. The free amine was employed without further purification. It was dissolved in THF (1.86 mL) together with Fmoc-Glu(OMe)-OH (0.178 g, 0.46 mmol) under argon. DIEA (0.16 mL, 0.93 mmol) and DEPBT (0.28 g, 0.93 mmol) were added to the mixture at 0 °C under argon. The mixture was stirred overnight at room temperature. The solution was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Silica gel flash column chromatography of the residue (8%

acetone in CH_2Cl_2) afforded a white solid (0.33 g, 85%). mp: 148-150 °C; $[\alpha]_D^{26}$: + 12.9 (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.32 (td, *J* = 7.4, 3.1 Hz, 2H), 7.28-7.20 (m, 2H), 7.08 (d, *J* = 6.6 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.82 (ddt, *J* = 16.3 Hz, 1H), 5.69 (d, *J* = 6.8 Hz, 1H), 5.26 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.18 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.63-4.48 (m, 6H), 4.39-4.32 (m, 3H), 4.11 (t, *J* =7.1 Hz, 1H), 3.91 (d, *J* = 5.8 Hz, 1H), 3.62 (s, 3H), 3.59-3.50 (m, 1H), 2.58-2.31 (m, 2H), 2.18-2.09 (m, 1H), 1.96-1.88 (m, 1H), 1.89-1.79 (m, 1H), 1.38-1.23 (m, 1H), 1.02 (dt, *J* = 15, 7.3 Hz, 1H), 0.81-0.75 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 171.5, 171.2, 169.3, 156.4, 147.5, 144.8, 143.8, 143.6, 141.3, 131.6, 127.8, 127.1, 125.1, 123.7, 120.1, 119.1, 72.2, 70.1, 67.3, 65.9, 56.9, 54.5, 52.7, 52.1, 47.1, 37.8, 30.4, 28.1, 25.1, 15.6, 11.6; IR (film) ν_{max}: 3287, 3070, 2964, 2877, 1737, 1684, 1642, 1523, 1450, 1347, 1254, 1199, 1108, 738; ESI MS *m/z* for $C_{40}H_{46}N_4O_{11}$ $[M+H]^+$: calculated 759.3241, found 759.3255.



(6*S*,9*S*,12*S*)-6-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-12-(((2*S*,3*R*)-1-(allyloxy)-3-methyl-1-oxopentan-2-yl)carbamoyl)-9-(3-methoxy-3-oxopropyl)-2,2-dimethyl-7,10-dioxo-3,3-diphenyl-4-oxa-8,11-diaza-3-silatridecan-13-yl 4-nitrobenzoate (23): **22** (0.24 g, 0.3 mmol) was dissolved in a solution of 20% piperidine in DMF (1.8 mL) and the mixture was stirred for 15 minutes. The volatiles were removed under reduced pressure. The free amine was employed without further purification. It was dissolved in THF (1.3 mL) together with **13** (0.19 g, 0.34 mmol) under argon. DIEA (0.12 mL, 0.69 mmol) and DEPBT (0.2 g, 0.69 mmol) were added to the mixture at 0 °C under argon. The mixture was stirred overnight at room

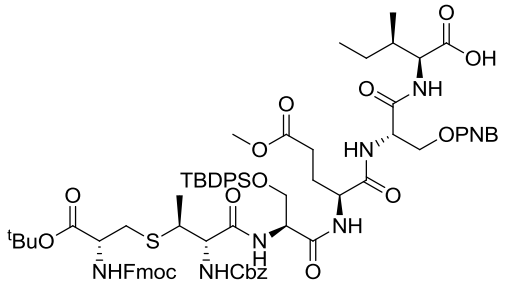
temperature. The solution was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Silica gel flash column chromatography of the residue (10% EtOAc in CH_2Cl_2) afforded the product as yellow solid (0.25 g, 75%). mp: 174-175 °C; $[\alpha]_D^{26}$: – 7 (c 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (d, *J* = 8.6 Hz, 2H), 7.79-7.70 (m, 3H), 7.62 (dd, *J* = 6.5, 1.4 Hz, 4H), 7.55 (d, *J* = 7.1 Hz, 2H), 7.47-7.30 (m, 11H), 7.29-7.25 (m, 2H), 7.05 (d, *J* = 8.5 Hz, 1H), 5.88 (ddt, *J* = 16.2, 10.5, 5.8 Hz, 1H), 5.59 (d, *J* = 5.3 Hz, 1H), 5.31 (ddd, *J* = 17.2, 2.9, 1.5 Hz, 1H), 5.22 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.75-4.62 (m, 2H), 4.59 (tt, *J* = 6.7, 2.7 Hz, 2H), 4.52-4.42 (m, 2H), 4.41-4.32 (m, 1H), 4.27-4.15 (m, 4H), 4.08 (dd, *J* = 10.3, 4.3 Hz, 1H), 3.92-3.85 (m, 2H), 3.68-3.65 (m, 1H), 3.48 (s, 3H), 2.51 (dd, *J* = 15.5, 9.7 Hz, 1H), 2.45-2.33 (m, 1H), 2.24-1.96 (m, 2H), 1.91-1.88 (m, 1H), 1.47-1.31 (m, 1H), 1.17-1.03 (m, 10H), 0.93-0.78 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.5, 171.1, 170.8, 170.5, 169.2, 156.5, 147.3, 145.1, 143.7, 141.3, 135.5, 135.5, 132.6, 132.4, 131.7, 130.1, 128.0, 127.9, 127.6, 127.1, 125.1, 125.1, 123.5, 120.1, 118.8, 71.8, 70.1, 67.6, 65.7, 63.8, 57.1, 56.8, 53.3, 52.8, 51.9, 47.0, 37.7, 30.3, 27.1, 26.9, 25.1, 19.3, 15.5, 11.6; IR (film) ν_{max}: 3284, 3070, 2932, 2859, 1738, 1634, 1521, 1345, 1112, 739; ESI MS *m/z* for $C_{59}H_{69}N_5O_{13}Si$ $[M+Na]^+$: calculated 1106.4558, found 1106.4792.



(2*S*,5*S*,8*S*,11*S*,14*S*,15*S*,18*R*)-1-allyl 19-tert-butyl 18-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-14-(((benzyloxy)carbonyl)amino)-2-((*R*)-sec-butyl)-11-(((tert-

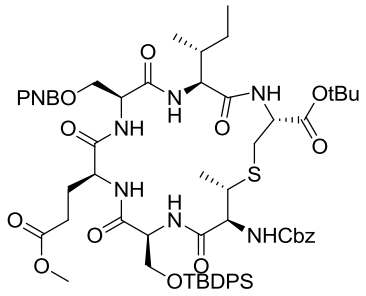
butyldiphenylsilyl)oxy)methyl)-8-(3-methoxy-3-oxopropyl)-15-methyl-5-(((4-nitrobenzoyl)oxy)methyl)-4,7,10,13-tetraoxo-16-thia-3,6,9,12-tetraazanonadecane-1,19-dioate (11): **23** (0.14 g, 0.13 mmol) was dissolved in a solution of 20% piperidine in DMF (0.9 mL) and the mixture was stirred for 15 minutes. The volatiles were removed under reduced pressure. The free amine was employed without further purification. It was dissolved in THF (0.5 mL) together with **12** (0.09 g, 0.14 mmol) under argon. DIEA (0.049 mL, 0.28 mmol) and DEPBT (0.084 g, 0.28 mmol) were added to the mixture at 0 °C under argon. The mixture was stirred overnight at room temperature. The solution was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Silica gel flash column chromatography of the residue (50% EtOAc in hexanes) afforded the product as a foam (0.14 g, 75%). $[\alpha]_D^{26}$: – 10.8 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.99 (bs, 1H), 7.67 (d, *J* = 7.5 Hz, 2H), 7.52 (dd, *J* = 16.0, 7.0 Hz, 6H), 7.41-7.27 (m, 12H), 7.25 (d, *J* = 7.1 Hz, 1H), 7.21-7.09 (m, 6H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.13 (d, *J* = 6.3 Hz, 1H), 5.93 (d, *J* = 7.3 Hz, 1H), 5.80 (ddd, *J* = 16.3, 11.0, 5.8 Hz, 1H), 5.23 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.14 (d, *J* = 10.4 Hz, 1H), 4.99 (d, *J* =11.9 Hz, 1H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.67-4.20 (m, 12H), 4.14 (dd, *J* = 17.5, 10.1 Hz, 2H), 3.86 (dd, *J* = 9.2, 4.6 Hz, 1H), 3.71 (d, *J* = 7.5 Hz, 1H), 3.64-3.53 (m, 1H), 3.43 (s, 3H), 3.07 (d, *J* = 11.5 Hz, 1H), 2.86 (dd, *J* = 13.4, 7.1 Hz, 1H), 2.64-2.41 (m, 1H), 2.41-2.20 (m, 1H), 2.05 (bs, 2H), 1.79 (bs, 1H), 1.38 (s, 9H), 1.30 (dd, *J* = 12.9, 7.3 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.09-0.97 (m, 1H), 0.94 (s, 9H), 0.77-0.70 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.3, 171.2, 171.0, 170.4, 169.7, 169.4, 156.4, 156.1, 147.4, 145.4, 144.0, 141.4, 135.7, 135.6, 135.6, 132.5, 132.2, 131.8, 130.3, 130.2, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.8, 127.2, 127.1, 125.2, 123.6, 120.1, 118.8, 83.0, 72.0, 70.1, 67.7, 67.3, 65.8, 63.4, 59.6, 56.9, 55.9, 55.0, 53.9, 53.1, 52.3, 47.2,

43.4, 37.7, 34.2, 30.7, 28.1, 26.9, 26.0, 25.1, 19.3, 18.4, 15.5, 11.6; IR (film) ν_{max}: 3283, 2932, 1723, 1629, 1520, 1345, 1251, 1151, 1111, 739, 702; ESI MS *m/z* for $C_{78}H_{95}N_7O_{18}SSi$ $[M+H]^+$: calculated 1478.6301, found 1478.6251.



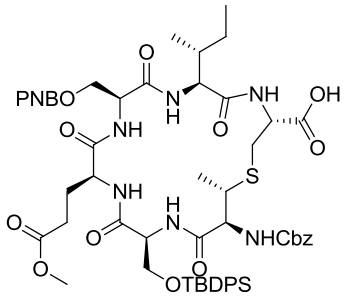
(5*R*,8*S*,9*S*,12*S*,15*S*,18*S*,21*S*)-9-(((benzyloxy)carbonyl)amino)-5-(tert-butoxycarbonyl)-21-((*R*)-sec-butyl)-12-(((tert-butyldiphenylsilyl)oxy)methyl)-1-(9H-fluoren-9-yl)-15-(3-methoxy-3-oxopropyl)-8-methyl-18-(((4-nitrobenzoyl)oxy)methyl)-3,10,13,16,19-pentaoxo-2-oxa-7-thia-4,11,14,17,20-pentaazadocosan-22-oic acid: Polymer supported PPh_3 (0.9 g, 2.7 mmol) was added to a solution of $Pd(OAc)_2$ (0 76 g, 0.33 mmol) in CH_2Cl_2 (15.4 mL). The mixture was stirred for 15 min under argon and added to a solution of **11** (1.7 g, 3.3 mmol) in CH_2Cl_2 (18.4 mL). Finally, $PhSiH_3$ (0.84 mL, 6.7 mmol) was added to the solution. The reaction mixture was stirred under argon for 5 hours at room temperature. The solution was filtered through a pad of celite and washed with EtOAc. The filtrate was evaporated under reduced pressure affording the product as a cream solid (1.6 g, 98%). mp: 138-139 °C; $[\alpha]_D^{26}$: –10 (c 1.45, $CHCl_3$); ^{1}H NMR (DMSO, 400 MHz) δ 8.46 (d, *J* = 7.9 Hz, 1H), 8.29 (d, *J* = 7.6 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 5.6 Hz, 2H), 7.66-7.48 (m, 7H), 7.40 (t, *J* = 6.1 Hz, 7H), 7.35-7.25 (m, 6H), 5.07 (d, *J* =12.5 Hz, 1H), 4.96 (d, *J* = 12.6 Hz, 1H), 4.74-4.47 (m, 5H), 4.39-4.13 (m, 5H), 4.08 (dd, *J* = 13.8, 8.5 Hz, 1H), 3.88 (dd, *J* = 9.6, 5.4 Hz, 1H), 3.80-3.70 (m, 1H), 3.67-3.60 (m, 1H), 3.53 (s, 3H), 3.14-3.02 (m, 1H), 2.98 (dd, *J* = 13.2, 4.7 Hz, 1H), 2.77 (dt, *J* = 20.9, 10.5 Hz,

2H), 2.36 (dd, *J* = 17.1, 9.1 Hz, 2H), 2.09-1.66 (m, 3H), 1.10 (s, 9H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.17-1.02 (m, 1H), 1.04 (d, *J* = 6.1 Hz, 1H), 0.90 (s, 9H), 0.84-0.78 (m, 6H); ^{13}C NMR (DMSO, 126 MHz) δ 172.8, 172.7, 170.5, 170.0, 169.9, 169.0, 168.8, 156.0, 155, 9, 146.7, 146.3, 143.8, 143.7, 140.7, 136.8, 135.1, 135.1, 132.6, 132.6, 129.7, 128.3, 127.9, 127.8, 127.7, 127.6, 127.0, 125.3, 123.2, 120.1, 81.0, 70.9, 70.1, 65.8, 65.7, 63.8, 59.1, 56.5, 54.7, 54.6, 52.5, 51.6, 51.2, 46.6, 42.3, 36.6, 31.4, 29.7, 27.9, 27.6, 26.5, 25.5, 24.6, 18.7, 18.7, 15.4, 11.2; IR (film) ν_{max}: 3287, 2962, 2931, 1727, 1633, 1520, 1345, 1251, 1153, 1112, 738, 702; ESI MS *m/z* for $C_{75}H_{91}N_7O_{18}SSi$ $[M+H]^+$: calculated 1438.5989, found 1438.5969.



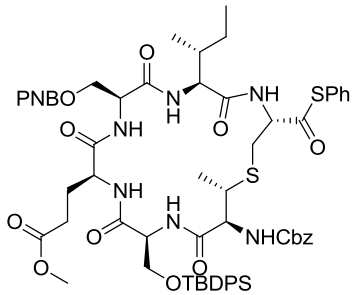
(3*R*,6*S*,9*S*,12*S*,15*S*,18*S*,19*S*)-tert-butyl 18-(((benzyloxy)carbonyl)amino)-6-((*R*)-sec-butyl)-15-(((tert-butyldiphenylsilyl)oxy)methyl)-12-(3-methoxy-3-oxopropyl)-19-methyl-9-(((4-nitrobenzoyl)oxy)methyl)-5,8,11,14,17-pentaoxo-1-thia-4,7,10,13,16-pentaazacyclononadecane-3-carboxylate (10): The free acid (0.04 g, 0.027 mmol) was dissolved in a solution of 20% piperidine in DMF (0.2 mL) and the solution was stirred for 15 min. The volatiles were removed under reduced pressure. The free amine was employed without further purification and it was dissolved in CH_2Cl_2:DMF (2:1) (10 mL). The mixture containing the amine was added over 8 h to a solution of PyBOP (0.072 g, 0.14mmol), DIEA (0.015 mL, 0.08 mmol) and DMAP (0.017 g, 0.13 mmol) in CH_2Cl_2:DMF (2:1) (18 mL) at room temperature under argon. The solution was stirred at room temperature for 3 days. The solution was diluted with EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$, and brine. The organic phase

was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was stirred in a 50% EtOAc in hexanes solution for an hour and the solids were filtered. The filtrate was evaporated. Silica gel flash column chromatography of the residue (20% acetone in CH_2Cl_2) afforded the product as a white foam (0.021 g, 65%). $[\alpha]_D^{26}$: – 13 (c 0.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 7.1 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 4H), 7.49-7.45 (m, 1H), 7.42 (d, *J* = 5.7 Hz, 2H), 7.37-7.26 (m, 8H), 7.23-7.18 (m, 5H), 6.77 (d, *J* = 6.7 Hz, 1H), 6.15 (d, *J* = 8.1 Hz, 1H), 5.09 (d, *J* = 12.1 Hz, 1H), 4.90 (d, *J* = 12.1 Hz, 1H), 4.68-4.38 (m, 6H), 4.29-4.26 (m, 2H), 4.07 (dt, *J* = 17.1, 8.6 Hz, 1H), 3.89 (dd, *J* = 9.1, 4.2 Hz, 1H), 3.78-3.66 (m, 1H), 3.67-3.58 (m, 1H), 3.46 (s, 3H), 3.41 (bs, 1H), 2.96 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.86 (dd, *J* = 14.0, 3.4 Hz, 1H), 2.52-2.25 (m, 2H), 2.23-2.05 (m, 1H), 2.04-1.83 (m, 1H), 1.38 (s, 9H), 1.32 (d, *J* = 2.3 Hz, 1H), 1.18 (d, *J* = 4.2 Hz, 3H), 0.94 (s, 9H), 0.95-0.87 (m, 1H), 0.83 (d, *J* = 6.3 Hz, 3H), 0.75 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 171.7, 171.4, 170.5, 170.1, 169.7, 169.1, 156.8, 147.6, 144.9, 135.8, 135.6, 135.5, 135.5, 132.2, 132.0, 130.3, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 123.8, 82.8, 72.3, 69.3, 67.7, 63.1, 60.3, 58.4, 54.9, 54.3, 54.1, 52.2, 44.6, 36.0, 33.9, 30.8, 28.0, 26.9, 19.3, 18.7, 15.9, 11.5; IR (film) ν_{max}: 3334, 2961, 2929, 2857, 1731, 1667, 1521, 1345, 1222, 1153, 1112, 701; ESI MS *m/z* for $C_{60}H_{79}N_7O_{15}SSi$ $[M+Na]^+$: calculated 1220.5022, found 1220.5055.

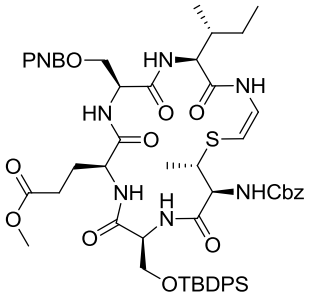


(3*R*,6*S*,9*S*,12*S*,15*S*,18*S*,19*S*)-18-(((benzyloxy)carbonyl)amino)-6-((*R*)-sec-butyl)-15-(((tert-butyldiphenylsilyl)oxy)methyl)-12-(3-methoxy-3-oxopropyl)-19-methyl-9-(((4-

nitrobenzoyl)oxy)methyl)-5,8,11,14,17-pentaoxo-1-thia-4,7,10,13,16-pentaazacyclononadecane-3-carboxylic acid (3): TFA (1.5 mL) was added at 0 °C to a solution of **10** (0.22 g, 0.18 mmol) in CH_2Cl_2 (2 mL). The solution was stirred at 0 °C for 2 hours and $NaHCO_3$ was added to the reaction mixture. The acid was extracted with EtOAc, washed with 5% HCl and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Silica gel flash column chromatography of the residue (5% MeOH in EtOAc) afforded the product as a yellowish foam (0.17 g, 80%). $[\alpha]_D^{26}$: – 4.65 (c 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, *J* =8.5 Hz, 2H), 7.85 (bs, 1H), 7.68-7.55 (m, 2H), 7.51-7.48 (m, 4H), 7.39 (bs, 1H), 7.40-7.24 (m, 8H), 7.24-7.19 (m, 3H), 7.19-7.13 (m, 3H), 7.13-7.01 (m, 1H), 6.01 (bs, 1H), 5.07 (d, *J* = 11.9 Hz, 1H), 4.84 (d, *J* = 12 Hz, 1H), 4.62-4.40 (m, 6H), 4.38-4.18 (m, 2H), 4.02 (d, *J* = 9.1 Hz, 1H), 3.91 (bs, 1H), 3.74-3.53 (m, 3H), 3.40 (s, 3H), 3.14-2.83 (m, 2H), 2.49-2.25 (m, 2H), 2.13-1.86 (m, 3H), 1.33 (bs, 1H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.02-0.92 (m, 1H), 0.91 (s, 9H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.70 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.6, 172.3, 171.8, 171.6, 170.8, 170.5, 170.2, 156.7, 147.5, 144.7, 135.4, 135.4, 132.0, 130.2, 130.1, 128.6, 128.5, 128.3, 128.1, 127.9, 127.9, 123.6, 72.0, 68.8, 67.8, 63.4, 59.8, 58.9, 55.5, 54.8, 54.2, 53.0, 52.2, 44.5, 35.8, 34.3, 30.5, 26.7, 26.3, 24.8, 19.1, 15.8, 11.2; IR (film) ν_{max}: 3330, 2961, 2040, 2858, 1731, 1668, 1521, 1346, 1220, 1111, 701; ESI MS *m/z* for $C_{56}H_{71}N_7O_{15}SSi$ $[M+Na]^+$: calculated 1164.4396, found 1164.4419.



((3R,6S,9S,12S,15S,18S,19S)-18-(((benzyloxy)carbonyl)amino)-6-((R)-sec-butyl)-15-(((tert-butyldiphenylsilyl)oxy)methyl)-12-(3-methoxy-3-oxopropyl)-19-methyl-5,8,11,14,17-pentaoxo-3-(((phenylthio)oxy)carbonyl)-1-thia-4,7,10,13,16-pentaazacyclononadecan-9-yl)methyl 4-nitrobenzoate (24): Thiophenol (23 µL, 0.22 mmol) was added to a solution of **3** (0.13 g, 0.11 mmol), PyBOP (88 mg, 0.17 mmol), and DIEA (29 µL, 0.17 mmol) in CH_2Cl_2 (1.1 mL) at 0 °C. The solution was warmed to room tempearature and left stirred for 20 h. The solution was diluted with EtOAc. The organic phase was washed with aq. sat. $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was dissolved in 50% acetonitrile:H_2O and purified by reverse-phase HPLC (40-90% acetonitrile:H_2O, 0.1% TFA over 10 min). Evaporation of the pure fractions provided the product as an oil (0.109 g, 78%). $[\alpha]_D^{26}$: –43.7 (c 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.99 (bs, 1H), 7.61-7.59 (m, 4H), 7.48-7.36 (m, 14H), 7.33-7.26 (m, 4H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.19 (d, *J* = 8.4 Hz, 1H), 5.19 (d, *J* = 12 Hz, 1 H), 4.97 (d, *J* = 12 Hz, 1H), 4.89 (bs, 1H), 4.66-4.56 (m, 4H), 4.45-4.43 (m, 2H), 4.16-4.14 (m, 1H), 3.95 (bs, 1H), 3.83-3.73 (m, 2H), 3.55 (s, 3H), 3.05 (bs, 2H), 2.51-2.39 (m, 2H), 2.18-2.00 (m, 4H), 1.51-1.45 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.09-1.06 (m, 1H), 1.02 (s, 9H), 0.97-0.95 (m, 3H), 0.85-0.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.2, 174.7, 172.3, 172.0, 170.9, 170.3,170.3, 156.9, 147.7, 144.6, 135.5, 134.7, 132.1, 130.4, 129.7, 129.4, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 126.8, 123.8, 73.3, 69.1, 67.9, 63.1, 60.2, 59.8, 58.7, 55.1, 54.4, 52.4, 44.7, 35.8, 34.0, 30.6, 26.9, 24.8, 19.3, 18.7, 16.0, 11.3; IR (film) ν_{max}: 3318, 2960, 2929, 1681, 1520, 1345, 1221, 1111, 745, 701; ESI MS *m/z* for $C_{62}H_{75}N_7O_{14}S_2Si$ $[M+H]^+$: calculated 1234.4661, found 1234.4663.



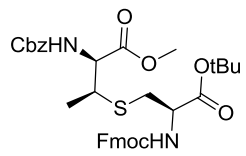
((6*S*,9*S*,12*S*,15*S*,18*S*,19*S*,*Z*)-18-(((benzyloxy)carbonyl)amino)-6-((*R*)-sec-butyl)-15-(((tert-butyldiphenylsilyl)oxy)methyl)-12-(3-methoxy-3-oxopropyl)-19-methyl-5,8,11,14,17-pentaoxo-1-thia-4,7,10,13,16-pentaazacyclononadec-2-en-9-yl)methyl 4-nitrobenzoate (2):

Method 1: DPPA (9.9 µL, 0.046 mmol) was added to a solution of **3** (0.024 g, 0.021 mmol) and DABCO (0.005 g, 0.046 mmol) in 1,4-dioxane (2.1 mL) at 0 °C under argon. The solution was heated at 94 °C overnight. The volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and purified by normal phase HPLC (R_t = 94 min, 0-4% isopropanol in CH_2Cl_2 over 120 min). Evaporation of the pure fractions provided the product as a foam (0.0057 g, 25%).

Method 2: $Pb(OAc)_4$ (0.047 g, 0.1 mmol) was added to a solution of **3** (0.024, 0.021 mmol), $Cu(OAc)_2$ (0.022 mg, 0.1 mmol) and pyridine (14 µL, 0.012 mmol) in THF (4 mL) at 0 °C under argon. The solution was allowed to warm to room temperature and stirred for 3.5 h. The solution was diluted with 8% TEA in EtOAc. The mixture was eluted through a pad of silica gel, washed with 8% TEA in EtOAc, and concentrated in *vacuo*. The residue was dissolved in CH_2Cl_2 and purified by normal phase HPLC (R_t = 94 min, 0-4% isopropanol in CH_2Cl_2 over 120 min). Evaporation of the pure fractions provided the product as a foam (0.0057 g, 25%).

$[\alpha]_D^{26}$: – 3 (c 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 100 MHz) δ 8.14 (d, J = 8 Hz, 2H) , 7.91-7.89 (m, 1H), 7.52-7.45 (m, 7H), 7.38-7.31 (m, 7H), 7.29-7.22 (m, 7H), 5.84-5.86 (m, 1H), 5.14 (d, J = 7

Hz, 1H), 5.11 (d, *J* = 9.2 Hz, 1H), 4.92 (d, *J* = 9.2 Hz, 1H), 4.62-4.56 (m, 2H), 4.53-4.50 (m, 1H), 4.45-4.31 (m, 5H), 4.12-4.10 (m, 1H), 3.87 (bs, 1H), 3.79-3.78 (m, 1H), 3.57 (bs, 1H), 3.48 (s, 3H), 2.36-2.29 (m, 2H), 2.06-2.02 (m, 2H), 1.98-1.95 (m, 1H), 1.37-1.35 (m, 1H), 1.19-1.16 (m, 1H), 1.07 (bs, 3H), 0.94 (s, 9H), 0.87 (d, *J* = 7 Hz, 3H), 0.76 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.5, 171.7, 170.7, 170.2, 169.8, 169.6, 156.8, 147.6, 144.6, 135.6, 135.4, 132.0, 131.8, 130.4, 128.6, 128.5, 128.3, 128.1, 128.1, 128.0, 123.8, 96.6, 72.3, 68.9, 67.8, 62.9, 60.4, 58.6, 55.4, 53.9, 52.2, 45.8, 35.3, 30.7, 26.9, 26.1, 24.9, 19.3, 16.9, 15.8, 11.1; IR (film) ν_{max}: 3311, 2923, 1855, 1700, 1668, 1523, 1345, 1258, 1108; ESI MS *m/z* for $C_{55}H_{69}N_7O_{13}SSi$ $[M+Na]^+$: calculated 1118.4341, found 1118.4297.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OtBu
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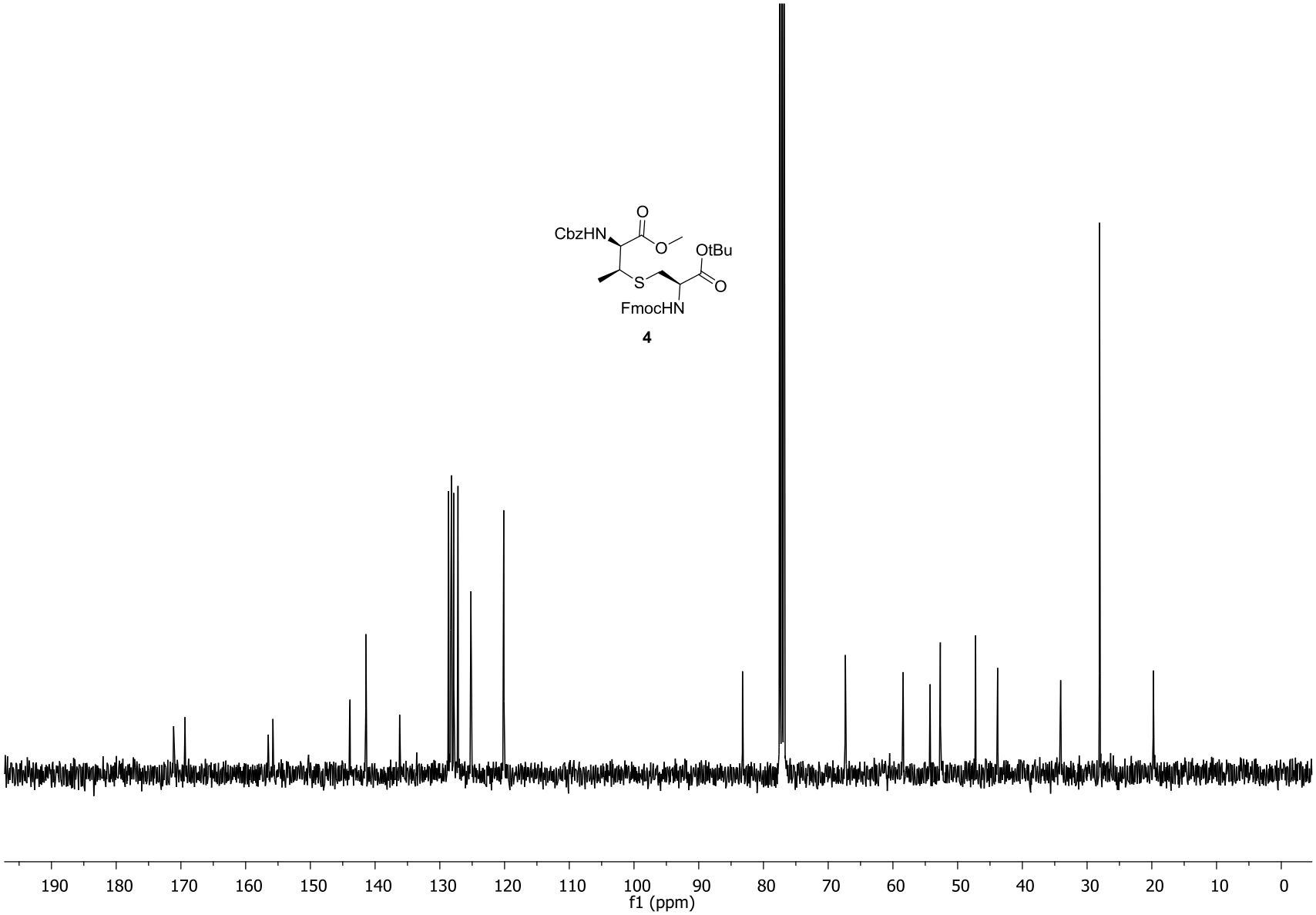
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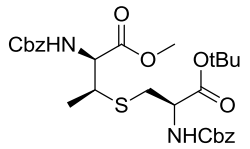
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OtBu
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5.5
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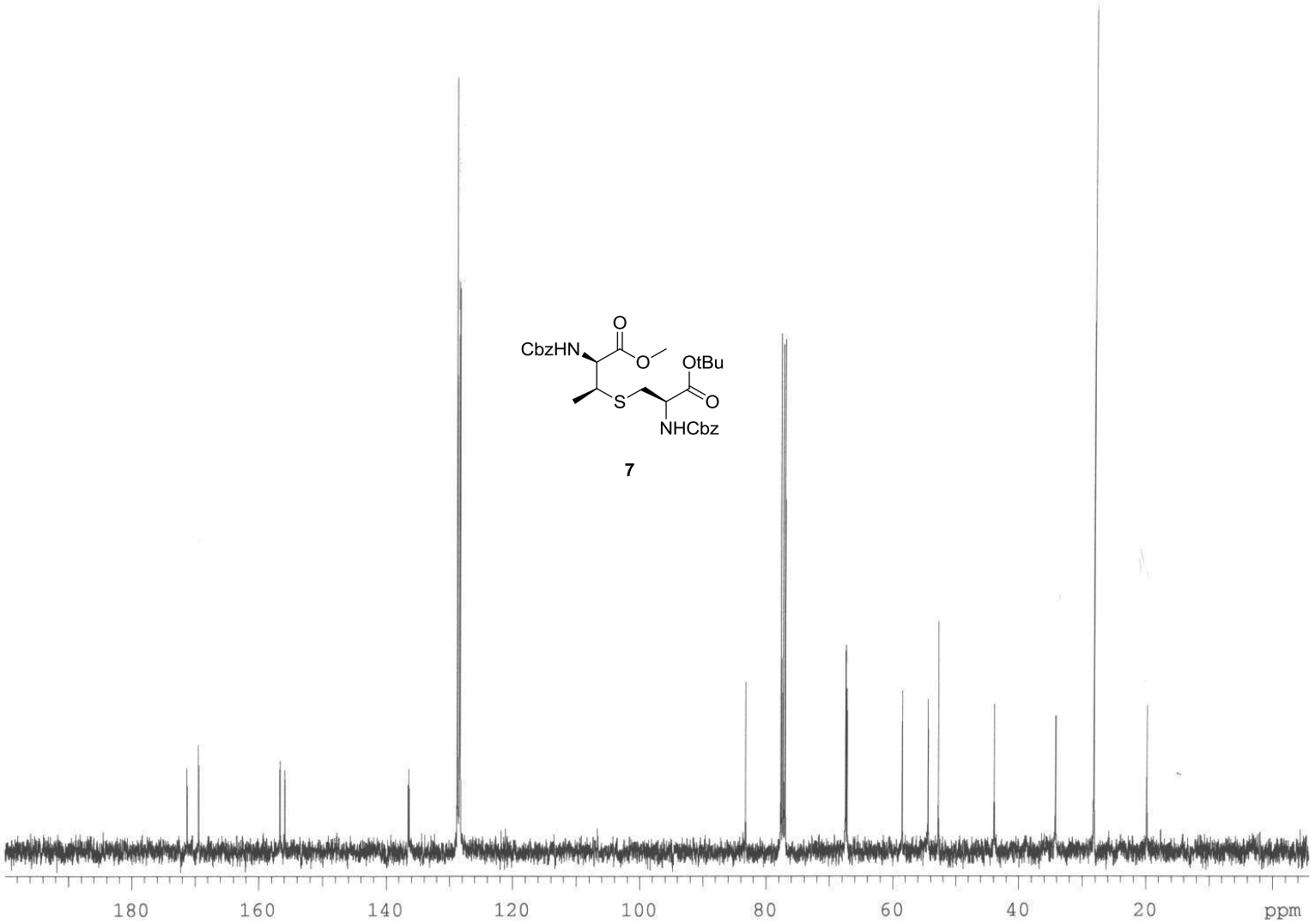
f1 (ppm)



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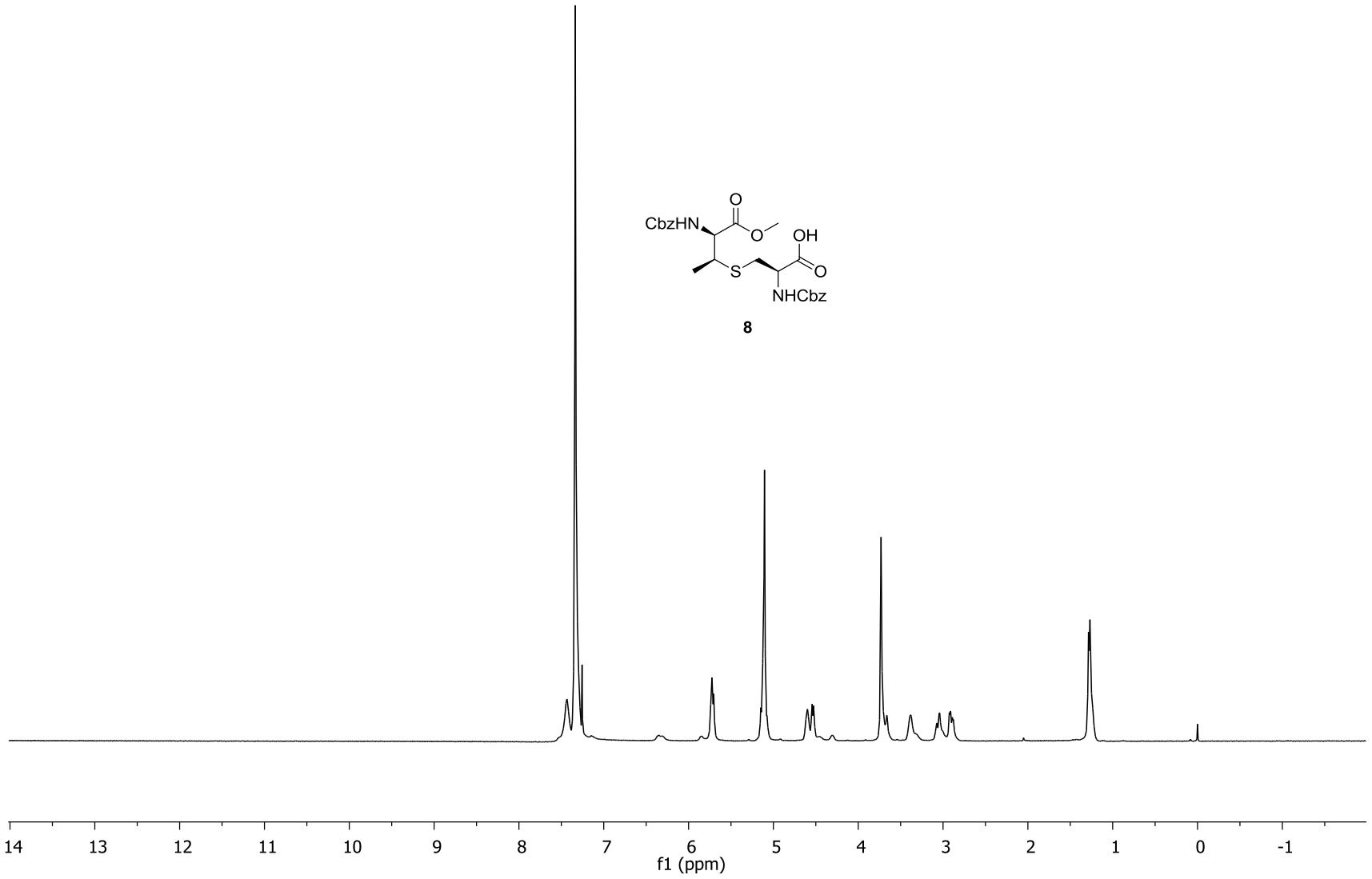
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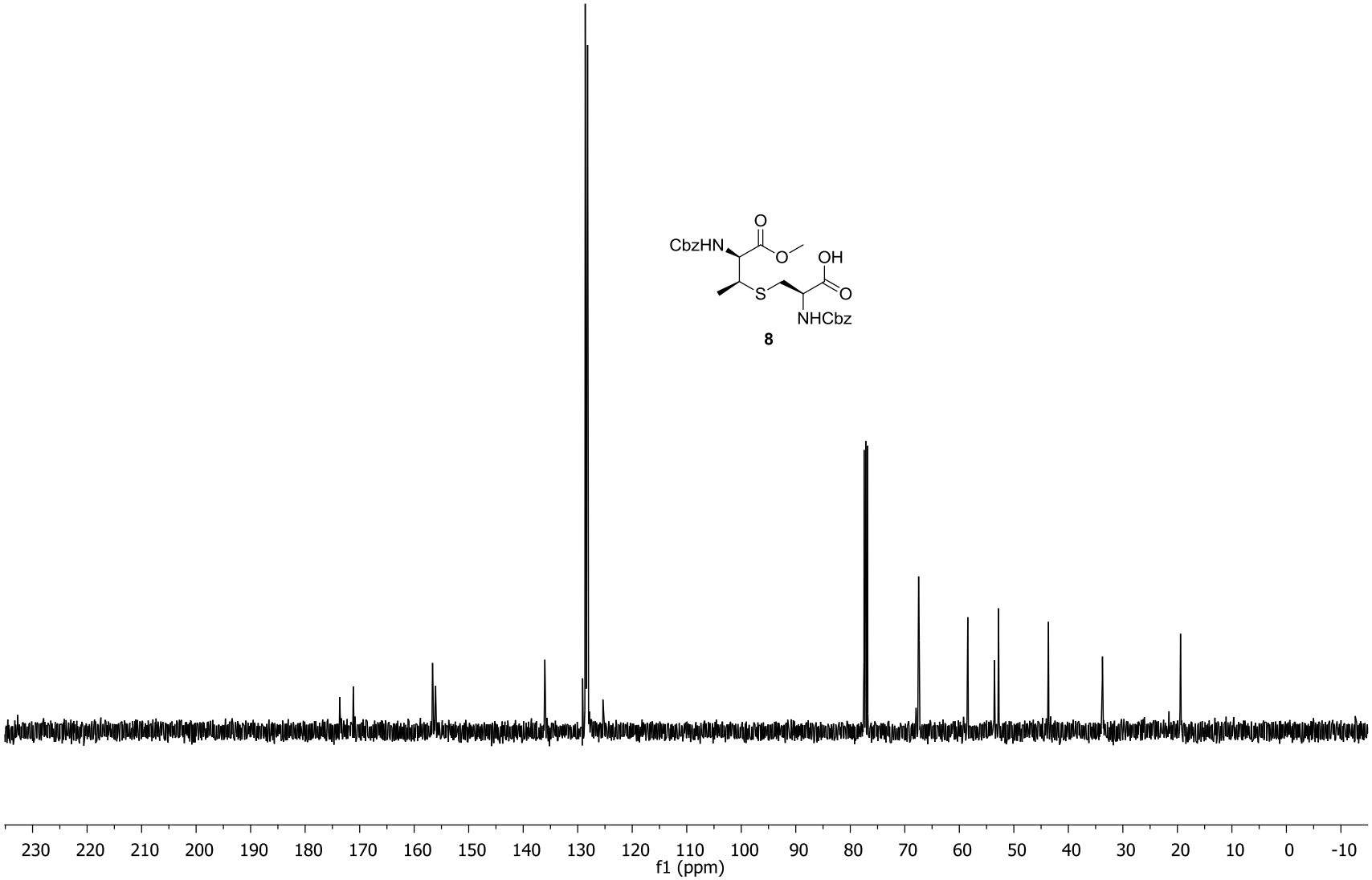
f1 (ppm)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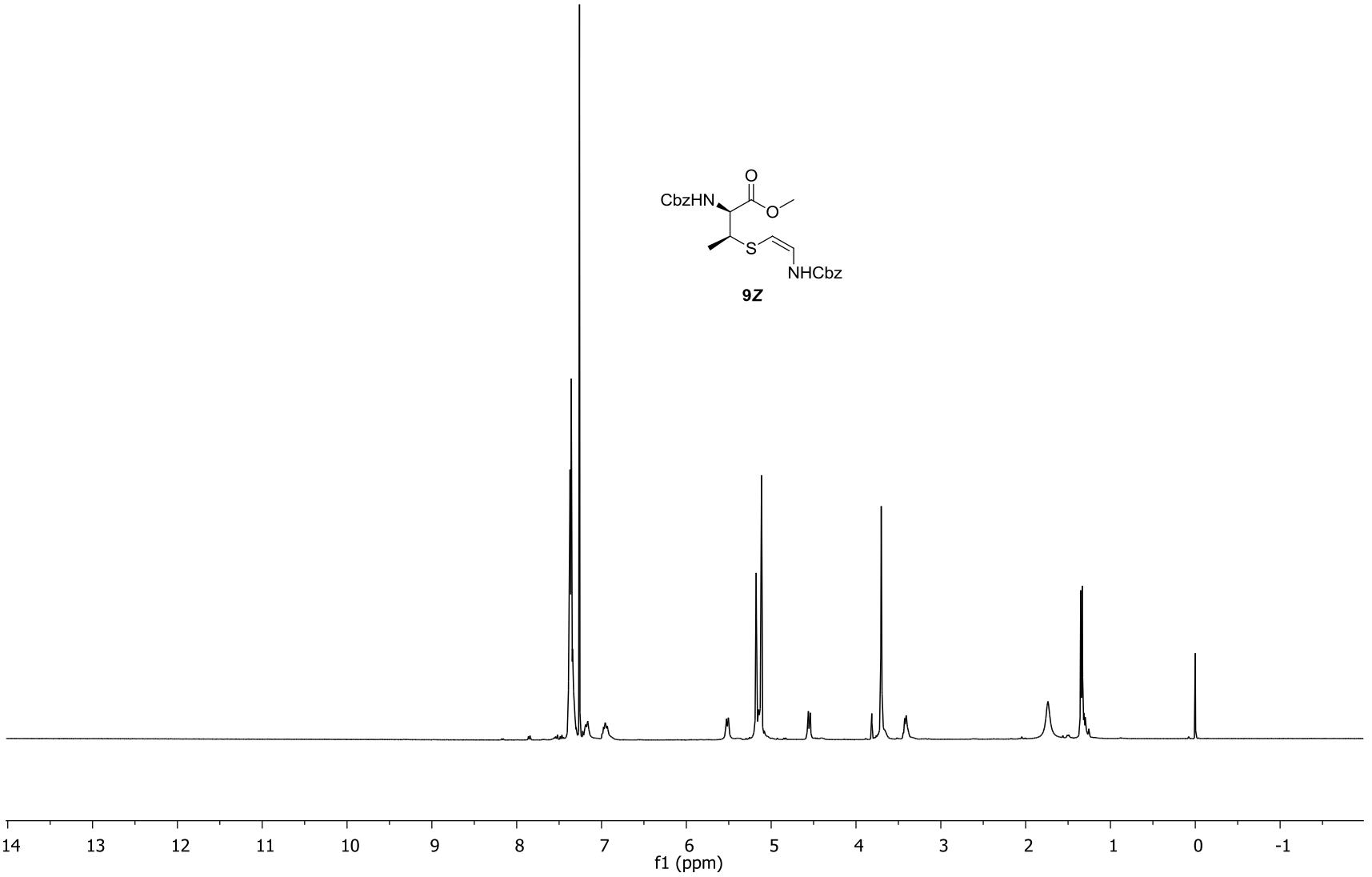

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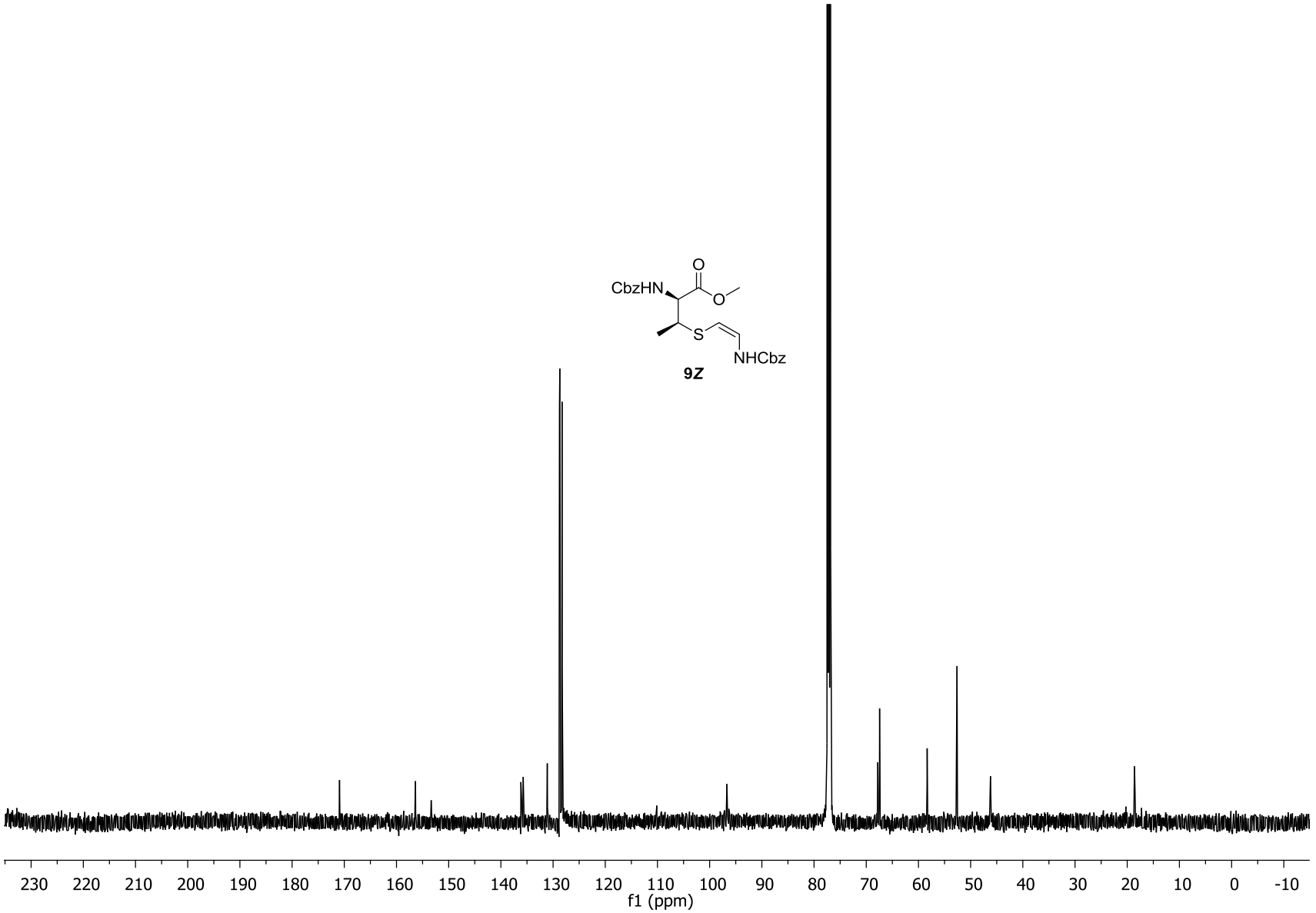
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S
NHCbz
9Z
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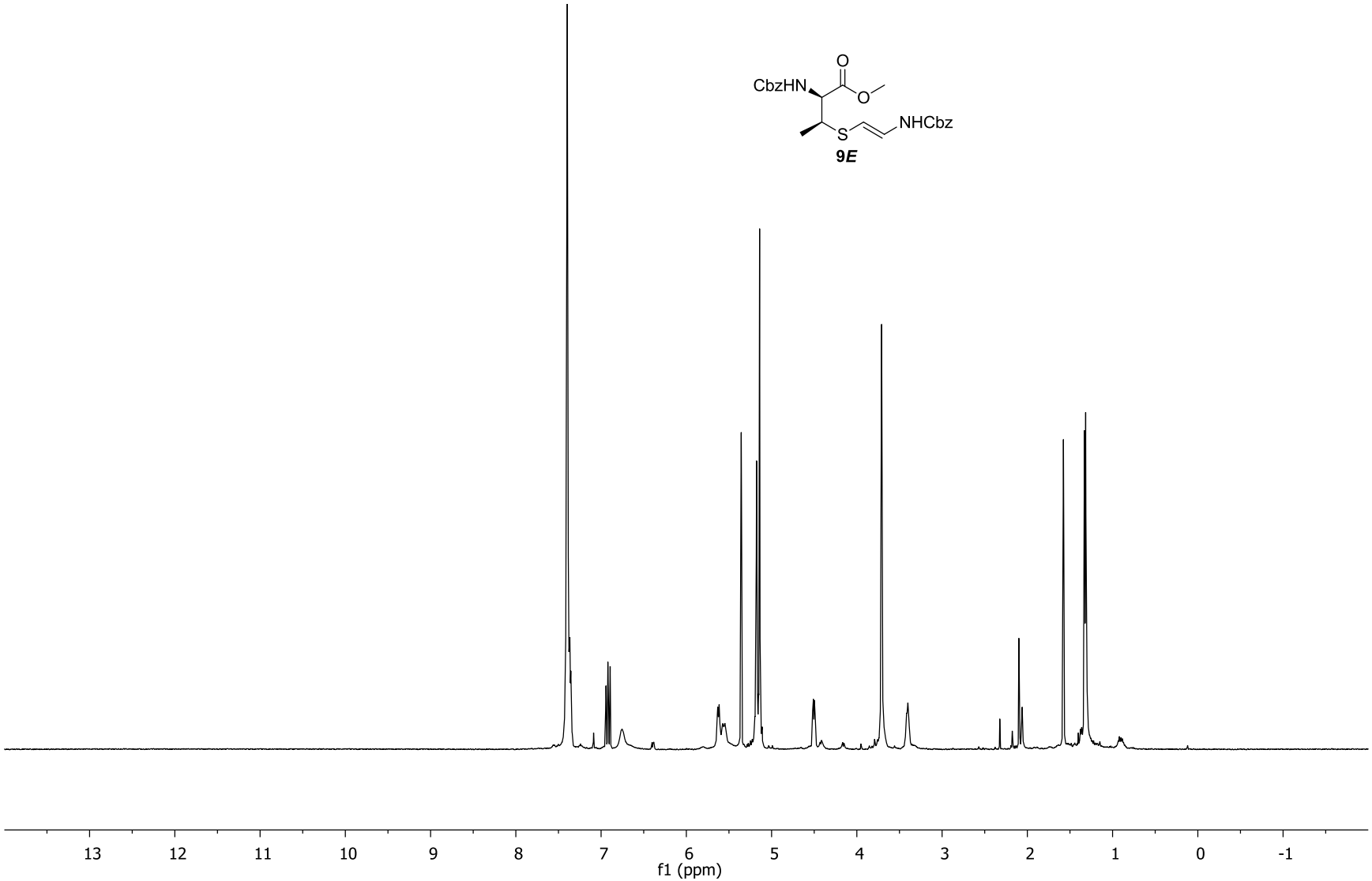
f1 (ppm)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O
S
NHCbz
9E
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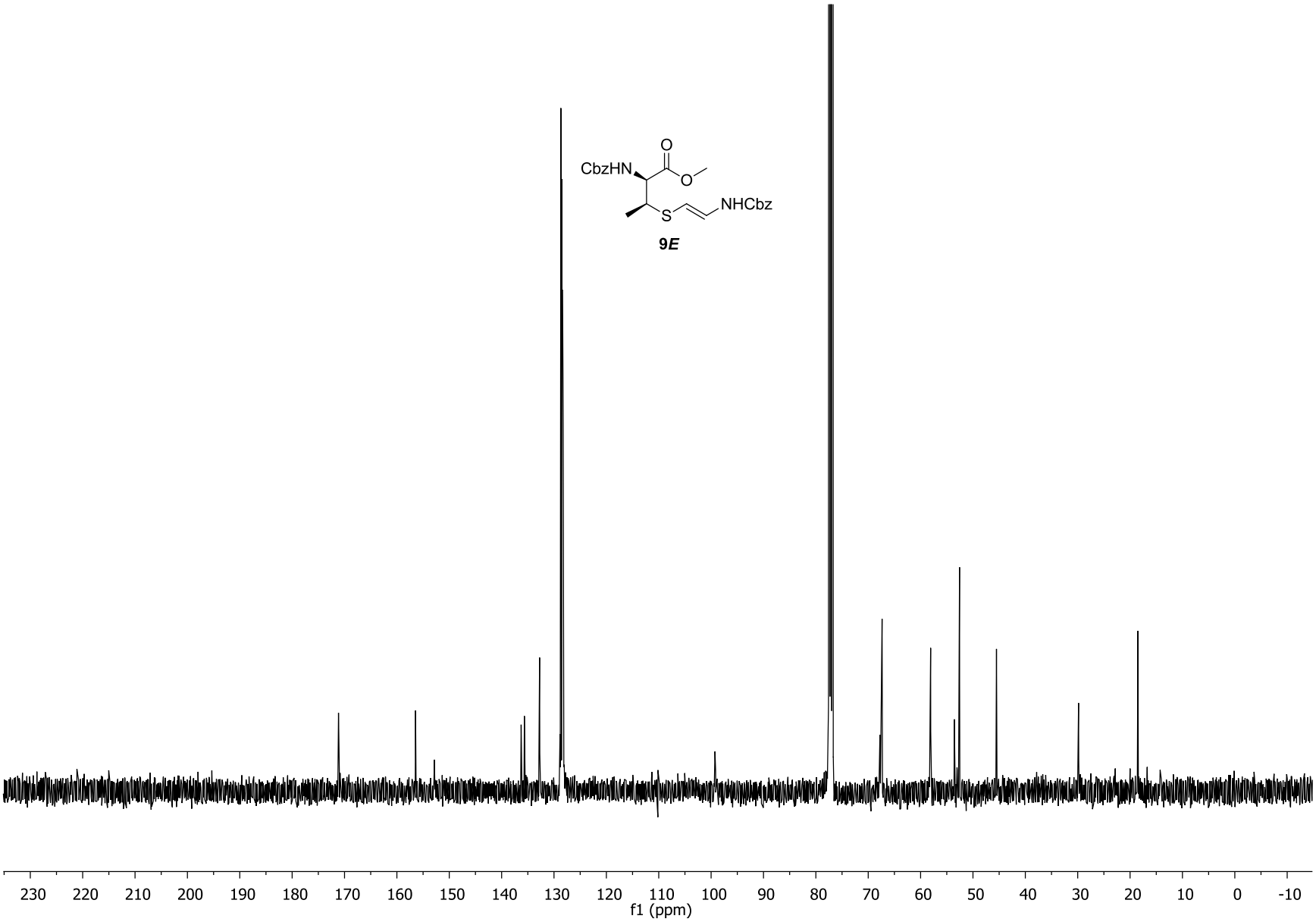
6
5
4
3
2
1
0
-1
f1 (ppm)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O
S
NHCbz
9E
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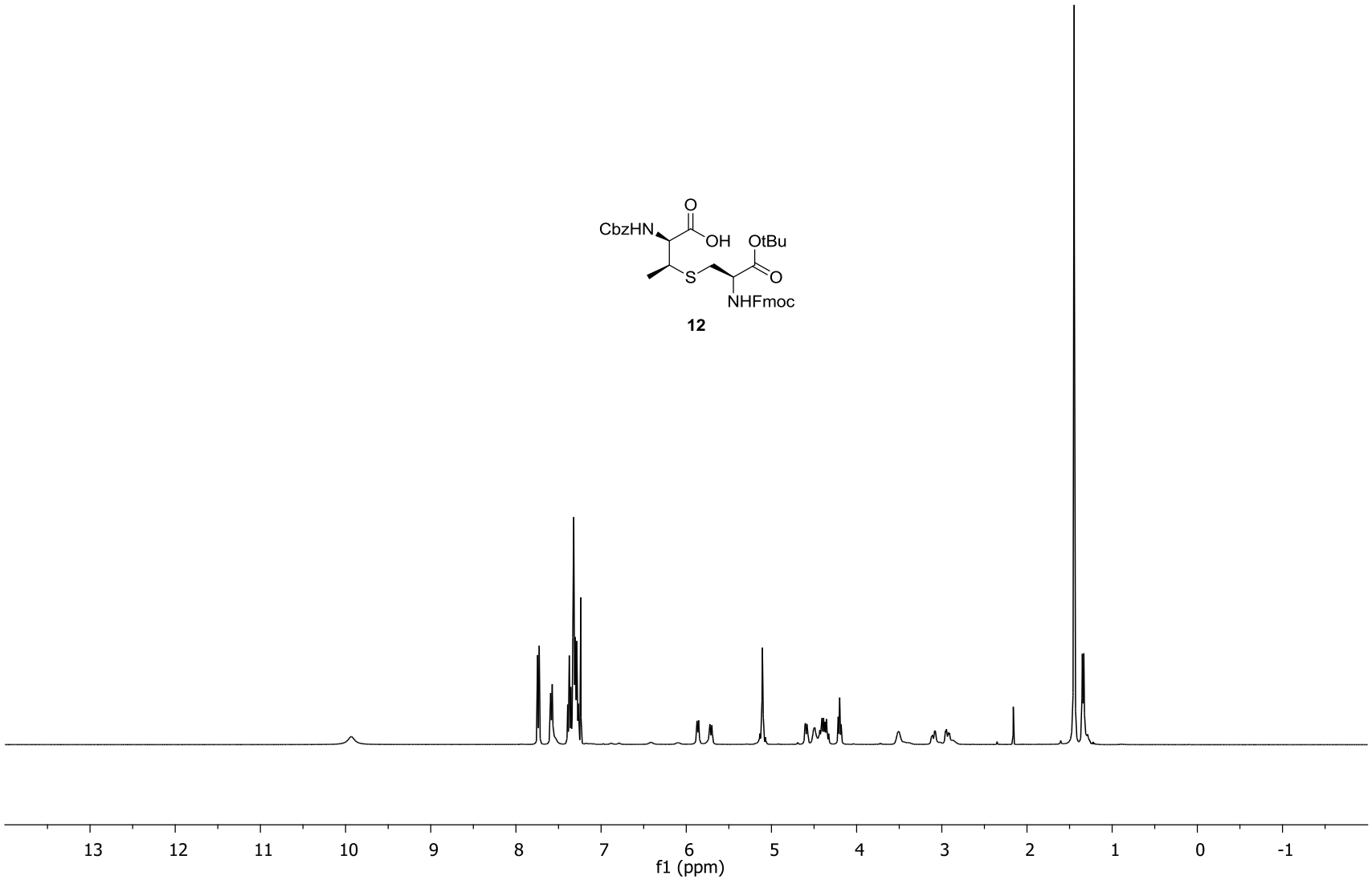
f1 (ppm)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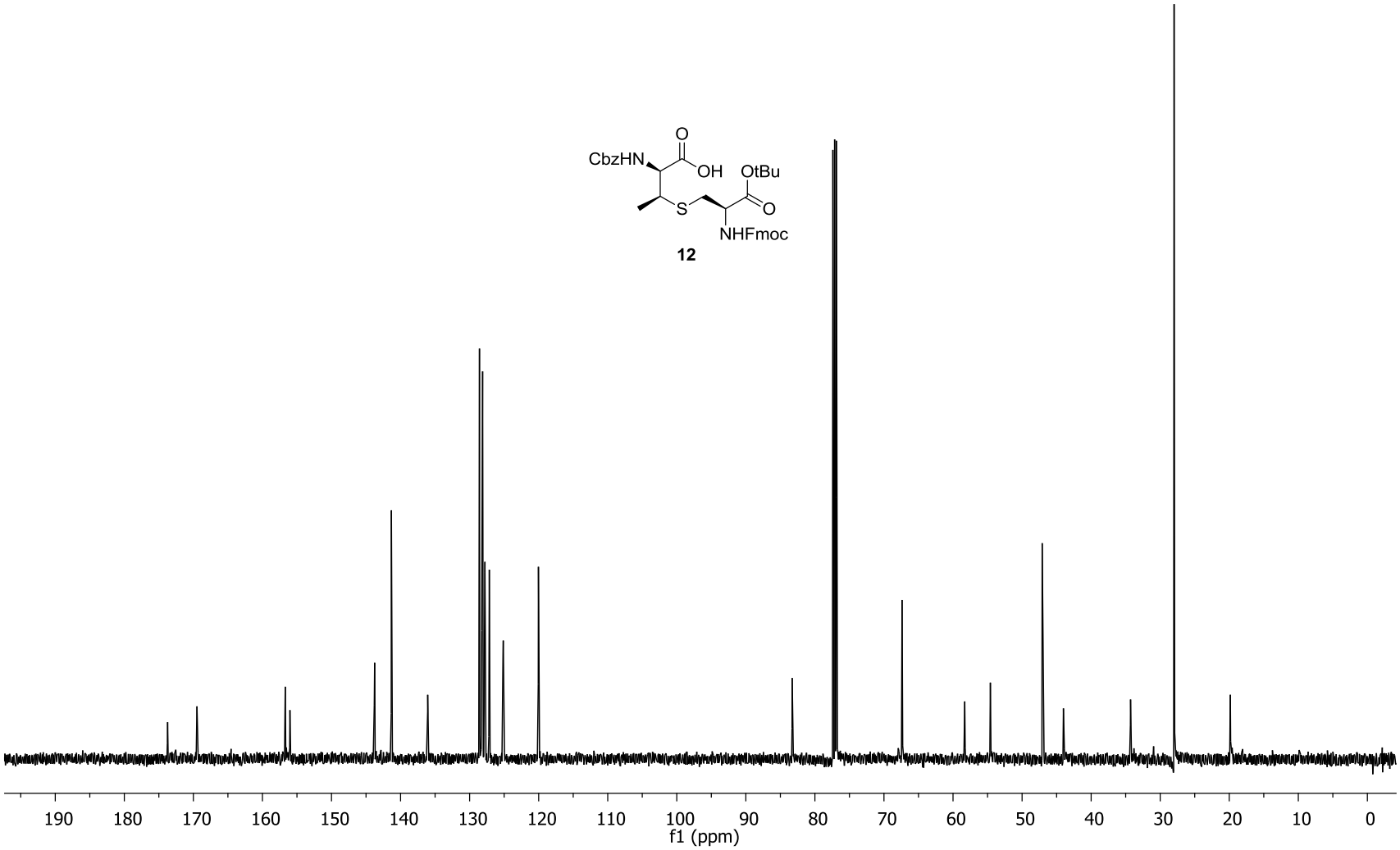
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NHFmoc
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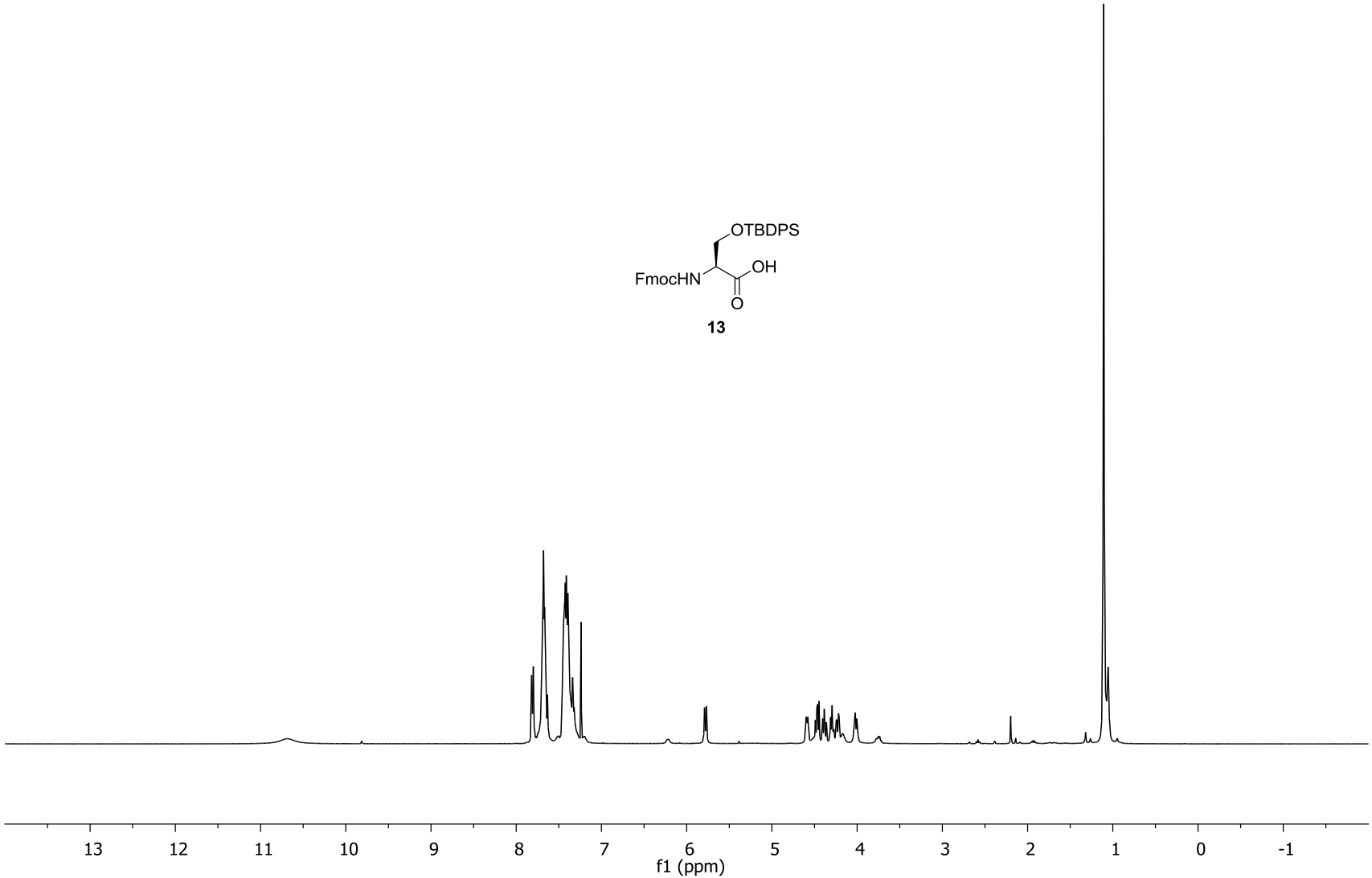
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4
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0
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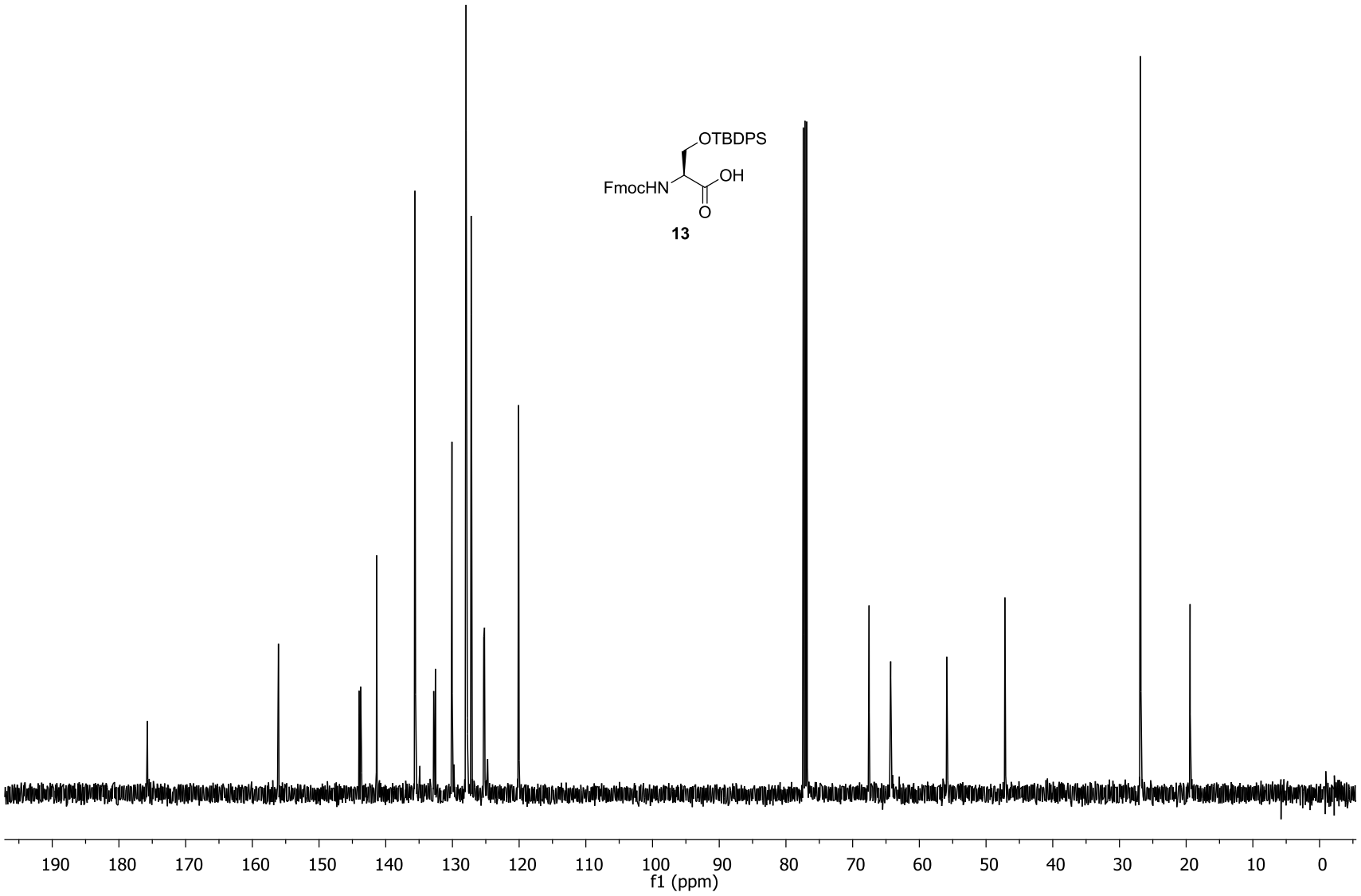
f1 (ppm)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FmocHN
OH
O
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100
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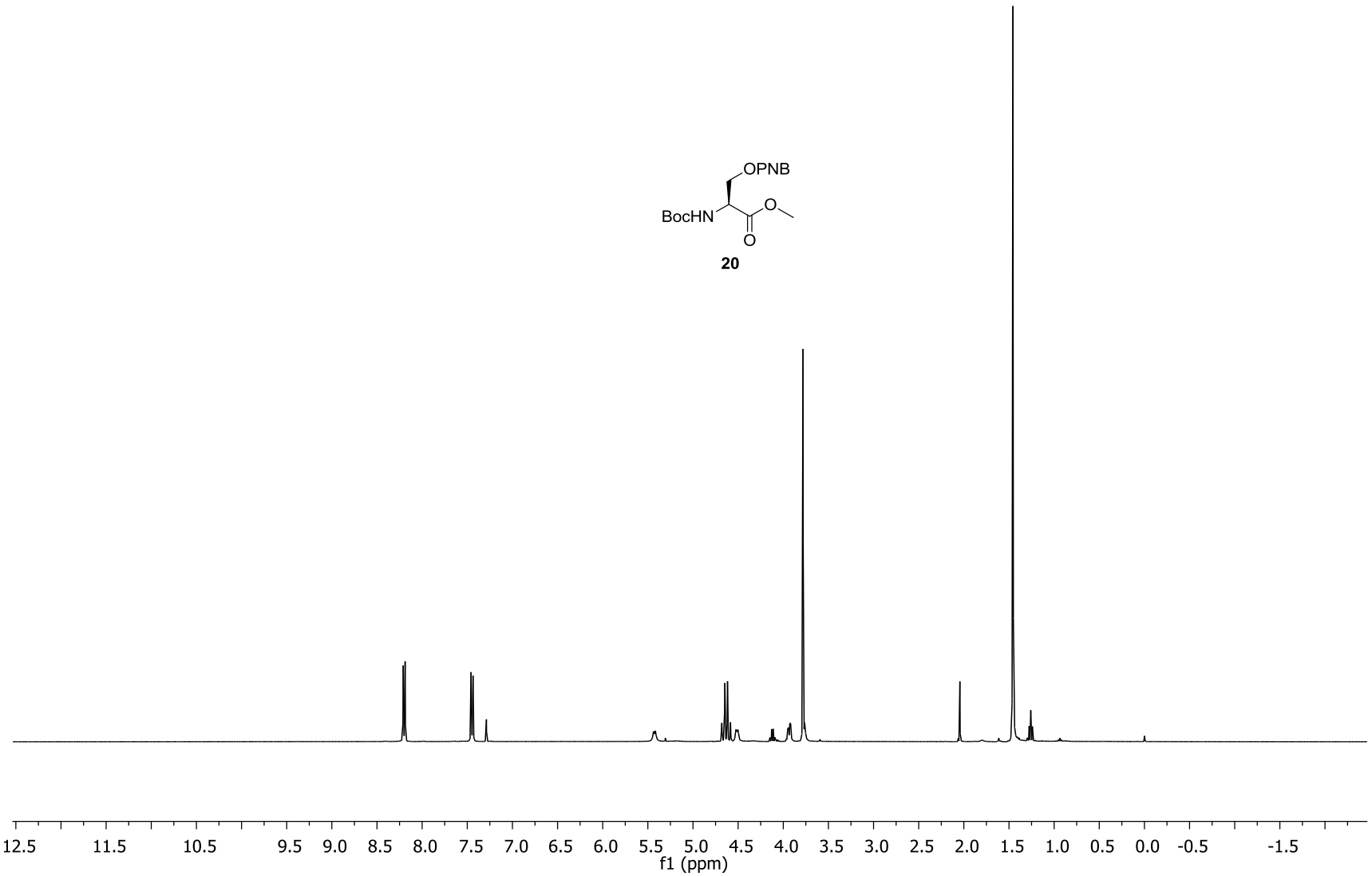
50
40
30
20
10
0
f1 (ppm)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BocHN
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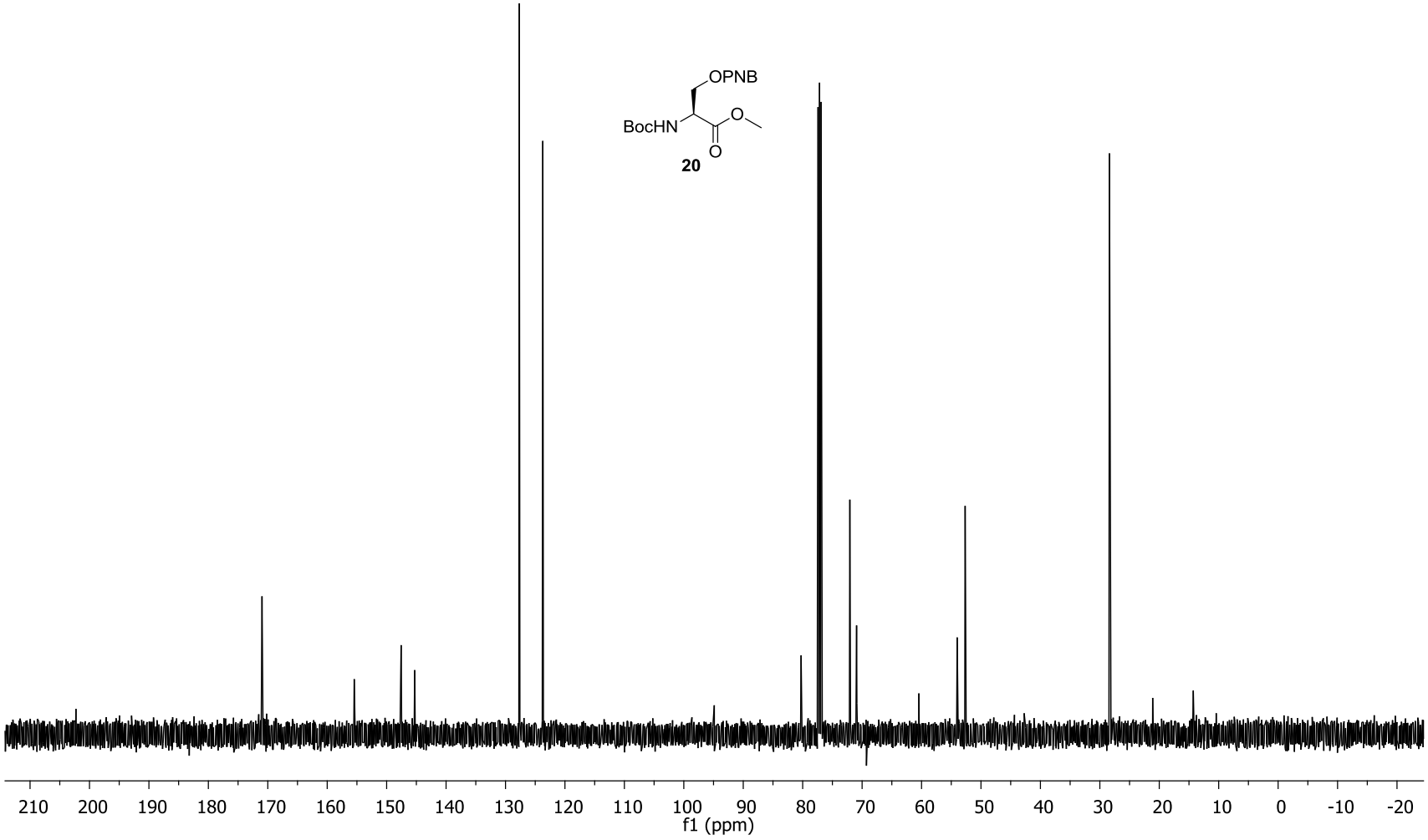
f1 (ppm)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BocHN
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O
20
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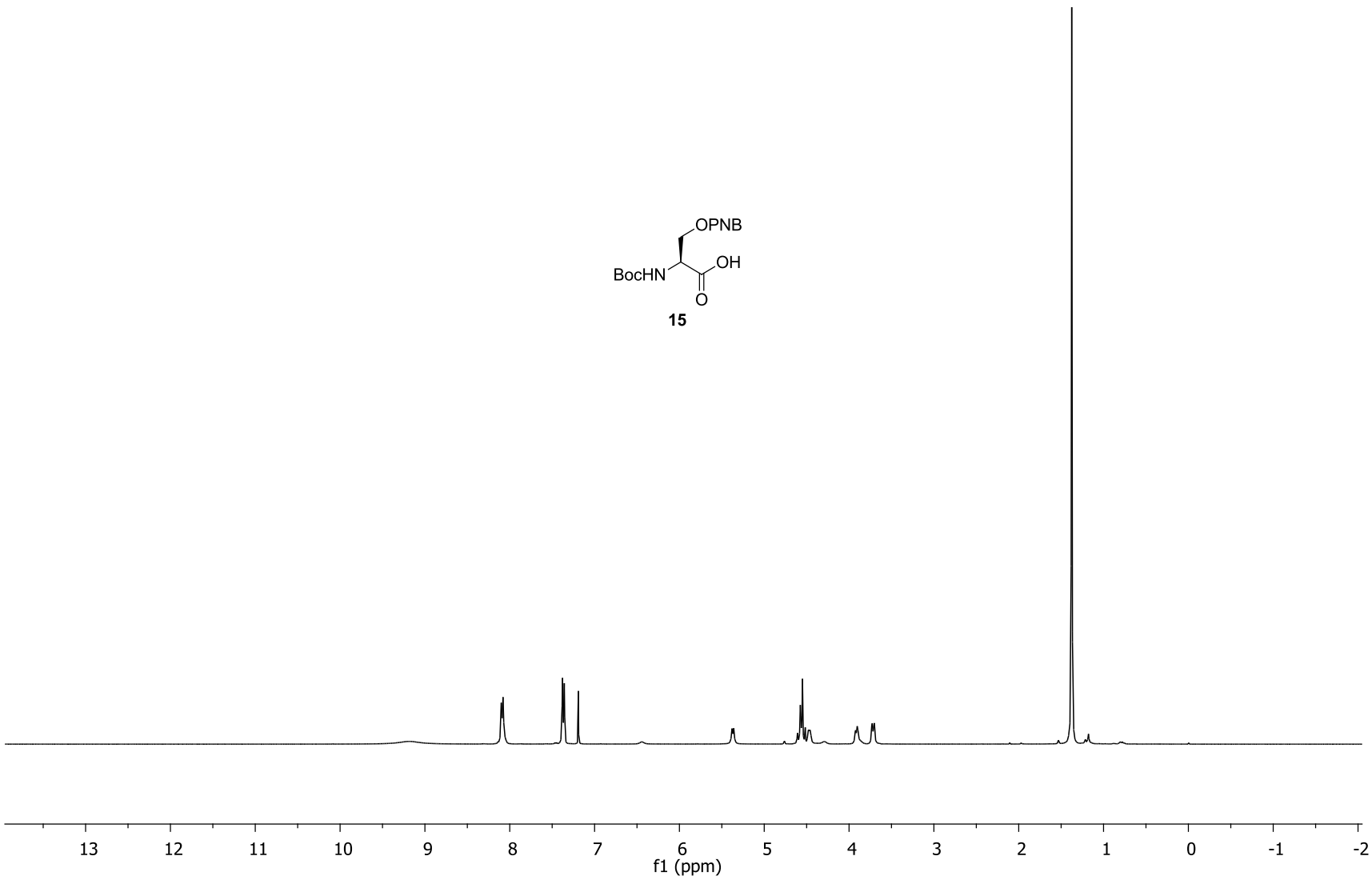
f1 (ppm)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BocHN
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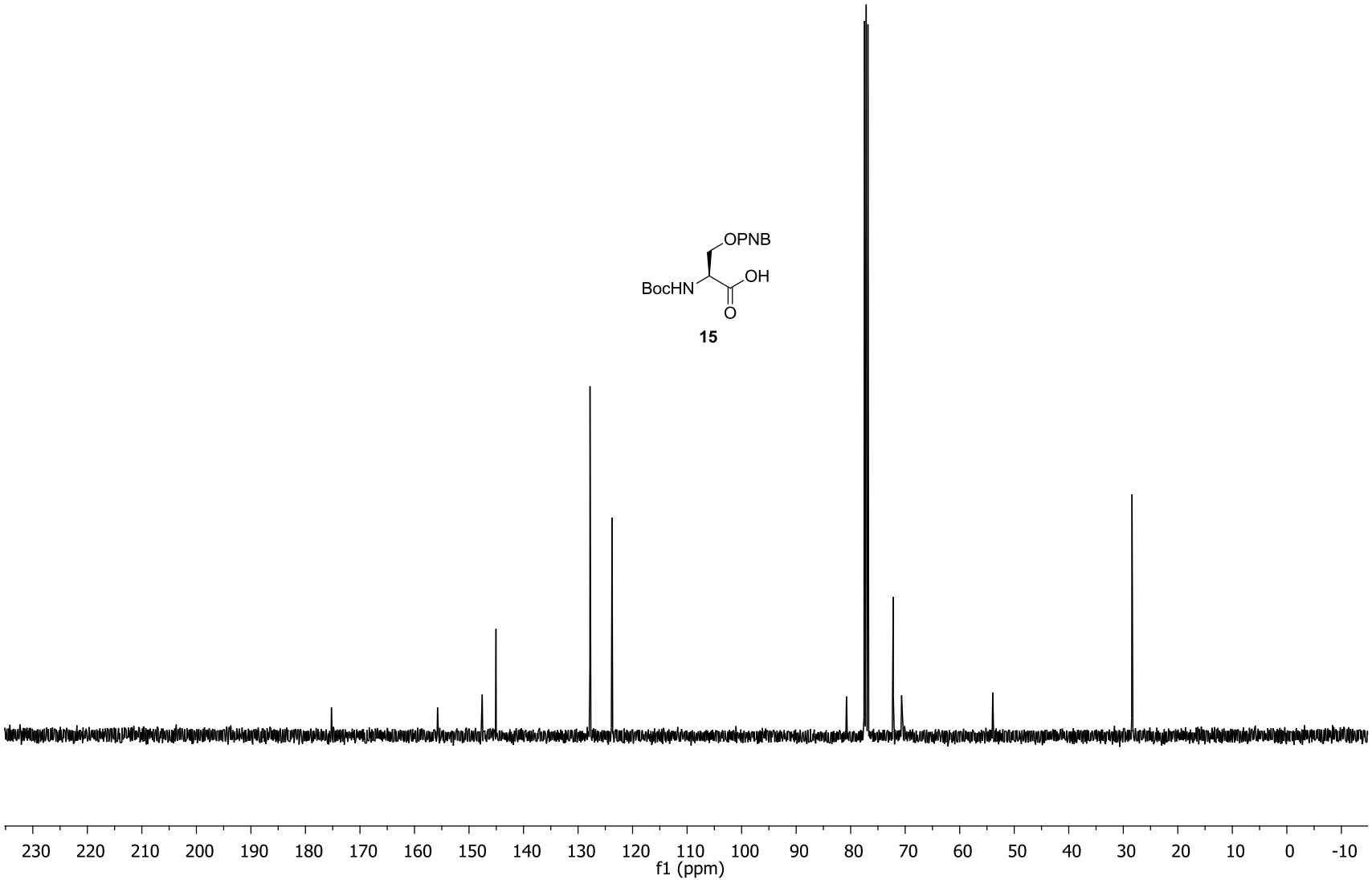
-1
-2
f1 (ppm)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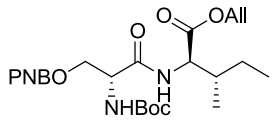
f1 (ppm)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OAll
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PNBO
N
H
NHBoc

21

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7.5
7.0
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6.0
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5.0
4.5
4.0
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0.0
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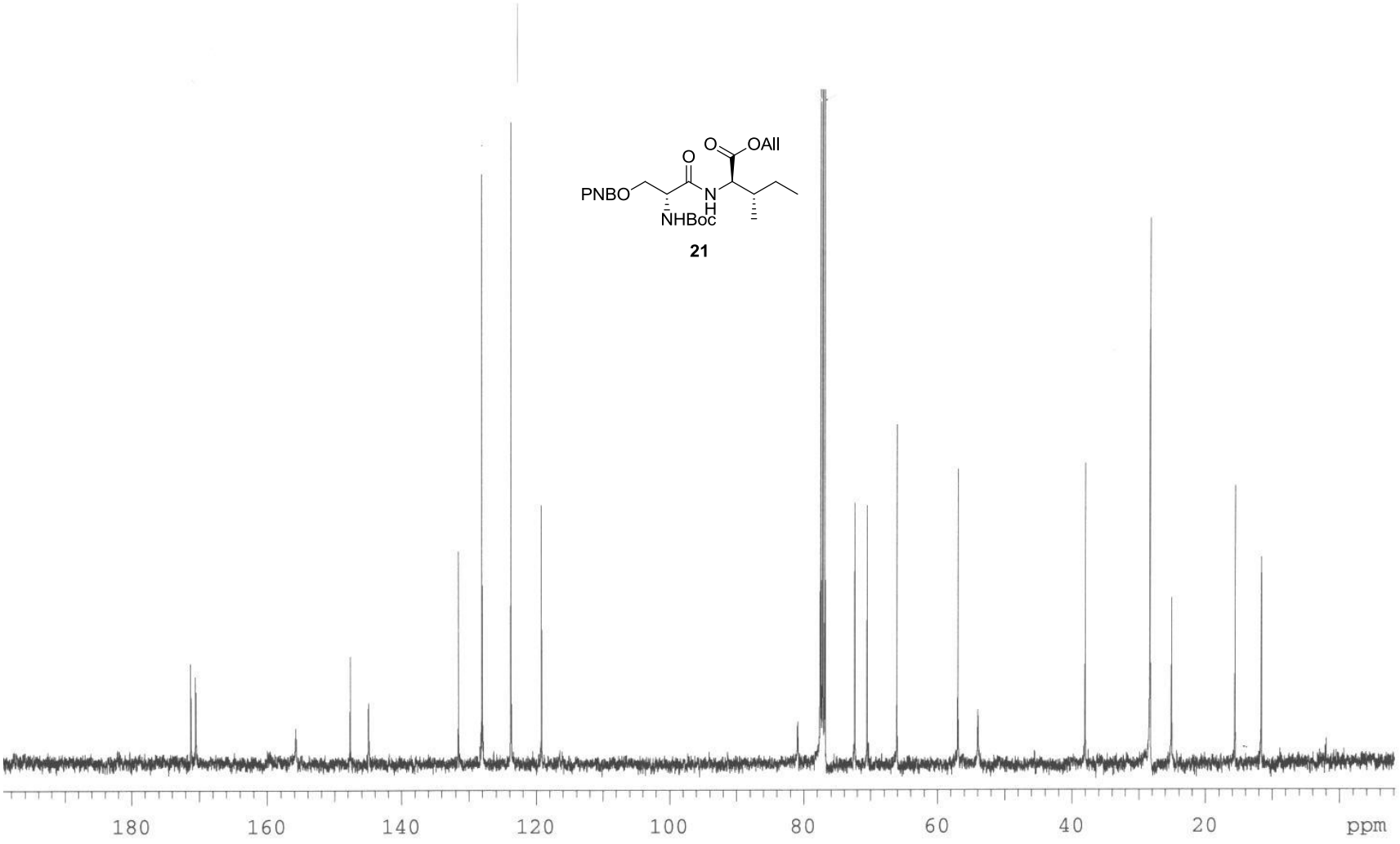
f1 (ppm)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PNBO
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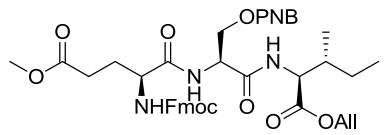
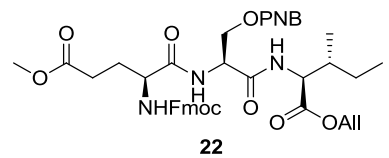
H
NHBoc
21
180
160
140
120
100
80
60
40
20
ppm

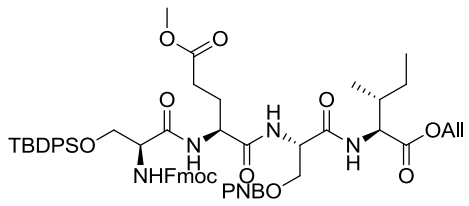


22

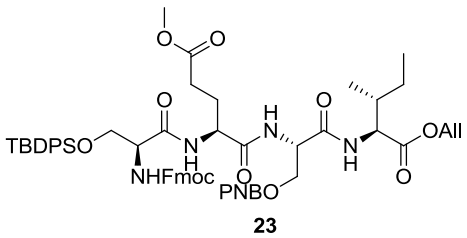

OPNB
O
O
O
N
H
H
N
O
NHFmoc
O
O
OAll

22

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

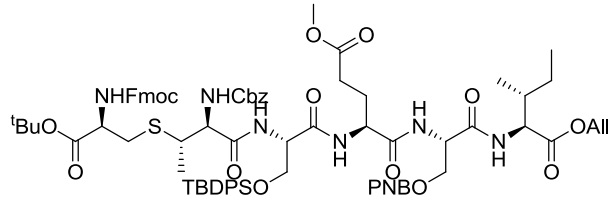


23


TBDPSO
NHFmoc
PNBO
OAll

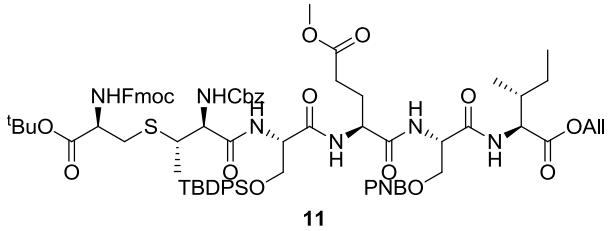
23

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


NHFmoc
NHCbz
tBuO
S
TBDPSO
PNBO
OAll

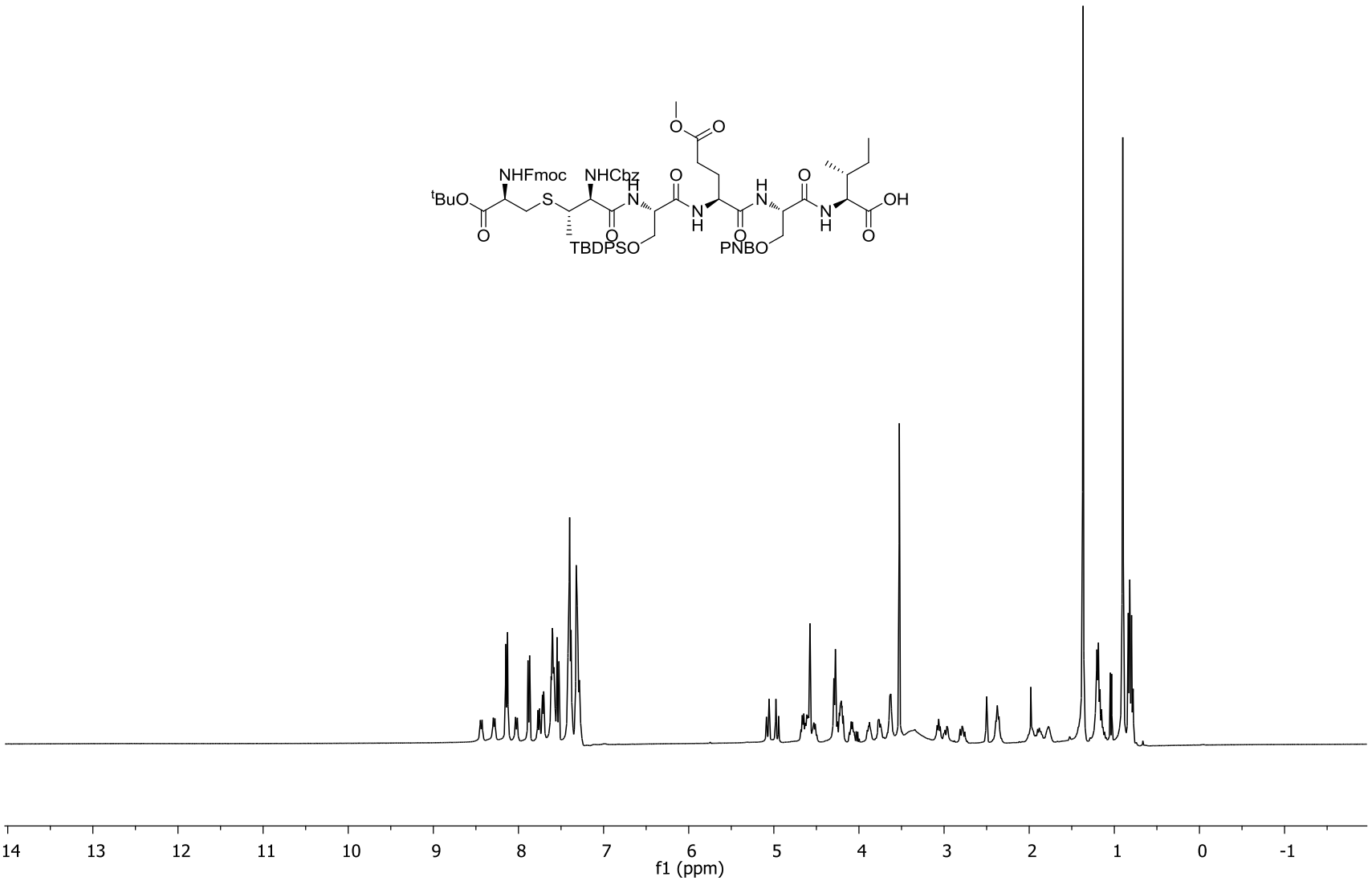
11

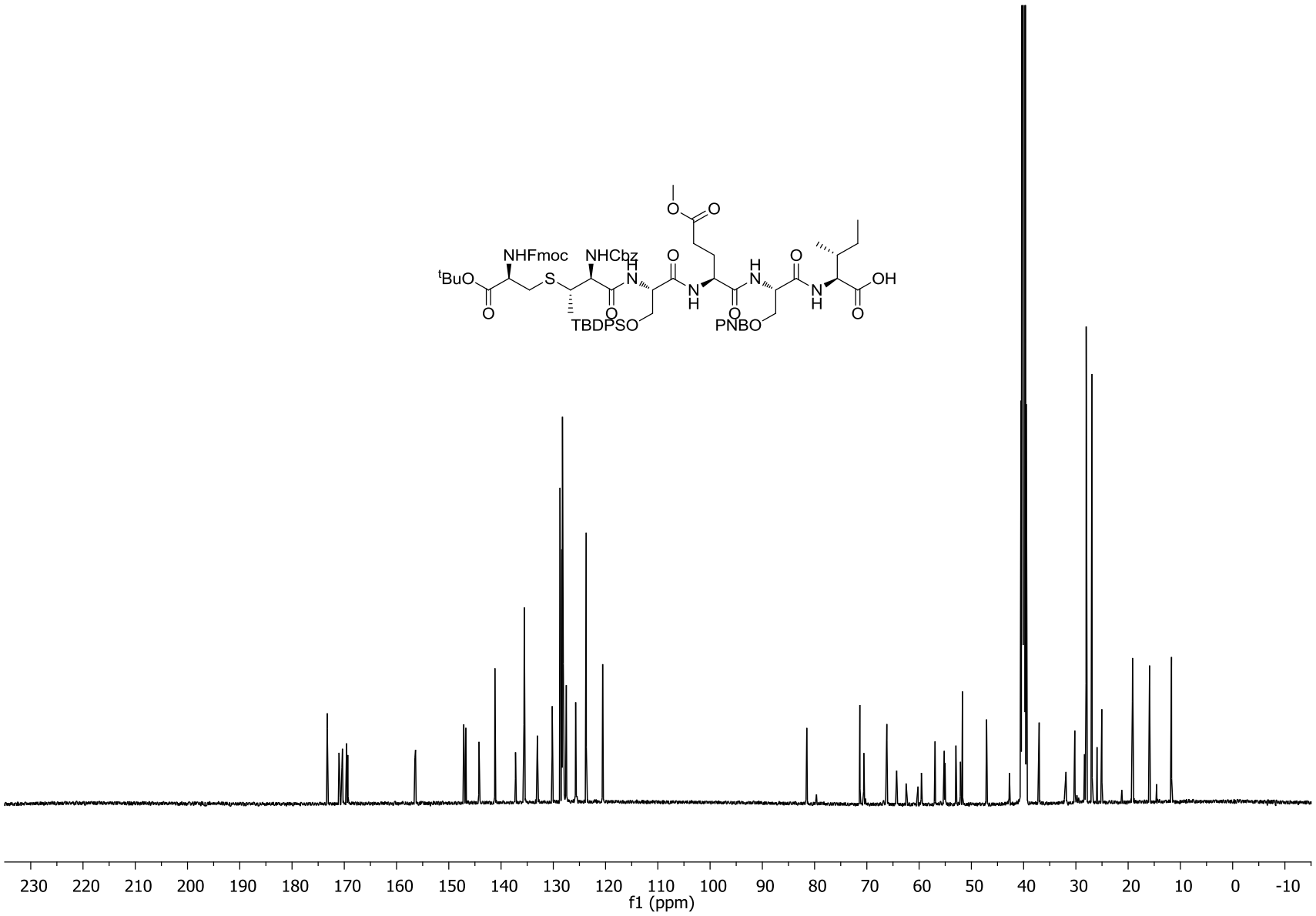
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

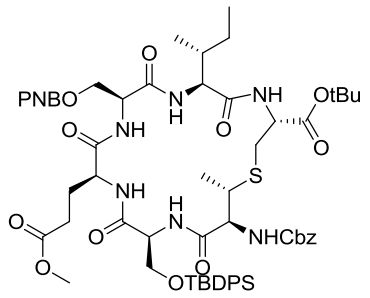

NHFmoc
NHCbz
tBuO
S
TBDPSO
PNBO
OAll

11

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

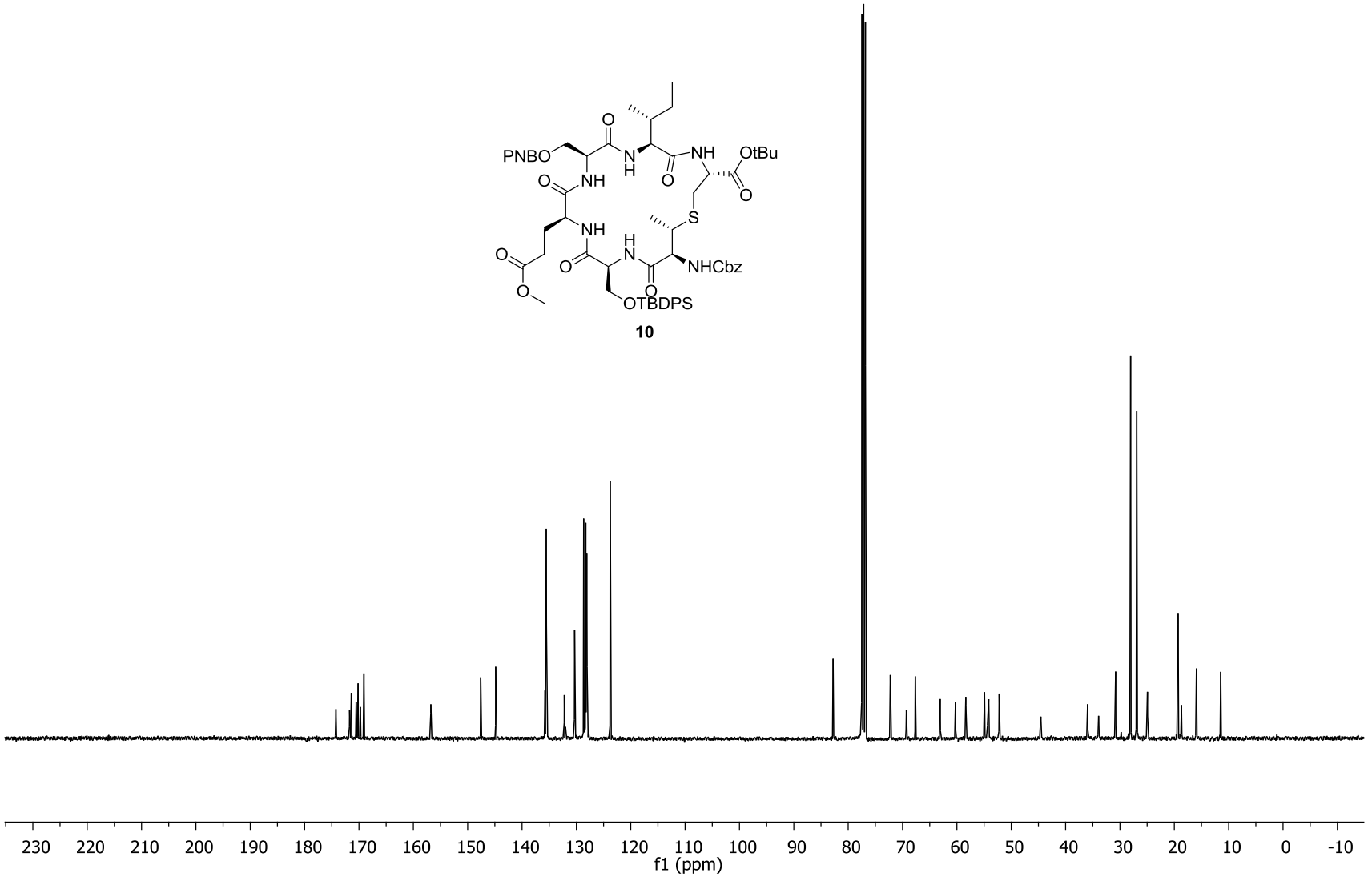

NHFmoc
NHCbz
tBuO
S
TBDPSO
PNBO
OH
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

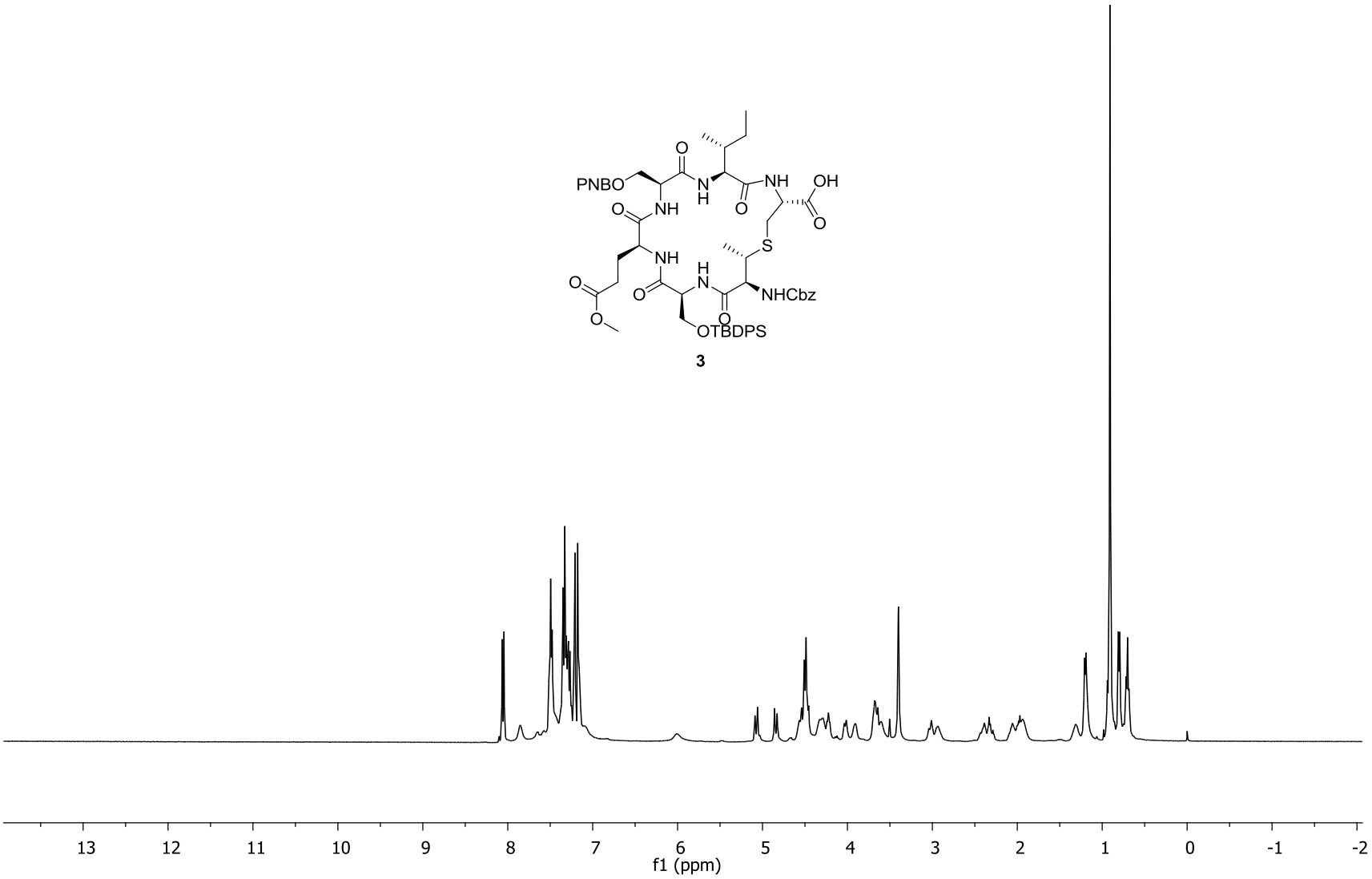

NHFmoc
NHCbz
tBuO
S
TBDPSO
PNBO
OH
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


PNBO
O
N
H
NH
OtBu
O
NH
O
O
S
NH
H
N
O
NHCbz
O
O
O
OTBDPS

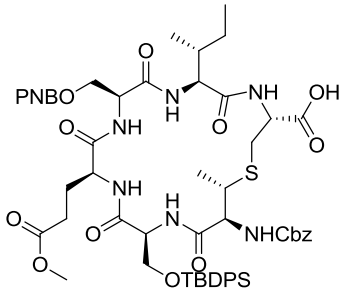
10

13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)


PNBO
O
N
H
NH
OtBu
O
O
NH
O
O
S
NH
H
N
O
NHCbz
O
O
O
OTBDPS
10
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

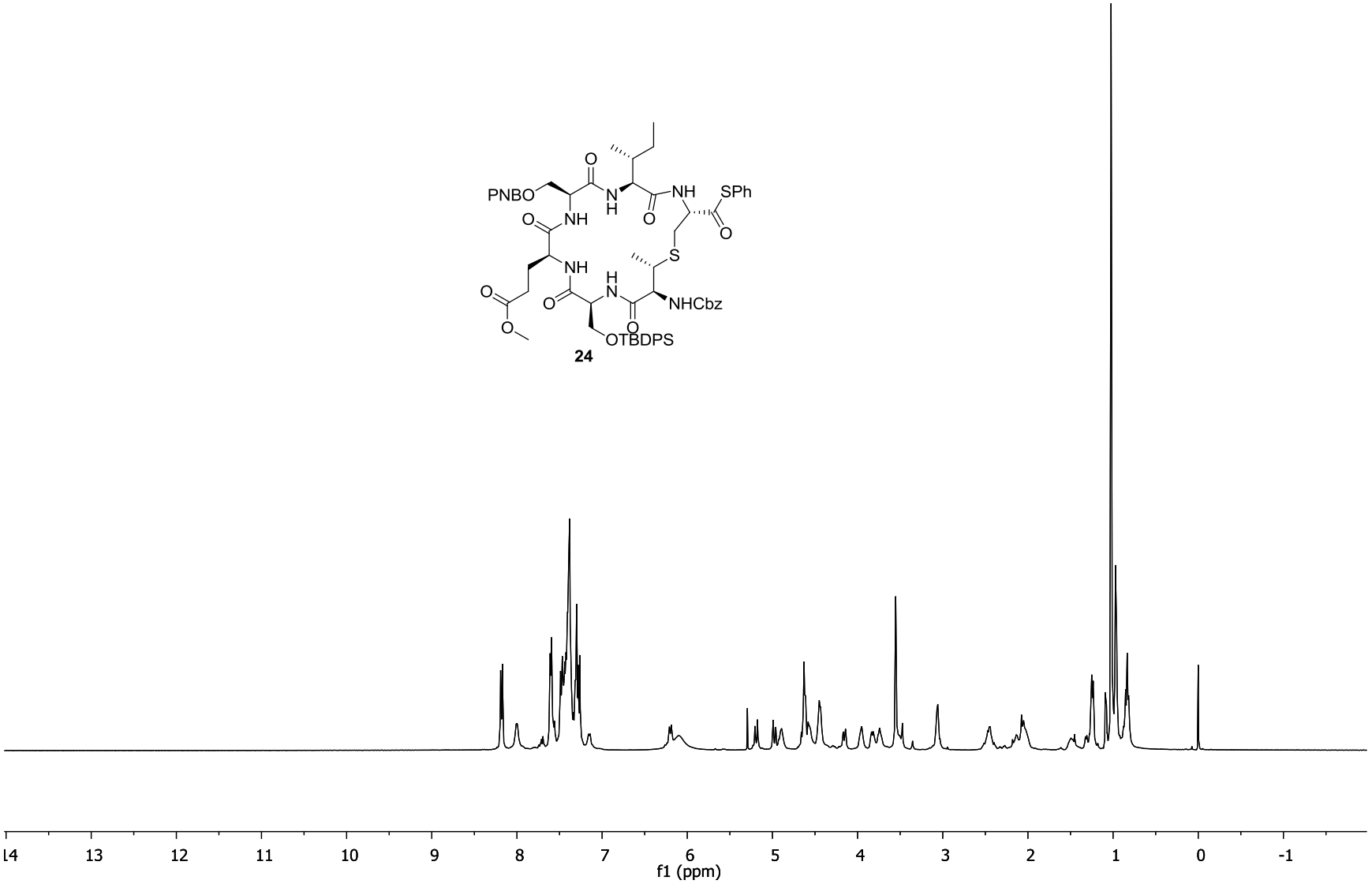

PNBO
NH
N
H
NH
OH
O
O
O
O
NH
S
NH
H
N
O
O
NHCbz
O
O
O
OTBDPS
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

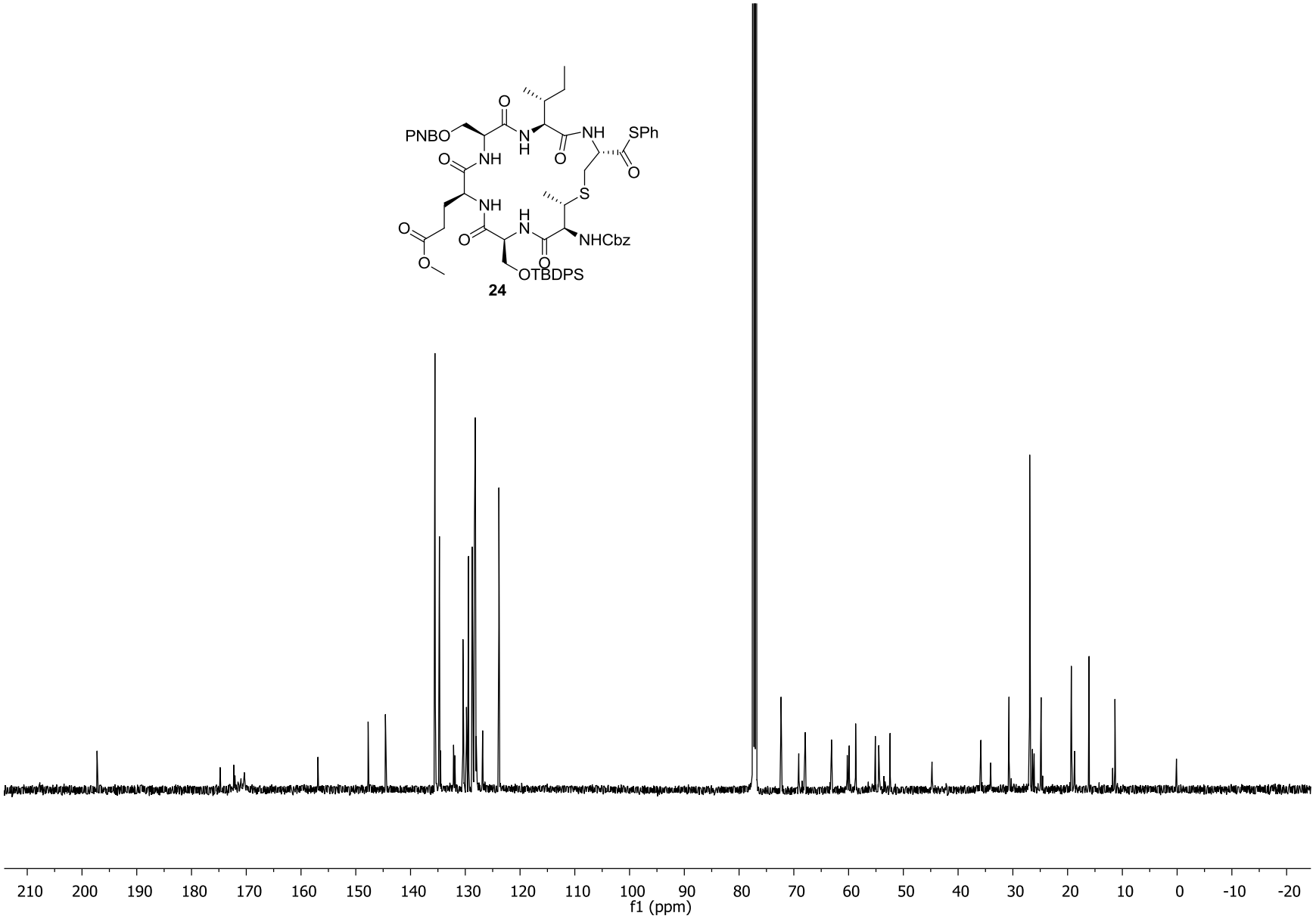
3

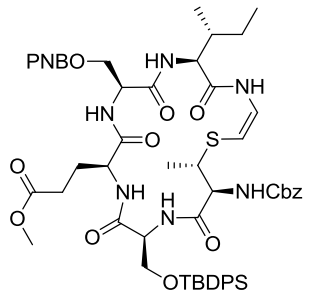

PNBO
O
N
H
NH
OH
O
NH
O
O
NH
S
O
H
N
NHCbz
O
O
O
OTBDPS

3

180
160
140
120
100
80
60
40
20
0 ppm

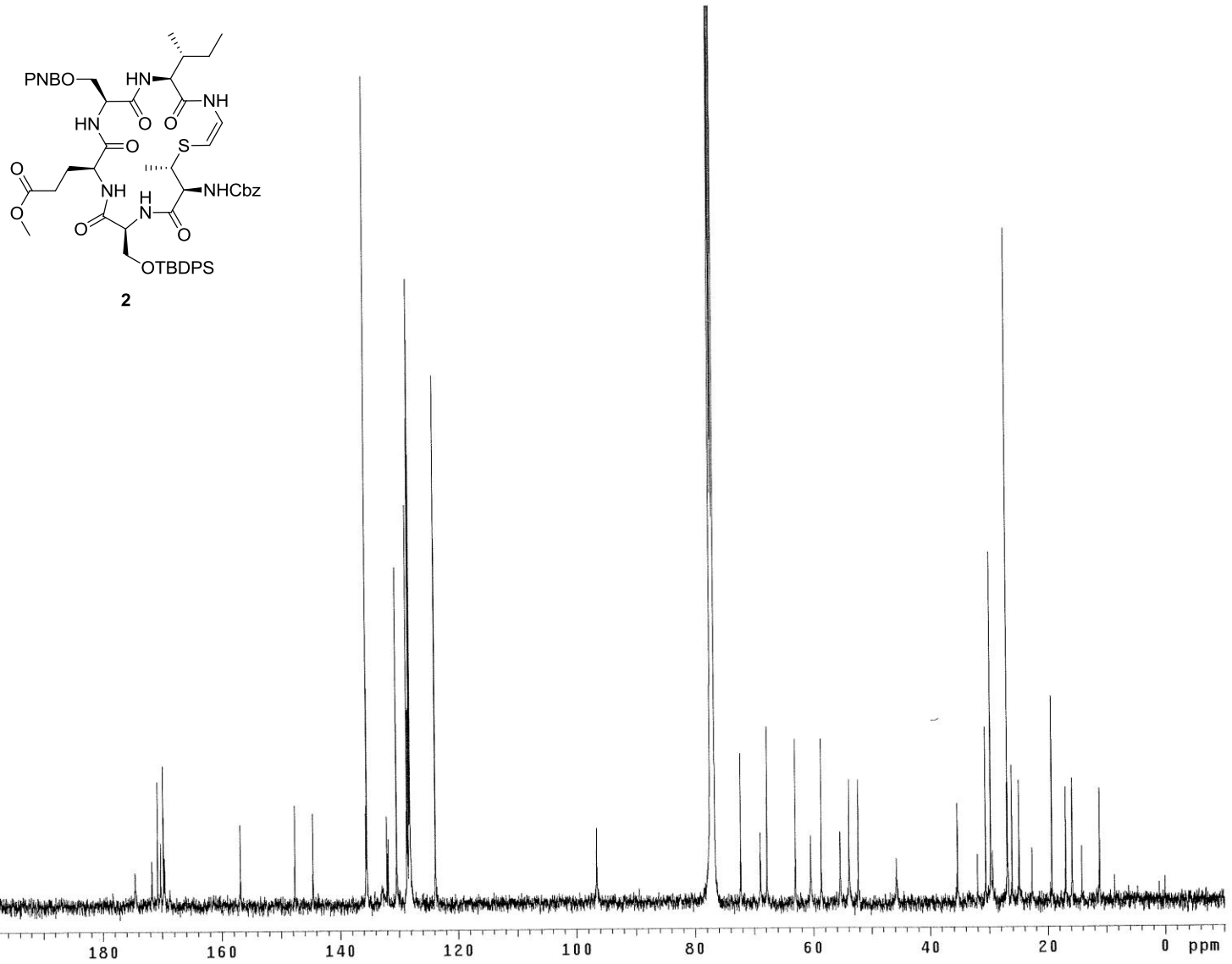

PNBO
NH
NH
NH
NH
SPh
S
NHCbz
OTBDPS
24
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


PNBO
O
N
H
NH
SPh
O
O
NH
O
O
S
NH
H
N
NHCbz
O
O
O
O
OTBDPS
24
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

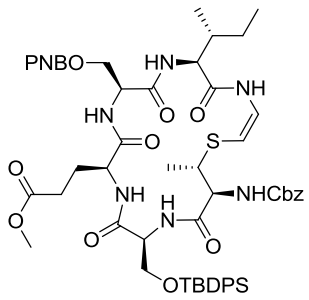

PNBO
HN
NH
HN
O
O
O
S
O
NH
NHCbz
H
N
O
O
O
OTBDPS

2

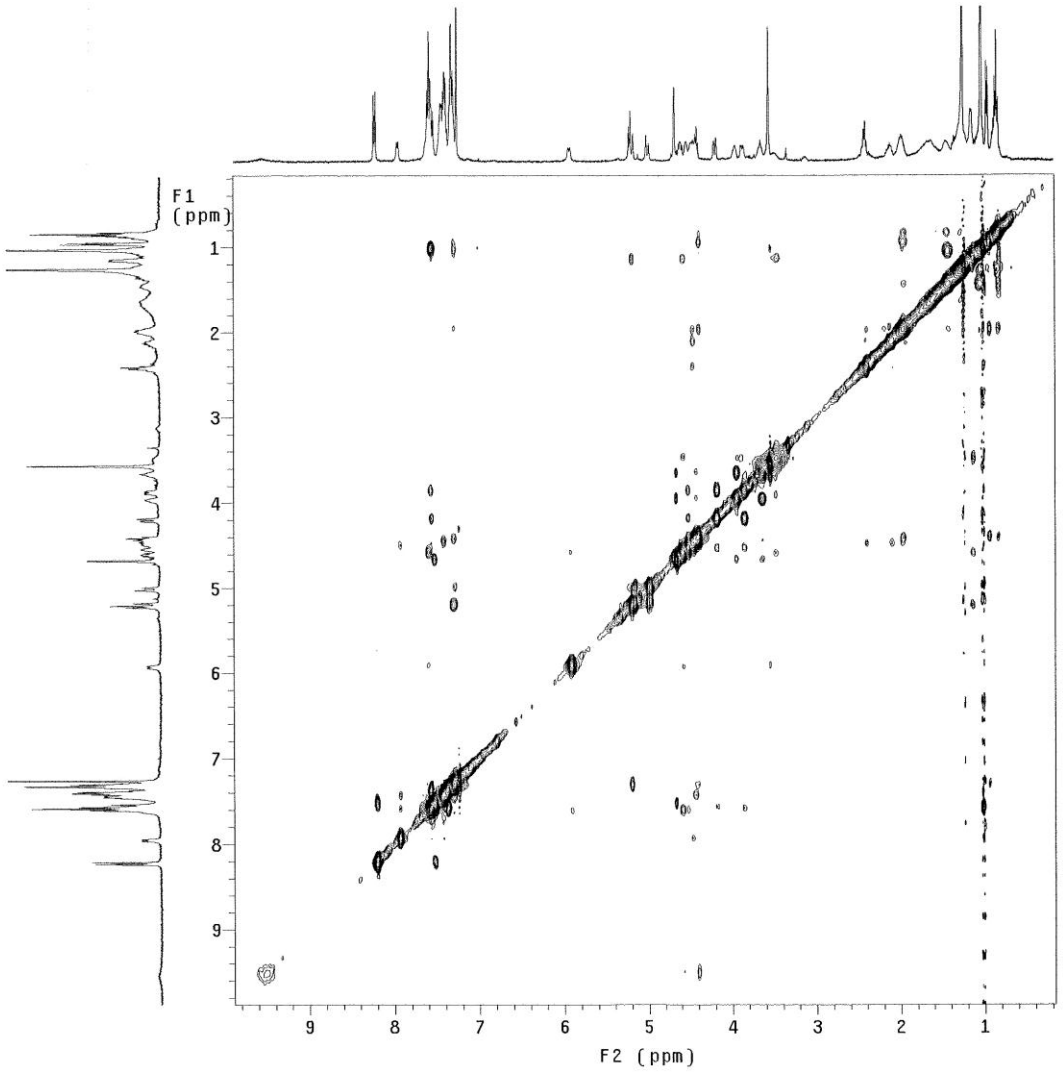
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

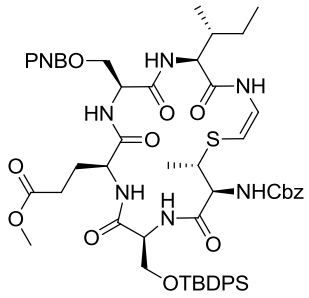

PNBO
HN
NH
HN
O
O
O
S
O
NH
NHCbz
O
N
H
O
O
OTBDPS
180
160
140
120
100
80
60
40
20
0
ppm

2

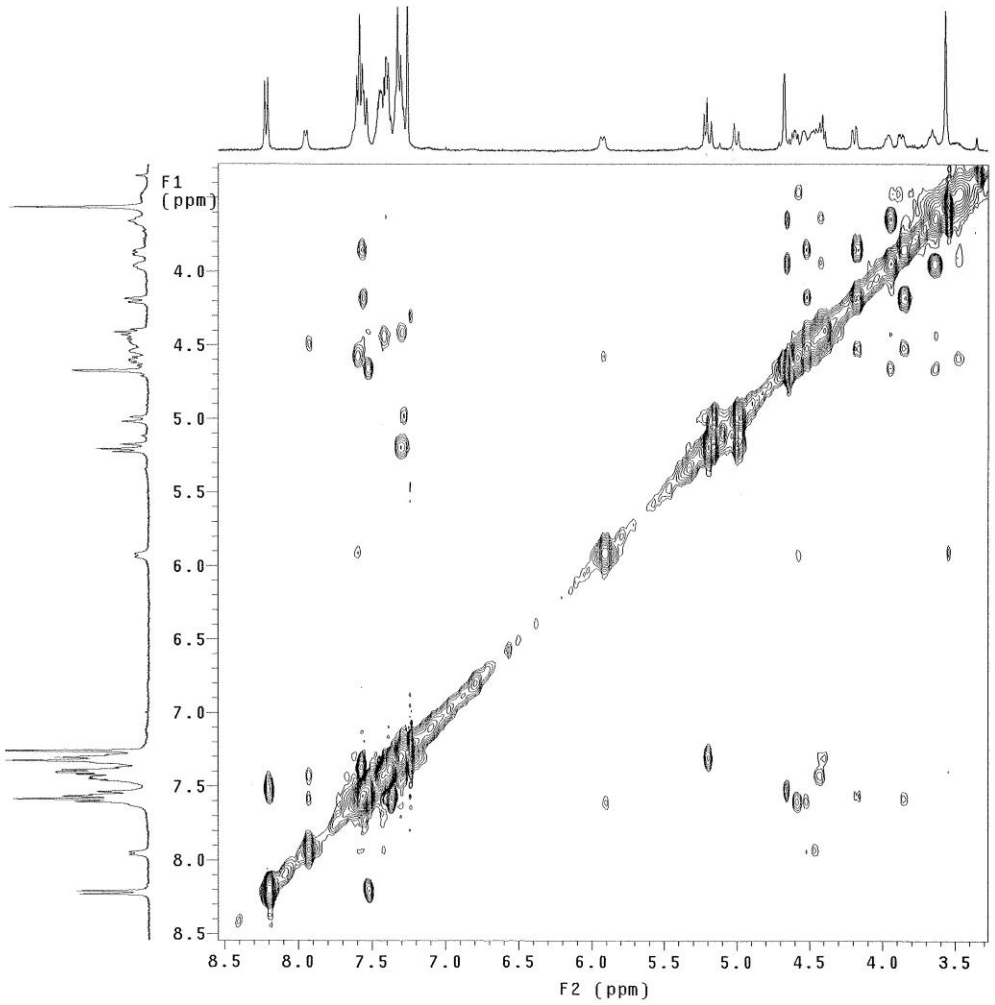

PNBO
HN
NH
HN
O
O
HN
O
S
O
NH
NHCbz
H
N
O
O
O
OTBDPS

2


F1
(ppm)
1
2
3
4
5
6
7
8
9
F2 (ppm)


PNBO
HN
NH
HN
O
O
O
S
O
NH
NHCbz
H
N
O
O
O
OTBDPS

2


F1
(ppm)
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
F2 (ppm)