In Situ Carboxyl Activation using a Silatropic Switch. A New Approach to Amide and Peptide Constructions.

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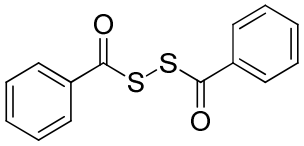
General Experimental. ^{1}H and ^{13}C NMR spectra were recorded on Inova 400 MHz spectrometers in deuteriochloroform ($CDCl_3$) with the solvent residual peak as internal reference unless otherwise stated ($CDCl_3$: ^{1}H = 7.26 ppm, ^{13}C = 77.23 ppm). Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent); coupling constants, *J*, are reported (Hz); integration is provided. Infrared spectra were recorded on a Nicolet 380 FT-IR spectrometer with a diamond plate. Peaks are reported (cm^{-1}) with the following relative intensities: vs (very strong), s (strong), m (medium), w (weak), and br (broad). Optical rotation values were measured at 20 ˚C on a Perkin Elmer Model 341 polarimeter with chloroform ($CHCl_3$) as solvent. Uncalibrated melting points were taken on a *Thomas-Hoover* melting point apparatus in open capillary tubes. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator. Visualization was accomplished by UV light, or with solutions of ninhydrin in ethanol or *p*-anisaldehyde in ethanol. Purification by chromatography was performed using Whatman 60Å 230-400 mesh SiO_2 with compressed air as a source of positive pressure. HPLC analyses were carried out using an Agilent 1100 system with a quaternary pump. Separations were achieved on DAICEL Chiralpak AS-RH or Chiralcel OD-RH, OJ-RH column. Solvents for reactions and chromatography were reagent grade and used as received. "Brine" refers to a saturated aqueous solution of NaCl. Solutions of NH_4Cl, $NaHCO_3$ refer to saturated aqueous solutions. Solvents used as reaction media were purchased in > 99% purity without further purification, unless otherwise specified.

Starting Materials. All protected amino acids, thiobenzoic acid, thioacetic acid, primary and secondary amines, 9-fluorenemethanol, *N*,*N*-dimethylaminopyridine (DMAP), *N*-phenyltriazolinedione, 1-admantanecarboxylic acid, *N,O*-bis(trimethylsilyl)acetamide (BSA), *N,N'*-dicyclohexylcarbodiimide (DCC), *N,N*-diisopropylethylamine (DIEA), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), chlorophenylsilane, 4-

toluenesulfonyl chloride, pyridine, diisobutylaluminium hydride (1.0 M in hexane), potassium thioacetate were purchased from Sigma-Aldrich and used without further purification. Thionicotinic acid was purchased from TCI.

1. Benzoyldisulfide Formation

Benzoyldisulfide.

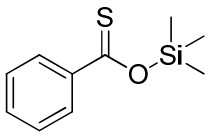


The disulfide was prepared from thiobenzoic acid using Elemes's method.[2] Crystallization of the reaction mixture using 1 : 3 ethyl acetate/hexanes gave the product as a white solid (376 mg, 60% yield). Mp 128-130 °C [Lit.[2] 132 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 1.2 Hz, 8.0 Hz, 2H), 7.66 (tt, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.53 (dt, *J* = 1.6 Hz, 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 135.5, 134.6, 129.2, 128.4; IR (cm^{-1}): 3368(w), 3063(w), 1699(m), 1679(vs), 1579(m), 1444(s), 1203(vs), 881(vs), 769(m), 673(m).

2. Control Experiments

a. *In Situ* Generation of *O*-Trimethylsilylthionobenzoate.

***S*-(Trimethylsilyl)benzothioate**.[3]



N,*O*-bis(trimethylsilyl)acetamide (BSA, 0.1 mL, 0.42 mmol) was added to a 10 mL flask containing thiobenzoic acid (0.045 mL, 0.38 mmol) in $CDCl_3$ (0.8 mL). The solution was allowed to stir at room temperature for 5 minutes and monitored by ^{1}H NMR. The proton NMR showed the disappearance of thiobenzoic acid resonances and the appearance of *S*-(trimethylsilyl)

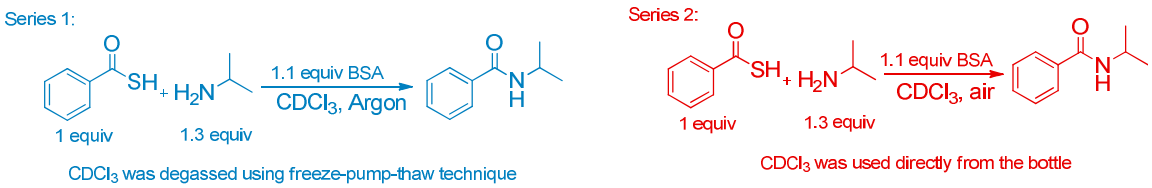
benzothioate resonances. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 2H), 0.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 139.6, 133.0, 128.9, 128.1, 0.3.

b. $CDCl_3$ Reactions, Degassed *vs.* Open to Air

$CDCl_3$ degassed reaction under argon: A sealed 10 mL flask was filled with argon. In between the addition of reagents, it was flushed several times with argon. Thiobenzoic acid (0.10 mL, 0.87 mmol), 4,4'-di-*tert*-butyl-1,1'-biphenyl (internal standard, 26 mg, 0.096 mmol), $CDCl_3$ (1.8 mL) degassed by freeze-pump-thaw technique, BSA (0.23 mL, 0.95 mmol) and isopropyl amine (0.092 mL, 1.13 mmol) were added to the flask sequentially. Then, 0.6 mL of the reaction mixture was transferred to a sealed NMR tube filled with argon. Proton NMR spectra were taken at different time points and the yield of the formed amide was determined based on the ratio to the internal standard (amide *ortho* protons chemical shift at 7.74 ppm; internal standard 9 CH_3 chemical shift at 1.36 ppm).

$CDCl_3$ reaction open to air: To a stirred solution of thiobenzoic acid (0.11 mL, 0.93 mmol), 4,4'-di-*tert*-butyl-1,1'-biphenyl (internal standard, 28 mg, 0.10 mmol) in $CDCl_3$ (1.9 mL) were added BSA (0.25 mL, 1.02 mmol) and isopropyl amine (0.098 mL, 1.20 mmol) sequentially at room temperature. Proton NMR spectra of the reaction mixture were taken at different time points and the yield of the formed amide was determined based on the ratio to the internal standard (amide *ortho* protons chemical shift at 7.74 ppm; internal standard 9 CH_3 chemical shift at 1.36 ppm).

The rates of the two reactions are depicted in Chart I.



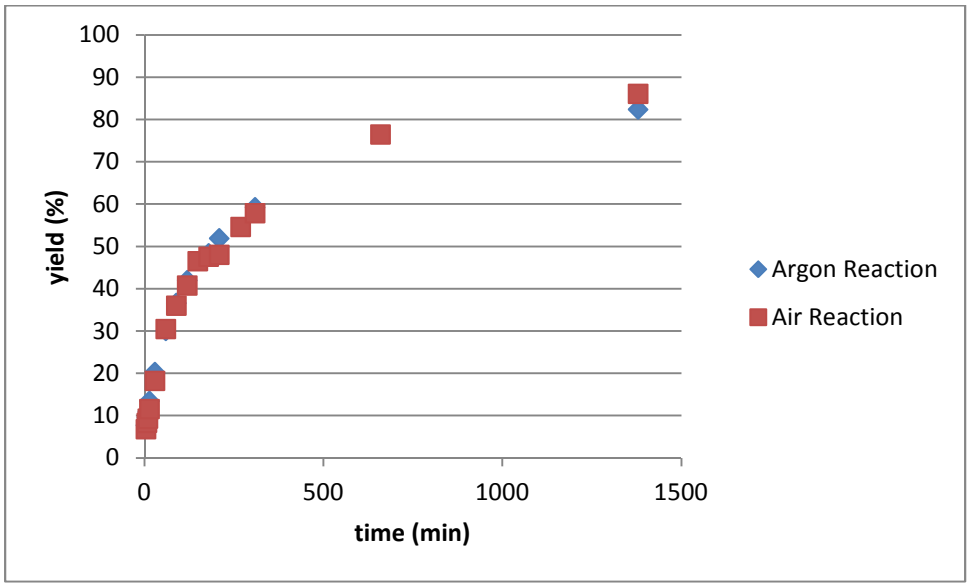


Chart I Reaction Rate Under Argon *vs.* Open to Air

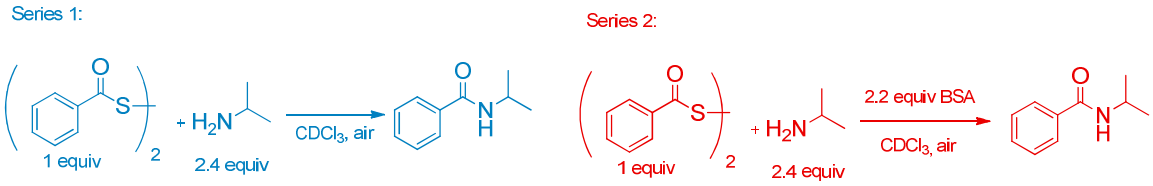
c. Bisbenzoyldisulfide Control Experiments

$CDCl_3$ Reaction of Bisbenzoyldisulfide without BSA: To a stirred solution of bisbenzoyldisulfide (80 mg, 0.29 mmol), 4,4'-di-*tert*-butyl-1,1'-biphenyl (internal standard, 18 mg, 0.065 mmol) in $CDCl_3$ (0.6 mL) was added isopropyl amine (0.061 mL, 0.70 mmol) at room temperature. Proton NMR spectra of the reaction mixture were taken at different time points and the yield of the formed amide was determined based on the ratio to the internal standard (amide *ortho* protons chemical shift at 7.74 ppm; internal standard 9 CH_3 chemical shift at 1.36 ppm).

$CDCl_3$ Reaction of Bisbenzoyldisulfide with BSA: To a stirred solution of bisbenzoyldisulfide (85 mg, 0.31 mmol), 4,4'-di-*tert*-butyl-1,1'-biphenyl (internal standard, 17 mg, 0.069 mmol) in

$CDCl_3$ (0.6 mL) were added BSA (0.084 mL, 0.34 mmol) and isopropyl amine (0.058 mL, 0.75 mmol) sequentially at room temperature. Proton NMR spectra of the reaction mixture were taken at different time points and the yield of the formed amide was determined based on the ratio to the internal standard (amide *ortho* protons chemical shift at 7.74 ppm; internal standard 9 CH_3 chemical shift at 1.36 ppm).

The rate of the two reactions was shown in Chart II.



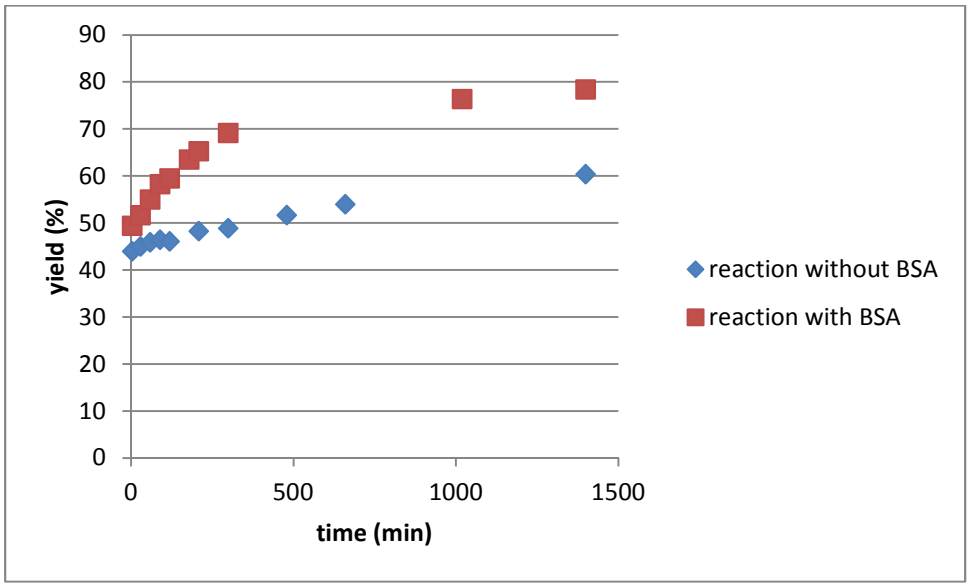
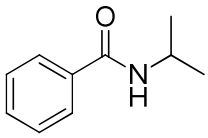


Chart II Reaction Rate of Bisbenzoyldisulfide without *vs.* with BSA

d. Isopropylbenzamide Formation, with *vs.* without BSA

***N*-**Isopropylbenzamide.[4]



Reaction with BSA: To a stirred solution of thiobenzoic acid (0.077 mL, 0.65 mmol) in THF (1.3 mL) were added BSA (0.16 mL, 0.65 mmol) and isopropyl amine (0.069 mL, 0.85 mmol) sequentially. After 3 h, the reaction was diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, it was purified by column chromatography (silica gel, 25% ethyl acetate in hexane) to give the product as a white solid (74 mg, 70% yield). R_f = 0.31, 25% EtOAc/hexanes. Mp 100-102 ^oC [Lit.[4] 101 ^oC]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 1.6 Hz, 6.8 Hz, 2H), 7.47 (tt, *J* = 1.2 Hz, 7.2 Hz, 1H), 7.42 (dt, *J* = 1.6 Hz, 7.2 Hz, 2H), 5.99 (br s, 1H), 4.28 (septet, *J* = 6.8 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 135.1, 131.4, 128.7, 127.0, 42.0, 23.0; IR (neat, cm^{-1}): 3291(m), 2970(w), 2931(w), 1630(s), 1531(s), 1346(m), 1288(m), 692(vs).

Control Reaction without BSA: To a solution of thiobenzoic acid (0.11 mL, 0.98 mmol) in THF (2 mL) was added isopropyl amine (0.10 mL, 1.27 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, the crude mixture was purified by column chromatography (silica gel, 25% ethyl acetate in hexane) to give the product as a white solid (22 mg, 14% yield).

e. Thiol Ester Control Experiments

Reaction between Thiol Ester and Amine without BSA: To a solution of thiobenzoic ethyl ester PhCOSEt (0.80 mmol) in THF (1.6 mL) was added isopropyl amine (0.085 mL, 1.04 mmol) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, ^1H NMR of the crude mixture showed trace formation of *N*-isopropylbenzamide. Purification by column chromatography (silica gel, 5% ethyl acetate in hexane) to recover PhCOSEt as a colorless oil (126 mg, 95% yield).

Reaction between Thiol Ester and Amine with BSA: To a solution of thiobenzoic ethyl ester PhCOSEt (0.78 mmol) in THF (1.6 mL) was added BSA (0.19 mL, 0.78 mmol) and isopropyl amine (0.083 mL, 1.01 mmol). Then the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, ^1H NMR of the crude mixture showed trace formation of *N*-isopropylbenzamide. Purification by column chromatography (silica gel, 5% ethyl acetate in hexane) to recover PhCOSEt as a colorless oil (125 mg, 96% yield).

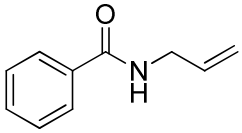
Competitive Reaction between Thiol Acid and Thiol Ester: To a solution of thiobenzoic ethyl ester PhCOSEt (0.24 mmol) and 4-methylthiobenzoic acid 4-MePhCOSH (0.24 mmol) in THF (0.6 mL) was added BSA (0.060 mL, 0.24 mmol) and isopropyl amine (0.040 mL, 0.48 mmol). Then the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, ^1H NMR of the crude mixture showed trace formation of *N*-isopropylbenzamide. Purification by column chromatography (silica gel, 5% ethyl acetate in hexanes followed by 30% ethyl acetate in hexanes) to recover PhCOSEt as a colorless oil (39.5

mg, 99% yield) and *N*-isopropyl-4-methylbenzamide as a white solid (37.4 mg, 88% yield). R_f = 0.30, 25% EtOAc/hexanes. Mp 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.01 (br s, 1H), 4.26 (septet, *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 141.8, 132.3, 129.3, 127.0, 42.0, 23.1, 21.6; IR (neat, cm^{-1}): 3303(m), 2972(w), 2931(w), 1628 (s), 1532(s), 1346(m), 1285(m), 1172(w).

3. General Procedure for the Synthesis of Simple Amides

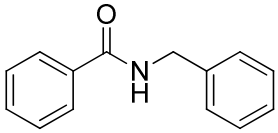
To a stirred solution of thiol acid (0.5 mmol), and BSA (0.5 mmol) in THF (1 mL) was added the amine (0.65 mmol). The reaction mixture was stirred for 3-24 h at room temperature then diluted with ethyl acetate and quenched with 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, the reaction residue was purified by chromatography to afford the desired amide.

***N*-Allylbenzamide**.[5] (Table 1 entry 1)



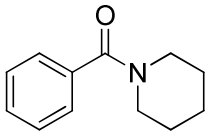
Prepared according to the general procedure, stirred at room temperature for 3 h and purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to give the product as a colorless oil (89 mg, 91% yield). R_f= 0.26, 25% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 1.6 Hz, 7.6 Hz, 2H), 7.48- 7.44 (m, 1H), 7.37 (dt, *J* = 1.2 Hz, 7.2 Hz, 2H), 6.72 (br s, 1H), 5.94-5.84 (m, 1H), 5.21 (dd, *J* = 17.2 Hz, 1.2 Hz, 1H), 5.13 (ddd, *J* = 10.0 Hz, 1.2 Hz, 1.2 Hz, 1H), 4.05-4.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 134.7, 134.4, 131.7, 128.7, 127.2, 116.7, 42.6; IR (cm^{-1}): 3305(br), 3066(w), 1634(s), 1532(vs), 1488(m), 1291(m), 692(vs).

***N*-Benzylbenzamide**.[6] (Table 1 entry 2)



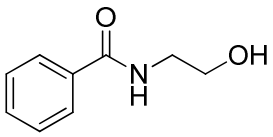
Prepared according to the general procedure, stirred at room temperature for 3 h and purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to give the product as a white solid (114 mg, 89% yield). R_f = 0.36, 25% EtOAc/hexanes. Mp 96-97 °C [Lit.[6] 98-104 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 0.8 Hz, 7.6 Hz, 2H), 7.46-7.42 (m, 1H), 7.36 -7.24 (m, 7H), 7.03 (br s, 1H), 4.54 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 138.6, 134.6, 131.7, 128.9, 128.7, 128.0, 127.7, 127.3, 44.2; IR (cm^{-1}): 3337(m), 2901(s), 2847(m), 1630(s), 1531(vs), 1450(s), 1283(s), 1001(m), 716(vs).

***N*-Benzoylpiperidine**.[7] (Table 1 entry 3)



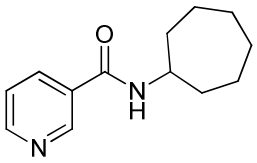
Prepared according to the general procedure, stirred at room temperature for 5 h and purified by column chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product as a colorless oil (84 mg, 74% yield). R_f = 0.40, 50% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (br s, 5H), 3.67 (br s, 2H), 3.30 (br s, 2H), 1.64-1.47 (br m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 25.8, 26.7, 43.3, 48.9, 127.0, 128.6, 129.5, 136.7, 170.5; IR (cm^{-1}): 2934(m), 2852(m), 1625(vs), 1428(s), 1273(s), 1109(m),707(s).

***N*-(2-Hydroxyethyl)benzamide**.[8] (Table 1 entry 4)



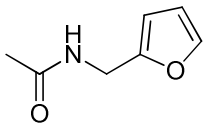
Prepared according to the general procedure, stirred at room temperature for 5 h and purified by column chromatography (silica gel, 8% methanol in dichloromethane) to give the product as a white solid (74 mg, 76% yield). R_f = 0.44, 10% MeOH/dichloromethane. Mp 58-59 °C [Lit.[8] 54-55 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.8 Hz, 1.6 Hz, 2H), 7.47-7.43 (m, 1H), 7.35 (dt, *J* = 1.6 Hz, 7.6 Hz, 2H), 7.07 (br s, 1H), 3.76-3.74 (m, 2H), 3.67 (br s, 1H), 3.57-3.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 134.3, 131.9, 128.8, 127.2, 62.1, 43.0; IR (cm^{-1}): 3302(br), 2938(w), 2876(w), 1635(s), 1537(vs), 1325(s), 1291(s), 1055(m), 1036(vs), 692(s).

***N*-Cycloheptylnicotinamide**. (Table 1 entry 5)



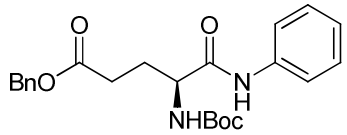
Prepared according to the general procedure, stirred at room temperature for 24 h and purified by column chromatography (silica gel, 60% ethyl acetate in hexanes) to give the product as a white solid (112 mg, 70% yield). R_f = 0.20, 75% EtOAc/hexanes. Mp 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.66-8.63 (m, 1H), 8.06 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 7.33 (dd, *J* = 4.8 Hz, 8.0 Hz, 1H), 6.32 (br s, 1H), 4.14-4.12 (m, 1H), 2.04-1.99 (m, 2H), 1.68-1.51 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 152.1, 148.1, 135.3, 130.9, 123.6, 51.4, 35.3, 28.2, 24.3; IR (cm^{-1}): 3317(m), 2930(s), 2859(m), 1630(vs), 1532(vs), 1322(m), 1026(m), 828(m), 709(vs), 672(s); HRMS (APCI$^+$) Calcd for $C_{13}H_{19}N_2O$ $[M+H]^+$: 219.1492. Found: 219.1495.

***N*-(Furan-2-ylmethyl)acetamide**.[9] (Table 1 entry 6)



Prepared according to the general procedure, stirred at room temperature for 3 h and purified by column chromatography (silica gel, 50% ethyl acetate in hexanes) to give the product as a yellow oil (114 mg, 82% yield). R_f = 0.25, 75% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.26 (m, 1H), 6.79 (br s, 1H), 6.24-6.23 (m, 1H), 6.14-6.12 (m, 1H), 4.31 (d, *J* = 5.6 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 151.6, 142.2, 110.6, 107.5, 36.6, 23.1; IR (cm^{-1}): 3271(br), 3079(w), 1649(vs), 1545(vs), 1286(s), 1147(m), 1017(m), 734(s).

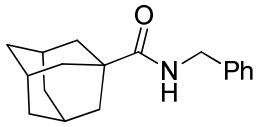
***N*-Phenyl-*N*-α-*tert*-butoxycarbonyl- γ-*tert*-benzyl ester L-glutamide**. (Table 1 entry 7)



Prepared according to the general procedure, stirred at room temperature for 24 h and purified by column chromatography (silica gel, 25% ethyl acetate in hexane) to give the product as a white solid (85 mg, 69% yield, HPLC of the crude reaction mixture showed no detectable epimerization). R_f = 0.38, 25% EtOAc/hexanes. Mp 101-104 °C; $[\alpha]^{20}_D$ -19.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.37-7.32 (m, 5H), 7.26 (t, *J* = 7.2 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 5.63 (d, *J* = 2.8 Hz, 1H), 5.11 (AB quartet, *J* = 12.4 Hz, 2H), 4.40 (br s, 1H), 2.65-2.49 (m, 2H), 2.23 (app sextet, *J* = 6.8 Hz, 1H), 2.06 (app sextet, *J* = 7.2 Hz, 1H), 1.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 170.3, 156.4, 137.9, 135.8, 129.1, 128.8, 128.6, 128.5, 124.6, 120.2, 80.6, 66.9, 54.6, 30.8, 28.5, 27.9; IR (cm^{-1}): 3315(m), 3313(m), 2977(w), 2928(w), 1723(s), 1686(m), 1666(vs), 1516(vs), 1445(s), 1157(vs), 1072(m), 754(s); HRMS (ESI^+) Calcd for $C_{23}H_{28}N_2O_5$ $[M+Na]^+$: 435.1890. Found: 435.1895.

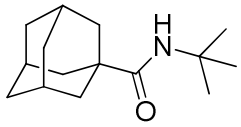
HPLC OJ-RH column: 50% acetonitrile in water over 20 min with a flow rate of 0.75 mL/min and 254 nm UV detection, retention time = 8.03 min (Boc-DL-Glu(OBn)-NH-Ph with retention times of 8.39 min and 10.51 min).

***N*-Benzyladamantane-1-carboxamide**.[10] (Table 1 entry 8)



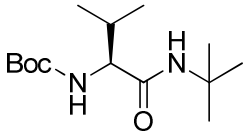
Prepared according to the general procedure, stirred at room temperature for 5 h and purified by column chromatography (silica gel, 20% ethyl acetate in hexanes) to give the product as a white solid (84 mg, 65% yield). R_f = 0.40, 25% EtOAc/hexanes. Mp 168-170 °C [Lit.[10] 172-173 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.29-7.24 (m, 3H), 5.89 (br s, 1H), 4.43 (d, *J* = 5.2 Hz, 2H), 2.04 (br m, 3H), 1.92-1.83 (m, 6H), 1.76-1.68 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 138.9, 128.9, 127.9, 127.6, 43.5, 40.9, 39.5, 36.7, 28.3; IR (cm^{-1}): 3336(m), 2901(s), 2847(s), 1631(s), 1530(vs), 1450(s), 1283(s), 1001(m), 716(s), 659(s).

***N*-(*tert*-Butyl)adamantane-1-carboxamide**.[11] (Table 1 entry 9)



Prepared according to the general procedure, stirred at room temperature for 23 h and purified by column chromatography (silica gel, 15% ethyl acetate in hexanes) to give the product as a white solid (78 mg, 81% yield). R_f = 0.64, 25% EtOAc/hexanes. Mp 175-178 °C [Lit.[11] 188-189 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (br s, 1H), 2.01 (br s, 3H), 1.81-1.78 (m, 6H), 1.73-1.64 (m, 6H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 50.7, 41.1, 39.6, 36.7, 29.0, 28.4; IR (cm^{-1}): 3328(m), 2899(vs), 2849(s), 1635(vs), 1533(vs), 1446(s), 1286(s), 1229(m), 637(m).

***N*-*tert*-Butoxycarbonyl-L-valyl-*tert*-butamide**.[12] (Table 1 entry 10)



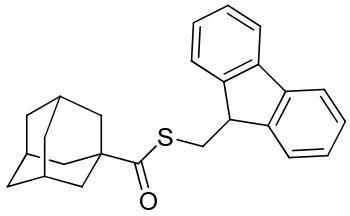
Prepared according to the general procedure, stirred at room temperature for 24 h and purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to give the product as a white solid (58 mg, 71% yield, HPLC of the crude reaction mixture showed no detectable epimerization). R_f = 0.54, 33% EtOAc/hexanes. Mp 118-120 °C [Lit.[12] 120-121 °C]; $[\alpha]^{20}_D$ -18.9 (*c* 1.0, MeOH) [Lit. $[\alpha]^{25}_D$ -19.0 (*c* 1.0, MeOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (br s, 1H), 5.07 (d, *J* = 6.8 Hz, 1H), 3.70 (dd, *J* = 6.8 Hz, 8.4 Hz, 1H), 2.08-2.00 (m, 1H), 1.43 (s, 9H), 1.33 (s, 9H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 156.2, 79.9, 60.7, 51.6, 31.3, 28.9, 28.5, 19.5, 18.2; IR (cm^{-1}): 3297(br), 2968(w), 2931(w), 1683(m), 1650(vs), 1530(s), 1363(m), 1251(m), 1171(s), 1019(m).

HPLC AS-RH column: 25% acetonitrile in water over 20 min with a flow rate of 0.75 mL/min and 210 nm UV detection, retention time = 12.54 min (Boc-DL-Val-NH-$C(CH_3)_3$ with retention times of 12.21 min and 14.42 min).

4. General Procedure for the Synthesis of 9-Fluorenylmethyl Thioesters of Amino Acids

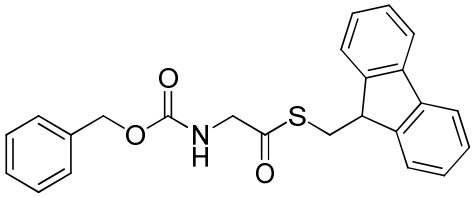
To the 2.0 M solution of 1-adamantanecarboxylic acid (1 equiv) or *N-tert*-butoxycarbonyl-α-amino acid (1 equiv), 9-fluorenylmethylthiol (1.2 equiv) and DMAP (0.1 equiv) in dichloromethane, was added a 2.0 M solution of DCC (1.1 equiv) in dichloromethane at 0 °C. The suspension was allowed to stir at 0 °C for one hour and then overnight at room temperature. The white solid was removed by filtration and washed with dichloromethane. The filtrate was concentrated under vacuum and purified by chromatography to afford the corresponding 9-fluorenylmethyl thioesters.

Adamantane 9-fluorenylmethyl thioester.



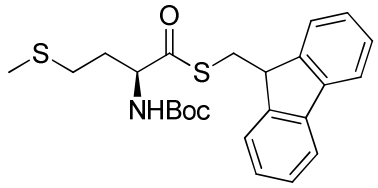
repared according to the general procedure and purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to give the product as a colorless foam (202 mg, 90% yield). R_f = 0.71, 16% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.0 Hz, 2H), 7.30 (dt, *J* = 1.2 Hz, 7.4 Hz, 2H), 4.12 (t, *J* = 6.0 Hz, 1H), 3.44 (d, *J* = 6.0 Hz, 2H), 2.02 (br m, 3H), 1.85-1.84 (m, 6H), 1.74-1.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 146.0, 141.3, 127.8, 127.2, 125.0, 120.0, 48.7, 47.3, 39.4, 36.6, 31.7, 28.4; IR (cm^{-1}): 2902(s), 2848(m), 1671(s), 1449(s), 1139(w), 987(w), 737(vs); HRMS (ESI^+) Calcd for $C_{25}H_{27}OS$ $[M+H]^+$: 375.1777. Found: 375.1779.

***N*-Benzyloxycarbonyl-glycine 9-fluorenylmethyl thioester**.



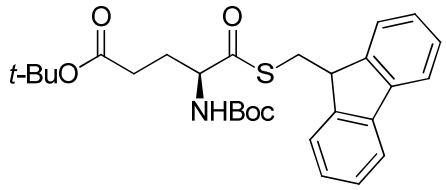
Prepared according to the general procedure and purified by column chromatography (silica gel, 15% ethyl acetate in hexanes) to give the product as colorless foam (309 mg, 93% yield). R_f = 0.22, 16% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.42-7.30 (m, 9H), 5.32 (t, *J* = 6.0 Hz, 1H), 5.13 (s, 2H), 4.17 (t, *J* = 5.8 Hz, 1H), 4.05 (d, *J* = 6.0 Hz, 2H), 3.55 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 156.3, 145.4, 141.3, 136.3, 128.8, 128.5, 128.4, 128.0, 127.4, 124.9, 120.2, 67.5, 50.9, 46.8, 32.3; IR (cm^{-1}): 3325(br), 3034(w), 2927(w), 1688(vs), 1509(m), 1448(m), 1235(s), 1156(m), 960(m), 736(vs), 696(m); HRMS (ESI^+) Calcd for $C_{24}H_{21}NO_3S$ $[M+Na]^+$: 426.1134. Found: 426.1143.

***N-tert*-Butoxycarbonyl-L-methioine 9-fluorenylmethyl thioester**.



Prepared according to the general procedure and purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to give the product as a white solid (323 mg, 97% yield). R_f = 0.37, 16% EtOAc/hexanes. Mp 88-90 °C; $[\alpha]^{20}_D$ -35.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.30 (ddt, *J* = 1.2 Hz, 2.4 Hz, 7.6 Hz, 2H), 5.06 (d, *J* = 8.8 Hz, 1H), 4.37 (app dt, *J* = 5.2 Hz, 8.0 Hz, 1H), 4.19 (t, *J* = 5.4 Hz, 1H), 3.60 (dd, *J* = 5.6 Hz, 14.0 Hz, 1H), 3.54 (dd, *J* = 5.8 Hz, 13.4 Hz, 1H), 2.35-2.32 (m, 2H), 2.03 (s, 3H), 1.94-1.86 (m, 1H), 1.72-1.63 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 155.2, 145.3, 141.4, 128.0, 127.3, 124.9, 120.1, 80.6, 60.1, 46.9, 32.2, 32.1, 29.9, 28.5, 15.6; IR (cm^{-1}): 3350(w), 2971(w), 2918(w), 1675(vs), 1504(s), 1446(m), 1364(m), 1250(m), 1159(m), 860(w), 734(vs); HRMS (ESI^+) Calcd for $C_{24}H_{29}NO_3S_2$ $[M+Na]^+$: 466.1481. Found: 466.1490.

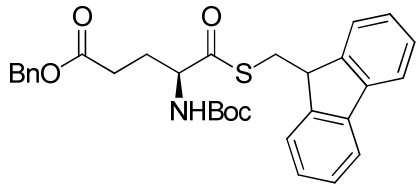
***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-butyl ester L-glutamine 9-fluorenylmethyl thioester**.



Prepared according to the general procedure and purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to give the product as a white solid (314 mg, 97% yield). R_f = 0.45, 16% EtOAc/hexanes. Mp 94-96 °C; $[\alpha]^{23}_D$ -32.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.29 (ddt, *J* = 1.2 Hz, 2.4 Hz,

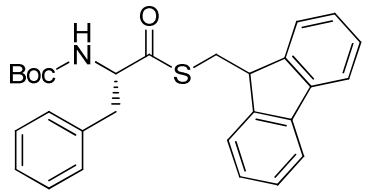
7.6 Hz, 2H), 5.20 (d, *J* = 8.0 Hz, 1H), 4.26 (dt, *J* = 4.8 Hz, 8.4 Hz, 1H), 4.16 (t, *J* = 5.8 Hz, 1H), 3.54 (dd, *J* = 5.6 Hz, 13.6 Hz, 1H), 3.48 (dd, *J* = 6.0 Hz, 13.2 Hz, 1H), 2.21-2.16 (m, 2H), 1.98-1.89 (m, 1H), 1.78-1.69 (m, 1H), 1.45 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 172.4, 155.4, 145.5, 141.4, 127.9, 127.3, 125.0, 120.1, 81.1, 80.4, 60.6, 46.9, 32.2, 31.7, 28.5, 28.3, 27.5; IR (cm^{-1}): 3303(br), 2976(w), 2930(w), 1719(vs), 1693(vs), 1524(m), 1448(m), 1366(m), 1248(s), 1147(vs), 1022(m), 736(vs); HRMS (ESI^+) Calcd for $C_{28}H_{35}NO_5S$ $[M+Na]^+$: 520.2128. Found: 520.2134.

***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-benzyl ester L-glutamine 9-fluorenylmethyl thioester**.



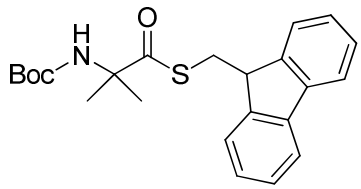
Prepared according to the general procedure and purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to give the product as a white solid (419 mg, 96% yield). R_f = 0.39, 16% EtOAc/hexanes. Mp 108-110 °C; $[\alpha]^{20}_D$ -24.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.36-7.26 (m, 9H), 5.11 (s, 2H), 5.09 (br s, 1H), 4.28 (dd, *J* = 8.0 Hz, 13.2 Hz, 1H), 4.17 (t, *J* = 5.2 Hz, 1H), 3.57 (dd, *J* = 5.0 Hz, 13.4 Hz, 1H), 3.52 (dd, *J* = 6.4 Hz, 14.4 Hz, 1H), 2.34-2.21 (m, 2H), 2.03-1.94 (m, 1H), 1.80-1.71 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 172.8, 155.3, 145.3, 141.4, 135.9, 128.8, 128.6, 128.5, 128.0, 127.3, 124.9, 120.1, 80.6, 66.8, 60.2, 46.9, 32.1, 30.3, 28.5, 27.7; IR (cm^{-1}): 3348(br), 2930(w), 1718(s), 1678(vs), 1499(s), 1447(m), 1250(m), 1164(s), 1148(s), 1080(m), 734(vs), 698(s), 622; HRMS (ESI^+) Calcd for $C_{31}H_{33}NO_5S$ $[M+Na]^+$: 554.1972. Found: 554.1978.

***N*-*tert*-Butoxycarbonyl-L-phenylalanine 9-fluorenylmethyl thioester**.



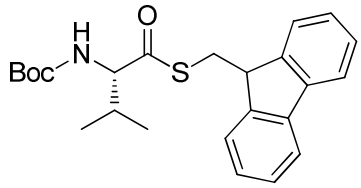
To a stirred solution of *N*-(tert-butoxycarbonyl)-L-phenylalanine (133 mg, 0.50 mmol), 9-fluorenyl-methylthiol (127 mg, 0.60 mmol) in DMF (5 mL) were added (benzotriazol-1-yloxy)tripyrrolidino phosphonium hexafluorophosphate (PyBop, 390 mg, 0.75 mmol) and diisopropylethylamine (DIEA, 162 mg, 1.25 mmol) at 0 ^{o}C sequentially. The reaction mixture was stirred at 0 °C for 30 min and warmed up to room temperature and stirred for 2.5 h. The reaction solution was washed with water and brine, dried with anhydrous Na_2SO_4, filtrated and then concentrated under reduced pressure. Purification by column chromatography (silica gel, 5% ethyl acetate in hexanes) to give the product as a colorless foam (225 mg, 98% yield). R_f = 0.45, 16% EtOAc/hexanes. $[\alpha]^{20}_{D}$ -35.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.27-7.23 (m, 3H), 7.07 (d, *J* = 6.4 Hz, 2H), 4.82 (d, *J* = 8.4 Hz, 1H), 4.58 (app dt, *J* = 6.0 Hz, 8.0 Hz, 1H), 4.17 (t, *J* = 5.8 Hz, 1H), 3.51 (d, *J* = 6.0 Hz, 2H), 3.00 (dd, *J* = 5.2 Hz, 14.4 Hz, 1H), 2.87 (dd, *J* = 7.8 Hz, 14.4 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 155.2, 145.6, 145.5, 141.3, 135.9, 129.5, 128.9, 127.9, 127.3, 125.1, 120.1, 80.6, 61.3, 46.8, 38.4, 32.6, 28.5; IR (cm^{-1}): 3338(w), 2976(w), 2928(w), 1681(s), 1494(m), 1449(m), 1365(m), 1247(m), 1160(s), 738(vs), 697(m); HRMS (ESI^+) Calcd for $C_{28}H_{29}NO_3S$ $[M+Na]^+$: 482.1760. Found: 482.1774.

***N-tert*-Butoxycarbonyl-α-aminoisobutyryl 9-fluorenylmethyl thioester**.[13]



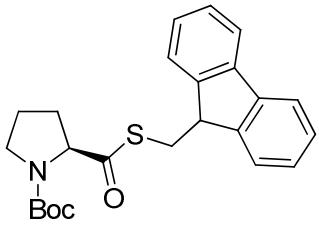
Prepared according to the general procedure and purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to give the product as a colorless foam (195 mg, 98% yield). R_f = 0.46, 16% EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.30 (app dt, *J* = 0.8 Hz, 7.6 Hz, 2H), 4.93 (s, 1H), 4.18 (t, *J* = 5.6 Hz, 1H), 3.50 (d, *J* = 5.6 Hz, 2H), 1.42 (s, 9H), 1.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 154.2, 145.8, 141.4, 127.8, 127.2, 125.1, 120.0, 80.3, 62.3, 47.2, 32.4, 28.6, 25.7; IR (cm^{-1}): 3351(br), 2977(w), 2929(w), 1690(vs), 1493(m), 1449(s), 1250(s), 1156(vs), 1077(s), 982(s), 739(vs).

***N-tert*-Butoxycarbonyl-L-valine 9-fluorenylmethyl thioester**.[13]



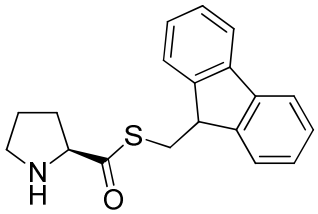
Prepared according to the general procedure and purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to give the product as a colorless foam (265 mg, 99% yield). R_f = 0.49, 16% EtOAc/hexanes. $[\alpha]^{20}_D$ -36.8 (*c* 1.0, $CHCl_3$) [Lit.[13] $[\alpha]^{23}_D$ -37.6 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.32-7.28 (m, 2H), 4.91 (d, *J* = 8.8 Hz, 1H), 4.21 (dd, *J* = 4.6 Hz, 9.2 Hz, 1H), 4.17 (t, *J* = 5.8 Hz, 1H), 3.59-3.51 (m, 2H), 2.15-2.05 (m, 1H), 1.45 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 155.7, 145.5, 141.4, 127.9, 127.3, 124.9, 120.1, 80.4, 65.6, 46.9, 32.1, 31.2, 28.5, 19.6, 16.9; IR (cm^{-1}): 3341(br), 2967(w), 2929(w), 1681(vs), 1492(s), 1448(s), 1365(s), 1249(m), 1160(vs), 999(m), 738(vs).

***N-tert*-Butoxycarbonyl-L-proline 9-fluorenylmethyl thioester**.[13]



Prepared according to the general procedure and purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to give the product as a white solid (244 mg, 96% yield, with a 5 : 9 ratio of two rotamers). R_f = 0.34, 16% EtOAc/hexanes. Mp 92-94 °C; $[\alpha]^{20}_D$ -92.3 (*c* 1.0, $CHCl_3$) [Lit.[13] $[\alpha]^{20}_D$ -72.9 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 2H), 7.65-7.60 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.31-7.28 (m, 2H), 4.39 (dd, *J* = 2.0 Hz, 8.4 Hz, 0.36H), 4.27-4.25 (dd, *J* = 2.8 Hz, 9.2 Hz, 0.64H), 4.17 (t, *J* = 5.6 Hz, 1H), 3.64-3.27 (m, 4H), 2.07-1.97 (m, 1H), 1.76-1.60 (m, 3H), 1.47 (s, 3.21H), 1.33 (s, 5.79H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 201.9, 154.7, 154.1, 145.8, 145.6, 145.5, 145.4, 141.5, 141.4, 127.9, 127.8, 127.3, 127.2, 127.1, 125.2, 125.1, 124.9, 124.8, 120.0, 119.9, 80.6, 80.4, 66.4, 66.1, 47.1, 47.0, 46.7, 31.9, 31.7, 31.6, 30.8, 28.7, 28.5, 24.1, 23.3; IR (cm^{-1}): 3037(w), 2975(w), 2926(w), 1689(vs), 1670(vs), 1446(m), 1386(s), 1363(s), 1162(m), 1099(m), 863(m), 751(m), 736(m).

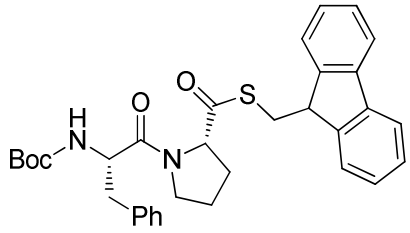
NH-L-Proline 9-fluorenylmethyl thioester.



N-tert-butoxycarbonyl-L-proline 9-fluorenylmethyl thioester (123 mg, 0.30 mmol) was dissolved in 40% TFA in dichloromethane (7 mL) and stirred at room temperature for 10 min. Dichloromethane was removed under vacuum and the residue was dissolved in ethyl acetate. The organic layer was washed with 20% aqueous sodium carbonate solution and brine. After drying

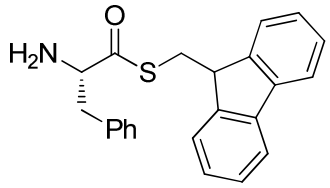
with anhydrous Na_2SO_4, the organic layer was filtrated and concentrated under reduced pressure to afford the free amine, which was applied immediately in the next step.

***N-tert*-Butoxycarbonyl-L-phenylalanyl-L-proline 9-fluorenylmethyl thioester**.



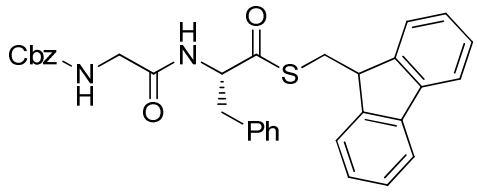
To a stirred solution of Boc-L-Phe-OH (103 mg, 0.39 mmol), freshly prepared NH-L-Pro-SFm (0.3 mmol) in DMF (3 mL) was added PyBop (234 mg, 0.45 mmol) and DIEA (0.12 mL, 0.75 mmol) at 0 ^{o}C sequentially. The reaction mixture was stirred at 0 °C for 30 min and warmed up to room temperature and stirred for 2.5 h. The reaction solution was washed with water and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated under reduced pressure. Purification by column chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product as a colorless foam (147 mg, 88% yield, with a 3 : 1 ratio of rotamer). R_f = 0.46, 33% EtOAc/hexanes. $[\alpha]^{20}_{D}$ -80.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.68 (m, 2H), 7.60-7.53 (m, 2H), 7.39-7.17 (m, 9H), 5.27 (d, *J* = 8.0 Hz, 0.74H), 4.98 (d, *J* = 7.8 Hz, 0.26H), 4.64-4.57 (m, 2H), 4.20 (t, *J* = 5.4 Hz, 0.74H), 4.10 (t, *J* = 5.4 Hz, 0.26H), 3.62-3.55 (m, 2H), 3.44-3.18 (m, 2H), 3.10-2.94 (m, 1H), 2.86-2.76 (m, 1H), 1.99-1.89 (m, 1H), 1.83-1.74 (m, 1H), 1.70-1.54 (m, 2H), 1.41 (s, 2.37H), 1.34 (s, 6.63H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 171.6, 155.5, 145.4, 141.5, 136.6, 129.8, 129.7, 129.6, 129.5, 129.4, 128.8, 128.7, 128.6, 127.9, 127.8, 127.3, 127.2, 127.1, 127.0, 125.0, 124.8, 120.0, 79.9, 66.1, 54.4, 53.3, 47.3, 47.2, 47.0, 38.9, 32.2, 31.8, 29.7, 28.5, 24.5; IR (cm^{-1}): 3305(br), 2975(w), 1785(w), 1694(vs), 1644(vs), 1496(m), 1447(s), 1248(m), 1163(vs), 1017(m), 742(vs), 699(s); HRMS (ESI^+) Calcd for $C_{33}H_{36}N_2O_4S$ $[M+Na]^+$: 579.2288. Found: 579.2293.

NH_2-L-Phenylalanine 9-fluorenylmethyl thioester.



Prepared according to the same procedure as NH-L-proline 9-fluorenylmethyl thioester. After drying with anhydrous Na_2SO_4 and filtration, the organic layer was concentrated under reduced pressure to afford the free amine, which was applied immediately in the next step.

***N*-Benzyloxycarbonyl-glycine-L-phenylalanine 9-fluorenylmethyl thioester**.



Prepared according to the same procedure as Boc-L-Phe-L-Pro-SFm and purified by column chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product as a colorless foam (248 mg, 90% yield). R_f = 0.58, 50% EtOAc/hexanes. $[\alpha]^{20}_D$ -30.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 6.2 Hz, 2H), 7.41-7.20 (m, 12H), 7.00 (br s, 2H), 6.30 (d, *J* = 7.6 Hz, 1H), 5.27 (br m, 1H), 5.10 (s, 2H), 4.87 (app q, *J* = 7.2 Hz, 1H), 4.15 (t, *J* = 6.0 Hz, 1H), 3.82 (dd, *J* = 5.6 Hz, 17.2 Hz, 1H), 3.76 (dd, *J* = 6.0 Hz, 16.8 Hz, 1H), 3.52 (d, *J* = 5.6 Hz, 2H), 3.00 (dd, *J* = 5.2 Hz, 14.0 Hz, 1H), 2.88 (dd, *J* = 7.2 Hz, 14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 168.8, 145.4, 141.4, 135.3, 129.4, 128.9, 128.8, 128.5, 128.3, 128.0, 127.5, 127.4, 127.3, 124.9, 124.8, 120.1, 67.5, 59.8, 46.8, 44.8, 38.4, 32.5; IR (cm^{-1}): 3292(br), 3032(w), 2927(w), 2160(w), 1666(vs), 1497(s), 1449(m), 1229(s), 1047(m), 737(s), 696(s); HRMS (ESI^+) Calcd for $C_{33}H_{30}N_2O_4S$ $[M+Na]^+$: 573.1819. Found: 573.1830.

5. General Procedure for the Synthesis of Amino Thiol acids

A solution of amino acid 9-fluorenylmethyl thioester in 40% piperidine in DMF (0.1 M solution) was stirred for 1 hour at room temperature. Then the reaction was diluted with ethyl acetate and neutralized by a 1 M HCl solution. The organic layer was washed by water and brine, then dried with anhydrous Na_2SO_4. After filtration and concentration under vacuum, the crude thiol acid was used without further purification.

6. General Procedure for the Synthesis of di- and tri Peptides

Method A: To a stirred solution of amino acid hydrochloride salt (0.33 mmol) with triethylamine (0.33 mmol) in THF (0.2 mL) was added the solution of amino thiol acid (0.25 mmol) and BSA (0.25 mmol) in THF (0.3 mL). The reaction was stirred for 8-63 h at room temperature and then diluted with ethyl acetate and quenched with a 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated on vacuum. Chromatographic purification afforded the desired peptides.

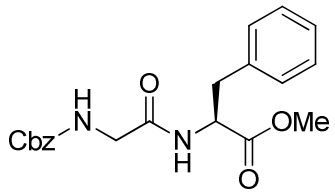
Method B: To a stirred solution of amino acid hydrochloride salt (0.33 mmol) with DIEA (0.33 mmol) in CH_3CN (0.2 mL) was added the solution of amino thiol acid (0.25 mmol) and BSA (0.25 mmol) in CH_3CN (0.3 mL). The reaction was stirred for 8-10 h at room temperature then diluted with ethyl acetate and quenched with a 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated under vacuum. Purification by column chromatography afforded the desired peptides.

Method C: To a stirred solution of amino thiol acid (0.25 mmol), $PhSiH_2Cl$ (0.28 mmol), amino acid hydrochloride salt (0.33 mmol) in CH_3CN (0.5 mL) was added DIEA (0.33 mmol) slowly. The reaction was stirred for 15 h at room temperature then diluted with ethyl acetate and quenched by a 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution

and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated under vacuum. Purification by column chromatography afforded the desired peptides.

Method D: To a stirred solution of amino thiol acid (0.25 mmol), $PhSiH_2Cl$ (0.28 mmol), amino acid hydrochloride salt (0.50 mmol) in CH_3CN (0.5 mL) was added DIEA (0.75 mmol) slowly. The reaction was stirred for 15 h at room temperature then diluted with ethyl acetate and quenched by 1M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated under vacuum. Purification by column chromatography afforded the desired peptides.

***N*-Benzyloxycarbonyl-glycyl-L-phenylalanine methyl ester**.[14] (Table 2 entry 1)

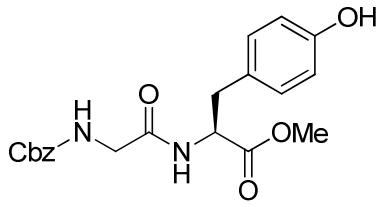


Path 1: Prepared according to Method A, stirred at room temperature for 10 h and purified by column chromatography (silica gel, 50% ethyl acetate in hexanes) to give the product as a colorless oil (87 mg, 78% yield, HPLC of the crude reaction mixture showed no detectable epimerization). R_f = 0.49, 66% EtOAc/hexanes. $[\alpha]^{20}_D$ +3.2 (*c* 1.0, DMF) [Lit.[15] $[\alpha]^{25}_D$ +2.7 (*c* 1.0, DMF)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 8H), 7.07 (d, *J* = 6.4 Hz, 2H), 6.54 (br s, 1H), 5.46 (br s, 1H), 5.11 (s, 2H), 4.87 (app dt, *J* = 6.0 Hz, 8.0 Hz, 1H), 3.87 (dd, *J* = 6.2 Hz, 17.6 Hz, 1H), 3.81 (dd, *J* = 6.0 Hz, 17.6 Hz, 1H), 3.71 (s, 3H), 3.13 (dd, *J* = 6.2 Hz, 14.2 Hz, 1H), 3.07 (dd, *J* = 6.2 Hz, 13.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 168.8, 156.7, 136.3, 135.8, 129.5, 128.8, 128.7, 128.5, 128.3, 127.4, 67.4, 53.3, 52.6, 44.6, 38.0; IR (cm^{-1}): 3306(br), 3030(w), 2951(w), 1722(vs), 1662(vs), 1516(vs), 1454(s), 1212(vs), 1176(s), 1047(s), 986(m), 739(s), 697(vs).

HPLC AS-RH column: 40% acetonitrile in water over 15 min with a flow rate of 0.7 mL/min and 210 nm UV detection, retention time = 9.70 min (Z-Gly-DL-Phe-OMe with retention times of 9.44 min and 12.07 min).

Path 2: To a stirred solution of L-phenylalanine methyl ester hydrochloride (84 mg, 0.39 mmol), Z-L-Arg-OH (92 mg, 0.30 mmol) with triethylamine (0.054 mL, 0.39 mmol) in THF (0.6 mL) were added freshly prepared Z-Gly-SH (68 mg, 0.30 mmol) and BSA (0.073 mL, 0.30 mmol) sequentially at room temperature. The reaction was stirred for 10 h at room temperature and then diluted with ethyl acetate and quenched with a 1 M HCl solution. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated on vacuum. Purification by column chromatography afforded the product Z-Gly-L-Phe-OMe (78 mg, 71% yield).

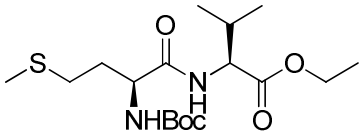
***N*-Benzyloxycarbonyl-glycyl-L-tyrosine methyl ester**. (Table 2 entry 2)



Prepared according to Method A, stirred at room temperature for 10 h and purified by column chromatography (silica gel, 50% ethyl acetate in hexanes) to give the product as a colorless oil (75 mg, 69% yield). R_f = 0.27, 66% EtOAc/hexanes. $[\alpha]^{20}_D$ +44.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 5H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.66 (d, *J* = 8.4 Hz, 2H), 6.59 (br s, 1H), 5.51 (br s, 1H), 5.11 (s, 2H), 4.83 (app dd, *J* = 5.8 Hz, 13.4 Hz, 1H), 3.87-3.77 (m, 2H), 3.73 (s, 3H), 3.05 (dd, *J* = 5.2 Hz, 14.4 Hz, 1H), 2.97 (dd, *J* = 6.4 Hz, 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 169.4, 157.0, 155.7, 136.2, 130.5, 128.8, 128.5, 128.3, 127.0, 115.9, 67.6, 53.5, 52.8, 44.5, 37.2; IR (cm^{-1}): 3306(br), 3014(w), 2952(w), 1706(s), 1660(vs), 1514(vs),

1442(s), 1216(vs), 1173(s), 1048(m), 750(s); HRMS (APCI$^+$) Calcd for $C_{20}H_{23}N_2O_6$ [M+H]$^+$: 387.1551. Found: 387.1557.

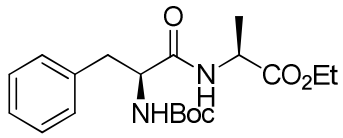
***N-tert*-Butoxycarbonyl-L-methionyl-L-valine ethyl ester**. (Table 2 entry 3)



Prepared according to Method B, stirred at room temperature for 10 h and purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to give the product as a white solid (78 mg, 83% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/DL = 99.4 : 0.6). R_f = 0.42, 33% EtOAc/hexanes. Mp 98-101 °C; $[\alpha]^{20}_D$ +4.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 7.6 Hz, 1H), 5.25 (d, *J* = 8.4 Hz, 1H), 4.48 (dd, *J* = 4.6 Hz, 8.6 Hz, 1H), 4.31 (app q, *J* = 6.8 Hz, 1H), 4.22-4.13 (m, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.22-2.14 (m, 1H), 2.01 (s, 3H), 2.08-2.01 (m, 1H), 1.98-1.89 (m, 1H), 1.42 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.6, 155.7, 80.3, 61.5, 57.4, 53.4, 31.5, 31.3, 30.3, 28.5, 19.2, 17.8, 15.3, 14.4; IR (cm^{-1}): 3303(br), 2970(m), 2932(w), 2160(w), 1743(vs), 1679(s), 1649(vs), 1531(s), 1366(s), 1293(m), 1203(s), 1148(s), 1050(m), 1025(m), 867(m); HRMS (ESI$^+$) Calcd for $C_{17}H_{32}N_2O_5S$ [M+Na]$^+$: 397.1924. Found: 399.1929.

HPLC AS-RH column: 30% acetonitrile in water over 25 min with a flow rate of 0.75 mL/min and 210 nm UV detection, retention time = 17.74 min (99.4%) and 24.73 (0.6%) (Boc-DL-Met-L-Val-OEt with retention times of 17.57 min and 24.50 min).

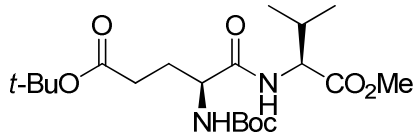
***N-tert*-Butoxycarbonyl-L-phenylalanyl-L-alanine ethyl ester**. (Table 2 entry 4)



Prepared according to Method B, stirred at room temperature for 12 h and purified by column chromatography (silica gel, 35% ethyl acetate in hexanes) to give the product as a white solid (66 mg, 72% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/LD = 99.5 : 0.5). R_f = 0.31, 33% EtOAc/hexanes. Mp 94-97 °C; $[\alpha]^{20}_D$ +3.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.19 (m, 5H), 6.51 (d, *J* = 5.2 Hz, 1H), 5.04 (d, *J* = 5.6 Hz, 1H), 4.48 (app quintet, *J* = 7.0 Hz, 1H), 4.39-4.35 (m, 1H), 4.21-4.10 (m, 2H), 3.06 (d, *J* = 6.4 Hz, 2H), 1.39 (s, 9H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 170.9, 155.6, 136.7, 129.6, 128.8, 127.1, 80.4, 61.7, 55.8, 48.4, 38.6, 28.4, 18.6, 14.3; IR (cm^{-1}): 3290(br), 2979(w), 2933(w), 2160(w), 1741(m), 1655(vs), 1530(s), 1366(m), 1159(vs), 1048(m), 1021(m), 698(m); HRMS (ESI^+) Calcd for $C_{19}H_{28}N_2O_5$ $[M+Na]^+$: 387.1890. Found: 387.1895.

HPLC AS-RH column: 30% acetonitrile in water over 15 min, 30-40% acetonitrile over 5 min, 40-50% acetonitrile over 5 min with a flow rate of 0.70 mL/min and 210 nm UV detection, retention time = 16.73 min (99.5%) and 23.58 (0.5%) (Boc-DL-Phe-L-Ala-OEt with retention times of 16.84 min and 23.88 min).

***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-butyl ester L-glutamyl-L-valine methyl ester**. (Table 2 entry 5)

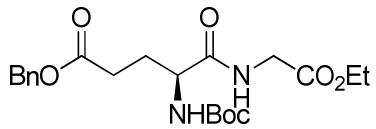


Prepared according to Method A, stirred at room temperature for 10 h and purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to give the product as a colorless oil (68 mg, 71% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/LD = 99.5 : 0.5). R_f = 0.39, 33% EtOAc/hexanes. $[\alpha]^{20}_D$ -10.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 6.90 (d, *J* = 8.0 Hz, 1H), 5.31 (d, *J* = 7.6 Hz, 1H), 4.48 (dd, *J* = 4.8 Hz, 8.8 Hz, 1H), 4.15 (app dd, *J* = 7.6 Hz, 13.2 Hz, 1H), 3.71 (s, 3H), 2.45-2.30 (m, 2H), 2.22-2.12 (m, 1H), 2.08-2.00 (m, 1H), 1.94-1.85 (m, 1H), 1.43 (s, 9H), 1.41 (s, 9H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.3, 171.9, 155.9, 81.1, 80.2, 57.4, 54.1, 52.3, 32.0, 31.2, 28.5, 28.3, 27.7, 19.2, 17.8; IR (cm^{-1}): 3309(br), 2974(w), 1727(s), 1659(s), 1520(m), 1366(s), 1250(m), 1148(vs), 1026(m); HRMS (ESI^+) Calcd for $C_{20}H_{36}N_2O_7$ $[M+Na]^+$: 439.2415. Found: 439.2422.

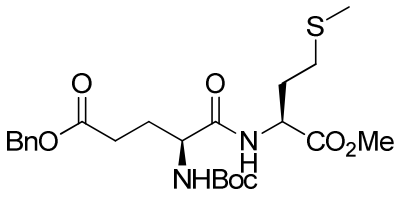
HPLC AS-RH column: 30% acetonitrile in water over 25 min then 40-100% acetonitrile over 4 min with a flow rate of 0.75 mL/min and 210 nm UV detection, retention time = 20.17 min (99.5%) and 24.65 (0.5%) (Boc-DL-Glu(O*t*Bu)-L-Val-OMe with retention times of 19.91 min and 24.22 min).

***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-benzyl ester L-glutamyl-glycine ethyl ester**. (Table 2 entry 6)



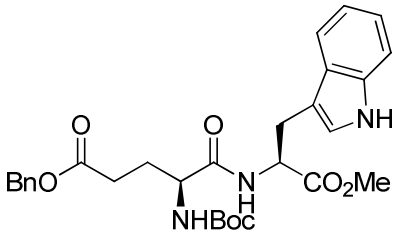
Prepared according to Method A, stirred at room temperature for 8 h and purified by column chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product as a white solid (80 mg, 76% yield). R_f = 0.51, 50% EtOAc/hexanes. Mp 80-82 °C; $[\alpha]^{20}_D$ -3.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 6.93 (br s, 1H), 5.42 (d, *J* = 5.6 Hz, 1H), 5.11 (s, 2H), 4.27 (app dd, *J* = 7.8 Hz, 13.4 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.03 (dd, *J* = 5.4 Hz, 18.2 Hz, 1H), 3.95 (dd, *J* = 5.4 Hz, 18.2 Hz, 1H), 2.59-2.44 (m, 2H), 2.21-2.12 (m, 1H), 1.99-1.91 (m, 1H), 1.41 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 172.1, 169.8, 155.9, 135.9, 128.8, 128.5, 128.4, 80.3, 66.7, 61.7, 53.7, 41.5, 30.6, 28.5, 28.2, 14.3; IR (cm^{-1}): 3285(br), 2979(w), 1735(s), 1668(s), 1649(s), 1518(s), 1367(s), 1202(s), 1159(vs), 1022(m), 746(m), 698(m); HRMS (ESI^+) Calcd for $C_{21}H_{30}N_2O_7$ $[M+Na]^+$: 445.1945. Found: 445.1949.

***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-benzyl ester L-glutamyl-L-methionine methyl ester**. (Table 2 entry 7)



Prepared according to Method A, stirred at room temperature for 10 h and purified by column chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product as a colorless oil (72 mg, 68% yield). R_f = 0.24, 33% EtOAc/hexanes. $[\alpha]^{20}_{D}$ +6.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 6.94 (d, *J* = 7.6 Hz, 1H), 5.32 (d, *J* = 7.6 Hz, 1H), 5.12 (s, 2H), 4.67 (app dt, *J* = 5.0 Hz, 7.8 Hz, 1H), 4.20 (app dd, *J* = 7.2 Hz, 13.6 Hz, 1H), 3.72 (s, 3H), 2.57-2.47 (m, 4H), 2.19-2.10 (m, 2H), 2.07 (s, 3H), 2.02-1.89 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 172.2, 171.7, 155.8, 135.9, 128.8, 128.5, 128.4, 80.4, 66.8, 53.8, 52.7, 51.7, 31.6, 30.6, 30.1, 28.5, 28.1, 15.6; IR (cm^{-1}): 3306(br), 2917(w), 1725(s), 1661(vs), 1516(s), 1444(m), 1366(s), 1213(s), 1162(vs), 1052(m), 697(m); HRMS (ESI^+) Calcd for $C_{23}H_{34}N_2O_7S$ $[M+Na]^+$: 505.1979. Found: 505.1985.

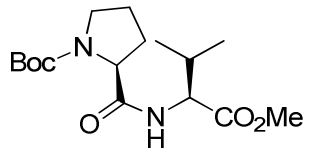
***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-benzyl ester L-glutamyl-L-tryptophan methyl ester**. (Table 2 entry 8)



Prepared according to Method A, stirred at room temperature for 8 h and purified by column chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product as a sticky oil (99

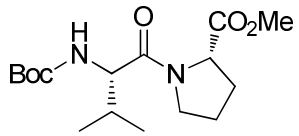
mg, 74% yield). R_f = 0.40, 50% EtOAc/hexanes. $[\alpha]^{20}_D$ +26.2 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.37-7.26 (m, 6H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.96 (s, 1H), 6.84 (br s, 1H), 5.34 (d, *J* = 6.4 Hz, 1H), 5.13-5.03 (m, 2H), 4.90 (dd, *J* = 6.4 Hz, 12.6 Hz, 1H), 4.22-4.17 (m, 1H), 3.64 (s, 3H), 3.33-3.23 (m, 2H), 2.46-2.32 (m, 1H), 2.25-2.17 (m, 1H), 2.05-1.78 (m, 1H), 1.87-1.78 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 172.4, 171.3, 155.9, 136.3, 136.0, 128.8, 128.6, 128.5, 127.5, 123.3, 122.4, 119.8, 118.6, 111.5, 109.8, 80.3, 66.7, 53.8, 52.9, 52.7, 30.4, 28.5, 28.1, 27.9; IR (cm^{-1}): 3325(br), 2931(w), 1712(vs), 1659(vs), 1501(s), 1454(m), 1365(m), 1248(s), 1160(vs), 1050(m), 740(s); HRMS (ESI^+) Calcd for $C_{29}H_{35}N_3O_7$ $[M+Na]^+$: 560.2367. Found: 560.2374.

***N-tert*-Butoxycarbonyl-L-prolyl-L-valine methyl ester.**[16] (Table 2 entry 9)



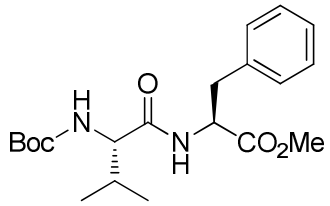
Prepared according to Method A, stirred at room temperature for 10 h and purified by column chromatography (silica gel, 33% ethyl acetate in hexanes) to give the product as a colorless oil (49 mg, 65% yield, with a 7 : 5 ratio of two rotamers). R_f = 0.30, 33% EtOAc/hexanes. $[\alpha]^{20}_D$ -88.0 (*c* 0.25, $CHCl_3$) [Lit.[16] $[\alpha]^{22}_D$ -88.4 (*c* 0.25, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (br s, 0.58H), 6.51 (br s, 0.42H), 4.49-4.44 (m, 1H), 4.32-4.24 (m, 1H), 3.69 (s, 3H), 3.45-3.30 (m, 2H), 2.18-2.19 (m, 2H), 1.91-1.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 156.1, 154.9, 80.5, 61.4, 59.8, 57.4, 52.2, 47.2, 31.5, 31.3, 28.5, 27.7, 24.9, 23.9, 19.2, 17.8; IR (cm^{-1}): 3305(w), 2968(w), 2876(w), 1742(m), 1692(vs), 1662(vs), 1547(m), 1397(s), 1364(m), 1158(s), 1118(m), 1011(w), 773(w); HRMS (ESI^+) Calcd for $C_{16}H_{28}N_2O_5$ $[M+Na]^+$: 351.1890. Found: 351.1894.

***N-tert*-Butoxycarbonyl-L-valyl-L-proline methyl ester.**[17] (Table 2 entry 10)



Prepared according to Method A, stirred at room temperature for 48 h and purified by column chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product as a colorless oil (55 mg, 70% yield, with a 7 : 1 ratio of two rotamers). R_f = 0.20, 33% EtOAc/hexanes. $[\alpha]^{20}_D$ -73.7 (*c* 1.0, $CHCl_3$) [Lit.[17] $[\alpha]^{25}_D$ -73.8 (*c* 1.51, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (d, *J* = 8.8 Hz, 1H), 4.50 (dd, *J* = 4.8 Hz, 8.4 Hz, 0.88H), 4.40 (dd, *J* = 3.4 Hz, 8.2 Hz, 0.12H), 4.30 (dd, *J* = 6.2 Hz, 9.4 Hz, 0.12H), 4.26 (dd, *J* = 6.2 Hz, 9.4 Hz, 0.88H), 3.79 -3.73 (m, 1H), 3.70 (s, 3H), 3.66-3.06 (m, 1H), 2.23-2.17 (m, 1H), 2.06-1.91 (m, 4H), 1.40 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.4, 156.1, 79.6, 58.9, 57.0, 52.4, 47.3, 46.4, 31.6, 31.5, 29.4, 29.2, 28.5, 25.2, 24.9, 19.5, 17.6; IR (cm^{-1}): 3306(br), 2972(w), 1745(s), 1703(s), 1639(vs), 1499(m), 1431(vs), 1365(m), 1164(vs), 1015(s).

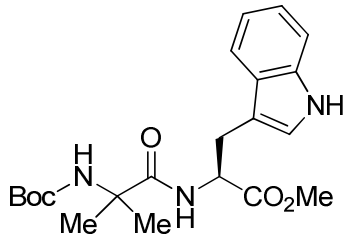
***N-tert*-Butoxycarbonyl-L-valyl-L-phenylalanine methyl ester.**[18] (Table 2 entry 11)



Prepared according to Method A, stirred at room temperature for 63 h and purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to give the product as a white solid (56 mg, 67% yield). R_f = 0.41, 33% EtOAc/hexanes. Mp 96-100 °C [Lit.[18] mp 101 °C]; $[\alpha]^{20}_D$ +38.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.20 (m, 3H), 7.09 (dd, *J* = 1.6 Hz, 8.0 Hz, 2H), 6.40 (br s, 1H), 5.05 (d, *J* = 6.0 Hz, 1H), 4.85 (app dd, *J* = 6.0 Hz, 13.6 Hz, 1H), 3.90 (t, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 3.11 (dd, *J* = 5.8 Hz, 13.6 Hz, 1H), 3.06 (dd, *J* = 5.8 Hz, 13.6 Hz, 1H), 2.09-2.02 (m, 1H), 1.42 (s, 9H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100

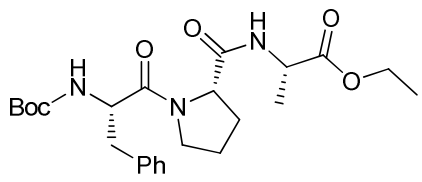
MHz, $CDCl_3$) δ 171.9, 171.5, 155.9, 135.9, 129.4, 128.8, 127.4, 80.0, 60.1, 53.3, 52.5, 38.2, 31.1, 28.5, 19.4, 17.9; IR (cm^{-1}): 3351(br), 3291(br), 2966(w), 2927(w), 1745(s), 1688(vs), 1655(vs), 1503(s), 1163(vs), 1017(s), 880(m), 699(s).

***N-tert*-Butoxycarbonyl-α-aminoisobutyryl-L-tryptophan methyl ester.**[13] (Table 2 entry 12)



Prepared according to Method A, stirred at room temperature for 54 h and purified by column chromatography (silica gel, 40% ethyl acetate in hexanes) to give the product as a colorless oil (66 mg, 74% yield). R_f = 0.30, 50% EtOAc/hexanes. $[\alpha]^{20}_D$ +35.7 (*c* 1.0, $CHCl_3$) [Lit.[13] $[\alpha]^{22}_D$ +37.2 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.01 (s, 1H), 6.89 (br s, 1H), 5.00 (s, 1H), 4.88 (app dt, *J* = 5.6 Hz, 7.2 Hz, 1H), 3.62 (s, 3H), 3.33 (dd, *J* = 6.0 Hz, 15.4 Hz, 1H), 3.27 (dd, *J* = 6.0 Hz, 15.4 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 172.7, 154.8, 136.3, 127.8, 123.3, 122.3, 119.6, 118.7, 111.5, 110.0, 56.9, 53.3, 52.5, 28.5, 27.9, 25.8; IR (cm^{-1}): 3324(br), 2979(w), 1693(s), 1659(s), 1503(s), 1438(m), 1364(s), 1250(s), 1159(vs), 1075(s), 741(vs).

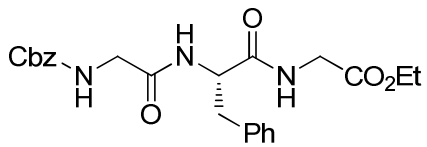
***N-tert*-Butoxycarbonyl-L-phenylalanyl-L-prolyl-L-alanine ethyl ester**. (Table 2 entry 13)



Prepared according to Method C, stirred at room temperature for 8 h and purified by column chromatography (silica gel, 50% ethyl acetate in hexanes) to give the product as a colorless oil (57 mg, 62% yield, with a 3 : 1 ratio of rotamers. HPLC of the crude reaction mixture showed the epimerization ratio LLL/LDL = 99.5 : 0.5). R_f = 0.46, 75% EtOAc/hexanes. $[\alpha]^{20}_D$ -34.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.0 Hz, 0.25H), 7.32-7.18 (m, 5.75H), 5.32 (d, *J* = 8.4 Hz, 0.75H), 5.12 (d, *J* = 5.2 Hz, 0.25H), 4.63 (app q, *J* = 7.4 Hz, 0.75H), 4.54 (app d, *J* = 4.8 Hz, 0.75H), 4.47 (app quintet, *J* = 7.2 Hz, 2.50H), 4.39 (app q, *J* = 7.2 Hz, 0.25H), 4.19 (dq, *J* = 2.2 Hz, 7.2 Hz, 1.50H), 4.09 (dq, *J* = 2.0 Hz, 7.2 Hz, 0.50H),3.56-3.41 (m, 2H), 3.03 (app dd, *J* = 7.4 Hz, 13.4 Hz, 1H), 2.92 (app dd, *J* = 6.4 Hz, 12.0 Hz, 1H), 2.31-2.27 (m, 1H), 1.98-1.79 (m, 3H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.38 (s, 9H), 1.27 (dt, *J* = 2.4 Hz, 7.0 Hz, 2.25H), 1.19 (dt, *J* = 2.0 Hz, 7.4 Hz, 0.75H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.0, 171.3, 171.1, 170.4, 155.8, 155.3, 136.4, 135.8, 129.7, 129.6, 129.1, 128.7, 127.7, 127.2, 80.3, 79.9, 77.5, 61.6, 60.8, 60.1, 54.4, 53.5, 48.7, 48.6, 47.5, 46.9, 39.6, 39.1, 30.9, 28.5, 27.3, 25.3, 22.2, 18.3, 17.0, 14.4; IR (cm^{-1}): 3306(br), 2977(w), 1688(s), 1638(vs), 1525(s), 1444(s), 1366(s), 1160(vs), 1019(m), 700(m); HRMS (ESI^+) Calcd for $C_{24}H_{35}N_3O_6$ $[M+Na]^+$: 484.2418. Found: 484.2422.

HPLC AS-RH column: 30% acetonitrile in water over 20 min with a flow rate of 0.70 mL/min and 210 nm UV detection, retention time = 10.98 min (99.5%) and 13.61 (0.5%) (Boc-L-Phe-DL-Pro-L-Ala-OEt with retention times of 10.83 min and 13.52 min).

***N*-Benzyloxycarbonyl-glycyl-L-phenylalanyl-glycine ethyl ester**.[19] (Table 2 entry 14)



Prepared according to Method D, stirred at room temperature for 15 h and purified by column chromatography (silica gel, 60% ethyl acetate in hexanes) to give the product as a colorless oil

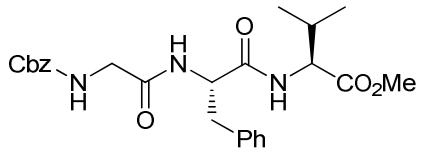
(64 mg, 73% yield, HPLC of the crude reaction mixture showed the epimerization ratio L/D = 97 : 3). R_f = 0.16, 66% EtOAc/hexanes. $[\alpha]^{20}_D$ -13.5 (*c* 2.0, EtOH) [Lit.[20] $[\alpha]^{25}_D$ -12.4 (*c* 2.0, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.15 (m, 11H), 7.03 (br s, 1H), 5.79 (br m, 1H), 5.07 (s, 2H), 4.82 (app q, *J* = 6.8 Hz, 1H), 4.12 (q, *J* = 6.8 Hz, 2H), 3.96 (dd, *J* = 5.2 Hz, 18.0 Hz, 1H), 3.86-3.76 (m, 3H), 3.10 (dd, *J* = 6.4 Hz, 13.6 Hz, 1H), 3.00 (dd, *J* = 7.6 Hz, 13.2 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 169.8, 169.6, 156.9, 136.6, 136.4, 129.5, 128.7, 128.4, 128.3, 127.2, 67.4, 61.7, 54.4, 44.6, 41.5, 38.4, 14.3; IR (cm^{-1}): 3292(br), 3065(w), 2935(w), 1723(s), 1649(vs), 1525(s), 1201(s), 1027(s), 739(m), 697(s); HRMS (ESI^+) Calcd for $C_{23}H_{27}N_3O_6$ $[M+Na]^+$: 464.1792. Found: 464.1798.

HPLC OD-RH column: 30% acetonitrile in water over 15 min, 30-40% acetonitrile over 5 min, then 40-50% acetonitrile over 5 min with a flow rate of 0.70 mL/min and 210 nm UV detection, retention time = 25.01 min (3%) and 26.47 min (97%) (Z-Gly-DL-Phe-Gly-OEt with retention times of 24.87 min and 26.39 min).

Path 2: Prepared according to Method B, stirred at room temperature for 15 h and purified by column chromatography (silica gel, 60% ethyl acetate in hexanes) to give the product as a sticky oil (53 mg, 80% yield, HPLC of the crude reaction mixture showed the epimerization ratio L/D = 96.2 : 3.8).

Path 3: Prepared according to Method C, stirred at room temperature for 15 h and purified by column chromatography (silica gel, 60% ethyl acetate in hexanes) to give the product as a sticky oil (55 mg, 60% yield, HPLC of the crude reaction mixture showed the epimerization ratio L/D = 96.8 : 3.2).

***N*-Benzyloxycarbonyl-glycyl-L-phenylalanyl-L-valine methyl ester**.[21] (Table 2 entry 15)

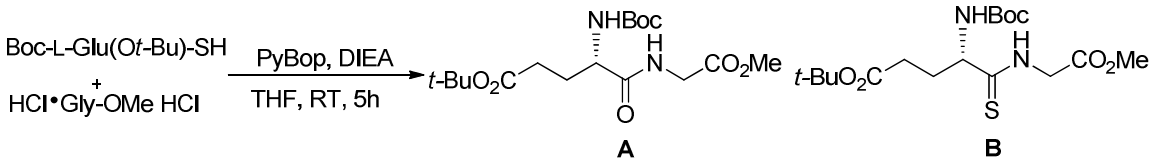


Path 1: Prepared according to Method D, stirred at room temperature for 15 h and purified by column chromatography (silica gel, 50% ethyl acetate in hexane) to give the product as a colorless oil (52 mg, 55% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/DL = 97 : 3). R_f = 0.33, 66% EtOAc/hexanes. $[\alpha]^{20}_D$ -15.0 (*c* 1.0, EtOH) [Lit.[22] $[\alpha]^{20}_D$ -14.1 (*c* 0.8, EtOH)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5H), 7.24-7.19 (m, 3H), 7.15 (d, *J* = 7.2 Hz, 2H), 6.98 (br s, 1H), 6.69 (br s, 1H), 5.65 (br s, 1H), 5.09 (s, 2H), 4.79 (app q, *J* = 7.0 Hz, 1H), 4.42 (dd, *J* = 5.6 Hz, 8.8 Hz, 1H), 3.85 (d, *J* = 4.0 Hz, 2H), 3.66 (s, 3H), 3.03 (d, *J* = 6.8 Hz, 2H), 2.09-2.02 (m, 1H), 0.83 (d, *J* = 6.8 Hz, 6H), 0.80 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 170.9, 169.2, 156.8, 136.5, 136.4, 129.5, 128.8, 128.7, 128.4, 128.3, 127.2, 67.4, 57.6, 54.7, 52.3, 44.6, 38.6, 31.3, 19.0, 18.0; IR (cm^{-1}): 3290(br), 3065(w), 2962(w), 1724(s), 1645(vs), 1520(s), 1212(s), 1148(m), 739(m), 697(m); HRMS (ESI^+) Calcd for $C_{25}H_{31}N_3O_6$ $[M+Na]^+$: 492.2105. Found: 492.2116.

HPLC AS-RH column: 30% acetonitrile in water over 15 min, 30-40% acetonitrile over 5 min, 40-50% acetonitrile over 5 min then 50-100% acetonitrile over 4 min with a flow rate of 0.70 mL/min and 210 nm UV detection, retention time = 19.08 min (97%) and 25.13 (3%) (Z-Gly-DL-Phe-L-Val-OMe with retention times of 18.99 min and 25.05 min).

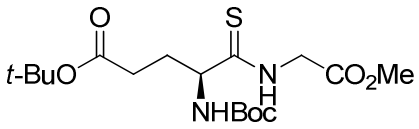
Path 2: Prepared according to Method B, stirred at room temperature for 15 h and purified by column chromatography (silica gel, 50% ethyl acetate in hexane) to give the product as a colorless oil (48 mg, 74% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/DL = 95.6 : 4.4).

Path 3: Prepared according to Method C, stirred at room temperature for 15 h and purified by column chromatography (silica gel, 50% ethyl acetate in hexane) to give the product as a colorless oil (56 mg, 50% yield, HPLC of the crude reaction mixture showed the epimerization ratio LL/DL = 96.2 : 3.8).



To a stirred solution of Boc-L-Glu(O*t*-Bu)-SH (83 mg, 0.26 mmol), glycine methyl ester hydrochloride salt (25 mg, 0.20 mmol) in THF (2 mL) was added PyBop (156 mg, 0.30 mmol) and DIEA (0.083 mL, 0.50 mmol) at 0 °C sequentially. The reaction mixture was stirred at 0 °C for 30 min and warmed up to room temperature and then stirred for 4.5 h. The reaction mixture was washed with water and brine, dried with anhydrous Na_2SO_4, then filtrated and concentrated under reduced pressure. Purification by column chromatography (silica gel, 30% ethyl acetate in hexane) gave compound **A** (30 mg, 40% yield) as a colorless oil (R_f = 0.25, 50% EtOAc/hexanes) and compound **B** (23 mg, 28% yield) as a colorless oil (R_f = 0.50, 50% EtOAc/hexanes).

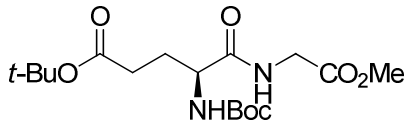
***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-butyl ester L-glutamyl-thioxo-glycine methyl ester**.



$[\alpha]^{20}_{D}$ -10.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 5.62 (d, *J* = 8.0 Hz, 1H), 4.54-4.50 (m, 2H), 4.34 (dd, *J* = 4.4 Hz, 18.4 Hz, 1H), 3.78 (s, 3H), 2.45-2.30 (m, 2H), 2.20-2.12 (m, 1H), 2.06-1.97 (m, 1H), 1.45 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 173.2, 168.9, 155.7, 81.3, 80.5, 60.3, 52.8, 47.0, 32.0, 31.0, 28.5, 28.3; IR (cm^{-1}): 3276(br),

2977(w), 1689(vs), 1499(m), 1444(m), 1366(vs), 1247(s), 1211(m), 1151(vs); HRMS (ESI^+) Calcd for $C_{17}H_{30}N_2O_6S$ $[M+Na]^+$: 413.1717. Found: 413.1722.

***N*-α-*tert*-Butoxycarbonyl-γ-*tert*-butyl ester L-glutamyl-glycine methyl ester**.



$[\alpha]^{20}_D$ -8.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (br s, 1H), 5.38 (d, *J* = 7.6 Hz, 1H), 4.19 (app dd, *J* = 7.4 Hz, 13.2 Hz, 1H), 4.05 (dd, *J* = 5.4 Hz, 18.0 Hz, 1H), 4.0 (dd, *J* = 5.4 Hz, 18.0 Hz, 1H), 3.73 (s, 3H), 2.44-2.29 (m, 2H), 2.13-2.04 (m, 1H), 1.95-1.86 (m, 1H), 1.43 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.3, 170.2, 155.9, 81.1, 80.3, 54.0, 52.5, 41.4, 31.9, 28.5, 28.3, 27.9; IR (cm^{-1}): 3307(br), 2977(w), 1720(s), 1664(s), 1515(m), 1366(s), 1208(m), 1149(vs), 1048(w), 1026(w); HRMS ($APCI^+$) Calcd for $C_{17}H_{31}N_2O_7$ $[M+H]^+$: 375.2126. Found: 375.2132.

Boc-L-Glu(O*t*-Bu)-Gly-OMe could also be prepared according to Method A, stirred at room temperature for 8 h and purified by column chromatography (silica gel, 30% ethyl acetate in hexane) to give compound **A** as an only product (64 mg, 74% yield).

7. References

(1) Current Address: Department of Chemistry, University of Chicago, 5735 South Ellis Avenue, Chicago, IL 60637

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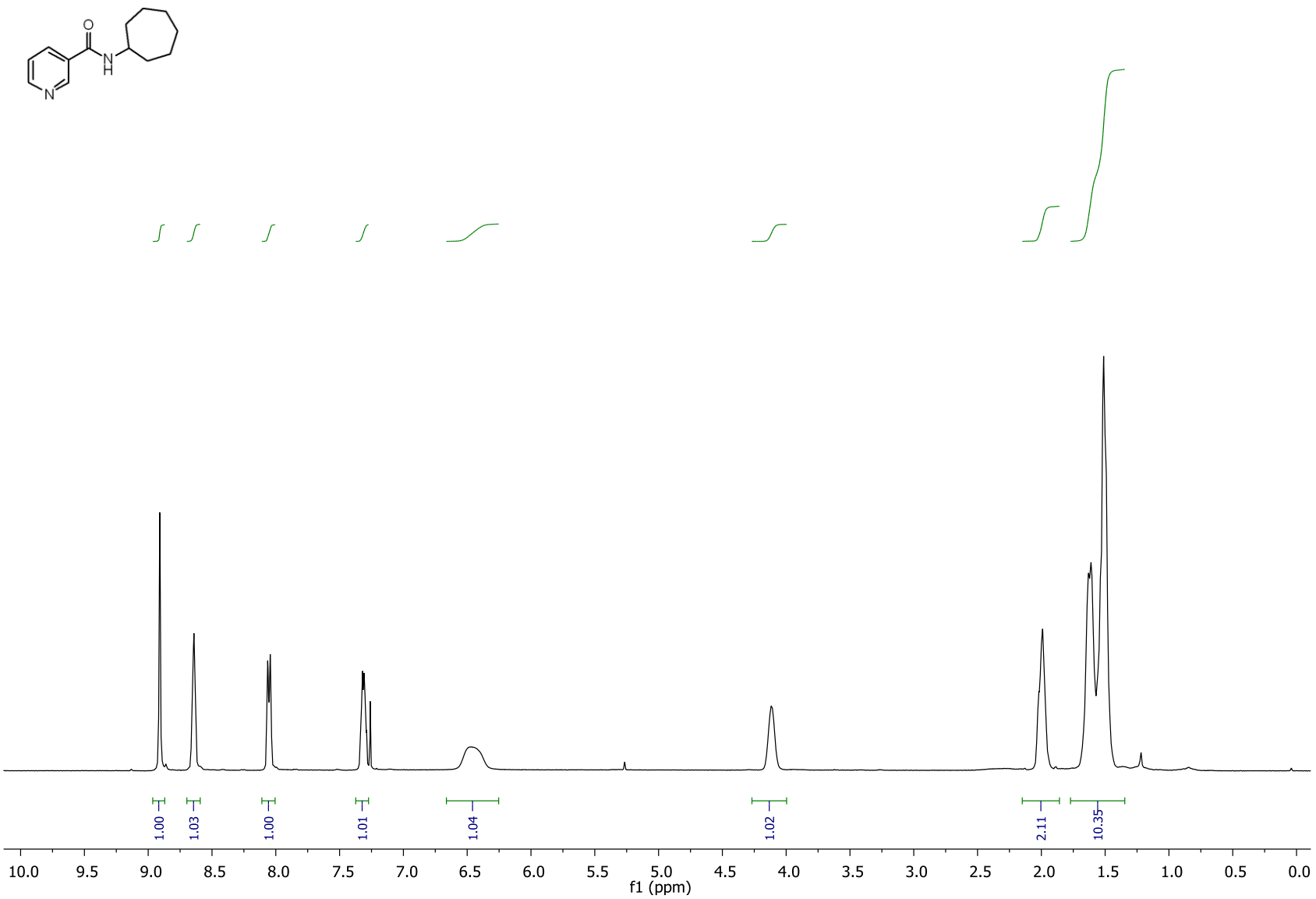
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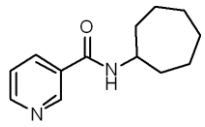
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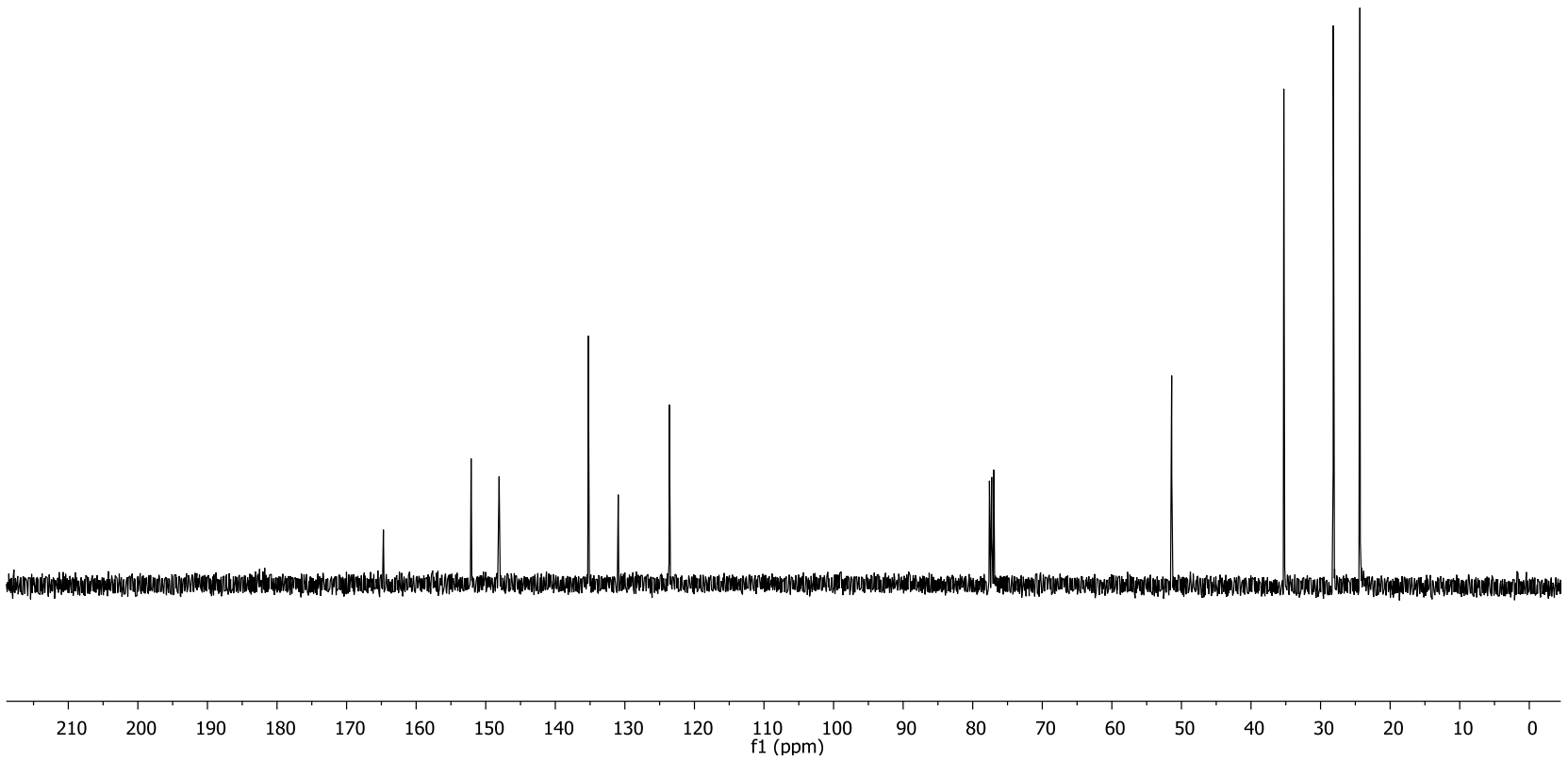
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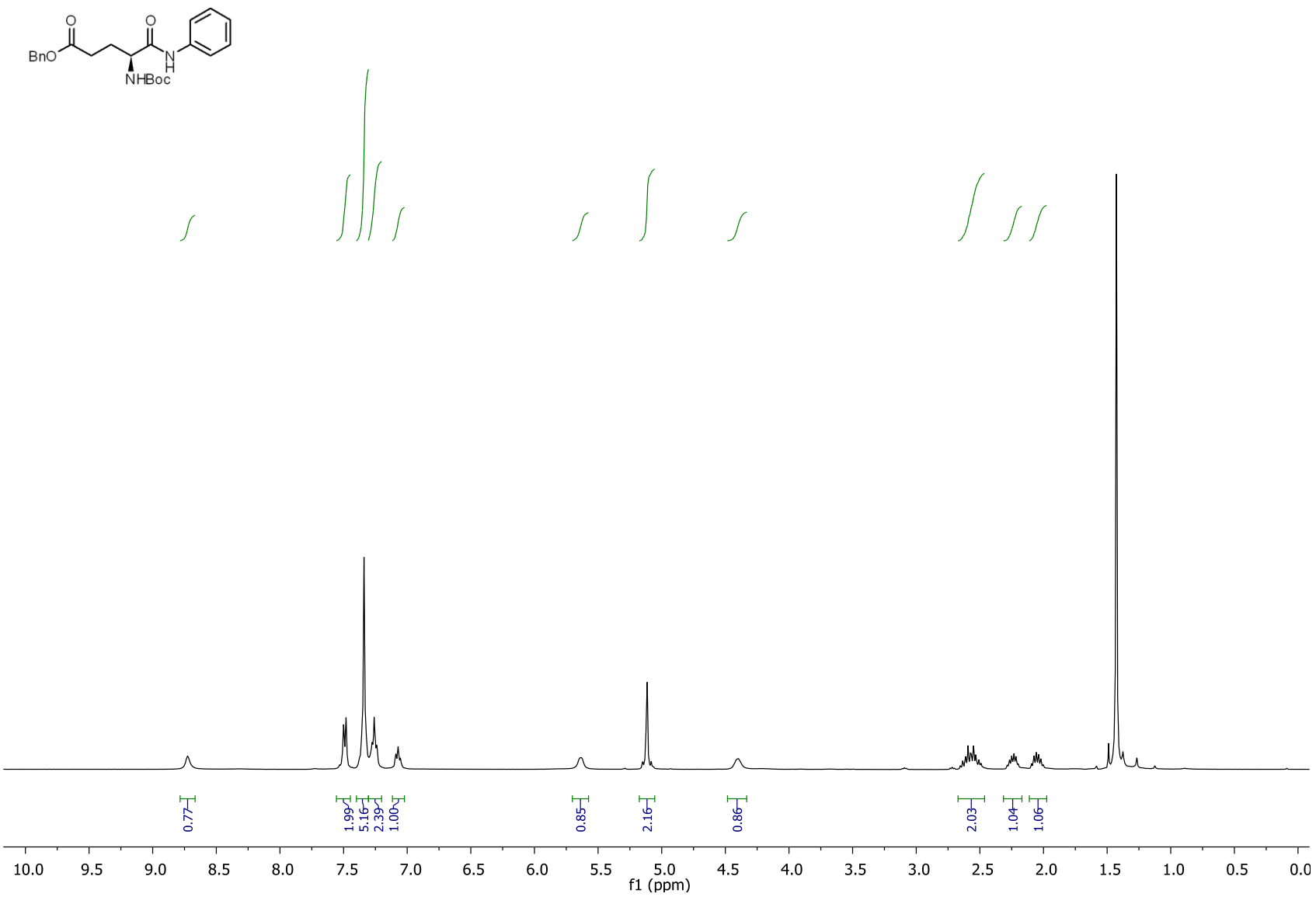
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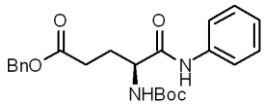
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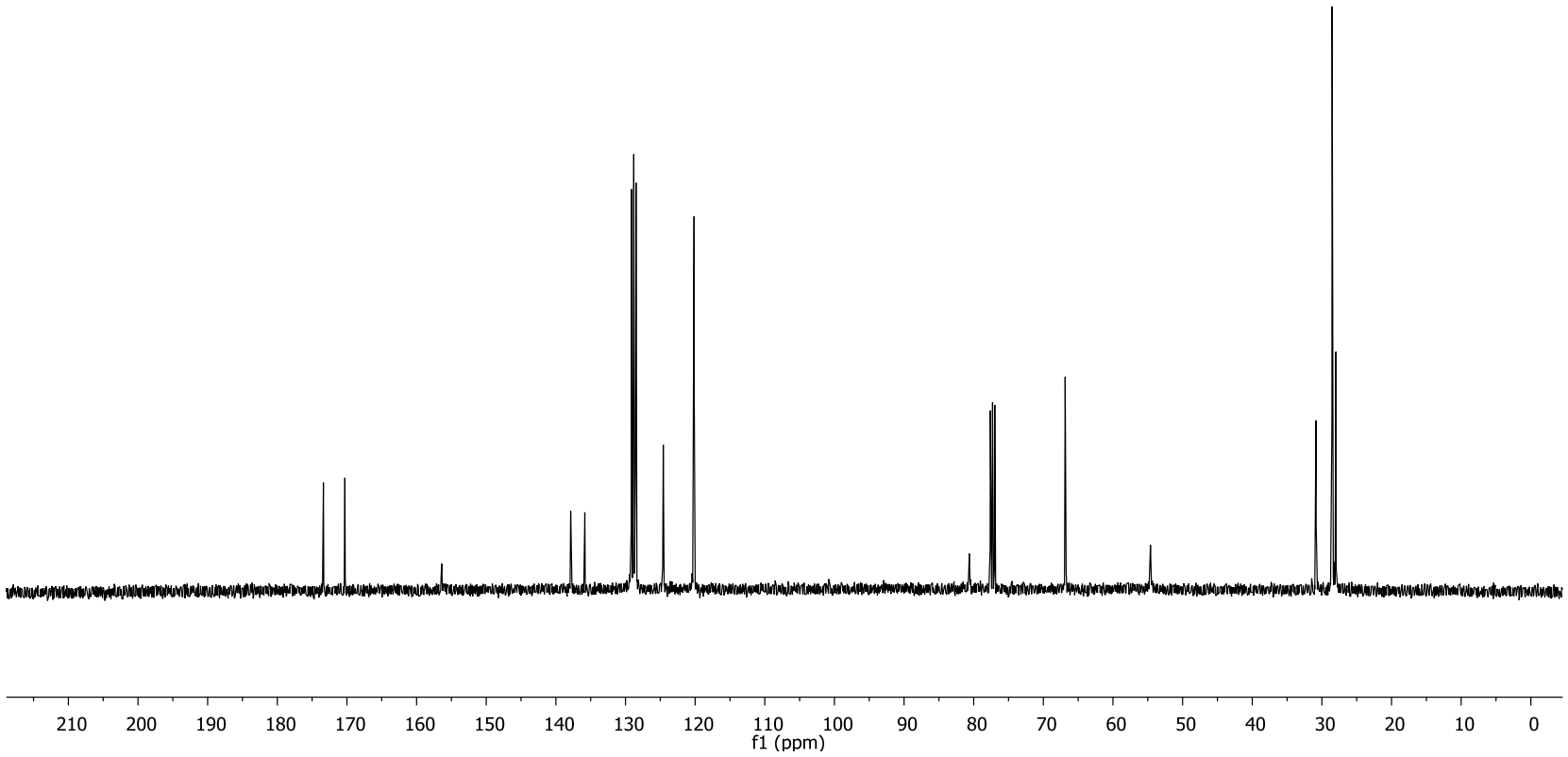
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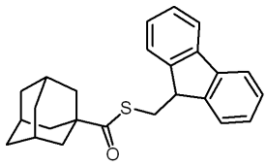
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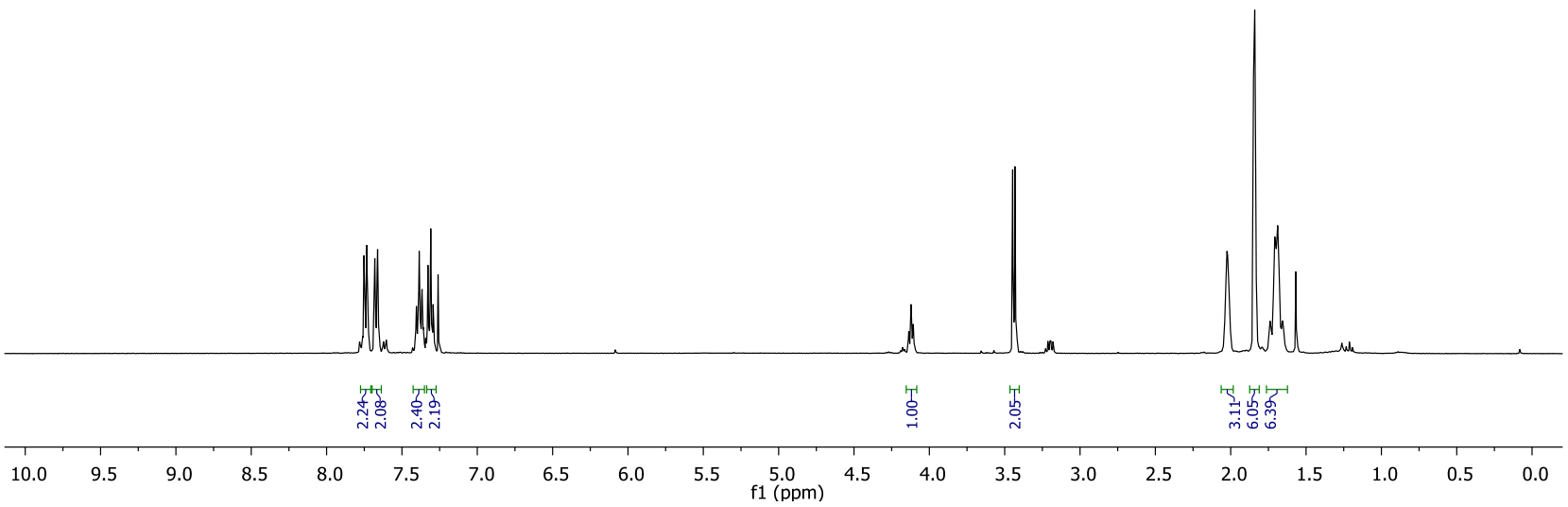
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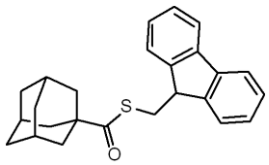
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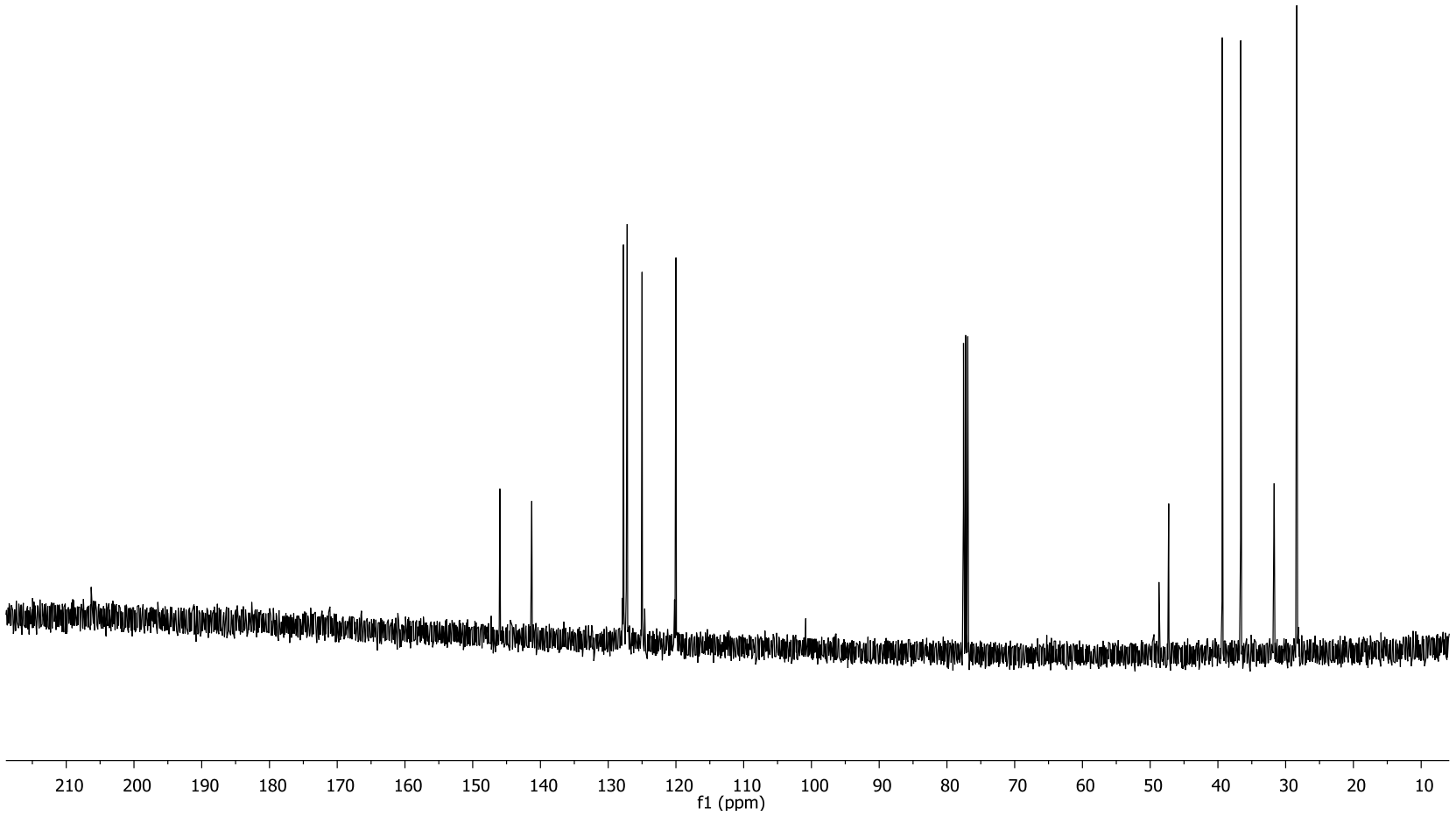
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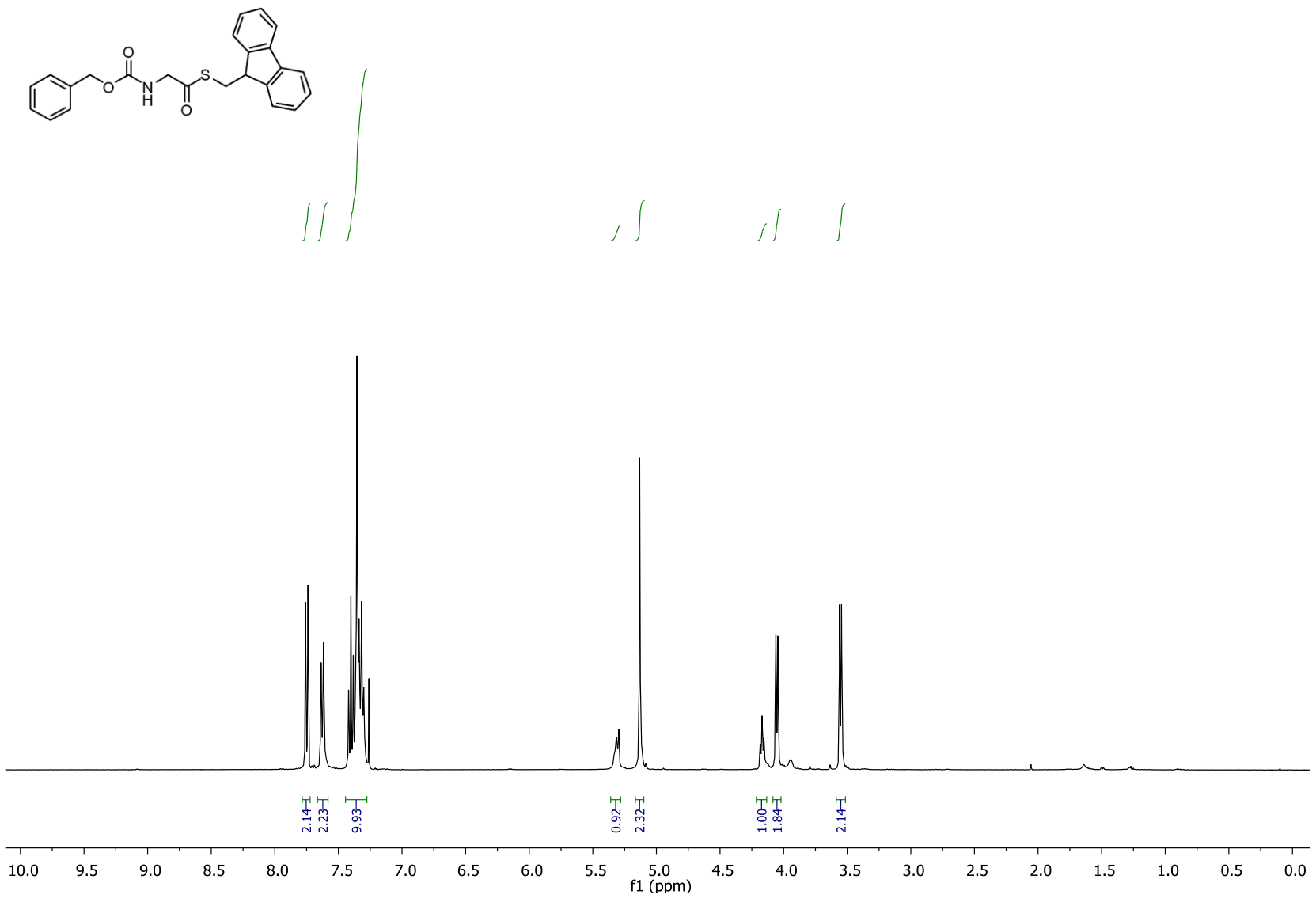
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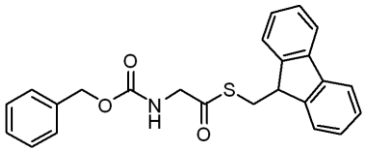
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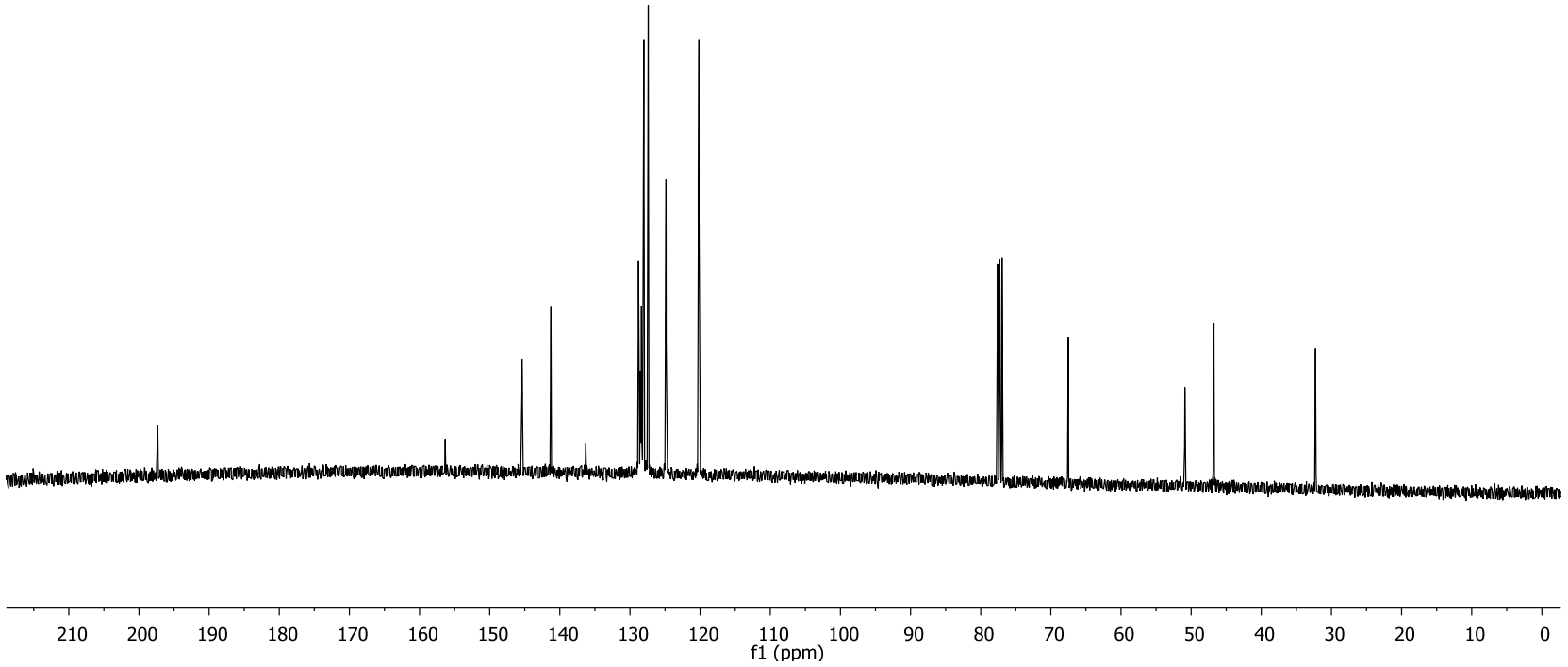
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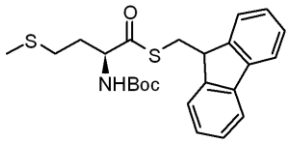
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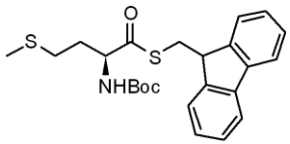
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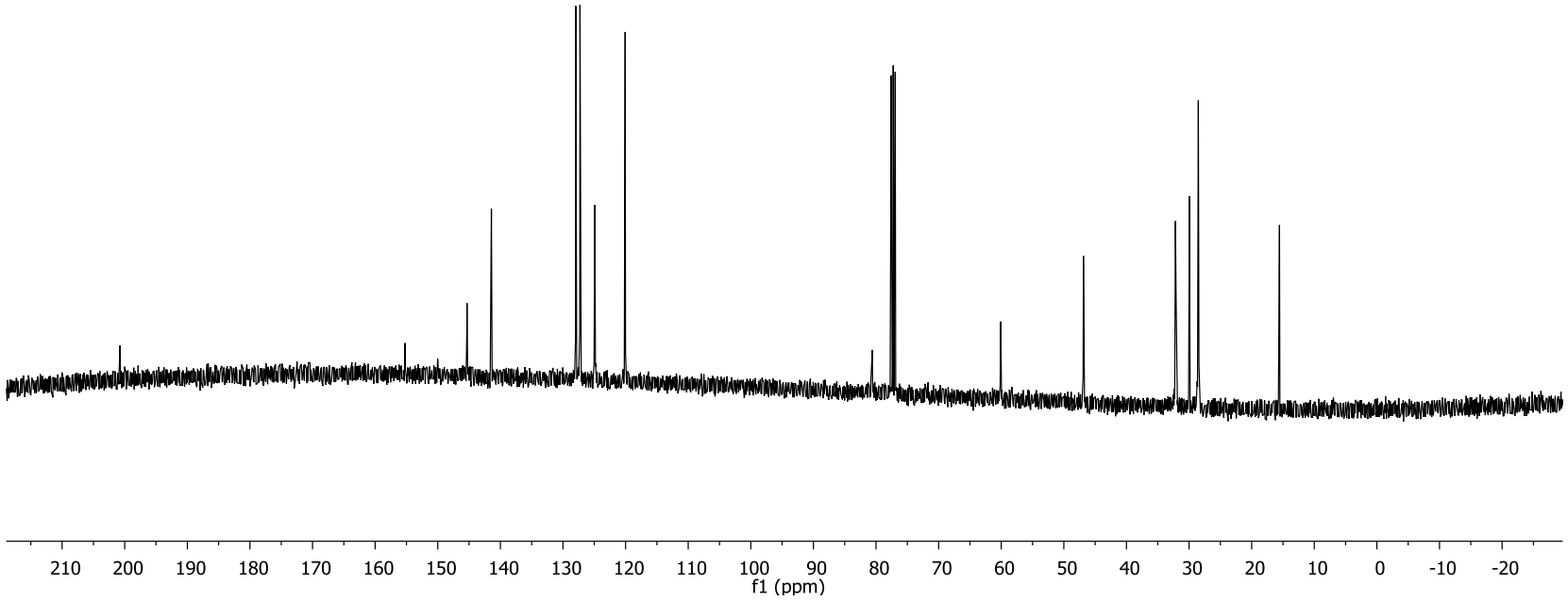
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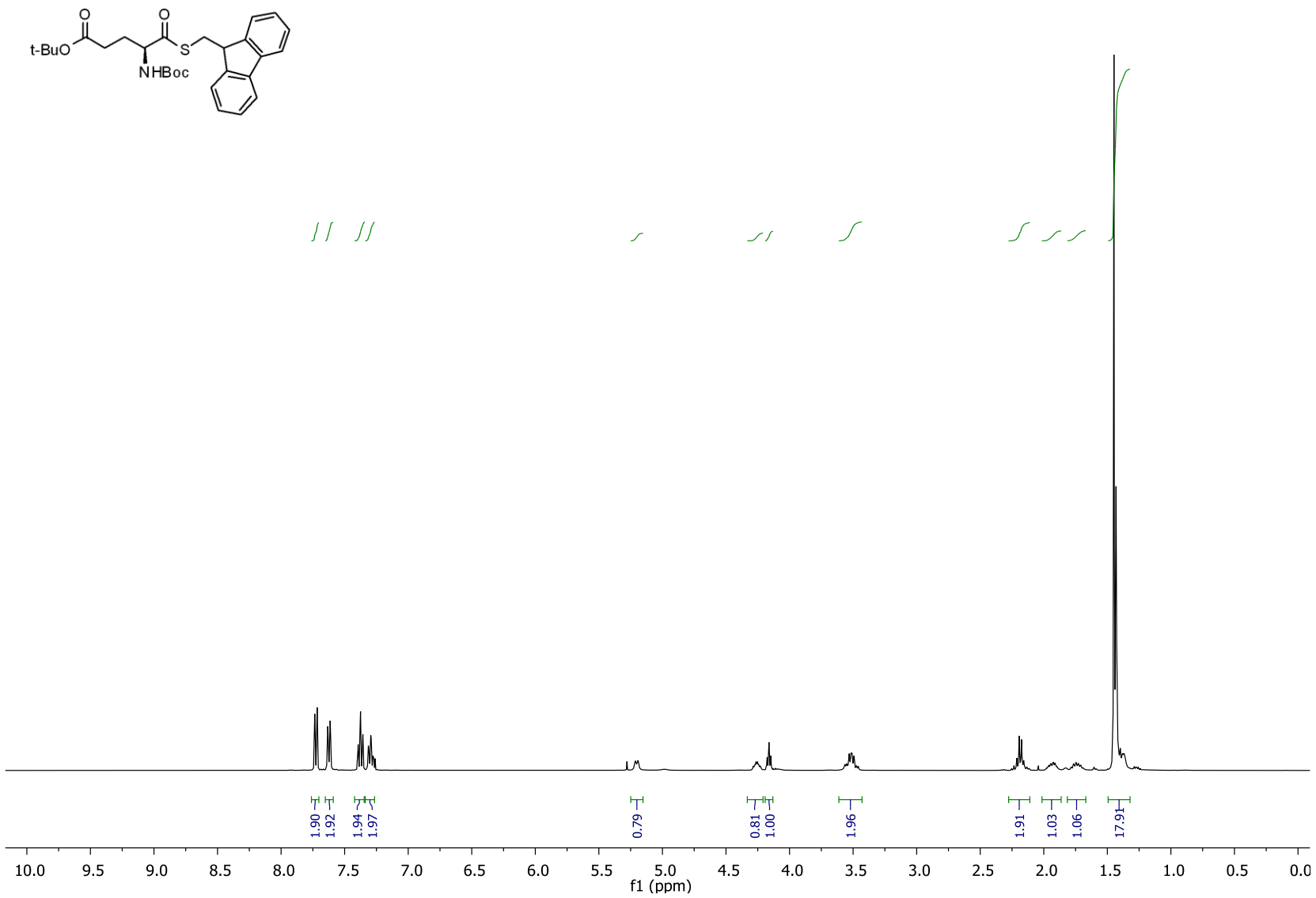
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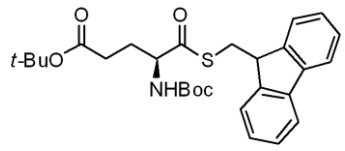
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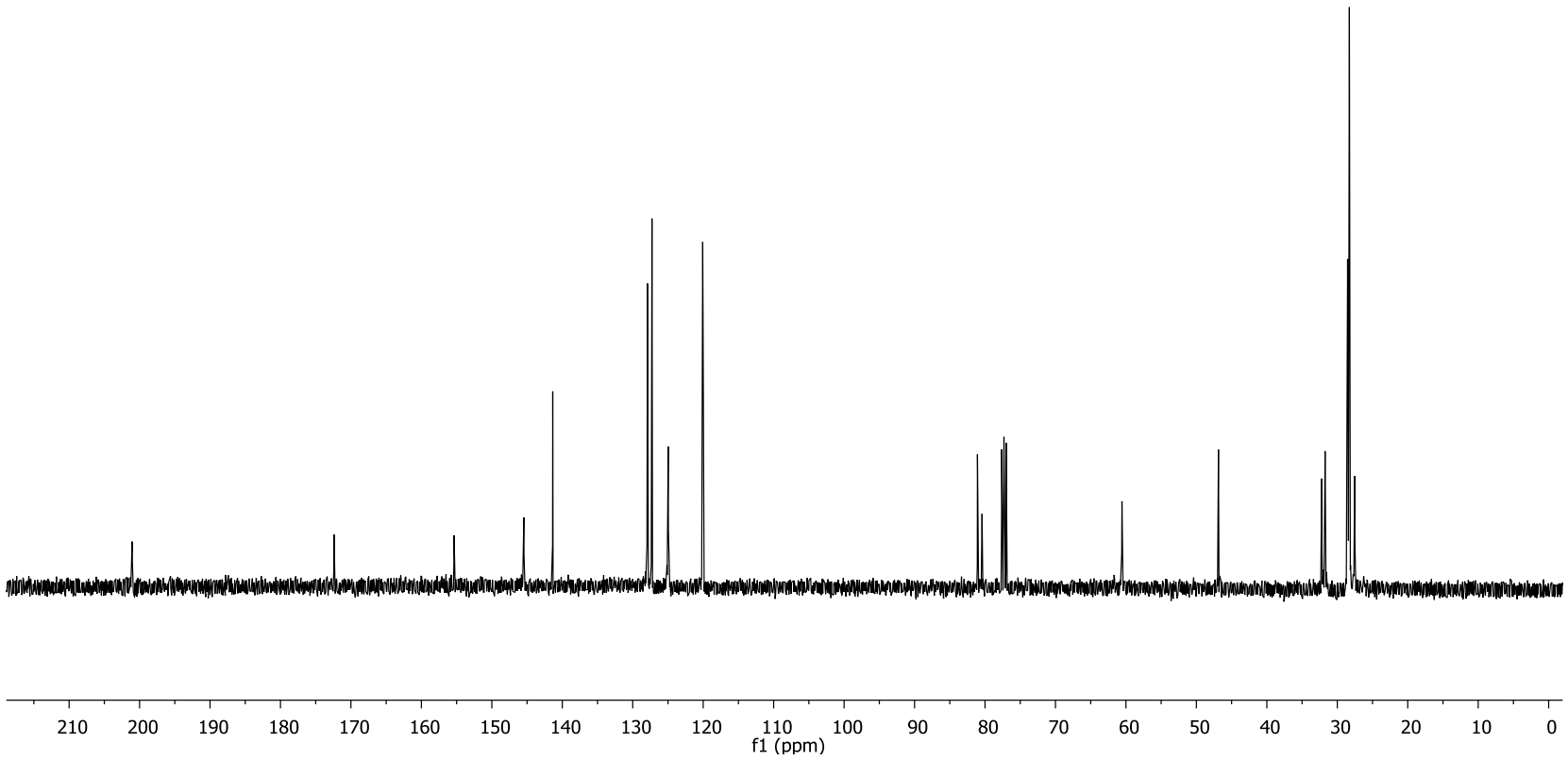
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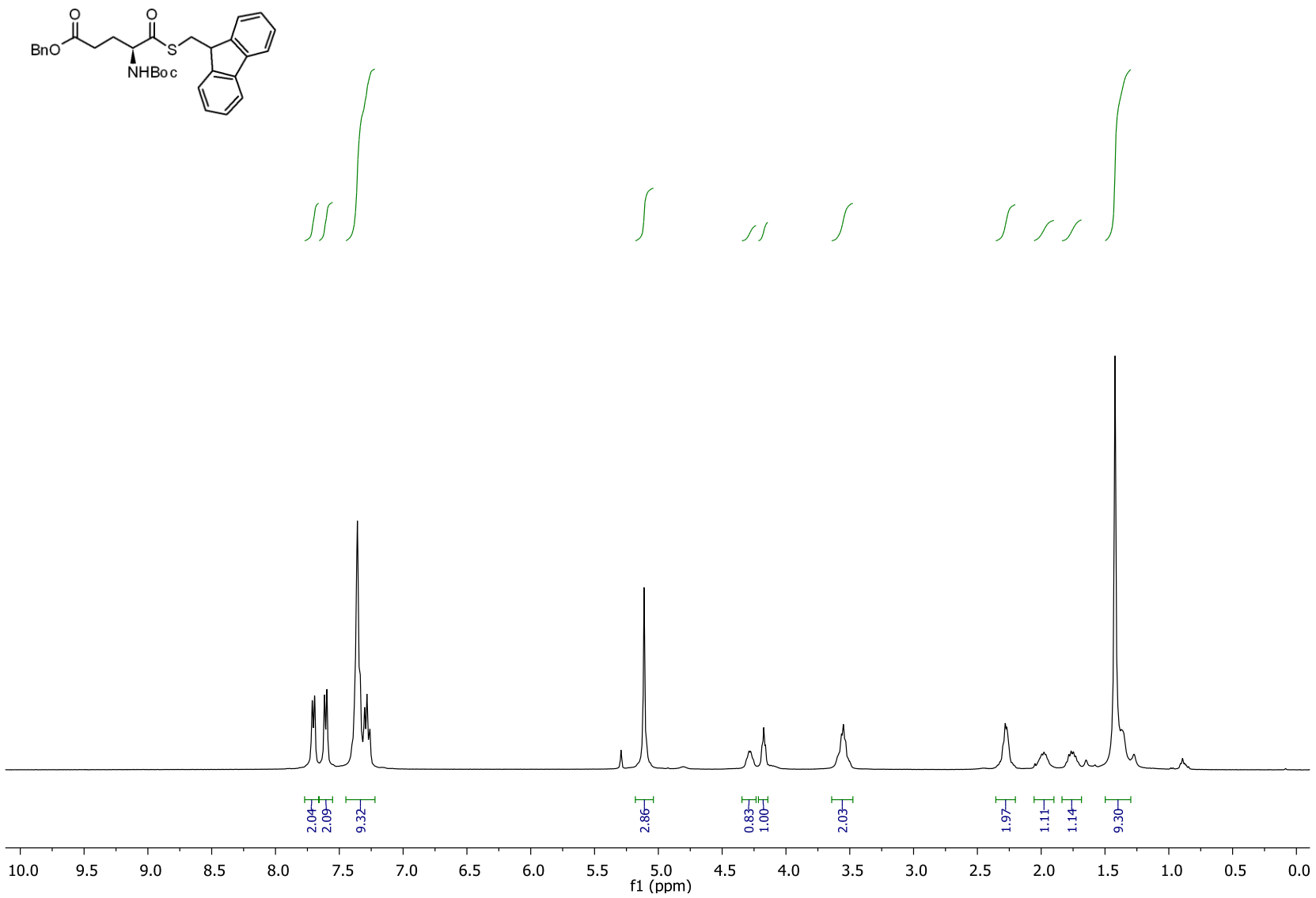
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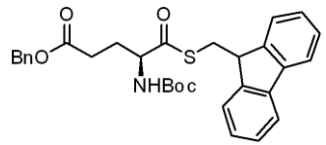
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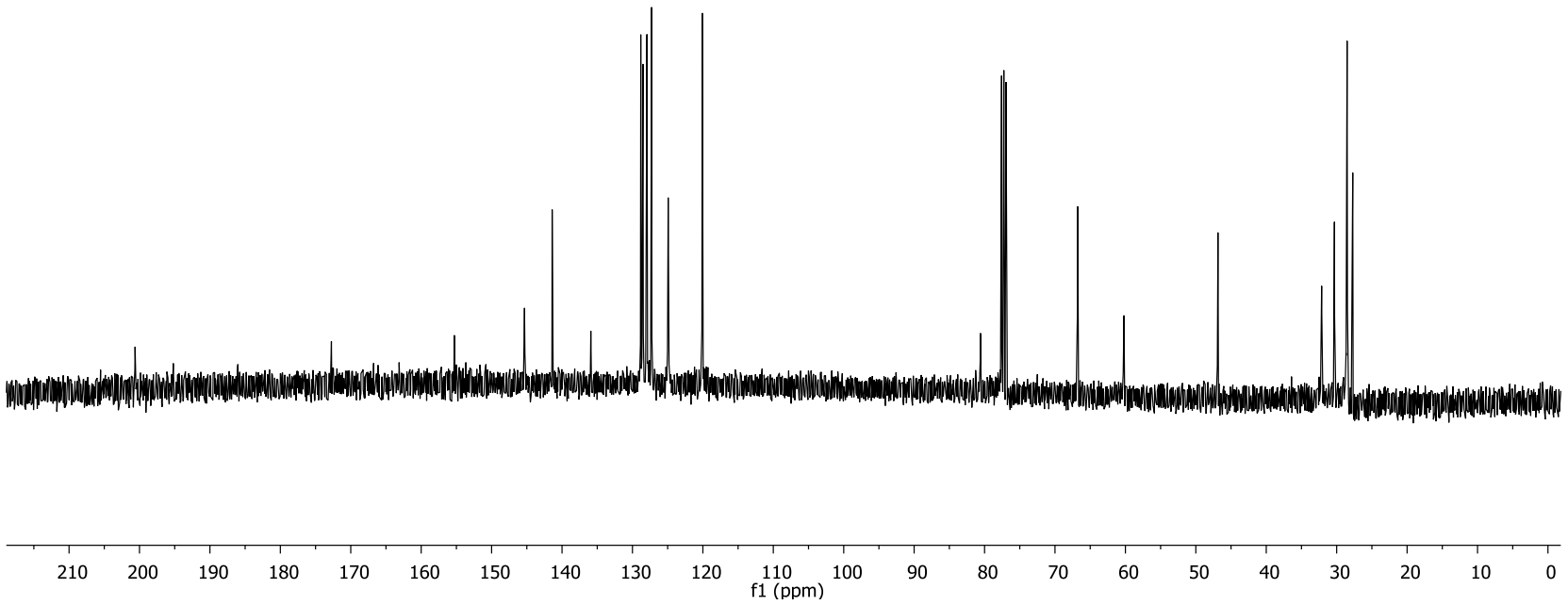
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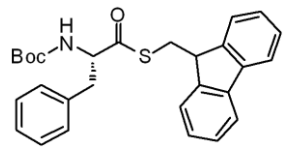
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H
O
S

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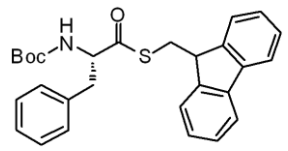
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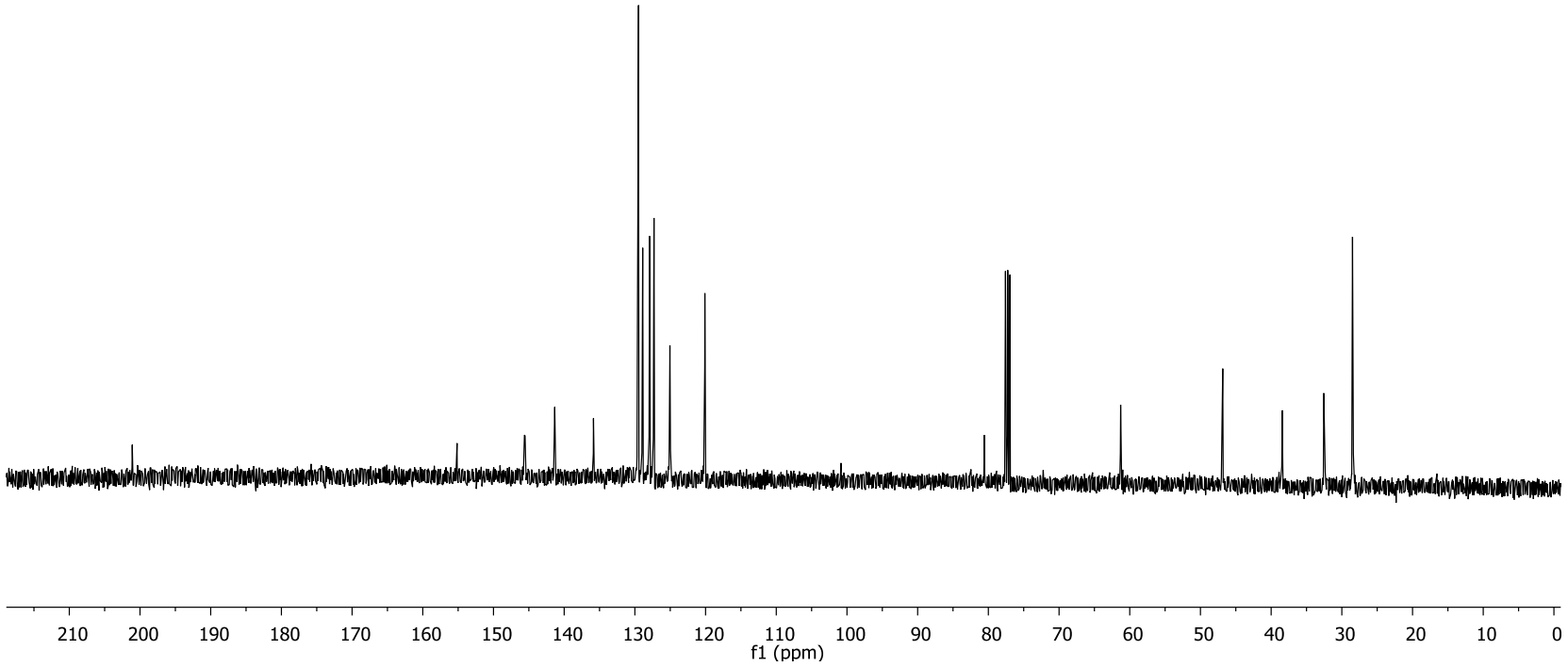
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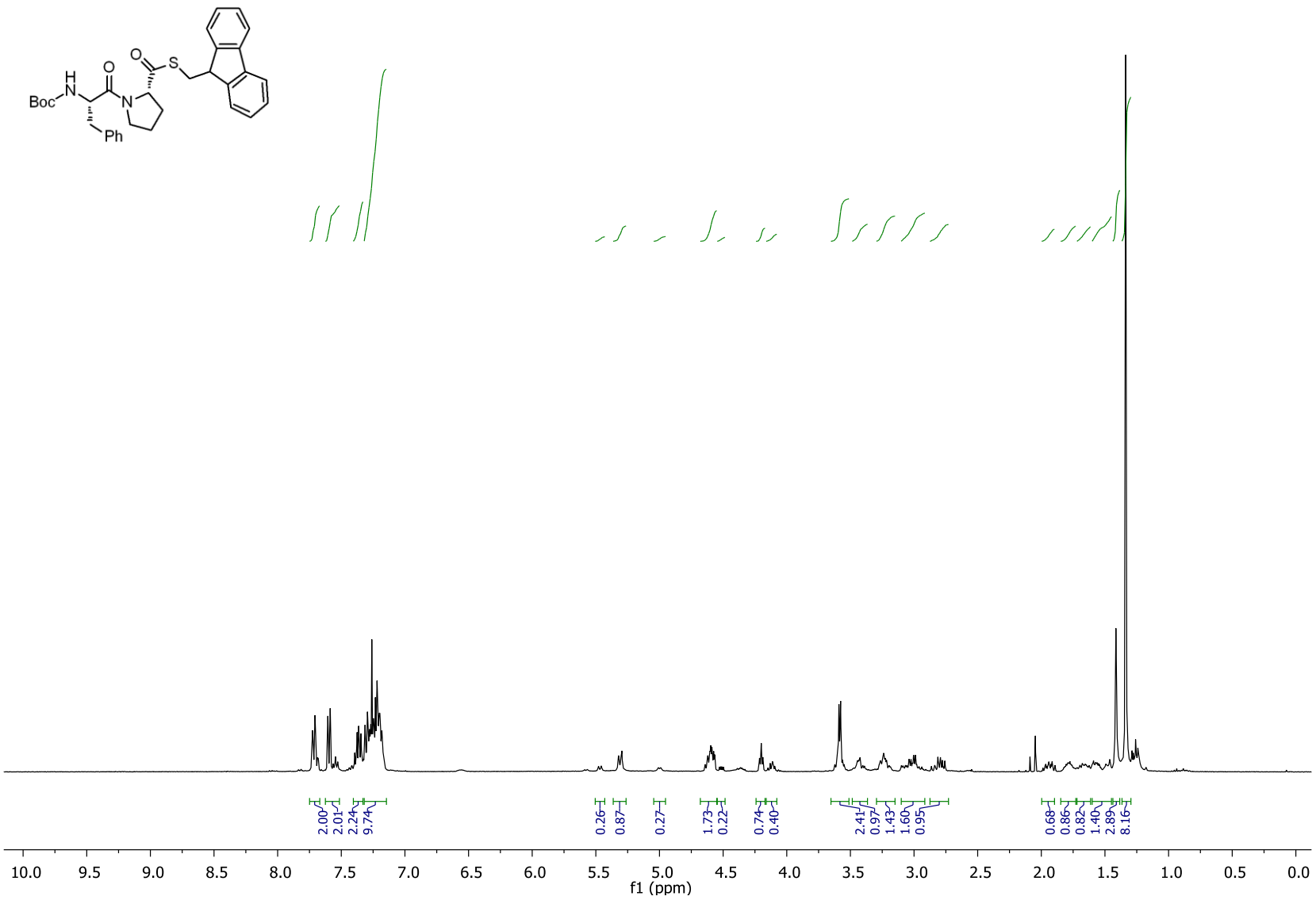
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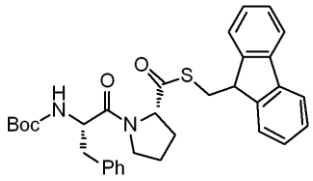
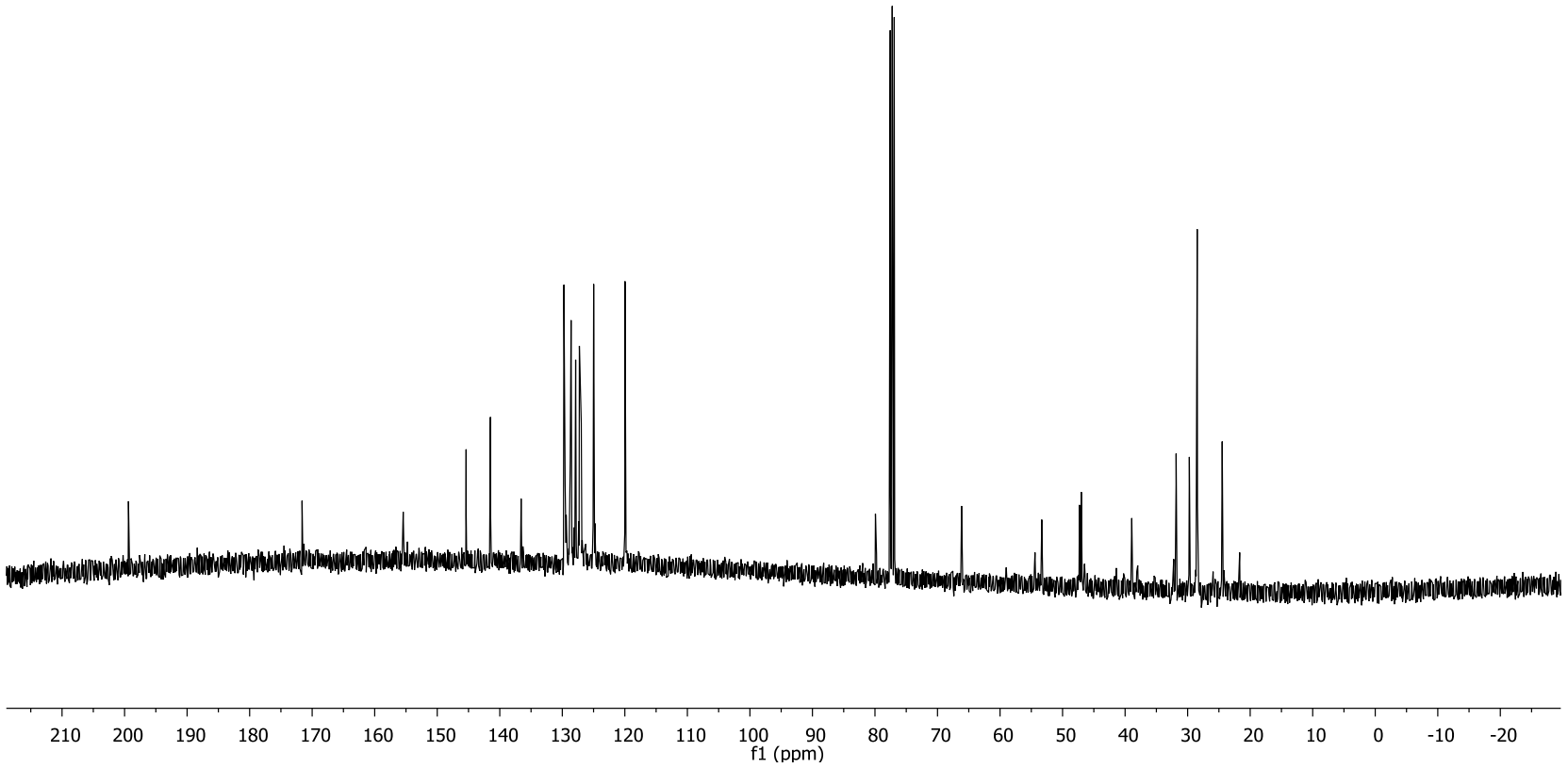
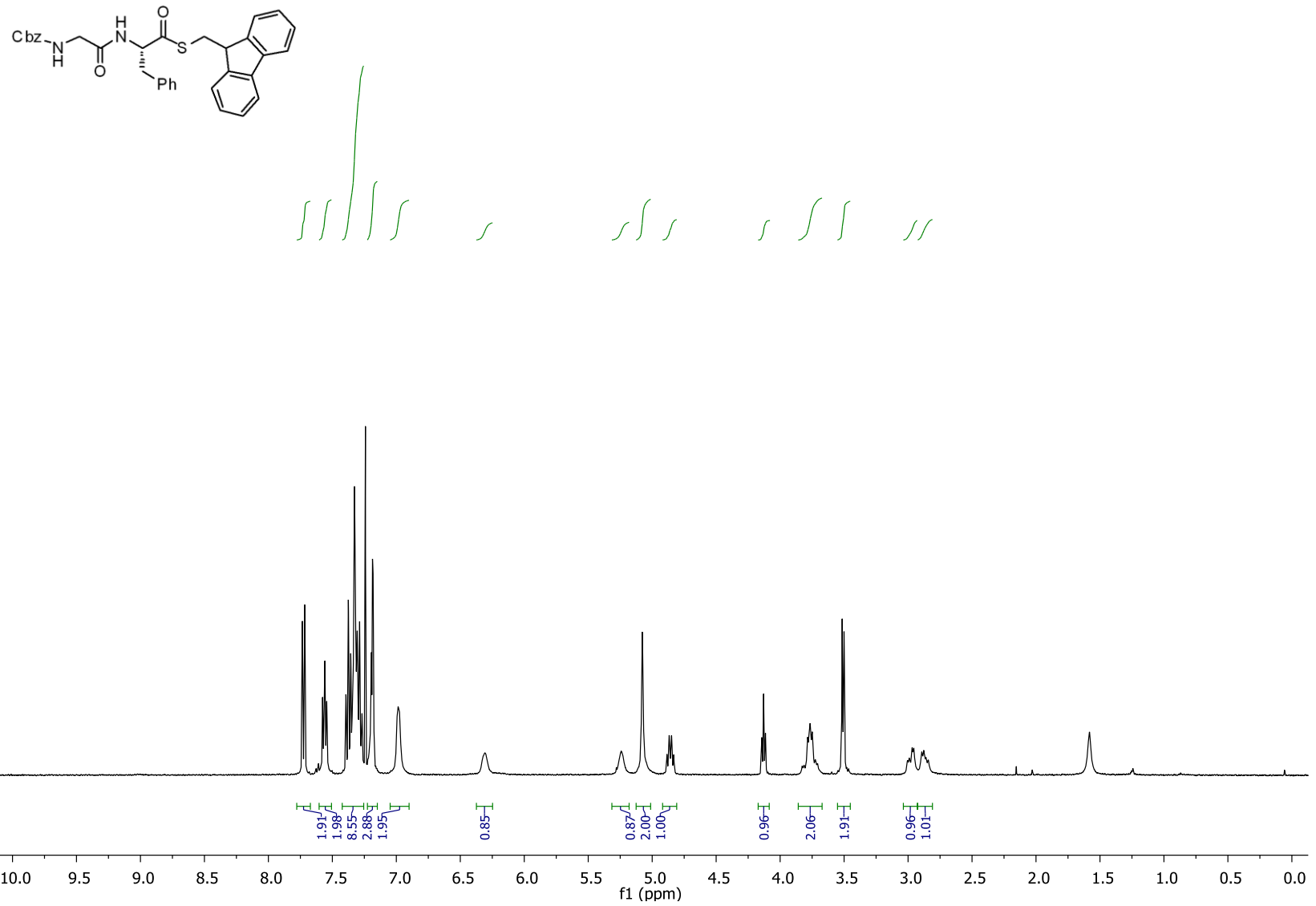
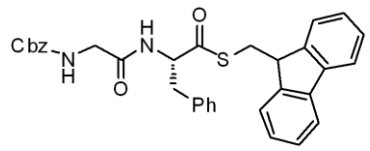
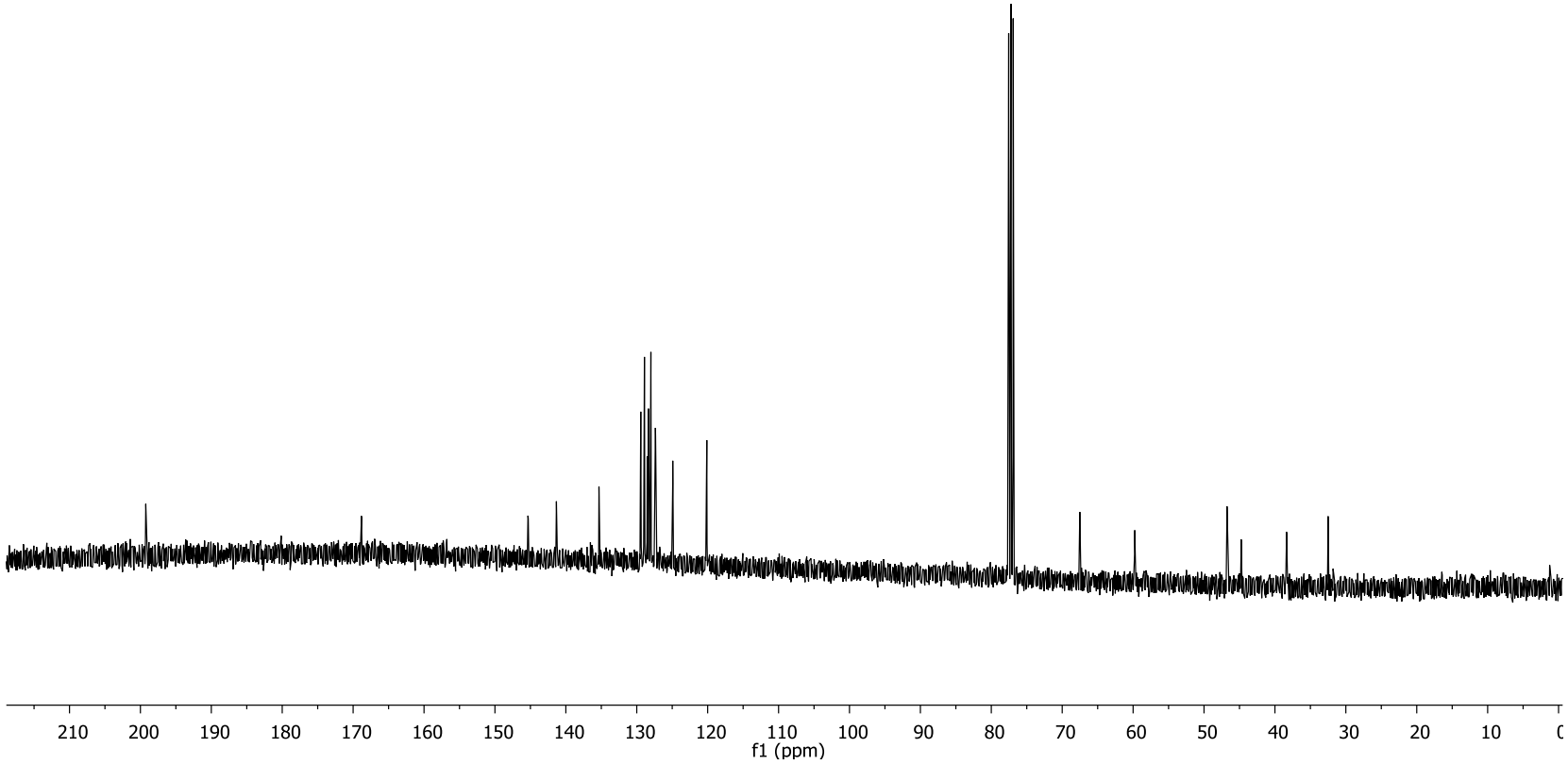
0.0
f1 (ppm)

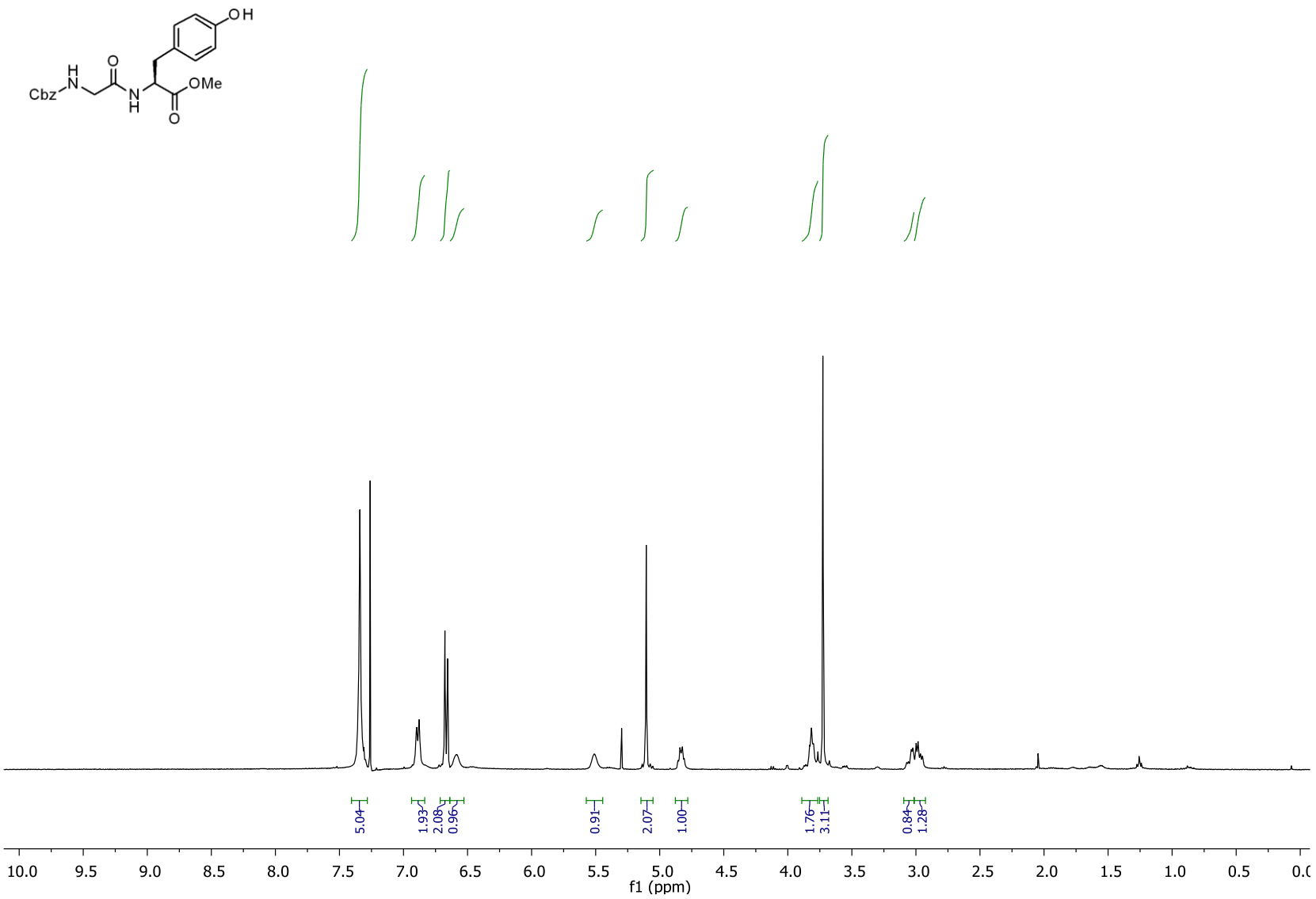

Boc
H
N
O
N
O
S
Ph

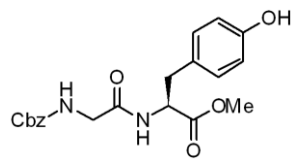

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

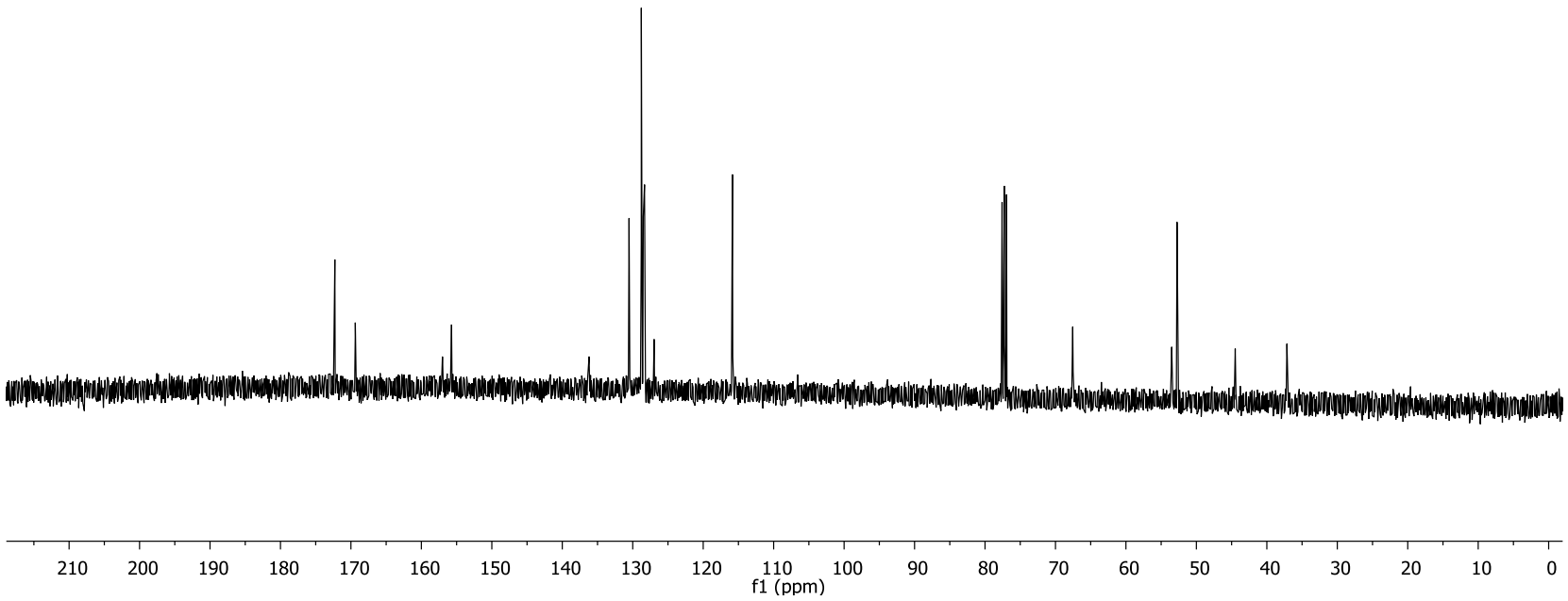

Cbz
N
H
O
H
N
O
S
Ph
1.91
1.98
8.55
2.88
1.95
0.85
0.87
2.00
1.00
0.96
2.06
1.91
0.96
1.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

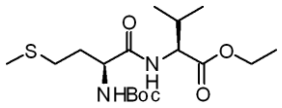

Cbz
N
H
O
H
N
O
S
Ph

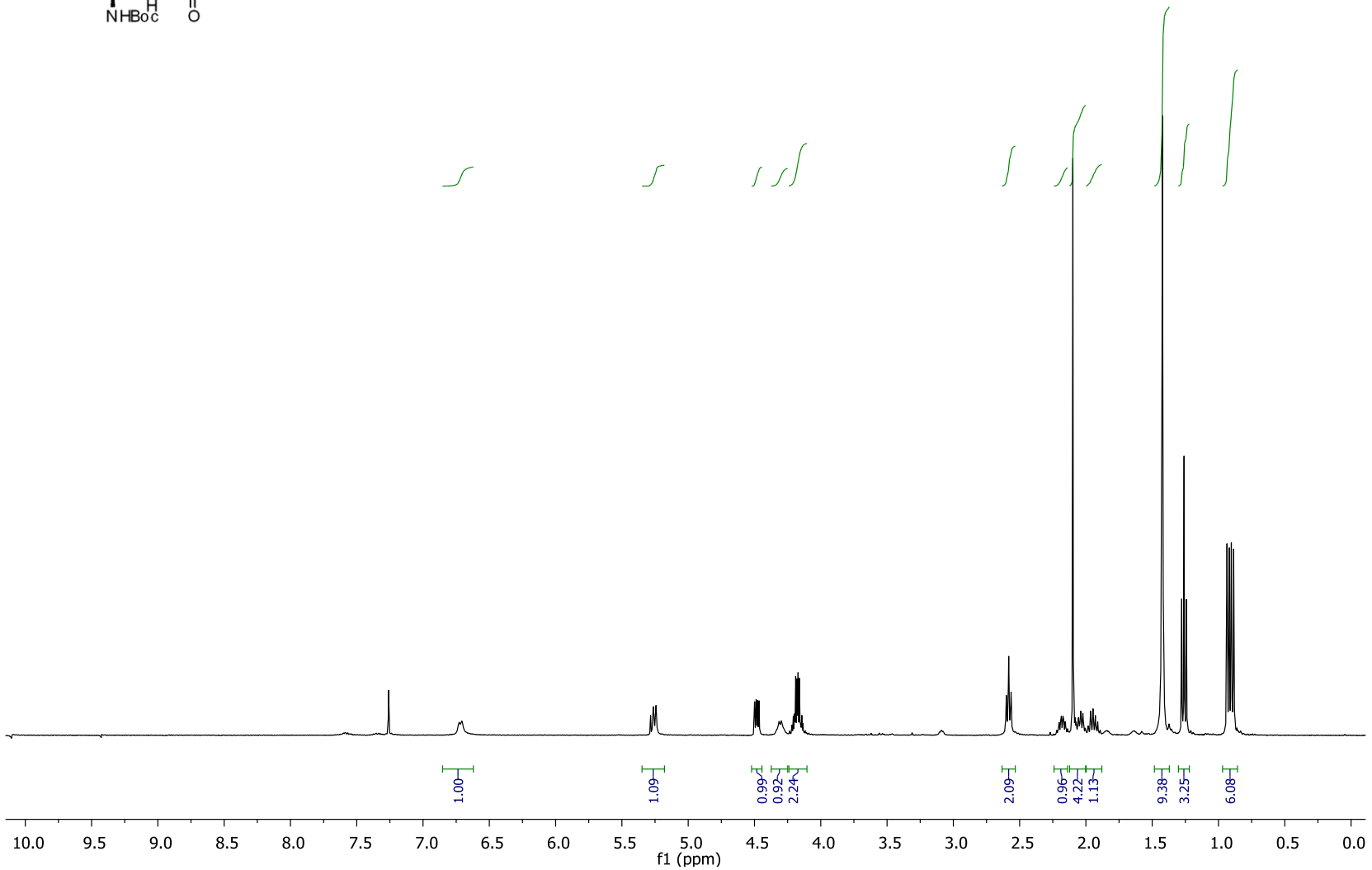

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

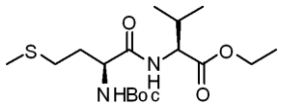

OH
Cbz
N
H
O
N
H
OMe
O
5.04
1.93
2.08
0.96
0.91
2.07
1.00
1.76
3.11
0.84
1.28
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


OH
H
N
Cbz
O
N
H
OMe
O

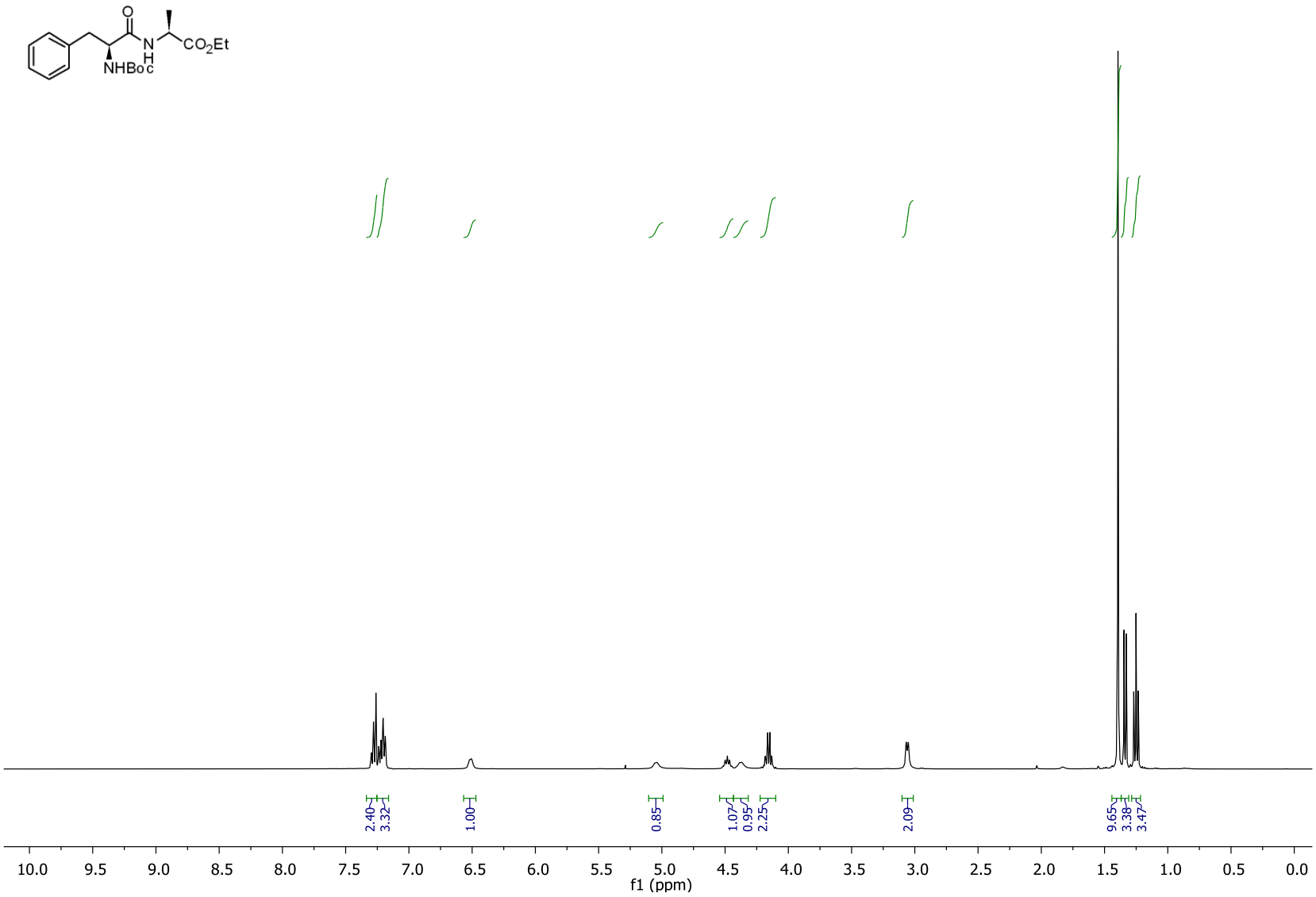

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

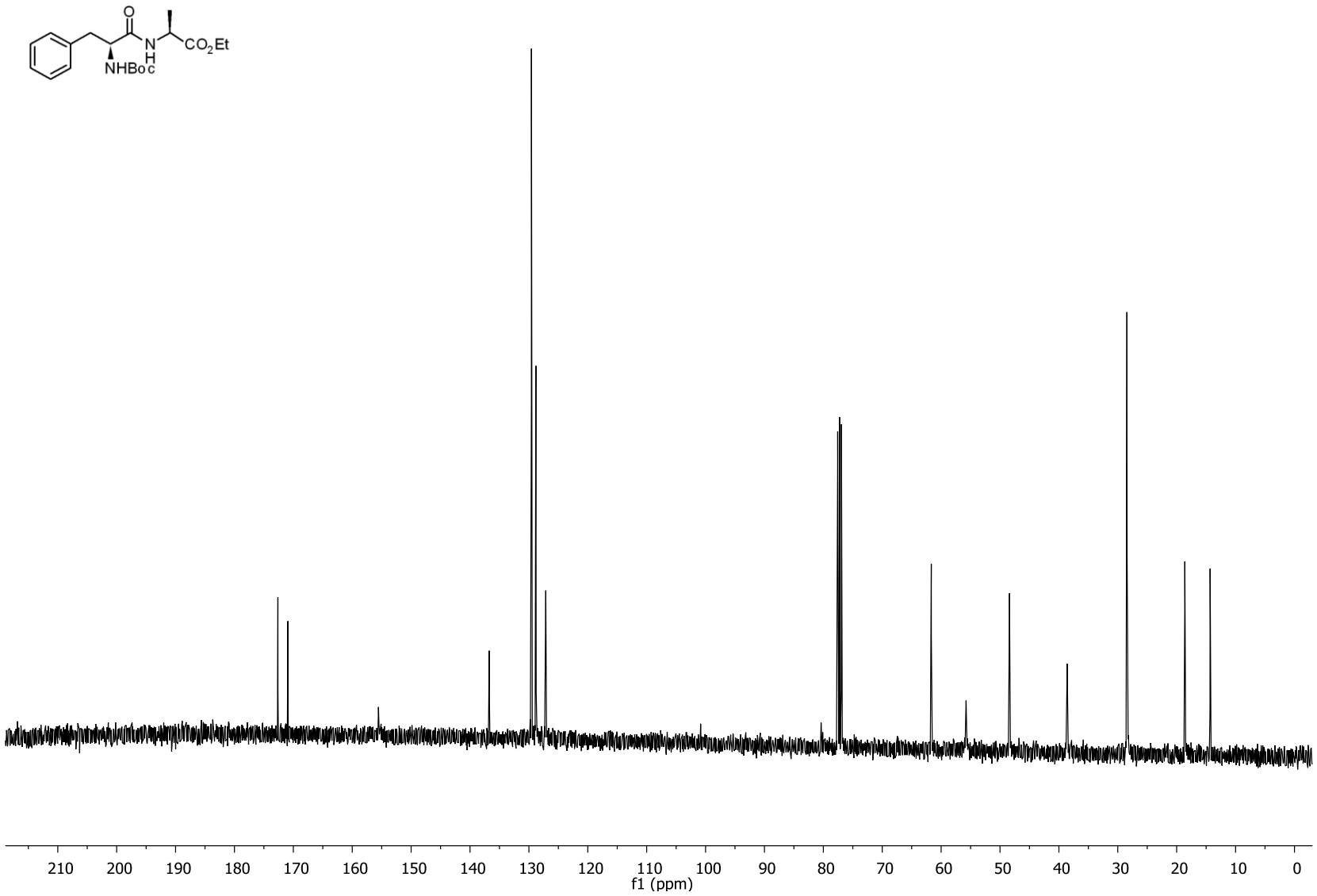

O
S
N
H
O
NHBoc
O

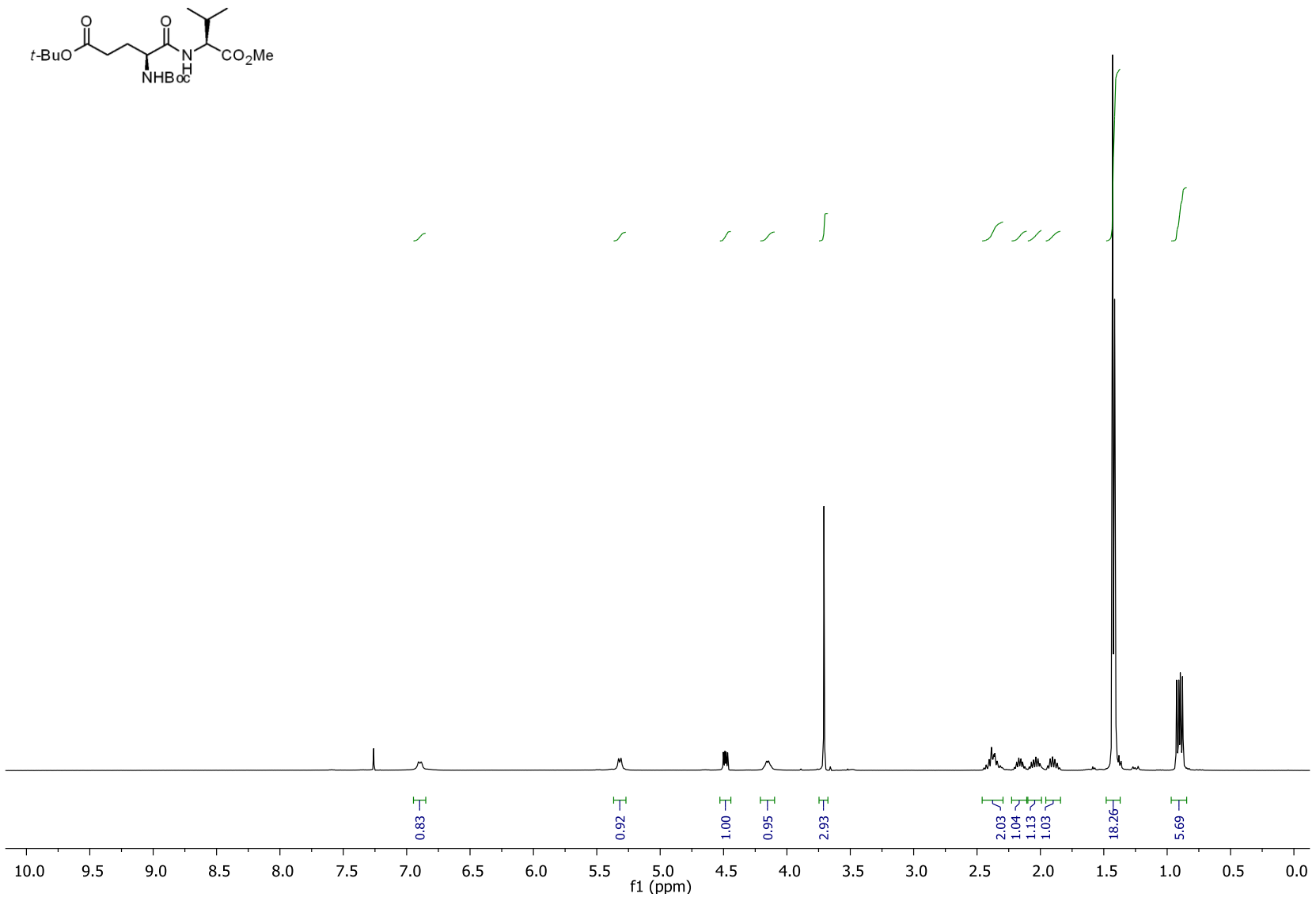

1.00
1.09
0.99
0.92
2.24
2.09
0.96
4.22
1.13
9.38
3.25
6.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

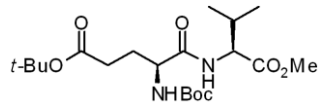

S
O
N
H
NHBoc
O
O

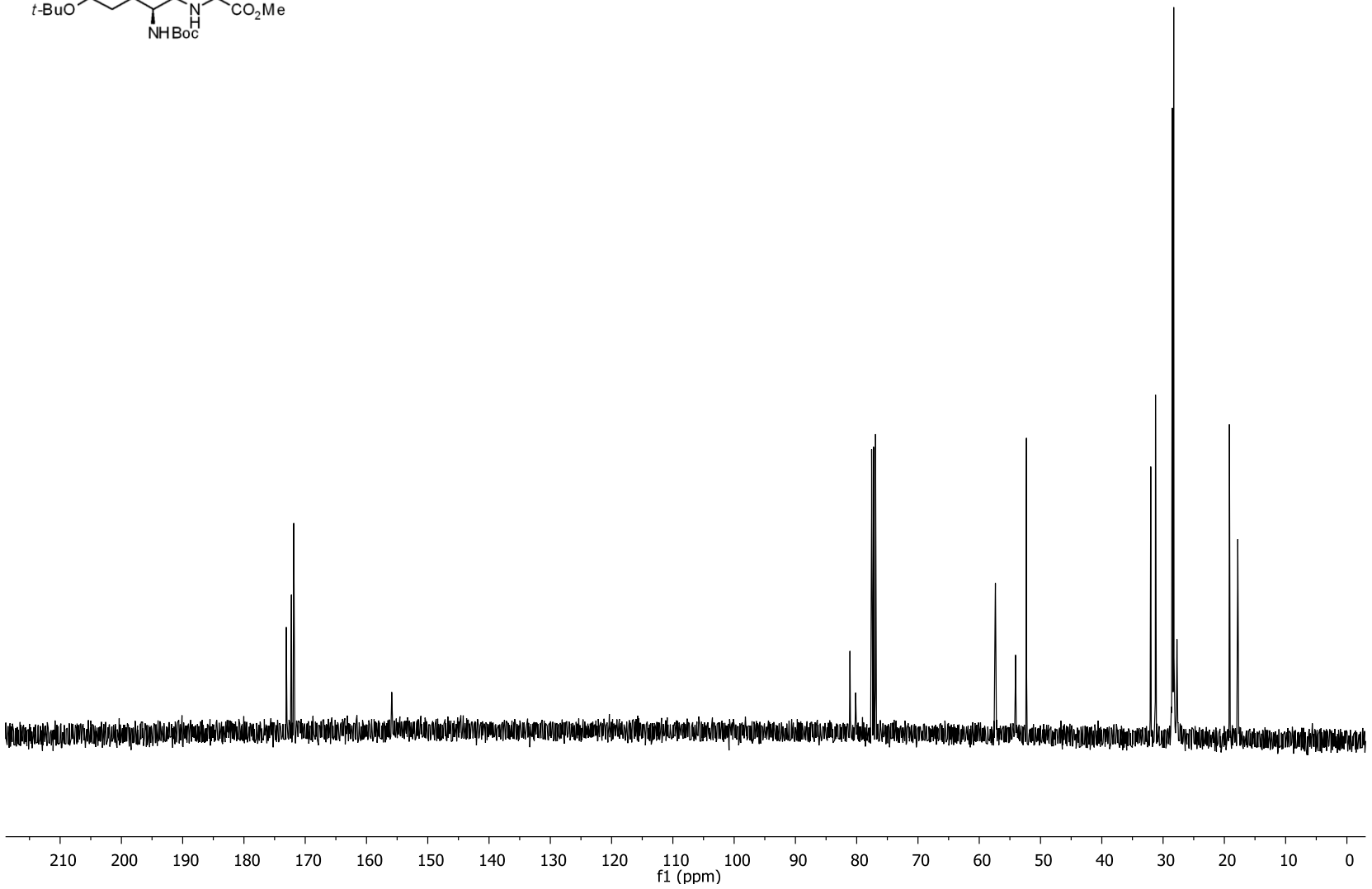
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

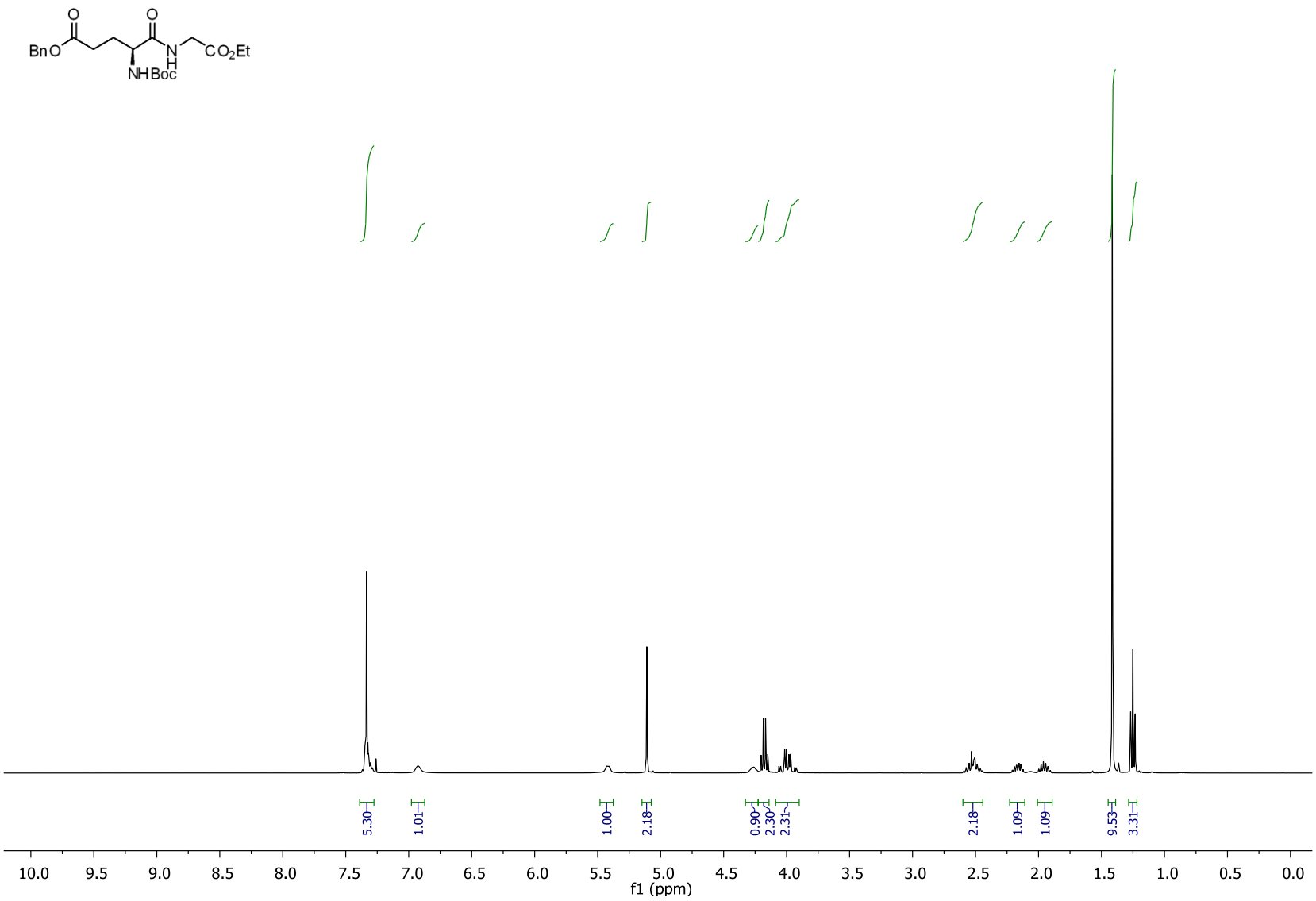

O
N
H
CO2Et
NHBoc
2.40
3.32
1.00
0.85
1.07
0.95
2.25
2.09
9.65
3.38
3.47
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

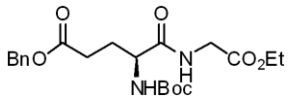

O
N
H
CO2Et
NHBoc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

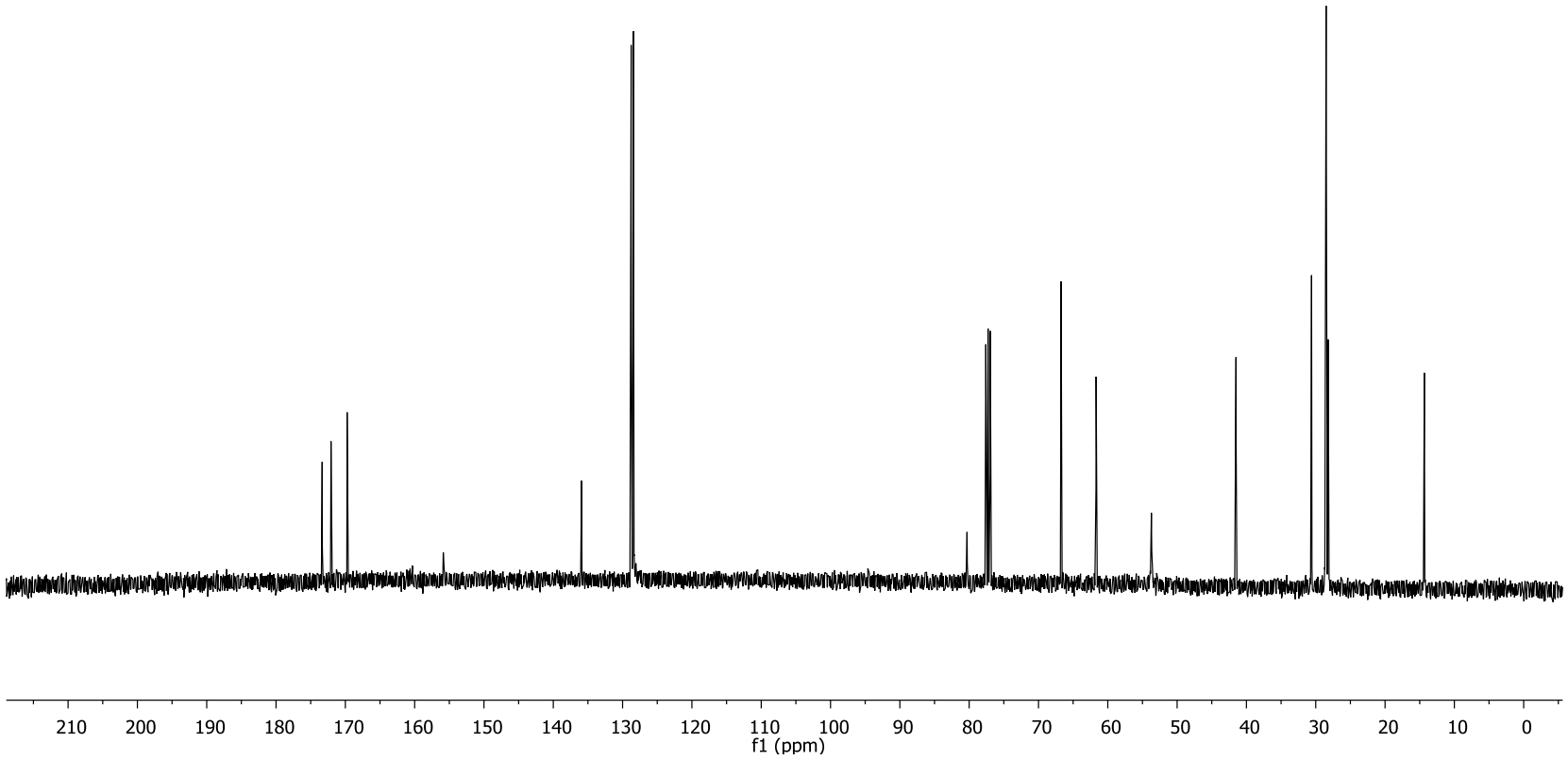

t-BuO
O
O
N
H
CO2Me
NHBoc
0.83
0.92
1.00
0.95
2.93
2.03
1.04
1.13
1.03
18.26
5.69
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

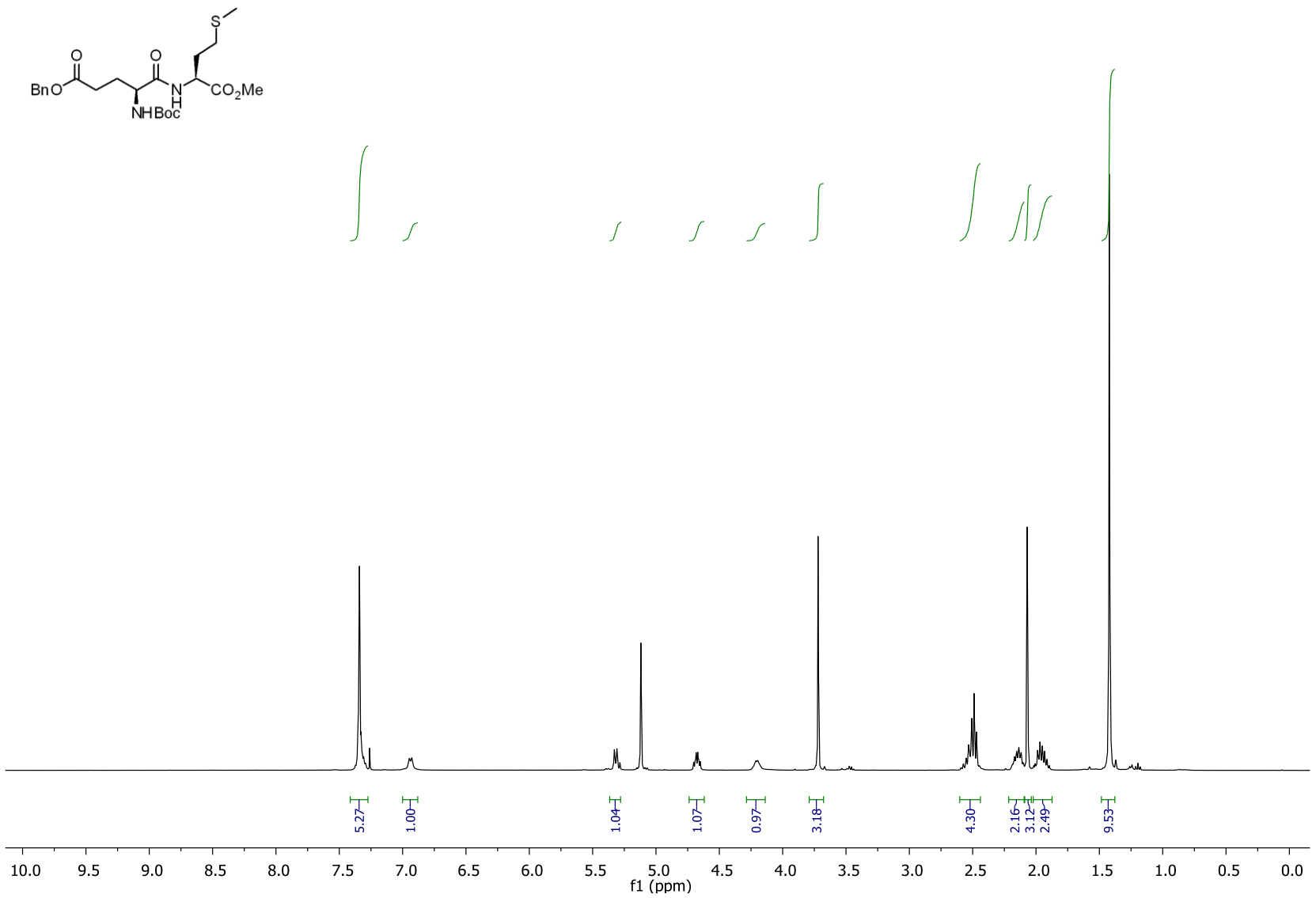

t-BuO
O
O
N
H
CO2Me
NHBoc

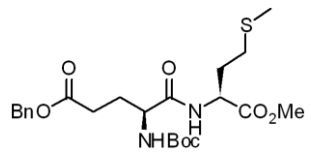

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

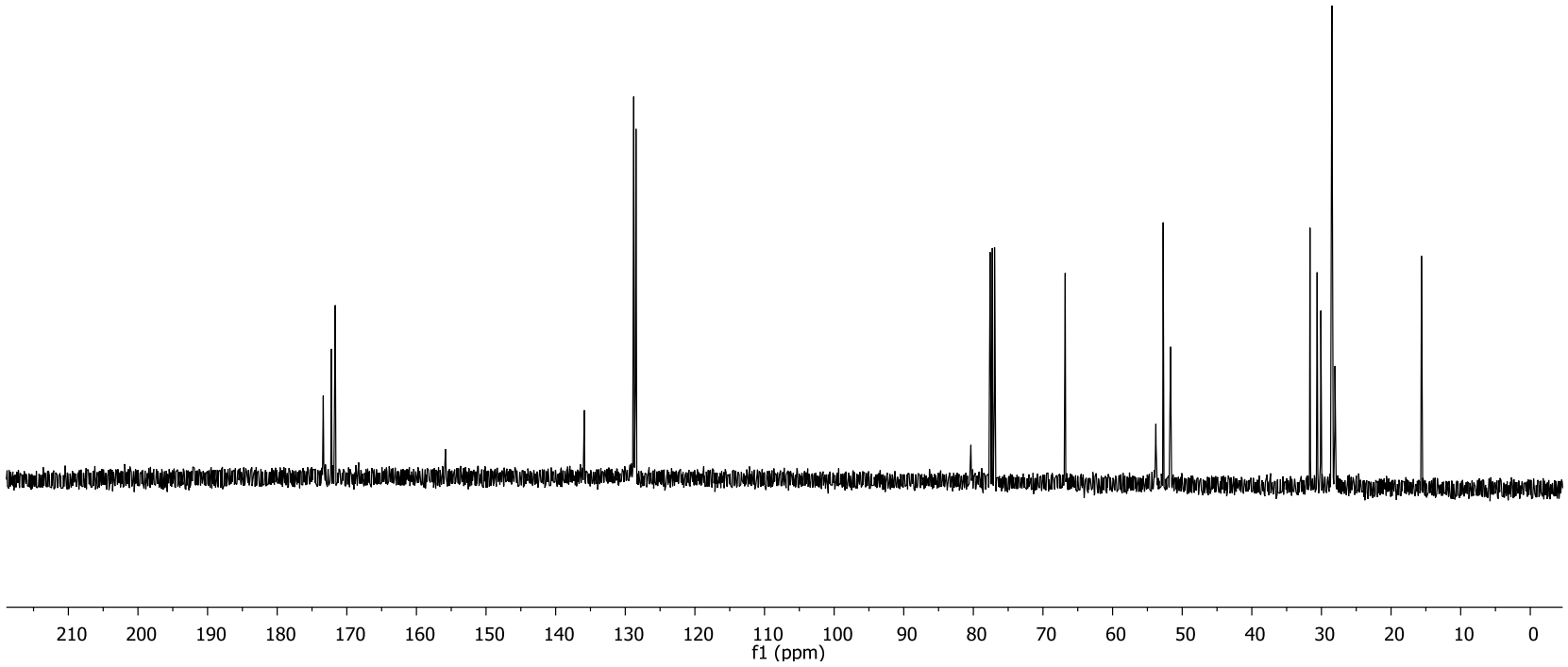

BnO
O
O
N
H
CO2Et
NHBoc
5.30
1.01
1.00
2.18
0.90
2.30
2.31
2.18
1.09
1.09
9.53
3.31
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

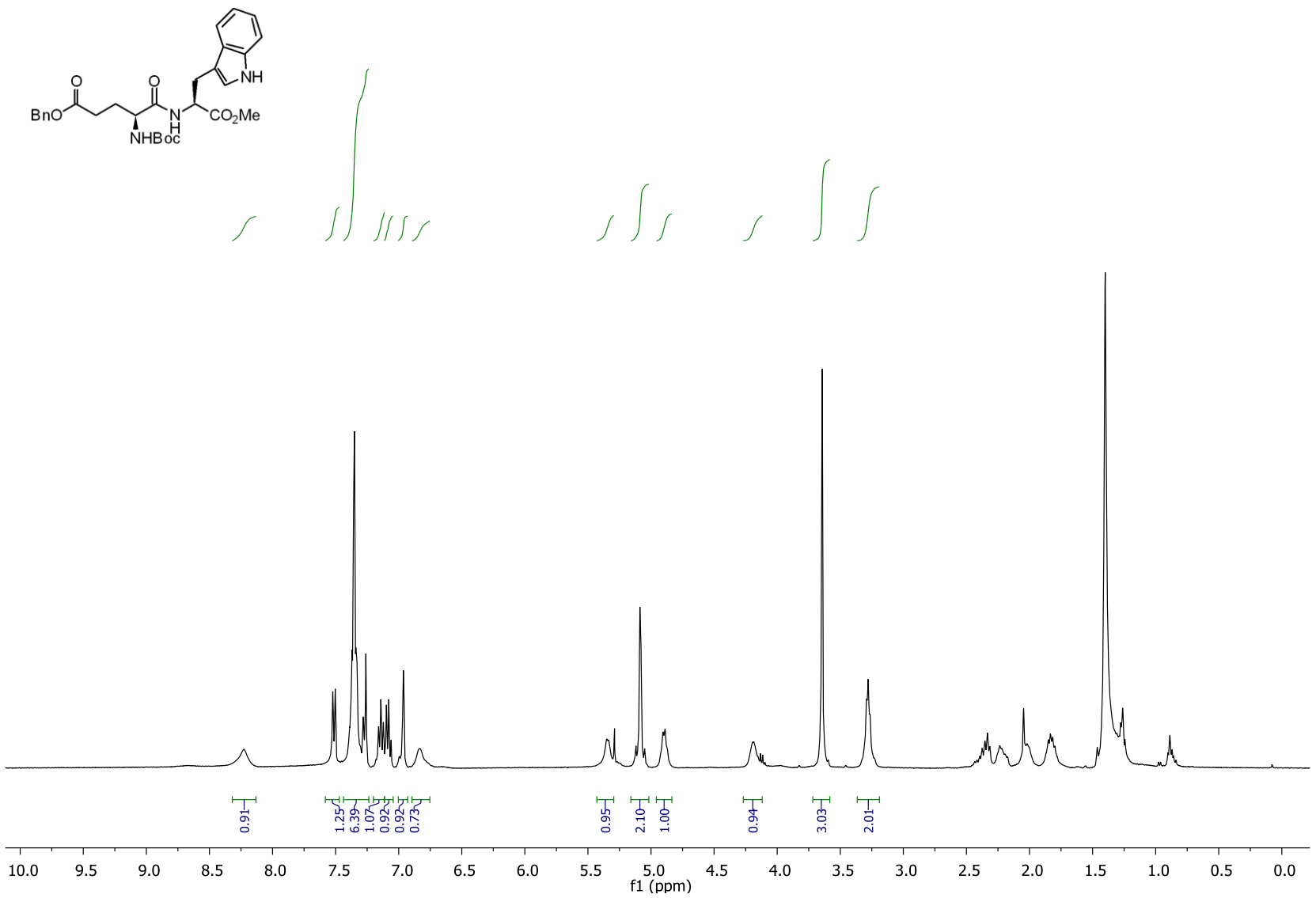

O
O
BnO
N
H
CO2Et
NHBoc

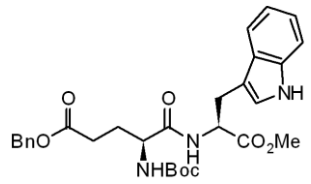

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

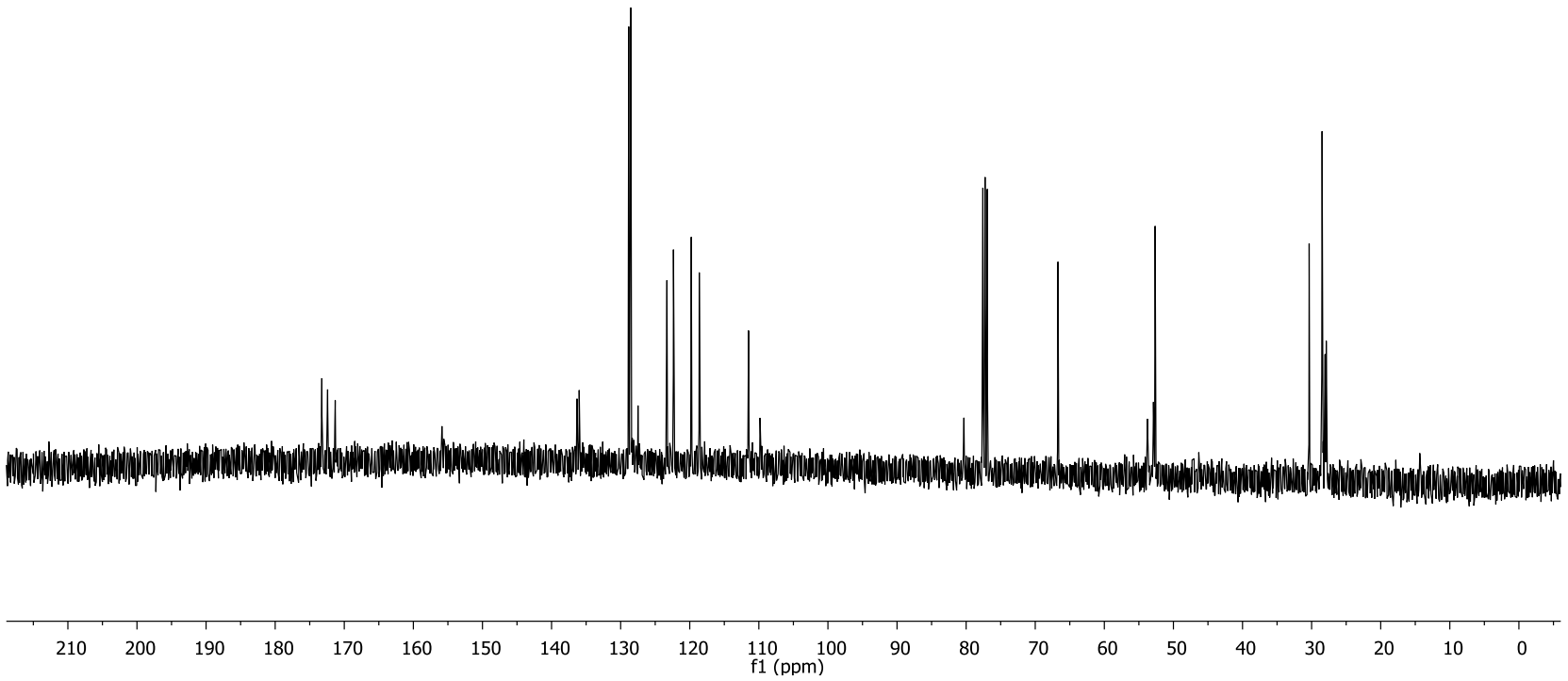

BnO
O
O
N
H
NHBoc
CO2Me
S
5.27
1.00
1.04
1.07
0.97
3.18
4.30
2.16
3.12
2.49
9.53
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

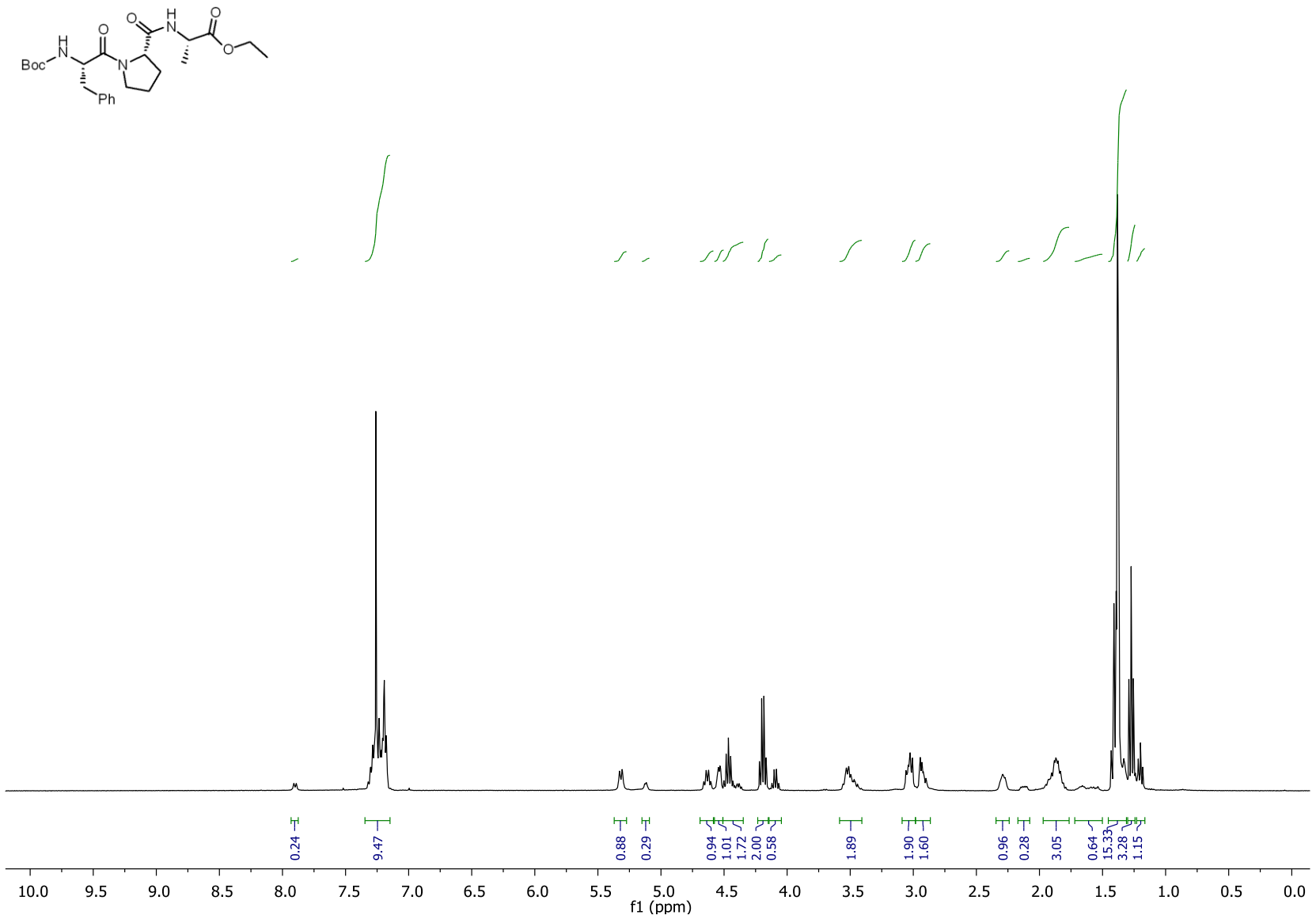

S
O
O
BnO
N
H
CO2Me
NHBoc

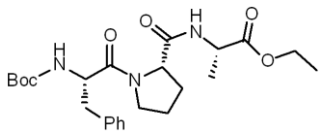

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

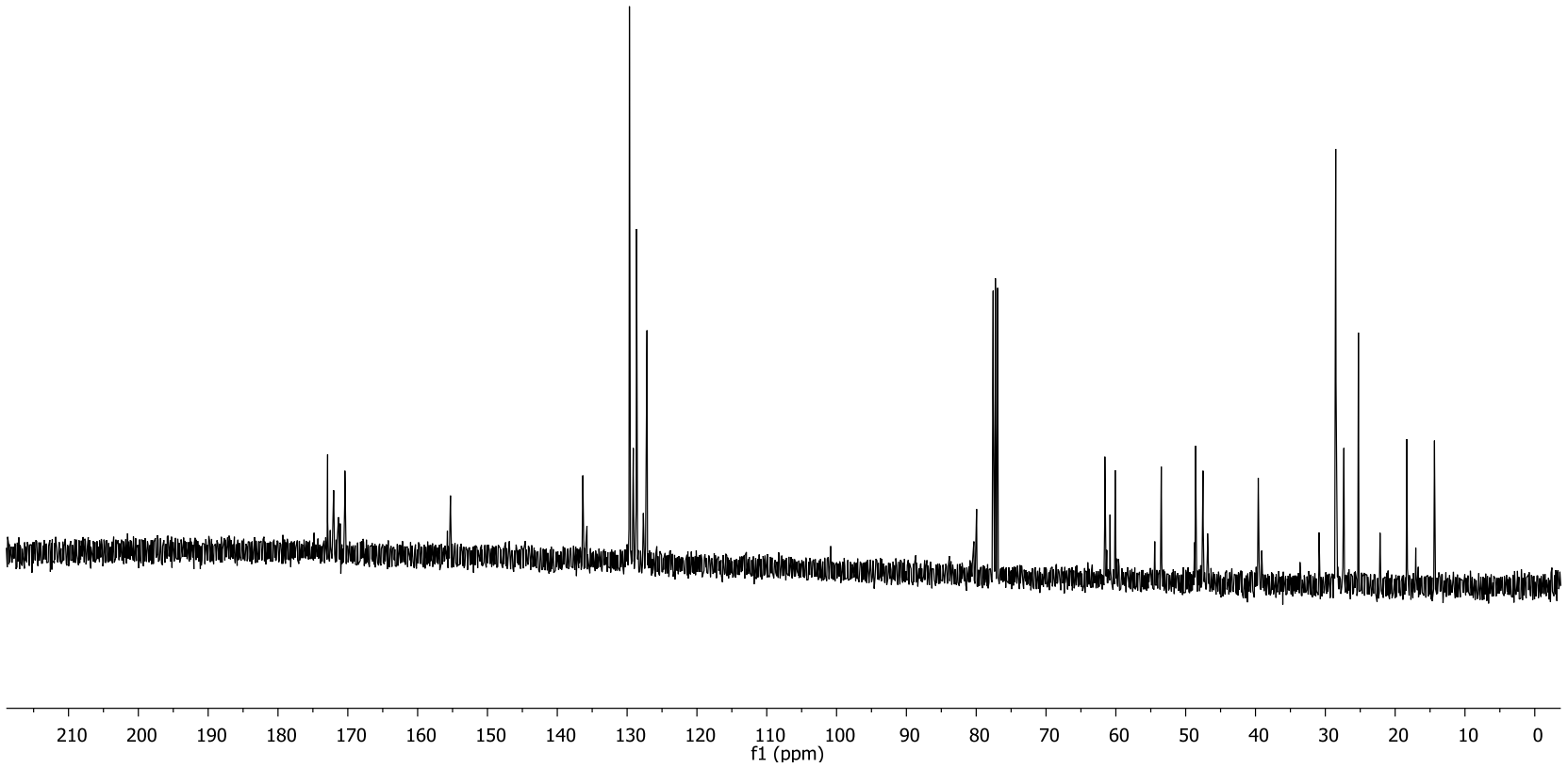

BnO
O
O
N
H
NHBoc
CO2Me
NH
0.91
1.25
6.39
1.07
0.92
0.92
0.73
0.95
2.10
1.00
0.94
3.03
2.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

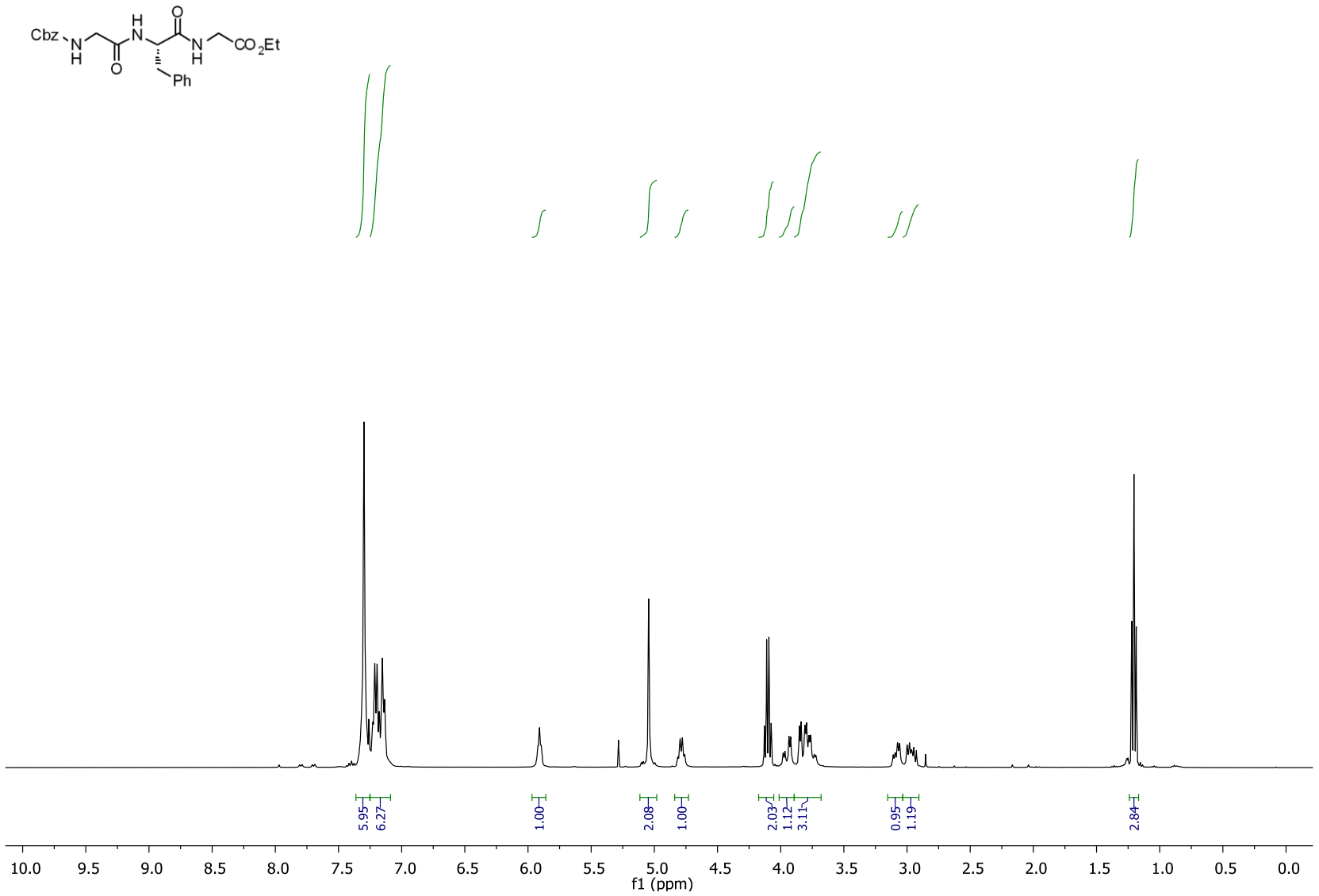

O
O
BnO
N
H
NH
CO2Me
NHBoc

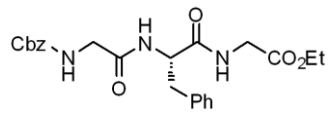

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

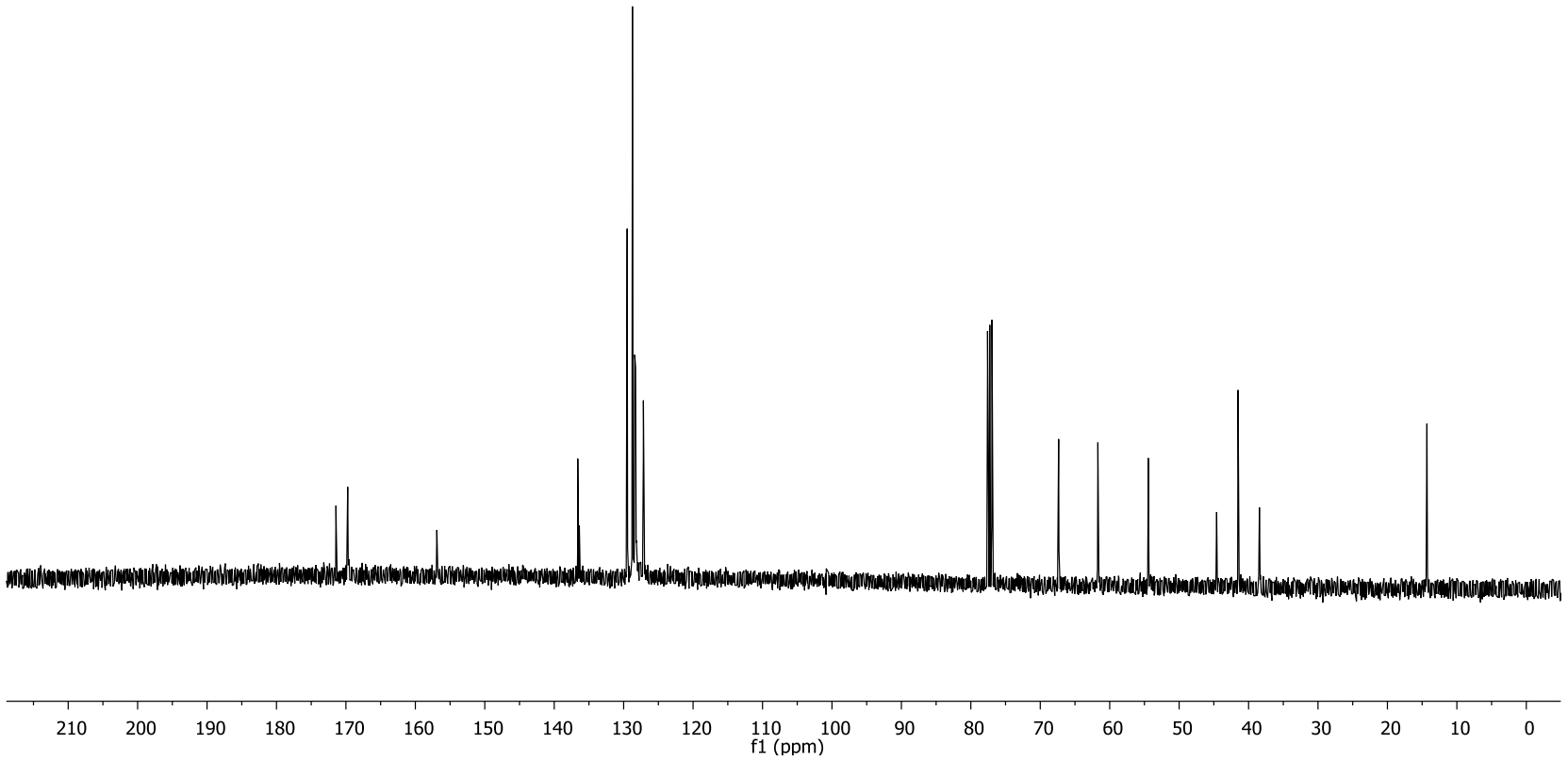

Boc
Ph
0.24
9.47
0.88
0.29
0.94
1.01
1.72
2.00
0.58
1.89
1.90
1.60
0.96
0.28
3.05
0.64
15.33
3.28
1.15
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

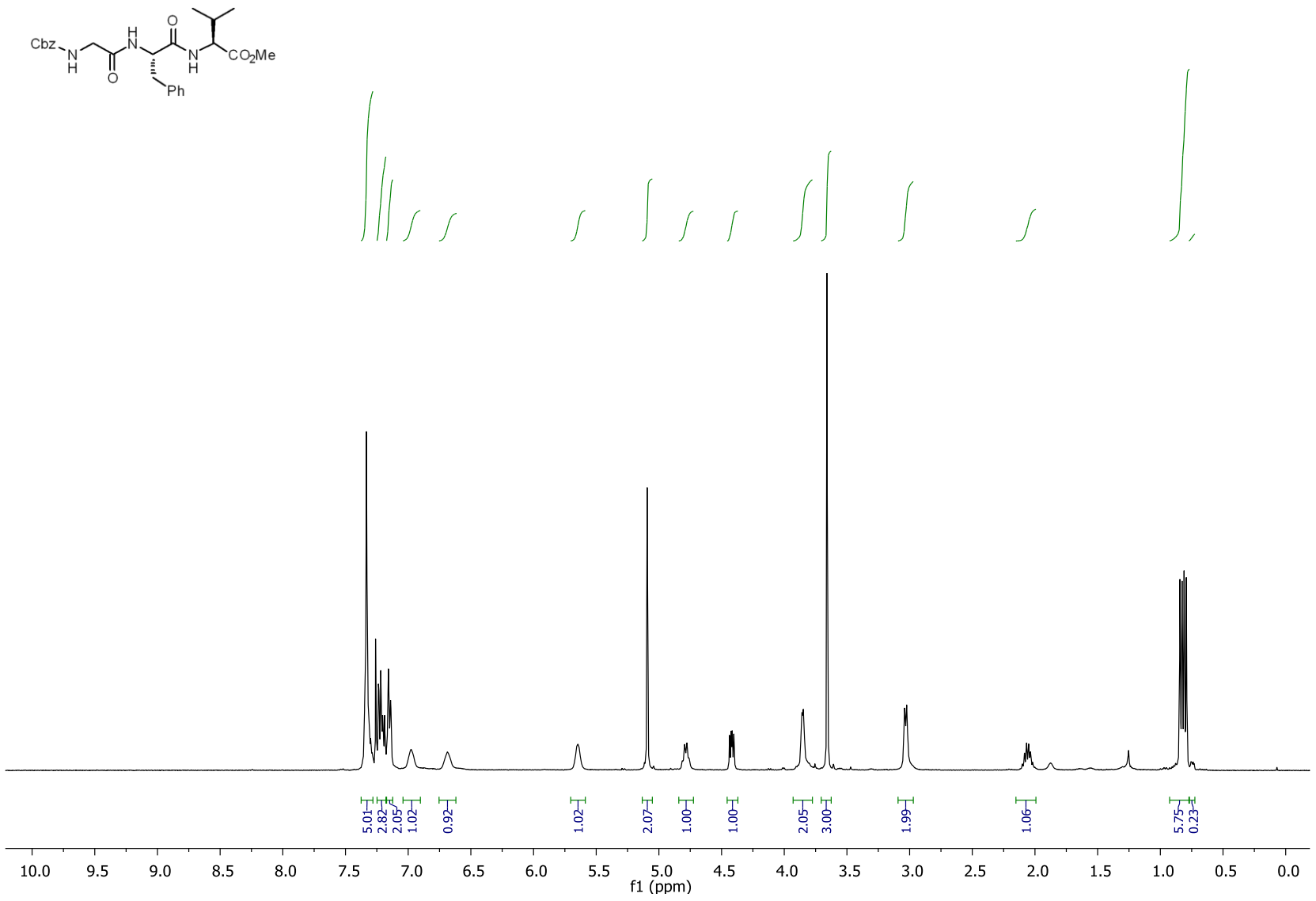

Boc
Ph

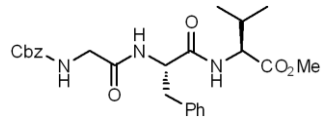

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

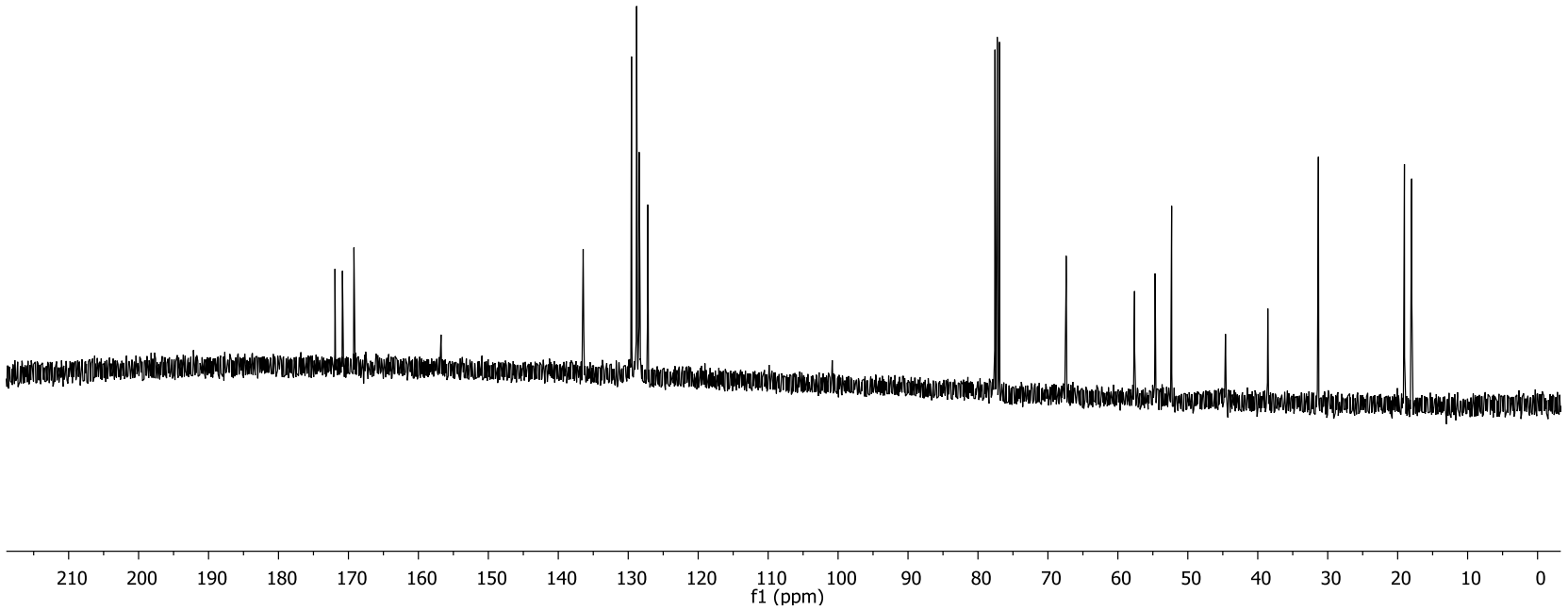

Cbz
N
H
O
H
N
O
H
N
CO2Et
Ph
5.95
6.27
1.00
2.08
1.00
2.03
1.12
3.11
0.95
1.19
2.84
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

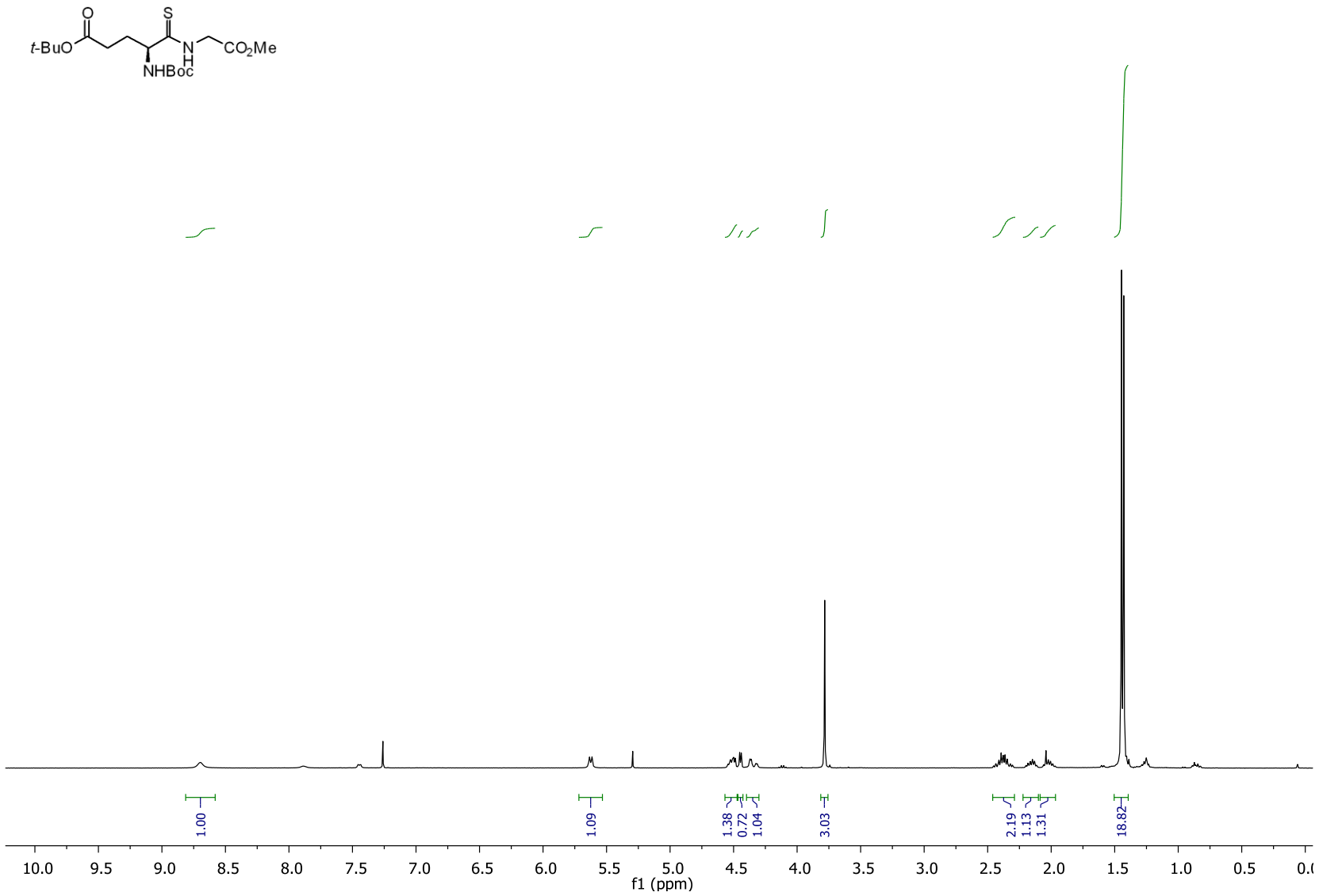

Cbz
N
H
O
H
N
O
N
H
CO2Et
Ph


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


Cbz
N
H
O
H
N
O
N
H
O
CO2Me
Ph
5.01
2.82
2.05
1.02
0.92
1.02
2.07
1.00
1.00
2.05
3.00
1.99
1.06
5.75
0.23
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Cbz
N
H
O
H
N
O
N
H
CO2Me
Ph


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


t-BuO
O
S
N
H
CO2Me
NHBoc
1.00
1.09
1.38
0.72
1.04
3.03
2.19
1.13
1.31
18.82
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
2.5
2.0
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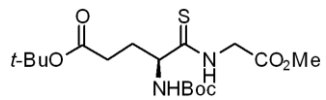
0.5
f1 (ppm)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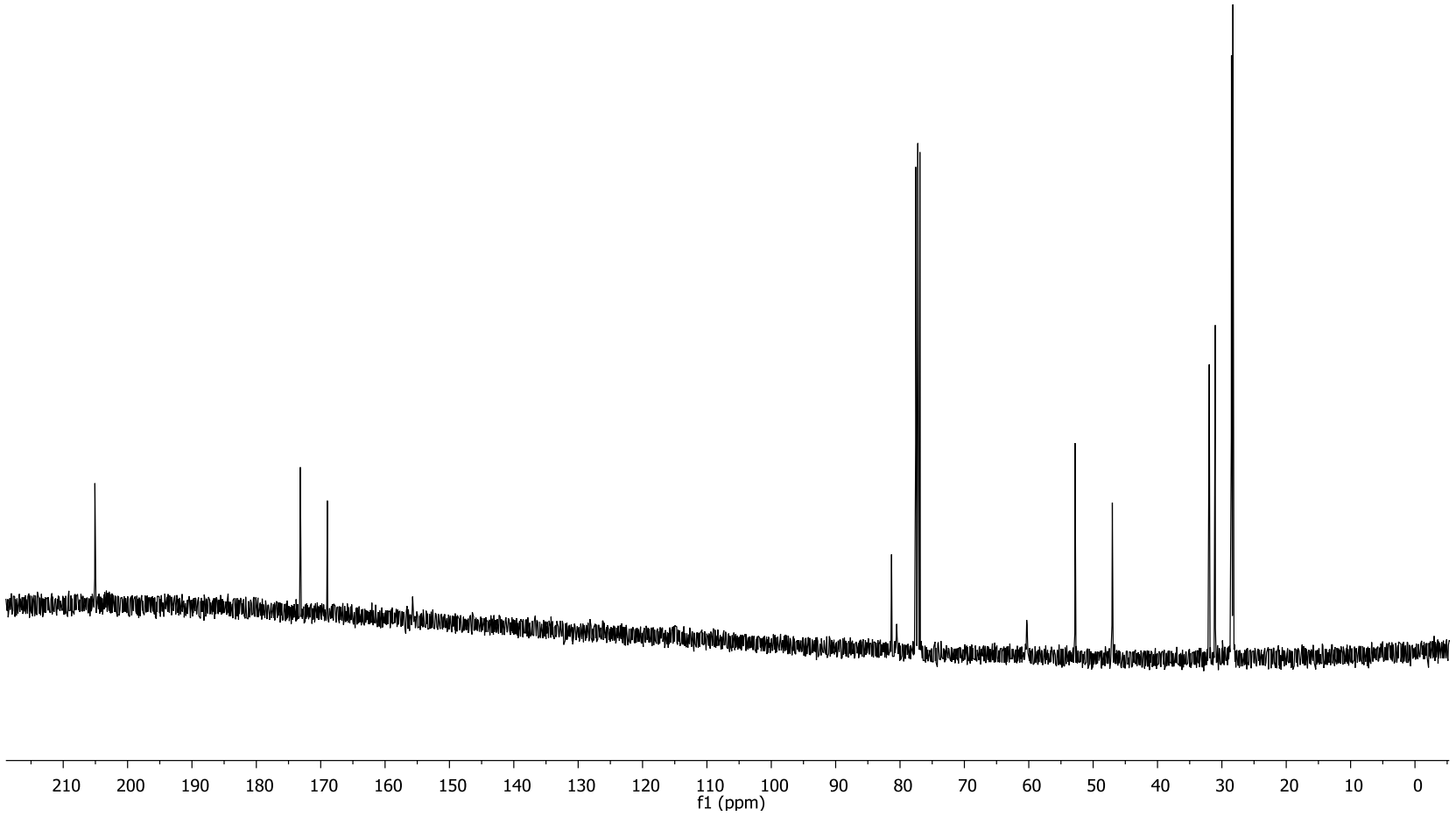
S
t-BuO
N
H
CO2Me
NHBoc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200
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180
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90
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50
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30
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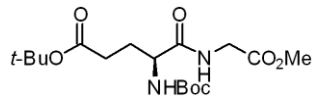
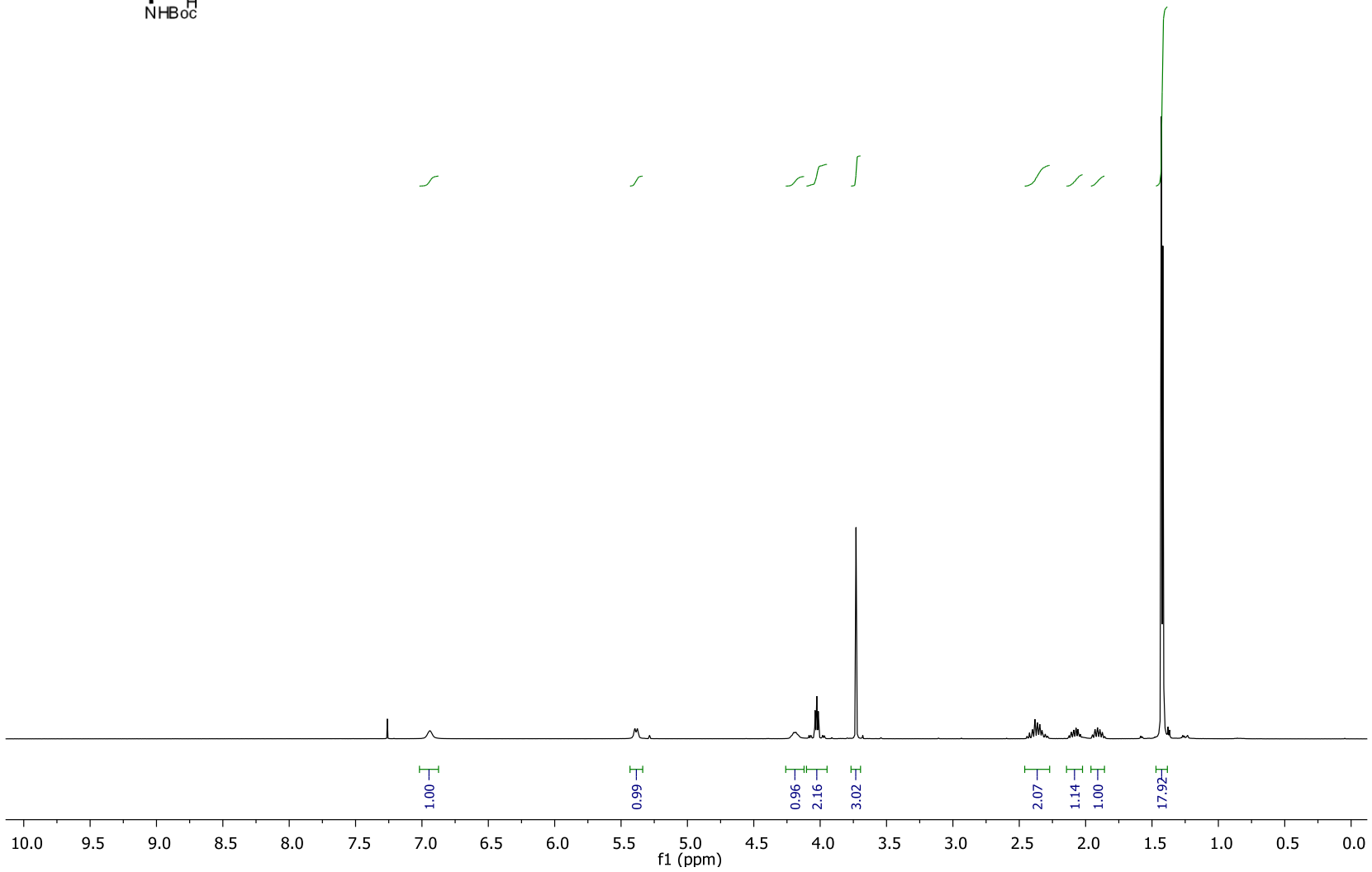
0
f1 (ppm)


t-BuO
O
O
N
H
CO2Me
NHBoc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3.02
2.07
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1.00
17.92
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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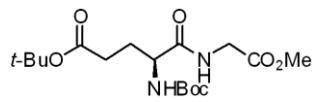
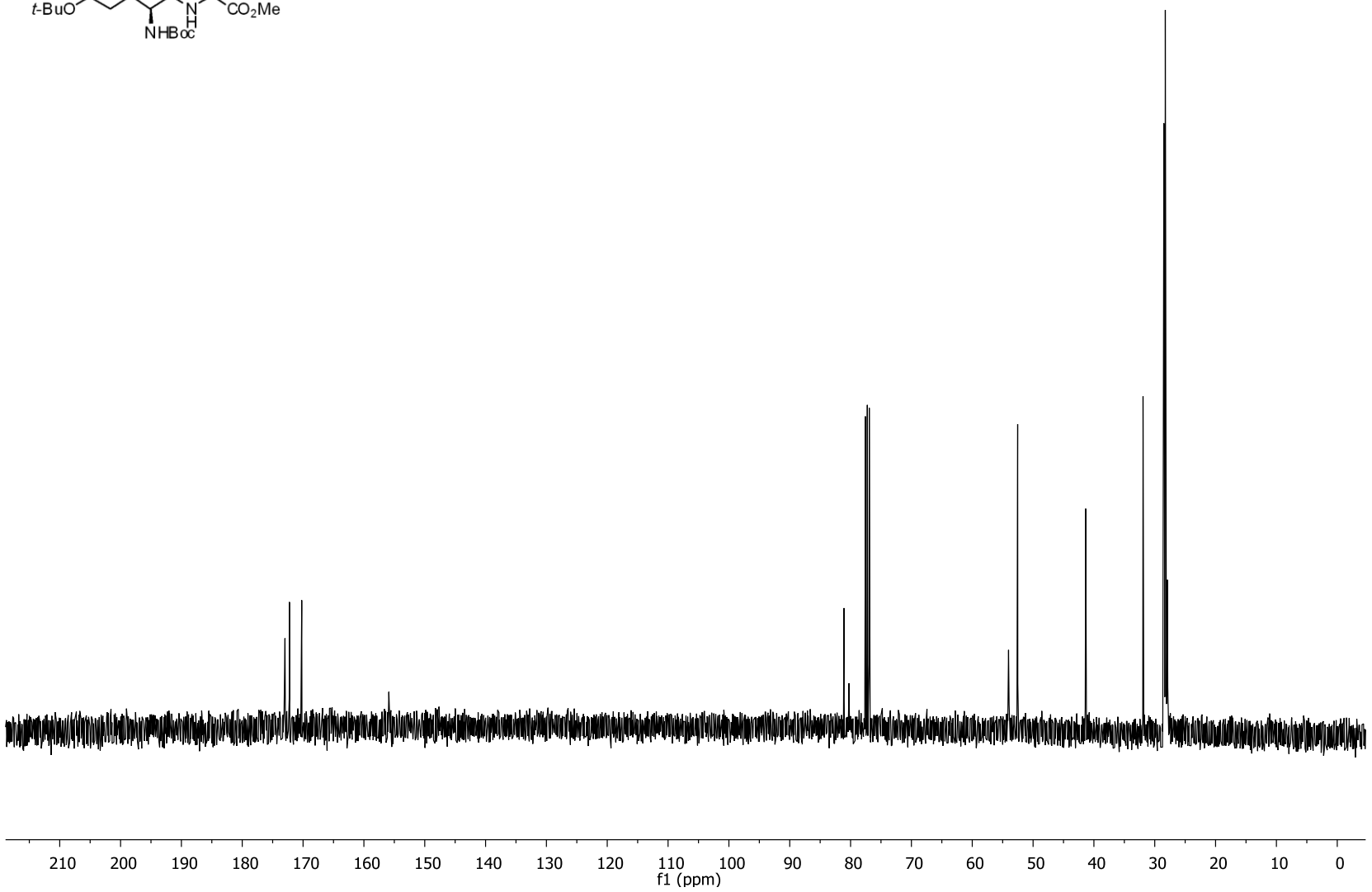
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
t-BuO
N
H
CO2Me
NHBoc


210
200
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10
0
f1 (ppm)