SUPPORTING INFORMATION

SYNTHESIS OF ORTHOGONALLY PROTECTED DISULFIDE BRIDGE MIMETICS

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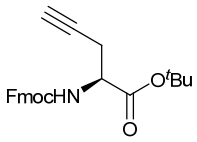
General considerations

Reactions were conducted with continuous magnetic stirring under an inert argon atmosphere unless otherwise stated. Glassware was oven-dried at >120 °C, and allowed to cool to room temperature under a positive argon pressure or vacuum. Cooling of reaction vessels to 0 °C was achieved by an ice-water bath and cooling to -15 °C was achieved by a dry ice-acetone bath. Protected allyl glycine **18** was prepared by a literature procedure.[1] All reagents (excluding solvents) were used as supplied. Dichloromethane (DCM) was freshly distilled over calcium hydride. Ethyl acetate, hexane, cyclohexane, toluene and acetone were not distilled prior to use. Anhydrous *N*,*N*-dimethylformamide and methanol were of commercial quality. Thin-layer chromatography was performed with TLC aluminium sheets with silica gel 60 F_{245}. Flash column chromatography was carried out using 0.040-0.063 mm silica gel with pre-absorption of the crude product onto silica.

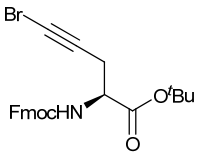
^{1}H and ^{13}C nuclear magnetic resonance experiments were carried out using a 300 MHz spectrometer. Chemical shifts are reported from the residual solvent peak. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), multiplet (m), broad (br) and apparent (ap.). Elemental analysis was performed by Robertson Microlit Laboratories. Where the percentage composition found was not within the required limits, accurate mass is reported instead of elemental analysis.

(*S*)-*tert*-Butyl 2-(9*H*-fluoren-9-ylmethoxycarbonylamino)pent-4-ynoate



Cyclohexane (7 mL) and *tert*-butyl-2,2,2-trichloroacetimidate (3.25 g, 14.9 mmol) were added to a stirred solution of compound **8** (1.00 g, 2.98 mmol) in ethyl acetate (14 mL). The reaction mixture was then stirred for 72 hours at room temperature. After this time, the solvent was removed *in vacuo* and the crude product was purified *via* flash column chromatography (9:1 hexane:ethyl acetate) to yield the *alkyne* (1.167 g, 99%) as a colourless oil. δ_H (300 MHz; $CDCl_3$) 7.77 (2H, d, *J* 7.3), 7.62 (2H, d, *J* 7.4), 7.41 (2H, ap. t, *J* 7.4), 7.32 (2H, ap. t, *J* 7.3), 5.67 (1H, d, *J* 7.9), 4.47-4.21 (4H, m), 2.77 (2H, dd, *J* 4.0 and 2.6), 2.04 (IH, s), 1.51 (9H, s); δ_C (75 MHz; $CDCl_3$) 169.5, 155.8, 144.03, 143.95, 141.5, 127.9, 127.3, 125.3, 120.2, 83.0, 78.7, 71.7, 67.4, 52.8, 47.3, 28.1, 23.2. Data consistent with literature.[2]

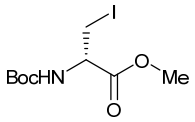
(*S*)-*tert*-Butyl 5-bromo-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)pent-4-ynoate, 7



N-Bromosuccinimide (631 mg, 3.54 mmol) and $AgNO_3$ (50 mg, 0.30 mmol) were added to a stirred solution of (*S*)-*tert*-butyl 2-(9*H*-fluoren-9-ylmethoxycarbonylamino)pent-4-ynoate (1.167 g, 2.98 mmol) in acetone (10.5 mL) under argon. The reaction mixture was stirred for 7 hours at room temperature. After this time, water (*ca.* 50 mL) was added and the suspension was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were then washed with water (ca. 50 mL) and brine (*ca.* 50 mL), dried over anhydrous sodium

sulphate and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (9:1 hexane:ethyl acetate) to yield *alkyne* **7** (1.098 g, 78%) as a pale yellow oil. ν_{max} (KBr)/cm^{-1} 3335 (br.), 3066, 2979, 2950, 1721, 1508, 1450, 1369, 1349, 1252, 1223, 1155, 1076, 1050, 843, 759, 740; δ_H (300 MHz; $CDCl_3$) 7.77 (2H, d, *J* 7.3), 7.61 (2H, d, *J* 7.4), 7.41 (2H, ap. t, *J* 7.3), 7.33 (2H, ap. tt *J* 7.4, 1.1), 5.65 (1H, d, *J* 7.5), 4.47-4.31 (3H, m), 4.25 (1H, ap.t, *J* 7.0), 2.78 (2H, d, *J* 4.5), 1.51 (9H, s); δ_C (75 MHz; $CDCl_3$) 169.4, 155.7, 144.1, 144.0, 141.5, 128.0, 127.3, 125.42, 125.36, 120.2, 83.2, 75.1, 67.4, 53.0, 47.4, 41.8, 28.2, 24.5; *m/z* LRMS (EI) 471 (^{81}Br-M^+, 60), 469 (^{79}Br-M^+, 60), 370 (95), 368 (100), 352 (65), 296 (35); HRMS (EI) 471.0859 (M^+. $C_{24}H_{24}{}^{81}BrNO_4$ requires 471.0872); $[\alpha]_D$ = +2.4 (*c* 0.5, MeOH).

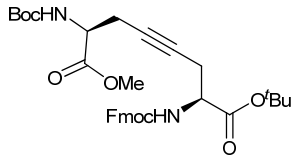
(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-iodopropanoate, 9



Triphenylphosphine (6.00 g, 22.9 mmol) and imidazole (1.55 g, 22.8 mmol) were dissolved in DCM (100 mL). The solution was cooled to 0 °C using an ice bath and iodine (5.80 g, 22.9 mmol) was added in three portions under argon. The solution was allowed to warm to room temperature and stirred at room temperature for 10 minutes. The solution was then cooled again to 0 °C and a solution of Boc-Ser-OMe **10** (4.08 g, 18.6 mmol) in DCM (16 mL) was added dropwise to the reaction mixture over 30 minutes. The reaction was then stirred at 0 °C for 30 minutes and then at room temperature for two hours. After this time, the reaction mixture was filtered through silica/celite pad, washing with 1:1 hexane:diethyl ether, and the solvent reduced *in vacuo* to yield the crude product. The crude product was purified *via* flash

column chromatography (9:1 hexane:diethyl ether) to yield *iodide* **9** (3.73 g, 61%) as a white amorphous solid. δ_H (300 MHz; $CDCl_3$) 5.34 (1H, br. s), 4.57-4.44 (1H, m), 3.80 (3H, s), 3.63-3.48 (2H, m), 1.46 (9H, s); δ_C (75 MHz; $CDCl_3$) 170.4, 155.2, 80.4, 54.0, 53.4, 28.6, 8.2. Data consistent with literature.[3]

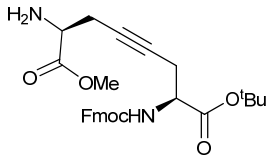
(2*S*,7*S*)-*tert*-Butyl 7-(*tert*-butoxycarbonylamino)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-7-(methoxycarbonyl)hept-4-ynoate, 6



Zinc dust (331 mg, 5.05 mmol) was weighed into a round bottomed flask. Iodine (12.8 mg, 0.05 mmol) was added and the flask was heated with a heat gun, under vacuum for ten minutes and then flushed with argon. The flask was evacuated and flushed with argon a further three times and cooled to 0 °C. Compound **9** (500 mg, 1.52 mmol) was dissolved in anhydrous DMF (1.5 mL) and added dropwise, *via* syringe, to the activated zinc at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 90 minutes to give the corresponding organozinc intermediate (TLC analysis was used to confirm the complete consumption of the starting material). In a separate flask, CuCN (118 mg, 1.32 mmol) and LiCl (112 mg, 2.63 mmol) were heated to 150 °C for two hours under argon and then cooled to room temperature. DMF (2.2 mL) was added and the solution stirred for five minutes to form the soluble CuCN·2LiCl complex. The copper complex was then cooled to -15 °C. Once the zinc insertion process was judged to have reached completion, stirring was ceased to allow the zinc powder to settle to the bottom of the flask. The supernatant was removed *via* syringe under argon (with care being taken to avoid the transfer of zinc) and

added dropwise to the copper complex at -15 °C. Compound **7** (476 mg, 1.01 mmol) was then dissolved in DMF (1.5 mL) and also added dropwise to the copper complex at -15 °C. The cooling bath was removed and the reaction mixture was stirred at room temperature for 16 hours under argon. After this time, water (*ca.* 50 mL) was added and the suspension was extracted with diethyl ether (3 × 100 mL), washed with brine (*ca.* 60 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (5:1 hexane:ethyl acetate) to yield *alkyne* **6** (376 mg, 63%) as an amorphous white solid. ν_{max} (KBr)/cm^{-1} 3376, 3358, 3064, 3038, 2977, 2934, 1746, 1737, 1704, 1516, 1439, 1389, 1362, 1219, 1168, 1058, 1016, 845, 759, 743; δ_H (300 MHz; $CDCl_3$) 7.82-7.65 (4H, m), 7.45-7.26 (4H, m), 6.23 (1H, d, *J* 8.5), 6.03 (1H, d, *J* 8.7), 4.65-4.15 (5 H, m), 3.71 (3H, s), 2.78-2.52 (4H, m), 1.52 (9H, s), 1.46 (9H, s); δ_C (75 MHz; $CDCl_3$) 172.2, 170.4, 156.1, 155.5, 144.1, 141.5, 127.9, 127.4, 127.3, 125.6, 125.5, 120.2, 120.1, 82.9, 80.1, 78.5, 78.2, 67.3, 53.01, 52.95, 52.3, 47.4, 28.6, 28.3, 24.2, 24.1; *m/z* LRMS (EI) 592 (M^+, 20), 492 (25), 391 (50), 269 (45), 241 (55), 178 (100); Anal. Calc. for $C_{33}H_{40}N_2O_8$: C, 66.87; H, 6.80; N, 4.73. Found: C, 66.76; H, 6.78; N, 4.70%; $[\alpha]_D$ = +11.6 (*c* 0.5, MeOH).

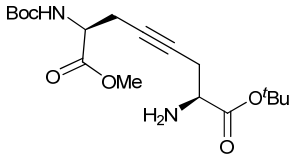
(2*S*,7*S*)-*tert*-Butyl 7-amino-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-7-(methoxycarbonyl)hept-4-ynoate, 11[4]



Anhydrous methanol (2.10 mL, 1.66 g, 5.19 mmol) was added dropwise to a stirred solution of acetyl chloride (3.60 mL, 3.97 g, 5.06 mmol) in ethyl actate (29 mL) under argon and the solution was stirred at room temperature for 20 minutes. In a separate flask, compound **6** (50

mg, 0.08 mmol) was added under argon. The 1.75 M HCl solution (1.1 mL) was then added to compound **6** and the reaction mixture stirred for 16 hours at room temperature. After this time, the solution was evaporated to give the crude product which was purified *via* flash column chromatography (99:1 chloroform:methanol) to yield *amine* **11** (38.4 mg, 92%) as a pale yellow oil. ν_{max} (KBr)/cm^{-1} 3375 (br.), 3065, 3042, 2978, 2952, 2855, 1746, 1740, 1731, 1715, 1517, 1505, 1451, 1369, 1350, 1222, 1156, 1106, 1057, 1017, 846, 760, 740; δ_H (300 MHz; $CDCl_3$) 7.79-7.63 (4H, m), 7.43-7.26 (4H, m), 6.07 (1H, d, *J* 8.7), 4.50-4.35 (3H, m), 4.24 (1H, t, *J* 7.1), 3.73 (3H, s), 3.61 (1H, ap. t, *J* 4.8), 2.74-2.52 (4H, m), 1.97 (2H, br. s), 1.49 (9H, s); δ_C (75 MHz; $CDCl_3$) 175.1, 170.1, 156.1, 144.2, 144.1, 141.5, 127.9, 127.31, 127.27, 125.48, 125.45, 120.2, 82.7, 79.1, 78.0, 67.3, 53.6, 53.1, 52.6, 47.4, 28.2, 25.4, 23.7; *m/z* LRMS (ESI) 515.2 ($M+Na^+$, 20), 493.2 (M+H, 100); HRMS (ESI) 493.2327 ($M+H^+$. $C_{28}H_{33}N_2O_6$ requires 493.2339); Anal. Calc. for $C_{28}H_{32}N_2O_6$: C, 68.28; H, 6.55; N, 5.69. Found: C, 68.94; H, 7.01; N, 5.45%.

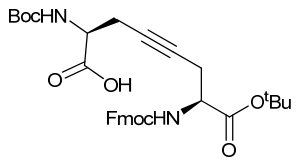
(2*S*,7*S*)-*tert*-Butyl 2-amino-7-(*tert*-butoxycarbonylamino)-7-(methoxycarbonyl)hept-4-ynoate, 12



Diethylamine (0.14 mL, 98 mg, 1.34 mmol) was added to a stirred solution of compound **6** (40 mg, 0.07 mmol) in anhydrous methanol (0.6 mL) at 0 °C. The ice bath was removed and the reaction mixture was stirred at room temperature for 5.5 hours. After this time, the solution was evaporated to give the crude product which was purified *via* flash column chromatography (99:1 chloroform:methanol) to yield *amine* **12** (24.5 mg, 98%) as a pale

yellow oil. ν_{max} (KBr)/cm^{-1} 3374, 2978, 2932, 1722, 1715, 1514, 1506, 1455, 1438, 1393, 1368, 1250, 1220, 1163, 1060, 1021, 849, 779; δ_H (300 MHz; $CDCl_3$) 5.77 (1H, d, *J* 8.7), 4.49 (1H, dt, *J* 8.8 and 4.3), 3.76 (3H, s), 3.47 (1H, ap. t, *J* 5.0), 2.78-2.46 (4H, m), 1.82 (2H, br. s), 1.47 (9H, s), 1.45 (9H, s); δ_C (75 MHz; $CDCl_3$) 173.8, 171.8, 155.5, 81.7, 80.1, 79.0, 77.8, 53.8, 52.8, 52.3, 28.6, 28.2, 25.5, 23.7; *m/z* LRMS (EI) 370 (M^+, 15), 269 (85), 169 (80), 57 (100); HRMS (EI) 370.2111 (M^+. $C_{18}H_{30}N_2O_6$ requires 370.2104).

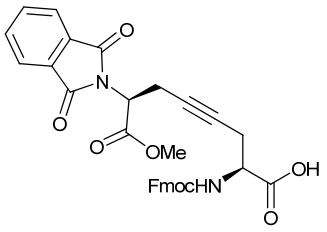
(2*S*,7*S*)-7-(*tert*-Butoxycarbonyl)-2-(*tert*-butoxycarbonylamino)-7-(9*H*-fluoren-9-ylmethoxycarbonylamino)hept-4-ynoic acid, 13[5]



Trimethyltinhydroxide (76.3 mg, 0.42 mmol) was added to a stirred solution of compound **6** (50 mg, 0.08 mmol) in 1,2-dichloroethane (2.0 mL) under argon. The reaction mixture was then heated at 70 °C for 4 hours. After this time, the reaction mixture was concentrated *in vacuo*, and the residue dissolved in ethyl acetate (ca. 15 mL). The organic phase was washed with 0.5 M $HCl_{(aq)}$ (3 × 15 mL) and brine (ca. 15 mL), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo.* The product was then dissolved in the minimum amount of ethyl acetate possible (ca. 0.3 mL) and an excess of hexane added (ca. 10 mL). The flask was then sealed and placed in a freezer overnight to yield white crystals. Collection of the crystals by filtration yielded *carboxylic acid* **13** (38.3 mg, 78%). Note: flash column chromatography resulted in the decomposition of compound **13**. mp 121.5-122.5 °C; ν_{max} (KBr)/cm^{-1} 3370 (br.), 2978, 2928, 2855, 1715, 1516, 1451, 1394, 1368, 1351, 1250, 1224, 1159, 1058, 847, 759, 740; δ_H (300 MHz; $CDCl_3$) 7.80-7.26 (8H, m), 6.02 (1H, d, *J* 8.7), 5.88

(1H, d, *J* 8.6), 4.65-4.05 (5H, m), 2.80-2.43 (4H, m), 1.49 (9H, s), 1.44 (9H, s); δ_C (75 MHz; $CDCl_3$) 173.7 170.4, 156.0, 155.7, 144.3, 143.9, 141.6, 141.5, 127.9, 127.3, 125.6, 125.4, 120.2, 83.0, 80.5, 78.4, 78.2, 67.2, 53.0, 52.1, 47.3, 28.5, 28.2, 23.7, 23.5. *m/z* LRMS (ESI) 601.3 ($M+Na^+$, 100); Anal. Calc. for $C_{32}H_{38}N_2O_8$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.17; H, 6.52; N, 4.79%.

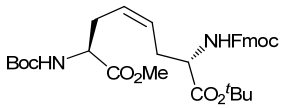
(2*S*,7*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-7-methoxycarbonyl-7-(phthalimido)hept-4-ynoic acid, 14



Trifluoroacetic acid (5.2 mL) was added dropwise to a stirred solution of compound **6** (120 mg, 0.20 mmol) in DCM (0.3 mL) at 0 °C. The reaction mixture was stirred for 4 hours at 0 °C. After this time, the solvent was removed *in vacuo* to give the crude deprotected product. Anhydrous toluene (20 mL) was then added followed by phthalic anhydride (33 mg, 0.22 mmol) and triethylamine (0.085 mL, 61 mg, 0.61 mmol). The mixture was refluxed under Dean-Stark conditions for 2.5 hours. The volatiles were evaporated *in vacuo* and the residue dissolved in ethyl acetate (ca. 60 mL). The organic phase was washed with 10% citric $acid_{(aq)}$ (ca. 15 mL), water (ca. 15 mL), saturated $NaHCO_{3(aq)}$ (ca. 15 mL) and brine (ca. 15 mL), dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography (19:1 chloroform:methanol) to yield *carboxylic acid* **14** (59 mg, 51%) as a pale yellow foam. ν_{max} (KBr)/cm^{-1} 3374 (br.), 3065, 2953, 2925, 1776, 1748, 1716, 1518, 1450, 1436, 1390, 1340, 1251, 1213, 1110, 1057, 977, 760, 741,

720; δ_H (300 MHz; $CDCl_3$) 7.88-7.20 (13H, m), 5.79 (1H, d, *J* 5.1), 5.04 (1H, t, *J* 7.5), 4.50-4.10 (4H, m), 3.69 (3H, s), 3.19-2.98 (2H, m), 2.80-2.42 (2H, m); δ_C (75 MHz; $CDCl_3$) 174.6, 168.5, 167.8, 156.2, 144.1, 143.9, 141.4, 134.6, 131.8, 127.9, 127.3, 125.51, 125.46, 124.4, 124.0, 120.2, 78.9, 77.5, 67.5, 53.2, 52.9, 51.2, 47.3, 22.8, 20.2; *m/z* LRMS (EI) 566 (M^+, 5), 316 (15), 178 (100), 147 (75); HRMS (EI) 566.1697 (M^+. $C_{32}H_{26}N_2O_8$ requires 566.1689).

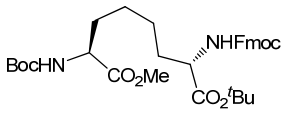
(2*S*,7*S*,*Z*)-*tert*-Butyl 7-(*tert*-butoxycarbonylamino)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-7-(methoxycarbonyl)hept-4-enoate, 15[6]



To a solution of compound **6** (100 mg, 0.17 mmol) in a 1:1 mixture of hexane/ethyl acetate (4 mL) was added palladium/barium sulphate (10% palladium by weight, 30 mg) under argon. A balloon fitted with a glass tap attachment was filled with argon and evacuated. The balloon was then filled with hydrogen and attached to the top of the flask. The inert atmosphere was then exchanged for hydrogen by briefly exposing the reaction vessel to vacuum (1-2 seconds) and filling the vessel with hydrogen through the balloon on the top. The evacuation of the atmosphere and filling with hydrogen was performed twice. The reaction was then left open to the balloon and stirred vigorously for 2 hours at room temperature. After this time, the balloon was removed and the reaction mixture diluted with ethyl acetate (ca. 15 mL), filtered through a celite pad, washing with ethyl acetate (ca. 40 mL), and reduced *in vacuo*. The crude product was purified *via* flash column chromatography (5:1 hexane:ethyl acetate) to yield *alkene* **15** (88 mg, 88%) as a colourless oil. ν_{max} (KBr)/cm^{-1} 3363 (br.), 3004, 2978, 2954, 2934, 1718, 1516, 1451, 1393, 1368, 1353, 1250, 1222, 1159, 1050, 1024, 846, 760, 741; δ_H (300 MHz; $CDCl_3$) 7.76 (2H, d, *J* 7.4), 7.61 (2H, m), 7.40 (2H, ap.t, *J* 7.3), 7.31 (2H, ap.t, *J*

7.4), 5.58-5.37 (3H, m), 5.14 (1H, d, *J* 7.8), 4.52-4.16 (5H, m), 3.72 (3H, s), 2.68-2.35 (4H, m), 1.47 (9H, s), 1.45 (9H, s); δ_C (75 MHz; $CDCl_3$) 172.6, 170.9, 155.9, 155.3, 144.1, 141.5, 127.9, 127.74, 127.69, 127.3, 125.4, 120.2, 82.6, 80.4, 67.3, 54.0, 53.2, 52.6, 47.4, 30.71, 30.67, 28.5, 28.3; *m/z* LRMS (EI) 594 (M^+, 10), 351 (25), 271 (35), 243 (100); Anal. Calc. for $C_{33}H_{42}N_2O_8$: C, 66.65; H, 7.12; N, 4.71. Found: C, 66.44; H, 7.06; N, 4.35%; $[\alpha]_D$ = +5.8 (*c* 0.5, MeOH).

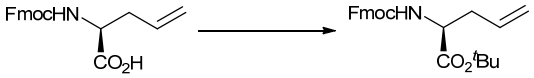
(2*S*,7*S*)-*tert*-Butyl 7-(*tert*-butoxycarbonylamino)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-7-(methoxycarbonyl)heptanoate, 16



To a solution of compound **6** (42 mg, 0.07 mmol) in ethyl acetate (2 mL) was added palladium on carbon (10% palladium by weight, 14 mg) under argon. A balloon fitted with a glass tap attachment was filled with argon and evacuated. The balloon was then filled with hydrogen and attached to the top of the flask. The inert atmosphere was then exchanged for hydrogen by briefly exposing the reaction vessel to vacuum (1-2 seconds) and filling the vessel with hydrogen through the balloon on the top. The evacuation of the atmosphere and filling with hydrogen was performed twice. The reaction was then left open to the balloon and stirred for 20 hours at room temperature. After this time, the reaction mixture was diluted with ethyl acetate (ca. 15 mL), filtered through a celite pad, washing with ethyl acetate (ca. 40 mL), and reduced *in vacuo*. The crude product was purified *via* flash column chromatography (5:1 hexane:ethyl acetate) to yield *alkane* **16** (42 mg, 99%) as a colourless oil.[7] ν_{max} (KBr)/cm^{-1} 3347 (br.), 3003, 2977, 2935, 2865, 1717, 1517, 1451, 1392, 1367, 1248, 1223, 1162, 1106, 1078, 1048, 848, 760, 741; δ_H (300 MHz; $CDCl_3$) 7.76 (2H, d, *J*

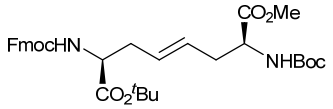
7.4), 7.60 (2H, d, *J* 7.3), 7.40 (2H, ap. t, *J* 7.4), 7.31 (2H, ap.t, *J* 7.3), 5.34 (1H, d, *J* 8.1), 5.03 (1H, d, *J* 8.0), 4.50-4.15 (5H, m), 3.73 (3H, s), 1.90-1.55 (4H, m), 1.47 (9H, s), 1.44 (9H, s), 1.43-1.26 (4H, m); δ_C (75 MHz; $CDCl_3$) 173.5, 171.8, 156.1, 155.6, 144.2, 144.1, 141.5, 127.9, 127.3, 125.3, 120.2, 82.4, 80.1, 67.1, 54.4, 53.5, 52.5, 47.4, 32.9, 32.8, 28.5, 28.3, 25.2, 24.9; *m/z* LRMS (EI) 596 (M^+, 5), 364 (20), 273 (100); Anal. Calc. for $C_{33}H_{44}N_2O_8 \cdot H_2O$: C, 64.48; H, 7.54; N, 4.56. Found: C, 64.63; H, 7.33; N, 4.38%; $[\alpha]_D$ = -14.4 (*c* 0.5, MeOH).

(*S*)-*tert*-Butyl 2-(9*H*-fluoren-9-ylmethoxycarbonylamino)pent-4-enoate, 17



A solution of *tert*-butyl trichloroacetimidate (7.772 g, 35.6 mmol) in cyclohexane (25 mL) was added to a solution of (*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)pent-4-enoic acid (3.000 g, 8.89 mmol) in ethyl acetate (54 mL). The reaction mixture was stirred at room temperature for 67 hours. After this time, the reaction mixture was concentrated *in vacuo* and purified *via* flash column chromatography (9:1 hexane:ethyl acetate) to yield *alkene* **17** (3.169 g, 91%) as a colourless oil. δ_H (300 MHz; $CDCl_3$) 7.77 (2H, d, *J* 7.4), 7.60 (2H, dd, *J* 7.4, 0.6), 7.40 (2H, ap. td, *J* 7.4, 0.6), 7.31 (2H, ap. td, *J* 7.4, 1.1), 5.80-5.64 (1H, m), 5.36 (1H, d, *J* 7.9), 5.15 (2H, ap. d, *J* 11.8), 4.48-4.29 (3H, m), 4.23 (1H, t, *J* 7.1), 2.66-2.45 (2H, m), 1.48 (9H, s); δ_C (75 MHz; $CDCl_3$) 171.0, 155.8, 144.1, 144.0, 141.5, 132.4, 127.9, 127.2, 125.3, 120.2, 119.3, 82.5, 67.2, 53.8, 47.4, 37.2, 28.3. Data consistent with literature.[8]

(2*S*,7*S*,*E*)-*tert*-Butyl 7-(*tert*-butoxycarbonylamino)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-7-(methoxycarbonyl)hept-4-enoate, 19[9]

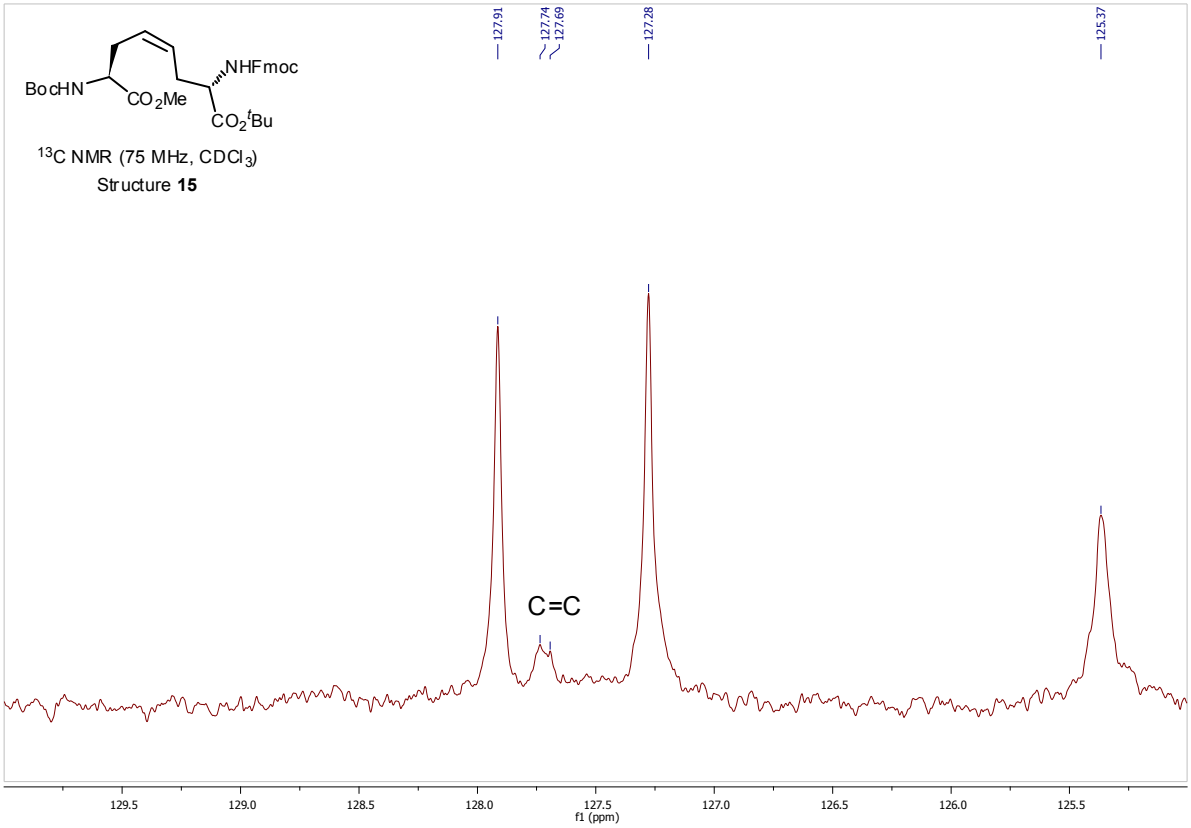


Compound **17** (335 mg, 0.852 mmol) and compound **18** (216 mg, 0.942 mmol) were added to an oven dried round bottomed flask under argon. DCM (8.5 mL) and Grubbs second generation catalyst (**20**) (73 mg, 0.085 mmol) were added and the reaction was refluxed for 6.5 hours under argon. The reaction mixture was allowed to cool to room temperature and $Pb(OAc)_4$ (112mg, 0.252 mmol) was added. The reaction mixture was stirred for 16 hours at room temperature. After this time, the reaction mixture was diluted with DCM (ca. 15 mL), filtered through a celite/silica (1:1) pad, washing with DCM (ca. 100 mL), and reduced *in vacuo*. The crude product was purified *via* flash column chromatography (9:1 toluene:diethyl ether) to yield *alkene* **19** (287 mg, 57%) as a colourless oil. ν_{max} (KBr)/cm^{-1} 3354 (br.), 3065, 3041, 2978, 2934, 1716, 1508, 1451, 1367, 1352, 1249, 1221, 1161, 1081, 972, 847, 760, 740, 703; δ_H (300 MHz; $CDCl_3$) 7.76 (2H, d, *J* 7.4), 7.63 (2H, d, *J* 7.3), 7.40 (2H, ap.t, *J* 7.4), 7.31 (2H, ap. td, *J* 7.3, 1.1), 5.52-5.35 (3H, m), 5.18 (1H, d, *J* 9.5), 4.50-4.18 (5H, m), 3.72 (3H, s), 2.57-2.37 (4H, m), 1.47 (9H, s), 1.44 (9H, s); δ_C (75 MHz; $CDCl_3$) 172.7, 170.9, 155.9, 155.4, 144.1, 141.5, 128.8, 128.6, 127.9, 127.3, 125.4, 120.2, 82.5, 80.2, 67.2, 54.0, 53.3, 52.5, 47.4, 35.83, 35.78, 28.5, 28.3; *m/z* LRMS (EI) 594 (M^+, 20), 550 (35), 494 (40), 465 (40), 393 (100), 351 (45); Anal. Calc. for $C_{33}H_{42}N_2O_8 \cdot 1.2H_2O$: C, 64.31; H, 7.26; N, 4.55. Found: C, 64.13; H, 7.33; N, 4.38%; $[\alpha]_D$ = +1.2 (*c* 0.5, MeOH).

Assignment of alkene geometry for compounds 15 and 19

Alkene carbon shifts in ^{13}C NMR spectra are, in general, higher for (*E*)-alkenes than the equivalent (*Z*)-alkenes. Kremminger and Undheim have shown this to be the case for the unprotected analogues of **15** and **19** (128.85 ppm for the (*E*)-isomer and 126.84 ppm for the (*Z*)-isomer of (2*S*,7*S*)-2,7-diamino-4-octenedioic acid dihydrochloride).[10] The ppm values of the alkene carbons are 127.74 and 127.69 for compound **15** and 128.77 and 128.62 for compound **19** (Figure 1).

Additionally, the IR spectra of compounds **15** and **19** can be used to assign the alkene stereochemistry (see Figure 2). The IR spectrum of compound **19** clearly shows a double bond absorption at 972 cm^{-1}. This peak corresponds to a C-H out of plane deformation of an (*E*)-alkene.[11] As predicted, this absorption is not present in the IR spectra of compound **15**.



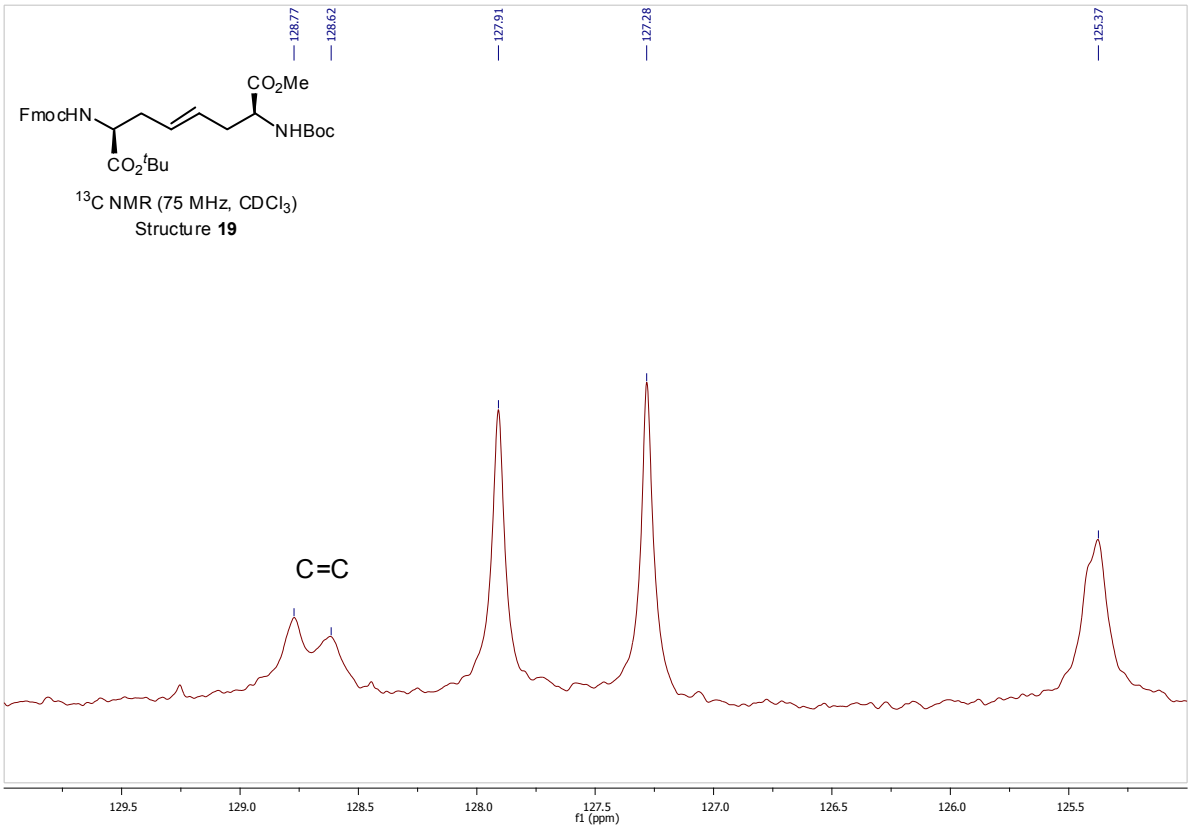


Figure 1. A section of the ^{13}C NMR spectra for compounds **15** and **19** with the alkene carbon peaks highlighted.

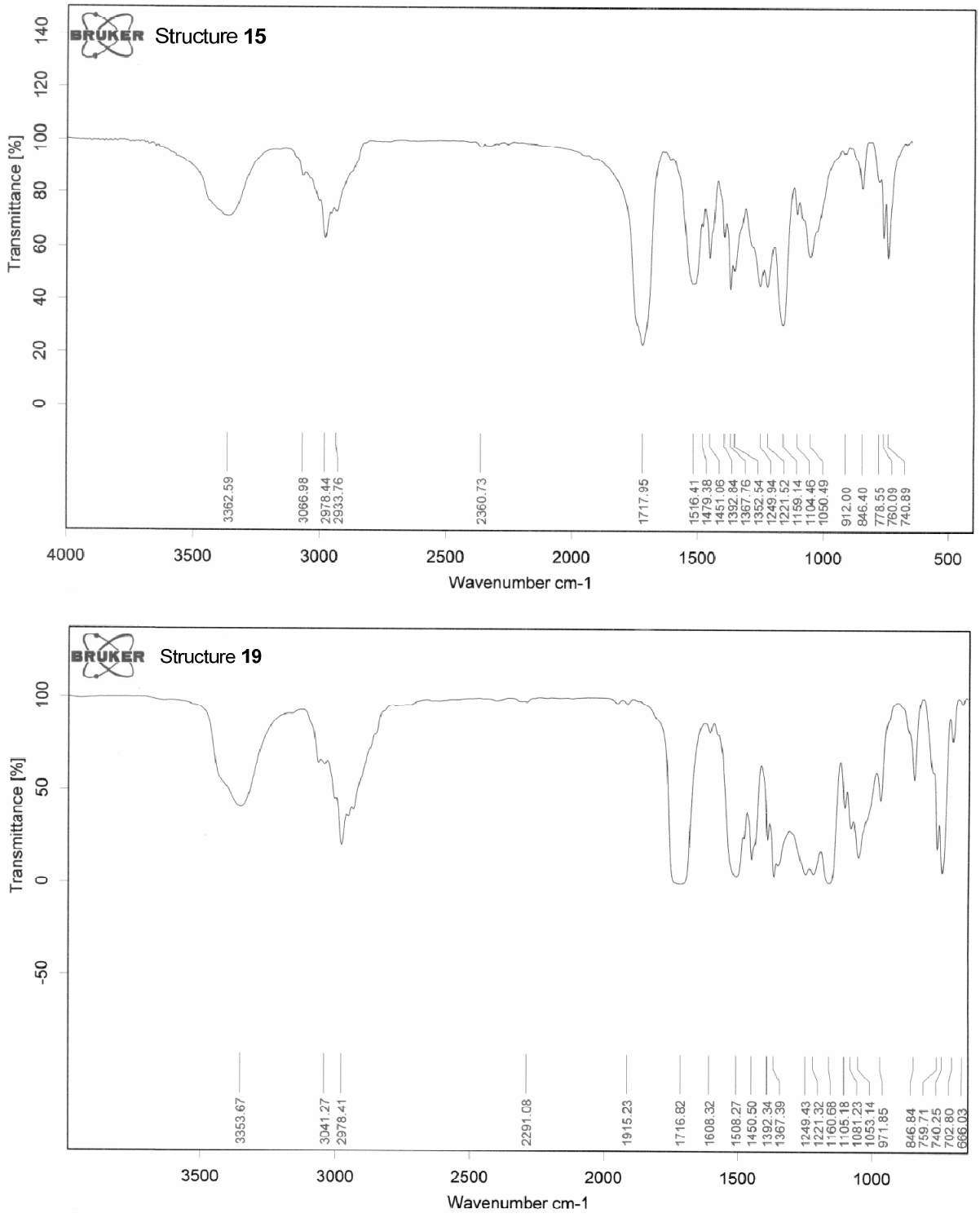


Figure 2. IR spectra for compounds **15** and **19**.

References

1. S. Collet, P. Bauchat, R. Danion-Bougot, D. Danion, *Tetrahedron: Asymmetry* **1998**, *9*, 2121.

2. M. D. Middleton, B. P. Peppers, S. T. Diver, *Tetrahedron* **2006**, *62*, 10528.

3. J. A. Bajgrowicz, A. El Hallaoui, R. Jacquier, C. Pigiere, P. Viallefont, *Tetrahedron* **1985**, *41*, 1833. This compound is commercially available from Sigma-Aldrich.

4. Procedure adapted from: K. R. West, K. D. Bake, S. Otto, *Org. Lett.* **2005**, *7*, 2615.

5. Procedure adapted from: K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee, B. S. Safina, *Angew. Chem. Int. Ed.* **2005**, *44*, 1378. Note: Nicolaou and co-workers reported that this method for the selective hydrolysis of methyl esters proceeds with nearly complete retention of stereochemistry (the least selective reaction reported yielded a product with a 94:6 diastereomeric ratio). Careful inspection of the ^{1}H and ^{13}C NMR spectra of compound **13** only indicates the formation of one diastereomer.

6. For the assignment of the alkene geometry in compound **15** see page 15.

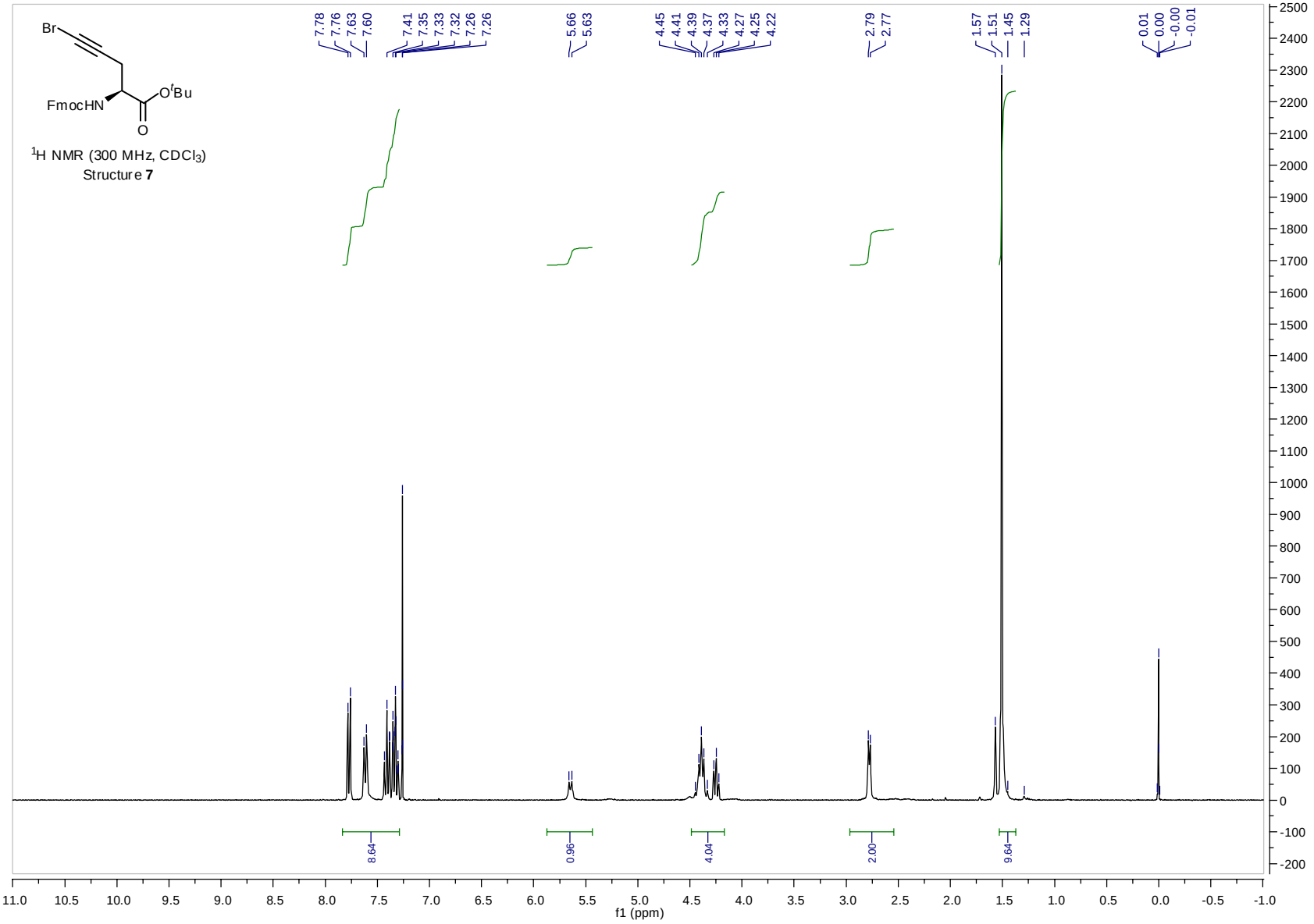
7. We did not observe the deprotection of the Fmoc group under these conditions (T. Maegawa, Y. Fujiwara, T. Ikawa, H. Hisashi, Y. Monguchi, H. Sajiki, *Amino Acids* **2009,** *36,* 493).

8. M. J. O'Donnell, F. Delgado, *Tetrahedron* **2001**, *57*, 6641.

9. For the assignment of the alkene geometry in compound **19** see page 15.

10. P. Kremminger and K. Undheim, *Tetrahedron* **1997,** *53,* 6925.

11. D. H. Williams, I. Fleming, *Spectroscopic methods in organic chemistry (Fourth edition revised),* **1989,** page 41.


Br
FmocHN
O
O^{t}Bu
^{1}H NMR (300 MHz, CDCl$_3$)
Structure **7**
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7.76
7.63
7.60
7.41
7.35
7.33
7.32
7.26
7.26
5.66
5.63
4.45
4.41
4.39
4.37
4.33
4.27
4.25
4.22
2.79
2.77
1.57
1.51
1.45
1.29
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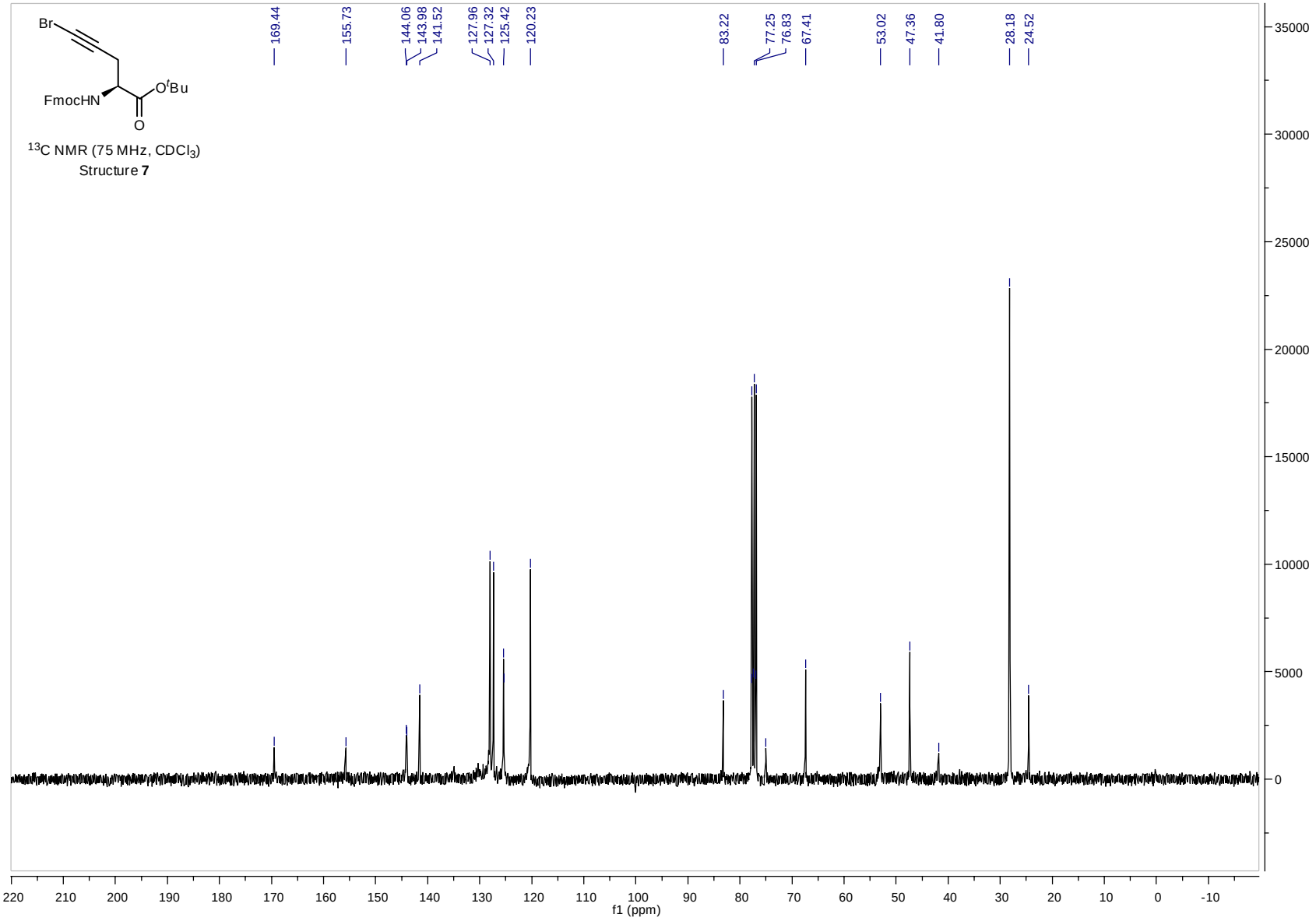
0.00
-0.00
-0.01
8.64
0.96
4.04
2.00
9.64
f1 (ppm)


Br
FmocHN
O
O^{t}Bu
^{13}C NMR (75 MHz, CDCl$_3$)
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143.98
141.52
127.96
127.32
125.42
120.23
83.22
77.25
76.83
67.41
53.02
47.36
41.80
28.18
24.52
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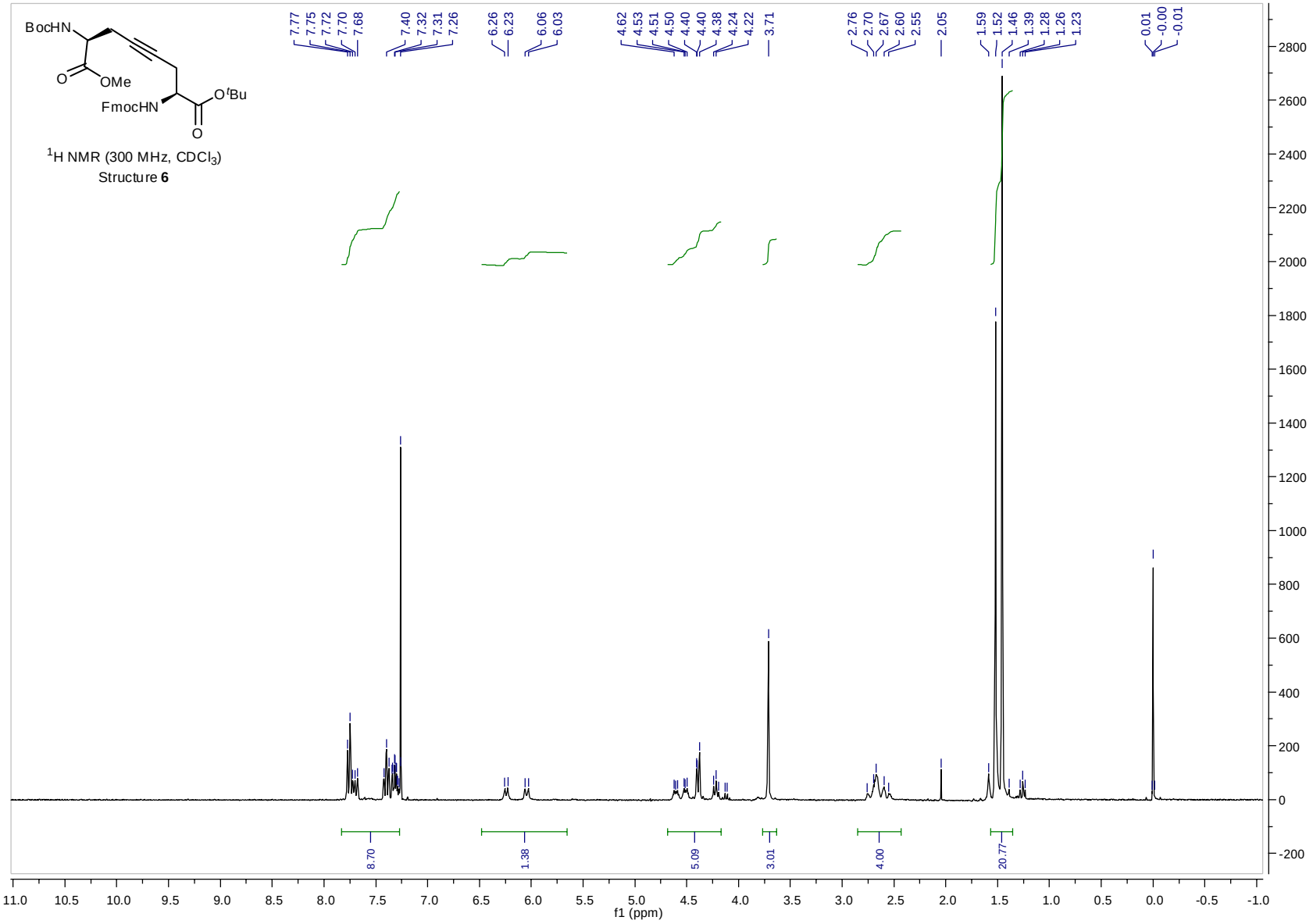
30000
25000
20000
15000
10000
5000
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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O
OMe
FmocHN
O
O
O^{t}Bu
^{1}H NMR (300 MHz, CDCl$_3$)
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7.72
7.70
7.68
7.40
7.32
7.31
7.26
6.26
6.23
6.06
6.03
4.62
4.53
4.51
4.50
4.40
4.40
4.38
4.24
4.22
3.71
2.76
2.70
2.67
2.60
2.55
2.05
1.59
1.52
1.46
1.39
1.28
1.26
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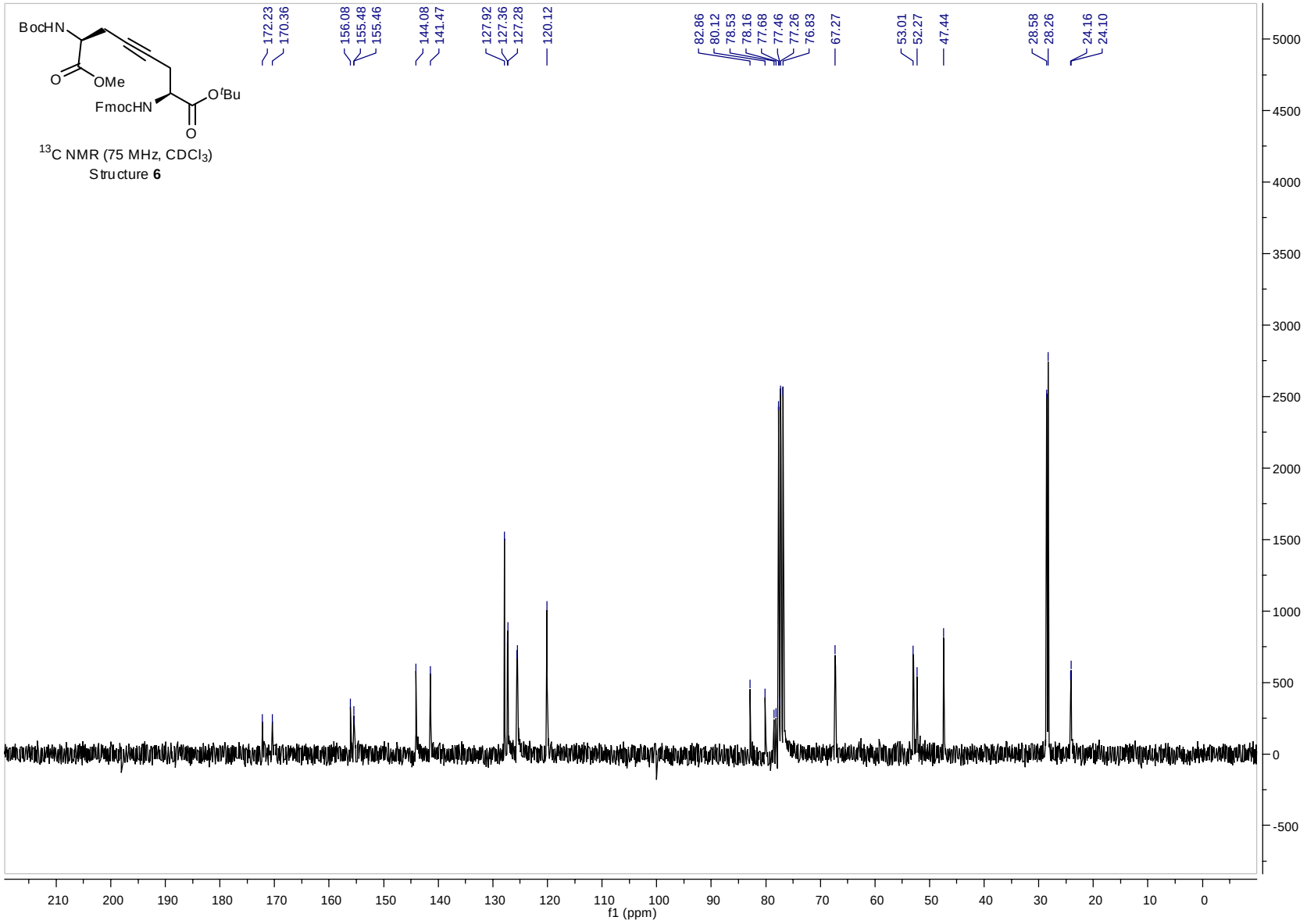
20.77
f1 (ppm)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FmocHN
O
O^{t}Bu
O
^{13}C NMR (75 MHz, CDCl$_3$)
Structure **6**
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155.48
155.46
144.08
141.47
127.92
127.36
127.28
120.12
82.86
80.12
78.53
78.16
77.68
77.46
77.26
76.83
67.27
53.01
52.27
47.44
28.58
28.26
24.16
24.10
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
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50
40
30
20
10
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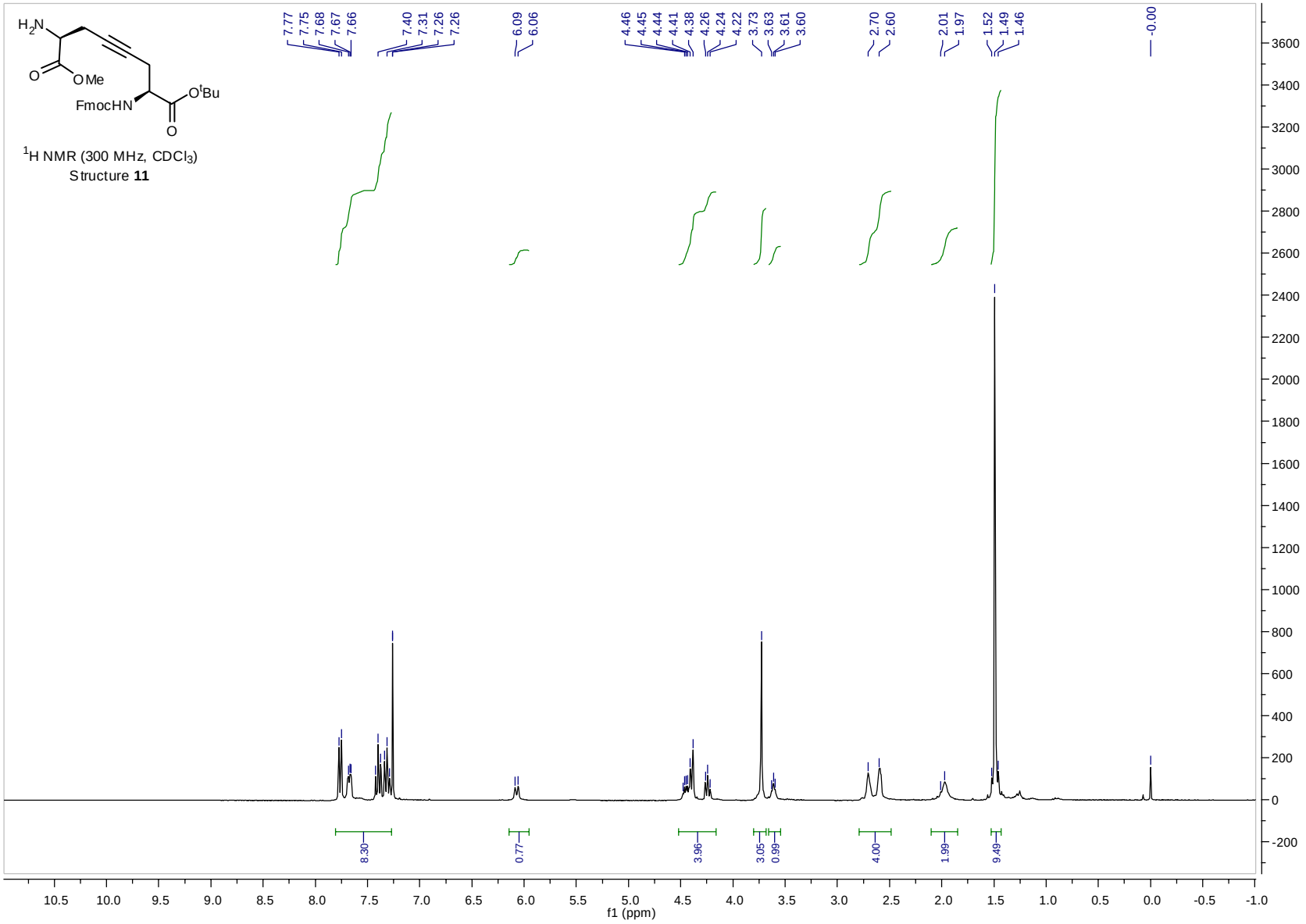
f1 (ppm)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O
OMe
FmocHN
O
OtBu
1H NMR (300 MHz, CDCl3)
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7.66
7.40
7.31
7.26
7.26
6.09
6.06
4.46
4.45
4.44
4.41
4.38
4.26
4.24
4.22
3.73
3.63
3.61
3.60
2.70
2.60
2.01
1.97
1.52
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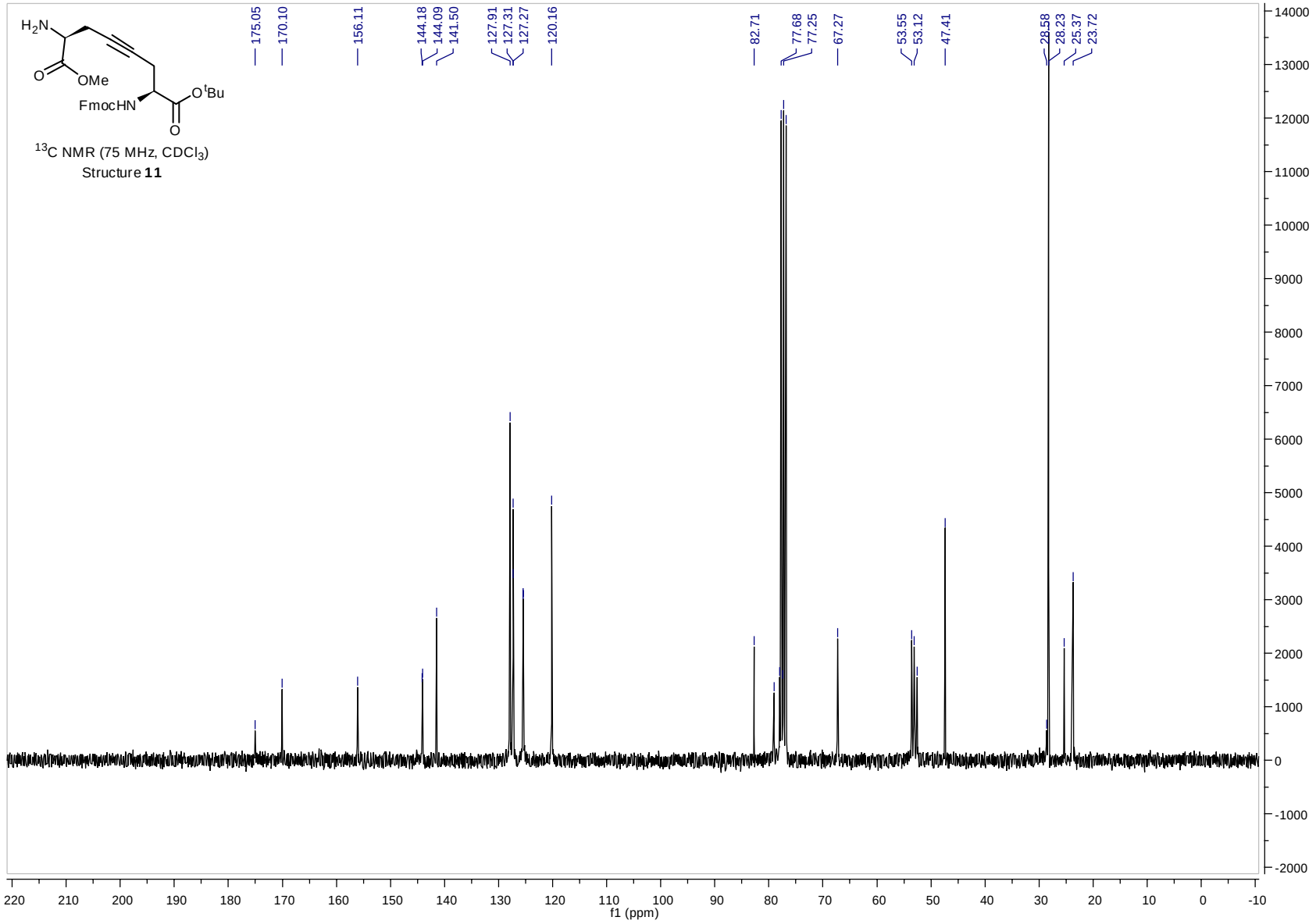
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O
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FmocHN
O
OtBu
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144.09
141.50
127.91
127.31
127.27
120.16
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67.27
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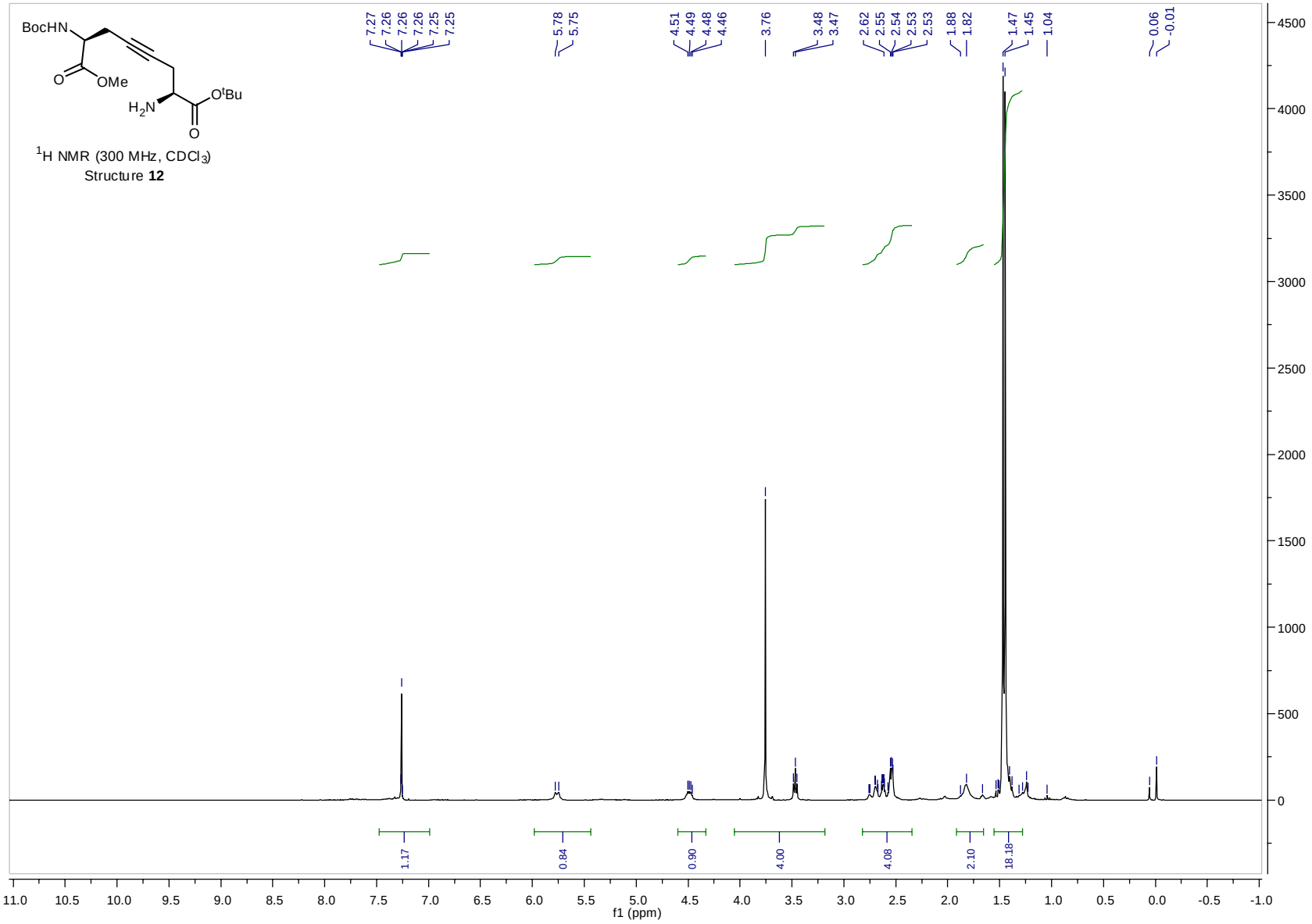
28.23
25.37
23.72
f1 (ppm)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OMe
H2N
OtBu
O
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4.51
4.49
4.48
4.46
3.76
3.48
3.47
2.62
2.55
2.54
2.53
2.53
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1.82
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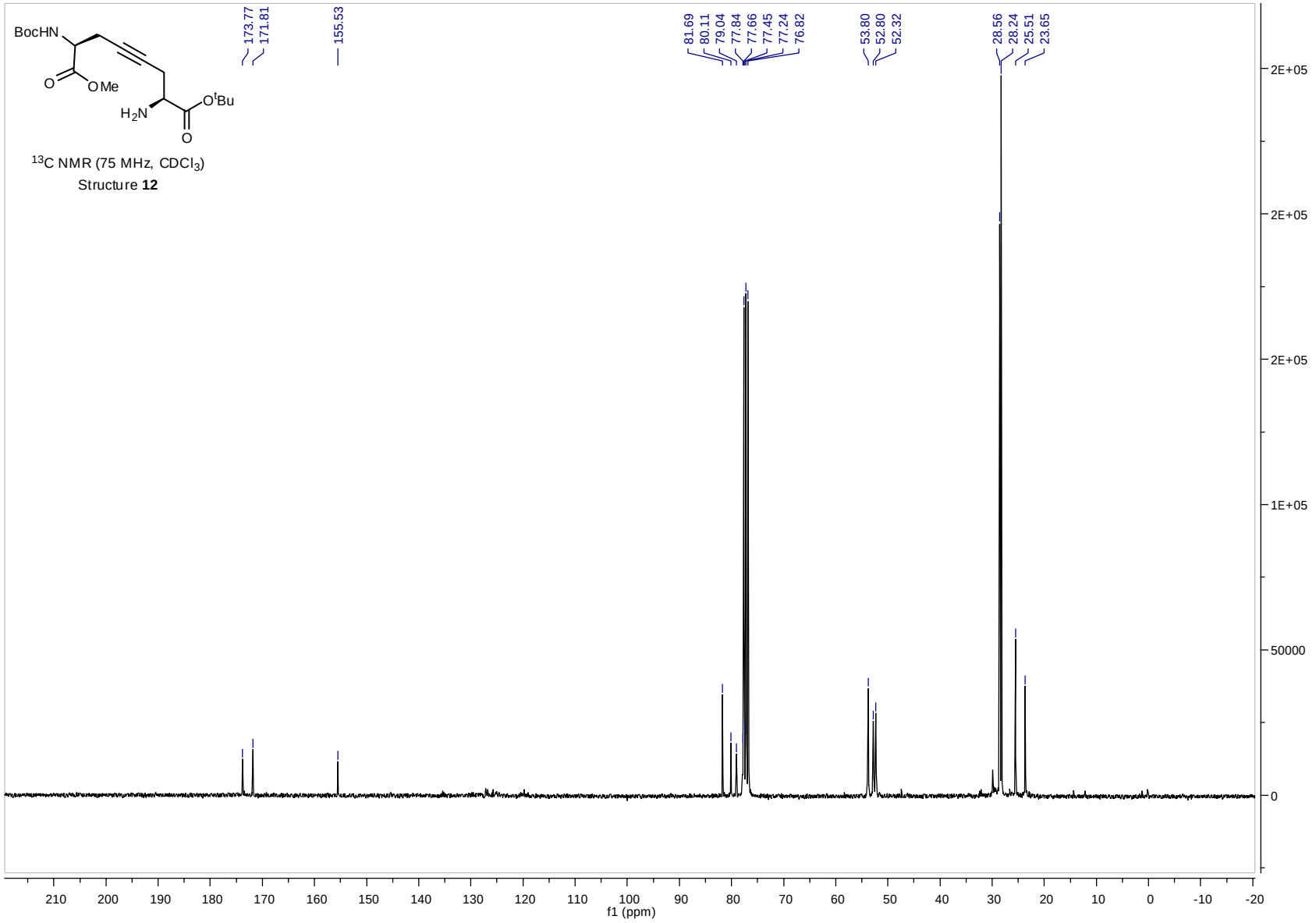
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OMe
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OtBu
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52.80
52.32
28.56
28.24
25.51
23.65
2E+05
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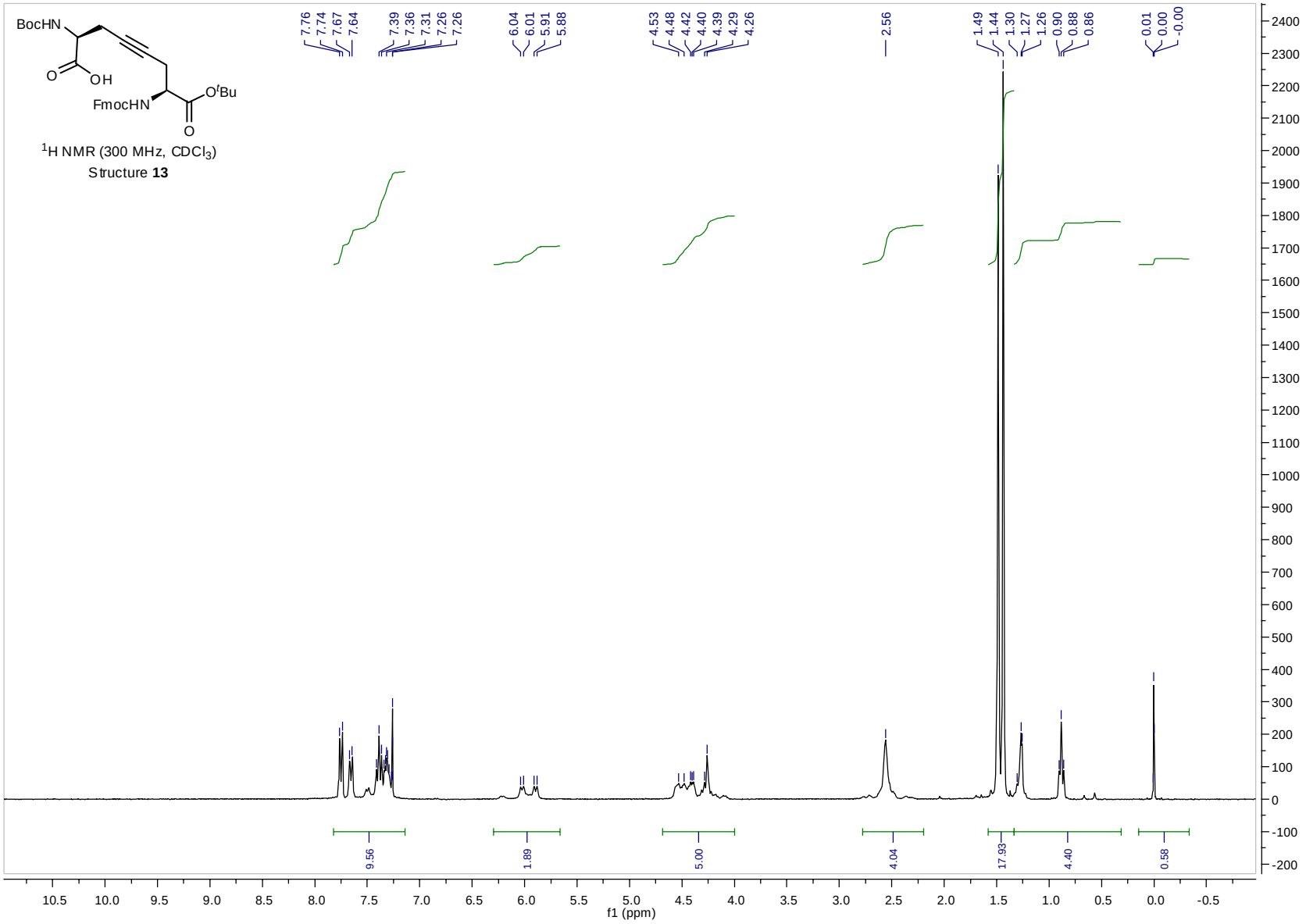
f1 (ppm)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OtBu
O
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7.26
7.26
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6.01
5.91
5.88
4.53
4.48
4.42
4.40
4.39
4.29
4.26
2.56
1.49
1.44
1.30
1.27
1.26
0.90
0.88
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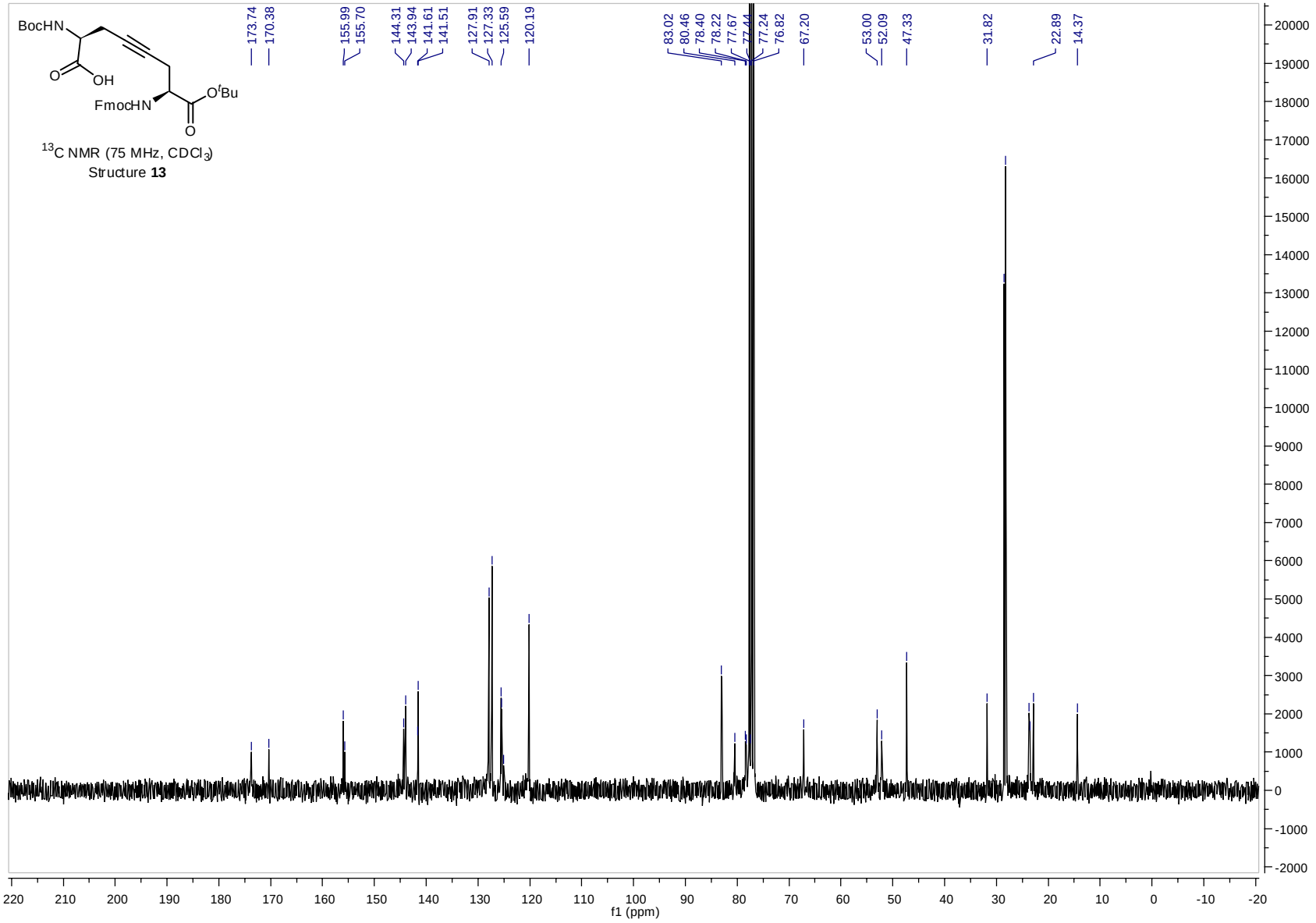
0.58
f1 (ppm)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OH
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O
O^{t}Bu
O
^{13}C NMR (75 MHz, CDCl$_3$)
Structure **13**
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170.38
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155.70
144.31
143.94
141.61
141.51
127.91
127.33
125.59
120.19
83.02
80.46
78.40
78.22
77.67
77.44
77.24
76.82
67.20
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52.09
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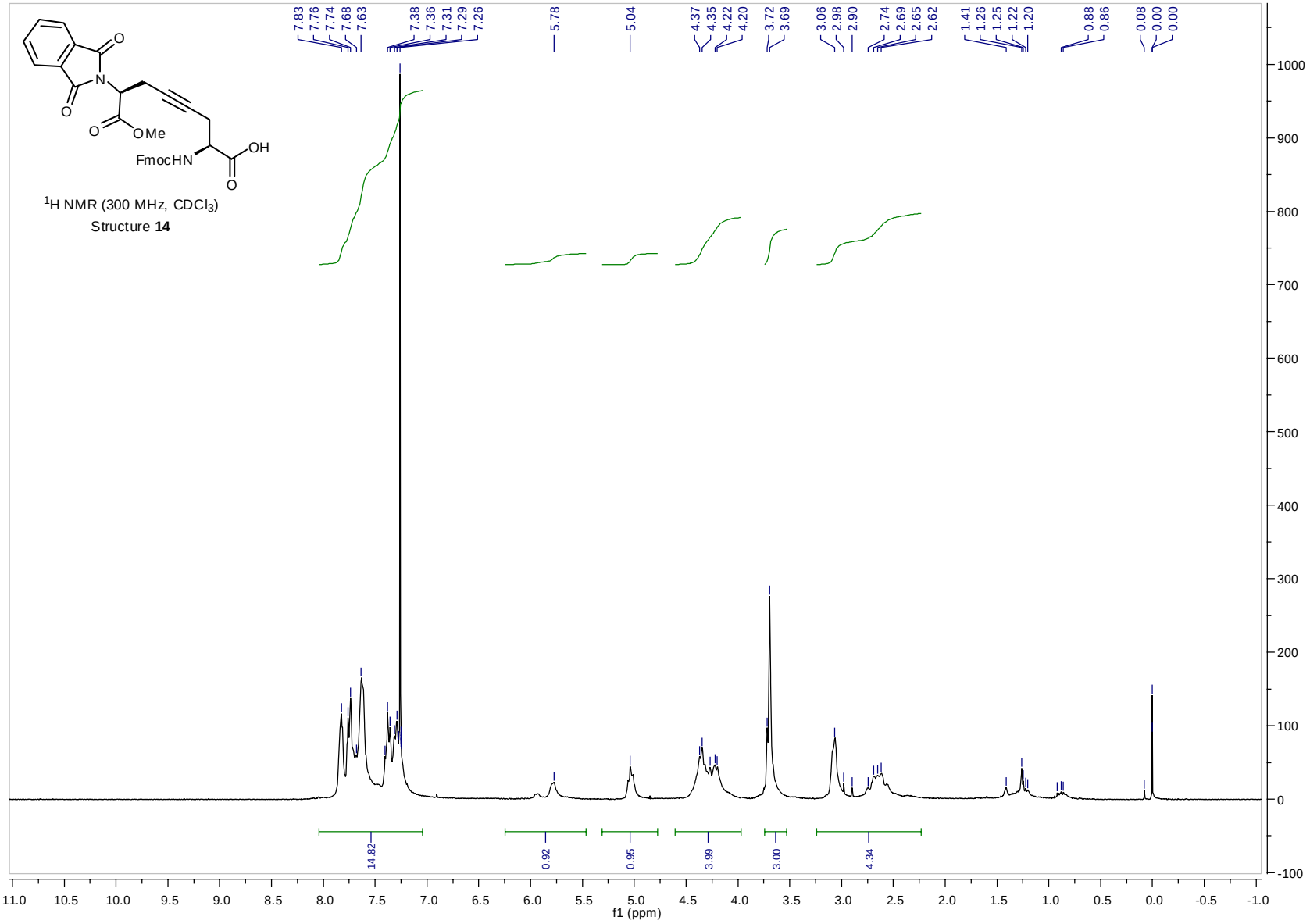
22.89
14.37
f1 (ppm)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4.37
4.35
4.22
4.20
3.72
3.69
3.06
2.98
2.90
2.74
2.69
2.65
2.62
1.41
1.26
1.25
1.22
1.20
0.88
0.86
0.08
0.00
0.00
O
N
O
O
O
OMe
FmocHN
OH
O
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Structure 14
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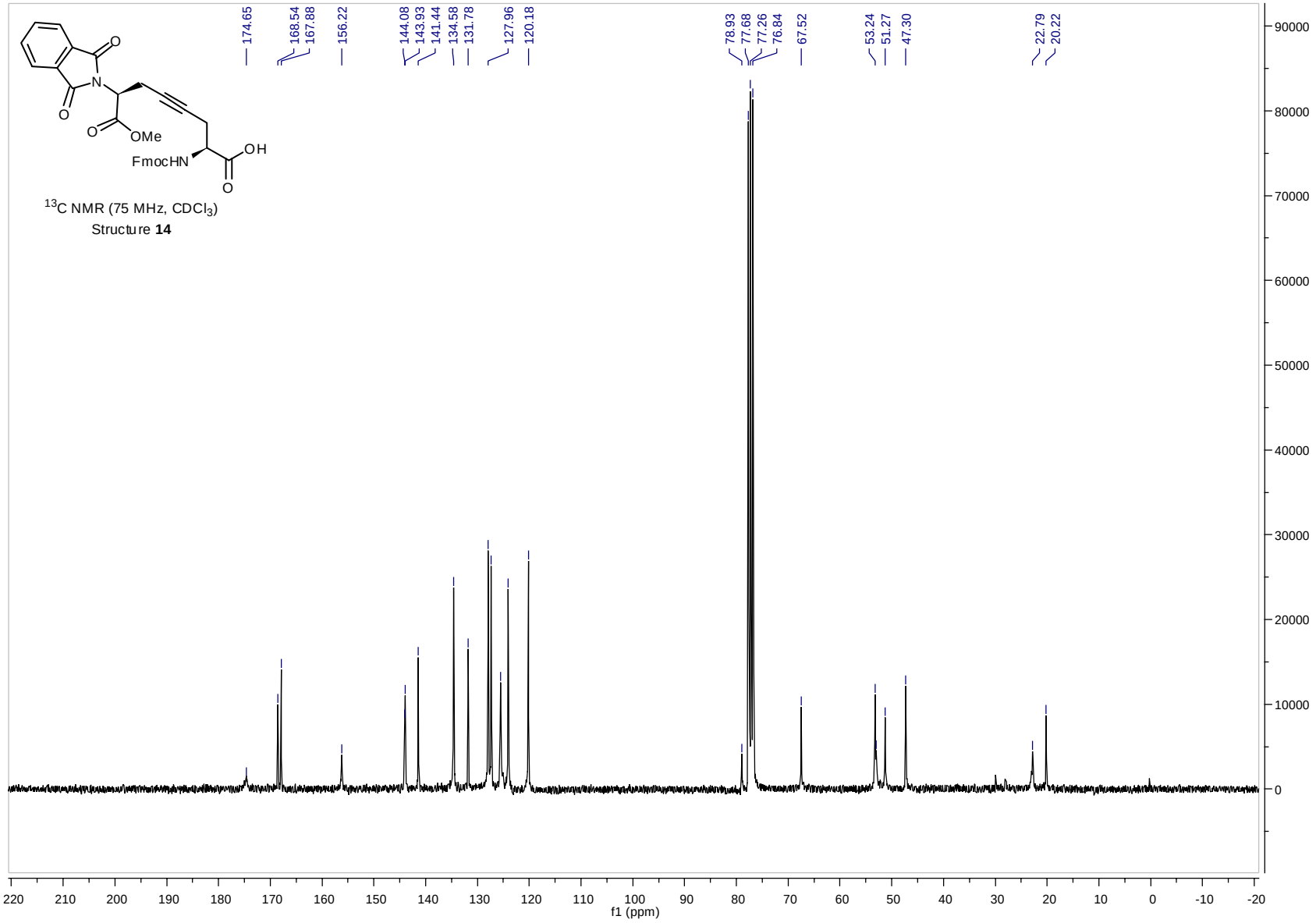
3.99
3.00
4.34
f1 (ppm)


174.65
168.54
167.88
156.22
144.08
143.93
141.44
134.58
131.78
127.96
120.18
78.93
77.68
77.26
76.84
67.52
53.24
51.27
47.30
22.79
20.22
O
N
O
O
OMe
FmocHN
OH
O
13C NMR (75 MHz, CDCl3)
Structure 14
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
220
210
200
190
180
170
160
150
140
130
120
110
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90
80
70
60
50
40
30
20
10
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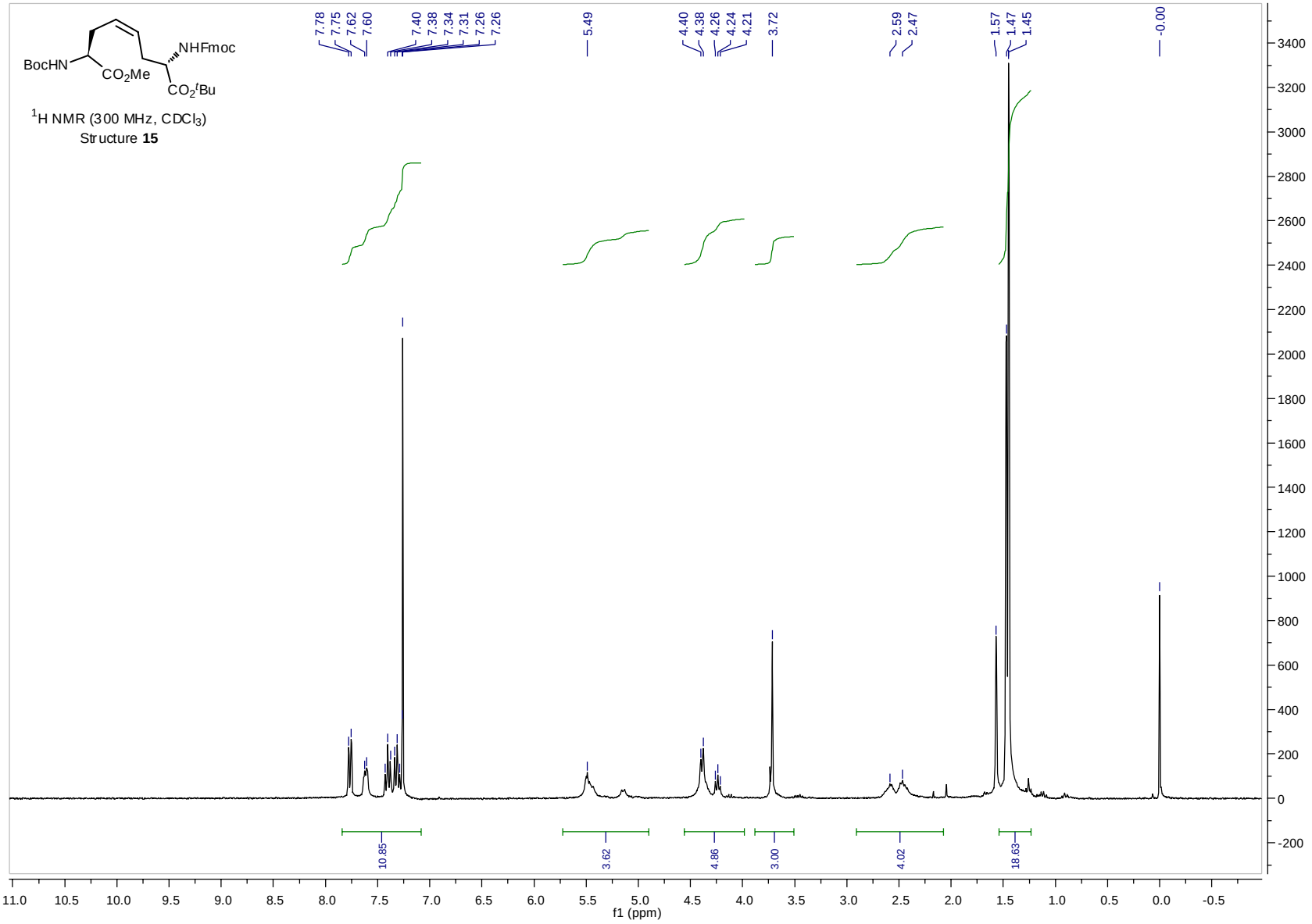
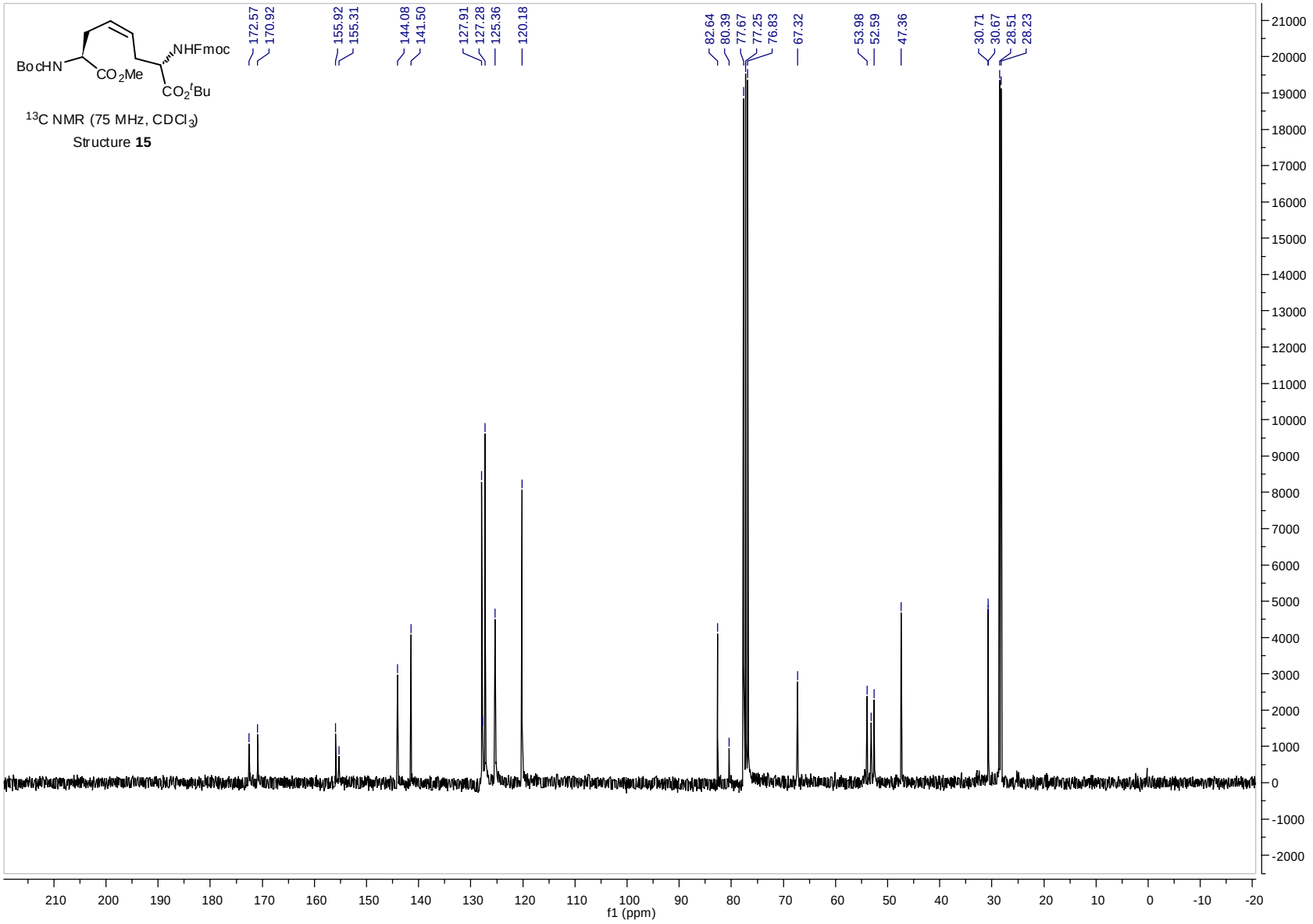
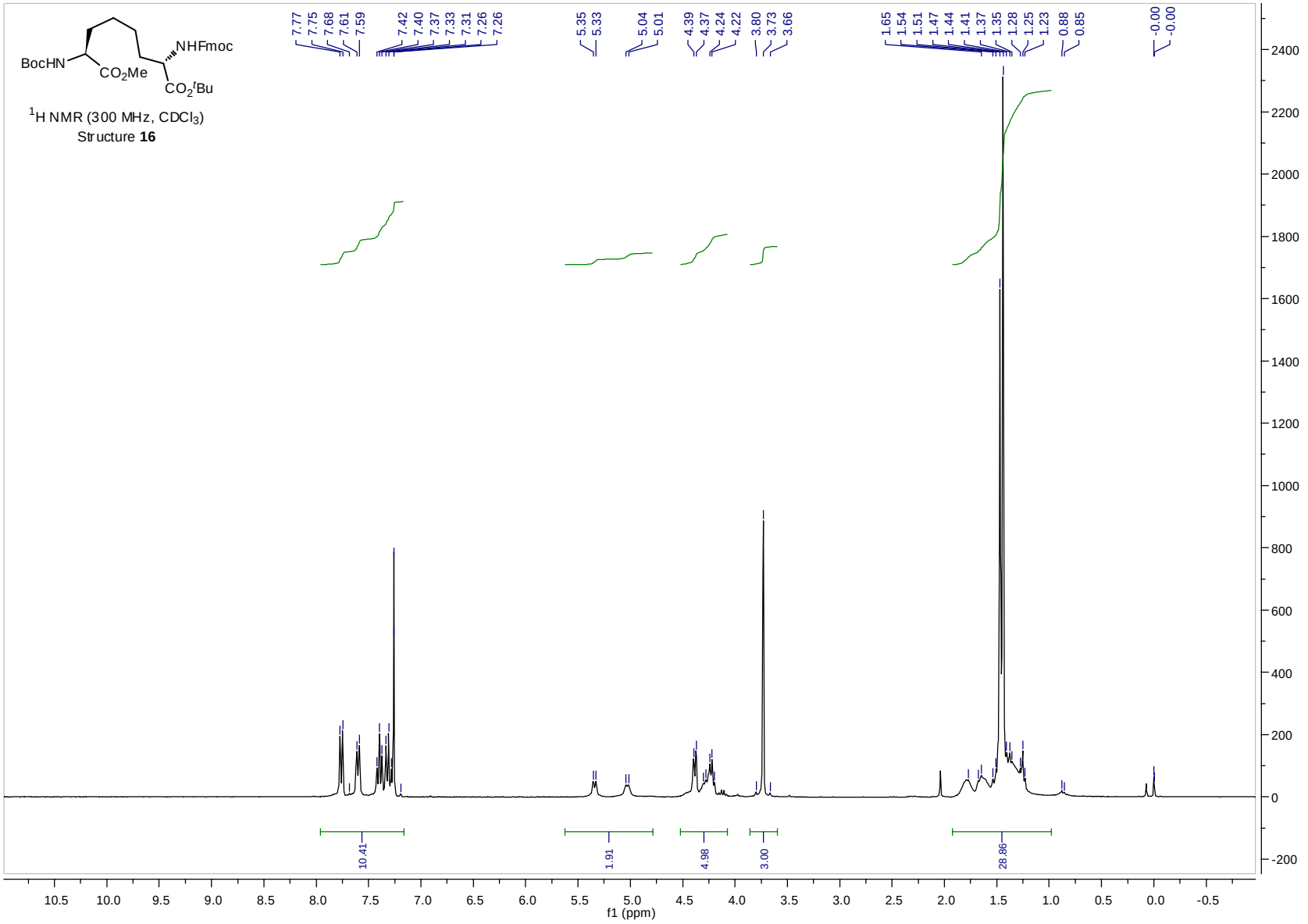
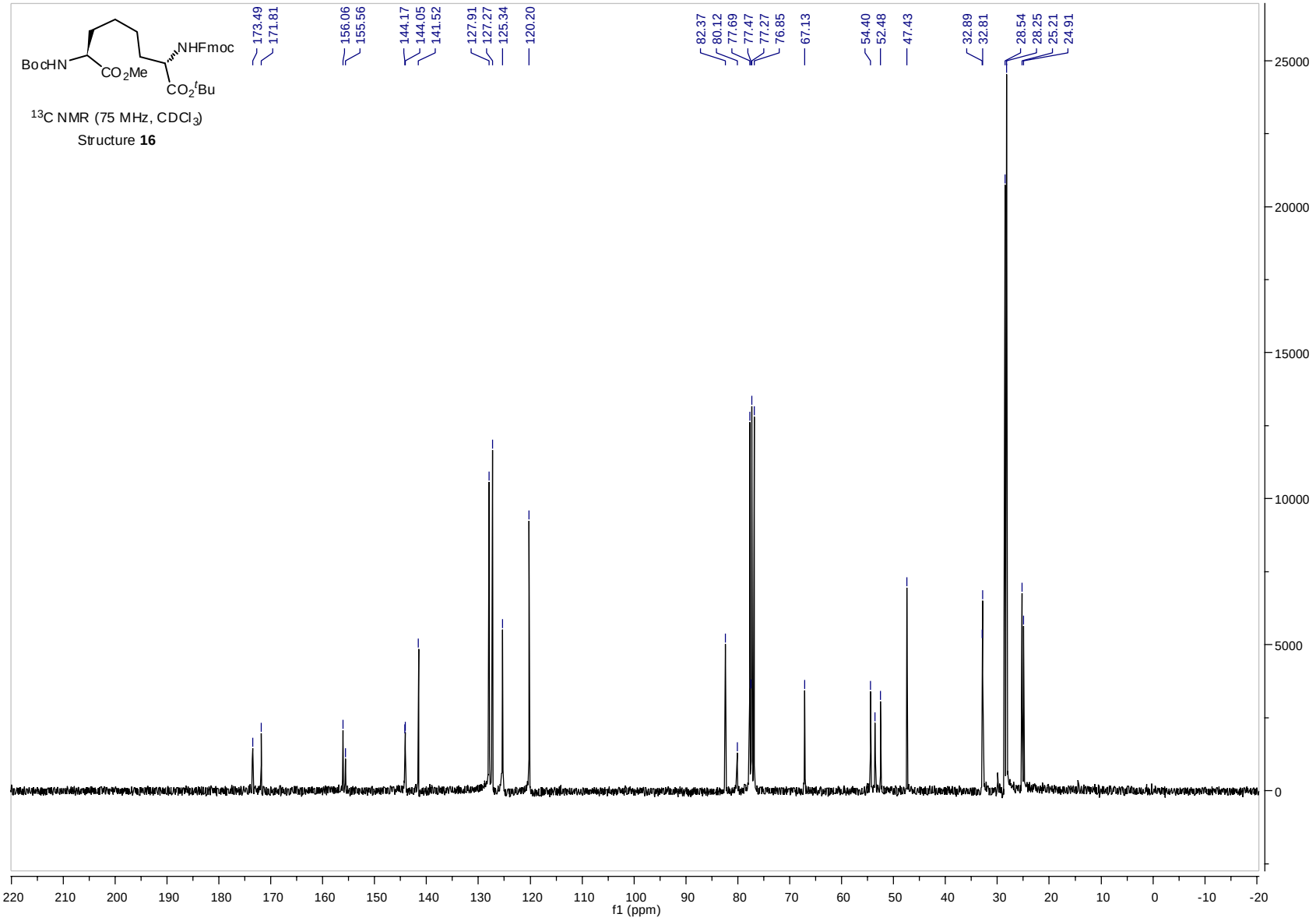
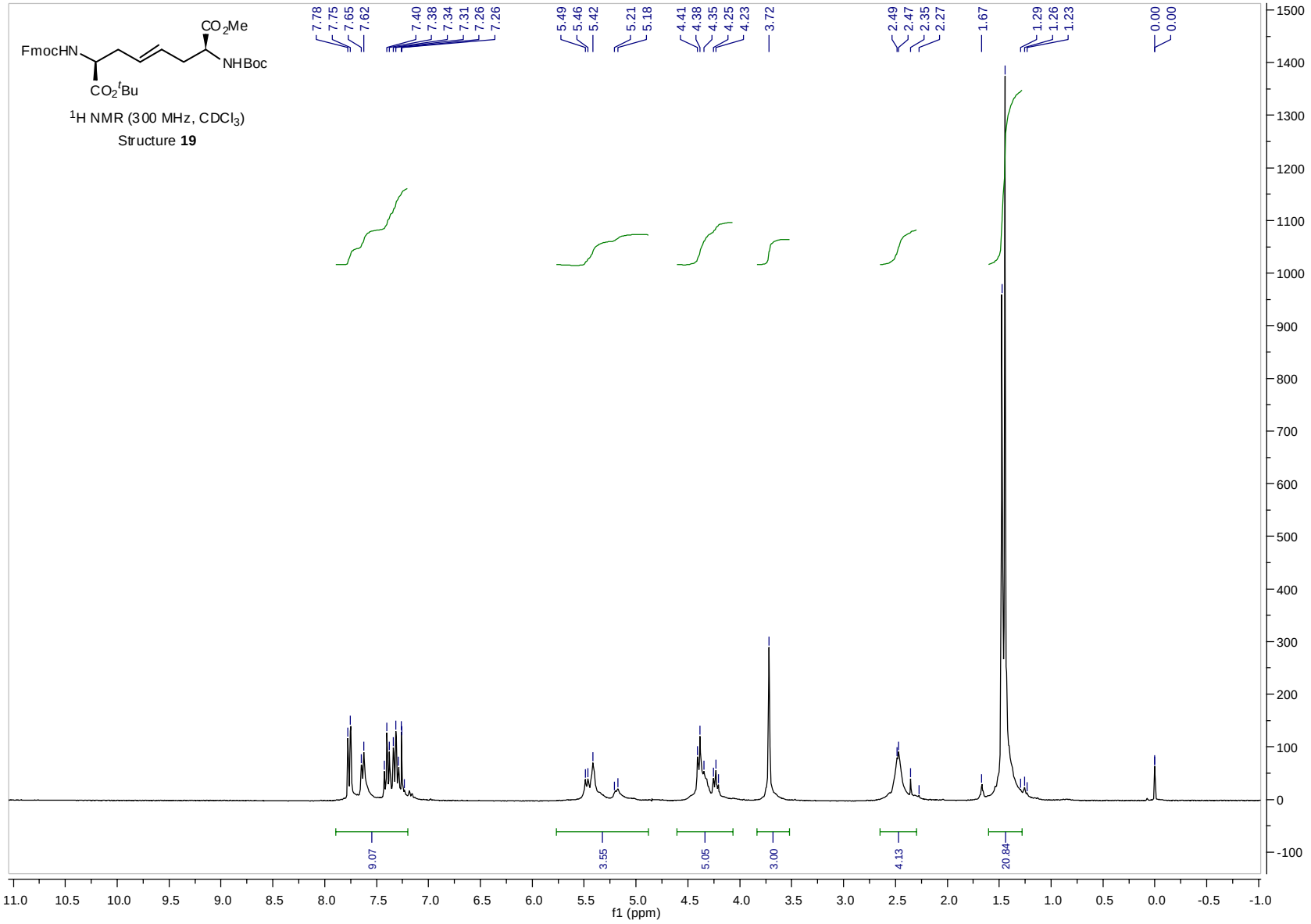
-10
-20
f1 (ppm)

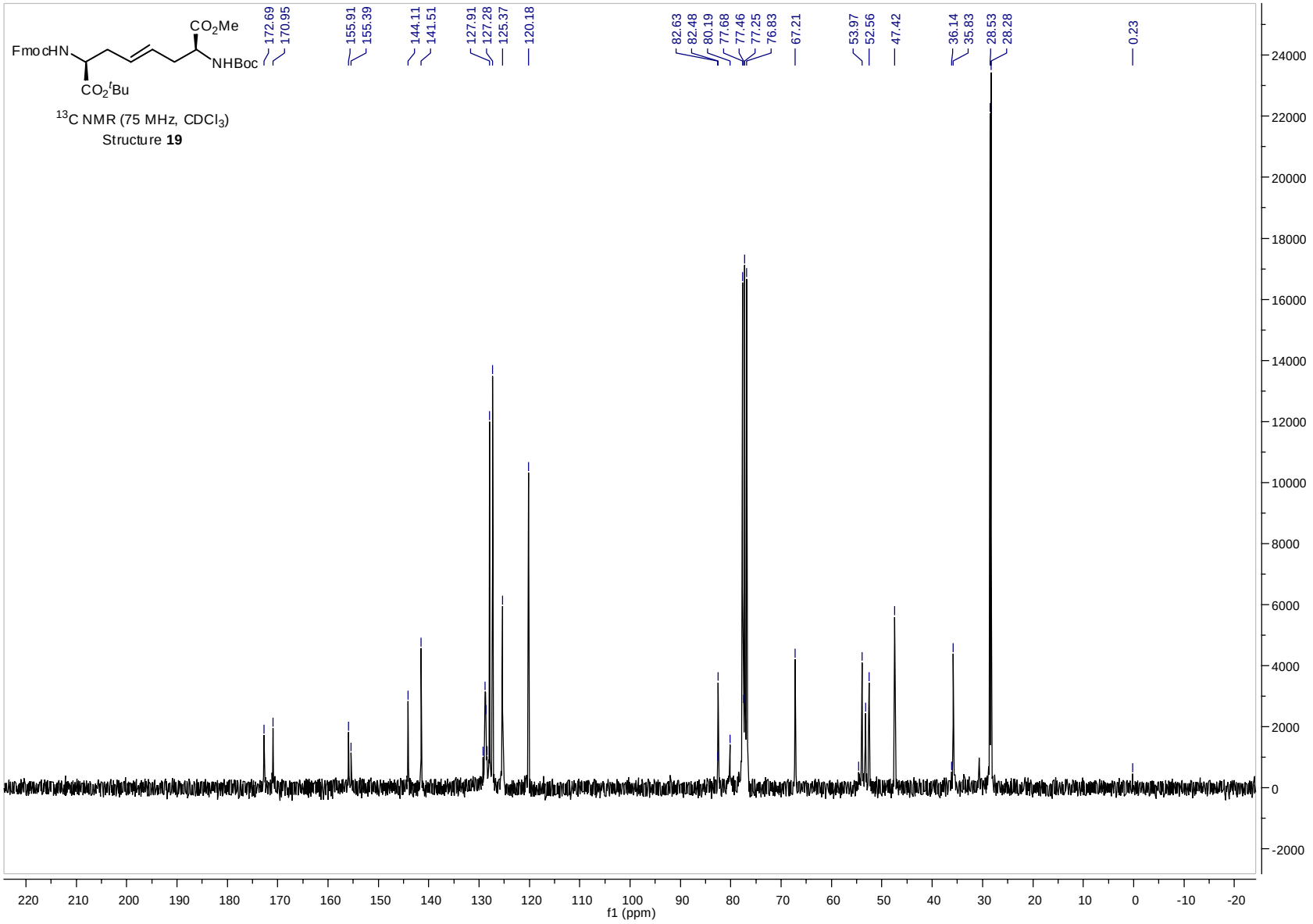

BocHN
NHFmoc
CO2Me
CO2tBu
1H NMR (300 MHz, CDCl3)
Structure 15
7.78
7.75
7.62
7.60
7.40
7.38
7.34
7.31
7.26
7.26
5.49
4.40
4.38
4.26
4.24
4.21
3.72
2.59
2.47
1.57
1.47
1.45
-0.00
10.85
3.62
4.86
3.00
4.02
18.63
f1 (ppm)


BocHN
CO2Me
NHFmoc
CO2tBu
13C NMR (75 MHz, CDCl3)
Structure 15
172.57
170.92
155.92
155.31
144.08
141.50
127.91
127.28
125.36
120.18
82.64
80.39
77.67
77.25
76.83
67.32
53.98
52.59
47.36
30.71
30.67
28.51
28.23
f1 (ppm)


BocHN
NHFmoc
CO2Me
CO2tBu
1H NMR (300 MHz, CDCl3)
Structure 16
7.77
7.75
7.68
7.61
7.59
7.42
7.40
7.37
7.33
7.31
7.26
7.26
5.35
5.33
5.04
5.01
4.39
4.37
4.24
4.22
3.80
3.73
3.66
1.65
1.54
1.51
1.47
1.44
1.41
1.37
1.35
1.28
1.25
1.23
0.88
0.85
-0.00
-0.00
10.41
1.91
4.98
3.00
28.86
f1 (ppm)


BocHN
CO2Me
NHFmoc
CO2tBu
13C NMR (75 MHz, CDCl3)
Structure 16
173.49
171.81
156.06
155.56
144.17
144.05
141.52
127.91
127.27
125.34
120.20
82.37
80.12
77.69
77.47
77.27
76.85
67.13
54.40
52.48
47.43
32.89
32.81
28.54
28.25
25.21
24.91
25000
20000
15000
10000
5000
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


FmocHN
CO2Me
NHBoc
CO2tBu
1H NMR (300 MHz, CDCl3)
Structure 19
7.78
7.75
7.65
7.62
7.40
7.38
7.34
7.31
7.26
7.26
5.49
5.46
5.42
5.21
5.18
4.41
4.38
4.35
4.25
4.23
3.72
2.49
2.47
2.35
2.27
1.67
1.29
1.26
1.23
0.00
0.00
9.07
3.55
5.05
3.00
4.13
20.84
f1 (ppm)


FmocHN
CO2Me
NHBoc
CO2tBu
13C NMR (75 MHz, CDCl3)
Structure 19
172.69
170.95
155.91
155.39
144.11
141.51
127.91
127.28
125.37
120.18
82.63
82.48
80.19
77.68
77.46
77.25
76.83
67.21
53.97
52.56
47.42
36.14
35.83
28.53
28.28
0.23
f1 (ppm)