Supporting Information

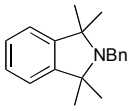
Synthesis of analogs of the radiation mitigator JP4-039 and visualization of BODIPY derivatives in mitochondria

Marie-Céline Frantz,[a] Erin M. Skoda,[a] Joshua R. Sacher,[a] Michael W. Epperly,[b] Julie Goff,[b] Joel S. Greenberger,[b] and Peter Wipf*[a,c]

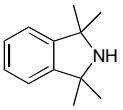
[a]*Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA,* [b]*Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA 15232, USA,* [c]*Department of Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA 15260, USA*

Contents

General Information. All moisture- and air-sensitive reactions were performed using syringe-septum cap techniques under an inert atmosphere (N_2 or argon) in glassware that was dried in an oven at 140 °C for at least 2 h prior to use. Reactions carried out at a temperature below 0 °C employed a brine/ice bath or a CO_2/acetone bath. All reagents and solvents were used as received unless otherwise specified. THF and Et_2O were distilled over sodium/benzophenone ketyl; MeOH was distilled over magnesium; benzene, acetonitrile and DME were distilled over CaH_2; DMF was distilled and stored over 4Å molecular sieves; pyridine and triethylamine were distilled over CaH_2 and stored over KOH; CH_2Cl_2 and toluene were purified using an alumina column filtration system. Analytical thin-layer chromatography (TLC) was performed on pre-coated SiO_2 60 F_{254} plates (250 µm layer thickness) available from Merck. Visualization was accomplished by UV irradiation at 254 nm and/or by staining with Vaughn's reagent (4.8 g $(NH_4)_6Mo_7O_{24}$•$4H_2O$ and 0.2 g $Ce(SO_4)_2$•$4H_2O$ in 100 mL of a 3.5 N H_2SO_4 solution), a $KMnO_4$ solution (1.5 g $KMnO_4$ and 1.5 g K_2CO_3 in 100 mL of a 0.1% NaOH solution), a ninhydrin solution (2 g ninhydrin in 100 mL EtOH), a PMA solution (5 g phosphomolybdic acid in 100 mL EtOH), or a *p*-anisaldehyde solution (2.5 mL *p*-anisaldehyde, 2 mL AcOH and 3.5 mL conc. aq. H_2SO_4 in 100 mL EtOH). Flash column chromatography was performed using SiO_2 60 (particle size 0.040–0.055 mm, 230–400 mesh, or Silicycle SiliaFlash® P60, 40-63 µm). Melting points were determined on a Laboratory Devices Mel-Temp II capillary melting point apparatus fitted with a Fluke 51 II digital thermometer. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Infrared spectra were recorded on a Smiths IdentifyIR ATR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 300 or 400 instrument at 300/75 MHz or 400/100 MHz, respectively. Chemical shifts were reported in parts per million (ppm) as referenced to residual solvent. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (app = apparent, b = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sext, = sextuplet, m = multiplet), number of protons, coupling constant(s). ^{13}C NMR were obtained using a proton-decoupled pulse sequence and are tabulated by observed peak. LC-MS analyses were performed on a Shimadzu UFLC instrument equiped with an Applied Biosystems MDS SCIEX API 2000 mass spectrometer (ESI), under the following conditions: column: Varian Polaris C18-A (100 x 4.6 mm, 5 µm) equilibrated at 40 °C; buffer A: 0.1% aqueous AcOH, buffer B: 0.1% AcOH in MeCN; 30 min gradient: 5% buffer B in buffer A for 1 min, then 5 to 95% buffer B in buffer A over 13 min, then 95% buffer B in buffer A for 4 min, then 95 to 5% buffer B in buffer A over 7 min, then 5% buffer B in buffer A for 5 min; flow rate: 0.2 mL/min; detection: TIC and/or UV λ = 254/280 nm. Mass spectra were obtained on a Waters Autospec double focusing mass spectrometer (EI) or a Waters Q-Tof mass spectrometer (ESI), at the University of Pittsburgh Mass Spectrometry facility. Experimental procedures and spectral details for compounds **11** and JP4-039 have previously been reported in *Org. Lett.* **2011**, *13*, 2318-2321.

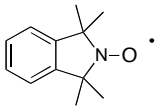


2-Benzyl-1,1,3,3-tetramethylisoindoline.[1] An oven-dried 250 mL, three-necked, round-bottom flask was flushed with nitrogen, and magnesium turnings (3.84 g, 156 mmol) were introduced, that were covered with dry Et_2O (9 mL). A solution of MeI (9.45 mL, 150 mmol) in dry Et_2O (80 mL) was then added dropwise *via* a dropping funnel while stirring over a period of 50 min. The resulting reaction mixture was then stirred for an additional 30 min, and then concentrated by slow distillation of solvent until the internal temperature reached 80 °C. The residue was allowed to cool to 60 °C, and a solution of *N*-benzylphtalimide (6.00 g, 25.0 mmol) in dry toluene (76 mL) was added dropwise *via* a dropping funnel with stirring at a sufficient rate to maintain this temperature. When the addition was complete, solvent was distilled slowly from the mixture until the temperature reached 108-110 °C. The reaction mixture was refluxed at 110 °C for 4 h, then concentrated again by further solvent distillation. It was then cooled to rt and diluted with hexanes. The resulting purple slurry was filtered through Celite and washed with hexanes. The combined yellow filtrate turned dark red-purple after standing in air overnight. It was then concentrated *in vacuo*. The resulting purple residue was passed through a short column of basic alumina (grade I, 70-230 mesh), eluting with hexanes (~1 L), to afford 2.58 g (39%) of the title compound as a colorless oil which solidified to give a white solid. Representative experimental data are as follows: mp 61.0-61.4 °C (lit. 63-64 °C from MeOH or EtOH); IR (neat) 3081, 3062, 3047, 3019, 3006, 2978, 2965, 2958, 2918, 2890, 2849, 2820, 1485, 1446, 1379, 1372, 1355, 1319, 1299, 1284, 1265, 1237, 1211, 1195, 1176, 1161, 1140, 1120, 1103, 1073, 1045, 1025, 945, 932, 904, 874, 827, 790, 760, 751, 742, 701, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (app d, 2 H, J = 7.2 Hz), 7.34-7.19 (m, 5 H), 7.18-7.11 (m, 2 H), 4.00 (s, 2 H), 1.31 (s, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 143.6, 128.5, 128.1, 127.0, 126.5, 121.5, 65.4, 46.5, 28.6; EI-MS *m/z* 265 (M^+, 25), 251 (100), 235 (53), 158 (69), 144 (86), 128 (60), 115 (67), 103 (67), 92 (86), 77 (65), 65 (84); HRMS (EI) *m/z* calcd for $C_{19}H_{23}N$ 265.1830, found 265.1824.

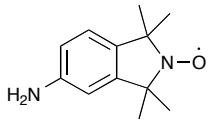


1,1,3,3-Tetramethylisoindoline.[1] 2-Benzyl-1,1,3,3-tetramethylisoindoline (3 x 621 mg, 7.02 mmol) was dissolved in AcOH (3 x 11 mL) in 3 separated Parr flasks, then 10% Pd/C (3 x 56.5 mg) was added. The flasks were placed in 3 high pressure reactors. The reactors were charged with H_2 and purged for 5 cycles and was finally pressurized with H_2 at 4 bars (60 psi). After stirring at rt for 3 h, the combined reaction mixtures were filtered through Celite, and the solvent removed *in vacuo*. The resulting residue was dissolved in water (5 mL) and the solution neutralized with 2.5 N aq. NaOH (pH 11.5), and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 1.16 g (95%) of the crude title compound as slightly yellow crystals. Representative experimental data are as follows: mp 36.0-36.5 °C (lit. 36-38 °C from $MeOH/H_2O$); IR (neat) 3064, 3036, 3013, 2956, 2920, 2861, 1478, 1459, 1441, 1414, 1372, 1359, 1314, 1297, 1241, 1209, 1178, 1165, 1139, 1124, 1105, 1023, 1001, 993, 932, 883, 764, 734, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.23 (m, 2 H), 7.18-7.11 (m, 2 H), 1.86 (bs, 1 H), 1.48 (s, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 127.2, 121.6, 62.9, 32.1.

[1] Griffiths, P. G.; Moad, G.; Rizzardo, E.; Solomon, D. H. *Aust. J. Chem.* **1983**, *36*, 397.



1,1,3,3-Tetramethylisoindolin-2-yloxyl (TMIO, 1).[1] To a solution of 1,1,3,3-tetramethylisoindoline (1.46 g, 8.33 mmol) in a 14:1 mixture of MeOH/MeCN (16.6 mL) were added successively $NaHCO_3$ (560 mg, 6.67 mmol), $Na_2WO_4 \cdot 2H_2O$ (83.3 mg, 0.25 mmol) and 30% aq. H_2O_2 (3.12 mL, 27.50 mmol). The resulting suspension was stirred at rt. After 18 h, a bright yellow suspension formed and 30% aq. H_2O_2 (3.00 mL, 26.44 mmol) was added. The reaction mixture was stirred for 2 days, then diluted with water and extracted twice with hexanes. The combined organic layers were washed with 1 M aq. H_2SO_4 and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 1.55 g (98%) of crude **1** as a yellow crystalline powder, that was carried on without further purification. Representative experimental data are as follows: mp 122-125 °C (softening point: 108 °C) (lit. 128-129°C from petroleum ether); IR (neat) 2971, 2922, 2859, 1670, 1482, 1465, 1450, 1427, 1372, 1353, 1316, 1295, 1278, 1165, 1120, 1109, 1021, 760, 678 cm^{-1}; EI-MS *m/z* 268 (100), 252 (30), 239 (43), 191 (M^+, 75), 155 (60); HRMS (EI) *m/z* calcd for $C_{12}H_{17}NO$ 191.1310, found 191.1306.



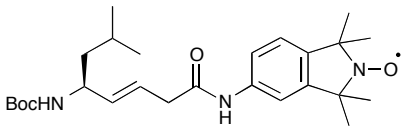
5-Amino-1,1,3,3-tetramethylisoindolin-2-yloxyl (5-amino-TMIO, 2).[2] Conc. H_2SO_4 (13.5 mL) was added dropwise *via* syringe to TMIO (1.34 g, 7.07 mmol, crude) cooled in an ice-water bath, forming a dark-red solution which was then warmed to 60 °C for 15 min and then cooled to 0 °C. Conc. HNO_3 (0.90 mL, 19.1 mmol) was added dropwise *via* syringe. When the reaction appeared complete, the yellow-orange solution was heated at 100 °C for 10 min, the color turning to red-orange. After cooling to rt, the reaction mixture was neutralized by careful addition to ice-cooled 2.5 N aq. NaOH (30 mL, final pH > 12). This aqueous phase was extracted with Et_2O until it became colorless and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 1.64 g (98%) of crude 5-nitro-1,1,3,3-tetramethylisoindolin-2-yloxyl[3] as a yellow-orange powder, that was carried on without further purification.

A flask containing a solution of 5-nitro-1,1,3,3-tetramethylisoindolin-2-yloxyl (1.50 g, 6.38 mmol, crude) in MeOH (75 mL) was purged and filled with argon, then 10% Pd/C (150 mg) was added. The flask was purged and filled 3 times with H_2, and the resulting black suspension was stirred at rt under H_2 (1 atm) for 4 h. The reaction mixture was then filtered through Celite, the Celite washed with MeOH, and the solution concentrated *in vacuo* to yield 1.38 g of the crude hydroxylamine as a yellow solid that was carried on without further purification. Representative experimental data are as follows: ^{1}H NMR (300 MHz, CD_3OD) δ 6.89 (d, 1 H, J = 8.1 Hz), 6.62 (dd, 1 H, J = 8.1, 2.1 Hz), 6.54 (d, 1 H, J = 2.1 Hz), 3.35 (s, 2 H), 1.35 (s, 6 H), 1.33 (s, 6 H); ^{13}C NMR (75 MHz, CD_3OD) δ 148.1, 147.4, 136.5, 123.3, 116.3, 110.0, 68.3, 68.0, 27.1, 26.8.

To a solution of the crude hydroxylamine (1.38 g, 6.38 mmol) in MeOH (75 mL) was added $Cu(OAc)_2 \cdot H_2O$ (26 mg, 0.128 mmol). The reaction mixture was stirred at rt under air for 1.5 h, the color turning to dark brown. The solvent was then removed *in vacuo*, the residue taken up in $CHCl_3$ and a small amount of MeOH to dissolve the insoluble material, and washed with water. The aqueous phase was extracted twice with $CHCl_3$, and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography of the residue on SiO_2 (6:4 to 5:5, hexanes/EtOAc) afforded 1.13 g (86%, 2 steps) of **2** as a yellow powder. Representative experimental data are as follows:

[2] Giroud, A. M.; Rassat, A. *Bull. Soc. Chim. Fr.* **1979**, *II*, 48.
[3] Bolton, R.; Gillies, D. G.; Sutcliffe, L. H.; Wu, X. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2049.

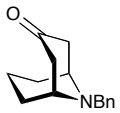
mp 192-194 °C (softening point: 189 °C) (lit. 198 °C from 1:2, benzene/petroleum ether); IR (neat) 3463, 3429, 3368, 3353, 3239, 3049, 2969, 2924, 2857, 1640, 1619, 1588, 1580, 1508, 1495, 1452, 1424, 1372, 1357, 1334, 1314, 1297, 1280, 1247, 1161, 1120, 1068, 1042, 943, 924, 885, 867, 820, 680 cm^{-1}; EI-MS *m/z* 205 (M^+, 75), 190 (90), 175 (58), 173 (68), 160 (100), 144 (65), 130 (63), 115 (43), 91 (35), 77 (36); HRMS (EI) *m/z* calcd for $C_{12}H_{17}N_2O$ 205.1341, found 205.1336.



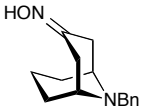
(*S*,*E*)-*N*-(1,1,3,3-Tetramethyl-2-oxo-isoindolin-5-yl)-5-(*tert*-butoxycarbonylamino)-7-methyloct-3-enamide (12). To a solution of the alcohol **10** (187 mg, 0.728 mmol) in acetone (7 mL) at 0 °C was slowly added a solution of Jones reagent (2.5 M, 0.73 mL, 1.82 mmol). The resulting dark suspension was stirred at 0 °C for 1 h, then diluted with Et_2O and water. The aqueous phase was separated and extracted with twice Et_2O. The combined organic layers were washed with water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 190 mg (96%) of the crude acid **11** as a slightly yellow oil, that was carried on without further purification.

To a solution of acid **11** (187 mg, 0.691 mmol, crude) in dry CH_2Cl_2 (8 mL) at 0 °C were added successively **2** (213 mg, 1.04 mmol), DMAP (93.7 mg, 0.760 mmol), HOBt•H_2O (103 mg, 0.760 mmol) and EDCI (162 mg, 0.829 mmol). The resulting yellowish solution was stirred at rt for 16 h, and then washed with sat. aq. NH_4Cl. The aqueous phase was separated and extracted once with CH_2Cl_2, and the combined organic layers were washed with 1 N aq. HCl (2x) and sat. aq. $NaHCO_3$ (1x), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography of the residue on SiO_2 (6:4, hexanes/EtOAc) afforded 221 mg (70%, 67% over 2 steps) of **12** as a pale orange foam: mp 78-79 °C (softening point: 70 °C); $[\alpha]_D^{22}$ +72.2 (*c* 0.5, CH_2Cl_2); IR (neat) 3310 (br), 2969, 2926, 2864, 1675, 1618, 1599, 1526, 1493, 1465, 1452, 1429, 1420, 1388, 1362, 1325, 1310, 1280, 1243, 1161, 1118, 1042, 1021, 969, 872, 826 cm^{-1}; EI-MS *m/z* 458 (M^+, 72), 428 (50), 372 (30), 342 (37), 175 (49), 160 (31), 91 (44), 73 (61), 69 (100); HRMS (EI) *m/z* calcd for $C_{26}H_{40}N_3O_4$ 458.3019, found 458.3011.

A sample of this nitroxide (44.8 mg, 0.0977 mmol) was dissolved in dry MeOH (0.9 mL) and L-ascorbic acid (17.4 mg, 0.0977 mmol) was added. The orange solution turned slighly yellow within a few minutes. After stirring at rt for 50 min, an additional amount of L-ascorbic acid (8.7 mg, 0.0488 mmol) was added, but a complete discoloration of the solution could not be achieved and a residual amount of starting material was seen on TLC. After stirring for 1.5 h, the solvent was removed *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 and washed with water. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 42.6 mg (95%) of the corresponding hydroxylamine (contaminated with nitroxide) as a pale yellow foam: ^{1}H NMR (300 MHz, CD_3OD, broad) δ 7.42 (s, 1 H), 7.36 (d, 1 H, *J* = 5.7 Hz), 7.09 (d, 1 H, *J* = 6.3 Hz), 6.65 (bs, 1 H), 5.75-5.68 (m, 1 H), 5.68-5.50 (m, 1 H), 4.08 (app bs, 1 H), 3.22-3.00 (m, 2 H), 1.65-1.56 (m, 1 H), 1.52-1.05 (m, 2 s at 1.41 and 1.38, 23 H), 0.91 (d, 6 H, *J* = 4.5 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 172.3, 158.0, 158.0, 147.0, 142.3, 139.2, 137.1, 124.0, 123.1, 120.8, 115.0, 79.9, 68.5, 68.2, 51.8, 45.3, 41.7, 29.0, 28.9, 26.9, 26.8, 25.9, 23.3, 22.7.

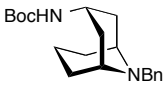


9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one (13).[4] A mecanically stirred solution of acetonedicarboxylic acid (3.24 g, 21.5 mmol) and glutaraldehyde (24% in water, 12.7 mL, 32.3 mmol) in H_2O (30 mL) was treated at 0 °C with benzylamine (2.0 mL, 17.9 mmol). The resulting pale yellow paste was vigorously stirred at rt under argon for 12 h. The brownish reaction mixture was then adjusted to pH < 2 with conc. HCl and the resulting clear brown solution heated to 60 °C for 1 h to complete decarboxylation. After cooling, the mixture was extracted with CH_2Cl_2 (3 x 30 mL). It was then adjusted to pH > 12 with solid NaOH and extracted with CH_2Cl_2 (4 x 50 mL). These combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography of the residue on SiO_2 (7:3, hexanes/EtOAc) afforded **13** (2.83 g, 69%) as a colorless crystalline solid. Representative experimental data are as follows: mp 70.3-70.5 °C (hexanes/EtOAc) (lit. 63-66 °C); IR (neat) 3062, 3025, 2934, 2921, 2874, 2846, 1689, 1493, 1456, 1441, 1415, 1403, 1362, 1338, 1329, 1320,1305, 1288, 1279, 1266, 1219, 1202, 1185, 1133, 1100, 1070, 1029, 1018, 984, 947, 911, 844, 766, 731, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.48-7.20 (m, 5 H), 3.91 (s, 2 H), 3.32 (app s, 2 H), 2.74 (dd, 2 H, J = 16.2, 6.6 Hz), 2.26 (d, 2 H, J = 16.2 Hz), 2.08-1.85 (m, 2 H), 1.65-1.40 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.9, 139.4, 128.6, 128.5, 127.3, 57.2, 53.7, 43.0, 29.5, 16.8; ESI-MS *m/z* 230 ($[M+H]^+$, 100), 172 (42); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NO$ (M+H) 230.1545, found 230.1550.



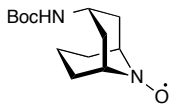
9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one oxime (14). To a solution of ketone **13** (2.40 g, 10.5 mmol) in EtOH (28 mL) were added NH_2OH•HCl (1.48 g, 20.9 mmol) and then 3 N aq. NaOH (7.0 mL, 20.9 mmol). The reaction mixture was refluxed under argon for 14 h, then diluted with CH_2Cl_2 and water. The layers were separated and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, and the insoluble material filtered and rinsed with CH_2Cl_2 to afford 1.42 g of a first crop of product as colorless crystals. Chromatography of the mother liquor on SiO_2 (8:2 to 4:6, hexanes/EtOAc) afforded 1.11 g of a second crop as a colorless crystalline solid. The total amount of **14** obtained was 2.53 g (99%): mp 135.4-135.7 °C (CH_2Cl_2); IR (neat) 3300-2500 (br), 3057, 3157, 2960, 2939, 2921, 2883, 2842, 1644, 1497, 1467, 1456, 1433, 1418, 1389, 1364, 1357, 1348, 1323, 1286, 1266, 1243, 1210, 1197, 1111, 1096, 1079, 1074, 1059, 1005, 980, 964, 952, 928, 900, 841, 760, 747, 723, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (bs, 1 H), 7.44-7.20 (m, 5 H), 3.88 (s, 2 H), 3.14-3.05 (m, 2 H), 3.03 (d, 1 H, J = 16.2 Hz), 2.73 (dd, 1 H, J = 15.4, 5.9 Hz), 2.38 (dd, 1 H, J = 16.3, 6.8 Hz), 2.25 (d, 1 H, J = 15.3 Hz), 2.05-1.73 (m, 3 H), 1.60-1.44 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.0, 139.7, 128.6, 128.5, 127.2, 57.0, 51.9, 51.2, 32.0, 29.8, 29.0, 25.9, 17.3; ESI-MS *m/z* 245 ($[M+H]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{15}H_{21}N_2O$ (M+H) 245.1654, found 245.1642.

[4] Mach, R. H.; Luedtke, R. R.; Unsworth, C. D.; Boundy, V. A.; Nowak, P. A.; Scripko, J. G.; Elder, S. T.; Jackson, J. R.; Hoffman, P. L.; Evora, P. H.; Rao, A. V.; Molinoff, P. B.; Childers, S. R.; Ehrenkaufer, R. L. *J. Med. Chem.* **1993**, *36*, 3707.



***tert*-Butyl 9-benzyl-9-azabicyclo[3.3.1]nonan-3-ylcarbamate (15).** A suspension of oxime **14** (1.30 g, 5.34 mmol) and $NiCl_2$ (69.2 mg, 0.534 mmol) in MeOH (25 mL) was treated at –20 °C with $NaBH_4$ (2.13 g, 53.4 mmol) portionwise. The resulting dark mixture was vigorously stirred between –20 and –10 °C under argon. After 1.5 h, a solution of $NaBH_4$ (1.70 g, 42.7 mmol) in water (5 mL) was added. The reaction mixture was stirred at the same temperature for 1.5 h, then warmed to rt. After stirring for 1 h at rt, the mixture was quenched carefully with acetone, then filtered over Celite and the brown solid rinsed with MeOH. The solution was concentrated *in vacuo*, and the residue was taken up in water, acidified with 6 N aq. HCl (pH < 2), extracted twice with Et_2O, then basified with solid NaOH (pH > 9) and extracted twice with $CHCl_3$. An emulsion formed with a white precipitate that was filtered over Celite. The combined chloroformed layers were washed with brine, dried (K_2CO_3), filtered and concentrated *in vacuo* to afford 1.49 g of the crude amine as a pale yellow oil that was carried on to the next step without further purification.

To a solution of this amine in dry CH_2Cl_2 (100 mL) were added Et_3N (2.25 mL, 16.0 mmol) and then Boc_2O (1.29 g, 5.87 mmol) at 0 °C. The reaction mixture was stirred at rt under argon for 18 h, then quenched with sat. aq. NH_4Cl and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2, and the insoluble material filtered to afford 481 mg of a first crop of **15** as a white powder. Chromatography of the mother liquor on SiO_2 (9:1 to 5:5, hexanes/EtOAc) afforded 4 other fractions of different purity for a total amount of 964 mg. The total amount of **15** obtained was *ca.* 1.44 g (82%, 2 steps). A sample of **15** was recrystallized in EtOH (*ca.* 4 mL) to afford colorless crystals. ^{1}H NMR showed a 3:1 mixture of stereoisomers: mp 153.6-155.0 °C (EtOH); IR (neat) 3312 (br), 3023, 2988, 2971, 2943, 2911, 2861, 2846, 2826, 2809, 1672, 1532, 1493, 1472, 1450, 1387, 1364, 1316, 1303, 1290, 1282, 1254, 1228, 1185, 1169, 1133, 1068, 1046, 1029, 1018, 874, 837, 766, 736, 699, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.18 (m, 5 H), 4.40-4.24 (m, 1 H), 4.24-4.00 (m, 1 H), 3.82 (s, 2 H), 3.07 (bd, 2 H, J = 11.1 Hz), 2.38 (ddd, 2 H, J = 12.0, 12.0, 6.3 Hz), 1.93 (d, 2 H, J = 6.3 Hz), 1.60-1.50 (m, 2 H), 1.46 (s, 9 H), 1.15 (app td, 2 H, J = 11.0, 3.0 Hz), 0.99 (app bd, 2 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 140.7, 128.5, 128.4, 126.9, 79.2, 56.0, 49.4, 42.9, 34.2, 28.7, 24.8, 14.5; ESI-MS *m/z* 331 ([M+H]$^+$, 100), 275 ([M–*t*-Bu+H]$^+$, 93); HRMS (ESI) *m/z* calcd for $C_{20}H_{31}N_2O_2$ (M+H) 331.2386, found 331.2392.

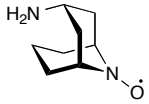


3-(*tert*-Butoxycarbonylamino)-9-azabicyclo[3.3.1]nonane *N*-oxyl (3-Boc-amino-ABNO, 16). A flask containing a suspension of the Bn-protected amine **15** (715 mg, 2.16 mmol) and AcOH (5 drops) in 10:1 EtOH/EtOAc (30 mL) was purged and filled 3 times with argon, then 10% Pd/C (143 mg) was added. The flask was purged and filled 3 times with H_2, and the resulting black suspension was stirred at 40-50 °C under H_2 (1 atm) for 3 h. The reaction mixture was then filtered through a pad of Celite, the Celite washed with EtOAc and MeOH, and the solution concentrated *in vacuo* to afford 591 mg of the crude amine as a white powder, that was carried on to the next step without further purification.

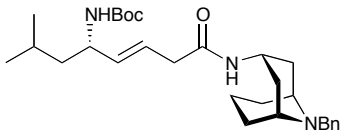
To a suspension of this amine (755 mg, 3.14 mmol) in MeCN (3.1 mL) was added Na_2WO_4•$2H_2O$ (523 mg, 1.57 mmol) and the mixture was stirred at rt for 30 min. After cooling to 0 °C, UHP (1.52 g, 15.7 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to rt. After stirring for 3.5 h at rt, water was added and the resulting mixture was extracted with $CHCl_3$ (3x). The combined organic layers were dried (K_2CO_3), filtered and concentrated *in vacuo*. The residue was taken up in EtOH, and the insoluble material filtered to afford 467 mg of a first

crop of **16** as a yellow powder. Chromatography of the mother liquor on SiO_2 (8:2 to 4:6, hexanes/EtOAc) afforded 120 mg of a second crop as a yellow powder. The total amount of **16** obtained was 587 mg (73%, 2 steps): mp 222.8 °C (sublimation); IR (neat) 3334 (br), 2969, 2947, 2870, 1677, 1525, 1389, 1366, 1351, 1307, 1292, 1273, 1252, 1232, 1225, 1167, 1131, 1116, 1068, 1046, 1036, 1019, 869, 846, 826, 779, 770, 753 cm^{-1}; ESI-MS *m/z* 298 ($[M_{red}+MeCN+H]^+$, 30), 278 ($[M+Na]^+$, 63), 275 (54), 263 (100), 257 ($[M_{red}+H]^+$, 20), 241 ($[M–O+H]^+$, 23), 222 (50), 212 (28); HRMS (ESI) *m/z* calcd for $C_{13}H_{23}N_2O_3Na$ (M+Na) 278.1606, found 278.1593.

A sample of nitroxide **16** (20.0 mg, 0.0783 mmol) was suspended in MeOH (0.8 mL) and L-ascorbic acid (13.9 mg, 0.0783 mmol) was added. The slightly yellow suspension became white within a few seconds. After stirring at rt for 40 min under argon, the solvent was removed *in vacuo*. The resulting residue was taken up in EtOAc and sonicated. The insoluble material was filtered, rinsed with EtOAc and MeOH, and dried, to yield 15.0 mg (75%) of the corresponding hydroxylamine as a white solid. Representative experimental data are as follows: ^{1}H NMR (DMSO-d_6, 400 MHz, 2:1 mixture of isomers) δ 7.93 (s, 0.8 H), 7.43 (s, 0.4 H), 6.57 (d, 0.4 H, J = 8.0 Hz), 6.45 (d, 0.7 H, J = 8.8 Hz), 4.40-4.25 (m, 0.8 H), 3.85-3.70 (m, 0.4 H), 3.40-3.20 (m, 1 H), 3.20-3.10 (m, 1 H), 2.23-2.02 (m, 2 H), 2.02-1.80 (m, 2 H), 1.70-1.53 (m, 2 H), 1.37 (s, 9 H), 1.25-1.14 (m, 1 H), 1.08 (app bt, 2 H, J = 11.2 Hz), 0.82 (app bd, 1 H, J = 11.6 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz, mixture of isomers) δ 154.8, 77.3, 77.1, 55.2, 53.3, 40.4, 33.2, 32.2, 30.8, 28.3, 28.1, 23.4, 13.0, 12.3.



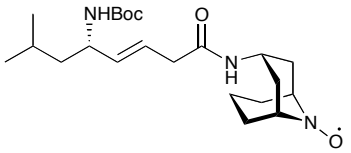
3-Amino-9-azabicyclo[3.3.1]nonane *N*-oxyl (3-amino-ABNO, 6). A mixture of Boc-protected amine 3-Boc-amino-ABNO (**16**, 200 mg, 0.783 mmol) in a 4.0 N solution of HCl in 1,4-dioxane (3.3 mL, 13.2 mmol) was stirred at 0 °C for 1 h and at rt for an additional 2 h. The suspension was then filtered and the solid rinsed with cold dry Et_2O, to give 167 mg of an off-white powder. It was dissolved in a minimum of 2.5 N aq. NaOH, and extracted with warm $CHCl_3$ (7x). The combined organic layers were dried (K_2CO_3), filtered and concentrated *in vacuo* to afford 110 mg (90%) of a red oil. Upon high vacuum and/or storage at rt for not more than 1 h, the product started to loose the red color characteristic for a nitroxide and became pale yellow. Thus, the title compound is unstable.



***tert*-Butyl (*S*,*E*)-8-(9-benzyl-9-azabicyclo[3.3.1]nonan-3-ylamino)-2-methyl-8-oxooct-5-en-4-ylcarbamate (18).** A suspension of oxime **14** (400 mg, 1.64 mmol) and $NiCl_2$ (21.2 mg, 0.164 mmol) in MeOH (8 mL) was treated at –15 °C with $NaBH_4$ (652 mg, 16.4 mmol) portionwise. The resulting dark mixture was vigorously stirred between –15 and 0 °C under argon. After 1.5 h, a solution of $NaBH_4$ (326 mg, 8.18 mmol) in water (1 mL) was added. The reaction mixture was stirred from 0 °C to rt. After 1 h, the reaction mixture was quenched carefully with acetone, then filtered over Celite and the brown solid rinsed with MeOH. The solution was concentrated *in vacuo*, and the residue was taken up in water, acidified with 6 N aq. HCl (pH < 2), extracted twice with Et_2O, then basified with solid NaOH (pH > 9) and extracted with $CHCl_3$ (3x). The combined chloroformed layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 416 mg of the crude amine as a yellow oil that was carried on to the next step without further purification.

To a solution of acid **11** (424 mg, 1.52 mmol, crude) in dry CH_2Cl_2 (18 mL) at 0 °C were added successively HOBt•H_2O (246 mg, 1.82 mmol), DMAP (206 mg, 1.67 mmol), a solution of this amine (403 mg, 1.59 mmol, crude) in dry CH_2Cl_2 (2

mL), and EDCI (356 mg, 1.82 mmol). The resulting mixture was stirred at rt under argon for 14 h, then washed with 2.5 N aq. NaOH (3x). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (8:2 to 4:6, hexanes/EtOAc) afforded 421 mg (57%, 3 steps) of **18** as a white powder: mp 115.0-115.4 °C; $[\alpha]_D^{23}$ +12.6 (*c* 1.0, CH_2Cl_2); IR (neat) 3338 (br), 3277 (br), 2924, 2867, 1681, 1635, 1519, 1495, 1467, 1452, 1435, 1389, 1364, 1349, 1327, 1307, 1277, 1252, 1163, 1137, 1081, 1060, 1044, 1025, 1010, 993, 964, 930, 874, 842, 760, 742, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.34 (m, 2 H), 7.33-7.27 (m, 2 H), 7.25-7.19 (m, 1 H), 5.95-5.80 (m, 1 H), 5.66 (dt, 1 H, *J* = 15.2, 7.2 Hz), 5.46 (dd, 1 H, *J* = 15.4, 6.6 Hz), 4.55-4.45 (m, 1 H), 4.41 (ddddd, 1 H, *J* = 12.0, 12.0, 8.4, 6.0, 6.0 Hz), 4.04 (app p, 1 H, *J* = 7.2 Hz), 3.82 (s, 2 H), 3.08 (app bd, 2 H, *J* = 10.4 Hz), 2.98 (d, 2 H, *J* = 7.2 Hz), 2.40-2.26 (m, 2 H), 2.06-1.87 (m, 3 H), 1.73-1.60 (m, 3 H), 1.58-1.49 (m, 1 H), 1.44 (s, 9 H), 1.34 (app td, 2 H, *J* = 7.3, 1.4 Hz), 1.03-0.92 (m, 2 H), 0.93 (d, 3 H, *J* = 6.8 Hz), 0.93 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 155.6, 140.6, 137.2, 128.6, 128.4, 126.9, 123.6, 79.5, 56.0, 51.6, 49.3, 49.3, 44.2, 42.0, 40.4, 33.5, 33.4, 28.6, 24.8, 24.7, 22.7, 14.5; ESI-MS *m/z* 527 (80), 506 ($[M+Na]^+$, 84), 484 ($[M+H]^+$, 67); HRMS (ESI) *m/z* calcd for $C_{29}H_{45}N_3O_3Na$ (M+Na) 506.3359, found 506.3336.

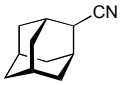


(*S*,*E*)-*N*-(9-Azabicyclo[3.3.1]nonan-9-oxo-3-yl)-5-(*tert*-butoxycarbonylamino)-7-methyloct-3-enamide (17). A solution of Bn-protected amine **18** (150 mg, 0.309 mmol) in 5:1 MeCN/H_2O (12 mL) was treated with CAN (339 mg, 0.618 mmol). The resulting red reaction mixture was stirred at rt under argon. After 3.5 h, more CAN (170 mg, 0.309 mmol) was added. After 19 h stirring, sat. aq. $NaHCO_3$ (12 mL) was added and stirring was continued for 15 min. The mixture was then extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 144 mg of the crude amine as a brownish residue, that was carried on to the next step without further purification.

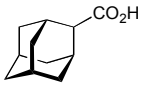
To a suspension of this amine (140 mg, 0.301 mmol) in 1:1 MeCN/MeOH (1.2 mL) was added Na_2WO_4•$2H_2O$ (50.2 mg, 0.151 mmol) and the mixture was stirred at rt for 30 min. After cooling to 0 °C, UHP (146 mg, 1.51 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to rt and stirred overnight. After 17 h, water was added and the resulting mixture was extracted twice with $CHCl_3$. The combined organic layers were dried (K_2CO_3), filtered and concentrated *in vacuo*. Chromatography on SiO_2 (5:5, hexanes/EtOAc to EtOAc) afforded 84.9 mg (69%, 2 steps) of **17** as orange microcrystals formed from an initial red oil. Representative experimental data are as follows: mp 140.2-141.0 °C (EtOAc); $[\alpha]_D^{23}$ +25.9 (*c* 1.0, CH_2Cl_2); IR (neat) 3292 (br), 2949, 2926, 2867, 1690, 1657, 1539, 1469, 1448, 1400, 1389, 1362, 1325, 1308, 1284, 1269, 1247, 1221, 1167, 1116, 1088, 1070, 1040, 1018, 977, 678 cm^{-1}; ESI-MS *m/z* 431 ($[M+Na]^+$, 77); HRMS (ESI) *m/z* calcd for $C_{22}H_{38}N_3O_4Na$ (M+Na) 431.2760, found 431.2736.

A sample of this nitroxide (10.0 mg, 0.0245 mmol) was dissolved in MeOH (0.3 mL) and L-ascorbic acid (4.4 mg, 0.0245 mmol) was added. The pale orange suspension became colorless within a few seconds. After stirring at rt for 30 min under argon, the solvent was removed *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 with some MeOH and washed twice with water. The combined aqueous layers were extracted with warm CH_2Cl_2 (4x), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 9.4 mg (94%) of the corresponding hydroxylamine as a white powder: ^1H NMR ($CDCl_3$, 400 MHz, 3:1 mixture of isomers) δ 6.02-5.91 (m, 0.25 H), 5.82 (app bd, 0.75 H, *J* = 6.0 Hz), 5.71-5.58 (m, 1 H), 5.52-5.41 (m, 1 H), 4.84 (ddddd, 0.75 H, *J* = 11.6, 11.6, 6.8, 6.8, 6.8 Hz), 4.52 (app bs, 1 H), 4.23

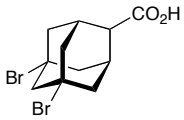
(app o, 0.25 H, J = 6.2 Hz), 4.09-3.97 (m, 1 H), 3.57 (app bd, 1.5 H, J = 9.6 Hz), 3.42 (app bd, 0.5 H, J = 10.0 Hz), 3.00-2.91 (m, 2 H), 2.51-2.38 (m, 0.6 H), 2.38-2.19 (m, 2 H), 2.05-1.88 (m, 0.5 H), 1.80-1.57 (m, 3 H), 1.56-1.46 (m, 2 H), 1.44 (s, 9 H), 1.34 (app td, 2 H, J = 7.3, 1.8 Hz), 1.38-1.26 (m, 1 H), 1.14 (app bt, 2 H, J = 12.4 Hz), 0.93 (d, 3 H, J = 6.8 Hz), 0.92 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, mixture of isomers) δ 170.6, 170.4, 155.6, 137.4, 137.3, 123.6, 123.5, 79.4, 55.9, 55.9, 54.1, 51.6, 51.5, 44.2, 40.3, 40.3, 39.7, 33.8, 33.8, 32.5, 31.2, 31.1, 29.9, 28.6, 24.8, 23.6, 22.9, 22.7, 14.3, 13.5, 12.8.



2-Adamantanecarbonitrile.[5] A 3-5 °C solution of 2-adamantanone (21.0 g, 137 mmol), TosMIC (35.5 g, 178 mmol) and EtOH (14 mL, 233 mmol) in DME (470 mL) was treated with portionwise addition of solid *t*-BuOK (39.2 g, 342 mmol), maintaining the internal temperature below 10 °C. After the addition, the resulting slurry reaction mixture was stirred at rt for 30 min and then at 35-40 °C for 30 min. The heterogeneous reaction mixture was filtered and the solid washed with DME. The filtrate was concentrated *in vacuo*, loaded to a short alumina column (activated, neutral, Brockmann I, 150 mesh, 7 cm thick x 15 cm height), and washed off with a 5:1 mixture of hexanes/CH_2Cl_2 (~1.5 L). The solution was concentrated *in vacuo* to afford 19.0 g (86%) of the title compound as a white powder: mp 170-174 °C (softening point: ~155 °C, sealed tube) (lit. 170-177 °C); IR (neat) 2903, 2851, 2229, 1468, 1450, 1355, 1342, 1239, 1111, 1098, 1073, 988, 976, 818, 807, 792 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 (app s, 1 H), 2.23-2.08 (m, 4 H), 2.00-1.80 (m, 4 H), 1.80-1.66 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 122.5, 37.2, 36.9, 36.8, 33.3, 30.6, 27.1, 27.0.



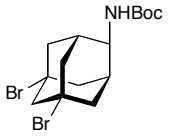
2-Adamantane carboxylic acid. A mixture of 2-adamantanecarbonitrile (18.9 g, 117 mmol) in AcOH (56 mL) and 48% HBr (224 mL) was stirred at 120 °C overnight. The reaction mixture was cooled at 4 °C, let stand for 4 h, then filtered. The solid was washed with water and dried under vacuum over silica gel overnight, to yield 20.6 g (98%) of the title compound as colorless crystals: mp 145.5-145.8 °C (sealed tube) (lit.[5] 143-144 °C); IR (neat) 3200-2400 (br), 2922, 2915, 2894, 2849, 2630, 2950, 1681, 1468, 1452, 1439, 1418, 1351, 1342, 1332, 1314, 1301, 1277, 1249, 1226, 1176, 1099, 1064, 1049, 984, 941, 926, 911, 831 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (s, 1 H), 2.55-2.47 (m, 1 H), 2.20 (app bs, 2 H), 1.87-1.64 (m, 10 H), 1.60-1.50 (m, 2 H).



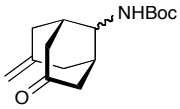
5,7-Dibromo-2-adamantane carboxylic acid (19).[6] A vigorously stirred 0 °C solution of $AlBr_3$ (18.9 g, 69.6 mmol), BBr_3 (2.40 g, 9.49 mmol) and Br_2 (40 mL) was treated portionwise with 2-adamantane carboxylic acid (5.70 g, 31.6 mmol). Upon completion of the addition, the reaction mixture was stirred at 70 °C for 48 h, then cooled in an ice bath, and quenched carefully with sat. aq. sodium bisulfite. Stirring was continued at rt overnight. The resultant pale brown suspension was filtered, the solid washed with water and dried overnight under vacuum at 60 °C to yield 10.95 g (quant.) of crude **19** as a beige powder. Representative experimental data are as follows: mp 230-232 °C (sealed tube); IR (neat)

[5] Oldenziel, O. H.; Wildeman, J.; van Leusen, A. M. *Org. Synth.* **1977**, *57*, 8.
[6] Rohde, J. J.; Pliushchev, M. A.; Sorensen, B. K.; Wodka, D.; Shuai, Q.; Wang, J.; Fung, S.; Monzon, K. M.; Chiou, W. J.; Pan, L.; Deng, X.; Chovan, L. E.; Ramaiya, A.; Mullally, M.; Henry, R. F.; Stolarik, D. F.; Imade, H. M.; Marsh, K. C.; Beno, D. W. A.; Fey, T. A.; Droz, B. A.; Brune, M. E.; Camp, H. S.; Sham, H. L.; Frevert, E. U.; Jacobson, P. B.; Link, J. T. *J. Med. Chem.* **2007**, *50*, 149.

3200-2400 (br), 2956, 2933, 2909, 2861, 1692, 1444, 1431, 1418, 1331, 1319, 1301, 1291, 1284, 1269, 1249, 1217, 1204, 1189, 1150, 1032, 1017, 995, 973, 945, 939, 928, 818, 803, 753, 745, 703, 663 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.56 (bs, 1 H), 2.85 (app d, 2 H, J = 12.9 Hz), 2.75-2.55 (m, 2 H), 2.50-2.35 (m, 2 H), 2.35-2.10 (m, 7 H); LC-MS (ESI) t_R 20.4 min, *m/z* 337 ([M–H]$^-$, 100).



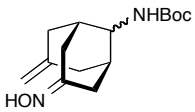
(5,7-Dibromo-adamantan-2-yl)-carbamic acid *tert*-butyl ester (20).[6] The reaction was performed in 3 separated batches. For each of them, a suspension of the acid **19** (7.80 g, 23.1 mmol) in dry toluene (117 mL) was treated successively with Et_3N (3.9 mL, 27.7 mmol) and DPPA (6.20 mL, 27.7 mmol). The resulting brown solution was stirred at 85 °C for 12 h. To a separated flask containing a solution of *t*-BuOK (5.28 g, 46.1 mmol) in dry THF (312 mL) at 0 °C was added the resulting isocyanate solution dropwise *via* a dropping funnel. The reaction mixture was allowed to warm to rt over 3 h, then quenched with water. The THF was removed *in vacuo*, and the resulting material was diluted with EtOAc. The organic layer was washed with 1 N aq. HCl, sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was sonicated in a minimum of anhydrous Et_2O, filtered and washed with cold Et_2O to yield **20** as a white powder. The 3 mother liquors were then combined and 2 additional filtrations afforded another fraction of **20** as an off-white powder. Chromatography of the residual mother liquor on SiO_2 (9:1, hexanes/EtOAc) afforded a white powder contaminated with a yellow oil. This residue was taken up in hexanes, filtered, and the white powder washed with hexanes. This resulting white powder was only an impurity. The mother liquor was concentrated *in vacuo* and again taken up in a small amount of hexanes. The solvent was removed from the insoluble white powder with a Pasteur pipet, to separate the product from the yellow oil. The white powder was dried to yield an additional fraction of **20**. The combined fractions afforded 21.6 g (77%) of **20** as a white powder. A sample of higher purity obtained after chromatography (recovered starting material from the next step) was used for analysis: mp 187.5-189.5 °C; IR (neat) 3250, 3146, 3125, 3000, 2974, 2959, 2932, 2876, 2862, 1681, 1476, 1457, 1388, 1366, 1345, 1332, 1292, 1275, 1256, 1250, 1230, 1157, 1079, 1042, 1021, 999, 842, 835, 820, 803, 775, 734, 725, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (bd, 1 H, J = 6.3 Hz), 3.75 (app bs, 1 H), 2.86 (s, 2 H), 2.47-2.10 (m, 10 H), 1.45 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 80.2, 60.2, 59.7, 59.0, 51.2, 46.4, 41.5, 38.8, 28.6; EI-MS *m/z* 411 (M^+, 9), 409 (M^+, 15), 407 (M^+, 8), 354 ([M–*t*-Bu]$^+$, 67), 352 ([M–*t*-Bu]$^+$, 56), 350 ([M–*t*-Bu]$^+$, 15), 274 ([M–*t*-Bu–Br]$^+$, 100), 272 ([M–*t*-Bu–Br]$^+$, 98), 230 ([M–Boc–Br]$^+$, 48), 228 ([M–Boc–Br]$^+$, 51), 213 ([M–NHBoc–Br]$^+$, 40), 211 ([M–NHBoc–Br]$^+$, 39), 148 ([M–Boc–2Br]$^+$, 41), 132 (54), 131 (76), 117 (43), 105 (50), 93 (52), 91 (80), 79 (65), 77 (68), 65 (37), 59 (79), 56 (87); HRMS (EI) *m/z* calcd for $C_{15}H_{24}Br_2NO_2$ 408.0174, found 408.0154.



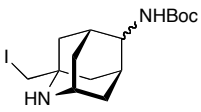
(7-Methylene-bicyclo[3.3.1]nonan-3-one-9-yl)-carbamic acid *tert*-butyl ester (21). The reaction was performed in 3 separated batches. A mixture of **20** (3 x 2.46 g, 18.0 mmol) and 2 N aq. NaOH (3 x 13.5 mL, 81.0 mmol, degassed) in dioxane (3 x 16.5 mL, degassed) was heated in a stainless steel Parr bomb at 160 °C (20 bar) under argon for 2 h. The crude mixtures were combined and the dioxane was removed *in vacuo*. The aqueous residue (pH > 12) was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to

afford 3.90 g of crude 9-amino-7-methylene-bicyclo[3.3.1]nonan-3-one[9] as a yellow solid, that was carried on without further purification.

To a solution of this amine (2.98 g, 18.0 mmol, crude) in dry CH_2Cl_2 (270 mL) was added Et_3N (7.60 mL, 54.0 mmol) and then Boc_2O (4.37 g, 19.8 mmol) at 0 °C. The reaction mixture was stirred at rt under nitrogen for 20 h, then quenched with sat. aq. NH_4Cl. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude was taken up in CH_2Cl_2 but was poorly soluble. A filtration afforded a white powder. The mother liquor was evaporated and taken up in a 7:3 hexanes/EtOAc mixture. After sonicaton, the white powder was filtered. This procedure was repeated one more time. Chromatography of the resulting mother liquor on SiO_2 (9:1 to 6:4, hexanes/EtOAc) afforded 964 mg of another fraction as a pale yellow powder. Since the 3 fractions from filtration were impure and still contained Et_3N, they were combined, dissolved in $CHCl_3$ (50 mL), washed with 5% aq. $CuSO_4$ (2 x 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography of the residue on SiO_2 (9:1 to 6:4, hexanes/EtOAc) afforded 1.624 g of the major isomer as a white powder, and 2.59 g (42%, 4 steps) of **21** were obtained, while 509 mg (~7%) of starting material **20** (45% yld b.r.s.m.) was recovered. Representative experimental data are as follows: mp 167.8-182.0 °C; IR (neat) 3271, 3131, 2971, 2930, 2849, 1685, 1478, 1452, 1437, 1407, 1385, 1364, 1351, 1316, 1250, 1239, 1215, 1161, 1142, 1109, 1073, 1064, 1044, 1017, 1008, 904, 857, 783, 773, 729, 710, 688, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 4:1 mixture of isomers) δ 4.93 (app bs, 0.2 H), 4.84 (s, 2 H), 4.74 (app bs, 0.8 H), 4.12 (app bs, 0.2 H), 3.96-3.87 (app m, 0.8 H), 2.65-2.12 (m, 10 H), 1.49 and 1.48 (2 s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, 4:1 mixture of isomers) δ 209.2, 155.6, 139.7, 139.7, 116.5, 115.9, 80.2, 51.4, 50.5, 47.0, 42.3, 41.0, 35.9, 35.0, 34.4, 28.6; ESI-MS *m/z* 288 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{15}H_{23}NO_3Na$ (M+Na) 288.1576, found 288.1567.

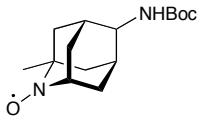


(7-Methylene-bicyclo[3.3.1]nonan-3-one oxime-9-yl)-carbamic acid *tert*-butyl ester (22). To a solution of ketone **21** (2.53 g, 9.53 mmol) in dry pyridine (18 mL) was added $NH_2OH•HCl$ (2.02 g, 28.6 mmol). The reaction mixture was stirred at rt under argon for 12 h. The solvent was removed *in vacuo*, and the residue diluted with EtOAc and then water was added. The layers were separated and the aqueous phase extracted with EtOAc. The combined organic layers were washed with 5% aq. $CuSO_4$ (8x), brine (2x), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography of the residue on SiO_2 (5:5, hexanes/EtOAc) followed by trituration in Et_2O afforded 2.41 g (90%) of **22** as a white powder: mp 60-86 °C; IR (neat) 3265 (br), 2971, 2924, 2833, 1690, 1515, 1508, 1498, 1450, 1437, 1388, 1364, 1249, 1161, 1077, 1062, 1040, 1012, 978, 965, 949, 921, 881, 777, 716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 4:1 mixture of isomers) δ 8.01 (bs, 1 H), 4.93 (app bs, 0.35 H), 4.90-4.70 (m, 0.65 H), 4.79 (s, 1 H), 4.68 (d, 1 H, J = 1.5 Hz), 3.86 (app bs, 1 H), 3.25 (d, 0.2 H, J = 15.9 Hz), 3.09 (d, 0.8 H, J = 16.5 Hz), 2.58-2.19 (m, 8 H), 2.19-1.93 (m, 1 H), 1.47 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, 4:1 mixture of isomers) δ 155.5, 141.1, 141.1, 113.2, 112.7, 80.0, 52.2, 51.4, 41.3, 40.5, 37.6, 35.7, 35.1, 34.2, 34.0, 32.6, 32.5, 31.6, 28.6, 24.9; ESI-MS *m/z* 281 ($[M+H]^+$, 65), 266 (50), 225 ($[M–t\text{-}Bu]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{15}H_{25}N_2O_3$ (M+H) 281.1865, found 281.1855.



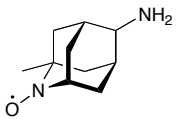
(1-Iodomethyl-2-azaadamantan-6-yl)-carbamic acid *tert*-butyl ester (23). To a mixture of oxime **22** (2.35 g, 8.39 mmol) and MoO_3 (1.70 g, 11.8 mmol) in dry MeOH (84 mL) at 0 °C under argon was added $NaBH_4$ (3.24 g, 83.9 mmol) portionwise. The resulting dark brown reaction mixture was stirred at 0-10 °C for 4 h, then quenched with acetone and filtered through Celite. The Celite was rinsed with acetone, and the filtrate was concentrated *in vacuo*. The resulting residue was diluted with water (100 mL) and EtOAc (200 mL), and filtered through Celite to break the emulsion. The organic layer was separated, washed with a few brine, dried (K_2CO_3), filtered and concentrated *in vacuo* to afford ~2.5 g of crude *tert*-butyl-3-amino-7-methylenebicyclo[3.3.1]nonan-9-ylcarbamate as a pale brown oily foam, that was carried on without further purifcation.

To a suspension of this amine (2.23 g, 8.39 mmol, crude) in dry MeCN (42 mL) at 0 °C under argon was added I_2 (2.13 g, 8.39 mmol). The reaction mixture was stirred at rt for 3 h and then quenched with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ (pH 8). The resulting yellow mixture was extracted with $CHCl_3$ (3x), and the combined organic layers were dried (K_2CO_3), filtered and concentrated *in vacuo*. Chromatography of the residue on SiO_2 (EtOAc to 9:1, EtOAc/MeOH) afforded 1.55 g (47%, 2 steps) of **23** as a dark orange powder: mp 125-138 °C; IR (neat) 3278 (br), 3269, 2967, 2918, 2868, 2853, 1701, 1670, 1541, 1448, 1444, 1431, 1388, 1362, 1351, 1295, 1280, 1269, 1250, 1217, 1200, 1167, 1118, 1086, 1077, 1045, 1012, 995, 891, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 3:1 mixture of isomers) δ 4.83 (app bs, 0.65 H), 4.75 (app bs, 0.35 H), 3.82-3.67 (m, 1 H), 3.24 (bs, 1 H), 3.19 (s, 1.5 H), 3.16 (s, 0.5 H), 2.20-2.07 (m, 1 H), 1.98-1.80 (m, 3 H), 1.80-1.60 (m, 6 H), 1.46 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, 3:1 mixture of isomers) δ 155.5, 79.7, 53.7, 49.0, 47.4, 47.2, 40.9, 36.1, 35.8, 32.4, 31.7, 30.8, 28.6, 23.7, 23.2; EI-MS *m/z* 392 (M^+, 18), 265 ($[M–I]^+$, 68), 209 ($[M–I–t\text{-}Bu]^+$, 88), 148 (100), 94 (80); HRMS (ESI) *m/z* calcd for $C_{15}H_{25}IN_2O_2$ 392.0961, found 392.0958.

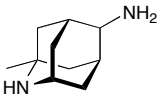


(1-Methyl-2-azaadamantane-*N*-oxyl-6-yl)-carbamic acid *tert*-butyl ester (6-Boc-amino-1-Me-AZADO, 24). The reaction was performed in 2 separated batches. A Parr flask was charged with the iodoalkane **23** (2 x 414 mg, 2.11 mmol), EtOH (2 x 10 mL) and 20% $Pd(OH)_2/C$ (2 x 82 mg). The flask was placed in a high pressure reactor. The reactor was charged with H_2 and purged for 5 cycles and finally pressurized with H_2 at 4 bar (60 psi), then heated at 50 °C. After stirring at 50 °C for 26 h, the reaction mixtures were combined and filtered through Celite, the Celite washed with MeOH, and the solution concentrated *in vacuo* to yield a dark reddish powder. The crude was dissolved in CH_2Cl_2 and washed with sat. aq. Na_2CO_3, dried (K_2CO_3), filtered and concentrated *in vacuo* to afford 556 mg (99%) of crude (1-methyl-2-azaadamantan-6-yl)-carbamic acid *tert*-butyl ester as a yellow solid, that was carried on without further purification.

A mixture of this amine (554 mg, 2.08 mmol, crude) and $Na_2WO_4•2H_2O$ (347 mg, 1.04 mmol) in MeOH (6 mL) was stirred at rt for 20 min then cooled to 0 °C and treated with 30% aq. H_2O_2 (2.36 mL, 20.8 mmol). The resulting reaction mixture was stirred at 0 °C for 30 min then allowed to warm to rt. After 4 h, the reaction mixture was cooled to 0 °C and treated again with H_2O_2 (0.70 mL, 6.24 mmol), then allowed to warm to rt. After an additional 6 h stirring at rt, the bright orange reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatograpy of the residue on SiO_2 (7:3 to 5:5, hexanes/EtOAc) afforded 345 mg (59%, 58% over 2 steps) of **24** as a red solid. Representative experimental data are as follows: mp 140-150 °C (softening point: 131 °C); IR (neat) 3265, 3138, 2999, 2969, 2922, 1688, 1474, 1448, 1383, 1362, 1286, 1275, 1252, 1163, 1137, 1079, 1066, 1045, 1008, 984, 958, 777, 727, 708 cm^{-1}; ESI-MS *m/z* 284 (70), 282 ($[M+H]^+$, 100); HRMS (ESI) *m/z* calcd for $C_{15}H_{26}N_2O_3$ (M+H) 282.1943, found 282.1941.

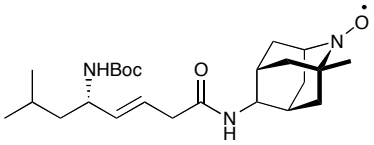


6-Amino-1-methyl-2-azaadamantane-*N*-oxyl (6-amino-1-Me-AZADO, 8). A solution of 6-Boc-amino-1-Me-AZADO (335 mg, 1.19 mmol) in a 4.0 N solution of HCl in 1,4-dioxane (5.0 mL, 20.0 mmol) was stirred at 0 °C for 1 h and at rt for an additional 2 h. Dioxane was removed *in vacuo* and the yellow residue was dissolved in 2.5 N aq. NaOH and extracted with CH_2Cl_2 until the organic layer became colorless. The combined organic layers were dried (K_2CO_3), filtered and concentrated *in vacuo* to afford 230 mg (quant.) of crude **8** as a red oil: LC-MS (ESI) t_R 7.71 min, *m/z* 183 ($[M_{red}+H]^+$), 166 ($[M–O+H]^+$).



6-Amino-1-methyl-2-azaadamantane (26). The reaction was performed in 2 separate batches. A Parr flask was charged with the iodoalkane **23** (2 x 494 mg, 2.52 mmol), EtOH (2 x 12 mL) and 20% $Pd(OH)_2/C$ (2 x 99.0 mg). The flask was placed in a high pressure reactor. The reactor was charged with H_2 and purged for 5 cycles and finally pressurized with H_2 at 4 bar (60 psi), then heated at 50 °C. After stirring at 50 °C for 22 h, the reaction mixtures were combined and filtered through Celite, the Celite washed with MeOH and EtOAc, and the solution concentrated *in vacuo*. The crude was dissolved in CH_2Cl_2 and washed with sat. aq. Na_2CO_3, dried (K_2CO_3), filtered and concentrated *in vacuo* to afford 638 mg (95%) of crude (1-methyl-2-azaadamantan-6-yl)-carbamic acid *tert*-butyl ester as a dark grey foam, that was carried on without further purification.

A mixture of (1-methyl-2-azaadamantan-6-yl)-carbamic acid *tert*-butyl ester (180 mg, 0.676 mmol, crude) in a 4.0 N solution of HCl in 1,4-dioxane (2.85 mL, 11.4 mmol) was stirred at 0 °C for 1 h and at rt for an additional 2.5 h. Dioxane was removed *in vacuo* and the residue was dissolved in 2.5 N aq. NaOH and extracted with $CHCl_3$ (3x). The combined organic layers were dried (K_2CO_3), filtered and concentrated *in vacuo* to afford 113 mg (quant.) of crude **26** as a dark brown oil, that was carried on without further purification.



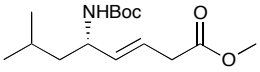
(*S*,*E*)-*N*-(1-Methyl-2-azaadamant-2-oxo-6-yl)-5-(*tert*-butoxycarbonylamino)-7-methyloct-3-enamide (25). To a solution of alcohol **10** (180 mg, 0.699 mmol) in acetone (8 mL) at 0 °C was slowly added a solution of Jones reagent (2.5 M, 0.70 mL, 1.75 mmol). The resulting dark suspension was stirred at 0 °C for 1 h, then diluted with Et_2O and water. The aqueous phase was separated and extracted with Et_2O (2x). The combined organic layers were washed with water (2x) and brine (1x), dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 189 mg (quant.) of the crude acid (**11**) as a colorless oil, that was carried on without further purification.

To a solution of this acid (58.7 mg, 0.216 mmol, crude) in dry CH_2Cl_2 (2.0 mL) at 0 °C were added successively HOBt•H_2O (35.1 mg, 0.260 mmol), DMAP (29.4 mg, 0.238 mmol), a solution of amine **26** (40.0 mg, 0.216 mmol) in dry CH_2Cl_2 (0.7 mL), and EDCI (50.0 mg, 0.260 mmol). The resulting mixture was stirred at rt under argon for 15 h, then the mixture was diluted with CH_2Cl_2, washed twice with 1 N aq. NaOH, dried (K_2CO_3), filtered and concentrated *in vacuo*. Chromatography of the residue on deactivated SiO_2 (EtOAc then 9:1, EtOAc/MeOH + 1% NH_4OH) afforded 54.0 mg

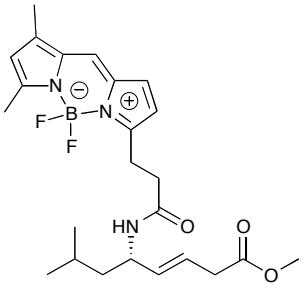
(59%) of *tert*-butyl (*S*,*E*)-8-(1-methyl-2-azaadamant-6-ylamino)-2-methyl-8-oxooct-5-en-4-ylcarbamate as a pale yellow foam.

To a mixture of this amine (54.0 mg, 0.129 mmol) in 1:1 MeCN/MeOH (0.6 mL) was added $Na_2WO_4 \cdot 2H_2O$ (21.4 mg, 0.0643 mmol), and the resulting mixture was stirred at rt for 20 min. After cooling to 0 °C, UHP (100 mg, 1.03 mmol) was added and the reaction mixture was stirred under air at 0 °C for 1 h then at rt for 12 h. Water was then added, and the resulting aqueous mixture was extracted with $CHCl_3$ (2x). The combined organic layers were dried (K_2CO_3), filtered and concentrated *in vacuo*. Flash chromatography of the residue on SiO_2 (5:5, hexanes/EtOAc to EtOAc) afforded 35.4 mg (63%) of **25**, 8.6 mg as red crystals (suitable for X-ray) and 26.8 mg as a red-orange foam: mp 154-156 °C (EtOAc); $[\alpha]_D^{23}$ +6.2 (*c* 1.0, CH_2Cl_2); IR (neat) 3308 (br), 2948, 2928, 2868, 1677, 1663, 1651, 1646, 1523, 1450, 1387, 1362, 1336, 1325, 1312, 1284, 1245, 1167, 1133, 1116, 1066, 1042, 1023, 1003, 969, 951 cm^{-1}; ESI-MS *m/z* 457 ($[M+Na]^+$, 63), 401 (51), 318 (33); HRMS (ESI) *m/z* calcd for $C_{23}H_{42}N_3O_4Na$ (M+Na) 457.2917, found 457.2884.

A sample of this nitroxide (4.0 mg, 0.00920 mmol) was dissolved in dry MeOH (0.2 mL) and L-ascorbic acid (1.6 mg, 0.00920 mmol) was added. Complete discoloration of the solution occured immediately. After stirring at rt for 15 min, the solvent was removed *in vacuo*. The resulting residue was dissolved in $CHCl_3$ and washed with water. The aqueous phase was extracted once with $CHCl_3$, and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 5.2 mg (>100%) of the corresponding hydroxylamine as a colorless solidified oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (bs, 1 H), 5.69 (dt, 1 H, *J* = 14.9, 7.3 Hz), 5.53 (dd, 1 H, *J* = 15.6, 5.6 Hz), 4.46 (app bs, 1 H), 4.14-4.03 (m, 1 H), 4.03-3.96 (m, 1 H), 3.27 (app bs, 1 H), 3.02 (d, 2 H, *J* = 7.2 Hz), 2.36-2.20 (m, 2 H), 2.07-1.70 (m, 8 H), 1.70-1.55 (m, 1 H), 1.43 (2 s, 9 H), 1.40-1.20 (m, 2 H), 1.11 (s, 3 H), 0.93 (app d, 6 H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 155.4, 137.8, 122.8, 79.5, 57.0, 56.3, 52.4, 51.1, 44.4, 42.9, 42.8, 40.4, 35.1, 35.0, 32.1, 31.2, 31.1, 30.7, 30.5, 30.5, 29.9, 29.8, 29.5, 28.6, 29.6, 26.4, 24.9, 23.3, 23.3, 22.9, 22.8, 22.6, 14.3.

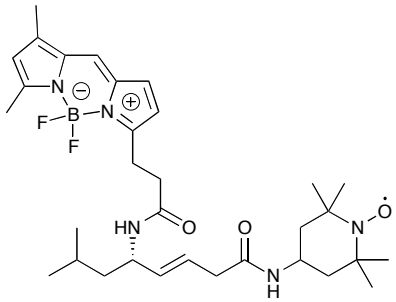


(*S*,*E*)-Methyl 5-((*tert*-butoxycarbonyl)amino)-7-methyloct-3-enoate (27). To a solution of the acid **11**, (142 mg, 0.523 mmol, crude) in acetonitrile (8.7 mL, 0.06 M) was added K_2CO_3 (362 mg, 5.23 mmol), followed by MeI (326 µL, 5.233 mmol). The resulting reaction mixture was stirred at rt under N_2 in the dark for 11 h, then quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic portion was washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography on SiO_2 (ISCO, 12 g column, liquid load in CH_2Cl_2, 0-100% EtOAc/hexanes gradient, eluted at 50% EtOAc/hexanes) afforded **27** as a colorless oil (159 mg, quant.): $[\alpha]_D^{20}$ –13.0 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) 3351 (br), 2952, 2932, 2867, 1737, 1692, 1512, 1452, 1435, 1389, 1364, 1327, 1245, 1159, 1118, 1081, 1042, 1016, 967 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (dtd, 1 H, *J* = 15.5, 6.9, 1.2 Hz), 5.49 (dd, 1 H, *J* = 15.2, 4.9 Hz), 4.39 (bs, 1 H), 4.23-4.00 (m, 1 H), 3.68 (s, 3 H), 3.07 (d, 2 H, *J* = 6.9 Hz), 1.72-1.59 (m, 1 H), 1.44 (s, 9 H), 1.39-1.25 (m, 2 H), 0.92 (d, 3 H, *J* = 6.6 Hz), 0.91 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 155.5, 135.6, 122.0, 79.5, 52.0, 50.4, 44.8, 37.7, 28.6, 24.9, 22.9, 22.6; HRMS (ESI) *m/z* calcd for $C_{18}H_{27}N_3O_4Na$ $(M+Na)^+$ 308.1838, found 308.1860.



(*S*,*E*)-5,5-Difluoro-3-(3-((8-methoxy-2-methyl-8-oxooct-5-en-4-yl)amino)-3-oxopropyl)-7,9-dimethyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (29). To a solution of ester **27** (150 mg, 0.526 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added TFA (0.4 mL, 5.26 mmol). The resulting colorless solution was stirred at rt. TLC analysis showed that the starting material had been consumed after 4 h. The reaction mixture was concentrated, and the residue was taken up CH_2Cl_2 and washed with 5% aq. Na_2CO_3 (pH 9). The aqueous layer was extracted once with CH_2Cl_2, and the combined organic portion was dried (K_2CO_3), filtered, and concentrated to afford 92.2 mg (95%, crude) of amine as a pale brownish oil, that was carried on without further purification.

A solution of activated ester **28** (BODIPY-FL-NHS, 224 mg, 0.576 mmol) and DIEPA (0.26 mL, 1.49 mmol) in dry CH_2Cl_2 (15 mL) was treated with a solution of amine (89.0 mg, 0.480 mmol, crude) in dry CH_2Cl_2 (5 mL). The resulting red solution was stirred at rt under N_2 for 9 h, then washed with water. The aqueous phase was extracted with CH_2Cl_2 until it became almost colorless. The combined organic portion was dried (Na_2SO_4), filtered, and concentrated. Chromatography on SiO_2 (75:25 to 6:4 to 5:5, hexanes/EtOAc) afforded 180 mg (82%) of **29** as a red, viscous oil that solidified to give a red crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1 H), 6.88 (d, 1 H, J = 4.0 Hz), 6.30 (d, 1 H, J = 4.0 Hz), 6.13 (s, 1 H), 5.58-5.62 (m, 2 H), 5.42 (dd, 1 H, J = 15, 6.0 Hz), 4.48 (dt, 1 H, J = 15, 7.3, 7.3 Hz), 3.67 (s, 3 H), 3.28 (t, 2 H, J = 7.3 Hz), 3.01 (d, 2 H, J = 6.9 Hz), 2.66 (t, 2 H, J = 7.3 Hz), 2.57 (s, 3 H), 2.26 (s, 3 H), 1.44 (m, 1H), 1.31 (ddd, 1 H, J = 7.2, 6.4, 2.4 Hz), 1.26 (ddd, 1 H, J = 7.2, 6.4, 1.6 Hz), 0.85 (dd, 6 H, J = 7.8, 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.0, 160.4, 157.6, 144.1, 135.3, 135.0, 133.6, 128.5, 124.0, 122.1, 120.6, 117.9, 52.0, 48.8, 44.2, 37.8, 36.3, 25.1, 24.8, 23.0, 22.4, 15.1, 11.5; HRMS (APCI) *m/z* calcd for $C_{24}H_{32}N_3O_3F_2BNa$ $(M+Na)^+$ 482.2402, found 482.2446.

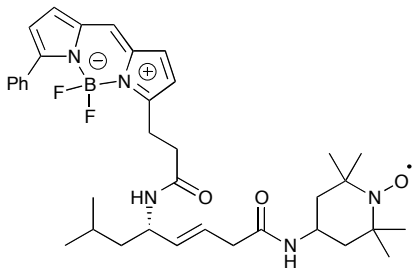


(*S*,*E*)-5,5-Difluoro-3-(3-((8-((1-oxo-2,2,6,6-tetramethylpiperidin-4-yl)amino)-2-methyl-8-oxooct-5-en-4-yl)amino)-3-oxopropyl)-7,9-dimethyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (30). To a vigorously stirred mixture of ester **29** (34.5 mg, 0.0751 mmol) and pig liver esterase (PLE, 17 U/mg, 7 mg) in acetone (1.5 mL) was added phosphate buffer (0.05 M, pH 7.0, 2.75 mL). The resulting heterogenous reaction mixture was vigorously stirred at rt overnight. TLC analysis (1:1 EtOAc:hexanes, $KMnO_4$) after 13 h showed only starting material. More PLE (7 mg) was added. The reaction mixture was allowed to stir for 10 d, and additional PLE was added after 3, 4, 5, and 7 d. After 10 d, TLC analysis showed completed consumption of starting material, and the reaction mixture was concentrated. Citric acid (~pH 3) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic portion was

dried (Na_2SO_4), filtered, and concentrated to give the crude, red solid (34.6 mg, quant). This solid was carried on to the next reaction without purification.

To the resulting acid (34.6 mg, 0.0777 mmol) in CH_2Cl_2 (1 mL) at 0 °C in the dark was added 4-amino TEMPO (20.0 mg, 0.117 mmol) in CH_2Cl_2 (1 mL) followed by DMAP (10.4 mg, 0.0855 mmol), HOBt-H_2O (13.1 mg, 0.0855 mmol), and EDCI (17.9 mg, 0.0932 mmol). The reaction mixture was allowed to warm to rt as it stirred overnight. The reaction mixture was washed with H_2O (3 mL) and sat. NH_4Cl (3 mL), and the aqueous portion was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic portion was dried (Na_2SO_4), filtered, and concentrated to give a crude, red oil (63 mg). The crude material was purified by chromatography on SiO_2 (ISCO, 4 g column, liquid load in CH_2Cl_2, 0-20% MeOH/CH_2Cl_2 gradient, eluted at 5% MeOH/CH_2Cl_2) to give a crude, impure orange oil (41 mg). The oil was then purified by chromatography on SiO_2 (ISCO, 4 g column, liquid load in CH_2Cl_2, 10-100% EtOAc/hexanes gradient, eluted at 100% EtOAc) to provide **30** as a reddish orange oil (26 mg, 56%): R_f = 0.41 (10% MeOH/CH_2Cl_2); IR (ATR) 3288, 2954, 2926, 1642, 1605, 1528, 1249, 1133, 1084, 999 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$, δ) 169.6, 168.5, 158.8, 154.3, 142.2, 134.8, 133.2, 131.2, 126.2, 121.9, 121.7, 118.8, 115.5, 48.8, 41.2, 34.5, 31.6, 27.5, 23.3, 22.4, 20.5, 2.3, 13.9, 9.5; HRMS (ESI) *m/z* calcd for $C_{32}H_{47}BN_5O_3F_2Na$ $(M+Na)^+$ 621.3638, found 621.3589.

A sample of this nitroxide (14.4 mg, 0.0241 mmol) in MeOH (1 mL) was added L-(+)-ascorbic acid (6.4 mg, 0.036 mmol). After stirring at rt for 2 h, the reaction mixture was concentrated. The resulting residue was dissolved in CH_2Cl_2 and washed once with water. The aqueous layers was extracted once with CH_2Cl_2, and the combined organic portion was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to yield the corresponding hydroxylamine as a red oil (12.2 mg, 85%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.87 (d, 1 H, *J* = 3.9 Hz), 6.64 (d, 1 H *J* = 7.2 Hz), 6.32 (d, 1 H, *J* = 3.9 Hz), 6.13 (s, 1 H), 6.03 (d, 1 H, *J* = 6.3 Hz), 5.54 (dt, 1 H, *J* = 15, 7.5, 7.5 Hz), 5.35 (dd, 1 H, *J* = 15, 6.6 Hz), 4.28 (m, 2 H), 3.25 (t, 2 H, 7.4 Hz), 2.89 (dd, 1 H, *J* = 7.2, 2.1 Hz), 2.69 (t, 1 H, *J* = 7.4 Hz), 2.55 (s, 3 H), 2.26 (s, 3 H), 2.04 (br s, 1 H), 1.50 (d, 4 H, *J* = 4.8 Hz), 1.28-1.30 (m, 3 H), 1.25 (s, 12 H), 0.84 (t, 6 H, *J* = 5.8 Hz).



(*S*,*E*)-5,5-Difluoro-3-(3-((8-((1-hydroxy-2,2,6,6-tetramethylpiperidin-4-yl)amino)-2-methyl-8-oxooct-5-en-4-yl)amino)-3-oxopropyl)-7-phenyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (BODIPY®-R6G-JP4-039, 33). To a solution of JP4-039 (125 mg, 0.294 mmol) in MeOH (3 mL) was added ascorbic acid (65 mg, 0.37 mmol). The orange solution became homogenous in less than 1 min. Stirring was continued 30 min, and the reaction mixture was concentrated. To the residue was added ethyl acetate (10 mL), water (5 mL), and 5% Na_2CO_3 (5 mL)). The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic portion was dried ($MgSO_4$) and evaporated, and the crude hydroxylamine was carried on to the next reaction.

To a solution of the crude hydroxylamine in CH_2Cl_2 (3 mL) at 0 °C was added trifluoroacetic acid (440 µL, 5.89 mmol). The solution was warmed to rt and stirred 4 h. The solvent and excess acid were evaporated, and the residue was dissolved in EtOAc (25 mL). The organic portion was washed with saturated Na2CO3 (2 x 5 mL) and brine (5 mL), dried over $MgSO_4$, and cocentrated to give the free amine as a white solid, which was carried on to the next reaction.

To BODIPY®-R6G-NHS (**31**) (50.0 mg, 0.114 mmol) was added a solution of the crude amine in CH_2Cl_2 (2 mL), followed by diisopropylethylamine (36 µL, 0.21 mmol). The resulting red solution was stirred at rt for 18 h, and the reaction mixture was concentrated. The residue was dissolved in MeOH (2 mL), and catalytic copper (II) acetate hydrate was added. The mixture was stirred open to air for 30 min, then poured into water (10 mL). The aqueous mixture was extracted with EtOAc, and the combined organics were dried over $MgSO_4$ and evaporated. The resulting residue was purified by chromatography on SiO_2 (1-5% MeOH/CH_2Cl_2) to provide BODIPY-R6G JP4-039 (**33**) (46 mg, 62%) as a red semisolid: IR (ATR) 3303, 2958, 2926, 2855, 1653, 1616, 1540, 1463, 1245, 1137, 1085 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{36}H_{48}BF_2N_5O_3$ 647.3813, found 647.3802. NMR spectra are severely broadened and not useful, so the compound was characterized as the hydroxylamine after reduction with ascorbic acid in methanol.

Analytical data for hydroxylamine **32**: ^{1}H NMR (600 MHz, $CDCl_3$ layered with 5% ascorbic acid in D_2O) δ 7.89 (dd, 2 H, *J* = 7.2, 1.2 Hz), 7.47 (m, 3 H), 7.25 (s, 1 H), 7.13 (d, 1 H, *J* = 4.2 Hz), 7.03 (d, 1 H, *J* = 4.2 Hz), 6.65 (d, 1 H, *J* = 4.2 Hz), 6.41 (d, 1 H, *J* = 3.6 Hz), 5.53 (m, 1H), 5.31 (dd, 1 H, *J* = 15.3, 6.9 Hz), 4.20 (m, 2 H), 3.27 (dd, 2 H, *J* = 6.9, 5.1 Hz), 2.90 (m, 2 H), 2.64 (q, 2 H, *J* = 6.8 Hz), 1.89 (m, 2 H), 1.47 (m, 1 H), 1.32–1.22 (m, 17 H), 0.83 (dd, 6 H, *J* = 8.4, 3.6 Hz,); ^{13}C NMR (150 MHz, $CDCl_3$ layered with 5% ascorbic acid in D_2O) δ 171.7, 170.5, 161.4, 136.7, 135.1, 132.5, 130.9, 130.0, 129.4, 128.5, 123.8, 12.6, 120.2, 101.3, 56.1, 50.6, 43.3, 40.2, 40.0, 35.9, 29.8, 35.2, 24.6, 22.6, 22.4, 20.4; HRMS (ESI) $[M+H]^+$ calcd for $C_{36}H_{49}BF_2N_5O_3$ 648.3891, found 648.3896.

X-Ray Crystallography Data for Compound 25.

Table S1. Crystal data and structure refinement for **25**.

Identification code	mf29229s	
Empirical formula	C24 H40 N3 O4	
Formula weight	434.59	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.8433(18) Å	α= 90°.
	b = 18.424(5) Å	β= 90°.
	c = 20.221(5) Å	γ = 90°.
Volume	2549.5(12) $Å^3$	
Z	4	
Density (calculated)	1.132 Mg/m^3	
Absorption coefficient	0.077 mm^{-1}	
F(000)	948	
Crystal size	0.27 x 0.25 x 0.18 mm^3	
Theta range for data collection	2.21 to 24.99°	
Index ranges	-8<=h<=8, -21<=k<=21, -24<=l<=24	
Reflections collected	20281	
Independent reflections	2581 [R(int) = 0.0592]	
Completeness to theta = 24.99°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9863 and 0.9796	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2581 / 0 / 288	
Goodness-of-fit on F^2	1.100	
Final R indices [I>2sigma(I)]	R1 = 0.0484, wR2 = 0.1258	
R indices (all data)	R1 = 0.0707, wR2 = 0.1371	
Absolute structure parameter	?	
Largest diff. peak and hole	0.183 and -0.147 $e.Å^{-3}$	

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for MCF292-29 (**25**). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	9677(4)	7238(1)	840(1)	61(1)
N(1)	7414(5)	6362(2)	920(2)	70(1)
C(1)	14877(9)	6353(3)	-2903(2)	110(2)
N(2)	3320(5)	5820(2)	2602(2)	72(1)
O(2)	1622(4)	5793(2)	2844(1)	84(1)
C(2)	16937(7)	6357(3)	-1884(2)	91(2)
O(3)	15174(4)	4187(1)	-520(1)	62(1)
N(3)	14139(4)	5171(2)	-1022(1)	54(1)
C(3)	15166(6)	6026(2)	-2215(2)	69(1)
O(4)	15157(4)	5257(1)	40(1)	62(1)
C(4)	13312(6)	6131(2)	-1813(2)	57(1)
C(5)	13401(5)	5912(2)	-1085(2)	49(1)
C(6)	11417(5)	5982(2)	-783(2)	52(1)
C(7)	10828(5)	6512(2)	-393(2)	50(1)
C(8)	8781(5)	6604(2)	-149(2)	54(1)
C(9)	8693(5)	6765(2)	582(2)	49(1)
C(10)	6973(6)	6477(3)	1624(2)	72(1)
C(11)	4995(10)	6830(2)	1712(2)	87(2)
C(12)	4680(11)	7011(2)	2443(2)	103(2)
C(13)	4778(6)	6333(2)	2856(2)	64(1)
C(14)	7051(6)	5790(3)	2022(2)	79(1)
C(15)	6743(7)	5968(4)	2753(2)	94(2)
C(16)	5536(9)	5285(2)	1808(2)	91(2)
C(17)	3594(7)	5605(3)	1908(2)	86(2)
C(18)	3405(7)	6296(4)	1504(2)	109(2)
C(19)	4341(8)	6473(3)	3587(2)	101(2)
C(20)	14845(5)	4906(2)	-456(2)	50(1)
C(21)	15660(6)	3735(2)	43(2)	62(1)
C(22)	17630(7)	3947(3)	320(2)	91(2)
C(23)	14055(9)	3773(2)	560(2)	99(2)
C(24)	15751(8)	2982(2)	-266(2)	84(1)

Table S3. Bond lengths [Å] and angles [°] for MCF292-29 (**25**).

O(1)-C(9)	1.219(4)
N(1)-C(9)	1.336(4)
N(1)-C(10)	1.471(4)
N(1)-H(1N)	0.93(4)
C(1)-C(3)	1.528(5)
C(1)-H(1A)	0.9700
C(1)-H(1B)	0.9700
C(1)-H(1C)	0.9700
N(2)-O(2)	1.262(4)
N(2)-C(13)	1.466(5)
N(2)-C(17)	1.471(5)
C(2)-C(3)	1.512(7)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
C(2)-H(2C)	0.9700
O(3)-C(20)	1.349(4)
O(3)-C(21)	1.451(4)
N(3)-C(20)	1.334(4)
N(3)-C(5)	1.462(4)
N(3)-H(3N)	0.91(3)
C(3)-C(4)	1.520(6)
C(3)-H(3A)	0.9900
O(4)-C(20)	1.214(4)
C(4)-C(5)	1.526(5)
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(5)-C(6)	1.495(5)
C(5)-H(5A)	0.9900
C(6)-C(7)	1.318(4)
C(6)-H(6A)	0.9400
C(7)-C(8)	1.495(5)
C(7)-H(7A)	0.9400
C(8)-C(9)	1.507(5)
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(10)-C(14)	1.501(6)

C(10)-C(11)	1.512(7)
C(10)-H(10A)	0.9900
C(11)-C(18)	1.526(7)
C(11)-C(12)	1.531(6)
C(11)-H(11A)	0.9900
C(12)-C(13)	1.504(6)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(13)-C(15)	1.517(7)
C(13)-C(19)	1.529(5)
C(14)-C(16)	1.458(7)
C(14)-C(15)	1.529(6)
C(14)-H(14A)	0.9900
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(16)-C(17)	1.468(7)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(17)-C(18)	1.517(7)
C(17)-H(17A)	0.9900
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(19)-H(19A)	0.9700
C(19)-H(19B)	0.9700
C(19)-H(19C)	0.9700
C(21)-C(22)	1.511(6)
C(21)-C(24)	1.522(5)
C(21)-C(23)	1.517(6)
C(22)-H(22A)	0.9700
C(22)-H(22B)	0.9700
C(22)-H(22C)	0.9700
C(23)-H(23A)	0.9700
C(23)-H(23B)	0.9700
C(23)-H(23C)	0.9700
C(24)-H(24A)	0.9700
C(24)-H(24B)	0.9700
C(24)-H(24C)	0.9700

C(9)-N(1)-C(10)	123.3(3)
C(9)-N(1)-H(1N)	121(2)
C(10)-N(1)-H(1N)	116(2)
C(3)-C(1)-H(1A)	109.5
C(3)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
C(3)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(2)-N(2)-C(13)	121.1(3)
O(2)-N(2)-C(17)	118.5(3)
C(13)-N(2)-C(17)	114.9(3)
C(3)-C(2)-H(2A)	109.5
C(3)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	109.5
C(3)-C(2)-H(2C)	109.5
H(2A)-C(2)-H(2C)	109.5
H(2B)-C(2)-H(2C)	109.5
C(20)-O(3)-C(21)	121.8(2)
C(20)-N(3)-C(5)	122.8(3)
C(20)-N(3)-H(3N)	116.1(19)
C(5)-N(3)-H(3N)	119.4(19)
C(2)-C(3)-C(4)	112.4(3)
C(2)-C(3)-C(1)	110.4(4)
C(4)-C(3)-C(1)	109.2(4)
C(2)-C(3)-H(3A)	108.3
C(4)-C(3)-H(3A)	108.3
C(1)-C(3)-H(3A)	108.3
C(3)-C(4)-C(5)	116.7(3)
C(3)-C(4)-H(4A)	108.1
C(5)-C(4)-H(4A)	108.1
C(3)-C(4)-H(4B)	108.1
C(5)-C(4)-H(4B)	108.1
H(4A)-C(4)-H(4B)	107.3
N(3)-C(5)-C(6)	111.0(3)
N(3)-C(5)-C(4)	110.2(3)
C(6)-C(5)-C(4)	109.6(3)
N(3)-C(5)-H(5A)	108.7

C(6)-C(5)-H(5A)	108.7
C(4)-C(5)-H(5A)	108.7
C(7)-C(6)-C(5)	125.9(3)
C(7)-C(6)-H(6A)	117.0
C(5)-C(6)-H(6A)	117.0
C(6)-C(7)-C(8)	124.6(3)
C(6)-C(7)-H(7A)	117.7
C(8)-C(7)-H(7A)	117.7
C(7)-C(8)-C(9)	112.6(3)
C(7)-C(8)-H(8A)	109.1
C(9)-C(8)-H(8A)	109.1
C(7)-C(8)-H(8B)	109.1
C(9)-C(8)-H(8B)	109.1
H(8A)-C(8)-H(8B)	107.8
O(1)-C(9)-N(1)	122.7(3)
O(1)-C(9)-C(8)	122.6(3)
N(1)-C(9)-C(8)	114.7(3)
N(1)-C(10)-C(14)	112.9(4)
N(1)-C(10)-C(11)	111.1(4)
C(14)-C(10)-C(11)	109.3(3)
N(1)-C(10)-H(10A)	107.8
C(14)-C(10)-H(10A)	107.8
C(11)-C(10)-H(10A)	107.8
C(10)-C(11)-C(18)	109.2(3)
C(10)-C(11)-C(12)	109.5(5)
C(18)-C(11)-C(12)	107.8(4)
C(10)-C(11)-H(11A)	110.1
C(18)-C(11)-H(11A)	110.1
C(12)-C(11)-H(11A)	110.1
C(13)-C(12)-C(11)	110.5(3)
C(13)-C(12)-H(12A)	109.6
C(11)-C(12)-H(12A)	109.6
C(13)-C(12)-H(12B)	109.6
C(11)-C(12)-H(12B)	109.6
H(12A)-C(12)-H(12B)	108.1
N(2)-C(13)-C(12)	108.1(4)
N(2)-C(13)-C(15)	105.7(4)
C(12)-C(13)-C(15)	109.3(4)

N(2)-C(13)-C(19)	108.3(3)
C(12)-C(13)-C(19)	112.8(4)
C(15)-C(13)-C(19)	112.4(4)
C(16)-C(14)-C(10)	110.7(4)
C(16)-C(14)-C(15)	109.0(4)
C(10)-C(14)-C(15)	109.4(4)
C(16)-C(14)-H(14A)	109.2
C(10)-C(14)-H(14A)	109.2
C(15)-C(14)-H(14A)	109.2
C(13)-C(15)-C(14)	110.5(3)
C(13)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15A)	109.5
C(13)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	108.1
C(14)-C(16)-C(17)	110.3(4)
C(14)-C(16)-H(16A)	109.6
C(17)-C(16)-H(16A)	109.6
C(14)-C(16)-H(16B)	109.6
C(17)-C(16)-H(16B)	109.6
H(16A)-C(16)-H(16B)	108.1
N(2)-C(17)-C(16)	110.8(4)
N(2)-C(17)-C(18)	106.1(4)
C(16)-C(17)-C(18)	109.9(4)
N(2)-C(17)-H(17A)	110.0
C(16)-C(17)-H(17A)	110.0
C(18)-C(17)-H(17A)	110.0
C(11)-C(18)-C(17)	109.4(3)
C(11)-C(18)-H(18A)	109.8
C(17)-C(18)-H(18A)	109.8
C(11)-C(18)-H(18B)	109.8
C(17)-C(18)-H(18B)	109.8
H(18A)-C(18)-H(18B)	108.3
C(13)-C(19)-H(19A)	109.5
C(13)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(13)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5

H(19B)-C(19)-H(19C)	109.5
O(4)-C(20)-N(3)	125.3(3)
O(4)-C(20)-O(3)	125.0(3)
N(3)-C(20)-O(3)	109.7(3)
O(3)-C(21)-C(22)	110.2(3)
O(3)-C(21)-C(24)	102.1(3)
C(22)-C(21)-C(24)	110.6(4)
O(3)-C(21)-C(23)	110.4(3)
C(22)-C(21)-C(23)	112.3(4)
C(24)-C(21)-C(23)	110.8(4)
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(21)-C(23)-H(23A)	109.5
C(21)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(21)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(21)-C(24)-H(24A)	109.5
C(21)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(21)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($Å^2$x 10^3) for MCF292-29 (**25**). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + \ldots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	57(2)	68(1)	57(1)	0(1)	4(1)	-8(1)
N(1)	76(2)	87(2)	46(2)	-15(2)	18(2)	-31(2)
C(1)	111(4)	164(5)	54(2)	20(3)	13(3)	6(4)
N(2)	61(2)	104(3)	51(2)	0(2)	11(2)	-21(2)
O(2)	57(2)	131(2)	63(2)	28(2)	12(1)	-14(2)
C(2)	73(3)	120(4)	79(3)	0(3)	26(3)	-8(3)
O(3)	85(2)	51(1)	51(1)	-3(1)	-15(1)	6(1)
N(3)	66(2)	53(2)	42(2)	-9(1)	-6(1)	7(1)
C(3)	74(3)	83(3)	49(2)	2(2)	13(2)	3(2)
O(4)	79(2)	61(1)	45(1)	-7(1)	-9(1)	-6(1)
C(4)	58(2)	63(2)	50(2)	1(2)	2(2)	8(2)
C(5)	49(2)	53(2)	45(2)	-3(1)	1(2)	-1(2)
C(6)	50(2)	56(2)	50(2)	-3(2)	2(2)	-4(2)
C(7)	54(2)	54(2)	44(2)	1(2)	6(2)	-2(2)
C(8)	51(2)	64(2)	47(2)	4(2)	9(2)	2(2)
C(9)	41(2)	57(2)	49(2)	4(2)	5(2)	3(2)
C(10)	72(3)	97(3)	49(2)	-21(2)	19(2)	-34(2)
C(11)	138(5)	61(2)	61(2)	16(2)	31(3)	24(3)
C(12)	166(6)	73(3)	71(3)	-3(2)	56(3)	14(3)
C(13)	61(2)	88(3)	41(2)	-4(2)	5(2)	-12(2)
C(14)	59(3)	120(4)	57(2)	7(3)	5(2)	27(3)
C(15)	67(3)	168(5)	47(2)	3(3)	-7(2)	10(3)
C(16)	143(5)	67(3)	64(3)	8(2)	29(3)	6(3)
C(17)	82(3)	120(4)	57(2)	-7(3)	0(2)	-46(3)
C(18)	59(3)	221(7)	49(2)	-2(3)	-5(2)	53(4)
C(19)	106(4)	147(4)	50(2)	-18(3)	22(2)	-33(4)
C(20)	49(2)	57(2)	42(2)	-4(2)	-4(2)	-4(2)
C(21)	71(3)	60(2)	55(2)	5(2)	-6(2)	6(2)
C(22)	84(3)	111(4)	79(3)	-7(3)	-25(2)	22(3)
C(23)	127(4)	71(3)	99(3)	2(2)	45(3)	-8(3)
C(24)	105(3)	63(2)	83(3)	6(2)	-3(3)	15(2)

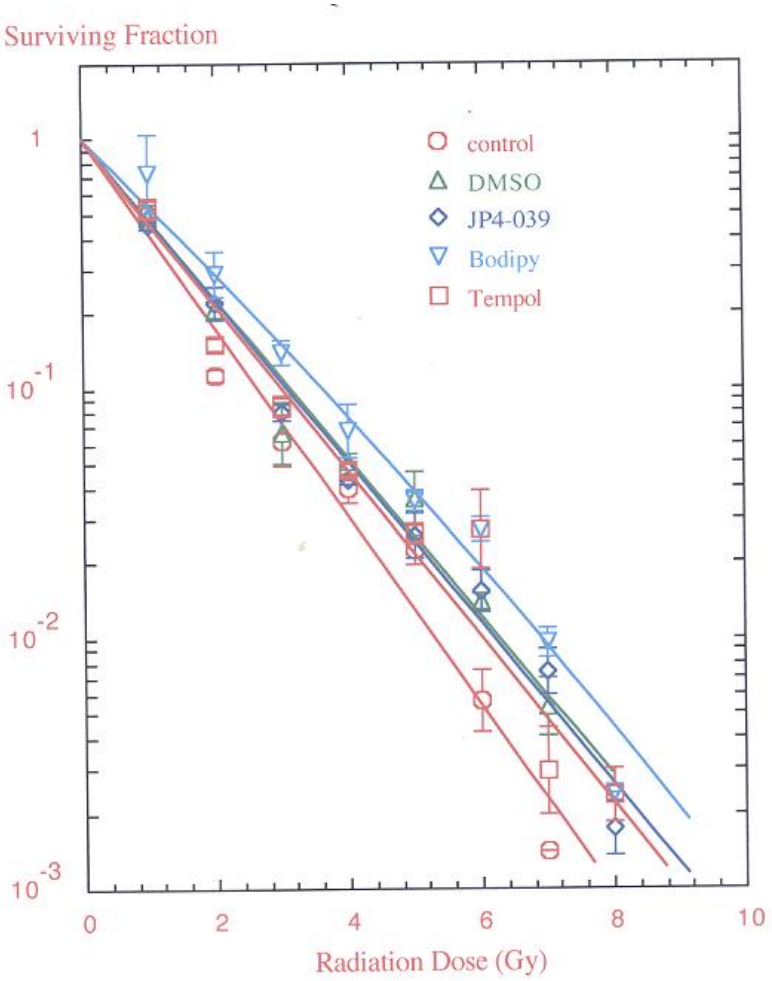
Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for MCF292-29 (**25**).

	x	y	z	U(eq)
H(1N)	6740(60)	5990(20)	714(19)	72(12)
H(1A)	16055	6285	-3162	164
H(1B)	14602	6868	-2862	164
H(1C)	13790	6114	-3120	164
H(2A)	17116	6138	-1452	137
H(2B)	16744	6875	-1834	137
H(2C)	18086	6268	-2153	137
H(3N)	13850(50)	4837(16)	-1341(16)	48(9)
H(3A)	15397	5499	-2266	83
H(4A)	12264	5852	-2024	69
H(4B)	12944	6644	-1836	69
H(5A)	14306	6244	-852	59
H(6A)	10507	5615	-879	62
H(7A)	11761	6856	-259	60
H(8A)	8042	6159	-239	65
H(8B)	8158	7002	-392	65
H(10A)	7970	6813	1804	87
H(11A)	4912	7277	1442	104
H(12A)	5686	7353	2590	124
H(12B)	3402	7242	2501	124
H(14A)	8347	5560	1964	95
H(15A)	6802	5521	3014	113
H(15B)	7787	6291	2906	113
H(16A)	5640	4833	2061	109
H(16B)	5717	5169	1339	109
H(17A)	2570	5255	1776	104
H(18A)	3537	6183	1032	131
H(18B)	2114	6512	1576	131
H(19A)	3074	6705	3628	151
H(19B)	5340	6787	3771	151
H(19C)	4330	6016	3824	151
H(22A)	18607	3919	-27	137

H(22B)	17979	3620	676	137
H(22C)	17569	4440	487	137
H(23A)	14020	4257	750	149
H(23B)	14312	3421	906	149
H(23C)	12806	3667	355	149
H(24A)	16775	2971	-597	126
H(24B)	14506	2871	-472	126
H(24C)	16029	2626	75	126

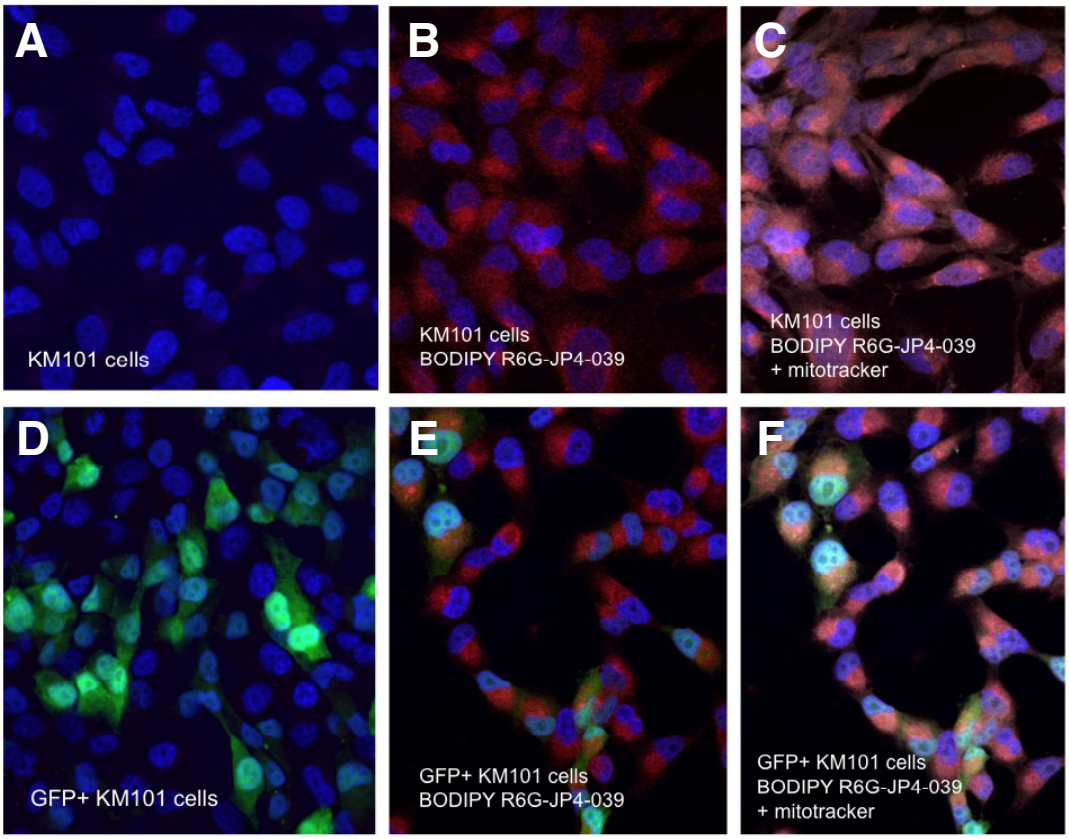
Irradiation survival curves in 32Dcl3 cells.

Procedure: Murine 32D cl 3 cells were suspended at 1 x10^5 cells and irradiated to doses of irradiation ranging from 0 to 8 Gy using a J. L. Shepherd Mark I cesium irradiator at a dose rate of 72 cGy per min. In some groups, nitroxides were added at a concentration of 10 µM either 1 h before irradiation or 10 min after irradiation. The cells were resuspended in methycellulose containing 10% serum and 15% WEHI-3 conditioned medium as a source of IL3, and incubated at 37 °C for 7 d, at which colonies of >50 cells were counted. The data was analyzed using linear quadratic and single-hit, multi-target models.



Data used to calculate D_0 and ñ for Organic and Biomolecular Chemistry manuscript.

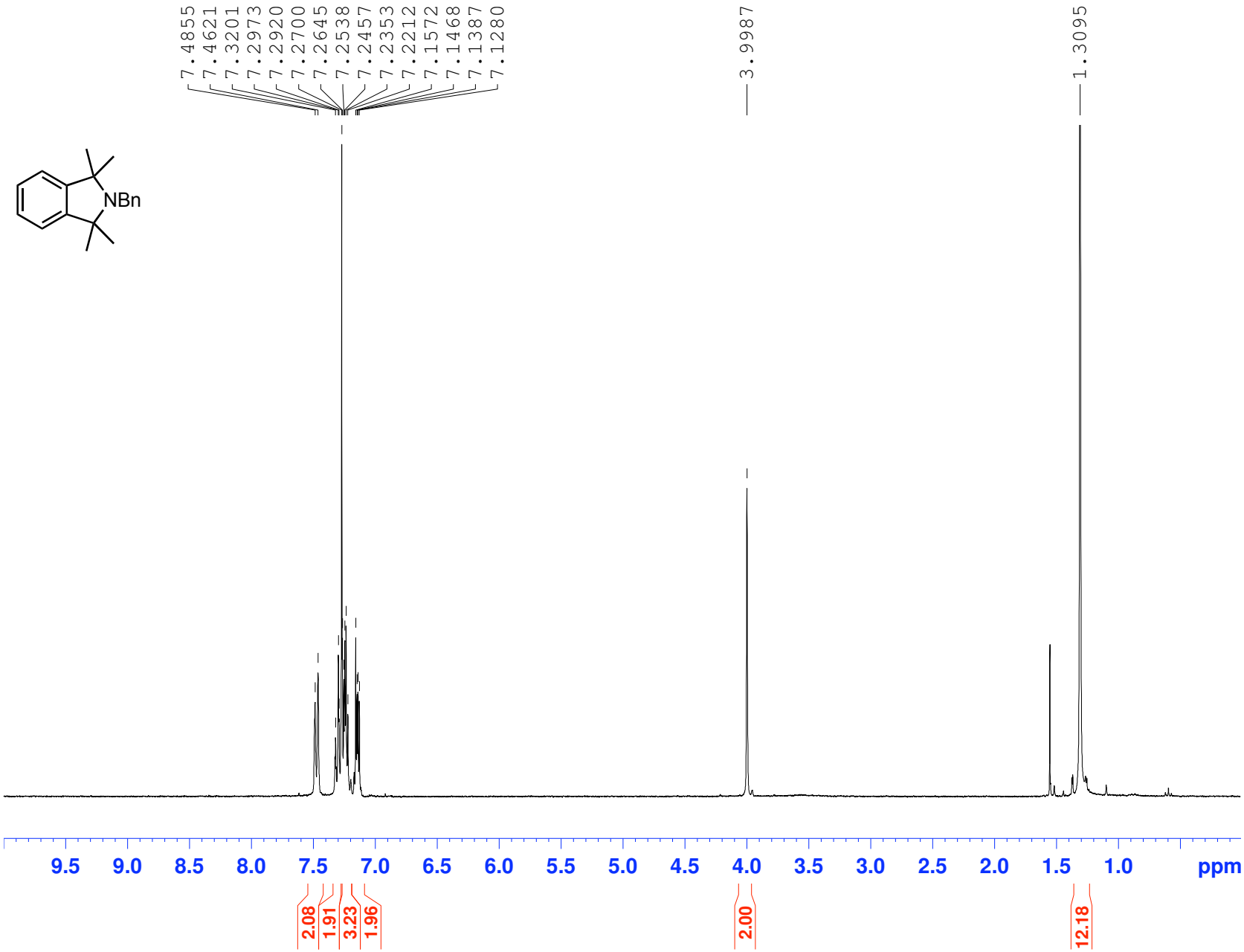
Compound	Before Irradiation		After Irradiation	
	D_0	ñ	D_0	ñ
Control	1.4	1.0	1.7	1.0
	1.3	1.0	1.8	1.0
	1.3	1.1	1.7	1.2
TEMPO	1.2	1.1	1.3	2.1
	1.3	1.0	1.6	1.0
	1.3	1.0	1.3	1.7
JP4-039	2.8	1.0	1.3	3.7
	2.3	1.0	1.2	3.2
	1.7	0.9	1.0	3.6
BODOPY®-FL-JP4-039	1.7	1.2	1.3	4.5
	2.8	1.4	1.4	3.4
	3.2	1.2	1.2	5.6
BODOPY®-R6G-JP4-039			1.3	4.2
			1.5	4.0
			1.6	2.2
TMIO	2.1	0.9	1.4	2.0
	1.6	1.0	1.2	2.9
	1.8	1.0	1.2	2.5
ABNO	4.3	1.0	1.5	1.8
	2.7	1.1	1.4	2.4
	2.3	1.0	1.2	2.1
1-Me-AZADO	3.5	1.0	1.5	2.6
	2.3	1.1	1.2	4.0
	2.1	0.9	1.3	1.5

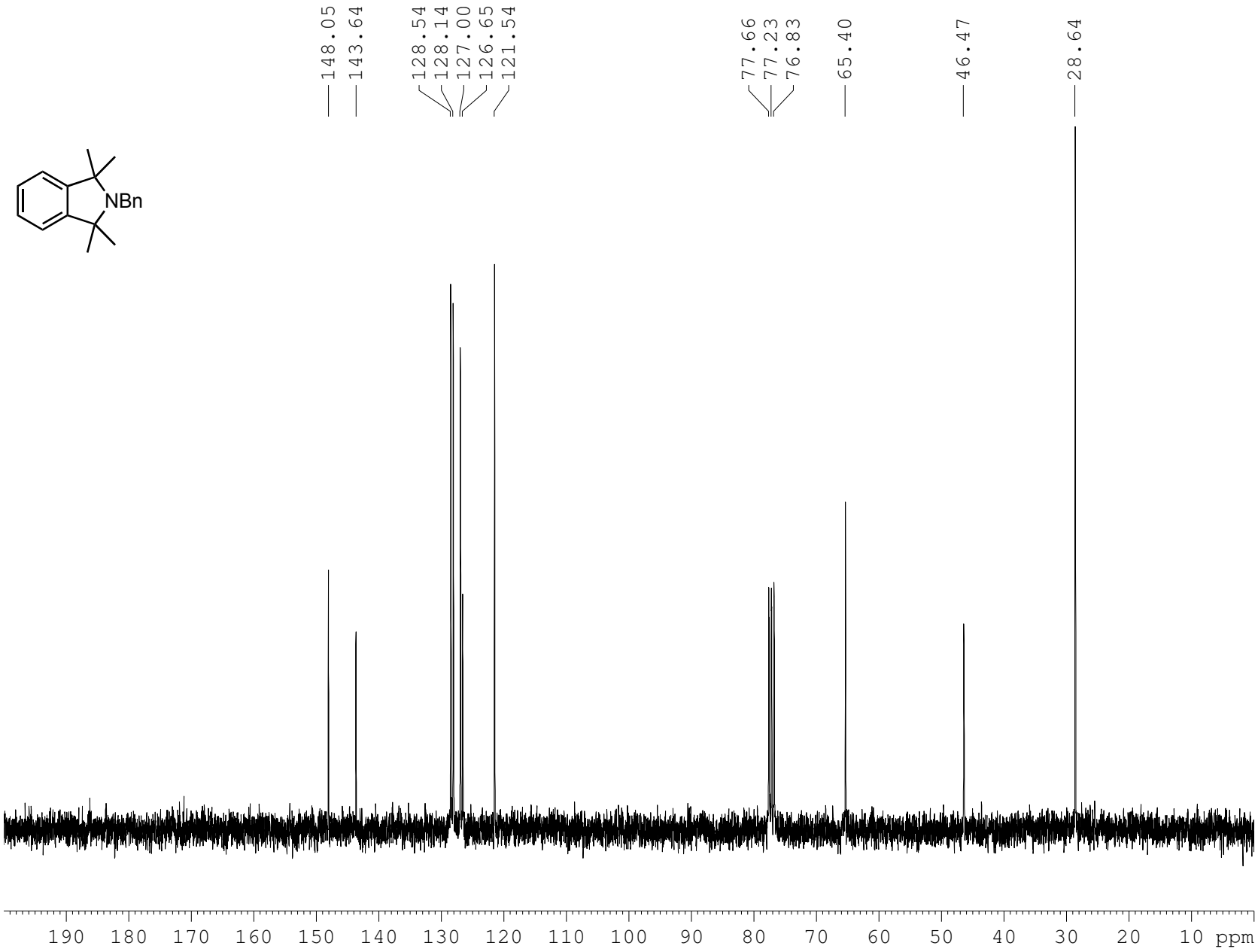


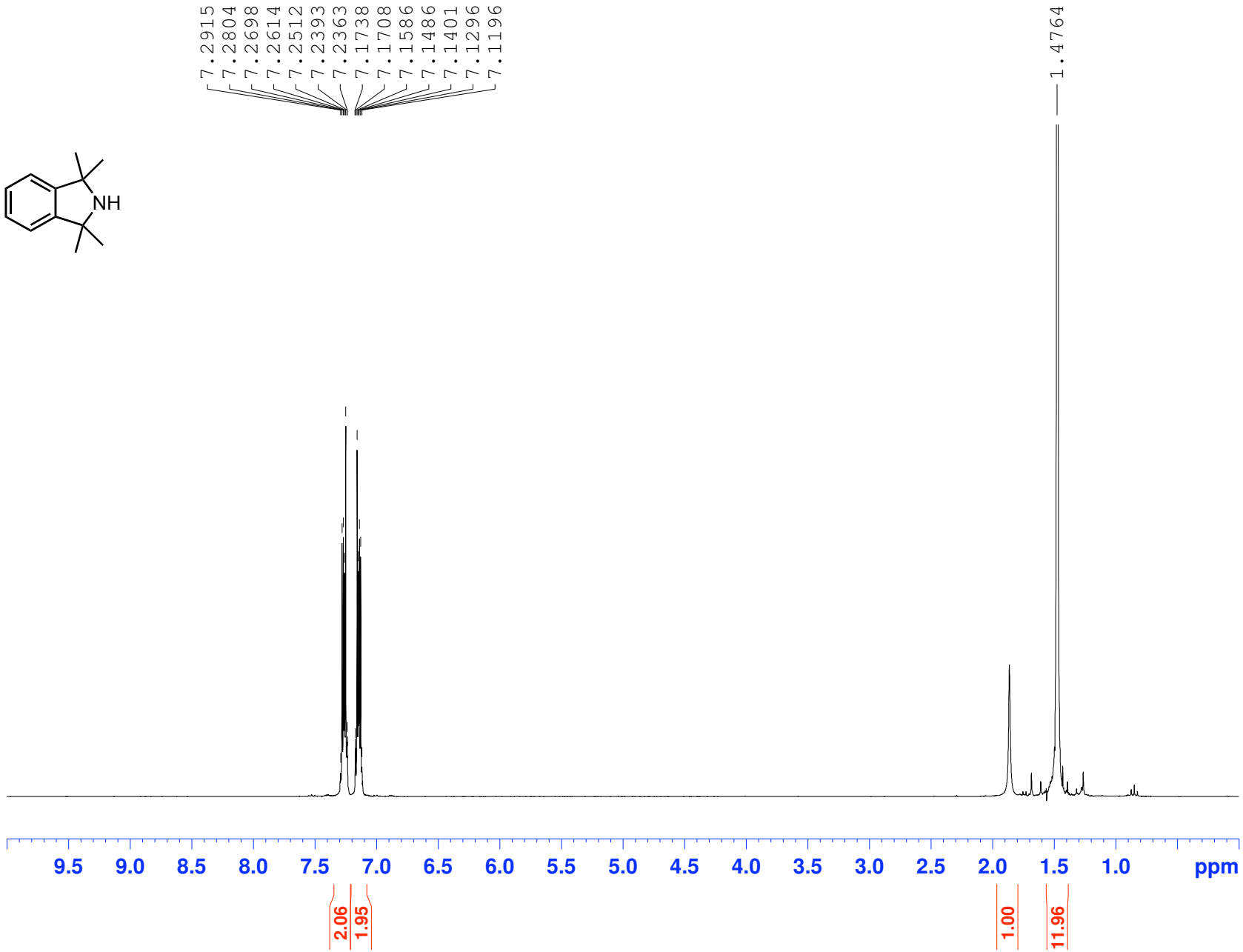
Visualization of **33** in KM101 cells. Panel A: Untreated KM101 cells. Panel B: KM101 cells incubated with BODIPY®-R6G-JP4-039 (**33**, red). Panel C: KM101 cells incubated with BODIPY®-R6G-JP4-039 (**33**, red) + MitoTracker Deep Red FM (grey). Panel D: GFP^+ KM101 cells. Panel E: GFP^+ KM101 cells incubated with BODIPY®-R6G-JP4-039 (**33**, red). Panel F: GFP^+ KM101 cells incubated with BODIPY®-R6G-JP4-039 (**33**, red) + MitoTracker Deep Red FM (grey).

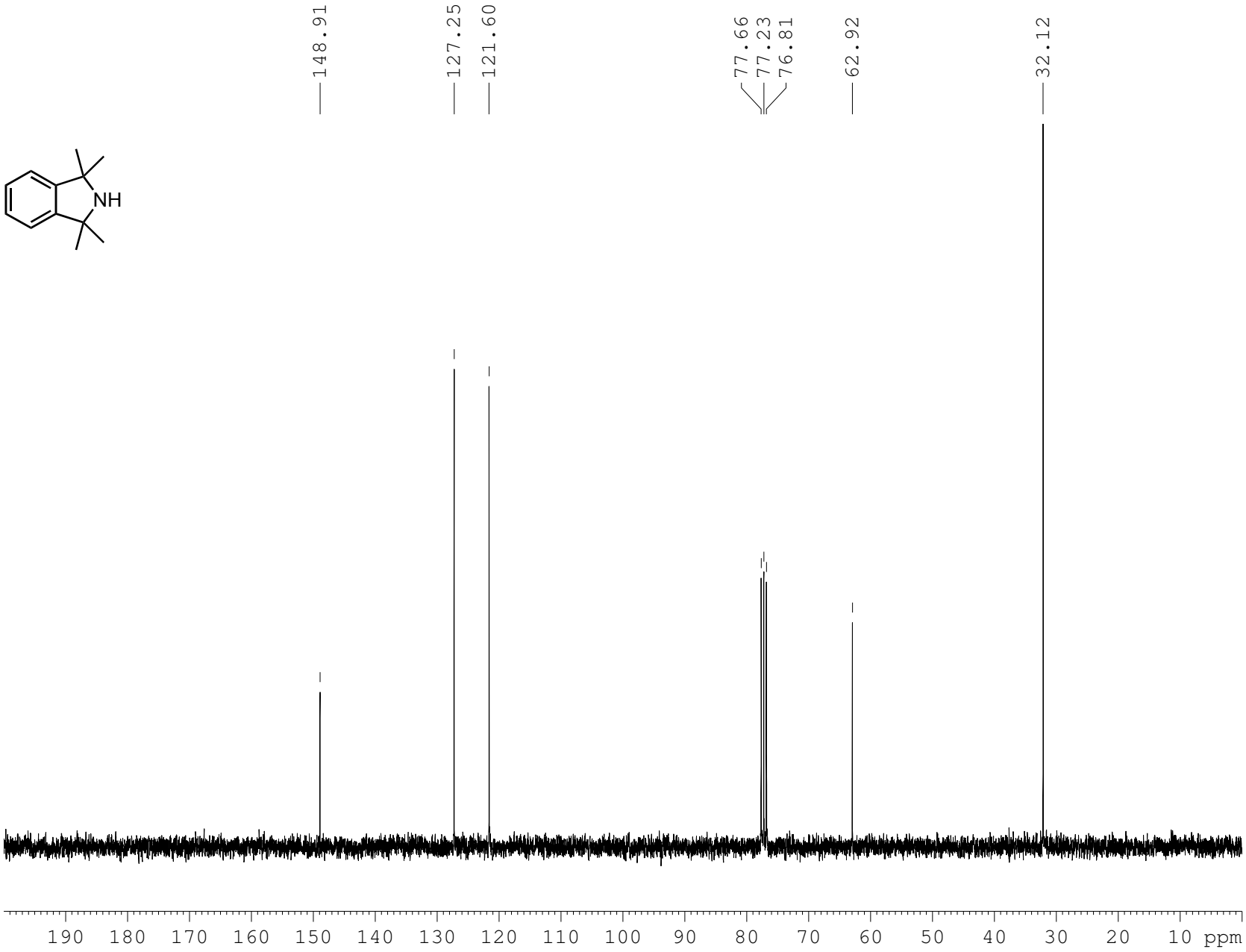
In Panels C and F, pink colors indicate co-localization of MitoTracker Deep Red FM and BODIPY®-R6G-JP4-039.

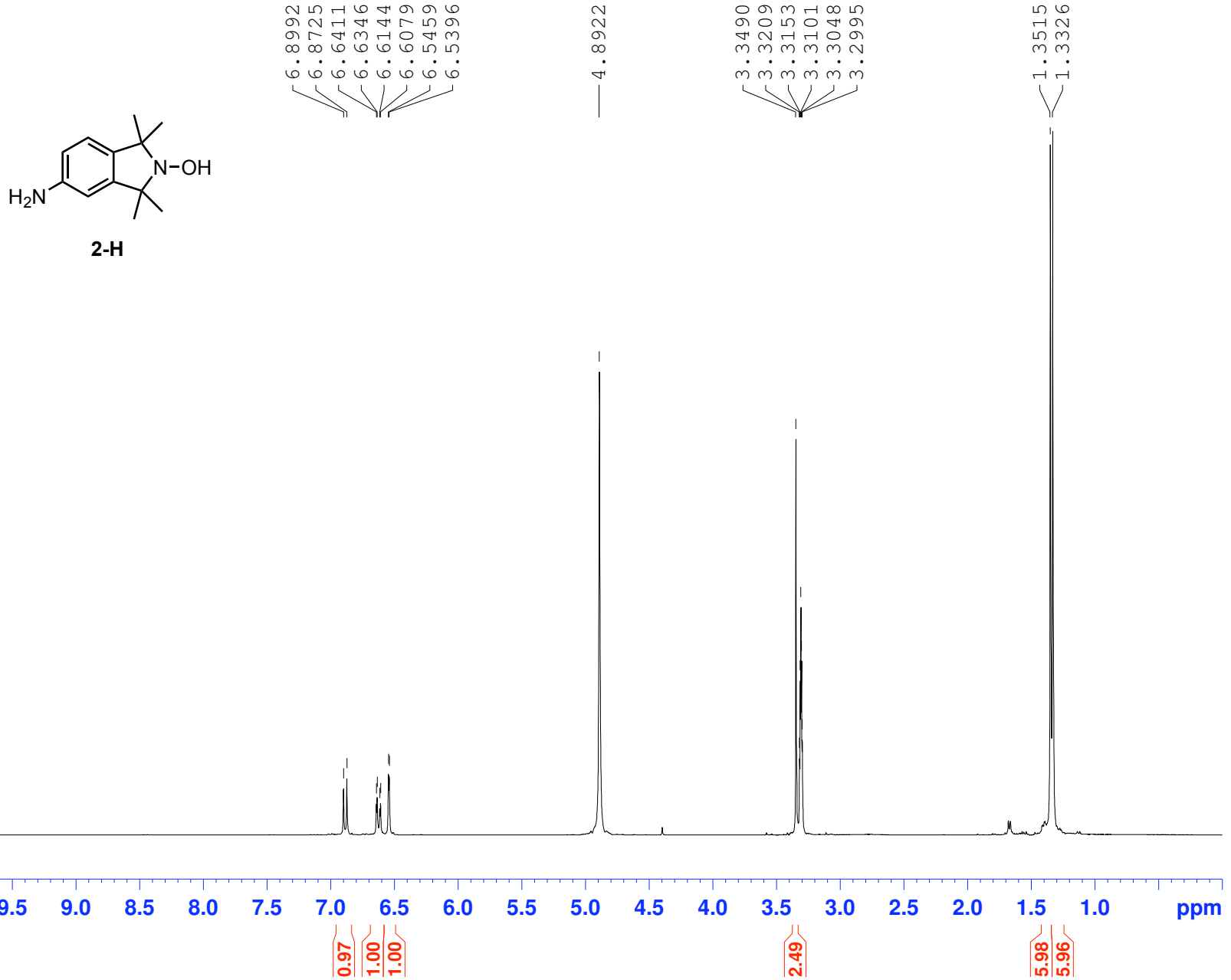
NMR Spectra



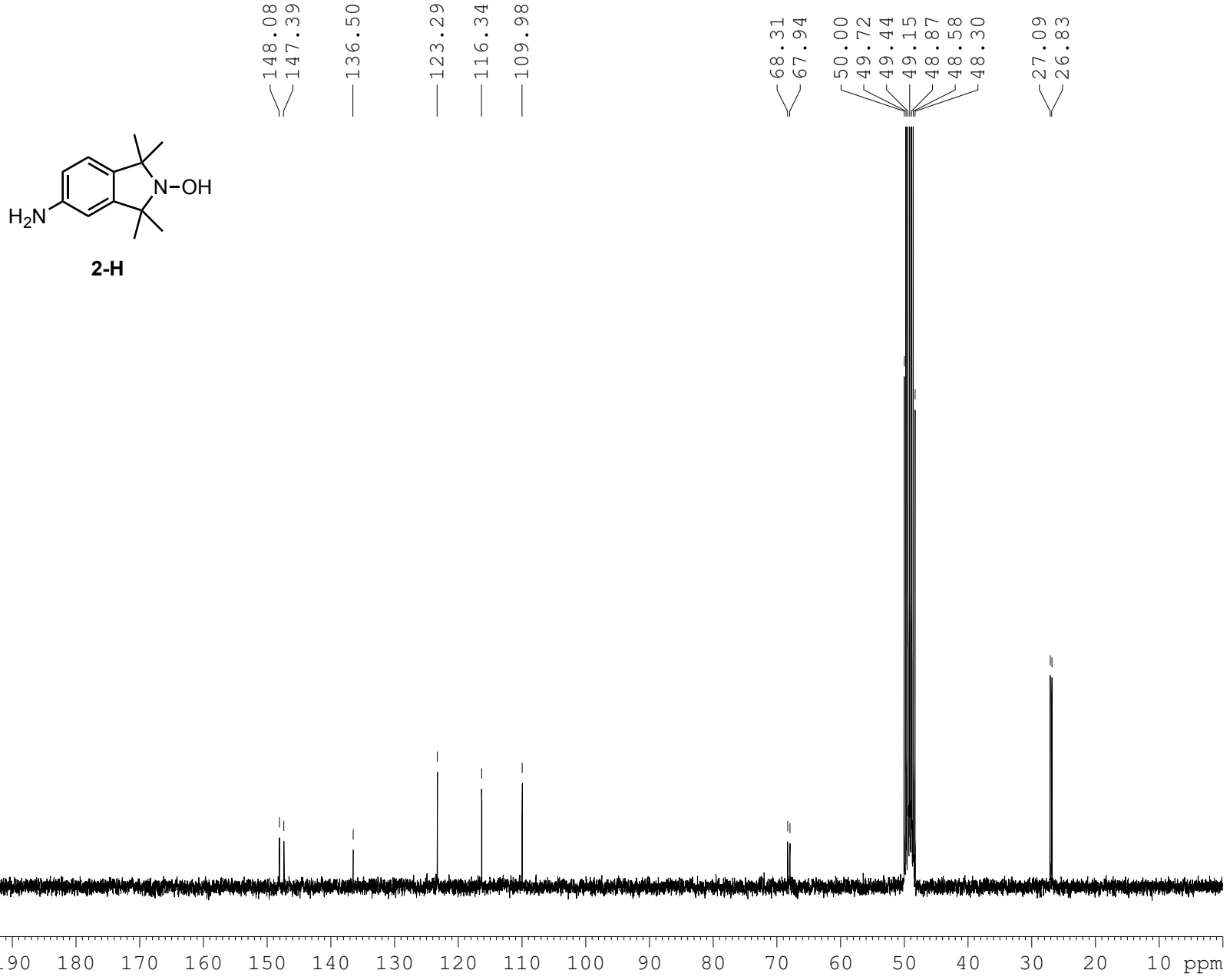




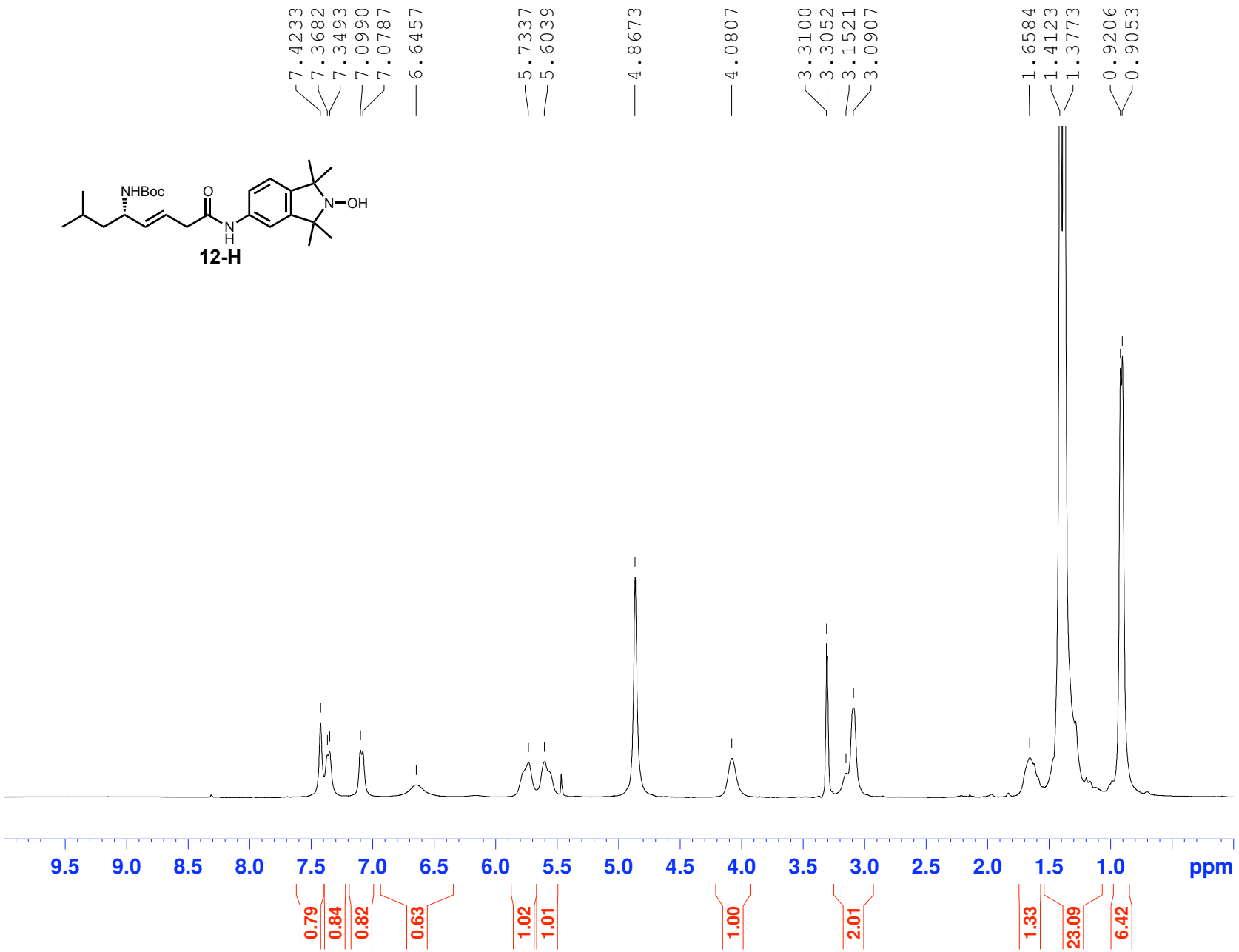


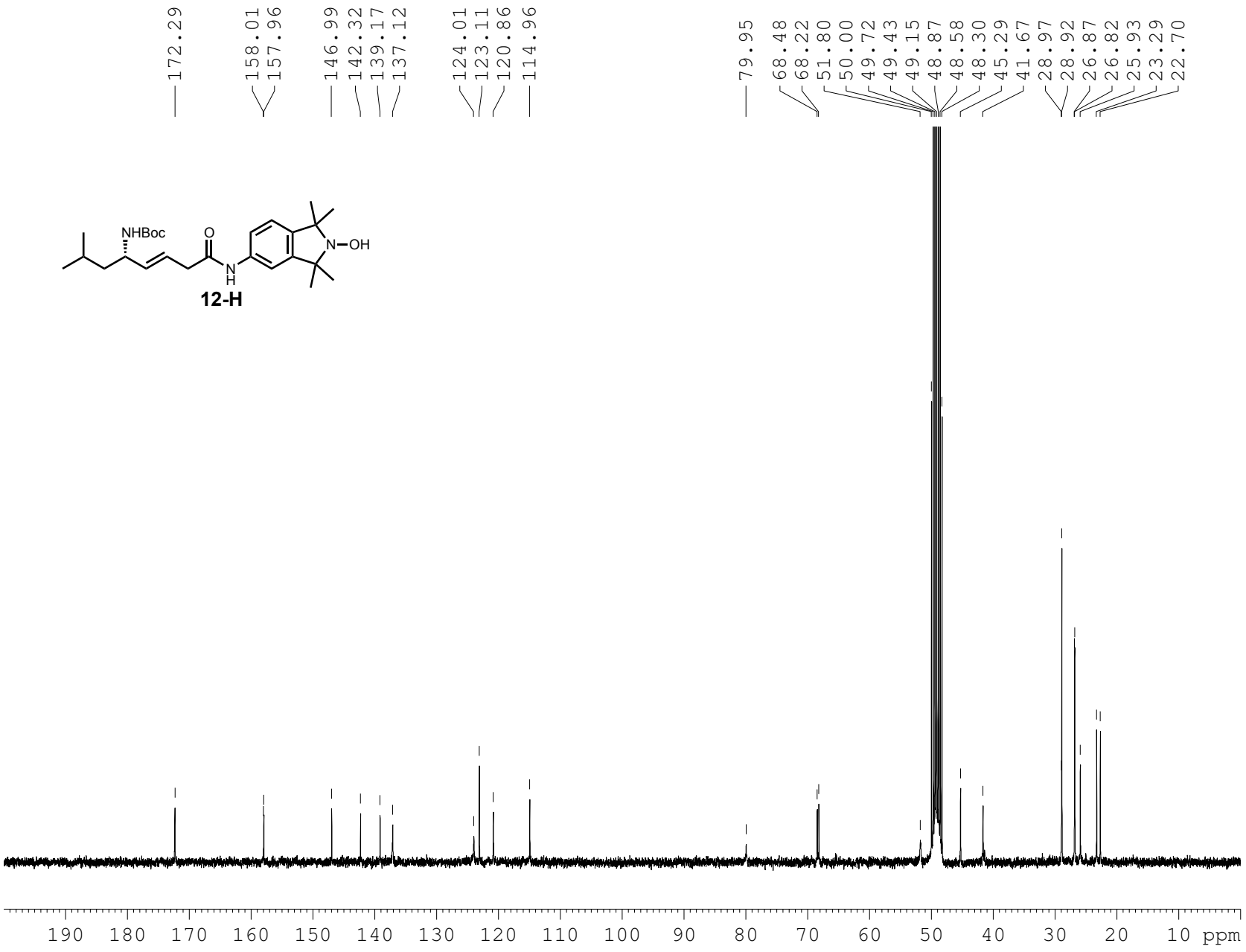


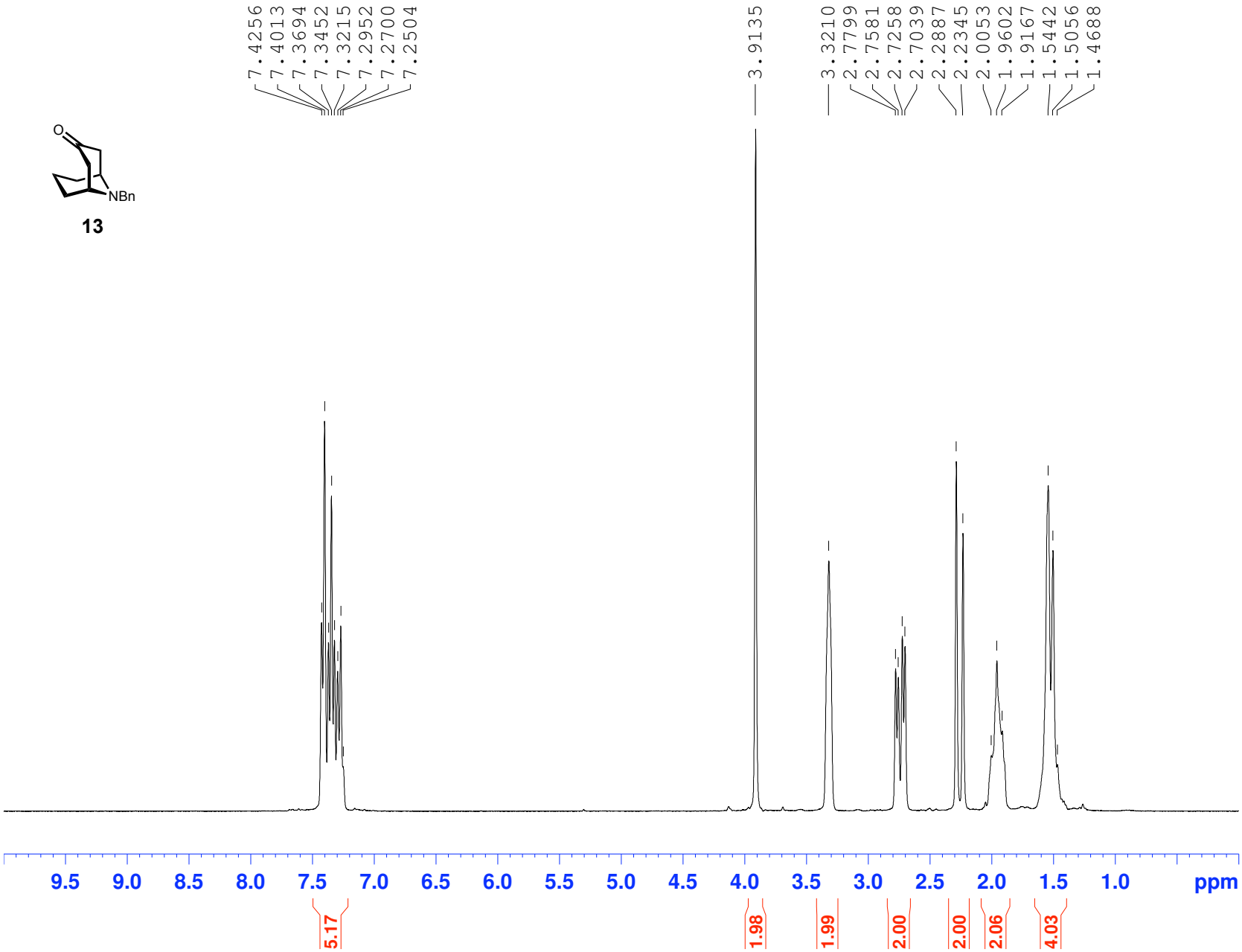
2-H

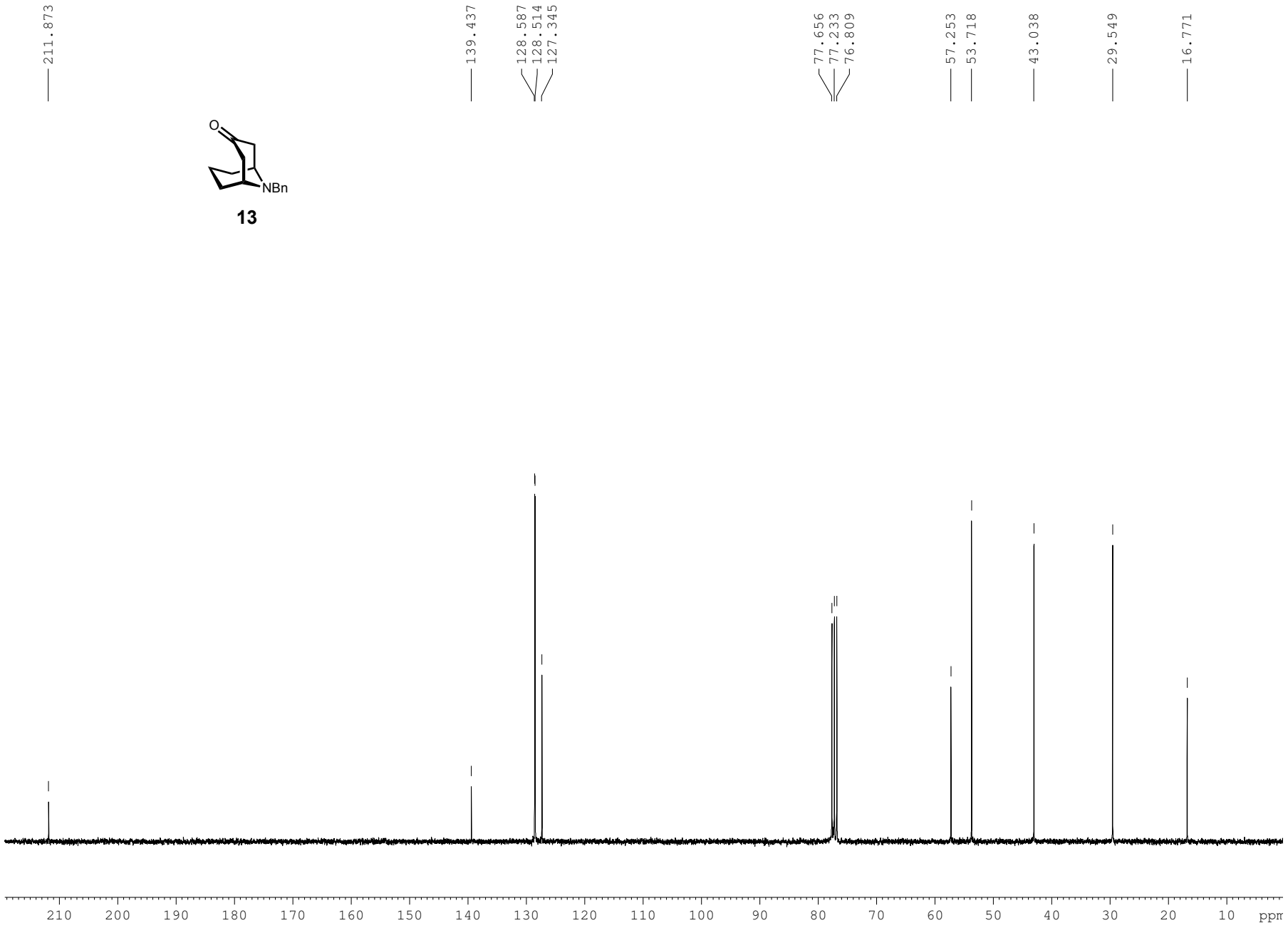


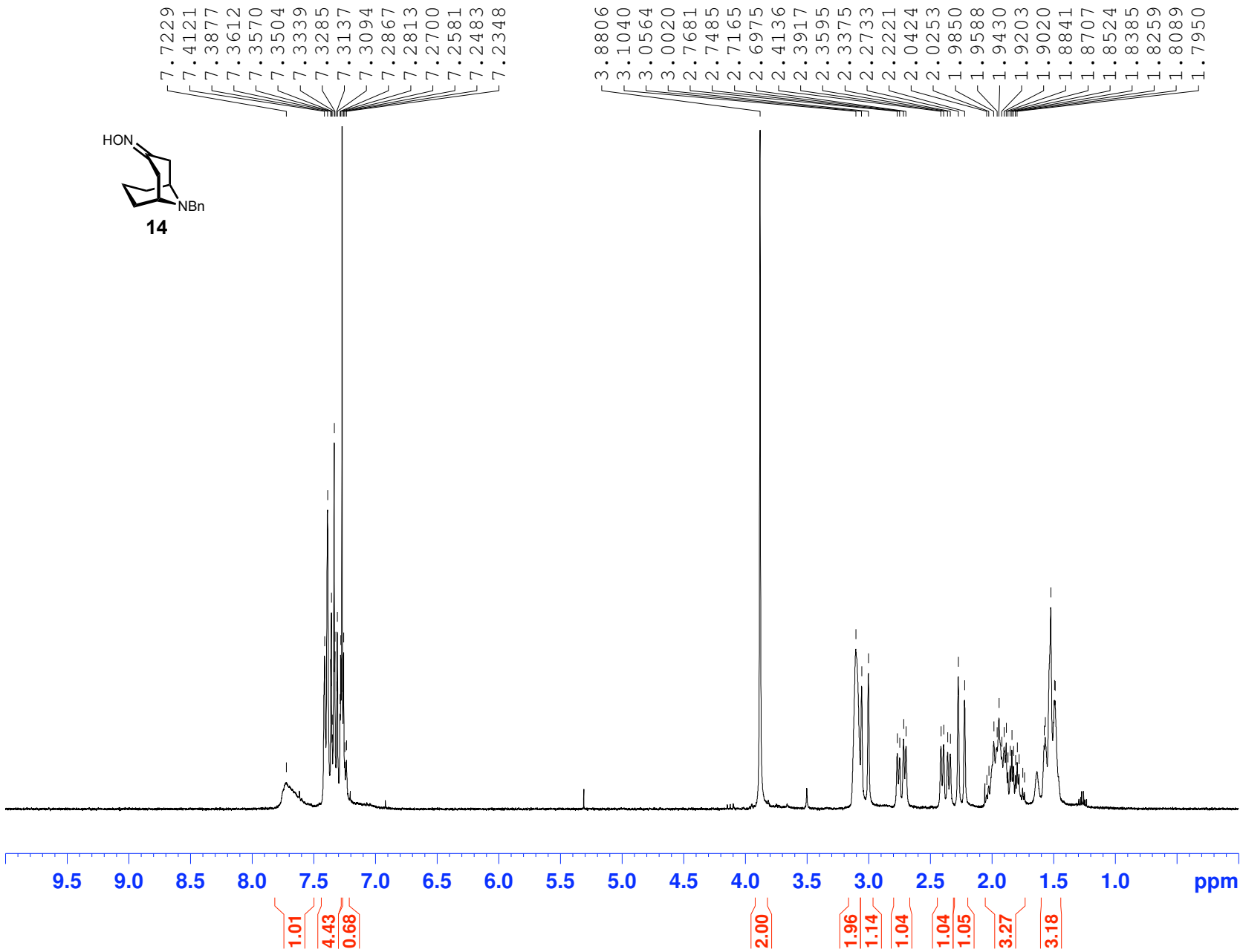
2-H

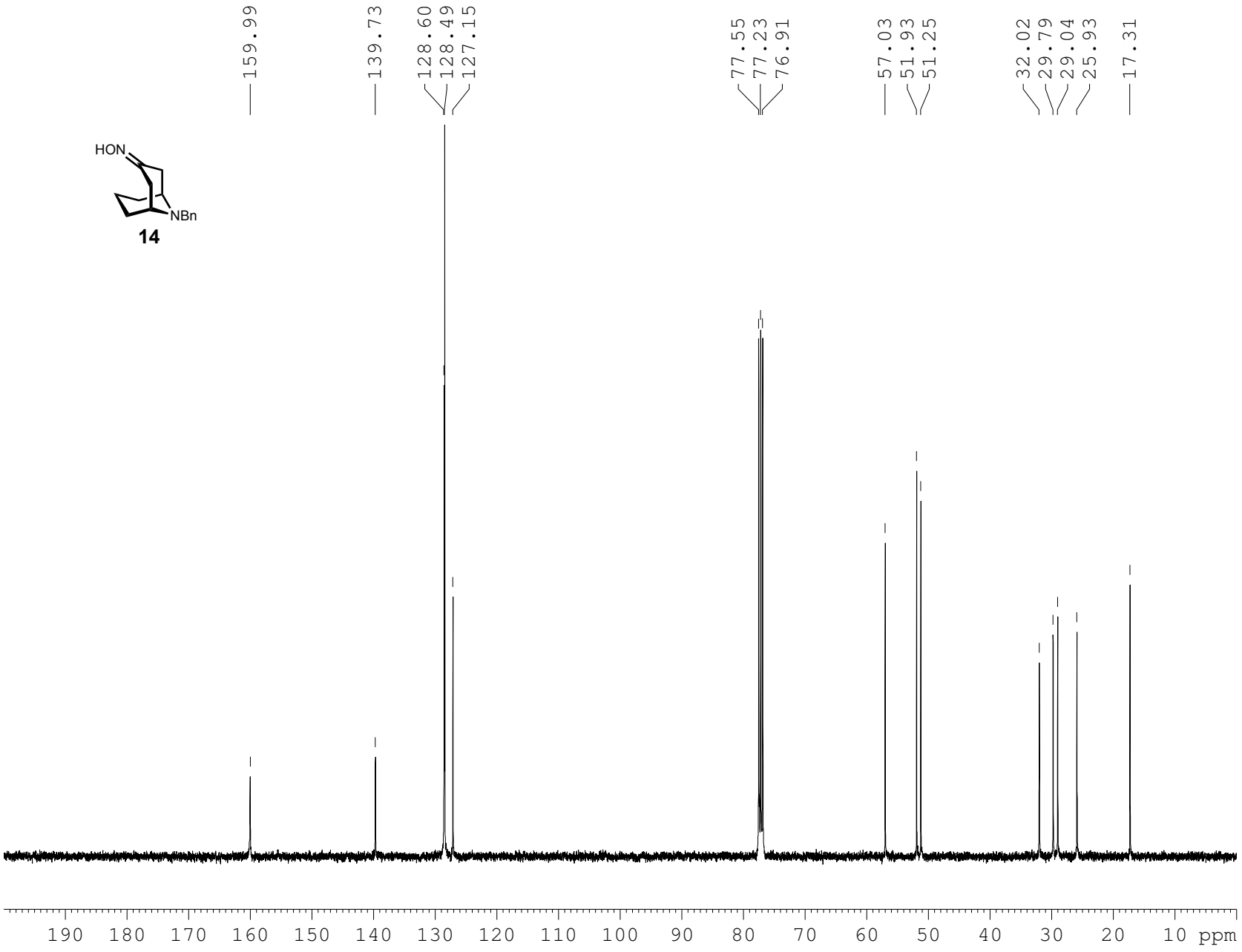


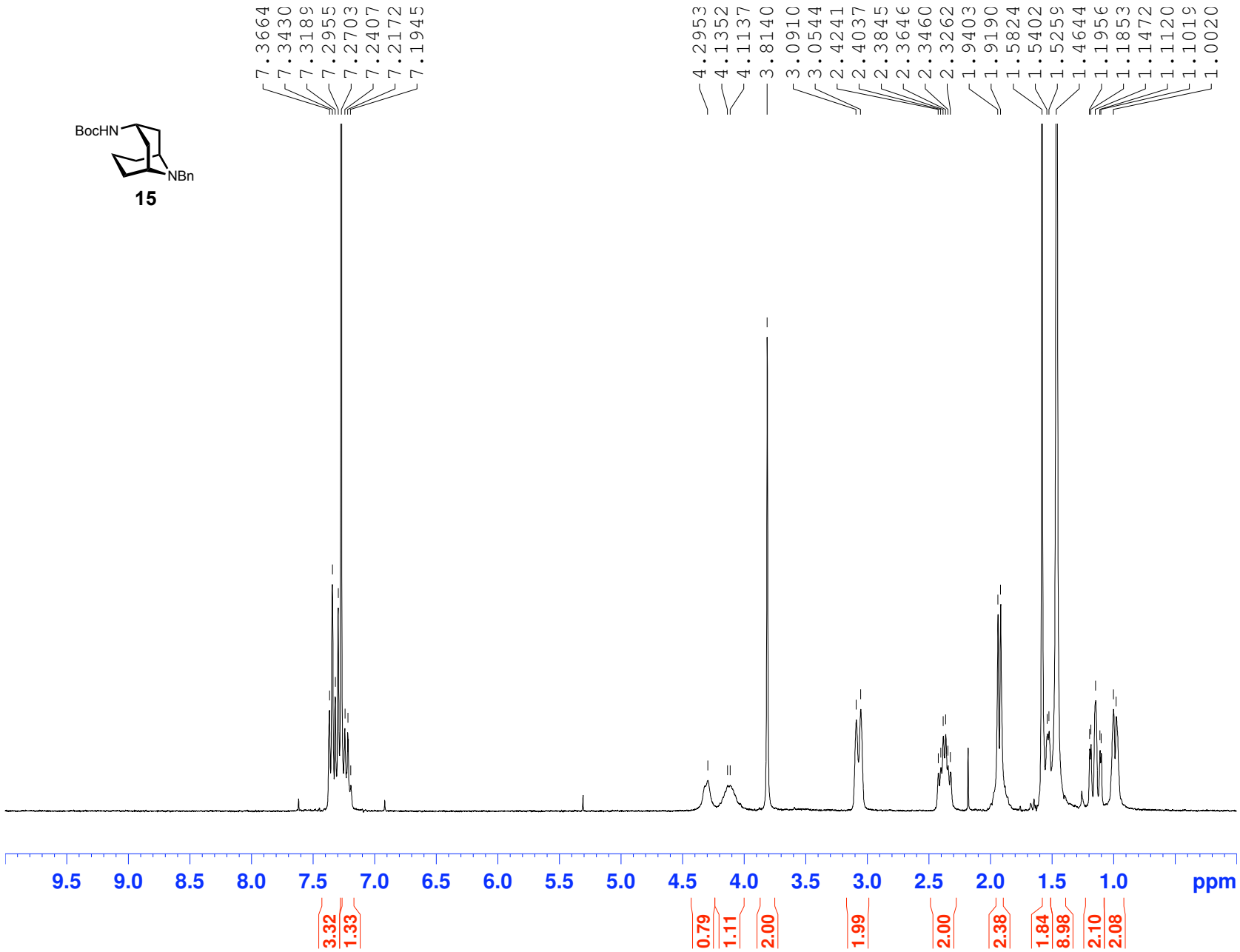


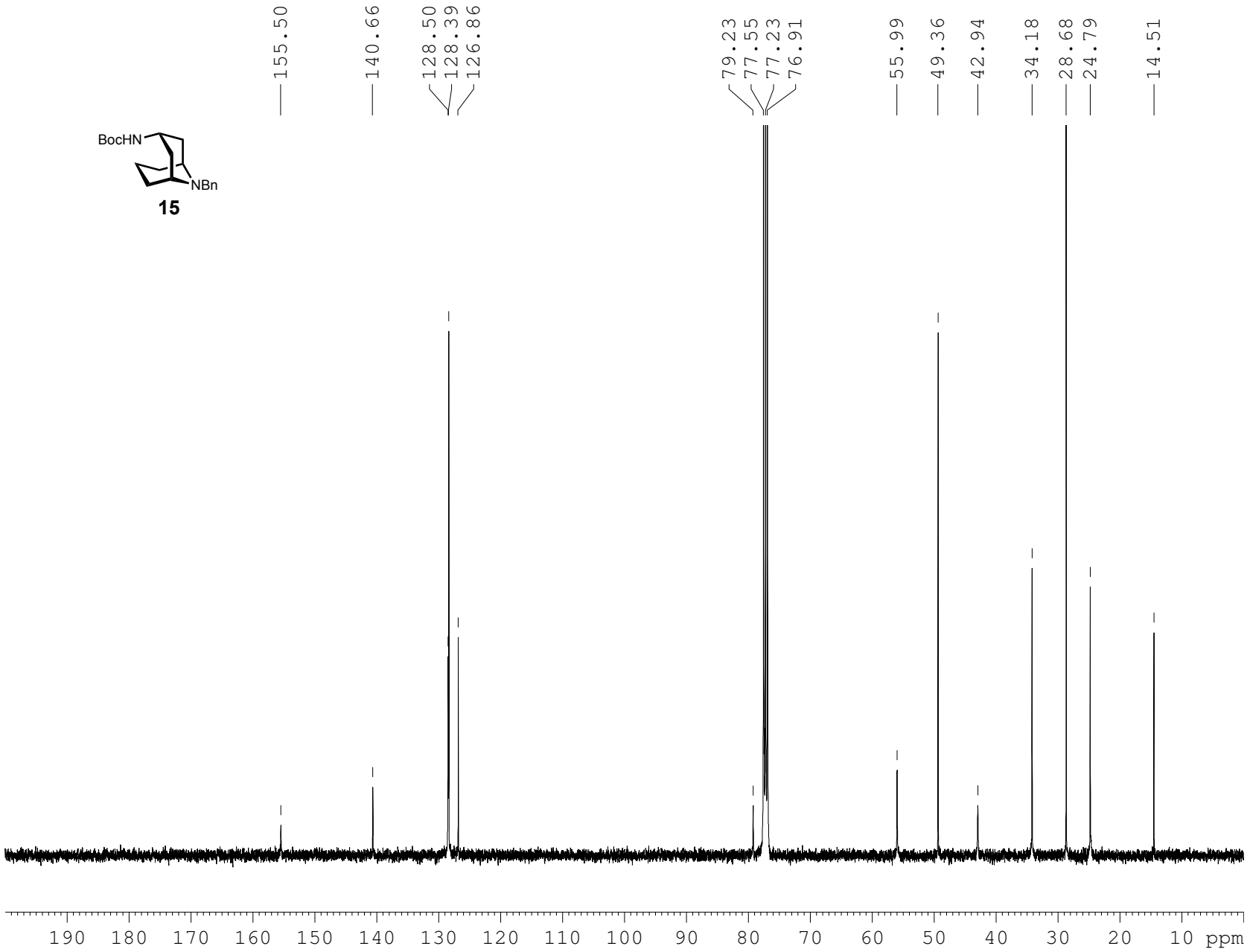


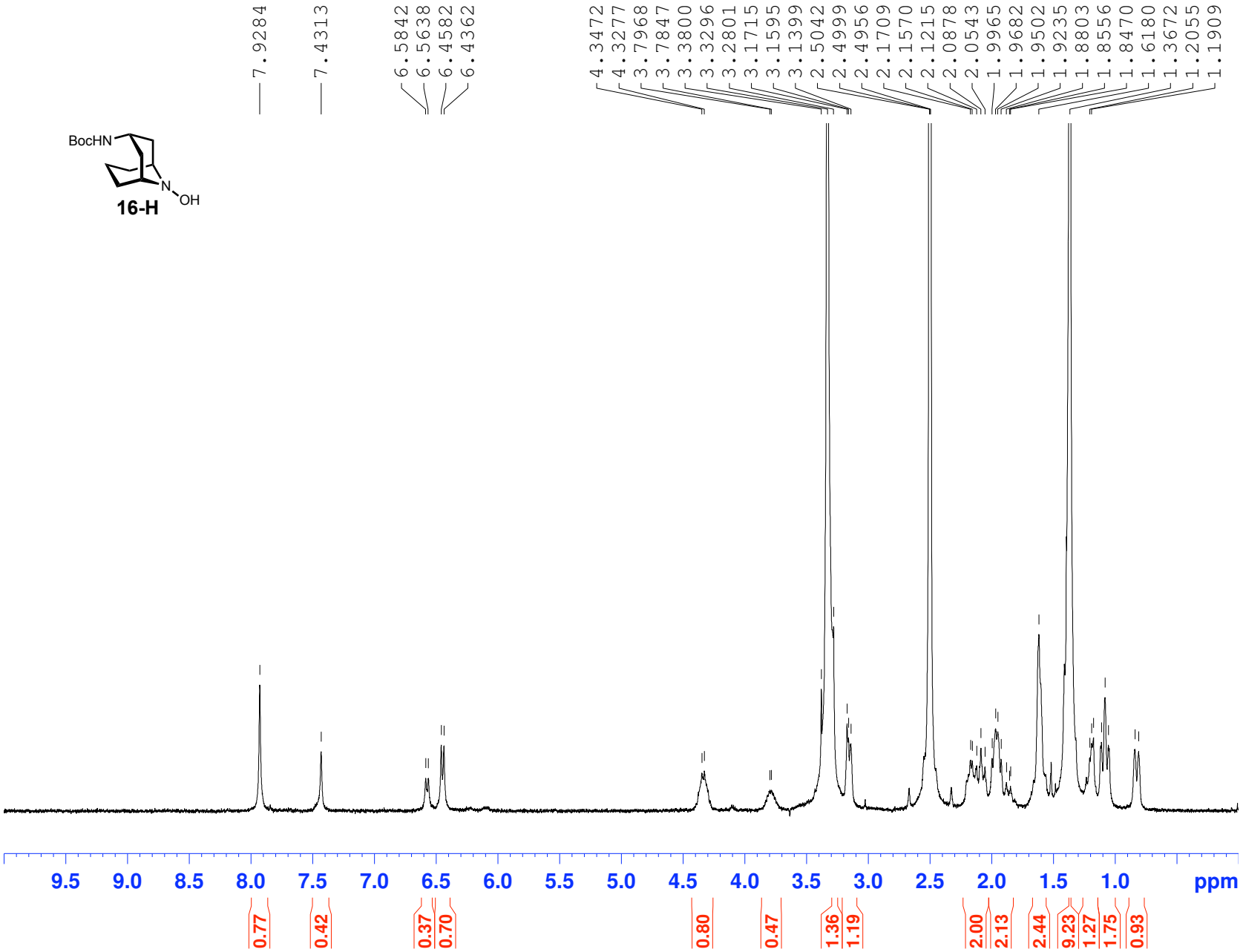


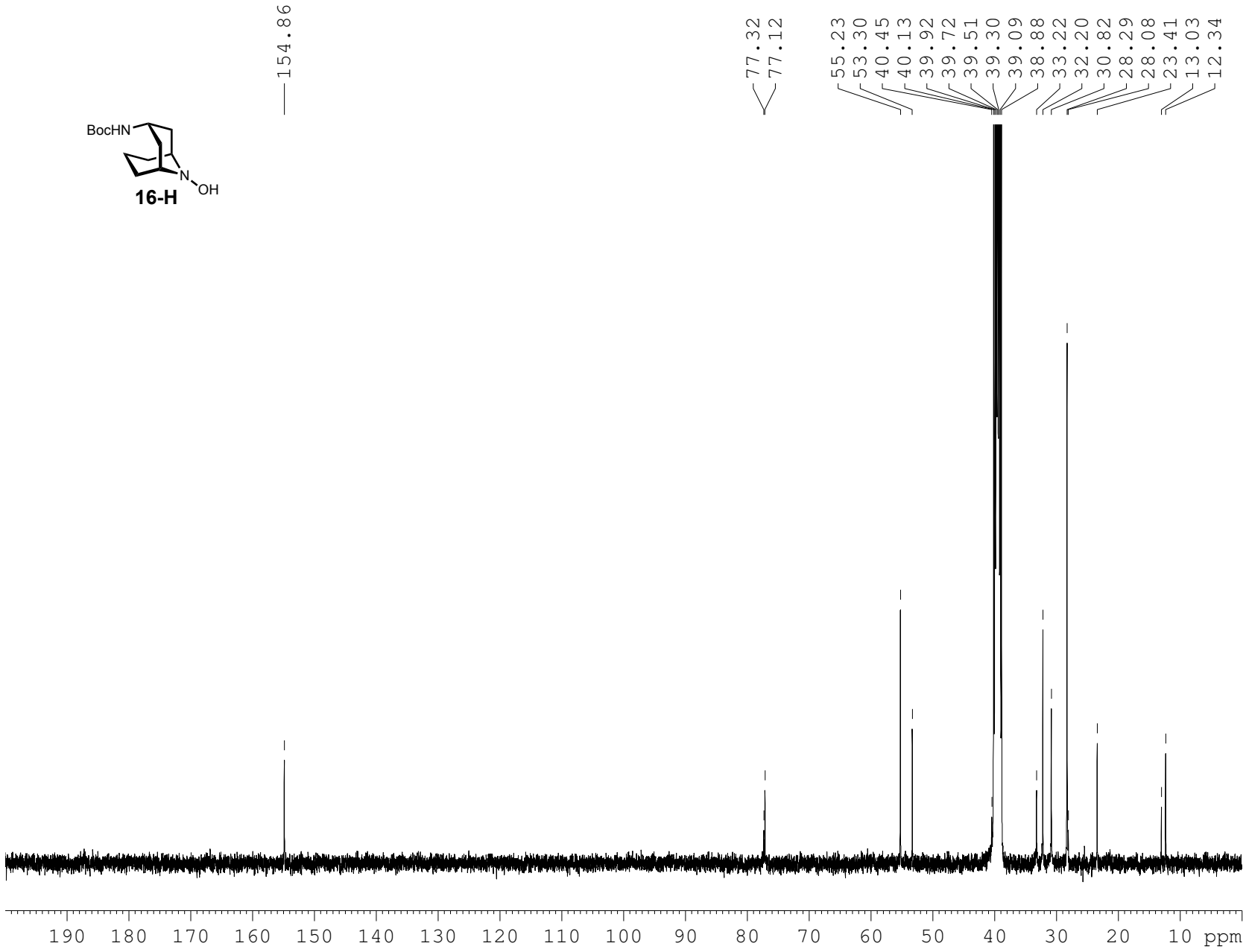


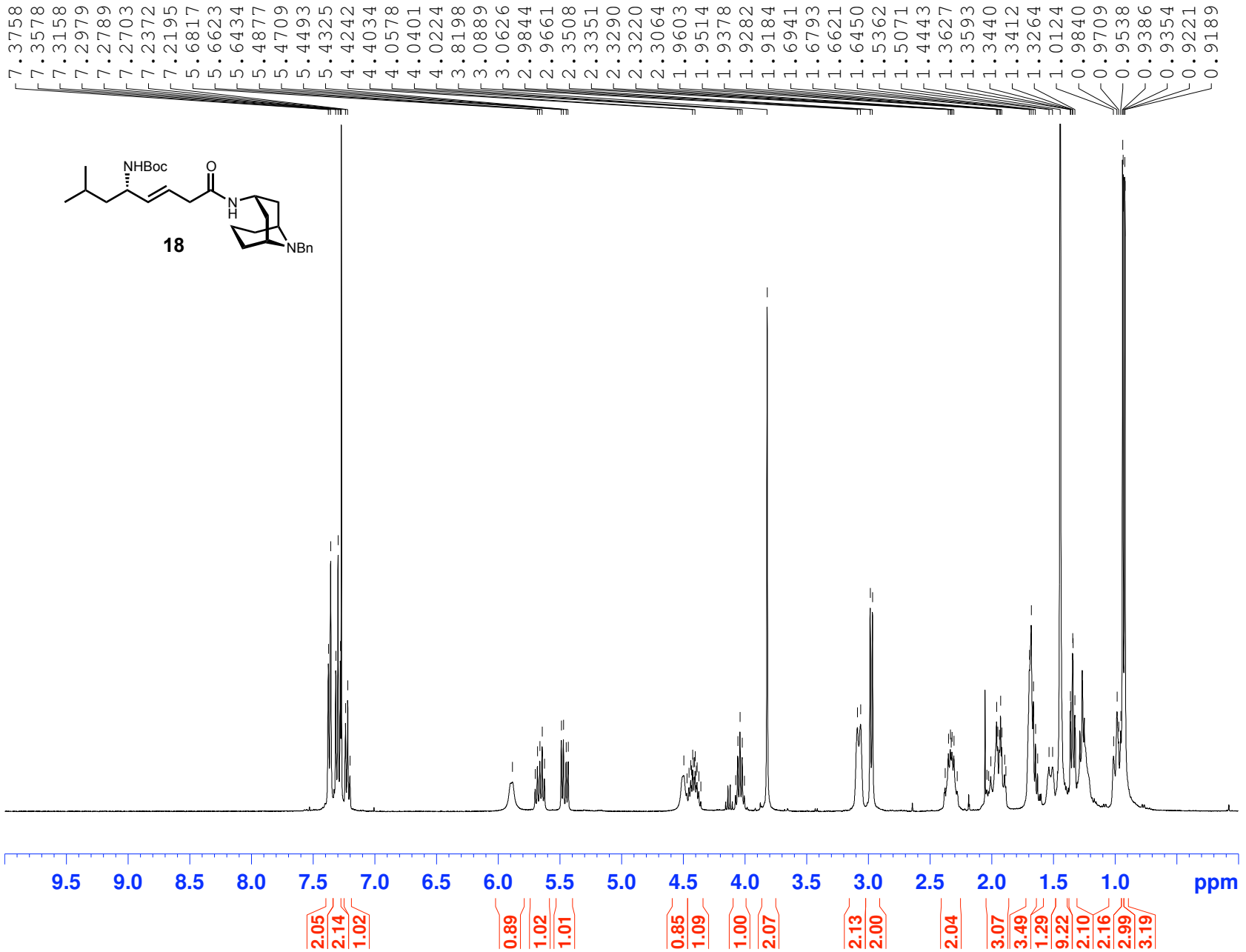


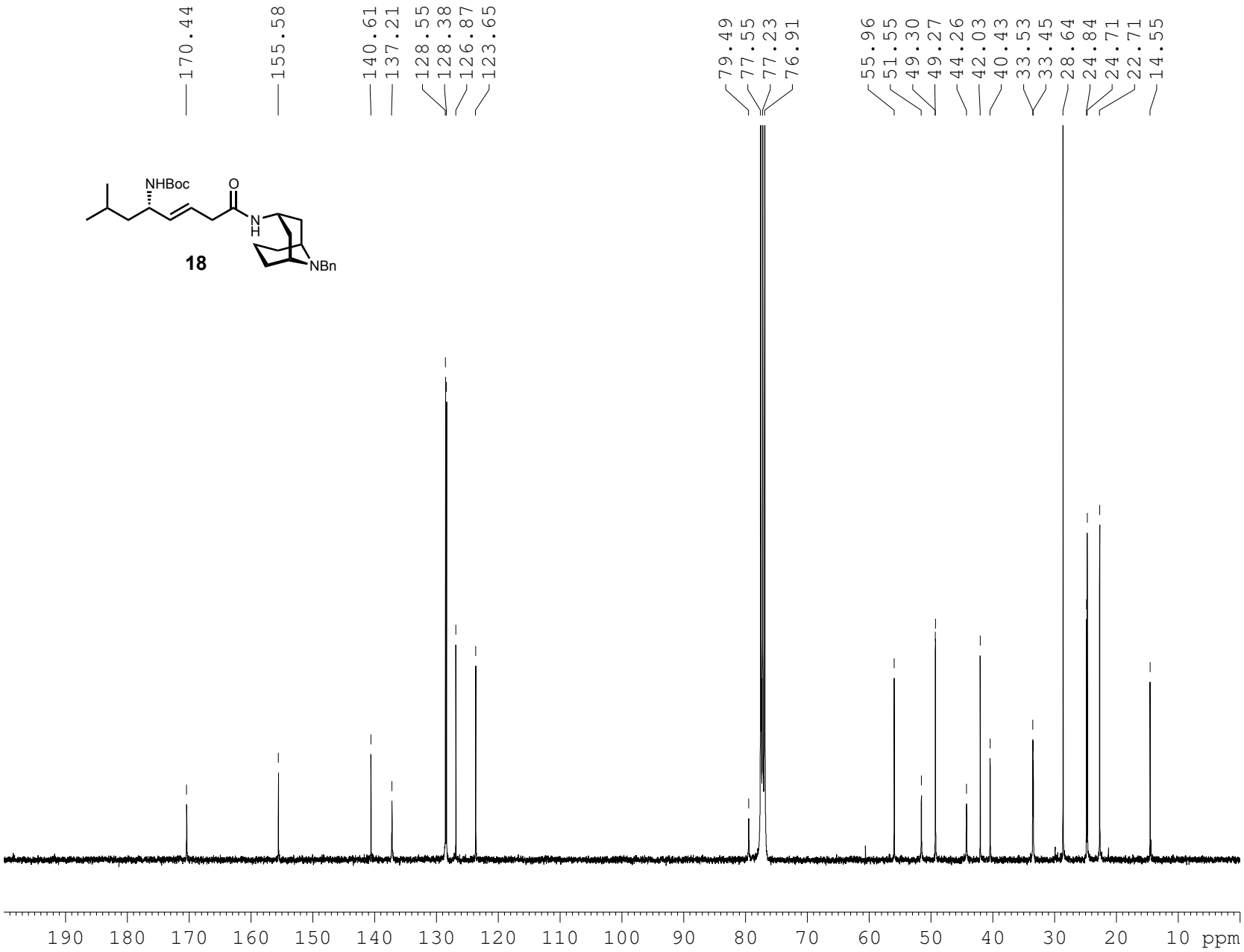


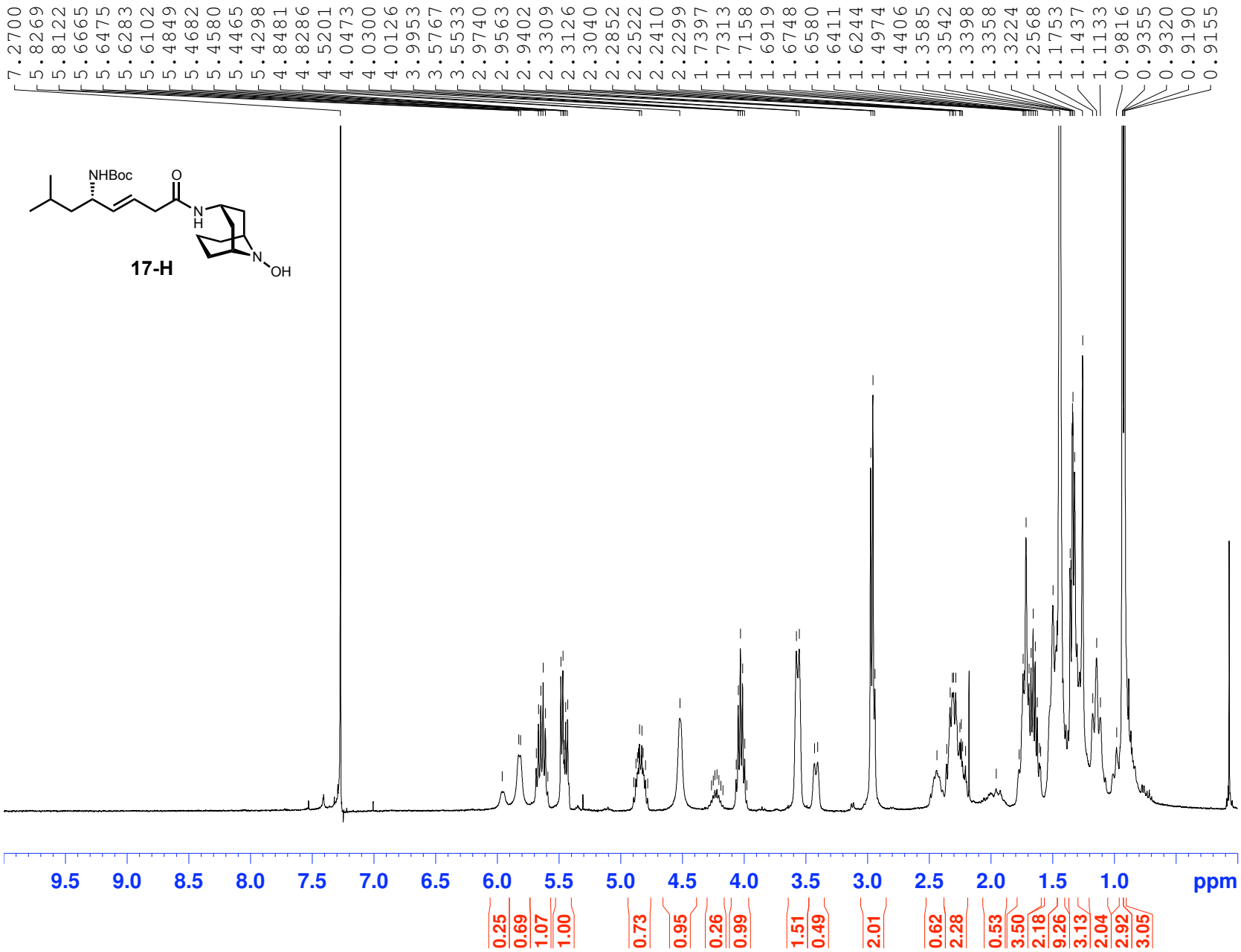


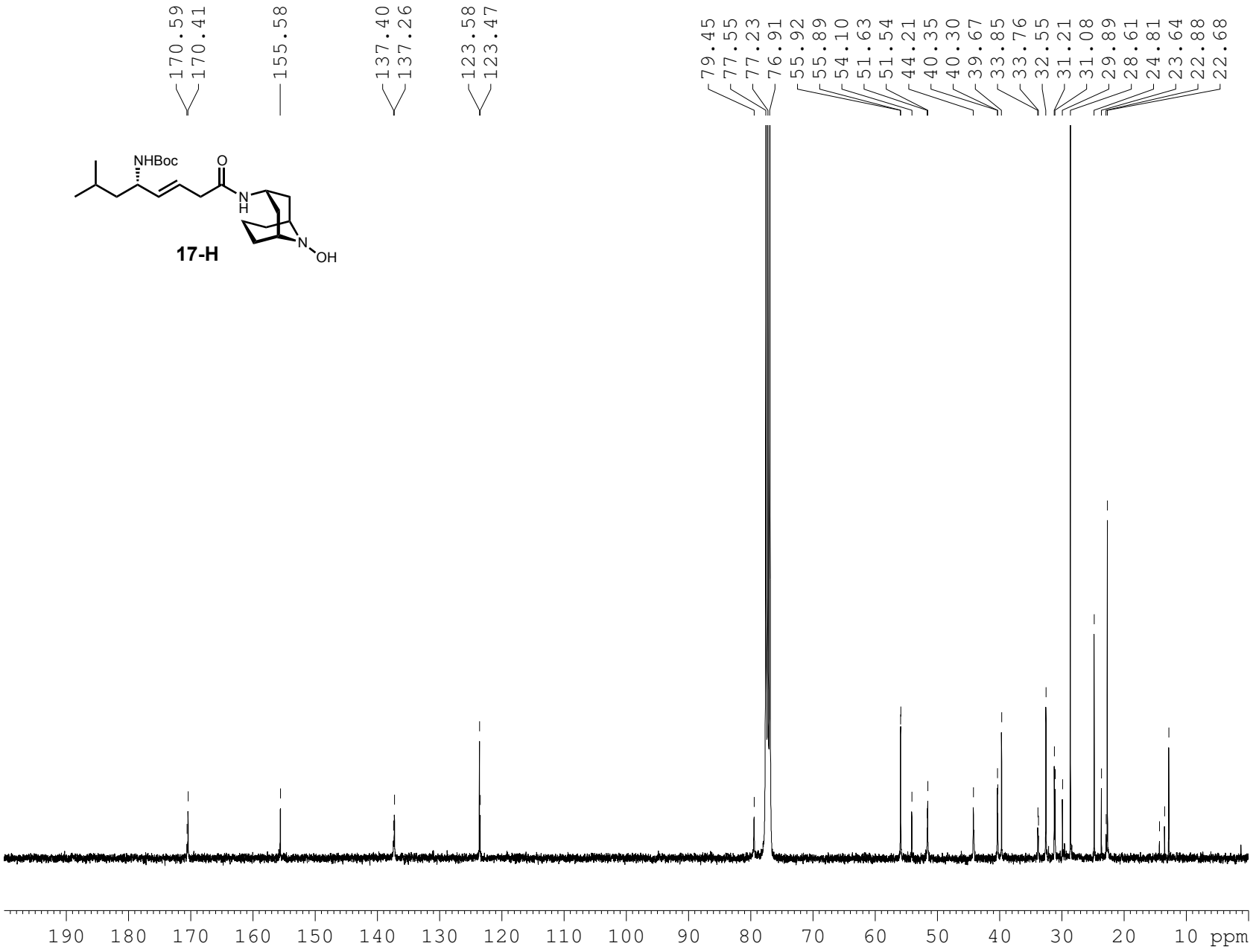


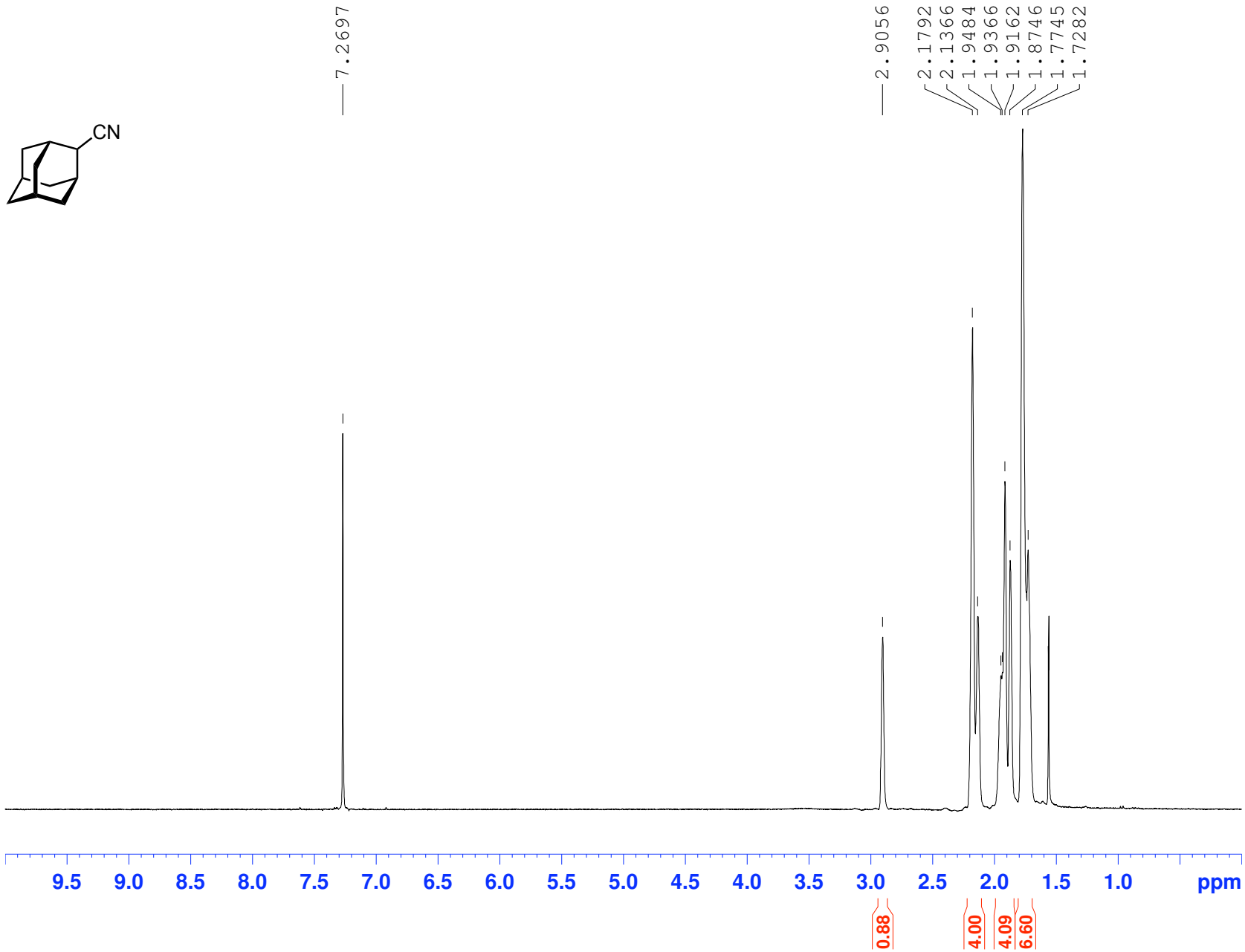


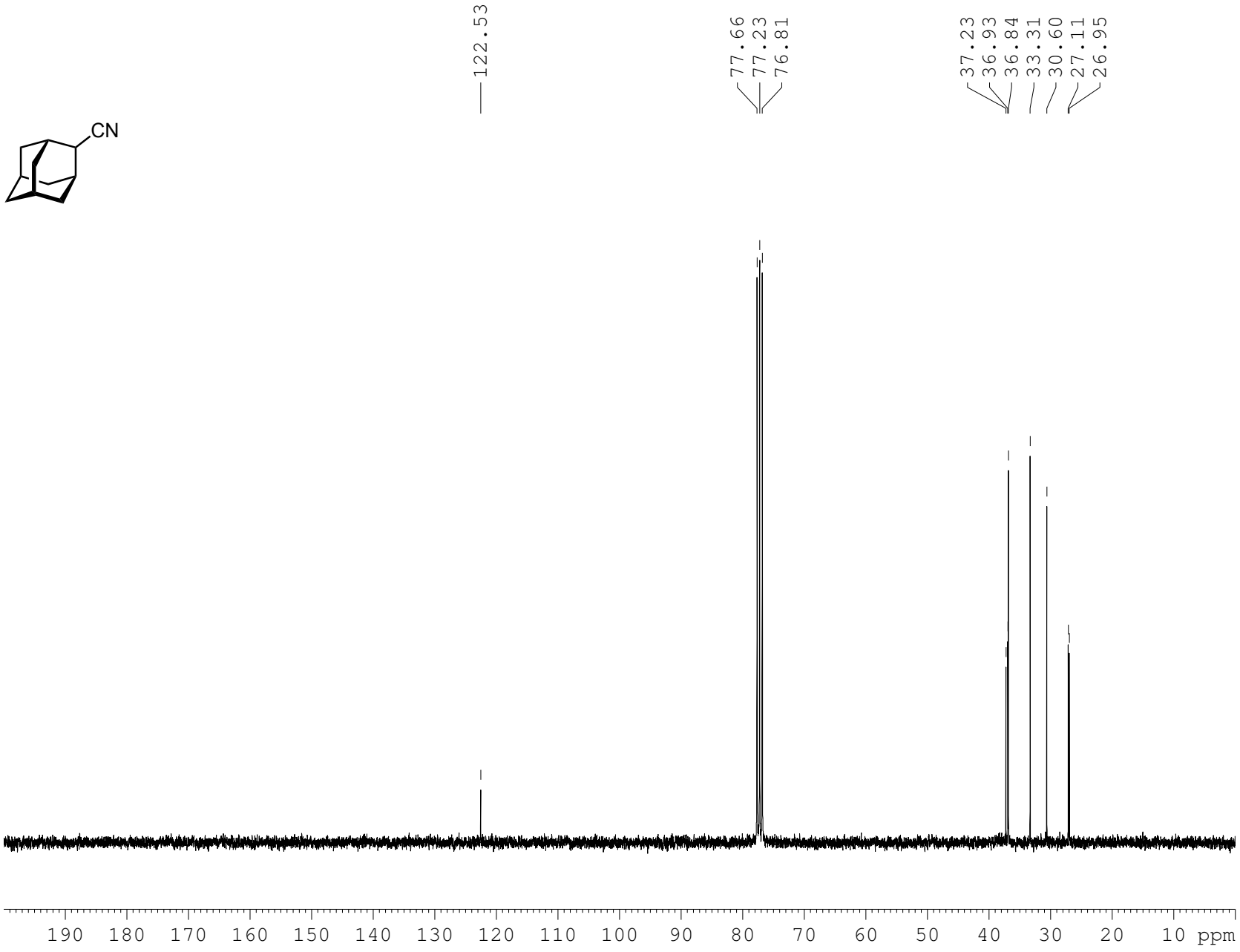


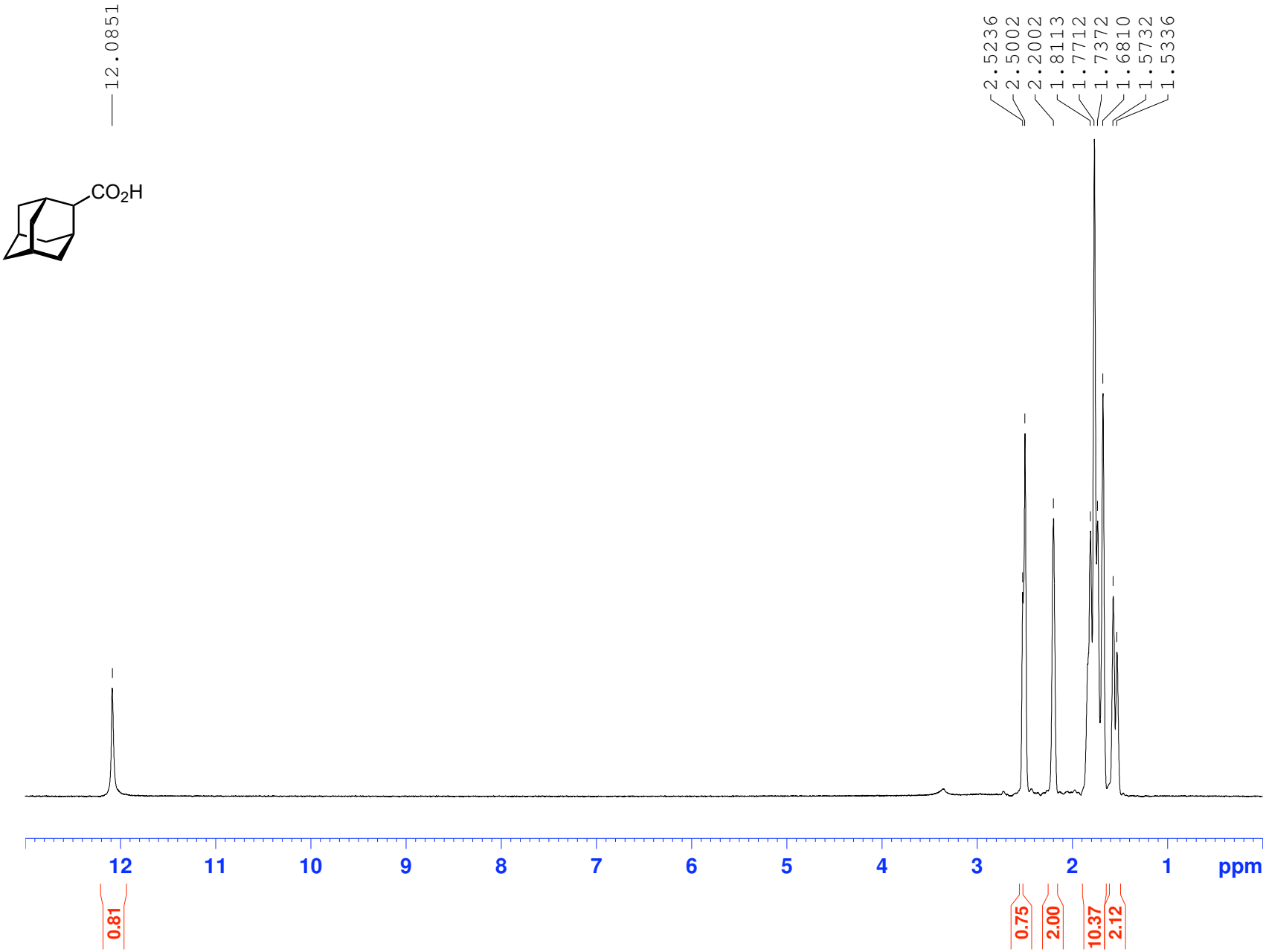


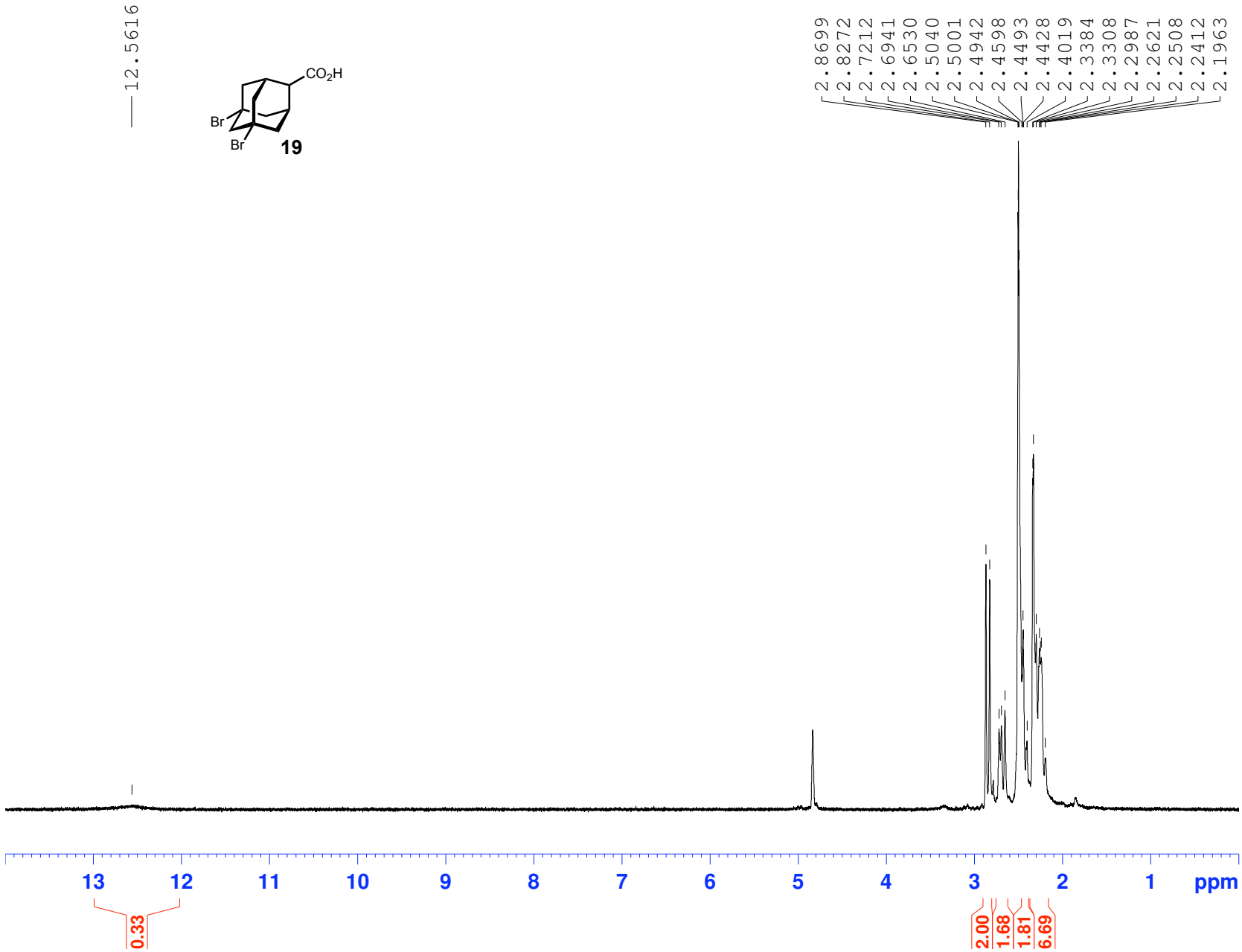


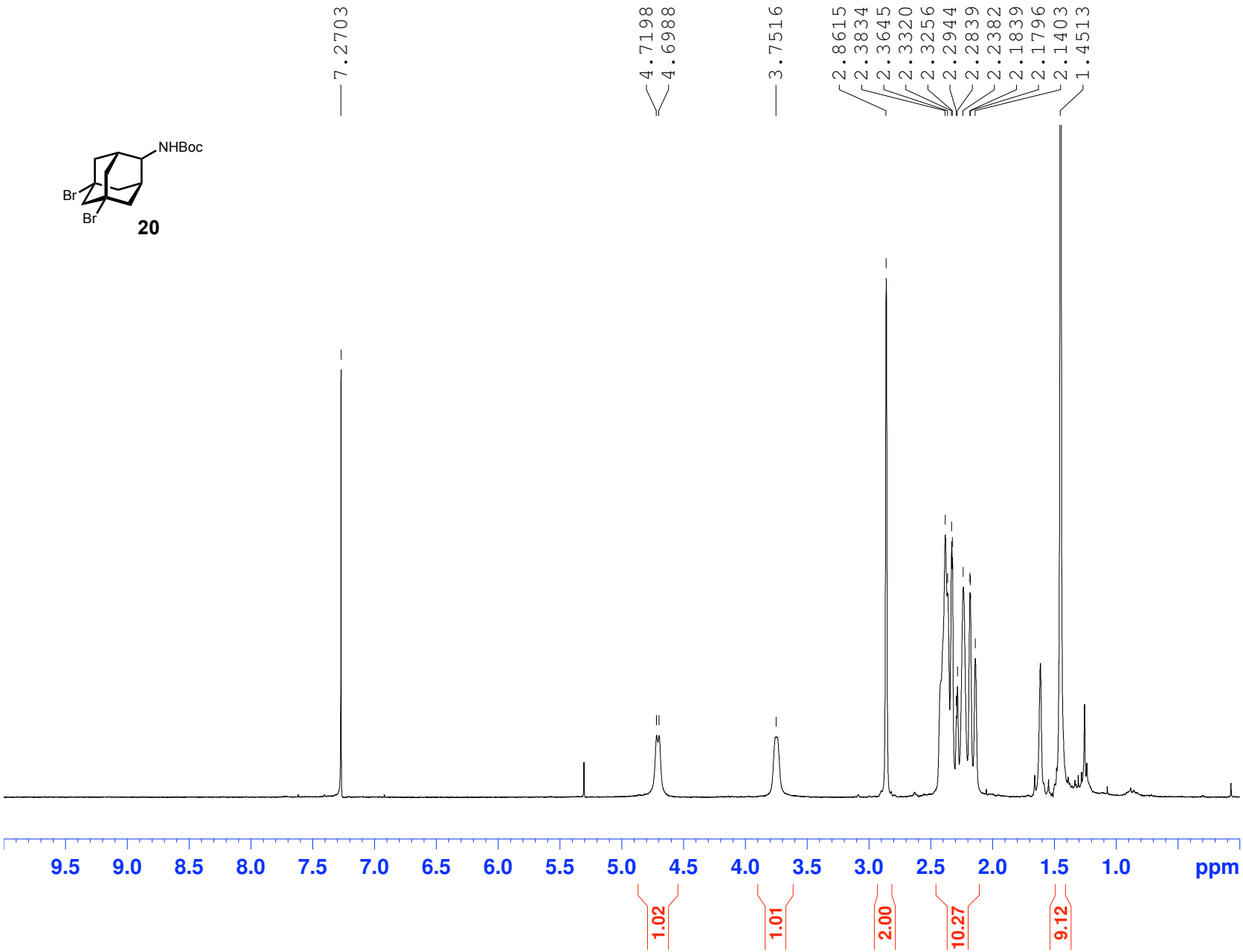


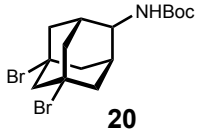












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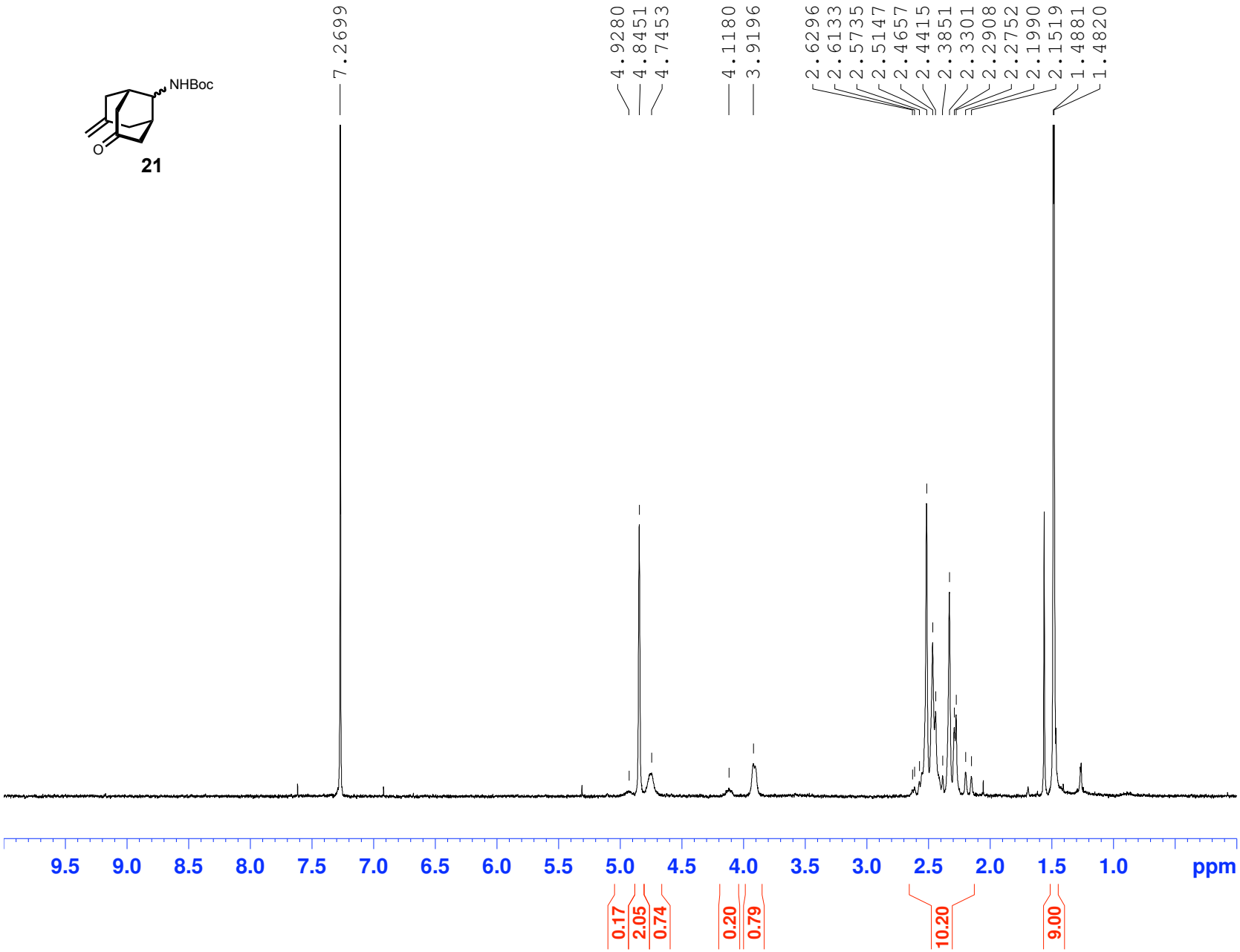

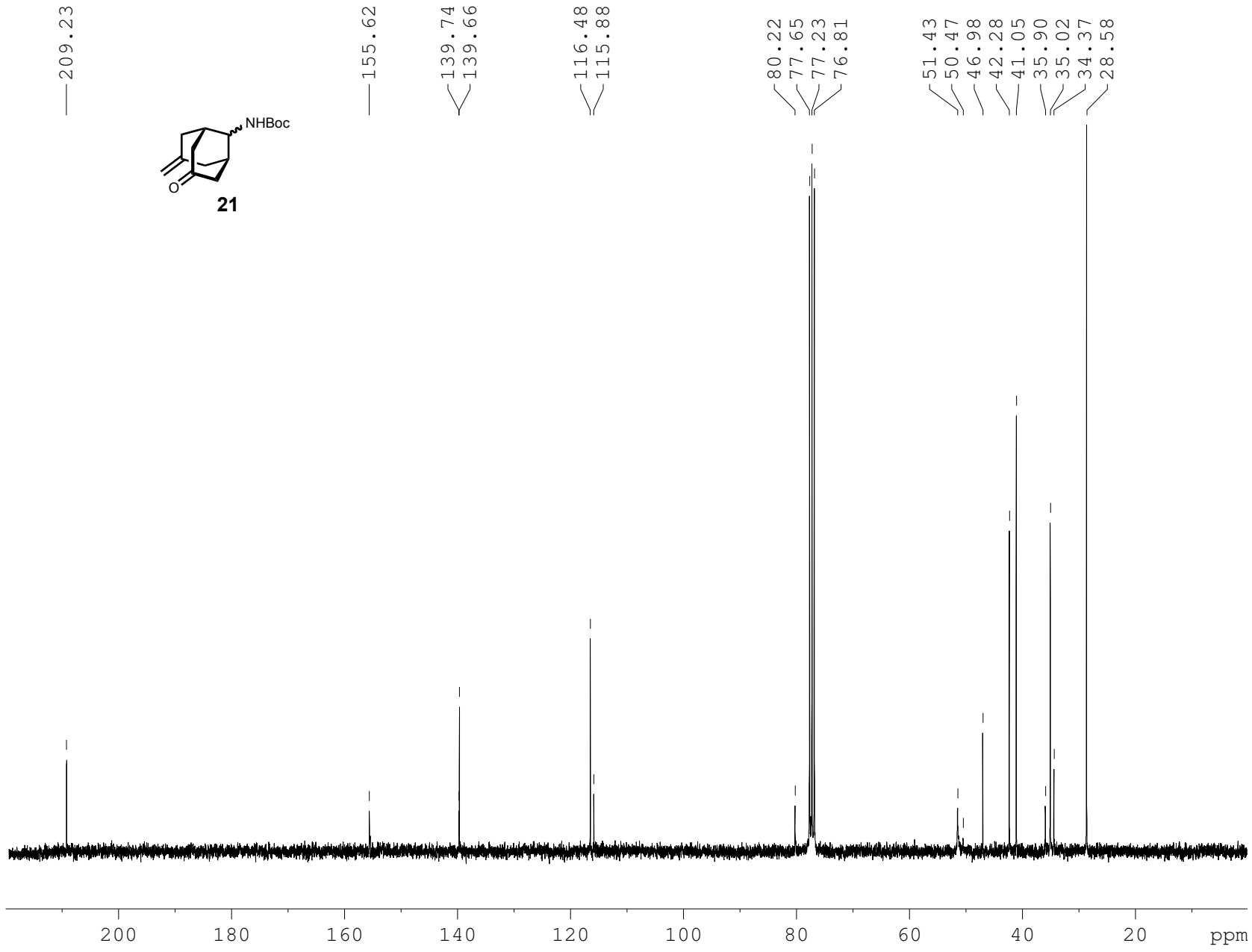

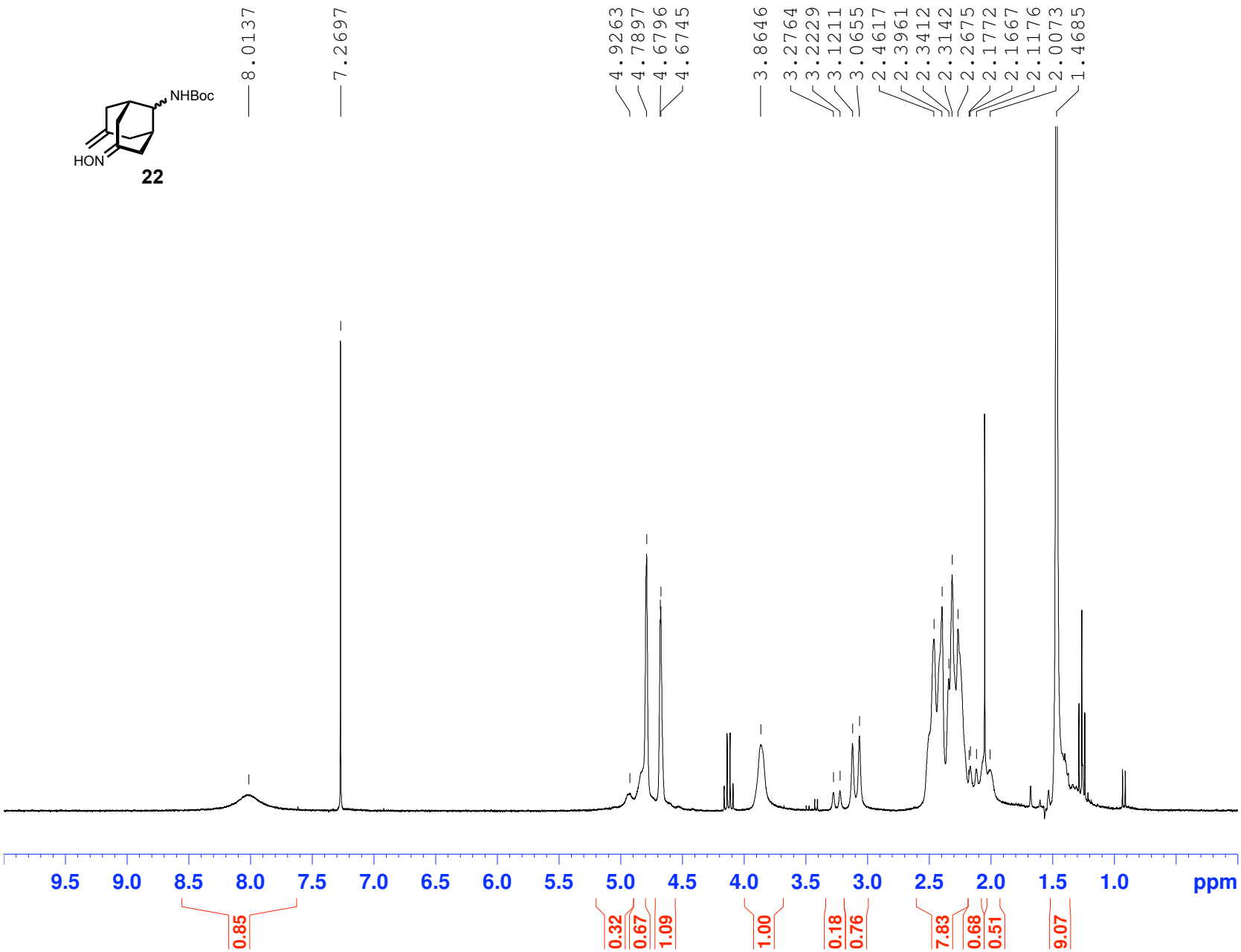

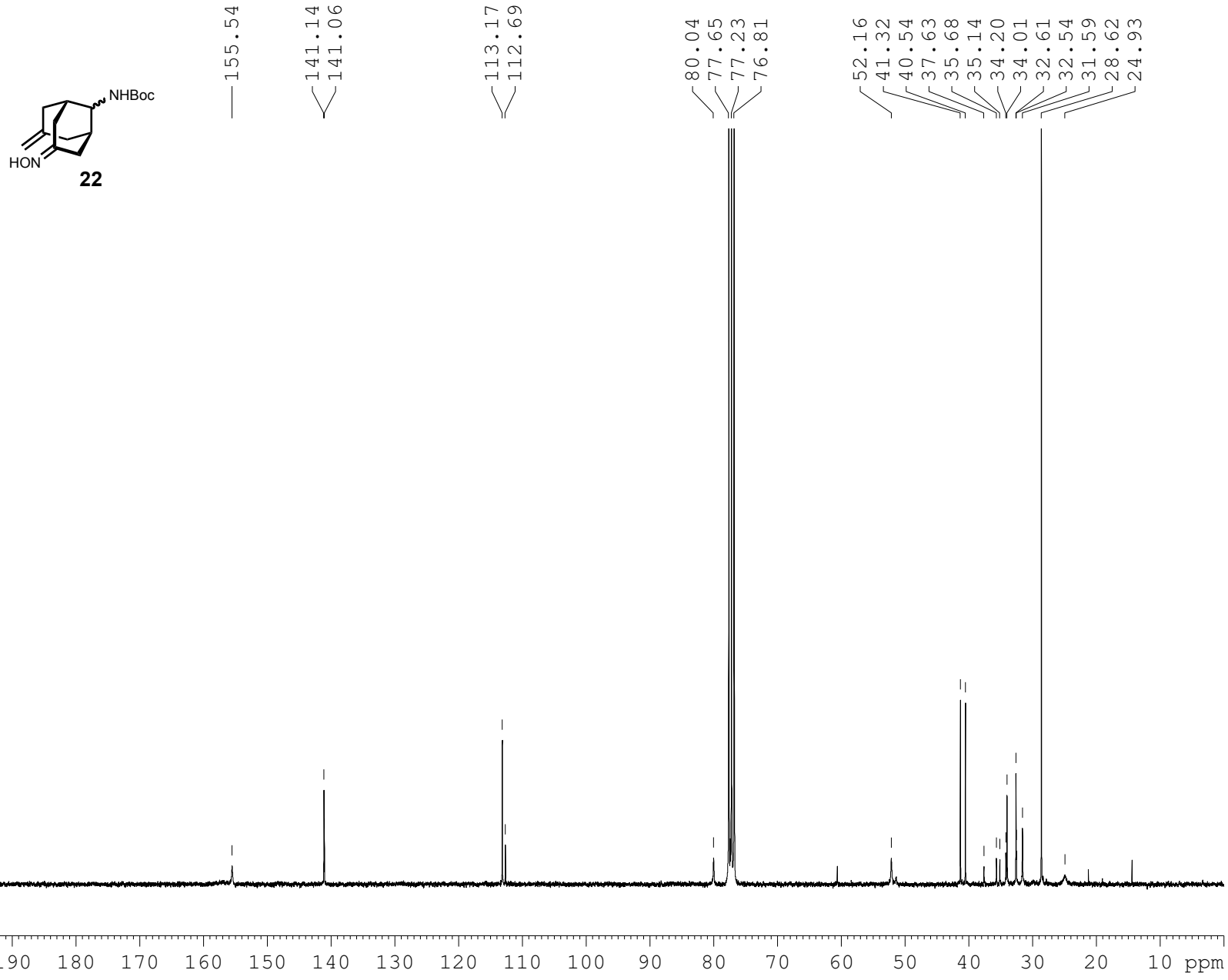

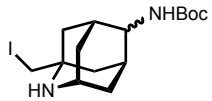

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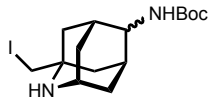

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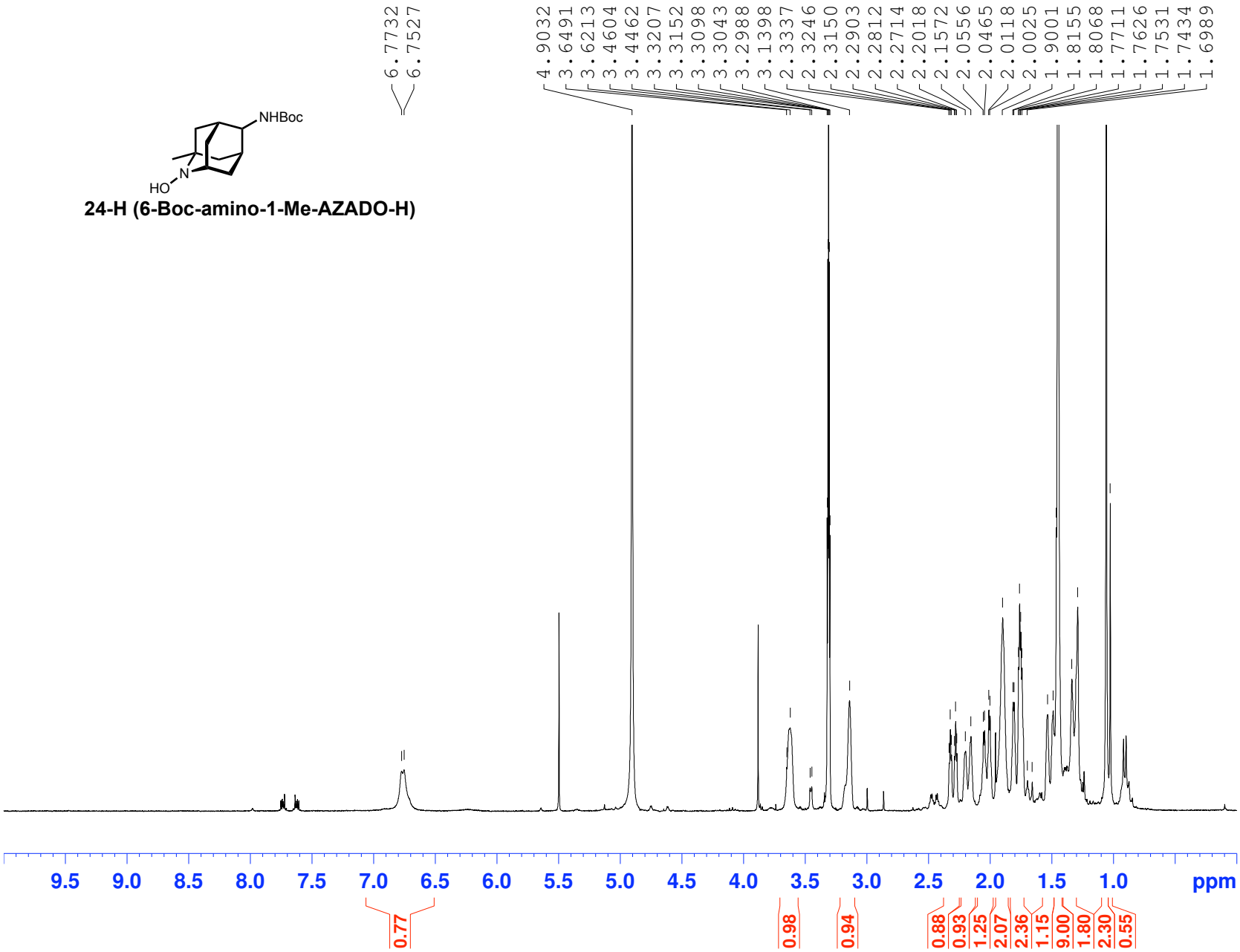
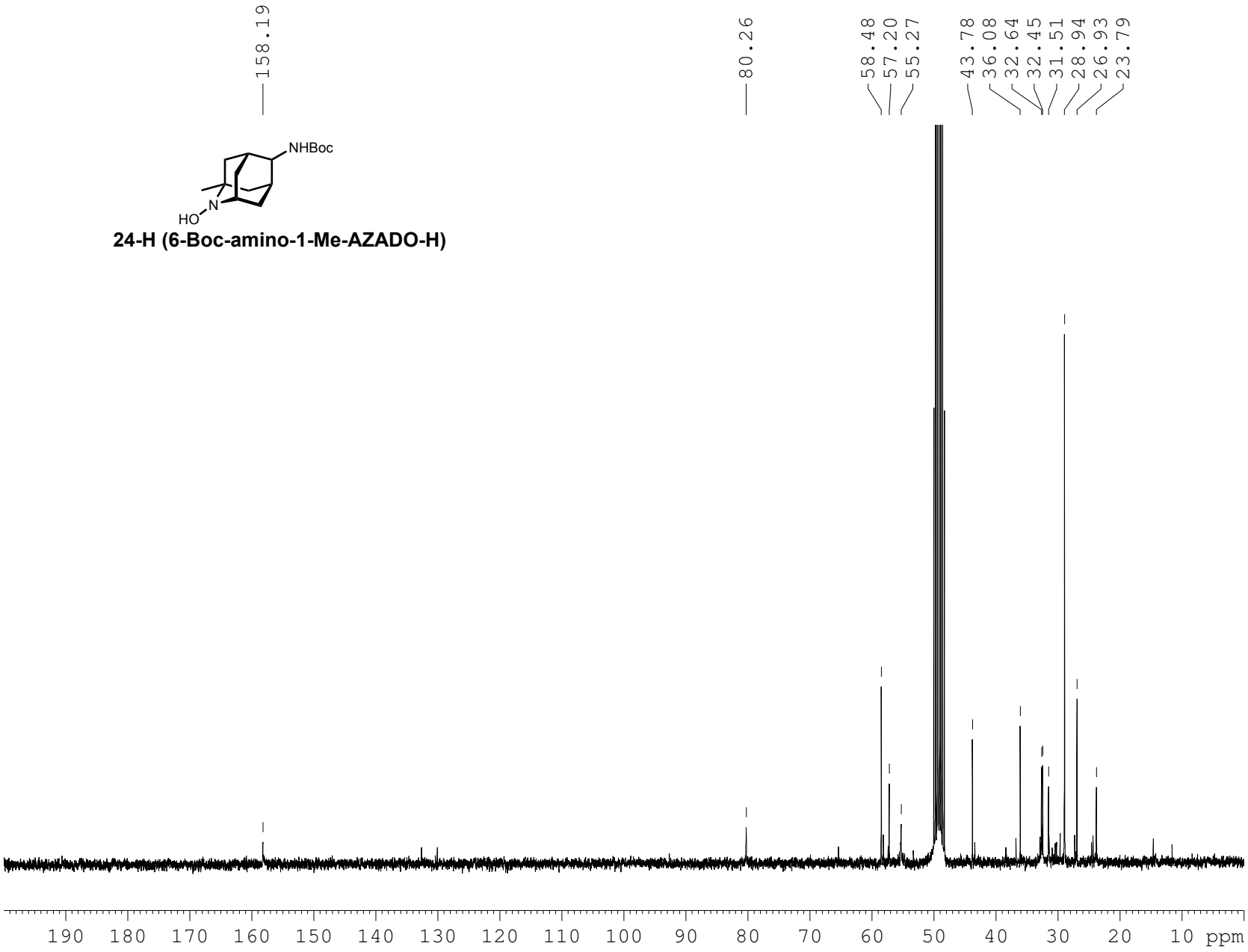
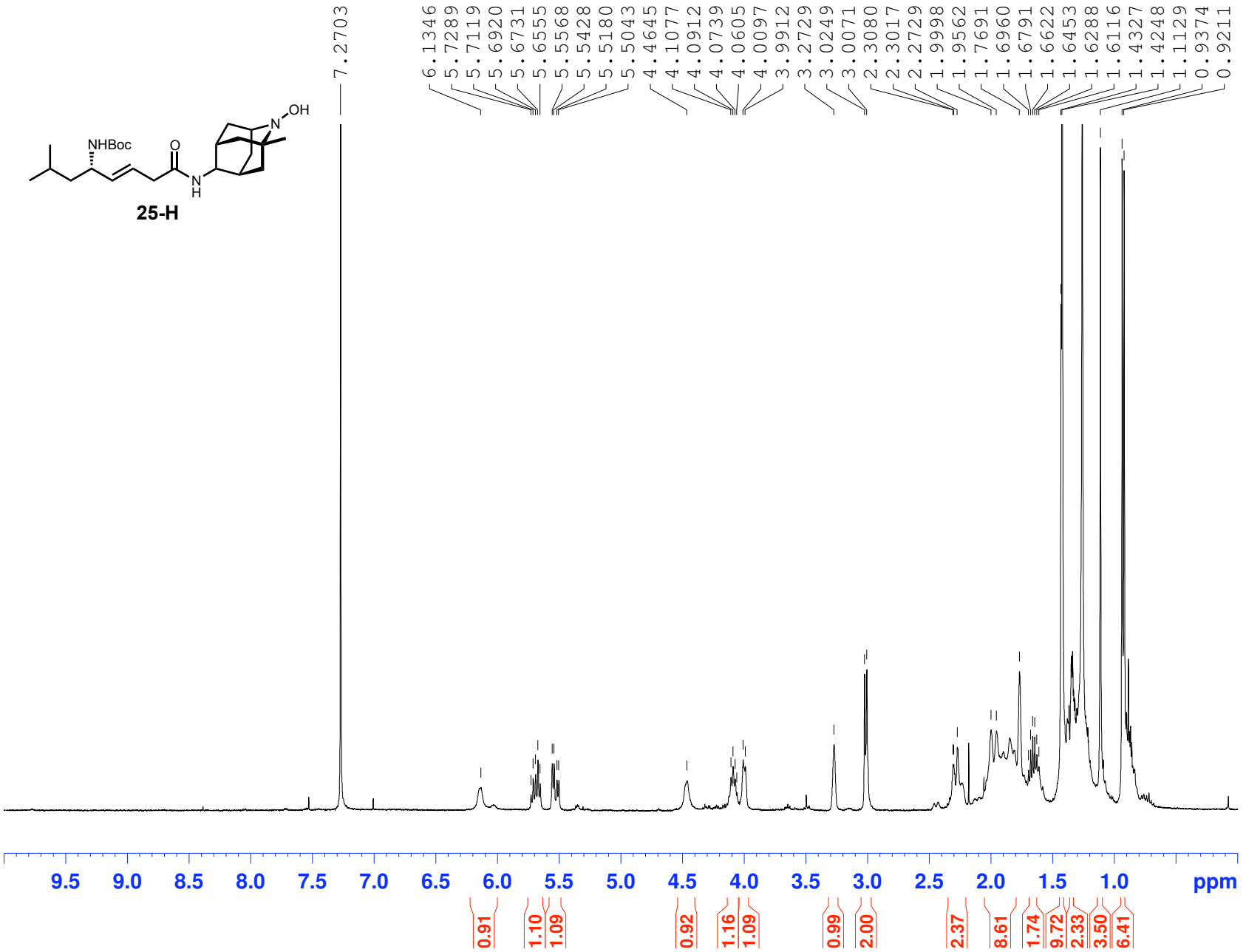
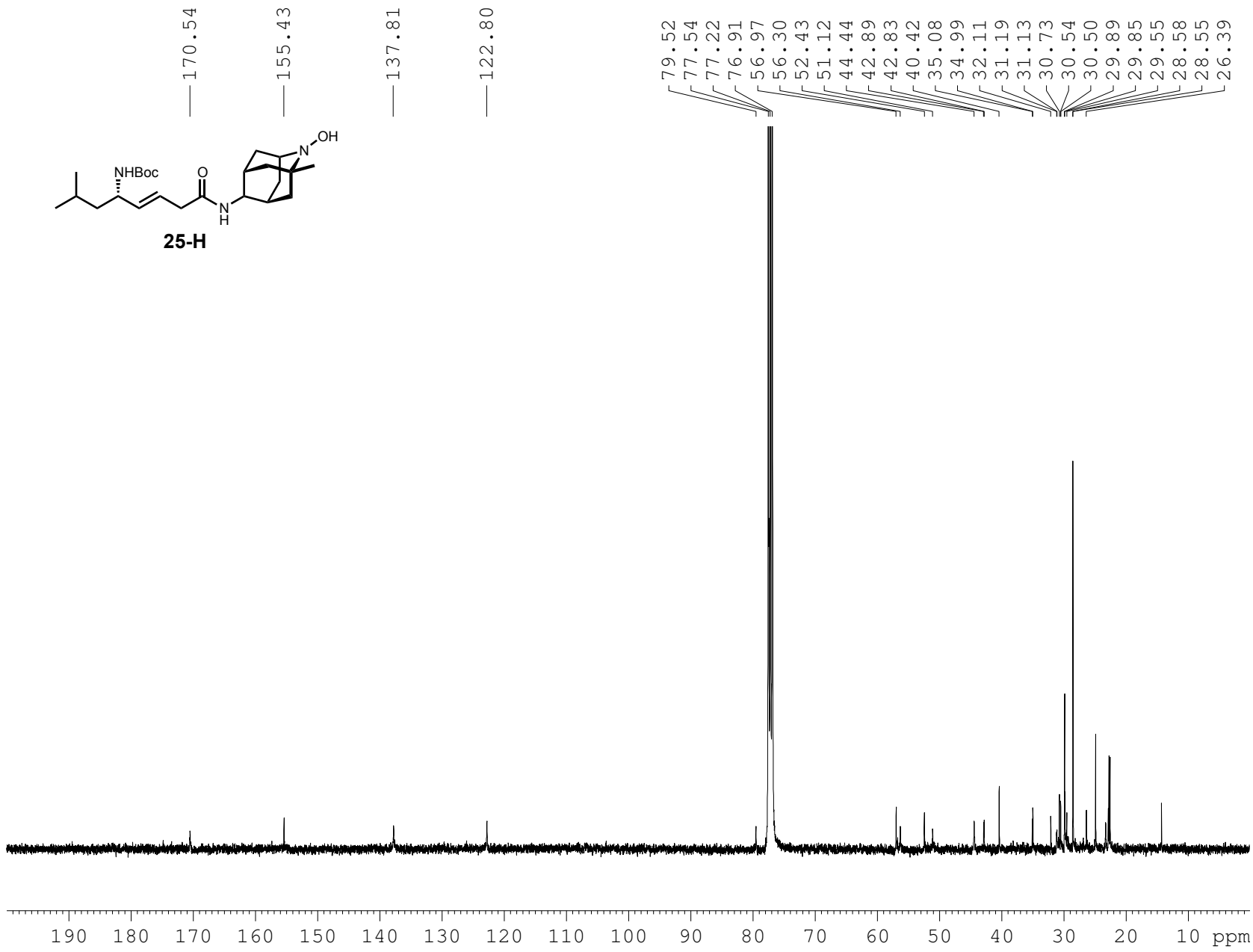


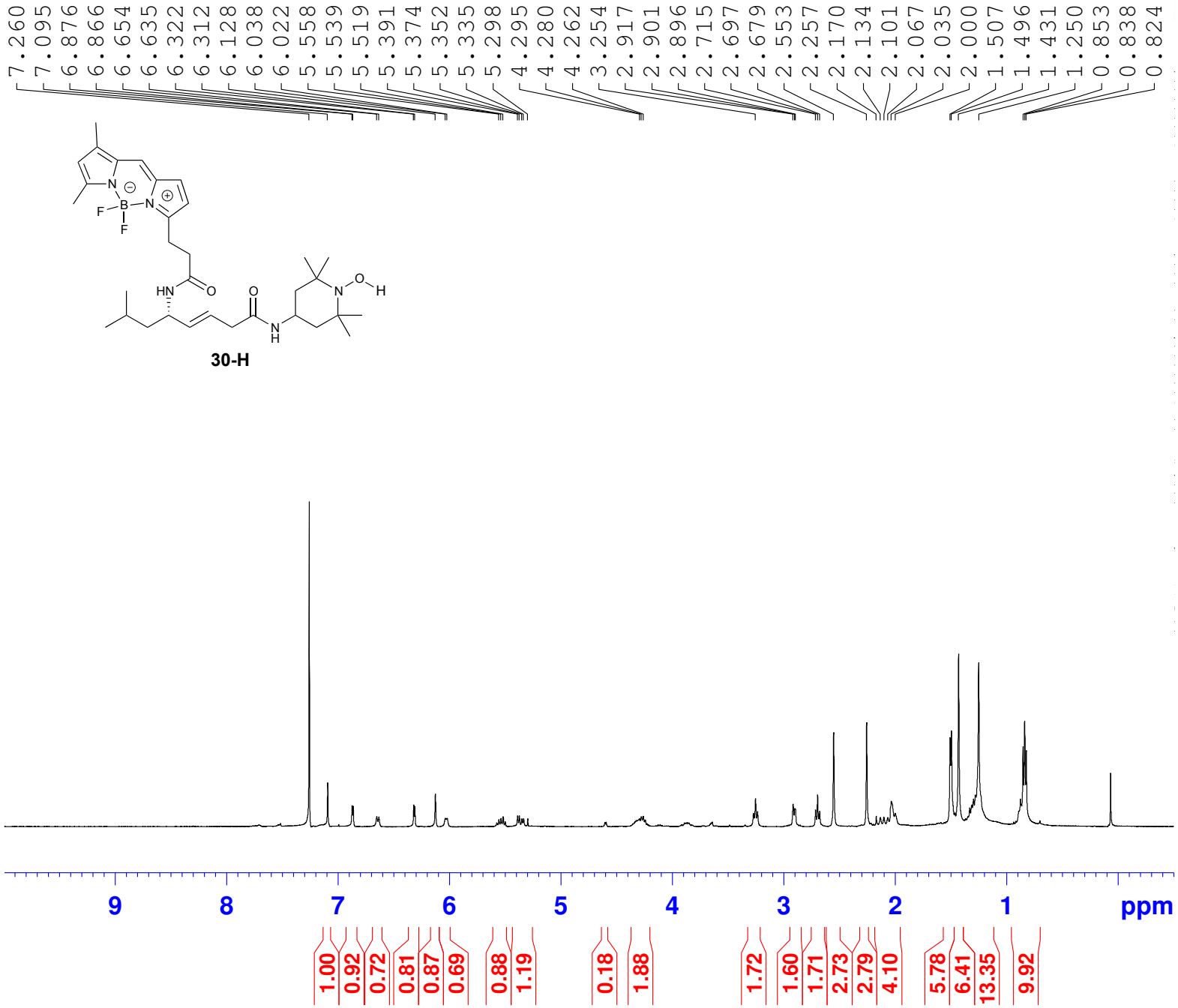
24-H (6-Boc-amino-1-Me-AZADO-H)



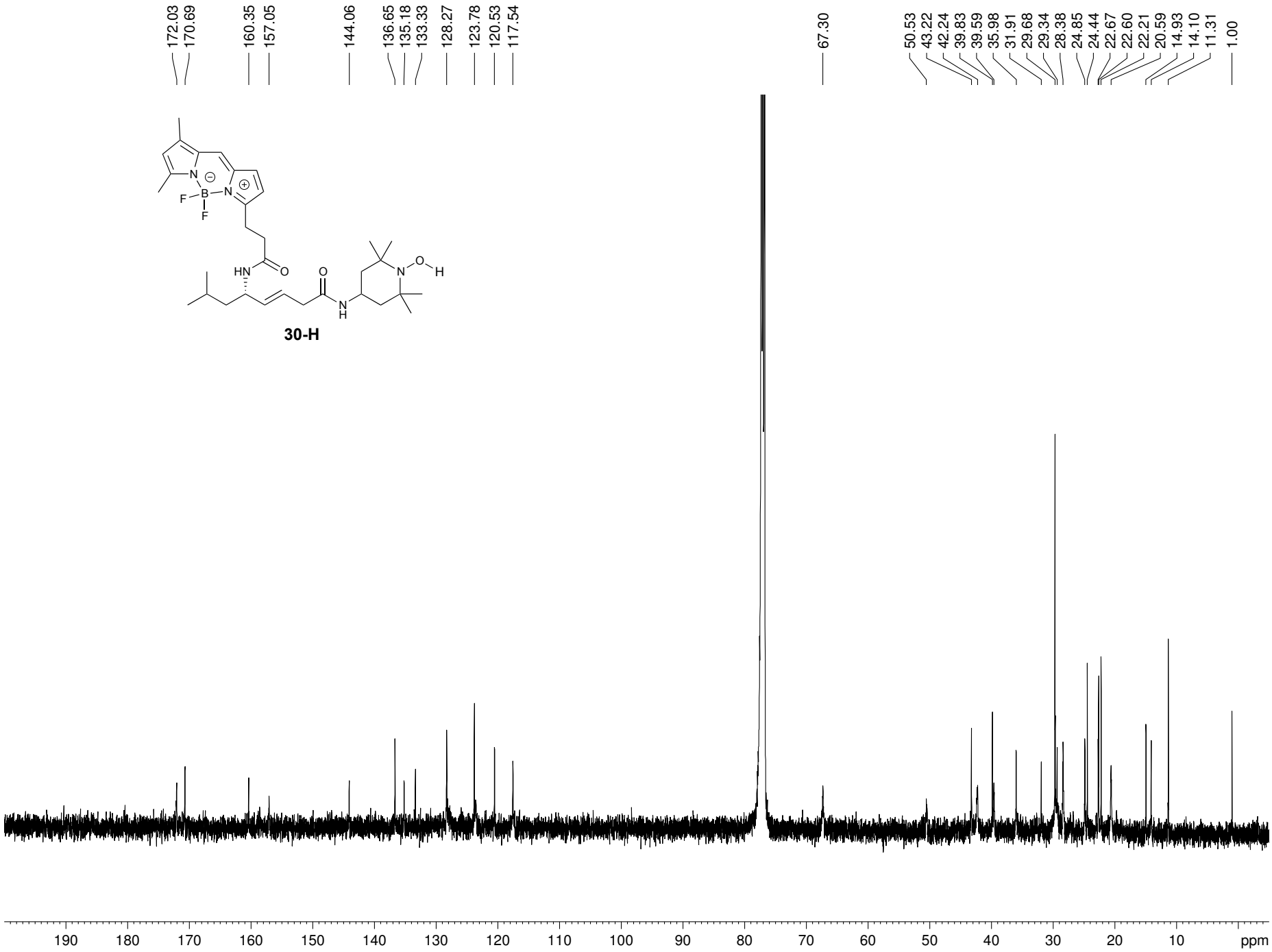
24-H (6-Boc-amino-1-Me-AZADO-H)



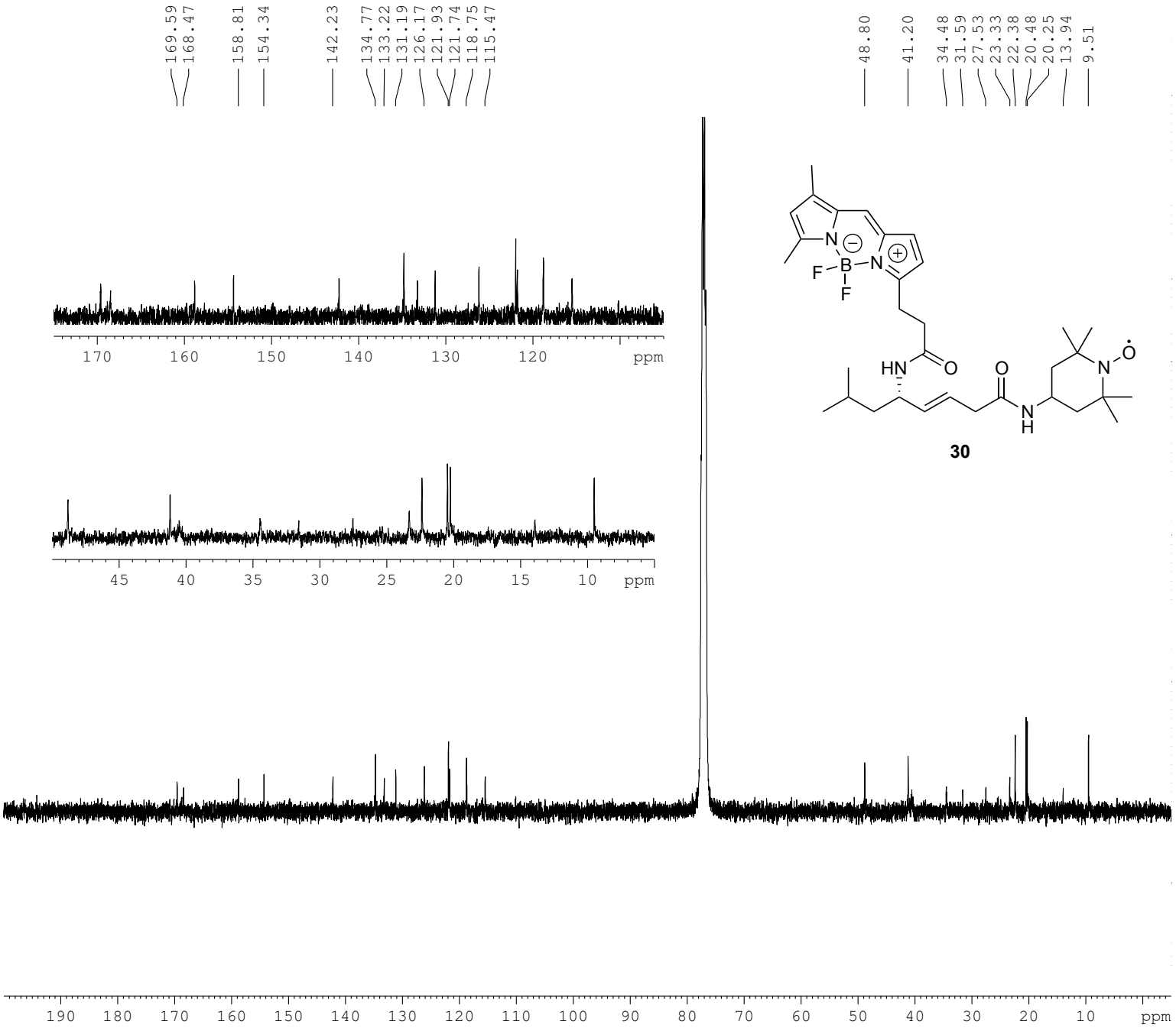




30-H



30-H



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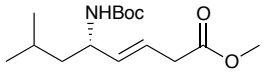

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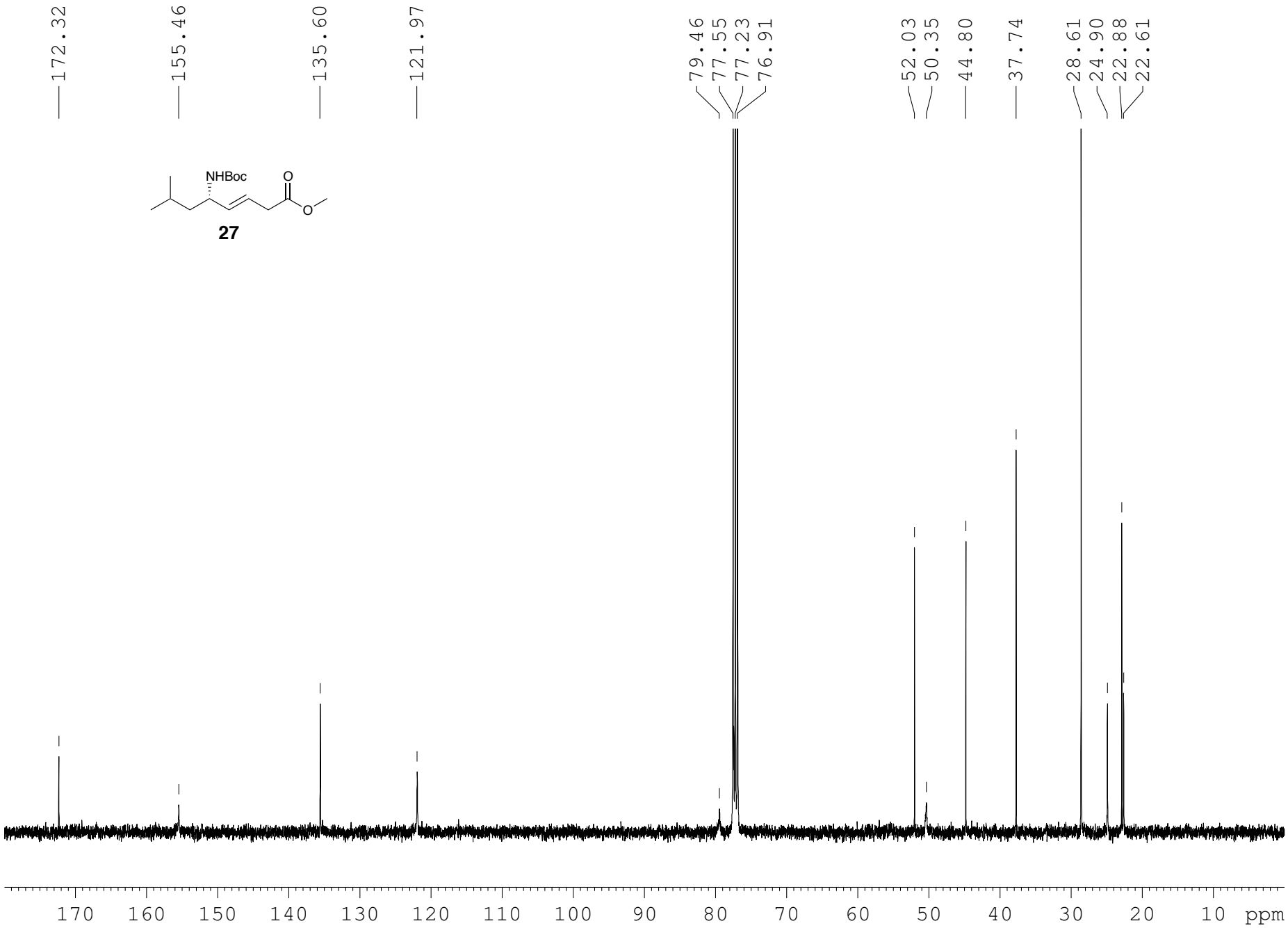

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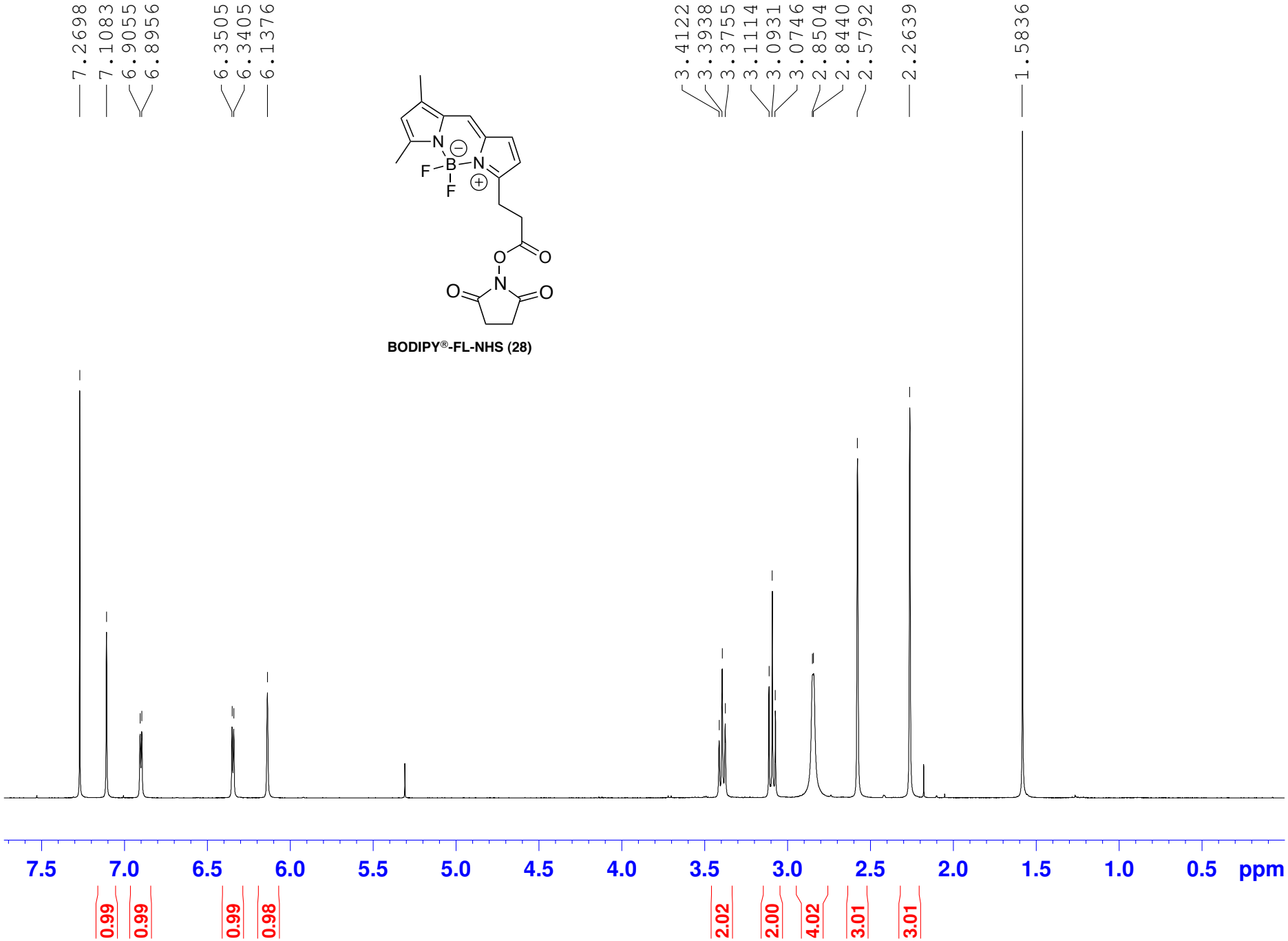
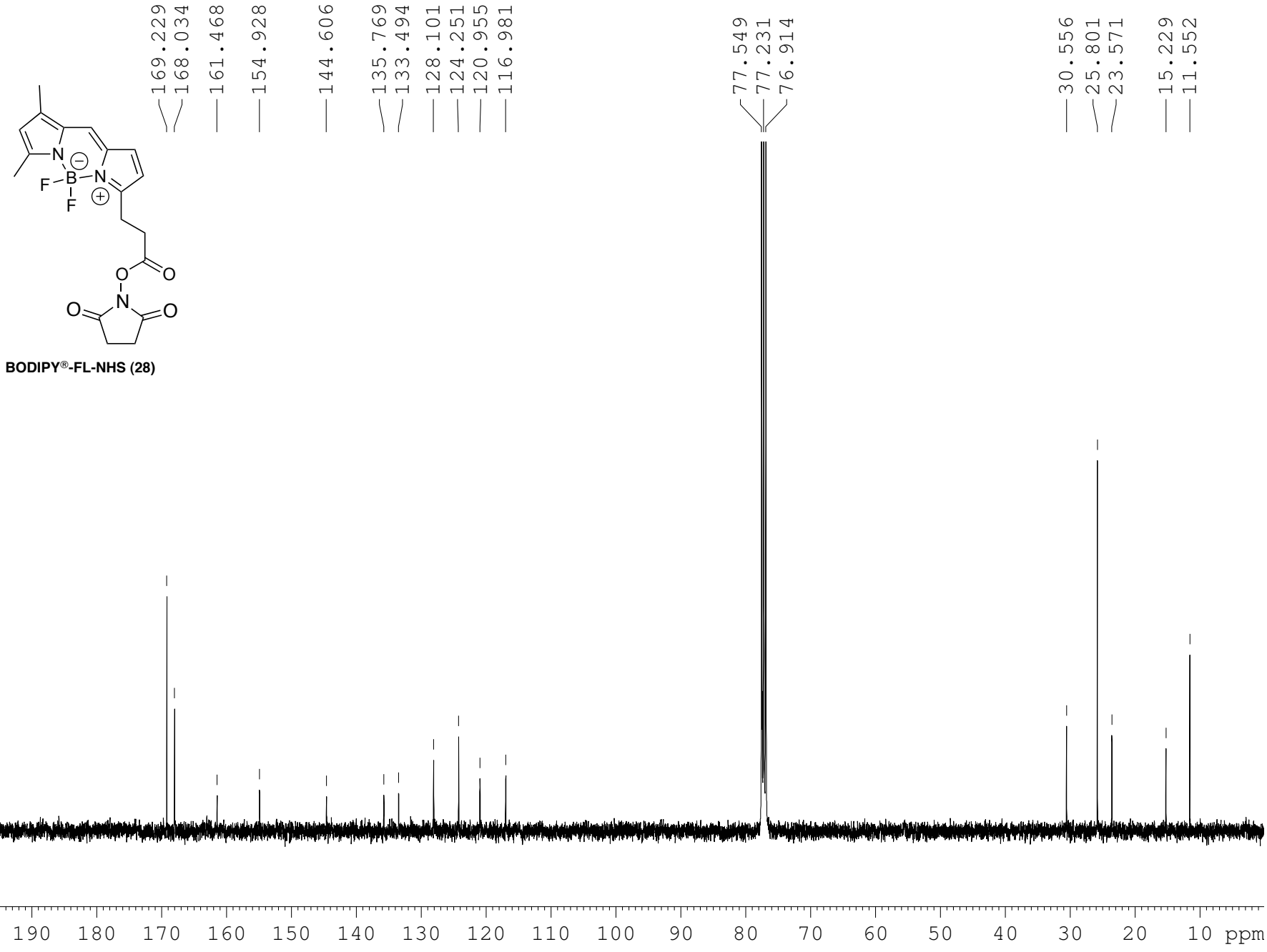
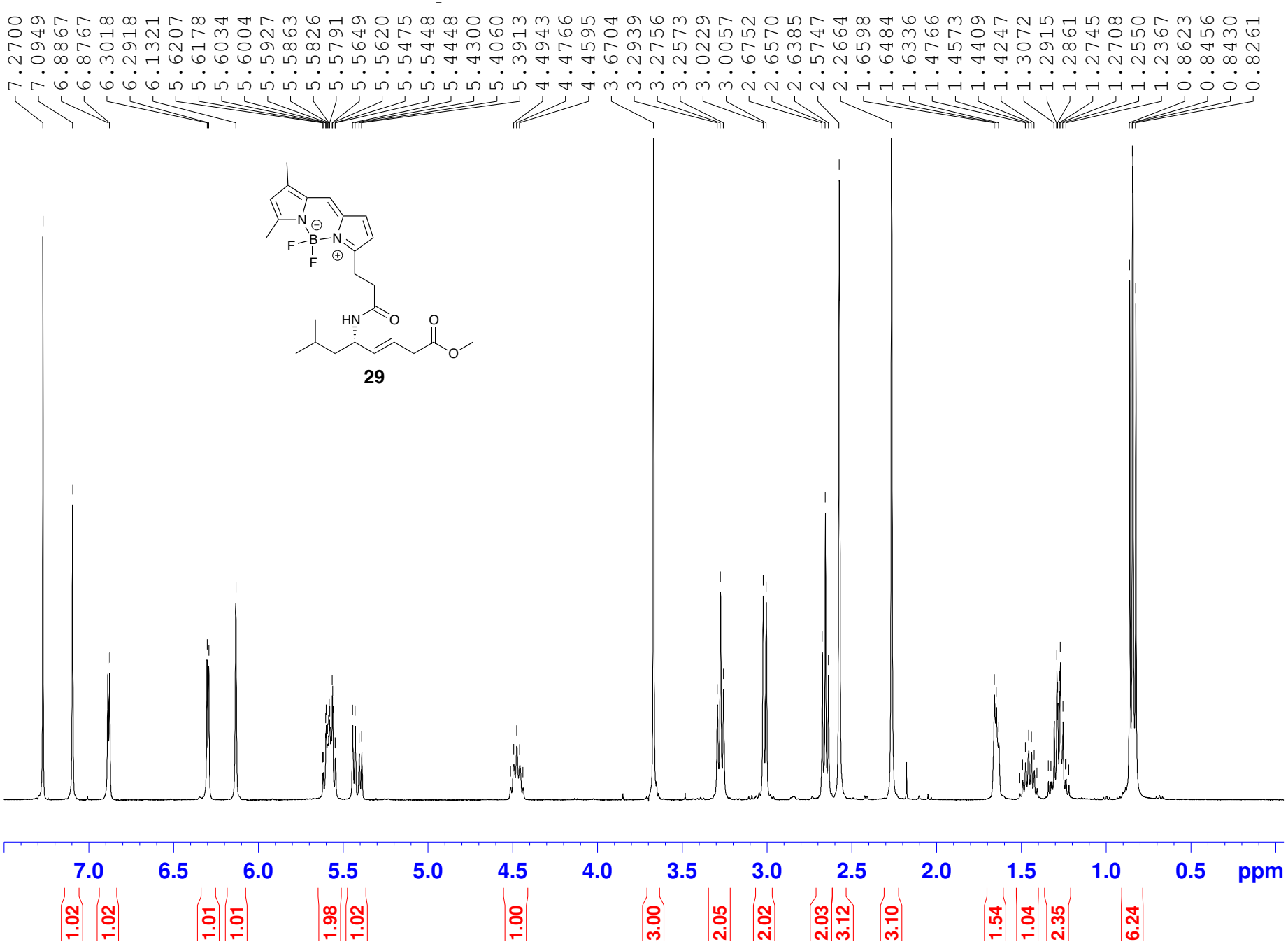
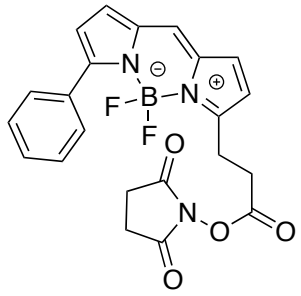


BODIPY®-FL-NHS (28)

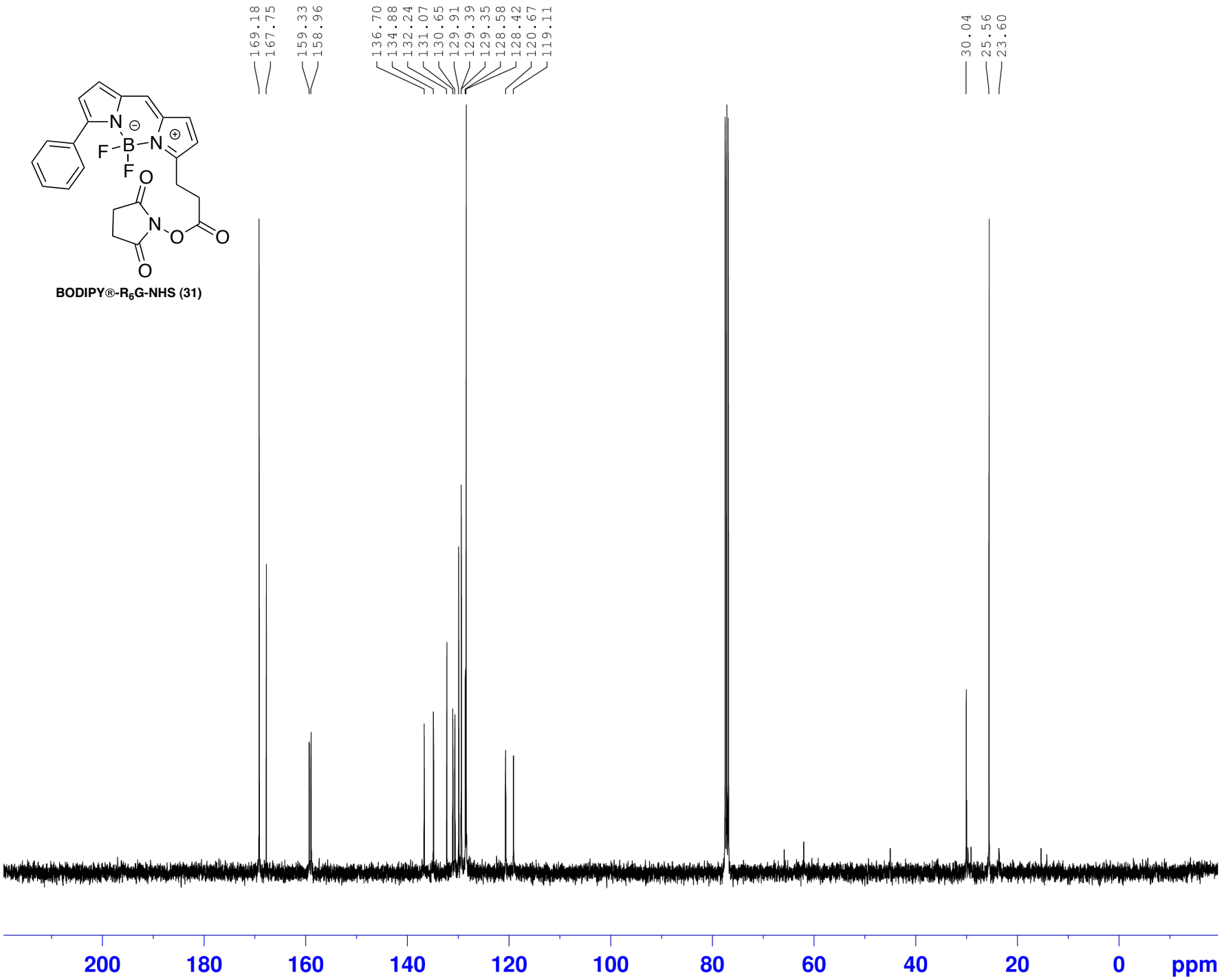


BODIPY®-FL-NHS (28)





BODIPY®-R_6G-NHS (31)



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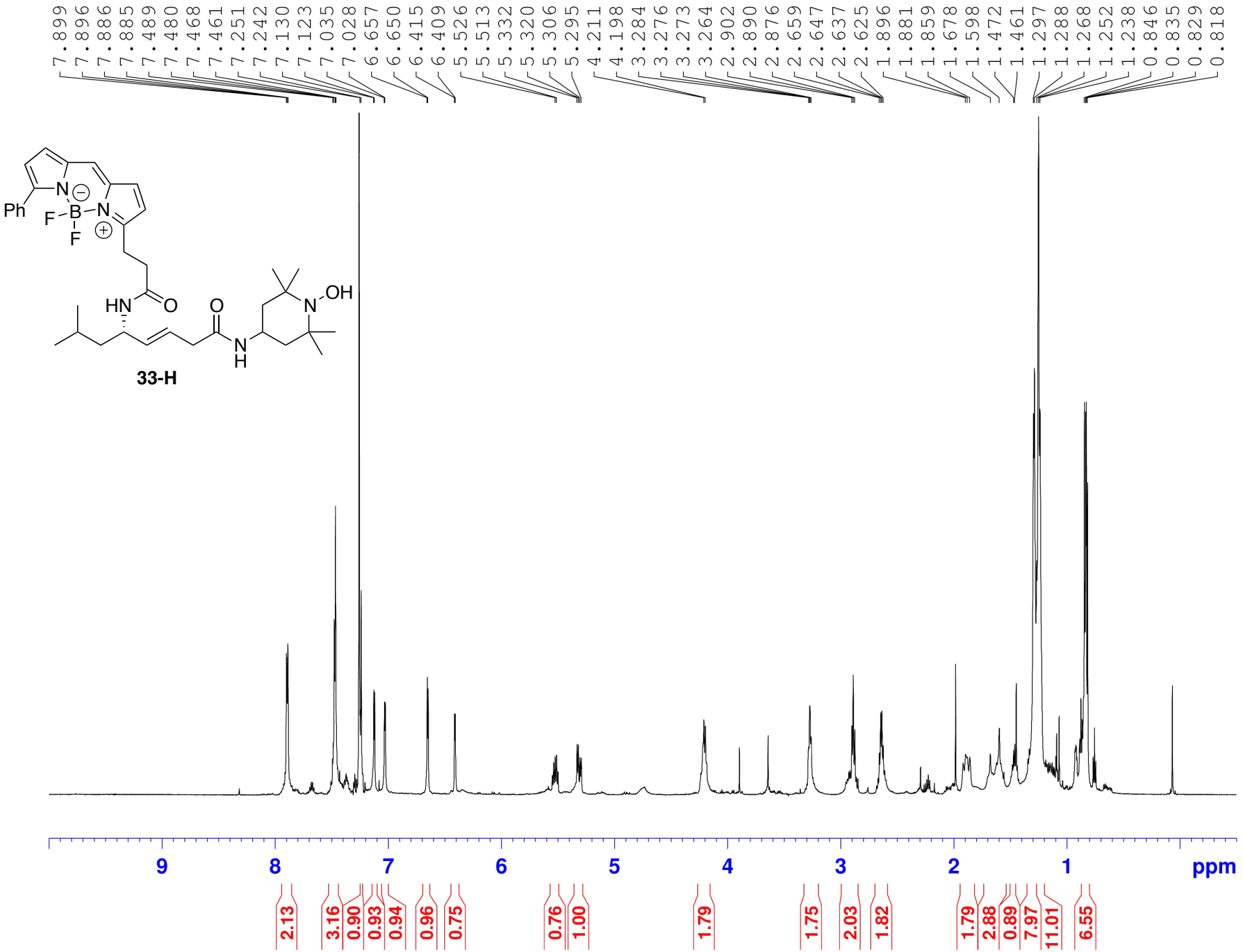

33-H