AMINO ACID DERIVED ENAMINONES: A STUDY IN RING FORMATION PROVIDING VALUABLE ASYMMETRIC SYNTHONS

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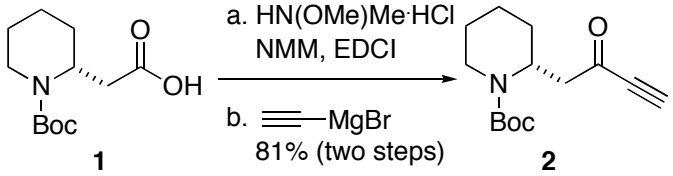
General experimental paragraph.

All commercially available reagents and solvents were used without further purification unless otherwise noted. Methylene chloride was dried by distillation from calcium hydride. Flash column chromatography was carried out on silica gel. TLC was conducted on silica gel 250 micron, F_{254} plates. ^{1}H NMR spectra were recorded on 400 MHz or 500 MHz NMR instruments. Chemical shifts are reported in ppm with the solvent as internal standard ($CDCl_3$: 7.28 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. ^{13}C NMR spectra were recorded on 100 MHz or 125 MHz NMR spectrometers with complete proton decoupling. Chemical shifts are reported in ppm with the solvent as internal standard ($CDCl_3$: 77.0 ppm). High-resolution mass spectrometry was performed by the University of Kansas Mass Spectroscopy Service Laboratory. All new compounds were determined to be >95% as determined by ^{1}H NMR spectroscopy.

Representative procedure for N-Boc ynone preparation.



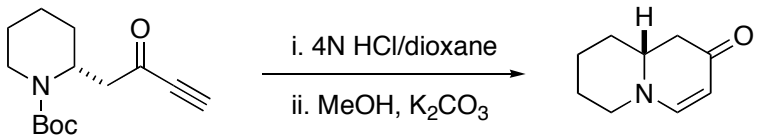
(*S*)-*tert*-Butyl 2-(2-(Methoxy(methyl)amino)-2-oxoethyl)piperidine-1-carboxylate (1a). (*R*)-2-(1-(*tert*-Butoxycarbonyl)piperidin-2-yl)acetic acid (**1**, 1.00 g, 4.0 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL) under argon atmosphere and cooled to –15 °C. To this solution was added *N*,*O*-dimethylhydroxylamine·HCl (0.42 g, 4.27 mmol) and *N*-

methylmorpholine (0.05 mL, 4.44 mmol) followed by EDCI (0.82 g, 4.27 mmol) in portions over 30 minutes then allowed to come to room temperature. After 2 hours the reaction was again cooled to 0 °C and quenched by the addition of an ice cold 10% HCl solution (25 mL) and allowed to stir at this temperature for 5 minutes. The reaction was diluted with water (50 mL) and extracted with CH_2Cl_2 (x3). The combined organic layers were washed with saturated $NaHCO_3$ (x1), dried over Na_2SO_4, filtered and concentrated. This crude material was purified via flash chromatography (3 hexane/1 EtOAc) to provide 1.14 g of the amide as an oily solid (96%): ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) □ 1.33-1.45 (bm, 1H) 1.43 (s, 9H), 1.44-1.52 (bm, 5H), 2.47-2.59 (m, 2H), 2.70 (bt, *J* = 13 Hz, 1H), 3.01 (s, 3H), 3.57 (s, 3H), 3.88 (bd, *J* = 13 Hz, 1H), 4.58 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) □ 19.3, 25.7, 28.8, 32.4, 33.1, 39.7, 48.0, 61.6, 79.7, 155.1, 172.6; IR (neat) 3564, 2933, 1690, 1447, 1255 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{14}H_{27}N_2O_4$: 287.1971, found 287.1957; $[\square]^{22}_D$ -6.0 (*c* = 1.0, $CHCl_3$).

(*R*)-*tert*-Butyl 2-(2-Oxobut-3-ynyl)piperidine-1-carboxylate (2). The Weinreb amide (**1a**, 0.72 g, 2.52 mmol) was dissolved in anhydrous THF (40 mL) under argon atmosphere and cooled to 0 °C. To this reaction vessel, was added dropwise, a 0.5 M solution of ethynyl magnesium bromide (12.6 mL, 6.3 mmol) in THF and allowed to come to room temperature. After 2 hours the reaction was judged complete by TLC (1 hexanes / 1 EtOAc) and again cooled to 0 °C. The reaction was quenched by the addition of an ice cold 10% HCl solution (15 mL) and allowed to stir at this temperature for 5 minutes. The reaction was diluted with water and extracted with EtOAc (x3). The combined organic layers were washed with saturated $NaHCO_3$ (x1), dried over Na_2SO_4,

filtered and concentrated. This crude material was purified via flash chromatography (8 hexane/1 EtOAc) to provide 0.53 g of a colorless oil (84%): ^{1}H NMR (500 MHz, $CDCl_3$) □ 1.41-1.51 (m, 2H), 1.44 (s, 9H), 1.59-1.76 (m, 4H), 2.77-2.84 (m, 2H), 2.87-2.90 (m, 1H), 3.29 (s, 1H), 4.01 (bs, 1H), 4.85 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) □ 18.8, 25.1, 28.3, 28.4, 39.1, 45.8, 47.4, 78.8, 79.8, 81.5, 154.5, 185.0; IR (neat) 3211, 2937, 2090, 1680, 1411, 1165 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[M+Na]^+$ $C_{14}H_{21}NO_3Na$: 274.1419, found 274.1419; $[\square]^{22}_D$ -38 (*c* = 0.65, $CHCl_3$).

Representative procedure for conversion of ynone to enaminone:



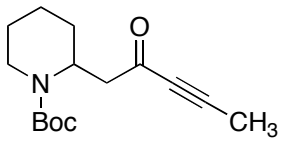
2 **3**

(*R*)-7,8,9,9a-Tetrahydro-1*H*-quinolizin-2(6*H*)-one (3). METHOD 1: Ynone (**2**, 72 mg, 0.48 mmol) was dissolved in a 4N HCl-dioxane solution (1.5 mL) and allowed to react for 15 minutes. After this time the dioxane and excess HCl were removed under reduced pressure and this residue placed under vacuum for 15 minutes. This material was then dissolved in MeOH (10 mL) and excess K_2CO_3 (a minimum of 4 equivalents) was added. The reaction was judged to be complete by TLC (10% MeOH/CH_2Cl_2) in 15 minutes. At this time CH_2Cl_2 was added, the reaction suction filtered, and the organic solvents concentrated. This residue was purified via flash chromatography (1-5% MeOH/CH_2Cl_2) to provide 37 mg (87%) of an off-white solid: Spectral data of the title compound was identical to that reported in the literature with the exception of optical rotation: $[\square]^{22}_D$ -135 (*c* = 0.925, $CHCl_3$). Comparison to the reported value, $[\square]^{22}_D$ -146 (*c*

= 0.885, $CHCl_3$), indicated an ee of 93%. This enantiomeric ratio was verified via chiral HPLC using a Baker Chiralcel OJ column. Conditions: isopropanol 2-15% in hexanes, 60 minutes, 0.5 mL/min, 30 °C. (-)-Enantiomer: R_t = 40.1 min; (+)-Enantiomer: R_t = 41.6 min. ee = 94%.[1]

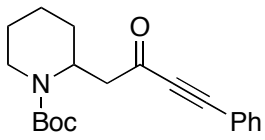
METHOD 2: The ynone **2** (28 mg, 0.11 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) under an argon atmosphere and cooled to –78 °C. A solution of TMS-I (0.03 mL, 0.11 mmol) in anhydrous CH_2Cl_2 (1 mL) was then added dropwise at this temperature. After 20 minutes at this temperature the reaction was allowed to warm to 0 °C and additional TMS-I (0.03-0.11 mmol) was added until all starting material was consumed (TLC, 3 hexanes / 1 EtOAc). After 20 minutes the reaction was judged complete and this mixture was concentrated under reduced pressure and placed under vacuum for 15 minutes. This residue was then dissolved in MeOH (5 mL) and excess K_2CO_3 was added. The reaction was monitored via TLC (10% MeOH/CH_2Cl_2) and judged complete after 30 minutes. At this time CH_2Cl_2 was added and the resultant slurry suction filtered the organic layer concentrated. This residue was purified via flash chromatography (5% MeOH/CH_2Cl_2) to provide 16 mg (95%) enaminone **3**. The enantiomeric excess using this method was not determined on this example.

Ynone characterization data (4-14):



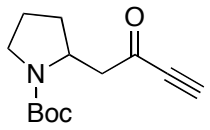
4

***tert*-Butyl 2-(2-Oxopent-3-ynyl)piperidine-1-carboxylate (4).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25-1.48 (m, 2H), 1.42 (s, 9H), 1.55-1.67 (m, 4H), 2.02 (s, 3H), 2.75-2.80 (m, 3H), 4.00 (bs, 1H), 4.81 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.1, 18.8, 25.2, 28.3, 39.2, 45.7, 47.6, 79.6, 80.3, 90.5, 154.6, 185.7; IR (neat) 2974, 2936, 2862, 2218, 1670, 1410, 1157 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{15}H_{24}NO_3$: 266.1756, found 266.1750.



5

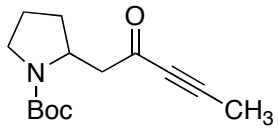
***tert*-Butyl 2-(2-Oxo-4-phenylbut-3-ynyl)piperidine-1-carboxylate (5).** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39-1.55 (m, 2H), 1.44 (s, 9H), 1.64-1.73 (m, 4H), 2.85 (dd, *J* = 14 Hz, 9 Hz, 2H), 2.97 (dd, *J* = 14 Hz, 7 Hz, 1H), 4.06 (bs, 1H), 4.89 (bs, 1H), 7.23-7.41 (m, 2H), 7.44-7.47 (m, 1H), 7.58 (d, *J* = 7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7, 25.2, 28.3, 39.1, 45.8, 47.8, 53.4, 79.6, 88.0, 91.0, 119.8, 128.5, 130.6, 133.0, 154.5, 185.6; IR (neat) 3410, 2359, 2202, 1654 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{20}H_{26}NO_3$: 328.1913, found 328.1907.



6

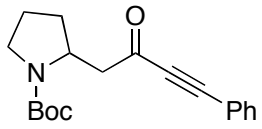
***tert*-Butyl 2-(2-Oxobut-3-ynyl)pyrrolidine-1-carboxylate (6).** ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 1.38 (s, 9H), 1.60-1.67 (bs, 1H), 1.72-1.80 (m, 2H), 2,00-2.09 (m, 1H),

2.52-2.59 (m, 1H), 3.19 (s, 1H), 3.22 (bm, 3H), 4.13-4.22 (bm, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 23.6, 28.4, 31.5, 46.8, 50.0, 53.4, 78.0, 79.5, 81.7, 154.5, 183.0; IR (neat) 3209, 2977, 2881, 2092, 1707, 1414, 1179 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[M+H]^+$ $C_{13}H_{20}NO_3$: 238.1443, found 238.1440.



7

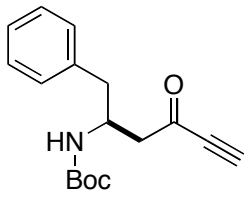
***tert*-Butyl 2-(2-Oxopent-3-ynyl)pyrrolidine-1-carboxylate (7).** ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) 1.43 (s, 9H), 1.64 (bs, 1H), 1.78-1.99 (m, 2H), 1.99 (s, 3H), 2.00-2.08 (m, 1H), 2.45-2.53 (m, 1H) 2.82-3.10 (bs, 1H), 3.28-3.40 (m, 2H), 4.20 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 3.8, 23.5, 28.4, 31.0, 46.6, 50.1, 53.6, 80.0, 80.5, 91.0, 154.5, 186.6; IR (neat) 2975, 2939, 2216, 1670, 1397, 1163 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{14}H_{22}NO_3$: 252.1600, found 252.1591.



8

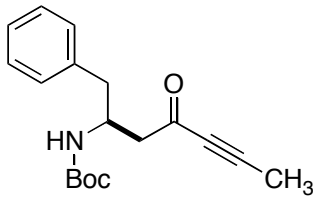
***tert*-Butyl 2-(2-Oxo-4-phenylbut-3-ynyl)pyrrolidine-1-carboxylate (8).** ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) 1.40 (s, 9H), 1.60-1.66 (bs, 1H) 1.66-1.75 (m, 2H), 1.96-2.02 (m, 1H), 2.55-2.61 (m, 1H), 3.00-3.12 (bs, 1H), 3.19-3.29 (bs, 2H), 4.12-4.18 (m, 1H), 7.18-7.21 (m, 2H), 7.25-7.28 (m, 1H), 7.38-7.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 23.5, 28.6, 31.4, 36.7, 50.4, 54.0, 56.8, 80.0, 88.2, 91.3, 120.1, 128.5, 130.6, 133.0, 154.4,

186.2; IR (neat) 2974, 2878, 2203, 1695, 1395, 1168 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{19}H_{24}NO_3$: 314.1756, found 314.1729.



9

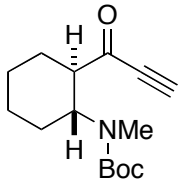
(*S*)-*tert*-Butyl 4-Oxo-1-phenylhex-5-yn-2-ylcarbamate (9). ^1H NMR (400 MHz, $CDCl_3$) □ 1.41 (s, 9H), 2.76-2.97 (m, 3H), 2.77-2.84 (m, 1H), 3.30 (s, 1H), 4.23-4.31 (m, 1H), 4.89 (d, *J* = 8 Hz, 1H), 7.18-7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 28.7, 40.6, 48.8, 49.0, 79.8, 79.9, 81.7, 127.1, 129.0, 129.8, 137.9, 155.5, 185.9; IR (neat) 3352, 3265, 2095, 1685 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[M+H]^+$ $C_{17}H_{22}NO_3$: 288.1600, found 288.1596; $[\square]^{22}_D$ -7.0 (*c* = 0.55, $CHCl_3$)



10

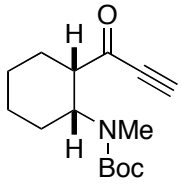
(*S*)-*tert*-Butyl 4-Oxo-1-phenylhept-5-yn-2-ylcarbamate (10). ^1H NMR (400 MHz, $CDCl_3$) □ 1.38 (s, 9H), 2.00 (s, 3H), 2.67 (d, *J* = 6 Hz, 2H), 2.75-2.92 (m, 2H), 4.23 (bs, 1H), 4.97 (d, *J* = 8 Hz, 1H), 7.08-7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 4.5, 28.7, 40.7, 48.7, 49.1, 79.6, 80.6, 91.5, 127.0, 128.9, 129.8, 138.2, 155.5, 186.6; IR (neat)

3350, 2975, 2929, 2219, 1699, 1164 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[M+H]^+$ $C_{18}H_{24}NO_3$: 302.1756, found 302.1761; $[\alpha]^{22}_D$ -2.0 (*c* = 0.65, $CHCl_3$).



+/- **11**

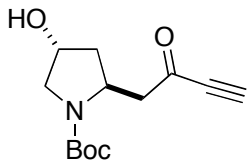
***tert*-Butyl Methyl((*trans*)-2-propioloylcyclohexyl)carbamate (11).** ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.15-1.29 (m, 2H), 1.32-1.73 (m, 2H), 1.46 (s, 9H), 1.79-1.89 (m, 3H), 1.93-1.98 (m, 1H), 2.75 (bs, 3H), 2.77-2.88 (m, 1H), 3.25 (s, 1H), 4.00-4.23 (bm, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C, rotomeric) δ 24.5, 25.1, 28.3, 28.8, 29.7, 55.3, 55.9, 56.8, 79.5, 80.2, 80.8, 155.1, 188.8; IR (neat) 3211, 2933, 2860, 2089, 1690, 1151 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{15}H_{24}NO_3$: 266.1756, found 266.1757.



+/- **12**

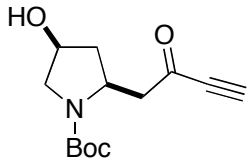
***tert*-Butyl Methyl((*cis*)-2-propioloylcyclohexyl)carbamate (12).** ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.15-1.8 (m, 5H), 1.46 (s, 9H), 1.87-1.90 (m, 1H), 2.04-2.09 (m, 1H), 2.14-2.18 (m, 1H), 2.79 (s, 3H), 3.18 (s, 1H), 3.44 (bs, 1H), 3.98 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C, rotomeric) δ 21.3, 25.7, 26.2, 27.7, 28.2, 29.5, 52.2, 56.1, 77.3, 79.5,

82.2, 155.6, 188.6; IR (neat) 3400, 2929, 2858, 2087, 1690, 1148 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{15}H_{24}NO_3$: 266.1756, found 266.1749.



13

(2*S*,4*R*)-*tert*-Butyl 4-Hydroxy-2-(2-oxobut-3-ynyl)pyrrolidine-1-carboxylate (13). ^1H NMR (400 MHz, $CDCl_3$, 50 °C) □ 1.42 (s, 9H), 1.76-1.82 (bm, 1H), 2.12-2.17 (bm, 1H), 2.66 (dd, *J* = 16 Hz, 9 Hz, 1H), 2.90 (bs, 1H), 3.20 (bs, 1H), 3.31 (s, 1H), 3.33-3.42 (m, 2H), 4.27-4.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 28.8, 40.7, 50.5, 52.6, 55.0, 69.4, 79.6, 80.4, 82.0, 155.0, 185.4; IR (neat) 3400, 3250, 2990, 2900, 2100, 1700, 1400 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{13}H_{20}NO_4$: 254.1392, found 254.1389; $[\square]^{22}_D$ -55 (*c* = 0.89, $CHCl_3$).

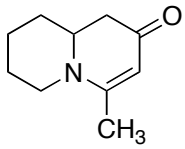


14

(2*S*,4*S*)-*tert*-Butyl 4-Hydroxy-2-(2-oxobut-3-ynyl)pyrrolidine-1-carboxylate (14). ^1H NMR (400 MHz, $CDCl_3$, 50 °C) □ 1.47 (s, 9H), 1.85 (bd, *J* = 14 Hz, 1H), 2.03 (s, 1H), 2.26 (ddd, *J* = 14 Hz, 9 Hz, 5Hz, 1H), 3.08 (dd, *J* = 16 Hz, 9 Hz, 1H), 3.23 (s, 1H), 3.38 (bd, *J* = 12 Hz, 2H), 3.59 (dd, *J* = 12 Hz, 5 Hz, 1H), 4.27-4.34 (m, 1H), 4.43-4.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 28.9, 39.7, 51.1, 53.1, 55.4, 70.8, 78.8, 80.4, 82.2,

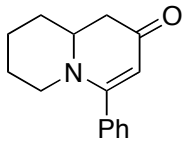
154.6, 186.0; IR (neat) 3400, 2975, 2090, 1680, 1400 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{13}H_{20}NO_4$: 254.1392, found 254.1393; $[\alpha]^{22}_D$ -4 (*c* = 0.6, $CHCl_3$).

Enaminone characterization data (15-25):



15

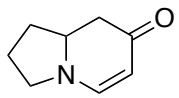
4-Methyl-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-one (15). ^1H NMR (400 MHz, $CDCl_3$) δ 1.37-1.86 (m, 6H), 1.95 (s, 3H), 2.25 (dd, *J* =10.6 Hz, 16.5 Hz, 1H), 2.48 (dd, *J* = 16.5 Hz, 5.7 Hz, 1H), 2.76-2.82 (m, 1H), 3.28-3.38 (m, 1H), 3.74-3.78 (m, 1H), 4.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 24.1, 26.1, 31.8, 43.2, 48.5, 59.0, 102.1, 163.4, 191.8; IR (neat) 3444, 2934, 2855, 1626, 1557 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[M+H]^+$ $C_{10}H_{16}NO$: 166.1232, found 166.1234.



16

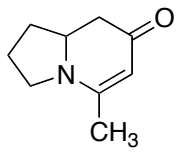
4-Phenyl-7,8,9,9a-tetrahydro-1*H*-quinolizin-2(6*H*)-one (16). ^1H NMR (500 MHz, $CDCl_3$) δ 1.46-1.50 (m, 2H), 1.56-1.60 (m, 1H), 1.75-1.80 (m, 2H), 1.88-1.98 (m, 1H), 2.47 (dd, *J* = 16 Hz, 11 Hz, 1H), 2.60-2.66 (m, 2H), 3.50-3.58 (m, 2H), 5.09 (s, 1H), 7.28-7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 25.9, 31.3, 42.6, 50.3, 58.6,

103.3, 127.0, 128.5, 128.9, 136.7, 165.9, 191.5; IR (neat) 2932, 2853, 1640, 1541 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[M+H]^+$ $C_{15}H_{18}NO$: 228.1388, found 228.1400.



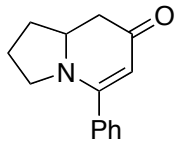
17

2,3,8,8a-Tetrahydroindolizin-7(1*H*)-one (17). ^1H NMR (400 MHz, $CDCl_3$) 1.61-1.70 (m, 1H), 1.86-1.95 (m, 1H), 2.05-2.10 (m, 1H), 2.21-2.44 (m, 3H), 3.42-3.54 (m, 2H), 3.66-3.76 (m, 1H), 4.91 (d, *J* = 7 Hz, 1H), 7.19 (d, *J* = 7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 24.8, 33.2, 41.9, 49.7, 58.5, 97.5, 150.4, 192.5; IR (neat) 3423, 297, 2879, 1617, 1559 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[M+H]^+$ $C_8H_{12}NO$: 138.1901, found 138.0911.



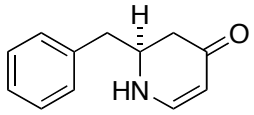
18

5-Methyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (18). ^1H NMR (400 MHz, $CDCl_3$) 1.61-1.70 (m, 1H), 1.82-1.95 (m, 1H), 2.01 (s, 3H), 2.05-2.10 (m, 1H), 2.21-2.42 (m, 3H), 3.42-3.47 (m, 1H), 3.52-3.57 (m, 1H), 3.70-3.80 (m, 1H), 4.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.9, 24.0, 33.1, 41.6, 47.3, 59.3, 98.4, 161.2, 191.7; IR (neat) 3397, 2918, 1597, 1531 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_9H_{14}NO$: 152.1075, found 152.1093.



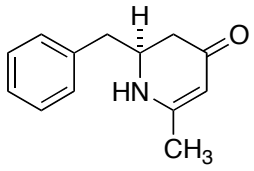
19

5-Phenyl-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (19). ^{1}H NMR (400 MHz, $CDCl_3$) □ 1.75-1.85 (m, 1H), 1.85-2.00 (m, 1H), 2.01-2.09 (m, 1H), 2.30-2.40 (m, 1H), 2.41-2.54 (m, 2H), 3.27-3.31 (m, 1H), 3.48-3.52 (m, 1H), 4.04-4.07 (m, 1H), 5.10, (s, 1H), 7.38-7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 24.9, 32.4, 41.9, 49.7, 59.3, 100.4, 128.0, 128.9, 130.2, 136.6, 163.3, 192.4; IR (neat) 3427, 2964, 2877, 1611, 1518, 1471 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{14}H_{16}NO$: 214.1232, found 214.1227.



20

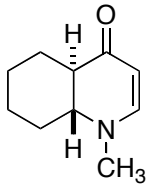
(*S*)-2-Benzyl-2,3-dihydropyridin-4(1*H*)-one (20). Spectral data was identical to the reported values: $[□]^{22}_{D}$ –150, (*c* = 0.65, $CHCl_3$); literature value = : $[□]^{22}_{D}$ –151, (*c* = 0.225, $CHCl_3$).[2]



21

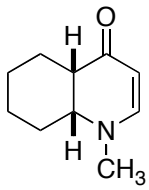
(*S*)-2-Benzyl-6-methyl-2,3-dihydropyridin-4(1*H*)-one (21). ^{1}H NMR (400 MHz, $CDCl_3$) □ 1.92 (s, 3H), 2.36 (dd, *J* = 16 Hz, 11.5 Hz, 1H), 2.48 (dd, *J* = 16 Hz, 5 Hz, 1H), 2.84-2.93 (m, 2H), 3.81-3.85 (m, 1H), 4.82 (s, 1H), 4.98 (s, 1H), 7.19-7.38 (m, 5H); ^{13}C

NMR (100 MHz, $CDCl_3$) □ 21.6, 40.8, 41.7, 54.7, 100.1, 127.5, 129.4, 129.6, 137.3, 161.2, 191.6; IR (neat) 3244, 1608, 1597, 1531 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[M+H]^+$ $C_{13}H_{16}NO$: 202.1232, found 202.1234; $[\square]^{22}_D$ -190 (*c* = 1.6, $CHCl_3$).



22

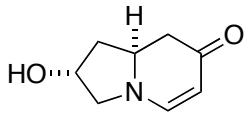
(*trans*)-1-Methyl-4a,5,6,7,8,8a-hexahydroquinolin-4(1*H*)-one (22). ^1H NMR (500 MHz, $CDCl_3$) □ 0.95-1.04 (m, 1H), 1.10-1.28 (m, 2H), 1.30-1.39 (m, 1H), 1.70-1.85 (m, 2H), 2.00-2.08 (m, 1H), 2.13-2.15 (m, 1H), 2.32-2.35 (m, 1H), 2.89 (s, 3H), 2.92-3.06 (m, 1H) 4.96 (d, *J* = 7 Hz, 1H), 6.98 (d, *J* = 7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 23.5, 23.8, 24.0, 29.2, 38.5, 47.4, 61.1, 97.3, 154.2, 193.0; IR (neat) 3417, 2924, 2856, 1634, 1590, 1191 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{10}H_{16}NO$: 166.1232, found 166.1235.



23

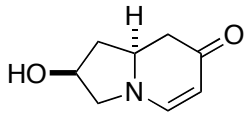
(*cis*)-1-Methyl-4a,5,6,7,8,8a-hexahydroquinolin-4(1*H*)-one (23). ^1H NMR (500 MHz, $CDCl_3$) □ 1.23-1.32 (m, 2H), 1.37-1.42 (m, 2H), 1.50-1.57 (m, 1H), 1.57-1.66 (m, 1H), 1.77-1.87 (m, 1H), 2.10-2.18 (m, 1H), 2.56-2.64 (m, 1H), 2.99 (s, 3H), 3.30-3.38 (m, 1H), 4.87 (d, *J* = 7 Hz, 1H), 6.83 (d, *J* = 7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 22.8,

23.8, 24.3, 29.0, 30.6, 45.0, 60.1, 96.7, 153.6, 192.0; IR (neat) 2930, 2855, 1631, 1590, 1207 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_{10}H_{16}NO$: 166.1232, found 166.1227.



24

(2*R*,8a*S*)-2-Hydroxy-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (24). ^1H NMR (400 MHz, $CDCl_3$) □ 1.84 (ddd, *J* = 15.5 Hz, 11.3 Hz, 4.2 Hz, 1H), 2.03 (dd, *J* = 12.9 Hz, 5.6 Hz, 1H), 2.36 (dd, *J* = 16.3 Hz, 16.3 Hz), 1H), 2.47 (dd, *J* = 16.1 Hz, 5.1 Hz, 1H), 3.00 (bs, 1H), 3.54 (d, *J* = 11.9 Hz, 1H), 3.75 (dd, *J* = 11.9 Hz, 4.4 Hz, 1H), 4.10-4.19 (m, 1H), 4.65 (t, *J* = 4.1 Hz, 1H), 5.00 (d, *J* = 7 Hz, 1H), 7.24 (d, *J* = 7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 41.3, 42.1, 56.4, 58.6, 70.3, 97.8, 151.2, 192.7; IR (neat) 3400, 1580 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_8H_{12}NO_2$: 154.0868, found 154.0853; [□]$^{22}_D$ -490 (*c* = 0.45, $CHCl_3$).

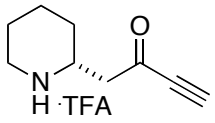


25

(2*R*,8a*R*)-2-Hydroxy-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (*ent*-25). ^1H NMR (400 MHz, D_3CCOCD_3) □ 1.74 (ddd, *J* = 15.5 Hz, 9 Hz, 6.5 Hz, 1H), 2.05-2.08 (m, 1H), 2.22 (dd, *J* = 15.8 Hz, 5 Hz, 1H), 2.38 (dd, *J* = 15.8 Hz, 15.8 Hz, 1H), 2.51 (ddd, *J* = 6.4 Hz, 12.6 Hz, 6.4 Hz, 1H), 3.36 (dd, *J* = 10.7 Hz, 5.5 Hz, 1H), 3.69 (dd, *J* = 10.7 Hz, 6.5 Hz, 1H), 3.74-3.81 (m, 1H), 4.50-4.56 (m, 1H), 4.75 (d, *J* = 7.4 Hz, 1H), 7.30 (d *J* = 7.4 Hz; ^{13}C NMR (100 MHz, D_3CCOCD_3) □ 41.4, 42.2, 57.0, 57.2, 70.0, 97.2, 150.1, 190.6; IR

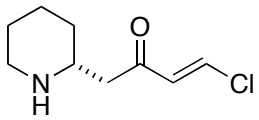
(neat) 3320, 2871, 1614, 1560 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[M+H]^+$ $C_8H_{12}NO_2$: 154.0868, found 154.0862; $[\alpha]^{22}_D$ +780 (*c* = 0.90, $CHCl_3$).

Additional Compounds (26, 29, 30):



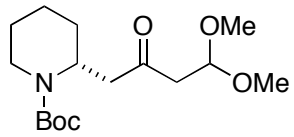
26

(*R*)-1-(Piperidin-2-yl)but-3-yn-2-one 2,2,2-Trifluoroacetic Acid (26). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.51-1.62 (m, 1H), 1.70 (dd, *J* = 24 Hz, 12 Hz, 1H), 1.77-1.99 (m, 4H), 3.00 (dd, *J* = 18 Hz, 6 Hz, 2H), 2.25 (bd, *J* = 18 Hz, 1H), 3.38 (s, 1H), 3.45-3.57 (bm, 2H), 9.22 (bd, *J* = 70 Hz, 2H-exchangable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 22.6, 28.7, 45.5, 48.1, 52.8, 81.0, 81.3, 183.2; IR (neat) 2958, 2097, 1678, 1203, 1136 cm^{-1}; HRMS (ES+) *m/z* calc'd for $[M+H]^+$ $C_9H_{14}NO$: 152.1075, found 152.1060.



29

(*R*,*E*)-4-Chloro-1-(piperidin-2-yl)but-3-en-2-one (29). ^{1}H NMR (400 MHz, CD_3OD) δ 1.55-1.80 (m, 3H), 1.81-1.99 (m, 3H), 2.96-3.17 (m, 3H), 3.30-3.41 (m, 2H), 3.50-3.64 (m, 1H), 6.66 (d, *J* = 13.7 Hz, 1H), 7.70 (d, *J* = 13.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 22.0, 22.3, 42.9, 45.0, 52.9, 132.4, 139.2, 194.8; IR (neat) 3400, 2951, 1674, 1585 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $[M+H]^+$ $C_9H_{15}NOCl$: 188.0842, found 188.0827; $[\alpha]^{22}_D$ +22 (*c* = 0.32, $CHCl_3$).

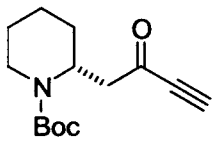


30

(*R*)-*tert*-Butyl 2-(4,4-Dimethoxy-2-oxobutyl)piperidine-1-carboxylate (30). ^{1}H NMR (400 MHz, $CDCl_3$) □ 1.38-1.68 (m, 6H), 1.46 (s, 9H), 2.63 (dd, *J* = 15 Hz, 6.3 Hz, 1H), 2.72-2.79 (m, 4H), 3.36 (s, 6H), 3.99 (bs, 1H), 4.73 (bs, 1H), 4.77 (t, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) □ 19.3, 25.7, 28.6, 28.8, 44.8, 47.0, 47.3, 54.2, 54.4, 80.0, 102.1, 155.2, 206.2; IR (neat) 3400, 2089, 1643 cm^{-1}; HRMS (ES+) *m*/*z* calc'd for $[M+H]^+$ $C_{16}H_{30}NO_5$: 316.2124, found 316.2118; $[\square]^{22}_D$ +9.0 (*c* = 0.50, $CHCl_3$).

References:

1. Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807-5809.
2. Comins, D. L.; Zhang, Y.; Joseph, S. P. *Org. Lett.* **1999**, *1*, 657-659.



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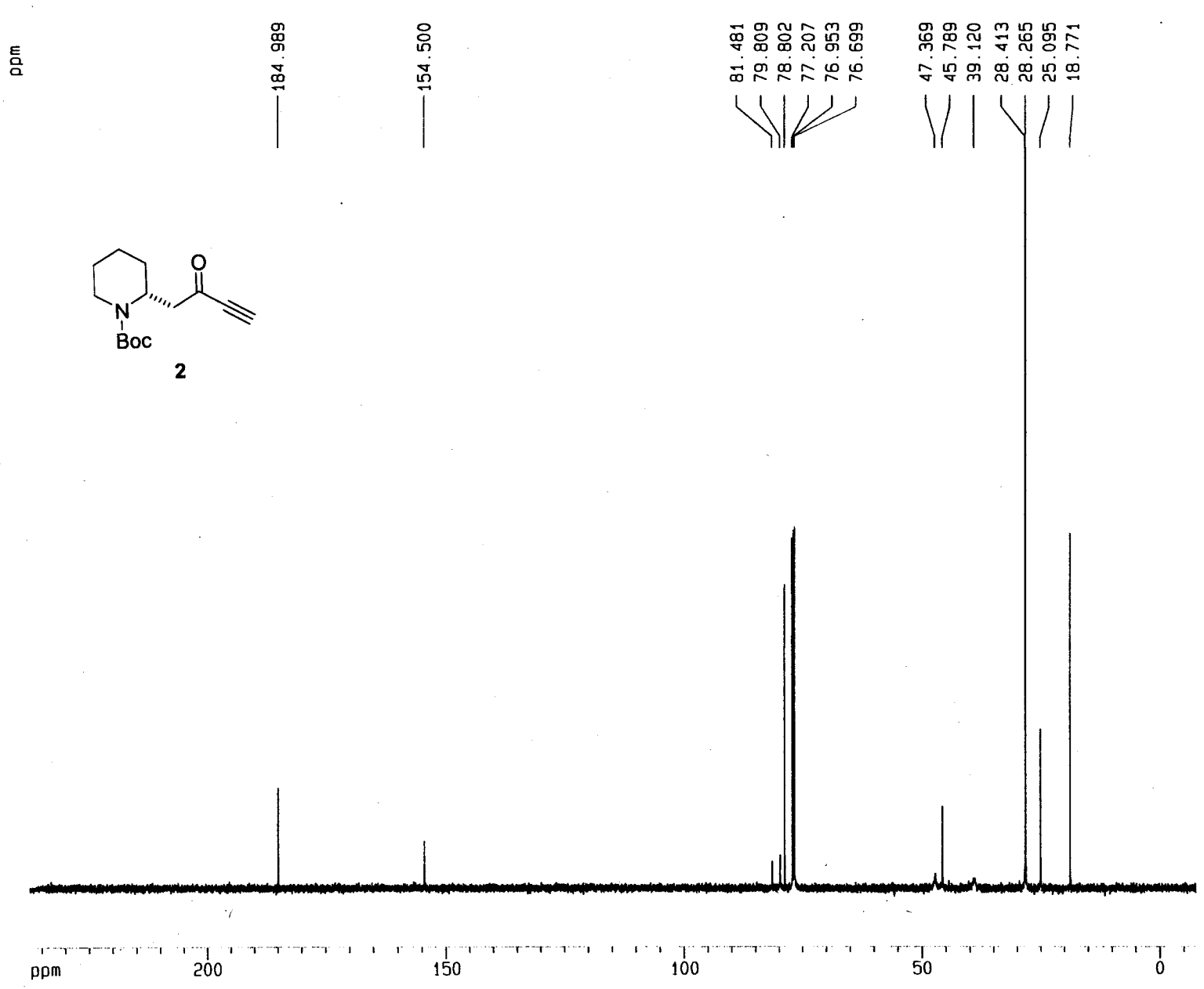


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F2 - Processing parameters
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F2                     -948.11 Hz
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HZCM                1572.32703 Hz/cm
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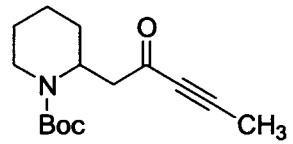

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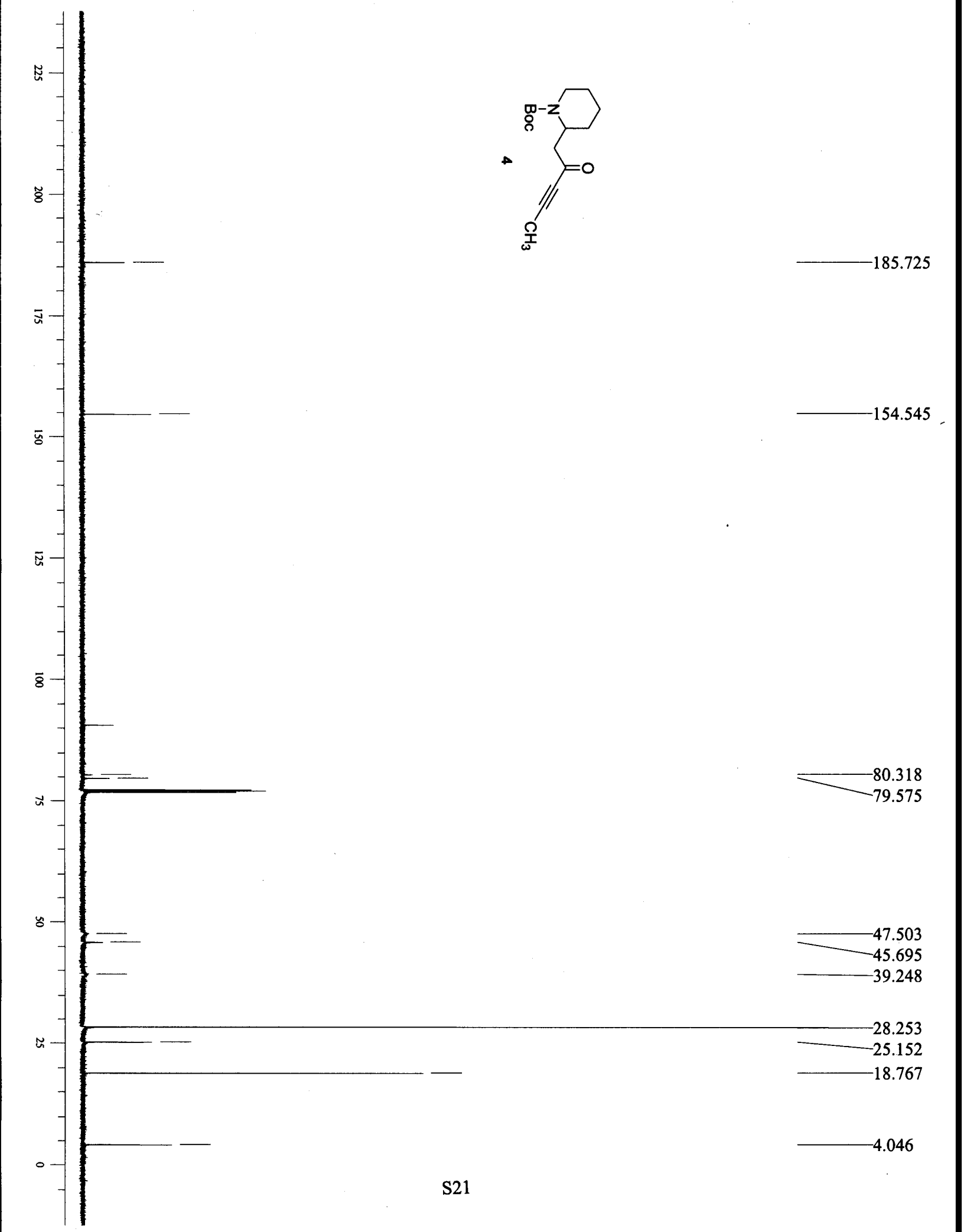
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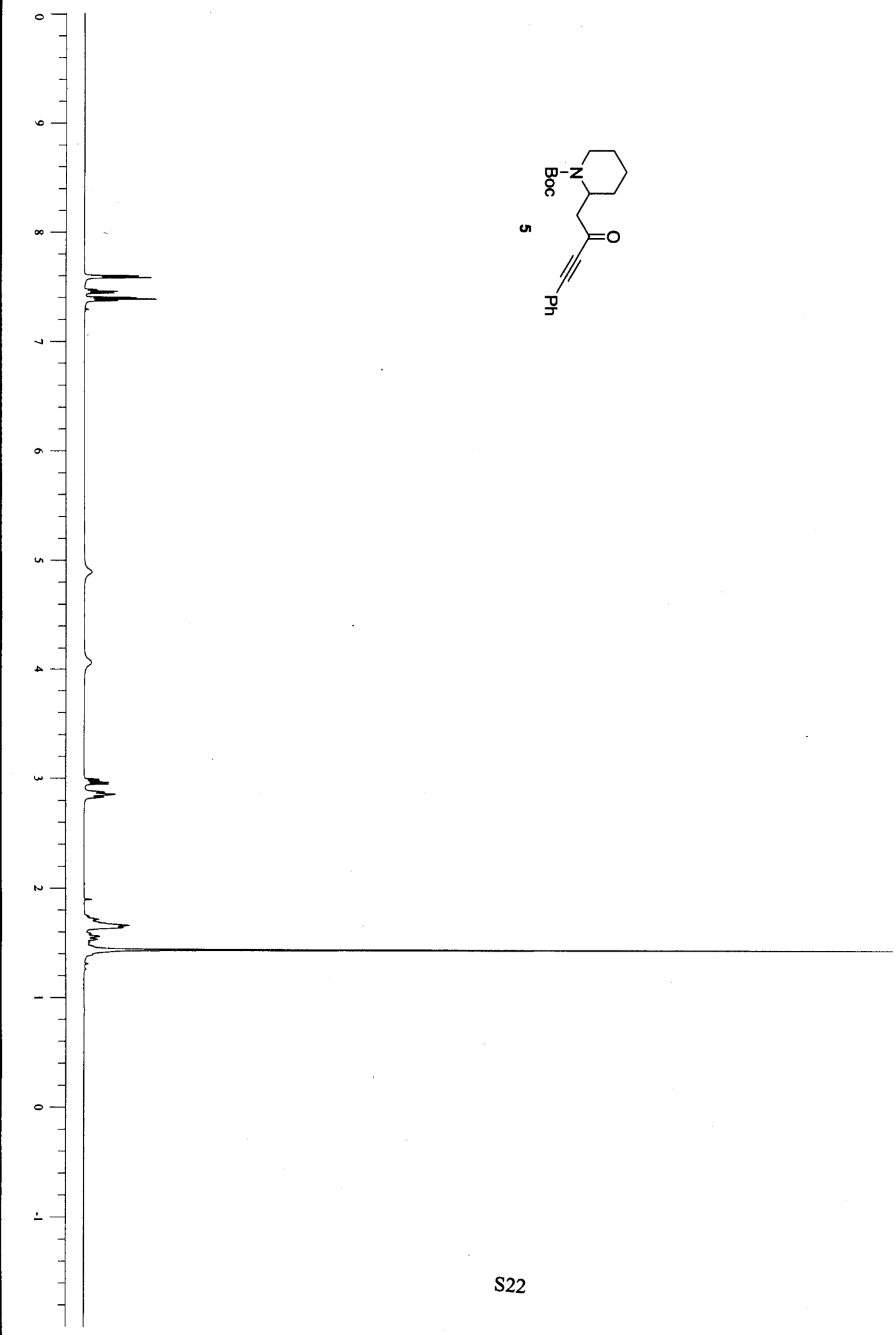
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Boc
O
Ph
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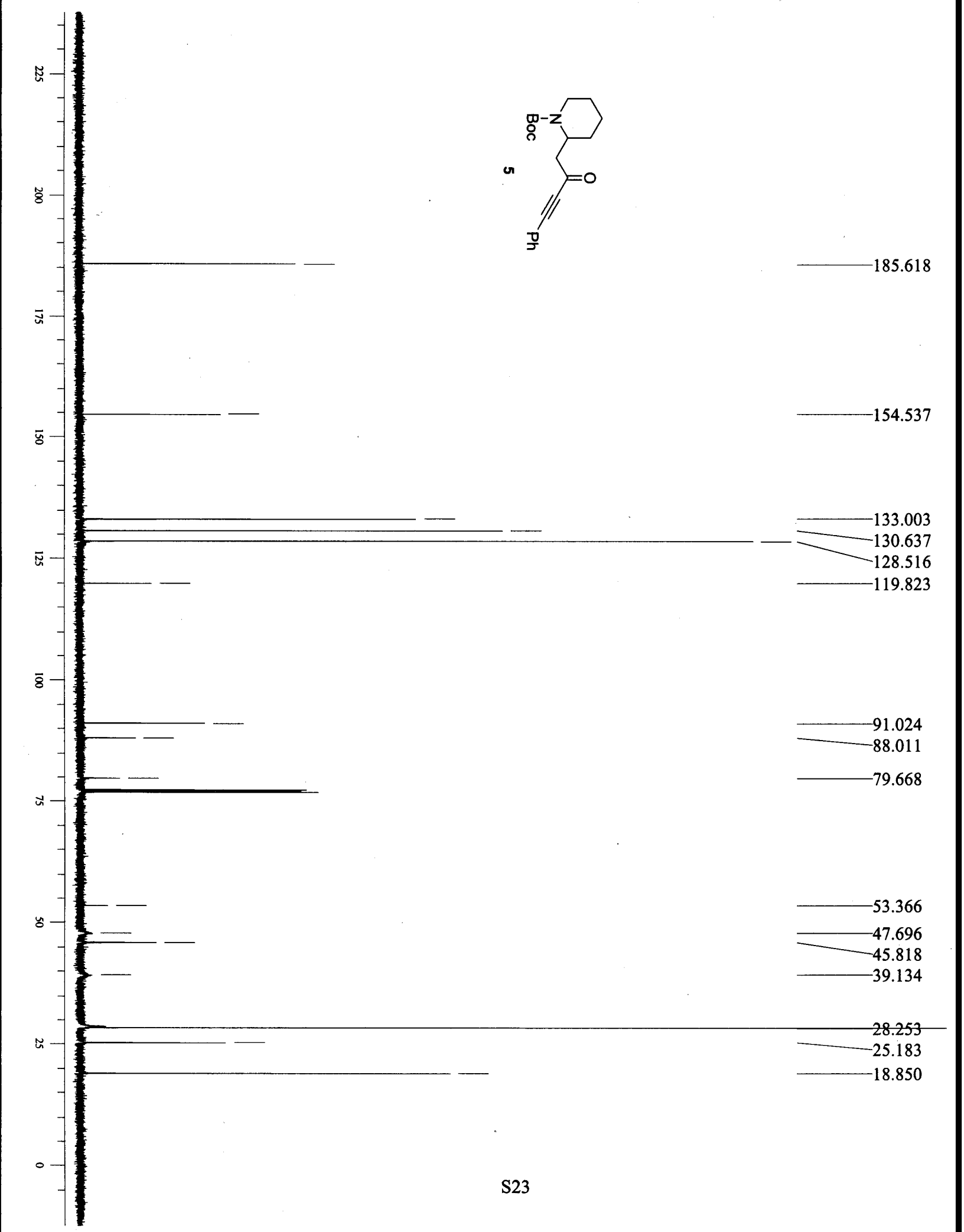
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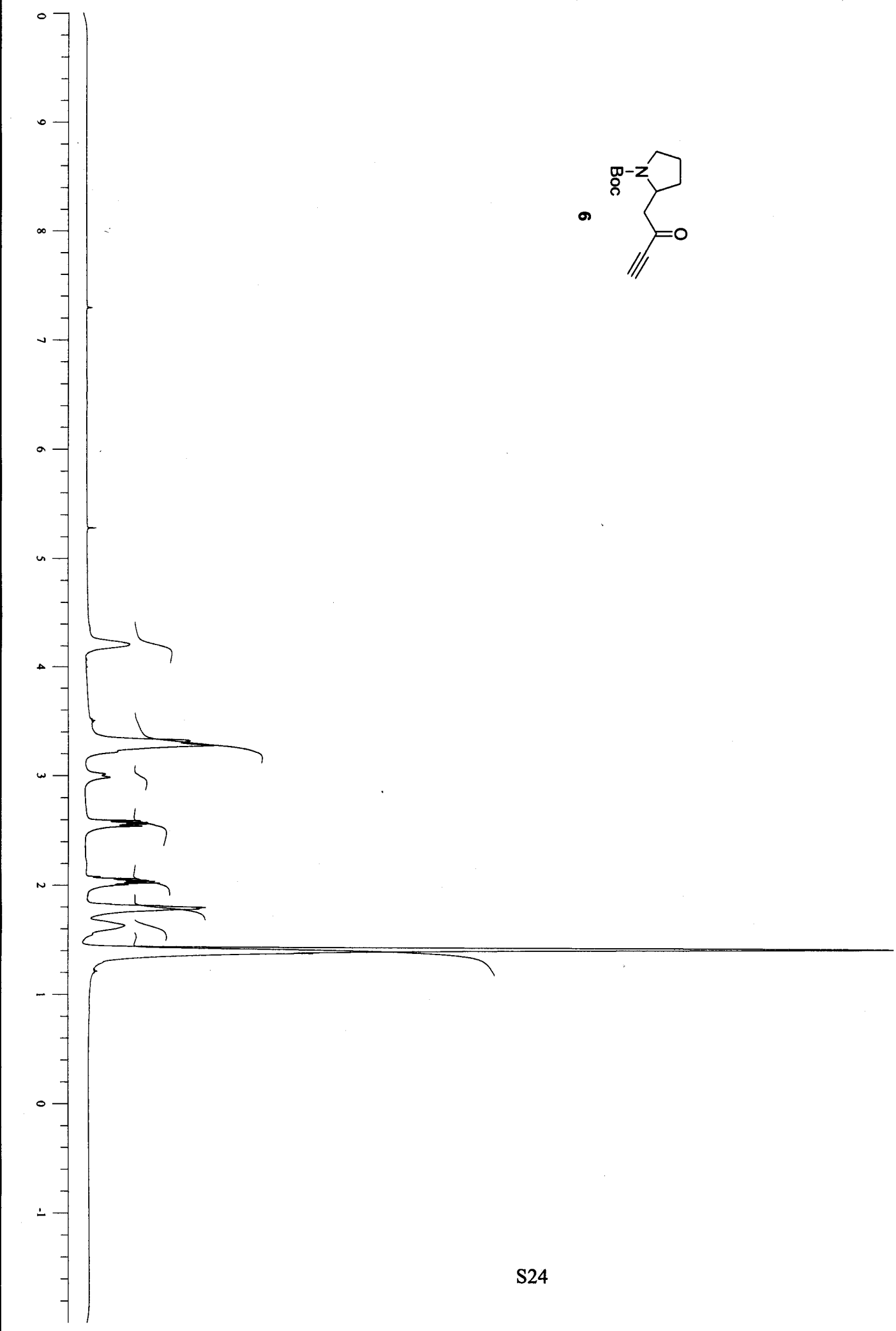
Boc
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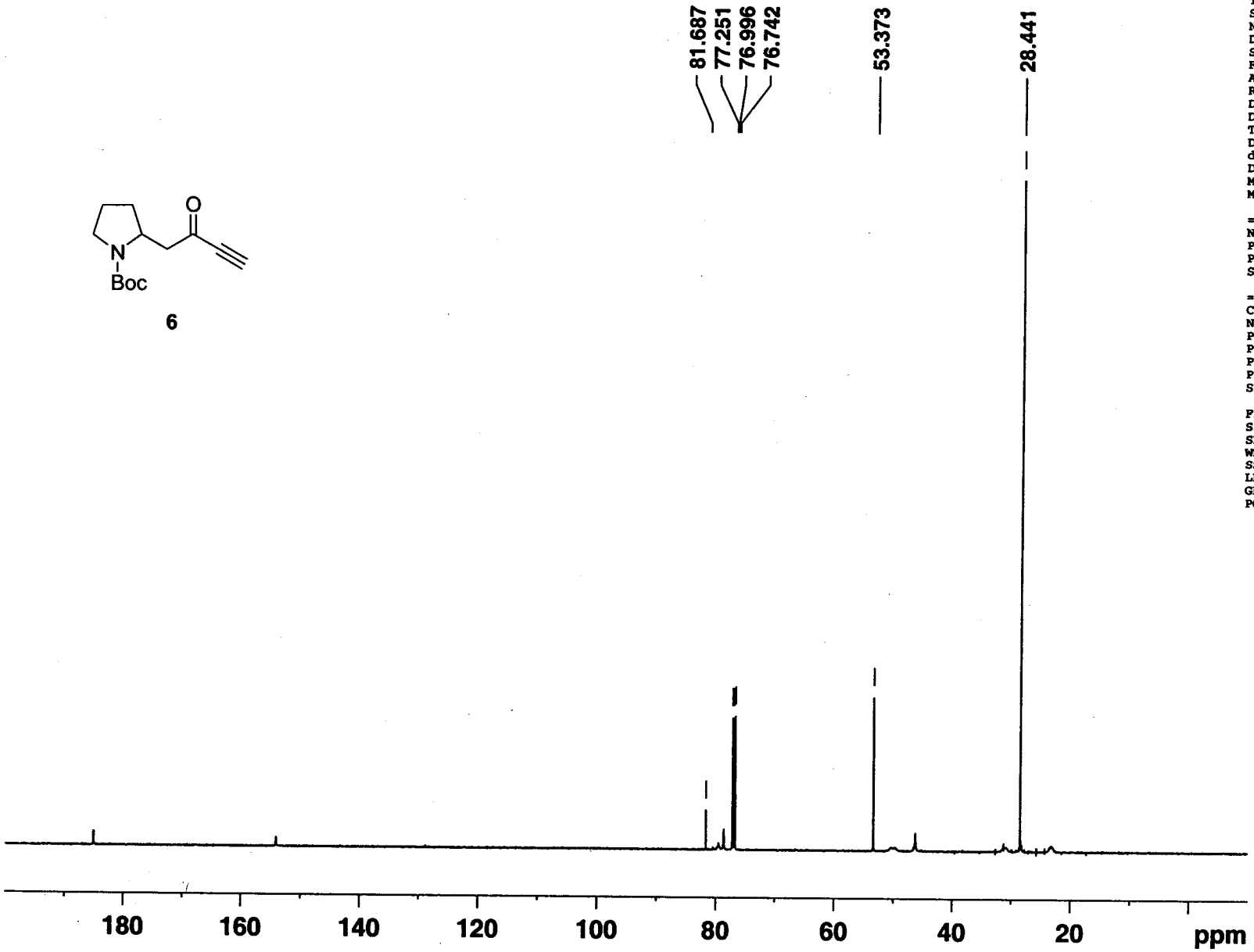
6

6

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SFO2                500.1325000 MHz

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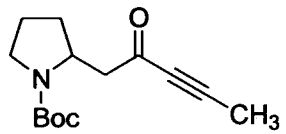
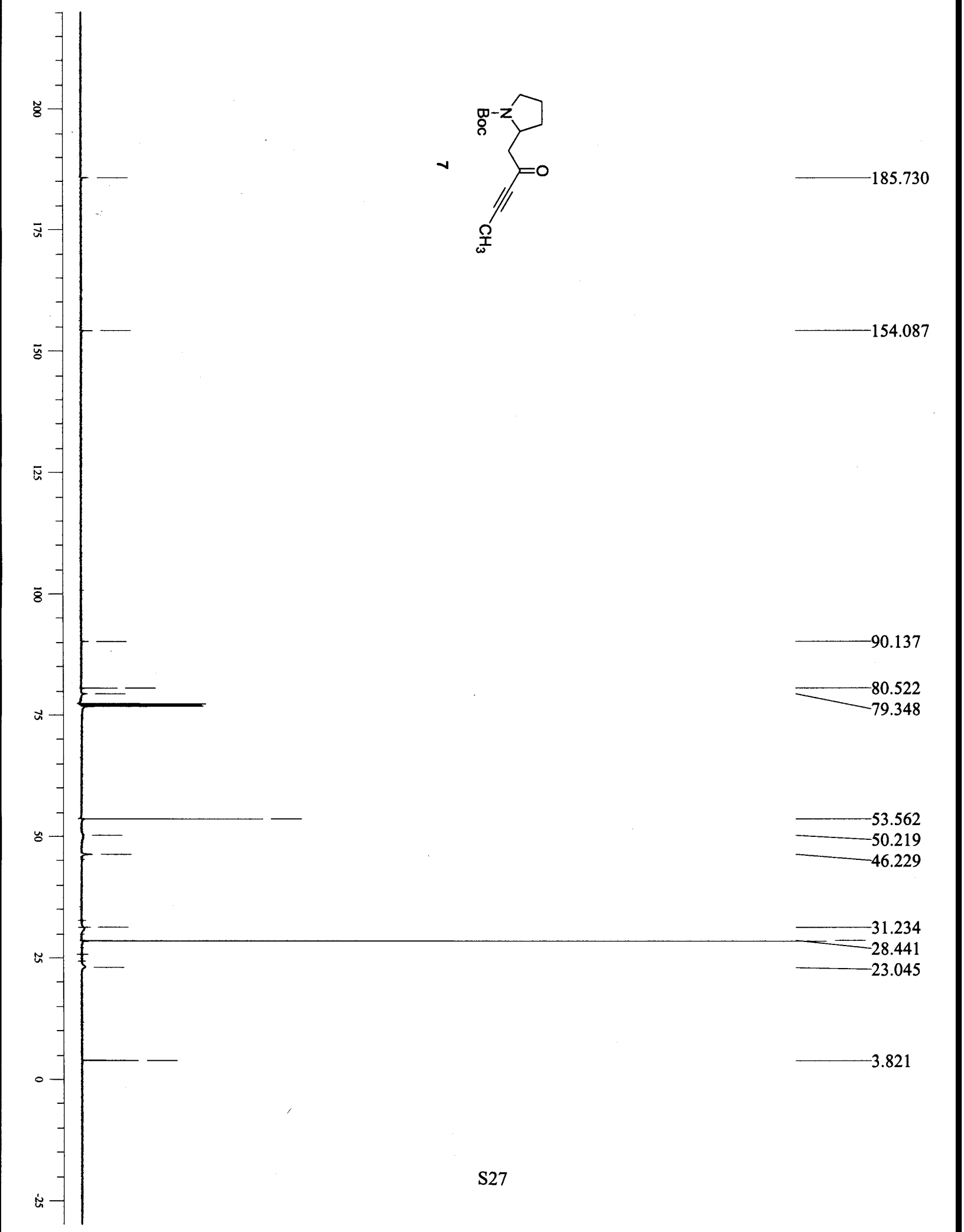


7


7
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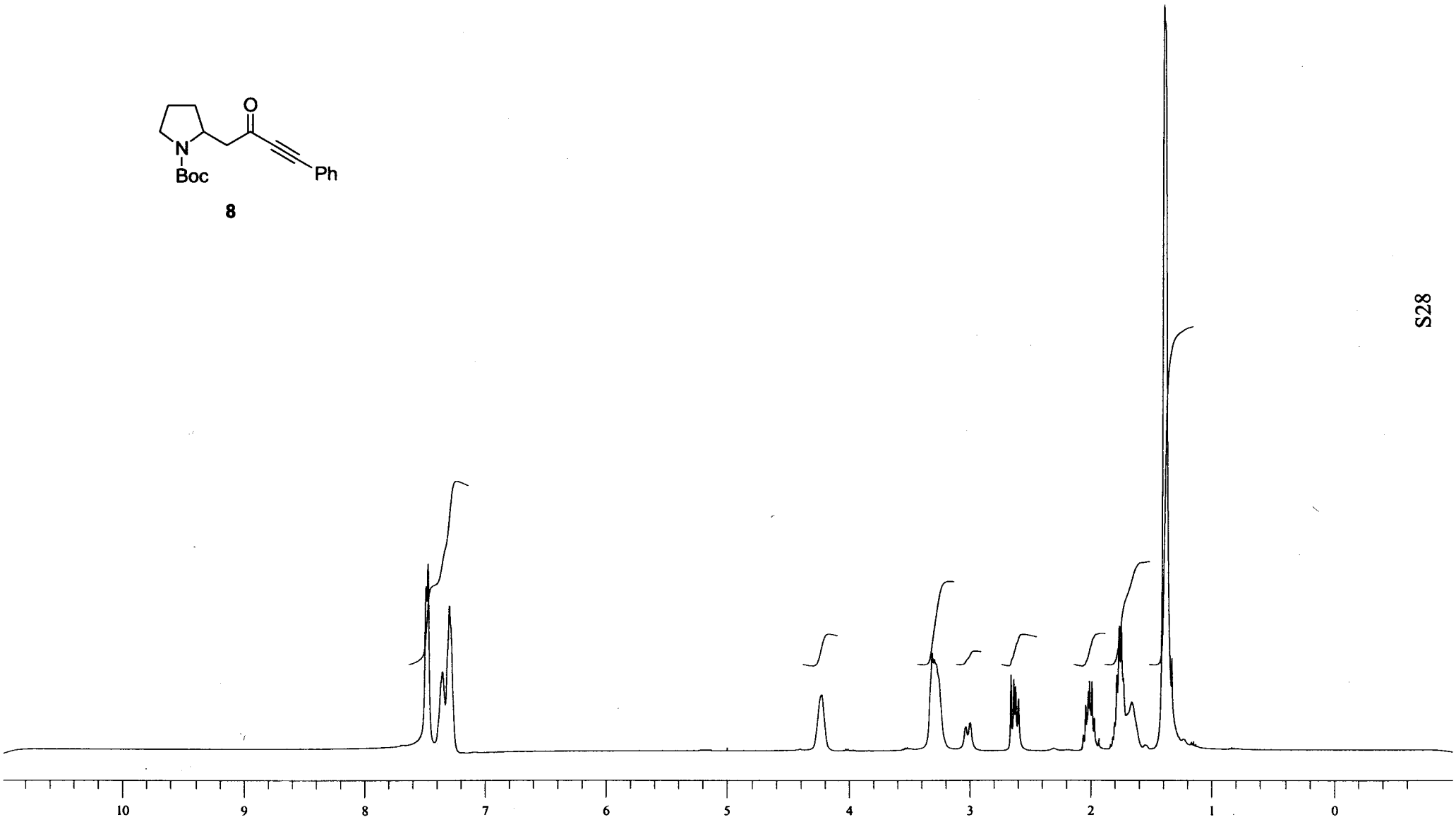
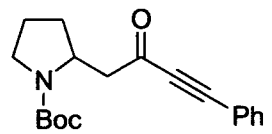
N
O
CH3
185.730
154.087
90.137
80.522
79.348
53.562
50.219
46.229
31.234
28.441
23.045
3.821
200
175
150
125
100
75
50
25
0
-25

8





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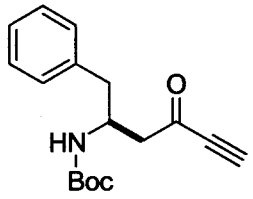
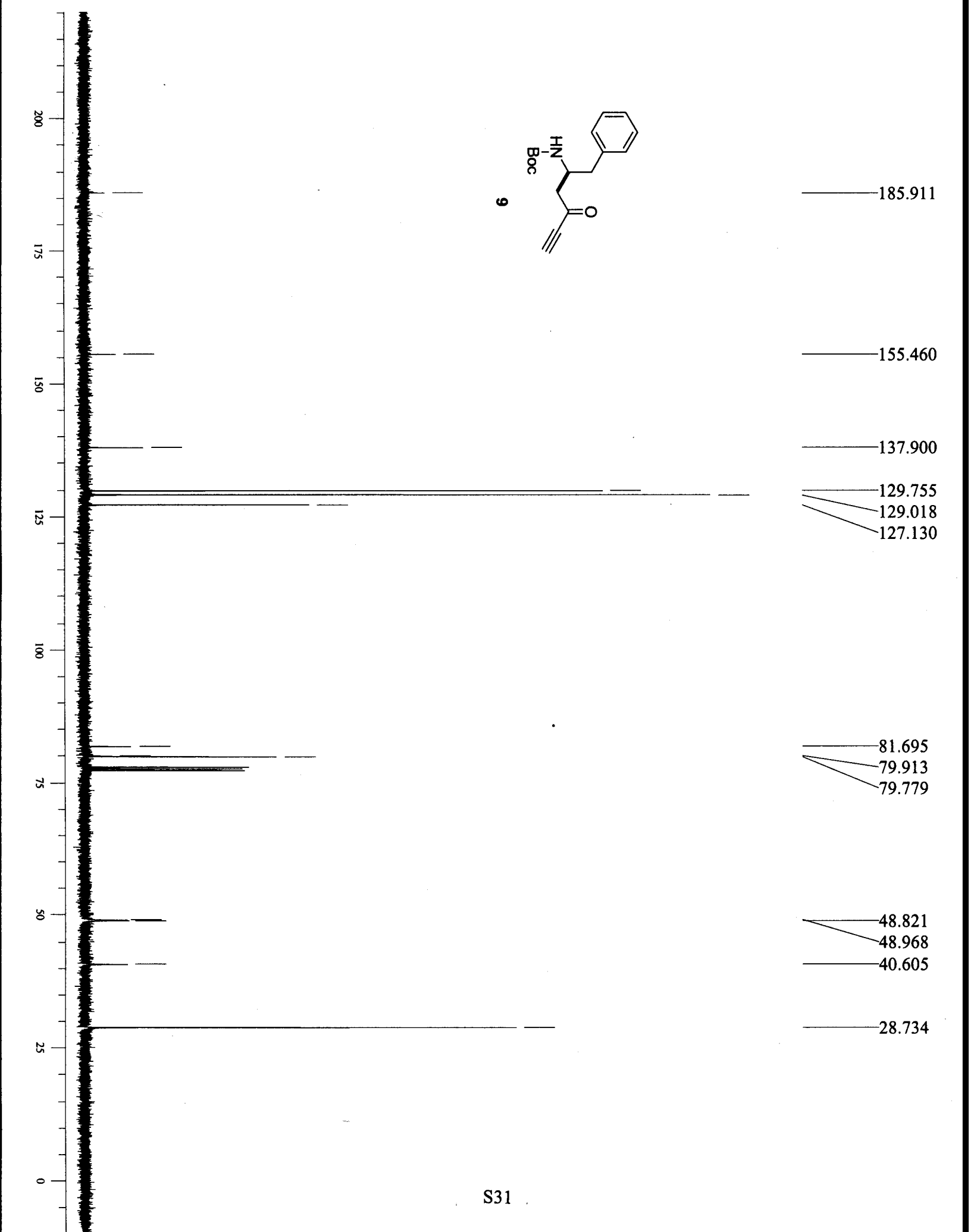
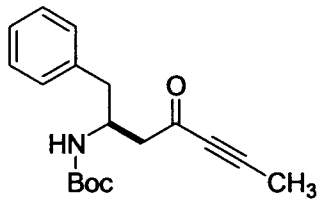
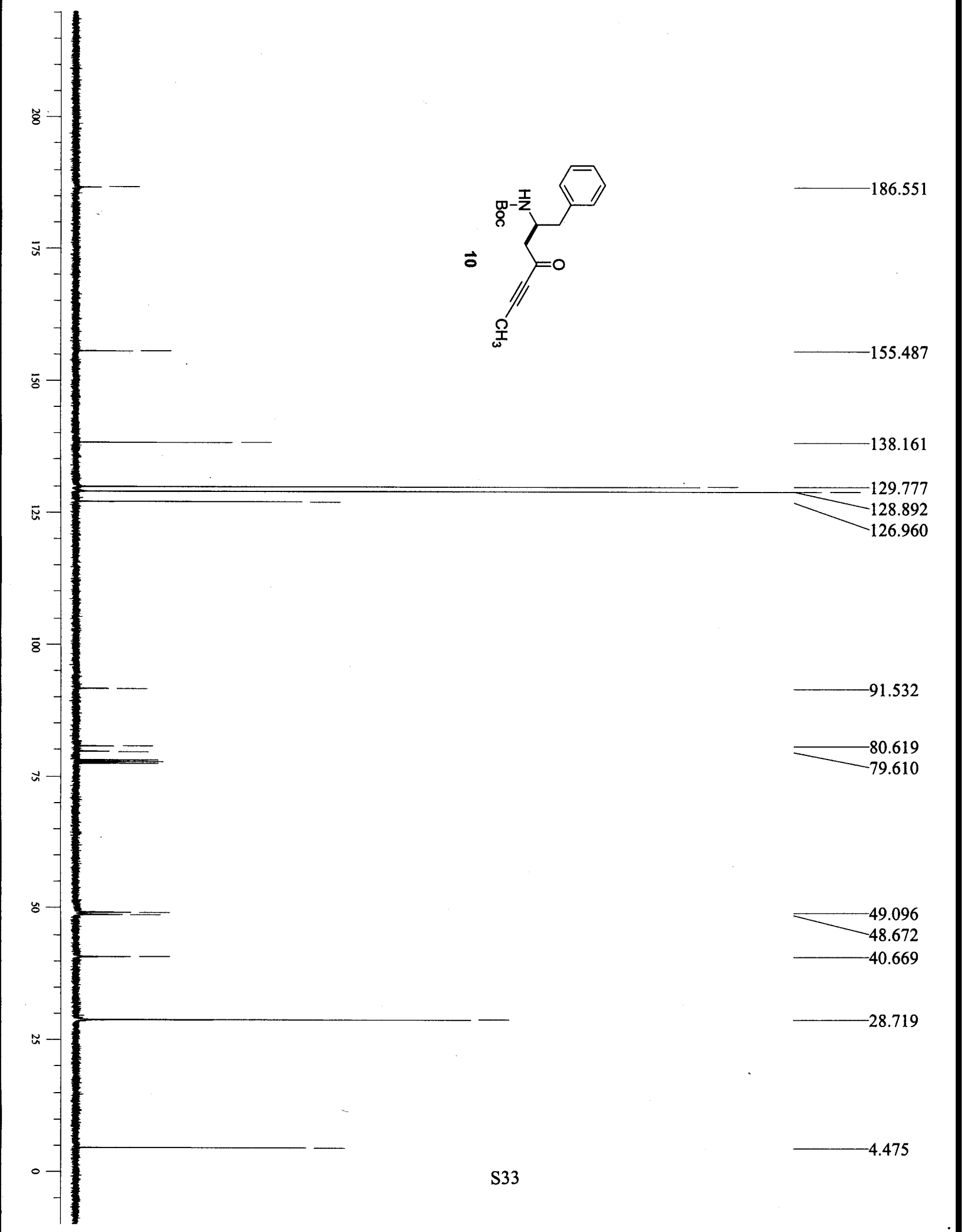


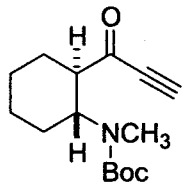
9


9
HN
Boc
O
185.911
155.460
137.900
129.755
129.018
127.130
81.695
79.913
79.779
48.821
48.968
40.605
28.734
200
175
150
125
100
75
50
25
0

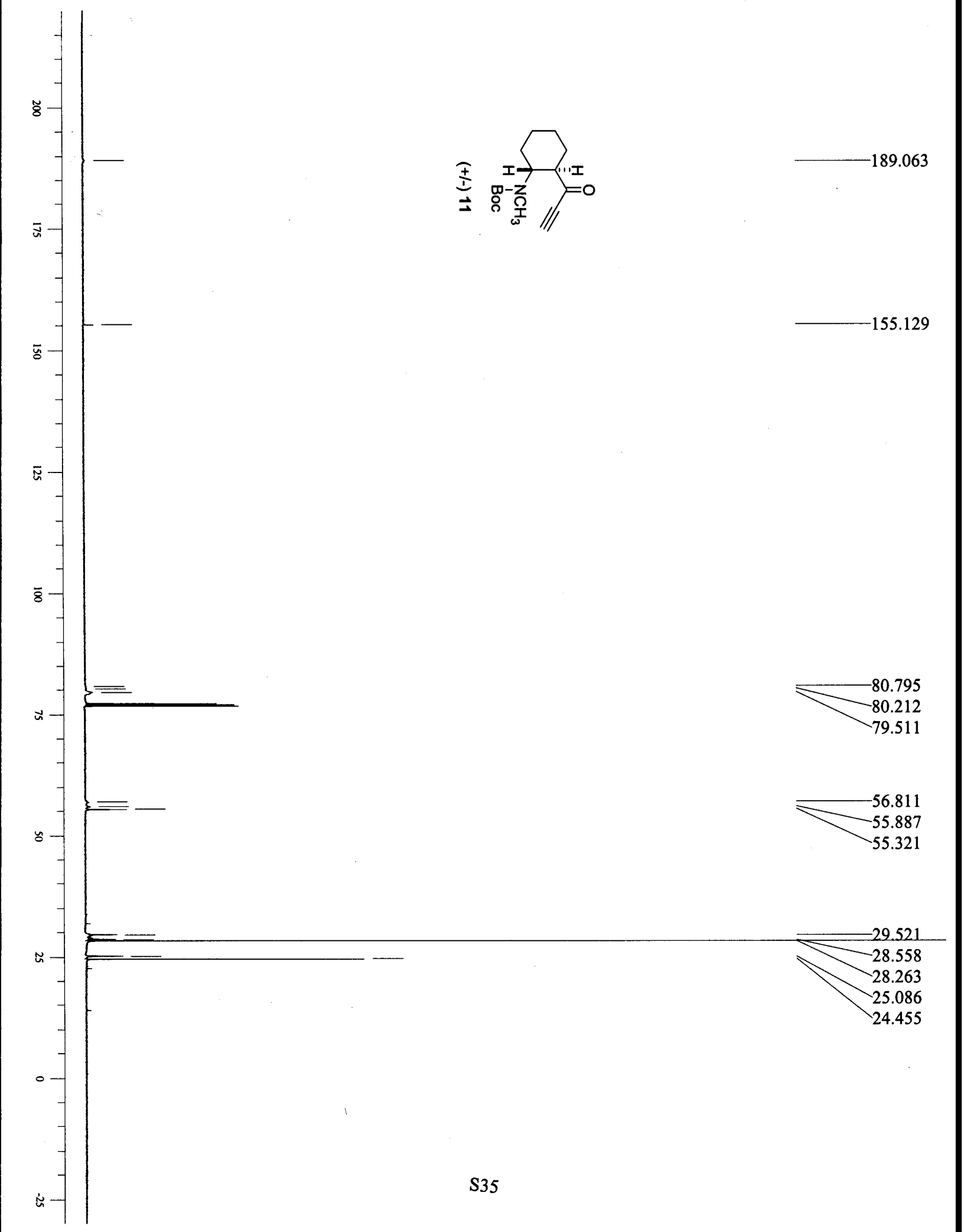


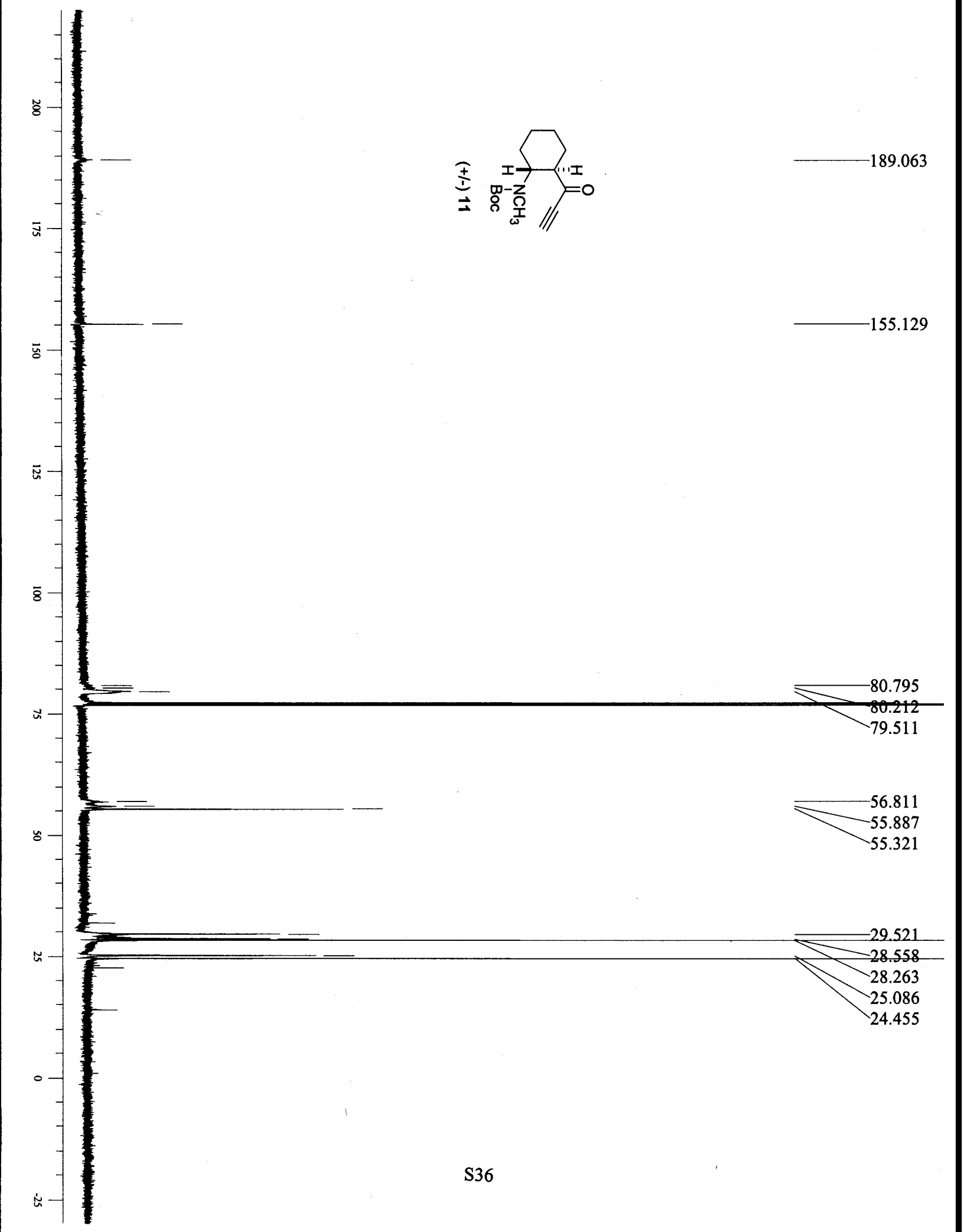
10

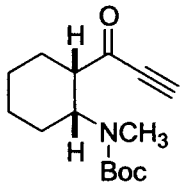

10
HN
Boc
O
CH3
186.551
155.487
138.161
129.777
128.892
126.960
91.532
80.619
79.610
49.096
48.672
40.669
28.719
4.475
200
175
150
125
100
75
50
25
0



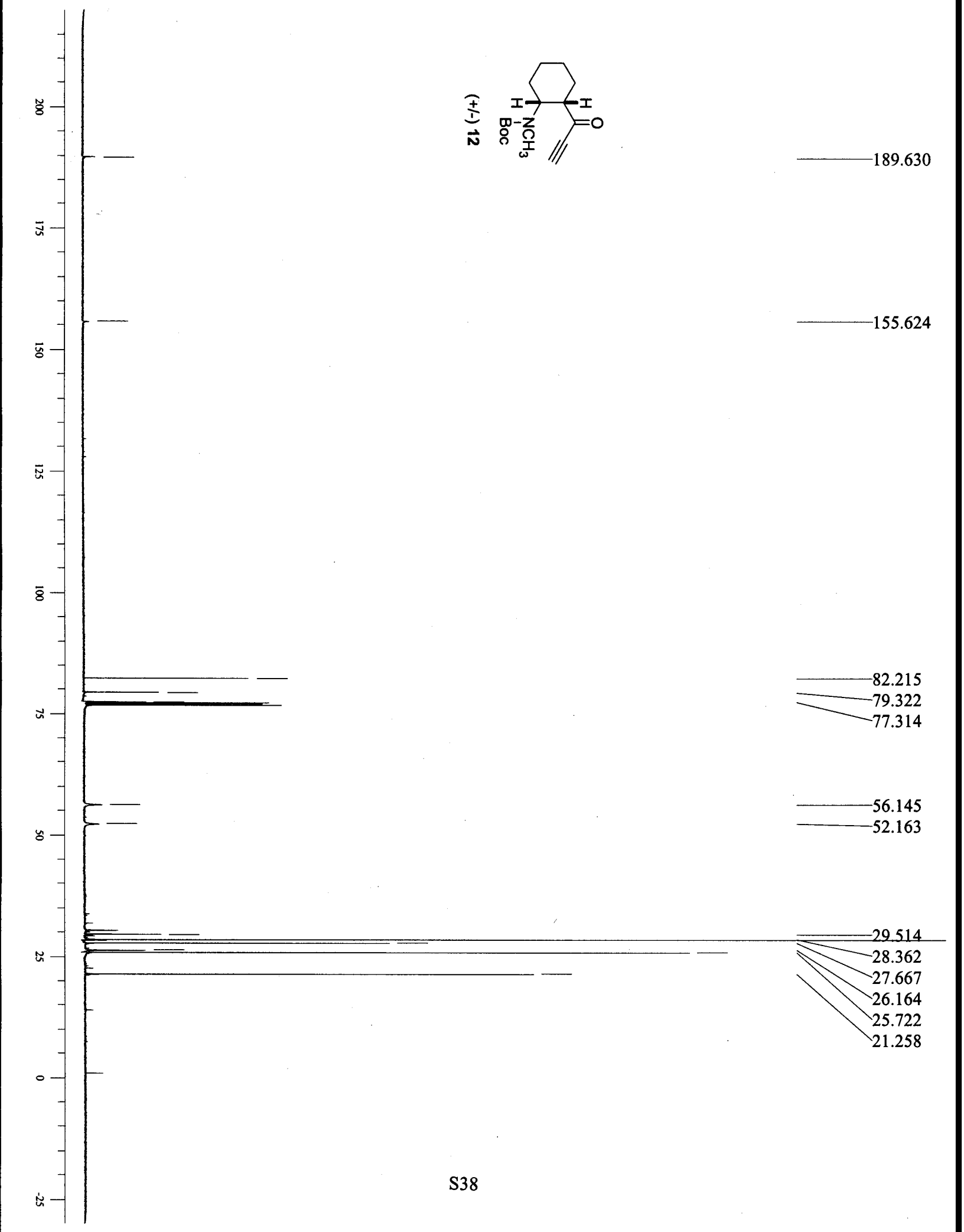
(+/-) **11**


(+/-) 11
189.063
155.129
80.795
80.212
79.511
56.811
55.887
55.321
29.521
28.558
28.263
25.086
24.455

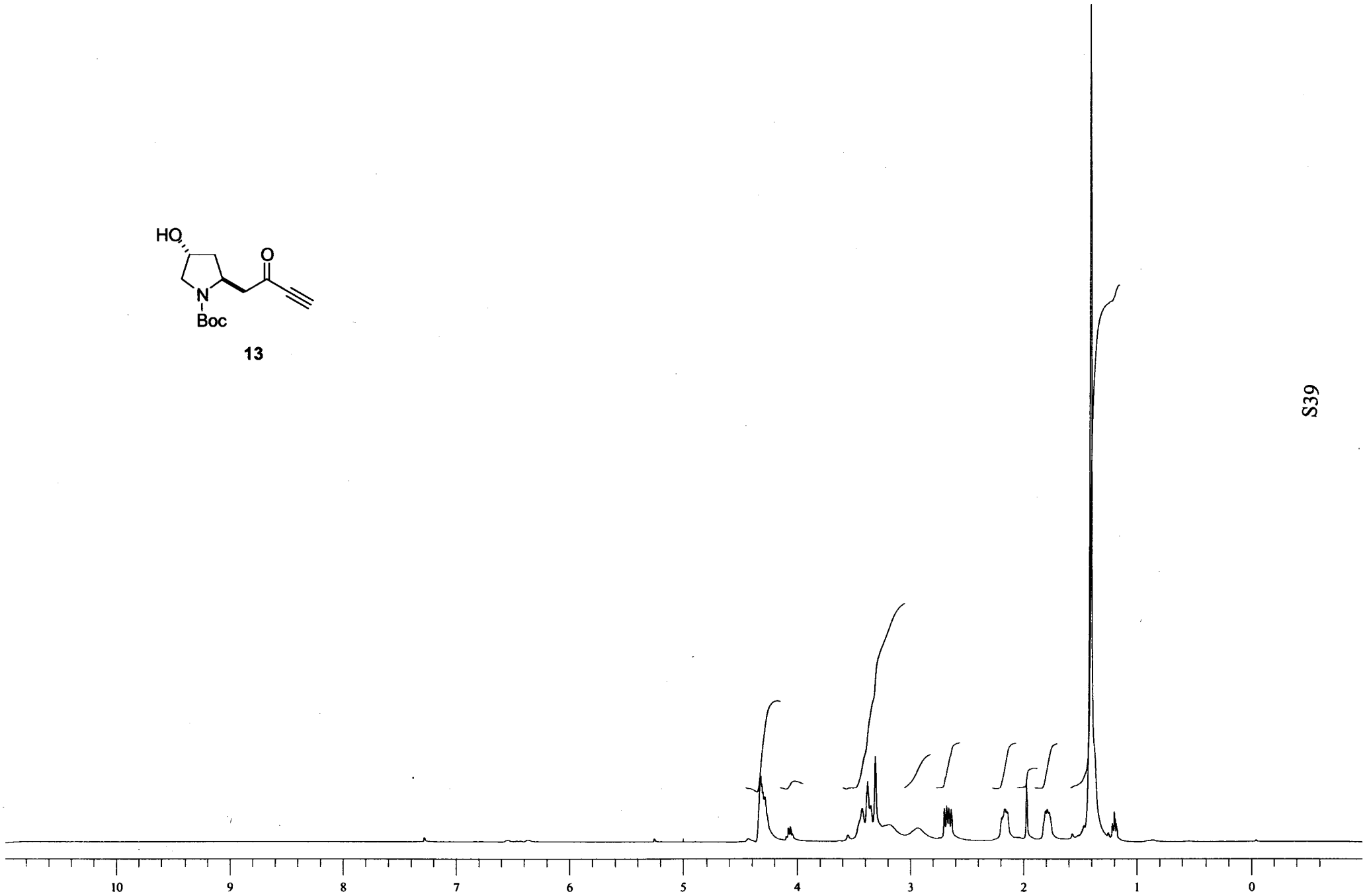

(+/-) 11
189.063
155.129
80.795
80.212
79.511
56.811
55.887
55.321
29.521
28.558
28.263
25.086
24.455
200
175
150
125
100
75
50
25
0
-25

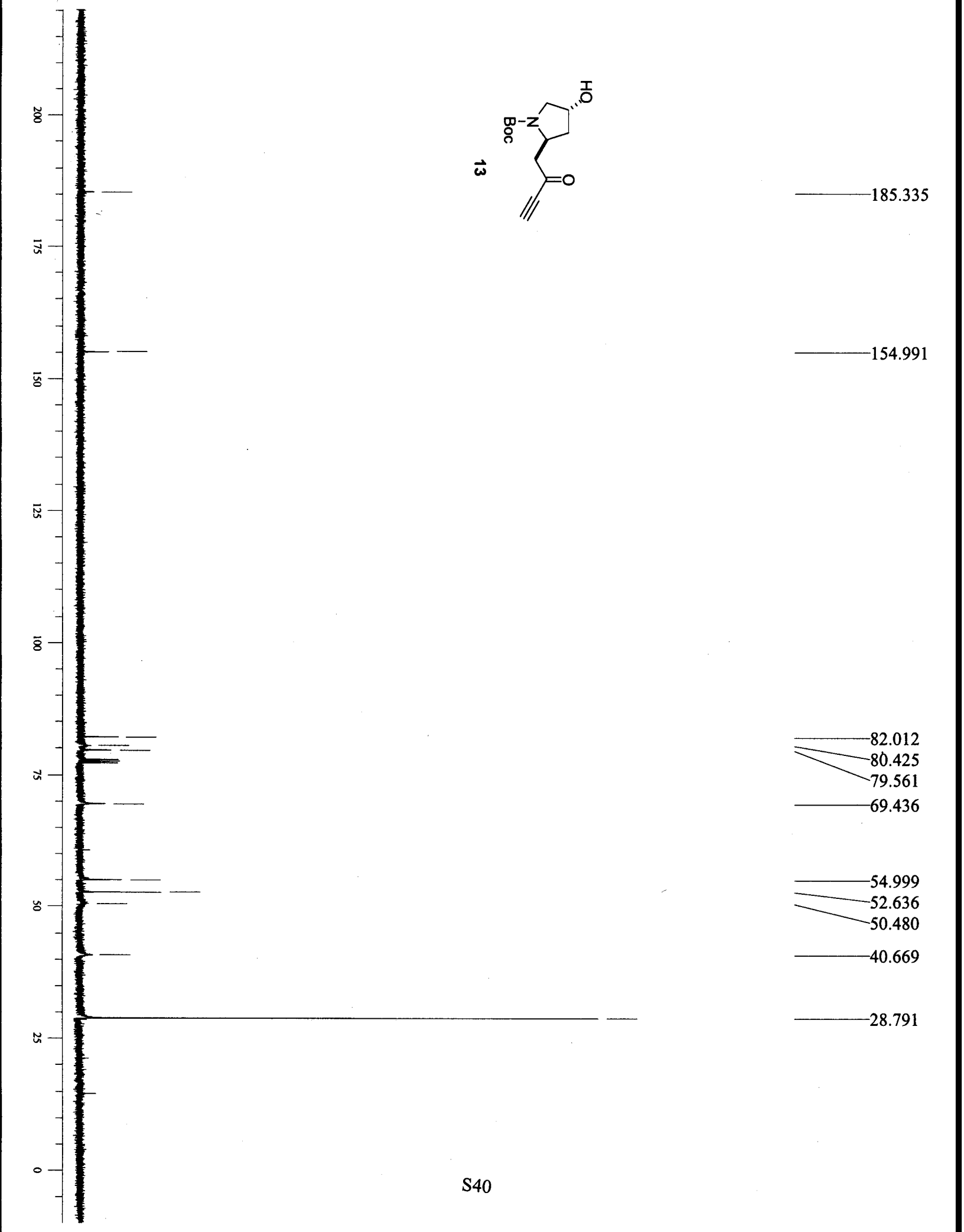


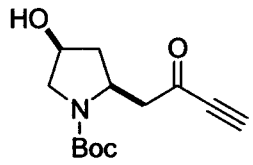
(+/-) **12**


(+/-) 12
H
H
NCH3
Boc
O
189.630
155.624
82.215
79.322
77.314
56.145
52.163
29.514
28.362
27.667
26.164
25.722
21.258
200
175
150
125
100
75
50
25
0
-25

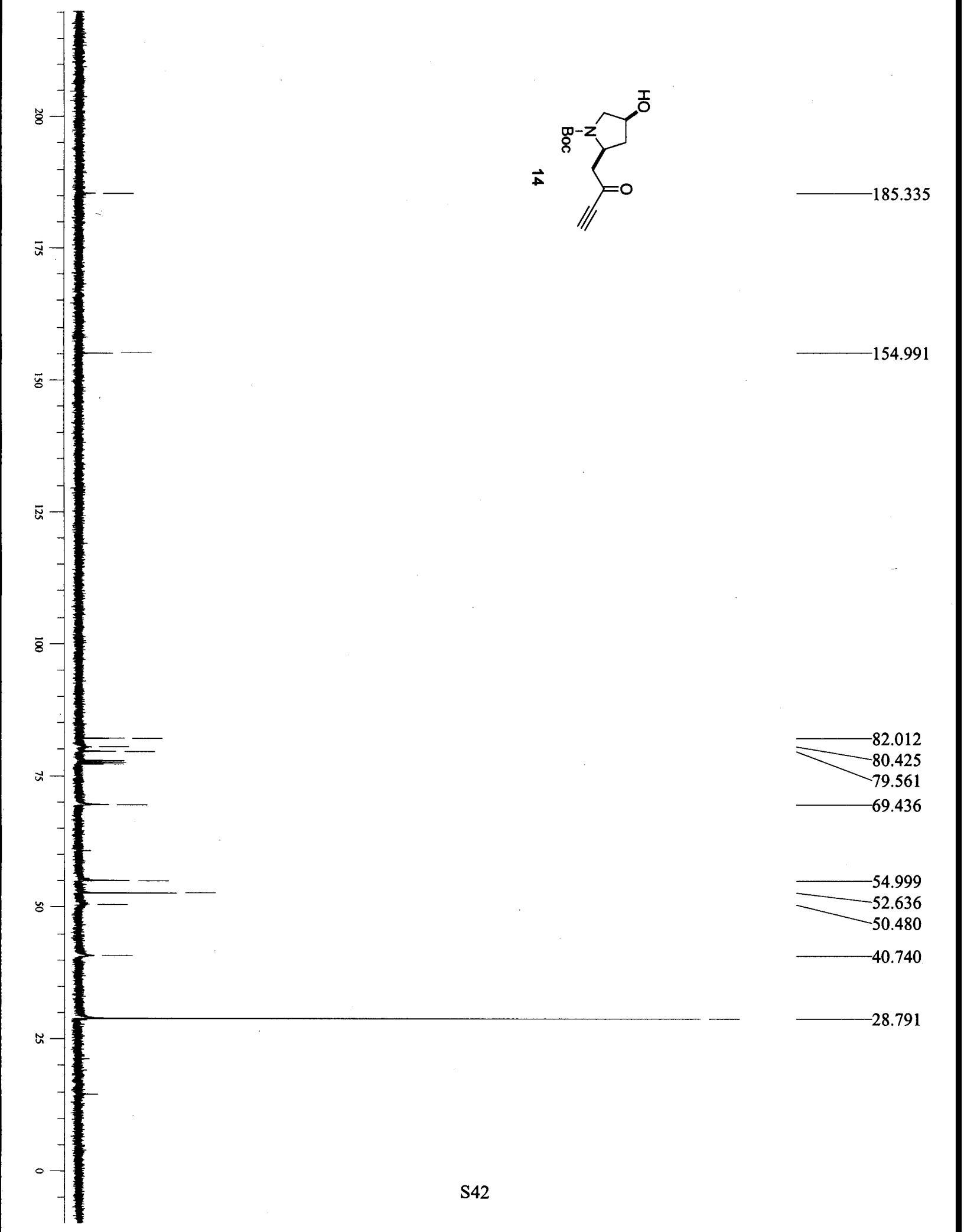
13

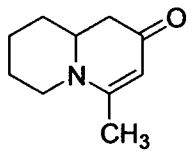



HO
N
Boc
O
13
185.335
154.991
82.012
80.425
79.561
69.436
54.999
52.636
50.480
40.669
28.791
200
175
150
125
100
75
50
25
0

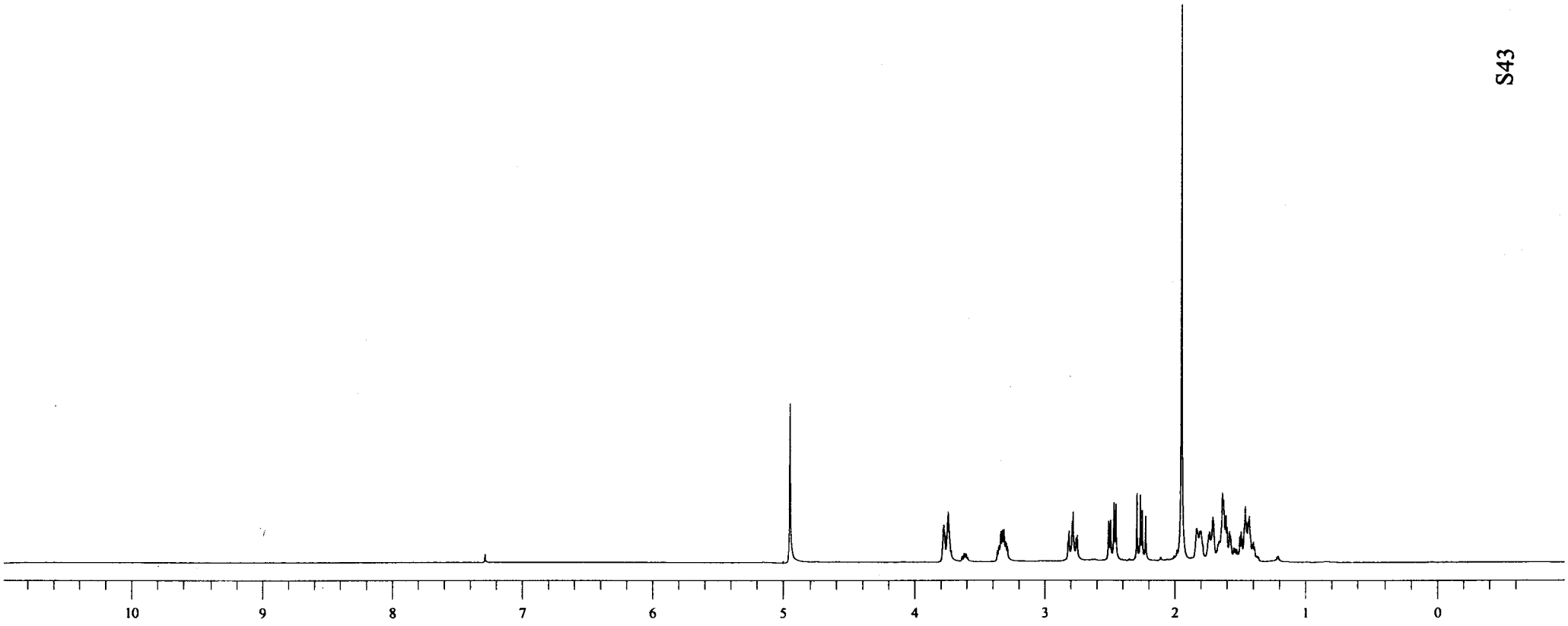


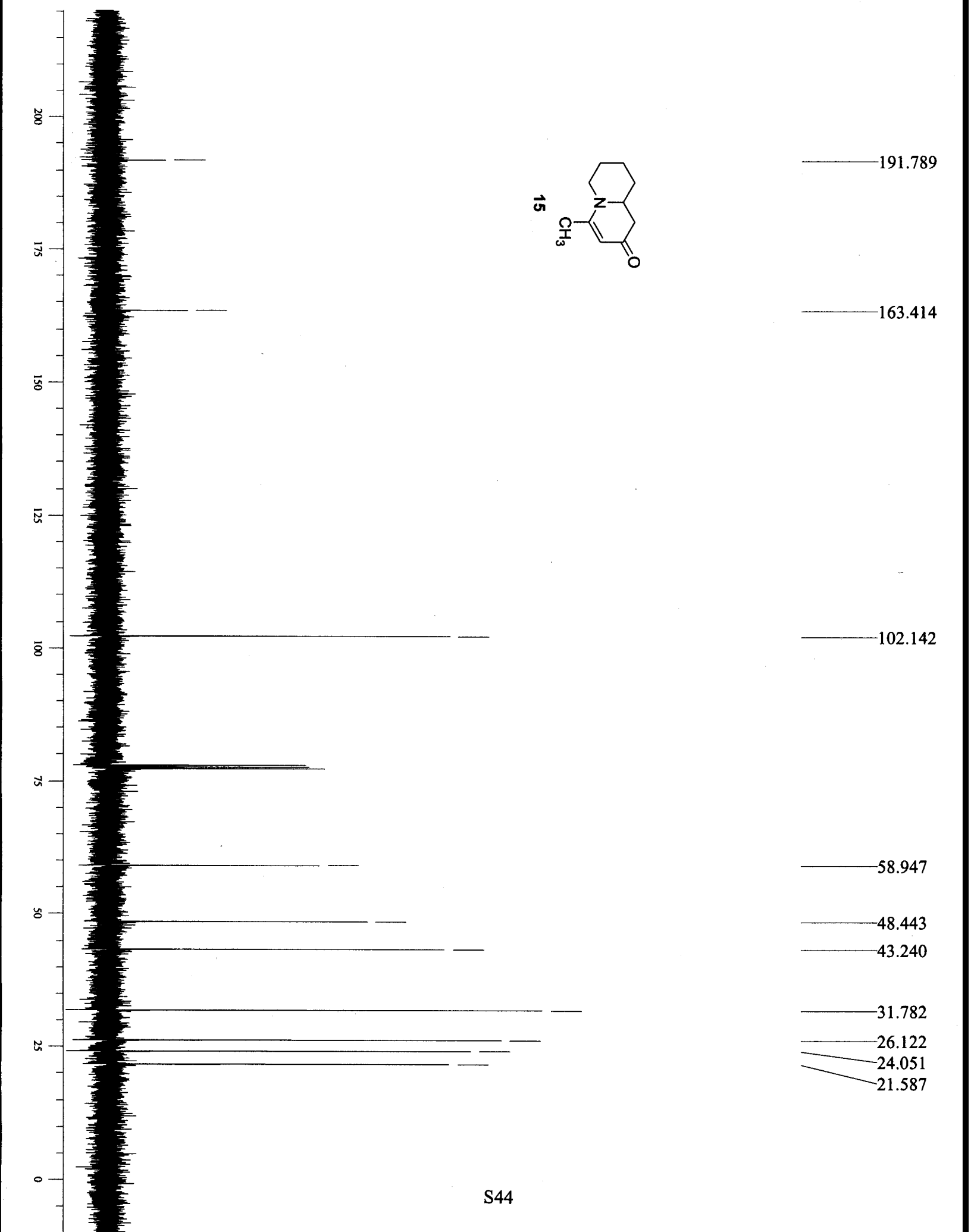
14

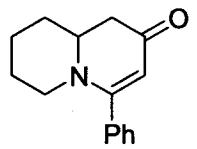

HO
N
Boc
O
14
185.335
154.991
82.012
80.425
79.561
69.436
54.999
52.636
50.480
40.740
28.791
200
175
150
125
100
75
50
25
0



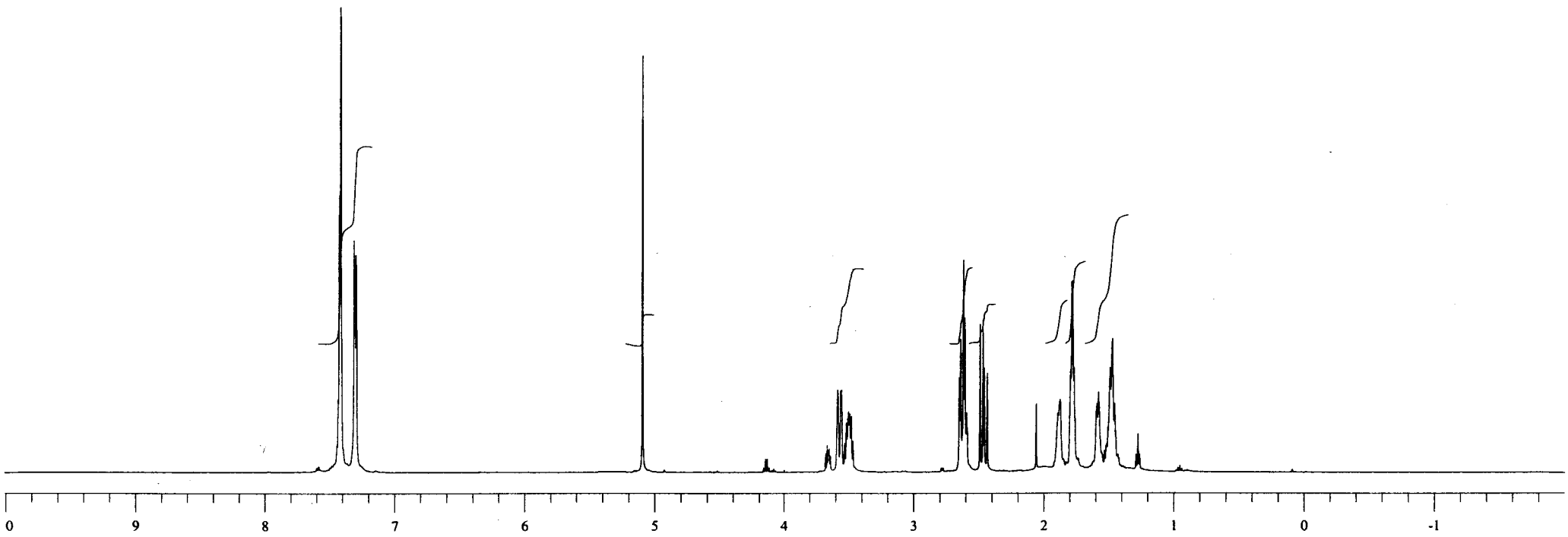
15

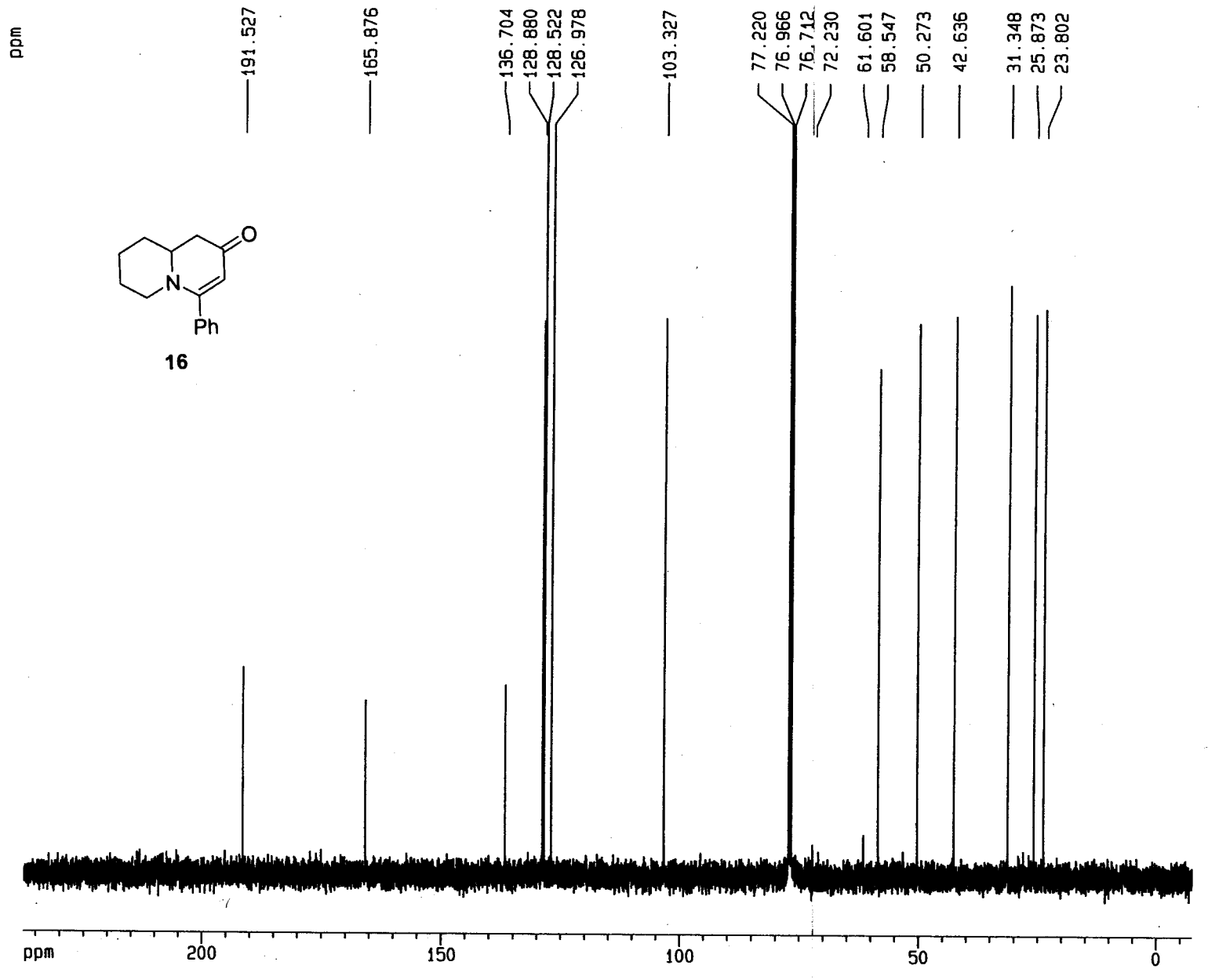



200
175
150
125
100
75
50
25
0
15
CH3
N
O
191.789
163.414
102.142
58.947
48.443
43.240
31.782
26.122
24.051
21.587



16






```
Current Data Parameters
NAME                  BJT4-31c
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20031023
Time                     16.39
INSTRUM                  spect
PROBHD     5 mm BBO BB-1H
PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                         328
DS                           4
SWH                  31446.541 Hz
FIDRES               0.479836 Hz
AQ                   1.0420883 sec
RG                        2048
DW                      15.900 usec
DE                       6.00 usec
TE                       300.0 K
D1                   0.10000000 sec
d11                  0.03000000 sec
d12                  0.00002000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                       6.50 usec
PL1                      5.00 dB
SFO1                125.7719472 MHz

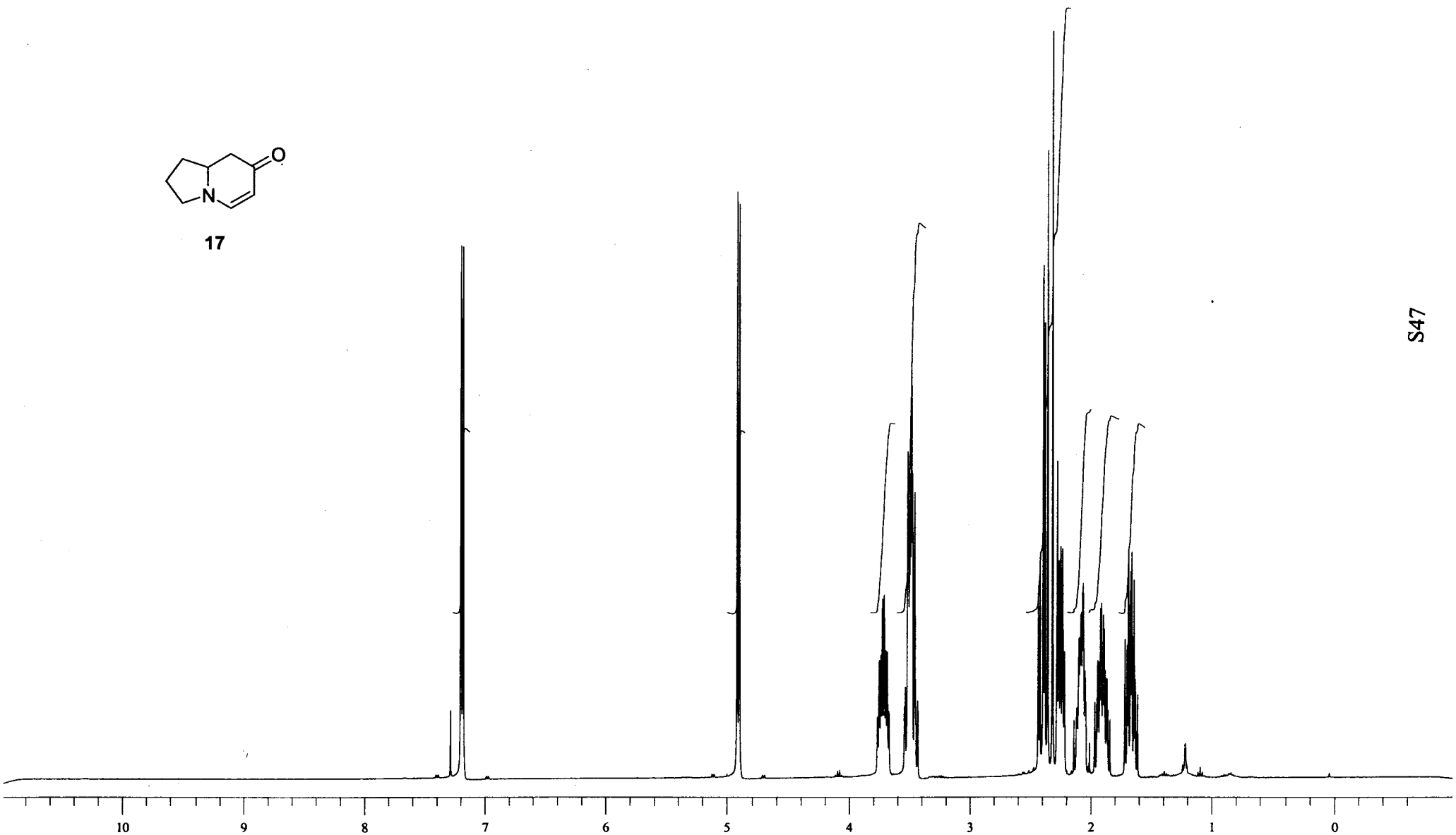
======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                   95.00 usec
PL2                     -4.00 dB
PL12                    19.00 dB
PL13                    30.00 dB
SFO2                500.1325000 MHz

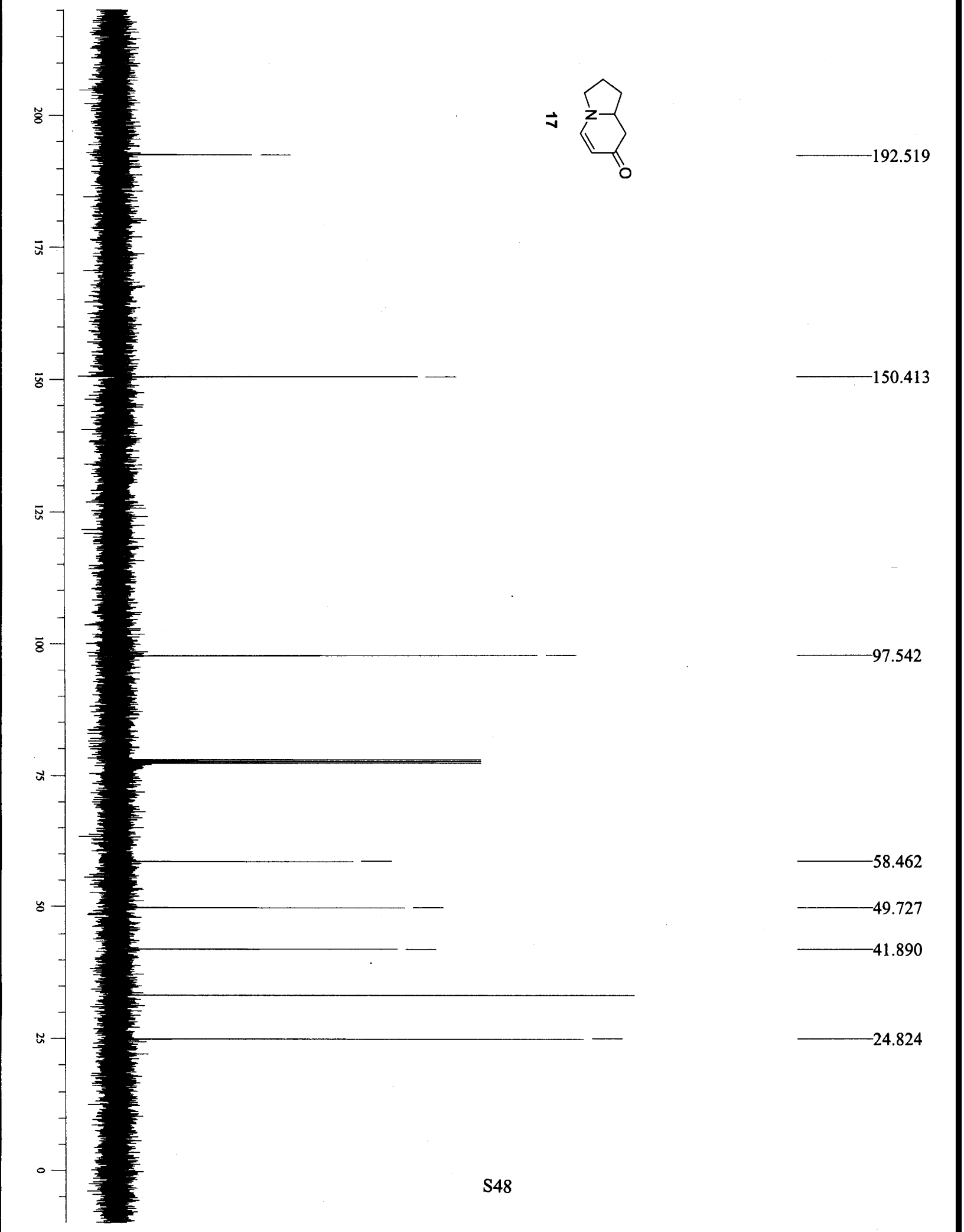
F2 - Processing parameters
SI                       65536
SF                  125.7578008 MHz
WDW                         EM
SSB                          0
LB                       1.00 Hz
GB                           0
PC                        1.40

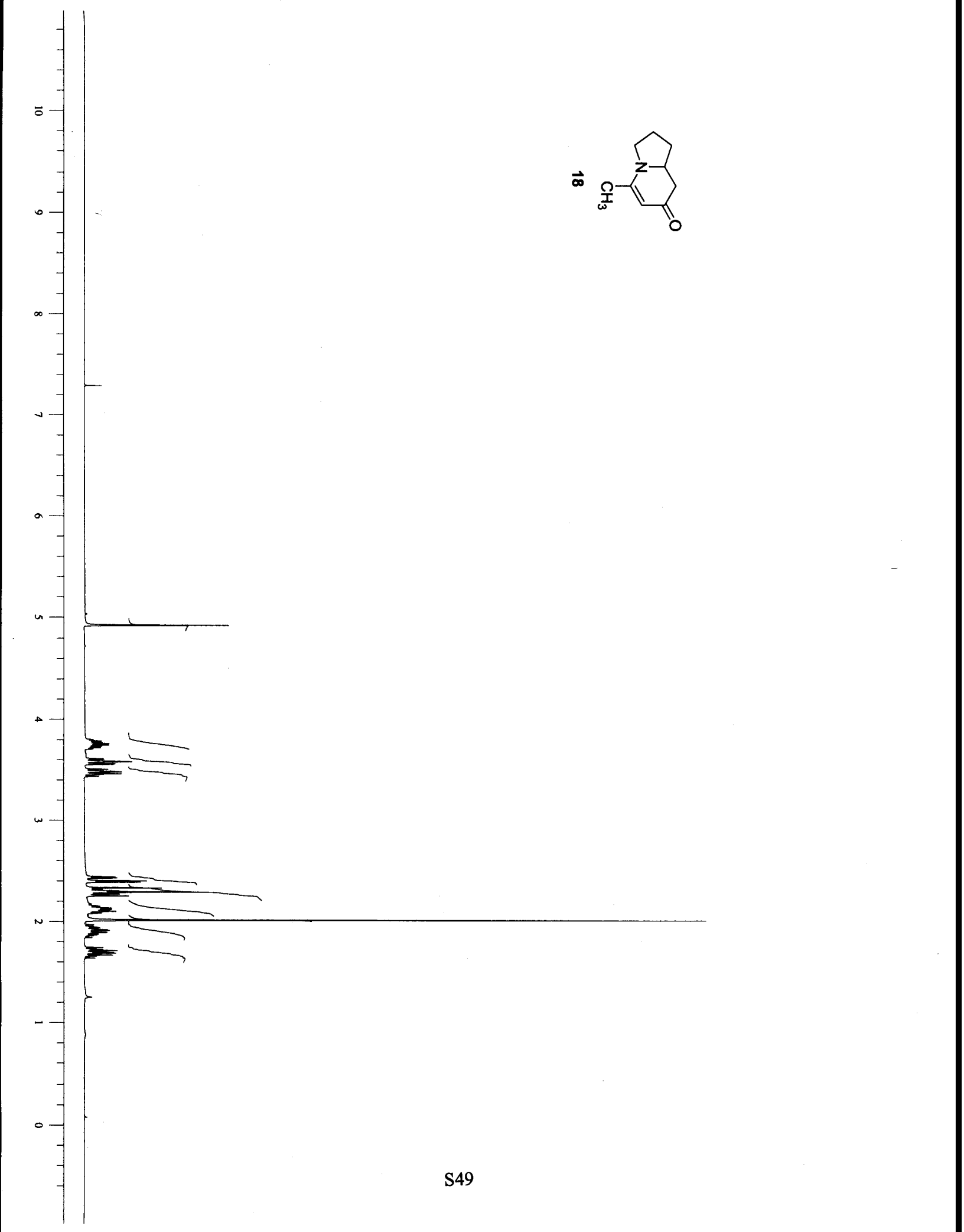
F1 - Processing parameters
SI                        1024
MC2                         QF
SF                  500.1300000 MHz
WDW                         no
SSB                          0
LB                       0.30 Hz
GB                           0

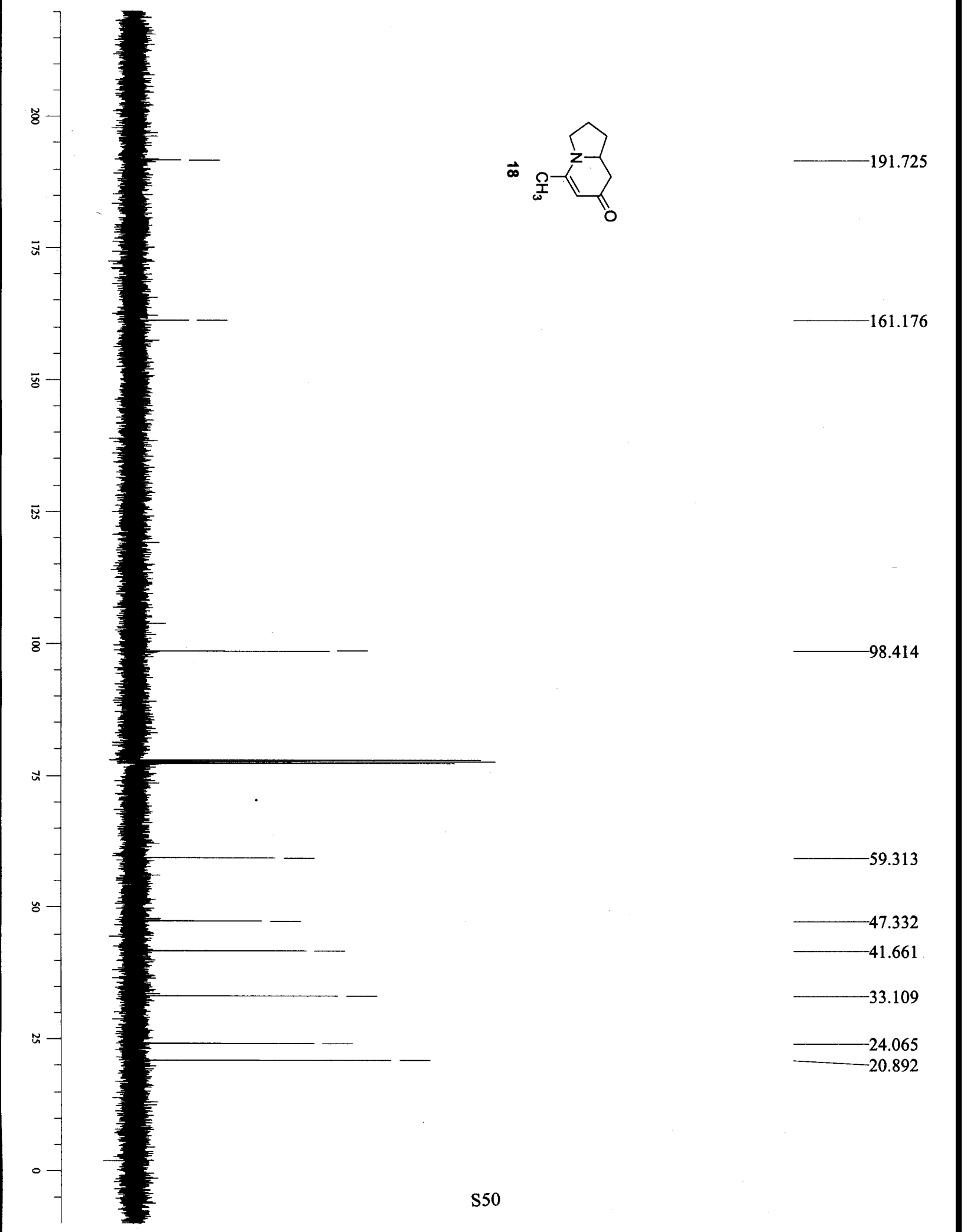
1D NMR plot parameters
CX                      20.00 cm
CY                       0.00 cm
F1P                    242.517 ppm
F1                   30498.43 Hz
F2P                     -7.539 ppm
F2                    -948.11 Hz
PPMCM                12.50282 ppm/cm
HZCM                1572.32703 Hz/cm
```

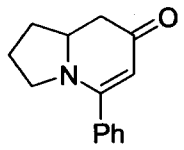
17



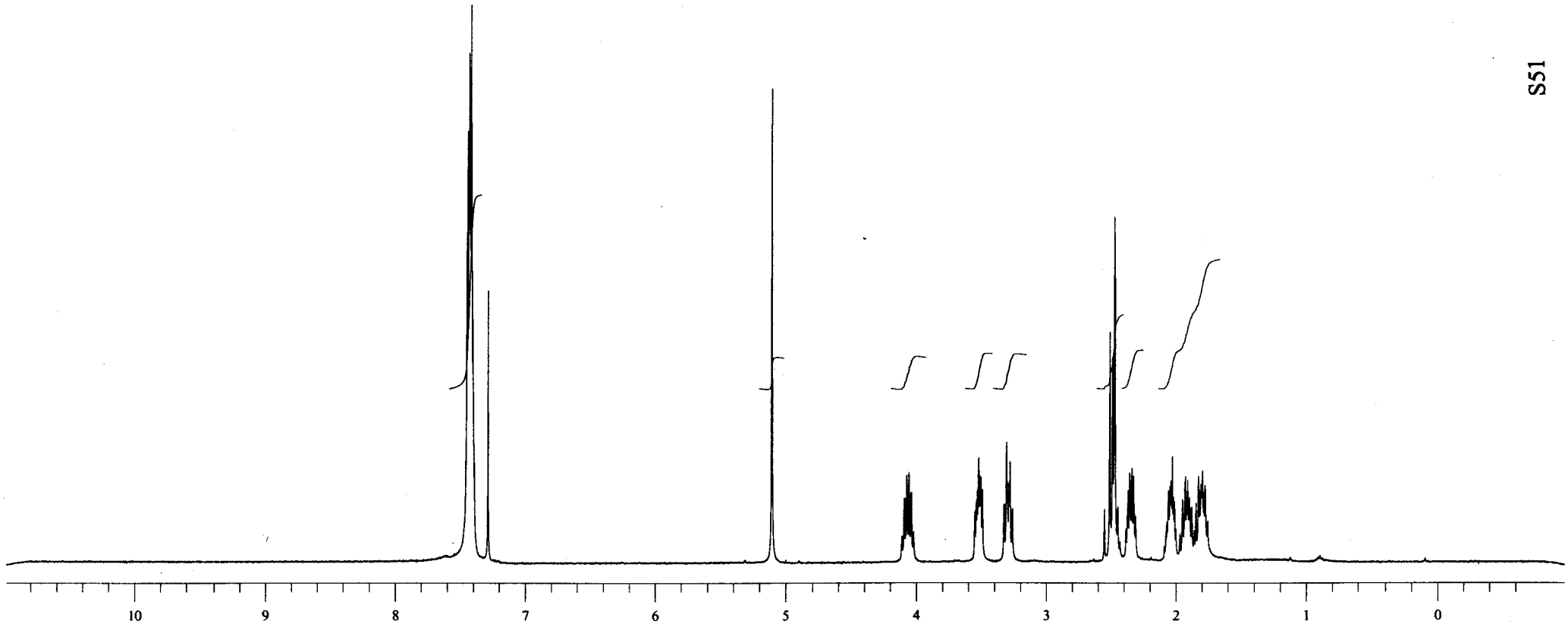

47
N
O
192.519
150.413
97.542
58.462
49.727
41.890
24.824
200
175
150
125
100
75
50
25
0

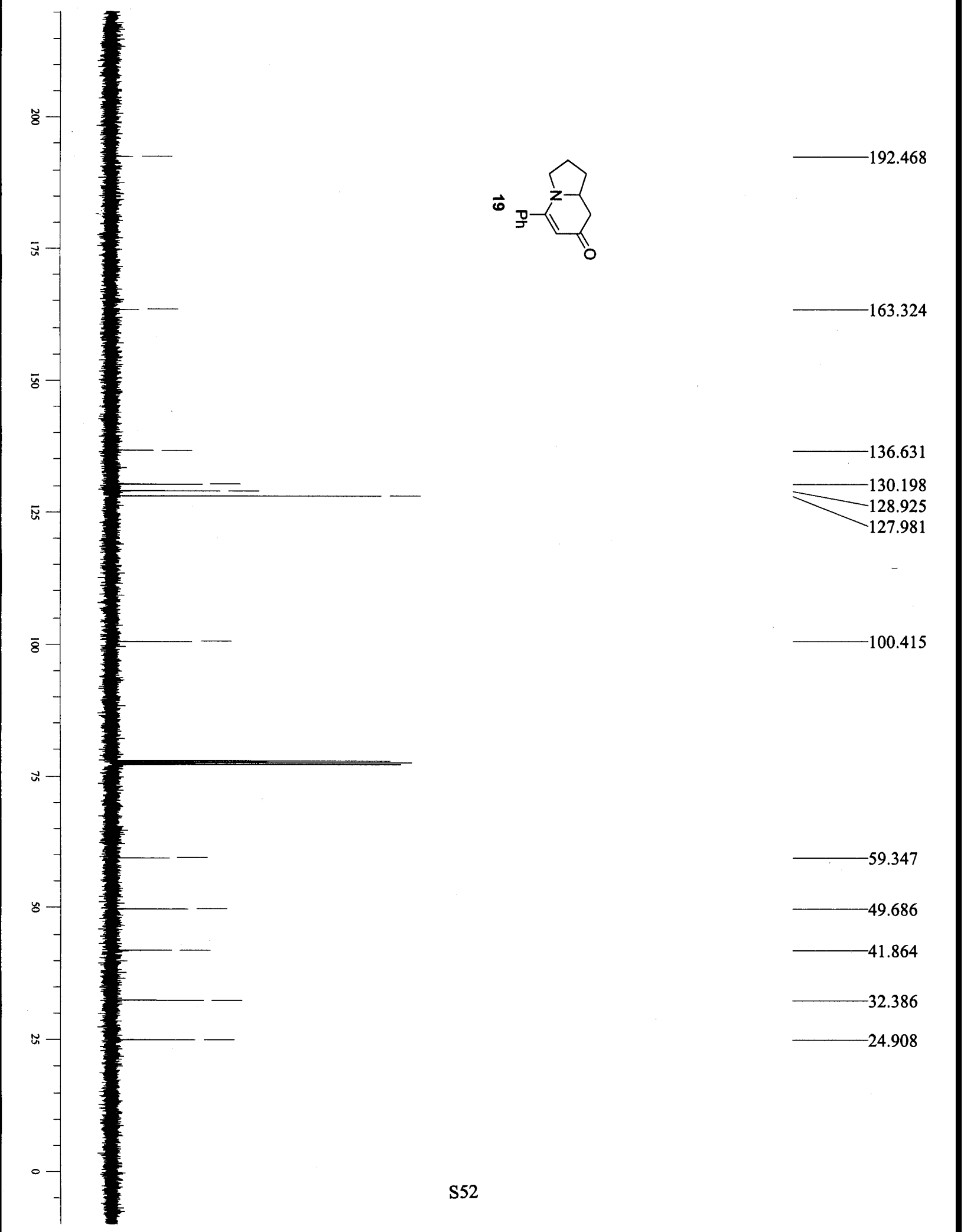

18
N
CH3
O


18
191.725
161.176
98.414
59.313
47.332
41.661
33.109
24.065
20.892



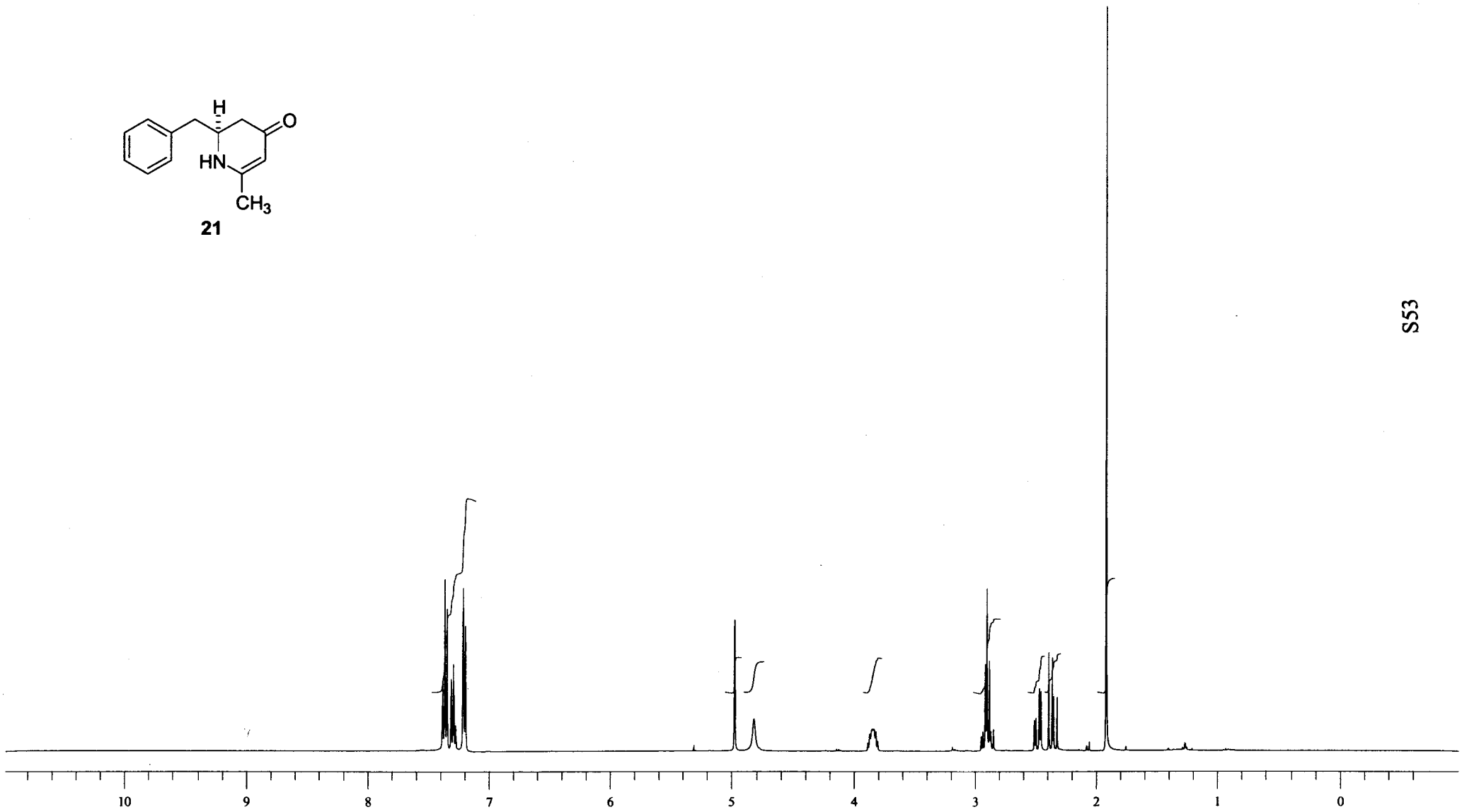
19

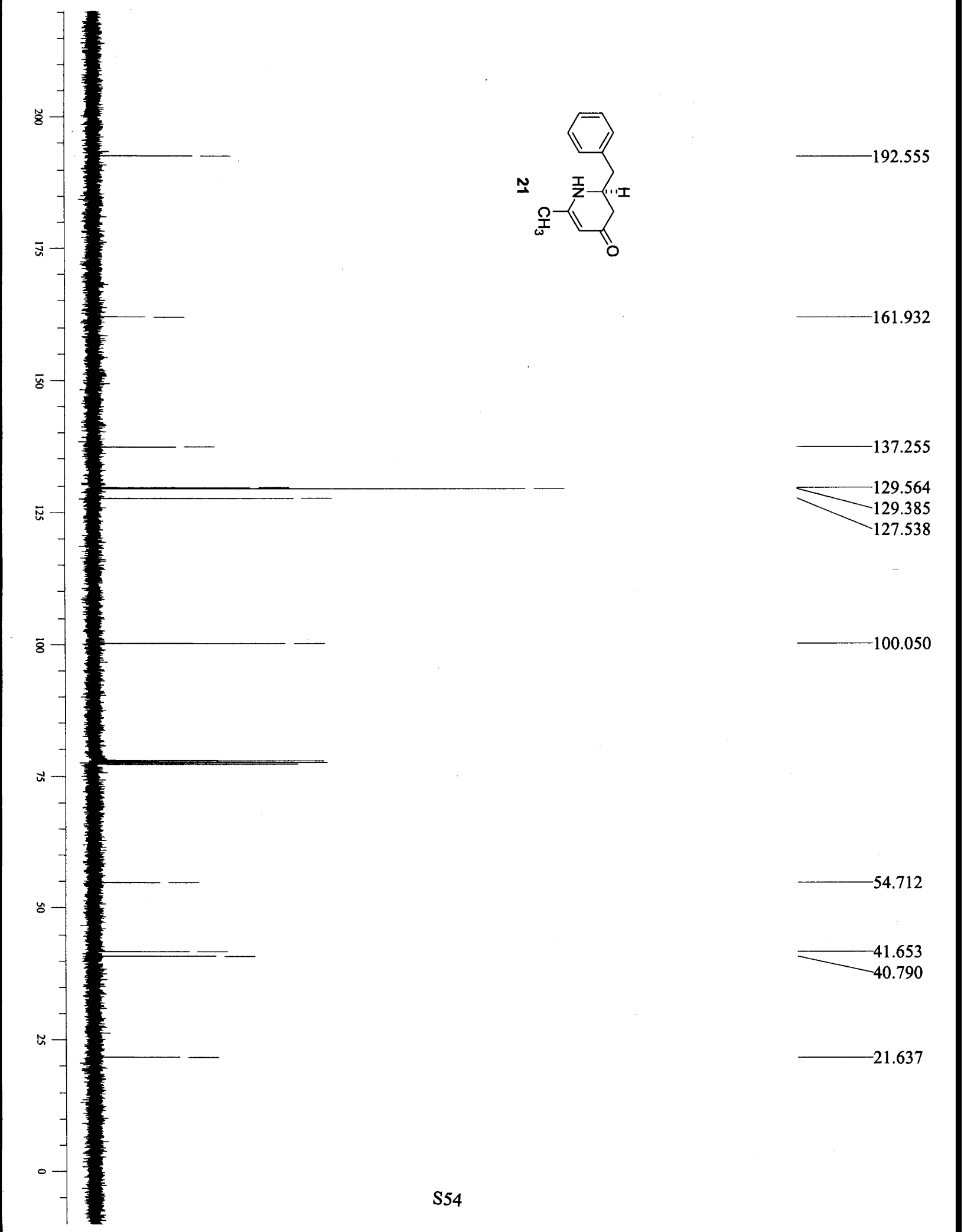



200
175
150
125
100
75
50
25
0
N
Ph
O
192.468
163.324
136.631
130.198
128.925
127.981
100.415
59.347
49.686
41.864
32.386
24.908

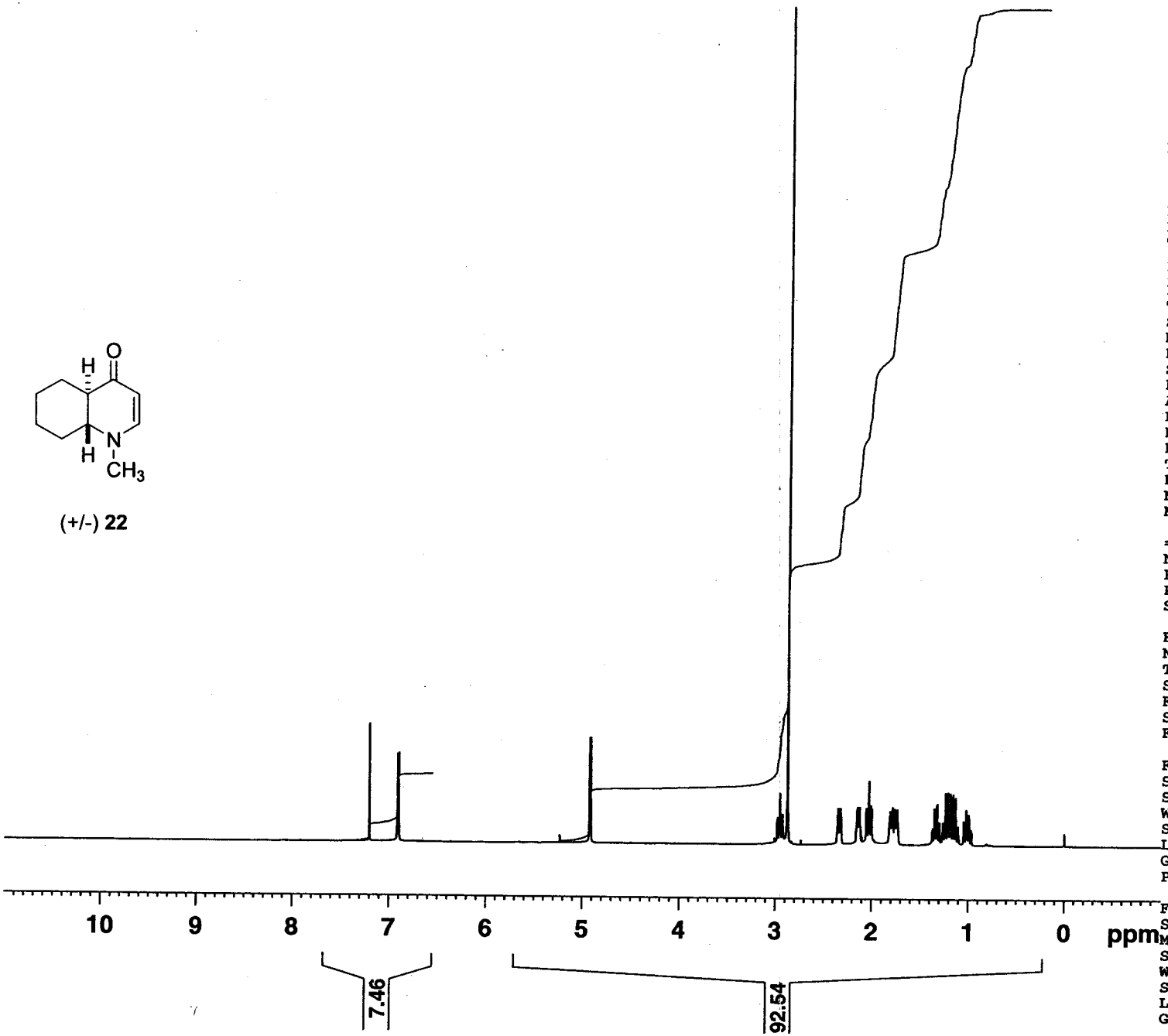
19

21




21
HN
CH3
O
H
200
175
150
125
100
75
50
25
0
192.555
161.932
137.255
129.564
129.385
127.538
100.050
54.712
41.653
40.790
21.637

(+/-) **22**




```
Current Data Parameters
NAME                  BJT_5_245C
EXPNO                          1
PROCNO                         1

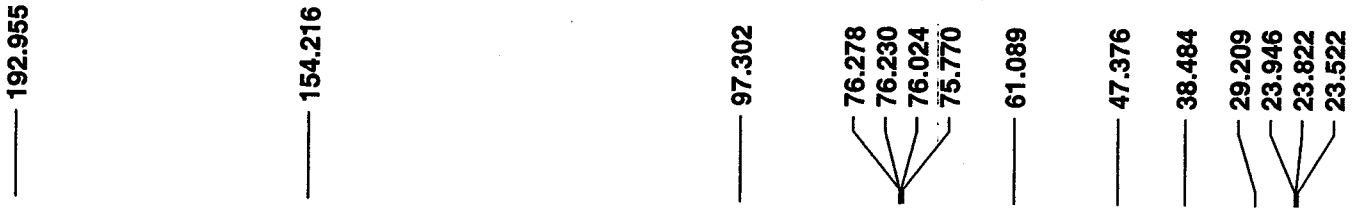
F2 - Acquisition Parameters
Date_                   20050728
Time                       13.03
INSTRUM                    spect
PROBHD   5 mm CPDUL 13C
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                            16
DS                             2
SWH                 10330.578 Hz
FIDRES                0.157632 Hz
AQ                    3.1720407 sec
RG                            64
DW                      48.400 usec
DE                       6.00 usec
TE                       300.0 K
D1                    1.00000000 sec
MCREST                0.00000000 sec
MCWRK                 0.01500000 sec

======== CHANNEL f1 ========
NUC1                          1H
P1                       15.00 usec
PL1                      -5.00 dB
SFO1                500.1330885 MHz

F1 - Acquisition parameters
ND0                            2
TD                           256
SFO1                 500.1325 MHz
FIDRES              23.475060 Hz
SW                     12.016 ppm
FnMODE               undefined

F2 - Processing parameters
SI                         32768
SF                  500.1300415 MHz
WDW                           EM
SSB                            0
LB                        0.30 Hz
GB                             0
PC                          1.00

F1 - Processing parameters
SI                          1024
MC2                           QF
SF                  500.1300000 MHz
WDW                       QSINE
SSB                            0
LB                        0.30 Hz
GB                             0
```



(+/-) **22**

```
Current Data Parameters
NAME                  BJT_5_245C
EXPNO                          2
PROCNO                         1

F2 - Acquisition Parameters
Date_                   20050728
Time                       13.15
INSTRUM                    spect
PROBHD    5 mm CPDUL 13C
PULPROG                 zgpg30
TD                         65536
SOLVENT                    CDCl3
NS                           512
DS                             4
SWH                    31446.541 Hz
FIDRES                 0.479836 Hz
AQ                     1.0420883 sec
RG                          8192
DW                        15.900 usec
DE                         6.00 usec
TE                        300.0 K
D1                     0.15000001 sec
d11                    0.03000000 sec
DELTA                  0.05000000 sec
MCREST                 0.00000000 sec
MCWRK                  0.01500000 sec

======== CHANNEL f1 ========
NUC1                         13C
P1                         10.00 usec
PL1                        -4.90 dB
SFO1                 125.7697360 MHz

======== CHANNEL f2 ========
CPDPRG2                  waltz16
NUC2                         1H
PCPD2                      80.00 usec
PL2                        -5.00 dB
PL12                        9.54 dB
PL13                       10.00 dB
SFO2                 500.1325000 MHz

F2 - Processing parameters
SI                         65536
SF                   125.7579179 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
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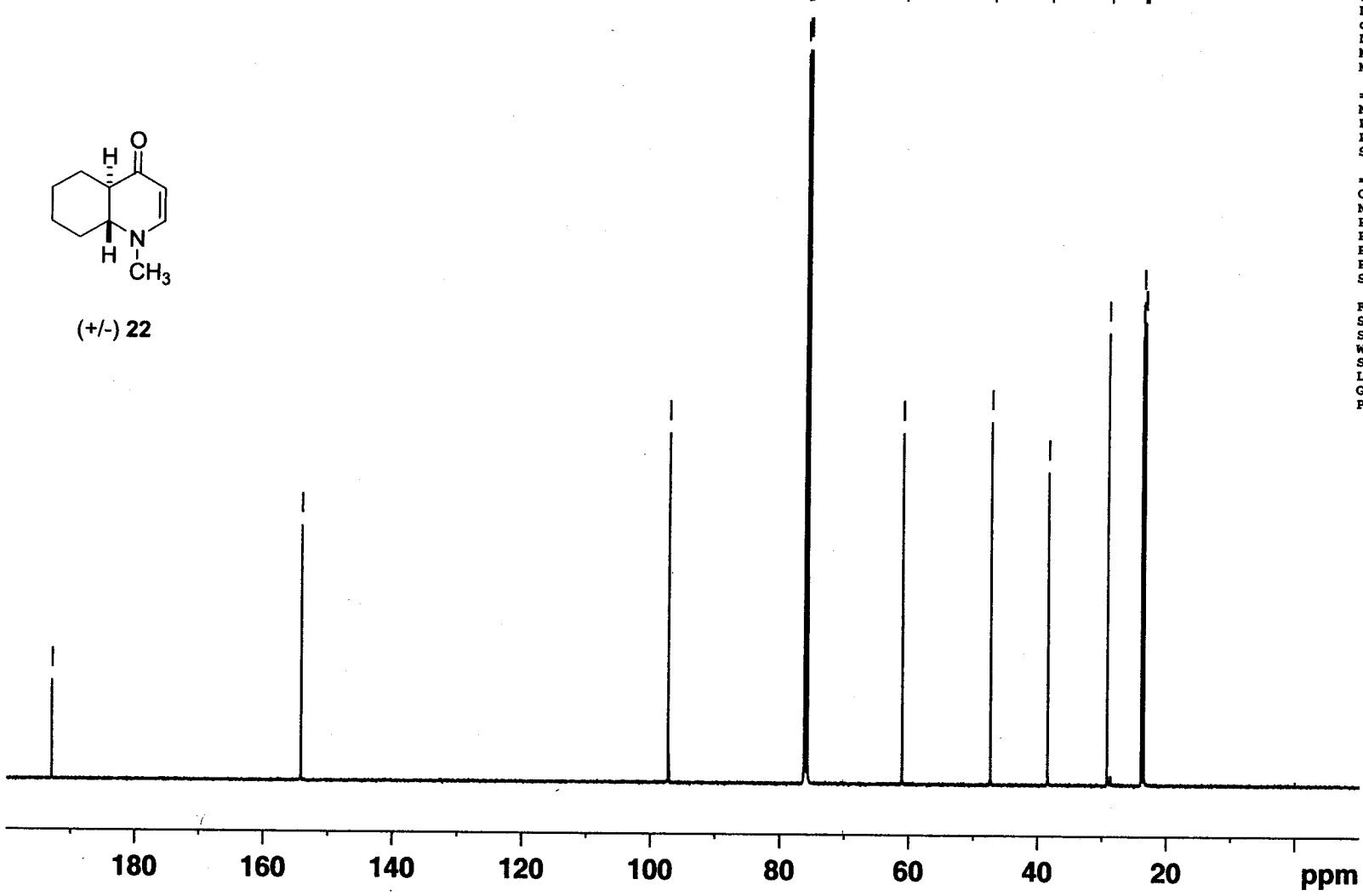
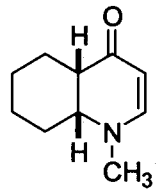
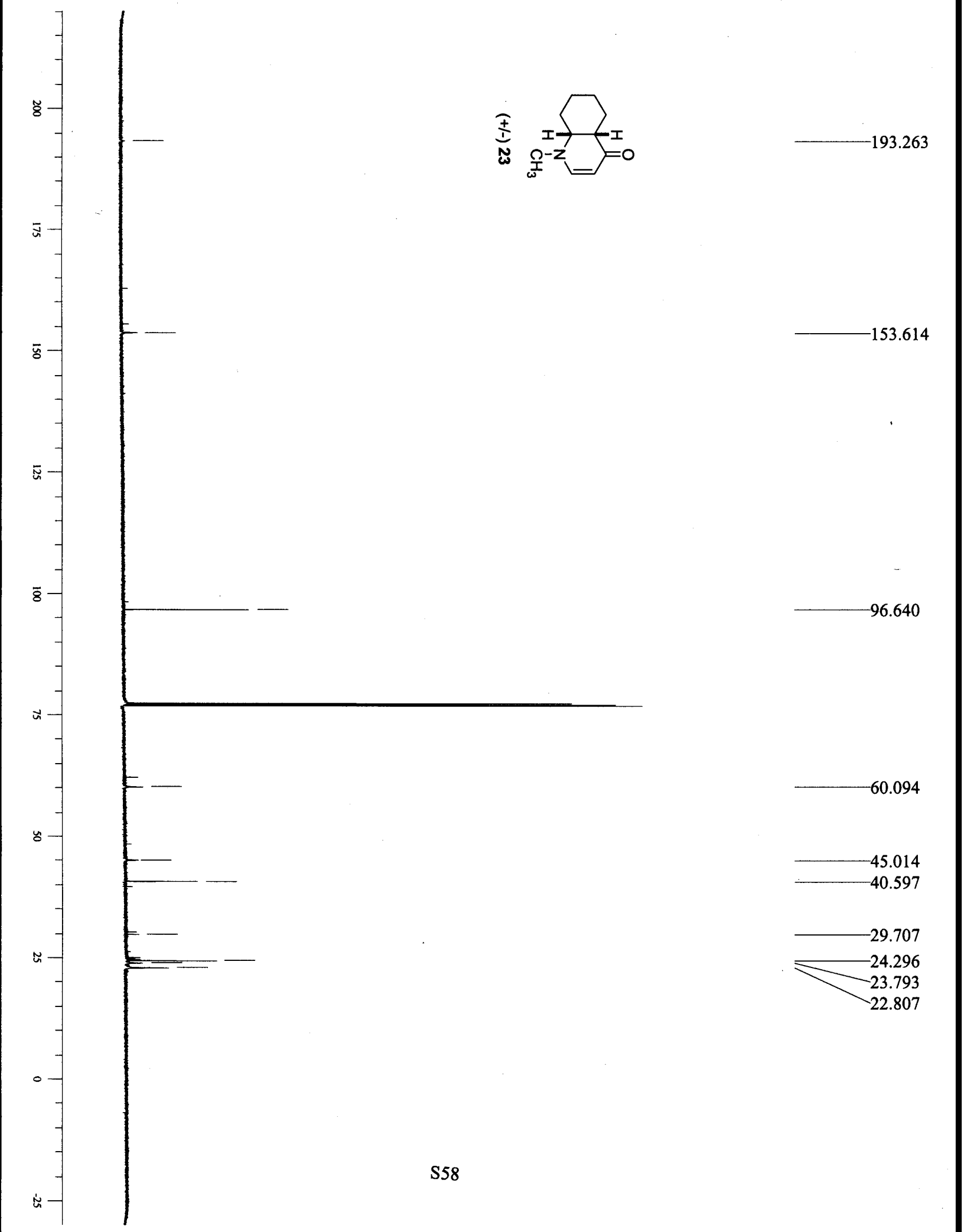
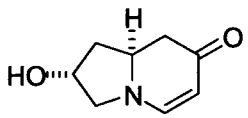


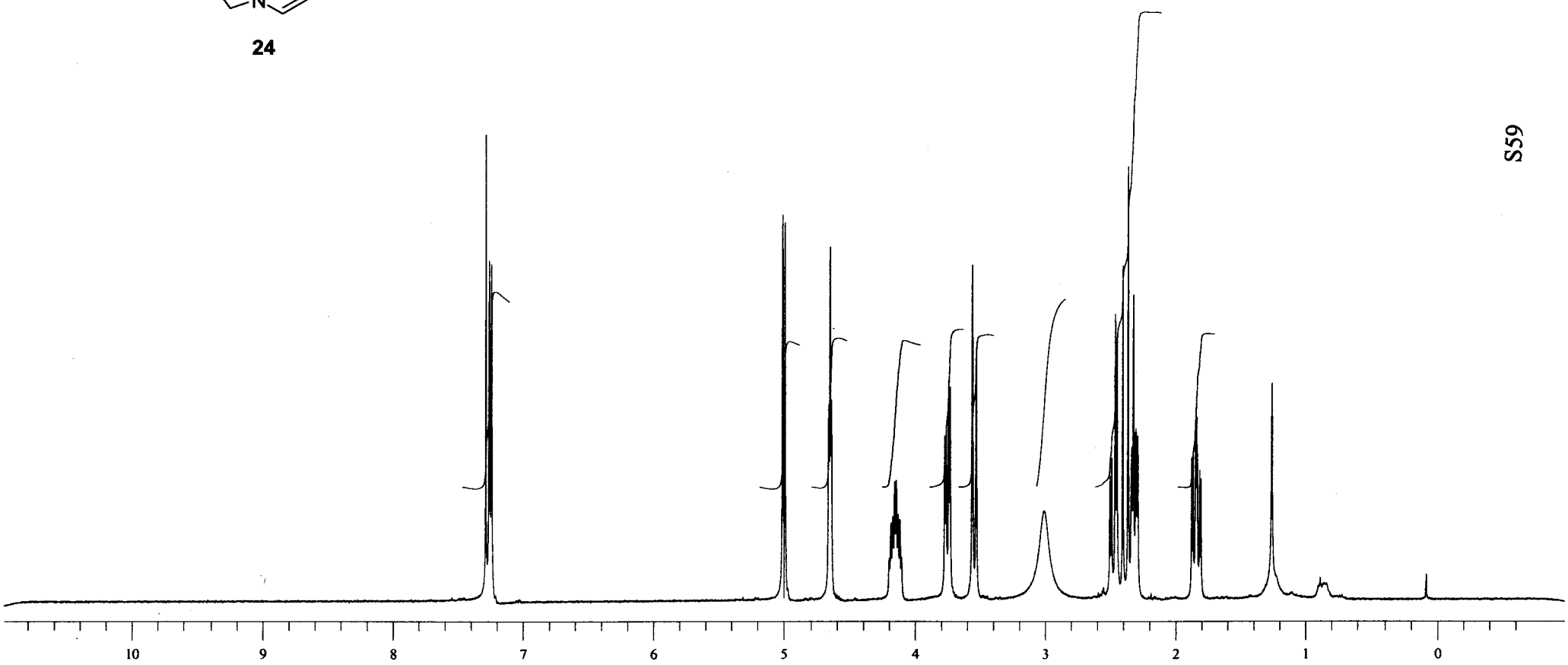


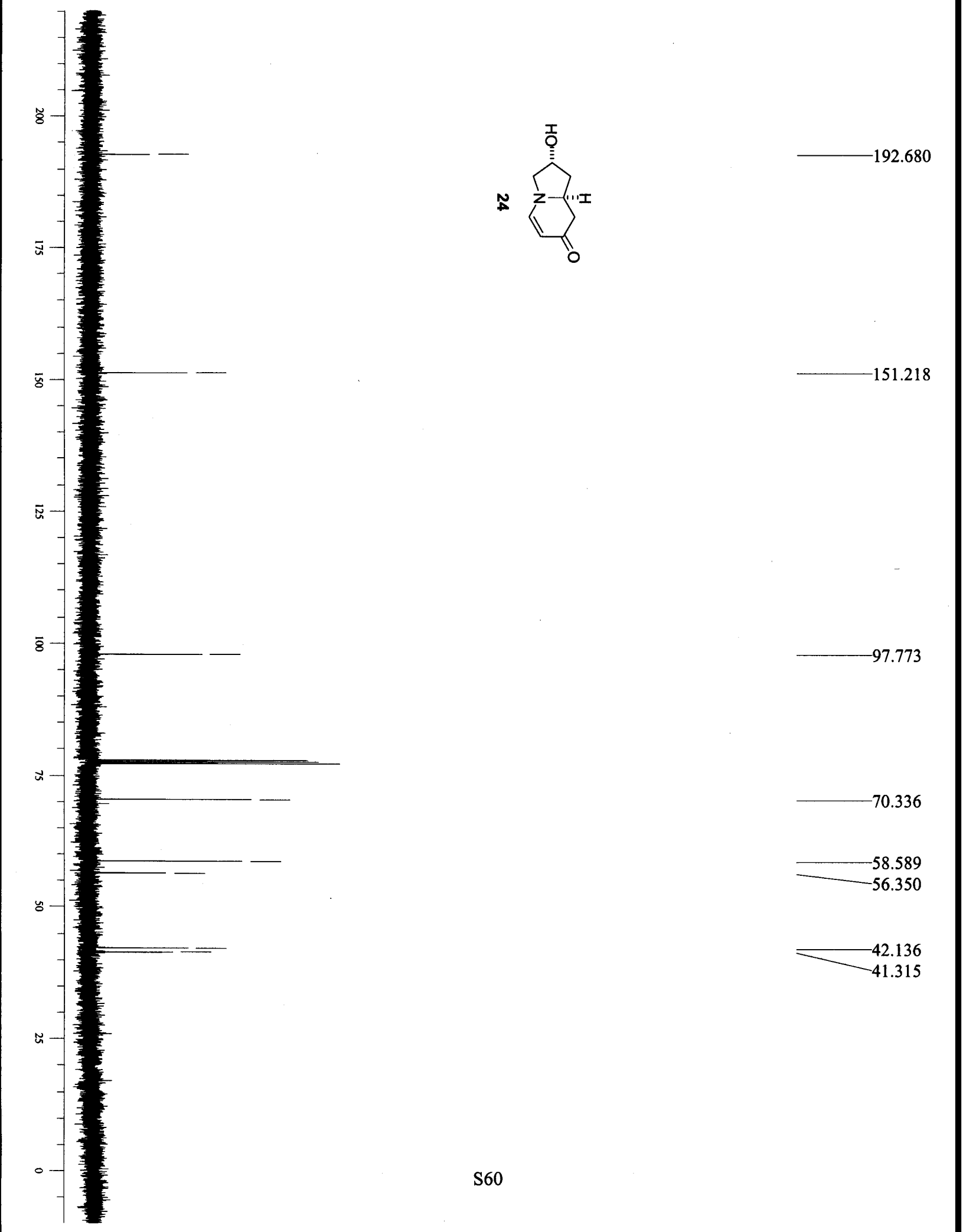
(+/-) **23**

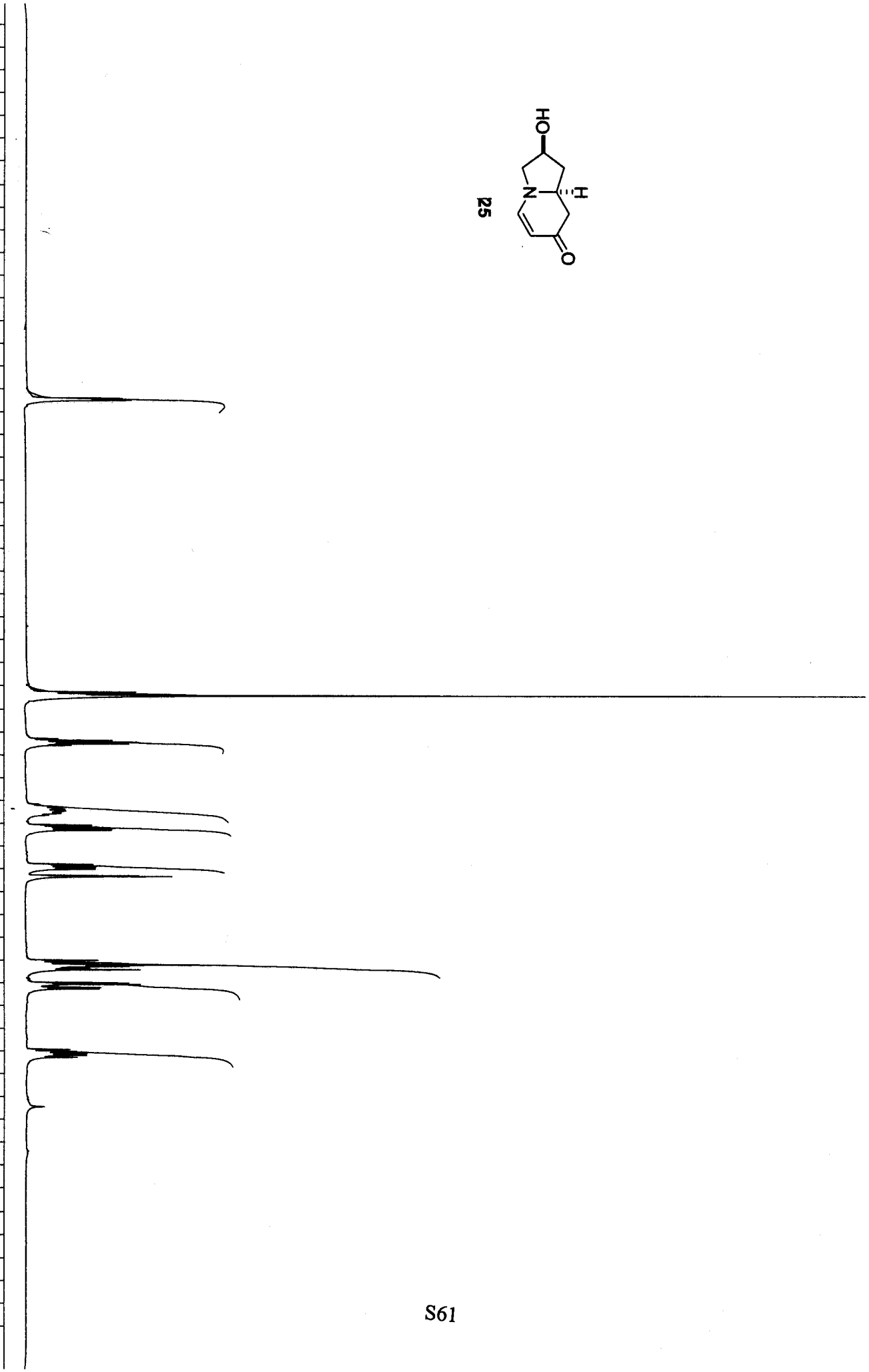

(+/-) 23
193.263
153.614
96.640
60.094
45.014
40.597
29.707
24.296
23.793
22.807
200
175
150
125
100
75
50
25
0
-25



24




200
175
150
125
100
75
50
25
0
HO
H
N
O
24
192.680
151.218
97.773
70.336
58.589
56.350
42.136
41.315



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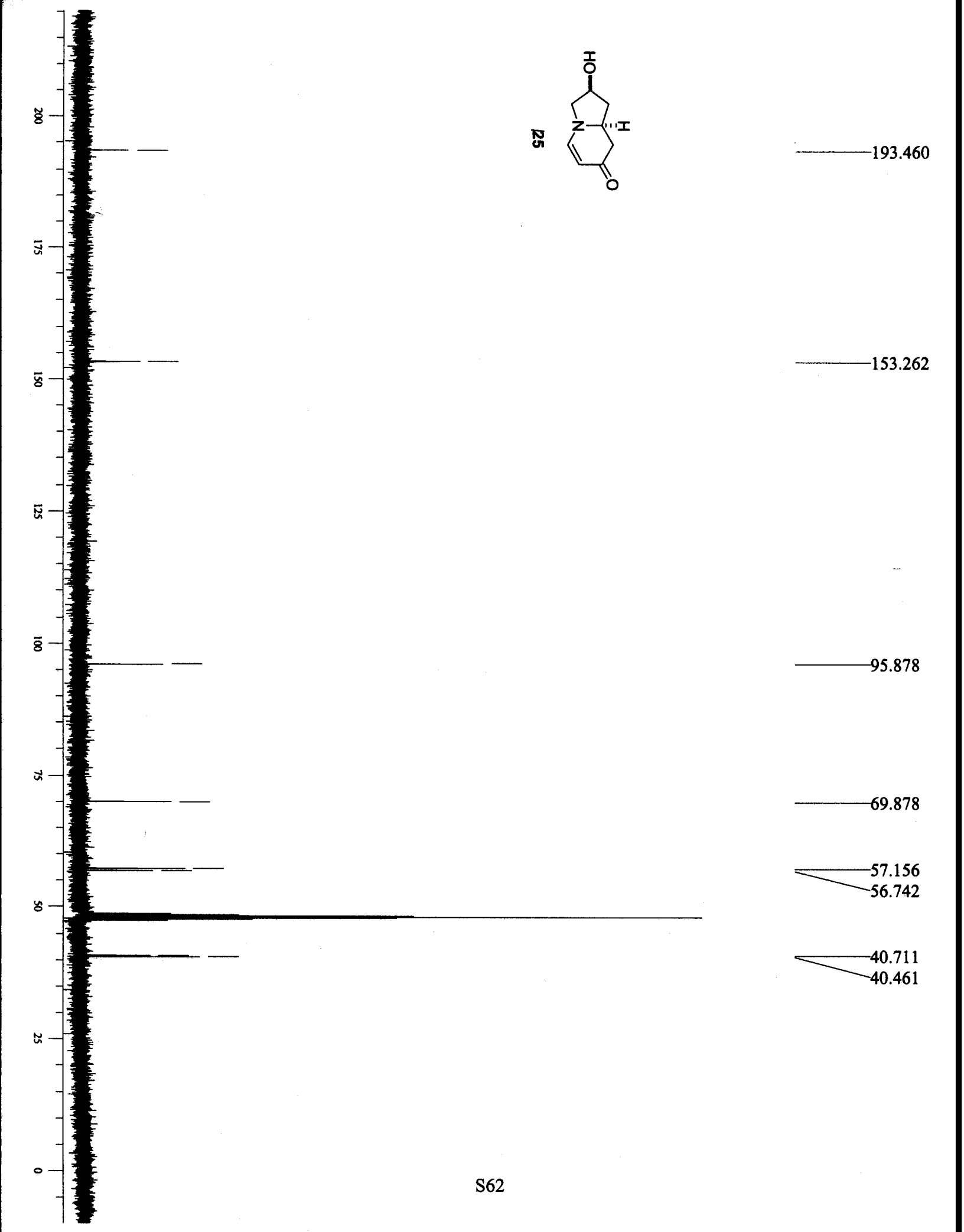
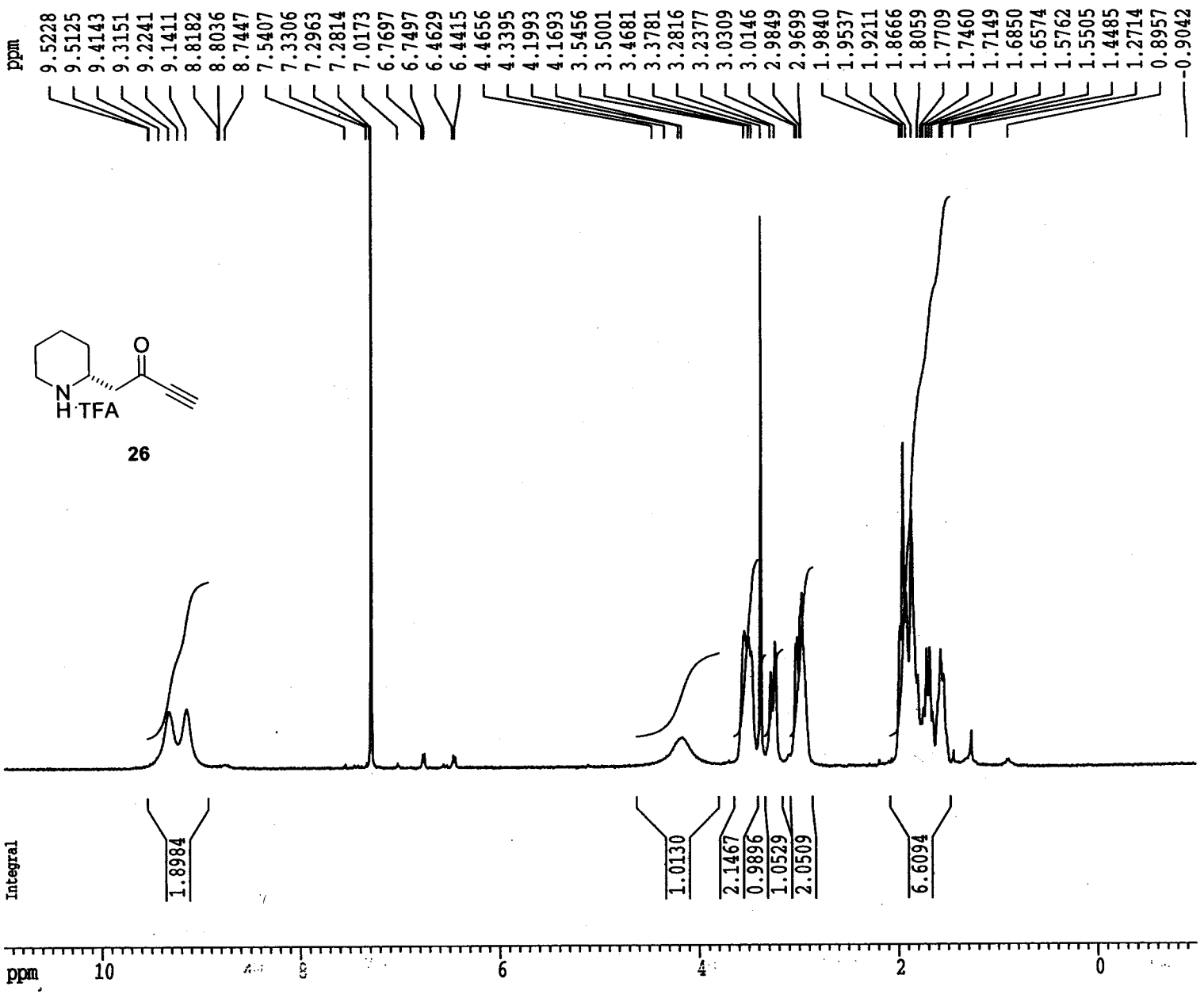

25
OH
N
H
O
193.460
153.262
95.878
69.878
57.156
56.742
40.711
40.461
200
175
150
125
100
75
50
25
0



Current Data Parameters

NAME	BJT5-215
EXPNO	3
PROCNO	1

F2 - Acquisition Parameters

Date_	20050711
Time	13.36
INSTRUM	drx400
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	456.1
DW	104.400 usec
DE	5.50 usec
TE	295.2 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

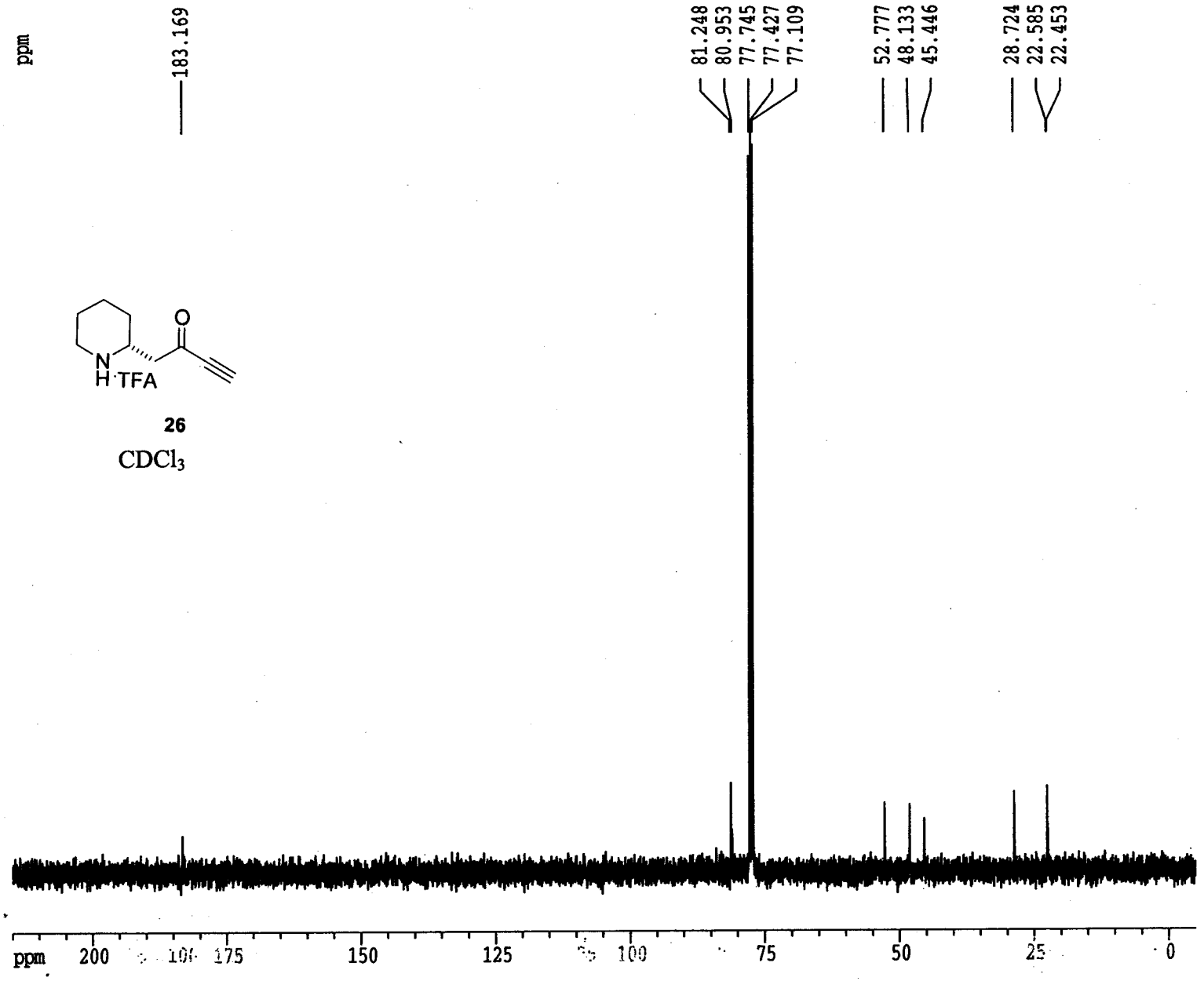
NUC1	1H
P1	9.35 usec
PL1	-4.00 dB
SFO1	400.1320007 MHz

F2 - Processing parameters

SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	11.000 ppm
F1	4401.43 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.60000 ppm/cm
HZCM	240.07800 Hz/cm



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$CDCl_3$

```
Current Data Parameters
NAME            BJT5-215
EXPNO                  4
PROCNO                 1

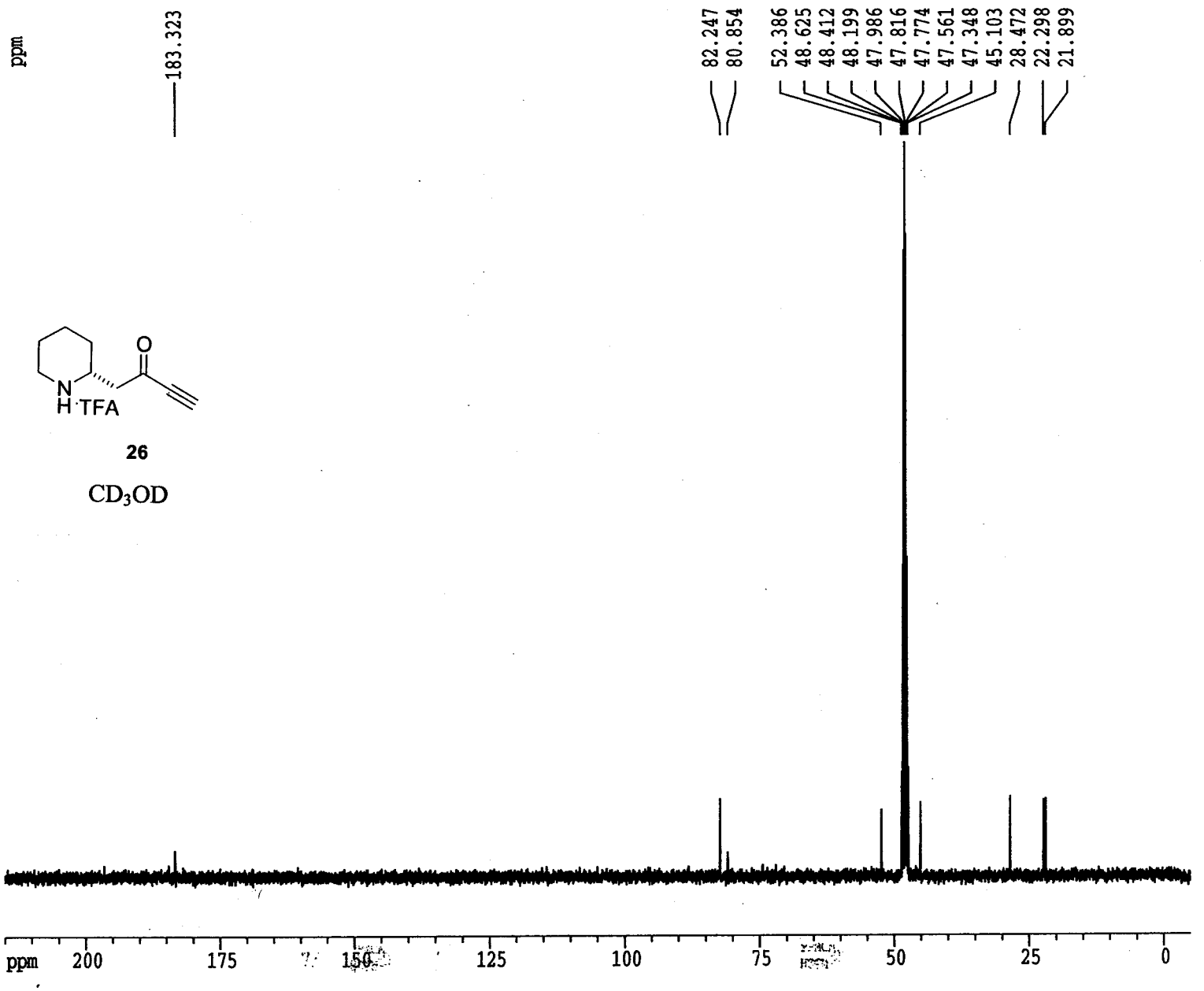
F2 - Acquisition Parameters
Date_           20050711
Time               13.39
INSTRUM           drx400
PROBHD   5 mm QNP 1H/13
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   400
DS                     4
SWH           23148.148 Hz
FIDRES         0.353213 Hz
AQ             1.4156276 sec
RG                 32768
DW                21.600 usec
DE                 5.50 usec
TE                296.2 K
D1            0.15000001 sec
d11           0.03000000 sec
DELTA         0.05000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                13C
P1                11.25 usec
PL1                2.00 dB
SFO1         100.6232933 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2            100.00 usec
PL2               -4.00 dB
PL12              16.58 dB
PL13              17.00 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                 65536
SF           100.6127290 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40

1D NMR plot parameters
CX                20.00 cm
CY                12.50 cm
F1P              215.000 ppm
F1             21631.74 Hz
F2P               -5.000 ppm
F2              -503.06 Hz
PPMCM           11.00000 ppm/cm
HZCM          1106.73999 Hz/cm
```



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CD_3OD

Current Data Parameters

NAME	BJT5-215
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20050529
Time	15.09
INSTRUM	drx400
PROBHD	5 mm QNP 1H/13
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	602
DS	4
SWH	23148.148 Hz
FIDRES	0.353213 Hz
AQ	1.4156276 sec
RG	32768
DW	21.600 usec
DE	5.50 usec
TE	294.2 K
D1	0.15000001 sec
d11	0.03000000 sec
DELTA	0.05000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	11.25 usec
PL1	2.00 dB
SFO1	100.6232933 MHz

======== CHANNEL f2 ========

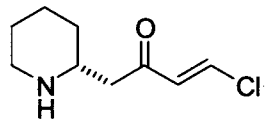
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	-4.00 dB
PL12	16.58 dB
PL13	17.00 dB
SFO2	400.1316005 MHz

F2 - Processing parameters

SI	65536
SF	100.6127290 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	215.000 ppm
F1	21631.74 Hz
F2P	-5.000 ppm
F2	-503.06 Hz
PPMCM	11.00000 ppm/cm
HZCM	1106.73999 Hz/cm



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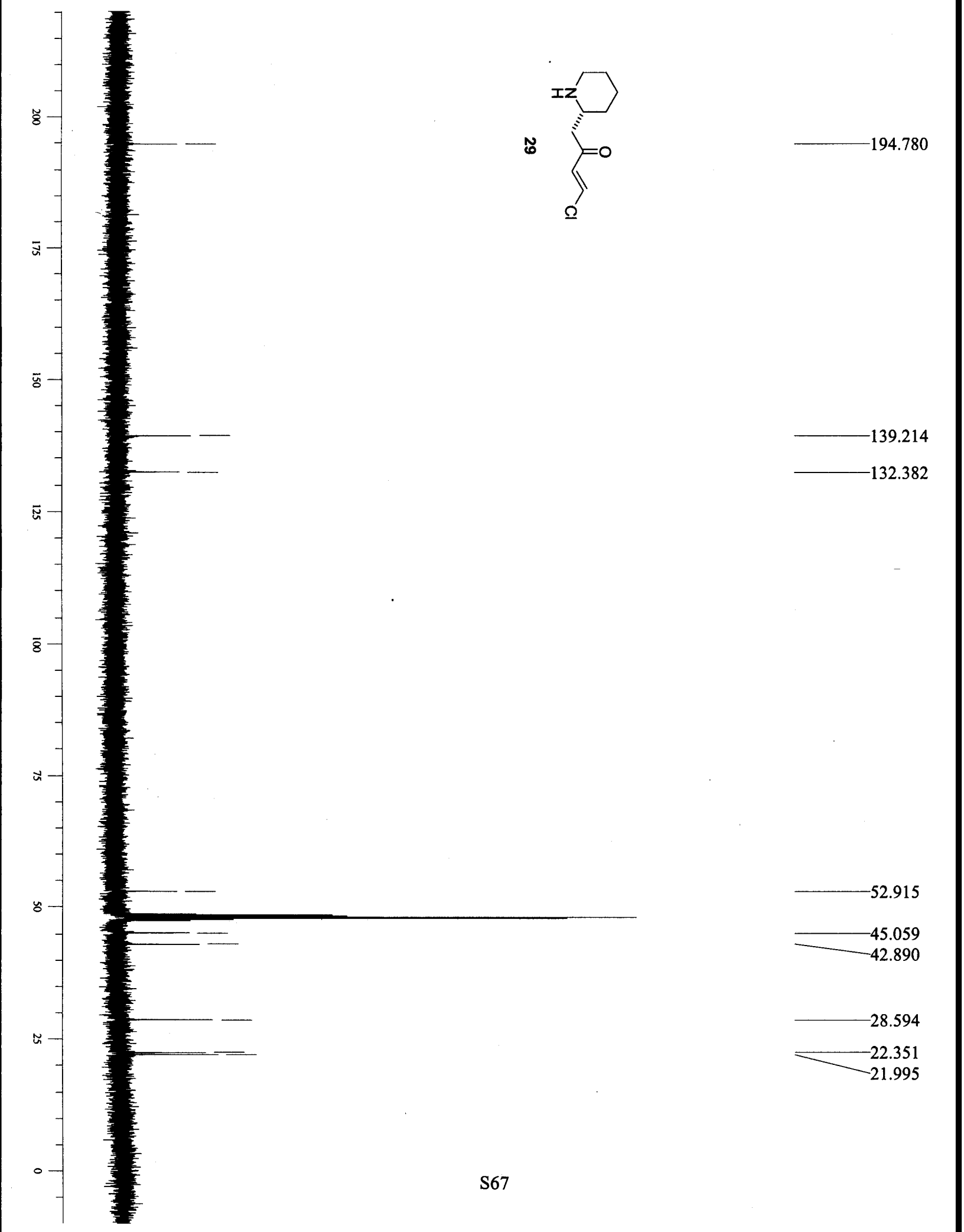
29
194.780
139.214
132.382
52.915
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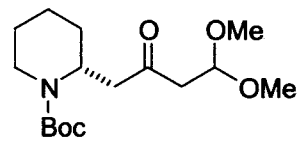
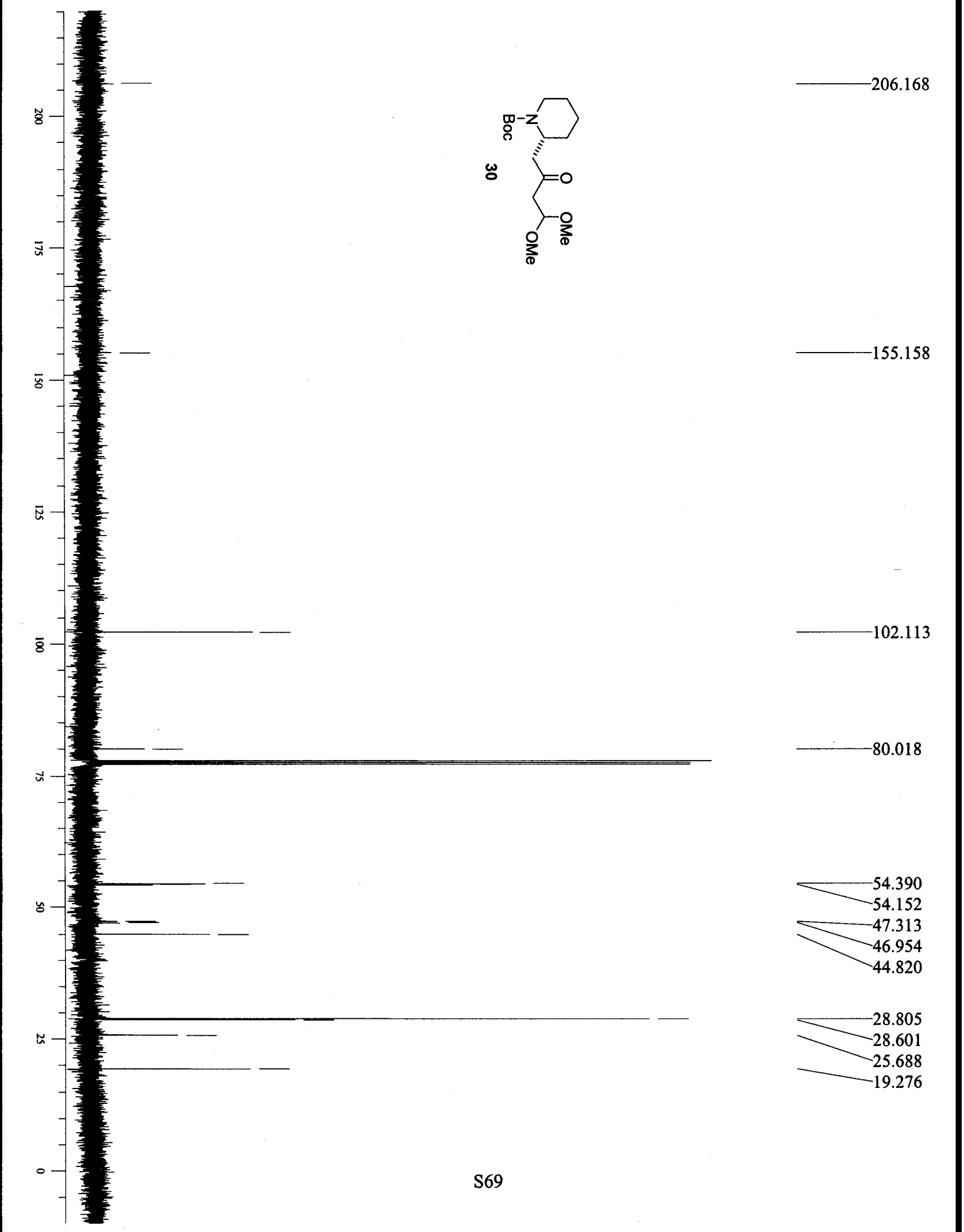
42.890
28.594
22.351
21.995
200
175
150
125
100
75
50
25
0



30


206.168
155.158
102.113
80.018
54.390
54.152
47.313
46.954
44.820
28.805
28.601
25.688
19.276
200
175
150
125
100
75
50
25
0
Boc
N
O
OMe
OMe

30