Supplementary Material (ESI) for Chemical Communications

SUPPORTING INFORMATION

A New Method for the Construction of the Hydroxylated Tropane Skeleton: Enantioselective Synthesis of (−)-Bao Gong Teng A

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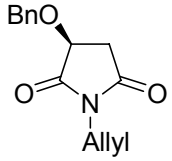
Contents

General Methods

Melting points were determined on a Yanaco MP-500 melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 341 automatic polarimeter. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian unity +500 NMR spectrometer or a Bruker AV 400 NMR spectrometer. Unless otherwise noted, ^{1}H NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. Mass spectra were recorded by Bruker Dalton Esquire 3000 plus and Finnigan Mat-LCQ (ESI direct injection). HRMS spectra were recorded on a Shimadzu LCMS-IT-TOF apparatus. Elemental analyses were performed using a Vario RL analyzer. Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl. Methylene dichloride was distilled from phosphorus pentoxide. Silica gel (zhifu, 300-400 mesh) from Yantai silica gel factory (China) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/ petroleum ether (PE) (60-90 °C) mixture.

Experimental Procedures

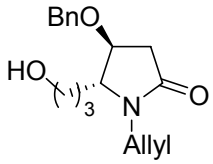
(*S*)-1-Allyl-3-(benzyloxy)pyrrolidine-2,5-dione (6).



To a suspension of (*S*)-1-allyl-3-(benzyloxy)pyrrolidine-2,5-dione[1] (8.80 g, 56.8 mmol) and Ag_2O (39.7 g, 171 mmol) in Et_2O (114 mL) was added BnBr (20.5 mL, 171 mmol). After stirring at dark for two days at room temperature, the mixture was filtered through celite and the residue concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2: PE = 3: 1) afforded compound **6** (13.1 g, 53.4 mmol, 94%) as a colorless oil. $[\alpha]_D^{17}$ –100.9 (*c* 1.60, $CHCl_3$); IR (film): 3083, 3058, 3031, 2979, 2932, 2868, 1784, 1712, 1644, 1497, 1455, 1429, 1396, 1333, 1289, 1253, 1196, 1124 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.67 (dd, *J* = 4.1, 18.3 Hz, 1H, H-4), 2.96 (dd, *J* = 8.2, 18.3 Hz, 1H, H-4), 4.09-4.12 (m, 2H, NCH_2), 4.37 (dd, *J* = 4.1, 8.2 Hz, 1H, H-3), 4.78 (d, *J* = 11.7 Hz, 1H, OCH_2Ph), 4.99 (d, *J* = 11.7 Hz, 1H, OCH_2Ph), 5.17-5.26 (m, 2H, $CH=CH_2$), 5.72-5.83 (m, 1H,

C*H*=CH_2), 7.29-7.41 (m, 5H, ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 36.2, 40.6, 72.0, 72.9, 118.5, 128.1, 128.2, 128.5, 130.3, 136.6, 173.6, 175.4; MS (ESI) *m/z* 268 ($M+Na^+$, 100%); Anal. calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.33; H, 6.14; N, 5.70.

(4*S*,5*R*)-1-Allyl-4-(benzyloxy)-5-(3-hydroxypropyl)pyrrolidin-2-one (8).

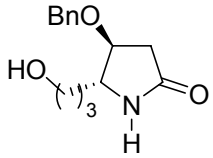


To a cooled solution (0 °C) of compound **6** (1.96 g, 8.00 mmol) in CH_2Cl_2 (64 mL) was added a 0.5 M solution of Grignard reagent **7** in THF (64 mL, 32.0 mmol), prepared from 3-*tert*-butyldimethylsilyloxypropyl bromide. After stirring at 0 °C for 8 h, the reaction was quenched with H_2O (20 mL). The aqueous phase was extracted with CH_2Cl_2 (4×60 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (EtOAc: PE = 1: 2) to afford the adduct (*N*,*O*-acetal) as a diastereomeric mixture in a combined yield of 94%, which, without further separation, was used in the next step.

To a cooled solution (–55 °C) of the diastereomeric mixture of *N*,*O*-acetals in CH_2Cl_2 (50 mL) were added successively Et_3SiH (16.8 mL, 110 mmol) and $BF_3{\cdot}OEt_2$ (5.2 mL, 44.2 mmol). After stirring at –55 °C for overnight, the mixture was allowed to slowly warm to room temperature and stirred for another 2 days. Saturated aqueous $NaHCO_3$ (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (4×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. After concentration in vacuo, the residue was purified by flash chromatography on silica gel (EtOAc: PE = 2: 1) to afford compound **8** (1.88 g, 6.51 mmol, 82%) as a colorless oil. $[\alpha]_D^{17}$ +50.5 (*c* 0.97, $CHCl_3$); IR (film): 3408, 3083, 3063, 3030, 2927, 2867, 1674, 1636, 1496, 1454, 1413, 1359, 1264, 1196, 1067 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.35-1.60 (m, 3H), 1.70-1.80 (m, 1H), 1.90-2.20 (br s, 1H, OH, D_2O exchangeable), 2.49 (dd, *J* = 2.0, 17.5 Hz, 1H, H-3), 2.68 (dd, *J* = 6.6, 17.5 Hz, 1H, H-3), 3.48 (dd, *J* = 7.0, 15.8 Hz, 1H, C*H*$_2$N), 3.62 (t, *J* = 6.3 Hz, 2H, C*H*$_2$OH), 3.65 (ddd, *J* = 2.0, 3.4, 7.1 Hz, 1H, H-5), 3.90 (ddd, *J* = 2.0, 2.0, 6.6 Hz, 1H, H-4), 4.35 (dd, *J* = 4.3, 15.8 Hz, 1H, C*H*$_2$N), 4.48 (d, *J* = 11.8 Hz, 1H, OC*H*$_2$Ph), 4.54

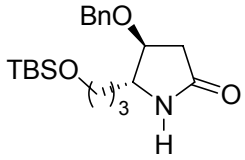
(d, *J* = 11.8 Hz, 1H, OC*H*$_2$Ph), 5.15-5.28 (m, 2H, CH=C*H*$_2$), 5.67-5.79 (m, 1H, C*H*=CH$_2$), 7.28-7.38 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 27.8, 37.2, 42.9, 62.2, 63.6, 70.7, 75.8, 117.8, 127.7, 127.9, 128.5, 132.3, 137.5, 172.3; MS (ESI) *m/z* 312 (M+Na$^+$, 100%); Anal. calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.50; H, 8.03; N, 4.84.

(4*S*,5*R*)-4-(Benzyloxy)-5-(3-hydroxypropyl)pyrrolidin-2-one (9).



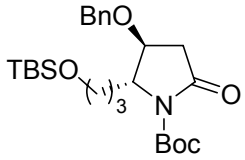
A mixture of compound **8** (1.92 g, 6.64 mmol) and $RhCl_3 \cdot xH_2O$ (107 mg) in EtOH (65 mL) was refluxed for 6 hours. After removal of the solvent, the residue was dissolved in H_2O/AcOH (45 mL /45 mL) and refluxed for another 48 hours. Water and the acetic acid were removed under reduced pressure. To the resulting residue in 40 mL EtOH (40 mL) was added AcCl (1.1 mL, 15.5 mmol) at 0 °C under nitrogen atmosphere. After stirring at room temperature for one day, the reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2 (100 mL). The organic phase was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (EtOAc: MeOH = 20: 1) to afford compound **9** (1.24 g, 4.98 mmol, 75%) as a colorless oil. $[\alpha]_D^{17}$ +59.8 (*c* 1.85, $CHCl_3$); IR (film): 3272, 3088, 3054, 3025, 2935, 2868, 1693, 1497, 1454, 1393, 1354, 1310, 1267, 1067, 1029 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.44-1.54 (m, 1H), 1.54-1.69 (m, 3H), 2.39 (dd, *J* = 3.9, 17.4 Hz, 1H, H-3), 2.62 (dd, *J* = 6.9, 17.4 Hz, 1H, H-3), 3.48 (br s, 1H, OH), 3.54-3.68 (m, 3H, C*H*$_2$OH and H-5), 3.86 (ddd, *J* = 3.6, 3.9, 6.9 Hz, 1H, H-4), 4.46 (d, *J* = 11.7 Hz, 1H, OC*H*$_2$Ph), 4.52 (d, *J* = 11.7 Hz, 1H, OC*H*$_2$Ph), 7.25-7.37 (m, 5H, ArH), 7.62 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 31.2, 37.1, 60.7, 61.7, 71.1, 79.0, 127.6, 127.8, 128.4, 137.3, 175.8; MS (ESI) *m/z* 272 (M+Na$^+$, 100%); Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.57; H, 7.66; N, 5.63.

(4*S*,5*R*)-4-(Benzyloxy)-5-(3-*tert*-butyldimethylsilyloxypropyl)pyrrolidin-2-one (10).



A mixture of hydroxy-lactam **9** (1.40 g, 5.62 mmol), imidazole (444 mg, 16.9 mmol), TBSCl (1.70 g, 11.3 mmol) and DMAP (50 mg) in anhydrous CH_2Cl_2 (8 mL) was stirred at room temperature under nitrogen atmosphere for 24 hours. After quenching with water (15 mL) at 0 °C, the aqueous phase was extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were washed successively with a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (EtOAc: PE = 1: 5) to afford compound **10** (1.73 g, 4.77 mmol, yield: 85%) as a colorless oil. $[\alpha]_D^{25}$ +29.3 (*c* 1.20, $CHCl_3$); IR (film): 3211, 3091, 3032, 2951, 2928, 2885, 2857, 1702, 1497, 1472, 1455, 1388, 1359, 1308, 1256, 1167, 1205, 1098, 1029, 1006 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.22 (s, 6H, $(CH_3)_2Si$), 1.06 (s, 9H, *t*-Bu), 1.65-1.90 (m, 4H, 2×CH_2), 2.57 (dd, *J* = 3.8, 17.3 Hz, 1H, H-3), 2.79 (dd, *J* = 7.0, 17.3 Hz, 1H, H-3), 3.74-3.85 (m, 3H, C*H*$_2$OTBS and H-5), 4.05 (ddd, *J* = 3.6, 3.8, 7.0 Hz, 1H, H-4), 4.66 (d, *J* = 11.8 Hz, 1H, OC*H*$_2$Ph), 4.71 (d, *J* = 11.8 Hz, 1H, OC*H*$_2$Ph), 7.43-7.54 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 (2C), 18.2, 25.9, 29.0, 31.4, 37.1, 60.6, 62.5, 71.1, 79.0, 127.6, 127.8, 128.4, 137.5, 175.4; MS (ESI) *m/z* 386 ($M+Na^+$, 100%); Anal. calcd for $C_{20}H_{33}NO_3Si$: C, 66.07; H, 9.15; N, 3.85. Found: C, 66.25; H, 9.13; N, 3.84.

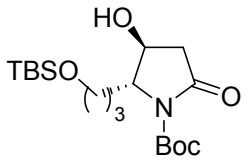
***tert*-Butyl (2*R*,3*S*)-3-(benzyloxy)-2-(3-*tert*-butyldimethylsilyloxypropyl)-5-oxopyrrolidine-1-carboxylate (11).**



To a mixture of compound **10** (1.21 g, 3.33 mmol), Et_3N (1.4 mL, 10.1 mmol) and DMAP (50 mg, 0.38 mmol) in anhydrous CH_2Cl_2 (6.7 mL) was added dropwise $(Boc)_2O$ (1.9 mL, 8.3 mmol) under nitrogen atmosphere at 0 °C. After stirring at room temperature for 24 hours, the reaction was quenched with water (20 mL) at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and

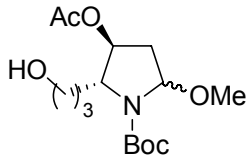
concentration in vacuo, the residue was purified by flash chromatography on silica gel (EtOAc: PE = 1: 7) to afford compound **11** (1.45 g, 3.13 mmol, 94%) as a colorless oil. $[\alpha]_D^{25}$ –34.5 (*c* 1.39, $CHCl_3$); IR (film): 3054, 3029, 2954, 2930, 2857, 1786, 1752, 1716, 1497, 1471, 1455, 1368, 1309, 1212, 1153, 1095, 1070, 1043, 1026 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H, 2×$SiCH_3$), 0.88 (s, 9H, *t*-BuSi), 1.37-1.60 (m, 3H), 1.53 (s, 9H, *t*-BuO), 1.74-1.86 (m, 1H), 2.59 (d, *J* = 18.1 Hz, 1H, H-3), 2.76 (dd, *J* = 5.6, 18.1 Hz, 1H, H-3), 3.61 (t, *J* = 6.1 Hz, 2H, TBSOCH_2), 3.83 (d, *J* = 5.6 Hz, 1H, H-4), 4.15 (dd, *J* = 3.5, 9.5 Hz, 1H, H-5), 4.51 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 4.54 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 7.26-7.38 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.4 (2C), 18.4, 26.1, 28.2, 28.9, 29.2, 38.5, 62.6, 64.4, 70.7, 74.2, 83.1, 127.8, 128.1, 128.7, 137.4, 149.9, 172.3; MS (ESI) *m/z* 486 ($M+Na^+$, 100%); Anal. calcd for $C_{25}H_{41}NO_5Si$: C, 64.76; H, 8.91; N, 3.02. Found: C, 64.92; H, 8.93; N, 3.01.

***tert*-Butyl (2*R*,3*S*)-3-hydroxy-2-(3-*tert*-butyldimethylsilyloxypropyl)-5-oxopyrrolidine-1-carboxylate (5).**



To a solution of compound **11** (1.449 g, 3.13 mmol) in 16 mL of ethanol was added 10% Pd/C (435 mg). The mixture was hydrogenated under 1 atm hydrogen pressure at room temperature for 36 h. The reaction mixture was filtered through celite and the filtrate was evaporated in vacuo. Flash chromatography (EtOAc: PE = 1: 2) of the residue afforded compound **5** (1.15 g, 3.09 mmol, 95%) as white crystals. M.p. = 96-97 °C (EtOAc/PE); $[\alpha]_D^{20}$ –44.1 (*c* 1.36, $CHCl_3$); IR (film) 3460, 2928, 2856, 1771, 1723, 1460, 1368, 1350, 1294, 1253, 1227, 1154, 1122, 1082, 1049, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H, 2×$SiCH_3$), 0.85 (s, 9H, *t*-BuSi), 1.36-1.47 (m, 1H), 1.49 (s, 9H, O*t*-Bu), 1.51-1.62 (m, 2H), 1.69-1.82 (m, 1H), 2.43 (d, *J* = 18.1 Hz, 1H, H-3), 2.78 (dd, *J* = 5.4, 18.1 Hz, 1H, H-3), 3.17 (d, *J* = 3.4 Hz, 1H, D_2O exchangeable, OH), 3.61 (t, *J* = 6.0 Hz, 2H, CH_2OTBS), 4.00 (dd, *J* = 3.5, 9.6 Hz, 1H, H-5), 4.14 (dd, *J* = 3.4, 5.4 Hz, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.2 (2C), 18.5, 26.1, 28.2, 28.9, 29.3, 41.3, 62.8, 67.6, 67.7, 83.2, 150.1, 173.2; MS (ESI) *m/z* 396 ($M+Na^+$, 100%); Anal. calcd for $C_{18}H_{35}NO_5Si$: C, 57.87; H, 9.44; N, 3.75. Found: C, 57.92; H, 9.43; N, 3.76.

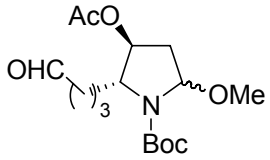
***tert*-Butyl (2*R*,3*S*)-3-acetoxy-2-(3-hydroxypropyl)-5-methoxypyrrolidine-1-carboxylate (12).**



To a solution of compound **5** (800 mg, 2.20 mmol) in 20 mL of methanol was added $NaBH_4$ (324 mg, 8.60 mmol) at 0 °C. After stirring at the same temperature for 1 hour, the reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL). The solvent was evaporated in vacuo. To the residue was added water (20 mL) and the aqueous phase extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration and concentration in vacuo, the residue and a catalytic amount of DMAP (40 mg, 0.33 mmol) were dissolved in anhydrous CH_2Cl_2 (10 mL). To this solution were added pyridine (520 mg, 0.5 mL, 6.58 mmol) and Ac_2O (890 mg, 0.80 mL, 8.72 mmol) at 0 °C. After stirring at room temperature for 2 hours, water (5 mL) was added at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed successfully with a 1 M solution of HCl (10 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in an I_2-MeOH solution (50 mL, 1% g/mL) and stirred at room temperature for 8 hours. The reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) at 0 °C. The solvent was evaporated in vacuo. To the resulting mixture was added water (20 mL) and the aqueous phase extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. Flash chromatography (EtOAc: PE = 2: 1) of the residue afforded compound **12** as a inseparable diastereomeric mixture (474 mg, 1.50 mmol, 68%). colorless oil; $[\alpha]_D^{20}$ –31.1 (*c* 3.8, $CHCl_3$); IR (film) 3461, 2976, 2937, 1741, 1701, 1442, 1391, 1367, 1316, 1241, 1169, 1130, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (1:1 diastereomeric mixture; a and b; determined by integration at δ 5.20-5.31 and 5.31-5.52) δ 1.49 (s, $9H_{a+b}$, O*t*-Bu), 1.55-1.85 (m, $4H_{a+b}$), 2.03 (s, $3H_{a+b}$, OAc), 2.06-2.18 (m, $1H_{a+b}$, H-3), 2.22-2.41 (m, $1H_{a+b}$, H-3), 3.32 (m, $1.5H_a$, OMe), 3.35 (m, $1.5H_b$, OMe), 3.67 (t, J = 5.9 Hz, $2H_{a+b}$, CH_2OH), 3.82-3.95 (m, 0.5H, H_a), 3.95-4.09 (m, 0.5H, H_b), 5.06-5.15 (m, $1H_{a+b}$), 5.20-5.31 (m, $0.5H_a$), 5.31-5.52 (m, $0.5H_b$); ^{13}C NMR (100 MHz, $CDCl_3$)

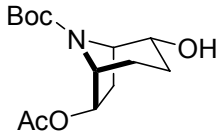
(1:1 diastereomeric mixture) δ 21.3, 28.5, 28.7, 29.0, 30.3, 38.3, 39.2, 55.9, 56.2, 62.6, 62.9, 63.5, 77.5, 77.9, 80.8, 88.9, 154.5, 153.4, 170.7; MS (ESI) *m/z* 340 ($M+Na^+$, 100%); Anal. calcd for $C_{15}H_{27}NO_6$: C, 56.77; H, 8.57; N, 4.41. Found: C, 56.59; H, 8.59; N, 4.40.

tert-Butyl (2*R*,3*S*)-3-acetoxy-2-(2-formylethyl)-5-methoxypyrrolidine-1-carboxylate (4).



To a solution of Dess-Martin periodinane (2.670 g, 6.30 mmol) in 20 mL of CH_2Cl_2 was added dropwise a 0.14 M CH_2Cl_2 solution of compound **12** (660 mg, 2.10 mmol) at 0 °C. The resulting solution was stirred at the room temperature for 0.5 hour and diluted with Et_2O (30 mL) at 0 °C. To the resulting mixture were added an aqueous solution (15 mL) of $Na_2S_2O_3$ (*ca.* 100-158 g/L) and $NaHCO_3$ (*ca.* 100 g/L), and the resulting mixture was stirred for 15 min. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration in vacuo, the residue was purified by flash chromatography on silica gel (EtOAc: PE = 1 : 2) to afford compound **2** (484 mg, 1.54 mmol, 73%) as a inseparable diastereomeric mixture in 1:1 ratio. colorless oil; $[\alpha]_D^{25}$ –31.4 (*c* 2.06, $CHCl_3$); IR (film): 2977, 2936, 2825, 2716, 1739, 1700, 1444, 1389, 1367, 1314, 1241, 1167, 1131, 1089 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) (1:1 diastereomeric mixture; a and b; determined by integration at δ 5.20-5.32 and 5.32-5.44) δ 1.49 (s, $9H_{a+b}$, O*t*-Bu), 1.85-2.08 (m, $2H_{a+b}$), 2.03 (s, $3H_{a+b}$, OAc), 2.08-2.20 (m, $1H_{a+b}$), 2.25-2.40 (m, $1H_{a+b}$), 2.47-2.65 (m, $2H_{a+b}$, CHOC*H*$_2$), 3.34 (s, $1.5H_a$, OMe), 3.37(s, $1.5H_b$, OMe), 3.86-3.95 (m, $0.5H_a$), 3.95-4.04 (m, $0.5H_b$), 5.05-5.12 (m, $1H_{a+b}$), 5.20-5.32 (m, $0.5H_a$), 5.32-5.44 (m, $0.5H_b$), 9.80 (s, $1H_{a+b}$, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) (1:1 diastereomeric mixture) δ 21.2, 25.8, 26.4, 28.5, 28.7, 36.1, 38.9, 40.2, 55.9, 56.3, 62.9, 80.7, 88.9, 154.5, 155.3, 170.6, 201.5; MS (ESI) *m/z* 338 ($M+Na^+$, 100%); Anal. calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.37; H, 7.97; N, 4.46.

(1*R*,2*R*,5*R*,6*S*)-6-Acetyloxy-8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]octan-2-ol (13).



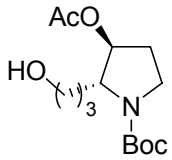
To a cooled solution (–50 °C) of compound **4** (460 mg, 1.46 mmol) in THF (60 mL) were added dropwise $BF_3{\cdot}OEt_2$ (0.52 mL, 4.20 mmol), and a 0.1 M solution of SmI_2 in THF (42 mL) containing *t*-BuOH (310 mg, 0.42 mL).[2] After stirring at the same temperature for 0.5 h, the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted with EtOAc (4×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc: PE = 1: 1) to afford compound **13** (233 mg, 0.82 mmol, yield: 56%) as white crystals, and an inseparable mixture, which was further purified by flash chromatography on silica gel (eluent: CH_2Cl_2: MeOH = 15: 1) to afford compound **14** (21 mg, 0.074 mmol, yield: 5%) as a colorless oil, and the reduced product **15** (46 mg, 0.16 mmol, yield: 11%).

Diastereomer **13**: M.p. = 113-114 ^oC (EtOAc/PE); $[\alpha]_D^{17}$ –51.2 (*c* 4.3, $CHCl_3$); IR (film): 3427, 2977, 2930, 2871, 1734, 1692, 1695, 1475, 1406, 1366, 1328, 1244, 1165, 1112, 1071, 1038 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (a 63:37 mixture of two rotamers; determined by integration at δ 3.70-3.78 and 3.78-3.85) δ 1.25-1.37 (m, 1H), 1.45 (s, 5.7 H, *t*-Bu), 1.48 (s, 3.3 H, *t*-Bu), 1.53-1.78 (m, 2H), 1.78-1.87 (m, 1H), 1.87-1.97 (m, 1H), 2.03 (s, 1.1H, OAc), 2.05 (s, 1.9 H, OAc), 2.47 (dd, *J* = 7.6, 14.5 Hz, 1H, H-7), 2.77 (br s, 0.37H, OH, D_2O exchangeable), 3.48 (br s, 0.63H, OH, D_2O exchangeable), 3.70-3.78 (m, 0.37 H), 3.78-3.85 (m, 0.63H), 3.97-4.02 (m, 0.63 H), 4.07-4.12 (m, 0.37 H), 4.17-4.22 (m, 0.37 H), 4.32 (dd, *J* = 3.0, 7.1 Hz, 0.63 H), 4.97 (dd, *J* = 2.2, 7.6 Hz, 1H, H-6); ^{13}C NMR (rotameric mixture) (125 MHz, $CDCl_3$) δ 21.3, 25.6, 26.1, 26.3, 26.8, 28.6, 31.5, 32.4, 58.7, 58.8, 59.2, 29.8, 66.9, 67.7, 76.6, 77.5, 80.1, 80.2, 153.8, 154.2, 171.1; MS (ESI) *m/z* 308 ($M+Na^+$, 100%); HRMS calcd for $C_{14}H_{23}NNaO_5$ [$M+Na^+$]: 308.1468; found: 308.1475.

Diastereomer **14**: $[\alpha]_D^{20}$ –31.7 (*c* 1.18, $CHCl_3$); IR (film): 3444, 2976, 2926, 2864, 1737, 1684, 1420, 1366, 1245, 1171, 1115, 1007 cm^{-1}; ^1H NMR (a 65:35 mixture of two rotamers; determined by integration at δ 4.30-4.42 and 4.42-4.53) (400 MHz,

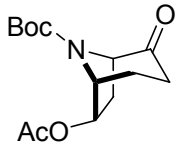
$CDCl_3$) δ 1.48 (s, 9H, *t*-Bu), 1.51-1.69 (m, 4H), 1.93 (ddd, *J* = 2.5, 7.9, 14.4 Hz, H-7), 2.04 (s, 3H), 2.12 (dd, *J* = 7.4, 14.4, Hz, H-7), 2.81 (br s, 1H, OH, D_2O exchangeable), 3.62-3.80 (m, 1H), 4.07-4.14 (m, 0.65H), 4.19-4.30 (m, 0.35H), 4.30-4.42 (m, 0.35H), 4.42-4.53 (m, 0.65H), 5.05 (dd, *J* = 2.5, 7.4 Hz, 1H, H-6); ^{13}C NMR (rotameric mixture) (100 MHz, $CDCl_3$) δ 21.3, 23.7, 24.2, 24.9, 28.7, 35.2, 35.8, 58.5, 59,7, 60.8, 69.2, 69.8, 76.2, 77.5, 80.5, 156.4, 171.0; MS (ESI) *m/z* 308 ($M+Na^+$, 100%); HRMS calcd for $C_{14}H_{23}NNaO_5$ $[M+Na]^+$: 308.1468; found: 308.1482.

tert-Butyl (2*R*,3*S*)-3-acetoxy-2-(3-hydroxypropyl)pyrrolidine-1-carboxylate (15).



Colorless oil; $[\alpha]_D^{25}$ –34.4 (*c* 1.19, $CHCl_3$); IR (film): 3445, 2976, 2936, 1739, 1694, 1478, 1402, 1366, 1242, 1171, 1121, 1023 cm^{-1}; ^{1}H NMR (rotameric mixture) (400 MHz, $CDCl_3$) δ 1.47 (s, 9H, *t*-Bu), 1.58-1.85 (m, 4H), 1.92-2.00 (m, 1H), 2.05 (s, 3H), 2.08-2.20 (m, 1H), 3.40-3.55 (m, 2H, H-5), 3.61-3.76 (m, 2H, OC*H*$_2$), 3.64-3.89 (m, 1H, H-2), 4.98-5.05 (m, 1H); ^{13}C NMR (rotameric mixture) (100 MHz, $CDCl_3$) 21.5, 28.7, 28.8, 28.9, 29.6, 29.7, 29.9, 44.3, 44.6, 62.3, 62.7, 63.1, 63.7, 78.0, 79.9, 154.9, 155.1, 170.8, 170.9; MS (ESI) *m/z* 310 ($M+Na^+$, 100%); Anal. calcd for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.37; H, 8.75; N, 4.88.

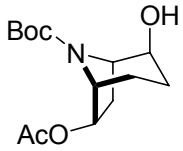
(1*R*,5*R*,6*S*)-6-Acetyloxy-8-(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-2-one (16).



To a solution of Dess-Martin periodinane (445 mg, 1.05 mmol) in 8 mL of CH_2Cl_2 was added dropwise a CH_2Cl_2 (5 mL) solution of compound **13** (120 mg, 0.42 mmol) at 0 °C. The resulting solution was stirred at room temperature for 0.5 hour and diluted with Et_2O (15 mL) at 0 °C. An aqueous solution (10 mL) of $Na_2S_2O_3$ (*ca.* 100-158 g/L) and $NaHCO_3$ (*ca.* 100 g/L) was added and the resulting mixture was stirred for 15 min. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4,

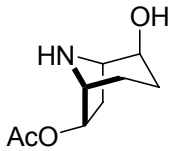
filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc: PE = 1 : 2) to afford compound **16** (102 mg, 0.36 mmol, 86%) as a colorless oil. $[\alpha]_D^{25}$ –43.4 (*c* 1.96, $CHCl_3$); IR (film): 2977, 2930, 1734, 1700, 1391, 1369, 1322, 1292, 1243, 1155, 1107, 1031, 1006 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) (a 60:40 mixture of two rotamers; determined by integration at δ 4.39-4.48 and 4.46-4.62) δ 1.46 (s, 9H, *t*-Bu), 1.92-2.00 (m, 1H), 2.08 (s, 3H, OAc), 2.18-2.35 (m, 3H), 2.37-2.45 (m, 2H, CH_2CO), 4.26-4.39 (m, 1H), 4.39-4.48 (m, 0.6H), 4.48-4.62 (m, 0.4H), 5.14 (dd, *J* = 2.9, 7.3 Hz, 1H, CHOAc); ^{13}C NMR (100 MHz, $CDCl_3$)) (a 60:40 mixture of two rotamers) δ 21.2, 26.1, 28.5, 32.8, 36.4, 59.0, 64.5, 76.4, 81.1, 154.1, 170.9, 204.8; MS (ESI) *m/z* 306 ($M+Na^+$, 100%); HRMS calcd for $C_{14}H_{21}NNaO_5$ [$M+Na^+$]: 306.1312; found: 306.1324.

(1*R*,2*S*,5*R*,6*S*)-6-Acetyloxy-8-(*tert*-butoxycarbonyl)-8-azabicyclo[3.2.1]octan-2-ol (12).



To a cooled solution (–78 °C) of compound **14** (30 mg, 0.11 mmol) in THF (3 mL) was added dropwise a THF solution of L-selectride (0.15 mmol, 0.15 mL, 1.0 M). After stirring for 0.5 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc: PE = 1: 1) to afford compound **12** as a colorless oil (26 mg, 0.091 mmol, 84%).

(1*R*,2*S*,5*R*,6*S*)-6-Acetyloxy-8-azabicyclo[3.2.1]octan-2-ol (1).

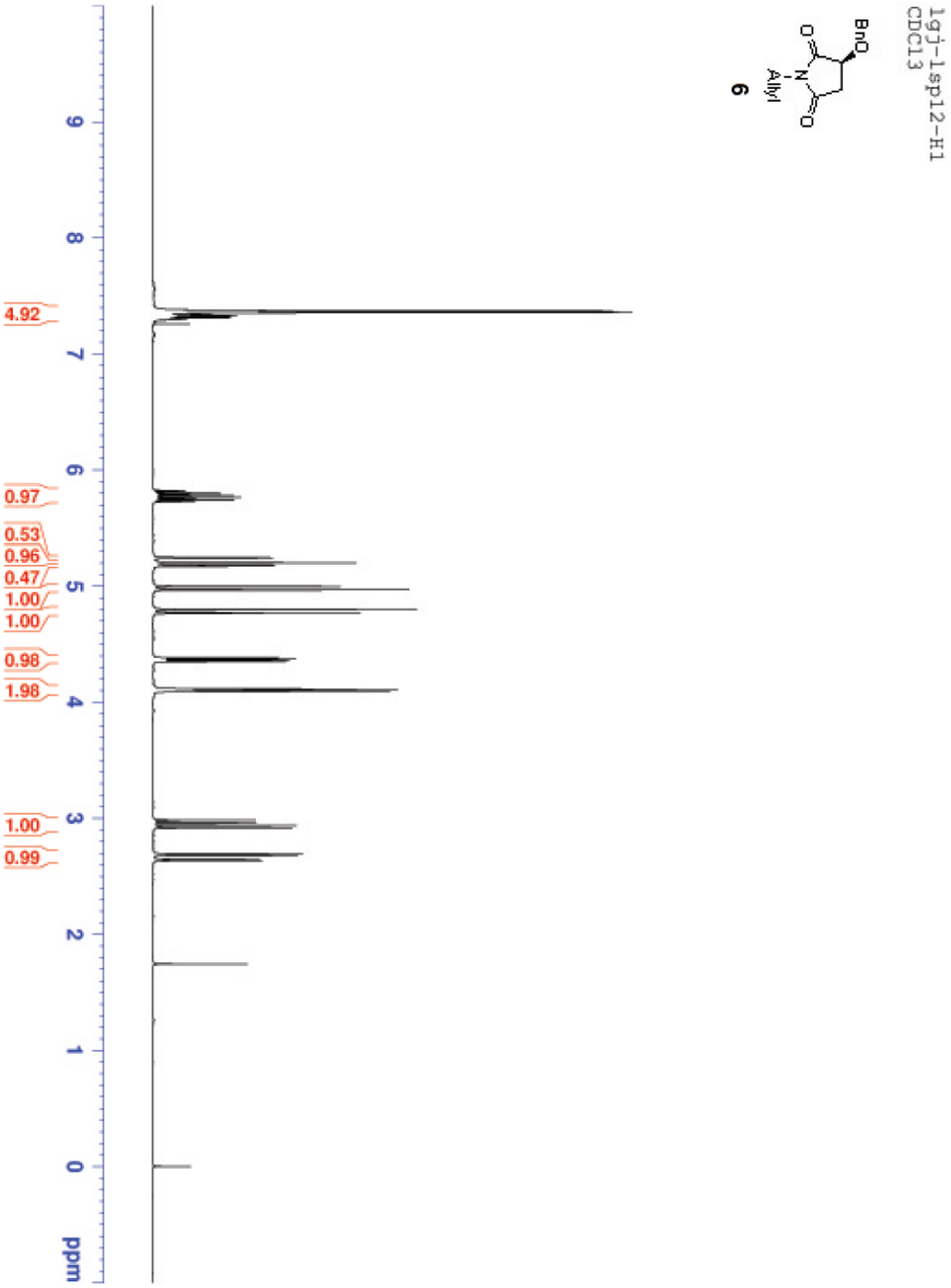


To a cooled solution (0 °C) of compound **14** (35 mg, 0.12 mmol) in CH_2Cl_2 (0.4 mL) was added dropwise 2,6-lutidine (45 mg, 0.42 mmol, 0.05 mL) and TMSOTf (69 mg, 0.31 mmol, 0.06 mL). After stirring at room temperature for 0.5 h, the reaction was

quenched with saturated aqueous NH_4Cl (2 mL) at 0 °C. The aqueous phase was extracted with Et_2O (4×5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was dissolved in THF (5 mL). To the resultant solution was added a solution of TBAF (0.15 mmol, 0.15 mL, 0.1 M in THF) at 0 °C. The resulting solution was stirred for 10 min and quenched with saturated aqueous NH_4Cl (2 mL) at 0 °C. The aqueous phase was extracted with Et_2O (3×5 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography on basic alumina (CH_2Cl_2: PE = 1: 2) to afford compound **1** (16 mg, 72%) as a colorless crystalline solid. M.p. = 75-76 ^oC (CH_2Cl_2/PE) (lit.[3] M.p. 76-78 ^oC). $[\alpha]_D^{24}$ –31.6 (*c* 0.59, EtOH) {lit.[3] $[\alpha]_D^{25}$ –29.6 (*c* 0.97, EtOH)}; IR (film): 3360, 2942, 2867, 1731, 1650, 1441, 1376, 1243, 1180, 1094, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.48-1.59 (m, 3H), 1.78 (ddd, *J* = 2.1, 6.7, 14.7 Hz, 1H, H-7), 1.83-1.92 (m, 1H), 2.04 (s, 3H, OAc), 2.16 (dd, *J* = 7.0, 14.7 Hz, 1H, H-7), 2.65 (br s, 2H, D_2O exchangeable, NH and OH), 3.27-3.33 (m, 1H, H-2), 3.53-3.58 (m, 2H, H-1 and H-5), 5.13 (dd, *J* = 2.1, 7.0 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ21.5, 25.0, 25.3, 37.4, 60.8, 61.4, 67.7, 78.3, 170.9; MS (ESI) *m/z* 186 ($M+H^+$, 100%); HRMS calcd for $C_9H_{16}NO_3$ [$M+H^+$]: 186.1125; found: 186.1121.

Reference

1. J. M. Luo, C. F. Dai, S. Y. Lin and P.-Q. Huang, *Chem. Asian. J.*, 2009, **4**, 328-335.
2. Y. G. Xiang, X. W. Wang, X. Zeng, Y. P. Ruan and P.-Q. Huang, *Chem. Commun.*, 2009, **45**, 7045-7047.
3. Y. Q. Zhang and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2006, **128**, 465-472.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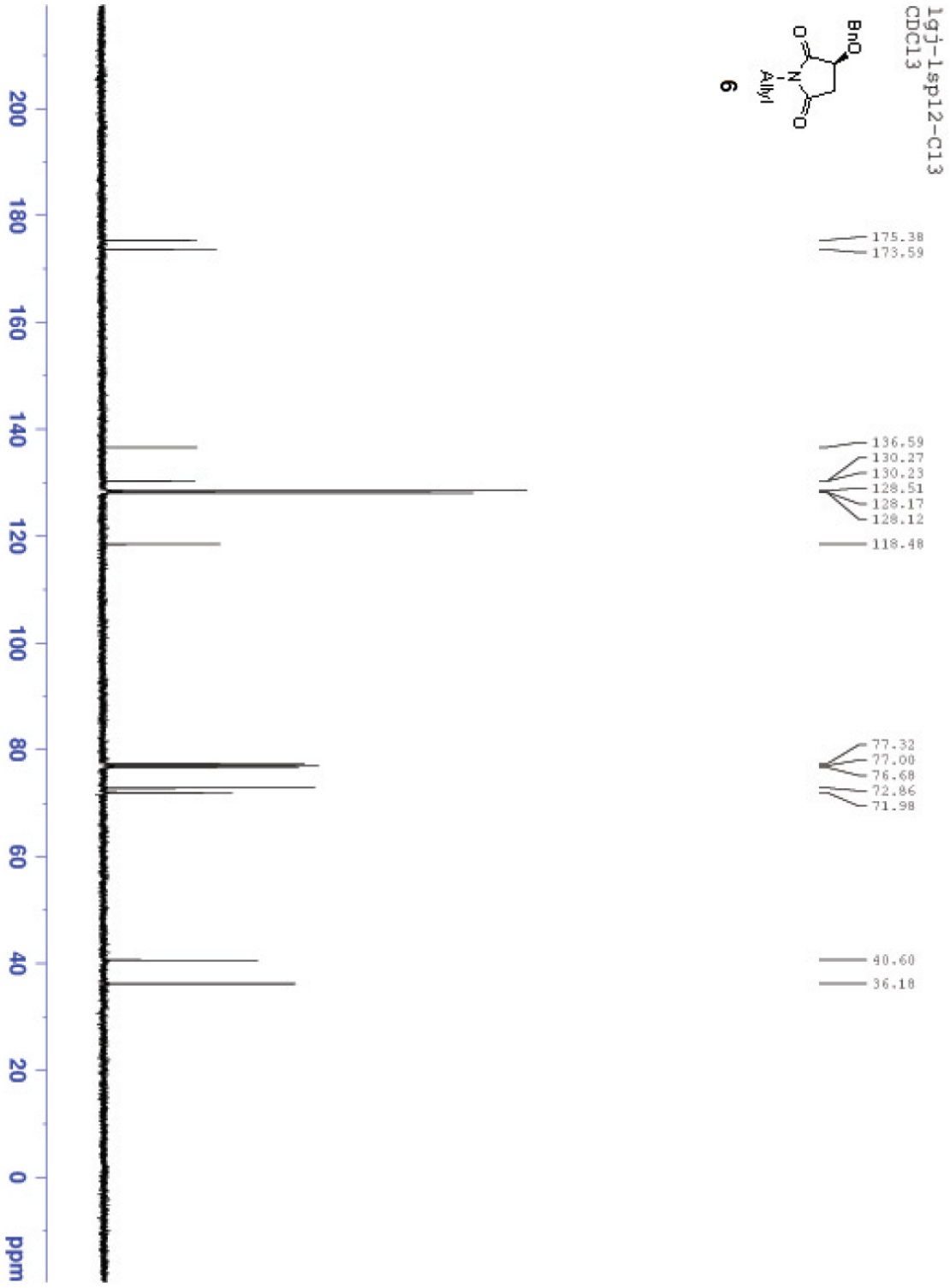
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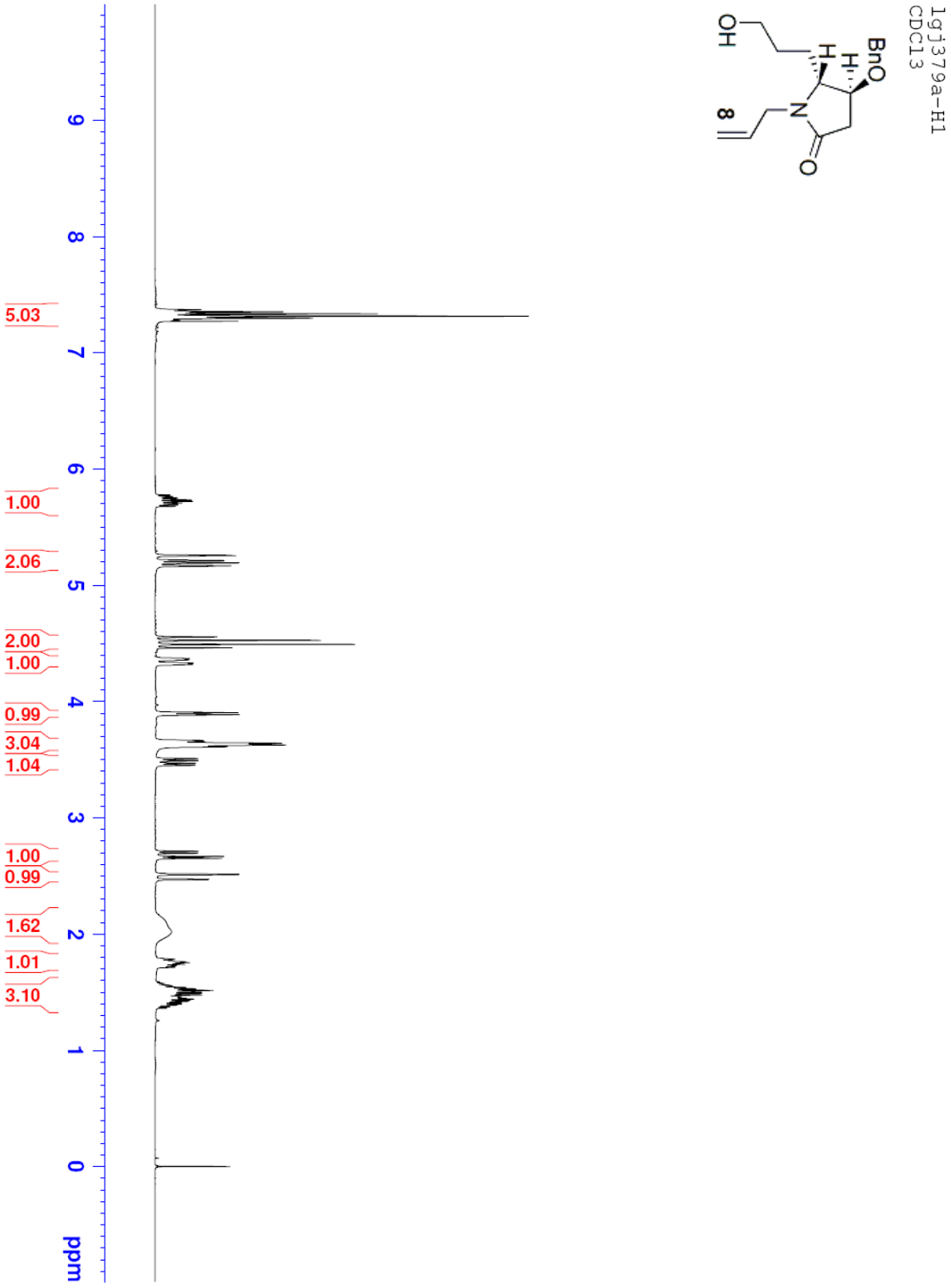
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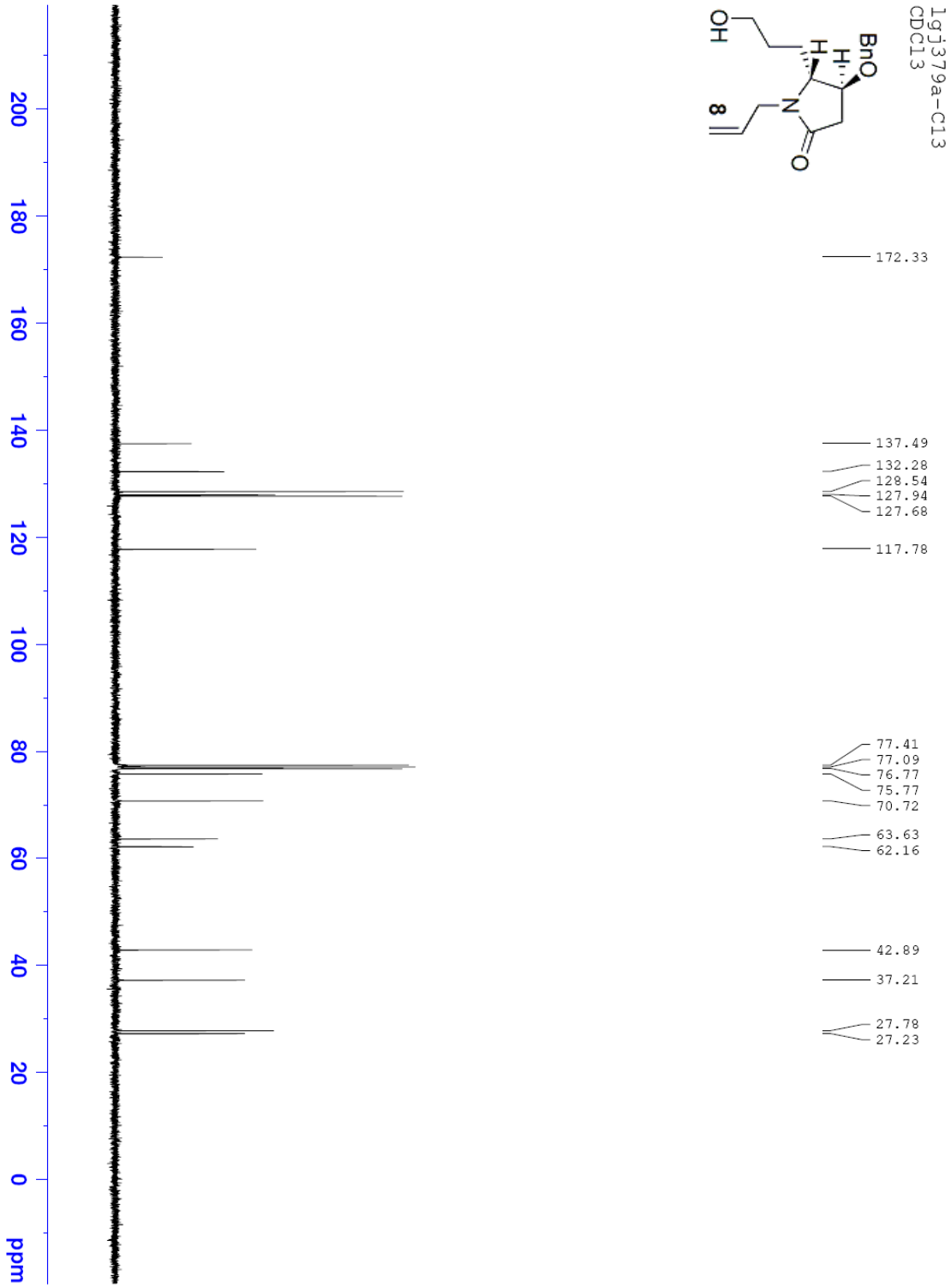
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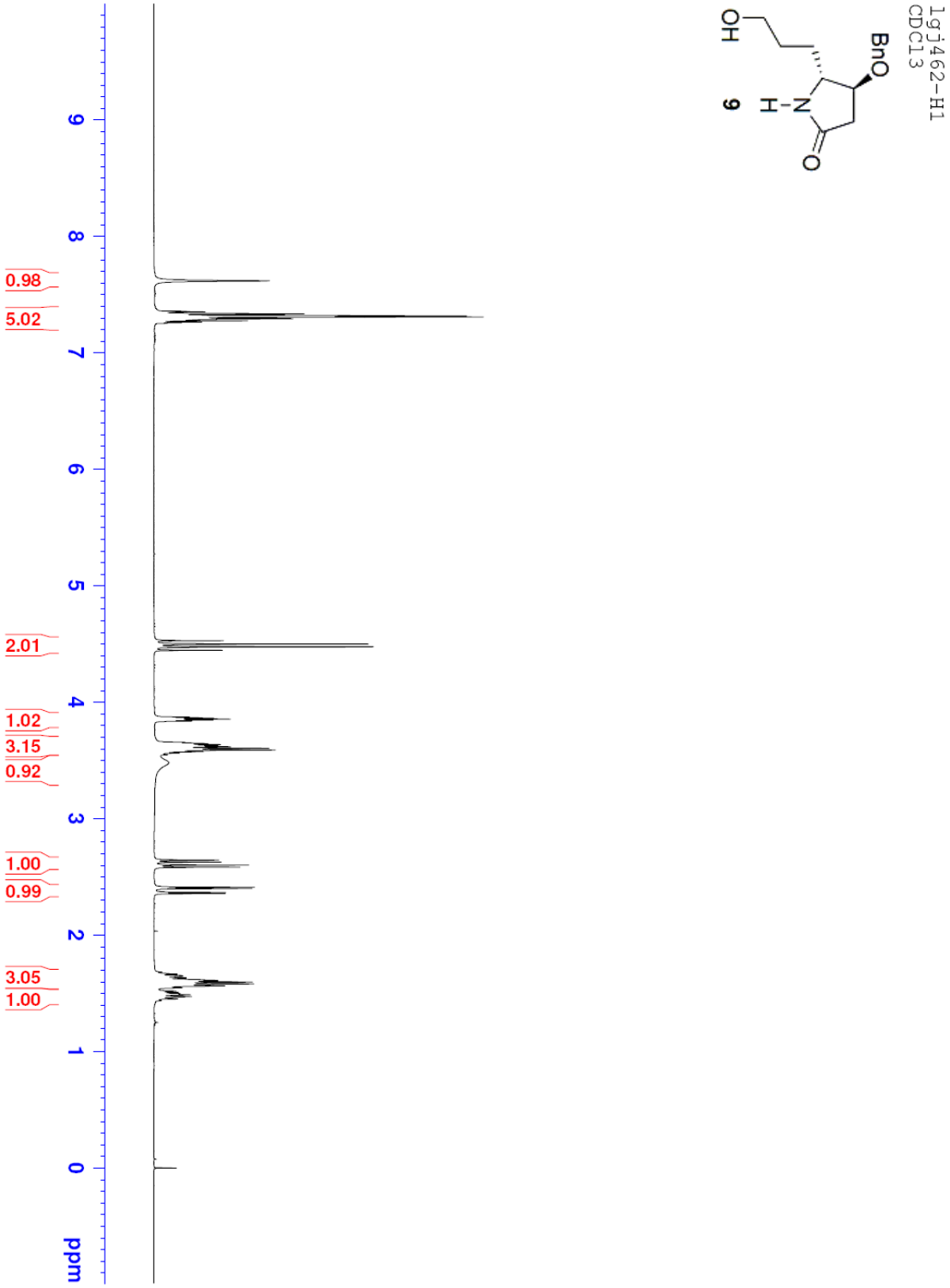
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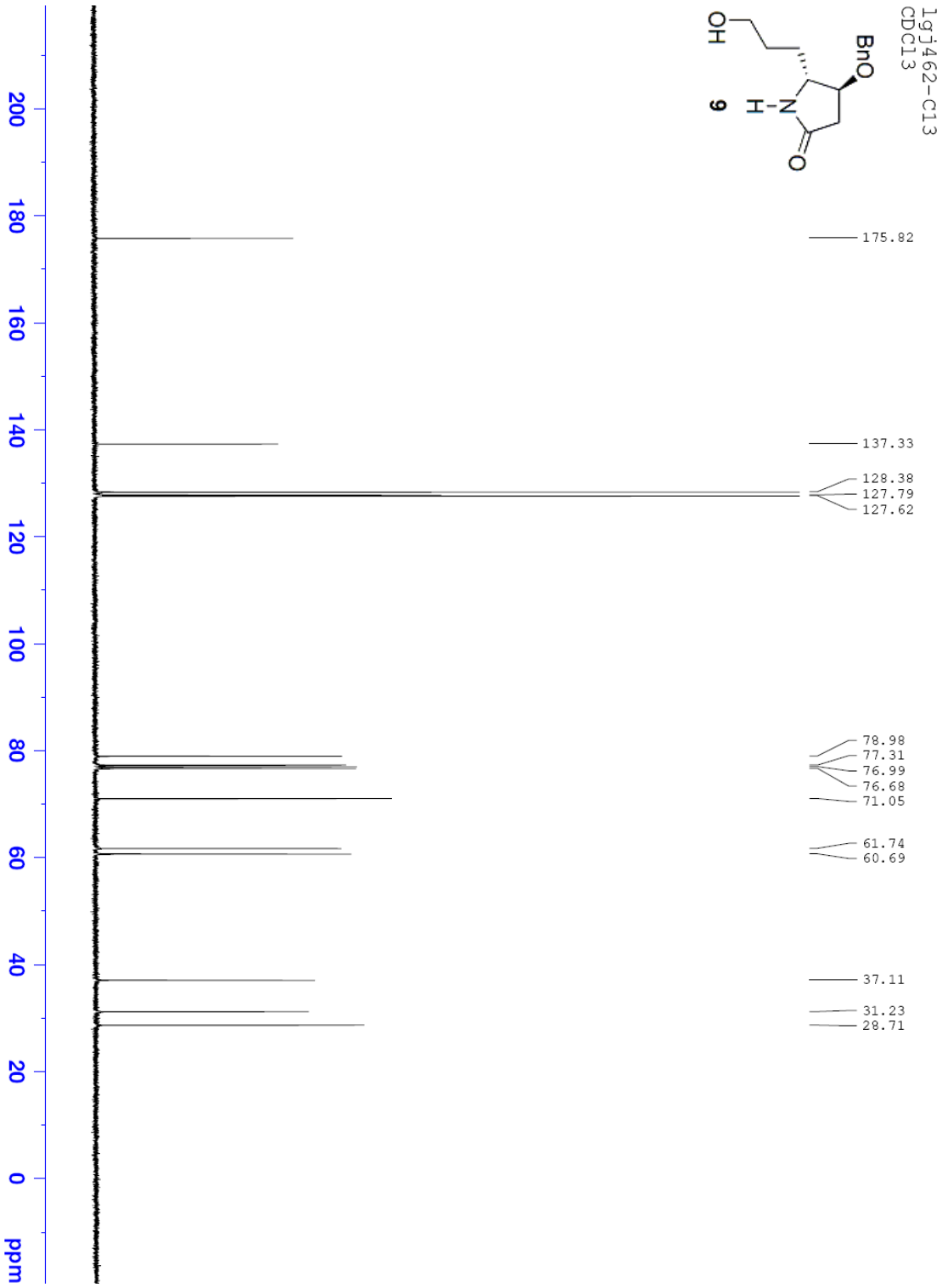
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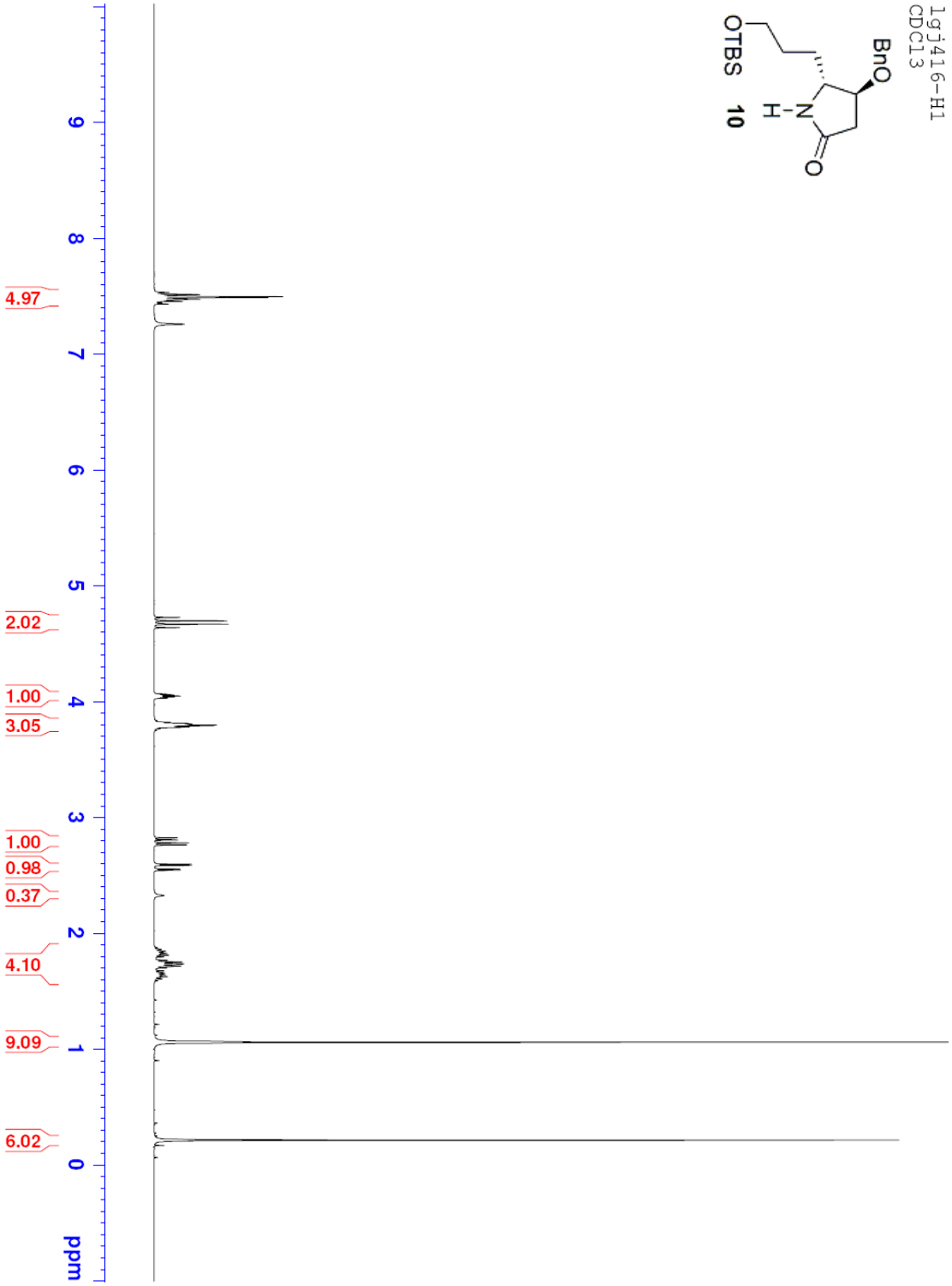
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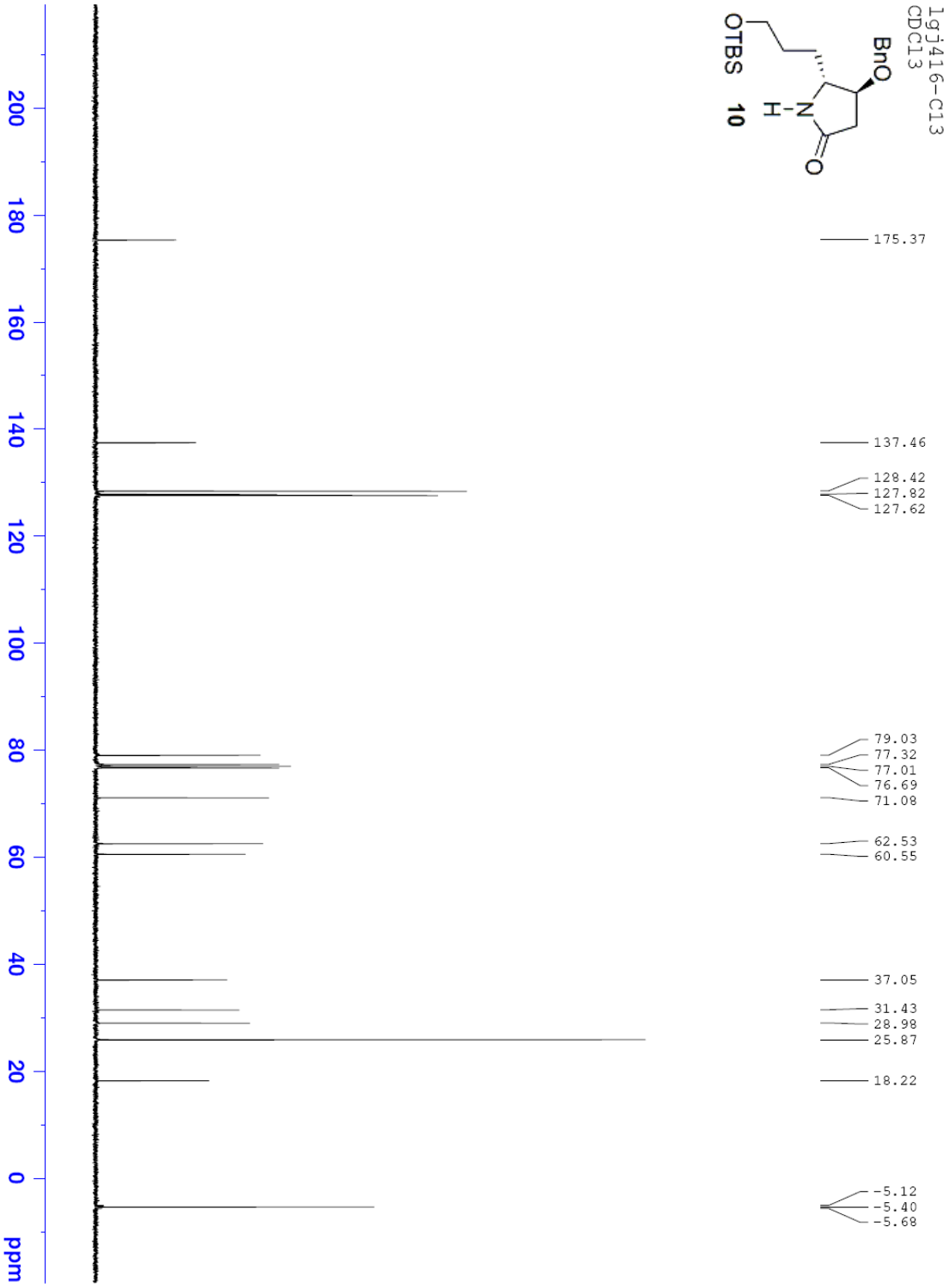
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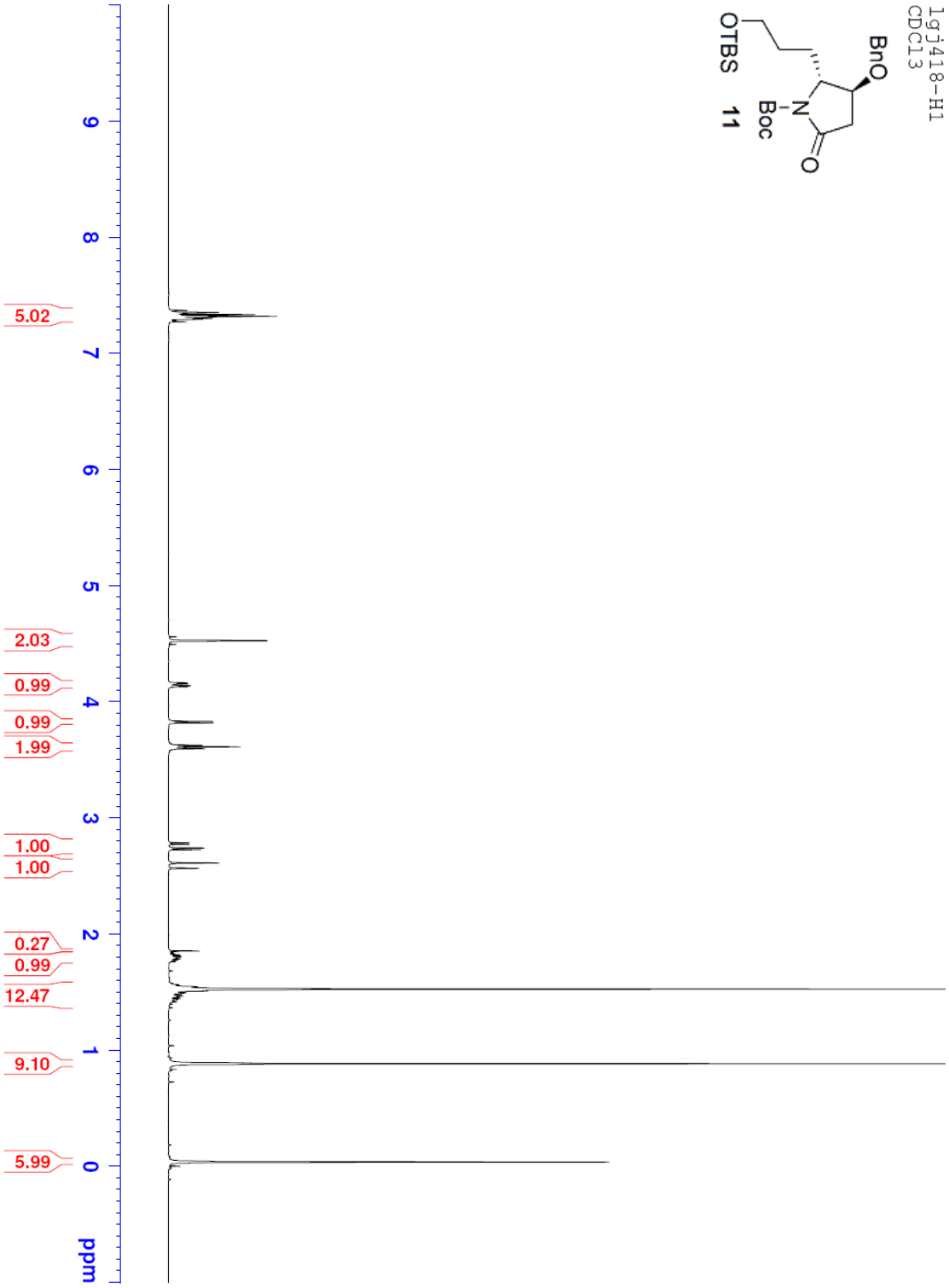
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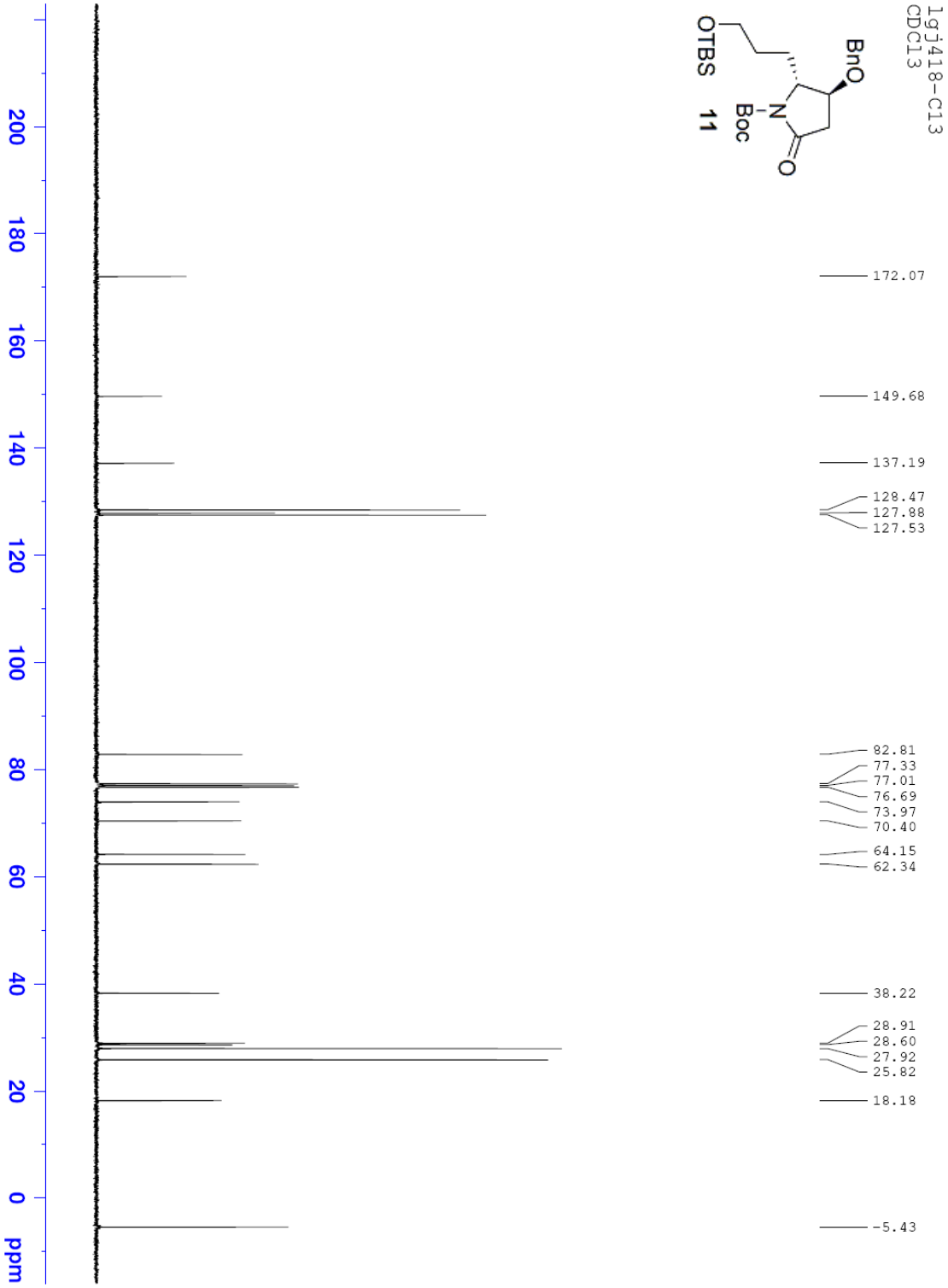
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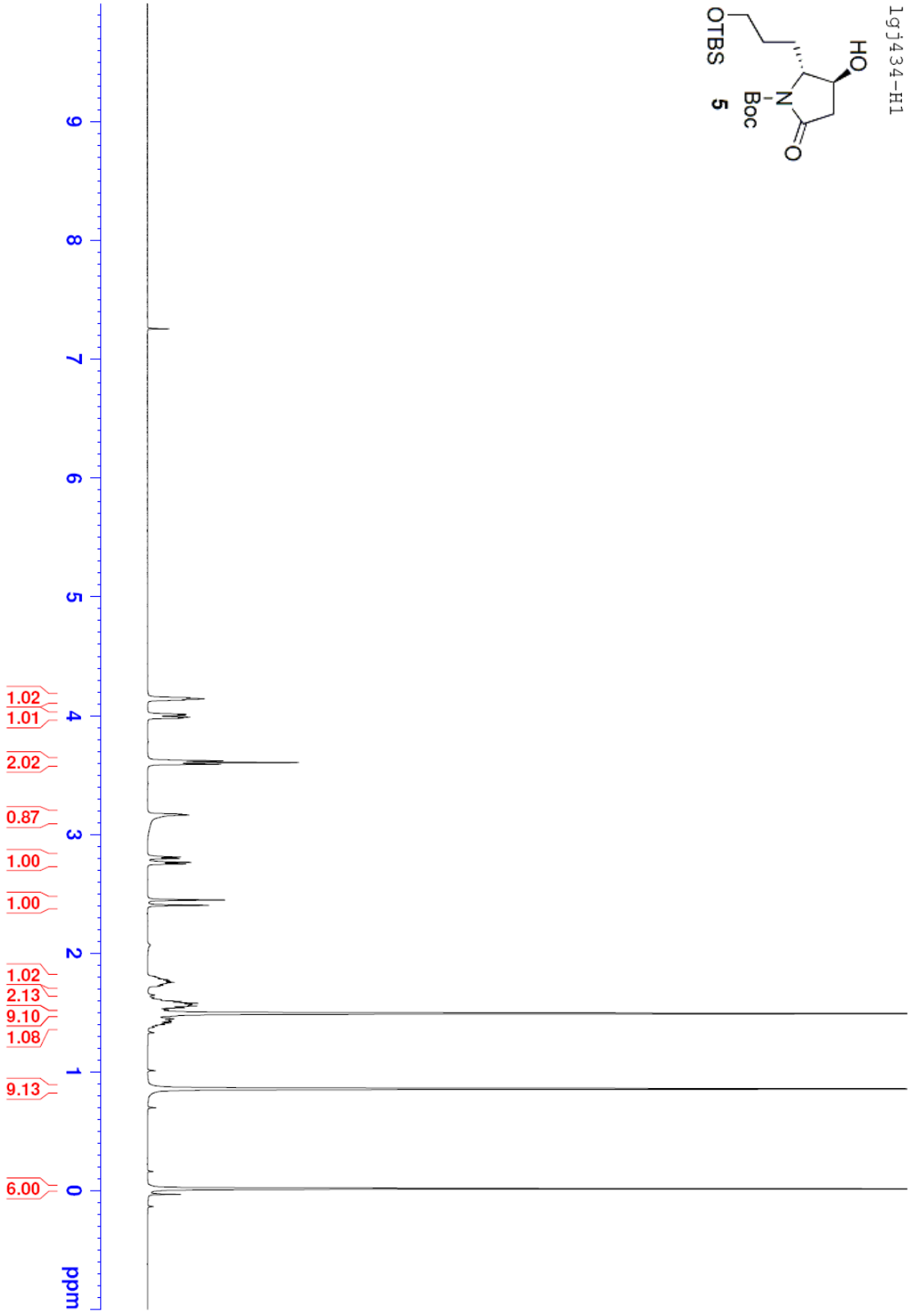
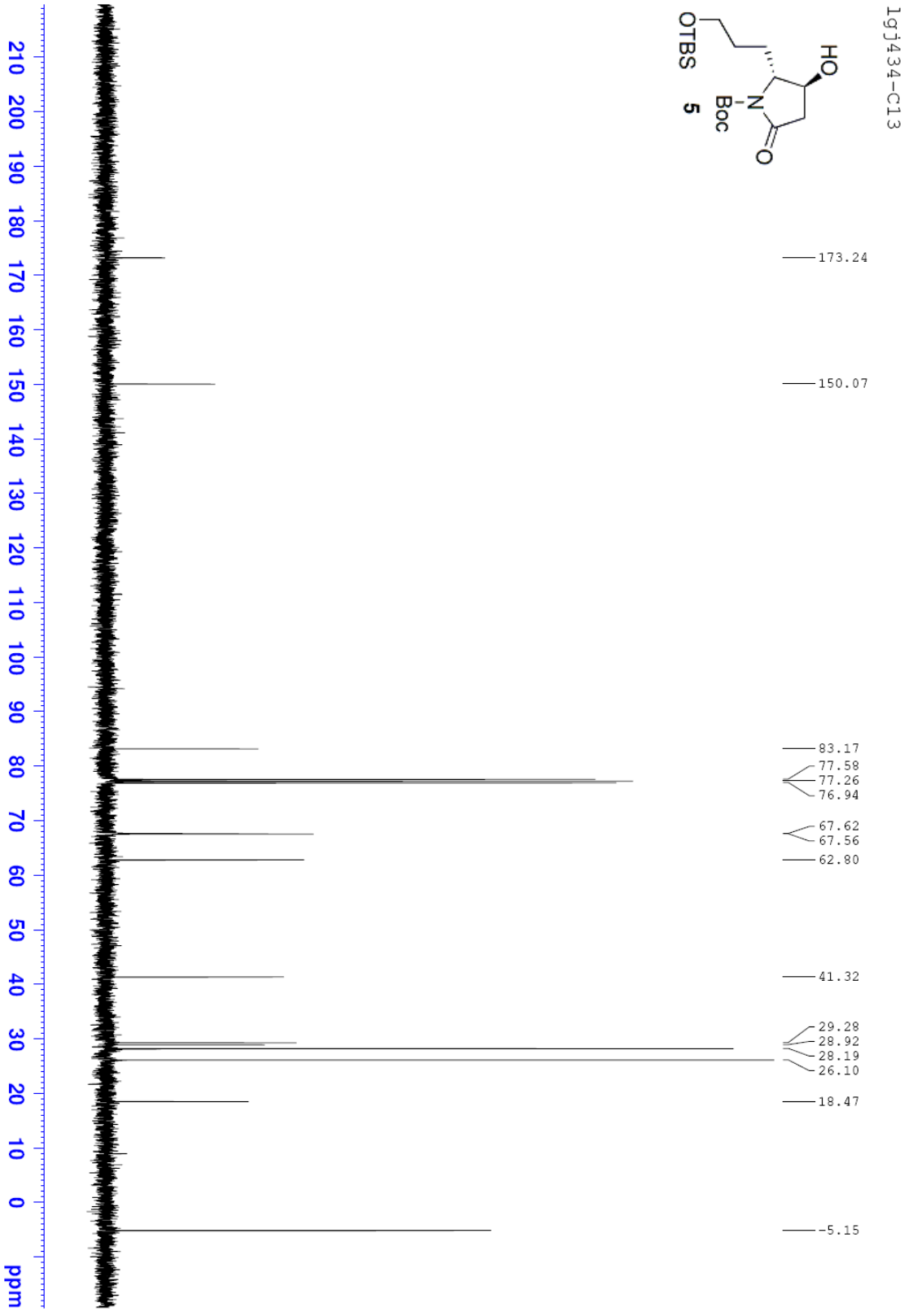
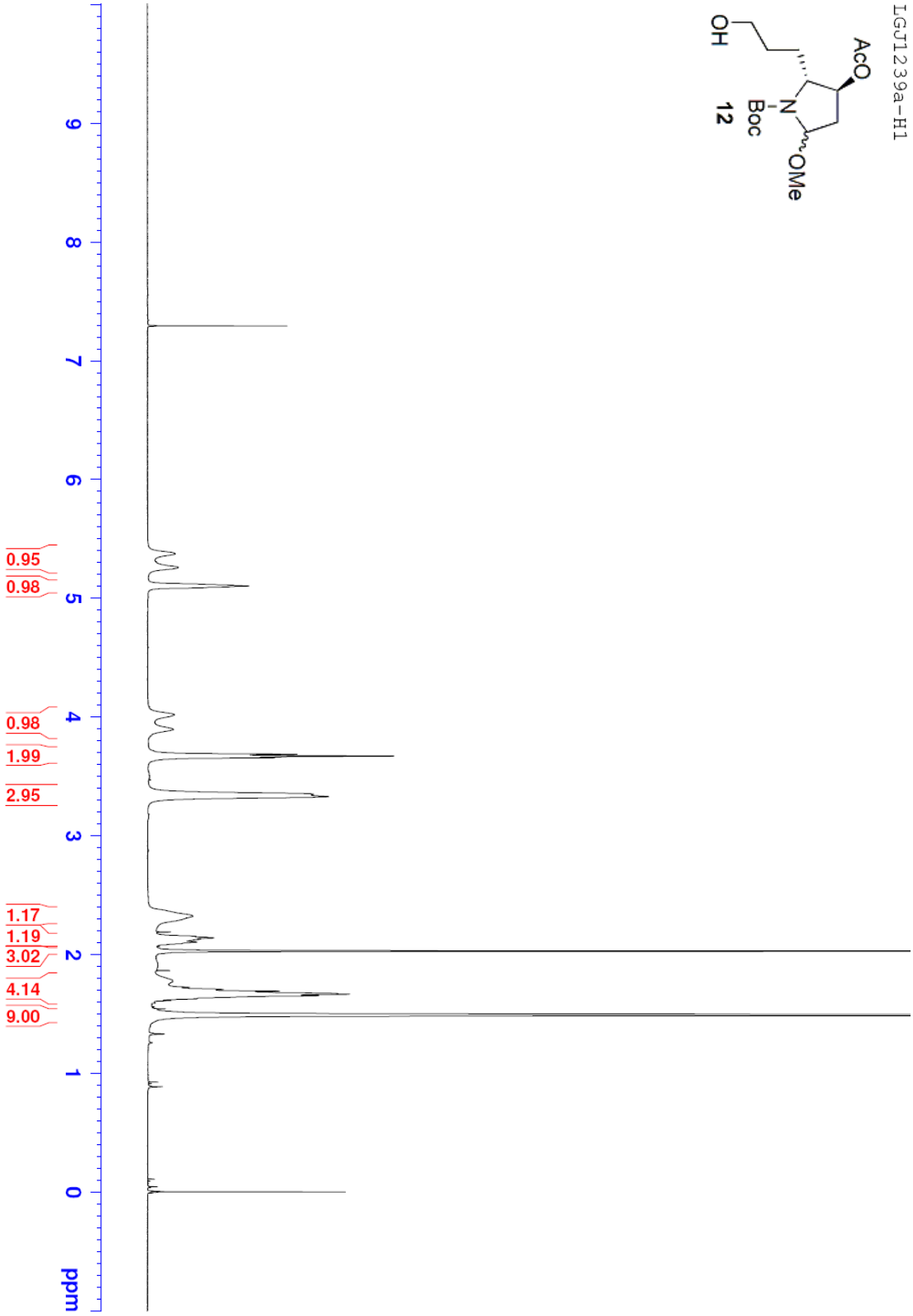
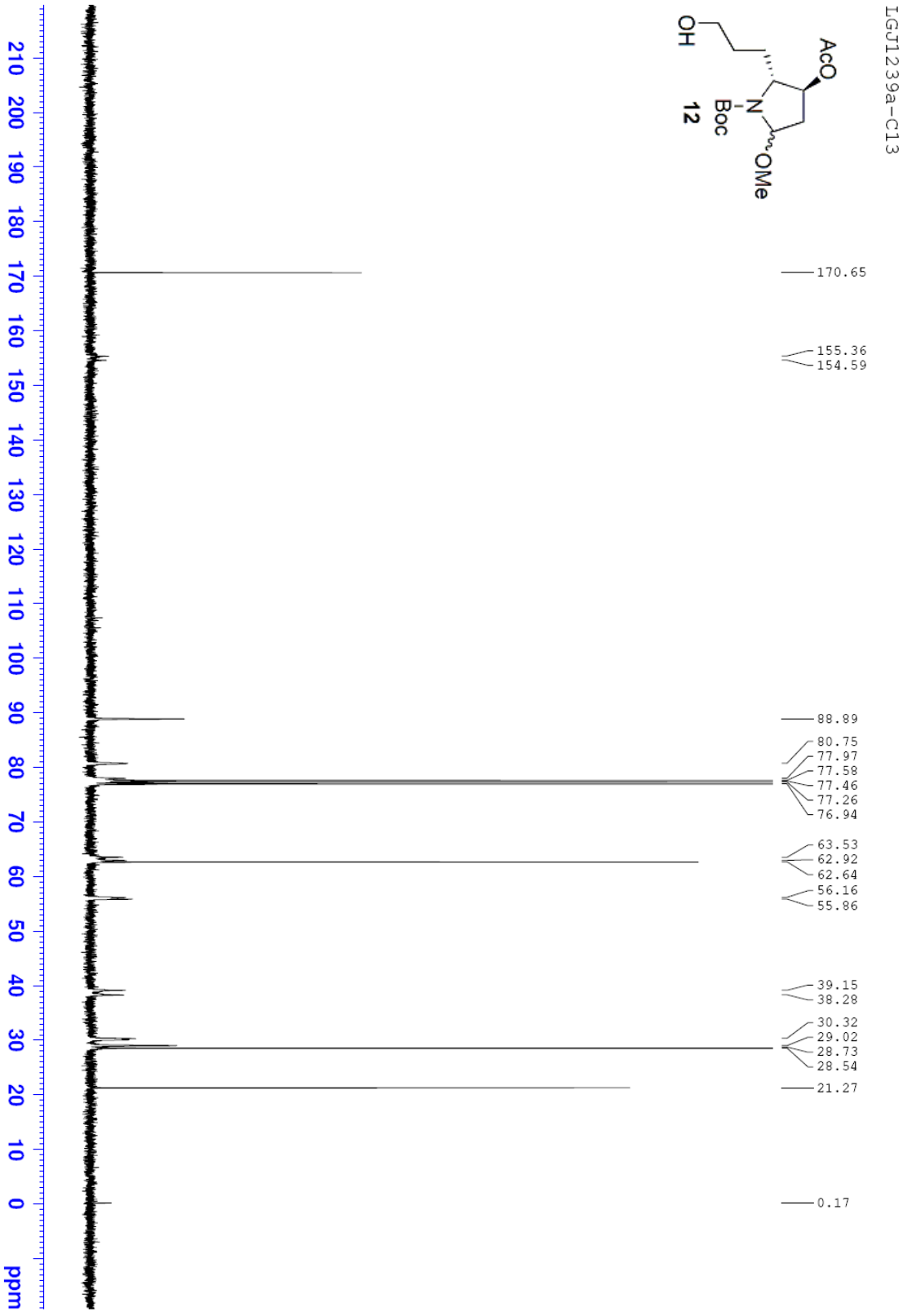
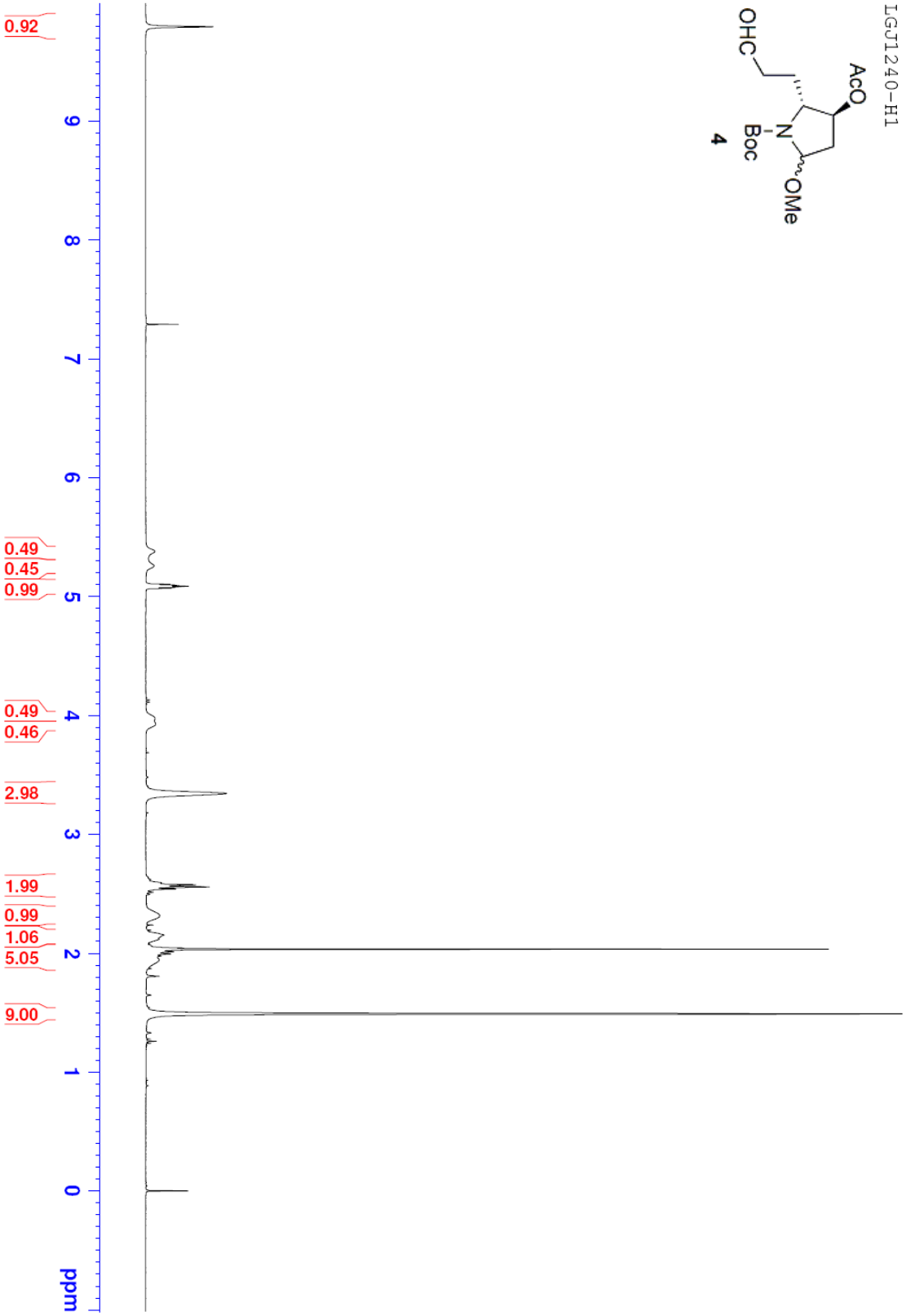
0
ppm
172.07
149.68
137.19
128.47
127.88
127.53
82.81
77.33
77.01
76.69
73.97
70.40
64.15
62.34
38.22
28.91
28.60
27.92
25.82
18.18
-5.43

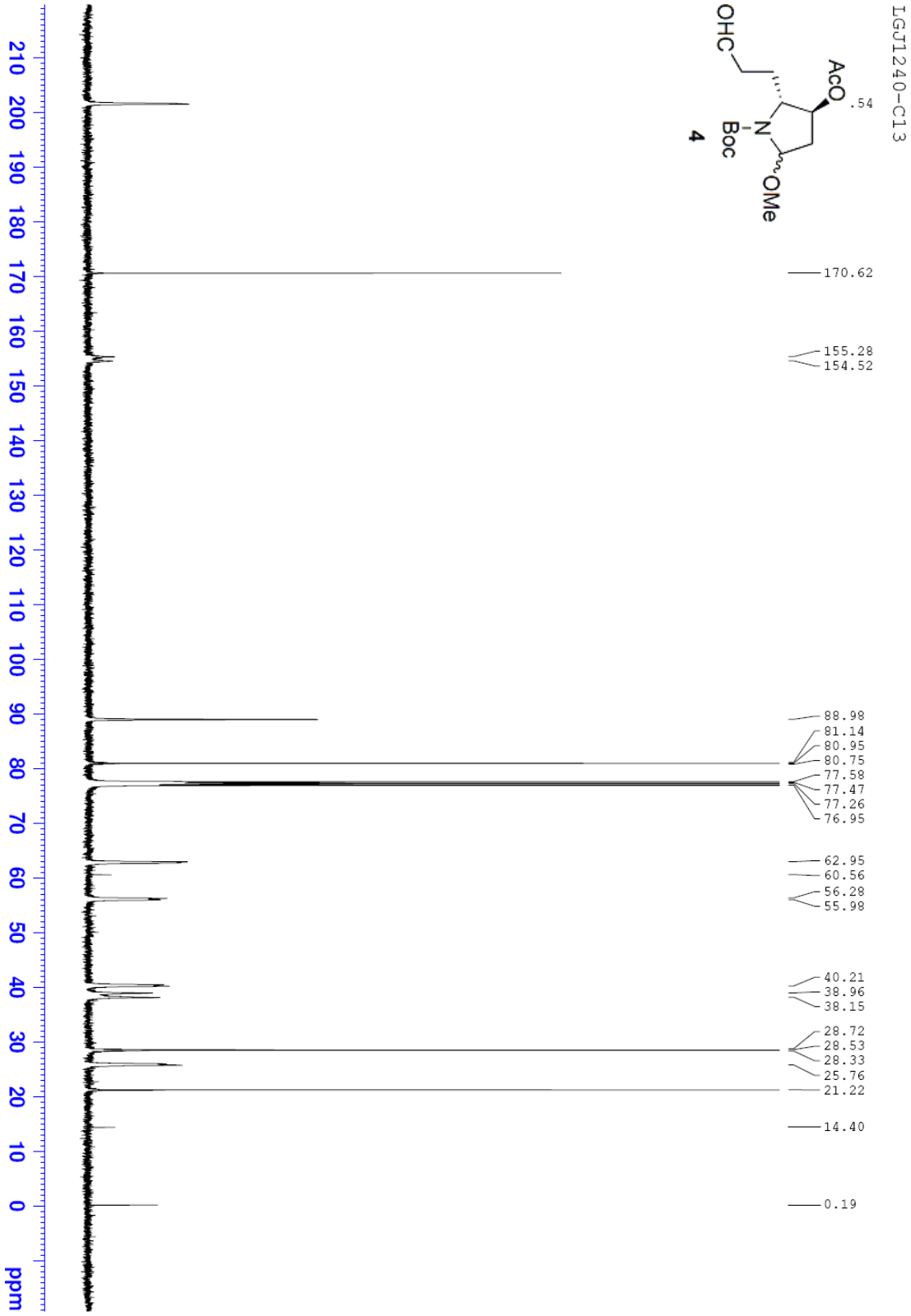

1gj434-H1
OTBS
5
N
Boc
O
HO
1.02
1.01
2.02
0.87
1.00
1.00
1.02
2.13
9.10
1.08
9.13
6.00
ppm

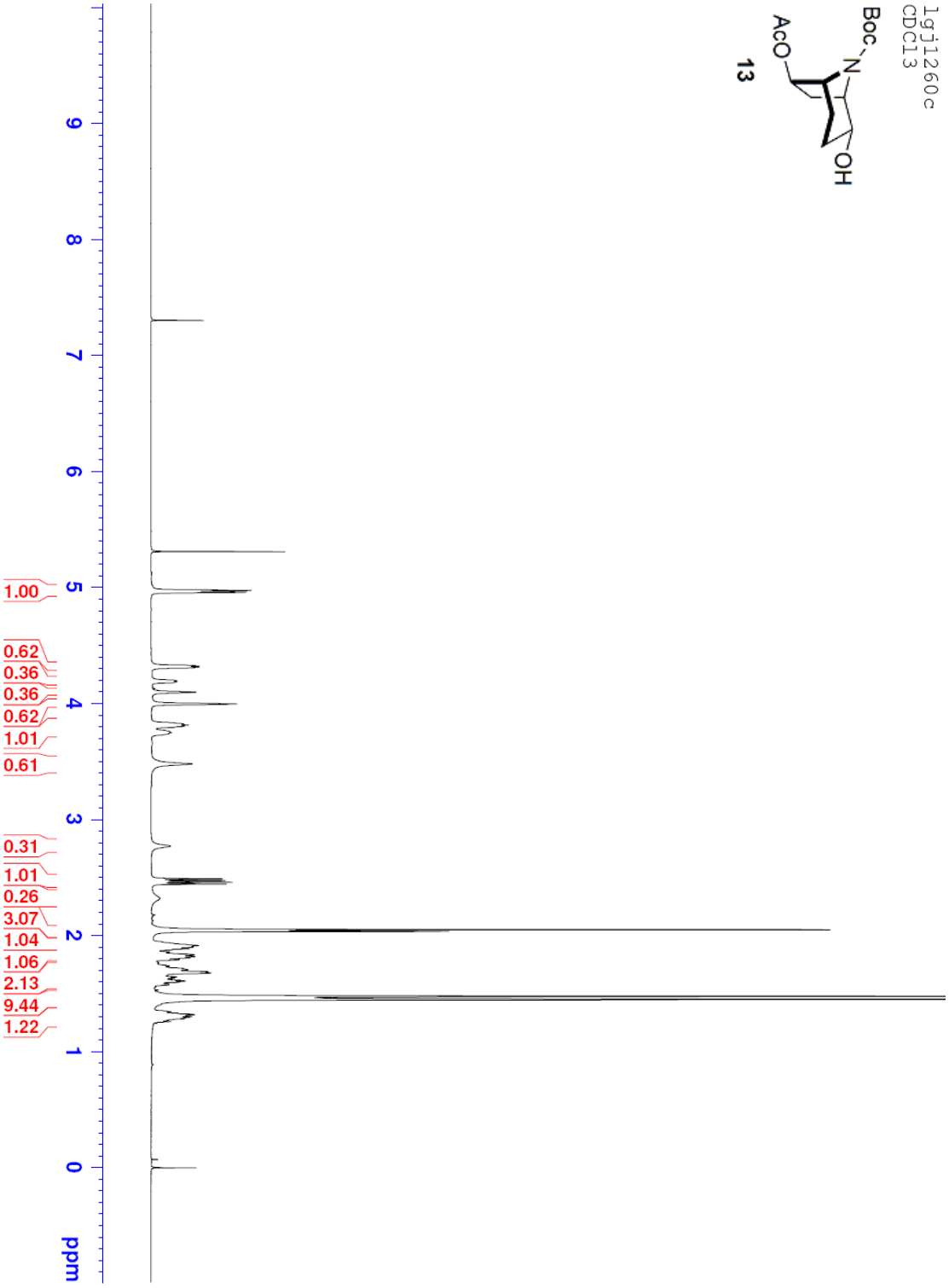

1gj434-C13
OTBS
5
Boc
N
O
HO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
173.24
150.07
83.17
77.58
77.26
76.94
67.62
67.56
62.80
41.32
29.28
28.92
28.19
26.10
18.47
-5.15

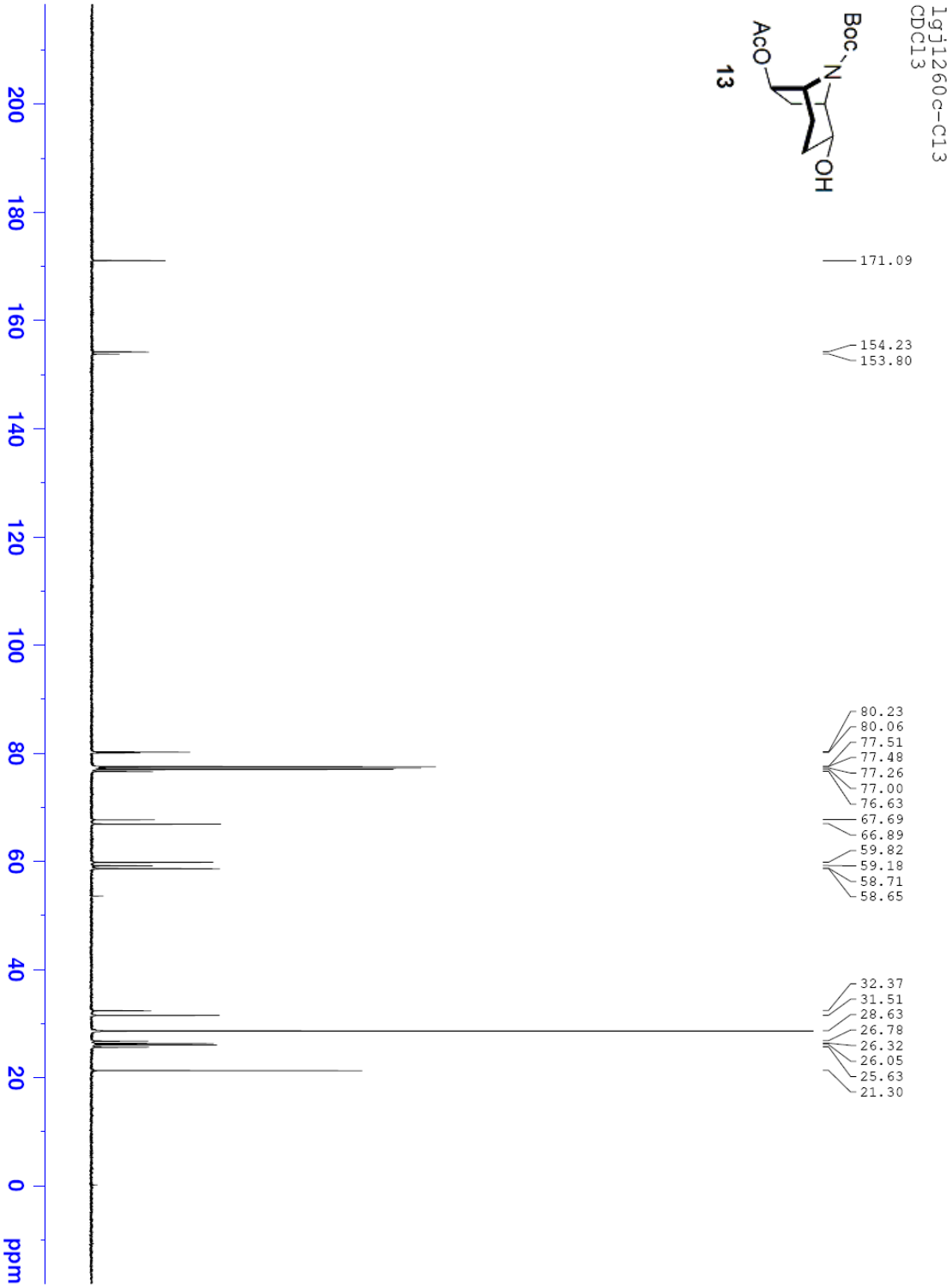

LGJ1239a-H1
AcO
OMe
N
Boc
OH
12
0.95
0.98
0.98
1.99
2.95
1.17
1.19
3.02
4.14
9.00
ppm

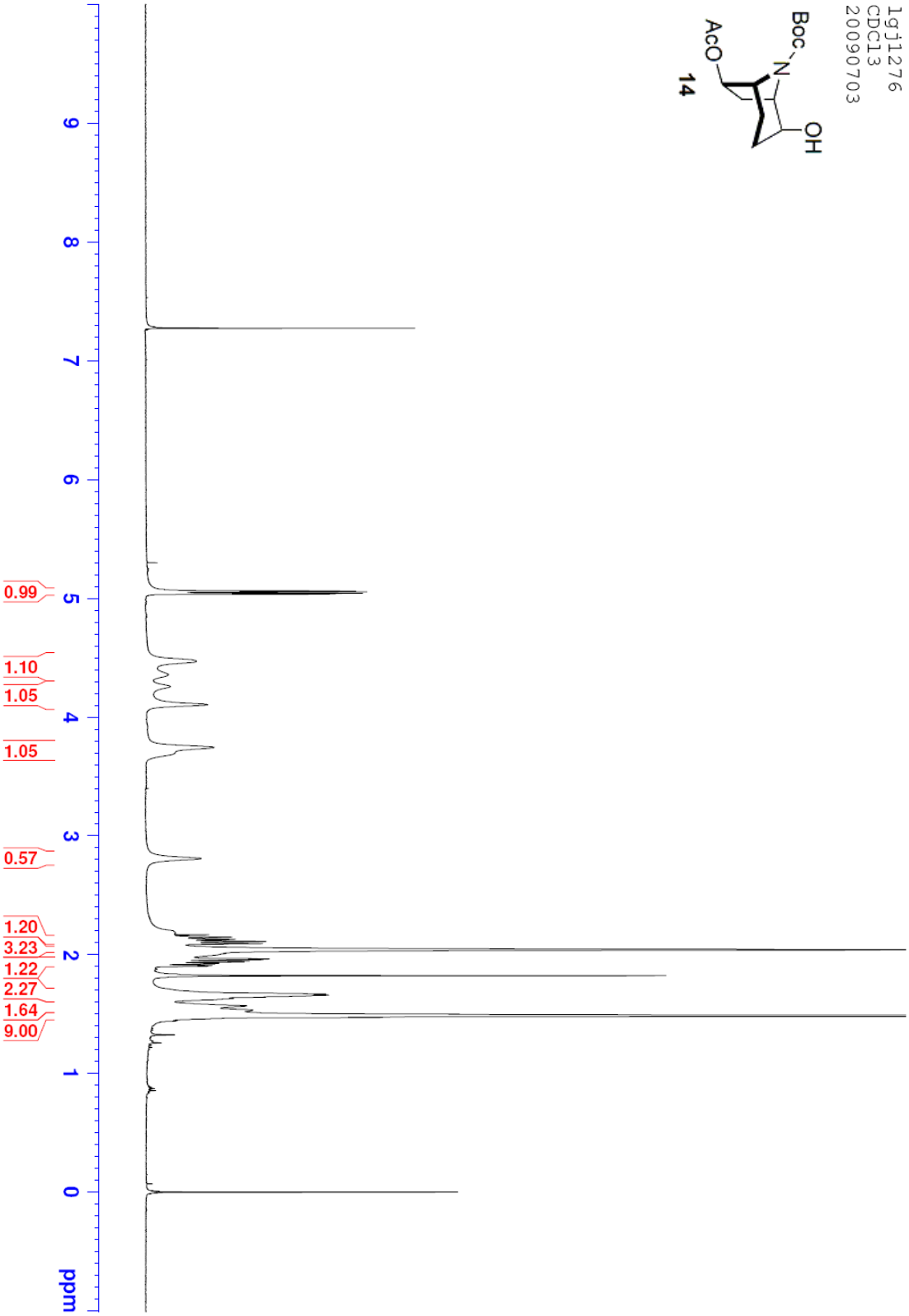

IGJ1239a-C13
AcO
OH
N
Boc
OMe
12
170.65
155.36
154.59
88.89
80.75
77.97
77.58
77.46
77.26
76.94
63.53
62.92
62.64
56.16
55.86
39.15
38.28
30.32
29.02
28.73
28.54
21.27
0.17
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

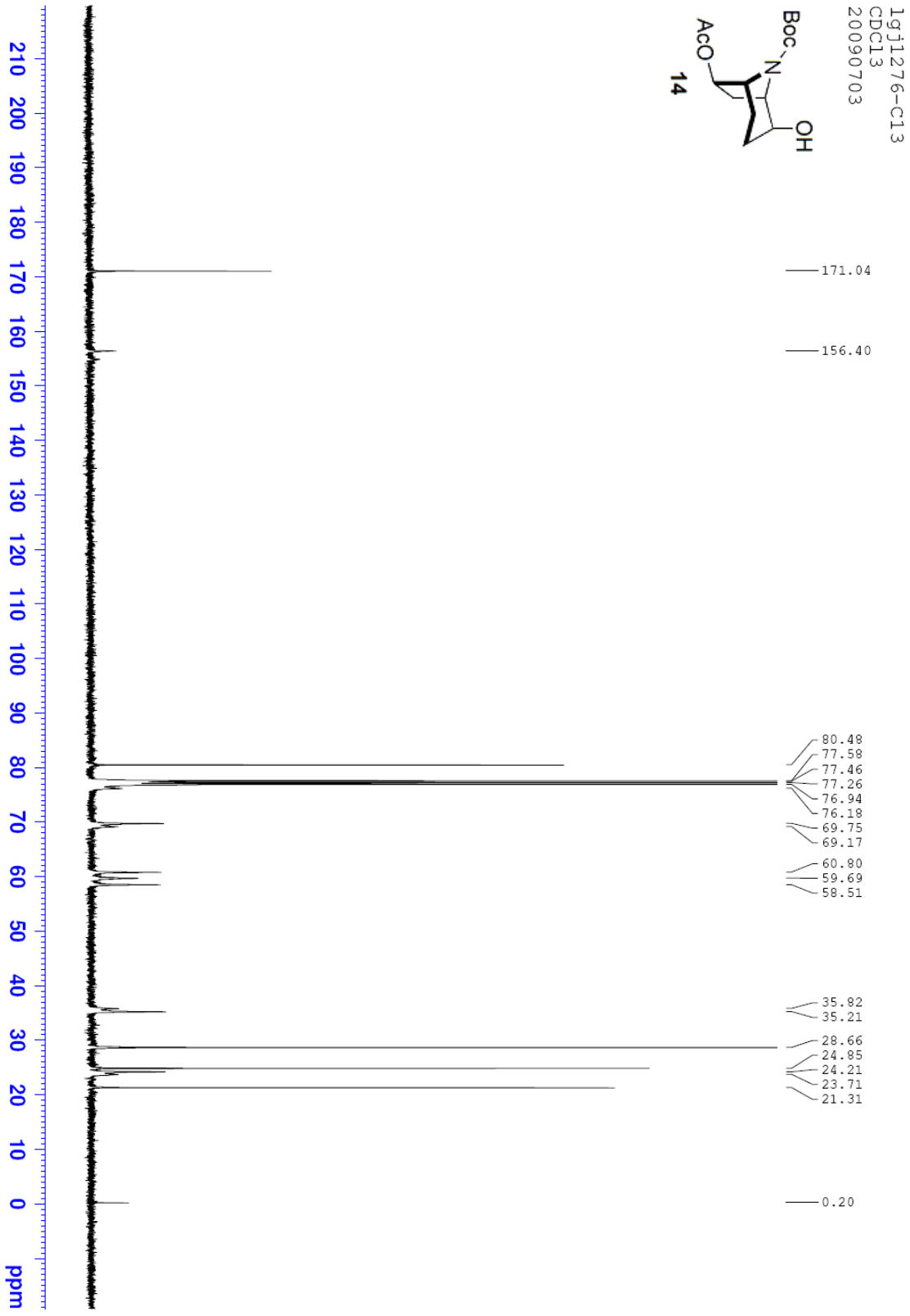

LGJ1240-H1
OHC
AcO
N
Boc
OMe
4
0.92
0.49
0.45
0.99
0.49
0.46
2.98
1.99
0.99
1.06
5.05
9.00
ppm

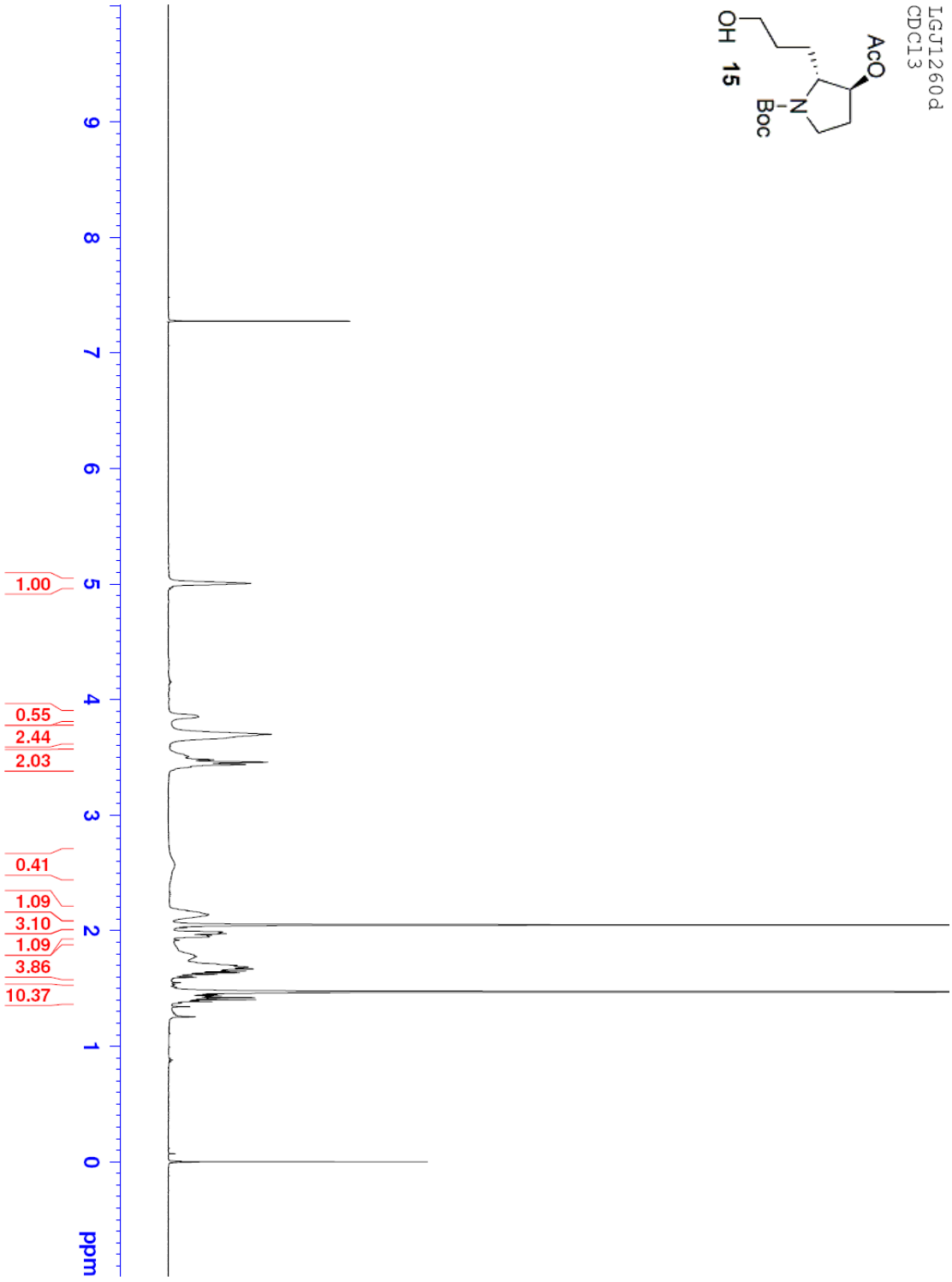

LGJ1240-C13
OHC
AcO
.54
N
Boc
OMe
4
170.62
155.28
154.52
88.98
81.14
80.95
80.75
77.58
77.47
77.26
76.95
62.95
60.56
56.28
55.98
40.21
38.96
38.15
28.72
28.53
28.33
25.76
21.22
14.40
0.19
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

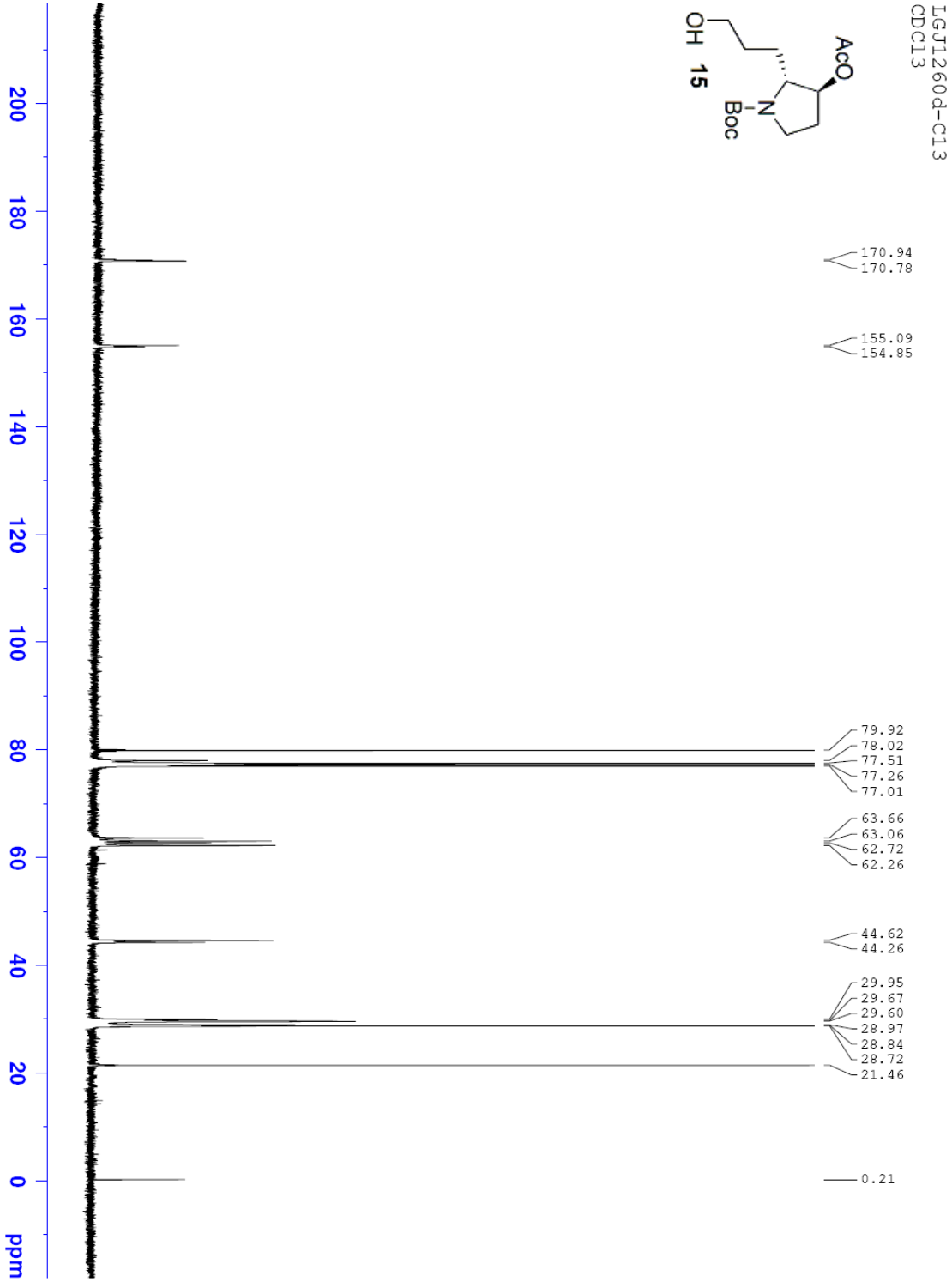

1gj1260c
CDCl3
Boc
N
AcO
OH
13
ppm
0
1
2
3
4
5
6
7
8
9
1.00
0.62
0.36
0.36
0.62
1.01
0.61
0.31
1.01
0.26
3.07
1.04
1.06
2.13
9.44
1.22

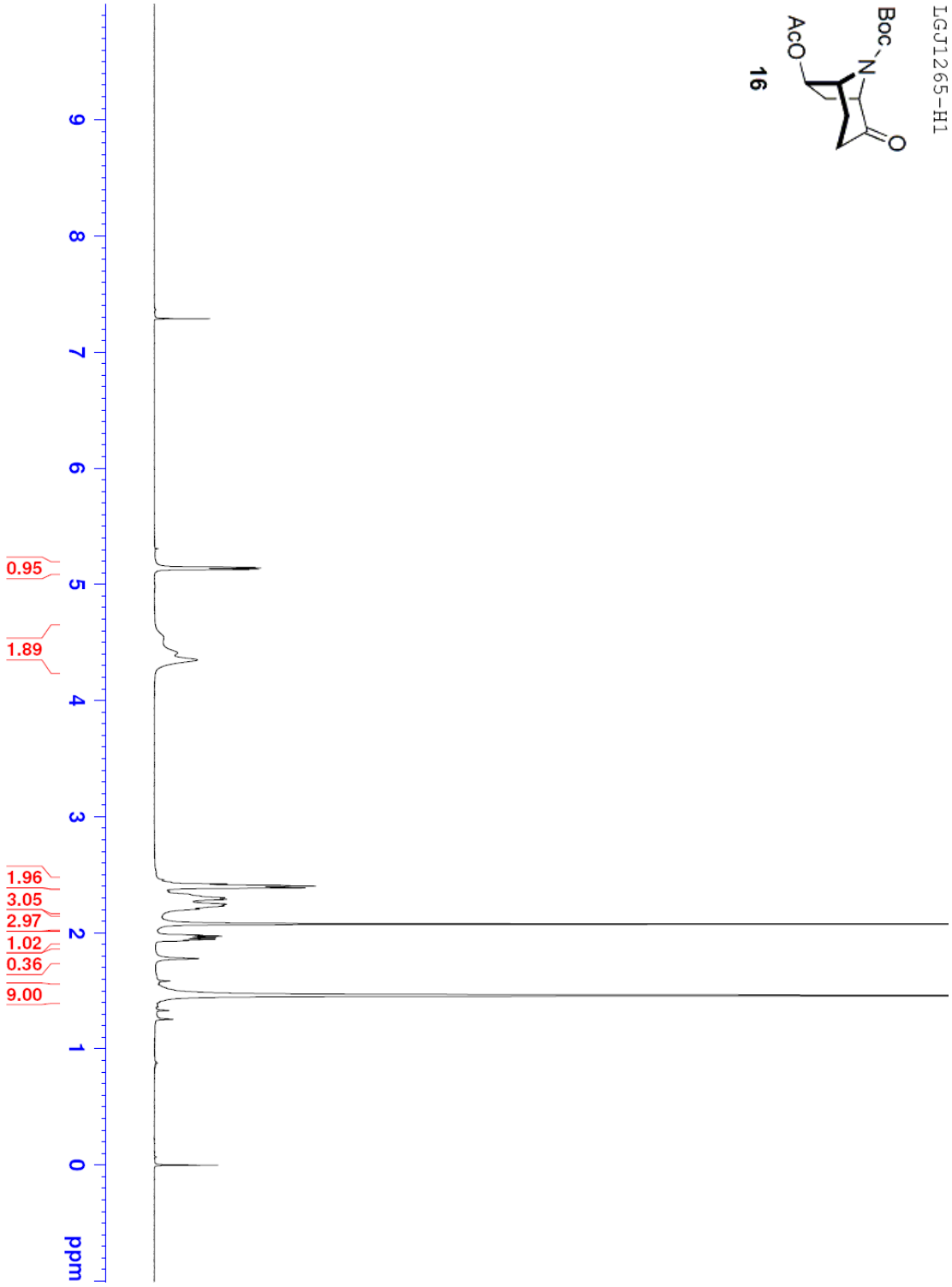

lgj1260c-C13
CDCl3
Boc
N
AcO
OH
13
171.09
154.23
153.80
80.23
80.06
77.51
77.48
77.26
77.00
76.63
67.69
66.89
59.82
59.18
58.71
58.65
32.37
31.51
28.63
26.78
26.32
26.05
25.63
21.30
200
180
160
140
120
100
80
60
40
20
0
ppm

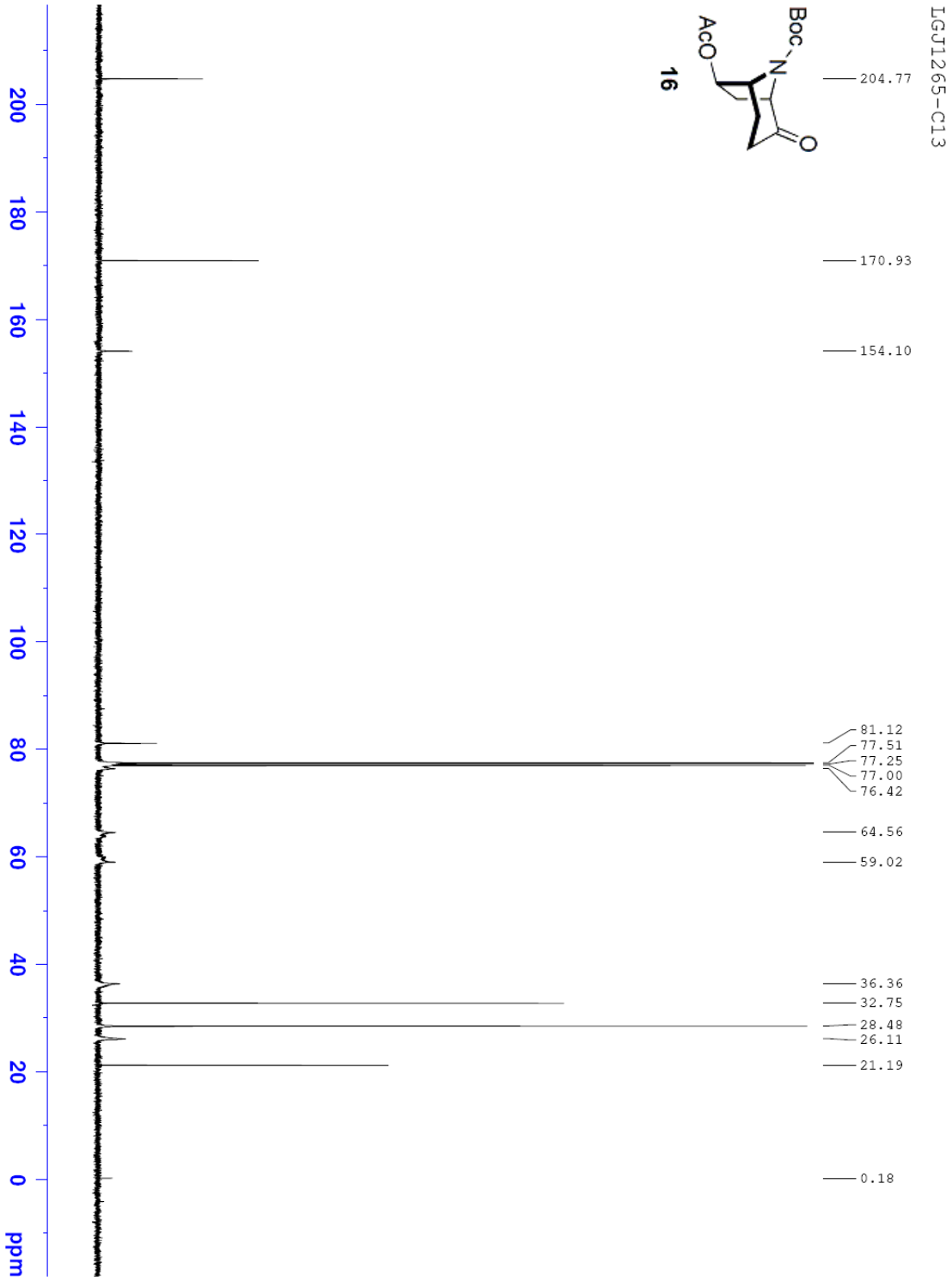

lgj1276
CDCl3
20090703
Boc
N
AcO
OH
14
0.99
1.10
1.05
1.05
0.57
1.20
3.23
1.22
2.27
1.64
9.00
9
8
7
6
5
4
3
2
1
0
ppm

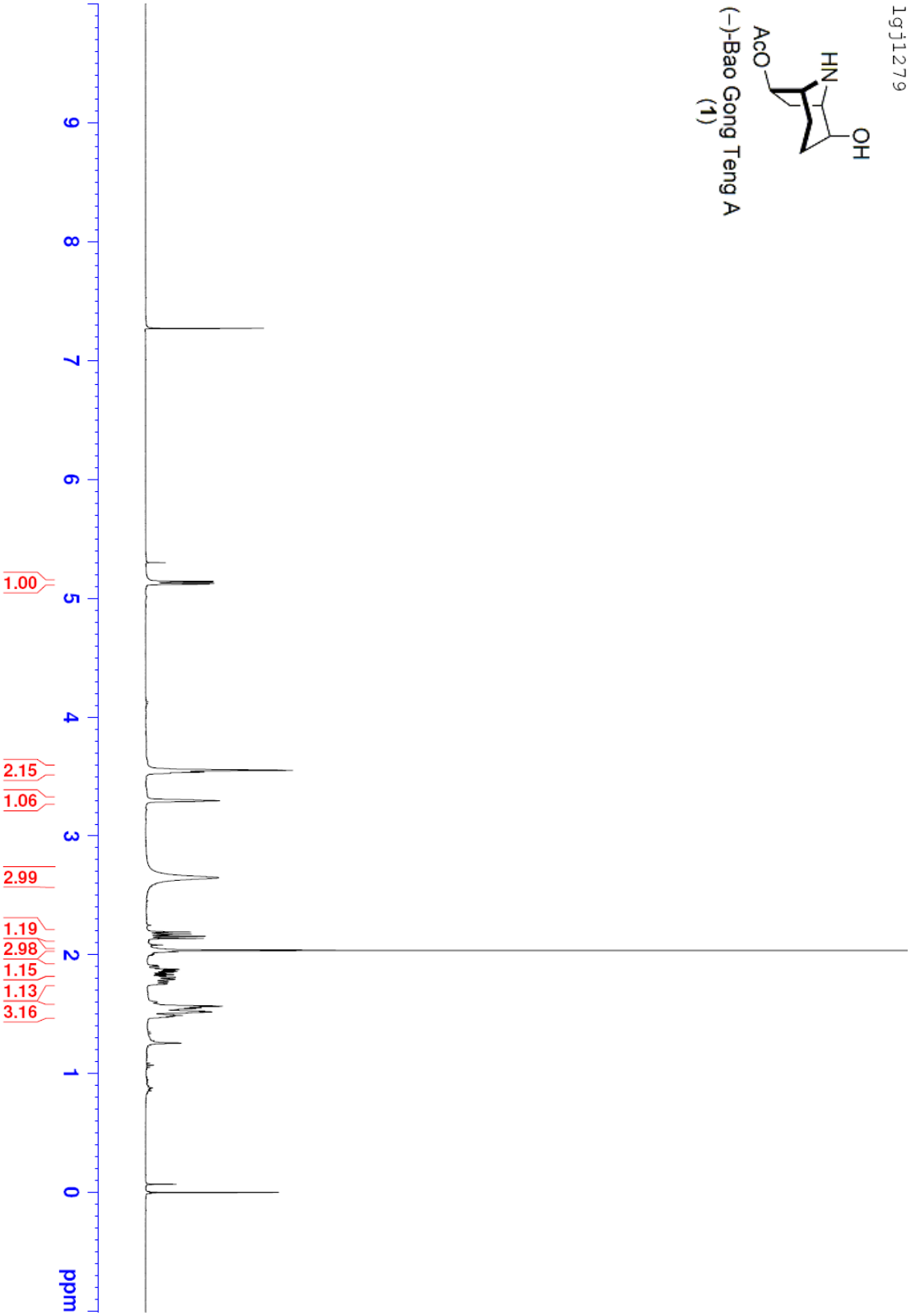

1gj1276-C13
CDC13
20090703
Boc
N
AcO
OH
14
171.04
156.40
80.48
77.58
77.46
77.26
76.94
76.18
69.75
69.17
60.80
59.69
58.51
35.82
35.21
28.66
24.85
24.21
23.71
21.31
0.20
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

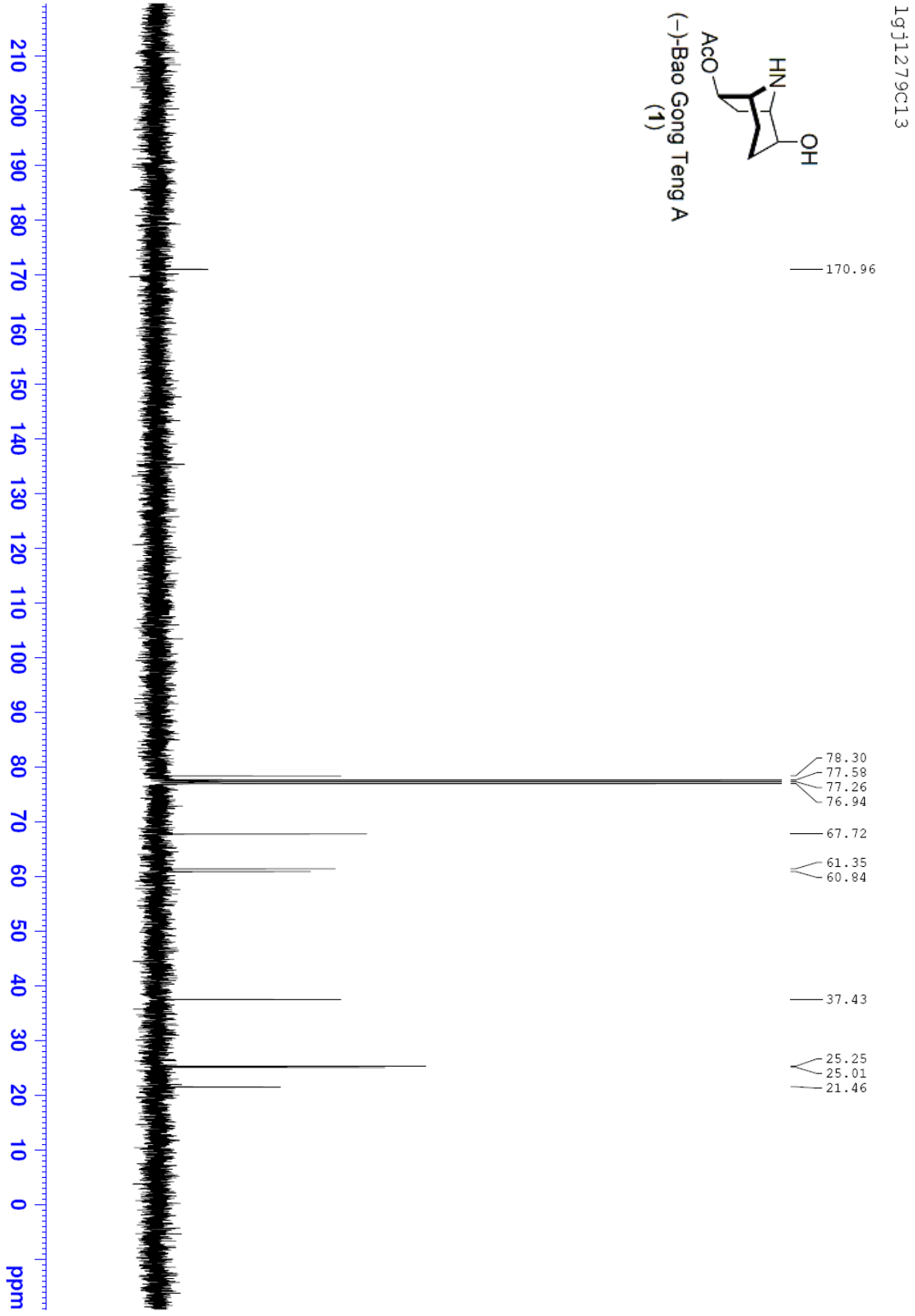

LGJ1260d
CDCl3
AcO
N
Boc
OH
15
1.00
0.55
2.44
2.03
0.41
1.09
3.10
1.09
3.86
10.37
9
8
7
6
5
4
3
2
1
0
ppm


LGJ1260d-C13
CDCl3
OH
15
N
Boc
AcO
170.94
170.78
155.09
154.85
79.92
78.02
77.51
77.26
77.01
63.66
63.06
62.72
62.26
44.62
44.26
29.95
29.67
29.60
28.97
28.84
28.72
21.46
0.21
200
180
160
140
120
100
80
60
40
20
0
ppm


LGJ1265-H1
16
Boc
N
O
AcO
0.95
1.89
1.96
3.05
2.97
1.02
0.36
9.00
ppm


LGJ1265-C13
16
AcO
Boc
N
O
204.77
170.93
154.10
81.12
77.51
77.25
77.00
76.42
64.56
59.02
36.36
32.75
28.48
26.11
21.19
0.18
200
180
160
140
120
100
80
60
40
20
0
ppm


1gj1279
(−)-Bao Gong Teng A
(1)
AcO
HN
OH
1.00
2.15
1.06
2.99
1.19
2.98
1.15
1.13
3.16
9
8
7
6
5
4
3
2
1
0
ppm


1gj1279C13
(−)-Bao Gong Teng A
(1)
AcO
HN
OH
170.96
78.30
77.58
77.26
76.94
67.72
61.35
60.84
37.43
25.25
25.01
21.46
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm