

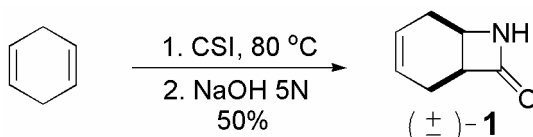
A safety problem was discovered for the protocol for preparing (±)-7-azabicyclo[4,2,0]oct-3-en-8-one (**1**).
A revised protocol has been published (*Org. Lett.* **2014**, *16*, 3848, DOI: 10.1021/ol5019097).

Supporting Information

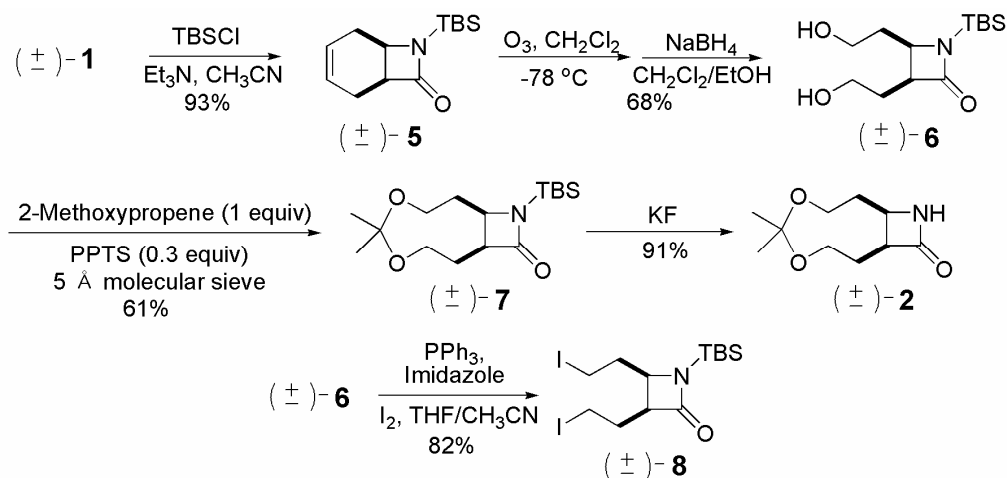
Synthesis of β -Lactams Bearing Functionalized Side Chains from a Readily Available Precursor

Myung-ryul Lee, Shannon S. Stahl* and Samuel H. Gellman*

General Methods. All chemicals and lipase bound to polyacrylate resin (Lipolase, L4777) were purchased from Sigma-Aldrich. ^1H , ^{13}C and ^{19}F NMR spectra were recorded at 300 MHz for proton, at 75 MHz for carbon and at 282.2 MHz for fluorine. Melting points were determined using a Thomas Hoover Uni-melt capillary melting point apparatus. Optical rotations were determined using a Perkin-Elmer 241 polarimeter.



(±)-7-Azabicyclo[4,2,0]oct-3-en-8-one (1**).** To 1,4-cyclohexadiene (25 g, 311.9 mmol) was added chlorosulfonyl isocyanate (44.2 g, 311.9 mmol) with stirring. The reaction mixture was stirred at 80 °C for 4 h and then cooled to room temperature. The reaction mixture was diluted with CH₂Cl₂ (30 mL) and poured into ice-water (mixture of water (250 mL) and ice); the pH was adjusted to 7 with 5 N NaOH. The aqueous solution was extracted several times with CH₂Cl₂. The combined organic layers were washed with brine and dried (MgSO₄). After filtration, the organic solution was concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent varied from 1:1 CH₂Cl₂/EtOAc to EtOAc) to give **1** in 50% yield as a solid: mp 122-125 °C; ^1H NMR (300 MHz CDCl₃) δ 5.93-5.83 (m, 1 H), 5.79-5.68 (m, 1 H), 5.59 (s, 1 H), 4.03-3.97 (m, 1 H), 3.42-3.35 (m, 1 H), 2.54-2.42 (m, 1 H), 2.41-2.28 (m, 1 H), 2.25-2.07 (m, 2 H); ^{13}C NMR (75 MHz, CDCl₃) δ 170.8, 125.8, 124.2, 47.7, 46.7, 26.8, 21.1; HRMS (*m/z*, ESI) calcd for C₇H₉NO (*M*)⁺ 123.0679, found 123.0678.



(±)-7-*tert*-Butyldimethylsilyl-7-azabicyclo[4,2,0]oct-3-en-8-one (5). To a stirred solution of **1** (5.2 g, 42.3 mmol) in acetonitrile (160 mL) was added TBSCl (6.7 g, 44.4 mmol), DMAP (2.0 g, 16.9 mmol), and TEA (8.6 g, 84.7 mmol). The reaction mixture was stirred for 6 h at room temperature. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc (250 mL). The organic solution was washed with 0.5 N HCl, H₂O, sat. NaHCO₃ and brine and then dried (MgSO₄). After filtration, the solution was concentrated *in vacuo*. The crude product was purified by silica column chromatography (5:1 hexane/EtOAc) to give **5** in 93% yield as a solid: mp 35-38 °C; ¹H NMR (300 MHz, CDCl₃) δ 5.91-5.82 (m, 1 H), 5.78-5.66 (m, 1 H), 3.91-3.85 (m, 1 H), 3.43-3.34 (m, 1 H), 2.51-2.31 (m, 2 H), 2.22-1.99 (m, 2 H), 0.94 (s, 9 H), 0.22 (s, 3 H), 0.20 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 174.8, 126.6, 124.2, 48.5, 48.1, 27.4, 26.0, 21.5, 18.1, -5.5, -6.1; HRMS (m/z, ESI) calcd for C₁₃H₂₃NOSi (M+H)⁺ 238.1544, found 238.1550.

(±)-1-*tert*-Butyldimethylsilyl-*cis*-3,4-bis-(2-hydroxyethyl)-azetidin-2-one (6). Compound **5** (7.1 g, 29.9 mmol) was dissolved in CH₂Cl₂ (210 mL), and the solution was cooled to -78 °C. O₃ was bubbled through a solution of **5** until the solution became pale blue, and then N₂ was bubbled through until the solution became colorless. EtOH (70 mL) and NaBH₄ (3.4 g, 89.7 mmol) were added to the solution at -78 °C, and the mixture was warmed to room temperature. The reaction mixture was allowed to stir for 10 h at room temperature. The reaction was quenched by addition of sat. aq. NH₄Cl, and then water (50 mL) was added. The mixture was extracted several times with CH₂Cl₂. The combined organic layers were dried (MgSO₄). After filtration, the solution was concentrated *in vacuo*. The crude product was purified by silica column

chromatography (eluent varied from EtOAc to 12:1 EtOAc/MeOH) to give **6** in 68% yield as an oil: ^1H NMR (300 MHz, CD_3OD) δ 3.87 (ddd, 1 H, $J = 9.3, 5.4, 3.3$ Hz), 3.80-3.49 (m, 4 H), 3.41 (ddd, 1 H, $J = 8.7, 7.2, 5.7$ Hz), 2.05-1.77 (m, 4 H), 0.97 (s, 9 H), 0.25 (s, 6 H); ^{13}C NMR (75 MHz, CD_3OD) δ 178.8, 61.0, 59.7, 51.9, 51.0, 35.6, 29.2, 26.8, 19.1, -5.1, -5.4; HRMS (m/z , ESI) calcd for $\text{C}_{13}\text{H}_{27}\text{NO}_3\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 296.1653, found 296.1658.

(±)-10-(tert-Butyldimethylsilyl)-5,5-dimethyl-4,6-dioxo-10-azabicyclo

[7.2.0]undecan-11-one (7). To a stirred solution of **6** (2.2 g, 8.0 mmol) and molecular sieves (10 g, 5 \square) in anhydrous CH_2Cl_2 (800 mL) was added 2-methoxypropene (0.75 g, 10.4 mmol) and pyridinium *p*-toluenesulfonate (0.61 g, 2.4 mmol) at 0 $^\circ\text{C}$. The mixture was then warmed to room temperature. After sitting overnight, the molecular sieves were filtered off using celite, and the filtrate was washed with sat. NaHCO_3 and dried (MgSO_4). After filtration, the solution concentrated *in vacuo*. The crude product was purified by silica column chromatography (3:1 hexane/EtOAc) to give **7** in 61% yield as a solid: mp 88-91 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 3.98 (ddd, 1 H, $J = 12.6, 3.0, 3.0$ Hz), 3.82 (ddd, 1 H, $J = 9.6, 5.4, 5.1$ Hz), 3.77-3.58 (m, 2 H), 3.53-3.34 (m, 2 H), 2.49-2.29 (m, 1 H), 2.08-1.84 (m, 2 H), 1.82-1.70 (m, 1 H), 1.40 (s, 3 H), 1.31 (s, 3 H), 0.94 (s, 9 H), 0.21 (s, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.6, 100.7, 64.5, 59.1, 56.2, 54.3, 33.7, 26.3, 25.9, 25.8, 24.8, 18.3, -5.1, -5.5; HRMS (m/z , ESI) calcd for $\text{C}_{16}\text{H}_{31}\text{NO}_3\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 336.1966, found 336.1954.

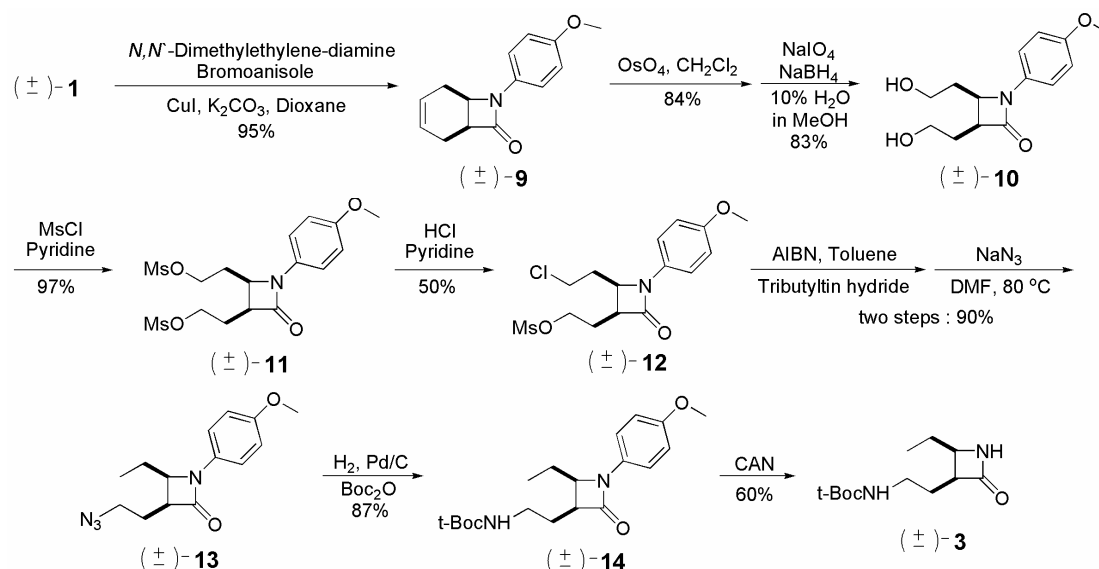
(±)-5,5-Dimethyl-4,6-dioxo-10-azabicyclo[7.2.0]undecan-11-one (2).

To a stirred solution of **7** (1.53 g, 4.9 mmol) in MeOH (120 mL) was added potassium fluoride (0.57 g, 9.8 mmol) at 0 $^\circ\text{C}$. The mixture was then warmed to room temperature. After 2 h the reaction mixture was concentrated *in vacuo*. The crude product was purified by silica column chromatography (EtOAc) to give **2** in 91% yield as a solid: mp 145-148 $^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3) δ 5.84 (s, 1 H), 3.98 (ddd, 1 H, $J = 12.6, 3.0, 2.7$ Hz), 3.91 (ddd, 1 H, $J = 11.1, 4.5, 3.0$ Hz), 3.81-3.60 (m, 2 H), 3.58-3.45 (m, 1 H), 3.40-3.30 (m, 1 H), 2.45-2.26 (m, 1 H), 2.20-2.00 (m, 1 H), 1.93-1.74 (m, 2 H), 1.41 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.0, 100.5, 63.5, 59.2, 53.7, 53.4, 32.6, 25.6, 25.4, 24.5; HRMS (m/z , ESI) calcd for $\text{C}_{10}\text{H}_{17}\text{NO}_3$ ($\text{M}+\text{Na}$) $^+$ 222.1101, found 222.1093.

(±)-1-tert-Butyldimethylsilyl-cis-3,4-bis-(2-iodoethyl)-azetidin-2-one (8).

To a stirred solution of triphenylphosphine (1.9 g, 7.3 mmol) and imidazole (0.79 g, 11.7

mmol) in anhydrous THF (10 mL) and acetonitrile (10 mL) was added iodine (1.8 g, 7.3 mmol) at room temperature. After 10 min, a solution of **6** (0.5 g, 1.8 mmol) in THF (10 mL) was added to the reaction mixture. After 4 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc. The organic solution was washed with 5% Na₂S₂O₅, H₂O and brine and then dried (MgSO₄). After filtration, the solution was concentrated *in vacuo*. The crude product was purified by silica column chromatography (6:1 hexane/EtOAc) to give **8** in 82% yield as an oil: ¹H NMR (300 MHz, CDCl₃) δ 3.78 (ddd, 1 H, *J* = 9.3, 5.7, 3.3 Hz), 3.54-3.39 (m, 2 H), 3.37-3.26 (m, 1 H), 3.18 (ddd, 1 H, *J* = 10.2, 7.5, 5.4 Hz), 2.99 (ddd, 1 H, *J* = 10.2, 9.0, 6.9 Hz), 2.33-1.95 (m, 4 H), 0.95 (s, 9 H), 0.24 (s, 3 H), 0.23 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 174.0, 53.0, 52.9, 35.2, 29.5, 26.1, 18.0, 2.9, 0.2, -5.3, -5.6; HRMS (*m/z*, ESI) calcd for C₁₃H₂₅I₂NOSi (*M*+Na)⁺ 515.9687, found 515.9679.



(±)-7-(4-Methoxyphenyl)-7-azabicyclo[4,2,0]oct-3-en-8-one (9). Compound **1** (5.0 g, 40.6 mmol), CuI (0.15 g, 0.8 mmol), K₂CO₃ (16.3 g, 117.7 mmol) were placed in a Schlenk tube, and the tube was evacuated and refilled with N₂. Dioxane (25 mL), 4-bromoanisole (15.2 g, 81.2 mmol), and *N,N*-dimethyl-1,2-ethylenediamine (0.79 g, 8.9 mmol) were added to the Schlenk tube under N₂. The Schlenk tube was sealed, and the mixture was allowed to stir for 20 h at 105 °C. After cooling, the reaction mixture was filtered through silica gel, which was then rinsed with EtOAc. The filtrate was concentrated *in vacuo*. The crude product was purified by silica column chromatography (1:1 hexane/EtOAc) to give **9** in 95% yield as a solid: mp 137-139 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.30 (d, 2 H, *J* = 9.0 Hz), 6.86 (d, 2 H, *J* = 9.0 Hz), 5.95-

5.84 (m, 1 H), 5.70-5.59 (m, 1 H), 4.40-4.34 (m, 1 H), 3.78 (s, 3 H), 3.52-3.43 (m, 1 H), 2.75-2.52 (m, 2 H), 2.28-2.14 (m, 2 H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.4, 155.8, 130.4, 126.5, 124.0, 118.5, 114.3, 55.3, 50.2, 46.6, 23.8, 21.3; HRMS (m/z , ESI) calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_2$ (M^+) $^+$ 229.1098, found 229.1101.

(\pm)-cis-3,4-bis-(2-Hydroxyethyl)-1-(4-methoxyphenyl)-azetidin-2-one (10).

To a stirred solution of **9** (2.0 g, 8.8 mmol) and 4-methylmorpholine N-oxide (3.1 g, 26.5 mmol) in CH_2Cl_2 (100 mL) was added a 4% aqueous OsO_4 solution (2.7 mL, 0.44 mmol) at room temperature. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (120 mL) and washed with 10% $\text{Na}_2\text{S}_2\text{O}_3$, sat. NaHCO_3 and brine. The combined aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried (MgSO_4) and, after filtration, concentrated *in vacuo*. The crude product was quickly purified by silica column chromatography (eluent varied from 1:1 $\text{CHCl}_3/\text{EtOAc}$ to 10:1 EtOAc/MeOH) to give 3,4-bis-hydroxy-7-(4-methoxyphenyl)-7-azabicyclo[4,2,0]octan-8-one in 84% yield as a solid. This material was carried directly on to the next reaction.

To a stirred solution of 3,4-bis-hydroxy-7-(4-methoxyphenyl)-7-azabicyclo[4,2,0]octan-8-one (2.0 g, 7.4 mmol) in MeOH (220 mL) containing 10 % water was added NaIO_4 (2.1 g, 9.7 mmol) at 0 °C. After 5 h at 0 °C, NaBH_4 (0.84 g, 22.3 mmol) was added to the reaction mixture, which was then warmed to room temperature. After 2 h, the reaction mixture was diluted with EtOAc (1 L) and washed with brine (200 mL). The organic layer was dried (MgSO_4), filtered and concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent varied from 1:1 $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ to 15:1 EtOAc/MeOH) to give **10** in 83% yield as a solid: mp 99-102 °C; ^1H NMR (300 MHz, CD_3OD) δ 7.33 (d, 2 H, J = 8.7 Hz), 6.92 (d, 2 H, J = 9.0 Hz), 4.39 (ddd, 1 H, J = 7.8, 5.4, 5.1 Hz), 3.85-3.72 (m, 5 H), 3.71-3.59 (m, 2 H), 3.49 (ddd, 1 H, J = 8.1, 7.8, 5.7 Hz), 2.15-2.00 (m, 1 H), 1.19-1.82 (m, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.8, 157.9, 131.6, 120.6, 115.3, 61.0, 59.8, 55.8, 53.4, 49.5, 32.3, 29.1; HRMS (m/z , ESI) calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_4$ ($\text{M}+\text{Na}$) $^+$ 288.1209, found 288.1208.

(\pm)-cis-3,4-bis-(2-Methanesulfonyloxyethyl)-1-(4-methoxyphenyl)-azetidin-2-one (11).

To a stirred solution of **10** (0.68 g, 2.6 mmol) in pyridine (8 mL) was added methanesulfonyl chloride (1.2 g, 10.3 mmol) at 0 °C. The reaction mixture was then warmed to room temperature. After 30 min, the reaction mixture was concentrated under a stream of N_2 . The concentrated residue was diluted with EtOAc and washed with 0.5 N HCl , H_2O and brine. The organic layer was dried (MgSO_4), filtered and

concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent varied from 1:1 CH₂Cl₂/EtOAc to 15:1 EtOAc/MeOH) to give **11** in 97% yield as a oil: ¹H NMR (300 MHz, CDCl₃) δ 7.26 (d, 2 H, *J* = 8.7 Hz), 6.89 (d, 2 H, *J* = 9.0 Hz), 4.60-4.44 (m, 2 H), 4.42-4.25 (m, 3 H), 3.79 (s, 3 H), 3.57 (ddd, 1 H, *J* = 8.4, 7.8, 6.3 Hz), 3.07 (s, 3 H), 3.04 (s, 3 H), 2.41-2.27 (m, 1 H), 2.25-2.04 (m, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 165.7, 156.3, 129.7, 119.1, 114.3, 67.9, 66.5, 55.2, 51.1, 47.5, 37.0, 36.8, 27.9, 24.7; HRMS (*m/z*, ESI) calcd for C₁₆H₂₃NO₈S₂ (M)⁺ 421.0860, found 421.0851.

(±)-*cis*-4-(2-Chloroethyl)-3-(2-methansulfonyloxyethyl)-1-(4-methoxyphenyl)-azetidin-2-one (12). To a stirred solution of **11** (2.8 g, 6.6 mmol) in pyridine (50 mL) was added 4 N HCl in dioxane (3.3 mL, 13.3 mmol) at 0 °C. The reaction mixture was then warmed to room temperature. After 14 h, the reaction mixture was concentrated under a stream of N₂. The concentrated residue was diluted with EtOAc and washed with 0.5 N HCl, H₂O and brine. The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by silica column chromatography (2:1:2 CH₂Cl₂/hexane/EtOAc) to give **12** in 38% yield as an oil. The recovered starting material (30 to 40%) was recycled by the same procedure to give **12** in total 50% yield as an oil: ¹H NMR (300 MHz, CDCl₃) δ 7.29 (d, 2 H, *J* = 9.3 Hz), 6.89 (d, 2 H, *J* = 9.0 Hz), 4.59-4.41 (m, 3 H), 3.79 (s, 3 H), 3.69-3.51 (m, 3 H), 3.08 (s, 3 H), 2.42-2.28 (m, 1 H), 2.23-2.04 (m, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 165.9, 156.4, 130.0, 119.2, 114.4, 67.8, 55.4, 51.6, 47.5, 41.5, 37.1, 31.5, 25.0; HRMS (*m/z*, ESI) calcd for C₁₅H₂₀ClNO₅S (M+Na)⁺ 384.0643, found 384.3652.

(±)-*cis*-3-(2-Azidoethyl)-4-ethyl-1-(4-methoxyphenyl)-azetidin-2-one (13). A reaction flask was charged with **12** (1.2 g, 3.2 mmol) and AIBN (0.1 g, 0.64 mmol) and then evacuated. Toluene (30 mL) was added, and the flask was filled with N₂. To the stirred reaction mixture was added tributyltinhydride (4.7 g, 16.1 mmol). A reflux condenser was then installed, and the mixture was warmed to 80 °C. After 12 h, the reaction mixture was concentrated *in vacuo*. The concentrated residue was purified by silica column chromatography (eluent varied from CHCl₃ to 1:1 Hexane/EtOAc) to give tributyltinhydride-contaminated *cis*-4-ethyl-3-(2-methansulfonyloxyethyl)-1-(4-methoxyphenyl)-azetidin-2-one, which was used for the next reaction without further purification.

To a stirred solution of the tributyltinhydride-contaminated *cis*-4-ethyl-3-(2-methansulfonyloxyethyl)-1-(4-methoxyphenyl)-azetidin-2-one described above in DMF

(15 mL) at 60-80 °C was added NaN₃ (2.1 g, 32.2 mmol). After 12 h, the reaction mixture was diluted with H₂O and extracted several times with EtOAc. The combined organic layers were washed with H₂O and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by silica column chromatography (2:1 hexane/EtOAc) to give **13** in 90% overall yield from **12** as a solid: mp 49-50 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.28 (d, 2 H, *J* = 9.0 Hz), 6.87 (d, 2 H, *J* = 9.0 Hz), 4.05 (ddd, 1 H, *J* = 9.3, 5.7, 3.9 Hz), 3.78 (s, 3 H), 3.74-3.64 (m, 1 H), 3.62-3.51 (m, 1 H), 3.40 (ddd, 1 H, *J* = 10.5, 5.7, 5.4 Hz), 2.16-1.84 (m, 3 H), 1.74-1.57 (m, 1 H), 1.00 (t, 3 H, *J* = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 166.1, 155.7, 130.5, 118.5, 113.9, 55.5, 54.9, 49.1, 48.1, 24.0, 20.9, 10.3; HRMS (*m/z*, ESI) calcd for C₁₄H₁₈N₄O₂ (*M*+Na)⁺ 297.1322, found 297.1319.

In order to confirm the regiochemistry of compound **13**, COSY 2D-NMR spectroscopy was performed; the data are shown below.

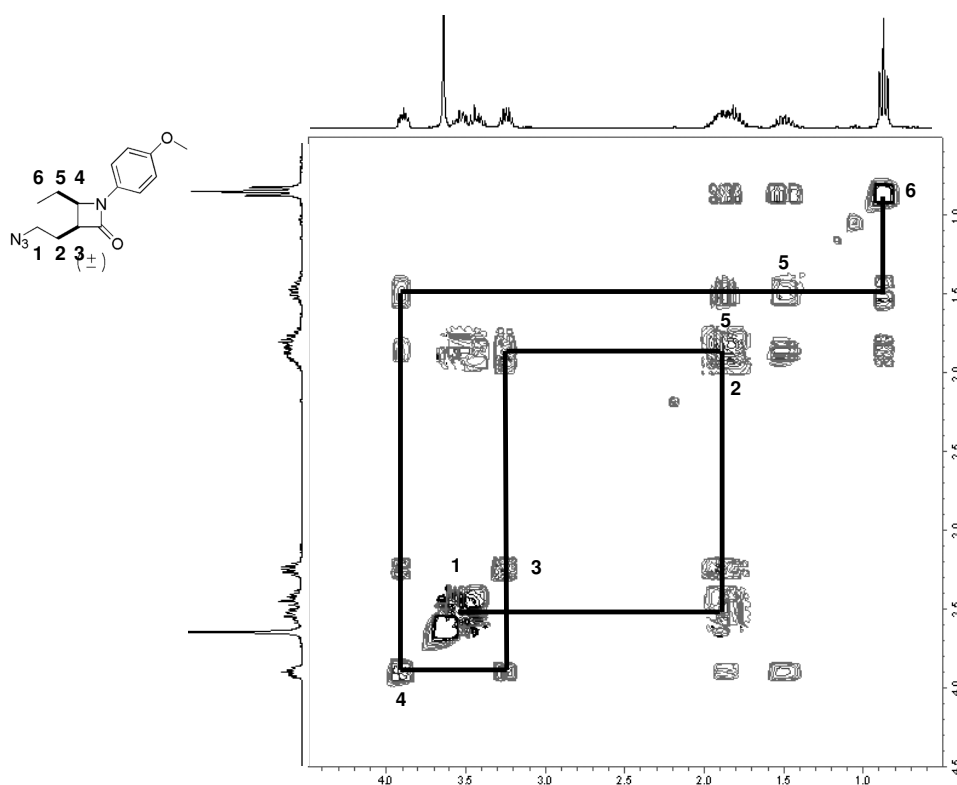
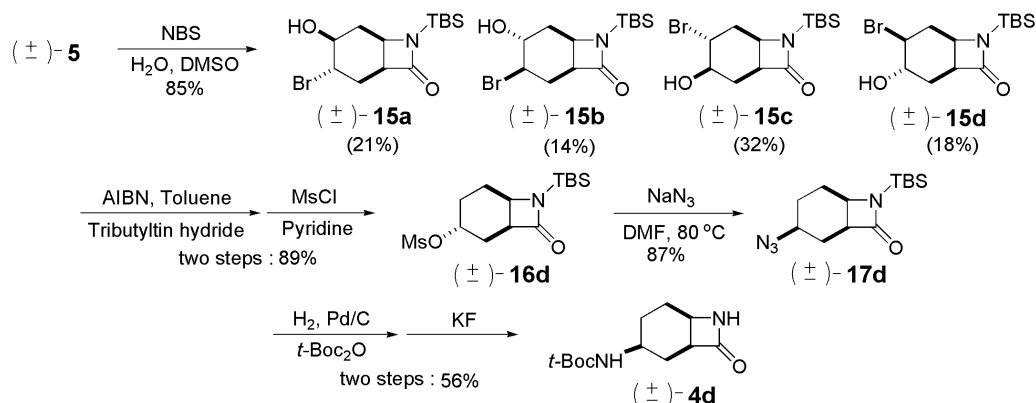


Figure S1. COSY data of **13**.

(±)-cis-3-(2-tert-Butoxycarbonylaminoethyl)-4-ethyl-1-(4-methoxyphenyl)-azetidin-2-one (14). A suspension of **13** (0.8 g, 2.9 mmol), Boc₂O (1.9 g, 8.7 mmol) and 10% Pd/C (wet, 0.64 g) in MeOH (10 mL) was shaken on a Parr hydrogenation apparatus under 50 psi H₂ at room temperature. After 12 h, the reaction mixture was

filtered through celite, and the pad was rinsed with MeOH. The combined filtrate was concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent varied from 3:3:1 CH₂Cl₂/hexane/EtOAc to 2:1 hexane/EtOAc) to give **14** in 87% yield as a solid.: mp 100-103 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.29 (d, 2 H, *J* = 9.0 Hz), 6.87 (d, 2 H, *J* = 9.3 Hz), 5.61 (s, 1 H), 4.03 (ddd, 1 H, *J* = 9.3, 5.7, 3.9 Hz), 3.78 (s, 3 H), 3.58-3.43 (m, 1 H), 3.38-3.15 (m, 2 H), 2.07-1.78 (m, 3 H), 1.75-1.56 (m, 1 H), 1.45 (s, 9 H), 0.99 (t, 3 H, *J* = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 167.2, 156.0, 155.9, 130.6, 118.7, 114.1, 78.5, 55.7, 55.1, 49.8, 39.0, 28.2, 24.7, 21.1, 10.5; HRMS (*m/z*, ESI) calcd for C₁₉H₂₈N₂O₄ (*M*)⁺ 348.2044, found 348.2039.

(±)-cis-3-(2-*tert*-Butoxycarbonylaminoethyl)-4-ethyl-azetidin-2-one (3). To a stirred solution of **14** (0.87 g, 2.5 mmol) in THF (4 mL) and acetonitrile (16 mL) was added a solution of ceric ammonium nitrate (CAN; 4.1 g, 7.5 mmol) in H₂O (20 mL) at 0 °C. After 30 min at 0 °C, the reaction was quenched by addition of 10% Na₂SO₃ and then water (20 mL) was added. The reaction mixture was extracted several times with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent varied from 1:1 hexane/EtOAc to 1:4 hexane/EtOAc) to give **3** in 60% yield as a solid: mp 88-90 °C; ¹H NMR (300 MHz, CDCl₃) δ 6.16 (s, 1 H), 5.46 (s, 1 H), 3.61 (ddd, 1 H, *J* = 9.3, 4.8, 4.5 Hz), 3.48-3.32 (m, 1 H), 3.26-3.07 (m, 2 H), 1.92-1.56 (m, 3 H), 1.55-1.46 (m, 1 H), 1.44 (s, 9 H), 0.96 (t, 3 H, *J* = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 172.0, 156.1, 78.7, 53.2, 51.0, 39.1, 28.3, 24.9, 24.0, 10.7; HRMS (*m/z*, ESI) calcd for C₁₂H₂₂N₂O₃ (*M*+Na)⁺ 265.1523, found 265.1527.



(±)-4-Bromo-7-*tert*-butyldimethylsilyl-3-hydroxy-7-azabicyclo[4,2,0]octan-8-one (15). To a stirred solution of **5** (1.2 g, 5.0 mmol) and H₂O (0.72 g, 40.1

mmol) in DMSO (23 mL) was added N-bromosuccinimide (0.98 g, 5.5 mmol) at 0 °C. The mixture was then warmed to room temperature. After 2 h, the reaction mixture was diluted with H₂O and extracted several times with EtOAc. The combined organic layers were washed with H₂O and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent varied from 5:1 to 1:1 hexane/EtOAc) to give **15a** (21%), a mixture of **15b** (14%) and **15c** (32%), and **15d** (18%). In order to determine the stereochemistries of **15a**, **15b**, **15c** and **15d**, these compounds were resynthesized using (*1S,6R*)-**5** and then crystallized (crystals of **15b** could not be obtained). Crystal structures were determined for enantiopure **15a**, **15c** and **15d** (shown below).

15a: ¹H NMR (300 MHz, CDCl₃) δ 4.20-4.07 (m, 1 H), 3.92-3.77 (m, 2 H), 3.49-3.39 (m, 1 H), 2.78-2.65 (m, 1 H), 2.61-2.40 (m, 2 H), 2.20-2.03 (m, 1 H), 1.85-1.70 (m, 1 H), 0.96 (s, 9 H), 0.27 (s, 3 H), 0.20 (s, 3 H).

15b and 15c: ¹H NMR (300 MHz, CDCl₃) δ 4.22 (ddd, 1 H (**15c**), *J* = 10.2, 8.1, 3.9 Hz), 4.08-3.85 (m, 2.2 H (**15b**=1.2 H, **15c**=1 H)), 3.81 (ddd, 1 H (**15c**), *J* = 5.7, 5.7, 2.7 Hz), 3.44-3.27 (m, 1.4 H (**15b**=0.4 H, **15c**=1 H)), 2.68-2.19 (m, 5.6 H (**15b**=1.6 H, **15c**=4 H)), 2.00 (ddd, 1 H (**15c**), *J* = 12.3, 7.8, 4.5 Hz), 1.76 (ddd, 0.4 H (**15b**), *J* = 15.0, 9.6, 6.0 Hz), 0.96 (s, 12.6 H (**15b**=3.6 H, **15c**=9 H)), 0.25 (s, 4.2 H (**15b**=1.2 H, **15c**=3 H)), 0.24 (s, 1.2 H (**15b**)), 0.20 (s, 3 H(**15c**)).

15d: mp 107-110 °C; ¹H NMR (300 MHz, CDCl₃) δ 4.06-3.88 (m, 2 H), 3.81-3.71 (m, 1 H), 3.56 (ddd, 1 H, *J* = 8.7, 6.0, 3.3 Hz), 2.82 (ddd, 1 H, *J* = 15.0, 7.2, 5.7 Hz), 2.54-2.42 (m, 2 H), 2.23 (ddd, 1 H, *J* = 15.3, 10.2, 5.4 Hz), 1.64 (ddd, 1 H, *J* = 14.4, 8.7, 8.4 Hz), 0.96 (s, 9 H), 0.29 (s, 3 H), 0.20 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 175.0, 71.7, 55.3, 48.2, 39.5, 29.0, 26.3, 18.6, -5.3, -5.4; HRMS (*m/z*, ESI) calcd for C₁₃H₂₄BrNO₂Si (*M*+Na)⁺ 356.0651, found 356.0657.

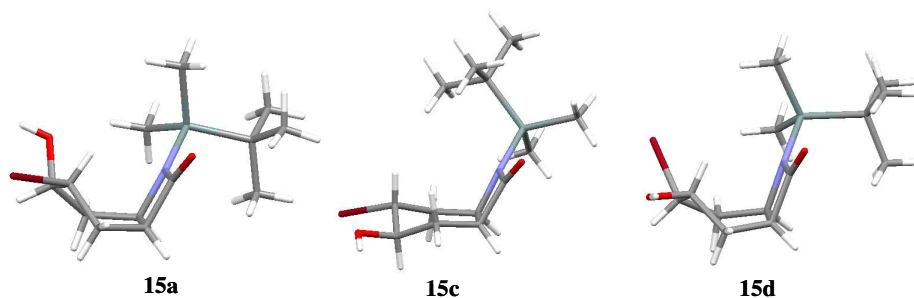


Figure S2. Crystal structure of **15a**, **15c** and **15d**.

(±)-7-tert-Butyldimethylsilyl-3-methansulfonyloxy-7-azabicyclo[4,2,0]octan-8-one (16d). A reaction flask was charged with **15d** (0.27 g, 0.8 mmol) and

AIBN (26.8 mg, 0.16 mmol) and evacuated. Toluene (15 mL) was added, and the flask was filled with N₂. To the stirring mixture was added tributyltinhydride (1.2 g, 4.1 mmol). A reflux condenser was then installed, and the mixture was warmed to 80 °C. After 12 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica column chromatography (eluent varied from CHCl₃ to 1:4 hexane/EtOAc) to give tributyltinhydride-contaminated 7-*tert*-butyldimethylsilyl-3-hydroxy-7-azabicyclo[4,2,0]octan-8-one, which was used for the next reaction without further purification.

To a stirred solution of the tributyltinhydride-contaminated 7-*tert*-butyldimethylsilyl-3-hydroxy-7-azabicyclo[4,2,0]octan-8-one described above in pyridine (2 mL) was added methanesulfonyl chloride (0.18 g, 1.6 mmol) at 0 °C. The mixture was then warmed to room temperature. After 30 min, the reaction mixture was concentrated under a stream of N₂. The residue was diluted with EtOAc, and the solution was washed with 0.5 N HCl, H₂O and brine. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by silica column chromatography (1:1 hexane/EtOAc) to give **16d** in 89% overall yield from **15d** as an oil: ¹H NMR (300 MHz, CDCl₃) δ 5.07-4.95 (m, 1 H), 3.84-3.75 (m, 1 H), 3.46-3.36 (m, 1 H), 3.00 (s, 3 H), 2.38-2.25 (m, 1 H), 2.20-1.93 (m, 3 H), 1.91-1.67 (m, 2 H), 0.96 (s, 9 H), 0.26 (s, 3 H), 0.19 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 174.9, 76.2, 47.2, 45.6, 38.4, 26.6, 26.1, 24.9, 23.5, 18.3, -5.5, -5.7; HRMS (m/z, ESI) calcd for C₁₄H₂₇NO₄SSi (M+Na)⁺ 356.1322, found 356.1311.

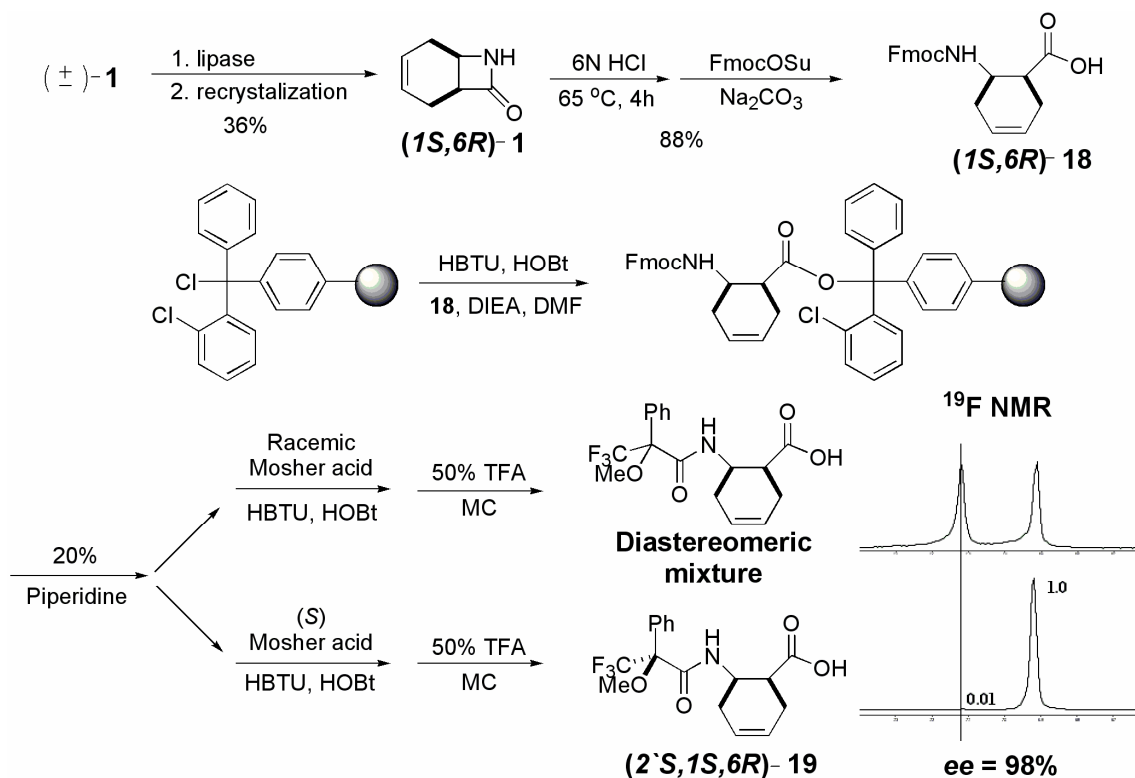
(±)-3-Azido-7-*tert*-butyldimethylsilyl-7-azabicyclo[4,2,0]octan-8-one (17d).

To a stirred solution of **16d** (0.24 g, 0.72 mmol) in DMF (3 mL) at 60-65 °C was added NaN₃ (0.23 g, 3.6 mmol). After 2 h, the reaction mixture was diluted with H₂O and extracted several times with EtOAc. The combined organic layers were washed with H₂O and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by silica column chromatography (3:1 hexane/EtOAc) to give **17d** in 87% yield as an oil: ¹H NMR (300 MHz, CDCl₃) δ 3.75-3.66 (m, 1 H), 3.62-3.48 (m, 1 H), 3.28 (ddd, 1 H, *J* = 9.3, 6.0, 5.7 Hz), 2.14-2.08 (m, 1 H), 1.98-1.68 (m, 5 H), 0.96 (s, 9 H), 0.24 (s, 3 H), 0.21 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 175.5, 56.2, 47.1, 45.9, 26.3, 26.1, 25.8, 24.6, 18.3, -5.5, -5.8; HRMS (m/z, ESI) calcd for C₁₃H₂₄N₄OSi (M+H)⁺ 281.1793, found 281.1786.

(±)-3-*tert*-Butoxycarbonylamino-7-azabicyclo[4,2,0]octan-8-one (4d).

A suspension of **17d** (0.18 g, 0.62 mmol), Boc₂O (0.54 g, 2.49 mmol) and 10% Pd/C (wet, 0.14 g) in MeOH (6 mL) was shaken on a Parr hydrogenation apparatus under 50 psi H₂

at room temperature. After 12 h, the reaction mixture was filtered through celite, and the bed was rinsed with MeOH. The filtrate was concentrated *in vacuo*. To a stirred solution of the concentrated residue in MeOH (10 mL) at 0 °C was added potassium fluoride (73 mg, 1.2 mmol). The mixture was then warmed to room temperature. After 2 h, the reaction mixture was concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent varied from 1:5 hexane/EtOAc to EtOAc) to give **4d** in 56% yield as a solid: mp 173-175 °C; ¹H NMR (300 MHz, CD₃OD) δ 3.79 (ddd, 1 H, *J* = 5.1, 4.8, 0.9 Hz), 3.50-3.36 (m, 1 H), 3.21 (ddd, 1 H, *J* = 10.2, 5.7, 5.1 Hz), 2.15-2.00 (m, 1 H), 1.97-1.86 (m, 1 H), 1.85-1.48 (m, 4 H), 1.42 (s, 9 H); ¹³C NMR (75 MHz, CD₃OD) δ 175.1, 157.6, 79.9, 47.4, 46.7, 46.4, 28.7, 27.7, 27.6, 26.4; HRMS (*m/z*, ESI) calcd for C₁₂H₂₀N₂O₃ (*M*+Na)⁺ 263.1367, found 263.1376.



(1S,6R)-7-Azabicyclo[4,2,0]oct-3-en-8-one (1). An Erlenmeyer flask (500 mL) was charged with **1** (5 g, 40.6 mmol), lipase on polyacrylate resin (10 g), H₂O (0.73 g, 40.6 mmol) and diisopropyl ether (200 mL). The reaction flask was sealed and agitated at 60 °C, for 12 h in a shaking incubator. The reaction mixture was filtered, and the isolated solids were rinsed with diisopropyl ether. The combined filtrate was concentrated *in vacuo*. The crude product was purified by silica column

chromatography (eluent varied from 1:1 hexane/EtOAc to EtOAc) and then recrystallized from CHCl₃ and diisopropyl ether to give (*1S,6R*)-**1** in 36% yield as a solid: mp 158-161 °C; [α]_D -28.2 (c 0.4, CHCl₃).

(1*S*,6*R*)-6-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-cyclohex-3-en-1-carboxylic acid (18**).** Compound (*1S,6R*)-**1** (0.15 g, 1.2 mmol) was dissolved in 6 N HCl (8 mL). The flask was fitted with a reflux condenser, and the reaction mixture was warmed to 65 °C. After 4 h, the reaction mixture was cooled in an ice bath and neutralized to pH 7 by addition of 10 N NaOH. The neutralized reaction mixture was stirred, and NaCO₃ (0.52 g, 4.9 mmol) and dioxane (6 mL) were added. A solution of FmocOSu (0.82 g, 2.4 mmol) in dioxane (6 mL) was then slowly added to the stirred reaction mixture at 0 °C. After the mixture had stirred overnight at room temperature, the pH was adjusted to 2 with 1 N HCl, and the acidified solution was then extracted several times with EtOAc. The combined organic layers were washed with H₂O and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified by silica column chromatography (eluent varied from CHCl₃ to EtOAc) to give **18** in 88 % yield as a solid: mp 74-80 °C; [α]_D +11.5 (c 3.0, CHCl₃); ¹H NMR (300 MHz CD₃OD) δ 7.78 (d, 2 H, *J* = 7.5 Hz), 7.67-7.53 (m, 2 H), 7.42-7.25 (m, 4 H), 5.75-5.55 (m, 2 H), 4.42-4.32 (m, 1 H), 4.31-4.15 (m, 3 H), 2.89-2.78 (m, 1 H), 2.62-1.96 (m, 4 H); ¹³C NMR (75 MHz, CD₃OD) δ 176.5, 157.8, 145.0, 144.9, 142.2, 128.5, 128.0, 127.9, 126.0, 125.9, 125.2, 120.7, 67.6, 48.1, 47.9, 42.5, 31.2, 26.1; HRMS (*m/z*, ESI) calcd for C₂₂H₂₁NO₄ (M+Na)⁺ 386.1363, found 386.1359.

Preparation of Mosher amide derivatives from **18.** After swelling of 2-chlorotriylchloride resin (1.2 mmol/g, 25 μ mol) in CH₂Cl₂, a solution of **18** (1.2 equiv), DIEA (3.3 equiv) in CH₂Cl₂ (1 mL) was added to the resin. After 2 h stirring, the resin was filtered and washed 3 times with CH₂Cl₂ and 3 times with DMF. The Fmoc group was removed by treating the resin with 20% piperidine in DMF twice, for 7 min each time. The resin was isolated by filtration and washed 3 times with CH₂Cl₂ and 3 times with DMF. A solution of racemic or (*S*)-Mosher acid (3 equiv), HBTU (3 equiv), HOBT (3 equiv) and DIEA (6 equiv) in DMF (1 mL) was added to the resin. After 4 h stirring, the resin was isolated by filtration and washed 3 times with CH₂Cl₂, 3 times with DMF and 3 times with CH₂Cl₂. The product was cleaved from the resin using 50% TFA in CH₂Cl₂ for 2 h. The deprotection solution was filtered, and the filtrate was concentrated under a stream of N₂. The crude product was directly used to determine the *ee* value of **19** using ¹⁹F NMR; TFA (5 μ L) was used as an internal standard.

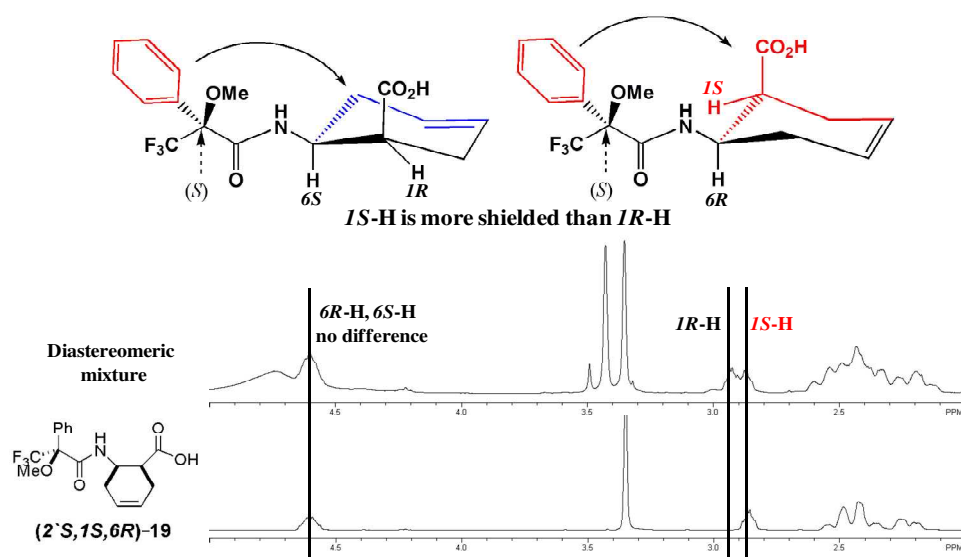
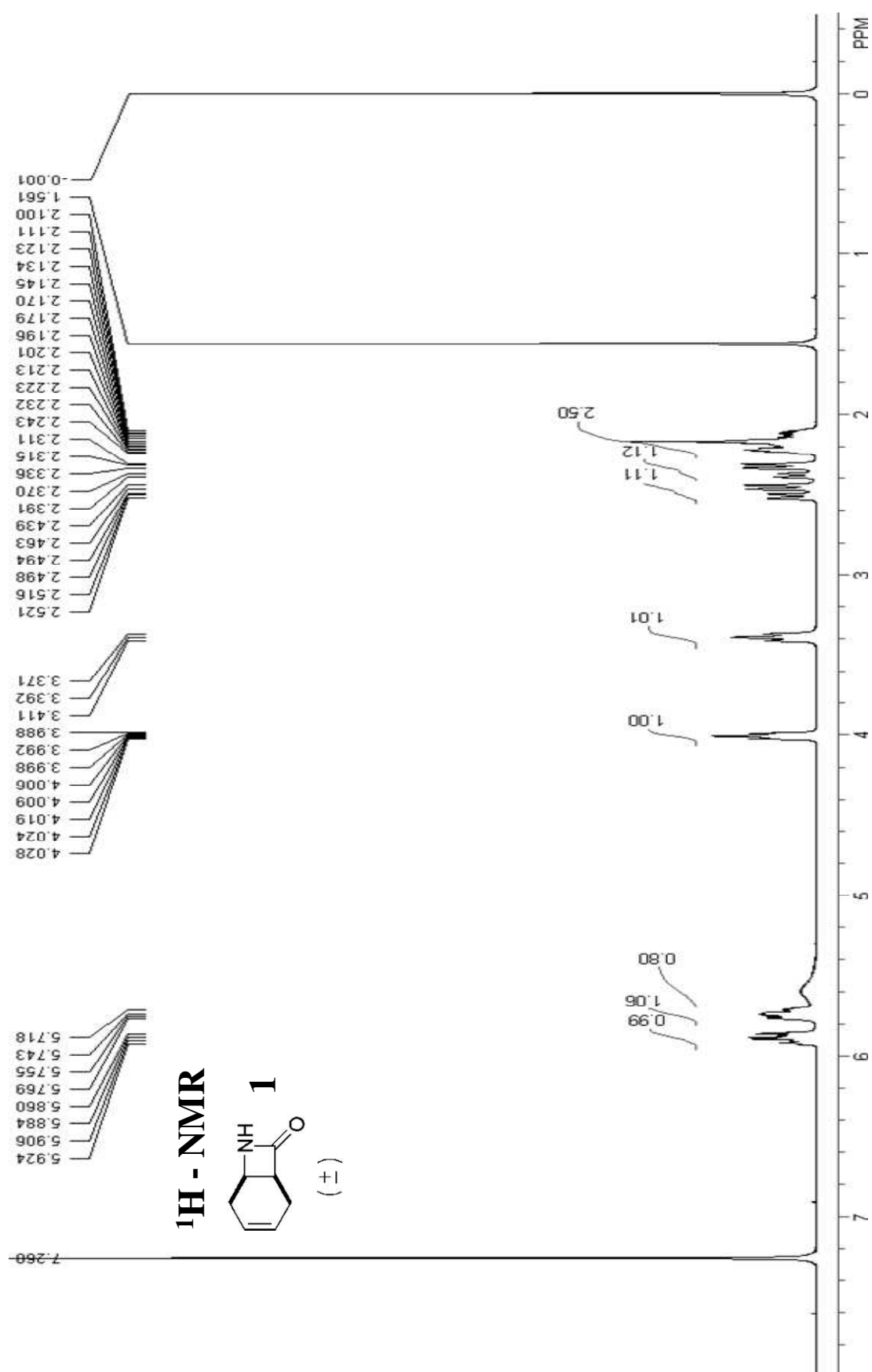
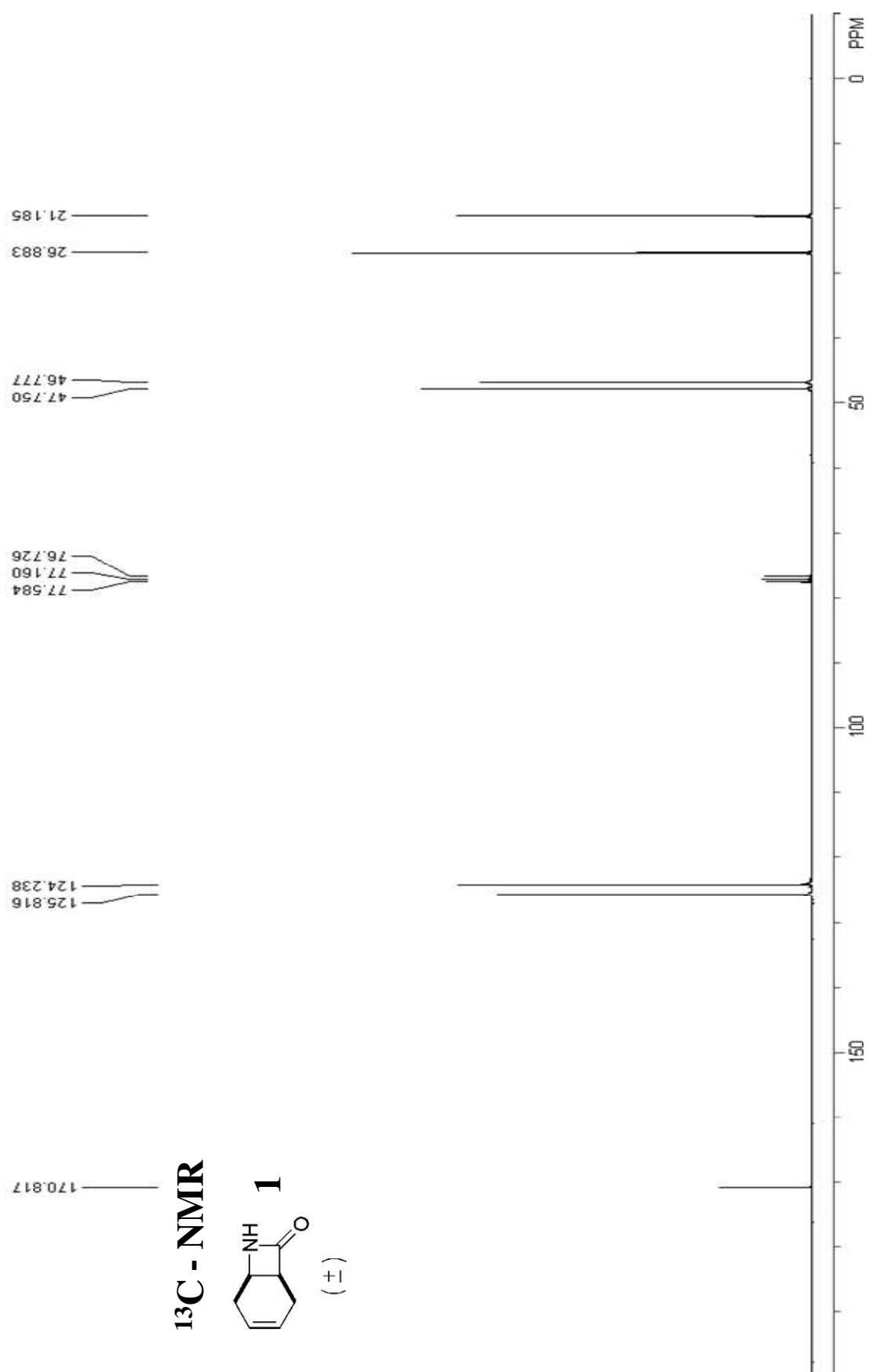
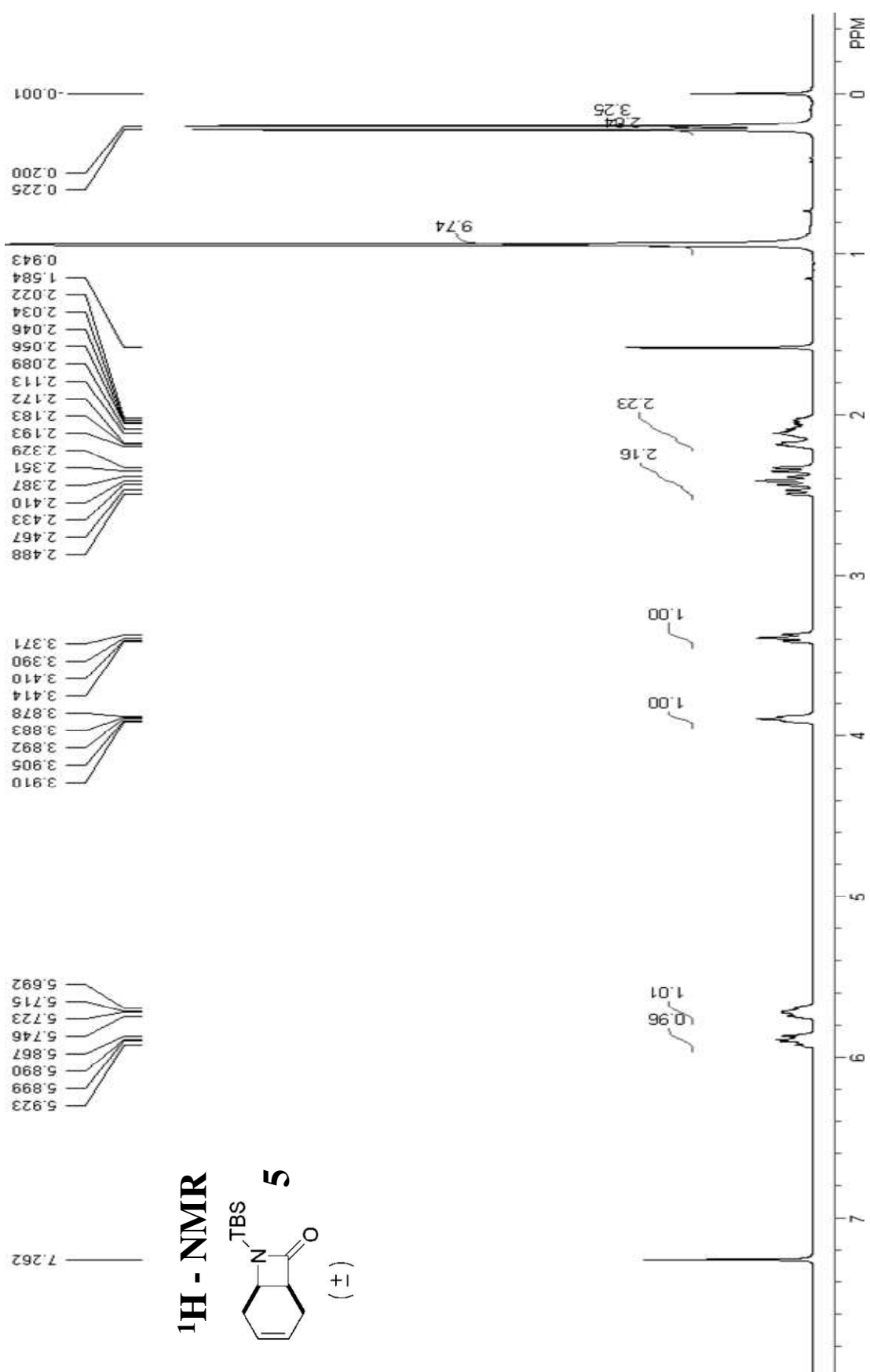
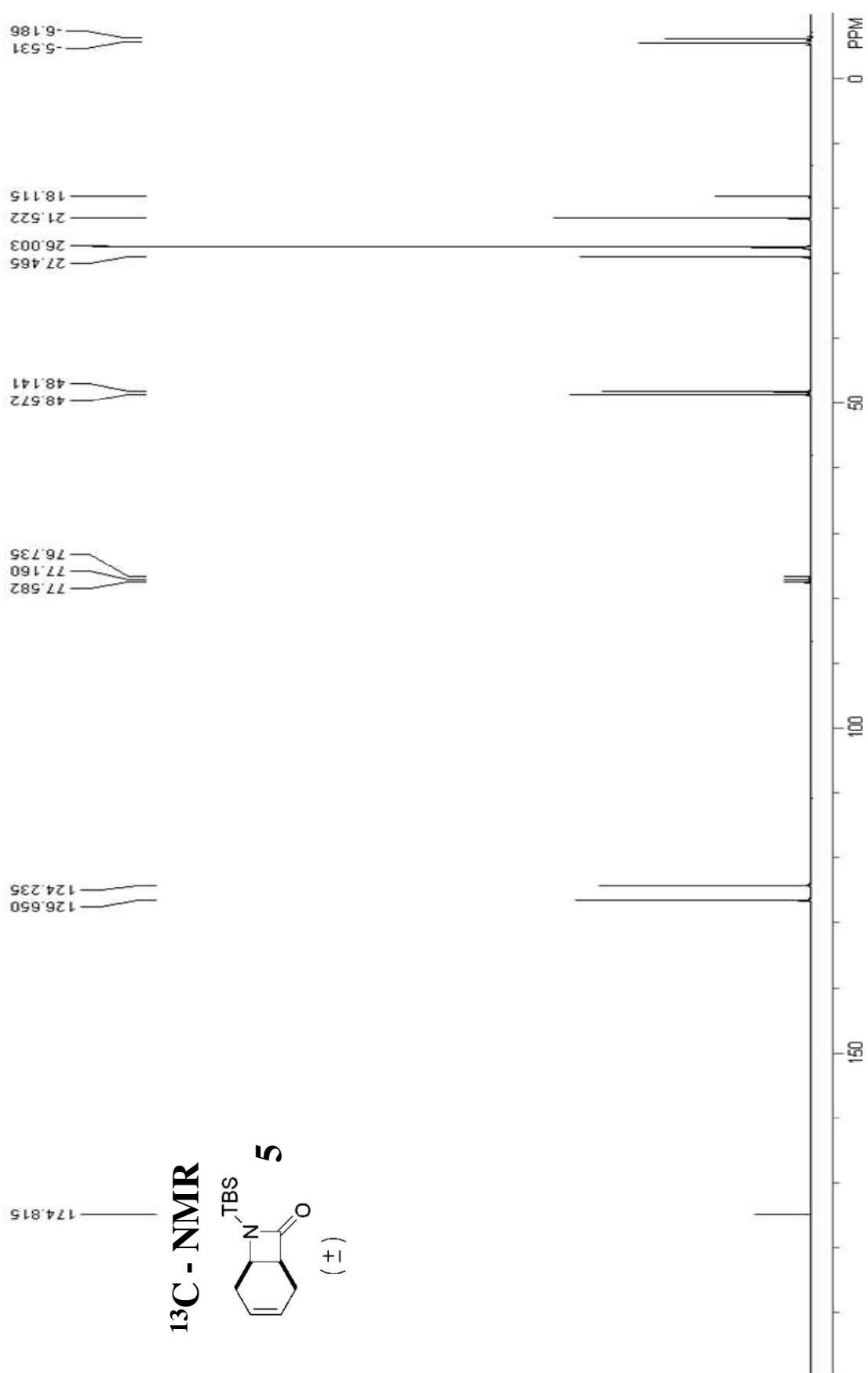


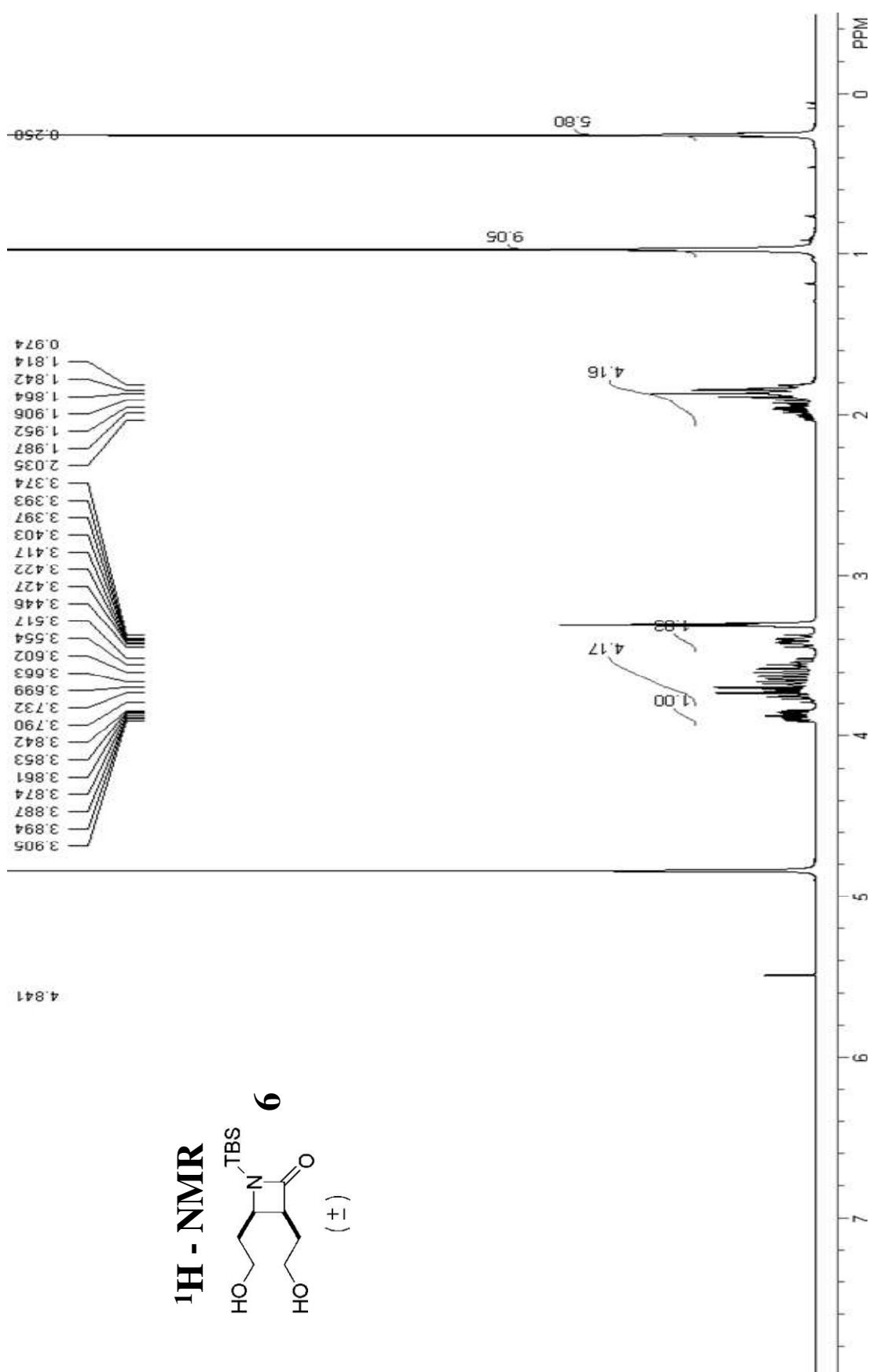
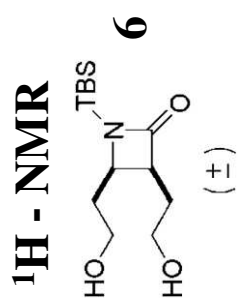
Figure S3. Determination of absolute configuration of (2'S,1S,6R)-19

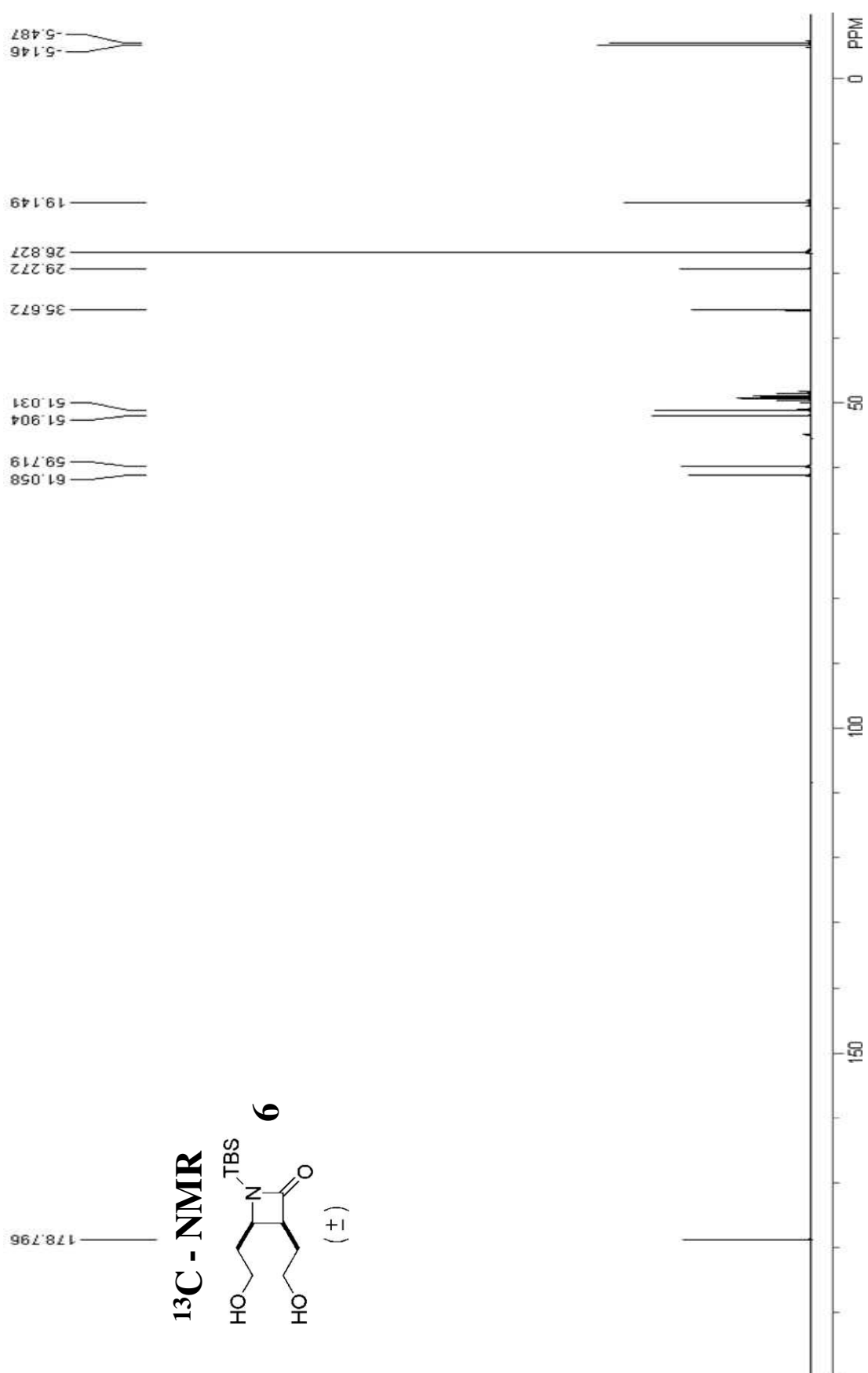


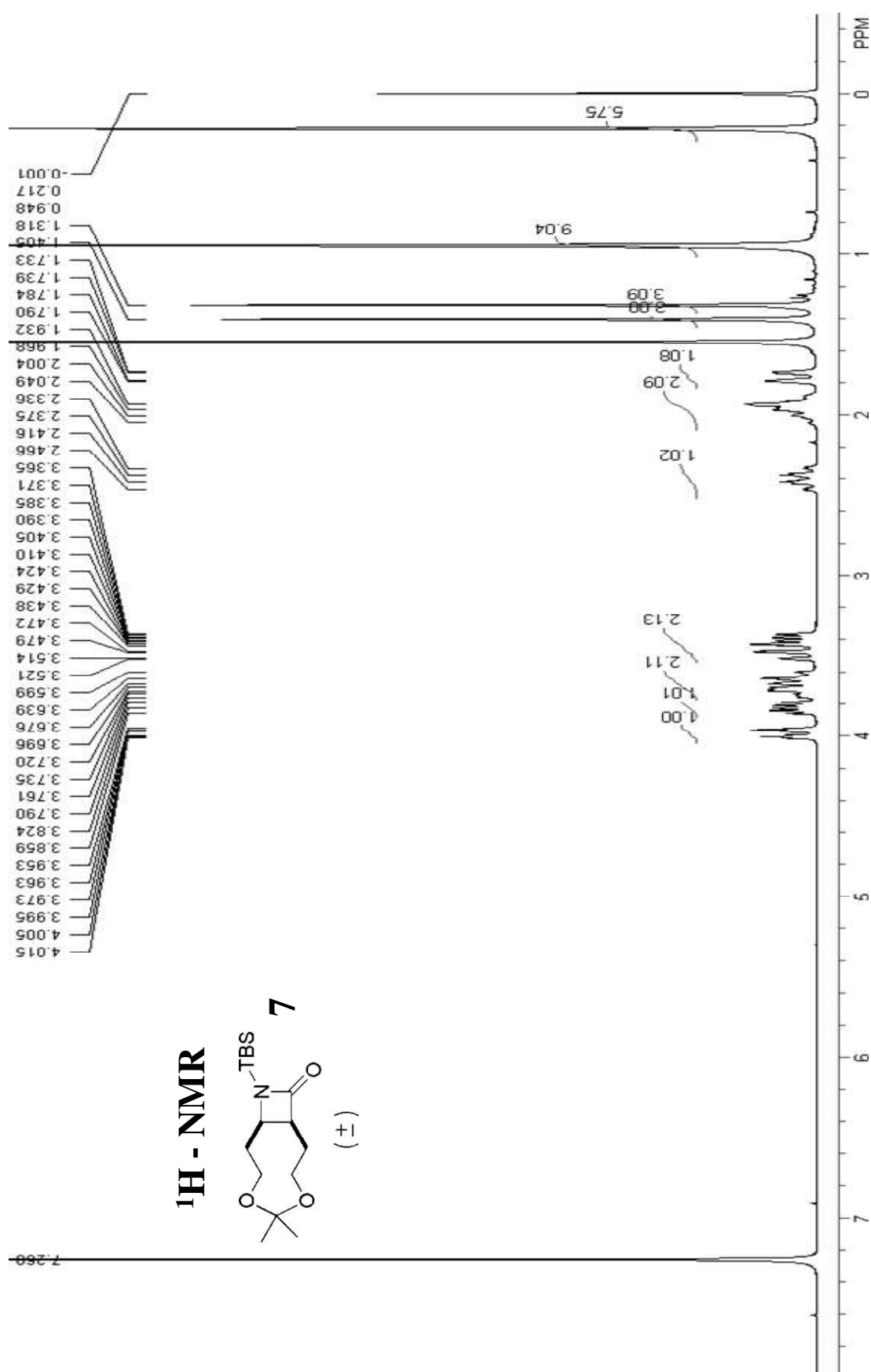


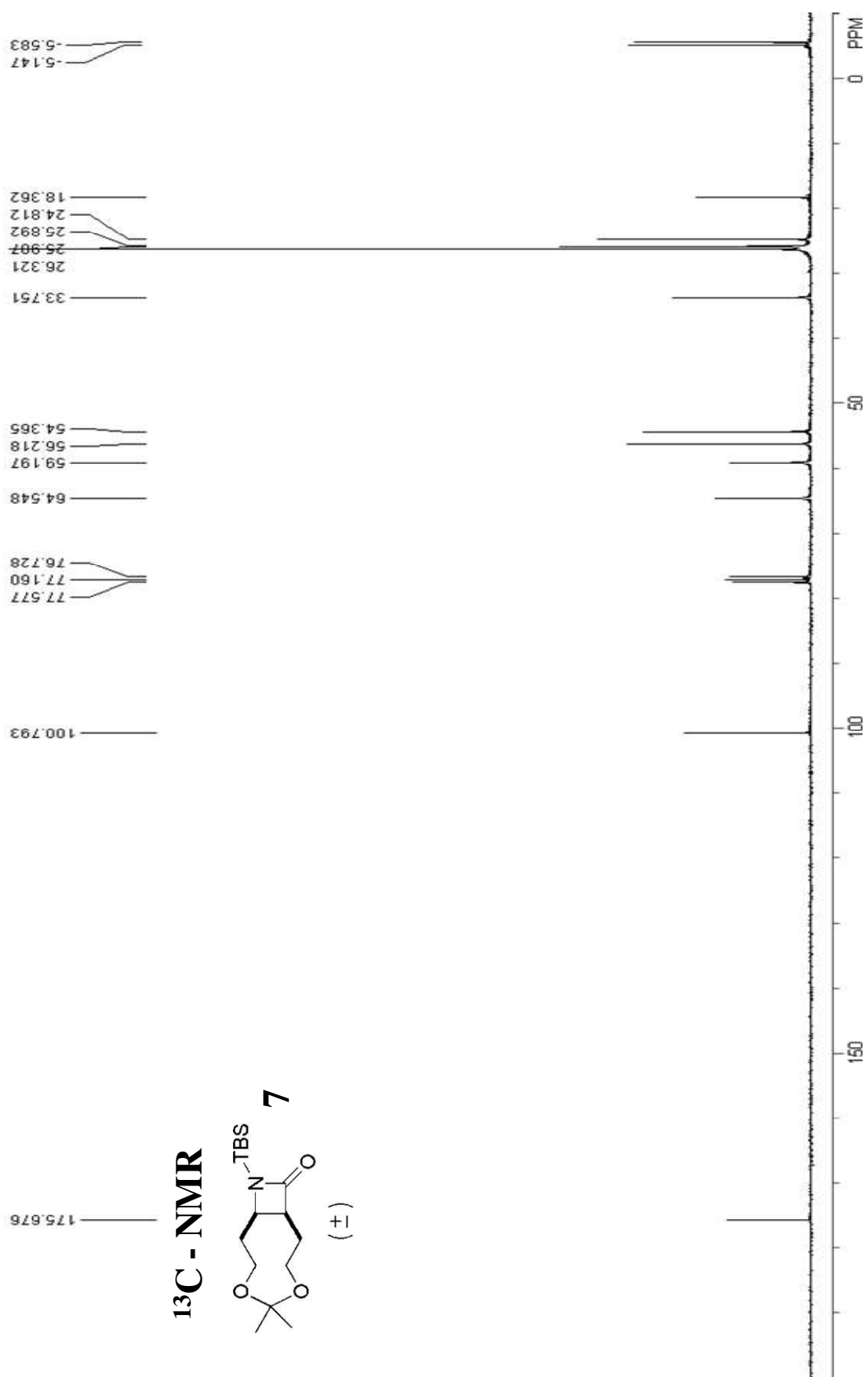


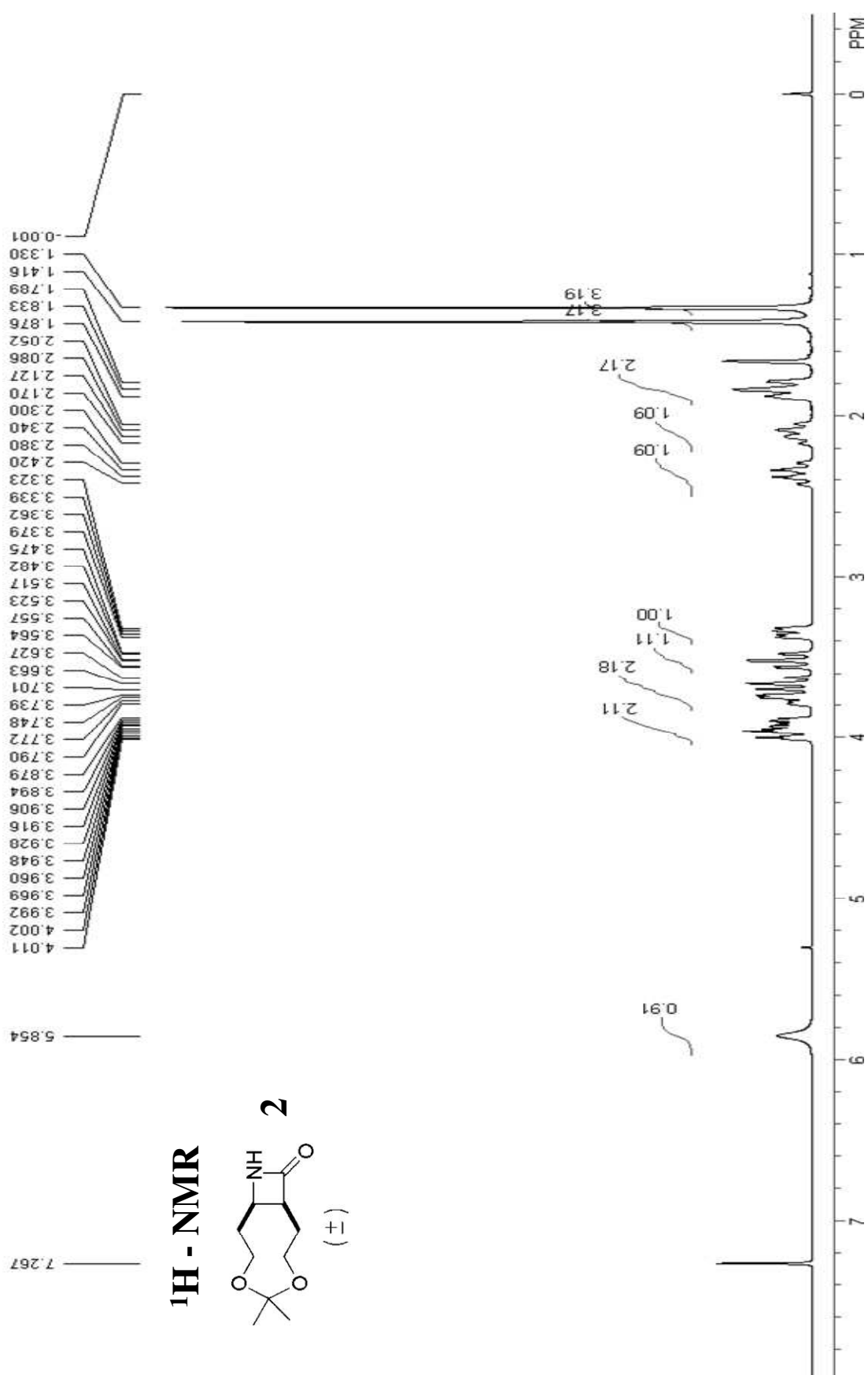


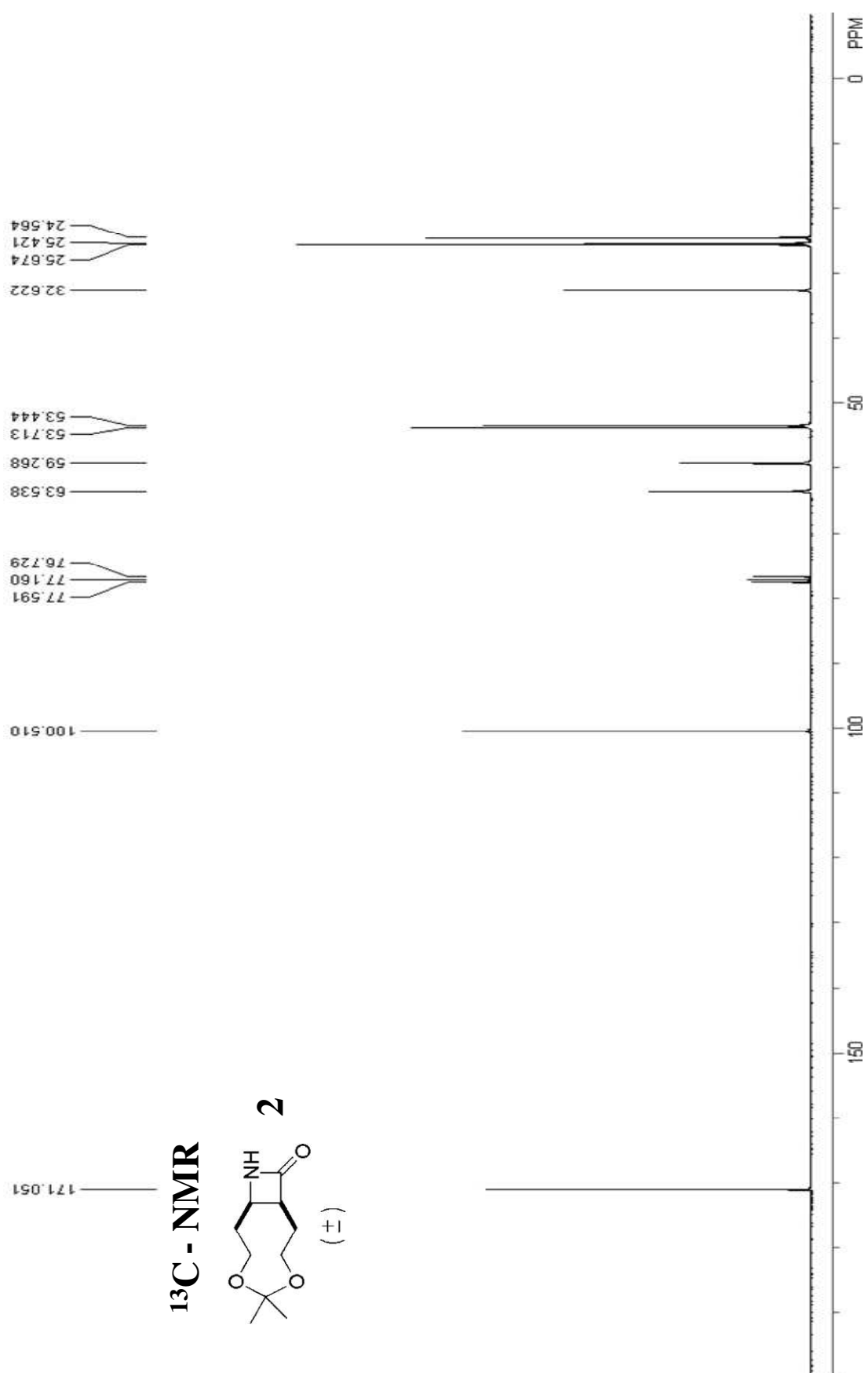


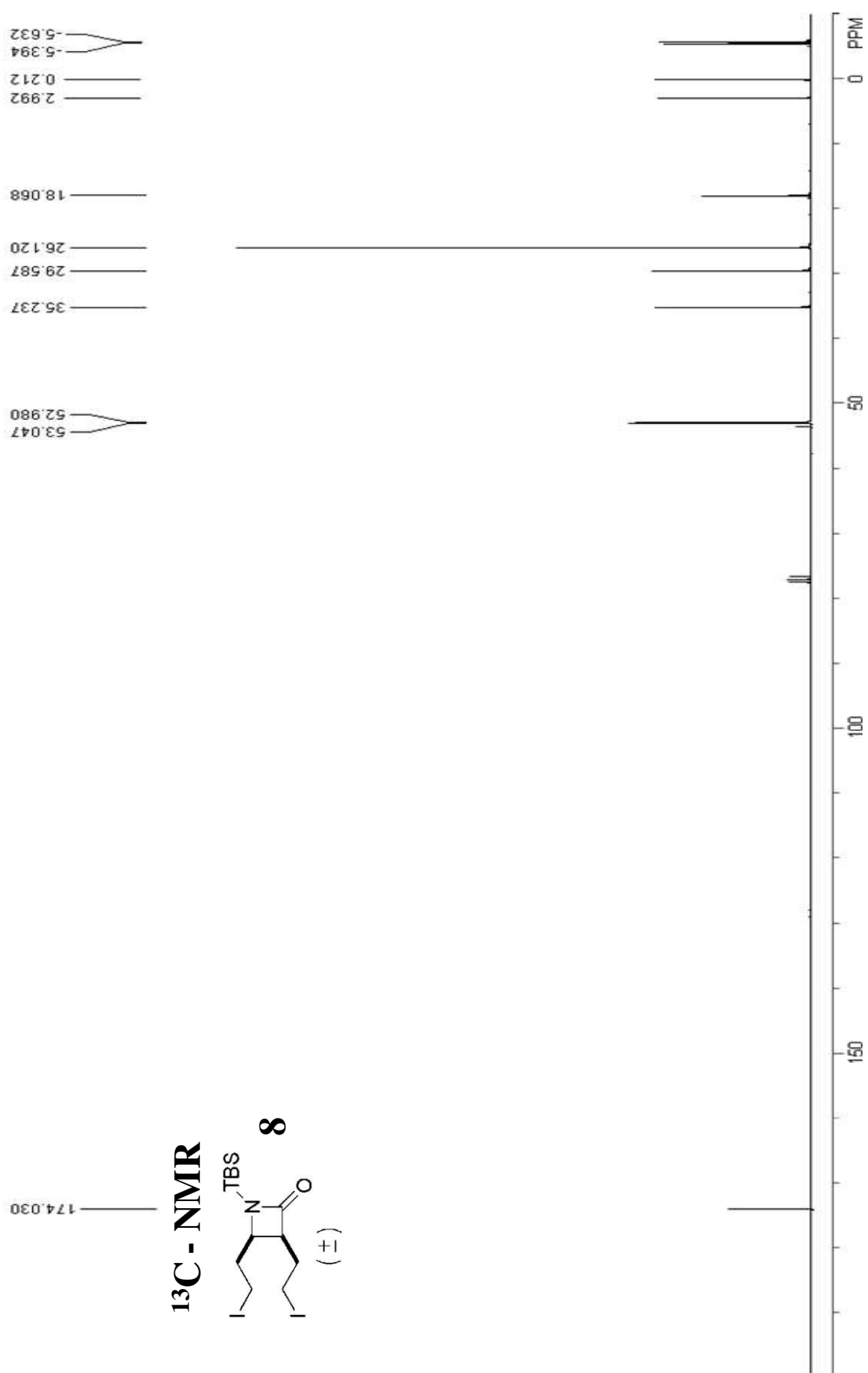


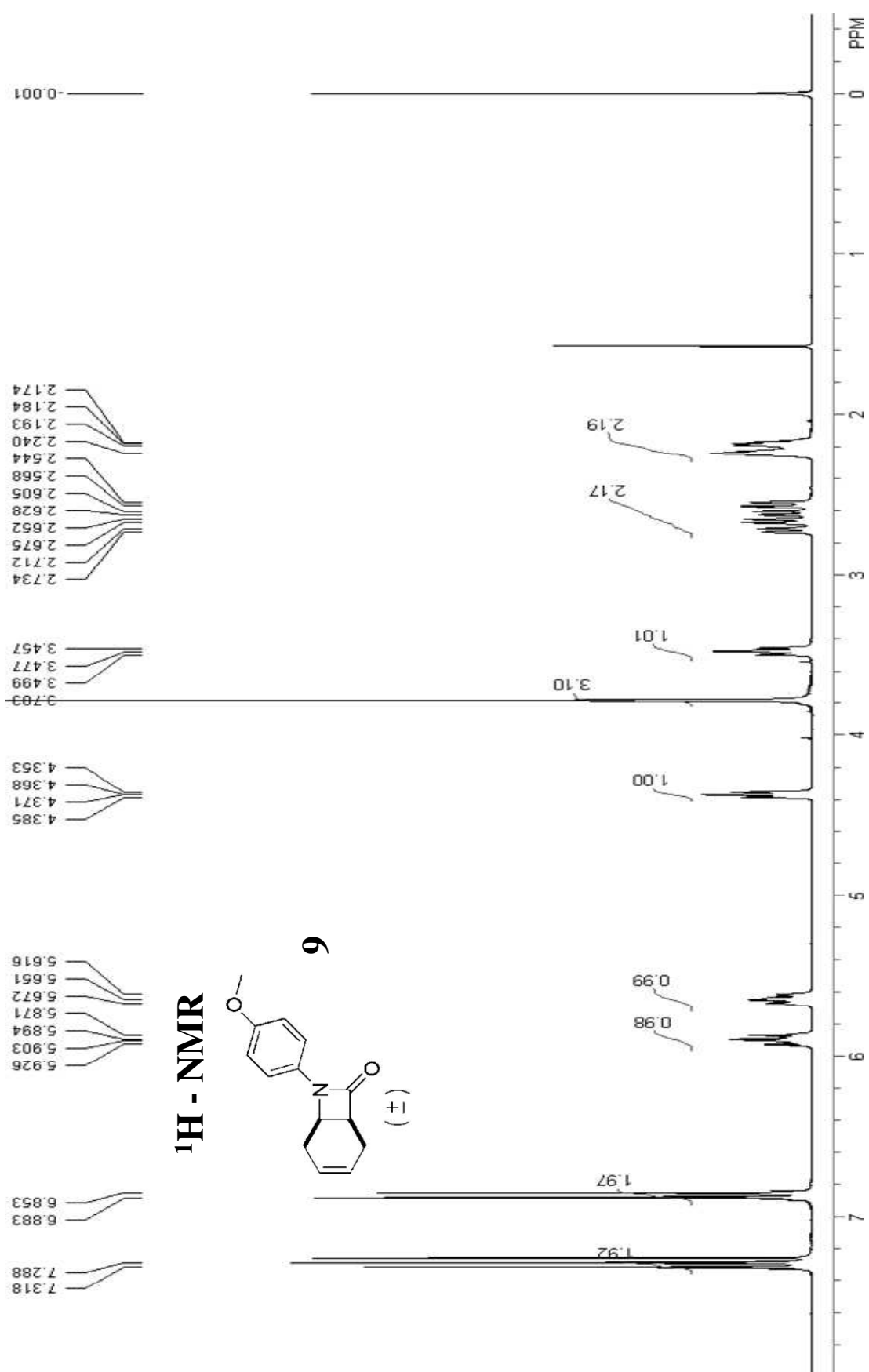


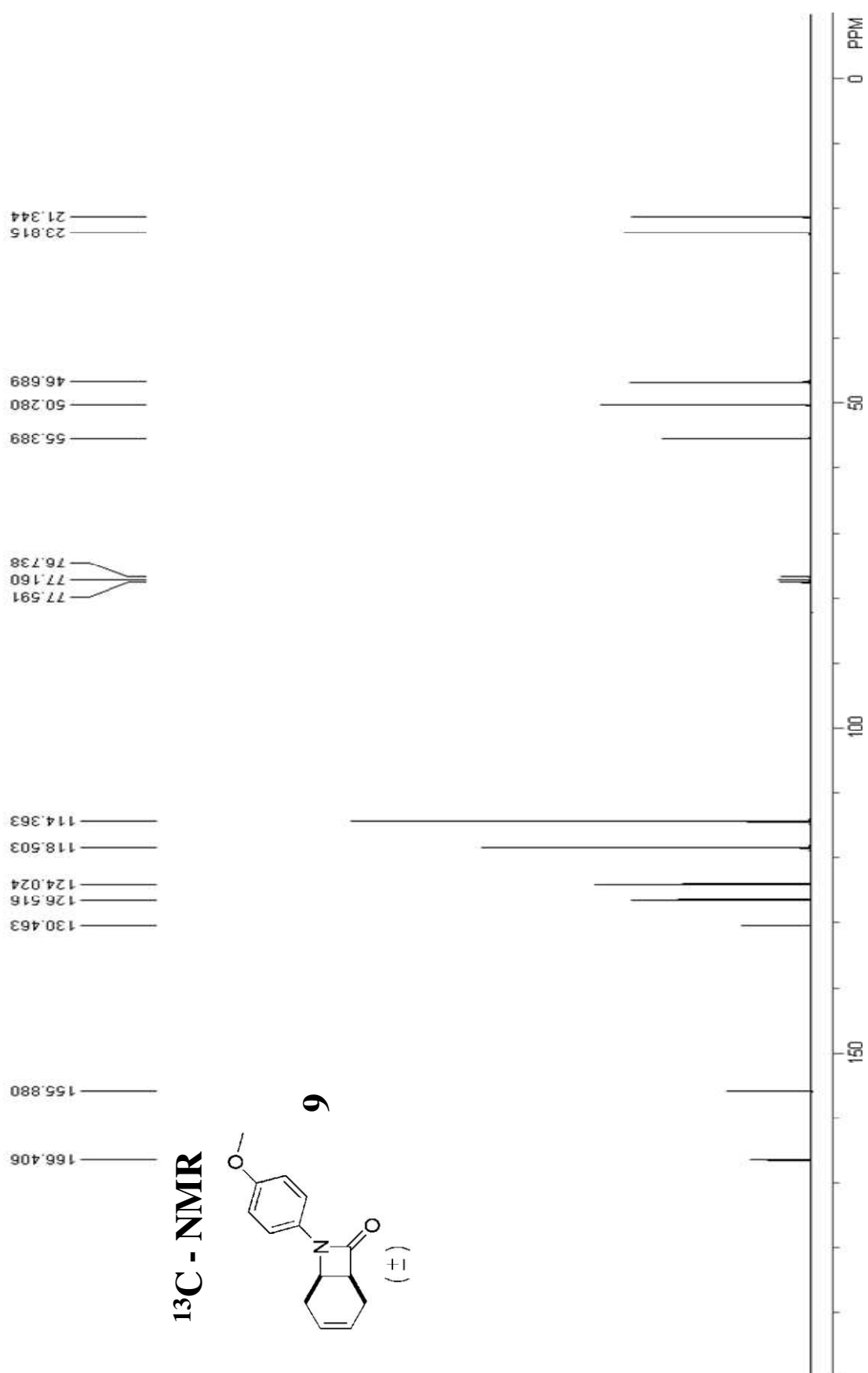


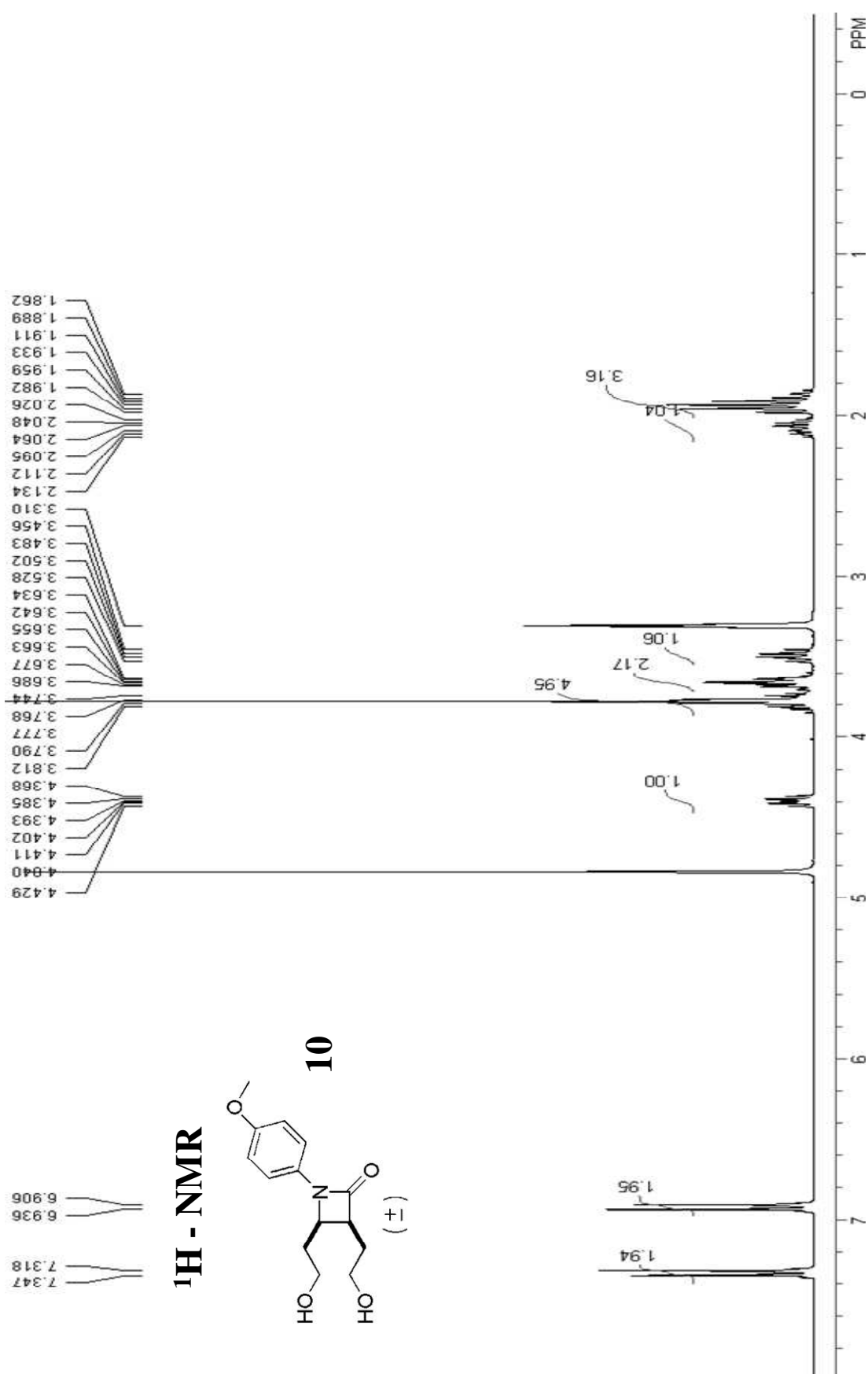


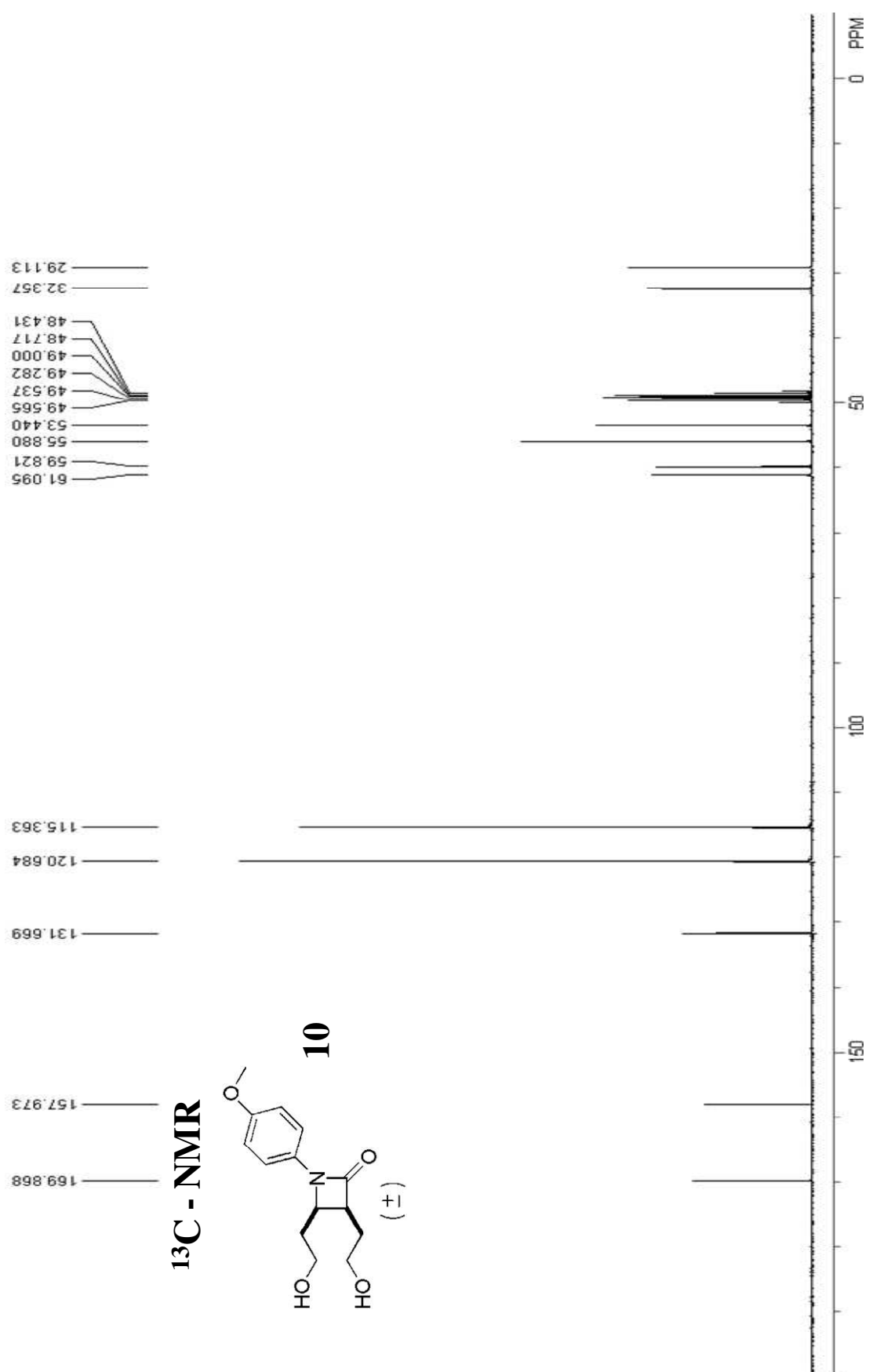


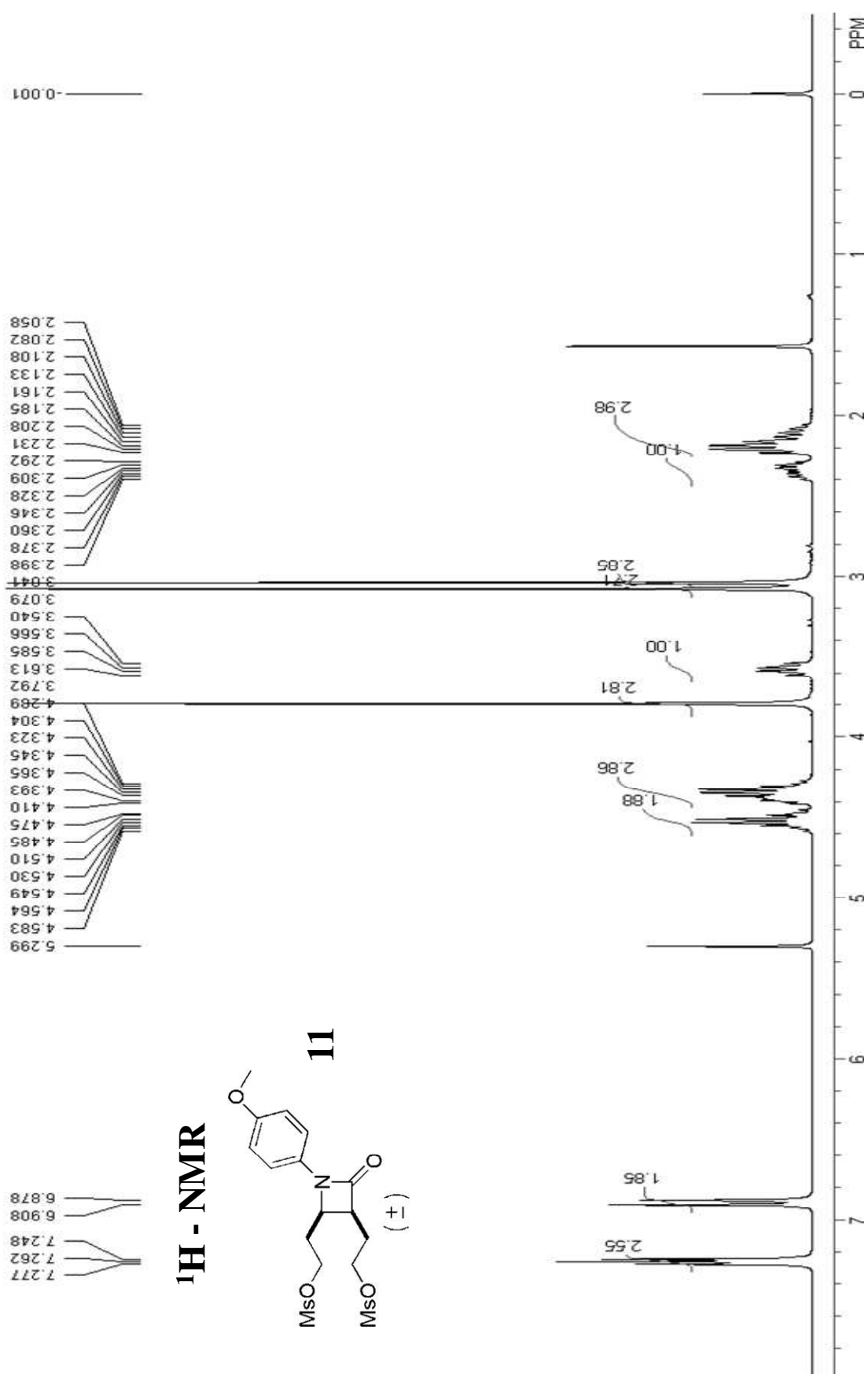


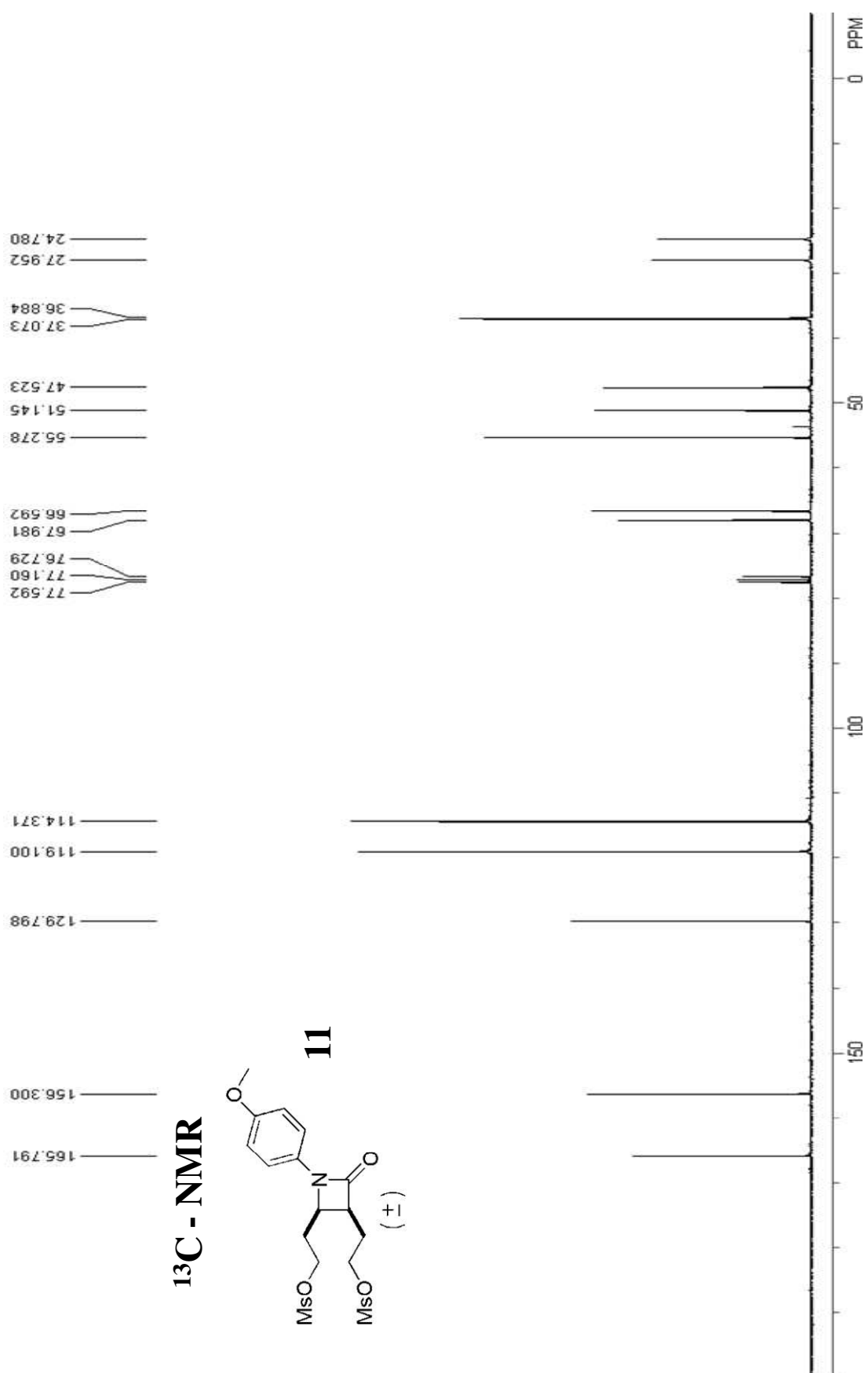


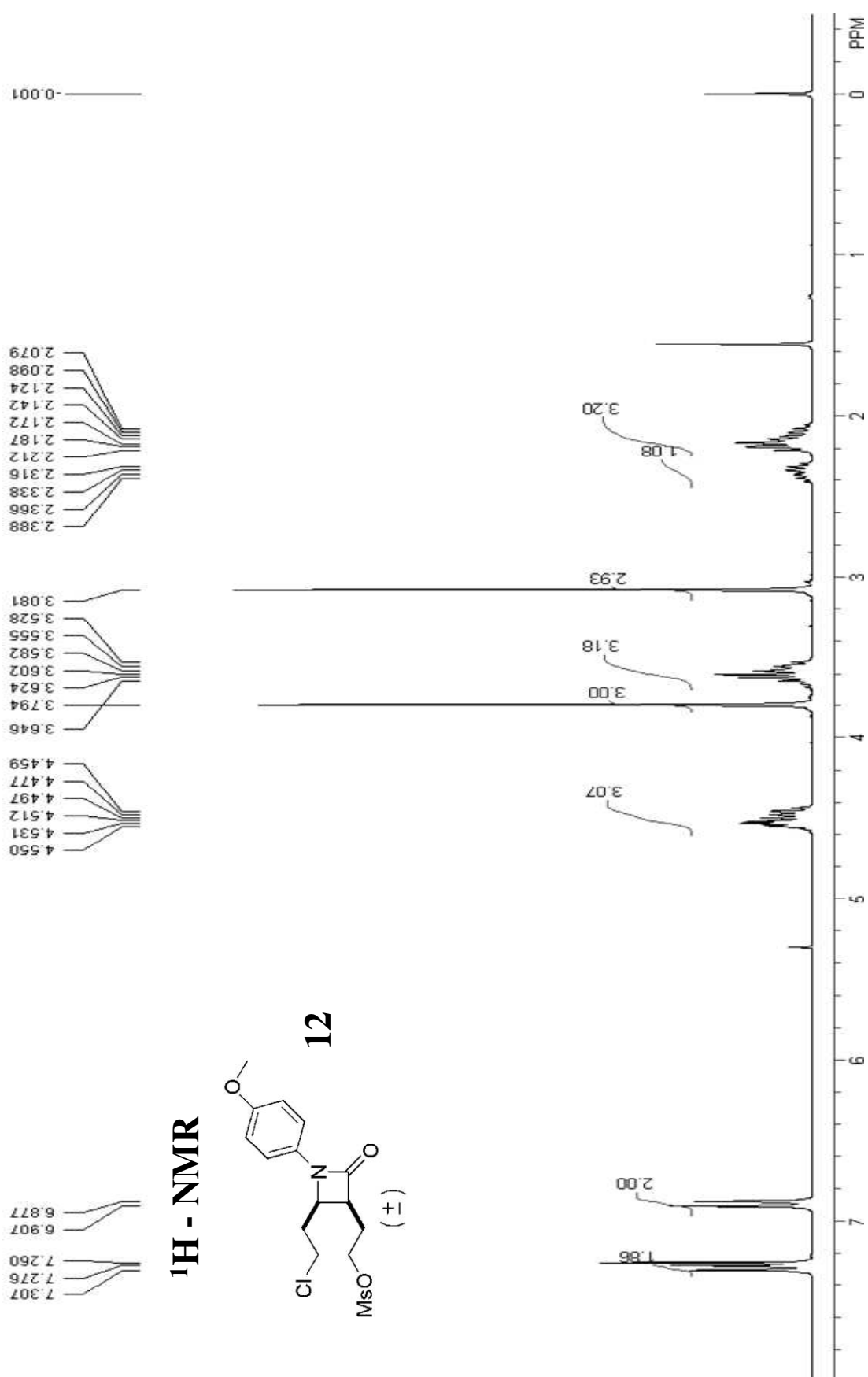


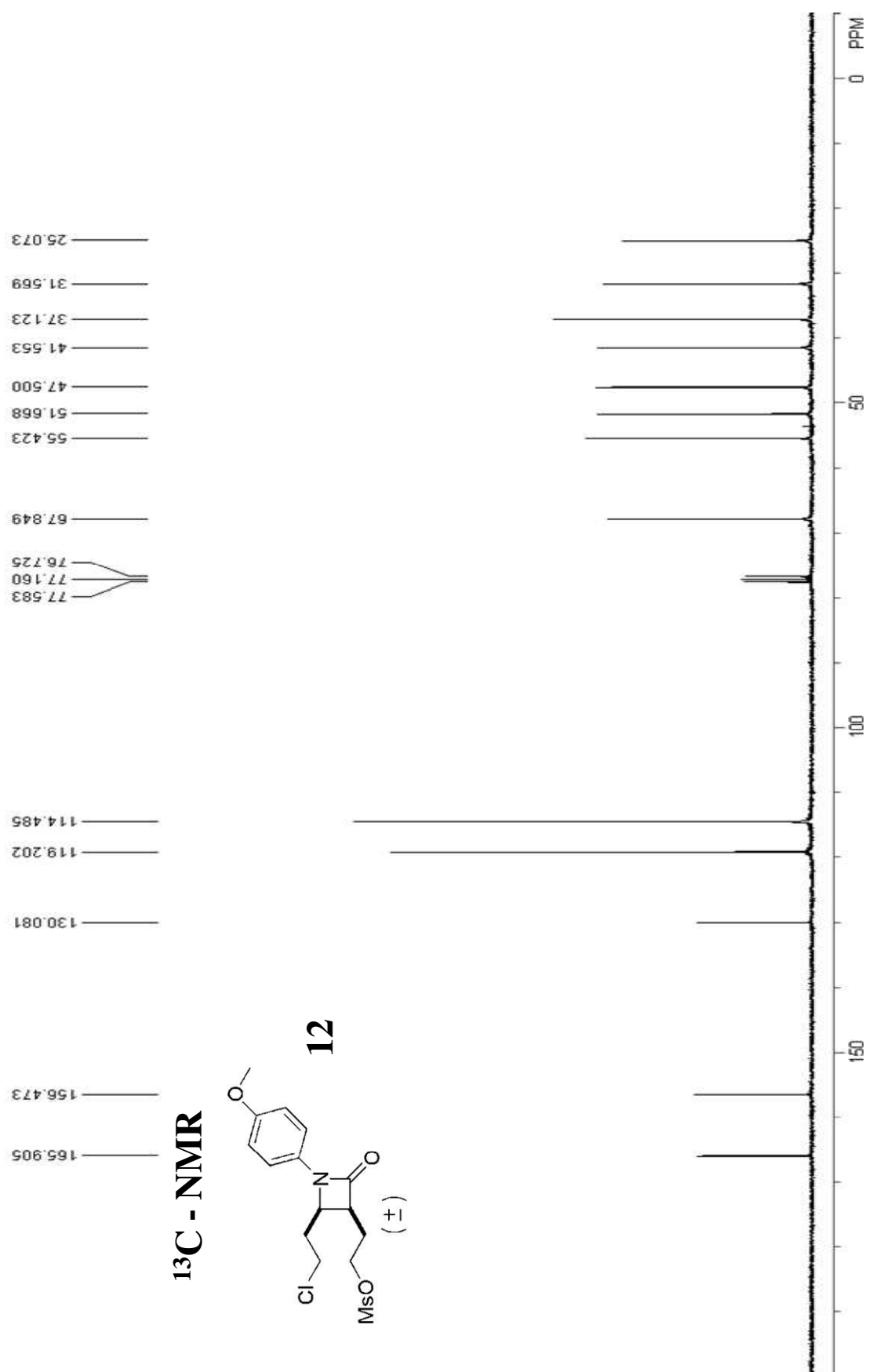


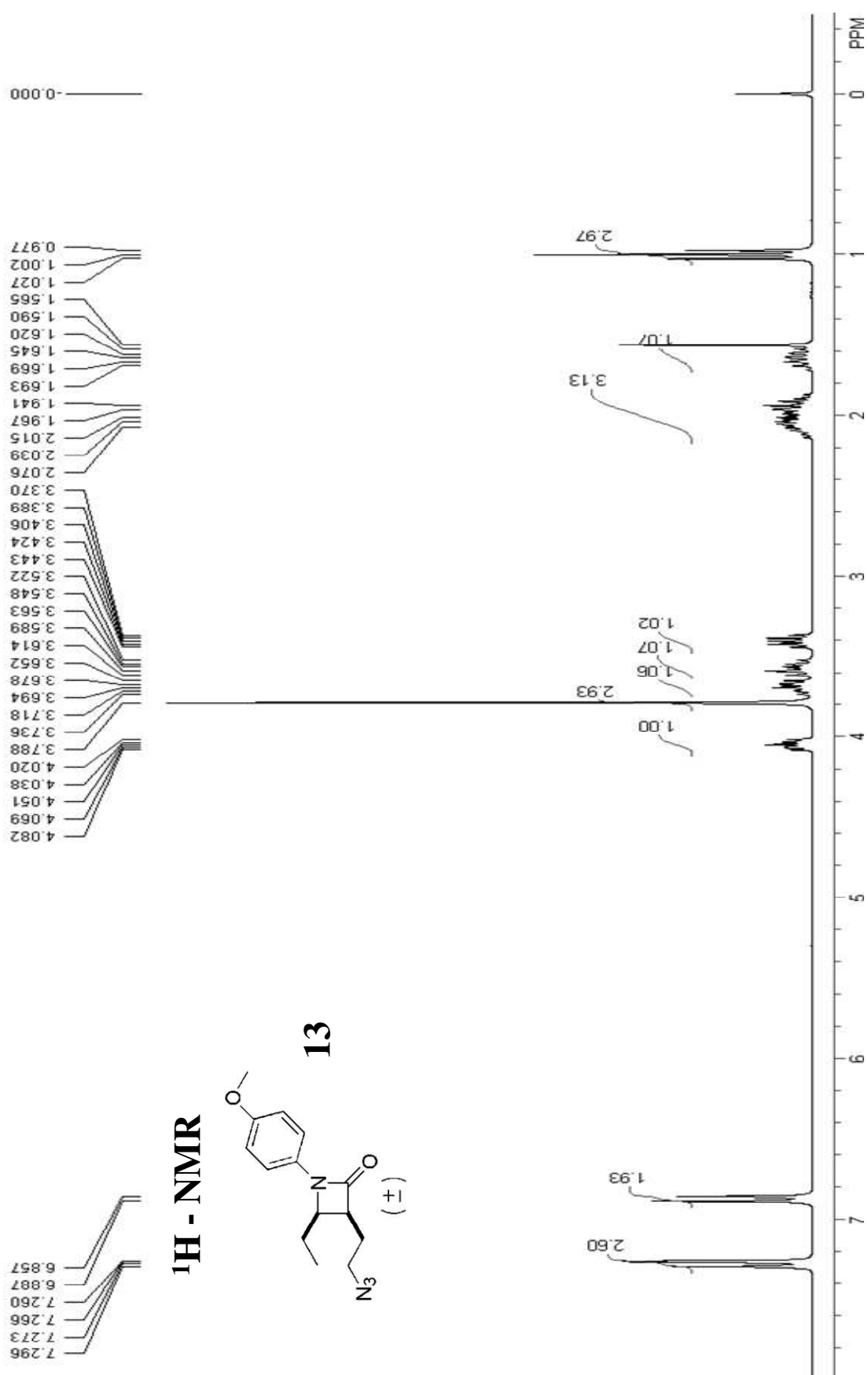


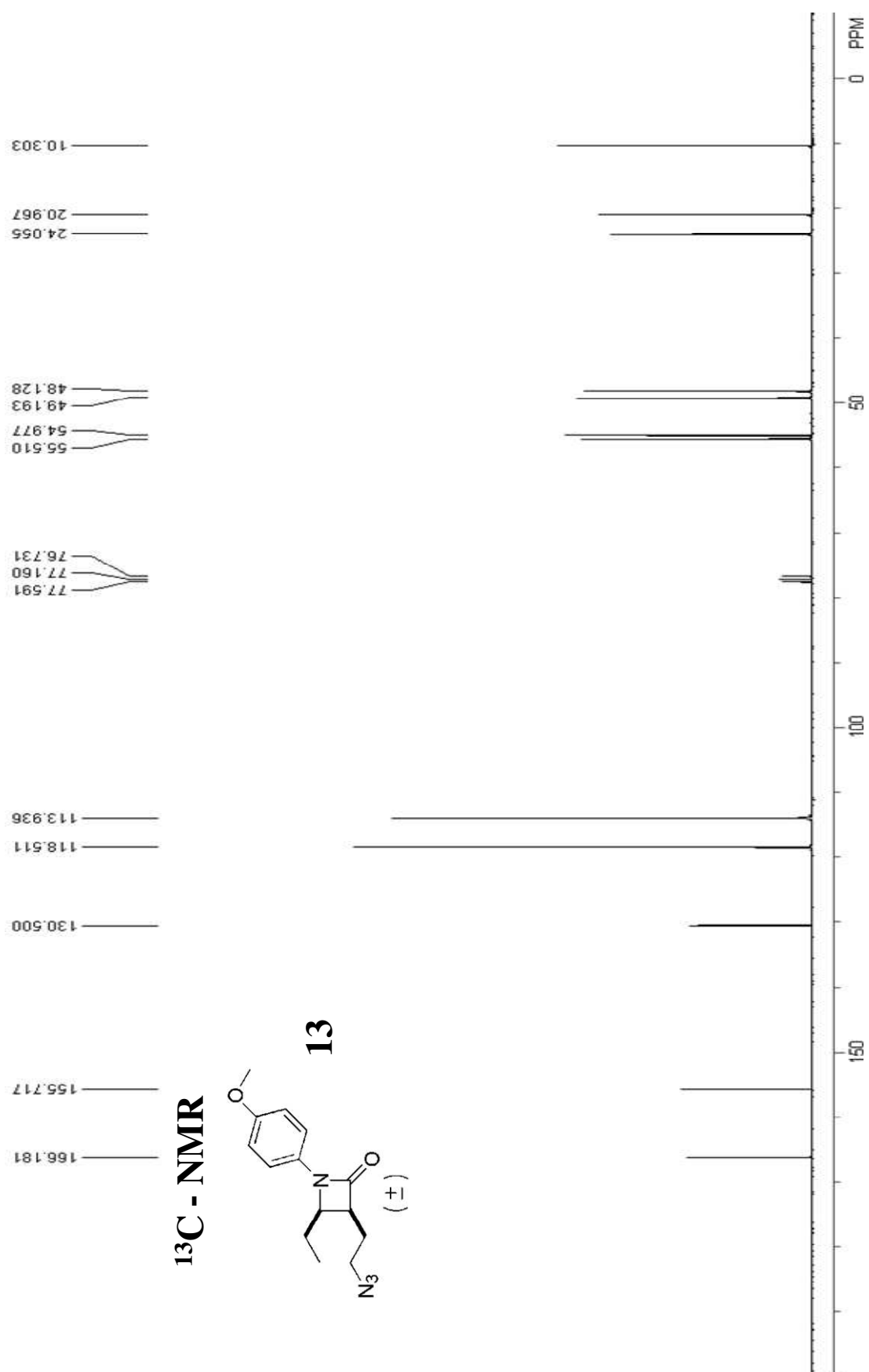


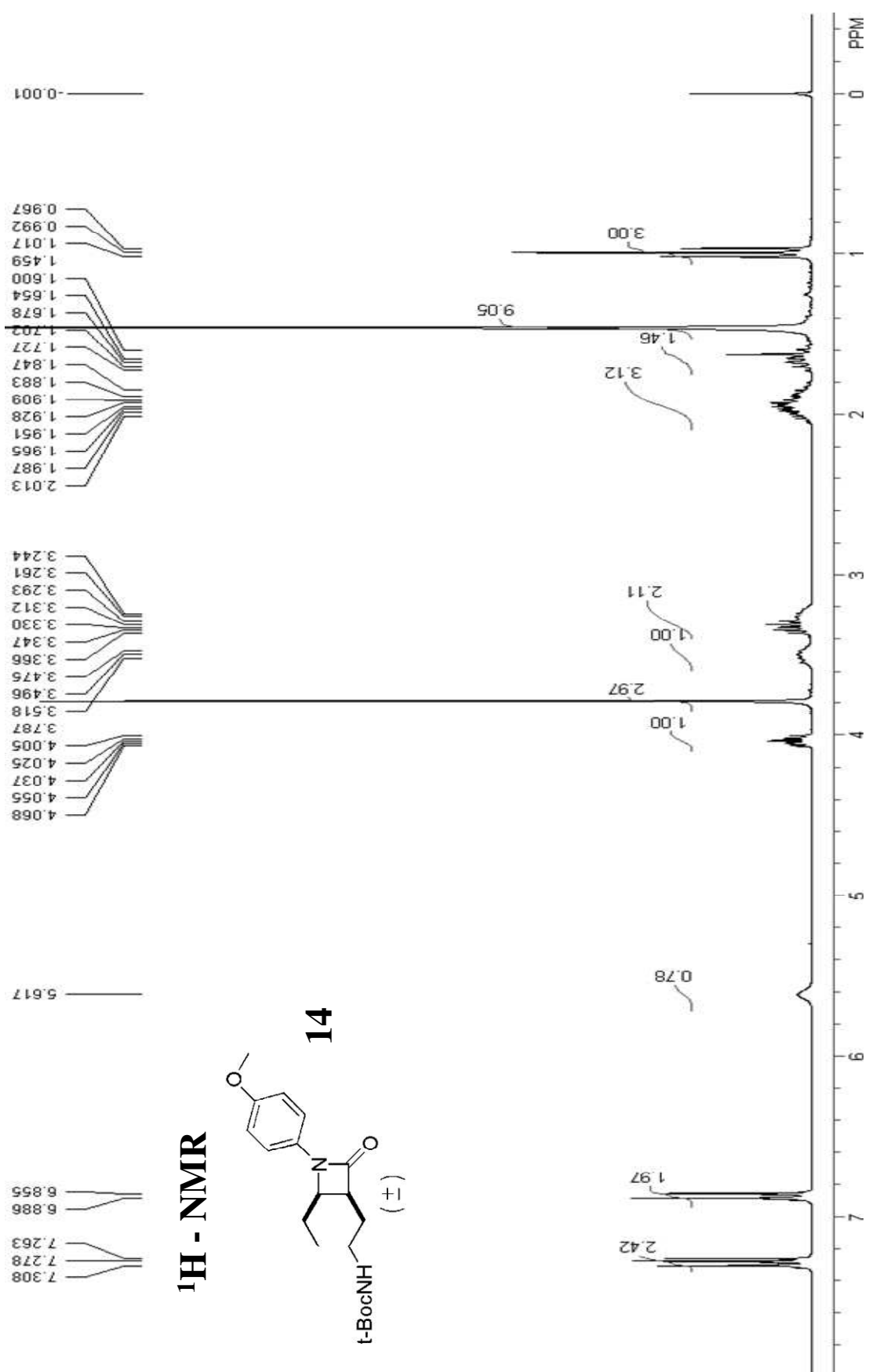


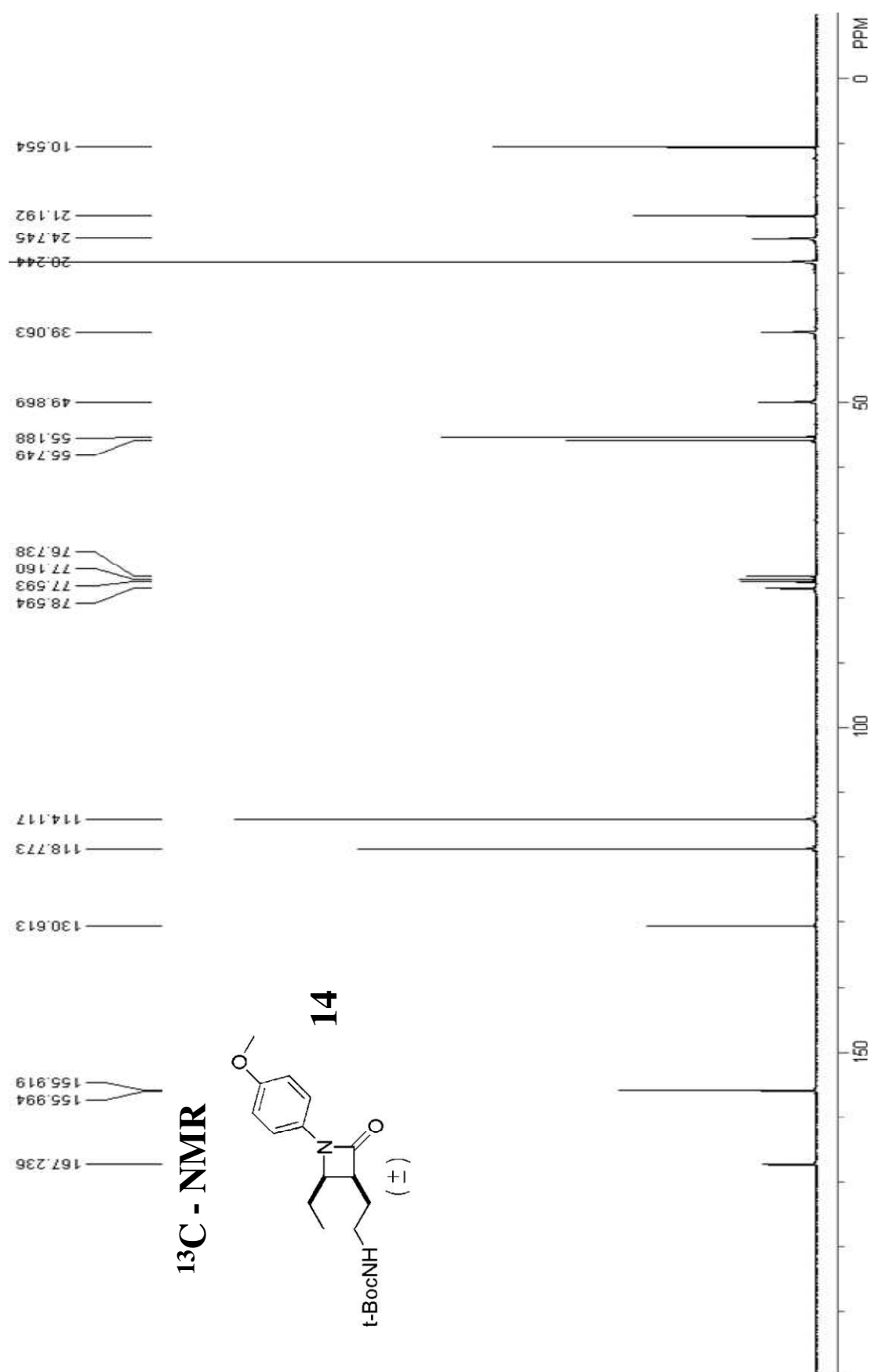


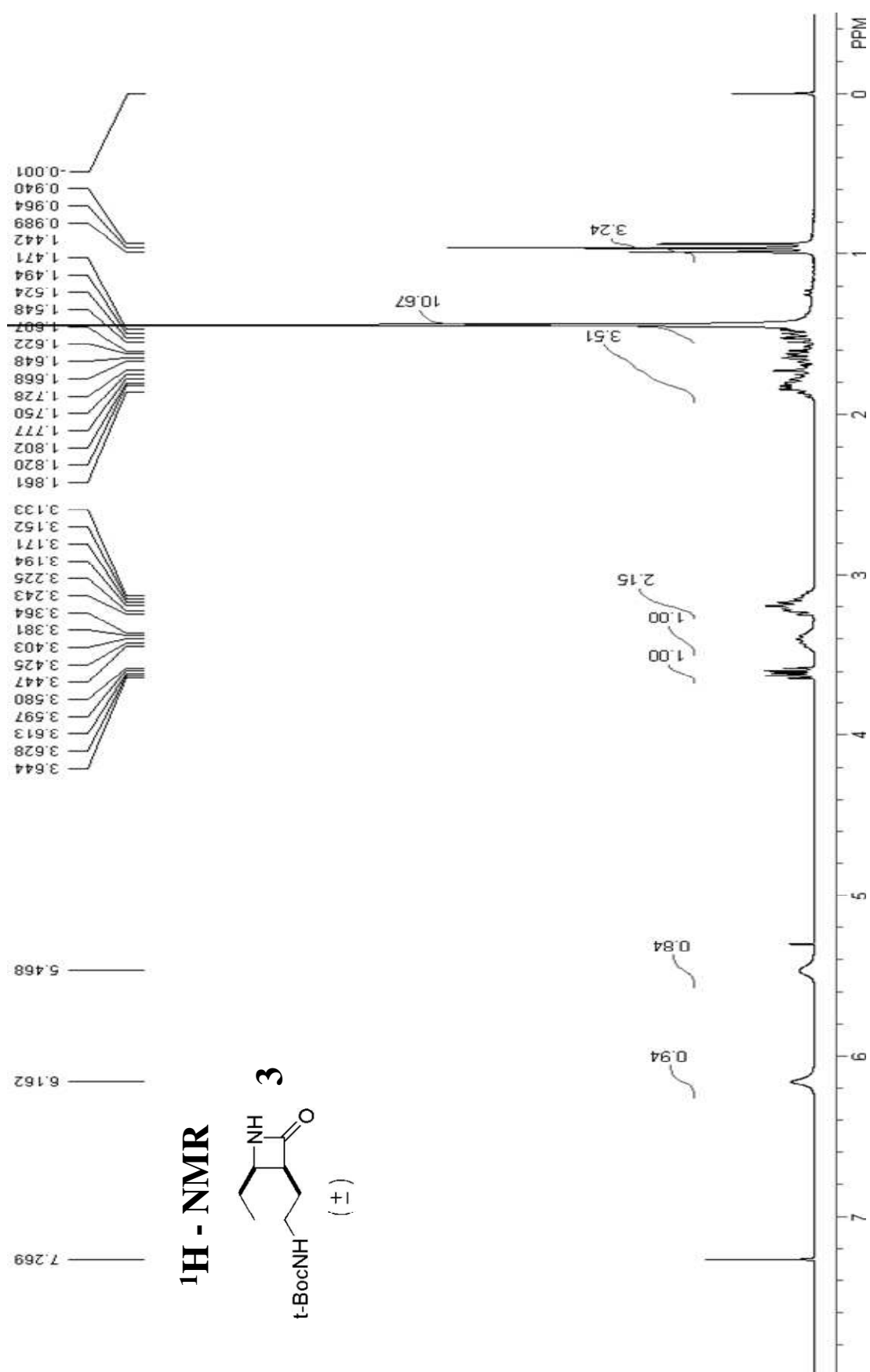


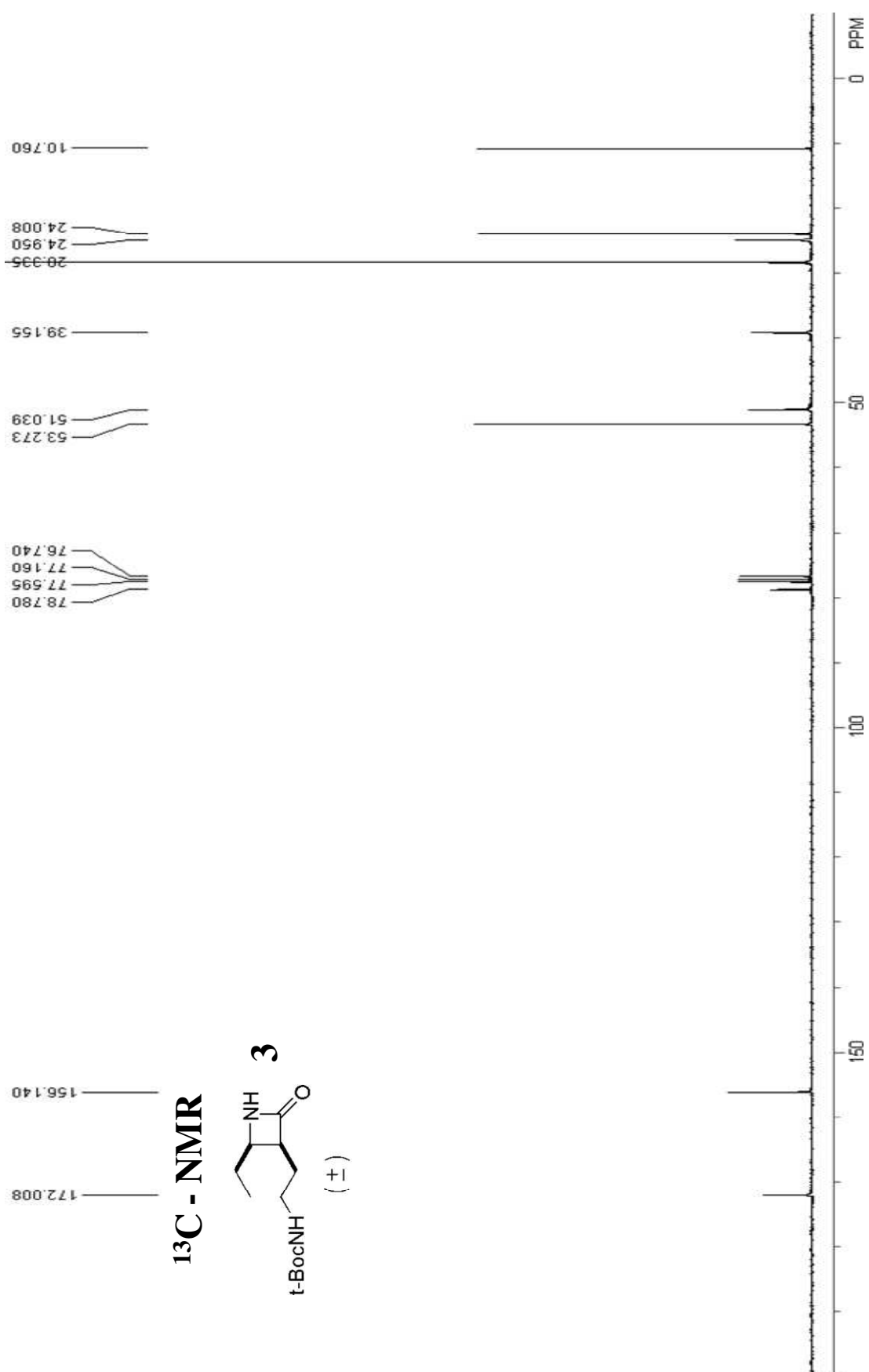


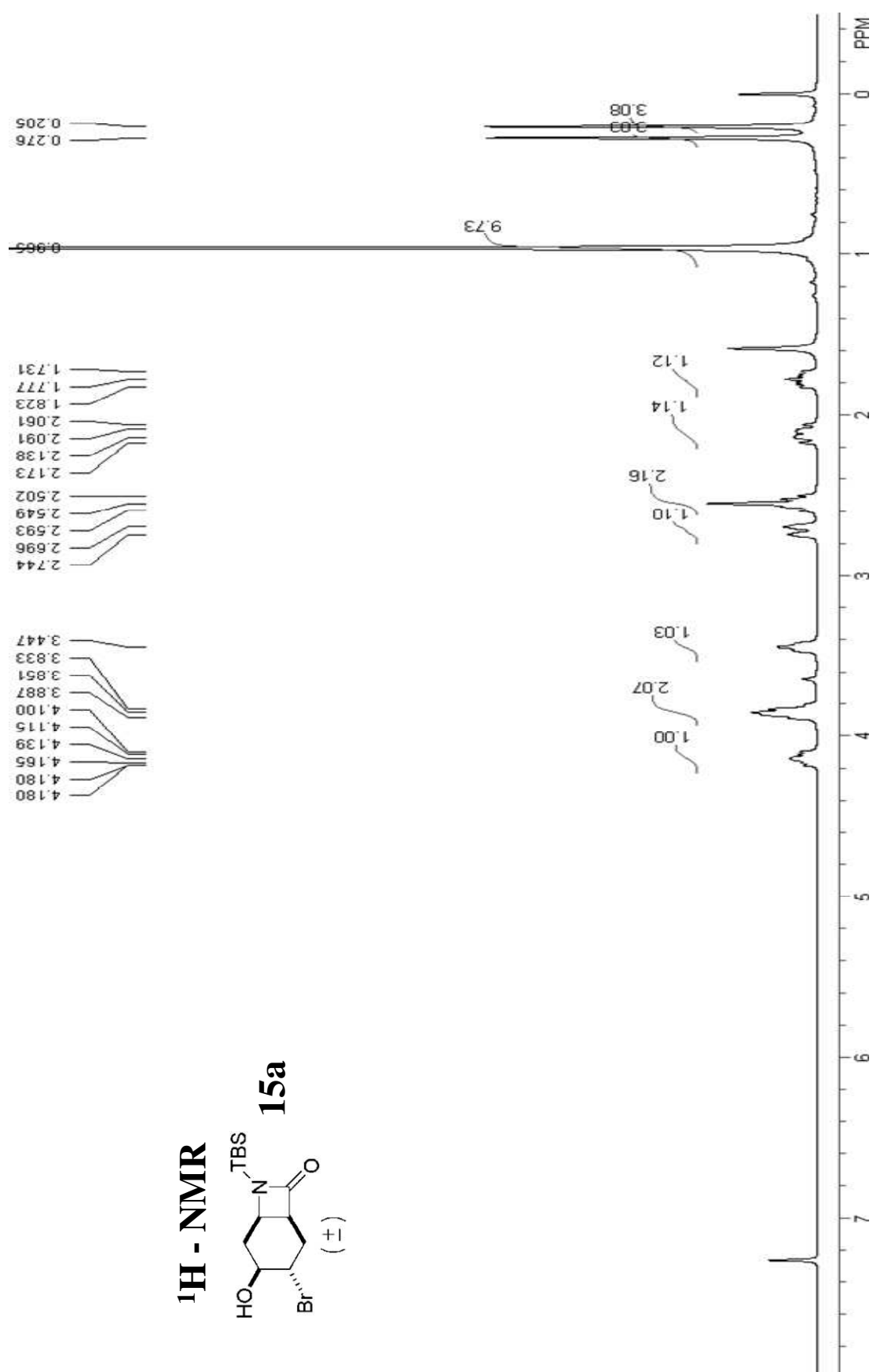
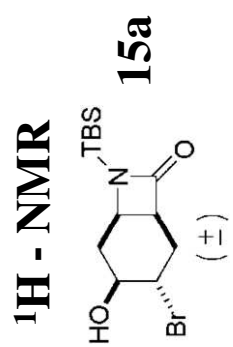




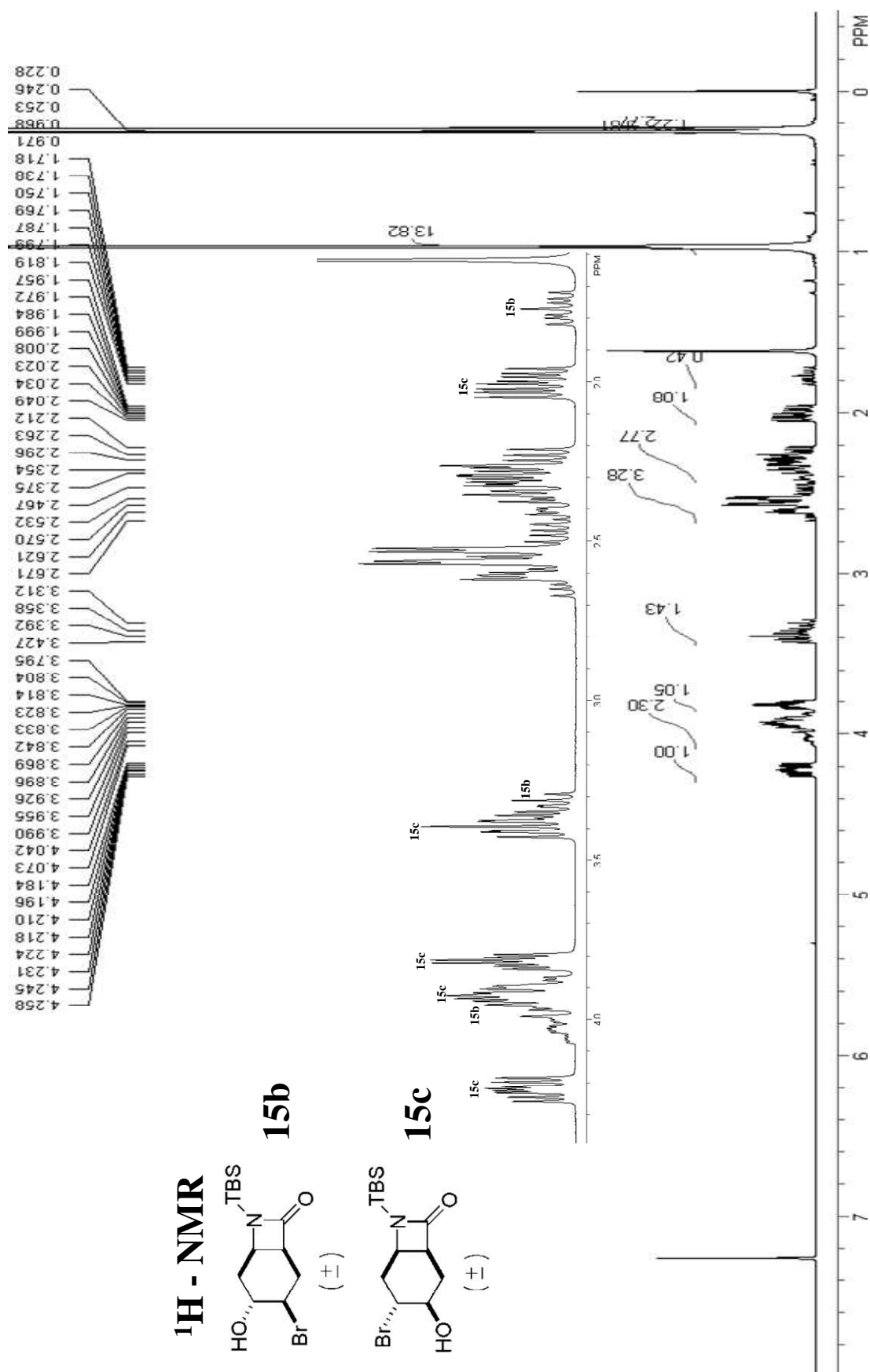
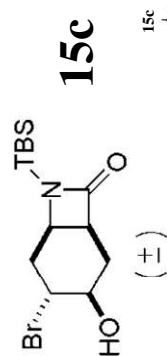
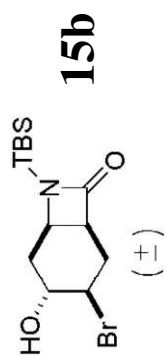


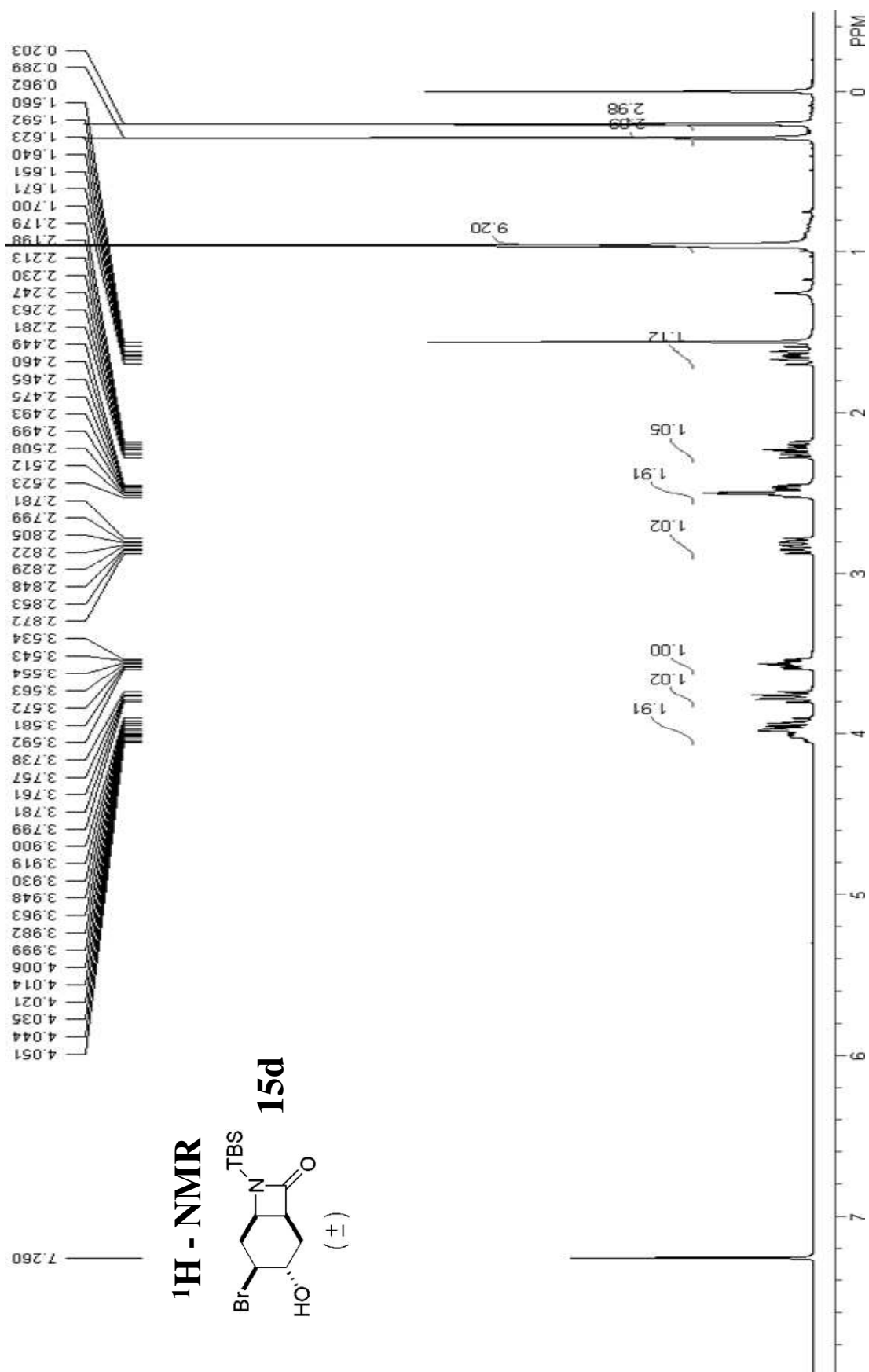


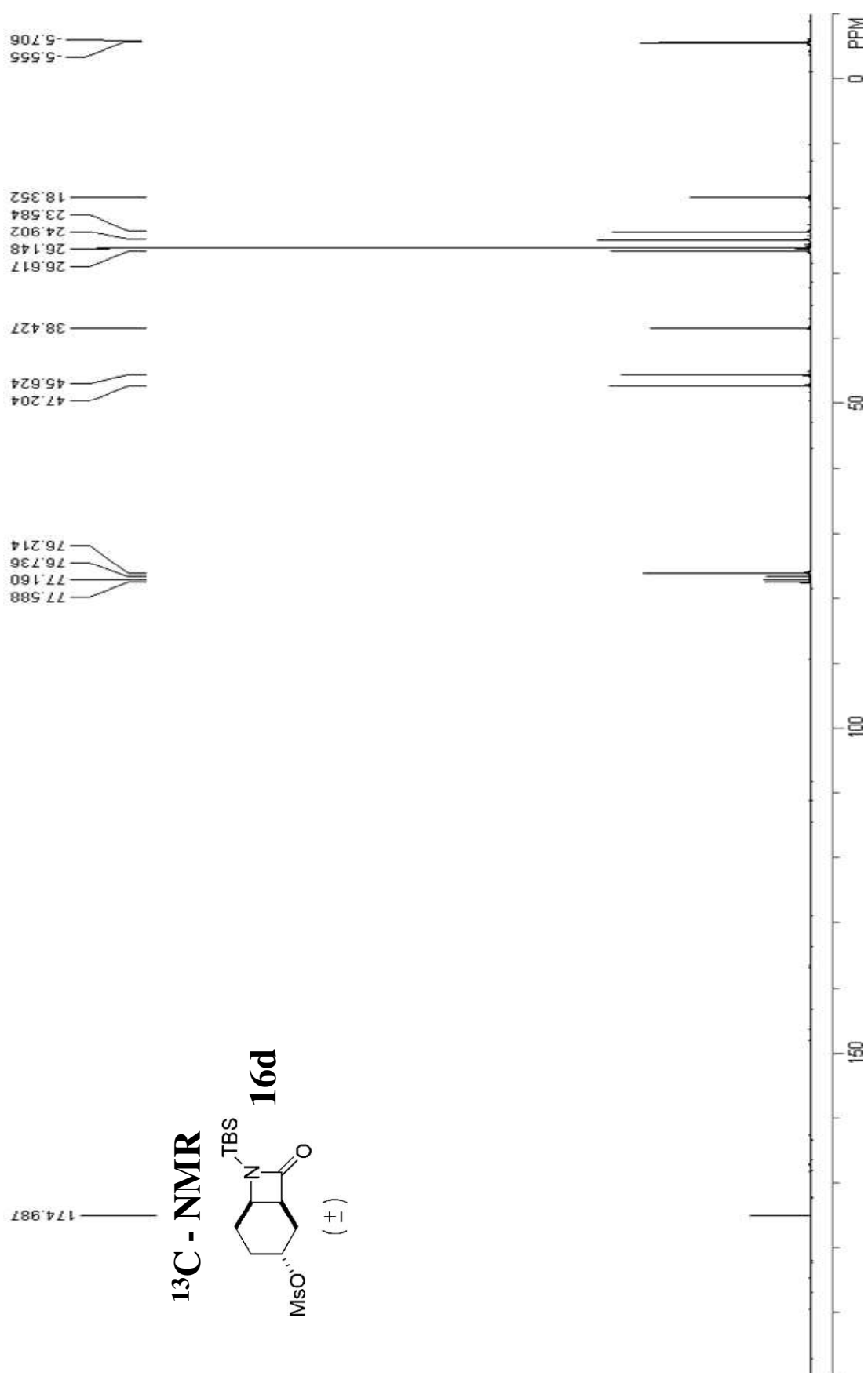


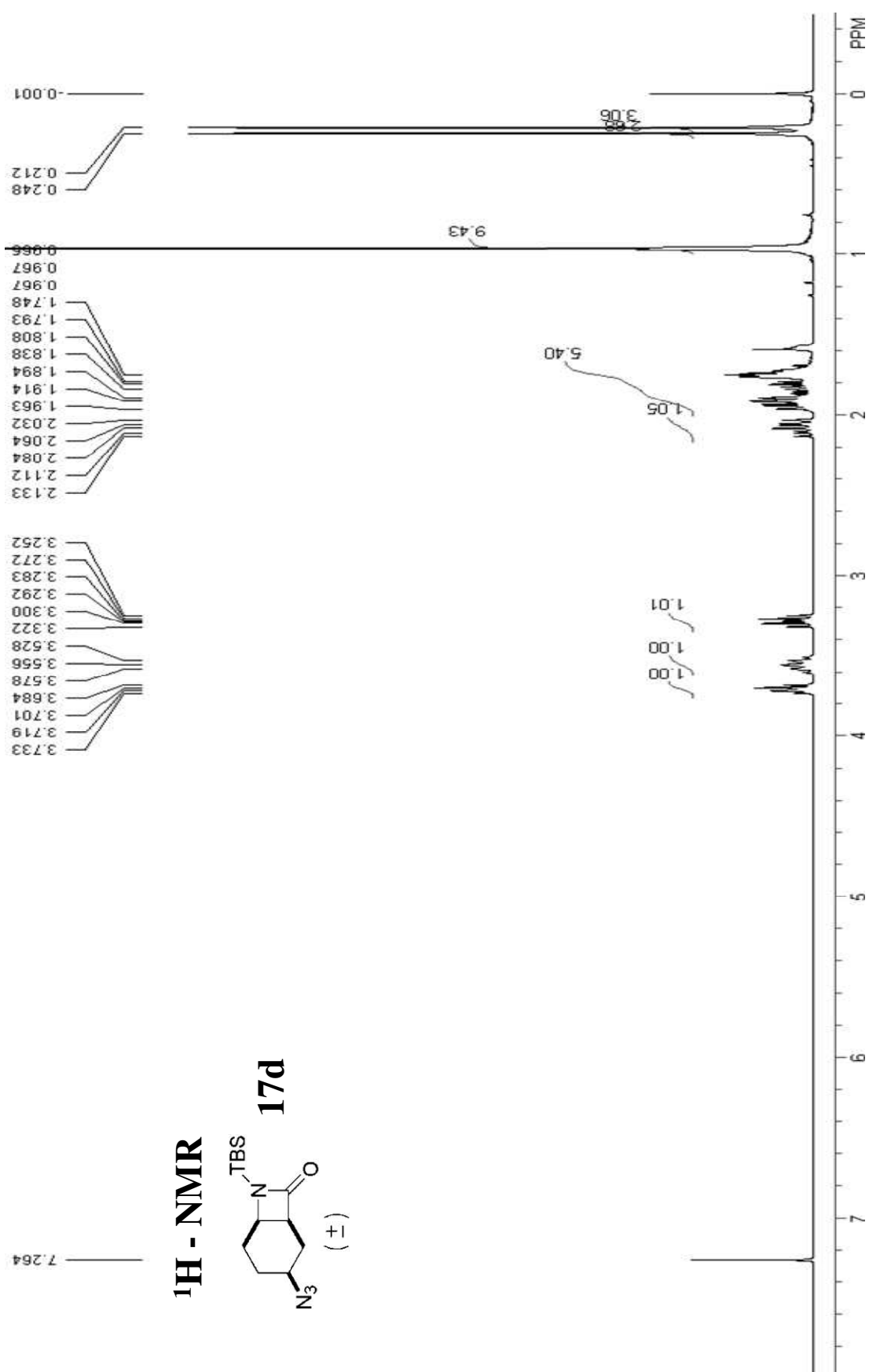


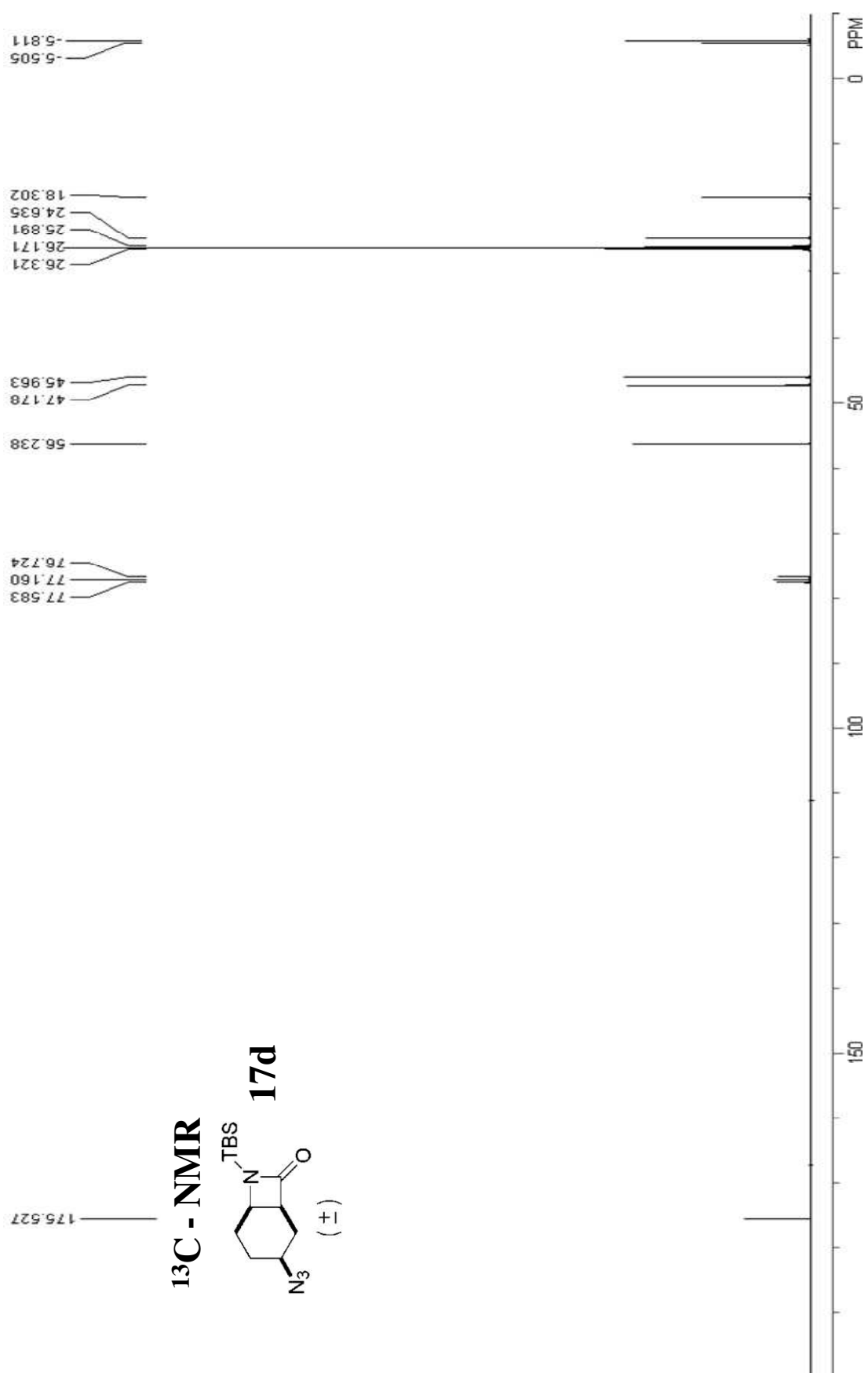
¹H - NMR

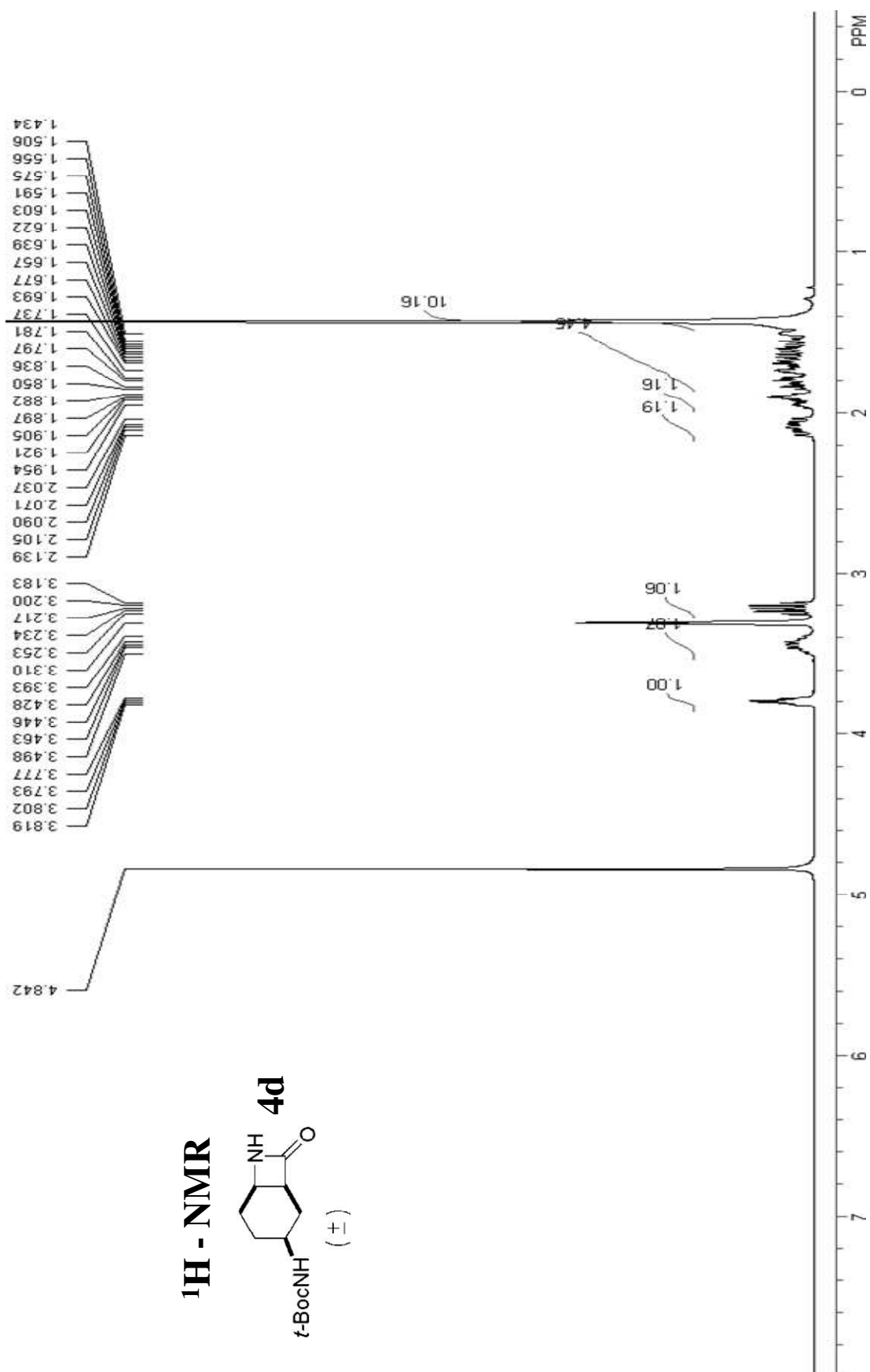
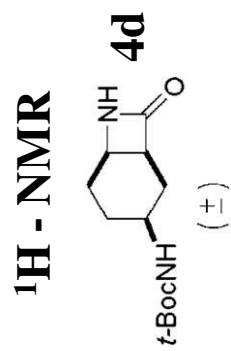


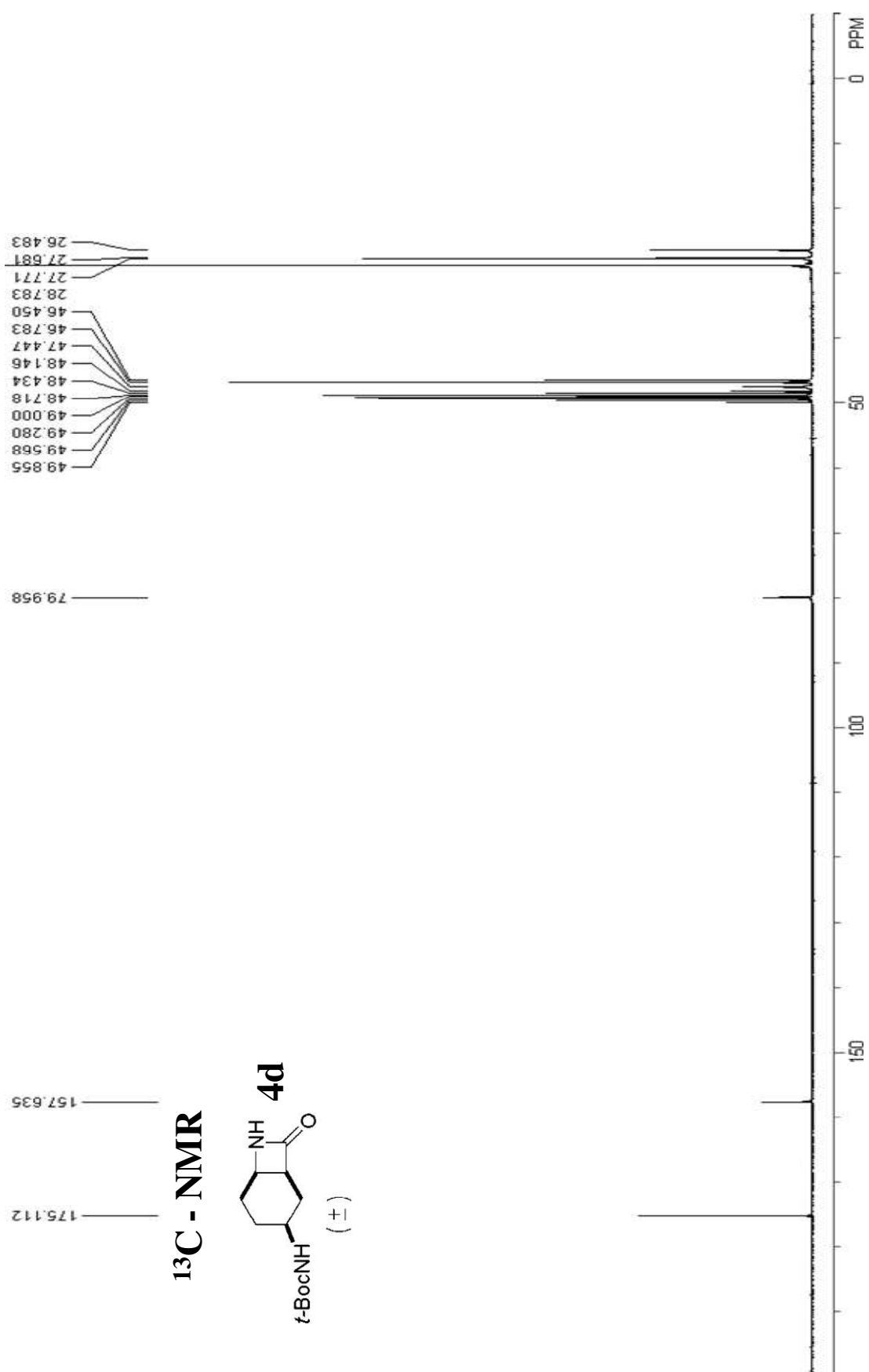


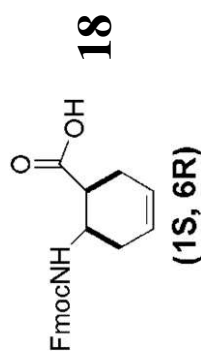
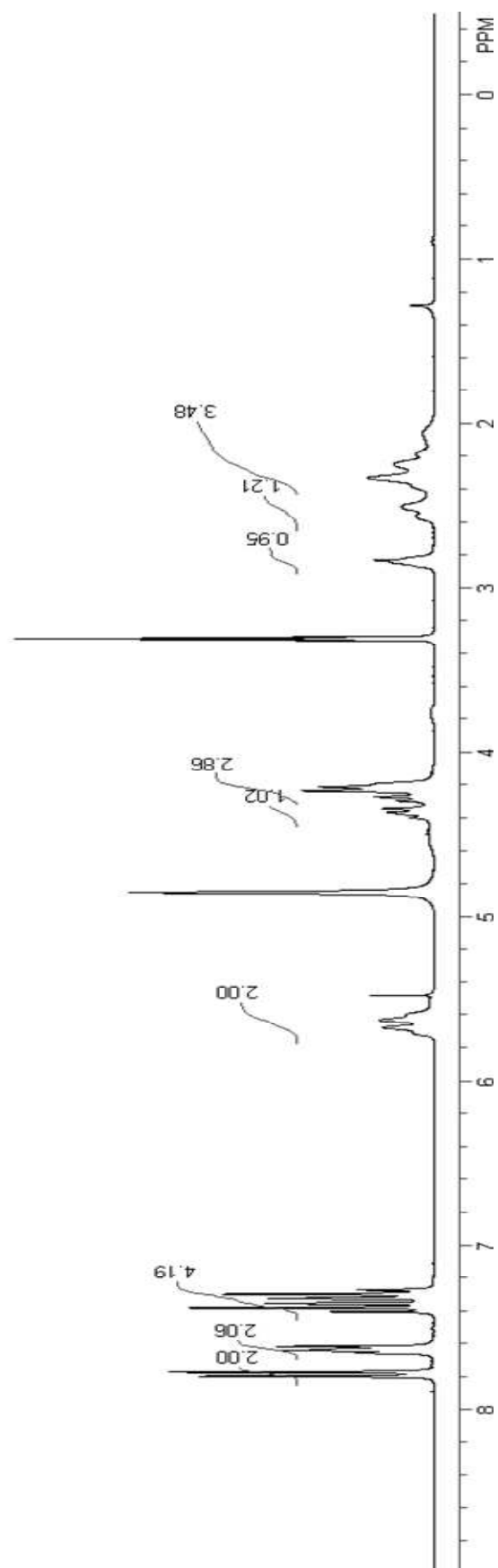












¹H - NMR

