Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supporting Information

Polyhydroxylated Homoazepanes and 1-Deoxy-homonojirimycin Analogues: Synthesis and Glycosidase Inhibition Study

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3,9-Di-*O*-benzyl-1,2-*O*-isopropylidene-5,6,7,8-tetradeoxy-a-D-*xylo*-nona-5-eno-1,4-furanose (11). To a cooled solution of sodium hydride (0.43 g, 10.78 mmol) in THF (2 cm^3) was added alcohol **10** (3.0 g, 8.98 mmol) in THF (30 cm^3) and stirred for half an hour. Benzyl bromide (1.28 cm^3, 10.78 mmol) and tetra *n*-butyl ammonium iodide (10 mg) were added and the resulting reaction mixture was allowed to warm at room temperature and stirred for 6 h. The reaction mixture was quenched by adding saturated ammonium chloride (10 cm^3) and THF was removed under reduced pressure and the residue obtained was extracted with chloroform (3 x 30 cm^3). Usual workup and chromatographic purification (*n*-hexane/ethyl acetate = 9.5/0.5) afforded **11** (3.6 g, 95%) as a thick liquid (Found: C, 73.54; H, 7.63. Cald for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60); R_f 0.56 (10% ethyl acetate-*n*-hexane); $[\alpha]_D^{25} - 43.2$ (*c* 1.25 in $CHCl_3$); $\nu_{max.}$(Neat)/cm^{-1} 1603, 1452, 1375, 1310 and 1215; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.32 (3H, s, C*H*$_3$), 1.50 (3H, s, C*H*$_3$), 1.73 (2H, quintet, *J* 6.6 Hz, *H*6a,b), 2.20 (2H, q, *J* 6.6 Hz, *H*7a,b), 3.49 (2H, t, *J* 6.6 Hz, *H*9a,b), 3.81 (1H, d, *J* 3.3 Hz, *H*3), 4.48 (2H, s, OC*H*$_2$Ph), 4.53 (1H, d, *J* 12.3 Hz, OC*H*$_2$Ph), 4.58 (1H, dd, *J* 7.5 and 3.3 Hz, *H*4), 4.61 (1H, d, *J* 3.6 Hz, *H*2), 4.64 (1H, d, *J* 12.3 Hz, OC*H*$_2$Ph), 5.69 (1H, dd, *J* 15.6 and 7.5 Hz, *H*5), 5.86 (1H, dt, *J* 15.6 and 6.6 Hz, *H*6), 5.93 (1H, d, *J* 3.6 Hz, *H*1), 7.25–7.36 (10H, m, Ar*H*'s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 25.8, 26.4 (2 x *C*H$_3$), 28.6, 28.7 (*C*7/*C*8), 69.1 (*C*9), 71.4, 72.3 (2 x OCH$_2$Ph), 80.8, 82.4, 83.0 (*C*2/*C*3/*C*4), 104.2 (*C*1), 110.7 (O*C*O), 123.8 (*C*6), 126.9 (strong), 127.0 (strong), 127.1, 127.2, 127.7 (strong), 127.8 (strong), 134.9 (*C*5), 137.1, 138.0 (Ar*C*'s).

3,9-Di-*O*-benzyl-1,2-*O*-isopropylidene-7,8-dideoxy-5,6-oxirano-b-L-*glycero*-D-*gluco*-nona-1,4-furanose (12a) and 3,9-di-*O*-benzyl-1,2-*O*-isopropylidene-7,8-dideoxy-5,6-oxirano-a-D-*glycero*-L-*ido*-nona-1,4-furanose (12b). To a solution of the olefin **11** (3.6 g, 8.49 mmol) in CH_2Cl_2 (60 cm^3) was added *m*-chloroperbenzoic acid (2.2 g, 12.74 mmol) at 0 °C and the resulting reaction mixture was allowed to warm at room temperature and stirred for 24 h. The reaction mixture was diluted by adding water (10 cm^3) and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 cm^3). The combined organic phase was washed

with 2N NaOH (10 cm^3) and worked up to afford a diastereomeric mixture of epoxides. Purification by column chromatography and first elution with (*n*-hexane/ethyl acetate = 9.6/0.4) gave **12a** (2.4 g, 64%) as a thick liquid (Found: C, 70.91; H, 7.29. Cald for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32); R_f 0.56 (20% ethyl acetate-*n*-hexane); $[\alpha]_D^{25} - 41.0$ (*c* 2.0 in $CHCl_3$); $\nu_{max.}$(Neat)/cm^{-1} 1454, 1375, 1217 and 1082; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.31 (3H, s, C*H*$_3$), 1.45 (3H, s, C*H*$_3$), 1.66–1.79 (4H, m, *H*7a,b and *H*8a,b), 3.00–3.03 (1H, m, *H*6), 3.07 (1H, dd, *J* 7.2 and 2.1 Hz, *H*5), 3.45 (2H, m, *H*9a,b), 3.78 (1H, dd, *J* 7.2 and 3.0 Hz, *H*4), 4.04 (1H, d, *J* 3.0 Hz, *H*3), 4.49 (2H, s, OC*H*$_2$Ph), 4.61 (1H, d, *J* 3.6 Hz, *H*2), 4.67 (2H, ABq, *J* 12.0 Hz, OC*H*$_2$Ph), 5.92 (1H, d, *J* 3.6 Hz, *H*1), 7.26–7.36 (10H, m, Ar*H*'s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 26.1, 26.3 (2 x *C*H$_3$), 26.8, 28.5 (*C*7/*C*8), 54.1, 58.5 (*C*5/*C*6), 69.5 (*C*9), 72.3, 72.8 (2 x O*C*H$_2$Ph), 81.3, 81.9, 82.6 (*C*2/*C*3/*C*4), 105.2 (*C*1), 111.7 (O*C*O), 127.4, 127.5, 127.51 (strong), 127.8 (strong), 128.2 (strong), 128.4 (strong), 137.2, 138.3 (Ar*C*'s). Further elution with (*n*-hexane/ethyl acetate = 9.5/0.5) afforded **12b** (1.2 g, 32%) as a thick liquid (Found: C, 70.93; H, 7.36. Cald for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32); R_f 0.41 (20% ethyl acetate-*n*-hexane); $[\alpha]_D^{25} - 20.0$ (*c* 0.5 in $CHCl_3$); $\nu_{max.}$(Neat)/cm^{-1} 1454, 1377, 1215, 1163 and 1024; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.32 (3H, s, C*H*$_3$), 1.46 (3H, s, C*H*$_3$), 1.66–1.81 (4H, m, *H*7a,b and *H*8a,b), 2.84 (1H, ddd, *J* 5.1, 3.6 and 2.1, *H*6), 3.06 (1H, dd, *J* 6.0 and 2.1 Hz, *H*5), 3.44–3.56 (2H, m, *H*9a,b), 3.85 (1H, dd, *J* 6.0 and 3.6 Hz, *H*4), 3.95 (1H, d, *J* 3.6 Hz, *H*3), 4.48 (2H, s, OC*H*$_2$Ph), 4.51 (1H, d, *J* 12.3 Hz, OC*H*$_2$Ph), 4.62 (1, d, *J* 3.9 Hz, *H*2), 4.71 (1H, d, *J* 12.3 Hz, OC*H*$_2$Ph), 5.98 (1H, d, *J* 3.9 Hz, *H*1), 7.27–7.36 (10H, m, Ar*H*'s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 25.8, 26.0 (2 x *C*H$_3$), 26.5, 28.1 (*C*7/*C*8), 54.1, 55.6 (*C*5/*C*6), 69.2 (*C*9), 71.4, 72.4 (2 x O*C*H$_2$Ph), 81.2, 81.8, 82.4 (*C*2/*C*3/*C*4), 104.9 (*C*1), 111.2 (O*C*O), 127.0, 127.1 (strong), 127.2 (strong), 127.5, 127.8 (strong), 128.0 (strong), 136.8, 138.0 (Ar*C*'s).

6-Azido-3,9-di-*O*-benzyl-1,2-*O*-isopropylidene-6,7,8-trideoxy-α-D-*glycero*-D-*gluco*-nona-1,4-furanose (13a). To a solution of epoxide **12a** (1.0 g, 2.27 mmol) in DMF (10 cm^3) was added sodium

azide (0.89 g, 13.64 mmol) and lithium chloride (0.57 g, 13.64 mmol) and the resulting reaction mixture was heated to 100 °C for 8 h. The reaction mixture was poured in an ice-water (50 cm^3) and extracted with ethyl acetate (3 x 20 cm^3). Purification by column chromatography (*n*-hexane/ethyl acetate = 9/1) gave **13a** (1.0 g, 91%) as a thick liquid (Found: C, 64.60; H, 6.87. Cald for $C_{26}H_{33}N_3O_6$: C, 64.58; H, 6.88); R_f 0.59 (20% ethyl acetate-*n*-hexane); $[\alpha]_D^{25}$ – 28.4 (*c* 2.25 in $CHCl_3$); $\nu_{max.}$(Neat)/cm^{-1} 3200–3600 (broad band), 2104, 1454, 1375 and 1217; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.32 (3H, s, C*H*$_3$), 1.47 (3H, s, C*H*$_3$), 1.62–1.88 (4H, m, *H*7a,b and *H*8a,b), 2.66 (1H, d, *J* 6.0 Hz, exchanges with D_2O, O*H*), 3.42–3.58 (3H, m, *H*6 and *H*9a,b), 4.09 (1H, dd, *J* 6.9 and 4.5 Hz, *H*5), 4.13 (1H, d, *J* 3.0 Hz, *H*3), 4.17 (1H, dd, *J* 6.9 and 3.0 Hz, *H*4), 4.51 (2H, s, OC*H*$_2$Ph), 4.52 (1H, d, *J* 11.4, Hz, OC*H*$_2$Ph), 4.63 (1H, d, *J* 3.6 Hz, *H*2), 4.73 (1H, d, *J* 11.4 Hz, OC*H*$_2$Ph), 5.96 (1H, d, *J* 3.6 Hz, *H*1), 7.27–7.40 (10H, m, Ar*H*'s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 26.0, 26.3 (2 x *C*H$_3$), 26.7, 26.9 (*C*7/*C*8), 65.0, 69.7 (*C*6/*C*9), 71.4, 72.0 (2 x O*C*H$_2$Ph), 72.9 (*C*5), 78.3, 81.7, 82.4 (*C*2/*C*3/*C*4), 104.9 (*C*1), 111.8 (O*C*O), 127.4, 127.5 (strong), 128.0 (strong), 128.2 (strong), 128.4, 128.7 (strong), 136.5, 138.3 (Ar*C*'s).

6-Azido-3,9-di-*O*-benzyl-1,2-*O*-isopropylidene-6,7,8-trideoxy-b-L-*glycero*-L-*ido*-nona-1,4-furanose (13b). The epoxide **12b** (1.0 g, 2.27 mmol) was reacted with sodium azide (0.89 g, 13.64 mmol) and lithium chloride (0.57 g, 13.64 mmol) as described in the synthesis of **13a** to afford **13b** (1.0 g, 92%) as a thick liquid (Found: C, 64.56; H, 6.91. Cald for $C_{26}H_{33}N_3O_6$: C, 64.58; H, 6.88); R_f 0.54 (20% ethyl acetate-*n*-hexane); $[\alpha]_D^{25}$ – 46.4 (*c* 1.25 in $CHCl_3$); $\nu_{max.}$(Neat)/cm^{-1} 3200–3600 (broad band), 2102, 1454, 1375 and 1078; δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.35 (3H, s, C*H*$_3$), 1.51 (3H, s, C*H*$_3$), 1.60–1.75 (2H, m, *H*7a,b), 1.81–1.98 (2H, m, *H*8a,b), 3.4–3.55 (1H, bs, exchanges with D_2O, O*H*), 3.46–3.55 (3H, m, *H*6 and *H*9a,b), 3.82 (1H, dd, *J* 7.5 and 3.0 Hz, *H*4), 4.07 (1H, d, *J* 3.0 Hz, *H*3), 4.33 (1H, dd, *J* 7.5 and 3.0 Hz, *H*5), 4.50 (2H, s, OC*H*$_2$Ph), 4.51 (1H, d, *J* 12.0 Hz, OC*H*$_2$Ph), 4.65 (1H, d, *J* 3.6 Hz, *H*2), 4.73 (1H, d, *J* 12.0, Hz, OC*H*$_2$Ph), 6.00 (1H, d, *J* 3.6 Hz, *H*1), 7.28–7.37 (10H, m, Ar*H*'s); δ_C (75 MHz; $CDCl_3$; Me_4Si)

26.0, 26.5 (2 x *C*H$_3$), 26.9, 27.0 (*C*7/*C*8), 63.4, 69.9 (*C*9/*C*6), 71.6, 72.0 (2 x O*C*H$_2$Ph), 72.9 (*C*5), 78.0, 82.1, 83.8 (*C*2/*C*3/*C*4), 104.7 (*C*1), 112.1 (O*C*O), 127.4, 127.5 (strong), 127.8 (strong), 128.2 (strong), 128.3, 128.7 (strong), 136.2, 138.3 (Ar*C*'s).

6-(*N*-Benzoxycarbonylamino)-6,7,8-trideoxy-1,2-*O*-isopropylidene-a-D-*glycero*-D-*gluco*-nona-1,4-furanose (14a). To a solution of **13a** (0.90 g, 1.86 mmol) in methanol (15 cm^3) was added ammonium formate (0.70 g, 11.18 mmol) and 10% Pd/C (0.30 g) and the resulting reaction mixture was refluxed for an hour. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to give thick oil. To a cooled solution of amino alcohol (0.50 g, 1.80 mmol) in methanol-water (10 cm^3, 9:1) was added sodium bicarbonate (0.45 g, 5.42 mmol) and benzyl chloroformate (0.37 g, 2.17 mmol) at 0 °C and the resulting reaction mixture was stirred for 12 h. Methanol was evaporated under reduced pressure and the residue was extracted with chloroform (3 × 20 cm^3). Usual workup and purification by column chromatography (*n*-hexane/ethyl acetate = 4/6) gave **14a** (0.58 g, 76%) as a white solid (Found: C, 58.41; H, 7.11. Cald for $C_{20}H_{29}NO_8$: C, 58.38; H, 7.10); R_f 0.54 (ethyl acetate); $[\alpha]_D^{25}$ + 6.0 (*c* 1.0 in $CHCl_3$); mp 124–126 °C (ethyl acetate); $\nu_{max.}$(KBr)/cm^{-1} 3200–3600 (broad band), 1688, 1533, 1450, 1377, 1256 and 1069; δ_H (300 MHz; $CHCl_3$ + D_2O; Me_4Si) 1.26 (3H, s, C*H*$_3$), 1.42 (3H, s, C*H*$_3$), 1.45–1.65 (3H, m, *H*7a,b and *H*8a), 1.75–1.85 (1H, m, *H*8b), 3.59 (2H, bt, *J* 4.5 Hz, *H*9a,b), 3.85 (1H, bt, *J* 4.5 Hz, *H*6), 3.94 (1H, dd, *J* 7.5 and 4.5 Hz, *H*5), 4.07 (1H, dd, *J* 7.5 and 2.4 Hz, *H*4), 4.33 (1H, d, *J* 2.4 Hz, *H*3), 4.47 (1H, d, *J* 3.6 Hz, *H*2), 5.06 (2H, s, OC*H*$_2$Ph), 5.90 (1H, d, *J* 3.6, Hz, *H*1) 7.23–7.28 (5H, m, Ar*H*'s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 26.1, 26.2 (2 x *C*H$_3$), 26.8, 28.5 (*C*7/*C*8), 53.8 (*C*9), 61.7 (*C*6), 67.0 (*C*5), 71.7 (O*C*H$_2$Ph), 75.1, 79.7, 84.8 (*C*2/*C*3/*C*3), 104.8 (*C*1), 111.6 (O*C*O), 127.9 (strong), 128.1, 128.4 (strong), 136.1 (Ar*C*'s), 157.2 (NH*C*O).

6-(*N*-Benzoxycarbonylamino)-6,7,8-trideoxy-1,2-*O*-isopropylidene-b-L-*glycero*-L-*ido*-nona-1,4-furanose (14b). The reaction of **13b** (0.90 g, 1.86 mmol) with ammonium formate (0.70 g, 11.18 mmol) and 10% Pd/C (0.30 g) in methanol (15 cm^3) followed by sodium bicarbonate (0.45 g, 5.42 mmol)

and benzyl chloroformate (0.37 g, 2.17 mmol) as described in the synthesis of **14a** afforded **14b** (0.52 g, 68%) as a white solid (Found: C, 58.36; H, 7.12. Cald for $C_{20}H_{29}NO_8$: C, 58.38; H, 7.10); R_f 0.48 (ethyl acetate); $[\alpha]_D^{25} - 26.7$ (*c* 0.45 in $CHCl_3$); mp 154–156 °C (ethyl aceate); $\nu_{max.}$(KBr)/cm^{-1} 3200–3600 (broad band), 1672, 1533, 1446, 1379, 1331 and 1248; δ_H (300 MHz; $CHCl_3$ + D_2O; Me_4Si) 1.31 (3H, s, C*H*$_3$), 1.46 (3H, s, C*H*$_3$), 1.46–1.76 (4H, m, *H*7a,b and *H*8a,b), 3.56–3.72 (2H, m, *H*9a,b), 3.84–3.96 (1H, m, *H*6), 4.09 (1H, t, *J* 3.9 Hz, *H*5), 4.15 (1H, dd, *J* 3.9 and 2.7 Hz, *H*4), 4.27 (1H, d, *J* 2.7 Hz, *H*3), 4.49 (1H, d, *J* 3.6 Hz, *H*2), 5.08 (2H, ABq, *J* 12.3 Hz, OC*H*$_2$Ph), 5.94 (1H, d, *J* 3.6 Hz, *H*1) 7.25–7.35 (5H, m, Ar*H*'s); δ_C (75 MHz; $CDCl_3$; Me_4Si) 26.3, 26.9 (strong), 28.6 (2 x *C*H$_3$ and *C*7/*C*8), 53.9, 62.0 (*C*6/*C*9), 67.1 (*C*5), 72.0 (O*C*H$_2$Ph), 76.3, 78.5, 85.0 (*C*2/*C*3/*C*4), 104.8 (*C*1), 111.8 (O*C*O), 128.0 (strong), 128.1, 128.4 (strong), 136.0 (Ar*C*'s), 157.2 (NH*C*O).

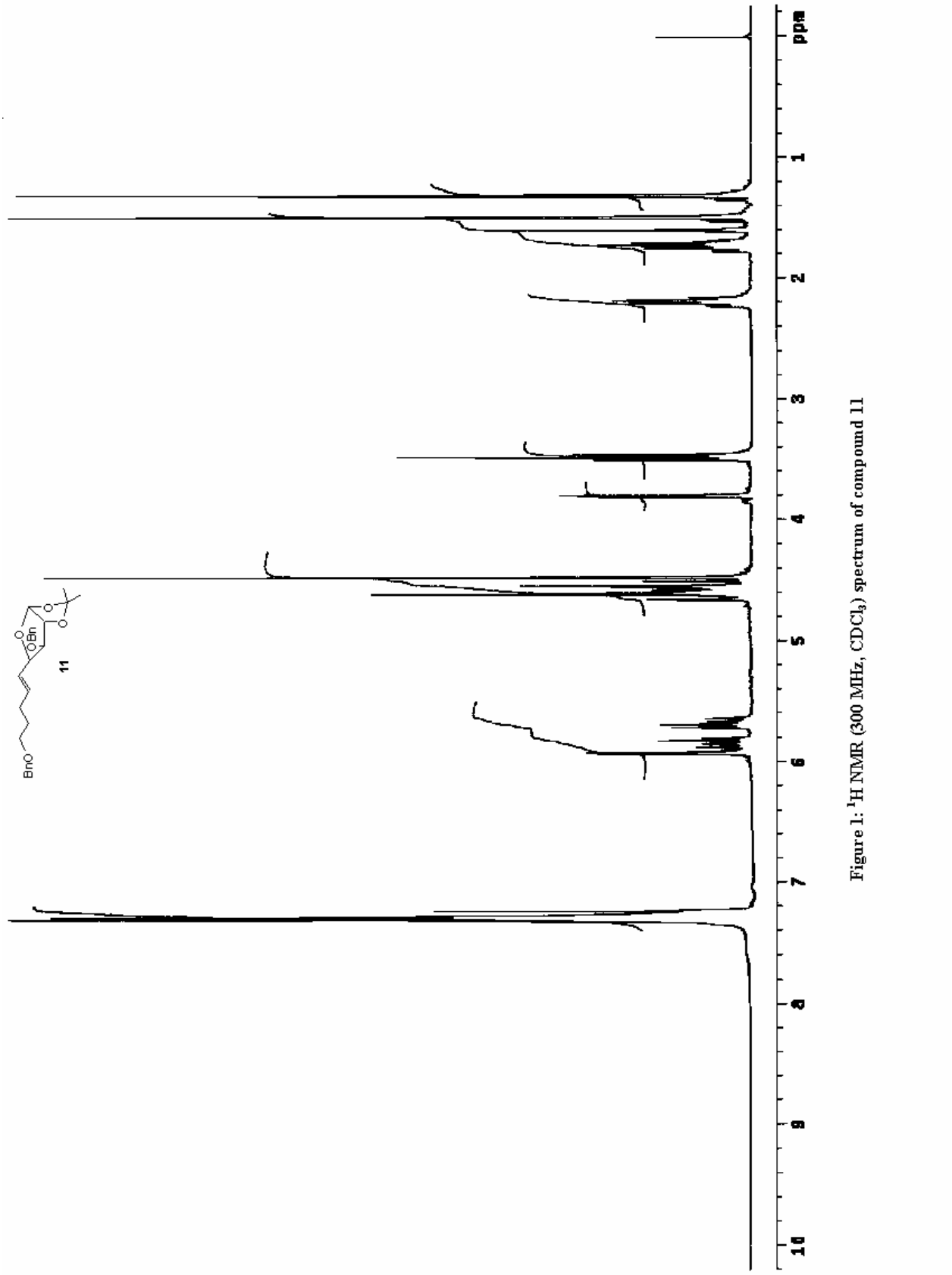

Figure 1: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 11

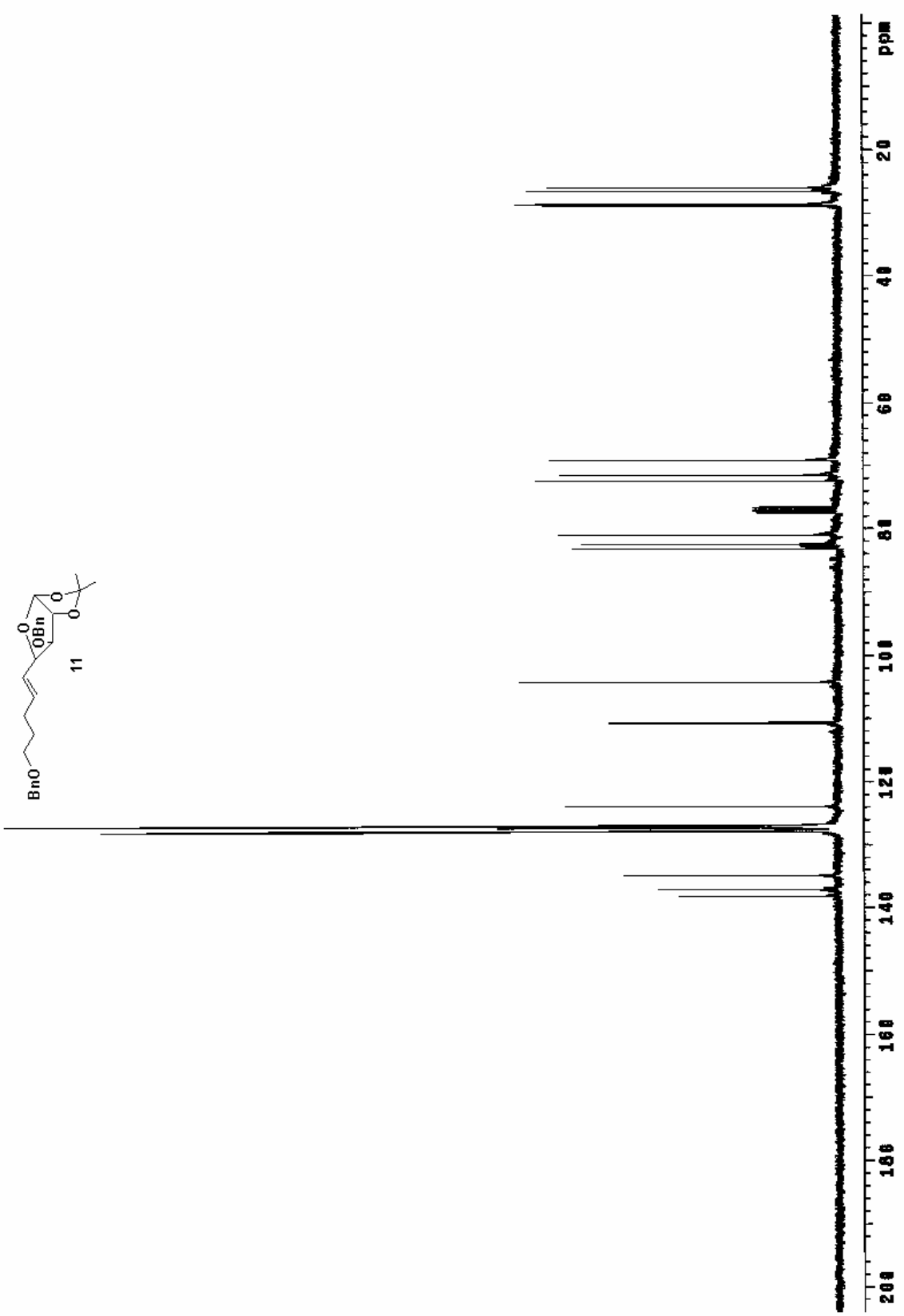

Figure 2: ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 11

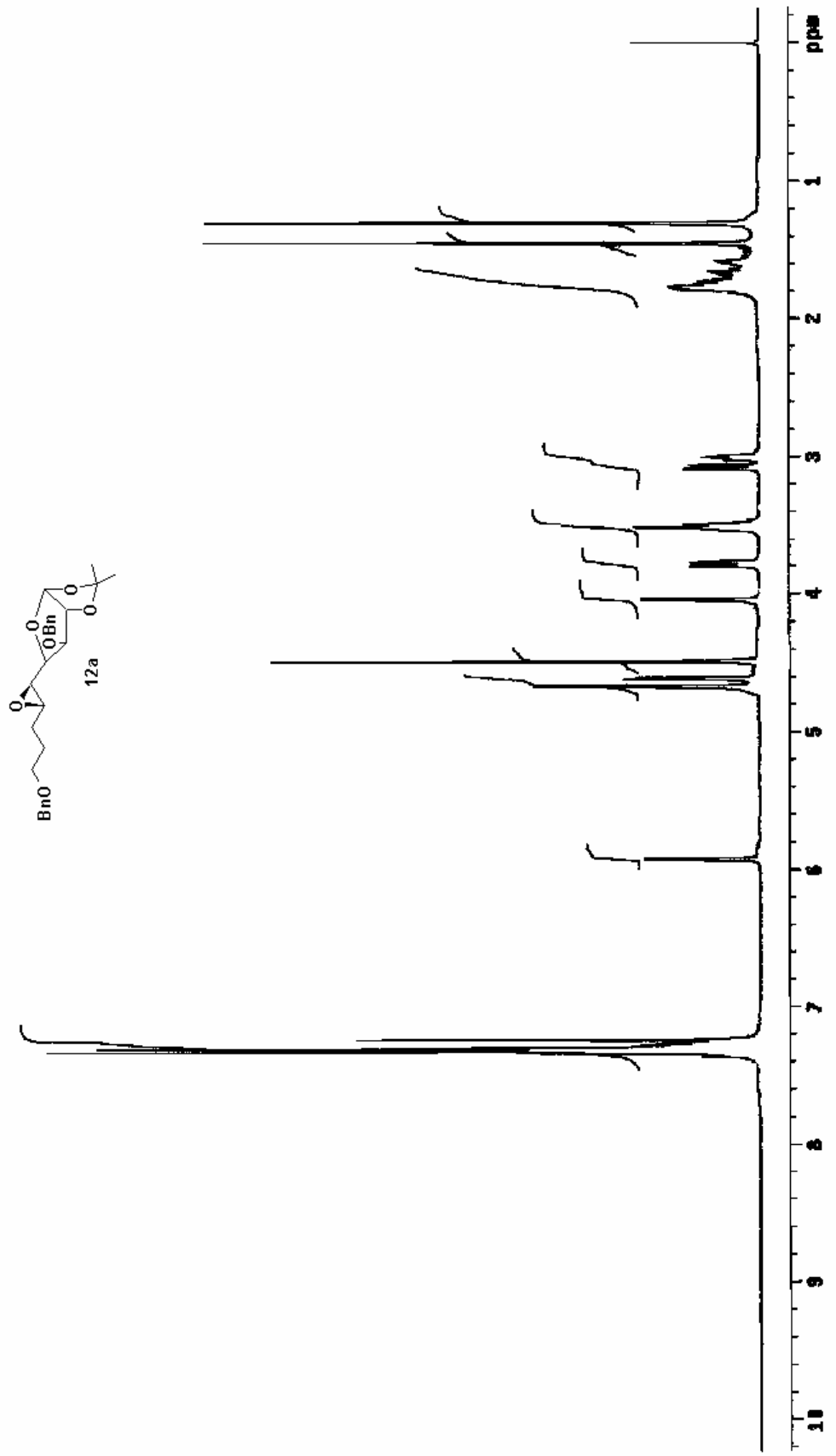

Figure 3: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 12a

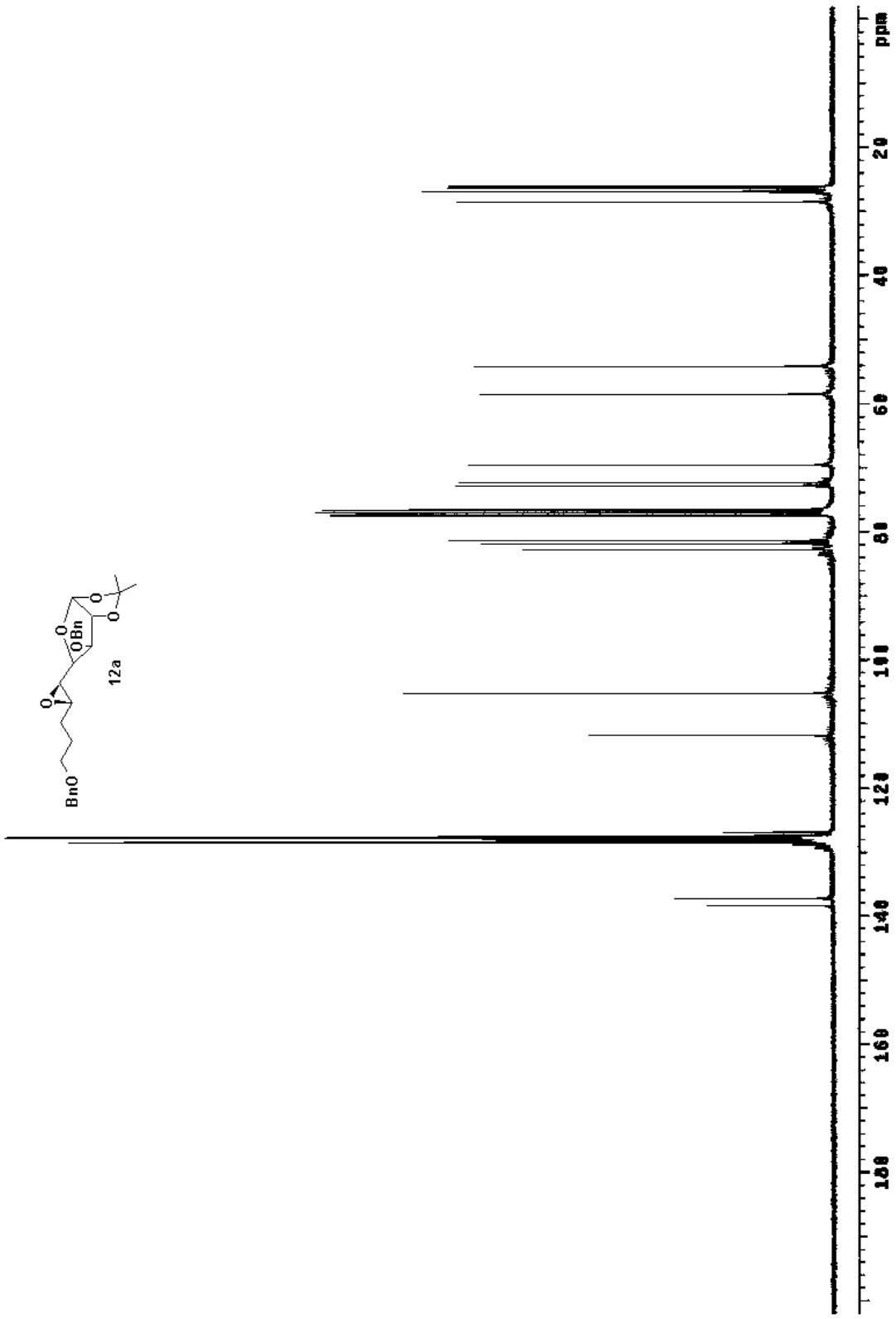

Figure 4: ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 12a

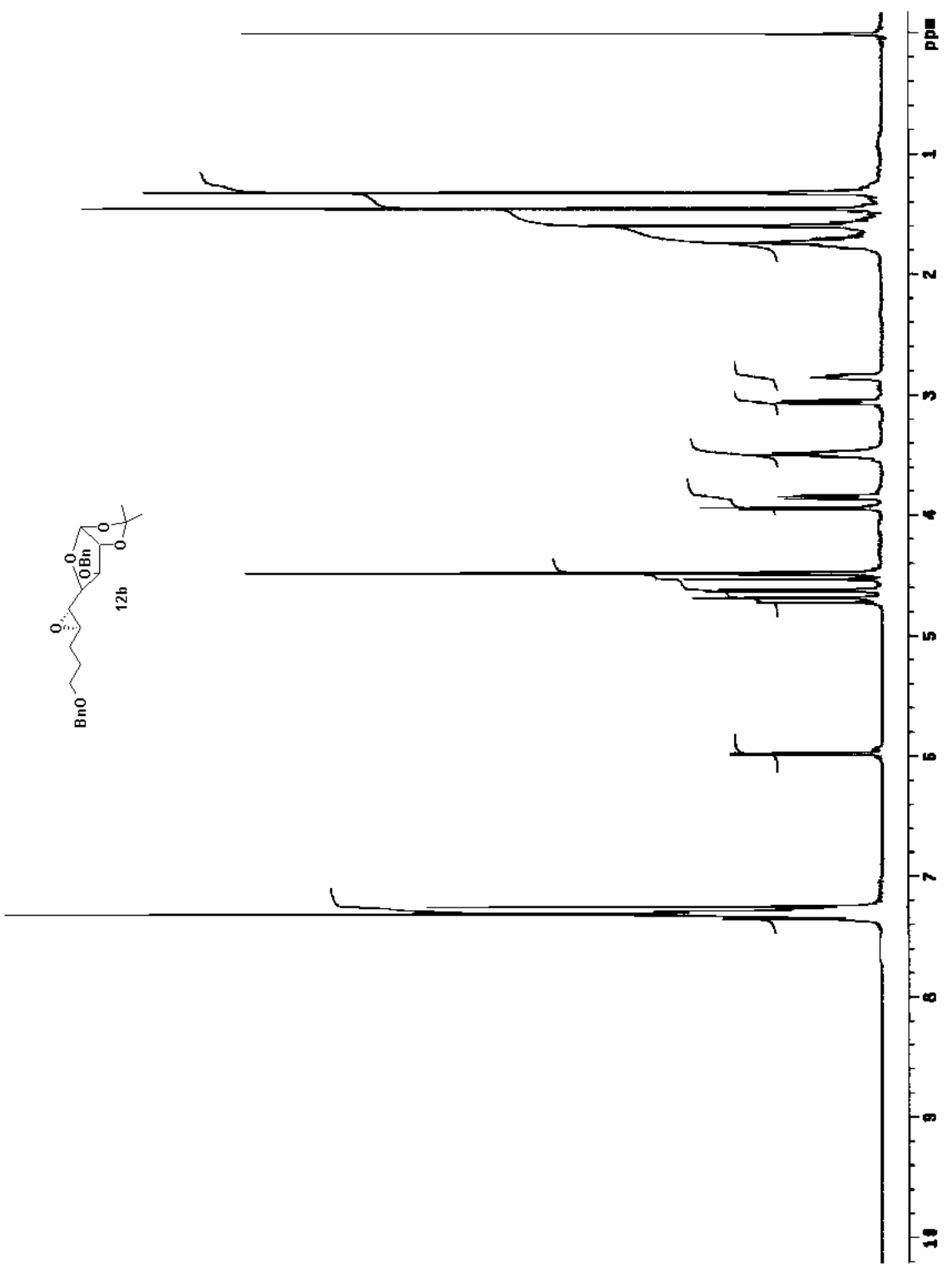

Figure 5: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 12b

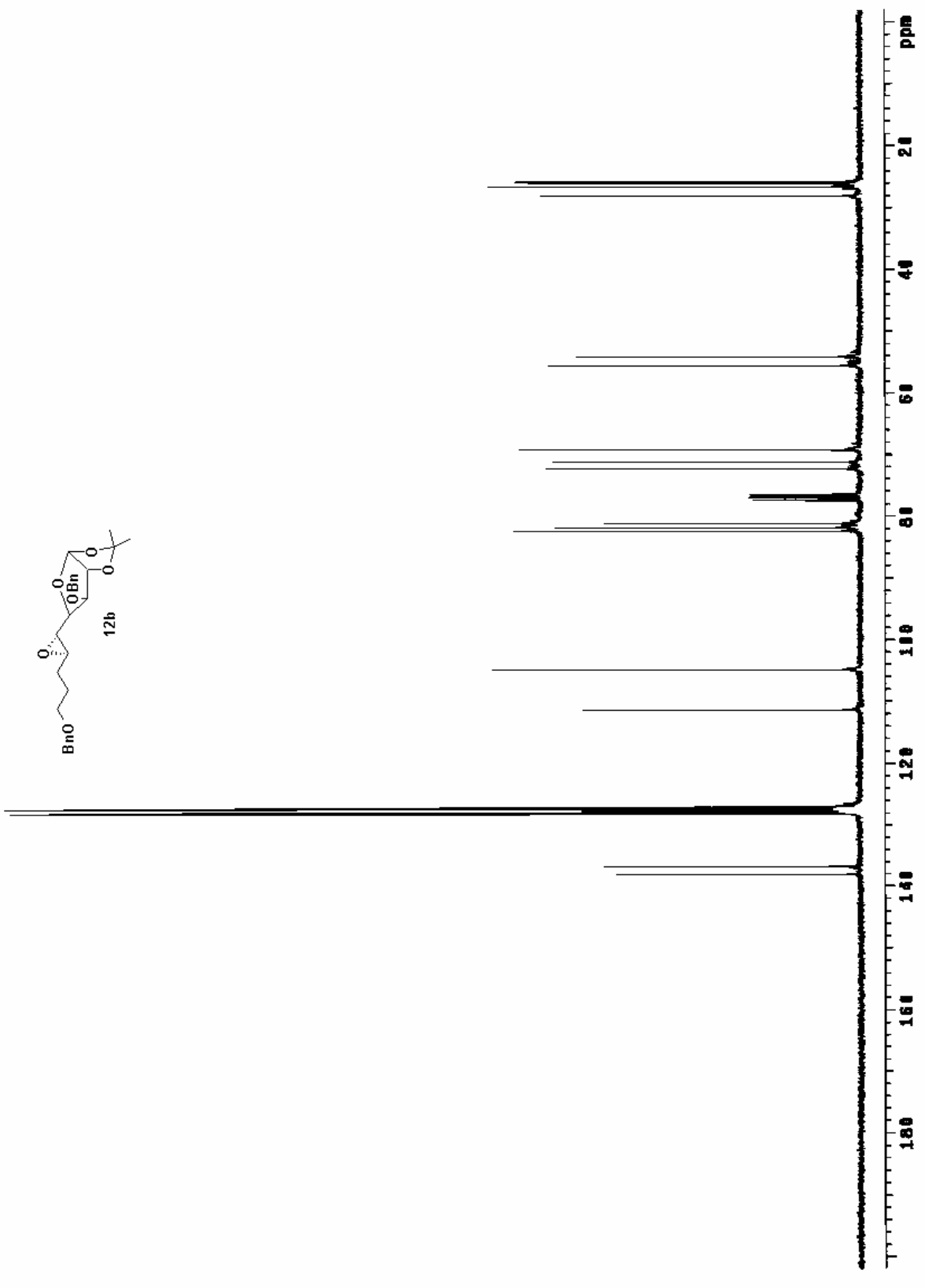

Figure 6: ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 12b

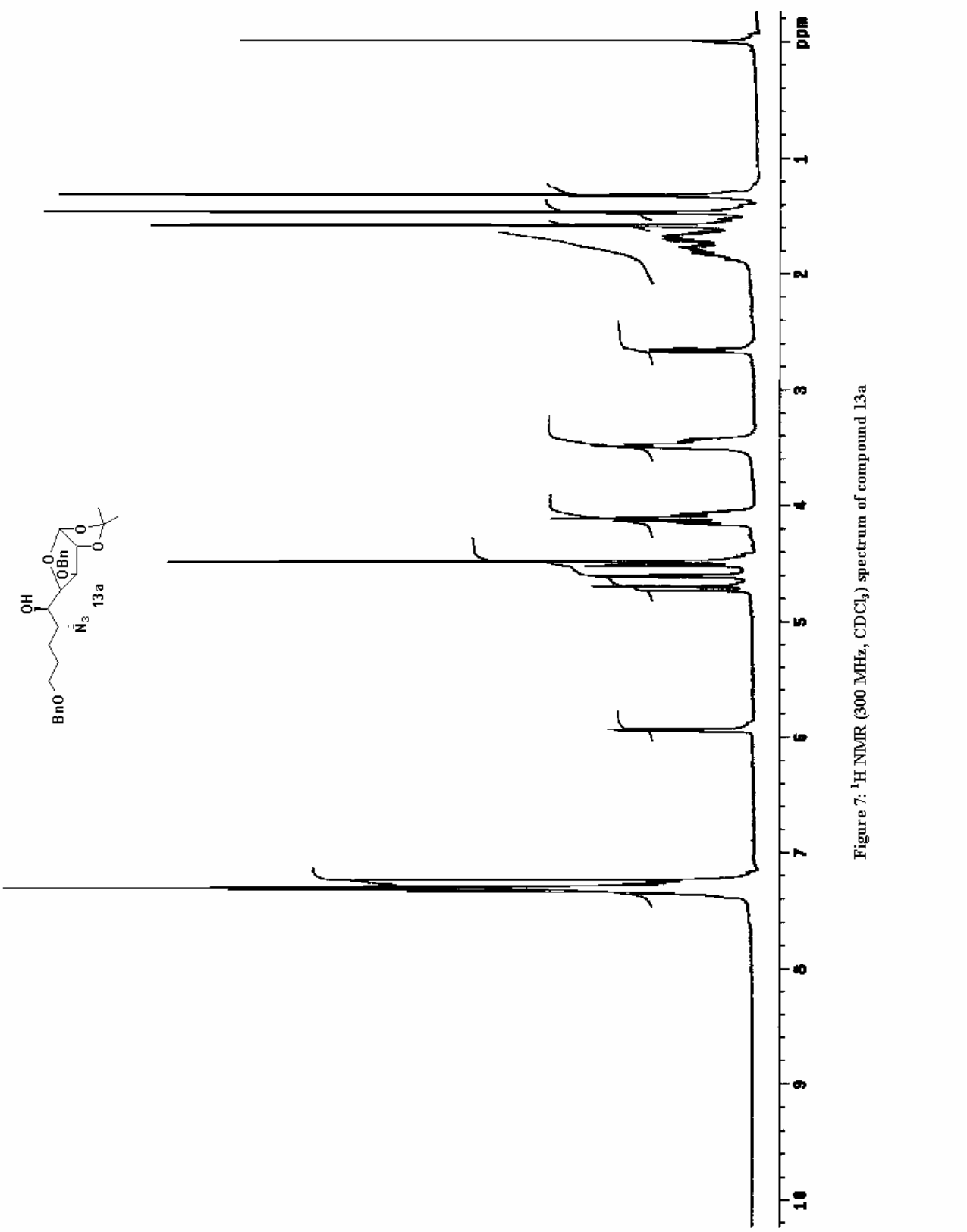

Figure 7: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 13a

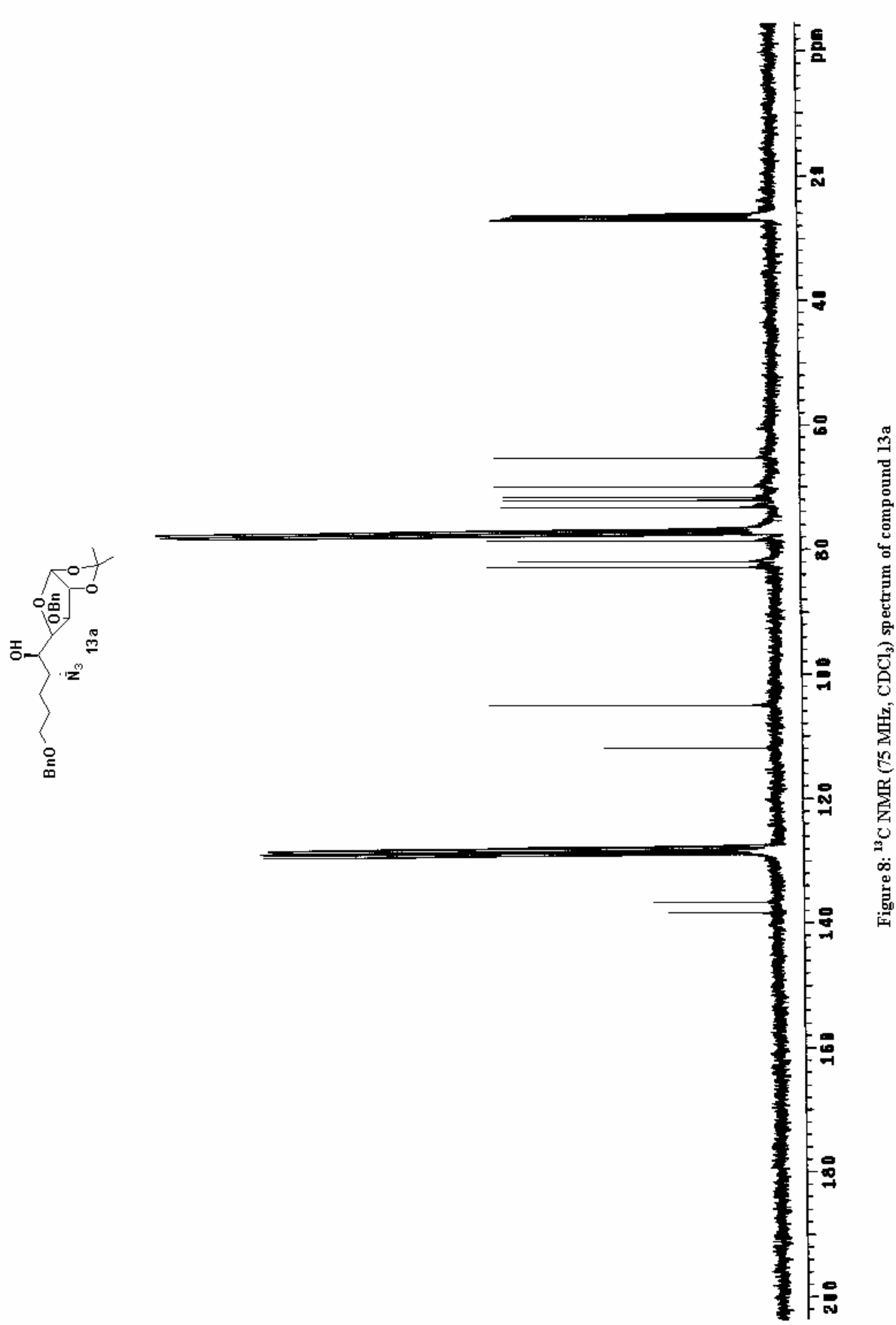

Figure 8: ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 13a

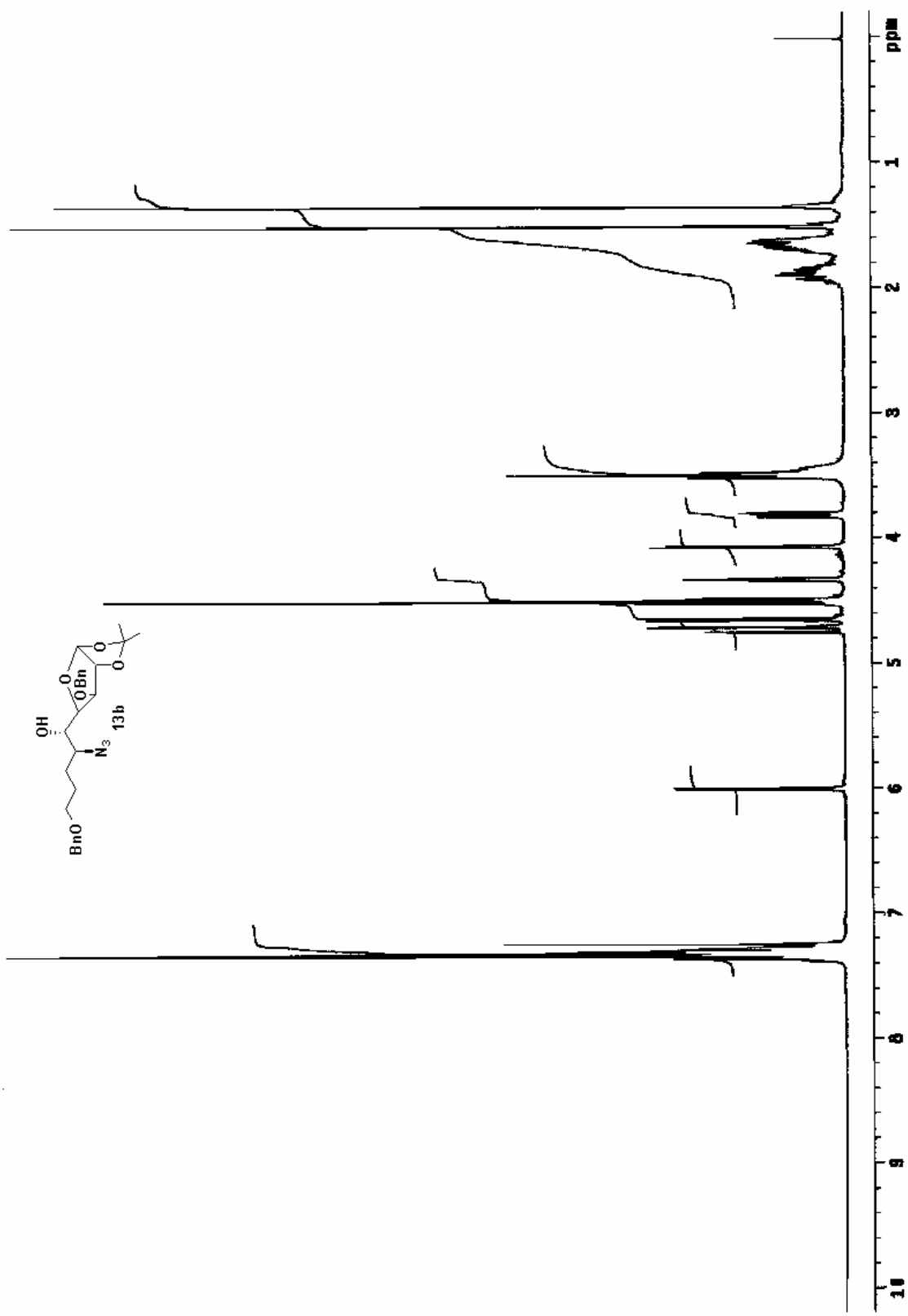

Figure 9: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 13b

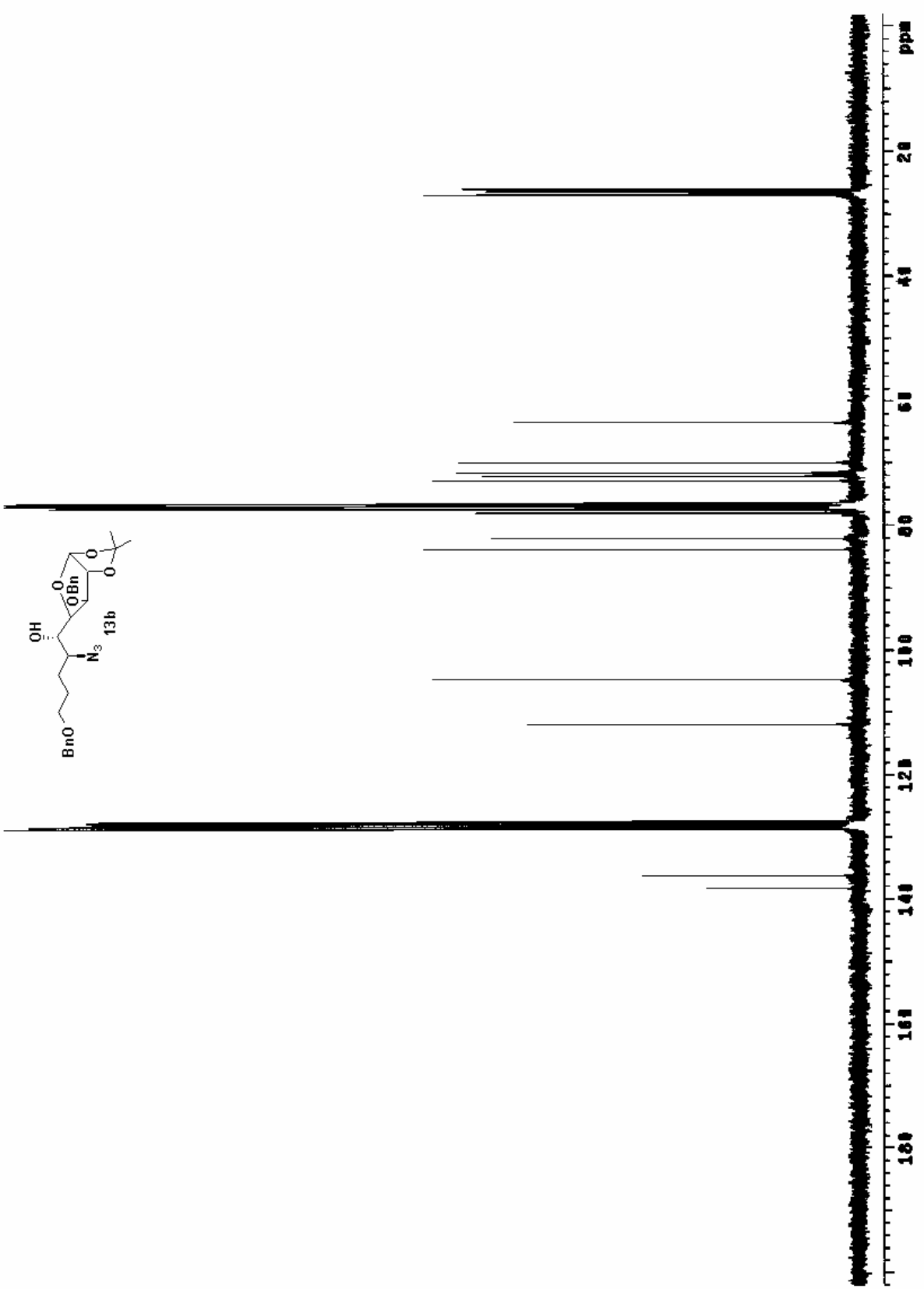

Figure 10: ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 13b

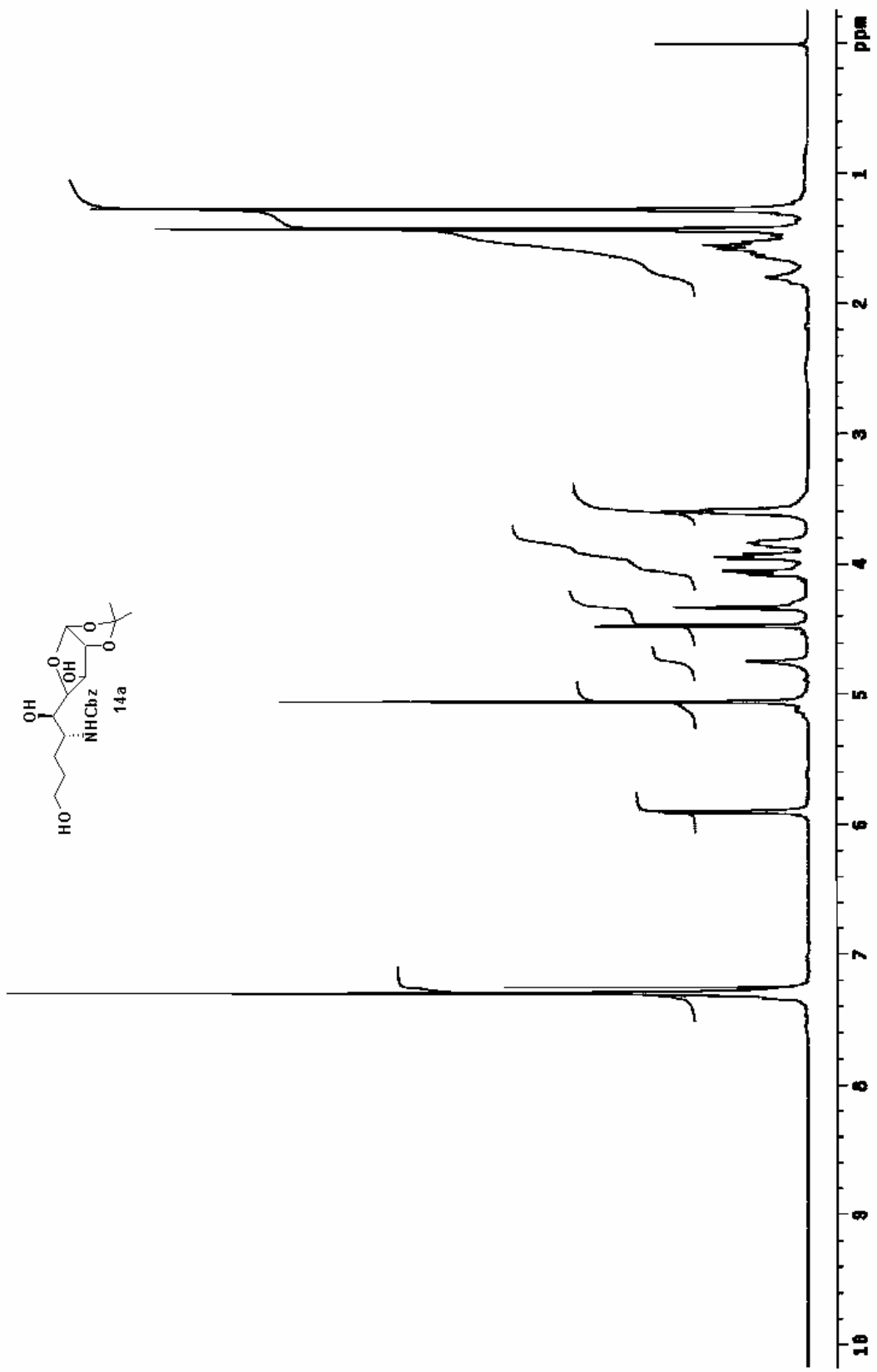

Figure 11: ^{1}H NMR (300 MHz, $CDCl_3 + D_2O$) spectrum of compound 14a

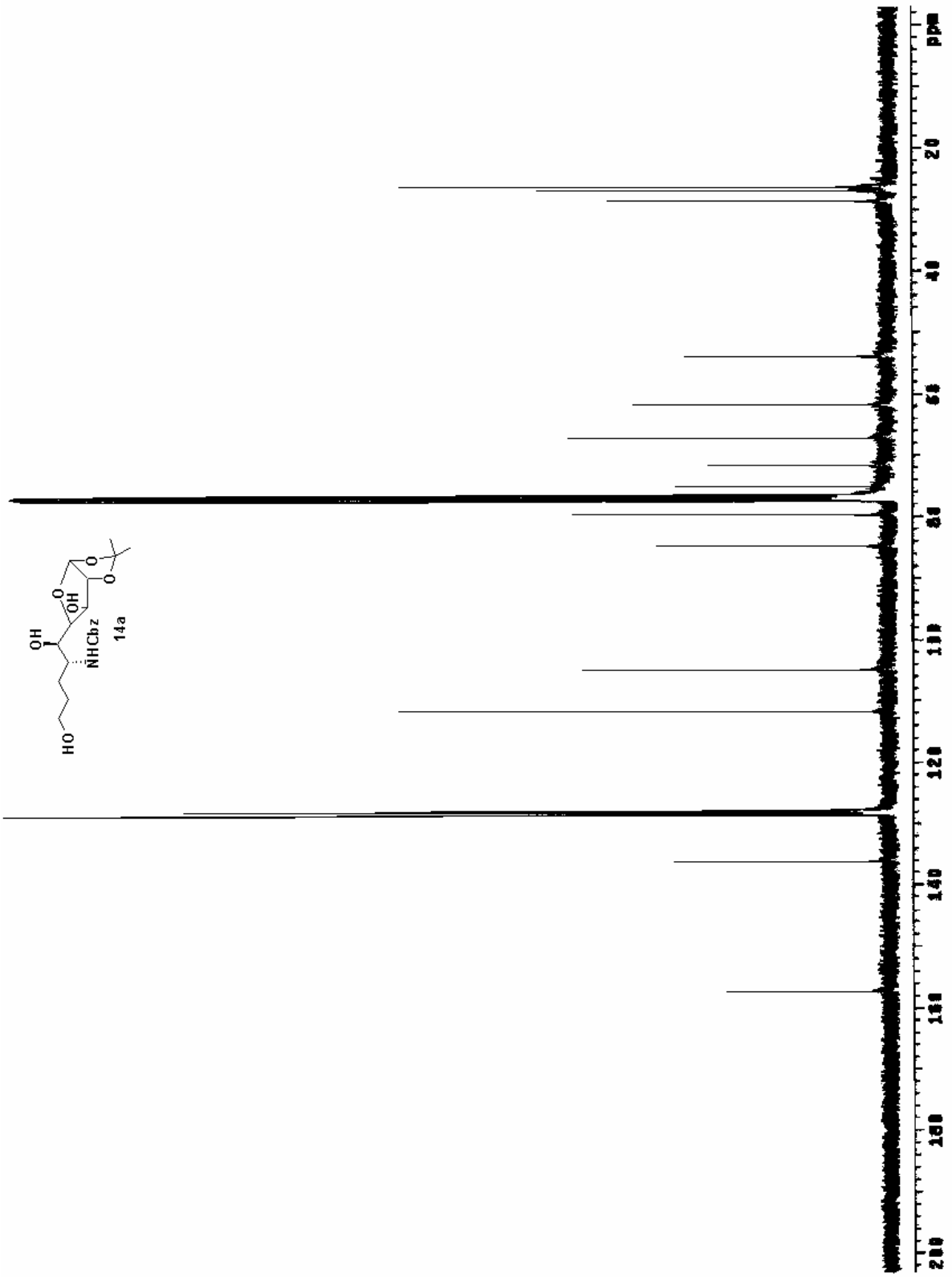

Figure 12: ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 14a

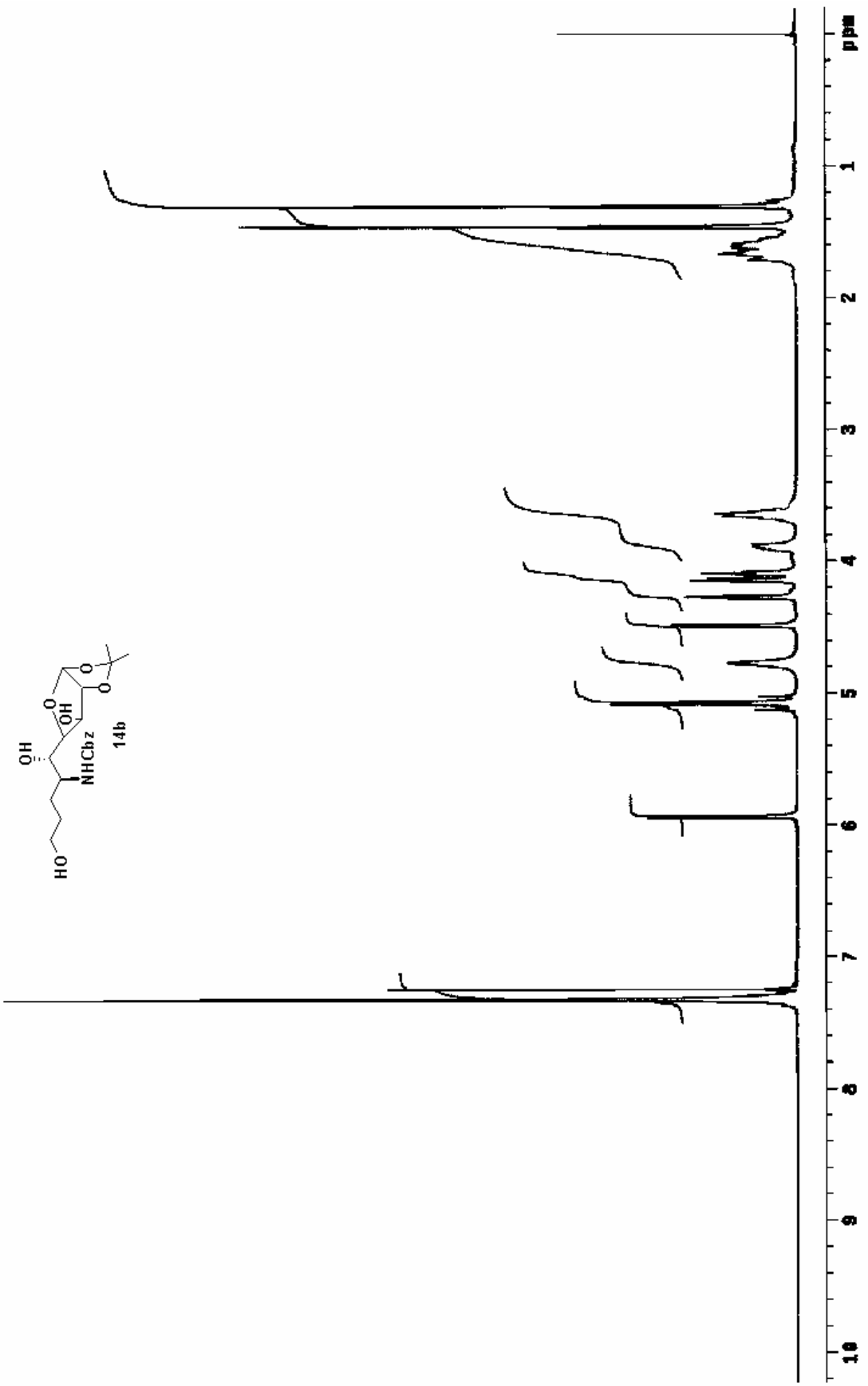

Figure 13: ^{1}H NMR (300 MHz, $CDCl_3 + D_2O$) spectrum of compound 14b

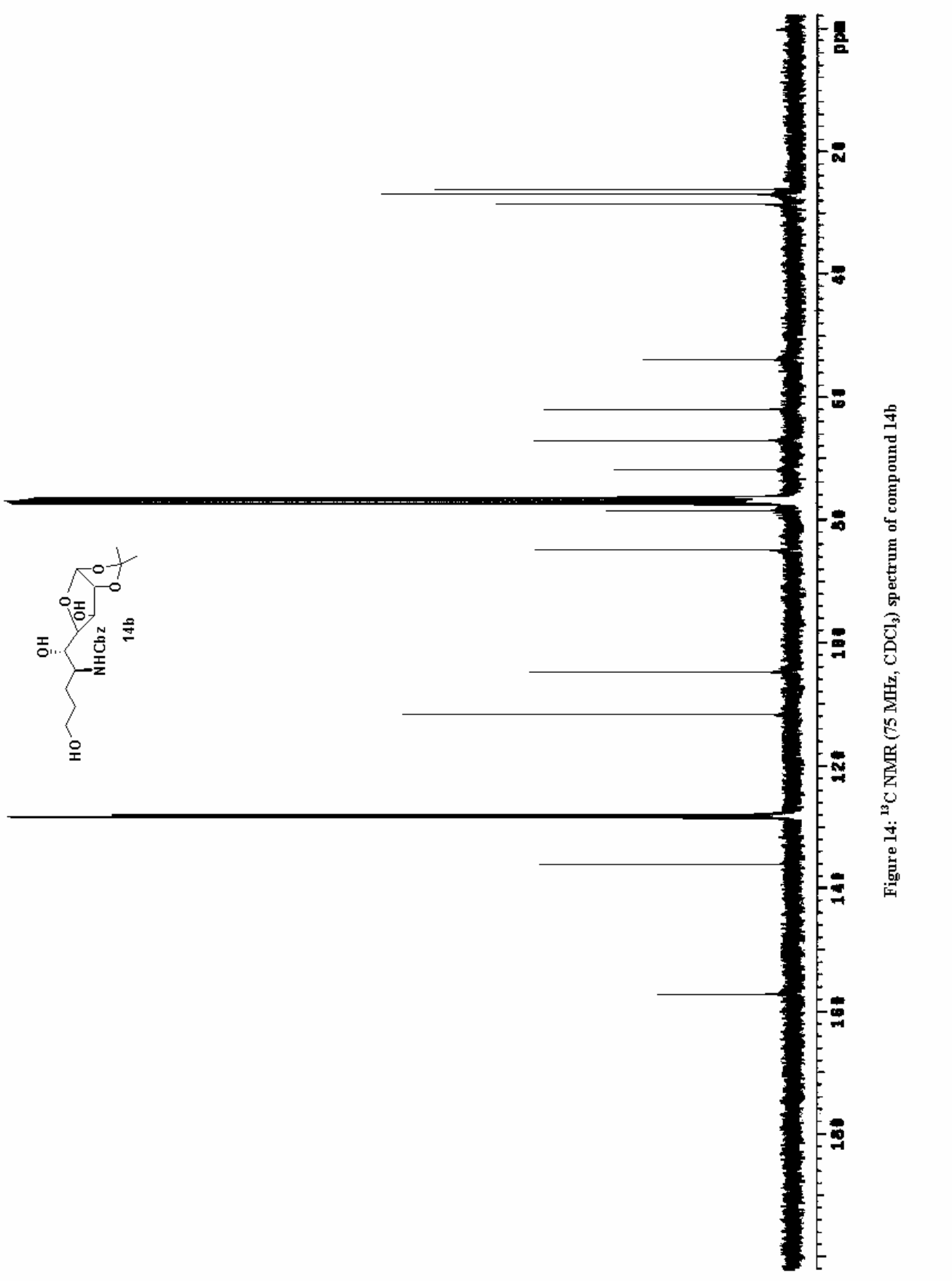

Figure 14: ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 14b

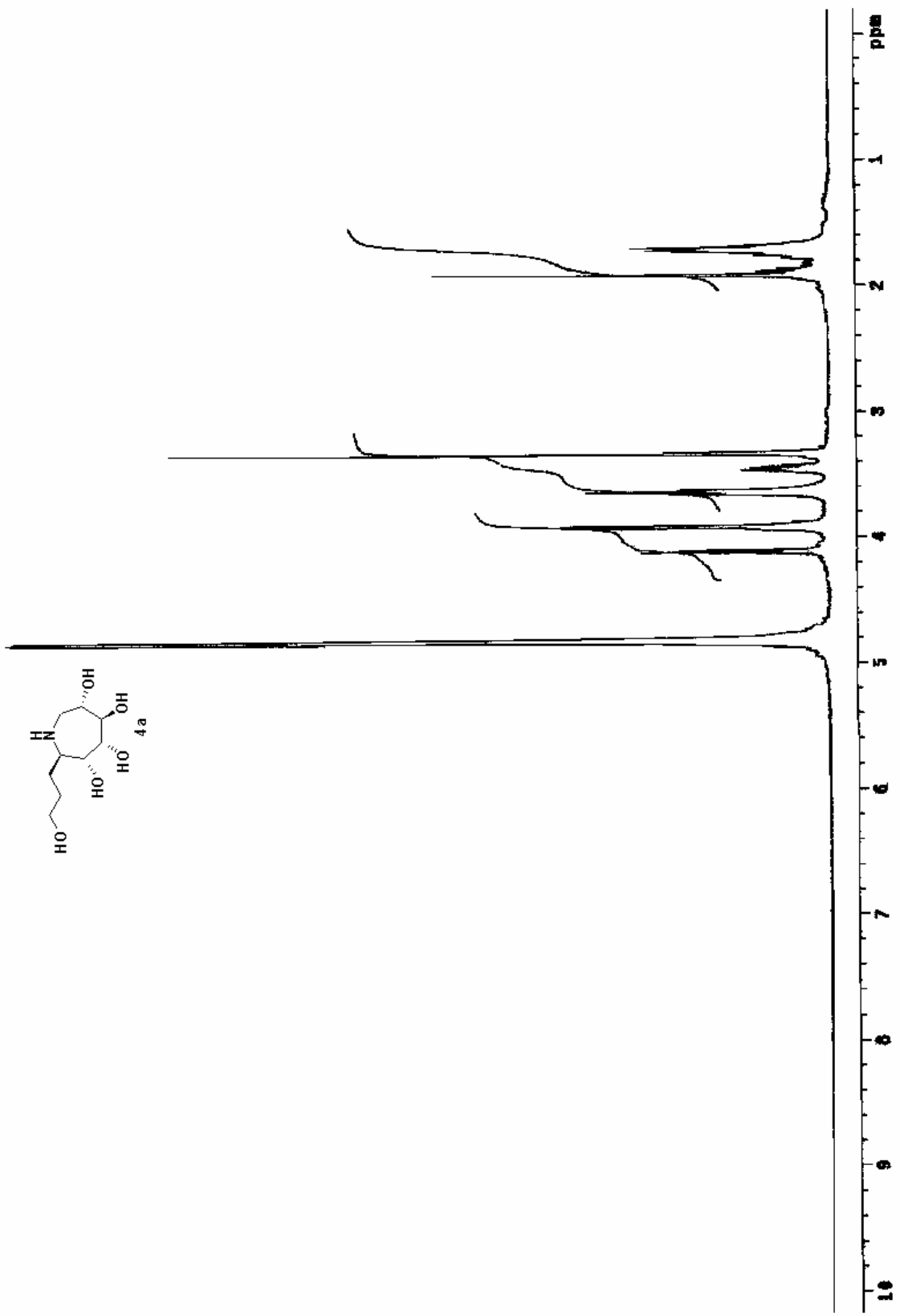

Figure 15: ^{1}H NMR (300 MHz, D_2O) spectrum of compound 4a

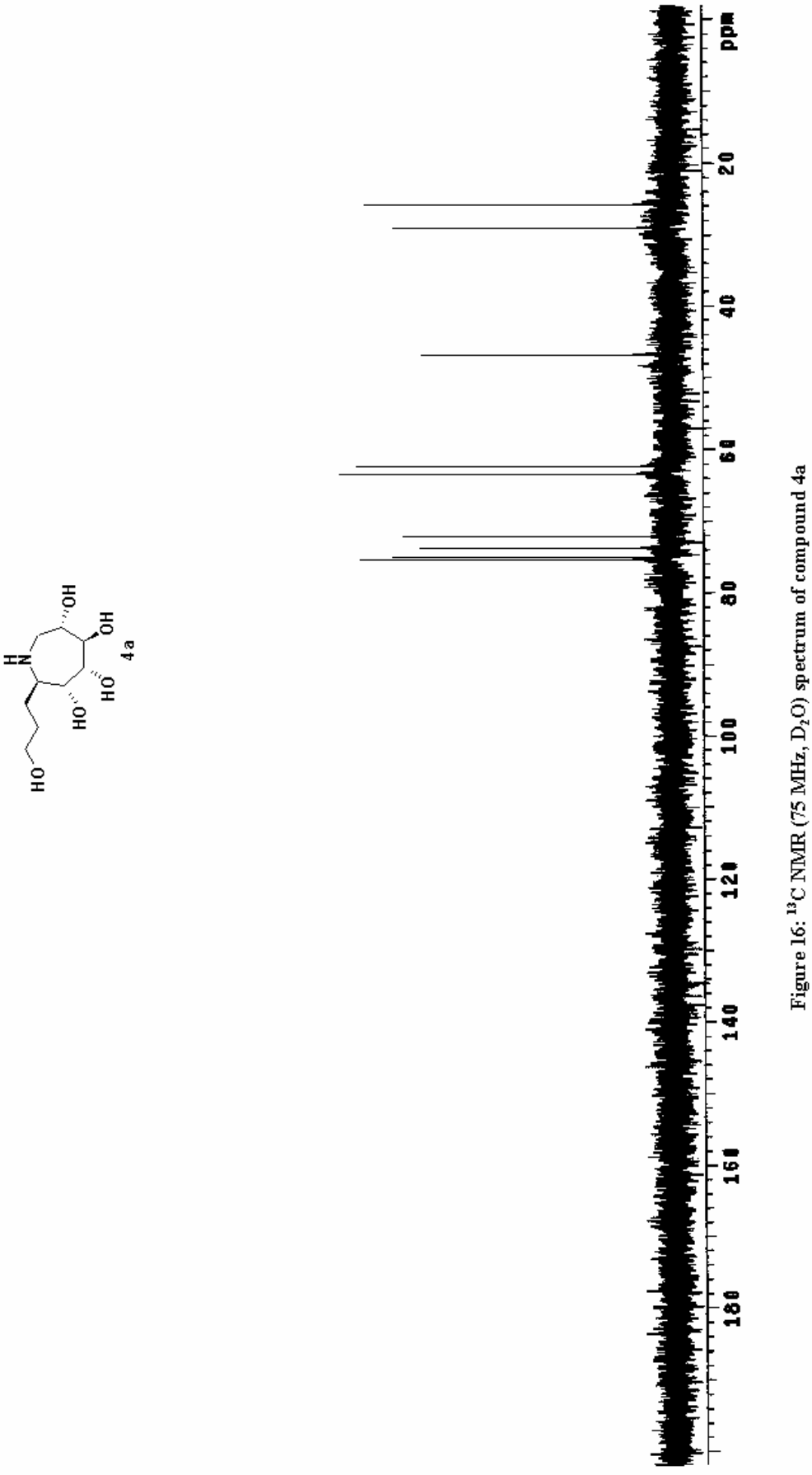

Figure 16: ^{13}C NMR (75 MHz, D_2O) spectrum of compound 4a

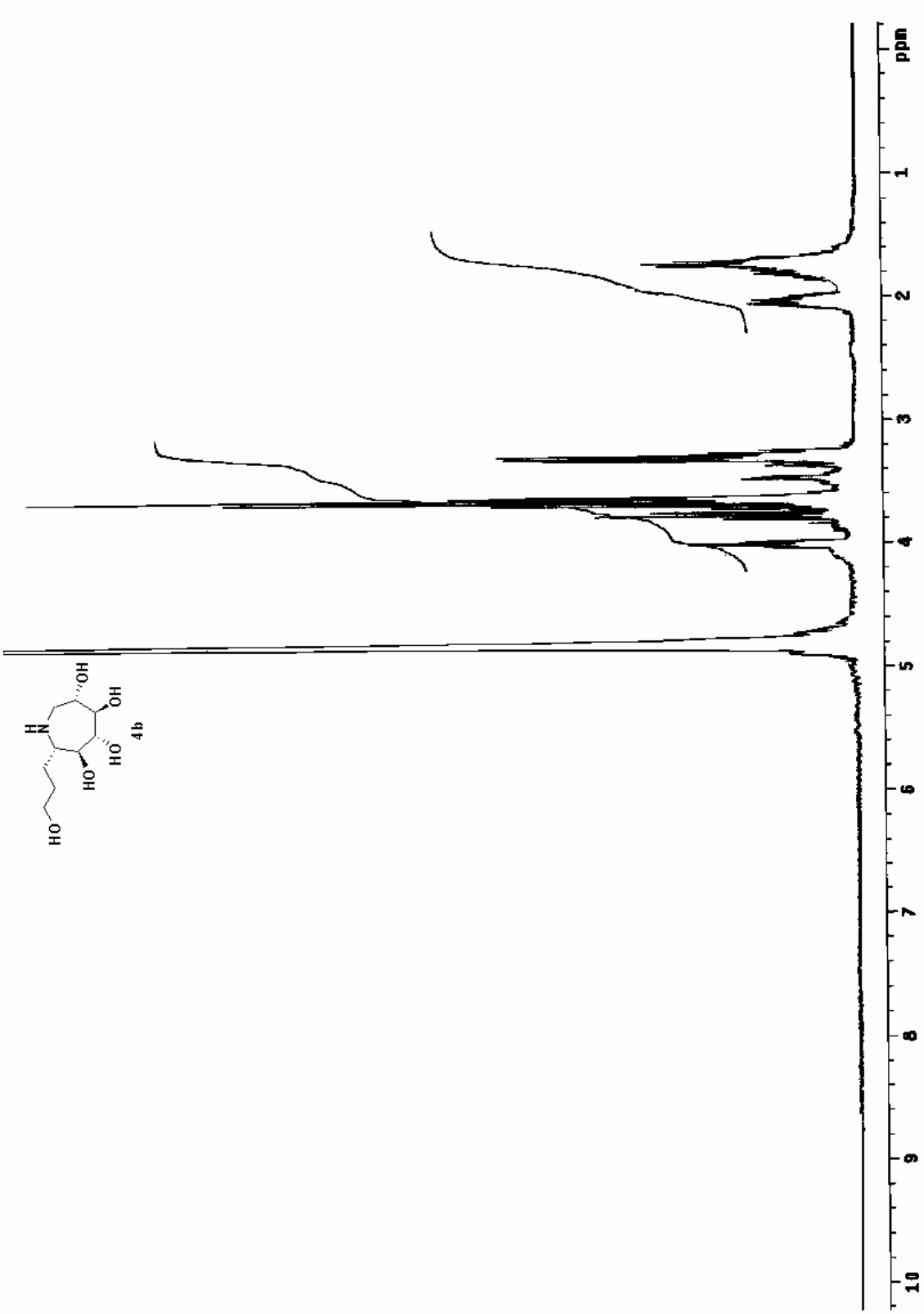

Figure 17: ^{1}H NMR (300 MHz, D_2O) spectrum of compound 4b

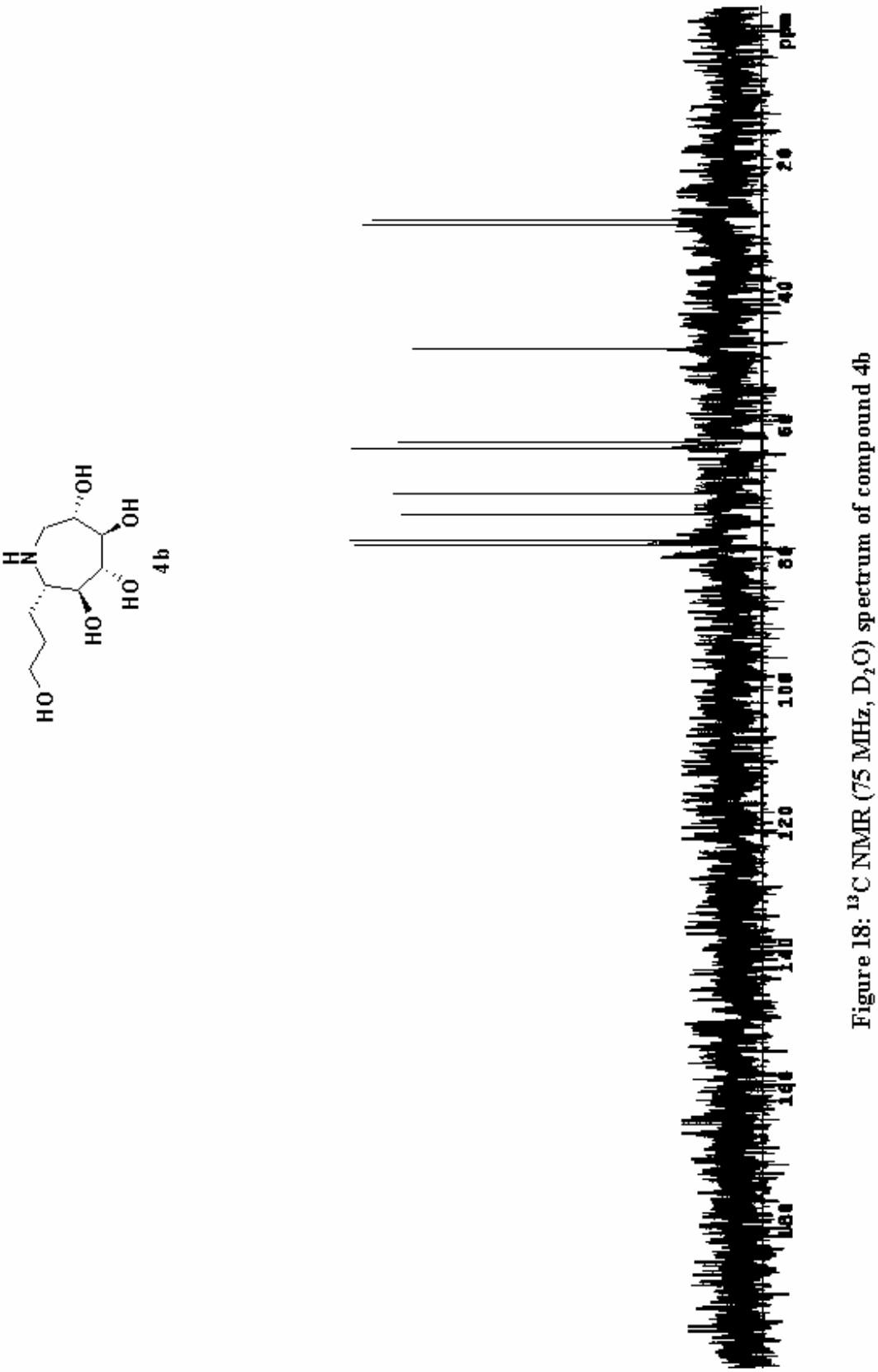

Figure 18: ^{13}C NMR (75 MHz, D_2O) spectrum of compound 4b

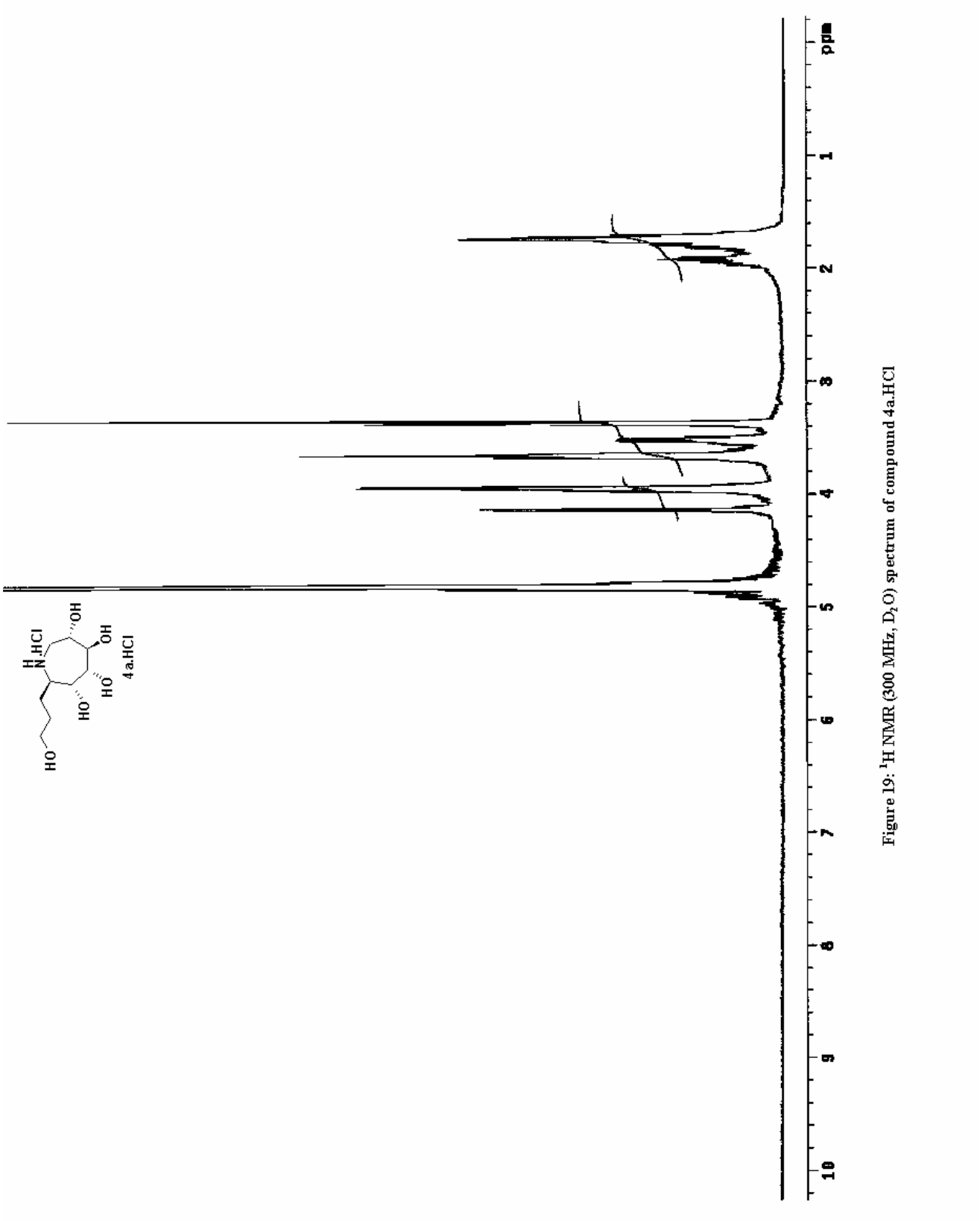

Figure 19: ^{1}H NMR (300 MHz, D_2O) spectrum of compound 4a.HCl

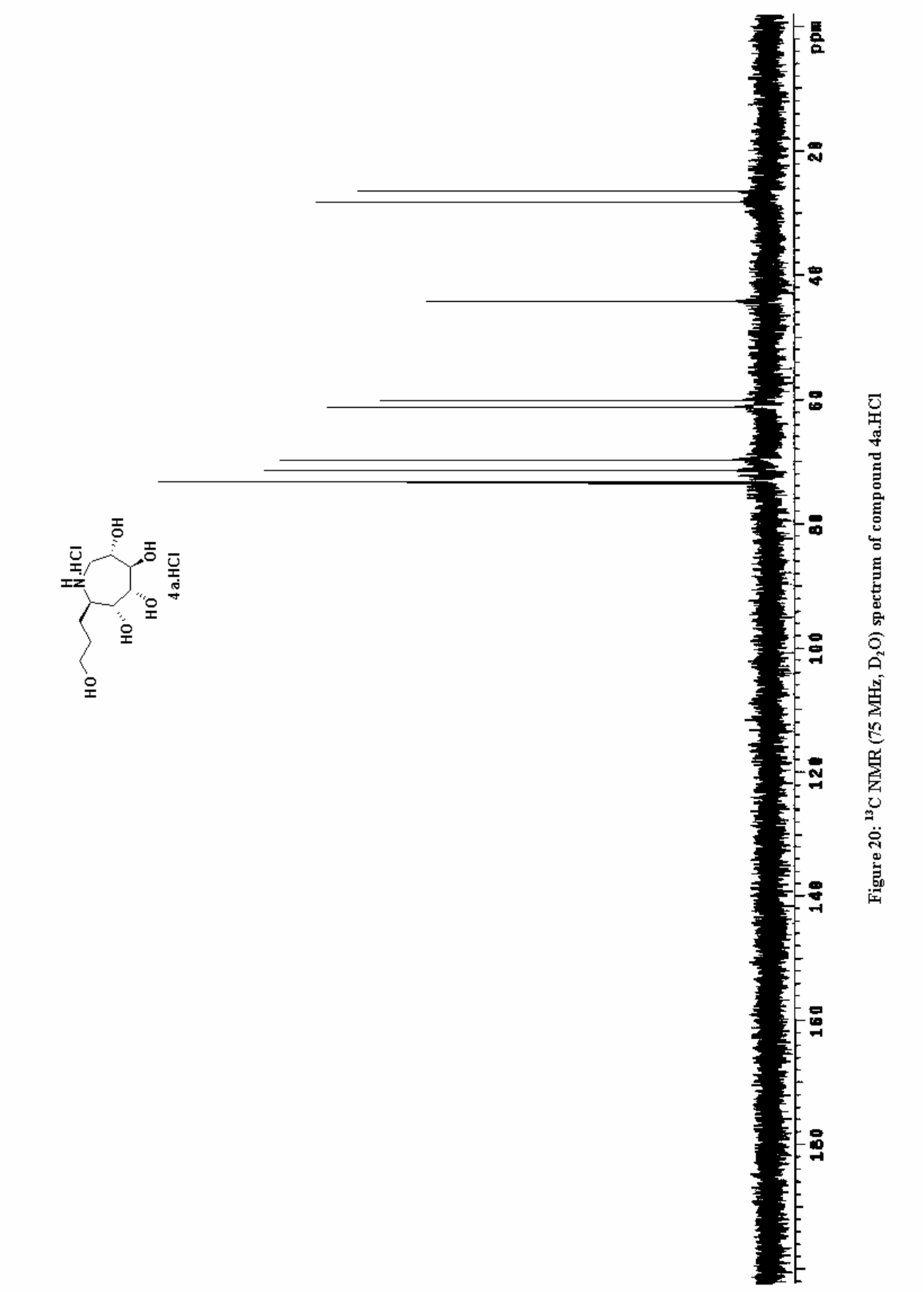

Figure 20: ^{13}C NMR (75 MHz, D_2O) spectrum of compound 4a.HCl

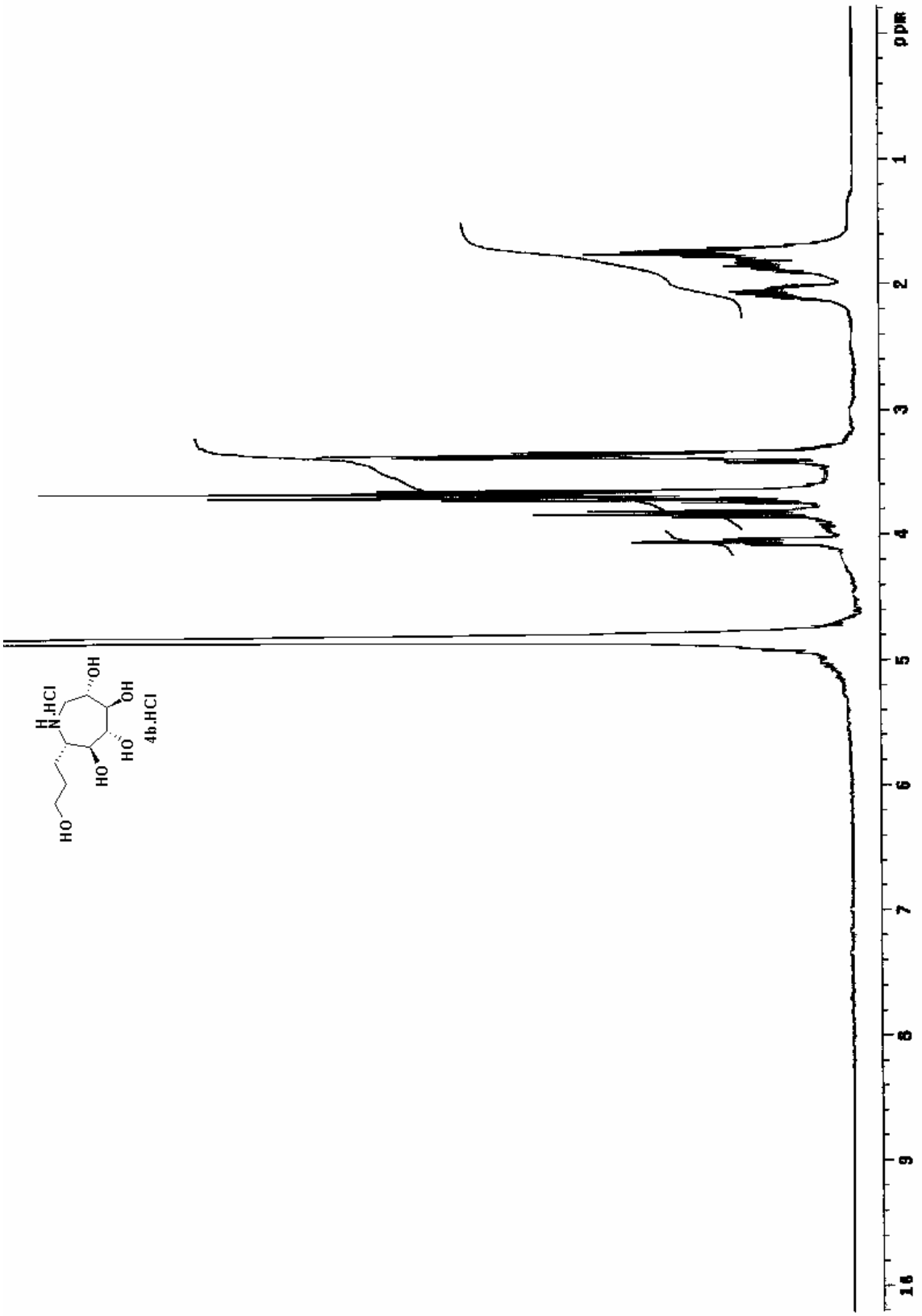

Figure 21: ^{1}H NMR (300 MHz, D_2O) spectrum of compound 4b.HCl

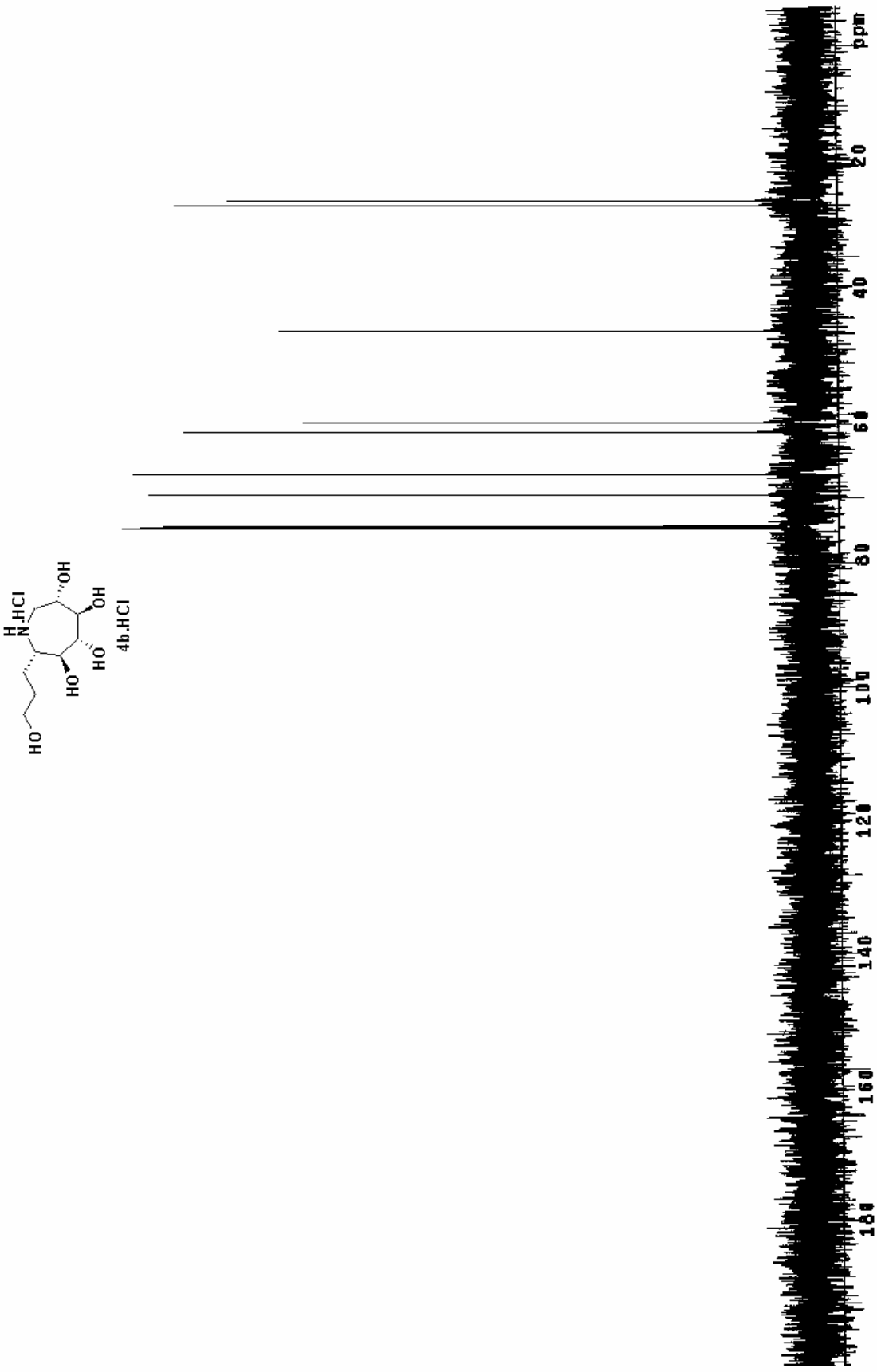

Figure 22: ^{13}C NMR (75 MHz, D_2O) spectrum of compound 4b.HCl

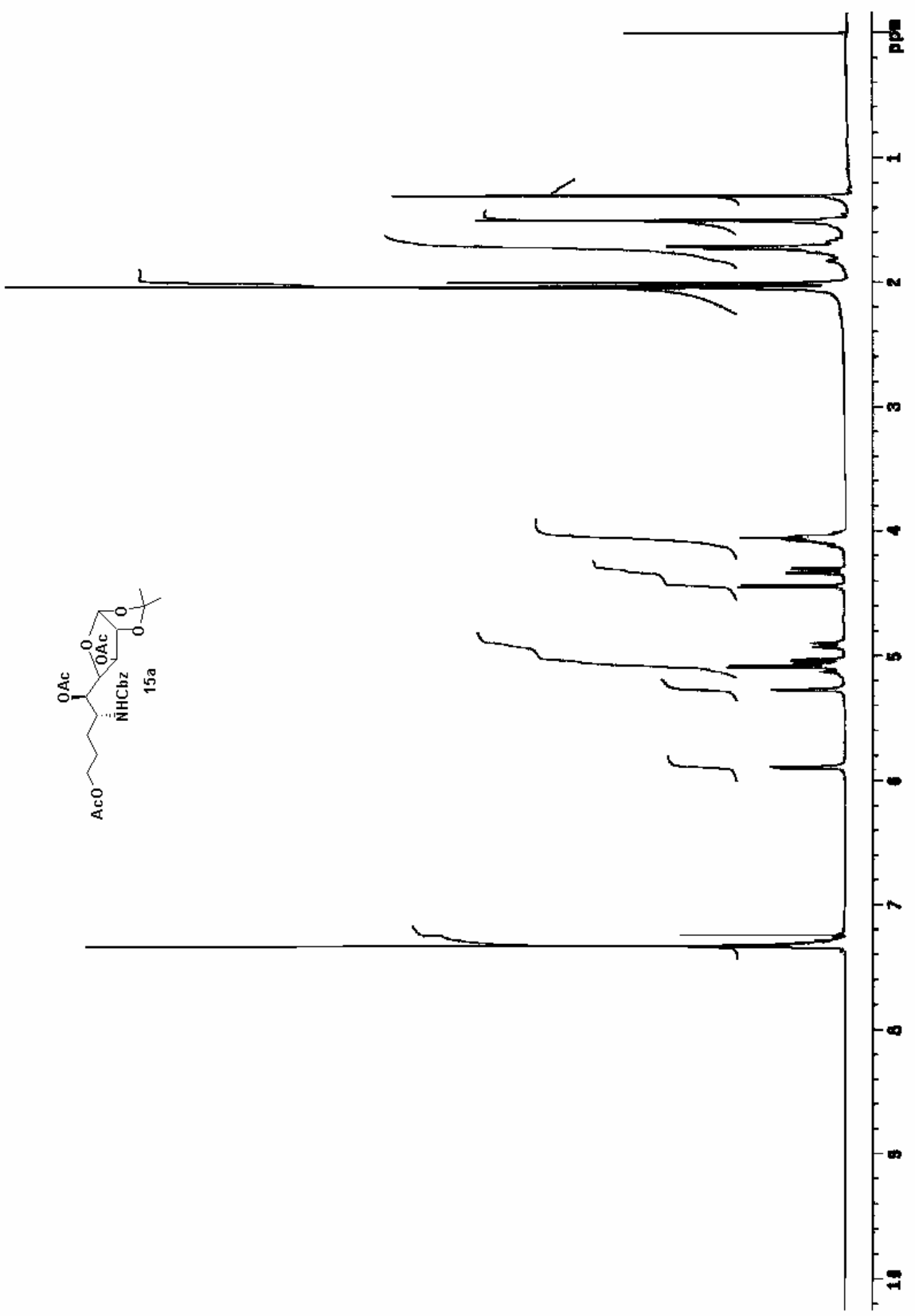

Figure 23: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 15a

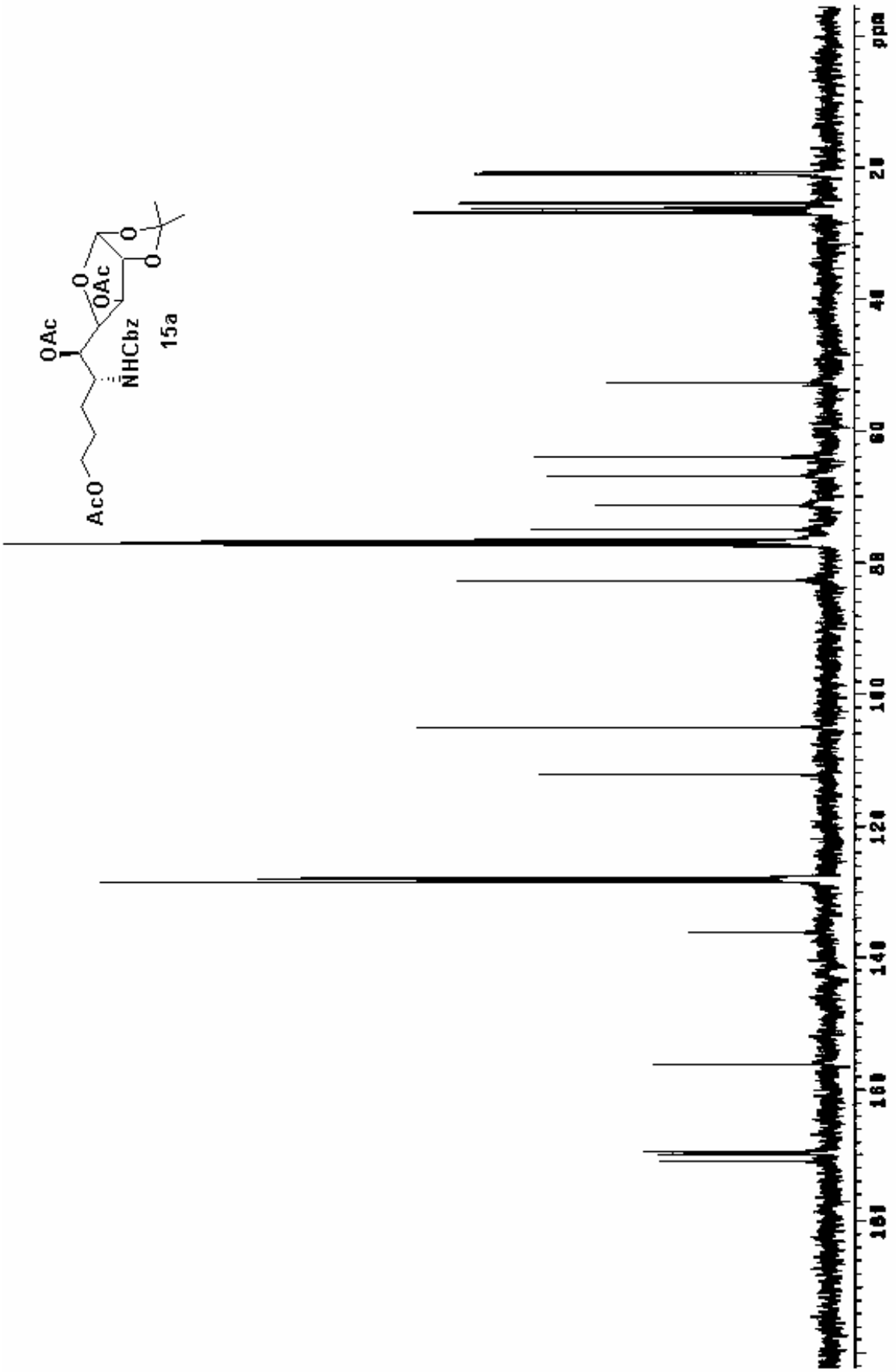

Figure 24: ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 15a

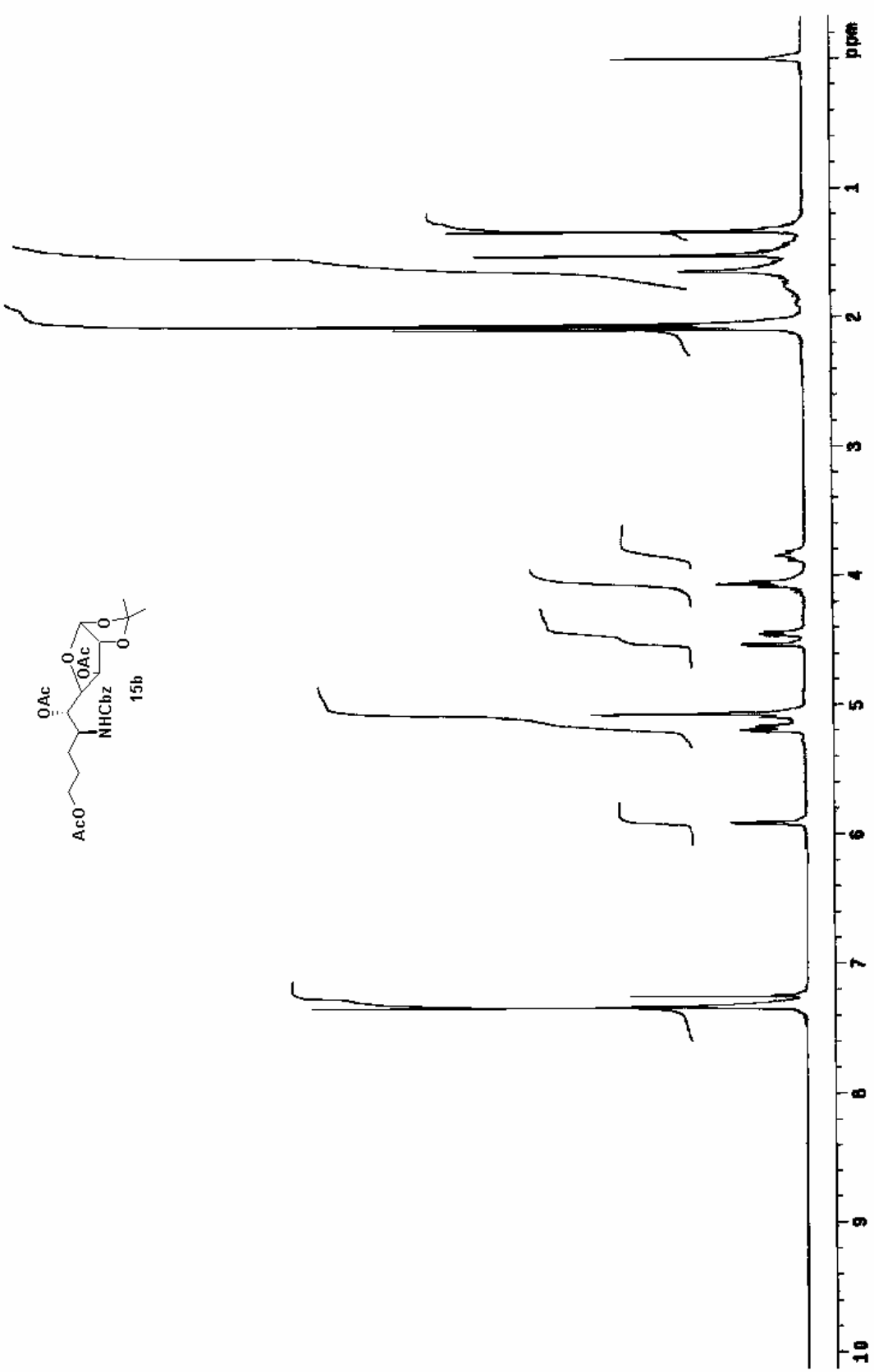

Figure 25: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound 15b

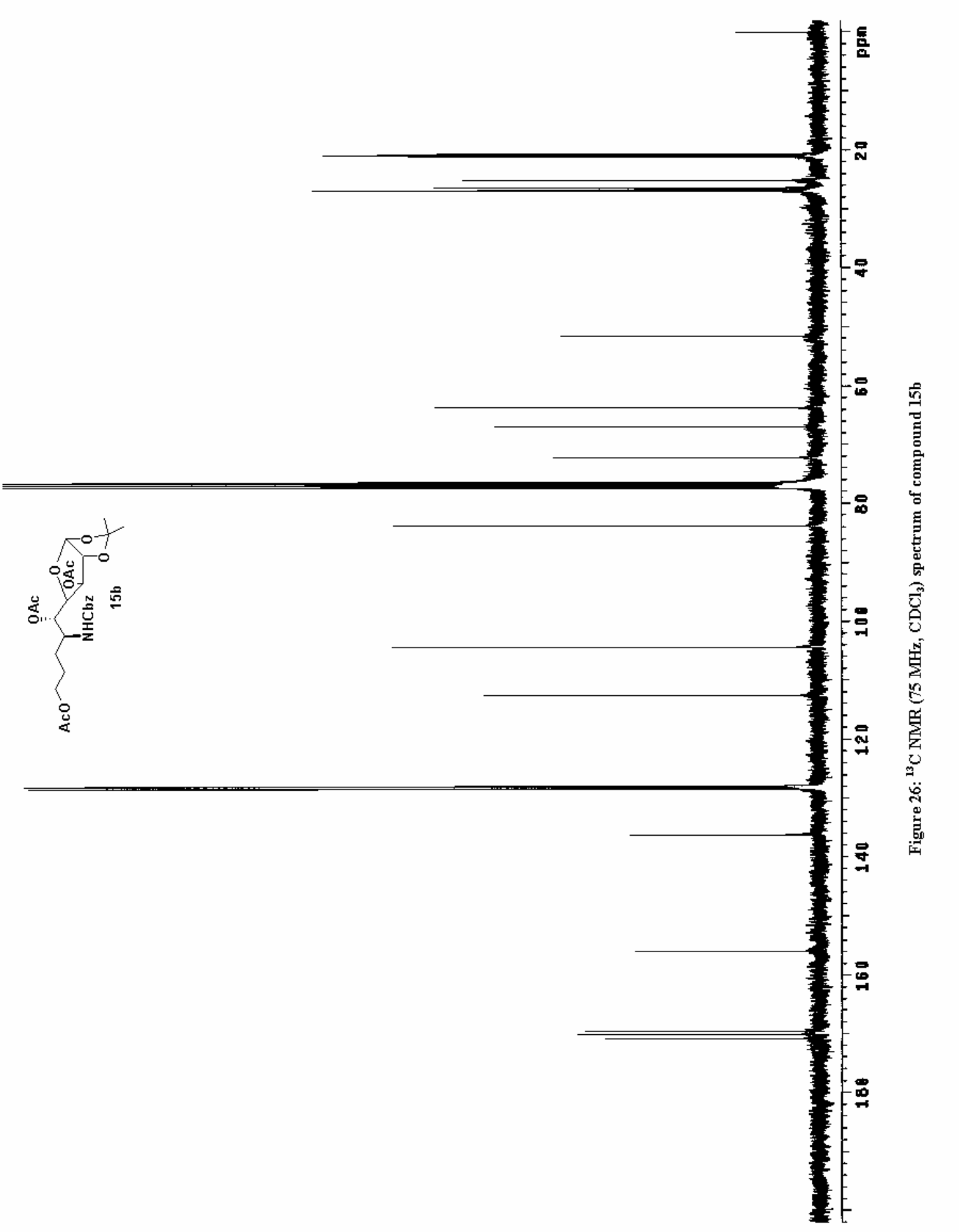

Figure 26: ^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound 15b

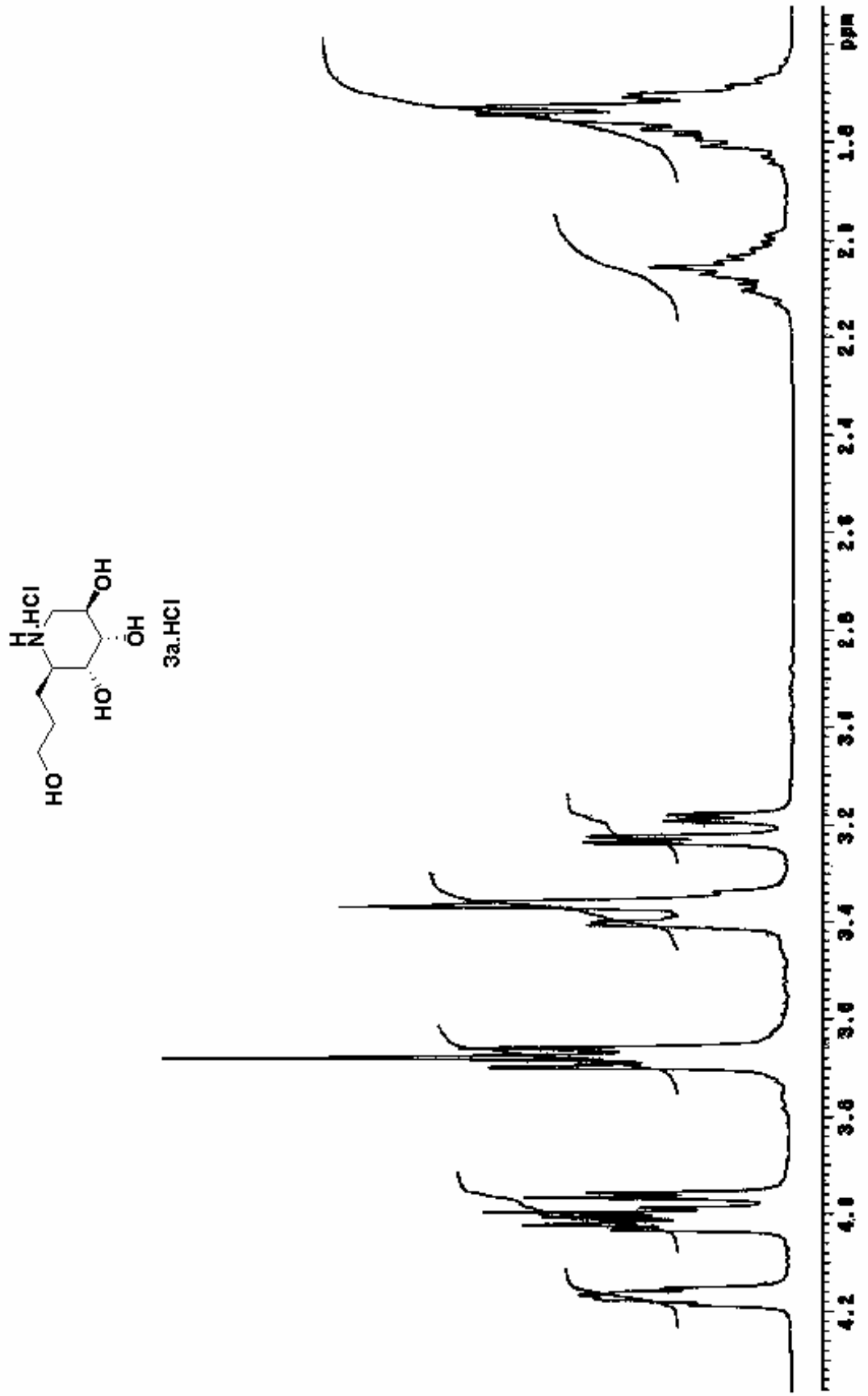

Figure 27: ^{1}H NMR (300 MHz, D_2O) spectrum of compound 3a.HCl

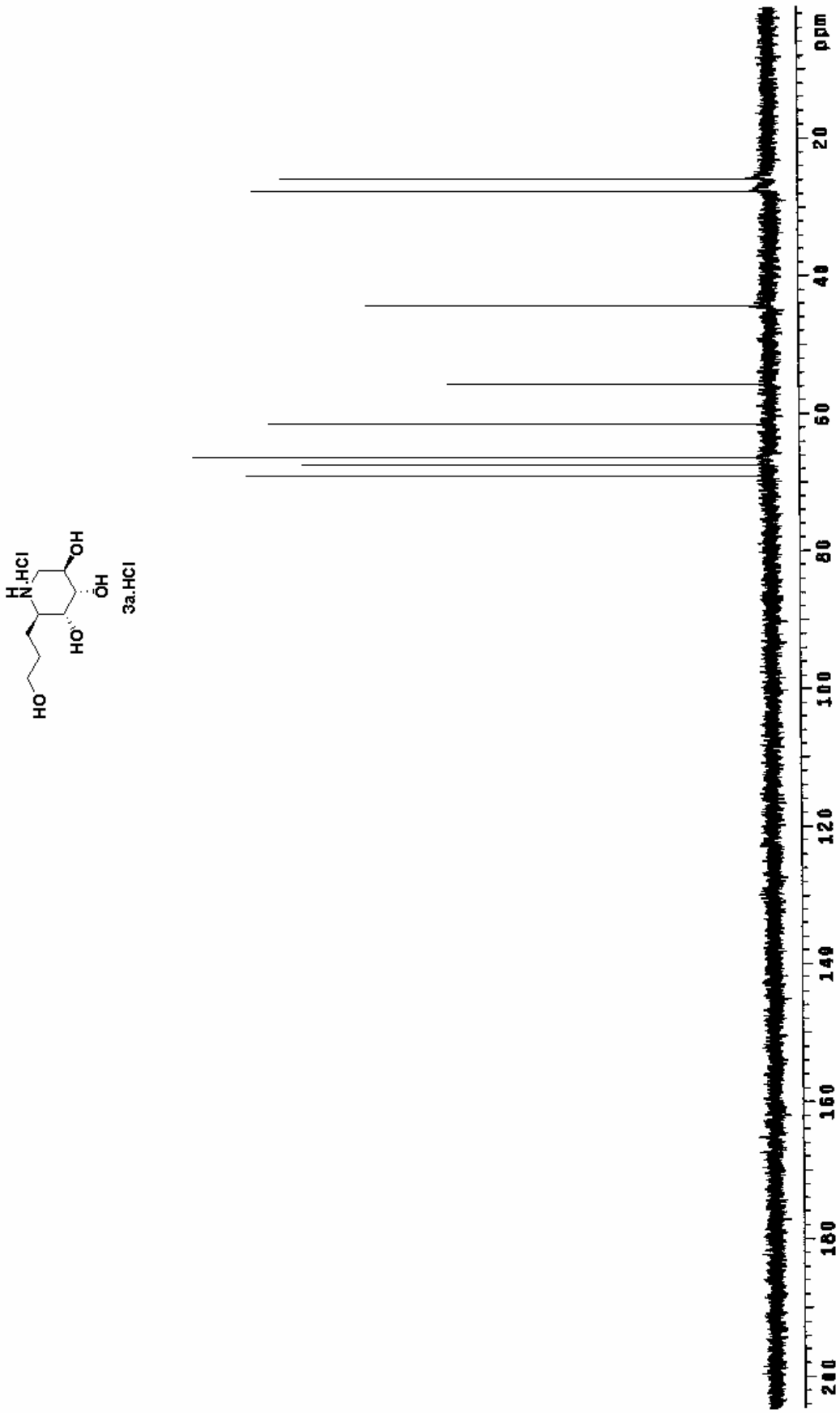

Figure 28: ^{13}C NMR (75 MHz, D_2O) spectrum of compound 3a.HCl

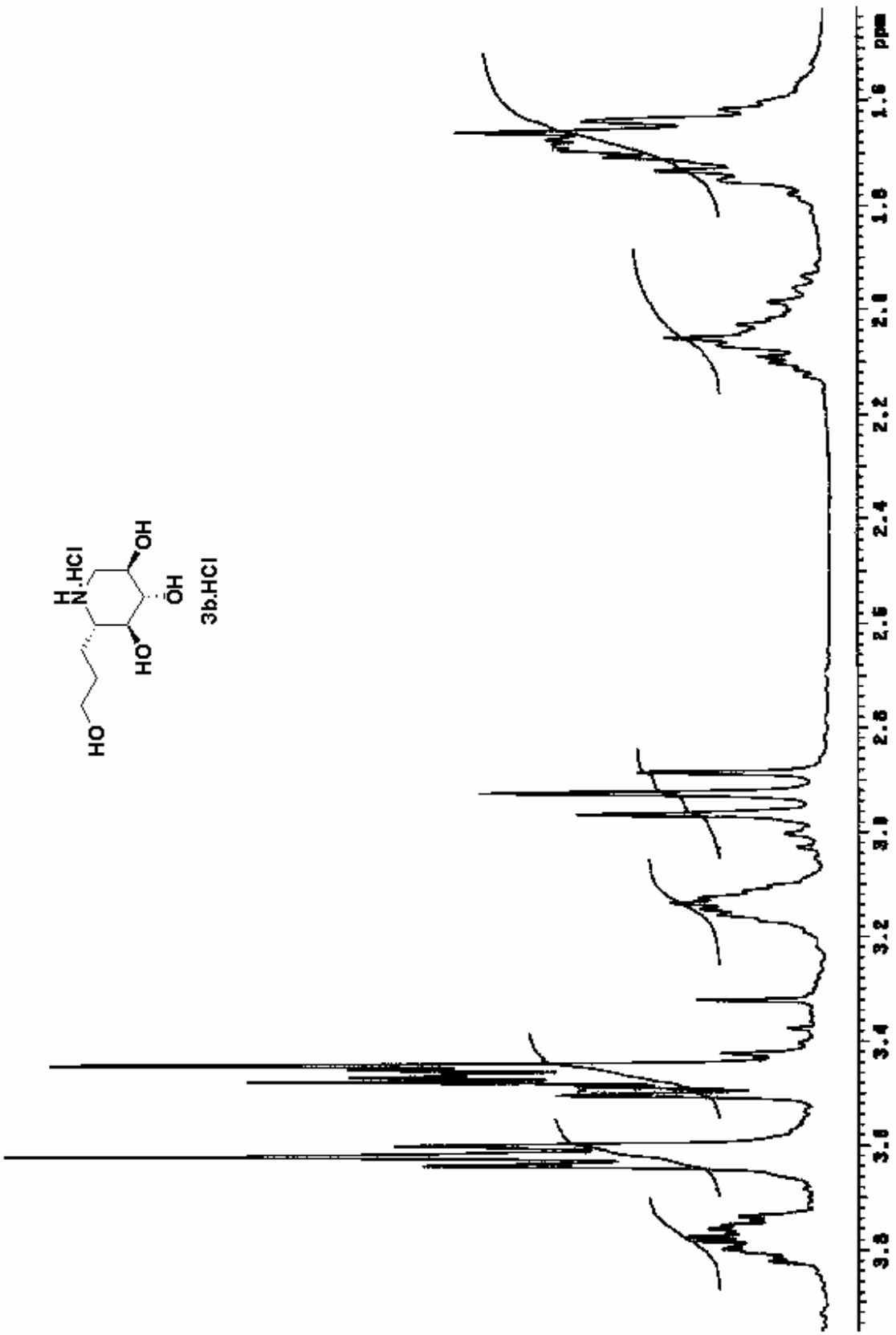

Figure 29: ^{1}H NMR (300 MHz, D_2O) spectrum of compound 3b.HCl

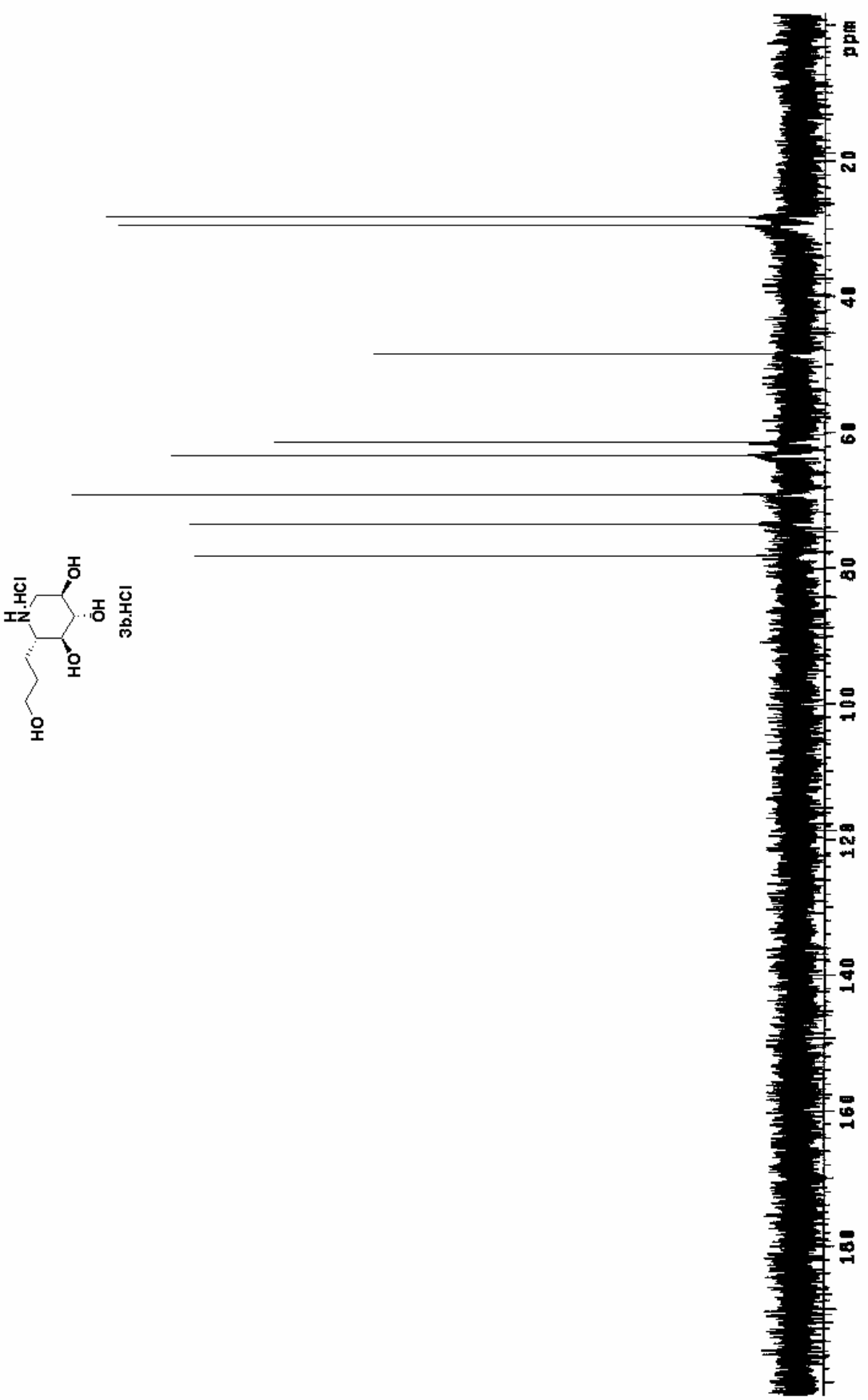

Figure 30: ^{13}C NMR (75 MHz, D_2O) spectrum of compound 3b.HCl

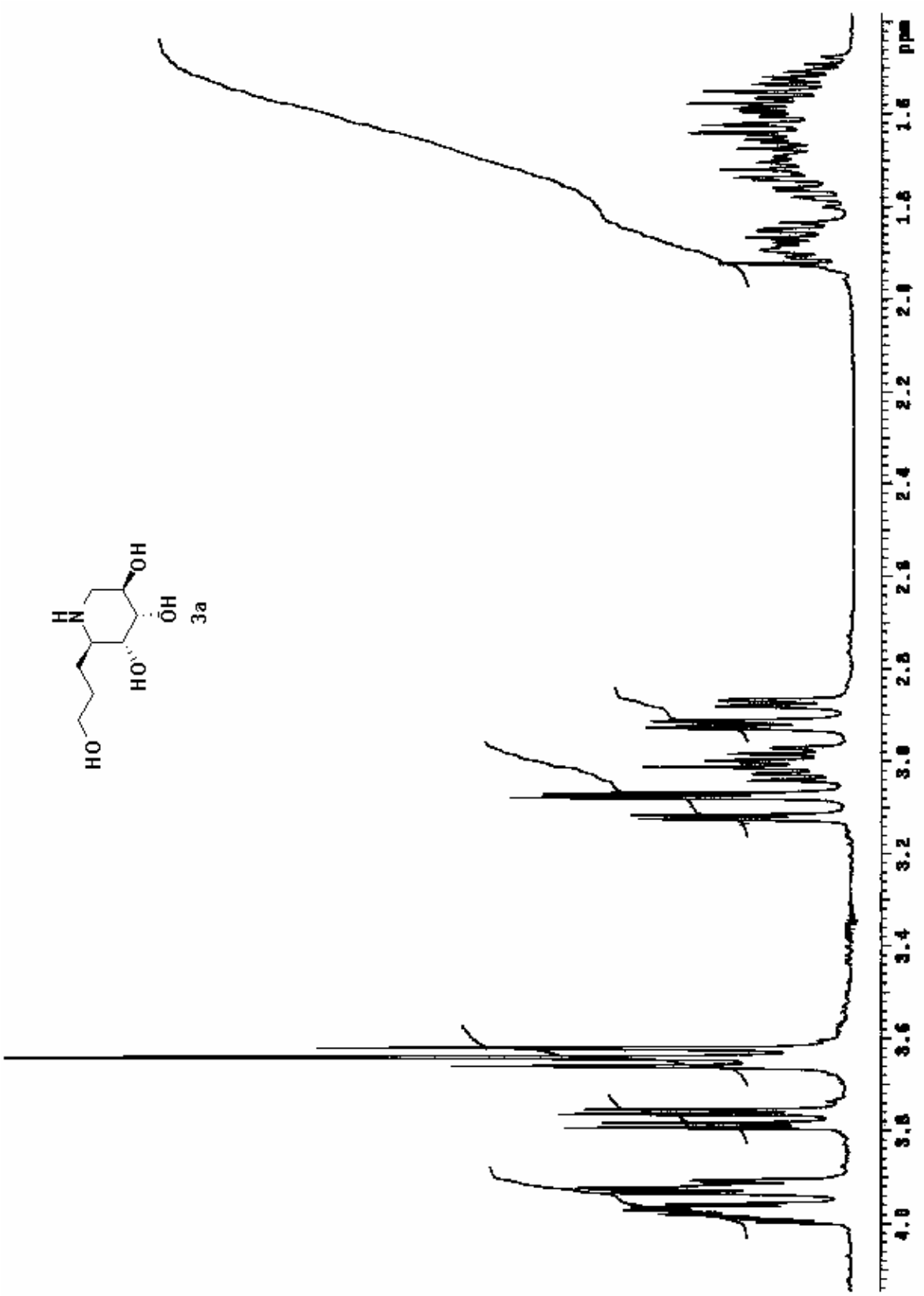

Figure 31: ^{1}H NMR (300 MHz, D_2O) spectrum of compound 3a

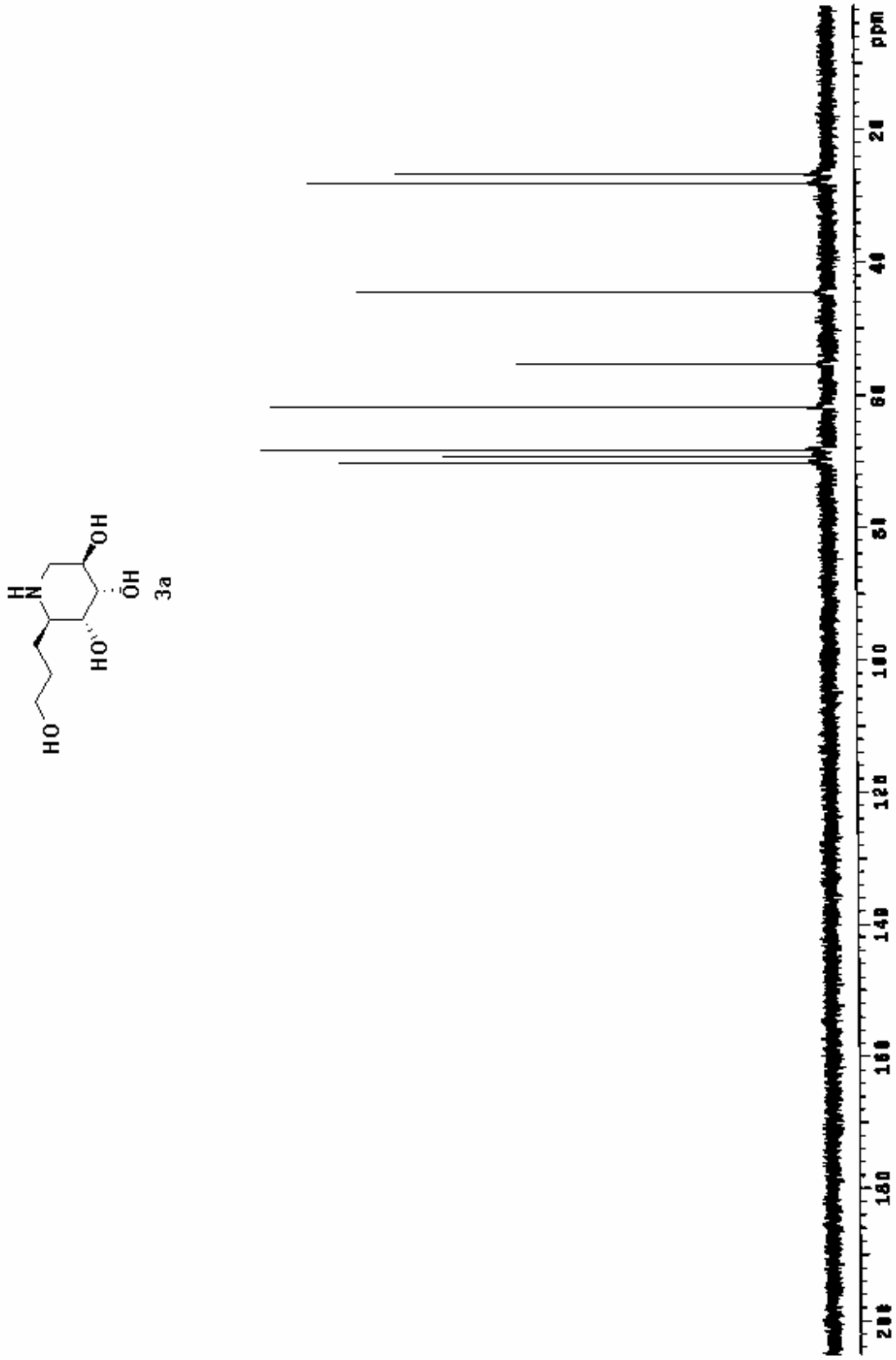

Figure 32: ^{13}C NMR (75 MHz, D_2O) spectrum of compound 3a

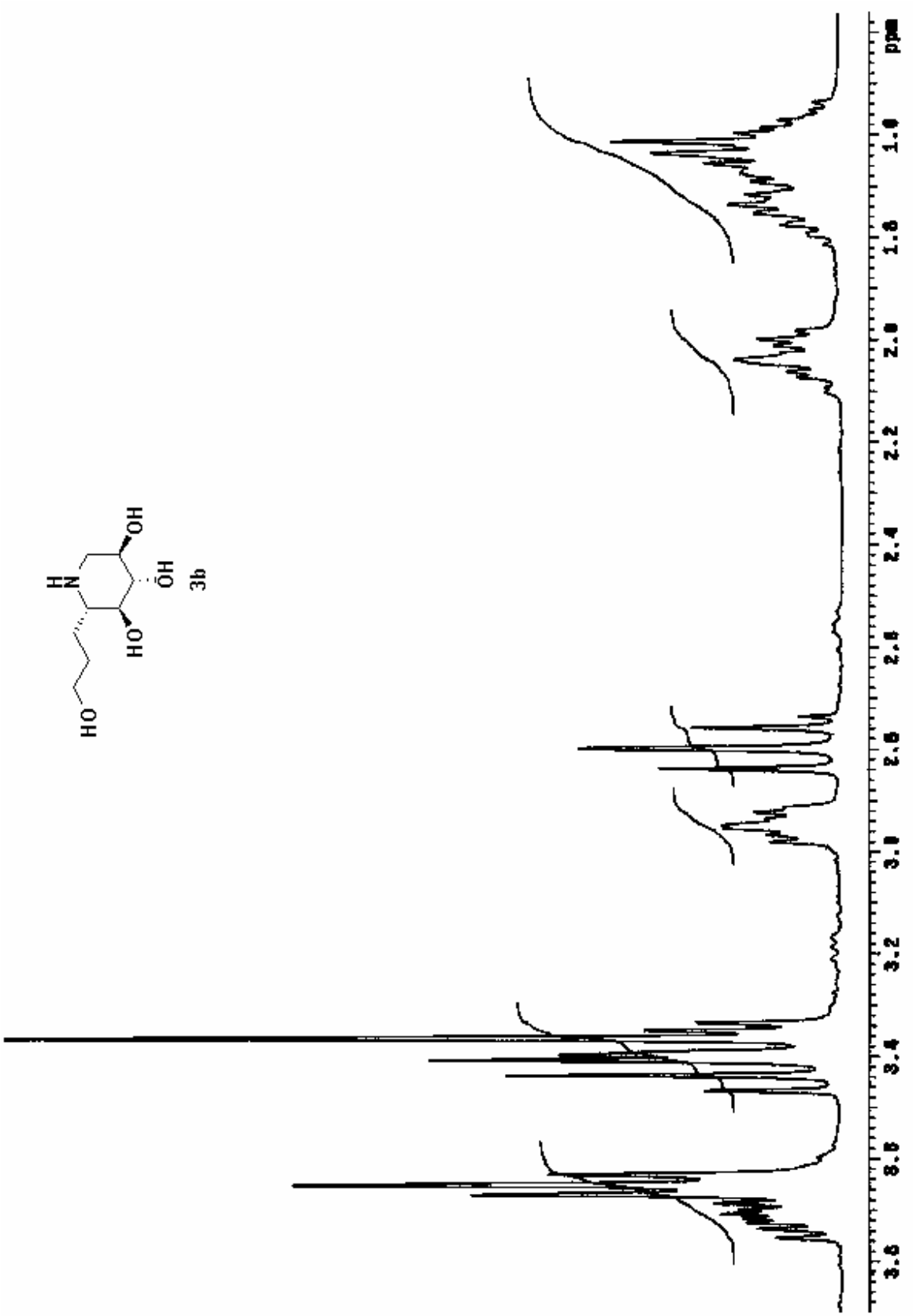

Figure 33: ^{1}H NMR (300 MHz, D_2O) spectrum of compound 3b

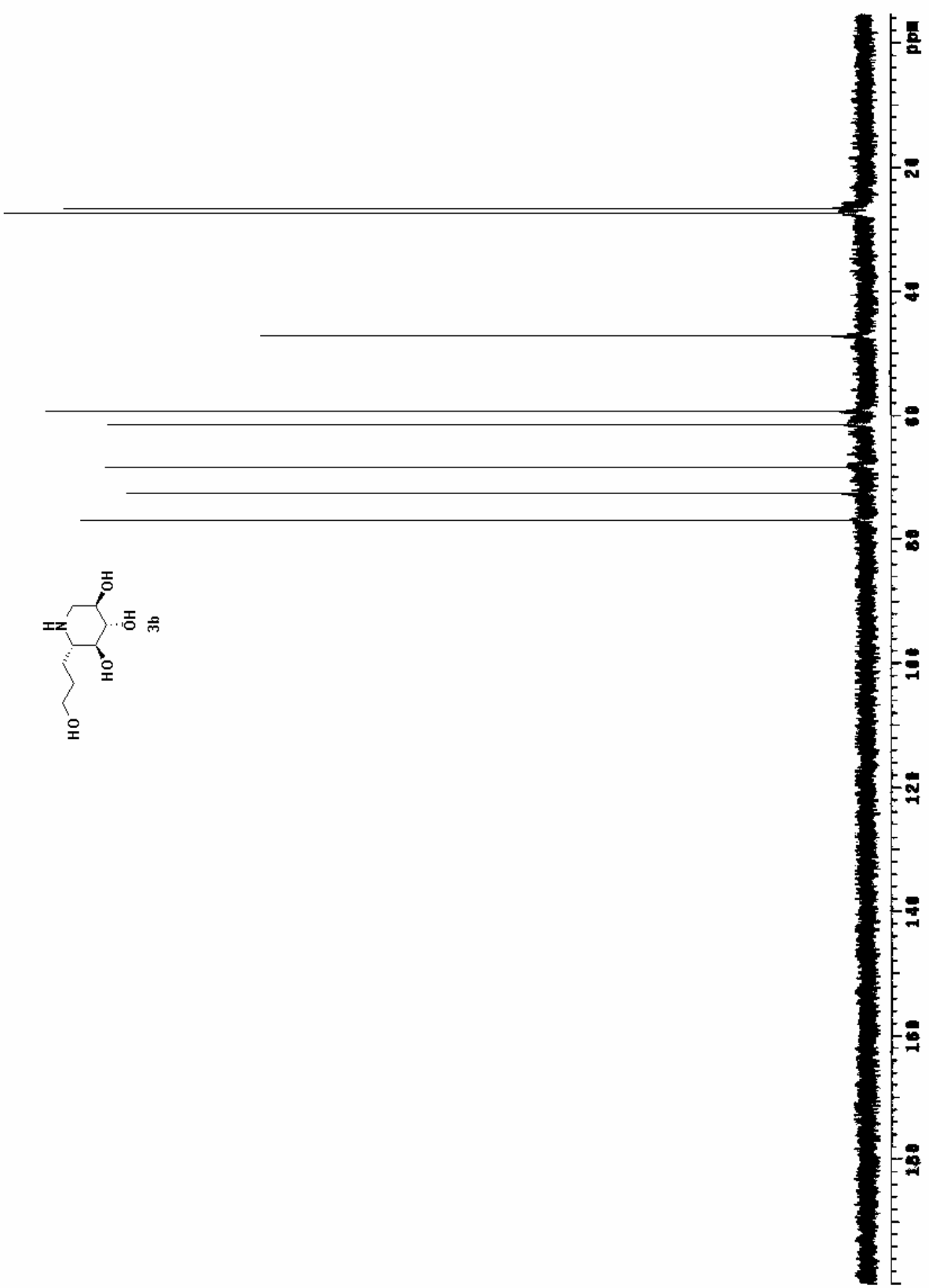

Figure 34: ^{13}C NMR (75 MHz, D_2O) spectrum of compound 3b