

ACCESSORY PUBLICATION FOR:

Synthesis and Biological Evaluation of a New Family of Constrained Azabicyclic Homocholine Analogues

Jill I. Halliday,^A Mary Chebib,^B and Malcolm D. McLeod^{C,D}

^ASchool of Chemistry, F11, University of Sydney, NSW 2006, Australia.

^BFaculty of Pharmacy, A15, University of Sydney, NSW 2006, Australia.

^CResearch School of Chemistry, Australian National University, Canberra, ACT 0200, Australia.

^DCorresponding author. Email: malcolm.mcleod@anu.edu.au

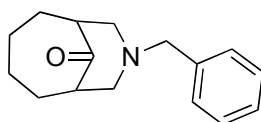
Contents

General Experimental	S2
Synthetic Procedures and Characterisation Data	S3–S18
Inhibitory Concentration (IC ₅₀) Response Curves	S19–S20
References	S21
¹ H and ¹³ C NMR Spectra	S22–S83

General Experimental

Infrared absorption spectra were obtained using a Shimadzu FTIR-84005 (Fourier Transform Infrared Spectrometer). Compounds were prepared as a thin film between 0.5 cm sodium chloride plates seated on a custom made perch in the apparatus. Absorption maxima (ν_{\max}) are expressed in wavenumbers (cm^{-1}). ^1H Nuclear magnetic resonance spectra were recorded using a Bruker Avance 200 (200.13 MHz), Bruker Avance 300 (300.13 MHz), Bruker DRX 400 (400.21 MHz) spectrometer or a Varian Gemini 300 and Varian Mercury 300 (300.06 MHz), and are recorded in parts per million (ppm) downfield shift from tetramethylsilane ($\delta_{\text{TMS}} = 0$), using residual chloroform solvent (δ 7.26) as internal reference. The data is reported as chemical shift (δ_{H}), relative integral, multiplicity (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, sext. = sextet, sept. = septet, m = multiplet), coupling constant (J Hz) and assignment. ^{13}C Nuclear magnetic resonance spectra were recorded using a Bruker Avance 300 (75.5 MHz), Bruker DRX 400 (100.6 MHz) or a Varian Gemini 300 and Varian Mercury 300 (75.5 MHz) spectrometer at ambient temperature with complete proton decoupling. Data is expressed in parts per million (ppm) downfield relative to tetramethylsilane ($\delta_{\text{TMS}} = 0$) using deuterated chloroform (δ 77.1) as an internal reference and is reported as chemical shift (δ_{C}). Low resolution mass spectra were recorded using positive ion electrospray ionization (ESI+) on a Finnigan PolarisQ ion trap or Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer or by electron ionisation (EI) on a VG AutoSpec M series sector mass spectrometer. Major fragments are quoted in the form x (y), where x is the mass to charge ratio (m/z) and y is the percentage abundance relative to the base peak. High resolution mass spectra were recorded using positive ion electrospray ionization (ESI+) on Bruker Apex 4.7T FTICR-MS or by electron ionisation (EI) on a VG AutoSpec M series sector mass spectrometer. Analytical thin layer chromatography (TLC) was performed using 0.2 mm thick aluminium-backed, pre-coated silica gel plates (Merck Kieselgel 60 F254). Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh ASTM), under a positive pressure of nitrogen. Solvent compositions were mixed v/v as specified.

8-Benzyl-8-azabicyclo[4.3.1]decan-10-one 6e

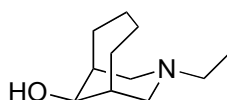


To a solution of *N,N*-bis(ethoxymethyl)benzylamine^[1,2] **5** ($R^1 = \text{Bn}$) (2.68 g, 12.0 mmol) and chlorotrimethylsilane (2.57 g, 23.7 mmol) in acetonitrile (80 mL) was added cycloheptanone (0.897 g, 8.00 mmol) and the mixture was stirred at room temperature for 48 h. The reaction was quenched by the addition of ice water (20 mL) and partitioned between diethyl ether (40 mL) and water (30 mL). The organic layer was then extracted with hydrochloric acid (0.5 M, 4 × 8 mL) and the combined aqueous extracts washed with diethyl ether (40 mL), cooled to 0 °C and the pH brought to 9 by the addition of concentrated ammonia solution (~4 mL). The organic material was then extracted with diethyl ether (3 × 50 mL) and the combined organic extracts were washed with brine (2 × 20 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to afford the *title compound* **6e** (0.647 g, 2.66 mmol, 33%) as a yellow oil. ν_{max} (NaCl)/ cm^{-1} 2916, 2851, 2802, 2766 (C–H), 1713 (C=O); ^1H NMR (300 MHz, CDCl_3) δ_{H} 7.36–7.26 (5H, m, NCH_2Ph), 3.52 (2H, s, NCH_2Ph), 2.85 (2H, d, J 11.1, H7A, H9A), 2.62 (2H, m, H1, H6), 2.44 (2H, m, H7B, H9B), 2.06 (2H, m, H2A, H5A), 1.79 (2H, m, H3A, H4A), 1.59 (2H, m, H2B, H5B), 1.42 (2H, m, H3B, H4B); ^{13}C NMR (50 MHz, CDCl_3) δ_{C} 212.5, 138.2, 128.6, 127.9, 126.8, 62.4, 59.3, 48.3, 31.0, 26.5; m/z (ESI+) 244 ($[\text{M}+\text{H}]^+$, 100); HRMS (ESI+) found 244.1697; $\text{C}_{16}\text{H}_{22}\text{NO}$ ($[\text{M}+\text{H}]^+$) requires 244.1701.

General Procedure for Sodium Borohydride Reduction

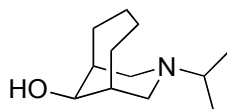
Sodium borohydride (2 eq) was added to a stirred solution of ketone (1 eq) in ethanol/water (4:1) at 0 °C, and the reaction stirred for 2 h. Concentrated hydrochloric acid was added dropwise to quench the excess sodium borohydride and the mixture concentrated under reduced pressure to remove ethanol. The aqueous solution was made basic (pH 10) by the addition of aqueous sodium hydroxide (3 M) and the organic material extracted by diethyl ether (3 ×). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give the crude alcohol. Purification by flash chromatography (ethyl acetate:hexane) then afforded the target compound.

(10s)-8-Ethyl-8-azabicyclo[4.3.1]decan-10-ol **7a**



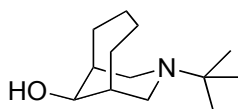
The reaction was conducted according to the general procedure using 8-ethyl-8-azabicyclo[4.3.1]decan-10-one^[3] **6a** (1.06 g, 5.85 mmol), sodium borohydride (0.441 g, 11.7 mmol) and ethanol/water (125 mL) to afford the *title compound* **7a** (0.867 g, 4.73 mmol, 81%) as a colourless solid after flash chromatography (1:4, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 3393 (O–H), 2967, 2904, 2755 (C–H); ^1H NMR (300 MHz, CD_3OD) δ_{H} 3.88 (1H, t, J 5.4, H10), 2.71 (2H, d, J 10.9, H7A, H9A), 2.25 (2H, q, J 7.2, NCH_2CH_3), 2.07–1.86 (8H, m, H1, H2A, H3A, H4A, H5A, H6, H7B, H9B), 1.68 (2H, m, H2B, H5B), 1.53 (2H, m, H3B, H4B), 1.04 (3H, t, J 7.2, NCH_2CH_3); ^{13}C NMR (50 MHz, CDCl_3) δ_{C} 76.2, 60.4, 52.4, 38.8, 31.7, 27.4, 13.0; m/z (ESI+) 184 ($[\text{M}+\text{H}]^+$, 100). Found 184.1701, $\text{C}_{11}\text{H}_{22}\text{NO}$ ($[\text{M}+\text{H}]^+$) requires 184.1693.

(10s)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-ol **7b**



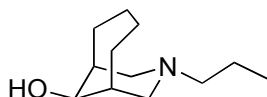
The reaction was conducted according to the general procedure using 8-isopropyl-8-azabicyclo[4.3.1]decan-10-one^[3] **6b** (1.01 g, 5.17 mmol), sodium borohydride (0.391 g, 10.3 mmol) and ethanol/water (100 mL) to afford the *title compound* **7b** (1.00 g, 5.07 mmol, 98%) as a colourless solid after flash chromatography (1:4, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 3261 (O–H), 2961, 2939, 2914, 2870, 2852 (C–H); ^1H NMR (300 MHz, CD_3OD) δ_{H} 3.83 (1H, t, J 5.4, H10), 2.69 (1H, sept. J 6.6, $\text{NCH}(\text{CH}_3)_2$), 2.63 (2H, dd, J 11.1, 2.2, H7A, H9A), 2.31 (2H, dd, J 11.3, 2.8, H7B, H9B), 2.06 (2H, m, H1, H6), 1.97–1.85 (4H, m, H2A, H3A, H4A, H5A), 1.68 (2H, m, H2B, H5B), 1.50 (2H, m, H3B, H4B), 0.98 (6H, d, J 6.6, $\text{NCH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CD_3OD) δ_{C} 76.8, 56.4, 55.4, 39.8, 32.7, 28.1, 18.3; m/z (ESI+) 198 ($[\text{M}+\text{H}]^+$, 100). Found 198.1858, $\text{C}_{12}\text{H}_{24}\text{NO}$ ($[\text{M}+\text{H}]^+$) requires 198.1852.

(10s)-8-tert-Butyl-8-azabicyclo[4.3.1]decan-10-ol **7c**^[3]



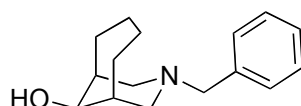
The reaction was conducted according to the general procedure using 8-*tert*-butyl-8-azabicyclo[4.3.1]decan-10-one^[3] **6c** (1.00 g, 4.78 mmol), sodium borohydride (0.724 g, 19.2 mmol) and methanol/water (50 mL) to afford the *title compound 7c* (0.613 g, 2.90 mmol, 61%) as a colourless solid after flash chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/cm⁻¹ 3273 (O–H), 2961, 2910, 2851, 2795, 2739 (C–H); ¹H NMR (300 MHz, CD₃OD) δ_{H} 3.83 (1H, t, *J* 5.5, H10), 2.88 (2H, dd *J* 8.6, 2.4, H7A, H9A), 2.19 (2H, dd, *J* 11.3, 2.6, H7B, H9B), 2.06 (2H, m, H1, H6), 1.99–1.85 (4H, m, H2A, H3A, H4A, H5A), 1.70 (2H, m, H2B, H5B), 1.50 (2H, m, H3B, H4B), 1.05 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CD₃OD) δ_{C} 76.9, 53.8 (2C), 39.9, 32.6, 28.2, 26.7; *m/z* (ESI+) 212 ([M+H]⁺, 100), 156 (17). Found 212.2009, C₁₃H₂₆NO ([M+H]⁺) requires 212.2009.

(10*s*)-8-Propyl-8-azabicyclo[4.3.1]decan-10-ol **7d**



The reaction was conducted according to the general procedure using 8-propyl-8-azabicyclo[4.3.1]decan-10-one^[3] **6d** (0.225 g, 1.15 mmol), sodium borohydride (0.0870 g, 2.30 mmol) and ethanol/water (15 mL) to afford the *title compound 7d* (0.192 g, 0.973 mmol, 85%) as a colourless solid after flash chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/cm⁻¹ 3366 (O–H), 2964, 2935, 2878 (C–H); ¹H NMR (300 MHz, CD₃OD) δ_{H} 3.89 (1H, t, *J* 5.4, H10), 2.71 (2H, d *J* 10.9, H7A, H9A), 2.17 (2H, t, *J* 7.0, NCH₂CH₂CH₃), 2.08 (2H, m, H1, H6), 2.02 (2H, dd, *J* 11.5, 3.0, H7B, H9B), 2.06–1.88 (4H, m, H2A, H3A, H4A, H5A), 1.72 (2H, m, H2B, H5B), 1.58–1.45 (2H, m, H3B, H4B), 1.49 (2H, sext., *J* 7.2, NCH₂CH₂CH₃), 0.94 (3H, t, *J* 7.4, NCH₂CH₂CH₃); ¹³C NMR (75 MHz, CD₃OD) δ_{C} 76.3, 61.8, 61.6, 39.8, 32.6, 28.0, 21.5, 12.5; *m/z* (ESI+) 198 ([M+H]⁺, 100). Found 198.1854, C₁₂H₂₄NO ([M+H]⁺) requires 198.1858.

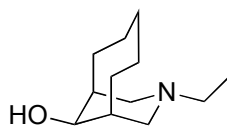
(10*s*)-8-Benzyl-8-azabicyclo[4.3.1]decan-10-ol **7e**



The reaction was conducted according to the general procedure using ketone **6e** (0.470 g, 1.93 mmol), sodium borohydride (0.146 g, 3.87 mmol) and ethanol/water (40 mL) to afford the *title compound 7e* (0.455 g, 1.85 mmol, 96%) as a colourless solid after flash chromatography (1:9, ethyl

acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 3339 (O–H), 2945, 2907, 2870, 2853, 2806 (C–H); ^1H NMR (200 MHz, CD_3OD) δ_{H} 7.31–7.20 (5H, m, $\text{NCH}_2\text{C}_6\text{H}_6$), 3.91 (1H, t, J 4.9, H10), 3.36 (2H, s, $\text{NCH}_2\text{C}_6\text{H}_6$), 2.67 (2H, d, J 10.6, H7A, H9A), 2.10–1.88 (8H, m, H1, H2A, H3A, H4A, H5A, H6, H7B, H9B), 1.75 (2H, m, H2B, H5B), 1.49 (2H, m, H3B, H4B); ^{13}C NMR (50 MHz, CD_3OD) δ_{C} 168.7, 158.2, 157.3, 156.0, 104.3, 92.6, 89.6, 67.9, 60.5, 56.2; m/z (ESI+) 246 ($[\text{M}+\text{H}]^+$, 100). Found 246.1851, $\text{C}_{16}\text{H}_{24}\text{NO}$ ($[\text{M}+\text{H}]^+$) requires 246.1858.

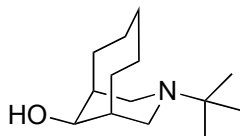
(11s)-9-Ethyl-9-azabicyclo[5.3.1]undecan-11-ol **7f**



The reaction was conducted according to the general procedure using 9-ethyl-9-azabicyclo[5.3.1]undecan-11-one^[3] **6f** (0.958 g, 4.90 mmol), sodium borohydride (0.371 g, 9.80 mmol) and ethanol/water (100 mL) to afford a mixture of epimers (1:4.2, 11r:11s) which was separated to give the *title compound* **7f** (0.492 g, 2.49 mmol, 51%) as a colourless oil after flash chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 3369 (O–H), 2966, 2933, 2908, 2847, 2799, 2762 (C–H); ^1H NMR (300 MHz, CD_3OD) δ_{H} 3.83 (1H, t, J 5.9, H11), 2.81 (2H, d, J 11.3, H8A, H10A), 2.31 (2H, q, J 7.2, NCH_2CH_3), 2.05 (2H, dd, J 11.7, 3.8, H8B, H10B), 1.95–1.88 (6H, m, H1, H2A, H3A, H5A, H6A, H7), 1.72–1.69 (5H, m, H2B, H3B, H4A, H5B, H6B), 1.34 (1H, m, H4B), 1.07 (3H, t, J 7.2, NCH_2CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ_{C} 58.2, 53.3, 38.7, 33.5, 30.6, 25.6, 12.8, 6.7; m/z (ESI+) 198 ($[\text{M}+\text{H}]^+$, 100). Found 198.1845, $\text{C}_{12}\text{H}_{24}\text{NO}$ ($[\text{M}+\text{H}]^+$) requires 198.1858.

A second fraction afforded the (11r) isomer (31.3 mg, 0.159 mmol, 3%) which was not investigated further.

(11s)-9-tert-Butyl-9-azabicyclo[5.3.1]undecan-11-ol **7g**

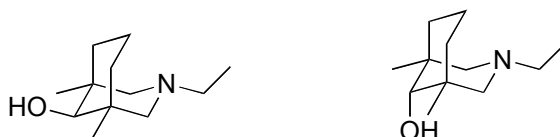


The reaction was conducted according to the general procedure using 9-tert-butyl-9-azabicyclo[5.3.1]undecan-11-one^[3] **6g** (118 mg, 0.528 mmol), sodium borohydride (39.9 mg, 1.06 mmol) and ethanol/water (10 mL) to afford the *title compound* **7g** (106 mg, 0.472 mmol, 89%) as a

colourless solid after flash chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 3339 (O–H), 2964, 2908, 2787 (C–H); ^1H NMR (300 MHz, CD_3OD) δ_{H} 3.83 (1H, m, H11), 2.98 (2H, d J 11.1, H8A, H10A), 2.25 (2H, m, H8B, H10B), 2.01–1.61 (11H, m, H1, H2, H3, H4A, H5, H6, H7), 1.43 (1H, m, H4B), 1.09 (9H, s, $\text{NC}(\text{CH}_3)_3$); ^{13}C NMR (50 MHz, CD_3OD) δ_{C} 76.1, 54.5, 51.4, 39.0, 33.4, 31.3, 26.6, 25.6; m/z (ESI+) 226 ($[\text{M}+\text{H}]^+$, 100), 170 (10). Found 226.2164, $\text{C}_{14}\text{H}_{28}\text{NO}$ ($[\text{M}+\text{H}]^+$) requires 226.2171.

(9s)-3-Ethyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol **10a** and

(9r)-3-ethyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol **11a**

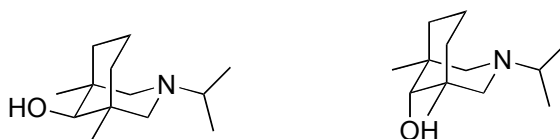


The reaction was conducted according to the general procedure using 3-ethyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-one^[3] **9a** (501 mg, 2.56 mmol), sodium borohydride (194 mg, 5.13 mmol) and ethanol/water (50 mL) to afford the *title compounds* as a mixture of epimers (1:2.2, 9r:9s) which was separated to give **10a** (306 mg, 1.55 mmol, 60%) as a colourless solid after flash chromatography (1:9 ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 3342 (O–H), 2966, 2945, 2922, 2870, 2800, 2770, 2748 (C–H); ^1H NMR (400 MHz, CDCl_3) δ_{H} 3.00 (1H, d, J 5.6, H9), 2.80–2.62 (1H, m, H7A), 2.73 (2H, dd, J 10.4, 1.3, H2A, H4A), 2.14 (2H, q, J 7.2, NCH_2CH_3), 1.80 (2H, d, J 10.4, H2B, H4B), 1.63–1.52 (3H, m, H6A, H7B, H8A), 1.41 (1H, bs, OH), 1.35 (2H, dd, J 13.8, 6.9, H6B, H8B), 1.01 (3H, t, J 7.2, NCH_2CH_3), 0.84 (6H, s, CCH_3); ^{13}C NMR (50 MHz, CDCl_3) δ_{C} 81.4, 66.3, 52.4, 36.2, 31.3, 25.5, 21.1, 13.0; m/z (ESI+) 198 ($[\text{M}+\text{H}]^+$, 100), 196 (32). Found 198.1853, $\text{C}_{12}\text{H}_{24}\text{NO}$ ($[\text{M}+\text{H}]^+$) requires 198.1858.

A second fraction afforded **11a** (117 mg, 0.593 mmol, 23%) as a colourless oil. ν_{\max} (NaCl)/ cm^{-1} 3441 (O–H), 2970, 2947, 2922, 2903, 2847, 2806 (C–H); ^1H NMR (300 MHz, CD_3OD) δ_{H} 3.02 (1H, s, H9), 2.80 (1H, m, H7A), 2.42 (2H, d, J 10.9, H2A, H4A), 2.23 (2H, q, J 7.2, NCH_2CH_3), 2.17 (2H, dd, J 11.0, 2.1, H2B, H4B), 1.65 (2H, ddd, J 13.6, 5.9, 0.8, H6A, H8A), 1.42–1.23 (3H, m, H6B, H7B, H8B), 1.04 (3H, t, J 7.2, NCH_2CH_3), 0.84 (6H, s, CCH_3); ^{13}C NMR (75 MHz, CD_3OD) δ_{C} 80.7, 59.5, 53.6, 41.3, 37.4, 25.7, 22.5, 13.0; m/z (ESI+) 198 ($[\text{M}+\text{H}]^+$, 100). Found 198.1858, $\text{C}_{12}\text{H}_{24}\text{NO}$ ($[\text{M}+\text{H}]^+$) requires 198.1858.

(9s)-3-Isopropyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol **10b** and

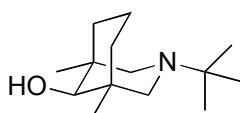
(9r)-3-isopropyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol **11b**



The reaction was conducted according to the general procedure using 3-isopropyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-one^[3] **9b** (236 mg, 1.13 mmol), sodium borohydride (259 mg, 6.86 mmol) and ethanol/water (10 mL) to afford the *title compounds* as a mixture of epimers (1:1.7, 9r:9s) which was separated to give alcohol **10b** (109 mg, 0.516 mmol, 46%) as a colourless solid after flash chromatography (1:9, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 3354 (O–H), 2968, 2947, 2922, 2903, 2854, 2789 (C–H); ^1H NMR (300 MHz, CD_3OD) δ_{H} 2.90 (1H, s, H9), 2.77 (1H, m, H7A), 2.66 (2H, dd, J 10.3, 1.3, H2A, H4A), 2.54 (1H, sept., J 6.6, $\text{CH}(\text{CH}_3)_2$), 2.09 (2H, dd, J 11.6, 2.3, H2B, H4B), 1.63 (2H, tdd, J 13.5, 6.5, 2.2, H6A, H8A), 1.35–1.22 (3H, m, H6B, H7B, H8B), 0.96 (6H, d, J 6.6, $\text{CH}(\text{CH}_3)_2$), 0.82 (6H, s, CCH_3); ^{13}C NMR (75 MHz, CD_3OD) δ_{C} 82.0, 62.8, 54.9, 36.9, 32.3, 25.8, 22.0, 18.4; m/z (ESI+) 212 ($[\text{M}+\text{H}]^+$, 100), 210 ($\text{M}-\text{H}^+$, 20). Found 212.2012, $\text{C}_{13}\text{H}_{26}\text{NO}$ ($[\text{M}+\text{H}]^+$) requires 212.2014.

A second fraction afforded alcohol **11b** (53 mg, 0.251 mmol, 22%) as a yellow oil. ν_{\max} (NaCl)/ cm^{-1} 3377, 3356 (O–H), 2962, 2928, 2870, 2851 (C–H); ^1H NMR (300 MHz, CD_3OD) δ_{H} 3.02 (1H, s, H9), 2.86 (1H, m, H7A), 2.56 (1H, sept., J 6.6, $\text{CH}(\text{CH}_3)_2$), 2.44 (2H, dd, J 10.9, 2.1, H2A, H4A), 2.32 (2H, d, J 10.7, H2B, H4B), 1.63 (2H, ddd, J 14.0, 6.3, 1.2, H6A, H8A), 1.45–1.19 (3H, m, H6B, H7B, H8B), 0.99 (6H, d, J 6.6, $\text{CH}(\text{CH}_3)_2$), 0.84 (6H, s, CCH_3); ^{13}C NMR (75 MHz, CD_3OD) δ_{C} 81.0, 55.3, 54.9, 41.6, 37.3, 25.8, 22.6, 18.7; m/z (ESI+) 212 ($[\text{M}+\text{H}]^+$, 25), 211 (40), 210 ($[\text{M}-\text{H}]^+$, 100). Found $[\text{M}-\text{H}]^+$ 210.1852, $\text{C}_{13}\text{H}_{24}\text{NO}$ ($[\text{M}-\text{H}]^+$) requires 210.1858.

(9s)-3-tert-Butyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-ol **10c**



The reaction was conducted according to the general procedure using *tert*-butyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-one^[3] **9c** (82.7 mg, 0.37 mmol), sodium borohydride (28.0 mg, 0.74 mmol) and ethanol/water (6 mL) to afford the *title compound* as a mixture of epimers (1:1.7, 9r:9s) which was separated to give **10c** (40.2 mg, 0.178 mmol, 48%) as a colourless solid. ν_{\max} (NaCl)/ cm^{-1} 3346 (O–H), 2968, 2949, 2907, 2868, 2851, 2791 (C–H); ^1H NMR (300 MHz,

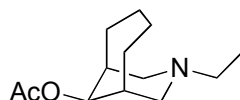
CD₃OD) δ_{H} 2.89 (1H, s, H9), 2.84 (1H, m, H7A), 2.84 (2H, d, J 11.4, H2A, H4A), 2.07 (2H, dd, J 11.7, 2.1, H2B, H4B), 1.64 (2H, tdd, J 13.2, 6.4, 2.0, H6A, H8A), 1.35–1.22 (3H, m, H6B, H7B, H8B), 1.02 (9H, s, NC(CH₃)₃), 0.81 (6H, s, CCH₃); ¹³C NMR (75 MHz, CD₃OD) δ_{C} 82.1, 59.9, 53.6, 36.9, 32.5, 26.6, 26.3, 22.1; m/z (ESI+) 226 ([M+H]⁺, 100), 170 (10). Found 226.2169, C₁₄H₂₈NO ([M+H]⁺) requires 226.2171.

The minor isomer **11c** was not isolated.

General Procedure for Acetylation

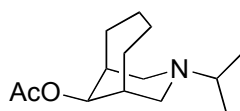
To a solution of alcohol (1 eq) and 4-(dimethylamino)pyridine (0.1 eq) in dichloromethane was added triethylamine (2 eq) and acetic anhydride (4 eq) under nitrogen. The reaction mixture was heated at reflux for 24 h at which time the reaction was quenched by the addition of saturated sodium hydrogen carbonate solution (10 mL) and the organic material extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give crude acetate which was subsequently purified by flash chromatography (ethyl acetate:hexane) to give the target compound.

(10s)-8-Ethyl-8-azabicyclo[4.3.1]decan-10-yl acetate **8a**



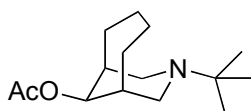
The reaction was conducted according to the general procedure using alcohol **7a** (67.0 mg, 0.366 mmol), 4-(dimethylamino)pyridine (5.0 mg, 0.0409 mmol), triethylamine (0.10 mL, 0.0728 g, 0.719 mmol), acetic anhydride (0.14 mL, 0.151 g, 1.48 mmol) and dichloromethane (2.5 mL) to afford the *title compound* **8a** (0.0696 g, 0.309 mmol, 85%) as a clear colourless oil after flash chromatography (1:9, ethyl acetate:hexane). ν_{max} (NaCl)/cm⁻¹ 2968, 2943, 2918, 2858, 2802, 2781, 2758 (C–H), 1740 (C=O); ¹H NMR (200 MHz, CDCl₃) δ_{H} 4.95 (1H, t, J 5.7, H10), 2.69 (2H, dd, J 11.1, 2.1, H7A, H9A), 2.31–2.20 (2H, m, H1, H6), 2.24 (2H, q, J 7.2, NCH₂CH₃), 2.07 (3H, s, OCOCH₃), 2.08 (2H, dd, J 11.1, 3.1, H7B, H9B), 1.91–1.77 (4H, m, H2A, H3A, H4A, H5A), 1.66–1.52 (4H, m, H2B, H3B, H4B, H5B), 1.02 (3H, s, NCH₂CH₃); ¹³C NMR (50 MHz, CDCl₃) δ_{C} 170.9, 78.2, 60.2, 52.5, 36.0, 32.1, 27.1, 21.7, 13.0; m/z (ESI+) 226 ([M+H]⁺, 100), 224 (27). Found 226.1804, C₁₃H₂₄NO₂ ([M+H]⁺) requires 226.1807.

(10s)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-yl acetate **8b**



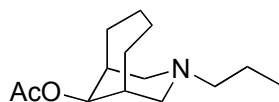
The reaction was conducted according to the general procedure using alcohol **7b** (0.100 g, 0.507 mmol), 4-(dimethylamino)pyridine (6.3 mg, 0.0516 mmol), triethylamine (0.14 mL, 0.103 g, 1.01 mmol), acetic anhydride (0.19 mL, 0.207 g, 2.02 mmol) and dichloromethane (5 mL) to afford the *title compound* **8b** (0.113 g, 0.473 mmol, 93%) as a clear colourless oil after flash chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2962, 2941, 2916, 2860, 2799, 2785, 2746 (C–H), 1736 (C=O); ^1H NMR (200 MHz, CDCl_3) δ_{H} 4.89 (1H, t, J 5.7, H10), 2.66 (1H, sept., J 6.6, $\text{NCH}(\text{CH}_3)_2$), 2.57 (2H, dd, J 11.3, 2.4, H7A, H9A), 2.34 (2H, dd, J 11.5, 3.1, H7B, H9B), 2.20 (2H, m, H1, H6), 2.03 (3H, s, OCOCH_3), 1.86–1.74 (4H, m, H2A, H3A, H4A, H5A), 1.62–1.49 (4H, m, H2B, H3B, H4B, H5B), 0.93 (6H, d, J 6.6, $\text{NCH}(\text{CH}_3)_2$); ^{13}C NMR (50 MHz, CDCl_3) δ_{C} 170.8, 78.6, 53.3, 54.4, 36.0, 32.1, 27.2, 21.7, 18.3; m/z (ESI+) 240 ($[\text{M}+\text{H}]^+$, 86), 238 (100). Found 240.1955, $\text{C}_{14}\text{H}_{26}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 240.1964.

(10s)-8-*tert*-Butyl-8-azabicyclo[4.3.1]decan-10-yl acetate **8c**^[3]



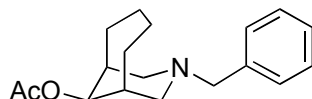
The reaction was conducted according to the general procedure using alcohol **7c** (0.112 g, 0.529 mmol), 4-(dimethylamino)pyridine (6.5 mg, 0.0532 mmol), triethylamine (0.15 mL, 0.109 g, 1.08 mmol), acetic anhydride (0.20 mL, 0.216 g, 2.12 mmol) and dichloromethane (2.5 mL) to afford the *title compound* **8c** (0.129 g, 0.509 mmol, 96%) as a clear colourless oil after flash chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2968, 2943, 2914, 2874, 2860, 2789 (C–H), 1738 (C=O); ^1H NMR (300 MHz, CDCl_3) δ_{H} 4.91 (1H, t, J 5.6, H10), 2.84 (2H, dd, J 8.5, 2.5, H7A, H9A), 2.27–2.20 (4H, m, H1, H6, H7B, H9B), 2.06 (3H, s, OCOCH_3), 1.94–1.77 (4H, m, H2A, H3A, H4A, H5A), 1.64–1.51 (4H, m, H2B, H3B, H4B, H5B), 1.02 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 170.9, 78.9, 53.3, 52.9, 36.3, 32.1, 27.3, 26.5, 21.8; m/z (ESI+) 254 ($[\text{M}+\text{H}]^+$, 100), 252 (25), 198 (23). Found 254.2105, $\text{C}_{15}\text{H}_{28}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 254.2120.

(10s)-8-Propyl-8-azabicyclo[4.3.1]decan-10-yl acetate **8d**



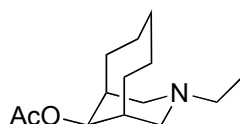
The reaction was conducted according to the general procedure using alcohol **7d** (80.2 mg, 0.406 mmol), 4-(dimethylamino)pyridine (5.7 mg, 0.0548 mmol), triethylamine (0.115 mL, 83.7 mg, 0.827 mmol), acetic anhydride (0.155 mL, 0.168 g, 1.64 mmol) and dichloromethane (5 mL) to afford the *title compound* **8d** (78.2 mg, 0.328 mmol, 81%) as a clear colourless oil after flash chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2941, 2918, 2874, 2860, 2804, 2779, 2752 (C–H), 1738 (C=O); ^1H NMR (200 MHz, CDCl_3) δ_{H} 4.94 (1H, t, J 5.7, H10), 2.63 (2H, dd, J 8.9, 2.2, H7A, H9A), 2.24–2.03 (4H, m, H1, H6, H7B, H9B), 2.13 (2H, q, J 7.2, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 2.06 (3H, s, OCOCH_3), 1.89–1.78 (4H, m, H2A, H3A, H4A, H5A), 1.65–1.38 (4H, m, H2B, H3B, H4B, H5B), 1.44 (2H, sext., J 7.1, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 0.90 (3H t, J 7.3, $\text{NCH}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (50 MHz, CDCl_3) δ_{C} 170.9, 78.92, 60.7, 60.6, 30.0, 32.1, 27.1, 21.7, 20.8, 12.4; m/z (ESI+) 240 ($[\text{M}+\text{H}]^+$, 29), 238 (100). Found 240.1951, $\text{C}_{14}\text{H}_{26}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 240.1964.

(10s)-8-Benzyl-8-azabicyclo[4.3.1]decan-10-yl acetate **8e**



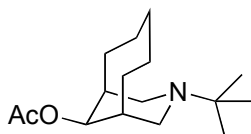
The reaction was conducted according to the general procedure using alcohol **7e** (198 mg, 8.07 mmol), 4-(dimethylamino)pyridine (9.8 mg, 0.080 mmol), triethylamine (0.22 mL, 163 mg, 1.61 mmol), acetic anhydride (0.30 mL, 0.329 g, 3.22 mmol) and dichloromethane (8 mL) to afford the *title compound* **8e** (227 mg, 0.790 mmol, 98%) as a colourless oil after flash chromatography (1:9, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2915, 2858, 2801 (C–H), 1732 (C=O); ^1H NMR (200 MHz, CDCl_3) δ_{H} 7.33–7.23 (5H, m, NCH_2Ph), 4.98 (1H, t, J 5.5, H10), 3.39 (2H, s, NCH_2Ph), 2.46 (2H, d, J 10.9, H7A, H9A), 2.23–1.48 (12H, m, H1, H2, H3, H4, H5, H6, H7B, H9B), 2.07 (3H, s, OCOCH_3); ^{13}C NMR (50 MHz, CDCl_3) δ_{C} 170.7, 139.2, 129.0, 128.3, 127.0, 77.8, 63.4, 60.2, 35.7, 31.6, 27.0, 21.5; m/z (ESI+) 288 ($[\text{M}+\text{H}]^+$, 100). Found 288.1958, $\text{C}_{18}\text{H}_{26}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 288.1964.

(11s)-9-Ethyl-9-azabicyclo[5.3.1]undecan-11-yl acetate **8f**



The reaction was conducted according to the general procedure using alcohol **7f** (102 mg, 0.514 mmol), 4-(dimethylamino)pyridine (6.3 mg, 0.051 mmol), triethylamine (104 mg, 1.03 mmol), acetic anhydride (210 mg, 2.06 mmol) and dichloromethane (5 mL) to afford the *title compound* **8f** (123 mg, 0.514 mmol, 99%) as a colourless oil after flash chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2966, 2914, 2795, 2764 (C–H), 1740 (C=O); ^1H NMR (300 MHz, CDCl_3) δ_{H} 4.96 (1H, m, H11), 2.72 (2H, d, J 10.4, H8A, H10A), 2.30 (2H, q, J 6.7, NCH_2CH_3), 2.13–2.09 (4H, m, H1, H7, H8B, H10B), 2.09 (3H, m, OCOCH_3), 1.79–1.67 (10H, m, H2, H3, H4, H5, H6), 1.04 (3H, t, J 6.7, NCH_2CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 170.6, 77.2, 57.4, 52.1, 35.0, 32.2, 30.9, 24.6, 21.6, 12.5; m/z (ESI+) 240 ($[\text{M}+\text{H}]^+$, 100). Found 240.1953, $\text{C}_{14}\text{H}_{26}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 240.1964.

(11s)-9-tert-Butyl-9-azabicyclo[5.3.1]undecan-11-yl acetate **8g**



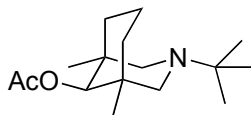
The reaction was conducted according to the general procedure using alcohol **7g** (84.1 mg, 0.373 mmol), 4-(dimethylamino)pyridine (5.0 mg, 0.041 mmol), triethylamine (75.7 mg, 0.748 mmol), acetic anhydride (152 mg, 1.49 mmol) and dichloromethane (3.7 mL) to afford the *title compound* **8g** (69.1 mg, 0.258 mmol, 69%) as a colourless oil after flash chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2966, 2916, 2868, 2795 (C–H), 1738 (C=O); ^1H NMR (200 MHz, CDCl_3) δ_{H} 4.97 (1H, t, J 5.4, H11), 2.87 (2H, d, J 11.3, H8A, H10A), 2.27 (2H, dd, J 11.5, 2.6, H8B, H10B), 2.07 (5H, m, H1, H7, OCOCH_3), 1.81–1.55 (10H, m, H2, H3, H4, H5, H6), 1.04 (9H, s, $\text{NC}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 170.7, 78.6, 53.5, 50.8, 35.6, 32.3, 31.2, 26.4, 24.5, 21.7; m/z (ESI+) 268 ($[\text{M}+\text{H}]^+$, 100), 212 (14). Found 268.2268, $\text{C}_{16}\text{H}_{30}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 268.2277.

(9s)-3-Ethyl-1,5-diethyl-3-azabicyclo[3.3.1]nonan-9-yl acetate **12a**



The reaction was conducted according to the general procedure using alcohol **10a** (97.9 mg, 0.496 mmol), 4-(dimethylamino)pyridine (6.8 mg, 0.056 mmol), triethylamine (102 mg, 1.0 mmol), acetic anhydride (206 mg, 2.0 mmol) and dichloromethane (2.0 mL) to afford the *title compound* **12a** (110 mg, 0.460 mmol, 92%) as a colourless oil after flash chromatography (1:4, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2967, 2929, 2755 (C–H), 1739 (C=O), 1241 (C–O); ^1H NMR (200 MHz, CDCl_3) δ_{H} 4.53 (1H, s, H9), 2.81–2.64 (1H, m, H7A), 2.71 (2H, d, J 11.7, H2A, H4A), 2.14 (2H, q, J 6.4, CH_2CH_3), 2.07 (3H, s, OCOCH_3), 1.89 (2H, dd, J 11.7, 2.2, H2B, H4B), 1.55 (2H, tdd, J 13.6, 6.5, 2.3, H6A, H8A), 1.40–1.22 (3H, m, H6B, H7B, H8B), 0.98 (3H, t, J 7.2, CH_2CH_3), 0.69 (6H, s, CCH_3); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 171.4, 81.9, 65.8, 52.2, 35.8, 32.2, 30.0, 25.2, 21.1, 13.0; m/z (ESI+) 240 ($[\text{M}+\text{H}]^+$, 100), 238 (89). Found 240.1958. $\text{C}_{14}\text{H}_{26}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 240.1964.

(9s)-3-tert-Butyl-1,5-dimethyl-3-azabicyclo[3.3.1]nonan-9-yl acetate **12c**

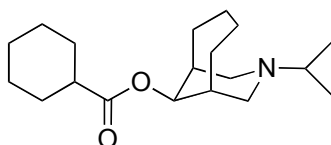


The reaction was conducted according to the general procedure using alcohol **10c** (81.5 mg, 0.317 mmol), 4-(dimethylamino)pyridine (4.4 mg, 0.036 mmol), triethylamine (73.4 mg, 0.725 mmol), acetic anhydride (148 mg, 1.45 mmol) and dichloromethane (3.6 mL) to afford the *title compound* **12c** (88.9 mg, 0.332 mmol, 92%) as a colourless oil after flash chromatography (1:9, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2966, 2926, 2910, 2872, 2853 (C–H), 1738 (C=O); ^1H NMR (200 MHz, CDCl_3) δ_{H} 4.52 (1H, s, H9), 2.91–2.76 (1H, m, H7A), 2.81 (2H, d, J 11.6, H2A, H4A), 2.16 (2H, dd, J 11.7, 1.9, H2B, H4B), 2.09 (3H, s, COOCH_3), 1.66–1.49 (2H, m, H6A, H8A), 1.41–1.25 (3H, m, H6B, H7B, H8B), 1.01 (9H, s, $\text{NC}(\text{CH}_3)_3$), 0.70 (6H, s, CCH_3); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 171.4, 82.3, 68.3, 53.0, 35.5, 32.3, 29.8, 26.0, 25.2, 21.2; m/z (ESI+) 268 ($[\text{M}+\text{H}]^+$, 100), 212 (21). Found 268.2270, $\text{C}_{16}\text{H}_{30}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 268.2277.

General Procedure for Esterification

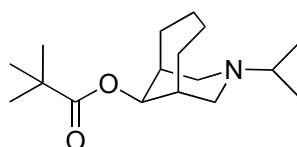
To a solution of alcohol (1 eq) and acid chloride (1.5 eq) in dichloromethane (0.25 M) at 0 °C was added triethylamine (2.1 eq) dropwise under nitrogen. The solution was warmed to room temperature and the reaction heated at reflux for 16 h at which time the reaction was quenched by the addition of saturated sodium hydrogen carbonate solution (10 mL) and the organic material extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give crude acetate which was subsequently purified by flash chromatography (ethyl acetate:hexane) to give the target compound.

(10s)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-yl cyclohexanecarboxylate **13**



The reaction was conducted according to the general procedure using alcohol **7b** (70.0 mg, 0.355 mmol), cyclohexanecarbonyl chloride (77.7 mg, 0.530 mmol), triethylamine (76.4 mg, 0.755 mmol) and dichloromethane (1.5 mL) to afford the *title compound* **13** (100 mg, 0.326 mmol, 92%) as a colourless oil after chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2961, 2930, 2854, 2799, 2787 (C–H), 1728 (C=O); ^1H NMR (300 MHz, CDCl_3) δ_{H} 4.93 (1H, t, J 5.6, H10), 2.69 (1H, sept., J 6.6, $\text{NCH}(\text{CH}_3)_2$), 2.60 (2H, d, J 11.3, H7A, H9A), 2.37 (2H, dd, J 11.5, 3.1, H7B, H9B), 2.31 (1H, m, H1'), 2.21 (2H, m, H1, H6), 1.94–1.22 (18H, m, H2, H3, H4, H5, H2', H3', H4', H5', H6'), 0.96 (6H, d, J 6.6, $\text{NCH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 175.7, 77.9, 55.3, 54.2, 43.8, 36.0, 32.0, 29.3, 27.1, 26.0, 25.7, 18.2; m/z (ESI+) 308 ($[\text{M}+\text{H}]^+$, 5), 306 (100). Found 308.2576, $\text{C}_{19}\text{H}_{34}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 308.2590.

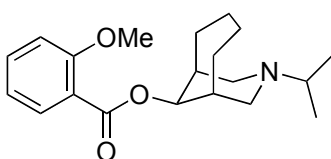
(10s)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-yl pivalate **14**



The reaction was conducted according to the general procedure using alcohol **7b** (70.1 mg, 0.355 mmol), pivaloyl chloride (64.6 mg, 0.536 mmol), triethylamine (76.4 mg, 0.755 mmol) and

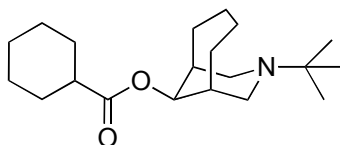
dichloromethane (1.5 mL) to afford the *title compound* **14** (99.0 mg, 0.352 mmol, 99%) as a colourless oil after chromatography (1:9, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2964, 2945, 2914, 2872, 2860, 2799, 2785 (C–H), 1726 (C=O); ^1H NMR (300 MHz, CDCl_3) δ_{H} 4.92 (1H, t, J 5.7, H10), 2.69 (1H, sept., J 6.6, $\text{NCH}(\text{CH}_3)_2$), 2.60 (2H, d, J 11.2, H7A, H9A), 2.37 (2H, dd, J 11.6, 2.7, H7B, H9B), 2.20 (2H, m, H1, H6), 1.91–1.78 (4H, m, H2A, H3A, H4A, H5A), 1.66–1.52 (4H, m, H2B, H3B, H4B, H5B), 1.22 (9H, s, $\text{OCOC}(\text{CH}_3)_3$), 0.96 (6H, d, J 6.6, $\text{NCH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 178.1, 78.0, 55.3, 54.2, 39.1, 36.0, 32.0, 27.5, 27.1, 18.2; m/z (ESI+) 282 ($[\text{M}+\text{H}]^+$, 38), 280 (100). Found 282.2421, $\text{C}_{17}\text{H}_{32}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 282.2433.

(10s)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-yl 2-methoxybenzoate **15**



The reaction was conducted according to the general procedure using alcohol **7b** (70.1 mg, 0.355 mmol), *o*-anisoyl chloride (90.5 mg, 0.531 mmol), triethylamine (76.4 mg, 0.755 mmol) and dichloromethane (1.5 mL) to afford the *title compound* **15** (95.4 mg, 0.288 mmol, 81%) as a colourless solid after chromatography (1:19, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2962, 2914, 2858, 2799, 2785 (C–H), 1724 (C=O), 1600 (C=C); ^1H NMR (300 MHz, CDCl_3) δ_{H} 7.85 (1H, dd, J 8.1, 1.8, H6'), 7.45 (1H, td, J 7.4, 1.1, H4'), 6.99–6.95 (2H, m, H3', H5'), 5.20 (1H, t, J 5.6, H10), 3.88 (3H, s, ArOCH_3), 2.71 (1H, sept., J 6.6, $\text{NCH}(\text{CH}_3)_2$), 2.64 (2H, d, J 11.1, H7A, H9A), 2.43 (2H, dd, J 11.6, 2.7, H7B, H9B), 2.36 (2H, m, H1, H6), 2.01–1.86 (4H, m, H2A, H3A, H4A, H5A), 1.80–1.69 (2H, m, H2B, H5B), 1.61–1.53 (2H, m, H3B, H4B), 0.98 (6H, d, J 6.6, $\text{NCH}(\text{CH}_3)_2$); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 165.7, 158.4, 133.4, 131.8, 120.8, 120.2, 112.0, 78.8, 55.8, 55.3, 54.2, 36.1, 32.0, 26.9, 18.1; m/z (ESI+) 685 (24), 354 (18), 332 ($[\text{M}+\text{H}]^+$, 100). Found 332.2214, $\text{C}_{20}\text{H}_{30}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) requires 332.2226.

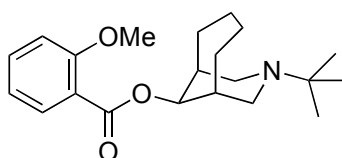
(10s)-8-Isopropyl-8-azabicyclo[4.3.1]decan-10-yl cyclohexanecarboxylate **16**



The reaction was conducted according to the general procedure using alcohol **7c** (100 mg, 0.473 mmol), cyclohexanecarbonyl chloride (106 mg, 0.721 mmol), triethylamine (98.3 mg, 0.971 mmol)

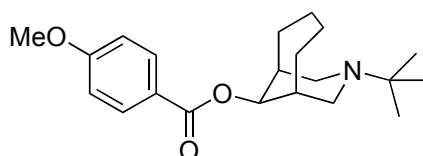
and dichloromethane (2.0 mL) to afford the *title compound 16* (105 mg, 0.327 mmol, 69%) as a clear colourless oil after chromatography (1:9, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2968, 2918, 2854, 2789, 2733, 2667 (C–H), 1728 (C=O); ^1H NMR (300 MHz, CDCl_3) δ_{H} 4.92 (1H, t, J 5.7, H10), 2.84 (2H, d, J 11.1, H7A, H9A), 2.31 (1H, tt, J 11.2, 3.6, H1'), 2.25 (2H, dd, J 11.1, 3.8, H7B, H9B), 2.20 (2H, m, H1, H6), 1.99–1.92 (4H, m, H2A', H3A, H4A, H6A'), 1.84–1.74 (4H, m, H2A, H3A', H5A, H5A'), 1.68–1.59 (3H, m, H3B, H4A', H4B), 1.55–1.41 (4H, m, H2B, H2B', H5B, H6B') 1.34–1.21 (3H, m, H3B', H4B', H5B'), 1.02 (9H, s, $\text{NC}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 175.7, 78.1, 53.1, 52.7, 43.9, 36.2, 31.9, 29.3, 27.1, 26.4, 26.0, 25.7; m/z (ESI+) 322 ($[\text{M}+\text{H}]^+$, 100), 266 (28). Found 322.2739, $\text{C}_{20}\text{H}_{36}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) requires 322.2746.

(10s)-8-tert-Butyl-8-azabicyclo[4.3.1]decan-10-yl 2-methoxybenzoate 17



The reaction was conducted according to the general procedure using alcohol **7c** (74.9 mg, 0.354 mmol), *o*-anisoyl chloride (90.5 mg, 0.531 mmol), triethylamine (76.4 mg, 0.755 mmol) and dichloromethane (1.5 mL) to afford the *title compound 17* (98.6 mg, 0.285 mmol, 81%) as a colourless solid after chromatography (1:9, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2968, 2943, 2912, 2856, 2787, 2733 (C–H), 1724 (C=O); ^1H NMR (300 MHz, CDCl_3) δ_{H} 7.85 (1H, d, J 7.2, H6'), 7.46 (1H, t, J 7.6, H4'), 7.00–6.96 (2H, m, H3', H5'), 5.19 (1H, t, J 4.9, H10), 3.89 (3H, s, ArOCH_3), 2.89 (2H, d, J 10.4, H7A, H9A), 2.35–2.31 (4H, m, H1, H6, H7B, H9B), 1.99–1.93 (4H, m, H2A, H3A, H4A, H5A), 1.77–1.68 (2H, m, H2B, H5B), 1.62–1.53 (2H, m, H3B, H4B), 1.05 (9H, s, $\text{NC}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 165.8, 159.5, 133.4, 131.9, 120.8, 120.2, 112.1, 79.1, 55.9, 53.1, 52.8, 36.3, 31.9, 27.0, 26.4; m/z (ESI+) 713 (48), 368 (25), 346 ($[\text{M}+\text{H}]^+$, 100), 290 (39). Found 346.2369, $\text{C}_{21}\text{H}_{32}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) requires 346.2382.

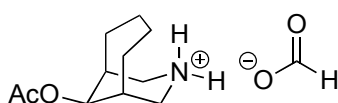
(10s)-8-tert-Butyl-8-azabicyclo[4.3.1]decan-10-yl 4-methoxybenzoate 18



The reaction was conducted according to the general procedure using alcohol **7c** (75.0 mg, 0.355 mmol), *p*-anisoyl chloride (90.4 mg, 0.530 mmol), triethylamine (76.4 mg, 0.755 mmol) and

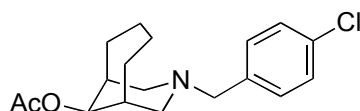
dichloromethane (1.5 mL) to afford the *title compound 18* (119 mg, 0.344 mmol, 97%) as a colourless solid after chromatography (1:9, ethyl acetate:hexane). ν_{\max} (NaCl)/ cm^{-1} 2968, 2947, 2918, 2854, 2799, 2787 (C–H), 1709 (C=O), 1606, 1510 (C=C); ^1H NMR (300 MHz, CDCl_3) δ_{H} 8.03 (2H, d, J 8.8, H2', H6'), 6.93 (2H, d, J 8.8, H3', H5'), 5.17 (1H, t, J 5.4, H10), 3.86 (3H, s, ArOCH_3), 2.90 (2H, d, J 11.2, H7A, H9A), 2.34 (4H, m, H1, H6, H7B, H9B), 2.08–1.85 (4H, m, H2A, H3A, H4A, H5A), 1.78–1.55 (4H, m, H2B, H3B, H4B, H5B), 1.05 (9H, s, $\text{NC}(\text{CH}_3)_3$); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 165.9, 163.4, 131.7, 123.6, 113.8, 78.9, 55.6, 53.2, 52.8, 36.4, 32.0, 27.3, 26.4; m/z (ESI+) 346 ($[\text{M}+\text{H}]^+$, 100), 290 (33). Found 346.2369, $\text{C}_{21}\text{H}_{32}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) requires 346.2382.

(10s)-10-Acetoxy-8-azoniabicyclo[4.3.1]decane formate **19**



Ammonium formate (87.8 mg, 1.39 mmol) was added to a solution of *N*-benzylamine **8e** (80.0 mg, 0.278 mmol) and an equal weight of palladium on charcoal (10% wt) in dry methanol (20 mL). The mixture was heated at reflux for 12 min under nitrogen. The mixture was allowed to cool to room temperature and filtered through a pad of celite, washing with methanol and dichloromethane. The volatile solvent was removed under reduced pressure to afford the *title compound 19* (48.7 mg, 0.200 mmol, 72%) as a colourless solid. ν_{\max} (NaCl)/ cm^{-1} 3354 (N–H), 2914, 2858, 2802, 2729 (C–H), 1734 (C=O); ^1H NMR (300 MHz, CD_3OD) δ_{H} 8.54 (1H, s, OCHO), 5.10 (1H, t, J 5.5, H10), 2.96–2.84 (4H, m, H7, H9), 2.21 (2H, m, H1, H6), 2.07 (3H, m, OCOCH_3), 1.97–1.74 (6H, m, H2, H3A, H4A, H5), 1.62–1.55 (2H, m, H3B, H4B); ^{13}C NMR (75 MHz, CD_3OD) δ_{C} 172.0, 170.4, 78.4, 52.9, 36.4, 31.8, 28.1, 21.2; m/z (ESI+) 198 ($[\text{M}-\text{OCHO}]^+$, 100). Found 198.1481, $\text{C}_{11}\text{H}_{20}\text{NO}_2$ ($[\text{M}-\text{OCHO}]^+$) requires 198.1489.

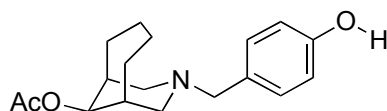
(10s)-8-(4-Chlorobenzyl)-8-azabicyclo[4.3.1]dec-10-yl acetate **20**



Sodium triacetoxyborohydride (73.9 mg, 0.348 mmol) was added to a solution of amine **19** (60.6 mg, 0.249 mmol) and *p*-chlorobenzaldehyde (35.0 mg, 0.249 mmol) in dichloroethane (2.5 mL) and the mixture stirred under nitrogen at room temperature for 30 h. The reaction was quenched by the addition of sodium bicarbonate (sat. 10 mL) and the organic material extracted into

dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give crude acetate which was subsequently purified by flash chromatography (1:19, ethyl acetate:hexane) to give the *title compound* **20** (67.0 mg, 0.208 mmol, 84%) as a colourless oil. ν_{\max} (NaCl)/ cm^{-1} 2917, 2858, 2797 (C–H), 1736 (C=O); ^1H NMR (300 MHz, CDCl_3) δ_{H} 7.27 (4H, s, ArH), 4.98 (1H, t, J 5.7, H10), 3.34 (2H, s, NCH_2Ar), 2.64 (2H, d, J 11.1, H7A, H9A), 2.23 (2H, m, H1, H6), 2.15 (2H, dd, J 11.4, 3.0, H7B, H9B), 2.08 (3H, s, OCOCH_3), 1.98–1.47 (8H, m, H2, H3, H4, H5); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 170.7, 137.7, 132.6, 130.3, 128.4, 77.6, 62.6, 60.1, 35.6, 31.6, 26.9, 21.5; m/z (ESI+) 324 (35), 322 ($[\text{M}+\text{H}]^+$, 100), 138 (30), 125 (32). Found 324.1556, $\text{C}_{18}\text{H}_{25}\text{NO}_2^{37}\text{Cl}$ ($[\text{M}+\text{H}]^+$) requires 324.1544; Found 322.1579, $\text{C}_{18}\text{H}_{25}\text{NO}_2^{35}\text{Cl}$ ($[\text{M}+\text{H}]^+$) requires 322.1574.

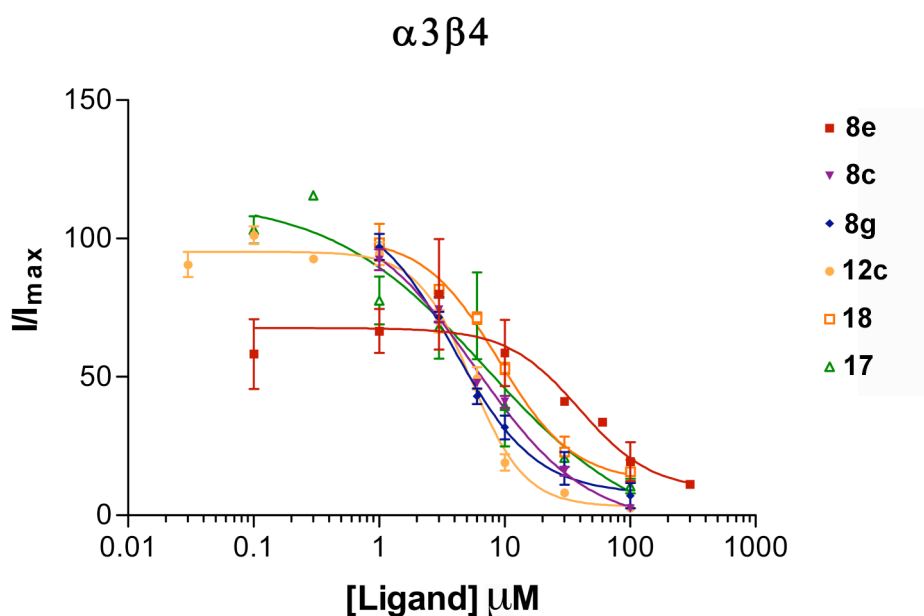
(10*s*)-8-(4-Hydroxybenzyl)-8-azabicyclo[4.3.1]dec-10-yl acetate **21**



Sodium triacetoxymethylborohydride (70.3 mg, 0.332 mmol) was added to a solution of ammonium salt **19** (57.9 mg, 0.238 mmol) and *p*-methoxybenzaldehyde (29.1 mg, 0.238 mmol) in dichloroethane (2.5 mL) and the mixture stirred under nitrogen at room temperature for 30 h. The reaction was quenched by the addition of sodium bicarbonate (sat. 10 mL) and the organic material extracted into dichloromethane (3 × 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give crude acetate which was subsequently purified by flash chromatography (1:4, ethyl acetate:hexane) to give the *title compound* **21** (71.3 mg, 0.235 mmol, 99%) as a colourless oil. ν_{\max} (NaCl)/ cm^{-1} 3401 (O–H), 2916, 2800 (C–H), 1735, 1708 (C=O); ^1H NMR (300 MHz, CDCl_3) δ_{H} 7.16 (2H, d, J 8.4, H2', H6'), 6.79 (2H, d, J 8.5, H3', H5'), 5.81 (1H, bs, OH), 5.00 (1H, t, J 5.7, H10), 3.30 (2H, s, NCH_2Ar), 2.65 (2H, d, J 11.2, H7A, H9A), 2.22 (2H, m, H1, H6), 2.11 (2H, m, H7B, H9B), 2.08 (3H, s, OCOCH_3), 2.08–1.45 (8H, m, H2, H3, H4, H5); ^{13}C NMR (75 MHz, CD_3OD) δ_{C} 171.2, 154.8, 131.1, 130.3, 115.1, 78.2, 62.6, 60.0, 35.7, 31.6, 26.9, 21.5; m/z (EI) 303 (M^+ , 30), 244 (51), 228 (34), 196 (32), 138 (48), 107 (100), 91 (45), 43 (37). Found 303.1834, $\text{C}_{18}\text{H}_{25}\text{NO}_3$ (M^+) requires 303.1834.

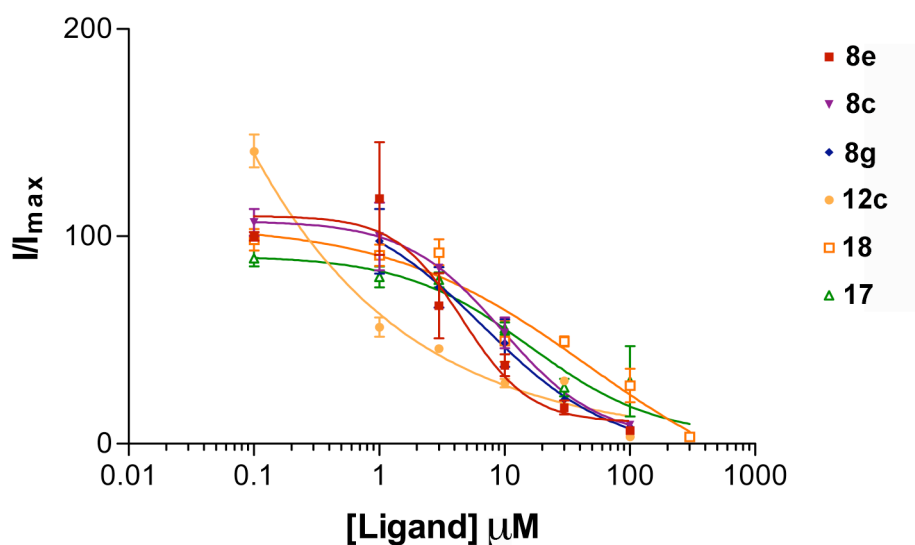
Inhibitory Concentration (IC₅₀) Response Curves ^[4]

The two-electrode voltage-clamp electrophysiology functional assay was conducted on esters **8c**, **8e**, **8g**, **12c**, **17** and **18** according to previously reported procedures^[4] with the following minor modifications. Oocytes were stored at 18 °C in frog ringer solution containing gentamycin (50 µM/mL), or calcium free frog ringer solution containing BaCl₂ (1.8 mM) and kanamycin (4 mg/L) for cells injected with $\alpha 7$ mRNA. Oocytes were continually superfused by frog ringer solution or calcium free frog ringer solution containing BaCl₂ (1.8 mM) and atropine (1 µM) for cells expressing $\alpha 7$ nAChR. Test compounds were applied to oocytes at intervals of 8–9 min. The amplitude of the current (*I*) recorded in response to each drug was normalised to the amplitude (*I_m*) of the current response to acetylcholine ($\alpha 3\beta 4$, 150 µM; $\alpha 4\beta 2$, 150 µM; $\alpha 7$, 300 µM).



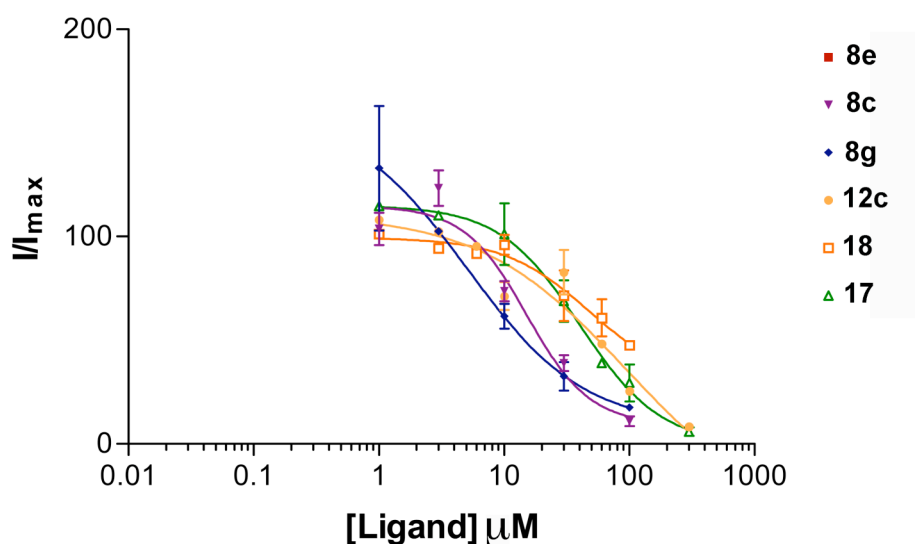
Inhibitory concentration (IC₅₀) response curves at rat $\alpha 3\beta 4$ receptor expressed in *Xenopus* oocytes of **8c**, **8e**, **8g**, **12c**, **17** and **18** in the presence of and normalized to the current response by acetylcholine (150 µM). Data are the mean \pm SEM (n >3 oocytes).

$\alpha 4\beta 2$



Inhibitory concentration (IC₅₀) response curves at rat $\alpha 4\beta 2$ receptor expressed in *Xenopus* oocytes of **8c**, **8e**, **8g**, **17** and **18** in the presence of and normalized to the current response by acetylcholine (100 μ M). Data are the mean \pm SEM (n >3 oocytes). Data for ester **12c** did not provide a good fit to the model and so was not reported.

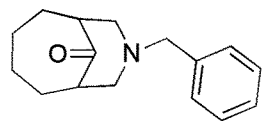
$\alpha 7$



Inhibitory concentration (IC₅₀) response curves at rat $\alpha 7$ receptor expressed in *Xenopus* oocytes of **8c**, **8g**, **12c**, **17** and **18** in the presence of and normalized to the current response by acetylcholine (300 μ M). Data are the mean \pm SEM (n >3 oocytes). The IC₅₀ inhibitory concentration response curve for ester **8e** was not completed.

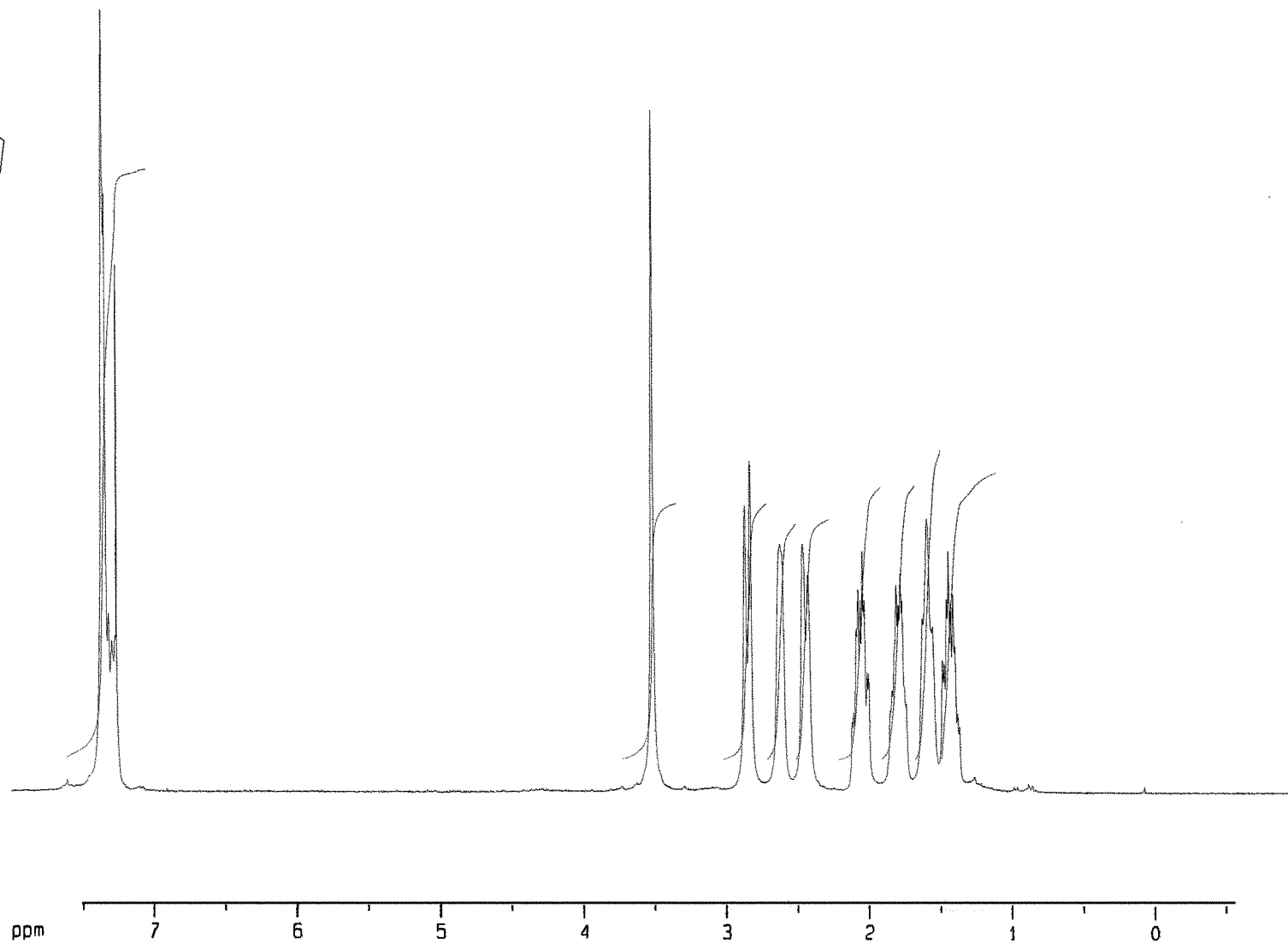
References:

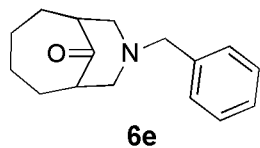
- [1] C. Brocke, M. A. Brimble, D. S.-H. Lin, M. D. McLeod, *Synlett* **2004**, 2359–2363.
- [2] D. L. Fields, J. B. Miller, D. D. Reynolds, *J. Org. Chem.* **1962**, 27, 2749–2753.
- [3] J. I. Halliday, M. Chebib, P. Turner, M. D. McLeod, *Org. Lett.* **2006**, 8, 3399–3401.
- [4] D. Barker, D. H.-S. Lin, J. E. Carland, C. P.-Y. Chu, M. Chebib, M. A. Brimble, G. P. Savage, M. D. McLeod, *Bioorg. Med. Chem.* **2005**, 13, 4565–4575.



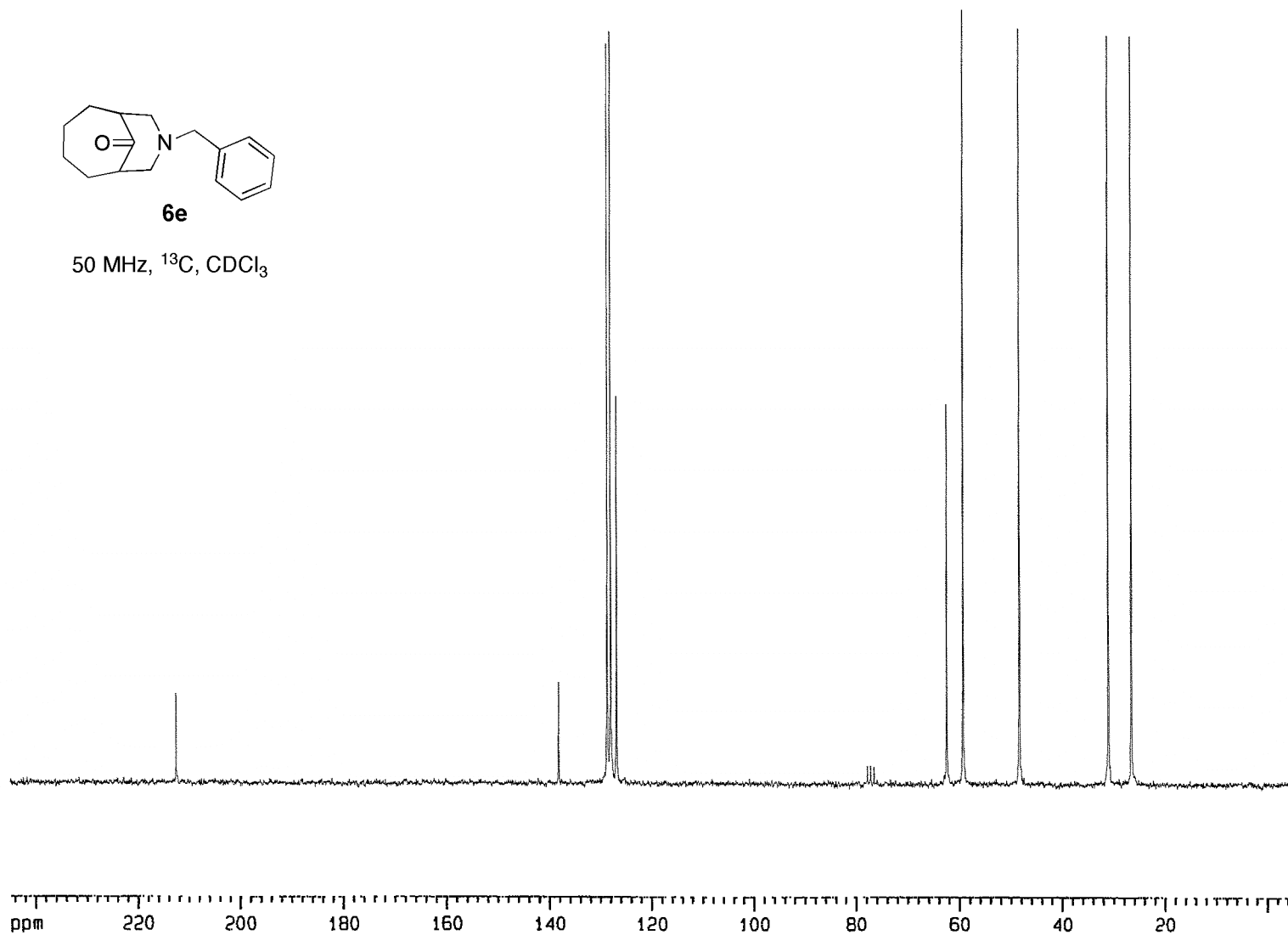
6e

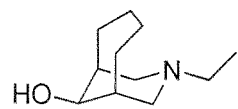
300 MHz, ^1H , CDCl_3





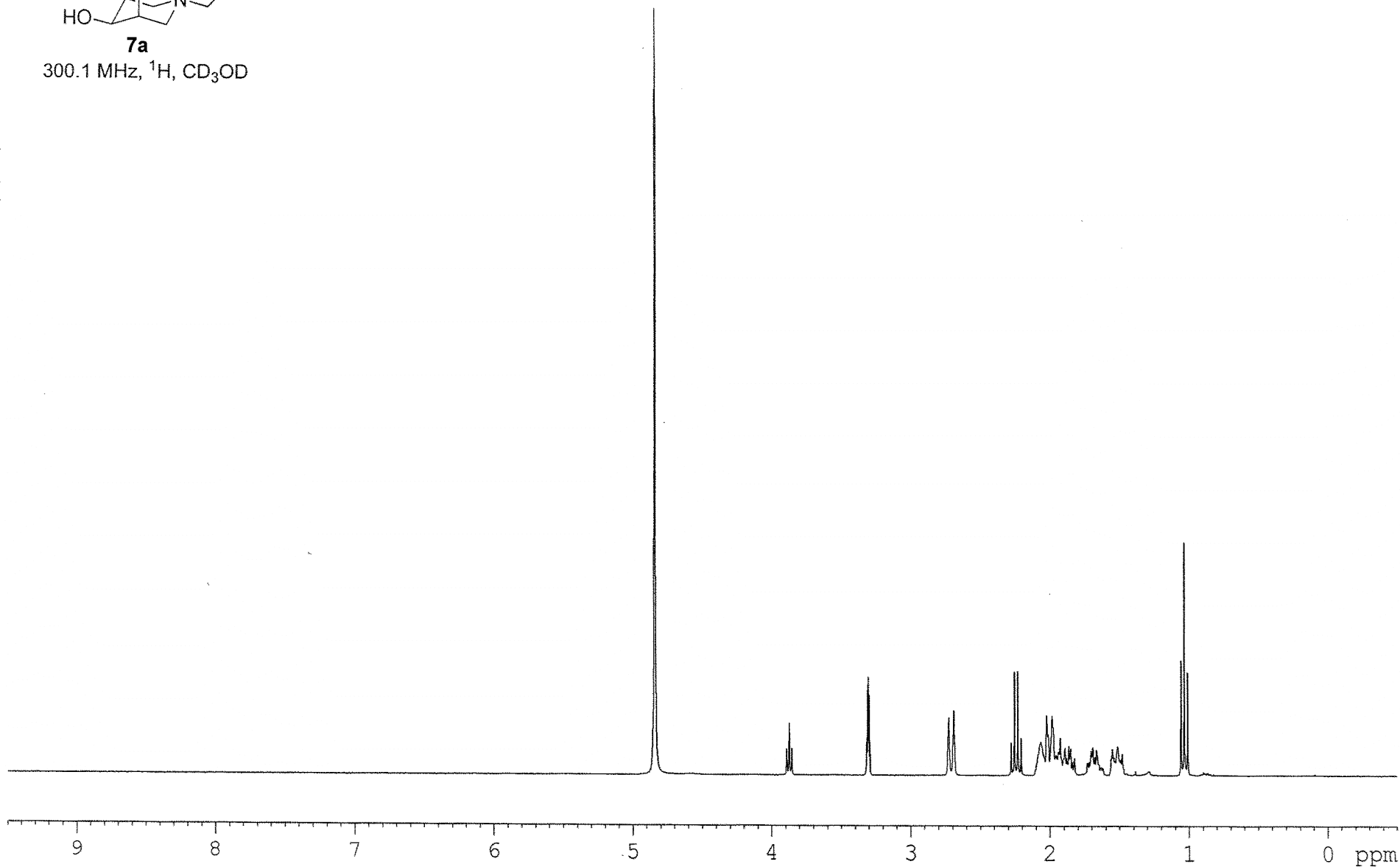
50 MHz, ^{13}C , CDCl_3

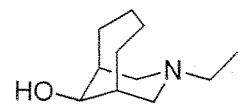




7a

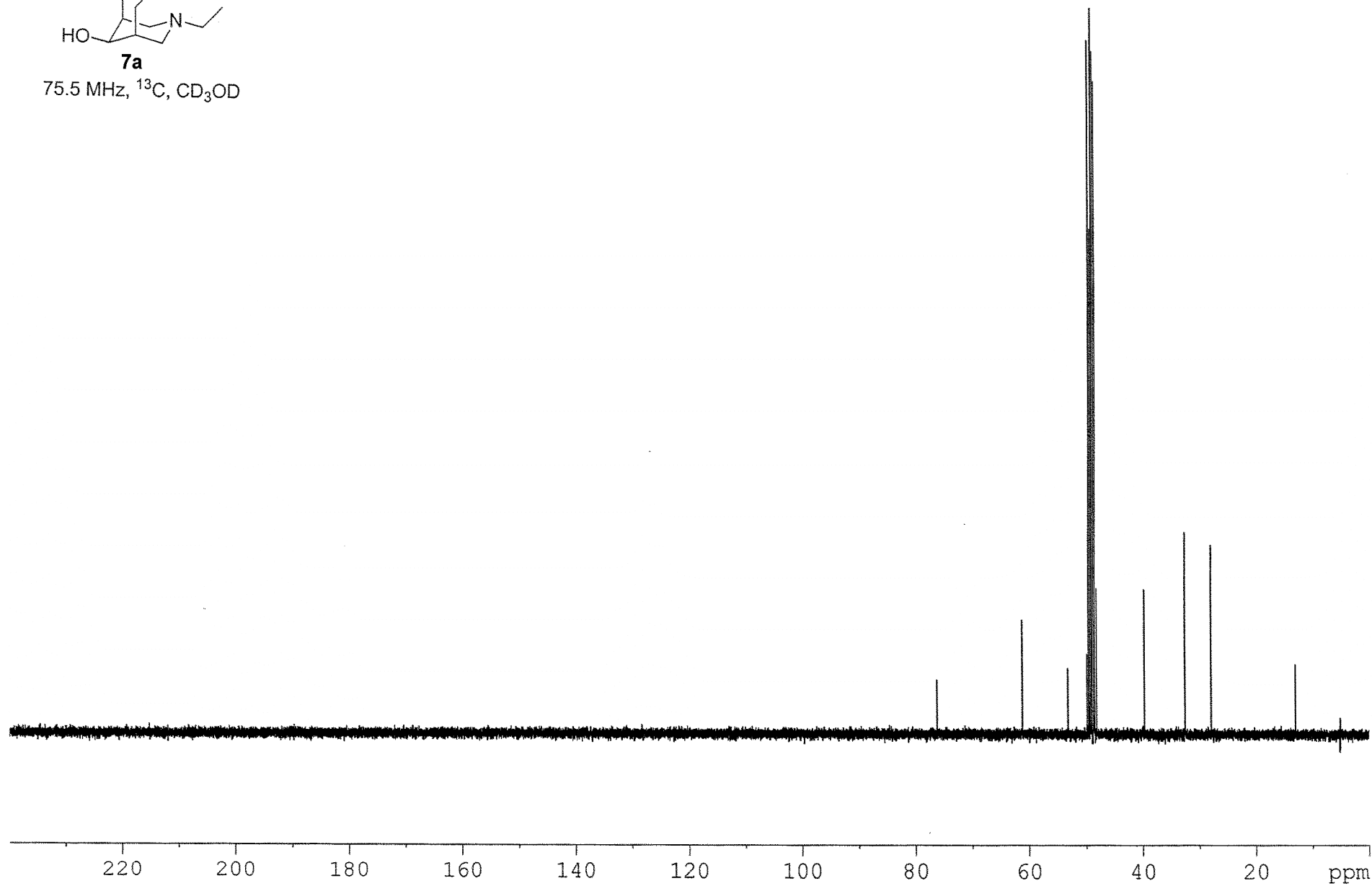
300.1 MHz, ¹H, CD₃OD

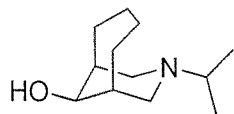




7a

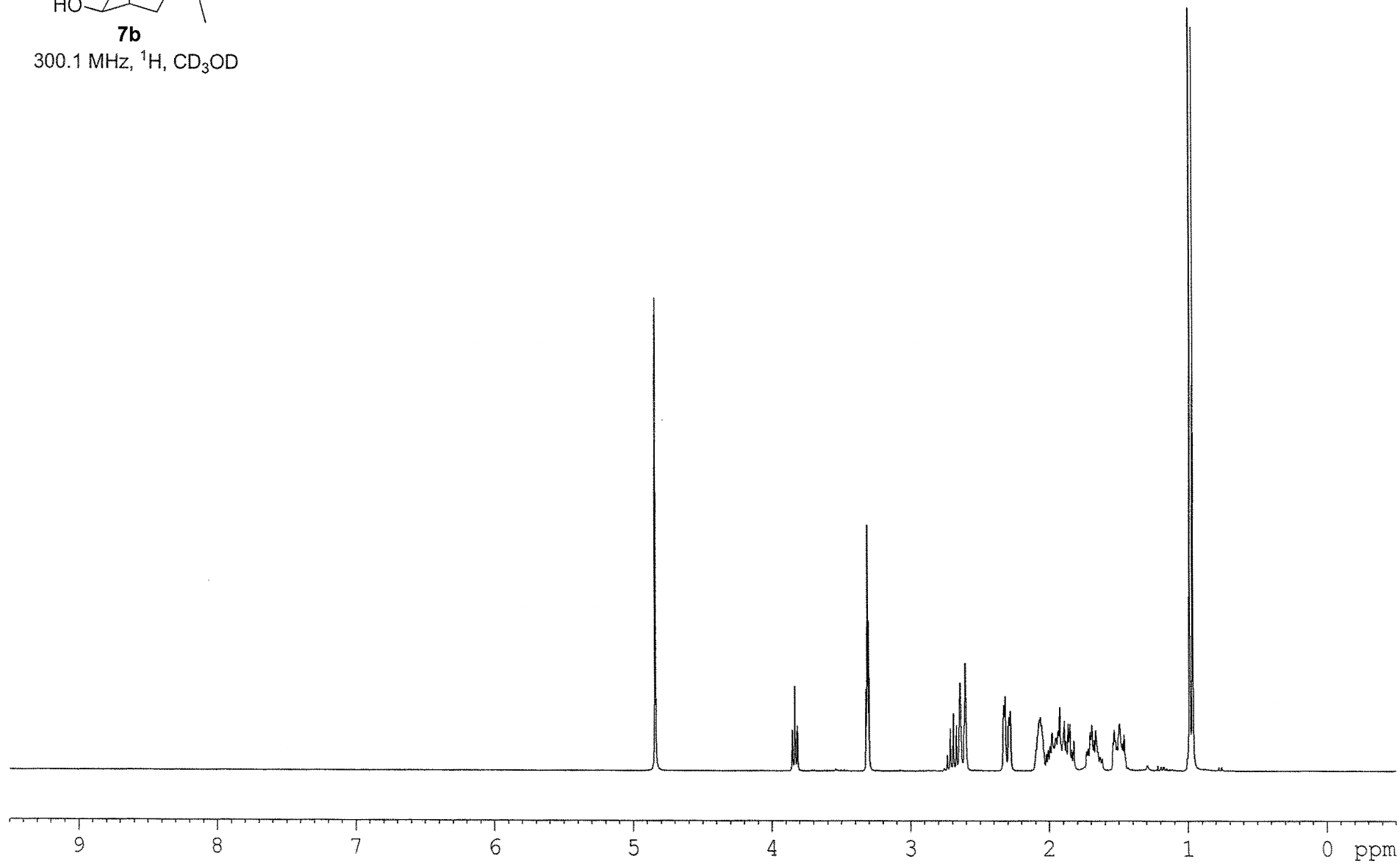
75.5 MHz, ^{13}C , CD_3OD

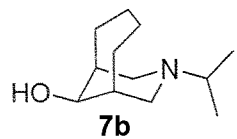




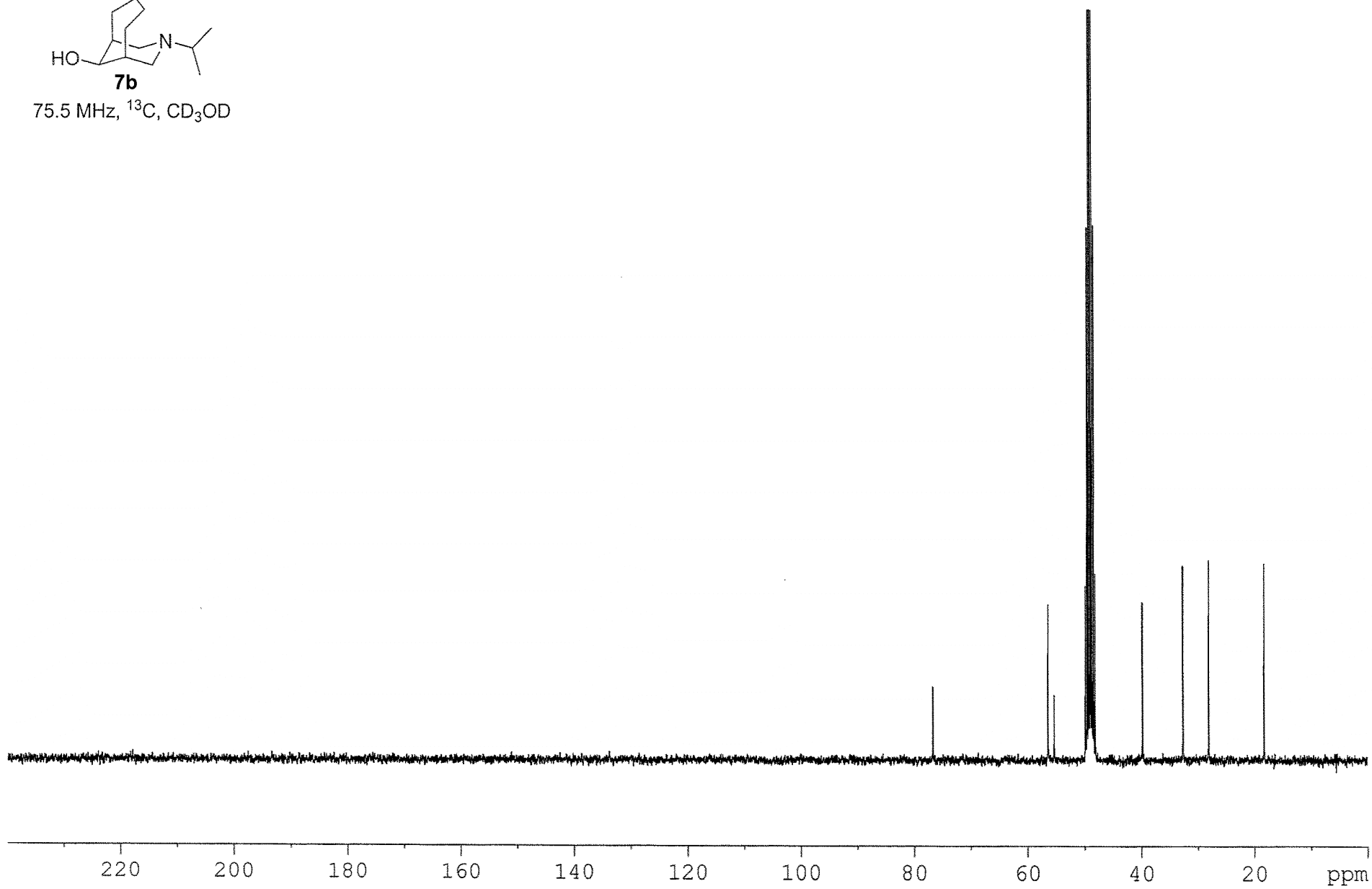
7b

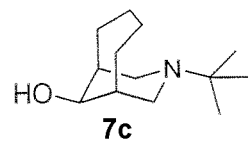
300.1 MHz, ^1H , CD_3OD



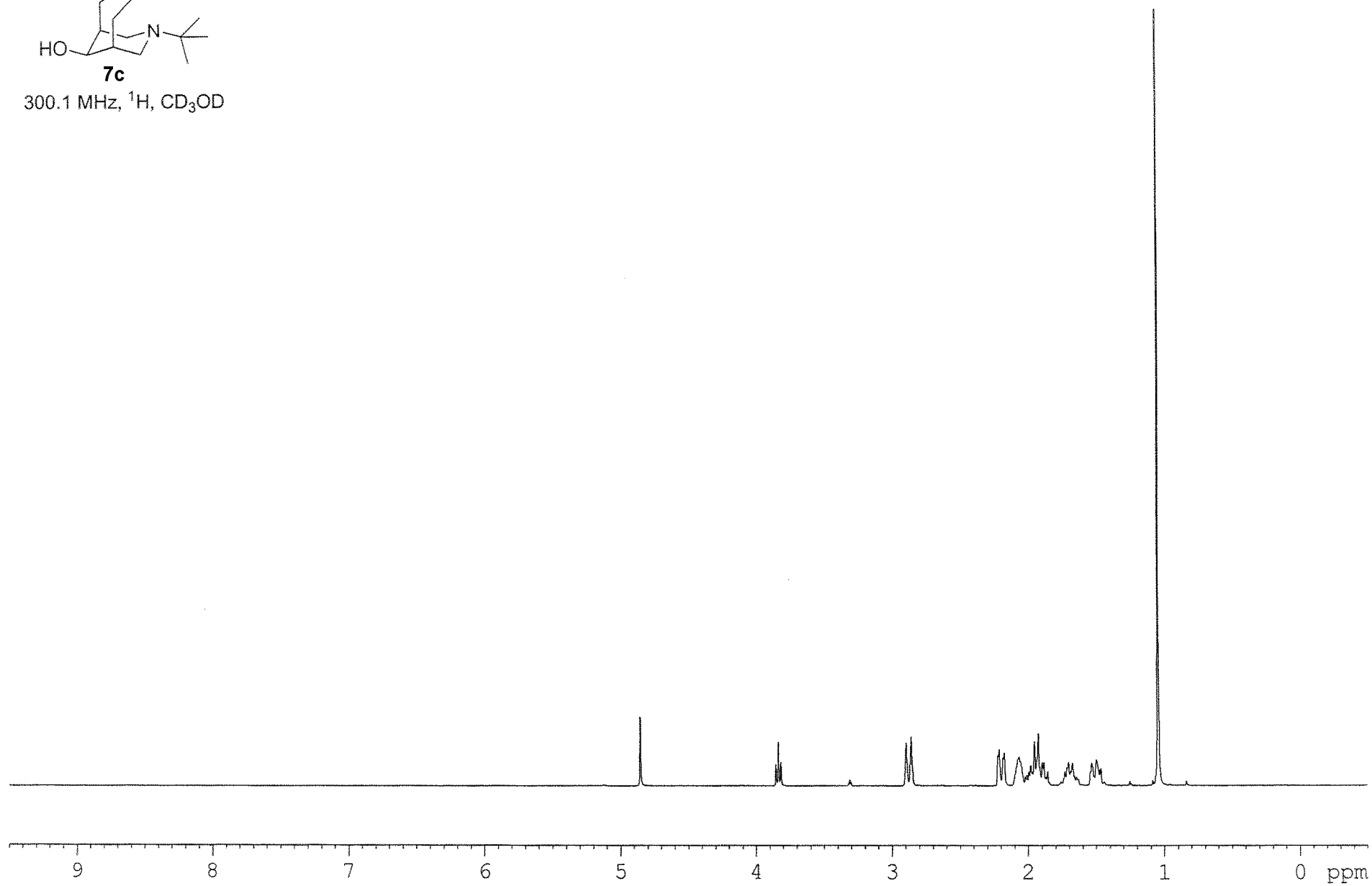


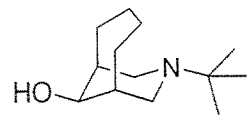
75.5 MHz, ^{13}C , CD_3OD





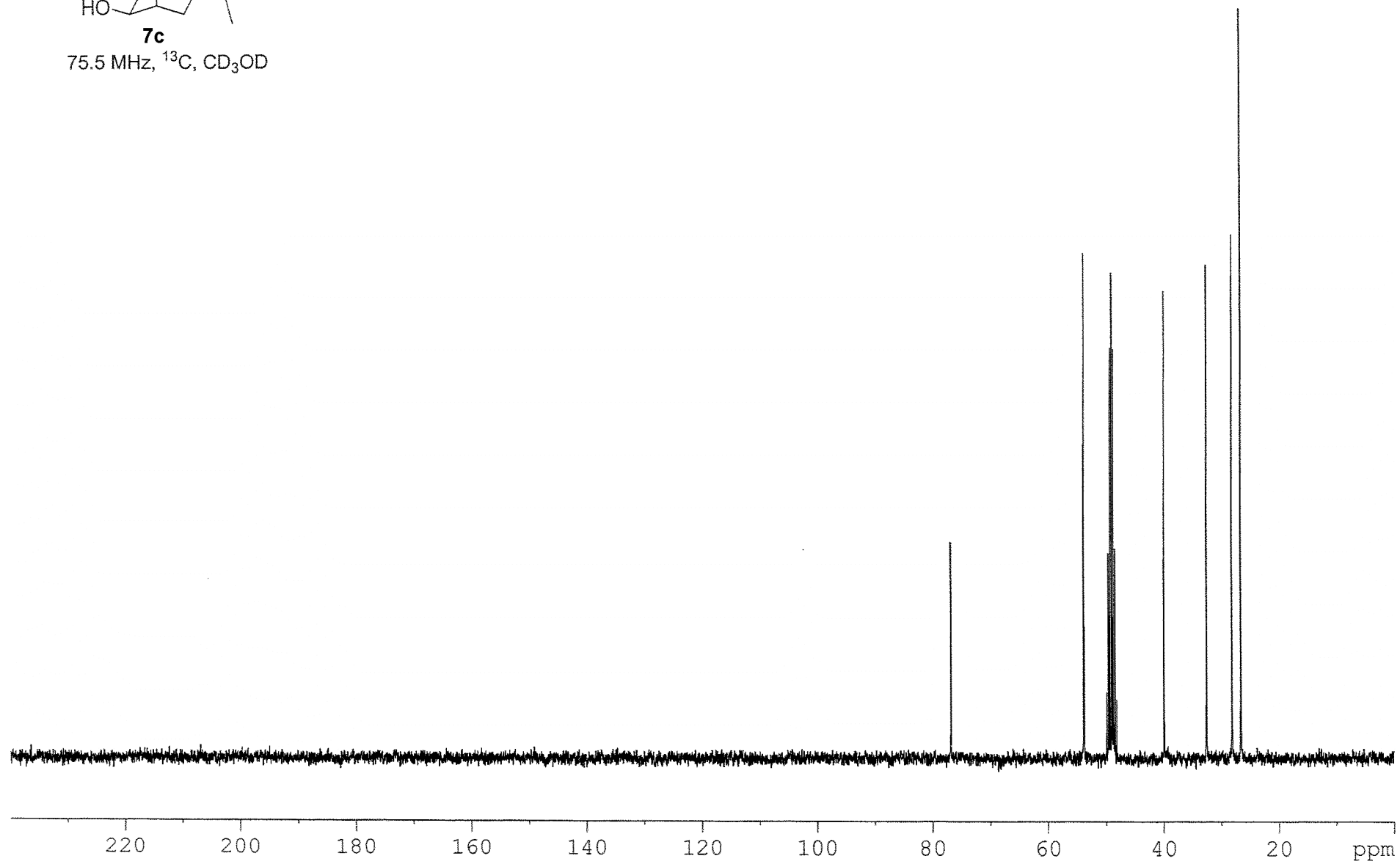
300.1 MHz, ^1H , CD_3OD

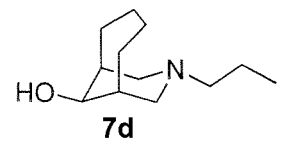




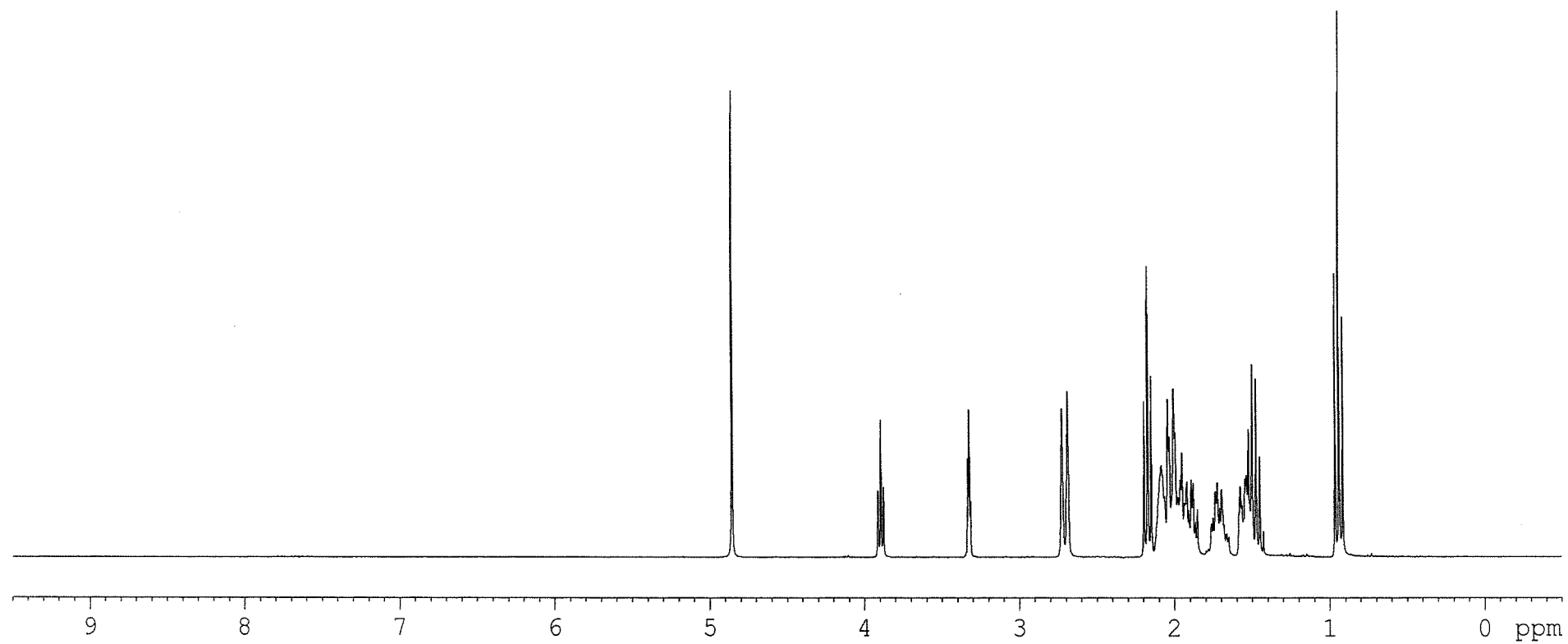
7c

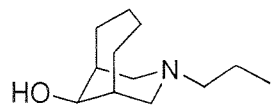
75.5 MHz, ^{13}C , CD_3OD





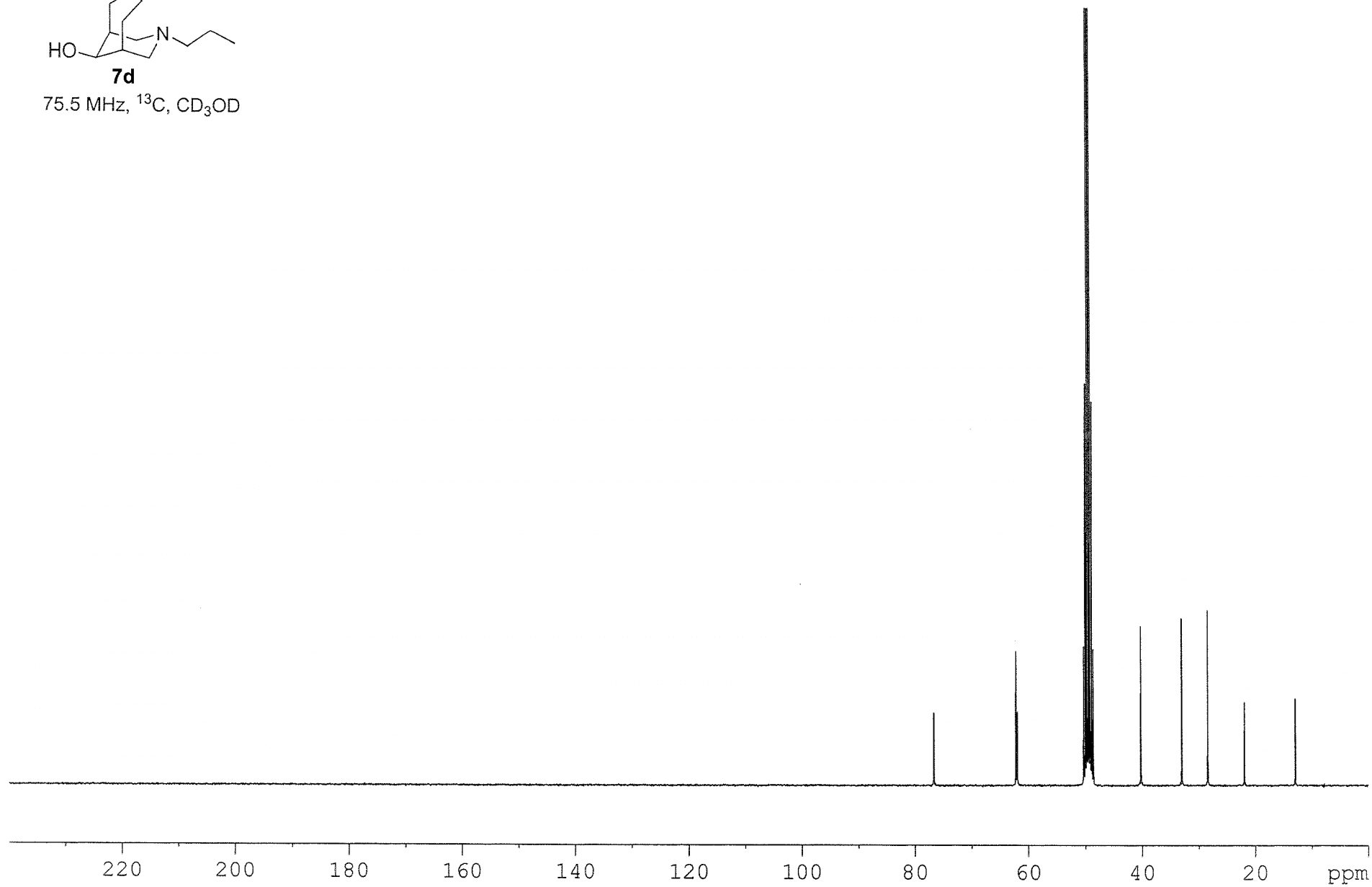
300.1 MHz, ^1H , CD_3OD

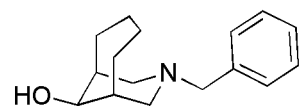




7d

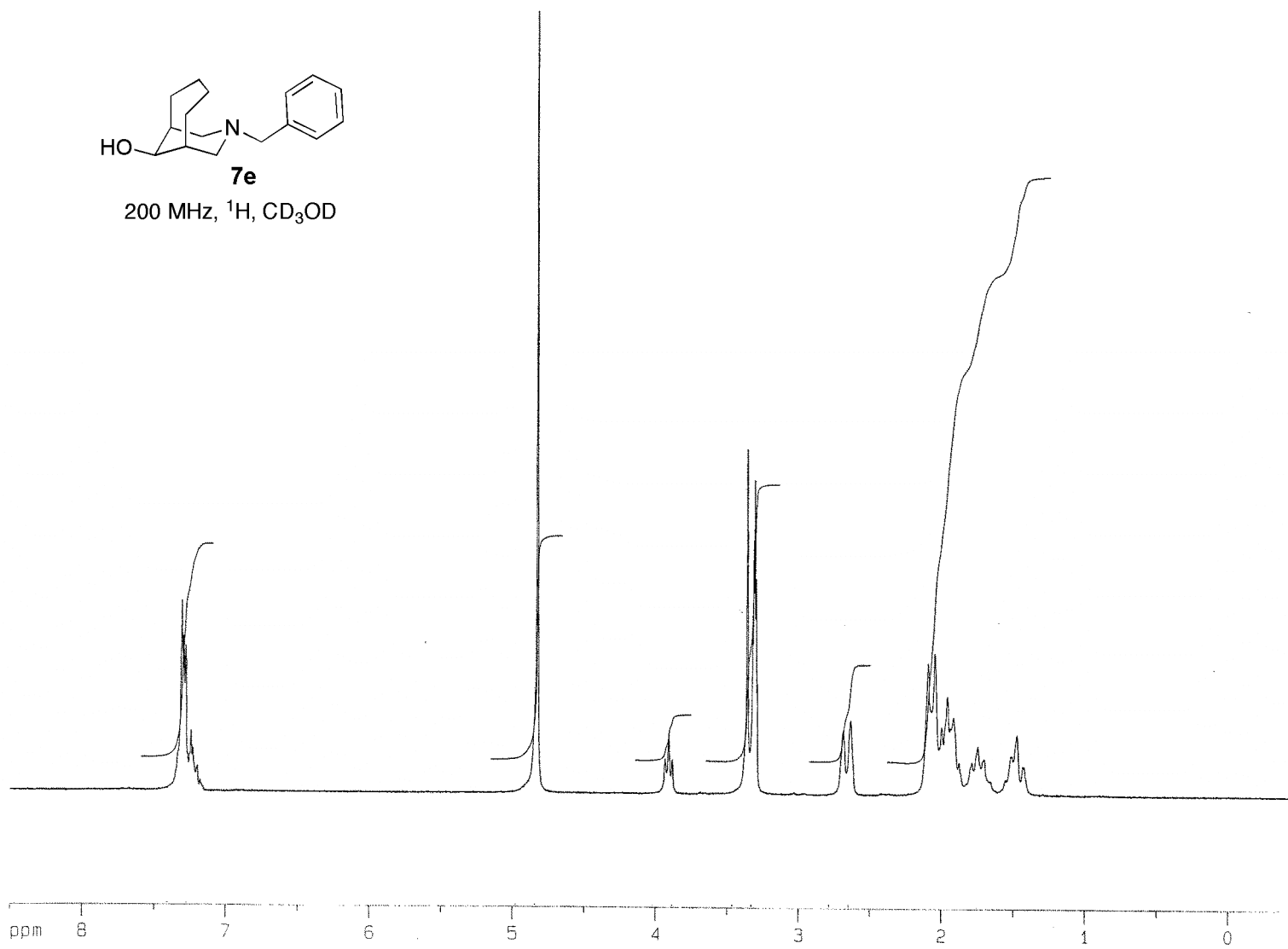
75.5 MHz, ^{13}C , CD_3OD

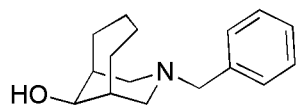




7e

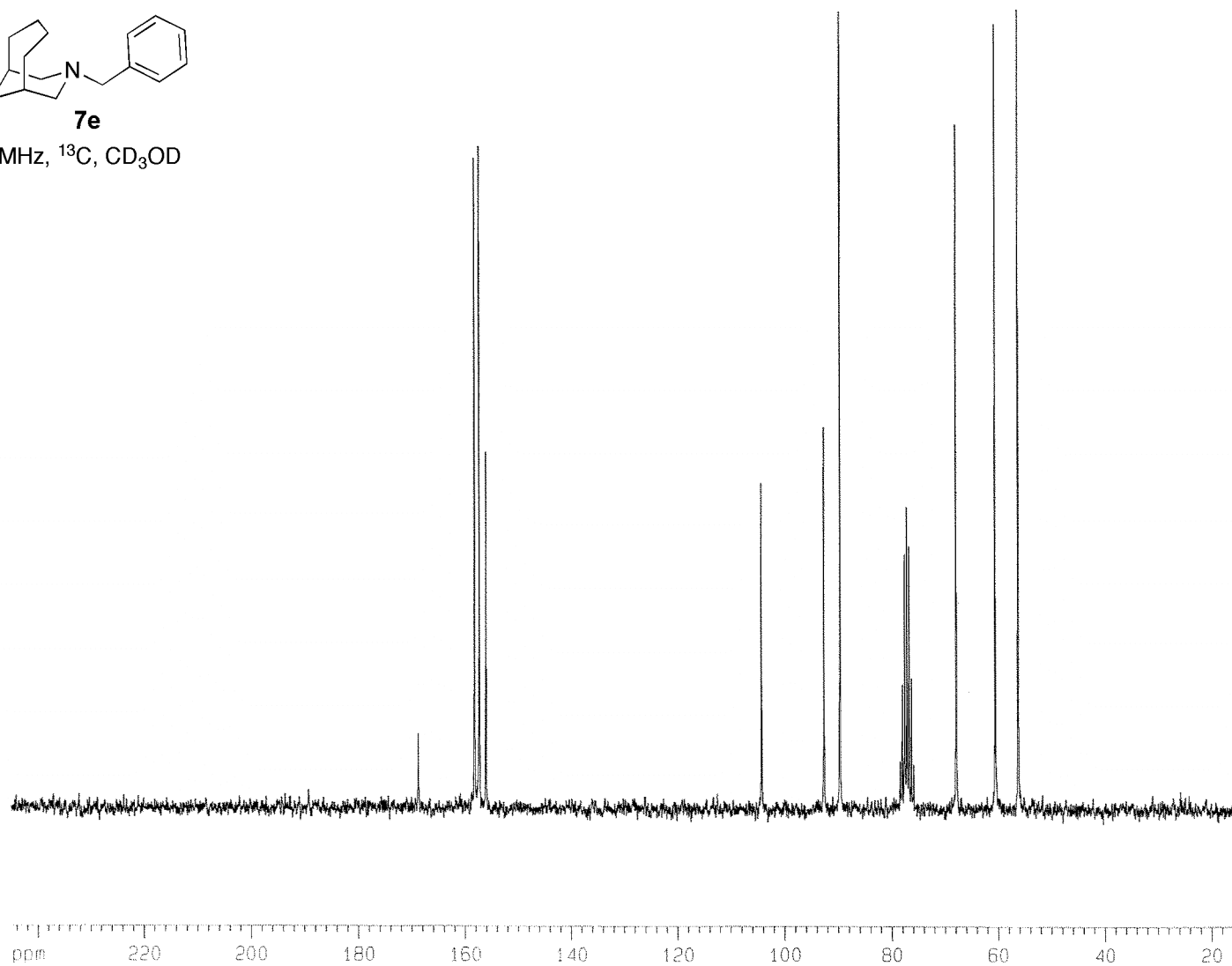
200 MHz, ^1H , CD_3OD

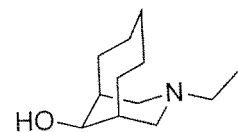




7e

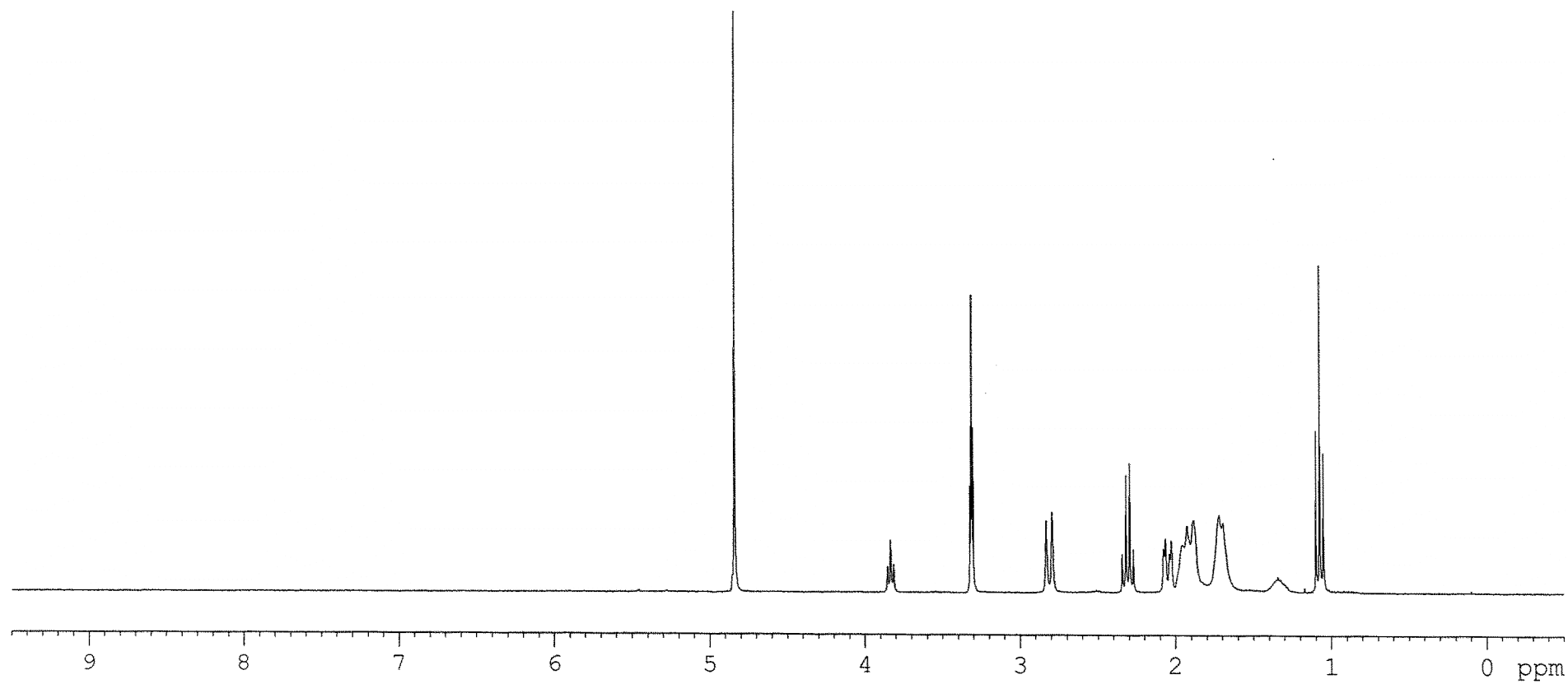
50 MHz, ^{13}C , CD_3OD

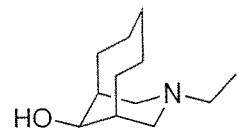




7f

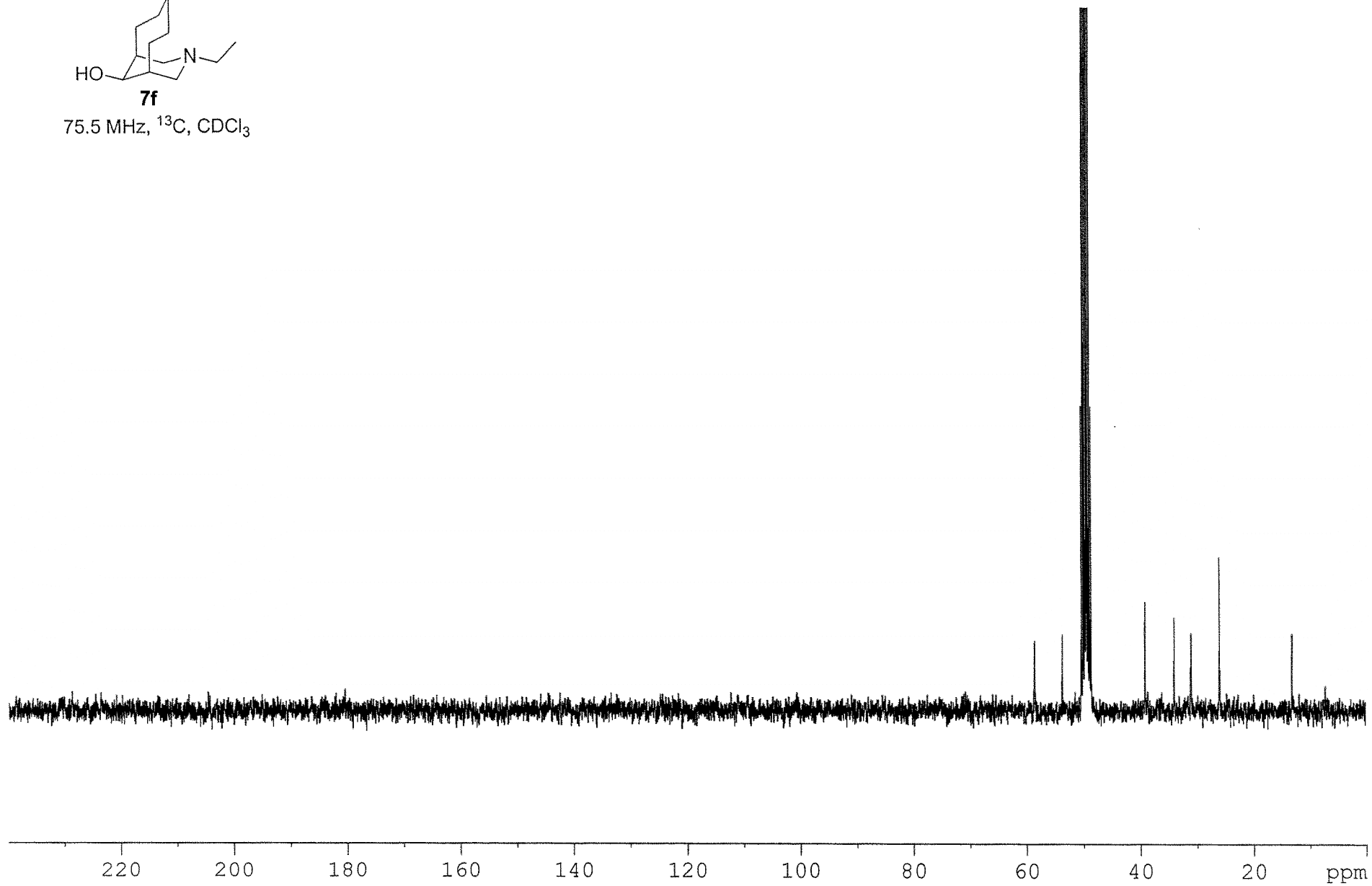
300.1 MHz, ^1H , CDCl_3

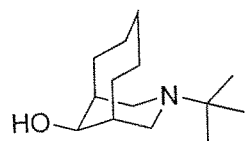




7f

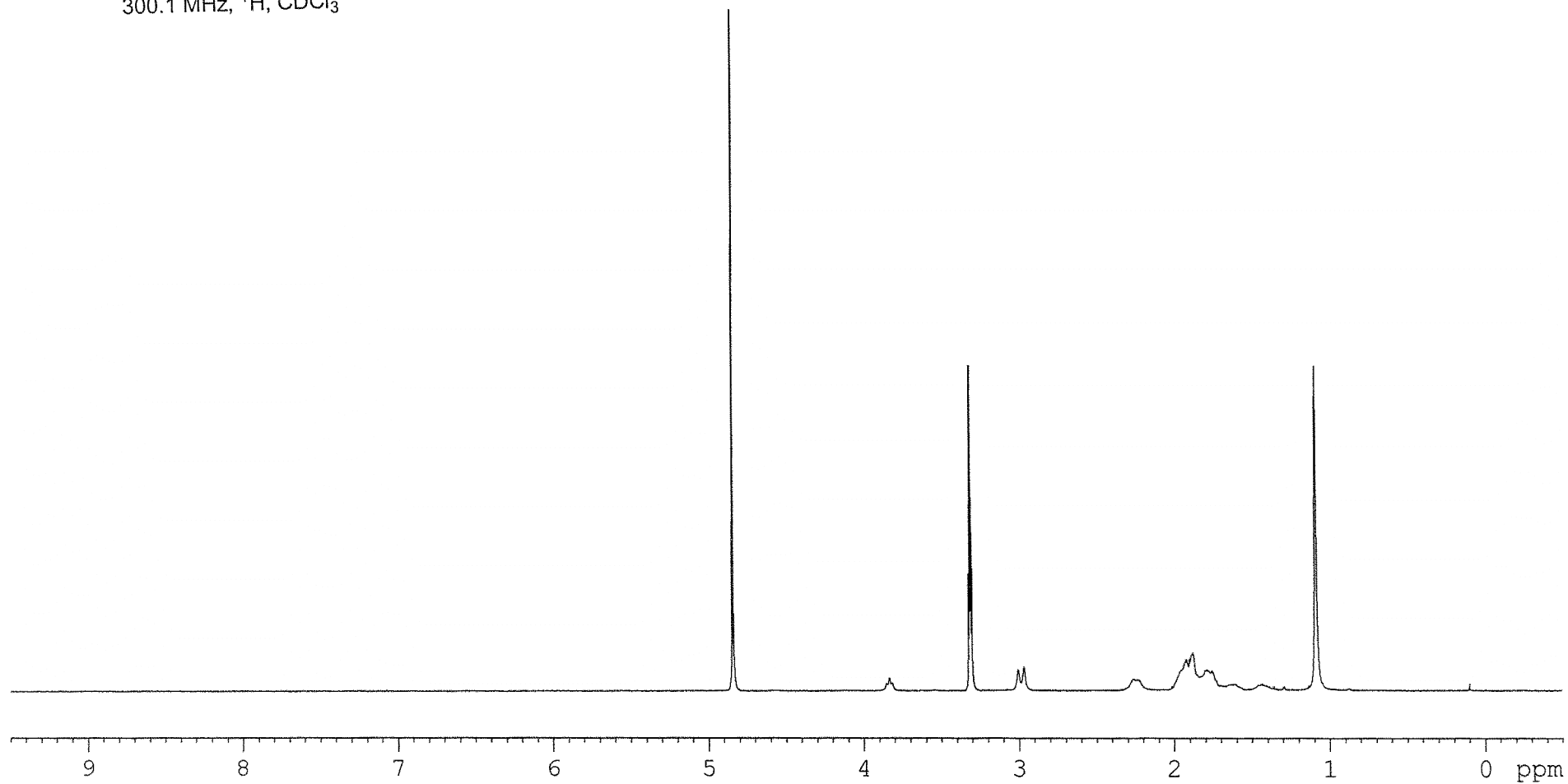
75.5 MHz, ^{13}C , CDCl_3

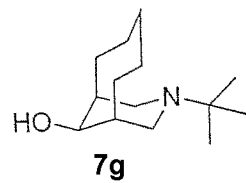




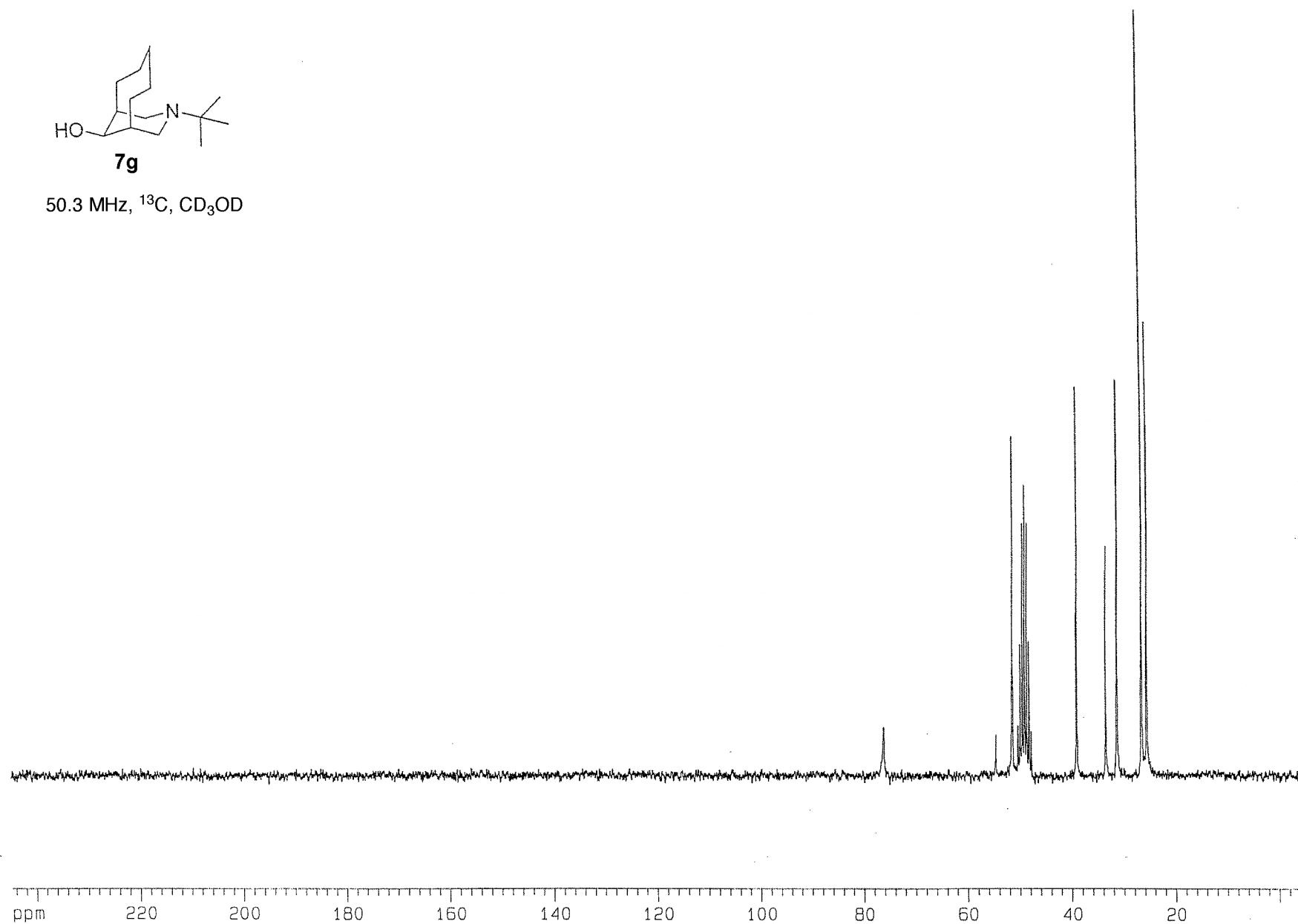
7g

300.1 MHz, ^1H , CDCl_3





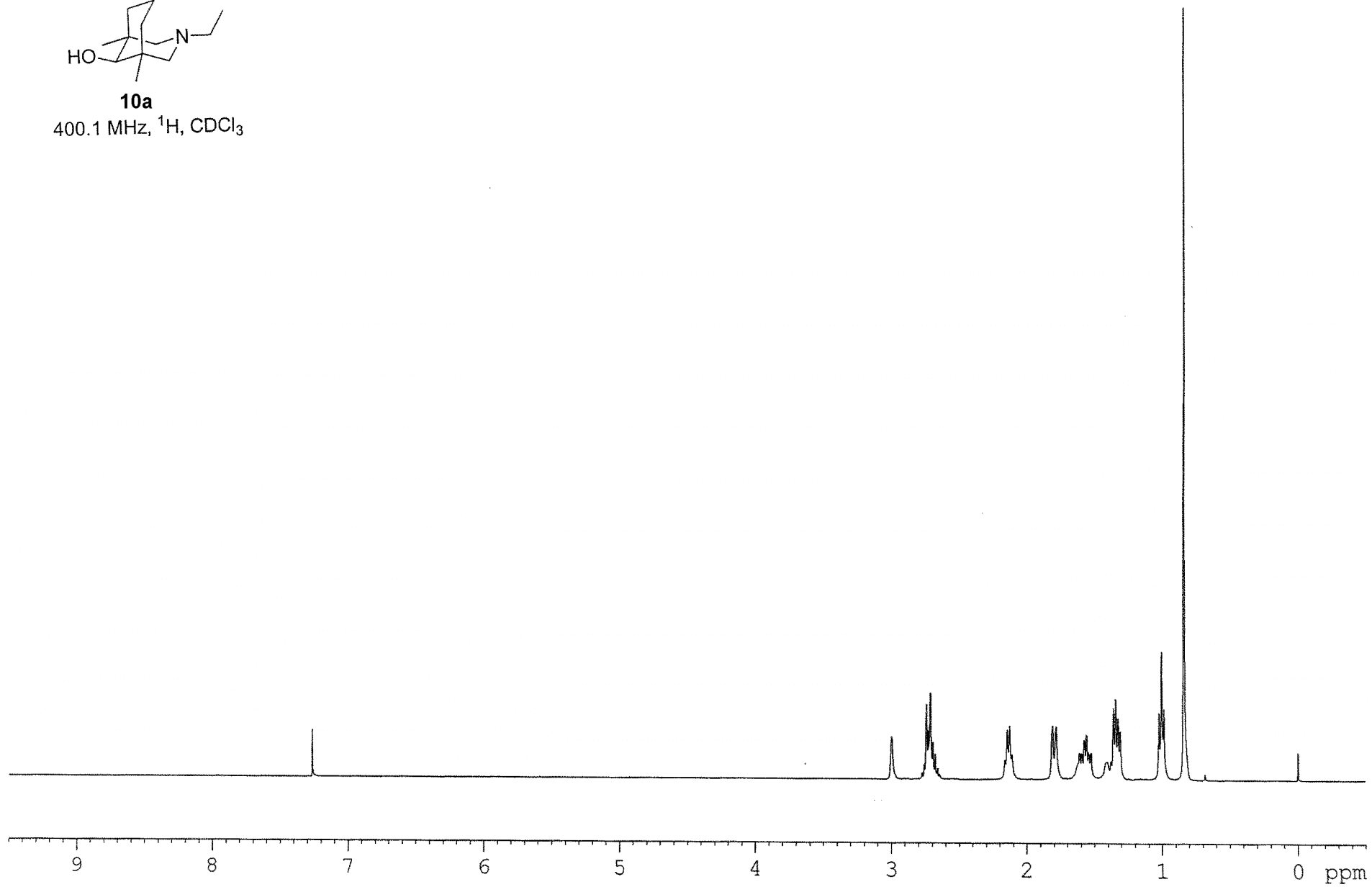
50.3 MHz, ^{13}C , CD_3OD





10a

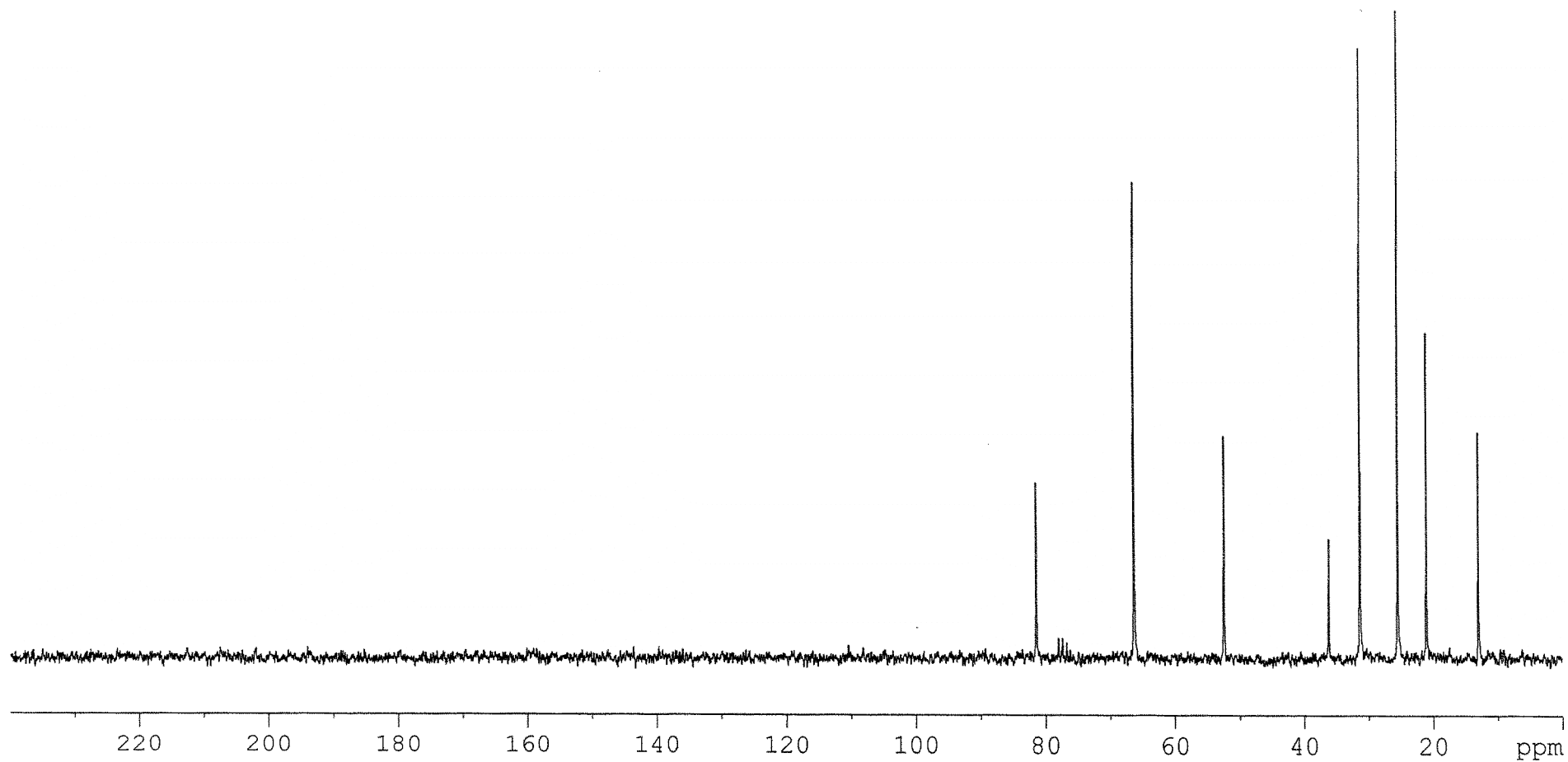
400.1 MHz, ^1H , CDCl_3

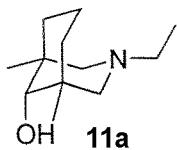




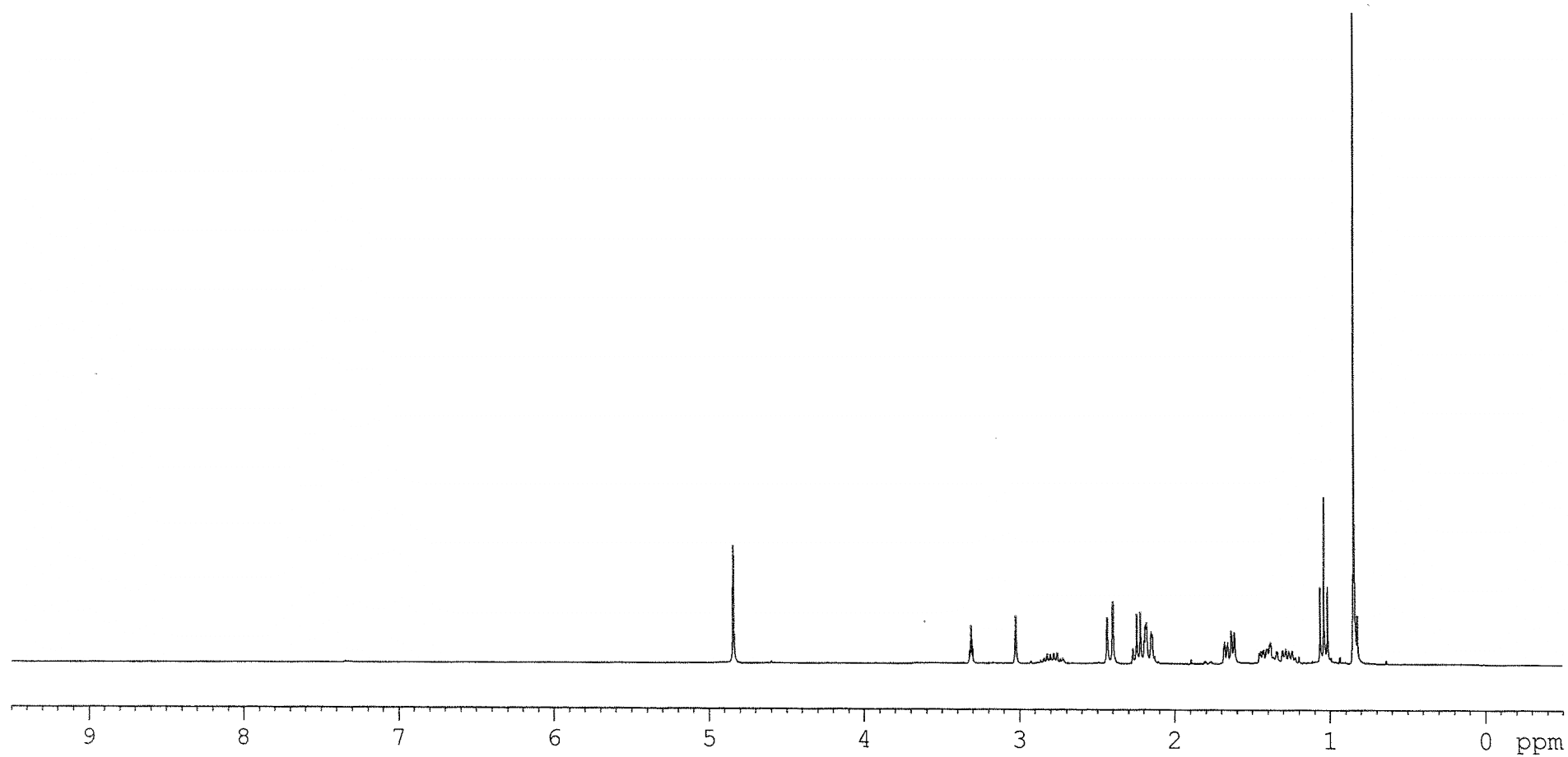
10a

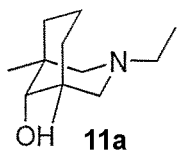
50.3 MHz, ^{13}C , CDCl_3



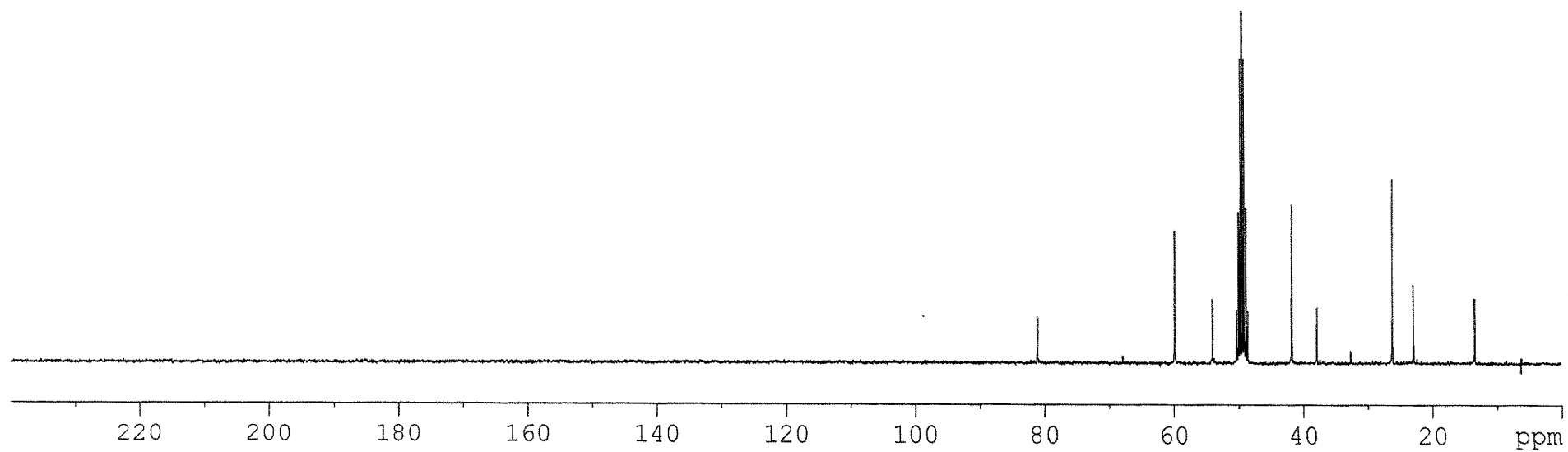


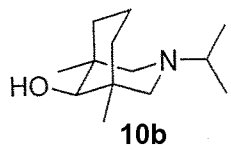
300.1 MHz, ^1H , CD_3OD



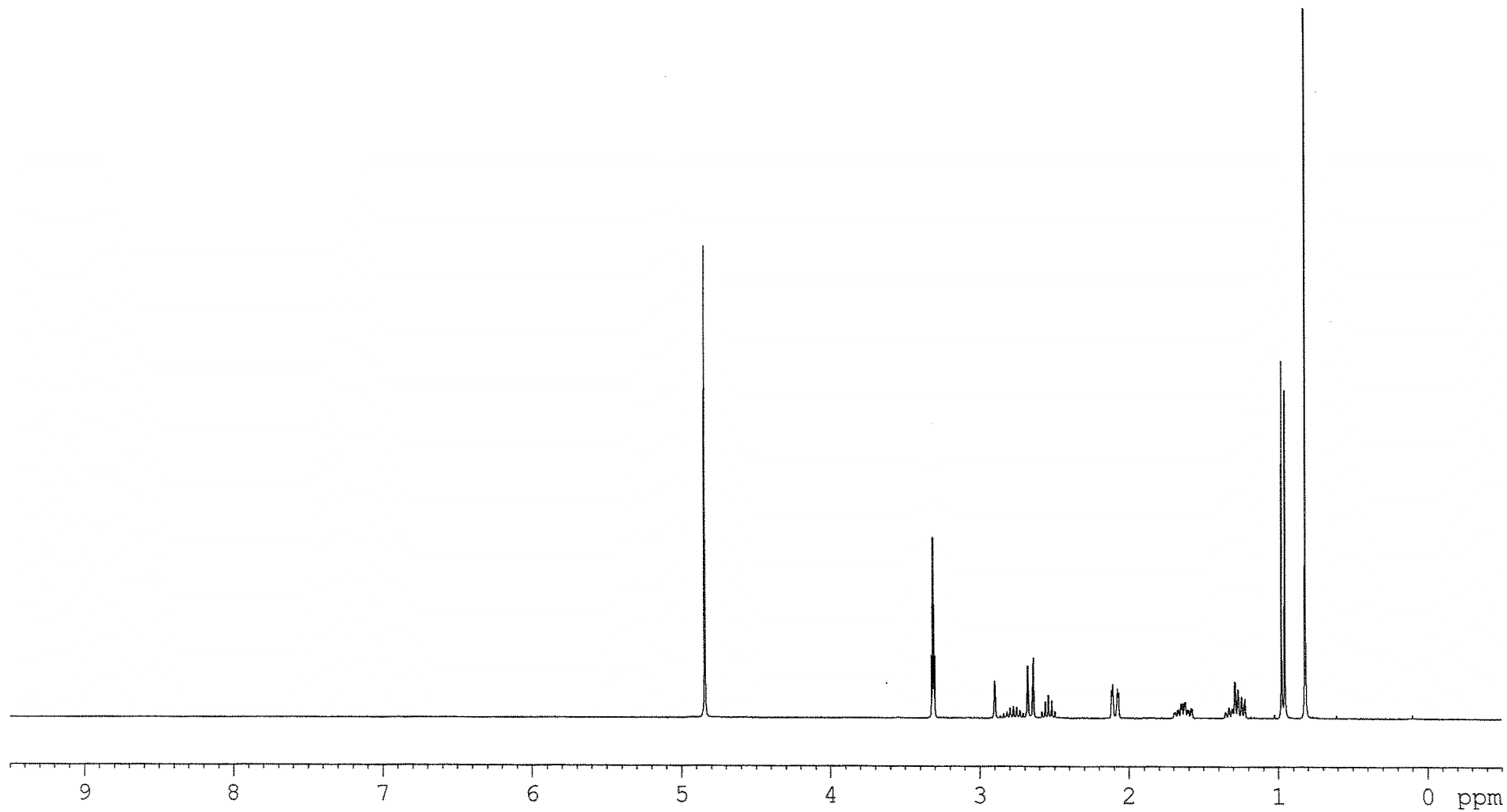


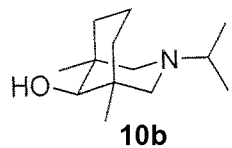
75.5 MHz, ^{13}C , CD_3OD



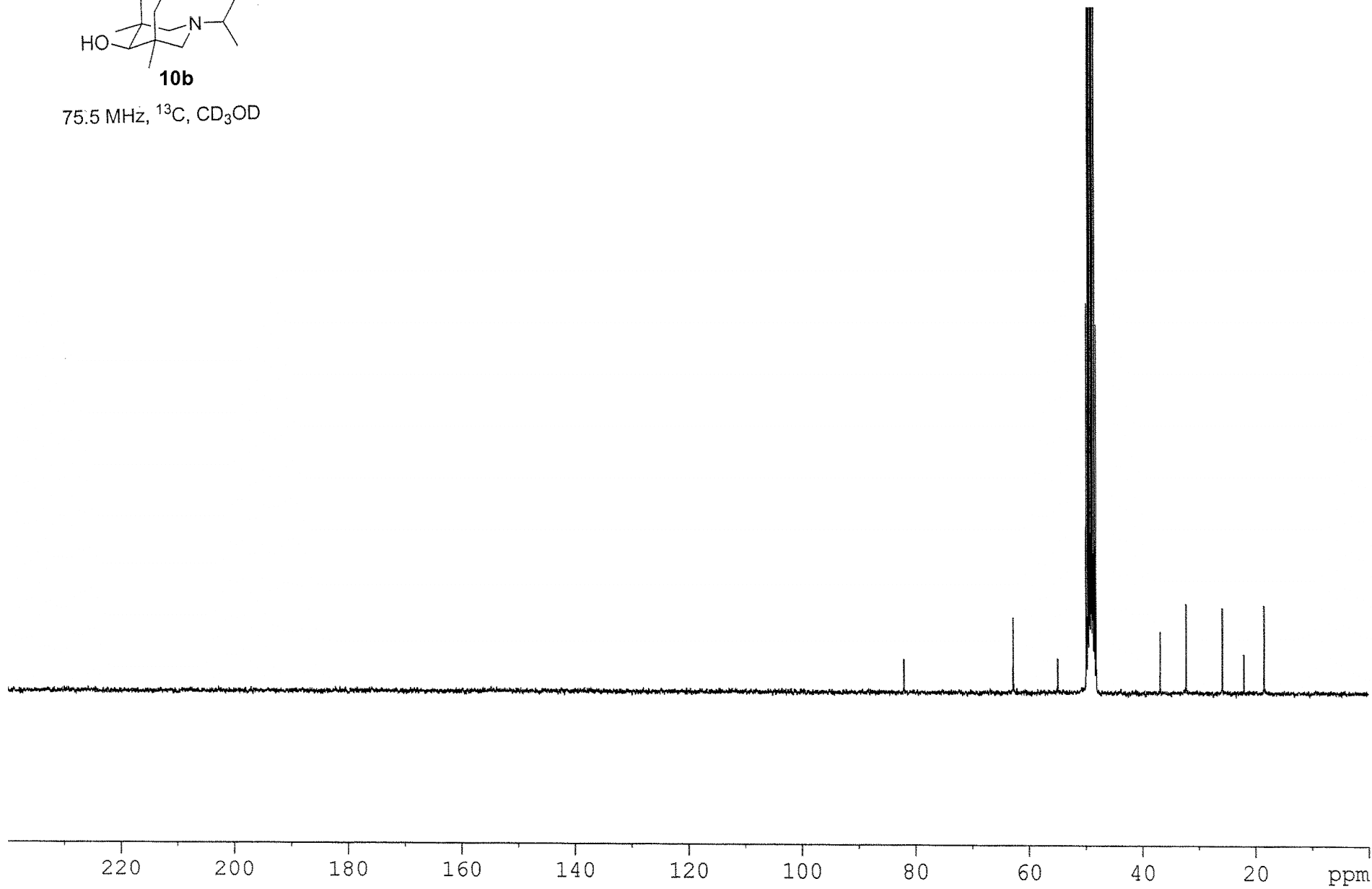


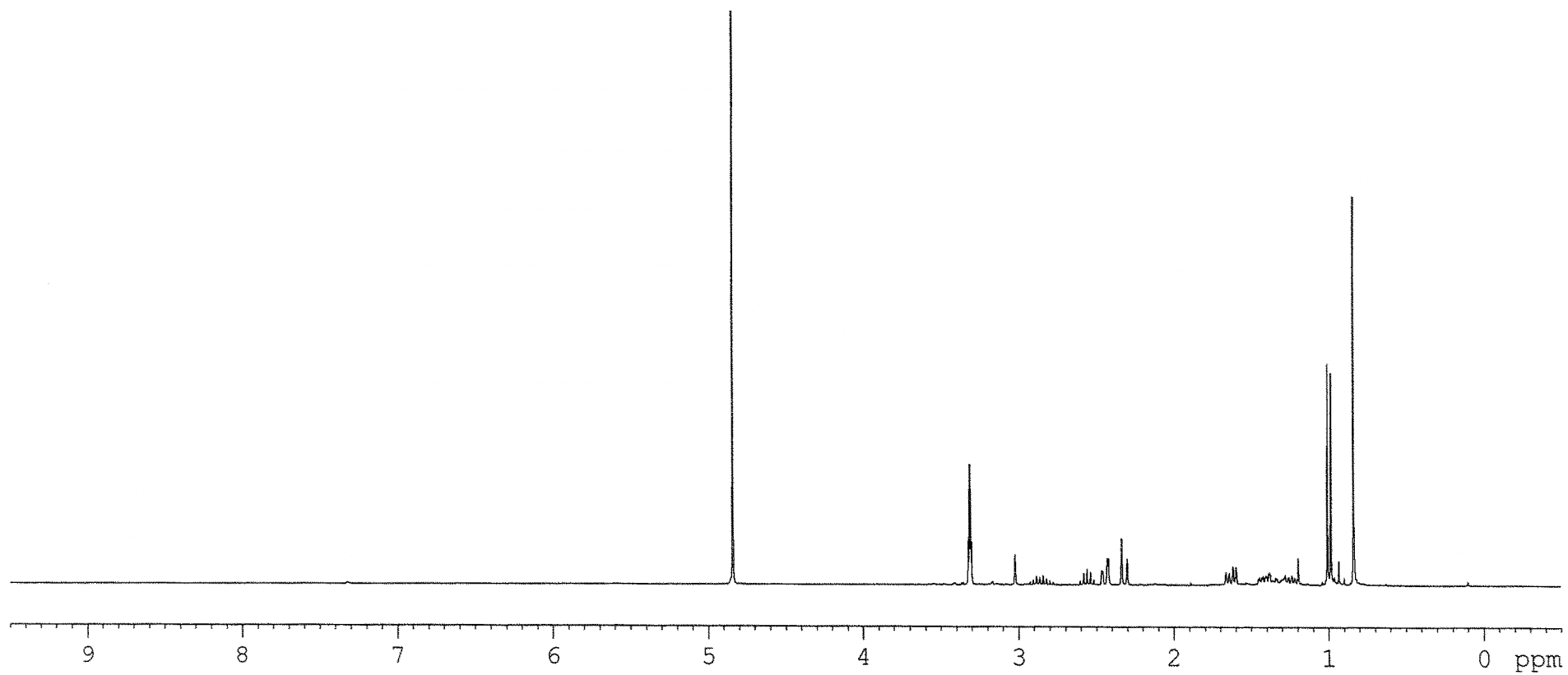
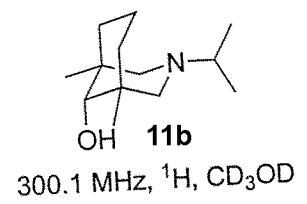
300.1 MHz, ¹H, CD₃OD

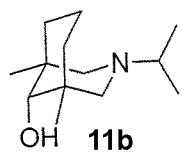




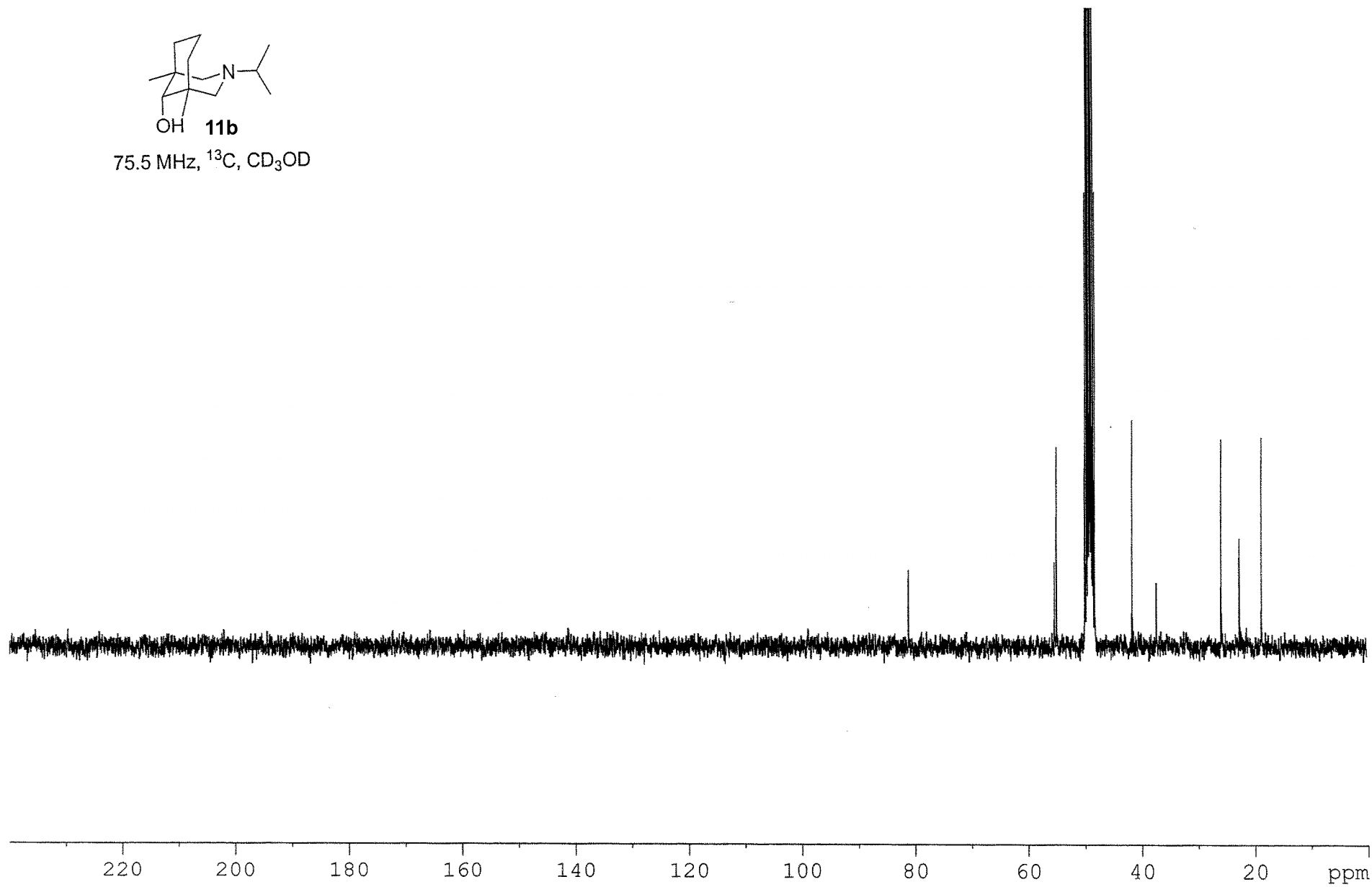
75.5 MHz, ^{13}C , CD_3OD

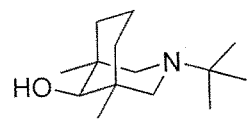






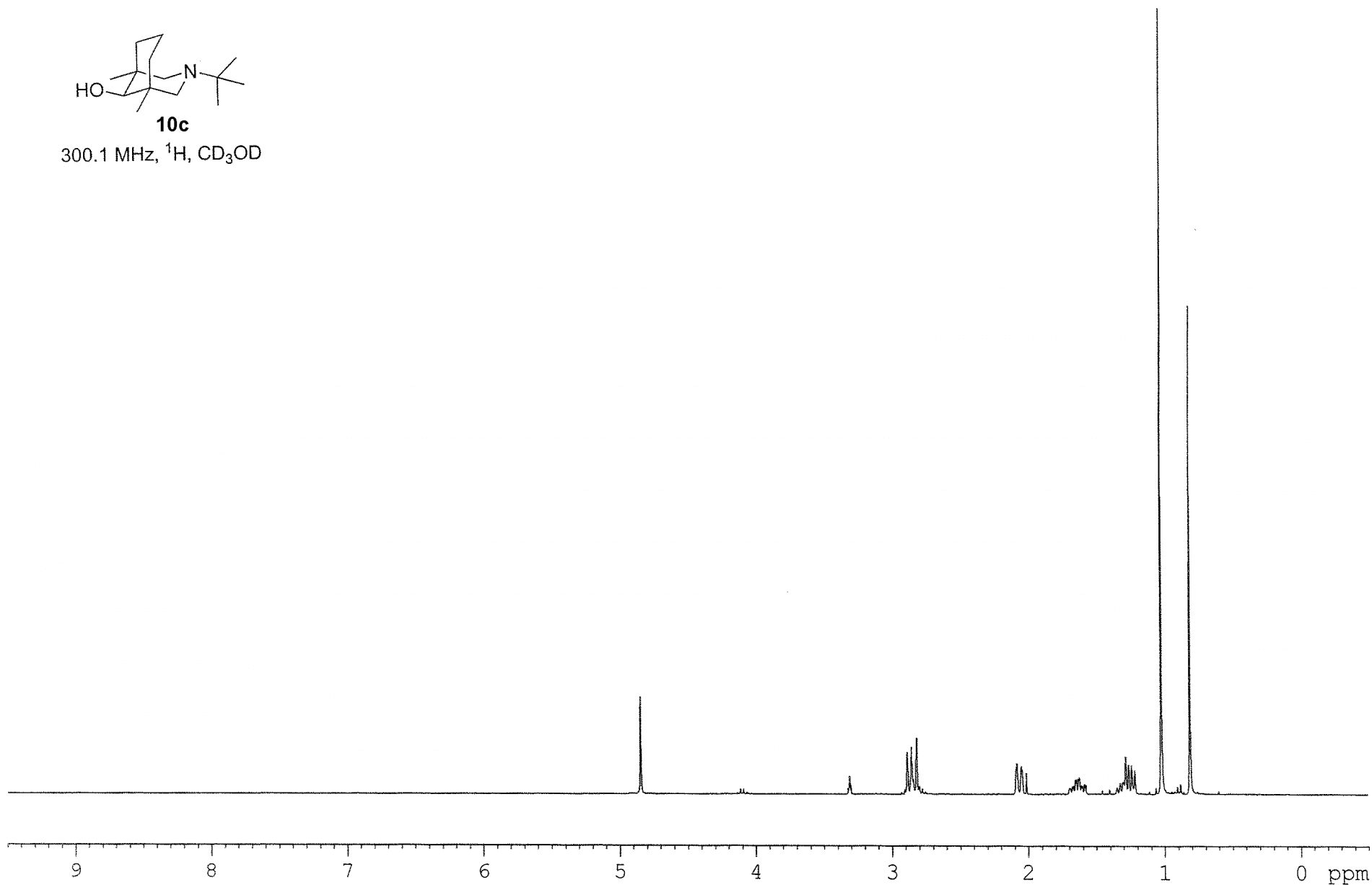
75.5 MHz, ^{13}C , CD_3OD

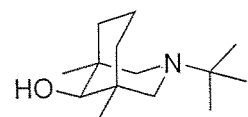




10c

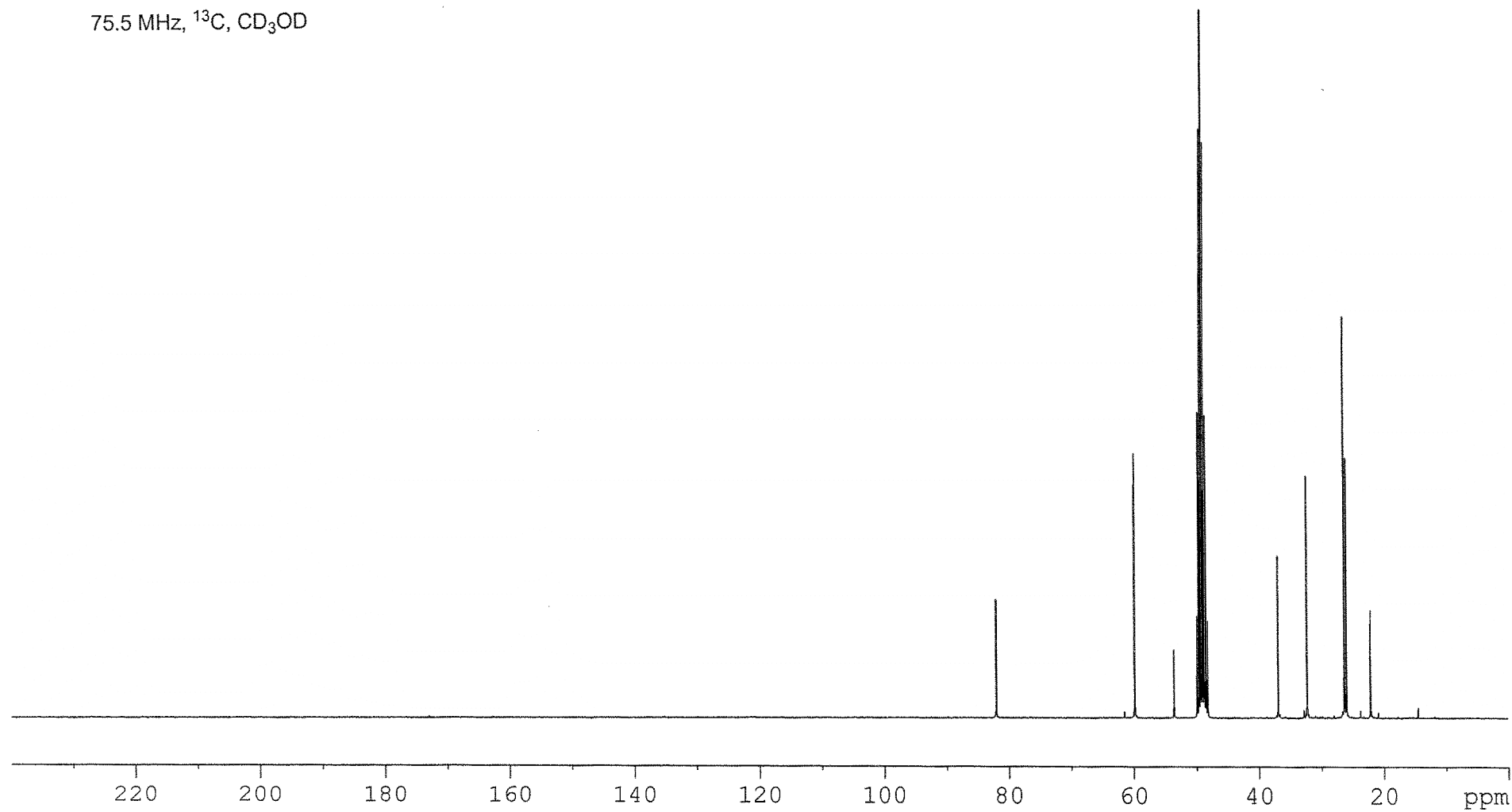
300.1 MHz, ^1H , CD_3OD

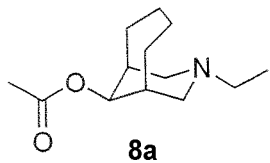




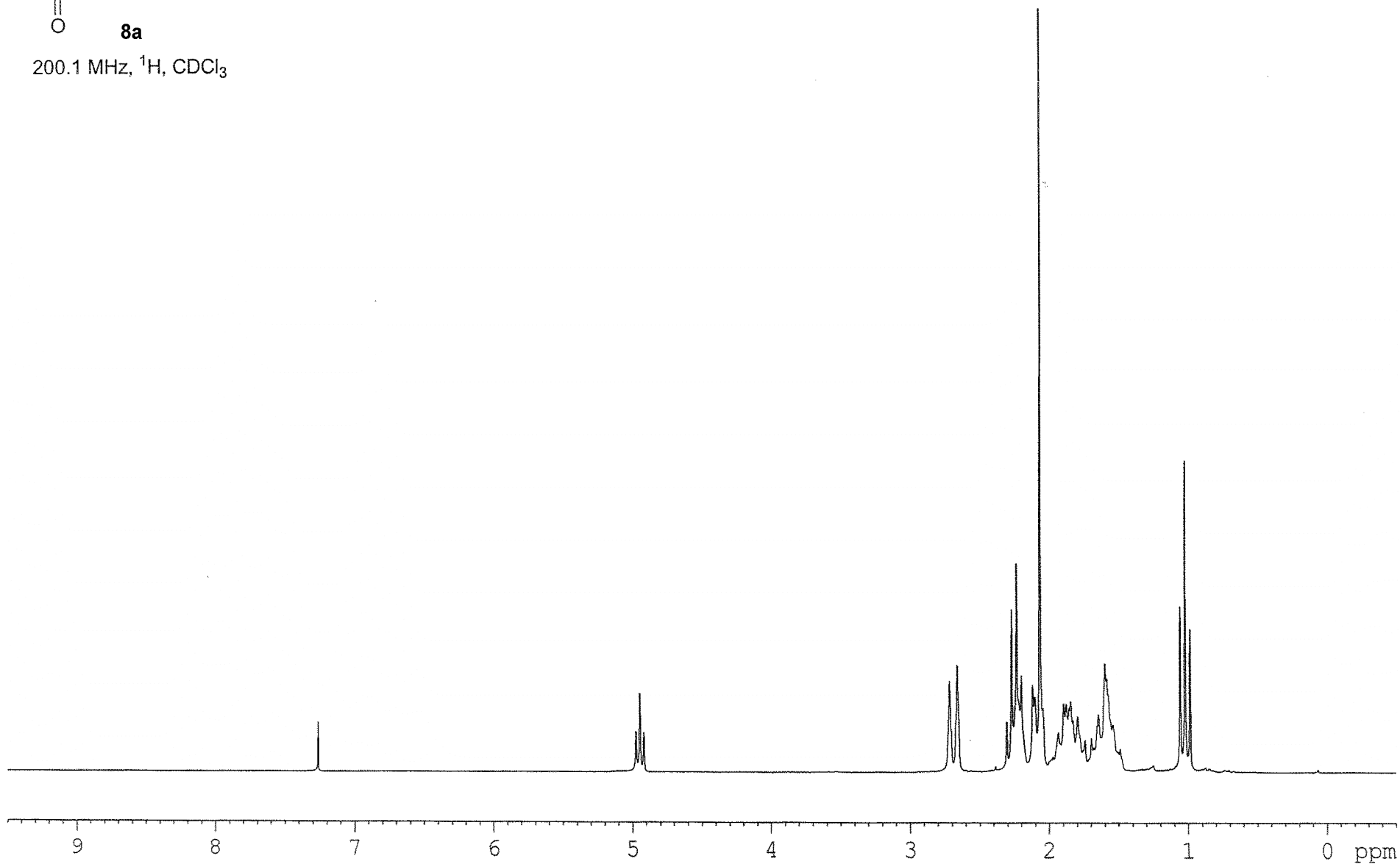
10c

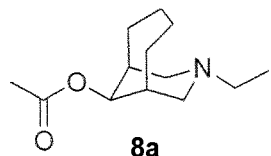
75.5 MHz, ^{13}C , CD_3OD



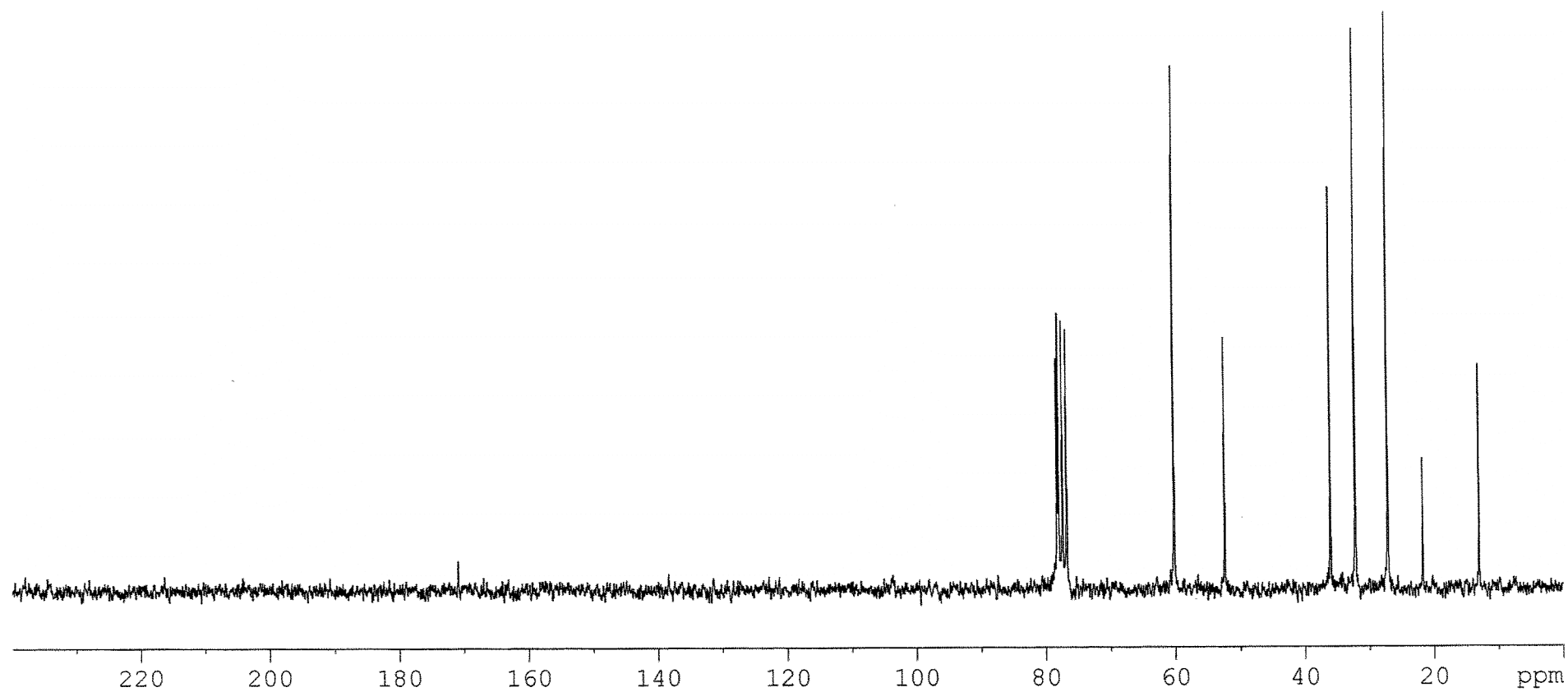


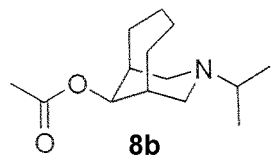
200.1 MHz, ^1H , CDCl_3



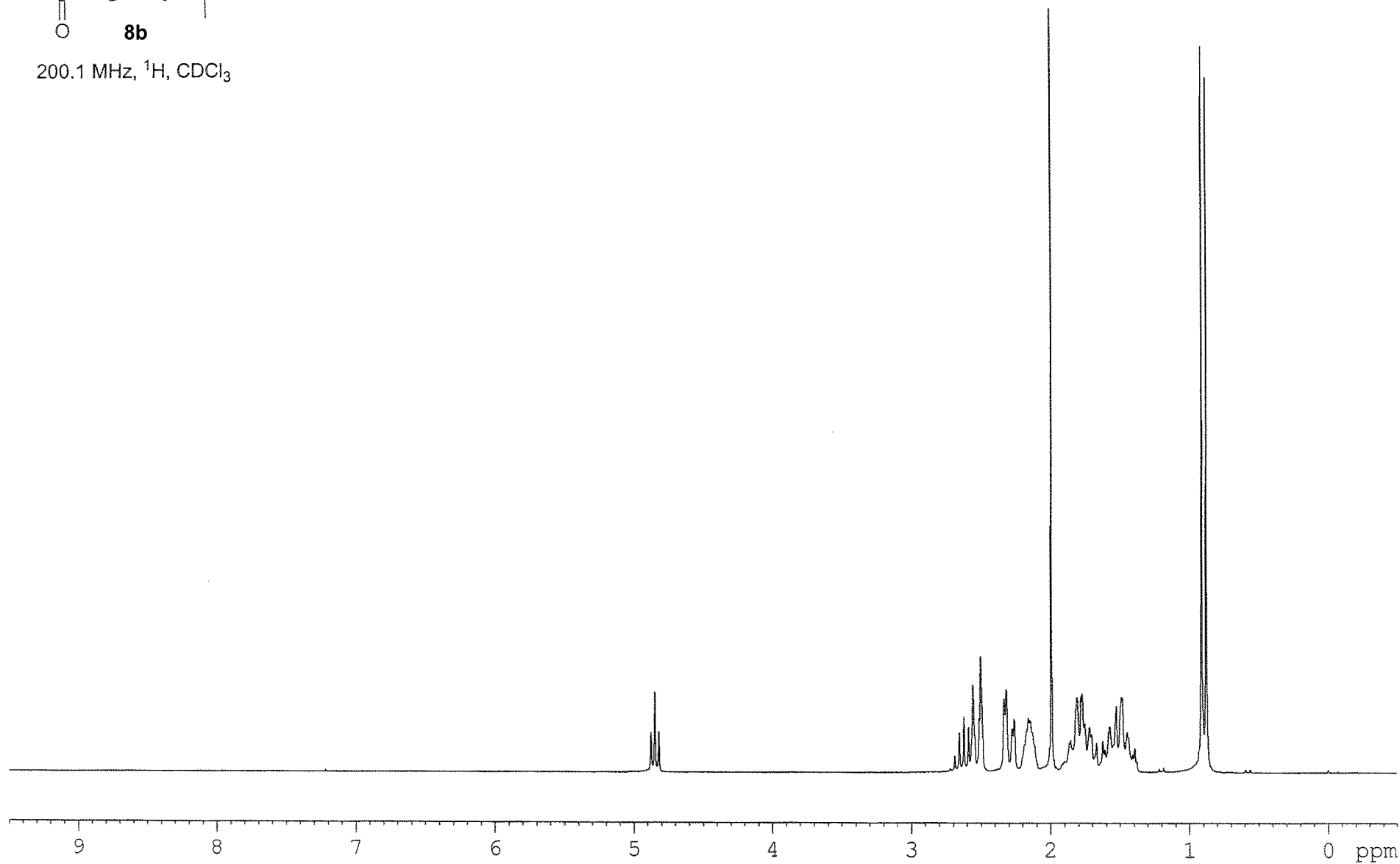


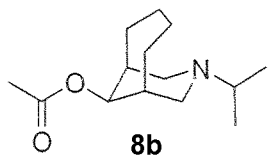
50.3 MHz, ^{13}C , CDCl_3



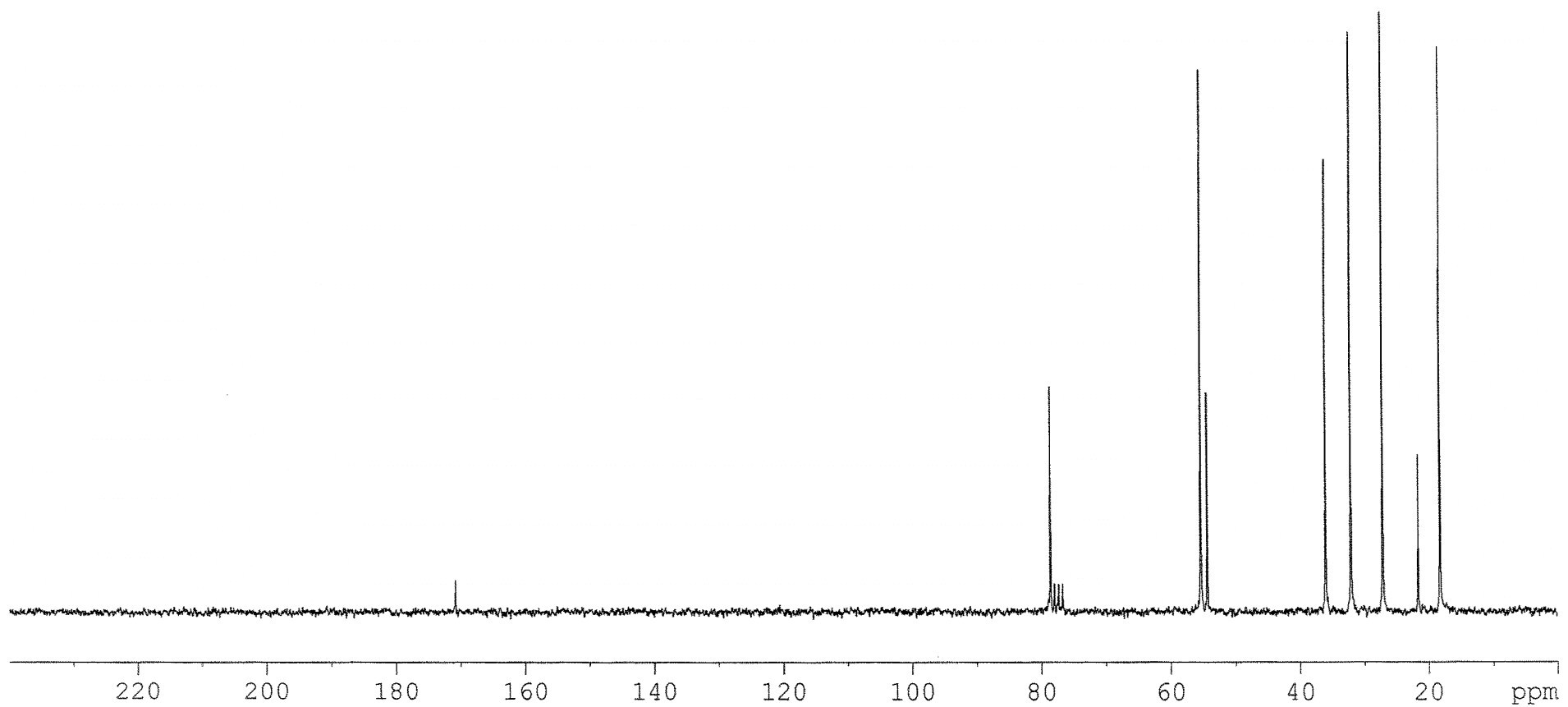


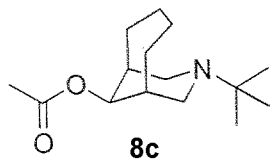
200.1 MHz, ^1H , CDCl_3



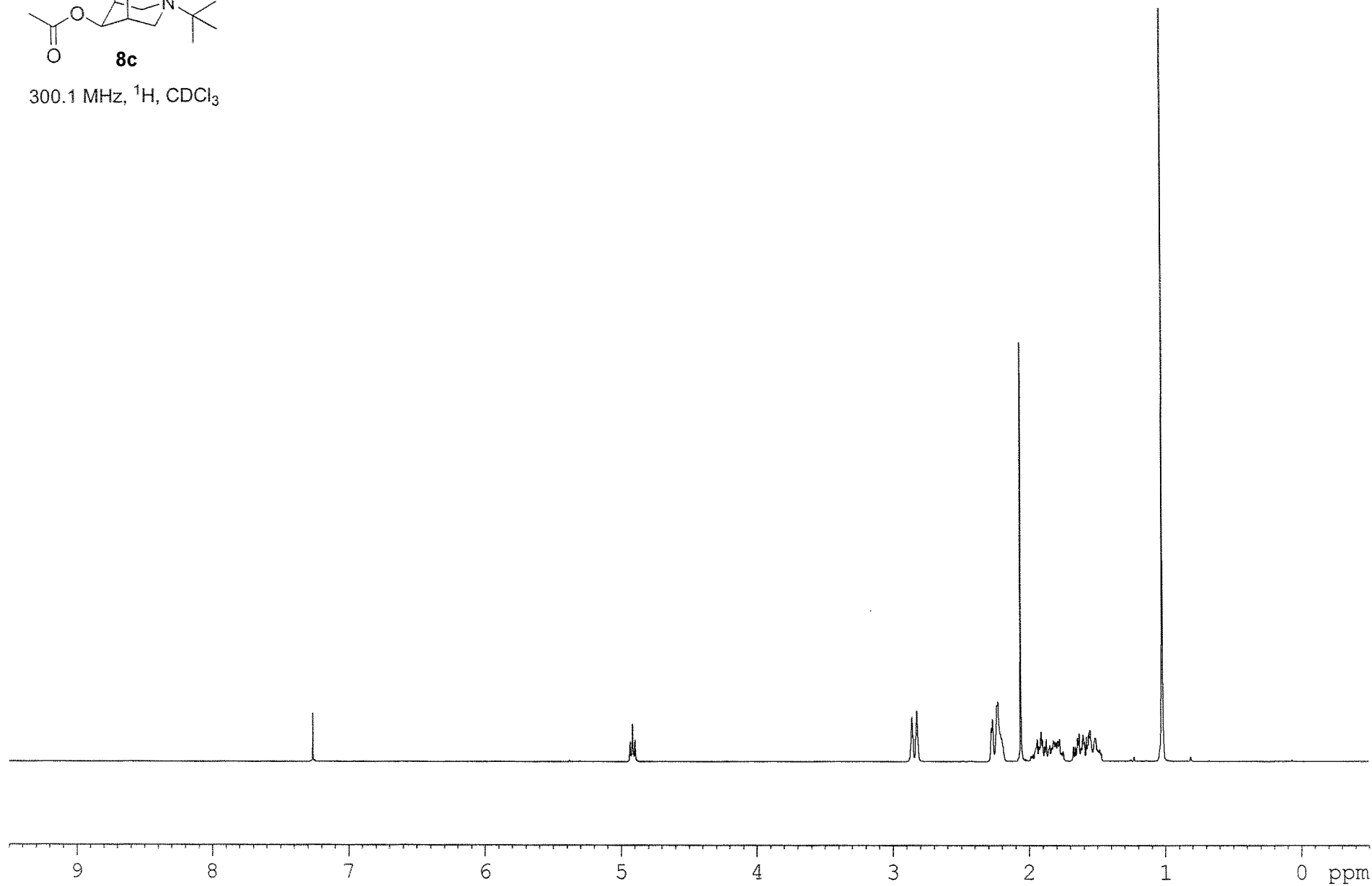


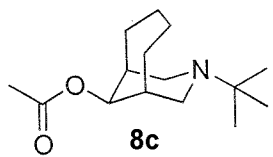
50.3 MHz, ^{13}C , CDCl_3



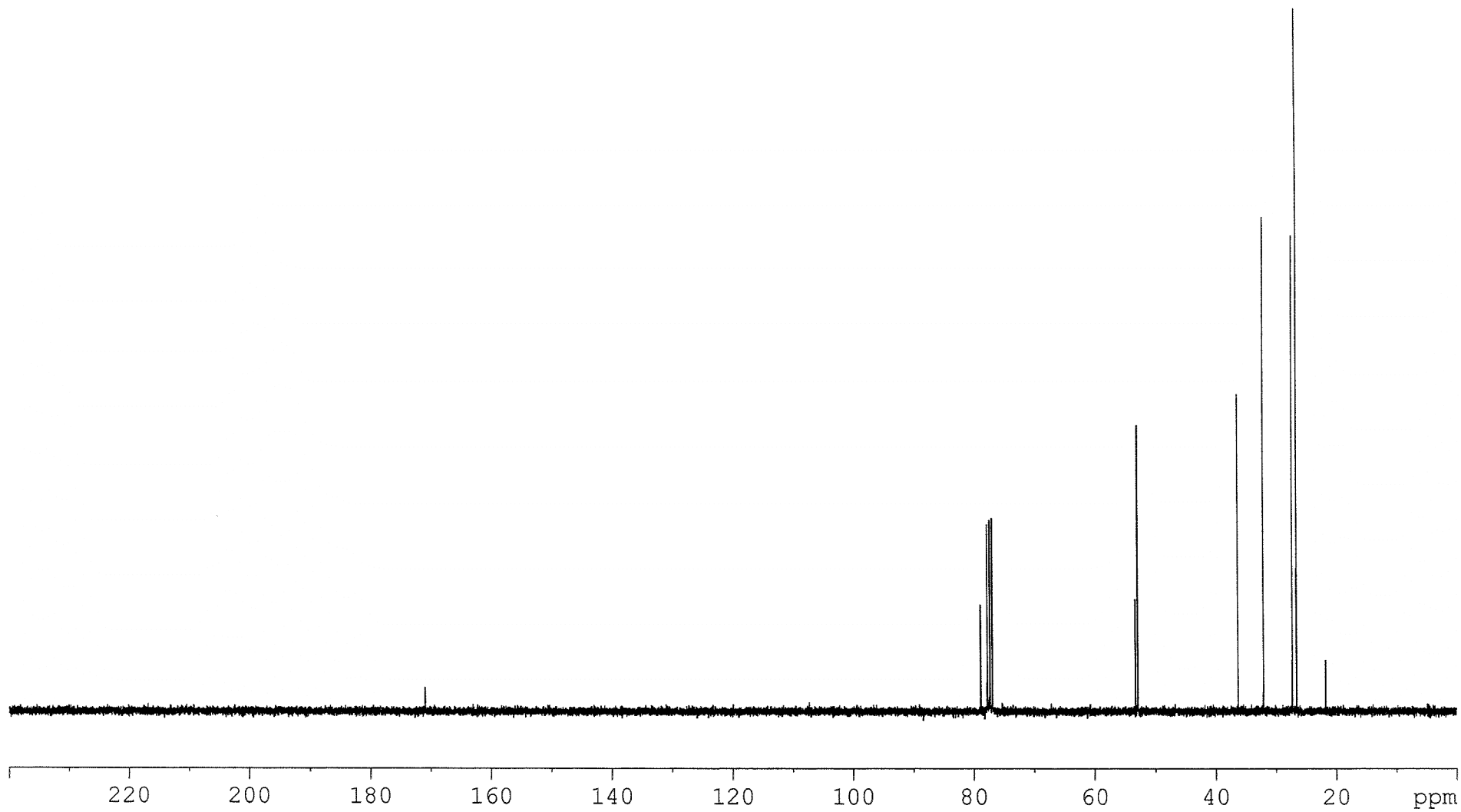


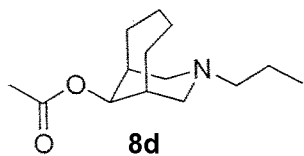
300.1 MHz, ^1H , CDCl_3



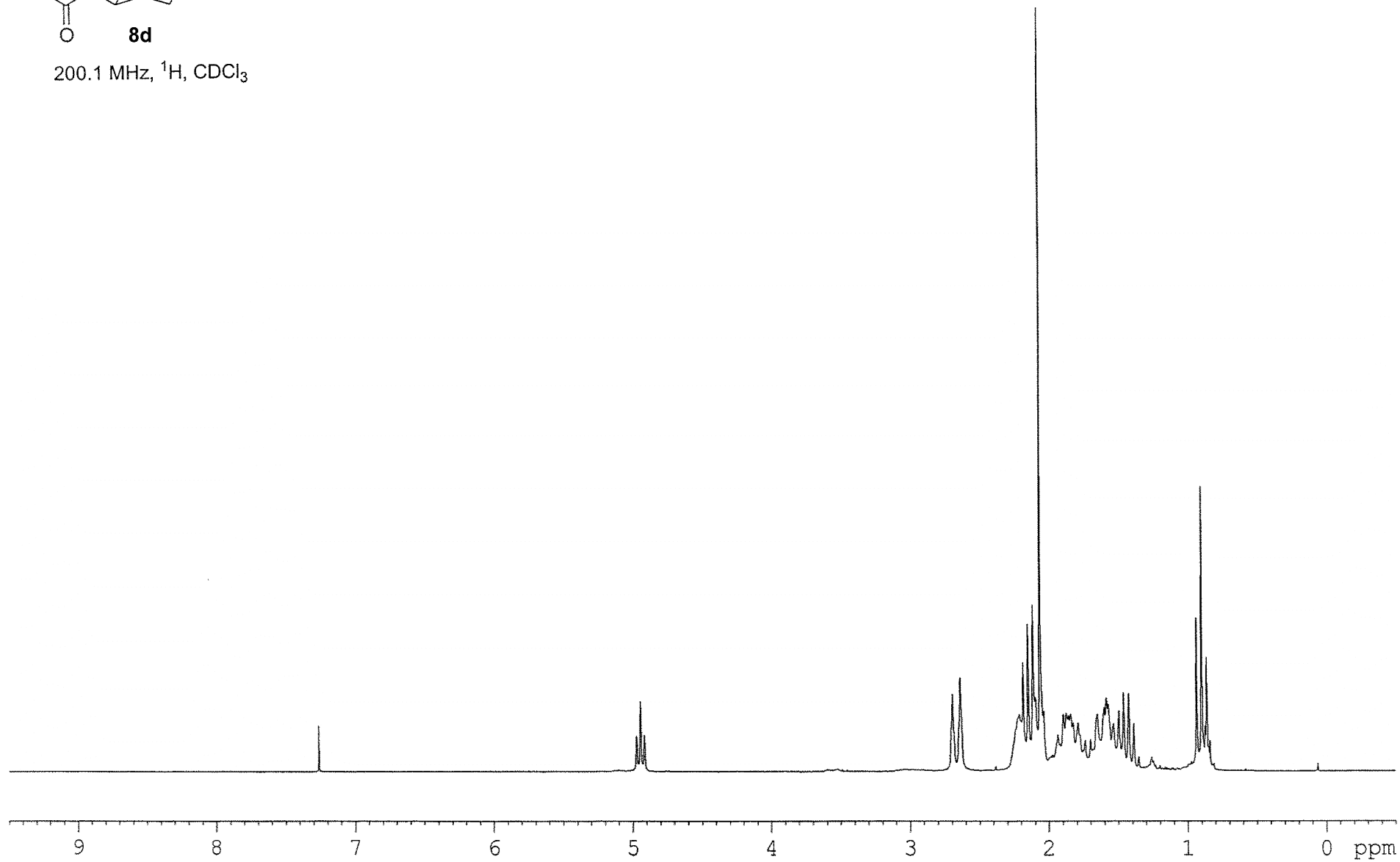


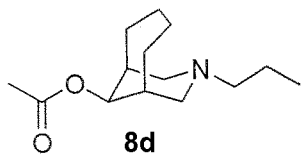
75.5 MHz, ^{13}C , CDCl_3



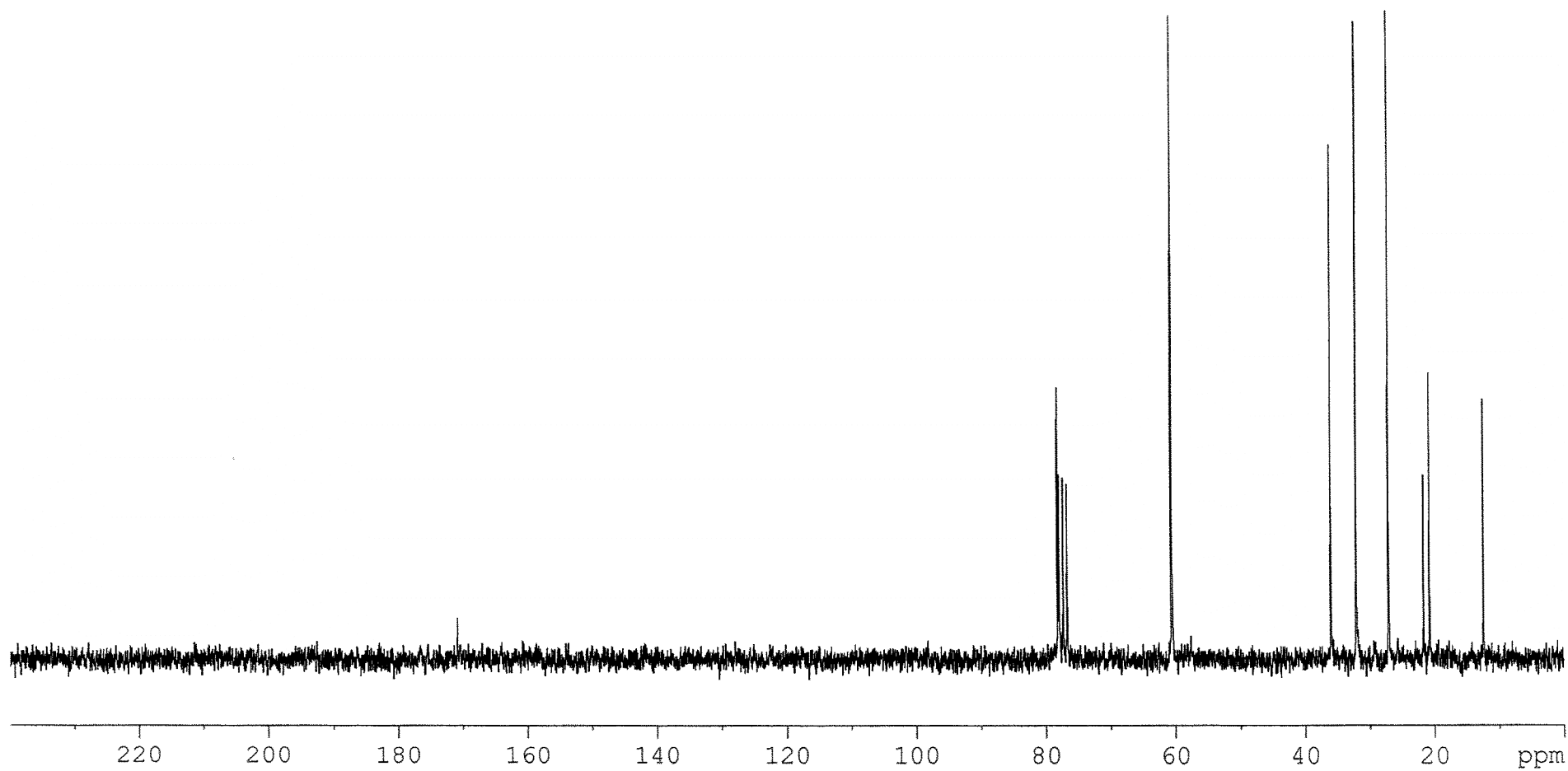


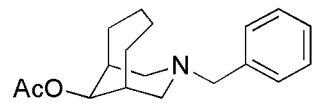
200.1 MHz, ^1H , CDCl_3





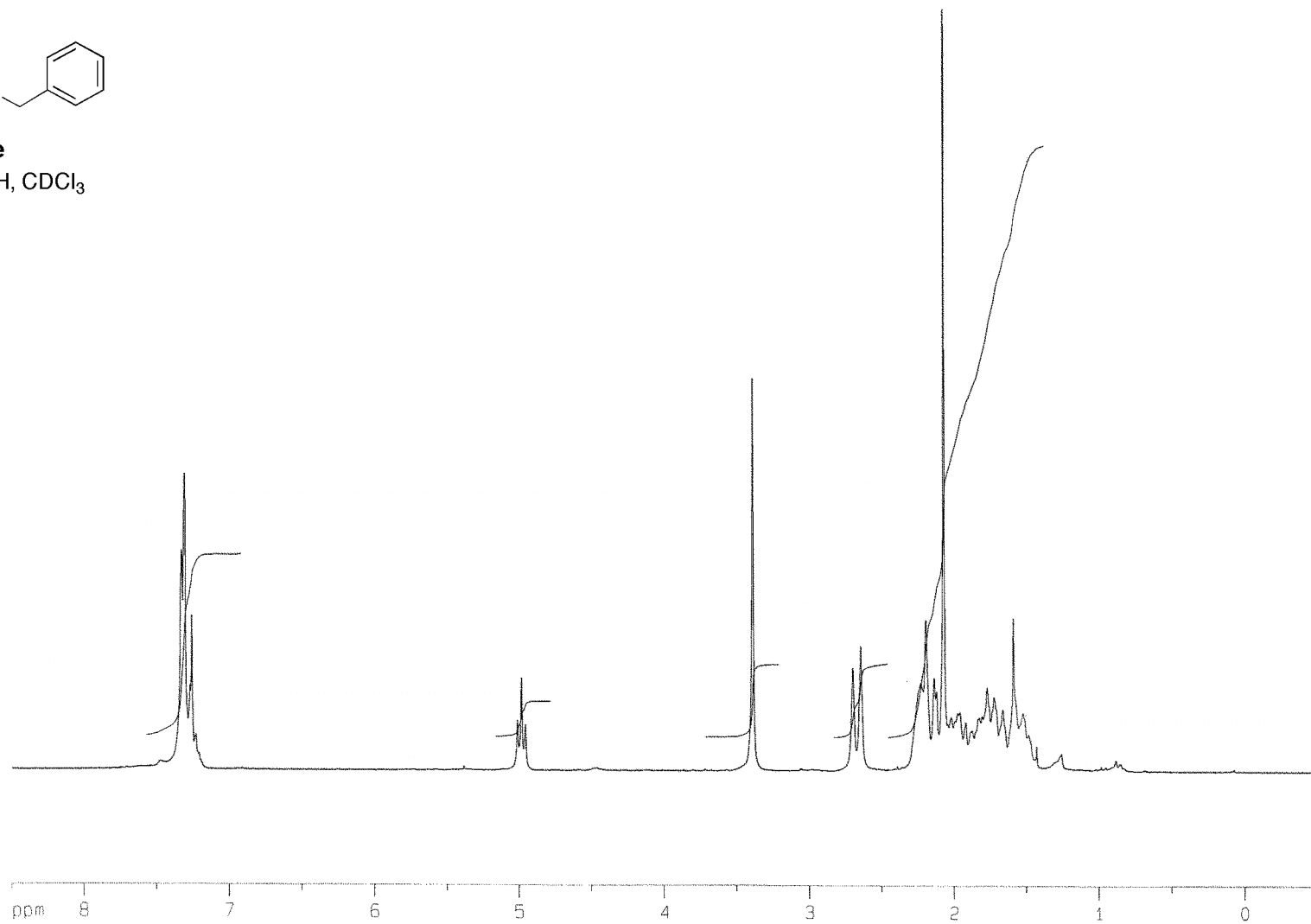
50.3 MHz, ^{13}C , CDCl_3

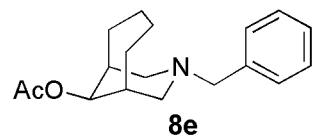




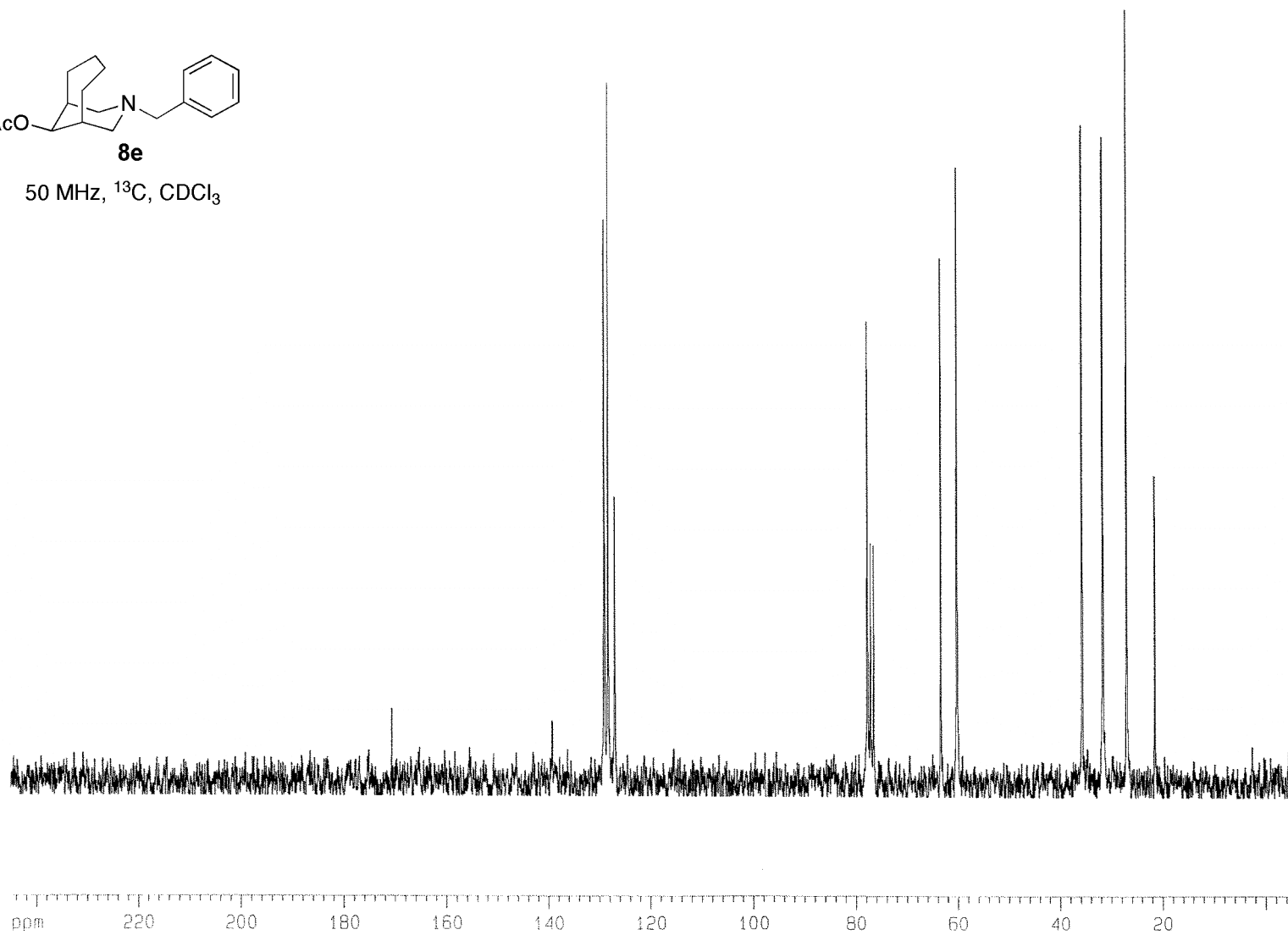
8e

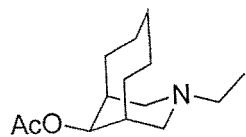
200 MHz, ¹H, CDCl₃





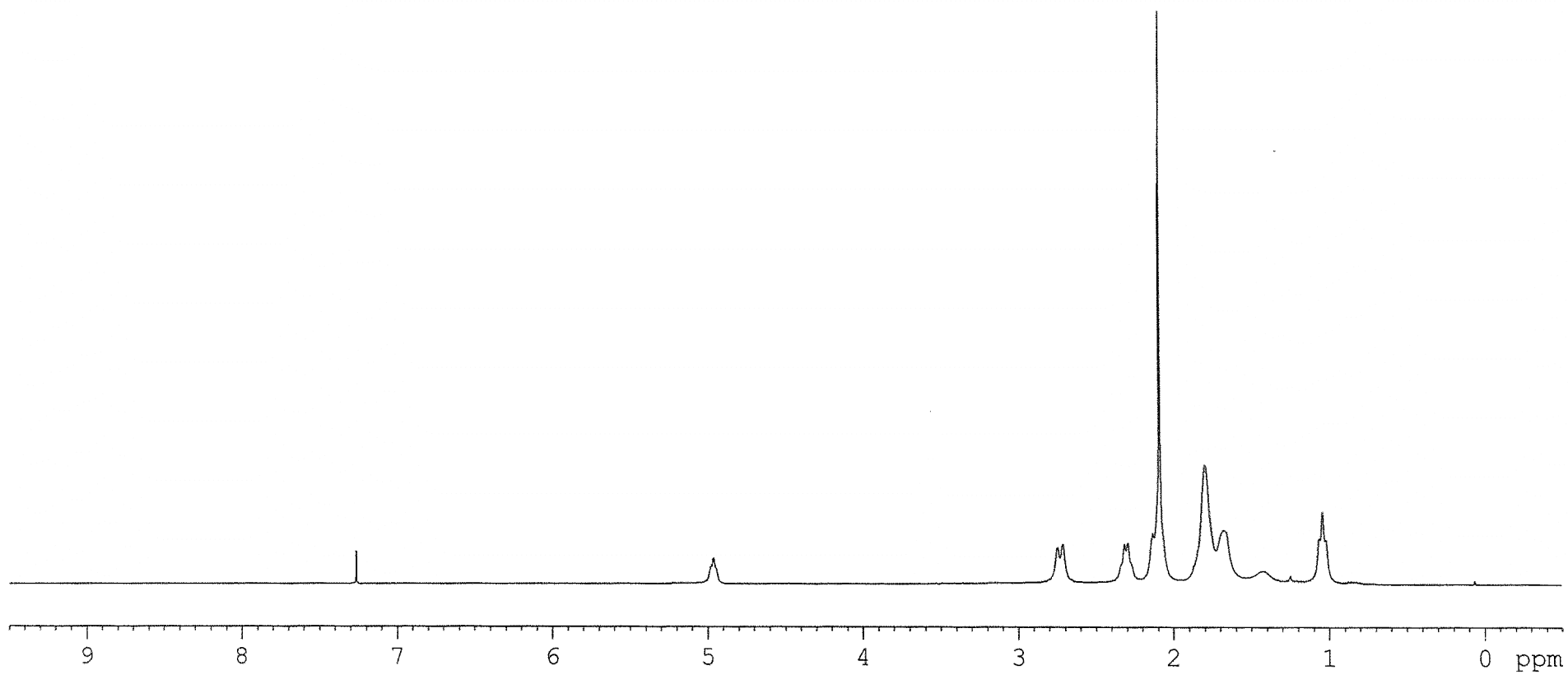
50 MHz, ^{13}C , CDCl_3

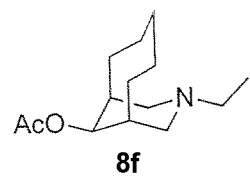




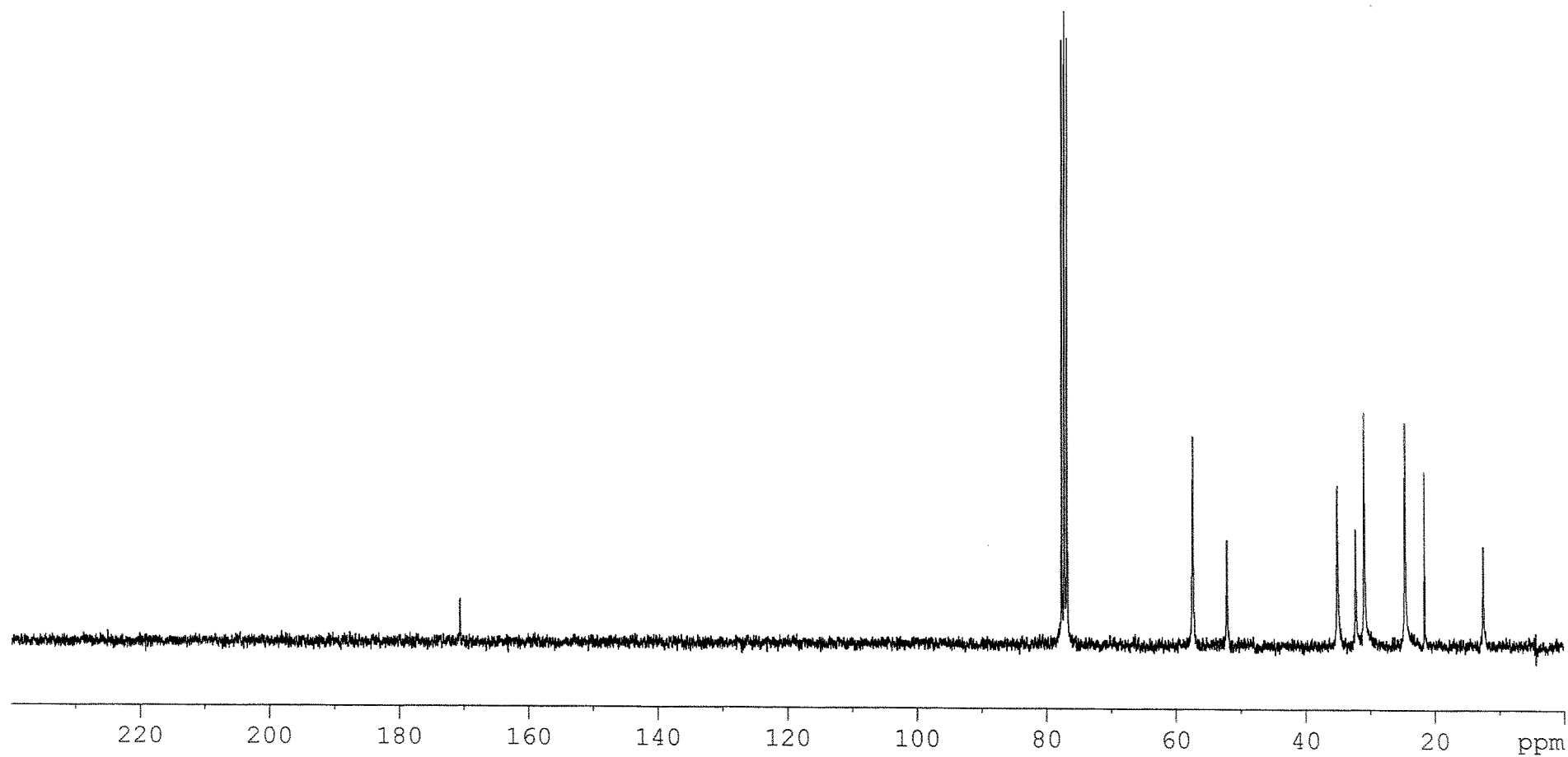
8f

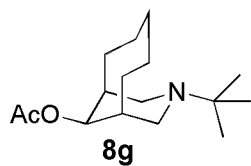
300.1 MHz, ^1H , CDCl_3



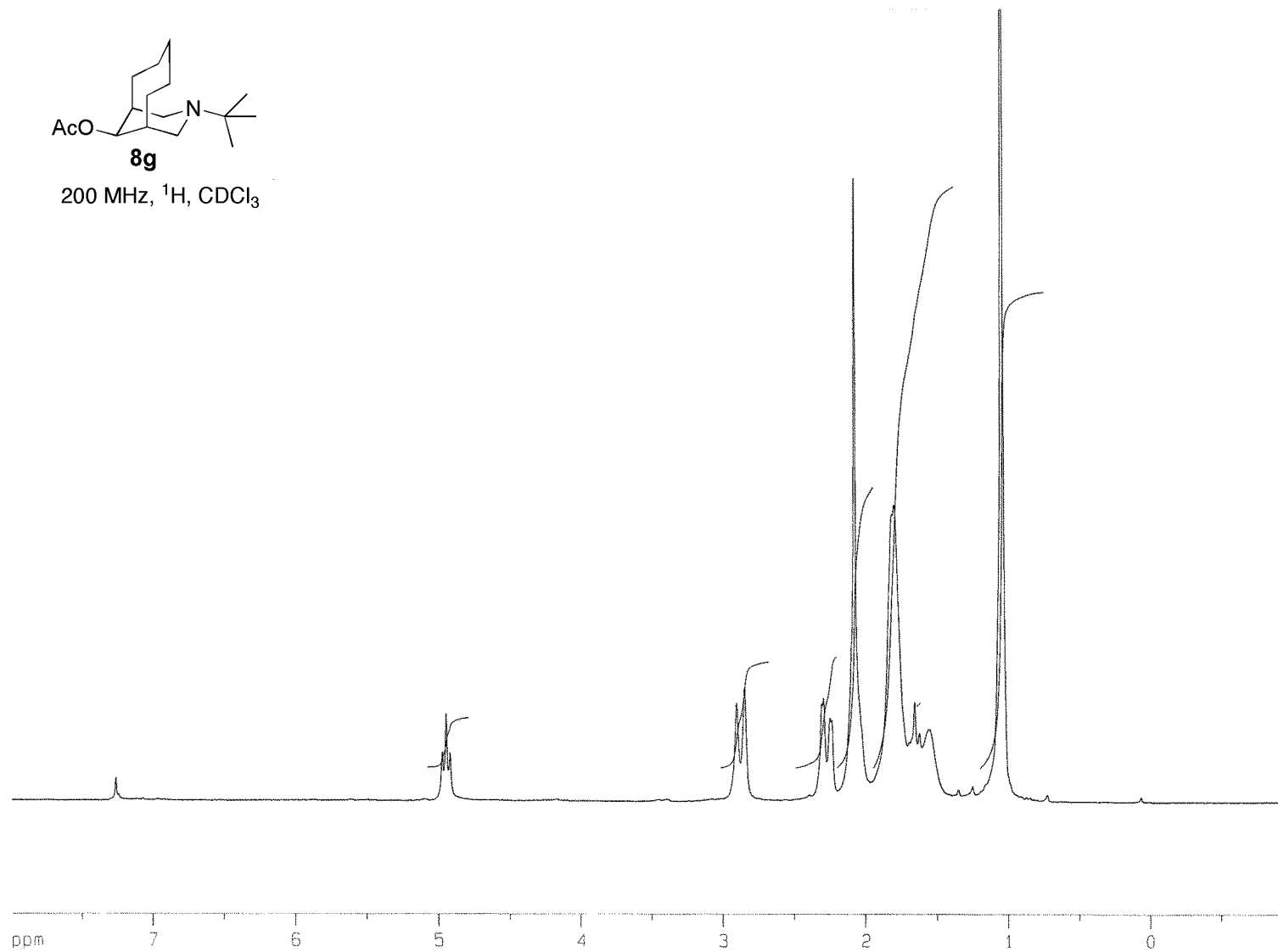


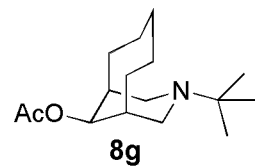
75.5 MHz, ^{13}C , CDCl_3



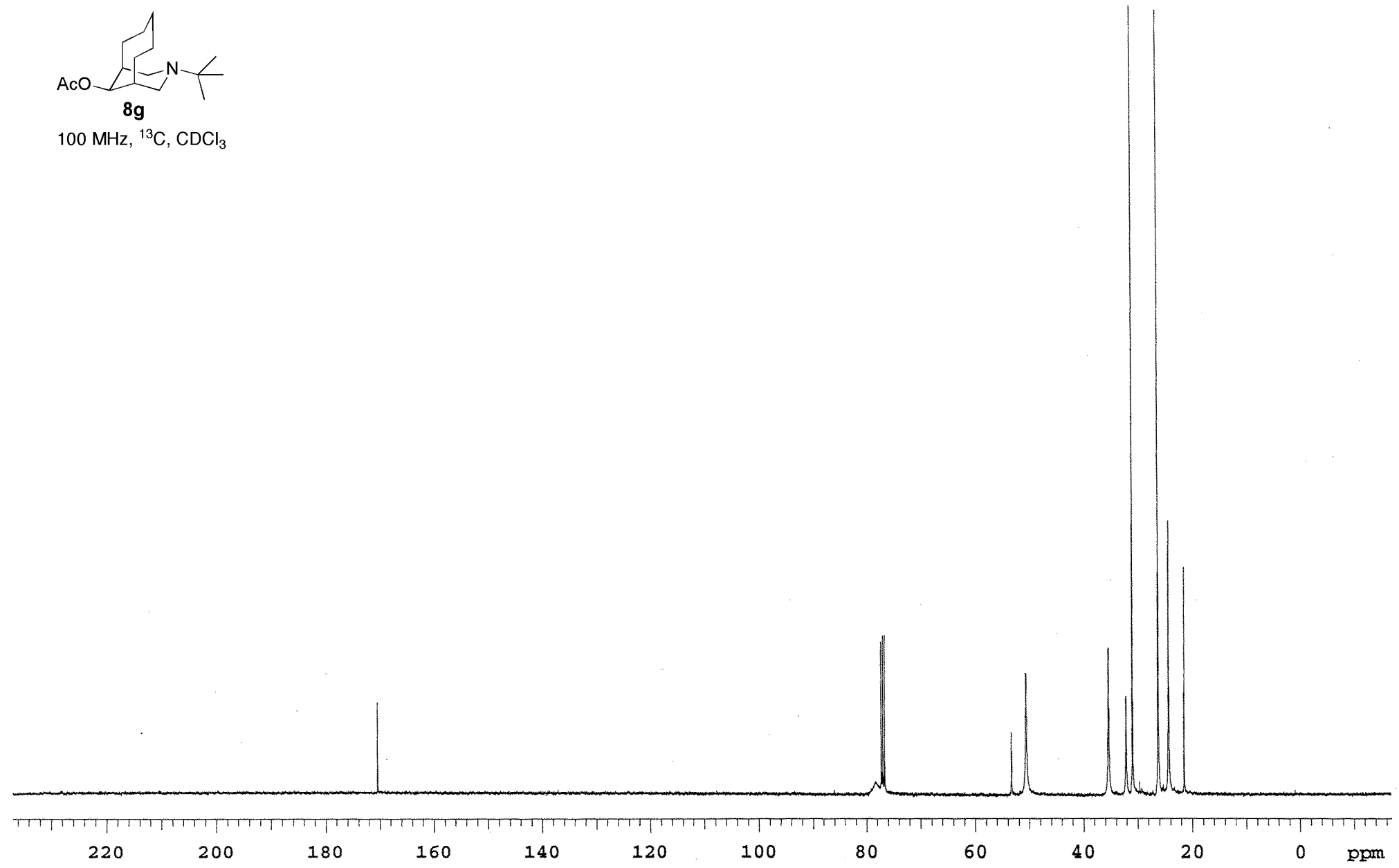


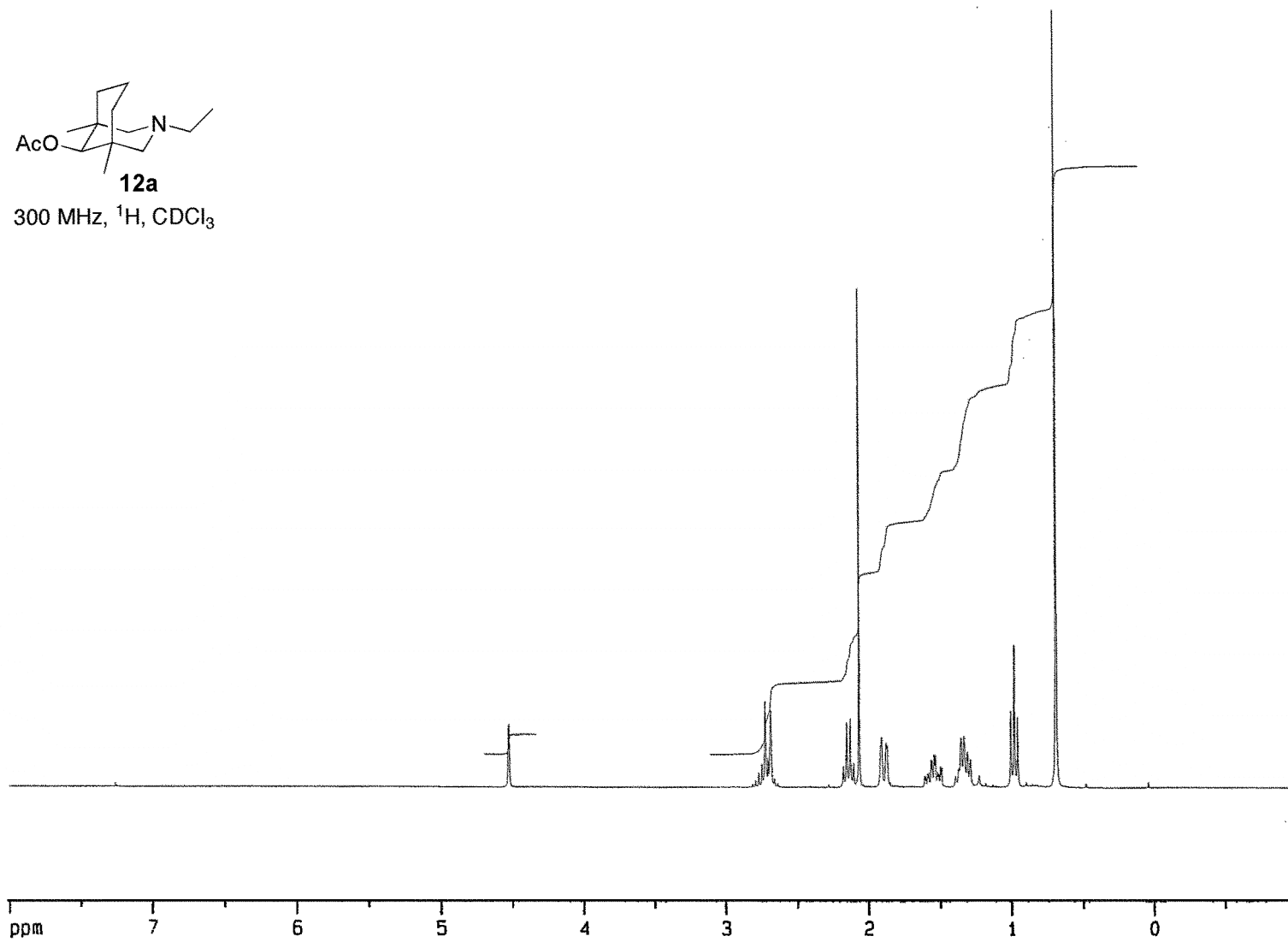
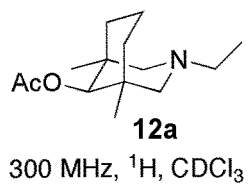
200 MHz, ¹H, CDCl₃

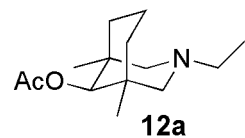




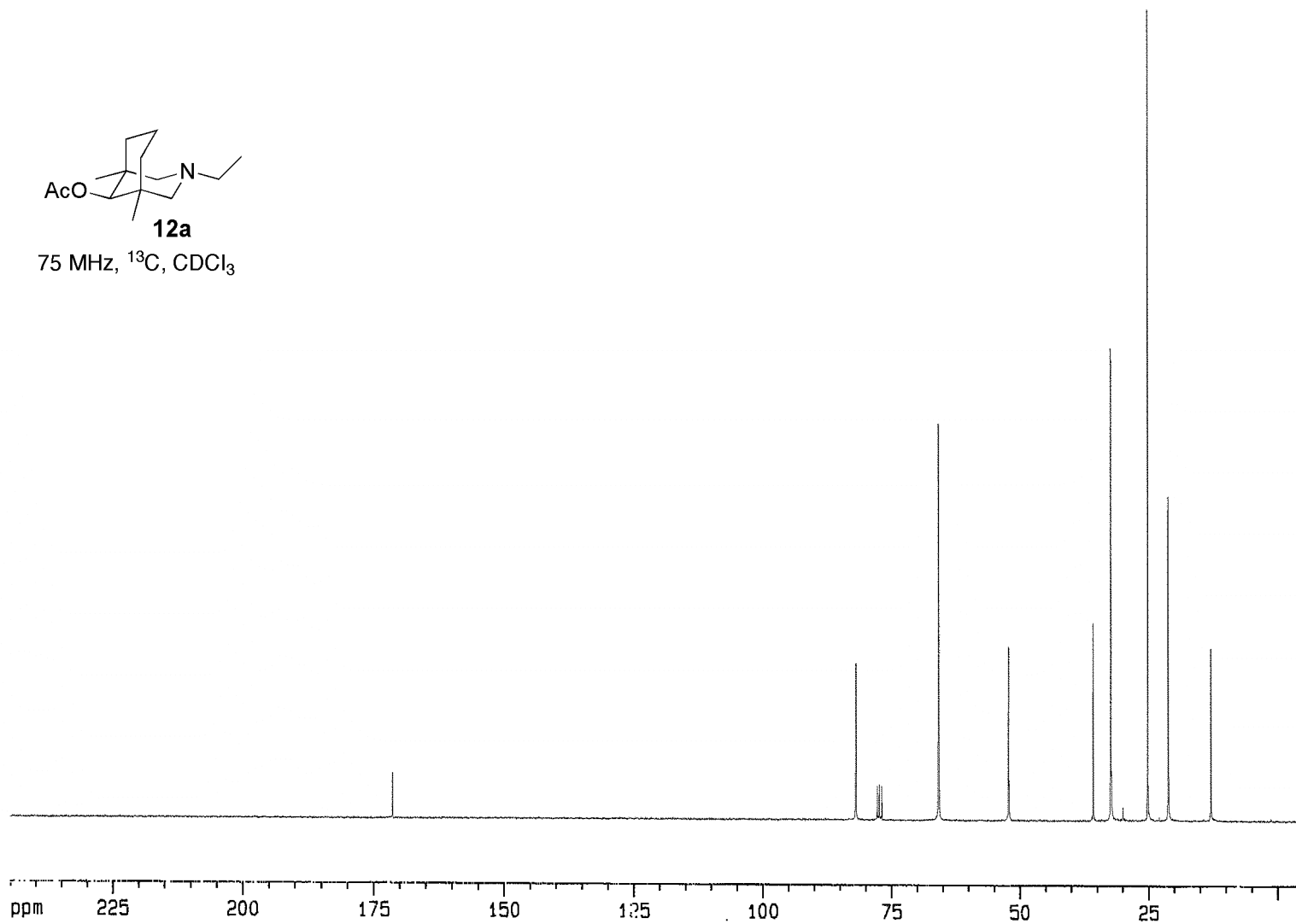
100 MHz, ¹³C, CDCl₃

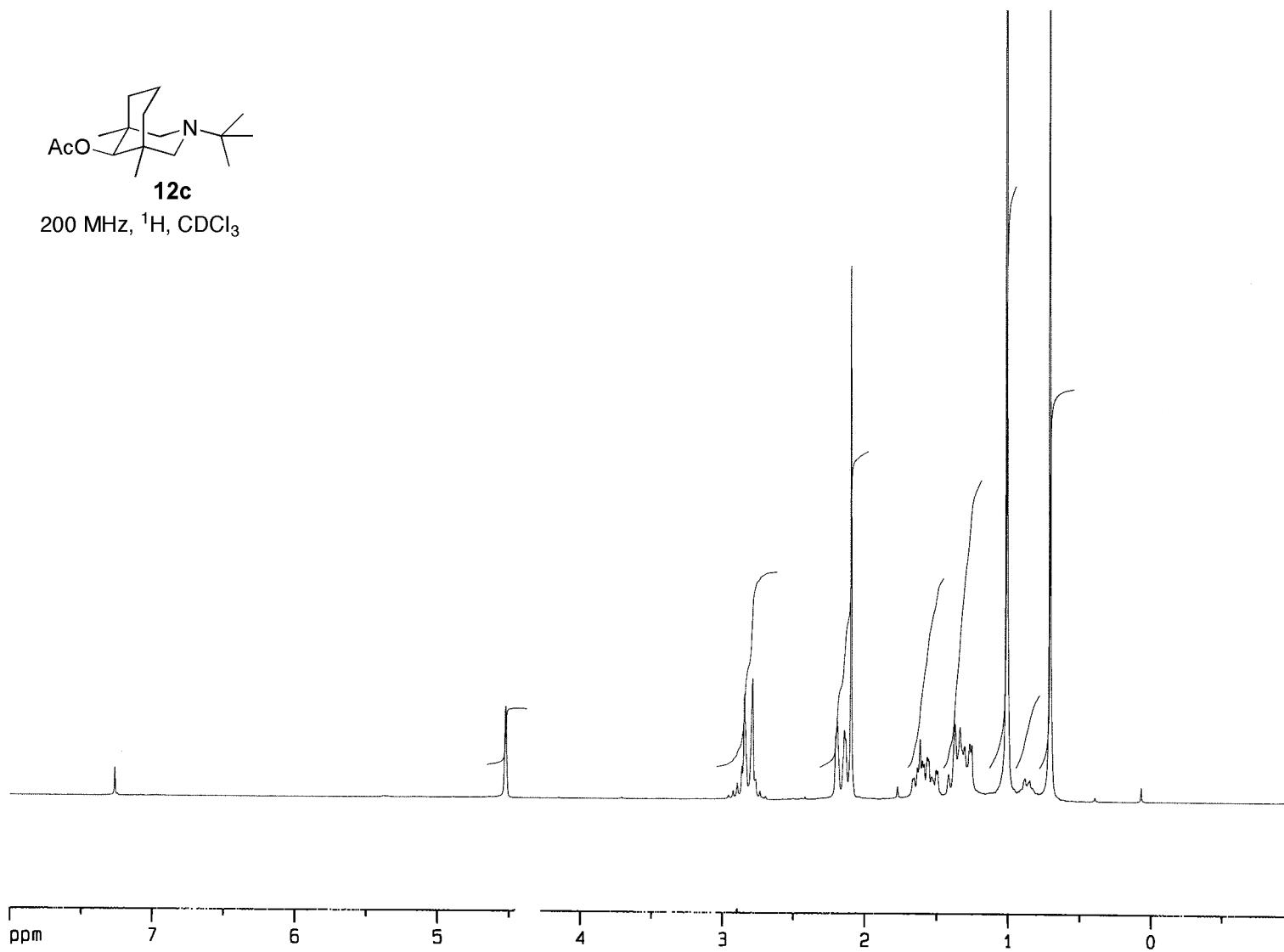
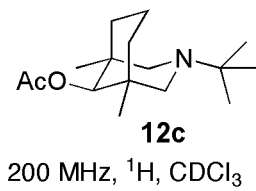


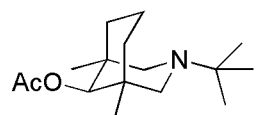




75 MHz, ^{13}C , CDCl_3

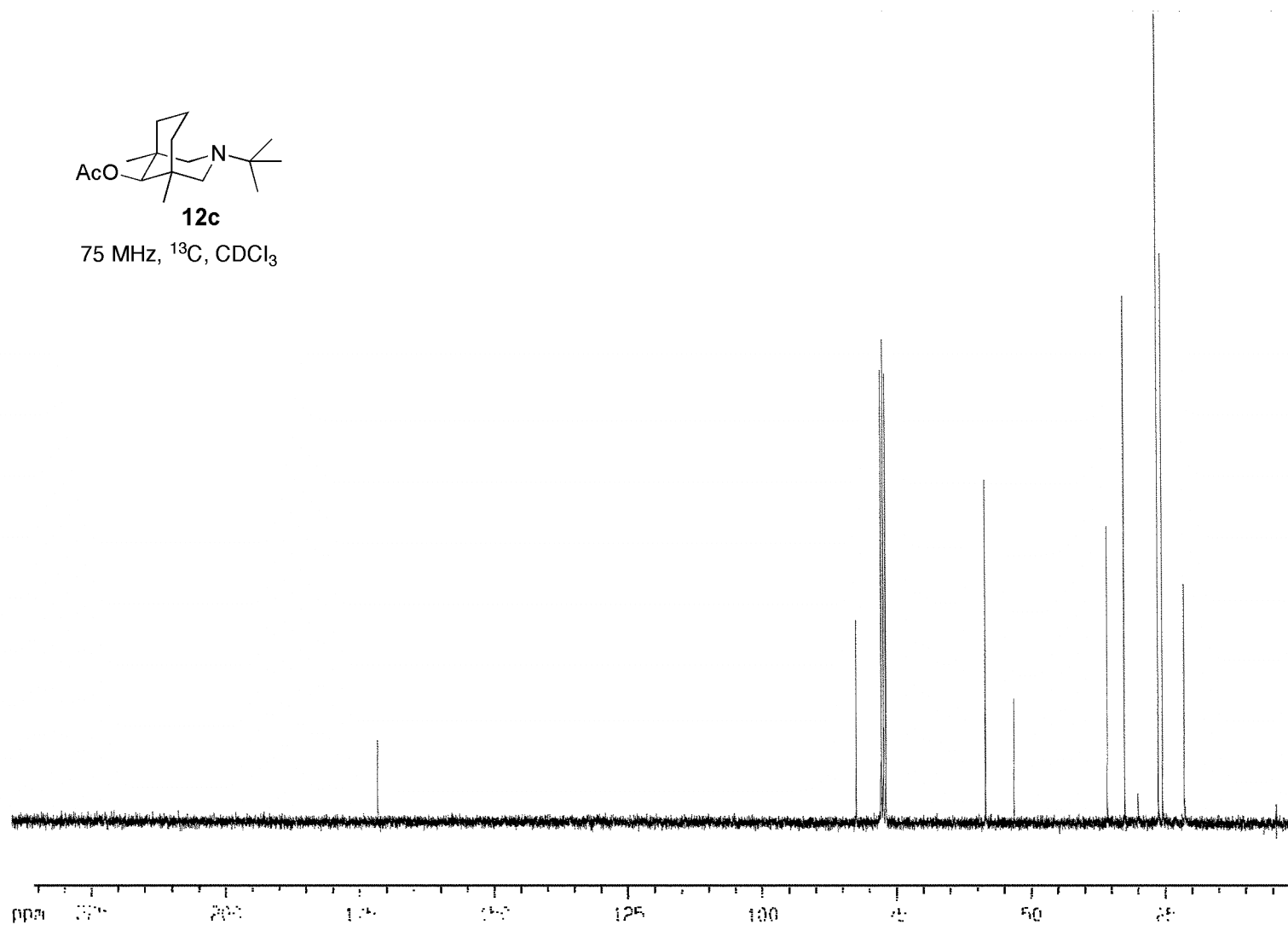


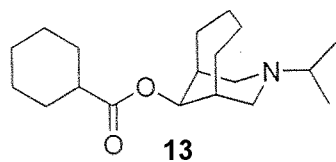




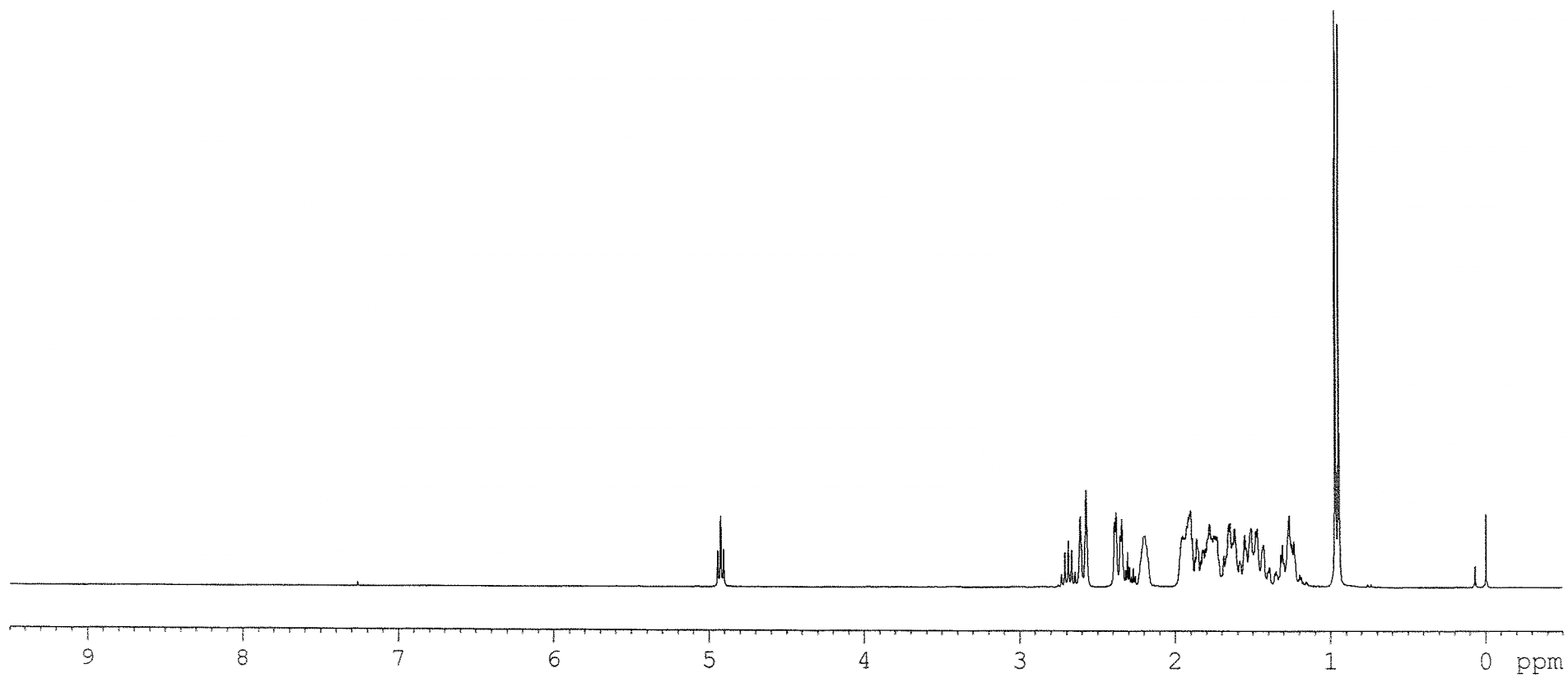
12c

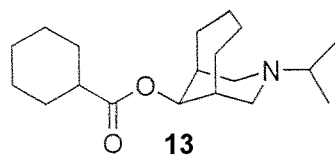
75 MHz, ^{13}C , CDCl_3



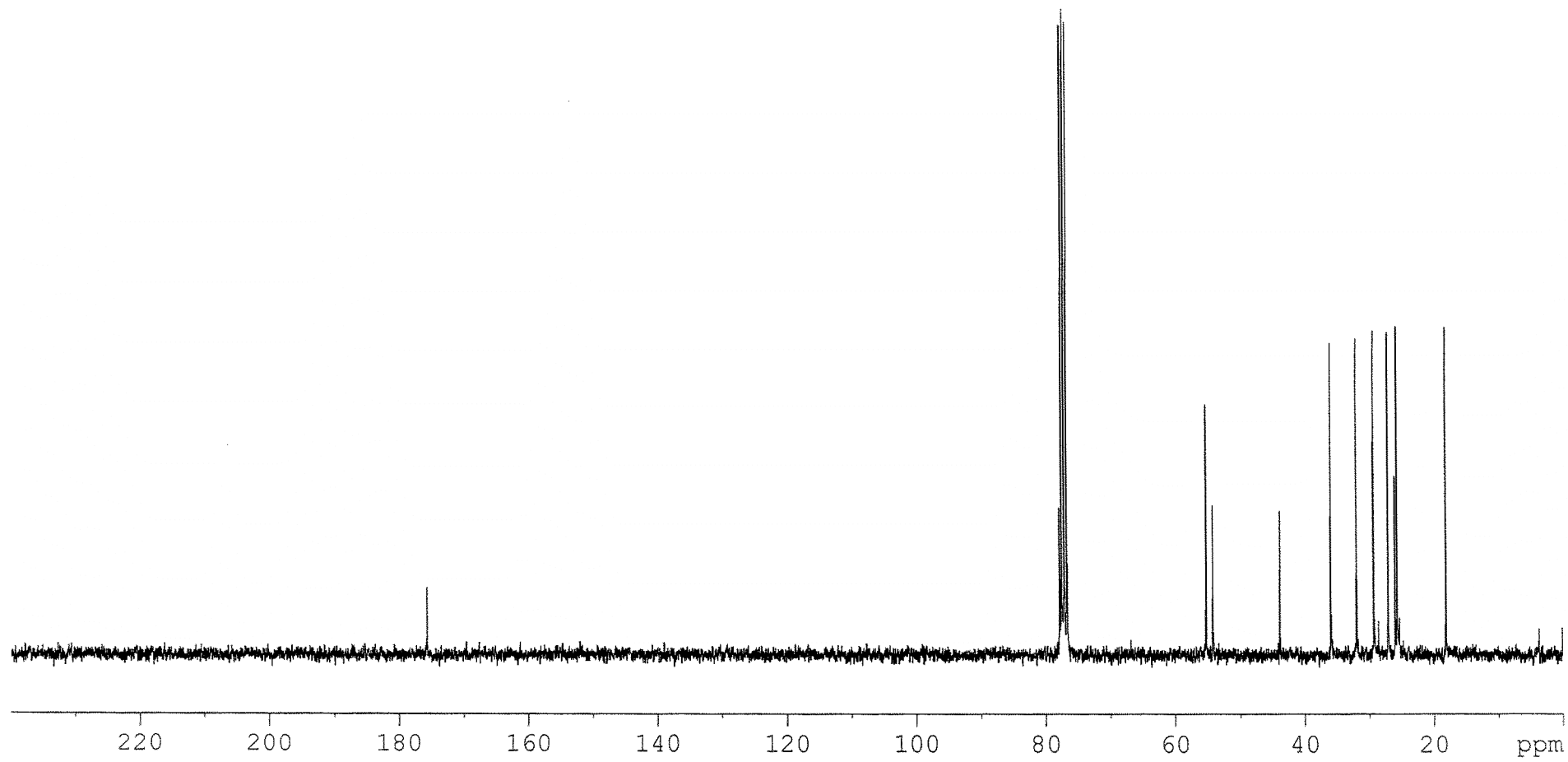


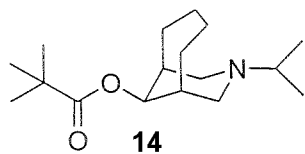
300.1 MHz, ^1H , CDCl_3



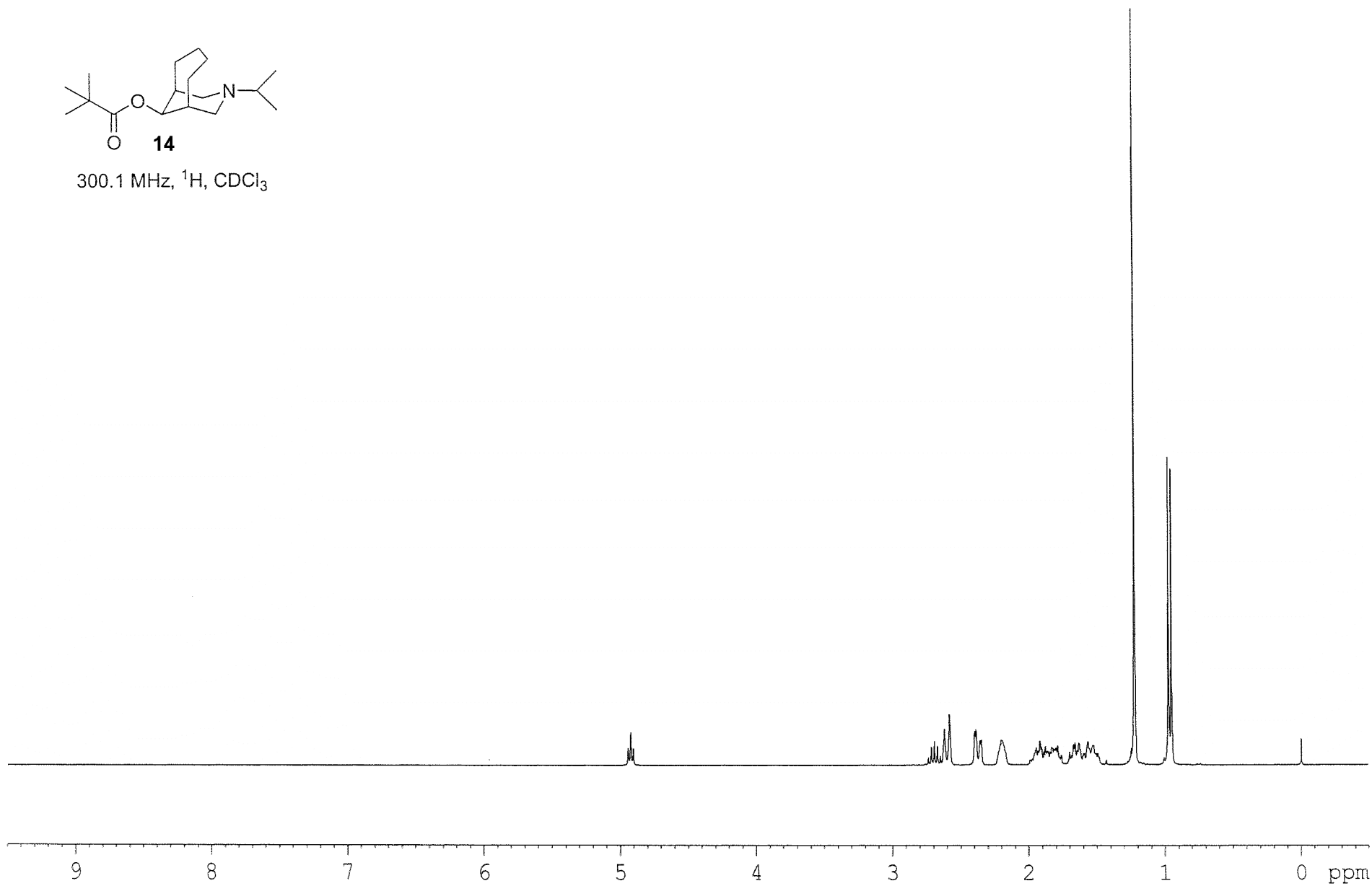


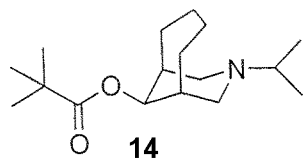
75.5 MHz, ^{13}C , CDCl_3



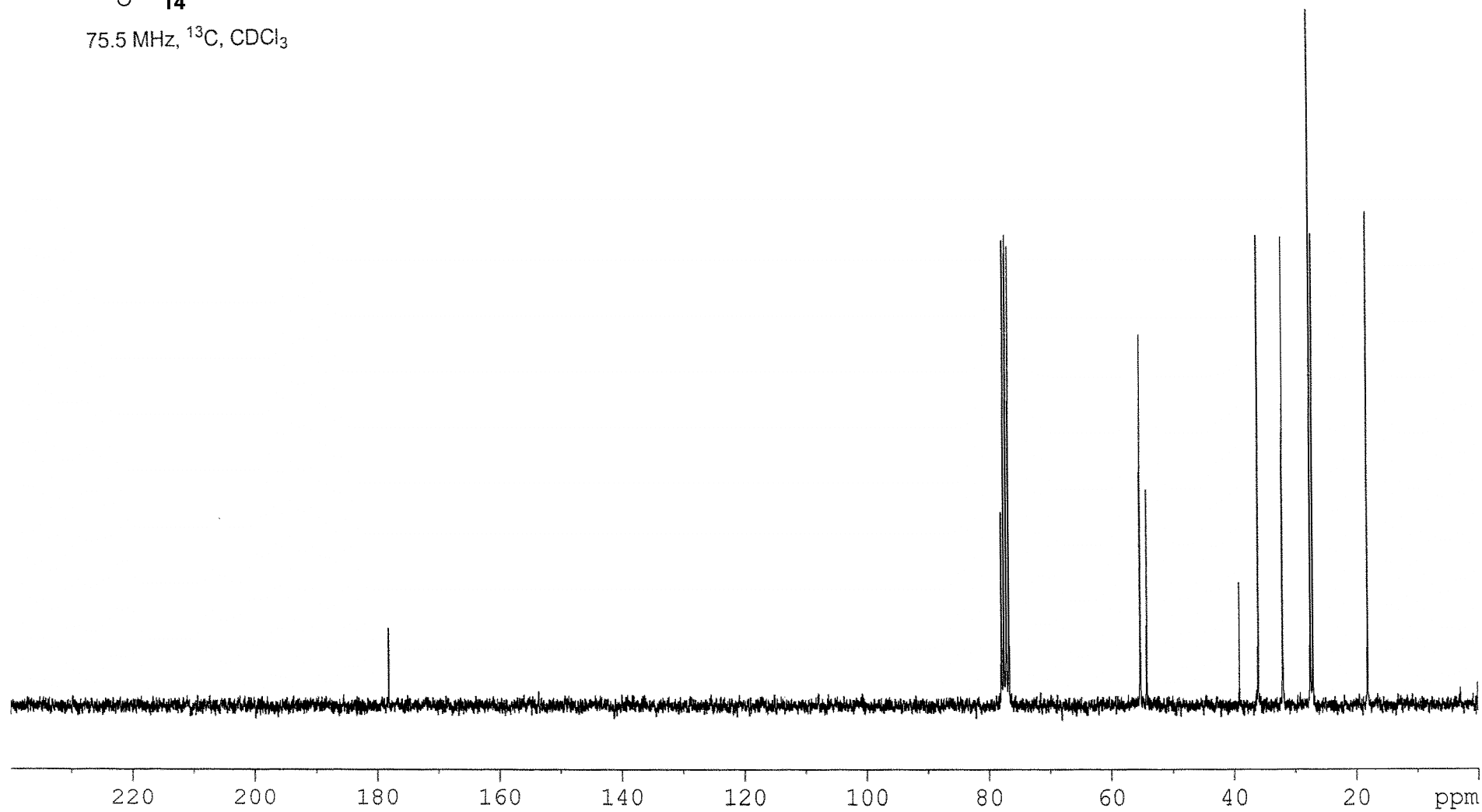


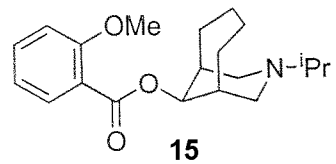
300.1 MHz, ¹H, CDCl₃



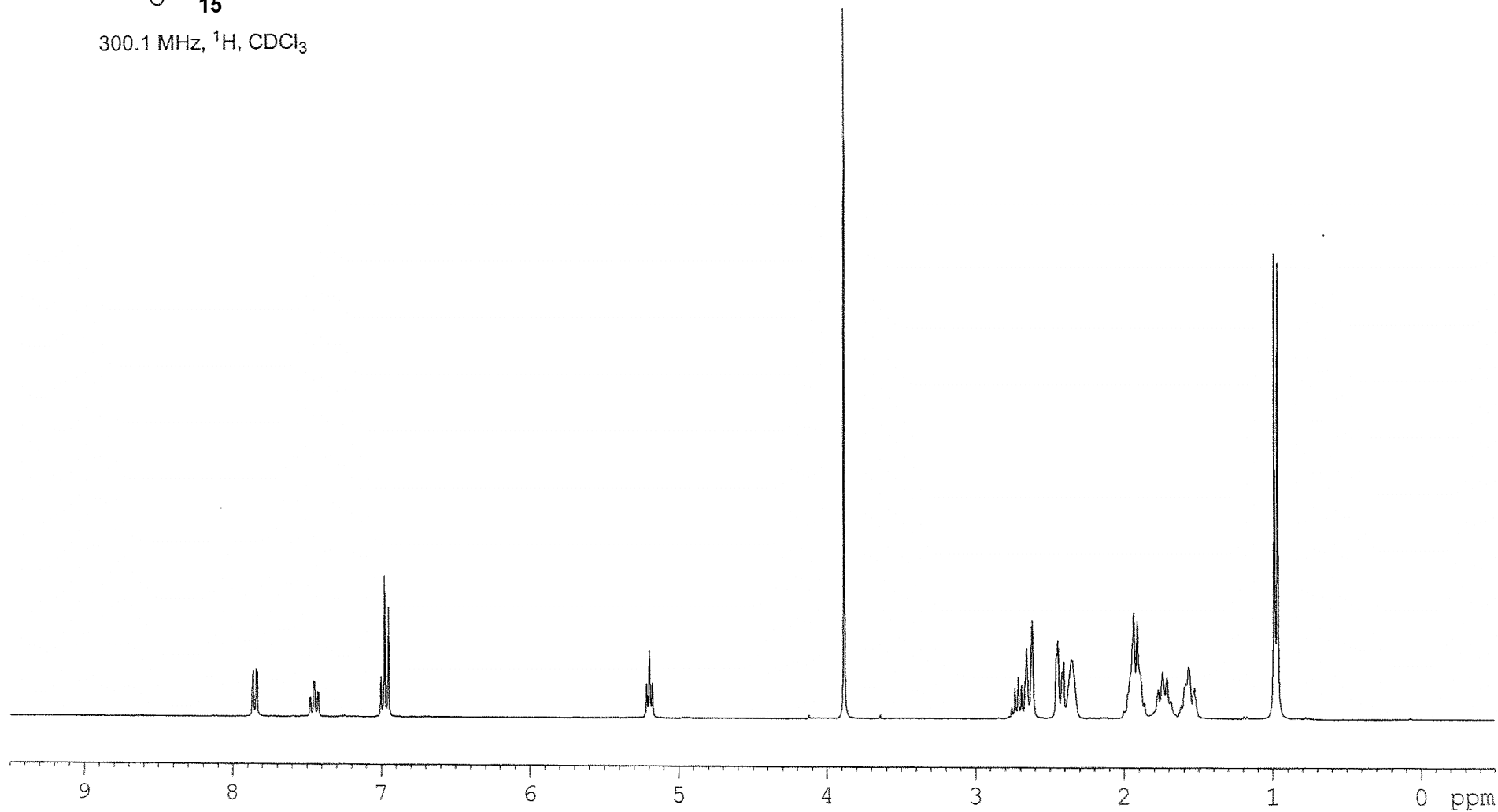


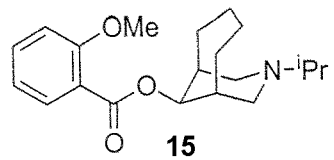
75.5 MHz, ^{13}C , CDCl_3



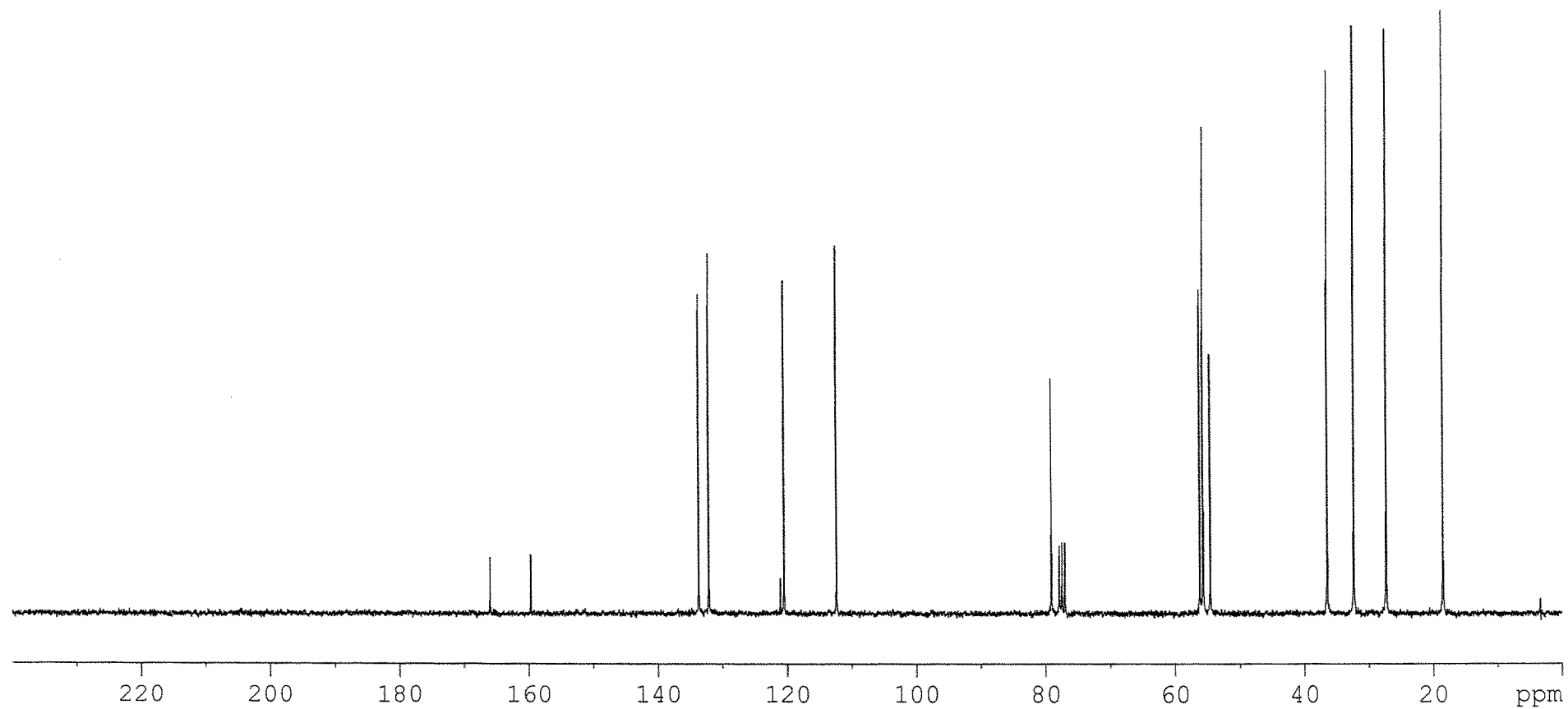


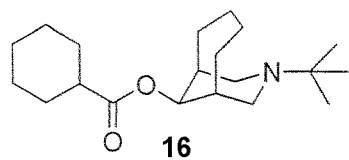
300.1 MHz, ¹H, CDCl₃



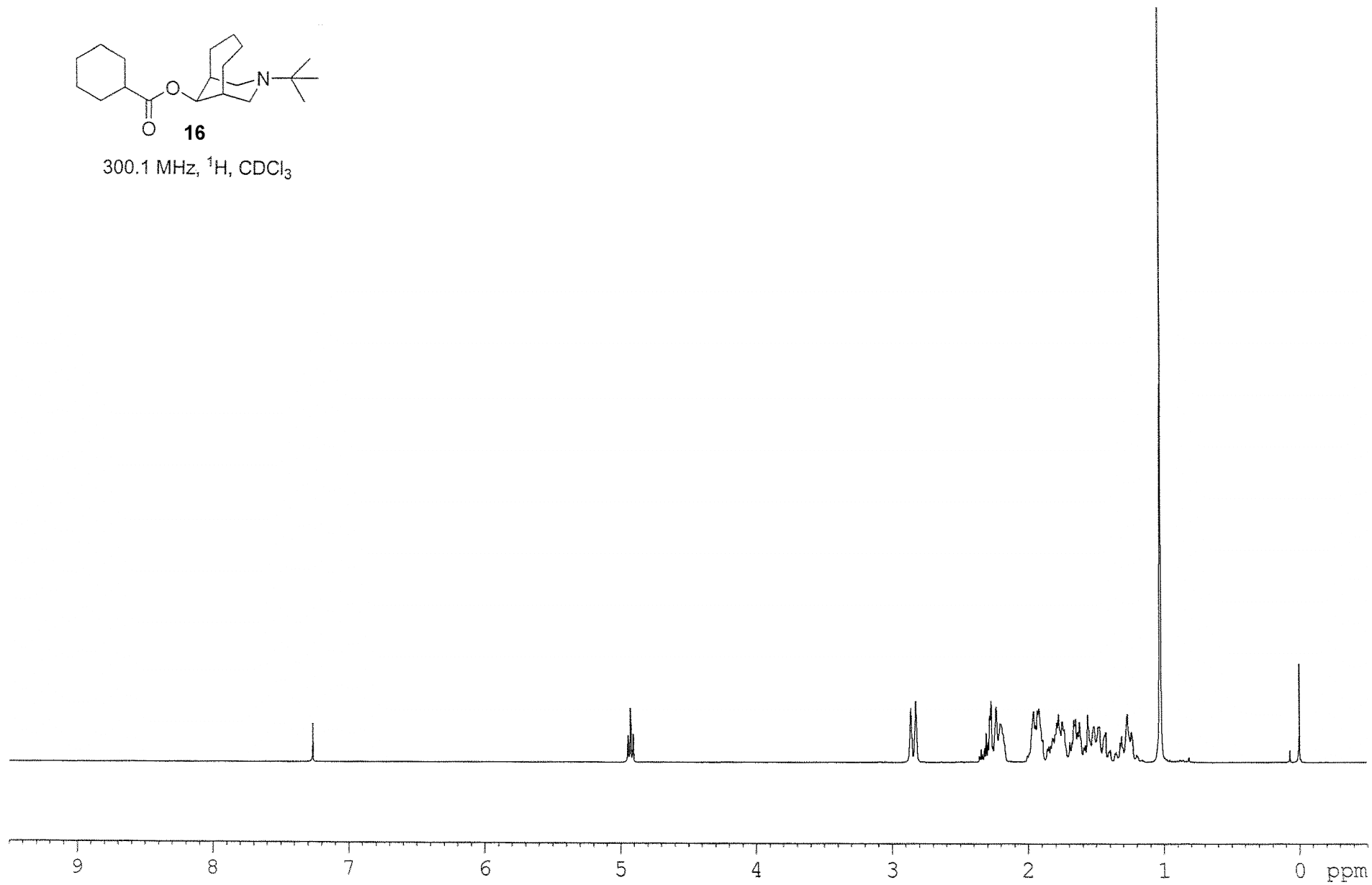


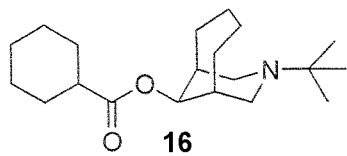
75.5 MHz, ^{13}C , CDCl_3



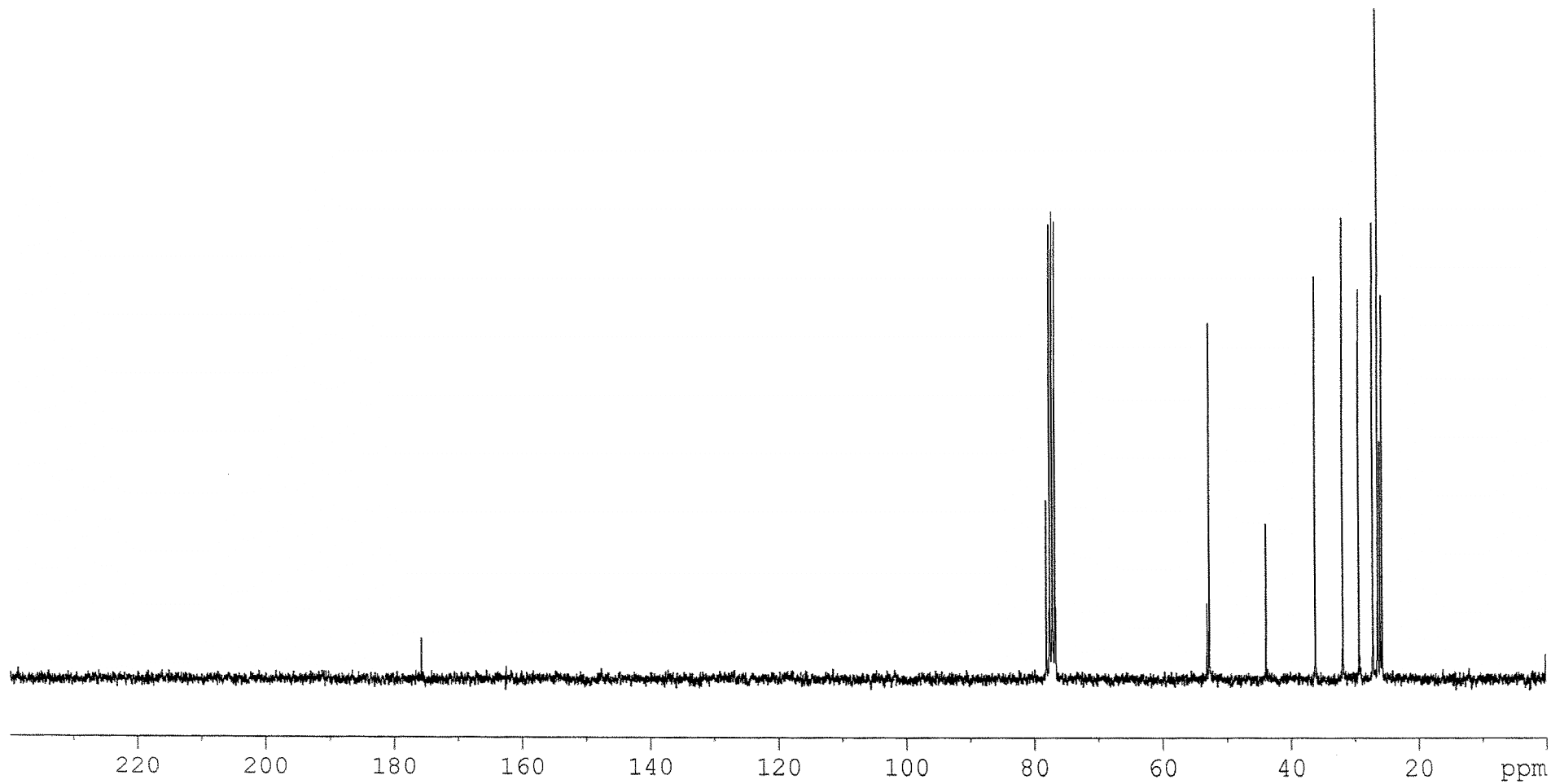


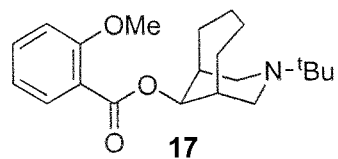
300.1 MHz, ^1H , CDCl_3



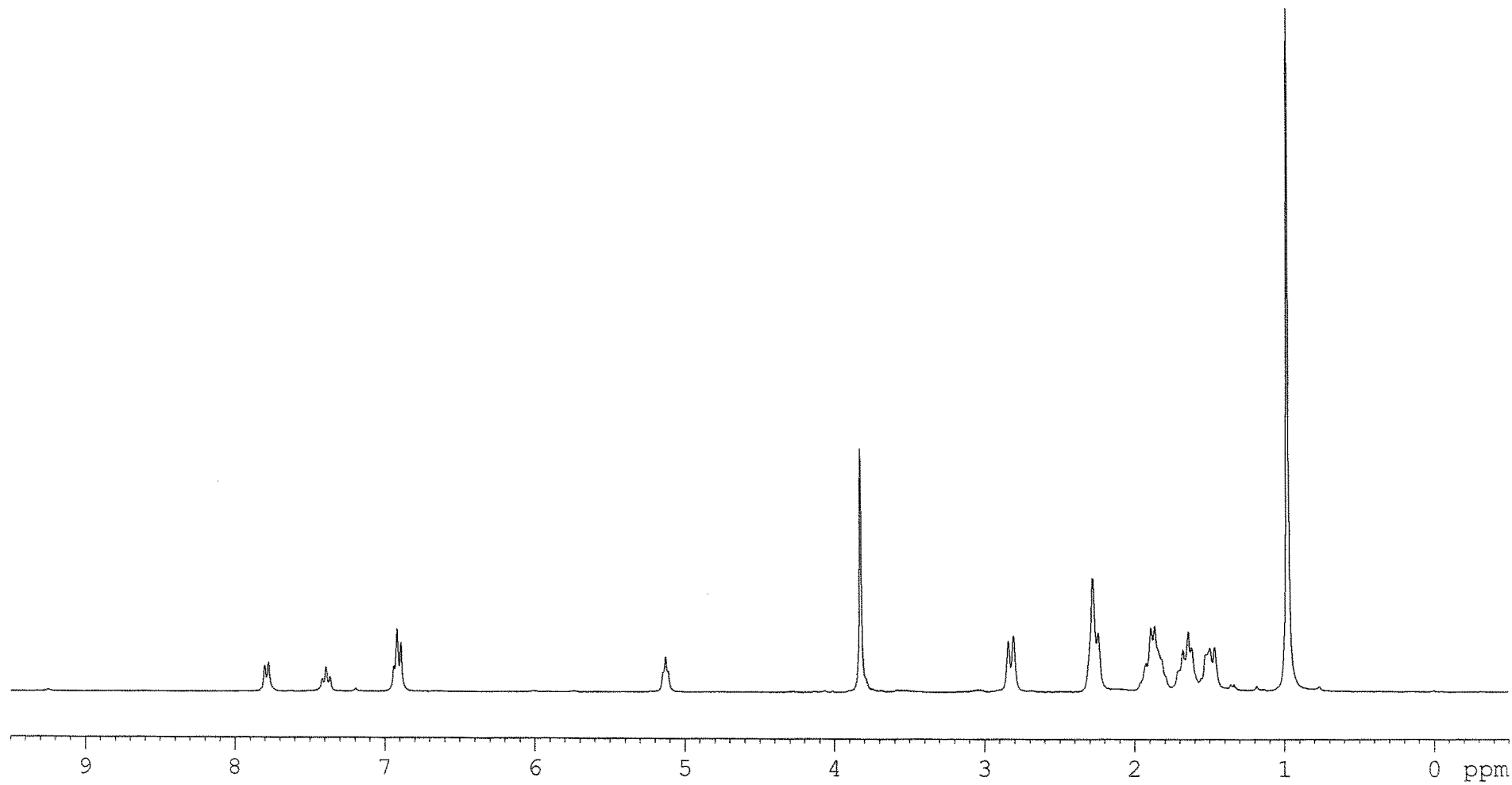


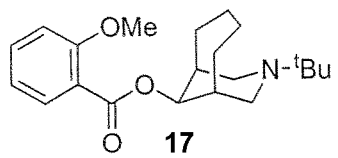
75.5 MHz, ^{13}C , CDCl_3



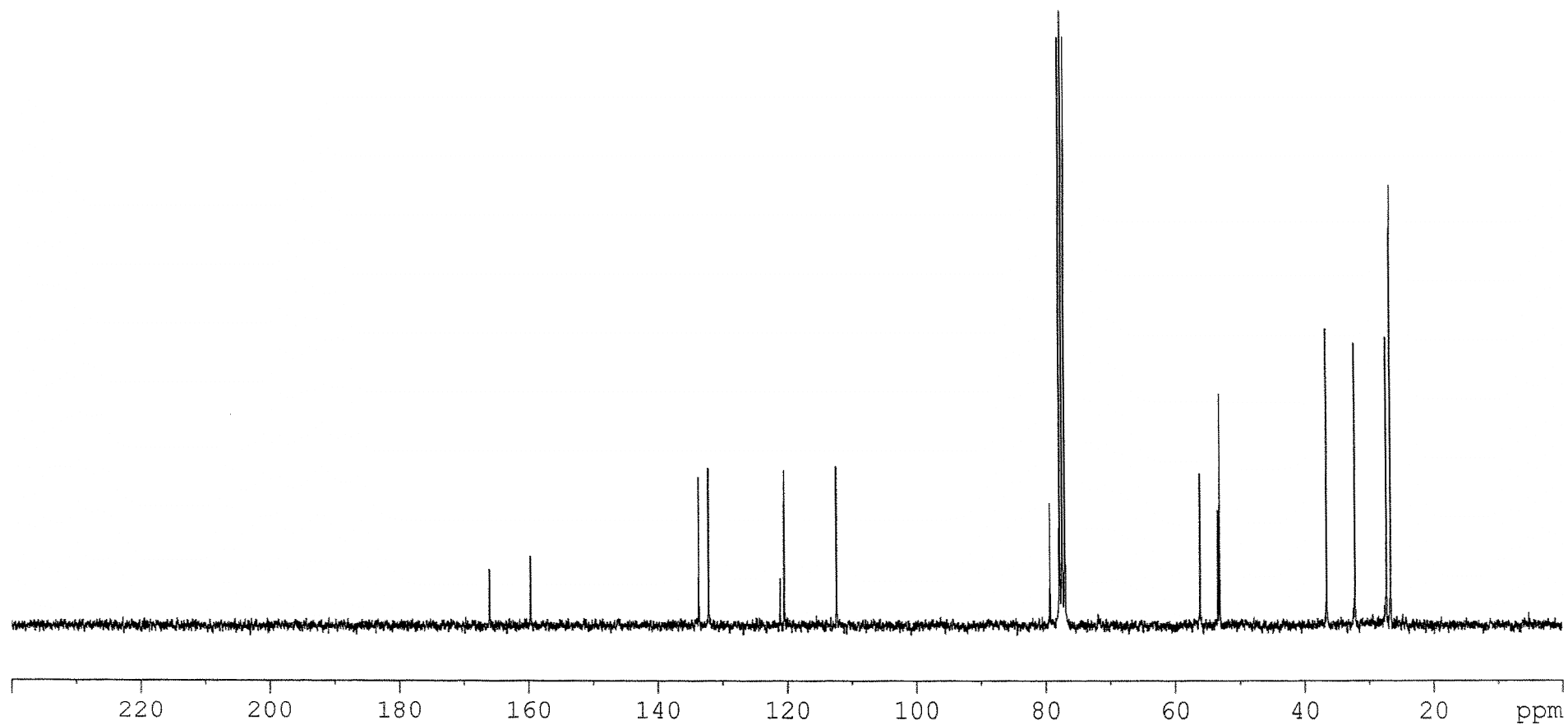


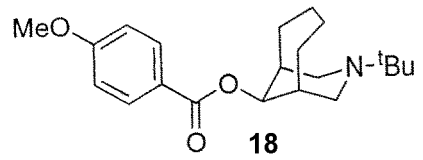
300.1 MHz, ¹H, CDCl₃



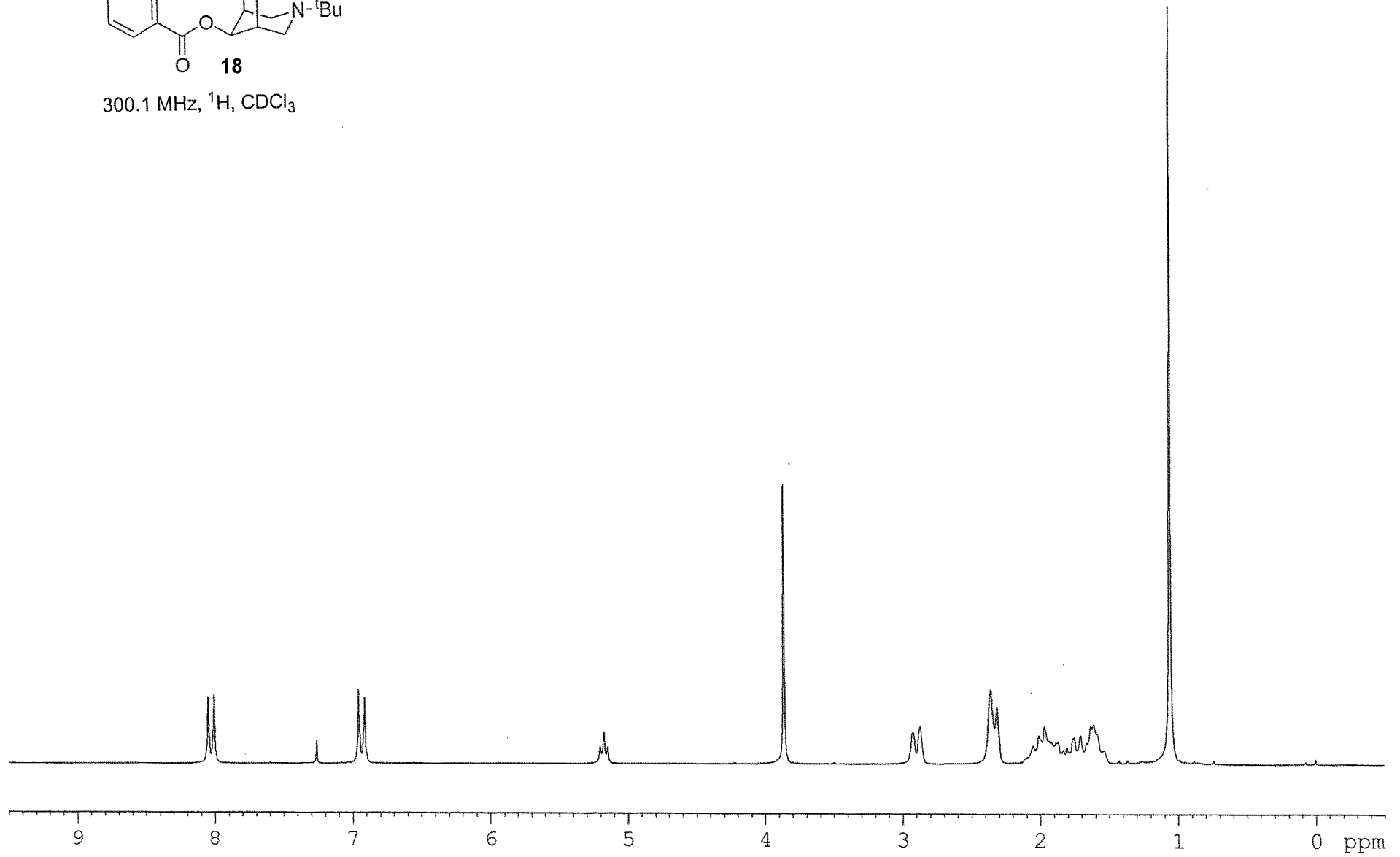


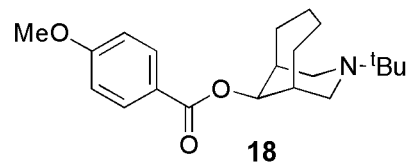
75.5 MHz, ^{13}C , CDCl_3



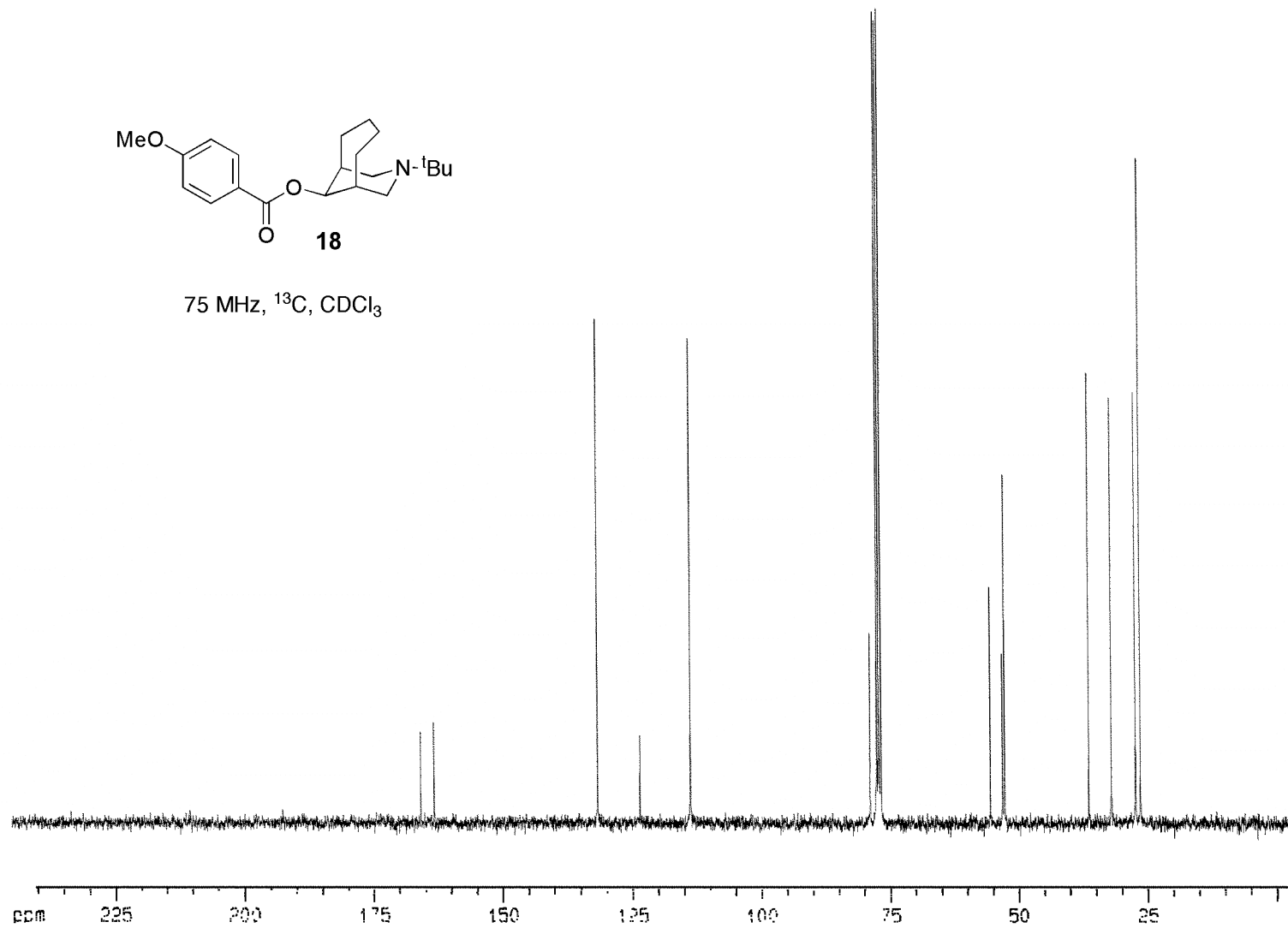


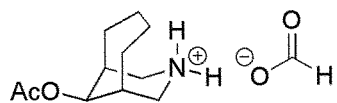
300.1 MHz, ¹H, CDCl₃





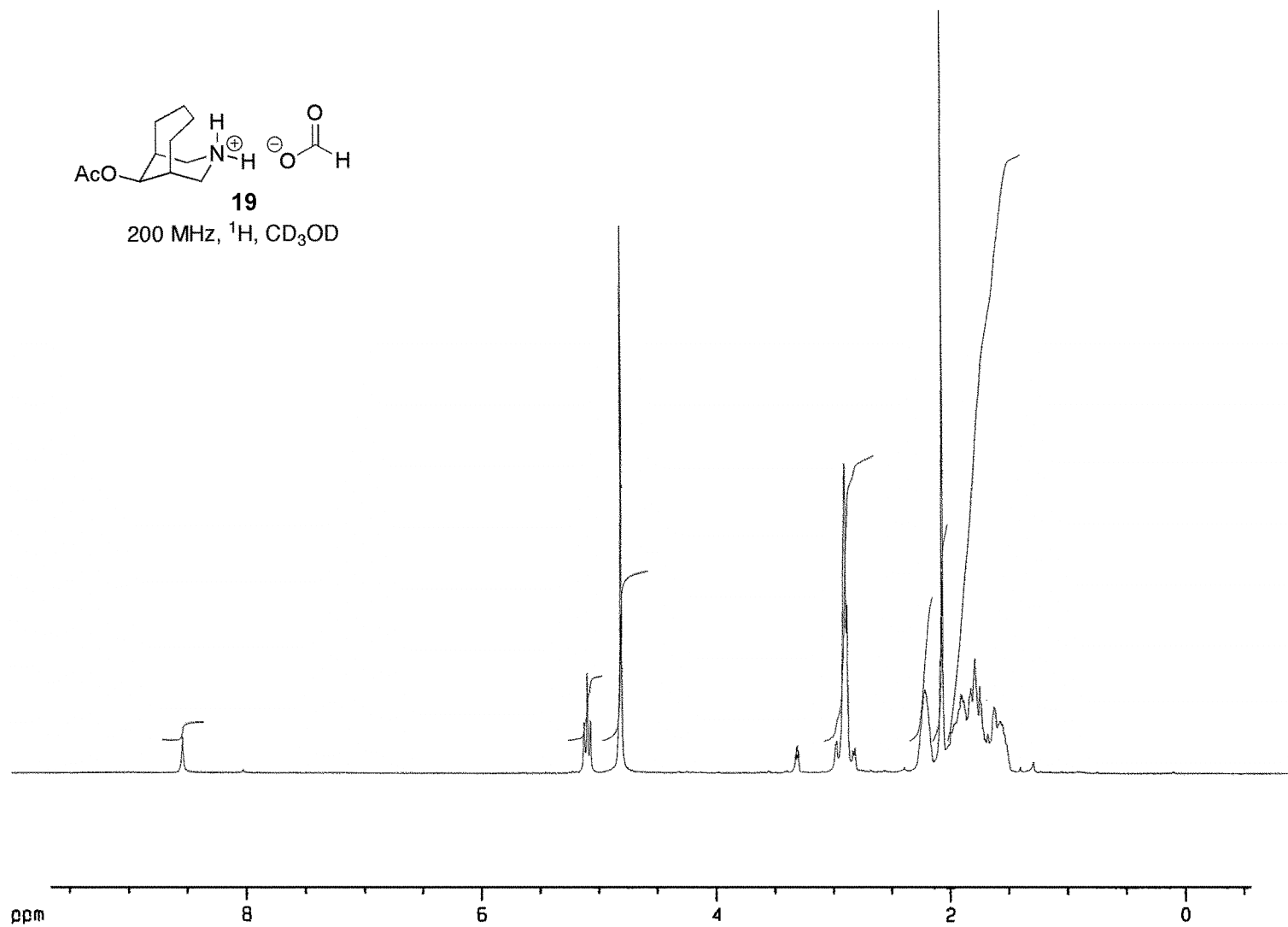
75 MHz, ^{13}C , CDCl_3

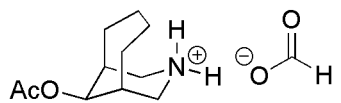




19

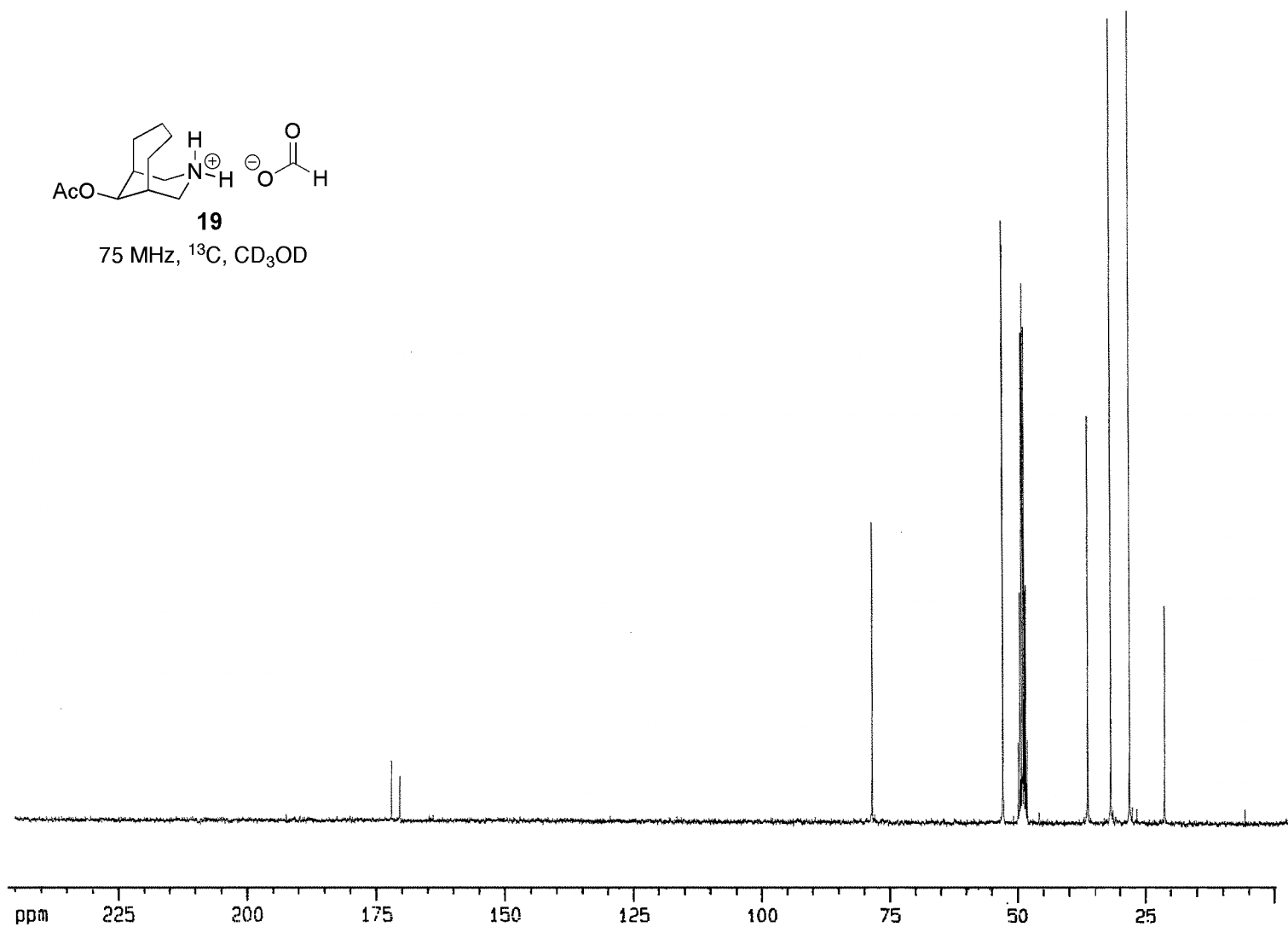
200 MHz, ^1H , CD_3OD

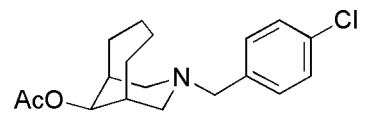




19

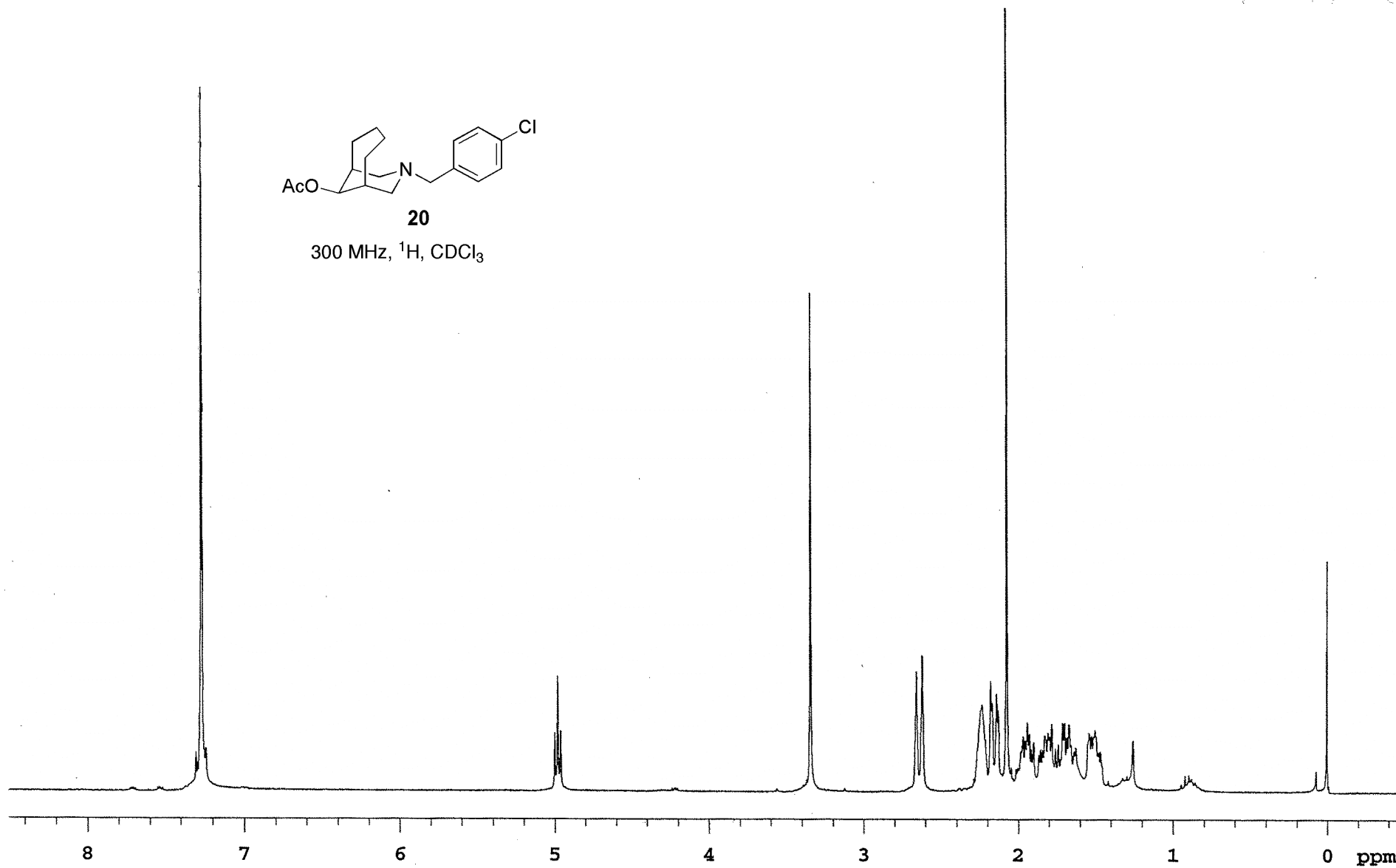
75 MHz, ^{13}C , CD_3OD

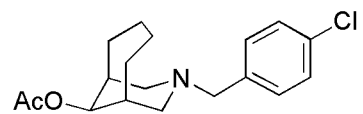




20

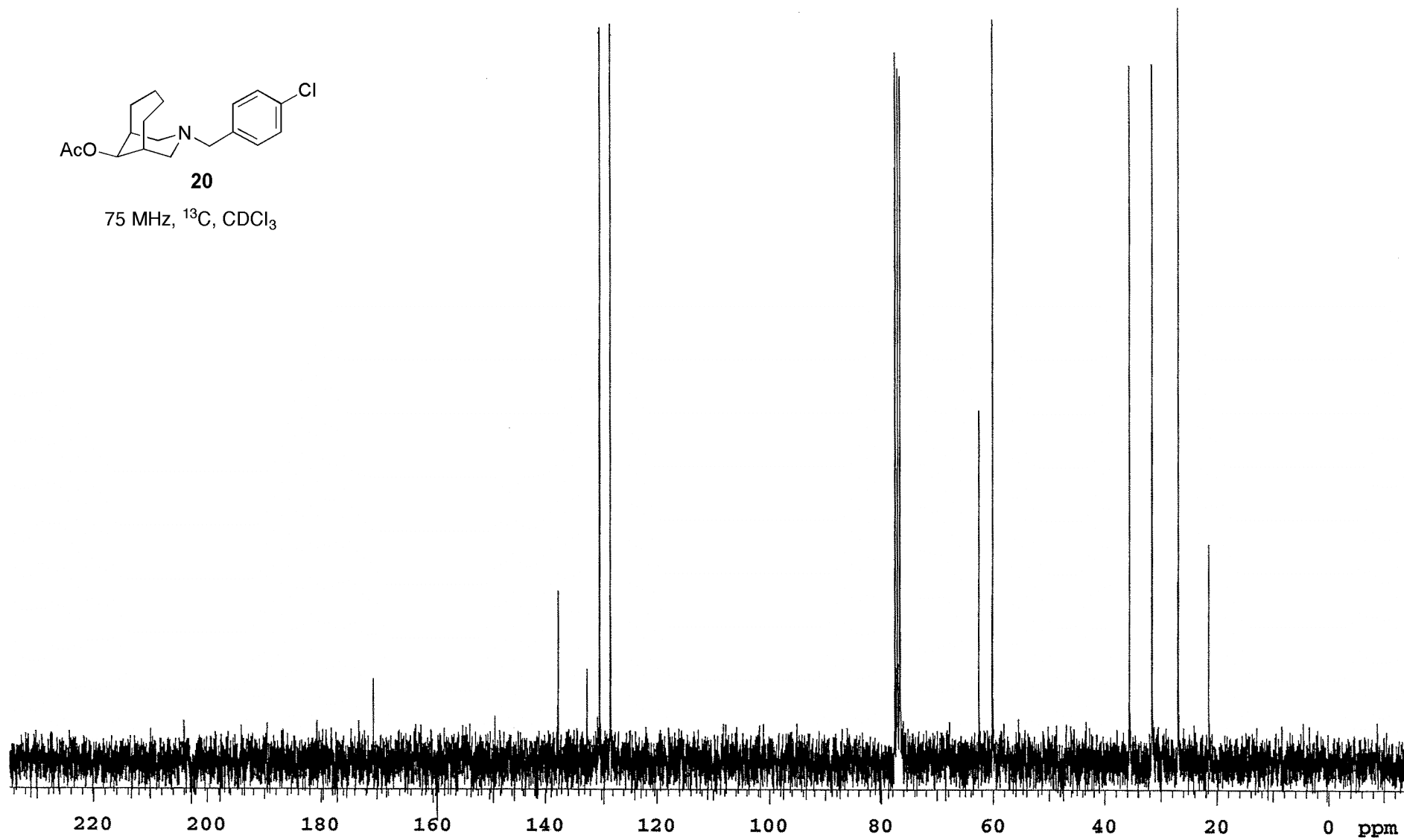
300 MHz, ^1H , CDCl_3

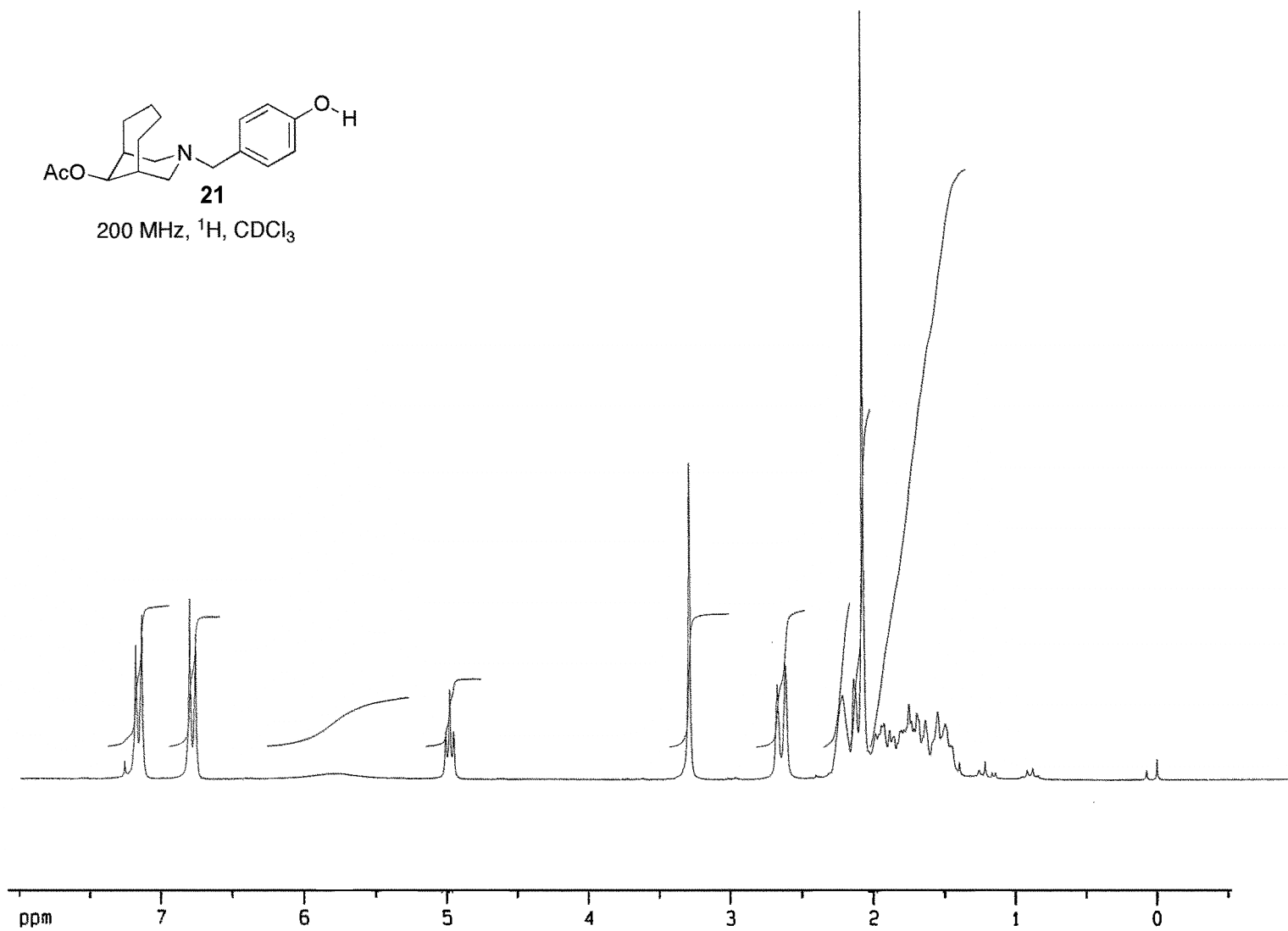
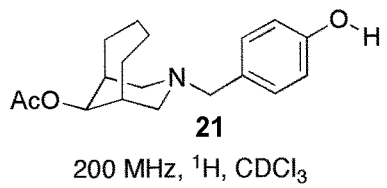


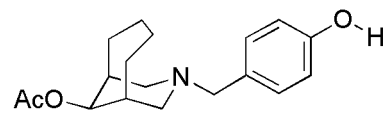


20

75 MHz, ^{13}C , CDCl_3







21

75 MHz, ^{13}C , CDCl_3

