Angewandte
Eine Zeitschrift der Gesellschaft Deutscher Chemiker
Chemie

Supporting Information

Enantioselective Catalysis Coupled with Stereodivergent Cyclization Strategies Enables Rapid Syntheses of (+)-Limaspermidine and (+)-Kopsihainanine A

Beau P. Pritchett[+], *Etienne J. Donckele*[+], *and Brian M. Stoltz**

anie_201707304_sm_miscellaneous_information.pdf

Table of Contents

Materials and Methods

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried glassware under an argon atmosphere using dry, deoxygentated solvents (distilled or passed over a column of activated alumina).[1] Commercially available reagents were used as received. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 40-63 nm) was used for flash chromatography. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and 77.16, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralpak (AD-H) or Chiracel (OD-H) columns obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode, or from the Caltech Center for Catalysis and Chemical

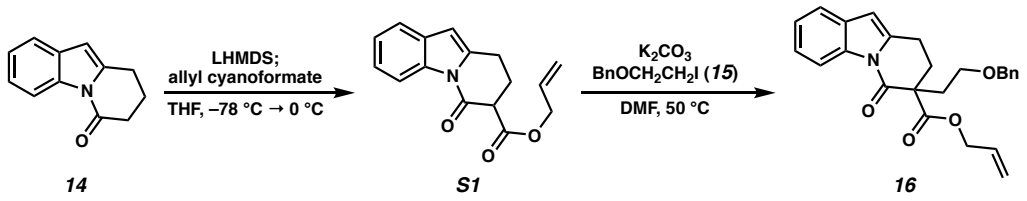
Synthesis using an Agilent 6200 series TOF with an Agilent G1978A Multimode source in mixed (Multimode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm.

Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Bis(cyclopentadienyl) zirconium chloride hydride was purchased from Strem Chemicals and stored at room temperature in a N_2-filled glovebox. Hydroxylamine-*O*-sulfonic acid was purchased from Sigma Aldrich and stored at –30°C in the glovebox freezer. MeOH was distilled from magnesium methoxide immediately prior to use. Triethylamine was distilled from calcium hydride immediately prior to use. (*S*)-$(CF_3)_3$-*t*-BuPHOX (**L1**),[2] tris(4,4'-methoxydibenzylideneacetone)dipalladium(0) $Pd_2(pmdba)_3$,[3] allyl cyanoformate,[4] and (2-benzyloxy)ethyl iodide (**15**)[5] were prepared by known methods.

List of Abbreviations:

DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene, TBD – 1,5,7-triazabicyclo[4.4.0]dec-5-ene, TBME – *tert*-butyl methyl ether, ee – enantiomeric excess, LHMDS – lithium bis(trimethylsilyl)amide, SFC – supercritical fluid chromatography, TFA – trifluoroacetic acid, THF – tetrahydrofuran, TLC – thin-layer chromatography

Experimental Procedures

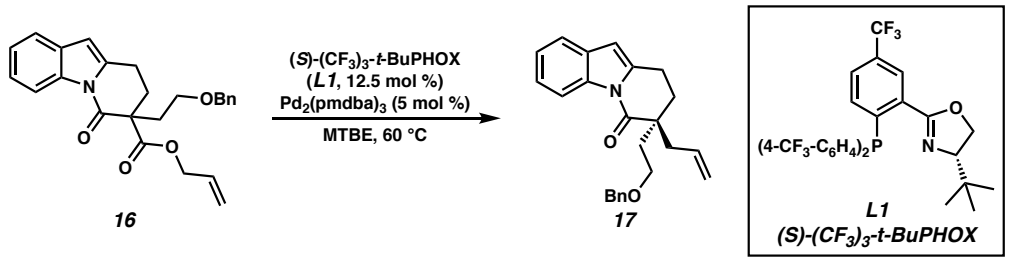


Allyl 6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (S1): A flame-dried round bottom flask was charged with LHMDS (3.34 g, 20.0 mmol, 2.0 equiv) and a magnetic stirring bar in a N_2-filled glove box. The flask was sealed, removed from the glovebox, fitted with an argon line, and suspended in a dry ice/acetone bath. THF (50 mL) was added slowly to the flask and allowed to stir until the LHMDS had been completely dissolved. A solution of heteroarene **14** (1.84 g, 10.0 mmol, 1.0 equiv) in THF (7 mL) was added dropwise, and the reaction was allowed to stir for 30 min at –78 °C. Allyl cyanoformate (1.32 mg, 12.0 mmol, 1.2 equiv) was then added dropwise, and the reaction mixture was allowed to warm slowly to 0 °C over 4 h. Once the cooling bath temperature reached 0 °C, saturated aqueous NH_4Cl (200 mL) was then added slowly and the mixture stirred for 20 min before being extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 15% acetone in hexanes) afforded tertiary β-amidoester **S5** (2.56 g, 96% yield) as a faintly yellow oil which solidified to an off-white amorphous solid upon storage at –30 °C: R_f = 0.35 (4:1 hexanes:acetone eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45–8.42 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.24 (m, 2H), 6.36 (td, *J* = 1.4, 0.7 Hz, 1H), 5.93 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.35 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.77–4.67 (m, 2H), 3.83 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.11 (dddd, *J* = 16.4, 8.1, 4.5, 1.4 Hz, 1H), 2.98

(dddd, J = 16.4, 8.5, 4.6, 1.5 Hz, 1H), 2.55–2.46 (m, 1H), 2.38–2.29 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 165.2, 137.0, 135.1, 131.5, 129.9, 124.51, 124.48, 120.0, 119.1, 116.7, 105.8, 66.5, 51.1, 25.3, 21.8; IR (Neat Film, NaCl) 3085, 3051, 2946, 2850, 1732, 1690, 1577, 1454, 1381, 1356, 1301, 1213, 1177, 1148, 1021, 977, 932, 802, 742 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{16}NO_3$ $[M+H]^+$: 270.1130, found 270.1140.

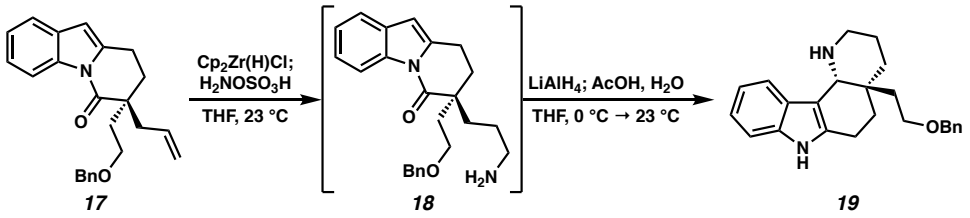
Allyl 7-(2-(benzyloxy)ethyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (16): To a solution of β-amidoester **S1** (727 mg, 2.70 mmol, 1.0 equiv) in DMF (9 mL) were added K_2CO_3 (522 mg, 3.78 mmol, 1.4 equiv) and iodide **15**[5] (990 mg, 3.78 mmol, 1.4 equiv) at 23 °C with stirring. The reaction mixture was placed in a pre-heated 50 °C oil bath. After 4 h, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH_4Cl (50 mL) was added, followed by extraction with EtOAc (3 x 100 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated. Flash column chromatography (SiO_2, 25% Et_2O in hexanes) afforded quaternary β-amidoester **16** (903 mg, 83% yield) as a clear colorless oil: R_f = 0.32 (7:3 hexanes:Et_2O eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49–8.43 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.22 (m, 2H), 7.23–7.18 (m, 5H), 6.31 (dt, J = 1.8, 0.9 Hz, 1H), 5.81 (ddt, J = 17.2, 10.5, 5.6 Hz, 1H), 5.21 (dq, J = 17.2, 1.5 Hz, 1H), 5.16 (dq, J = 10.5, 1.3 Hz, 1H), 4.64–4.56 (m, 2H), 4.46 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 3.74 (t, J = 6.3 Hz, 2H), 3.07 (dtd, J = 16.7, 4.7, 1.1 Hz, 1H), 2.96 (dddd, J = 16.6, 11.7, 4.6, 1.8 Hz, 1H), 2.59–2.49 (m, 2H), 2.41 (dt, J = 14.3, 6.1 Hz, 1H), 2.27 (ddd, J = 13.5, 11.8, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 167.9, 138.2, 137.2, 135.4, 131.4, 130.2, 128.4, 127.64, 127.62, 124.30, 124.28, 119.9, 118.9, 116.8, 105.3, 73.1, 66.8, 66.4, 55.3, 34.7, 30.3, 20.9; IR (Neat Film,

NaCl) 3066, 3032, 2930, 2855, 1728, 1701, 1597, 1577, 1451, 1353, 1333, 1301, 1171, 1093, 1026, 973, 798, 733, 695 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{25}H_{26}NO_4$ $[M+H]^+$: 404.1856, found 404.1865.



(*S*)-7-Allyl-7-(2-(benzyloxy)ethyl)-8,9-dihydropyrido[1,2-*a*]indol-6(7*H*)-one (17): A flame-dried 100 mL Schlenk Flask was charged with $Pd_2(pmdba)_3$ (56 mg, 51.1 μmol, 0.05 equiv), (*S*)-$(CF_3)_3$-*t*-BuPHOX (**L1**, 77 mg, 0.13 mmol, 0.125 equiv), and a magnetic stirring bar in a N_2-filled glove box. The flask was then charged with TBME (28 mL) and stirred at 23 °C for 30 minutes, generating a dark purple solution. To the preformed catalyst solution was added a solution of **16** (417 mg, 1.03 mmol, 1.0 equiv) in TBME (3 mL, including washings). The flask was sealed, removed from the glovebox, and placed in a preheated 60 °C oil bath with stirring. Full consumption of starting material was achieved after 8 h, as determined by TLC analysis. The crude reaction mixture was stripped onto silica gel, and purified by flash column chromatography (SiO_2, 12% Et_2O → 25% Et_2O in hexanes) to afford α-quaternary DHPI **17** (305 mg, 82% yield) as a faintly yellow oil: R_f = 0.5 (7:3 hexanes:Et_2O eluent); 94% *ee*, $[\alpha]_D^{25}$ +22.6 (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.49–8.46 (m, 1H), 7.49–7.46 (m, 1H), 7.30–7.25 (m, 2H), 7.25–7.20 (m, 5H), 6.30 (q, *J* = 1.3 Hz, 1H), 5.82 (ddt, *J* = 16.0, 11.2, 7.4 Hz, 1H), 5.15 (t, *J* = 1.1 Hz, 1H), 5.14–5.11 (m, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 3.69 (dt, *J* = 9.6, 6.9 Hz, 1H), 3.62 (ddd, *J* = 9.6, 7.2, 5.7 Hz, 1H), 3.05

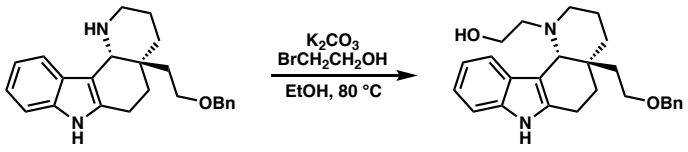
(ddd, J = 7.5, 5.9, 1.3 Hz, 2H), 2.66 (ddt, J = 13.9, 7.0, 1.3 Hz, 1H), 2.49–2.42 (m, 1H), 2.29 (dt, J = 14.2, 7.1 Hz, 1H), 2.12–2.03 (m, 2H), 1.99 (ddd, J = 14.2, 6.9, 5.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 138.3, 137.7, 135.3, 133.2, 130.2, 128.4, 127.62, 127.59, 124.02. 123.96, 119.8, 119.3, 116.7, 104.7, 73.2, 66.7, 45.6, 40.9, 35.4, 29.5, 19.9; IR (Neat Film, NaCl) 3062, 3028, 2930, 2856, 1693, 1639, 1595, 1574, 1451, 1433, 1355, 1299, 1181, 1097, 1026, 1001, 915, 797, 733, 695 cm^{-1}; HRMS (ESI/APCI) m/z calc'd for $C_{24}H_{26}NO_2$ $[M+H]^+$: 360.1958, found 360.1962; SFC conditions: 15% i-PrOH, 2.5 mL/min, Chiralcel OD-H column, λ = 210 nm, t_R (min): major = 8.83, minor = 9.71.



(4a*R*,11c*R*)-4a-(2-(Benzyloxy)ethyl)-2,3,4,4a,5,6,7,11c-octahydro-1*H*-pyrido[3,2-*c*]carbazole (19): A flame-dried round bottom flask was charged with α-quaternary DHPI **17** (98 mg, 0.273 mmol, 1.0 equiv), THF (1.4 mL), and a magnetic stirring bar in a N_2-filled glovebox. To this solution was added bis(cyclopentadienyl) zirconium chloride hydride (84 mg, 0.325 mmol, 1.2 equiv), and the mixture was stirred at 23 °C for 30 min. A second portion of bis(cyclopentadienyl) zirconium chloride hydride (14 mg, 54 μmol, 0.2 equiv) was added, and the reaction mixture was stirred for an additional 30 min at which point a brown solution was observed. Hydroxylamine-*O*-sulfonic acid (46 mg, 0.406 mmol, 1.5 equiv) was added, the vial was sealed and removed from the glovebox, and stirring was resumed at 23 °C in a fume hood for an additional 10 min. The reaction mixture was then cooled to 0 °C and $LiAlH_4$ (0.82 mL, 1.0 M in THF, 0.82 mmol, 3.0 equiv) was added over five minutes. The reaction was stirred at 0 °C for 15 minutes

before careful quenching with H_2O (2.2 mL) and AcOH (6.6 mL). Stirring was continued at 23 °C for 12h, at which point complete equilibration to the desired Pictet–Spengler product (**19**) was observed by LCMS. The mixture was basified with 2N NaOH until pH > 12, and was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford crude *cis*-fused tetracycle **19** (96 mg), which was carried on without further purification.

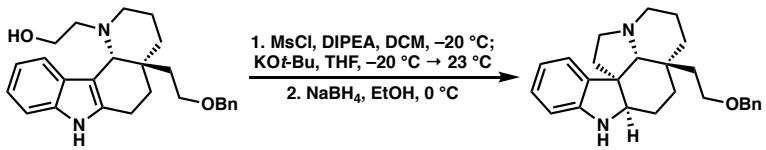
An analytical sample of **19** was obtained after flash column chromatography (SiO_2, 2% Et_3N in EtOAc): off-white foam; R_f = 0.45 (19:1 EtOAc:Et_3N eluent); $[\alpha]_D^{25}$ – 23.1 (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.35–7.24 (m, 6H), 7.14–7.01 (m, 2H), 4.45 (s, 2H), 3.75 (s, 1H), 3.61–3.54 (m, 2H), 3.01 (d, *J* = 12.2 Hz, 1H), 2.80–2.72 (m, 3H), 2.36 (app q, *J* = 10.2 Hz, 1H), 1.85–1.75 (m, 2H), 1.65–1.43 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 136.3, 134.1, 128.5, 127.60, 127.57, 127.5, 121.0, 119.3, 117.6, 112.1, 110.6, 73.0, 66.9, 56.7, 46.3, 36.7, 35.1, 34.4, 25.4, 22.8, 20.3; IR (Neat Film, NaCl) 3401, 3295, 3147, 3057, 3030, 2926, 2854, 1622, 1588, 1495, 1466, 1452, 1364, 1328, 1101, 1028, 1011, 806, 739, 697 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{24}H_{29}N_2O$ $[M+H]^+$: 361.2274, found 361.2287.



19 ***20***

Ethanolamine 209: To a solution of crude *cis*-fused tetracycle **19** (96 mg, 0.266 mmol, 1.0 equiv) in EtOH (8.9 mL) were added 2-bromoethanol (0.15 mL, 2.11 mmol, 8.0 equiv), K_2CO_3 (295 mg, 2.11 mmol, 8.0 equiv) and a magnetic stirring bar. The suspension was heated to 80 °C and stirred for 4 h, at which point full consumption of

starting material was observed by TLC analysis. The suspension was concentrated to dryness, partitioned between H_2O (75 mL) and EtOAc (75 mL), and extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1% Et_3N in EtOAc) gave ethanolamine **20** (68 mg, 62% yield in two steps from **17**) as tan foam: R_f = 0.5 (19:1 EtOAc:Et_3N eluent); $[\alpha]_D^{25}$ +17.8 (*c* 1.28, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.42–7.38 (m, 1H), 7.32–7.28 (m, 2H), 7.27–7.22 (m, 4H), 7.12–7.05 (m, 2H), 4.40 (d, *J* = 11.9 Hz, 1H), 4.37 (d, *J* = 11.9 Hz, 1H), 3.56–3.42 (m, 3H), 3.24 (s, 1H), 3.17–3.07 (m, 3H), 2.87–2.72 (m, 3H), 2.26–2.17 (m, 2H), 1.89–1.74 (m, 2H), 1.66–1.51 (m, 3H), 1.48–1.41 (m, 1H), 1.30 (ddd, *J* = 14.1, 8.3, 5.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 136.2, 135.4, 129.9, 128.5, 127.62, 127.57, 121.1, 119.6, 117.8, 110.6, 110.5, 73.0, 67.0, 63.2, 58.0, 54.2, 52.3, 36.84, 36.82, 35.8, 25.2, 22.1, 20.5; IR (Neat Film, NaCl) 3406, 3212, 3178, 3107, 3060, 3031, 2943, 2871, 1619, 1584, 1496, 1452, 1366, 1329, 1305, 1246, 1187, 1104, 1075, 1038, 983, 903, 870, 741, 697 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{26}H_{33}N_2O_2$ $[M+H]^+$: 405.2537, found 405.2541.

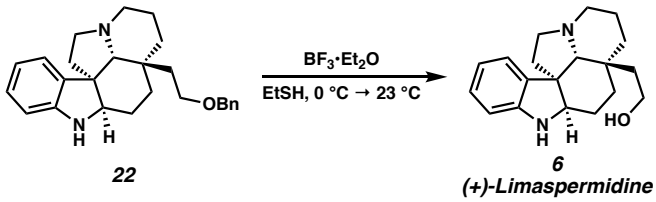


20 ***22***

***O*-Benzyl Limaspermidine (22)**: To a solution of primary alcohol **20** (64 mg, 158 μmol, 1.0 equiv) and *N,N*-diisopropylethylamine (DIPEA, 36 μL, 206 μmol, 1.3 equiv) in CH_2Cl_2 (3.1 mL) was added methanesulfonyl chloride (MsCl, 12.5 μL, 161 μmol, 1.02 equiv) dropwise at –15 °C (ice/MeOH bath). After stirring at –15 °C for 45 min, KO*t*-Bu (0.79 mL, 0.5 M in THF, 0.395 mmol, 2.5 equiv) was added and the reaction mixture was

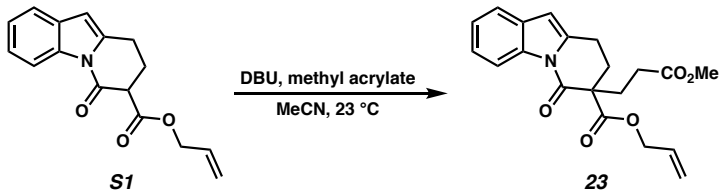
allowed to warm to 0 °C over a period of 2 h. The reaction mixture was quenched with brine (25 mL), and extracted with EtOAc (5 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was dissolved in EtOH (4.8 mL) and the resulting solution cooled to 0 °C. $NaBH_4$ (30 mg, 0.79 mmol, 5.0 equiv) was added in three equal portions over 10 min. After stirring at 0 °C for 15 additional min, the reaction mixture was removed from the ice bath and stirring was continued for a further 3 h. Sodium citrate dihydrate (233 mg, 0.79 mmol, 5.0 equiv) and H_2O (5 mL) were added, and the mixture was stirred at 23 °C for 30 min. The reaction mixture was partitioned between H_2O (20 mL) and EtOAc (20 mL), and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 8% MeOH in CH_2Cl_2) gave *O*-benzyl 10imaspermidine (**22**, 44.6 mg, 73% yield) as faint yellow oil: R_f = 0. 22 (19:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ +10.0 (*c* 0.44, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.0, 6.5 Hz, 2H), 7.27–7.23 (m, 1H), 7.22–7.19 (m, 2H), 7.08 (d, *J* = 7.4 Hz, 1H), 7.02 (td, *J* = 7.6, 1.3 Hz, 1H), 6.74 (td, *J* = 7.3, 1.0 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 12.0 Hz, 1H), 3.51 (dd, *J* = 11.0, 6.2 Hz, 1H), 3.44 (ddd, *J* = 9.6, 8.1, 5.9 Hz, 1H), 3.40–3.35 (m, 1H), 3.15–3.10 (m, 1H), 3.05 (d, *J* = 11.0 Hz, 1H), 2.35–2.22 (m, 2H), 2.27 (s, 1H), 2.08–1.93 (m, 2H), 1.86 (ddd, *J* = 14.5, 8.3, 6.5 Hz, 1H), 1.80–1.70 (m, 1H), 1.66 (ddt, *J* = 13.0, 6.4, 3.1 Hz, 2H), 1.54–1.42 (m, 3H), 1.31–1.19 (m, 2H), 1.08–1.03 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 138.6, 135.4, 128.4, 127.7, 127.5, 127.4, 123.0, 119.4, 110.6, 72.8, 71.0, 66.2, 65.6, 53.9, 53.6, 53.0, 38.7, 36.9, 35.6, 35.5, 28.4, 24.4, 21.9; IR (Neat Film, NaCl) 3361, 3027, 2928, 2857, 2779, 2722, 1606, 1481, 1462, 1363, 1332, 1259, 1176, 1095, 1026,

740, 697 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{26}H_{33}N_2O$ $[M+H]^+$: 389.2587, found 389.2592.



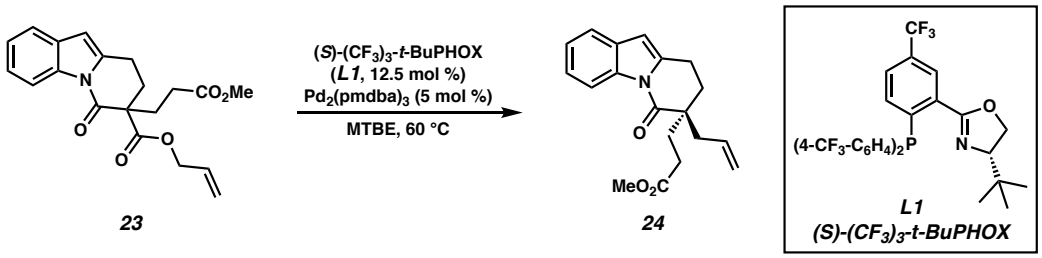
(+)-Limaspermidine (2): To a solution of *O*-benzyl 11imaspermidine (**22**, 21 mg, 54 μmol, 1.0 equiv) in EtSH (1.8 mL) was added BF_3•Et_2O (133 μL, 1.07 mmol, 20 equiv) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was transferred to a pre-heated 30 °C oil bath and stirred for an additional 4 h. After cooling to 23 °C and quenching with saturated aqueous $NHCO_3$ (5 mL) and H_2O (5 mL), the mixture was stirred for an additional 2 h, then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 8% MeOH in CH_2Cl_2) furnished (+)-limaspermidine (**2**, 13.5 mg, 84% yield) as an off-white amorphous solid: R_f = 0. 27 (9:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ +22.6 (*c* 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.01 (td, *J* = 7.6, 1.3 Hz, 1H), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 3.63 (td, *J* = 10.0, 5.4 Hz, 1H), 3.58–3.48 (m, 2H), 3.16–3.10 (m, 1H), 3.04 (app dt, *J* = 10.9, 2.2 1H), 2.34–2.22 (m, 3H), 2.06 (td, *J* = 13.8, 3.5 Hz, 1H), 1.99 (ddd, *J* = 12.4, 10.9, 2.9 Hz, 1H), 1.81–1.67 (m, 3H), 1.65 (d, *J* = 13.5 Hz, 1H), 1.54–1.44 (m, 3H), 1.27 (td, *J* = 13.4, 4.6 Hz, 1H), 1.19 (ddd, *J* = 14.2, 9.3, 5.4 Hz, 1H), 1.04 (dd, *J* = 13.7, 3.8 Hz, 1H), 0.92 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 135.4, 127.5, 122.9, 119.3, 110.6, 70.8, 65.5, 58.8, 53.9, 53.6, 53.0, 40.6, 38.7, 35.62, 35.55, 28.4, 24.4, 21.9; IR (Neat Film, NaCl) 3308, 3149, 2930, 2858, 2816, 2793, 1607, 1466, 1320, 1256, 1216, 1166,

1041, 1015, 900, 749 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{27}N_2O$ $[M+H]^+$: 299.2118, found 299.2114.



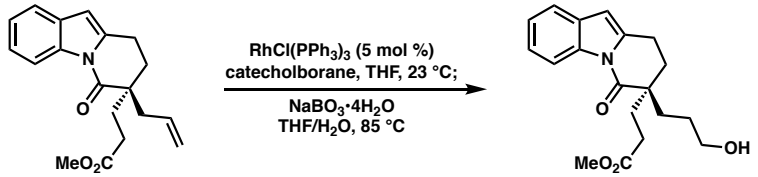
Allyl 7-(3-methoxy-3-oxopropyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (23): To a solution of β-amidoester **S1** (530 mg, 1.96 mmol, 1.0 equiv) in MeCN (13.1 mL) were added methyl acrylate (0.36 mL, 3.92 mmol, 2.0 equiv) and DBU (15 μL, 98 μmol, 0.05 equiv) at 23 °C with stirring. After 90 min, starting material was completely consumed as determined by TLC analysis. Saturated aqueous NH_4Cl (100 mL) was added, followed by extraction with EtOAc (3 x 150 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), then dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 25% acetone in hexanes) afforded quaternary β-amidoester **23** (670 mg, 96% yield) as a light yellow oil: R_f = 0.33 (3:1 hexanes:acetone eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47–8.44 (m, 1H), 7.47–7.45 (m, 1H), 7.31–7.24 (m, 2H), 6.32 (dt, *J* = 1.7, 0.9 Hz, 1H), 5.83 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.24 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.65 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.67 (s, 3H), 3.09 (dtd, *J* = 16.8, 4.9, 1.1 Hz, 1H), 2.96 (dddd, *J* = 16.7, 11.5, 4.8, 1.8 Hz, 1H), 2.68 (ddd, *J* = 15.8, 9.3, 6.5 Hz, 1H), 2.55 – 2.47 (m, 2H), 2.44 (ddd, *J* = 10.7, 5.6, 3.9 Hz, 2H), 2.13 (ddd, *J* = 13.4, 11.4, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 170.9, 167.5, 136.8, 135.3, 131.2, 130.1, 124.44, 124.42, 120.0, 119.2, 116.8, 105.6, 66.5, 55.6, 52.0, 30.6, 30.0, 29.9, 20.8; IR (Neat Film, NaCl) 2951, 2854, 1738, 1704, 1600, 1577, 1455, 1375, 1357, 1315, 1227, 1176, 1087, 1034,

989, 935, 802, 755 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{20}H_{22}NO_5$ $[M+H]^+$: 356.1492, found 356.1498.



Methyl ®-3-(7-allyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-7-yl)propanoate (24): A flame-dried 250 mL Schlenk Flask was charged with $Pd_2(pmdba)_3$ (90 mg, 82.1 μmol, 0.05 equiv), (*S*)-$(CF_3)_3$-*t*-BuPHOX (**L1**, 120 mg, 0.202 mmol, 0.125 equiv), and a magnetic stirring bar in a N_2-filled glove box. The flask was then charged with TBME (42 mL) and stirred at 23 °C for 30 minutes, generating a dark purple solution. To the preformed catalyst solution was added a solution of **23** (580 mg, 1.63 mmol, 1.0 equiv) in TBME (7 mL, including washings). The flask was sealed, removed from the glovebox, and placed in a preheated 60 °C oil bath with stirring. Full consumption of starting material was achieved after 12 h, as determined by TLC analysis. The crude reaction mixture was stripped onto silica gel, and purified by flash column chromatography (SiO_2, 25% Et_2O in hexanes) to afford α-quaternary DHPI **24** (456 mg, 90% yield) as a yellow oil: R_f = 0.29 (7:3 hexanes:Et_2O eluent); 92% *ee*, $[\alpha]_D^{25}$ –4.2 (*c* 0.89, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.47–8.43 (m, 1H), 7.47–7.44 (m, 1H), 7.29–7.22 (m, 2H), 6.30 (td, *J* = 1.4, 0.7 Hz, 1H), 5.85–5.75 (m, 1H), 5.18–5.16 (m, 1H), 5.15–5.14 (m, 1H), 3.64 (s, 3H), 3.07 (td, *J* = 6.7, 1.4 Hz, 2H), 2.63 (ddt, *J* = 14.1, 7.1, 1.2 Hz, 1H), 2.53–2.39 (m, 3H), 2.18–2.03 (m, 3H), 2.01–1.91 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 172.9, 137.4, 135.3, 132.8, 130.2, 124.14, 124.11, 119.9, 119.6, 116.7, 105.0, 51.9, 45.8, 40.2,

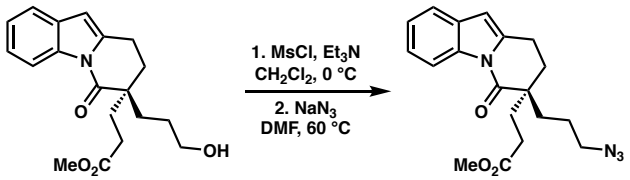
30.5, 29.6, 29.2, 19.7; IR (Neat Film, NaCl) 3459, 3376, 3077, 2948, 2865, 1731, 1694, 1639, 1597, 1575, 1452, 1358, 1310, 1258, 1176, 1101, 1031, 996, 920, 879, 800, 757, 644 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found 312.1584; SFC conditions: 7% *i*-PrOH, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 15.71, minor = 14.34.



24 ***25***

Primary alcohol 25: To a solution of DHPI **24** (1.2 g, 3.85 mmol, 1.0 equiv) in THF (38 mL) were added $RhCl(PPh_3)_3$ (176 mg, 0.19 mmol, 0.05 equiv) and catecholborane (7.6 mL, 1.0 M in THF, 7.6 mmol, 2.0 equiv) sequentially at 23 °C. After stirring at 23 °C for 30 min, H_2O (10 mL) and $NaBO_3•4H_2O$ (2.9 g, 18.8 mmol, 5.0 equiv) were added. The reaction mixture was transferred to a pre-heated 85 °C oil bath and stirred for 15 min. After cooling to 23 °C, the resulting suspension was filtered. The filter cake was washed with THF, and the filtrate was concentrated to dryness. The residue was partitioned between CH_2Cl_2 (40 mL) and H_2O (40 mL), and the aqueous layer was extracted with CH_2Cl_2 (40 mL). The combined organic layers were washed with 1N aq. NaOH (3 x 40 mL) and brine (40 mL), dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 20% Et_2O in CH_2Cl_2) afforded alcohol **25** as a yellow oil (1.09 g, 86%): R_f = 0.21 (4:1 CH_2Cl_2:Et_2O eluent); $[\alpha]_D^{25}$ +10.9 (*c* 1.23, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.44–8.41 (m, 1H), 7.47–7.44 (m, 1H), 7.29–7.21 (m, 2H), 6.29 (app q, *J* = 1.1 Hz, 1H), 3.66–3.61 (m, 2H), 3.64 (s, 3H), 3.07 (ddt, *J* = 7.2, 5.8, 1.3, 2H), 2.52–2.36 (m, 2H), 2.17–2.02 (m, 3H), 2.00–1.88 (m, 2H), 1.77–1.69 (m, 2H), 1.66–1.59 (m,

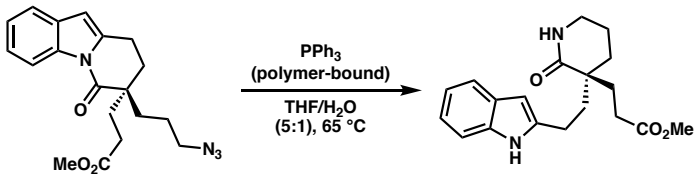
2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 173.4, 137.3, 135.2, 130.2, 124.13, 124.10, 119.9, 116.7, 105.1, 62.8, 51.9, 45.6, 31.6, 30.6, 29.7, 29.2, 27.1, 19.7; IR (Neat Film, NaCl) 3449, 2948, 2869, 1736, 1695, 1598, 1575, 1454, 1379, 1356, 1335, 1311, 1181, 1056, 1024, 819, 802, 758 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{24}NO_4$ $[M+H]^+$: 330.1700, found 330.1705.



25 ***26***

Azide 26: To a solution of alcohol **25** (1.1 g, 3.33 mmol, 1.0 equiv) and Et_3N (1.5 mL, 10.76 mmol, 3.2 equiv) in CH_2Cl_2 (24 mL) was added methanesulfonyl chloride (MsCl, 0.28 mL, 3.62 mmol, 1.09 equiv) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, then was quenched with sat. aq. $NaHCO_3$ (10 mL). After stirring for an additional 15 min, the aqueous layer was separated and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was dissolved in DMF (24 mL), and NaN_3 (240 mg, 3.69 mmol, 1.1 equiv) was added. The suspension was stirred at 60 °C for 1h, at which point complete consumption of starting material was determined by TLC analysis. The reaction mixture was cooled to 23 °C, diluted with H_2O (20 mL), and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with H_2O (2×20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. Flash column chromatography (SiO_2, 20% EtOAc in hexanes) afforded azide **26** as a yellow oil (1.04 g, 88% over two steps): R_f = 0.33 (3:1 hexanes:EtOAc eluent); $[\alpha]_D^{25}$ –65.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45–8.41 (m, 1H), 7.49–7.43 (m, 1H), 7.31–7.21 (m, 2H), 6.31 (app q, *J* = 1.3

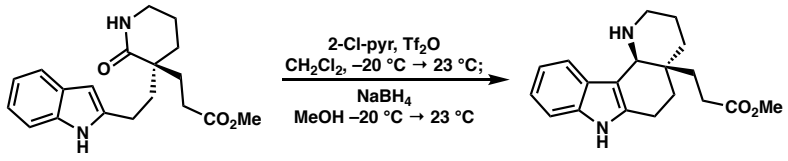
Hz, 1H), 3.65 (s, 3H), 3.32 (td, *J* = 6.4, 1.3 Hz, 2H), 3.09 (dddd, *J* = 7.2, 5.7, 4.4, 1.5 Hz, 2H), 2.50–2.37 (m, 2H), 2.18–2.06 (m, 2H), 2.06–1.96 (m, 2H), 1.95–1.84 (m, 1H), 1.77–1.61 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 172.8, 137.1, 135.3, 130.2, 124.23, 124.19, 119.9, 116.7, 105.2, 52.0, 51.8, 45.6, 32.7, 30.5, 29.8, 29.1, 23.7, 19.7; IR (Neat Film, NaCl) 2949, 2868, 2096, 1736, 1694, 1597, 1575, 1454, 1380, 1356, 1336, 1312, 1302, 1262, 1179, 1027, 1000, 819, 803, 758 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{23}N_4O_3$ $[M+H]^+$: 355.1765, found 355.1767.



26 *27*

Methyl ®-3-(3-(2-(1*H*-indol-2-yl)ethyl)-2-oxopiperidin-3-yl)propanoate (27): To a solution of azide **26** (700 mg, 1.97 mmol, 1.0 equiv) in THF (20 mL) and H_2O (4 mL) was added polymer-bound PPh_3 (1.31 g, ~3 mmol/g loading, 3.94 mmol, 2.0 equiv) in one portion. The reaction mixture was placed in a pre-heated oil bath and stirred at 65 °C for 4 h. After cooling to 23 °C, the reaction mixture filtered, washing with EtOAc, and the filtrate was concentrated to dryness. Flash column chromatography (SiO_2, 4% MeOH in CH_2Cl_2) afforded δ-lactam **27** as a light yellow foam (525 mg, 81%): R_f = 0.27 (19:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ –21.4 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.30–7.27 (m, 1H), 7.10 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 7.04 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.21 (s, 1H), 5.85 (br s, 1H), 3.66 (s, 3H), 3.32 (td, *J* = 5.7, 2.1 Hz, 2H), 2.86 (ddd, *J* = 14.6, 11.1, 5.8 Hz, 1H), 2.69 (ddd, *J* = 15.0, 11.0, 4.5 Hz, 1H), 2.42 (h, *J* = 8.5 Hz, 2H), 2.16 (ddd, *J* = 13.7, 11.2, 4.6 Hz, 1H), 2.01 (t, *J* = 8.2 Hz, 2H), 1.91–1.80 (m, 4H), 1.77–1.68 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$)

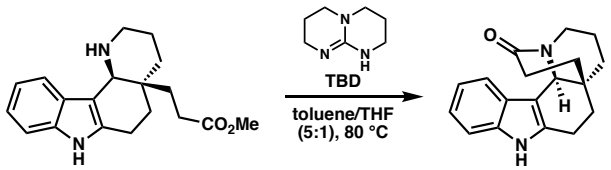
δ 176.0, 174.1, 139.5, 136.2, 128.7, 121.1, 119.8, 119.5, 110.7, 99.4, 51.9, 44.3, 42.8, 37.5, 33.2, 30.2, 29.4, 23.6, 19.5; IR (Neat Film, NaCl) 3287, 3054, 2949, 2870, 1731, 1645, 1551, 1489, 1456, 1417, 1289, 1173, 1094, 1061, 1012, 910, 782, 748 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{25}N_2O_3$ $[M+H]^+$: 329.1860, found 329.1868.



27 ***28***

***Trans*-fused tetracycle 28**: To a solution of δ-lactam **27** (111 mg, 0.338 mmol, 1.0 equiv) in CH_2Cl_2 (8.4 mL) were added 2-chloropyridine (39 μL, 0.405 mmol, 1.2 equiv) and triflic anhydride (63 μL, 0.372 mmol, 1.1 equiv) at –20 °C (dry ice in H_2O/MeOH (7:3) bath). After 15 min, the reaction mixture was removed from the cooling bath and stirring continued for a further 15 min. At this time, the reaction mixture was cooled back to –20 °C and a solution of $NaBH_4$ (64 mg, 1.69 mmol, 5.0 equiv) in MeOH (8.4 mL) was added dropwise over a period of two minutes. The reaction was diluted with CH_2Cl_2 and quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The biphasic mixture was poured into H_2O (25 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1% MeOH → 8% MeOH in CH_2Cl_2) afforded *trans*-fused tetracycle **28** (89 mg, 84% yield) as a yellow foam: R_f = 0.22 (9:1 CH_2Cl_2:MeOH eluent); $[\alpha]_D^{25}$ +21.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.9 Hz, 1H), 7.82 (br s, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.07 (ddd, *J* = 8.1, 7.1, 1.4 Hz, 1H), 7.01 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 3.96 (app t, *J* = 2.0 Hz, 1H), 3.61 (s, 3H), 3.33–3.26 (m, 1H), 2.91 (td, *J* = 12.9, 3.8 Hz, 1H), 2.75 (dddd, *J* = 20.2, 11.8, 6.2, 3.1 Hz, 1H), 2.65 (ddt, *J* =

16.7, 6.4, 1.4 Hz, 1H), 2.30 (ddd, *J* = 14.8, 12.1, 5.5 Hz, 1H), 2.20 (ddd, *J* = 14.8, 11.9, 4.8 Hz, 1H), 1.98 (td, *J* = 13.4, 12.7, 5.3 Hz, 1H), 1.78–1.69 (m, 3H), 1.62–1.42 (m, 3H), 1.35–1.23 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 136.1, 133.1, 127.2, 120.9, 120.5, 119.2, 110.8, 110.4, 64.1, 51.8, 47.2, 35.5, 33.6, 32.0, 29.0, 22.5, 20.6, 20.3; IR (Neat Film, NaCl) 3395, 3177, 3054, 2926, 2856, 1731, 1619, 1579, 1465, 1435, 1317, 1250, 1198, 1174, 1142, 1109, 1014, 875, 856, 739, 693 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{19}H_{25}N_2O_2$ $[M+H]^+$: 313.1911, found 313.1905.



28 ***29***

Pentacyclic lactam 29: In an N_2-filled glovebox, an oven-dried scintillation vial was charged with a magnetic stirring bar, *trans*-fused tetracycle **28** (56 mg, 0.179 mmol, 1.0 equiv), toluene (2.2 mL), THF (0.44 mL), and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 25 mg, 0.179 mmol, 1.0 equiv) at 23 °C. The vial was sealed and removed from the glovebox and placed in a pre-heated 80 °C heating block. After stirring for 5 h at 80 °C, the reaction mixture was cooled to 23 °C and stripped onto silica gel. Flash column chromatography (SiO_2, 2% MeOH in CH_2Cl_2) afforded lactam **29** (32.5 mg, 65% yield) as a white amorphous solid: R_f = 0.32 (19:1 CH_2Cl_2:MeOH eluent); recrystallized by slow evaporation from absolute ethanol; $[\alpha]_D^{25}$ –17.5 (*c* 0.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.72–7.67 (m, 1H), 7.26 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.11 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.02 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 4.41 (dd, *J* = 12.9, 5.6 Hz, 1H), 4.33 (app t, *J* = 2.0 Hz, 1H), 3.15 (td, *J* = 12.8, 3.3 Hz, 1H), 3.02 (dddd, *J* = 13.6, 11.1, 6.6, 3.2 Hz, 1H), 2.76 (ddt, *J* = 17.2, 5.8, 1.7 Hz, 1H), 2.11–2.04 (m, 2H), 2.01–

1.83 (m, 4H), 1.73–1.67 (m, 2H), 1.59–1.48 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.1, 136.3, 133.2, 125.1, 121.9, 120.3, 119.8, 111.2, 110.4, 64.4, 53.8, 39.9, 37.0, 35.0, 34.6, 27.8, 22.5, 19.8; IR (Neat Film, NaCl) 3273, 3059, 2924, 2853, 1657, 1464, 1409, 1328, 1245, 1163, 1131, 1075, 910, 846, 804, 738 cm^{-1}; HRMS (ESI/APCI) *m/z* calc'd for $C_{18}H_{21}N_2O$ $[M+H]^+$: 281.1648, found 281.1649.

Dunitz–Winkler Distortion Parameters for Bridgehead Lactam 29

Single crystal X-ray diffraction enabled the calculation of amide distortion parameters (χ_C, χ_N, and τ)[6] for strained lactam **29**. We calculated a pyramidalization parameter χ_N of 50.5°. The carbonyl carbon was found to exhibit a slight deviation from planarity with a distortion parameter χ_C of 6.5°. The torsion angle about the C–N bond, τ, was determined to be 23.5°.

^{1}HNMR Data Comparison of Synthetic (+)-Limaspermidine (2) (Table S1)

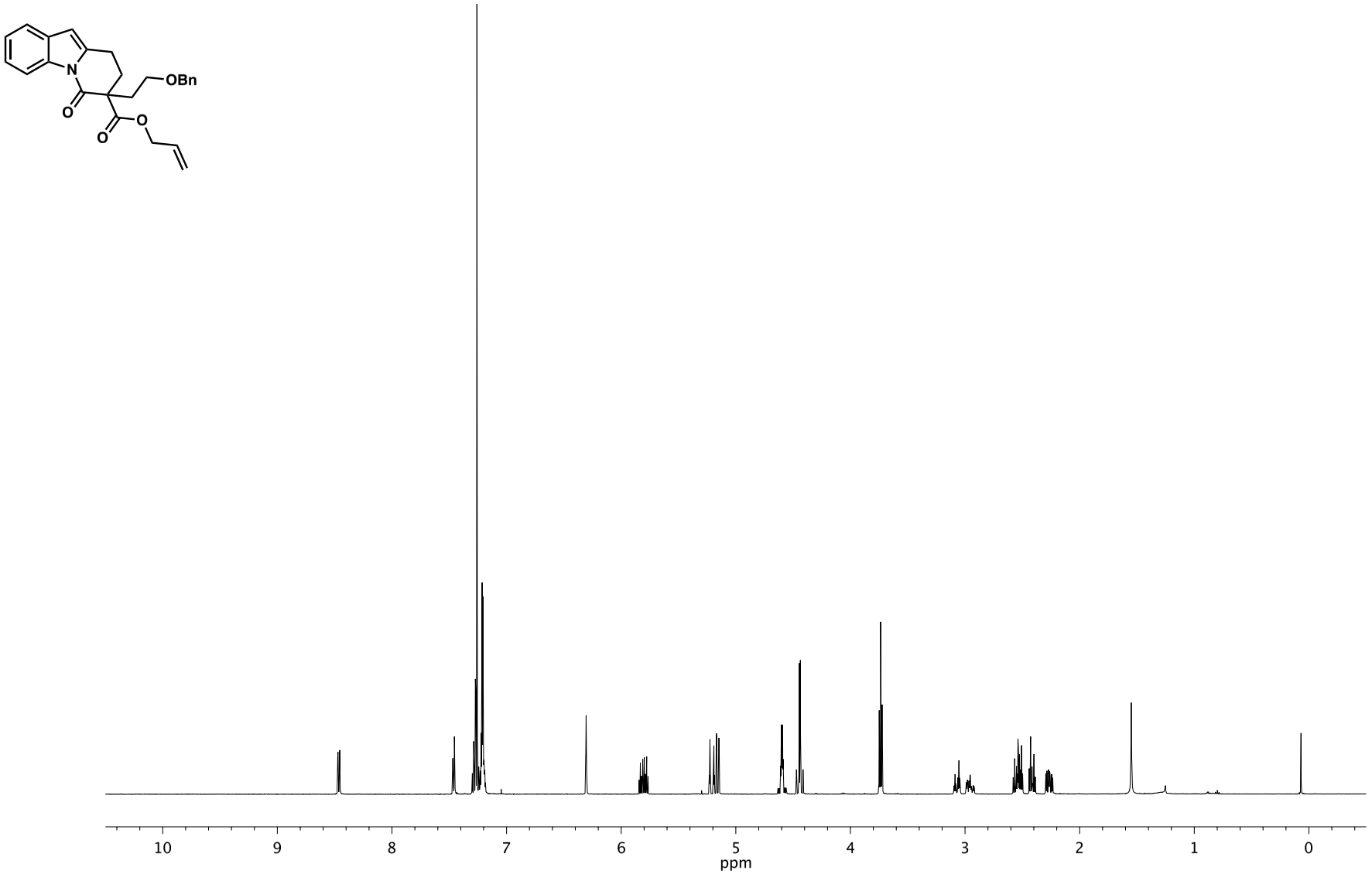
This Work	**Movassaghi's Report[7]**
^{1}H NMR (500 MHz, $CDCl_3$)	*^{1}H NMR (400 MHz, $CDCl_3$)*
7.08 (dd, *J* = 7.4, 1.2 Hz, 1H)	7.08 (d, *J* = 7.7 Hz, 1H)
7.01 (td, *J* = 7.6, 1.3 Hz, 1H)	7.01 (app td, *J* = 7.6, 1.3 Hz, 1H)
6.73 (td, *J* = 7.4, 1.0 Hz, 1H)	6.73 (app td, *J* = 7.4, 1.0 Hz, 1H)
6.64 (d, *J* = 7.7 Hz, 1H)	6.64 (d, *J* = 7.7 Hz, 1H)
3.63 (td, *J* = 10.0, 5.4 Hz, 1H)	3.63 (td, *J* = 10.0, 5.5 Hz, 1H)
3.58–3.48 (m, 2H)	3.58–3.47 (m, 2H)
3.16–3.10 (m, 1H)	3.17–3.08 (m, 1H)
3.04 (app dt, *J* = 10.9, 2.2 Hz, 1H)	3.05 (d, *J* = 11.1 Hz, 1H)
2.34–2.22 (m, 3H)	2.37–2.17 (m, 3H)
2.06 (td, *J* = 13.8, 3.5 Hz, 1H)	2.16–1.90 (m, 2H)
1.99 (ddd, *J* = 12.4, 10.9, 2.9 Hz, 1H)	
1.81–1.67 (m, 3H)	1.87–1.58 (m, 5H)
1.65 (d, *J* = 13.5 Hz, 1H)	
1.54–1.44 (m, 3H)	1.58–1.37 (m, 3H)
1.27 (td, *J* = 13.4, 4.6 Hz, 1H)	1.37–1.12 (m, 2H)
1.19 (ddd, *J* = 14.2, 9.3, 5.4 Hz, 1H)	
1.04 (dd, *J* = 13.7, 3.8 Hz, 1H)	1.03 (d, *J* = 13.7 Hz, 1H)
0.92 (br s, 1H)	0.89 (br s, 1H)

^{13}CNMR Data Comparison of Synthetic (+)-Limaspermidine (2) (Table S2)

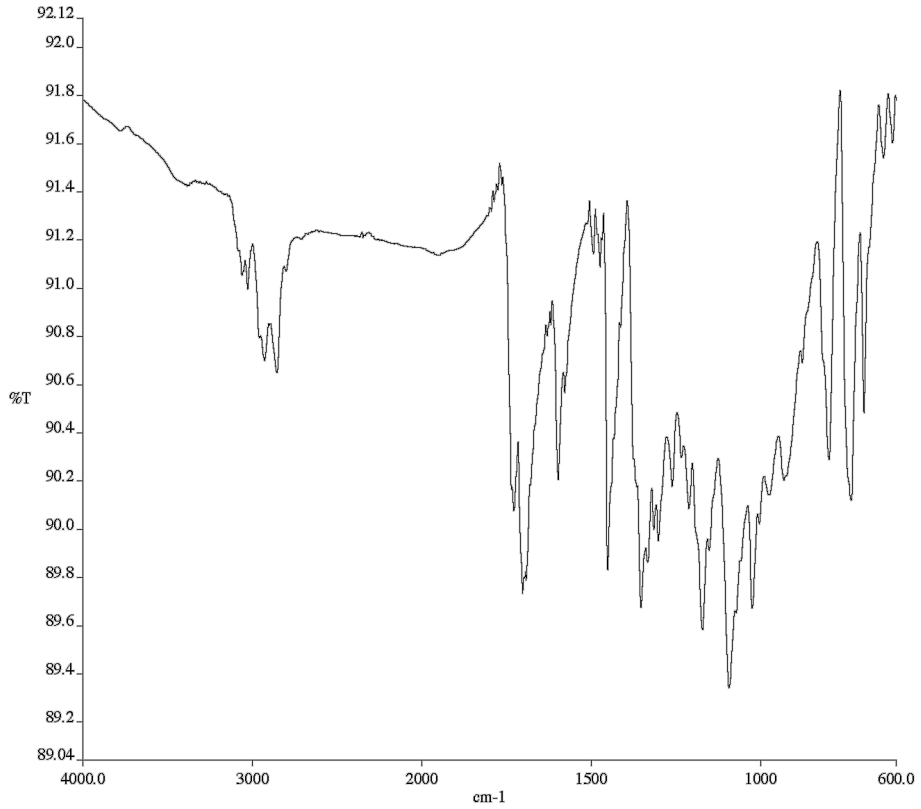
This Report	**Movassaghi's Report**[7]
^{13}C NMR (126 MHz, $CDCl_3$)	*^{13}C NMR (125 MHz, $CDCl_3$)*
149.6	149.6
135.4	135.4
127.5	127.5
122.9	122.9
119.3	119.3
110.6	110.6
70.8	70.8
65.5	65.5
58.8	58.8
53.9	53.9
53.6	53.6
53.0	53.0
40.6	40.7
38.7	38.7
35.62	35.6
35.55	35.6
28.4	28.4
24.4	24.5
21.9	21.9

Notes and References

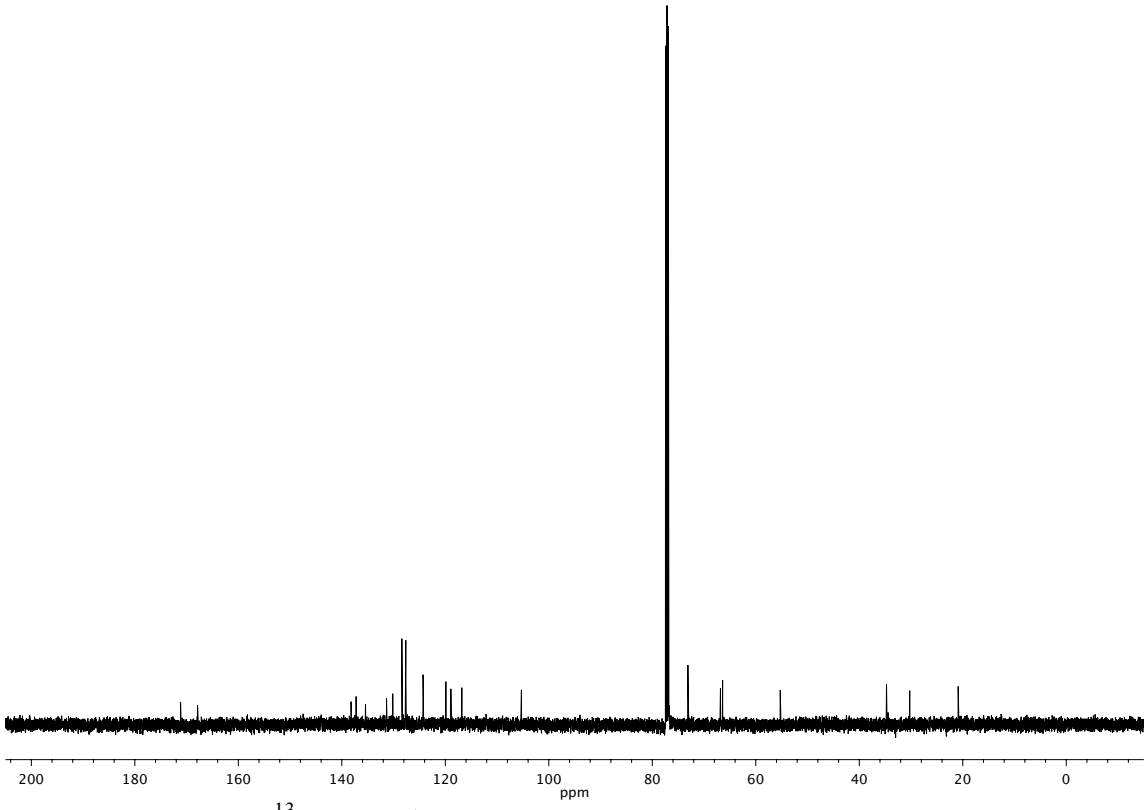
1. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
2. McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554.
3. (a) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253–256. (b) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435–4438.
4. Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486–3487.
5. Procedure adapted from: King, B. W. Lactam Derivatives as Inhibitors of Matrix Metalloproteinases and/or TNF-Alpha Converting Enzyme. US Patent 2004266751, December 30, 2004.
6. For the definition of amide bond deformation, see: Dunitz, J. D.; Winkler, F. K. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1975**, *31*, 251–263.
7. White, K. L.; Movassaghi, M. *J. Am. Chem. Soc.* **2016**, *138*, 11383–11389.



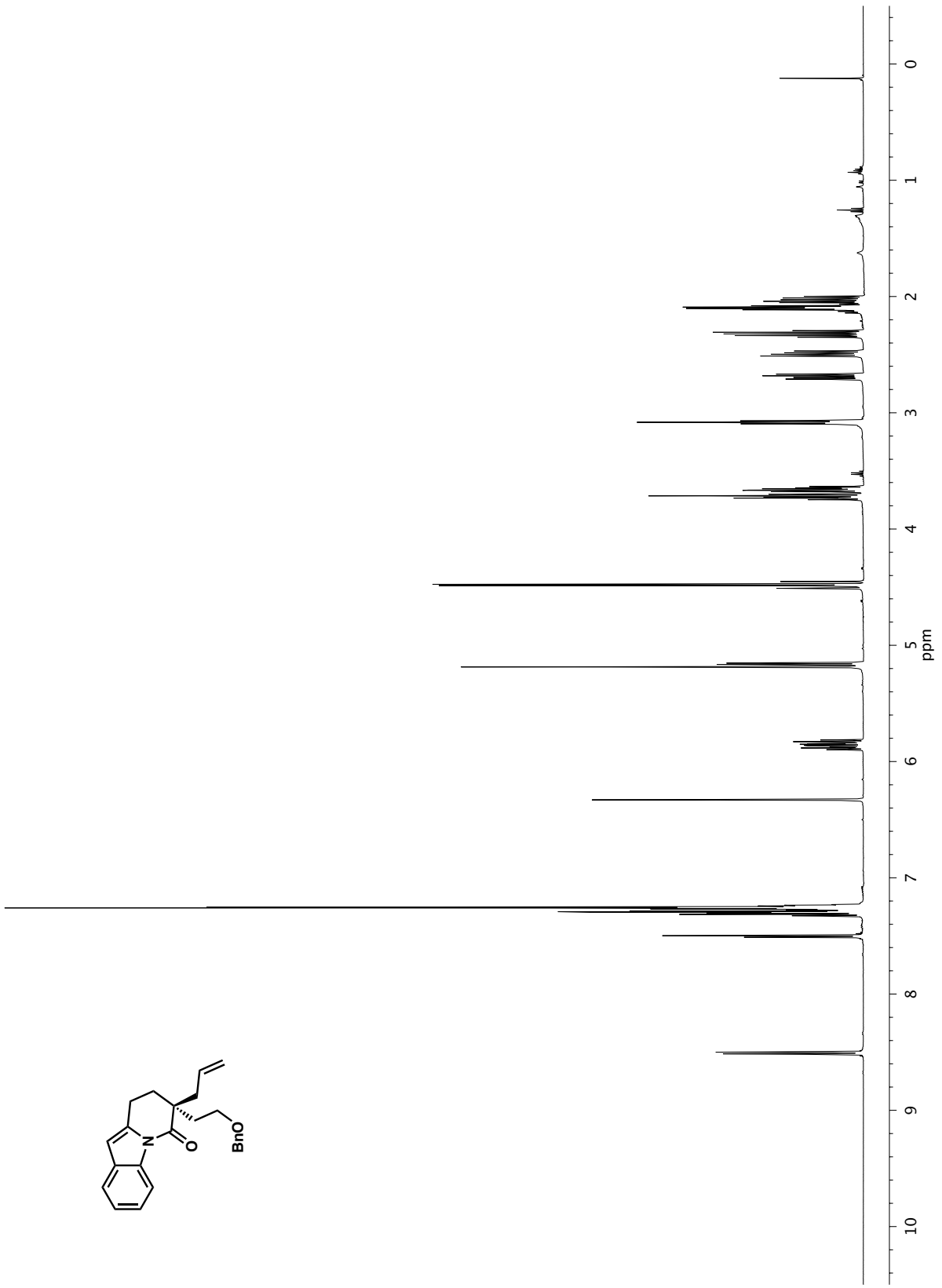
^{1}H NMR (500 MHz, $CDCl_3$) of compound **16**.



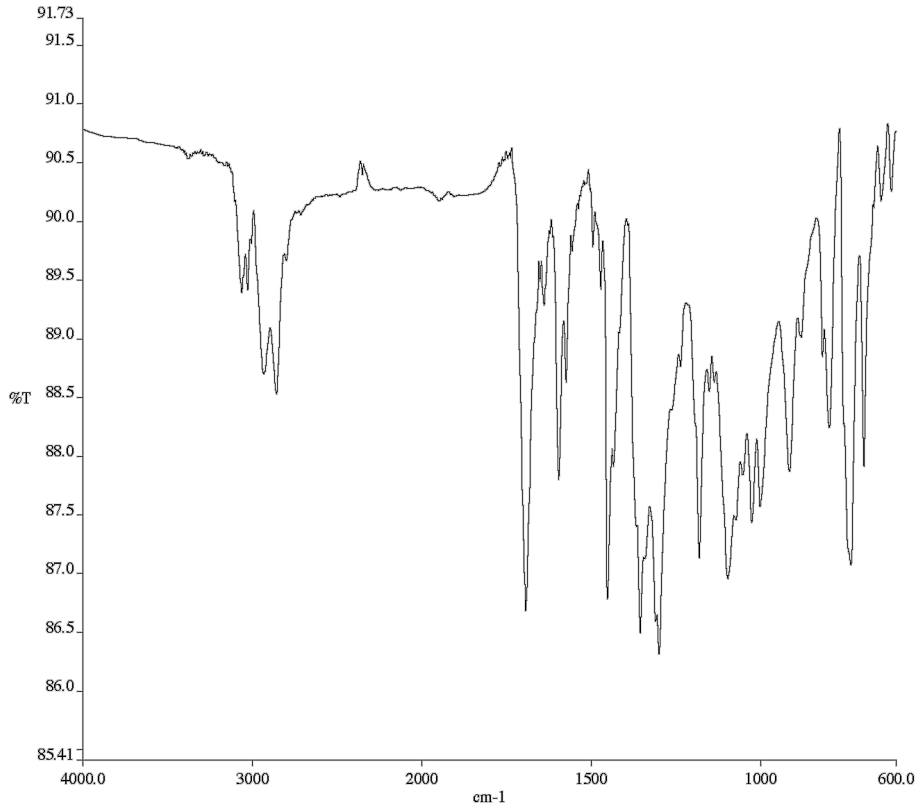
Infrared spectrum (Thin Film, NaCl) of compound **16**.



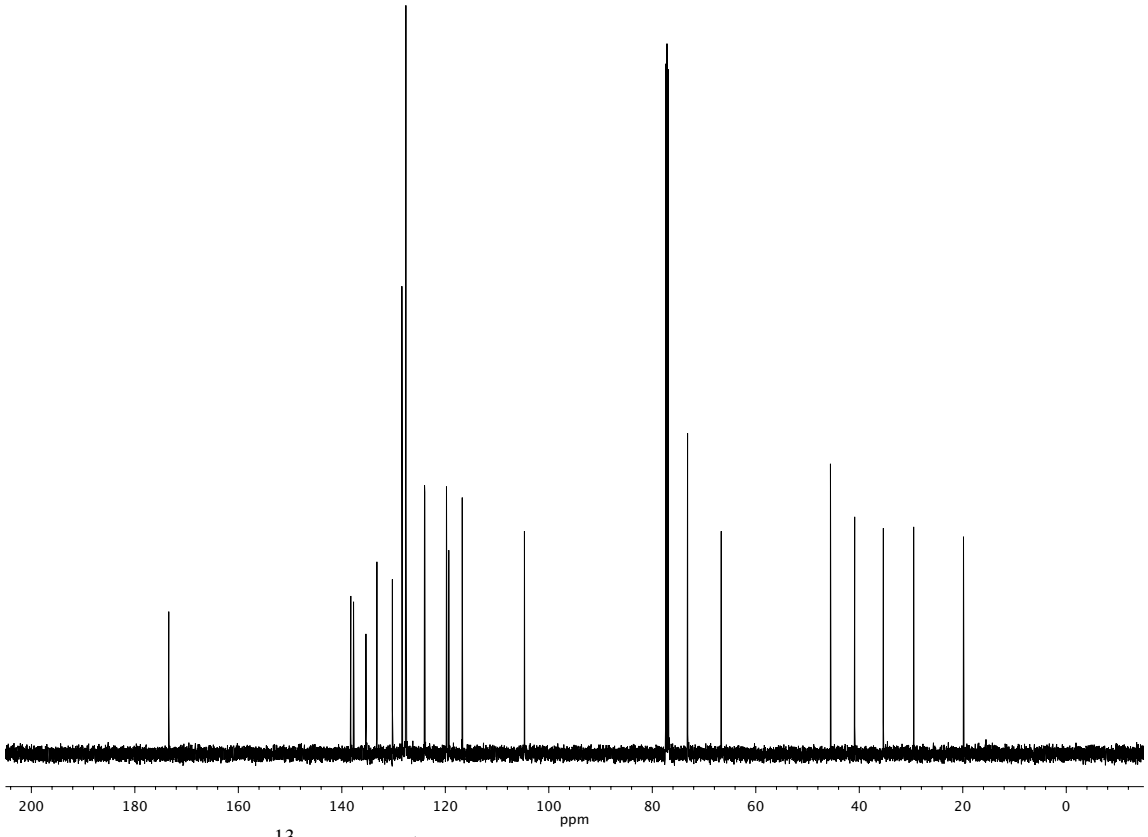
^{13}C NMR (126 MHz, $CDCl_3$) of compound **16**.



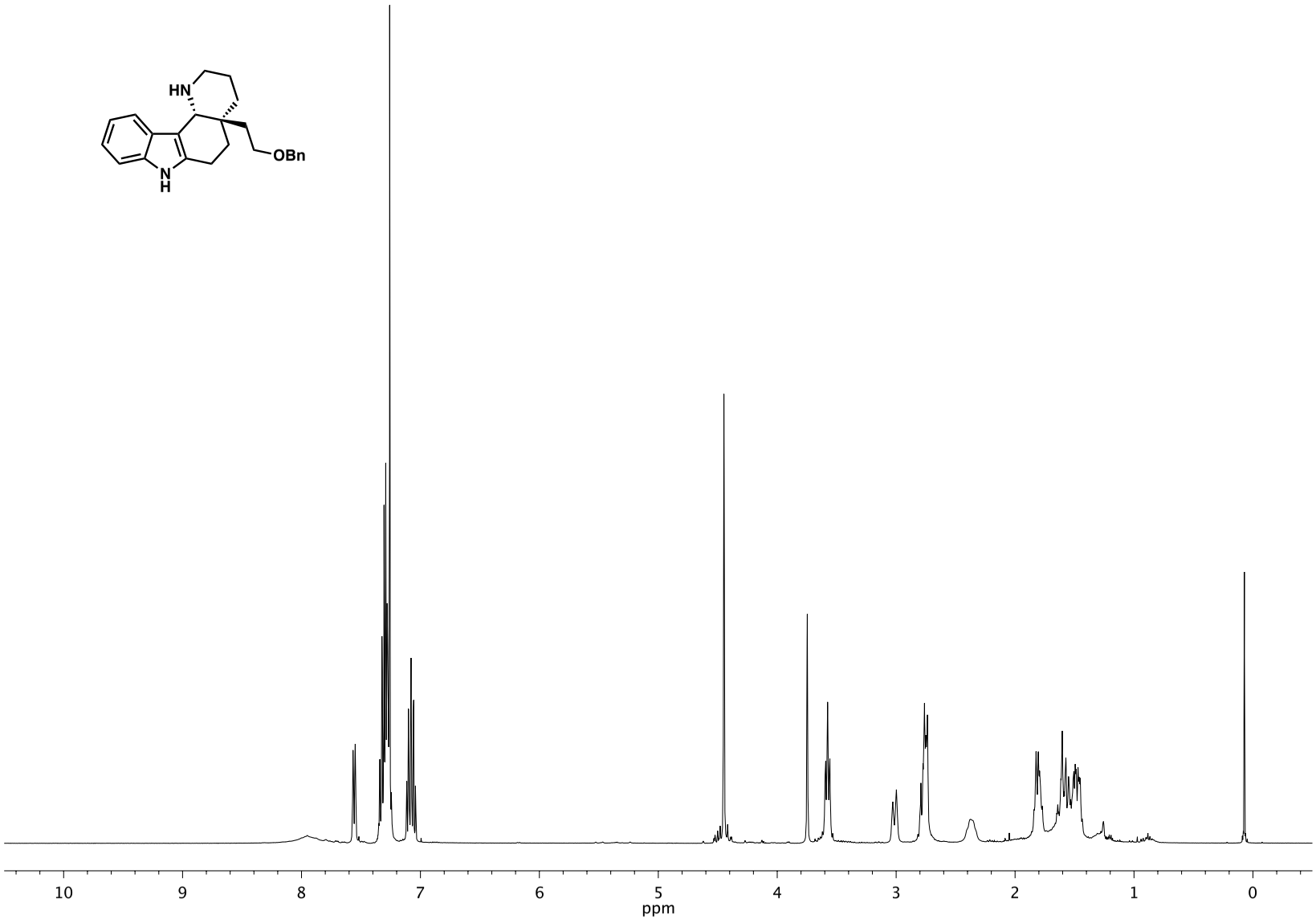
^{1}H NMR (500 MHz, $CDCl_3$) of compound **17**.



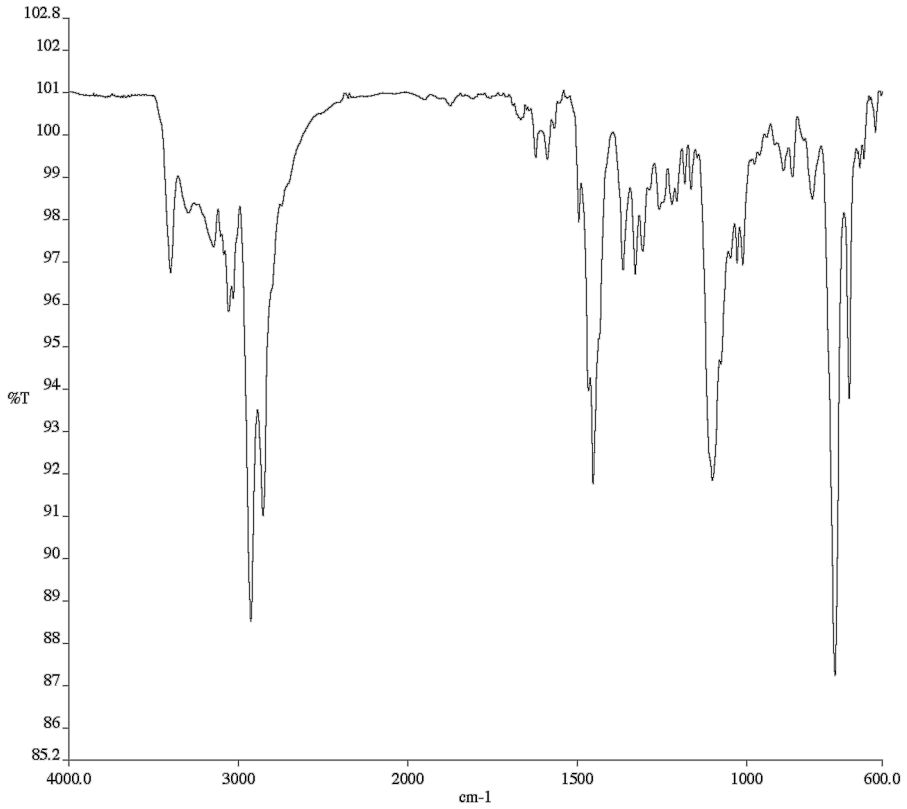
Infrared spectrum (Thin Film, NaCl) of compound **17**.



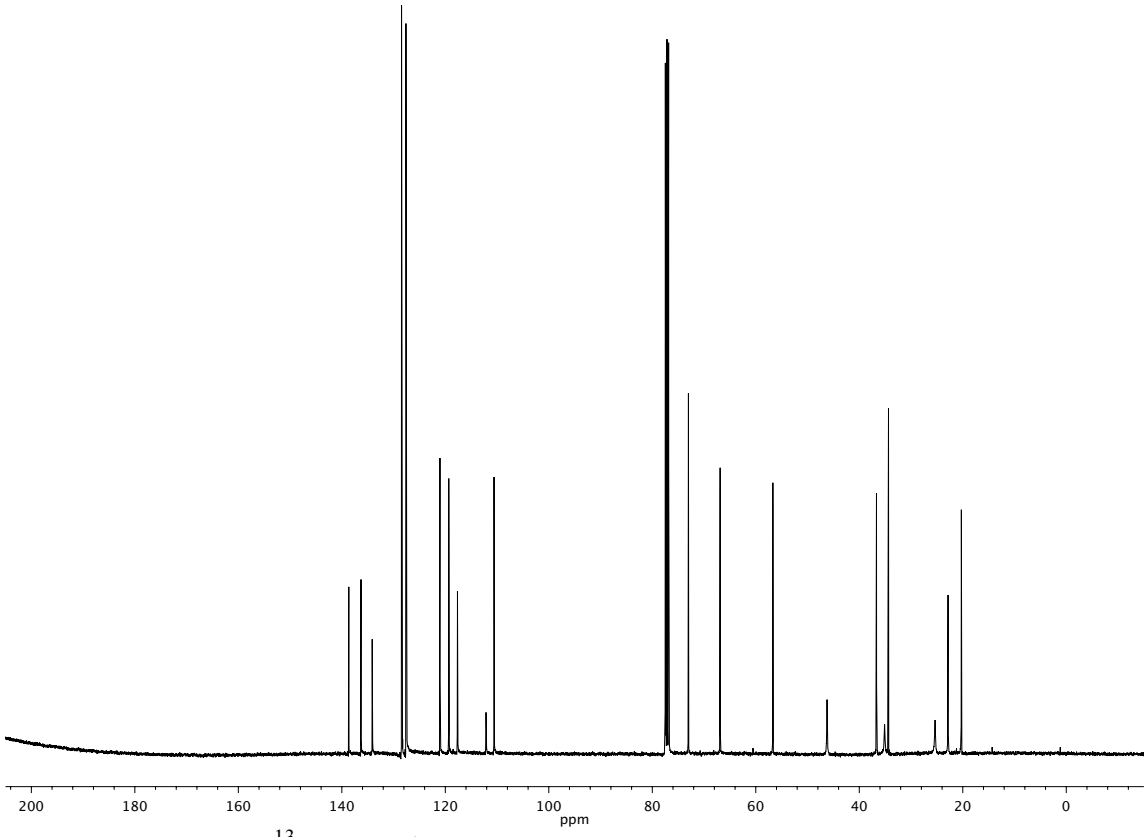
^{13}C NMR (126 MHz, $CDCl_3$) of compound **17**.



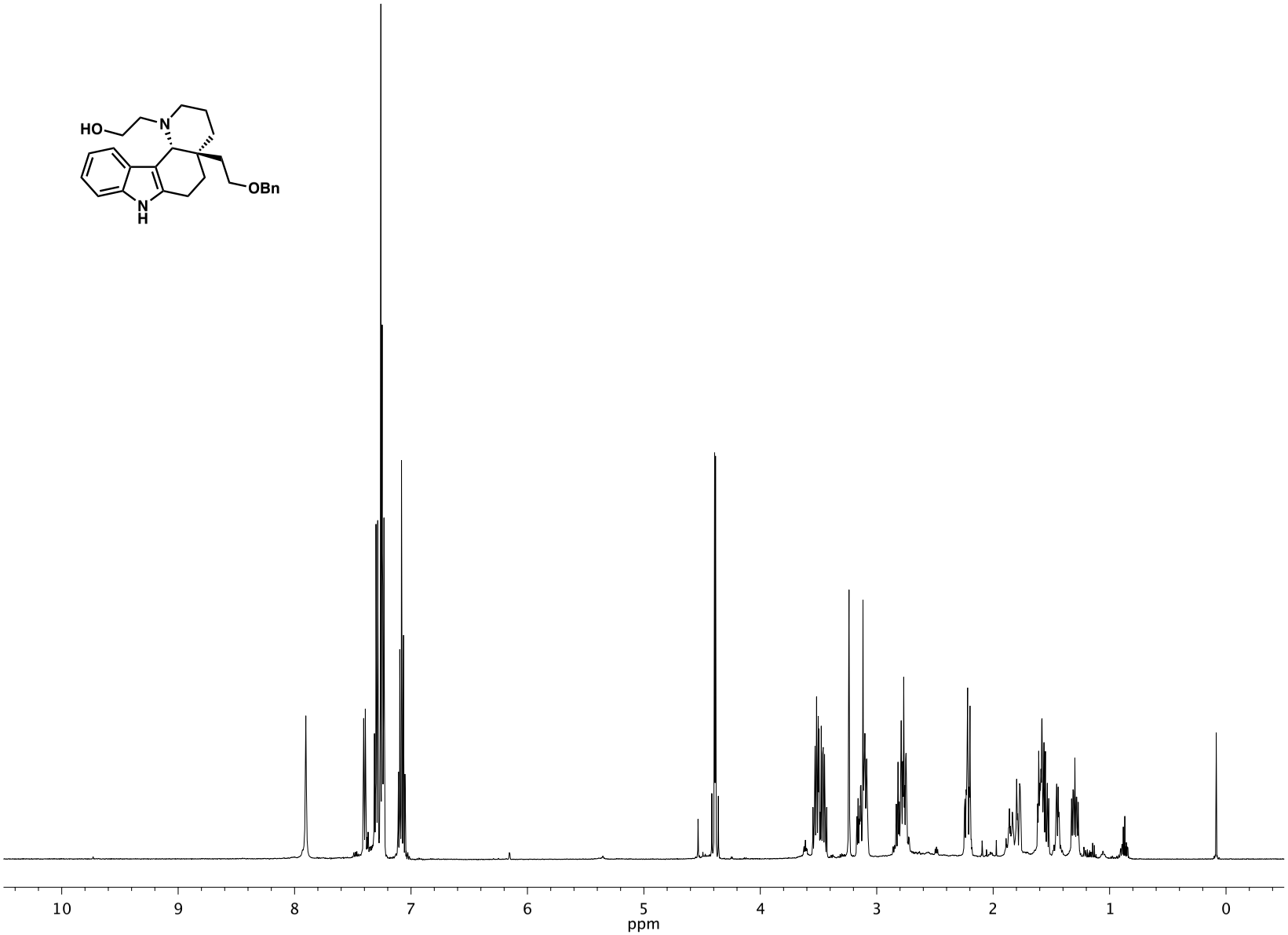
^{1}H NMR (400 MHz, $CDCl_3$) of compound **19**.



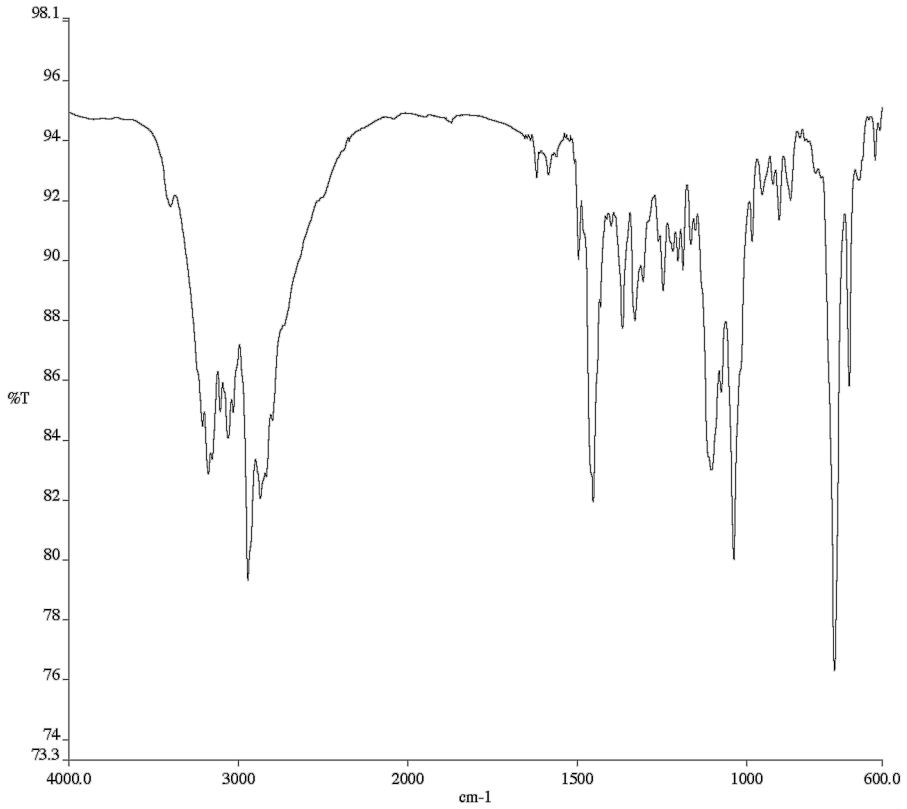
Infrared spectrum (Thin Film, NaCl) of compound **19**.



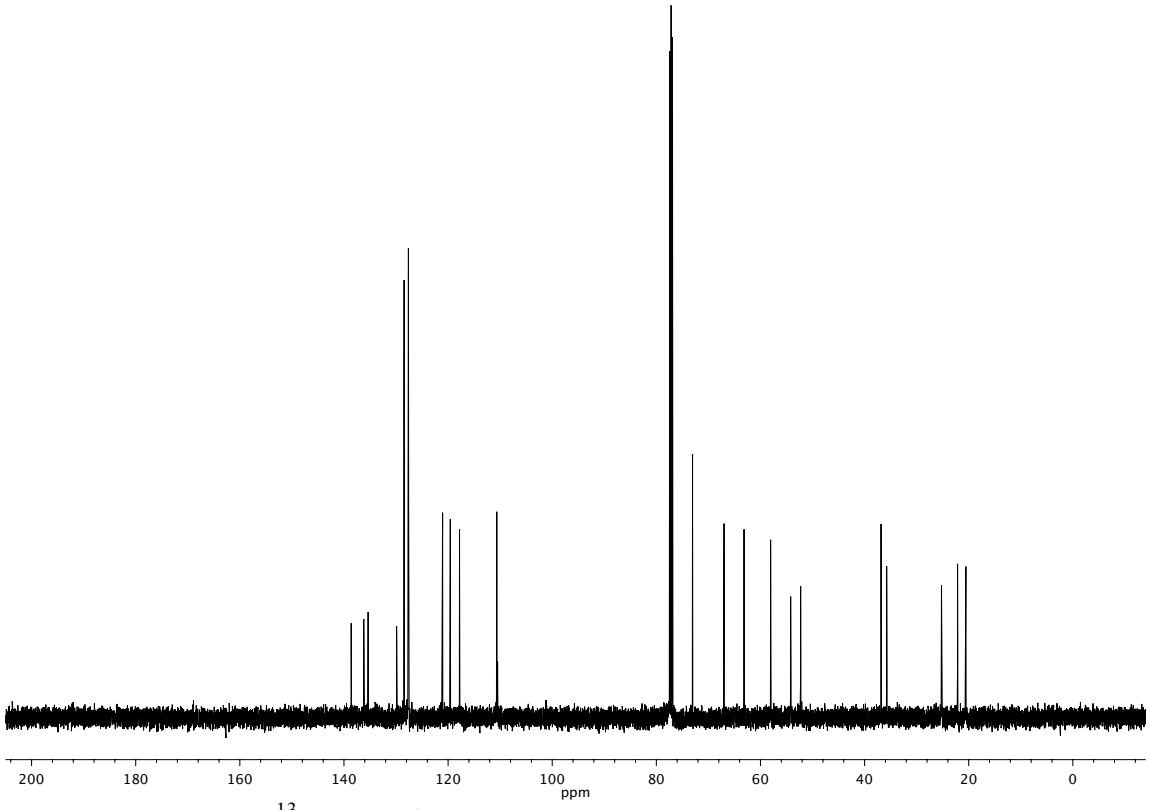
^{13}C NMR (101 MHz, $CDCl_3$) of compound **19**.



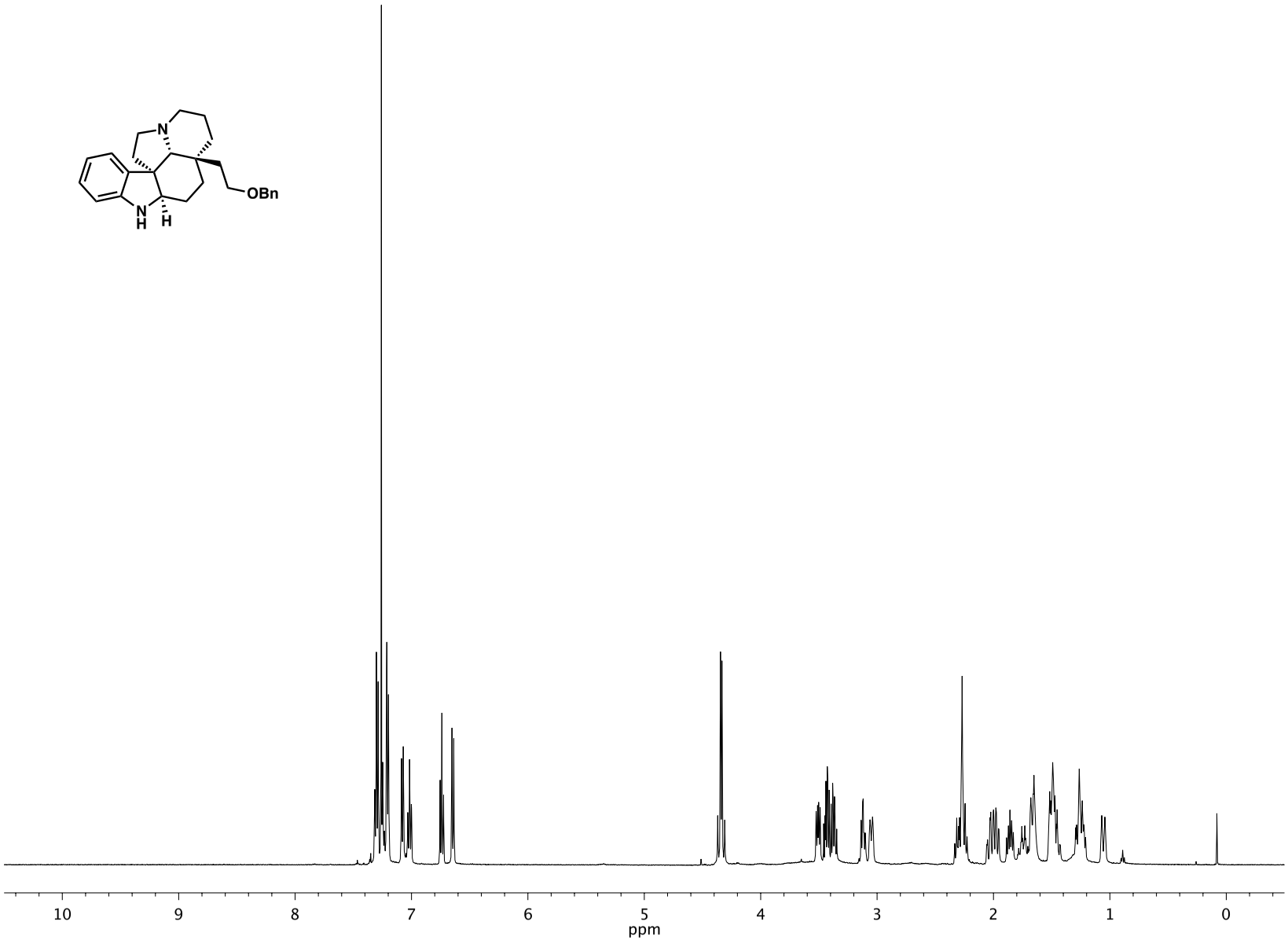
^{1}H NMR (500 MHz, $CDCl_3$) of compound **20**.



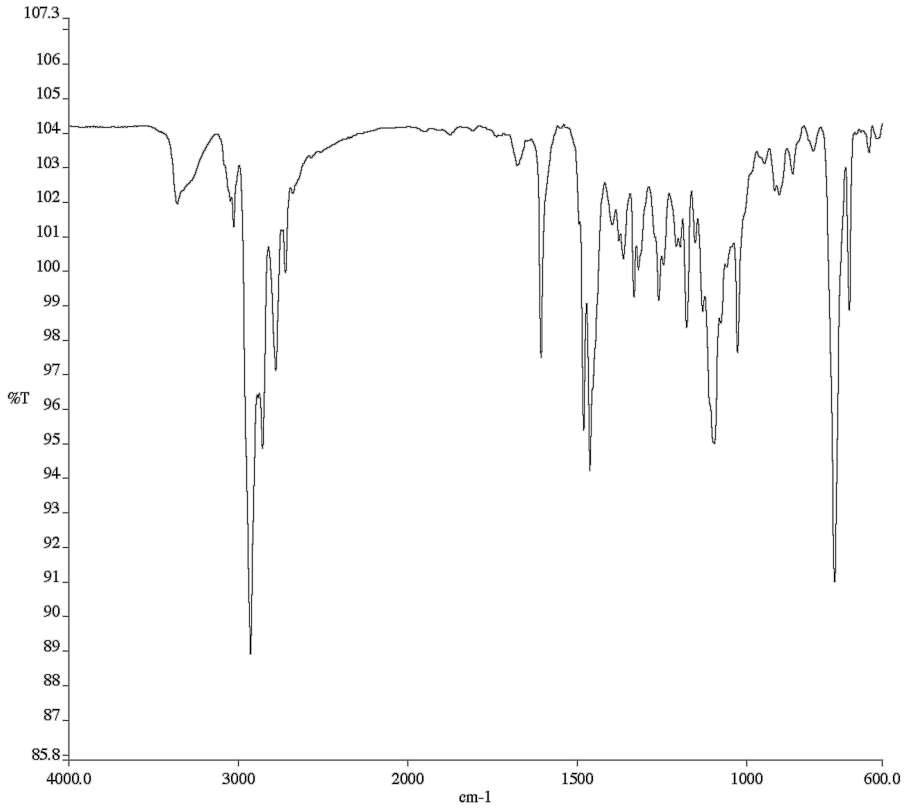
Infrared spectrum (Thin Film, NaCl) of compound **20**.



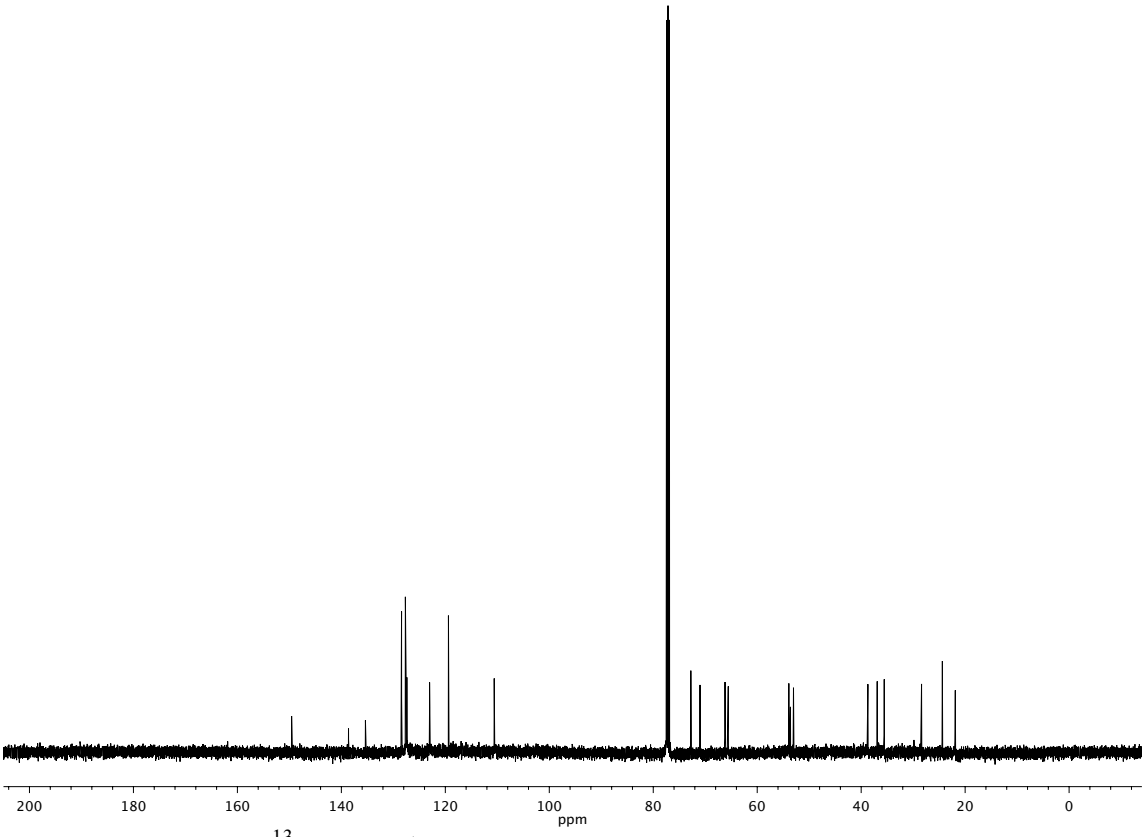
^{13}C NMR (126 MHz, $CDCl_3$) of compound **20**.



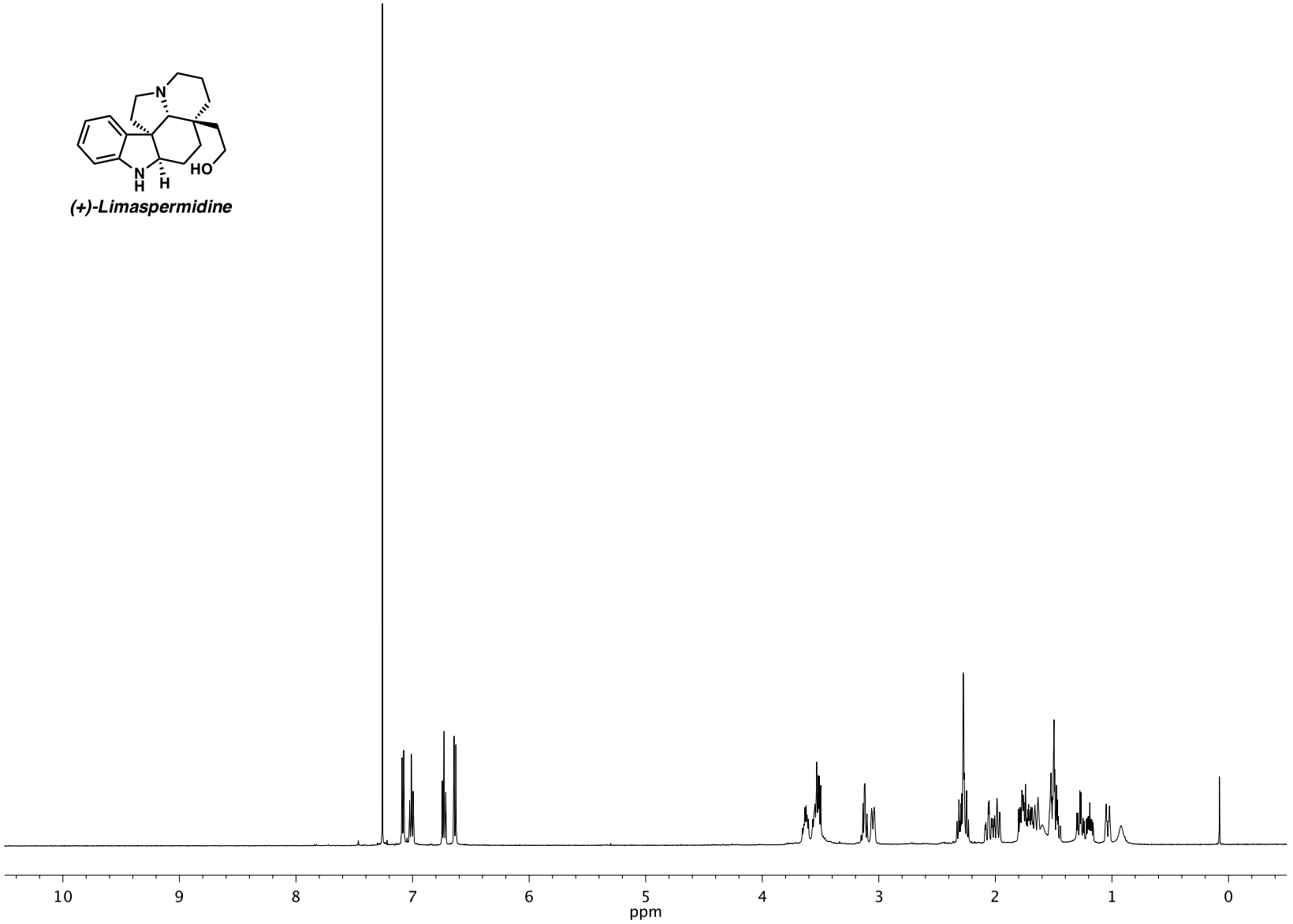
^{1}H NMR (500 MHz, $CDCl_3$) of compound **22**.



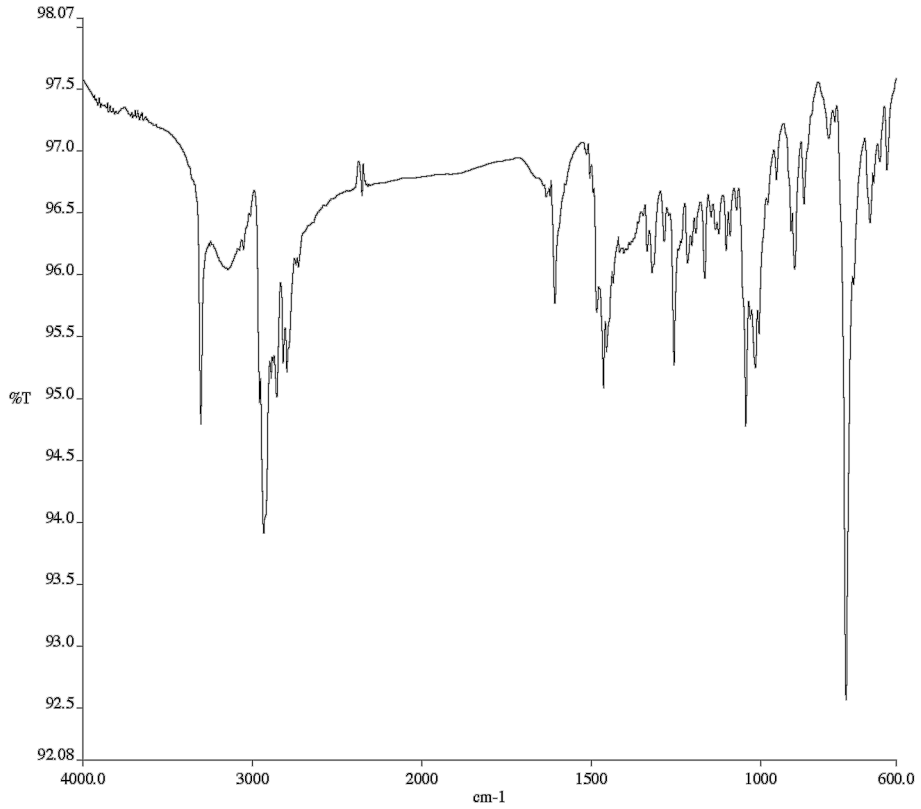
Infrared spectrum (Thin Film, NaCl) of compound **22**.



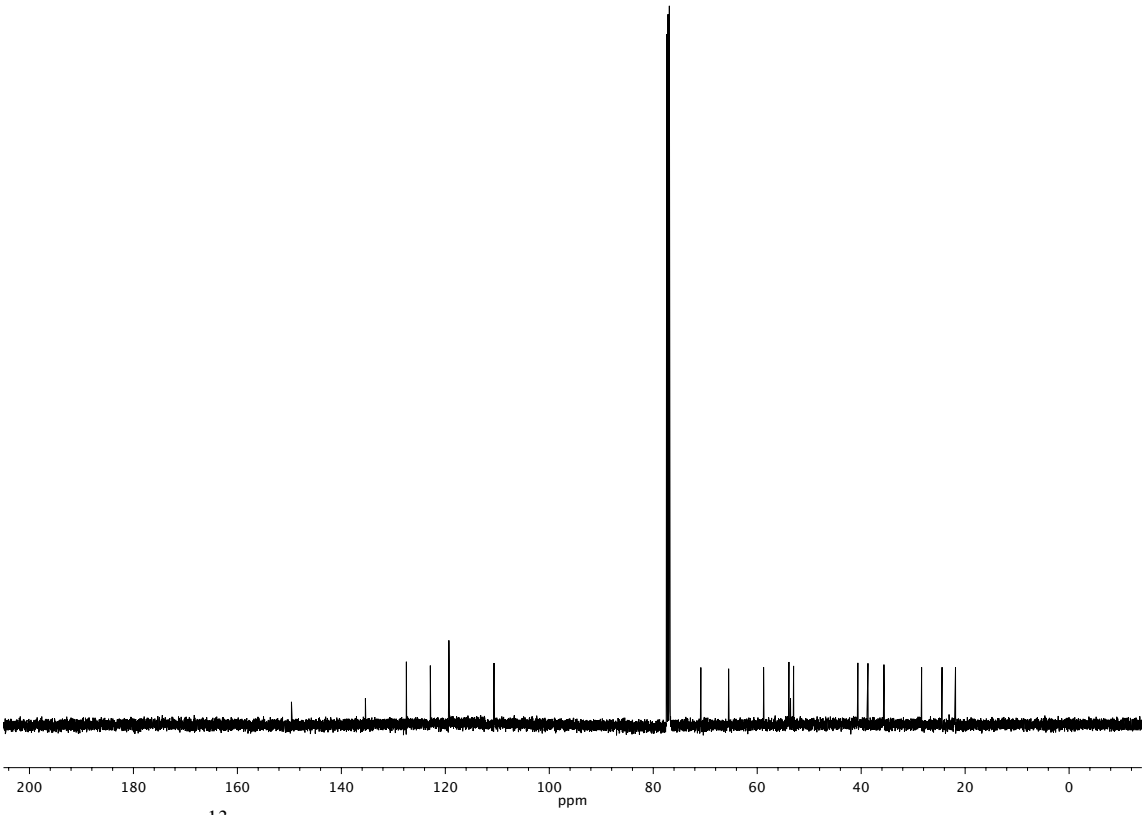
^{13}C NMR (126 MHz, $CDCl_3$) of compound **22**.



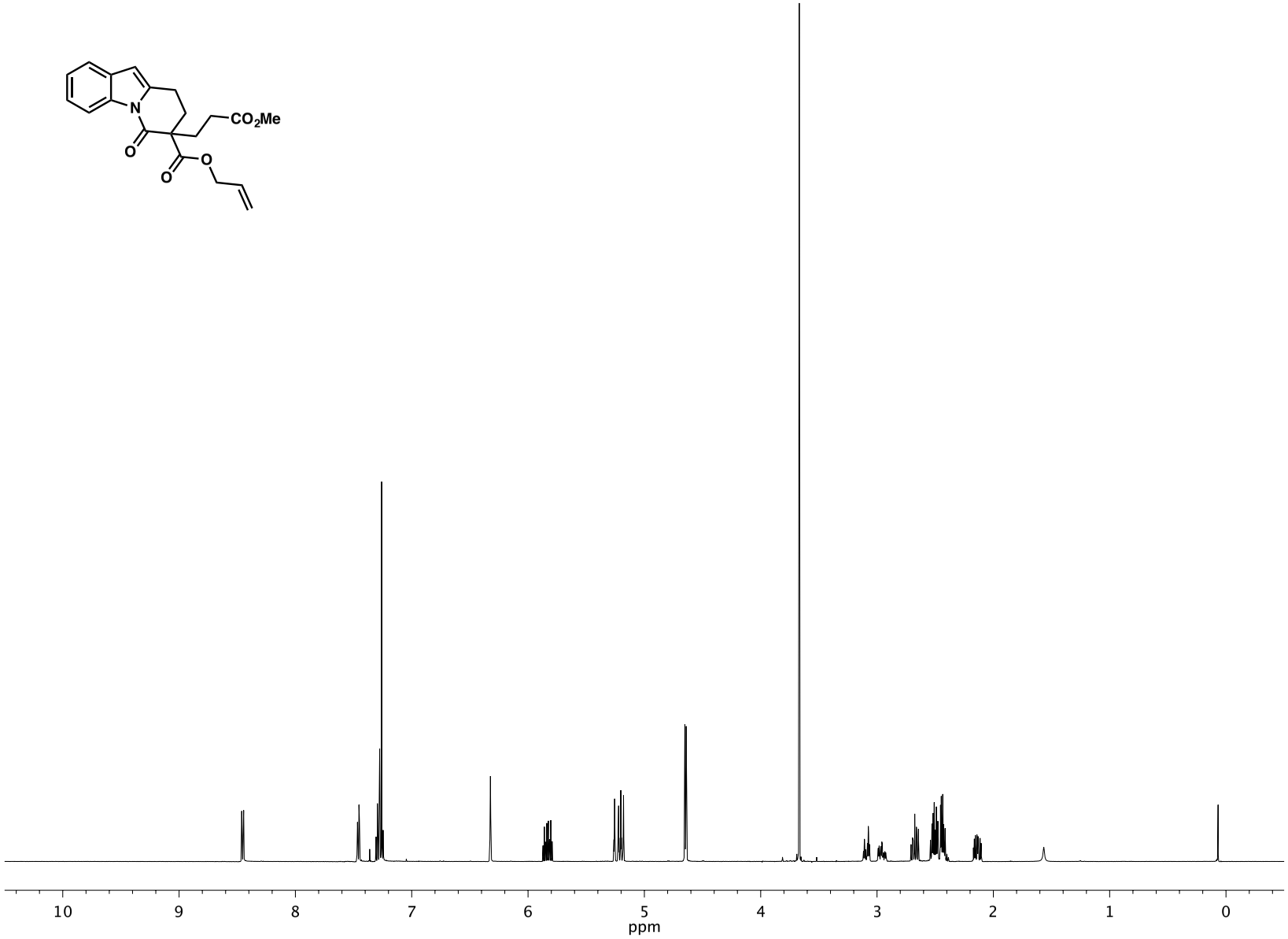
^{1}H NMR (500 MHz, $CDCl_3$) of (+)-Limaspermidine (**2**).



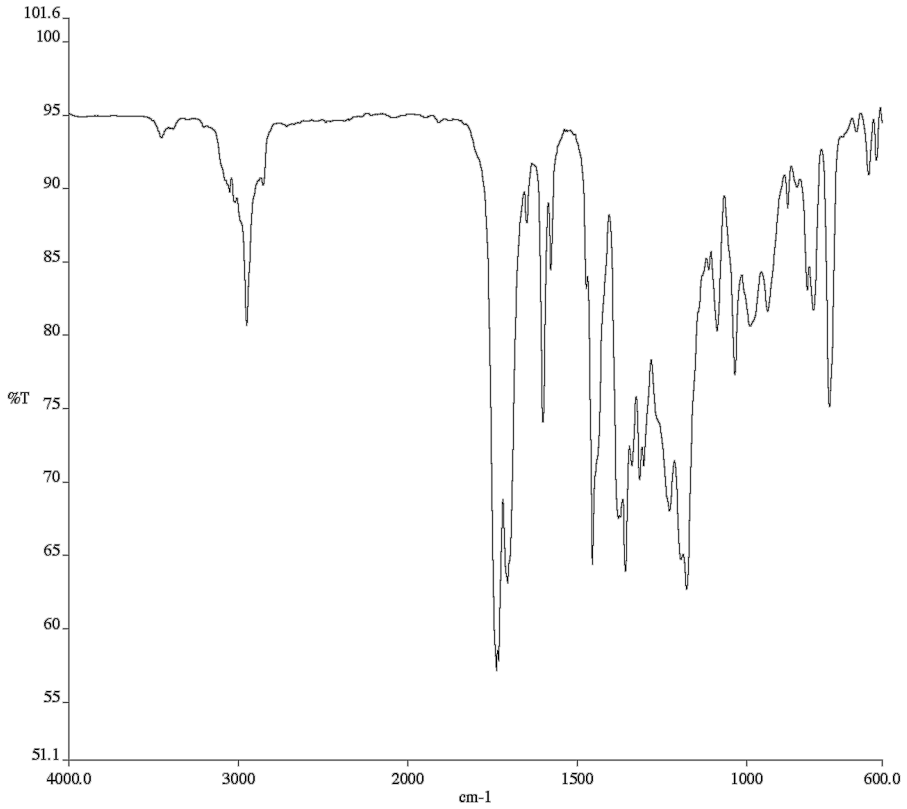
Infrared spectrum (Thin Film, NaCl) of (+)-Limaspermidine (**2**).



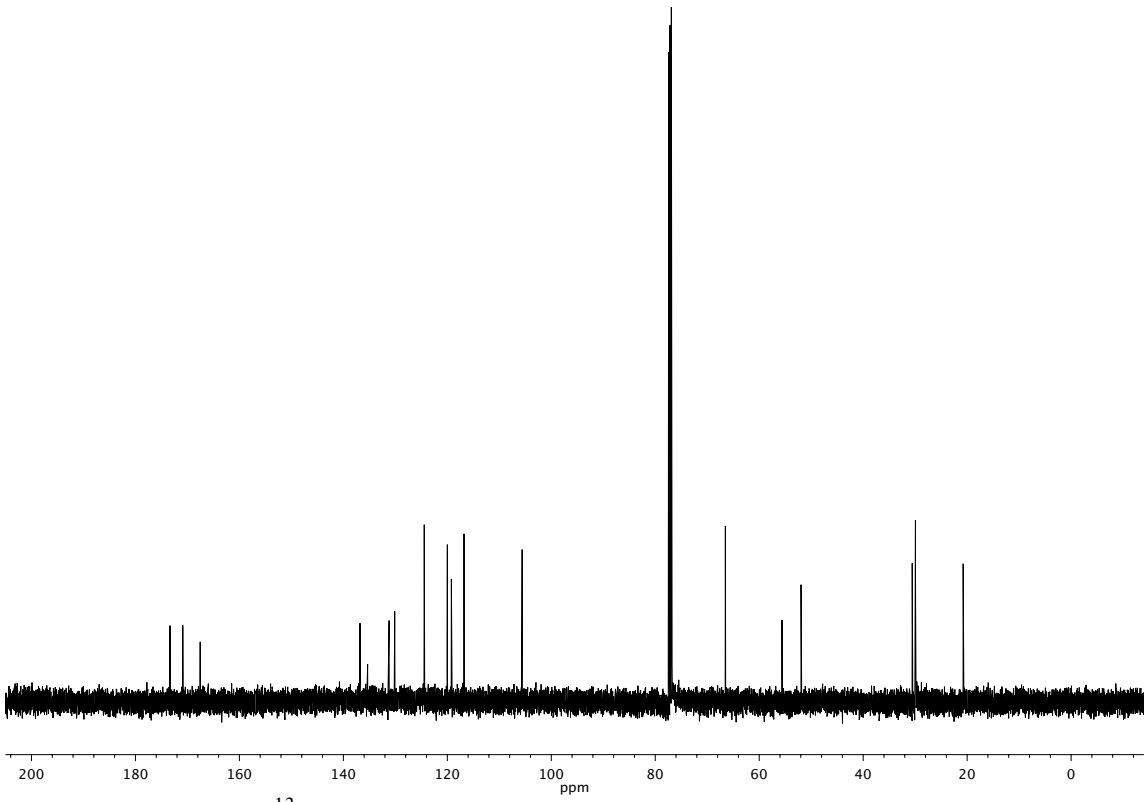
^{13}C NMR (126 MHz, $CDCl_3$) of (+)-Limaspermidine (**2**).



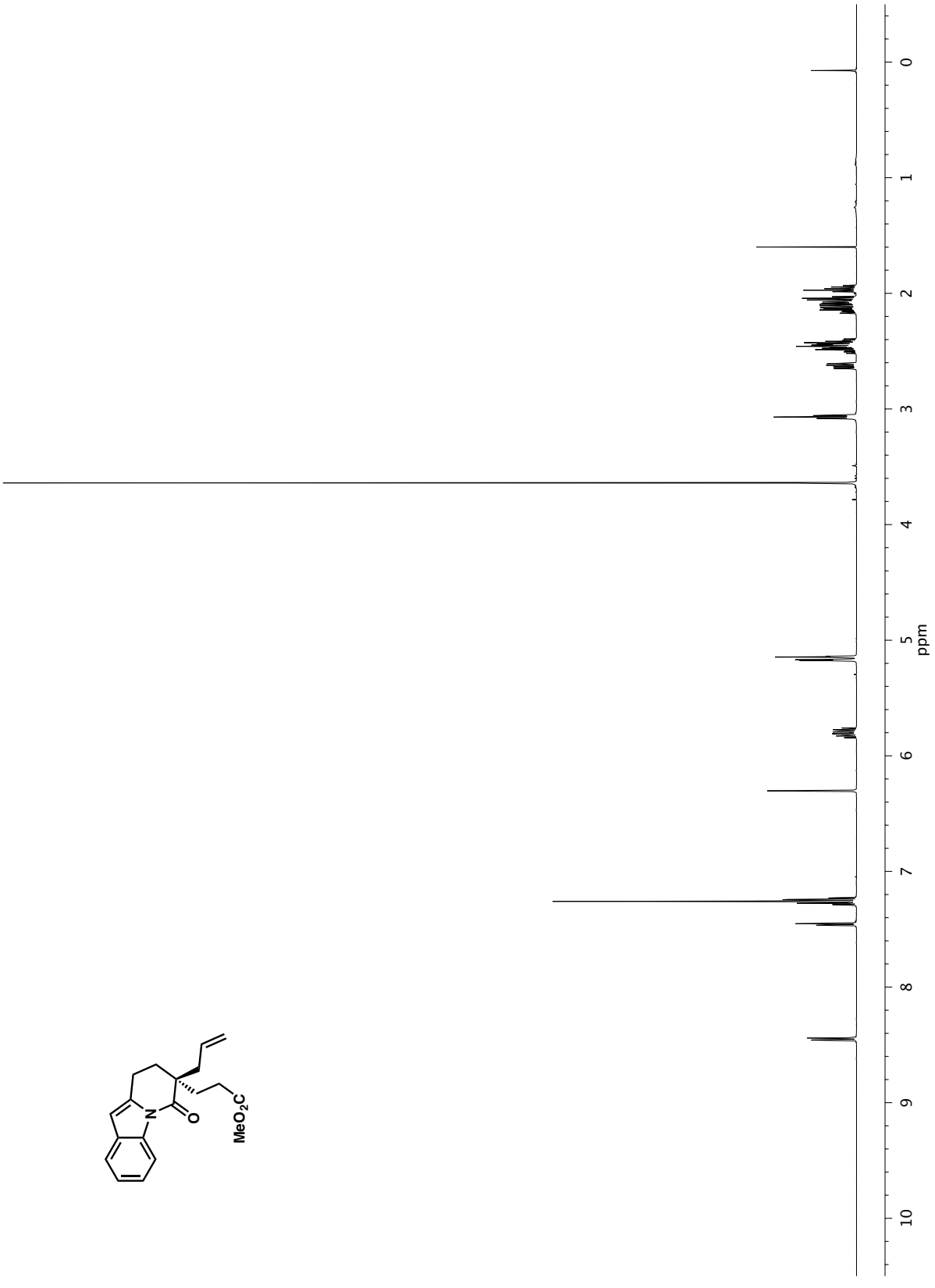
^{1}H NMR (500 MHz, $CDCl_3$) of compound **23**.



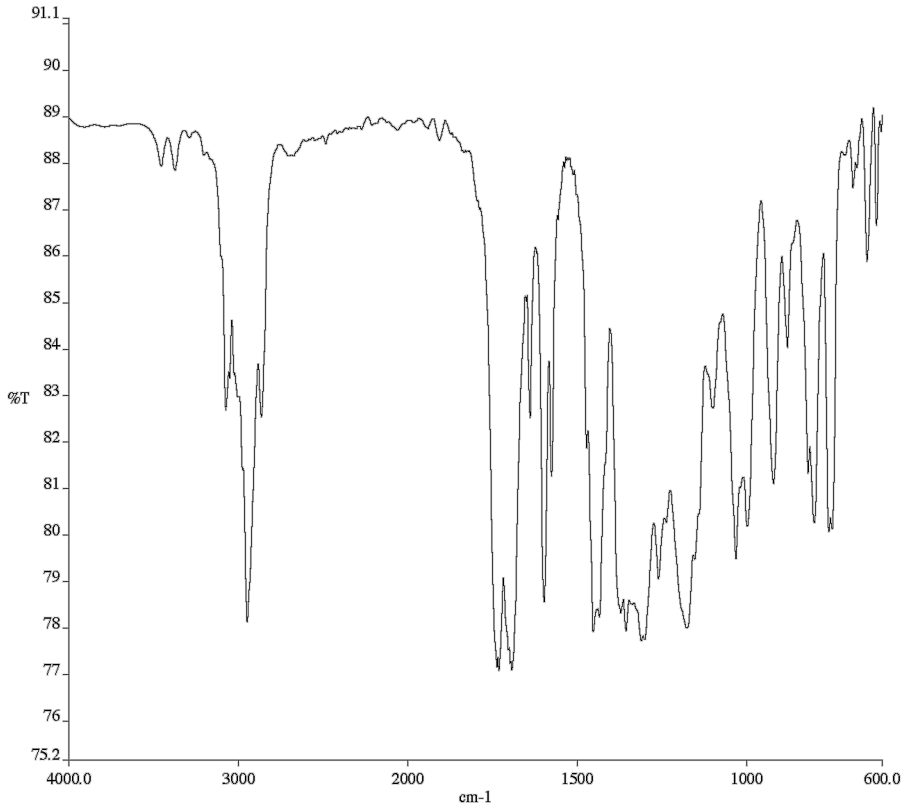
Infrared spectrum (Thin Film, NaCl) of compound **23**.



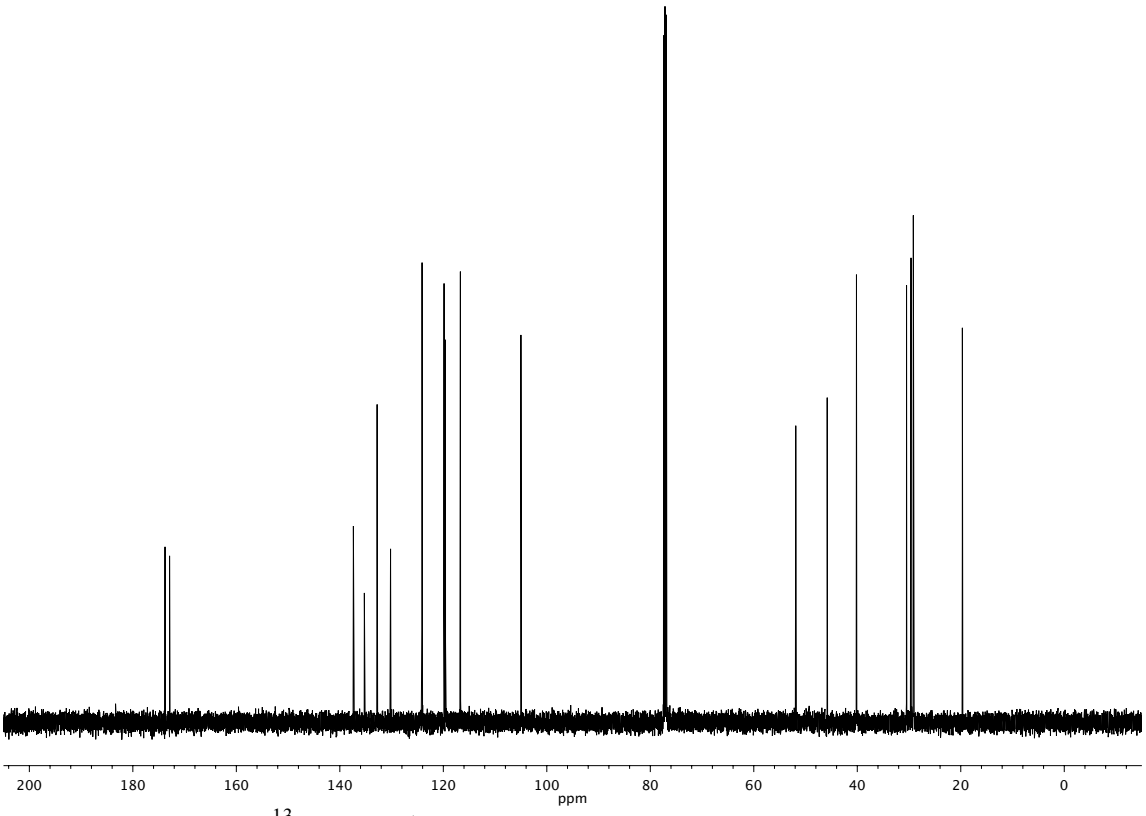
^{13}C NMR (126 MHz, $CDCl_3$) of compound **23**.



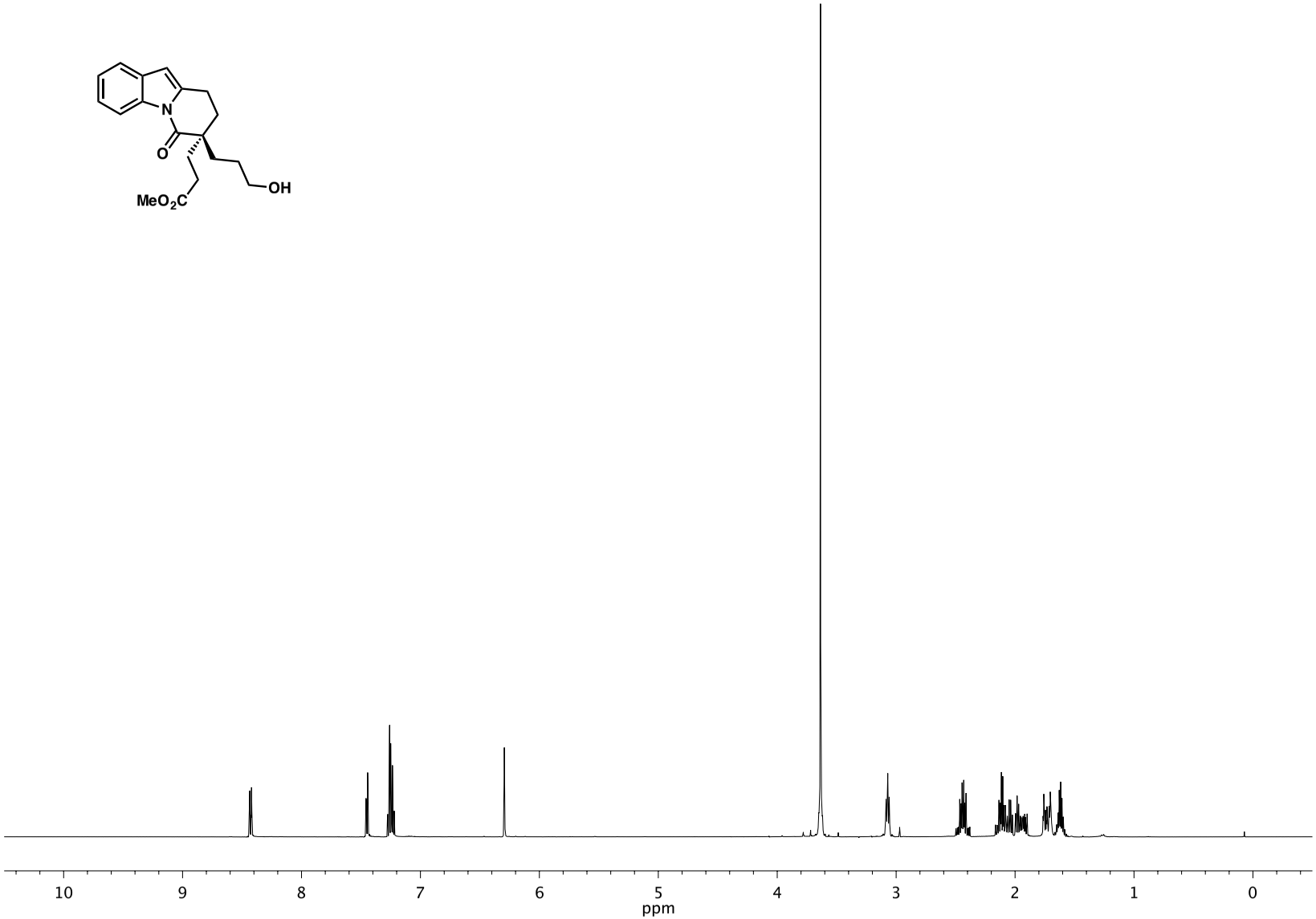
^{1}H NMR (500 MHz, $CDCl_3$) of compound **24**.



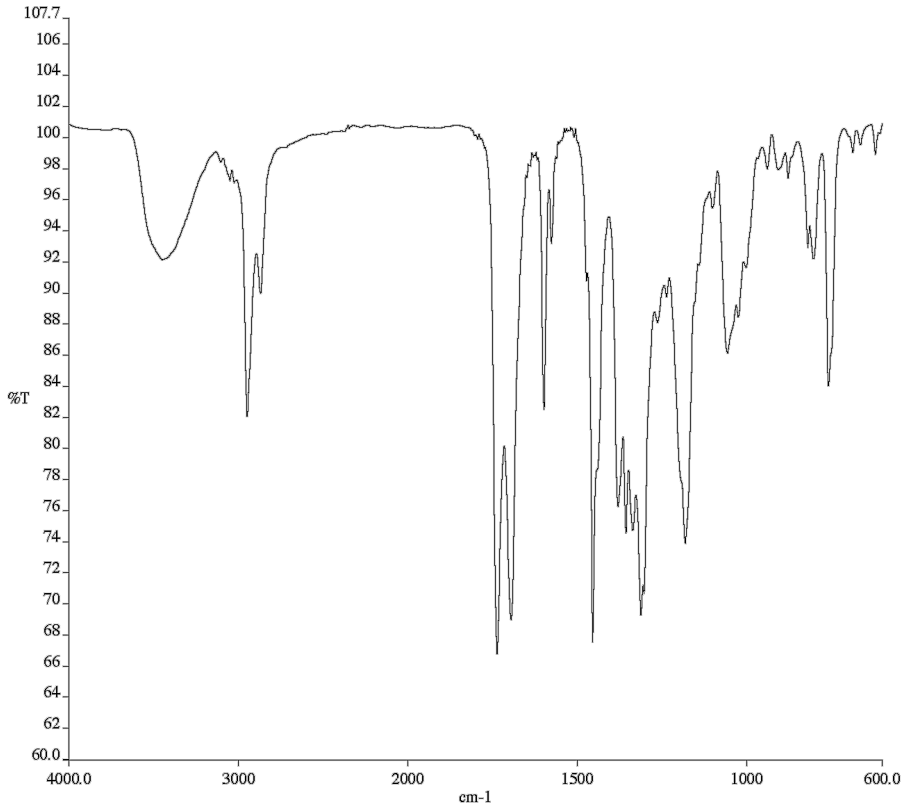
Infrared spectrum (Thin Film, NaCl) of compound **24**.



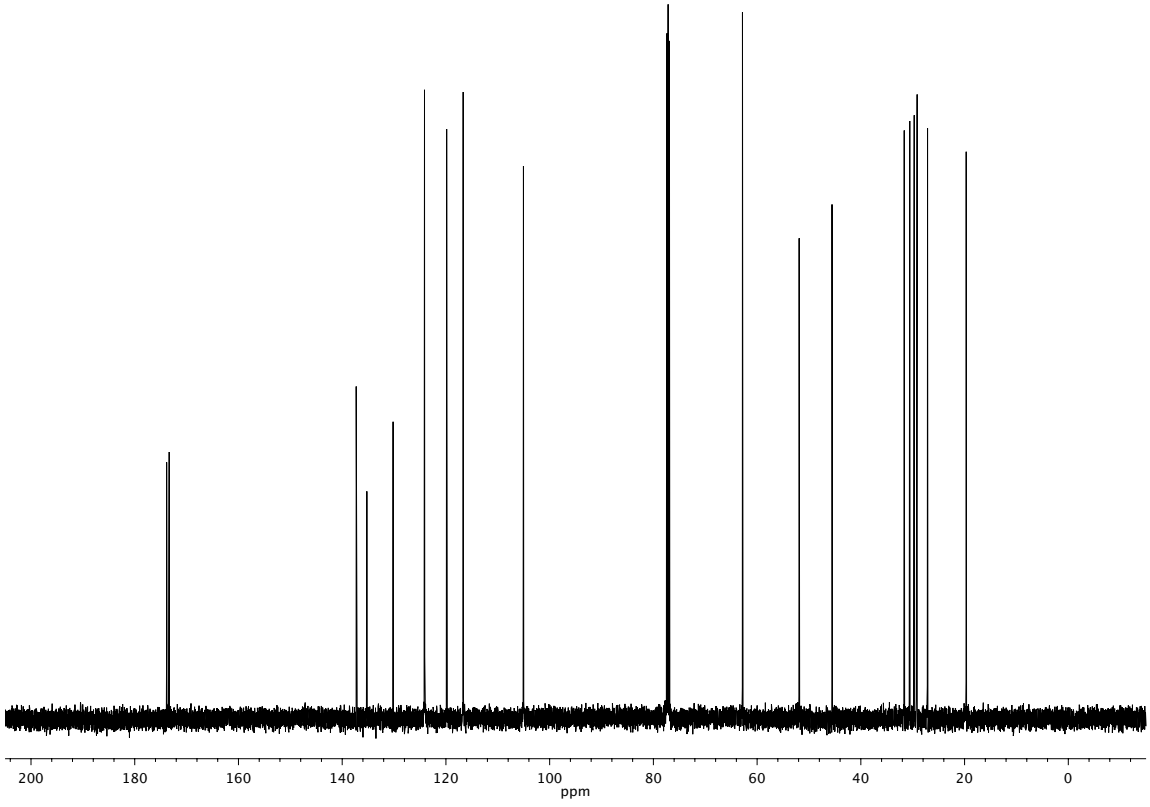
^{13}C NMR (126 MHz, $CDCl_3$) of compound **24**.



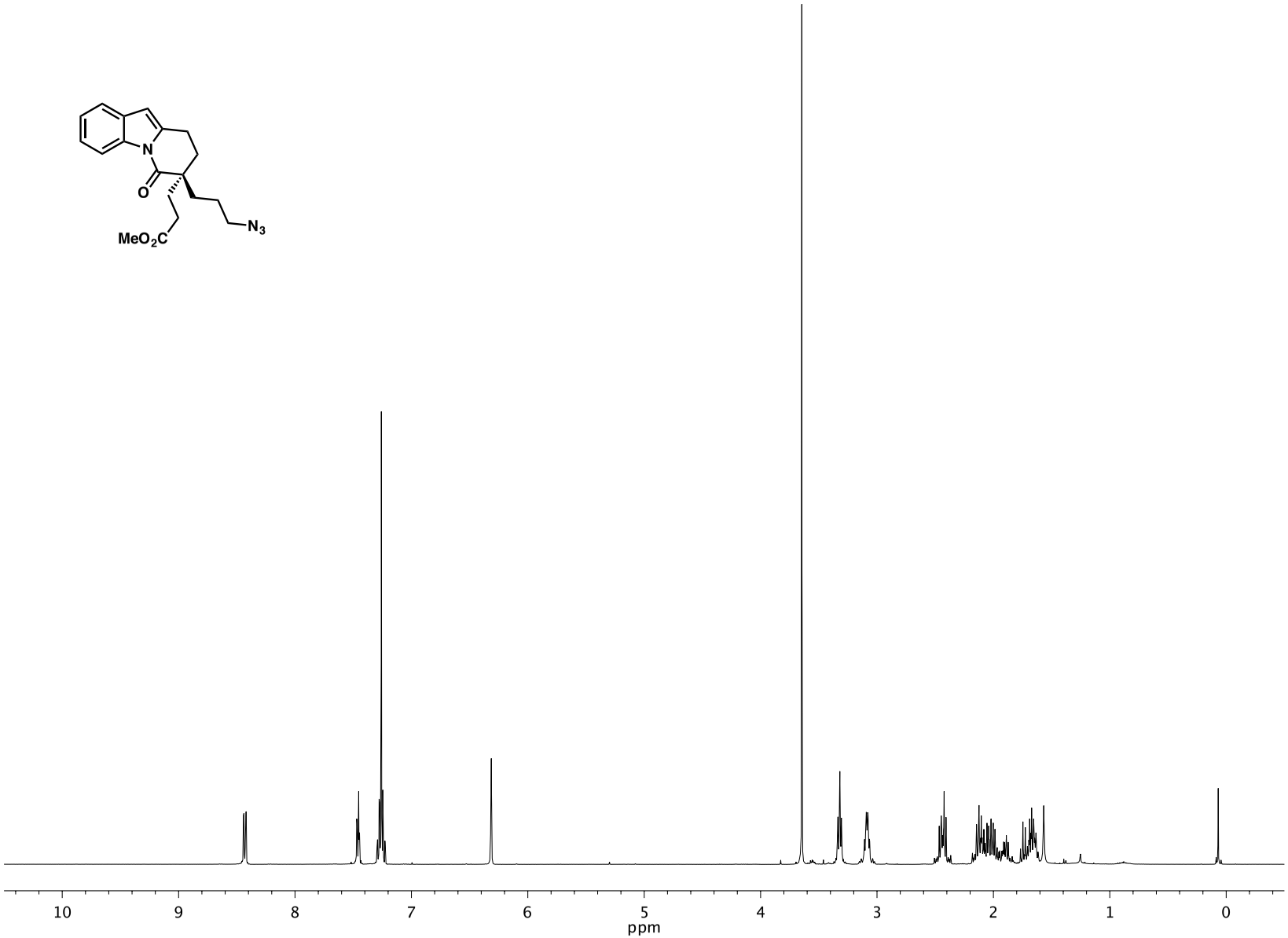
^{1}H NMR (500 MHz, $CDCl_3$) of compound **25**.



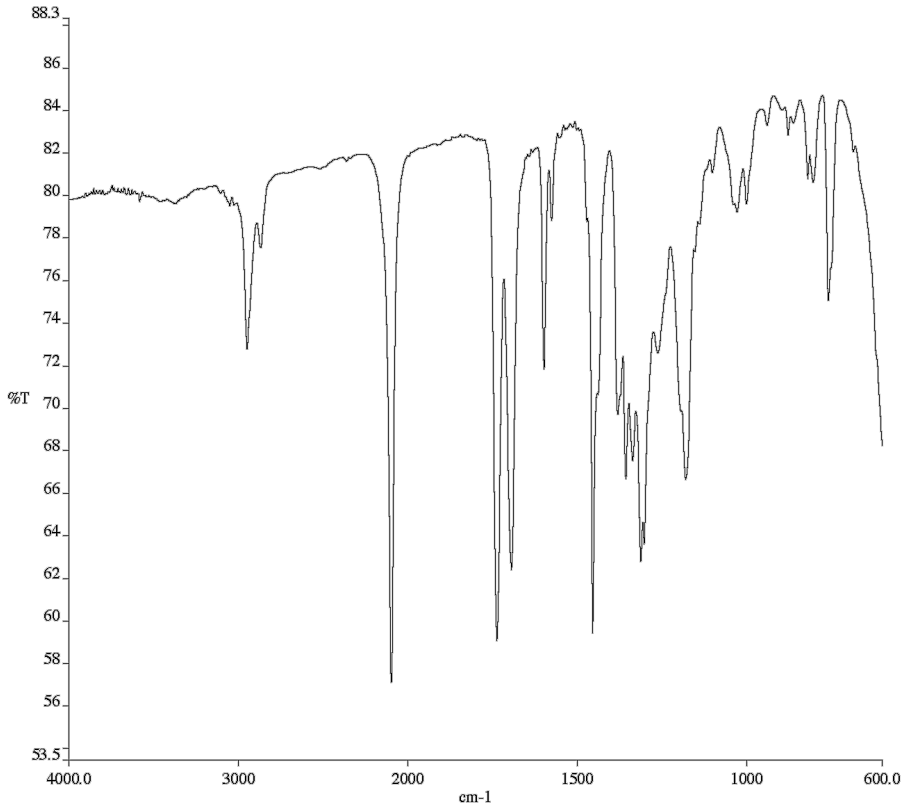
Infrared spectrum (Thin Film, NaCl) of compound **25**.



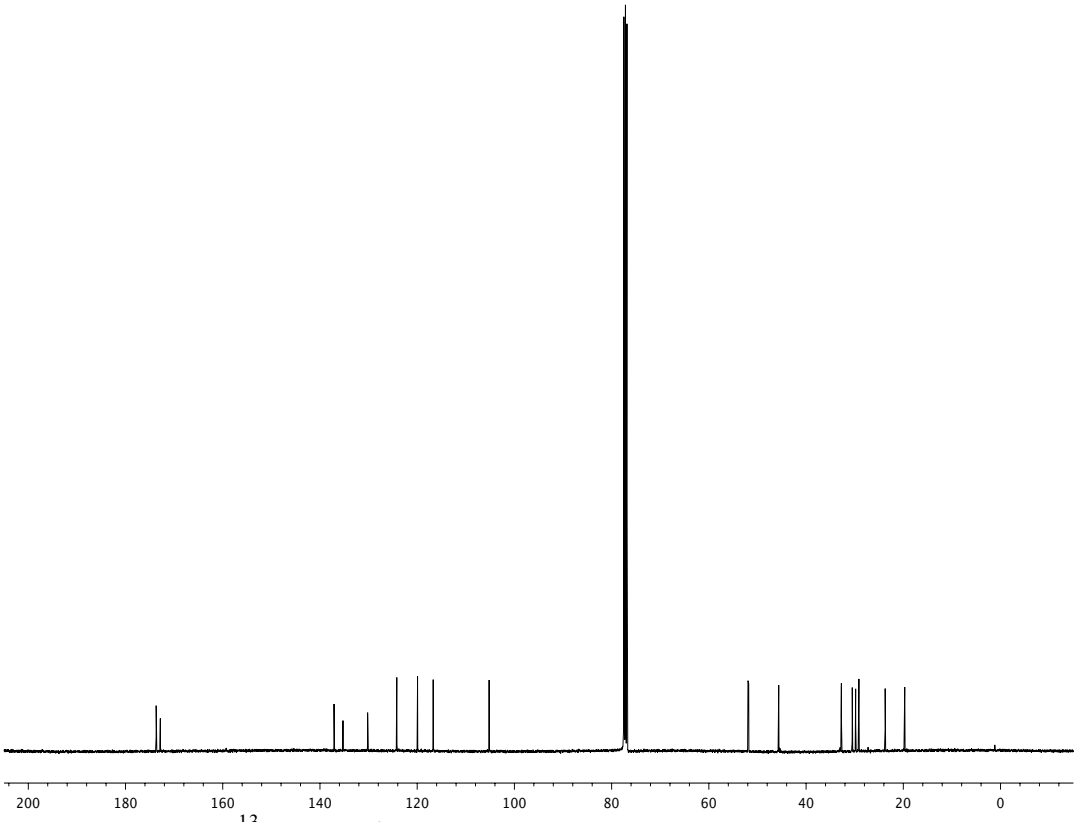
^{13}C NMR (126 MHz, $CDCl_3$) of compound **25**.



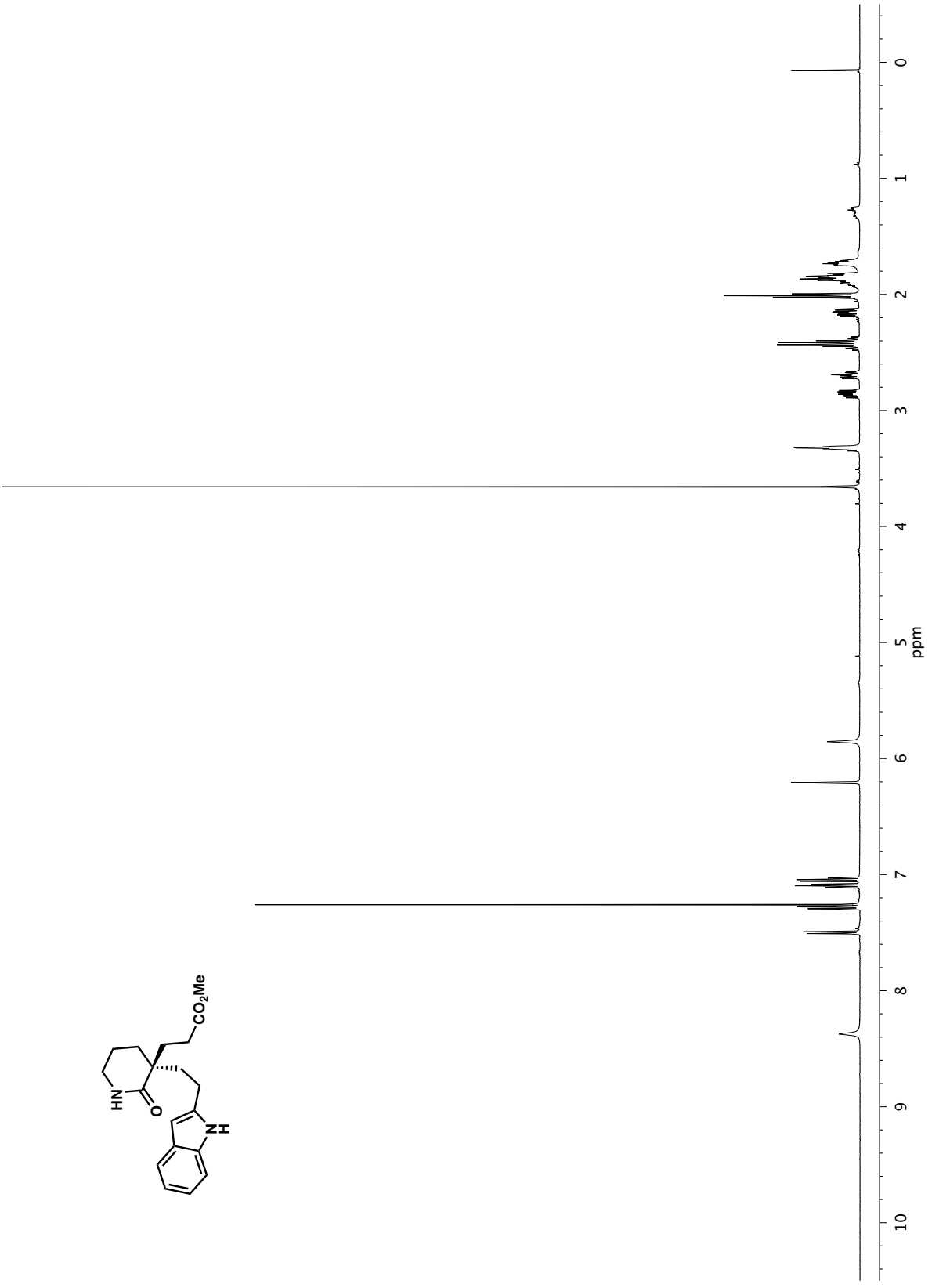
^{1}H NMR (400 MHz, $CDCl_3$) of compound **26**.



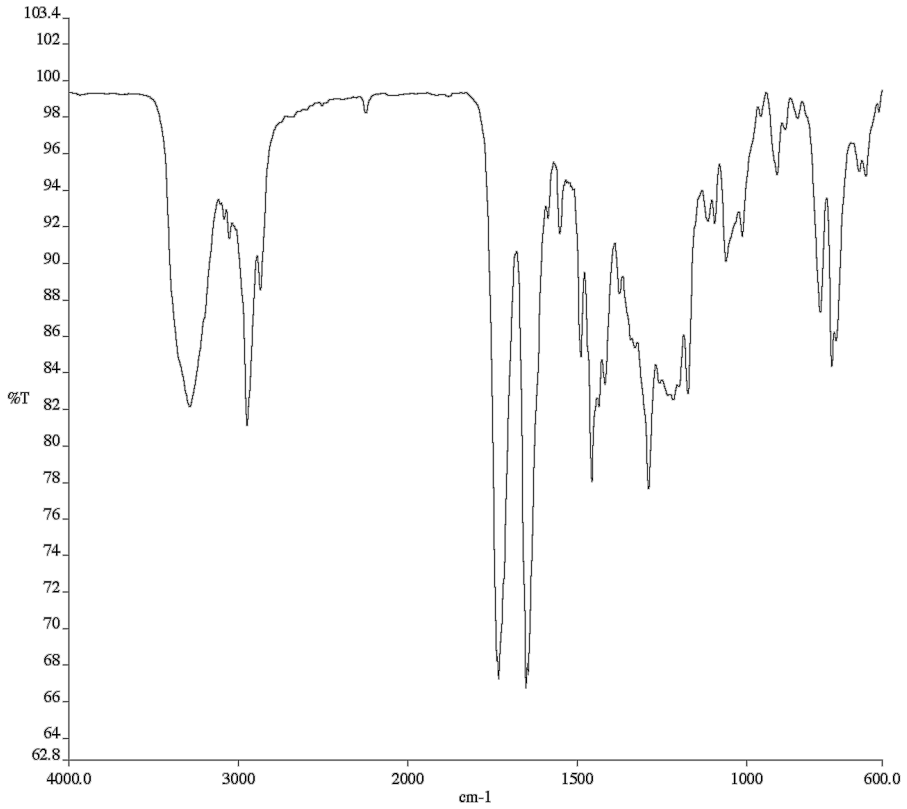
Infrared spectrum (Thin Film, NaCl) of compound **26**.



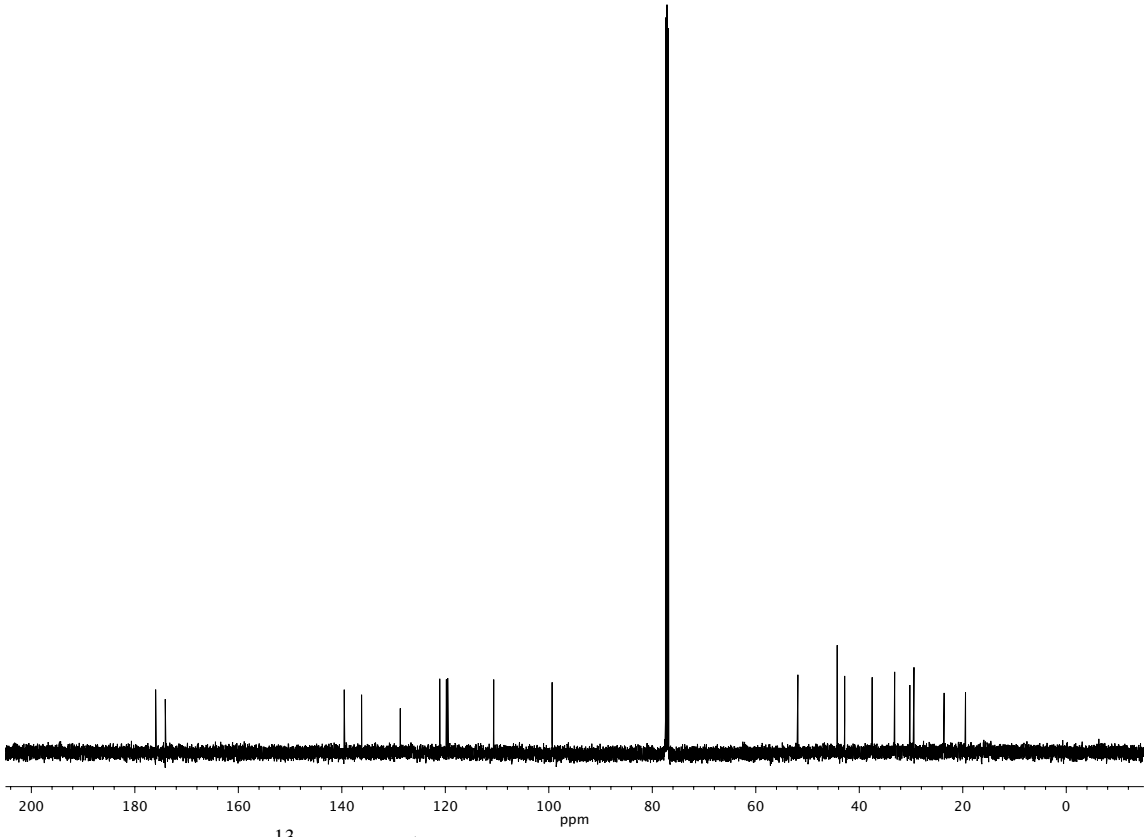
^{13}C NMR (101 MHz, $CDCl_3$) of compound **26**.



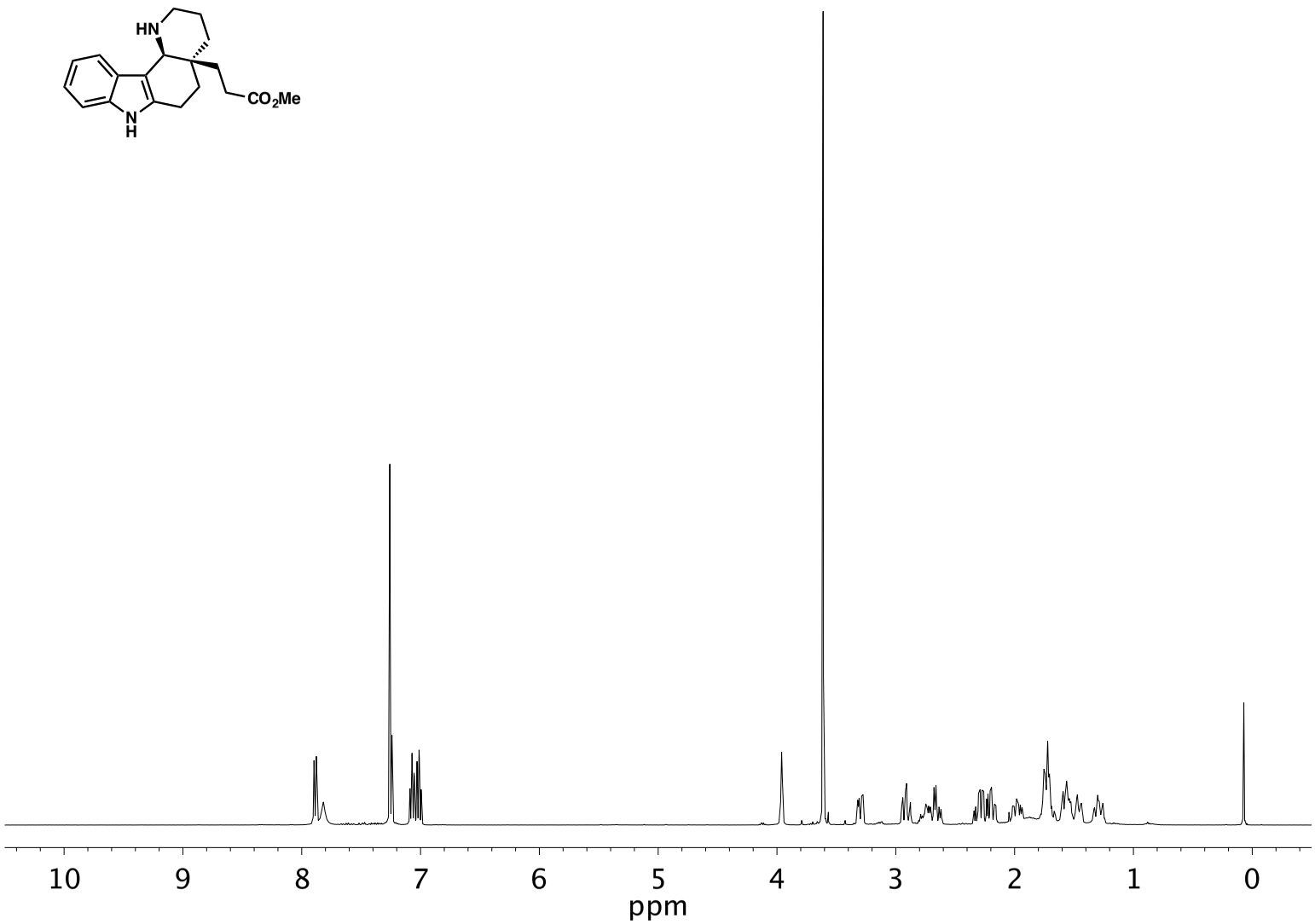
^{1}H NMR (500 MHz, $CDCl_3$) of compound **27**.



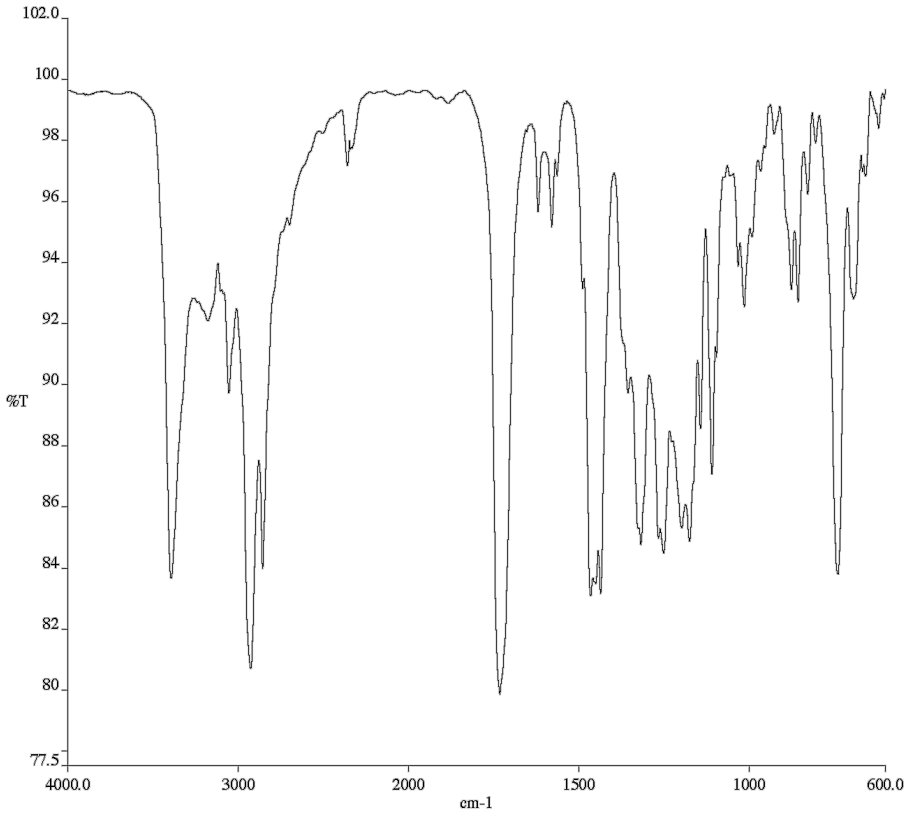
Infrared spectrum (Thin Film, NaCl) of compound **27**.



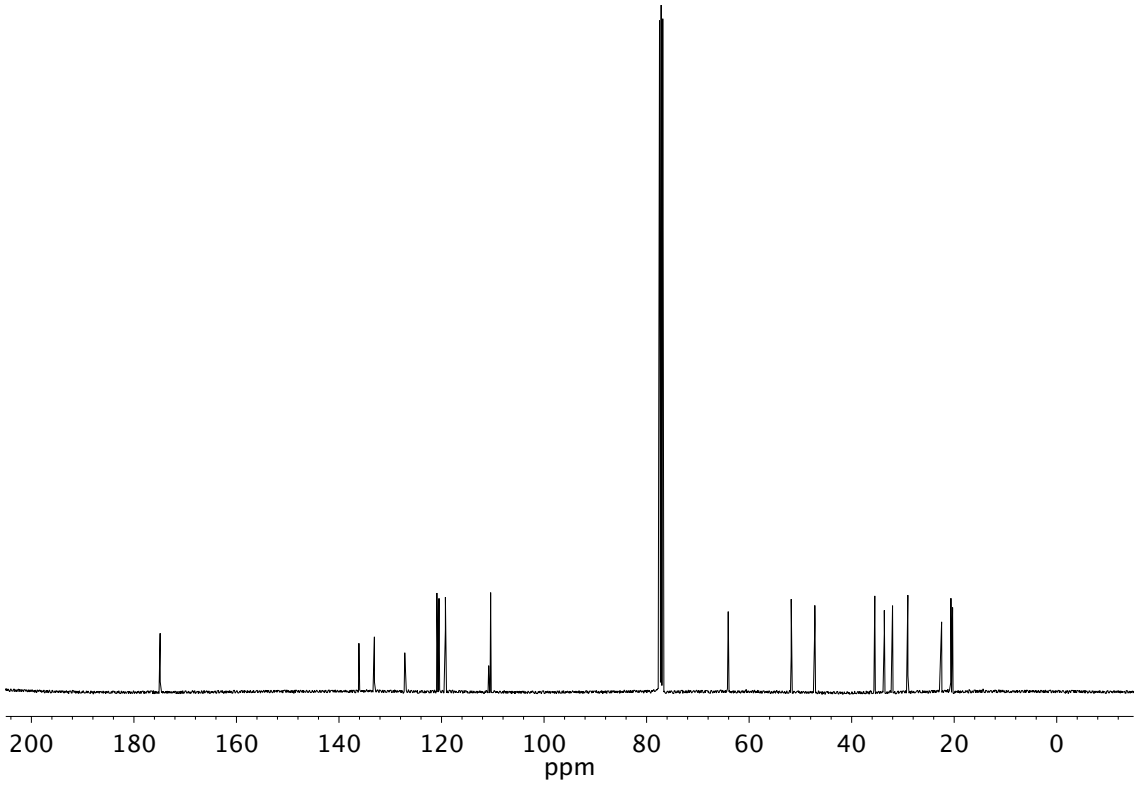
^{13}C NMR (126 MHz, $CDCl_3$) of compound **27**.



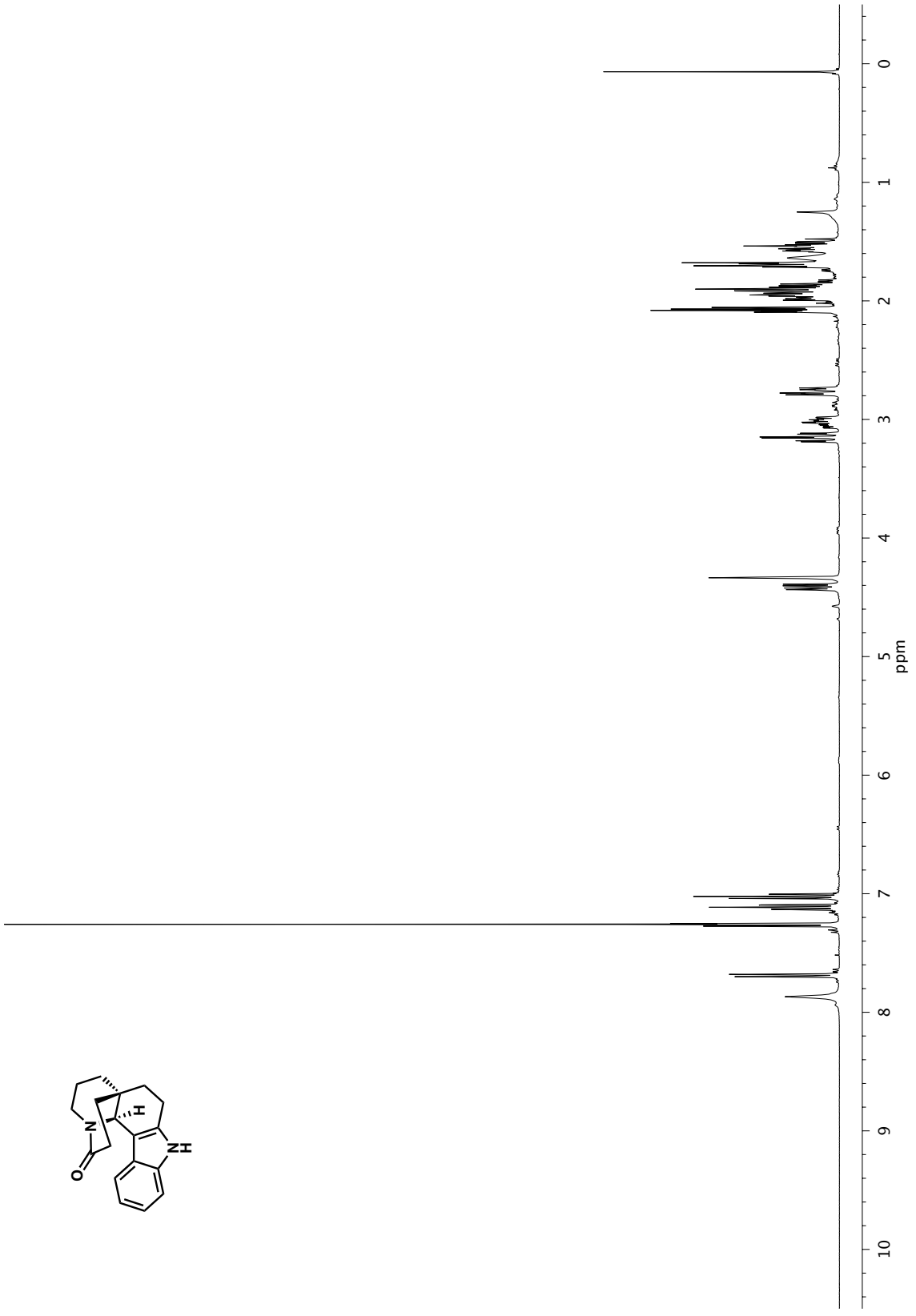
^{1}H NMR (400 MHz, $CDCl_3$) of compound **28**.



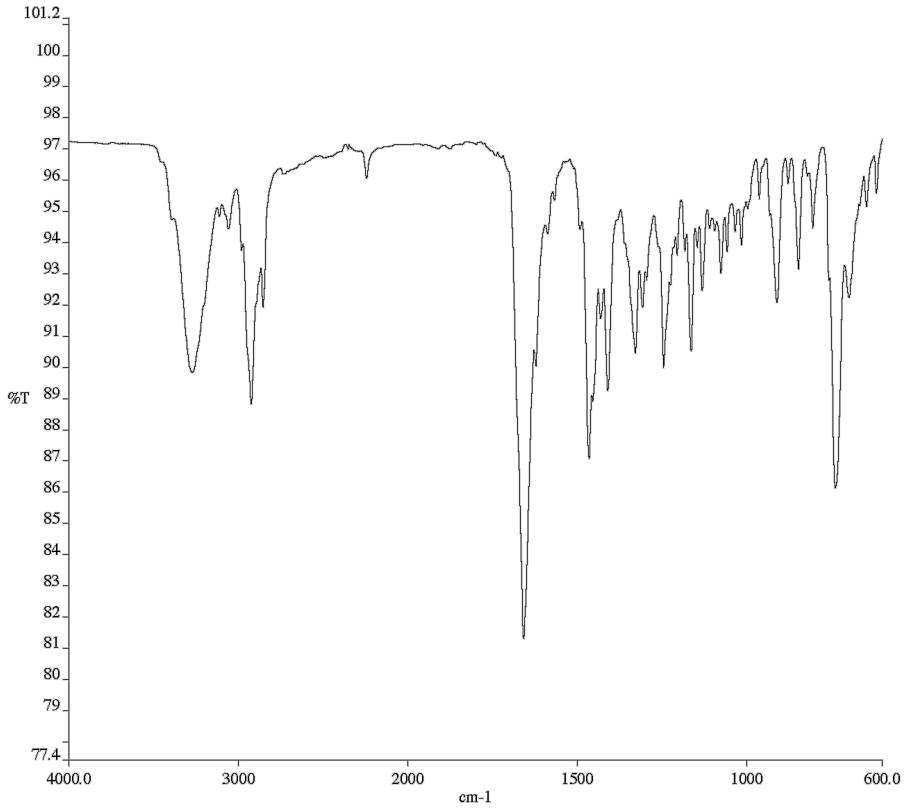
Infrared spectrum (Thin Film, NaCl) of compound **28**.



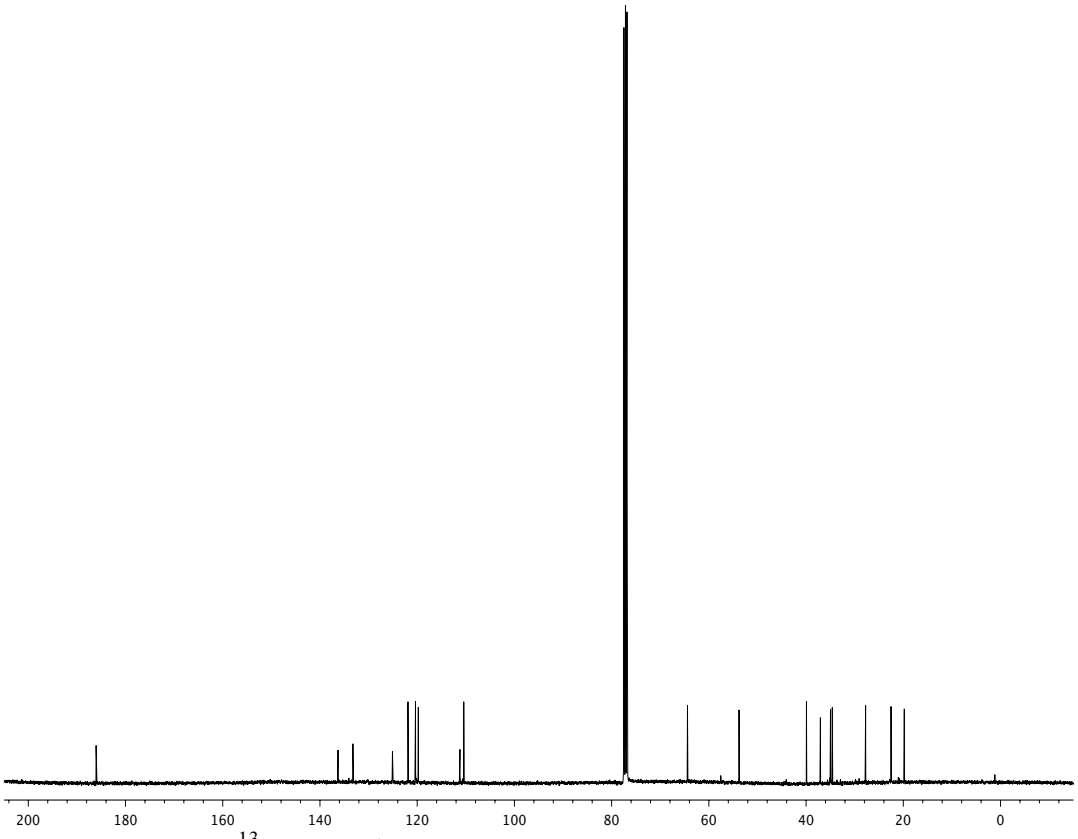
^{13}C NMR (101 MHz, $CDCl_3$) of compound **28**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **29**.



Infrared spectrum (Thin Film, NaCl) of compound **29**.



^{13}C NMR (101 MHz, $CDCl_3$) of compound **29**.