Electronic Supplementary Information for

Stereoselective Synthesis of Spirotryprostatin A

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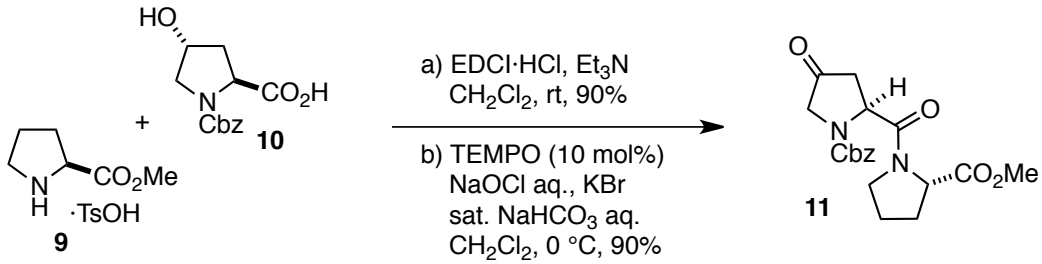
General. All non-aqueous reactions were carried out under an inert atmosphere of argon in oven-dried glassware unless otherwise noted. Dehydrated diethyl ether, tetrahydrofuran, methylene chloride and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Dehydrated methanol, ethanol and acetonitrile were also purchased from Wako Pure Chemical Industries, Ltd. and stored over activated MS3A. All other reagents were commercially available and used without further purification. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60F_{254}. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40-100 μm) purchased from Kanto Chemical Co., Inc. ^{1}H and ^{13}C NMR were recorded on a JEOL ECX-400 spectrometer. Preparative thin layer chromatography (PTLC) separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F_{254}. All ^{1}H NMR spectra are reported in units, parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are indicated in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77.0 ppm or central line of the septet for DMSO-d_6 at 39.52 ppm. Infrared spectra (IR) were recorded on a FT/IR-4100 Fourier Transform Infrared Spectrophotometer, and are reported in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-T100LP AccuTOF LC-plus in positive electrospray ionization (ESI) method or direct analysis real time (DART) method using PEG as the internal standard. Optical rotations were measured on a JASCO P-2200 Digital Polarimeter at room temperature, using the sodium D line. Melting points, determined on a Yanaco Micro Melting Point Apparatus, are uncorrected.

(*S*)-benzyl 2-((*S*)-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)-4-oxopyrrolidine-1-carboxylate (11)



To a stirred solution of *N*-Cbz-*trans*-4-hydroxy-L-proline (**10**, 60.7 g, 229 mmol) and L-proline methyl ester *p*-toluenesulfonate salt (**9**, 47.7 g, 158 mmol) in CH_2Cl_2 (760 mL) were added EDCI·HCl (65.8 g, 343 mmol) and Et_3N (38.3 mL, 275 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h, then quenched with saturated NH_4Cl aq. (760 mL) and partitioned between CH_2Cl_2 (240 mL) and water (240 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (300 mL) twice. The combined organic extract was washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/1 to MeOH/EtOAc = 1/10) to afford dipeptide **S1** (53.4 g, 142 mmol, 90%) as a yellow oil.

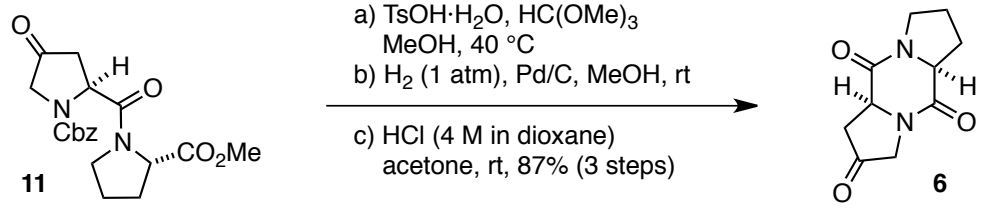
R*f* = 0.31 (MeOH/EtOAc = 1/10, PMA); $[\alpha]^{25}_{D}$ –68 (*c* = 0.88, $CHCl_3$); IR (neat) 3421, 2952, 2361, 1744, 1700, 1647, 1558, 1541, 1421, 1359, 1199, 1174, 1123 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz): (**1.4:1 mixture of two rotamers**) (***major***) δ 7.34–7.26 (m, 5H), 5.15 (d, *J* = 12.8 Hz, 1H), 5.07 (d, *J* = 12.8 Hz, 1H), 4.71 (dd, *J* = 7.8, 7.3 Hz, 1H), 4.62–4.58 (m, 1H), 3.89 (dd, *J* = 7.3, 6.9 Hz, 1H), 3.78–3.31 (m, 4H), 3.72 (s, 3H), 2.29–2.14 (m, 2H), 2.09–1.76 (m, 4H) (***minor***) δ 7.34–7.26 (m, 5H), 5.12 (d, *J* = 11.9 Hz, 1H), 4.96 (d, *J* = 11.9 Hz, 1H), 4.62 (dd, *J* = 7.8, 7.3 Hz, 1H), 4.62–4.58 (m, 1H), 4.31 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.78–3.31 (m, 4H), 3.70 (s, 3H), 2.29–2.14 (m, 2H), 2.09–1.76 (m, 2H), 1.67–1.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 100MHz): (***major* and *minor***) δ 172.7 (C), 172.4 (C), 171.2 (C), 170.9 (C), 155.0 (C), 154.3 (C), 136.5 (C), 136.3 (C), 128.4 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 70.2 (CH), 69.6 (CH), 67.4 (CH_2), 67.0 (CH_2), 58.8 (CH_2), 58.6 (CH_2), 56.8 (CH_2), 56.2 (CH_2), 55.5 (CH), 54.8 (CH), 52.2 (CH_3), 52.2 (CH_3), 46.7 (CH_2), 46.5 (CH_2), 38.5 (CH_2), 37.7 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 24.9 (CH_2), 24.5 (CH_2); HRMS (ESI): calcd for $C_{19}H_{24}O_6N_2Na$ ($[M+Na]^+$): 399.1532, found 399.1525.

To a stirred solution of **S1** (25.6 g, 68.0 mmol), TEMPO (1.00 g, 6.80 mmol) and KBr (809 mg, 6.80 mmol) in CH_2Cl_2 (170 mL) and saturated Na_2CO_3 aq. (170 mL) were added 3.5 M

NaOCl aq. (58 mL, 204 mmol) at 0 °C. The resulting mixture was stirred vigorously at 0 °C for 30 min, then quenched with saturated $Na_2S_2O_3$ aq. (170 mL) and partitioned between CH_2Cl_2 (350 mL) and water (170 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (200 mL) twice. The combined organic extract was washed with brine (70 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/1 to 0/1) to afford **11** (23.0 g, 61.4 mmol, 90%) as yellow crystals.

R*f* = 0.60 (EtOAc, Ce-PMA); M.p. 103.8–104.6 °C; $[\alpha]^{25}_{D}$ –26 (*c* = 1.32, $CHCl_3$); IR (neat) 2954, 1764, 1743, 1710, 1653, 1446, 1416, 1359, 1198, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) (**2.1:1 mixture of two rotamers**) (***major***) δ 7.35–7.26 (m, 5H), 5.26 (d, *J* = 11.9 Hz, 1H), 5.09 (d, *J* = 11.9 Hz, 1H), 4.96 (dd, *J* = 12.8, 8.2 Hz, 1H), 4.56 (dd, *J* = 8.7, 4.1 Hz, 1H), 4.13–3.90 (m, 3H), 3.71 (s, 3H), 3.71–3.63 (m, 1H), 2.87–2.77 (m, 1H), 2.64–2.60 (m, 1H), 2.29–2.20 (m, 1H), 2.10–1.97 (m, 3H) (***minor***) δ 7.35–7.26 (m, 5H), 5.26 (d, *J* = 11.9 Hz, 1H), 5.09 (d, *J* = 11.9 Hz, 1H), 5.03 (dd, *J* = 12.8, 11.5 Hz, 1H), 4.38–4.37 (m, 1H), 4.13–3.90 (m, 1H), 3.71–3.63 (m, 1H), 3.69 (s, 3H), 3.46–3.42 (m, 2H), 2.87–2.77 (m, 1H), 2.64–2.60 (m, 1H), 2.10–1.97 (m, 4H); (DMSO-d_6, 100 °C) δ 7.38–7.32 (m, 5H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.05 (d, *J* = 12.4 Hz, 1H), 5.02 (d, *J* = 9.2 Hz, 1H), 4.34–4.26 (m, 1H), 3.90 (d, *J* = 18.1 Hz, 1H), 3.76 (d, *J* = 18.1 Hz, 1H), 3.60 (s, 3H), 3.60–3.49 (m, 2H), 3.09 (dd, *J* = 18.4, 9.2 Hz, 1H), 2.28 (d, *J* = 18.4 Hz, 1H), 2.17–2.01 (m, 1H), 1.96–1.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) (***major* and *minor***) δ 207.5 (C), 207.0 (C), 171.6 (C), 171.4 (C), 170.0 (C), 169.9 (C), 154.4 (C), 153.4 (C), 135.5 (C), 135.4 (C), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 127.2 (CH), 67.1 (CH_2), 66.8 (CH_2), 58.2 (CH), 58.0 (CH), 54.2 (CH), 54.0 (CH), 52.6 (CH_2), 52.2 (CH_2), 51.6 (CH_3), 51.6 (CH_3), 46.3 (CH_2), 46.0 (CH_2), 40.1 (CH_2), 39.6 (CH_2), 28.3 (CH_2). 28.1 (CH_2), 24.3 (CH_2), 24.0 (CH_2); (DMSO-d_6, 100 °C) δ 207.5 (C), 171.3 (C), 169.7 (C), 153.6 (C), 136.0 (C), 127.8 (CH), 127.4 (CH), 127.1 (CH), 66.2 (CH_2), 58.0 (CH), 54.3 (CH), 52.4 (CH_2), 51.2 (CH_3), 45.9 (CH_2), 39.9 (CH_2), 27.9 (CH_2). 23.9 (CH_2); HRMS (ESI) calcd for $C_{19}H_{22}O_6N_2Na$ ($[M+Na]^+$) 397.1376, found 397.1361.

(5a*S*,10a*S*)-hexahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-2,5,10(3*H*)-trione (6)



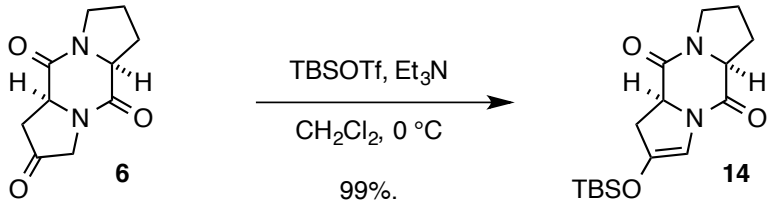
To a stirred solution of **11** (12.5 g, 33.3 mmol) and TsOH·H_2O (3.16 g, 16.6 mmol) in MeOH (150 mL) were added $CH(OMe)_3$ (7.3 mL, 67 mmol) at room temperature. The resulting mixture was stirred at 40 °C for 1 h before quenching with saturated Na_2CO_3 aq. (150 mL) and partitioned between EtOAc (300 mL) and water (100 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (200 mL) twice. The combined organic extract was washed with water (200 mL) and brine (60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was used in the next reaction without further purification.

A mixture of the crude product and 10% Pd/C (M-type (wet, 50% water, Kawaken), 3.50 g, 1.66 mmol) was added MeOH (150 mL) under Argon atmosphere. The flask was charged with hydrogen gas (1 atm) at room temperature and the resulting suspension was vigorously stirred for 30 min. The reaction mixture was filtered through a Celite pad and the filtrate was stirred at 40 °C for 2 h. The reaction mixture was concentrated *in vacuo* to give a crude product, which was used for the next step without further purification.

To a stirred solution of the crude product in acetone (120 mL) were added 4 M HCl in 1,4-dioxane (15.0 mL) at 0 °C and the mixture was stirred at room temperature for 4 h. The white precipitates were collected in a Büchner funnel using suction filtration, washed with cold acetone (10 mL) twice and dried under vacuum to give the first crop of **6** (3.7 g, 17.8 mmol, 53%). Concentration of the mother liquor and recrystallization from acetone provided a second crop of **6** (0.64 g, 3.08 mmol, 9%). Concentrated mother liquor was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford another fraction of **6** (1.67 g, 8.03 mmol, 24%). The overall yield is 87% in three steps (6.01 g, 28.8 mmol).

R*f* = 0.29 (MeOH/EtOAc = 1/10, Ce-PMA); M.p. 204.8–205.3 °C; $[\alpha]^{27}_{D}$ –190 (*c* = 1.15, $CHCl_3$); IR (neat): 1764, 1660, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 4.68 (dd, *J* = 9.2, 8.7 Hz, 1H), 4.26 (dd, *J* = 8.3, 7.8 Hz, 1H), 4.14 (d, *J* = 19.7 Hz, 1H), 3.79 (d, *J* = 19.7 Hz, 1H), 3.61 (dd, *J* = 8.7, 5.2 Hz, 2H), 3.13 (dd, *J* = 19.2, 9.4 Hz, 1H), 2.93 (dd, *J* = 19.2, 8.7 Hz, 1H), 2.45–2.38 (m, 1H), 2.26–2.16 (m, 1H), 2.12–1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 206.2 (C), 166.8 (C), 164.5 (C), 59.6 (CH), 57.4 (CH), 52.1 (CH_2), 45.7 (CH_2), 39.2 (CH_2), 27.8 (CH_2), 22.9 (CH_2); HRMS (DART) calcd for $C_{10}H_{13}N_2O_3$ ($[M+H]^+$) 209.0926, found 209.0920.

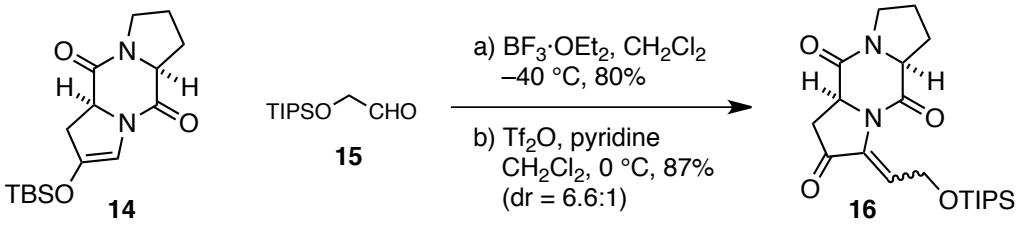
(5a*S*,10a*S*)-7-((*tert*-butyldimethylsilyl)oxy)-1,2,3,5a,6,10a-hexahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-5,10-dione (14)



To a stirred solution of **6** (6.00 g, 28.8 mmol) in CH_2Cl_2 (280 mL) was added TBSOTf (7.90 mL, 34.6 mmol) and Et_3N (12.1 mL, 86.5 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 2.5 h. The reaction mixture was quenched with saturated Na_2CO_3 aq. (280 mL) and partitioned between EtOAc (500 mL) and water (220 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (250 mL) twice. The combined organic extract was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/1 to 0/1) to afford **14** (9.22 g, 28.6 mmol, 99%) as white crystals.

R*f* = 0.64 (MeOH/EtOAc = 1/10, UV, Ce-PMA); M.p. 109.0–109.9 °C; $[\alpha]^{27}_D$ +18 (*c* = 1.01, $CHCl_3$); IR (neat) 2930, 2359, 1677, 1640, 1436, 1255, 931, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 6.18 (s, 1H), 4.61 (dd, *J* = 10.5, 9.6 Hz, 1H), 4.17 (dd, *J* = 8.3, 7.8 Hz, 1H), 3.60–3.56 (m, 2H), 3.30–3.28 (m, 1H), 2.75 (dd, *J* = 16.5, 11.0 Hz, 1H), 2.38–2.20 (m, 2H), 2.06–1.89 (m, 2H), 0.93 (s, 9H), 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 165.2 (C), 161.8 (C), 145.0 (C), 105.4 (CH), 60.0 (CH), 58.3 (CH), 45.5 (CH_2), 33.7 (CH_2), 27.8 (CH_2), 25.4 (CH_3), 23.3(CH_2), 18.0 (C), –4.8 (CH_3), –4.9 (CH_3); HRMS (ESI) calcd for $C_{16}H_{30}N_2O_3SiNa$ ($[M+Na]^+$) 345.1610, found 345.1598.

(5a*S*,10a*S*)-3-(2-((triisopropylsilyl)oxy)ethylidene)hexahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-2,5,10(3*H*)-trione (16)

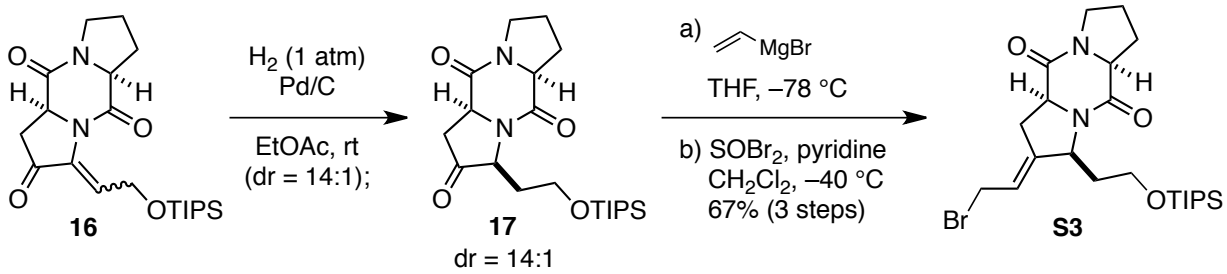


To a stirred solution of **14** (8.13 g, 25.2 mmol) and aldehyde **15** (8.18 g, 37.8 mmol) in CH_2Cl_2 (200 mL) was added $BF_3{\cdot}OEt_2$ (4.60 mL, 50.4 mmol) at −78 °C and the resulting mixture was stirred at –40 °C for 3 h. The reaction mixture was quenched with saturated NH_4Cl aq. (200 mL) and partitioned between CH_2Cl_2 (200 mL) and water (100 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (300 mL) twice. The combined organic extract was washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/1 to MeOH/EtOAc = 1/10) to afford 4:1 diastereomixtures of aldol (8.58 g, 20.2 mmol, 80%) as a clear viscous oil.

To a stirred solution of aldol (8.55 g, 20.1 mmol) and pyridine (6.50 mL, 80.5 mmol) in CH_2Cl_2 (200 mL) were added Tf_2O (4.10 mL, 24.2 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with saturated NH_4Cl aq. (200 mL) and partitioned between EtOAc (300 mL) and water (100 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (200 mL) twice. The combined organic extract was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/1 to 0/1) to afford inseparable diastereomixtures (6.6:1) of **16** (7.14 g, 17.6 mmol, 87%) as a yellow viscous oil.

R*f* = 0.52 (EtOAc, UV, Ce-PMA); IR (neat) 2943, 2866, 1742, 1676 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) (***major***) δ 6.30 (dd, J = 6.9, 3.7 Hz, 1H), 4.82 (dd, J = 17.9, 3.7 Hz, 1H), 4.70 (dd, J = 9.2, 8.2 Hz, 1H), 4.38 (dd, J = 17.9, 6.9 Hz, 1H), 4.34 (dd, J = 8.2, 6.9 Hz, 1H), 3.64–3.61 (m, 2H), 3.12 (dd, J = 19.7, 8.2 Hz, 1H), 2.93 (dd, J = 19.7, 9.2 Hz, 1H), 2.42–2.22 (m, 2H), 2.11–1.90 (m, 2H), 1.16–1.05 (m, 21H); ^{13}C NMR ($CDCl_3$, 100MHz) (***major***) δ 195.1 (C), 164.5 (C), 164.0 (C), 129.5 (C), 125.2 (CH), 62.1 (CH_2), 59.5 (CH), 57.3 (CH), 46.0 (CH_2), 37.0 (CH_2), 27.8 (CH_2), 22.9 (CH_2), 18.0 (CH_3), 11.9 (CH); HRMS (ESI) calcd for $C_{21}H_{34}O_4N_2SiNa$ ($[M+Na]^+$) 429.2186, found 429.2197.

(3*S*,5a*S*,10a*S*,*E*)-2-(2-bromoethylidene)-3-(2-((triisopropylsilyl)oxy)ethyl)octahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-5,10-dione (S3)



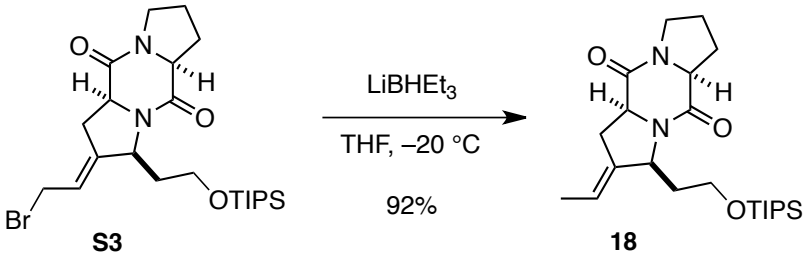
A mixture of **16** (7.14 g, 17.6 mmol) and 10% Pd/C (M-type (wet, 50% water, Kawaken), 3.70 g, 1.76 mmol) was added MeOH (150 mL) under Argon atmosphere. The flask was charged with hydrogen gas (1 atm) at room temperature and the resulting suspension was vigorously stirred for 30 min. The reaction mixture was filtered through a Celite pad and the filtrate was stirred at 40 °C for 2 h. The reaction mixture was concentrated *in vacuo* to give **17**, which was used for the next step without further purification.

To a stirred solution of **17** in THF (85 mL) was added 1.0 M vinyl magnesium bromide solution in THF (35.1 mL, 35.1 mmol) at −78 °C. The resulting mixture was stirred at –78 °C for 30 min and quenched with saturated NH_4Cl aq. (85 mL). The resulting mixture was partitioned between EtOAc (50 mL) and water (10 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (100 mL) twice. The combined organic extract was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product which was used in the next reaction without further purification.

To a stirred solution of the crude product and pyridine (14.3 mL, 175 mmol) in CH_2Cl_2 (85 mL) was added $SOBr_2$ (6.70 mL, 52.7 mmol) in one portion at −20 °C and the resulting mixture was stirred at –20 °C for 20 min. The reaction mixture was quenched with saturated NH_4Cl aq. (85 mL) and partitioned between EtOAc (85 mL) and water (30 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (100 mL) twice. The combined organic extract was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/1 to 0/1) to afford **S3** (5.86 g, 11.7 mmol, 67% in three steps) as a yellow viscous oil.

R*f* = 0.62 (MeOH/EtOAc = 1/10, Ce-PMA); $[\alpha]^{25}_D$ –23 (*c* = 0.90, $CHCl_3$); IR (neat) 2942, 2865, 1671, 1460, 1671, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 5.84 (tm, *J* = 8.2 Hz, 1H), 4.67 (dm, *J* = 6.0 Hz, 1H), 4.25 (dd, *J* = 10.5, 7.3 Hz, 1H), 4.12 (dd, *J* = 8.2, 7.8 Hz, 1H), 4.00 (d, *J* = 8.2 Hz, 2H), 3.75–3.66 (m, 2H), 3.58–3.54 (m, 2H), 3.04 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.86 (ddm, *J* = 15.6, 10.5 Hz, 1H), 2.39–2.29 (m, 2H), 2.23–2.13 (m, 1H), 2.08–1.88 (m, 2H), 1.75–1.67 (m, 1H), 1.05–1.04 (m, 21H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 167.1 (C), 165.9 (C), 142.6 (C), 120.6 (CH), 60.7 (CH), 60.1 (CH), 59.2 (CH), 59.2 (CH), 45.0 (CH_2), 36.0 (CH_2), 27.9 (CH_2), 27.7 (CH_2), 23.3 (CH_2), 17.9 (CH_3), 11.8 (CH); HRMS (ESI) calcd for $C_{23}H_{39}O_3N_2BrSiNa$ ($[M+Na]^+$) 521.1811, found 521.1816.

(3*S*,5a*S*,10a*S*,*E*)-2-ethylidene-3-(2-((triisopropylsilyl)oxy)ethyl)octahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-5,10-dione (18)

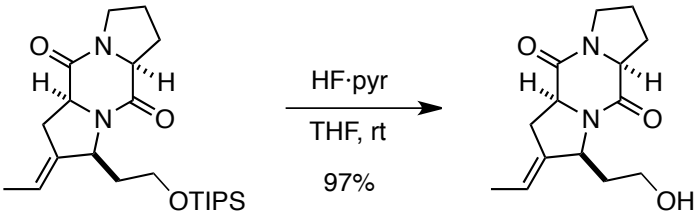


S3 **18**

To a stirred solution of **S3** (3.22 g, 6.45 mmol) in THF (64 mL) was added 1.0 M $LiBHEt_3$ solution in THF (12.9 mL, 12.9 mmol) at −20 °C. The resulting mixture was stirred at –20 °C for 30 min, then quenched with saturated NH_4Cl aq. (64 mL). The reaction mixture was partitioned between EtOAc (100 mL) and water (30 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (80 mL) twice. The combined organic extract was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/1 to 0/1) to afford **18** (2.50 g, 5.94 mmol, 92%) as a yellow oil.

R*f* = 0.68 (MeOH/EtOAc = 1/10, Ce-PMA); $[\alpha]^{19}_{D}$ –68 (*c* = 1.69, $CHCl_3$); IR (neat) 2942, 2866, 1673, 1417 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 5.54–4.46 (m, 1H), 4.55–4.53 (m, 1H), 4.17 (dd, *J* = 11.0, 7.3 Hz, 1H), 4.10 (dd, *J* = 8.7, 7.8 Hz, 1H), 3.70–3.66 (m, 2H), 3.57–3.54 (m, 2H), 2.93 (dd, *J* = 15.6, 7.3 Hz, 1H), 2.71 (dd, *J* = 15.6, 11.0 Hz, 1H), 2.38–2.12 (m, 3H), 2.06–1.86 (m, 2H), 1.69 (d, *J* = 6.9 Hz, 3H), 1.69–1.62 (m, 1H), 1.07–1.04 (m, 21H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 167.2 (C), 166.5 (C), 136.3 (C), 119.3 (CH), 61.0 (CH), 60.4 (CH), 59.6 (CH_2), 59.3 (CH), 45.0 (CH_2), 36.3 (CH_2), 27.9 (CH_2), 27.8 (CH_2), 23.4 (CH_2), 17.9 (CH_3), 14.3 (CH_3), 11.9 (CH); HRMS (ESI) calcd for $C_{23}H_{40}O_3N_2SiNa$ ($[M+Na]^+$) 443.2706, found 443.2714.

(3*S*,5a*S*,10a*S*,*E*)-2-ethylidene-3-(2-hydroxyethyl)octahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-5,10-dione (19)

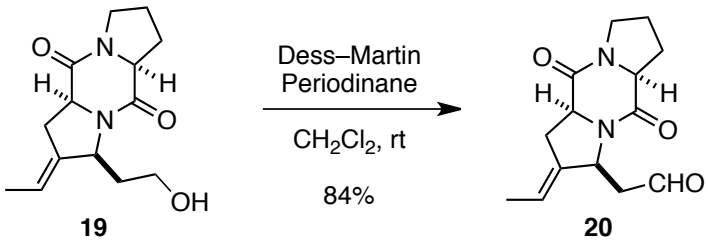


18 **19**

To a stirred solution of **18** (1.28 g, 3.04 mmol) in THF (30 mL) was added 30% HF·pyridine (4.0 mL) at 0 °C. The resulting mixture was stirred at room temperature for 3 h and quenched with saturated NH_4Cl aq. (30 mL) The resulting mixture was partitioned between CH_2Cl_2 (50 mL) and water (10 mL). The organic phase was collected and the aqueous phase was extracted with 10% MeOH in CH_2Cl_2 solution (60 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford **19** (780 mg, 2.95 mmol, 97%) as a yellow viscous oil.

R*f* = 0.33 (MeOH/EtOAc = 1/10, Ce-PMA); $[\alpha]^{18}_{D}$ –133 (*c* = 0.72, $CHCl_3$); IR (neat) 3415, 2880, 1659, 1425 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 5.51 (qm, *J* = 6.8 Hz, 1H), 4.58 (dd, *J* = 6.4, 6.4 Hz, 1H), 4.19 (dd, *J* = 11.0, 7.4 Hz, 1H), 4.14 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.36–3.46 (m, 4H), 3.34 (brs, 1H), 2.94 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.78–2.70 (m, 1H), 2.41–2.33 (m, 1H), 2.25–2.15 (m, 1H), 2.07–1.86 (m, 3H), 1.79–1.70 (m, 1H), 1.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 169.2 (C), 166.4 (C), 137.3 (C), 119.1 (CH), 60.9 (CH), 60.8 (CH), 59.0 (CH_2), 58.6 (CH), 45.1 (CH_2), 39.9 (CH_2), 28.1 (CH_2), 27.1 (CH_2), 23.5 (CH_2), 14.3 (CH_3); HRMS (ESI) calcd for $C_{14}H_{20}O_3N_2Na$ ($[M+Na]^+$) 287.1372, found 287.1366.

2-((3*S*,5a*S*,10a*S*,*E*)-2-ethylidene-5,10-dioxodecahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazin-3-yl)acetaldehyde (20)

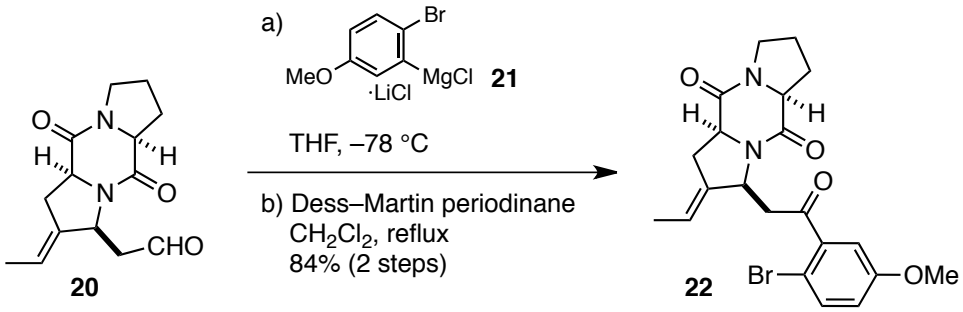


19 **20**

To a stirred solution of **19** (430 mg, 1.63 mmol) in CH_2Cl_2 (16 mL) was added Dess-Martin periodinane (1.00 g, 2.44 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 15 min. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aq. (6 mL) and stirred for 10 min at 0 °C. The mixture was added saturated Na_2CO_3 aq. (10 mL) and partitioned between CH_2Cl_2 (30 mL) and water (5 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (25 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford **20** (361 mg, 1.38 mmol, 84%) as a yellow viscous oil.

R*f* = 0.37 (MeOH/EtOAc = 1/10, Ce-PMA); $[\alpha]^{25}_{D}$ –23 (*c* = 0.66, $CHCl_3$); IR (neat) 2881, 2359, 1719, 1664, 1423 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 9.73 (dd, *J* = 1.8, 1.4 Hz, 1H), 5.61–5.55 (m, 1H), 4.83–4.81 (m, 1H), 4.25 (dd, *J* = 9.2, 9.2 Hz, 1H), 4.13 (dd, *J* = 8.7, 7.8 Hz, 1H), 3.64–3.52 (m, 2H), 3.04–2.95 (m, 2H), 2.87–2.75 (m, 2H), 2.38–2.30 (m, 1H), 2.19–1.89 (m, 3H), 1.69 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 198.9 (CH), 167.5 (C), 166.1 (C), 136.7 (C), 120.4 (CH), 60.6 (CH), 60.4 (CH), 56.5 (CH), 48.7 (CH_2), 45.2 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 23.3 (CH_2), 14.5 (CH_3); HRMS (ESI) calcd for $C_{14}H_{18}O_3N_2Na$ ($[M+Na]^+$) 285.1215, found 285.1210.

(3*S*,5a*S*,10a*S*,*E*)-3-(2-(2-bromo-5-methoxyphenyl)-2-oxoethyl)-2-ethylideneoctahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-5,10-dione (22)

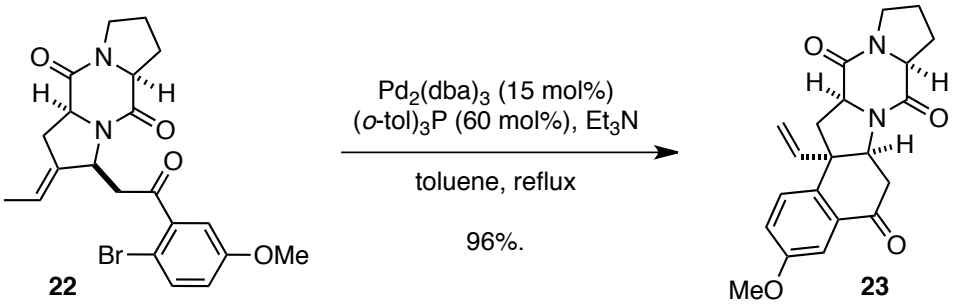


To a stirred solution of the 2-bromo-3-methoxy iodobenzene (1.50 g, 4.89 mmol) in THF (8 mL) was added 1.3 M *i*-PrMgBr·LiCl solution in THF (3.1 mL, 4.07 mmol) at –78 °C. The reaction mixture was stirred for 30 min at 20 °C to give the solution of **21**. To a stirred solution of **20** (361 mg, 1.38 mmol) in THF (7.0 mL) was added **21** at –78 °C by cannulation and the resulting mixture was stirred at −78 °C for 45 min. The reaction mixture was quenched with saturated NH_4Cl aq. (7.0 mL) and partitioned between EtOAc (15 mL) and water (5 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (10 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was used in the next reaction without further purification.

To a stirred solution of the crude product in CH_2Cl_2 (14 mL) was added Dess-Martin periodinane (1.40 g, 3.26 mmol) at room temperature and the resulting mixture was stirred at refluxing temperature for 30 min. The reaction mixture was quenched with saturated $Na_2S_2O_3$ aq. (6 mL) and stirred for 10 min at 0 °C. The resulting mixture was added saturated Na_2CO_3 aq. (8 mL) and partitioned between CH_2Cl_2 (20 mL) and water (5 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (15 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1/1 to 0/1) to afford **22** (518 mg, 1.16 mmol, 84% in two steps) as a yellow viscous oil.

R*f* = 0.40 (MeOH/EtOAc = 1/10, UV, Ce-PMA); $[\alpha]^{25}_{D}$ –47 (*c* = 0.96, $CHCl_3$); IR (neat) 2937, 2339, 1665, 1422 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 7.44 (d, *J* = 8.7 Hz, 1H), 6.95 (d, *J* = 2.7 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.70–5.63 (m, 1H), 4.98–4.96 (m, 1H), 4.24 (dd, *J* = 10.3, 7.6 Hz, 1H), 4.13 (dd, *J* = 8.2, 7.8 Hz, 1H), 3.81 (s, 3H), 3.62 (dd, *J* = 17.0, 3.2 Hz, 1H), 3.59–3.54 (m, *2*H), 3.32 (dd, *J* = 17.0, 8.2 Hz, 1H), 2.97 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.88-2–79 (m, 1H), 2.37–2.29 (m, 1H), 2.18–1.86 (m, 3H), 1.67 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 200.6 (C), 167.3 (C), 166.2 (C), 158.7 (C), 141.6 (C), 136.2 (C), 134.5 (CH), 120.8 (CH), 117.9 (CH), 114.1 (CH), 109.0 (C), 60.6 (CH), 60.4 (CH), 57.7 (CH), 55.6 (CH_3), 46.2 (CH_2), 45.1 (CH_2), 28.2 (CH_2), 27.8 (CH_2), 23.3 (CH_2), 14.5 (CH_3); HRMS (ESI) calcd for $C_{21}H_{25}O_6N_2BrNa$ ($[M+Na]^+$) 469.0739, found 469.0750.

(6a*S*,8a*S*,13a*S*,14a*S*)-3-methoxy-14a-vinyl-6,6a,8a,9,10,11,14,14a-octahydrobenzo[*e*]pyrrolo[1',2':4,5]pyrazino[1,2-*a*]indole-5,8,13(13a*H*)-trione (23)

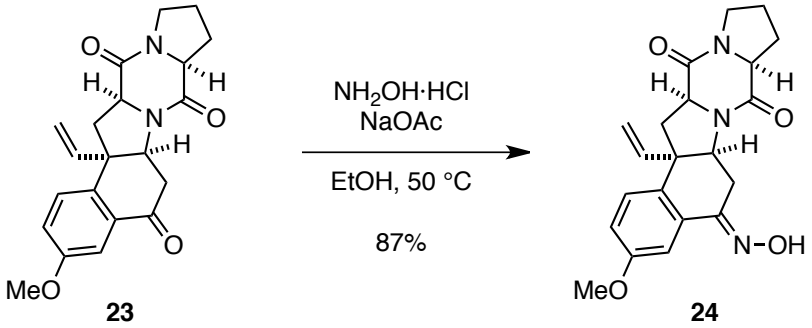


22 23

To a stirred solution of **22** (277 mg, 0.620 mmol), (*o*-tol)$_3$P (113 mg, 0.372 mmol) and Pd$_2$(dba)$_3$ (85.2 mg, 0.093 mmol) in toluene (6.2 mL) were added Et$_3$N (0.26 mL, 1.86 mmol) at room temperature and the resulting mixture was stirred at refluxing temperature for 2 h. The reaction mixture was quenched with saturated NH$_4$Cl aq. (6 mL) and partitioned between CH$_2$Cl$_2$ (50 mL) and water (10 mL). The organic phase was collected and the aqueous phase was extracted with 10% MeOH in CH$_2$Cl$_2$ solution (60 mL) twice. The combined organic extract was dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford **23** (219 mg, 0.597 mmol, 96%) as a yellow viscous oil.

R*f* = 0.33 (MeOH/EtOAc = 1/10, UV, Ce-PMA); $[\alpha]^{22}_{D}$ +167 (*c* = 0.75, CHCl$_3$); IR (neat) 2952, 2360, 1667, 1607, 1494, 1416, 1287 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400MHz) δ 7.40 (d, *J* = 2.8 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.14 (dd, *J* = 8.7, 2.8 Hz, 1H), 5.94 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.34 (d, *J* = 10.6 Hz, 1H), 5.29 (d, *J* = 17.4 Hz, 1H), 4.55 (dd, *J* = 11.0, 5.5 Hz, 1H), 4.43 (dd, *J* = 9.6, 7.3 Hz, 1H), 4.15 (dd, *J* = 8.2, 7.8 Hz, 1H), 3.84 (s, 3H), 3.52–3.48 (m, 2H), 3.42 (dd, *J* = 15.6, 5.5 Hz, 1H), 2.77 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.70 (dd, *J* = 13.7, 9.6 Hz, 1H), 2.62 (dd, *J* = 15.6, 11.0 Hz, 1H), 2.34–2.18 (m, 2H), 2.05–1.88 (m, 2H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 194.6 (C), 166.9 (C), 166.1 (C), 158.8 (C), 142.2 (CH), 134.9 (C), 132.0 (C), 130.7 (CH), 122.5 (CH), 115.1 (CH$_2$), 108.6 (CH), 61.0 (CH), 60.6 (CH), 60.1 (CH), 55.5 (CH$_3$), 49.3 (C), 45.1 (CH$_2$), 40.0 (CH$_2$), 35.1 (CH$_2$), 27.3 (CH$_2$), 23.5 (CH$_2$); HRMS (ESI) calcd for C$_{21}$H$_{22}$O$_4$N$_2$Na ([M+Na]$^+$) 389.1477, found 389.1489.

(6a*S*,8a*S*,13a*S*,14a*S*,*E*)-5-(hydroxyimino)-3-methoxy-14a-vinyl-6,6a,8a,9,10,11,14,14a-octahydrobenzo[*e*]pyrrolo[1',2':4,5]pyrazino[1,2-*a*]indole-8,13(5*H*,13a*H*)-dione (24)

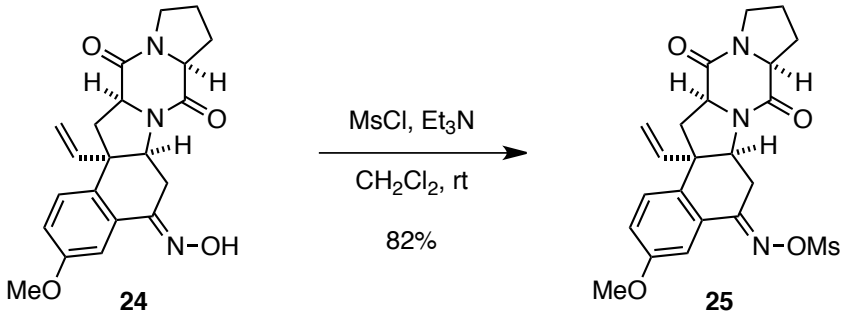


23 **24**

To a stirred solution of **23** (211 mg, 0.575 mmol) in EtOH (5.8 mL) was added $NH_2OH{\cdot}HCl$ (120 mg, 1.73 mmol) and NaOAc (142 mg, 1.73 mmol) at room temperature and the resulting mixture was stirred at 50 °C for 20 min. The reaction was quenched with saturated NH_4Cl aq. (6 mL) and partitioned between CH_2Cl_2 (10 mL) and water (6 mL). The organic phase was collected and the aqueous phase was extracted with 10% MeOH in CH_2Cl_2 solution (6 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford **24** (190 mg, 0.499 mmol, 87%) as a yellow viscous oil.

R*f* = 0.44 (MeOH/EtOAc = 1/10, UV, Ce-PMA); $[\alpha]^{20}_D$ +112 (*c* = 0.92, $CHCl_3$); IR (neat) 3290, 3002, 2876, 1661, 1419 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 8.72 (brs, 1H), 7.28 (d, *J* = 2.8 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 6.90 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.83 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.26 (d, *J* = 17.4 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.39 (dd, *J* = 11.4, 5.5 Hz, 1H), 4.38 (dd, *J* = 11.0, 6.9 Hz, 1H), 4.28 (dd, *J* = 14.2, 5.5 Hz, 1H), 4.18 (dd, *J* = 8.2, 7.8 Hz, 1H), 3.79 (s, 3H), 3.59–3.49 (m, 2H), 2.74 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.52 (dd, *J* = 13.7, 11.0 Hz, 1H), 2.38–2.24 (m, 2H), 2.08–1.88 (m, *2*H), 1.91 (dd, *J* = 14.2, 11.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 167.4 (C), 166.5 (C), 158.3 (C), 151.5 (C), 142.9 (CH), 130.9 (C), 130.7 (C), 130.1 (C), 117.8 (CH), 113.9 (CH_2), 107.2 (CH), 60.7 (CH), 60.0 (CH), 59.9 (CH), 55.3 (CH_3), 49.3 (C), 45.2 (CH_2), 35.1 (CH_2), 27.4 (CH_2), 24.4 (CH_2), 23.6 (CH_2); HRMS (ESI) calcd for $C_{21}H_{23}O_4N_3Na$ ($[M+Na]^+$) 404.1586, found 404.1599.

(6a*S*,8a*S*,13a*S*,14a*S*,*E*)-3-methoxy-5-(((methylsulfonyl)oxy)imino)-14a-vinyl-6,6a,8a,9,10,11,14,14a-octahydrobenzo[*e*]pyrrolo[1',2':4,5]pyrazino[1,2-*a*]indole-8,13(5*H*,13a*H*)-dione (25)

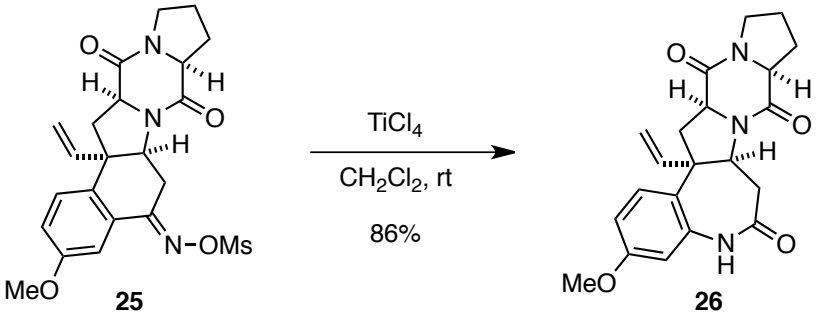


24 **25**

To a stirred solution of **24** (190 mg, 0.499 mmol) in CH_2Cl_2 (2.5 mL) was added Et_3N (0.2 mL, 1.50 mmol) and MsCl (0.13 mL, 0.998 mmol) at room temperature. The resulting mixture was stirred at room temperature for 30 min, then quenched with saturated NH_4Cl aq. (3 mL) and partitioned between CH_2Cl_2 (3 mL) and water (2 mL). The organic phase was collected and the aqueous phase was extracted with 10% MeOH in CH_2Cl_2 solution (3 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford **25** (188 mg, 0.409 mmol, 82%) as a yellow viscous oil.

R*f* = 0.46 (MeOH/EtOAc = 1/10, UV, Ce-PMA); $[\alpha]^{19}_D$ +76 (*c* = 1.16, $CHCl_3$); IR (neat) 2971, 1668, 1495, 1416, 1366, 1296, 1239, 1182 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 7.40 (d, *J* = 2.7 Hz, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.05 (dd, *J* = 9.2, 2.7 Hz, 1H), 5.89 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 5.26 (d, *J* = 17.4 Hz, 1H), 4.39 (dd, *J* = 10.1, 7.4 Hz, 1H), 4.34 (dd, *J* = 10.5, 5.5 Hz, 1H), 4.14 (dd, *J* = 8.2, 7.8 Hz, 1H), 4.01 (dd, *J* = 15.1, 5.5 Hz, 1H), 3.83 (s, 3H), 3.52–3.49 (m, 2H), 3.24 (s, 3H), 2.73 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.55 (dd, *J* = 13.8, 10.1 Hz, 1H), 2.37 (dd, *J* = 15.1, 10.5 Hz, 1H), 2.35–2.20 (m, 2H), 2.08–1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 167.1 (C), 166.1 (C), 159.7 (C), 158.5 (C), 142.0 (CH), 132.4 (C), 130.7 (CH), 127.6 (C), 119.7 (C), 115.1 (CH_2), 108.6 (CH), 60.6 (CH), 59.9 (CH), 59.6 (CH), 55.5 (CH_3), 49.4 (C), 45.2 (CH_2), 36.7 (CH_3), 35.3 (CH_2), 27.3 (CH_2), 26.4 (CH_2), 23.5 (CH_2); HRMS (ESI) calcd for $C_{22}H_{25}O_6N_3SNa$ ($[M+Na]^+$) 482.1362, found 482.1349.

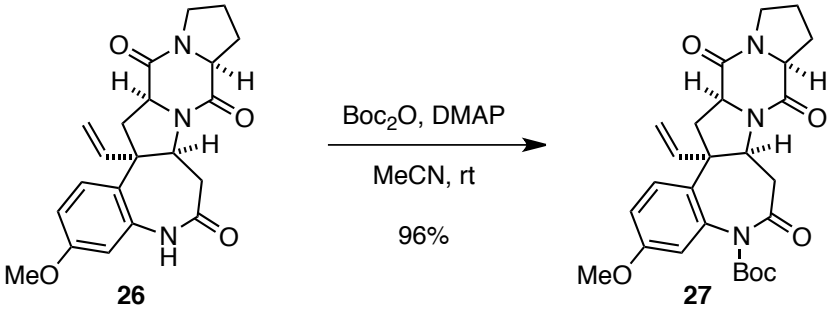
(7a*S*,9a*S*,14a*S*,15a*S*)-3-methoxy-15a-vinyl-7,7a,9a,10,11,12,15,15a-octahydro-5*H*-benzo[*b*]pyrrolo[1'',2'':4',5']pyrazino[1',2':1,5]pyrrolo[3,2-*d*]azepine-6,9,14(14a*H*)-trione (26)



To a stirred solution of **25** (114 mg, 0.247 mmol) in CH_2Cl_2 (2.5 mL) was added 1.0 M $TiCl_4$ solution in CH_2Cl_2 (1.0 mL, 0.98 mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 h, then quenched with saturated NH_4Cl aq. (3 mL) and partitioned between CH_2Cl_2 (3 mL) and water (2 mL). The organic phase was collected and the aqueous phase was extracted with 10% MeOH in CH_2Cl_2 solution (3 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford **26** (80.9 mg, 0.212 mmol, 86%) as a yellow viscous oil.

R*f* = 0.16 (MeOH/EtOAc = 1/10, UV, Ce-PMA); M.p. 239.0–239.9 °C; $[\alpha]^{23}_D$ +156° (*c* = 0.60, $CHCl_3$); IR (neat) 3234, 2984, 2360, 2338, 1671 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 7.38 (brs, 1H), 7.30 (d, *J* = 8.7 Hz, 1H), 6.71 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.50 (d, *J* = 2.3 Hz, 1H), 6.07 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.39 (d, *J* = 10.5 Hz, 1H), 5.22 (d, *J* = 17.4 Hz, 1H), 4.66 (dd, *J* = 4.6, 3.2 Hz, 1H), 4.22 (dd, *J* = 11.0, 6.8 Hz, 1H), 4.14 (dd, *J* = 8.2, 7.8 Hz, 1H), 3.80 (s, 3H), 3.64–3.57 (m, 2H), 3.52–3.46 (m, 1H), 3.12–2.98 (m, 2H), 2.56–2.53 (m, 1H), 2.38–2.22 (m, 3H), 1.97–1.85 (m 1H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 171.5 (C), 167.4 (C), 166.3 (C), 159.4 (C), 141.7 (CH), 137.4 (C), 131.0 (CH), 125.4 (C), 114.5 (CH_2), 110.7 (CH), 109.1 (CH), 65.4 (CH), 60.8 (CH), 58.1 (CH), 55.4 (CH_3), 52.6 (C), 45.2 (CH_2), 35.4 (CH_2), 34.4 (CH_2), 28.0 (CH_2), 23.4 (CH_2); HRMS (ESI) calcd for $C_{21}H_{23}O_4N_3Na$ ($[M+Na]^+$) 404.1586, found 404.1583.

(7a*S*,9a*S*,14a*S*,15a*S*)-*tert*-butyl 3-methoxy-6,9,14-trioxo-15a-vinyl-6,7,7a,9,9a,10,11,12,14,14a,15,15a-dodecahydro-5*H*-benzo[*b*]pyrrolo[1'',2'':4',5']pyrazino[1',2':1,5]pyrrolo[3,2-*d*]azepine-5-carboxylate (27)

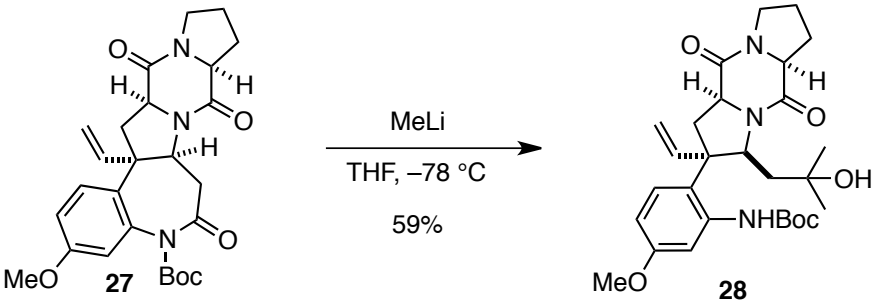


26 **27**

To a stirred solution of **26** (80.9 mg, 0.212 mmol) in MeCN (1.0 mL) was added Boc_2O (69.4 mg, 0.318 mmol) and DMAP (2.6 mg, 0.021 mmol) at room temperature and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated NH_4Cl aq. (1 mL) and partitioned between CH_2Cl_2 (2 mL) and water (2 mL). The organic phase was collected and the aqueous phase was extracted with 10% MeOH in CH_2Cl_2 solution (3 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 0/1 to 1/10) to afford **27** (98.1 mg, 0.204 mmol, 96%) as a yellow viscous oil.

R*f* = 0.37 (MeOH/EtOAc = 1/10, UV, Ce-PMA); $[\alpha]^{24}_D$ +103 (*c* = 0.62, $CHCl_3$); IR (neat) 1772, 1730, 1671, 1611, 1413, 1288, 1243, 1148 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) (**10:1 mixture of two rotamers**) (***major***) δ 7.31 (d, *J* = 9.2 Hz, 1H), 6.81 (dd, *J* = 9.2, 2.3 Hz, 1H), 6.73 (d, *J* = 2.3 Hz, 1H), 6.14 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.49 (d, *J* = 11.0 Hz, 1H), 5.29 (d, *J* = 17.4 Hz, 1H), 4.59 (dd, *J* = 3.7, 3.7 Hz, 1H), 4.22 (dd, *J* = 11.0, 7.3 Hz, 1H), 4.12 (dd, *J* = 8.2, 7.4 Hz, 1H), 3.80 (s, 3H), 3.69–3.62 (m, 1H), 3.51–3.45 (m, 1H), 3.22 (dd, *J* = 12.8, 3.7 Hz, 1H), 3.03 (dd, *J* = 14.2, 11.0 Hz, 1H), 2.37–2.25 (m, 2H), 2.31 (dd, *J* = 12.8, 3.7 Hz, 1H), 2.30 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.10–2.00 (m, 1H), 1.95–1.84 (m, 1H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 100MHz) (***major***) δ 168.3 (C), 167.7 (C), 165.9 (C), 159.3 (C), 151.0 (C), 141.2 (CH), 138.9 (C), 130.1 (CH), 127.5 (CH), 115.0 (CH_2), 113.7 (CH), 112.7 (CH). 84.5 (C), 65.1 (CH), 60.7 (CH), 58.5 (CH), 55.5 (CH_3), 51.9 (C), 45.2 (CH_2), 36.5 (CH_2), 33.9 (CH_2), 28.2 (CH_2), 27.7 (CH_3), 23.3 (CH_2); HRMS (ESI) calcd for $C_{26}H_{31}O_6N_3Na$ ($[M+Na]^+$) 504.2111, found 504.2130.

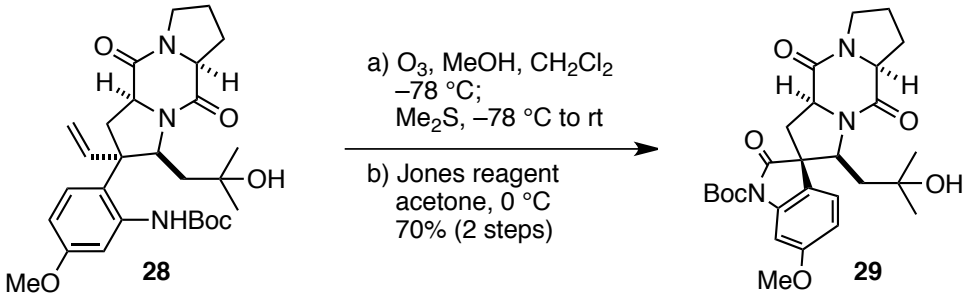
***tert*-butyl (2-((2*S*,3*S*,5a*S*,10a*S*)-3-(2-hydroxy-2-methylpropyl)-5,10-dioxo-2-vinyldecahydro dipyrrolo[1,2-*a*:1',2'-*d*]pyrazin-2-yl)-5-methoxyphenyl)carbamate (28)**



To a stirred solution of **27** (27.0 mg, 0.056 mmol) in THF (0.5 mL) was added 1.11 M MeLi solution in Et_2O (0.11 mL, 0.118 mmol) at −78 °C and the resulting mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with saturated NH_4Cl aq. (1.0 mL) and partitioned between 17% MeOH in CH_2Cl_2 (1.0 mL) and water (0.5 mL). The organic phase was collected and the aqueous phase was extracted with 17% MeOH in CH_2Cl_2 (1.5 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by PTLC (*n*-hexane/EtOAc/MeOH = 5/4/1) to afford **28** (17.0 mg, 0.033 mmol, 59%) as a pale yellow oil.

R*f* = 0.38 (MeOH/EtOAc = 1/10, UV, Ce-PMA); $[\alpha]^{22}_D$ –142 (*c* = 0.73, $CHCl_3$); IR (neat) 3402, 2974, 1731, 1680, 1654, 1522, 1465, 1418, 1233, 1156, 1042, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 7.48 (d, *J* = 2.8 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 6.72 (brs, 1H), 6.66 (dd, *J* = 8.7, 2.8 Hz, 1H), 5.94 (dd, *J* = 17.9, 10.5 Hz, 1H), 5.39 (d, *J* = 10.5 Hz, 1H), 5.28 (d, *J* = 17.9 Hz, 1H), 4.86 (dd, *J* = 8.2, 2.7 Hz, 1H), 4.22-4.16 (m, 1H), 4.19 (dd, *J* = 11.4, 11.4 Hz, 1H), 4.02 (brs, 1H), 3.82 (s, 3H), 3.62–3.49 (m, 2H), 2.86 (dd, *J* = 11.4, 11.4 Hz, 1H), 2.35–2.21 (m, 3H), 2.05–1.89 (m, 2H), 1.49 (s, 9H), 1.22–1.13 (m, 2H), 1.20 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 170.1 (C), 166.5 (C), 159.8 (C), 152.3 (C), 141.7 (CH), 137.2 (C), 128.2 (CH), 121.3 (C), 115.2 (CH_2), 109.8 (C), 108.4 (C), 80.8 (C), 67.8 (C), 61.2 (CH), 58.1 (CH), 55.9 (CH), 55.3 (CH_3), 54.9 (C), 46.0 (CH_2), 45.0 (CH_2), 34.1 (CH_2), 30.7 (CH_3), 28.3 (CH_3), 28.0 (CH_3), 27.5 (CH_2), 23.7 (CH_2); HRMS (ESI) calcd for $C_{26}H_{39}O_6N_3Na$ ($[M+Na]^+$) 536.2737, found 536.2722.

(2*S*,3*S*,5a*S*,10a*S*)-*tert*-butyl 3-(2-hydroxy-2-methylpropyl)-6'-methoxy-2',5,10-trioxo-3,5,5a,6,7,8, 10,10a-octahydro-1*H*-spiro[dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-2,3'-indoline]-1'-carboxylate (29)

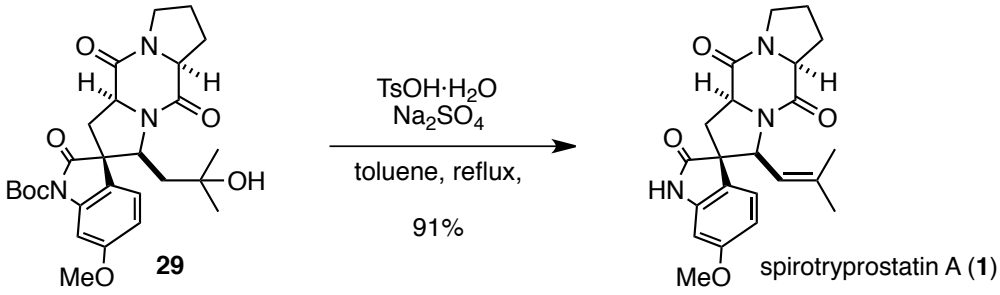


To a stirred solution of **28** (9.4 mg, 0.018 mmol) in CH_2Cl_2 (1 mL) and MeOH (1 mL) was cooled to –78 °C and ozone was passed through the solution for 2 min until complete consumption of the starting material was observed on TLC analysls. The reaction flask was purged with argon, and Me_2S (0.1 mL, 1.34 mmol) was added and the reaction mixture was warmed to room temperature. After stirring for 12 h, the reaction mixture was concentrated under reduced pressure and the crude product was used in the next reaction without further purification.

To a stirred solution of the crude product in acetone (0.6 mL) were added 2.7 M Jones reagent (17 μL, 0.045 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and the reaction was quenched with 2-propanol (50 μL). Cold 1 M HCl aq. (0.1 mL) was added to dissolve the chromium waste and the mixture was partitioned between 17% MeOH in CH_2Cl_2 (1 mL) and water (1 mL). The organic phase was collected and the aqueous phase was extracted with 17% MeOH in CH_2Cl_2 (2 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by PTLC (MeOH/EtOAc = 1/20) to afford **29** (6.5 mg, 0.013 mmol, 70% in two steps) as a clear oil.

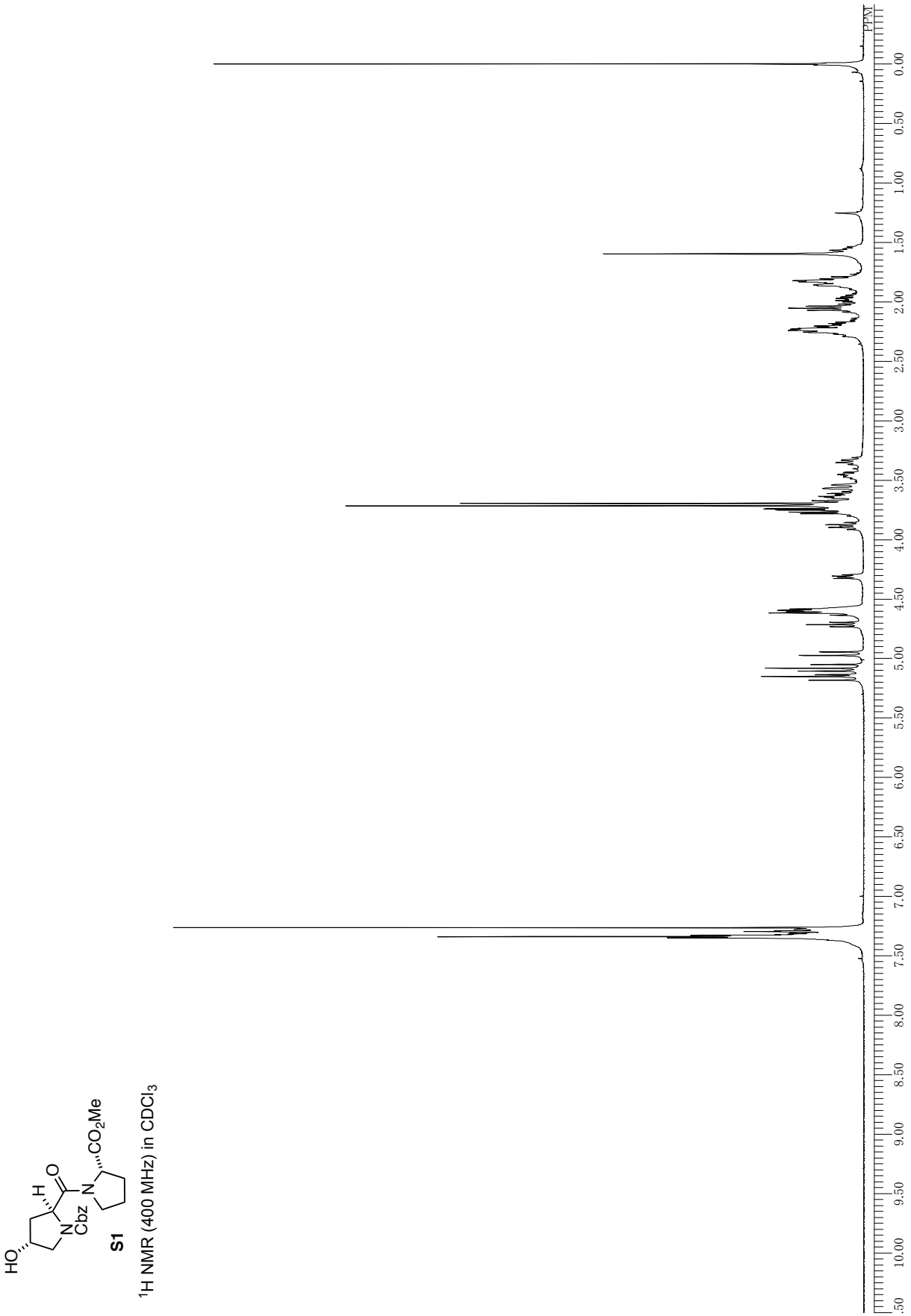
R*f* = 0.46 (MeOH/EtOAc = 1/10, UV, Ce-PMA); $[\alpha]^{22}_D$ –107 (*c* = 0.27, $CHCl_3$); IR (neat) 3384, 2973, 1792, 1763, 1734, 1671, 1654, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 7.54 (d, *J* = 2.3 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 6.72 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.92 (dd, *J* = 9.2, 7.4 Hz, 1H), 4.38 (dd, *J* = 5.0, 4.6 Hz, 1H), 4.37 (brs, 1H), 4.29 (dd, *J* = 8.2, 7.8 Hz, 1H), 3.84 (s, 3H), 3.61-3.58 (m, 2H), 2.65 (dd, *J* = 13.7, 9.2 Hz, 1H), 2.48 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.41–2.33 (m, 1H), 2.29–2.19 (m, 1H), 2.11–1.94 (m, 2H), 1.85–1.84 (m, 2H), 1.64 (s, 9H), 1.10 (s, 3H), 0.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 177.1 (C), 168.5 (C), 166.1 (C), 160.7 (C), 148.8 (C), 141.2 (C), 125.6 (CH), 117.4 (C), 110.0 (CH), 102.0 (CH), 85.0 (C), 68.6 (C), 61.0 (CH), 59.6 (CH), 59.0 (CH), 55.6 (CH), 55.4 (C), 45.2 (CH_2), 43.5 (CH_2), 34.3 (CH_2), 31.4 (CH_3), 28.1 (CH_3), 27.6 (CH_2), 26.9 (CH_3), 23.6 (CH_2); HRMS (ESI) calcd for $C_{27}H_{35}O_7N_3Na$ ($[M+Na]^+$) 536.2373, found 536.2386.

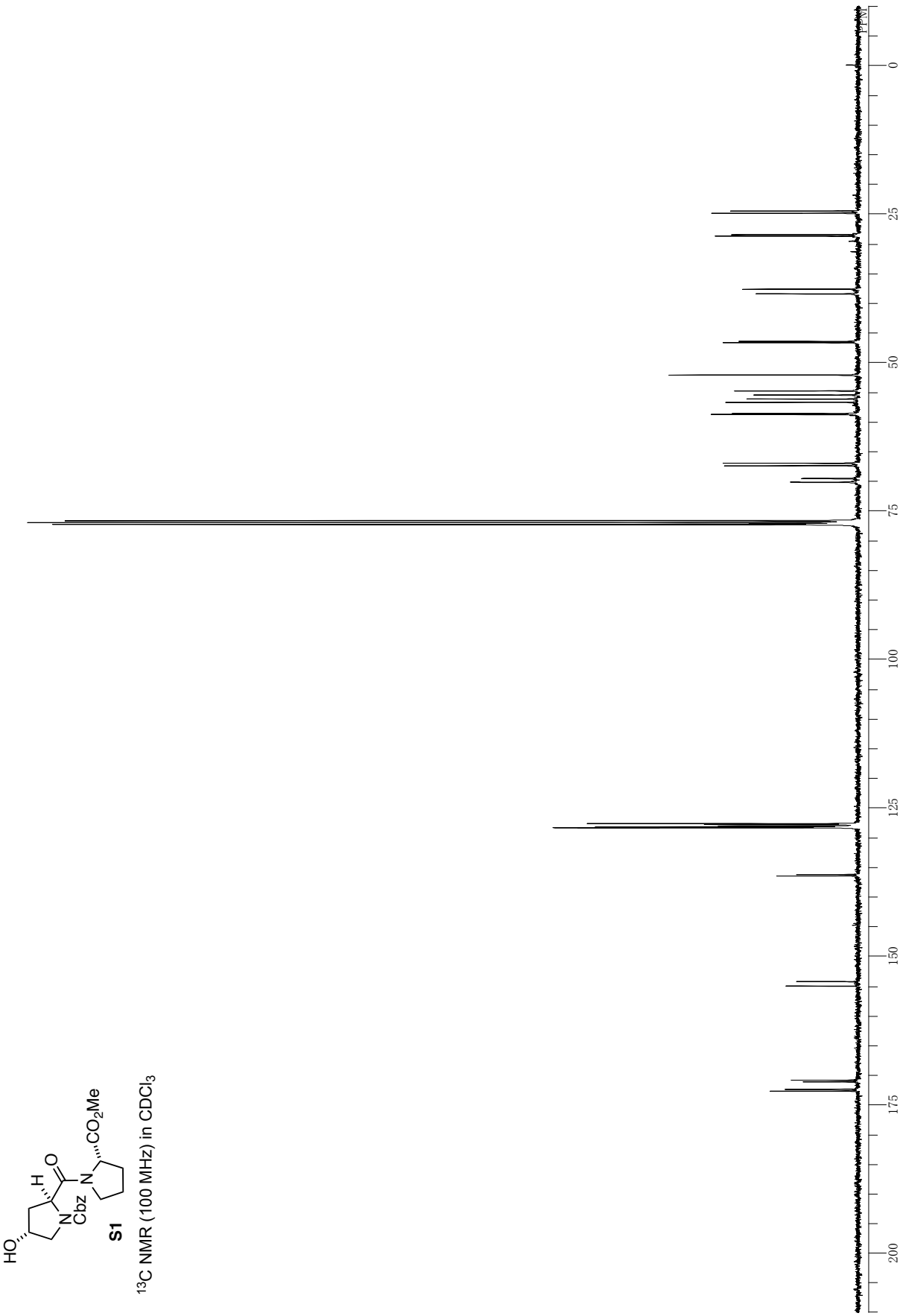
Spirotryprostatin A (1)

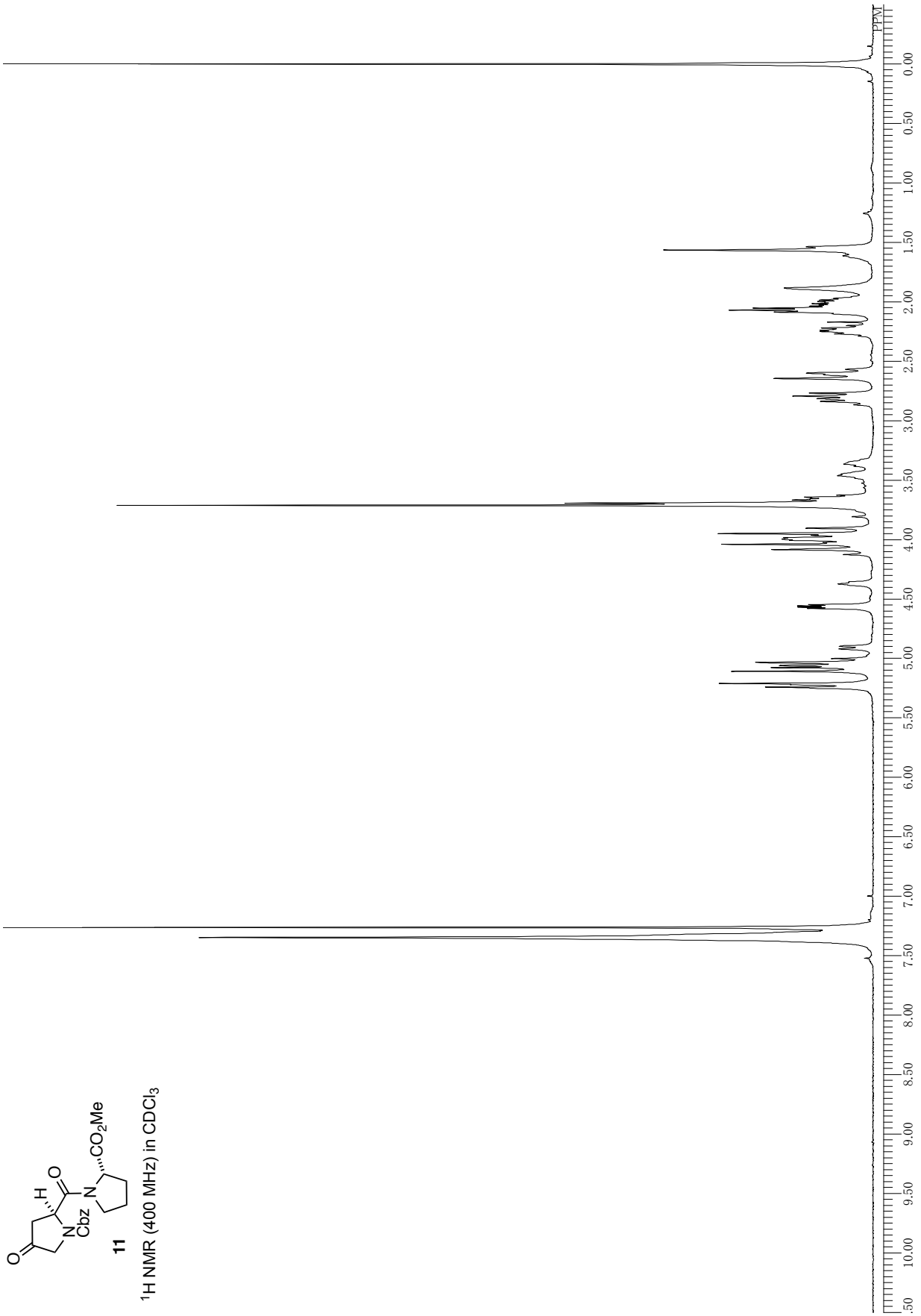


To a stirred solution of **29** (5.3 mg, 0.010 mmol) and Na_2SO_4 (5.0 mg) in toluene (1.0 mL) was added $TsOH·H_2O$ (5.9 mg, 0.030 mmol) at room temperature and the resulting mixture was stirred at refluxing temperature for 19 h. The reaction mixture was quenched with saturated $NaHCO_3$ aq. (0.5 mL) and partitioned between 17% MeOH in CH_2Cl_2 (0.5 mL) and water (0.5 mL). The organic phase was collected and the aqueous phase was extracted with 17% MeOH in CH_2Cl_2 solution (1 mL) twice. The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by PTLC (*n*-hexane/EtOAc/MeOH = 5/4/1) to afford spirotryprostatin A (**1**) (3.6 mg, 0.0091 mmol, 91%) as a clear oil.

R*f* = 0.45 (MeOH/$CHCl_3$ = 1/20, UV, PMA); $[\alpha]^{24}_D$ –109 (*c* = 0.18, $CHCl_3$); IR (neat) 2923, 1718, 1671, 1632, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 7.62 (brs, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.50 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 5.03 (dm, *J* = 10.0 Hz, 1H), 5.00 (dd, *J* = 10.5, 6.8 Hz, 1H), 4.78 (d, *J* = 10.0 Hz, 1H), 4.28 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.80 (s, 3H), 3.64–3.54 (m, 2H), 2.61 (dd, *J* = 13.3, 10.5 Hz, 1H), 2.39 (dd, *J* = 13.3, 6.8 Hz, 1H), 2.37–2.25 (m, 2H), 2.08–1.91 (m, 2H), 1.65 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 180.8 (C), 167.1 (C), 166.9 (C), 160.4 (C), 141.6 (C), 138.4 (C), 127.3 (CH), 121.3 (CH), 118.7 (C), 106.7 (CH), 96.6 (CH), 61.0 (CH), 60.2 (CH), 60.2(C), 58.5 (CH), 55.5 (CH_3), 45.2 (CH_2), 34.3 (CH_2), 27.4 (CH_2), 25.5 (CH_3), 23.7 (CH_2), 18.0 (CH_3); HRMS (ESI) calcd for $C_{22}H_{25}O_4N_3Na$ ($[M+Na]^+$) 418.1743, found 418.1758.


HO
H
O
N
Cbz
N
CO2Me
S1
1H NMR (400 MHz) in CDCl3
PPM
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
8.00
8.50
9.00
9.50
10.00


HO
H
O
N
Cbz
N
CO2Me
S1
13C NMR (100 MHz) in CDCl3
200
175
150
125
100
75
50
25
0

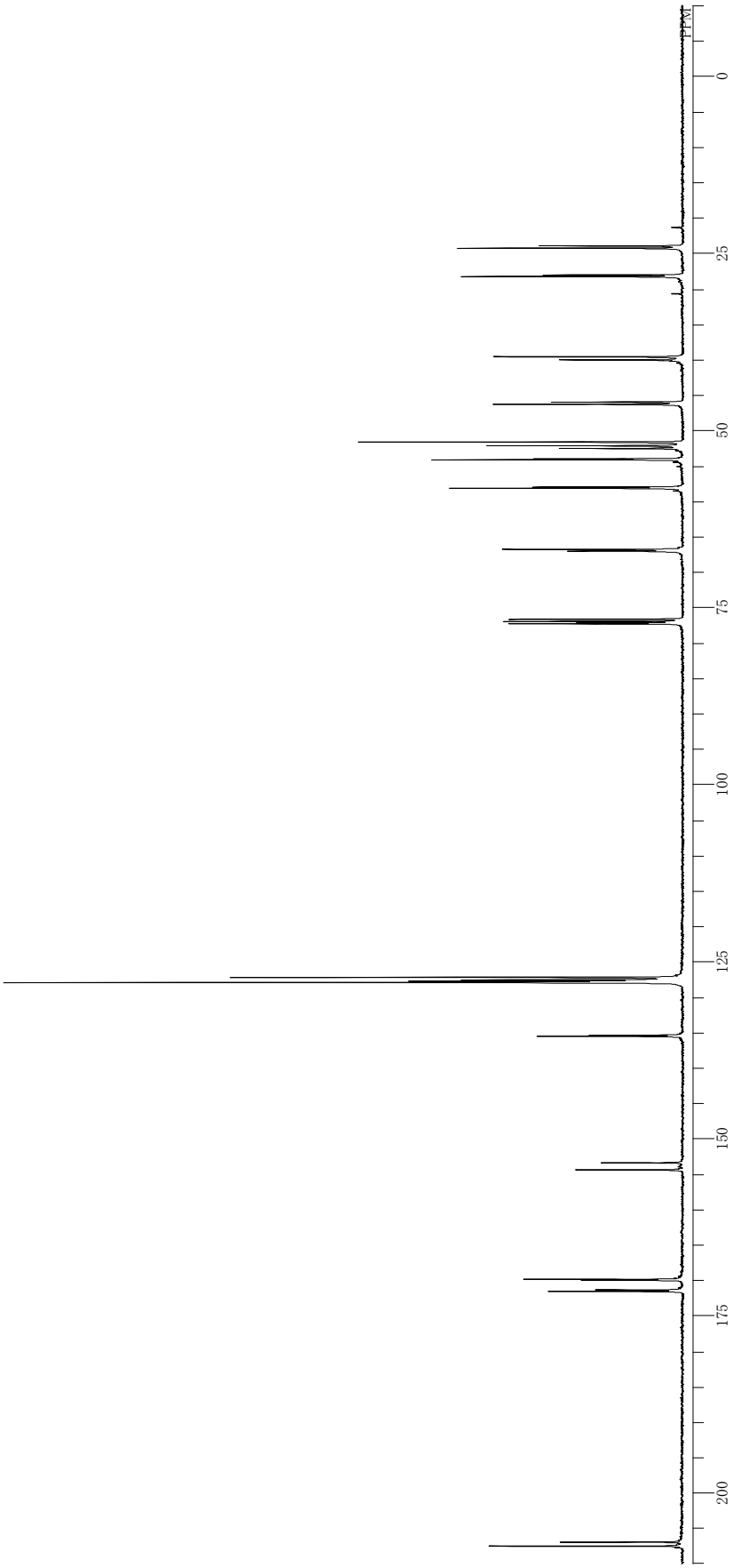


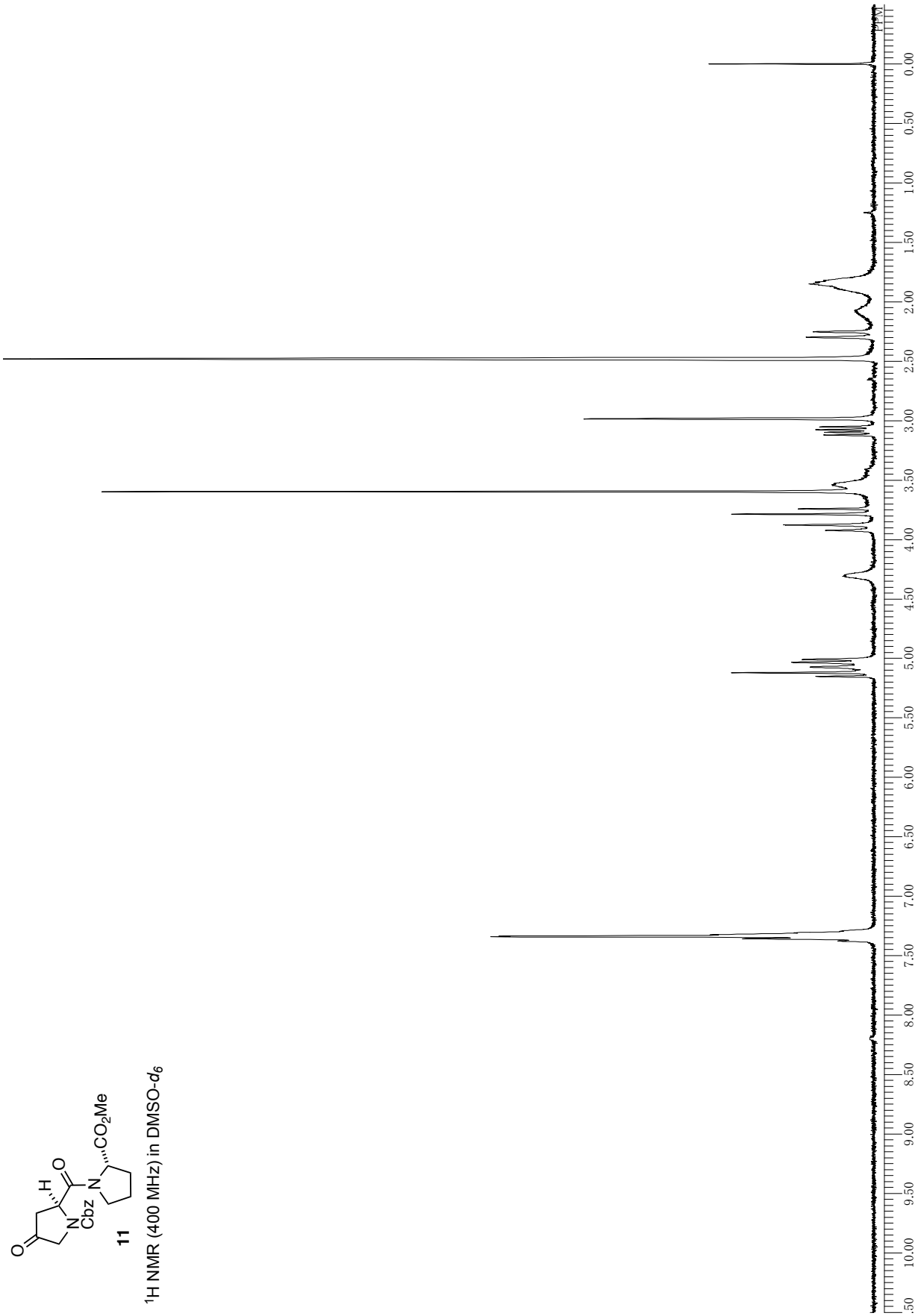
11

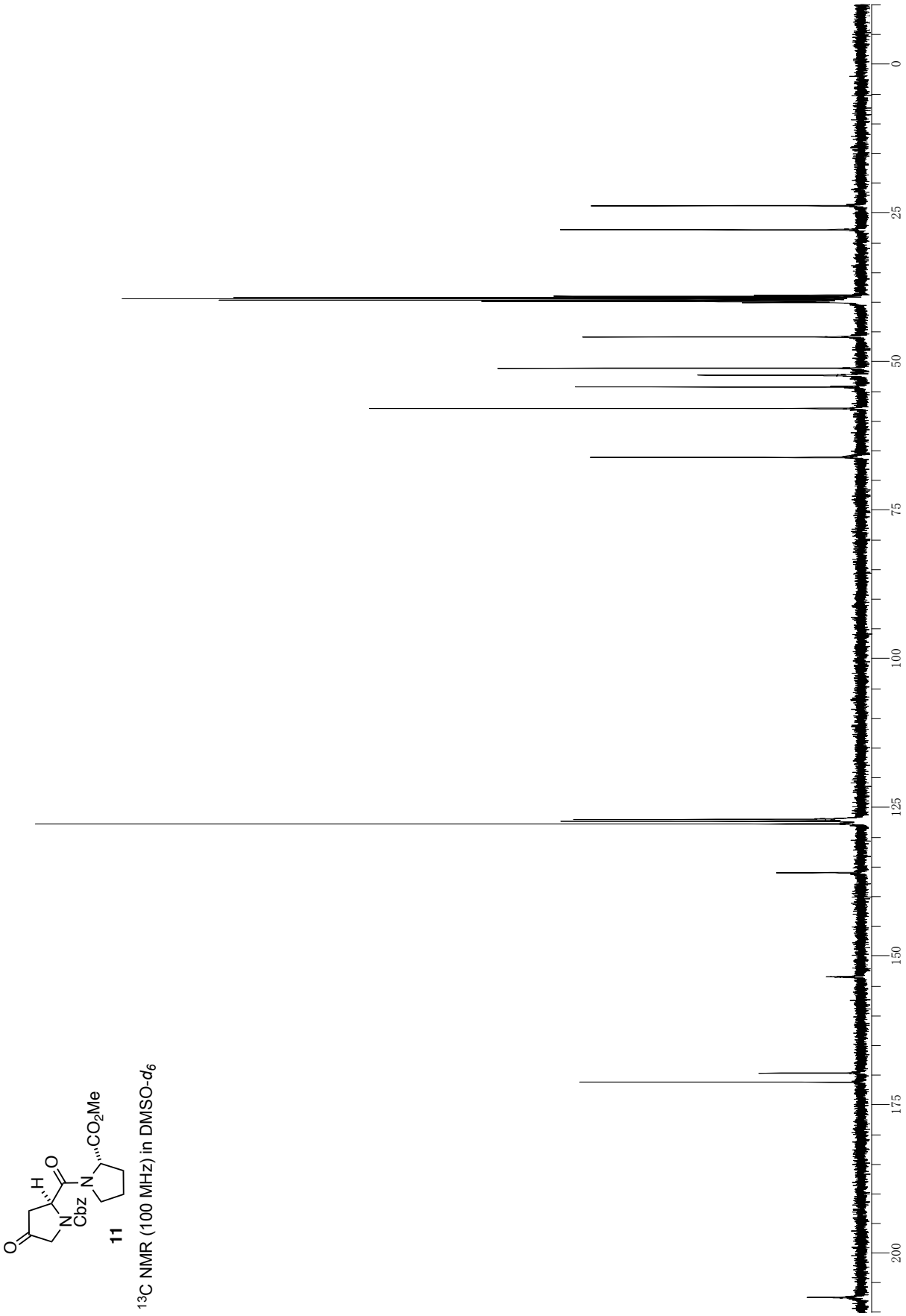
^{1}H NMR (400 MHz) in $CDCl_3$

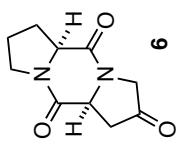
11

^{13}C NMR (100 MHz) in $CDCl_3$



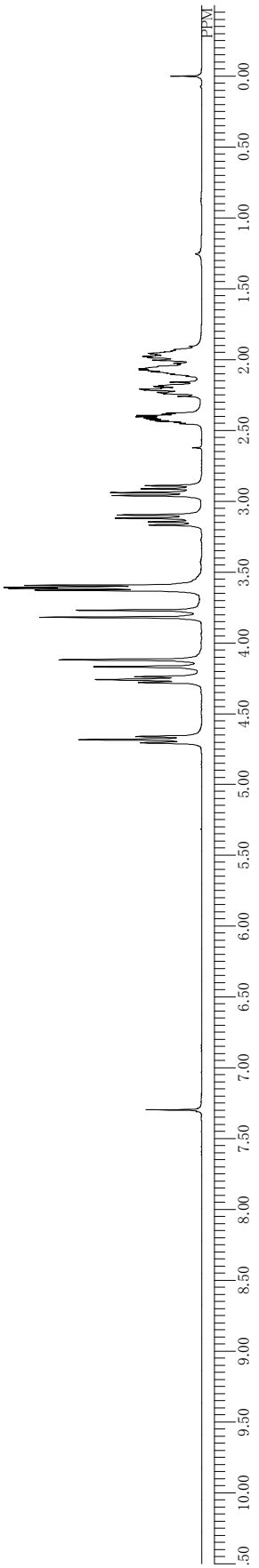

CO2Me
H
O
N
Cbz
N
O
11
1H NMR (400 MHz) in DMSO-d6
11.50
10.00
9.50
9.00
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

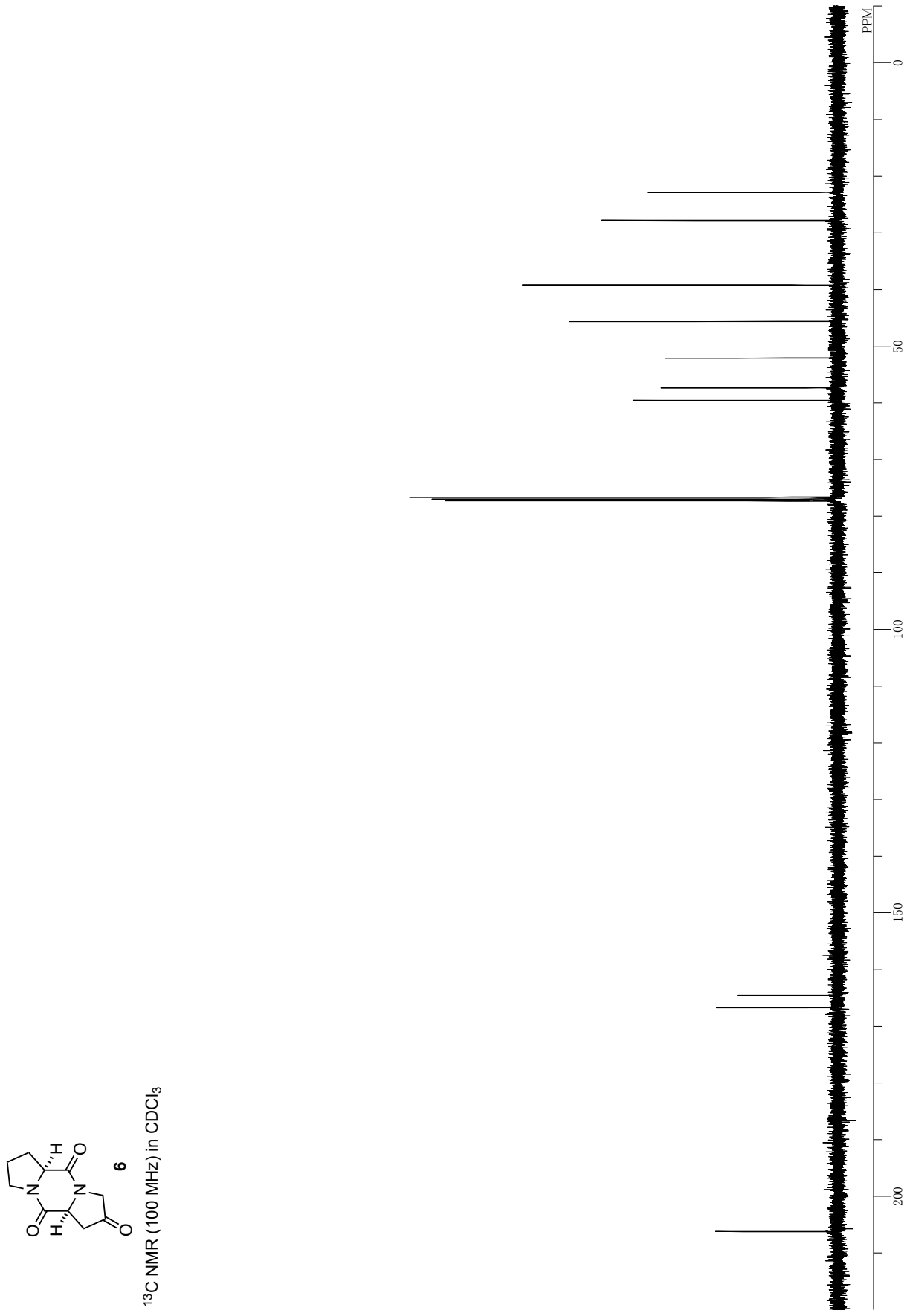

0
25
50
75
100
125
150
175
200
CO2Me
H
O
N
Cbz
N
O
11
13C NMR (100 MHz) in DMSO-d6



6

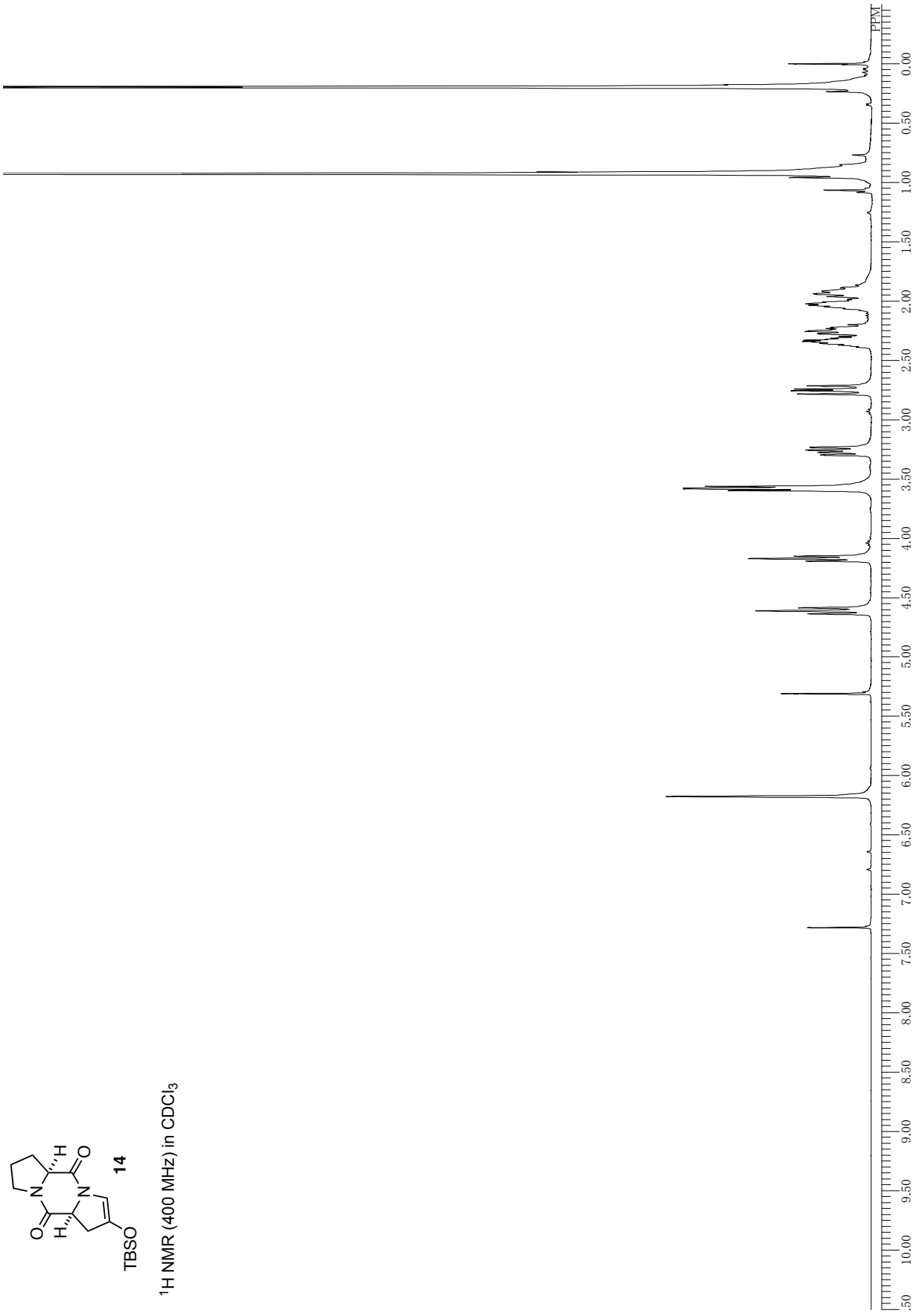
^{1}H NMR (400 MHz) in $CDCl_3$





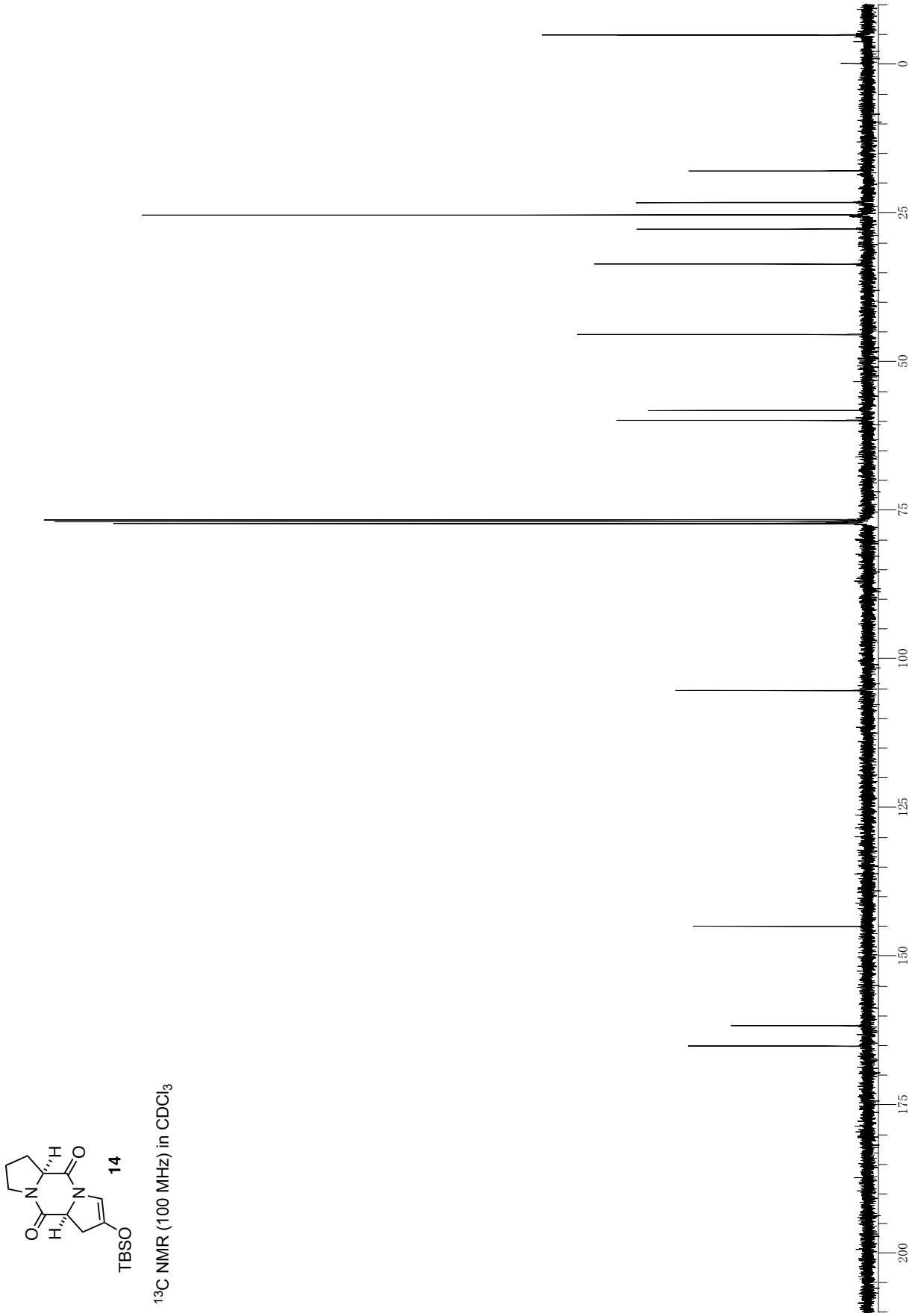
6

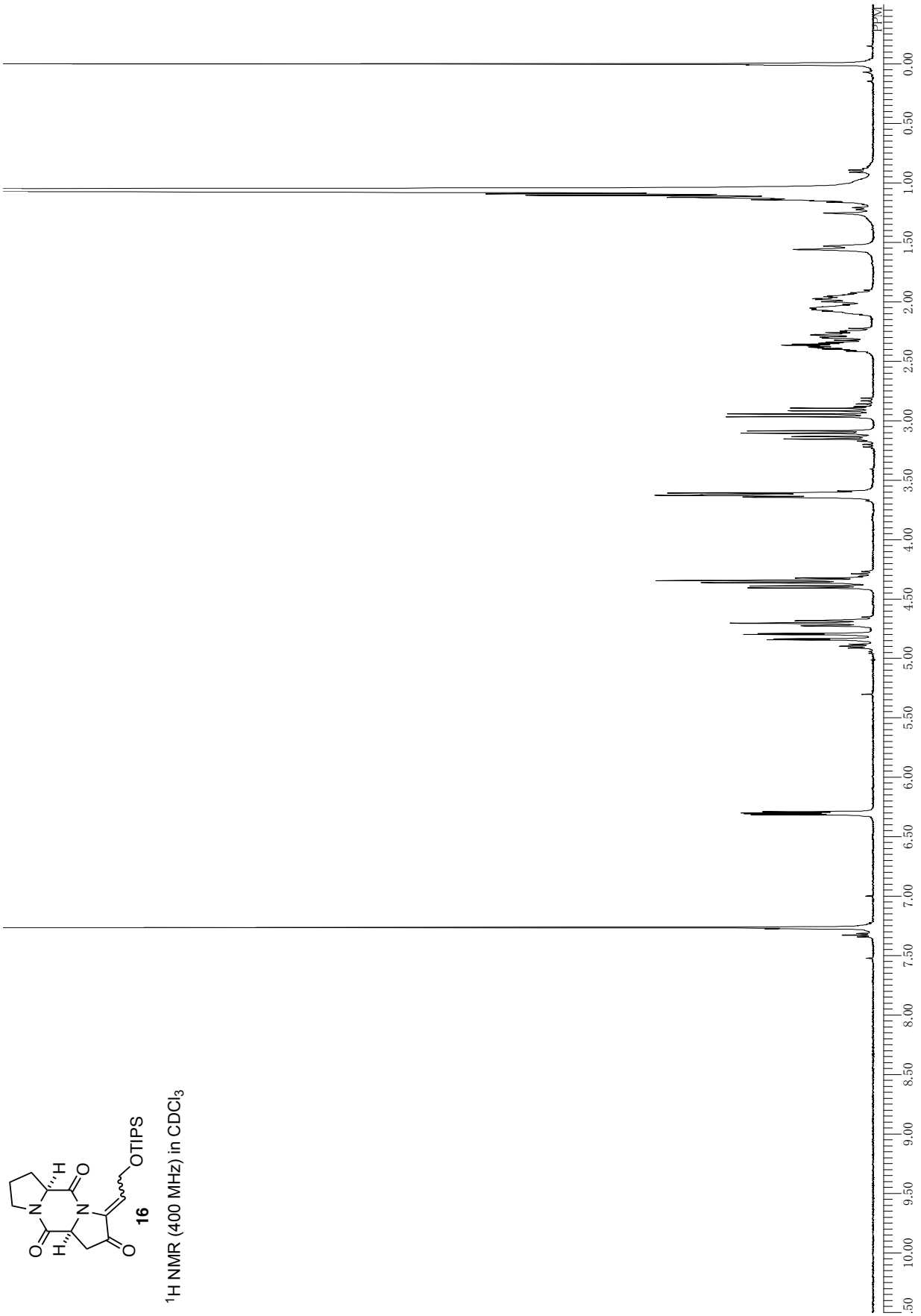
^{13}C NMR (100 MHz) in $CDCl_3$

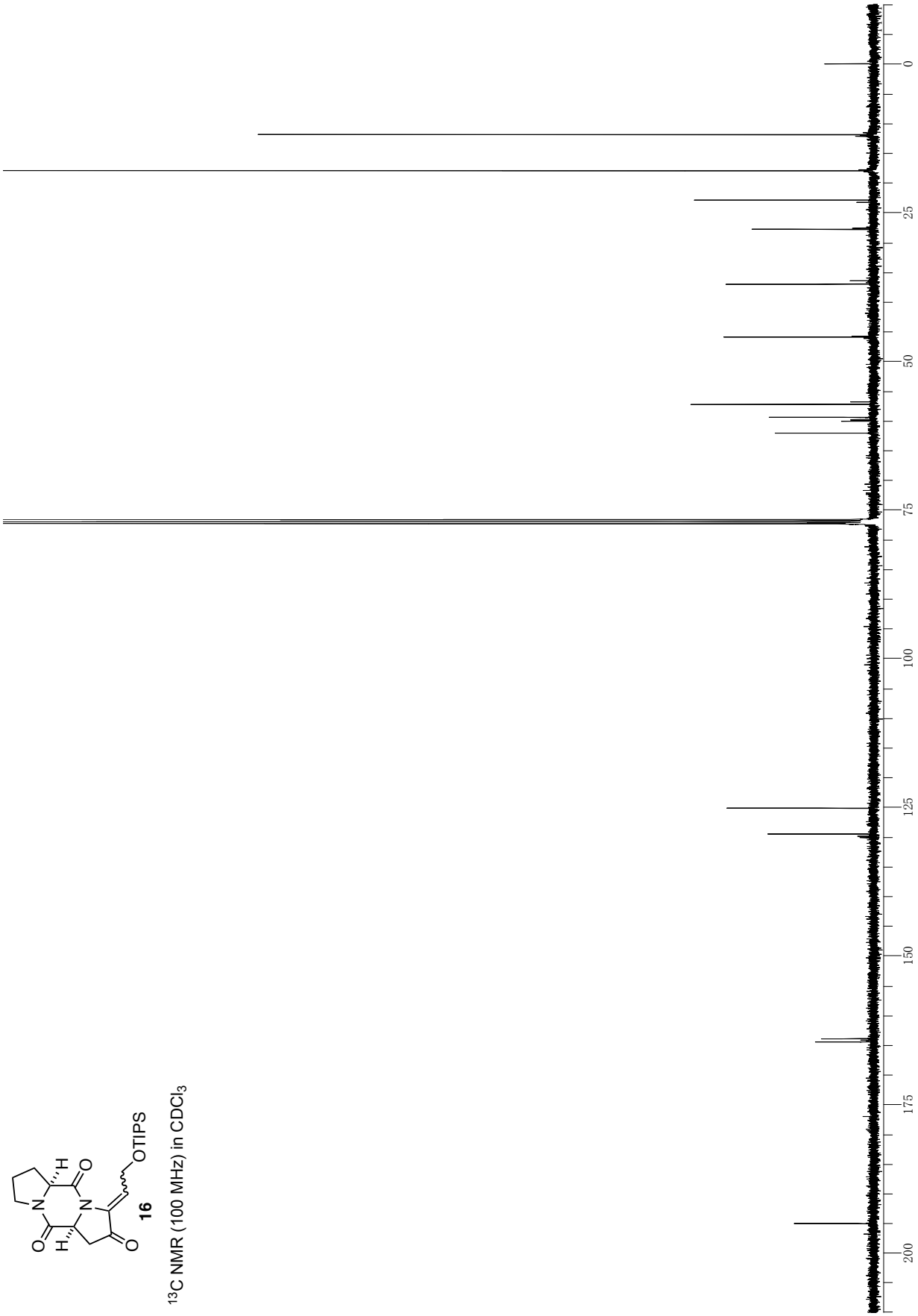


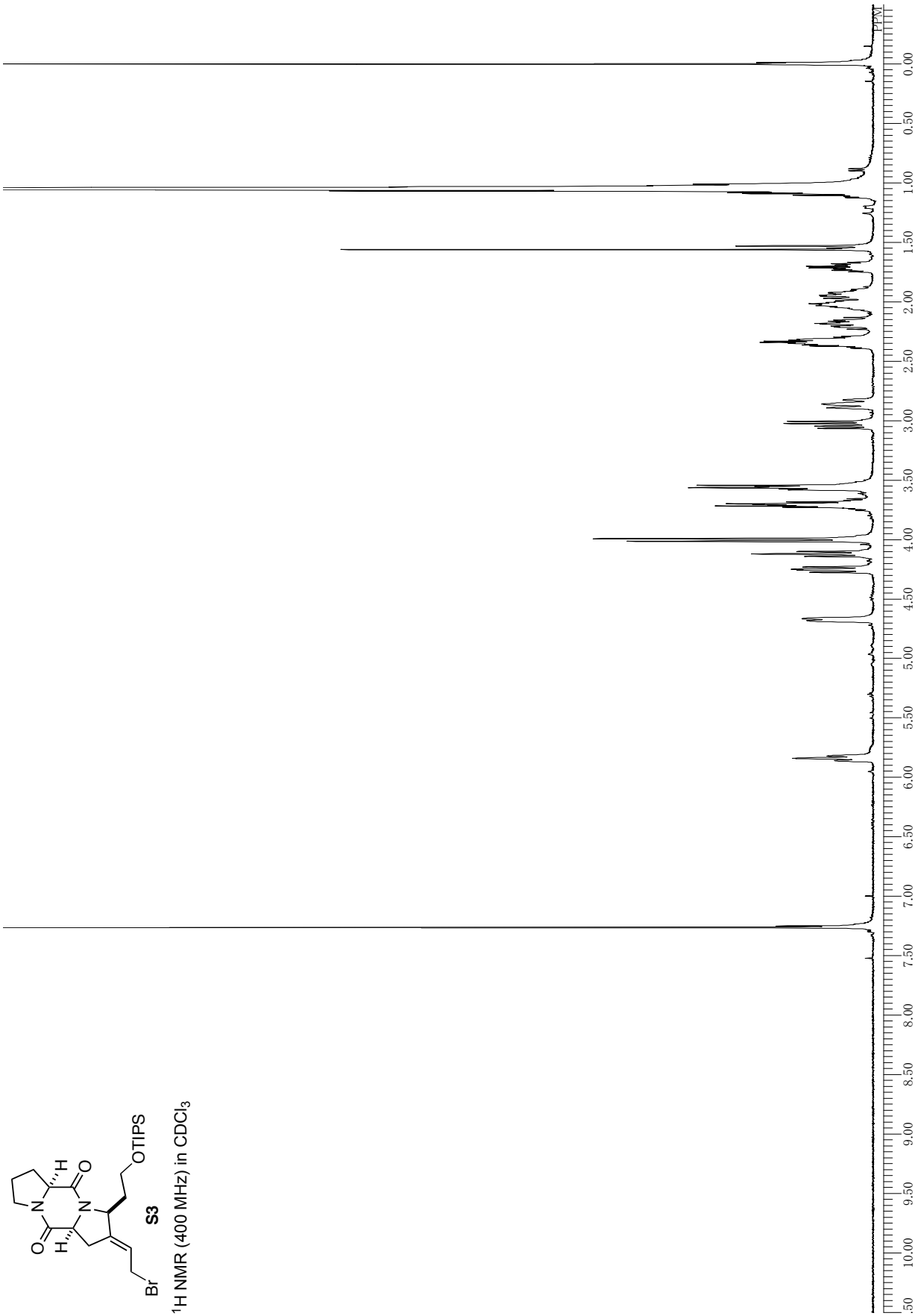
14

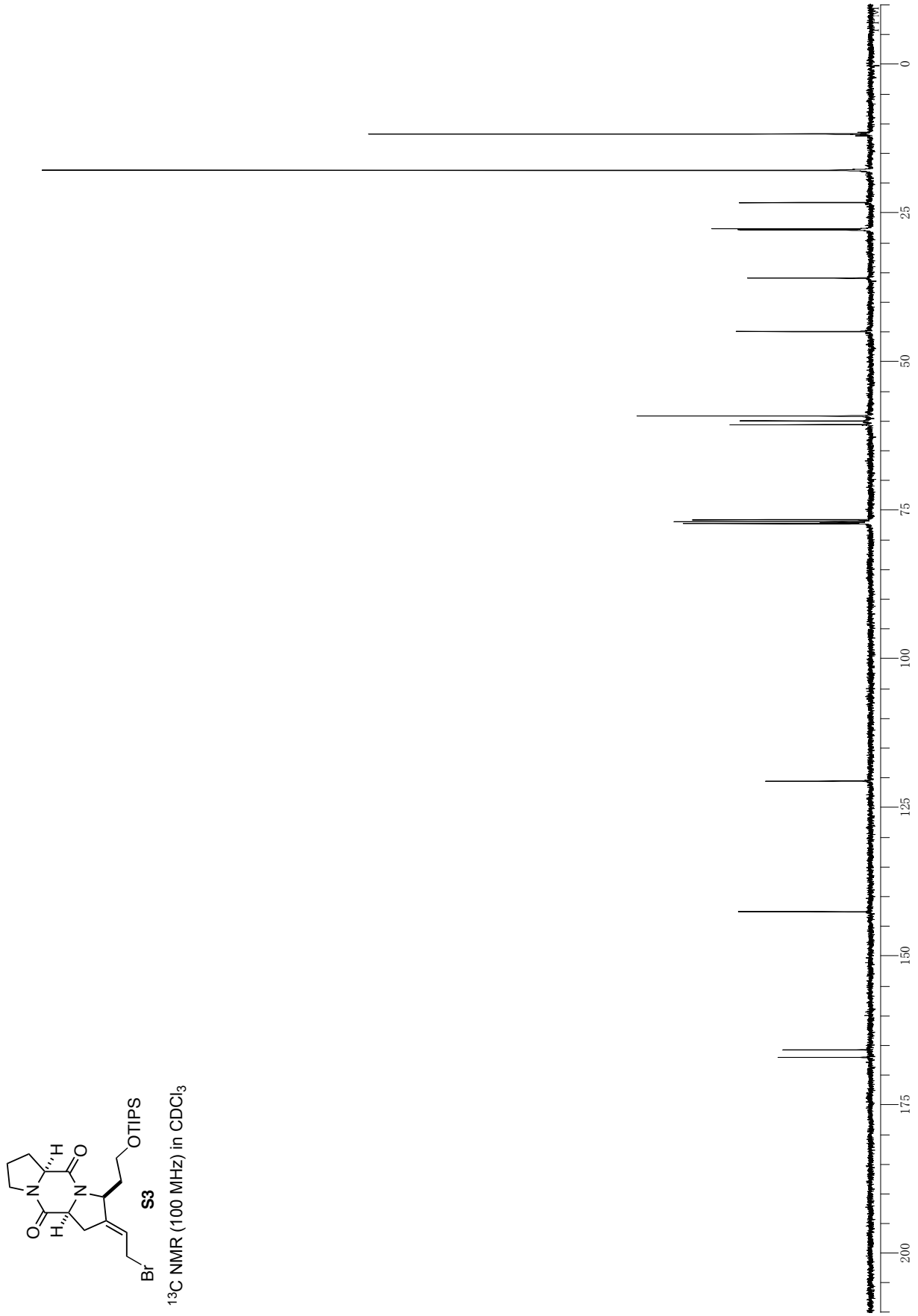
^{1}H NMR (400 MHz) in $CDCl_3$

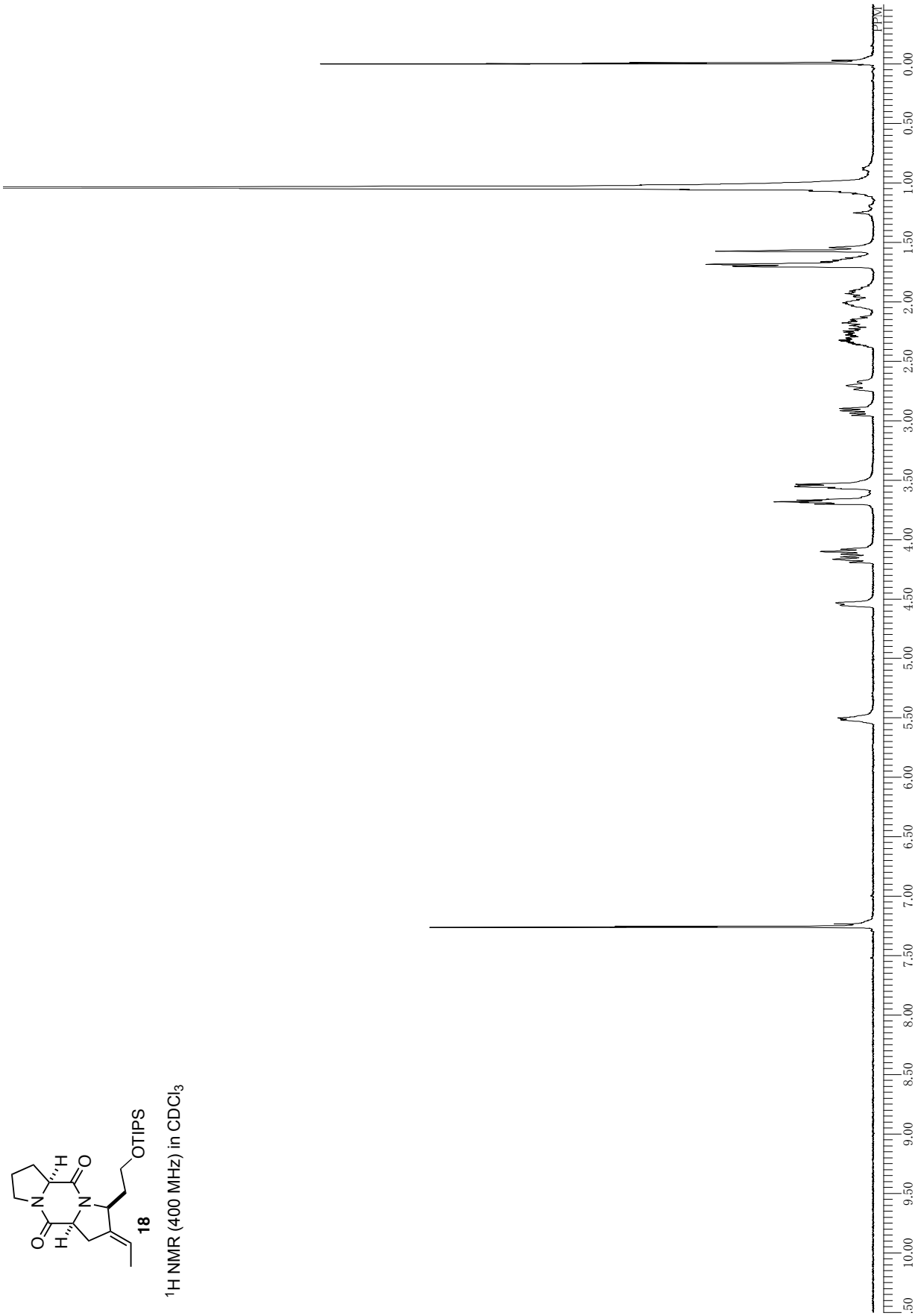

14
TBSO
^{13}C NMR (100 MHz) in $CDCl_3$
0
25
50
75
100
125
150
175
200


OTIPS
16
^{1}H NMR (400 MHz) in $CDCl_3$
PPM
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
8.00
8.50
9.00
9.50
10.00


OTIPS
16
^{13}C NMR (100 MHz) in $CDCl_3$
0
25
50
75
100
125
150
175
200

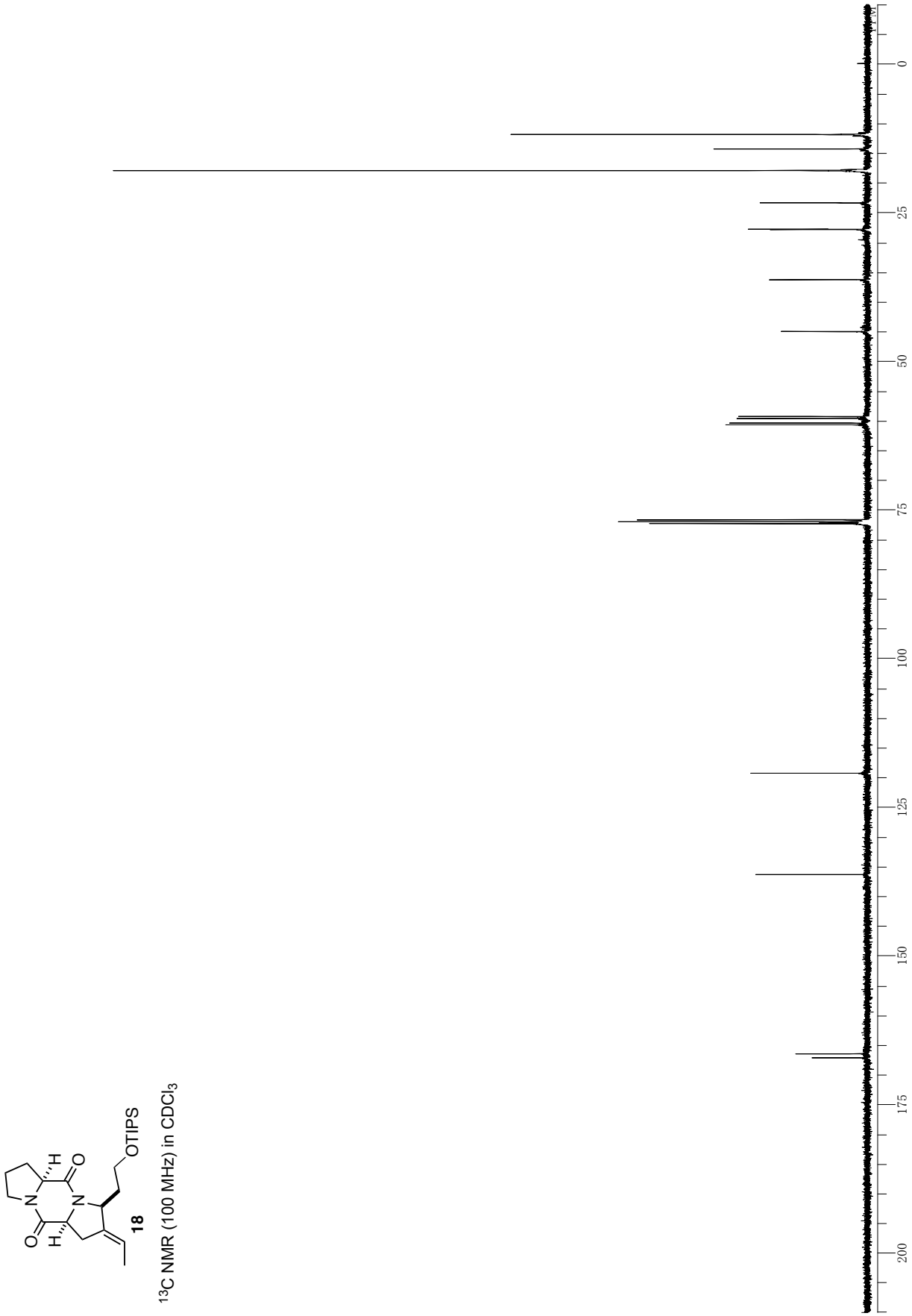

PPM
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
8.00
8.50
9.00
9.50
10.00
.50
OTIPS
Br
S3
^{1}H NMR (400 MHz) in $CDCl_3$

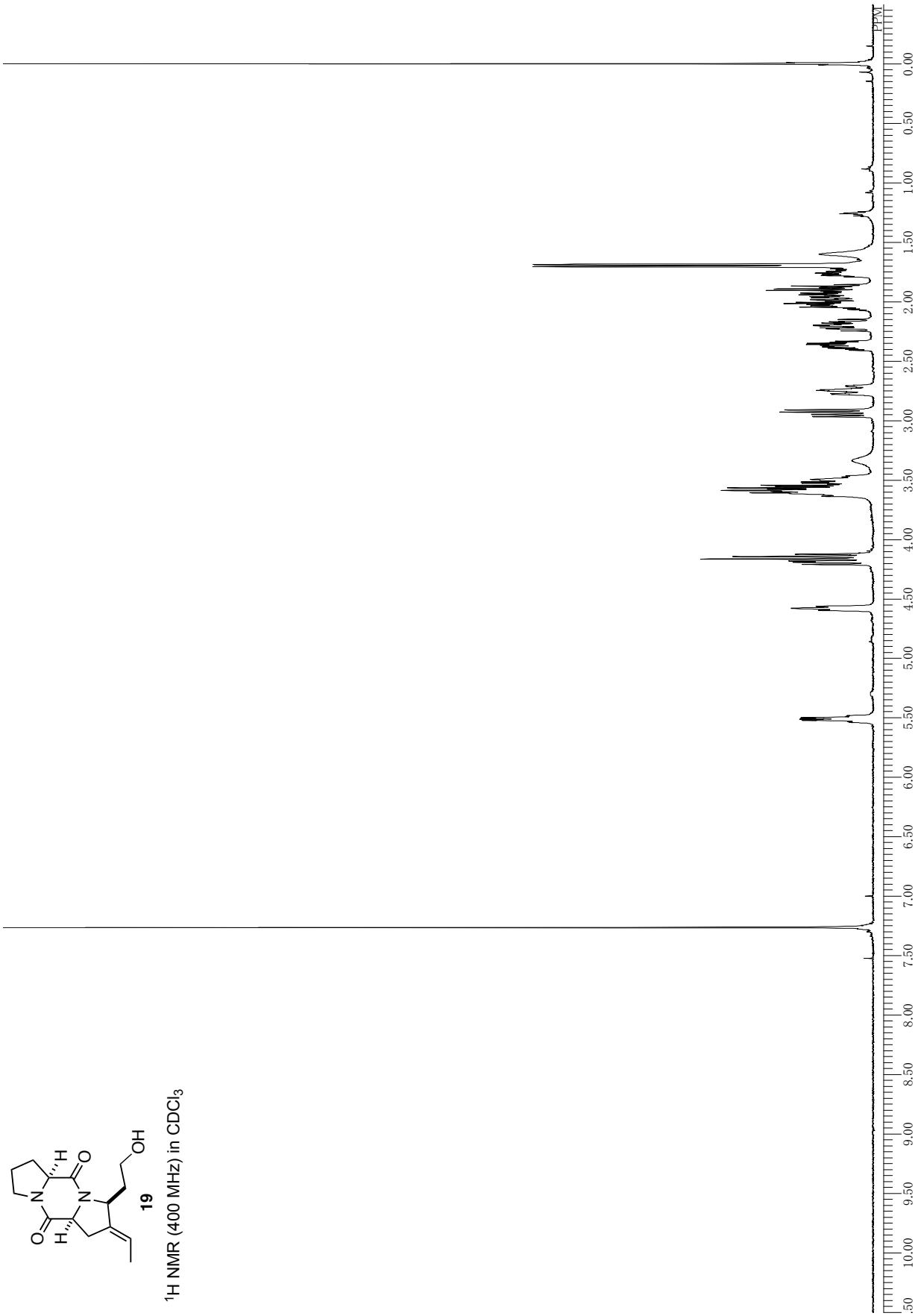

OTIPS
Br
S3
^{13}C NMR (100 MHz) in $CDCl_3$
200
175
150
125
100
75
50
25
0



18

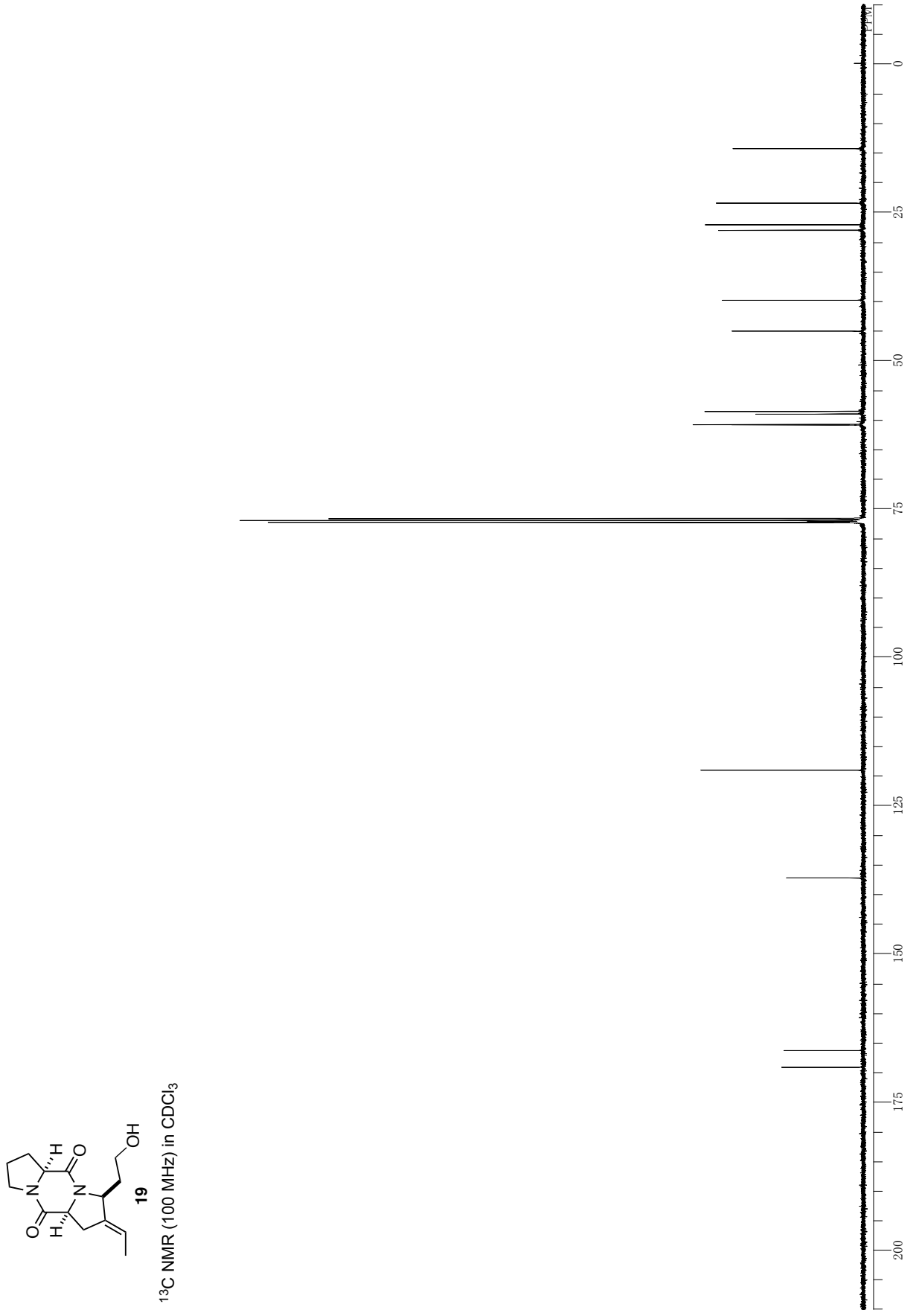
^{1}H NMR (400 MHz) in $CDCl_3$

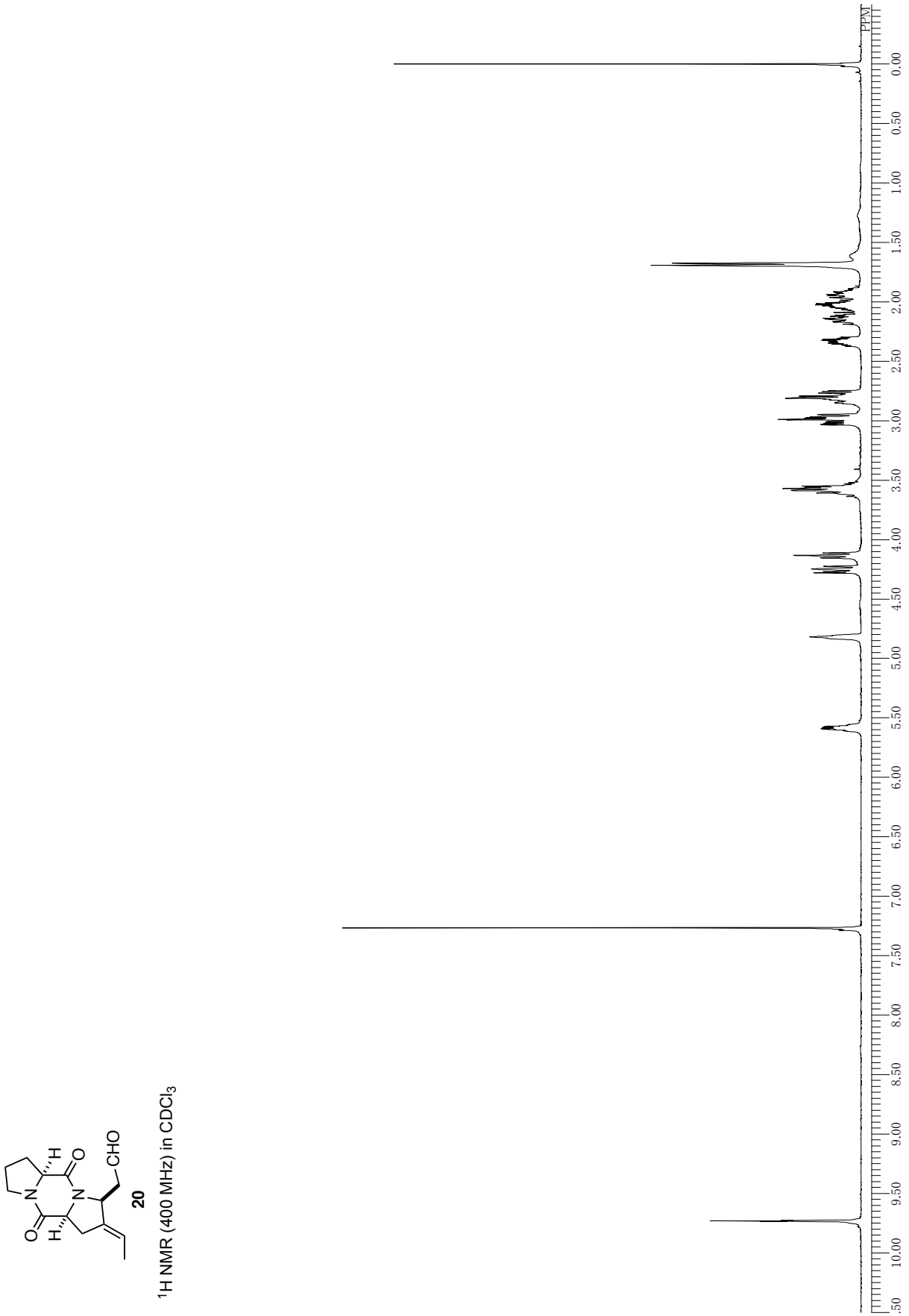

OTIPS
18
^{13}C NMR (100 MHz) in $CDCl_3$
0
25
50
75
100
125
150
175
200



19

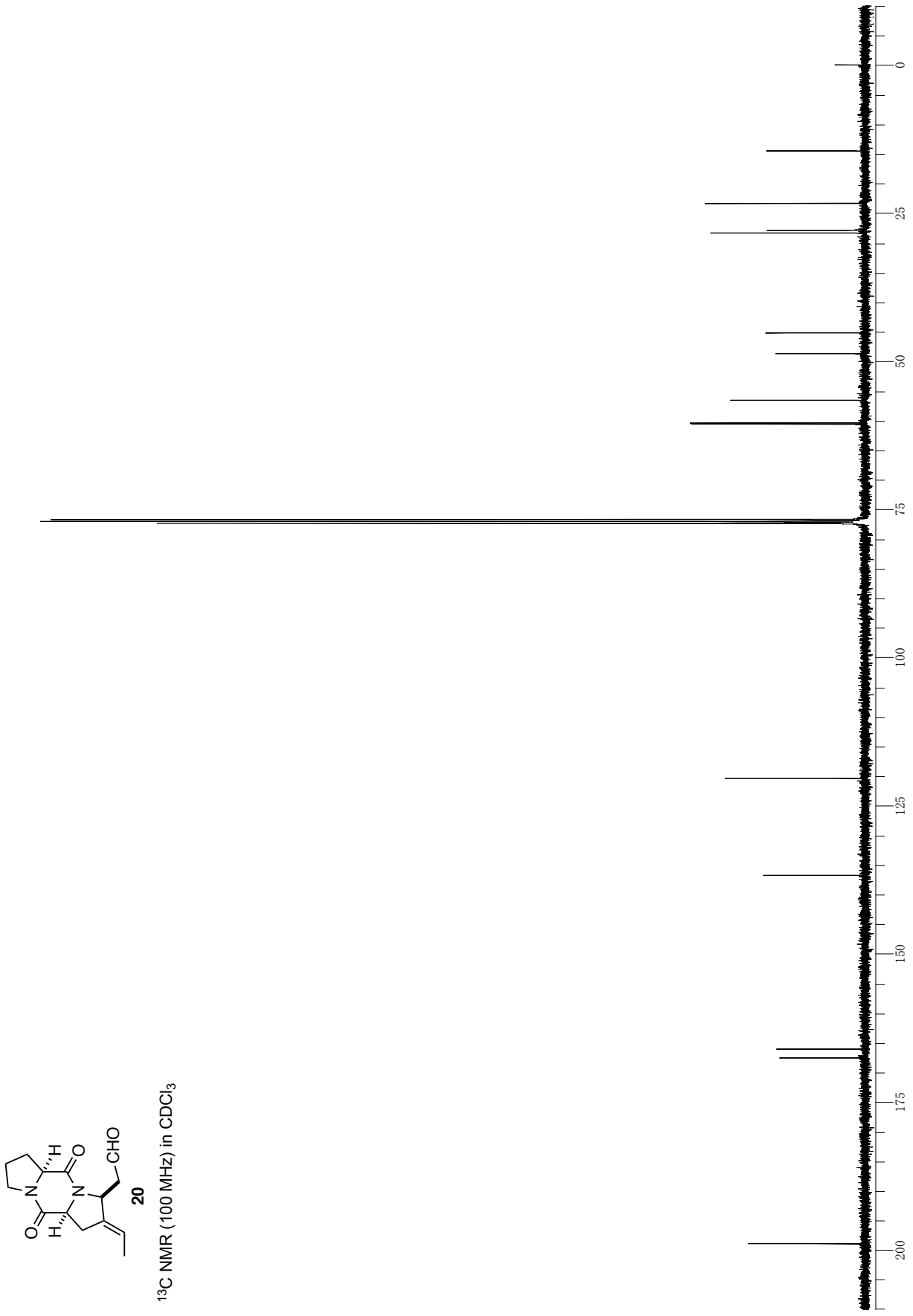
^{1}H NMR (400 MHz) in $CDCl_3$

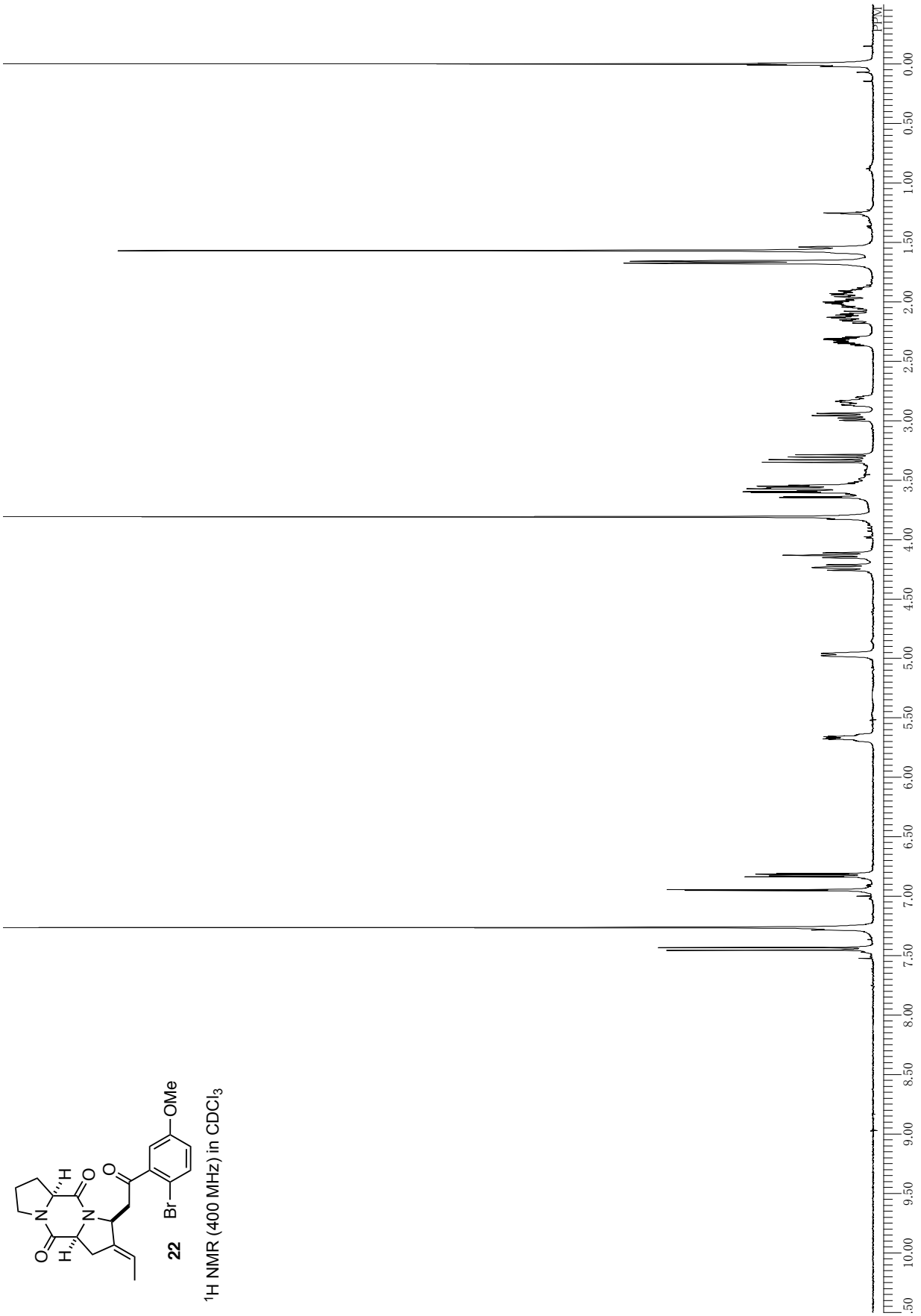

OH
H
O
N
N
H
O
19
^{13}C NMR (100 MHz) in $CDCl_3$
0
25
50
75
100
125
150
175
200



20

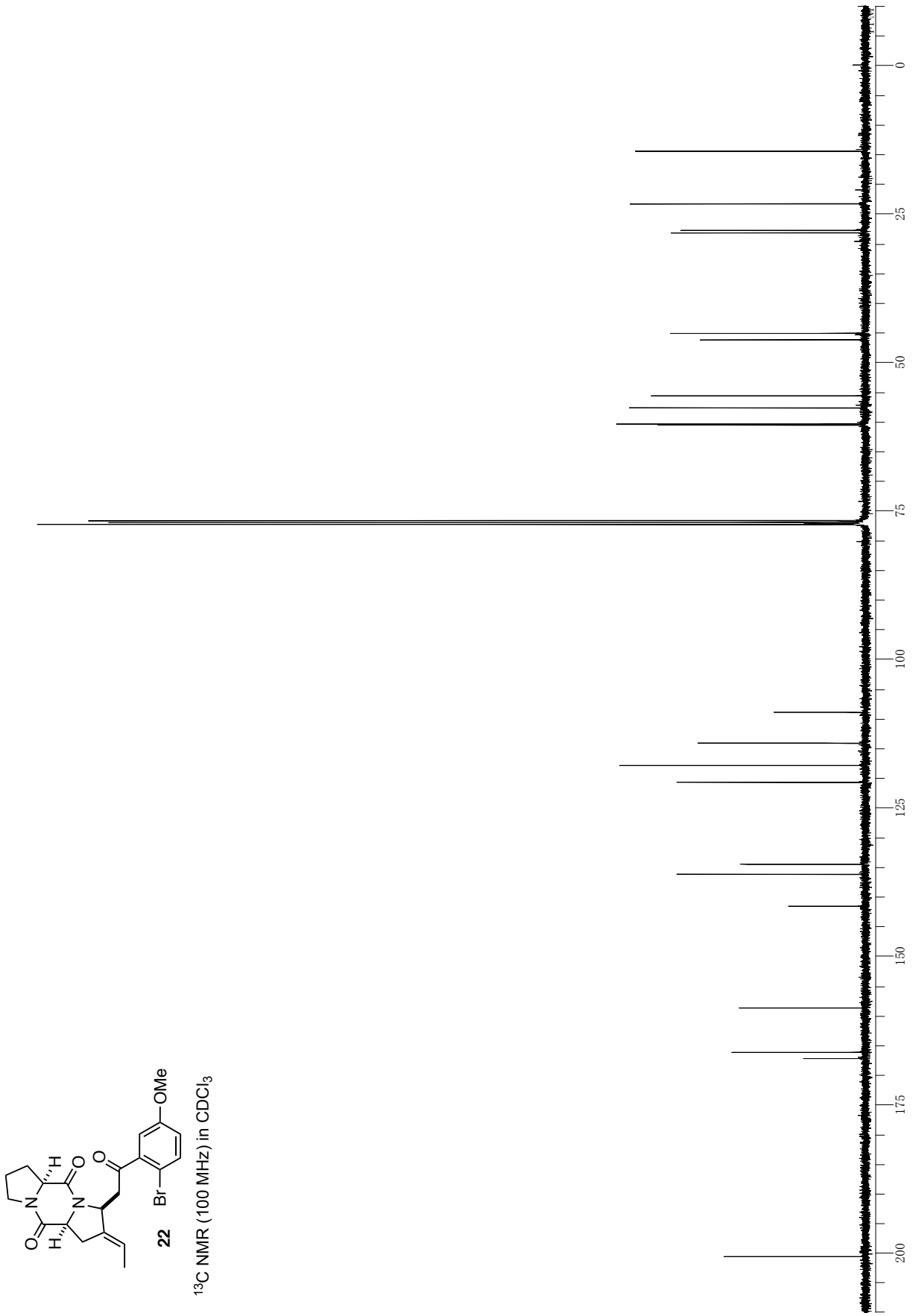
^{1}H NMR (400 MHz) in $CDCl_3$


CHO
H
O
N
N
O
H
20
^{13}C NMR (100 MHz) in $CDCl_3$
0
25
50
75
100
125
150
175
200



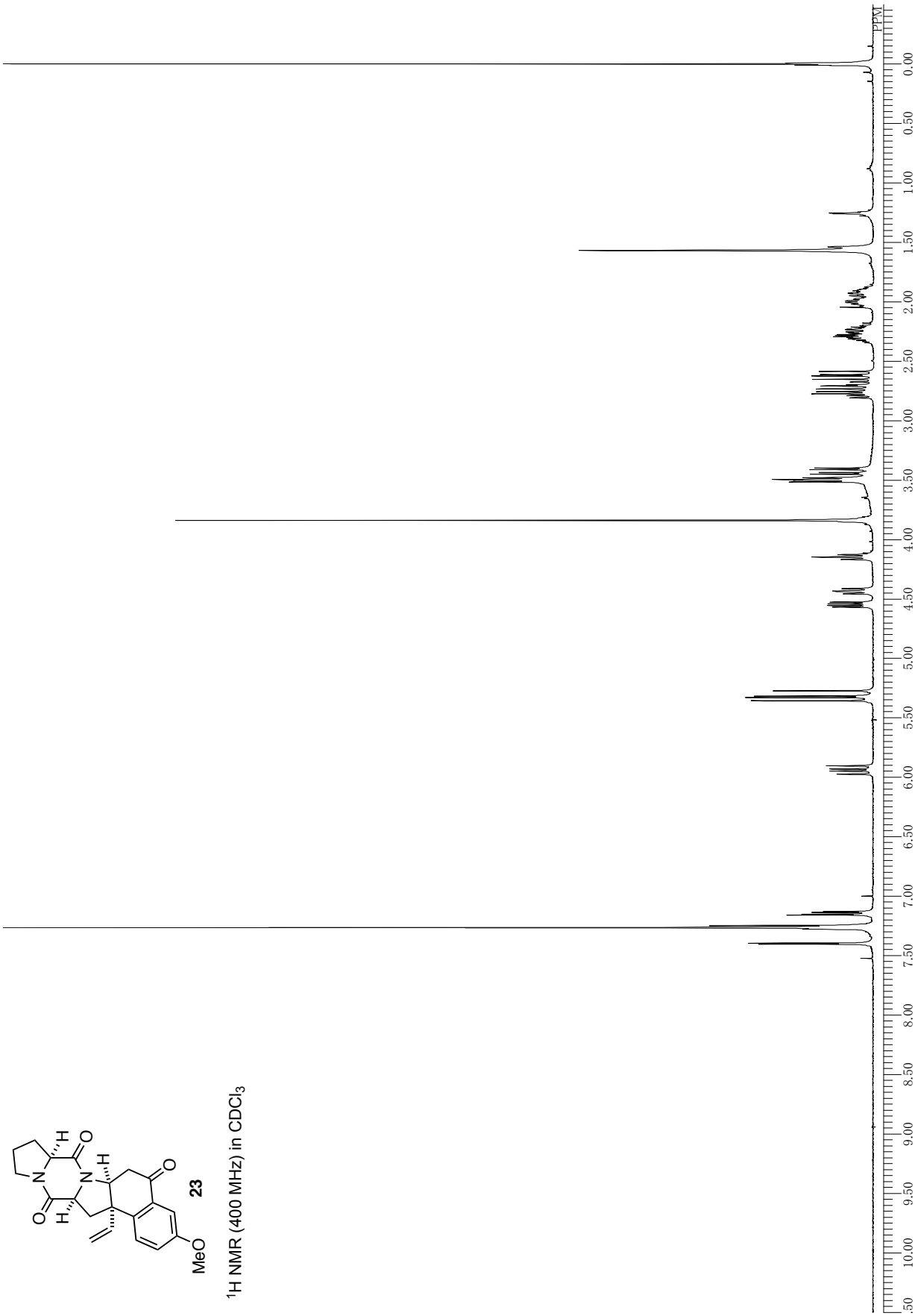
22

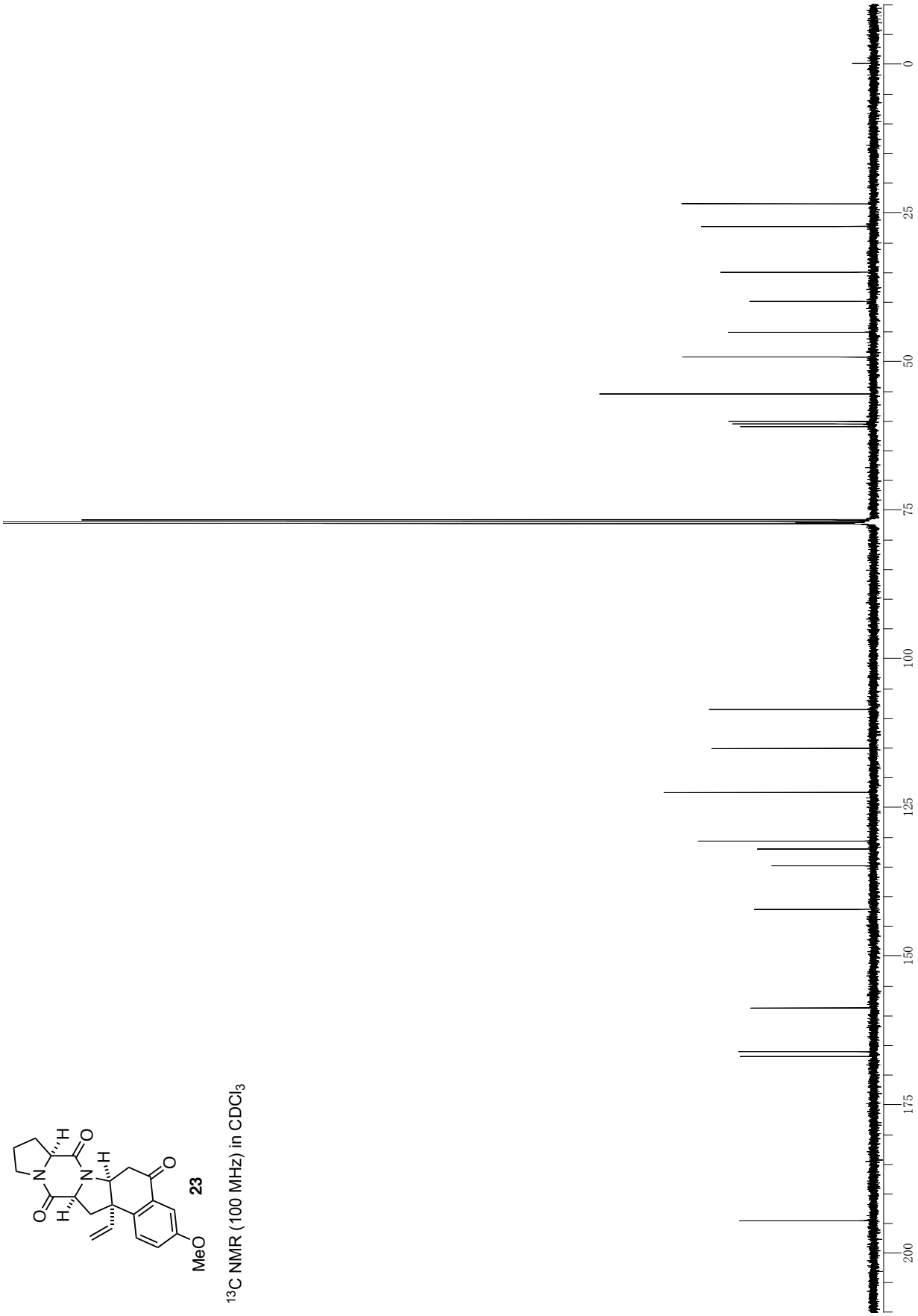
^{1}H NMR (400 MHz) in $CDCl_3$



22

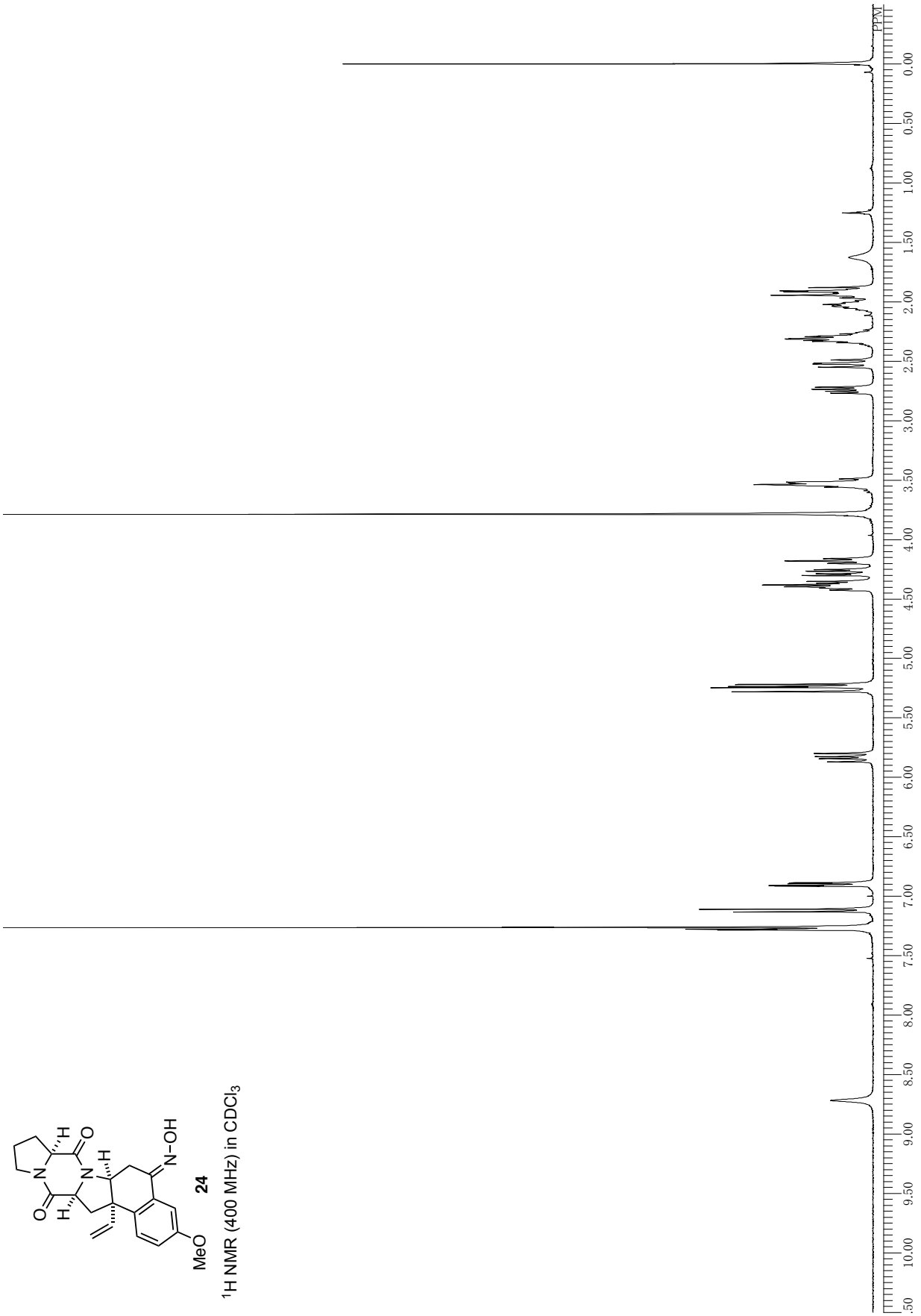
^{13}C NMR (100 MHz) in $CDCl_3$


MeO
23
^{1}H NMR (400 MHz) in $CDCl_3$
PPM
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
8.00
8.50
9.00
9.50
10.00



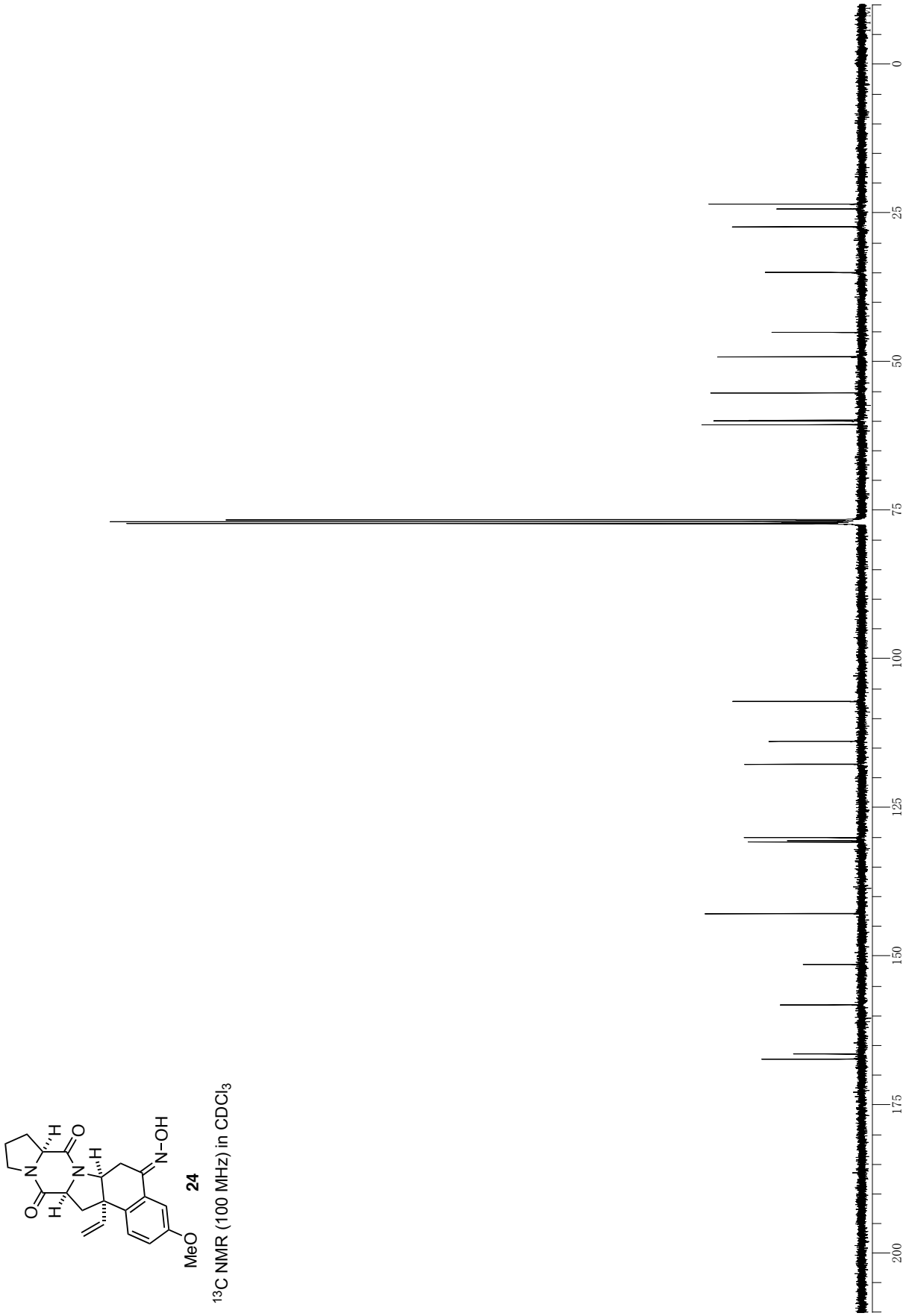
23

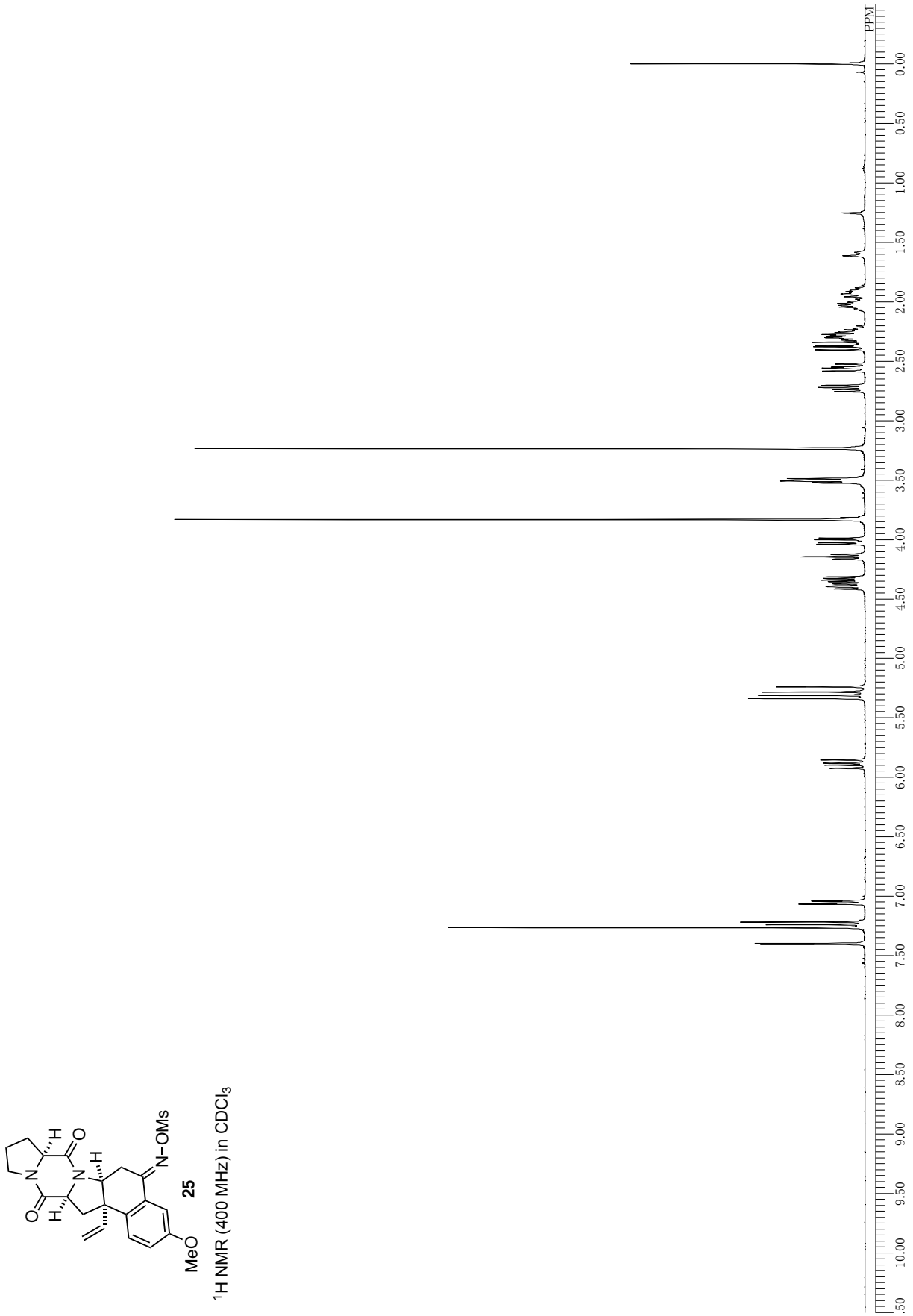
^{13}C NMR (100 MHz) in $CDCl_3$



24

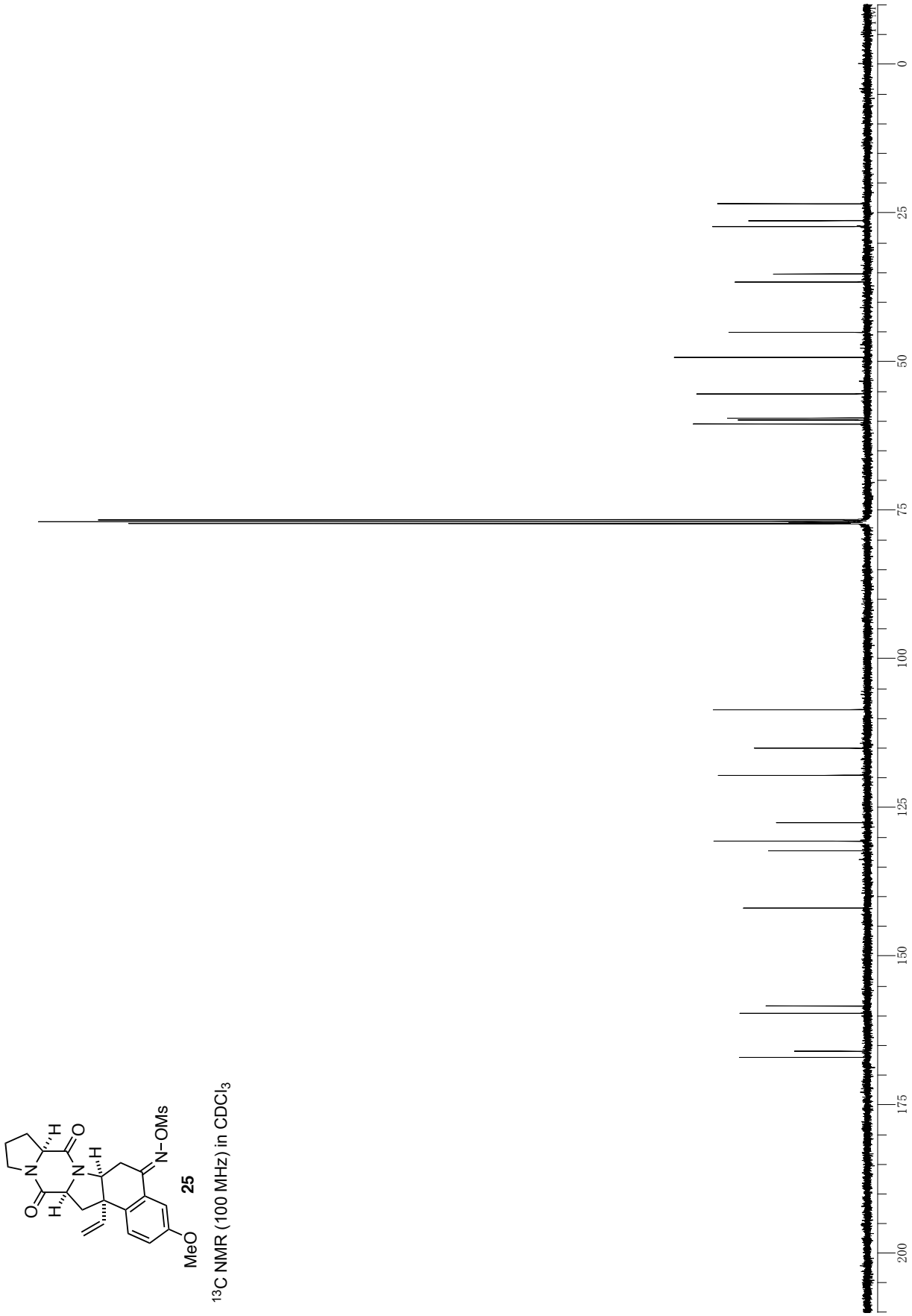
^{1}H NMR (400 MHz) in $CDCl_3$

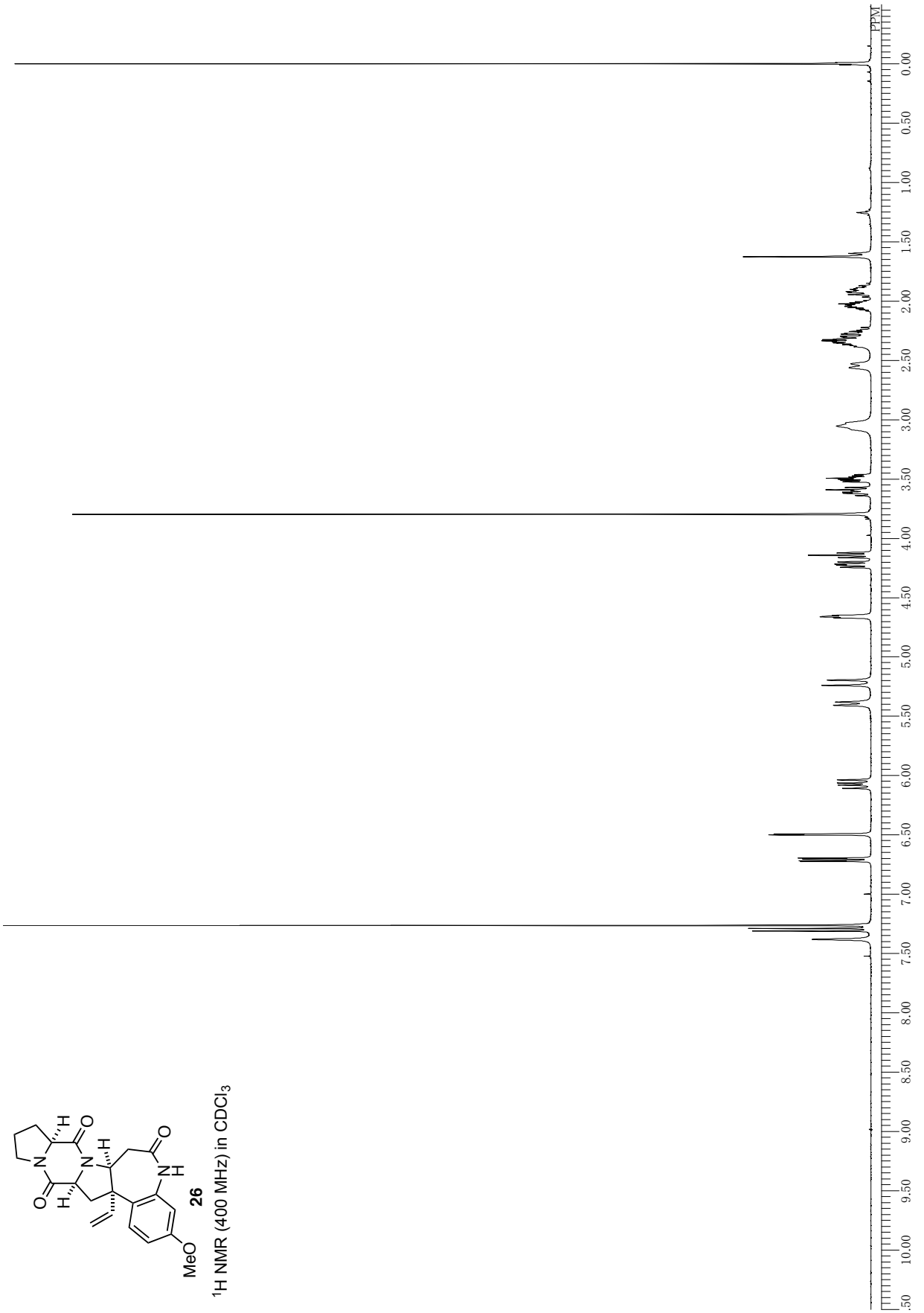

N–OH
MeO
24
^{13}C NMR (100 MHz) in $CDCl_3$
200
175
150
125
100
75
50
25
0



25

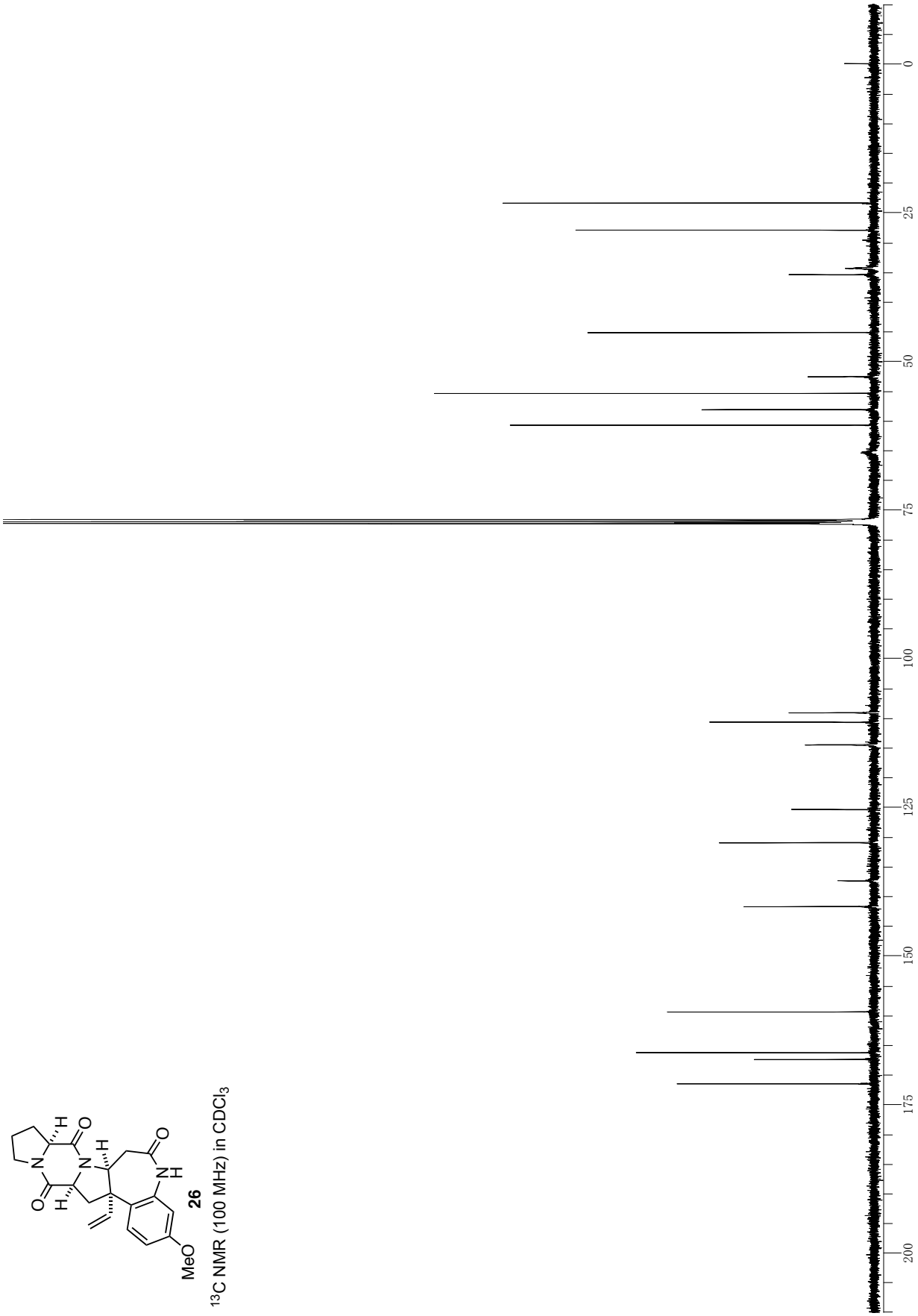
^{1}H NMR (400 MHz) in $CDCl_3$


N–OMs
MeO
25
^{13}C NMR (100 MHz) in $CDCl_3$
0
25
50
75
100
125
150
175
200



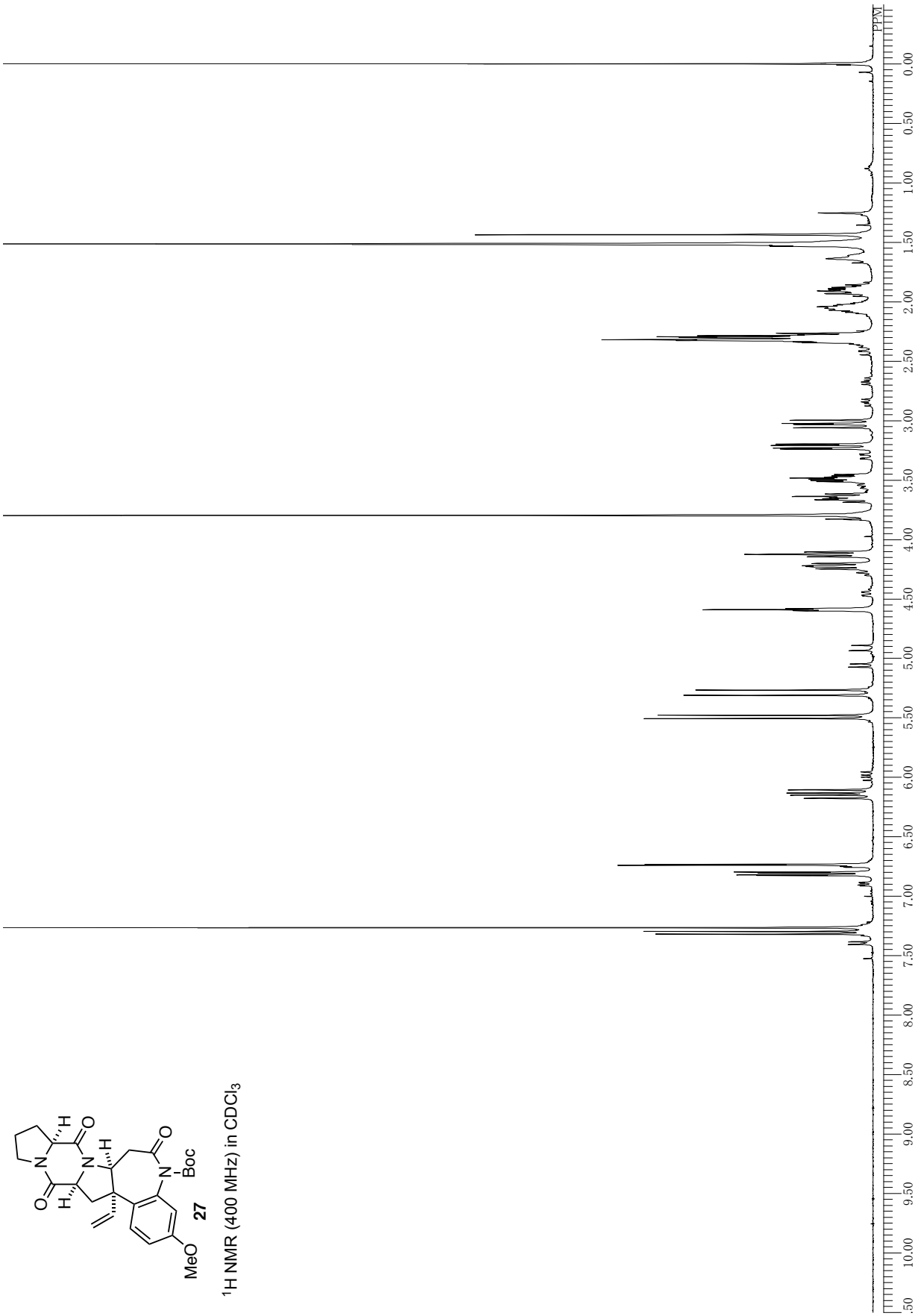
26

^{1}H NMR (400 MHz) in $CDCl_3$



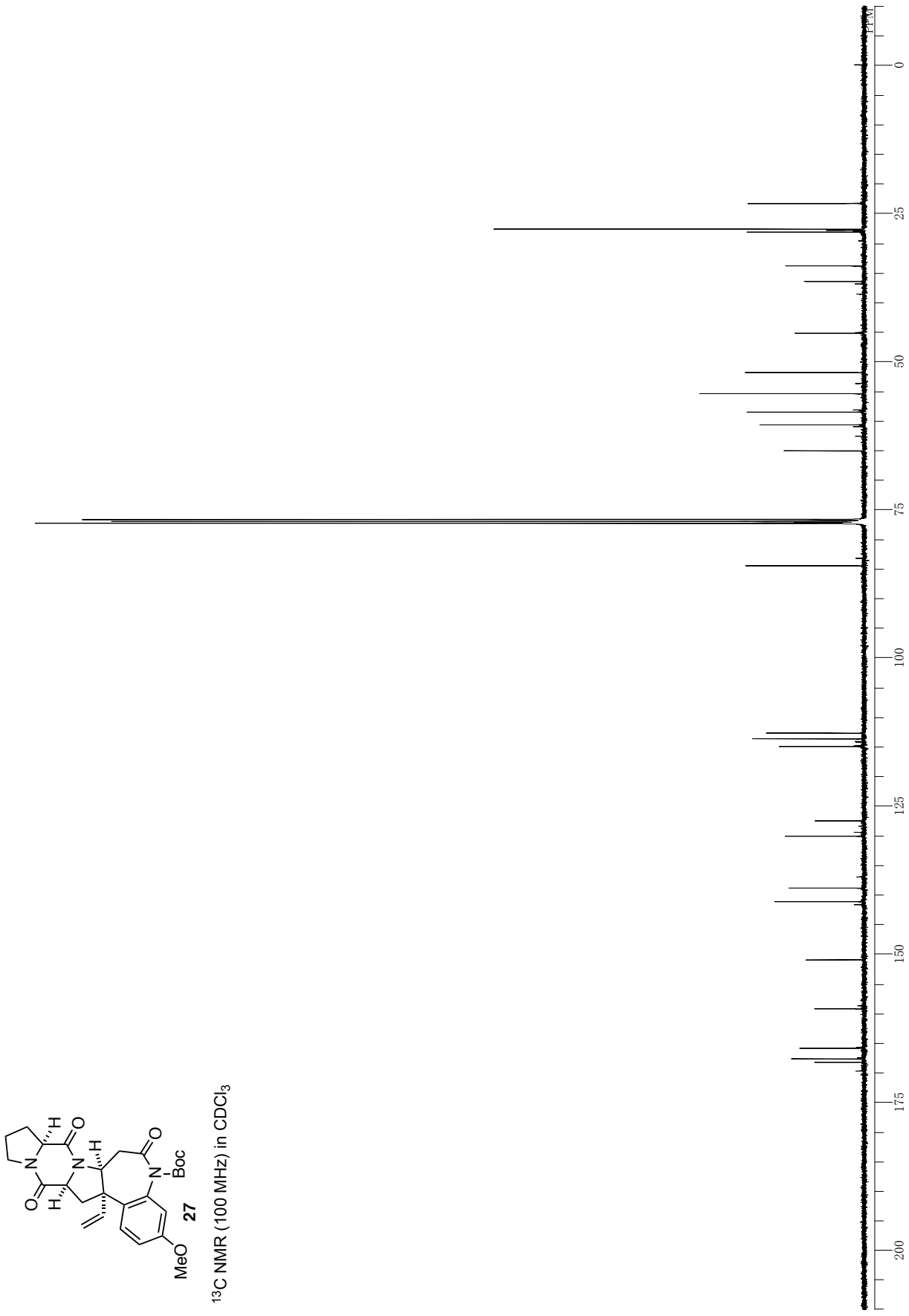
26

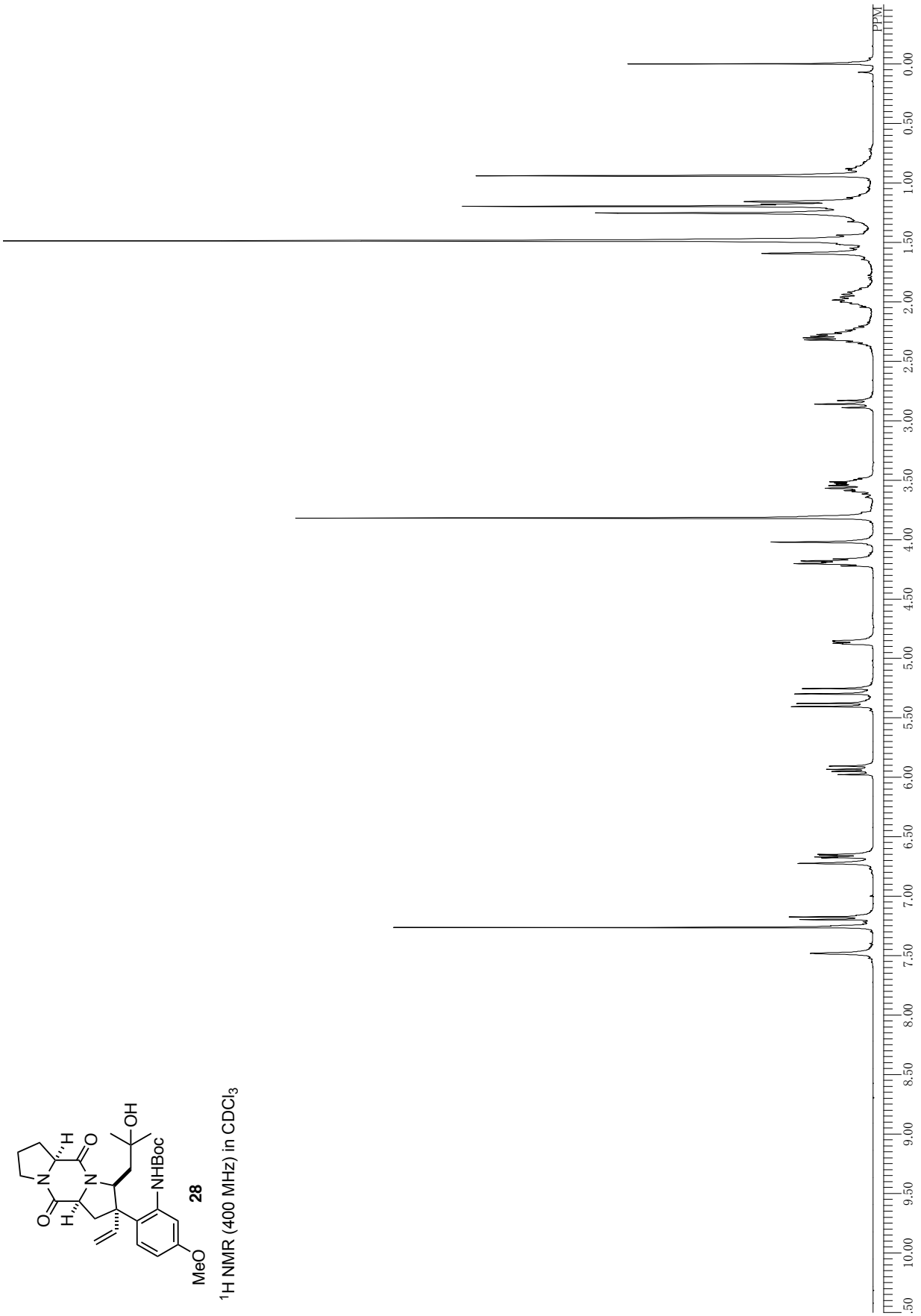
^{13}C NMR (100 MHz) in $CDCl_3$



27

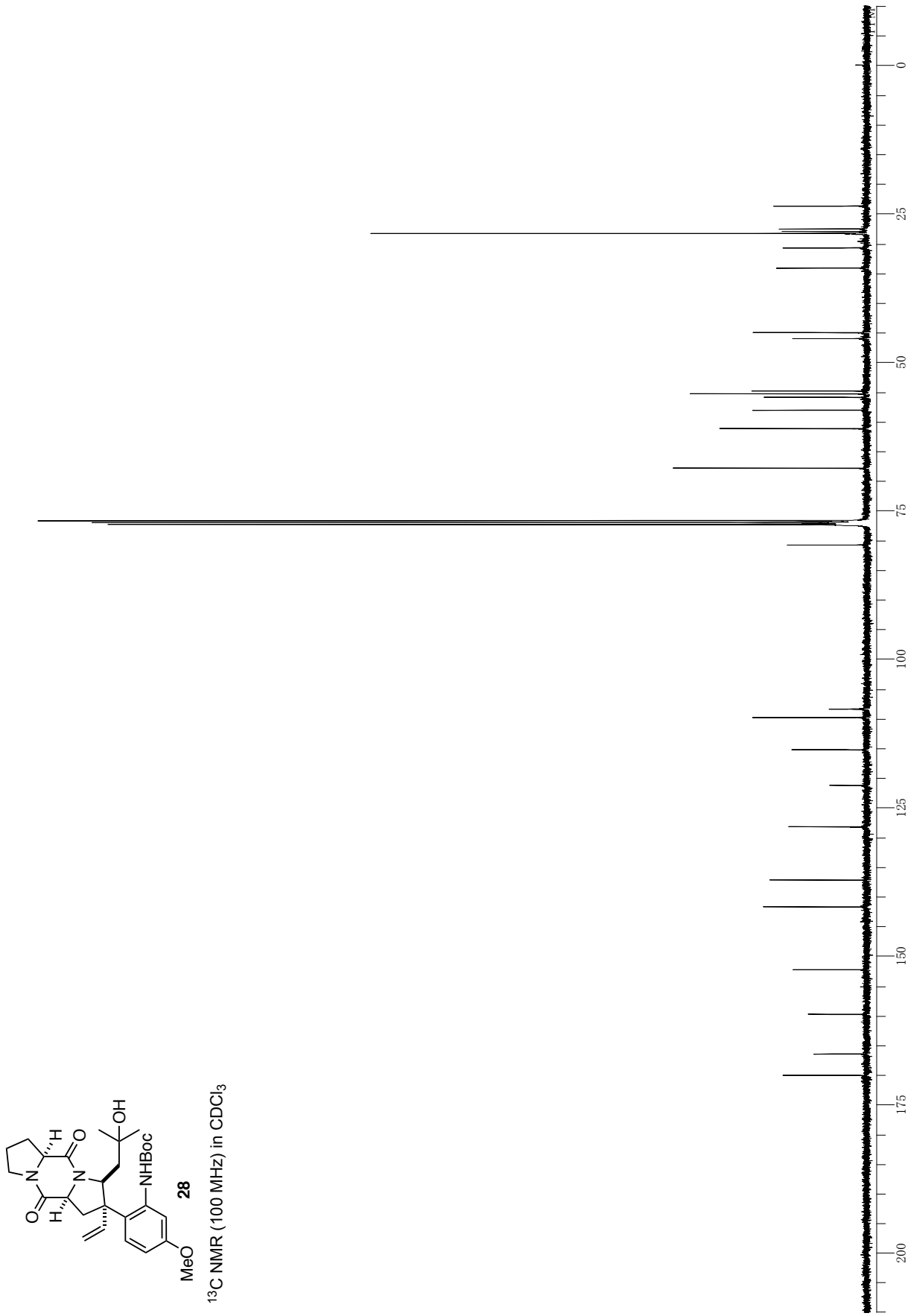
^{1}H NMR (400 MHz) in $CDCl_3$

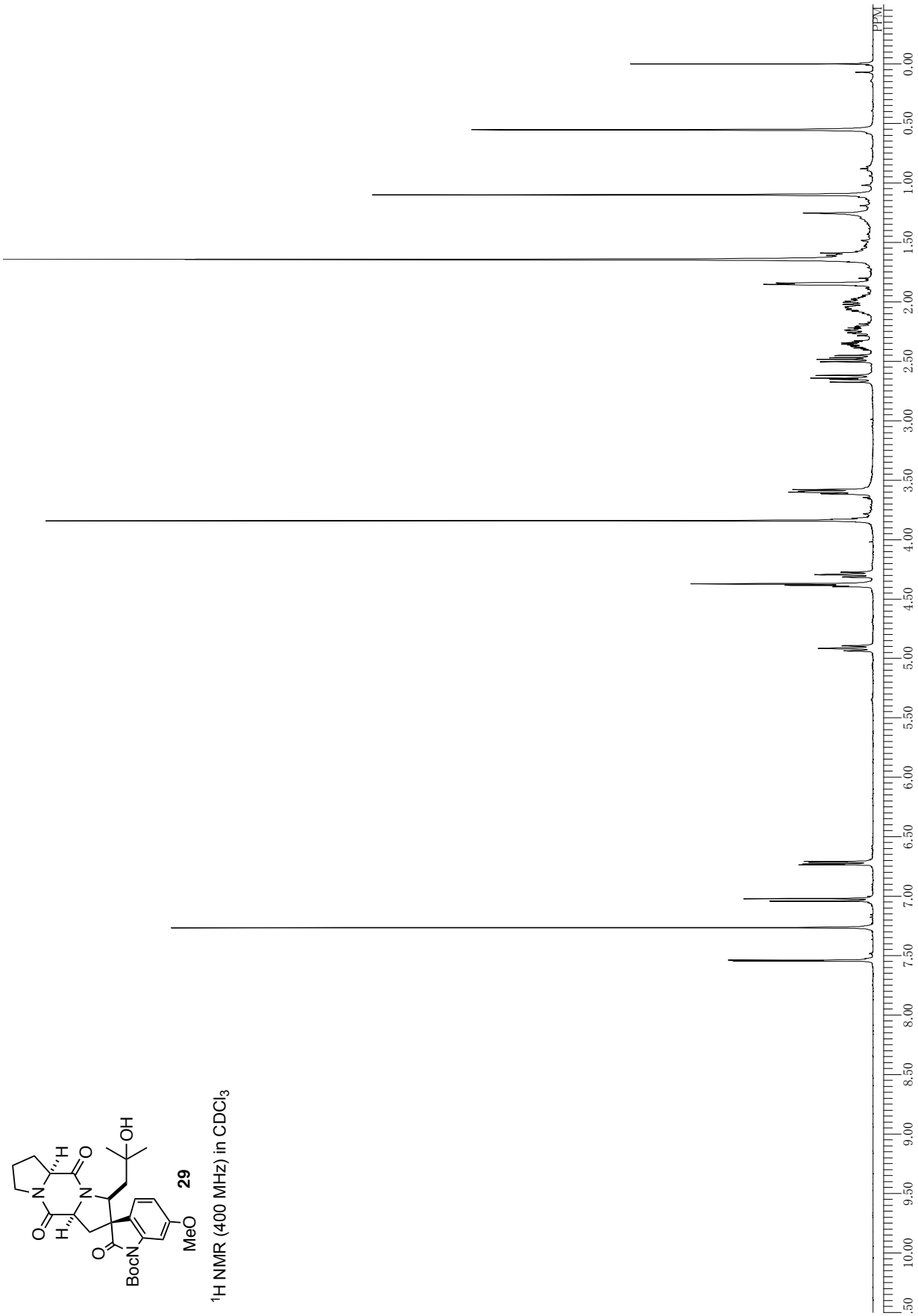

Boc
MeO
27
^{13}C NMR (100 MHz) in $CDCl_3$
0
25
50
75
100
125
150
175
200



28

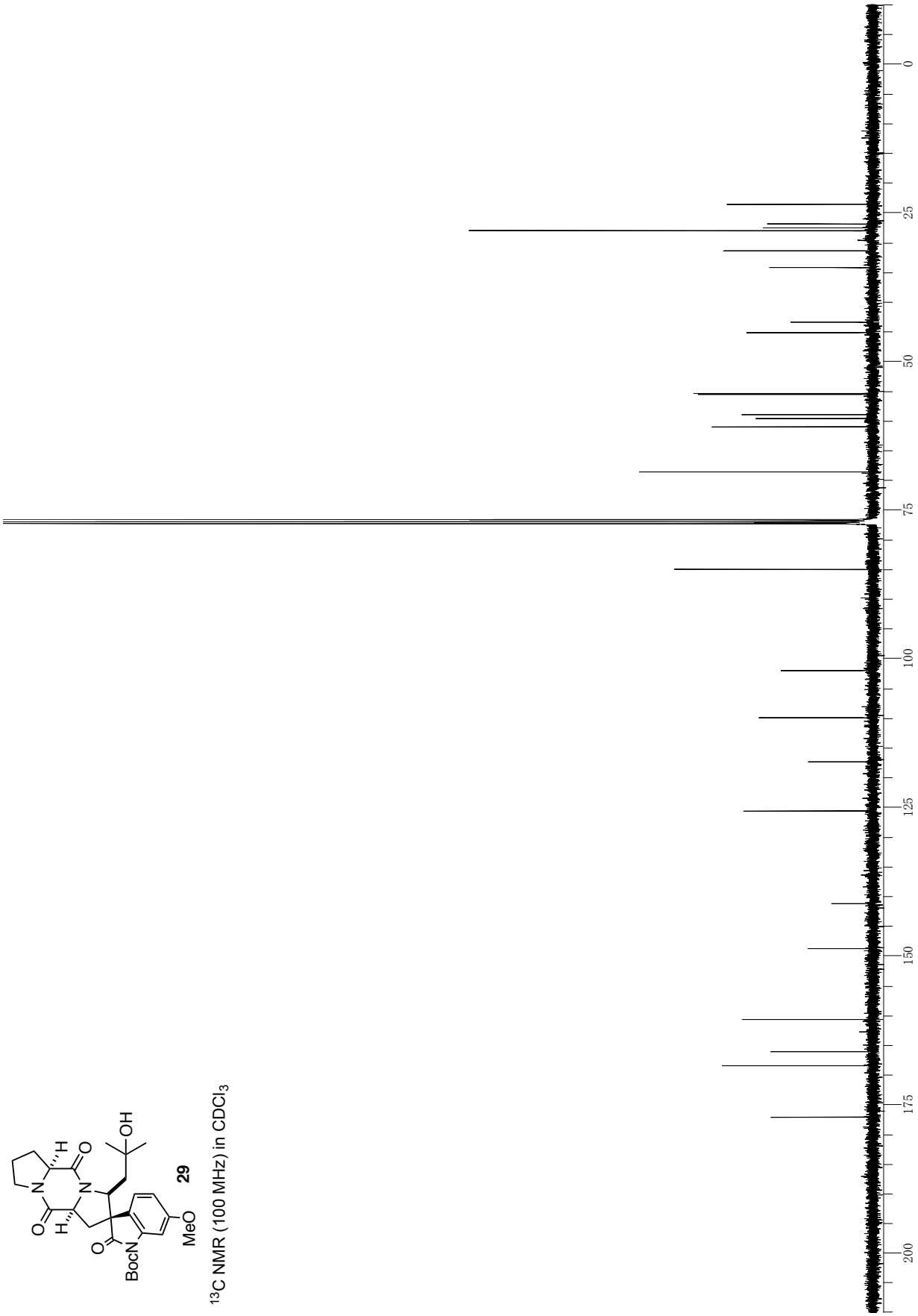
^{1}H NMR (400 MHz) in $CDCl_3$


OH
NHBoc
MeO
28
^{13}C NMR (100 MHz) in $CDCl_3$
200
175
150
125
100
75
50
25
0



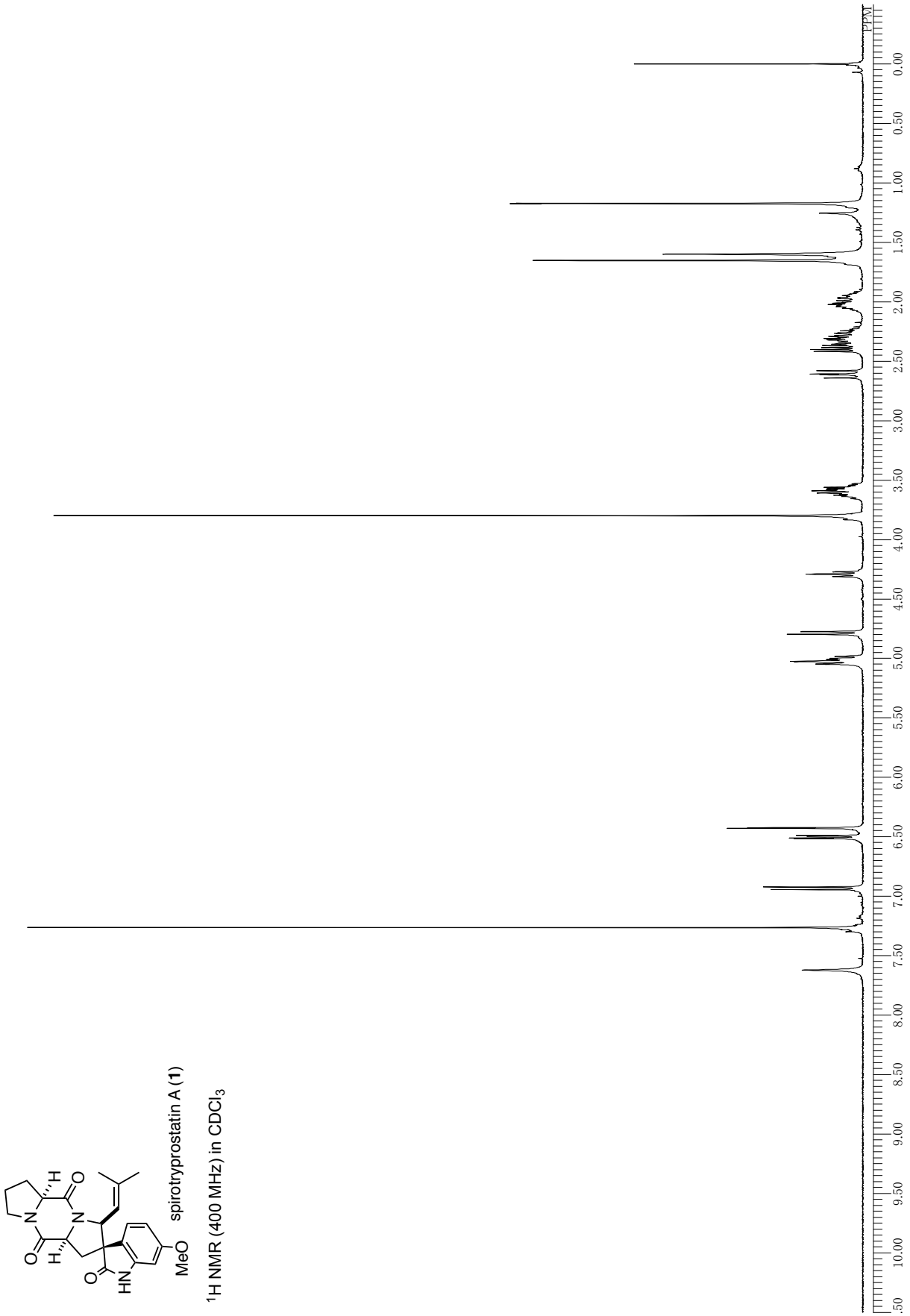
29

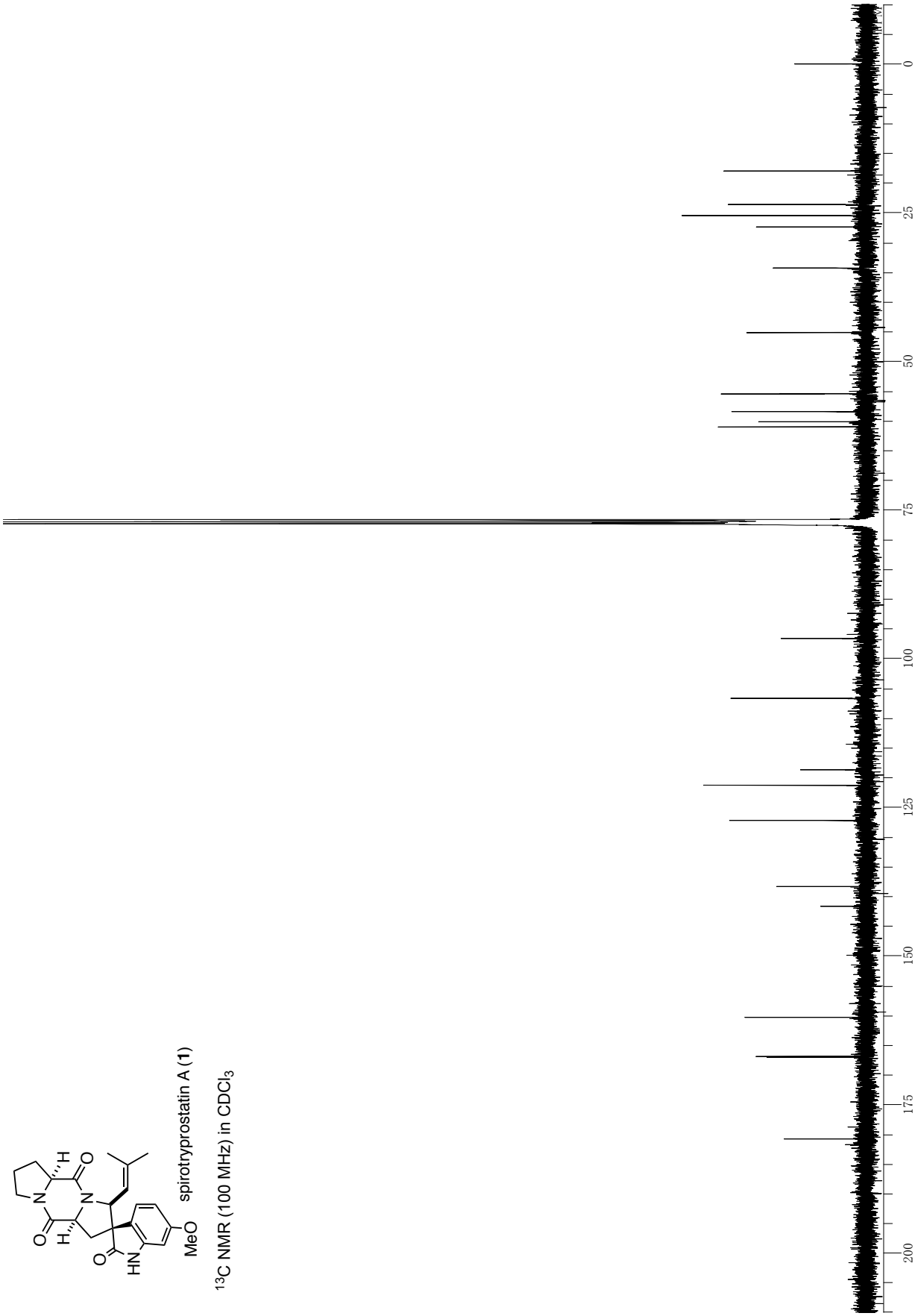
^{1}H NMR (400 MHz) in $CDCl_3$



29

^{13}C NMR (100 MHz) in $CDCl_3$


spirotryprostatin A (1)
^{1}H NMR (400 MHz) in $CDCl_3$
MeO
HN
PPM
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
8.00
8.50
9.00
9.50
10.00


spirotryprostatin A (1)
^{13}C NMR (100 MHz) in $CDCl_3$
MeO
HN
O
N
H
0
25
50
75
100
125
150
175
200