Supplementary Information for

Development of a Route to Chiral Epidithiodioxopiperazine Moieties and Application to the Asymmetric Synthesis of (+)-*Hyalodendrin*

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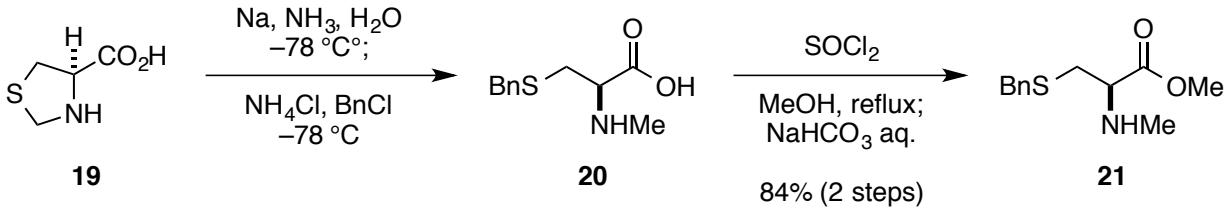
General. All non-aqueous reactions were carried out under an inert atmosphere of argon in oven-dried glassware unless otherwise noted. Dehydrated tetrahydrofuran, methylene chloride and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Dehydrated methanol 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 m) purchased from Kanto Chemical Co., Inc. ^{1}H and ^{13}C NMR were recorded on a JEOL ECX-400 or ECS-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. 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.

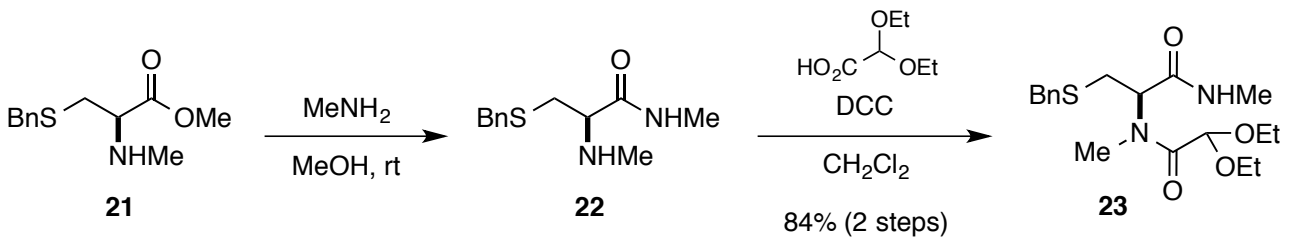
methyl *S*-benzyl-*N*-methyl-*L*-cysteinate (21)



To a stirred solution of (–)-thiazolidine-4-carboxylic acid[1] (**13**, 5.00 g, 37.5 mmol) in liquid ammonia (200 mL) and water (0.75 mL) at –78 °C was added sodium in small pieces until dark blue color persisted throughout the solution for 15 min. The blue color was discharged with solid NH_4Cl and was added BnCl (7.0 mL, 61 mmol). After the mixture was stirred for 2 h at the same temperature, the reaction was warmed to rt and ammonia was allowed to evaporate. The residue was dissolved in minimal amount of 10 M NaOH aq. Et_2O (40 mL) was added and the organic phase was discarded. The aqueous phase was adjusted to pH 6 with 12 M HCl aq and the precipitate was collected with suction filtration. Crystals were washed with ice-cold water (10 mL) and ether (10 mL). To the crude residue in MeOH (190 mL) was added $SOCl_2$ (8.16 mL, 112 mmol) at 0 °C. After refluxing for 24 h, the mixture was quenched with $NaHCO_3$ aq. (200 mL) at 0 °C and partitioned between CH_2Cl_2 (200 mL) and water (200 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 (150 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 afford **15** (7.54 g, 31.5 mmol, 84%) as a colorless oil.

R*f* = 0.24 (EtOAc only, UV, Ce-PMA); $[\alpha]^{25}_{D}$ +12.5 (*c* = 1.59, $CHCl_3$); IR (neat, cm^{-1}) 3330, 3027, 2948, 2797, 1736, 1601, 1493, 1452, 1340, 1199, 1172, 1113, 1070, 1007, 964, 771; ^1H NMR ($CDCl_3$) δ 7.32–7.23 (m, 5H), 3.73 (s, 2H), 3.73 (s, 3H), 3.30 (dd, *J* = 6.9, 6.0 Hz, 1H), 2.74 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.68 (dd, *J* = 14.0, 6.9 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.8, 137.9, 128.8, 128.4, 127.0, 62.6, 51.9, 36.6, 34.6, 33.9; HRMS (DART) calcd for $C_{12}H_{18}NO_2S$ 240.1058 ($[M+H]^+$), found 240.1051.

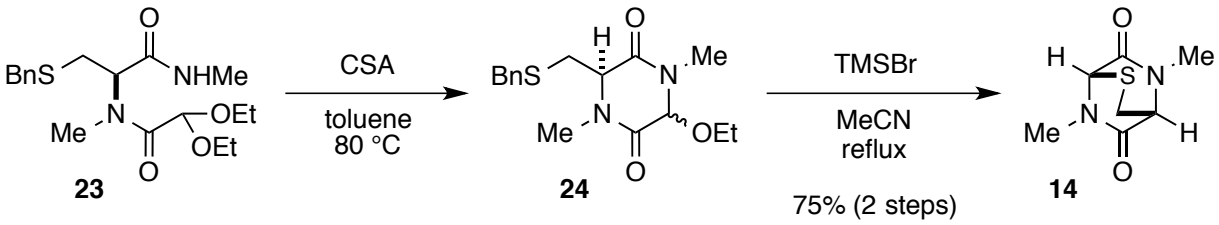
(*R*)-3-(benzylthio)-2-(2,2-diethoxy-*N*-methylacetamido)-*N*-methylpropanamide (23)



To a stirred solution of **15** (6.08 g, 25.4 mmol) was added 40 % methylamine in methanol solution (10.9 mL) at room temperature. The reaction mixture was allowed to stir for 24 h and concentrated *in vacuo*. The crude residue of *N*-methyl amide **22** was used in the next reaction without further purification. To a solution of crude **22** in CH_2Cl_2 (127 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (7.52 g, 36.4 mmol) and diethoxyacetic acid[2] (3.95 g, 26.7 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 15 min and the reaction was quenched with sat. $NaHCO_3$ aq. (150 mL). The resulting solution was partitioned between CH_2Cl_2 (100 mL) and water (100 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (100 mL) twice. The combined organic extract was washed with brine (150 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 afford **23** (7.84 g, 21.3 mmol, 84%, >99% ee) as a yellow oil. The enantiometric excess was determined by HPLC analysis with a chiral HPLC column (DAICEL CHIRALCEL AD-H, 5.0% 2-propanol in *n*-hexane, 1.0 mL/min, 210 nm). The retention times corresponding to **23** and its enantiomer are 19.9 and 27.3 min, respectively.

R*f* = 0.57 (EtOAc only, UV, Ce-PMA); $[\alpha]^{25}_{D}$ –123 (*c* = 1.12, $CHCl_3$); IR (neat, cm^{-1}) 3324, 2976, 2930, 1652, 1545, 1492, 1451, 1408, 1373, 1297, 1092, 1062, 916; (*5:3 mixture of two rotamers*) (***major***) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.21 (m, 5H), 6.80–6.70 (br s, 1H), 5.09–5.03 (m, 1H), 4.96 (s, 1H), 3.96–3.58 (m, 4H), 3.70 (s, 2H), 3.12–3.06 (m, 1H), 2.79 (d, *J* = 4.6 Hz, 3H), 2.70 (s, 3H), 1.35–1.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6, 167.6, 138.3, 128.9, 128.5, 127.0, 104.5, 65.1, 62.8, 58.2, 36.9, 30.1, 28.5, 25.9, 15.0; (***minor***) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.21 (m, 5H), 6.17–6.06 (br s, 1H), 5.09–5.03 (m, 1H), 5.04 (s, 1H), 3.96–3.58 (m, 4H), 3.70 (s, 2H), 3.12–3.06 (m, 1H), 2.97 (s, 3H), 2.96–2.93 (m, 2H), 2.75 (d, *J* = 5.0 Hz, 3H), 1.35–1.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5, 168.9, 137.7, 128.8, 128.5, 127.1, 99.5, 65.1, 62.6, 55.4, 35.8, 30.1, 28.5, 26.1, 15.0; HRMS (ESI) calcd for $C_{18}H_{28}N_2NaO_4S$ ($[M+Na]^+$) 391.1667, found 391.1661.

(1S,4R)-5,7-dimethyl-2-thia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (14)



To a stirred solution of **17** (7.84 g, 21.3 mmol) in toluene (106 mL) was added CSA (4.94 g, 21.3 mmol) at room temperature. The reaction mixture was allowed to warm to 80 °C and stirred for 5 h. The reaction was quenched with saturated $NaHCO_3$ aq. (50 mL) and partitioned between EtOAc (100 mL) and water (100 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (150 mL) twice. Combined organic extract was washed with brine (100 mL), dried over sodium sulfate and filtered. The filtrate was concentrated *in vacuo* to give **18** as a 4:1 mixture of diastereomers. The residue was used in the next step without purification. Aliquot of the crude mixture was purified for characterization purpose.

(***major***) 97% ee, The enantiometric excess was determined by HPLC analysis with a chiral HPLC column (DAICEL CHIRALCEL AD-H, 10.0% 2-propanol in *n*-hexane, 1.0 mL/min, 210 nm). The retention times corresponding to **24** (*major*) and its enantiomer are 26.7 and 36.9 min, respectively. R*f* = 0.48 (EtOAc only, UV, Ce-PMA); $[\alpha]^{25}_D$ +13.0 (*c* = 1.67, $CHCl_3$); IR (neat, cm^{-1}) 3060, 3027, 2976, 2930, 2385, 2301, 1677, 1479, 1454, 1400, 1325, 1252, 1156, 1120, 1066, 1008, 916, 773 ^{1}H NMR ($CDCl_3$) δ 7.34–7.30 (m, 3H), 7.28–7.23 (m, 2H), 4.70 (s, 1H), 3.88 (dd, *J* = 6.4, 6.0 Hz, 1H), 3.79 (dd, *J* =14.2, 6.9 Hz, 1H), 3.76 (s, 2H), 3.72 (dd, *J* = 14.2, 6.9 Hz , 1H), 3.03 (s, 3H), 3.03–3.01(m, 2H), 3.01 (s, 3H), 1.18 (t, *J* = 6.9 Hz, 3H) ; ^{13}C NMR ($CDCl_3$) δ 167.6, 163.4, 137.7, 129.1, 128.7, 127.4, 87.4, 66.0, 63.0, 37.0, 35.9, 34.1, 33.0, 15.1; HRMS (ESI) calcd for $C_{16}H_{22}N_2NaO_3S$ ($[M+Na]^+$) 345.1249, found 345.1249.

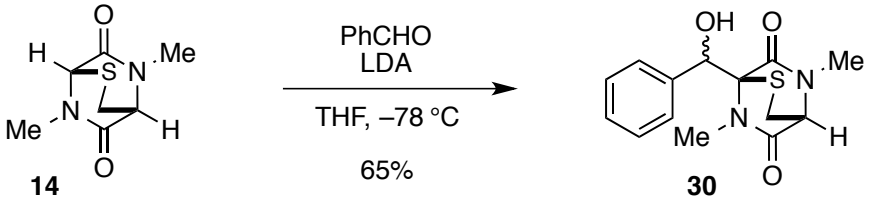
(***minor***) 97% ee, The enantiometric excess was determined by HPLC analysis with a chiral HPLC column (DAICEL CHIRALCEL AD-H, 10.0% 2-propanol in *n*-hexane, 1.0 mL/min, 210 nm). The retention times corresponding to **24** (*minor*) and its enantiomer are 30.8 and 46.9 min, respectively. R*f* = 0.40 (EtOAc only, UV, Ce-PMA); $[\alpha]^{25}_D$ +37.7 (*c* = 1.20, $CHCl_3$); IR (neat, cm^{-1}) 3329, 3028, 2976, 2930, 1672, 1543, 1453, 1398, 1326, 1252, 1153, 1069, 1004, 933, 771; ^{1}H NMR ($CDCl_3$) δ 7.33–7.25 (m, 5H), 5.05 (s, 1H), 4.20 (t, *J* = 3.7, 2.3 Hz, 1H), 3.79–3.75 (m, 1H), 3.65 (s, 2H), 3.60–3.56 (m, 1H), 3.23 (dd, *J* = 14.2, 2.3 Hz, 1H), 3.03 (s, 3H), 2.94 (dd, *J* = 14.2, 3.7 Hz, 1H), 2.85 (s, 3H), 1.26 (dd, *J* = 7.3, 6.9 Hz, 3H) ; ^{13}C NMR ($CDCl_3$) δ 165.3, 163.6, 137.6, 129.1,

128.7, 127.5, 84.7, 63.6, 61.4, 37.1, 33.9, 31.5, 31.1, 15.1; HRMS (ESI) calcd for $C_{16}H_{22}N_2NaO_3S$ ($[M+Na]^+$) 345.1249, found 345.1249.

To a stirred solution of crude residue of **24** in MeCN (250 mL) was added TMSBr (30 mL, 108 mmol) at room temperature. The reaction mixture was refluxed for 5 h and quenched with saturated $NaHCO_3$ aq. at 0 °C. The mixture was partitioned between 20% MeOH in $CHCl_3$ (100 mL) and water (250 mL). The organic phase was collected and the aqueous phase was extracted with 20% MeOH in $CHCl_3$ (100 mL) twice. 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 (EtOAc only) to afford **14** (4.2 g) as an orange solid. Recrystallization from EtOAc afforded **14** (2.97 g, 15.9 mmol, 75%) as a white crystals (> 99% ee). The enantiometric excess was determined by HPLC analysis with a chiral HPLC column (DAICEL CHIRALCEL AD-H, 10% 2-propanol in *n*-hexane, 1.0 mL/min, 210 nm). The retention times corresponding to **14** and its enantiomer are 37.6 and 32.2 min, respectively.

R*f* = 0.38 (EtOAc only, UV, Ce-PMA); M.p. 190.4–194.8 °C; $[\alpha]^{25}_D$ –5.60 (*c* = 1.11, $CHCl_3$); IR (neat, cm^{-1}) 3327, 2995, 2931, 1682, 1447, 1392, 1288, 1244, 1202, 1163, 1013, 938, 830; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.70 (s, 1H), 4.37 (dd, *J* = 3.6, 2.8 Hz, 1H), 3.46 (dd, *J* = 11.0, 3.6 Hz, 1H), 3.17 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.07 (s, 3H), 3.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 165.4, 63.1, 62.5, 32.6, 31.6, 30.9; HRMS (ESI) calcd for $C_7H_{11}N_2O_2S$ ($[M+H]^+$) 187.0541, found 187.0549.

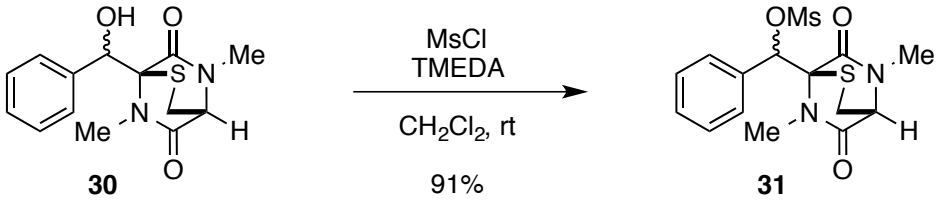
(1S,4R)-1-(hydroxy(phenyl)methyl)-5,7-dimethyl-2-thia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (30)



To a stirred solution of **14** (1.00 g, 5.37 mmol) in THF (153 mL) and benzaldehyde (1.09 mL, 10.7 mol) was added LDA (0.8 M, 13.4 mL, 10.7 mmol) at –78 °C. After stirring for 30 min at the same temperature, the reaction mixture was warmed to 0 °C and quenched with NH_4Cl aq. (150 mL). The resulting solution was partitioned between CH_2Cl_2 (100 mL) and water (100 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (300 mL) twice. 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 = 3/2) to afford **30** (876 mg, 3.00 mmol, 56%) as a colorless oil (*3:1 mixture of two diastereomers*).

R*f* = 0.52 (EtOAc only, UV, Ce-PMA); IR (neat, cm^{-1}) 3444, 3009, 2932, 2361, 2338, 1964, 1781, 1683, 1548, 1450, 1380, 1328, 1243, 1092, 1049, 1028, 971, 945, 913, 875, 856, 815, 761; (***major***) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68–7.24 (m, 5H), 5.41 (d, *J* = 8.3 Hz , 1H), 4.67 (d, *J* = 8.3 Hz, 1H), 4.48 (dd, *J* = 3.6, 2.3 Hz, 1H), 3.52 (dd, *J* = 11.0, 3.6 Hz, 1H), 3.17 (dd, *J* = 11.0, 2.3 Hz, 1H), 3.16 (s, 3H), 2.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 167.3, 137.9, 128.6, 128.0, 127.9, 72.9, 72.7, 61.7, 32.8, 32.0, 27.8; (***minor***) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68–7.24 (m, 5H) , 5.28 (d, *J* = 11.9 Hz, 1H), 4.37 (dd, *J* = 4.1, 1.8 Hz , 1H), 3.31 (s, 3H), 3.25 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.08 (s, 3H), 3.02 (dd, *J* = 11.0, 1.8Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 167.0, 137.9, 128.6, 128.0, 127.9, 74.6, 71.2, 61.3, 31.9, 31.8, 26.9; HRMS (ESI) calcd for $C_{14}H_{16}N_2NaO_3S$ ($[M+Na]^+$) 315.0779, found 315.0781.

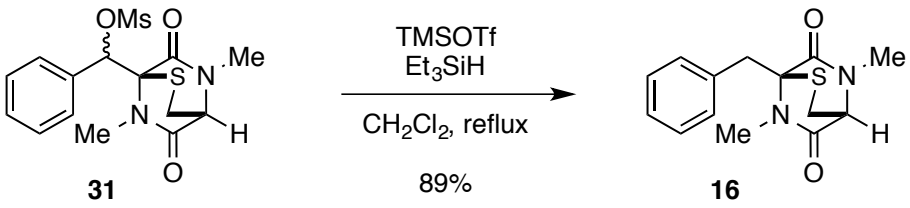
((1S,4R)-5,7-dimethyl-6,8-dioxo-2-thia-5,7-diazabicyclo[2.2.2]octan-1-yl)(phenyl)methyl methanesulfonate (31)



To a stirred solution of **30** (876 mg, 3.00 mmol) in CH_2Cl_2 (15 mL) was added TMEDA (900 μL, 6.00 mmol) and methanesulfonyl chloride (464 μL, 6.00 mmol) at room temperature and resulting mixture was stirred at room temperature for 40 min. The reaction was quenched with NH_4Cl aq. (15 mL) and partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (40 mL) twice. 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 afford **31** (1.02 g, 2.75 mmol, 92%) as a colorless oil (*single diastereomer*).

R*f* = 0.29 (*n*-hexane/EtOAc = 1/2, UV, Ce-PMA); IR (neat, cm^{-1}) 3370, 3017, 2937, 2370, 2336, 1781, 1693, 1452, 1423, 1359, 1279, 1242, 1202, 1174, 1101, 999, 960, 930, 889, 820, 803, 756; ^1H NMR ($CDCl_3$) δ 7.70–7.60 (m, 2H), 7.45–7.35 (m, 3H), 6.67 (s, 1H), 4.42 (m, 1H), 3.44 (dd, *J* = 11.4, 3.4 Hz, 1H), 3.15 (s, 3H), 3.11 (s, 3H), 3.11–3.08 (m, 1H), 3.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.5, 165.2, 134.2, 129.3, 128.5, 128.1, 80.2, 72.2, 61.1, 39.6, 33.1, 32.5, 29.2; HRMS (ESI) calcd for $C_{15}H_{18}N_2NaO_5S_2$ ($[M+Na]^+$) 393.0555, found 393.0574.

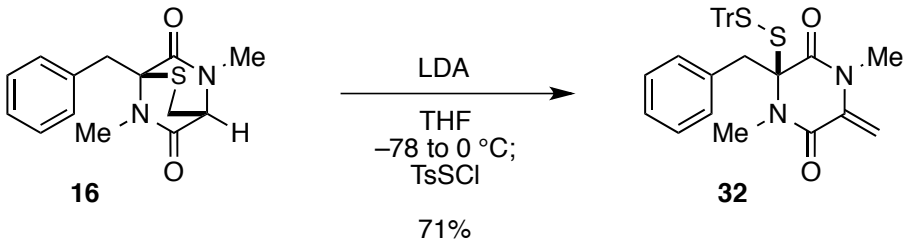
(1S,4R)-1-benzyl-5,7-dimethyl-2-thia-5,7-diazabicyclo[2.2.2]octane-6,8-dione (16)



To a stirred solution of **31** (796 mg, 2.15 mmol) and triethylsilane (2.14 mL, 12.9 mmol) in CH_2Cl_2 (10.7 mL) was added TMSOTf (2.33 mL, 12.9 mmol) at room temperature and the reaction mixture was heated to reflux for 3 h. The reaction mixture was quenched with saturated $NaHCO_3$ aq. (10 mL) and partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (20 mL) twice. 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 = 3/1) to afford **16** (390 mg, 1.41 mmol, 66%) as a yellow oil.

R*f* = 0.52 (EtOAc only, UV, Ce-PMA); $[\alpha]^{25}_{D}$ –24.4 (*c* = 1.31, $CHCl_3$); IR (neat, cm^{-1}) 2931, 2360, 1689, 1496, 1453, 1380, 1247, 1174, 1093, 958; ^{1}H NMR ($CDCl_3$) δ 7.40–7.38 (m, 2H), 7.32–7.23 (m, 3H), 4.43 (dd, *J* = 3.7, 2.1 Hz, 1H), 3.71 (d, *J* = 15.6 Hz, 1H), 3.60 (d, *J* = 15.6 Hz, 1H), 3.41 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.12 (s, 3H) 3.10 (dd, *J* = 11.0, 2.1 Hz, 1H), 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 166.3, 134.6, 129.6, 127.9, 126.7, 70.4, 61.5, 35.8, 32.2, 32.0, 27.1; HRMS (ESI) calcd for $C_{14}H_{16}N_2NaO_2S$ ($[M+Na]^+$) 299.0830, found 299.0839.

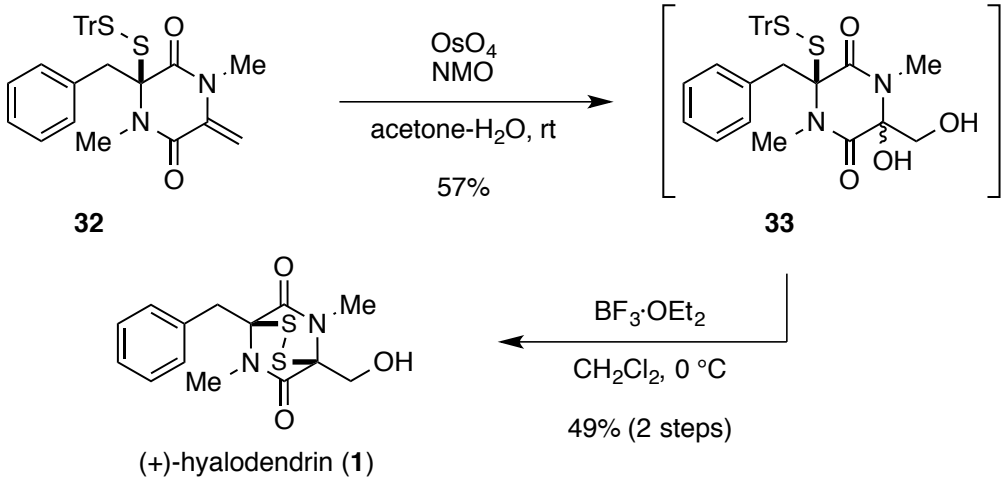
(S)-3-benzyl-1,4-dimethyl-6-methylene-3-(trityldisulfanyl)piperazine-2,5-dione (32)



To a stirred solution of **16** (361 mg, 1.31 mmol) in THF (37 mL) was added LDA (0.8 M, 1.63 mL, 1.31 mmol, 1.0 eq.) at –78 °C and the solution was stirred at 0 °C for 10 min and TrSCl (812 mg, 2.61 mmol) was added. The resulting mixture was quenched with saturated NH_4Cl aq. and partitioned between CH_2Cl_2 (15 mL) and water (15 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (30 mL) twice. 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 = 5/1) to afford **32** (514 mg, 0.933 mmol, 71%) as a yellow oil.

R*f* = 0.26 (*n*-hexane/EtOAc = 1/5, UV, Ce-PMA); $[\alpha]^{25}_{D}$ +149 (*c* = 1.31, $CHCl_3$); IR (neat, cm^{-1}) 3058, 3028, 2927, 2338, 1679, 1612, 1492, 1443, 1362, 1275, 1216, 1084, 1033, 885, 759; ^1H NMR ($CDCl_3$) δ 7.35–7.24 (m, 15H), 7.14–7.10 (m, 3H), 6.87–6.86 (m, 2H), 5.60 (s, 1H), 4.58 (s, 1H), 3.47 (d, *J* = 14.4 Hz, 1H), 2.96 (s, 3H), 2.87 (s, 3H), 2.47 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 162.7, 158.7, 143.4, 135.6, 134.1, 130.4, 129.2, 128.5, 127.9, 127.4, 127.3, 101.9, 78.4, 72.8, 40.6, 30.7, 30.1; HRMS (ESI) calcd for $C_{33}H_{30}N_2NaO_2S_2$ ($[M+Na]^+$) 573.1646, found 573.1620.

hyalodendrin (1)



To a stirred solution of **32** (106.5 mg, 0.193 mmol) in 50% aqueous acetone (0.97 mL) was added OsO_4 (480 μL, 0.04 M in *t*-BuOH, 0.019 mmol) and NMO (45.3 mg, 0.387 mmol) at room temperature. After stirring for 5 h at 50 °C, the resulting solution was added Na_2SO_3 aq. (1 mL) and partitioned between CH_2Cl_2 (1 mL) and water (1 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (2 mL) twice. Combined organic extract was washed with brine (2 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **33** as a colorless oil (*1:1 mixture of two diastereomers*). Aliquot of the crude mixture was purified for characterization purpose.

(*less polar*) R*f* = 0.28 (*n*-hexane/EtOAc = 1/1, UV, Ce-PMA); $[\alpha]^{25}_{D}$ +133 (*c* = 1.00, $CHCl_3$); IR (neat, cm^{-1}); 1651, 1441, 1384, 1219, 1081, 856, 771 ^{1}H NMR ($CDCl_3$) δ 7.42–7.24 (m, 15H), 7.42–7.20 (m, 3H), 6.87–6.85 (m, 2H), 3.65–3.55 (m, 2H), 3.46 (d, *J* = 14.4 Hz, 1H), 2.99 (br s, 1H), 2.86 (s, 3H), 2.77 (s, 3H), 2.42 (br s, 1H), 2.07 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 167.4, 164.8, 143.4, 134.1, 130.3, 129.3, 128.6, 128.0, 127.5, 127.3, 82.7, 76.5, 72.8, 65.2, 39.9, 30.6, 27.8; HRMS (ESI) calcd for $C_{33}H_{32}N_2NaO_4S_2$ ($[M+Na]^+$) 607.1701, found 607.1717.

(*more polar*) R*f* = 0.23 (*n*-hexane/EtOAc = 1/1, UV, Ce-PMA); $[\alpha]^{25}_{D}$ +92.7 (*c* = 0.92, $CHCl_3$); IR (neat, cm^{-1}); 3403, 3014, 1653, 1443, 1385, 1240, 1080, 762; ^{1}H NMR ($CDCl_3$) δ 7.39–7.26 (m, 15H), 7.20–7.19 (m, 3H), 6.96–6.89 (m, 2H), 3.81 (br s, 1H), 3.50 (d, *J* = 14.2 Hz, 1H), 3.19 (dd, *J* = 11.6, 10.2 Hz, 2H), 2.83 (s, 3H), 2.78 (s, 3H), 2.33 (d, *J* = 14.2 Hz, 1H), 2.29 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.19 (dd, *J* = 10.2, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 167.4, 164.0, 143.5, 134.1, 130.3, 129.7, 128.7, 128.0, 127.8, 127.3, 82.0, 76.4, 72.9, 64.9, 40.1, 30.6, 28.1; HRMS (ESI) calcd for $C_{33}H_{32}N_2NaO_4S_2$ ($[M+Na]^+$) 607.1701, found 607.1717.

To a solution of crude **33** in CH_2Cl_2 (0.97 mL) was added $BF_3 \cdot OEt_2$ (41 μL, 0.386 mmol) at –78 °C and the solution was allowed to warm to 0 °C. After stirring for 15 min at the same temperature, the reaction was quenched with saturated $NaHCO_3$ aq. (0.3 mL) and partitioned between 20% MeOH in $CHCl_3$ (1 mL) and water (1 mL). The organic phase was collected and the aqueous phase was extracted with 20% MeOH in $CHCl_3$ (2 mL) twice. Combined organic extract was washed with brine (2 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 afford (+)-hyalodendrin (**1**) (30.4 mg, 0.094 mmol, 49%) as a yellow oil.

R*f* = 0.70 (*n*-hexane/EtOAc = 1/1, UV, Ce-PMA); $[\alpha]^{25}_D$ +36.7 (*c* = 0.60, $CHCl_3$); IR (neat, cm^{-1}); 3464, 2925, 2852, 2359, 2340, 1682, 1497, 1454, 1415, 1345, 1257, 1108, 1069, 821; ^1H NMR ($CDCl_3$) δ 7.34–7.26 (m, 5H), 4.39 (dd, *J* = 12.8, 6.4, 1H), 4.32 (dd, *J* = 12.8, 9.2 Hz, 1H), 4.09 (d, *J* = 16.0 Hz, 1H), 3.63 (d, *J* = 16.0 Hz, 1H), 3.49 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.21 (s, 3H), 2.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.9, 165.6, 134.1, 129.1, 128.7, 127.4, 75.7, 75.3, 61.3, 36.9, 28.6, 27.5; HRMS (ESI) calcd for $C_{14}H_{16}N_2NaO_3S_2$ ($[M+Na]^+$) 347.0500, found 347.049.

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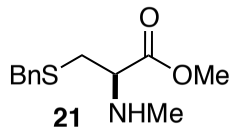
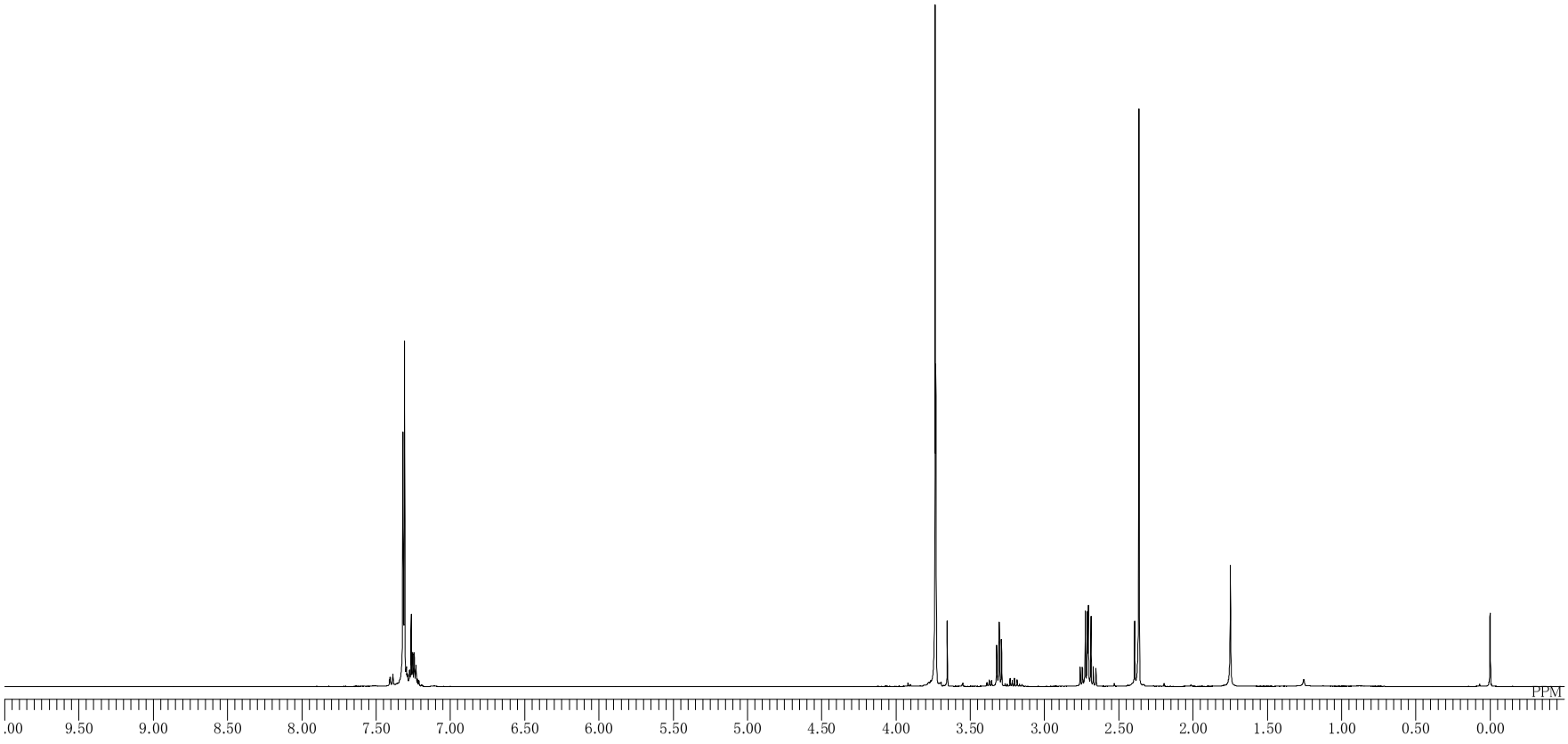
[1] N. Pellegrini, B. Refouvelet, G. Crini, O. Blacque, M. M. Kubicki and J.-F. Robert, *Chem. Pharm. Bull.*, 1999, **47**, 950-955.

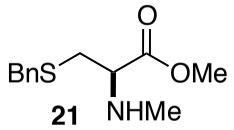
[2] A. Pinto, P. Conti, G. Grazioso, L. Tamborini, U. Madsen, B. Nielsen and C. De Micheli, *Eur. J. Med. Chem.*, 2011, **46**, 787-793.



21

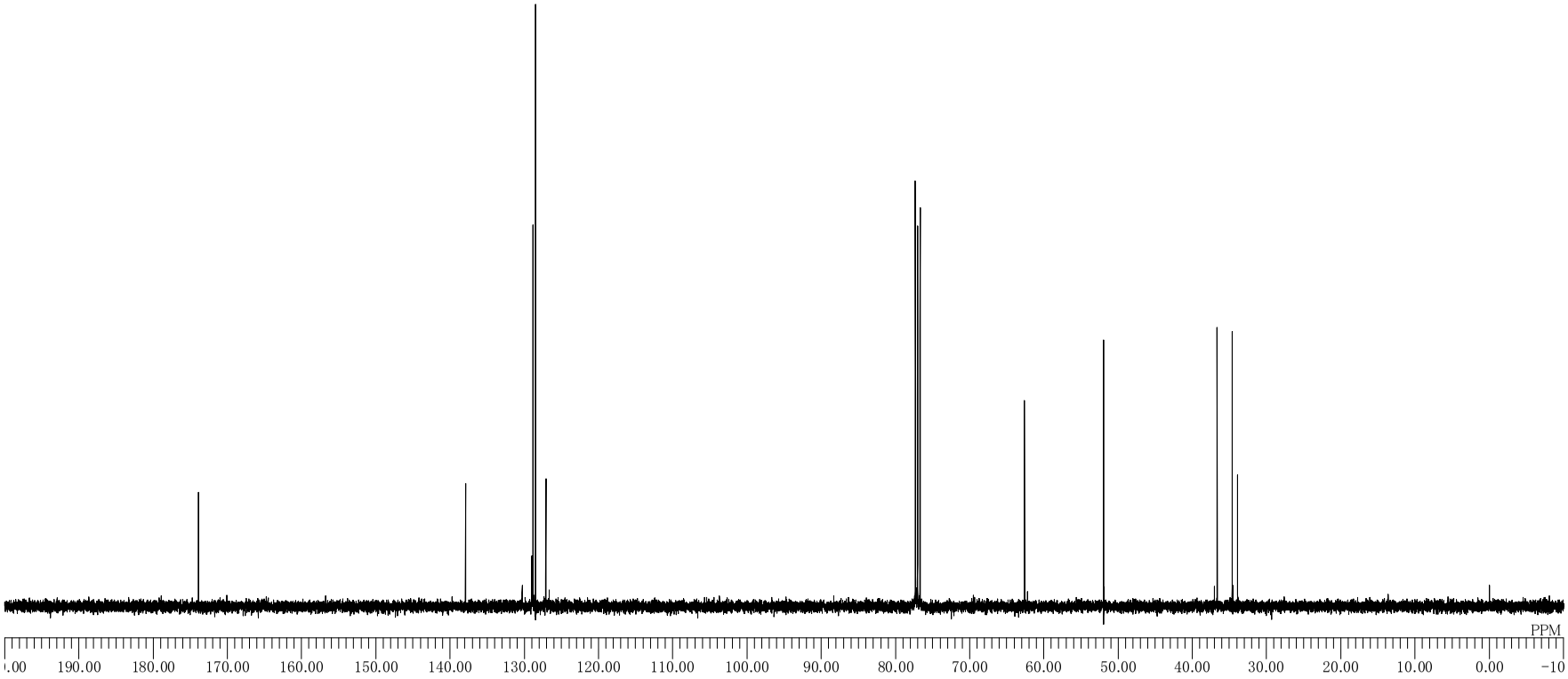
^{1}H NMR (400 MHz) in $CDCl_3$

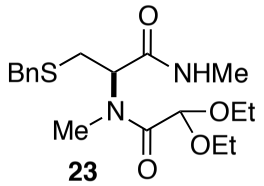




21

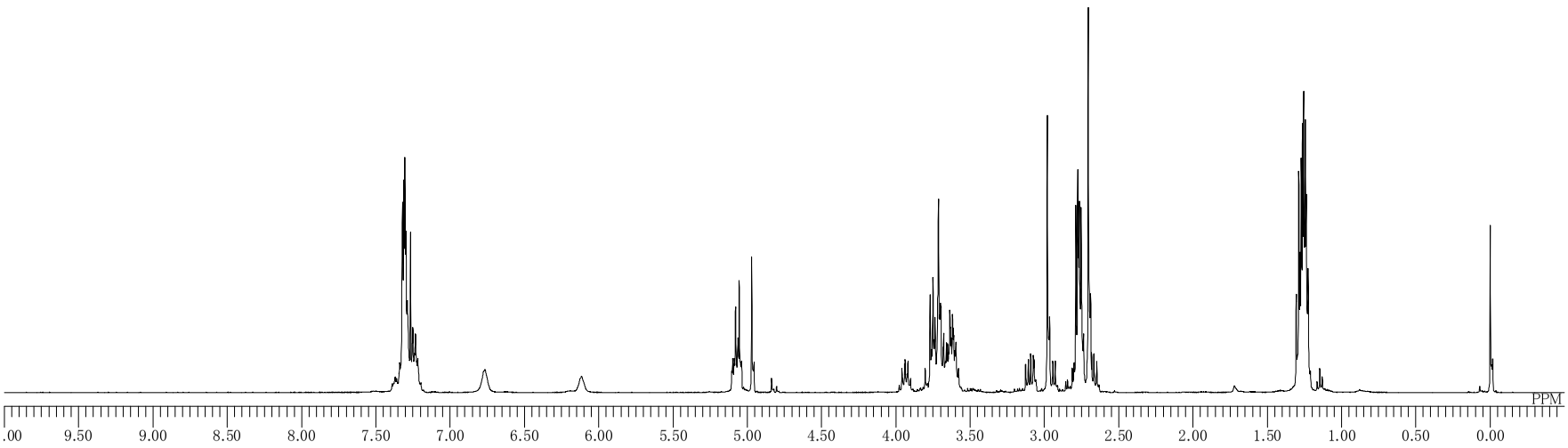
^{13}C NMR (100 MHz) in $CDCl_3$

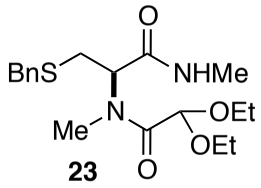




23

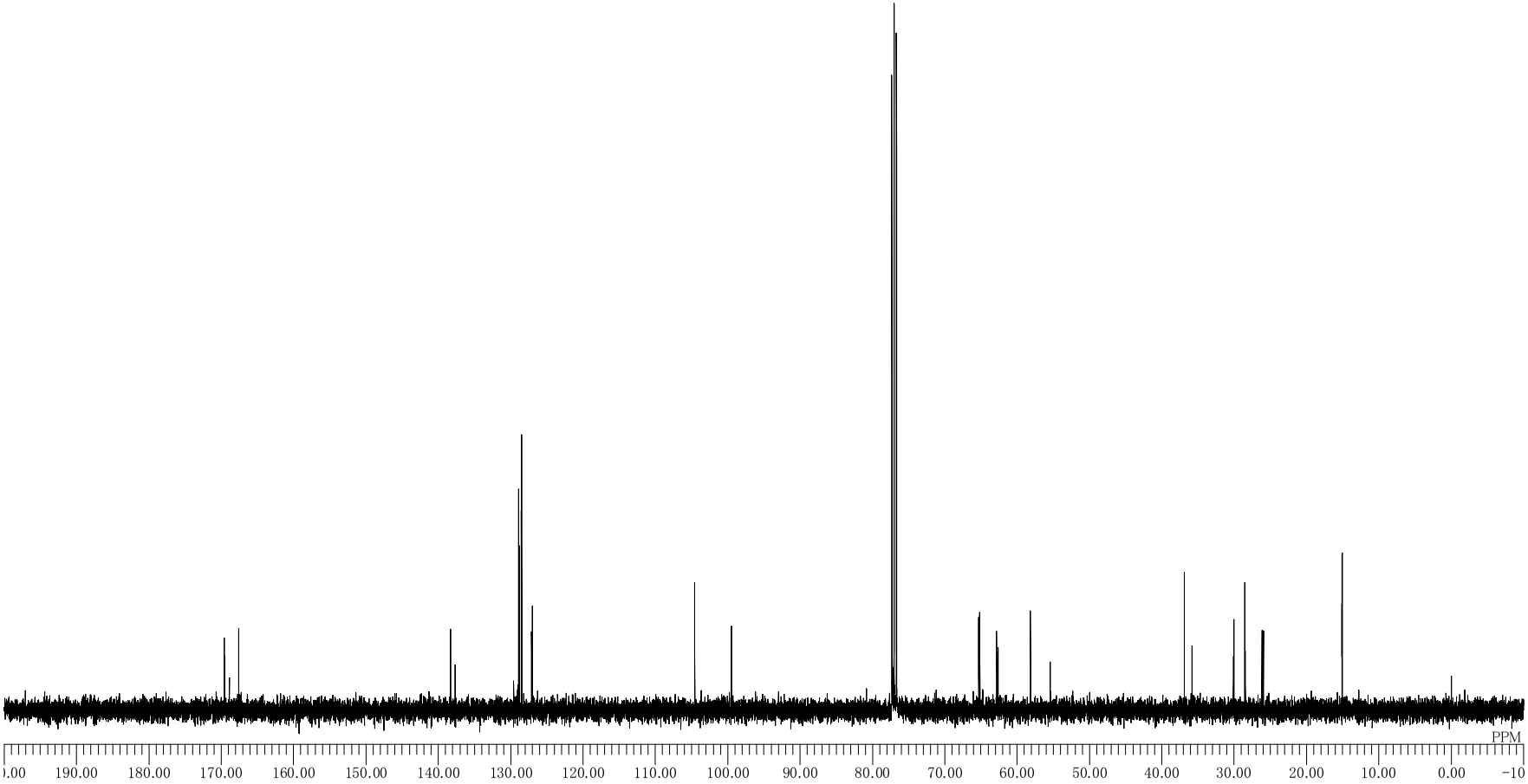
^{1}H NMR (400 MHz) in $CDCl_3$

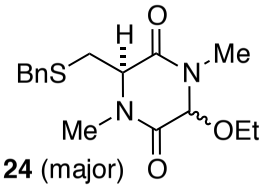




23

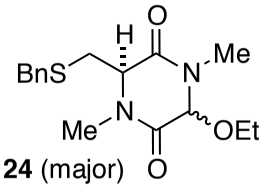
^{13}C NMR (100 MHz) in $CDCl_3$





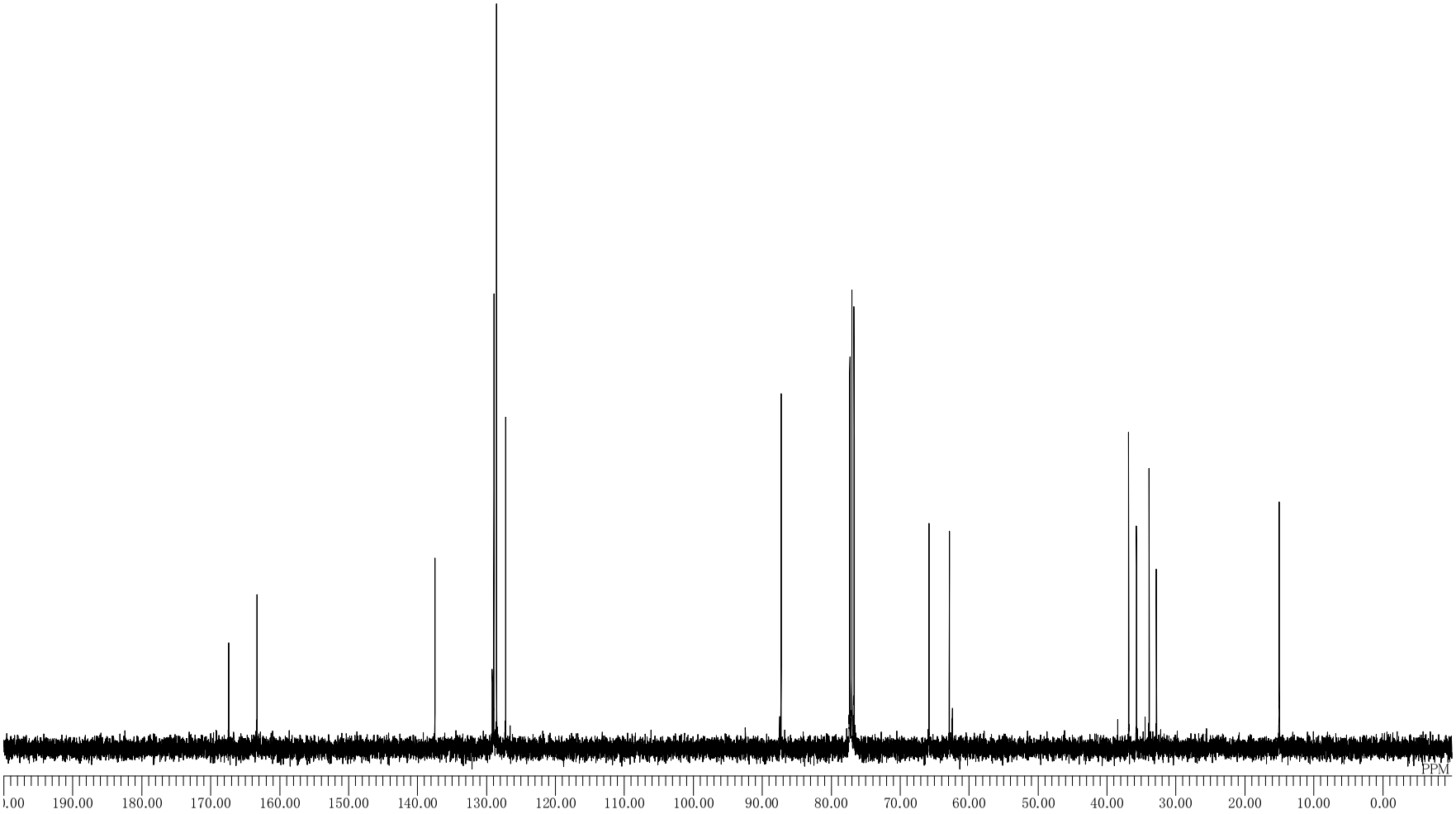
24 (major)

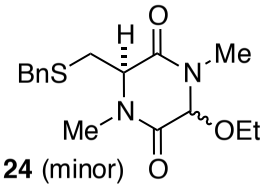
^{1}H NMR (400 MHz) in $CDCl_3$



24 (major)

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





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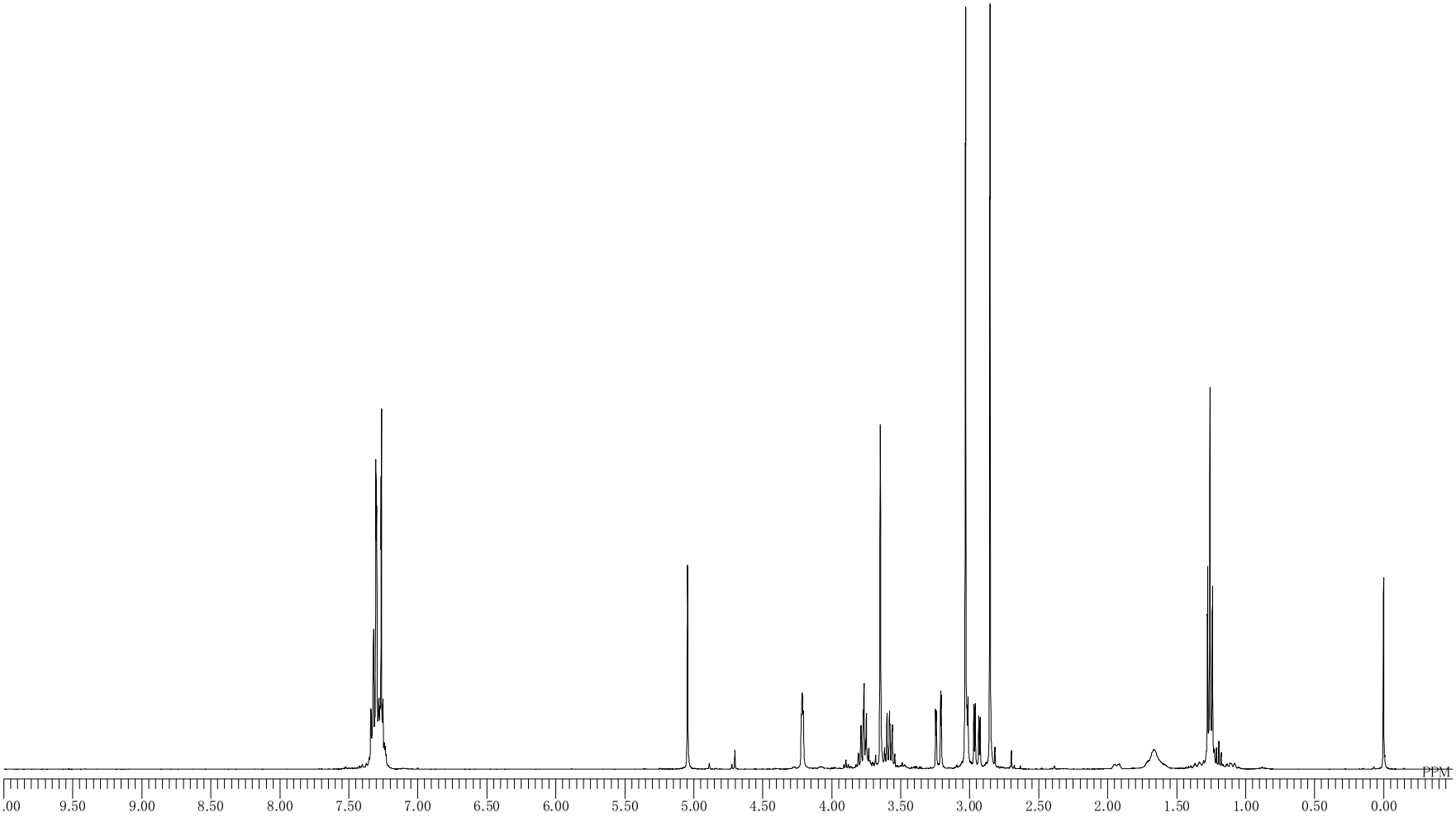
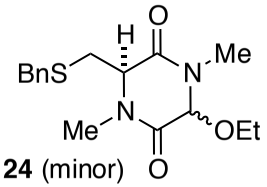
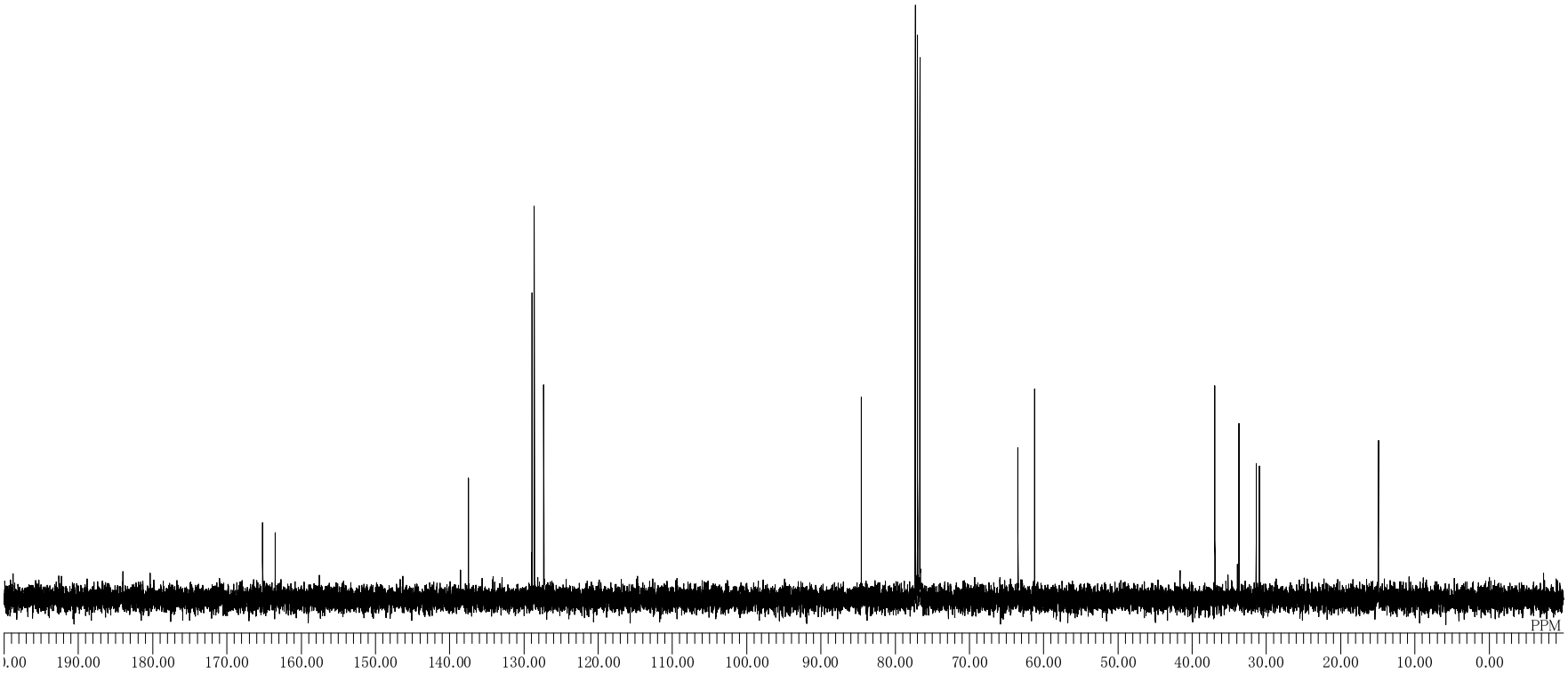
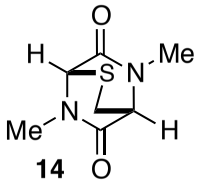




24 (minor)

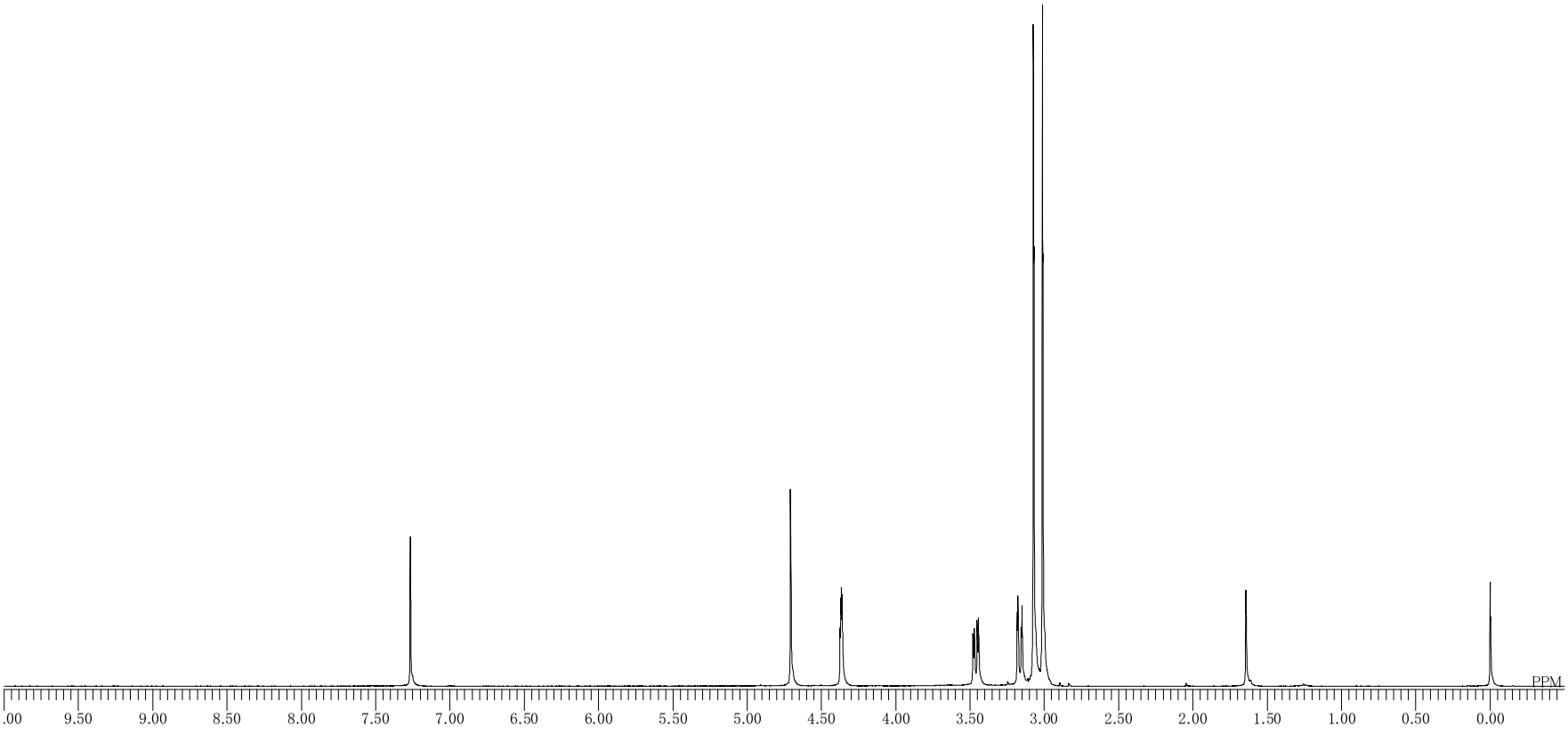
^{13}C NMR (100 MHz) in $CDCl_3$

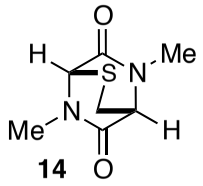




14

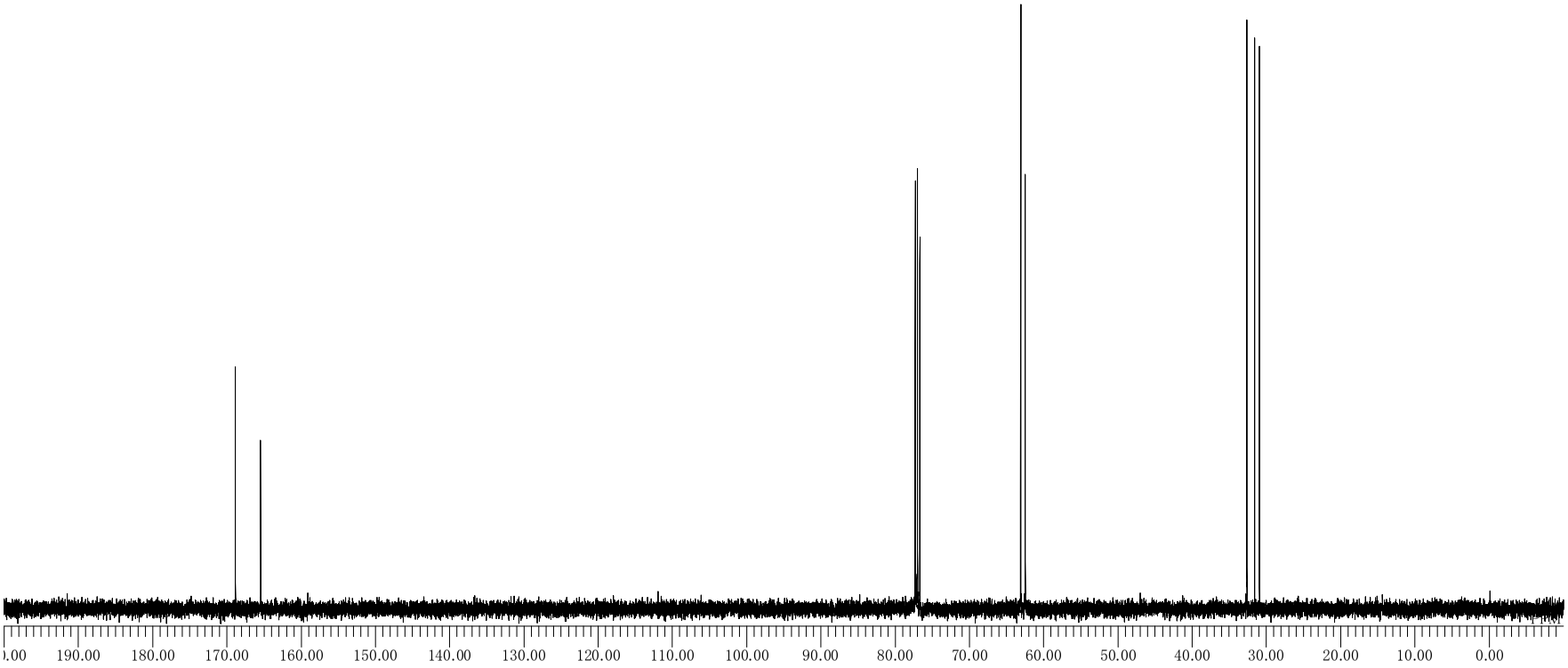
^{1}H NMR (400 MHz) in $CDCl_3$

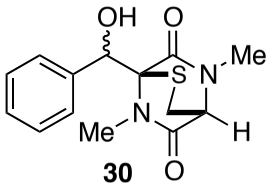




14

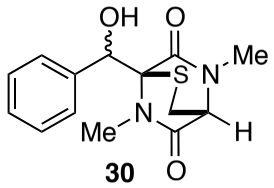
^{13}C NMR (100 MHz) in $CDCl_3$





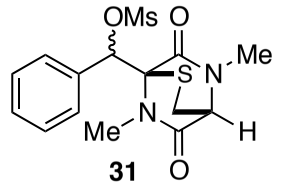
30

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



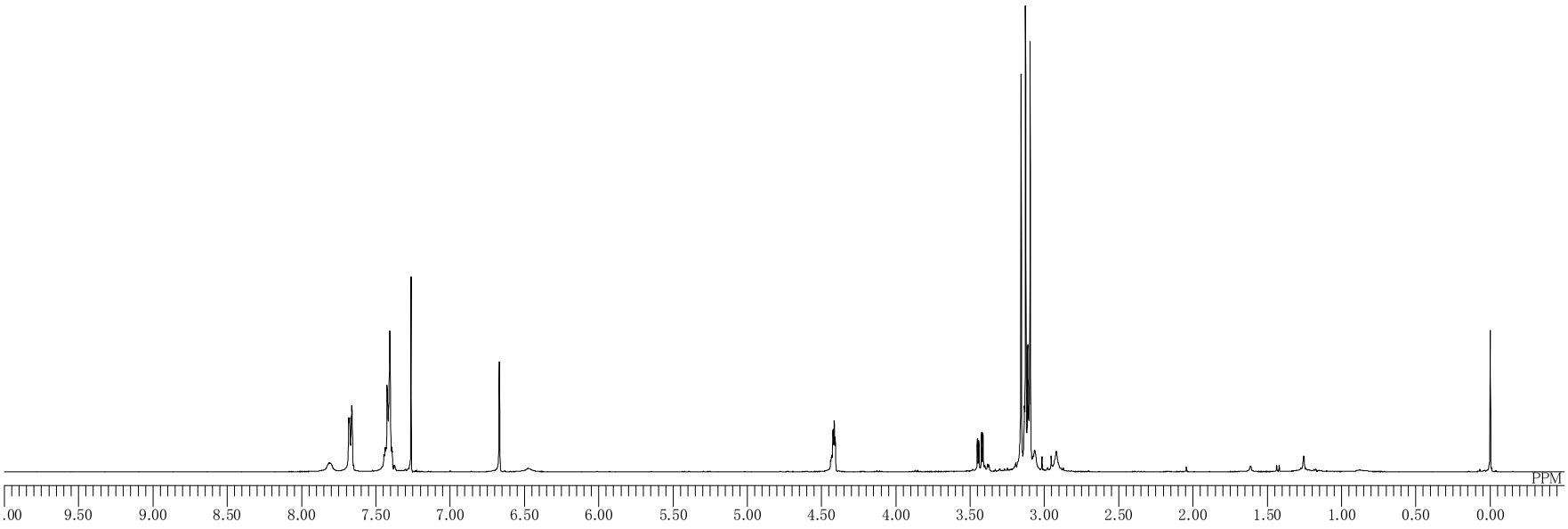
30

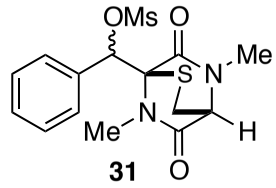
^{13}C NMR (100 MHz) in $CDCl_3$



31

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





31

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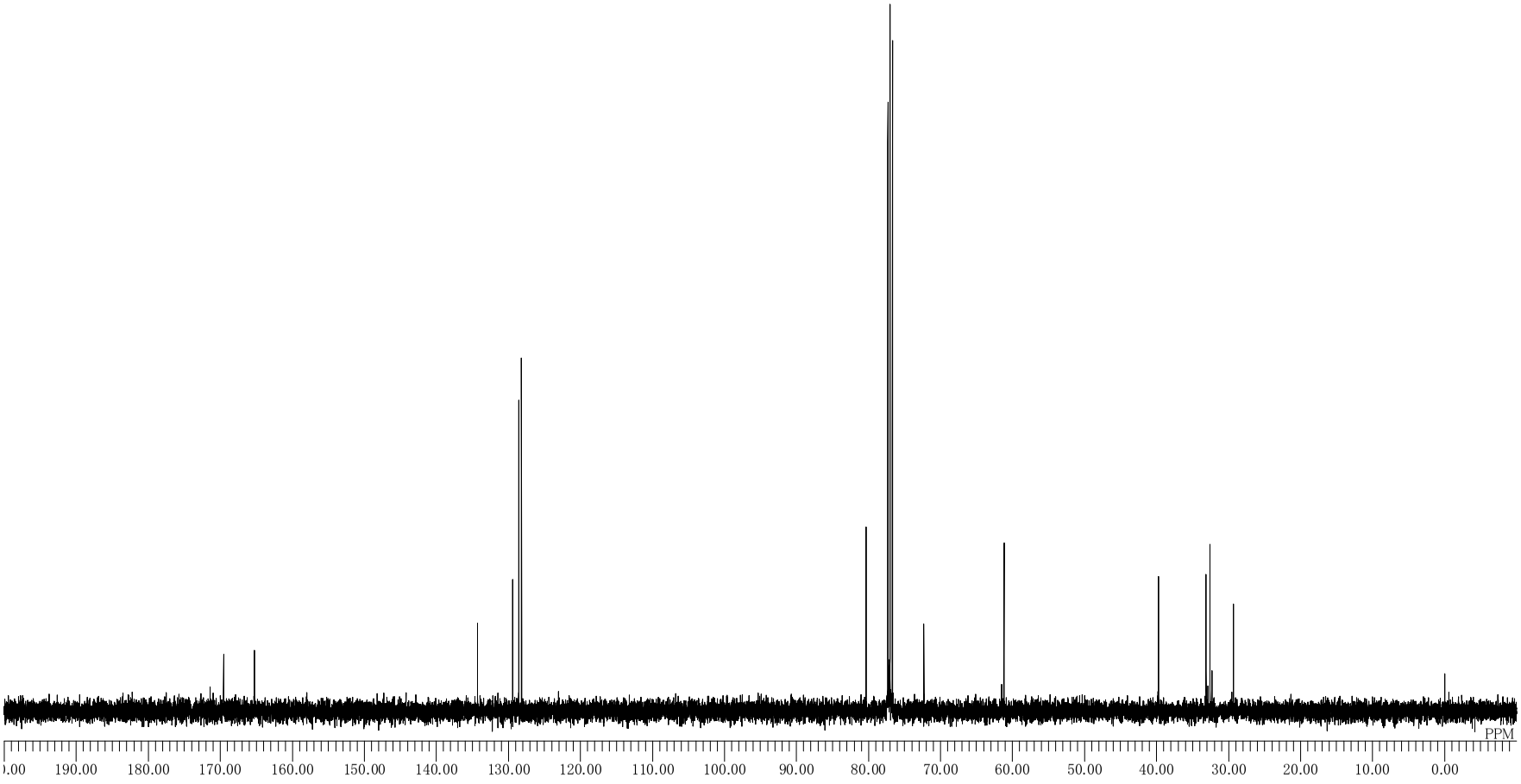
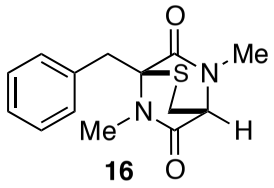
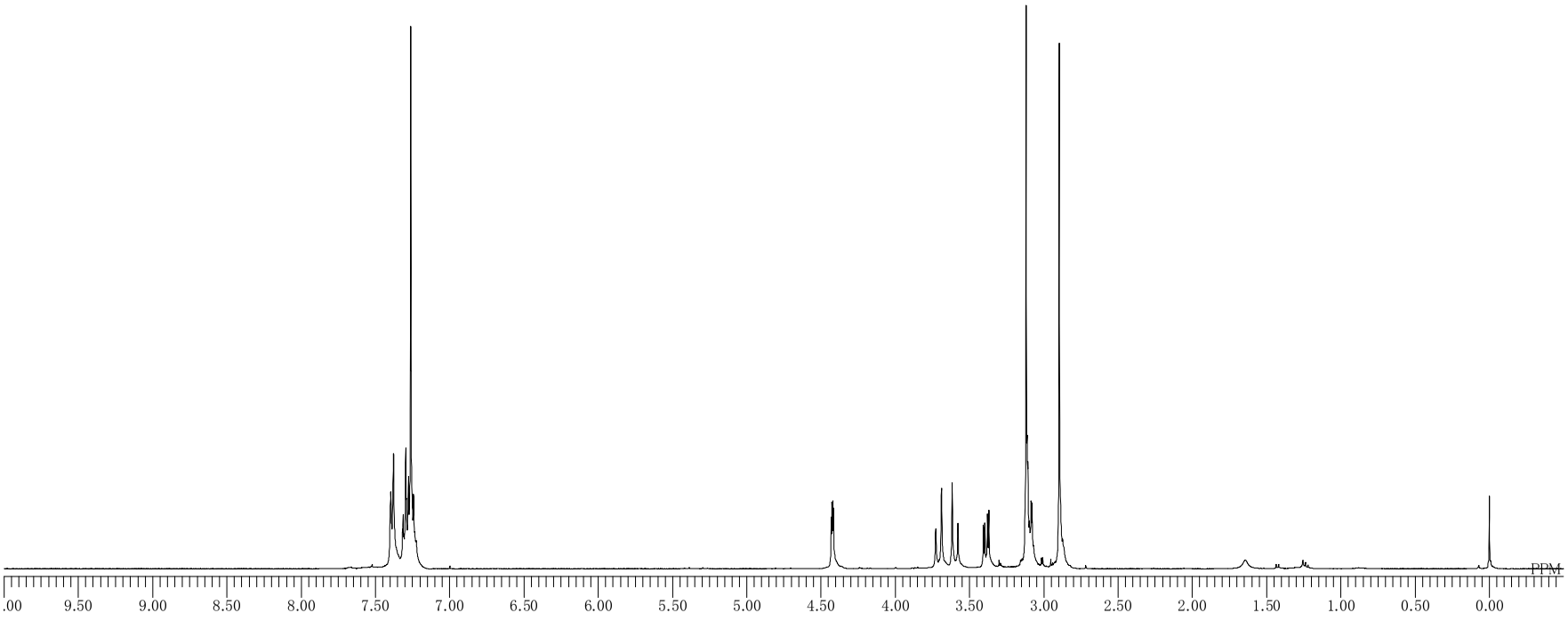
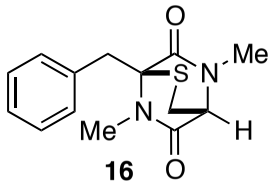




16

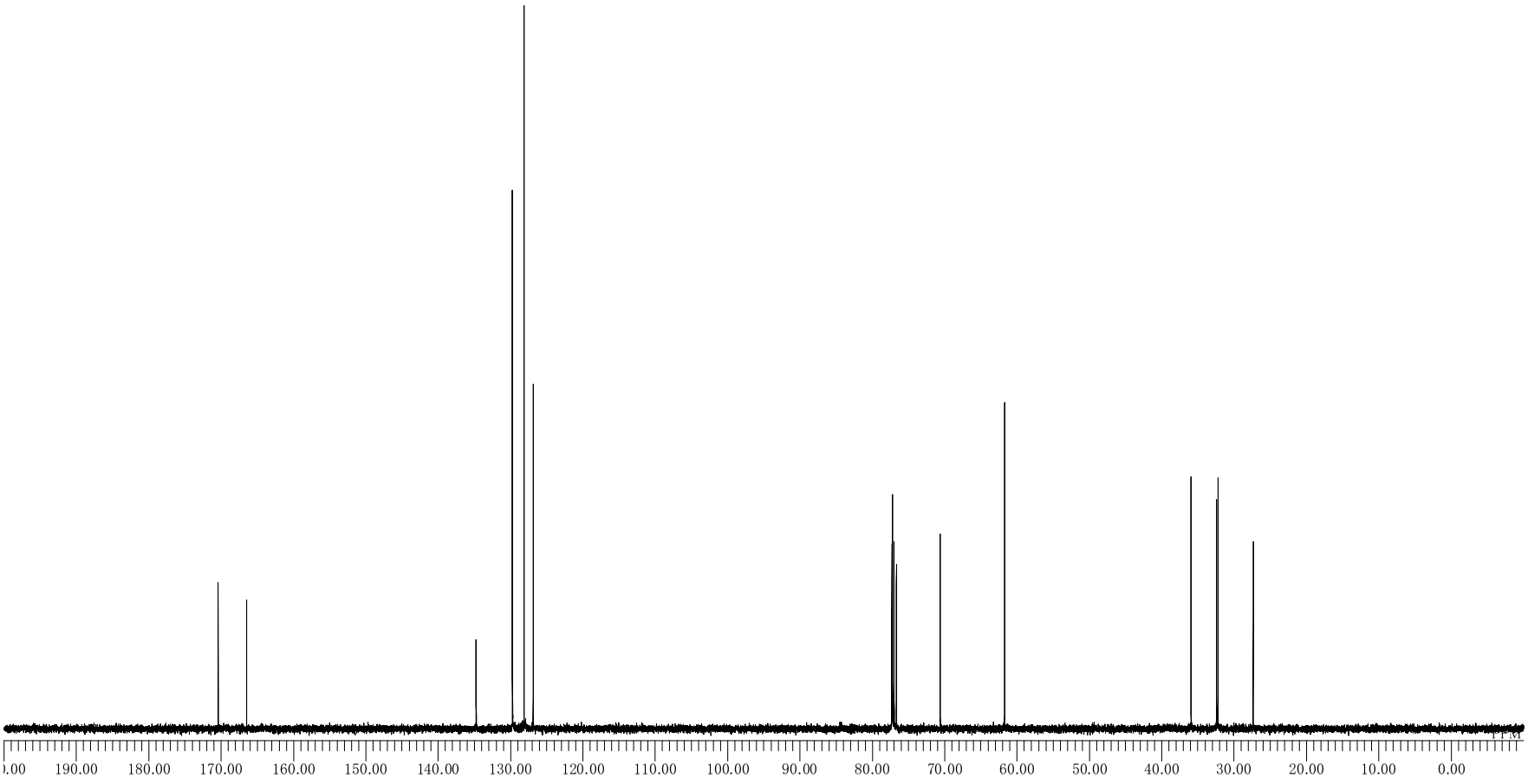
^{1}H NMR (400 MHz) in $CDCl_3$

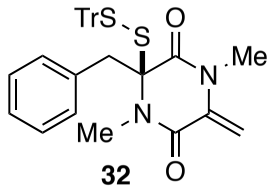




16

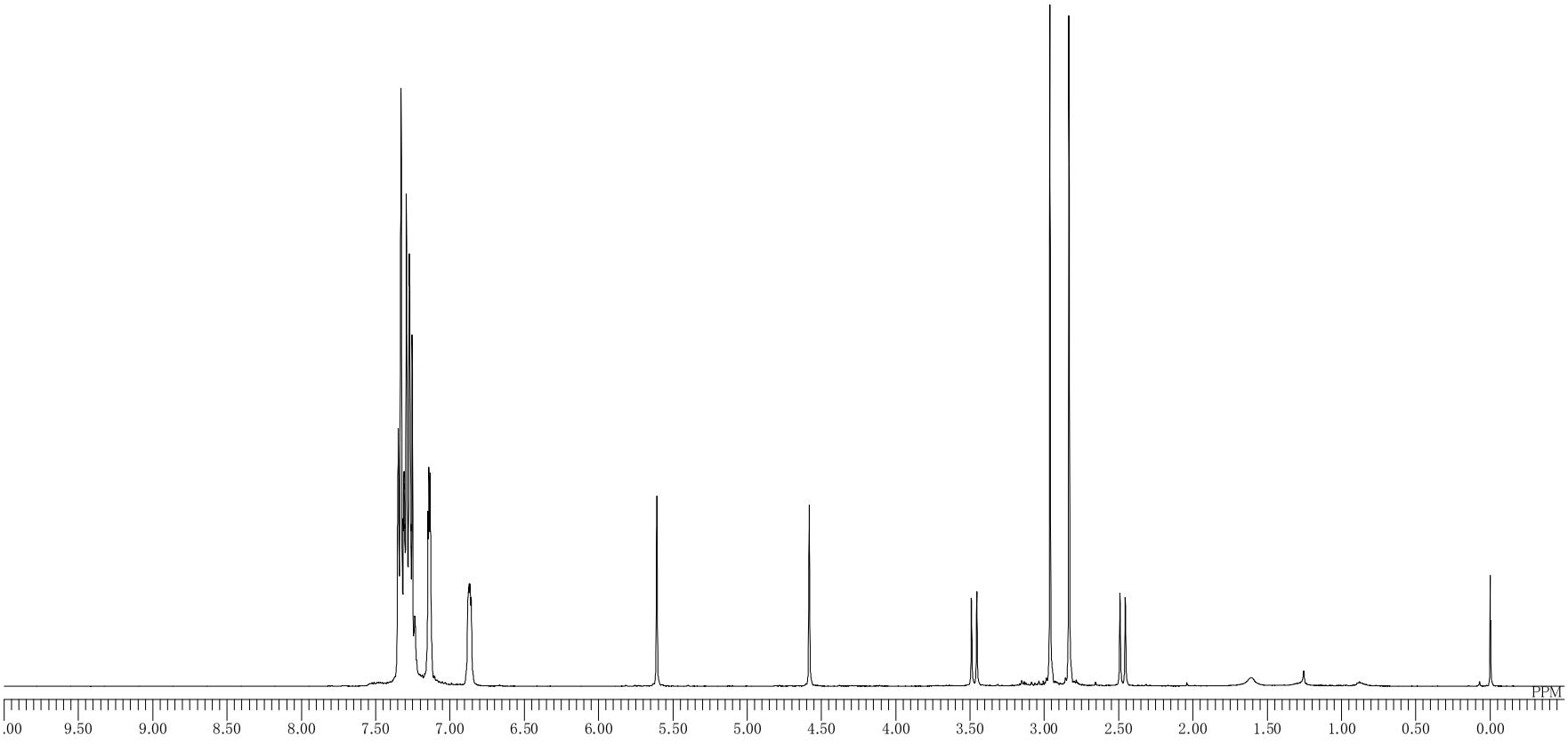
^{13}C NMR (100 MHz) in $CDCl_3$

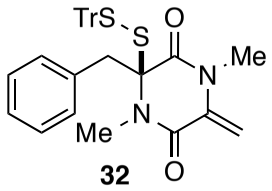




32

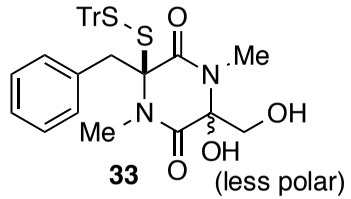
^{1}H NMR (400 MHz) in $CDCl_3$





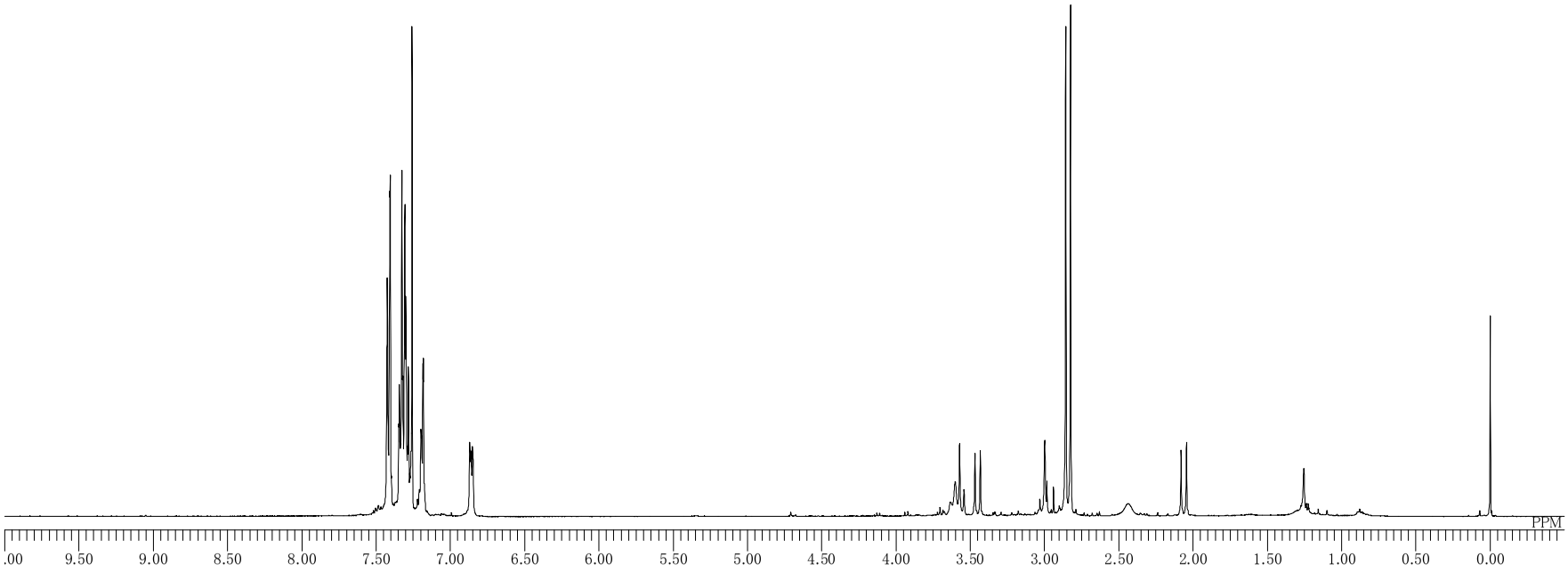
32

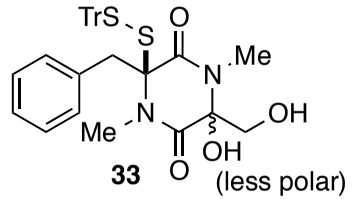
^{13}C NMR (100 MHz) in $CDCl_3$



33 (less polar)

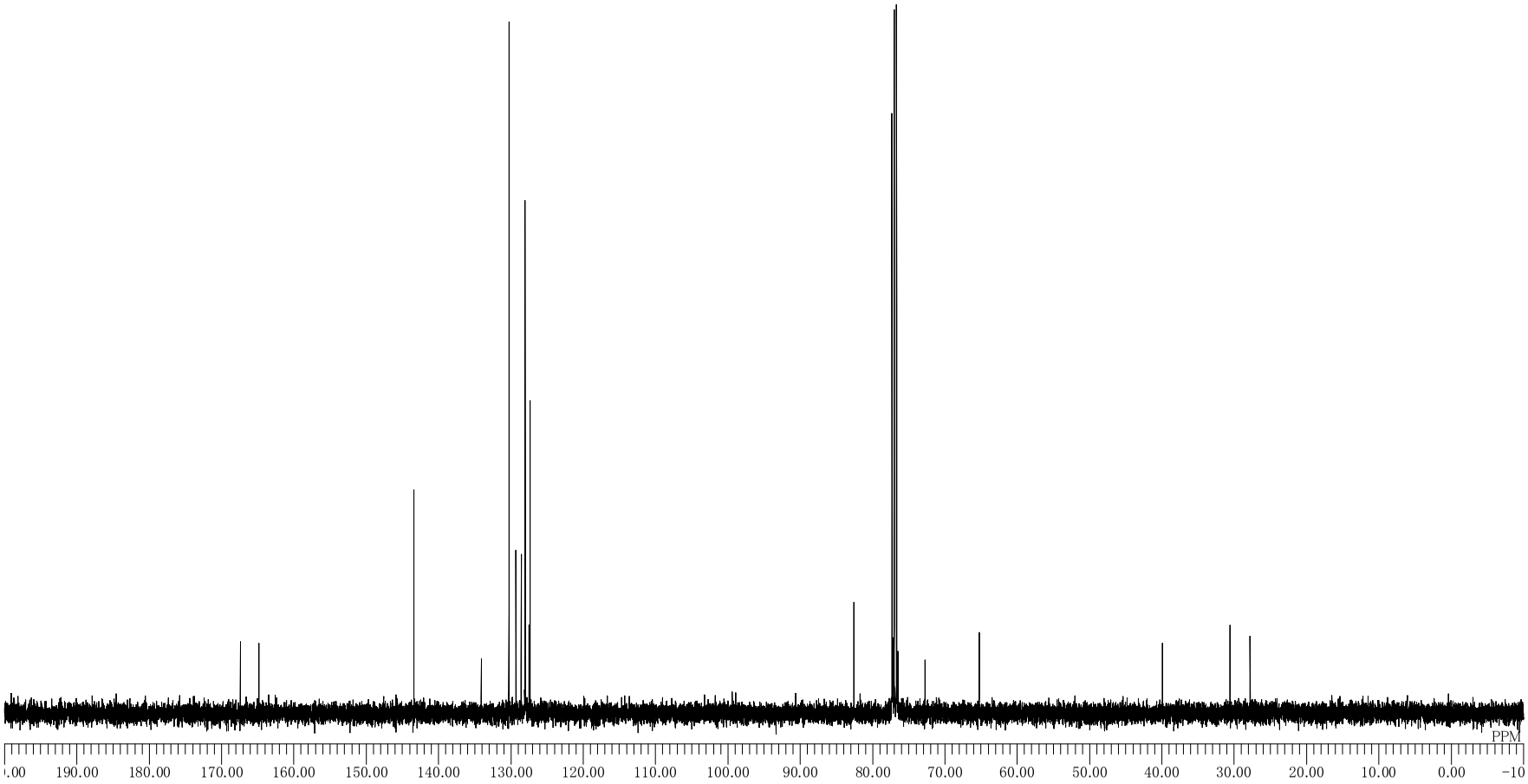
^{1}H NMR (400 MHz) in $CDCl_3$

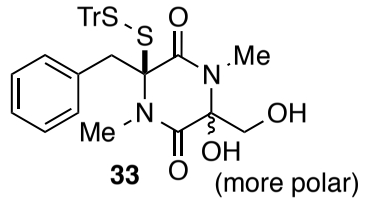




33 (less polar)

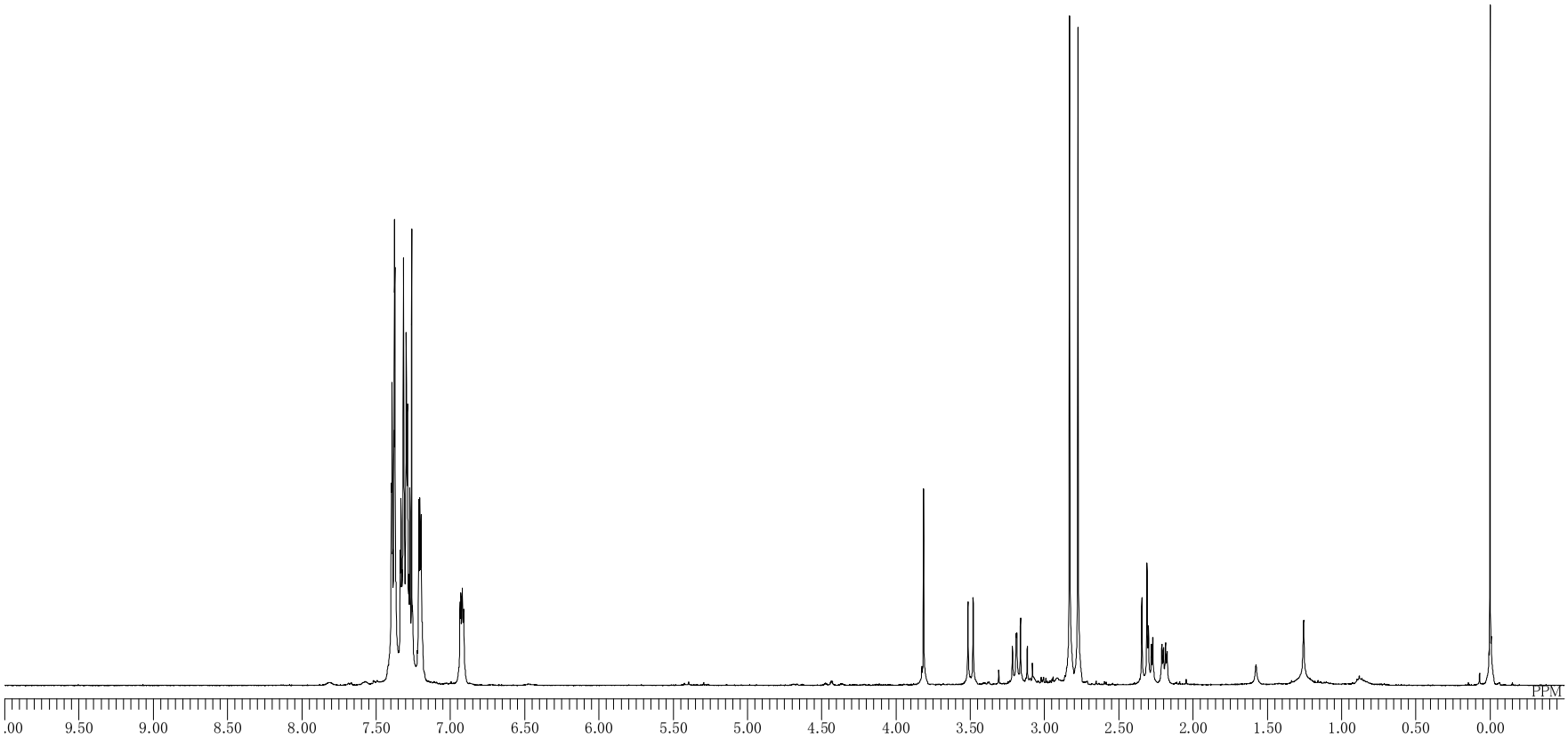
^{13}C NMR (100 MHz) in $CDCl_3$

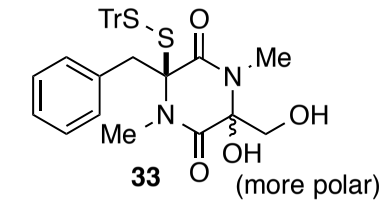




33 (more polar)

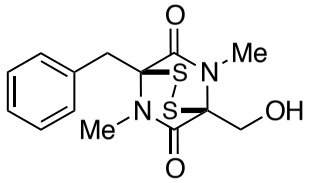
^{1}H NMR (400 MHz) in $CDCl_3$





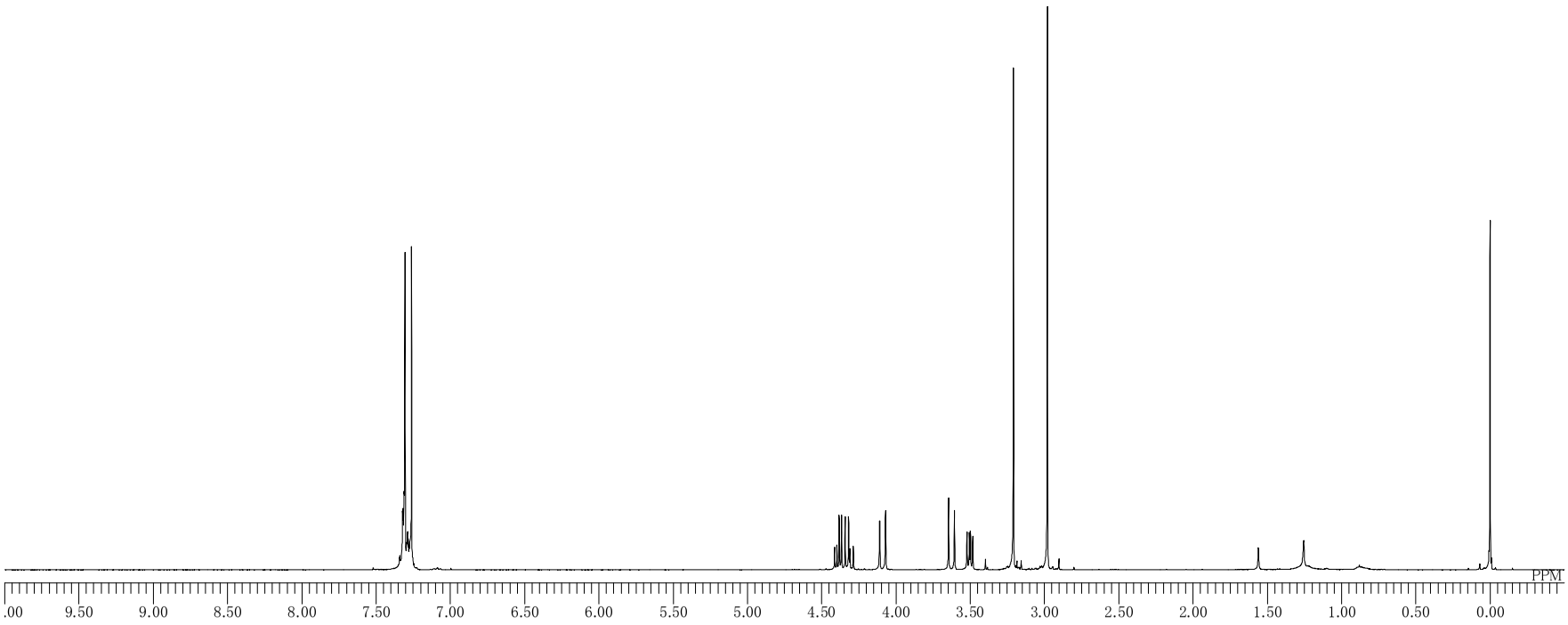
33 (more polar)

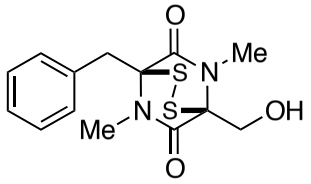
^{13}C NMR (100 MHz) in $CDCl_3$



(+)-hyalodendrin (**1**)

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





(+)-hyalodendrin (**1**)

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