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Supporting Information

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Asymmetric Total Synthesis of Pinnaic Acid

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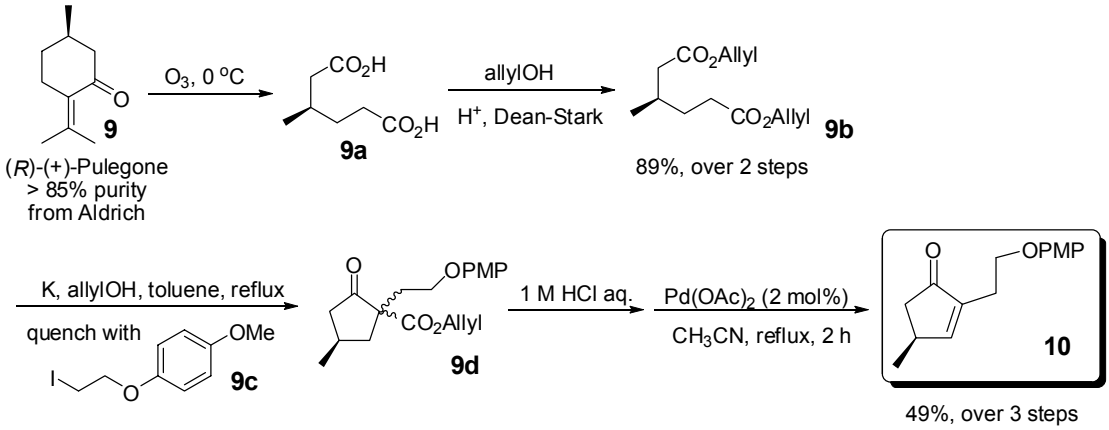
General Procedure Reagents were used as received from commercial suppliers unless otherwise indicated. All reactions were carried out under an atmosphere of N_2 or Ar unless otherwise indicated. THF was distilled from sodium/benzophenone prior to use. Alternatively, CH_2Cl_2, benzene, toluene, DMF, MeCN, MeOH, Et_2O, THF, EtOH, DMSO, and pyridine were purchased as dehydrated solvents and stored with active molecular sieves 3A or 4A under Ar prior to use for reactions. All solvents for work-up procedure were used as received. All inorganic salt solutions are aqueous unless otherwise stated. "Brine" refers to saturated aqueous NaCl solution. "Evaporation" refers to removal of solvent under reduced pressure (10-100 mmHg) with a rotary evaporator, followed by a period under high vacuum (< 0.1 mmHg) unless otherwise indicated. Column chromatography was performed with Fuji Silysia silica gel FL-60D. Analytical thin-layer chromatography (TLC) was performed with glass TLC plates (Merck 0.25mm coated silica gel $60F_{254}$ plates). Visualization was accomplished with UV light, phosphomolybdic acid, *p*-anisaldehyde or ninhydrin solution staining and subsequent hearting.

Melting points were uncorrected and measured with a Yanaco MP-J3 melting point apparatus. Boiling points were uncorrected and recorded during distillation. Optical rotations were measured with a JASCO DIP-1000 polarimeter. IR spectra were recorded on a JASCO FT/IR-230 spectrometer with samples prepared as a thin film on NaCl plates (for liquids and oil). Proton nuclear magnetic resonance (^{1}H NMR) data were acquired at 400 MHz on JEOL JNM-A400, 600 MHz on JEOL JNM-A600 or 800MHz on JEOL JNM-ECP800. Carbon nuclear magnetic resonance (^{13}C NMR) data were acquired at 100 MHz on JEOL JNM-A400, 150 MHz on JEOL JNM-A600 or 201MHz on JEOL JNM-ECP800. Data for ^{1}H NMR spectra are reported in the following format: chemical shift (multiplicity, coupling constant, number of atoms). Chemical shifts are indicated in parts per million (ppm) downfield from tetramethylsilane (TMS, $\delta = 0.00$) with residual undeuterated solvent peaks as internal reference, for ^{1}H NMR $CHCl_3$ (7.26), CHD2OD (3.31) or CHD_5 (7.16) and deuterated solvent peaks shifts for ^{13}C NMR $CDCl_3$ (77.0), C_6D_6 (128.4). Multiplicities are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) comp (overlapping signals of chemical nonequivalent protons), b (broad) or combinations of those. Coupling constants (*J*) are in hertz. Mass spectra are fast atom bombardment (FAB). HRFABMS were recorded on a JEOL JMS-700 spectrometer. The matrix used in HRFABMS analysis was *m*-nitrobenzyl alcohol (NBA).

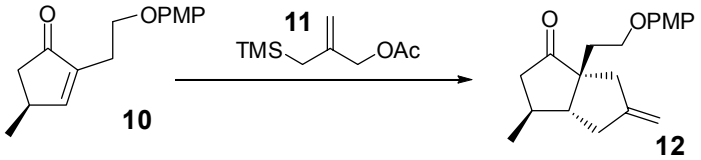


Scheme 1. Preparation of *(S)*-cyclopentanone **10** from *(R)*-pulegone

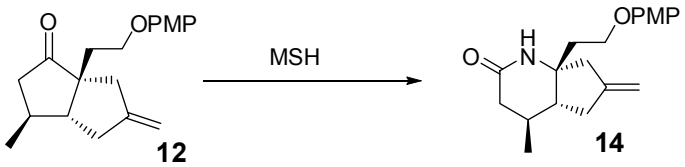
Diallyl ester 9b: Under slow stirring, O_3 was passed through a solution of (*R*)-(+)-pulegone **9** (30.0 g, 197 mmol; >85% purity from Aldrich, the purity is not the enantiomeric purity but due to the other chiral or achiral impurities) in ethyl acetate (350 mL), acetic acid (350 mL) and H_2O (24 mL) at 0°C, until no starting material was found on TLC (about 4 h). Excess O_3 was removed by a stream of N_2 for 10 min. Evaporation of the solvent afforded the crude dicarboxylic acid **9a** together with some pulegone-ozonide. A solution of concentrated sulfuric acid (0.5 mL) in allyl alcohol (450 mL) was added and the mixture was heated at reflux with a Dean-Stark trap for 4.5 h. Evaporation of the solvent gave a residue, which was distilled to afford ester **9b** (41.9 g, 89% over 2 steps) as a colorless oil, bp 115-130°C (150 Pa); $[\alpha]^{22}_{D}$ +3.0 (*c* 0.45, acetone); IR (film) ν_{max} 3084, 2960, 2876, 1738, 1731, 1648, 1177, 1156, 992, 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 16.8, 10.4, 6.0 Hz, 2 H), 5.32 (ddd, *J* = 16.8, 1.6, 0.8 Hz, 2 H), 5.24 (ddd, *J* = 10.4, 2.4, 1.2 Hz, 2 H), 4.58 (ddd, *J* = 6.0, 2.4, 1.6 Hz, 4 H), 2.37 (m, 2 H), 2.35 (dd, *J* = 15.2, 6.4 Hz, 1 H), 2.29 (dd, *J* = 15.2, 8.0 Hz, 1 H), 2.01 (m, 1 H), 1.72 (m, 1 H), 1.56 (m, 1 H), 0.97 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.4, 132.20, 132.18, 118.25, 118.21, 65.1, 65.0, 41.3, 31.8, 31.5, 29.9, 19.3; HRMS (FAB) calcd for $C_{13}H_{21}O_4$ $(M + H)^+$ 241.1440, found 241.1418.

Cyclopentenone 10: Toluene (90 mL) and potassium spheres (7.50 g, 192 mmol) were placed in a flask. Allyl alcohol (3.2 mL, 50 mmol) was added dropwise over 10 min. A vigorous exothermic reaction ensued. After the generation of H_2 gas ceased, the mixture was cooled to room temperature and a solution of ester **9b** (41.9 g, 175 mmol) in toluene (45 mL) was added followed by refluxing for 1 h. During the refluxing, toluene (180 mL) was added to maintain an efficient stirring. Next, a distillation head was attached and allyl alcohol was slowly removed as a toluene azeotrope. The reaction solution gradually changed to a solid mass; however, heating was continued until the distillation head temperature reached 110°C. The mixture was cooled to room temperature and toluene (180 mL) was added followed by a solution of ICH_2CH_2OPMP **9c** (53.4 g, 192 mmol) in toluene (180 mL). The mixture was heated with refluxing for 10 h, and then 4.5 M aqueous HCl (40 mL) was added dropwise for quenching at 0°C. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic phase was washed with water (150 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was diluted with acetone (600 mL) and mixed with 1 M aqueous HCl (300 mL). The

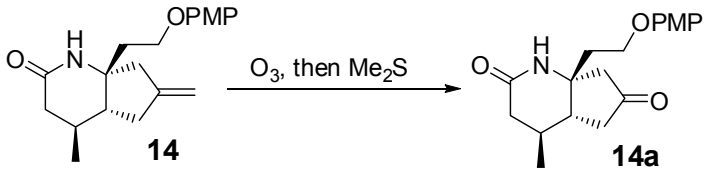
reaction was stirred at room temperature for 4 h, and then acetone was evaporated out and the aqueous residue was extracted with Et_2O (3 x 250 mL). The combined organic phase was washed with 1 M aqueous $NaHCO_3$ (250 mL) and brine (250 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (acetone/hexanes = 4:100). Collecting the fractions of the R_f range from 0.35 to 0.28 (acetone/hexanes = 15:100) afforded a mixture of several isomers. The mixture was dissolved in acetonitrile (4 mL) and a solution of $Pd(OAc)_2$ (0.75 g, 3.3 mmol) in acetonitrile (12 mL) was added. The reaction solution was then immersed in a preheated 90°C oil bath and stirred for 90 min. The reaction mixture was passed through a silica gel pad eluting with ethyl acetate to afford about a 2:1 mixture of **10** and 2-(2-(4-methoxyphenoxy)ethyl)-3-methylcyclopentenone. Purification by column chromatography (acetone/hexanes = 4:100 to 10:100) afforded cyclopentenone **10** (21.1 g, 49% over 3 steps) as a white solid, mp = 40.5°C.; $[\alpha]^{22}_D$ –58.2 (*c* 1.35, acetone); R_f = 0.19 (acetone/hexanes = 10:1); IR (film) ν_{max} 3044, 2956, 2872, 1702, 1634, 1508, 1230, 1040, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (dt, *J* = 2.4, 1.2 Hz, 1 H), 6.83 (m, 4 H), 4.05 (t, *J* = 6.0 Hz, 2 H), 3.76 (s, 3 H), 2.91 (dddq, *J* = 6.4, 2.4, 2.0, 7.2 Hz, 1 H), 2.64 (dd, *J* = 18.8, 6.4 Hz, 1 H), 2.63 (dt, *J* = 1.2, 6.0 Hz, 2 H), 1.97 (dd, *J* = 18.8, 2.0 Hz 1 H), 1.17 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 164.8, 153.8, 152.8, 141.5, 115.5, 114.6, 66.2, 55.7, 43.0, 33.6, 24.9, 20.2; HRMS (FAB) calcd for $C_{15}H_{19}O_3$ $(M + H)^+$ 247.1334, found 247.1347.



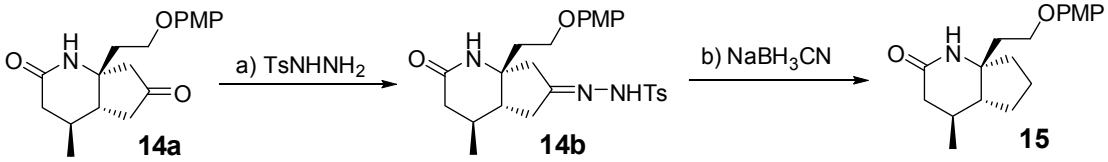
Alkene 12: To $Pd(OAc)_2$ (1.00 g, 4.43 mmol) in THF (5 mL) was added dropwise $(i\text{-PrO})_3P$ (7.7 mL, 31 mmol) at 0°C. The reaction mixture was stirred for 30 min, and then TMM precusor **11** (9.2 mL, 44 mmol) was added. The above mixture was added to a solution of cyclopentenone **10** (5.45 g, 22.1 mmol) in THF (1.5 mL). The reaction mixture in a sealed flask was then frozen by immersion of the flask in liquid N_2. When the solution was completely frozen, the flask was opened to the high vacuum and pumped 2-3 minutes, with the flask still immersed in liquid N_2. The flask was then closed and warmed until the solution had completely melted. This process was repeated three times and after the last cycle the flask was backfilled with an argon gas. The degassed reaction mixture was heated with refluxing for 2 h. Evaporation of the solvent gave a residue, which was purified by column chromatography (acetone/hexanes = 4:100) to afford alkene **12** (5.31 g, 80%) as a colorless oil, $[\alpha]^{20}_D$ –43.1 (*c* 1.33, $CHCl_3$); R_f = 0.29 (acetone/hexanes = 15:100); IR (film) ν_{max} 3076, 2958, 2922, 1736, 1508, 1230, 1040, 823 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.80 (m, 4 H), 4.92 (s, 1 H), 4.90 (s, 1 H), 3.94 (m, 2 H), 3.76 (s, 3 H), 2.62 (dddd, *J* = 16.2, 7.2, 3.2, 2.4 Hz, 1 H), 2.51 (dd, *J* = 17.4, 7.8 Hz, 1 H), 2.48 (ddd, *J* = 16.8, 4.8, 2.8 Hz, 1 H), 2.36 (d, *J* = 16.2 Hz, 1 H), 2.28 (d, *J* = 16.8 Hz, 1 H), 2.24 (dd, *J* = 8.4, 6.6 Hz, 1 H), 2.21 (dd, *J* = 7.8, 7.2 Hz, 1 H), 2.00 (dd, *J* = 17.4, 12.0 Hz, 1 H), 1.84 (ddd, *J* = 14.4, 6.6, 5.4 Hz 1 H), 1.77 (m, 1 H),1.09 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.6, 153.8, 152.7, 149.4, 115.1, 114.6, 108.1, 64.9, 59.0, 55.7, 52.6, 46.8, 41.7, 36.5, 34.3, 33.8, 19.0; HRMS (FAB) calcd for $C_{19}H_{25}O_3Na$ $(M + Na)^+$ 323.1623, found 323.1639.



Lactam (14): To ketone **12** (0.13 g, 0.43 mmol) and molecular sieves 4A (0.2 g) in CH_2Cl_2 (0.5 mL) was added a solution of newly prepared[1] MSH (*O*-mesitylsulfonylhydroxylamine, 0.14 g, 0.65 mmol) in CH_2Cl_2 (1 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 h. Alumina (Merck, activity I; 0.3 g) was added and the stirring was continued for a further 1 h. After filtration and evaporation of the solvent, the residue was purified by column chromatography (CH_2Cl_2/hexanes = 0:1 to 1:1 to 1:0 then MeOH/CH_2Cl_2 =10:100) to afford lactam **14** (0.060 g, 43%) as a yellow oil, together with the recovered starting material ketone **12** (0.075 g, 57%). R_f = 0.28 (MeOH/CH_2Cl_2 = 3:100); ^{1}H NMR (600 MHz, $CDCl_3$) δ6.83 (dd, J = 13.8, 9.0 Hz, 4 H), 6.63 (br, 1 H), 4.91 (s, 1 H), 4.88 (s, 1 H), 4.05 (m, 2 H), 3.76 (s, 3 H), 2.62 (dd, J = 16.2, 7.8 Hz, 1 H), 2.56 (m, 2 H), 2.42 (d, J = 17.4 Hz, 1 H), 2.38 (dd, J = 17.4, 2.4 Hz, 1 H), 2.08 (ddd, J = 15.0, 7.2, 6.0 Hz, 1 H), 1.95 (dd, J = 16.8, 11.2 Hz, 1 H), 1.87 (ddd, J = 9.6, 4.8, 4.8 Hz, 1 H), 1.79 (m, 1 H), 1.76 (m, 1 H), 0.99 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ220.6, 153.8, 152.7, 149.4, 115.1, 114.6, 108.1, 64.9, 59.0, 55.7, 52.6, 46.8, 41.7, 36.5, 34.3, 33.8, 19.0; HRMS (FAB) calcd for $C_{19}H_{26}NO_3$ $(M + H)^+$ 315.1913, found 316.1873.

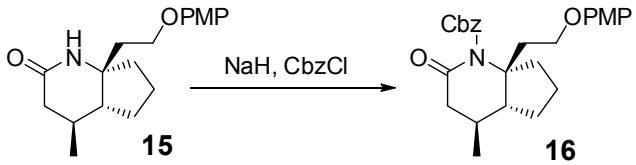


Ketone 14a: A slow O_3 flow was passed through the solution of alkene **14** (1.10 g, 3.49 mmol) in methanol (100 mL) at -78°C until the starting material was consumed by monitoring with TLC (about 1 h). Excess ozone was removed under a stream of N_2 for 10 min and then Me_2S (13 mL) was added dropwise at -78°C. The reaction mixture was allowed to rise to room temperature naturally over about 10 min and then concentrated under vacuum. The residue was purified by column chromatography (MeOH/CH_2Cl_2 = 0:100 to 1:100 to 5:100) to afford ketone **14a** (0.91 g, 82%) as a yellow oil, R_f = 0.37 (MeOH/CH_2Cl_2 = 3:100); ^{1}H NMR (600 MHz, $CDCl_3$) δ7.59 (br, 1 H), 6.81 (s, 4 H), 4.07 (m, 2 H), 3.75 (s, 3 H), 2.60 (dd, J = 19.8, 7.8 Hz, 1 H), 2.57 (dd, J = 30.6, 18.6 Hz, 2 H), 2.43 (d, J = 19.8 Hz, 1 H), 2.42 (dd, J = 17.4, 4.2 Hz, 1 H), 2.16 (m, 2 H), 2.01 (dd, J = 17.4, 12.0 Hz, 1 H), 1.96 (ddd, J = 15.0, 4.8, 4.2 Hz, 1 H), 1.82 (m, 1 H), 1.02 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ213.7, 171.4, 154.1, 152.1, 115.3, 114.6, 64.3, 60.5, 55.5, 51.0, 44.5, 40.9, 39.6, 38.5, 29.5, 19.3; HRMS (FAB) calcd for $C_{18}H_{24}NO_4$ $(M + H)^+$ 318.1705, found 318.1734.



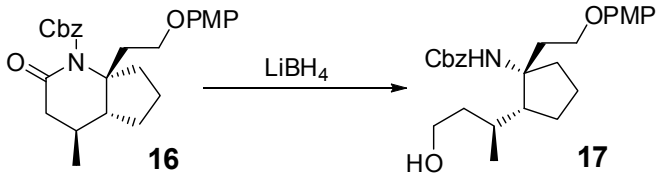
Lactam 15: Ketone **14a** (1.29 g, 4.07 mmol) and *p*-toluenesulfonhydrazide ($TsNHNH_2$, 1.53 g, 8.15 mol) in methanol (15 mL) was stirred at 50°C for 13 h. After evaporation of the solvent, the

residue was dissolved in THF (14 mL) and mixed with $NaBH_3CN$ (1.54 g, 24.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.092 g, 0.48 mmol). The reaction mixture was heated with refluxing for 19 h. The reaction was quenched at 0°C by addition of H_2O (20 mL) and CH_2Cl_2 (20 mL). After stirring at room temperature for a further 30 min, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phase was washed with 1 M aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (acetone/hexanes =1:4 to 1:1 to 1:0) to afford lactam **15** (0.75 g, 60%) as a yellow oil, R_f = 0.29 (acetone/hexanes = 2:5); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.82 (m, 4 H), 6.80 (br, 1 H), 4.02 (m, 2 H), 3.75 (s, 3 H), 2.29 (dd, J = 16.8, 3.0 Hz, 1 H), 2.07 (ddd, J = 14.4, 7.2, 6.0 Hz, 1 H), 1.85-1.94 (m, 4 H), 1.69-1.77 (m, 4 H), 1.59 (m, 2 H), 1.00 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 153.9, 152.5, 115.3, 114.6, 64.9, 64.0, 55.6, 49.1, 41.1, 40.1, 38.5, 32.1, 29.5, 22.6, 20.1; HRMS (FAB) calcd for $C_{18}H_{26}NO_3$ $(M + H)^+$ 304.1913, found 304.1931.



15 **16**

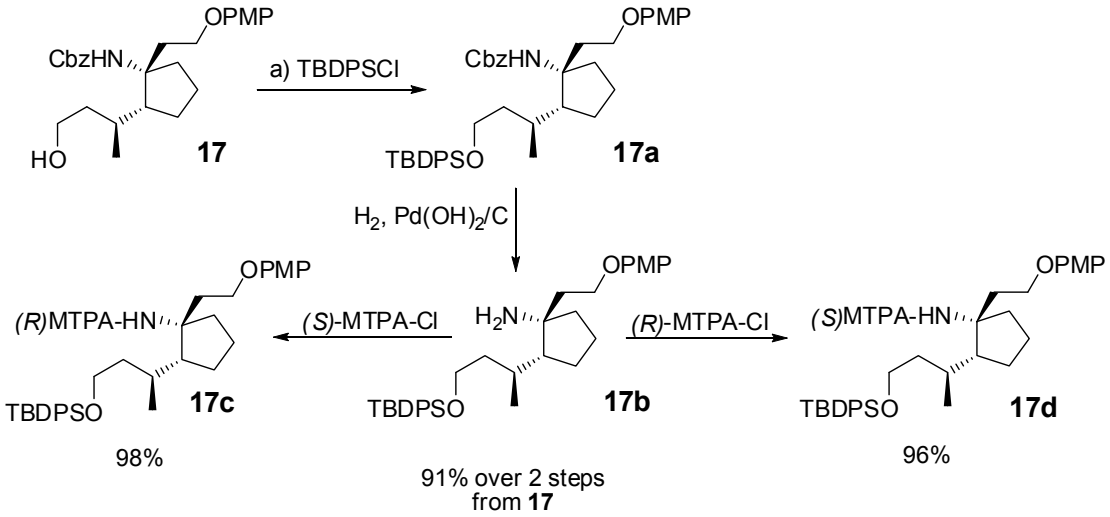
Cbz-lactam 16: To a solution of lactam **15** (0.372 g, 1.23 mmol) and NaH (60% in mineral oil, 0.15 g, 3.7 mmol) in THF (10 mL) was added CbzCl (0.35 mL, 2.5 mmol) at room temperature. The reaction mixture was heated with refluxing for 7 h. Saturated aqueous NH_4Cl (15 mL) and ethyl acetate (15 mL) were added at 0°C. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic phase was washed with brine (40 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (EtOAc/hexanes = 15:100 to 40:100) to afford Cbz-lactam **16** (0.469 g, 87%) as a colorless oil, $[\alpha]^{26}_D$ +110 (c 0.93, $CHCl_3$); R_f = 0.28 (EtOAc/hexanes = 30:100); IR (film) ν_{max} 3040, 2960, 2878, 1731, 1708, 1507, 1456, 1229, 1040, 824, 739, 699 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42-7.29 (m, 5 H), 6.78 (m, 4 H), 5.26 (s, 2 H), 3.99 (t, J = 6.0, 2 H), 3.74 (s, 3 H), 2.48 (ddd, J = 15.0, 5.4, 5.4 Hz, 1 H), 2.42 (dd, J = 17.4, 3.6 Hz, 1 H), 2.12 (m, 1 H), 2.06-2.03 (m, 3 H), 1.80 (m, 1 H), 1.73 (m, 1 H), 1.64 (m, 1 H), 1.53 (m, 2 H), 0.96 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 156.0, 153.9, 152.4, 135.2, 128.5, 128.3, 128.2, 115.2, 114.7, 69.5, 68.9, 65.0, 55.7, 50.2, 40.8, 40.7, 40.0, 31.6, 30.5, 23.1, 19.3; HRMS (FAB) calcd for $C_{26}H_{31}NO_5$ (M^+) 437.2202, found 437.2169.



16 **17**

Alcohol 17: Lactam **16** (28.4 mg, 0.0650 mmol), LiBr (23 mg, 0.26 mmol) and $NaBH_4$ (11 mg, 0.29 mmol) in THF (1.5 mL) were stirred at 50°C for 7 h. Saturated aqueous NH_4Cl (3 mL) and ethyl ether (3 mL) were added at 0°C. After stirring at room temperature for 30 min, the layers were separated and the aqueous layer was extracted with ethyl ether (2 x 3 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum to afford alcohol **17** (28.7

mg, 100%) as a colorless oil, R_f = 0.31 (EtOAc/hexanes = 30:100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 6.81 (m, 4 H), 5.22 (br, 1 H), 5.04 (m, 2 H), 3.99 (t, J = 2.4, 2 H), 3.75 (s, 3 H), 3.70 (ddd, J = 10.8, 6.4, 6.4 Hz, 1 H), 3.58 (ddd, J = 10.8, 6.4, 6.4 Hz, 1 H), 2.64 (ddd, J = 14.4, 6.4, 6.4 Hz, 1 H), 2.10 (br, 1 H), 1.97-1.89 (m, 5 H), 1.76 (m, 1 H), 1.70-1.54 (m, 4 H), 1.38 (ddd, J = 13.6, 13.2, 6.4 Hz, 1 H), 0.86 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 153.7, 152.8, 136.6, 128.4, 128.00, 127.98, 115.3, 114.5, 66.3, 65.6, 64.3, 60.4, 55.7, 51.9, 39.5, 37.4, 37.2, 28.3, 26.0, 21.4, 17.5; HRMS (FAB) calcd for $C_{26}H_{36}NO_5$ $(M+H)^+$ 442.2593, found 442.2617.



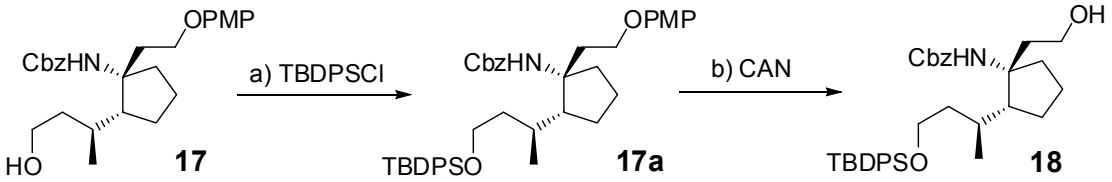
Scheme 2. EE determination of **17** by modified Mosher's method.
By comparison of ^{1}H NMR spectrum of **17c** and **17d**, no diastereomeric peak was found in each spectra. Therefore **17** was determined as more than 98% ee.

Amine 17b: To alcohol **17** (0.016 g, 0.036 mmol) and DMAP (0.002 g, 0.02 mmol) in CH_2Cl_2 (0.5 mL) were added Et_3N (0.050 mL, 0.36 mmol) and TBDPSCl (0.02 mL, 0.08 mmol) at 0°C. The reaction mixture was stirred at room temperature for 4 h. Next, 1 M aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was dissolved in ethanol (3 mL) and acetic acid (0.01 mL). Pd $(OH)_2$/C (5 wt% from N. E. CHEMCAT Co., Tokyo, Japan, 53% H_2O containing, 0.03 g, 0.006 mmol) was added at 0°C. After stirring at 40°C for 11 h, Et_3N (0.1 mL) was added and the reaction mixture was passed through a silica gel pad eluting with Et_3N/EtOH (1:100). After evaporation of the solvent, the residue was purified by column chromatography (Et_3N/CH_2Cl_2 = 0:100 to 5:100) to afford amine **17b** (17.8 mg, 91% over 2 steps) as a yellow oil, R_f = 0.05 (acetone/CH_2Cl_2 = 3:100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4 H), 7.41-7.35 (m, 6 H), 6.83 (m, 4 H), 4.06 (m, 2 H), 3.76 (s, 3 H), 3.70 (m, 2 H), 2.09 (ddd, J = 14.0, 7.6, 6.4 Hz, 1 H), 1.82-1.66 (m, 6 H), 1.52-1.48 (m, 3 H), 1.42-1.33 (m, 2 H), 1.05 (s, 9 H), 0.86 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 153.1, 135.59, 135.57, 133.98, 133.95, 129.6, 127.6, 115.3, 114.6, 66.0, 62.1, 61.4, 55.7, 53.5, 41.8, 40.5, 40.3, 28.5, 26.9, 26.6, 21.1, 19.2, 18.0.

***(R)*-MTPA-amide 17c**: To amine **17b** (8.7 mg, 0.016 mmol) and DMAP (2.0 mg, 0.016 mmol) in CH_2Cl_2 (0.2 mL) were added Et_3N (0.1 mL, 0.7 mmol) and *(S)*-MTPA-Cl (12.5 μL, 0.066 mmol)

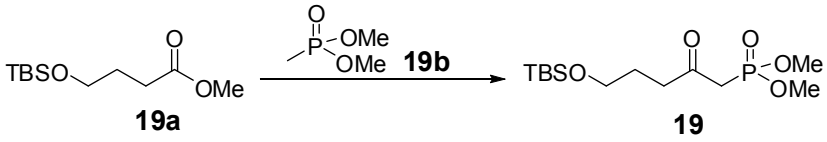
at 0°C. The reaction mixture was stirred at room temperature for 6 h and then quenched with absolute MeOH (1 mL) at 0°C. After evaporation of the solvent, the residue was purified by a short column chromatography (acetone/hexanes =1:10 to 3:10) to afford *(R)*-MTPA-amide **17c** (11.9 mg, 98%) as a colorless oil, R_f = 0.46 (acetone/hexanes = 3:10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (m, 4 H), 7.51 (m, 2 H), 7.41-7.35 (m, 9 H), 7.18 (br, 1 H), 6.78 (m, 4 H), 3.97 (m, 2 H), 3.76 (s, 3 H), 3.70 (ddd, J = 10.2, 6.6, 3.6 Hz, 1 H), 3.63 (ddd, J = 10.2, 6.6, 3.6 Hz, 1 H), 2.44 (ddd, J = 13.8, 7.2, 6.6 Hz, 1 H), 2.30 (ddd, J = 13.8, 7.8, 6.0 Hz, 1 H), 2.10 (ddd, J = 13.8, 6.6, 6.0 Hz, 1 H), 1.93-1.89 (m, 2 H), 1.80 (m, 1 H), 1.80 (m, 2 H), 1.61 (m, 1 H), 1.53-1.47 (m, 2 H), 1.43 (m, 1 H), 1.04 (s, 9 H), 0.81 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 153.8, 152.8, 135.55, 135.53, 133.9, 132.9, 129.6, 129.3, 128.5, 127.6, 127.4, 115.3, 114.6, 65.5, 65.0, 62.0, 55.7, 54.9, 53.2, 40.1, 38.2, 36.4, 28.8, 26.9, 26.1, 21.9, 19.2, 16.8.

***(S)*-MTPA-amide 17d**: To amine **17b** (9.1 mg, 0.016 mmol) and DMAP (2.0 mg, 0.016 mmol) in CH_2Cl_2 (0.2 mL) were added Et_3N (0.1 mL, 0.7 mmol) and *(R)*-MTPA-Cl (12.5 μL, 0.066 mmol) at 0°C. The reaction mixture was stirred at room temperature for 6 h and then quenched with absolute MeOH (1 mL) at 0°C. After evaporation of the solvent, the residue was purified by a short column chromatography (acetone/hexanes =1:10 to 3:10) to afford *(S)*-MTPA-amide **17d** (12.2 mg, 96%) as a colorless oil, R_f = 0.46 (acetone/hexanes = 3:10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66-7.64 (m, 4 H), 7.48 (m, 2 H), 7.41-7.30 (m, 12 H), 6.76 (m, 4 H), 3.92 (t, J = 6.6 Hz, 2 H), 3.75 (s, 3 H), 3.69 (m, 1 H), 3.634 (m, 1 H), 2.43 (ddd, J = 14.4, 6.6, 6.6 Hz, 1 H), 2.33 (ddd, J = 13.2, 7.8, 5.4 Hz, 1 H), 2.05 (ddd, J = 15.0, 6.6, 6.0 Hz, 1 H), 1.91-1.85 (m, 2 H), 1.79-1.69 (m, 3 H), 1.66-1.58 (m, 2 H), 1.52-1.43 (m, 2 H), 1.03 (s, 9 H), 0.83 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 153.8, 152.8, 135.54, 135.52, 133.9, 132.6, 129.58, 129.55, 129.2, 128.5, 127.6, 127.5, 115.3, 114.6, 65.5, 65.0, 62.1, 55.7, 55.0, 53.4, 40.2, 38.3, 36.4, 28.9, 26.9, 26.3, 21.9, 16.9, 1.0.

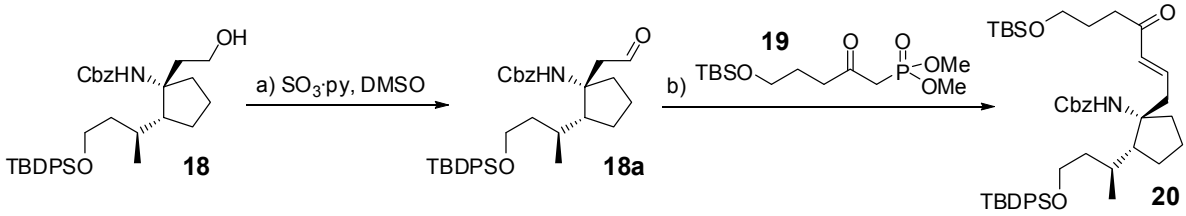


Alcohol 18: To alcohol **17** (0.446 g, 1.01 mmol) and DMAP (0.013 g, 0.10 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (0.22 mL, 1.5 mmol) and TBDPSCl (0.39 mL, 1.5 mmol) at 0°C. The reaction mixture was stirred at room temperature for 4 h. Next, 1 M aqueous $NaHCO_3$ (10 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was dissolved in CH_3CN (24 mL) and H_2O (6 mL). $(NH_4)_2Ce(NO_3)_6$ (CAN, 1.0 g, 1.82 mmol) was added and the reaction mixture was stirred at 0°C for 45 min. $CHCl_3$ (20 mL) and H_2O (20 mL) were added. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 x 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (acetone/CH_2Cl_2 = 0:100 to 5:100) to afford alcohol **18** (0.439 g, 76% over 2 steps) as a yellow oil, $[\alpha]^{28}_D$ -10.3 (c 1.13, $CHCl_3$); R_f = 0.43 (acetone/CH_2Cl_2 = 3:100); IR (film) ν_{max} 3441, 3356, 3076, 2958, 2858, 1710, 1504, 1426, 1255, 1110, 1084, 702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66

(m, 4 H), 7.41-7.30 (m, 11 H), 5.05 (br, 1 H), 5.00 (d, J = 12.6 Hz, 2 H), 3.69 (dd, J = 15.0, 6.0 Hz, 2 H), 3.65 (m, 2 H), 2.36 (br, 1 H), 2.15 (ddd, J = 14.4, 6.0, 6.0 Hz, 1 H), 1.80 (dddd, J = 13.2, 13.2, 7.8, 5.4 Hz, 2 H), 1.73-1.68 (m, 4 H), 1.65 (m, 1 H), 1.56 (m, 1 H), 1.53-1.46 (m, 2 H), 1.35 (m, 1 H), 1.03 (s, 9 H), 0.81 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.0, 136.7, 135.57, 135.55, 133.92, 133.89, 129.6, 128.5, 128.1, 128.0, 127.6, 66.3, 64.2, 61.9, 59.8, 54.5, 42.6, 40.0, 36.9, 28.5, 26.9, 26.5, 21.8, 19.1, 17.4; HRMS (FAB) calcd for $C_{35}H_{47}NO_4SiNa$ $(M+Na)^+$ 596.3172, found 596.3210.

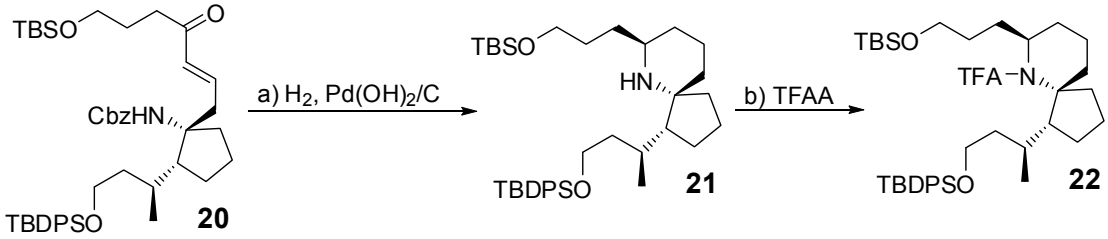


Phosphonate 19: To dimethyl methylphosphonate **19b** (1.29 g, 10.4 mmol) in THF (11 mL) was added dropwise *n*-BuLi (1.6 M in hexane, 5.34 mL, 8.55 mmol) at -78°C. After stirring at -78°C for 30 min, a solution of methyl 4-(*tert*-butyldimethylsilyloxy)butanoate[2] **19a** in THF (8 mL) was added dropwise at -78°C. After stirring at -78°C for further 30 min, aqueous NH_4Cl (15 mL) and ethyl acetate (15 mL) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (acetone/hexanes = 20:100) to afford 1.36 g (97%) phosphonate **19** as a colorless oil, R_f = 0.12 (acetone/hexanes = 10:100); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.76 (d, J = 11.4 Hz, 6 H), 3.60 (t, J = 6.0 Hz, 2 H), 3.09 (d, J = 22.8 Hz, 2 H), 2.67 (t, J = 7.2 Hz, 2 H), 1.78 (tt, J = 6.0, 7.2 Hz, 2 H), 0.86 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.7 (d, J = 6.15 Hz), 61.8, 52.9 (d, J = 6.15 Hz), 41.2 (d, J = 165 Hz), 40.9, 26.6, 25.9, 18.2, -5.4.

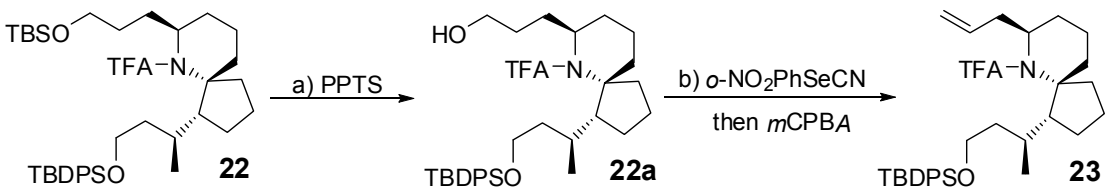


Ketone 20: To alcohol **18** (48.2 mg, 0.0840 mmol) in DMSO (0.15 mL) were added Et_3N (0.14 mL, 1.0 mmol) and a DMSO (0.8 mL) solution of SO_3 pyridine complex (53 mg, 0.34 mmol) at room temperature. After stirring at room temperature for 1 h, toluene (2 mL) was added and H_2O (2 mL) was added dropwise at 0°C. After stirring at room temperature for further 30 min, the layers were separated and the aqueous layer was extracted with toluene (2 x 3 mL). The combined organic phase was washed with 0.5 M aqueous $KHSO_4$ (2 x 5 mL), 1 M aqueous $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was mixed with LiCl (17 mg, 0.40 mmol) and THF (1 mL). Et_3N (0.041 mL, 0.29 mmol) and a THF (1 mL) solution of phosphate **19** (82 mg, 0.25 mmol) was added at 0°C, and the reaction mixture was stirred at 30°C for 2 h. Saturated aqueous NH_4Cl (4 mL) and ethyl acetate (4 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 4 mL). The combined organic phase was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography

(acetone/CH_2Cl_2 = 0:100 to 1:100) to afford α,β-unsaturated ketone **20** (64.6 mg, 100% 2 steps) as a colorless oil, $[\alpha]^{29}_D$ -10.3 (*c* 0.97, $CHCl_3$); R_f = 0.50 (acetone/hexanes = 30:100); IR (film) ν_{max} 3076, 2958, 2858, 1728, 1699, 1498, 1256, 1104, 837, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4 H), 7.41-7.29 (m, 11 H), 6.77 (dt, *J* = 16.0, 7.2 Hz, 1 H), 6.10 (d, *J* = 16.0 Hz, 1 H), 5.01 (s, 2 H), 4.80 (br, 1 H), 3.66 (dd, *J* = 14.0, 6.8 Hz, 2 H), 3.62 (t, *J* = 6.0 Hz, 2 H), 3.12 (m, 1 H), 2.56 (t, *J* = 7.2 Hz, 2 H), 2.36 (dd, *J* = 14.0, 7.6 Hz, 1 H), 1.94 (m, 1 H), 1.85-1.76 (m, 4 H), 1.71-1.66 (m, 5 H), 1.50 (m, 2 H), 1.32 (m, 1 H), 1.04 (s, 9 H), 0.89 (s, 9 H), 0.78 (d, *J* = 6.4 Hz, 3 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 155.0, 142.6, 136.6, 135.5, 133.90, 133.87, 132.89, 129.5, 128.4, 128.1, 128.0, 127.6, 66.2, 64.6, 62.2, 61.9, 52.0, 40.8, 39.5, 37.3, 36.6, 28.9, 27.0, 26.9, 26.3, 25.9, 21.3, 19.1, 18.3, 16.8, -5.3; HRMS (FAB) calcd for $C_{46}H_{67}NO_5Si_2Na$ $(M + Na)^+$ 792.4455, found 792.4429.

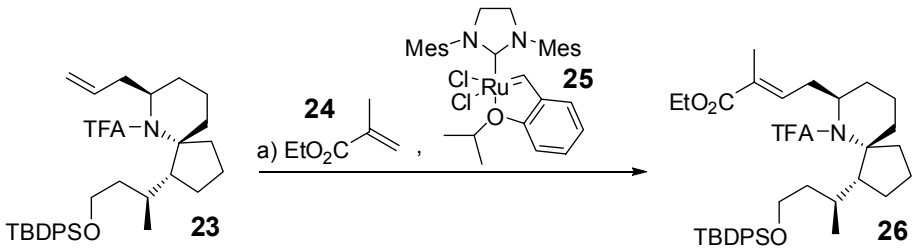


Amide 22: To ketone **20** (0.374 g, 0.485 mmol) in ethanol (5 mL) were added acetic acid (0.2 mL, 3.35 mmol) and Pd $(OH)_2$/C (5 wt% from N. E. CHEMCAT Co., Tokyo, Japan, 53% H_2O containing, 0.45 g, 0.097 mmol) at 0°C. The reaction mixture was stirred at 25°C for 24 h. Et_3N (0.5 mL) was added and the reaction mixture was passed through a silica gel pad eluting with Et_3N/EtOH (1:100). After evaporation of the solvent, the residue was dissolved with $ClCH_2CH_2Cl$ (5 mL) and *i*-Pr_2NEt (1.0 mL, 5.7 mmol). TFAA (0.50 mL, 3.5 mmol) was added at 0°C, and the reaction mixture was stirred at 0°C for 5 min. Saturated aqueous NH_4Cl (10 mL) and $CHCl_3$ (10 mL) were added. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 x 10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (acetone/hexanes = 1:100) to afford TFA-amide **22** (0.349 g, 81% over 2 steps) as a yellow oil, $[\alpha]^{25}_D$ -6.9 (*c* 0.70, $CHCl_3$); R_f = 0.56 (acetone/hexanes = 10:100); IR (film) ν_{max} 3076, 2958, 2856, 1686, 1426, 1199, 1140, 1101, 838, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.42-7.35 (m, 6 H), 3.90 (d, *J* = 10.8 Hz, 1 H), 3.65-3.55 (m, 4 H), 2.23-2.11 (m, 2 H), 2.01-1.96 (m, 3 H), 1.84-1.79 (m, 3 H), 1.71-1.62 (m, 5 H), 1.56-1.53 (m, 4 H), 1.40-1.26 (m, 3 H), 1.03 (s, 9 H), 0.87 (s, 9 H), 0.73 (d, *J* = 6.8 Hz, 3 H), 0.01 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.6 (q, *J* = 34.5 Hz), 135.5, 134.0, 133.8, 129.53, 129.49, 127.7, 127.6, 117.0 (q, *J* = 288 Hz), 69.0, 62.7, 62.5, 59.7, 54.4 (q, *J* = 3.6 Hz), 40.1, 36.0, 34.9, 31.6, 31.3, 30.8, 30.1, 26.8, 25.9, 24.5, 22.8, 19.1, 18.7, 18.2, 14.2, -5.36, -5.38; HRMS (FAB) calcd for $C_{40}H_{62}F_3NO_3Si_2Na$ $(M + Na)^+$ 740.4118, found 740.4097.

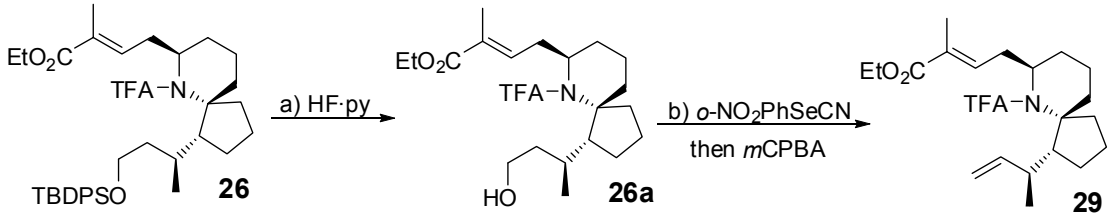


Alkene 23: TBS ether **22** (21.8 mg, 0.030 mmol) and PPTS (23 mg, 0.09 mmol) in ethanol (0.3

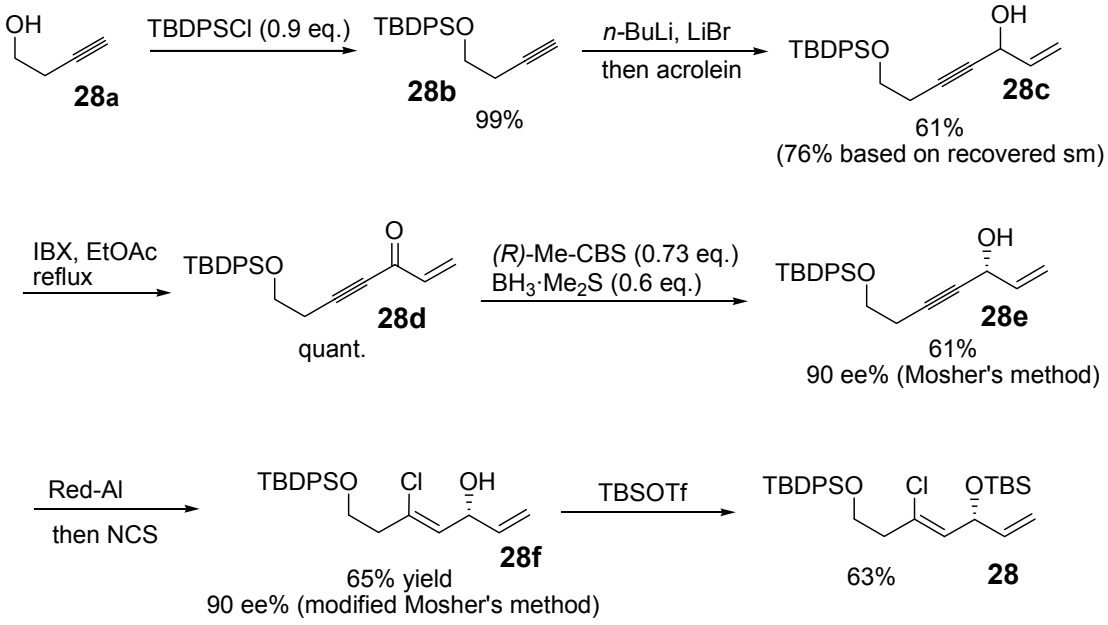
mL) were stirred at 25°C for 13 h. Next, 1 M aqueous $NaHCO_3$ (3 mL) and $CHCl_3$ (3 mL) were added. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 x 3 mL). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was dissolved in THF (0.3 mL), and *o*-nitrophenyl selenocyanate (8.2 mg, 0.036 mmol) and. *n*-Bu_3P (0.009 mL, 0.036 mmol) were added at 0°C. The reaction mixture was stirred at room temperature for 1 h. To the mixture, *m*CPBA (65% purity, 0.019 g, 0.072 mmol) was added at 0°C and stirred at room temperature for 2 h. Saturated aqueous $Na_2S_2O_3$ (2 mL) and CH_2Cl_2 (2 mL) were added at 0°C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic phase was washed with saturated aqueous Na_2CO_3 (5 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (acetone/hexanes = 0:100 to 1:100 to 3:100) to afford alkene **23** (15.7 mg, 88%, 2 steps) as a yellow oil, $[\alpha]^{29}_D$ +27.5 (*c* 1.90, $CHCl_3$); R_f = 0.62 (acetone/hexanes = 10:100); IR (film) ν_{max} 3078, 2958, 2852, 1688, 1427, 1208, 1139, 1104, 1088, 701 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.64 (m, 4 H), 7.42-7.35 (m, 6 H), 5.71 (m, 1 H), 5.14 (d, *J* = 18.6 Hz, 1 H), 5.11 (d, *J* = 11.2 Hz, 1 H), 3.89 (d, *J* = 9.6 Hz, 1 H), 3.68 (ddd, *J* = 11.2, 9.0, 5.4 Hz, 1 H), 3.57 (ddd, *J* = 9.0, 6.6, 6.6 Hz, 1 H), 2.70 (m, 1 H), 2.62 (ddd, *J* = 13.2, 12.0, 12.0 Hz, 1 H), 2.25-2.09 (m, 3 H), 1.92 (m, 1 H), 1.85-1.80 (m, 2 H), 1.75 (m, 2 H), 1.68-1.58 (m, 3 H), 1.50 (m, 1 H), 1.39-1.25 (m, 3 H), 1.02 (s, 9 H), 0.74 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.6 (q, *J* = 33.3 Hz), 135.50, 135.47, 134.4, 134.0, 133.8, 129.5, 129.4, 127.60, 127.56, 118.0, 117.0 (q, *J* = 287 Hz), 69.0, 62.6, 59.8, 53.9 (q, *J* = 3.6 Hz), 40.3, 40.2, 35.8, 35.0, 31.2, 30.2, 29.7, 26.8, 24.5, 22.4, 19.1, 18.9, 14.1, 14.0; HRMS (FAB) calcd for $C_{34}H_{46}F_3NO_2SiNa$ $(M + Na)^+$ 608.3148, found 608.3176.



Ester 26: A mixture of azaspiro-compound **23** (93.7 mg, 0.160 mmol), Hoveyda-Grubbs 2nd generation metathesis catalyst **25** (10 mg, 0.016 mmol) and ethyl methacrylate **24** (0.40 mL, 3.2 mmol) was heated with refluxing for 13 h. After the evaporation of excess ethyl methacrylate, the residue was purified by column chromatography (CH_2Cl_2/benzene = 5:100 to 30:100) to afford α,β-unsaturated ester **26** (80.3 mg, 75% over 2 steps) as a colorless oil, $[\alpha]^{23}_D$ -12.2 (*c* 1.76, $CHCl_3$); R_f = 0.38 (CH_2Cl_2/benzene = 10:100); IR (film) ν_{max} 3078, 2958, 2852, 1716, 1692, 1427, 1200, 1178, 1112, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 4 H), 7.40-7.33 (m, 6 H), 6.61 (m, 1 H), 4.22 (dq, *J* = 1.2, 7.2 Hz, 2 H), 4.10 (d, *J* = 11.0 Hz, 1 H), 3.70 (ddd, *J* = 9.6, 9.2, 5.2 Hz, 1 H), 3.58 (ddd, *J* = 9.6, 9.2, 6.0 Hz, 1 H), 2.85 (dd, *J* = 22.0, 12.8 Hz, 1 H), 2.72 (m, 1 H), 2.26-2.04 (m, 4 H), 2.03 (s, 3 H), 1.83-1.63 (m, 7 H), 1.48 (m, 1 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 1.46-1.26 (m, 3 H), 1.01 (s, 9 H), 0.73 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 157.6 (q, *J* = 33.8 Hz), 136.6, 135.43, 135.39, 133.8, 133.7, 130.3, 129.53, 129.48, 127.56, 127.53, 116.9 (q, *J* = 288 Hz), 69.1, 62.6, 60.7, 59.7, 53.4 (q, *J* = 3.7 Hz), 40.4, 35.8, 35.1, 35.0, 31.2, 30.2, 29.7, 26.8, 24.5, 22.2, 19.0, 18.8, 14.3, 14.2, 12.7; HRMS (FAB) calcd for $C_{38}H_{52}F_3NO_4SiNa$ $(M + Na)^+$ 694.3515, found 694.3507.



Alkene 29: To TBDPS ether **26** (80.3 mg, 0.12 mmol) and pyridine (0.6 mL) in a polypropylene container were added HF-pyridine complex (HF 70%, pyridine 30%, 0.3 mL) at 0°C. The reaction mixture was stirred at 25°C for 50 h. Next, 1 M aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (5 mL) were added to the reaction at 0°C. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 x 5 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was dissolved in THF (2 mL), and at 0°C, *o*-nitrophenyl selenocyanate (65 mg, 0.29 mmol) and *n*-Bu_3P (0.072 mL, 0.29 mmol) were added and the reaction mixture was stirred at room temperature for 3 h. To the mixture, *m*CPBA (65% purity, 0.15 g, 0.56 mmol) was added at 0°C and stirred at room temperature for a further 2 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (4 mL) and CH_2Cl_2 (4 mL) at 0°C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The combined organic phase was washed with saturated aqueous Na_2CO_3 (5 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (CH_2Cl_2/benzene = 0:100 to 30:100 to 50:100) to afford alkene **29** (44.7 mg, 90% over 2 steps) as a colorless oil, $[\alpha]^{20}_D$ -43.5 (*c* 1.56, $CHCl_3$); R_f = 0.46 (acetone/hexanes = 10:100); IR (film) ν_{max} 3078, 2958, 2872, 1716, 1684, 1424, 1259, 1197, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.57 (dt, J = 1.5, 6.4 Hz, 1 H), 5.74 (ddd, J = 17.2, 10.0, 9.2 Hz, 1 H), 4.94 (dd, J = 17.2, 1.2 Hz, 1 H), 4.91 (dd, J = 10.0, 2.0 Hz, 1 H), 4.21 (q, J = 7.2 Hz, 2 H), 3.92 (d, J = 12.6 Hz, 1 H), 2.77 (m, 1 H), 2.61 (m, 1 H), 2.32-2.08 (m, 4 H), 1.87 (s, 3 H), 1.91-1.62 (m, 8 H), 1.50 (dq, 6.8, 10.0 Hz, 1 H), 1.38 (m, 1 H), 1.31 (t, J = 7.2 Hz, 3 H), 0.95 (d, J = 6.8, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 157.4 (q, J = 37.3 Hz), 145.6, 137.0, 130.0, 116.9 (q, J = 287 Hz), 113.7, 68.7, 60.7, 59.6, 53.4 (q, J = 3.3 Hz), 39.5, 36.0, 34.8, 34.6, 31.7, 24.4, 23.2, 22.6, 14.21, 14.18, 12.6; HRMS (FAB) calcd for $C_{22}H_{32}F_3NO_3Na$ $(M + Na)^+$ 438.2232, found 438.2209.



Scheme 3. Preparation of the chiral lower side chain **28** by CBS asymmetric reduction

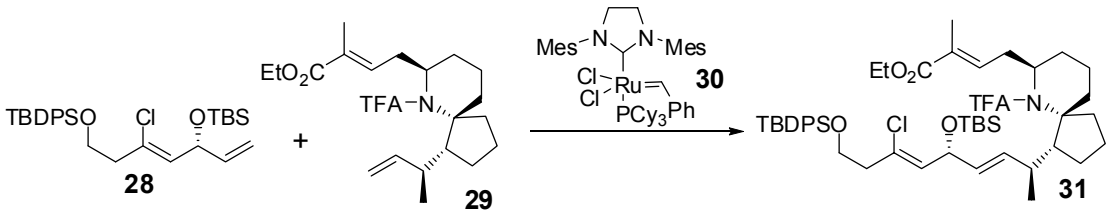
TBDPS ether 28b: To alcohol **28a** (0.60 mL 7.9 mmol) and DMAP (0.090 g, 0.72 mmol) in CH_2Cl_2 (9 mL) were added Et_3N (1.5 mL, 11 mmol) and TBDPSCl (1.89 mL, 7.27 mmol) at 0°C. After stirring at room temperature for 7 h, the reaction mixture was passed through a silica gel pad eluting with CH_2Cl_2. Evaporation of the solvent afforded TBDPS ether **28b** (2.22 g, 99%) as a colorless oil, R_f = 0.74 (acetone/hexanes = 20:100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.67 (m, 4 H), 7.43-7.36 (m, 6 H), 3.78 (d, J = 6.8 Hz, 2 H), 2.45 (dt, J = 2.8, 6.8 Hz, 2 H), 1.94 (t, J = 2.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.5, 129.7, 127.7, 81.5, 69.3, 62.3, 26.8, 22.6, 19.2.

Alcohol 28c: To alkyne **28b** (0.50 g, 1.62 mmol) in THF (3.3 mL) was dropped *n*-BuLi (1.6 M in hexane, 1.20 mL, 1.92 mmol) at -78°C. The reaction mixture was stirred at -78°C for 20 min, and then allowed to rise to room temperature. To the mixture, LiBr[3] (0.071 g, 0.81 mmol) was added with stirring at room temperature for a further 20 min. The reaction mixture was cooled to -78°C again and a solution of acrolein (>90% monomer, 0.137 mL, 2.05 mmol) in THF (0.55 mL) was added dropwise over 1 h. Upon completion of the addition, stirring was continued at -78°C for a further 1 h. Saturated aqueous NH_4Cl (10 mL) and Et_2O (10 mL) were added at -78°C. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography (acetone/hexanes = 1:100 to 10:100 to 20:100) to afford alcohol **28c** (0.36 g, 61%) as a colorless oil together with the starting material alkyne **28b** (0.10 g, 20%). R_f = 0.29 (acetone/hexanes = 20:100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.45-7.36 (m, 6 H), 5.93 (ddd, J = 16.8, 10.0, 5.4 Hz, 1 H), 5.42 (ddd, J = 16.8, 1.2, 1.2 Hz, 1 H), 5.17 (ddd, J = 10.0, 1.2, 1.2 Hz, 1 H), 4.82 (m, 1 H), 3.78 (t, J = 6.8 Hz, 2 H), 2.51 (dt, J = 2.0, 6.8 Hz, 2 H), 0.89 (d, J = 6.0, 1 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.6, 133.5, 129.7, 127.7, 116.1, 84.1, 80.1, 63.4, 62.3, 26.8, 22.9, 19.2.

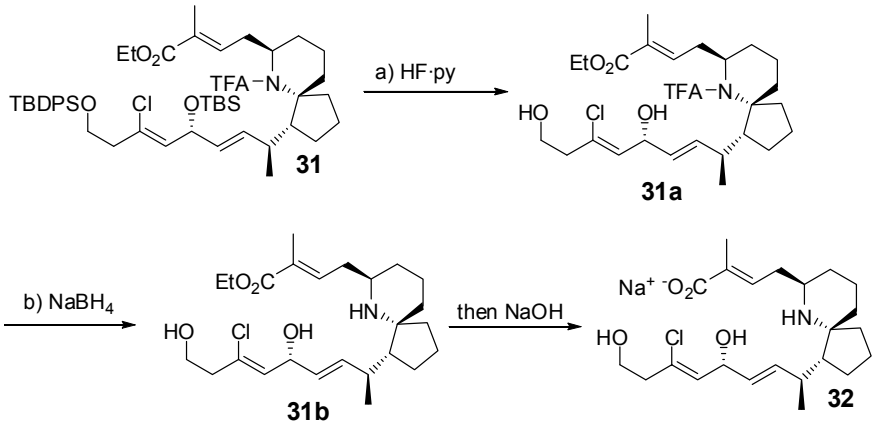
Chiral alcohol 28e: Alcohol **28c** (0.96 g, 2.6 mmol) and IBX (1.50 g, 5.26 mmol) in EtOAc (16 mL) were heated with refluxing for 11 h. The reaction mixture was passed through a silica gel pad eluting with CH_2Cl_2. Evaporation of the solvent gave a residue, which was dissolved in THF (4 mL) and added dropwise at -40°C within 1 h to the mixture of *(R)*-Me-CBS (1.0 M in THF, 1.9 mL, 1.9 mmol), THF (8 mL) and $BH_3{\cdot}SMe_2$ (2.0 M in THF, 0.78 mL, 1.56 mmol). Upon completion of the addition, stirring was continued for 5 min and then absolute methanol (2 mL) was slowly added for quenching. After evaporation of the solvent, the residue was purified by column chromatography (acetone/benzene = 2:100) to afford chiral alcohol **28e** (0.59 g, 61% over 2 steps) as a colorless oil, R_f = 0.29 (acetone/hexanes = 20:100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.45-7.36 (m, 6 H), 5.93 (ddd, J = 16.8, 10.0, 5.4 Hz, 1 H), 5.42 (ddd, J = 16.8, 1.2, 1.2 Hz, 1 H), 5.17 (ddd, J = 10.0, 1.2, 1.2 Hz, 1 H), 4.82 (m, 1 H), 3.78 (t, J = 6.8 Hz, 2 H), 2.51 (dt, J = 2.0, 6.8 Hz, 2 H), 1.89 (d, J = 6.0, 1 H), 1.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.6, 133.5, 129.7, 127.7, 116.1, 84.1, 80.1, 63.4, 62.3, 26.8, 22.9, 19.2.

Chloroalkene 28f: To hydroxyalkyne **28e** (0.55 g, 1.52 mmol) in THF (6 mL) was added dropwise Red-Al[4] (3.3 M in toluene, 0.51 mL, 1.54 mmol) at -78°C. The reaction mixture was allowed to rise to room temperature and stirred for 4 h. To the mixture, *N*-chlorosuccinimide (NCS, 0.27 g, 2.0 mmol) was added at -78°C, and stirring was continued for a further 5 h. Next, absolute methanol (1 mL) was added for quenching. After evaporation of the solvent, the residue was purified by column chromatography (acetone/benzene = 1:100 to 2:100) to afford chloroalkene **28f** (0.40 g, 65%) as a colorless oil, R_f = 0.50 (acetone/benzenes = 5:100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.43-7.36 (m, 6 H), 5.88 (ddd, J = 16.8, 10.0, 5.6 Hz, 1 H), 5.62 (d, J = 8.0 Hz, 1 H), 5.33 (d, J = 16.8 Hz, 1 H), 5.14 (d, J = 10.0 Hz, 1 H), 5.09 (m, 1 H), 3.85 (dd, J = 10.0, 6.0 Hz, 2 H), 2.55 (m, 2 H), 1.69 (br, 1 H), 1.04 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 135.6, 133.6, 133.5, 129.67, 129.66, 128.6, 127.67, 127.65, 115.2, 70.4, 60.8, 42.6, 26.8, 19.2.

Lower side chain unit 28: To a solution of secondary alcohol **28f** (0.19 g, 0.47 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (0.13 mL, 0.93 mmol) and TBSOTf (0.16 mL, 0.70 mmol) at 0°C. After stirring at room temperature for 20 minutes, absolute ethanol (0.2 mL) was added for quenching at 0°C. After evaporation of the solvent, the residue was purified by column chromatography (benzene/hexanes = 10:100 to 30:100) to afford lower side chain unit **28** (0.15 g, 63%) as a colorless oil, R_f = 0.21 (benzene/hexanes = 10:100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.44-7.36 (m, 6 H), 5.81 (ddd, J = 16.8, 10.4, 5.2 Hz, 1 H), 5.54 (d, J = 7.6 Hz, 1 H), 5.29 (ddd, J = 16.8, 1.6, 1.2 Hz, 1 H), 5.08 (m, 1 H), 5.05 (ddd, J = 10.4, 1.6, 1.2 Hz, 1 H), 3.82 (ddd, J = 12.8, 6.8, 3.2 Hz, 2 H), 2.56 (ddd, J = 14.4, 7.6, 6.8 Hz, 1 H), 2.51 (ddd, J = 14.4, 7.6, 6.8 Hz, 1 H), 1.03 (s, 9 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 135.6, 133.6, 130.9, 129.6,127.6, 113.6, 71.1, 61.0, 42.5, 26.8, 25.8, 19.2, -4.7, -4.8; HRMS (FAB) calcd for $C_{29}H_{43}{}^{35}ClO_2Si_2Na$ $(M + Na)^+$ 537.2388, found 537.2357.



Fully protected pinnaic acid 31: A mixture of azaspiro-segment **29** (9.3 mg, 0.022 mmol), Grubbs 2nd generation metathesis catalyst **30** (15 mg, 0.017 mmol), and the lower side chain unit **28** (63.1 mg, 0.122 mmol) in degassed toluene (0.3 mL) was heated at 90°C for 24 h. Evaporation of the solvent gave a residue, which was purified by column chromatography (benzene/hexane = 1:1 to CH_2Cl_2/benzene = 0:100 to 5:100) to afford fully protected pinnaic acid **31** (8.1 mg, 40%) as a yellow oil, together with the recovered starting material **29** (3.9 mg, 42%). $[\alpha]^{18}_D$ -15.1 (*c* 0.33, $CHCl_3$); R_f = 0.37 (CH_2Cl_2/benzene = 10:100); IR (film) ν_{max} 3077, 2958, 2856, 1716, 1688, 1656, 1476, 1428, 1259, 1200, 1140, 1116, 838, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4 H), 7.43-7.38 (m, 6 H), 6.59 (dd, *J* = 6.4, 9.6 Hz, 1 H), 5.62 (ddd, *J* = 1.6, 8.0, 15.2 Hz, 1 H), 5.49 (d, *J* = 7.6 Hz, 1 H), 5.35 (dd, *J* = 4.4, 15.2 Hz, 1 H), 4.98 (ddd, *J* = 1.6, 4.4, 7.6 Hz, 1 H), 4.25 (dq, *J* = 1.6, 7.2 Hz, 2 H), 3.91 (m, 1 H), 3.80 (dq, *J* = 2.0, 6.4 Hz, 2 H), 2.70 (m, 1 H), 2.66 (m, 1 H), 2.51 (t, *J* = 6.4 Hz, 2 H), 2.20-2.12 (m, 4 H), 1.90 (s, 3 H), 1.87-1.66 (m, 7 H), 1.46 (m, 1 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.34-1.25 (m, 2 H), 1.03 (s, 9 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.85 (s, 9 H), 0.01 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 157.5 (q, *J* = 33.3 Hz), 137.4, 136.9, 135.5, 133.5, 130.7, 130.3, 130.1, 129.7, 129.2, 127.7, 127.5, 116.9 (q, *J* = 287 Hz), 70.6, 68.8, 61.3, 60.7, 59.6, 53.4 (q, *J* = 3.6 Hz), 42.5, 36.4, 36.0, 35.3, 34.4, 31.6, 26.8, 25.8, 24.5, 23.2, 21.6, 19.1, 18.2, 14.3, 14.2, 12.9, -4.5, -4.8; HRMS (FAB) calcd for $C_{49}H_{71}{}^{35}ClF_3NO_5Si_2Na$ $(M + Na)^+$ 924.4409, found 924.4403; calcd for $C_{49}H_{71}{}^{37}ClF_3NO_5Si_2Na$ $(M + Na)^+$ 926.4381, found 926.4363



Pinnaic acid Na salt 32: To fully protected pinnaic acid **31** (6.7 mg, 0.0074 mmol) and pyridine (0.36 mL) in a polypropylene container was added HF-pyridine complex (HF 70%, pyridine 30%, 0.12 mL) at 0°C. The reaction mixture was stirred at 25°C for 25 h. Next, 1 M aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (5 mL) were added to the reaction at 0°C. The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2 x 5 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was diluted with absolute ethanol (0.2 mL) and mixed with $NaBH_4$ (0.015 g, 0.39 mmol). The reaction mixture was stirred at 25°C for 14 h to

generate ethyl ester **31b** before the addition of aqueous NaOH (2.5 M, 0.4 mL) at 0°C. The alkaline reaction was stirred at 25°C for 7 h and then at 40°C for a further 11 h. The reaction mixture was allowed to cool to room temperature and then loaded onto a short column of silica gel, which was eluted with MeOH/$CHCl_3$ (1:10 to 2:10 to 5:10 to 10:10) to afford pinnaic acid Na salt **32** (2.8 mg, 86% over 2 steps) as a colorless oil, R_f = 0.20 (MeOH/$CHCl_3$ = 3:7); ^{1}H NMR (600 MHz, CD_3OD) δ 6.48 (dt, J = 1.2, 7.2 Hz, 1 H), 5.76 (d, J = 7.8 Hz, 1 H), 5.66 (ddd, J = 15.6, 7.2, 1.2 Hz, 1 H), 5.53 (dd, J = 15.6, 6.6 Hz, 1 H), 4.94 (dd, J = 7.8, 7.2 Hz, 1 H), 3.74 (m, 2 H), 2.76 (m, 1 H), 2.56 (dt, J = 1.8, 6.6 Hz, 1 H), 2.34-2.28 (m, 2 H), 2.24 (m, 1 H), 1.84 (s, 3 H), 1.71-1.57 (m, 8 H), 1.46 (ddd, J = 5.4, 6.6, 11.4 Hz, 1 H), 1.39-1.26 (m, 4 H), 1.11 (m, 1 H), 0.99 (d, J = 6.6 Hz, 3 H); HRMS (FAB) calcd for $C_{23}H_{37}{}^{35}ClNO_4$ $(M + H)^+$ 426.2411, found 426.2394; calcd for $C_{23}H_{37}{}^{37}ClNO_4$ $(M + H)^+$ 428.2381, found 428.2391.

References:

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[2] G. Solladié, A. Almario, *Tetrahedron: Asymmetry* **1995**, *6*, 559-576.

[3] J. Mulzer, M. Berger, *J. Org. Chem.* **2004**, *69*, 891-898.

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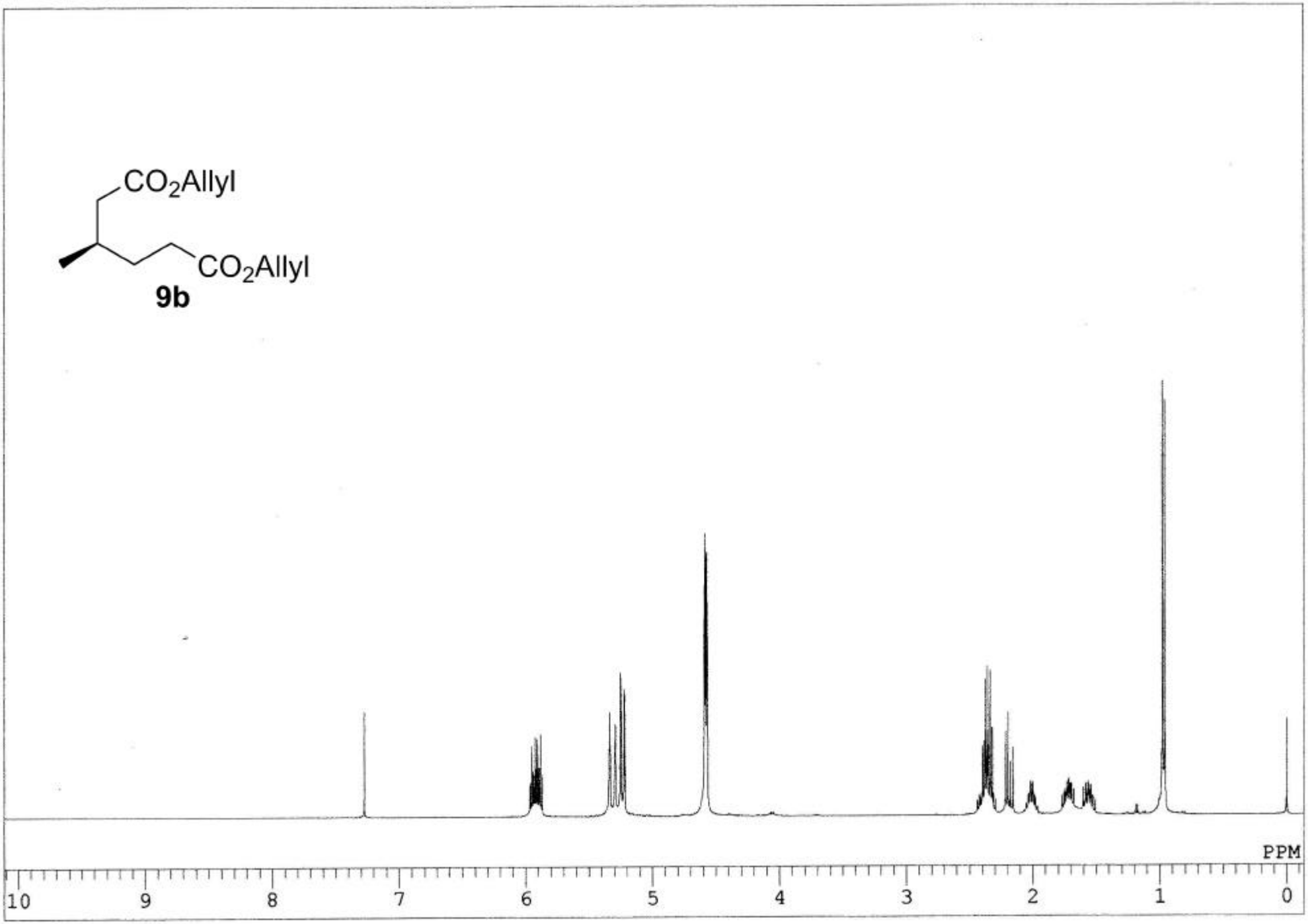
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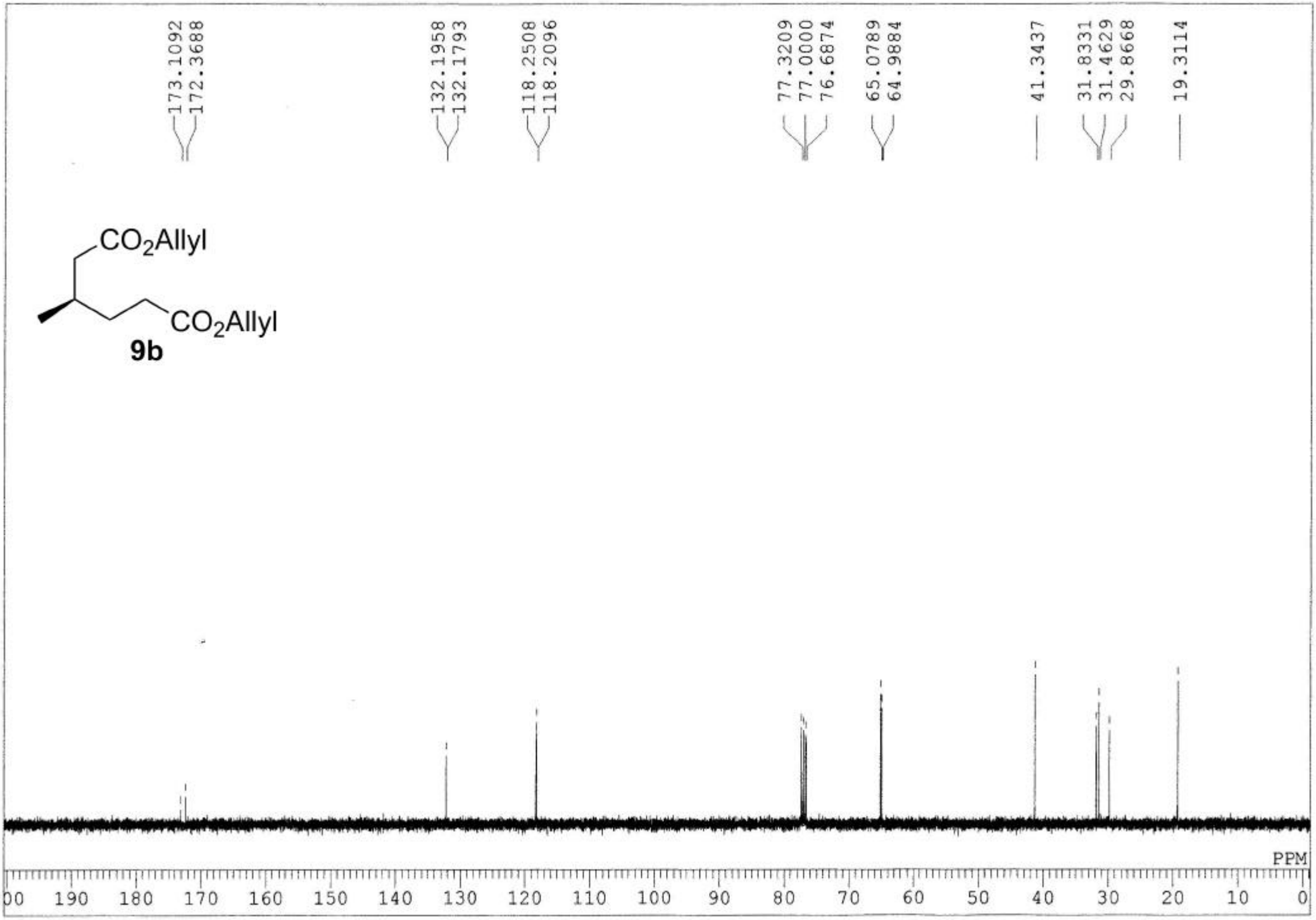
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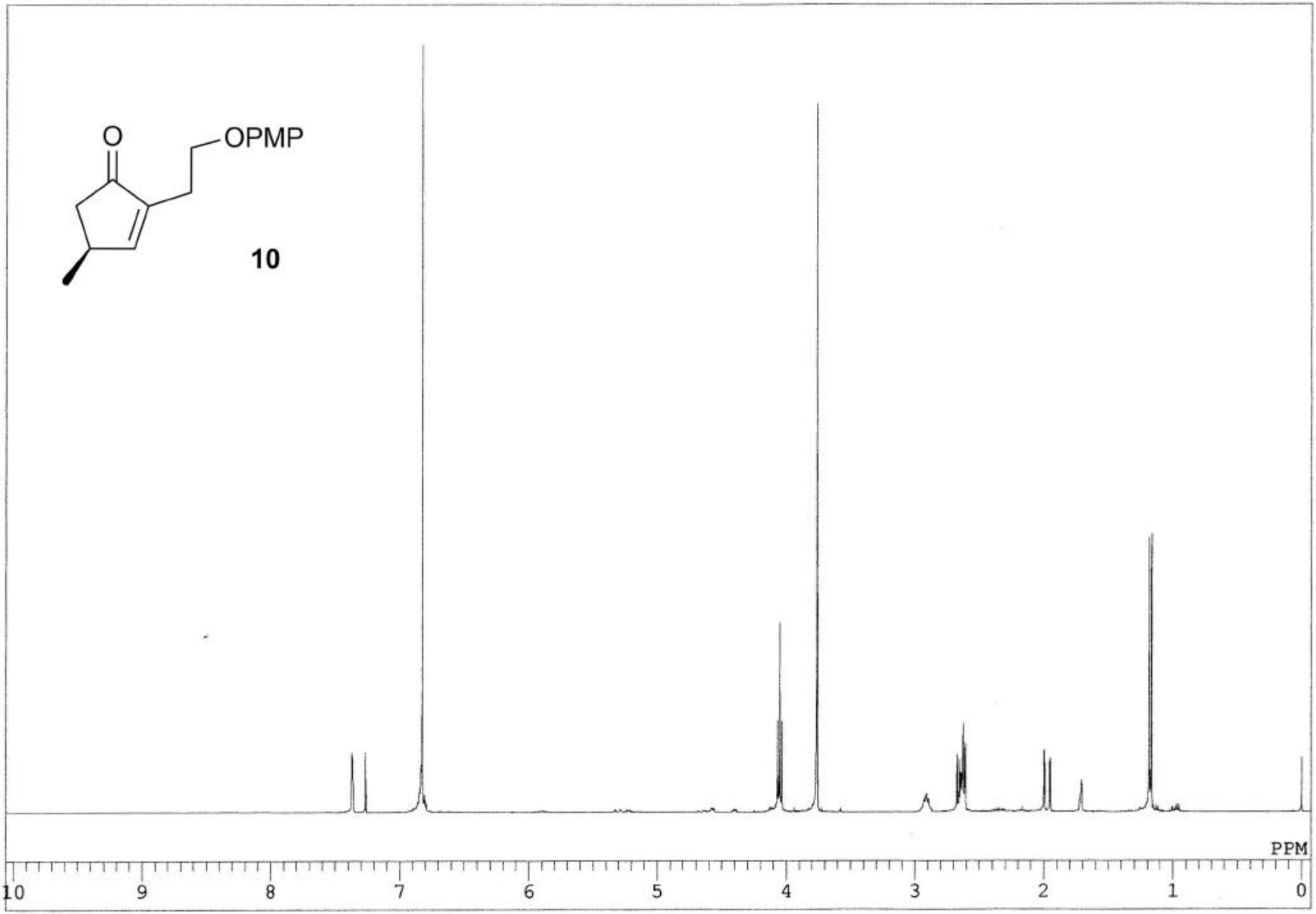
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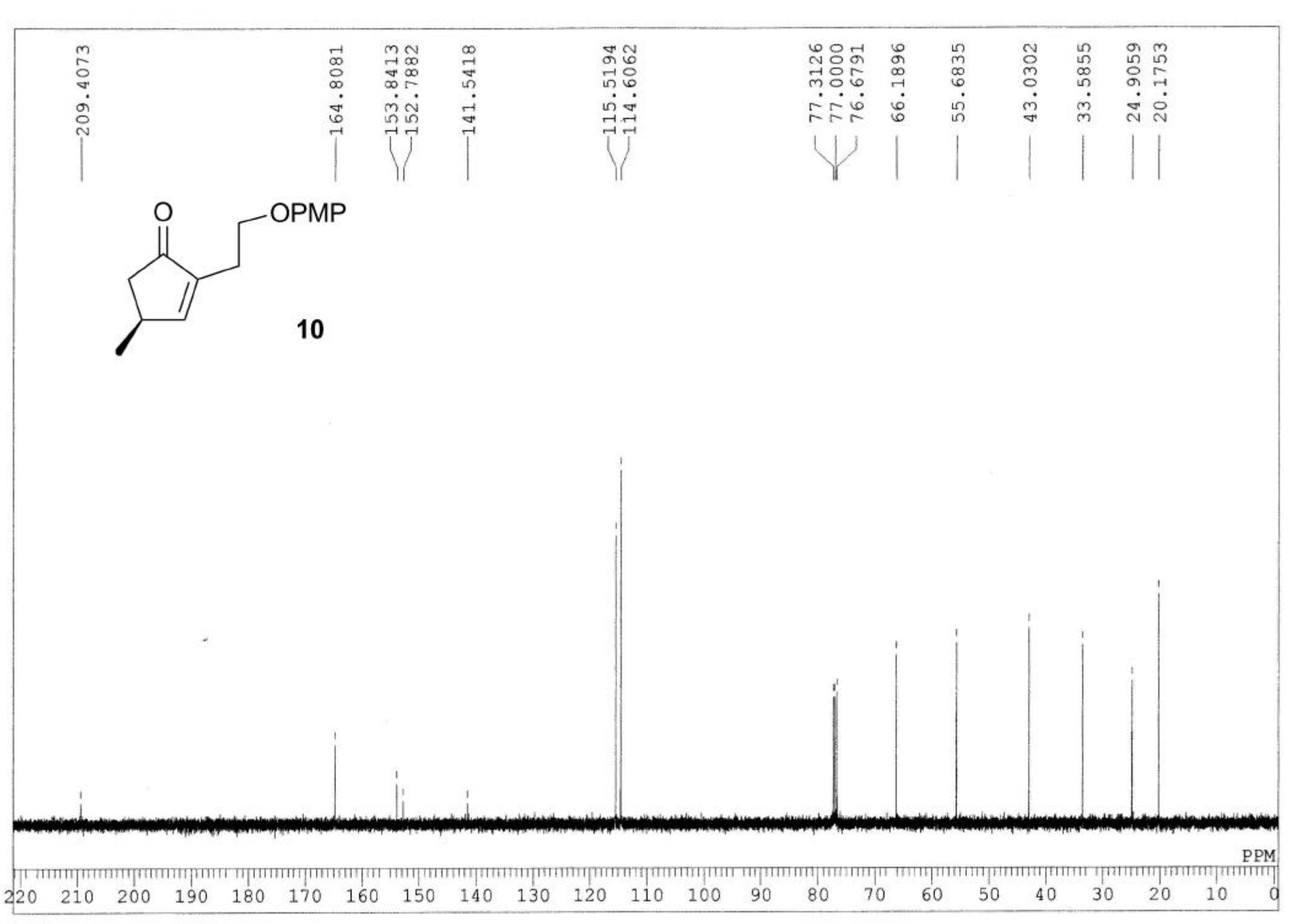
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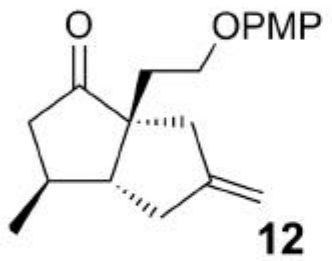

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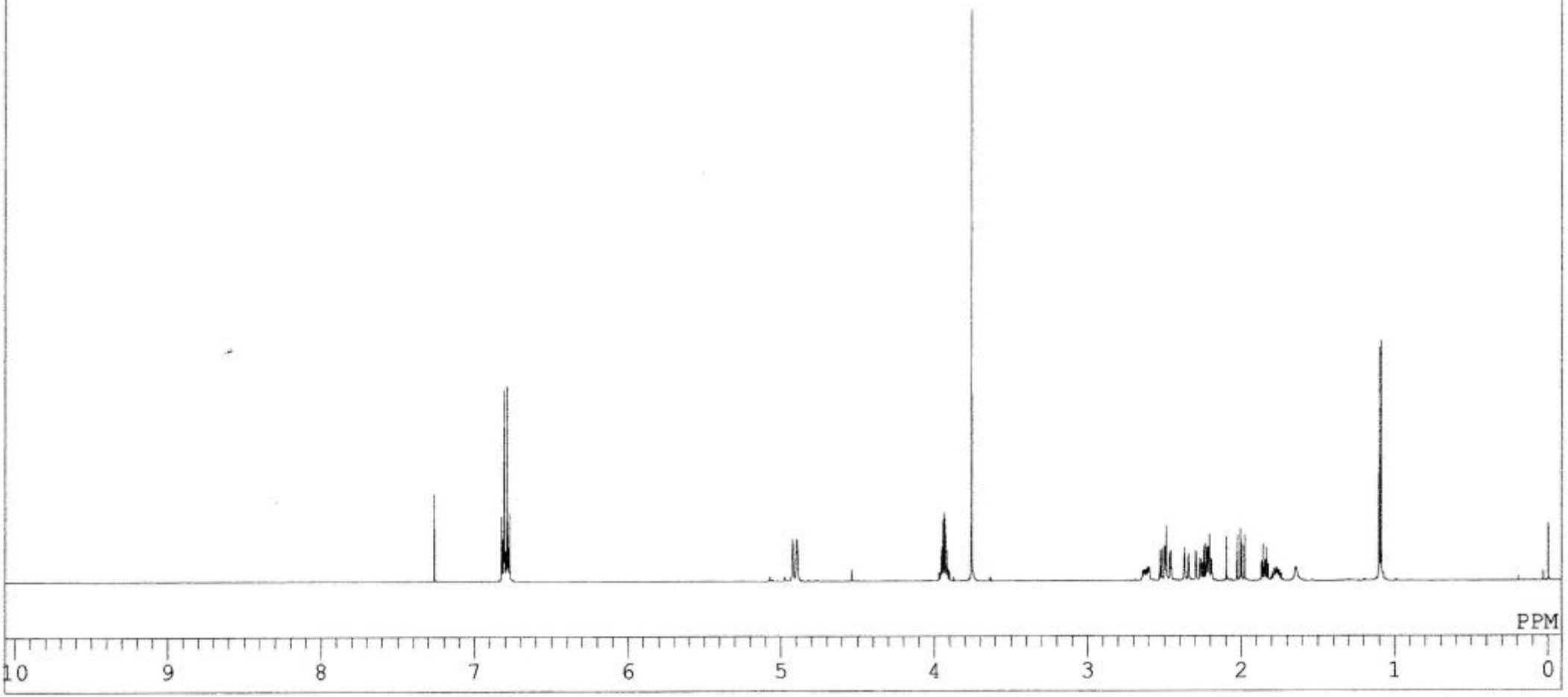

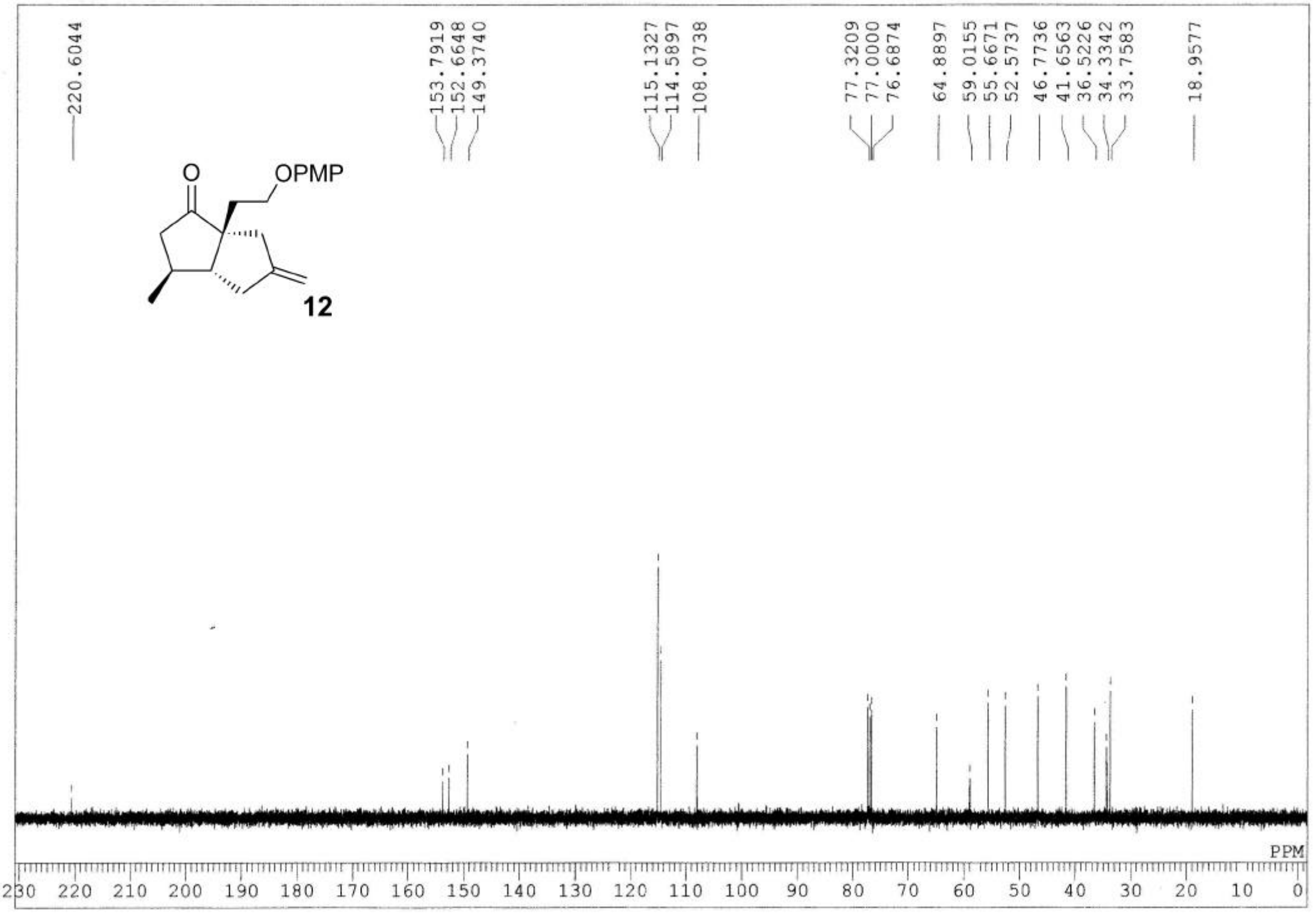
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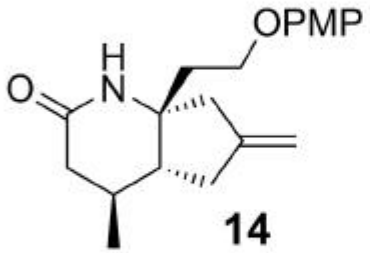

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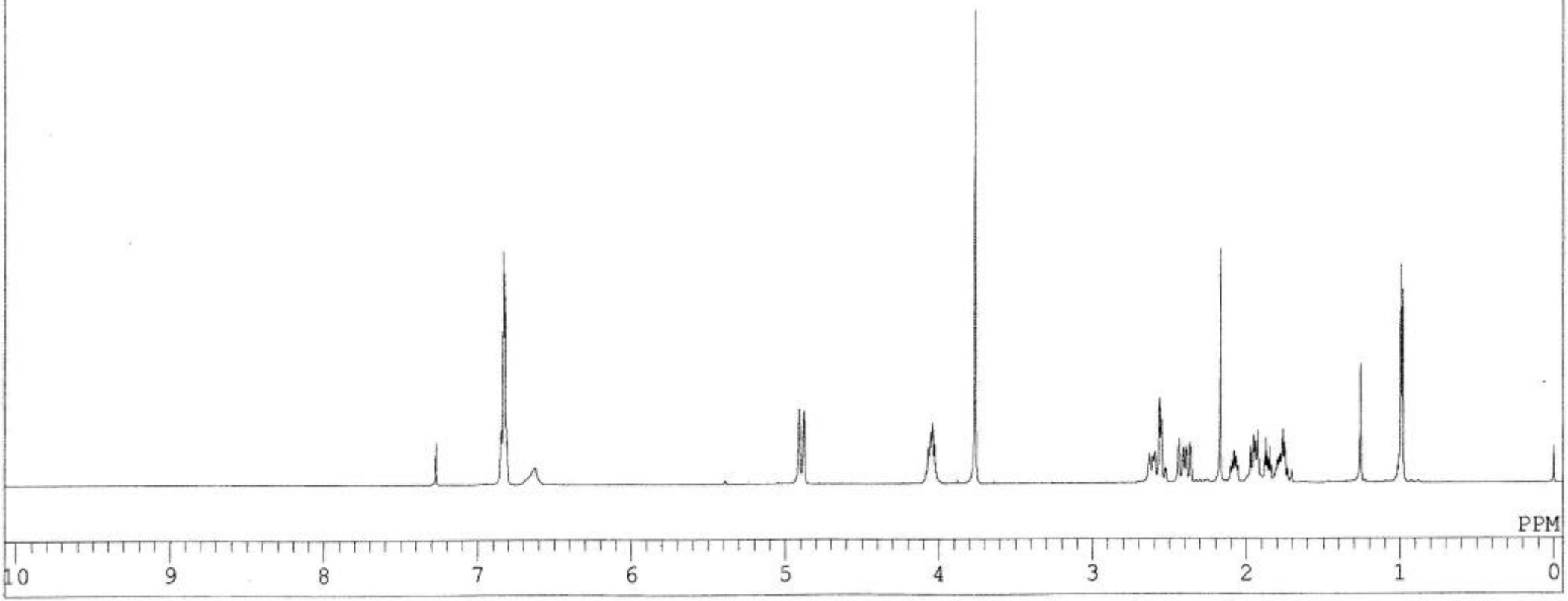

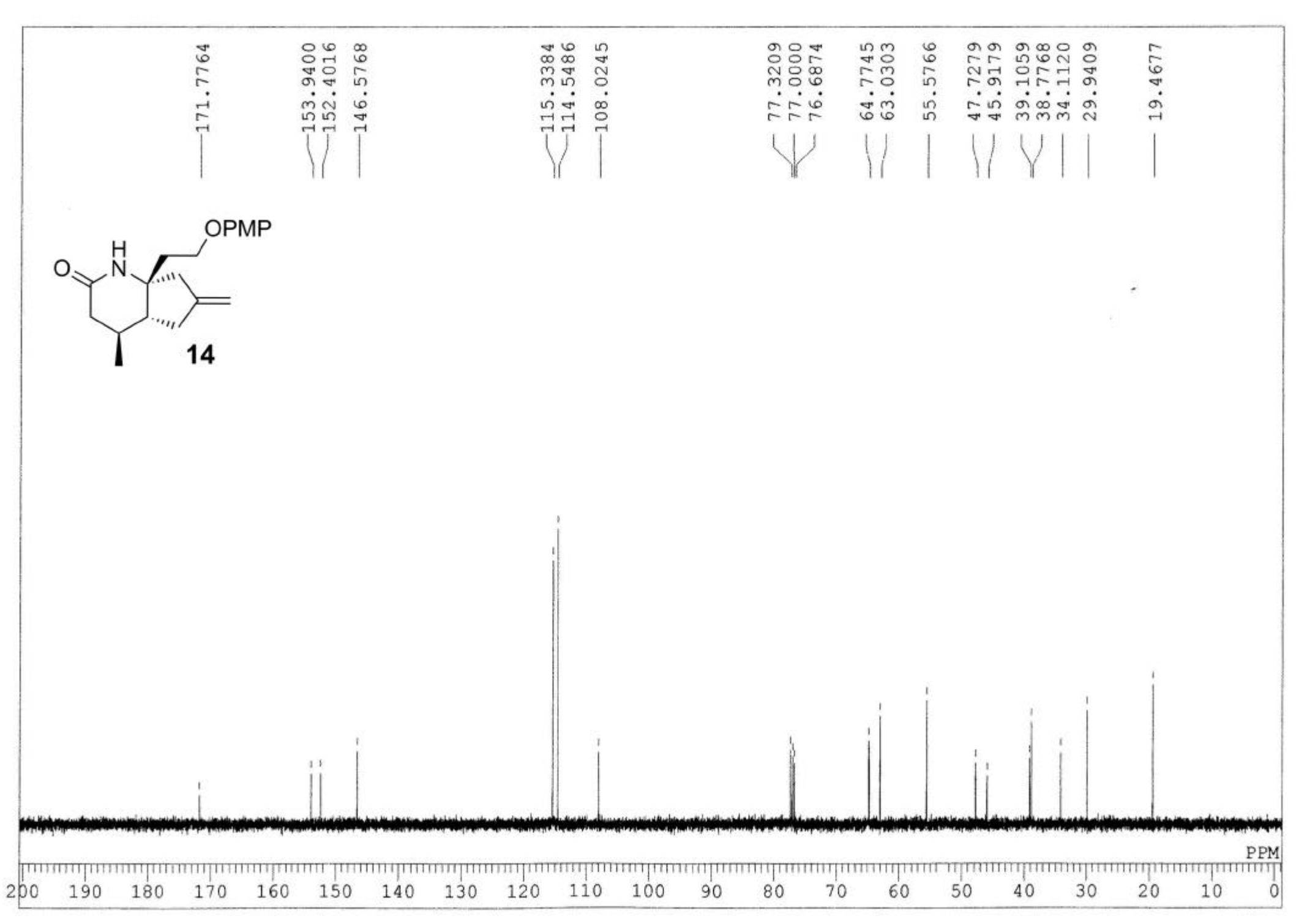
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PPM
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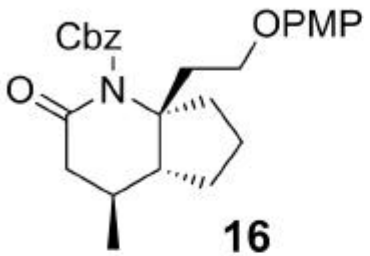

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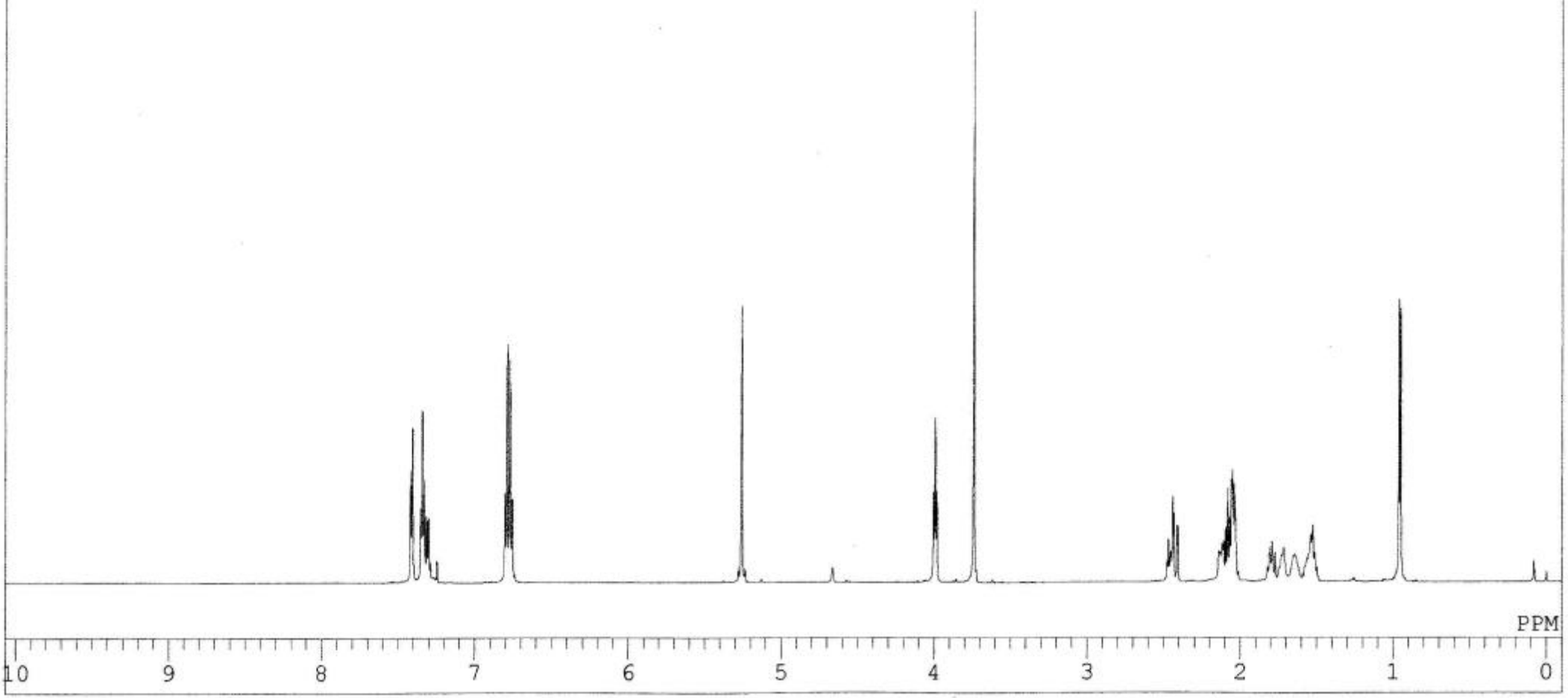

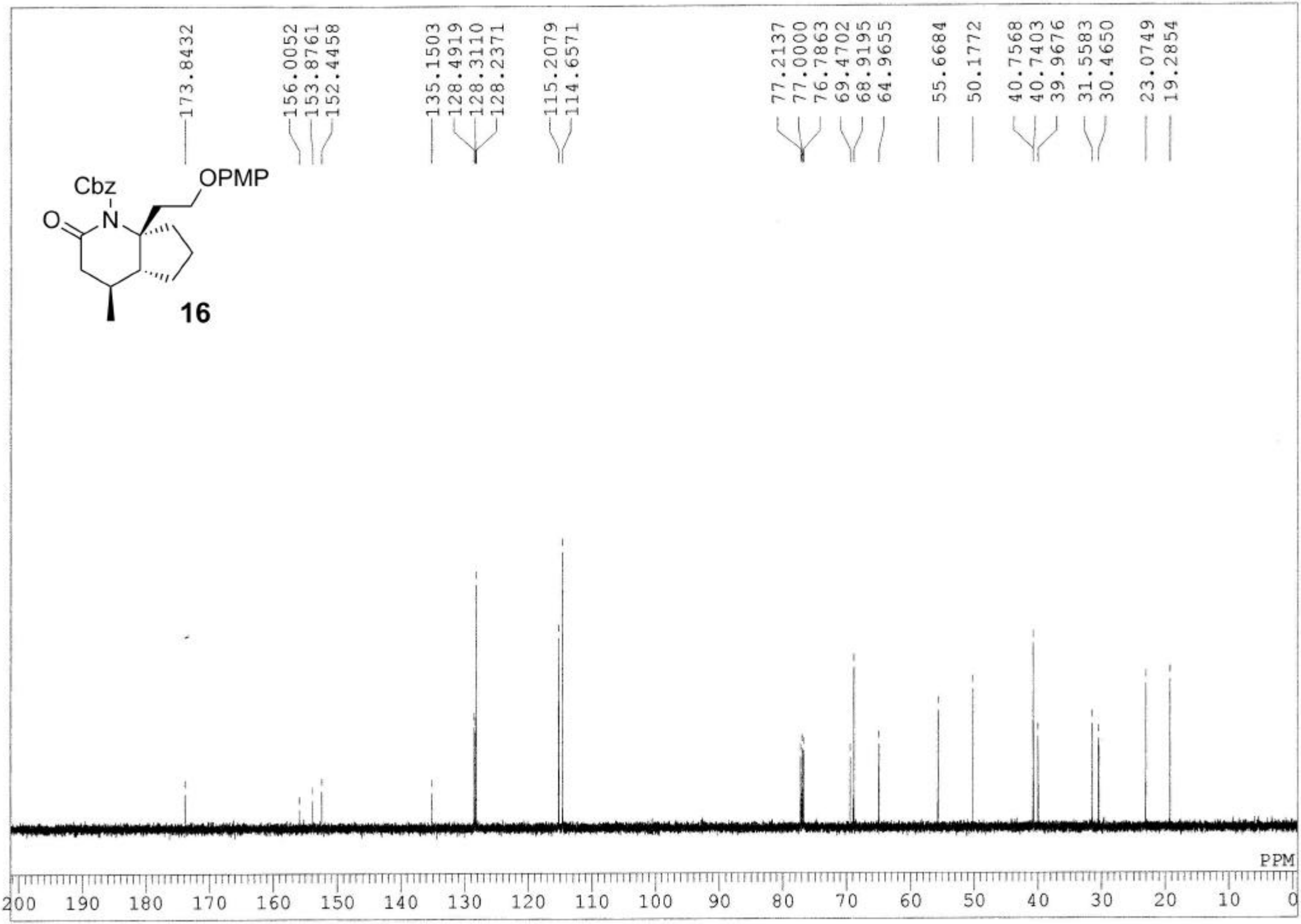
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Cbz
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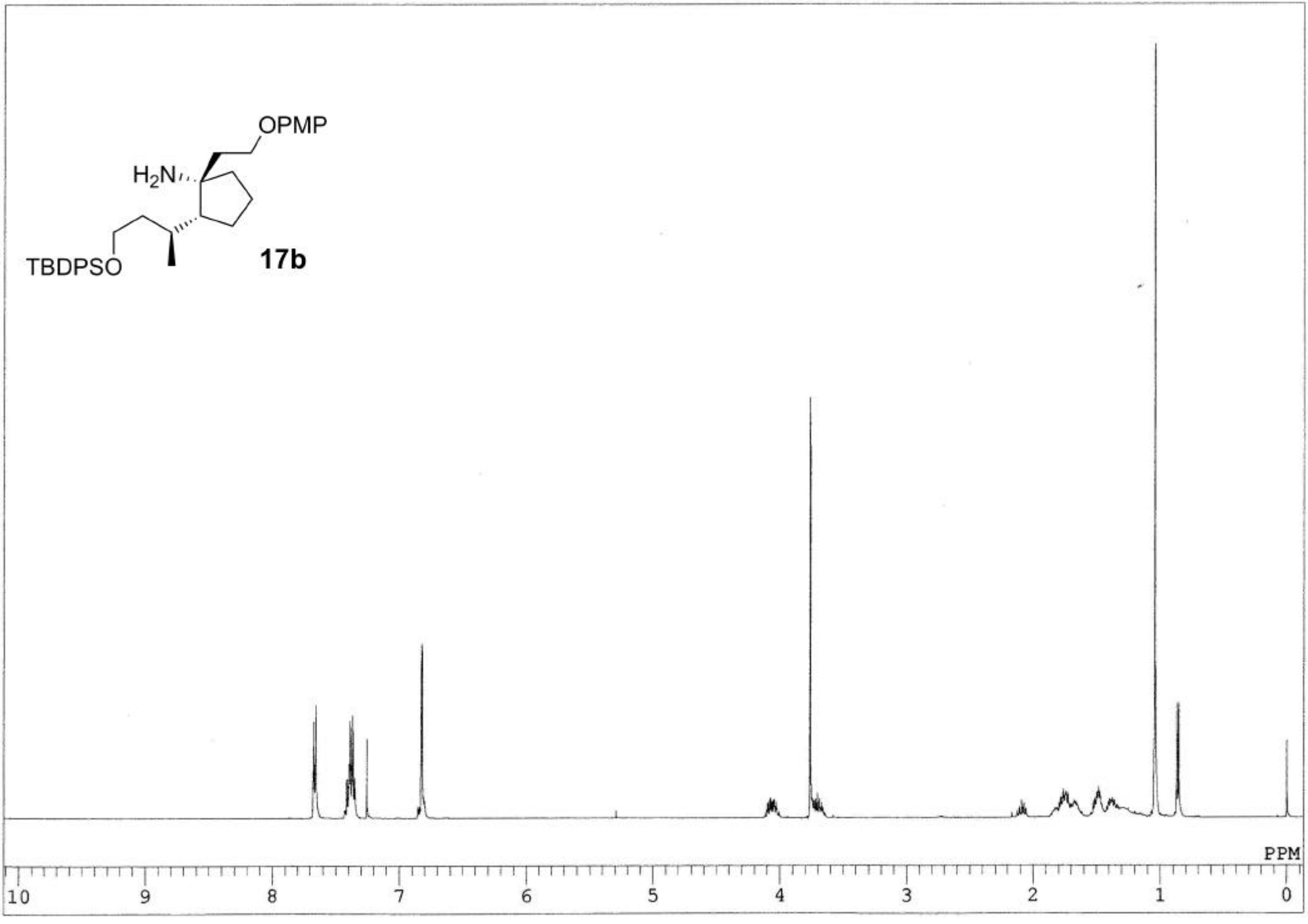
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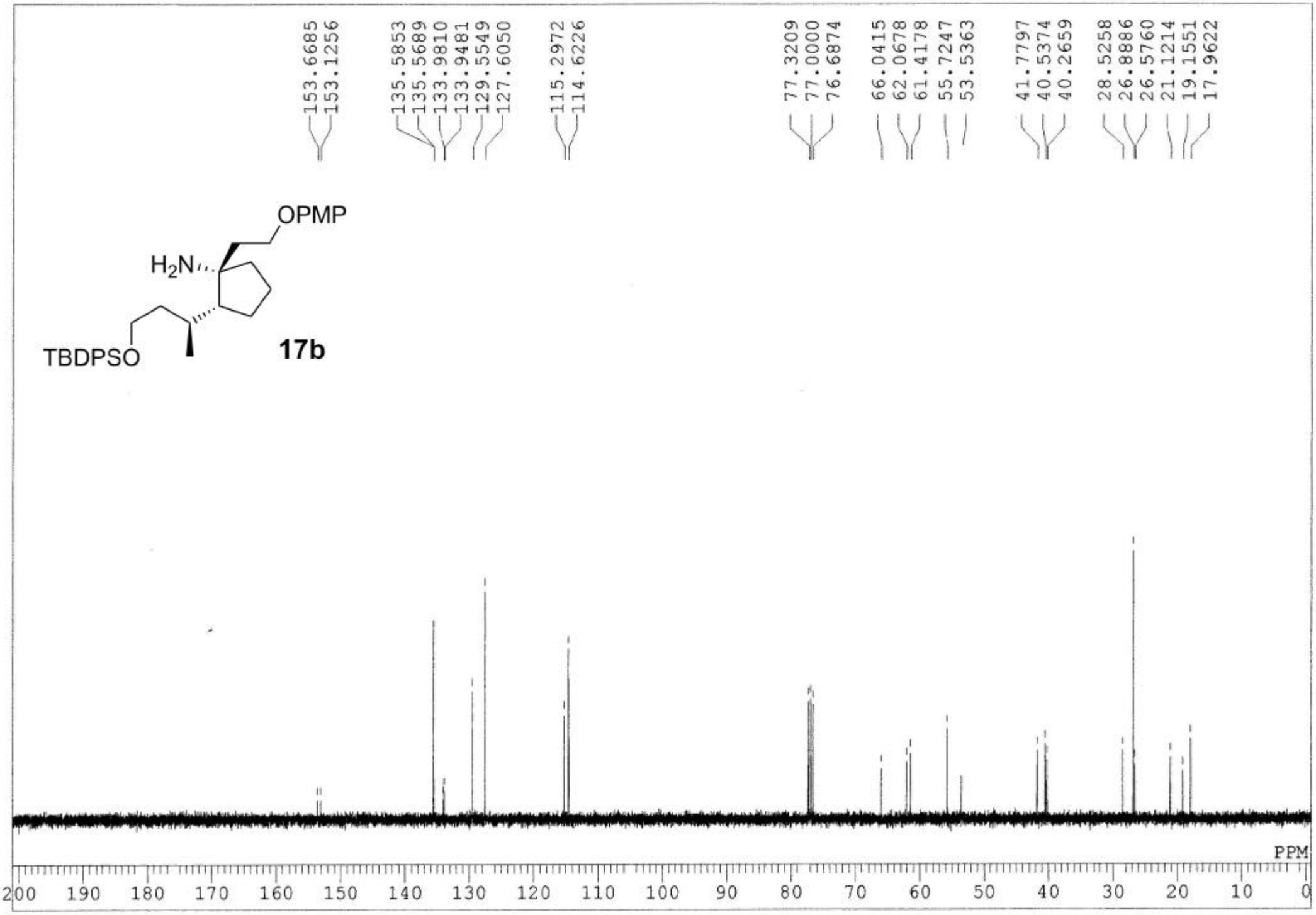
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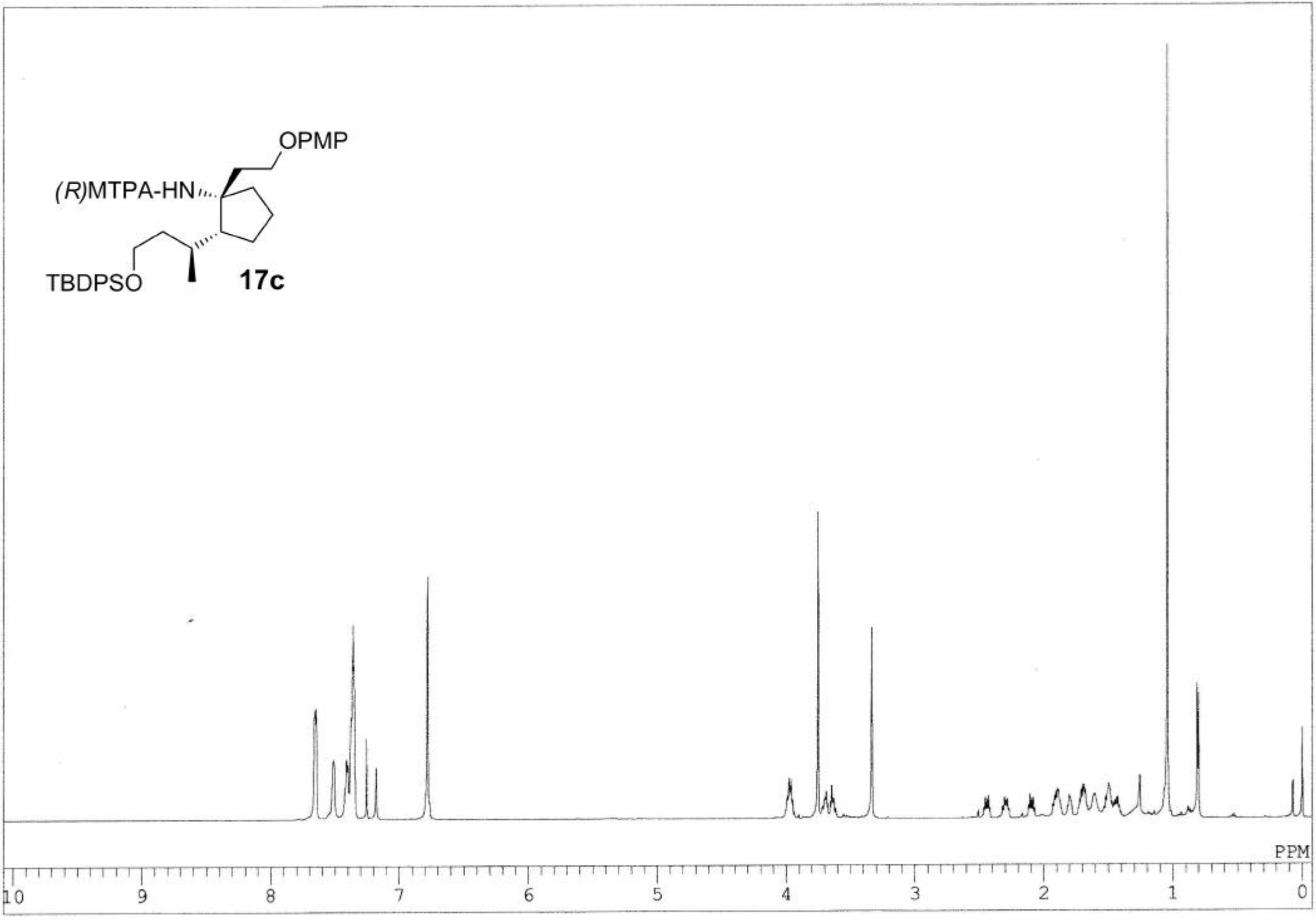
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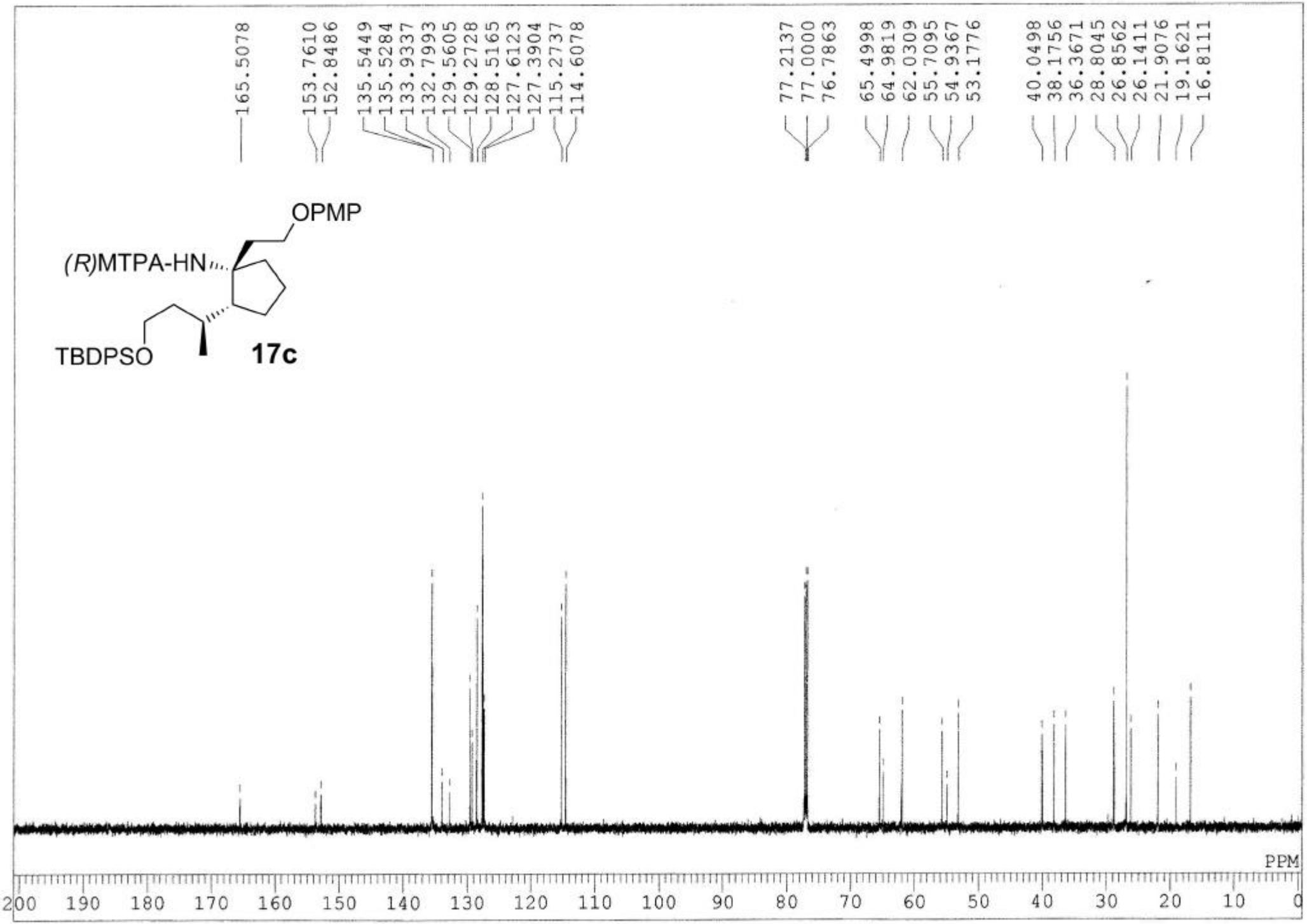
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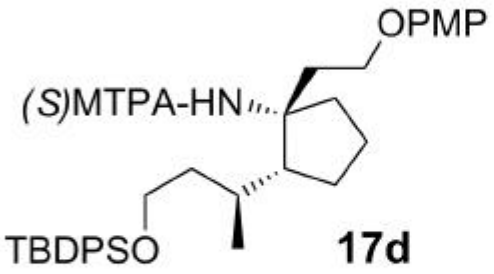

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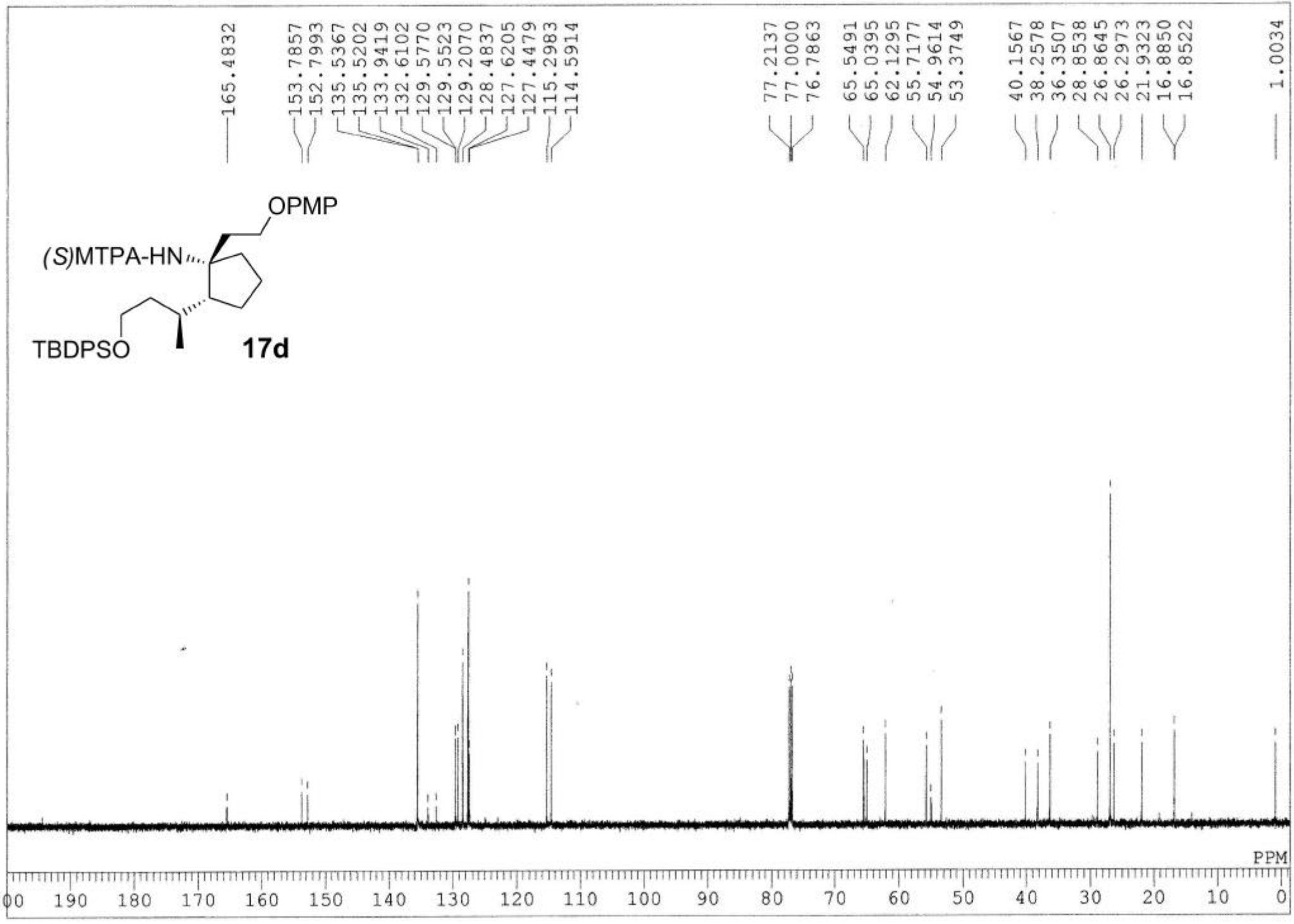
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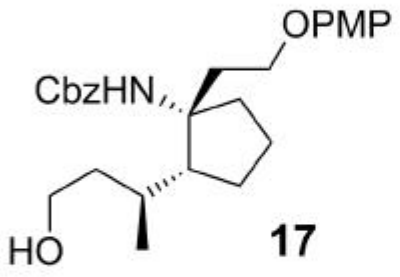

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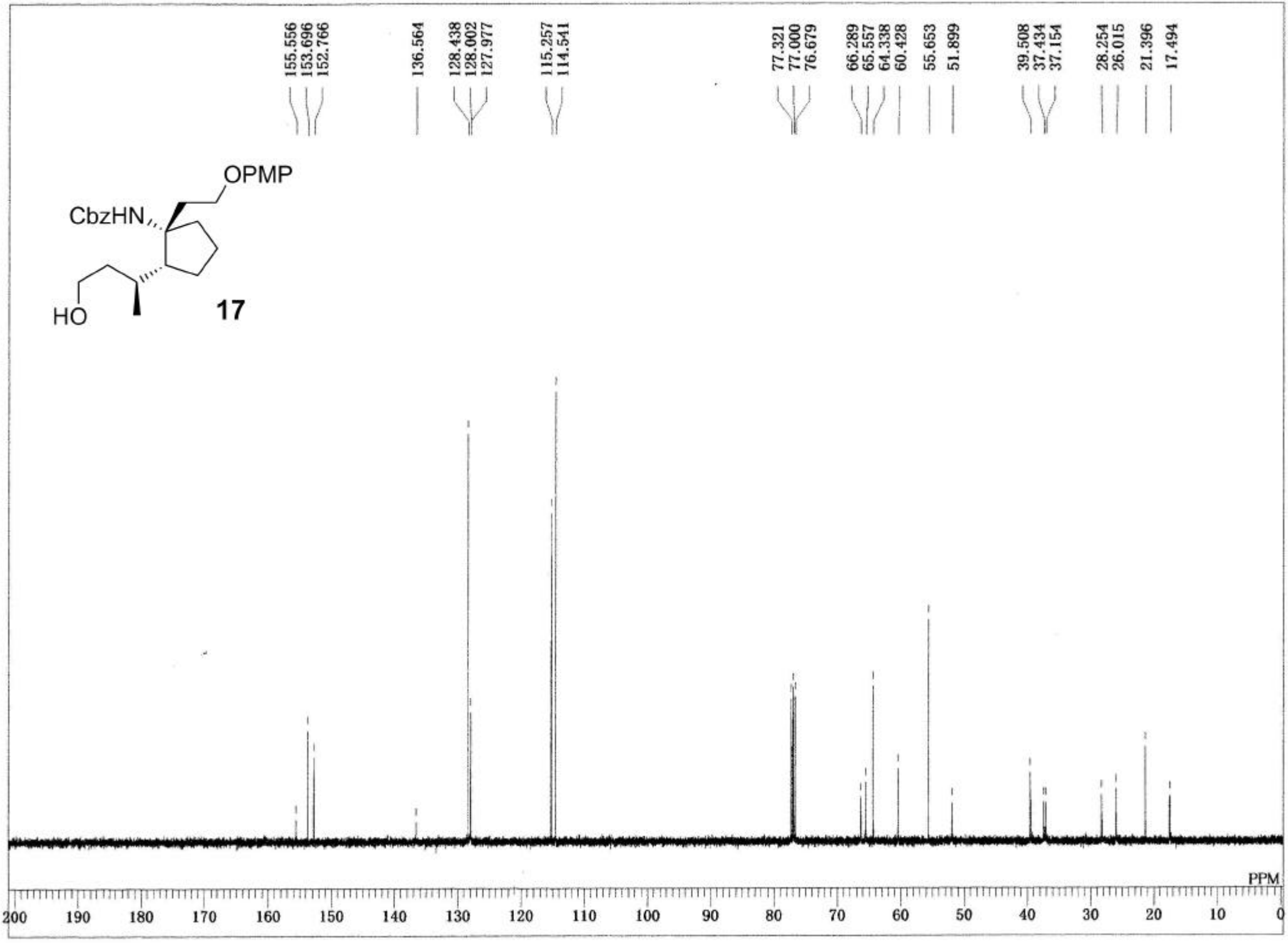
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CbzHN
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PPM
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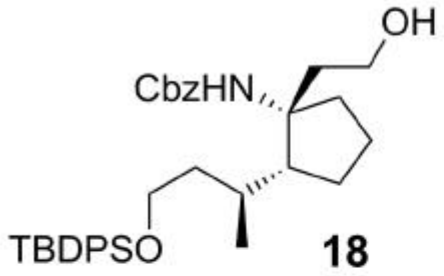

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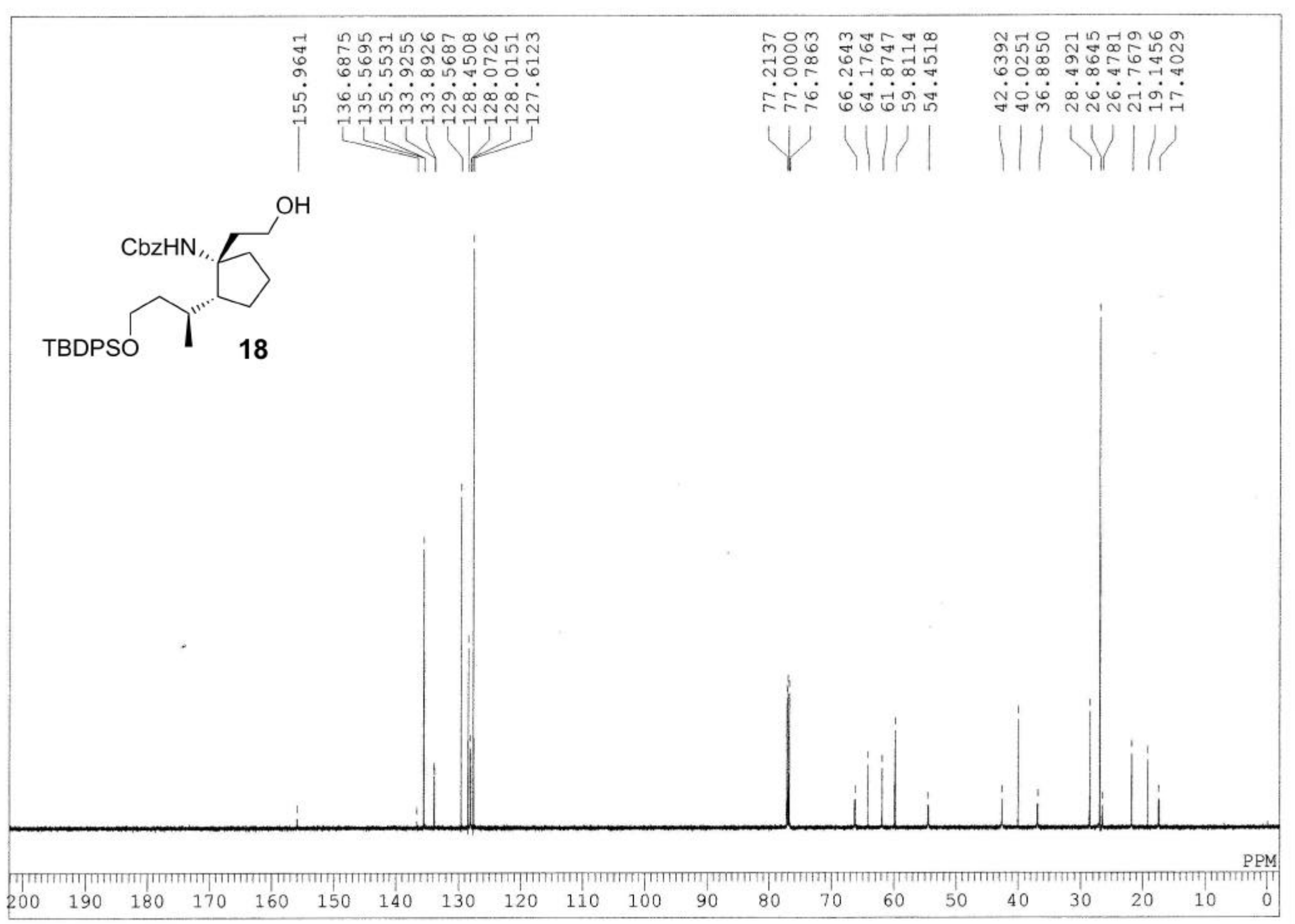
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CbzHN
TBDPSO
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PPM
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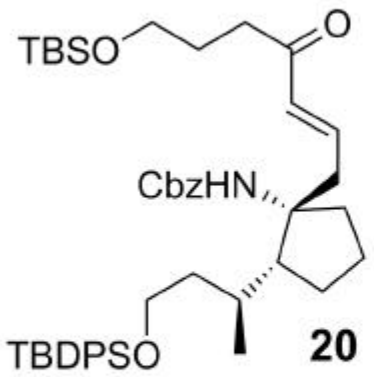

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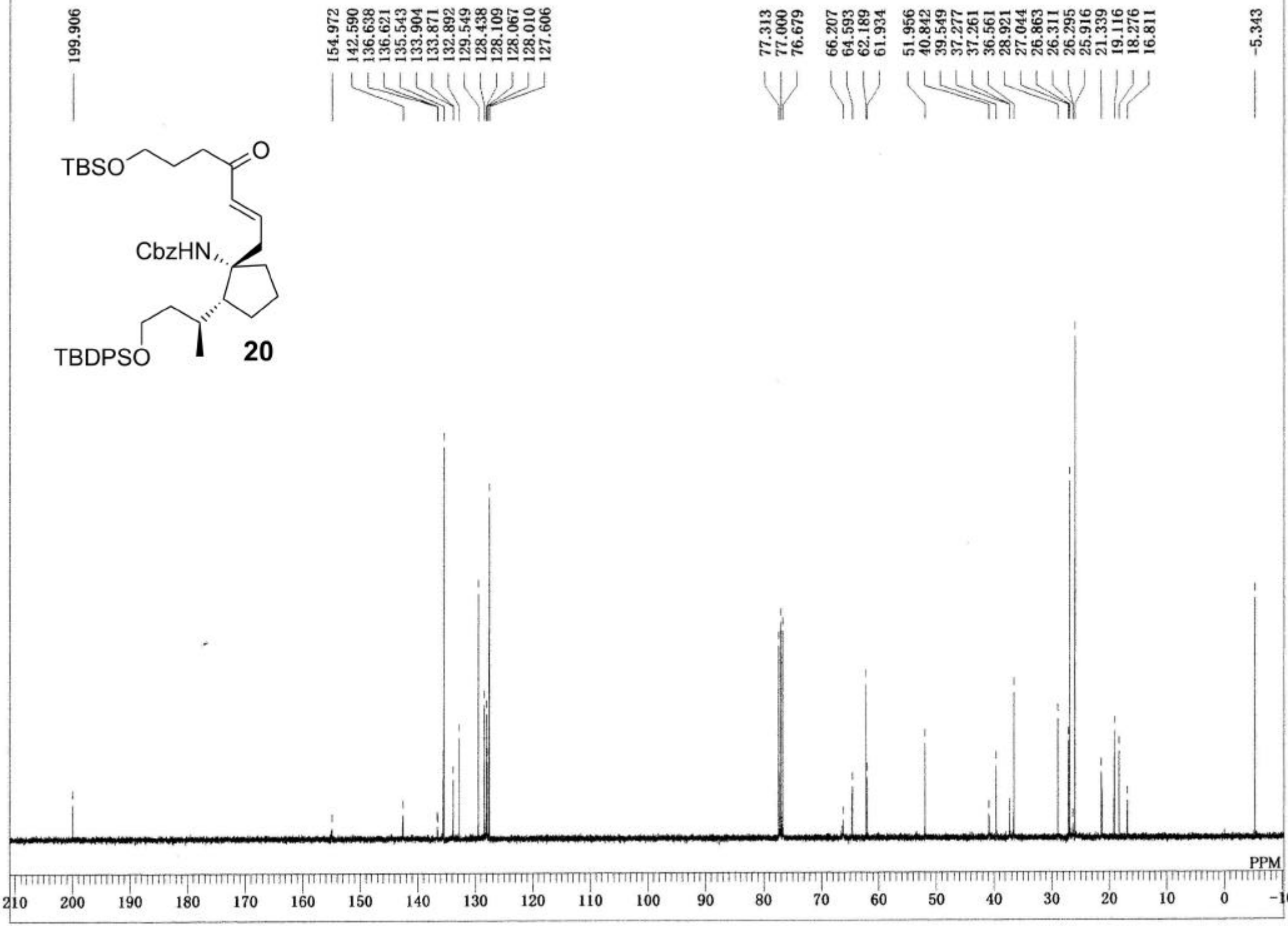
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CbzHN
TBDPSO
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PPM
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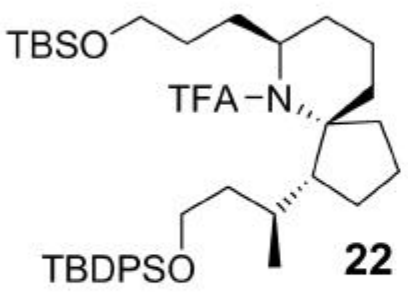
-10



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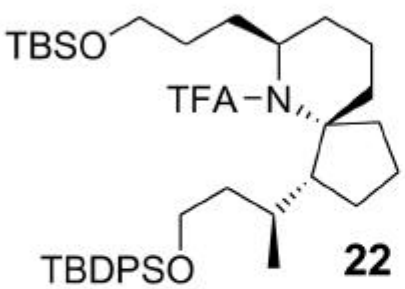

22

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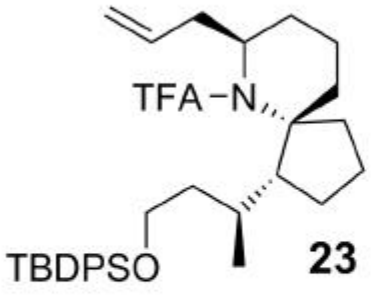
PPM



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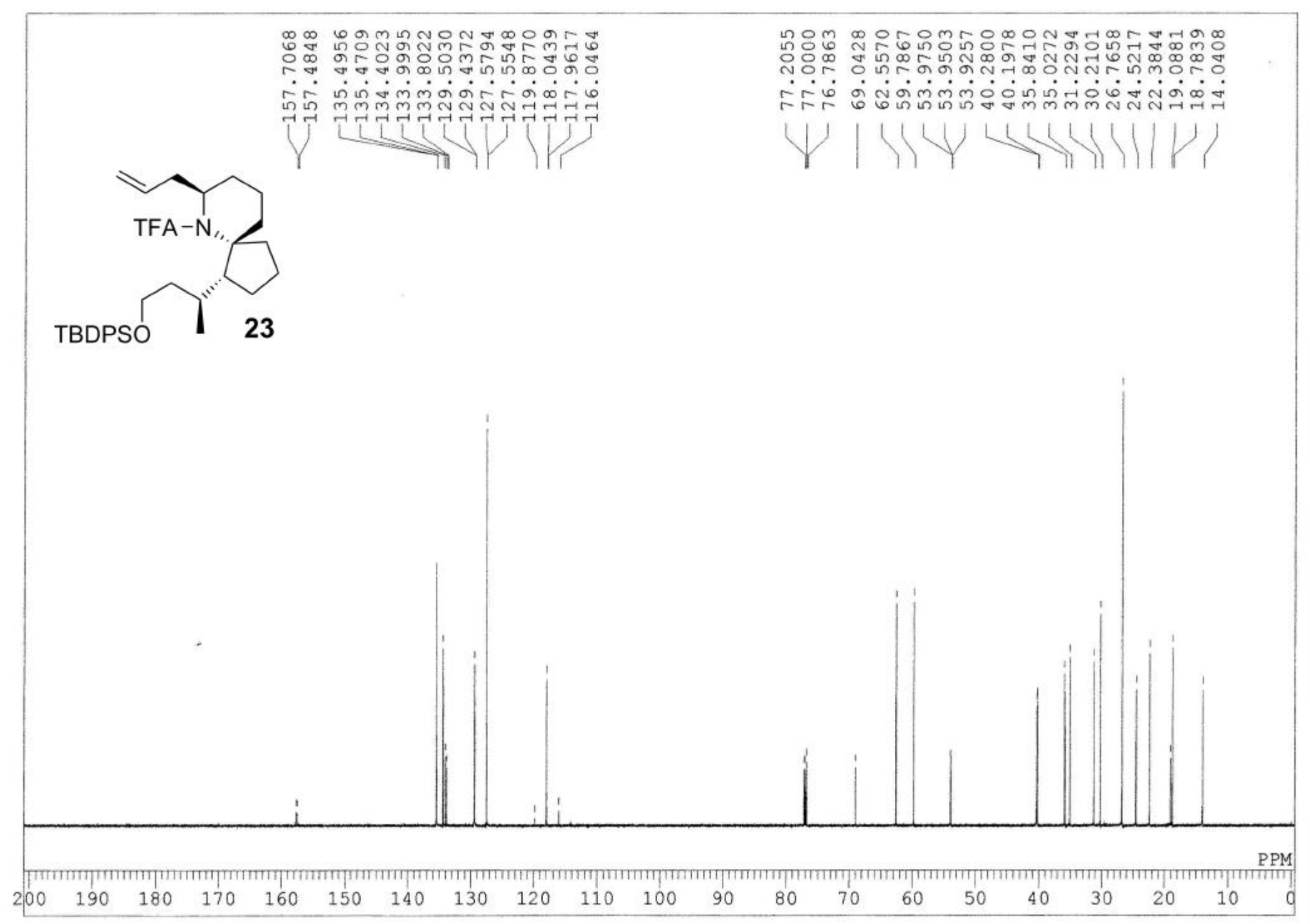
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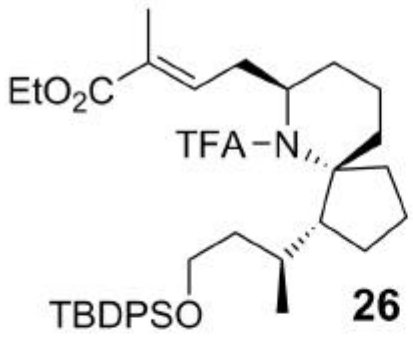

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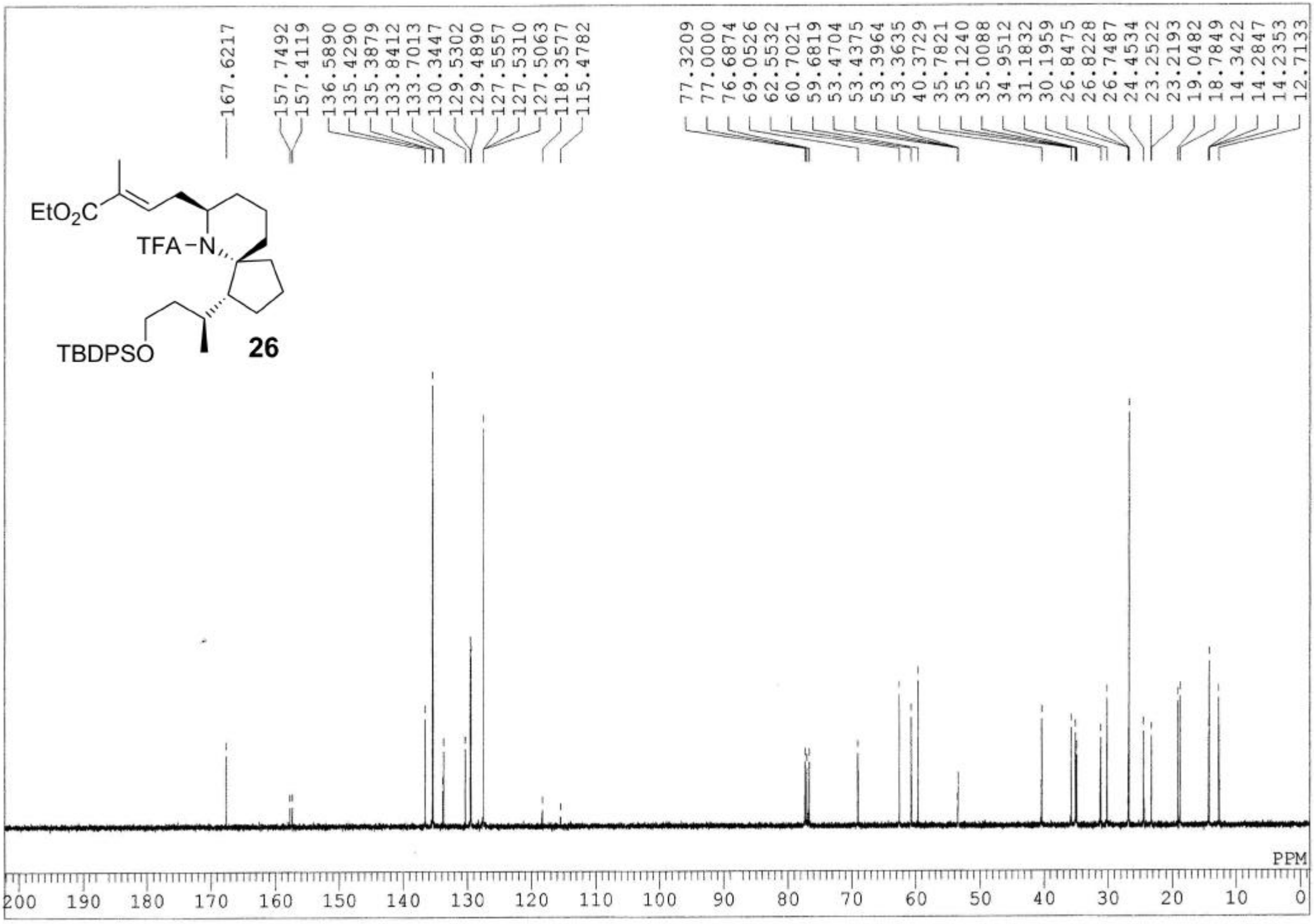
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PPM
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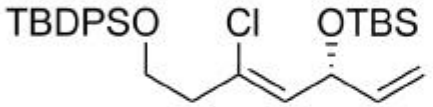

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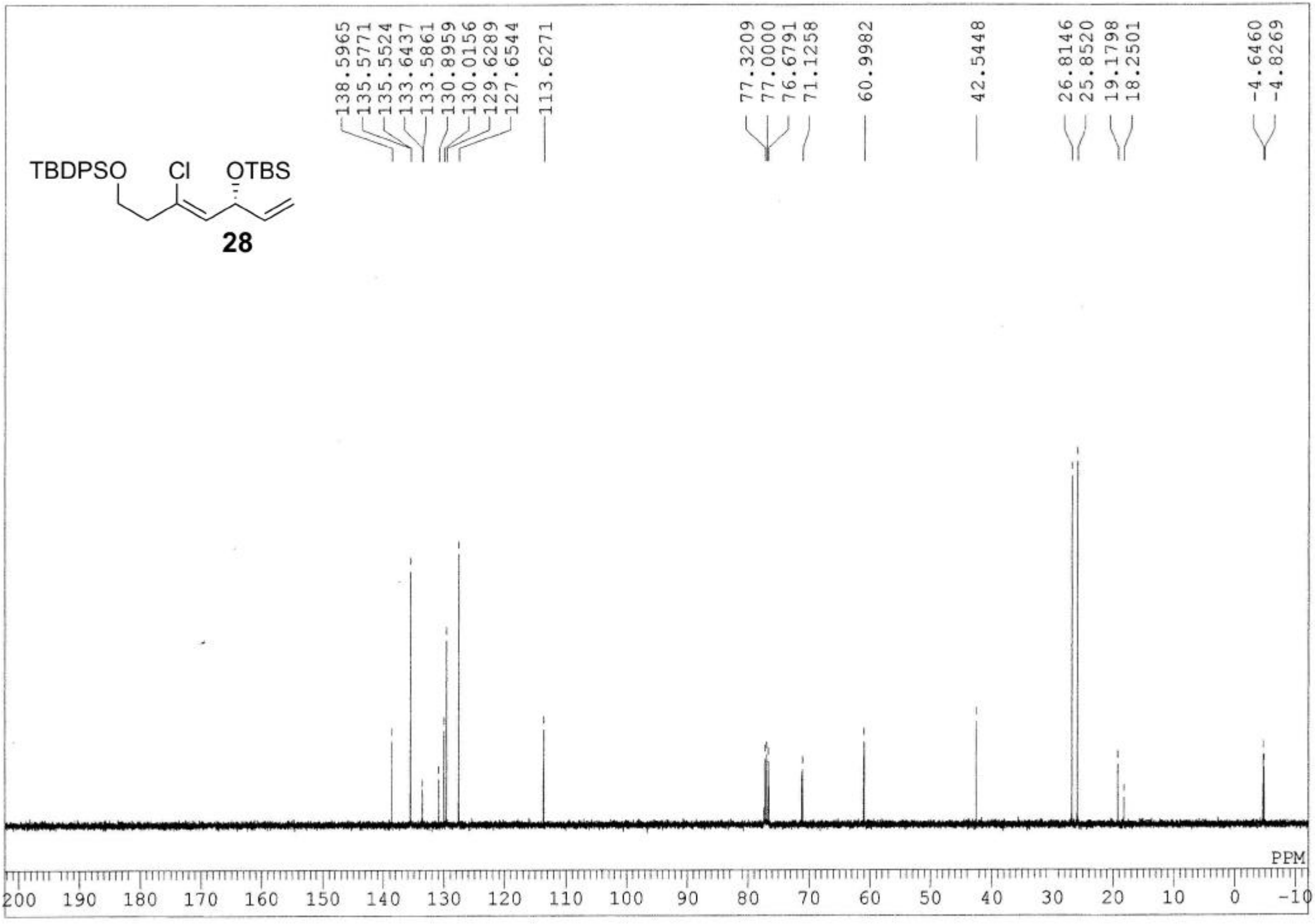
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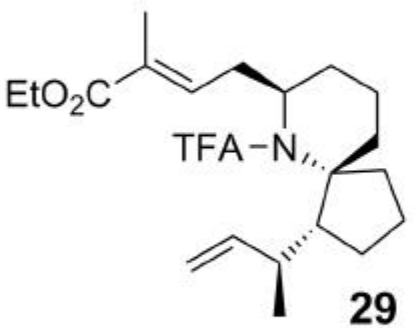

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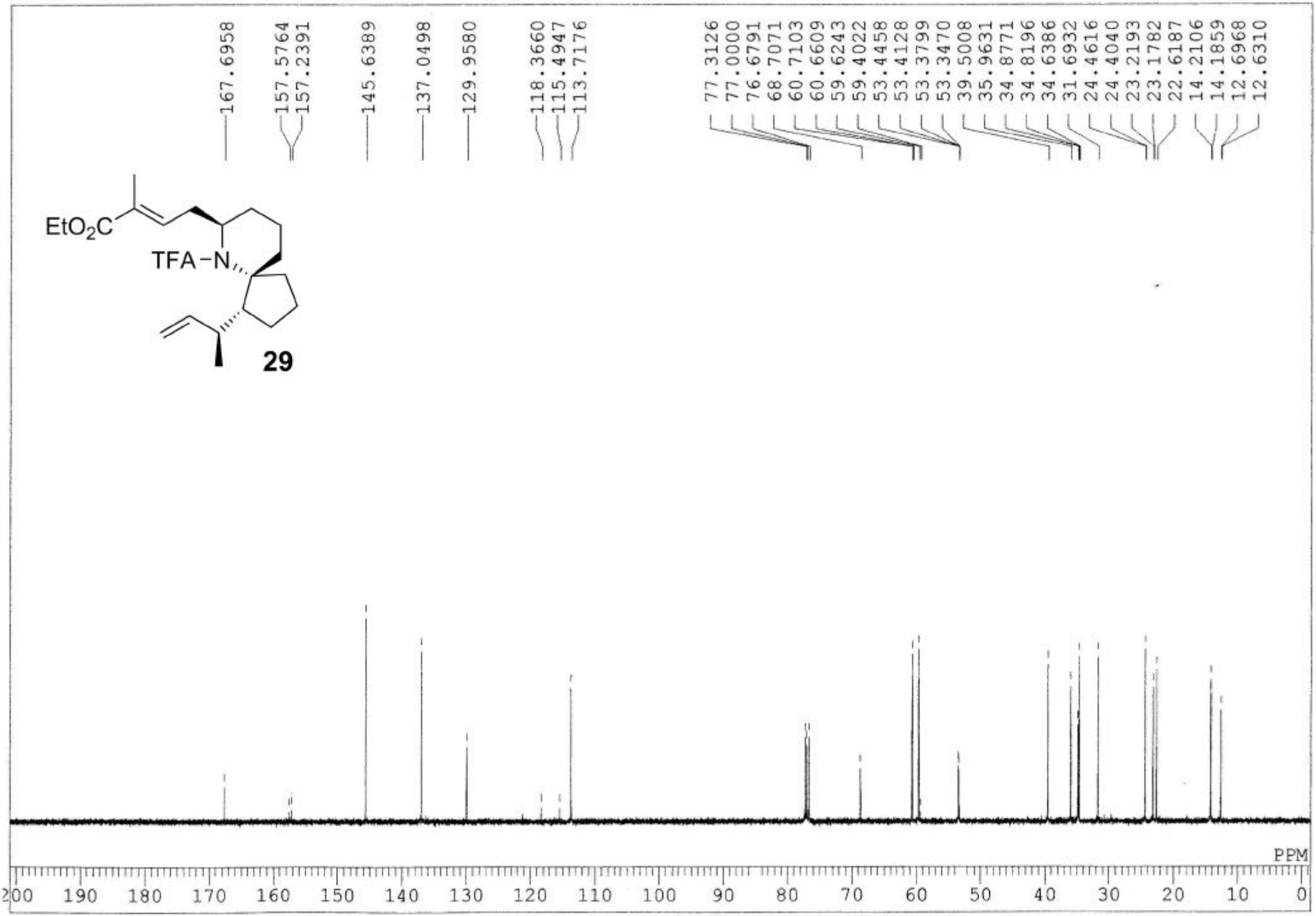
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PPM
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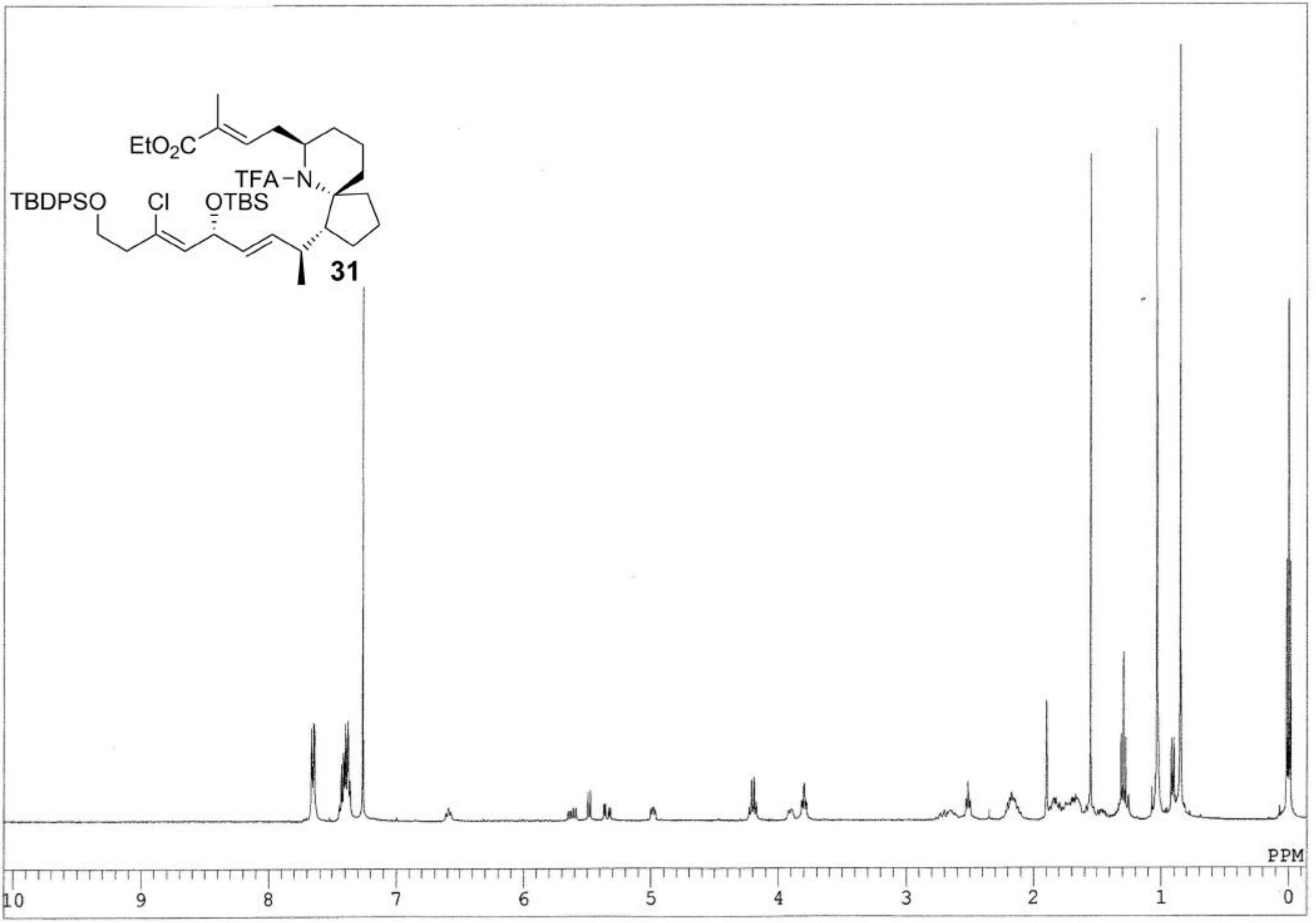
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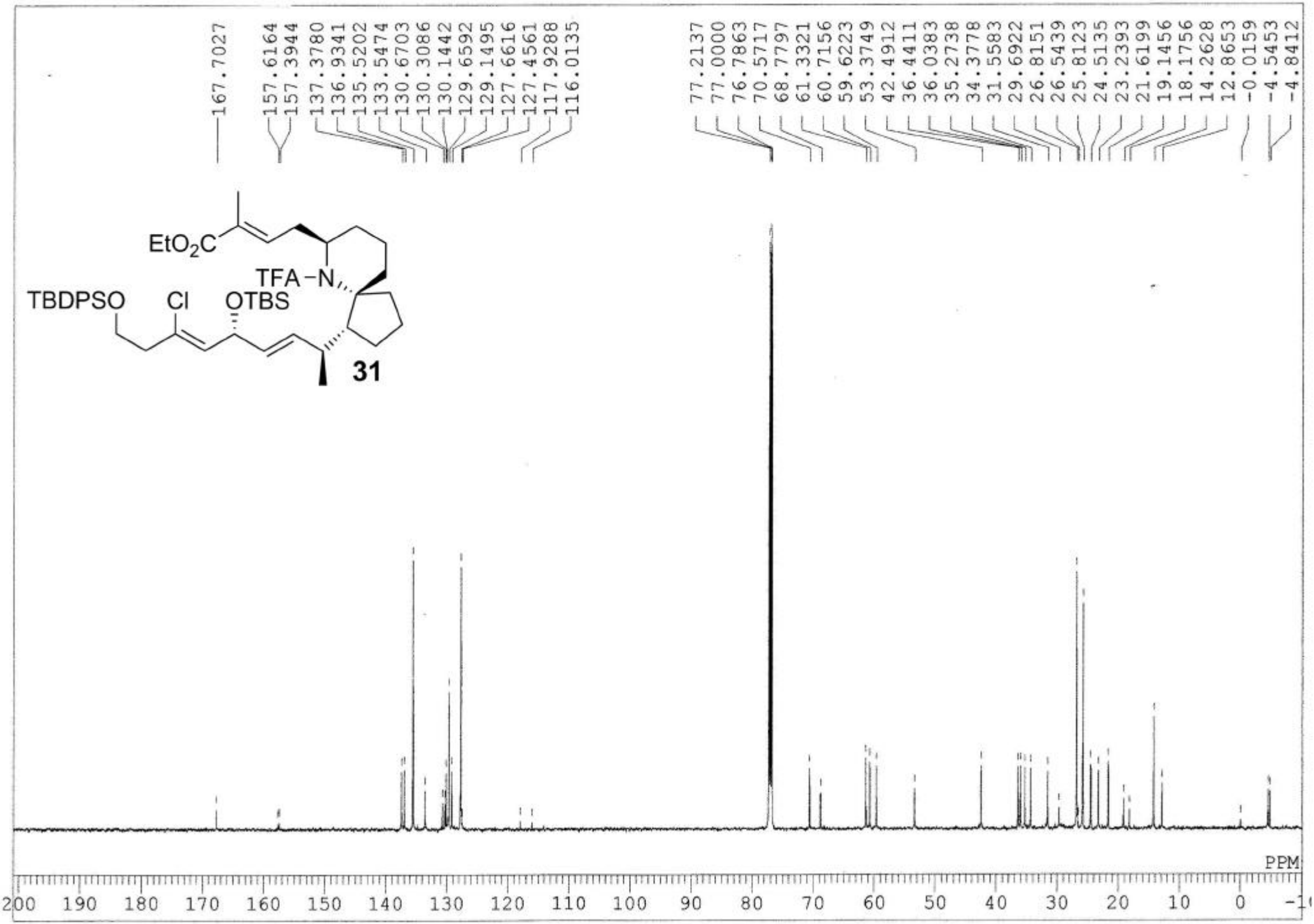
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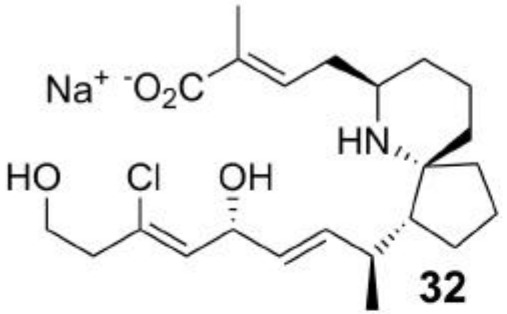

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