Supporting Information

Synthetic Studies on Densanins: Stereoselective Construction of a Pyrrolidine Ring Containing a Quaternary Carbon

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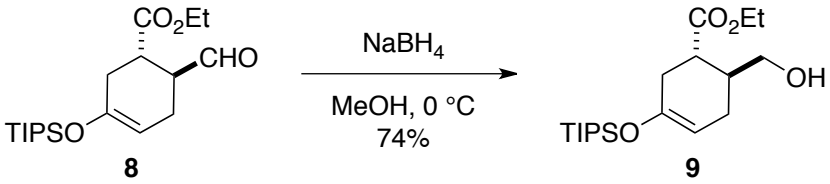
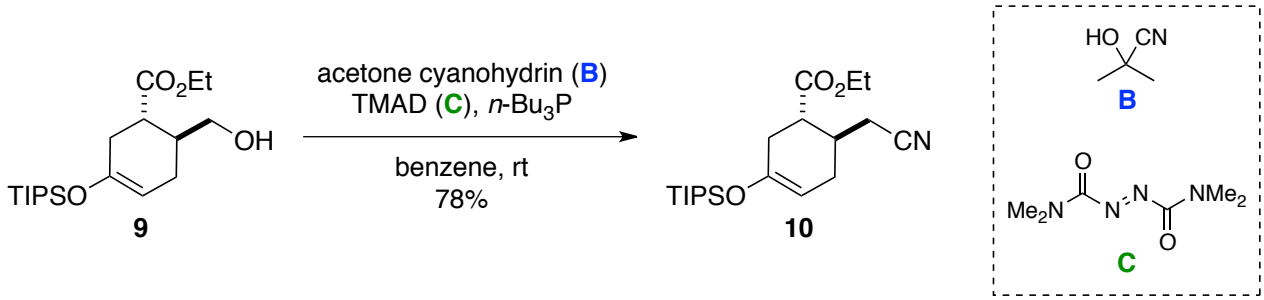
General Remarks: Nuclear magnetic resonance (NMR) spectra were determined on a JEOL-ECS400 instrument (400 and 100 MHz for ^{1}H and ^{13}C NMR, respectively). Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfields from tetramethylsilane (δ) as the internal standard or relative to a residual proton peak of the solvent at 7.26 ppm for chloroform-d_1, or at 7.16 ppm for benzene-d_6. Coupling constants for ^{1}H-NMR are reported in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Chemical shifts for ^{13}C NMR were reported in ppm relative to the center line of the triplet at 77.0 ppm for chloroform-d_1 or the center line of the triplet at 128.06 ppm for benzene-d_6. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 Fourier Transform Infrared Spectrophotometer and were 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 with sodium trifluoroacetate as the internal standard. Optical rotations were measured on JASCO P-2200 Polarimeter at room temperature using the sodium D line. Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F254. Preparative TLC separations were performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F254 unless otherwise noted. Flash chromatography separations were performed on KANTO CHEMICAL Silica Gel 60 (spherical, 40-100 mesh) unless otherwise noted. Reagents were commercial grades and were used without any purification. Dehydrated tetrahydrofuran, diethyl ether and dichloromethane were purchased from Kanto Chemicals Co., Inc., and were purified using a Glass Contour Solvent System. *N*,*N*-Dimethylformamide was purchased from Kanto Chemicals Co., Inc. and stored over activated MS4A. Dehydrated methanol was also purchased from Kanto Chemicals Co., Inc. and stored over activated MS3A. All reactions sensitive to oxygen or moisture were

conducted under an argon atmosphere. Preparation of compound **8** and determination of its optical purity were carried out according to the literature.[1] Starting from 20.0 g of **6** (156 mmol) and 42.4 g of **7** (187 mmol) by using (*S*)-Hayashi-Jørgensen catalyst, instead of (*R*)-catalyst, 46.9 g of **8** (132 mmol, 85%, >99:1 er) was obtained as a yellow oil. $[\alpha]_D^{24}$ = +18.6 (*c* 0.30, $CHCl_3$).

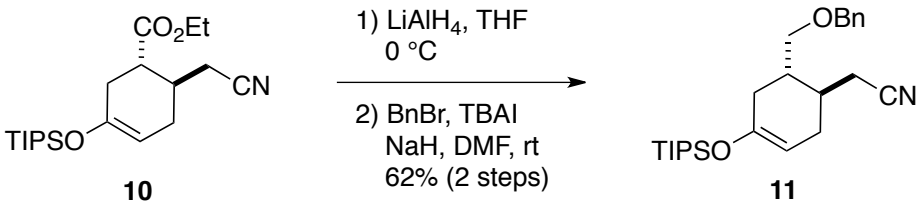


To a stirred solution of **8** (44.0 g, 124 mmol) in MeOH (250 mL) was added $NaBH_4$ (3.78 g, 124 mmol) at 0 °C under argon. After stirring for 1 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl (200 mL) at 0 °C, and the mixture was extracted with Et_2O (300 mL×5). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 4:1-3:1) to afford **9** (32.6 g, 91.5 mmol, 74%) as a yellow oil. $[\alpha]_D^{22}$ = +26.5 (*c* 0.30, $CHCl_3$); IR (film) 3462 (br), 2943, 2867, 1734, 1670, 1200, 1034, 883, 683; ^{1}H NMR ($CDCl_3$) δ 4.86-4.82 (m, 1H), 4.24-4.11 (m, 2H), 3.62 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.58 (dd, *J* = 11.4, 4.8 Hz, 1H), 2.60 (ddd, *J* = 10.2, 10.2, 5.6 Hz, 1H), 2.51-2.43 (m, 1H), 2.26-2.11 (m, 2H), 2.05-1.92 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.19-1.11 (m, 3H), 1.07 (d, *J* = 6.0 Hz, 18H); ^{13}C NMR ($CDCl_3$) δ 175.3 (C), 148.4 (C), 101.3 (CH), 65.2 (CH_2), 60.7 (CH_2), 42.8 (CH), 38.5 (CH), 32.1 (CH_2), 26.3 (CH_2), 18.0 (CH_3), 14.2 (CH_3), 12.6 (CH); HRMS (ESI) 379.2269 (calcd for $C_{19}H_{36}NNaO_4Si$ 379.2281). [KU04107]

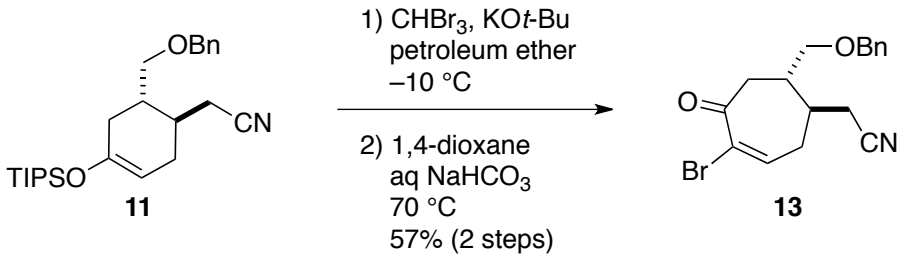


To a stirred solution of **9** (21.9 g, 61.3 mmol), acetone cyanohydrin (**B**, 8.80 mL, 91.9 mmol), *n*-Bu_3P (23.9 mL, 91.9 mmol) in benzene (620 mL) was added TMAD (**C**, 16.7 g, 91.9 mmol) at 0 °C under argon. After stirring for 24 h at room temperature, the reaction was quenched with H_2O (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (200 mL×3). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 14:1) to afford **10** (17.5 g, 47.9 mmol, 78%) as a yellow oil. $[\alpha]_D^{23}$ = +54.3 (*c* 1.00,

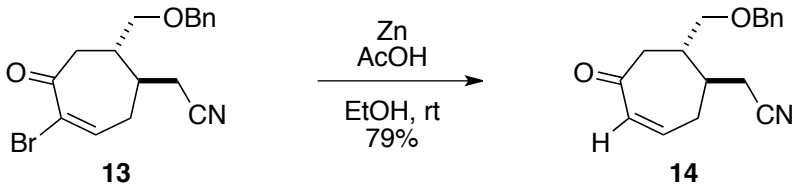
$CHCl_3$); IR (film) 2945, 2868, 1733, 1676, 1465, 1367, 1328, 1203, 1179, 1019, 882; ^{1}H NMR ($CDCl_3$) δ 4.80-4.77 (m, 1H), 4.23-4.10 (m, 2H), 2.60 (ddd, *J* = 9.6, 9.6, 6.0 Hz, 1H), 2.52-2.24 (m, 5H), 2.24-2.13 (m, 1H), 2.08-2.00 (m, 1H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.20-1.06 (m, 21H); ^{13}C NMR ($CDCl_3$) δ 173.6 (C), 148.3 (C), 117.8 (C), 100.0 (CH), 60.9 (CH_2), 44.1 (CH), 32.0 (CH), 31.8 (CH_2), 28.4 (CH_2), 21.3 (CH_2), 17.8 (CH_3), 14.1 (CH_3), 12.5 (CH); HRMS (ESI) 388.2274 (calcd for $C_{20}H_{35}NNaO_3Si$ 388.2284). [KU04155]



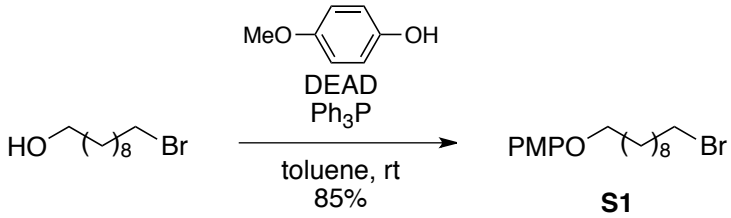
To a suspension of $LiAlH_4$ (3.67 g, 94.6 mmol) in THF (270 mL) was slowly added **10** (17.3 g, 47.3 mmol) in THF (200 mL) via cannula at 0 °C under argon. After stirring for 1 h at same temperature, the reaction mixture was diluted with THF (1.00 L) and quenched by sequential addition of H_2O (3.7 mL), 15% NaOH aq. (3.7 mL), and H_2O (11 mL) at 0 °C. After stirring for 2 4, the resulting mixture was filtered through a Celite pad (washed with Et_2O), and concentrated *in vacuo*. The residue (15.6 g) was dissolved in DMF, and the resulting solution was slowly added at 0 °C over 15 min via cannula to a suspension of NaH (55% oil dispersion, 4.13 g, 94.6 mmol), BnBr (11.5 mL, 94.6 mmol), and TBAI (4.37 g, 11.8 mmol) in DMF (200 mL). After stirring for 2 h at room temperature, the reaction mixture was diluted with Et_2O (1.0 L) and quenched with saturated aqueous NH_4Cl (150 mL) and H_2O (150 mL) at 0 °C. The mixture was extracted with Et_2O (300 mL×3). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 9:1) to afford **11** (12.1 g, 29.2 mmol, 62% in 2 steps) as a colorless oil. This material included impurities derived from the TIPS group. $[\alpha]_D^{23}$ = +33.4 (*c* 2.27, $CHCl_3$); IR (film) 2944, 2866, 1673, 1464, 1366, 1199, 1095, 883, 685; ^{1}H NMR ($CDCl_3$) δ 7.38-7.27 (m, 5H), 4.79-4.75 (m, 1H), 4.50 (s, 2H), 3.48 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.41 (dd, *J* = 9.6, 4.8 Hz, 1H), 2.46 (dd, *J* = 17.2, 4.0 Hz, 1H), 2.39 (dd, *J* = 17.2, 6.4 Hz, 1H), 2.27-2.21 (m, 1H), 2.11-2.10 (m, 2H), 2.04-1.99 (m, 3H), 1.18-1.05 (m, 21H); ^{13}C NMR ($CDCl_3$) δ 149.2 (C), 138.1 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 118.9 (C), 100.2 (CH), 73.2 (CH_2), 71.7 (CH_2), 37.5 (CH), 32.1 (CH), 31.6 (CH_2), 28.5 (CH_2), 21.1 (CH_2), 18.0 (CH_3), 12.5 (CH); HRMS (ESI) 436.2644 (calcd for $C_{25}H_{39}NNaO_2Si$ 436.2648). [KU04156, KU04157]



To a stirred solution of **11** (12.0 g, 29.0 mmol) and KO*t*-Bu (26.9 g, 232 mmol) in petroleum ether (190 mL) was slowly added $CHBr_3$ (15.4 mL, 175 mmol) over 2 h at –10 °C under argon. After stirring for 1 h at the same temperature, the reaction mixture was filtered through a Celite pad (washed with Et_2O) and concentrated *in vacuo*. The residue was dissolved in a 5:1 mixture of 1,4-dioxane and saturated aqueous $NaHCO_3$ (180 mL). The resulting mixture was heated at 70 °C for 1 h. After cooling to room temperature, the resulting mixture was extracted with EtOAc (200 mL×5). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 2:1) to afford **13** (5.77 g, 16.6 mmol, 57% in 2 steps) as a brown oil. $[\alpha]_D^{23}$ = +50.9 (*c* 1.05, $CHCl_3$); IR (film) 3032, 2865, 2245, 1681, 1603, 1454, 1423, 1362, 1105, 881, 741, 700; ^{1}H NMR ($CDCl_3$) δ 7.40-7.27 (m, 6H), 4.48 (s, 2H), 3.49 (dd, *J* = 9.4, 4.8 Hz, 1H), 3.38 (dd, *J* = 9.4, 6.4 Hz, 1H), 2.87 (dd, *J* = 14.4, 4.8 Hz, 1H), 2.81 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.70-2.57 (m, 2H), 2.57 (dd, *J* = 17.2, 4.8 Hz, 1H), 2.45 (dd, *J* = 17.2, 8.0 Hz, 1H), 2.25-2.17 (m, 1H), 2.04-1.95 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 192.7 (C), 145.4 (CH), 137.5 (C), 128.8 (C), 128.5 (CH), 127.9 (CH), 127.6 (CH), 118.1 (C), 73.5 (CH_2), 72.6 (CH_2), 44.0 (CH_2), 38.6 (CH), 37.0 (CH), 32.8 (CH_2), 23.5 (CH_2); HRMS (ESI) 370.0411 (calcd for $C_{17}H_{18}{}^{79}BrNNaO_2$ 370.0419). [KU04165]

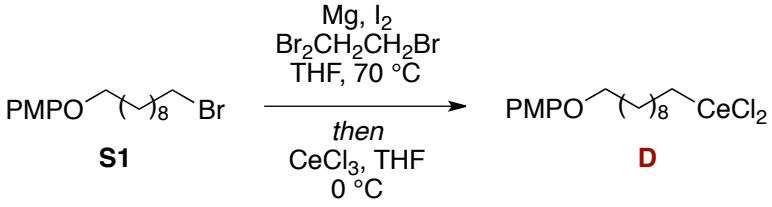


To a stirred solution of **13** (3.79 g, 10.9 mmol) in EtOH (200 mL) was added Zn dust (18.5 g, 272 mmol) and NH_4Cl (2.96 g, 54.4 mol) at 0 °C under argon. After stirring for 1 h at room temperature, the reaction mixture was filtered through a Celite pad. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 2:1-3:2) to afford **14** (2.31 g, 8.58 mmol, 79%) as a yellow oil. $[\alpha]_D^{23}$ = +21.1 (*c* 0.30, $CHCl_3$); IR (film) 2917, 2861, 1667, 1455, 1106, 741, 699; ^{1}H NMR ($CDCl_3$) δ 7.37-7.28 (m, 5H), 6.74 (ddd, *J* = 11.6, 6.6, 6.6 Hz, 1H), 6.12 (d, *J* = 11.6 Hz, 1H), 4.49 (s, 2H), 3.48 (dd, *J* = 9.4, 5.6 Hz, 1H), 3.37 (dd, *J* = 9.4, 6.8 Hz, 1H), 2.73 (dd, *J* = 14.4, 4.4 Hz, 1H), 2.68-2.63 (m, 3H), 2.56 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.43 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.24-2.16 (m, 1H), 2.00-1.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 200.8 (C), 144.6 (CH), 137.6 (C), 134.6 (CH), 128.4 (CH), 127.7 (CH), 127.5 (CH), 118.4 (C), 73.3 (CH_2), 73.1 (CH_2), 45.1 (CH_2), 38.4 (CH), 37.5 (CH), 31.4 (CH_2), 23.4 (CH_2); HRMS (ESI) 292.1303 (calcd for $C_{17}H_{19}NNaO_2$ 292.1314). [KU04170]



S1

To a stirred solution of 10-bromodecanol (13.7 mL, 88.3 mmol), *p*-methoxyphenol (7.12 g, 88.3 mmol) and Ph_3P (14.6 g, 85.64 mmol) in toluene (286 mL) was added DEAD in toluene (2.2 M, 26 mL, 88.3 mmol) at room temperature under argon. After stirring for 1 h at the same temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 19:1). The resulting solid was crystallized from *n*-hexane to afford **S1** (25.9 g, 75.4 mmol, 85%) as a colorless solid. mp. 60.7 °C; IR (film) 2934, 2852, 1512, 1241, 1853, 1038, 908, 825, 731; ^{1}H NMR ($CDCl_3$) δ 6.83 (s, 4H), 3.90 (t, *J* = 6.6 Hz, 2H), 3.77 (s, 3H), 3.41 (t, *J* = 6.8 Hz, 2H), 1.85 (dt, *J* = 14.8, 6.8 Hz, 2H), 1.75 (dt, *J* = 14.8, 6.8 Hz, 2H), 1.48-1.39 (m, 4H), 1.37-1.26 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 153.6 (C), 153.2 (C), 115.4 (CH), 114.6 (CH), 68.6 (CH_2), 55.7 (CH_3), 34.1 (CH_2), 32.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 28.1 (CH_2), 26.0 (CH_2).

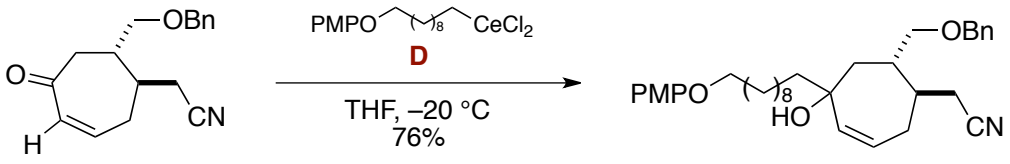


S1 **D**

In a flask, anhydrous $CeCl_3$ (17.7 g, 72.0 mmol) and THF (120 mL) was charged, and the resulting mixture was sonicated for 1 h at room temperature, and then cooled to 0 °C (flask A).

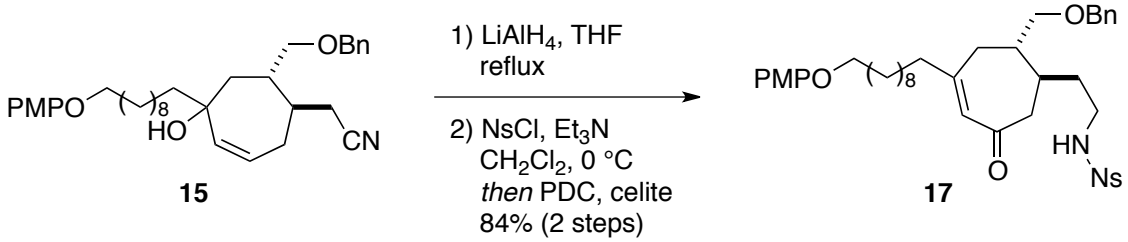
In another flask, a Grignard reagent was prepared according to the following procedure. To a vigorously stirred mixture of Mg (1.17 g, 48.0 mmol), 1,2-dibromoethane (1 drop), and I_2 (1 grain) in THF (40 mL) was slowly added **S1** (8.24 g, 24.0 mmol) in THF (80 mL) over 1.5 h at 70 °C under argon. After stirring for another 1 h at 70 °C, the resulting mixture was cooled to 40 °C.

The hot solution of a Grignard reagent was slowly transported to the flask A, which was cooled at 0 °C with stirring, via cannula over 30 min. The resulting suspension was stirred at 0 °C for 1 h. The resulting solution containing organocerium reagent **D** (0.1 M in THF, 240 mL) was used for the next step.



14 **15**

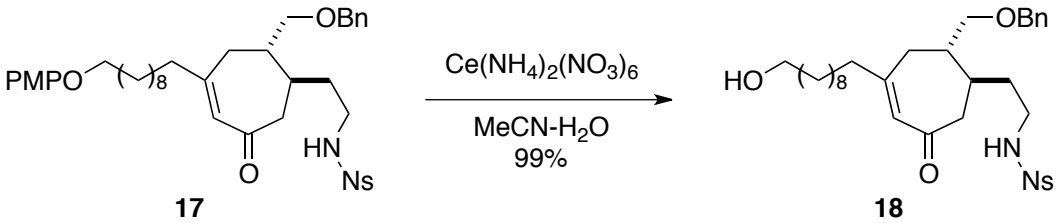
To a stirred solution of **14** (2.20 g, 8.17 mmol) in THF (100 mL) was added the above organocerium reagent **D** in THF (240 mL, 24.0 mmol) at –20 °C under argon. After stirring for 1 h at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl (100 mL) at –20 °C, and the resulting mixture was extracted with Et_2O (100 mL×5). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 9:1-5:1) to afford a diastereomeric mixture of tertiary alcohols **15** (dr = 1:1, 3.31 g, 6.20 mmol, 76%) as a yellow oil. $[\alpha]_D^{24}$ = +27.1 (*c* 1.03, $CHCl_3$); IR (film) 3482 (br), 2928, 2854, 1508, 1467, 1232, 1106, 1039, 825, 741, 699; ^{1}H NMR ($CDCl_3$) δ 7.38-7.27 (m, 5H), 6.82 (s, 4H), 5.68-5.60 (m, 1H), 5.57 (d, *J* = 12.0 Hz, 1/2H), 5.44 (ddd, *J* = 11.6, 2.4, 1.8 Hz, 1/2H), 4.56 (d, *J* = 12.0 Hz, 1/2H), 4.50 (s, 1H), 4.48 (d, *J* = 12.0 Hz, 1/2H), 3.89 (t, *J* = 6.4 Hz, 2H), 3.76 (s, 3H), 3.56 (dd, *J* = 9.4, 4.4 Hz, 1/2H), 3.48 (dd, J = 9.4, 4.8 Hz, 1/2H), 3.40 (dd, *J* = 9.2, 5.6 Hz, 1/2H), 3.34 (dd, *J* = 9.2, 6.0 Hz, 1/2H), 2.77 (brs, 1H), 2.55 (dd, *J* = 17.2, 4.4 Hz, 1/2H), 2.51-2.45 (m, 1/2H), 2.41-2.31 (m, 3/2H), 2.30-2.26 (m, 1H), 2.18 (dd, *J* = 8.4, 3.6 Hz, 1/2H), 2.14 (dd, *J* = 8.4, 3.2 Hz, 1/2H), 2.09-2.03 (m, 1H), 1.98 (dd, *J* = 14.6, 11.2 Hz, 1/2H), 1.91-1.79 (m, 3/2H), 1.78-1.71 (m, 5/2H), 1.55-1.40 (m, 4H), 1.37-1.23 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 153.6 (C), 153.2 (C), 138.6 (CH), 138.1 (C), 137.5 (C), 137.4 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 125.7 (CH), 124.1 (CH), 119.6 (C), 118.8 (C), 115.3 (CH), 114.5 (CH), 76.0 (C), 74.5 (CH_2), 74.4 (C), 73.6 (CH_2), 73.2 (CH_2), 73.1 (CH_2), 68.6 (CH_2), 55.7 (CH_3), 44.5 (CH_2), 42.6 (CH_2), 40.1 (CH_2), 39.9 (CH), 39.1 (CH_2), 37.6 (CH), 37.1 (CH), 36.4 (CH), 30.1 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.1 (CH_2), 26.0 (CH_2), 23.8 (CH_2), 23.4 (CH_2), 23.3 (CH_2), 22.1 (CH_2); HRMS (ESI) 556.3378 (calcd for $C_{34}H_{47}NNaO_4$ 556.3403). [KU04187]



15 **17**

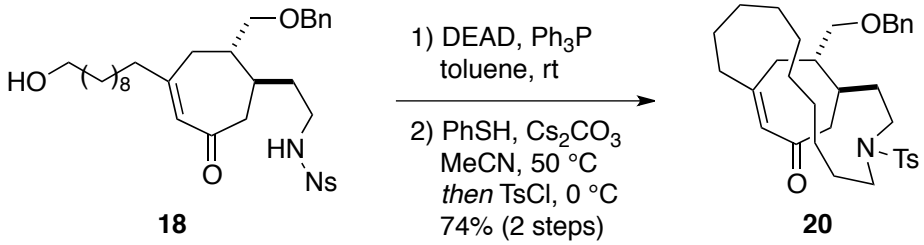
To a suspension of $LiAlH_4$ (927 mg, 23.9 mmol) in THF (20 mL) was slowly added **15** (2.84 g, 5.32 mmol) in THF (33 mL) via cannula at 0 °C under argon. The resulting mixture was heated at 75 °C for 1 h, before the reaction mixture was diluted with THF (100 mL) and quenched by sequential addition of H_2O (1 mL), 15% aqueous NaOH (1 mL), and H_2O (3 mL) at 0 °C. After stirring for 4 h vigorously, the resulting mixture was filtered through a Celite pad (washed with Et_2O), and concentrated *in vacuo*. The residue was

dissolved with CH_2Cl_2 (53 mL). To this solution were added Et_3N (1.12 mL, 7.98 mmol) and NsCl (1.37 g, 5.85 mmol) at 0 °C. After stirring for 1 h at the same temperature, PDC (3.93 g, 10.64 mmol) and Celite (4.0 g) were added to the resulting mixture at 0 °C. After stirring for another 2 h at room temperature, the reaction mixture was filtered through a Celite pad (washed with CH_2Cl_2). The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 5:2-3:2) to afford **17** (3.21 g, 4.45 mmol, 84% in 2 steps) as a yellow oil. $[\alpha]_D^{24}$ = +7.90 (*c* 1.175, $CHCl_3$); IR (film) 2928, 2855, 1647, 1542, 1508, 1460, 1362, 1231, 1168, 1102, 1038, 736; ^{1}H NMR ($CDCl_3$) δ 8.12-8.09 (m, 1H), 7.83-7.81 (m, 1H), 7.74-7.69 (m, 2H), 7.38-7.28 (m, 5H), 6.82 (s, 4H), 5.88 (s, 1H), 5.48 (t, *J* = 6.3 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 3.90 (t, *J* = 6.8 Hz, 2H), 3.76 (s, 3H), 3.36 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.30 (dd, *J* = 9.2, 6.8 Hz, 1H), 3.16 (td, *J* = 6.8, 6.3 Hz, 2H), 2.63 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.54-2.40 (m, 3H), 2.17 (t, *J* = 7.6 Hz, 2H), 1.84-1.57 (m, 5H), 1.50-1.40 (m, 5H), 1.35-1.24 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 201.4 (C), 163.7 (C), 153.6 (C), 153.3 (C), 148.0 (C), 137.9 (C), 133.6 (C), 133.5 (CH), 132.8 (CH), 131.1 (CH), 129.5 (CH), 128.5 (CH), 127.8 (CH), 127.7 (CH), 125.3 (CH), 115.4 (CH), 114.6 (CH), 73.3 (CH_2), 73.2 (CH_2), 68.6 (CH_2), 55.7 (CH_3), 45.1 (CH_2), 43.5 (CH), 41.6 (CH_2), 41.5 (CH_2), 34.7 (CH_2), 34.4 (CH_2), 32.4 (CH), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.2 (CH_2), 26.0 (CH_2); Two methylene carbons were not observed perhaps because of overlapping; HRMS (ESI) 743.3319 (calcd for $C_{40}H_{52}N_2NaO_8S$ 743.3342). [KU04197-199]

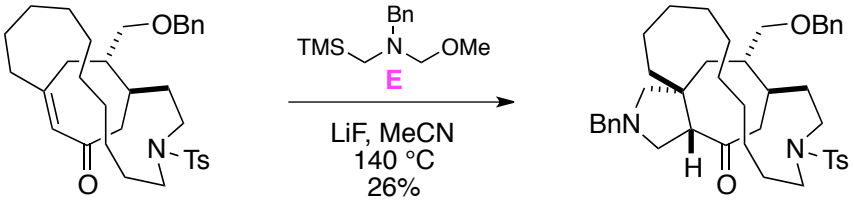


To a stirred solution of **17** (953 mg, 1.32 mmol) in acetonitrile (8 mL) was added ceric ammonium nitrate (1.98 g, 3.44 mmol) in water (2 mL) at 0 °C. After stirring at the same temperature for 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL) at 0 °C. The resulting mixture was partitioned between EtOAc (15 mL) and water (5 mL). The aqueous layer was extracted five times with EtOAc (15 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 1:1-1:2) to afford **18** (804 mg, 1.31 mmol, 99%) as a pale yellow oil. $[\alpha]_D^{25}$ = +7.14 (*c* 1.06, $CHCl_3$); IR (film) 3350 (br), 2927, 2854, 1644, 1542, 1455, 1416, 1363, 1166, 1094, 740, 588; ^{1}H NMR ($CDCl_3$) δ 8.11-8.08 (m, 1H), 7.83-7.81 (m, 1H), 7.73-7.71 (m, 2H), 7.38-7.29 (m, 5H), 5.88 (s, 1H), 5.56 (t, *J* = 6.0 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 3.63 (t, *J* = 6.6 Hz, 2H), 3.36 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.30 (dd, *J* = 9.0, 7.2 Hz, 1H), 3.14 (td, *J* = 6.8, 6.0 Hz, 2H), 2.63 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.54-2.41 (m, 3H), 2.17 (t, *J* = 7.6 Hz, 2H), 1.83-1.70 (m, 2H), 1.66-1.41 (m, 6H), 1.35-1.23 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 201.5 (C), 163.9 (C), 147.9 (C), 137.9

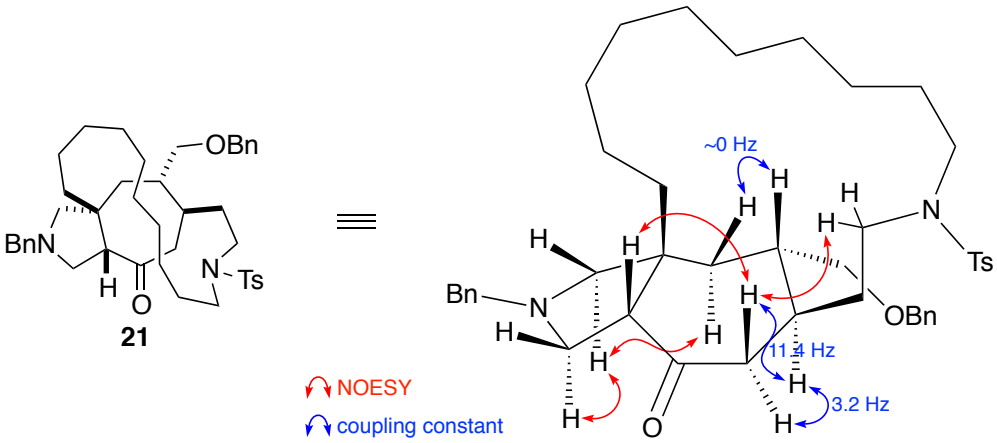
(C), 133.6 (C), 133.5 (CH), 132.8 (CH), 131.1 (CH), 129.4 (CH), 128.4 (CH), 127.7 (CH), 127.7 (CH), 125.2 (CH), 73.2 (CH_2), 73.1 (CH_2), 62.9 (CH_2), 45.0 (CH_2), 43.5 (CH), 41.5 (CH_2), 41.5 (CH_2), 34.7 (CH_2), 34.3 (CH_2), 32.7 (CH_2), 32.3 (CH), 29.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 27.1 (CH_2), 25.6 (CH_2); One methylene carbon was not observed perhaps because of overlapping; HRMS (ESI) 637.2940 (calcd for $C_{33}H_{46}N_2NaO_7S$ 637.2924). [KU04293]



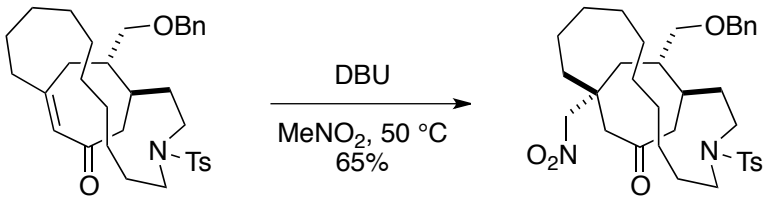
To a solution of **18** (764 mg, 1.24 mmol) and Ph_3P (814 mg, 3.11 mmol) in toluene (1.3 L) was added DEAD in toluene (2.2 M, 1.41 mL, 3.11 mmol) dropwise over 5 min at room temperature under argon. After stirring for 1 h, the reaction mixture was concentrated. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 3:1-1:1) to afford **19** and diethyl hydrazine-1,2-dicarboxylate (1.30 g) as a pale yellow solid. This material was dissolved in acetonitrile (12.5 mL), and to this solution were added Cs_2CO_3 (857 mg, 2.48 mmol) and PhSH (130 μL, 1.24 mmol) at 0 °C. The resulting mixture was heated at 50 °C for 1 h. After cooling to 0 °C, TsCl (498 mg, 2.48 mmol) was added to the resulting mixture at 0 °C. After stirring at room temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (20 mL) at 0 °C, and the mixture was extracted with EtOAc (20 mL×3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 3:1-2:1) to afford **20** (521 mg, 921 μmol, 74% in 2 steps) as a yellow oil. $[\alpha]_D^{25}$ = –28.9 (*c* 1.05, $CHCl_3$); IR (film) 2928, 2855, 1650, 1456, 21339, 1159, 1092, 737, 549; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.39-7.29 (m, 7H), 5.99 (s, 1H), 4.54 (s, 2H), 3.44 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.40 (dd, *J* = 9.0, 6.8 Hz, 1H), 3.26 (ddd, *J* = 12.8, 8.0, 7.6 Hz, 1H), 3.18 (ddd, *J* = 13.6, 13.2, 3.6 Hz, 1H), 2.87-2.70 (m, 3H), 2.60 (dd, *J* = 14.0, 13.6 Hz, 1H), 2.49 (ddd, *J* = 14.8, 4.4, 1.2 Hz, 1H), 2.42 (s, 3H), 2.38 (dd, *J* = 15.2, 3.2 Hz, 1H), 2.32-2.28 (m, 2H), 1.91-1.72 (m, 3H), 1.70-1.51 (m, 3H), 1.49-1.38 (m, 3H), 1.33-1.15 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 201.3 (C), 162.6 (C), 143.0 (C), 138.2 (C), 136.2 (C), 131.3 (CH), 129.6 (CH), 128.4 (CH), 127.6 (CH), 127.4 (CH), 127.0 (CH), 74.3 (CH_2), 73.1 (CH_2), 50.0 (CH_2), 47.7 (CH_2), 44.6 (CH_2), 43.6 (CH), 40.1 (CH_2), 37.8 (CH_2), 34.0 (CH), 34.0 (CH_2), 27.6 (CH_2), 27.5 (CH_2), 27.3 (CH_2), 26.9 (CH_2), 26.4 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 21.5 (CH_3); One methylene carbon was not observed perhaps because of overlapping; HRMS (ESI) 588.3108 (calcd for $C_{34}H_{47}NNaO_4S$ 588.3124). [KU04294, KU04296, KU04297]



To a stirred solution of **20** (23.8 mg, 42.1 μmol) and amine **E** (40.0 μL, 150 μmol) in MeCN (80.0 μL) was added LiF (3.3 mg, 127 μmol, 3.0 eq.) under argon. The resulting mixture was stirred at 140 °C for 5 h, before it was diluted with CH_2Cl_2 (1mL) and quenched with saturated aqueous $NaHCO_3$ (500 μL) and brine (500 μL) at 0 °C., The mixture was extracted with CH_2Cl_2 (2 mL×4). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (*n*-hexane/EtOAc = 2:1, then benzene/EtOAc = 4:1) to afford **21** (7.5 mg, 10.7 μmol, 26%) as a yellow oil. IR (film) 2925, 2854, 1702, 1650, 1539, 1513, 1455, 1338, 1156; ^{1}H NMR (benzene-d_6) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.22-7.04 (m, 8H), 6.84 (d, *J* = 8.0 Hz, 2H), 4.14 (d, *J* = 12.0 Hz, 1H), 4.09 (d, *J* = 12.0 Hz, 1H), 3.60-3.51 (m, 1H), 3.45 (d, *J* = 12.0 Hz, 1H), 3.45 (d, *J* = 13.2 Hz, 1H), 3.38 (d, *J* = 13.2 Hz, 1H), 3.31 (ddd, *J* = 14.0, 7.2, 7.2 Hz, 1H), 3.14-3.10 (m, 2H), 2.82 (dd, *J* = 8.8, 6.4 Hz, 1H), 2.78-2.70 (m, 2H), 2.64 (dd, *J* = 8.8, 8.0 Hz, 1H), 2.53 (d, *J* = 9.2 Hz, 1H), 2.41 (dd, *J* = 8.0, 7.2 Hz, 1H), 2.15 (dd, *J* = 11.0, 3.2 Hz, 1H), 2.09 (dd, *J* = 11.4, 11.0 Hz, 1H), 1.91 (s, 3H), 1.85 (d, *J* = 8.4 Hz, 1H), 1.83-1.73 (m, 2H), 1.69-1.54 (m, 5H), 1.51-1.40 (1H), 1.36-1.10 (m, 16H); ^{13}C NMR (benzene-d_6) δ 207.8 (C), 142.6 (C), 139.7 (C), 139.4 (C), 138.6 (C), 129.7 (CH), 128.9 (CH), 74.8 (CH_2), 73.5 (CH_2), 68.0 (CH_2), 62.7 (CH), 60.5 (CH_2), 54.4 (CH_2), 47.3 (CH_2), 46.7 (CH_2), 44.1 (C), 44.0 (CH_2), 40.6 (CH_2), 39.4 (CH_2), 37.4 (CH), 37.4 (CH), 31.9 (CH_2), 30.2 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 27.9 (CH_2), 27.8 (CH_2), 27.1 (CH_2), 25.4 (CH_2), 22.3 (CH_2), 21.1 (CH_3); Some peaks for methine carbons in the aromatic rings overlapped with the peaks of benzene-d_6; HRMS (ESI) 699.4190 (calcd for $C_{43}H_{59}N_2O_4S_1$ [M+H] 699.4196). The starting material **20** was partially recovered (8.4 mg, 14.8 μmol, 35%) as a yellow oil. [KU04365]



Selected NOESY correlations (red arrows) and coupling constants (blue arrows) of **21**

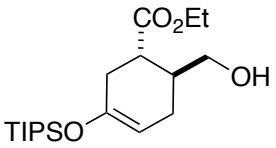


20 **22**

To a stirred solution of **20** (46.0 mg, 81.3 μmol) in $MeNO_2$ (2 mL) was added DBU (60.0 μL, 401 μmol) at room temperature under argon. The resulting mixture was stirred at 50 °C for 24 h, before the reaction was quenched with saturated aqueous NH_4Cl (2 mL) at 0 °C. The resulting mixture was extracted with EtOAc (2 mL×3). The combined organic extracts were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by MPLC on silica gel (*n*-hexane/Et_2O) to afford **22** (32.9 mg, 52.5 μmol, 65%) as a yellow oil. The starting material **20** was partially recovered (14.1 mg, 24.9 μmol, 31%) as a yellow oil. $[\alpha]_D^{23}$ = –1.24 (*c* 1.07, $CHCl_3$); IR (film) 2926, 2855, 1670, 1548, 1457, 1338, 1159, 738, 654, 549; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.37-7.28 (m, 7H), 4.52 (s, 2H), 4.29 (s, 2H), 3.39 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.32 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.28-3.19 (m, 2H), 2.91 (ddd, *J* = 12.2, 12.2, 4.4 Hz, 1H), 2.84-2.72 (m, 2H), 2.73 (d, *J* = 12.0 Hz, 1H) 2.42 (s, 3H), 2.34 (d, *J* = 11.6 Hz, 1H), 2.13 (d, *J* = 12.0 Hz, 1H), 1.93-1.55 (m, 6H), 1.43-1.19 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 209.0 (C), 143.0 (C), 138.1 (C), 136.0 (C), 129.6 (CH), 128.4 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 84.3 (CH_2), 74.6 (CH_2), 73.1 (CH_2), 53.4 (CH_2), 49.6 (CH_2), 47.9 (CH_2), 42.5 (CH_2), 39.5 (CH), 38.3 (C), 35.9 (CH_2), 35.8 (CH_2), 33.7 (CH_2), 33.5 (CH), 28.9 (CH_2), 27.5 (CH_2), 27.3 (CH_2), 27.1 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 25.3 (CH_2), 21.5 (CH_3), 20.6 (CH_2); HRMS (ESI) 649.3256 (calcd for $C_{35}H_{50}N_2NaO_6S$ 649.3287). [KU04299]

Reference

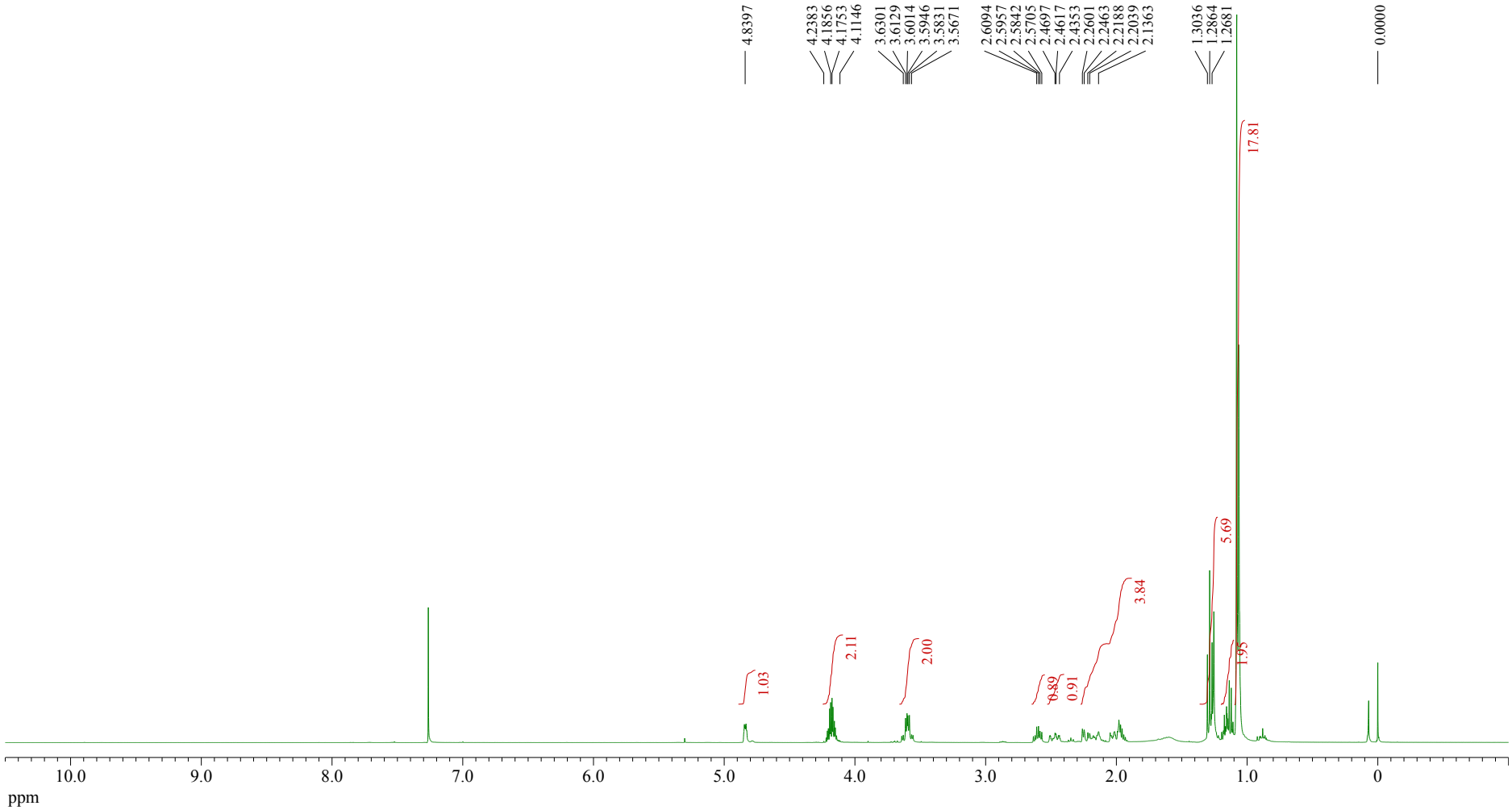
(1) L. You, X.-T. Liang, L.-M. Xu, Y.-F. Wang, J.-J. Zhang, Q. Su, Y.-H. Li, B. Zhang, S.-L. Yang, J.-H. Chen, and Z. Yang, *J. Am. Chem. Soc.,* 2015, **137**, 10120.

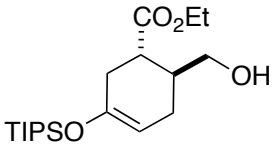


9

^{1}H-NMR

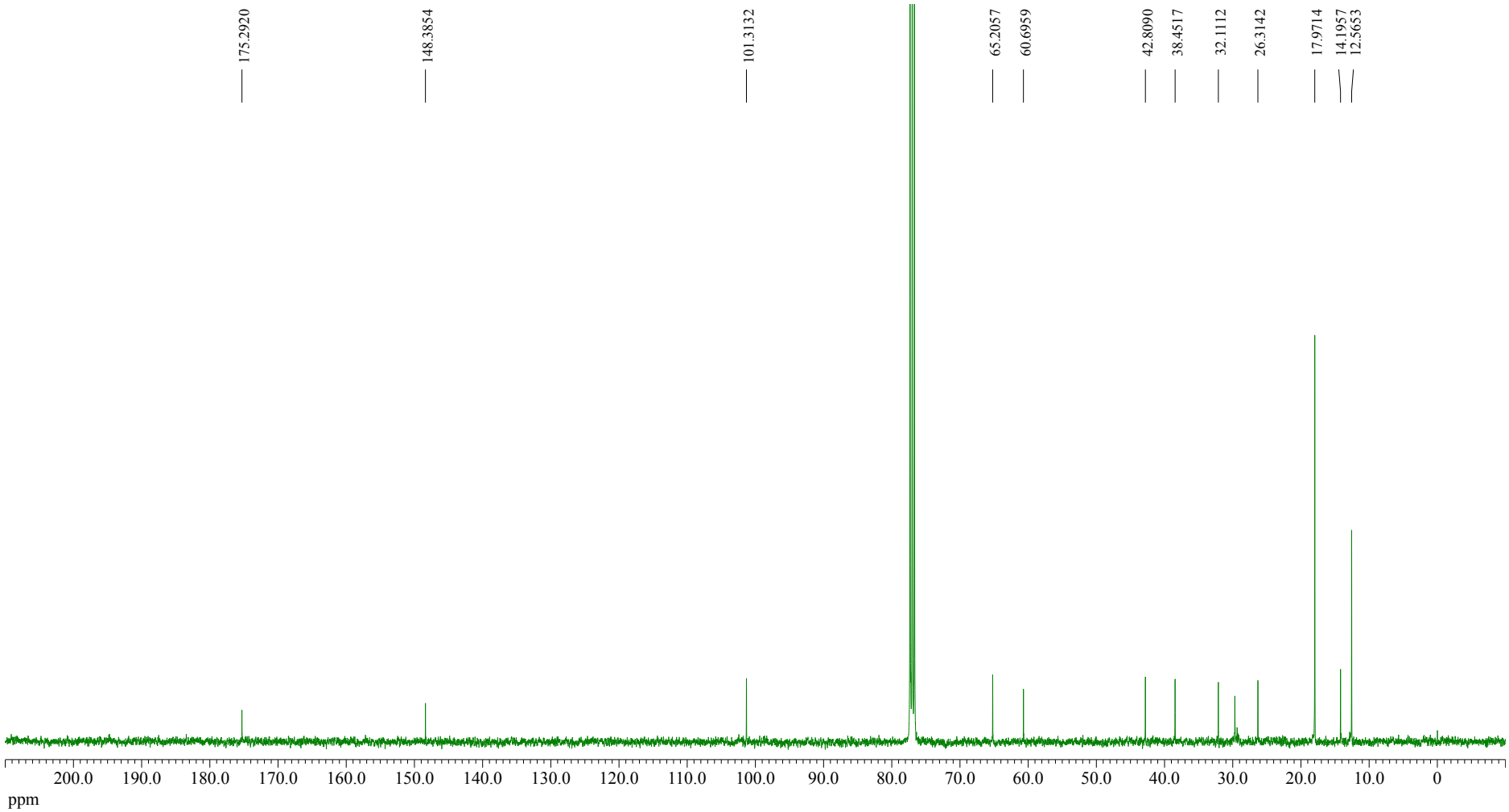
(400 MHz, $CDCl_3$)

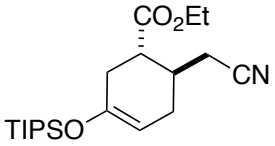




9

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

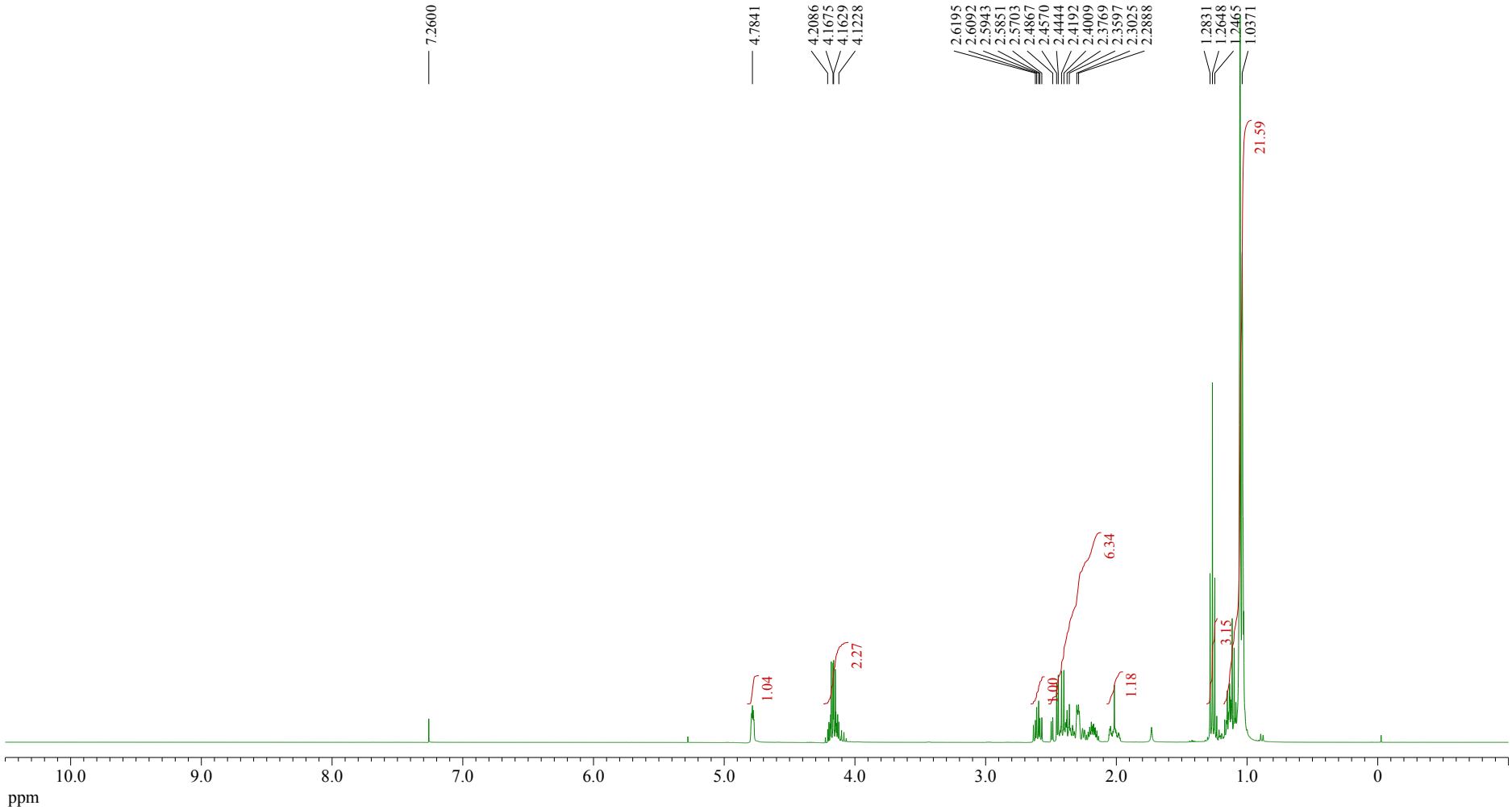


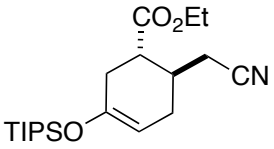


10

^{1}H-NMR

(400 MHz, $CDCl_3$)

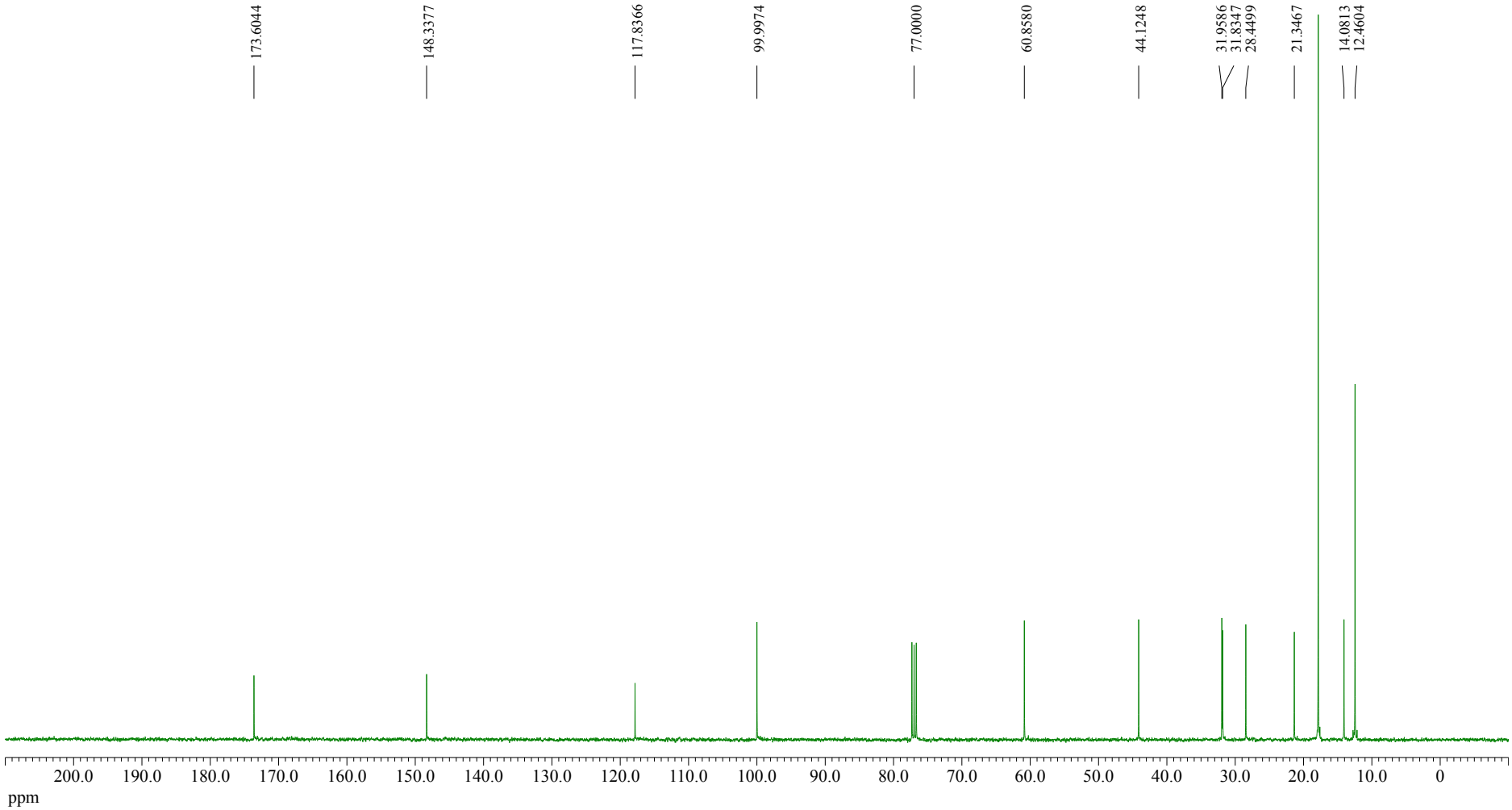


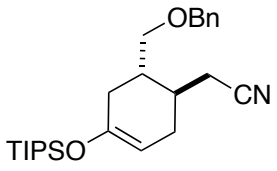


10

^{13}C-NMR

(100 MHz, $CDCl_3$)

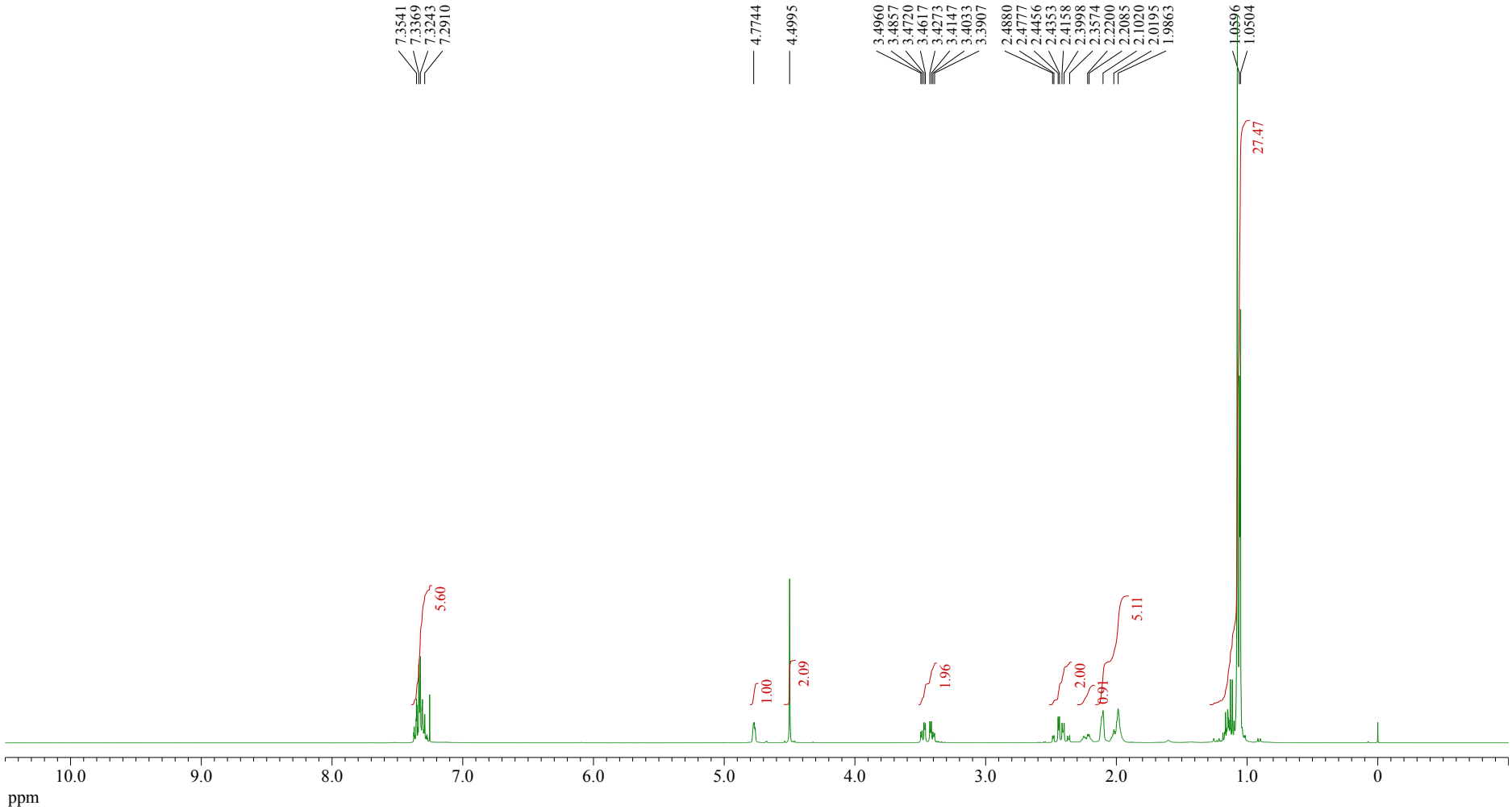


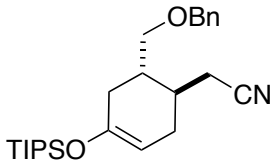


11

^{1}H-NMR

(400 MHz, $CDCl_3$)

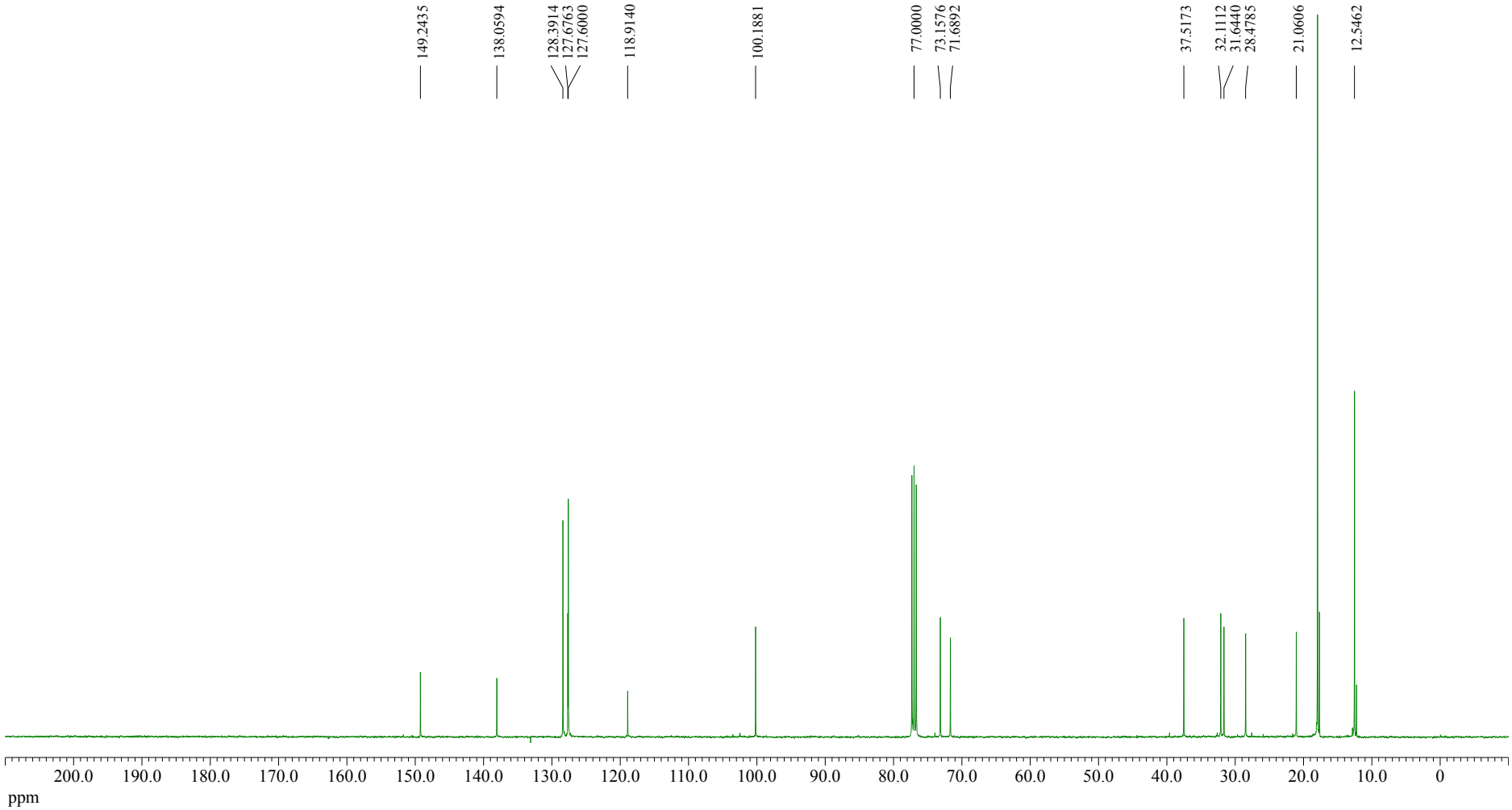


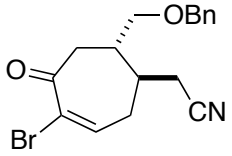


11

^{13}C-NMR

(100 MHz, $CDCl_3$)

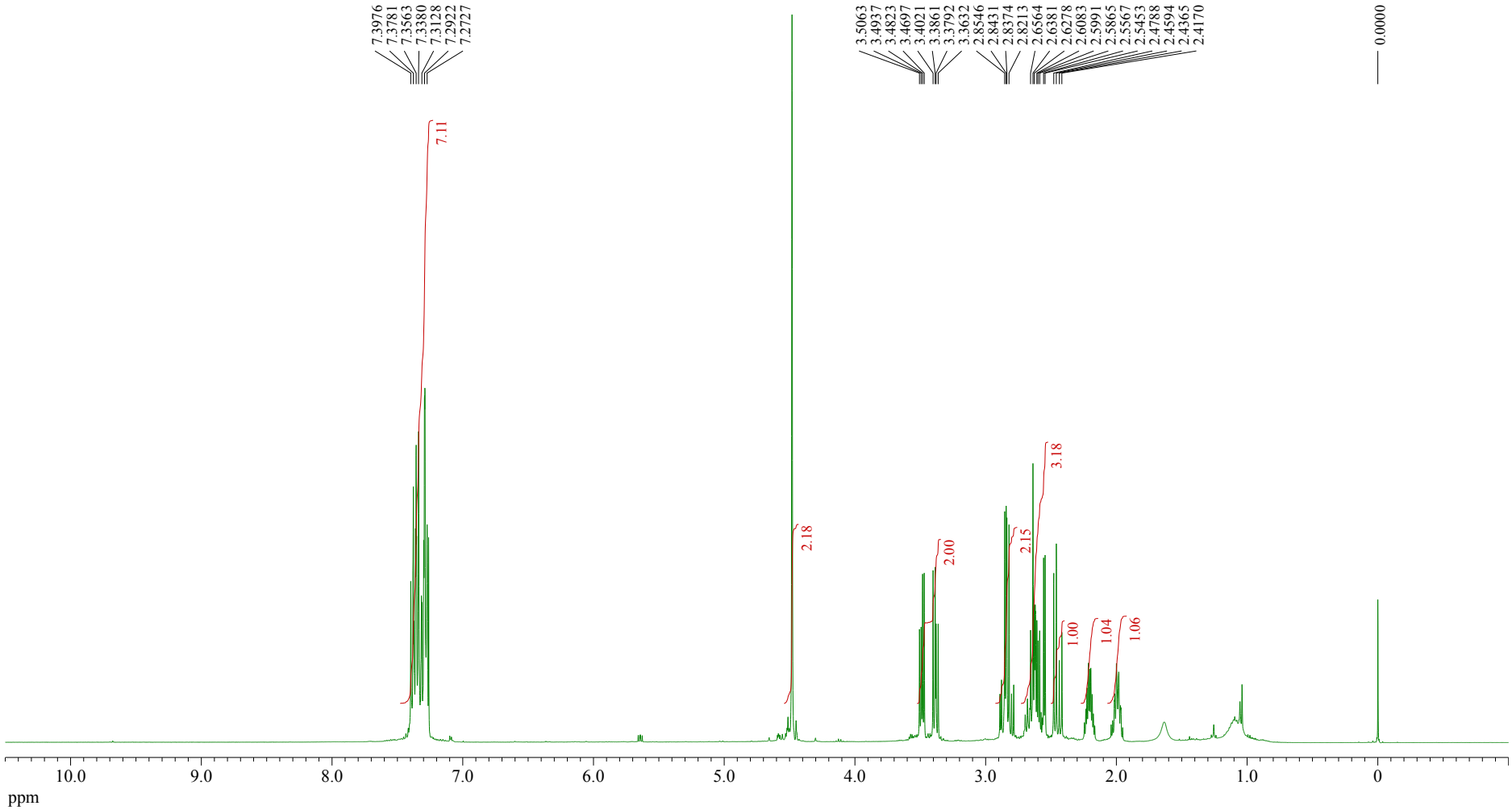


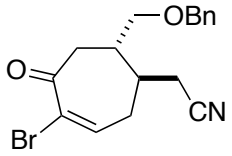


13

^{1}H-NMR

(400 MHz, $CDCl_3$)

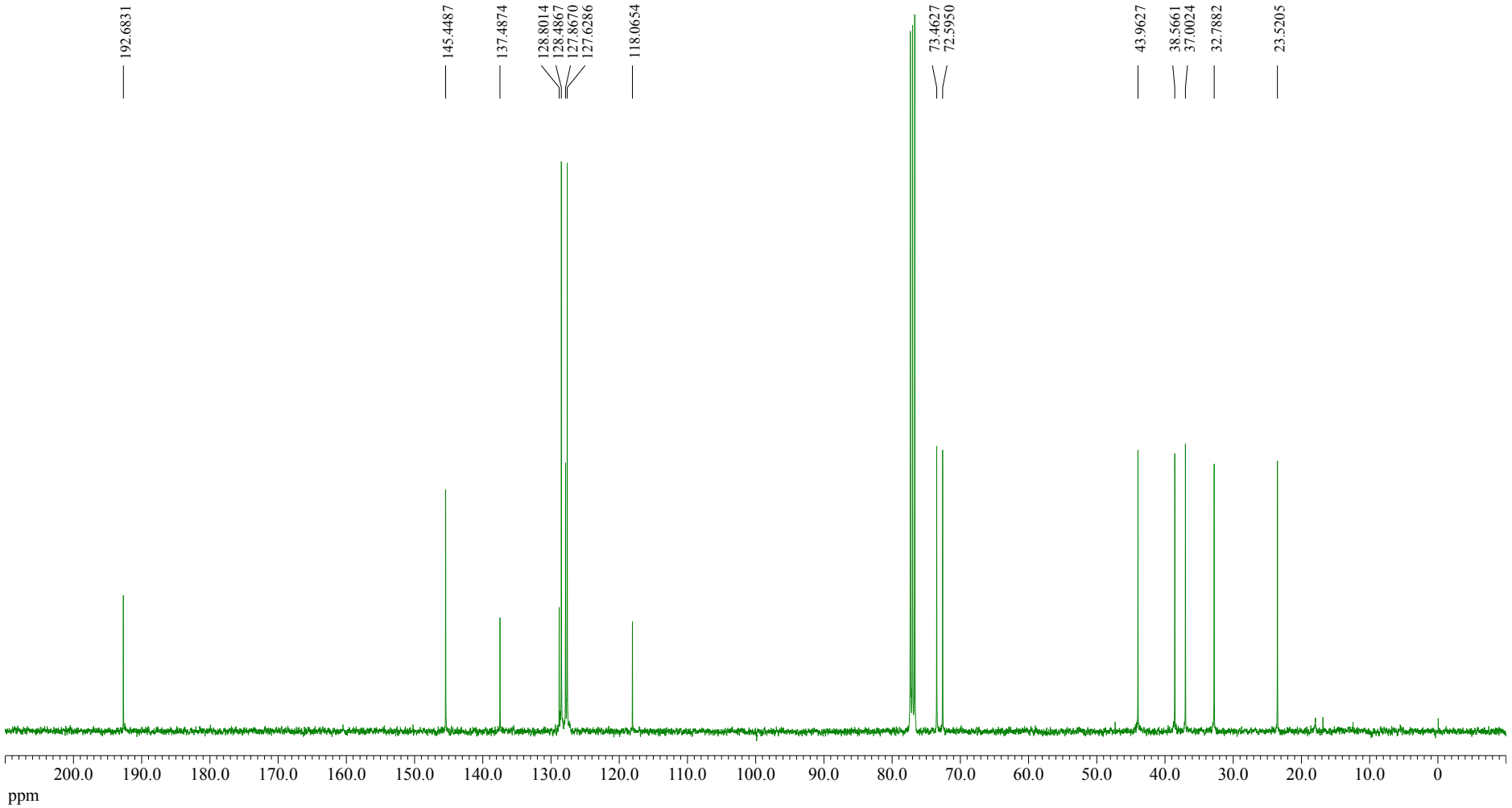


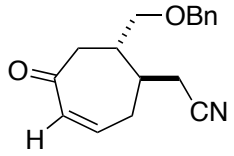


13

^{13}C-NMR

(100 MHz, $CDCl_3$)

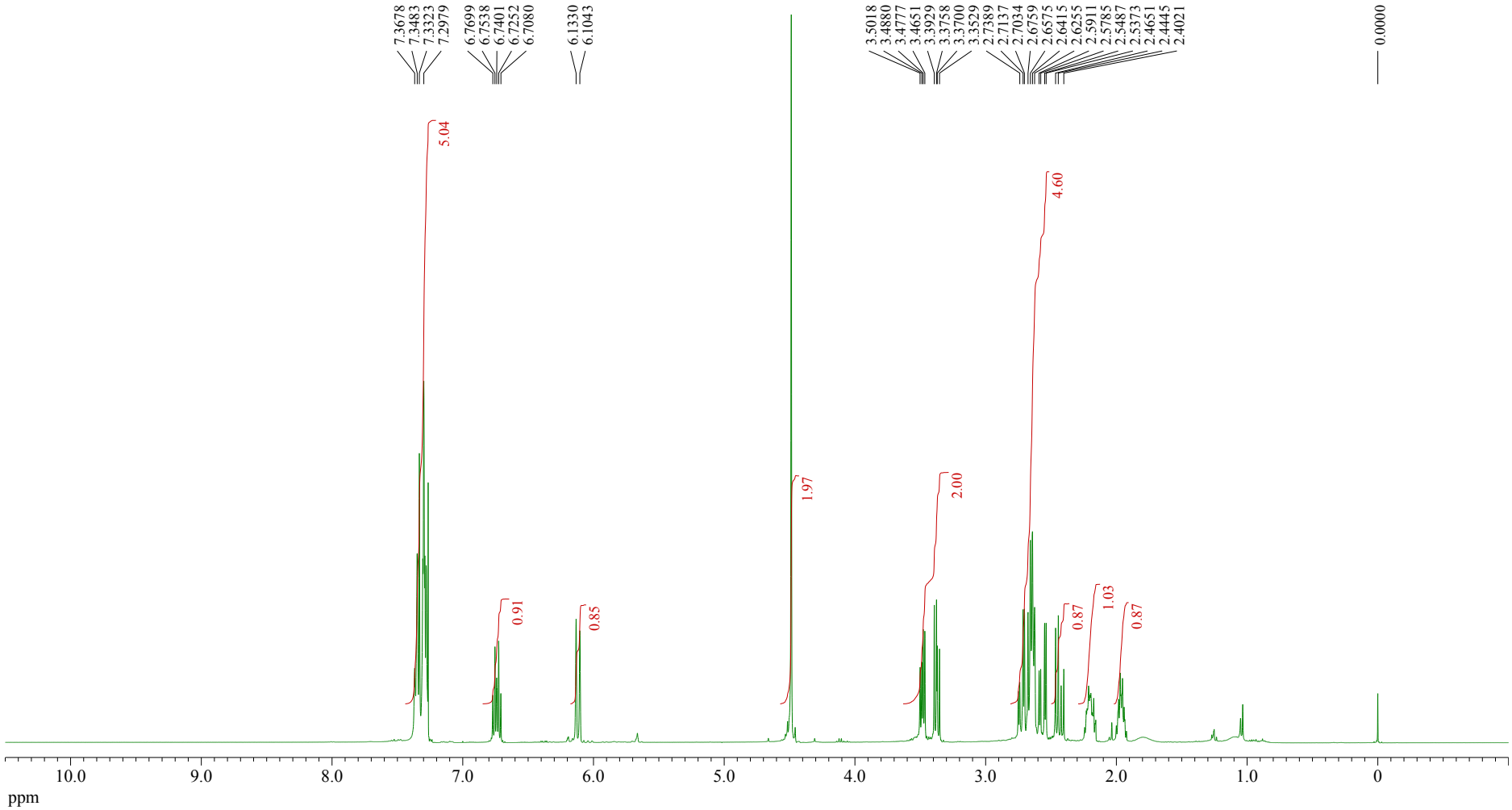


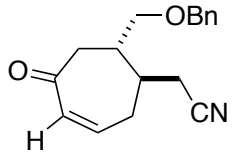


14

^{1}H-NMR

(400 MHz, $CDCl_3$)

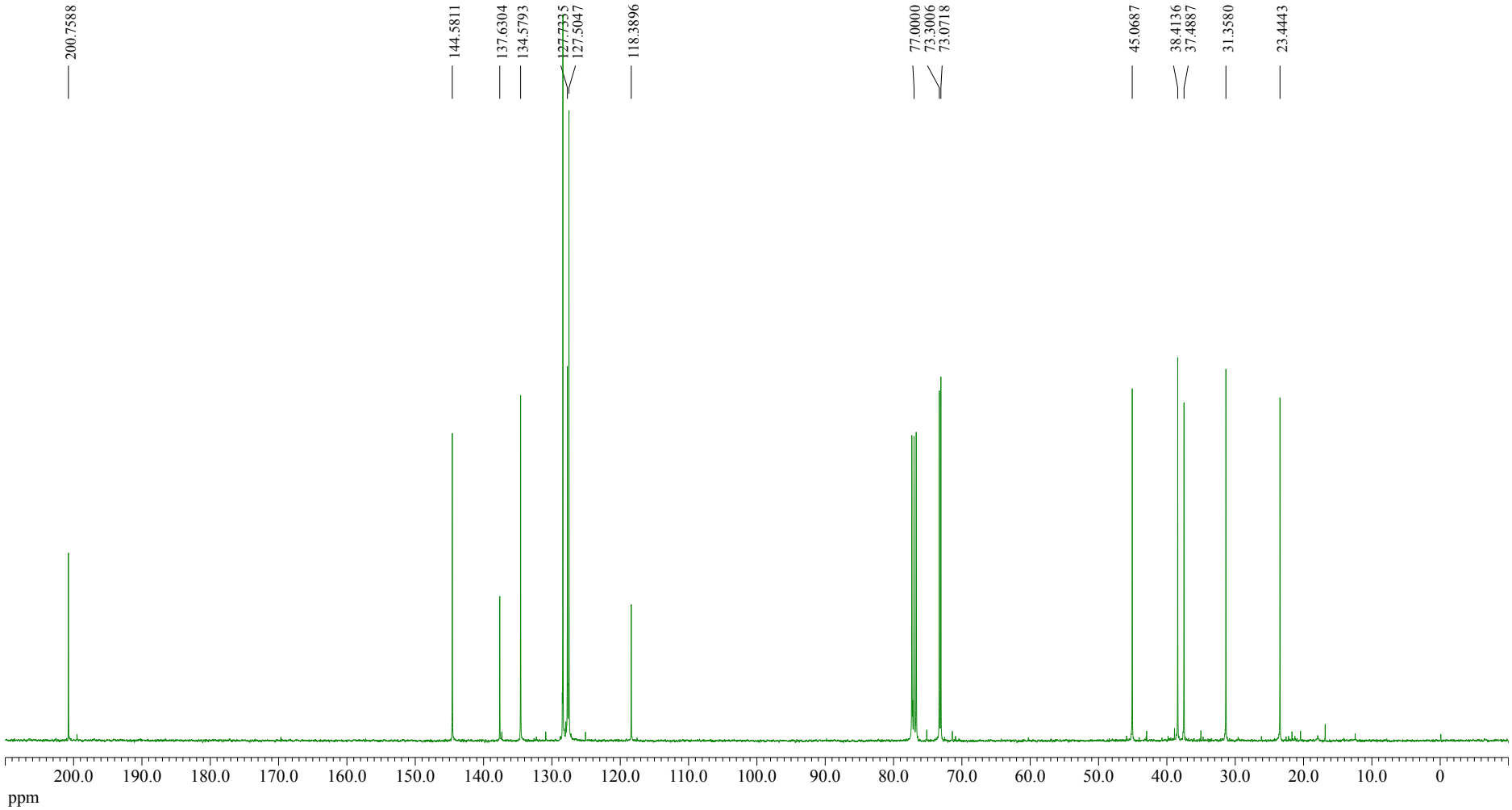


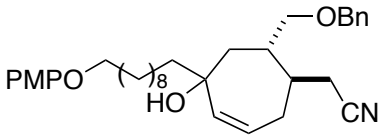


14

^{13}C-NMR

(100 MHz, $CDCl_3$)

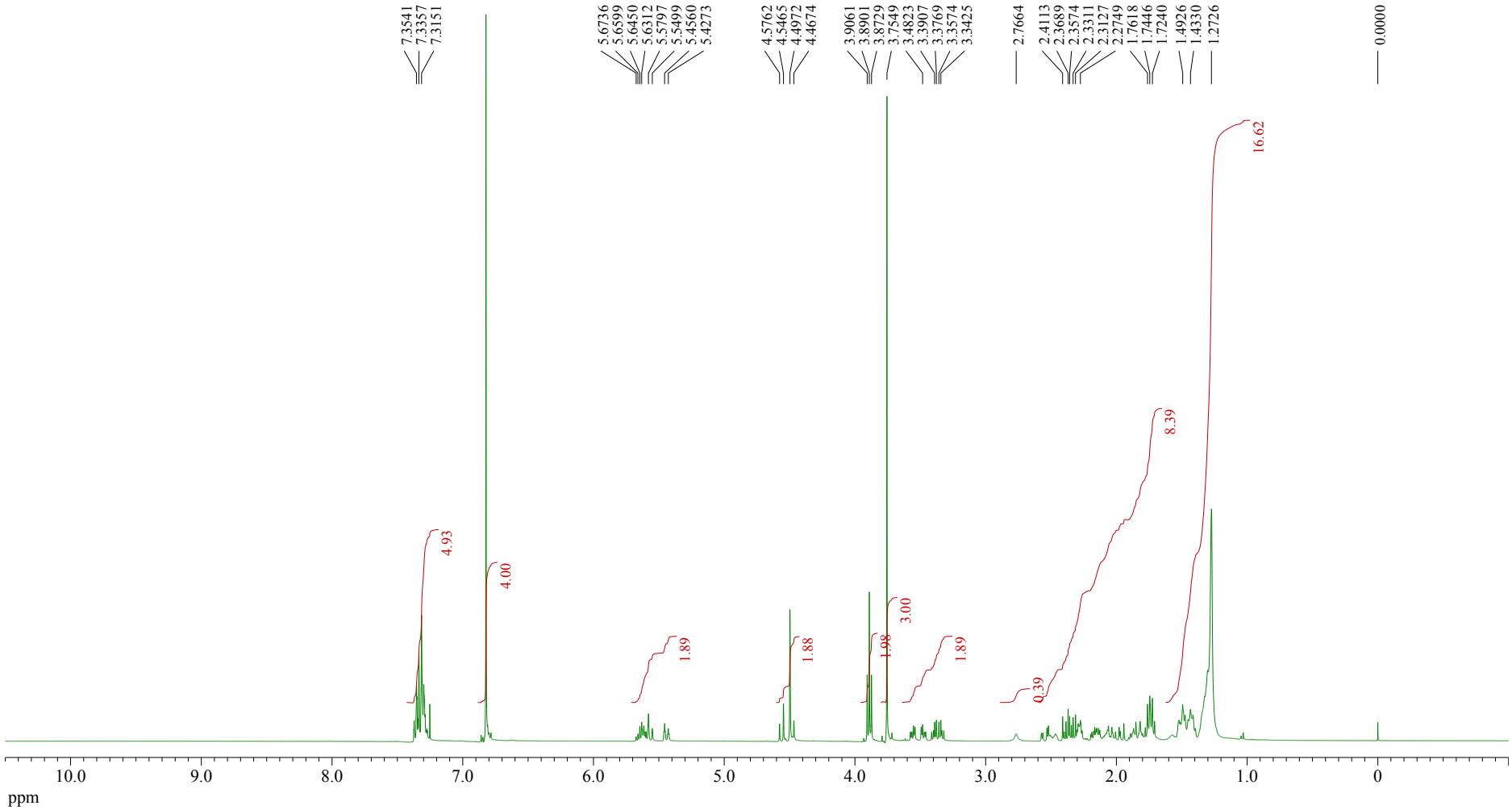


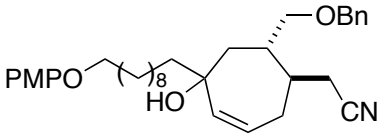


15

^{1}H-NMR

(400 MHz, $CDCl_3$)

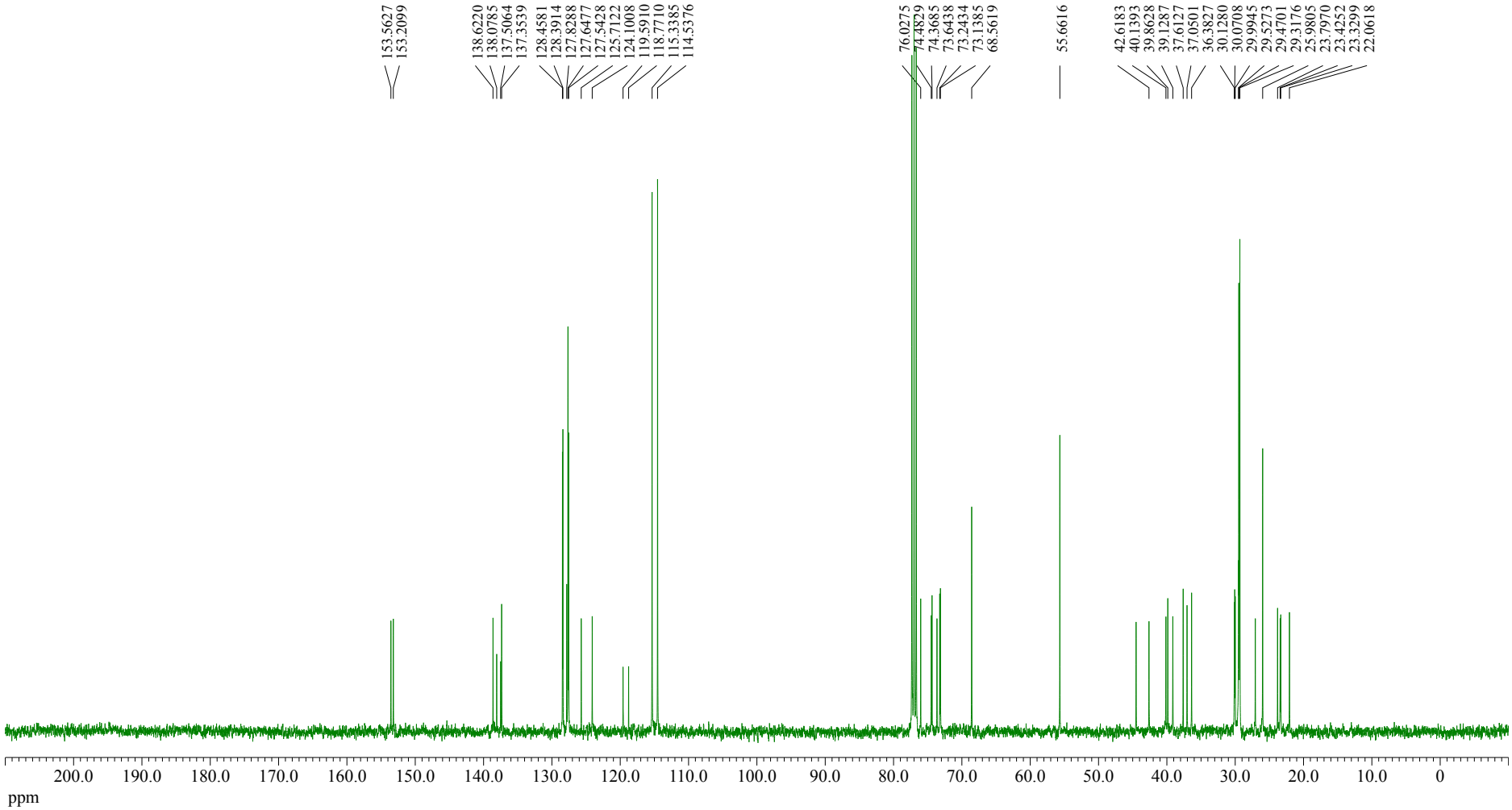


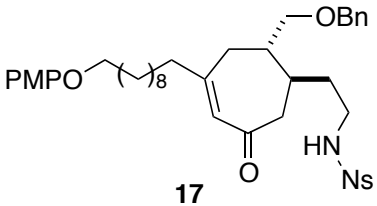


15

^{13}C-NMR

(100 MHz, $CDCl_3$)

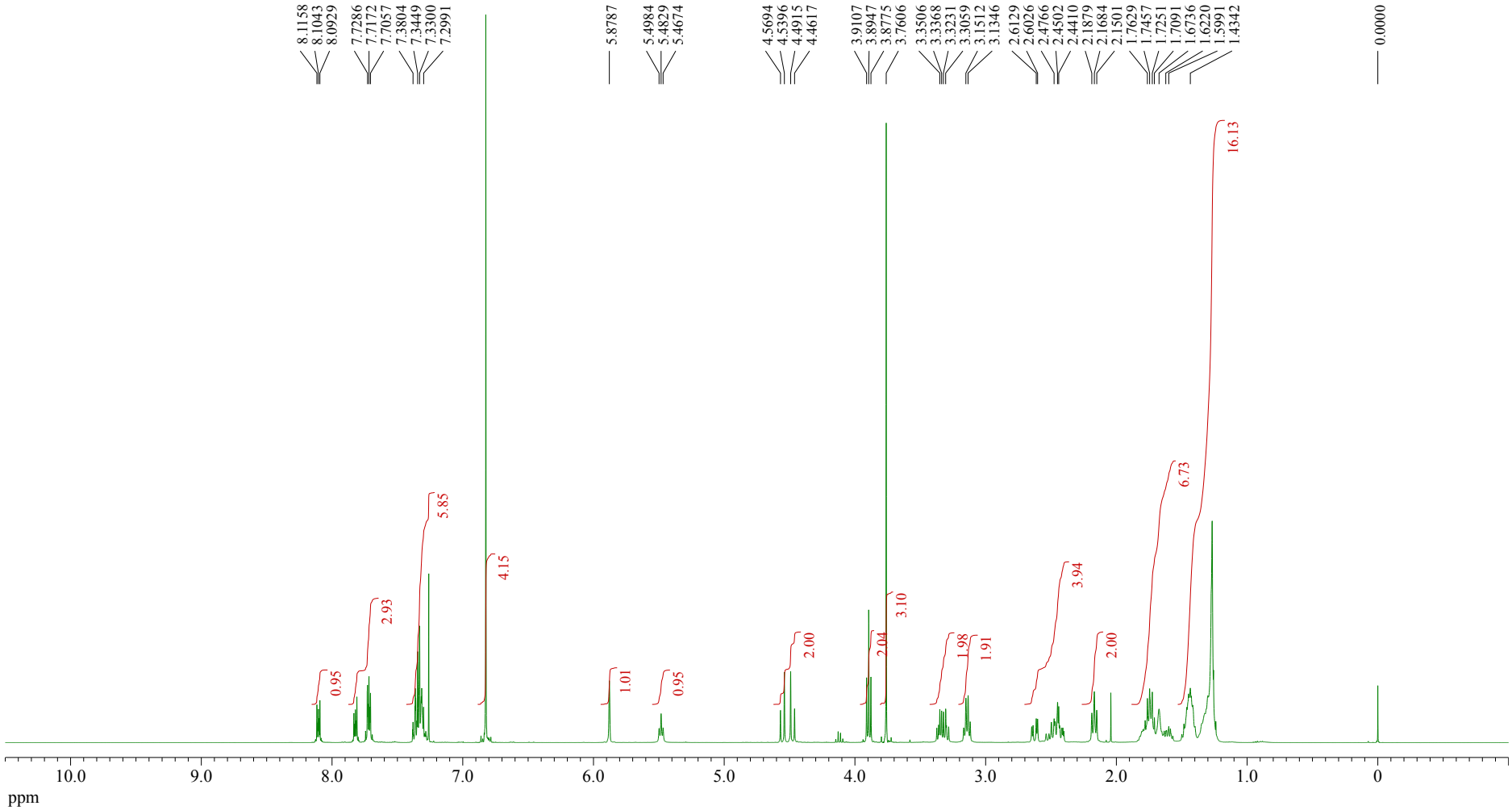


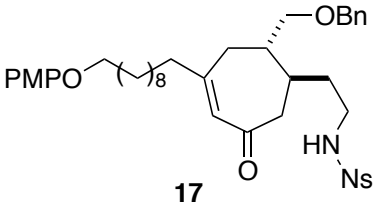


17

^{1}H-NMR

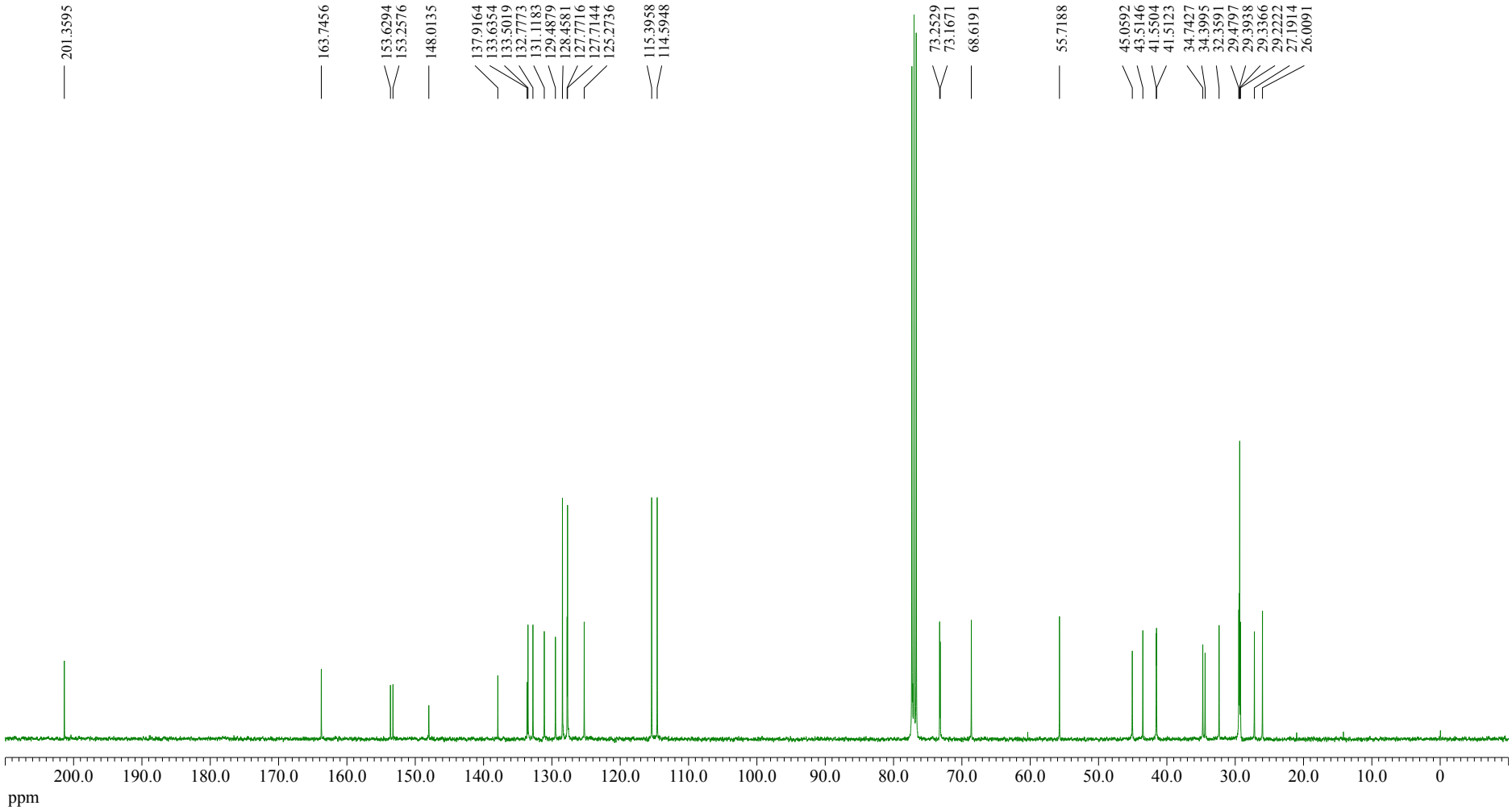
(400 MHz, $CDCl_3$)

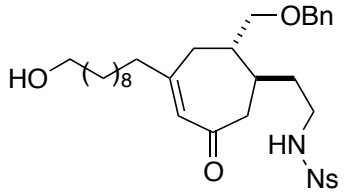




17

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

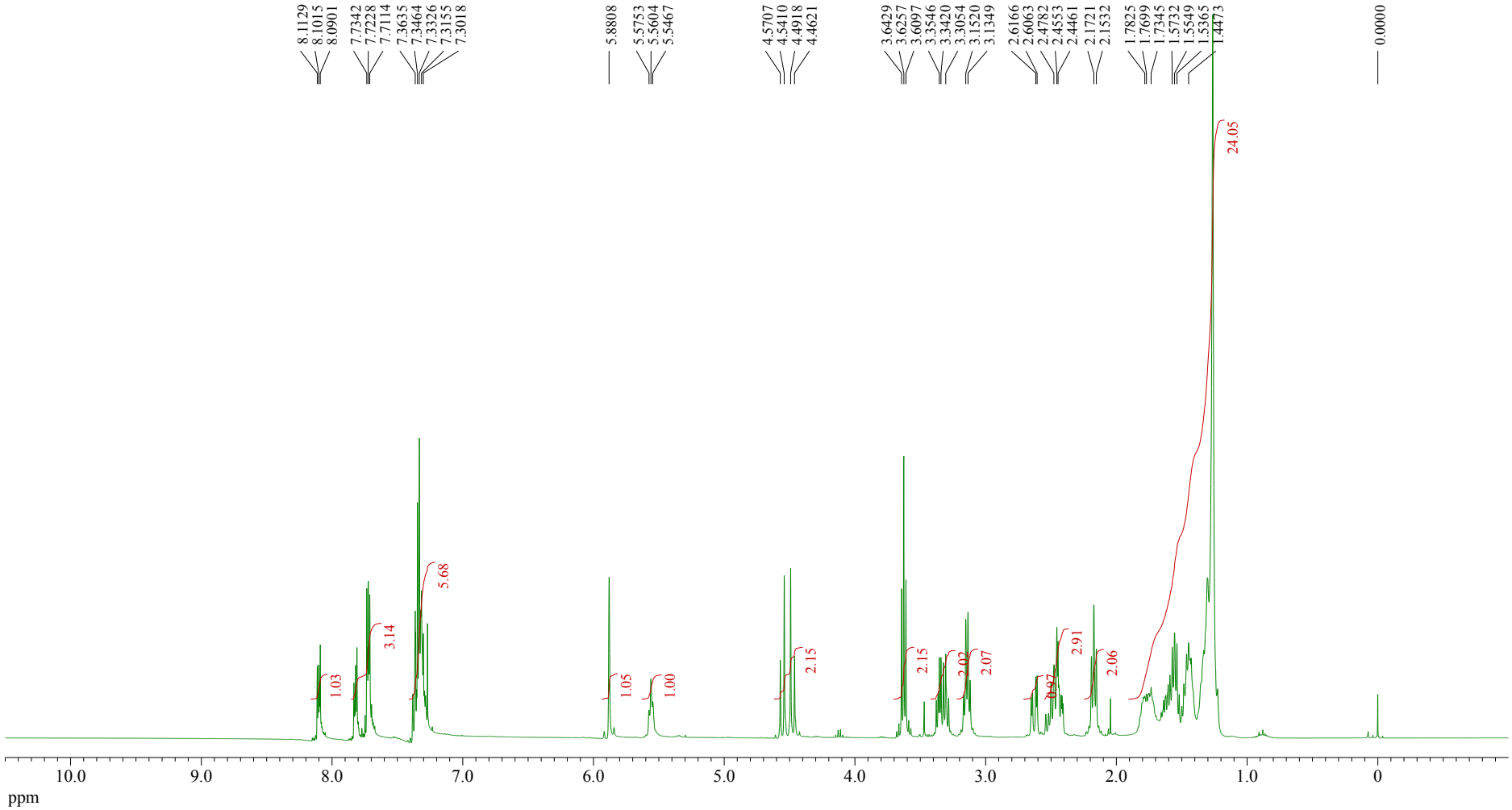


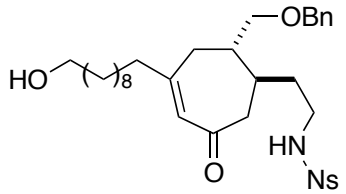


18

^{1}H-NMR

(400 MHz, $CDCl_3$)

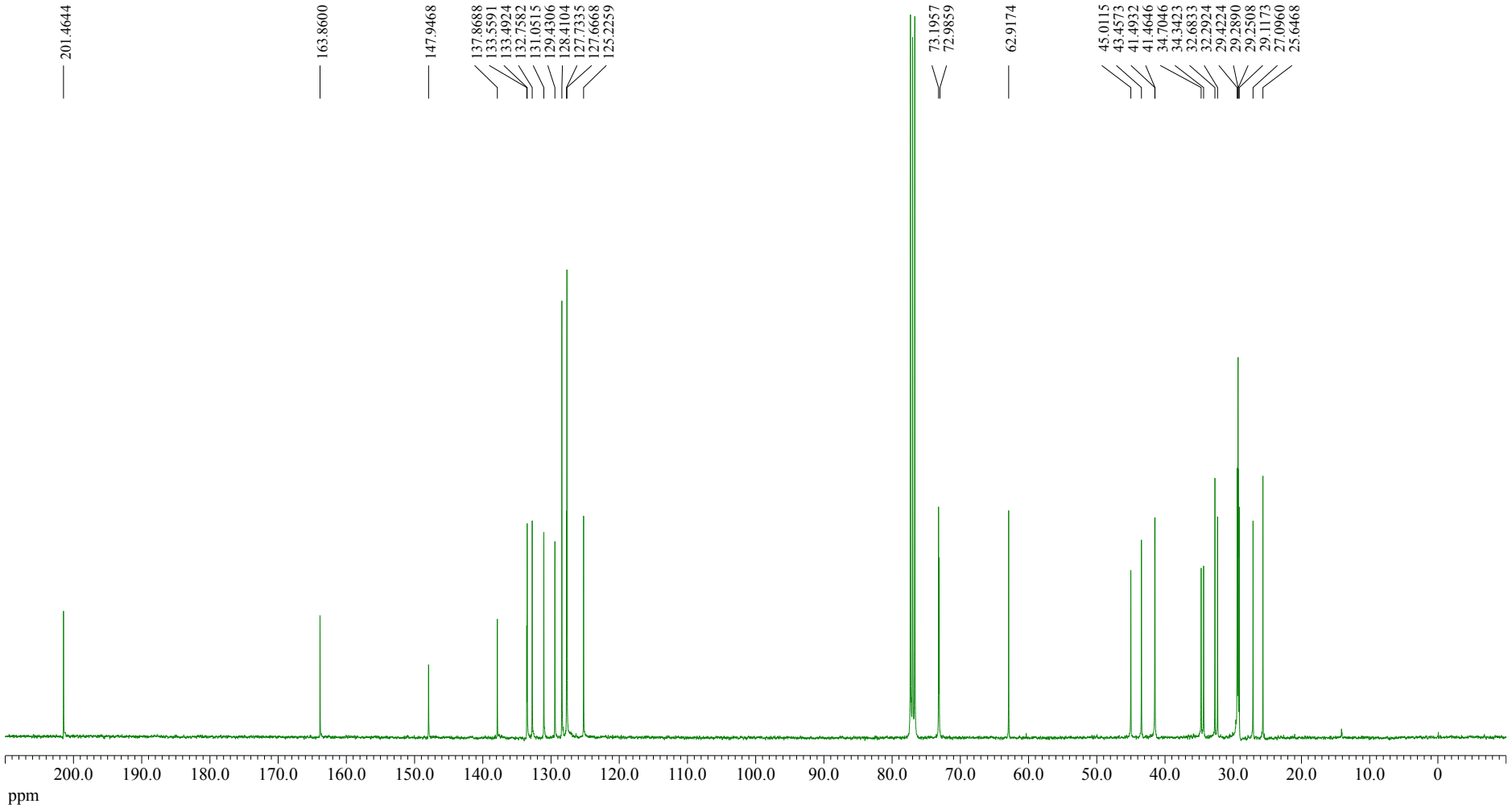


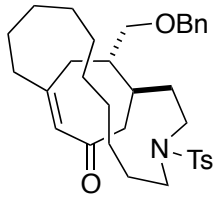


18

^{13}C-NMR

(100 MHz, $CDCl_3$)

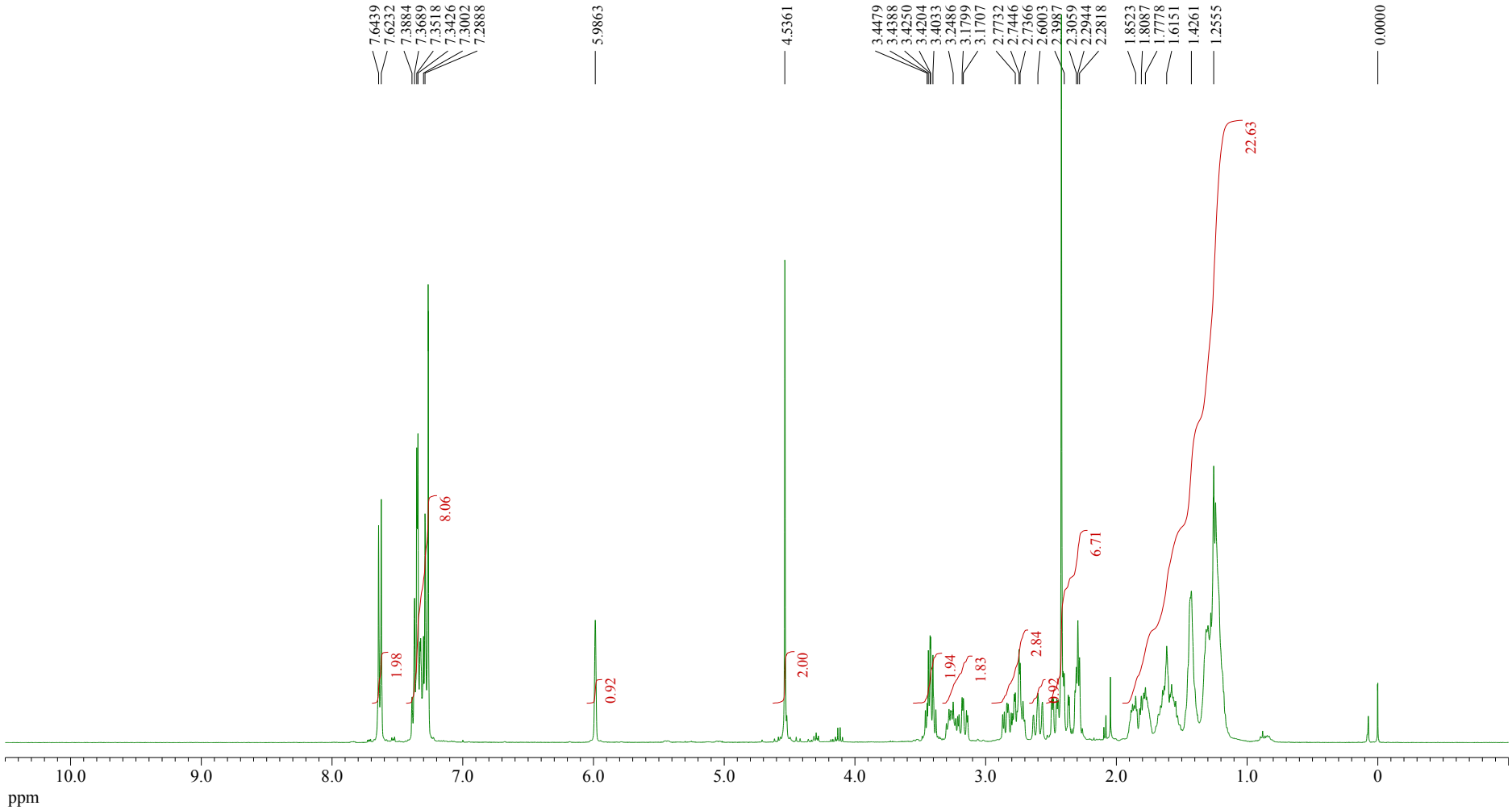


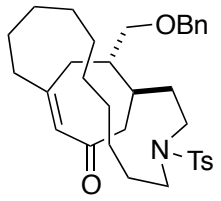


20

^{1}H-NMR

(400 MHz, $CDCl_3$)

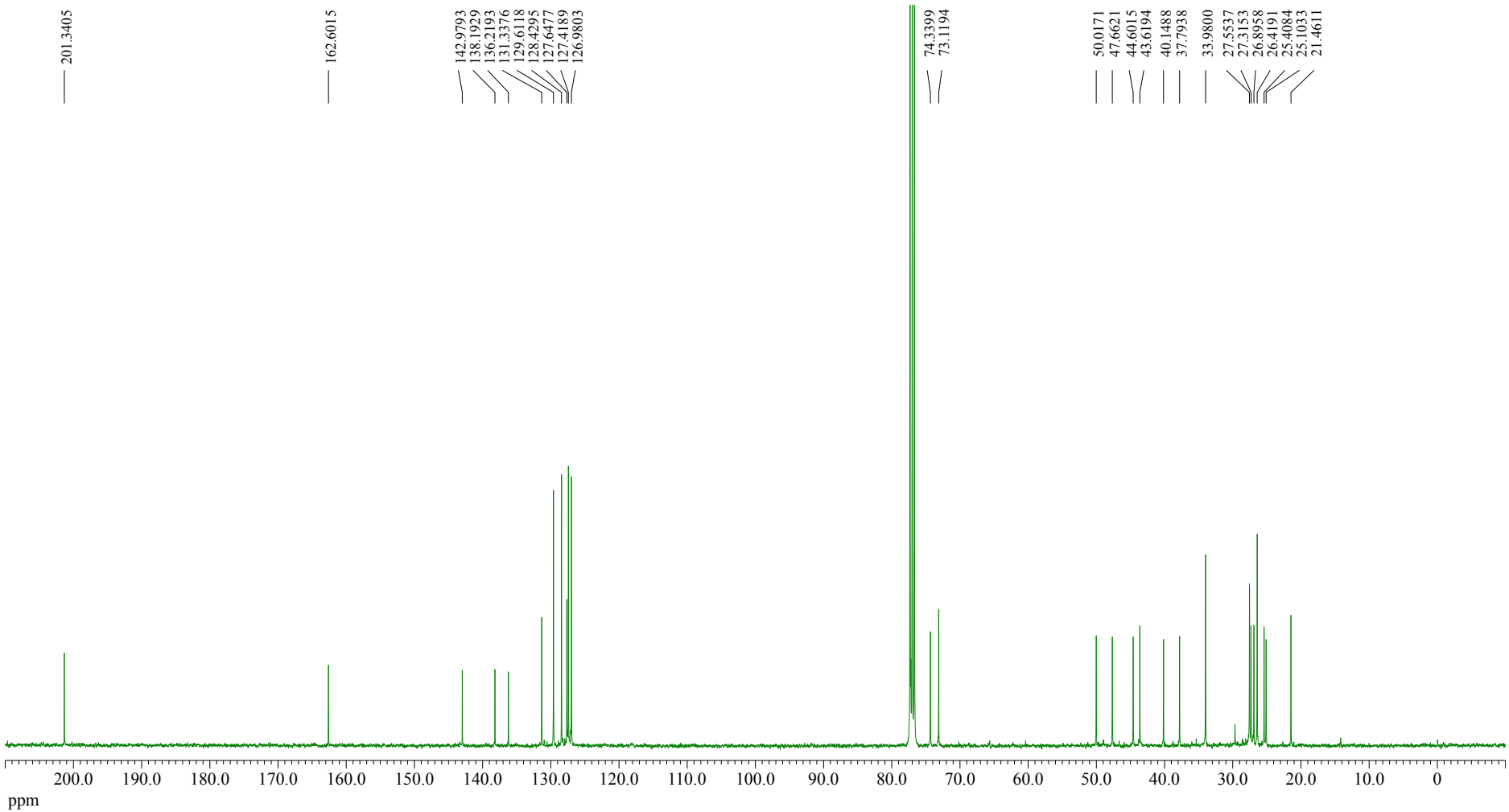


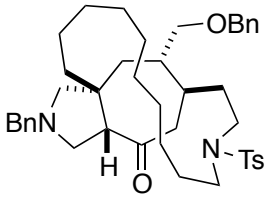


20

^{13}C-NMR

(100 MHz, $CDCl_3$)

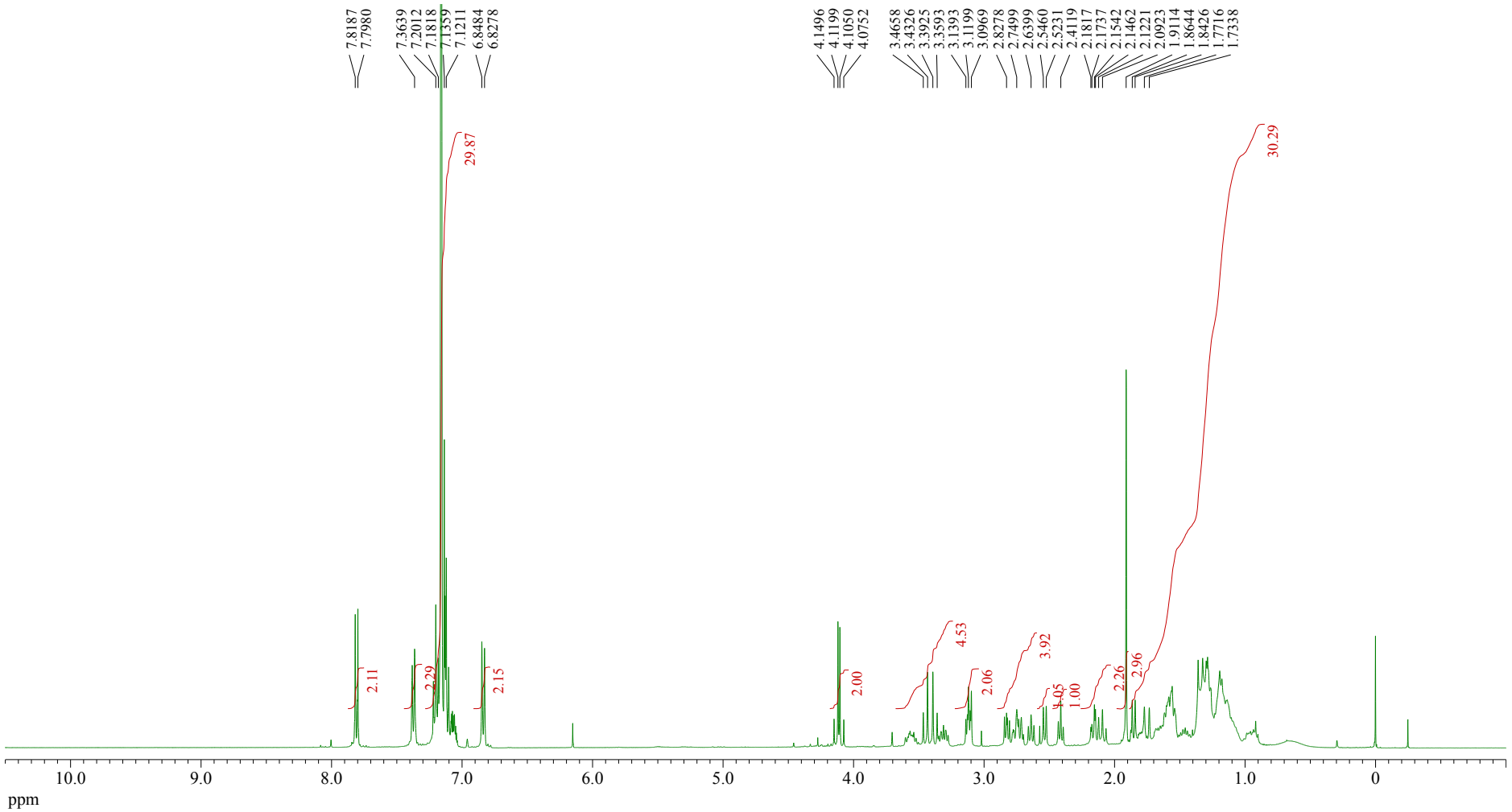


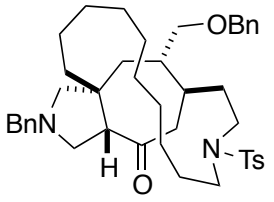


21

^{1}H-NMR

(400 MHz, benzene-d_6)

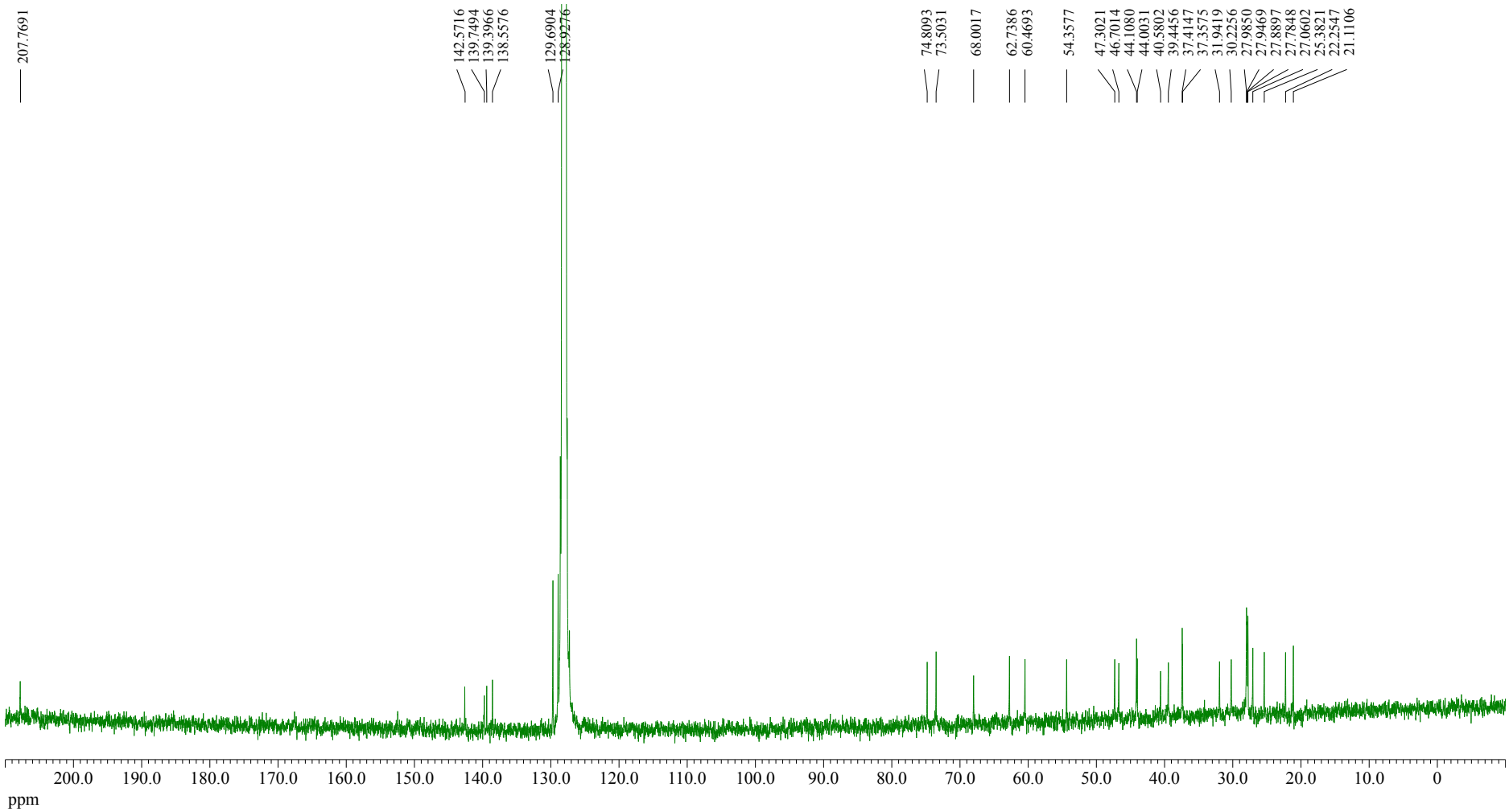


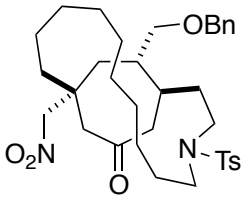


21

^{13}C-NMR

(100 MHz, benzene-d_6)

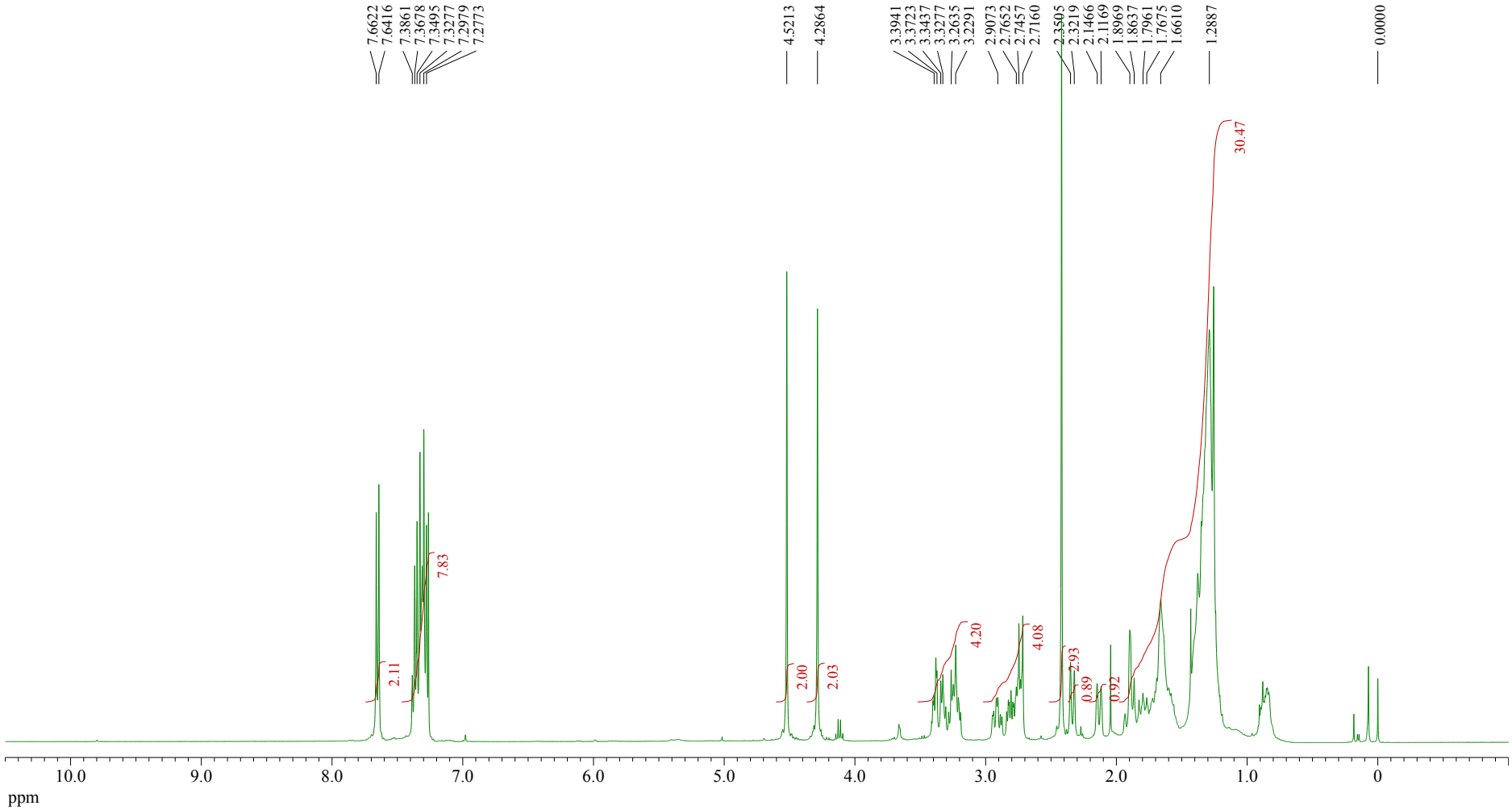


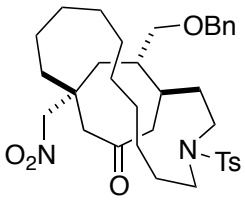


22

^{1}H-NMR

(400 MHz, $CDCl_3$)





22

^{13}C-NMR

(100 MHz, $CDCl_3$)