Supplementary Information

Asymmetric synthesis of two hydroxylated pyrrolizidines from a *C*-allyl epoxypyrrolidine

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EXPERIMENTAL PROCEDURES

General : All non-aqueous reactions were conducted under an atmosphere of nitrogen with magnetic stirring using freshly distilled solvents, unless otherwise indicated. THF, DCM and Et_2O were dried by distillation before use. Analytical thin layer chromatography (TLC) was performed on Silica gel 60 F254 plates produced by Merck. Visualization was accomplished with UV light and phosphomolybdic acid or potassium permanganate followed by heating. Optical rotations were measured on a JASCO P-2000 digital polarimeter at the sodium lamp (λ = 589 nm) D line. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 1725X spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 300 spectrometer respectively at 300 MHz and at 75 MHz in deuterated solvents. Mass spectra (MS) were obtained with thermoQuest TSQ 7000 spectrometer. High-resolution mass spectra (HRMS) recorded with a thermofinnigan MAT 95 XL spectrometer.

(2*S*,3*R*)-1-Benzyl-2-(prop-2-en-1-yl)pyrrolidin-3-ol (8).

A solution of epoxypyrrolidine **4** (354 mg, 1.65 mmol) in dry Et_2O (6 mL) was added slowly to a suspension of $LiAlH_4$ (119 mg, 2.98 mmol) in dry Et_2O (20 mL) at 0 °C under nitrogen. The suspension was stirred for two hours at room temperature and then treated at 0 °C with water (120 µL), 15% aqueous NaOH (120 µL), and water (360 µL). The residue was filtered through celite® and the filtrate

was concentrated *in vacuo*. Purification by flash column chromatography (eluent: 95:5:0.15 DCM/MeOH/Et_3N) provided **8** as a pale yellow oil (320.3 mg, 89%).

$[\alpha]_D^{25}$ + 60.3 (*c* 1.0; $CHCl_3$); ^1H NMR ($CDCl_3$) δ_H 7.38-7.22 (m, 5H), 6.05-5.88 (m, 1H), 5.18 (dq, *J* = 17.0, 1.4 Hz, 1H), 5.13 (ddt, *J* = 10.0, 2.1, 1.0 Hz, 1H), 4.10 (ddd, *J* = 7.1, 3.9, 2.6 Hz, 1H), 4.03 (1H, d, *J* = 13.0 Hz), 3.39 (d, *J* = 12.8 Hz, 1H), 2.85 (ddd, *J* = 9.2, 7.8, 2.0 Hz, 1H), 2.54-2.42 (m, 3H), 2.31-1.96 (m, 3H), 1.63 (ddt, *J* = 13.4, 7.3, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ_C 138.8 (Cq), 135.1 (CH), 128.5 (CH), 128.3 (CH), 128.4(CH), 116.6 (CH_2), 75.5 (CH), 71.4 (CH), 58.1 (CH_2), 51.0 (CH_2), 35.8 (CH_2), 32.3 (CH_2); MS (CI NH_3) m/z 218.1 (100); HRMS (CI CH_4) calcd. for $C_{37}H_{46}NO_3Si$: 218.1531, found 218.1541.

(2*S*,3*R*)-1-Benzyl-3-*tert*-butyldiphenylsilyloxy-2-(prop-2-en-1-yl)pyrrolidine (9).

The pyrrolidinol **8** (280.3 mg, 1.3 mmol) and imidazole (353 mg, 4.0 eq) were dissolved in anhydrous DMF (2 mL) and cooled to 0 °C. *Tert*-butyldiphenylchlorosilane (402 µL, 1.0 eq) was slowly added and the resulting solution was stirred for 24 hours at room temperature. Then water (10 mL) was added and extractions were done with Et_2O. The organic layer was washed with water, aqueous saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The crude compound was purified by flash chromatography (eluent: from 1:1:98 to 3.5:3.5:93 EtOAc/THF/PE) to give compound **9** as a pale yellow oil (500 mg, 85%).

$[\alpha]_D^{25}$ + 26.1 (*c* 2.0; $CHCl_3$); ^1H NMR ($CDCl_3$) δ_H 7.89-7.69 (m, 5H), 7.61-7.29 (m, 10H), 5.76 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 4.99 (ddt, *J* = 10.4, 2.3, 1.0 Hz, 1H), 4.95 (ddt, *J* = 16.9, 2.1, 1.5 Hz, 1H), 4.20 (dt, *J* = 5.0, 3.1 Hz, 1H), 4.06 (d, *J* = 12.8 Hz, 1H), 3.43 (d, 1H, *J* = 12.8 Hz), 2.96-2.88 (m, 1H), 2.82-2.62 (m, 2H), 2.16 (t, *J* = 6.6 Hz, 2H), 1.83-1.72 (m, 2H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ_C 139.6 (Cq), 136.1 (CH), 136.0 (CH), 135.4 (CH), 135.0 (CH), 134.5 (Cq), 134.2 (Cq), 129.7 (CH), 129.2 (CH), 128.3 (CH), 127.8 (CH), 127.8 (3 CH), 127.7 (CH), 116.6 (CH_2), 77.0 (CH), 72.5 (CH), 59.5 (CH_2), 52.0 (CH_2), 36.7 (CH_2), 33.3 (CH_2), 26.7 (CH_3), 19.1 (Cq); MS (CI NH_3) m/z 456.2 (100); HRMS (CI CH_4) calcd. for $C_{30}H_{38}NOSi$: 456.2723, found 456.2739.

3-[(2*S*,3*R*)-1-Benzyl-3-(*tert*-butyldiphenylsilyloxy)pyrrolidin-2-yl]propan-1-ol) (10).

At 0 °C, 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 5 mL, 2.5 eq) was added to the alcene **9** (455,7 mg, 1 mmol) in anhydrous THF (5 mL). The reaction mixture was first stirred at 0 °C for 10 minutes and then at room temperature for 16 hours. EtOH (3.5 mL) was added slowly followed by a 3 M aqueous solution of NaOH (2.5 mL) and a 30% aqueous solution of H_2O_2 (2.5 mL). The solution was stirred for 16 hours at room temperature. Aqueous layer was extracted with ethyl acetate and organic layer was washed with water and brine, dried with Na_2SO_4. After solvent removal, the residue was purified by flash column chromatography (eluent: 5:95 MeOH/DCM) to give compound **10** as a pale yellow oil (423.4 mg, 90%).

$[\alpha]_D^{25}$ + 20.1 (*c* 2.2; $CHCl_3$); ^1H NMR ($CDCl_3$) δ_H 7.63-7.72 (m, 4H), 7.51-7.24 (m, 11H), 4.24-4.17 (m, 1H), 4.06 (d, *J* = 12.6 Hz, 1H), 3.49 (d, *J* = 12.8 Hz, 1H), 3.50-3.32 (m, 2H), 2.97-2.86 (m, 1H), 2.74-2.59 (m, 2H), 1.95-1.18 (m, 7H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$) δ_C

137.5 (Cq), 135.9 (CH), 135.8 (CH), 134.0 (CH), 133.9 (Cq), 129.8 (CH), 129.5 (CH), 128.4 (CH), 127.7 (CH), 127.5 (CH), 76.1 (CH), 72.9 (CH), 62.6 (CH_2), 59.8 (CH_2), 51.8 (CH_2), 36.4 (CH_2), 33.3 (CH_2), 28.5 (CH_2), 27.0 (CH_3), 19.1 (Cq); HRMS (CI CH_4) calcd. for $C_{30}H_{40}NO_2Si$: 474.2828, found 474.2838.

3-[(2*S*,3*R*)-3-(*tert*-Butyldiphenylsilyloxy)pyrrolidin-2-yl]propan-1-ol (11).

To a suspension of pyrrolidine **10** (211.7 mg, 0.45 mmol) and 10% Pd/C (214.0 mg) in dry MeOH (16 mL) was added anhydrous ammonium formate (283.5 mg, 10 eq) in a single portion. The reaction mixture was refluxed for 2 hours and then cooled to room temperature. To this solution was added anhydrous K_2CO_3 (230.3 mg, 3.6 eq). The reaction was stirred for 2 hours and then filtered over celite®. After solvent removal, the residue was purified by flash chromatography (eluent: 5:95 MeOH/DCM with 1% NH_3) to yield compound **11** as a pale yellow oil (118.9 mg, 70%).

$[\alpha]_D^{25}$ + 2.2 (*c* 1.0; $CHCl_3$)**;** ^{1}H NMR ($CDCl_3$) δ_H 7.72-7.63 (m. 4H), 7.51-7.37 (m, 6H), 4.06 (dt, *J* = 5.0, 2.5 Hz, 1H), 3.87-3.37 (sl, 2 H), 3.61 (ddd. *J* = 11.1, 5.5, 3.6 Hz, 1H), 3.43 (ddd, *J* = 11.3, 8.7, 3.0 Hz, 1H), 3.23 (dt, *J* = 11.4, 7.9 Hz, 1H), 3.00-2.86 (m, 2 H), 1.93-1.73 (m, 2 H), 1.69-1.27 (m, 3H), 1.10 (s, 9H)**;** ^{13}C NMR ($CDCl_3$) δ_C 135.8 (CH), 134.0 (Cq), 129.8 (CH), 129.7 (CH) 127.8 (CH), 127.7 (CH), 78.5 (CH). 67.3 (CH), 62.8 (CH_2), 43.6 (CH_2), 34.5 (CH_2), 31.0 (CH_2), 30.7 (CH_2), 27.0 (CH_3), 19.1 (Cq).

(1*R*,7a*S*)-1-(*tert*-Butyldiphenylsilyloxy)hexahydro-1*H*-pyrrolizine (12).

To a stirred solution of compound **11** (62.4 mg, 0.2 mmol) in anhydrous DMF (2 mL) were added PPh_3 (90 mg, 2.0 eq), CCl_4 (31 µL, 2.0 eq) and Et_3N (44 µL, 2.0 eq). The reaction was allowed to stir for 24 hours at room temperature and then MeOH (1.5 mL) was added. The reaction was stirred for an additional hour and then water (2 mL) was added. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated at reduced pressure. Flash column chromatography (eluent: 4:96 MeOH/DCM) provided compound **12** (30.0 mg, 50%).

$[\alpha]_D^{25}$ −11.7 (*c* 1.0; $CHCl_3$); ^1H NMR ($CDCl_3$) δ_H 7.72-7.64 (m, 4H), 7.51-7.34 (m, 6H), 3.95 (td. *J* = 4.9, 3.3 Hz, 1H), 3.40 (td, *J* = 7.4, 3.0 Hz, 1H), 3.24 (dt, *J* = 10.8, 6.0 Hz, 1H), 3.04-2.95 (m, 1H), 2.55 (dt, *J* = 10.9, 6.0 Hz, 1H), 2.43-2.32 (m, 1H), 1.84-1.54 (m, 5H), 1.07 (s, 10H); ^{13}C NMR ($CDCl_3$) δ_C 135.9 (Cq), 135.8 (CH), 134.3 (Cq), 134.2 (Cq), 129.6 (CH), 127.58 (CH), 79.3 (CH), 72.7 (CH), 55.2 (CH_2), 52.6 (CH_2), 34.0 (CH_2), 30.2 (CH_2), 26.9 (CH_3), 26.1 (CH_2), 19.1 (Cq); HRMS (CI CH_4) calcd for $C_{23}H_{32}NOSi$: 366.2253, found 366.2251.

(1*R*,7a*S*)-1-Hydroxypyrrolizidine (13).

A solution of compound **12** (174 mg, 0.47 mmol) and TBAF (75 µL) in THF (5 mL) were stirred for 6 h. After removal of the solvent, the crude product was purified by flash chromatography (eluent: from 0:100 to 10:90 MeOH/DCM with 1% NH_3) to give compound **13** (47 mg, 80%).

$[\alpha]_D^{25}$ – 28.1 (*c* 0.5; $CHCl_3$); [Lit.[1a] $[\alpha]_D^{24}$ – 26.0 (*c* 2.3; $CHCl_3$); lit.[1b] $[\alpha]_D^{20}$ – 31.6 (*c* 0.5; $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ_H 3.97 (td, *J* = 5.2, 3.5 Hz, 1H), 3.37-3.28 (m, 1H), 3.22 (dt, *J* = 10.8, 6.7 Hz, 1H), 3.00 (ddd, *J* = 10.6, 6.6, 5.6 Hz, 1H), 2,58 (dt, *J* = 10.9, 6.6 Hz, 1H), 2.50 (ddd, *J* = 10.6, 7.7, 6.8 Hz, 1H), 2.09-1.93 (m, 2H), 1.83-1.67 (m, 3H), 1.48-1.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ_C 77.2 (CH), 72.5 (CH), 55.3 (CH_2), 52.6 (CH_4), 34.0 (CH_2), 30.4 (CH_2), 25.7 (CH_2); MS (CI NH_3) 128.1 (100).

3-[(1*S*,2*S*,5*R*)-3-Benzyl-6-oxa-3-azabicyclo[3.1.0]hex-2-yl]propan-1-ol (14).

At 0 °C, 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 183 mL, 3.2 eq) was added to the alkene **4** (616.5 mg, 2.85 mmol) in dried THF (6 mL). The reaction mixture was first stirred at 0 °C for 10 minutes and then at room temperature for 1 hour. EtOH (10 mL) was added slowly followed by an aqueous solution of 3 M NaOH (7.5 mL) and a 30% aqueous solution of H_2O_2 (7.5 mL). The solution was stirred for 16 hours at room temperature. Aqueous layer was extracted with ethyl acetate and organic layer was washed with water and brine, dried with Na_2SO_4. After solvent removal, the residue was purified by flash column chromatography (eluent: from 0:100 to 4:96 and 5:95 MeOH/DCM) to give compound **14** as a pale yellow oil (590.0 mg, 88%).

$[\alpha]_D^{25}$ + 10.3 (*c* 1.6; $CHCl_3$); IR (neat) ν 3367, 3026, 2924, 1223 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 7.31-7.13 (m, 5H), 3.81 (d, *J* = 13.0 Hz, 1H), 3.76 (d, *J* = 13.0 Hz, 1H), 3.60 (d, *J* = 2.8 Hz, 1H), 3.57-3.39 (m, 2H), 3.44 (d, *J* = 2.8 Hz, 1H), 3.05 (dd, *J* = 9.1 Hz, 3.6 Hz, 1H), 2.97 (dd, *J* = 13.7, 0.7 Hz, 1H), 2.87 (d, *J* = 13.7 Hz, 1H), 1.66-1.42 (m, 3H), 1.40-1.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ_C 138.8 (Cq), 129.4 (CH), 128.4 (CH),

[1] a) Shono, T.; Kise, N.; Tanabe, T. *J. Org. Chem.* **1988,** 53, 1364-1367; b) Murray, A.; Proctor, G. R.; Murray, P. J. *Tetrahedron* **1996,** 52, 3757-3766.

127.3 (CH), 64.7 (CH), 63.5 (CH_2), 62.6 (CH_2), 61.1 (CH), 57.7 (CH), 52.1 (CH_2), 29.1 (CH_2), 28.5 (CH_2); HRMS (CI CH_4) calcd for $C_{14}H_{20}NO_2$ 234.1494, found 234.1503.

3-[(1*S*,2*S*,5*R*)-6-Oxa-3-azabicyclo[3.1.0]hex-2-yl]propan-1-ol (15).

To compound **14** (89.9 mg, 0.38 mmol) in MeOH (5 mL) was added $Pd(OH)_2$ (17.2 mg) and 48% aqueous HF (50 µL). The suspension was stirred for 12 hours under 12 psi H_2 and then filtered over celite® and washed with MeOH. Removal of the solvent led to the desired compound **15** (47 mg, 85%).

^{1}H NMR (MeOD) δ_H 3.65-3.61 (bt, 2H), 3.51 (dd, *J* = 2. 8, 0.8 Hz, 1H), 3.46 (td, *J* = 6.1, 4.2 Hz, 2H), 3.40 (d, *J* = 2.7 Hz, 1H), 3.06 (dd, J = 5.6, 8.3 Hz, 1 H), 2.94 (d, *J* = 13.3 Hz, 1H), 2.61 (d, *J* = 13.3 Hz, 1H), 1.83-1.69 (m, 1H), 1.58-1.33 (m, 3H); HRMS (CI CH_4) calcd for $C_7H_{14}NO_2$ 144.1025, found 144.1036.

(1*S*,2*S*,5*R*)-3-Benzyl-2-(3-*tert*-butyldiphenylsilyloxypropyl)-6-oxa-3-azabicyclo[3.1.0]hexane (17).

The pyrrolidinol **14** (1.15 g, 4.9 mmol) and imidazole (1.33 g, 4.0 eq) were dissolved in anhydrous DMF (10 mL) and cooled to 0 °C. *Tert*-butyldiphenylchlorosilane (1.3 mL, 1.0 eq) was slowly added and the resulting solution was stirred for 24 hours at room temperature. Then water (5 mL) was added and extractions were done with Et_2O. The organic layer was washed with water, saturated

$NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The crude compound was purified by flash chromatography (eluent: 2:8:90 to 8:32:60 EtOAc/DCM/PE) to give **17** as a pale yellow oil (2.20 g, 95%).

$[\alpha]_D^{25}$ + 5.8 (*c* 0,8; $CHCl_3$); ^1H NMR ($CDCl_3$) δ_H 7.80-7.74 (m, 4H), 7.55-7.24 (m, 11H), 3.96-3.80 (m, 2H), 3.73 (td, *J* = 6.2 Hz, 2.0 Hz, 2H); 3.68 (d, *J* = 2.8 Hz, 1H), 3.55 (d, *J* = 2.8 Hz, 1H), 3.18-3.12 (m, 1H), 3.10 (d, *J* = 10.2 Hz, 1H), 3.14 (dd, *J* = 7.6, 5.7 Hz, 1H), 3.10 (d, *J* = 13.4 Hz, 1H), 2.94 (d, *J* = 13.5 Hz, 1H), 1.90-1.54 (m, 2H), 1.66-1.35 (m, 2H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$) δ_C 138.5 (Cq), 135.7 (CH), 134.1 (Cq), 129.7 (CH), 128.6 (CH), 128.3 (CH), 127.7 (CH), 126.8 (CH), 64.7 (CH), 63.8 (CH_2), 63.2 (CH_2), 61.4 (CH), 57.9 (CH), 53.5 (CH_2), 29.4 (CH_2), 28.1 (CH_2), 27.2 (CH_3), 19.3 (Cq); MS (CI NH_3) m/z 472.2 (100); HRMS (CI CH_4) calcd for $C_{30}H_{38}NO_2Si$: 472.2672, found 472.2691.

(2*S*,3*S*,4*S*)-1-Benzyl-4-(benzyloxy)-2-[3-(*tert*-butyldiphenylsilyloxy)propyl]pyrrolidin-3-ol (18).

To a solution of epoxypyrrolidine **17** (123.1 mg, 0.26 mmol) and benzylic alcohol (31 µL, 1.1 eq) in dried dioxane (1 mL) was added ytterbium trifluoromethanesulfonate (159 mg, 1 eq) under inert atmosphere. The suspension was warmed to 80-90 °C for 16 hours. An aqueous saturated solution of NH_4Cl (5 mL) was added and the mixture was stirred for 30 minutes. The aqueous layer was extracted with Et_2O and then the organic layers were washed with water and brine. After removal of the solvent, the residue was purified by flash chromatography (eluent: from 60:32:8 to 40:48:12 PE/DCM/EtOAc) to give the compound **18** (91.1 mg, 62%).

$[\alpha]_D^{25}$ + 32.8 (*c* 1.7; $CHCl_3$); ^1H NMR ($CDCl_3$) δ_H 7.76-7.69 (m, 4H), 7.49-7.26 (m, 16H), 4.61-4.49 (m, 2H), 4.05 (dd, *J* = 6.0, 3.0 Hz, 1H), 4.03 (d, *J* = 13.2 Hz, 1H), 3.83 (dt, *J* = 6.9 Hz, 2.5 Hz, 1H), 3.76 (td, *J* = 5.8, 2.1 Hz, 2H), 3.26 (d, *J* = 13.2 Hz, 1H), 2.98 (dd, *J* = 10.7, 2.1 Hz, 1H), 2.57 (dd, *J* = 10.7, 6.8 Hz, 1H), 2.49-2.38 (m, 1H), 2.17-1.98 (sl, 1 H, OH), 1.97-1.67 (m, 4H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$) δ_C 138.4 (Cq), 138.3 (Cq), 135.6 (CH), 133.9 (Cq), 129.6 (CH), 128.9 (CH), 128.4 (CH), 128,3 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.0 (CH), 83.9 (CH), 81.3 (CH), 71.2 (CH_2), 69,5 (CH), 64.3 (CH_2), 57.5 (CH_2), 56.8 (CH_2), 27.9 (CH_2), 26.9 (CH_3), 26.3 (CH_2), 19.2 (Cq); MS (CI NH_3) 580.3 (100); HRMS (CI CH_4) calcd for $C_{37}H_{46}NO_3Si$: 580.3247, found 580.3273.

(2*S*,3*R*,4*S*)-4-(Benzyloxy)-2-(3-(*tert*-butyldiphenylsilyloxy)propyl)pyrrolidin-3-ol (19).

To a suspension of pyrrolidine **18** (162 mg, 0.28 mmol) and 10% Pd/C (162 mg) in dry MeOH (2 mL) was added anhydrous ammonium formate (176.9 mg, 10 eq) in a single portion. The reaction mixture was refluxed for 2 hours and then cooled to room temperature. To this solution was added anhydrous K_2CO_3 (139.1 mg, 4 eq). The reaction was stirred for 2 hours and then filtered over celite®. After solvent removal, the residue was purified by flash chromatography (eluent: 5:95 MeOH/DCM with 1% NH_3) to yield compound **19** as a pale yellow oil (98.3 mg, 72%).

$[\alpha]_D^{25}$ + 7.1 (*c* 1.3; $CHCl_3$); ^1H NMR ($CDCl_3$) δ_H 7.72-7.65 (m, 4 H), 7.48-7.27 (m, 11H), 4.56 (s, 2H), 3.92-3.83 (m, 2H), 3.72 (pseudo-t, *J* = 5.6 Hz, 2H), 3.17-3.09 (m, 1H), 3.08-3.01 (m, 1H), 2.88 (pseudo-q, *J* = 4.7 Hz, 1H), 2.70 (s, 2 H), 1.84-1.55 (m, 4H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$) δ_C 138.1 (Cq), 135.6 (CH), 133.9 (Cq), 133.8 (Cq), 129.6 (CH),128.5 (CH), 127.8 (CH), 127.7 (CH), 86.6 (CH), 81.9 (CH), 71.3

(CH_2), 66.1 (CH), 63.8 (CH_2), 50.4 (CH_2), 29.9 (CH_2), 26.9 (CH_3), 19.2 (Cq); MS (CI NH_3) 490.2 (100); HRMS (CI CH_4) calcd for $C_{30}H_{40}NO_3Si$: 490.2777, found 490.2767.

(2*S*,3*R*,4*S*)-4-(Benzyloxy)-2-(3-hydroxypropyl)pyrrolidin-3-ol (20).

A solution of compound **19** (98.3 mg, 0.20 mmol) in MeOH (3 mL) was added to a solution of NH_4F•HF (60 µL). The mixture was stirred for 12 hours and then silica (150 mg) was added. The suspension was filtered over celite® and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (eluent: from 5:95 to 20:80 MeOH/DCM with 1% NH_3) led to compound **20** (47.1 mg, 94%).

$[\alpha]_D^{25}$ + 8.0 (*c* 1.5; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ_H 7.41-7,27 (m, 5H); 4.61-4.50 (m, 2H) ; 4.12-4.05 (sl, 1H), 3.92-3.84 (m, 2 H), 3.71-3.52 (m, 2H), 3.16-3.08 (m, 1H), 3.05-2.96 (m, 1H) ; 2.93-2.85 (m, 1H) ; 1.89-1.50 (m, 4H); ^{13}C NMR ($CDCl_3$) δ_C 138.0 (Cq), 128.5 (CH), 127.8 (CH), 127.7 (CH), 86.6 (CH), 81.6 (CH), 71.4 (CH_2), 66.0 (CH), 62.3 (CH_2), 50.3 (CH_2), 30.8 (CH_2), 30.4 (CH_2); MS (CI NH_3) 252.1 (100); HRMS (CI CH_4) calcd for $C_{14}H_{22}NO_3$: 252.1600, found 252.1606.

(2*S*,3*R*,4*S*)-4-(Benzyloxy)-2-(3-hydroxypropyl)pyrrolidin-3-ol (22).

A solution of compound **18** (243.2 mg, 0.42 mmol) in MeOH (5 mL) was added to a solution of NH_4F•HF (0.2 mL). The mixture was stirred for 12 hours and then silica (620 mg) was added. The suspension was filtered over celite® and the filtrate was concentrated

under reduced pressure. Purification by flash column chromatography (eluent: from 5:95 to 20:80 MeOH/DCM with 1% NH_3) led to compound **22** (144.7 mg, 100%).

$[\alpha]_D^{25}$ + 9.2 (*c* 0.8; $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ_H 7.42-7.23 (m, 10H), 4,51 (s, 2 H), 4,15 (dd, *J* = 7.3, 3.5 Hz, 1H), 4.10 (d, *J* = 12.8 Hz, 1H), 3.85 (dt, *J* = 7.0, 3.0 Hz, 1H), 3.75-3.60 (m, 2 H), 3.59-3.38 (sl, 2H), 3.20 (d, *J* = 13.0 Hz, 1H), 2.95 (dd, *J* = 11.1, 2.3 Hz, 1H), 2.55 (dd, *J* = 11.1 Hz, 7.2 Hz, 1H), 2.51-2.43 (m, 1H), 2.01-1.88 (m, 1H), 1.88-1.67 (m, 3H); ^{13}C NMR ($CDCl_3$) δ_C 138.2 (Cq), 137.9 (CH), 129.0 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 83.3 (CH), 79.7 (CH), 71,3 (CH_2), 69.2 (CH), 62.9 (CH_2), 58.2 (CH_2), 56.7 (CH_2), 27.6 (CH_2), 26.8 (CH_2); MS (CI NH_3) 342.2 (100).

(1*S*,2*S*,7a*S*)-4-Benzyl-2-(benzyloxy)-1-hydroxyhexahydro-1*H*-pyrrolizidinium *p*-toluenesulfonate (23).

To a solution of diol **22** (83.0 mg ; 0.24 mmol) and tosyl chloride (51.0 mg ; 1.1 eq) in anhydrous DCM (0.5 mL) was added anhydrous pyridine (0.35 mL; 4.33 mmol; 18.0 eq). The mixture was stirred for 24 hours at room temperature. Then solvents were co-evaporated with CCl_4. Purification with Dowex 50W-X8 led to compound **23** (89.6 mg, 74%).

^{1}H NMR ($CDCl_3$) δ_H 7.85 (d, 2 H), 7.55 (d, 2H), 7.37-7.11 (m, 10H), 4.84-4.66 (AB syst., *J* = 12.9 Hz, 2H), 4.53-4.47 (m, 2H), 4.42 (AB syst., 2H), 4.38 (m, 1H); 4.23, (dd, J= 4.8, 13.2 Hz, 1H); 3.96 (m, 1H), 3.50 (d, J= 13.2 Hz, 1H), 3.47 (m, 1H); 2.30 (m, 1H), 2.04 (m, 1H), 2.01 (m, 1H), 1.98 (m, 1H). ^{13}C NMR ($CDCl_3$) δ_C ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.32 (Cq), 139.64 (Cq), 136.89 (Cq), 132.62 (CH), 129.31 (CH),

129.16 (CH), 128.77 (CH), 128.52 (CH), 128.00 (CH), 127.67 (CH), 125.96 (CH), 84.52 (CH), 84.18 (CH), 77.51 (CH), 71.98 (CH2), 69.39 (CH2), 67.22 (CH2), 63.68 (CH2), 28.56 (CH2), 24.08 (CH2), 21.28 (CH_3).

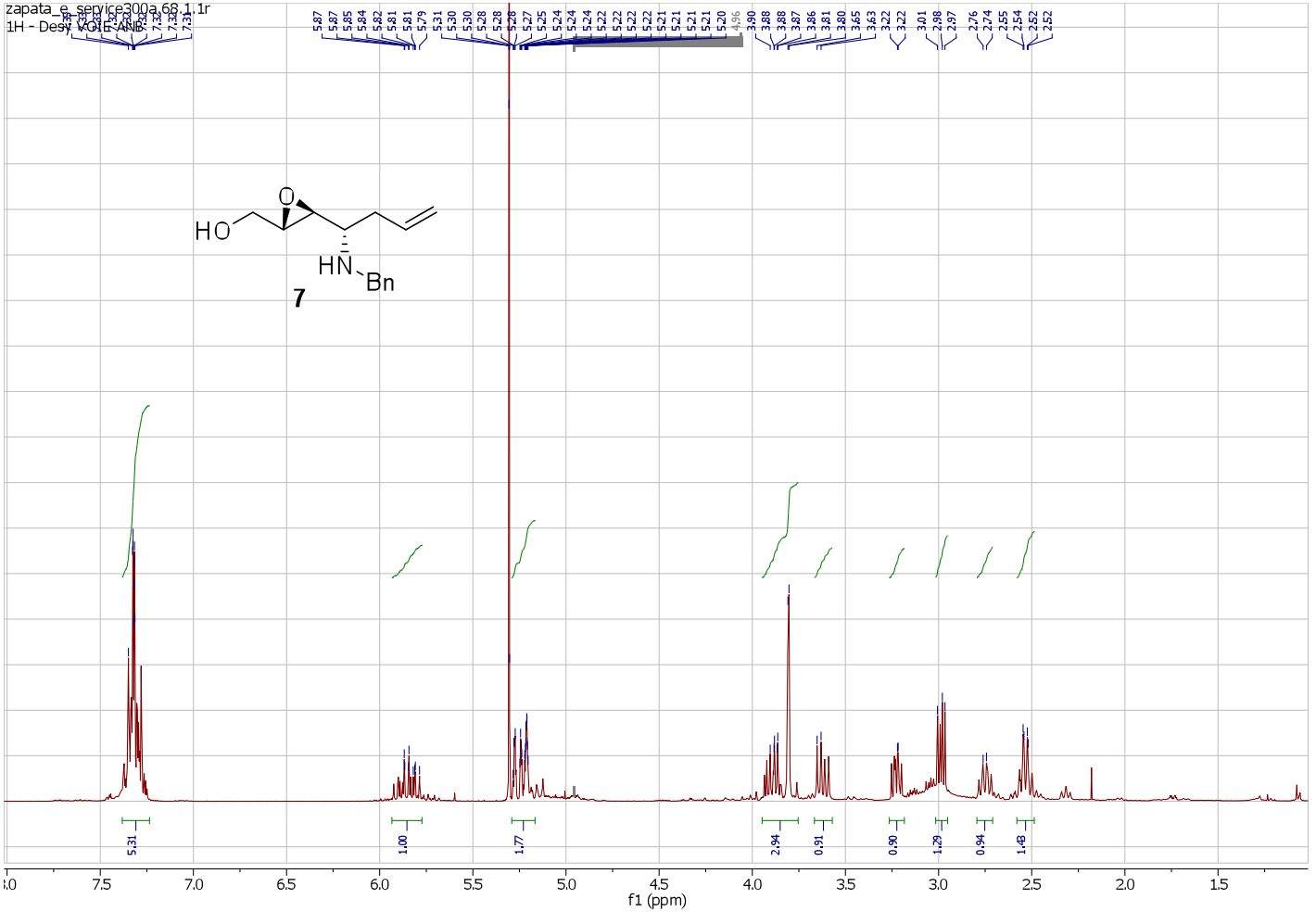
(1S,2S,7aS)-1,2-Dihydroxypyrrolizidine (all-(*S*)-1).

To a suspension of pyrrolizidinium **23** (117 mg, 0.22 mmol) and 10% Pd/C (52 mg) in dry MeOH (4 mL) was added anhydrous ammonium formate (88.1 mg, 1.0 eq) in a single portion. The reaction mixture was refluxed for 2 hours and then cooled to room temperature. To this solution was added anhydrous K_2CO_3 (57.3 mg, 2.0 eq). The reaction was stirred for 2 hours and then filtered over celite®. After solvent removal, the residue was purified by flash chromatography (eluent: 5:95 MeOH/DCM with 1% NH_3) to yield compound all-(*S*)-**1** as a pale yellow oil (30.0 mg, 100%).

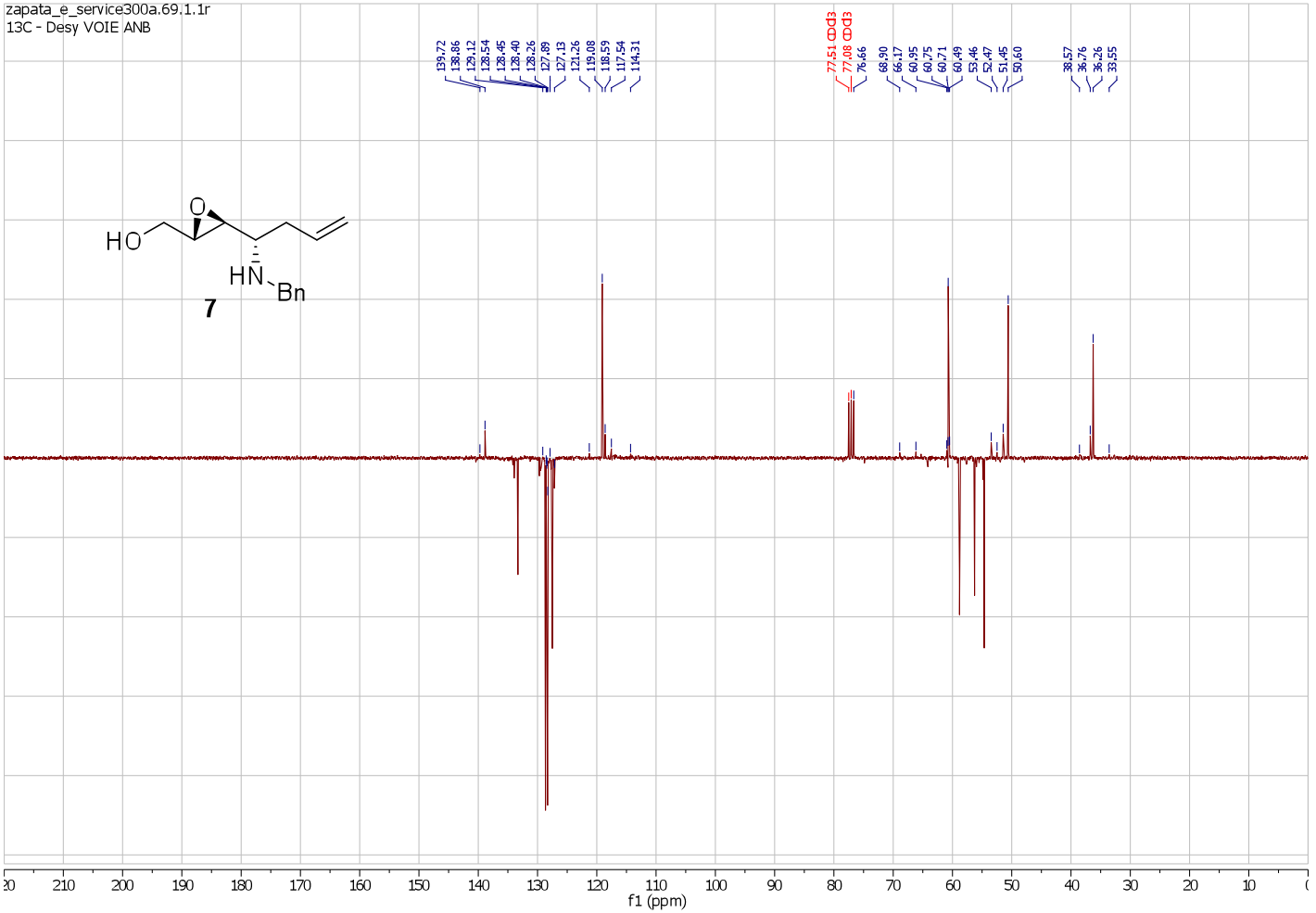
$[\alpha]_D^{25}$ + 1.5 (*c* 0.9; MeOH) [Lit.[2a] $[\alpha]_D^{24}$ – 3.4 (*c* 0.5; MeOH); lit.[2b] $[\alpha]_D^{23}$ + 11 (*c* 0.5; MeOH); lit.[2c] $[\alpha]_D^{23}$ + 11.3 (*c* 0.5; MeOH)]; ^{1}H NMR (MeOD) δ_H 4.90 (s, 2 H), 4.12 (q, *J* = 5,3 Hz, 1H), 3.78 (t, *J* = 4.8 Hz, 1H), 3.47-3.36 (m, 1H), 3.37 (dd, *J* = 11.1, 5.5 Hz, 1H), 3.14 (dt, *J* = 10.8, 5.6 Hz, 1H), 2.95-2.83 (m, 1H), 2.73 (dd, *J* = 11.1, 5.8 Hz, 1H), 2.13-1.72 (m, 4H); ^{13}C NMR (MeOD) δ_C 80.8 (CH), 77.2 (CH), 70.8 (CH). 58.2 (CH_2), 55.6 (CH_2), 29.7 (CH_2), 25.0 (CH_2); MS (CI NH_3) 144.1 (100); HRMS (CI CH_4) calcd for $C_7H_{14}NO_2$: 144.1025, found 144.1020.

[2] a) Ha, D. C.; Yun C. S.; Lee, Y. *J. Org. Chem.* **2000**, 65, 621-623; b) Izquierdo, I.; Plaza, M. T.; Tamayo, J. A. *Tetrahedron-Asymmetry* **2004,** 15, 3635-3642; c) Du-a-Man, S.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Eur. J. Org. Chem.* **2014,** 1708-1715.

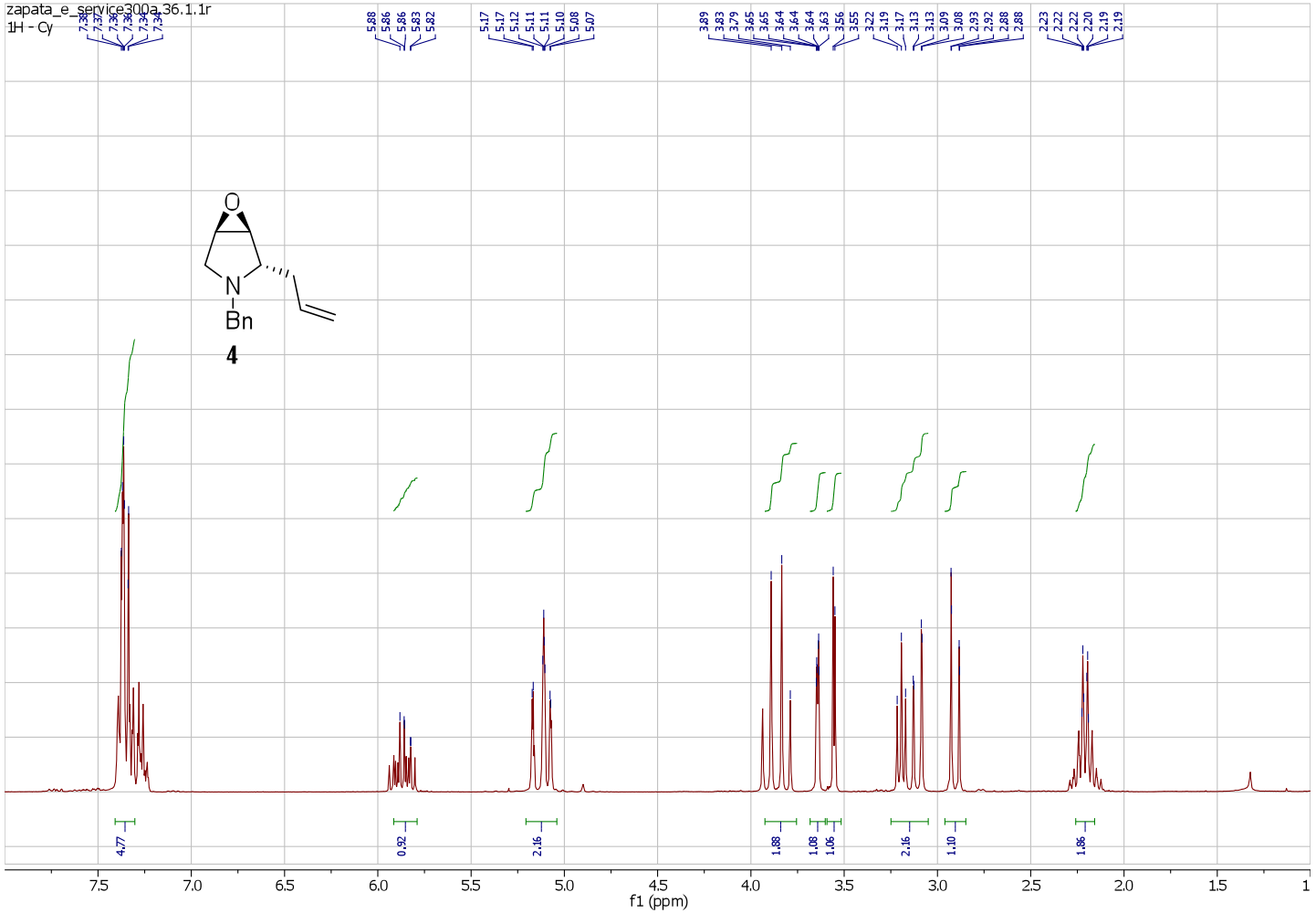
Copies of the ^{1}H and ^{13}C NMR spectra of all new compounds



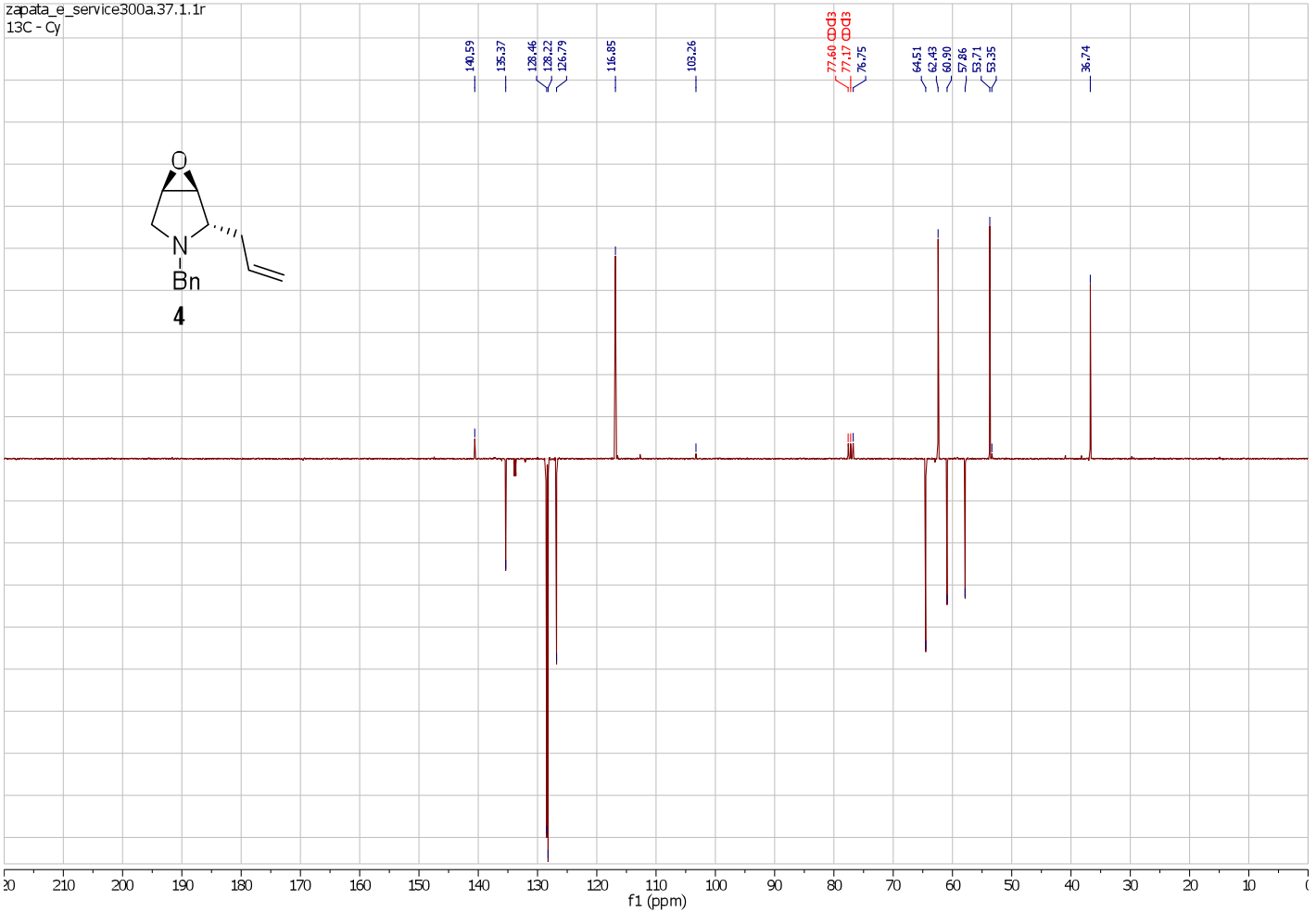
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **7**



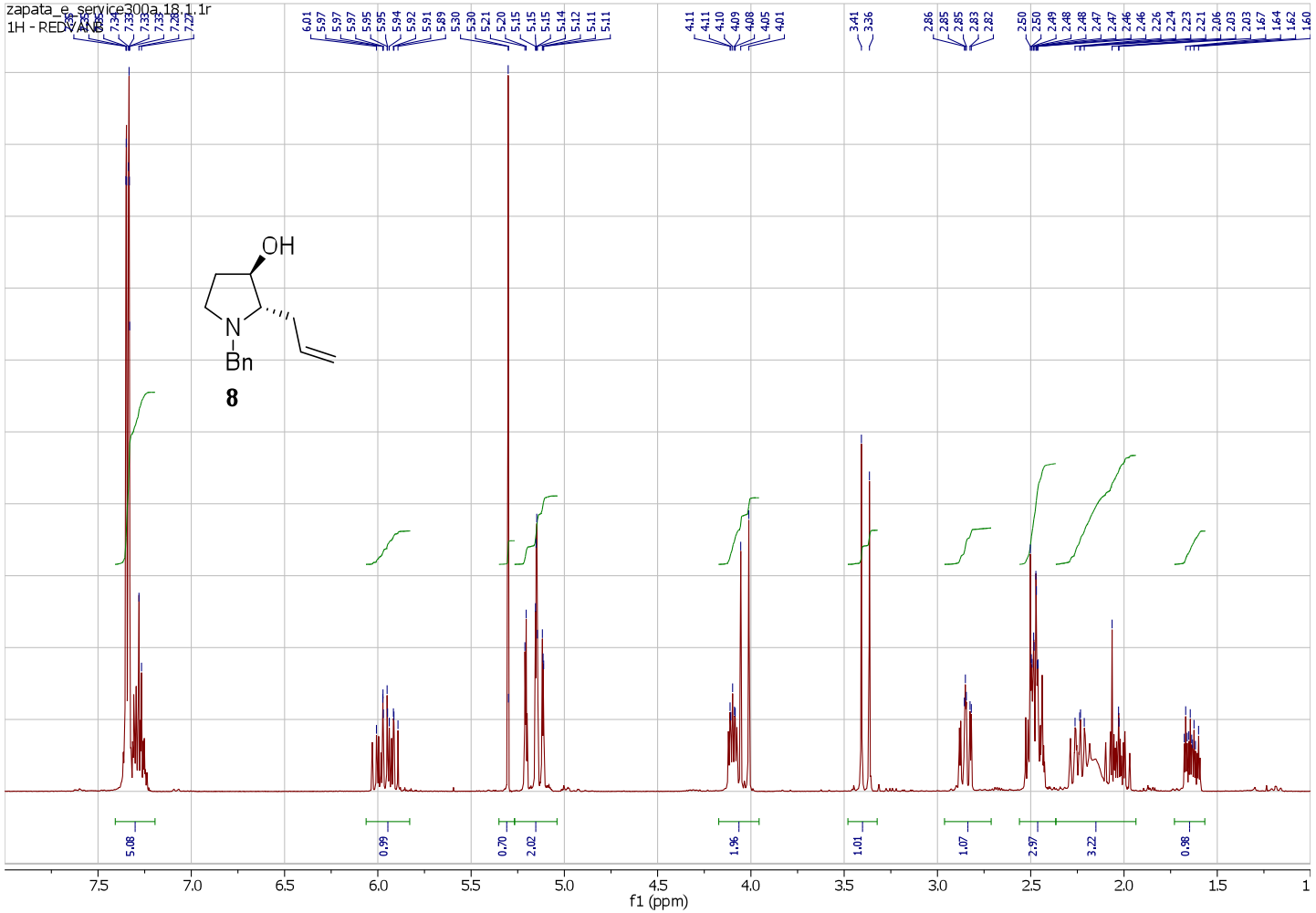
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **7**



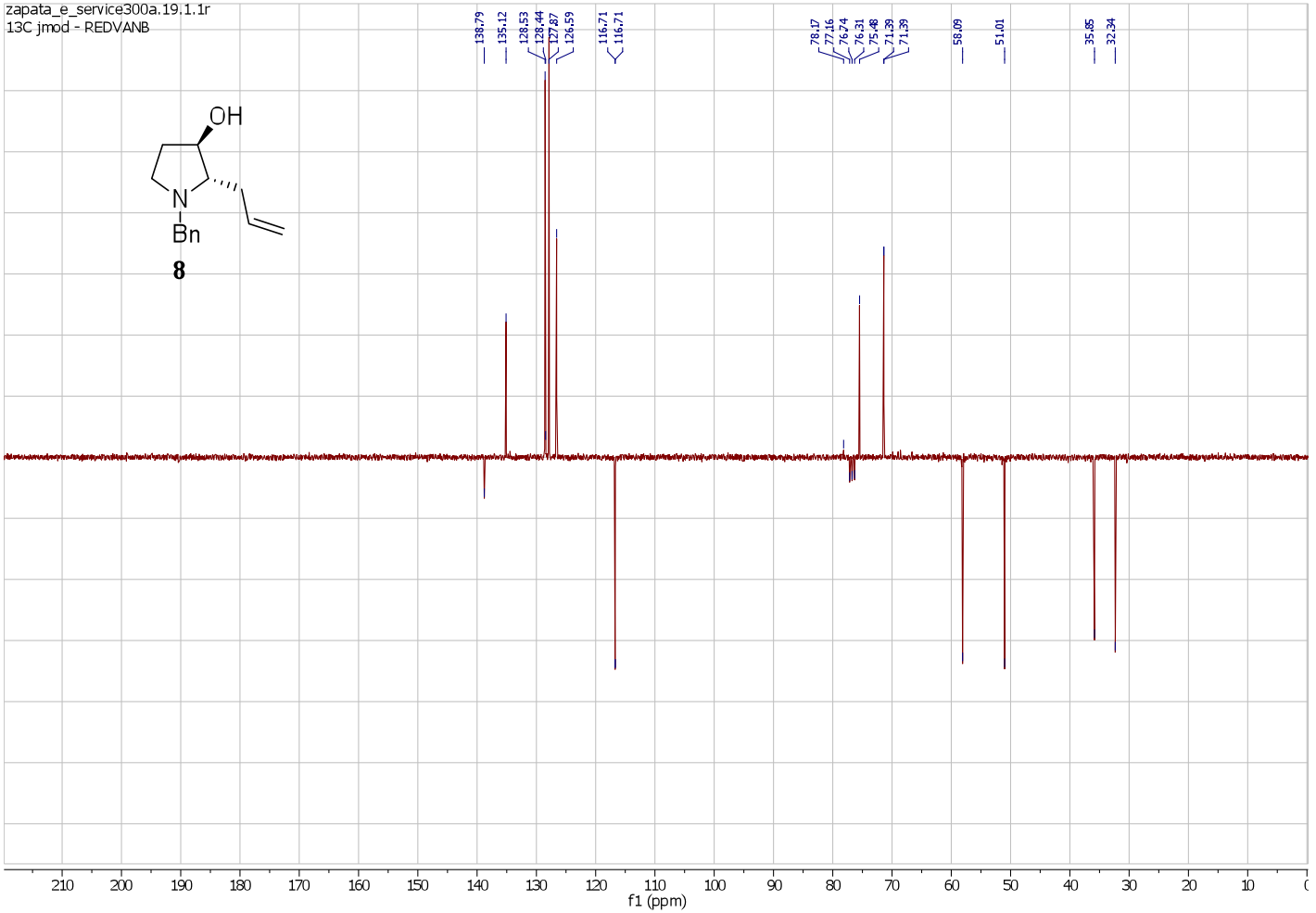
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **4**



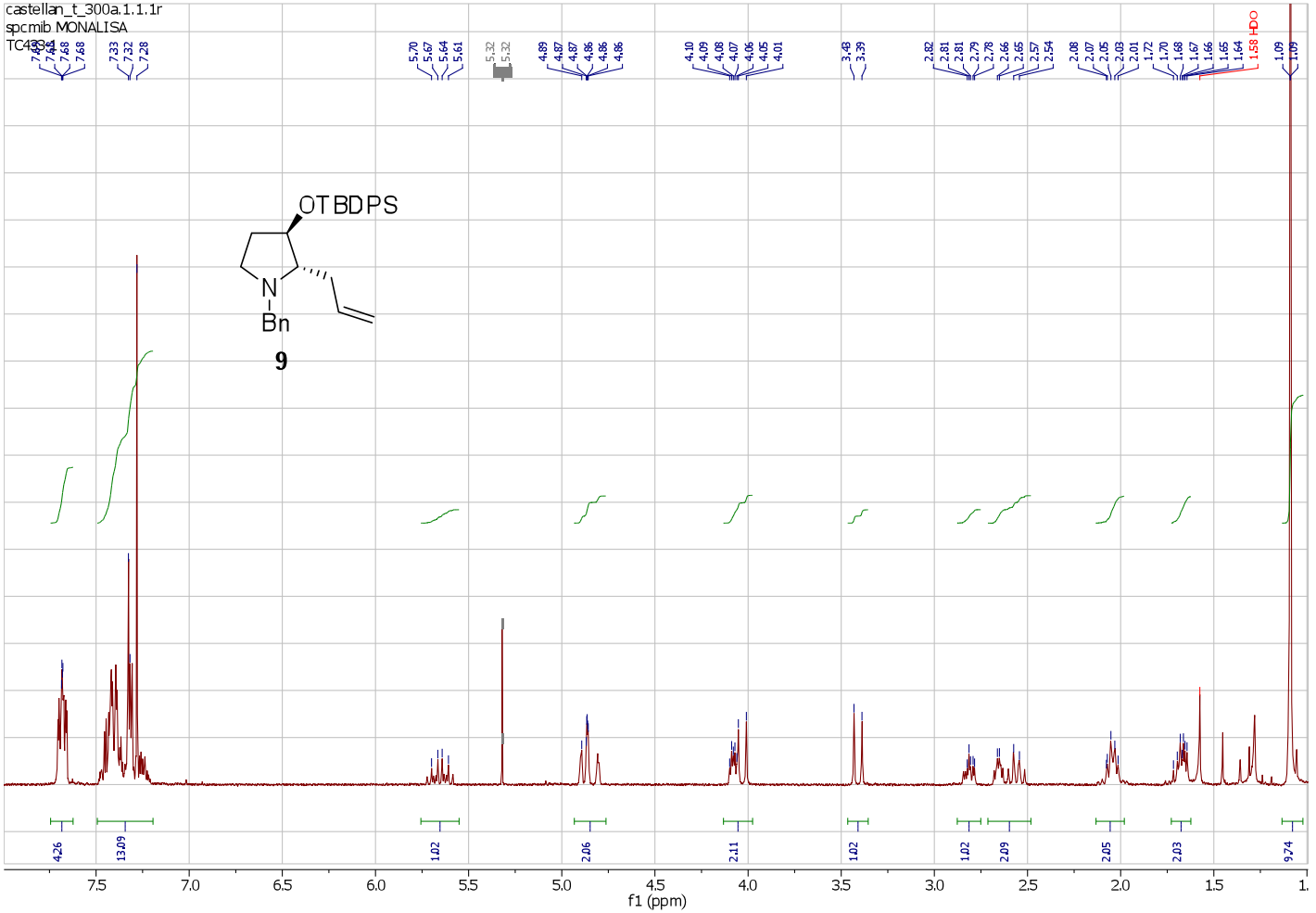
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **4**



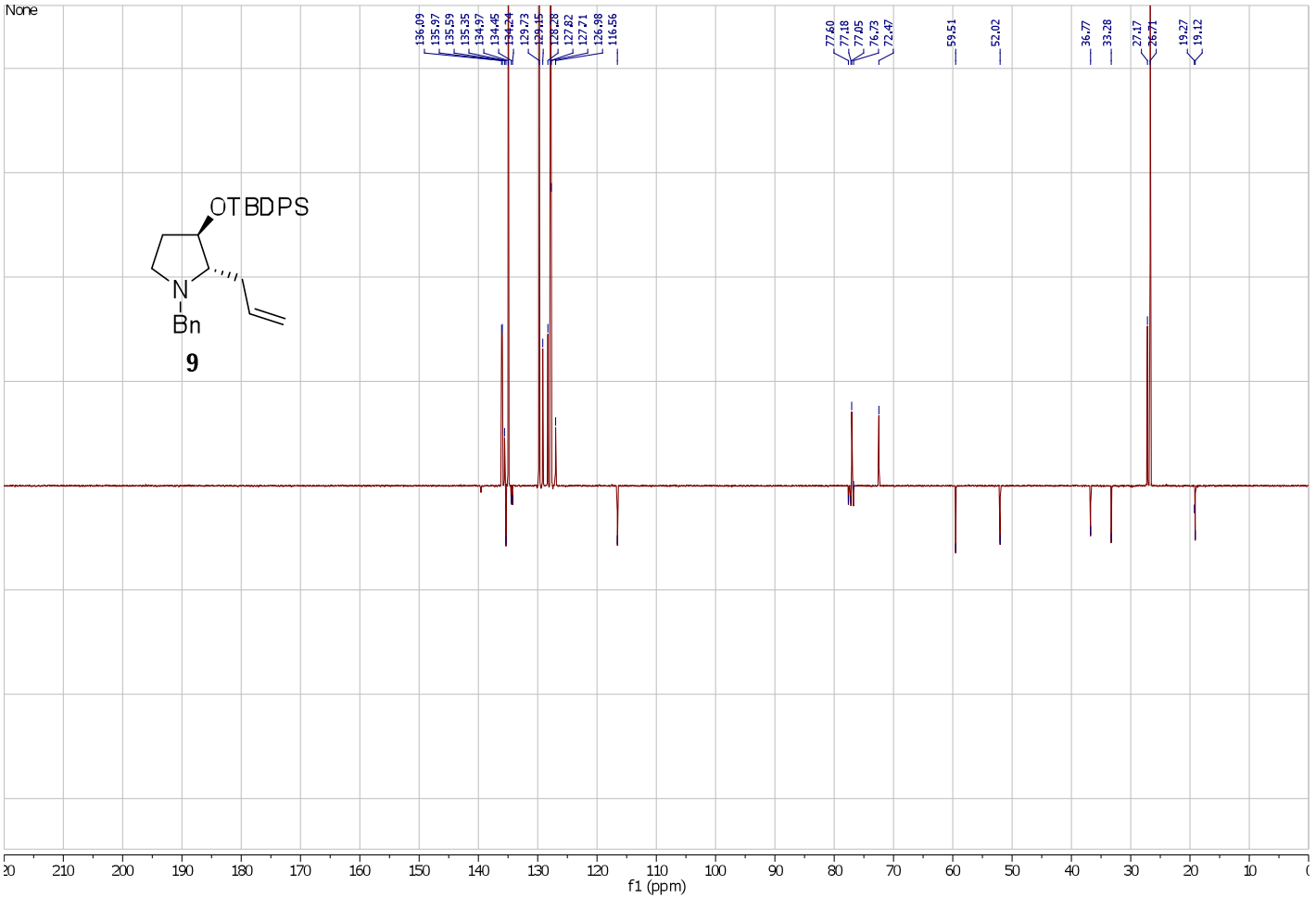
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **8**



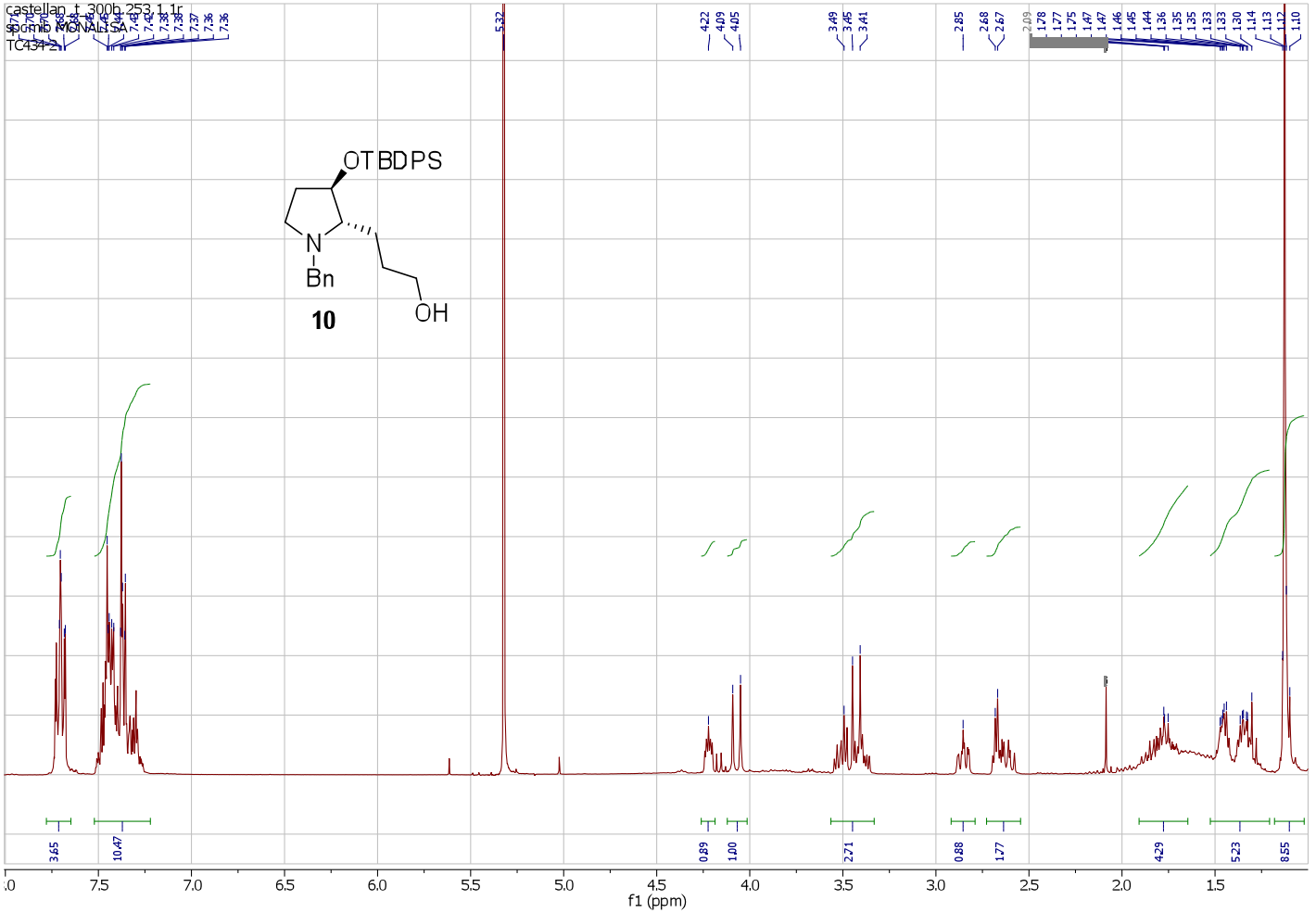
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **8**



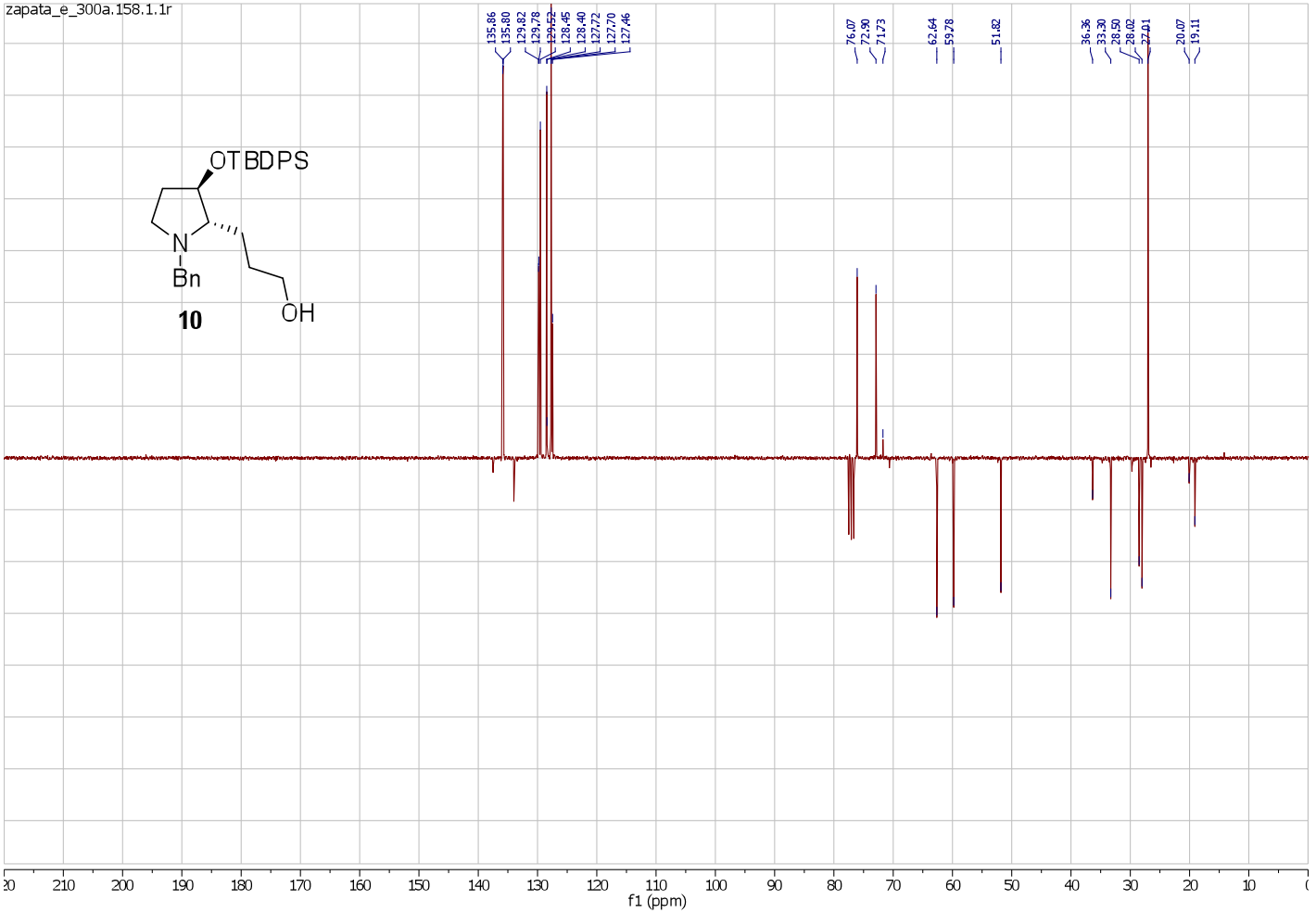
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **9**



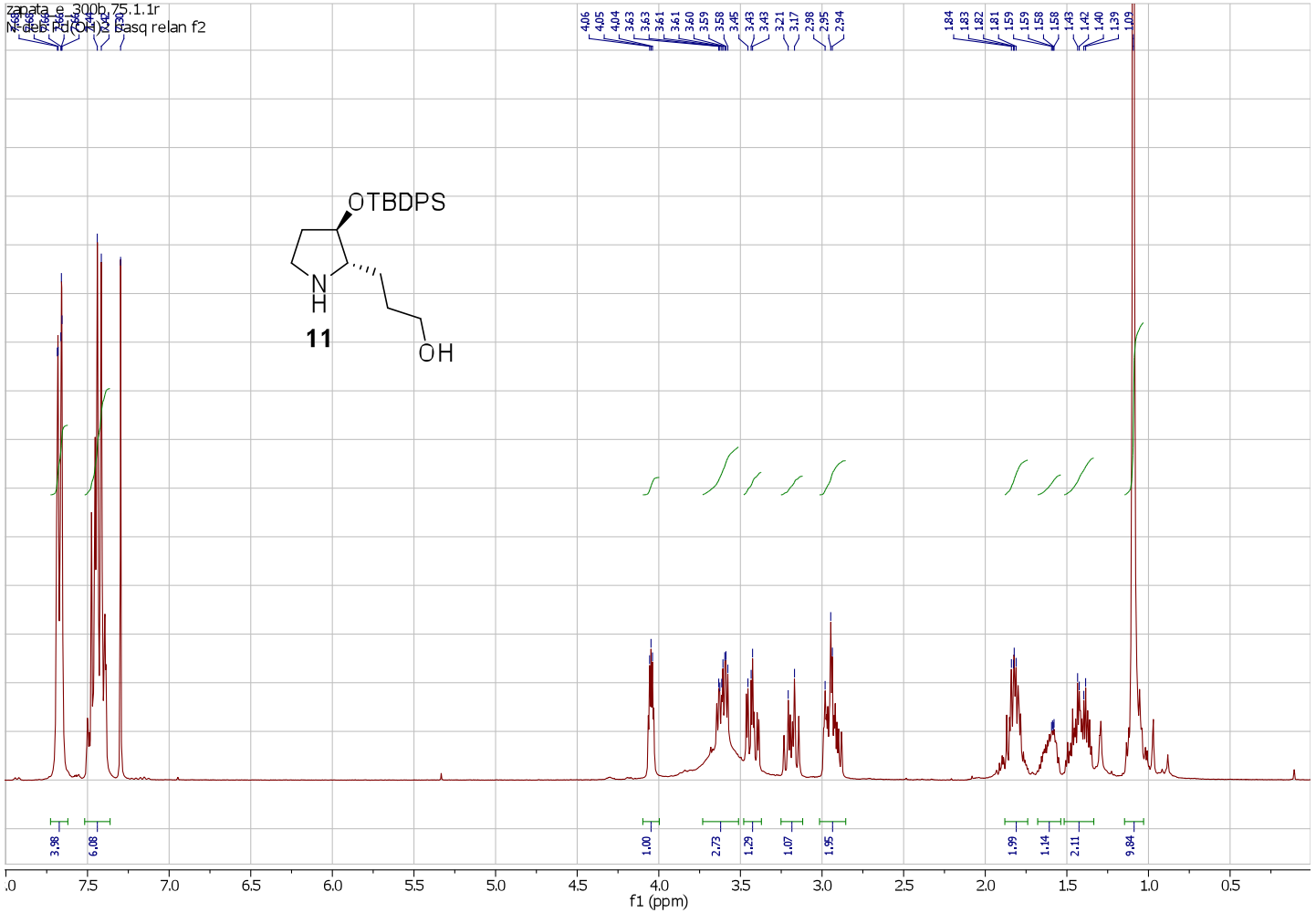
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **9**



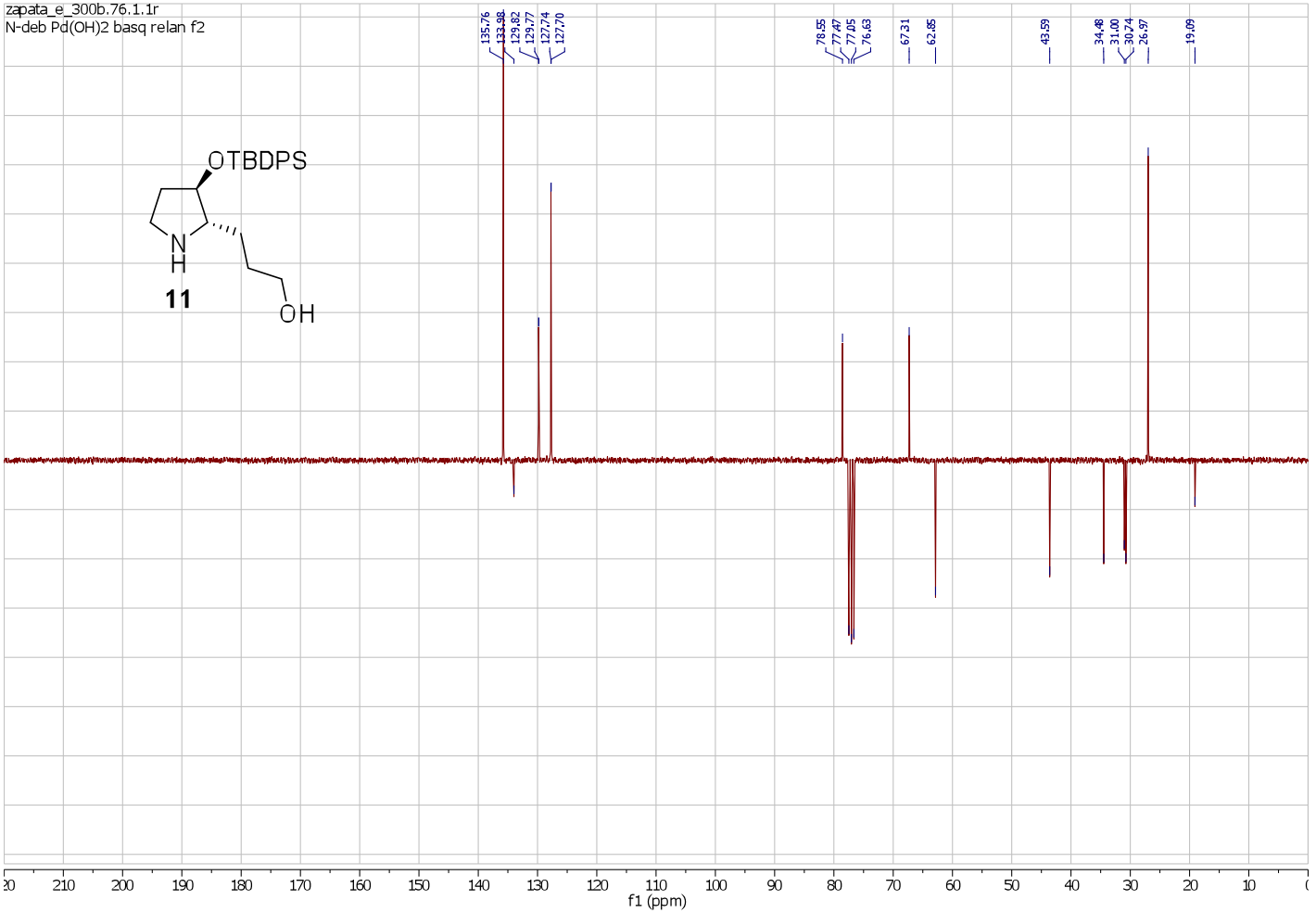
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **10**



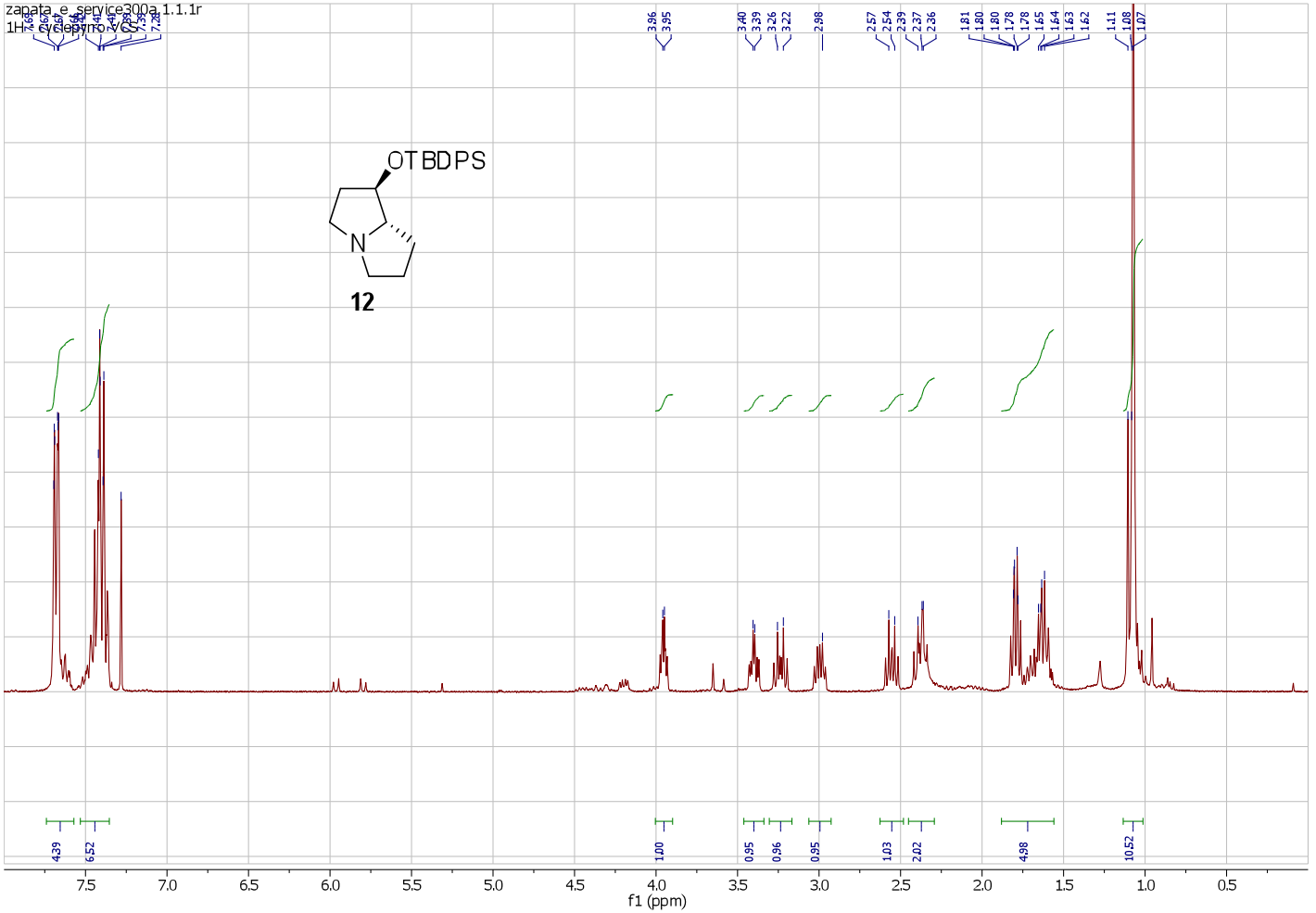
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **10**



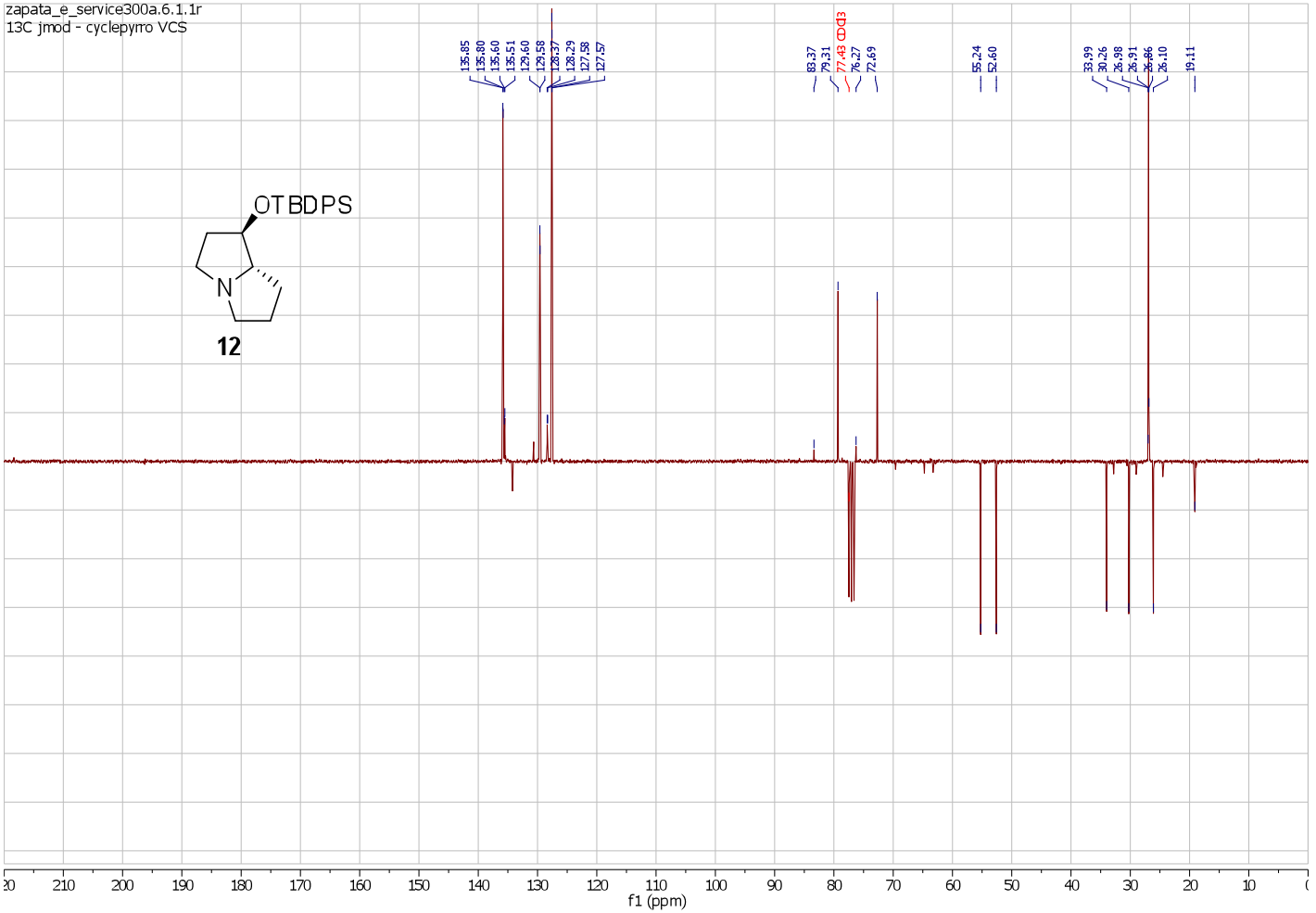
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **11**



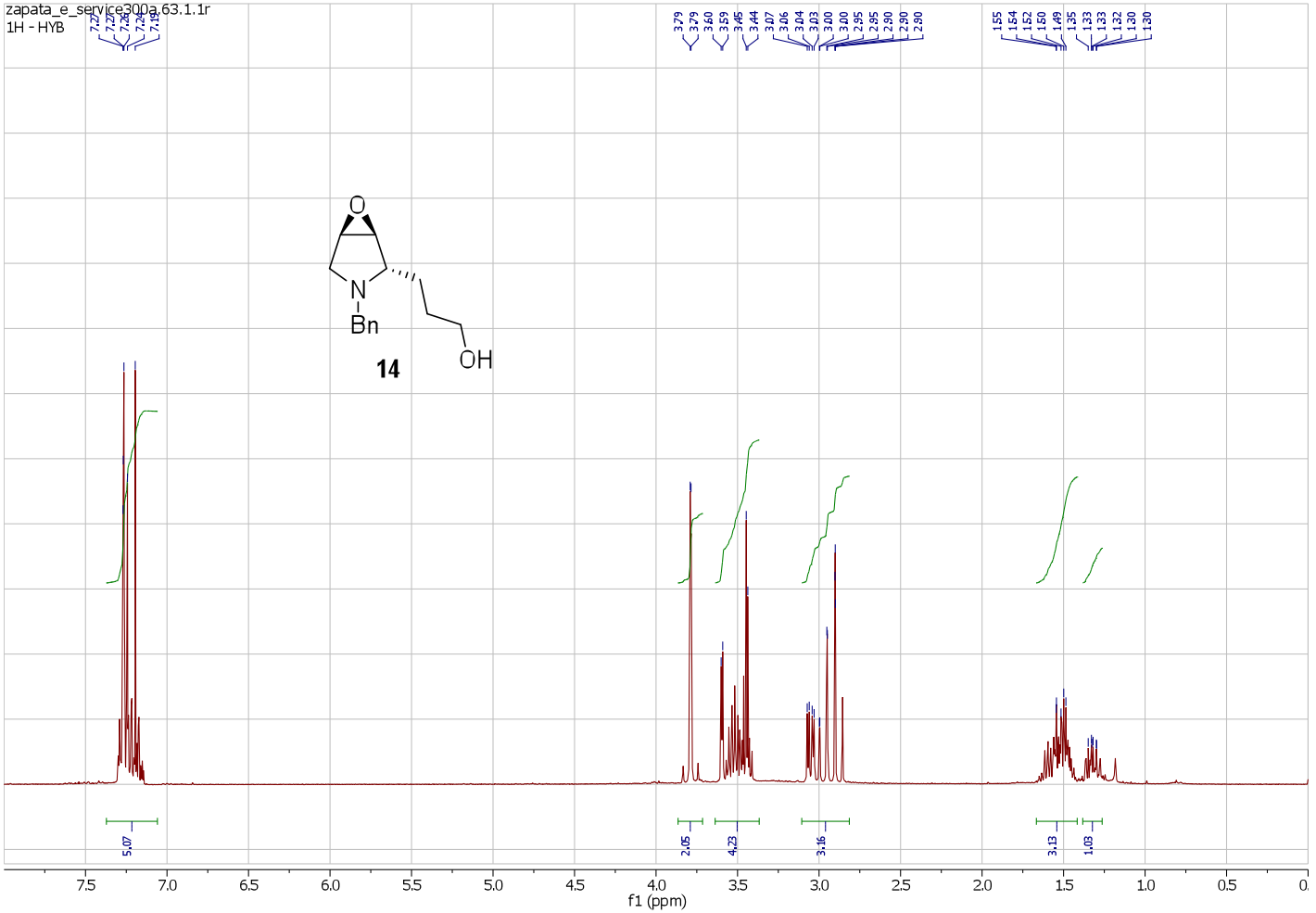
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **11**



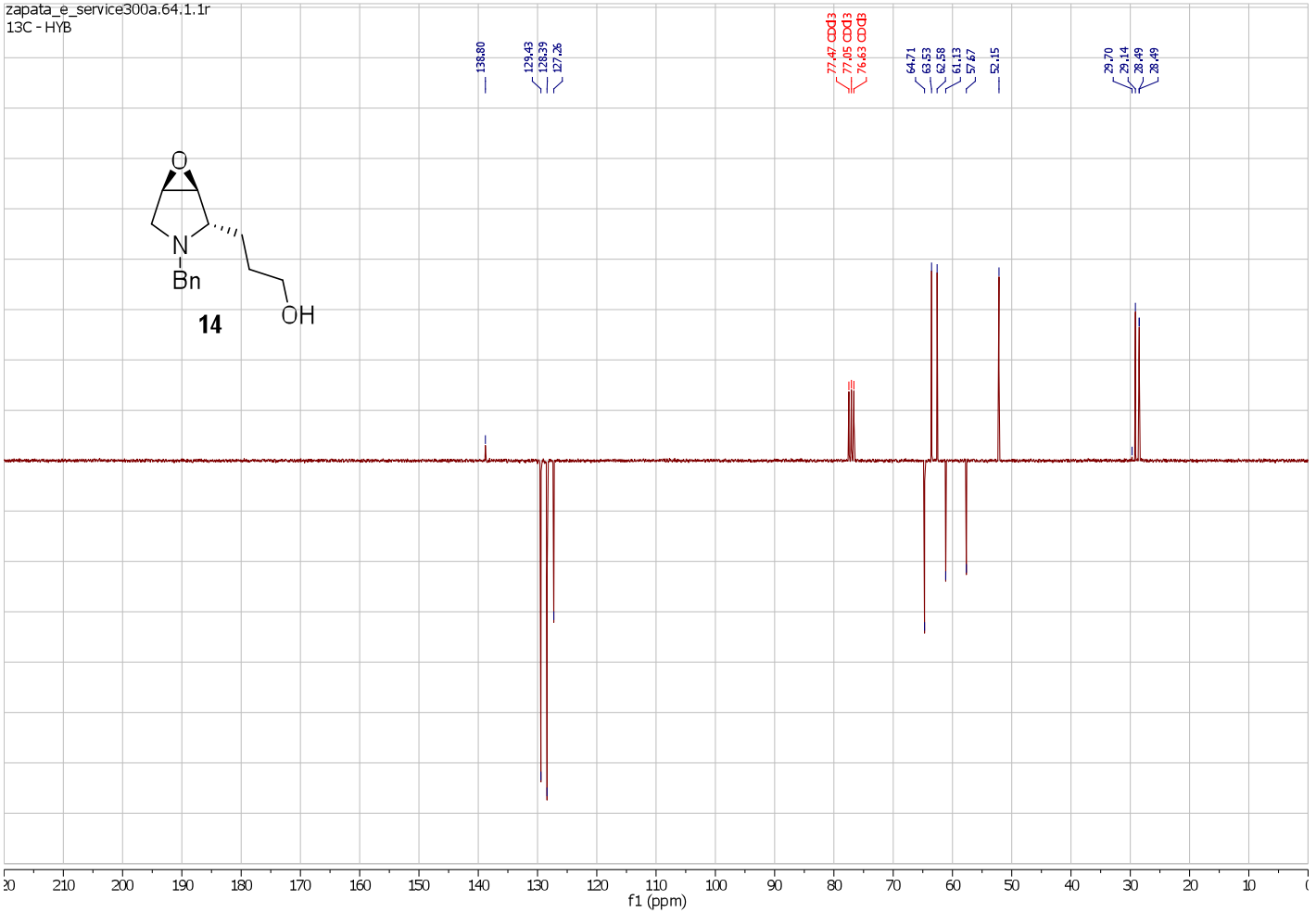
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **12**



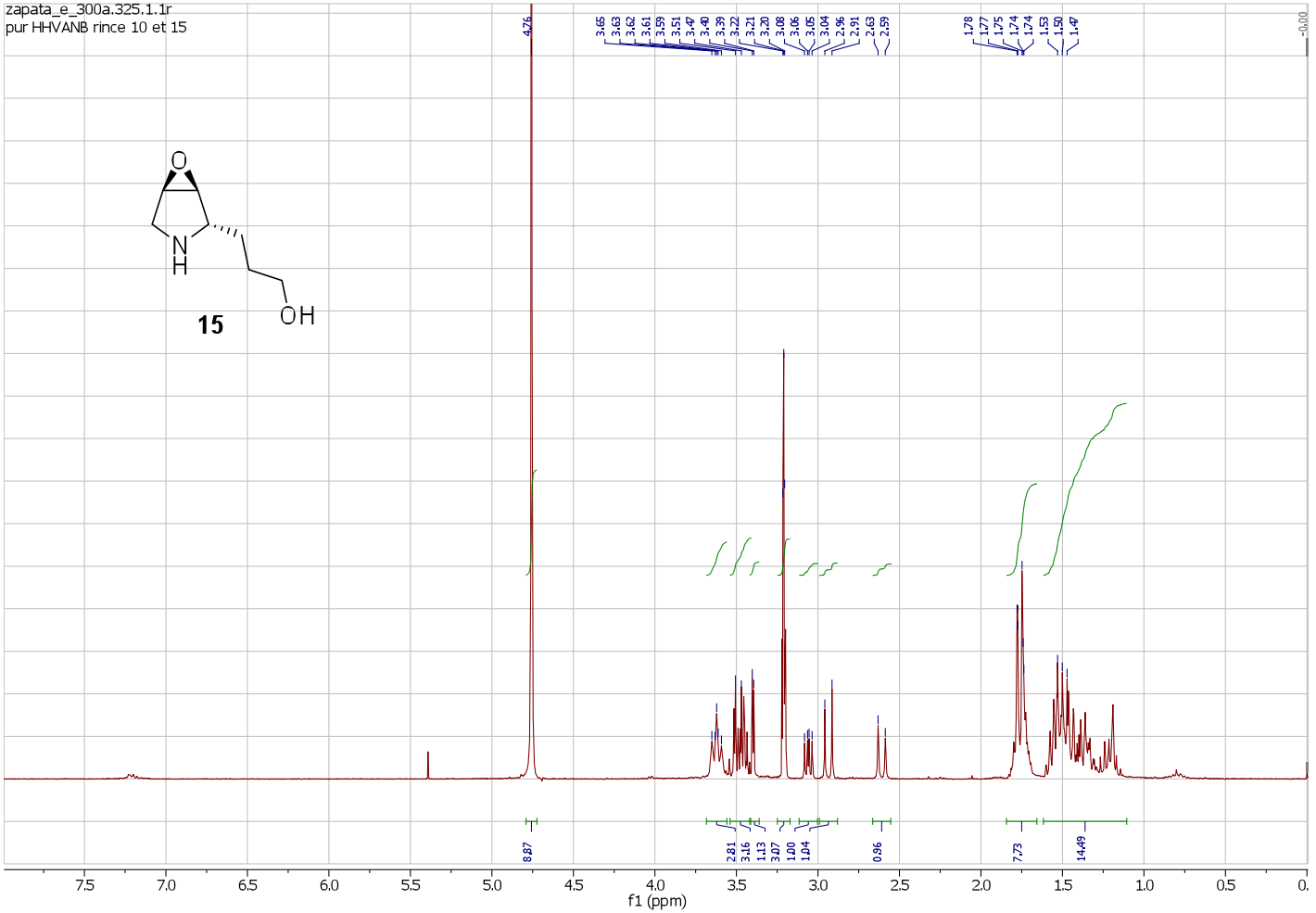
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **12**



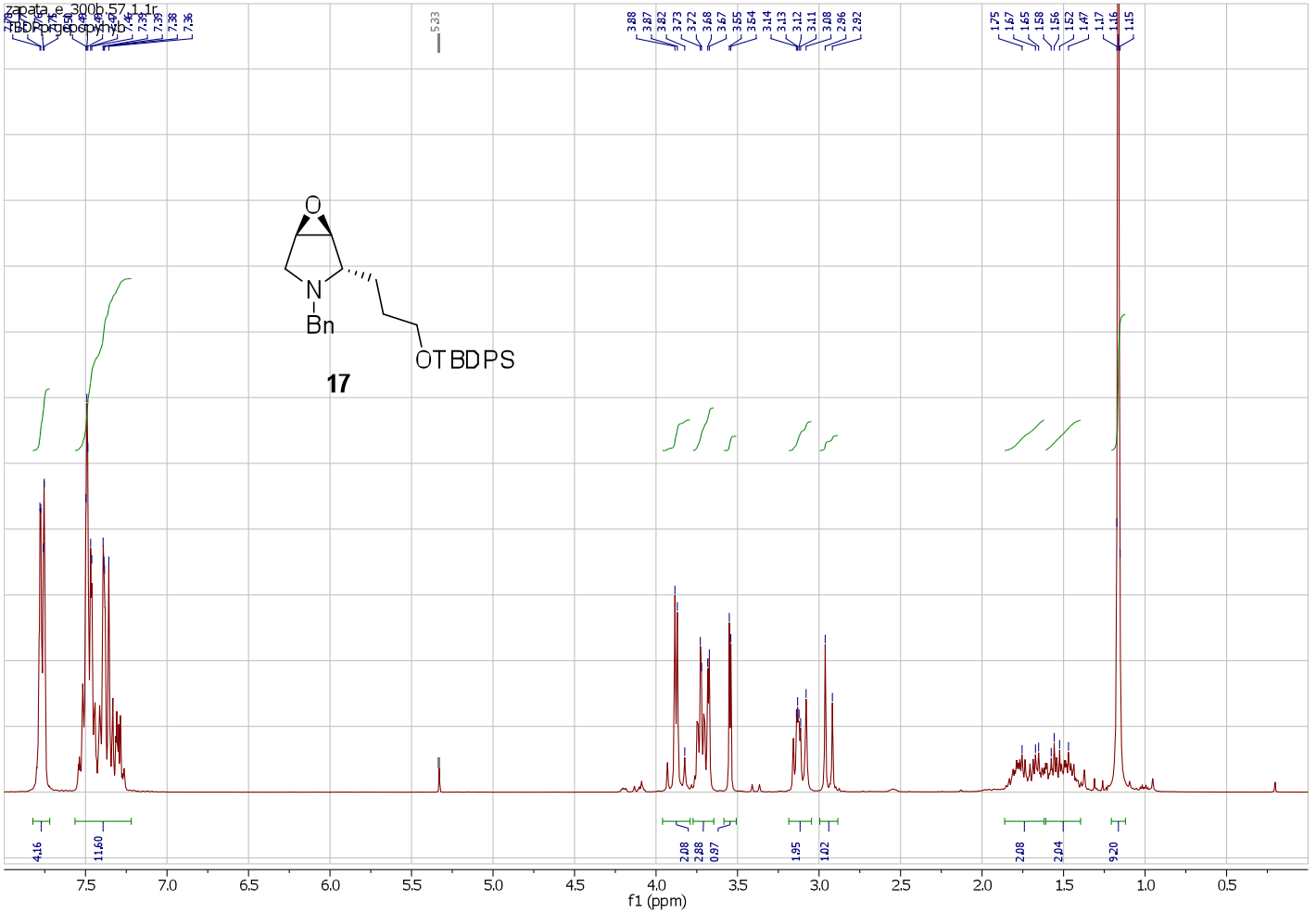
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **14**



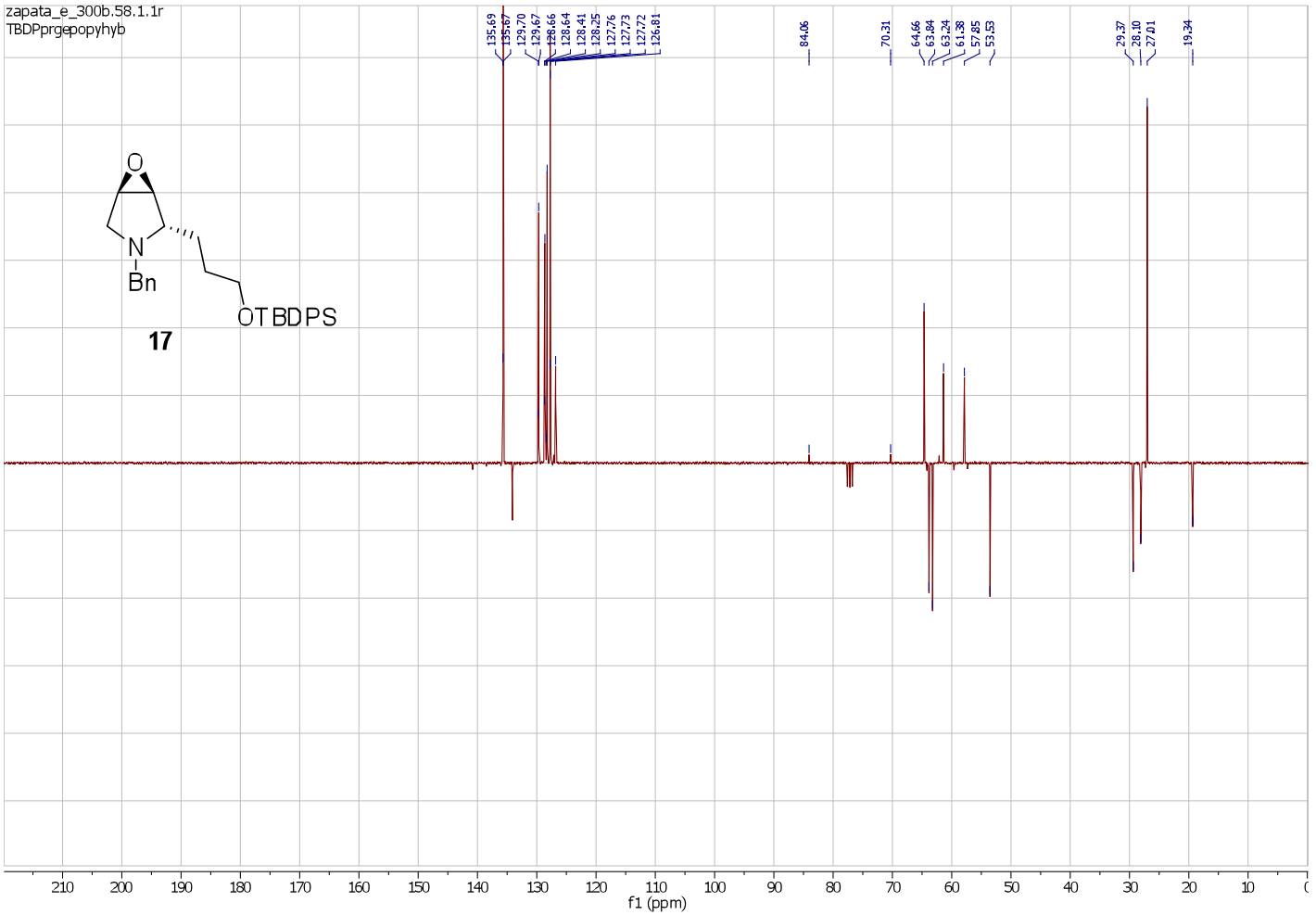
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **14**



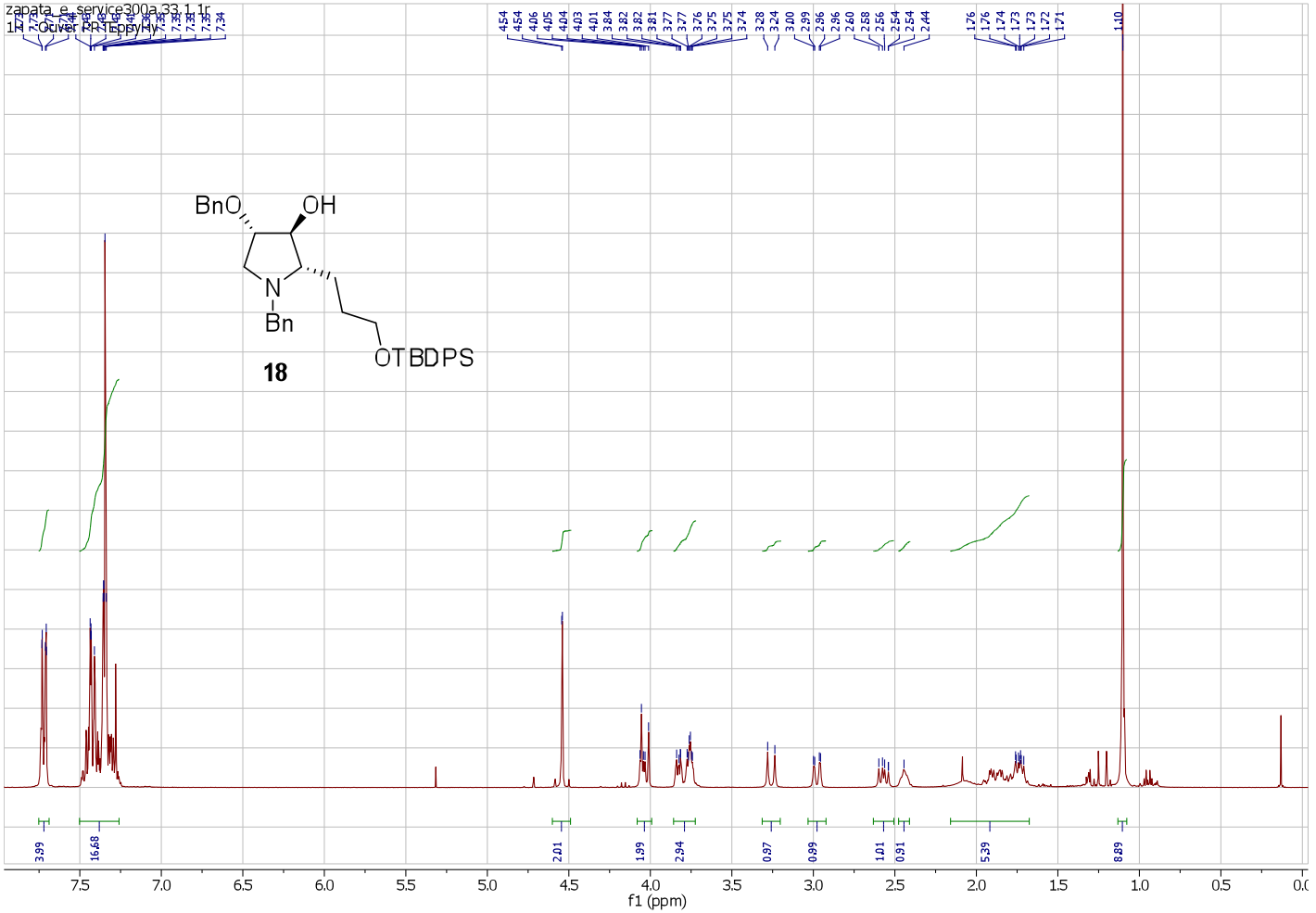
^{1}H NMR (300MHz, MeOH) spectrum of compound **15**



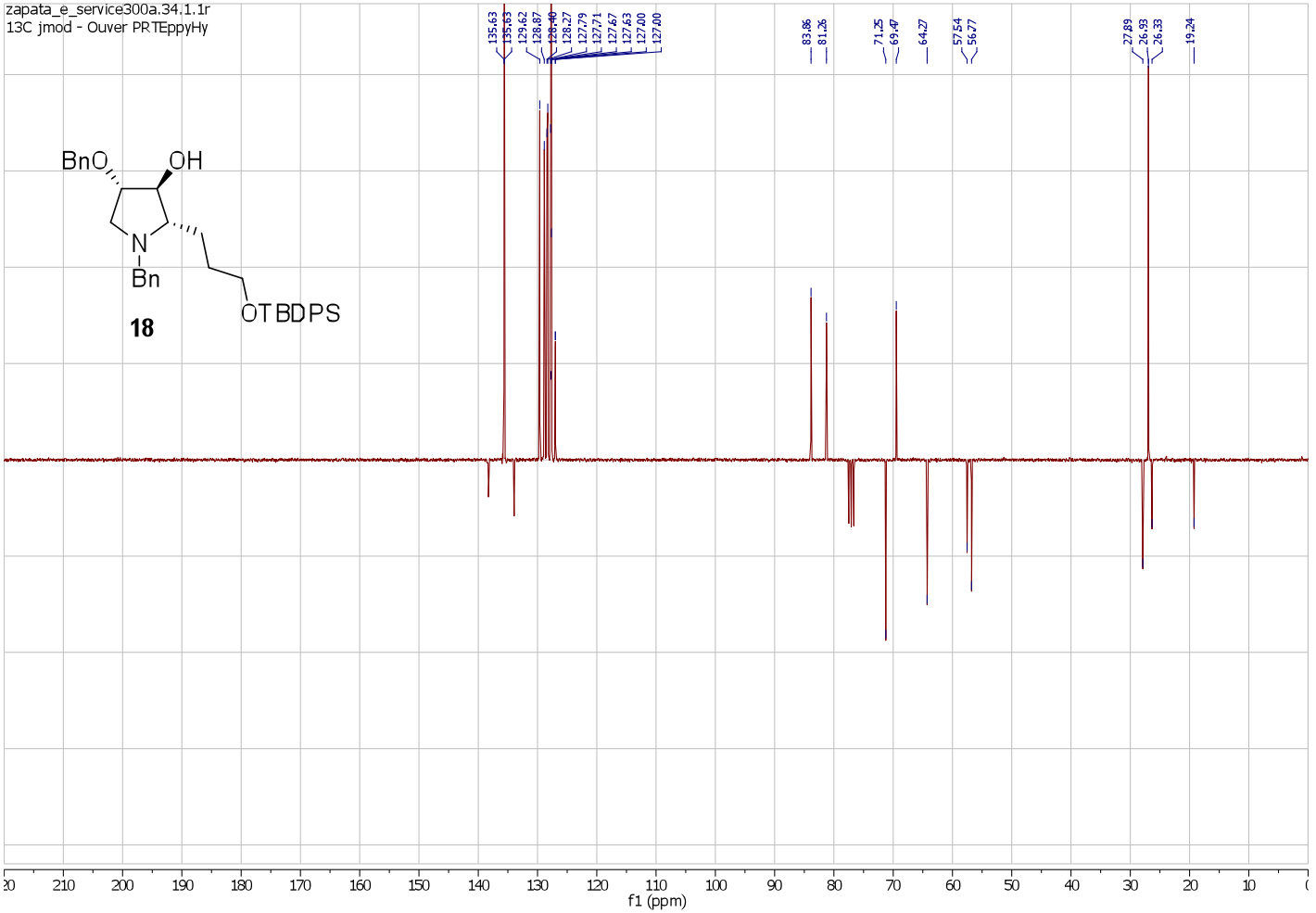
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **17**



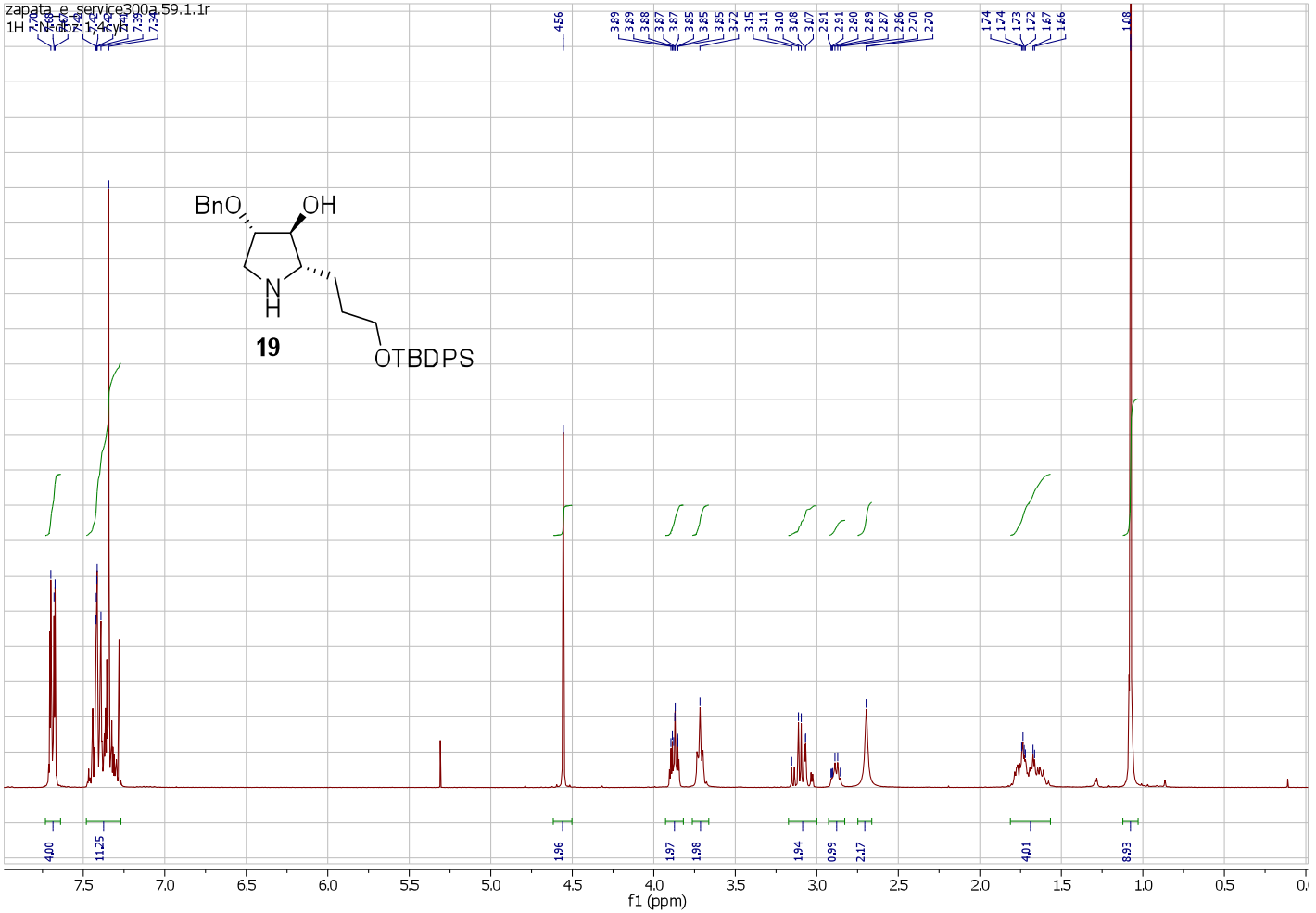
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **17**



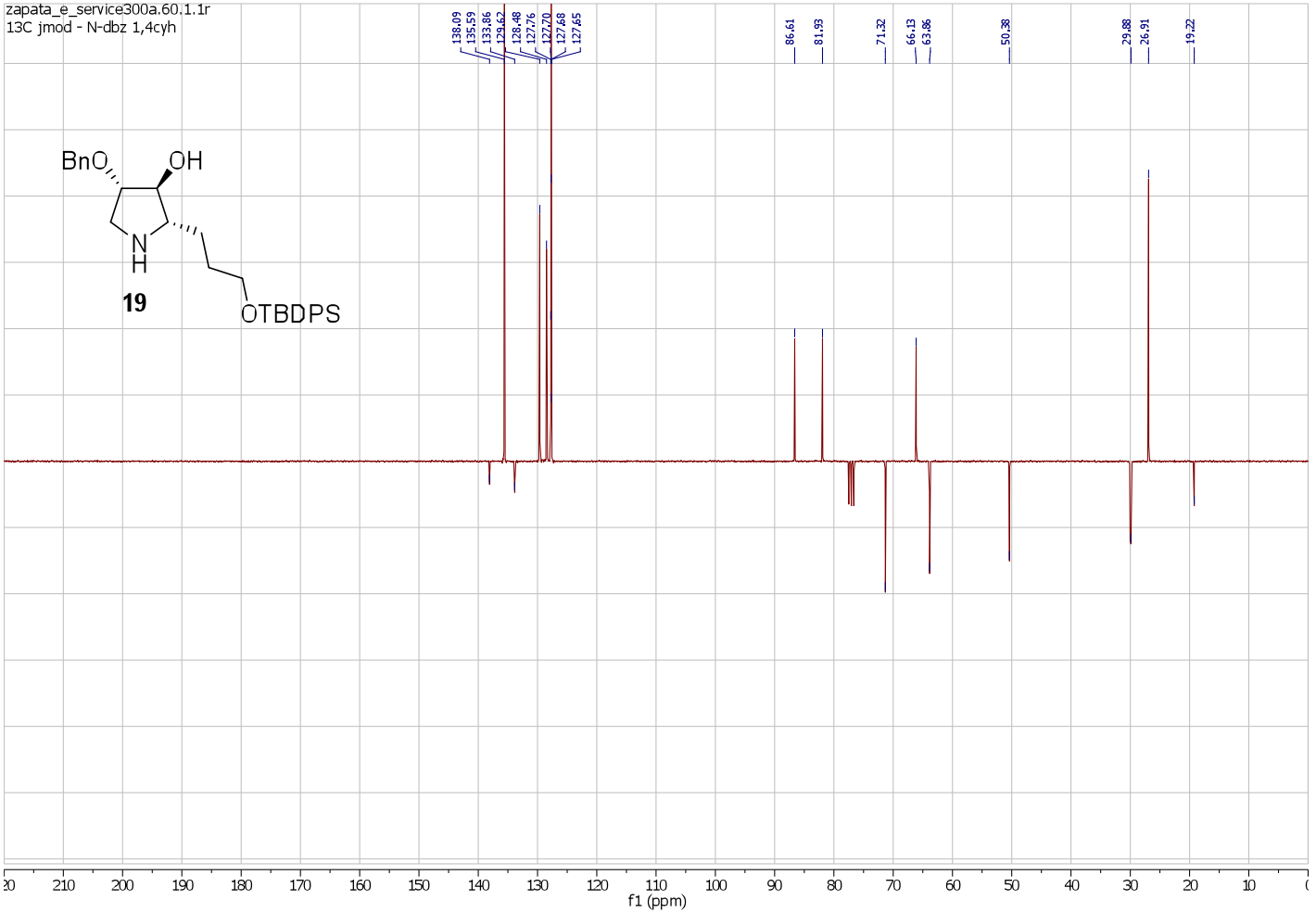
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **18**



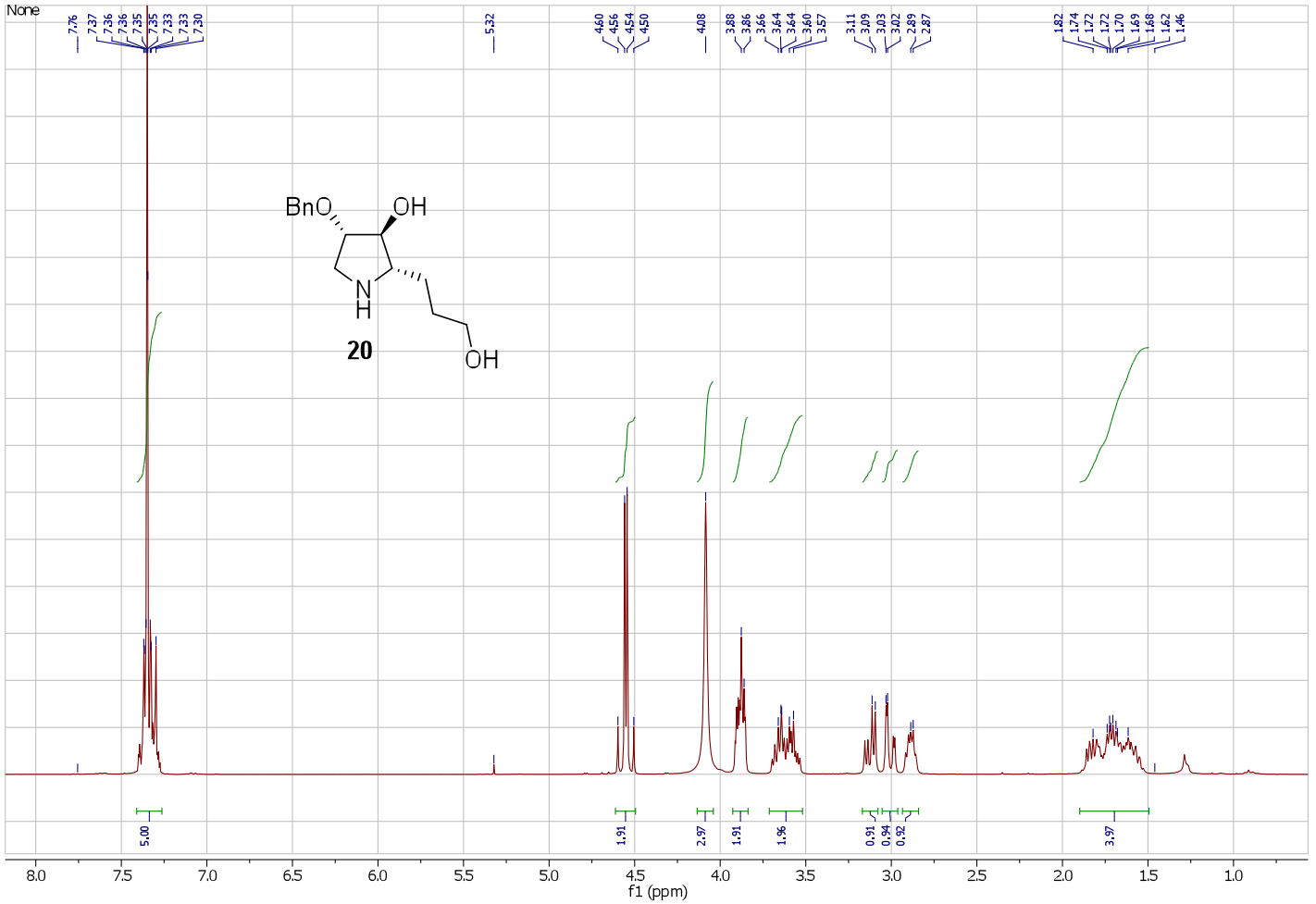
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **18**



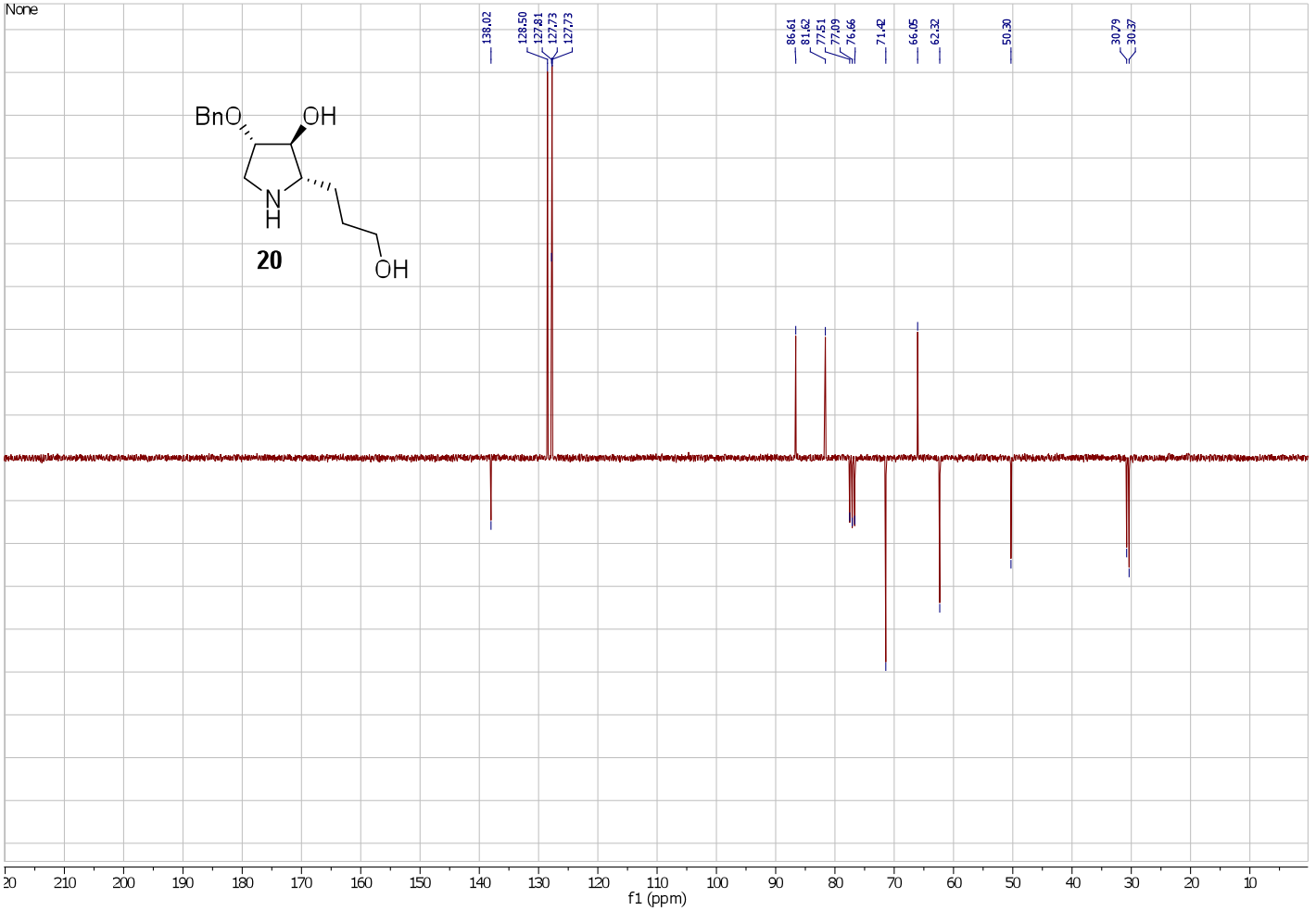
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **19**



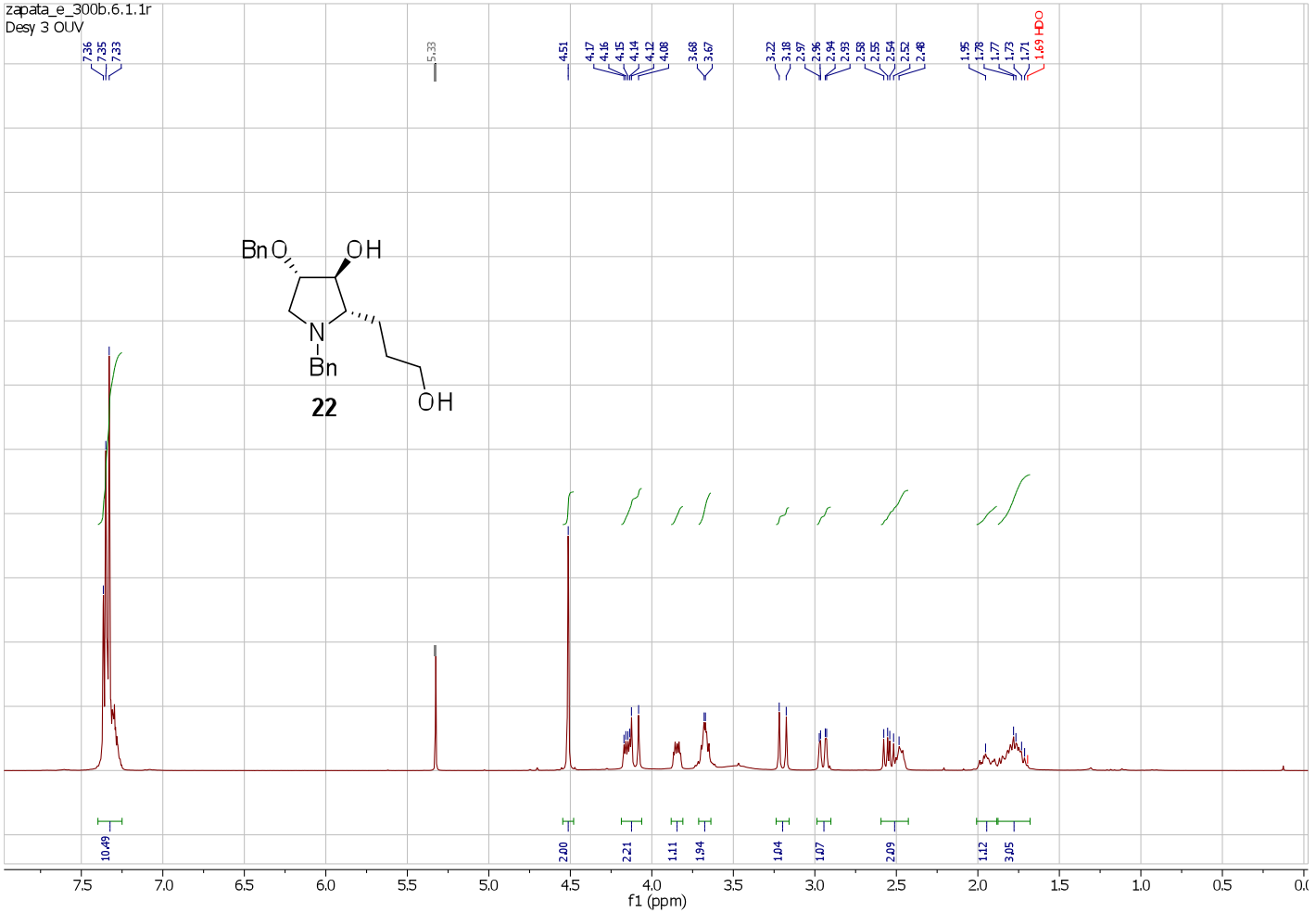
^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **19**



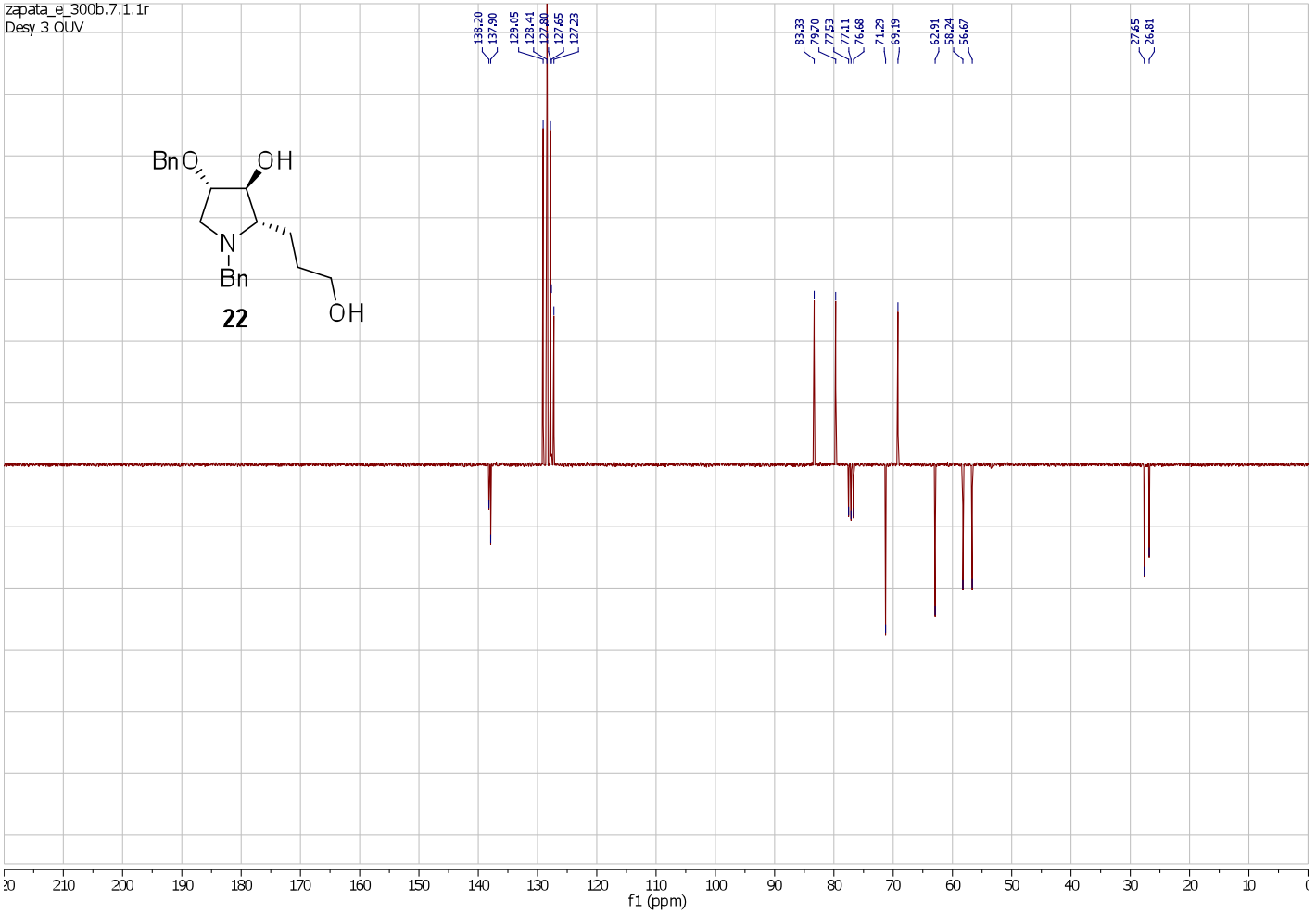
^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **20**



^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **20**



^{1}H NMR (300MHz, $CDCl_3$) spectrum of compound **22**



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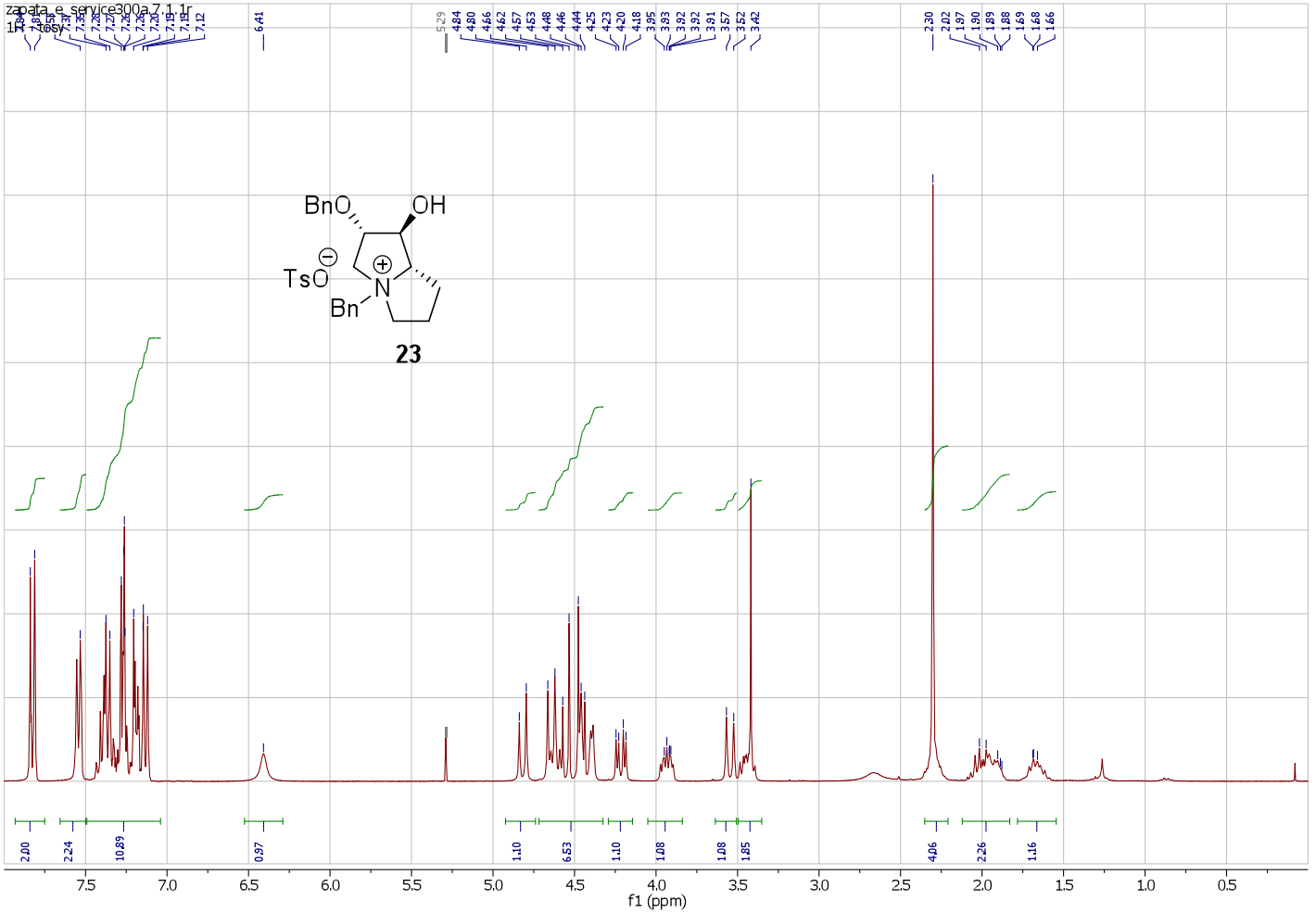

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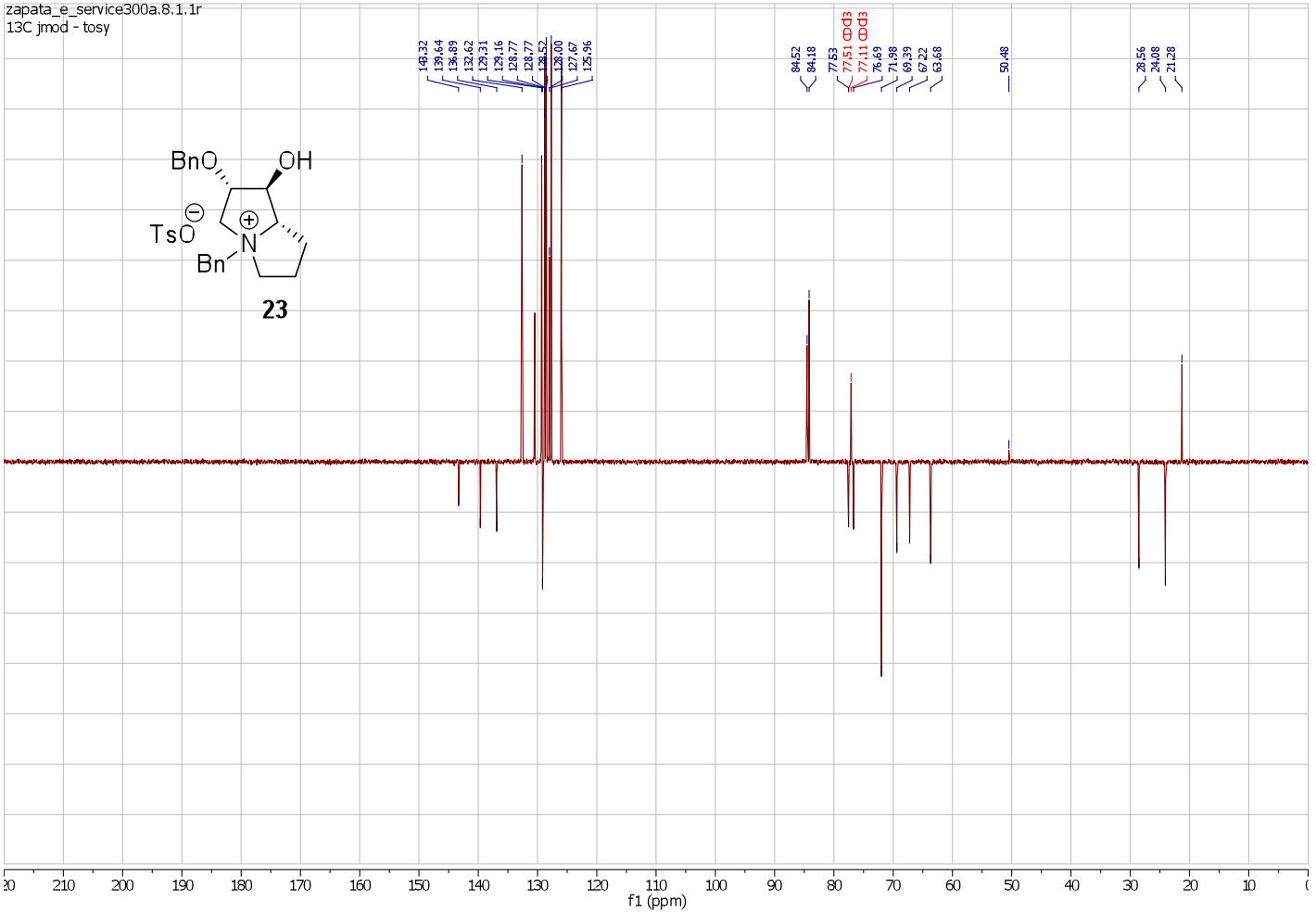

^{13}C NMR (75MHz, $CDCl_3$) spectrum of compound **23**