Levonantradol: Stereoselective Synthesis and Structural Analysis

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EXPERIMENTAL SECTION

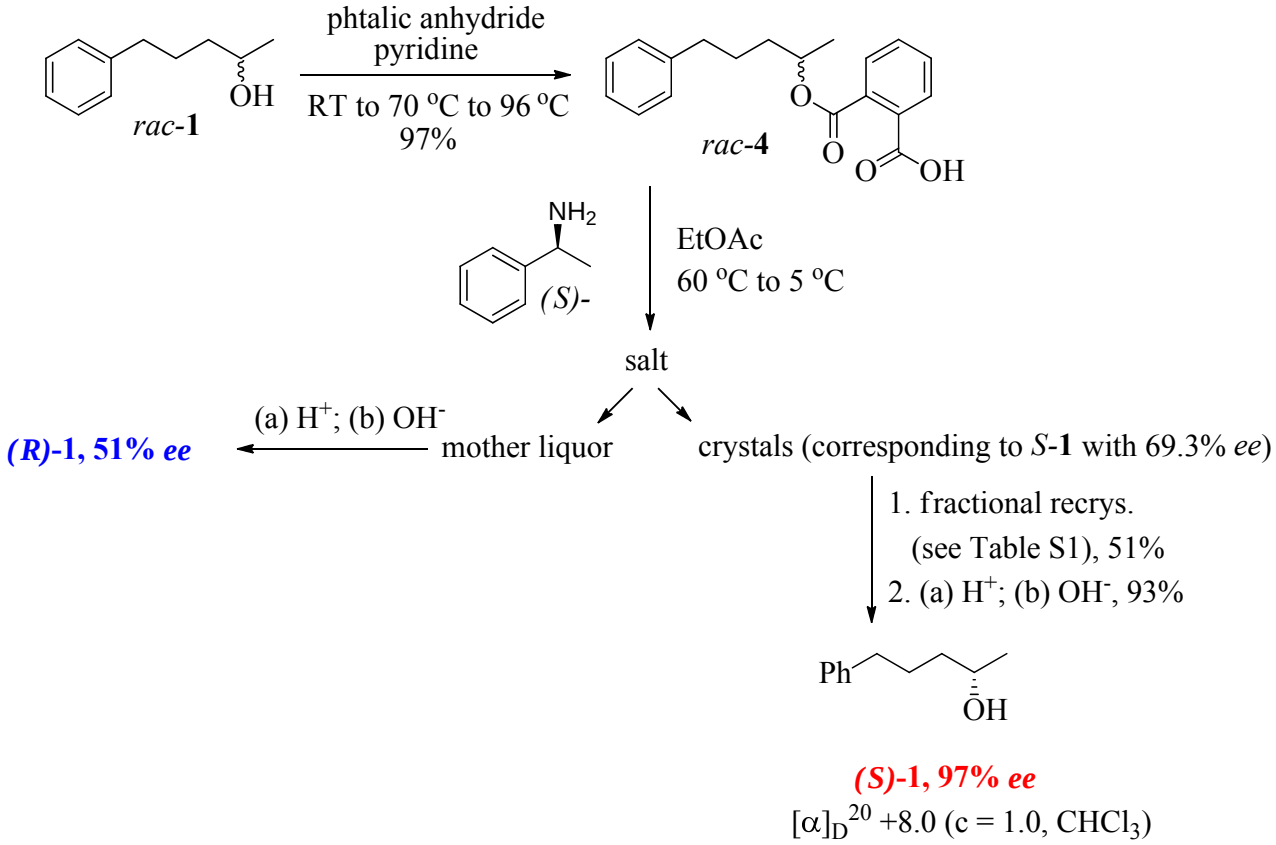
General

Solvents were dried by passing through the columns of molecular sieves in a solvent purification system (Innovative Technology Inc.). Unless otherwise stated, materials obtained from commercial suppliers were used without purification. Preparative separations were performed on silica gel (Geduran® Si 60) by column chromatography. TLCs were performed using silica gel 60 F_{254} aluminium sheets and visualised with molybdate dip or exposure to UV light (λ = 254 nm). ^{1}H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 125 MHz) spectra were recorded at 25 °C on Bruker Avance™ 400 or 500 MHz spectrometers. Chemical shifts (δ) were reported in ppm. ^{1}H NMR spectra were referenced to residual proton resonances in the deuterated $CDCl_3$ (δ_H = 7.26) or acetone-d_6 (δ_H = 2.05), and ^{13}C NMR spectra to $CDCl_3$ (δ_C = 77.0) or acetone-d_6 (δ_C = 29.8). Infrared spectra of neat solids or liquids were recorded on a Perkin Elmer FTIR spectrometer (Spectrum 100), equipped with a beam-condensing accessory. High-resolution mass spectra (HRMS) were recorded on Micromass Autospec Premier, Micromass LCT Premier, or VG Platform II spectrometers using chemical ionisation (CI) or electrospray ionisation (ESI) techniques at the Mass Spectroscopy Service of Imperial College London. $[\alpha]_D$ values were determined using an Optical Activity Ltd polarimeter at 20 ˚C. Melting points (m.p.) were determined using an Electrothermal Gallenhamp apparatus fitted with a calibrated thermometer with an error of ±2 °C, and are uncorrected. HPLC

chromatograms were recorded using Hewlett Packard HP1050 machines fitted with CHIRACEL™ or CHIRALPAK™ columns. Elemental analyses were performed by the Analytical Services at London Metropolitan University, U.K.

(±)-5-Phenyl-2-pentanol (*rac*-**1**),[1] methyl (*E*)-but-2-enoylcarbamate (**6**)[2] and [(*R*-BINAP)Pd(μ-OH)]$_2$[OTf]$_2$[3] were prepared by previously reported procedures.

Resolution of racemic 5-phenyl-2-pentanol, 1



Scheme S1 Resolution of monophtalate derivative **4** of racemic 5-phenyl-2-pentanol **1** via diastereomeric salts with (*S*)-α-methylbenzylamine.

5-Phenyl-2-pentanol phthalate, 4. Phthalic anhydride (5.36 g, 36.16 mmol) was added in one portion to a solution of (±)-5-phenyl-2-pentanol, *rac*-**1** (5.94 g, 36.16 mmol) in dry pyridine (6.01 g, 75.95 mmol). The reaction mixture was

stirred for 10 min at r.t., 20 min at 70 ˚C, then heated at 96 ºC for 4 h. When the reaction was complete (NMR) the mixture was diluted with H_2O (50 mL), EtOAc (50 mL) and 10% aq. HCl (150 mL). The organic layer was separated, and the aqueous layer extracted with EtOAc (2×50 mL). The combined organic layer was washed with 10% aq. HCl (50 mL), H_2O (50 mL), brine (50 mL), dried over $MgSO_4$, and evaporated in vacuo to give the desired phthalate derivative *rac*-**4** as a colourless viscous oil. Yield 10.94 g (97%); R_f = 0.6 (EtOAc); ν_{max}/cm^{-1}: 2937 m, 1695 s, 1600 m, 1580 m, 1495 m, 1453 m, 1412 m, 1380 m, 1355 m, 1284 s, 1125 s, 1071 s, 1038 m, 923 m, 855 m, 797 m, 742 s, 698 s, 639 m; δ_H (400 MHz, $CDCl_3$): 10.35 (1H, br s, CO_2H), 7.89 (1H, dd, *J* = 7.5, 1.6 Hz), 7.67 (1H, dd, *J* = 7.5, 1.6 Hz), 7.59 (1H, td, *J* = 7.5, 1.6 Hz), 7.55 (1H, td, *J* = 7.5, 1.6 Hz), 7.25 (2H, t, *J* = 7.4 Hz), 7.17–7.14 (3H, m), 5.24–5.16 (1H, m, C*H*Me), 2.63 (2H, t, *J* = 7.2, CH_2Ph), 1.81-1.58 (4H, m, 2×CH_2), 1.34 (3H, d, *J* = 6.2, Me); δ_c (100 MHz, $CDCl_3$): 172.4 (CO_2), 167.7 (CO_2), 142.1 (Cq), 133.9 (Cq), 132.2, 130.6, 129.9, 129.7 (Cq), 128.7, 128.4, 128.3, 125.8, 72.8 (CH), 35.6 (CH_2), 35.3 (CH_2), 27.1 (CH_2), 19.5 (Me); *m/z* (HRMS-ESI): found: 313.1419; calculated for $C_{19}H_{21}O_4$ $[M+H]^+$: 313.1440.

Preparation and resolution of the diastereomeric (*S*)-5-phenyl-2-pentanol phthalate·(*S*)-α-methylbenzylamine salt.

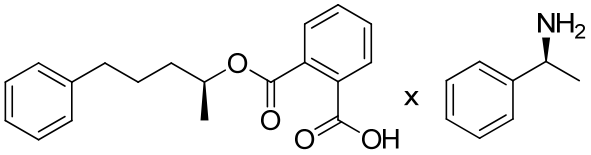


Table S1 Fractional recrystallisation of the diastereomeric salt.

	Fraction recrystallised	Solvent	*ee*, %* (crystals)	*ee*, %* (mother liquor)
1	Crystals after salt formation	EtOAc (15 mL/g)	(*S*)-**1**, 84	(*R*)-**1**, 6
2	Crystals after first recrystallization	EtOAc + MeOH (12 + 2 mL/g)	(*S*)-**1**, 97	(*S*)- **1**, 75.5
3	Mother liquor after second recrystallization	EtOAc	(*S*)-**1**, 87	(*S*)-**1**, 22
4	Crystals after third	EtOAc + MeOH	(*S*)-**1**, 97	-

recrystallization

*Determined by chiral HPLC of the alcohol **1**, using Chiracel OJ column (1.0 mL/min, 254 nm, 95:5 hexane/IPA)

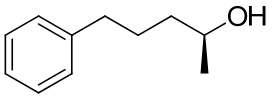
Preparation: (±)-5-Phenyl-2-pentanol phthalate *rac*-**4** (10.79 g, 34.53 mmol) was dissolved in EtOAc (35 mL) and heated up to 60 °C. A solution of (*S*)-α-methylbenzylamine (4.185 g, 34.53 mmol) was dissolved in EtOAc (35 mL), heated up to 60 °C and added to the warm phthalate solution with gentle stirring. When the addition was complete, stirring was discontinued and the solution was allowed to cool slowly down to r.t., left for 4 h, and then left in the fridge (5 ºC) overnight. The precipitate formed was filtered off and dried in air to give 6.22 g of the desired salt (see Scheme S1).*

Resolution: The collected salt was recrystallised from EtOAc (15 mL/g). This yielded 5.01 g of the product with 84% de, which was filtered off and dried in air (Table S1, entry 1). The collected crystals were then recrystallised from EtOAc + MeOH (12 + 2 mL/g) to provide 3.06 g of the desired (*S,S*)-salt in 97% de (Table S1, entry 2). The mother liquor collected was concentrated (1.95 g) and subsequently recrystallised from EtOAc (15 mL/g) and EtOAc + MeOH (12 + 2 mL/g) to give an additional 0.74 g of (*S,S*)-salt in 97% de (Table S1, entries 3 and 4 respectively). Total combined yield = 3.80 g (51%), a white flaky solid; $[\alpha]_D^{20}$ = +4.7 (c = 1.07, $CHCl_3$, 97% *de*); m.p. 131–132 ˚C; ν_{max}/cm^{-1}: 2927 m, 2858 m, 2672 w, 2524 w, 1708 s, 1622 m, 1526 s, 1495 s, 1453 m, 1397 s, 1386 s, 1301 m, 1269 s, 1187 m, 1162 m, 1137 s, 1092 m, 1072 s, 991 m, 829 m, 795 m, 762 s, 740 s, 711 s, 695 s, 652 m; δ_H (400 MHz, $CDCl_3$): 8.50 (br s, 3H, NH_2+CO_2H), 7.54 (1H, d, *J* = 7.0 Hz), 7.30–7.11 (13H, m), 4.99–4.92 (1H, m, OC*H*Me), 4.23 (1H, q, *J* = 6.7 Hz, CH–N), 2.56 (2H, t, *J* = 7.2 Hz, CH_2Ph), 1.72–1.49 (4H, m, 2×CH_2), 1.46 (3H, d, *J* = 6.7 Hz, NCH*Me*), 1.17 (3H, d, *J* = 6.2 Hz, OCH*Me*); δ_c (100 MHz, $CDCl_3$): 174.0 (CO_2), 168.1 (CO_2), 142.2 (Cq), 140.6 (Cq), 139.4 (Cq), 131.0 (Cq), 130.6, 128.7, 128.4, 128.35,

128.3, 128.2, 128.0, 127.8, 126.6, 125.8, 71.5 (OCH), 51.1 (NCH), 35.7 (CH_2), 35.5 (CH_2), 27.2 (CH_2), 21.7 (Me), 19.8 (Me); Anal. calcd. for $C_{27}H_{31}NO_4$: C, 74.80; H, 7.21; N, 3.23%. Found: C, 74.74; H, 7.16; N, 3.18%.

***Note:** The discarded mother liquors were combined and used further for the recovery of the starting chiral (*S*)-α-methylbenzylamine.

(*S*)-5-Phenyl-2-pentanol, (*S*)-1.



(S)-

1.5M aq. HCl (65 mL) was added to a solution of the isolated (*S*)-5-phenyl-2-pentanol phthalate (*S*)-α-methylbenzylamine salt (3.80 g, 8.77 mmol) in Et_2O (65 mL), and the reaction mixture was vigorously stirred for 5 min at r.t. The ethereal layer was separated, washed with 1.5M aq. HCl (2 × 65 mL), dried over $MgSO_4$ and concentrated to give 2.74 g (100%) of phthalate (*S*)**-4** as a colourless viscous oil; $[\alpha]_D^{20}$ = +36.8 (c = 0.87, $CHCl_3$) at 97% *ee*. The combined aqueous phases were concentrated in vacuum to recover (*S*)-α-methylbenzylamine hydrochloride in a quantitative yield (2.73 g, 100%). The obtained phthalate (*S*)**-4** was suspended in 3.75 M aq. NaOH (35 mL), refluxed for 5 min, cooled down to r.t. and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (hexane/ether = 1:1) to afford the desired alcohol (*S*)**-1** as a colourless oil (1.34 g, 93%). R_f = 0.40 (hexane/ether = 1:1); Chiral HPLC (Chiracel OJ column, 1.0 mL/min, 254 nm, 95/5 hexane:IPA): t_R = 9.36 (*S*-isomer), 11.9 (*R*-isomer) min; $[\alpha]_D^{20}$ = +8.0 (c = 1.0; $CHCl_3$, 97% *ee*) {lit.[1] $[\alpha]_D^{20}$ = +8.45 (c = 1.0, $CHCl_3$)}; ν_{max}/cm^{-1}: 3340 m, 3027 w, 2966 m, 2932 m, 2859 m, 1604 w, 1496 m, 1453 m, 1373 m, 1311 w, 1177 w, 1127 m, 1088 m, 1011 m, 941 m, 862 w, 799 w, 747 s, 697 s; δ_H (400 MHz, $CDCl_3$): 7.30–7.25 (2H, m), 7.20–7.15 (3H, m), 3.85–3.77 (1H, m, CH),

2.63 (2H, t, J = 7.7 Hz, CH_2Ph), 1.80–1.41 (5H, m, 2×CH_2 and OH), 1.18 (3H, d, J = 6.1 Hz, Me); δ_c (100 MHz, $CDCl_3$): 142.4 (Cq-Ph), 128.4 (CH-Ph), 128.3 (CH-Ph), 125.8 (CH-Ph), 68.1 (CH), 38.9 (CH_2), 35.9 (CH_2), 27.6 (CH_2), 23.6 (Me); *m/z* (HRMS-CI): found: 182.1549; calculated for $C_{11}H_{20}NO$ $[M+NH_4]^+$: 182.1545.

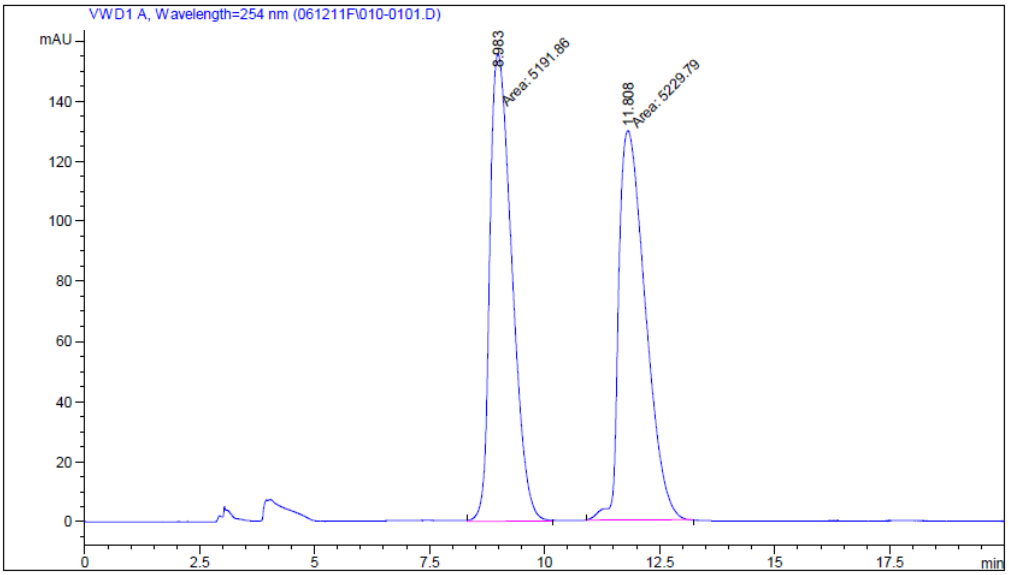


Figure S1. Chiral HPLC chromatogram of (*Rac*)-**1.**

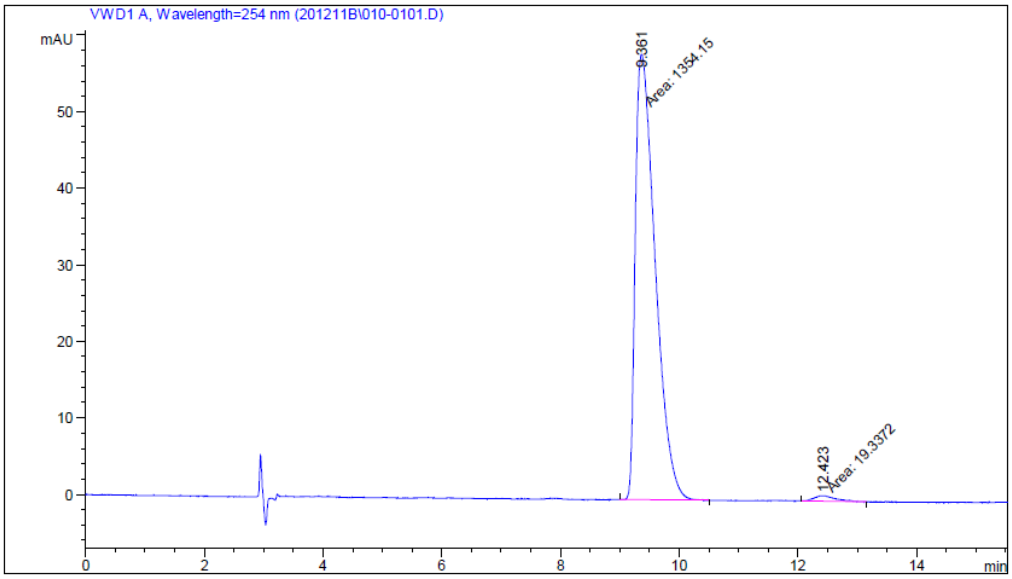
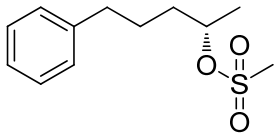
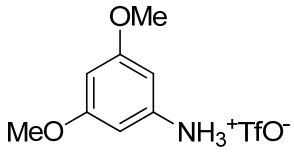


Figure S2 Chiral HPLC chromatogram of (*S*)-**1** after resolution (97% *ee*).

(*S*)-5-phenyl-2-pentanol mesylate, 5.

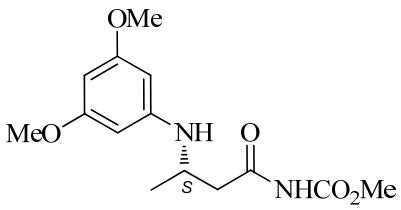


(*S*)-5-Phenyl-2-pentanol (*S*)-**1** (0.739 g, 4.50 mmol) and methanesulfonyl chloride (0.567 g, 4.95 mmol) were dissolved in dry THF (6 mL) under a dry N_2 atmosphere. The solution was cooled to 0 °C, before triethylamine (0.726 g, 9.0 mmol) was added dropwise. The reaction mixture was then allowed to warm up to r.t. and stirred for 1 h. When the reaction was complete (TLC), the mixture was diluted with Et_2O (20 mL), washed with H_2O (3×10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the desired mesylate **5** (1.054 g, 97%) as pale-yellow oil, which solidified upon standing. $[\alpha]_D^{20}$ = +4.6 (c = 1.72, $CHCl_3$); m.p. 29.0–30.5 ˚C; ν_{max}/cm^{-1}: 3034 w, 2987 w, 2939 w, 2859 w, 1603 m, 1495 m, 1456 m, 1429 w, 1385 m, 1360 m, 1335 s, 1270 w, 1171 s, 1127 m, 1088 m, 1010 w, 984 m, 971 s, 920 s, 895 s, 850 s, 820 m, 808 m, 794 s, 757 s, 705 s; δ_H (400 MHz, $CDCl_3$): 7.30–7.26 (2H, m), 7.21–7.16 (3H, m), 4.86–4.78 (1H, m, OC*H*Me), 2.97 (3H, s, $MeSO_2$), 2.65 (2H, t, *J* = 7.2 Hz, C*H*$_2$Ph), 1.82–1.60 (4H, m, 2×CH_2), 1.40 (3H, d, *J* = 6.3 Hz, Me); δ_c (100 MHz, $CDCl_3$): 141.7 (Cq), 128.4 (CH-Ph), 126.0 (CH-Ph), 80.0 (CH), 38.7 ($MeSO_2$), 36.1 (CH_2), 35.4 (CH_2), 26.9 (CH_2), 21.2 (Me); *m/z* (HRMS-CI): found: 260.1319; calculated for $C_{12}H_{22}NO_3S$: $[M+NH_4]^+$: 260.1320.



3,5-Dimethoxyaniline triflate. Trifluoromethanesulfonic acid (4.41 g, 29.4 mmol) was added dropwise to the solution of 3,5-dimethoxyaniline (4.50 g, 29.4 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C. The resulting suspension was allowed to warm up to r.t. and stirred for 1 h, before it was diluted with Et_2O (50 mL) and filtered through a sintered glass filter. The collected precipitate

was washed with Et_2O (35 mL) and dried under high vacuum to afford the desired triflate (8.59 g, 96%) as a white powder. m.p. 206.0–207.5 ˚C; ν_{max}/cm^{-1}: 2979 m, 2631 w, 1635 m, 1583 m, 1526 m, 1491 m, 1455 m, 1433 m, 1358 m, 1264 s, 1225 s, 1208 s, 1186 s, 1176 s, 1158 s, 1052 s, 1024 s, 926 m, 846 s, 831 m, 810 m, 765 m, 678 m, 628 s; δ_H (two rotamers) (400 MHz, acetone-d_6): 6.80 and 6.75 (2H, d, J = 2.2 Hz, H-2 and H-6), 6.69 and 6.61 (1H, d, J = 2.2 Hz, H-4), 3.85 and 3.84 (6H, s, 2×OMe), 3.03 (3H, br s, NH_2+H^+); δ_c (100 MHz, acetone-d_6): 161.8 (Cq), 136.6 (Cq), 102.9, 101.9, 55.4 (OMe); Anal. calcd. for $C_9H_{12}F_3NO_5S$: C, 35.65; H, 3.99; N, 4.62%. Found: C, 35.59; H, 3.88, N, 4.71%.



Methyl (*S*)-3-(3,5-dimethoxy-phenylamino)butanoyl carbamate, 7. Methyl (*E*)-but-2-enoylcarbamate (2.863 g, 20.0 mmol), 3,5-dimethoxyaniline triflate (9.10 g, 30.0 mmol) and [(*R*-BINAP)Pd(μ-OH)]$_2$[OTf]$_2$ catalyst (716 mg, 0.4 mmol) were cooled to –15 ºC under N_2 and dry THF (40 mL) was added in two portions. The reaction mixture was stirred at –10 ºC for 48 h, and then at 0 ˚C for 24 h. Upon completion (TLC), the reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (2×70 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated. The residual brown oil was purified on SiO_2 (hexane/EtOAc = 1:1) to give 5.49 g (93%) of product as a viscous yellow oil, which slowly crystallised on standing to give a tan powder (97.5% *ee*). The obtained crystalline material was recrystallised from dry toluene (12 mL/g), from which the adduct **7** was obtained in 74% yield with 100% *ee* from mother liquor. R_f = 0.3 (hexane/EtOAc = 1:1); Chiral HPLC (Chiracel OD-H column, 1.0 mL/min, 254 nm, 9:1 hexane/IPA): t_R = 30.6 (*S*-isomer), 38.3 (*R*-isomer) min; $[\alpha]_D^{20}$ = –

3.4 (c = 0.88, $CHCl_3$, 100% ee); m.p. 64–65 °C; ν_{max}/cm^{-1}: 3355 m, 3272 m, 2956 m, 2836 w, 1756 s, 1702 w, 1600 s, 1516 s, 1481 s, 1457 s, 1371 m, 1303 w, 1273 m, 1224 s, 1199 s, 1175 s, 1148 s, 1101 m, 1064 s, 1046 s, 984 m, 929 m, 806 m, 780 s, 770 s, 685 s; δ_H (400 MHz, $CDCl_3$): 7.88 (1H, br s, $NHCO_2$), 5.89 (1H, t, *J* = 2.1 Hz, H-4'), 5.82 (2H, d, *J* = 2.1 Hz, H-2' and H-6'), 4.00–3.96 (1H, m, H-3), 3.85 (1H, br s, NH), 3.76 (3H, s, CO_2Me), 3.74 (6H, s, 2×OMe), 3.05 (1H, dd, *J* = 15.8, 5.9 Hz, H-2), 2.87 (1H, dd, *J* = 15.8, 5.9 Hz, H-2), 1.29 (3H, d, *J* = 6.3 Hz, Me); δ_c (100 MHz, $CDCl_3$): 172.6 (CO_2), 161.8 (C-3'+C-5'), 152.2 (Cq), 148.7 (Cq), 92.5 (C-2' and C-6'), 90.2 (C4'), 55.2 (2×OMe), 53.1 (OMe), 46.0 (CHN), 42.2 (CH_2), 20.8 (Me); *m/z* (HRMS-ESI): found: 297.1454; calculated for $C_{14}H_{21}N_2O_5$ $[M+H]^+$: 297.1450.

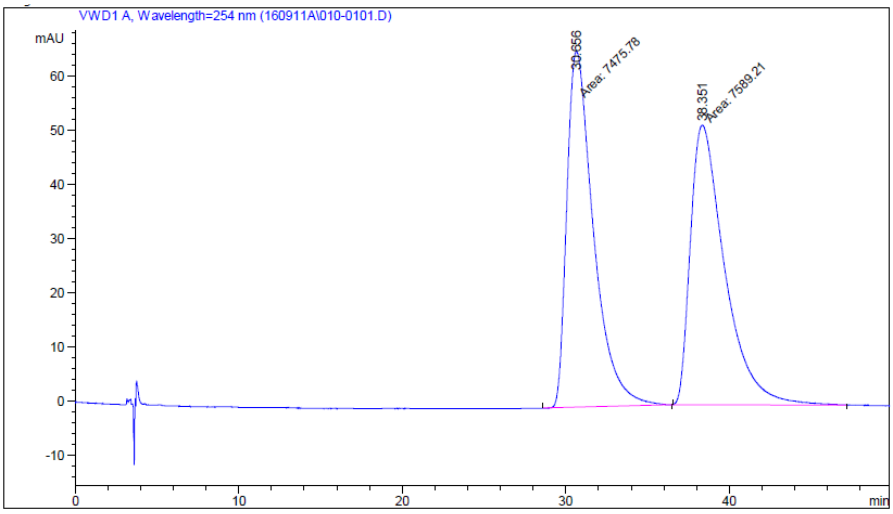


Figure S3 Chiral HPLC chromatogram of (*rac*)-**7**.

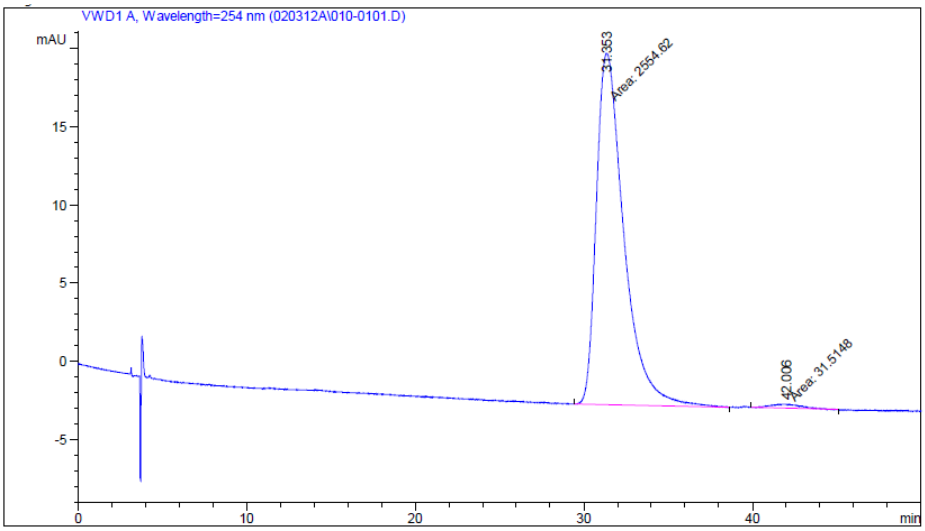


Figure S4 Chiral HPLC chromatogram of (*S*)-**7** after reaction (97.5% *ee*).

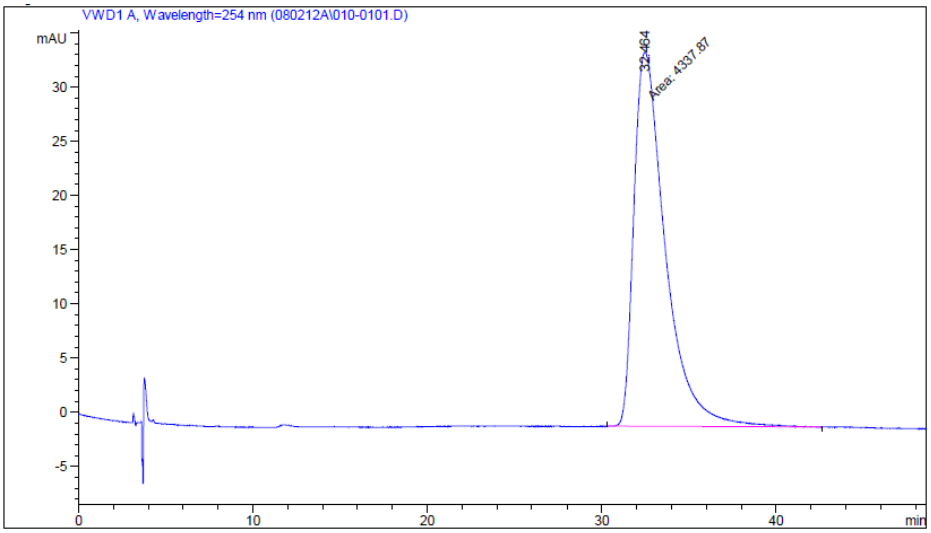
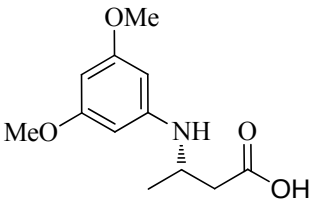
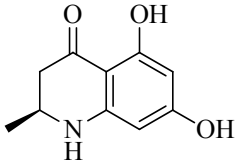


Figure S5 Chiral HPLC chromatogram of the Michael adduct recovered from the mother liquor after recystallisation (100% *ee*).

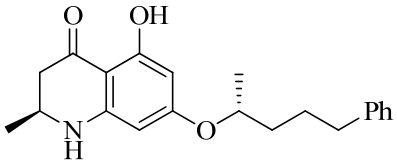


(*S*)-3-(3,5-Dimethoxy-phenylamino)butanoic acid, 8. Methyl (*S*)-3-(3,5-dimethoxy-phenylamino)butanoyl carbamate **7** (1.00 g, 3.37 mmol) was dissolved in dry MeOH (10 mL), to which a 1 M KOH/MeOH solution (6.7 mL) was added dropwise. The reaction mixture was stirred for 3 h at ambient temperature and then concentrated *in vacuo*. The residue was dissolved in 5 mL of H_2O and washed with Et_2O (3 × 10 mL). The aqueous layer was then acidified to pH 5–6 and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated to give 0.67 g (83%) of **8** as a viscous yellow oil. $[\alpha]_D^{20}$ = +22.2 (c = 0.54, $CHCl_3$); ν_{max}/cm^{-1}: 3365 w, 2966 m, 2841 w, 1707 m, 1593 s, 1516 m, 1456 m, 1416 m, 1292 m, 1254 m, 1201 s, 1174 s, 1147 s, 1059 s, 981 m, 926 m, 809 s, 683 m; δ_H (400 MHz, $CDCl_3$): 6.88 (2H, br s, CO_2H and NH), 5.92 (1H, t, *J* = 2.2 Hz, H-4'), 5.84 (2H, d, *J* = 2.2 Hz, H-2' and H-6'), 3.95–3.84

(1H, m, C*H*N), 3.75 (6H, s, 2×OMe), 2.66 (1H, dd, *J* = 15.5, 5.7 Hz, H-2), 2.50 (1H, dd, *J* = 15.5, 6.5 Hz, H-2), 1.30 (3H, d, *J* = 6.5 Hz, Me); δ_c (100 MHz, $CDCl_3$): 176.4 (CO_2), 161.8 (C-3'+C-5'), 148.3 (C-1'), 92.9 (C-2'+C-6'), 90.7 (C-4'), 55.2 (OMe), 46.3 (CHN), 40.5 (CH_2), 20.6 (Me); *m/z* (HRMS-ESI): found: 240.1237; calculated for $C_{12}H_{18}NO_4$ $[M+H]^+$: 240.1236.



(*S*)-5,7-Dihydroxy-2-methyl-2,3-dihydroquinolin-4(1*H*)-one, 2. Under a N_2 atmosphere, the β-aminoacid derivative **8** (1.042 g, 4.36 mmol) was dissolved in a mixture of AcOH/HBr (78 mL; 1:1 v/v) and refluxed for 1.5 h. After cooling to r.t., it was concentrated under reduced pressure. The residue was quenched with brine (7 mL), basified to pH 6–7 and extracted with EtOAc (4 × 30 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated. The residue was triturated with ether to afford the desired compound **2** (0.720 g, 86%) as air-sensitive yellow crystals. $[\alpha]_D^{20}$ = –141.5 (c = 0.65, MeOH); m.p. 153–155 ˚C; R_f = 0.3 (hexane/EtOAc = 3:2); ν_{max}/cm^{-1}: 3377 m, 3108 m, 1634 s, 1591 s, 1521 s, 1463 s, 1408 m, 1379 m, 1355 s, 1282 s, 1258 s, 1124 s, 1089 m, 1039 m, 908 m, 808 s, 766 s, 750 s, 658 m, 634 m; δ_H (400 MHz, acetone-d_6): 12.70 (1H, s, OH), 9.08 (1H, s, OH), 6.00 (1H, br s, NH), 5.71 (1H, d, *J* = 2.1 Hz, H-6 or H-8), 5.58 (1H, d, *J* = 2.1 Hz, H-6 or H-8), 3.75–3.66 (1H, m, H-2), 2.95 (3H, s, Me), 2.49 (1H, ddd, *J* = 16.5, 4.5, 1.4 Hz, H-3), 2.39 (1H, dd, *J* = 16.5, 12.4 Hz, H-3), 1.27 (3H, d, *J* = 6.3 Hz, Me); δ_c (100 MHz, acetone-d_6): 197.1 (C=O), 165.8 (Cq), 165.2 (Cq), 154.8 (Cq), 100.7 (Cq), 92.1 (C-6 or C-8), 91.2 (C-6 or C-8), 48.1 (C-2), 44.1 (CH_2), 20.2 (Me); *m/z* (HRMS-ESI): found: 194.0816; calculated for $C_{10}H_{12}NO_3$ $[M+H]^+$: 194.0817.



(*S*)-5-Hydroxy-2-methyl-7-[(*R*)-5-phenyl-2-pentyloxy]-2,3-dihydroquinolin-4(1*H*)-one, 9. Under a N_2 atmosphere, a mixture of **2** (0.367 g, 1.90 mmol), mesylate **5** (0.483 g, 2.00 mmol) and K_2CO_3 (anhydrous) (0.552 g, 3.99 mmol) was dissolved in dry DMF (3 mL). The suspension was stirred at 80–82 ºC for 2.5 h. On completion (TLC), the reaction mixture was cooled down to r.t., diluted with H_2O (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (5 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting brown oil was purified by column chromatography (hexane/EtOAc = 4:1, R_f = 0.30) to afford 0.565 g (88%) of **9** as a viscous pale-yellow oil. Chiral HPLC (Chiralpak AD–H column, 1.0 mL/min, 230 nm; 9:1 hexane/IPA): t_R = 12.8 min, 15.2 (epimer); $[\alpha]_D^{20}$ = –91 (c = 0.44, $CHCl_3$, 97% *ee*); ν_{max}/cm^{-1}: 3367 m, 3027 w, 2931 m, 2860 w, 1638 s, 1594 s, 1571 s, 1511 m, 1495 m, 1452 m, 1396 m, 1380 m, 1350 s, 1286 s, 1266 m, 1208 m, 1158 s, 1130 s, 1078 m, 1010 m, 909 m, 812 s, 747 s, 698 s, 660 m, 628 m; δ_H (400 MHz, $CDCl_3$): 12.54 (1H, s, OH), 7.30–7.26 (2H, m, Ph), 7.20–7.16 (3H, m, Ph), 5.76 (1H, d, *J* = 2.2 Hz, H-8 or H-6), 5.54 (1H, d, *J* = 2.2 Hz, H-8 or H-6), 4.39–4.31 (1H, m, OC*H*Me), 4.20 (1H, br s, NH), 3.77–3.68 (1H, m, H-2), 2.63 (2H, t, *J* = 7.3 Hz, CH_2Ph), 2.56 (1H, ddd, *J* = 16.5, 4.2, 1.2 Hz, H-3), 2.46 (1H, dd, *J* = 16.5, 12.4 Hz, H-3), 1.80–1.55 (4H, m, 2×CH_2), 1.30 (3H, d, *J* = 6.3 Hz, Me), 1.27 (3H, d, *J* = 6.1 Hz, OCH*Me*); δ_c (100 MHz, $CDCl_3$): 197.1 (C=O), 166.2 (Cq), 165.2 (Cq), 153.4 (Cq), 142.1 (Cq), 128.4 (CH-Ph), 128.34 (CH-Ph), 125.84 (CH-Ph), 101.6 (Cq), 92.6 (C-8 or C-6), 91.8 (C-8 or C-6), 73.8 (O*C*HMe), 48.5 (C-2), 44.6 (C-3), 35.8 (CH_2), 35.7 (*C*H_2Ph), 27.2 (CH_2), 21.3 (Me-2), 19.8 (OCH*Me*); HRMS (ESI) *m/z*: found: 340.1900; calculated for $C_{21}H_{26}NO_3$ $[M+H]^+$: 340.1913.

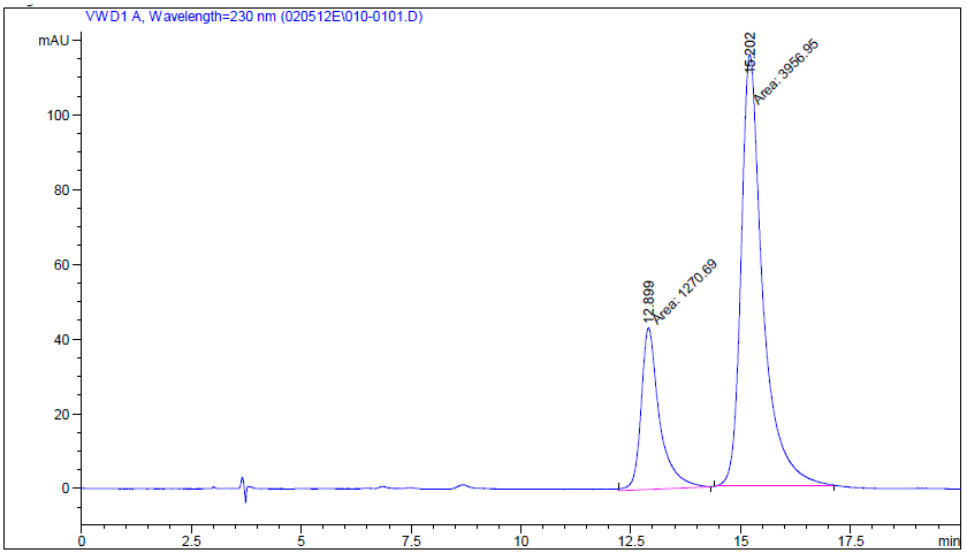


Figure S6. Chiral HPLC chromatogram of *epi*-**9** in 51% *ee* (sample prepared using optically pure **2** and (*R*)-**5** with 51% *ee*)

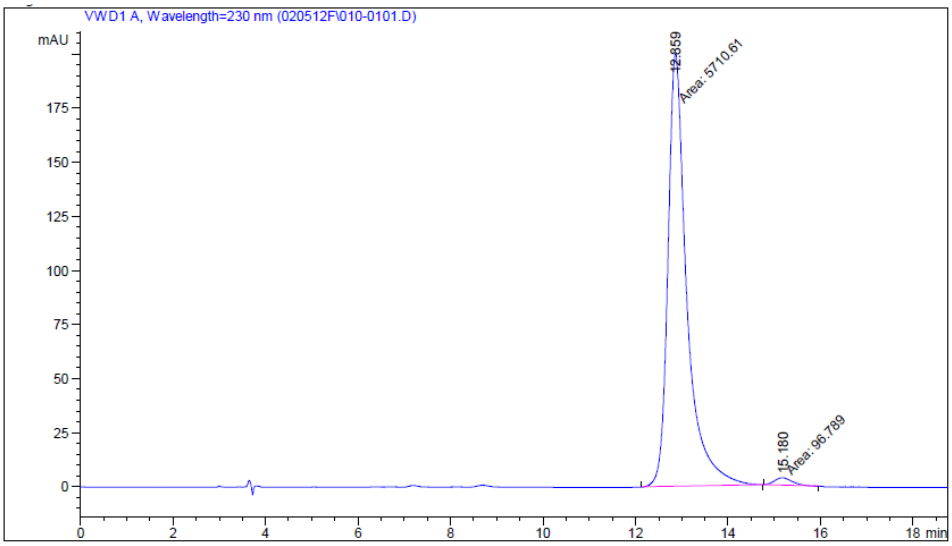
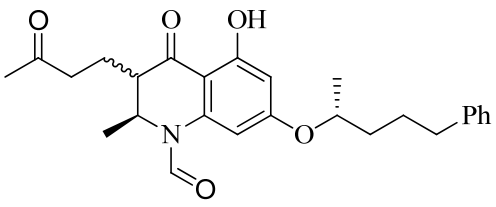


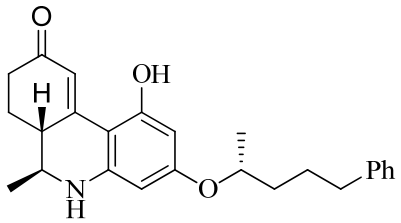
Figure S7 Chiral HPLC chromatogram of **9** (97% *ee*, prepared from optically pure **2** and (*S*)-**5** with 97% *ee*)



(2*S*)-1-Formyl-5-hydroxy-2-methyl-4-oxo-3-(3-oxobutyl)-7-[(*R*)-5-phenyl-2-pentyloxy]-2,3-dihydroquinoline, 10. Sodium hydride (0.230 g, 5.75 mmol;

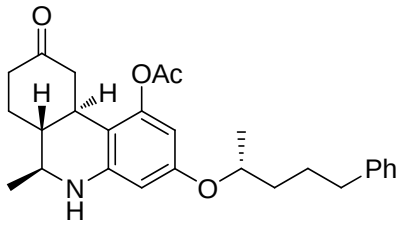
60% in mineral oil) was washed with dry hexane (3 × 5 mL) under an atmosphere of dry N_2 and suspended in dry toluene (5 mL). Methyl formate (2.76 g, 46.0 mmol) was added, and the reaction mixture was stirred for 5 min at r.t., before a solution of **9** (0.391 g, 1.15 mmol) in dry toluene (5 mL) was added dropwise. The resulting suspension was stirred at r.t. for 20 h. On completion (TLC) the bright-orange mixture was acidified to pH = 3–4 by the addition of 1M aq. HCl (12 mL), and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The orange oil residue (0.455 g) was dissolved in dry CH_2Cl_2 (10 mL) under a dry N_2 atmosphere. Methyl vinyl ketone (1.21 g, 17.3 mmol) was added, followed by triethylamine (58 mg, 0.58 mmol). The reaction mixture was stirred at r.t. for 20 h, concentrated *in vacuo* and subjected to the flash column chromatography (hexane/EtOAc = 1:1). The resulting colourless oil (0.485 g) contained a mixture of *bis*- and *mono*-formylated products (ratio = 13:1, determined by ^{1}H NMR) was dissolved in MeOH (10 mL), cooled down to 0 ºC and K_2CO_3 (anhydrous) (0.100 g, 0.73 mmol) was added in one portion. Stirring was continued at 0 ºC for 4 h, after which the reaction mixture was filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc = 2:1 to 1:1) to afford **10** as a viscous colourless oil (0.382 g, 76% over three steps). R_f = 0.45 (hexane/EtOAc = 1:1); $[\alpha]_D^{20}$ = +53.3 (c = 0.75, $CHCl_3$); ν_{max}/cm^{-1}: 2935 m, 1715 m, 1683 s, 1615 s, 1569 s, 1496 m, 1448 m, 1412 m, 1370 s, 1286 s, 1253 s, 1216 s, 1166 s, 1130 m, 1079 m, 1029 m, 977 w, 925 w, 810 s, 715 s; δ_H (400 MHz, $CDCl_3$) (mixture of stereoisomers, ratio = 3:2): 12.72 and 12.69 (1H, s, OH), 8.85 and 8.77 (1H, s, CHO), 7.30–7.26 (2H, m, Ph), 7.20–7.16 (3H, m, Ph), 6.18–6.15 (2H, m, H-6 and H-8), 5.16–5.09 and 5.03–4.98 (1H, m, H-2), 4.47–4.36 (1H, m), 2.86–2.78 (1H, m), 2.66–2.16 (5H, m), 2.19 and 2.14 (3H, s, OMe), 1.87–1.52 (5H, m), 1.32 and 1.32 (3H, d, J = 6.0 Hz, Me), 1.25 and 1.13 (3H, d, J = 6.9 Hz, Me); δ_c (100 MHz, $CDCl_3$): 207.7 (C=O), 207.2 (C=O),

200.0 (C=O), 199.4 (C=O), 166.4 (Cq), 166.0 (Cq), 165.61 (Cq), 165.57 (Cq), 160.3 (CH=O), 159.5 (CH=O), 141.9 (Cq), 141.3 (Cq), 128.39, 128.38, 125.9, 103.2 (Cq), 101.9 (Cq), 97.9, 97.8, 97.4, 97.3, 74.8 (O*C*HMe), 74.7 (O*C*HMe), 50.8, 49.1, 49.0, 48.5, 41.6 (CH_2), 40.0 (CH_2), 35.8 (CH_2), 35.7 (CH_2), 30.2, 30.1, 27.2 (CH_2), 24.6 (CH_2), 20.2 (CH_2), 19.6 (Me), 17.8 (Me), 12.7 (Me); *m/z* (HRMS-ESI): found: 438.2283; calculated for $C_{26}H_{32}NO_5$ $[M+H]^+$: 438.2280.



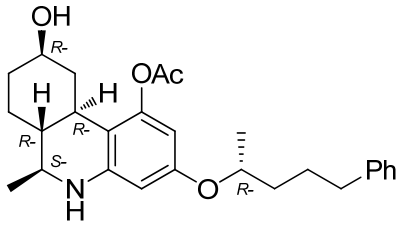
(6*S*,6a*R*)-5,6,6a,7-Tetrahydro-1-hydroxy-6-methyl-3-[(*R*)-5-phenyl-2-pentyloxy]-benzo[c]quinoline-9(8*H*)-one, 11. Sodium metal (0.626 g, 27.20 mmol) was dissolved in dry MeOH (42 mL) under a dry N_2 atmosphere. A solution of the diketone **10** (0.282 g, 0.64 mmol) in dry MeOH (10 mL) was added dropwise, and the reaction mixture was refluxed for 48 h. On completion (TLC), the reaction mixture was cooled down to r.t., quenched by the addition of acetic acid (1.63 g, 27.2 mmol) and concentrated *in vacuo*. The solid residue was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The brown oily residue contained ~5:1 mixture of *R*- and *S*- stereoisomers at C-6a (^{1}H NMR). It was subjected to the column chromatography (hexane/EtOAc = 1:1) to afford **11** as a single isomer, as a bright yellow powder (0.176 g, 70%). A solution of the title compound was found to decompose in air slowly at room temperature. R_f = 0.25 (hexane/EtOAc = 1:1); $[\alpha]_D^{20}$ = –282.7 (c = 0.75, $CHCl_3$); m.p. 183–184 ºC; ν_{max}/cm^{-1}: 3420 w, 3365 w, 2942 m, 2861 m, 1596 m, 1558 s, 1478 s, 1455 m, 1443 s, 1411 m, 1365 m, 1353 m, 1293 m, 1236 s, 1211 s, 1163 s, 1118 s, 1080 m, 1037 m, 954 w, 890 s, 800 s, 780 w, 630 s; $\underline{\delta_H}$ (400 MHz, $CDCl_3$): 11.15 (1H, s, OH), 7.91 (1H, d, *J* = 1.5 Hz, =CH), 7.29–7.25 (2H, m, Ph), 7.19–7.15

(3H, m, Ph), 6.10 (1H, d, *J* = 2.4 Hz, H-2 or H-4), 5.55 (1H, d, *J* = 2.4 Hz, H-2 or H-4), 4.39–4.32 (1H, m, OC*H*Me), 4.06 (1H, s, NH), 3.12–3.05 (1H, m, H-6), 2.63 (2H, t, *J* = 7.2 Hz, CH_2Ph), 2.61–2.56 (1H, m), 2.48–2.31 (2H, m), 2.25–2.18 (1H, m), 1.82–1.54 (5H, m), 1.29 (3H, d, *J* = 6.2 Hz, Me), 1.26 (3H, d, *J* = 6.1 Hz, Me); δ_c (100 MHz, $CDCl_3$): 203.1 (C=O), 162.2 (Cq), 162.0 (Cq), 157.5 (Cq), 150.4 (Cq), 142.3 (Cq), 128.5 (CH-Ph), 128.3 (CH-Ph), 125.7 (CH-Ph), 118.9 (C-10), 101.1 (C-10a), 95.1 (C-2 or C-4), 92.1 (C-2 or C-4), 73.2 (O*C*HMe), 51.7 (C-6), 42.9 (C-6a), 36.0 (CH_2), 35.9 (CH_2), 35.7 (CH_2), 27.2 (CH_2), 25.8 (CH_2), 19.9 (2×Me); *m/z* (HRMS-ESI): found: 392.2230; calculated for $C_{25}H_{30}NO_3$ $[M+H]^+$: 392.2226.



(6*S*,6a*R*,10a*R*)-5,6,6a,7,10,10a-Hexahydro-1-acetoxy-6-methyl-3-[(*R*)-5-phenyl-2-pentyloxy]-benzo[c]quinoline-9(8*H*)-one, 12. Ammonia gas was condensed at –70 ºC into an oven-dried two-neck round bottom flask to give 8 mL of liquid ammonia. A piece of lithium wire (0.022 g, 3.17 mmol) was added and the mixture was stirred for 15 min at –70 ºC under a dry N_2 atmosphere, forming a dark blue solution. A solution of the enone **11** (0.124 g, 0.32 mmol) in dry THF (2 mL) was then added dropwise, and stirring was continued for 20 min at –70 ºC. The reaction was quenched by the addition of dry NH_4Cl (0.300 g). The cooling bath was removed, and the reaction mixture was allowed to reach r.t., whereupon it was gently heated at 40 ˚C to remove residual ammonia. The resulting yellowish semi-solid was partitioned between EtOAc (10 mL) and H_2O (10 mL). The organic phase was separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic phases were washed with H_2O (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford 0.117 g of a white solid. This was dissolved in dry CH_2Cl_2 (3 mL) under a N_2 atmosphere,

followed by the addition of 4-DMAP (0.043 g, 0.35 mmol) and triethylamine (35 mg, 0.35 mmol). The resulting solution was cooled to 0 ºC, and acetic anhydride (0.036 g, 0.35 mmol) was added dropwise. Stirring was continued at 0 ºC for 1 h. Upon completion (TLC), the mixture was diluted with CH_2Cl_2 (5 mL) and poured into H_2O (10 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with 5% aq. $NaHCO_3$ (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The viscous brown oily residue was found to contain ~2:1 mixture of the *trans*-/*cis*- stereoisomers (^{1}H NMR), which was subjected to the column chromatography (hexane/EtOAc = 2:1) to afford **12** (76 mg, 55% over two steps) as the *trans*-isomer, as a colourless foam. Attempts to isolated the *cis*-isomer was unsuccessful. R_f = 0.27 (hexane/EtOAc = 2:1); $[\alpha]_D^{20}$ = –129.2 (c = 0.65, $CHCl_3$); ν_{max}/cm^{-1}: 3382 w, 2932 m, 2868 m, 1763 m, 1706 s, 1619 s, 1579 m, 1510 m, 1479 m, 1454 m, 1368 m, 1323 m, 1302 m, 1265 m, 1192 s, 1173 s, 1155 s, 1123 s, 1081 s, 1027 s, 892 m, 826 m, 750 m; δ_H (400 MHz, $CDCl_3$): 7.29–7.25 (2H, m, Ph), 7.19–7.16 (3H, m, Ph), 5.98 (1H, d, *J* = 2.4 Hz, H-2 or H-4), 5.96 (1H, d, *J* = 2.4 Hz, H-2 or H-4), 4.26–4.19 (1H, m, OC*H*Me), 3.79 (1H, br s, NH), 3.27 (1H, ddd, *J* = 2.0, 3.0, 14.8 Hz), 3.05 (1H, dq, *J* = 6.2, 8.7, H-6), 2.73 (1H, ddd, *J* = 3.3, 10.6, 13.4 Hz), 2.62 (2H, t, *J* = 7.2 Hz, C*H*$_2$Ph), 2.55 (1H, ddt, *J* = 2.0, 5.4, 15.4 Hz), 2.39 (1H, ddd, *J* = 7.3, 12.5, 15.4 Hz), 2.30 (3H, s, OAc), 2.25–2.16 (2H, m), 1.81–1.53 (5H, m), 1.41 (1H, qd, *J* = 5.5, 12.5 Hz), 1.23 (6H, virtual t, *J* = 6.3, 6.2 Hz, 2×Me); δ_c (100 MHz, $CDCl_3$): 210.7 (C=O), 169.0 (C(O)Me), 157.8 (Cq), 150.8 (Cq), 147.6 (Cq), 142.3 (Cq), 128.4 (CH-Ph), 128.3 (CH-Ph), 125.8 (CH-Ph), 108.3 (Cq), 100.3 (C-2 or C-4), 99.4 (C-2 or C-4), 73.7 (O*C*HMe), 50.4 (C-6), 46.7 (CH_2), 46.1, 40.4 (CH_2), 38.9, 35.9 (CH_2), 35.7 (CH_2), 27.3 (CH_2), 27.1 (CH_2), 21.3 (C(O)*Me*), 19.9 (Me), 19.8 (Me); *m/z* (HRMS-ESI): found: 436.2, 75; calculated for $C_{27}H_{34}NO_4$ $[M+H]^+$: 436.2488.



(6*S*,6a*R*,9*R*,10a*R*)-5,6,6a,7,8,9,10,10a-Octahydro-1-acetoxy-9-hydroxy-6-methyl-3-[(*R*)-5-phenyl-2-pentyloxy]-benzo[c]quinoline (levonantradol). A solution of the ketone **12** (62 mg, 0.14 mmol) in a mixture of EtOH/THF (1:1 v/v, 2 mL) was cooled down to –70 ºC, whereupon sodium borohydride (16 mg, 0.43 mmol) was added in one portion, and the mixture was stirred at –60 ºC for 30 min. Upon completion (TLC), the mixture was quenched by the addition of sat. aq. NH_4Cl (2 mL), warmed to r.t., diluted with H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc = 1:1) to afford levonantradol (59 mg, 95%) as a colourless foam. R_f = 0.27 (hexane/EtOAc = 1:1); Chiral HPLC (Chiralpak AS column, 1.0 mL/min, 254 nm, 9:1 hexane/IPA): t_R = 21.3 min; $[\alpha]_D^{20}$ = –112.1 (c = 0.66, $CHCl_3$, 99% *ee*); ν_{max}/cm^{-1}: 3385 m, 2932 m, 2862 m, 1738 m, 1619 s, 1579 m, 1478 m, 1452 m, 1371 s, 1334 m, 1301 m, 1267 m, 1209 s, 1158 s, 1115 s, 1069 m, 1029 s, 893 m, 825 m; δ_H (500 MHz, $CDCl_3$): 7.22–7.18 (m, 2H, Ph), 7.12–7.09 (m, 3H, Ph), 5.84 (d, *J* = 2.6 Hz, 1H, H-2 or H-4), 5.83 (d, *J* = 2.6 Hz, 1H, H-2 or H-4), 4.19–4.11 (m, 1H, OC*H*Me), 3.68–3.61 (m, 2H, H-9 and NH), 2.93–2.86 (m, 1H, H-6), 2.85–2.78 (m, 1H, H-10), 2.55 (t, *J* = 7.3 Hz, 2H, CH_2Ph), 2.34–2.28 (m, 1H, H-10a), 2.21 (s, 3H, OAc), 2.08–2.06 (m, 1H, H-8), 1.90–1.85 (m, 1H, H-7), 1.74–1.56 (m, 3H, CH_2CH_2CH$_2$Ph), 1.53–1.45 (m, 1H, CH_2CH$_2$CH$_2$Ph), 1.36 (br s, 1H, OH), 1.32–1.22 (m, 1H, H-8), 1.18–1.05 (m, 2H, H-6a, H-10), 1.17 (d, 3H, *J* = 6.1 Hz, OCH*Me*), 1.08 (d, 3H, *J* = 6.2 Hz, Me-6), 1.04–0.94 (m, 1H, H-7); δ_c (125 MHz, $CDCl_3$): 169.0 (*C*(O)Me), 157.4 (C-3), 151.0 (C-1), 147.7 (NH-*C*-C-4), 142.3 (Cq-Ph), 128.4 (CH-Ph), 128.3 (CH-Ph), 125.7 (CH-Ph), 109.3 (C-

10a-*C*-C-1), 100.1 (C-2 or C-4), 99.3 (C-2 or C-4), 73.6 (O*C*HMe), 70.9 (C-9), 50.6 (C-6), 46.6 (C-6a), 40.1 (C-10), 38.3 (C-10a), 36.0 ($CH_2CH_2CH_2Ph$), 35.7 (CH_2Ph+C-8), 27.3 ($CH_2CH_2CH_2Ph$), 26.6 (C-7), 21.3 (C(O)CH_3), 20.0 (Me-6), 19.8 (OCH*Me*); *m/z* (HRMS-ESI): found: 438.2642; calculated for $C_{27}H_{36}NO_4$ $[M+H]^+$: 438.2644.

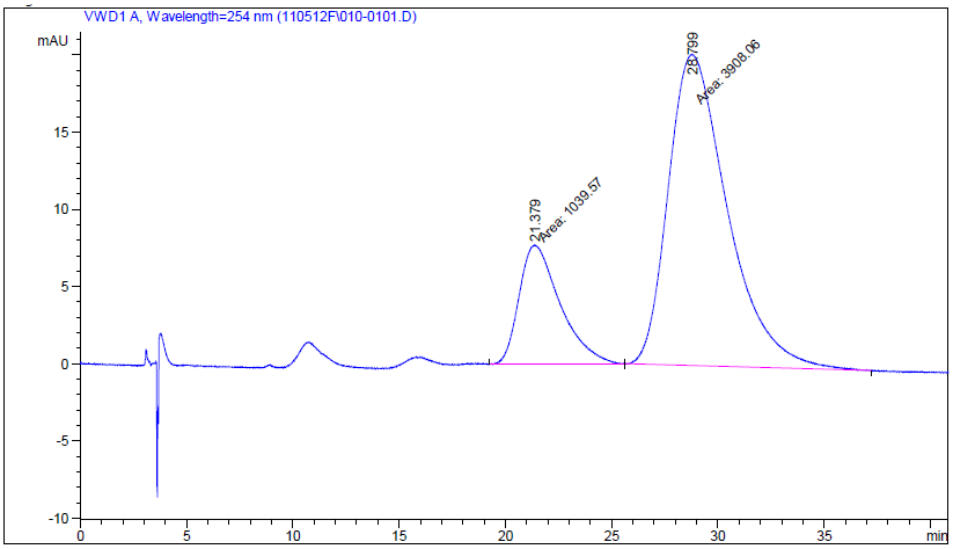


Figure S10. Chiral HPLC chromatogram of *epi*-levonantradol (58% *ee*, sample prepared from *epi*-**9** with 51% *ee*, see figure S6)

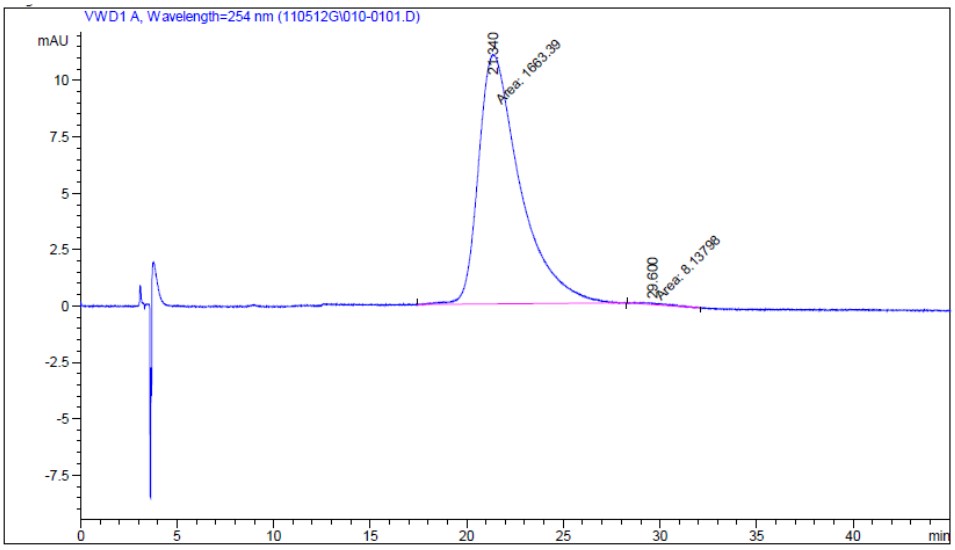
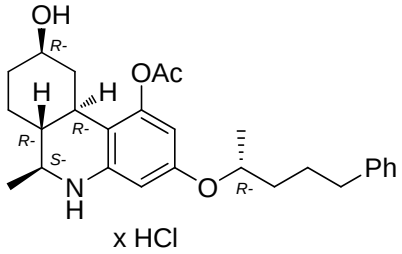
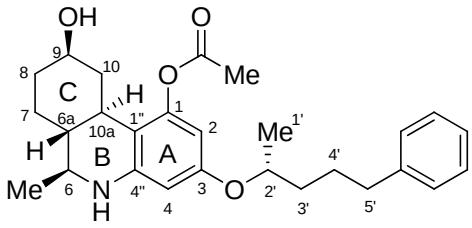


Figure S11 Chiral HPLC chromatogram of levonantradol (99% *ee*, prepared using **9** with 97% *ee*, see figure S7).



(6*S*,6a*R*,9*R*,10a*R*)-5,6,6a,7,8,9,10,10a-Octahydro-1-acetoxy-9-hydroxy-6-methyl-3-[(*R*)-5-phenyl-2-pentyloxy]-benzo[c]quinoline hydrochloride, levonantradol hydrochloride. 4M HCl in dry 1,4-dioxane (40 μL, 0.16 mmol) was added dropwise to a solution of levonantradol (35.0 mg, 0.08 mmol) in dry ether (4 mL) at 0 ºC. The resulting white suspension was effectively stirred for 10 min at r.t.; the precipitate formed was filtered off, washed with dry ether (2 × 5 mL) and dried in high vacuum (0.05 mmHg) to give levonantradol hydrochloride (35.7 mg, 94%) as an off-white powder. $[\alpha]_D^{25}$ = –94.3 (c = 0.35, MeOH), m.p. 119–120 ˚C {lit.[4] $[\alpha]_D^{20}$ = –98.57 (c = 0.351, MeOH), m.p. 120–125 ˚C}; ν_{max}/cm^{-1}: 3335 m, 2930 m, 2865 m, 2585 m, 1767 m, 1628 m, 1583 m, 1506 m, 1452 m, 1371 m, 1315 m, 1286 m, 1269 m, 1194 s, 1152 s, 1120 s, 1042 s, 1023 s, 893 m; ^{1}H NMR signals of the HCl salt are broad; δ_c (100 MHz, $CDCl_3$): 168.4 (*C*(O)Me), 157.3 (Cq), 150.8 (Cq), 142.4 (Cq), 128.6 (CH-Ph), 128.3 (CH-Ph), 125.6 (CH-Ph), 110.7 (C-2 and C-4), 106.9 (Cq), 74.4 (O*C*HMe), 70.3 (C-9), 54.8 (C-6), 44.1, 39.3 (CH_2), 38.2, 35.8 (CH_2), 35.5 (CH_2), 35.4 (CH_2), 27.3 (CH_2), 26.2 (CH_2), 21.3 (C(O)*C*H_3), 19.6 (Me), 16.7 (Me); *m/z* (HRMS-ESI): found: 438.2642; calculated for $C_{27}H_{36}NO_4$ $[M–Cl]^+$: 438.2644.

Table S1. NMR assignment of ^{1}H and ^{13}C resonances of levonantradol.[a]



H_α and H_β are methylene protons in ring C that are *anti-* and *syn-* to the OH substituent (at C-9), respectively.

^{1}H			**^{13}C**	
Assignment	δ_H *(observed)*/ppm	δ_H *(predicted)*/ppm	**Assignment**	δ_C/ppm
OAc	2.21 (3H, s)		C-1	151.0
H-2 & H-4	5.84 (1H, d, J = 2.6 Hz) 5.83 (1H, d, J = 2.6 Hz)	5.41, 5.67	OAc	169.0 (C=O), 21.3 (Me)
NH	3.65 (1H, br s, NH)		C-1''	109.3
H-6	2.89 (1H, dq, J = 9.4, 6.2 Hz)	2.71 ^{3}J(6-6a) = 8.7, ^{3}J(6-Me) = 6.0[b]	C-2 & C-4	100.1 and 99.3
Me	1.08 (3H, d, J = 6.2 Hz)		C-3	157.4
H-6a	1.13–1.18 (1H, m, overlapped with H-1')	0.74	C-4''	147.7
H-7α	0.99 (1H, dddd, J = 12.9, 12.7, 12.6, 3.6 Hz)	0.74 ^{2}J(7α-7β) = -13.2, ^{3}J(7α-8α) = 13.1, ^{3}J(7α-6a) = 11.4, ^{3}J(7α-8β) = 3.9.	C-6	50.6
H-7β	1.88 (1H, dddd, J = 12.9, 4.3, 3.7, 3.0 Hz)	1.62 ^{2}J(7β-7α) = -13.2, ^{3}J(7β-8α) = 4.5, ^{3}J(7β-6a) = 2.9, ^{2}J(7β-8β) = 3.3.	Me	20.0
H-8α	2.08–2.06 (1H, m)	1.72	C-6a	46.6
H-8β	1.27 (1H, dddd, J = 12.7, 12.5, 11.1, 4.3	0.99 ^{2}J(8β-8α) = -12.5,	C-7	26.6

	Hz)	^{3}(8β-7α) = 13.1, ^{3}J(8β-9) = 9.6, ^{3}J(8β-7β) = 4.5.		
H-9	3.68–3.61 (1H, m, overlapped with NH)	3.60	C-8	35.7
OH	1.36 (1H, br s)		C-9	70.9
H-10α	2.81 (1H, ddt, *J* = 12.4, 4.5, 2.4 Hz)	2.51 ^{2}J(10α-10β) = -13.2, ^{3}J(10α-9) = 4.4, ^{3}J(10α-10α) = 2.2, ^{3}J(10α-8α) = 1.9.	C-10	40.1
H-10β	1.12–1.05 (1H, m, overlapped with Me)	0.49	C-10a	38.3
H-10a	2.31 (1H, ddd, *J* = 11.7, 10.6, 2.4 Hz)	2.16 10a-10β = 11.1, 10a-6a = 10.0, 10a-10α = 2.2.	C-1’	19.8
H-1’	1.17 (3H, d, *J* = 6.0 Hz)		C-2’	73.6
H-2’	4.15 (1H, app. sextet, *J* = 6.0 Hz)		C-3’	36.0
H-3’ & H-4’	1.74–1.56 (3Hm m) 1.53–1.45 (1H, m)		C-4’	27.3
H-5’	2.55 (2H, t, *J* = 7.3 Hz, 2H)		C-5’	35.7
Ph	7.22–7.18 (2H, m) 7.12–7.09 (3H, m)		Ph	142.3 (*ipso*-C), 128.4, 128.3 (*meta*-CH), 125.7 (*para*-CH).

[a] Assignments made on the basis of ^{1}H, ^{13}C, dept135, COSY, HSQC, HMBC and NOESY experiments performed on 500 MHz Bruker Avance™ spectrometer at 25 °C; $CDCl_3$ was used as a solvent. [b] average of 3 predicted ^{3}J(HH) values of 3.4, 2.9 and 11.9 Hz.

NOE experiments for levonantradol

The relative stereochemistry of the octahydro-benzo[c]quinoline core was confirmed by three separate NOE experiments (500 MHz, $CDCl_3$):

1. Irradiation of H-6 proton at 2.97 ppm showed its proximity to H-7α (axial), H-9, H-10a and methyl group at C-6 (Figure S12).

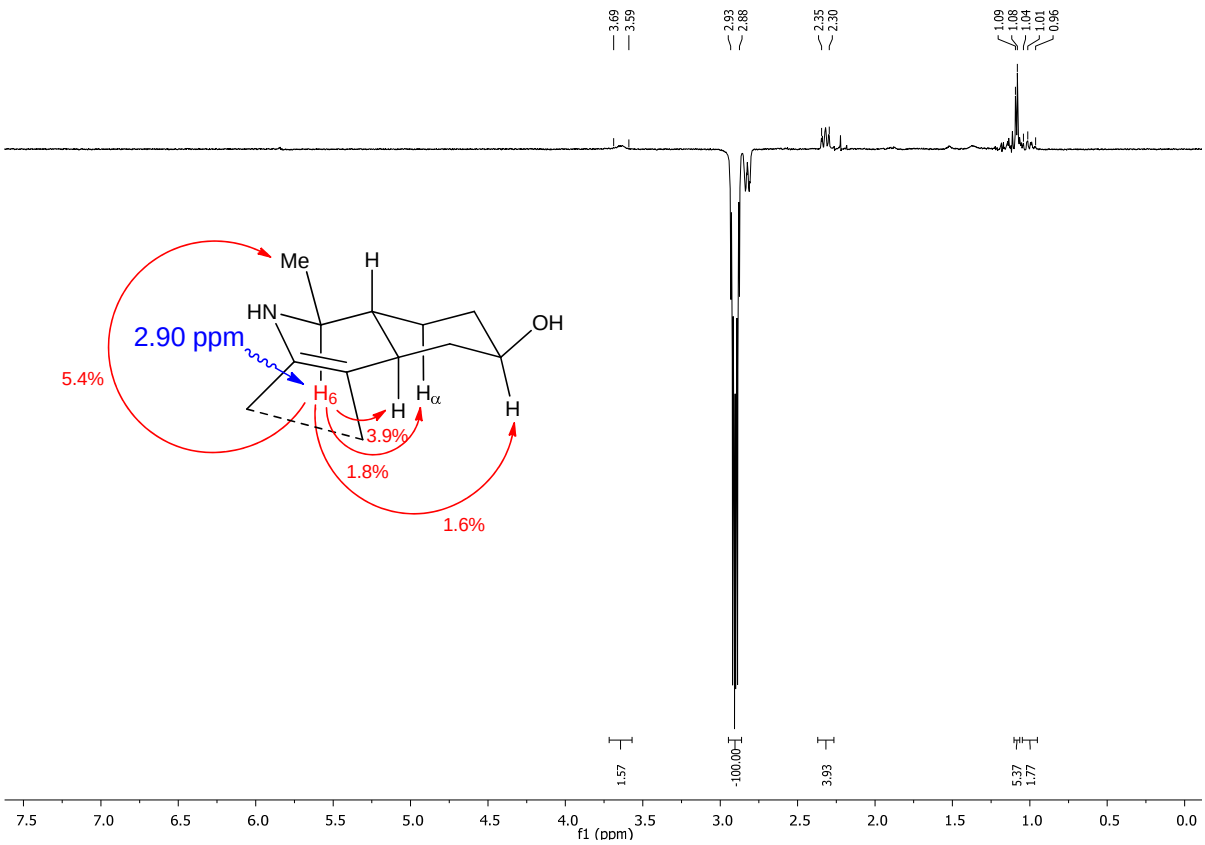


Figure S12 NOE values observed by irradiation of H-6.

2. Irradiation of H-9 proton at 3.65 ppm showed its proximity to H-10a, thus (Figure S13). This also allowed α-protons at C-7 (axial), C-8 (equatorial) and C-10 (equatorial) to be unambiguously located in ^{1}H NMR spectrum.

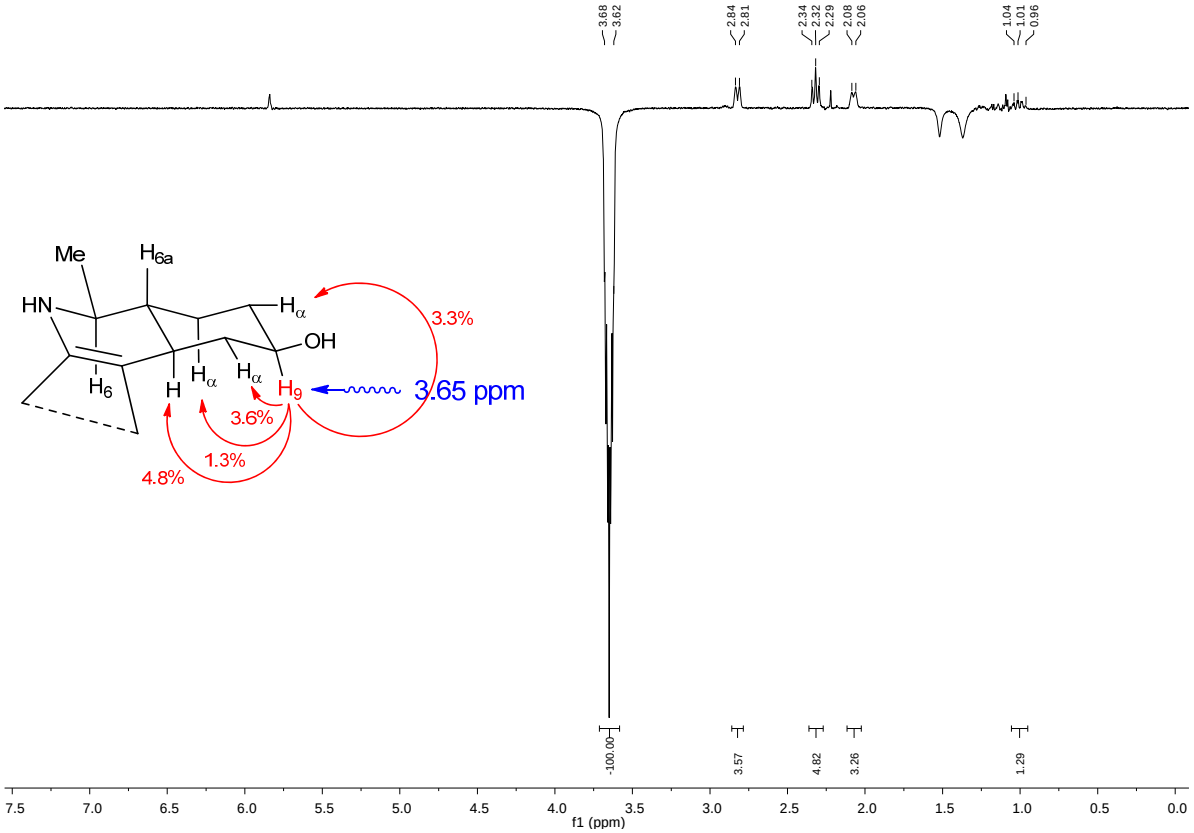


Figure S13 NOE values observed by irradiation of H-9, the remaining part of the molecule was omitted for clarity.

3. Irradiation of H-10a proton at 2.31 ppm showed its proximity to H-9 and H-6 (Figure S14). Correct assignments of α-protons at C-7 (axial) and C-10 (equatorial) were also confirmed.

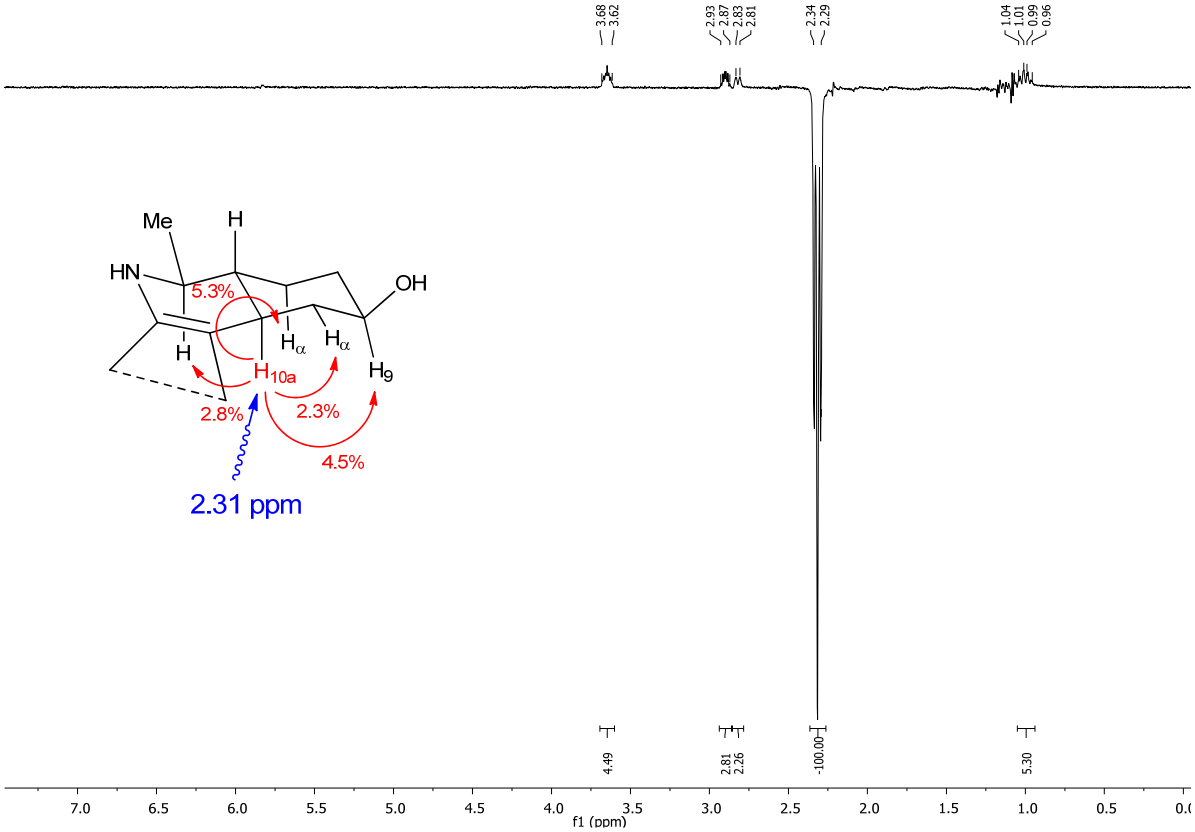


Figure S14 NOE values observed by irradiation of H-10a, the remaining part of the molecule was omitted for clarity.

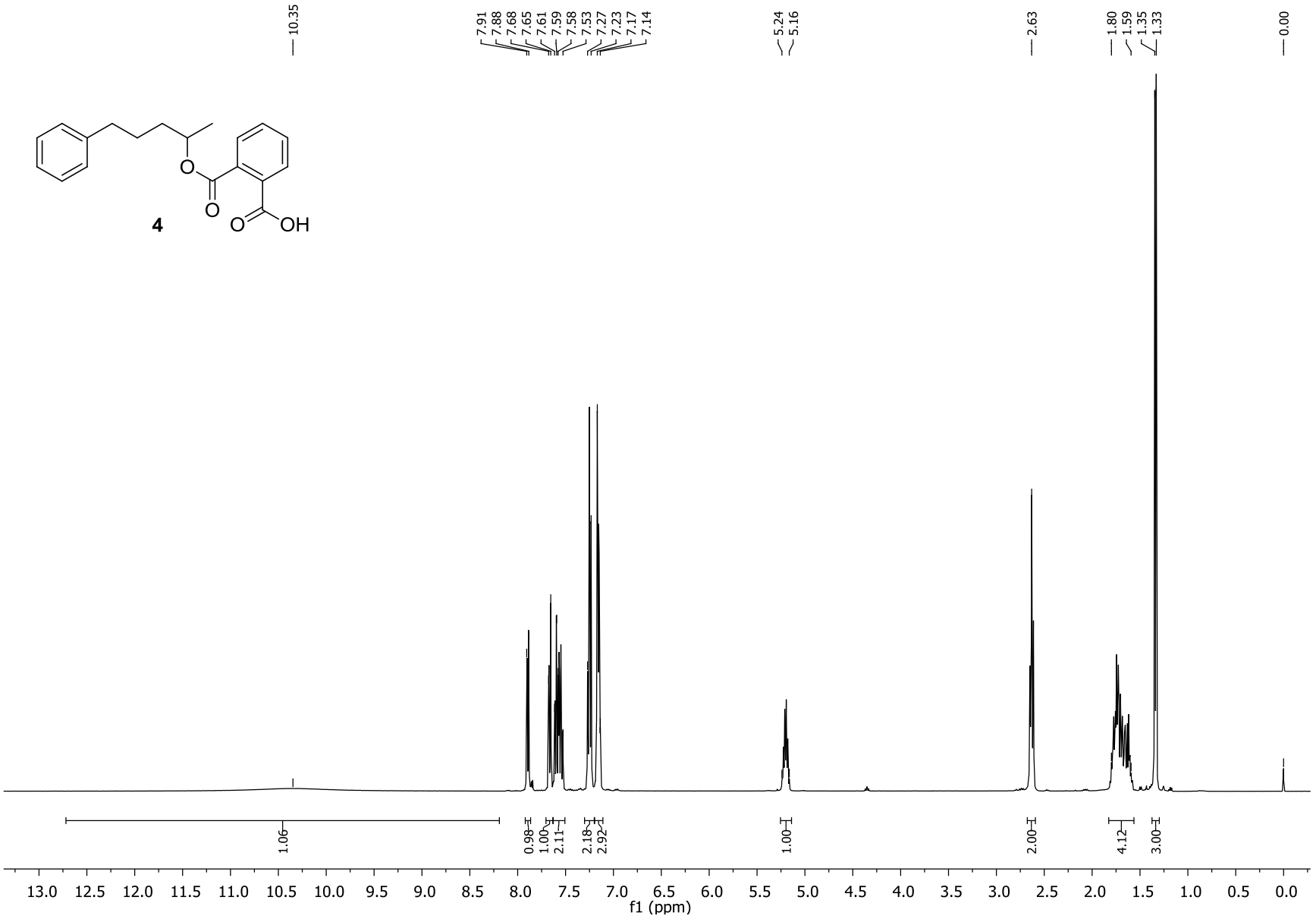
References

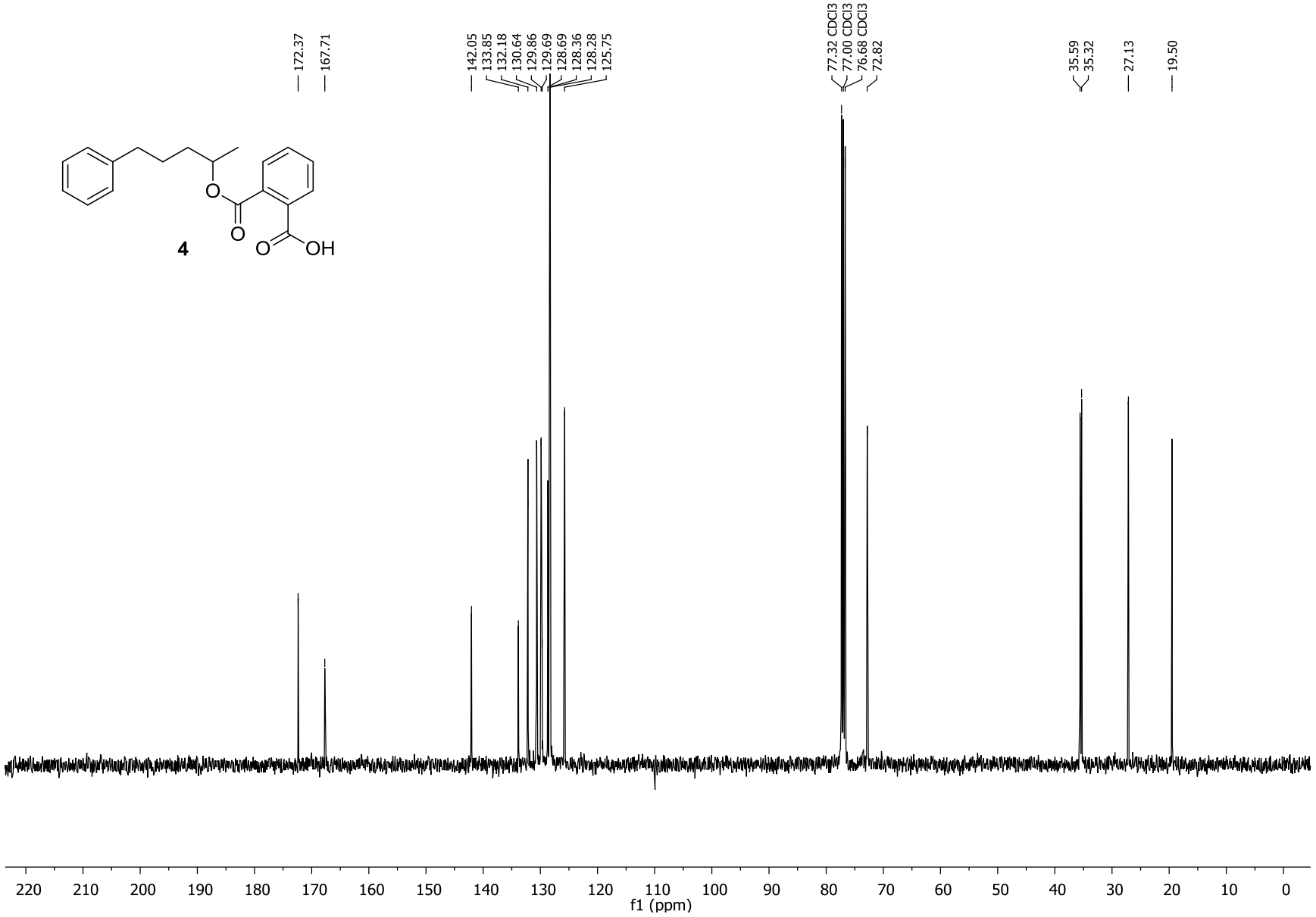
(1) Moore, B. S., *US Pat.* 4306285, **1983.**

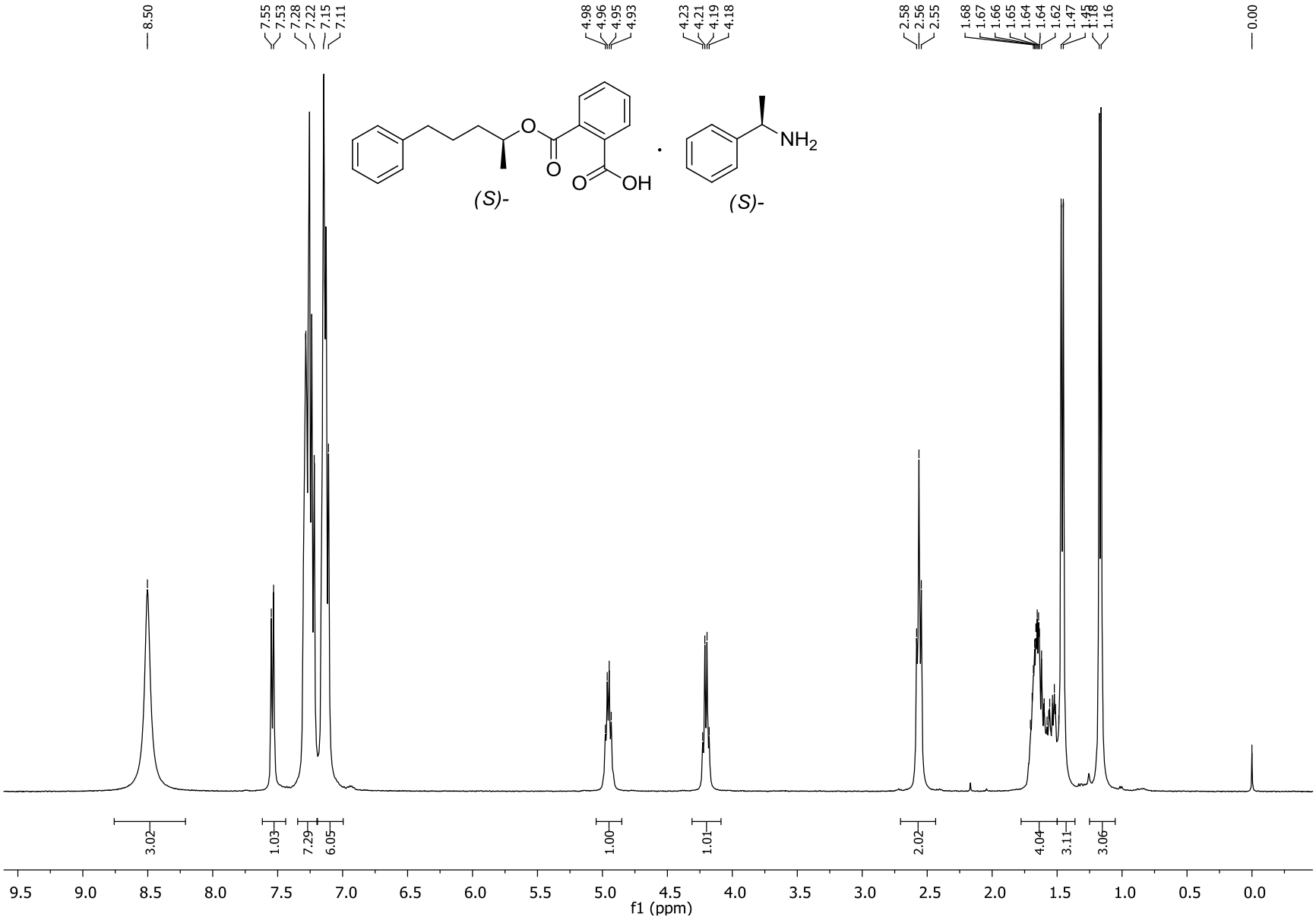
(2) Li, K. L.; Cheng, X. H.; Hii, K. K. *Eur. J. Org. Chem.* **2004**, 959-964.

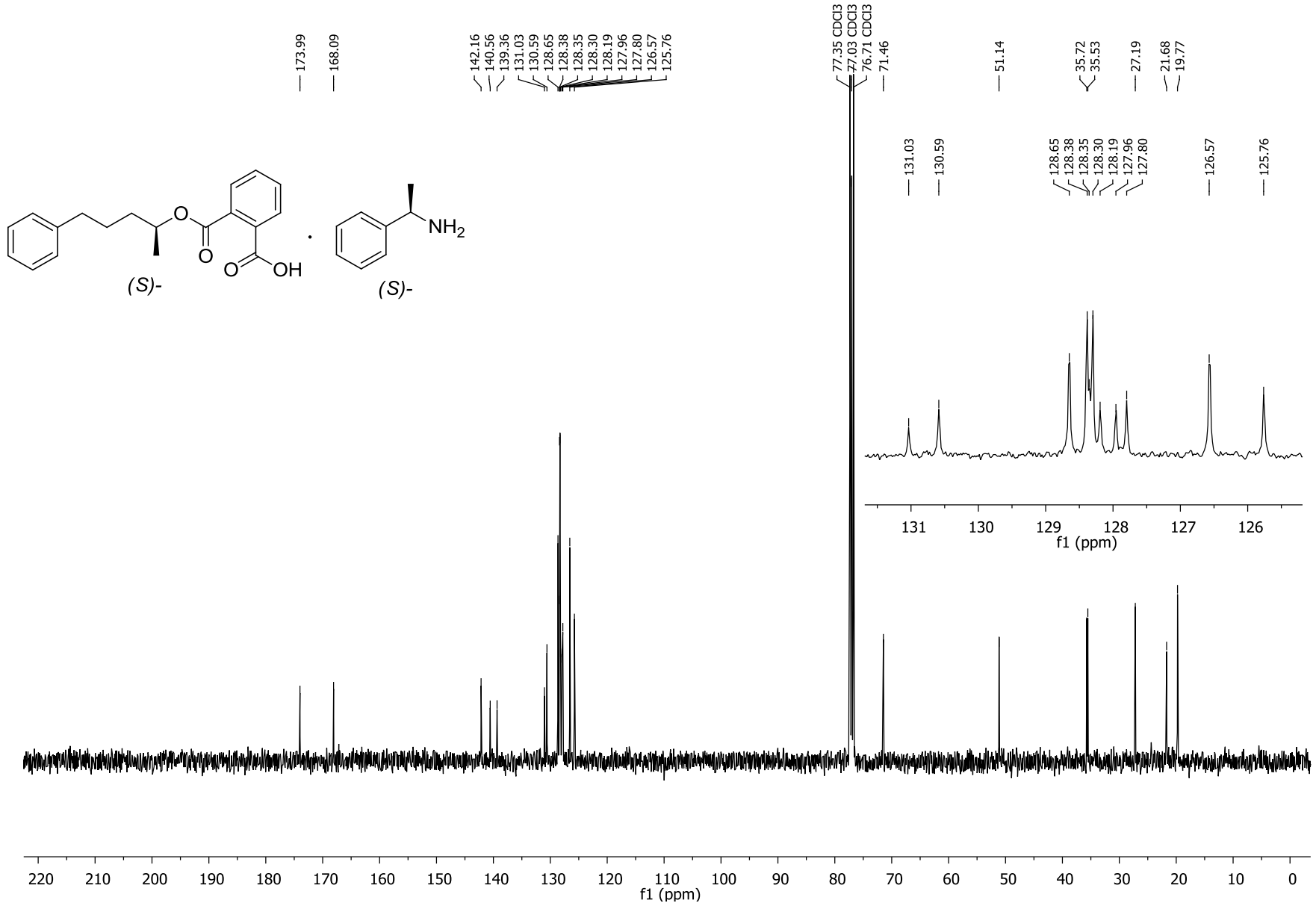
(3) A. E. Sheshenev, A. M. R. Smith, K. K. Hii, *Nat. Protocol* **2012,** *7*, 1765–1773.

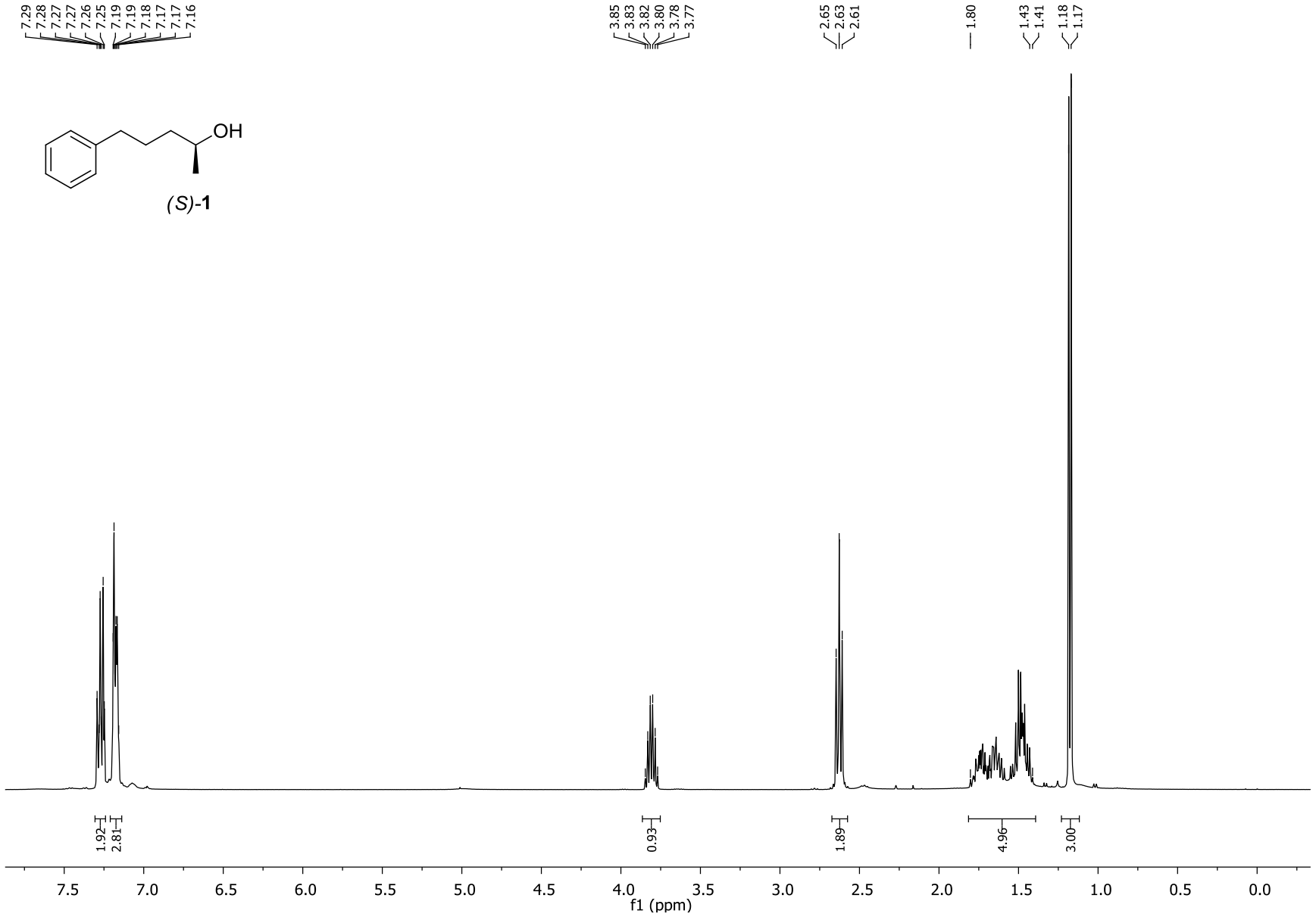
(4) Pfizer Inc., *GB Pat.*, GB 1579228, **1977**.

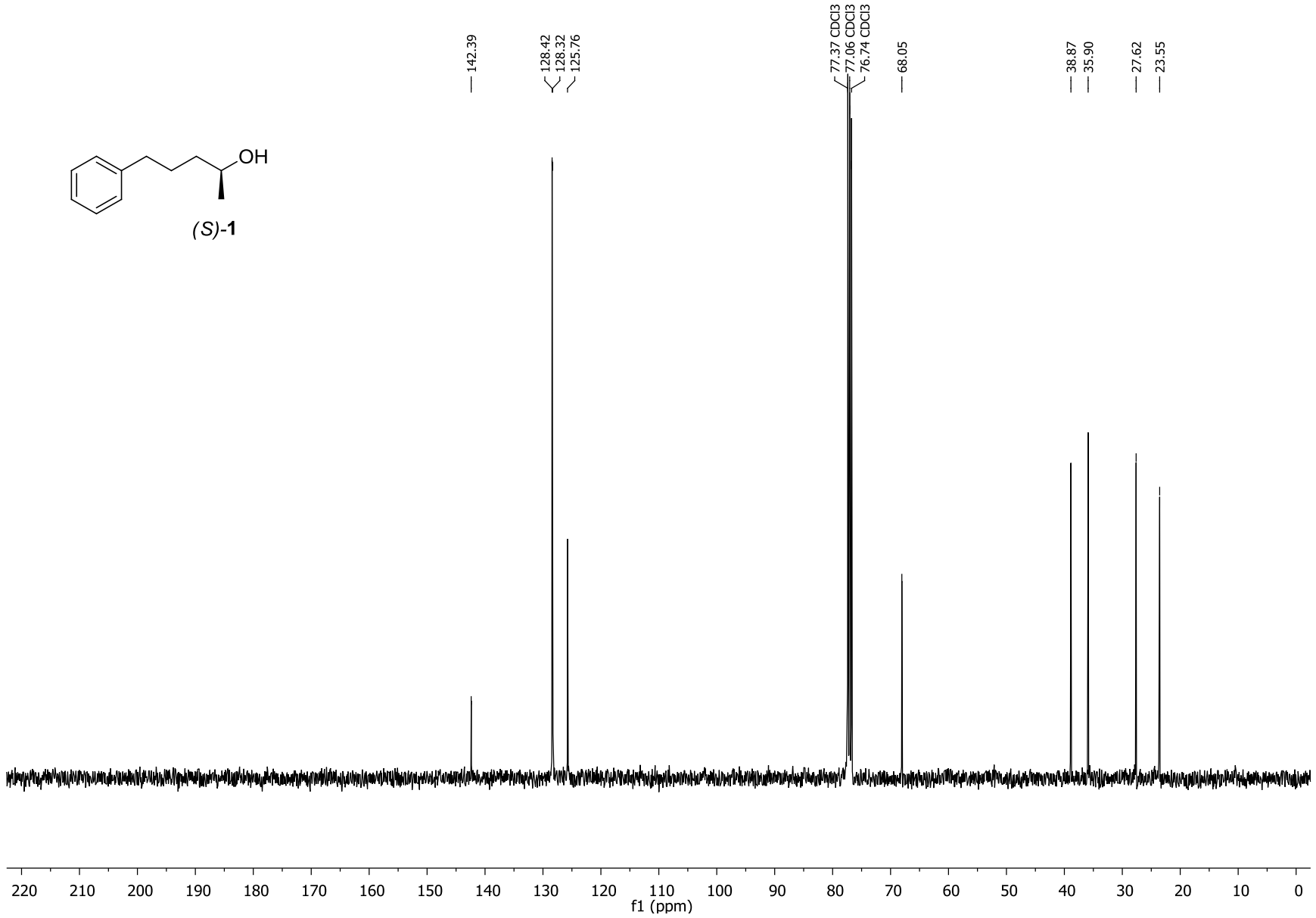


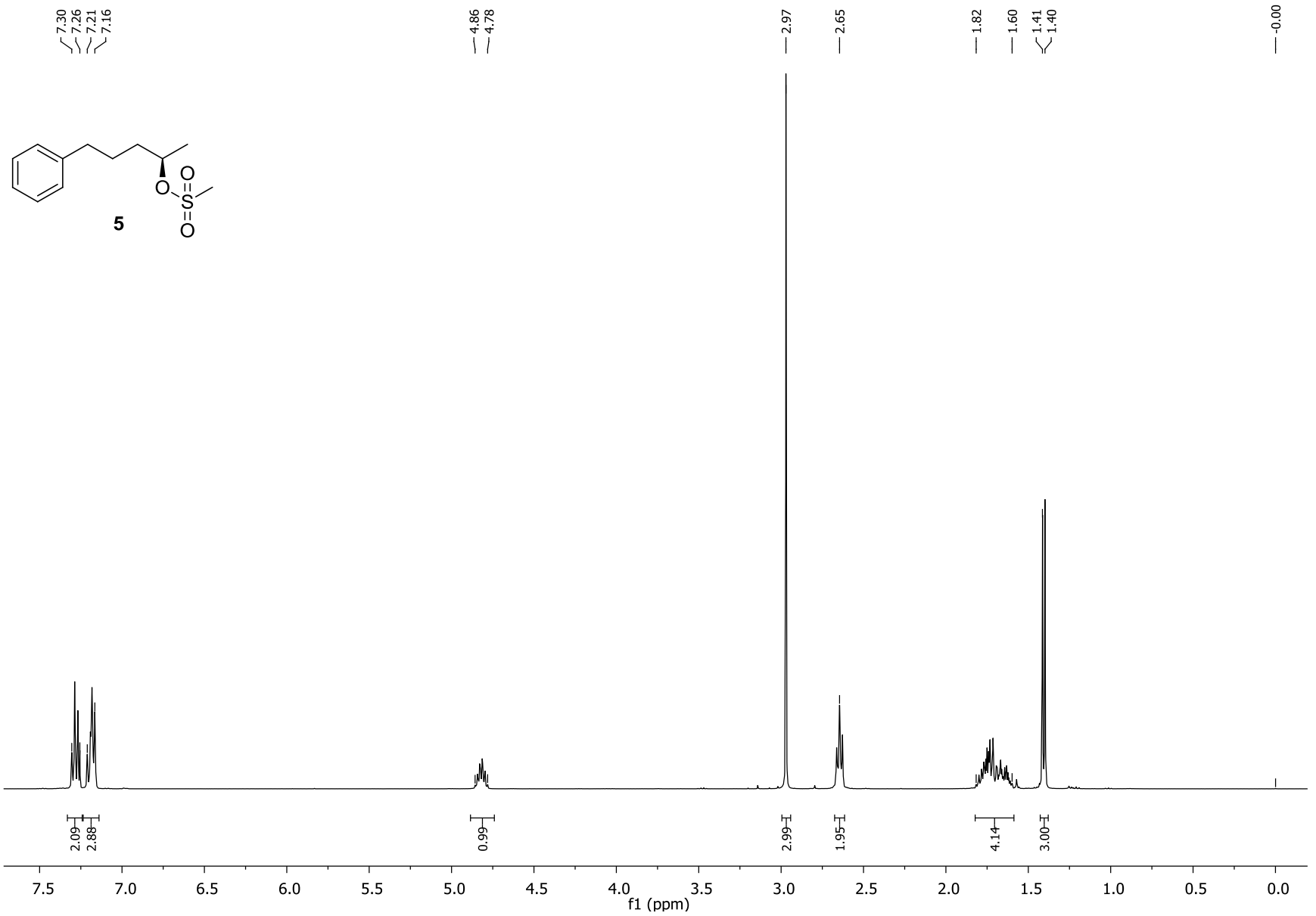


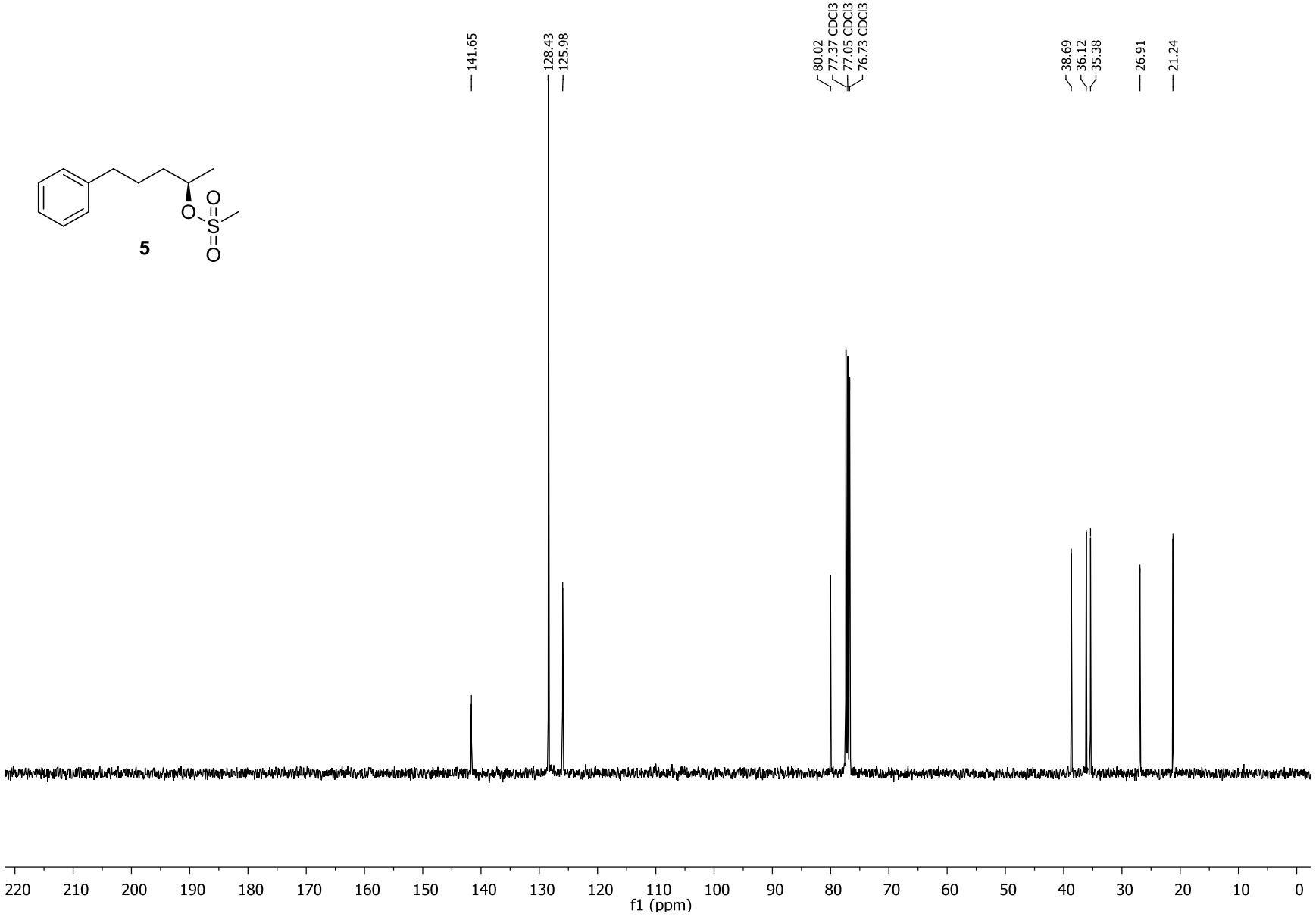


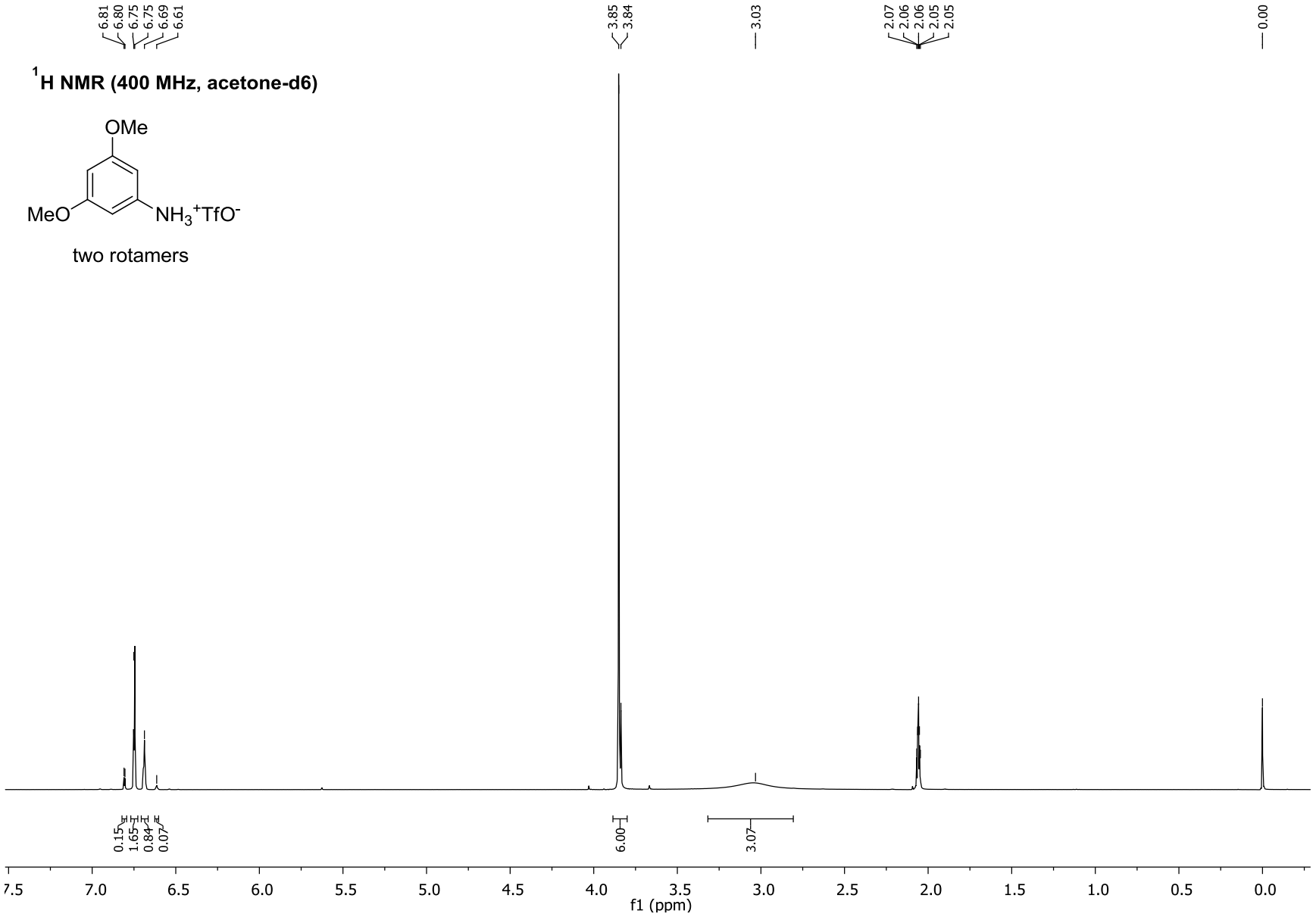


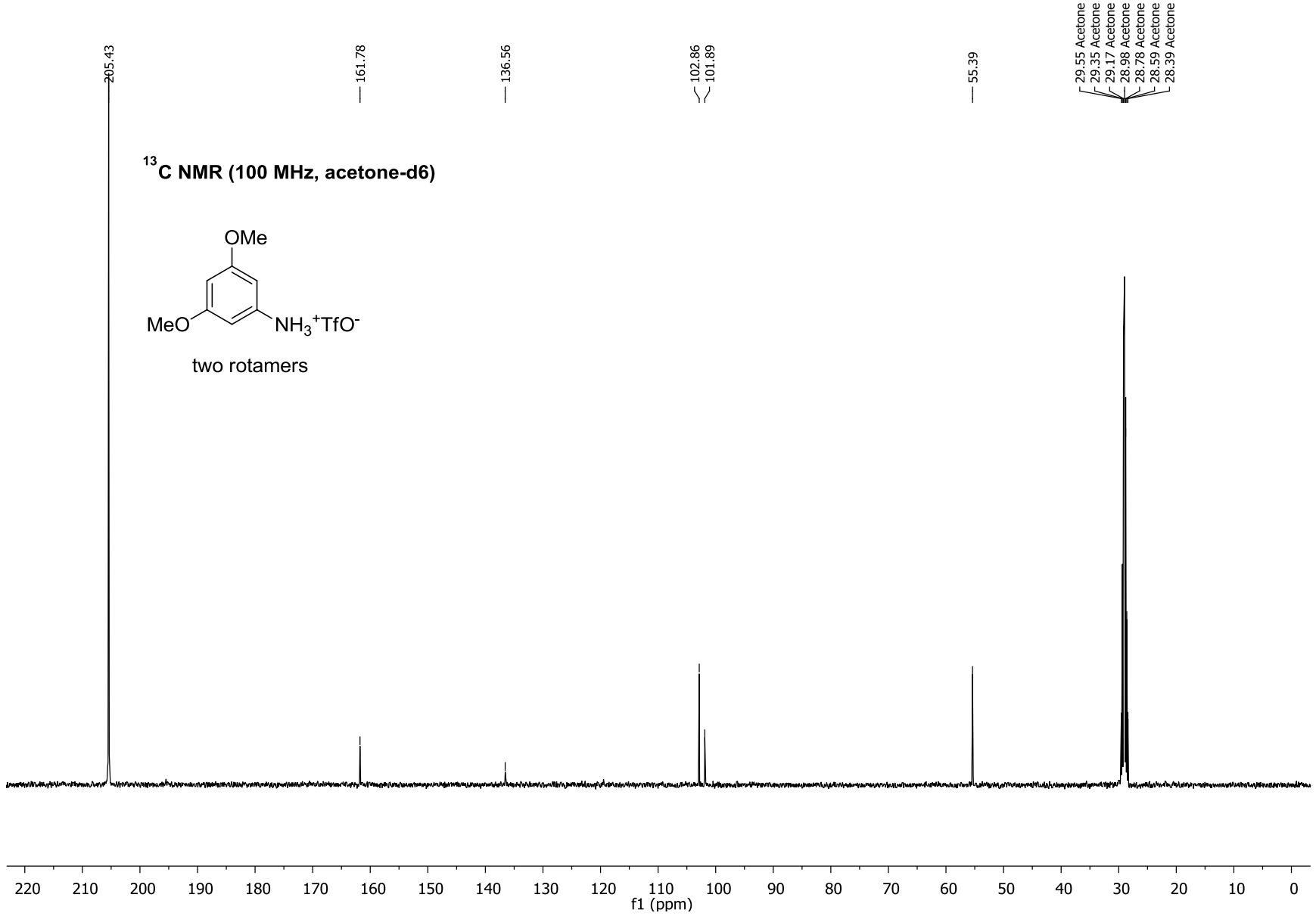


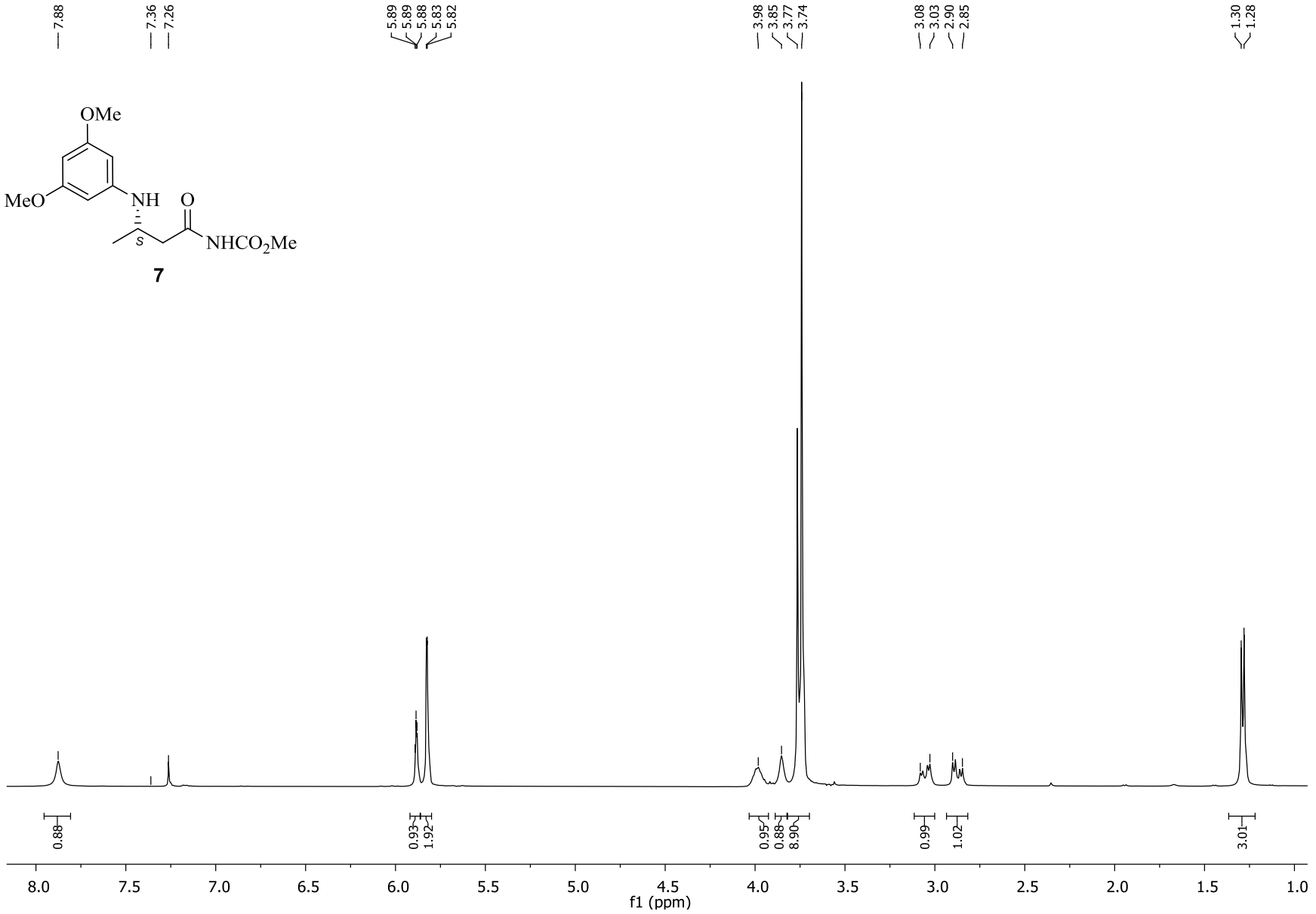


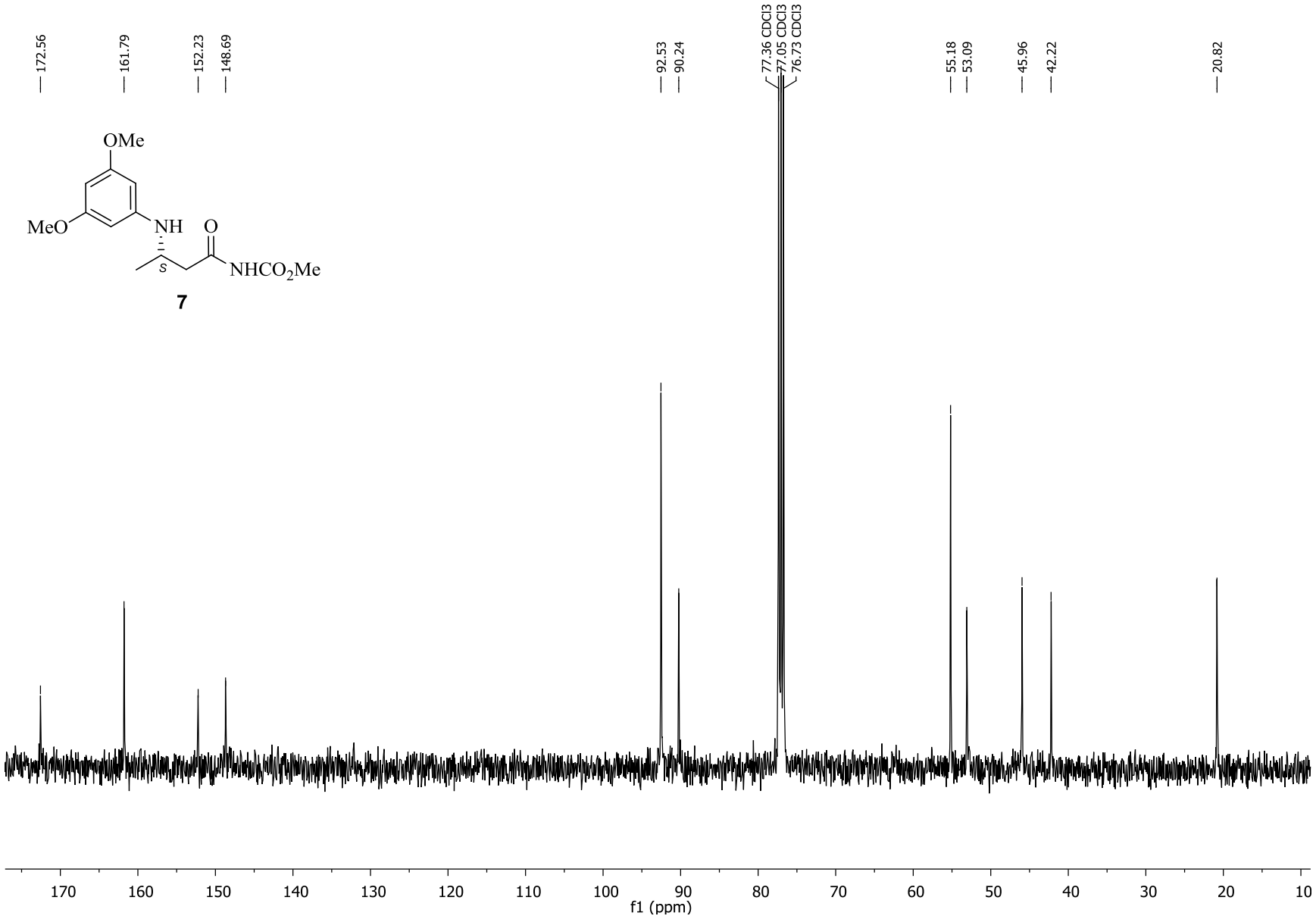


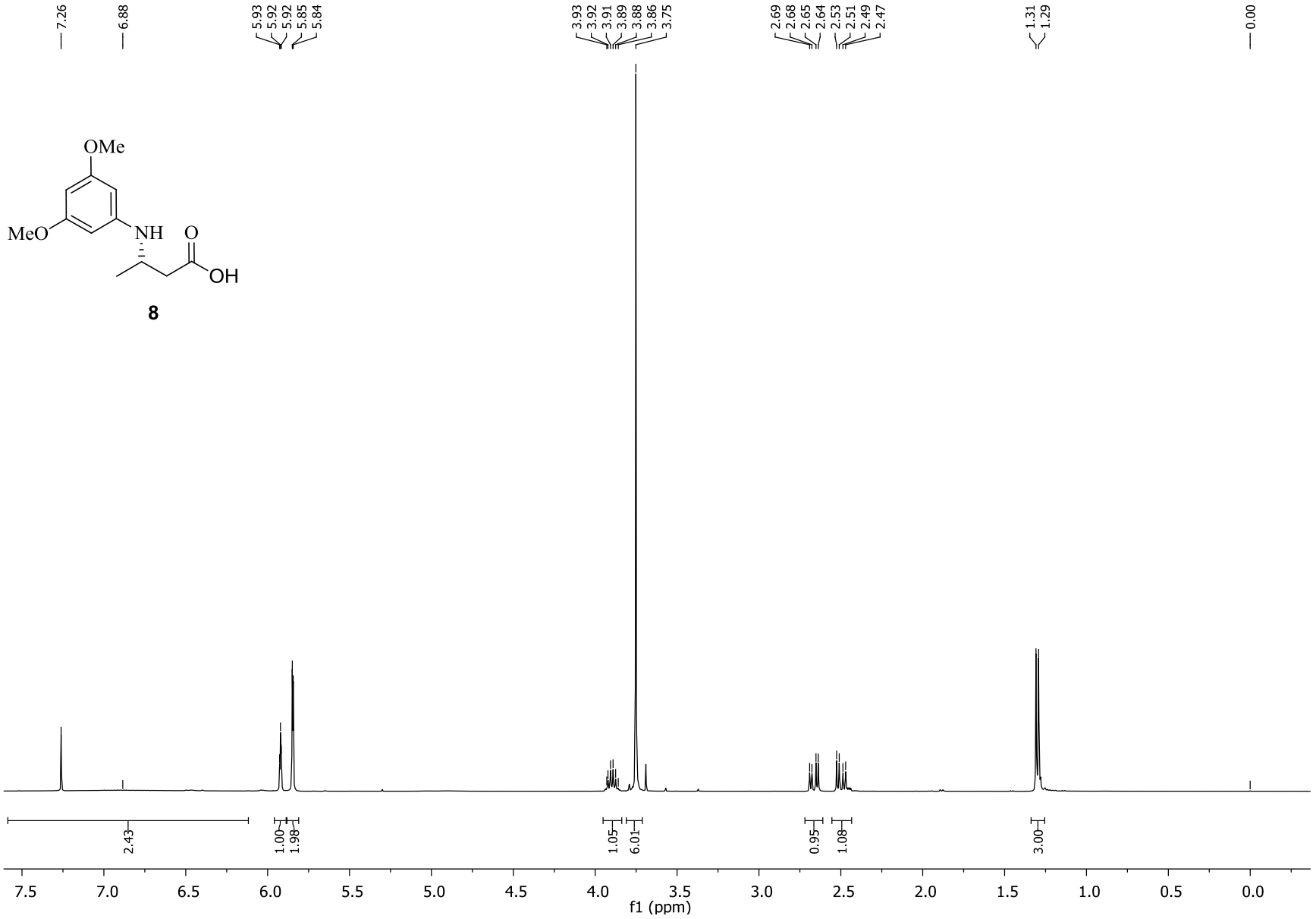












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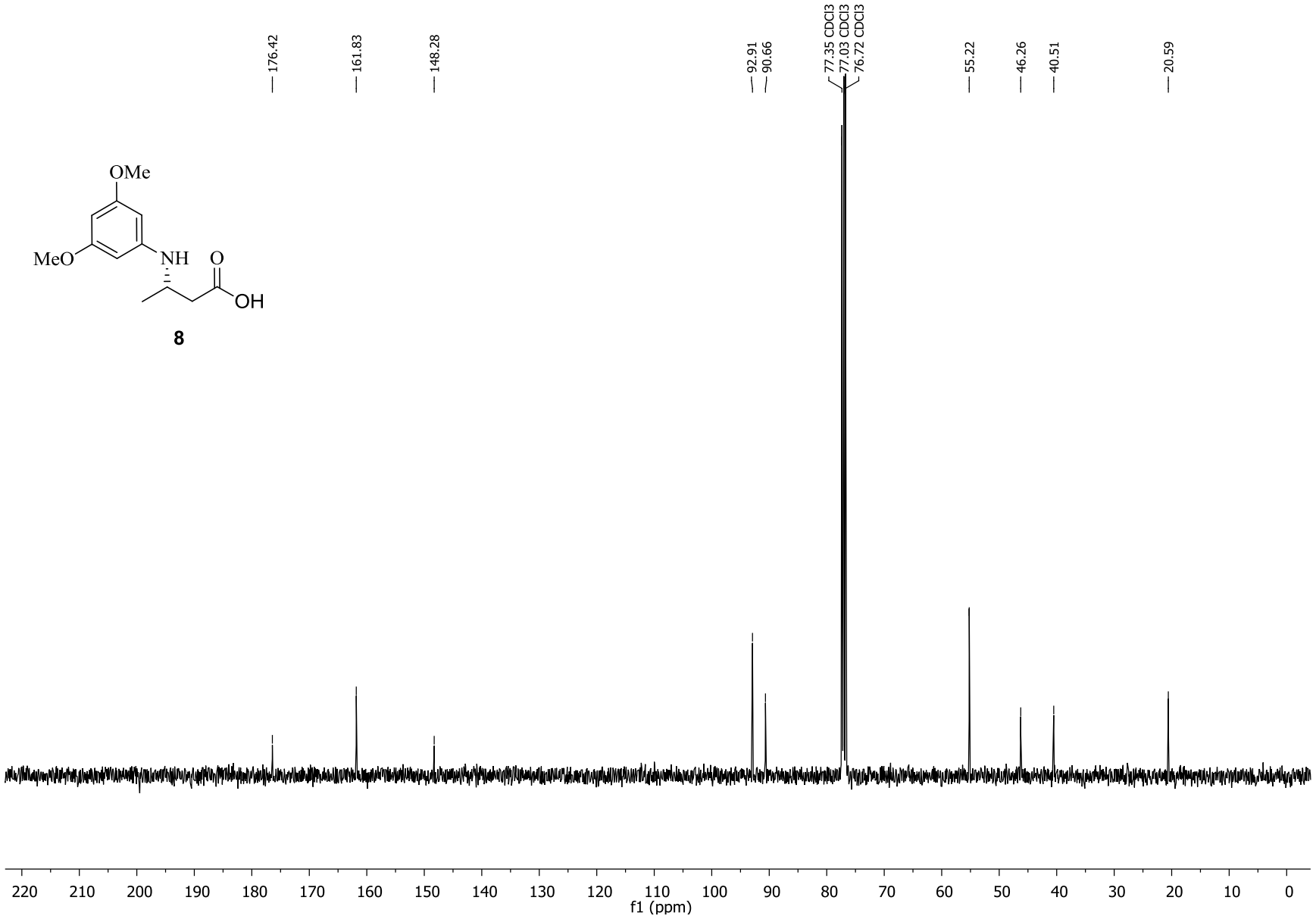
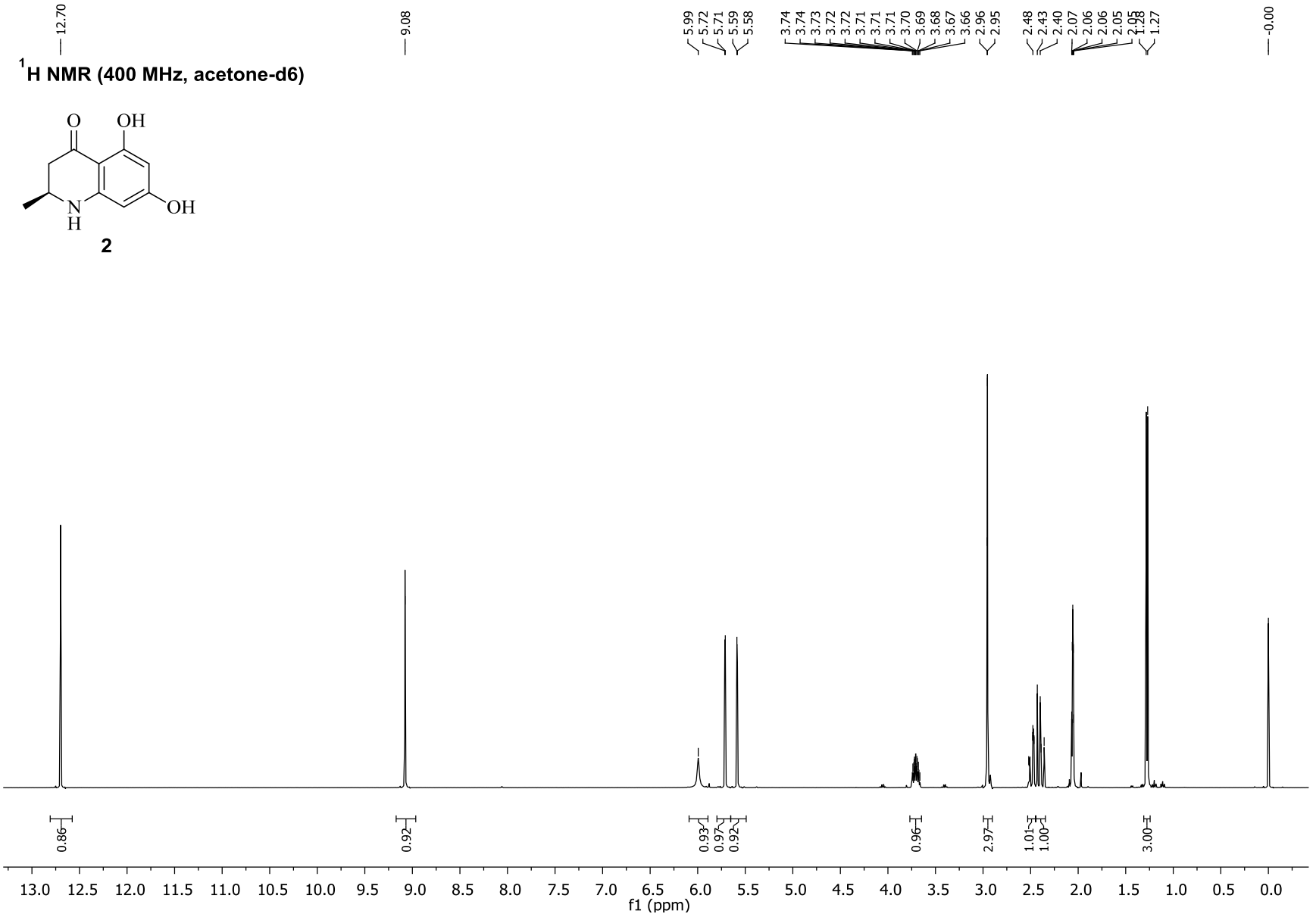
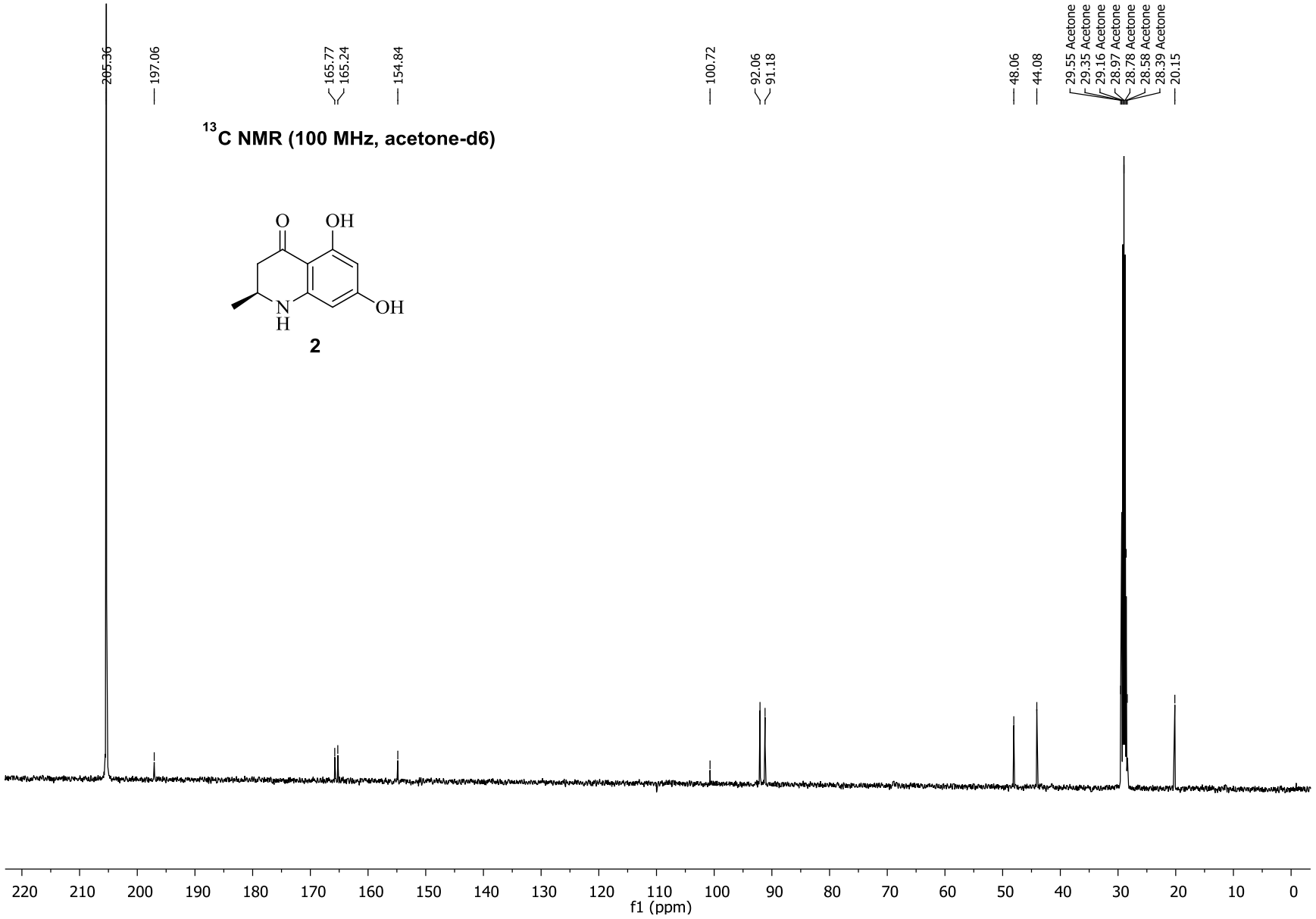
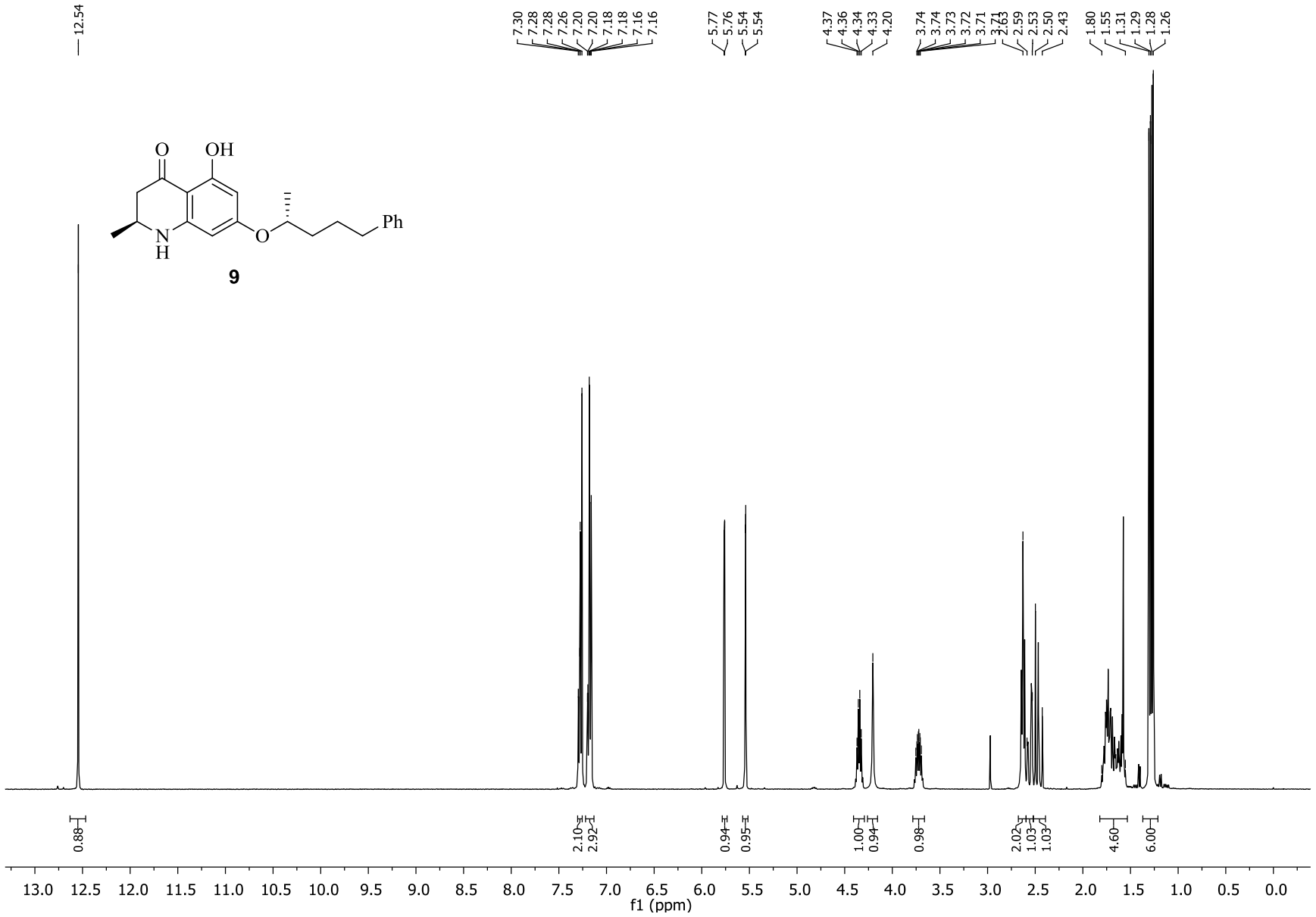


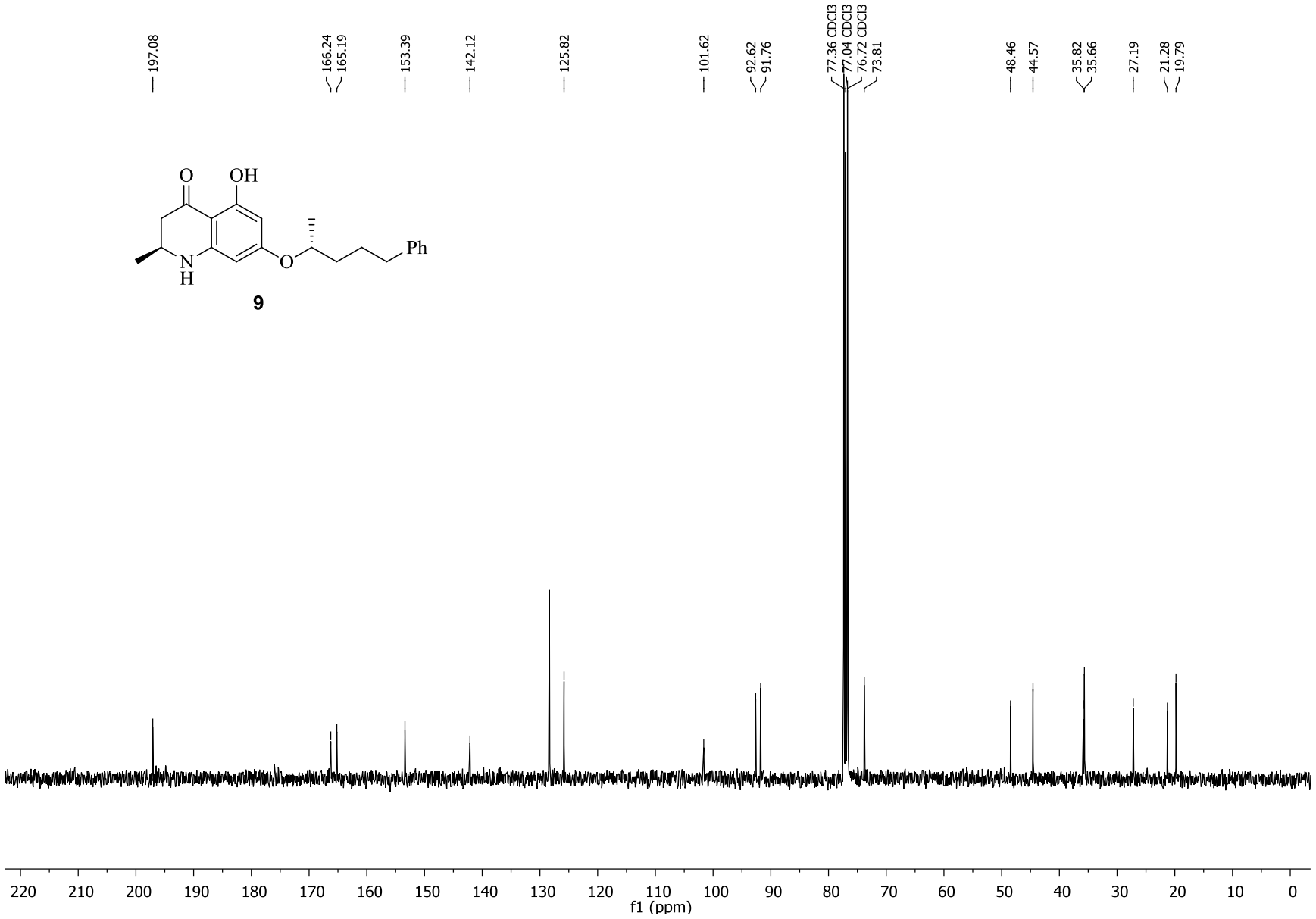


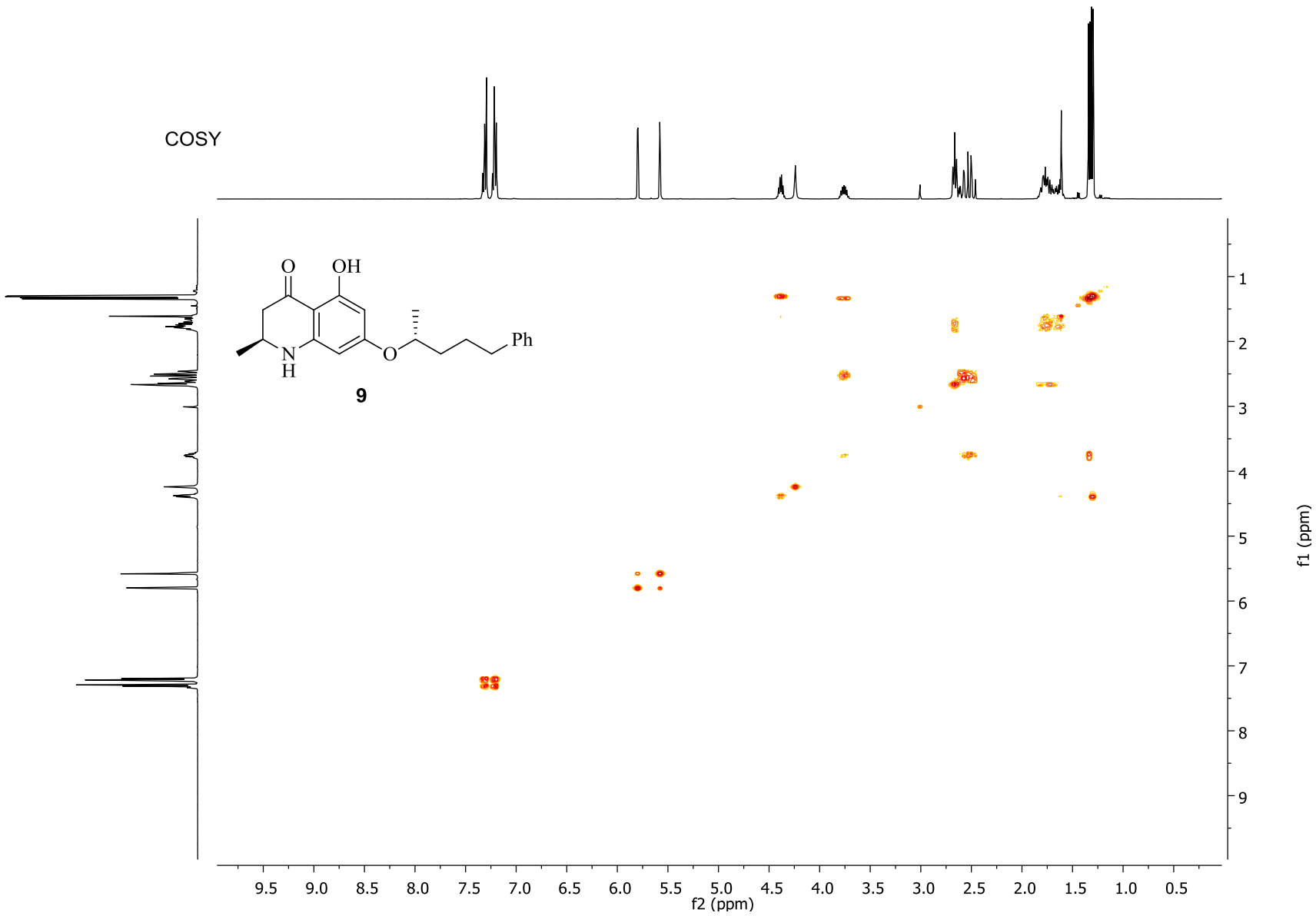
^{1}H NMR (400 MHz, acetone-d6)

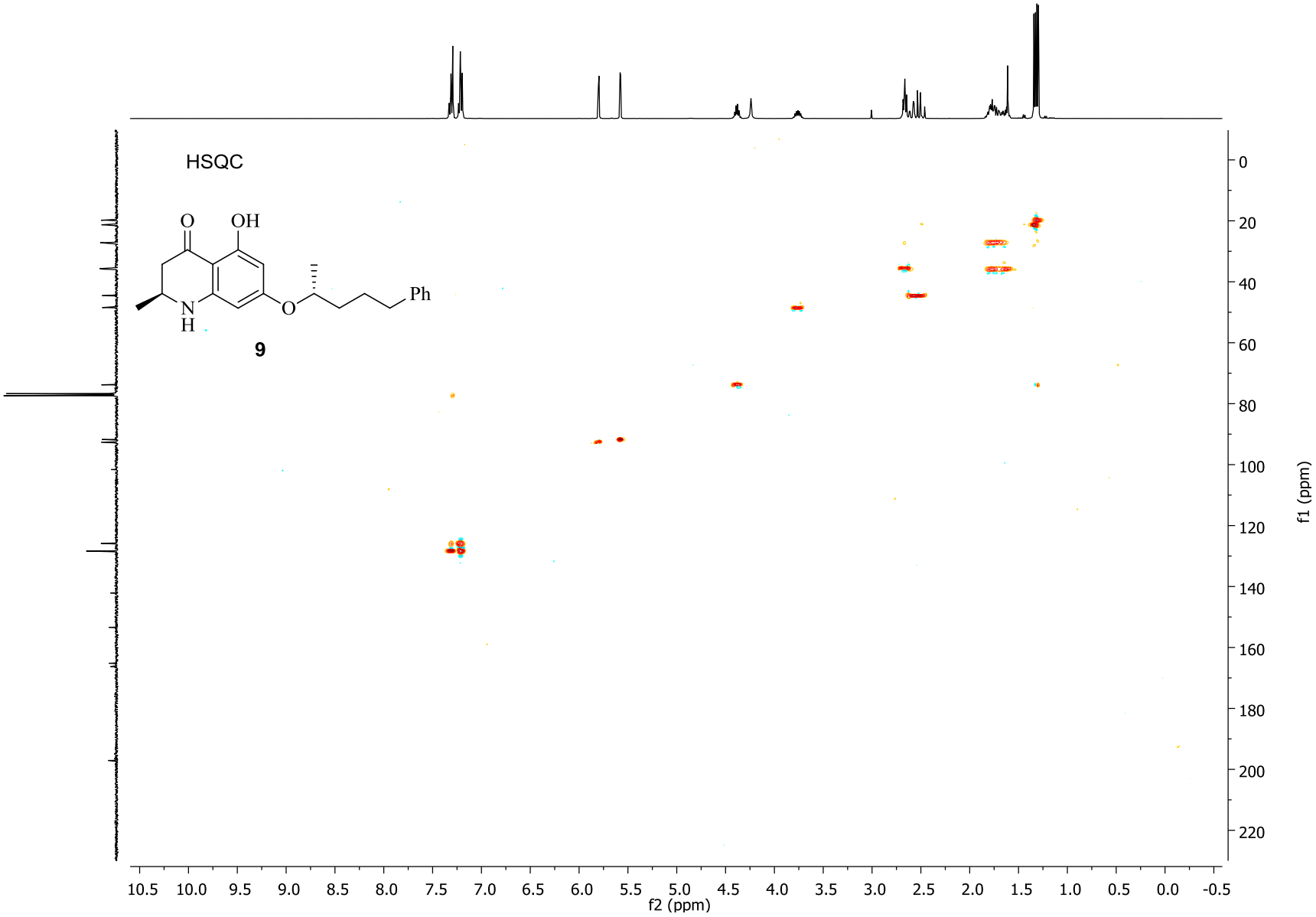
2

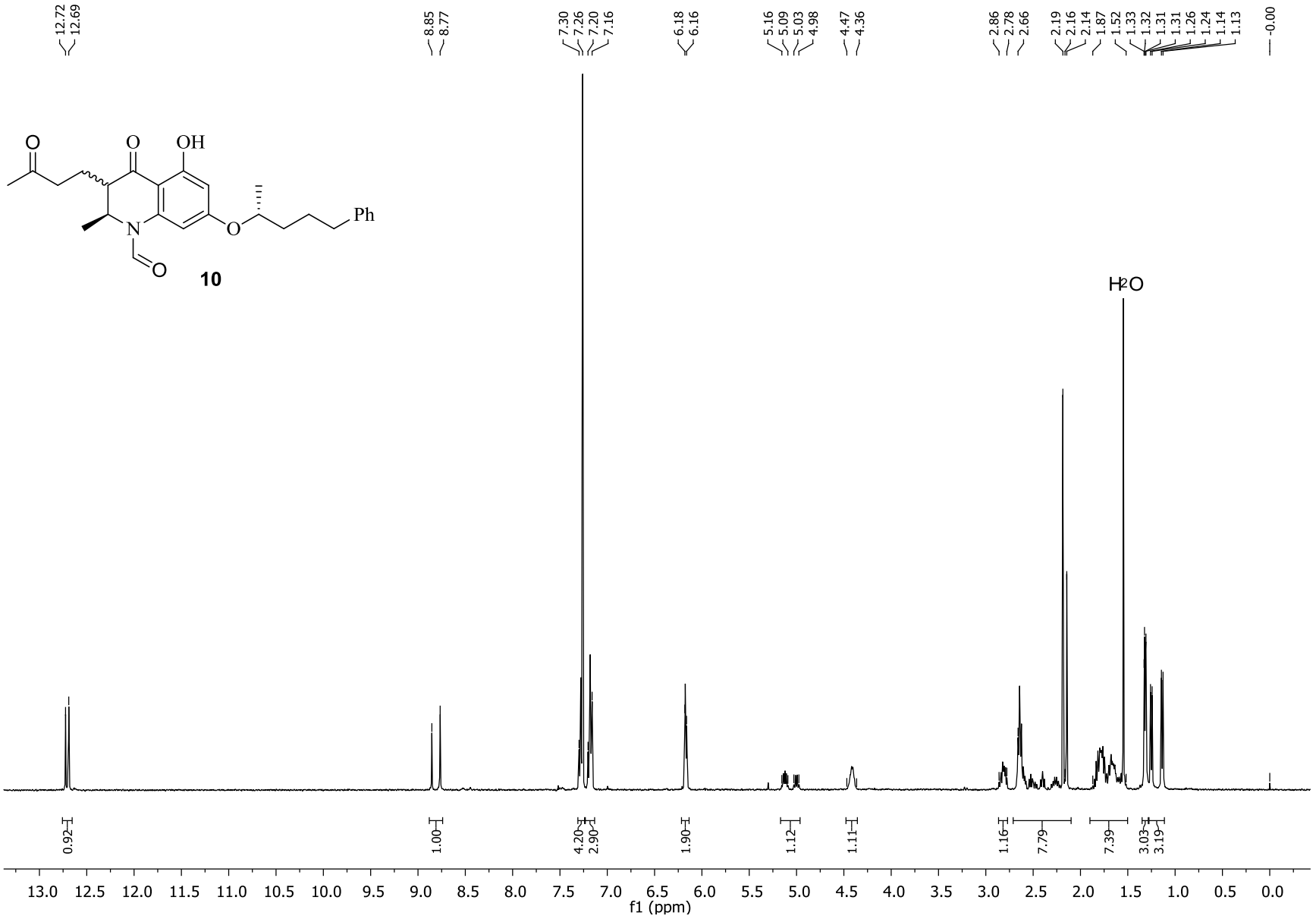

205.36
197.06
165.77
165.24
154.84
100.72
92.06
91.18
48.06
44.08
29.55 Acetone
29.35 Acetone
29.16 Acetone
28.97 Acetone
28.78 Acetone
28.58 Acetone
28.39 Acetone
20.15
13C NMR (100 MHz, acetone-d6)
O
OH
N
H
OH
2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

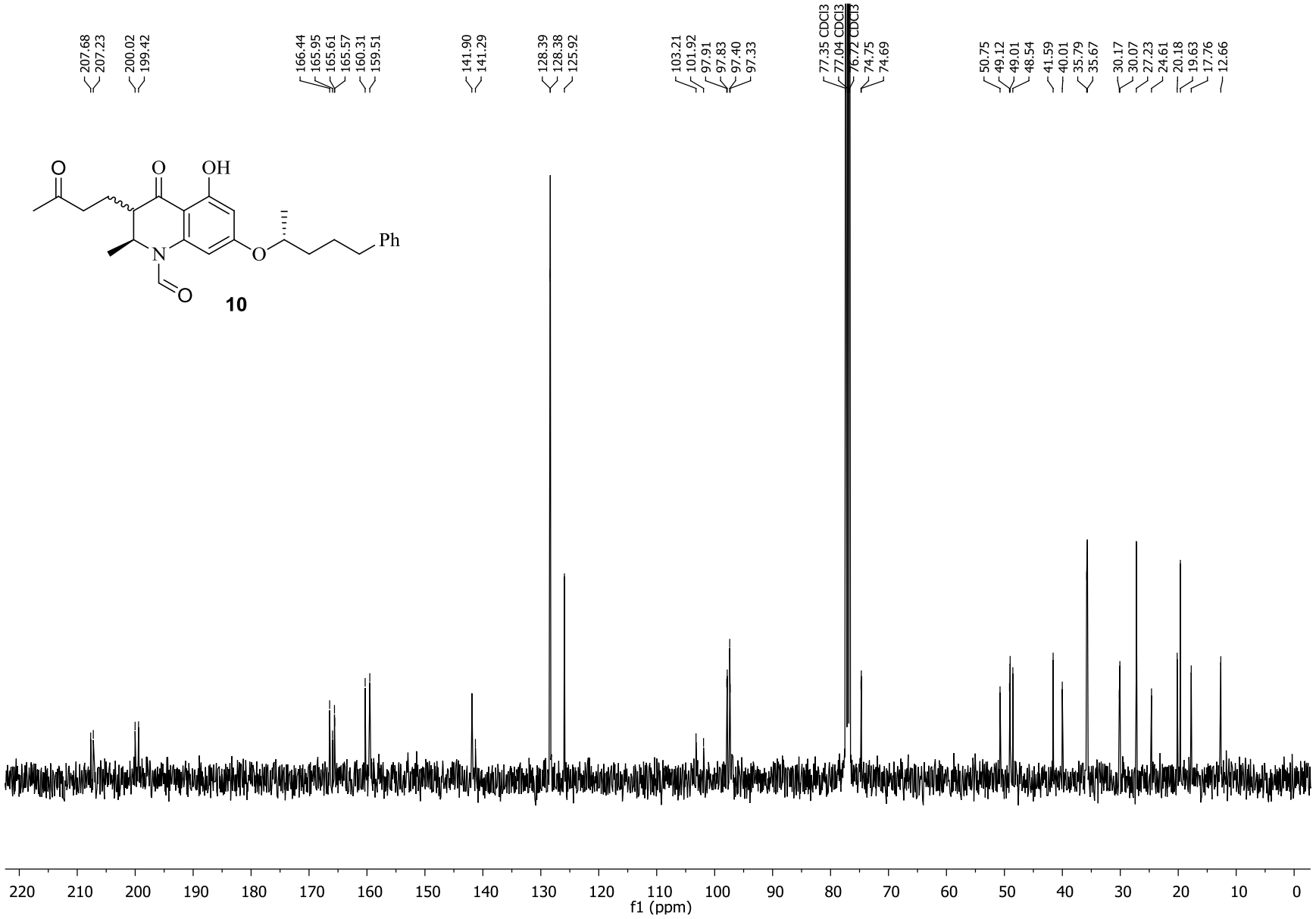


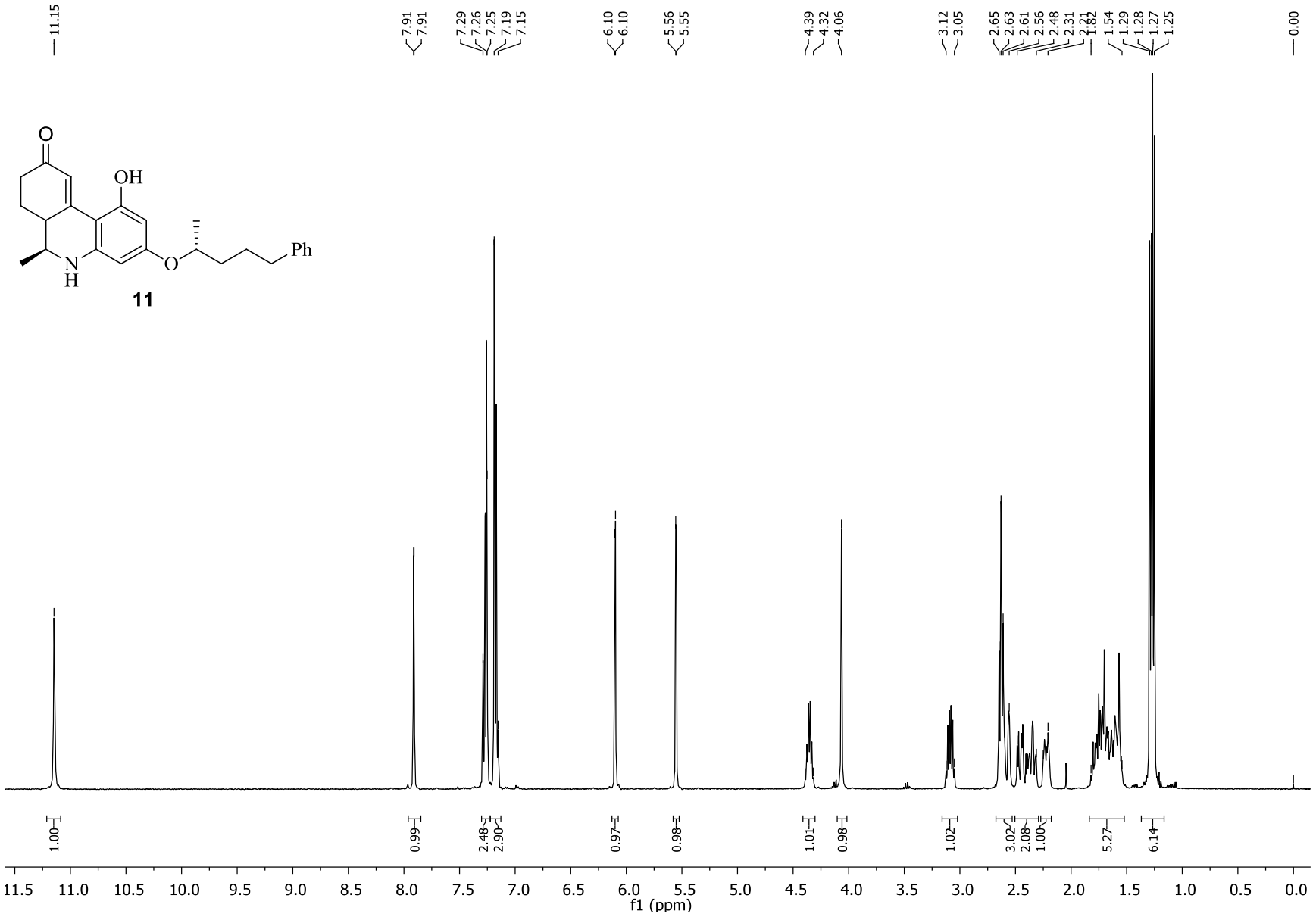

197.08
166.24
165.19
153.39
142.12
125.82
101.62
92.62
91.76
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
73.81
48.46
44.57
35.82
35.66
27.19
21.28
19.79
O
OH
N
H
O
Ph
9
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

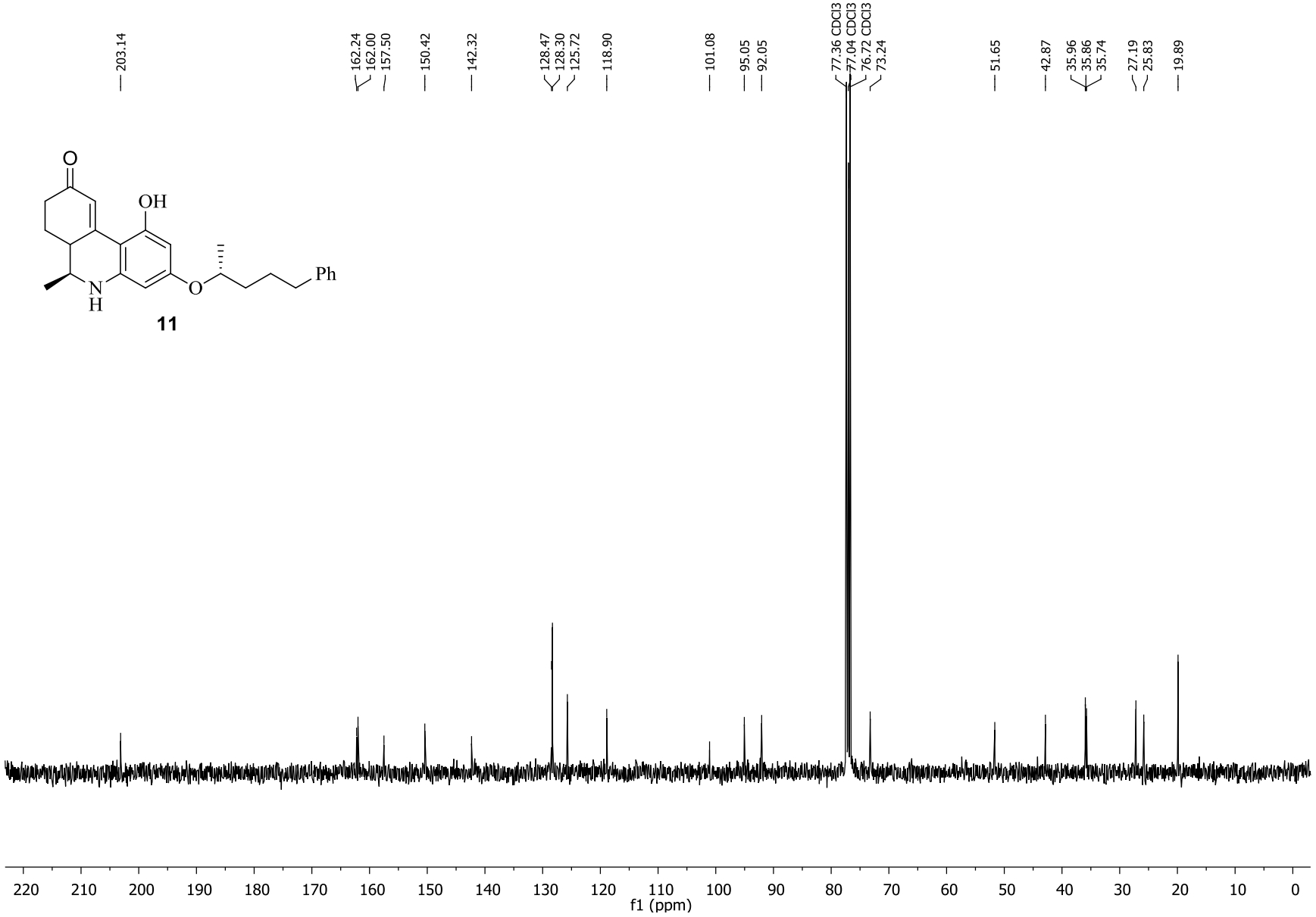


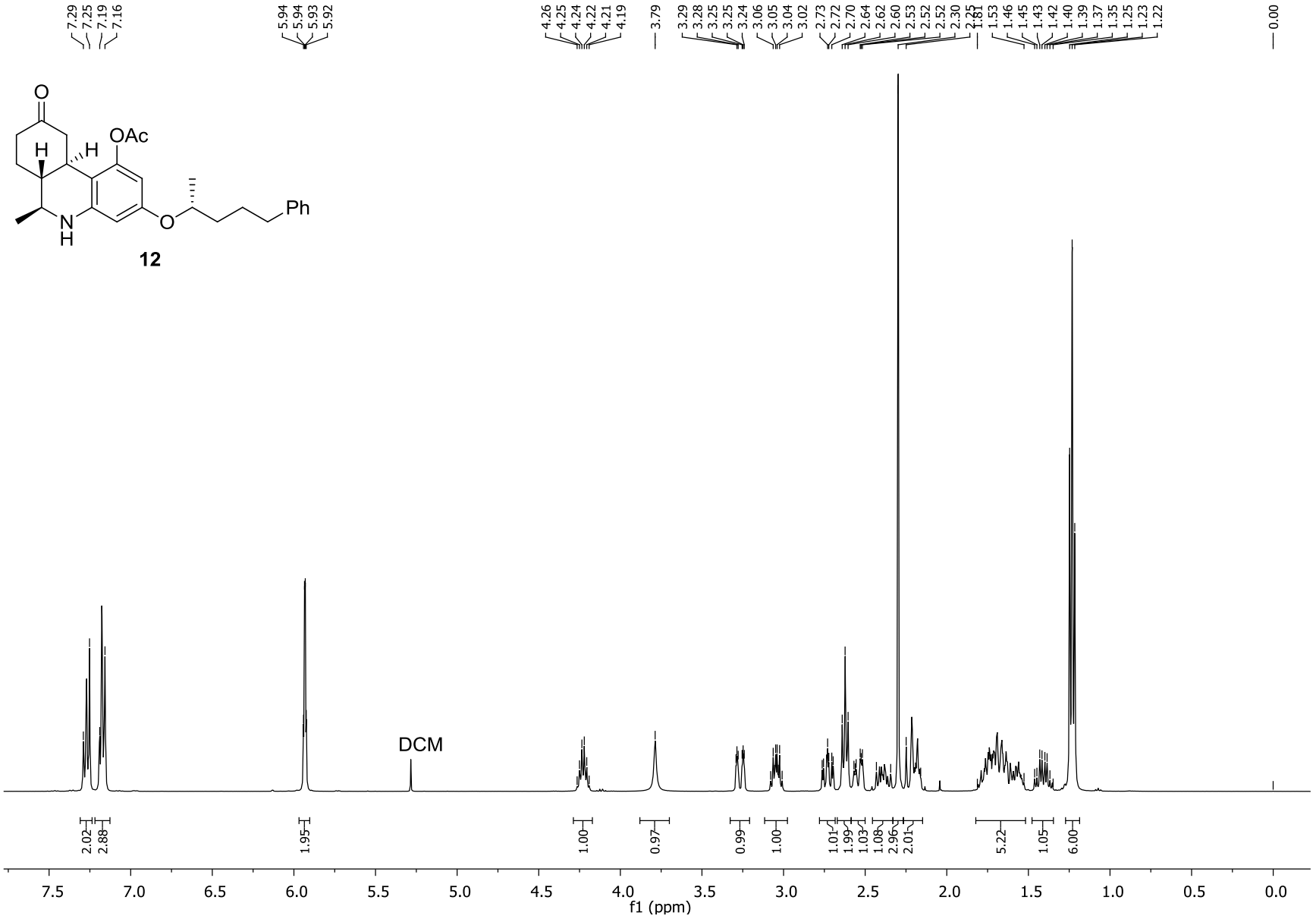


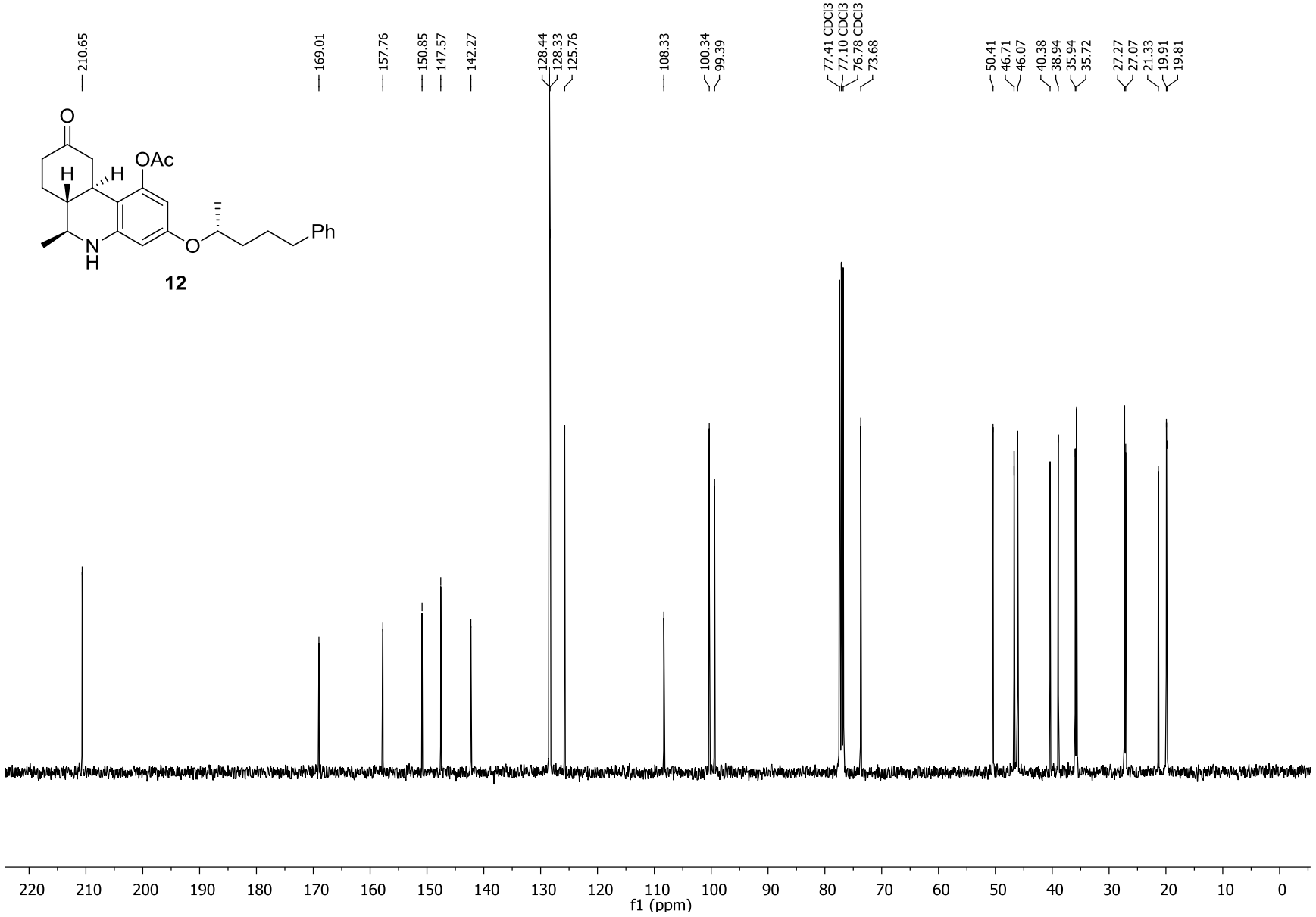


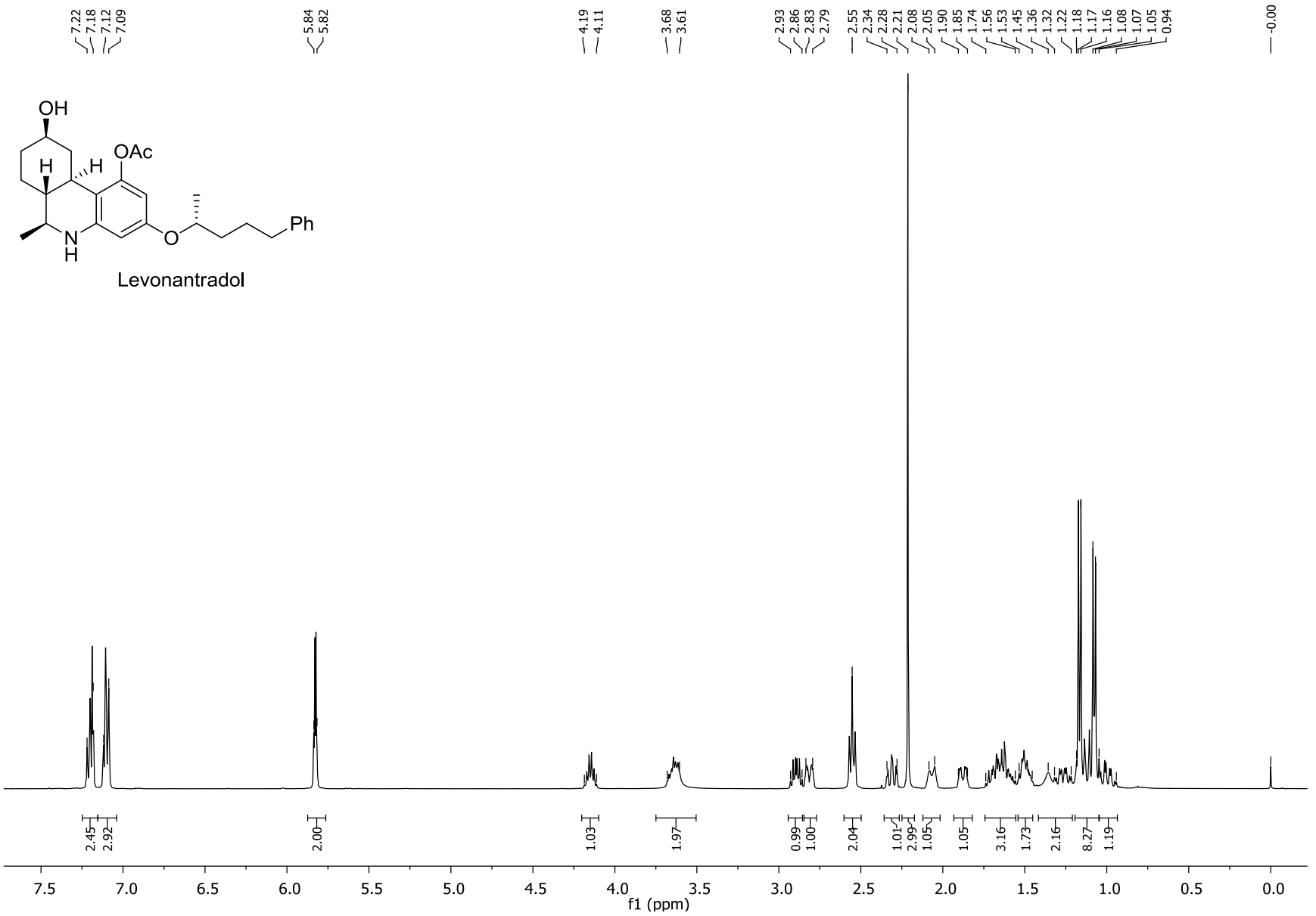


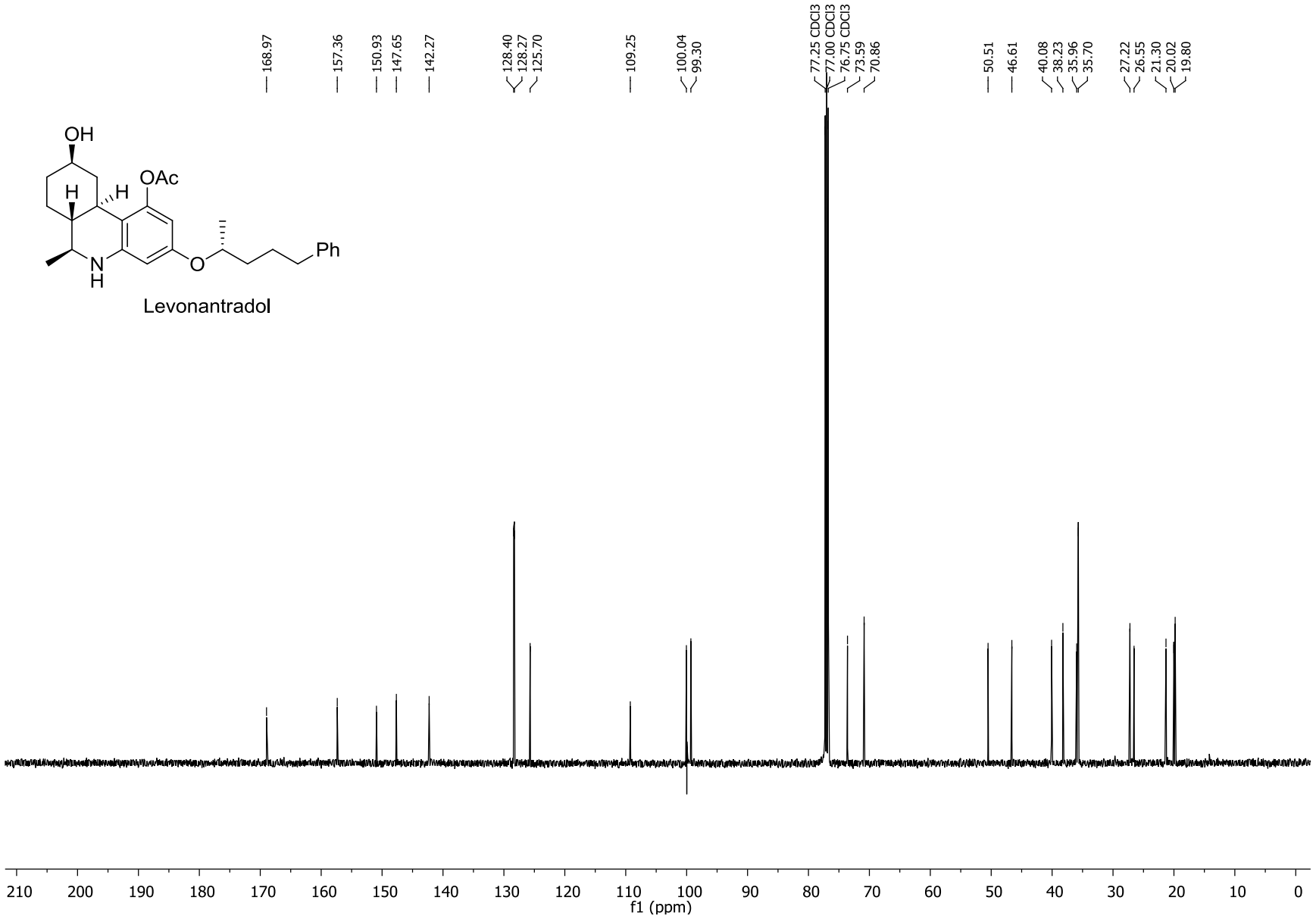


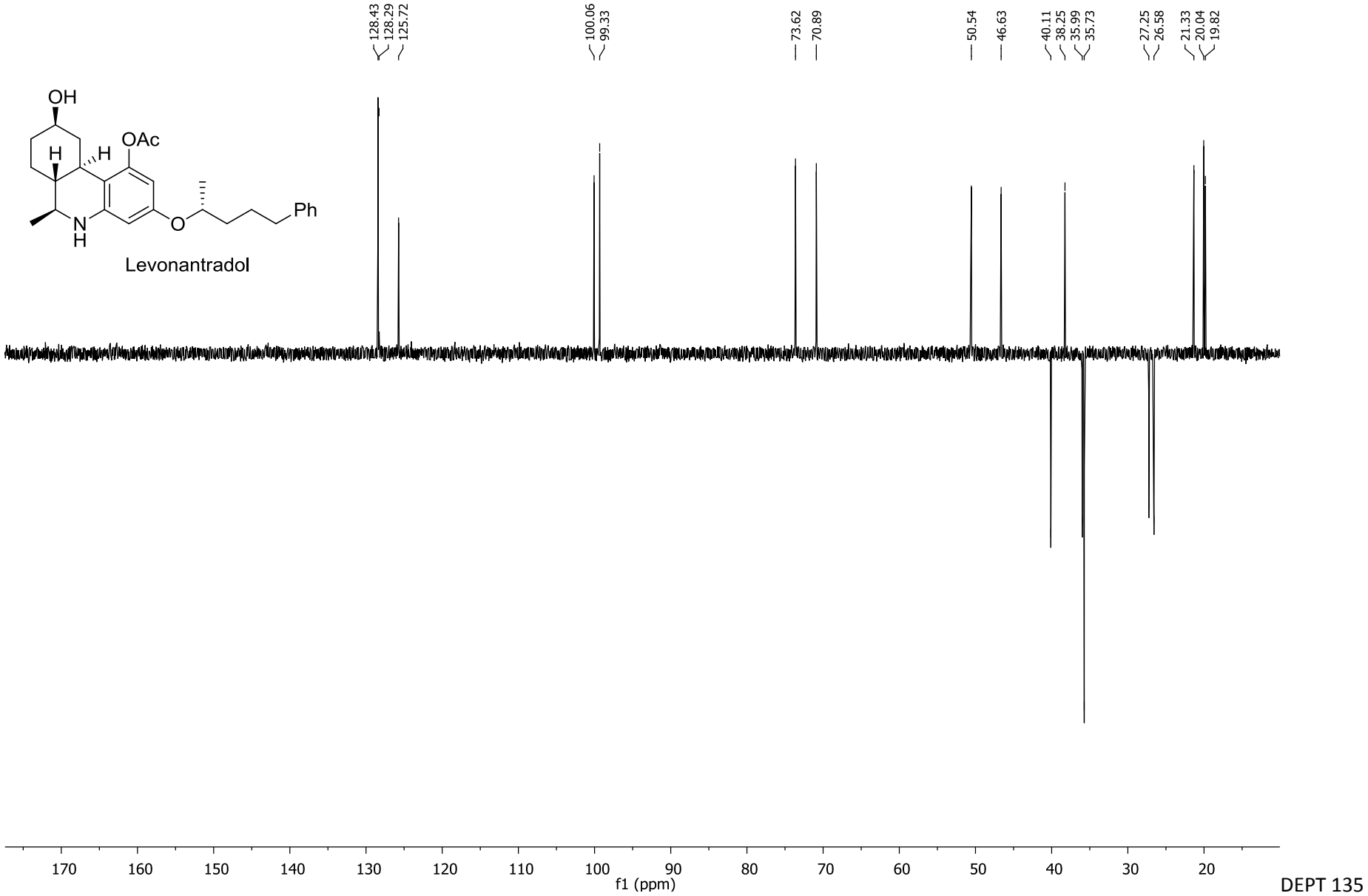












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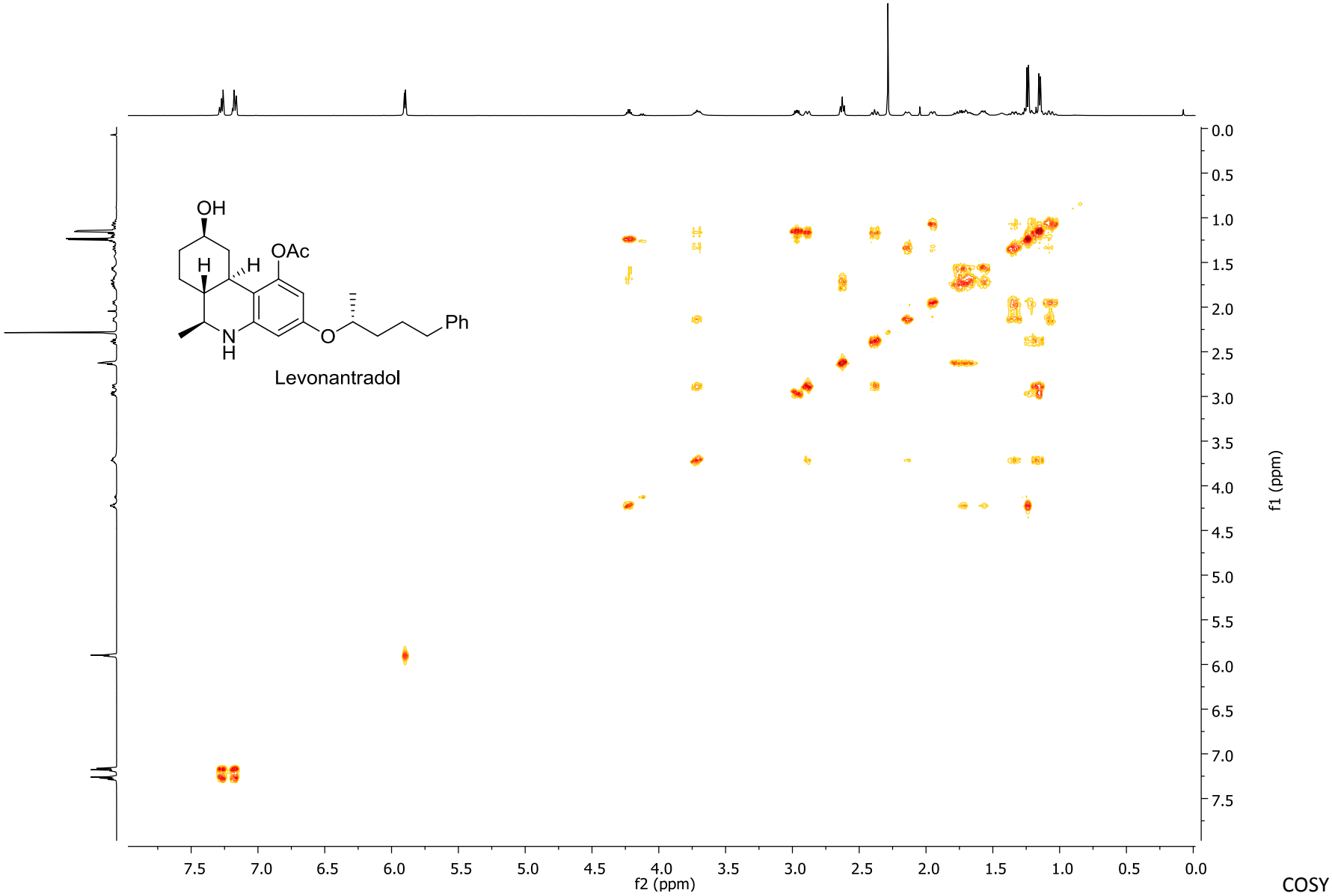

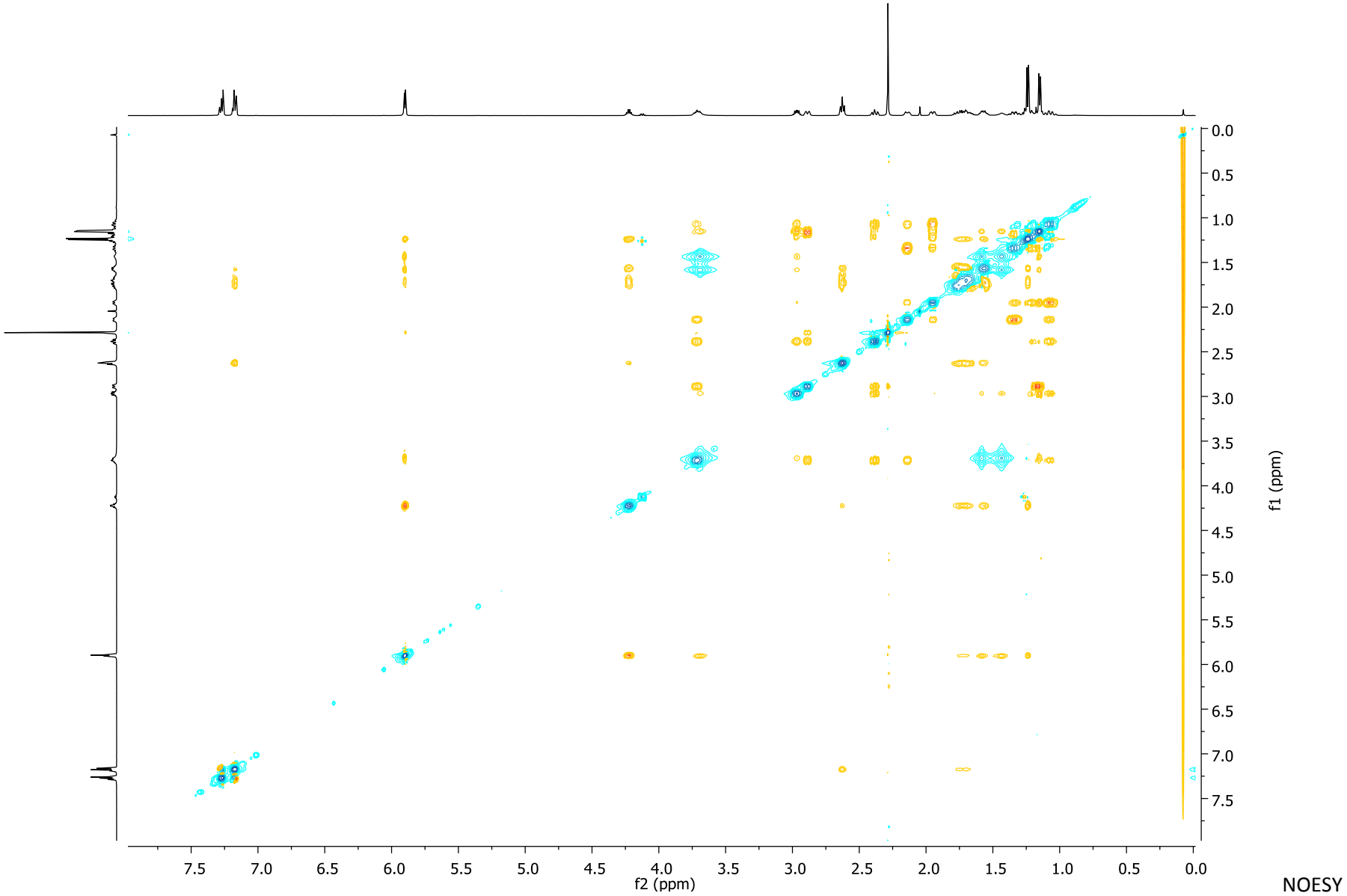

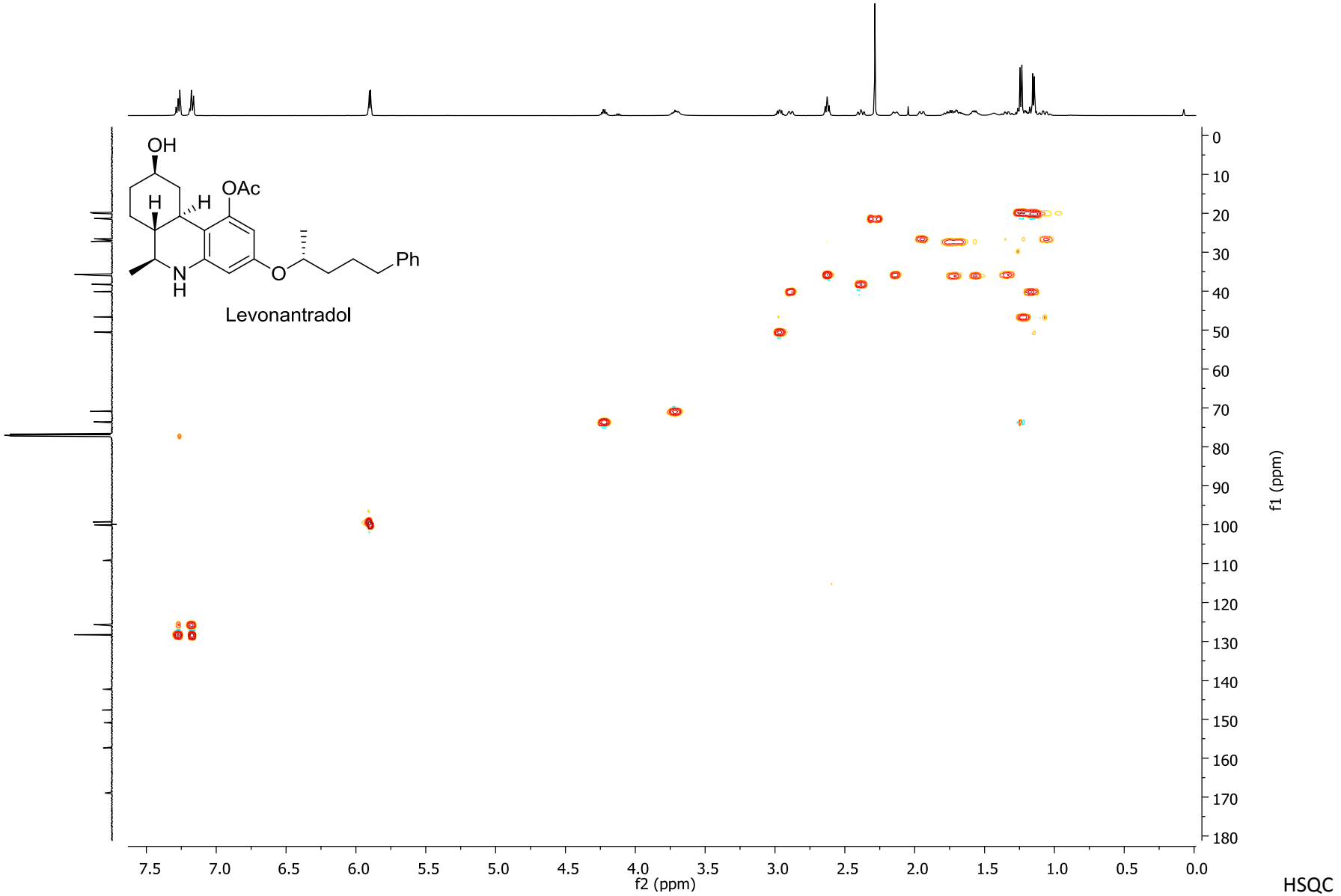

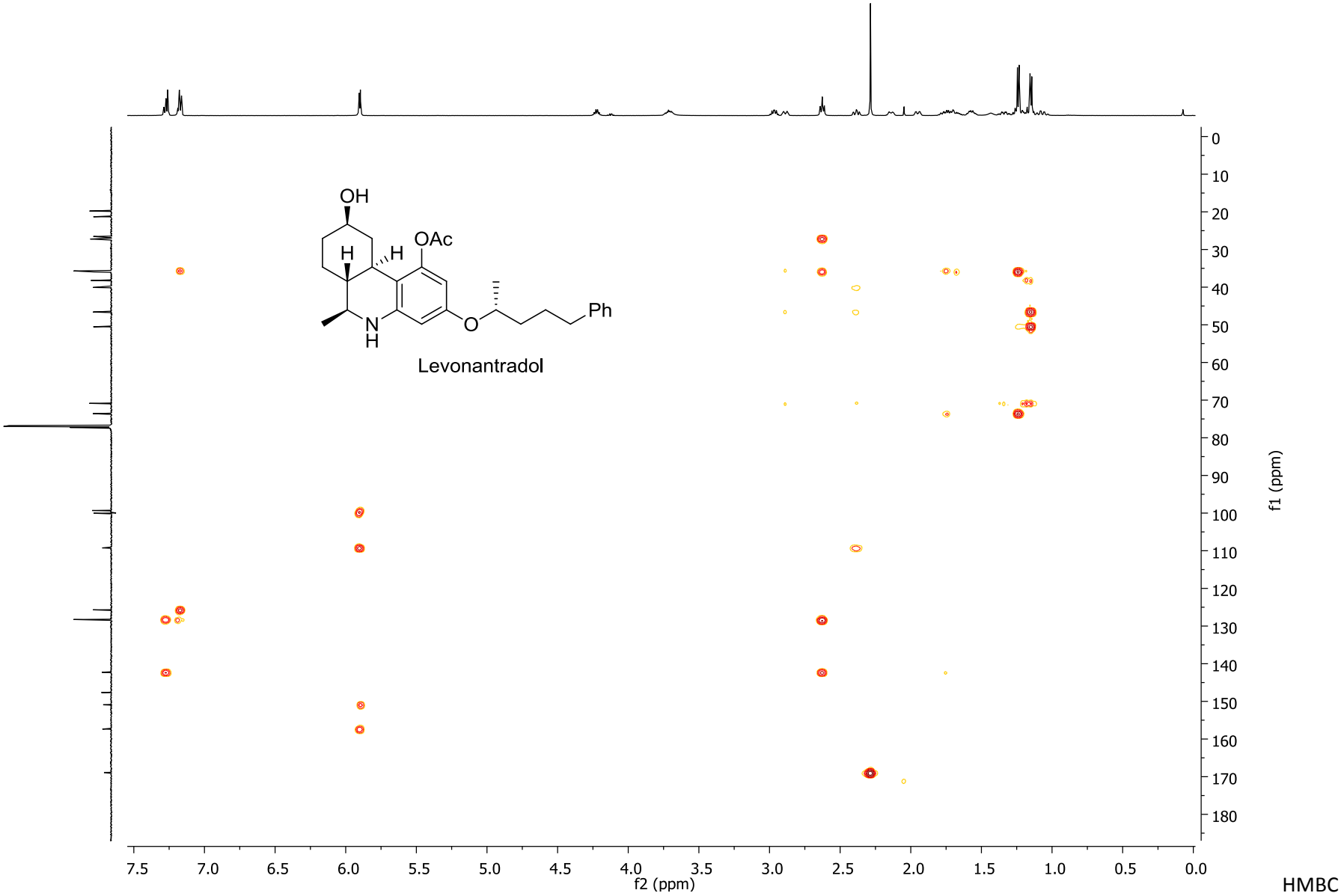

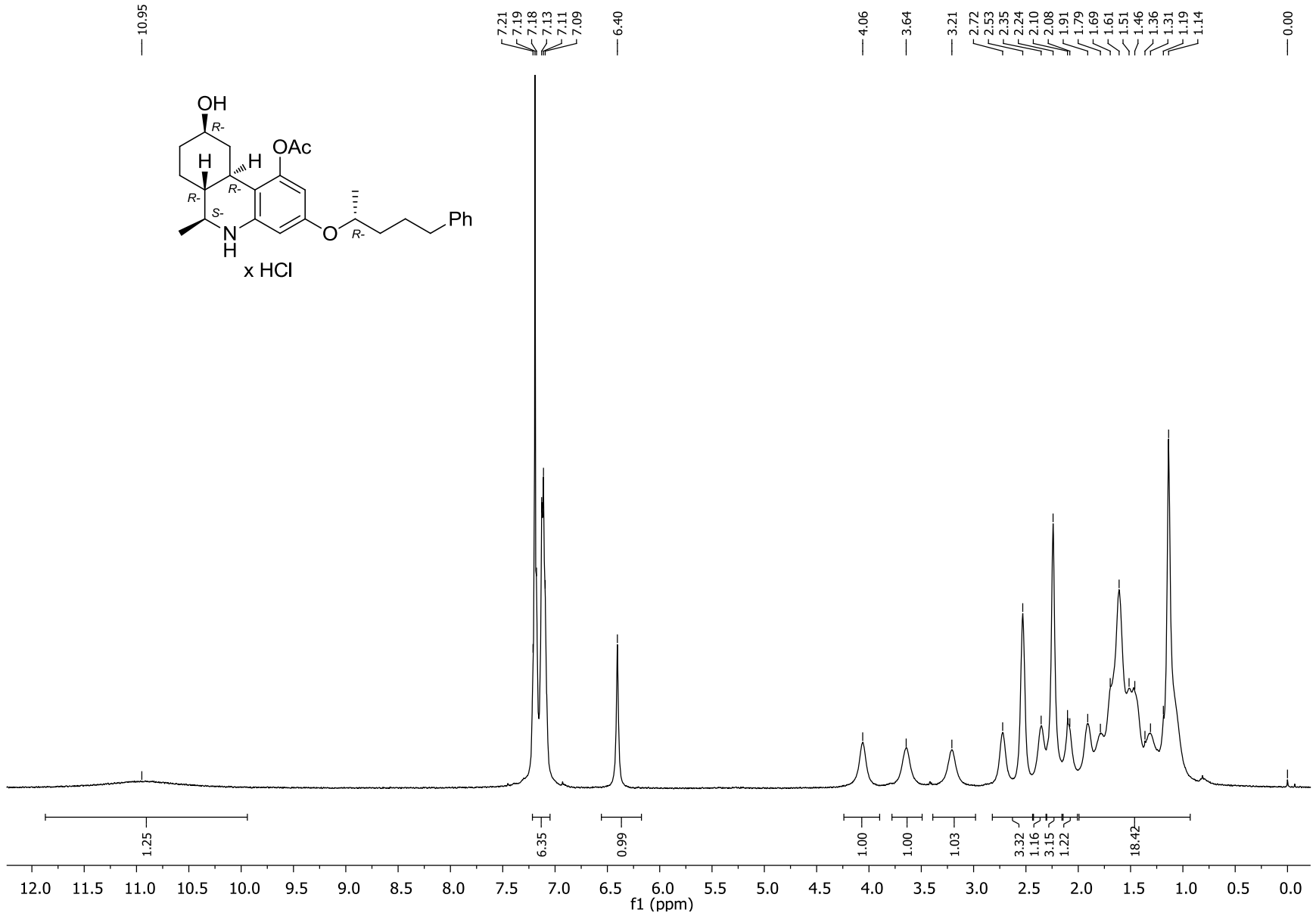

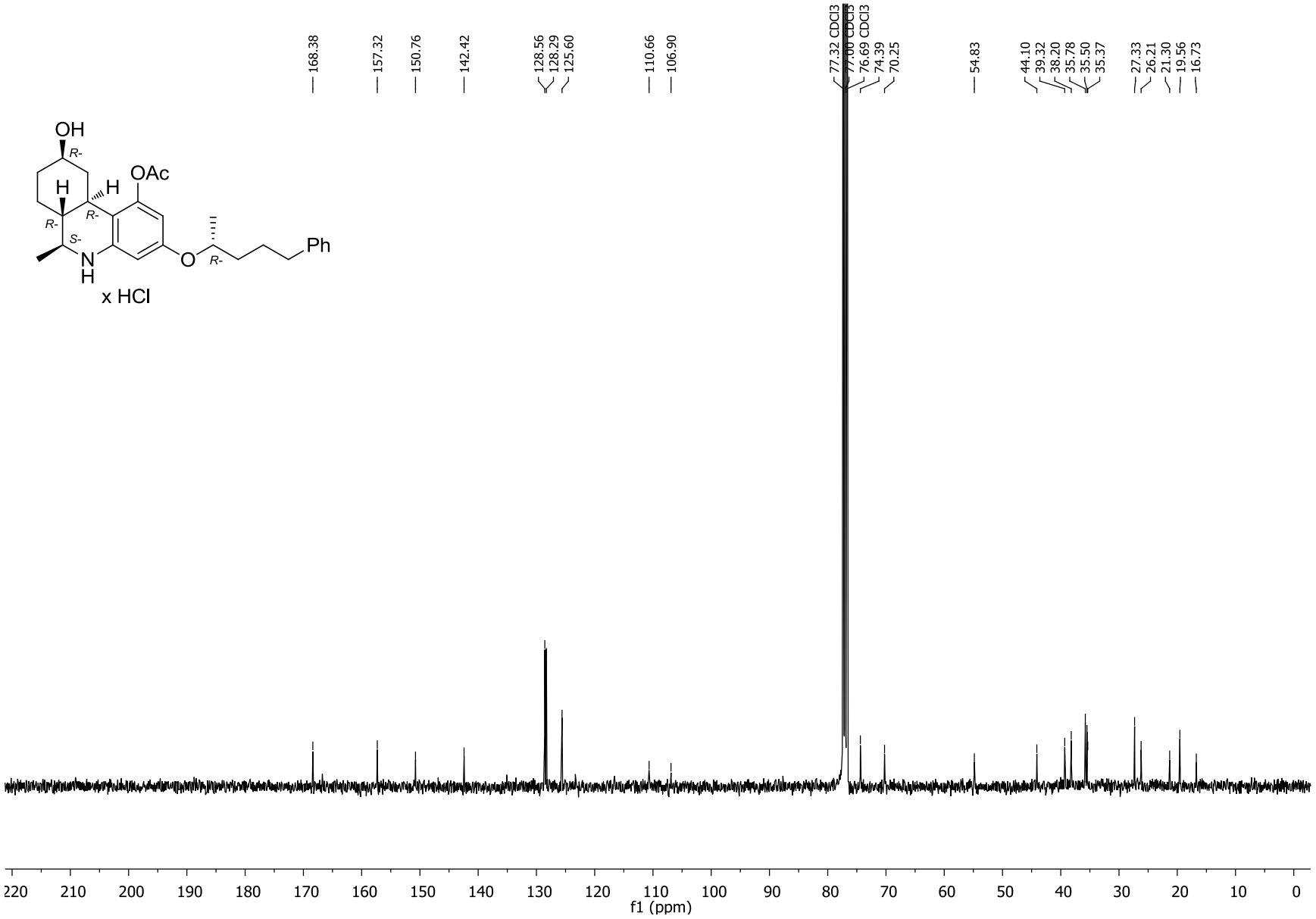
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142.42
128.56
128.29
125.60
110.66
106.90
77.32 CDCl3
77.00 CDCl3
76.69 CDCl3
74.39
70.25
54.83
44.10
39.32
38.20
35.78
35.50
35.37
27.33
26.21
21.30
19.56
16.73
OH
R-
H
H
OAc
R-
R-
S-
N
H
O
R-
Ph
x HCl
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)