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SUPPORTING INFORMATION

Heck reaction on Morita-Baylis-Hillman adduct: diastereoselective synthesis of pyrrolizidinones and pyrrolizidines

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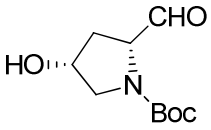
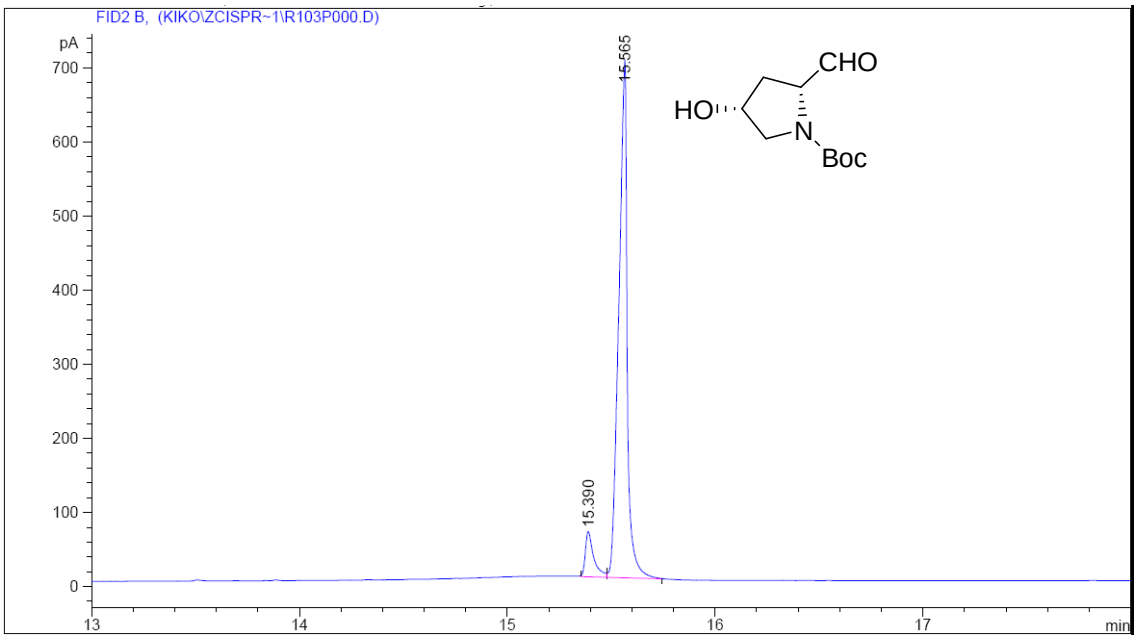
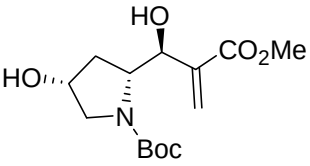
ATTACHMENT 1

Experimental procedures



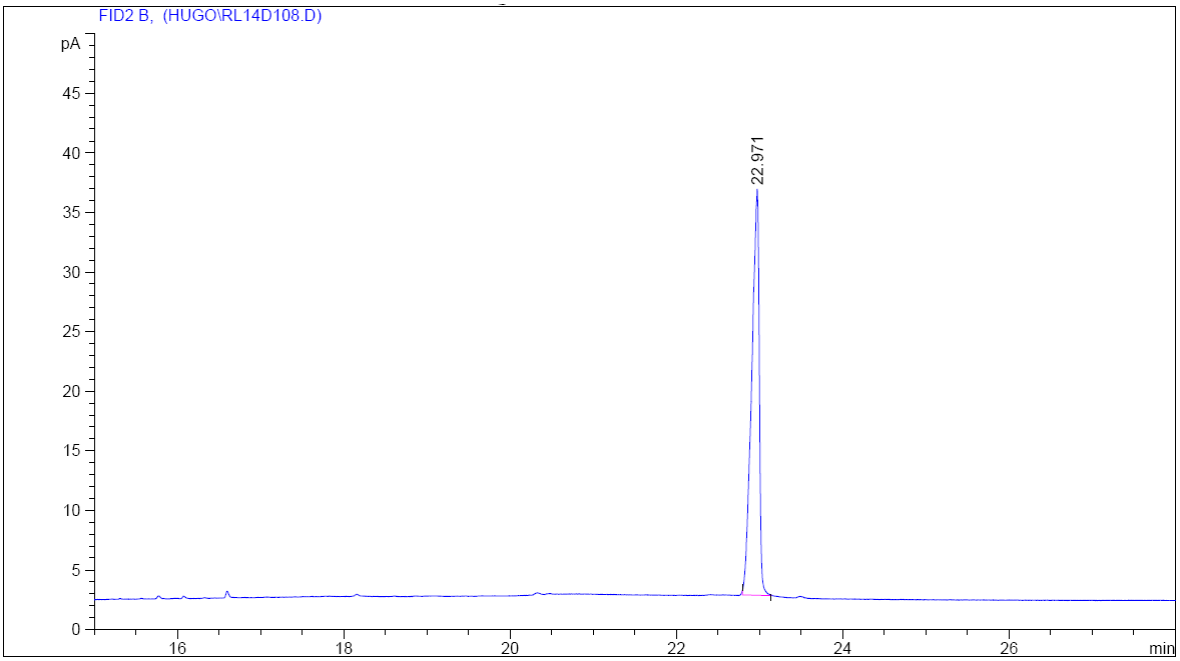
(2*R*,4*R*)-*tert*-Butyl 2-formyl-4-hydroxypyrrolidine-1-carboxylate (7): A stirred solution of (2*R*,4*R*)-1-*tert*-butyl 2-ethyl 4-methoxypyrrolidine-1,2-dicarboxylate (0.25 g, 0.96 mmol, see attachment I for experimental details) in anhydrous dichloromethane (5 mL), at -84 ºC and under argon atmosphere, was slowly added (during 5 minutes) a toluene solution of DIBAL-H (1.0 mol/L solution, 1.9 ml, 2.89 mmol). The mixture was stirred for 20 min. At the same temperature and the evolution was followed by TLC. The cooling bath was removed and a saturated solution of sodium acetate (5 mL) was added. The reaction medium was poured into a stirred mixture of ethyl ether (50 mL) and saturated ammonium chloride (10 mL). After 2h, the gel formed was filtered over a pad of Celite® and the aqueous filtrate was extracted again with ethyl ether. The organic phases were combined, dried over anhydrous Na_2SO_4 and evaporated. The residue was quickly filtered over a tiny amount of silica gel (Hexane : AcOEt 40:60 to 20:80), to provide aldeyde **7**, as colorless oil (0.190 g) in 92 % yield. Hydroxy-aldehyde **7** should be stored at -20 ºC or used immediately after be prepared. $[\alpha]_D^{20}$ +45 (c 1.5; MeOH); IR (Film, ν_{max}): 3377, 2974, 2931, 2838, 1728, 1646, 1428, 1370, 1279 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6, 90 ºC) δ 1.42 (9H, s), 1.89 (1H, m), 2.23 (1H, m), 3.31 (1H, dd); 3.42 (1H, dd), 4.04 (1H, m), 4.27 (1H, m), 9.47 (1H, s); ^{13}C NMR (62.5 MHz, DMSO-d_6, 90 ºC) δ 28.5, 38.1, 55.2, 64.1, 68.7, 79.7, 154.7, 202.8; HRMS (ESI-TOF) Calcd. for $C_{10}H_{18}NO_4$ $[M + H]^+$ 216.1236. Found 216.1245. GC conditions: HP chiral, flow 1.5 mL/min; 100 °C; 10 °C/min up to 230 ºC; pos run: 230 °C/15 min); T_R = 15.57 min (**2**); dr = 1:12.

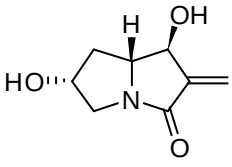




2*R*,4*R*)-*tert*-Butyl 4-hydroxy-2-((*S*)-1-hydroxy-2-(methoxycarbonyl)allyl)pyrrolidine-1-carboxylate (8): A mixture of hydroxy-aldehyde **7** (0.23 g, 1.069 mmol), DABCO (0.12 g, 1.069 mmol) and ethyl acrylate (2 mL) was sonicated for

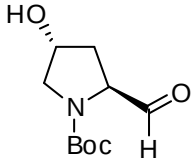
96 h (followed by GC). Then, the excess of methyl acrylate was removed under reduced pressure (**CAUTION**: this operation should be performed under an efficient fume hood). The residue was diluted with dichloromethane (20 mL). The organic phase was washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4 and evaporated. The crude residue was purified by flash silica gel column chromatography (Hexane : CH_2Cl_2 : AcOEt – 3.0:5.0:3.0) to provide adduct **8** (0.258 g), as a colorless oil, in 80 % yield. $[\alpha]_D^{20}$ -2 (c 1.5; MeOH); IR (Film, ν_{max}): 3387, 2970, 2958, 2933, 2355, 2332, 1715, 1666, 1413, 1368, 1155, 1090; ^{1}H NMR (250 MHz, DMSO-d_6, 90 °C) δ 1.43 (s, 9H), 1.74 (dt, *J* = 13.9, 4.3 Hz, 1H), 1.92 (m, 1H), 3.10 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.57 (dd, *J* = 11.2, 5.9 Hz, 1H), 3.71 (s, 3H), 4.05 (m, 2H), 4.94 (m, 1H), 5.87 (t, *J* = 1.6 Hz, 1H), 6.17 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6, 90 ºC) δ 27.8, 32.9, 50.8, 54.8, 58.6, 67.4, 68.0, 78.0, 124.0, 142.2, 153.2, 165.6; HRMS (ESI-TOF) Calcd. for $C_{14}H_{24}NO_6$ $[M + H]^+$ 302.1604. Found 302.1681; GC conditions: HP chiral, flow 1.5 mL/min; 100 °C; 10 °C/min up to 230 ºC; pos run: 230 °C/15 min); T_R = 22.97 min.



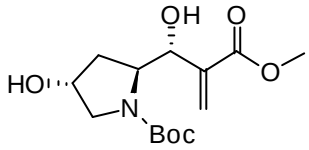


(1*S*,6*R*,7a*R*)-1,6-dihydroxy-2-methylenetetrahydro-1*H*-pyrrolizin-3(2*H*)-one (11): To a stirred solution of Morita-Baylis-Hillman adduct **8** (0.20 g, 0.66 mmol) in toluene (3 mL), at 0 °C, was added concentrated HCl (0.1 mL, 3.31 mmol). The resulting mixture was further stirred for 5-7 min. Then, a 35% solution of NaOH was added (0.46 mL, 4 mmol) and the reaction was further stirred for 30 min, at room temperature. The medium was neutralized to pH 7 (10% HCl solution) and the solvents were removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography (CH_2Cl_2 : MeOH - 95:05) to give pyrrolizidinone **11** (0.06 g) as a white solid, in 57 % yield. $[\alpha]_D^{20}$ -5 (c 2; EtOH); M.p. 93-94° C; IR (KBr): ν 3396, 3205, 2985, 2946, 2883, 1654, 1442 cm^{-1}. ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 1.67 (m, *J* = 13.4, 6.4, 4.4 Hz, 1H, H-7A), 2.35 (ddd, *J* = 13.4, 7.3, 5.6 Hz, 1H, H-7B), 3.17 (dd, *J* = 12.2, 5.2 Hz, 1H,

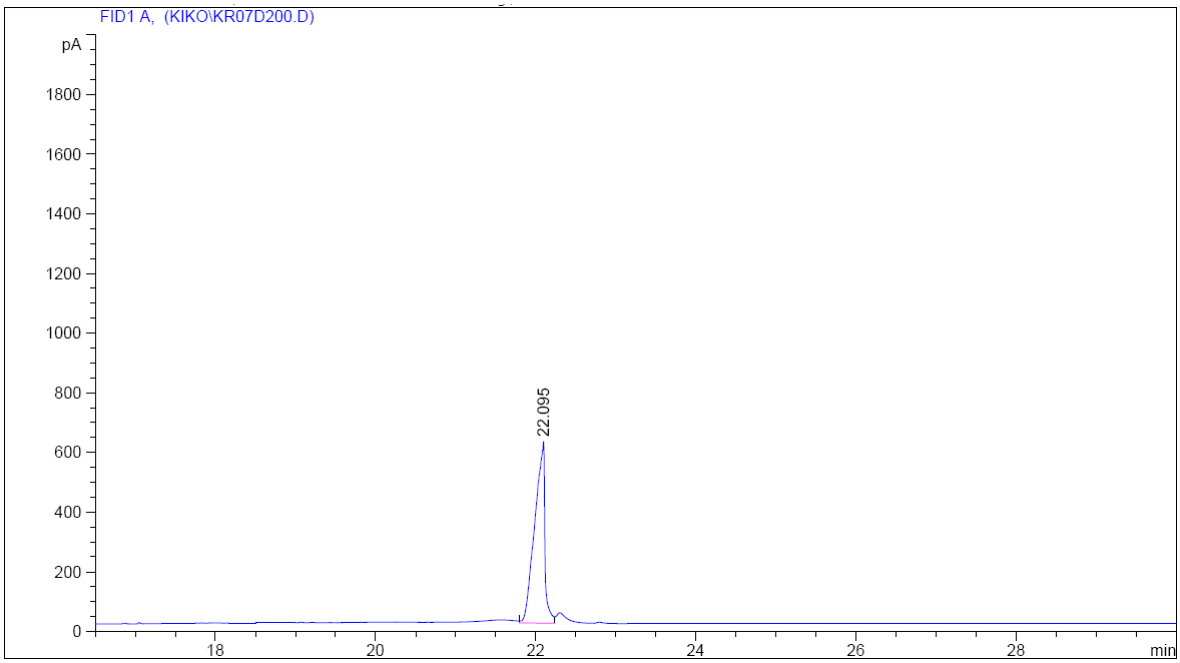
H-5B), 3.57 (dd, *J* = 12.2, 2.9 Hz, 1H, H-5A), 3.62 (ddd, *J* = 7.3, 6.4, 5.2 Hz, 1H, H-7a), 4.51 (m, *J* = 5.2, 3.2 Hz, 1H, H-6), 4.61 (m, *J* = 5.2, 2.9 Hz, 1H, H-1), 5.47 (d, *J* = 2.6 Hz, 1H, CH_2), 5.82 (d, *J* = 3.0 Hz, 1H, CH_2); ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$) δ 38.3, 51.6, 65.7, 71.9, 75.7, 114.8, 148.4, 168.3; HRMS (ESI-TOF) Calcd. for $C_8H_{12}NO_3$ $[M + H]^+$ 170.0817. Found 170.0864.

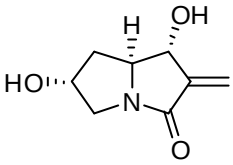


(2*S*,4*R*)-tert-butyl 2-formyl-4-hydroxypyrrolidine-1-carboxylate (9): A stirred solution of (2*S*,4*R*)-1-*tert*-butyl 2-ethyl 4-methoxypyrrolidine-1,2-dicarboxylate (0.25 g, 0.96 mmol, *compound **III**, for details, see attachment I at the end of this supporting informations*) in anhydrous dichloromethane (5 mL), at -84 ºC and under argon atmosphere, was slowly added (during 5 minutes) a toluene solution of DIBAL-H (1.0 mol/L solution, 1.9 ml, 2.89 mmol). The mixture was stirred for 20 min. At the same temperature. The reaction evolution was followed by TLC. The cooling bath was removed and a saturated solution of sodium acetate (5 mL) was added. The reaction medium was poured into a stirred mixture of ethyl ether (50 mL) and saturated ammonium chloride (10 mL). After 2h, the gel formed was filtered over a pad of Celite® and the aqueous filtrate was extracted again with ethyl ether. The organic phases were combined, dried over anhydrous Na_2SO_4 and evaporated. The residue was quickly filtered over a tiny amount of silica gel (Hexane : AcOEt 40:60 to 20:80), to provide aldeyde **9**, as colorless oil (0.188 g) in 91 % yield. Hydroxy-aldehyde **9** should be stored at -20 ºC or used immediately after be prepared. $[\alpha]_D^{20}$ -54.5 (c 1.5; MeOH); IR (Film, ν_{max}): 3395, 2978, 2933, 1736, 1669, 1409, 1365, 1160, 1123 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, 90 ºC) δ 1.42 (s, 9H), 1.96 (m, 2H), 3.43 (m, 2H), 4.14 (m, 1H), 4.25 (m, 1H), 9.43 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, 90 ºC) δ 28.5, 35.8, 55.5, 64.0, 68.7, 79.9, 154.2, 200.7; HRMS (ESI-TOF) Calcd. for $C_{10}H_{18}NO_4$ $[M + H]^+$ 216.1236. Found 216.1365. GC conditions: HP chiral, flow 1.5 mL/min; 100 °C; 10 °C/min up to 230 ºC; pos run: 230 °C/15 min); T_R = 15.39 min.

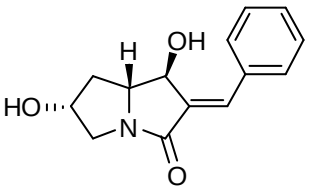


(2*S*,4*R*)-*tert*-butyl 4-hydroxy-2-((*R*)-1-hydroxy-2-(methoxycarbonyl)allyl)pyrrolidine-1-carboxylate (10): A mixture of hydroxy-aldehyde **9** (0.23 g, 1.069 mmol), DABCO (0.12 g, 1.069 mmol) and ethyl acrylate (2 mL) was sonicated for 96 h (followed by GC). Then, the excess of methyl acrylate was removed under reduced pressure (**CAUTION**: this operation should be performed under an efficient fume hood). The residue was diluted with dichloromethane (20 mL). The organic phase was washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4 and evaporated. The crude residue was purified by flash silica gel column chromatography (Hexane : CH_2Cl_2 : AcOEt – 3.0:5.0:3.0) to provide adducts **8** (0.206 g, see above for full spectral characterization) and **10** (0.052 g, spectral data below), as a colorless oil, in 70 % yield.
$[\alpha]_D^{20}$ -11 (c 1.5; MeOH); IR (Film, ν_{max}): 3402, 2879, 2952, 1720, 1670, 1417, 1368, 1273, 1163, 1092 cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6, 90 °C) δ 1.45 (s, 9H), 1.52 (m, 1H), 1.98 (dt, *J* = 12.0, 5.9 Hz, 1H), 3.30 (m, 2H), 3.71 (s, 3H), 4.07 (m, 1H), 4.23 (s, 1H), 4.90 (s, 2H), 5.86 (s, 1H), 6.12 (s, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6, 90 ºC) δ 27.8, 33.2, 50.8, 55.0, 58.4, 67.8, 68.1, 77.7, 123.6, 142.0, 153.5, 165.7; HRMS (ESI-TOF) Calcd. for $C_{14}H_{24}NO_6$ $[M + H]^+$ 302.1604. Found 302.1634. GC conditions: HP chiral, flow 1.5 mL/min; 100 °C; 10 °C/min up to 230 ºC; pos run: 230 °C/15 min); T_R = 22.09 min.



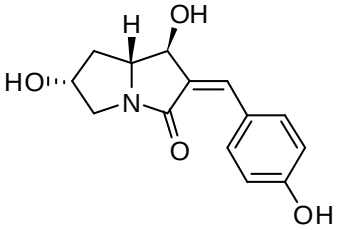


(1*R*,6*R*,7a*S*)-1,6-dihydroxy-2-methylenetetrahydro-1*H*-pyrrolizin-3(2*H*)-one (12): To a stirred solution of Morita-Baylis-Hillman adduct **10** (0.05 g, 0.165 mmol) in toluene (1 mL), at 0 °C, was added concentrated HCl (300 μL, 1.1 mmol). The resulting mixture was further stirred for 5-7 min. Then, a 35% solution of NaOH was added (0.16 mL, 1 mmol) and the reaction was further stirred for 30 min, at room temperature. The medium was neutralized to pH 7 (10% HCl solution) and the solvents were removed under reduced pressure. The crude residue was purified by flash silica gel column chromatography (CH_2Cl_2 : MeOH - 95:05) to give pyrrolizidinone **12** (0.012 g) as a white solid, in 55 % yield. $[\alpha]_D^{20}$ -12 (c 2; DMSO); IR (Film, ν_{max}): ν 3377, 3206, 2985, 2946, 2928, 1657, 1440 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 1.59 (ddd, *J* = 13.0, 10.8, 5.1 Hz, H-7B), 2.16 (dd, *J* = 13.0, 5.6 Hz, H-7A), 3.03 (d, *J* = 13.1 Hz, H-5A), 3.73 (dd, *J* = 13.0, 5.2 Hz, H-5B), 3.89 (dt, *J* = 10.5, 5.2 Hz, H-7a), 4.53 (dt, *J* = 5.1, 2.7 Hz, H-1), 4.59 (t, *J* = 5.1 Hz, H-6), 5.49 (d, *J* = 2.5 Hz, 1H, CH_2), 5.83 (d, *J* = 2.9 Hz, 1H, CH_2); ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$) δ 39.3, 51.6, 66.6, 72.8, 74.2, 116.9, 148.5, 167.9; HRMS (ESI-TOF) Calcd. for $C_8H_{12}NO_3$ $[M + H]^+$ 170.0817. Found 170.0862.



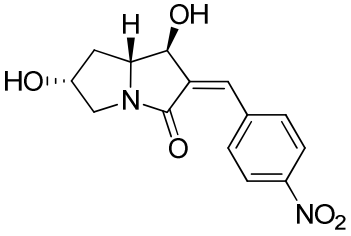
(1*S*,6*R*,7a*R*,*E*)-2-benzylidene-1,6-dihydroxytetrahydro-1*H*-pyrrolizin-3(2*H*)-one (14): To a solution of pyrrolizidinone **11** (0.13 g, 0.77 mmol) in DMF (3 mL) was added iodobenzene (0.184 g, 0.92 mmol, 0.1 mL) de iodobenzeno, triethylamine (0.218 g, 2.16 mmol, 0.3 mL) and Nájera palladacycle **13** (0.5 mol%, 0.004 mmol, 0.003 g). The resulting dark brown solution was stirred for 5h, at 110-120 °C. Then the solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography (CH_2Cl_2:MeOH – solvent gradient: 0:100 to 97:03), to provide benzylidene-pyrrolizidinone **14** (0.14 g), as a colorless oil, in 76 %. $[\alpha]_D^{20}$ + 40 (c 1, MeOH); IR (Film, ν_{max}): 3427, 3195, 2940, 2855, 1668, 1634, 1493, 1424,

1268, 1156, 1067 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 1.30 (m, *J* = 13.8, 9.1, 5.4 Hz, 1H, H-7A), 2.38 (m, *J* = 13.8, 6.8 Hz, 1H, H-7B), 3.27 (dd, *J* = 12.3, 6.1 Hz, 1H, H-5B), 3.56 (dd, *J* = 12.3, 3.3 Hz, 1H, H-5A), 3.69 (ddd, *J* = 9.1, 7.4, 1.8 Hz, 1H, H-7a), 4.47 (qd, *J* = 6.1, 3.3 Hz, 1H, H-6), 4.91 (dd, *J* = 1.8 Hz, 1H, H-1), 7.35 (d, *J* = 2.1 Hz, 1H, CH), 7.41 (m, 3H, Ph), 7.79 (m, 2H, Ph); ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$) δ 38.1, 52.1, 68.2, 70.1, 72.0, 129.2, 130.3, 131.3, 134.1, 134.2, 137.1, 172.1; HRMS (ESI-TOF) Calcd. for $C_{14}H_{16}NO_3$ $[M + H]^+$ 246.1130. Found 246.1168.



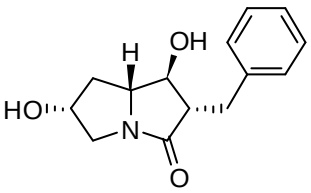
1*S*,6*R*,7a*R*,*Z*)-1,6-dihydroxy-2-(4-hydroxybenzylidene)tetrahydro-1*H*-pyrrolizin-3(2*H*)-one (15): To a solution of pyrrolizidinone **11** (0.25 g, 1.48 mmol) in DMF (3 mL) was added 4-iodophenol (0.49 g, 2.22 mmol), triethylamine (0.746 g, 7.39 mmol, 1.0 mL), Cy_2NMe (0.216 g, 1.11 mmol, 0.24 mL) and Najera palladacycle **13** (0.5 mol%, 0.007 mmol, 0.006 g). The resulting brown solution was stirred for 8 h, at 110-120 °C. After, the solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography (CH_2Cl_2:MeOH – solvent gradient 0:100 to 97:03) to give hydroxybenzylidene-pyrrolizidinone **15** (0.20 g), as a colorless oil, in 51 % yield. $[\alpha]_D^{20}$ + 32 (c 1, MeOH); IR (Film, ν_{max}): 3333, 2941, 1668, 1633, 1603, 1515, 1432, 1413, 1274, 1175, 1066 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 1.36 (m, *J* = 13.3, 9.3, 5.7 Hz, 1H, H-7A), 2.50 (dt, *J* = 13.3, 6.8 Hz, 1H, H-7B), 3.39 (dd, *J* = 12.6, 6.3 Hz, 1H, H-5B), 3.55 (dd, *J* = 12.6, 3.4 Hz, 1H, H-5A), 3.78 (t, *J* = 8.3 Hz, 1H, H-7a), 4.60 (m, 1H, H-6), 5.07 (t, *J* = 1.8 Hz, 1H, H-1), 6.89 (d, *J* = 8.7 Hz, 2H, Ar), 7.28 (d, *J* = 1.8 Hz, 1H, CH), 7.59 (d, *J* = 8.7 Hz, 2H, Ar); ^{13}C NMR (62,5 MHz, $(CD_3)_2CO$) 39.9, 53.5, 68.8, 70.7, 73.0, 116.4, 127.4, 132.5, 133.8, 136.3, 159.6, 172.4; HRMS (ESI-TOF) Calcd. for $C_{14}H_{16}NO_4$ $[M + H]^+$ 262.1079. Found 262.1122.

(1*S*,6*R*,7a*R*,*Z*)-1,6-dihidroxi-2-(4-nitrobenzilideno)tetrahidro-1*H*-pirrolizin-3(2*H*)-ona (**16**):

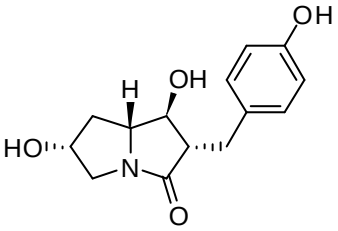


To a solution of pyrrolizidinone **11** (0.30 mmol, 0.05 g) em DMF (3 mL) were added 4-nitro-iodobenzene (1.5 equiv., 0.44 mmol, 0.11 g), triethylamine (5.0 equiv., 1.48 mmol, 0.2 mL), *N*-Methyl-dicyclohexylamine (Cy_2NMe, 0.75 equiv., 0.22 mmol, 0.04 mL), Nájera´s palladacycle I (**13**, 0.5 mol%, 0.002 mmol, 0.001 g). The resulting solution was stirred at 110-120 °C for 8 hs. After that, the solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography (230-400 mesh; CH_2Cl_2 : MeOH - 0:100 to 95:05) to afford 0.07 of benzylidene-pyrrolizididinone **16**, as a colorless oil, in 83% yield. $[\alpha]_D^{20}$ + 28° (c 2, MeOH); IR (Film, ν_{max}): 3308, 2974, 2924, 2864, 1699, 1671, 1644, 1596, 1523, 1513, 1435, 1381, 1346, 1314, 1264, 1244, 1220, 1202, 1133, 1104, 1075, 1055 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.49 (ddd, *J* = 13.2, 8.3, 5.1 Hz, 1H, H-7A); 2.49 (ddd, *J* = 13.3, 7.4, 6.2 Hz, 1H, H-7B); 3.38 (dd, *J* = 12.4, 5.8 Hz, 1H, H-5B); 3.68 (dd, *J* = 12.4, 3.0 Hz, 1H, H-5A); 3.80 (td, *J* = 8.1, 2.4 Hz, 1H, H-7a); 4.56 (qd, *J* = 5.8, 3.3 Hz 1H, H-6); 5.01 (t, *J* = 2.4 Hz, 1H, H-1); 7.45 (d, *J* = 2.3 Hz, 1H, CH); 8.01 (d, *J* = 8.8 Hz, 2H, Ar); 8.26 (d, *J* = 8.9 Hz, 2H, Ar); ^{13}C NMRN (62.5 MHz, CD_3CN) 39.2; 53.3; 68.4; 71.5; 72.5; 124.3;

132.4; 133.2; 140.5; 141.8; 148.6; 170.9; HRMS (ESI-TOF) *m/z* Calc. for $C_{14}H_{15}N_2O_5$ [M + H]$^+$: 291.0981. Found 291.0989.



(1*S*,2*S*,6*R*,7a*R*)-2-benzyl-1,6-dihydroxytetrahydro-1*H*-pyrrolizin-3(2*H*)-one (18): In a Parr® hydrogenation reactor was added a methanolic solution (5 mL) of pyrrolizidinone **14** (0.06 g, 0.24 mmol), followed by the addition of 10% Pd/C catalyst (20 mol%, 0.012 g). The reaction was stirred under a hydrogen pressure of 200 psi for 25 h, at room temperature. After that, the medium was filtered over a pad of Celite®. The solid was washed with methanol and the combined organic phases were evaporated. The residue was purified by flash silica gel column chromatography (CH_2Cl_2:MeOH – solvent gradient: 0:100 to 97:03) to afford reduced benzyl-pyrrolizidinone **18** (0.06 g), as a white solid, in 97 %. $[\alpha]_D^{20}$ + 51 (c 1, MeOH); M. p. 135-136° C; IR (KBr, ν_{max}): 3404, 3232, 2987, 2936, 2897, 2871, 1670, 1447, 1416, 1375, 1300, 1263, 1222,1175, 1121 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.55 (dddd, *J* = 13.4, 5.3, 4.0, 1.0 Hz, 1H), 2.25 (ddd, *J* = 13.4, 8.0, 5.4 Hz, 1H), 2.93 (m, 2H), 3.02 (m, *J* = 7.5, 1.8 Hz, 1H), 3.08 (ddd, *J* = 12.0, 4.9, 1.3 Hz, 1H), 3.52 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.64 (m, *J* = 8.0, 7.0, 5.3 Hz, 1H), 3.88 (dd, *J* = 9.4, 7.0 Hz, 1H), 4.41 (m, *J* = 5.1, 4.0, 3.0 Hz, 1H), 7.15 (m, 1H), 7.23 (m, 2H), 7.29 (m, 2H); ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$) δ 34.4, 38.6, 52.3, 54.0, 65.6, 72.4, 80.6, 126.5, 128.7, 130.3, 141.0, 175.6; HRMS (ESI-TOF) Calcd. for $C_{14}H_{18}NO_3$ [M + H]$^+$ 248.1287. Found 248.1286.

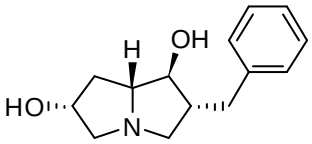


(1*S*,2*S*,6*R*,7a*R*)-1,6-dihydroxy-2-(4-hydroxybenzyl)tetrahydro-1*H*-pyrrolizin-3(2*H*)-one (20): The same experimental procedure described previously was used to obtain pyrrolizidinone **20** (0.059 g), as a colorless oil, in 95 % yield. Reaction time: 48 h; $[\alpha]_D^{20}$ 185 (c 1, MeOH); IR (Film, ν_{max}): 3351, 3031, 2923, 1669, 1515, 1443, 1366, 1237, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 1.44 (m, 1H, H-7A), 2.22 (ddd, *J* = 13.3, 7.0, 5.6 Hz, 1H, H-7B), 2.73 (td, *J* = 31.8, 7.3, 3.6 Hz, 1H, CH_2), 2.84 (m, *J* = 31.8, 13.3, 8.0 Hz, CH_2, *J* = 8.6, 7.0, 4.4 Hz, H-2, 2H), 3.06 (m, *J* = 12.1, 5.2 Hz, 1H, H-5B), 3.36 (dd, *J* = 12.1, 3.1 Hz, 1H, H-5A), 3.60 (q, $J_{1,7a=7a,7A=7a,7B}$ = 7.0, Hz, 1H, H-7a), 3.84 (dd, $J_{1,2}$ = 8.9, $J_{1,7a}$ = 7.0 Hz, 1H, H-1), 4.40 (m, *J* = 5.1, 9.0 Hz, 1H, H-6), 6.65 (m, *J* = 5.5 Hz, 2H, Ph), 7.03 (m, *J* = 5.5 Hz, 2H, Ph); ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$) δ 32.5, 37.6, 50.8, 53.8, 65.0, 72.0, 78.7, 115.5, 130.5, 131.0, 155.1, 175.9; HRMS (ESI-TOF) Calcd. for $C_{14}H_{18}NO_4$ [M + H]$^+$ 264.1236. Found 264.1318.

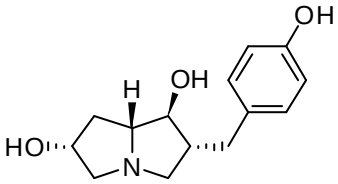
General experimental procedure for the amide carbonyl reduction of pyrrolizidinones 14, 15, 18, 20:

For example, to a solution of pyrrolizidinone **18** (0.063 g, 0.25 mmol) in anhydrous THF (5 mL) was added a freshly prepared solution of AlH_3 in THF (1 mol/L, 10 equiv., 2.5 mmol, 2.3 mL). *The AlH_3 solution was prepared as follow: A solution of $LiAlH_4$ (2,4 mol/L, 2.5 mL, THF) was added, at 0° C, to a solution of $AlCl_3$ (2 mmol, 0.27 g) in anydrous THF (5 mL). The resulting solution was stirred for 40 min).* After addition, the reaction medium was stirred for 30-60 min, at room temperature. Then, the medium was quenched with a saturated solution of Na_2SO_4 and filtered over a pad of Celite® and the solvents were removed under reduced pressure. The residue was purified by neutral alumina column

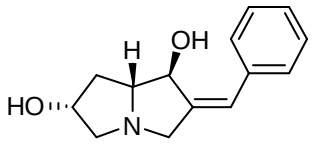
chromatography (eluting system CH_2Cl_2:MeOH 9,0:1,0) for compounds **18** and **20**, and eluting system CH_2Cl_2:MeOH:NH_4OH (30 %) 7,8:2,0:0,2) for compounds **16** e **17**, to provide the corresponding pyrrolizidines **19** in 80% yield, **21** in 53% yield, **22** in 50% yield and **23** in 21% yield.



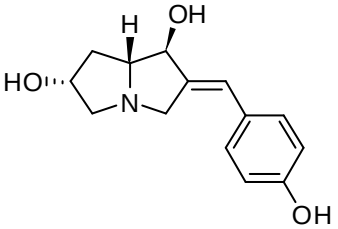
(1*S*,2*R*,6*R*,7a*R*)-2-benzylhexahydro-1*H*-pyrrolizine-1,6-diol (19): a colorless oil; $[\alpha]_D^{20}$ - 197 (c 1, MeOH); IR (Film, ν_{max}): 3325, 2926, 2899, 1447, 1383, 1296, 1114, 1073 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.82 (dt, *J* = 13.6, 4.3 Hz, 1H, H-7A), 2.16 (ddd, *J* = 13.6, 8.3, 5.4 Hz, 1H, H-7B), 2.31 (m, 1H, H-2), 2.59 (m, *J* = 14.0, 9.8 Hz (CH_2), *J* = 11.8, 4.0 Hz (H-5B), *J* = 11.0 Hz (H-3) 3H), 2.92 (dd, *J* = 11.8, 4.5 Hz, 1H, H-5A), 3.03 (m, *J* = 14.0, 4.1 Hz (CH_2), *J* = 11.0 Hz (H-3), 2H), 3.24 (td, $J_{1,7a}$ = 7.7, 4.8 Hz, 1H, H-7a), 3.88 (dd, $J_{1,2}$ = 9.5, $J_{1,7a}$ = 7.7 Hz, 1H, H-1), 4.39 (quin, *J* = 4.5 Hz, 1H, H-6), 7.26 (t, *J* = 6.9 Hz, 3H, Ph), 7.35 (t, *J* = 7.4 Hz, 2H, Ph); ^{13}C(100 MHz, D_2O) δ 35.7, 37.1, 48.6, 58.0, 60.3, 68.6, 73.1, 80.8, 126.3, 128.6, 128.9, 140.2; HRMS (ESI-TOF) calcd for $C_{14}H_{20}NO_2$ $[M + H]^+$ 234.1494, found 234.1491.



(1*S*,2*R*,6*R*,7a*R*)-2-(4-hydroxybenzyl)hexahydro-1*H*-pyrrolizine-1,6-diol (21): a colorless oil; $[\alpha]_D^{20}$ - 62 (c 1, MeOH); IR (Film, ν_{max}): 3333, 2927, 2594, 1613, 1596, 1514, 1444, 1365, 1247, 1117, 1088 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.99 (d, *J* = 13.2, 4.0 Hz, 1H, H-7A) 2.22 (ddd, *J* = 13.9, 8.9, 5.0 Hz, 1H, H-7B), 2.33 (m, 1H, H-2), 2.53 (dd, *J* = 13.9, 8.8 Hz, 1H, CH_2), 2.84 (dd, *J* = 12.1, 11.0 Hz, 1H, H-3), 2.91 (m, *J* = 13.9, 4.0 Hz (CH_2), *J* = 12.4, 3.8 Hz (H-5A), 2H), 3.16 (dd, *J* = 12.4, 4.1 Hz, 1H, H-5B), 3.38 (dd, *J* = 10.6, 6.9 Hz, 1H, H-3), 3.60 (td, *J* = 8.5, 3.4 Hz, 1H, H-7a), 3.98 (dd, $J_{1,2}$ = 9.6, $J_{1,7a}$ = 8.0 Hz, 1H, H-1), 4.49 (m, 1H, H-6), 6.78 (m, *J* = 8.5 Hz, 2H, Ar), 7.06 (d, *J* = 8.5 Hz, 2H, Ar); ^{13}C(100 MHz, D_2O) δ 33.8, 36.5, 47.8, 58.3, 60.3, 69.9, 72.4, 79.4, 115.8, 130.1, 130.3, 155.2. HRMS (ESI-TOF) Calcd. for $C_{14}H_{20}NO_3$ $[M + H]^+$ 250.1443. Found 250.1461.



(1*S*,6*R*,7a*R*,*Z*)-2-benzylidenehexahydro-1*H*-pyrrolizine-1,6-diol (22): a colorless oil; $[\alpha]_D^{20}$ -73 (c 1, MeOH); IR (Film, ν_{max}): 3406, 2925, 2855, 1646, 1495, 1448 1108, 1019 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 1.58 (m, *J* = 13.9, 8.4, 6.0 Hz, 1H, H-7A), 2.55 (m, *J* = 13.9, 8.4, 6.5 Hz, 1H, H-7B), 3.02 (dd, *J* = 11.9, 5.2 Hz, 1H, H-5B), 3.71 (dd, *J* = 11.9, 5.8 Hz, 1H, H-5A), 4.03 (d, *J* = 15.3 Hz, 1H, H-3), 4.22 (t, $J_{7a,7A=7a,7B}$ = 8.4 Hz, 1H, H-7a), 4.50 (quin, *J* = 5.8 Hz, 1H, H-6), 4.57 (d, *J* = 15.3 Hz, 1H, H-3), 4.70 (s, 1H, H-1), 6.79 (s, 1H, CH), 7.29 (t, *J* = 7.3 Hz, 1H, Ph), 7.37 (t, *J* = 7.5 Hz, 2H, Ph), 7.60 (d, *J* = 7.4 Hz, 2H, Ph); ^{13}C NMR (62.5 MHz, $(CD_3)_2CO$) δ 39.2, 60.0, 61.6, 71.6, 74.1, 75.8, 127.0, 127.7, 129.0, 129.6, 137.8, 142.8; HRMS (ESI-TOF) Calcd. for $C_{14}H_{18}NO_2$ $[M + H]^+$ 232.1338. Found 232.1380.

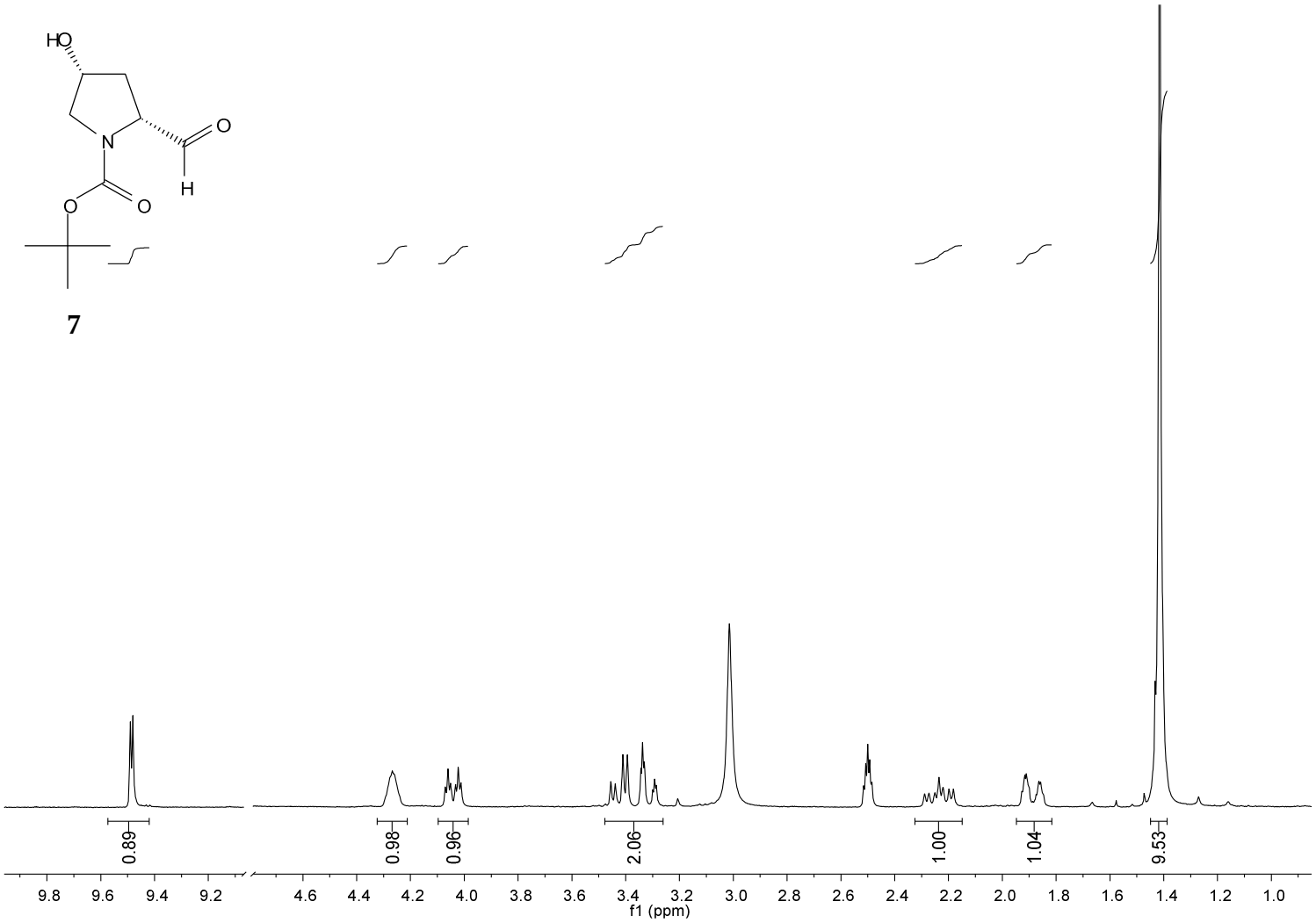


(1*S*,6*R*,7a*R*,*E*)-2-(4-hydroxybenzylidene)hexahydro-1*H*-pyrrolizine-1,6-diol (23): a colorless oil; $[\alpha]_D^{20}$ - 48 (c 0.7, MeOH); IR (Film, ν_{max}): 3431, 2923, 2852, 1628, 1603, 1509, 1416, 1384, 1364, 1268, 1242 cm^{-1}; ^1H NMR (400 MHz, D_2O)

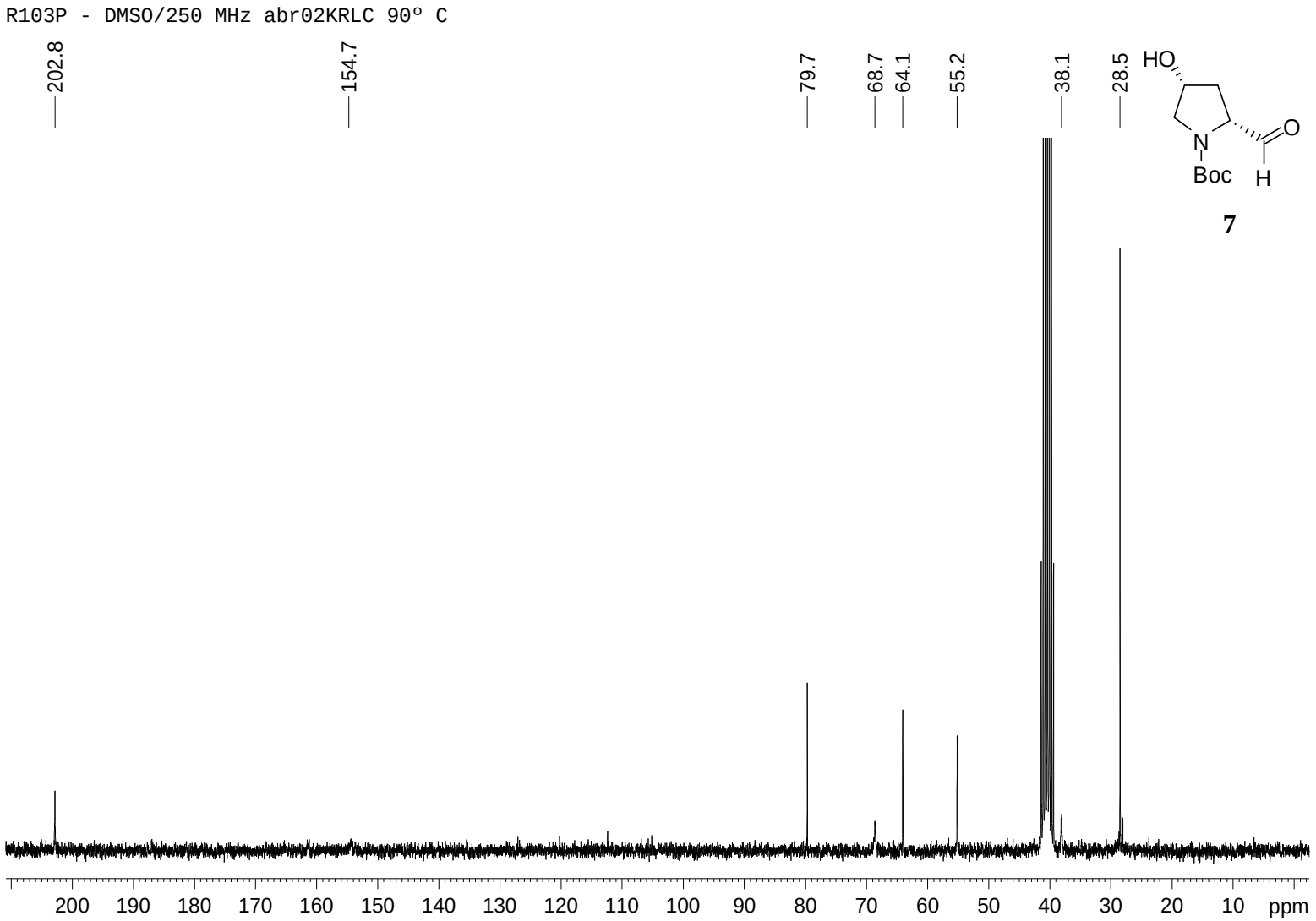
δ 1.77 (m, *J* = 13.6, 11.5, 5.6 Hz, 1H, H-7A), 2.46 (m, *J* = 13.9, 7.3 Hz, 1H, H-7B), 2.74 (dd, *J* = 11.5, 5.1 Hz, 1H, H-5B), 3.30 (dd, *J* = 11.5, 5.6 Hz, 1H, H-5A), 3.43 (m, *J* = 11.5, 7.0, 4.3 Hz, 1H, H-7a), 3.85 (d, *J* = 16.0, 1.5 Hz, 1H, H-3), 4.17 (d, *J* = 16.0 Hz, 1H, H-3), 4.47 (m, *J* = 5.6 Hz 1H, H-6), 4.70 (d, *J* = 4.3 Hz, 1H, H-1), 6.67 (s, 1H, CH), 6.83 (d, *J* = 8.5 Hz, 2H, Ar), 7.18 (d, *J* = 8.5 Hz, 2H, Ar); ^{13}C NMR (125 MHz, D_2O) δ 36.9, 55.3, 61.0, 69.5, 71.6, 79.5, 116.9, 126.1, 126.8, 130.6, 137.0, 159.5; HRMS (ESI-TOF) Calcd. for $C_{14}H_{18}NO_3$ $[M + H]^+$ 248.1287. Found 248.1289.

References:

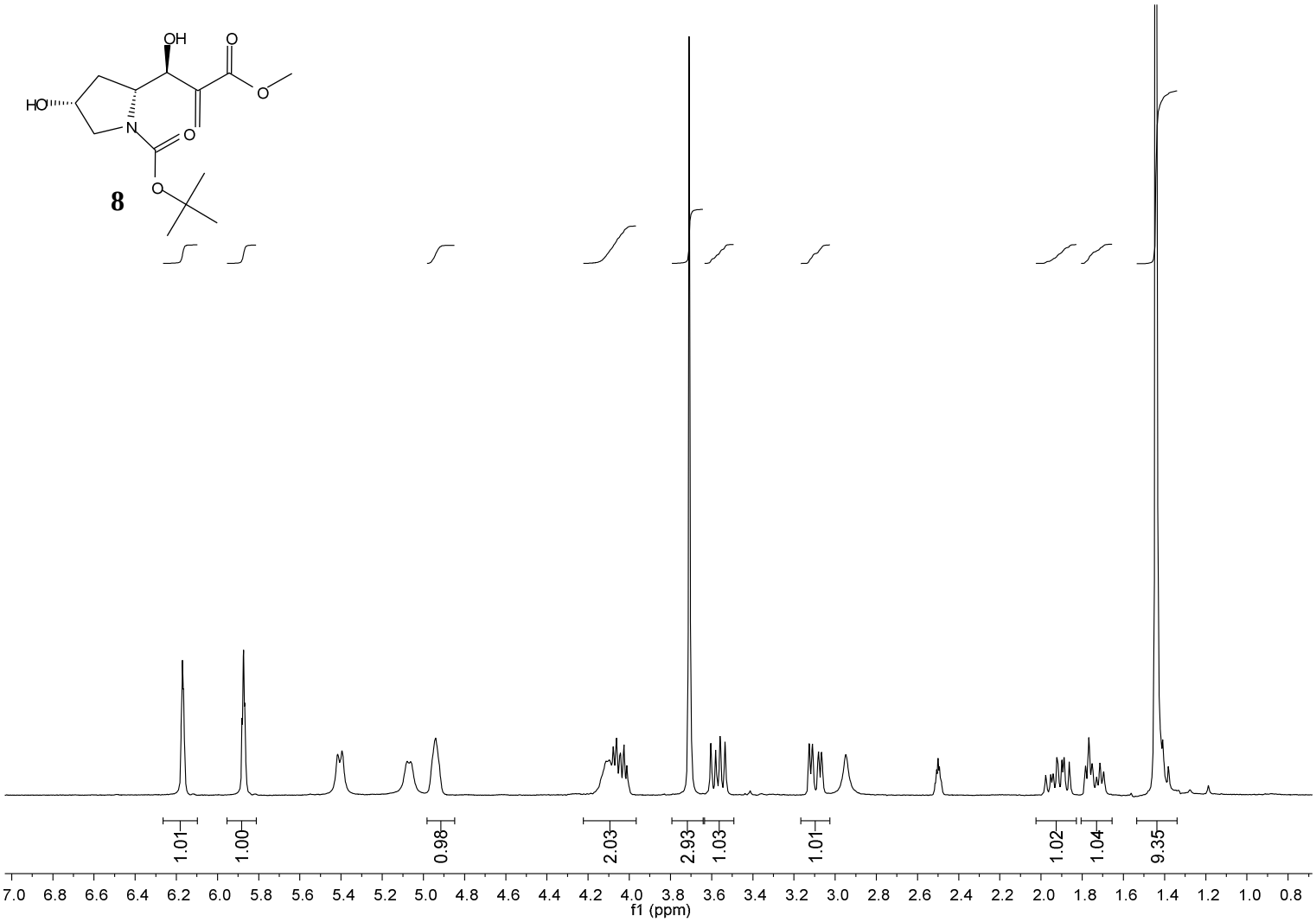
1. Kimura, R.; Nagano, T.; Kinoshita, H. *Bull. Chem. Soc. Jpn* **2002**, *75*, 2517-2525.



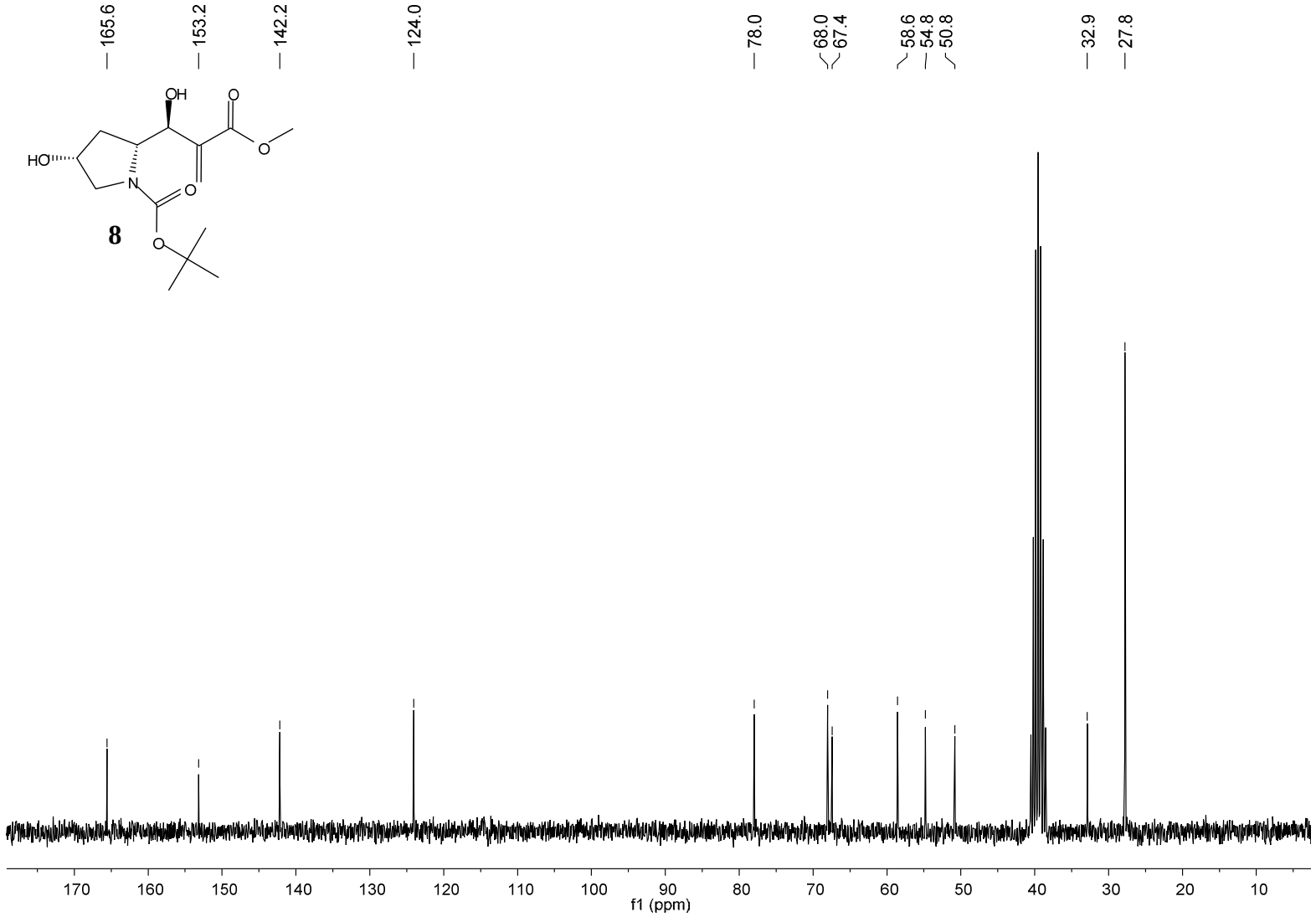
^{1}H NMR (250 MHz, DMSO-d_6, 90 ºC) spectrum of *cis*-4-hydroxy-(*D*)-prolinal **7**.



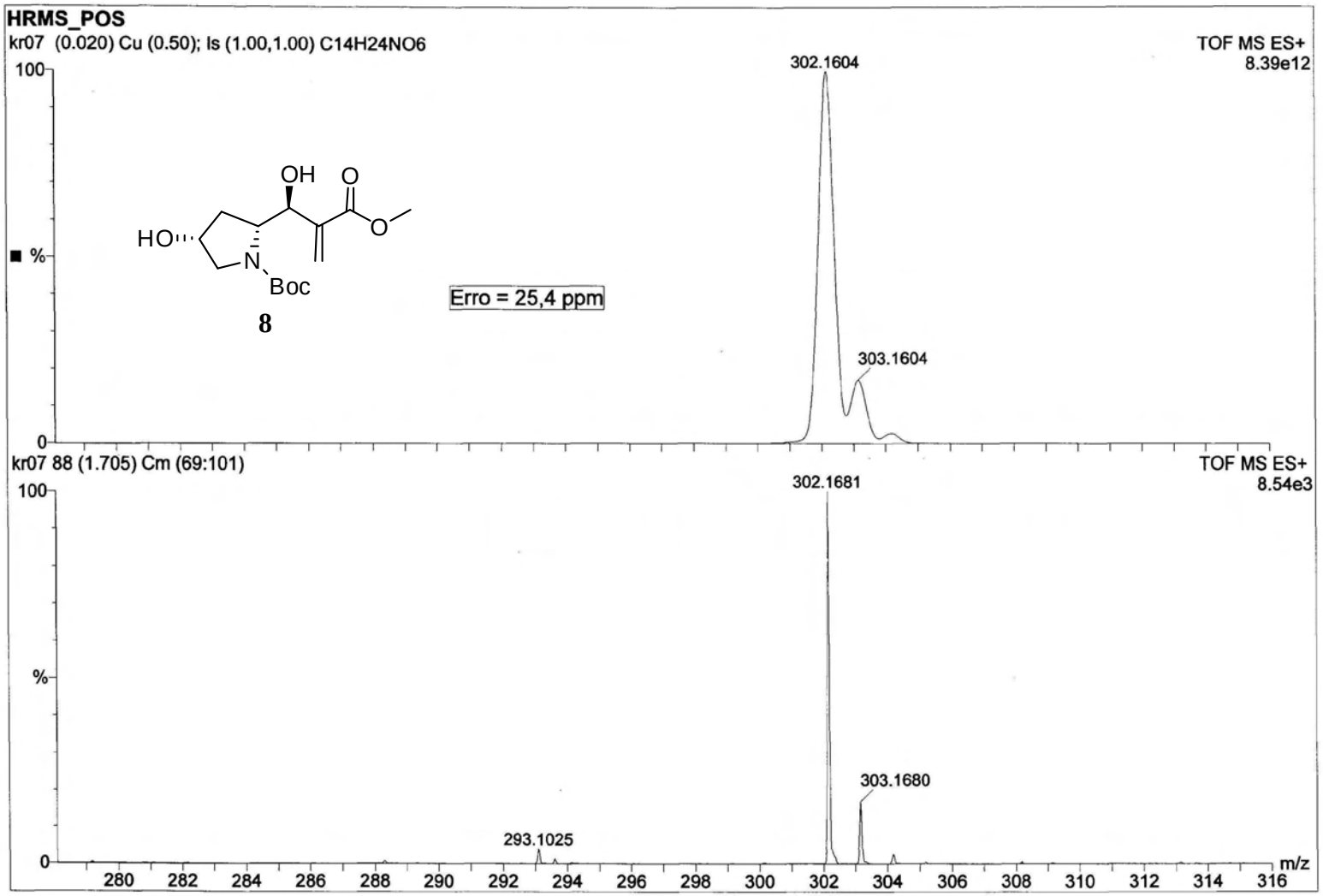
^{13}C NMR (62.5 MHz, DMSO-d_6, 90 ºC) spectrum of *cis*-4-hydroxy-(*D*)-prolinaldehyde **7**.



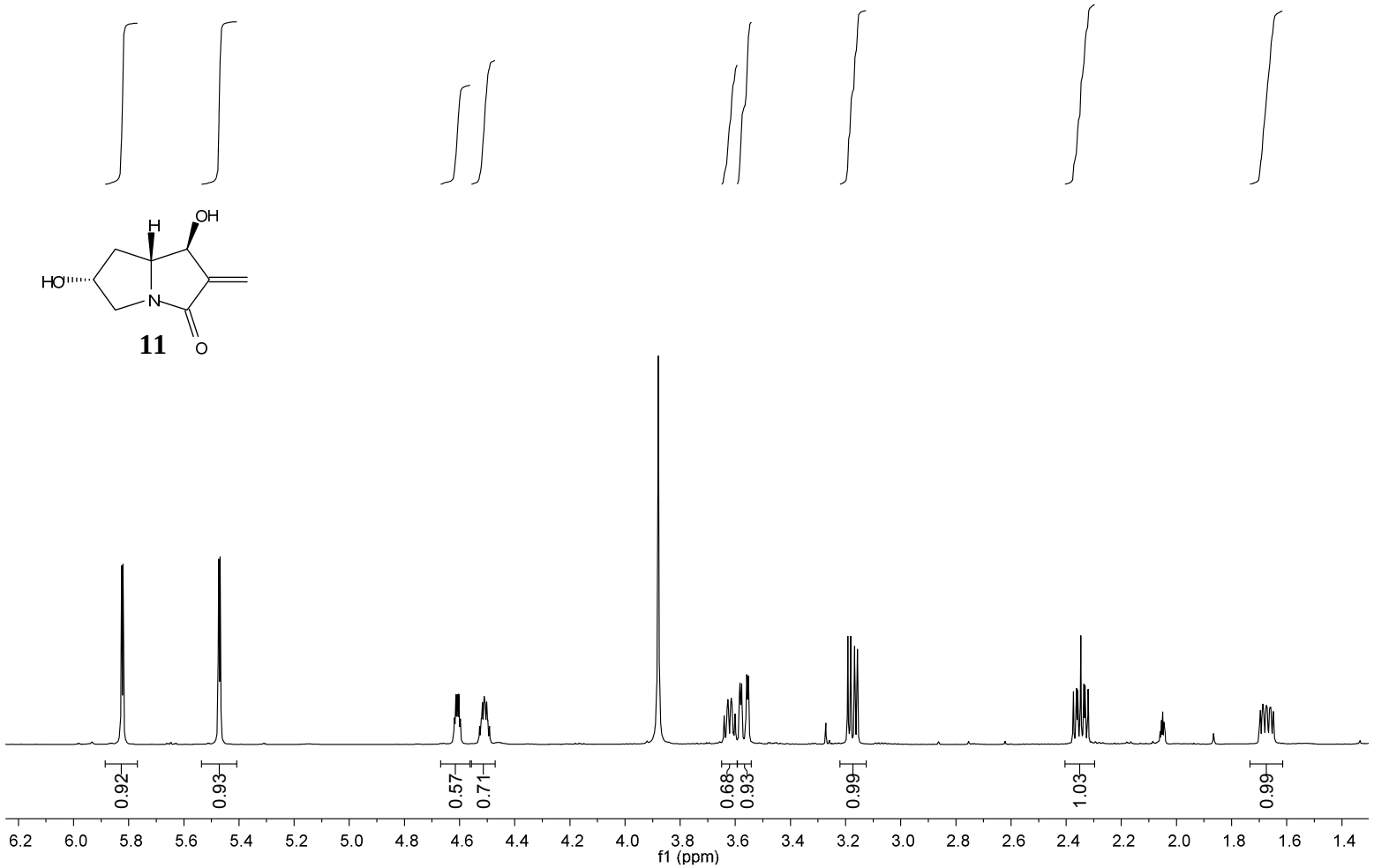
^{1}H NMR (250 MHz, DMSO-d_6, 90 ºC) spectrum of MBH adduct **8**.



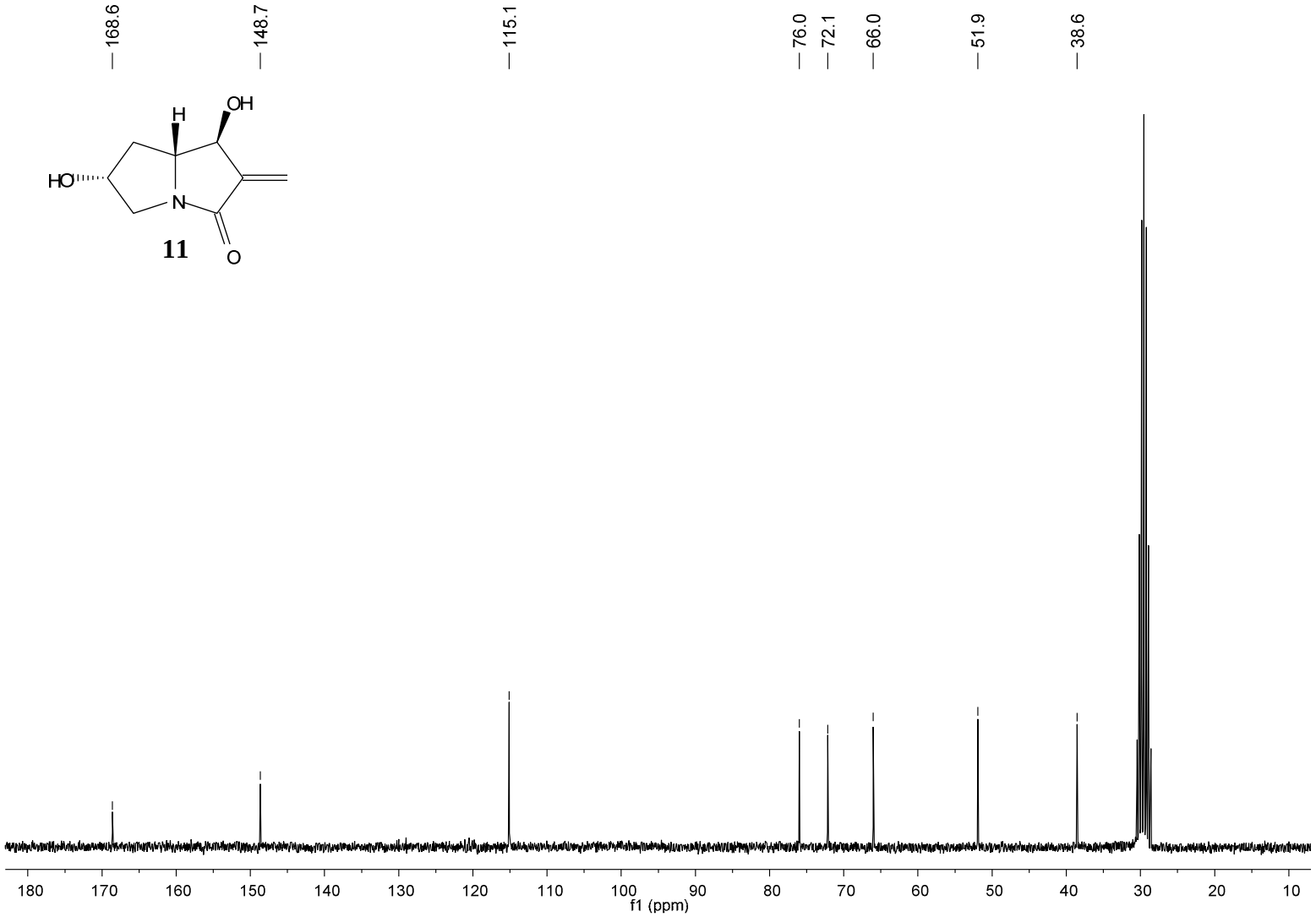
^{13}C NMR (62.5 MHz, DMSO-d_6, 90 ºC) spectrum of MBH adduct **8**.



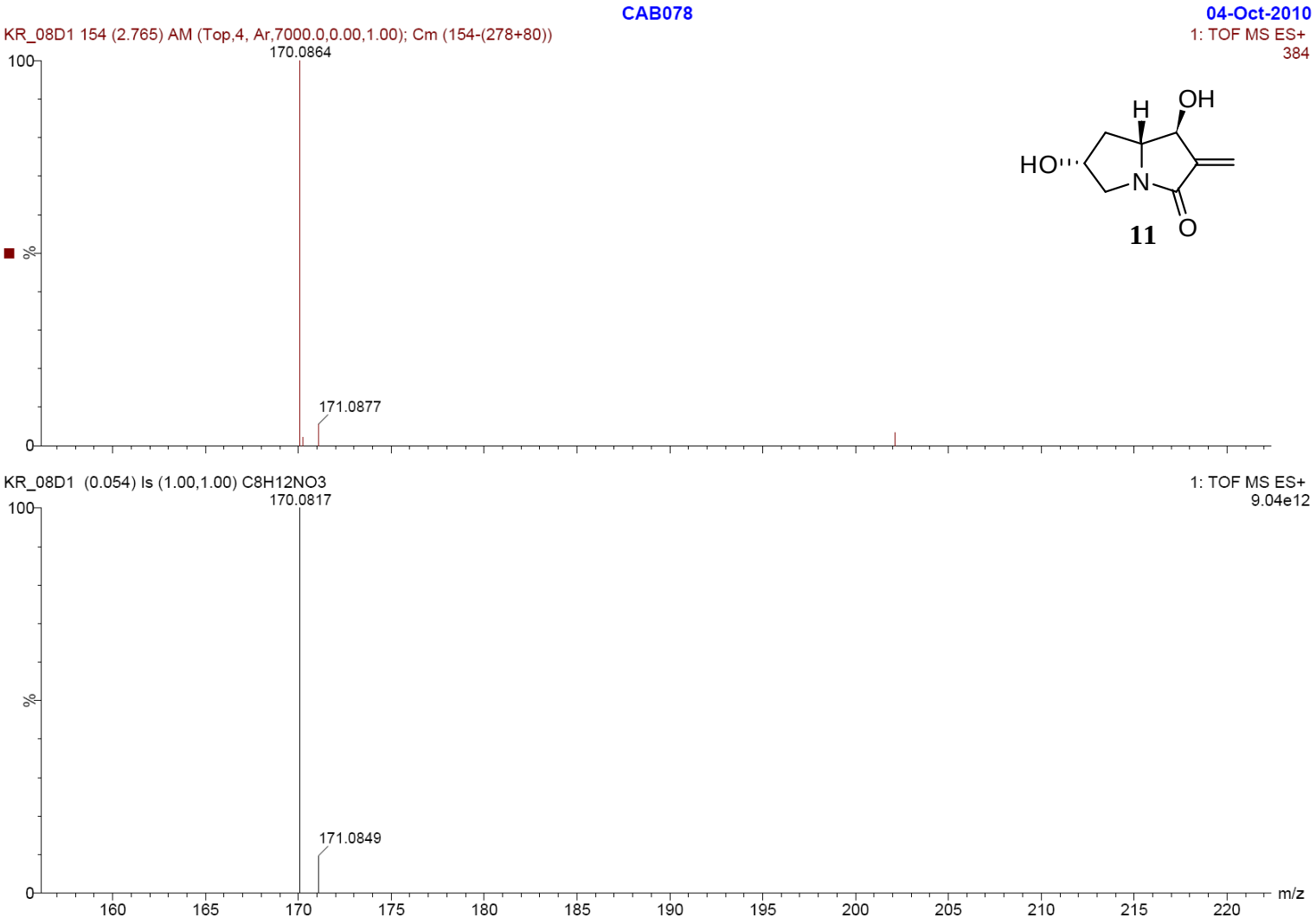
HRMS (ESI) of MBH adduct **8**.



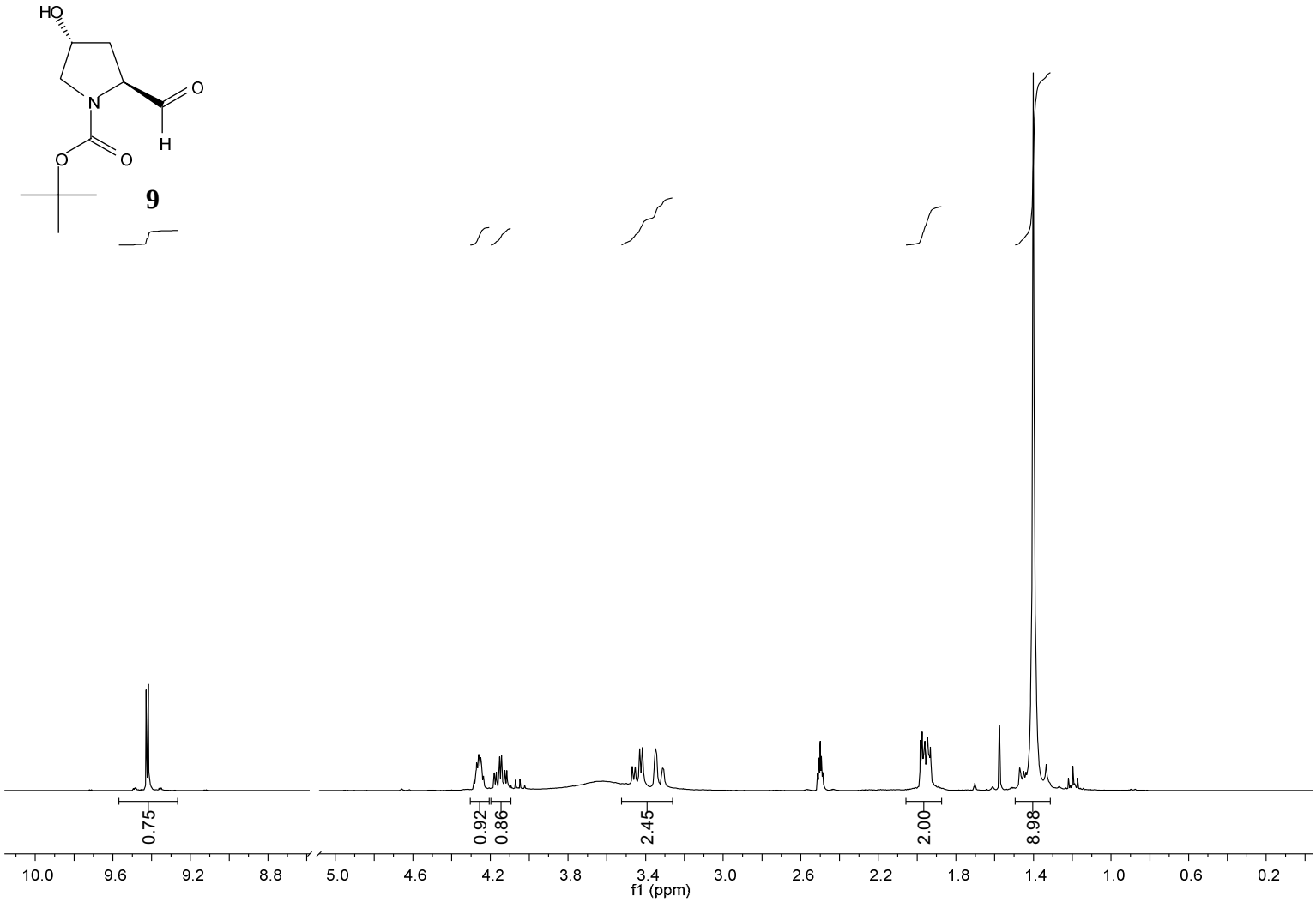
^{1}H NMR (500 MHz, $(CD_3)_2CO$) spectrum of pyrrolizidinone **11**.



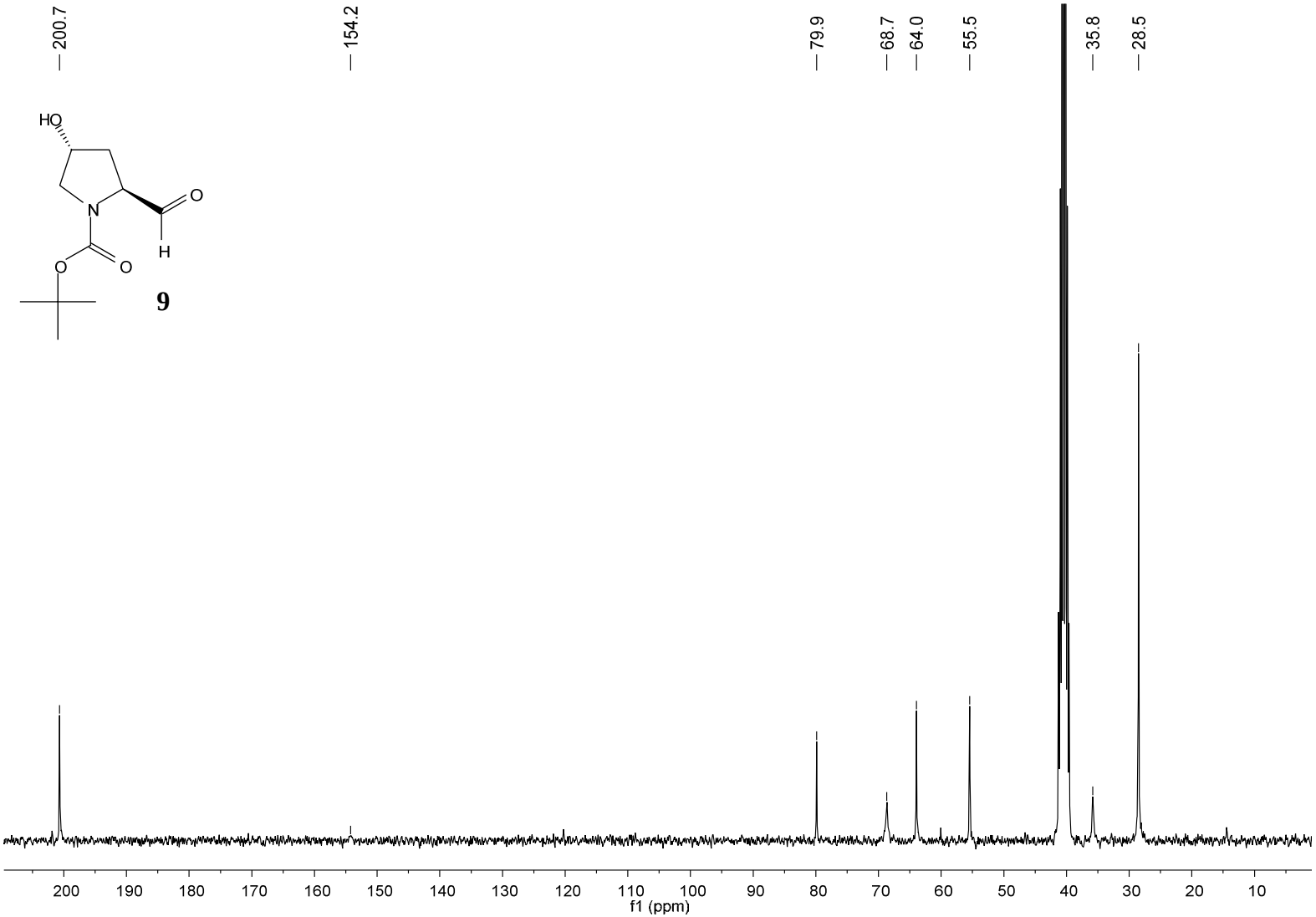
^{13}C NMR (62.5 MHz, $(CD_3)_2CO$) spectrum of pyrrolizidinone **11**.



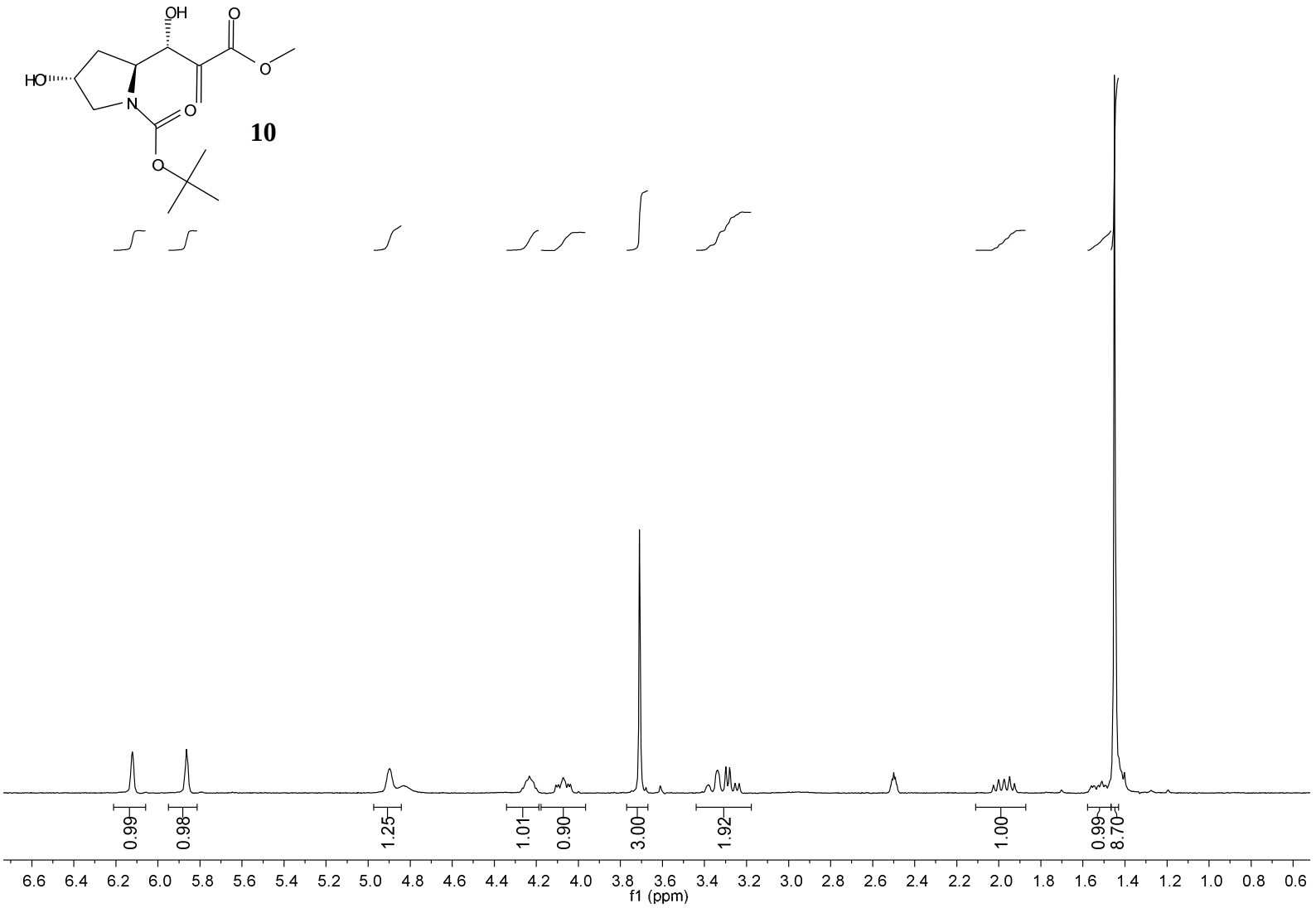
HRMS (ESI) of pyrrolizidinone **11**.



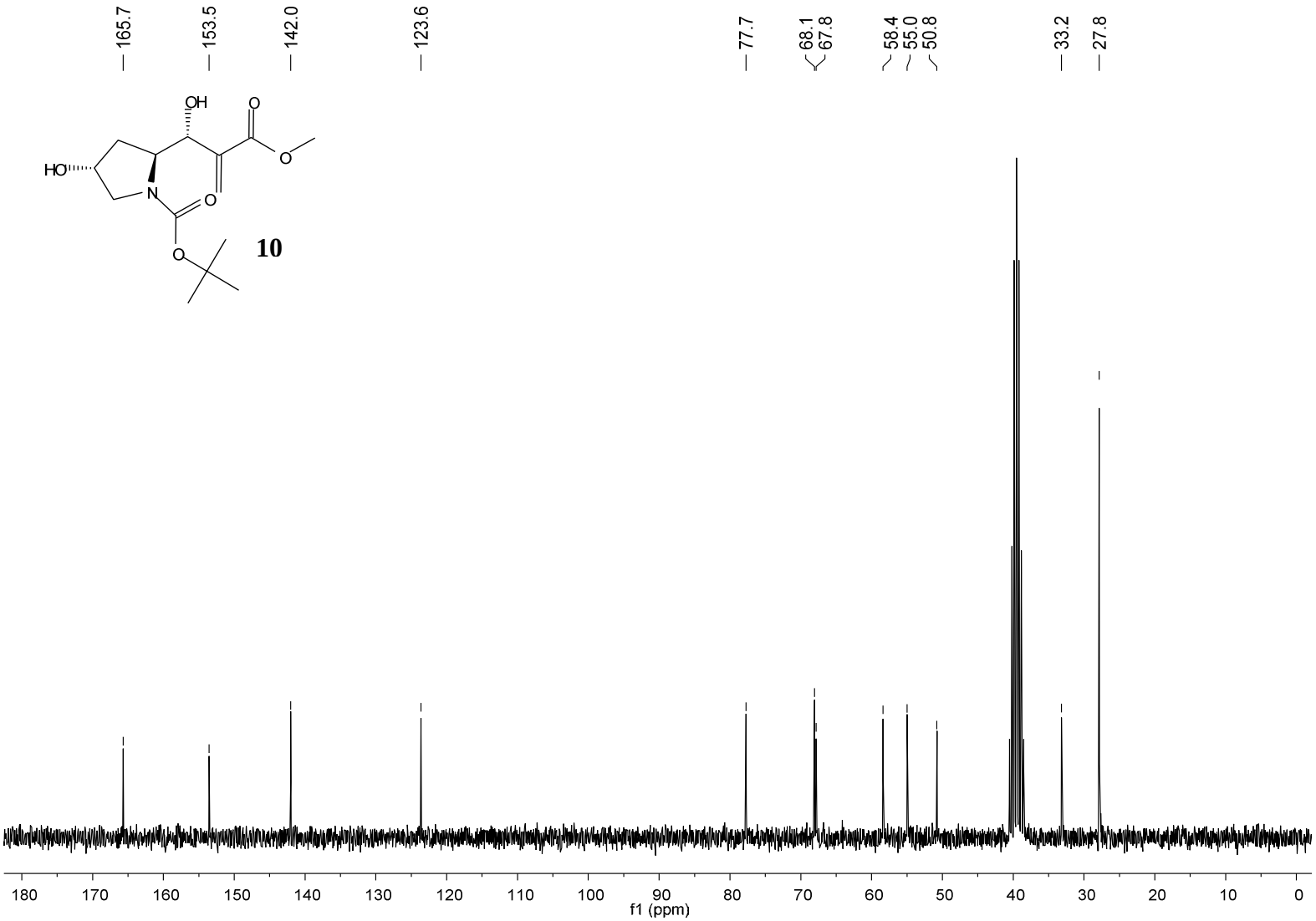
^{1}H NMR (300 MHz, DMSO-d_6, 90 ºC) spectrum of *trans*-hydroxy-prolinal **9**.



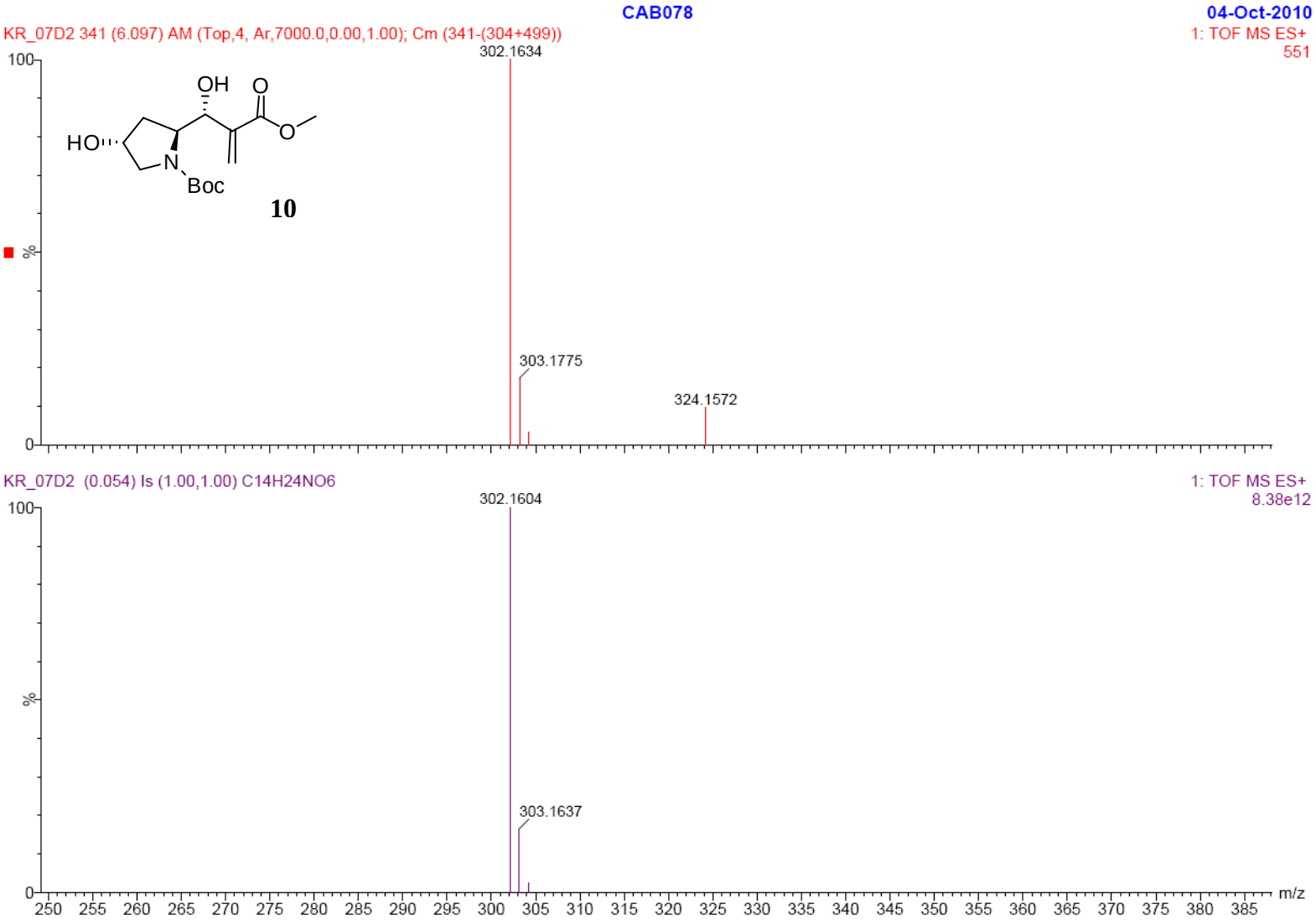
^{13}C NMR (75 MHz, DMSO-d_6, 90 ºC) spectrum of *trans*-hydroxy-prolinal **9**.



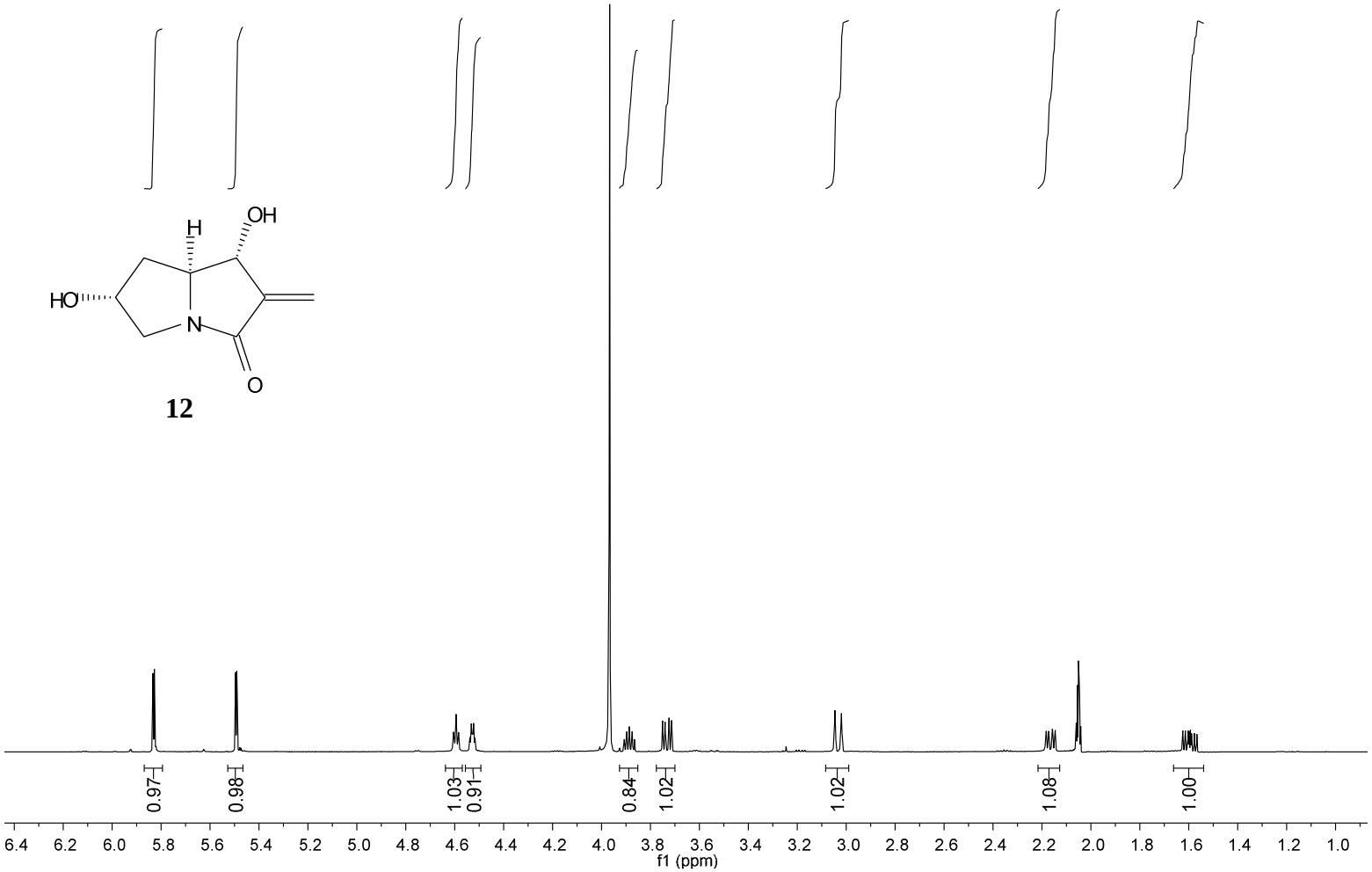
^{1}H NMR (250 MHz, DMSO-d_6, 90 ºC) spectrum of MBH adduct **10**.



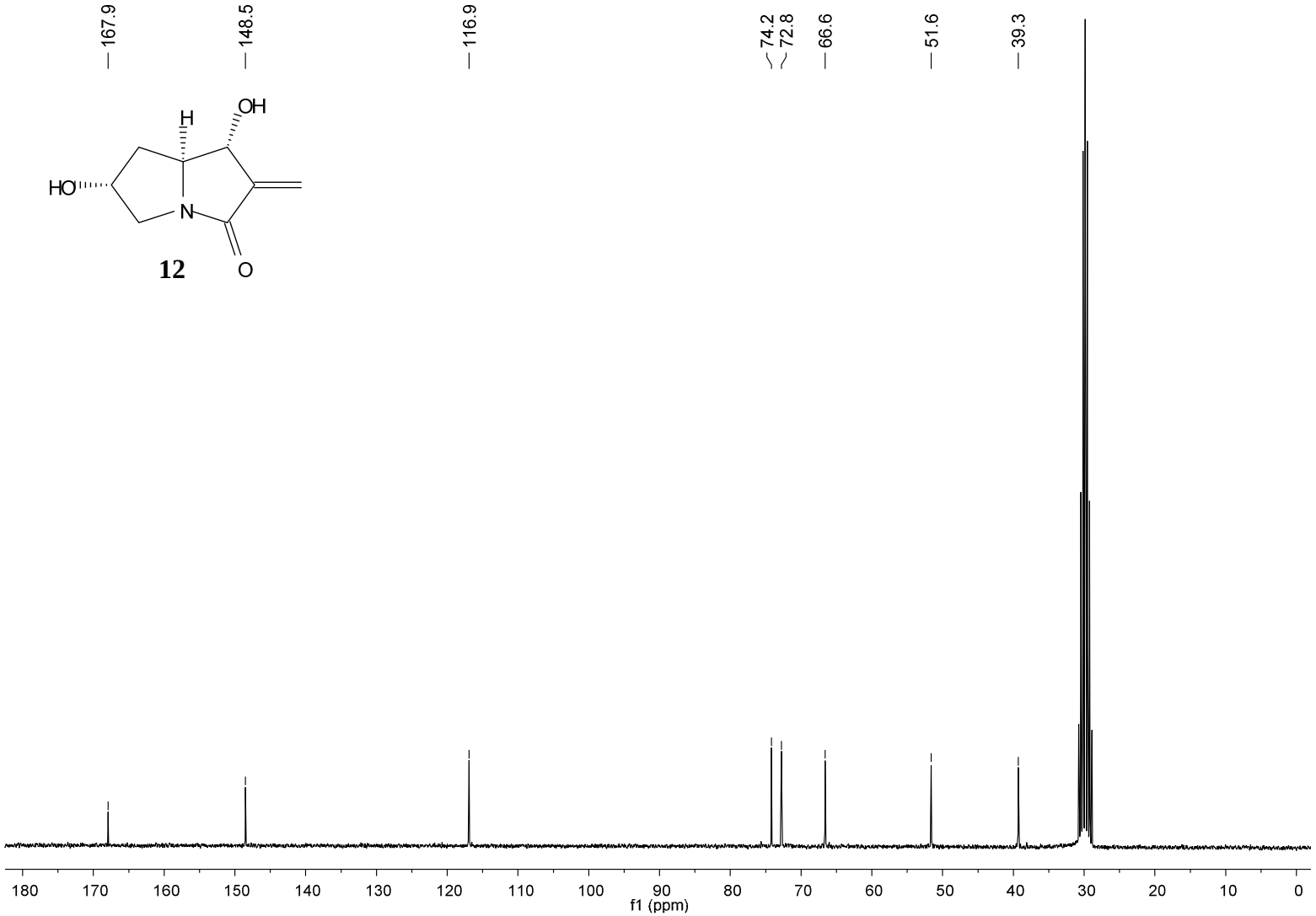
^{13}C NMR (62.5 MHz, DMSO-d_6, 90 ºC) spectrum of MBH adduct **10**.



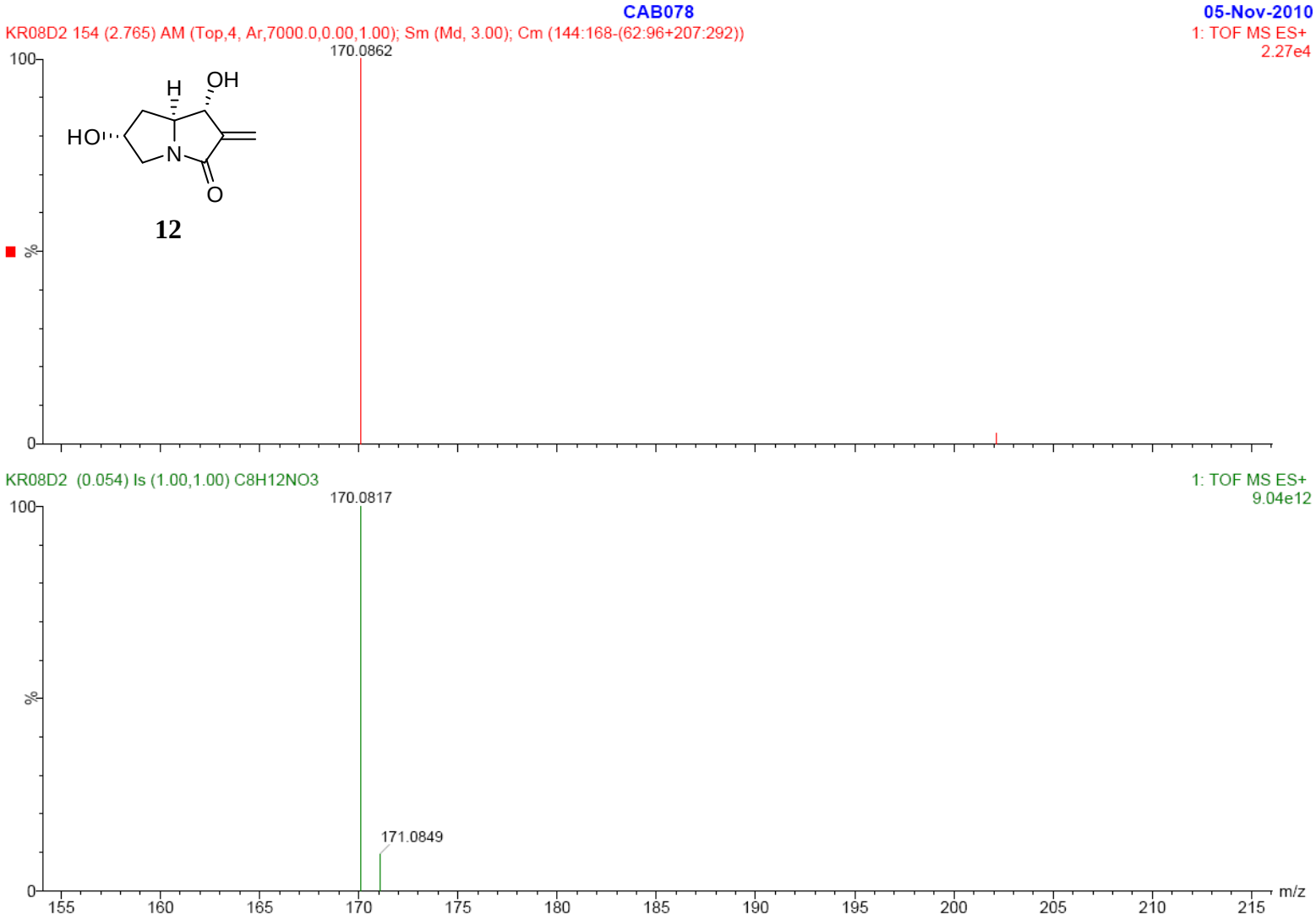
HRMS (ESI) of MBH adduct **10**.



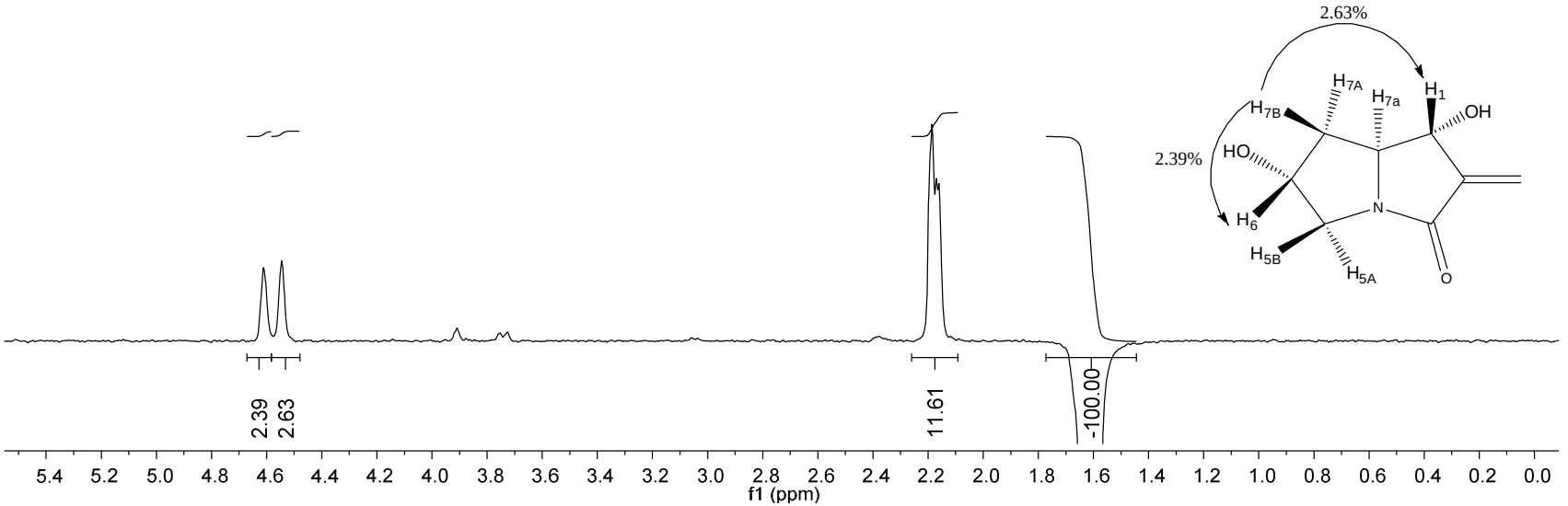
^{1}H NMR (500 MHz, $(CD_3)_2CO$) spectrum of pyrrolizidinone **12**.



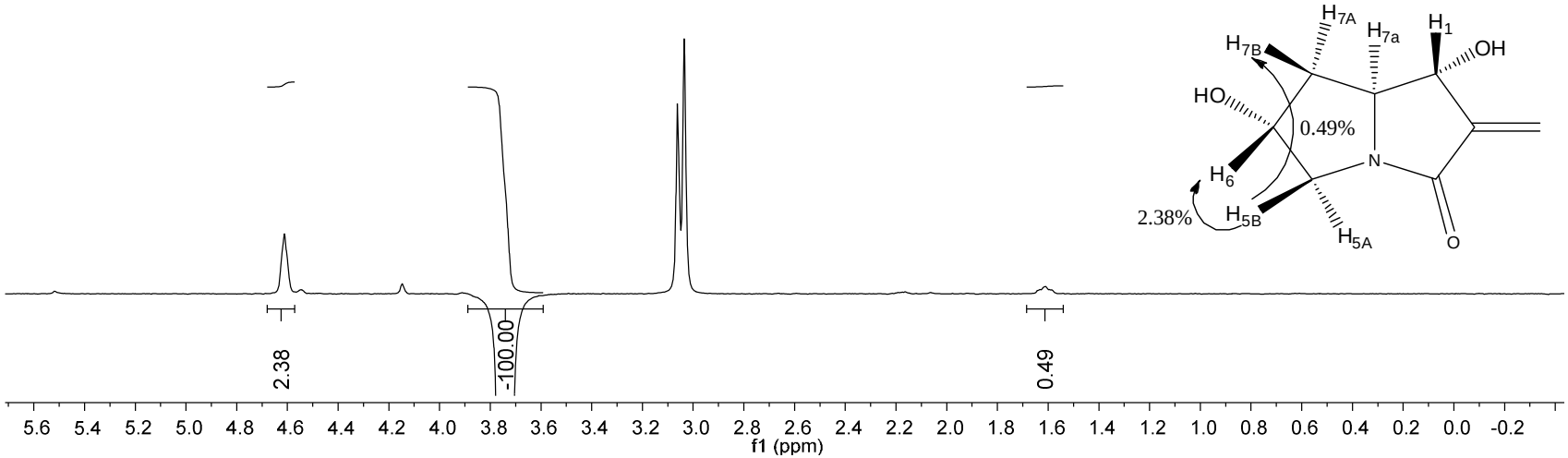
^{13}C NMR (62.5 MHz, $(CD_3)_2CO$) spectrum of pyrrolizidinone **12**.



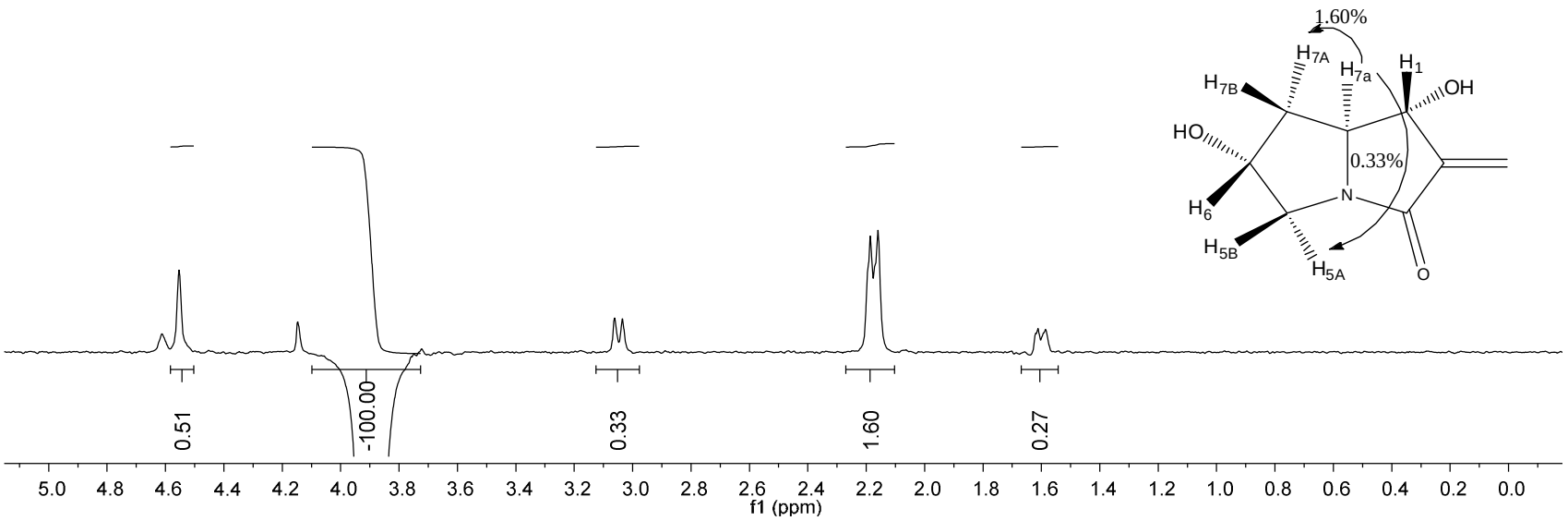
HRMS (ESI) of pyrrolizidinone **12**.



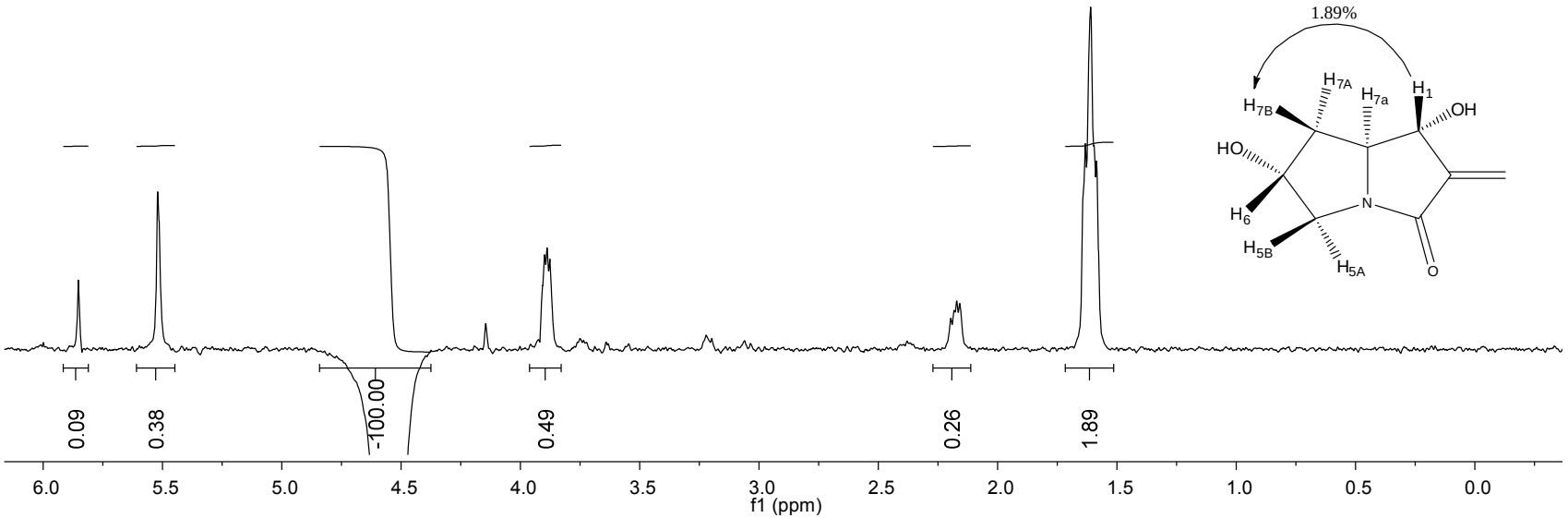
nOe [500 MHz, $(CD_3)_2CO$)] spectrum of pyrrolizidinone **12**, irradiation at 1.59 ppm, H-7B.



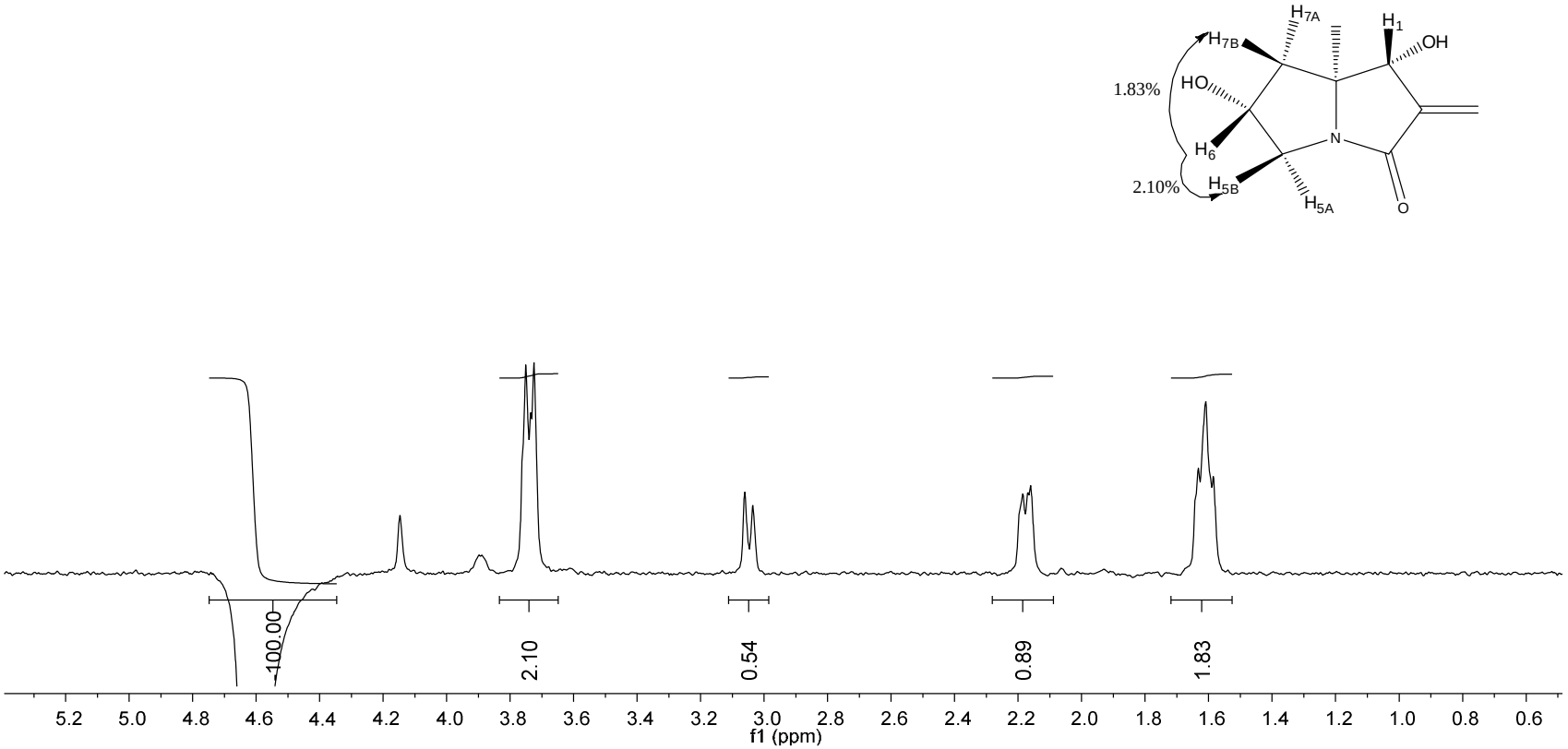
nOe [500 MHz, $(CD_3)_2CO$)] spectrum of pyrrolizidinone **12**, irradiation at 3.73 ppm, H-5B.



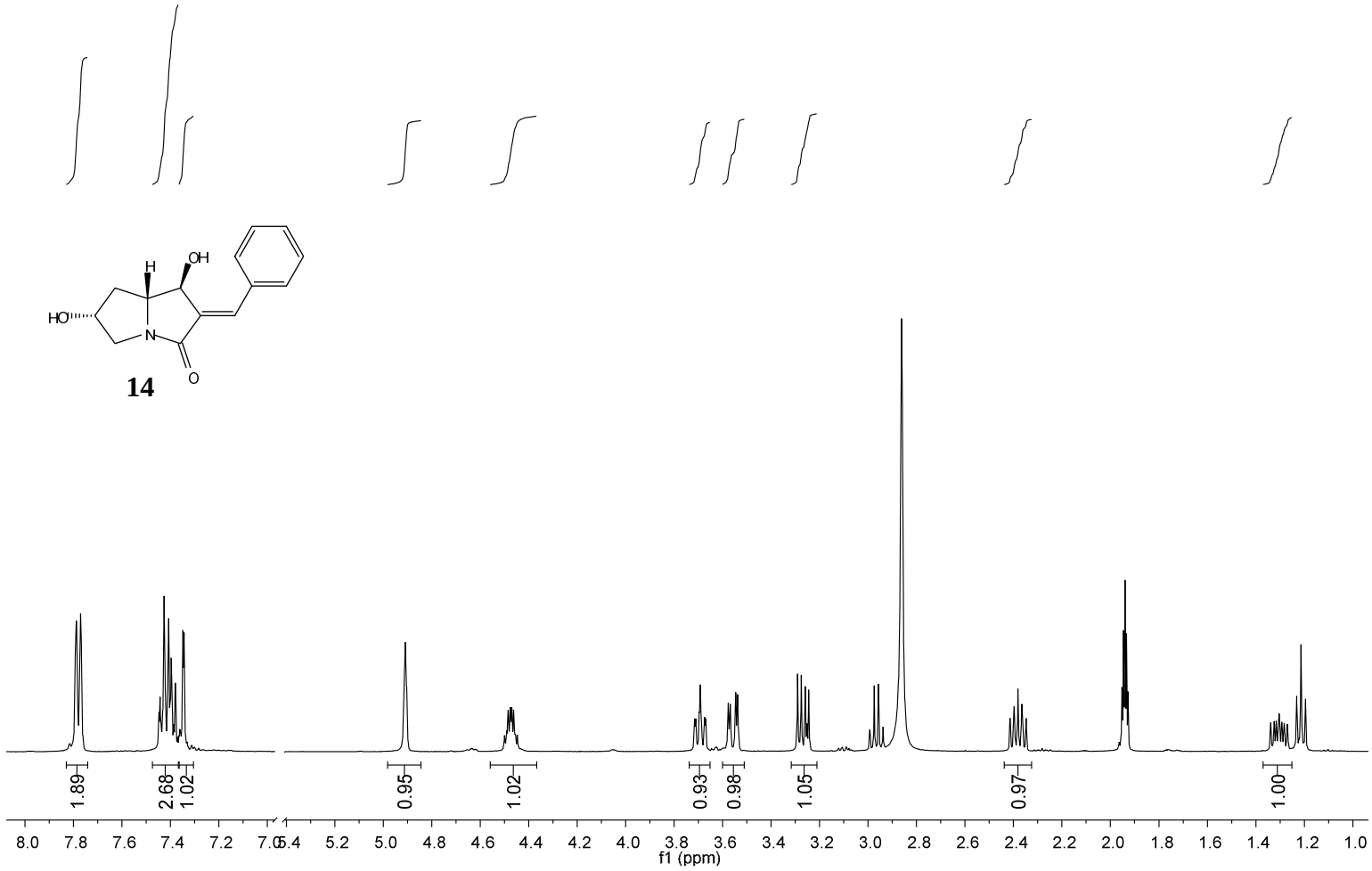
nOe [500 MHz, $(CD_3)_2CO$)] spectrum of pyrrolizidinone **12**, irradiation at 3.89 ppm, H-7a.



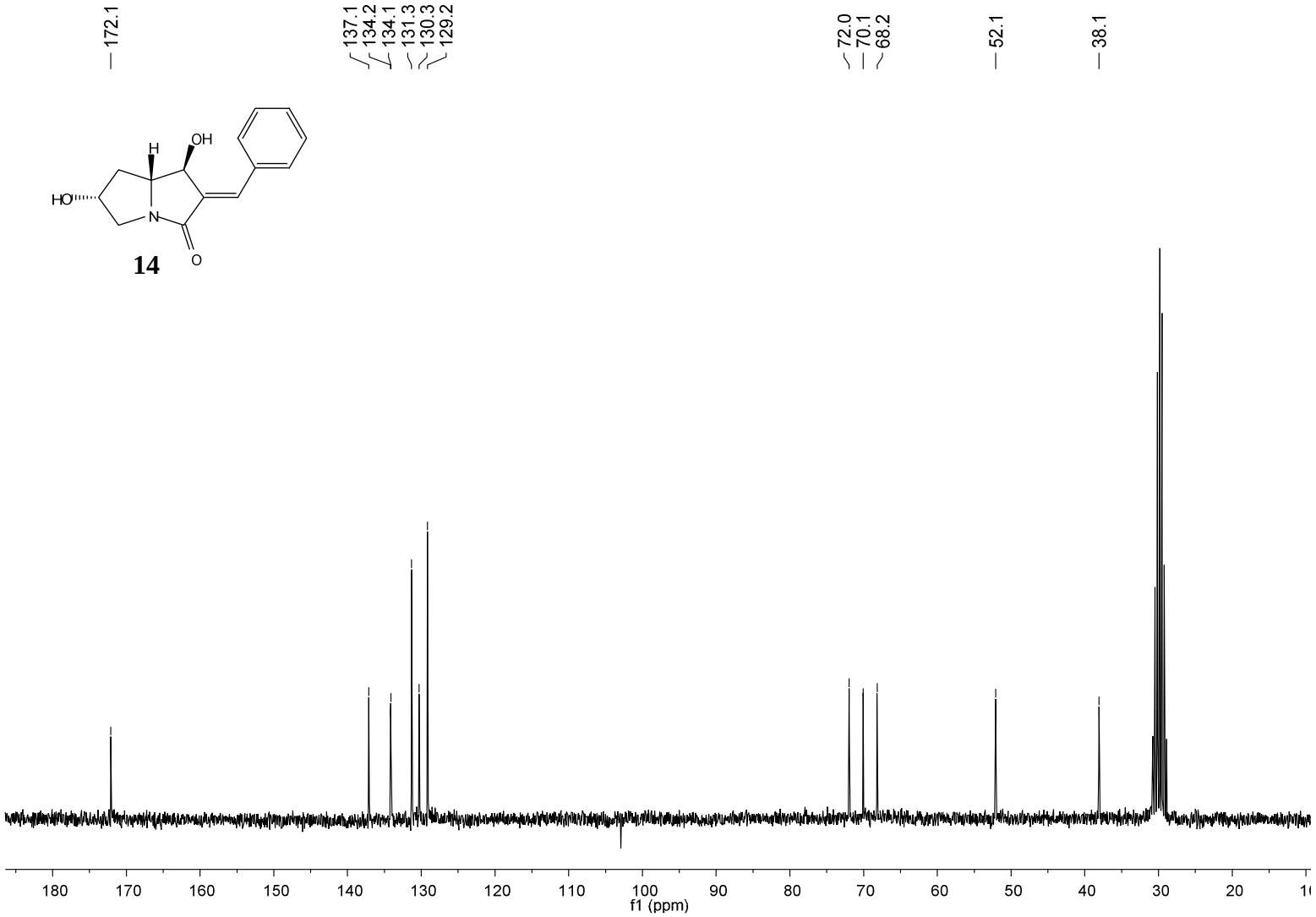
nOe [(500 MHz, $(CD_3)_2CO$] spectrum of pyrrolizidinone **12**, irradiation at 4.53 ppm, H-1)



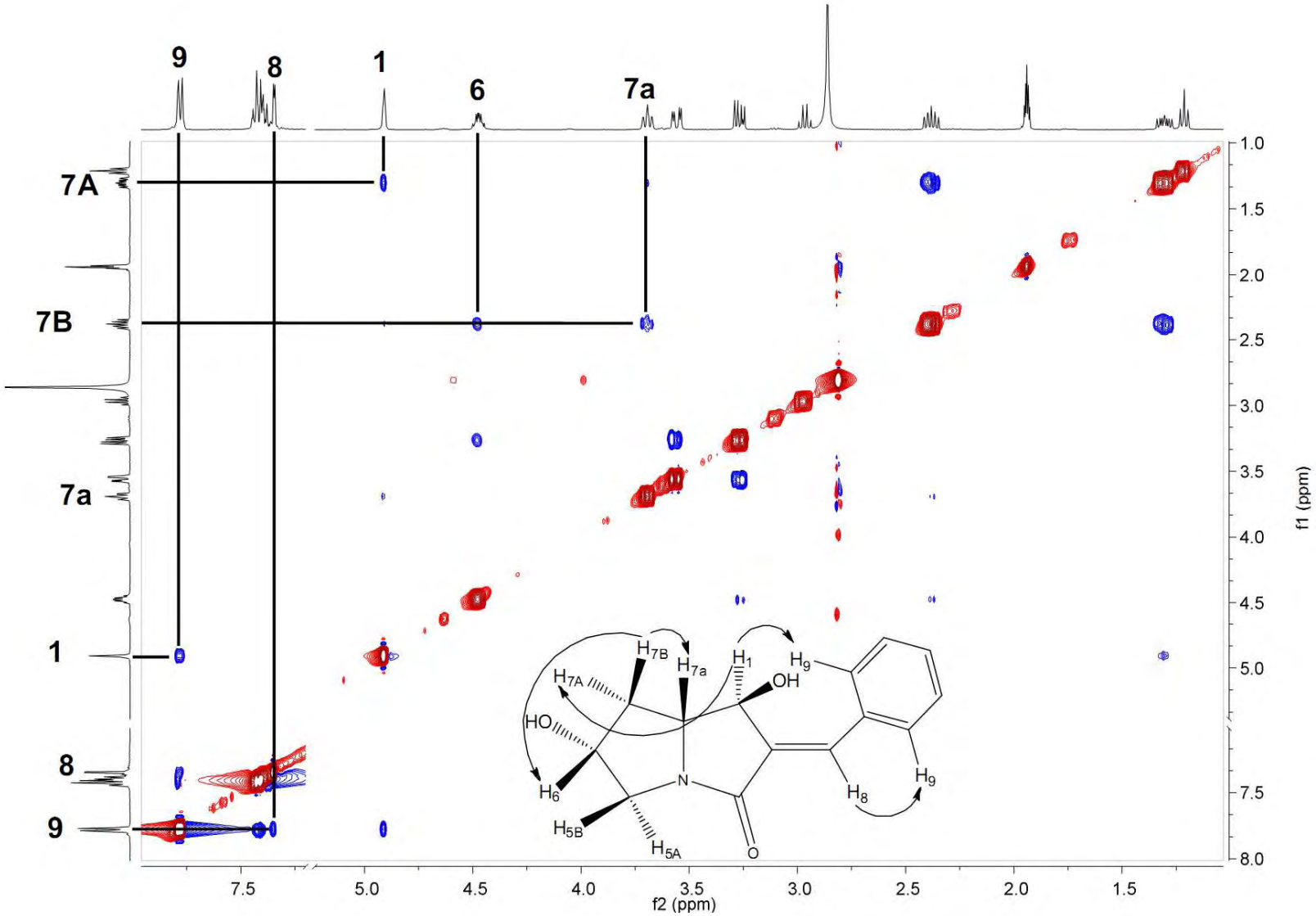
nOe [500 MHz, $(CD_3)_2CO$] spectrum of pyrrolizidinone **12**, irradiation at 4.59 ppm, H-6)



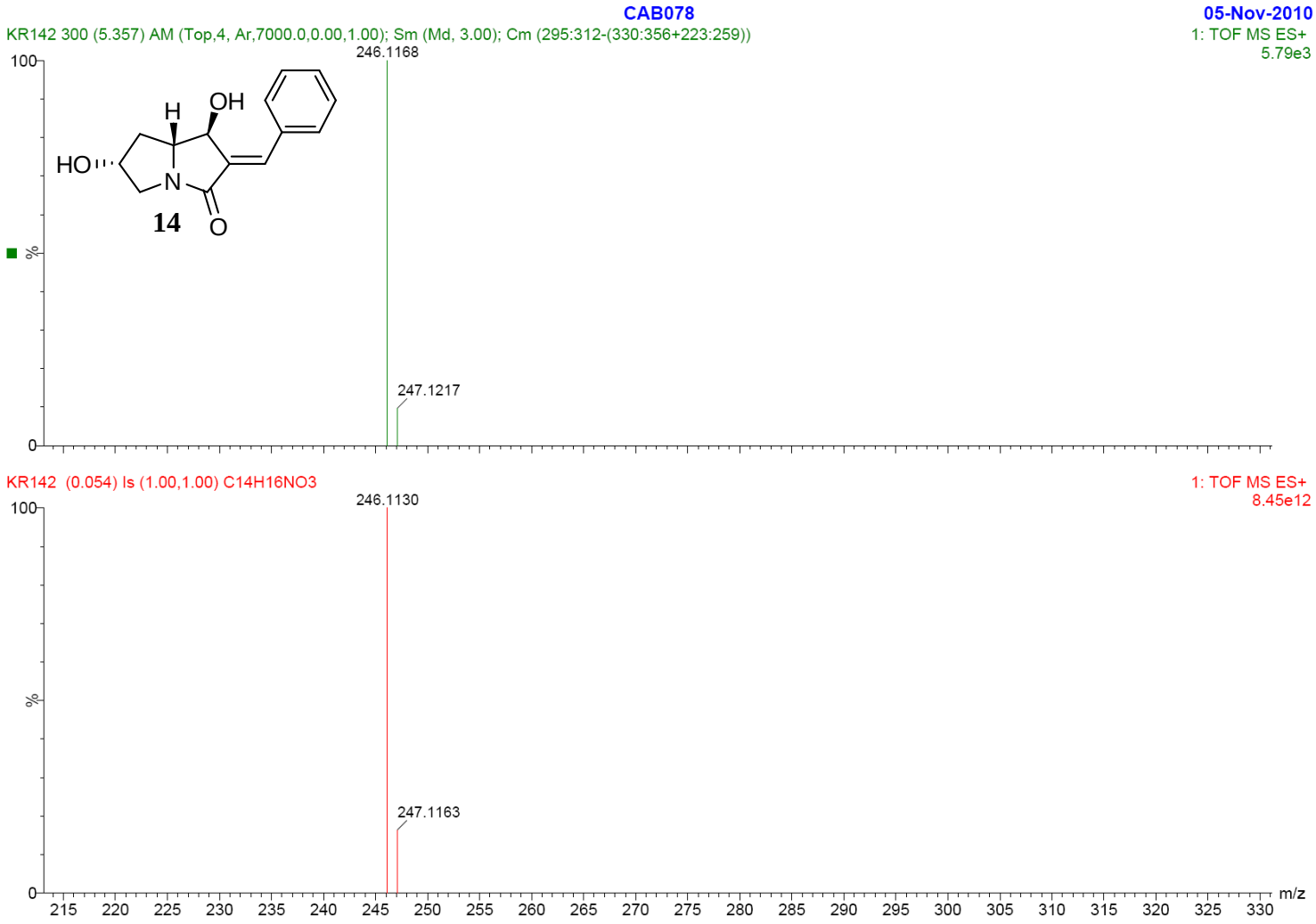
^{1}H NMR (400 MHz, CD_3CN) spectrum of benzylidene-pyrrolizidinone **14**.



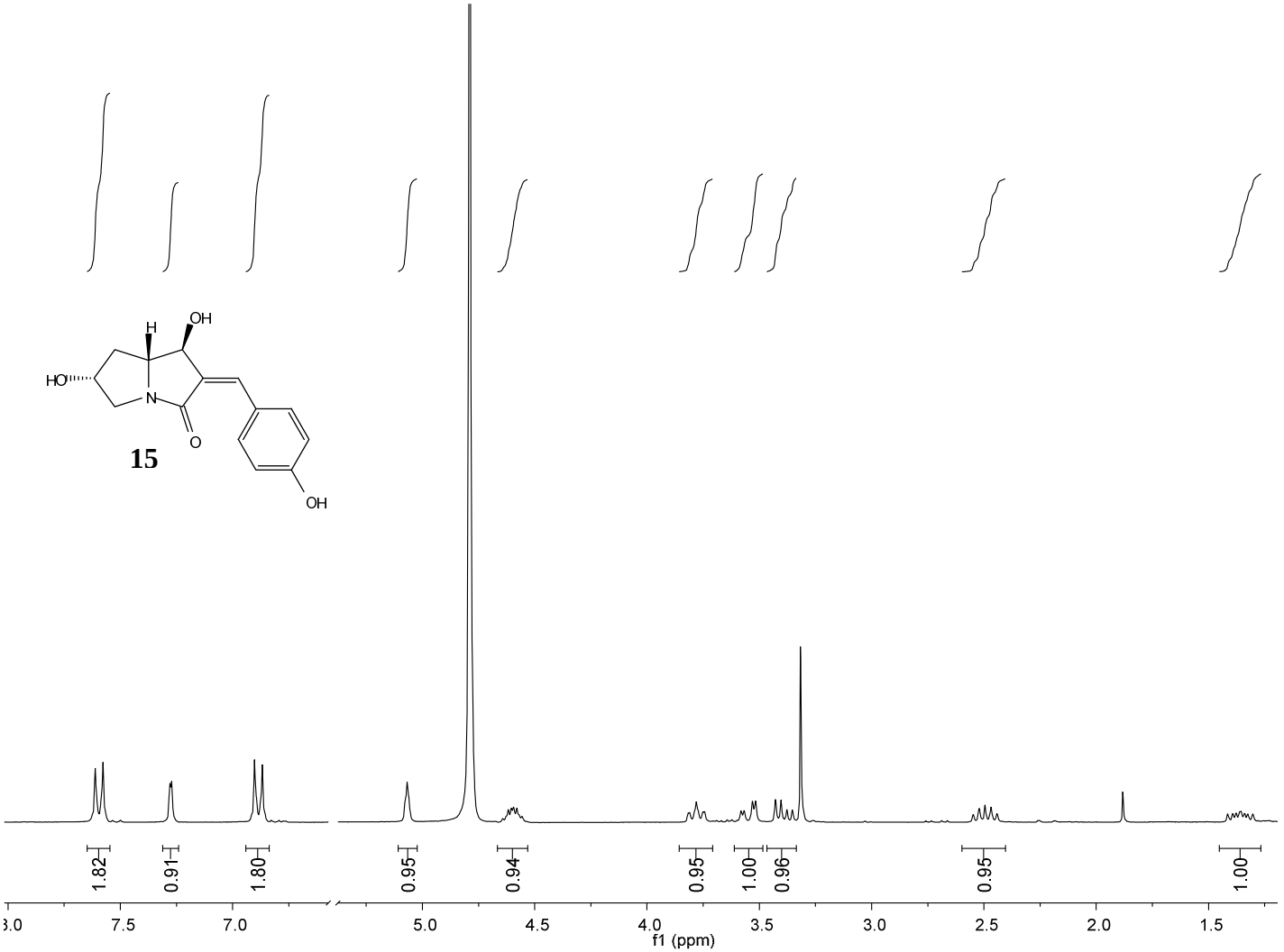
^{13}C NMR [62.5 MHz, $(CD_3)_2CO$)] spectrum of benzylidene-pyrrolizidinone **14**.



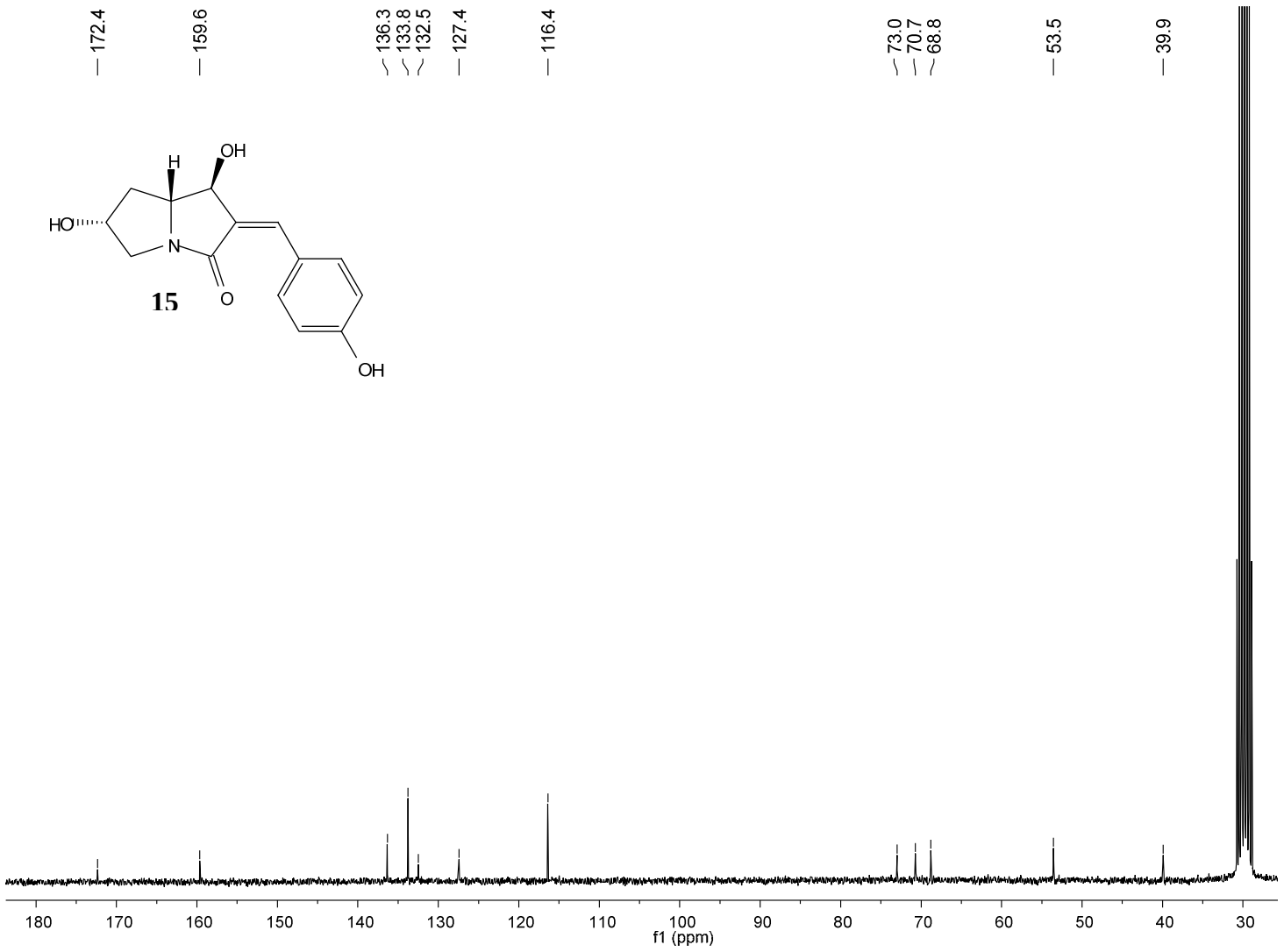
2-D NOESY (400 MHz, CD_3CN) spectrum of benzylidene-pyrrolizidine **14**.



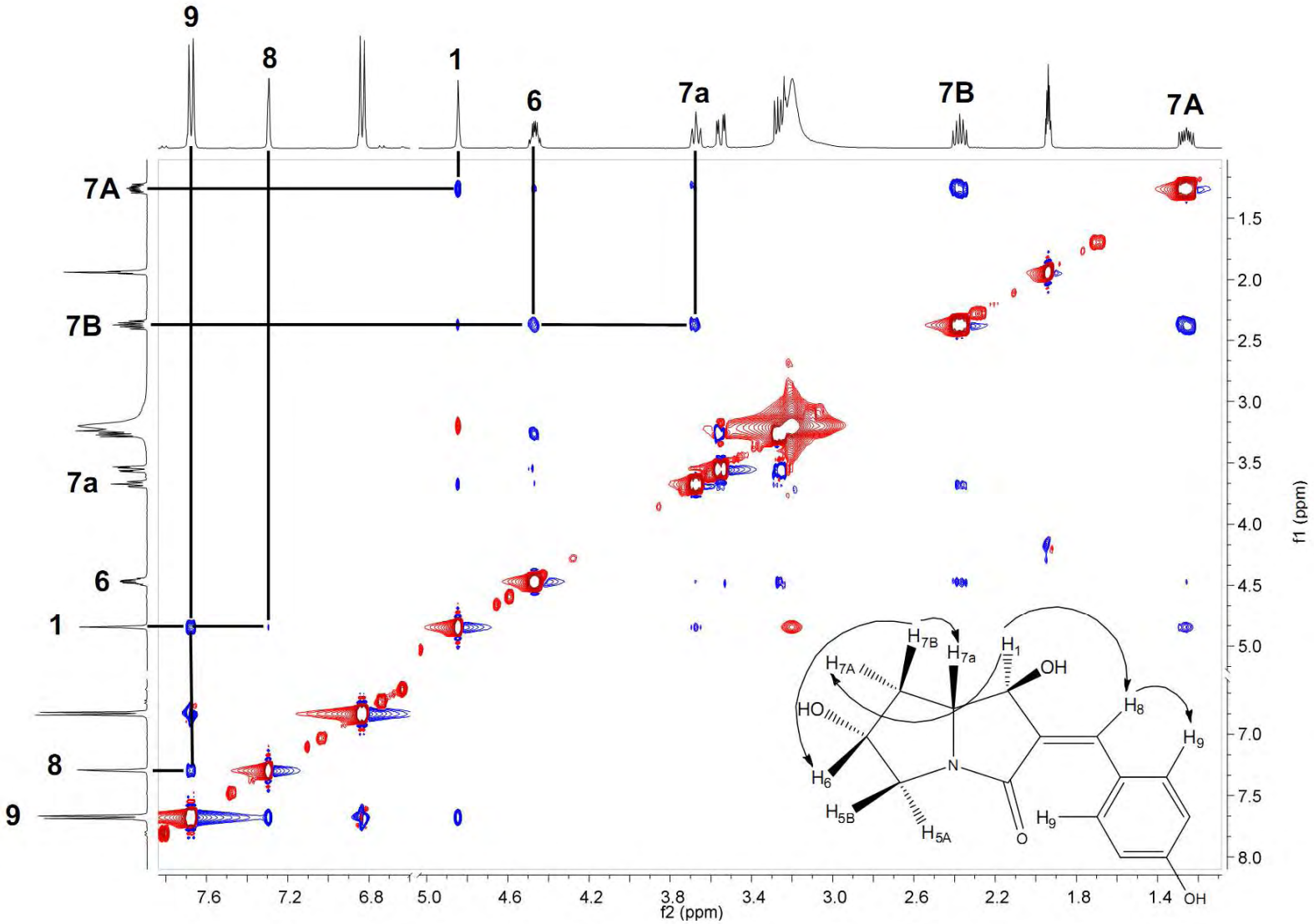
HRMS (ESI) of benzylidene-pyrrolizidinone **14**.



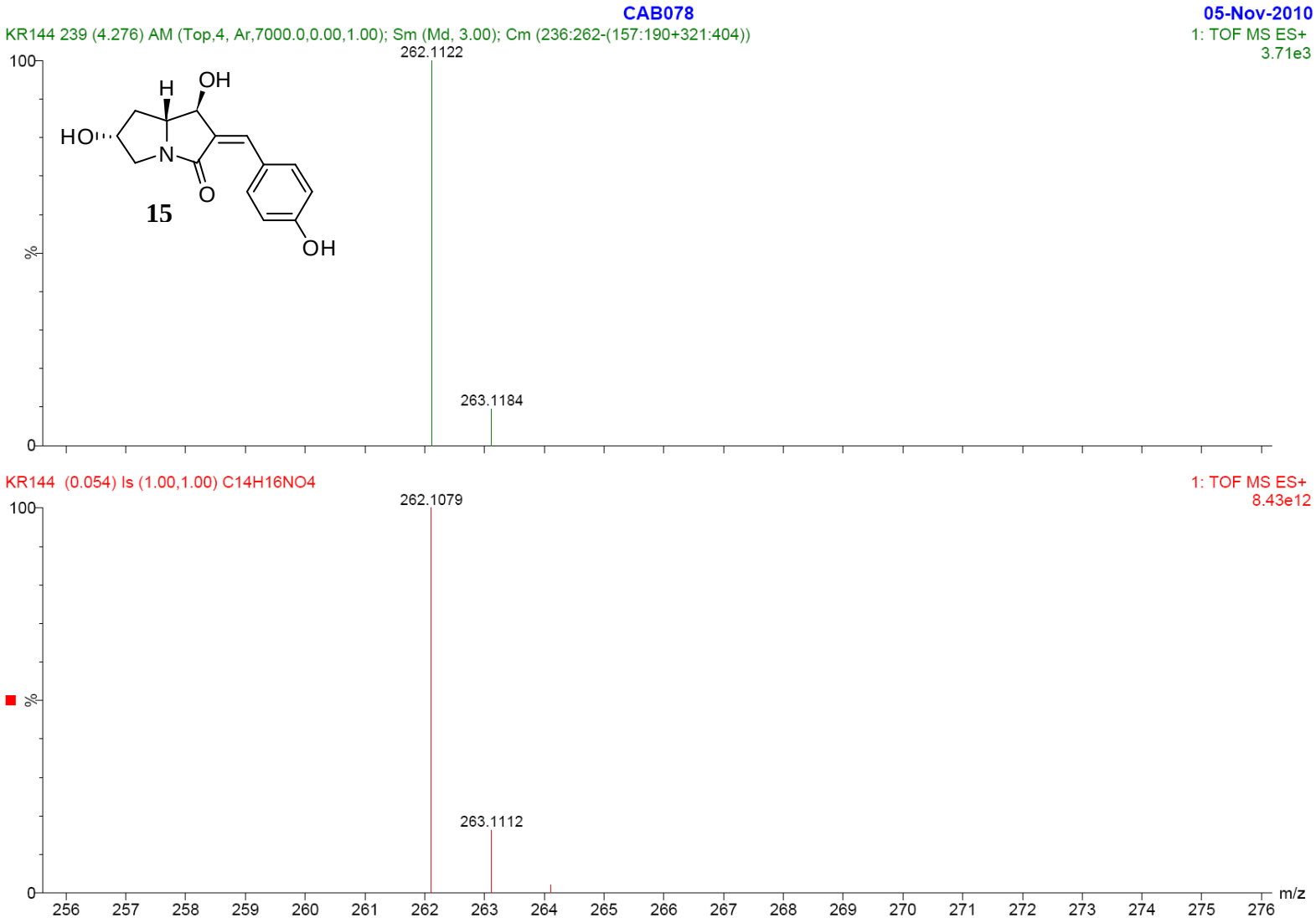
^{1}H NMR (250 MHz, D_2O) spectrum of hydroxy-benzylidene-pyrrolizidinone **15**.



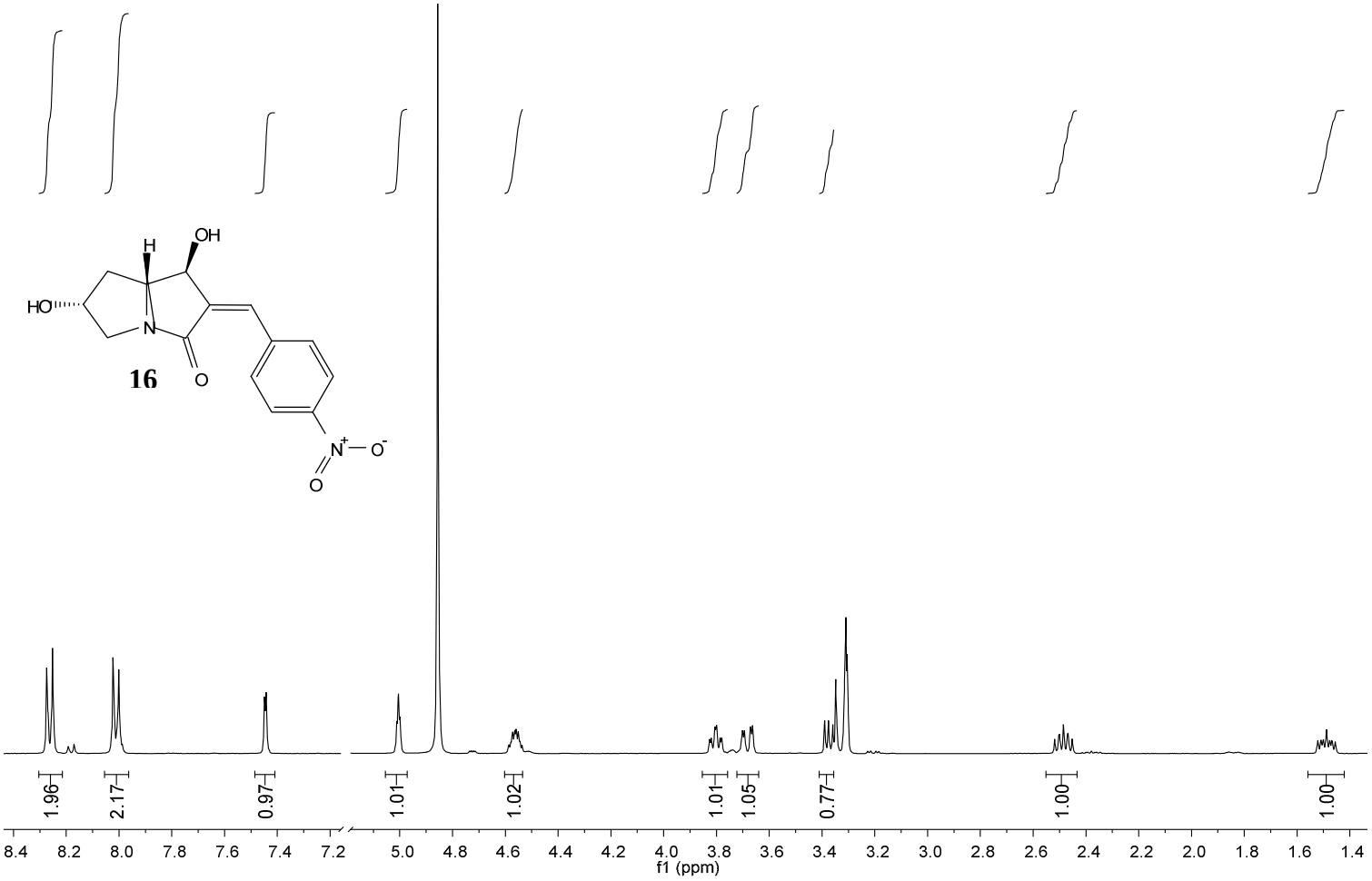
^{13}C NMR [62.5 MHz, $(CD_3)_2CO$)] spectrum of hydroxy-benzylidene-pyrrolizidinone **15**.



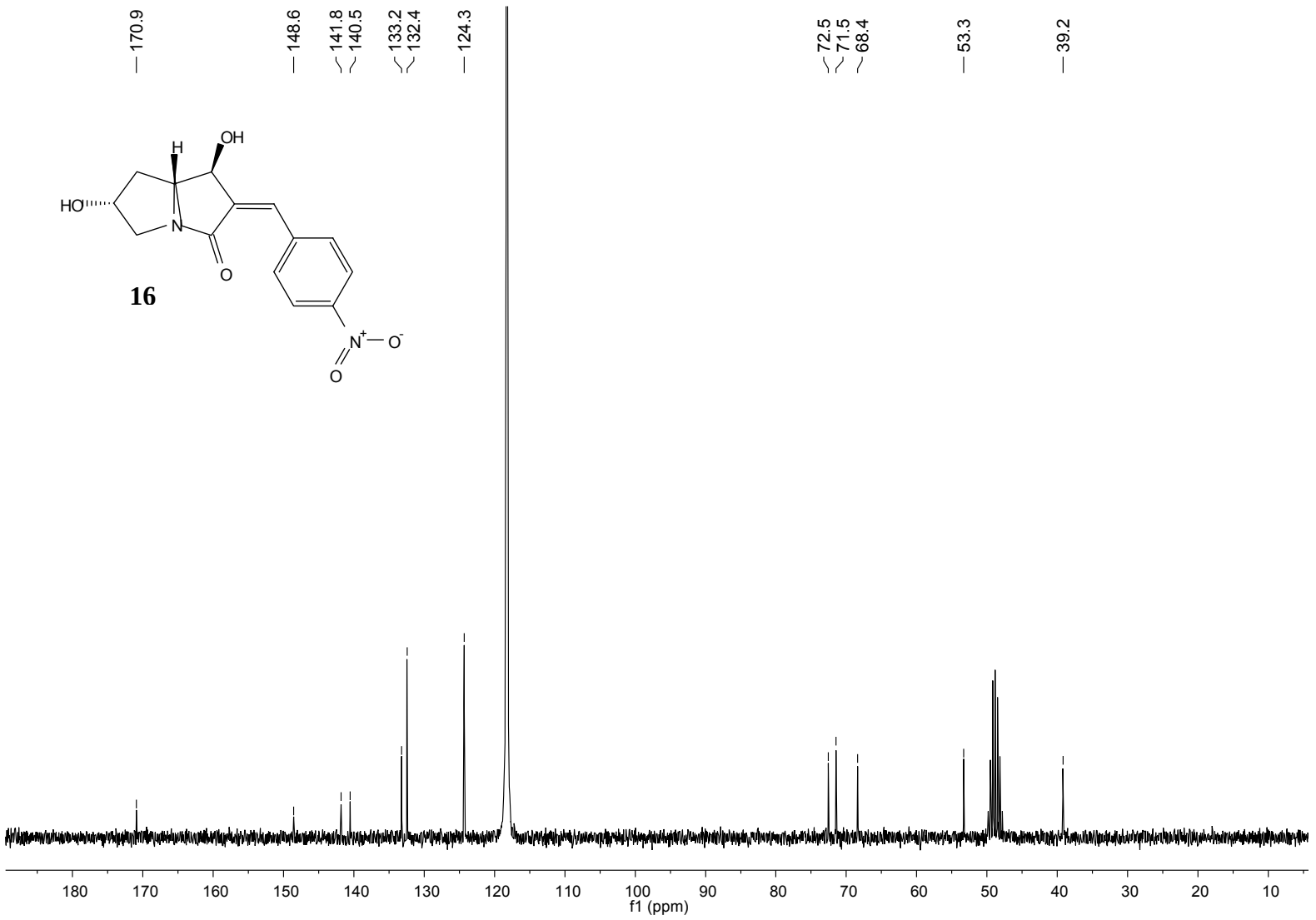
2-D NOESY (400 MHz, D_2O) spectrum of hydroxy-benzylidene-pyrrolizidinone **15**.



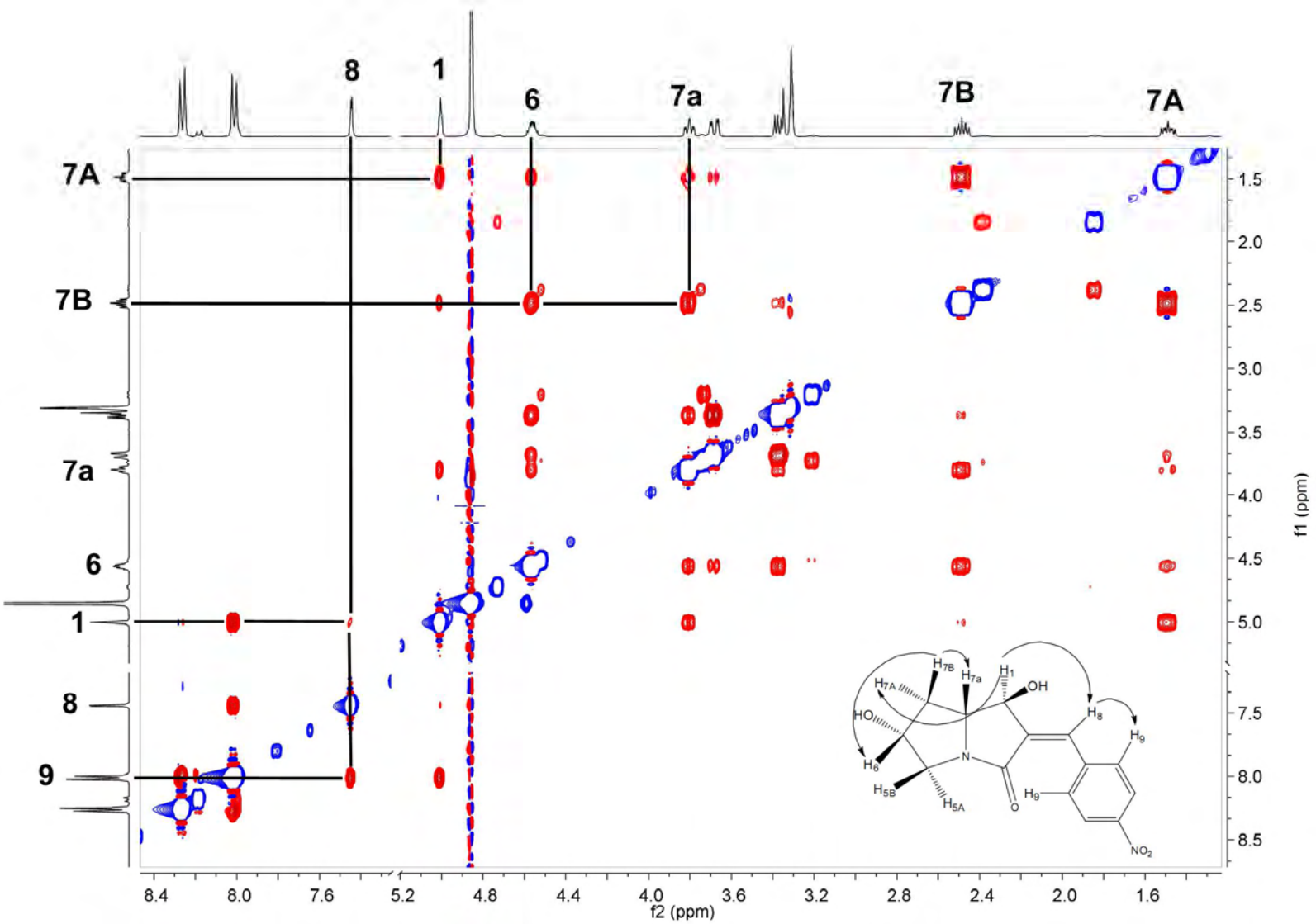
HRMS (ESI) of hydroxy-benzylidene-pyrrolizidinone **15**.



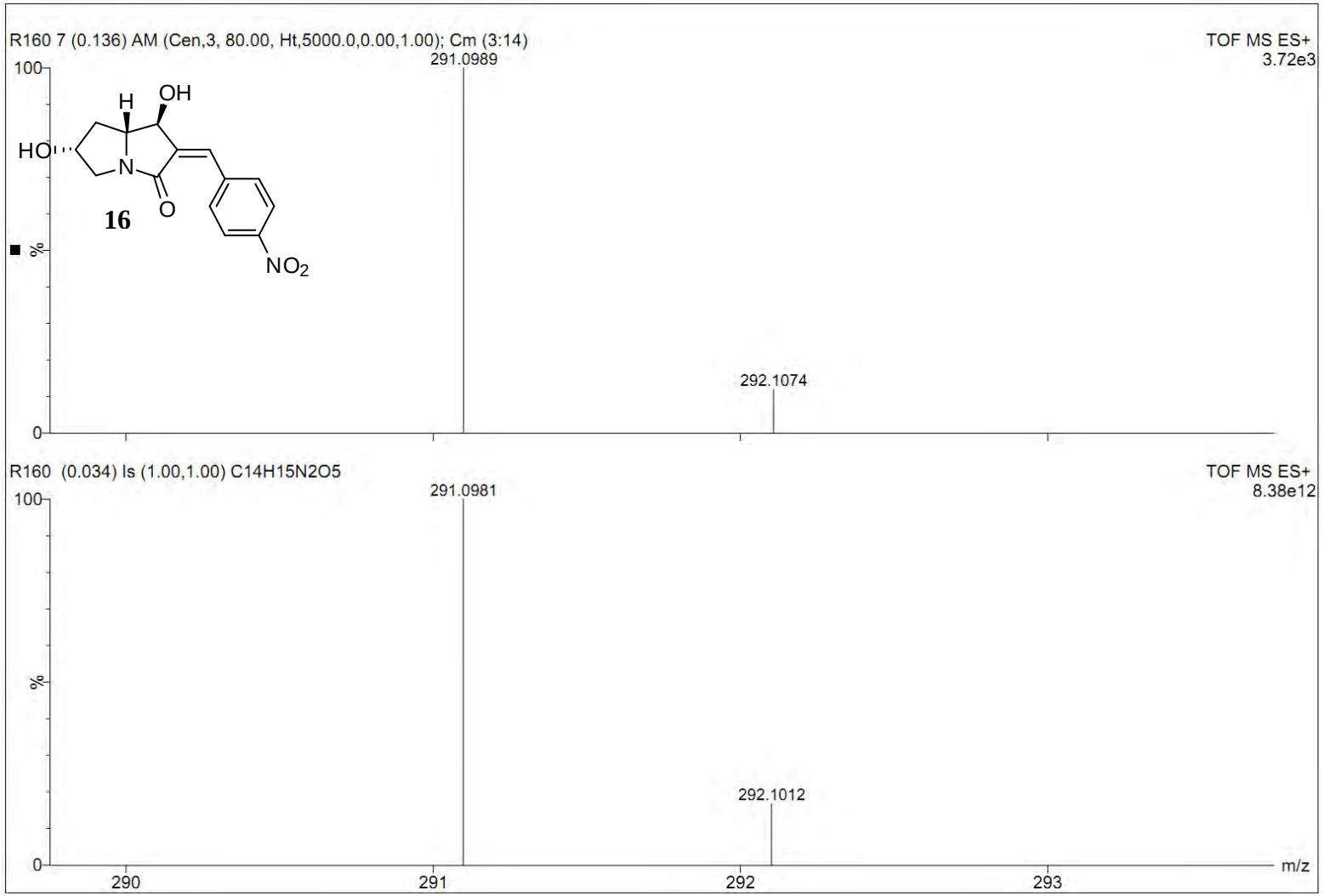
^{1}H NMR (400 MHz, CD_3OD) spectrum of *p*-nitro-benzylidene-pyrrolizidinone **16**.



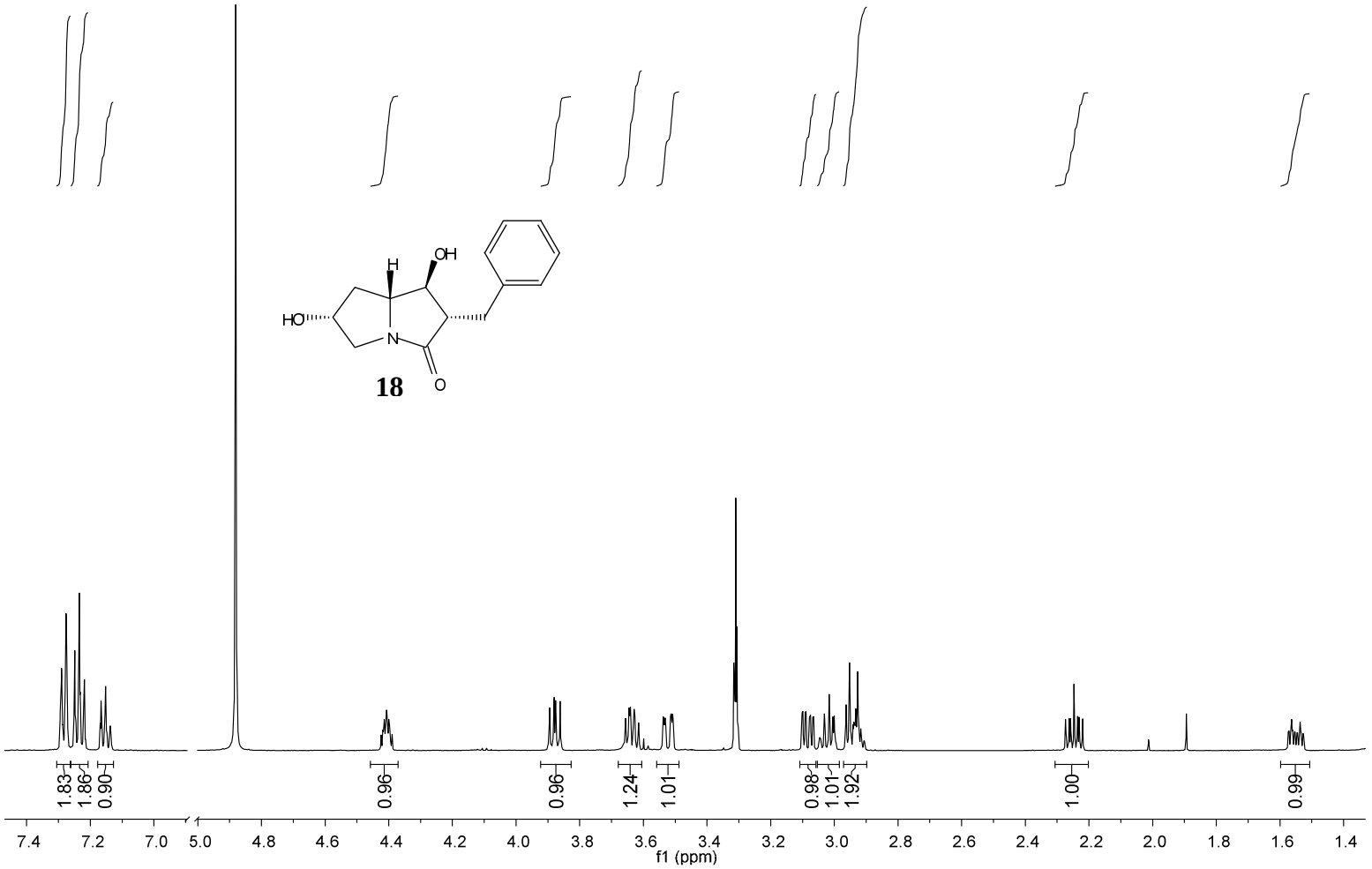
^{13}C NMR (62.5 MHz, CD_3CN) spectrum of *p*-nitro-benzylidene-pyrrolizidinone **16**.



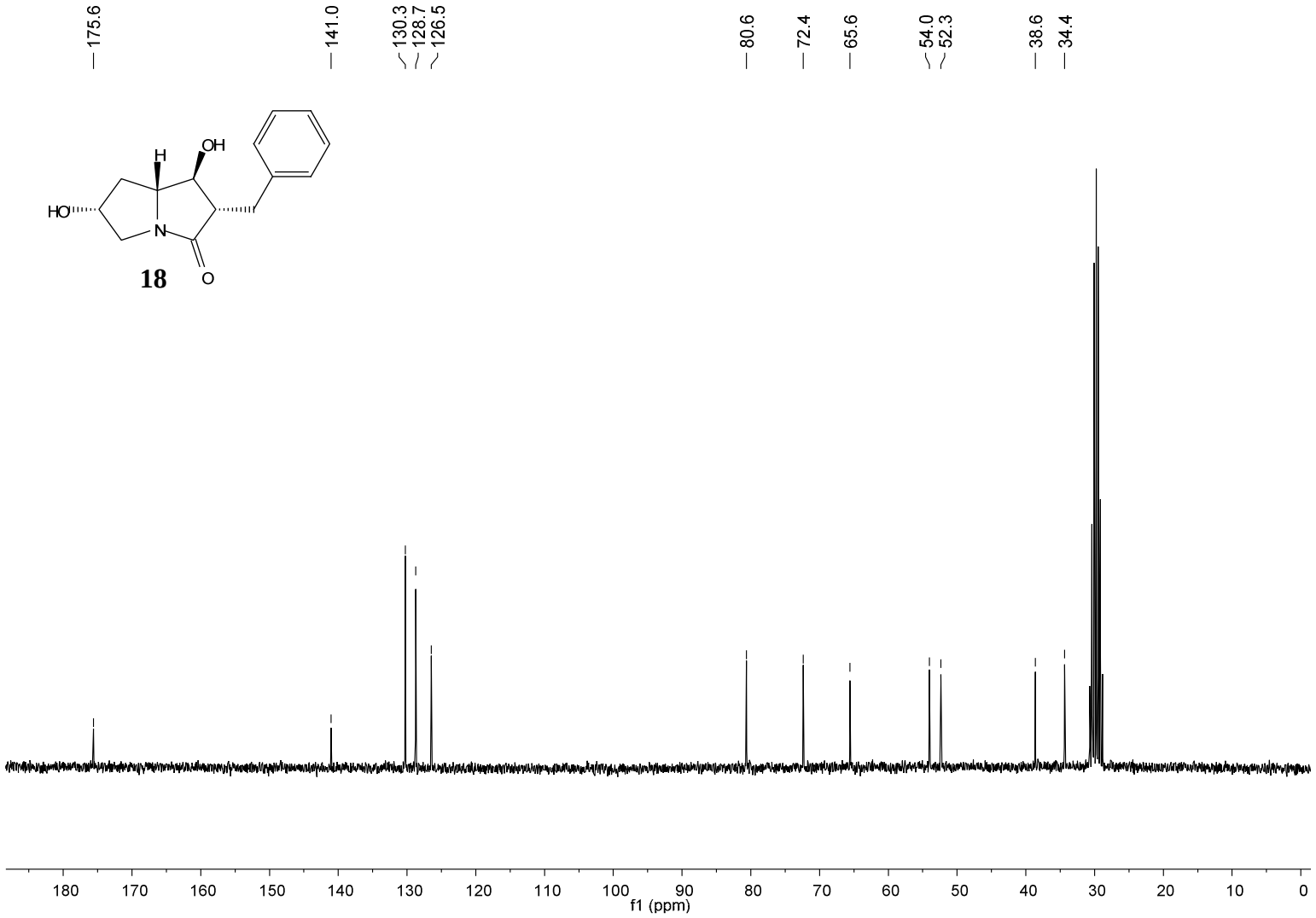
2D-NOESY (400 MHz, CD_3OD) spectrum of *p*-nitro-benzylidene-pyrrolizidinone **16**.



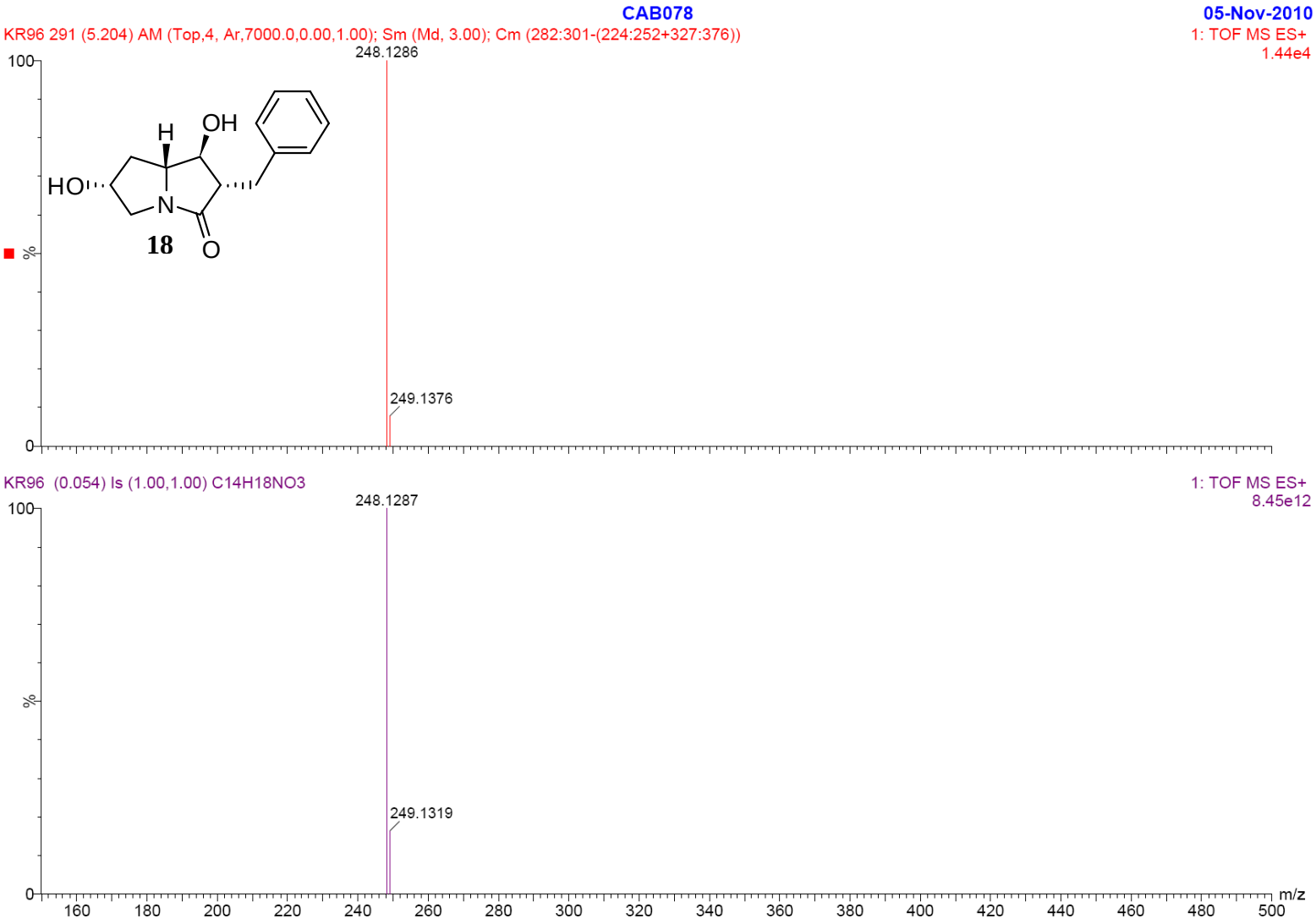
HRMS (ESI) of *p*-nitro-benzylidene-pyrrolizidinone **16**.



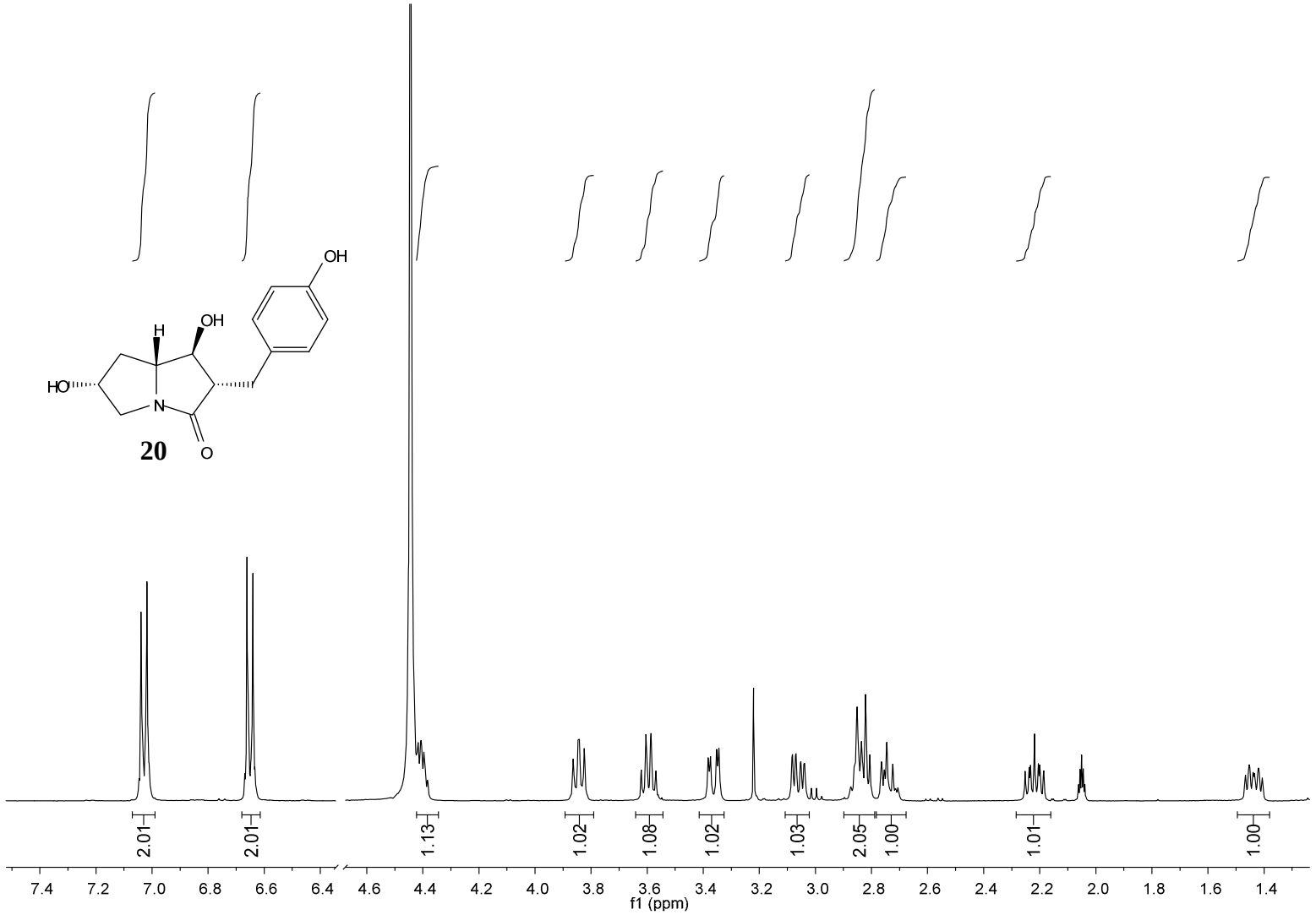
^{1}H NMR (500 MHz, CD_3OD) spectrum of benzyl-pyrrolizidinone **18**.



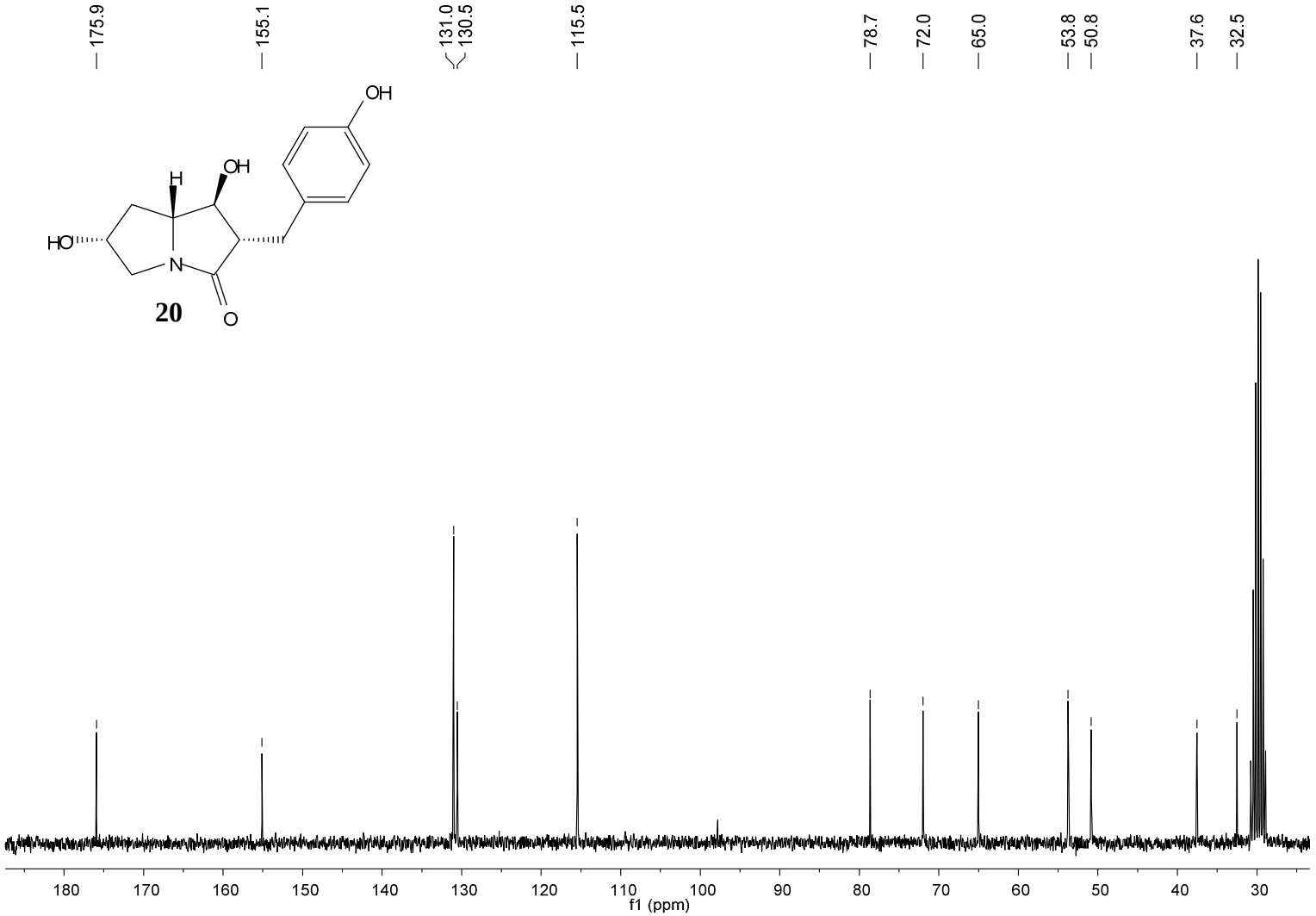
^{13}C NMR [62.5 MHz, $(CD_3)_2CO$)] spectrum of benzyl-pyrrolizidinone **18**.



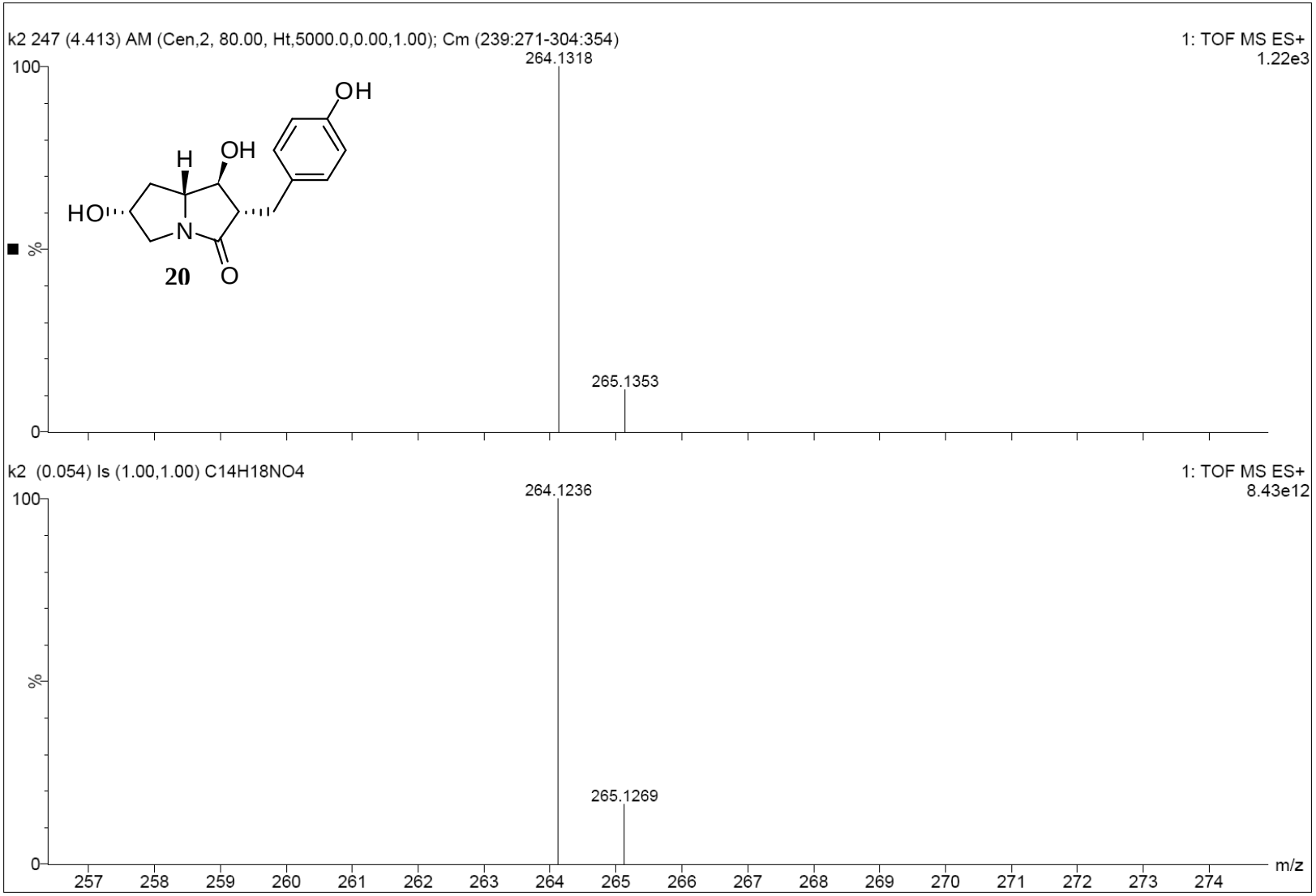
HRMS (ESI) of benzyl-pyrrolizidinone **18**.



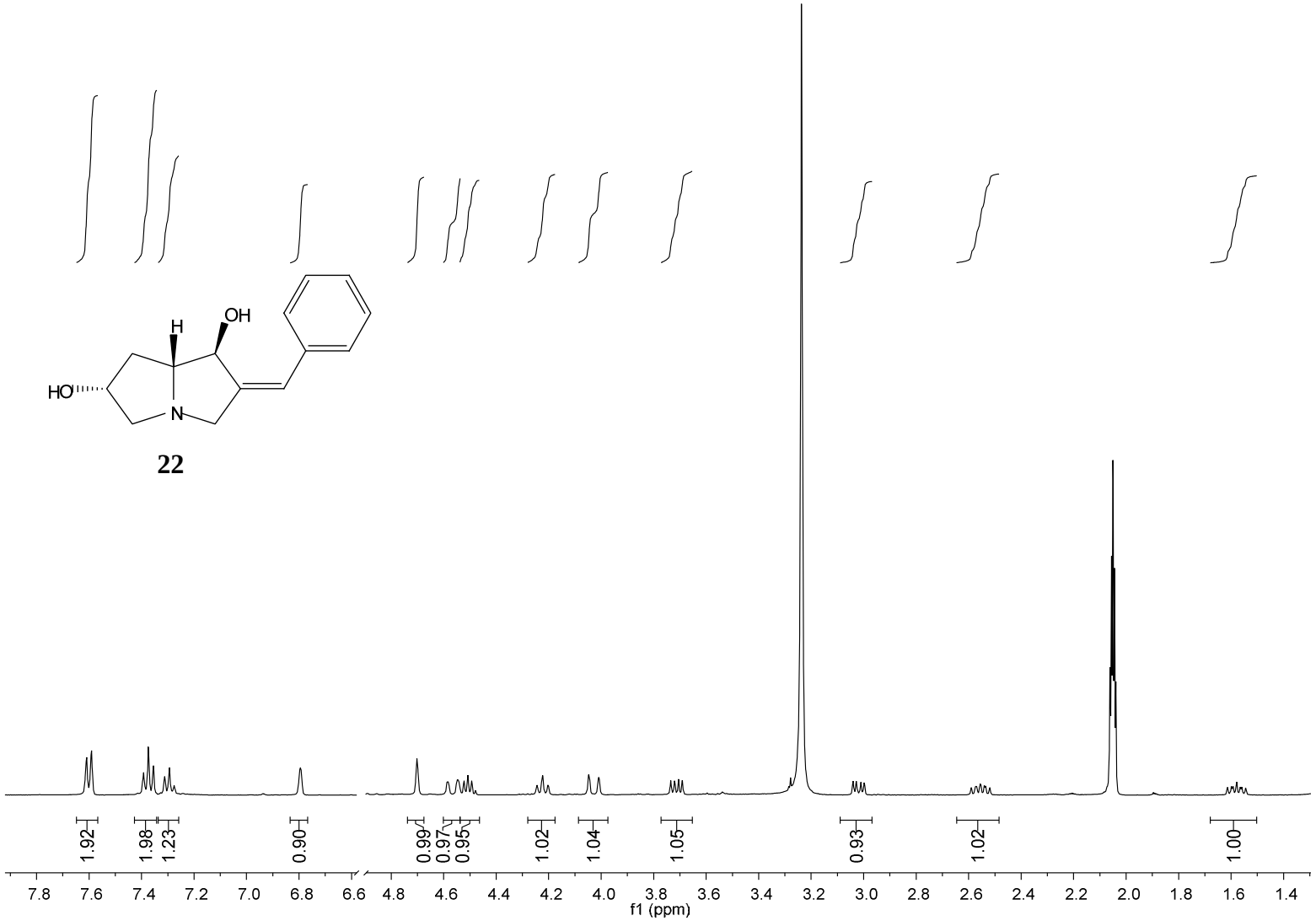
^{1}H NMR [400 MHz, $(CD_3)_2CO$] spectrum of hydroxy-benzyl-pyrrolizidinone **20**.



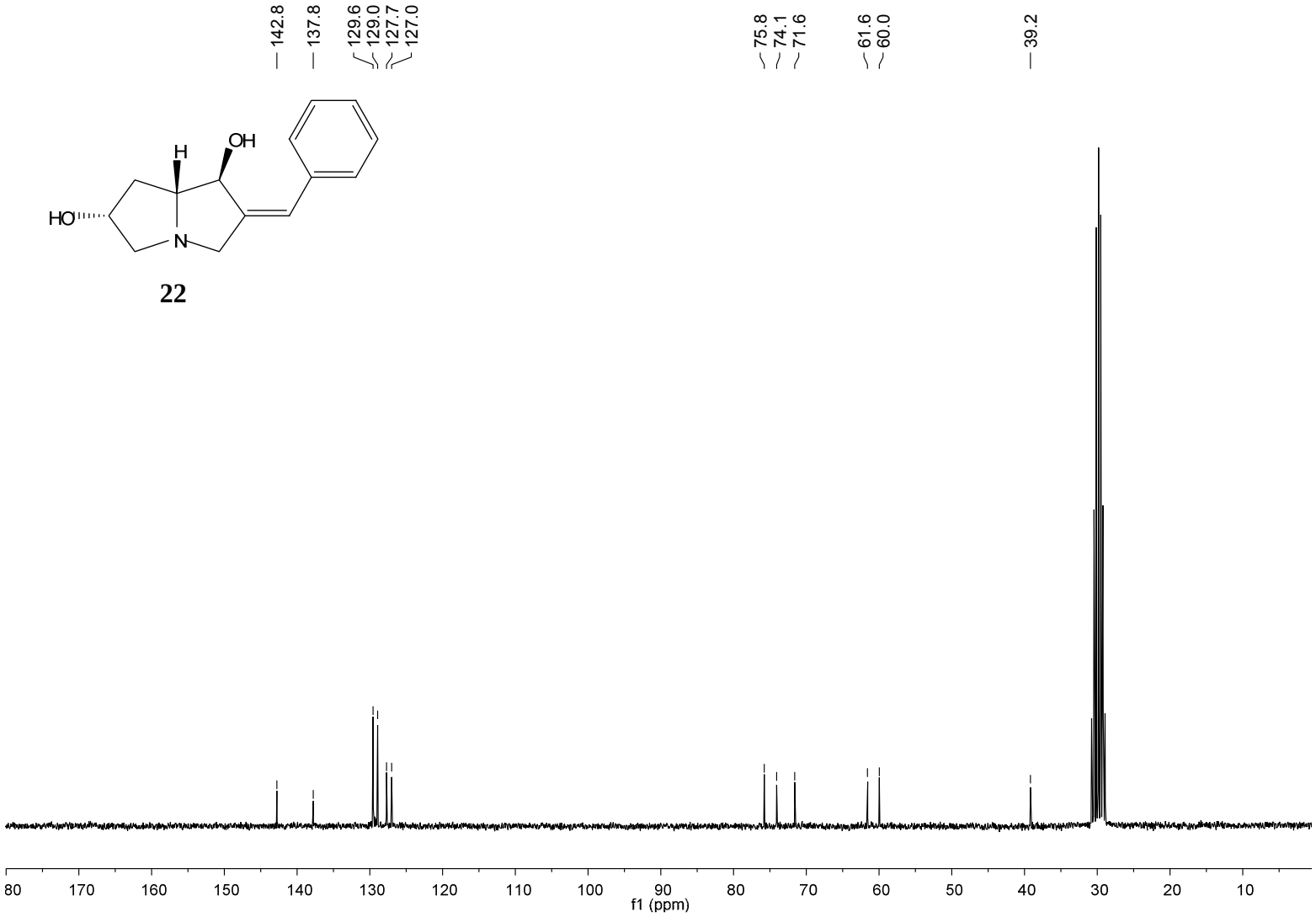
^{13}C NMR [62.5 MHz, $(CD_3)_2CO$)] spectrum of hydroxy-benzyl-pyrrolizidinone **20**.



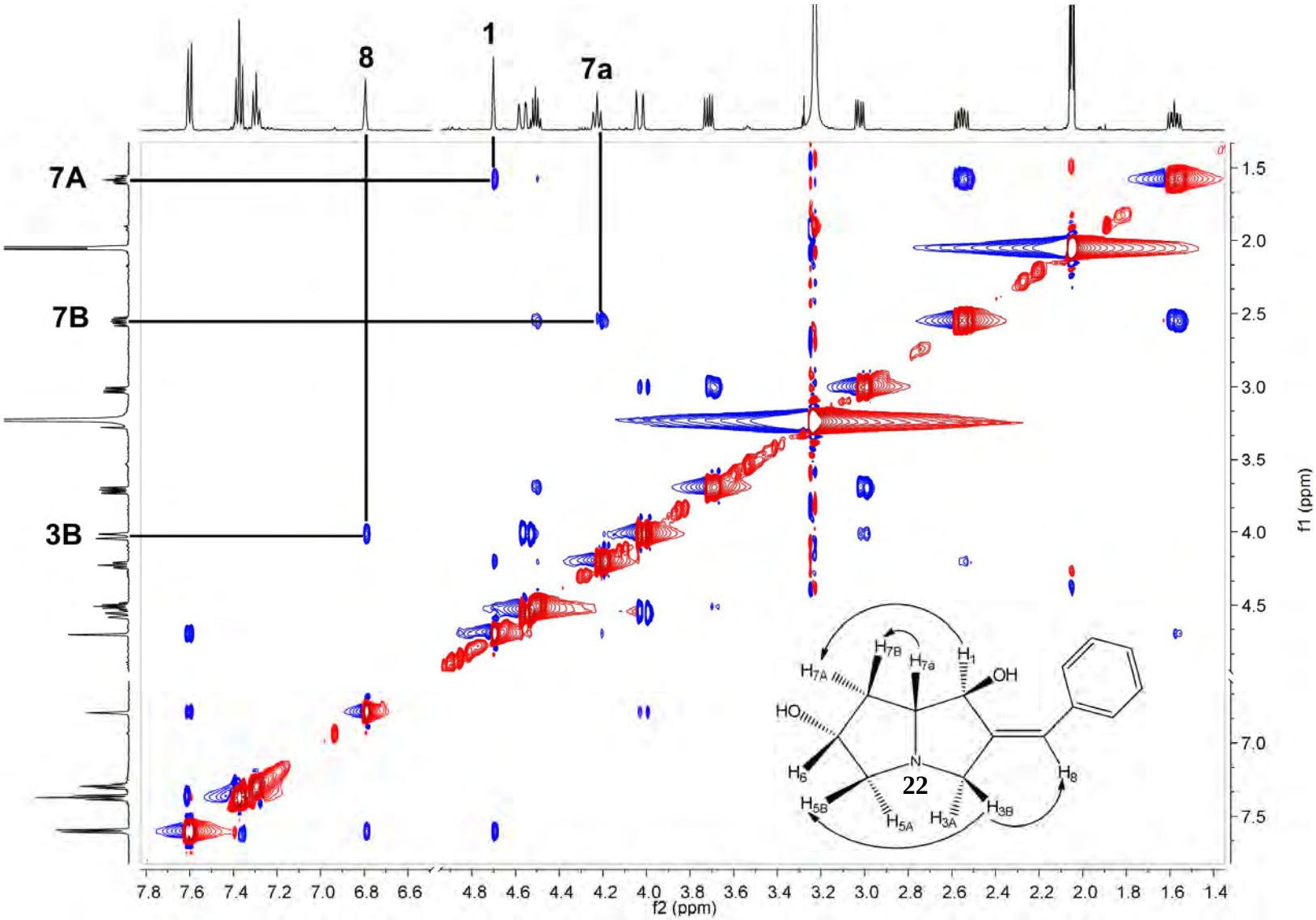
HRMS (ESI) of hydroxy-benzyl-pyrrolizidinone **20**.



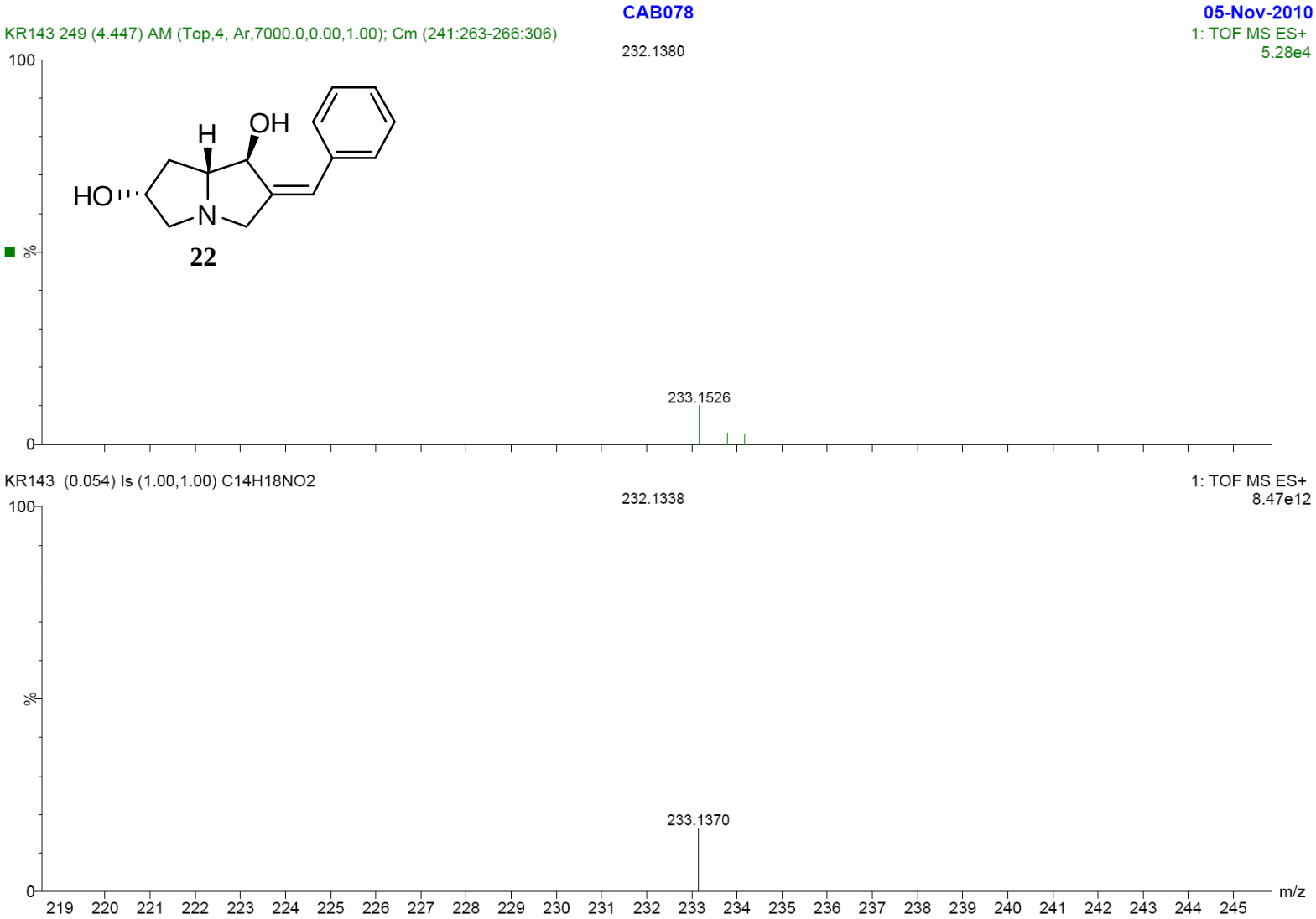
^{1}H NMR [400 MHz, $(CD_3)_2CO$)] spectrum of benzylidene-pyrrolizidine **22**.



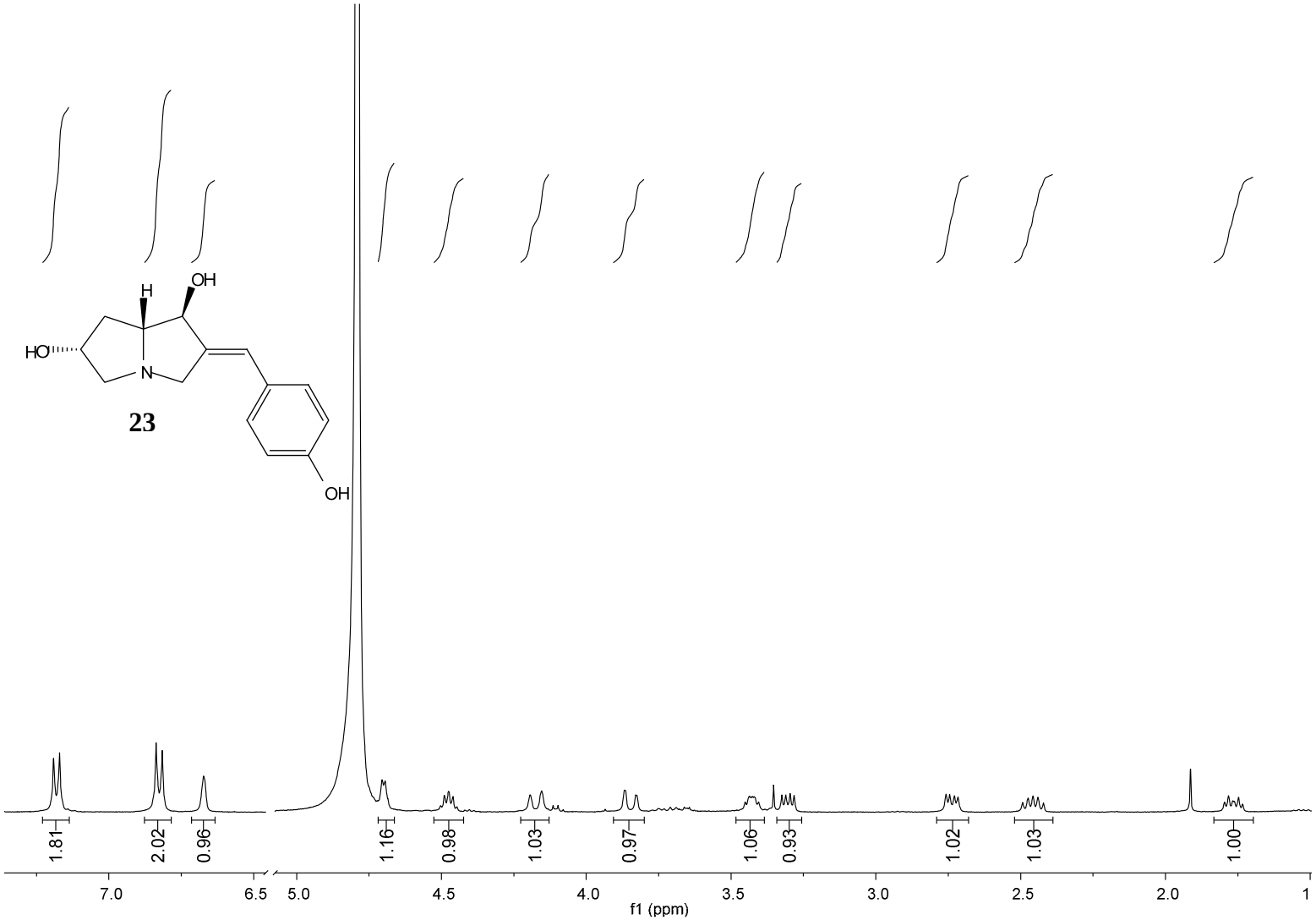
^{13}C NMR [(62.5 MHz, $(CD_3)_2CO$)] spectrum of benzylidene-pyrrolizidine **22**.



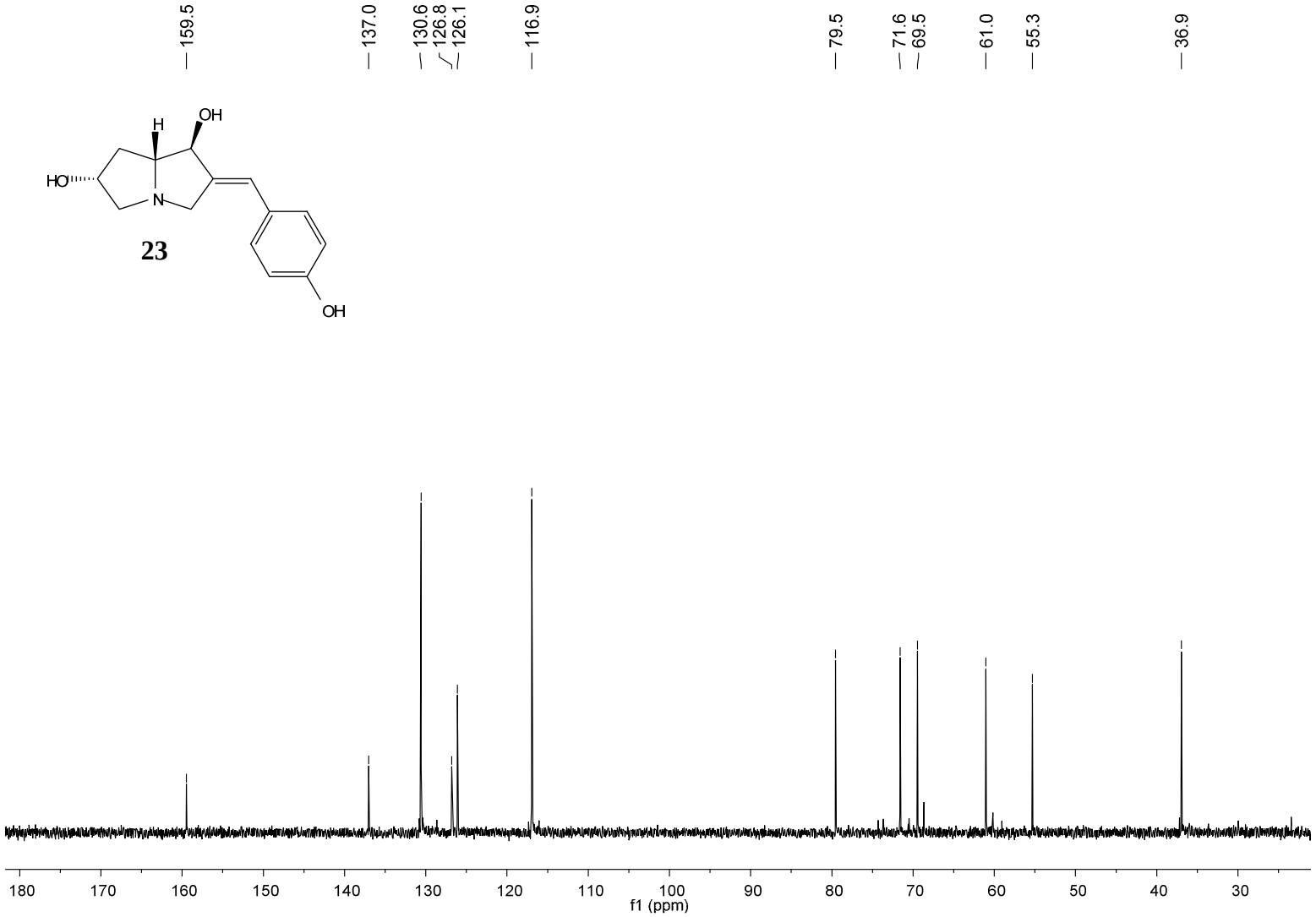
2D-NOESY [400 MHz, $(CD_3)_2CO$)] spectrum of benzylidene-pyrrolizidine **22**.



HRMS (ESI) of benzylidene-pyrrolizidine **22**.

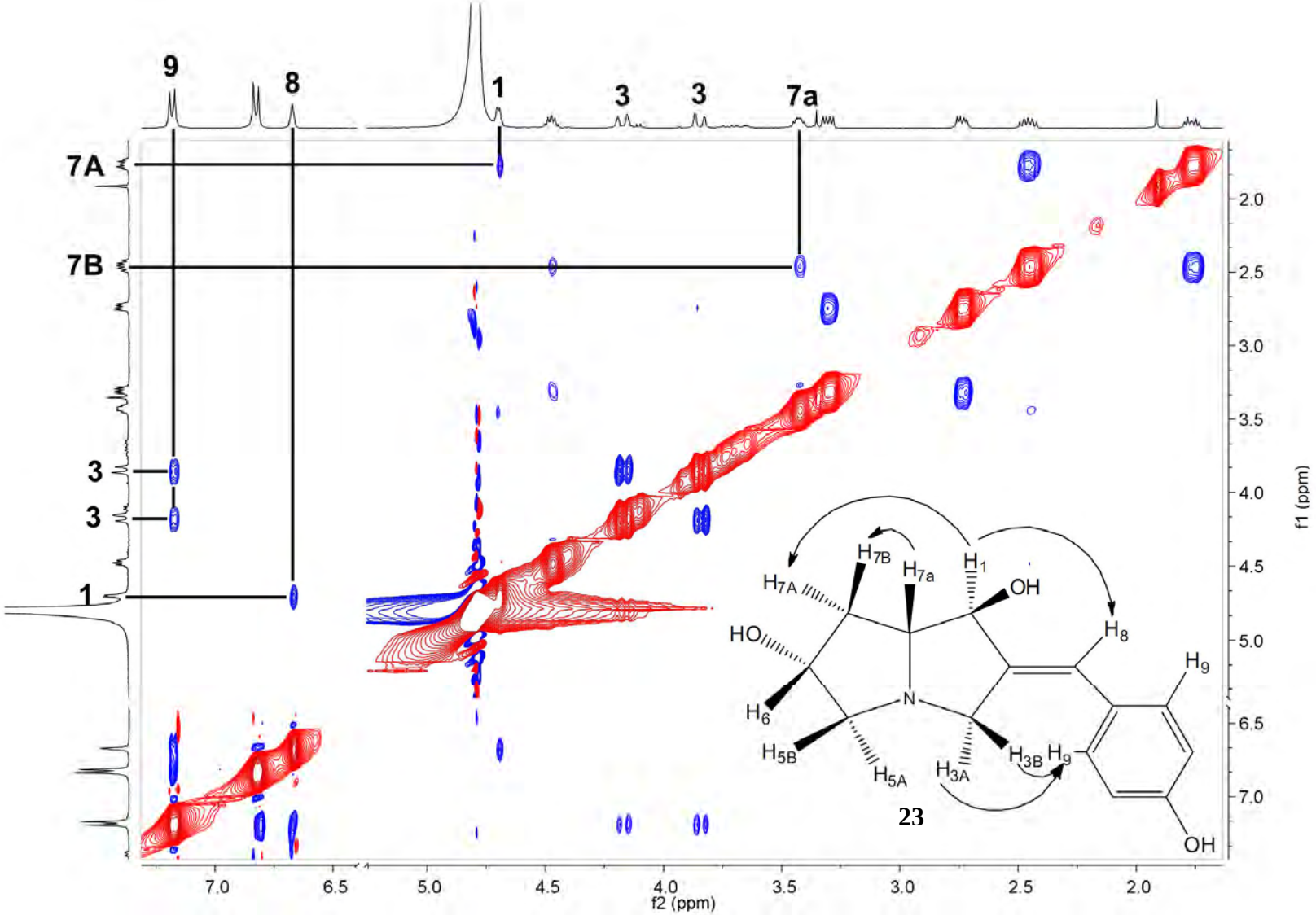


^{1}H NMR (400 MHz, D_2O) spectrum of hydroxy-benzylidene-pyrrolizidine **23**.

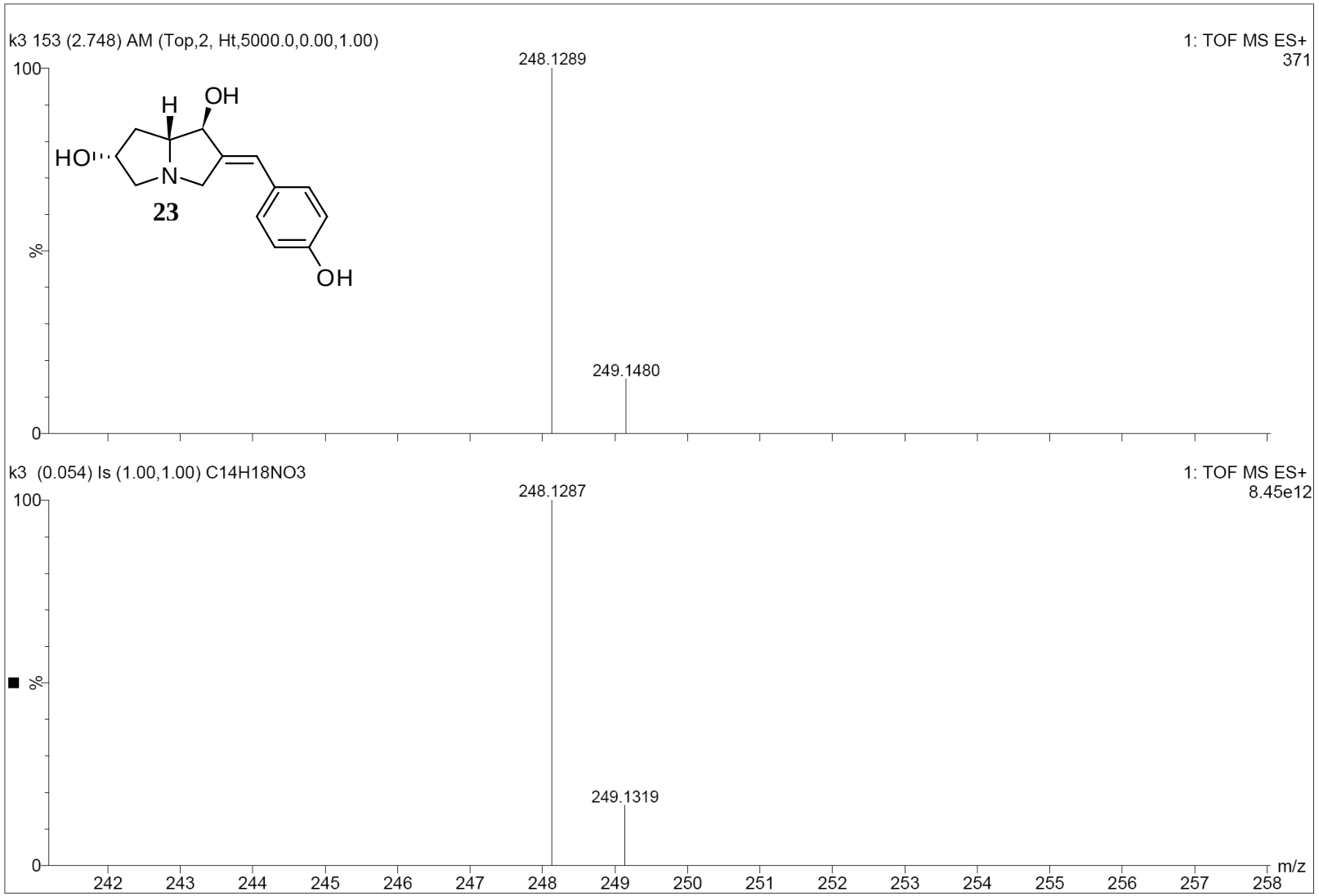


23

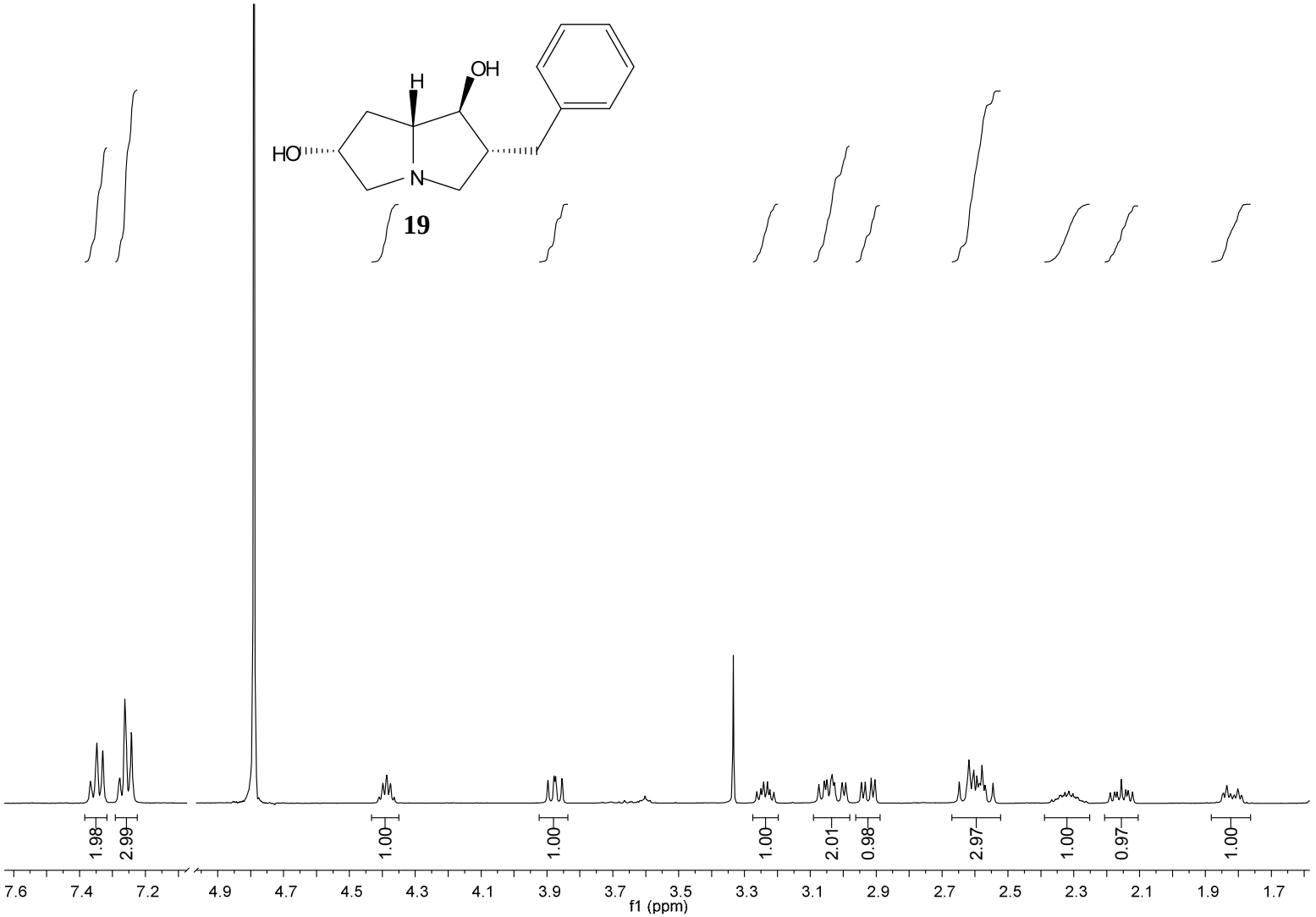
^{13}C NMR (125 MHz, D_2O) spectrum of hydroxy-benzylidene-pyrrolizidine **23**.



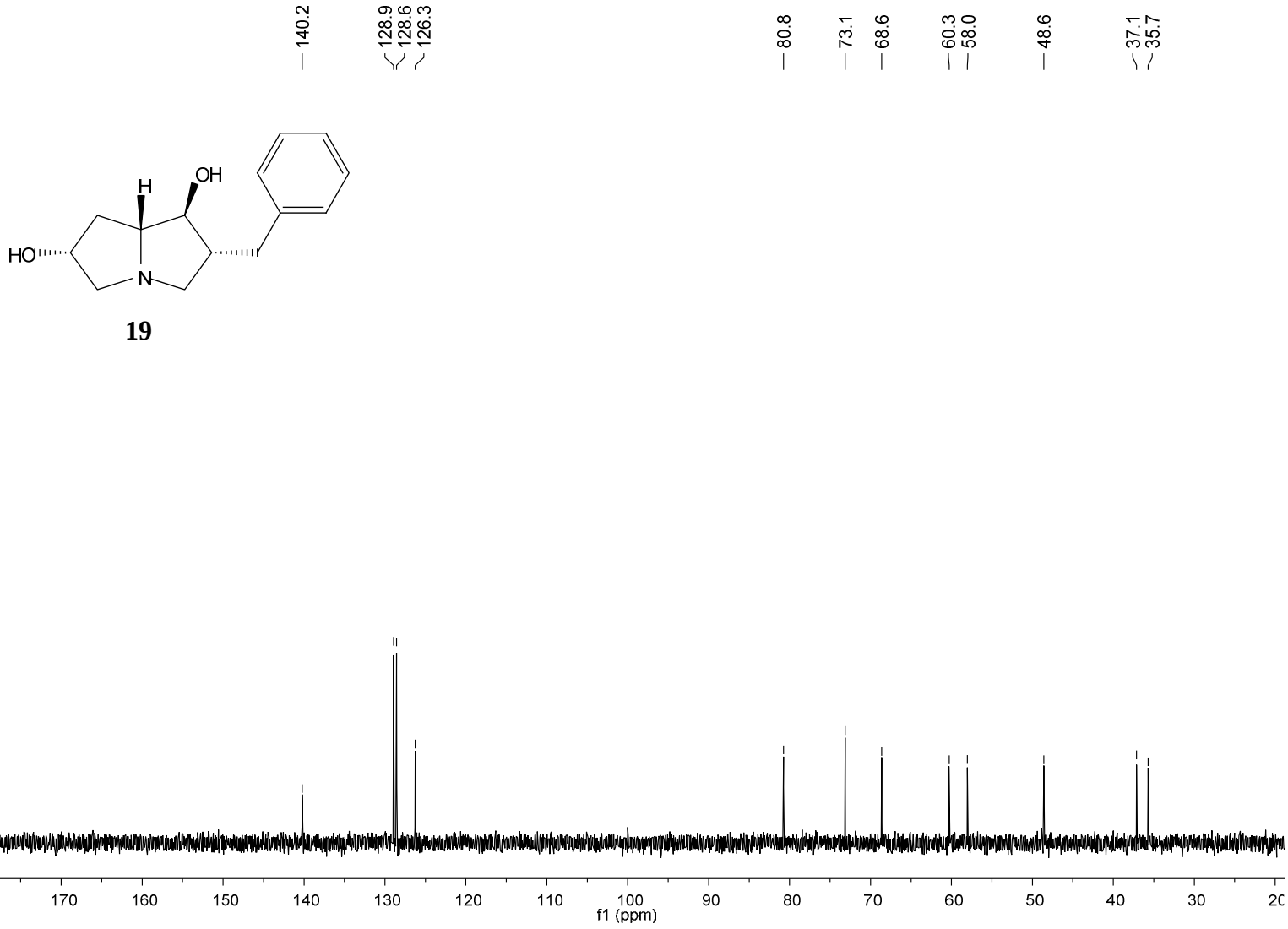
2D-NOESY (400 MHz, D_2O) spectrum of hydroxy-benzylidene-pyrrolizidine **23**.



HRMS (ESI) of hydroxy-benzylidene-pyrrolizidine **23**.

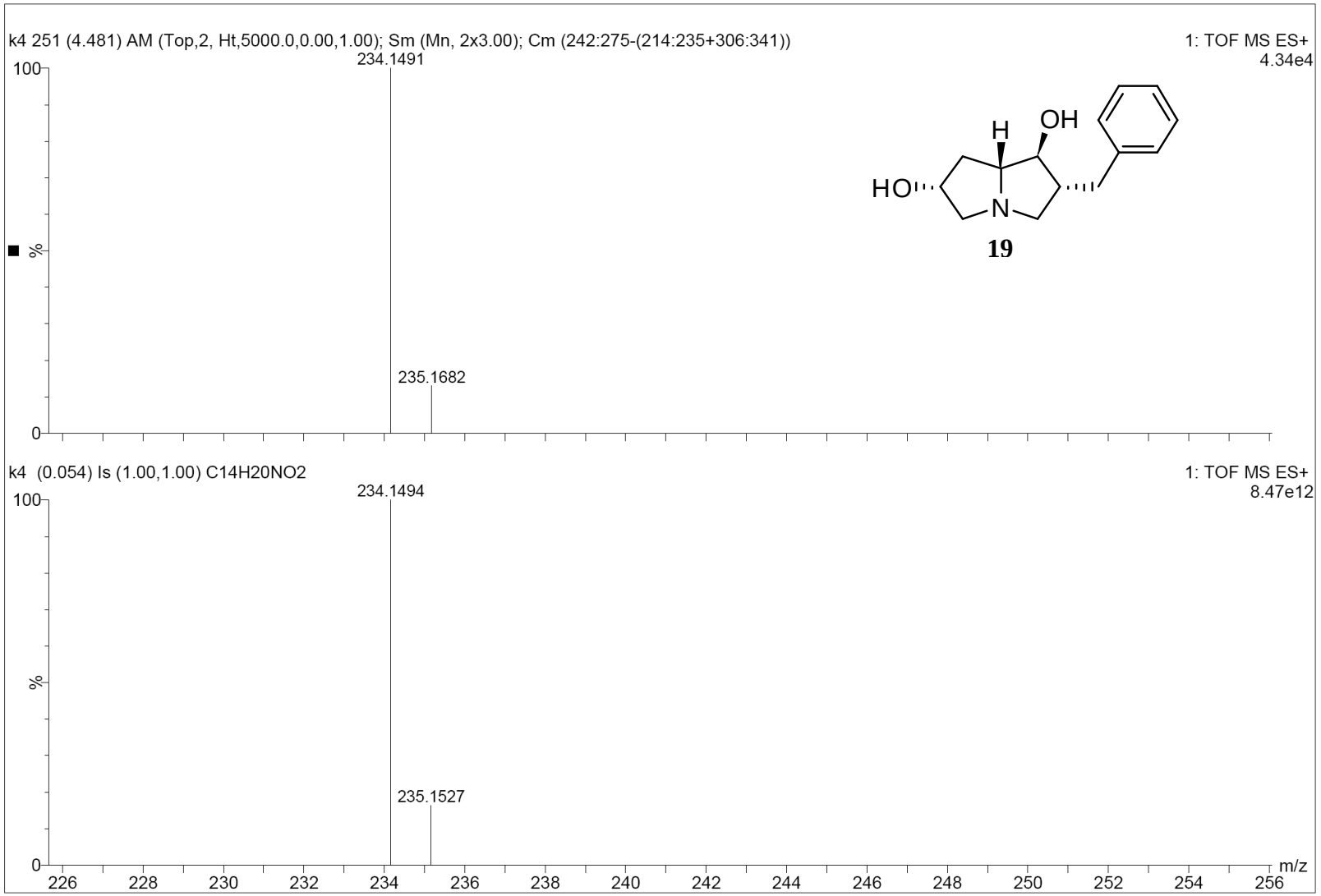


^{1}H NMR (400 MHz, D_2O) spectrum of benzyl-pyrrolizidine **19**.

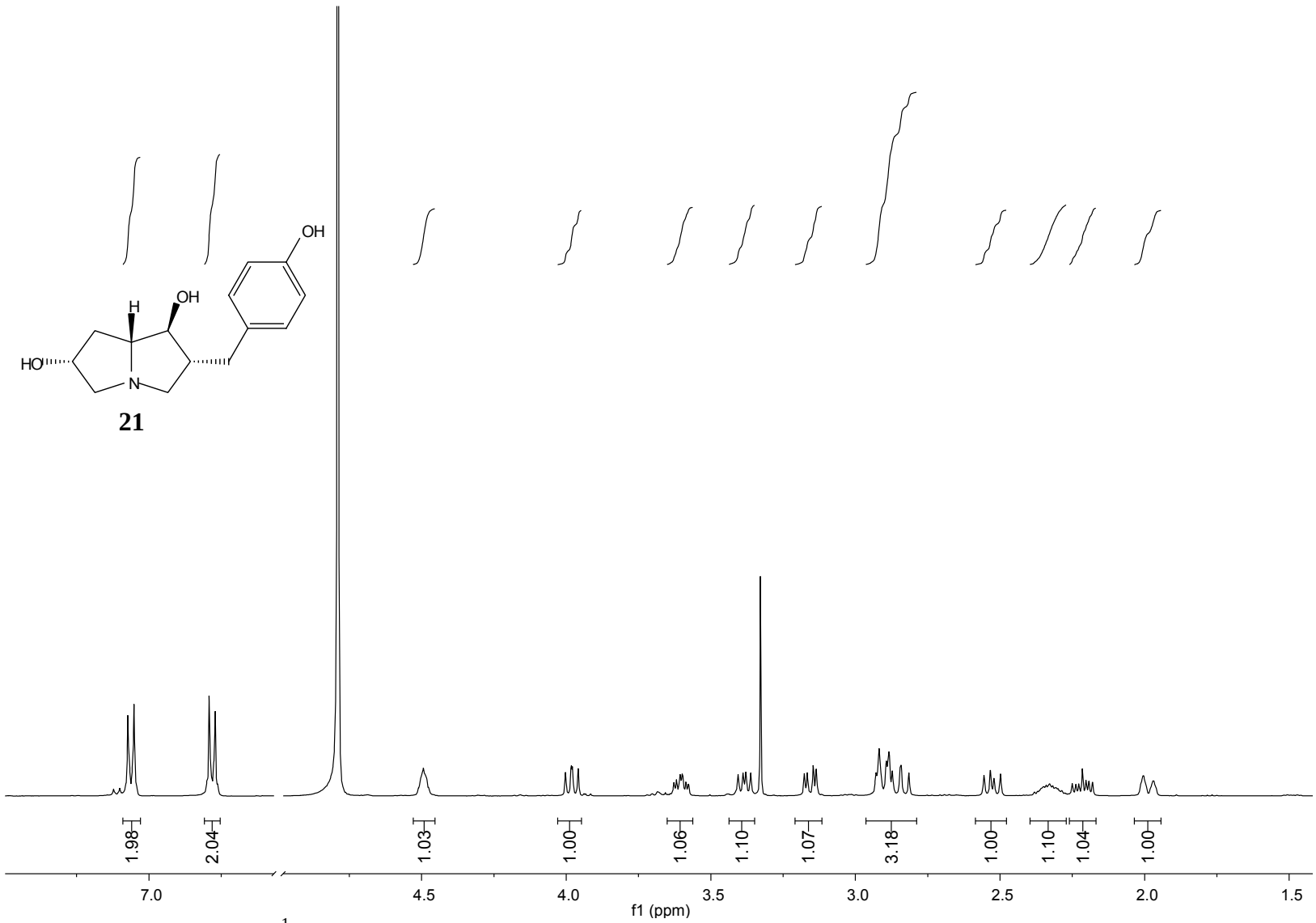


19

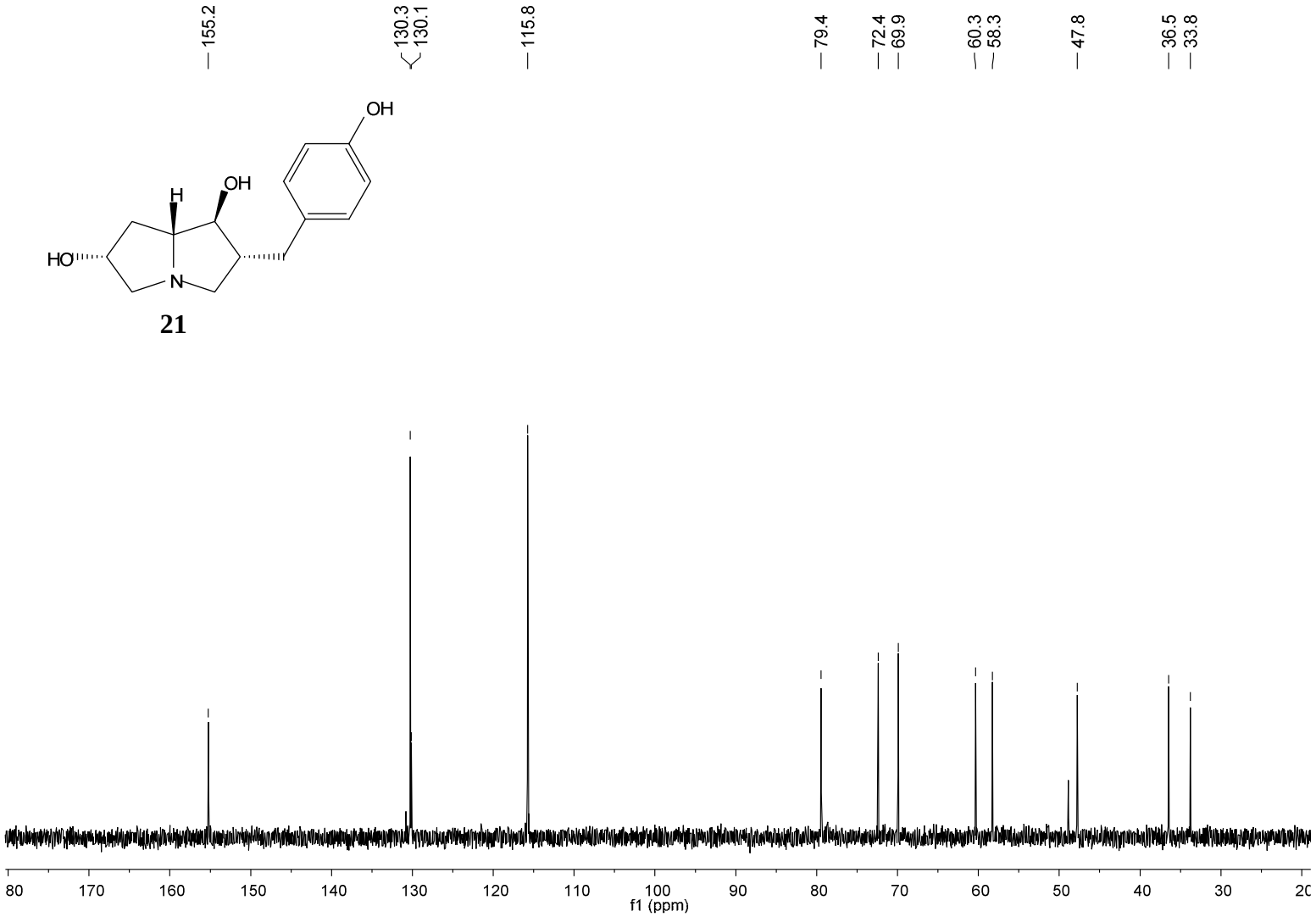
^{13}C NMR (100 MHz, D_2O) spectrum of benzyl-pyrrolizidine **19**.



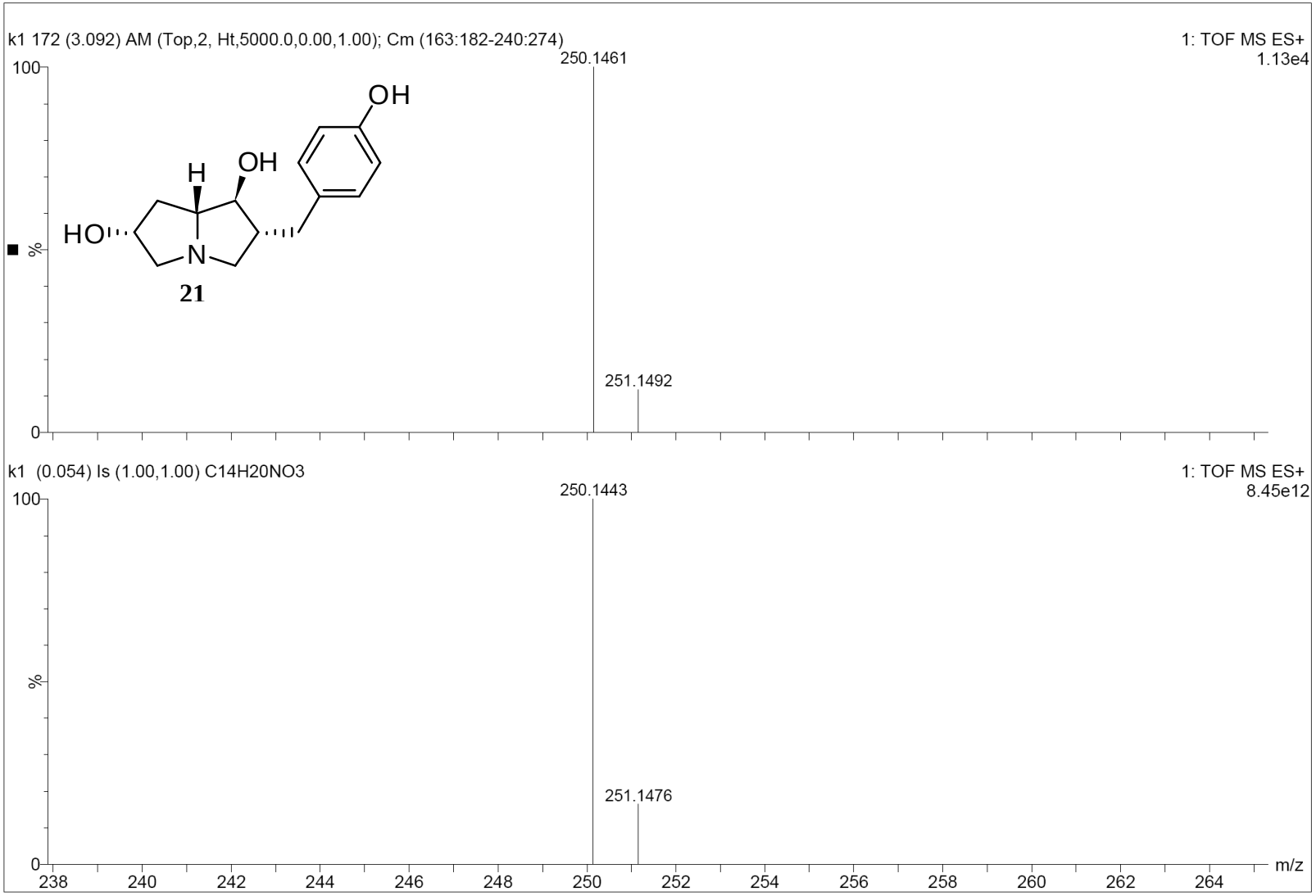
HMRS (ESI) of benzyl-pyrrolizidine **19**.



^{1}H NMR (400 MHz, D_2O) spectrum of hydroxy-benzyl-pyrrolizidine **21**.



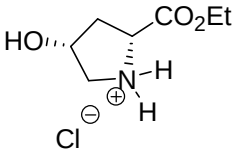
^{13}C NMR (100 MHz, D_2O) spectrum of hydroxy-benzyl-pyrrolizidine **21**.



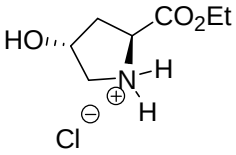
HRMS (ESI) of hydroxy-benzyl-pyrrolizidine **21**.

ATTACHMENT 1

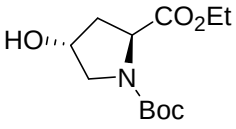
NOTE: In this part of our supporting information we have included the experimental procedure for the preparation the intermediates used for the synthesis of our asymmetric aldehydes. They appear here because these compounds are not cited in the manuscript. In order to differentiate these compounds from those described in our manuscript they were numbered using roman numbers.



(2*R*,4*R*)-2-(ethoxycarbonyl)-4-hydroxypyrrolidinium chloride (I): To a solution of commercial *cis*-4-hydroxy-D-proline or *trans*-4-hydroxy-L-proline (0.50 g, 3.81 mmol) in ethanol (10 mL), at 0 ºC, was slowly dropped thionyl chloride (0.31 mL, 0.513 g, 4.31 mmol). After that, the cooling bath was removed and the resulting solution was refluxed for 12h and cooled to room temperature. The resulting crystals was filtered, washed with ethyl ether and dried under reduced pressure. The filtrate was diluted with ethyl ether to obtain crystals that were filtered, washed with ethyl ether and dried. The crystals were combined to afford 0.73 g of the corresponding ester in 98 % yield. $[\alpha]_D^{20}$ +18 (c 2; H_2O); Lit.[1] $[\alpha]_D^{20}$ +20.37 (c 2; H_2O); M. p. 143° C; IR (KBr, ν_{max}): ν 3303, 2975, 2940, 1727, 1581, 1380, 1247, 1094 cm^{-1}. ^1H NMR (250 MHz, D_2O) δ 1.29 (3H, t), 2.48 (2H, m), 3.46 (2H, m), 4.31 (2H, q), 4.64 (1H, m); ^{13}C NMR (62,5 MHz, D_2O) δ 12.8, 36.6, 53.1, 58.2, 63.6, 68.6, 170.0. HRMS (ESI-TOF) Calcd. for $C_7H_{14}NO_3$ $[M + H]^+$ 160.0974. Found 160.0927.



(2*S*,4*R*)-2-(ethoxycarbonyl)-4-hydroxypyrrolidinium chloride (II): $[\alpha]_D^{20}$ -29,2º (c 3; H_2O); Lit.[2] $[\alpha]_D^{20}$ -28º (c 3; H_2O); M. p. 144° C; IR (KBr, ν_{max}): ν 3309, 2949, 2864, 2700, 2598, 1732, 1274, 1237 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.33 (t, 3H), 2.19 (ddd, 1H), 2.43 (m, 1H), 3.31 (m, 1H), 3.45 (dd, 1H), 4.32 (q, 2H), 4.58 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 14.3, 38.6, 55.0, 59.5, 64.0, 70.6, 170.2; HRMS (ESI-TOF) Calcd. for $C_7H_{14}NO_3$ $[M + H]^+$ 160.0974. Found 160.1016.

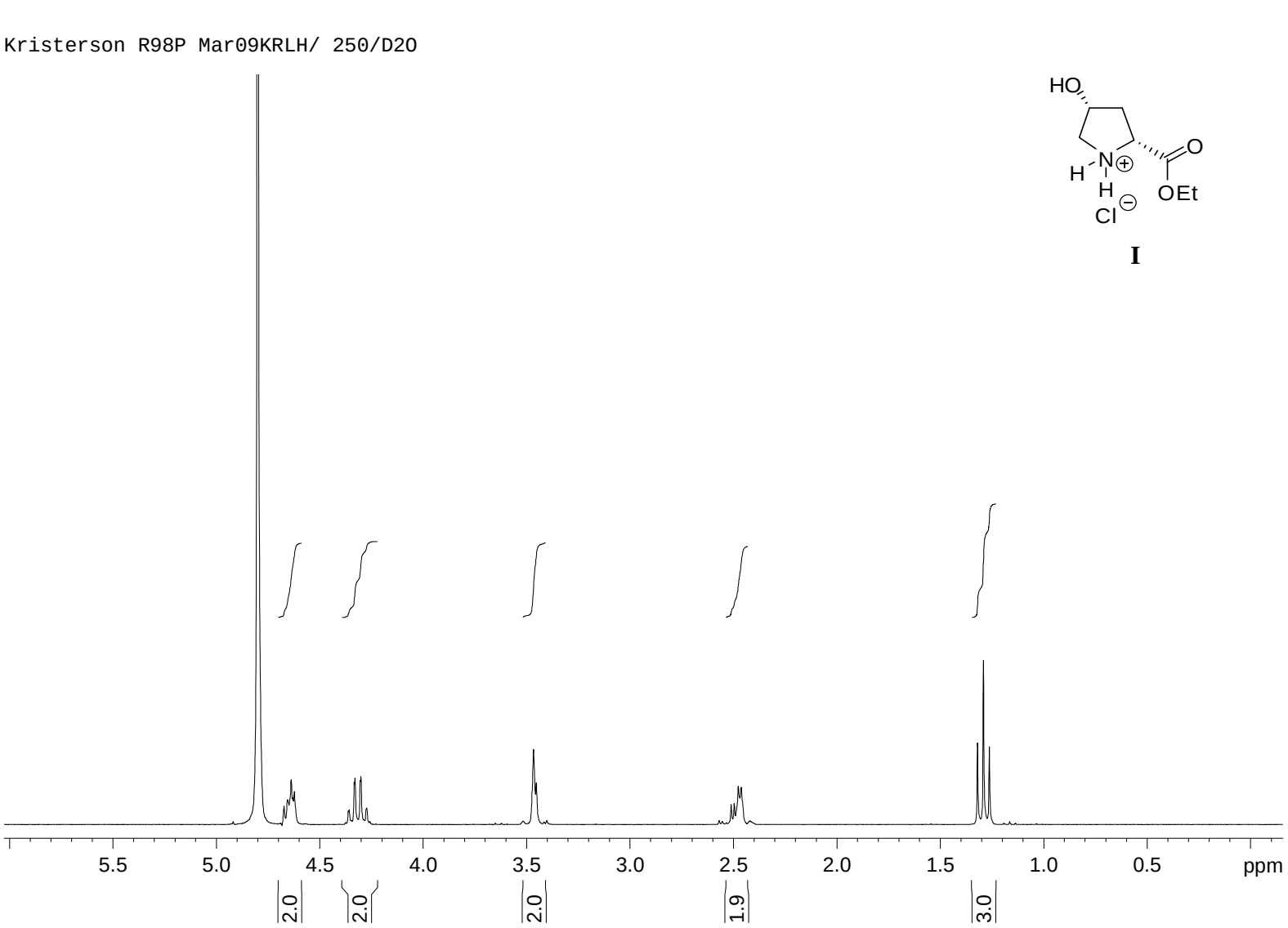


(2*S*,4*R*)-1-*tert*-butyl 2-ethyl 4-hydroxypyrrolidine-1,2-dicarboxylate (III): To a solution of the ester **II** (0.3 g, 1.53 mmol) in methanol (15 mL) was added di-*terc*-butyldicarbonate (Boc_2O, 0.4 g, 1.84 mmol) and $NaHCO_3$ (0.386 g, 4.60 mmol). The resulting suspension was immersed in a ultrasound bath for 4 h. The development of the reaction was followed by the CO_2 releasing. After that, the solvent was removed and the residue was dissolved in cooled distilled water (10 mL) and the solution was acidified with a saturated solution of $KHSO_4$ until pH 2 and extracted with ethyl acetate. The organic phase was separated, dried over anhydrous Na_2SO_4 and removed under reduced pressure to give 0.42 g of **III**, as a colorless oil, in 91 % yield $[\alpha]_D^{20}$ -69.1 (c 2; EtOH); Lit.[3] $[\alpha]_D^{20}$ -67.8 (c 2; EtOH); IR (film, ν_{max}): 3436, 2976, 2933, 1744, 1703, 1679, 1401, 1192, 1155 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 90 ºC) δ 1.21 (t, 3H), 1.38 (s, 9H), 2.06 (m, 2H), 3.33 (m, 2H), 4.12 (q, 2H), 4.26 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, 90 ºC) δ 13.5, 27.6, 38.2, 54.1, 57.4, 59.8, 67.7, 78.5,

152.9, 172.0; HRMS (ESI-TOF) Calcd. for $C_{12}H_{22}NO_5$ $[M + H]^+$ 260.1498. Found 260.1473.

References:

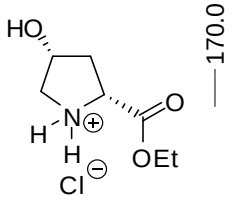
1. Di Cesare, P.; Jacquet, J. –P.; Essiz, M.; Remuzon, P.; Bouzard, D.; Weber, A. EP 87-114686, 1987.10.08. (*CAS* **1987**, *112*:118793).
2. Merck KGaA – Chemicals – ChemDAT. Product info.: *L*-4-Hydroxyproline ethyl ester hydrochloride: 824456. http://www.merck-chemicals.com/.
3. Baker, G.L.; Fritschel, S.J.; Stille, J.R.; Stille, J.K. *J. Org. Chem.* **1981**, *46*, 2954-2960.



I

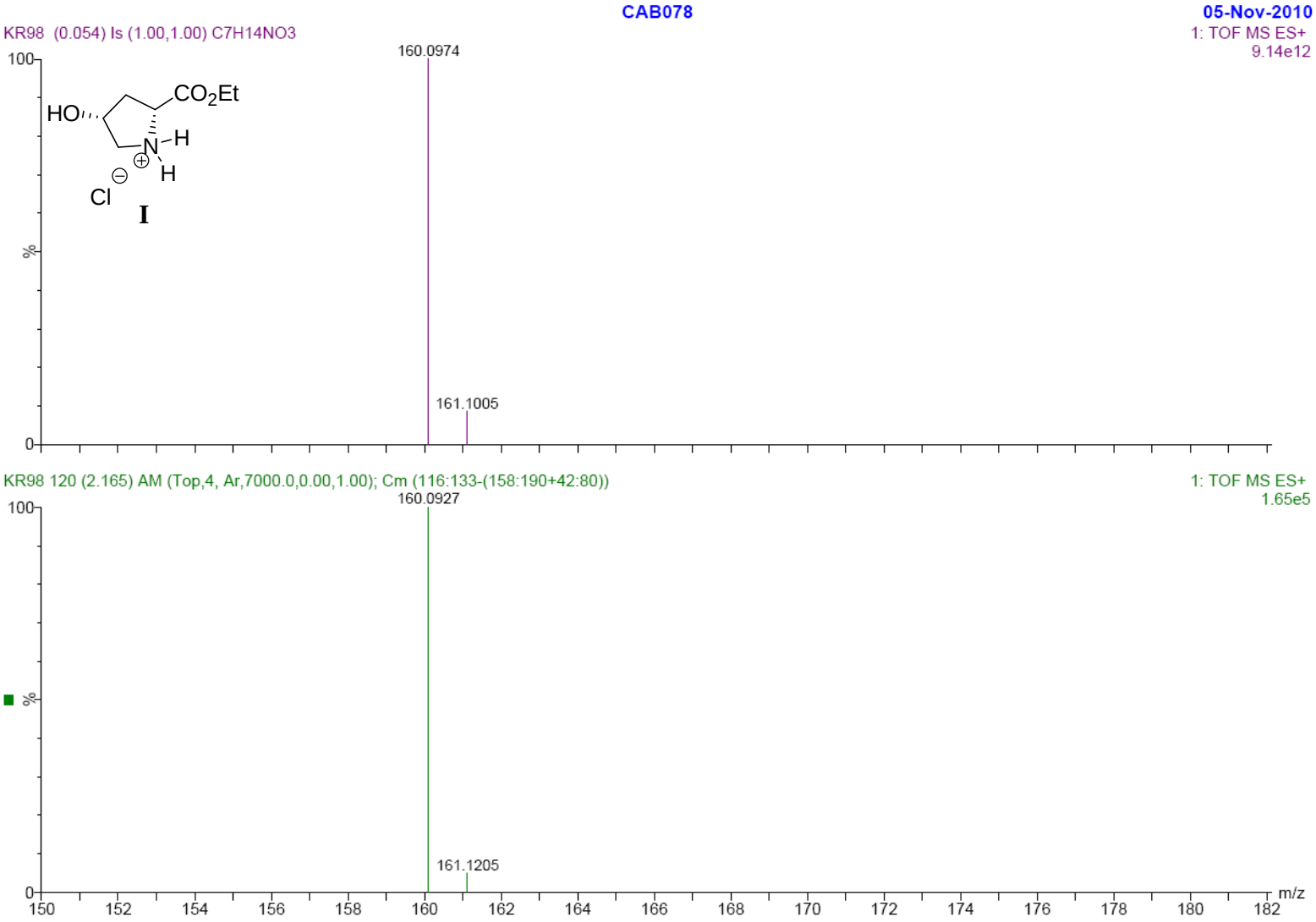
^{1}H NMR (250 MHz, D_2O) spectrum of ester **I**.

Kristerson R98P Mar09KRLC/ 250/D2O

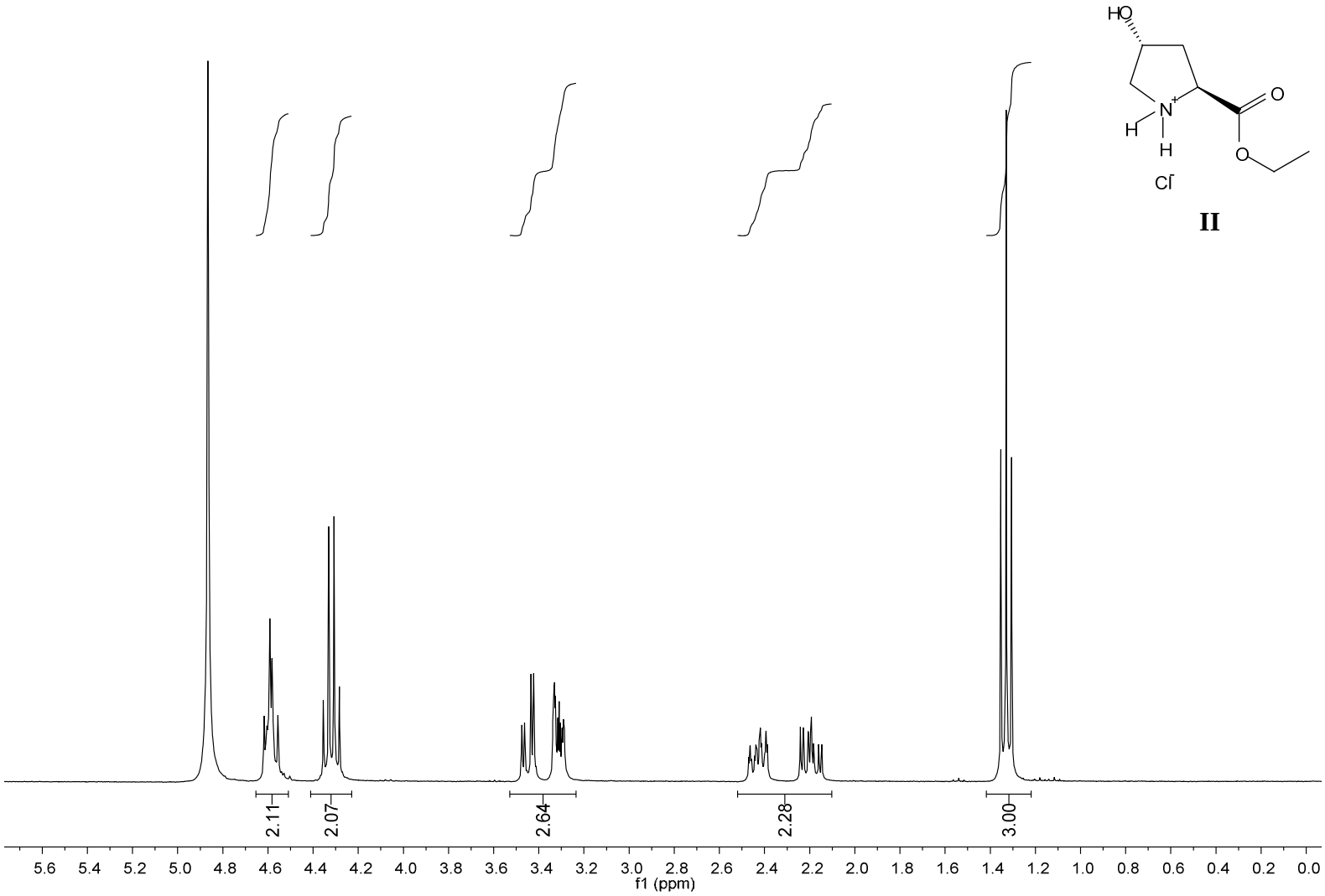


I

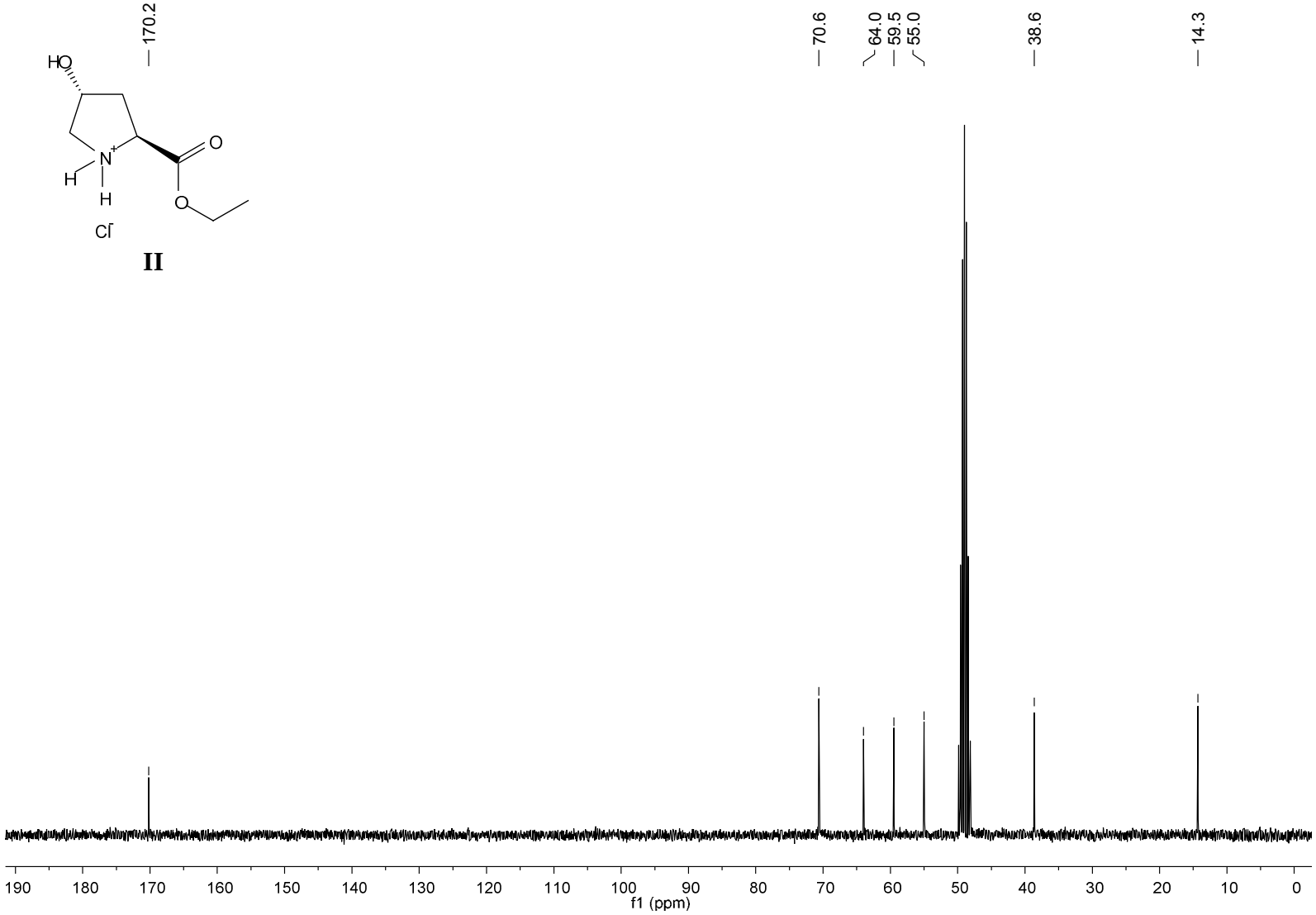
^{13}C NMR (62.5 MHz, D_2O) spectrum of ester **I**.



HRMS (ESI) of ester **I**.

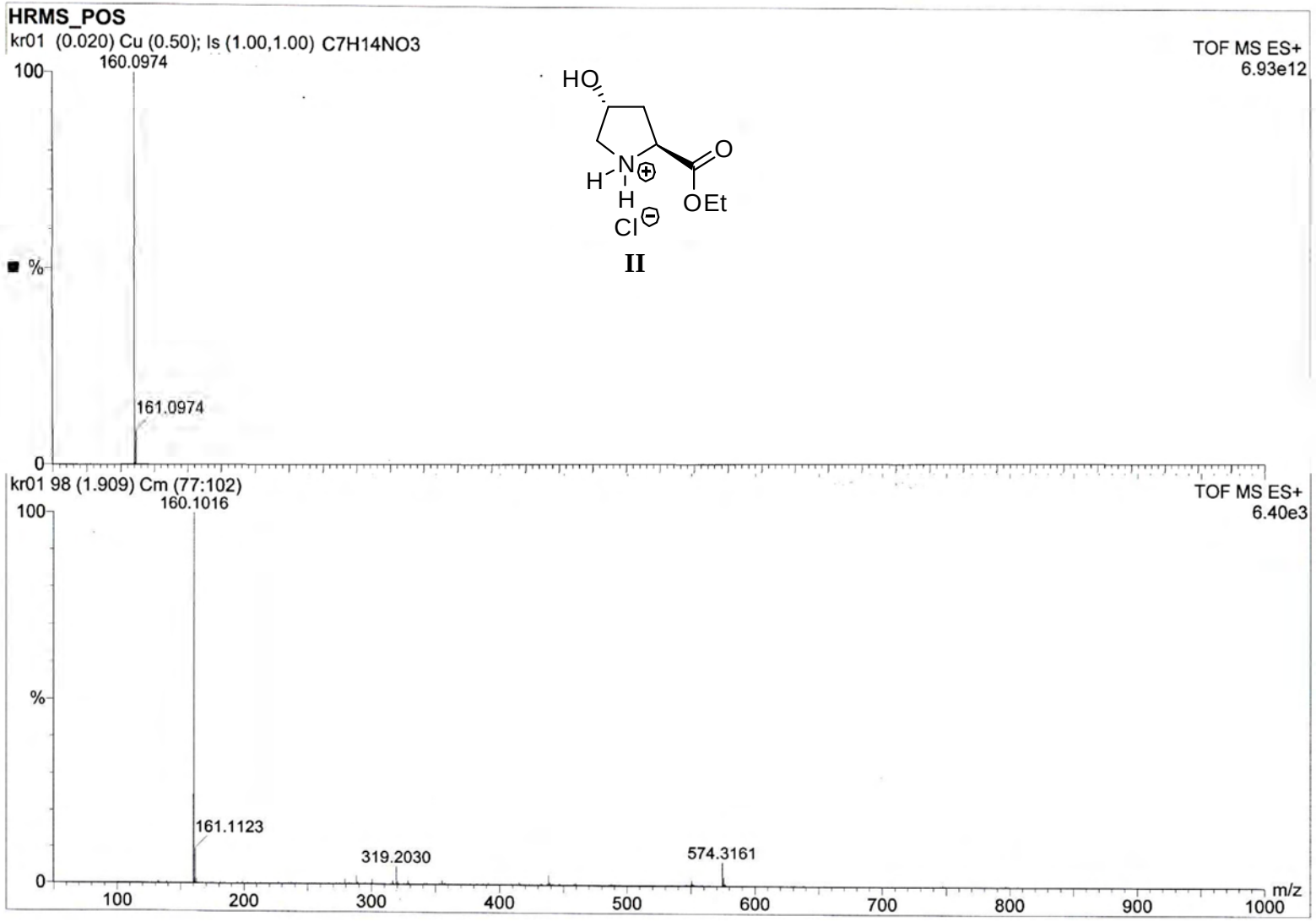


^{1}H NMR (300 MHz, CD_3OD) spectrum of ester **II**.



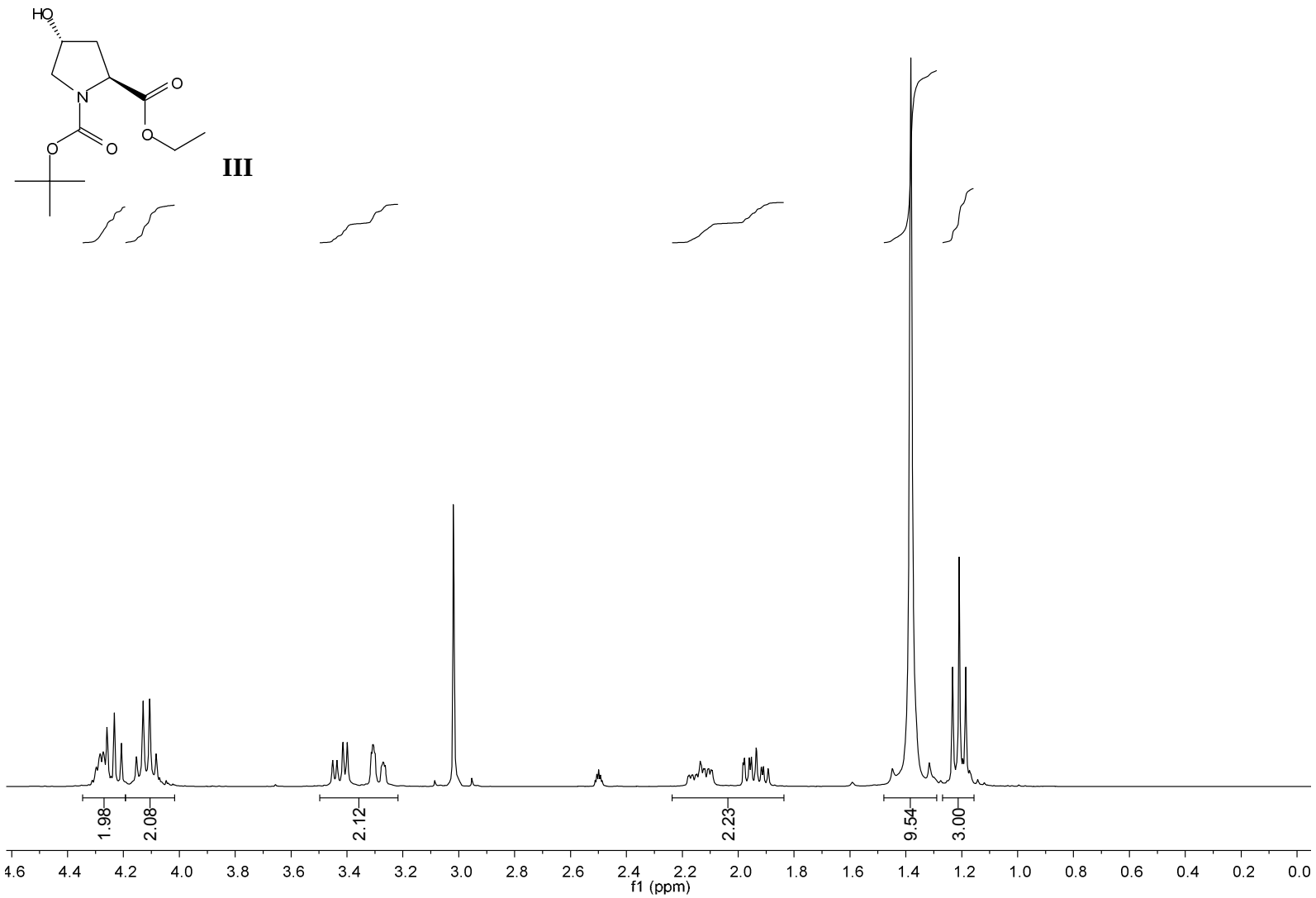
II

^{13}C NMR (75 MHz, CD_3OD) spectrum of ester **II**.

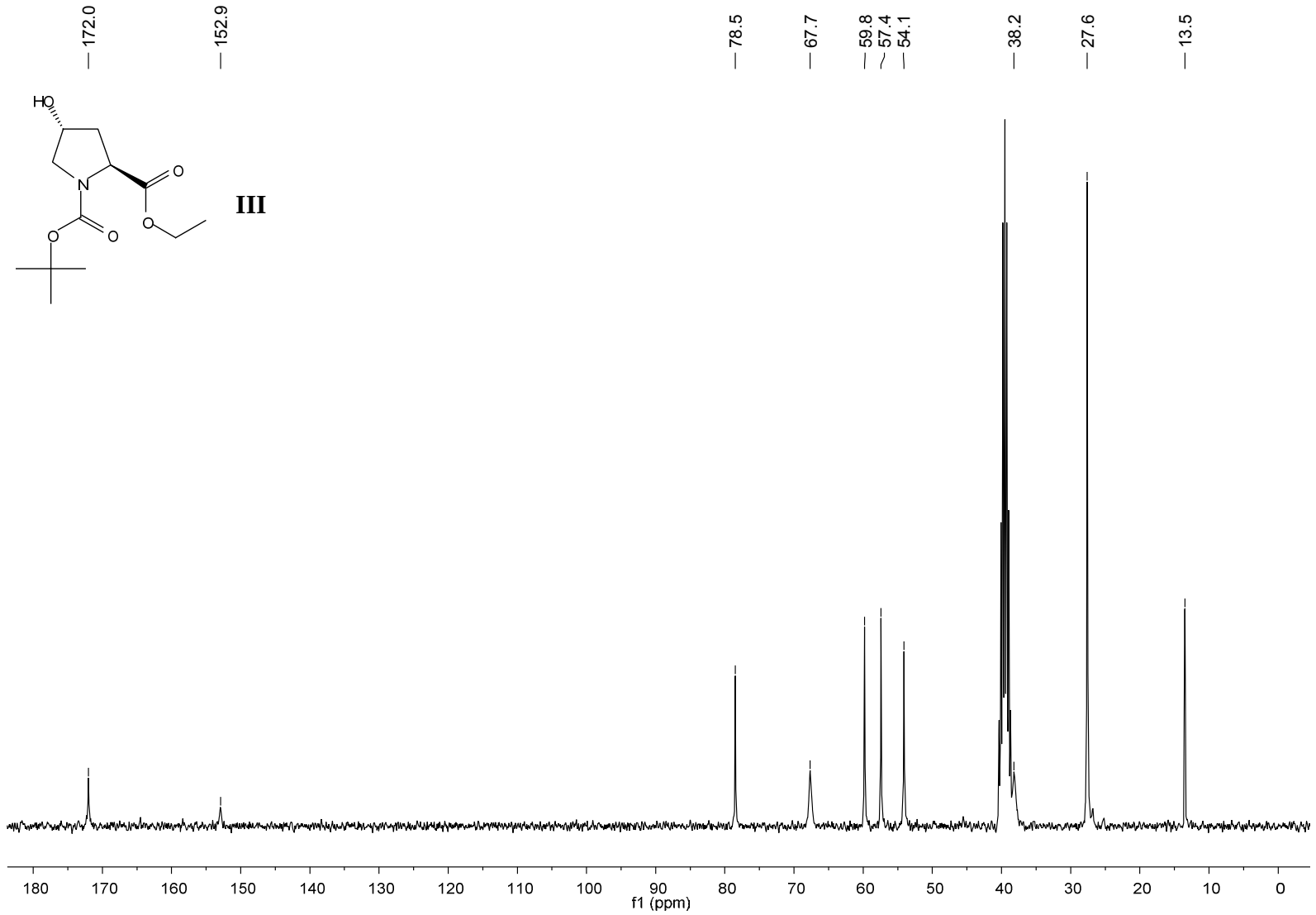


II

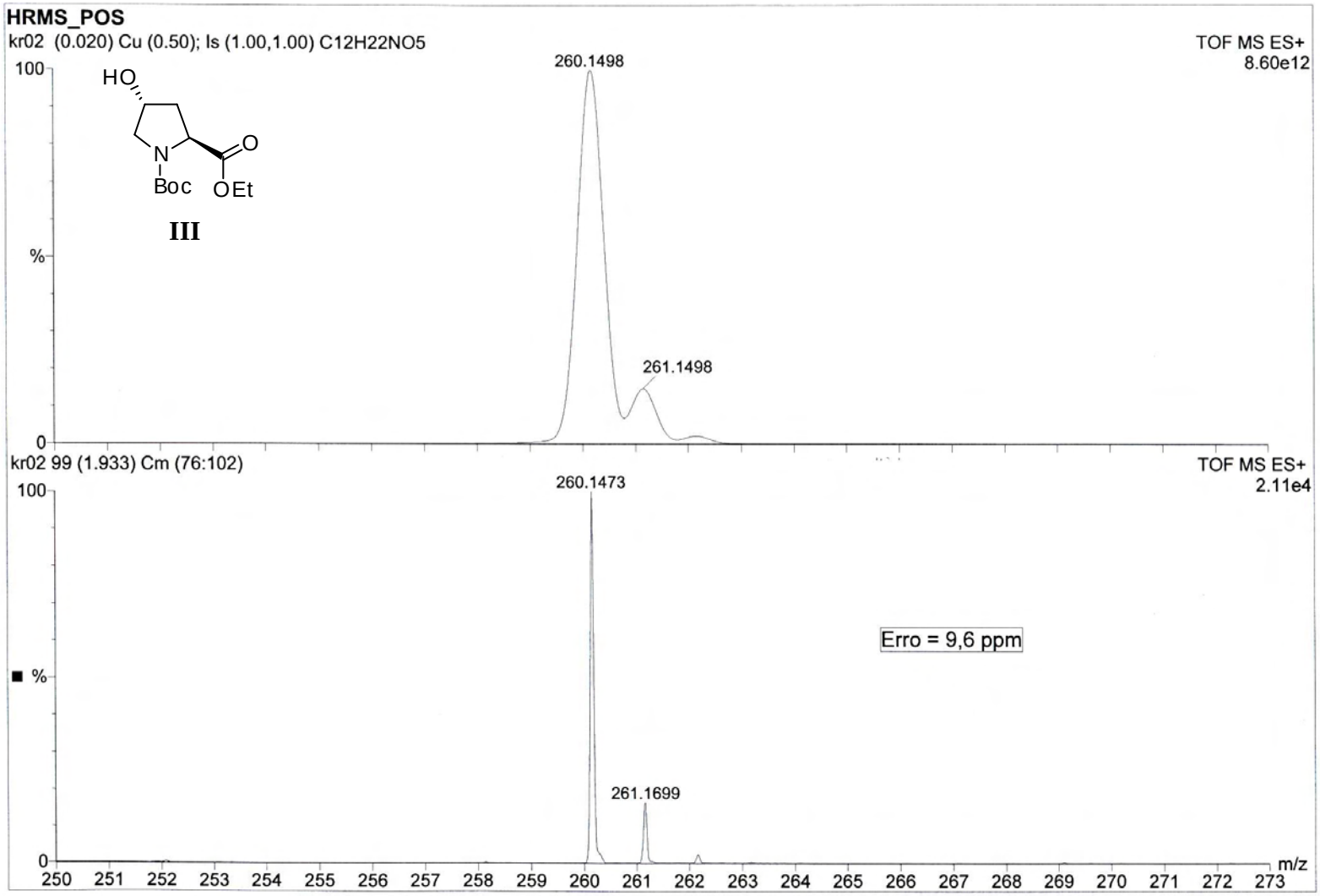
HRMS (ESI) of ester **II**.



^{1}H NMR (300 MHz, DMSO-d_6, 90 ºC) spectrum of ester **III**.



^{13}C NMR (75 MHz, DMSO-d_6, 90 ºC) spectrum of ester **III**.



HRMS (ESI) of ester **III**.