Asymmetric Allylboration of Cyclic Imines and Applications to Alkaloid Synthesis

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Supporting Information

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General Experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Dichloromethane was freshly distilled from calcium hydride. Tetrahydrofuran, diethyl ether, and toluene were freshly distilled from sodium/benzophenone. Chiral 3,3′-disubstituted binaphthols were synthesized using procedures from a previous report.[1] Cyclic imines were prepared according to literature procedures.[2] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz, respectively. Mass spectra were recorded on a Kratos MA890 mass spectrometer using electron impact (EI, 70 ev) ionization unless otherwise specified. Optical rotations were recorded in cells with 10 cm path length on a Perkin-Elmer 241 digital polarimeter.

General procedure for the allylboration of cyclic imines:

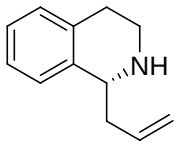
To a solution of the appropriate 3,3′-disubstitutedbinaphthol (0.35 mmol) in THF (5 mL) was added triallylborane[1] (46 mg, 0.34 mmol) dropwise. The reaction was stirred at room temperature for 2 hours then brought to reflux for 1 hour (2 hours for **2e-h**). The allylboronate solution was cooled to room temperature and concentrated under reduced pressure. The resulting white solid was dissolved in toluene (5 mL) and THF (1 mL) and the solution was cooled to -78 ^{o}C. A solution of the imine (0.21 mmol, 0.1 - 0.5 M) in THF was added dropwise over 2 minutes. The reaction was stirred at -78 ^{o}C for 24 hours and warmed to room temperature for an additional 24 hours. MeOH (5 mL) and aqueous NH_4Cl were used to quench the reaction. The organic phase was washed with brine and dried over Na_2SO_4. Purification using flash column chromatography on silica gel

(EtOAc/MeOH/NH_4OH) gave the desired homoallylic amine and the chiral ligand in their pure forms.

Alternatively, the reaction mixture could be extracted with 2 M HCl (5 x 5 mL). The chiral ligand was recovered from the organic phase. The aqueous phase was then basified using 1 M NaOH and extracted with diethyl ether (5 x 5 mL). The combined ethereal extracts were dried over Na_2SO_4 and evaporation of the solvent gave the homoallylic amine.

The enantiomeric purities of the products were determined by HPLC analysis (4.6 x 250 mm ChiralCel OD, hexane/*i*-PrOH = 99.5/0.5 ~ 98/2) of their trifluoroacetamides unless otherwise specified.

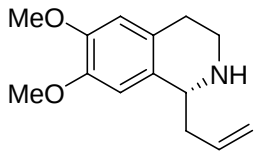
(*R*)-1-Allyl-1,2,3,4-tetrahydroisoquinoline (3a).



$[\alpha]^{25}_{589}$ +91 (95% *ee*, c 0.51, THF) [lit.[3] (*S* enantiomer): $[\alpha]^{25}_{589}$ -98.1 (94.8% *ee*, c 0.93, THF)]; IR (neat): 3304, 3073, 3018, 1639,1583, 913, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.92 (s, br, 1H), 2.43-3.02 (m, 5H), 3.22 (dt, J = 11.1 Hz, 5.4 Hz, 1H), 4.03 (dd, J = 3.3 Hz, 9.0 Hz, 1H), 5.09-5.22 (m, 2H), 5.83 (m, 1H), 7.04-7.17 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 135.5, 135.3, 129.2, 125.9, 125.9, 125.7, 117.8, 55.0, 41.0, 40.5, 29.9; Enantiomeric excess was determined by HPLC analysis of its trifluoroacetamide: (hexane/*i*-PrOH = 99/1, flow rate = 1 mL/min), t_R = 13.1 min (*R*), t_R = 19.5 min (*S*); $[\alpha]^{25}_{589}$ -116.5 (95% *ee*, c 1.68, $CHCl_3$)[lit.[3] (*S* enantiomer): $[\alpha]^{27}_{589}$

+121.24 (94.8% *ee*, c 1.43, $CHCl_3$)]; IR (neat): 3079, 2913, 1689, 1642, 1462, 1270, 1197, 1179, 1141, 921, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 5.7 : 1 mixture of rotamers): δ 2.50-3.18 (m, 4H), 3.36 (dt, J = 4.8 Hz, 11.4 Hz, 0.15H), 3.60 (dt, J = 3.9 Hz, 12.8 Hz, 0.85H), 3.95-4.60 (m, 1H), 4.99-5.22 (m, 2.30H), 5.48-6.02 (m, 1.70H), 7.03-7.42 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, 5.7 : 1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 156.2 (q, J = 35.3 Hz), *135.3*, 135.2, 133.6, *133.0*, *132.8*, 132.5, *129.2*, 128.8, *127.5*, 127.1, 126.6, *126.3*, *118.4*, 118.2, 116.7 (q, J = 288.5 Hz), *56.4*, 53.3, *41.6*, 40.9, 39.6, *37.3*, 29.0, *27.3*; MS *m/z* (relative intensity): 228 (M^+-allyl, 100).

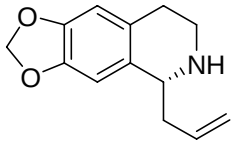
(*R*)-1-Allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3b).



$[\alpha]^{25}_{589}$ +87.6 (98% *ee*, c 0.69, THF); IR (neat): 3333, 3072, 1639, 1610, 1515, 1261, 1224, 1118, 915, 857, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, br, 1H), 2.30-3.15 (m, 6H), 3.72 (s, 6H), 3.85 (dd, J = 2.1 Hz, 8.4 Hz, 1H), 4.98-5.16 (m, 2H), 5.72 (m, 1H), 6.45 (s, 1H), 6.54 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.1, 146.9, 135.4, 130.3, 127.2, 117.6, 111.5, 108.8, 55.7, 55.5, 54.5, 40.8, 40.5, 29.2; MS *m/z* (relative intensity): 233 (M^+, 0.5), 232, (M^+-H, 2.5), 192 (M^+-allyl, 100); Enantiomeric excess was determined by HPLC analysis of its trifluoroacetamide: (hexane/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 17.6 min (*S*), t_R = 23.6 min (*R*); $[\alpha]^{25}_{589}$ -113.8 (98% *ee*, c 0.65, $CHCl_3$) [lit.[3] (*S* enantiomer): $[\alpha]^{25}_{589}$ +106.8 (95% *ee*, c 1.29, $CHCl_3$)]; IR (neat): 3075, 2937, 2837, 1688, 1642, 1520, 1464, 1256, 1232, 1178, 1195, 1178, 1140, 1118, 915, 857, 778,

754, 668, 654 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 6.1:1 mixture of rotamers): δ 2.48-2.78 (m, 3H), 2.86-3.02 (m, 1H), 3.29 (dt, J = 4.9 Hz, 12.6 Hz, 0.14H), 3.56 (ddd, J = 4.2 Hz, 12.2 Hz, 14.1 Hz, 0.86H), 3.82 (s, 3H), 3.83 (s, 3H), 3.95-4.05 (m, 0.86H), 4.53 (m, 0.14H), 4.88 (t, J = 7.1 Hz, 0.14H), 4.98-5.13 (m, 2H), 5.51 (dd, J = 5.2 Hz, 9.2 Hz, 0.86H), 5.69-5.88 (m, 1H), 6.54 (s, 0.14H), 6.56 (s, 0.86H), 6.59 (s, 0.14H), 6.60 (s, 0.86H); ^{13}C NMR (75 MHz, $CDCl_3$, 6.1:1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 155.9 (q, J = 35.6 Hz), *148.4*, 148.1, 147.8, *147.5*, 133.7, *133.2*, *127.2*, 127.1, *124.9*, 124.5, *118.8*, 118.2, 116.5 (q, J = 287.9 Hz), *111.5*, 111.1, 109.7, *109.5*, 56.0, 55.9, 53.0, *41.7*, 40.9, 39.6, *37.2*, 28.7, *27.0*; MS *m/z* (relative intensity): 228 (M^+-allyl, 100).

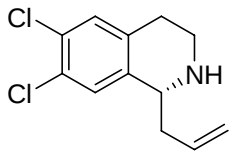
(*R*)-5-Allyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (3c).



$[\alpha]^{25}_{589}$ +97.8 (98% *ee*, c 0.91, THF); IR (neat): 3305, 3073, 2910, 1638, 1503, 1484, 1248, 1229, 1040, 936, 861, 805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.74 (s, br, 1H), 2.31-3.22 (m, 6H), 3.89 (dd, J = 2.7 Hz, 8.4 Hz, 1H), 5.07-5.15 (m, 2H), 5.79 (m, 1H), 5.84 (s, 2H), 6.50 (s, 1H), 6.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.6, 145.5, 135.4, 131.6. 128.4, 117.8, 108.7, 105.9, 100.5, 55.0, 40.9, 40.6, 30.0; MS *m/z* (relative intensity): 217 (M^+, 0.3), 216, (M^+-H, 1.6), 176 (M^+-allyl, 100); HRMS *m/z* Calcd. for $C_{13}H_{14}NO_2$ (M^+-H): 216.1025. Found: 216.1027; Enantiomeric excess was determined by HPLC analysis of its trifluoroacetamide: (hexane/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 19.8 min (*S*), t_R = 22.1 min (*R*); $[\alpha]^{25}_{589}$ -94.1 (98% *ee*, c 1.31, $CHCl_3$); IR (neat):

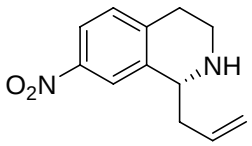
2910, 1690, 1642, 1506, 1487, 1240, 1199, 1140, 1040, 923, 864, 753, 668, 650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 6.3:1 mixture of rotamers): δ 2.48-3.04 (m, 4H), 3.32 (dt, J = 4.6 Hz, 11.6 Hz, 0.14H), 3.55 (dt, J = 3.5 Hz, 11.3 Hz, 0.86H), 3.91-4.52 (m, 1H), 4.82-5.54 (m, 3H), 5.70-5.86 (m, 1H), 5.89 (s, 2H), 6.53-6.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 6.3:1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 156.0 (q, J = 30.0 Hz), *149.0*, 146.8, 146.6, *144.4*, 133.6, *133.1*, *128.4*, 128.3, *126.4*, 125.9, *119.0*, 118.4, 116.6 (q, J = 285 Hz), *108.9*, 108.4, 106.9, *106.7*, 101.1, *56.0*, 53.4, *41.7*, 41.0, 39.7, *37.3*, 29.2, *27.4*; MS *m/z* (relative intensity): 313 (M^+, 1.5), 272 (M^+-allyl, 100); HRMS *m/z* Calcd. for $C_{15}H_{14}F_3NO_3$ (M^+-H): 313.0926. Found: 313.0934.

(*R*)-1-Allyl-6,7-dichloro-1,2,3,4-tetrahydroisoquinoline (3d).



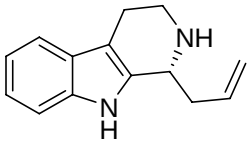
$[\alpha]^{25}_{589}$ +117.6 (95% *ee*, c 0.91, THF); IR (neat): 3339, 3076, 2926, 1640, 1472, 1136, 917, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.75 (s, br, 1H), 2.31-3.33 (m, 6H), 3.90 (dd, J = 3.0 Hz, 8.7 Hz, 1H), 5.08-5.15 (m, 1H), 5.74 (m, 1H), 7.11 (s, 1H), 7.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 135.8, 134.8, 130.9, 129.7, 129.5, 127.9, 118.6, 54.6, 40.7, 40.4, 29.3; MS *m/z* (relative intensity): 241 (M^+, 0.3), 240, (M^+-H, 1.1), 200 (M^+-allyl, 100); HRMS *m/z* Calcd. for $C_{12}H_{12}NCl_2$ (M^+-H): 240.0347. Found: 240.0345; Enantiomeric excess was determined by ^{19}F NMR of its MTPA-amide [δ -69.55 (*R*), -70.75 (S)].

(*R*)-1-Allyl-7-nitro-1,2,3,4-tetrahydroisoquinoline (3e).



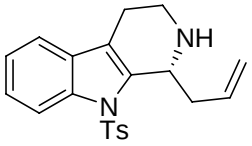
$[\alpha]^{25}_{589}$ +144 (99% *ee*, c 3.4, $CHCl_3$); IR (neat): 3344, 3074, 2927, 1640, 1587, 1518, 1345, 1279, 1134, 903, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.03 (s, br, 1H), 2.44-3.32 (m, 6H), 4.08 (dd, J = 3.1 Hz, 8.6 Hz, 1H), 5.14-5.24 (m, 2H), 5.81 (m, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.97 (dd, J = 2.1 Hz, 8.0 Hz, 1H); 8.05 (d, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.2, 143.4, 140.0, 134.4, 130.2, 121.3, 121.0, 118.9, 55.0, 40.4, 40.2, 30.1; MS *m/z* (relative intensity): 218 (M^+, 0.1), 217, (M^+-H, 0.6), 177 (M^+-allyl, 100), 131 (M^+-NO_2-allyl, 37); HRMS *m/z* Calcd. for $C_9H_9N_2O_2$ (M^+-allyl): 177.0664. Found: 177.0662; Enantiomeric excess was determined by HPLC analysis of its trifluoroacetamide: (hexane/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 28.0 min (*S*), t_R = 29.8 min (*R*). $[\alpha]^{25}_{589}$ -137 (99% *ee*, c 1.67, $CHCl_3$); IR (neat): 2959, 1692, 1640, 1525, 1467, 1346, 1282, 1260, 1195, 1158, 1141, 1045, 1000, 944, 928, 895, 834, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 5.6:1 mixture of rotamers): δ 2.52-2.79 (m, 2H), 2.89-3.16 (m, 2H), 3.35 (ddd, J = 5.4 Hz, 11.1 Hz, 13.5 Hz, 0.18H), 3.60 (ddd, J = 4.8 Hz, 11.1 Hz, 14.4 Hz, 0.82H), 4.02-4.65 (m, 1H), 4.99-5.85 (m, 4H), 7.25-7.36 (m, 1H), 7.95-8.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 5.6:1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 156.0 (q, J = 36.0 Hz), 146.6, *146.3*, *140.7*, 140.3, 136.8, *136.7*, 132.6, *132.0*, *130.5*, 130.0, *122.4*, 122.3, 122.0, *121.9*, *119.9*, 119.1, 116.3 (q, J = 288 Hz), *56.0*, 53.0, *41.3*, 40.6, 38.9, *36.3*, 29.3, *27.5*; MS *m/z* (relative intensity): 314 (M^+, 0.1), 273 (M^+-allyl, 100); HRMS *m/z* Calcd. for $C_{11}H_8F_3N_2O_3$ (M^+-allyl): 273.0487. Found: 273.0496.

(*R*)-1-Allyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (3f).



^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, br, 1H), 2.44-3.43 (m, 6H), 4.14 (t, J = 6.3 Hz, 1H), 5.16-5.30 (m, 2H), 5.87 (m, 1H), 7.08-7.22 (m, 2H), 7.27 (d, J = 7.2 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 8.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 135.6, 134.9, 127.3, 121.5, 119.2, 118.5, 118.1, 116.9, 110.8, 109.1, 51.9, 42.6, 39.3, 22.6; **3f** was derivatized by sequential treatment with $(CF_3CO)_2O$/pyridine and TsCl/NaH. Enantiomeric excess was then determined by chiral HPLC analysis of that derivative: (hexane/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 8.7 min (*S*), t_R = 19.7 min (*R*).); $[\alpha]^{25}_{589}$ -173.2 (94% *ee*, c 0.50, $CHCl_3$); IR (neat): 3074, 2959, 2925, 1692, 1643, 1598, 1452, 1377, 1208, 1174, 1143, 1089, 1041, 1022, 800, 756, 666, 584, 572, 543 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 5:1 mixture of rotamers): δ 2.27 (s, 2.5H), 2.28 (s, 0.5H), 2.42-2.91 (m, 3H), 3.11-3.66 (m, 2H), 4.08-4.80 (m, 1H), 5.04-5.16 (m, 2H), 5.68-5.98 (m, 1.17H), 6.39 (dd, *J* = 2.8 Hz, 10.6 Hz, 0.83H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.19-7.36 (m, 3H), 7.55 (d, *J* = 8.3 Hz, 0.34H), 7.67 (d, *J* = 8.3 Hz, 1.66H), 8.09 (d, *J* = 8.1 Hz, 0.17H), 8.17 (d, J = 8.3 Hz, 0.83H); ^{13}C NMR (75 MHz, $CDCl_3$, 5:1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 156.6 (q, *J* = 36.0 Hz), *145.3*, 145.2, *136.9*, 136.7, *134.7*, 134.3, 134.0, 133.5, *133.0*, 130.0, 129.9, *129.5*, *129.4*, 126.8, *126.5*, *125.5*, 125.3, 124.3, *119.0*, *118.8*,118.6, 118.2, 117.2, 115.6, *115.4*, 116.5 (q, *J* = 269 Hz), *54.2*, 51.0, *39.9*, 39.2, 38.2, *36.0*, *22.7*, 22.2, 21.6, *20.4*; MS *m/z* (relative intensity): 462 (M^+, 1.2), 421 (M^+-allyl, 100); HRMS *m/z* Calcd. for $C_{20}H_{16}F_3N_2O_3S$ (M^+-allyl): 421.0834. Found: 421.0831.

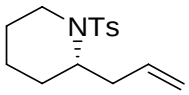
(*R*)-1-Allyl-9-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (3g).



$[\alpha]^{25}_{589}$ -202.4 (94% *ee*, c 1.8, $CHCl_3$); IR (neat): 3337, 3070, 2925, 1639, 1597, 1450, 1366, 1172, 754, 667, 584, 573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.06 (s, br, 1H), 2.26 (s, 3H), 2.41-3.15 (m, 6H), 4.53 (d, *J* = 9.3 Hz, 1H), 5.14-5.20 (m, 2H), 5.94 (m, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.19-7.34 (m, 3H), 7.51 (d, *J* = 8.1 Hz, 2H), 8.11 (d, *J* = 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 137.8, 136.8, 136.0, 134.9, 130.7, 129.6, 126.4, 124.5, 123.8, 119.3, 118.3, 117.7, 115.5, 52.6, 39.0, 37.2, 22.5, 21.5; MS(CI) *m/e* (relative intensity): 367 ($[M+1]^+$, 100), 325(M^+-allyl, 14), 192 (M^+-allyl, 100); HRMS *m/z* Calcd for $C_{18}H_{17}N_2O_2S$ (M^+-allyl): 325.1011. Found: 325.1012; Enantiomeric excess was determined by HPLC analysis of its trifluoroacetamide: (hexane/*i*-PrOH = 98/2, flow rate = 1 mL/min), t_R = 8.7 min (*S*), t_R = 19.7 min (*R*); $[\alpha]^{25}_{589}$ -173.2 (94% *ee*, c 0.50, $CHCl_3$); IR (neat): 3074, 2959, 2925, 1692, 1643, 1598, 1452, 1377, 1208, 1174, 1143, 1089, 1041, 1022, 800, 756, 666, 584, 572, 543 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 5:1 mixture of rotamers): δ 2.27 (s, 2.5H), 2.28 (s, 0.5H), 2.42-2.91 (m, 3H), 3.11-3.66 (m, 2H), 4.08-4.80 (m, 1H), 5.04-5.16 (m, 2H), 5.68-5.98 (m, 1.17H), 6.39 (dd, *J* = 2.8 Hz, 10.6 Hz, 0.83H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.19-7.36 (m, 3H), 7.55 (d, *J* = 8.3 Hz, 0.34H), 7.67 (d, *J* = 8.3 Hz, 1.66H), 8.09 (d, *J* = 8.1 Hz, 0.17H), 8.17 (d, J = 8.3 Hz, 0.83H); ^{13}C NMR (75 MHz, $CDCl_3$, 5:1 mixture of rotamers, signals for the minor isomer are in *italic* style): δ 156.6 (q, *J* = 36.0 Hz), *145.3*, 145.2, *136.9*, 136.7, *134.7*, 134.3, 134.0, 133.5, *133.0*, 130.0, 129.9, *129.5*, *129.4*, 126.8, *126.5*, *125.5*,

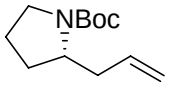
125.3, 124.3, *119.0*, *118.8*,118.6, 118.2, 117.2, 115.6, *115.4*, 116.5 (q, J = 269 Hz), *54.2*, 51.0, *39.9*, 39.2, 38.2, *36.0*, *22.7*, 22.2, 21.6, *20.4*; MS *m/z* (relative intensity): 462 (M^+, 1.2), 421 (M^+-allyl, 100); HRMS *m/z* Calcd. for $C_{20}H_{16}F_3N_2O_3S$ (M^+-allyl): 421.0834. Found: 421.0831.

(*S*)-2-allyl-1-tosylpiperidine (3h).



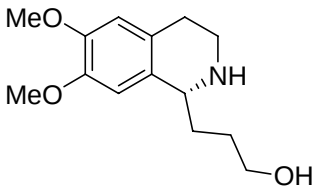
Allylation of imine **1h** (0.24 mmol) was accomplished according to the general procedure. To the crude reaction mixture was added TsCl (381 mg, 2 mmol) and DMAP (244 mg, 2 mmol). The reaction was stirred at room temperature overnight. Solvent was removed under reduced pressure. The residue was purified by column chromatography (1:1 hexane/EtOAc) to give 43 mg of **3i** (65%). $[\alpha]^{25}_{589}$ -42.2 (91% *ee*, c 2.22, CH_2Cl_2) [lit.[3] (*R* enantiomer): $[\alpha]^{27}_{589}$ +35.1 (89.4% *ee*, c 0.40, CH_2Cl_2)]; IR (neat): 3066, 2941, 2865, 1628, 1600, 1452, 1380, 1326, 1150, 926, 814, 658, 550 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.16-1.60 (m, 6H), 2.26 (t, J = 7.7 Hz, 2H), 2.38 (s, 3H), 2.94 (dt, J = 2.6 Hz, 13.7 Hz, 1H), 3.73 (dd, J = 3.7 Hz, 13.7 Hz, 1H), 4.07 (m, 1H), 4.97-5.02 (m, 2H), 5.65 (m, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.7, 138.7, 134.9, 129.5, 126.9, 117.0, 52.4, 40.6, 33.9, 26.5, 24.5, 21.4, 18.1; MS (CI) *m/z* (relative intensity): 280 ($[M+1]^+$, 100), 238, (M^+-allyl, 37); Enantiomeric excess was determined by HPLC analysis: (hexane/*i*-PrOH = 99.5/0.5, flow rate = 1 mL/min), t_R = 47.5 min (*R*), t_R = 51.2 min (*S*).

(*S*)-*tert*-butyl 2-allylpyrrolidine-1-carboxylate (3i)



Allylation of imine **1i** (0.20 mmol) was accomplished according to the general procedure. To the crude reaction mixture was added $(Boc)_2O$ (436 mg, 2 mmol) and NEt_3 (0.2 mL). The reaction was stirred at room temperature overnight. Solvent was removed under reduced pressure. The residue was purified by column chromatography (3:1 hexane/EtOAc) to give 30 mg of **3i** (71%). $[\alpha]^{25}_{589}$ -45.4 (92% *ee*, c 1.26, $CHCl_3$) [lit.[4] $[\alpha]^{25}_{589}$ -32.4 (c 1.56, $CHCl_3$)]; IR (neat): 3077, 2976, 1694, 1641, 1394, 1366, 1173, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.54-1.84 (m, 4H), 2.00-2.55 (m, 2H), 3.21-3.42 (m, 2H), 3.66-3.85 (m, 1H), 4.98-5.05 (m, 2H), 5.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1, 28.5, 30.0, 38.1, 45.6, 53.7, 78.8, 116.9, 135.2, 145.0; MS *m/z* (relative intensity): 211 (M^+, 0.1), 170 (M^+-allyl, 42), 114 (100); Enantiomeric excess was determined by HPLC analysis: (hexane/*i*-PrOH = 99.5/0.5, flow rate = 0.3 mL/min), t_R = 30.0 min (*R*), t_R = 32.3 min (*S*).

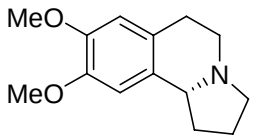
(*R*)-3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-1-ol



To a solution of amine **3b** (110 mg, 0.47 mmol) in THF (2 mL) was added 9-BBN (3 mL, 0.5 M in THF) dropwise. The reaction was stirred at room temperature for 3 hours. A mixture of aqueous NaOH (3 M, 5 mL) and 30% H_2O_2 (5 mL) were added at room temperature. The exothermic reaction caused the temperature to quickly rise to 55 ^oC and

this temperature was maintained for 25 minutes with external heat. The reaction mixture was then cooled to room temperature and extracted with Et_2O (3 x 5 mL). The combined ethereal extracts were washed with brine (10 mL) and dried over Na_2SO_4. Purification by flash column chromatography (10:1 CH_2Cl_2/MeOH, 0.5% NH_4OH) gave the intermediate alcohol (96 mg, 81 %). IR (neat): 3303, 2934, 1611, 1515, 1257, 1223, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.62-2.00 (m, 4H), 2.56-2.81 (m, 2H), 2.95-3.22 (m, 2H), 3.46-3.66 (m, 2H), 3.81 (s, 6H), 3.91 (dd, J = 4.5 Hz, 7.2 Hz, 1H), 4.72 (s, br, 2H), 6.52 (s, 1H), 6.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.5, 147.4, 130.2, 126.6, 111.6, 109.3, 62.8, 56.0, 55.8, 55.4, 39.7, 35.5, 30.5, 28.6; MS *m/z* (relative intensity): 251 (M^+, 0.5), 250 (M^+-H, 2.4), 232 (M^+-H-H_2O, 6.5), 192 (M^+-$CH_2CH_2CH_2OH$, 100). HRMS *m/z* Calcd. for $C_{14}H_{20}NO_3$ (M^+-H): 250.1443. Found: 250.1444.

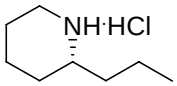
(+)-Crispine A (4).



The alcohol was stirred with PPh_3 (262 mg, 1.0 mmol), CBr_4 (331 mg, 1.0 mmol) and *i*-Pr_2NEt (0.3 mL) in THF (10 mL) at room temperature for 2 hours, followed by removal of the solvent under reduced pressure. Flash column chromatography (3:1 EtOAc/MeOH, 1% NH_4OH) yielded the title compound (73 mg, 66% yield for 2 steps). $[\alpha]^{25}_{589}$ +96.9 (c 1.1, $CHCl_3$) [lit.[5] $[\alpha]^{23}_{589}$ +100.4 (>99% *ee*, c 1, $CHCl_3$)]; IR(neat): 3303, 2934, 1611, 1515, 1257, 1223, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.62-2.00 (m, 3H), 2.23-2.37 (m, 1H), 2.48-2.77 (m, 3H), 2.92-3.21 (m, 3H), 3.41 (t, J = 8.4 Hz, 1H), 3.82 (s, 6H), 6.54 (s, 1H), 6.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 147.1, 130.9, 126.2,

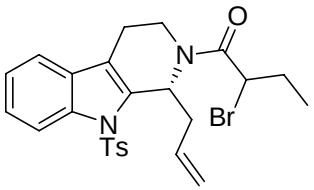
111.2, 108.8, 62.9, 55.9, 55.8, 53.0, 48.2, 30.4, 27.9, 22.2; MS *m/z* (relative intensity): 233 (M^+, 43), 232 (M^+-H, 100), 205 (M^+-C_2H_4, 43), 190 (M^+-$CH_2CH_2CH_2OH$, 33).

_R_-(-)-Coniine·HCl (5).



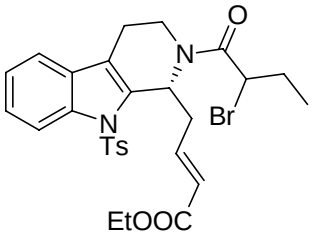
Allylation of imine **1h** (0.32 mmol) was accomplished according to the general procedure. To the crude reaction mixture was added 10% Pd/C (5 mol%) and MeOH (3 mL). The suspension was stirred at room temperature under H_2 atmosphere for 12 hours before the addition of HCl/Et_2O (4 mL, 0.5 M). (*R*)-(-)-Coniine·HCl (**5**) was obtained after column chromatography on silica gel (10:1 ~ 6:1 CH_2Cl_2/MeOH). $[\alpha]^{25}_{589}$ -6.8 (c 0.34, EtOH) [lit.[6] $[\alpha]^{22}_{589}$ -7.1 (c 1.0, EtOH)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, J = 7.3 Hz, 3H), 1.20-1.95 (m, 10H), 2.65-2.94 (m, 2H), 3.23-3.42 (m, 1H), 9.10 (s, br, 1H), 9.34 (s, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 57.0, 44.6, 35.2, 28.0, 22.3, 22.0, 18.4, 13.6; Enantiomeric excess was determined by HPLC analysis of its *p*-toluenesulfonamide: (hexane/*i*-PrOH = 99/1, flow rate = 1 mL/min), t_R = 25.0 min (*S*), t_R = 27.1 min (*R*); $[\alpha]^{25}_{589}$ -34.5 (c 1.0, benzene) [lit.[7] (for *S* enantiomer): $[\alpha]^{24}_{589}$ +39.6 (c 0.53, benzene)]; IR (neat): 3063, 3021, 2937, 2871, 1598, 1337, 1151, 1093, 932, 815, 712, 694, 653, 599, 552 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, J = 7.3 Hz, 3H), 1.10-1.65 (m, 10H), 2.39 (s, 3H), 2.96 (t, J = 13.5 Hz, 1H), 3.71 (dd, J = 3.7 Hz, 13.5 Hz, 1H), 3.95-4.06 (m, 1H), 7.25 (d, J = 7.8 Hz, 2H), 7.69 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 139.3, 129.5, 126.9, 52.7, 40.5, 31.6, 27.3, 24.4, 21.4, 19.6, 18.4, 13.9; MS (CI) *m/z* (relative intensity): 282 (M^+, 100), 238 (M^+-$CH_2CH_2CH_3$, 31).

1-((*R*)-1-Allyl-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-b]indol-2(9*H*)-yl)-2-bromobutan-1-one (6).



A solution of amine **3g** (220 mg, 0.60 mmol) in CH_2Cl_2 (20 mL) was treated with DCC (1.18 g, 5.72 mmol), 2-bromobutyric acid (957 mg, 5.73 mmol) and DMAP (20 mg) at -10 ^oC. The reaction was allowed to warm to room temperature for 2 hours. Solid material was filtered off and the filtrate was washed with 10% $NaHCO_3$ (aq.). Removal of the volatiles gave the crude amide **6** in quantitative yield. This crude material was used without further purification.

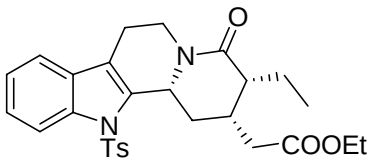
(*E*)-Ethyl 4-((*R*)-2-(2-bromobutanoyl)-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-yl)but-2-enoate (7).



The resulting compound **6** was dissolved in dioxane/H_2O (3:1, 15 mL). 2,6-Lutidine (0.15 mL), OsO_4 (0.6 mL, 0.022 M in water) and $NaIO_4$ (510 mg, 4.68 mmol) were added and the mixture was stirred at room temperature for 4 hours. The reaction mixture was then diluted with EtOAc (10 mL) and water (10 mL). The organic phase was separated and the aqueous phase was washed with EtOAc (3 x 10 mL). The combined organic phases

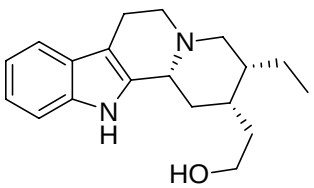
were washed with saturated Na_2SO_3 and brine then dried over Na_2SO_4. Following removal of the solvent, the crude aldehyde was taken up in CH_2Cl_2 (10 mL) and treated with Ph_3P=CHCOOEt (0.28 g, 0.8 mmol) at room temperature for 2 hours. Solvent was then removed under reduced pressure. Flash column chromatography (2:1 EtOAc/hexane) afforded the title compound (288 mg, 82% yield for three steps). ^{1}H NMR (300 MHz, DMSO, mixture of diastereomers and rotamers) δ 0.75-0.89 (m, 3H), 1.15 (t, J = 7.1 Hz, 3H), 1.79-2.26 (m, 5H), 2.57-3.23 (m, 4H), 3.43-3.61 (m, 1H), 3.94-4.68 (m, 2H), 4.76-5.64 (m, 1H), 5.81-7.08 (m, 3H), 7.15-7.48 (m, 5H), 7.55-7.69 (m, 1.74H), 7.74-7.81 (m, 0.26H), 7.94 (d, J = 8.4 Hz, 0.13H), 8.01 (d, J = 8.2 Hz, 0.87H); ^{13}C NMR (75 MHz, $CHCl_3$, signals for the major isomer) 167.8, 165.9, 144.9, 144.0, 136.7, 134.8, 133.9, 129.7, 129.6, 129.3, 126.7, 125.0, 124.1, 118.5, 118.0, 115.4, 67.0, 60.1, 48.8, 44.7, 37.4, 28.8, 21.5, 20.4, 14.2, 12.1; MS (ESI) *m/z* (relative intensity): 558 (M^++H, 100), 238 (M^+-$CH_2CH_2CH_3$, 31); HRMS *m/z* Calcd. for $C_{28}H_{32}BrN_2O_5S$ (M^++H): 587.1215. Found: 587.1207.

Ethyl 2-((2*S*,3*R*,12b*R*)-3-ethyl-4-oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acetate (8).



To a solution of compound **7** (220 mg, 0.375 mmol) in THF (35 mL) at -78 ^{o}C was added *n*-BuLi (0.414 mmol, 0.28 mL, 1.48 M in hexane) dropwise. The resulting clear solution was stirred at that temperature for an additional 2 minutes. The reaction was quenched with a minimum amount of saturated NH_4Cl solution. Evaporation of the solvent gave an oily residue that was purified by flash column chromatography (2:1 EtOAc/hexane) to afford the title compound (**8**) as a single diastereomer (119 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, J = 7.4 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 1.45-1.81 (m, 3H), 2.12 (dd, J = 9.4 Hz, 15.5 Hz, 1H), 2.23 (s, 3H), 2.38 (dd, J = 5.7 Hz, 15.5 Hz, 1H), 2.45-2.81 (m, 5H), 3.05 (dt, J = 13.5 Hz, 5.2 Hz, 1H), 4.01-4.12 (m, 2H), 4.96-5.11 (m, 2H), 7.04 (d, J = 8.2 Hz, 2H), 7.15-7.32 (m, 3H), 7.41 (d, J = 8.2 Hz, 2H), 8.06 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 172.0, 144.9, 138.1, 135.7, 133.2, 130.2, 129.2, 126.4, 125.2, 124.5, 123.1, 118.6, 116.3, 60.5, 53.7, 45.3, 38.5, 36.9, 35.6, 31.1, 21.7, 21.4, 20.7, 14.1, 12.8.

***ent*-Corynantheidol (9).**



Ester **8** (110 mg, 0.216 mmol) was dissolved in THF (35 mL). LAH (130 mg, 15 equiv.) was added in 4 portions during the course of 2 hours. The suspension was stirred at ambient temperature over night. The reaction was then cooled to 0 ^{o}C and unreacted LAH quenched carefully with saturated NH_4Cl. Removal of solid by filtration resulted in a clear solution that was concentrated to an oily residue. Purification by flash column chromatography (12:1 CH_2Cl_2/MeOH, 0.5% NH_4OH) gave the desired compound (**9**) as a white solid (57 mg, 88%), which has spectroscopic properties identical to those reported in the literature. $[\alpha]_D^{20}$ +93.2 (c 0.65, pyridine) [lit.[8] for corynantheidol: $[\alpha]_D^{20}$ -93.0 (c 0.52, pyridine)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H), 1.17-1.94 (m, 8H), 2.24 (s, br, 1H), 2.32 (dd, J = 2.2 Hz, 11.5 Hz, 1H), 2.46-2.75 (m, 2H), 2.86-3.15 (m, 4H), 3.71 (dt, J = 2.5 Hz, 6.5 Hz, 2H), 7.04-7.15 (m, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 7.3 Hz, 1H), 8.05 (s, br, 1H). MS (EI) *m/z* (relative intensity): 298 (M^+, 85), 297 (M^+-H, 100); HRMS *m/z* Calcd. for $C_{19}H_{25}NO_2$ (M^+-H): 297.1967. Found: 297.1974.

References

[1] Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2002**, *6*, 2701.

[2] (a) For syntheses of electron rich 3,4-dihydroisoquinolines, see: Rohloff, J. C.; Dyson, N. H.; Gardner, J. O.; Alfredson, T. V.; Sparacino, M. L.; Robinson, J. *J. Org. Chem.* **1993**, *58*, 1935. (b) For syntheses of electron poor 3,4-dihydroisoquinolines, see: Pelletier, J. C.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 616. (c) For the synthesis of 3,4-dihydro-β-carboline, see: Bertrand, M.; Poissonnet, G.; Thérét-Bettiol, M.; Gaspard, C.; Werner, G. H.; Pfeiffer, B.; Renard, P.; Leonce, S.; Dodd, R. H. *Bioorg. Med. Chem.* **2001**, *9*, 2155. (d) For the synthesis of 3,4-dihydro-9-(*p*-toluenesulfonyl)-β-carboline, see: Rey, A. W.;

Szarek, W. A.; Maclean, D. B. *Can. J. Chem.* **1992**, *70*, 2922. (e) For the synthesis of 1-pyrroline, see: Ochiai, M.; Inenaga, M.; Nagao, Y.; Moriarty, R. M.; Vaid, R. K.; Duncan, M. P. *Tetrahedron Lett.* **1988**, *29*, 6917. (f) For the synthesis of Δ^1-piperideine, see: Scully, F. E. *J. Org. Chem.* **1980**, *45*, 1515.

[3] Nakamura, M.; Hirai, A.; Makamura E. *J. Am. Chem. Soc*. **1996**, *118*, 8489.

[4] Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621.

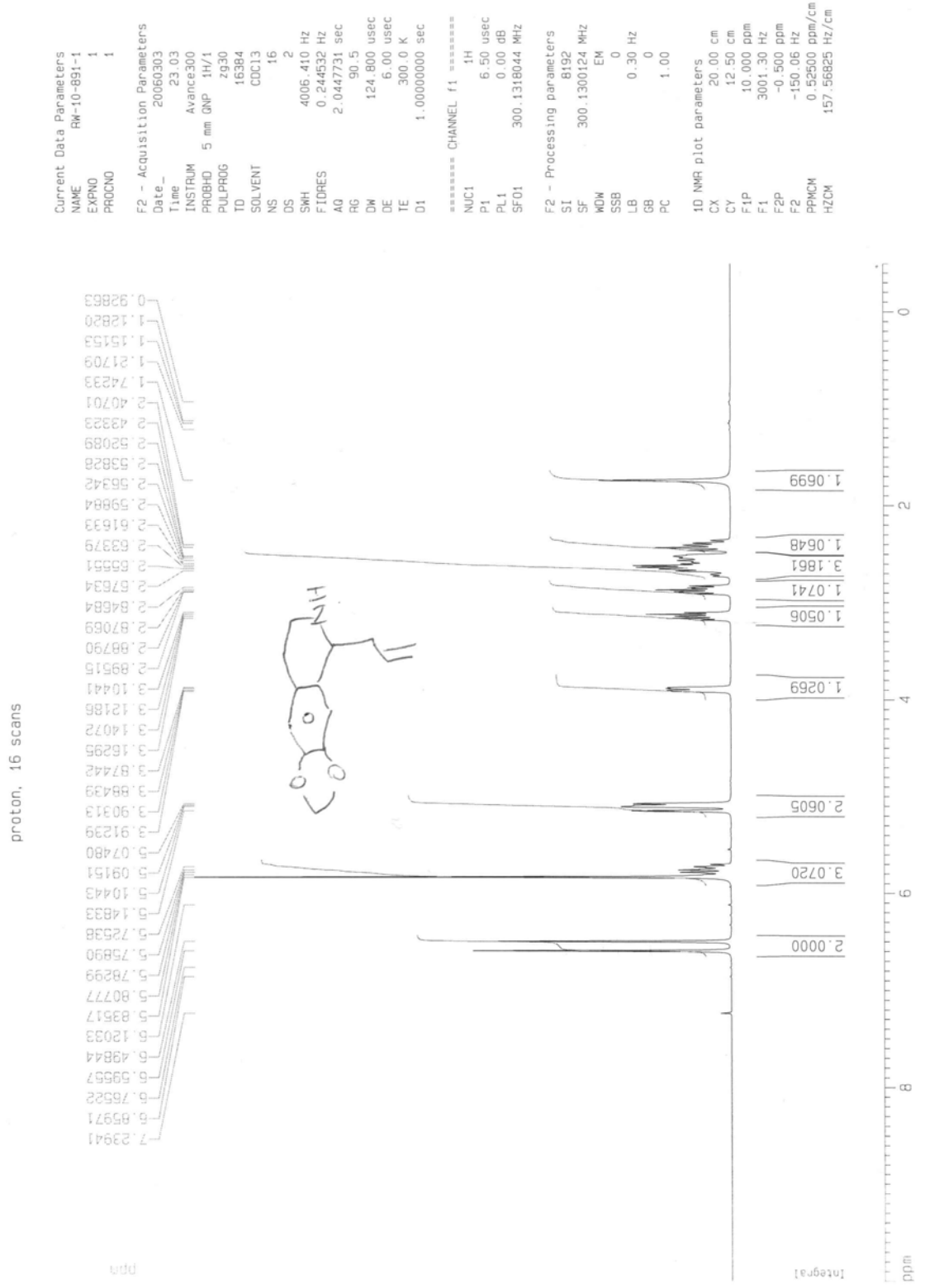
[5] Szawkalo, J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Drabowicz, J.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 3619.

[6] Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919.

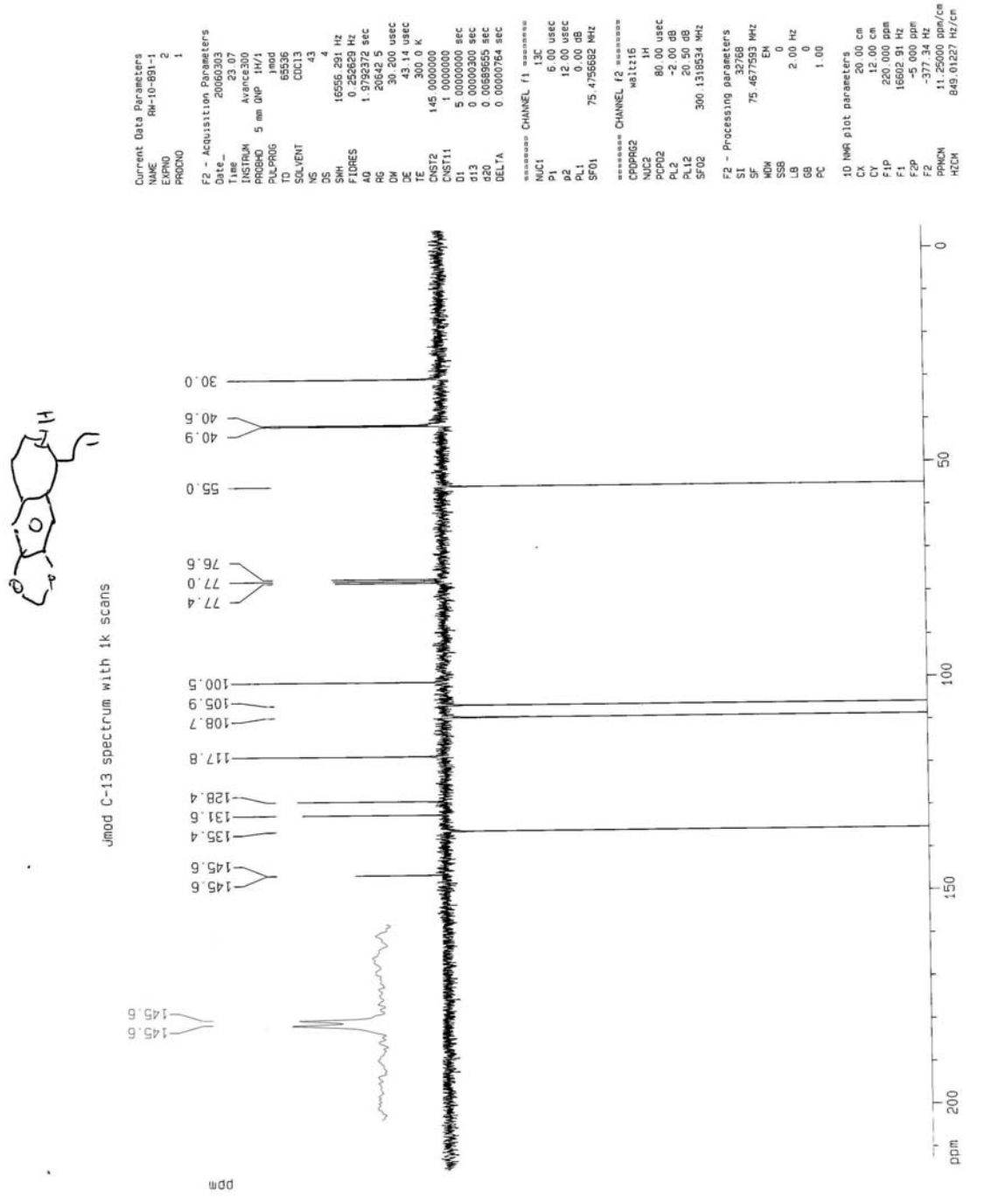
[7] Gallagher, T.; Eskici, M. *Synlett* **2000**, 1368.

[8] Beard, R. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2091.

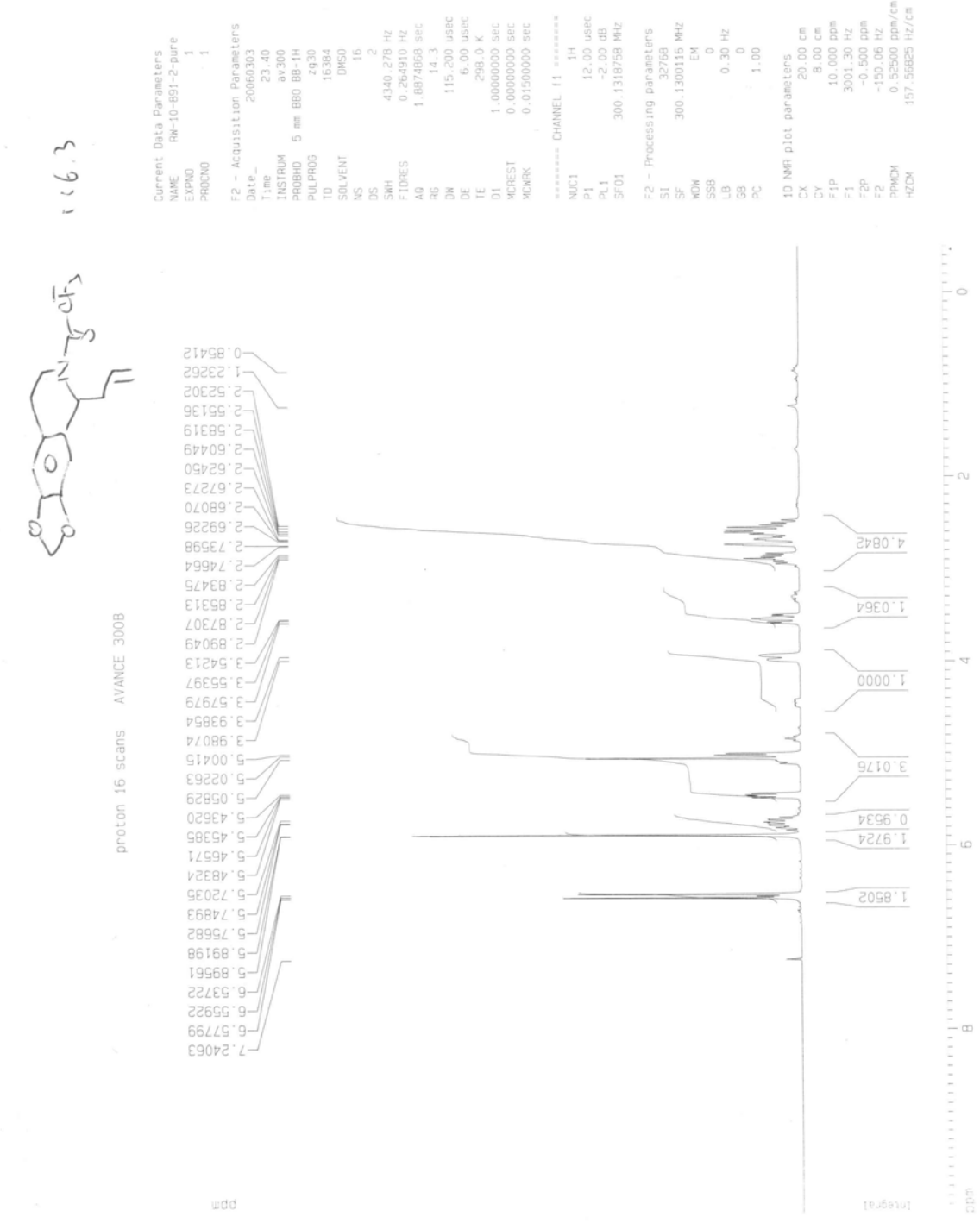
^{1}H NMR spectrum of compound 3c.



^{13}C NMR spectrum of compound 3c.



^{1}H NMR spectrum of the trifluoroacetamide of compound 3c.



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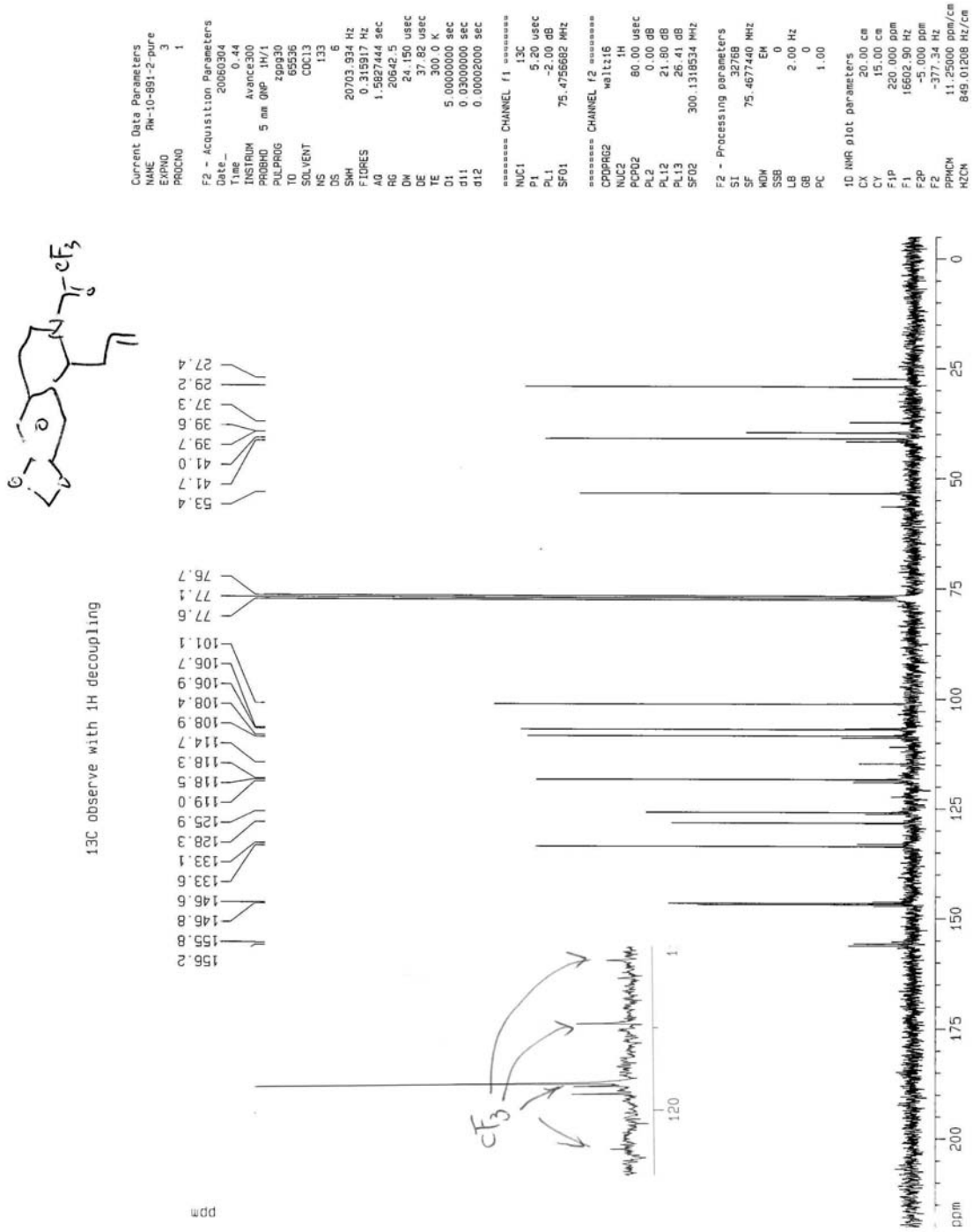
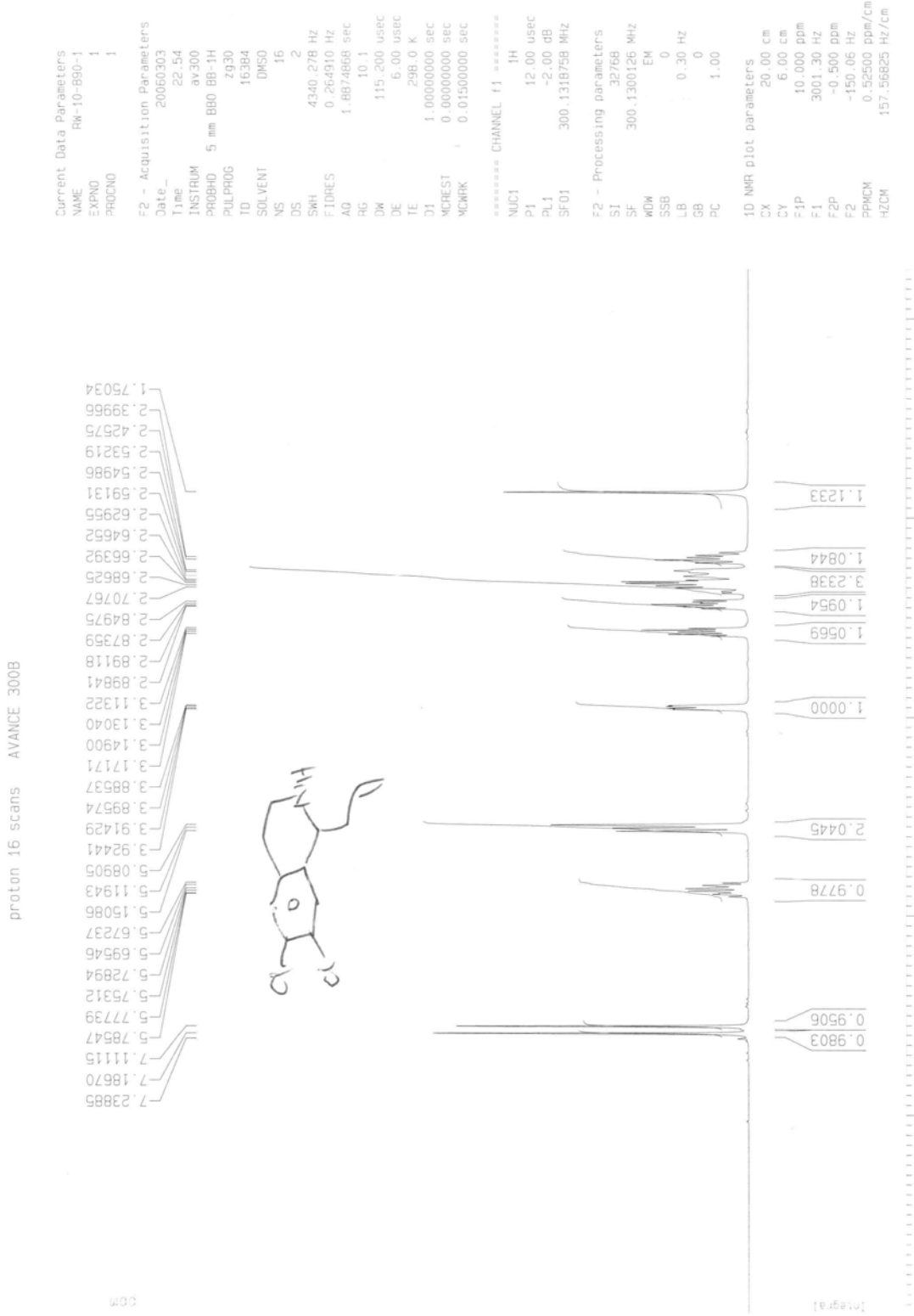
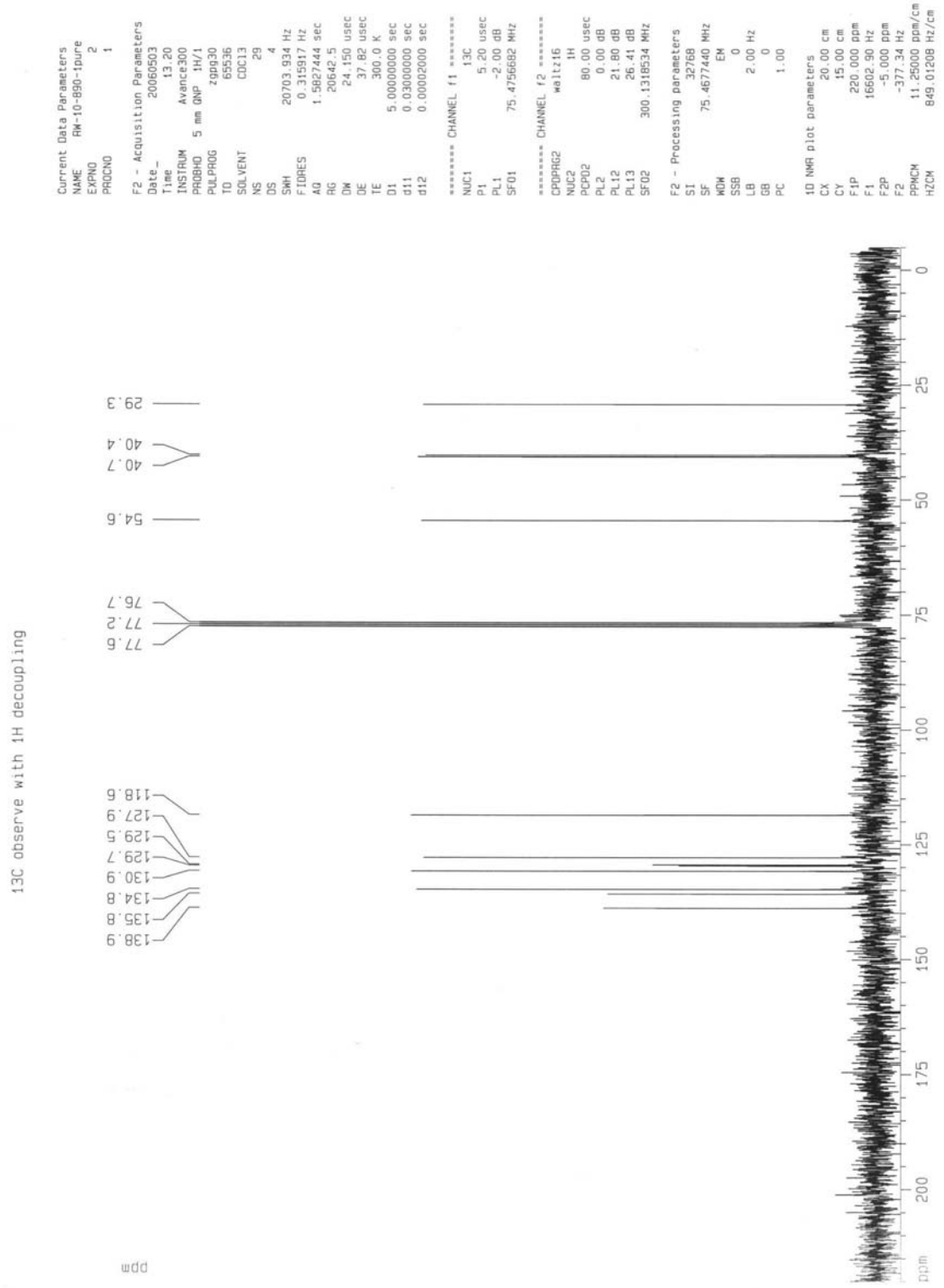


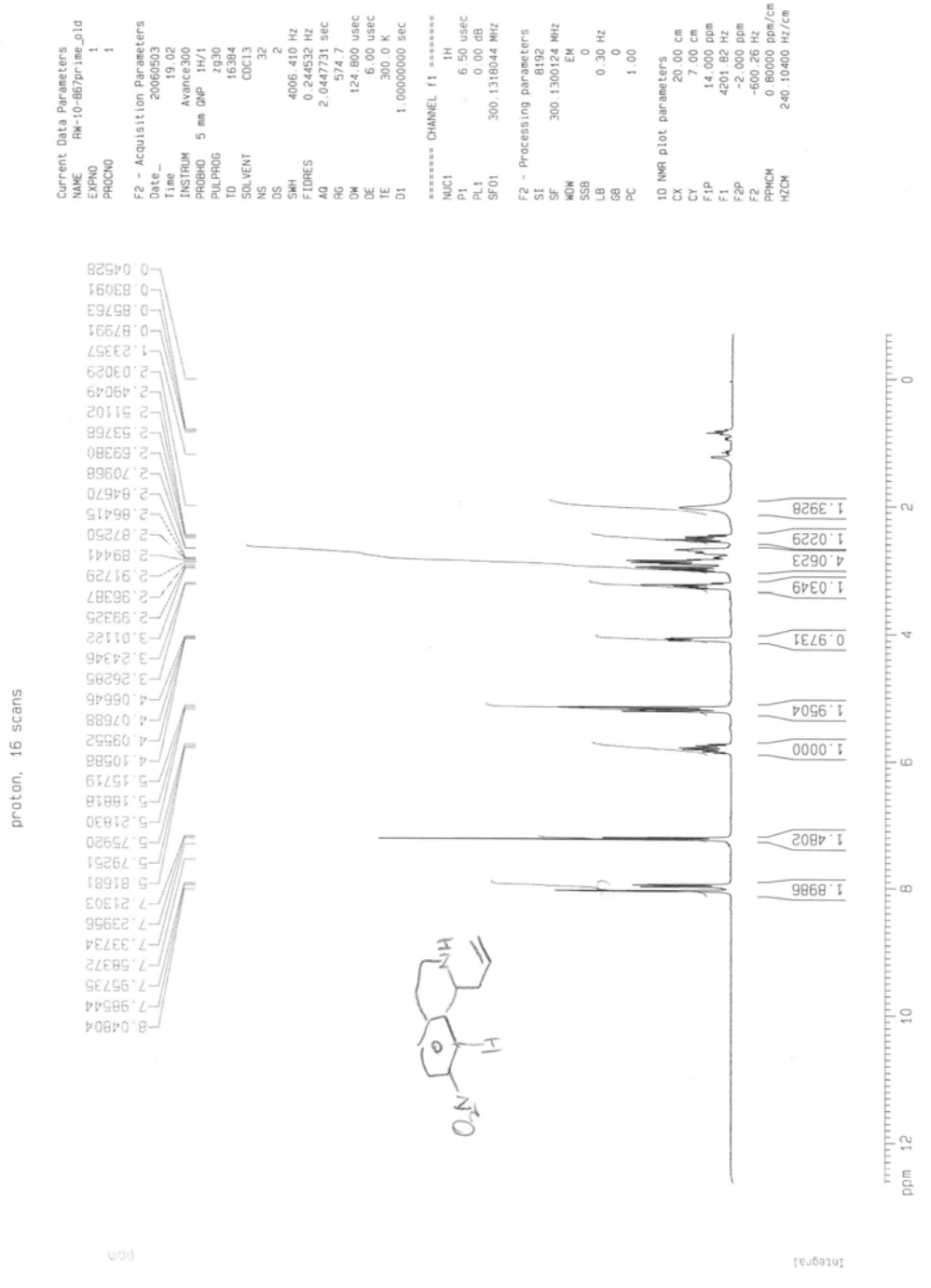
^{1}H NMR spectrum of compound 3d.



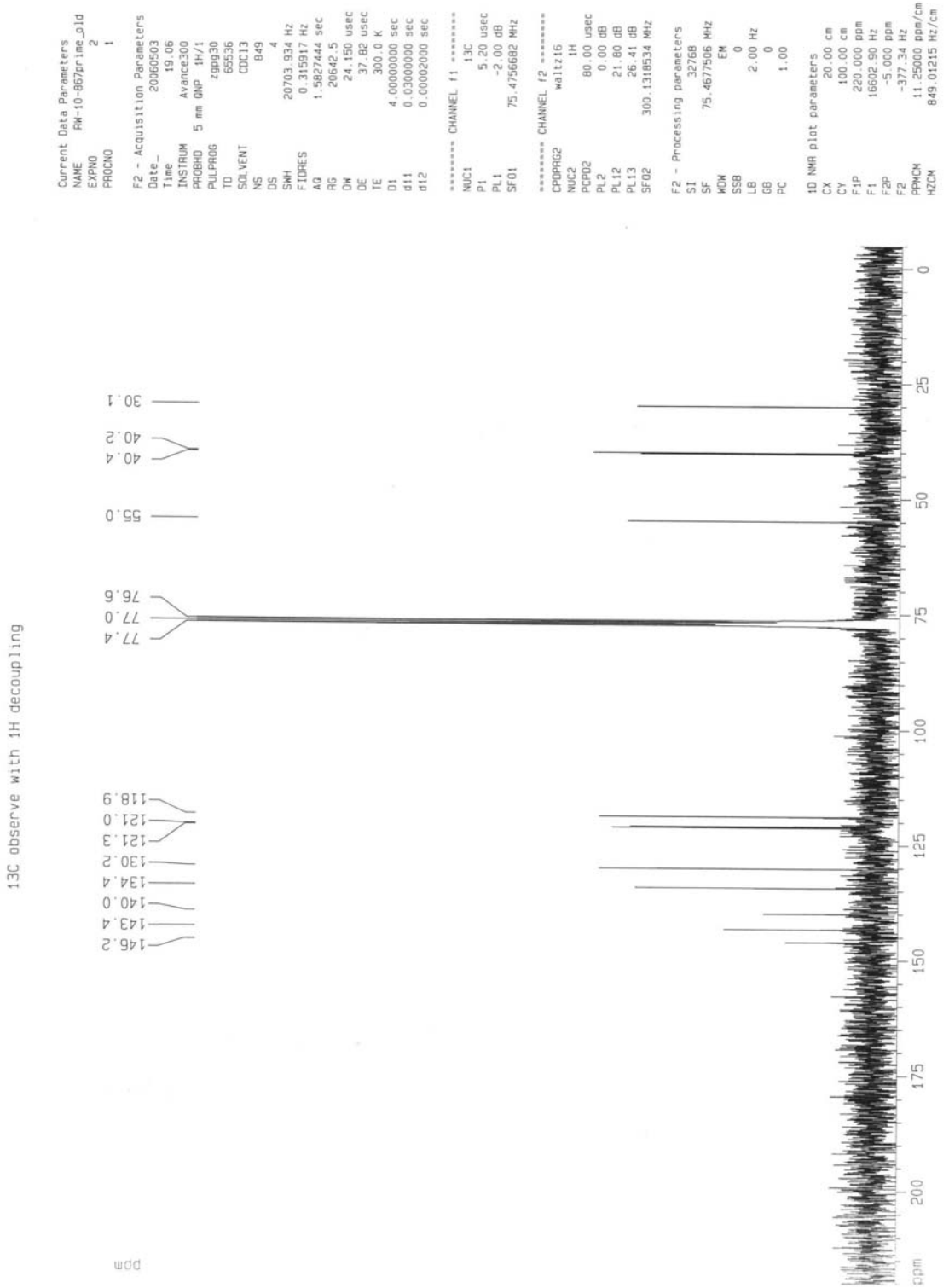
^{13}C NMR spectrum of compound 3d.



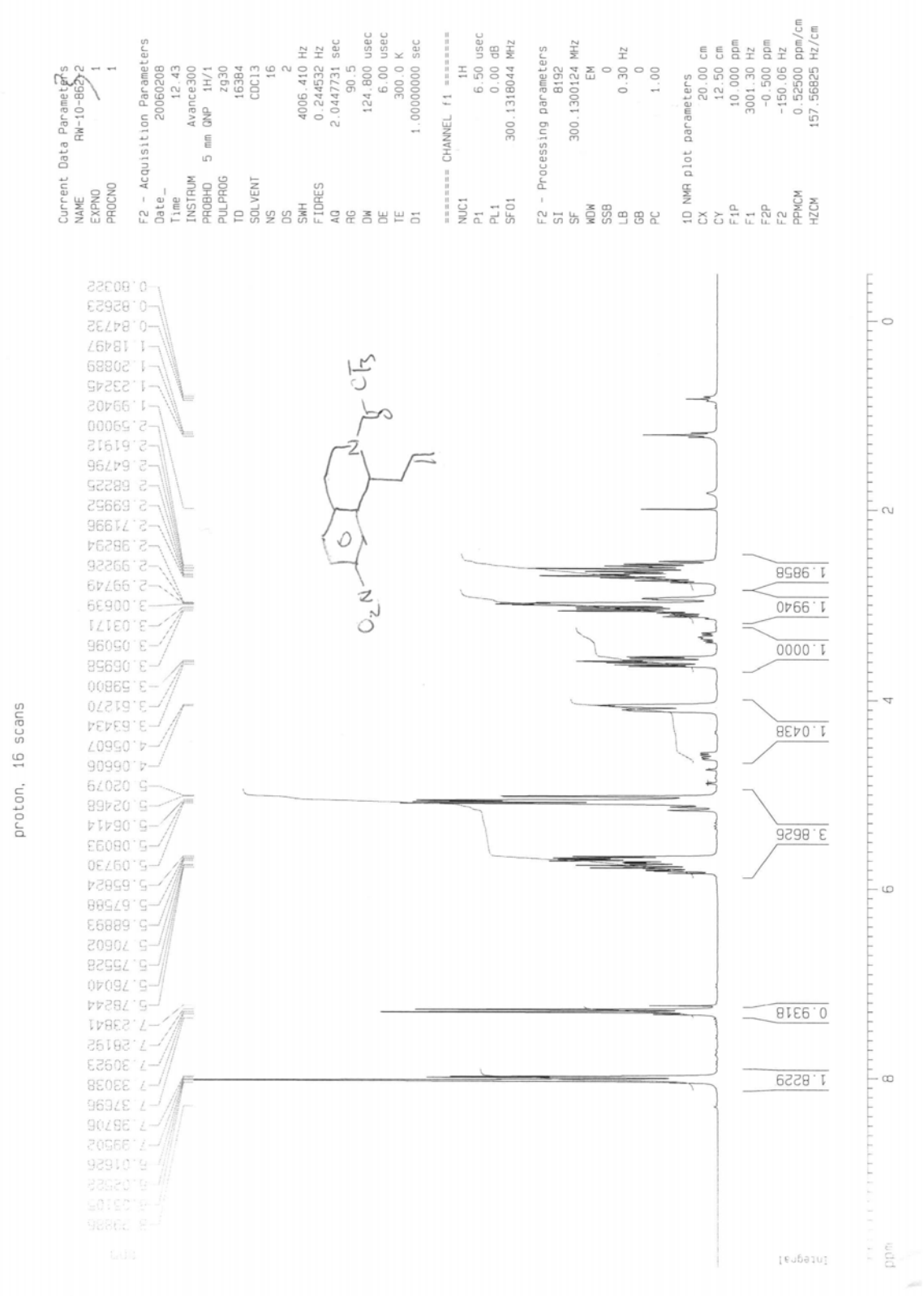
^{1}H NMR spectrum of compound 3e.



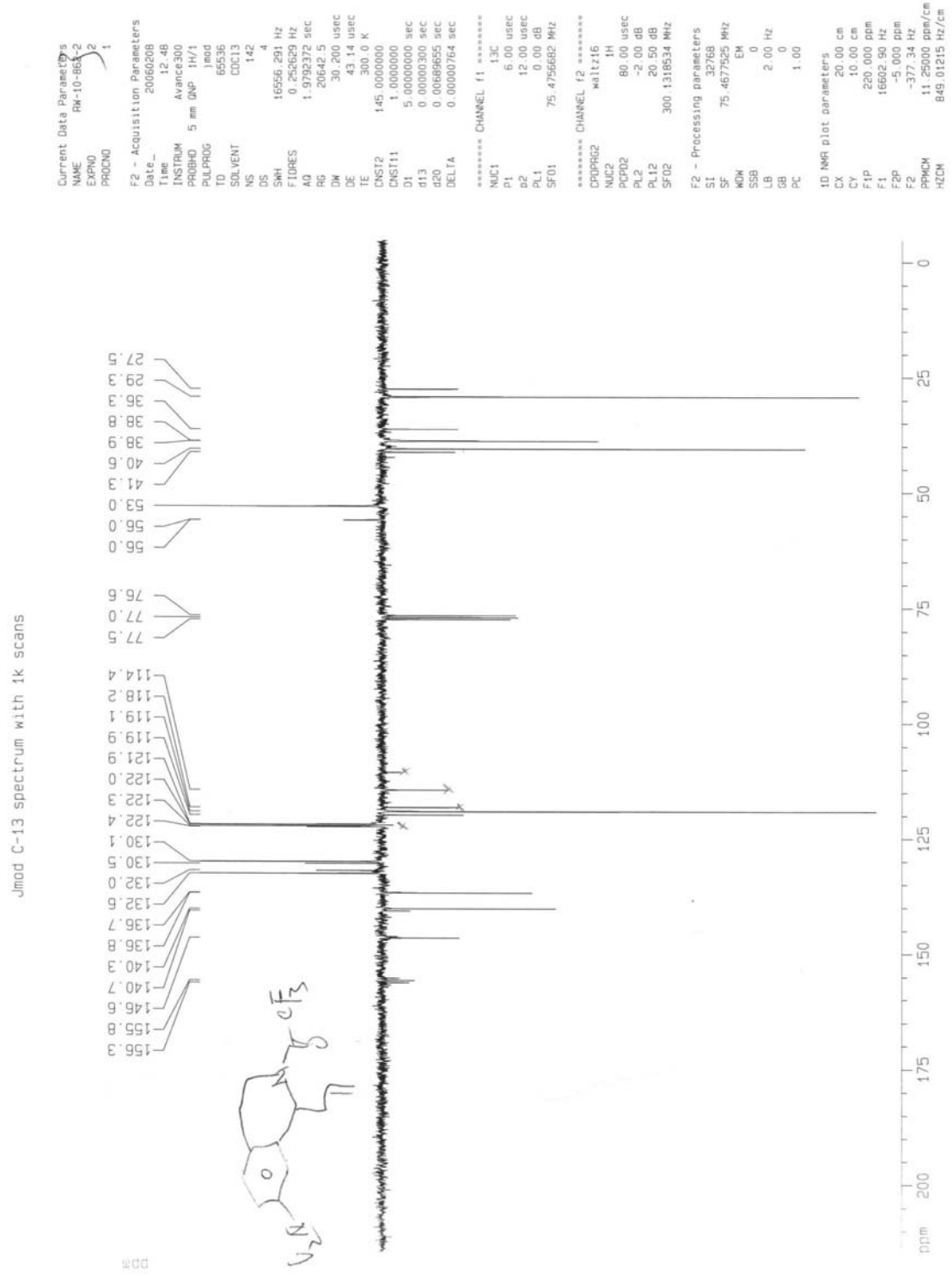
^{13}C NMR spectrum of compound 3e.



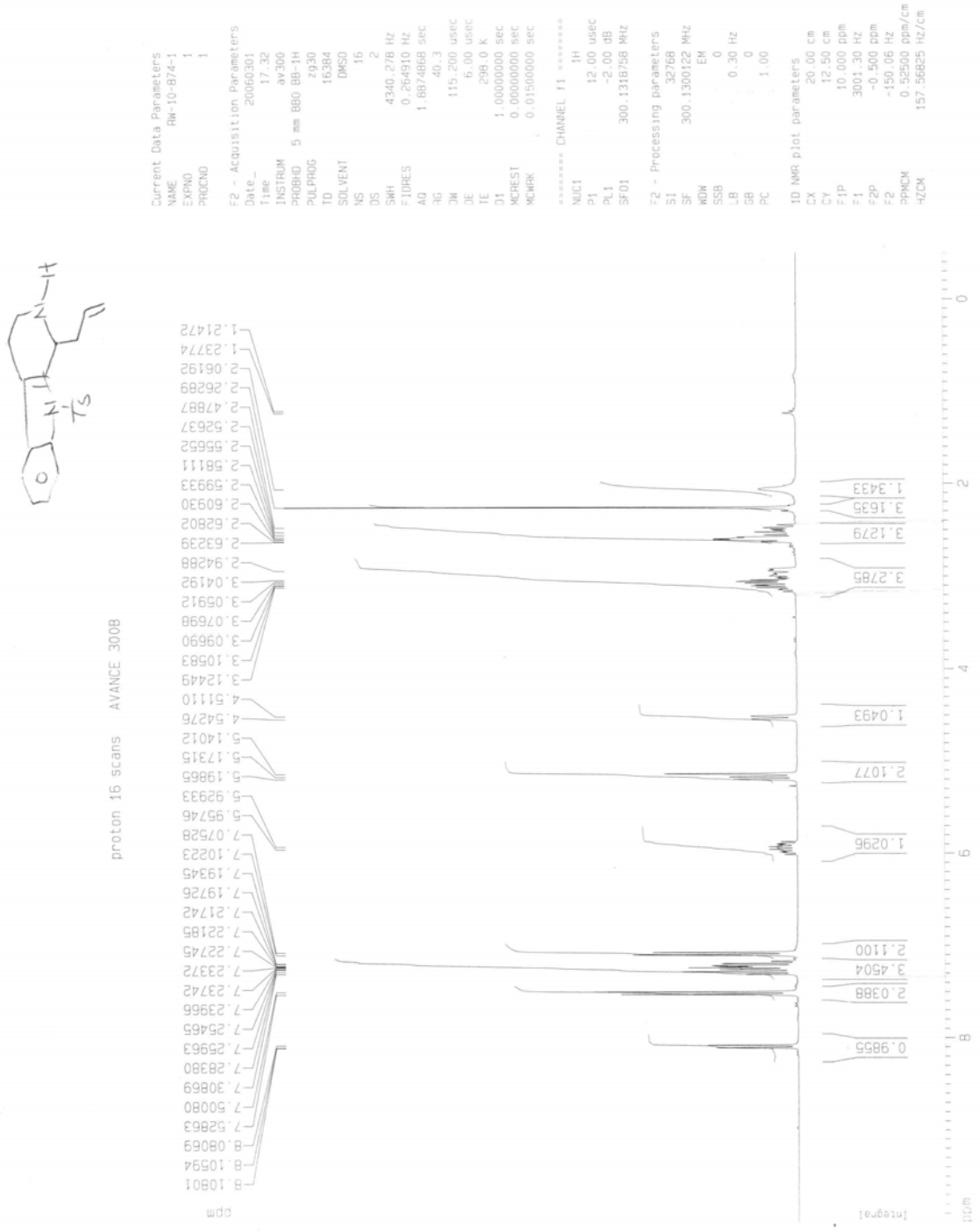
^{1}H NMR spectrum of the trifluoroacetamide of compound 3e.



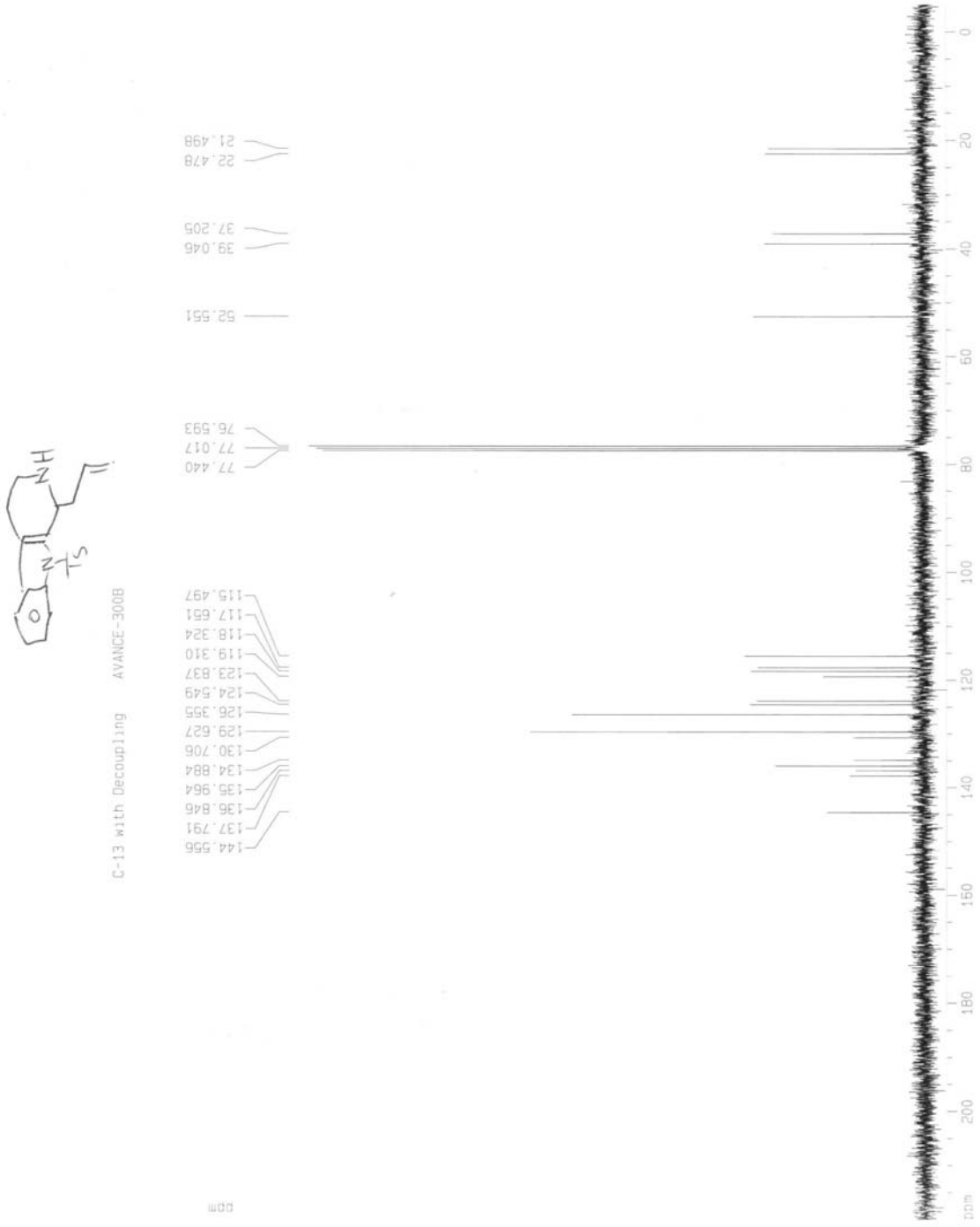
^{13}C NMR spectrum of the trifluoroacetamide of compound 3e.



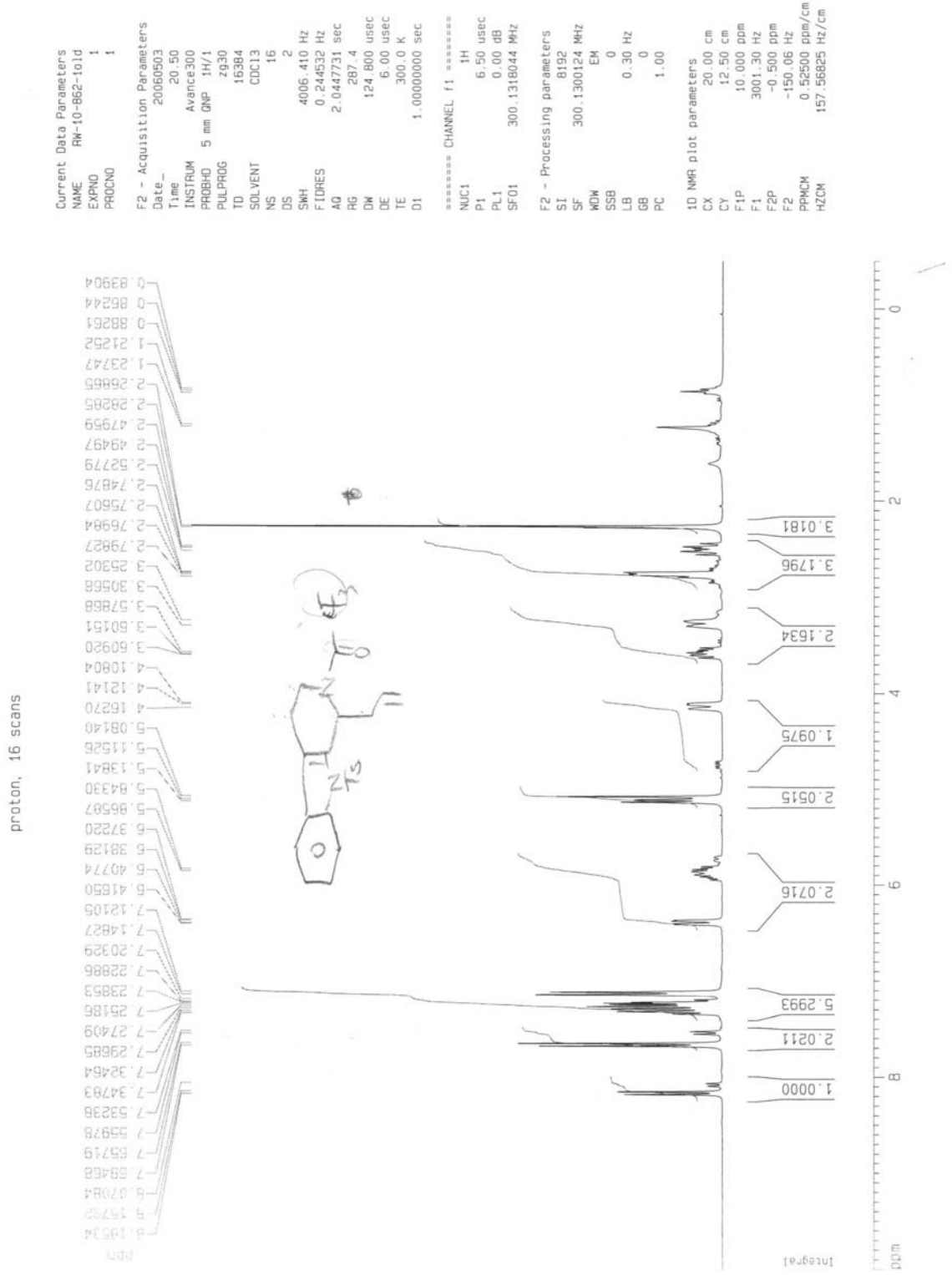
^{1}H NMR spectrum of compound 3g.



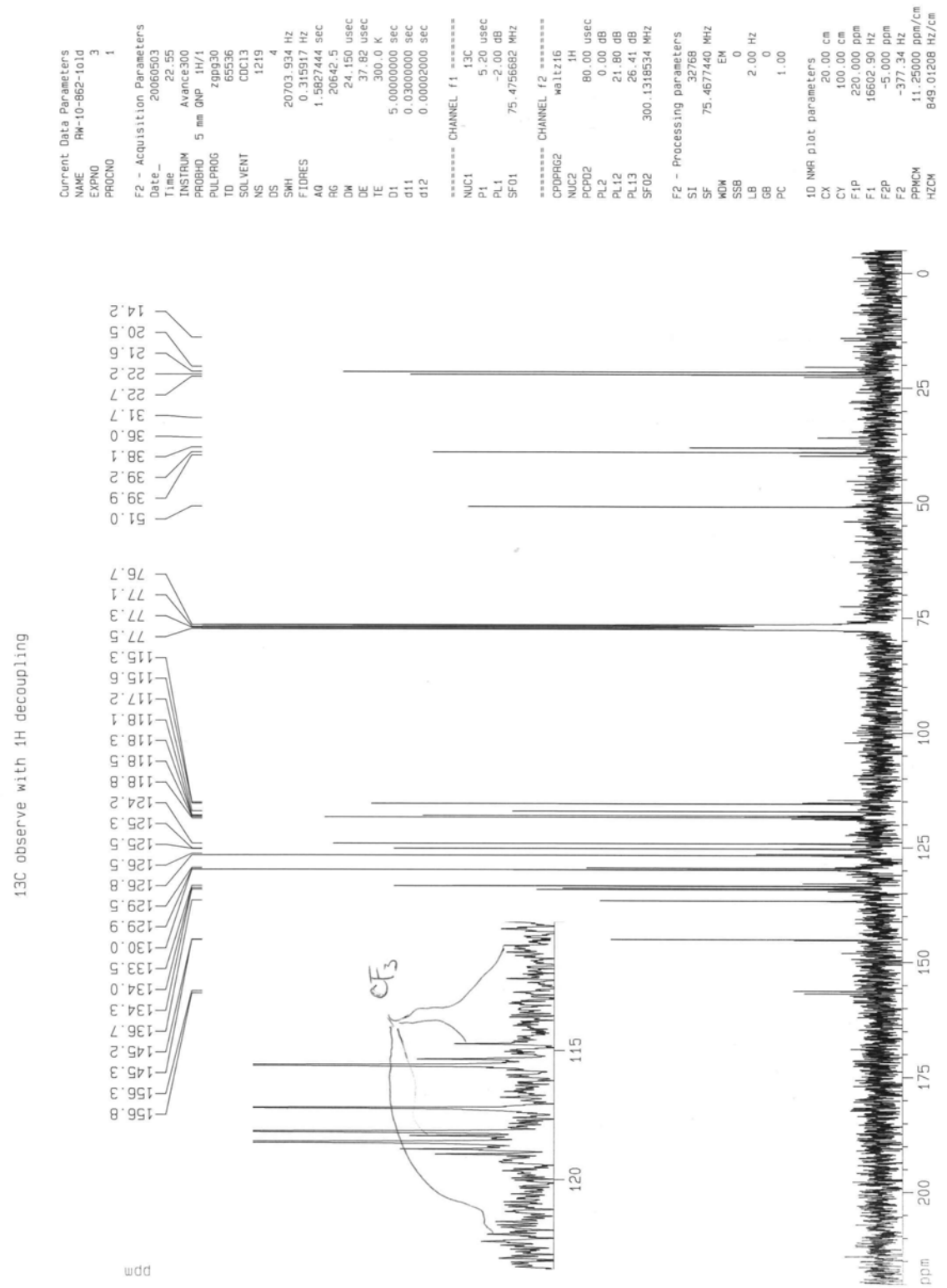
^{13}C NMR spectrum of compound 3g.



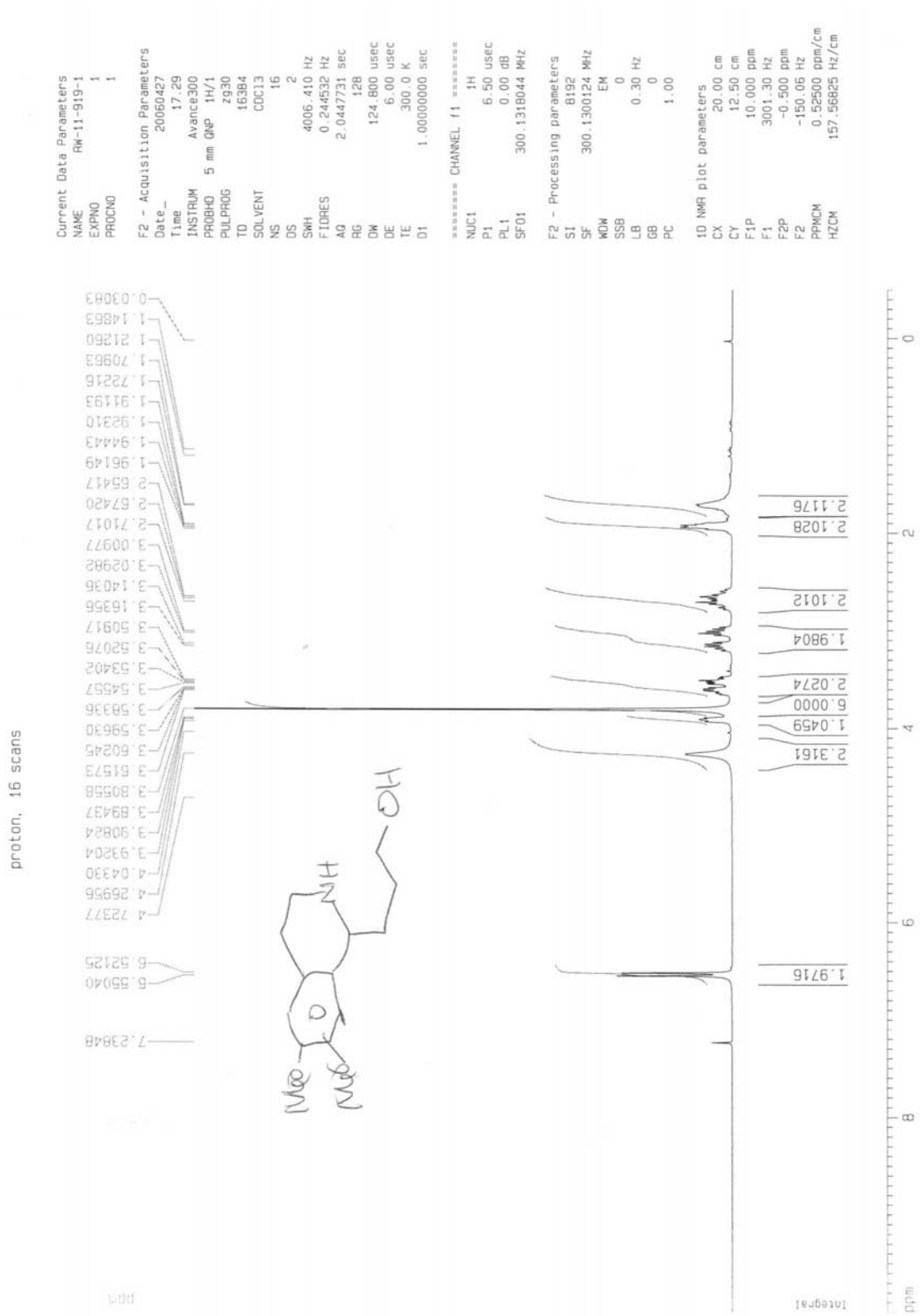
^{1}H NMR spectrum of the trifluoroacetamide of compound 3g.



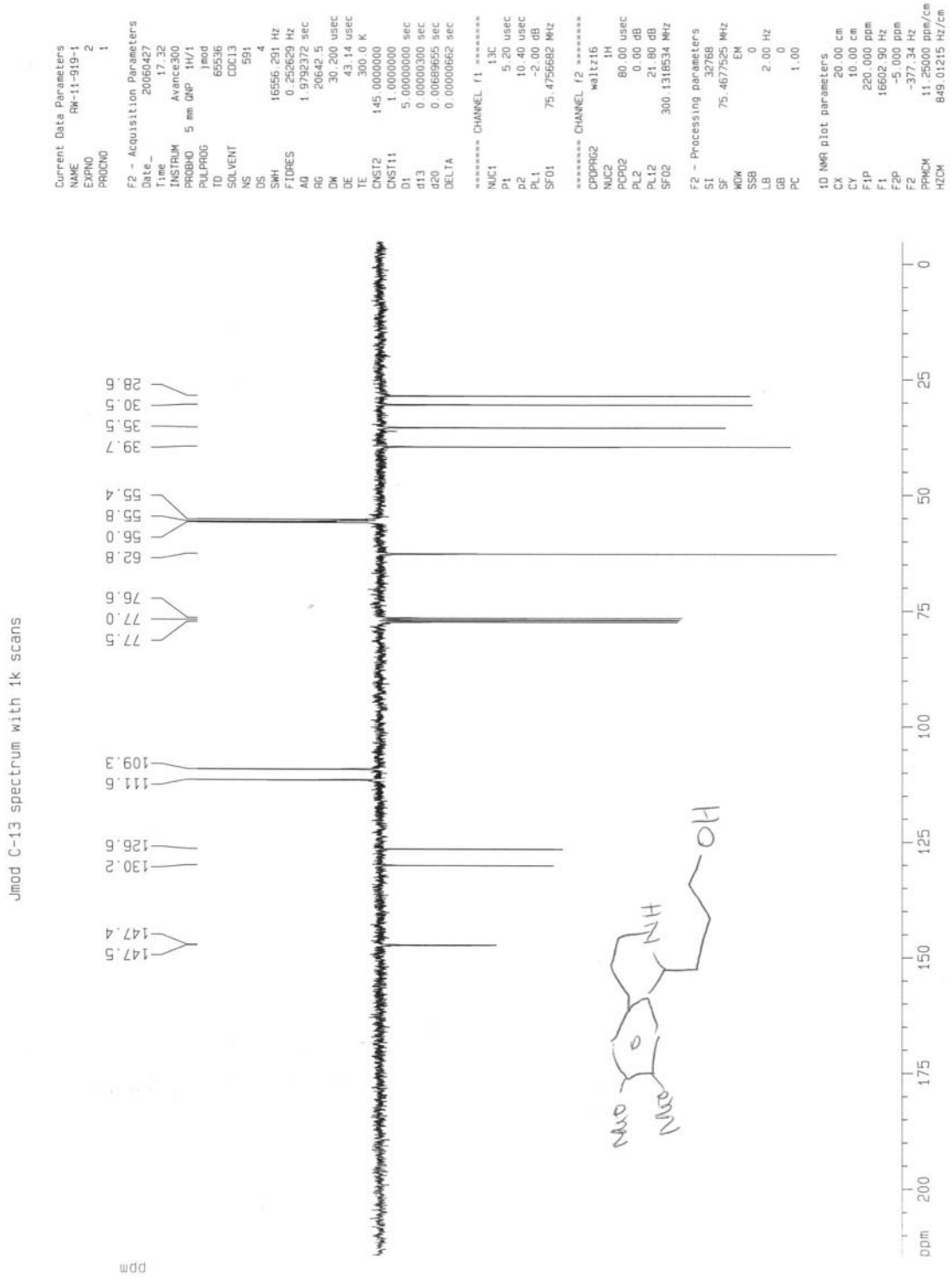
^{13}C NMR spectrum of the trifluoroacetamide of compound 3g.



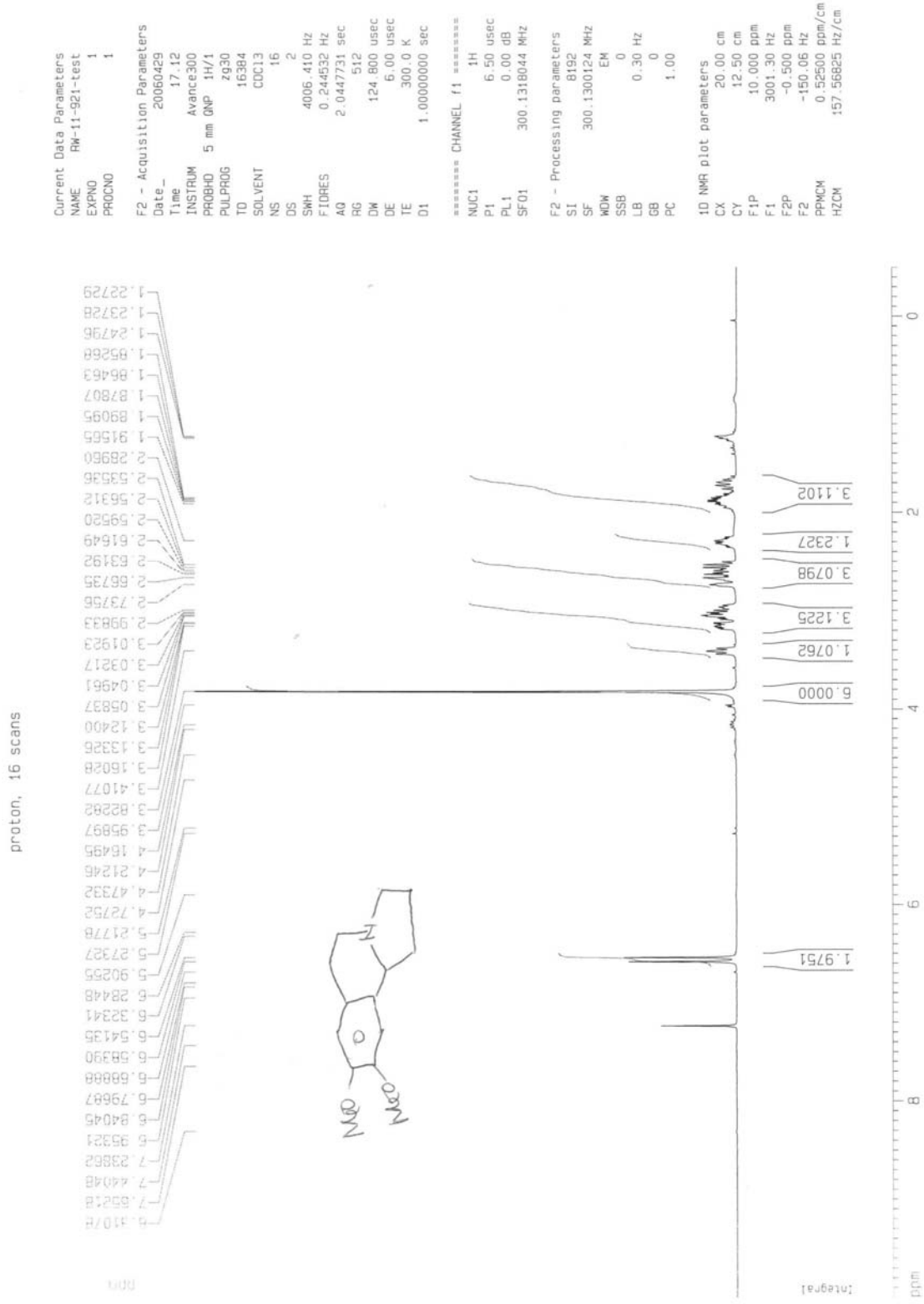
^{1}H NMR of (*R*)-3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-1-ol



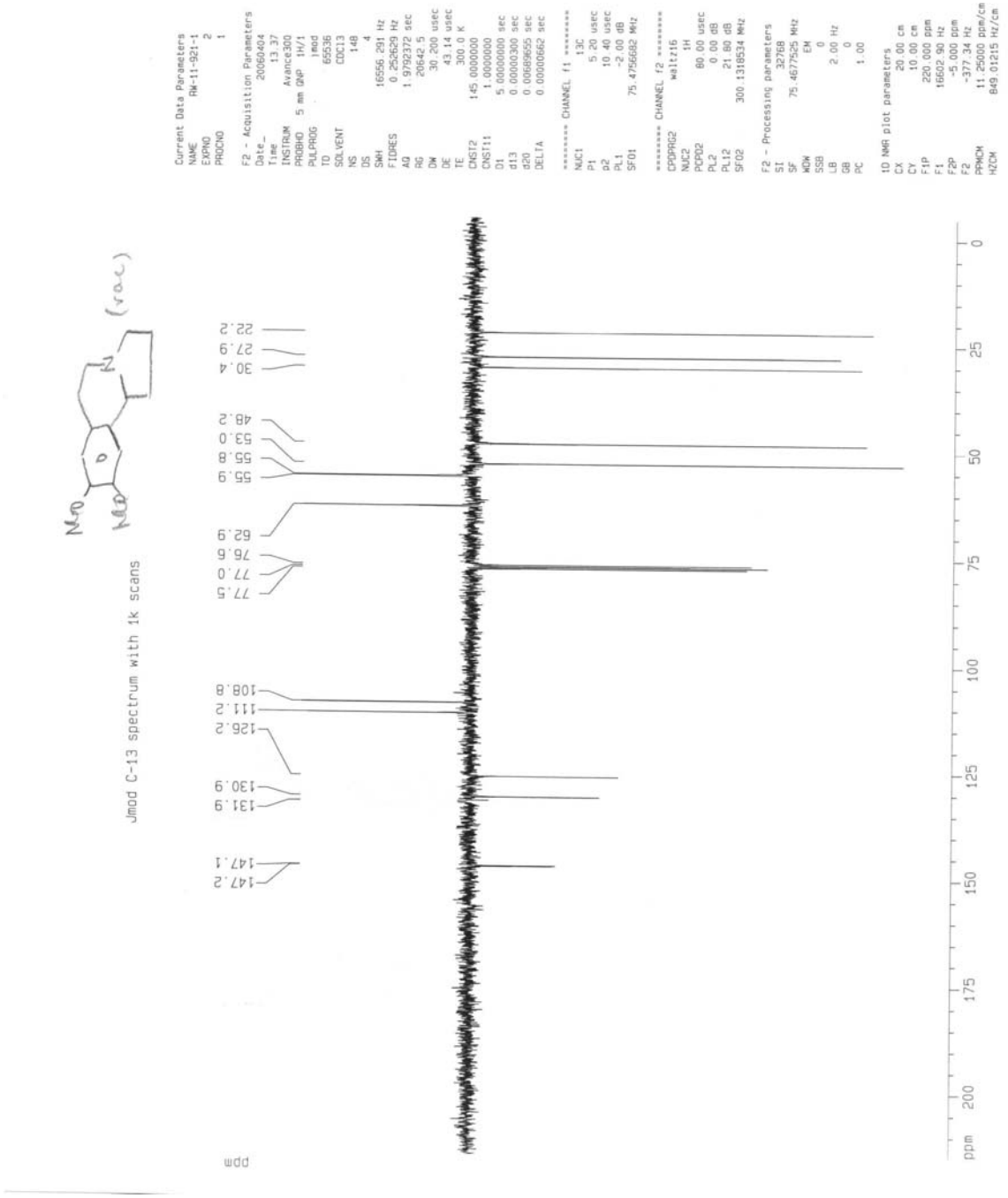
^{13}C NMR of (*R*)-3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-1-ol



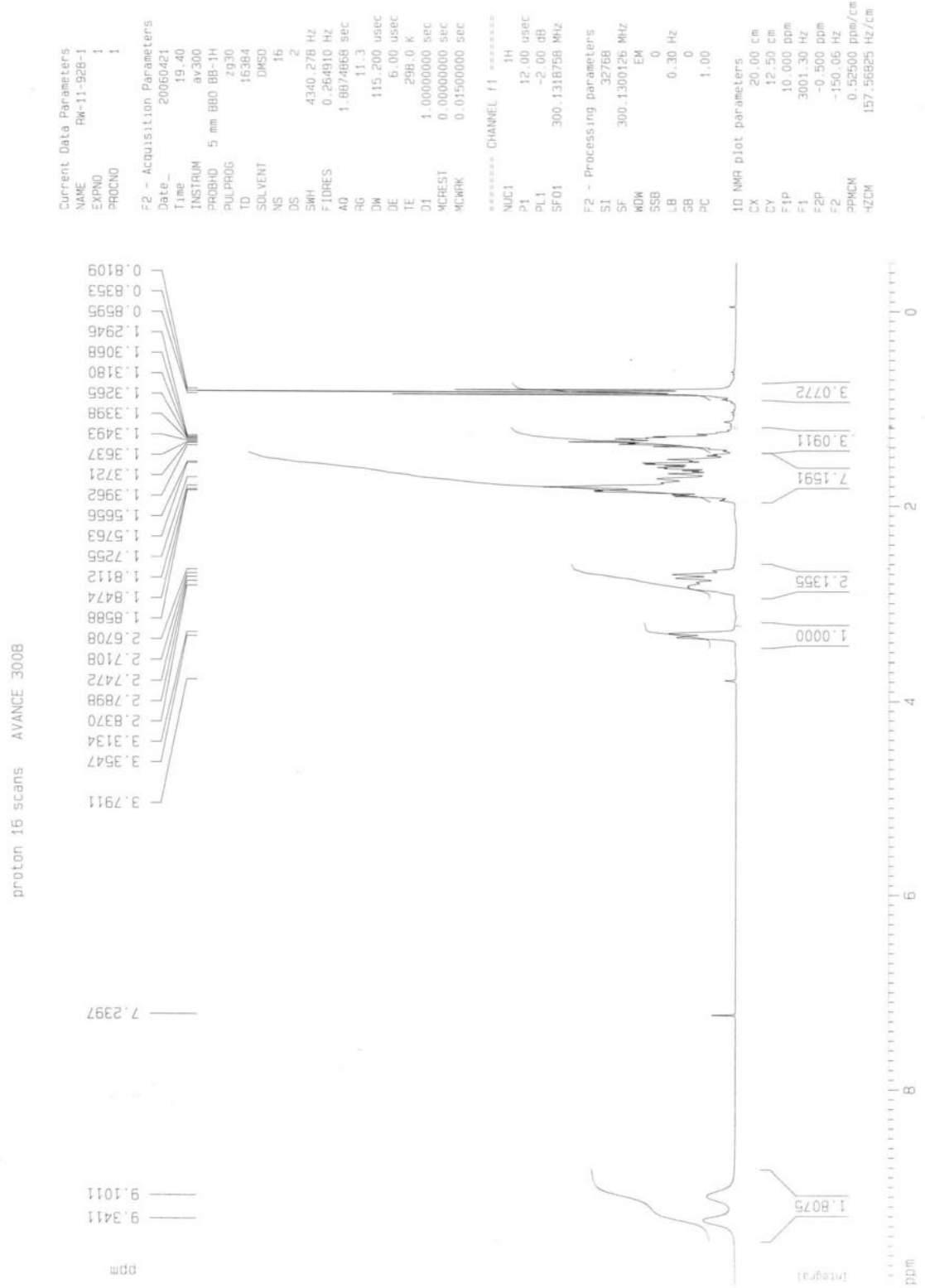
^{1}H NMR spectrum of compound 4.



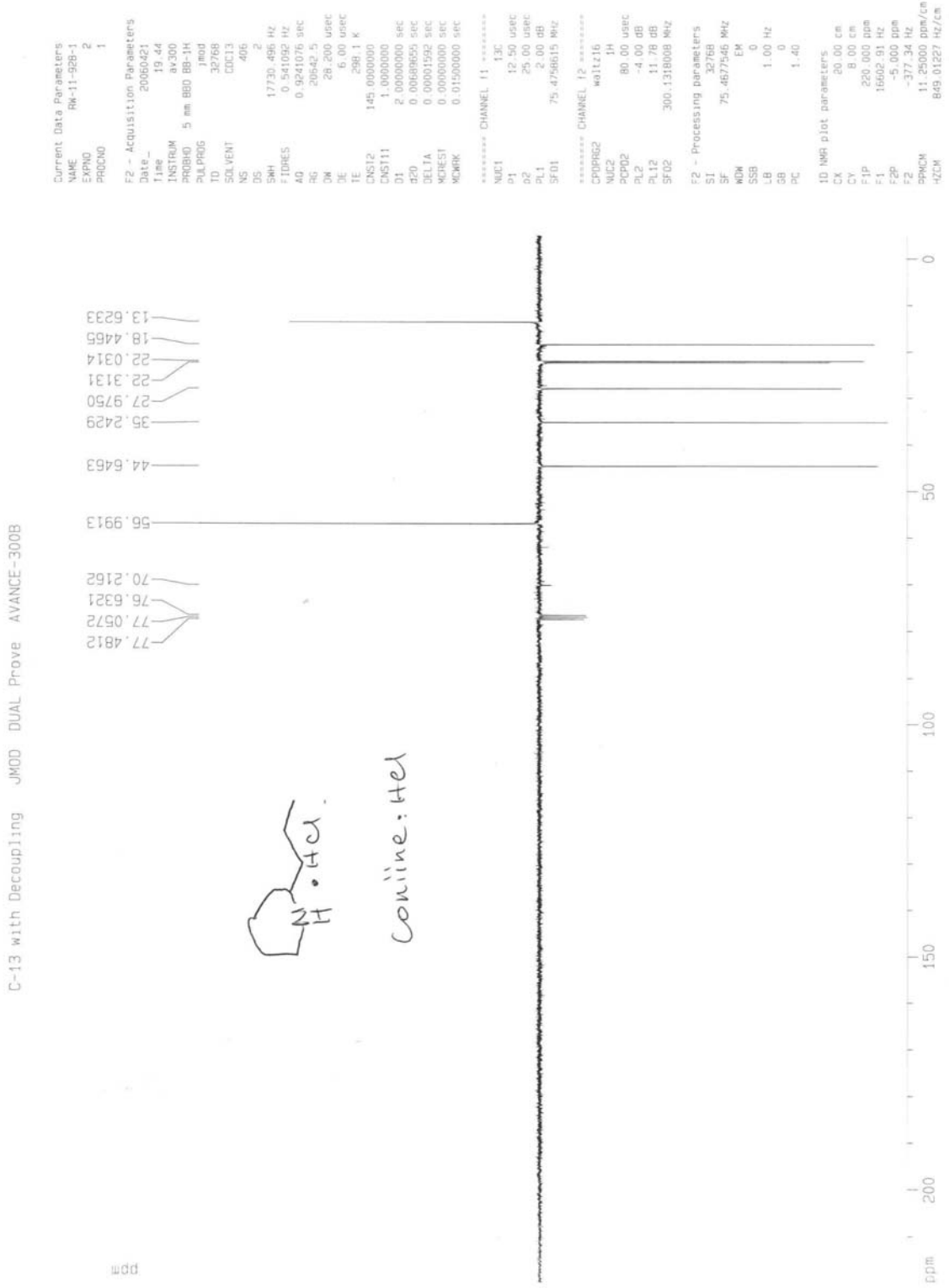
^{13}C NMR spectrum of compound 4.



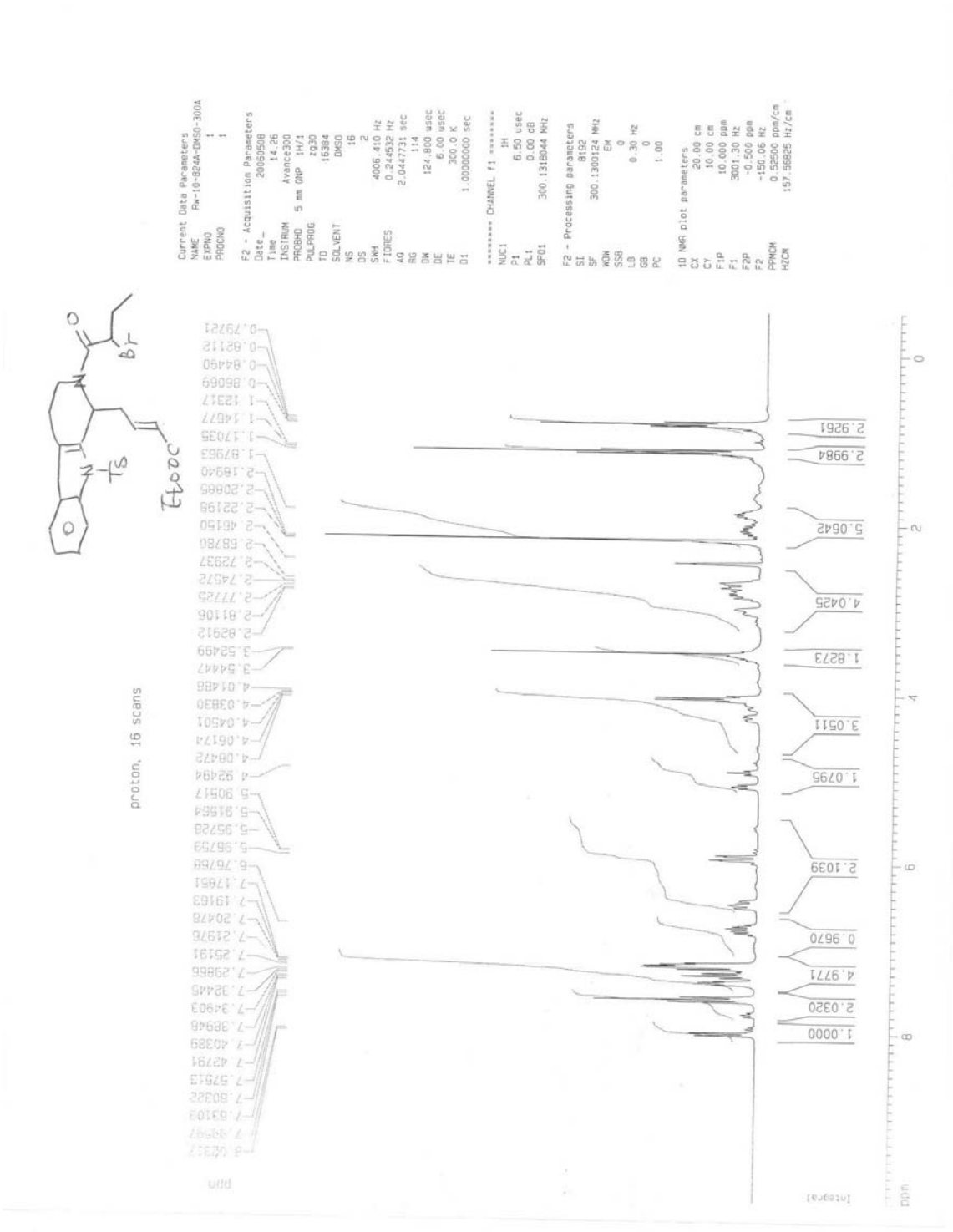
^{1}H NMR spectrum of compound 5 [(*R*)-Coniine].



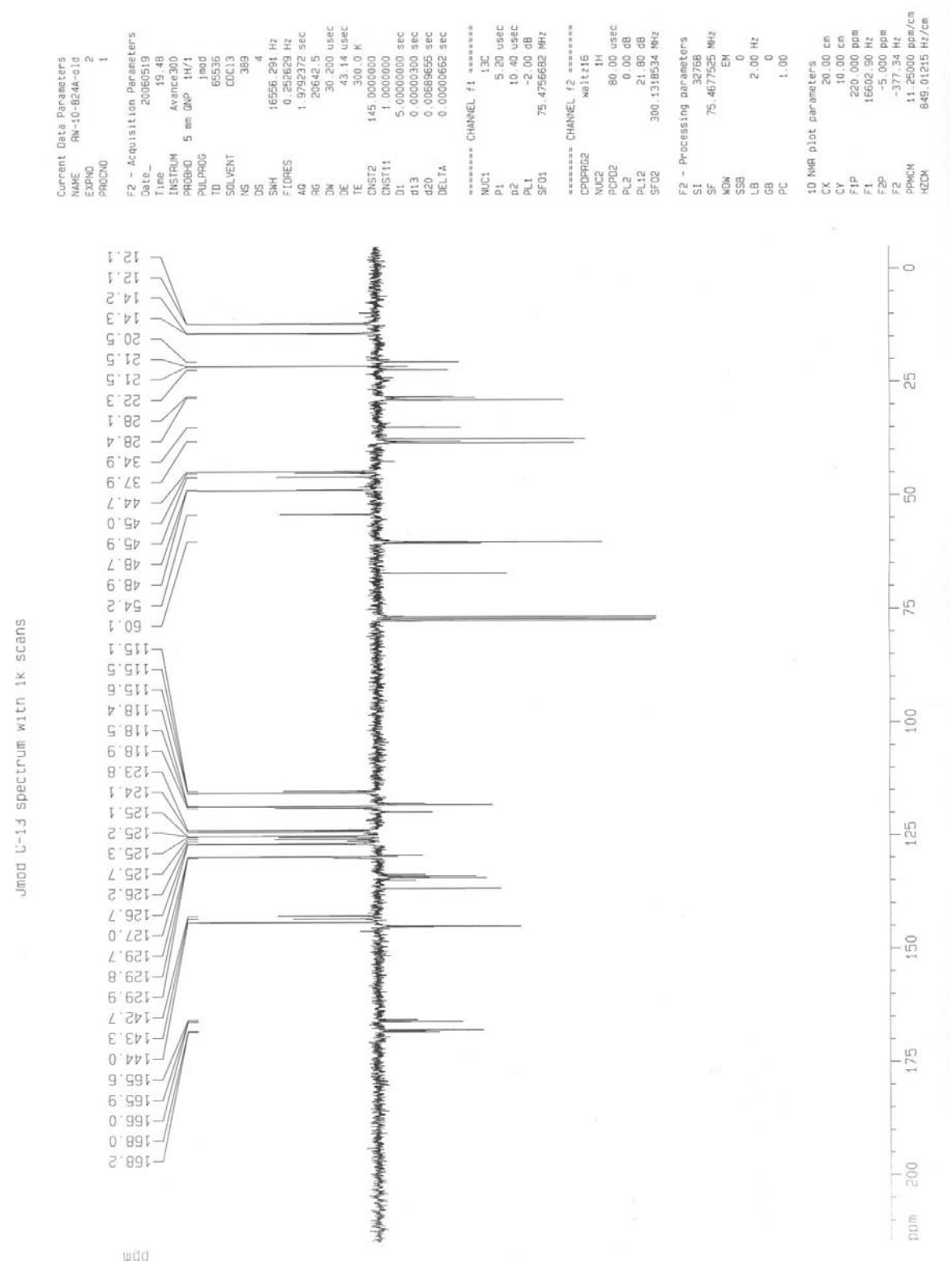
^{13}C NMR spectrum of compound 5.



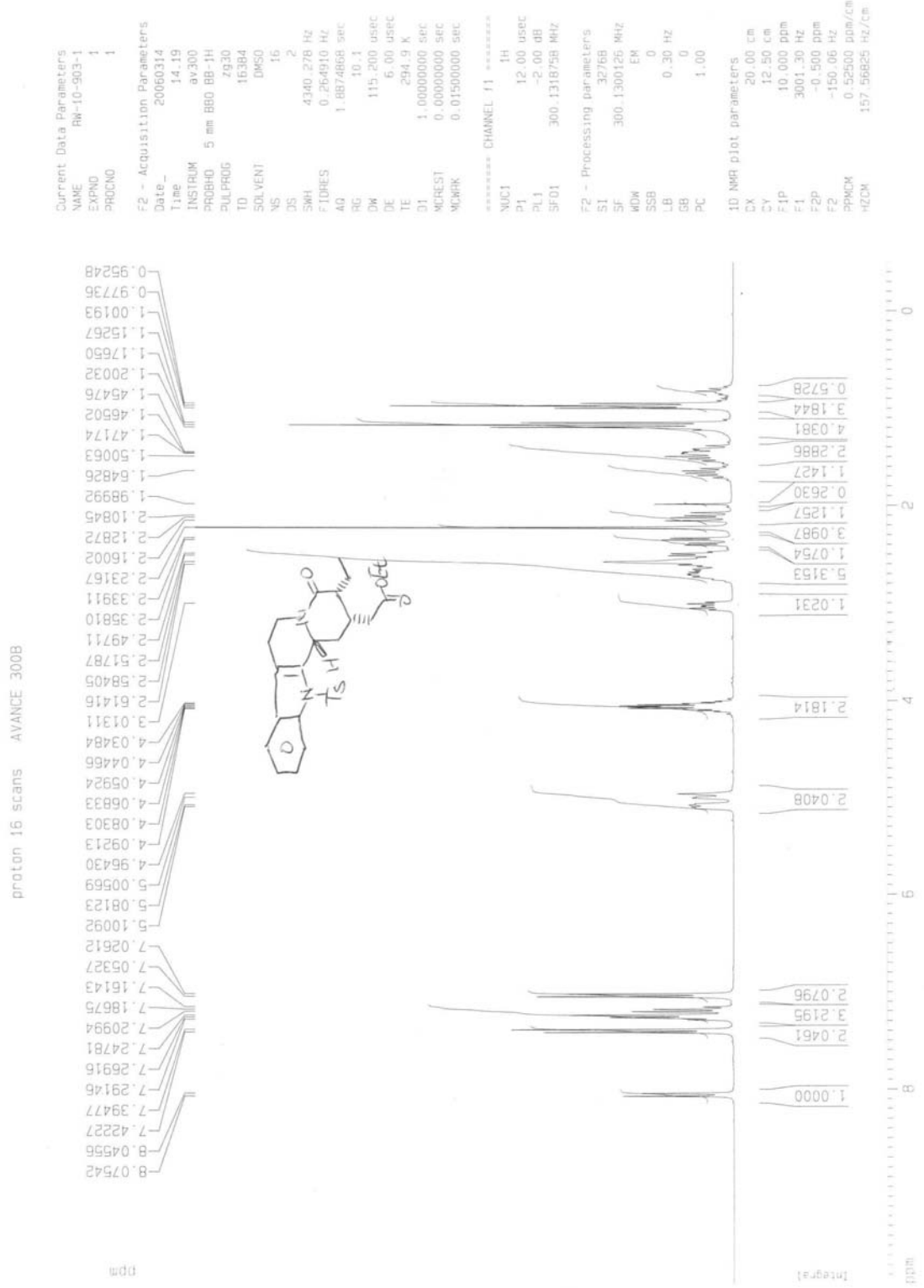
^{1}H NMR spectrum of compound 7.



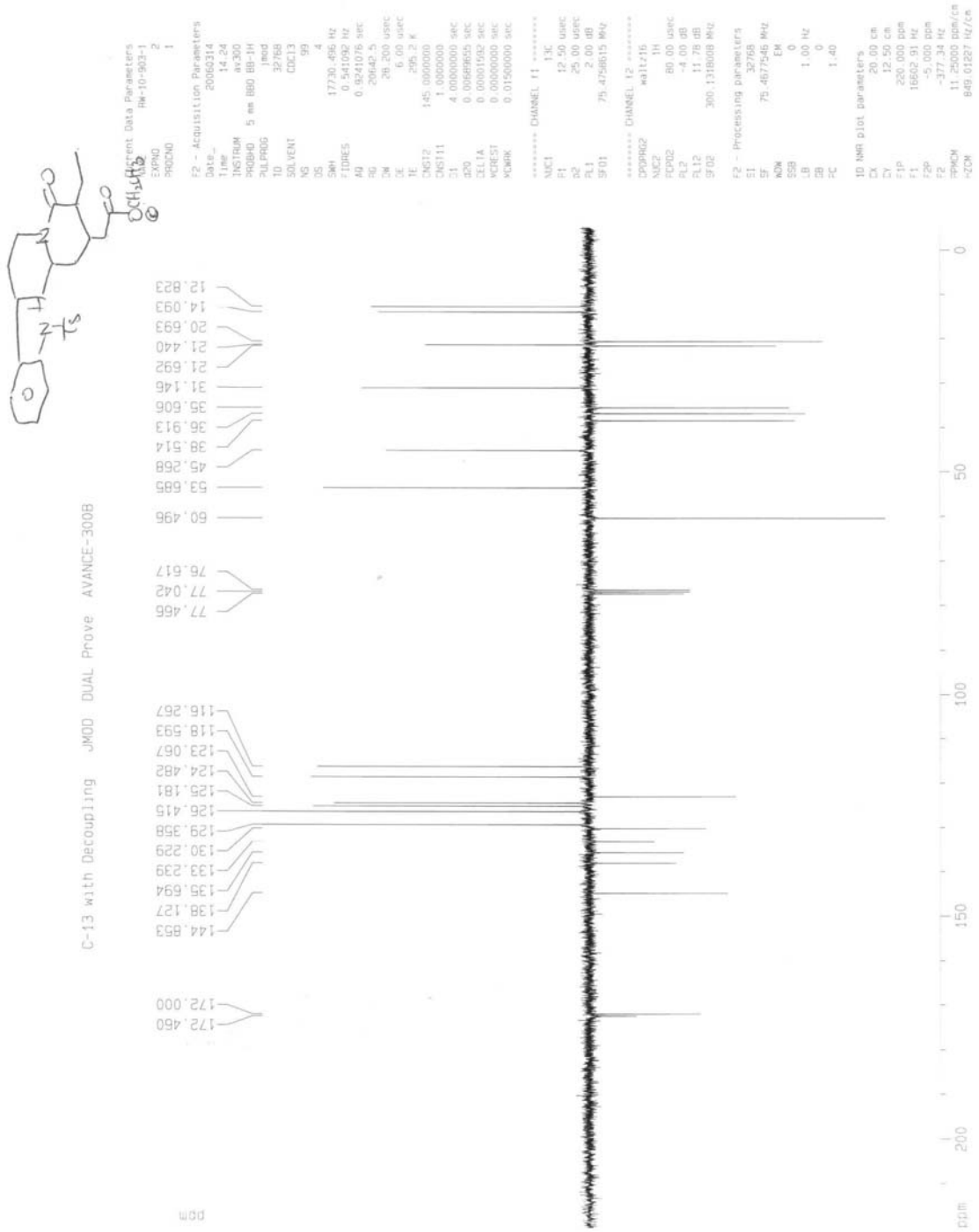
^{13}C NMR spectrum of compound 7.



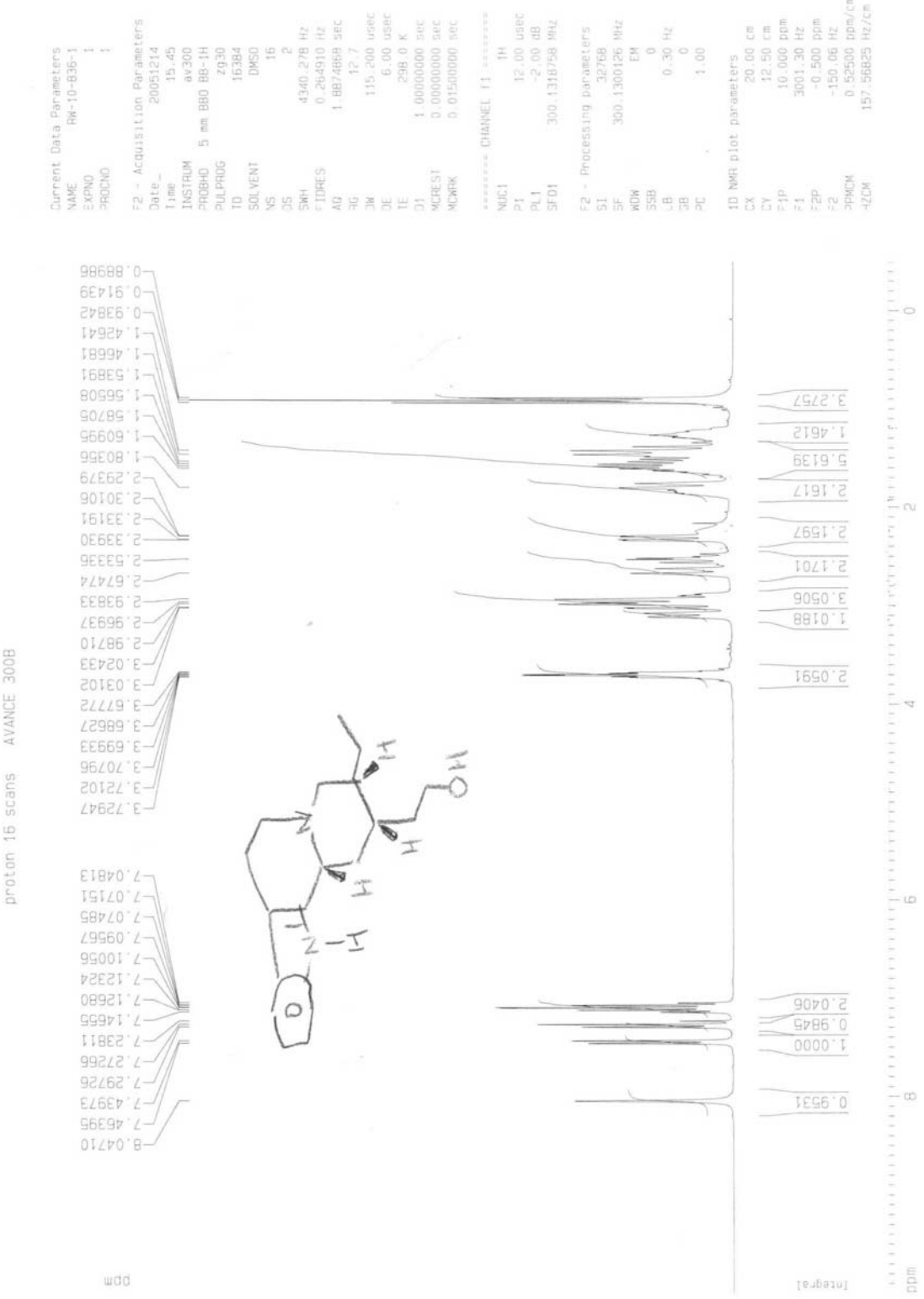
^{1}H NMR spectrum of compound 8.



^{13}C NMR spectrum of compound 8.



^{1}H NMR spectrum of compound 9 (*ent*-corynantheidol).



^{13}C NMR spectrum of compound 9 (*ent*-corynantheidol).