

Supplementary Information

Regio- and diastereocontrolled C–H insertion of chiral γ - and δ -lactam diazoacetates. Application to the asymmetric synthesis of (8*S*,8*aS*)-8-hydroxyindolizidine.

Gao-jun Fan, Zhongyi Wang and Andrew G. H. Wee*

Department of Chemistry and Biochemistry, University of Regina, Regina, Saskatchewan, S4S 0A2, Canada.

Experimental procedures and spectral data of new compounds:

ESI-1–ESI-9

NMR spectral data of new compounds:

ESI-10–ESI-45

Preparation of *p*-TSHACl. *p*-TsNHN=CHCO₂H was prepared, according to the House-Blankley method,^{5a} from 98% glyoxylic acid (28.5 g, 0.31 mol) in water (250 mL), and *p*-toluenesulfonylhydrazine (47.9 g, 0.26 mol) in aqueous 2.5 M hydrochloric acid (125 mL). The crude, dried hydrazone (60 g) was used for the next step reaction without further purification.

The heating period is critical to the success of this reaction. To the suspension of the above glyoxylic acid *p*-toluenesulfonylhydrazone (15.0 g, 62 mmol) in dry toluene (75 mL) was added thionyl chloride (9 mL, 123 mmol). The reaction mixture was heated at 80 °C for 25 min, during which time gas evolution was not observed. Gas evolution started when the reaction temperature was gradually increased to 90 °C, and then ceased. Most of the suspended solid had dissolved after 20 min. The solution became yellow-orange. The oil bath was removed after an additional 5 min at 90 °C. Toluene was removed under reduced pressure and the residual solid was treated with hot toluene and the solid mass is broken up to give a fine suspension. Upon cooling, the solid was filtered with suction and washed quickly with cold toluene to give first crop of crude product. The filtrate was concentrated and then treated with hot toluene again to get second crop of crude product. The combined crude product

was recrystallized using a minimum volume of hot toluene and petroleum ether to give totally 11.4 g (two steps 68%) of *p*-TSHACl as pale yellow prisms.

Compound (S)-3: Compound **2** (1.0 g, 4.87 mmol) and (tosylhydrazone)acetyl chloride (1.9 g, 7.3 mmol) were dissolved in dry CH₂Cl₂ and the solution was cooled to 0 °C in an ice-water bath. *N,N*-Dimethylaniline (0.93 mL, 7.3 mmol) was added dropwise via syringe. After the mixture was stirred at 0 °C for 20 min, *i*-Pr₂NEt (4.2 mL) was added. After stirring at 0 °C for 50 min, the reaction mixture was washed with saturated aqueous citric acid solution, brine and then saturated aqueous NaHCO₃ solution. The organic layer was dried (Na₂SO₄), filtered, concentrated and the residue was purified by flash chromatography (1:1 pet. ether:EtOAc and then EtOAc to yield (*S*)-**3** (R_f [EtOAc] = 0.42, 1.28 g, 98%) as a red oil. $[\alpha]_D^{25} +25.0$ (*c* 5.90, CHCl₃); IR (neat) 2097, 1690, 1637, 1378, 1173 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.18-7.36 (m, 5 H), 5.20 (six, *J* = 3.6, 8.7 Hz, 1 H), 4.72 (d, *J* = 12.6 Hz, 1 H), 4.70 (s, 1 H), 4.47 (d, *J* = 14.4 Hz, 1 H), 3.44 (dd, *J* = 3.6, 13.2 Hz, 1 H), 3.29 (ddd, *J* = 1.5, 3.6, 13.5 Hz, 1 H), 2.40-2.70 (m, 2 H), 1.95-2.15 (m, 2 H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.4, 165.7, 136.3, 128.3, 127.6, 127.2, 66.4, 50.4, 49.4, 46.1, 27.4, 25.3; HRMS calcd for C₁₄H₁₅N₃O₃ 273.1113, found 273.1120.

General Procedure for Rh(II)-Catalyzed Reaction. The appropriate Rh(II) catalyst (2 mol %) was dried under vacuum at 80 °C for 1 h and then cooled to rt. Dry CH₂Cl₂ (2 mL) was added and the mixture was heated (oil bath) to reflux. A solution of the appropriate lactam diazoacetate (0.2 mmol) in dry CH₂Cl₂ (2 mL) was added dropwise, via syringe pump, over a period of 1 h. After addition was complete, the mixture was refluxed for an additional 1 h. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography: For the δ lactam diazoacetates, (*S*)-**3** and (*R*)-**9**: EtOAc, 10:1 and then 5:1 EtOAc:MeOH to give compound **4**, **5**, **6** and then **7** or **10**, **11** and then **12** subsequently; for the γ-lactam diazoacetate (*S*)-**15**: 1:1 pet. ether:EtOAc, EtOAc and then 10:1 EtOAc:MeOH to give subsequently compounds **16**, **17** and then **18**. See Tables 1 and 2 for details.

Compound 4 (R_f [EtOAc] = 0.42): light yellow needles, mp: 131-132 °C; $[\alpha]_D^{22} +50.0$ (*c* 1.90, CHCl₃); IR 1778, 1642, 1202, 1166 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.18-7.38 (m, 5 H), 5.28 (d, *J* = 15.0 Hz, 1 H), 4.84 (ddd, *J* = 3.7, 3.7, 7.0 Hz, 1 H), 4.11 (ddd, *J* = 3.4, 7.4, 7.4 Hz, 1 H), 3.97 (d, *J* = 15.0 Hz, 1 H), 2.75 (dd, *J* = 7.7, 18.1 Hz, 1 H), 2.45-2.68 (m, 3 H), 2.32 (ddd, *J* = 4.6, 9.1, 18.9 Hz, 1 H), 2.00 (dddd, *J* = 3.2, 5.0, 11.8, 14.8 Hz, 1 H); ¹³C NMR (CDCl₃, 50 MHz) δ 173.9 (C), 169.1 (C), 135.9 (C), 128.9 (CH), 128.0 (CH), 127.9 (CH), 75.6 (CH), 54.7 (CH), 47.5 (CH₂), 35.7 (CH₂), 26.5 (CH₂), 24.0 (CH₂); HRMS calcd for C₁₄H₁₅NO₃ 245.1052, found 245.1047.

Compound 5 (R_f [EtOAc] = 0.15): $[\alpha]_D^{22}$ -44.2 (c 1.30, CHCl_3); IR 1754, 1649, 1472, 1437, 1178 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.19-7.38 (m, 5 H), 4.80-4.86 (m, 1 H), 4.83 (d, J = 14.4 Hz, 1 H), 4.36 (d, J = 14.6 Hz, 1 H), 3.44 (d, J = 3.2 Hz, 2 H), 3.06-3.19 (m, 1 H), 2.83 (dd, J = 10.9, 18.7 Hz, 1 H), 2.54 (dd, J = 5.6, 15.4 Hz, 1 H), 2.47 (dd, J = 4.4, 15.4 Hz, 1 H), 2.36 (dd, J = 6.0, 18.7 Hz, 1 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 175.0 (C), 169.6 (C), 136.2 (C), 128.7 (CH), 128.1 (CH), 127.7 (CH), 76.6 (CH), 50.0 (CH_2), 49.0 (CH_2), 36.0 (CH_2), 33.5 (CH_2), 30.6 (CH); HRMS calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_3$ 245.1052, found 245.1060.

Compound 6 (R_f [10:1 EtOAc:MeOH] = 0.36): colorless oil: $[\alpha]_D^{23}$ +8.3 (c 2.10, CHCl_3); IR 1724, 1635, 1494 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ (E/Z -mixture): 7.09-7.30 (m, 26 H), 6.64 (s, 2 H), 6.12 (s, 3.2 H), 5.10-5.20 (m, 5.2 H), 4.63 (d, J = 14.7 Hz, 2 H), 4.60 (d, J = 14.7 Hz, 3.2 H), 4.45 (d, J = 14.7 Hz, 2 H), 4.42 (d, J = 14.7 Hz, 3.2 Hz), 3.42 (dd, J = 3.8, 13.4 Hz, 3.2 Hz), 3.35 (dd, J = 4.2, 8.1 Hz, 2 H), 3.15-3.32 (m, 5.2 H), 2.30-2.70 (m, 10.4 H), 1.80-2.15 (m, 10.4 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.6, 168.4, 164.2, 163.6, 136.4, 136.3, 133.5, 129.9, 128.6 (x2), 128.0 (x2), 127.6, 127.5, 67.5, 67.3, 50.3, 50.2, 49.9, 49.8, 27.7, 27.6, 25.4, 25.2; HRMS calcd for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_6$ 490.2104, found 490.2112.

Compound 7 (R_f [10:1 EtOAc:MeOH] = 0.24): red oil, $[\alpha]_D^{23}$ +53.3 (c 1.50, CHCl_3); IR 2919, 1748, 1643, 1490, 1202, 1137 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.19-7.36 (m, 10 H), 5.19-5.26 (m, 2 H), 4.68 (d, J = 14.6 Hz, 2 H), 4.48 (d, J = 14.6 Hz, 2 H), 4.13 (d, J = 16.6 Hz, 2 H), 4.03 (d, J = 16.6 Hz, 2 H), 3.46 (dd, J = 3.8, 13.4 Hz, 2 H), 3.29 (dd, J = 3.2, 13.5 Hz, 2 H), 2.44-2.70 (m, 4 H), 2.00-2.14 (m, 4 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 168.7, 168.4, 136.4, 128.6, 128.0, 127.6, 67.9, 67.1, 50.3, 49.8, 27.3, 25.5; HRMS calcd for $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_7$ 508.2210, found 508.2210.

Compound 8 (R_f [10:1 EtOAc:MeOH] = 0.33): Compound **2** (329 mg, 1.6 mmol), Ph_3P (755 mg, 2.9 mmol) and $\text{ClCH}_2\text{CO}_2\text{H}$ (273 mg, 2.9 mmol) were dissolved in dry CH_2Cl_2 (15 mL). DEAD (0.46 mL, 2.9 mmol) was added dropwise to the solution and the resulting pale yellow solution was stirred at rt for 4 h. The reaction mixture was concentrated and the residue was purified by flash chromatography (1:1 pet. ether:EtOAc and then EtOAc to give a mixture of chloroacetate contaminated with trace amounts of Ph_3PO . The chloroacetate was hydrolyzed using K_2CO_3 (662 mg, 4.8 mmol) in methanol (15 mL). Methanol was evaporated and CH_2Cl_2 was added to the residue. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The crude product was purified by chromatography (10:1 EtOAc:MeOH) to give **8** (230 mg, 70 %) as a colorless crystals. mp (pet. ether:EtOAc): 136-137 $^\circ\text{C}$, $[\alpha]_D^{22}$ +17.4 (c 3.30, CHCl_3); IR (CHCl_3) 3284 (br), 1607, 1272 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 7.10-7.40 (m, 5 H), 4.56 (s, 2 H), 4.02-4.15 (m, 1 H), 3.40 (dd, J = 3.8, 12.5

Hz, 1 H), 3.10 (ddd, $J = 0.9, 5.1, 12.5$ Hz, 1 H), 2.60 (dt, $J = 7.7, 17.7$ Hz, 1 H), 2.45 (dt, $J = 6.4, 17.7$ Hz, 1 H), 1.80-2.05 (m, 2 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 169.3, 136.7, 128.6, 128.0, 127.4, 63.9, 53.6, 50.0, 28.7, 28.1; HRMS calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2$ 205.1103, found 205.1101.

Compound (R)-9 (prepared as described for (S)-3, R_f [EtOAc] = 0.42): Red oil; $[\alpha]_{\text{D}}^{25} -22.0$ (c 5.90, CHCl_3); IR (neat) 2954, 2108, 1689, 1637, 1490, 1384, 1178 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 7.14-7.34 (m, 5 H), 5.17 (six, $J = 3.5, 8.2$ Hz, 1 H), 4.71 (s, 1 H), 4.70 (d, $J = 14.2$ Hz, 1 H), 4.42 (d, $J = 14.7$ Hz, 1 H), 3.43 (dd, $J = 3.8, 13.4$ Hz, 1 H), 3.25 (ddd, $J = 0.9, 3.4, 13.4$ Hz, 1 H), 2.30-2.70 (m, 2 H), 1.85-2.15 (m, 2 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 168.4, 165.7, 136.3, 128.4, 127.7, 127.3, 66.4, 50.5, 49.5, 46.3, 27.5, 25.4; HRMS calcd for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3$ 273.1113, found 273.1118.

Compound 10 (R_f [EtOAc] = 0.42): light yellow oil, $[\alpha]_{\text{D}}^{22} -48.4$ (c 1.60, CHCl_3); IR 1778, 1642, 1449, 1202, 1167 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.18-7.38 (m, 5 H), 5.28 (d, $J = 15.0$ Hz, 1 H), 4.84 (ddd, $J = 3.7, 3.7, 7.0$ Hz, 1 H), 4.11 (ddd, $J = 3.4, 7.4, 7.4$ Hz, 1 H), 3.97 (d, $J = 15.0$ Hz, 1 H), 2.75 (dd, $J = 7.7, 18.1$ Hz, 1 H), 2.45-2.68 (m, 3 H), 2.32 (ddd, $J = 4.6, 9.1, 18.9$ Hz, 1 H), 2.00 (dddd, $J = 3.2, 5.0, 11.8, 14.8$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 173.9, 169.0, 135.9, 128.9, 128.0, 127.9, 75.5, 54.7, 47.5, 35.6, 26.4, 24.0; HRMS calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_3$ 245.1052, found 245.1059.

Compound 11 (R_f [EtOAc] = 0.15): $[\alpha]_{\text{D}}^{22} +36.4$ (c 1.10, CHCl_3); IR 1778, 1654, 1178 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.19-7.38 (m, 5 H), 4.80-4.86 (m, 1 H), 4.83 (d, $J = 14.4$ Hz, 1 H), 4.36 (d, $J = 14.6$ Hz, 1 H), 3.44 (d, $J = 3.2$ Hz, 2 H), 3.06-3.19 (m, 1 H), 2.83 (dd, $J = 10.9, 18.7$ Hz, 1 H), 2.54 (dd, $J = 5.6, 15.4$ Hz, 1 H), 2.47 (dd, $J = 4.4, 15.4$ Hz, 1 H), 2.36 (dd, $J = 6.0, 18.7$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 174.9, 169.7, 136.2, 128.7, 128.0, 127.7, 76.6, 50.1, 49.0, 36.0, 33.5, 30.6; HRMS calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_3$ 245.1052, found 245.1058.

Compound 12 (R_f [10:1 EtOAc:MeOH] = 0.24): red oil, $[\alpha]_{\text{D}}^{22} -53.0$ (c 1.50, CHCl_3); IR 1748, 1644, 1490 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.19-7.36 (m, 10 H), 5.20-5.28 (m, 2 H), 4.72 (d, $J = 14.7$ Hz, 2 H), 4.46 (d, $J = 14.7$ Hz, 2 H), 4.13 (d, $J = 17.3$ Hz, 2 H), 4.03 (d, $J = 17.3$ Hz, 2 H), 3.46 (dd, $J = 3.8, 13.4$ Hz, 2 H), 3.30 (dd, $J = 3.5, 13.4$ Hz, 2 H), 2.40-2.70 (m, 4 H), 2.00-2.15 (m, 4 H).

Compound (S)-15 (prepared as described for (S)-3 in 98% yield, R_f [EtOAc] = 0.53): Yellow oil; IR 2105, 1686, 1380, 1181 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 7.10-7.40 (m, 5 H), 5.30-5.40 (m, 1 H), 4.74 (s, 1 H), 4.48 (dd, $J = 14.8$ Hz, 2 H), 3.61 (dd, $J = 5.8, 11.6$ Hz, 1 H), 3.26 (dd, $J = 1.8, 11.7$ Hz, 1 H), 2.82 (dd, $J = 6.9, 17.8$ Hz, 1 H), 2.55 (dd, $J = 2.2, 17.8$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 171.3, 165.7, 135.5, 128.5, 127.7, 127.5, 67.2, 52.7, 46.3, 46.0, 37.7; HRMS calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3$ 259.0957, found 259.0955.

Compound 16 (R_f [EtOAc] = 0.40): light yellow powder: mp: 114-116 °C; $[\alpha]_D^{22}$ -38.9 (c 0.90, CHCl₃); IR 1782, 1692, 1399, 1159 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.17-7.38 (m, 5 H), 5.03 (ddd, J = 3.9, 3.9, 5.6 Hz, 1 H), 4.97 (d, J = 15.0 Hz, 1 H), 4.19 (ddd, J = 2.0, 5.9, 5.9 Hz, 1 H), 4.02 (d, J = 15.0 Hz, 1 H), 2.81 (d, J = 3.9 Hz, 2 H), 2.69 (dd, J = 2.0, 18.4 Hz, 1 H), 2.60 (dd, J = 6.0, 18.4 Hz, 1 H); ¹³C NMR (CDCl₃, 50 MHz) δ 173.7 (C), 171.2 (C), 135.0 (C), 129.0 (CH), 128.1 (CH), 128.0 (CH), 75.5 (CH), 57.3 (CH), 44.6 (CH₂), 37.1 (CH₂), 32.6 (CH₂); HRMS calcd for C₁₃H₁₃NO₃ 231.0895, found 231.0895.

Compound 17 (R_f [10:1 EtOAc:MeOH] = 0.44): $[\alpha]_D^{22}$ -13.6 (c 1.10, CHCl₃); IR 1752, 1686, 1195, 1135 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.18-7.38 (m, 10 H), 5.30-5.40 (m, 2 H), 4.50 (d, J = 14.8 Hz, 2 H), 4.44 (d, J = 14.8 Hz, 2 H), 4.10 (s, 4 H), 3.63 (dd, J = 5.9, 11.7 Hz), 3.24 (dd, J = 1.9, 11.7 Hz, 2 H), 2.85 (dd, J = 7.0, 17.9 Hz, 2 H), 2.55 (dd, J = 2.3, 17.9 Hz, 2 H); ¹³C NMR (CDCl₃, 50 MHz) δ 171.1, 168.9, 135.5, 128.7, 127.9, 127.8, 67.9, 67.7, 52.5, 46.2, 37.6; HRMS calcd for C₂₆H₂₈N₂O₇ 480.1897, found 480.1904.

Compound 18: IR 1719, 1690, 1255, 1155 cm⁻¹; *E*-isomer (R_f [10:1 EtOAc:MeOH] = 0.52): $[\alpha]_D^{22}$ +16.7 (c 0.30, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 7.20-7.38 (m, 10 H), 6.77 (s, 2 H), 5.35-5.42 (m, 2 H), 4.53 (d, J = 14.7 Hz, 2 H), 4.47 (d, J = 14.7 Hz, 2 H), 3.66 (dd, J = 5.9, 11.7 Hz), 3.28 (dd, J = 1.9, 11.7 Hz, 2 H), 2.88 (dd, J = 7.0, 17.9 Hz, 2 H), 2.58 (dd, J = 2.3, 17.9 Hz, 2 H); ¹³C NMR (CDCl₃, 75 MHz) δ 171.2, 164.0, 135.6, 133.6, 128.8, 128.1, 127.9, 68.1, 52.6, 46.3, 37.7; *Z*-isomer (R_f [10:1 EtOAc:MeOH] = 0.51): ¹H NMR (CDCl₃, 300 MHz) δ 7.18-7.36 (m, 10 H), 6.23 (s, 2 H), 5.29-5.36 (m, 2 H), 4.52 (d, J = 14.7 Hz, 2 H), 4.39 (d, J = 14.7 Hz, 2 H), 3.61 (dd, J = 5.8, 11.8 Hz), 3.31 (dd, J = 1.8, 11.7 Hz, 2 H), 2.82 (dd, J = 7.0, 17.8 Hz, 2 H), 2.58 (dd, J = 1.0, 17.5 Hz, 2 H); ¹³C NMR (CDCl₃, 75 MHz) δ 171.3, 164.4, 135.7, 130.0, 128.8, 128.1, 127.8, 67.9, 52.5, 46.3, 37.4.

Compound 19: Commercial Red-Al[®] solution (0.25 mL, 65 wt% in toluene) was diluted with dry toluene (5 mL). To a solution of lactone **8a** (240 mg, 0.98 mmol) in dry THF (20 mL) was added, dropwise, the diluted Red-Al solution (4.3 mL, 0.68 mmol) at -78 °C under argon. The mixture at -78 °C 4 h, at which time methanol (1.0 mL) and then saturated aqueous NH₄Cl (8 mL) were added. The reaction mixture was allowed to warm slowly to rt. The organic layer was separated and the aqueous layer was back-extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography (2:1 CH₂Cl₂:Acetone) to give unreacted **4** (19 mg) and a diastereomeric mixture of lactol **19** (R_f = 0.35, 209 mg, 94%) as a colorless oil: IR (neat) 3354 (br.), 2931, 1625 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz), δ (major diastereomer): 7.12-7.30 (m, 5 H), 5.50 (d, J = 4.8 Hz, 1 H), 5.08 (d, J = 14.8 Hz, 1 H), 4.40-4.48 (m, 1

H), 3.98 (q, $J = 7.6$ Hz, 1 H), 3.94 (d, $J = 15.0$ Hz, 1 H), 1.60-2.45 (m, 6 H); δ (minor diastereomer): 7.12-7.30 (m, 5 H), 5.44 (t, $J = 3.6, 3.4$ Hz, 1 H), 5.34 (d, $J = 15.0$ Hz, 1 H), 4.22-4.30 (m, 1 H), 3.80 (d, $J = 15.0$ Hz, 1 H), 3.71 (q, $J = 5.3$ Hz, 1H), 2.62-2.76 (m, 1 H), 1.60-2.45 (m, 5 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ (major) 171.2, 136.8, 128.6, 128.1, 127.5, 97.0, 72.5, 57.6, 48.1, 41.6, 27.5, 24.8; (minor) 171.1, 136.7, 128.3, 128.0, 127.4, 97.6, 75.3, 57.5, 47.3, 39.0, 27.1, 24.5; HRMS calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3$ 247.1208, found 247.1208.

Compound 20: $\text{Ph}_3\text{P}^+\text{CH}_2\text{OMe Cl}^-$ (1.67 g, 4.86 mmol) was suspended in dry THF (20 mL) and cooled to -60 °C. BuLi (2.2 mL, 4.45 mmol, 2M in hexane) was added, dropwise, to the suspension. After addition was complete, the resulting red solution was gradually warmed (~ 40 min) to -20 °C and then re-cooled to -40 °C. A solution of **19** (500 mg, 2.0 mmol) in dry THF (4 mL) was added via cannula and after addition was complete, the reaction temperature was gradually increased to rt (2 h). Saturated aqueous NH_4Cl (10 mL) was added and the organic layer was separated and the aqueous layer was back-extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash chromatography (1:1 then 1:3 pet. ether: EtOAc and finally EtOAc) to afford a 5.5:1 ratio of *Z*:*E* diastereomeric mixture of the enol ether (R_f [1:3 pet. ether:EtOAc] = 0.16, 407 mg, 74%). IR (neat) 3366 (br.), 2931, 1613 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz), δ (*E*-isomer): 7.10-7.30 (m, 5 H), 6.22 (d, $J = 12.6$ Hz, 1 H), 5.20 (d, $J = 15.1$ Hz, 1 H), 4.62 (dt, $J = 8.0, 15.1$ Hz, 1 H), 3.70-4.10 (m, 2 H), 3.40 (s, 3 H), 3.12-3.30 (m, 1 H), 1.50-2.60 (m, 6 H); δ (*Z*-isomer): 7.10-7.30 (m, 5 H), 5.88 (d, $J = 6.2$ Hz, 1 H), 5.16 (d, $J = 15.3$ Hz, 1 H), 4.30 (dd, $J = 7.8, 14.2$ Hz, 1 H), 3.70-4.10 (m, 2 H), 3.50 (s, 3 H), 3.12-3.30 (m, 1 H), 1.50-2.60 (m, 6 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ (*E*-isomer) 169.9, 148.4, 136.8, 128.2, 127.2, 126.9, 99.0, 66.0, 59.4, 55.6, 48.4, 28.3, 27.0, 25.0; (*Z*-isomer) 170.1, 147.7, 137.0, 128.1, 127.1, 126.8, 102.2, 65.8, 60.1, 55.6, 47.4, 28.0, 25.1, 23.2; HRMS calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$ 275.1521, found 275.1526.

A solution of the above alcohol (370 mg, 1.34 mmol) in dry 1,2-dichloroethane (20 mL) containing Bu_4NI (5 mg) was cooled to 0 °C, and *i*- Pr_2NEt (0.94 mL, 5.36 mmol) and MOMCl (0.2 mL, 2.7 mmol) were added. Then the solution was refluxed overnight. The reaction mixture was cooled to rt and then at 0 °C. Saturated aqueous Na_2CO_3 (1 mL) and brine (5 mL) were added to the reaction mixture and the organic layer was separated and dried over Na_2SO_4 . After removing the solvent, the resulting oil was purified by flash column eluted with pet. ether:EtOAc (1:1-1:2) to give 381 mg of MOM ether **20** (R_f [1:2 pet. ether:EtOAc] = 0.31) as colorless oil in 89 % yield: $[\alpha]_D^{23} -36.9$ (*c* 1.10, CH_2Cl_2); IR (neat) 2931, 1637 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz), δ (*E*-isomer): 7.16-7.38 (m, 5 H), 6.31 (d, $J = 12.6$ Hz, 1 H), 5.40 (d, $J = 14.3$ Hz, 1 H), 4.66-4.80 (m, 1 H), 4.48-4.64 (m, 2 H), 4.02 (d, J

= 15.0 Hz, 1 H), 3.72-3.88 (m, 1 H), 3.53 (s, 3 H), 3.30-3.48 (m, 1 H), 3.32 (s, 3 H), 1.85-2.75 (m, 6 H); δ (Z-isomer): 7.16-7.38 (m, 5 H), 5.97 (d, $J = 6.2$ Hz, 1 H), 5.46 (d, $J = 14.7$ Hz, 1 H), 4.48-4.64 (m, 2 H), 4.32-4.48 (m, 1 H), 4.00 (d, $J = 15.0$ Hz, 1 H), 3.72-3.88 (m, 1 H), 3.61 (s, 3 H), 3.30-3.48 (m, 1 H), 3.32 (s, 3 H), 1.85-2.75 (m, 6 H); ^{13}C NMR (CDCl_3 , 75 MHz), δ (Z-isomer): 168.8, 147.3, 137.0, 127.8, 127.2, 126.5, 102.0, 94.8, 72.1, 58.8, 57.4, 54.8, 47.6, 28.2, 23.0, 22.8; δ (E-isomer): 168.7, 148.3, 136.8, 127.9, 127.1, 126.6, 98.4, 94.9, 72.1, 58.5, 55.2, 54.9, 48.2, 28.1, 27.0, 22.7; HRMS calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_4$ (MH^+) 320.1862, found 320.1864.

Compound 21: Sodium metal (166 mg, 7.2 mmol) was added to liquid NH_3 (20 mL) at -78 °C under argon. The mixture was stirred for 10 min, and a solution of *N*-benzyl lactam **20** (380 mg, 1.2 mmol) in THF (2 mL) was added, dropwise, via cannula. The solution was stirred at -78 °C for 3 h and then solid NH_4Cl (250 mg) was added. The solution was gradually warmed to rt, the residue was extracted with CH_2Cl_2 . The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography (2:1 CH_2Cl_2 :Acetone) to give the debenzylated lactam ($R_f = 0.33$, 272 mg, 100%) as a colorless oil: $[\alpha]_D^{22} +11.1$ (c 0.50, CHCl_3); IR (neat) 3200, 2931, 1660 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 6.58 (s, 1 H), 6.35 (s, 1 H), 6.16 (d, $J = 12.6$ Hz, 1 H), 5.80 (d, $J = 6.2$ Hz, 1 H), 4.35-4.55 (m, 5 H), 4.03-4.15 (q, $J = 7.0$ Hz, 1 H), 3.60-3.73 (m, 2 H), 3.36 (s, 3 H), 3.29 (s, 3 H), 3.16 (s, 6 H), 3.05-3.25 (m, 2 H), 1.70-2.40 (m, 10 H), 1.40-1.60 (m, 2 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 171.2, 171.1, 149.6, 148.6, 100.1, 96.8, 95.1, 95.0, 69.7, 69.5, 59.2, 56.4, 56.1, 55.5, 55.4, 55.3, 29.7, 26.3, 26.2, 26.1, 24.4, 24.3; HRMS calcd for $\text{C}_{11}\text{H}_{20}\text{NO}_4$ (MH^+) 230.1392, found 230.1401.

The debenzylated lactam (270 mg, 1.18 mmol) was dissolved in THF (8 mL) and aqueous 1M HCl (4 mL) was added. The mixture was stirred at rt for 3 h and then solid Na_2CO_3 was added. The organic layer was separated and aqueous layer was back-extracted with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was dissolved in 95% EtOH (10 mL) and treated with NaBH_4 (90 mg, 2.38 mmol). After 3 h, the mixture was quenched with saturated aqueous NH_4Cl (1 mL). The mixture was evaporated and then extracted with CH_2Cl_2 . The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by flash chromatography (5:1 EtOAc:MeOH) to give **21** ($R_f = 0.31$, 188 mg, 76 %). A small amount of starting material (10 mg) was also obtained. $[\alpha]_D^{23} +23.0$ (c 0.65, CHCl_3); IR (neat) 3284 (br.), 2930, 1651 cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ 6.97 (br. s, 1 H), 4.73 (d, $J = 7.0$ Hz, 1 H), 4.62 (d, $J = 7.0$ Hz, 1 H), 3.84-3.94 (m, 1 H), 3.68-3.76 (m, 2 H), 3.40-3.50 (m, 1 H), 3.39 (s, 3 H), 2.50-2.00 (m, 3 H), 1.80-1.60 (m, 5 H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 172.1, 95.2, 70.2, 62.1, 56.4, 56.0, 28.6, 28.5, 26.7, 24.4; HRMS calcd for $\text{C}_{10}\text{H}_{19}\text{NO}_4$ 217.1314, found 217.1323.

Compound 22a: A mixture of **21** (185 mg, 0.85 mmol), tosyl chloride (243 mg, 1.3 mmol), Et₃N (0.23 mL, 1.7 mmol) and DMAP (10 mg) in dry CH₂Cl₂ (10 mL) was stirred at rt for 20 h under argon. The reaction mixture was washed with saturated aqueous NH₄Cl and the organic layer was separated and dried (Na₂SO₄), filtered and concentrated. The residue was purified by column chromatography (2:1 CH₂Cl₂:Acetone) to give the tosylate (R_f = 0.25, 286 mg, 91%) as a colorless oil: [α]²³_D +18.8 (c 0.80, CHCl₃); IR (neat) 2930, 1658 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.77 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 6.26 (br. s, 1 H), 4.70 (d, *J* = 7.0 Hz, 1 H), 4.58 (d, *J* = 7.0 Hz, 1 H), 4.04 (t, *J* = 6.0 Hz, 2 H), 3.78-3.90 (m, 1 H), 3.35 (s, 4 H), 2.44 (s, 3 H), 2.05-2.60 (m, 3 H), 1.64-1.88 (m, 4 H), 1.38-1.56 (m, 1 H); ¹³C NMR (CDCl₃, 50 MHz) δ 171.6, 144.8, 132.8, 129.8, 127.8, 95.2, 69.8, 69.5, 56.0, 55.9, 27.8, 26.8, 24.9, 24.2, 21.6; HRMS calcd for C₁₇H₂₆NO₆S (MH⁺) 372.1481, found 372.1491.

Prewashed NaH (56 mg, 60% in dispersion oil) was suspended in dry THF (7 mL) and a solution of the above tosylate (263 mg, 0.70 mmol) in dry THF (3 mL) was added via canula. The mixture was stirred at rt and the reaction was monitored by TLC. After the starting material was consumed, the mixture was cooled in ice-water bath and saturated aqueous NH₄Cl (5 mL) was carefully added. The organic layer was separated and aqueous layer was back-extracted with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude residue was purified by column chromatography (2:1 CH₂Cl₂:Acetone) to give the indolizidinone **22a** (R_f = 0.32, 134 mg, 95%) as a colorless oil: [α]²²_D +1.88 (c 4.0, CHCl₃); IR 2943, 1631, 1455 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.73 (d, *J* = 6.9 Hz, 1 H), 4.62 (d, *J* = 6.9 Hz, 1 H), 4.01 (quint, *J* = 2.1, 4.0 Hz, 1 H), 3.40-3.62 (m, 3 H), 3.39 (s, 3 H), 2.28-2.52 (m, 2 H), 2.20 (dddd, *J* = 2.2, 4.0, 8.7, 14.2 Hz, 1 H), 1.64-2.02 (m, 5 H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.7, 95.0, 68.6, 62.1, 55.8, 45.1, 27.5, 26.6, 25.5, 22.0; HRMS calcd for C₁₀H₁₇NO₃ 199.1208, found 199.1207.

Compound 22b: MOM ether **22a** (80 mg, 0.40 mmol) was dissolved in 1 M methanolic HCl (5 mL) and the mixture was heated at 60-65 °C (oil bath) for 100 min. The reaction mixture was cooled to rt, solid Na₂CO₃ was added and the reaction mixture was concentrated. The residue was extracted with MeOH and the methanol extract was filtered through a pad of Celite. The filtrate was concentrated and the crude alcohol was purified by column chromatography (10:1 EtOAc:MeOH) to afford **22b** (R_f = 0.12, 59 mg, 95 %) as a white solid. mp: 104-105 °C, Lit.^{13e} mp 98-100 °C; [α]²²_D - 44.4 (c 2.70, CHCl₃), Lit.^{13e} [α]²²_D - 30.6 (c 2, CHCl₃); IR 3378 (br.), 1601, 1478 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.13 (quint, *J* = 2.2, 4.2 Hz, 1 H), 3.40-3.58 (m, 3 H), 2.91 (s, 1 H), 2.51 (ddd, *J* = 7.4, 11.8, 18.5 Hz, 1 H), 2.33 (ddd, *J* = 0.4, 7.4, 17.9 Hz, 1 H), 2.08 (dddd, *J* = 1.7, 3.9, 7.3, 14.1 Hz, 1 H), 1.64-

2.02 (m, 5 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 169.3, 63.2, 62.6, 45.2, 28.3, 27.5, 26.1, 22.0; HRMS calcd for $\text{C}_8\text{H}_{13}\text{NO}_2$ 155.0946, found 155.0946.

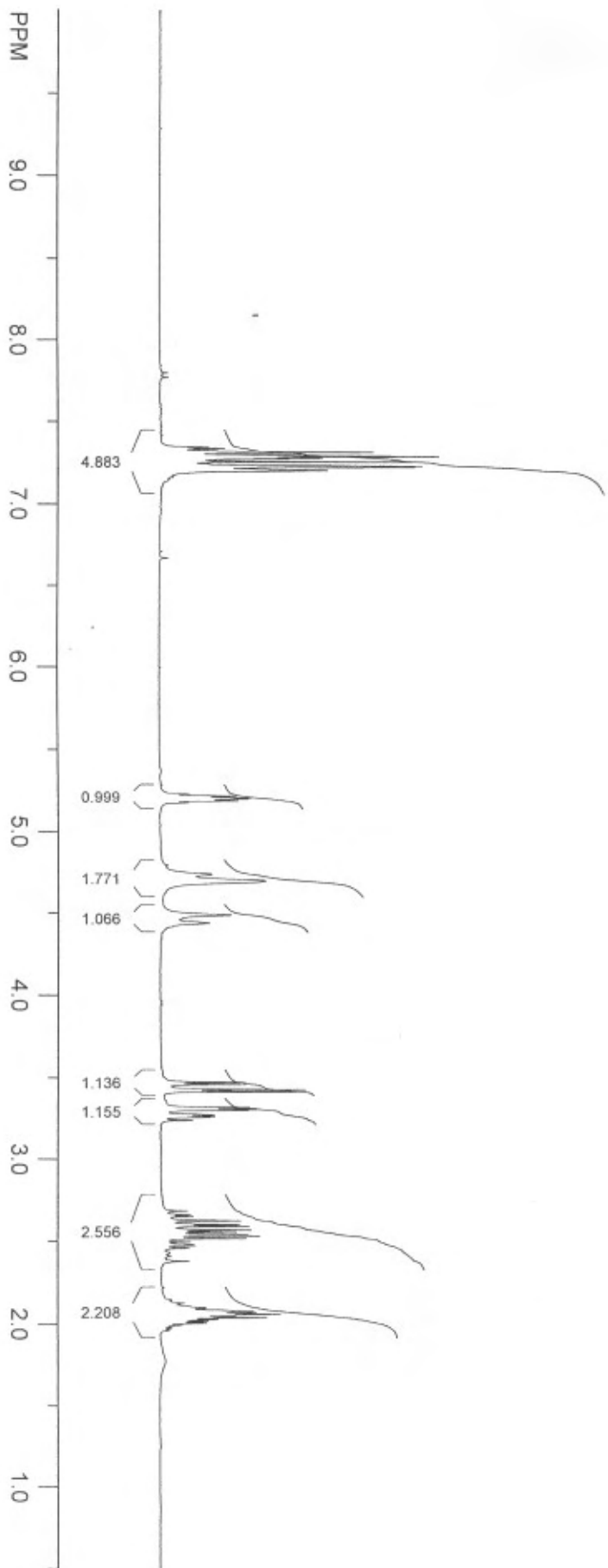
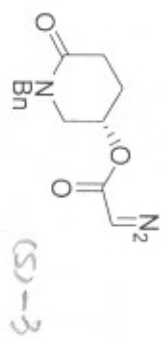
Indolizidine (23): The indolizidinone **22b** (17 mg, 0.11 mmol) was dissolved in dry THF (2 mL) and cooled to 0 °C. $\text{BH}_3\cdot\text{SMe}_2$ in ether (0.35 mL, 5 M) was added dropwise to the solution and the mixture was stirred at 0 °C for 30 min and then at rt for 22 h. The reaction mixture was cooled to 0 °C and then EtOH (4 mL) was carefully added. The reaction mixture was concentrated and the resulting white solid was redissolved in EtOH (8 mL) and refluxed for 24 h. The mixture was cooled to rt and five drops of concentrated HCl was added. EtOH was removed under reduced pressure and the resulting white solid was dissolved in distilled water (5 mL) and washed with CH_2Cl_2 . The aqueous solution was concentrated and the residue was purified using ion exchange chromatography (Dowex 50x2-400 ion exchange resin, 200-400 mesh, eluent: water and then 5% NH_4OH solution). The combined fractions containing **23** (R_f [MeOH] = 0.06) was concentrated by fractional distillation using a vigreux column. The remaining aqueous mixture was treated with three drops of concentrated HCl and then evaporated under reduced pressure to afford **23.HCl** (20 mg, 88%) as a white solid. mp: 128-130 °C; $[\alpha]_D^{22} +12.5$ (c 0.60, CH_3OH); IR 3354 (br.) cm^{-1} ; ^1H NMR (D_2O , 300 MHz) δ 4.30 (s, 1 H), 3.540-3.70 (m, 2 H), 3.22-3.36 (m, 1 H), 2.90-3.12 (m, 2 H), 1.66-2.24 (m, 8 H); ^{13}C NMR (CD_3OD , 75 MHz) δ 70.5 (CH), 64.0 (CH), 54.1 (CH_2), 53.0 (CH_2), 30.8 (CH_2), 24.8 (CH_2), 20.4 (CH_2), 19.1 (CH_2); HRMS calcd for $\text{C}_8\text{H}_{16}\text{NO}$ (MH^+) 142.1232, found 142.1229.

$\text{Rh}_2(\text{S-PTTL})_4$: dirhodium(II) tetrakis[*(S)*-*N*-phthaloyl-*tert*-leucinante]

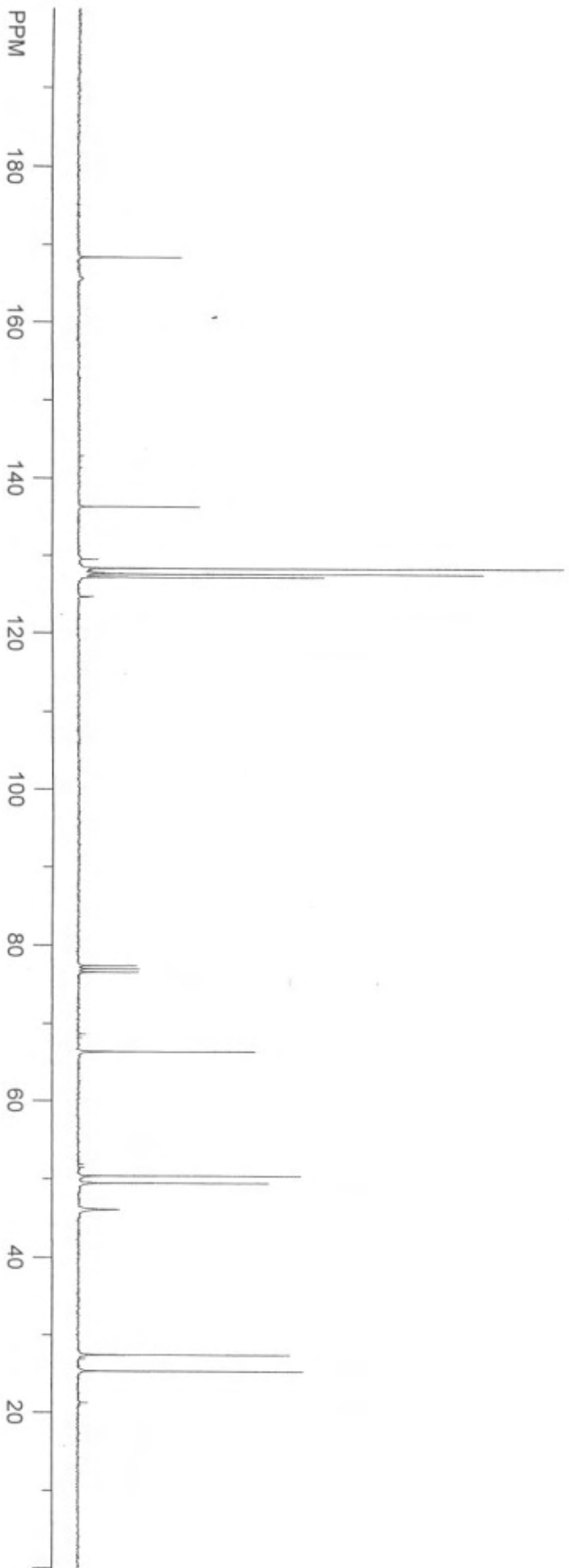
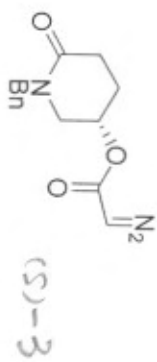
$\text{Rh}_2(\text{5R-MEPY})_4$: dirhodium(II) tetrakis[methyl (*5R*)-pyroglutamate]

$\text{Rh}_2(\text{4R-MEOX})_4$: dirhodium(II) tetrakis[methyl 4(*R*)-2-oxazolidinone-4-carboxylate]

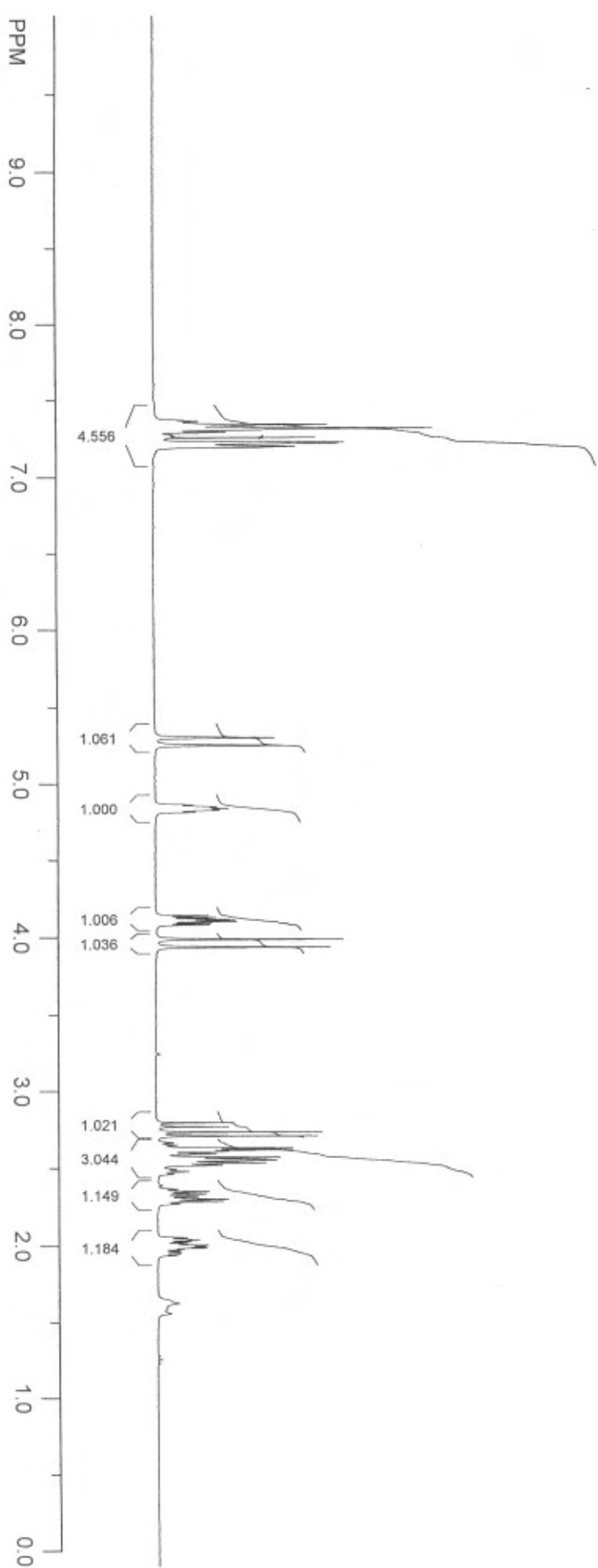
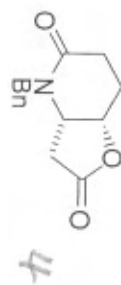
$\text{Rh}_2(\text{4R-MPPIM})_4$: dirhodium(II) tetrakis[methyl 4(*R*)-1-(3-phenylpropanoyl)-2-imidazolidinone-4-carboxylate]



GFA30

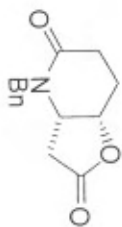


GFA113A

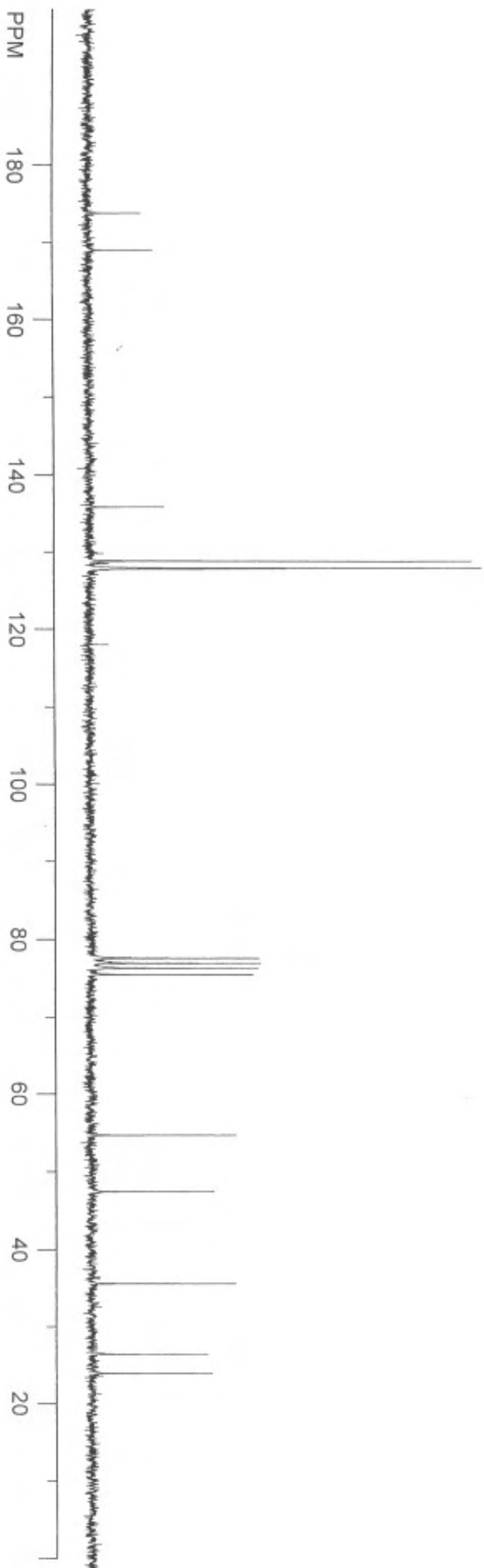


ESI-12

GFA113A



4

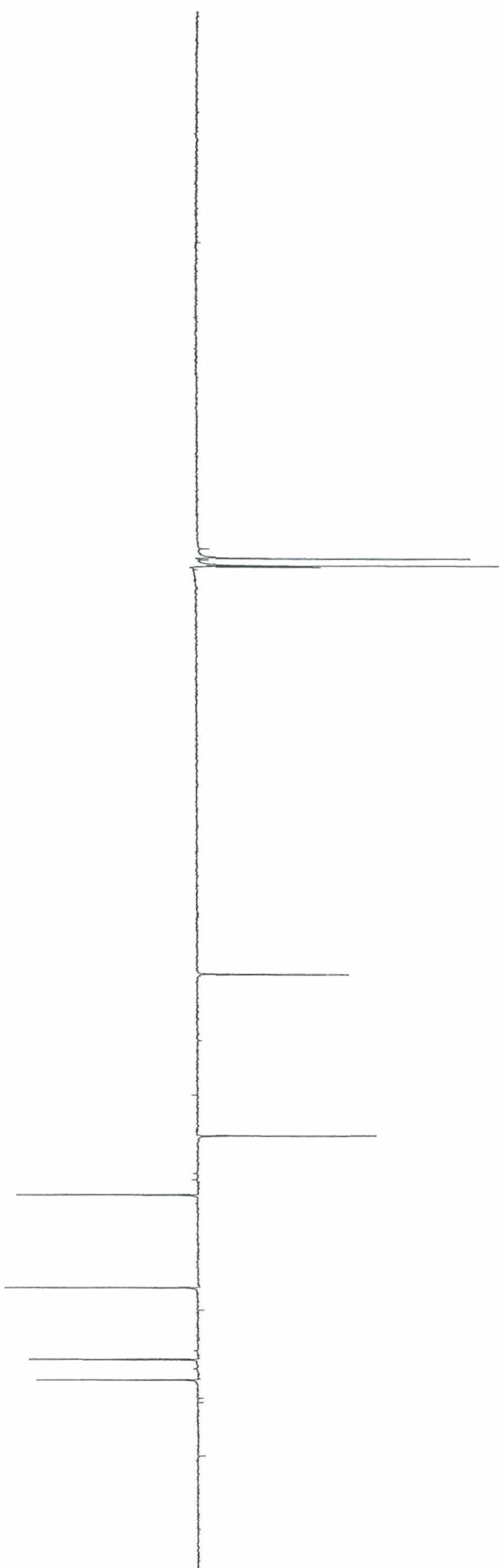


DEPT-135

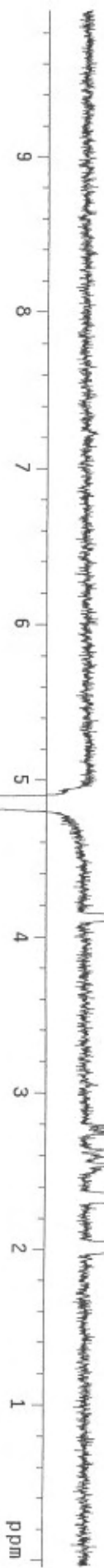
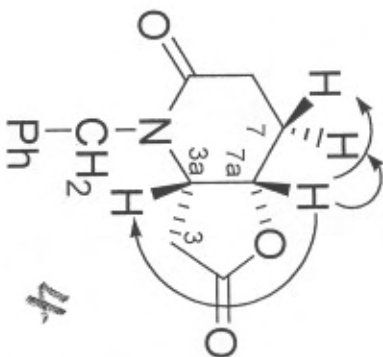


4

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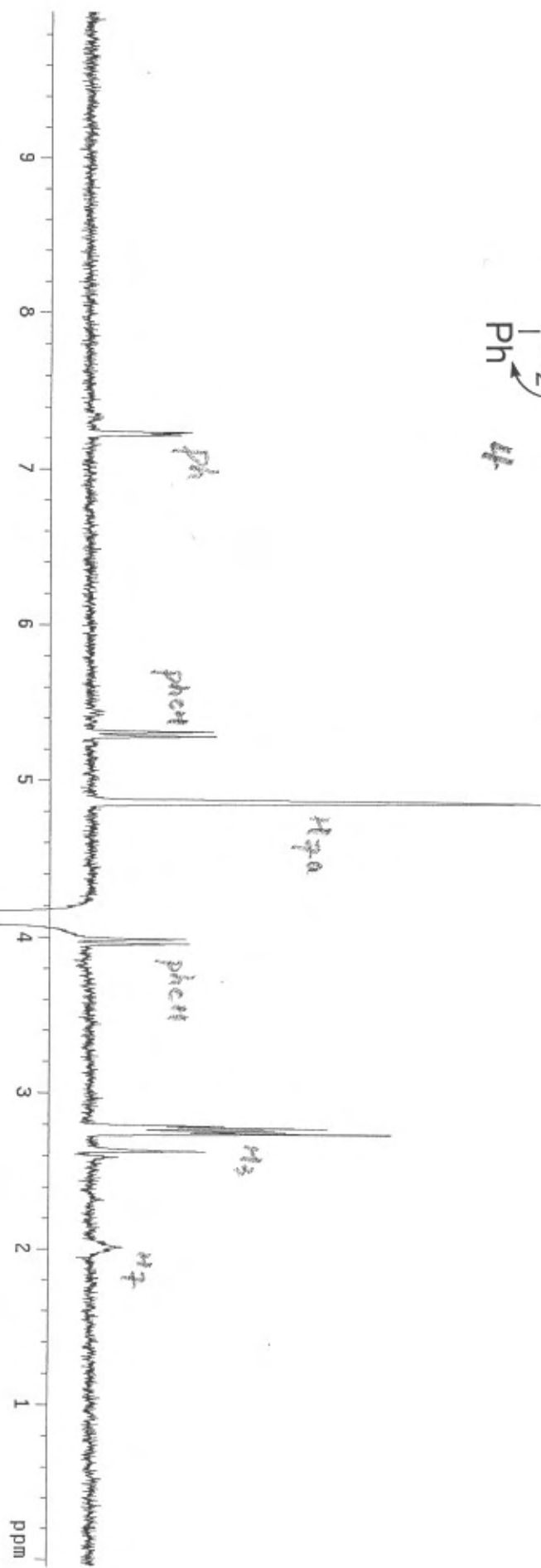
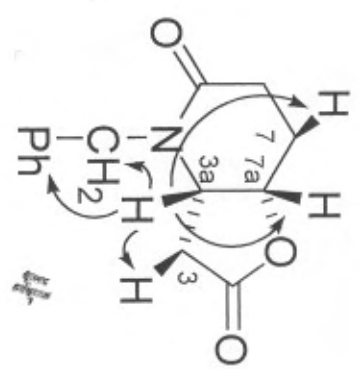


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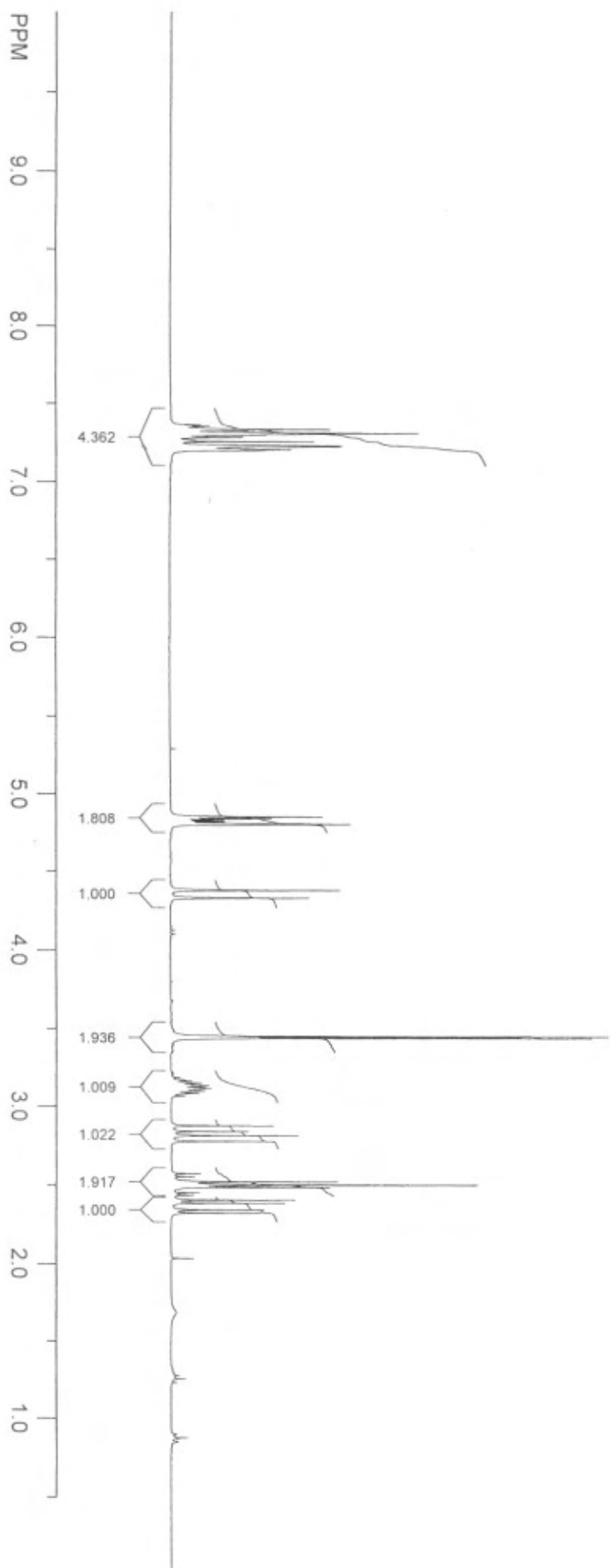
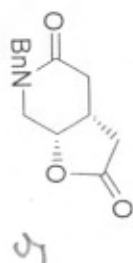


H_{3a}

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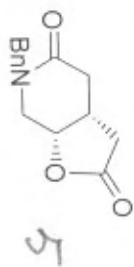


GFA46B

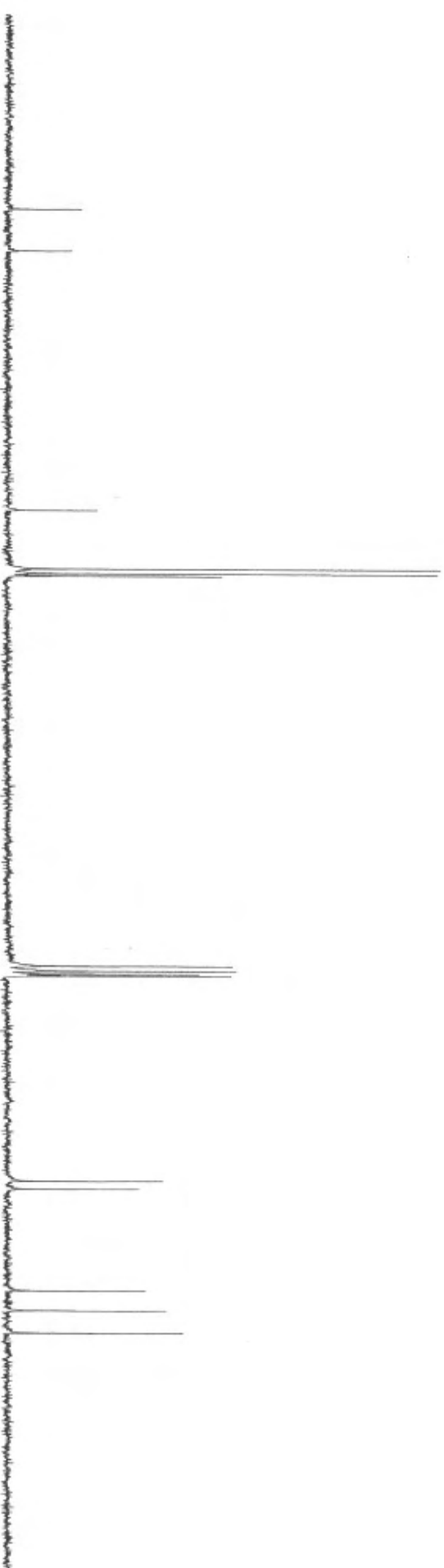


ESI-17

GFA046B

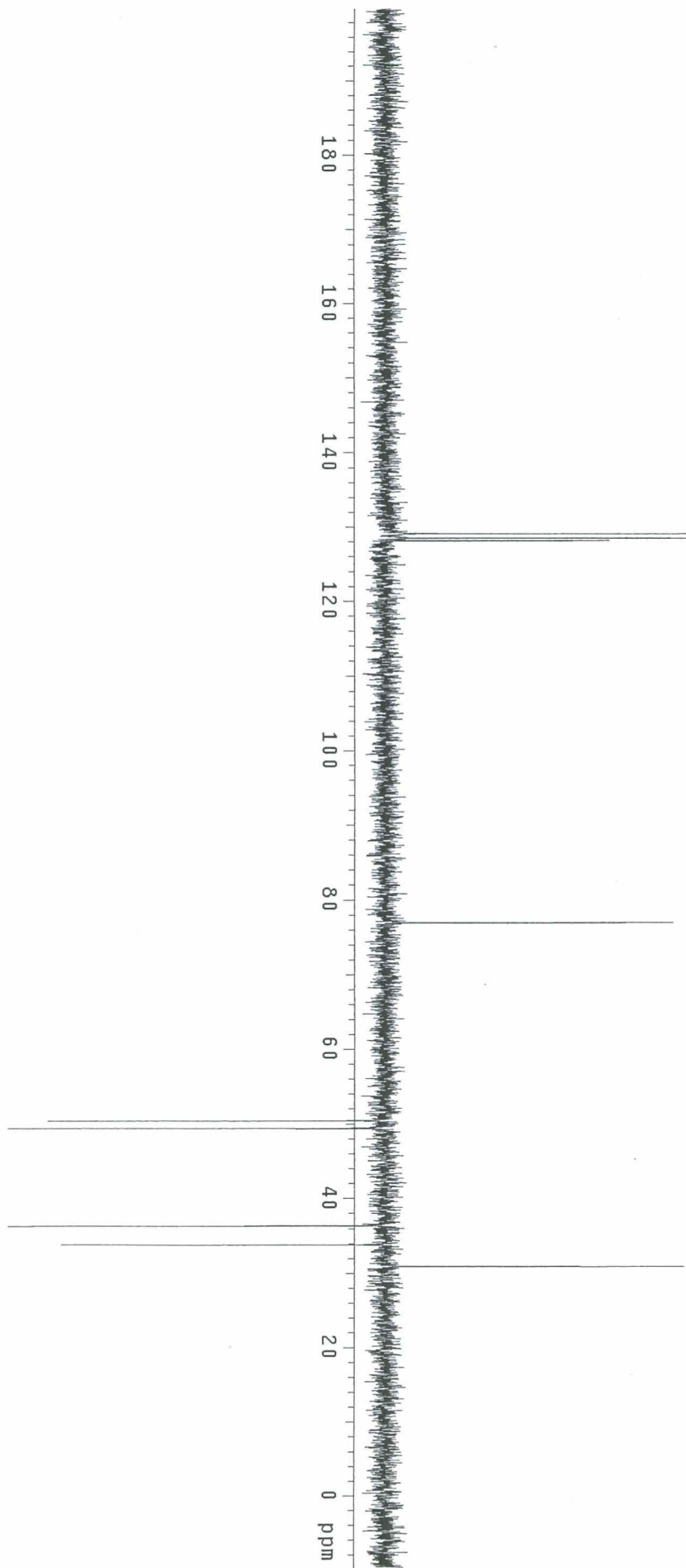
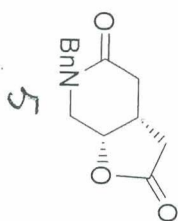


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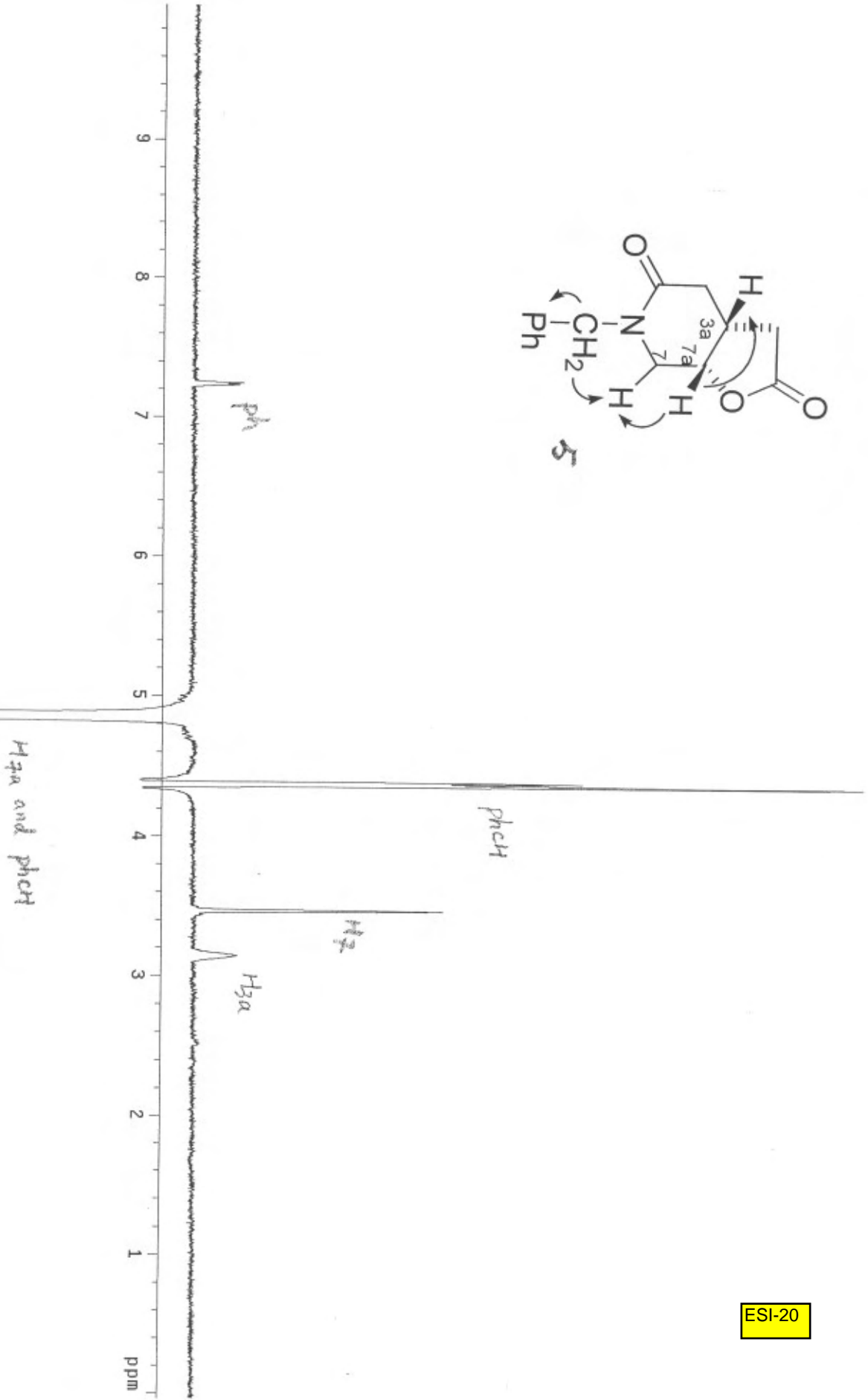
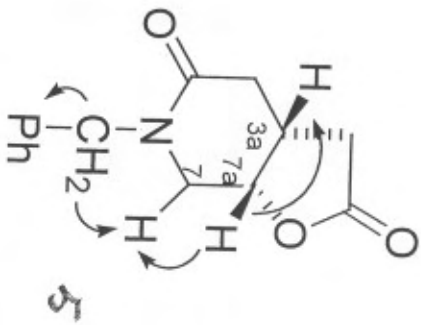


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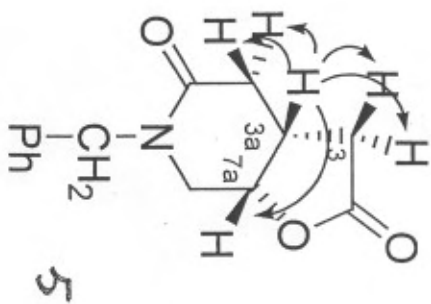
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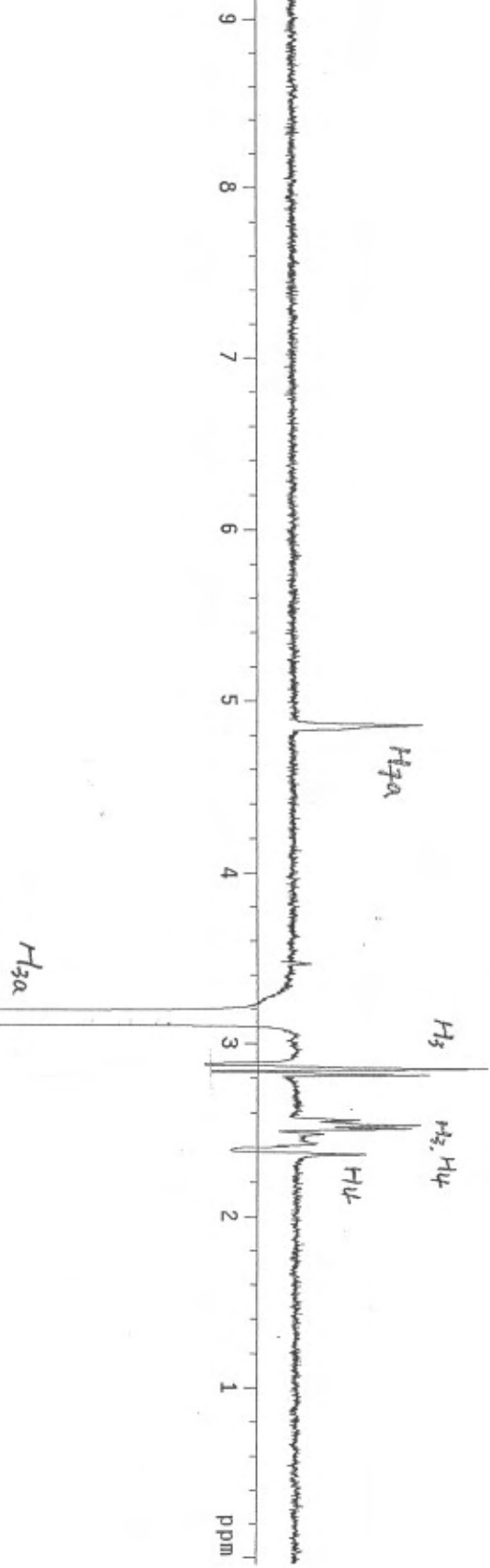
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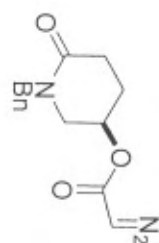
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5

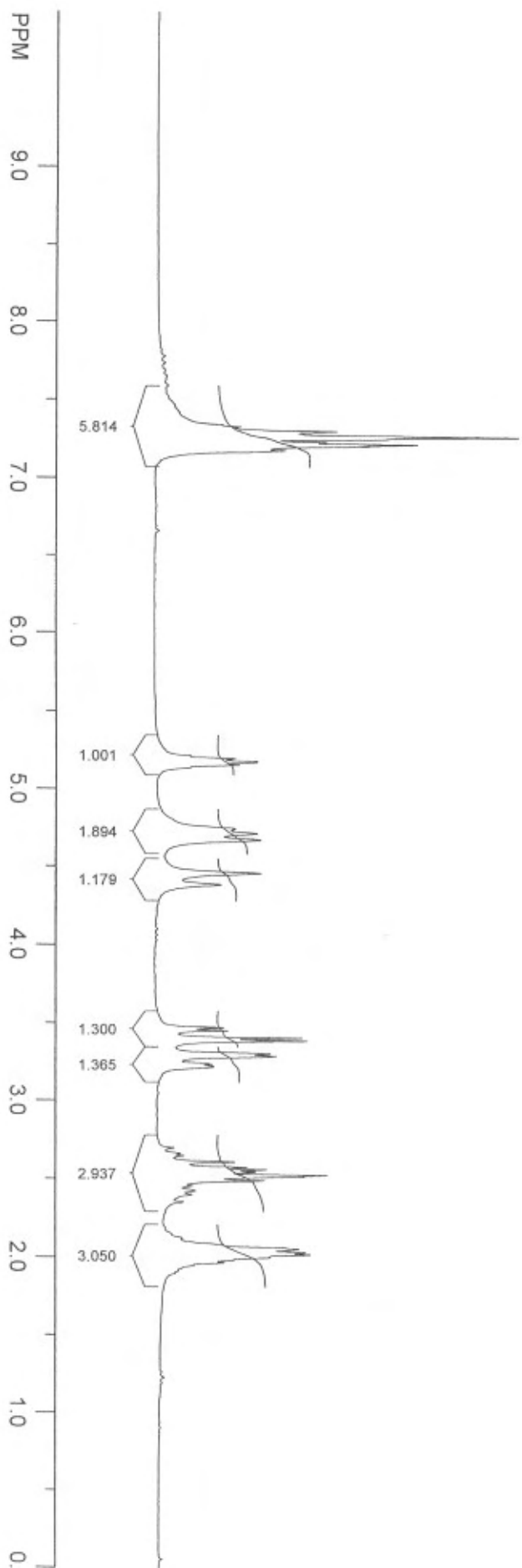


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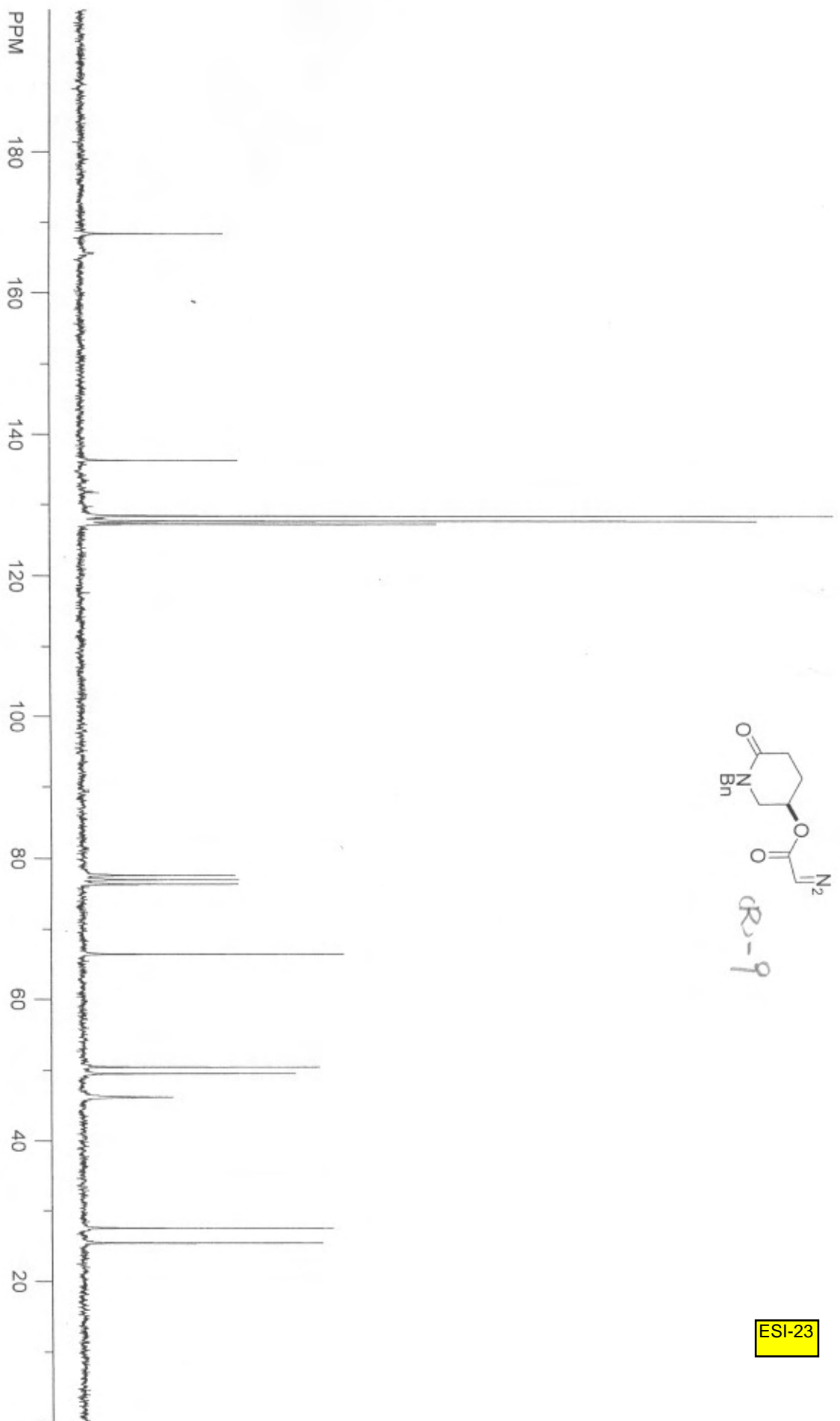
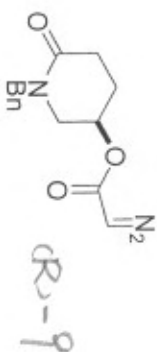


CR-9

ESI-22

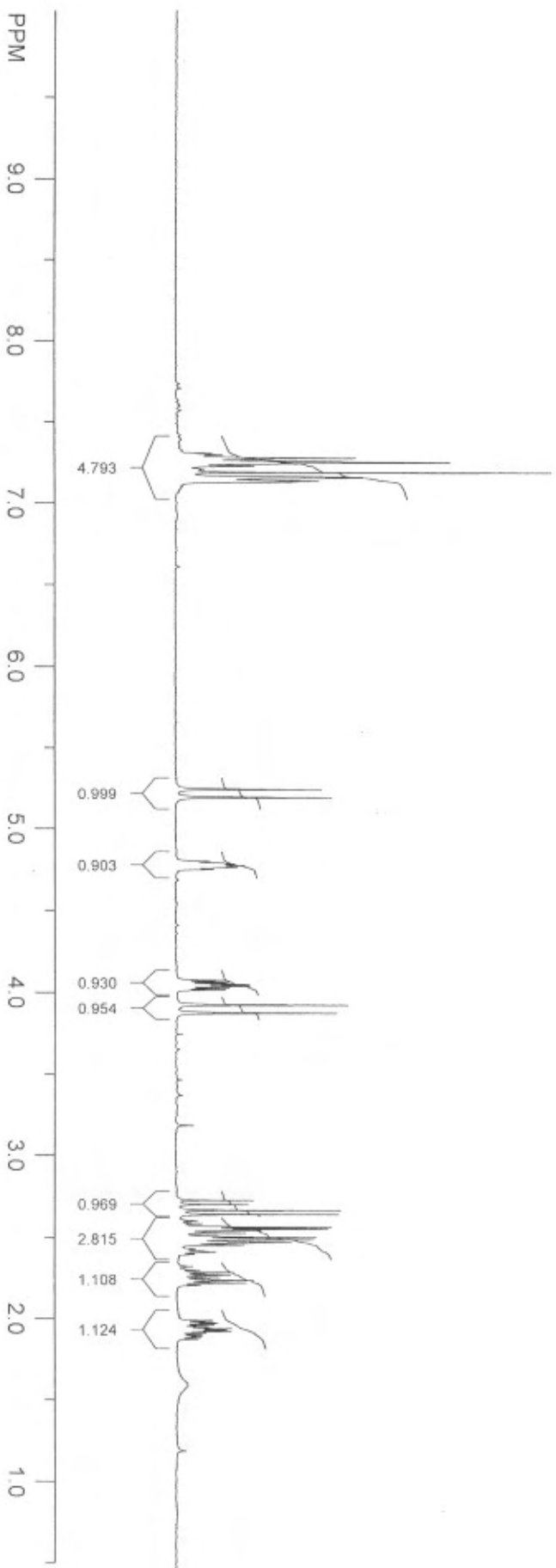
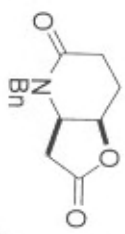


GF B066A



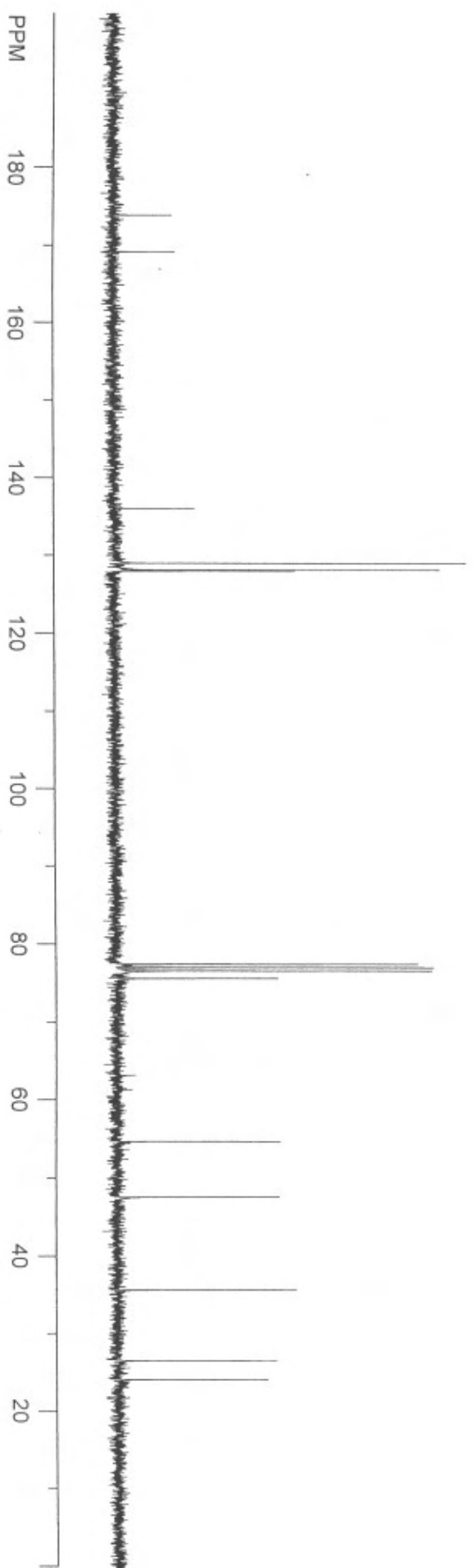
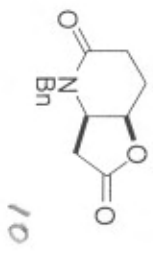
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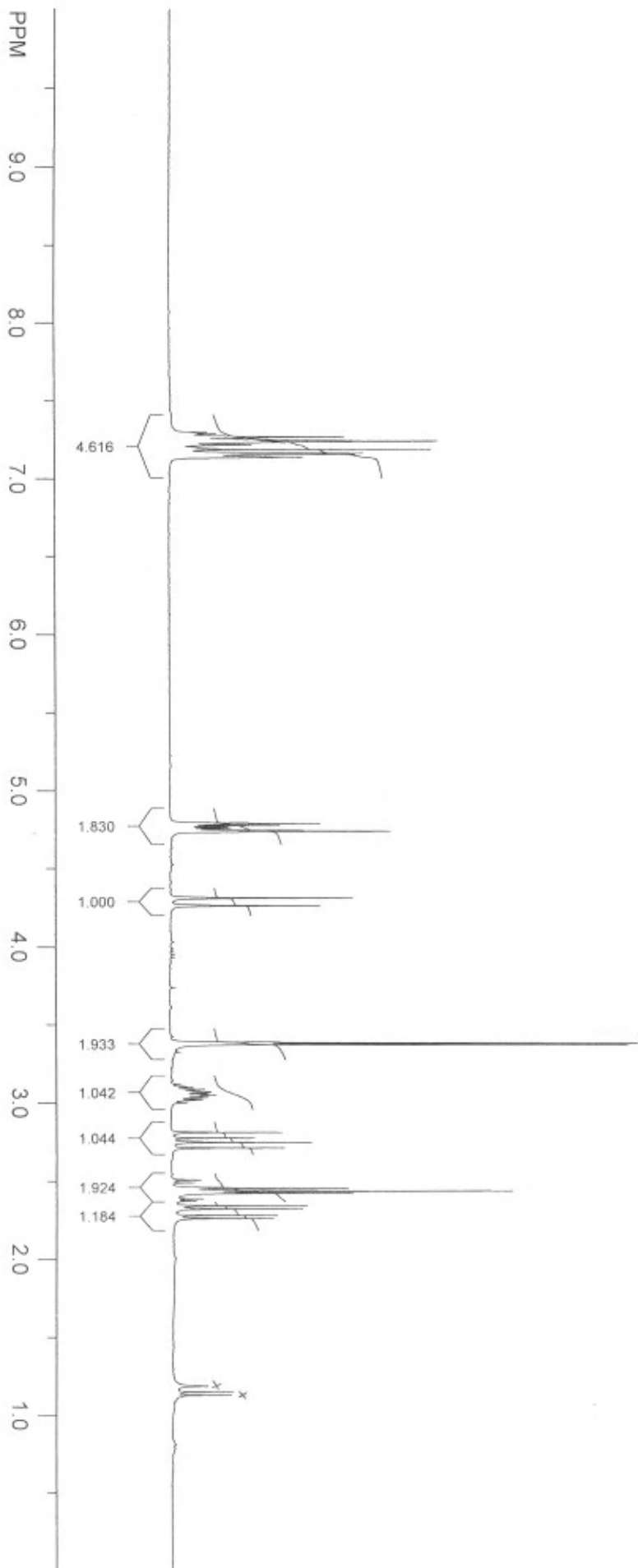
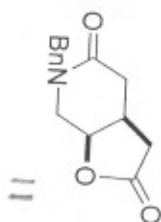


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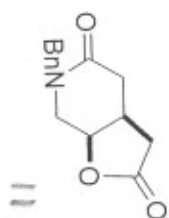


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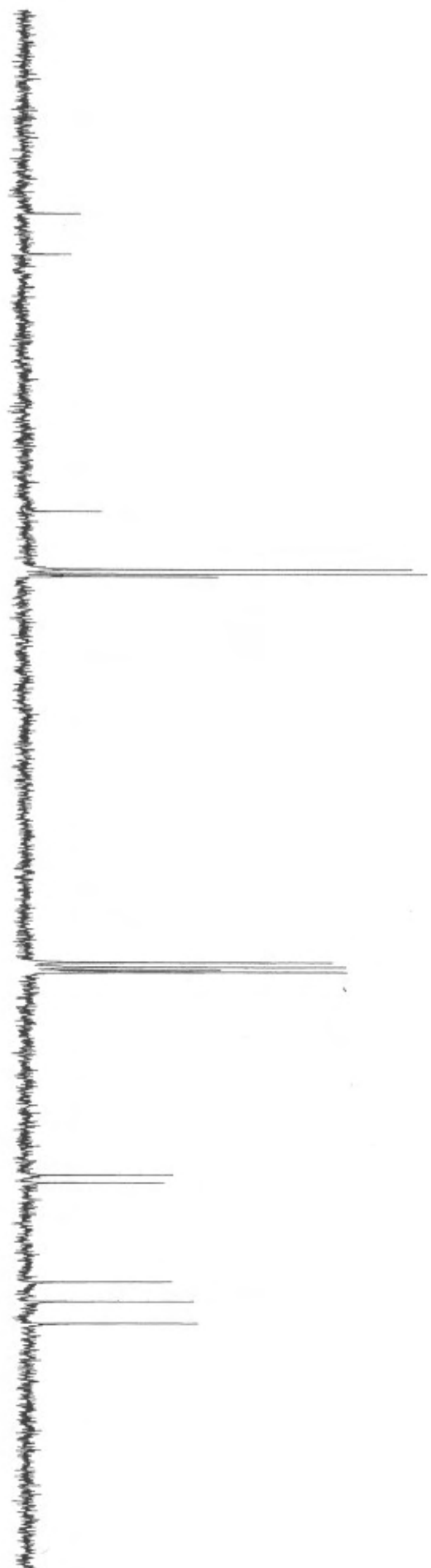


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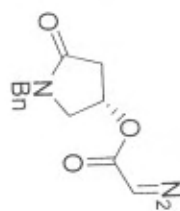
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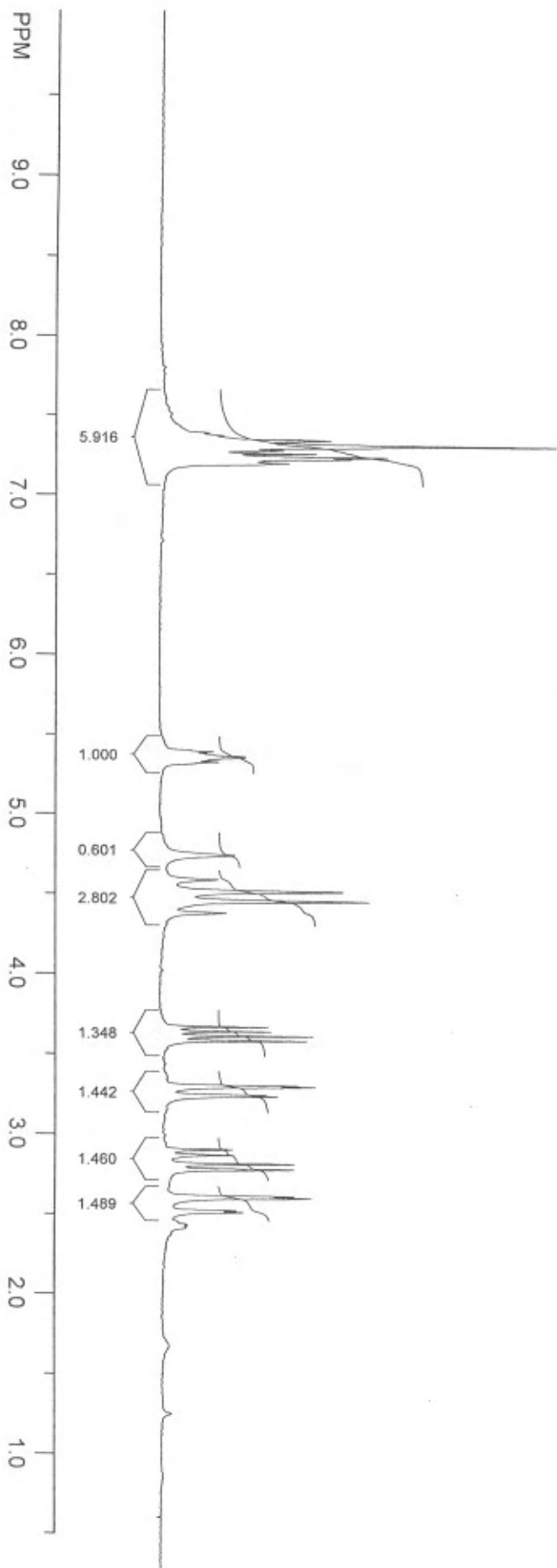
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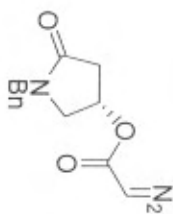
ESI-27



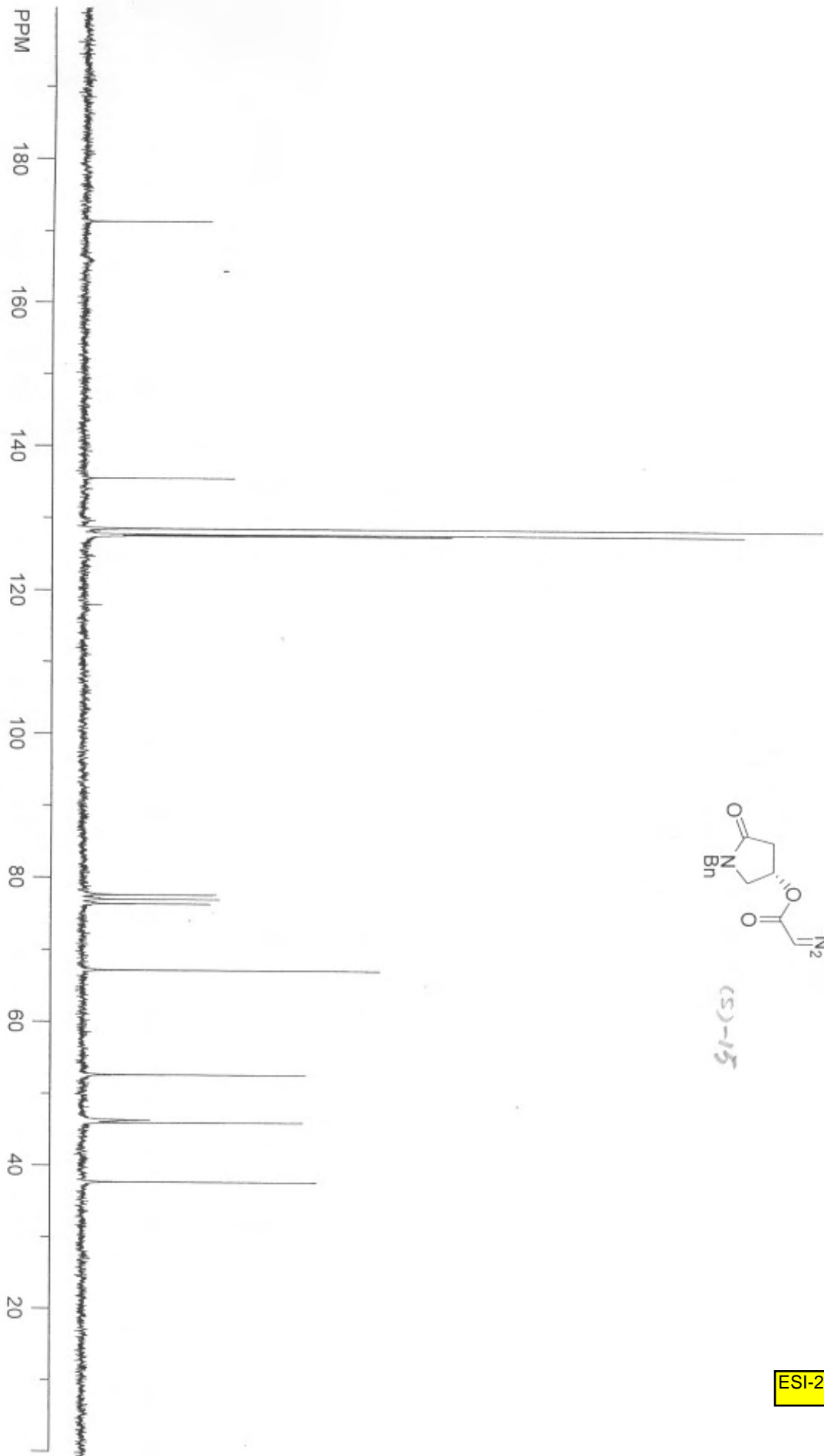
(S)-15



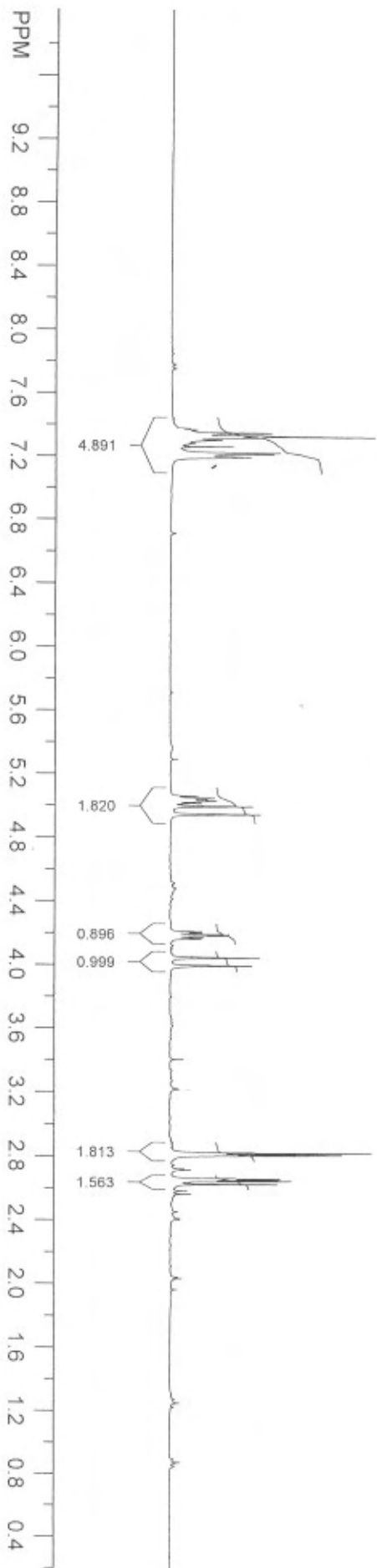
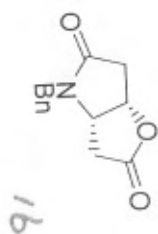
GFA059



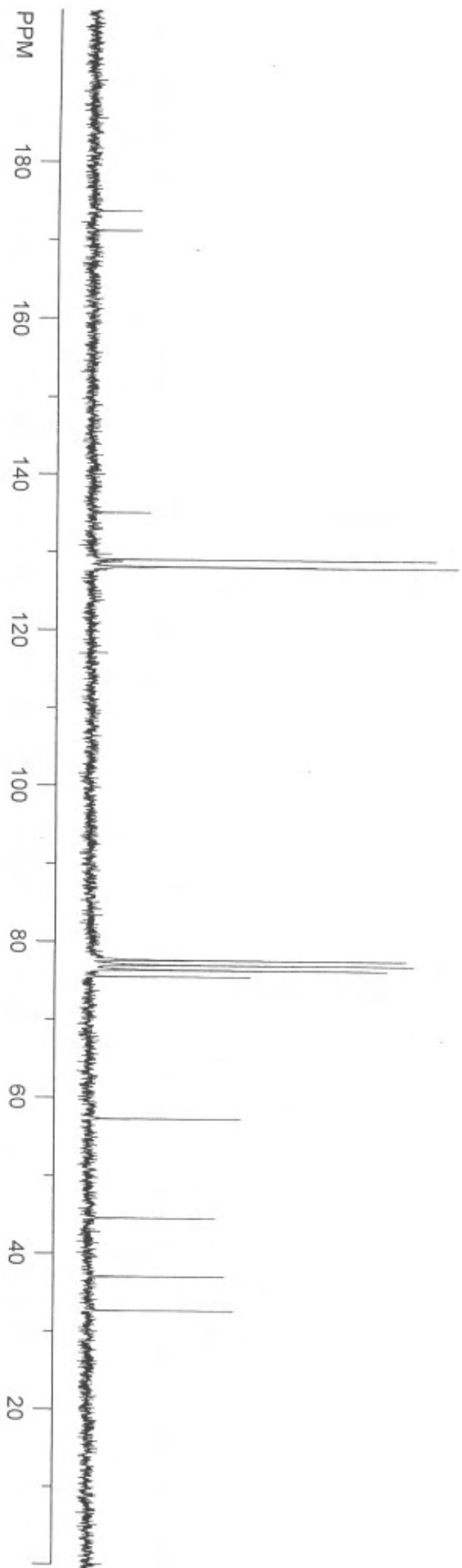
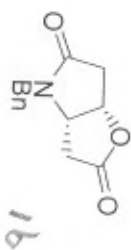
(S)-15



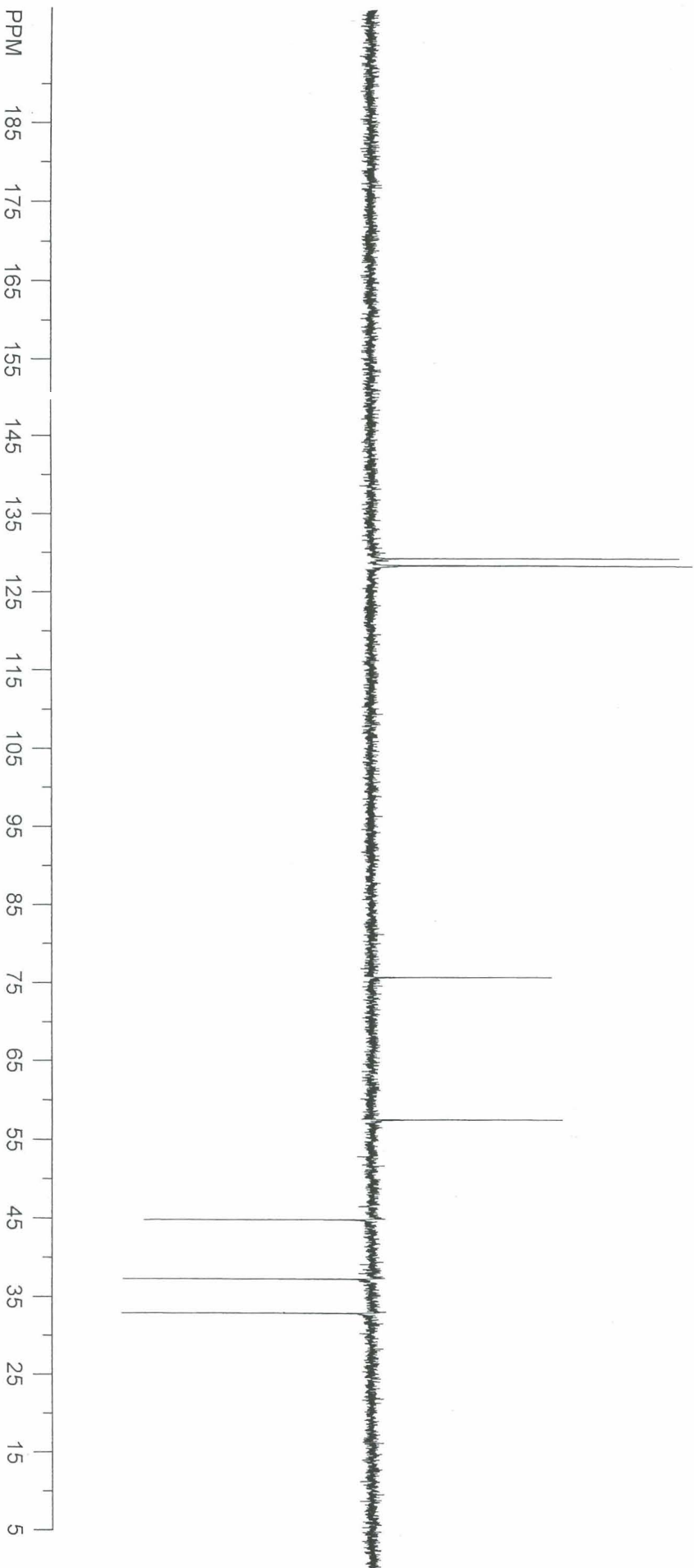
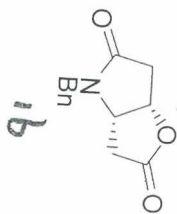
ESI-29



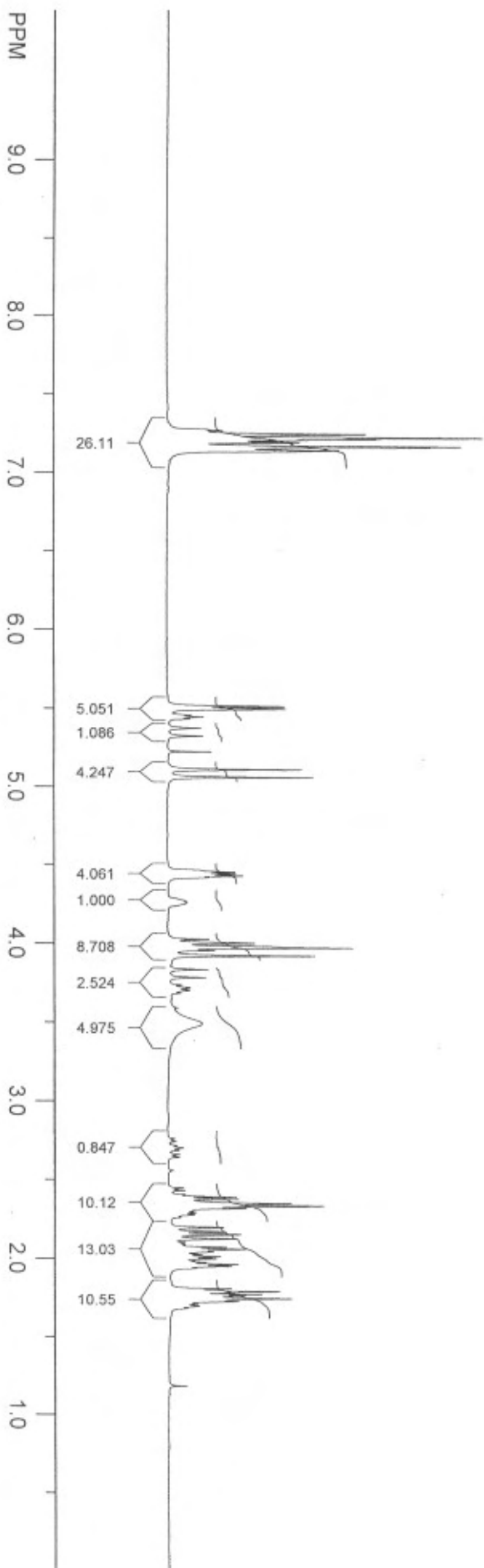
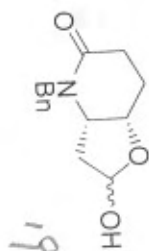
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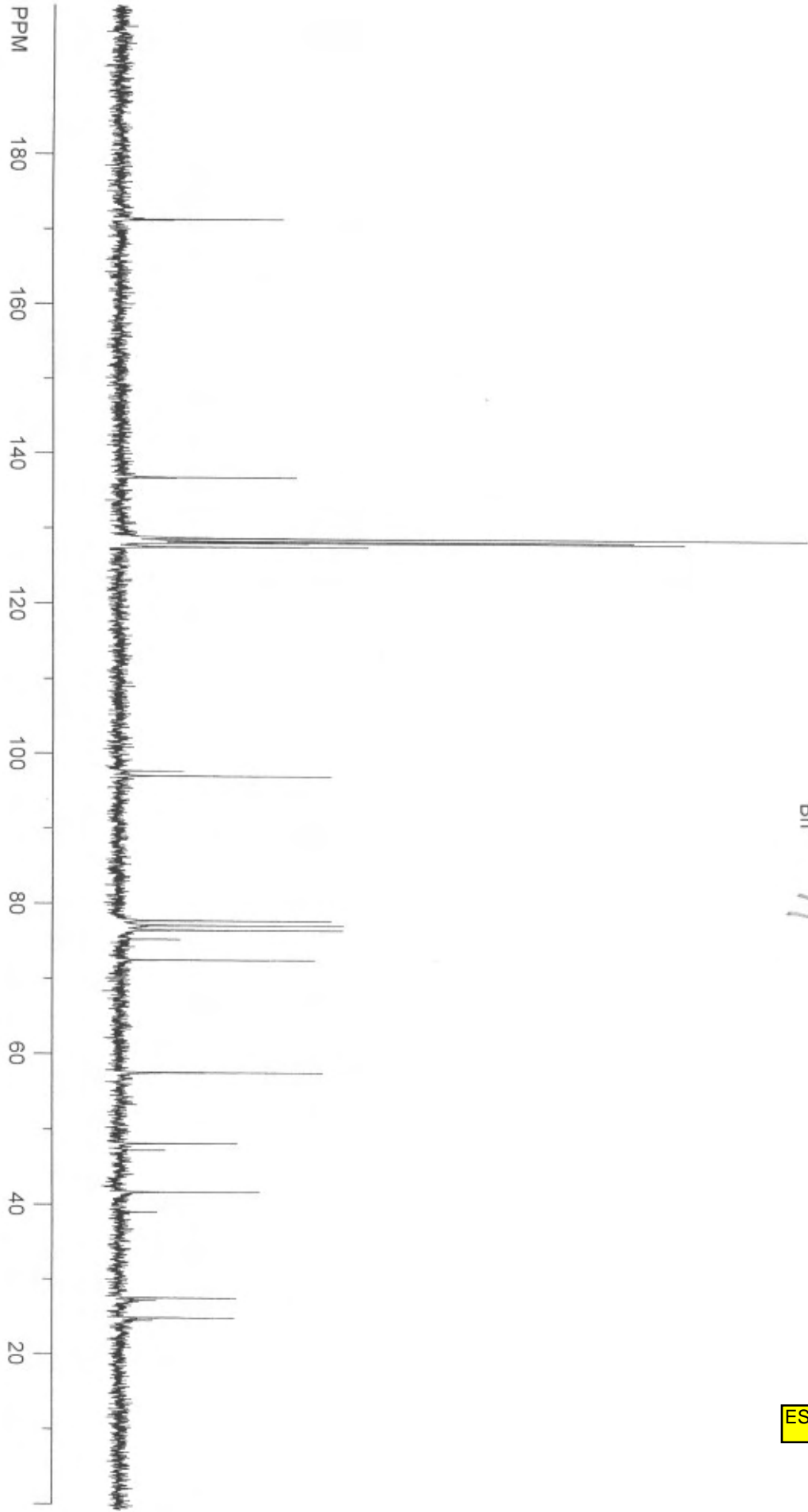
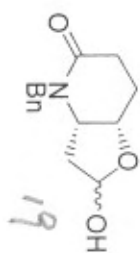
DEPT-135



GFB70

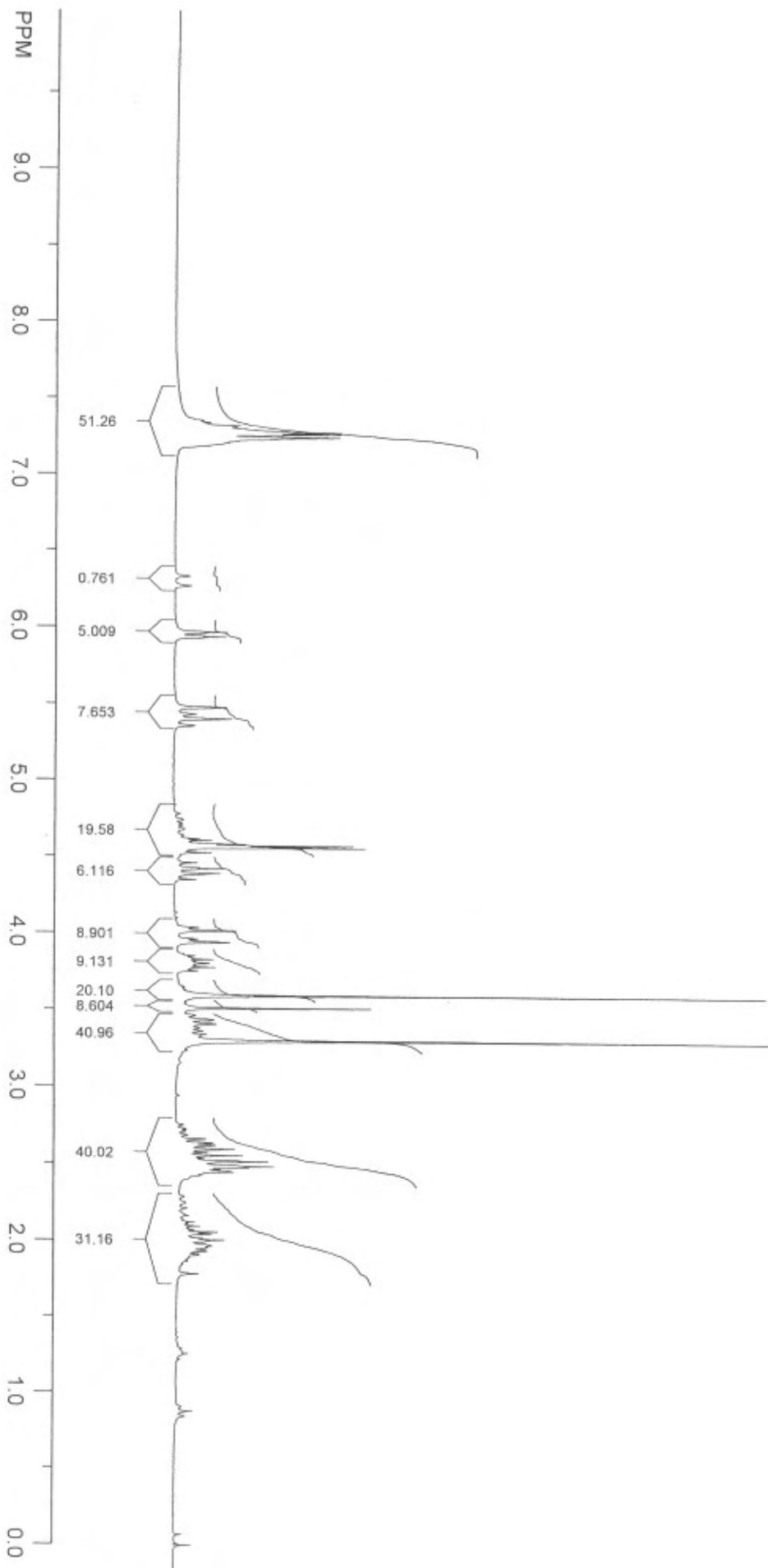
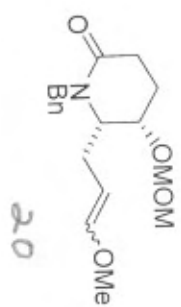


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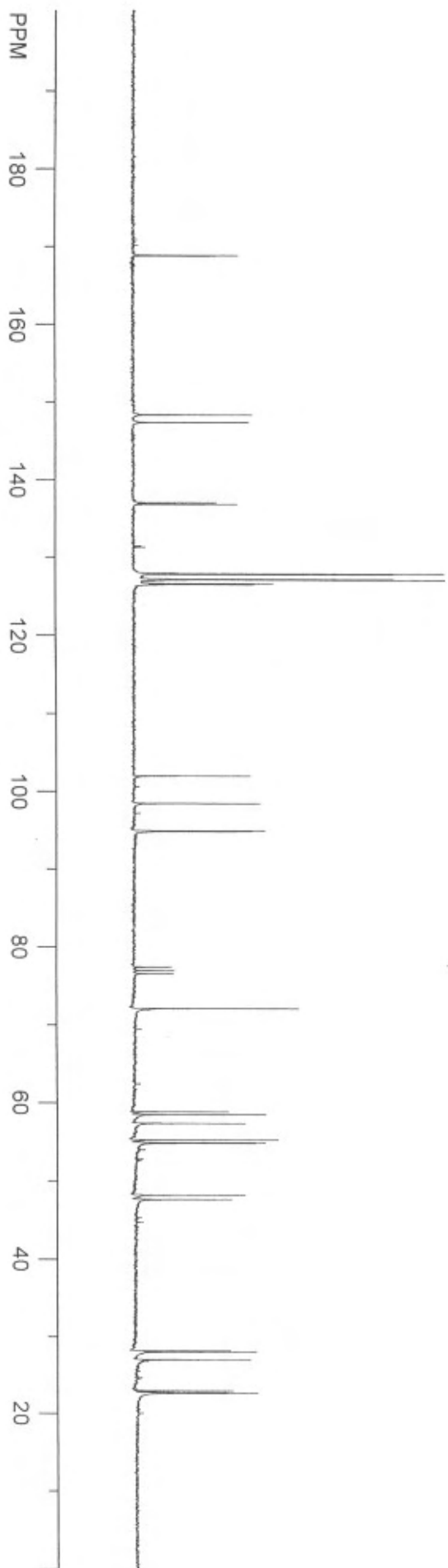
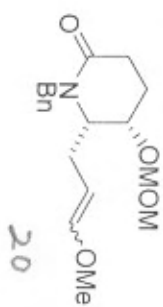
ESI-34

GFBI170A

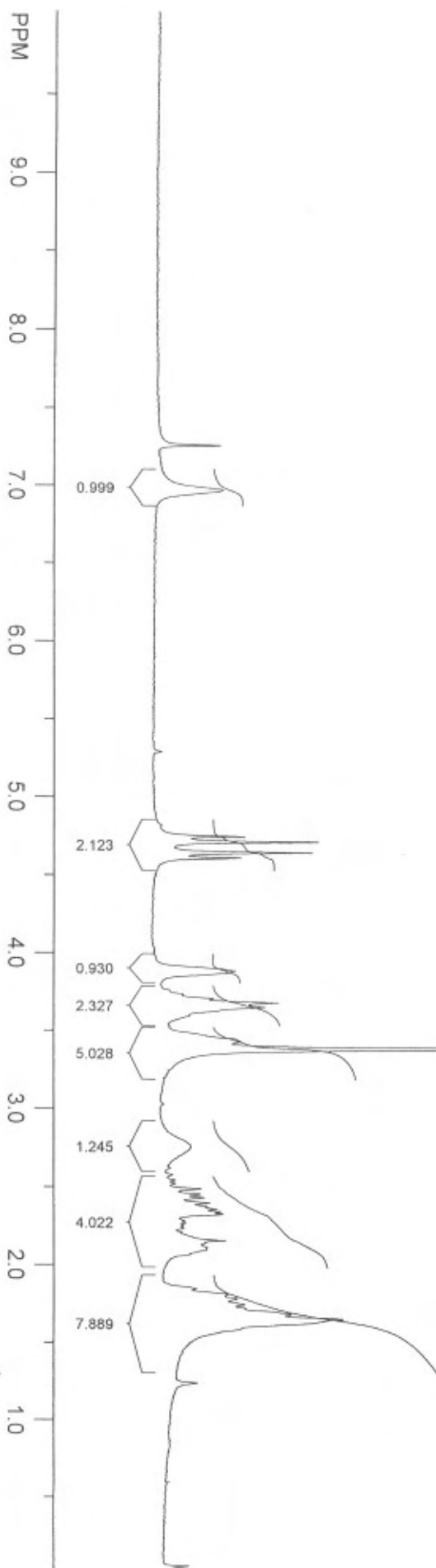
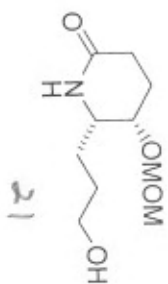


ESI-35

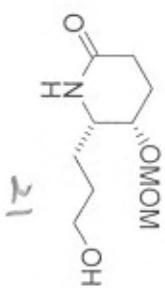
GFBS0-C



ESI-36

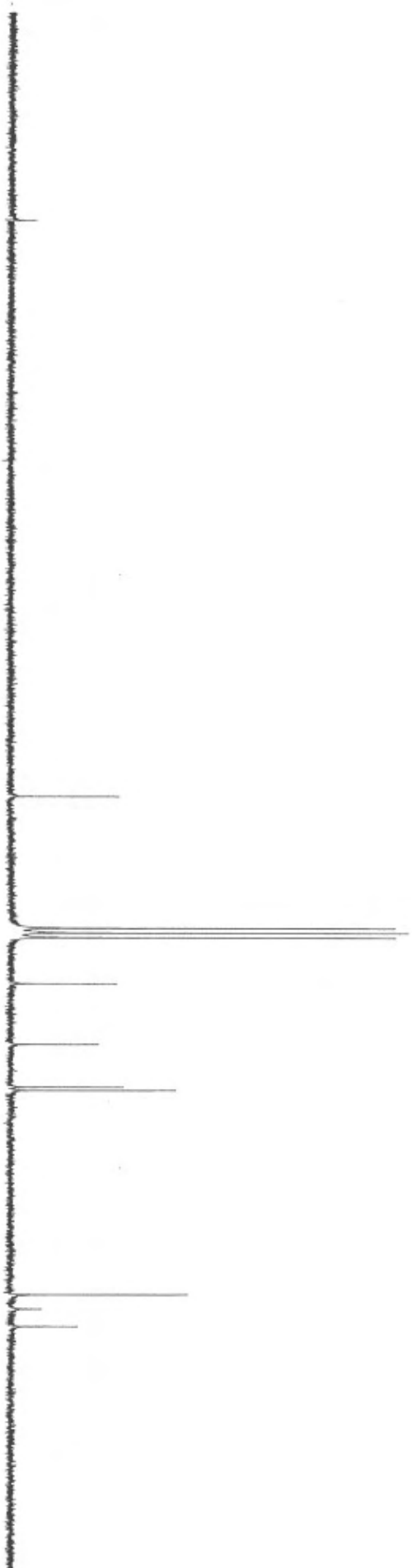


GFB28-C

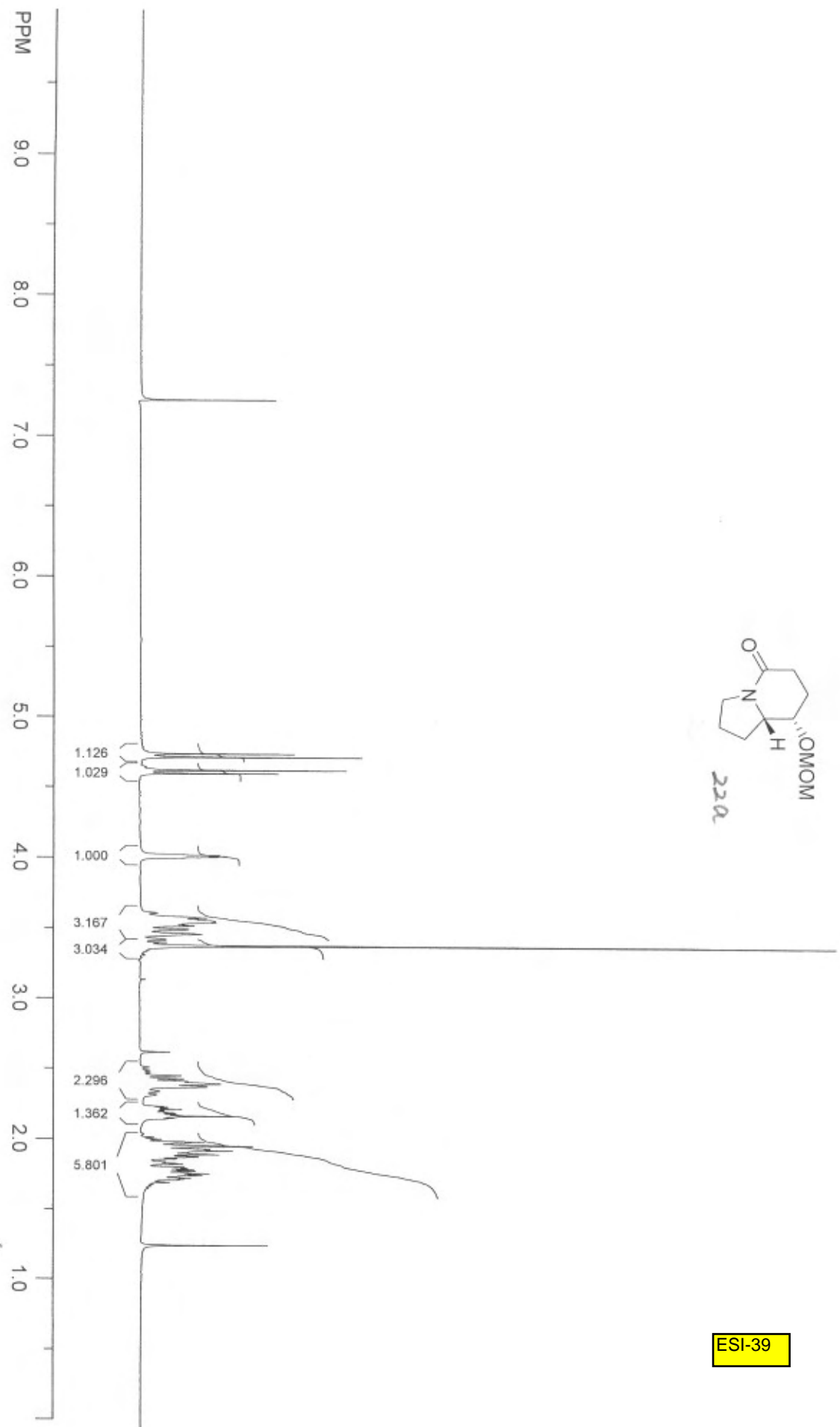
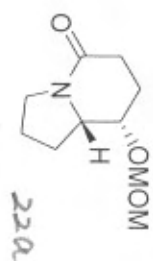


ESI-38

PPM 180 160 140 120 100 80 60 40 20 0

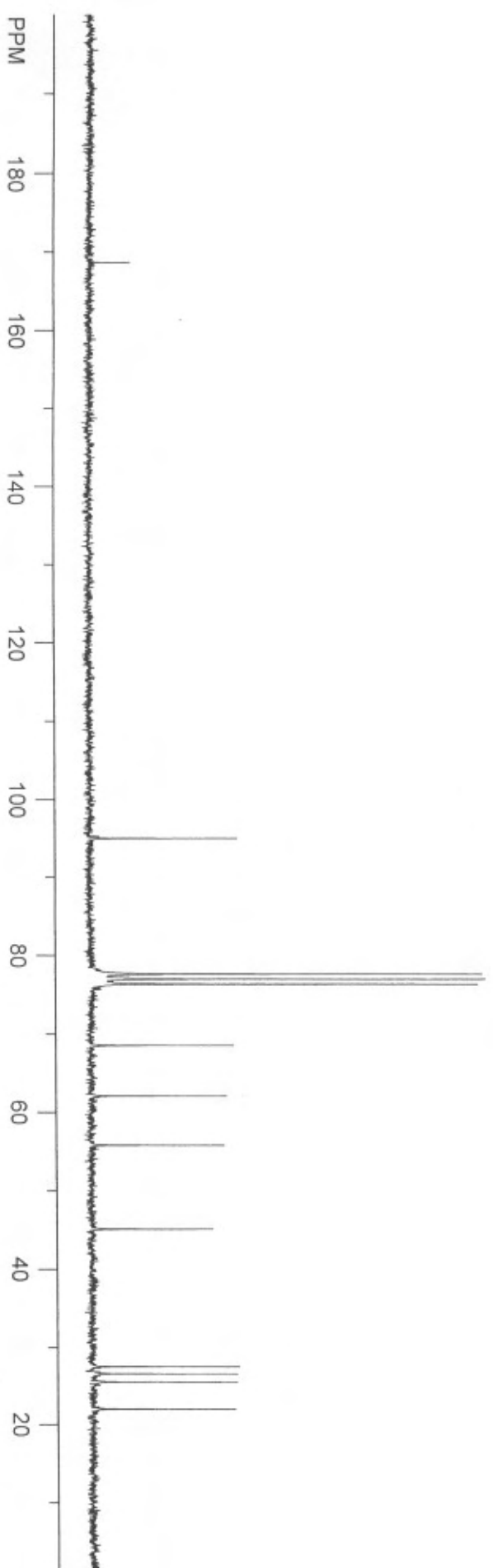
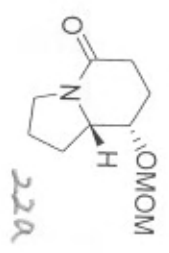


GFB54B



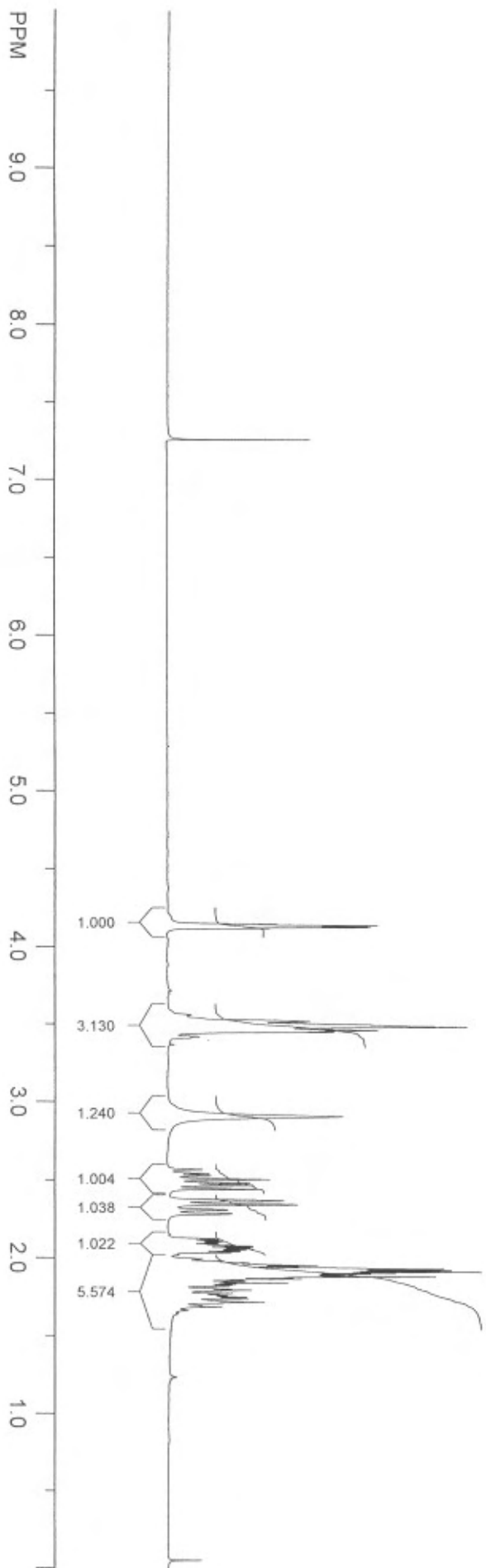
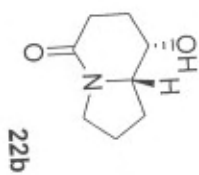
ESI-39

GFBS4B



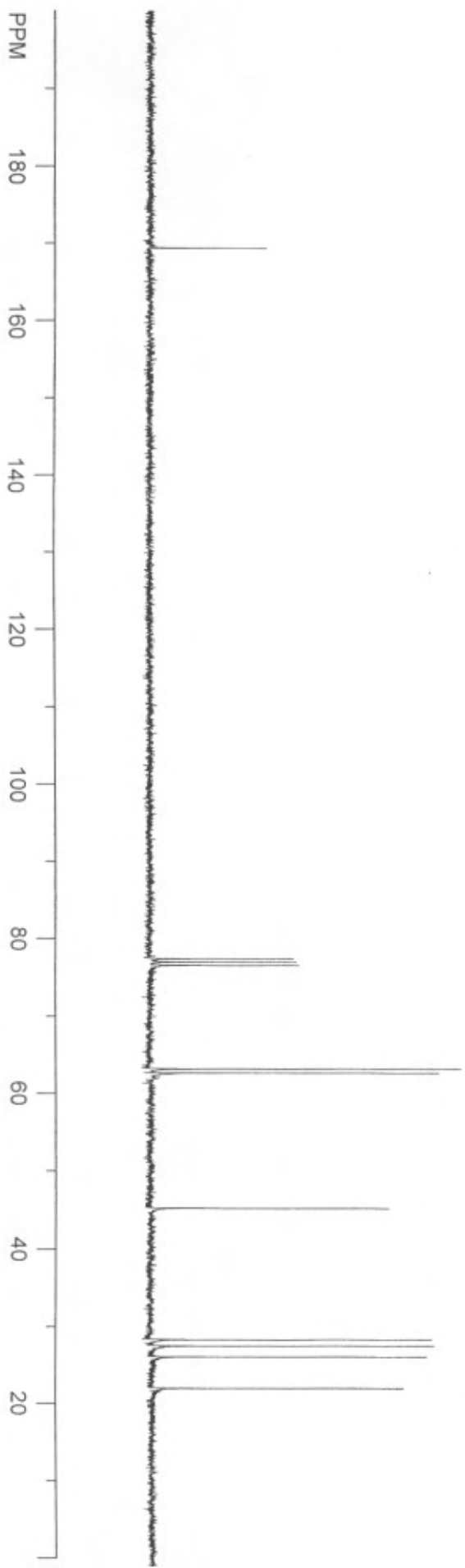
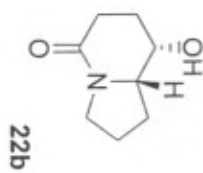
ESI-40

GFB60



ESI-41

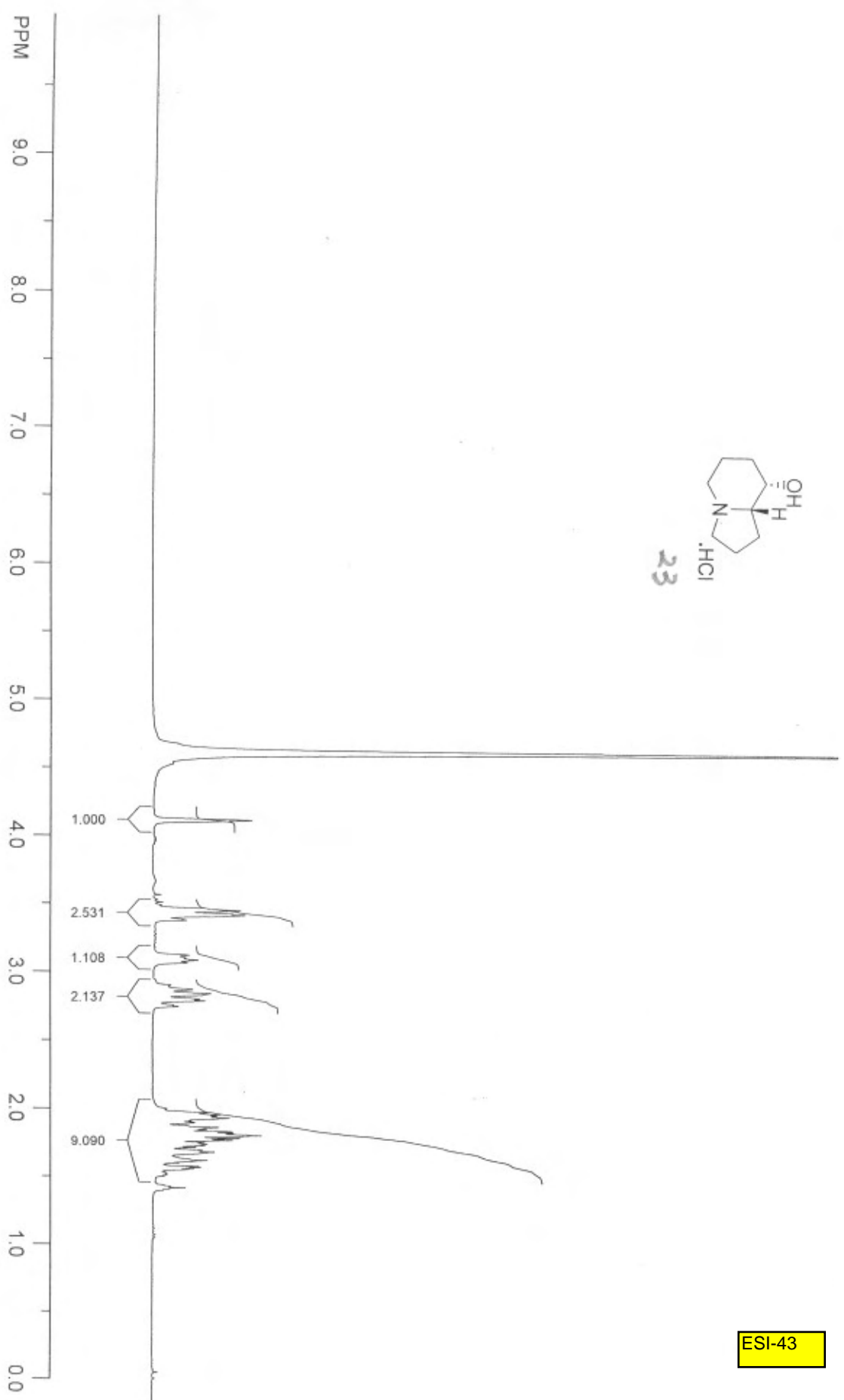
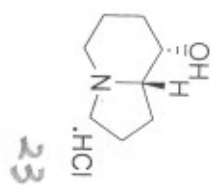
GFB60-C



ESI-42

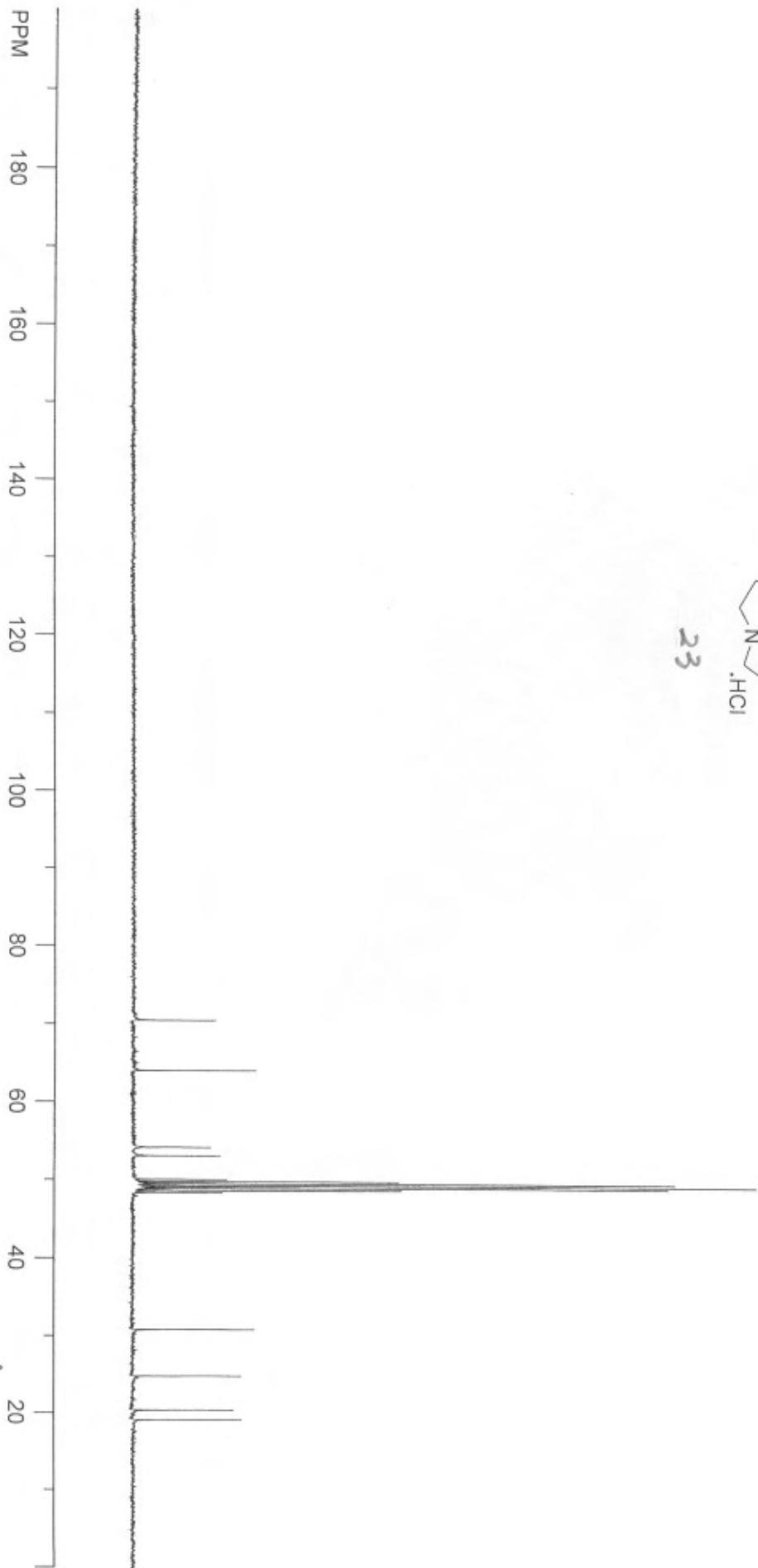
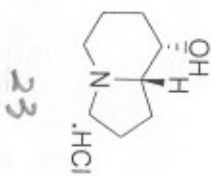
GFB69

D₂O



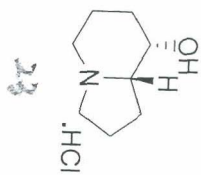
ESI-43

GFB69C-3
CD₃OD



ESI-44

DEPT-135



ESI-45