Synthesis of the indolizino[7,6-c]quinoline alkaloid isaindigotidione

Malik Hellal and Gregory D. Cuny*

Laboratory for Drug Discovery in Neurodegeneration,
Harvard NeuroDiscovery Center, Brigham & Women's Hospital and
Harvard Medical School, 65 Landsdowne Street, Cambridge, Massachusetts 02139

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General information. All reactions were carried out under an atmosphere of argon in flame-dried or oven-dried glassware with magnetic stirring. Purification of products was performed on an automated system using disposable silica gel columns. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ninhydrin solution, $KMnO_4$ or anisaldehyde staining followed by heating. ^{1}H NMR spectra were recorded on a 500 MHz spectrometer and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm or DMSO-d6 at 2.54 ppm). Data are reported as: (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on a 100 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm or DMSO-d_6 at 39.0 ppm). High-resolution mass spectra were obtained on MALDI-FT-ICR MS, using 150 mg/mL 2,5-dihydroxybenzoic acid dissolved in MeOH/H_2O (50:50) as matrix.

Materials. All reagents and solvents were purchased from commercial sources and used without further purification. $[Rh(C_2H_4)Cl_2]_2$, 1,3-bis(diphenylphosphino)propane (dppp), (S)- and (R)-BINAP, (R,R,R)-DOLEFIN, phenylboronic acid, 3,4,5-trimethoxyboronic acid are commercially available and used without further purification. The following starting materials were made according to literature procedures: E-(S)-*tert*-butyl 2-(3-ethoxy-3-oxopropo-1-enyl)pyrrolidine-1-carboxylate (**7**),[1] 4-benzyloxy-3,5-dimethoxy boronic acid (**6c**).[2]

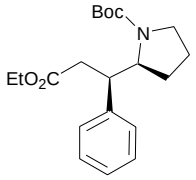
General procedure for the synthesis of 8a – c:

A 25 mL Schlenk flask was charged with [Rh(bis-ethylene)Cl]$_2$ (3 mol %) and ligand (7 mol %) and flushed under argon. A solution of 1,4-dioxane/water (4 ml of 10/1) was added and the mixture was stirred for five minutes. Arylboronic acid (4.0 equiv) and cesium carbonate (1.0 equiv) were added and the mixture was stirred for a further five minutes. Compound **7** (1.0 mmol) was added as a solution of 1,4-dioxane/water (4 mL of 10/1) and the mixture was heated at 60 °C for 24 h. The reaction mixture was filtered through silica gel and then concentrated under reduced pressure. The resulting material was purified by flash chromatography on silica gel (5 to 20 % of EtOAc in cyclohexane). The diastereomeric ratio was determined by integration of the signals corresponding to the CH_3 of the carbonyl functionality for **8a**, or the OCH_3 for **8b** and **8c** from the N-deprotected pyrrolidines.

(1) Zoute, L.; Kociok-Köhn, G.; Frost, C. G. *Org. Lett.* **2009**, *11*, 2491.

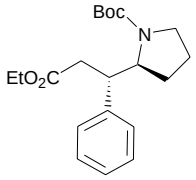
(2) a) Percec, V.; Holerca, M. N.; Nummelin, S.; Morrison, J. J.; Glodde, M.; Smidrkal, J. ; Peterca, M.; Rosen, B. M.; Uchida, S.; Balagurusamy, V. S. K.; Sienkowska, M. J. ; Heiney, P. A. *Chem. Eur. J.* **2006**, *12*, 6216. b) Radix, S.; Barret, R. *Tetrahedron*, **2007**, *63*, 12379. c) Moleele, S. S.; Michael, J. P.; de Koning, C. B. *Tetrahedron*, **2006**, *62*, 2831.

2-(2-Ethoxycarbonyl-1-phenylethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (R,S)-8a.



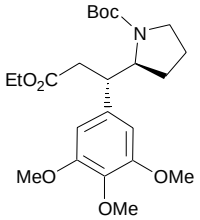
^{1}H NMR ($CDCl_3$) δ: 7.32-7.27 (m, 2H), 7.25-7.16 (m, 3H), 4.26-3.92 (m,3H), 3.91-3.73 (m, 1H), 3.61-3.04 (m, 2H), 2.80-2.64 (m, 2H), 1.79-1.61 (m, 4H), 1.56-1.44 (m, 9H), 1.11 (t, 3H, *J*=7.0 Hz); **^{13}C NMR** ($CDCl_3$) δ: 172.6, 155.3, 141.2, 128.7, 128.5, 128.2, 126.9, 63.6, 62.1, 60.5, 47.8, 44.9, 28.7, 28.5, 27.8, 14.3; **HRMS** (MALDI-TOF) Calcd for $C_{20}H_{29}NO_4Na$ $[M+Na]^+$: 370.1989 ; Found: 370.1991. **$[\alpha]^{20}_D$** -21.3 (*c* 1.07, CH_3OH).

2-(2-Ethoxycarbonyl-1-phenylethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (S,S)-8a.



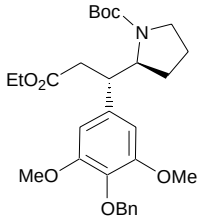
^{1}H NMR ($CDCl_3$) δ: 7.32-7.27 (m, 2H), 7.25-7.16 (m,3H), 4.20-3.94 (m, 3H), 3.43-3.24 (m, 2H), 3.16-3.03 (m, 1H), 2.92-2.80 (m, 1H), 2.69-2.51 (m, 1H), 1.77-1.60 (m, 4H), 1.59-1.48 (m, 9H), 1.16-1.04 (m, 3H); **^{13}C NMR** ($CDCl_3$) δ: 171.4, 156.1, 141.1, 128.8, 128.6, 128.5, 127.0, 62.5, 61.9, 60.5, 46.1, 38.3, 28.8, 28.5, 14.3; **HRMS** (MALDI-TOF) $C_{20}H_{29}NO_4Na$ $[M+Na]^+$: 370.1989 ; Found: 370.1991. **$[\alpha]^{20}_D$** -29.6 (*c* 0.93, CH_3OH).

2-[2-Ethoxycarbonyl-1-(3,4,5-trimethoxyphenyl)ethyl]pyrrolidine-1-carboxylic acid tert-butyl *ester* (S,S)-8b.



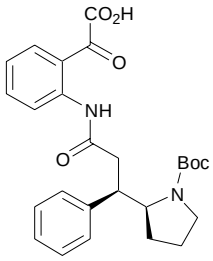
^{1}H NMR ($CDCl_3$) δ: 6.41 (d, 2H, *J*=15.5 Hz), 4.19-3.95 (m, 3H), 3.84 (s, 6H), 3.82 (s, 3H), 3.42-3.05 (m, 3H), 2.89-2.80 (m, 1H), 2.66-2.47 (m, 1H), 1.79-1.60 (m, 4H), 1.58 (s, 6H), 1.49 (s, 3H), 1.20-1.08 (m, 3H); **^{13}C NMR** ($CDCl_3$) δ: 173.0, 156.0, 153.6, 153.3, 137.7, 137.0, 105.5, 104.9, 79.5, 61.9, 61.1, 56.5, 46.8, 46.4, 38.4, 28.8, 14.4; **HRMS** (MALDI-TOF) Calcd for $C_{23}H_{35}NO_7Na$ $[M+Na]^+$: 460.2306 ; Found: 460.2298. **$[\alpha]^{20}_D$** -11.7 (*c* 0.87, CH_3OH).

2-[1-(4-Benzyloxy-3,5-dimethoxyphenyl)-2-ethoxycarbonylethyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (S,S)-8c.



^{1}H NMR ($CDCl_3$) δ: 7.48-7.44 (m, 2H), 7.33-7.27 (m, 3H), 6.39 (d, 2H, *J*=19.0 Hz), 5.01-4.97 (m, 2H), 4.17-3.94 (m, 3H), 3.80 (s, 6H), 3.38-3.22 (m, 2H), 3.16-2.97 (m, 1H), 2.86-2.77 (m, 1H), 2.66-2.50 (m, 1H), 1.77-1.60 (m, 4H), 1.59-1.47 (m, 9H), 1.19-1.08 (m, 3H); **^{13}C NMR** ($CDCl_3$) δ: 172.8, 153.7, 153.6, 138.1, 137.6, 135.9, 128.7, 128.3, 128.0, 105.6, 104.5, 103.7, 79.4, 75.1, 61.8, 60.6, 56.4, 46.9, 46.6, 46.1, 38.4, 28.8, 23.5, 22.6, 14.4; **HRMS** (MALDI-TOF) Calcd for $C_{29}H_{39}NO_7Na$ $[M+Na]^+$: 536.2619 ; Found: 536.2627. **$[\alpha]^{20}_D$** -37.5 (*c* 0.53, CH_3OH).

2-[2-(2-Oxalylphenylcarbamoyl)-1-phenylethyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (10).

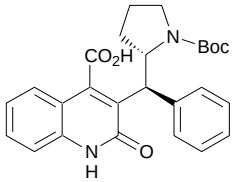


A solution of **(R,S)-8a** (300 mg, 0.86 mmol) in 1,2-dimethoxyethane/H_2O (15 mL of 2/1) and LiOH (54 mg, 1.29 mmol) was stirred at 80 ^oC for 2 h. After cooling, the organic solvent was removed in vacuo and the solution was acidify to pH 3 with HCl (1N) and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated to yield the acid as yellowish oil. The product was used without further purification. Under an argon atmosphere, isatin **4** (152 mg, 1.04 mmol) was added to the acid in anhydrous CH_2Cl_2 (10 mL) at 0 °C, followed by EDCI (174 mg, 0.91 mmol) and DMAP (20 mg, 0.09 mmol). The reaction was allowed to warm to room temperature and then stirred overnight. The solvent was removed in vacuo, then the mixture was diluted in EtOAc (20 mL), washed with HCl (1N, 5 mL), saturated $NaHCO_3$ (2x5 mL), and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, evaporated and dried under reduce pressure to yield a yellow solid. To this material was added water (15 mL) following by K_2CO_3 (179 mg, 1.29 mmol). The mixture was heated at 100 ^oC for 60 min. After cooling to 0 ^oC, the reaction was acidified to pH 3 with HCl (1N). The aqueous solution was extracted with EtOAc (2 x 20 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by chromatography on silica gel (3 to 20 % MeOH in CH_2Cl_2) to yield **10** (338 mg, 0.72 mmol, 84 %) as a yellow solid.

^{1}H NMR (DMSO-d_6) δ: 11.92 (s, 1H), 8.38 (b, 1H), 7.75 (d, 1H, *J*=7.5 Hz), 7.43 (t, 1H, *J*=7.5 Hz), 7.31-7.25 (m, 4H), 7.20-7.15 (m, 2H), 7.06 (t, 1H, *J*=8.0 Hz), 4.02-3.89 (m, 1H), 3.88-3.79 (m, 1H), 3.33-3.29 (m, 1H), 3.18-3.09 (m, 1H), 2.92-2.68 (m, 2H), 1.89-

1.58 (m, 4H), 1.49-1.131 (m, 9H); **^{13}C NMR** (DMSO-d_6) δ: 200.5, 170.2, 168.4, 140.6, 133.8, 133.4, 128.2, 128.0, 126.4, 122.1, 119.4, 79.2, 61.7, 46.9, 44.1, 36.8, 29.0, 28.1, 27.1, 22.3; **HRMS** (MALDI-TOF) Calcd for $C_{26}H_{30}N_2O_6Na$ $[M+Na]^+$: 489.1996 ; Found: 489.1982. **$[\alpha]^{20}_D$** -35.5 (*c* 0.6, CH_3OH).

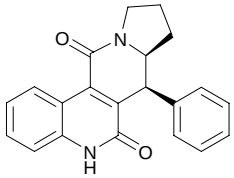
3-[(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)phenylmethyl]-2-oxo-1,2-dihydro-quinoline-4-carboxylic acid (11).



To a solution of **10** (300 mg, 0.64 mmol) under an argon atmosphere in anhydrous DMF (7 mL) was added t-BuOK (216 mg, 1.93 mmol) by portion. The mixture was heated to 80 ^oC for 4 h. After cooling to 0 ^oC, HCl (1N) was added until pH 3. The acidic solution was extracted with EtOAc (2 x 20 mL). The organic layers were combined, washed twice with 5 % aqueous LiCl (5 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by chromatography on silica gel (3 to 20 % MeOH in CH_2Cl_2 + AcOH 0.5 %) to yield **11** (161 mg, 0.36 mmol, 56 %) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 11.38 (b, 1H), 7.78-7.56 (m, 2H), 7.45 (d, 1H, *J*=7.5 Hz), 7.30 (t, 1H, *J*=7.5 Hz), 7.26-7.19 (m, 1H), 7.17-7.00 (m, 4H), 5.52 (b, 1H), 3.86 (b, 1H), 3.46-3.35 (m, 2H), 3.22-3.05 9m, 1H), 2.38-2.22 (m, 1H), 1.75-1.52 (m, 3H), 1.25-1.02 (m, 9H); **^{13}C NMR** (DMSO-d_6) δ: 172.9, 161.7, 153.7, 138.2, 136.7, 131.8, 129.8, 128.3, 127.4, 126.0, 125.5, 121.7, 121.4, 116.3, 114.8, 77.5, 75.8, 62.8, 30.1, 27.9, 27.6, 21.1, 18.6; **HRMS** (MALDI-TOF) Calcd for $C_{26}H_{28}N_2O_5Na$ $[M+Na]^+$: 471.1890 ; Found: 471.1889. **$[\alpha]^{20}_D$** -16.0 (*c* 0.87, CH_3OH).

7-Phenyl-5,7,7a,8,9,10-hexahydro-5,10a-diazacyclopenta[b]phenanthrene-6,11-dione (12).



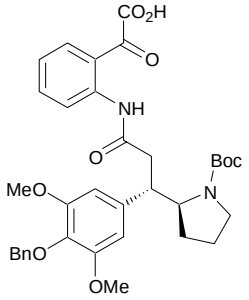
Method A: A mixture of **11** (50 mg, 0.11) in $SOCl_2$ (0.5 mL) was refluxed for 1 h. After cooling to room temperature, the solvent was removed in vacuo, then the mixture was diluted in EtOAc (10 mL), washed with HCl (1N, 5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude product was purified by chromatography on silica gel (2 to 5 % MeOH in CH_2Cl_2) to yield **12** (32 mg, 0.10 mmol, 87 %) as a yellow solid.

Method B: To a solution of **11** (36 mg, 0.08 mmol) at 0 ^oC in MeOH (1.5 mL) was added drop-wise conc. HCl (0.5 mL). The solution was warmed slowly to room temperature and stirred for 2 h. The solvent was removed in vacuo and the residue was dried under reduce pressure. Then, the yellowish powder was dissolved in anhydrous DMF (2 mL) and

cooled to 0 °C. EDCI (18 mg, 0.1 mmol) was added, following by NEt_3 (13 μL, 0.1 mmol) and DMAP (2 mg, 0.02 mmol). The reaction was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue was dissolved in EtOAc, washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by chromatography on silica gel (2 to 5 % MeOH in CH_2Cl_2) to yield **12** (21 mg, 0.06 mmol, 79 %) as a yellow solid.

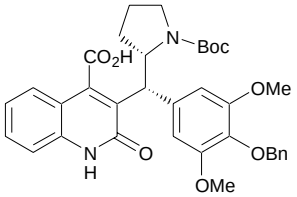
^{1}H NMR (DMSO-d_6) δ: 12.11 (b, 1H), 8.91 (d, 1H, *J*=8.0 Hz), 7.52 (td, 1H, *J*=2.5 and 7.0 Hz), 7.35 (d, 1H, *J*=8.0 Hz), 7.33-7.29 (m, 2H), 7.27-7.22 (m, 2H), 7.05 (d, 2H, *J*=7.0 Hz), 4.45 (d, 1H, *J*=4.5 Hz), 4.25-4.19 (m, 1H), 3.62-3.55 (m, 1H), 3.16-3.08 (m, 1H), 2.07-2.00 (m ,1H), 1.74-1.64 (m ,1H), 1.59-1.51 (m, 1H), 1.34-1.20 (m, 1H); **^{13}C NMR** (DMSO-d_6) δ: 161.4, 160.0, 138.3, 136.4, 135.3, 134.8, 130.0, 129.1, 128.4, 127.2, 122.0, 116.2, 115.4, 58.4, 45.6, 41.2, 28.3, 22.5; **HRMS** (MALDI-TOF) Calcd for $C_{21}H_{19}N_2O_2$ $[M+H]^+$: 331.1441 ; Found: 331.1433. **$[\alpha]^{20}_D$** -77.4 (*c* 0.27, CH_3OH).

2-[1-(4-Benzyloxy-3,5-dimethoxyphenyl)-2-(2-oxalylphenylcarbamoyl)ethyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (3).



Starting from **(S,S)-8c** (260 mg, 0.51 mmol), the same method as was used to prepare **10** afforded **3** (194 mg, 0.31 mmol, 61 %) as a yellow solid.
^{1}H NMR (DMSO-d_6) δ: 11.70-11.34 (m, 1H), 8.40-8.23 (m, 1H), 7.69 (d, 1H, *J*=7.5 Hz), 7.53 (t, 1H, *J*=7.5 Hz), 7.42-7.37 (m, 2H), 7.35-7.23 (m, 3H), 7.13 (t, 1H, *J*=7.5 Hz), 6.48 (d, 2H, *J*=8.5 Hz), 4.83 (s, 2H), 4.06-3.93 (m, 1H), 3.73 (s, 6H), 3.59-3.51 (m, 2H), 3.22-3.15 (m, 2H), 2.80-2.76 (m, 2H), 1.78-1.53 (m, 4H), 1.51-1.36 (m, 9H); **^{13}C NMR** (DMSO-d_6) δ: 201.1, 170.0, 152.7, 140.4, 137.8, 134.9, 134.0, 133.1, 127.9, 127.5, 122.3, 119.7, 105.5, 78.7, 73.8, 61.1, 55.9, 46.3, 44.4, 43.9, 28.1, 27.2, 22.1; **HRMS** (MALDI-TOF) Calcd for $C_{35}H_{40}N_2O_9Na$ $[M+Na]^+$: 655.2626 ; Found: 655.2620. **$[\alpha]^{20}_D$** -45.9 (*c* 0.27, CH_3OH).

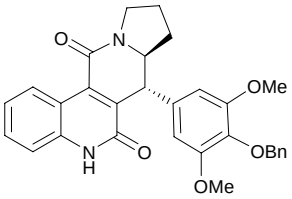
3-[(4-Benzyloxy-3,5-dimethoxyphenyl)-(1-*tert*-butoxycarbonylpyrrolidin-2-yl)methyl]-2-oxo-1,2-dihydroquinoline-4-carboxylic acid (2).



Starting from **3** (317 mg, 0.50 mmol), the same method as was used to prepare **11** afforded **2** (191 mg, 0.31 mmol, 62 %) as a white solid.

^{1}H NMR (DMSO-d_6) δ: 9.80 (s, 1H), 7.74-7.59 (m, 1H), 7.48-7.24 (m, 6H), 7.12-7.04 (m, 1H), 6.95-6.62 (m, 2H), 6.52-6.44 (m, 1H), 4.94-4.68 (m, 3H), 3.80-3.54 (m, 6H), 3.49-3.36 (m, 2H), 3.29-3.18 (m, 1H), 3.03-2.72 (m, 1H), 1.63-.144 (m, 4H), 1.37-1.22 (m, 9H); **^{13}C NMR** (DMSO-d_6) δ: 181.6, 154.6, 151.5, 140.4, 138.3, 134.6, 133.1, 128.0, 127.7, 127.4, 125.4, 123.3, 113.6, 105.5, 79.3, 73.7, 55.9, 55.7, 46.5, 31.2, 29.0, 28.0, 22.1, 19.1; **HRMS** (MALDI-TOF) Calcd for $C_{35}H_{38}N_2O_8Na$ $[M+Na]^+$: 637.2520 ; Found: 637.2503. **$[\alpha]^{20}_D$** -26.4 (*c* 0.33, CH_3OH).

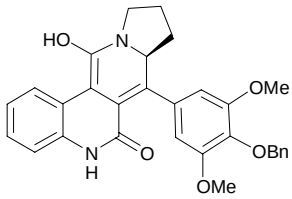
7-(4-Benzyloxy-3,5-dimethoxyphenyl)-5,7,7a,8,9,10-hexahydro-5,10a-diazacyclopenta[b]phenanthrene-6,11-dione (14).



To a solution of **2** (123 mg, 0.20 mmol) at 0 ^oC in MeOH (1.5 mL) was added drop-wise conc. HCl (0.5 mL). The solution was warmed slowly to room temperature and stirred for 2 hours. The solvent was removed in vacuo and the residue was dried under reduce pressure. Then, the yellowish powder was dissolved in anhydrous toluene (4 mL) and $SOCl_2$ (32 mL, 0.44 mmol) was added. The reaction was heated at 80 ^oC for 1 h. The solvent was removed in vacuo and the residue was dissolved in EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by chromatography on silica gel (1 to 5 % MeOH in CH_2Cl_2) to yield **14** (46 mg, 0.11 mmol, 54 %) as white solid.

^{1}H NMR (DMSO-d_6) δ: 11.72 (s, 1H), 8.76 (d, 1H, *J*=8.0 Hz), 7.49-7.41 (m, 3H), 7.37-7.32 (m, 2H), 7.31-7.26 (m, 2H), 7.17 (td, 1H, *J*=1.0 and 8.0 Hz), 6.51 (s, 2H), 4.84 (s, 2H), 3.96 (d, 1H, *J*=12.3 Hz), 3.88-3.86 (m, 1H), 3.73-3.60 (m ,1H), 3.68 (s, 6H), 3.59-3.49 (m, 1H), 1.99-1.92 (m, 1H), 1.90-1.82 (m, 1H), 180-1.68 (m, 2H); **^{13}C NMR** (DMSO-d_6) δ: 160.3, 159.4, 152.6, 138.5, 138.1, 138.0, 135.7, 135.0, 134.7, 129.6, 128.0, 127.8, 127.6, 121.5, 116.6, 115.0, 105.0, 73.9, 61.5, 55.9, 48.8, 45.7, 32.0, 22.1; **HRMS** (MALDI-TOF) Calcd for $C_{30}H_{29}N_2O_5$ $[M+H]^+$: 497.2071 ; Found: 497.2066. **$[\alpha]^{20}_D$** -117.7 (*c* 0.13, CH_3OH).

7-(4-Benzyloxy-3,5-dimethoxyphenyl)-11-hydroxy-7a,8,9,10-tetrahydro-5H-5,10a-diazacyclopenta[b]phenanthren-6-one (15).

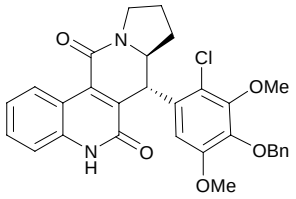


Method A: To a solution of **2** (37 mg, 0.06 mmol) at 0 ^oC in MeOH (1 mL) was added drop-wise conc. HCl (0.3 mL) The solution was warmed slowly to room temperature and stirred for 2 h. The solvent was removed in vacuo and the residue was dried under reduce pressure. Then, the yellowish powder was dissolved in anh DMF and cooled to 0 ^oC. EDCI (14 mg, 0.07 mmol) followed by NEt_3 (17 μL, 0.12 mmol) were added and the

reaction was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue was dissolved in EtOAc, washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by chromatography on silica gel (1 to 5 % MeOH in CH_2Cl_2) to yield **14** (10 mg, 0.020 mmol) and **15** (15 mg, 0.030 mmol).

Method B: To a solution of **2** (37 mg, 0.06 mmol) at 0 ^oC in MeOH (1 mL) was added drop-wise conc. HCl (0.3 mL) The solution was warmed slowly to room temperature and stirred for 2 h. The solvent was removed in vacuo and the residue was dried under reduce pressure. Then, the yellowish powder was dissolved in anhydrous DMF and cooled to 0 ^oC. HBTU (27 mg, 0.07 mmol) followed by DIEA (21 μL, 0.12 mmol) were added and the reaction was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue was dissolved in EtOAc, washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by chromatography on silica gel (1 to 5 % MeOH in CH_2Cl_2) to yield **14** (4 mg, 0.008 mmol) and **15** (23 mg, 0.046 mmol).
^{1}H NMR (DMSO-d_6) δ: 10.17 (s, 1H), 7.49 (d, 1H, *J*=8.0 Hz), 7.46-7.43 (m, 2H), 7.39-7.34 (m, 2H), 7.33-7.29 (m, 1H), 7.27 (td, 1H, *J*=1.5 and 8.0 Hz), 6.98 (td, 1H, *J*=1.5 and 8.0 Hz), 6.90 (d, 1H, *J*=8.0 Hz), 6.61 (s, 2H), 6.05 (b, 1H), 4.84 (s, 2H), 3.95 (td, 1H, J=5.0 and 10.5 Hz), 3.75 (s, 6H), 3.54-3.46 (m, 1H), 3.45-3.39 (m, 1H), 1.86-1.78 (m,1H), 1.76-1.66 (m, 1H), 1.60-1.53 (m, 1H), 1.36-1.27 (m, 1H); **^{13}C NMR** (DMSO-d_6) δ: 167.4, 152.5, 138.0, 136.9, 135.4, 134.2, 129.2, 128.0, 127.8, 127.1, 124.8, 122.0, 115.4, 105.9, 73.7, 62.9, 56.0, 52.9; 46.3, 44.8, 31.5, 29.0, 21.5; **HRMS** (MALDI-TOF) Calcd for $C_{30}H_{29}N_2O_5$ $[M+H]^+$: 497.2071 ; Found: 497.2064. **$[\alpha]^{20}_D$** -22.6 (*c* 0.27, CH_3OH).

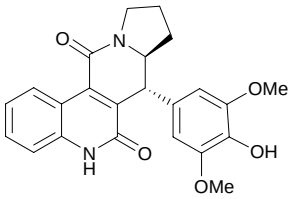
7-(4-Benzyloxy-2-chloro-3,5-dimethoxyphenyl)-5,7,7a,8,9,10-hexahydro-5,10a-diaza cyclopenta[b]phenanthrene-6,11-dione (16).



A solution of **2** (62 mg, 0.1 mmol) in $SOCl_2$ (1.0 mL) was heated to 80 ^oC for 1h. After cooling to room temperature, $SOCl_2$ was evaporated. The mixture was dissolved in EtOAc, washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by chromatography on silica gel (2 to 5 % MeOH in CH_2Cl_2) to yield **14** (14 mg, 0.028 mmol, 28%) as a white solid and **16** (28 mg, 0.053 mmol, 52%) as a white solid.
^{1}H NMR (DMSO-d_6) δ: 11.75 (s, 1H), 8.81 (d, 1H, *J*=8.5 Hz), 7.50-7.46 (m, 3H), 7.42-7.38 (m, 2H), 7.36-7.30 (m, 2H), 7.21 (t, 1H, *J*=8.0 Hz), 6.60 (s, 1H), 4.96 (s, 2H), 4.58 (d, 1H, *J*=12.5 Hz), 4.04-3.96 (m, 1H), 3.83 (s, 3H), 3.70-3.65 (m, 1H), 3.61 (s, 3H), 3.59-3.53 (m, 1H), 2.00-1.69 (m, 4H); **^{13}C NMR** (DMSO-d_6) δ: 162.4, 157.2, 153.5, 149.4, 139.7, 138.9, 138.5, 136.1, 135.6, 133.3, 129.8, 129.2, 128.2, 127.1, 121.3, 116.6,

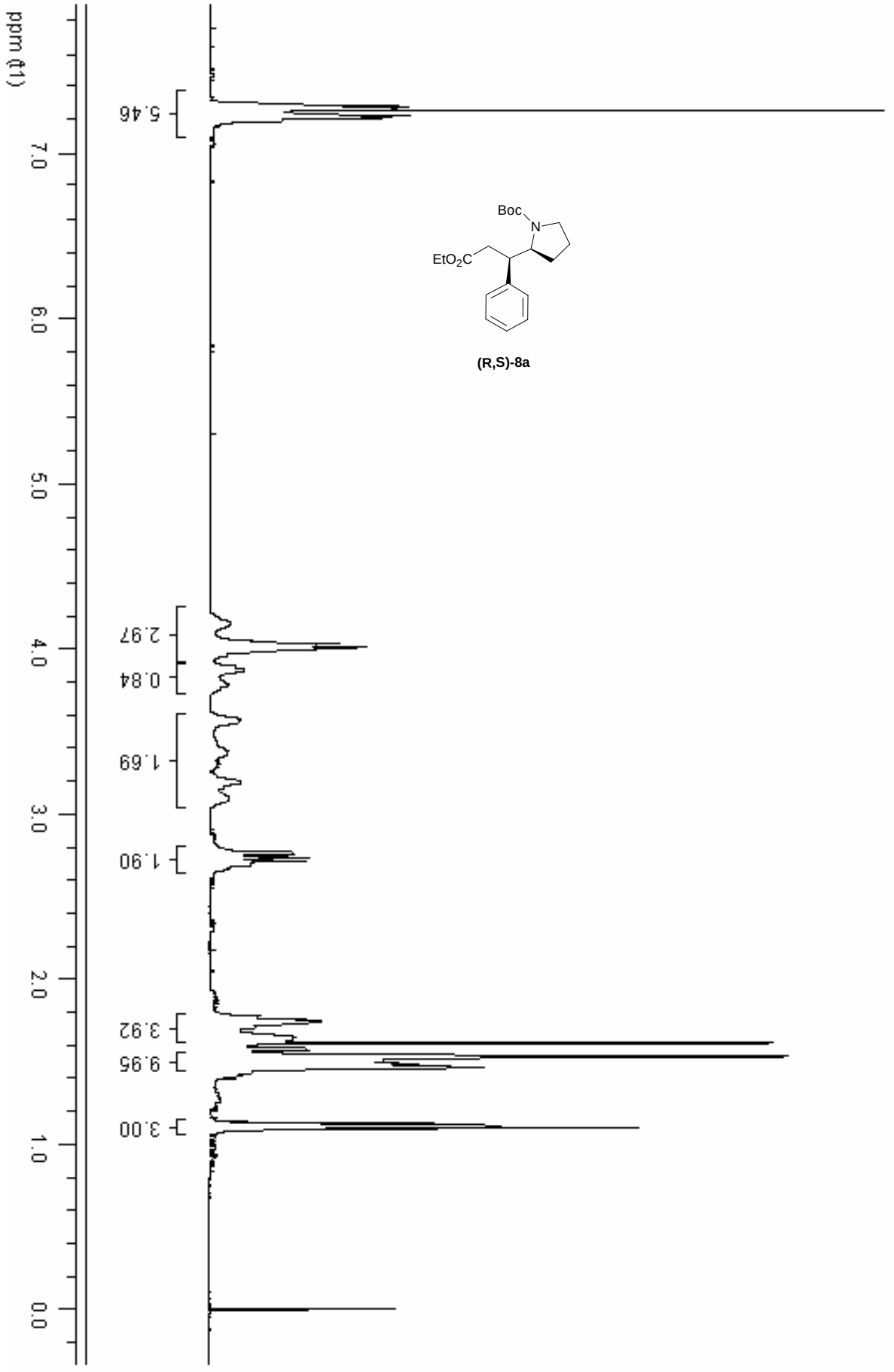
114.7, 108.8, 75.1, 60.9, 54.8, 48.9, 47.6, 31.7, 22.7; **HRMS** (MALDI-TOF) Calcd for $C_{30}H_{28}N_2O_5Cl$ $[M+H]^+$: 531.1681 ; Found: 531.1699. **$[\alpha]^{20}_D$** -100.0 (*c* 0.13, CH_3OH).

Isaindigotidione (1).



Compound **14** (30 mg, 0.06 mmol) was dissolved in methanol (2 mL) in a 10 mL flask containing 10% Pd/C (3 mg). The flask was flushed with H_2, a H_2 filled balloon attached, and the mixture was stirred for 10 h at room temperature. The reaction mixture was filtered through a short pad of silica gel and Celite, and the filtered cake was rinsed with MeOH. The clear filtrate was concentrated and the residue was purified by flash chromatography (2 to 5 % MeOH in CH_2Cl_2) to afford **1** (21 mg, 0.05 mmol, 86%) as a yellowish solid.

^{1}H NMR (DMSO-d_6) δ: 11.72 (s, 1H), 8.75 (d, 1H, *J*=8.0 Hz), 8.08 (s, 1H), 7.47 (t, 1H, *J*=7.5 Hz), 7.31 (d, 1H, *J*=8.0 Hz), 7.18 (t, 1H, *J*=7.5 Hz), 6.43 (s, 2H), 3.89 (d, 1H, *J*=12.0 Hz), 3.84-3.78 (m, 1H), 3.71-3.68 (m, 1H), 3.67 (s, 6H), 3.58-3.52 (m, 1H), 1.97-1-91 (m, 1H), 188.1.81 (m, 1H), 1.79-1.69 (m, 2H); **^{13}C NMR** (DMSO-d_6) δ: 160.3, 159.4, 147.6, 138.5, 135.6, 135.3, 133.8, 132.1, 129.6, 127.6, 121.5, 116.6, 115.0, 105.1, 61.7, 56.0, 48.5, 45.7, 32.0, 22.1; **HRMS** (MALDI-TOF) Calcd for $C_{23}H_{23}N_2O_5$ $[M+H]^+$: 407.1602 ; Found: 407.1606. **$[\alpha]^{20}_D$** -128.5 (*c* 0.13, CH_3OH) and +108.0 (*c* 0.10, DMSO).


ppm (t1)
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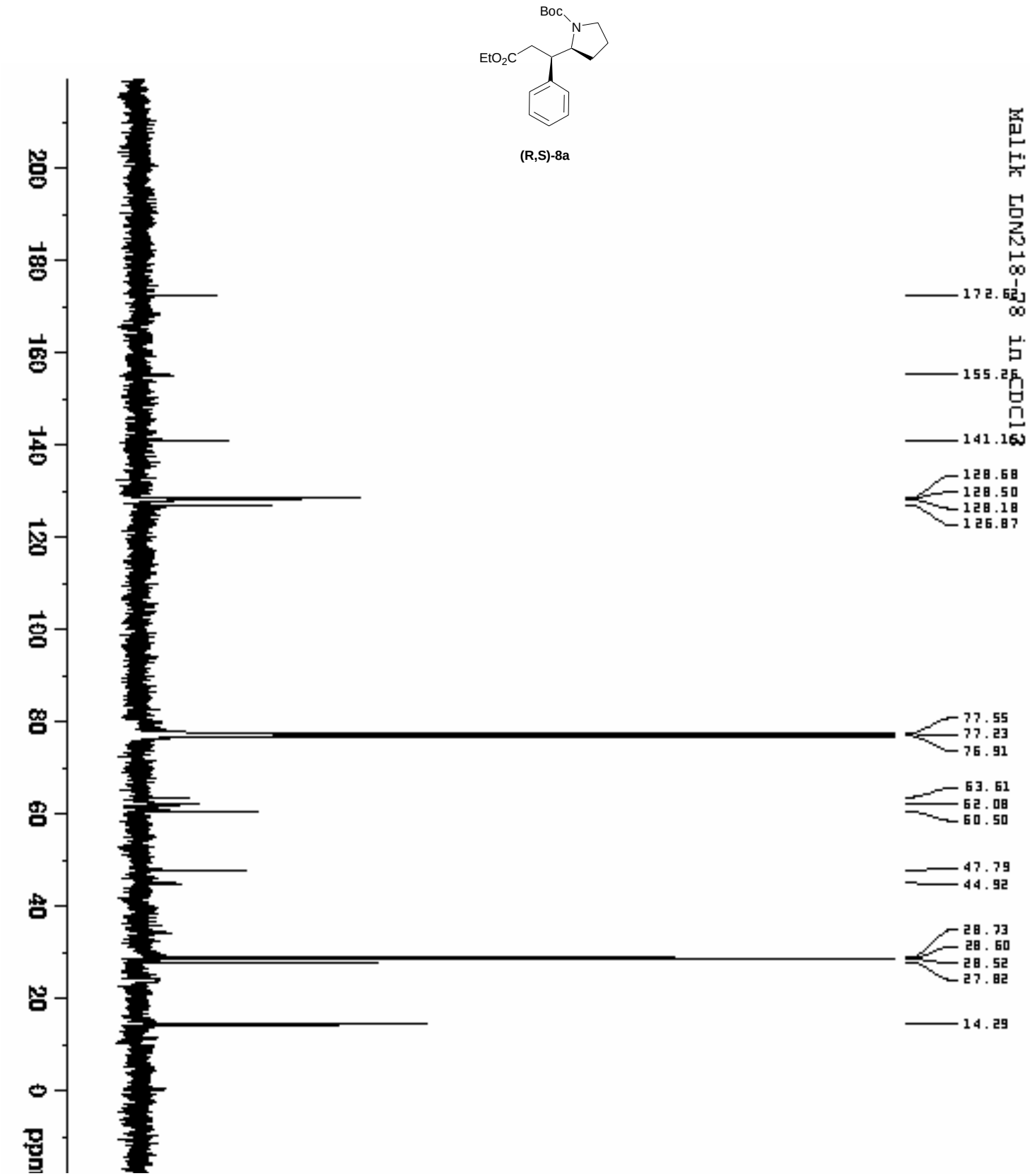
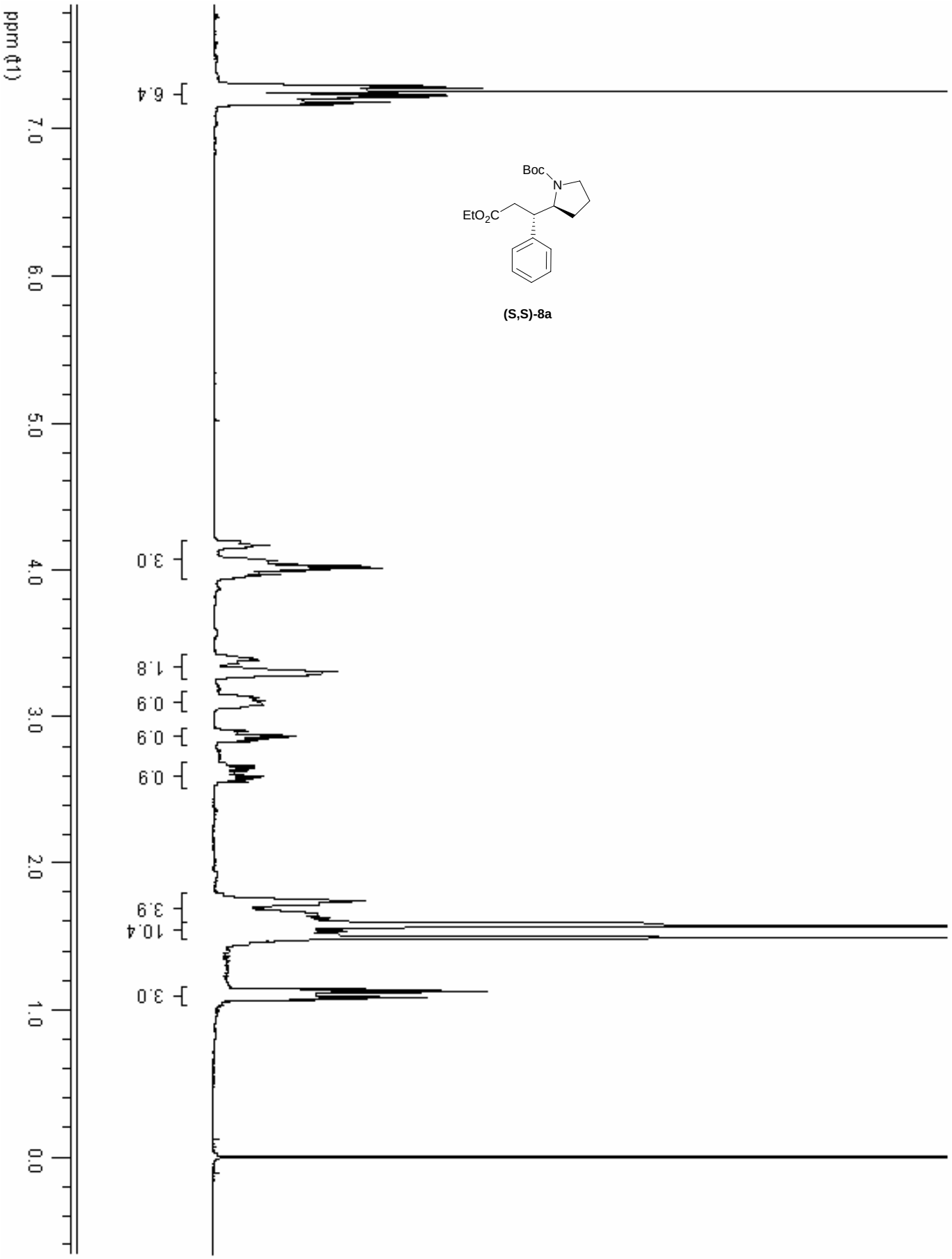
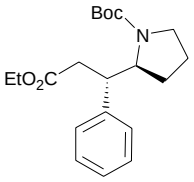
6.0
5.0
4.0
3.0
2.0
1.0
0.0
5.46
2.97
0.84
1.69
1.90
3.92
9.95
3.00
Boc
N
EtO2C

(R,S)-8a

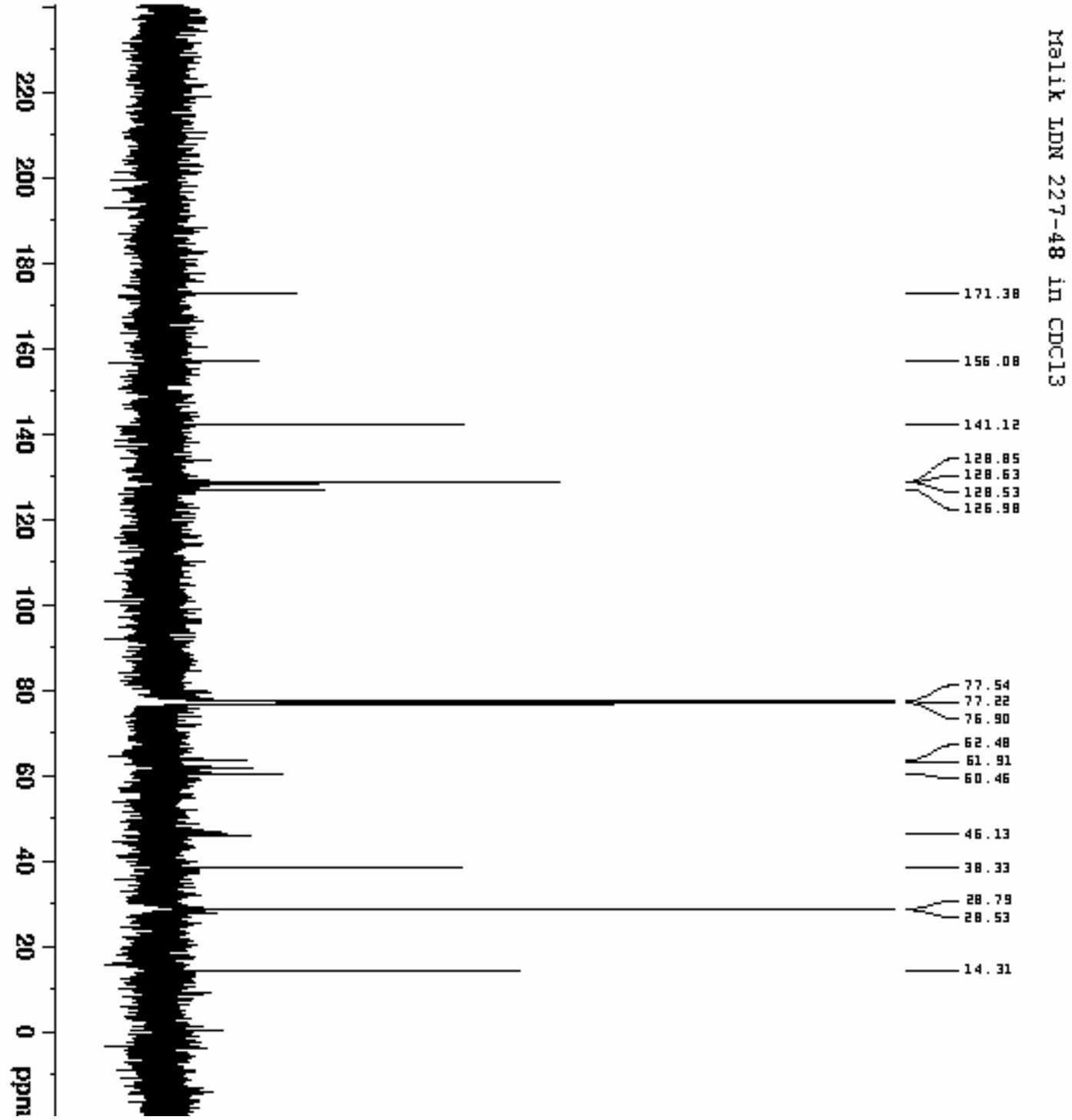

Boc
N
EtO2C
(R,S)-8a
Malik LDN218-28 in CDCl3
172.62
155.25
141.16
128.68
128.50
128.18
126.87
77.55
77.23
76.91
63.61
62.08
60.50
47.79
44.92
28.73
28.60
28.52
27.82
14.29
200
180
160
140
120
100
80
60
40
20
0
ppm

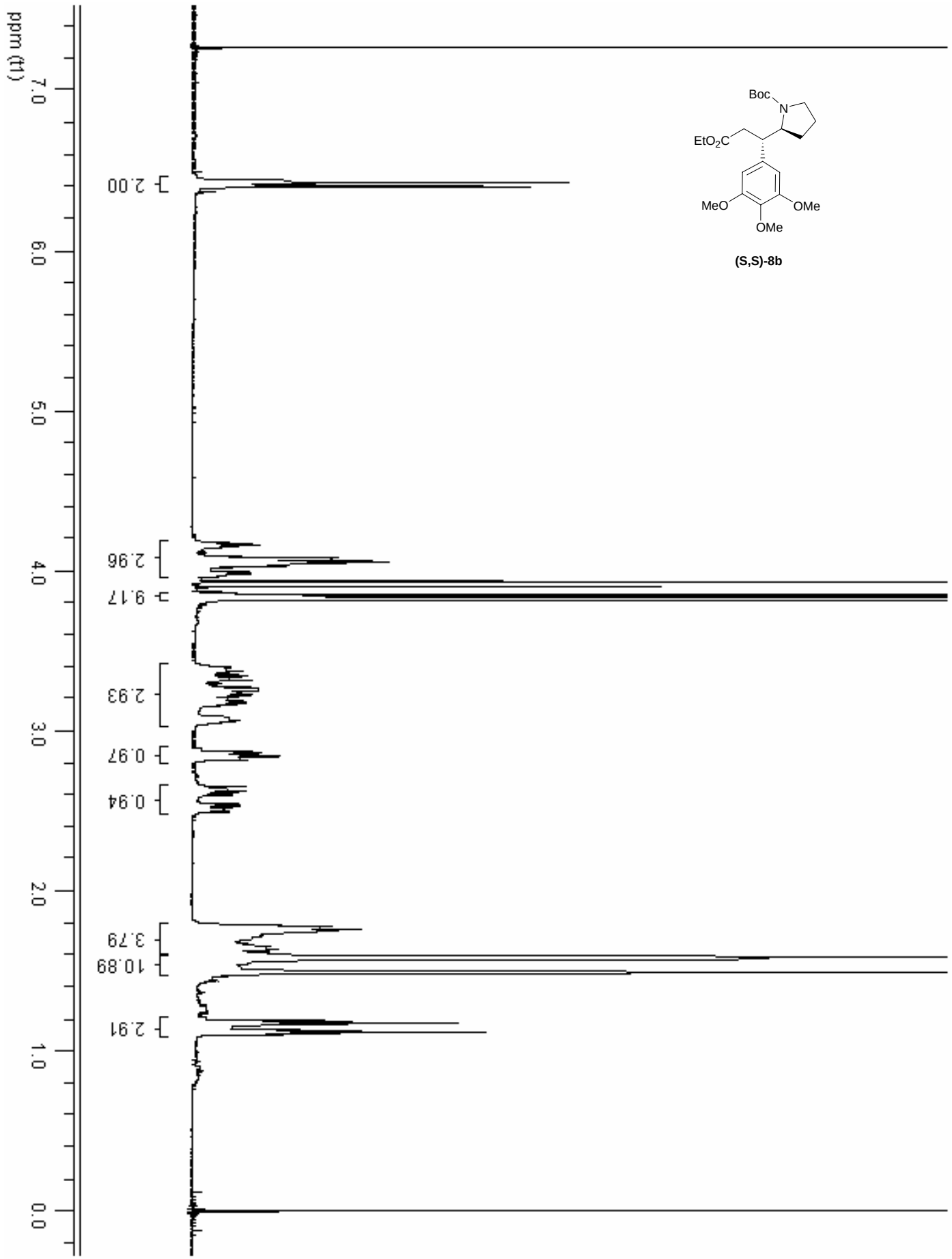


(S,S)-8a


Boc
N
EtO2C

(S,S)-8a


Malik LDN 227-48 in CDCl3
171.38
156.08
141.12
128.85
128.63
128.53
126.98
77.54
77.22
76.90
62.48
61.91
60.46
46.13
38.33
28.79
28.53
14.31
220
200
180
160
140
120
100
80
60
40
20
0
ppm


ppm (t1)
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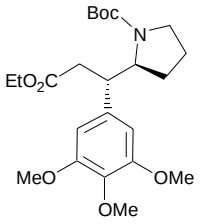
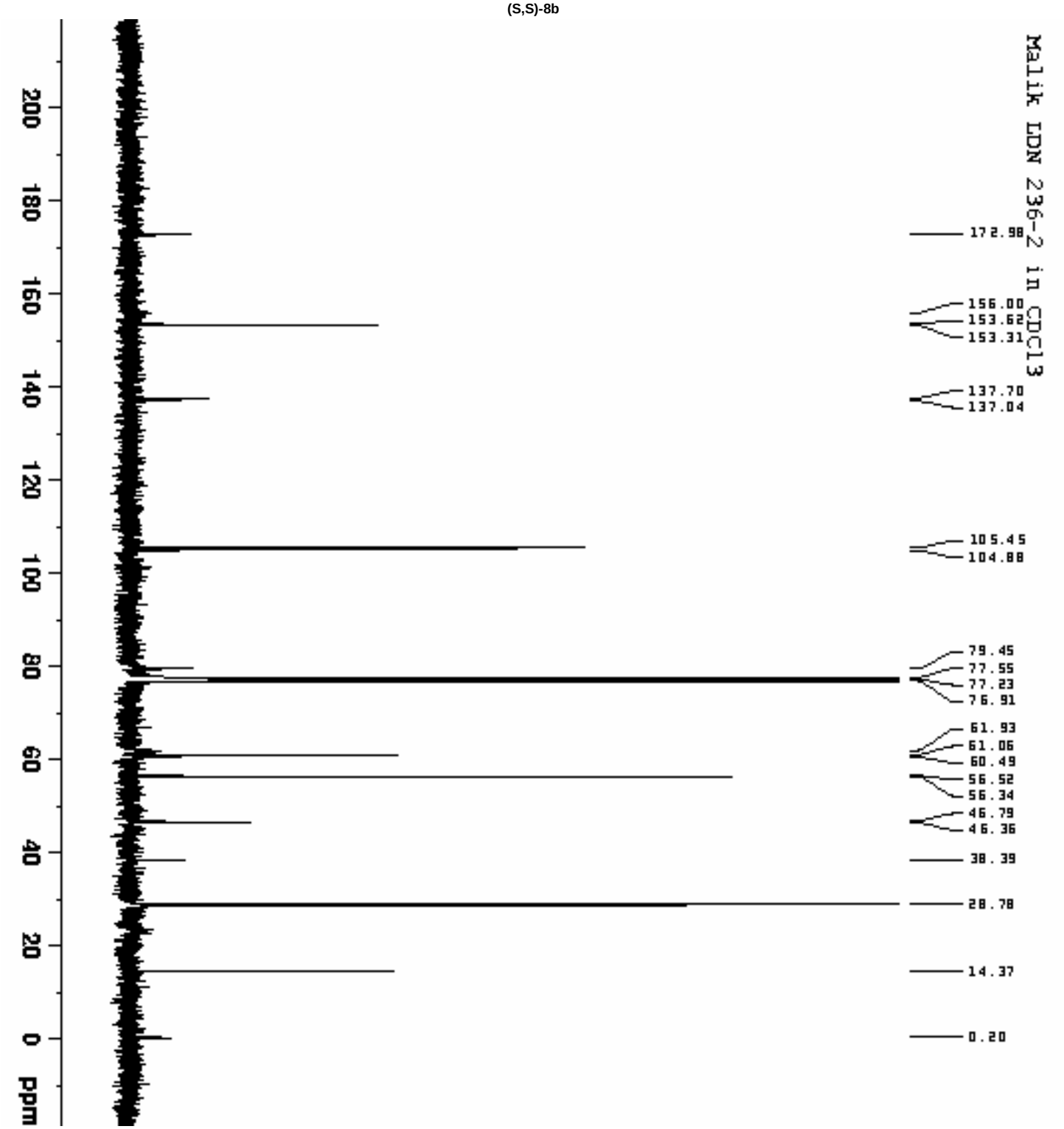
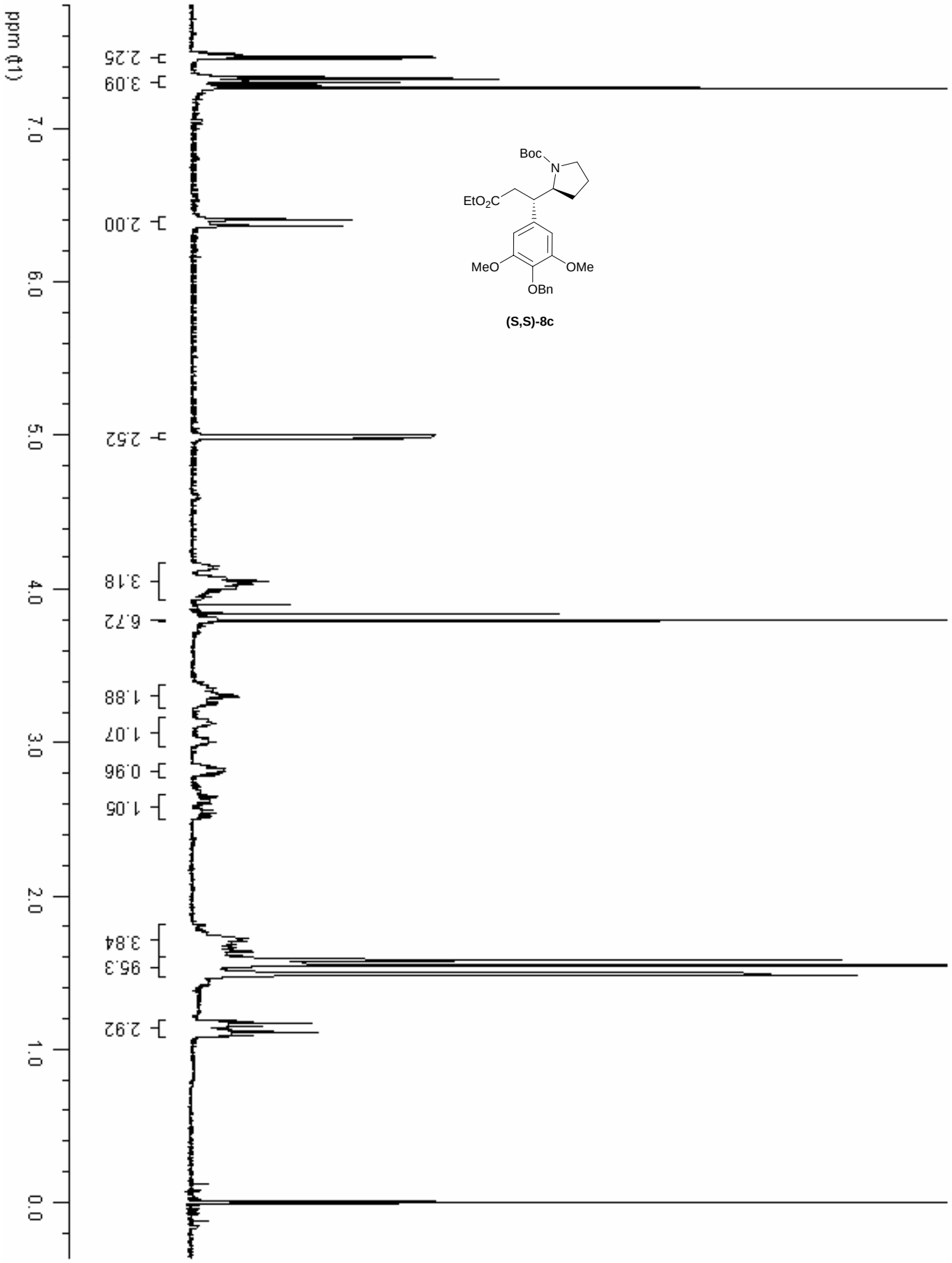
6.0
5.0
4.0
3.0
2.0
1.0
0.0
2.00
2.96
9.17
2.93
0.97
0.94
3.79
10.89
2.91
Boc
N
EtO2C
MeO
OMe
OMe

(S,S)-8b


Boc
N
EtO2C
MeO
OMe
OMe

(S,S)-8b


Malik LDN 236-2 in CDCl3
172.98
156.00
153.62
153.31
137.70
137.04
105.45
104.88
79.45
77.55
77.23
76.91
61.93
61.06
60.49
56.52
56.34
46.79
46.36
38.39
28.78
14.37
0.20
200
180
160
140
120
100
80
60
40
20
0
ppm


ppm (t1)
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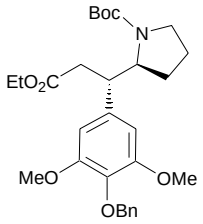
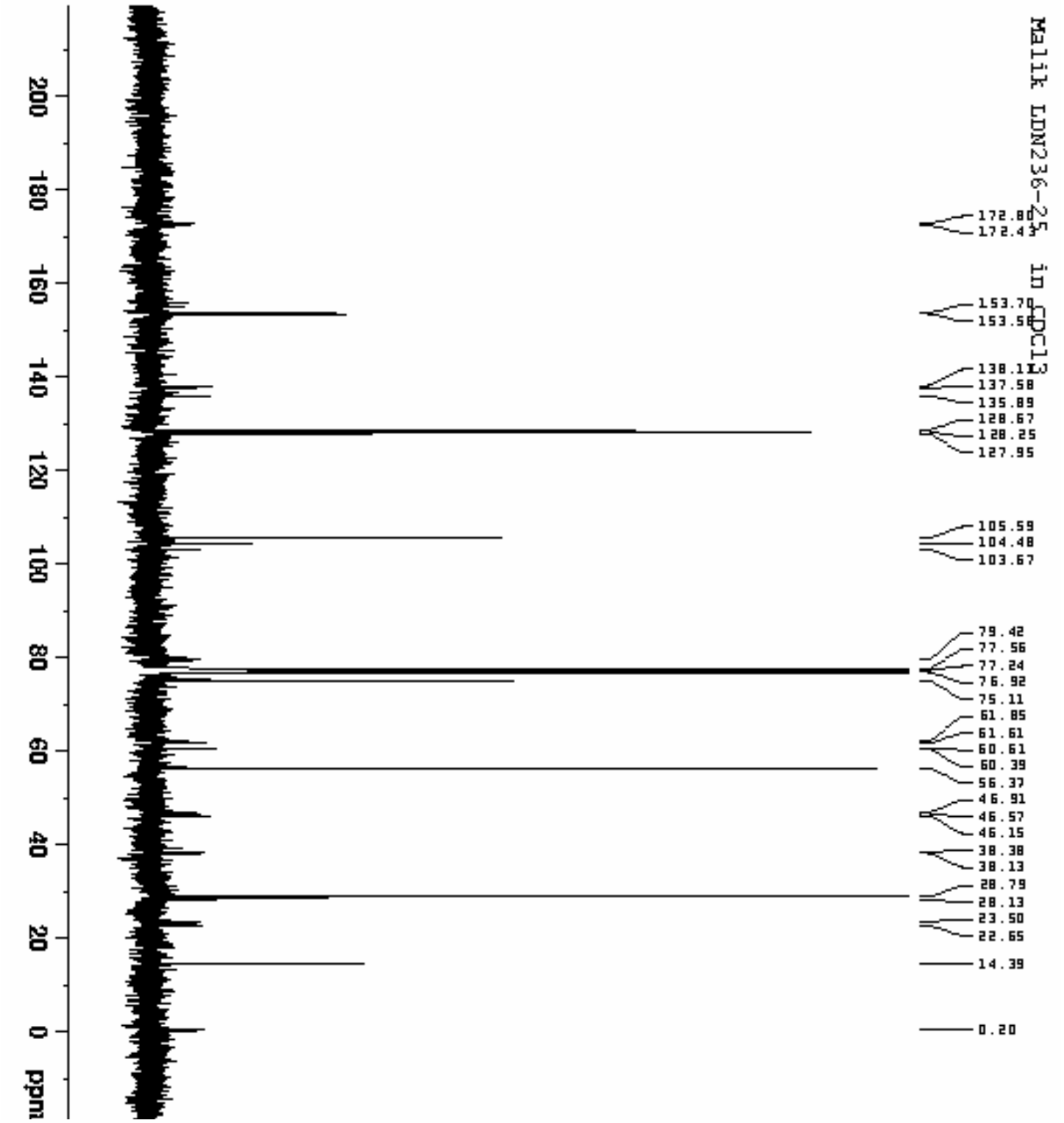
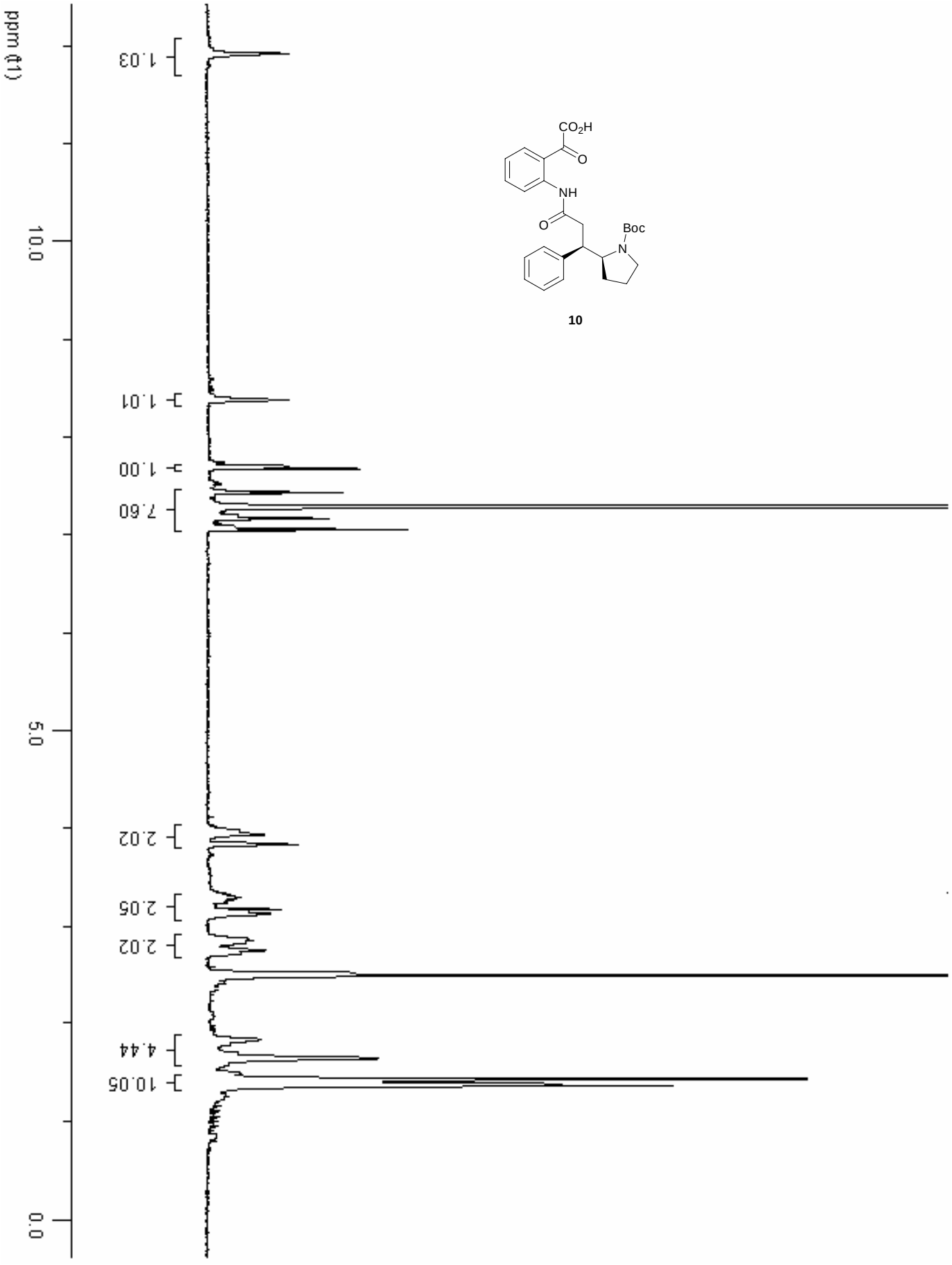
6.0
5.0
4.0
3.0
2.0
1.0
0.0
2.25
3.09
2.00
2.52
3.18
6.72
1.88
1.07
0.96
1.05
3.84
95.3
2.92
Boc
N
EtO2C
MeO
OMe
OBn

(S,S)-8c


Boc
N
EtO2C
MeO
OMe
OBn

(S,S)-8c


Malik LDN236-25, in CDCl3
172.81
172.43
153.70
153.58
138.11
137.58
135.89
128.67
128.25
127.95
105.59
104.48
103.67
79.42
77.56
77.24
76.92
75.11
61.85
61.61
60.61
60.39
56.37
46.91
46.57
46.15
38.38
38.13
28.79
28.13
23.50
22.65
14.39
0.20
200
180
160
140
120
100
80
60
40
20
0
ppm


ppm (t1)
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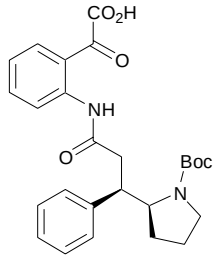
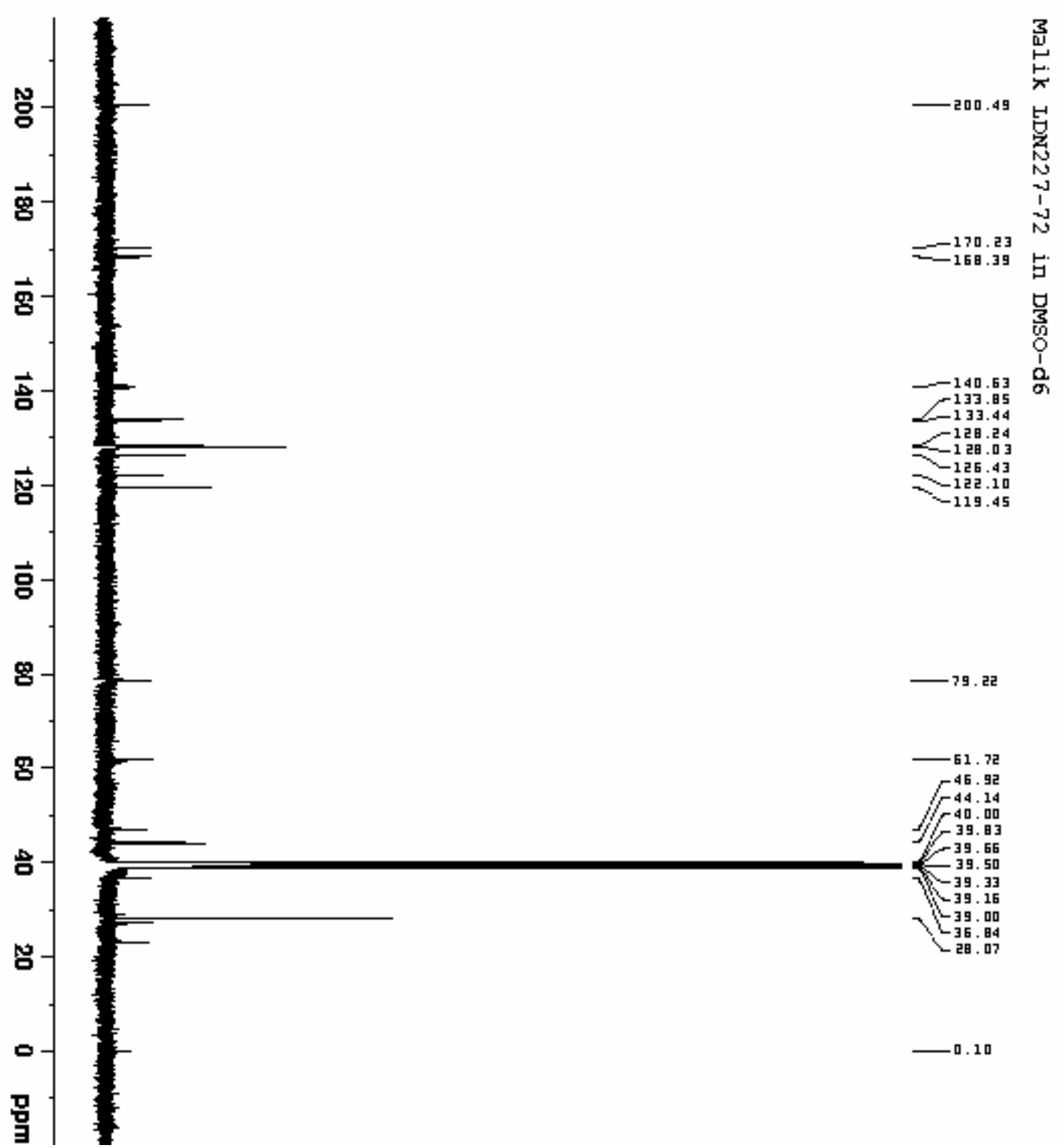
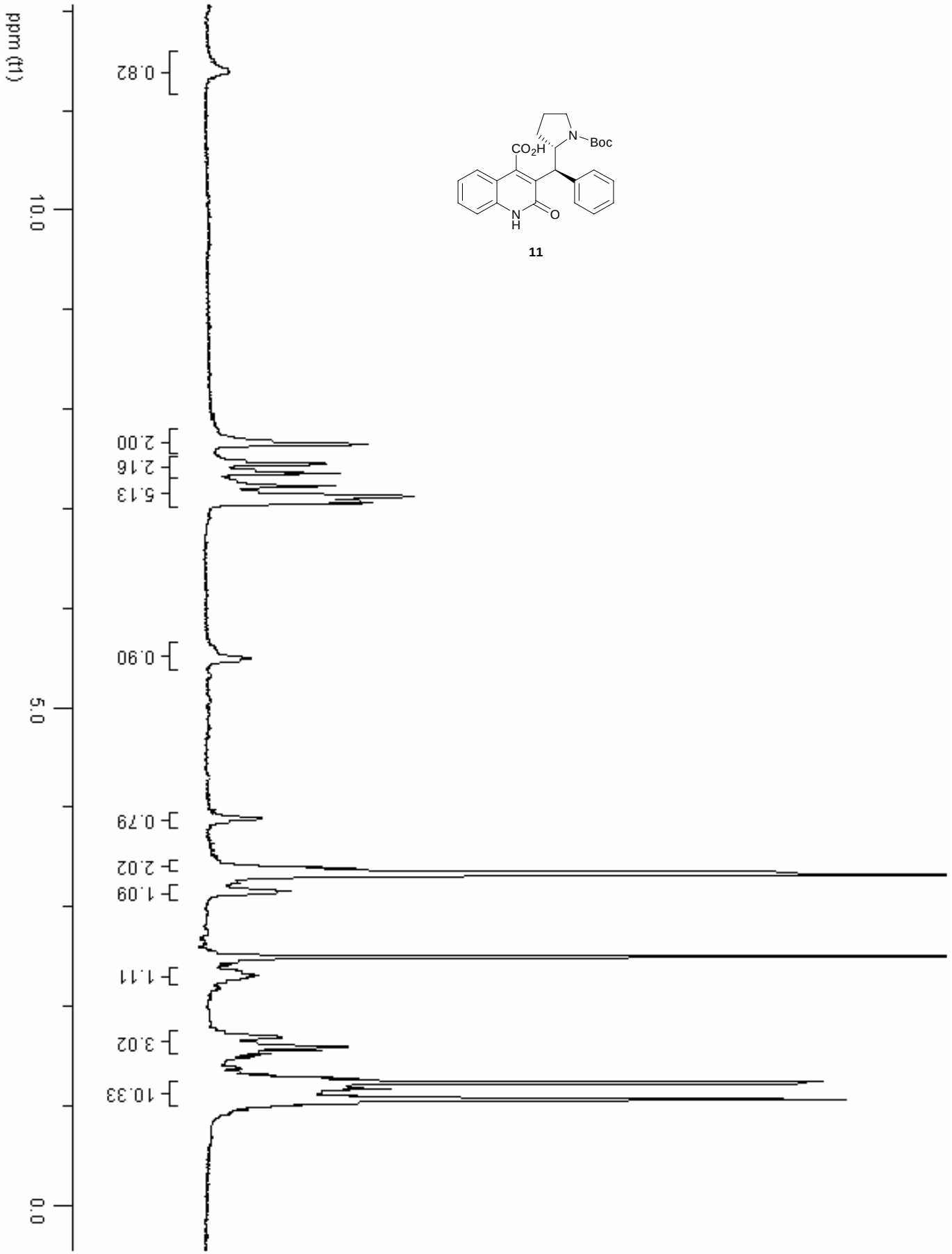
5.0
0.0
1.03
1.01
1.00
7.60
2.02
2.05
2.02
4.44
10.05
CO2H
O
NH
O
Boc
N

10


CO2H
O
NH
O
Boc
N

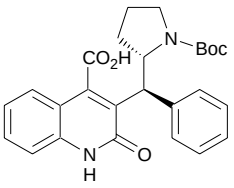
10


Malik LDN227-72 in DMSO-d6
200.49
170.23
168.39
140.63
133.85
133.44
128.24
128.03
126.43
122.10
119.45
79.22
61.72
46.92
44.14
40.00
39.83
39.66
39.50
39.33
39.16
39.00
36.84
28.07
0.10
200
180
160
140
120
100
80
60
40
20
0
ppm

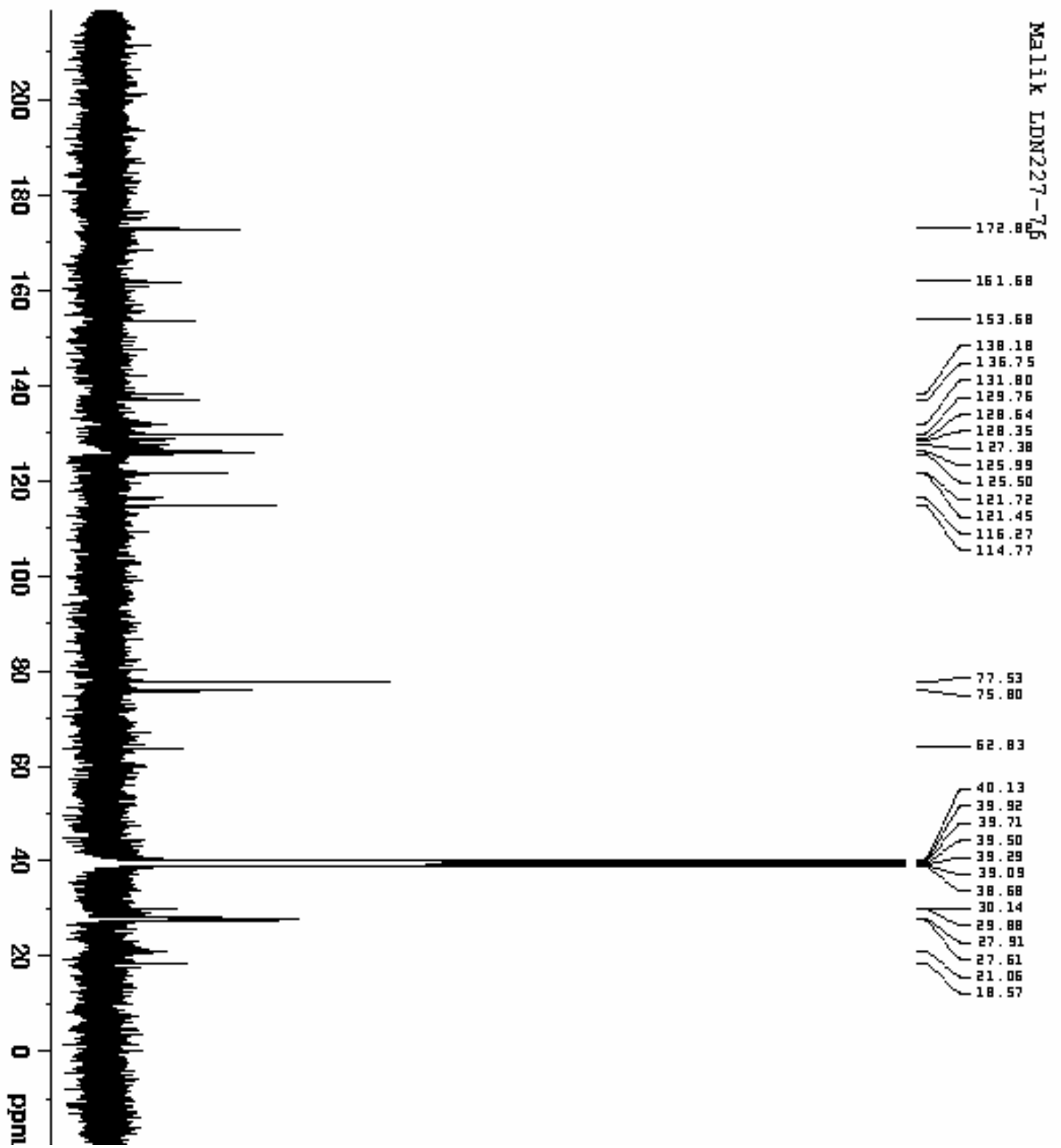

ppm (t1)
10.0
5.0
0.0
0.82
2.00
2.16
5.13
0.90
0.79
2.02
1.09
1.11
3.02
10.33

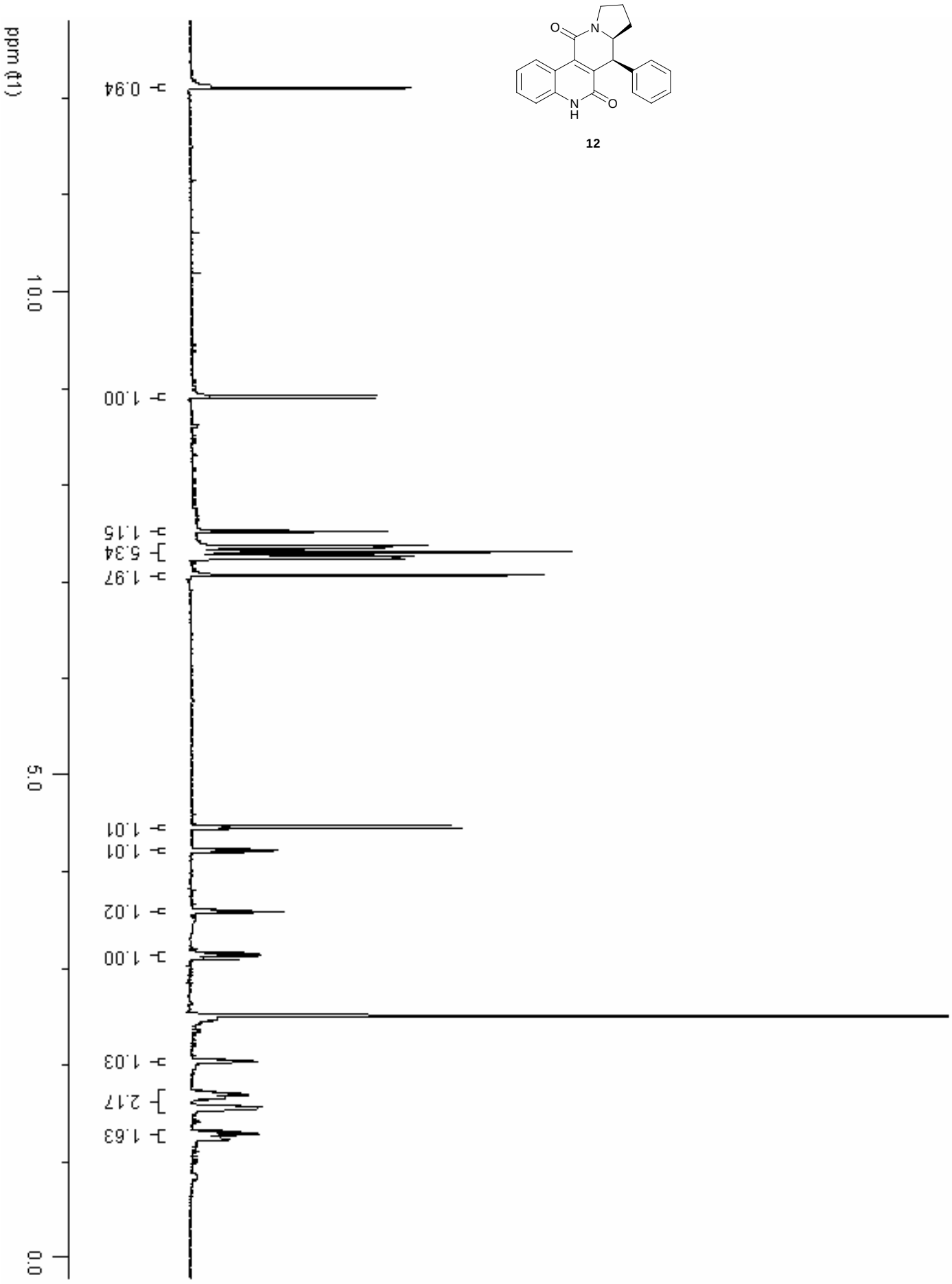
CO2H
N
Boc
N
H
O

11


CO2H
N
Boc
N
H
O

11


Malik LDN227-7g
172.88
161.68
153.68
138.18
136.75
131.80
129.76
128.64
128.35
127.38
125.99
125.50
121.72
121.45
116.27
114.77
77.53
75.80
62.83
40.13
39.92
39.71
39.50
39.29
39.09
38.68
30.14
29.88
27.91
27.61
21.06
18.57
200
180
160
140
120
100
80
60
40
20
0
ppm


ppm (t1)
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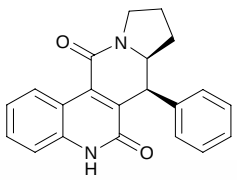
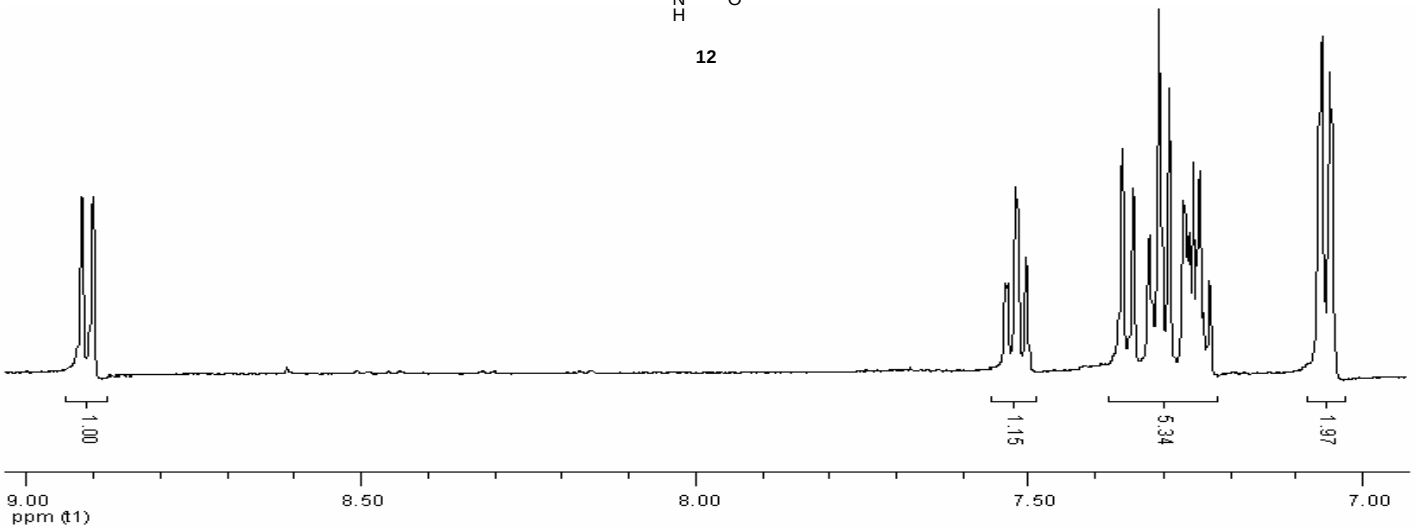
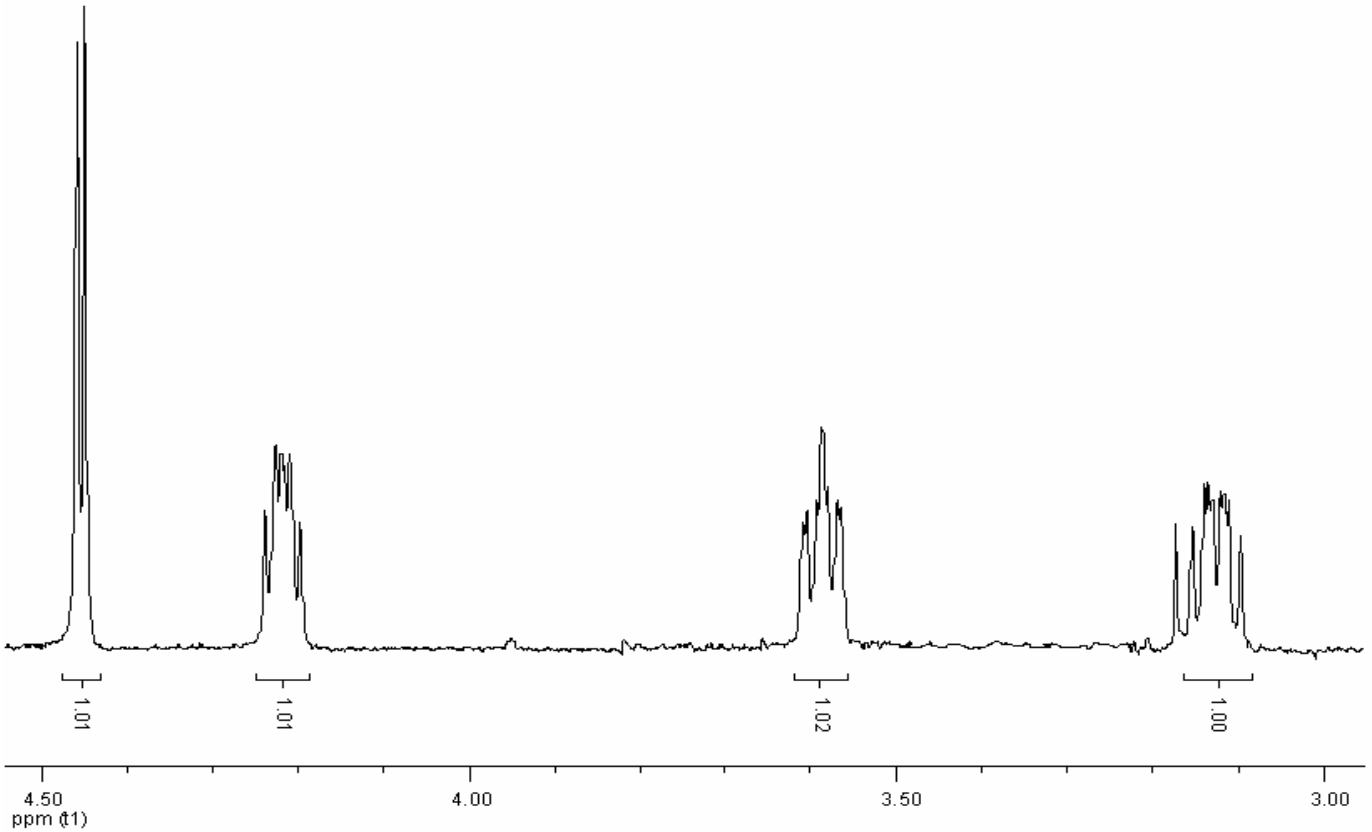
5.0
0.0
0.94
1.00
1.15
5.34
1.97
1.01
1.01
1.02
1.00
1.03
2.17
1.63
O
N
O
N
H

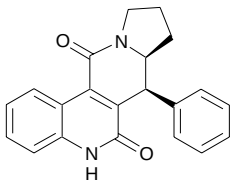
12


O
N
O
N
H

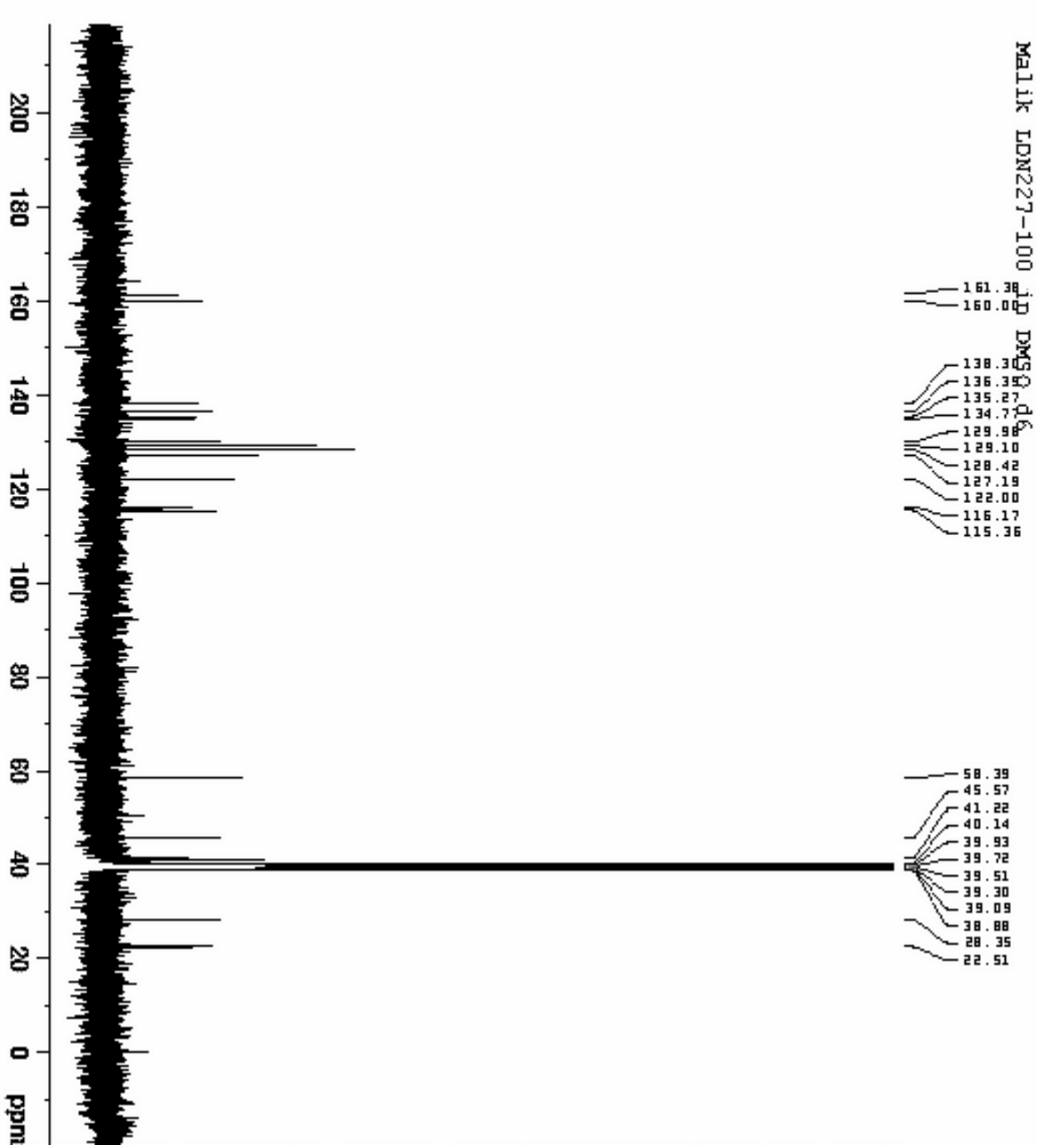
12

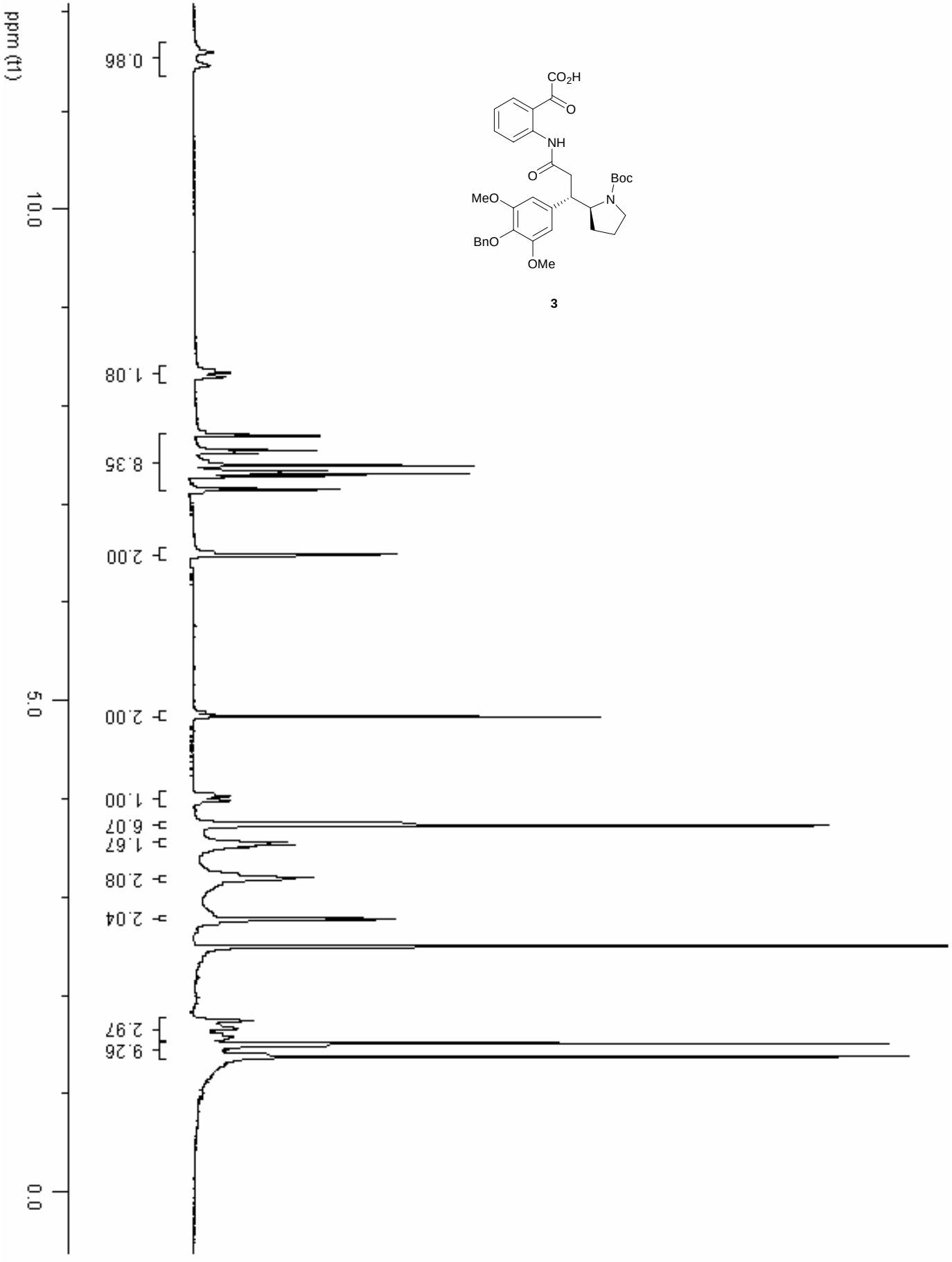

1.00
1.15
5.34
1.97
9.00
8.50
8.00
7.50
7.00
ppm (t1)


1.01
1.01
1.02
1.00
4.50
4.00
3.50
3.00
ppm (t1)


O
N
N
H
O

12


Malik LDN227-100 jp DMSO d6
161.38
160.08
138.39
136.39
135.27
134.71
129.98
129.10
128.42
127.19
122.00
116.17
115.36
58.39
45.57
41.22
40.14
39.93
39.72
39.51
39.30
39.09
38.88
28.35
22.51
200
180
160
140
120
100
80
60
40
20
0
ppm


ppm (t1)
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0.0
0.86
1.08
8.35
2.00
2.00
1.00
6.07
1.67
2.08
2.04
2.97
9.26
CO2H
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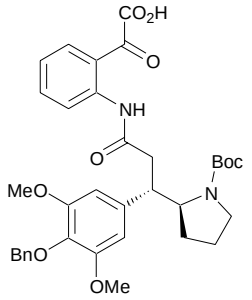
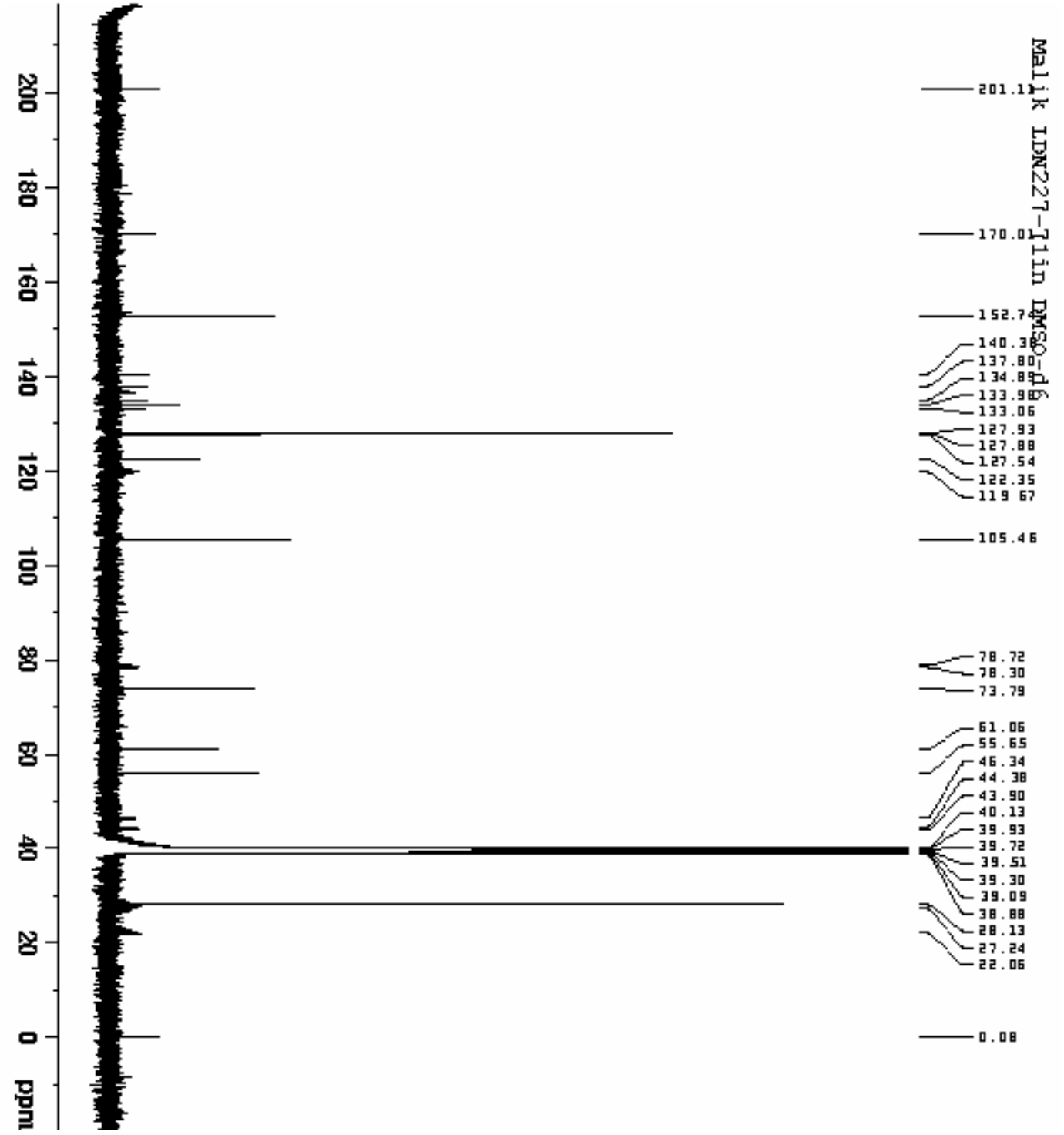
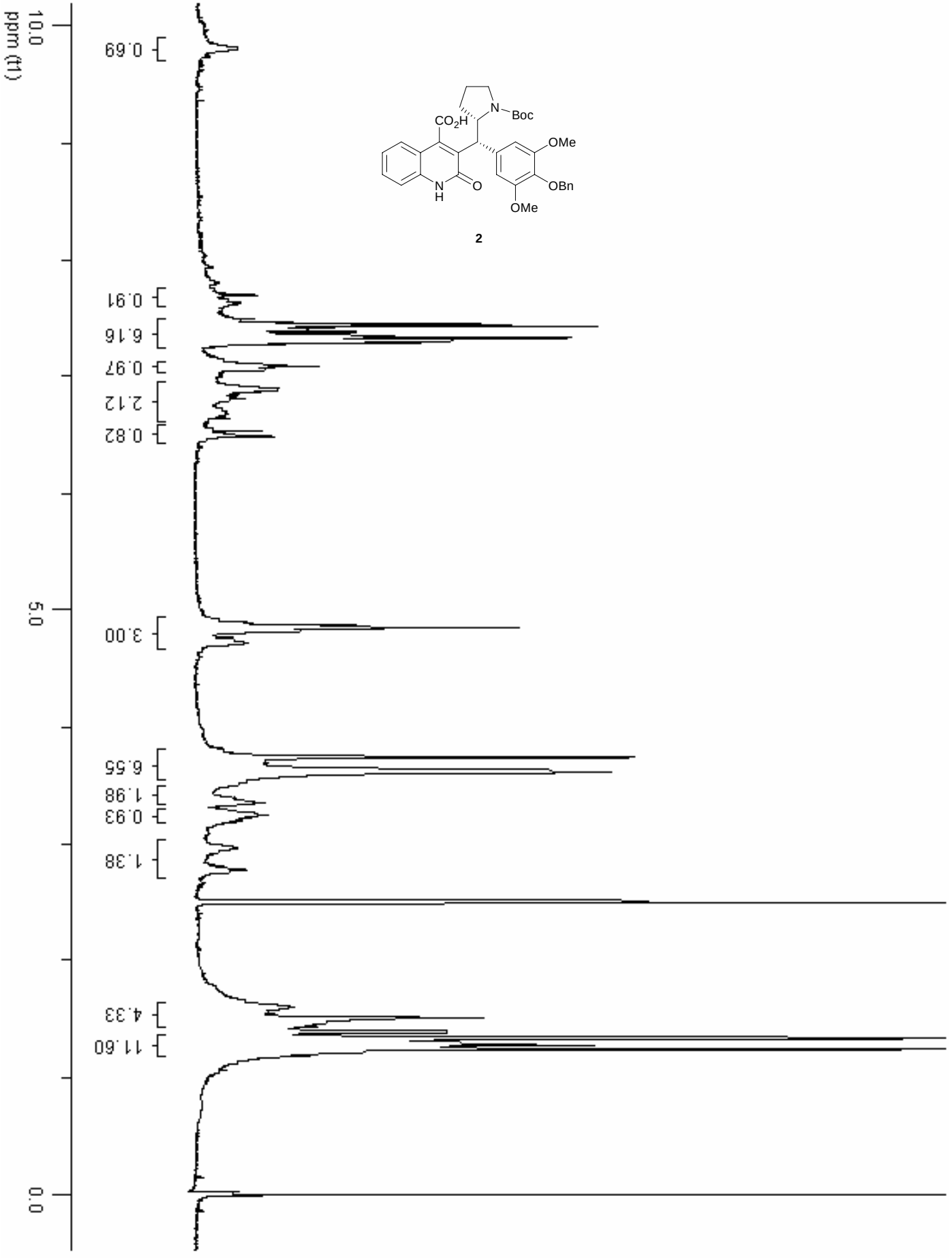
NH
O
Boc
N
MeO
BnO
OMe

3

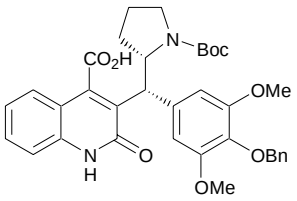

CO2H
O
NH
O
Boc
N
MeO
BnO
OMe

3

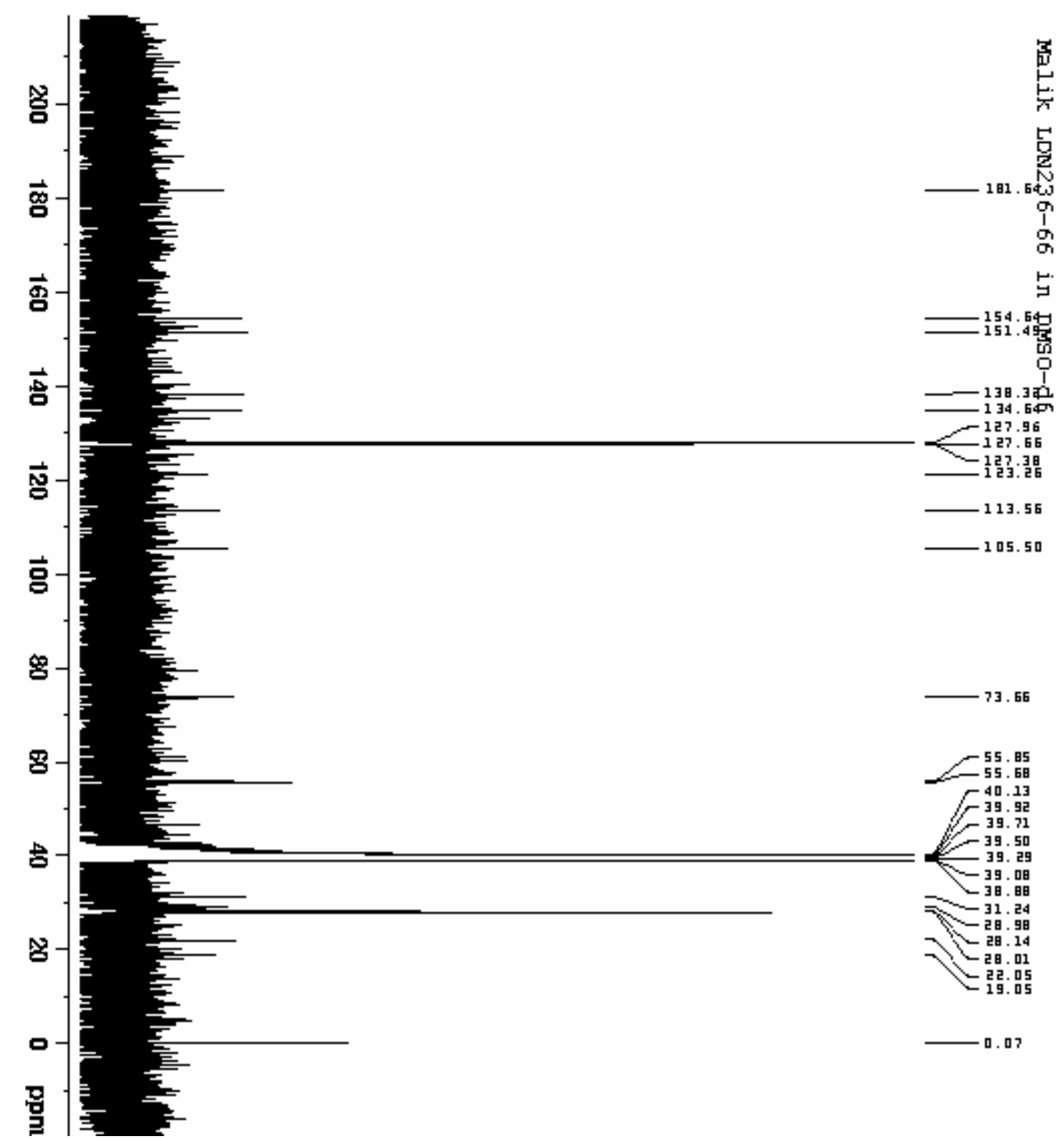

Malik LDN227-7lin DMSO-d6
201.11
170.01
152.77
140.38
137.80
134.88
133.98
133.06
127.93
127.88
127.54
122.35
119.67
105.46
78.72
78.30
73.79
61.06
55.65
46.34
44.38
43.90
40.13
39.93
39.72
39.51
39.30
39.09
38.88
28.13
27.24
22.06
0.08
200
180
160
140
120
100
80
60
40
20
0
ppm

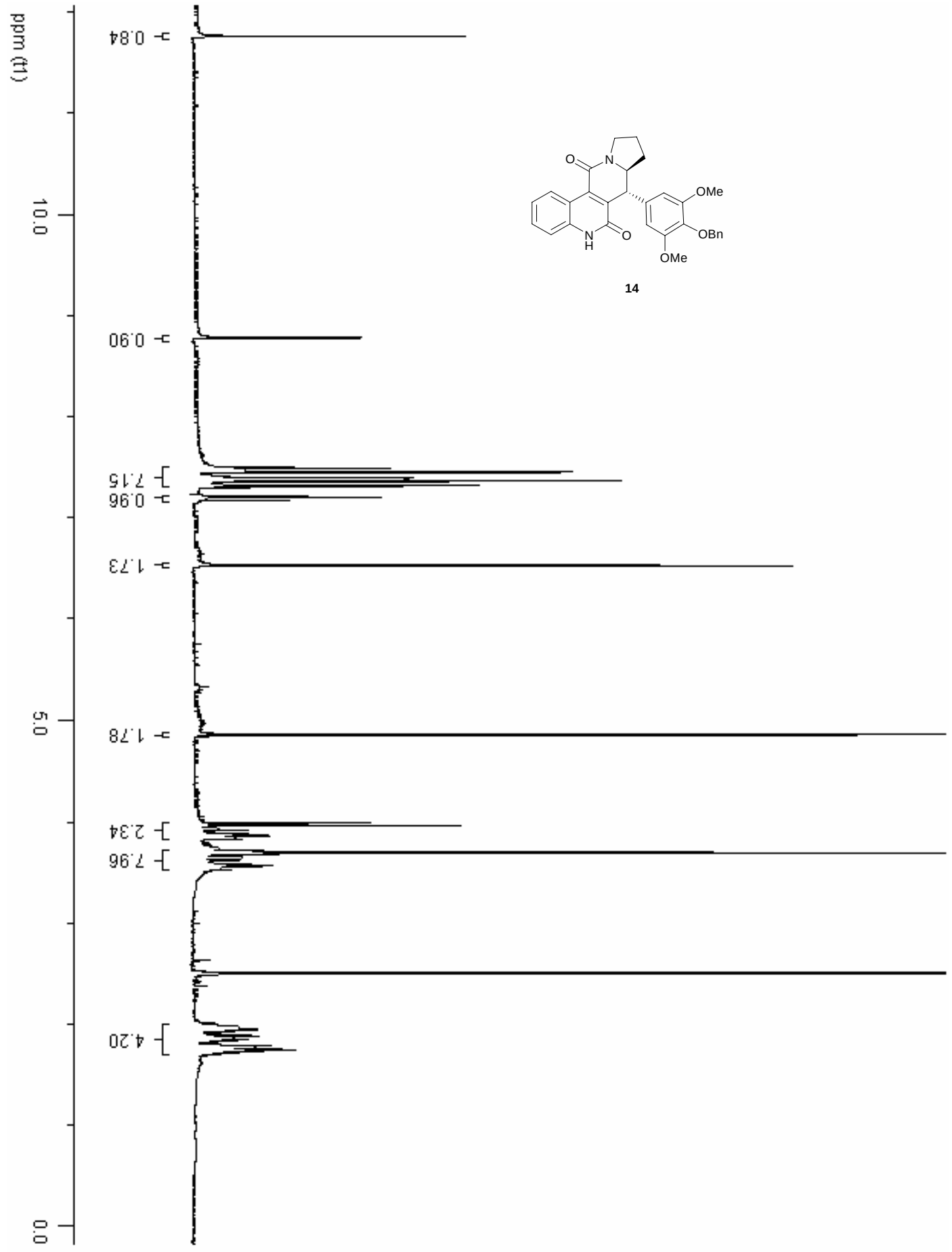

10.0
ppm (t1)
5.0
0.0
0.69
0.91
6.16
0.97
2.12
0.82
3.00
6.55
1.98
0.93
1.38
4.33
11.60
CO2H
N
Boc
OMe
OBn
OMe
N
H
O

2

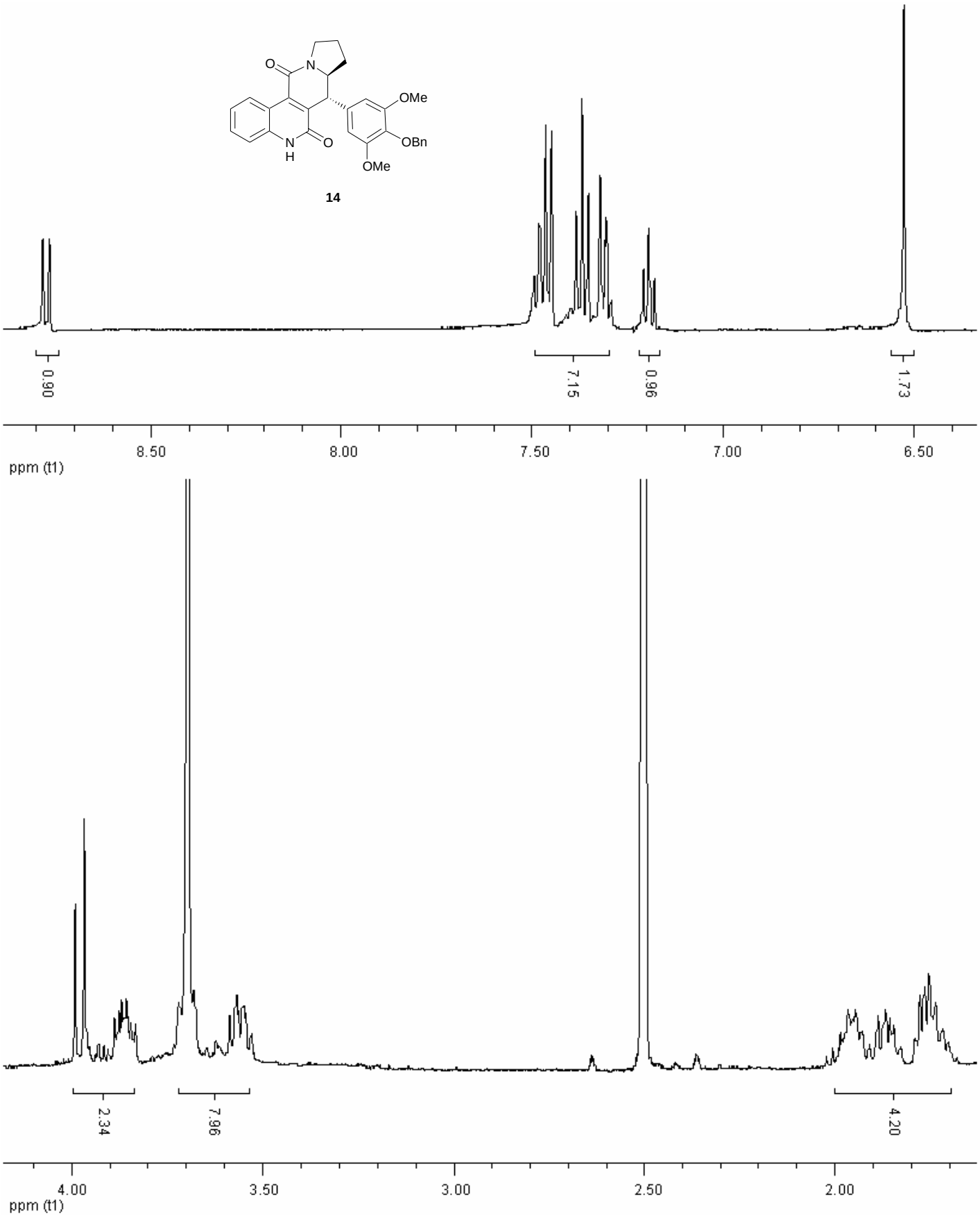

CO2H
N
Boc
OMe
OBn
OMe
N
H
O

2

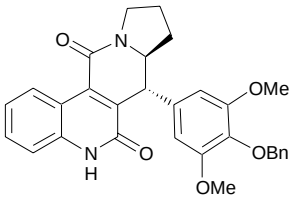

Malik LDN236-66 in DMSO-d6
181.66
154.64
151.49
138.34
134.64
127.96
127.66
127.38
123.26
113.56
105.50
73.66
55.85
55.68
40.13
39.92
39.71
39.50
39.29
39.08
38.88
31.24
28.98
28.14
28.01
22.05
19.05
0.07
200
180
160
140
120
100
80
60
40
20
0
ppm


ppm (t1)
10.0
5.0
0.0
0.84
0.90
7.15
0.96
1.73
1.78
2.34
7.96
4.20
O
N
OMe
OBn
OMe
N
H
O

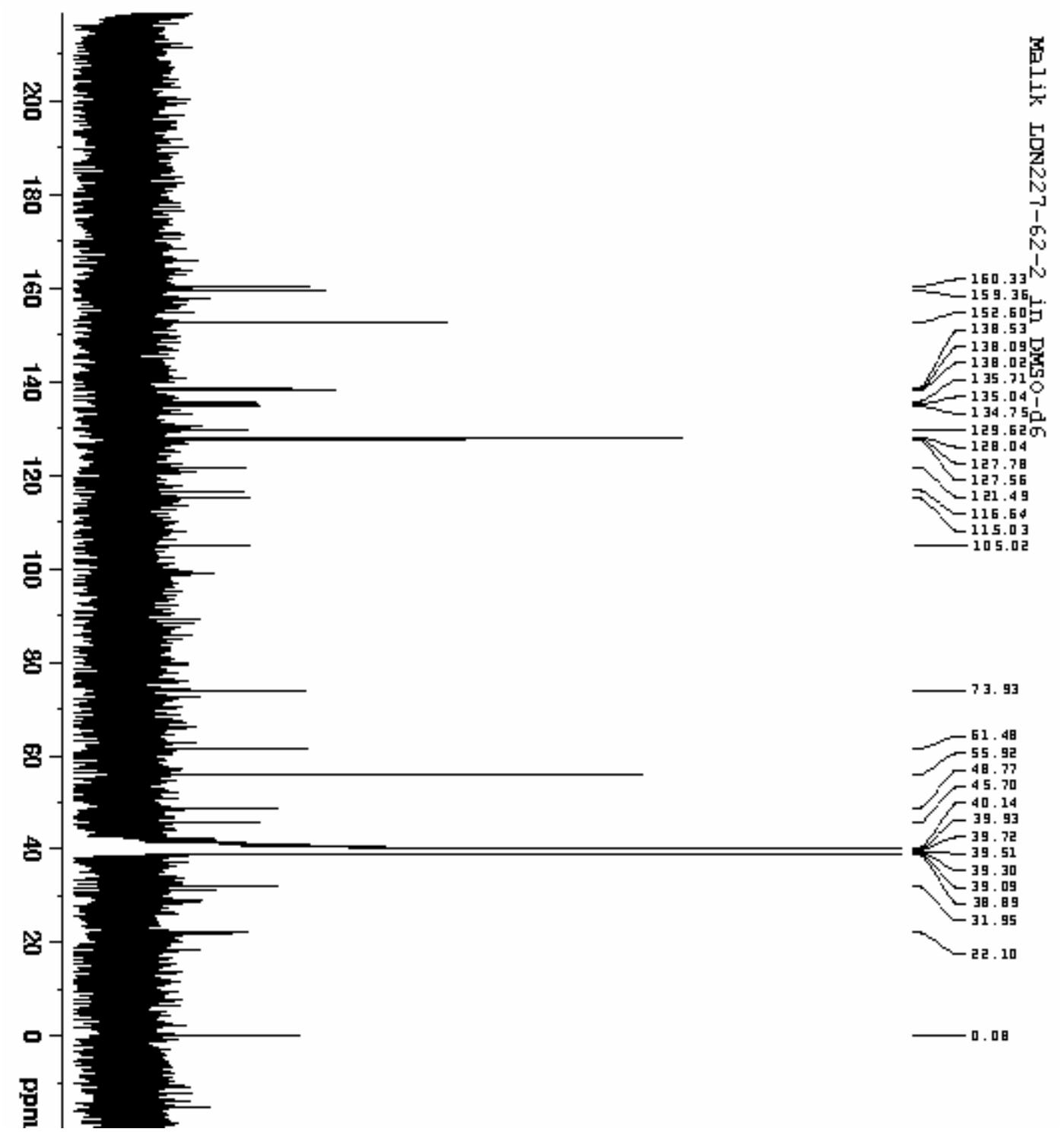
14

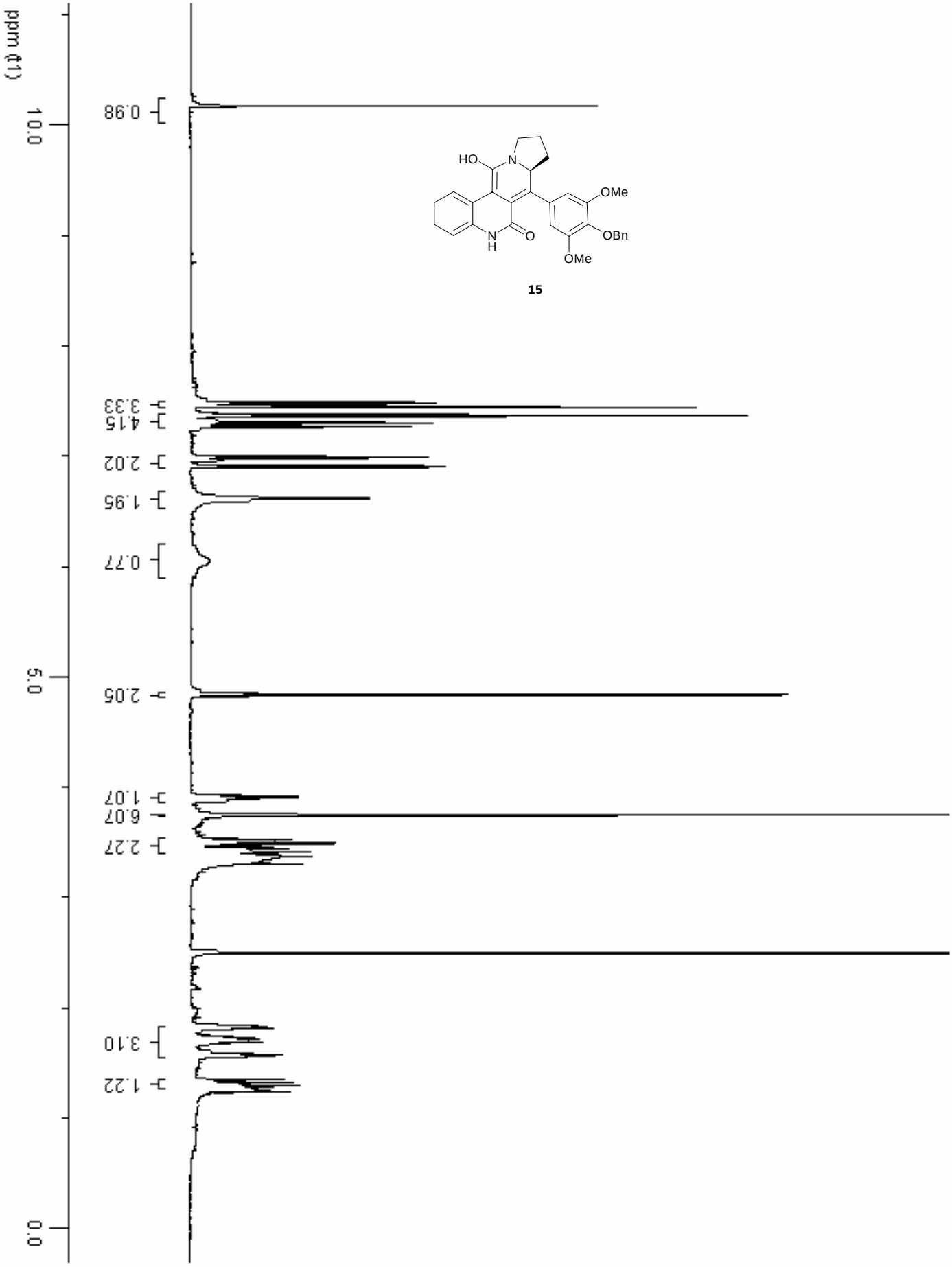

O
N
OMe
OBn
N
H
O
OMe
0.90
7.15
0.96
1.73
8.50
8.00
7.50
7.00
6.50
ppm (t1)
2.34
7.96
4.20
4.00
3.50
3.00
2.50
2.00
ppm (t1)

14

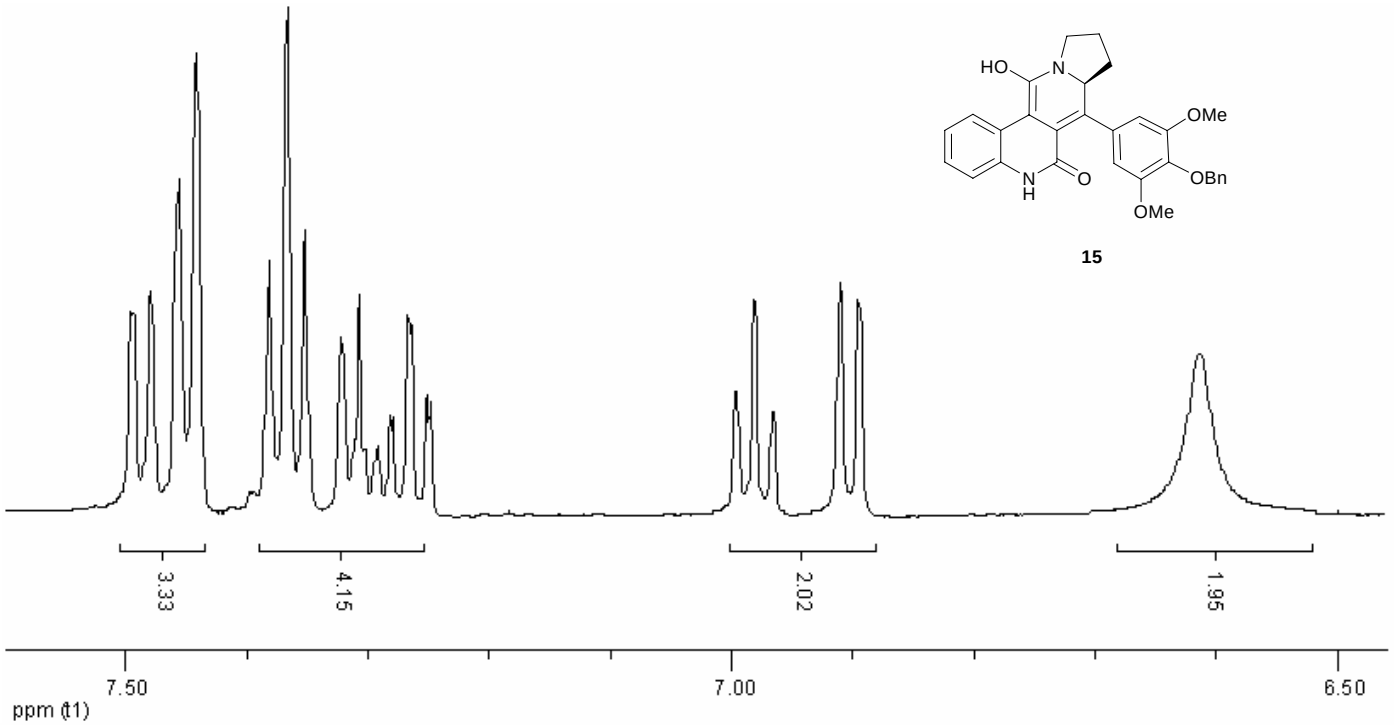

O
N
OMe
OBn
N
H
O
OMe

14

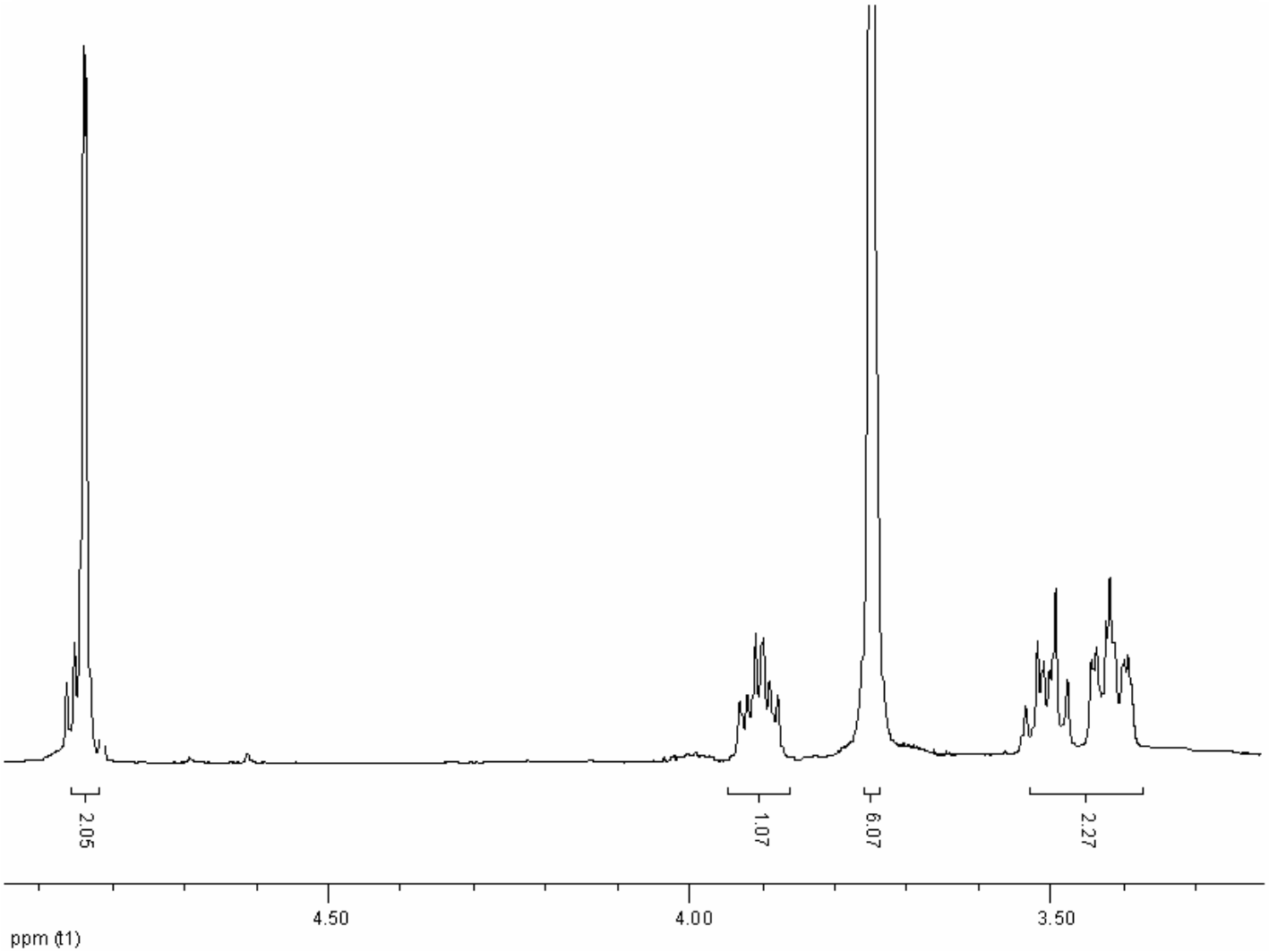

Malik LDN227-62-2 in DMSO-d6
160.33
159.36
152.60
138.53
138.09
138.02
135.71
135.04
134.75
129.62
128.04
127.78
127.56
121.49
116.64
115.03
105.02
73.93
61.48
55.92
48.77
45.70
40.14
39.93
39.72
39.51
39.30
39.09
38.89
31.95
22.10
0.08
200
180
160
140
120
100
80
60
40
20
0
ppm

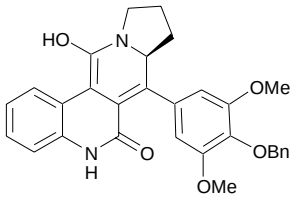

ppm (t1)
10.0
5.0
0.0
0.98
3.33
4.15
2.02
1.95
0.77
2.05
1.07
6.07
2.27
3.10
1.22
HO
N
OMe
OBn
OMe
N
H
O

15

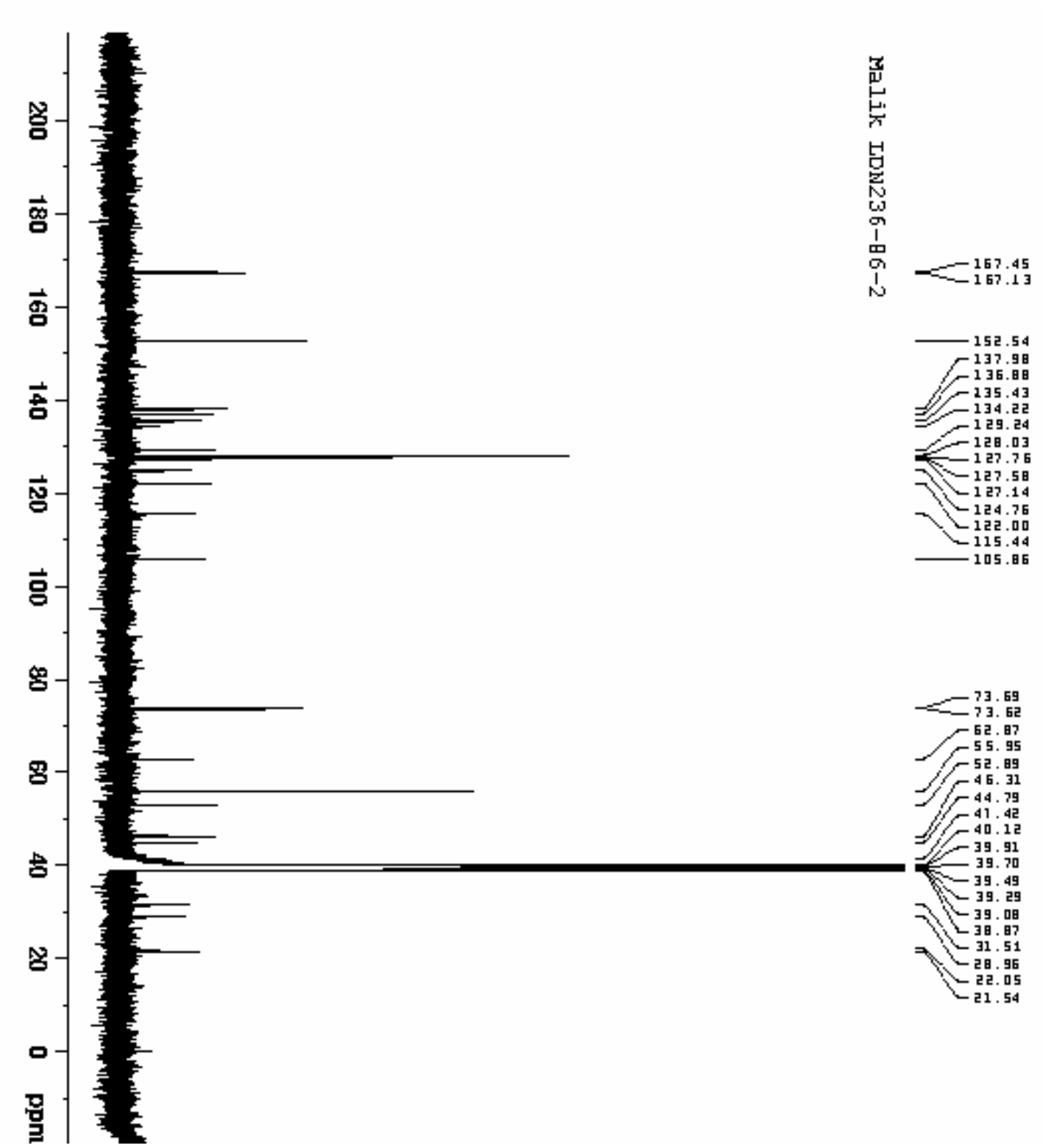

HO
N
OMe
OBn
OMe
N
H
O
3.33
4.15
2.02
1.95
7.50
7.00
6.50
ppm (t1)

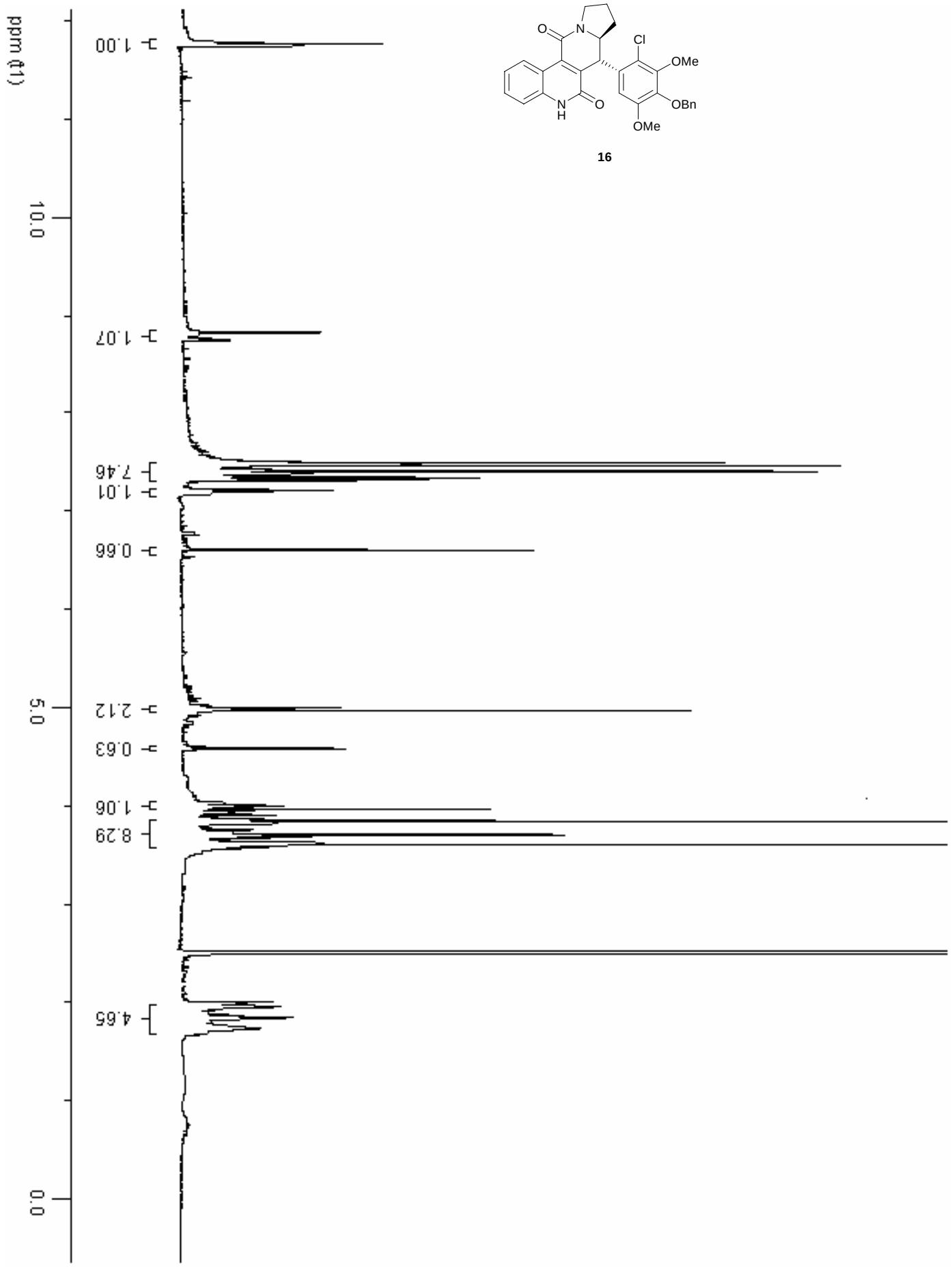
15


2.05
1.07
6.07
2.27
4.50
4.00
3.50
ppm (t1)

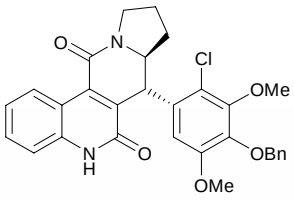

HO
N
OMe
OBn
N
H
O
OMe

15

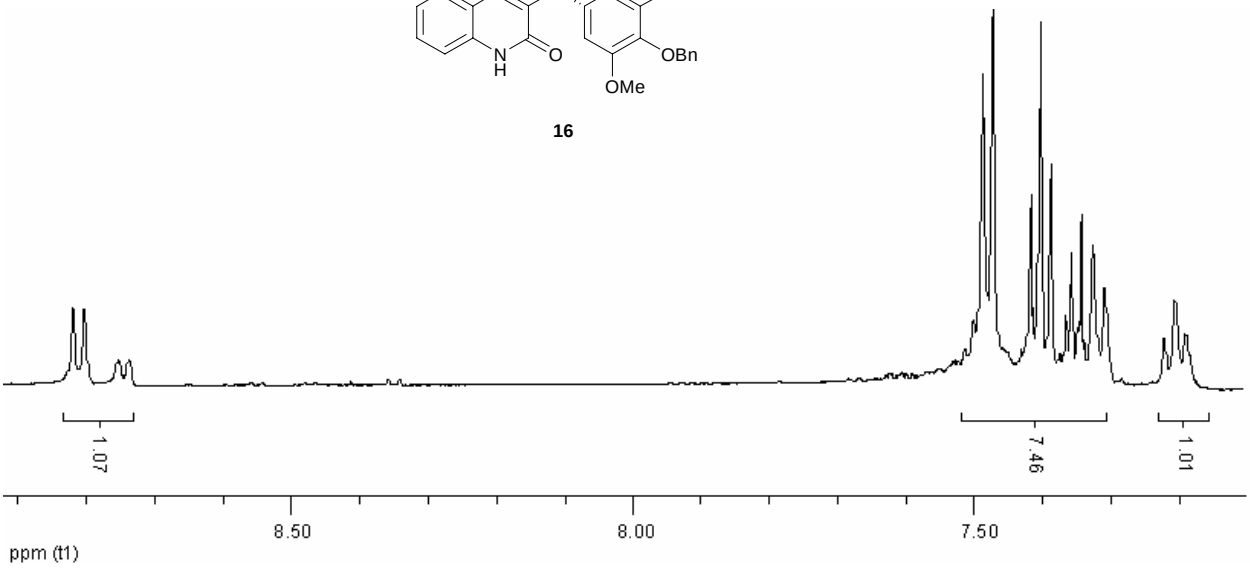

Malik LDN236-B6-2
167.45
167.13
152.54
137.98
136.88
135.43
134.22
129.24
128.03
127.76
127.58
127.14
124.76
122.00
115.44
105.86
73.69
73.62
62.87
55.95
52.89
46.31
44.79
41.42
40.12
39.91
39.70
39.49
39.29
39.08
38.87
31.51
28.96
22.05
21.54
200
180
160
140
120
100
80
60
40
20
0
ppm

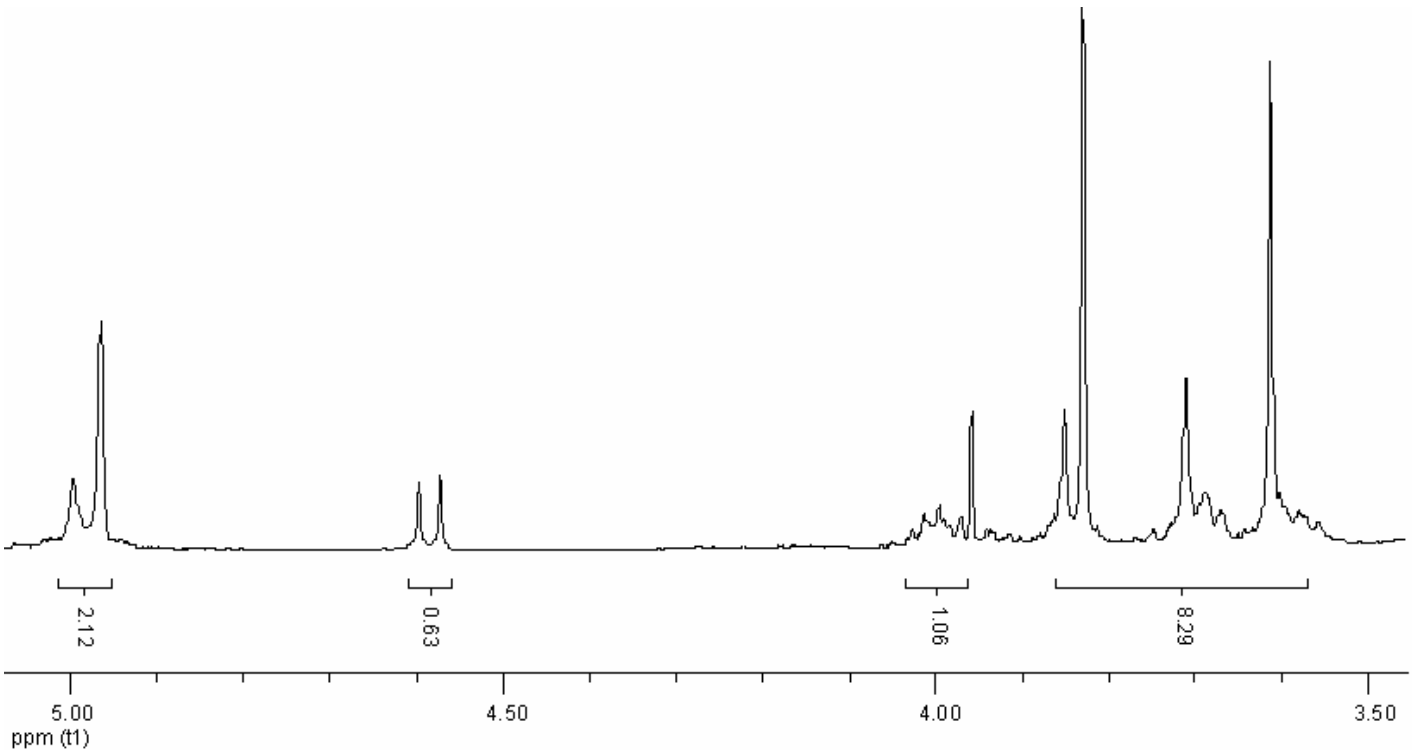

ppm (t1)
10.0
5.0
0.0
1.00
1.07
7.46
1.01
0.66
2.12
0.63
1.06
8.29
4.65
O
N
Cl
OMe
OBn
OMe
N
H
O

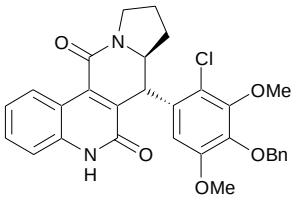
16


O
N
Cl
OMe
OBn
OMe
N
H
O

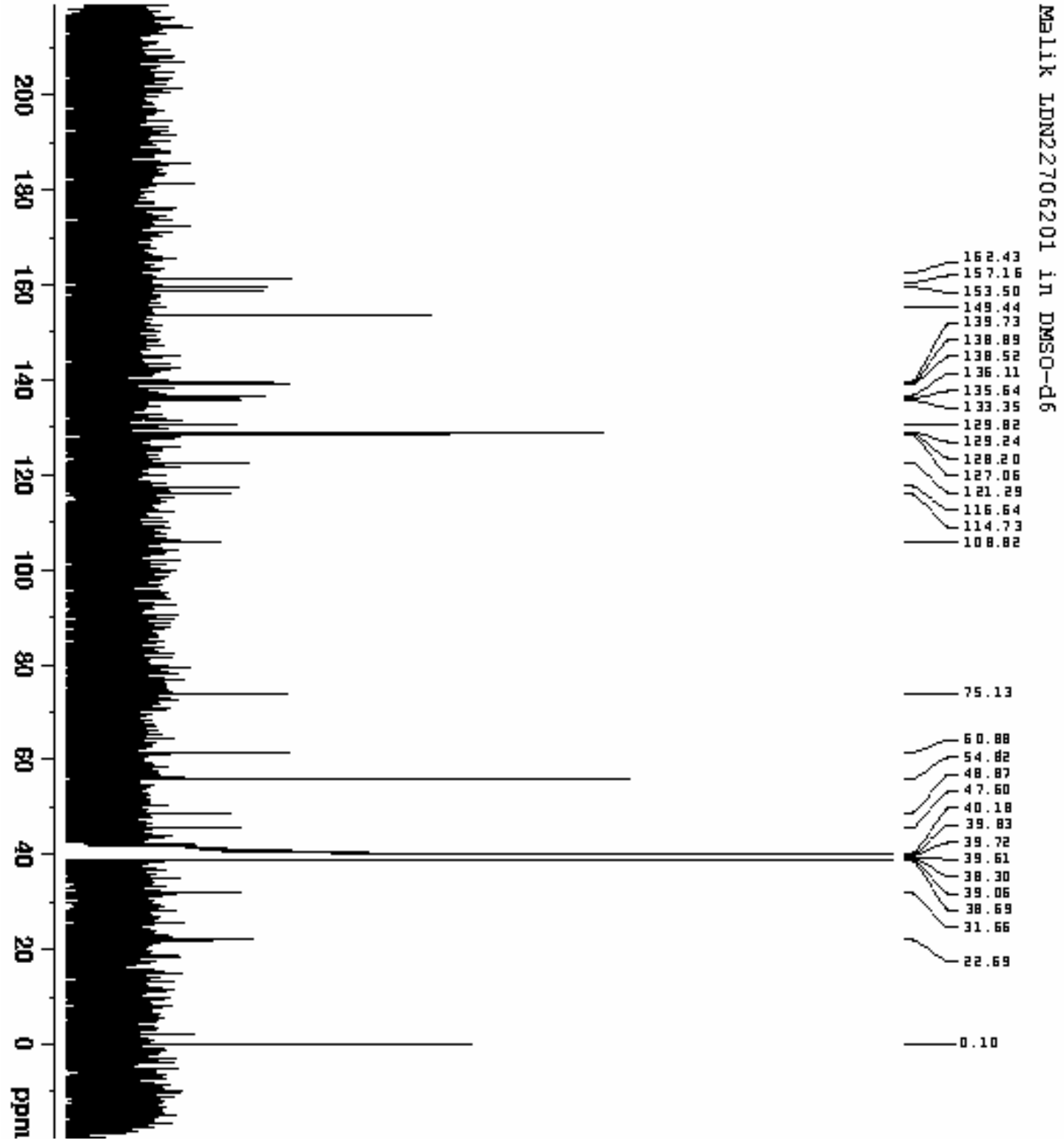
16


1.07
7.46
1.01
8.50
8.00
7.50
ppm (t1)

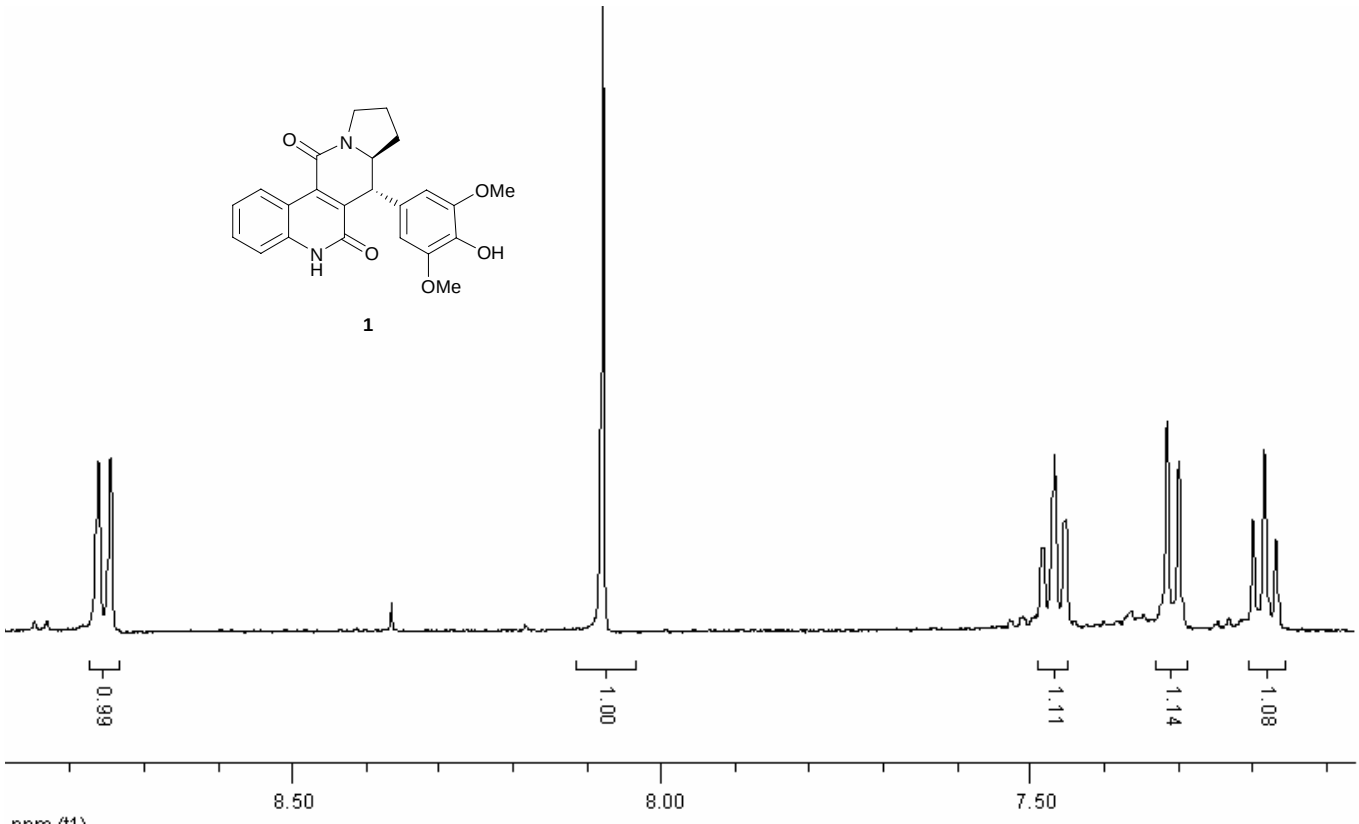

2.12
0.63
1.06
8.29
5.00
4.50
4.00
3.50
ppm (t1)


O
N
Cl
OMe
OBn
N
H
O
OMe

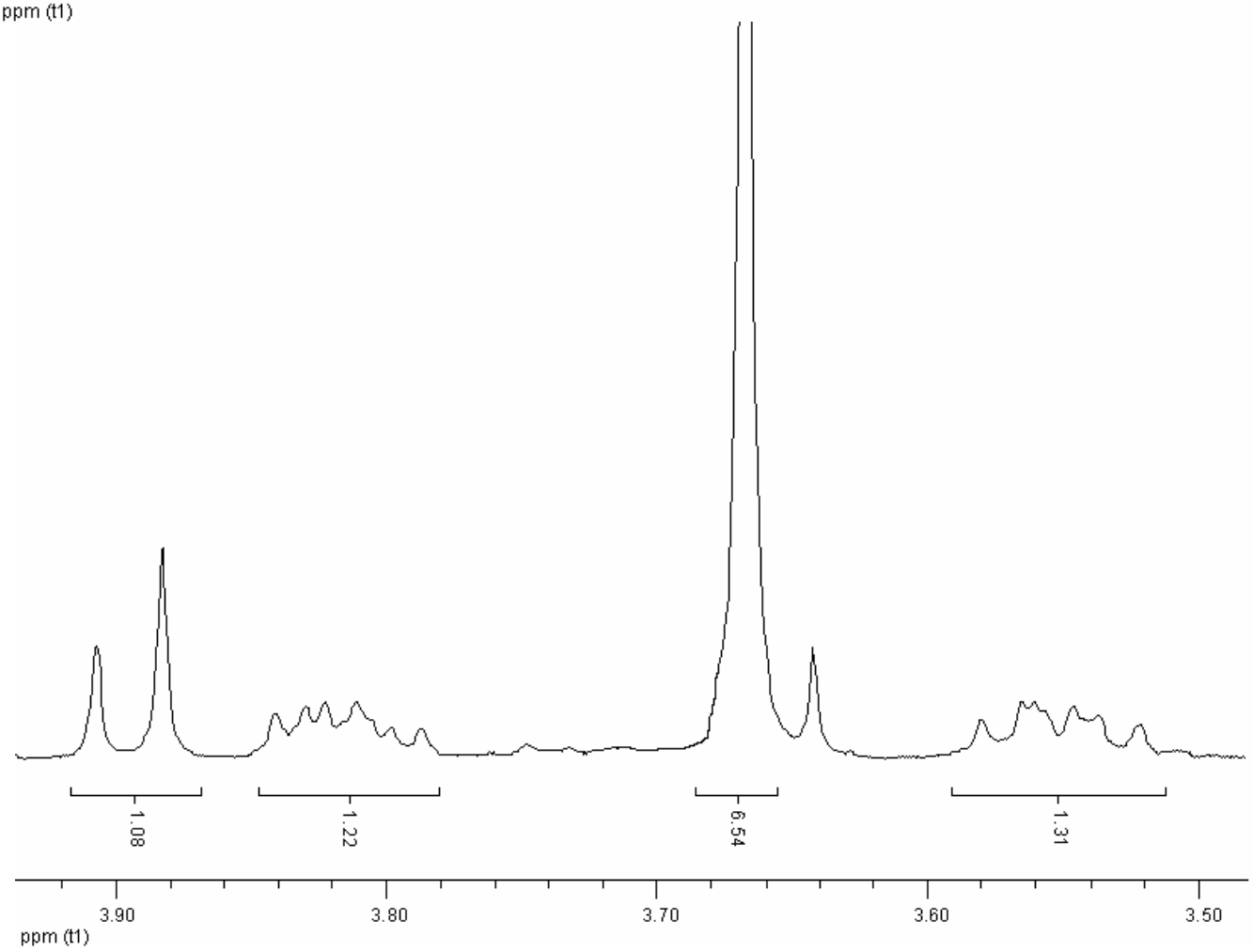
16

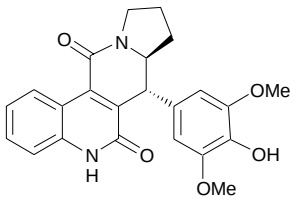

Malik IDN22706201 in DMSO-d6
162.43
157.16
153.50
149.44
139.73
138.89
138.52
136.11
135.64
133.35
129.82
129.24
128.20
127.06
121.29
116.64
114.73
108.82
75.13
60.88
54.82
48.87
47.60
40.18
39.83
39.72
39.61
38.30
39.06
38.69
31.66
22.69
0.10
200
180
160
140
120
100
80
60
40
20
0
ppm

ppm (t1)
10.0
5.0
0.0
0.96
0.99
1.00
1.11
2.31
2.04
2.35
8.66
4.10

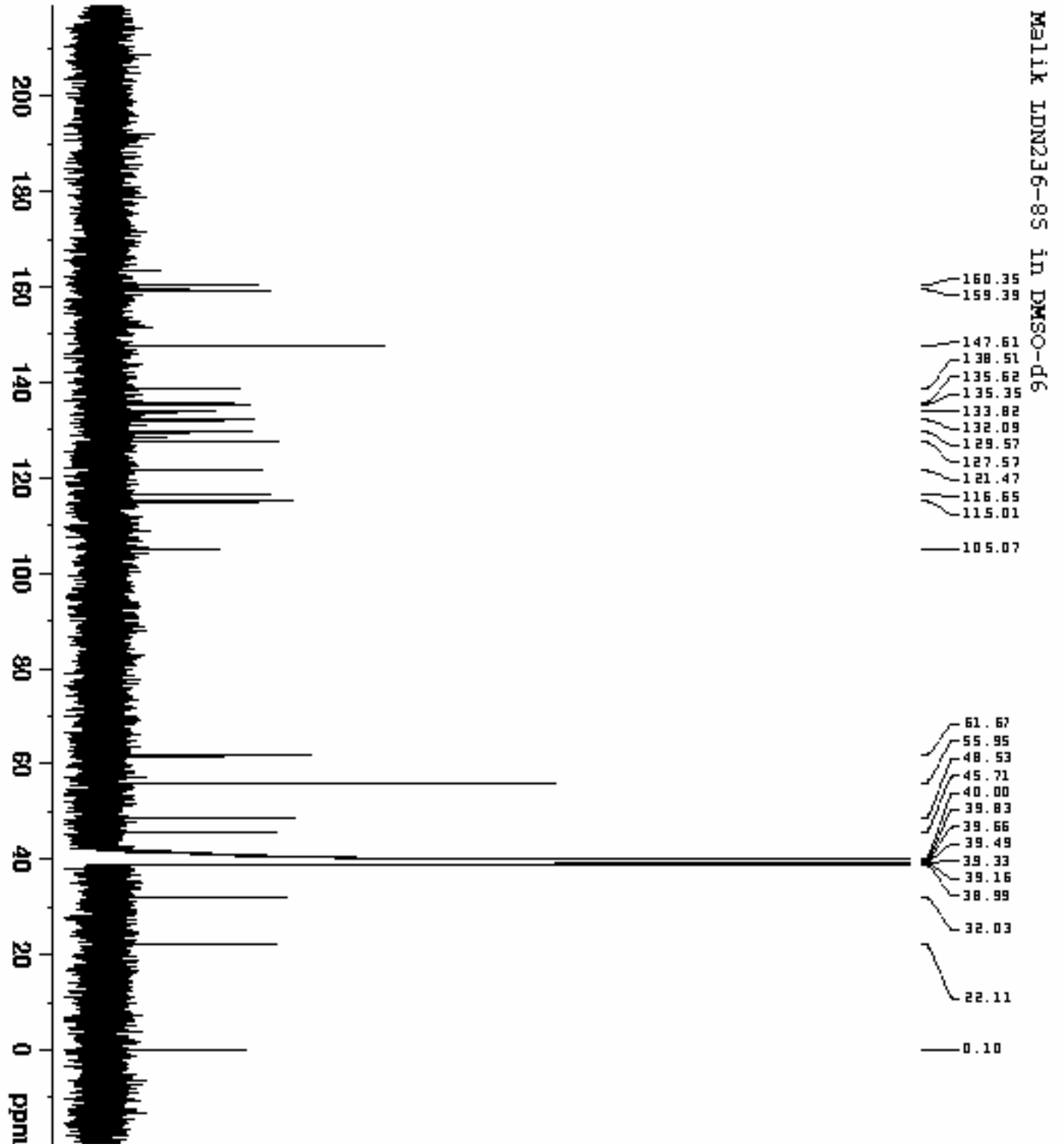

O
N
OMe
OH
N
H
O
OMe
0.99
1.00
1.11
1.14
1.08
8.50
8.00
7.50
ppm (t1)

1


1.08
1.22
6.54
1.31
3.90
3.80
3.70
3.60
3.50
ppm (t1)


O
N
OMe
OH
N
H
O
OMe

1


Malik LDN236-8S in DMSO-d6
160.35
159.39
147.61
138.51
135.62
135.35
133.82
132.09
129.57
127.57
121.47
116.65
115.01
105.07
61.67
55.95
48.53
45.71
40.00
39.83
39.66
39.49
39.33
39.16
38.99
32.03
22.11
0.10
200
180
160
140
120
100
80
60
40
20
0
ppm